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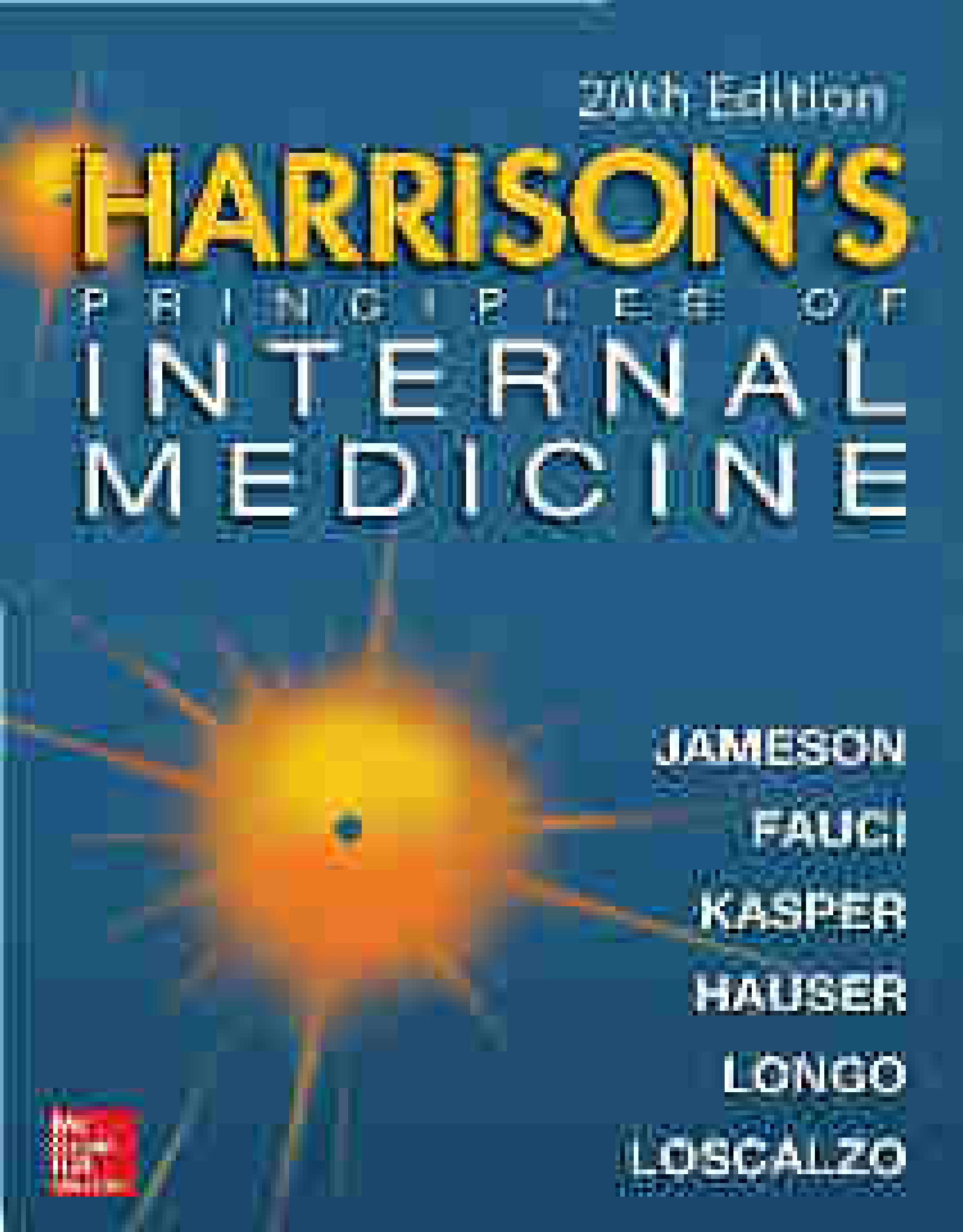

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Preface

The Editors are pleased to present the 20th edition of *Harrison's Principles of Internal Medicine.* This 20th edition is a true landmark in medicine, spanning 68 years and multiple generations of trainees and practicing clinicians. While medicine and medical education have evolved, readers will appreciate how this classic textbook has retained enduring features that have distinguished it among medical texts—a sharp focus on the clinical presentation of disease, expert in-depth summaries of pathophysiology and treatment, and highlights of emerging frontiers of science and medicine. Indeed, *Harrison's* retains its conviction that, in the profession of medicine, we are all perpetual students and lifelong learning is our common goal.

Harrison's is intended for learners throughout their careers. For *students*, Part 1, Chapter 1 begins with an overview of "The Practice of Medicine." In this introductory chapter, the editors continue the tradition of orienting clinicians to the *science* and the *art* of medicine, emphasizing the values of our profession while incorporating new advances in technology, science, and clinical care. Part 2, "Cardinal Manifestations and Presentation of Diseases" is a signature feature of *Harrison's*. These chapters eloquently describe how patients present with common clinical conditions, such as headache, fever, cough, palpitations, or anemia, and provide an overview of typical symptoms, physical findings, and differential diagnosis. Mastery of these topics prepares students for subsequent chapters on specific diseases they will encounter in courses on pathophysiology and in clinical clerkships. For *residents* and *fellows* caring for patients and preparing for board exams, *Harrison's* remains a definitive source of trusted content written by internationally renowned experts. Trainees will be reassured by the depth of content, comprehensive tables, and illuminating figures and clinical algorithms. Many exam questions are based on key testing points derived from *Harrison's* chapters. A useful companion book, *Harrison's Self-Assessment and Board Review*, includes over 1000 questions, offers comprehensive explanations of the correct answer, and provides links to the relevant chapter in the textbook. *Practicing clinicians* must keep up with an ever-changing knowledge base and clinical guidelines as part of lifelong learning. Clinicians can trust that chapters are updated extensively with each edition of *Harrison's*. The text is an excellent point-of-care reference for clinical questions, differential diagnosis, and patient management. In addition to the expanded and detailed Treatment sections, *Harrison's* continues its tradition of including "Approach to the Patient" sections, which provide an expert's overview of the practical management of common but often complex clinical conditions.

This edition has been modified extensively in its format as well as its content. We have reincorporated chapters that in previous editions were available only online. The 20th edition marks the return of *Harrison's* "Further Reading" citations at the end of each chapter, providing references carefully selected by our contributors. The authors and editors have rigorously curated and synthesized the vast amount of information that comprises general internal medicine—and each of the major specialties—into a highly readable and informative two-volume book. Readers will appreciate the concise writing style and consistency of format that have always characterized *Harrison's*. This book has a sharp focus on essential information with a goal of providing clear and definitive answers to clinical questions.

In addition to the printed book, *Harrison's* is available on multiple digital platforms, including eBook and app versions, and via an online subscription available through McGraw-Hill's popular Access Medicine (*www.accessmedicine.com*) collection. The digital editions feature an array of supplementary videos, databases, and photographic atlases as well as new literature updates, tutorials, animations, and audio discussions covering key topics in medicine. *Harrison's Manual of Medicine* is a condensed pocket version of clinical essentials derived from the more comprehensive *Harrison's Principles of Internal Medicine*. The *Manual* is also available as an eBook and an app and via Access Medicine. Together, these platforms form a potent *Harrison's* collection of reference, test prep, and point-of-care online content.

In the 20th edition, examples of new chapters include "Promoting Good Health," focusing on prevention and practical lifestyle changes to enhance longevity and well-being; "Health Care Systems in Developed Countries," providing a comparison of health delivery models from around the world; "Pharmacogenomics," applying new approaches for selecting precision medicines and appropriate doses; "Bacterial Resistance to Antimicrobial Agents," highlighting the widespread and often inappropriate use of antibiotics in clinical care and agriculture; "LGBT Health," outlining strategies to enhance access and care models for populations with distinctive health care needs; "Neuromyelitis Optica," summarizing disorders with similarities to multiple sclerosis but requiring different treatments; "Worldwide Changes in Patterns of Infectious Disease," reviewing the dynamic evolution of new infectious diseases and the containment of older disorders, some of which have plagued humankind for centuries; and "Approach to the Medical Consultation," providing practical advice to ensure that the consultant addresses the needs of the referring clinician. In addition to these and other new topics, the 20th edition presents a fascinating new series of chapters entitled "Frontiers," which foreshadows cutting-edge science that will change medical practice in the near term. Examples of new Frontier chapters include "Telomere Disease," "The Role of Epigenetics in Disease and Treatment," "The Role of Circadian Biology in Health and Disease," and "Behavioral Economics and Health."

In addition to these new topics, major advances in each subspecialty of internal medicine have been incorporated into this edition. Of particular note in this 20th edition are critical updates in the classic chapter on HIV/AIDS, which offers a clinically pragmatic focus as well as a comprehensive and analytical approach to pathogenesis. The updates cover the latest treatment protocols and address the issue of combination prevention modalities, making the chapter the most up-to-date treatise on HIV disease available.

Readers will find expanded coverage of neurodegenerative diseases, highlighting important advances in their classification and management and delineating new mechanisms responsible for the deposition and spread of pathogenic protein aggregates in these disorders. Practical guidance for the use of highly effective therapies for multiple sclerosis is another highlight of the new edition. The chapter on chronic hepatitis discusses in detail the dramatic new discoveries in the use of direct-acting antiviral agents for the treatment and cure of chronic hepatitis C virus disease; these agents are responsible for some of the most exciting therapeutic advances in medicine today.

The promise of the Human Genome Project continues to be realized in clinical medicine. This is reflected throughout the book but particularly highlighted by advances in our understanding of genetic heterogeneity of cancers, including molecular nosology that distinguishes distinct entities that share histologic similarities. The tools of genetics also inform the use of therapies targeting specific genetic lesions and immune system activation. Genetic counseling for patients with genetic predisposition to cancer (e.g., BRCA 1/2) is informing prevention strategies and reducing cancer risk. Our understanding of the microbiome, its relevance to normal physiology and disease pathogenesis, and its implications for treatment of a variety of diseases is expanding rapidly, and these advances are captured in a completely rewritten chapter "The Human Microbiome" and a thoroughly updated chapter "Microbial Genomics and Infectious Disease." The classification and management of diabetes has been thoroughly updated on the basis of new studies, clinical guidelines, and treatments. Updated guidelines for testosterone management and replacement are based on the results of new clinical trials.

We have many people to thank for their efforts in producing this book. First, the authors have done a superb job of producing authoritative chapters that synthesize vast amounts of scientific and clinical data to create informative and practical approaches to managing patients. In today's information-rich, rapidly evolving environment, they have ensured that this information is current. We are most

grateful to our colleagues who work closely with each editor to facilitate communication with the authors and help us keep *Harrison's* content current. In particular, we wish to acknowledge the expert support of Patricia Conrad, Patricia L. Duffey, Gregory K. Folkers, Julie B. McCoy, Elizabeth Robbins, Anita Rodriguez, and Stephanie Tribuna. Scott Grillo and James Shanahan, our long-standing partners at McGraw-Hill Education's Professional Publishing group, have inspired the creative and dynamic evolution of *Harrison's*, guiding the development of the book and its related products in new formats. Kim Davis, as Managing Editor, has adeptly ensured that the complex production of this multi-authored textbook proceeded smoothly and efficiently. Priscilla Beer and Armen Ovsepyen oversaw the production of our videos and animations. Jeffrey Herzich, along with other members of the McGraw-Hill Education staff, shepherded the production of this new edition.

We are privileged to have compiled this 20th edition and are enthusiastic about all that it offers our readers. We learned much in the process of editing *Harrison's* and hope that you will find this edition uniquely valuable as a clinical and educational resource.

The Editors

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1 The Practice of Medicine

The Editors

ENDURING VALUES OF THE MEDICAL PROFESSION

No greater opportunity, responsibility, or obligation can fall to the lot of a human being than to become a physician. In the care of the suffering, [the physician] needs technical skill, scientific knowledge, and human understanding.... Tact, sympathy, and understanding are expected of the physician, for the patient is no mere collection of symptoms, signs, disordered functions, damaged organs, and disturbed emotions. [The patient] is human, fearful, and hopeful, seeking relief, help, and reassurance.

—*Harrison's Principles of Internal Medicine*, 1950

The practice of medicine has changed in significant ways since the first edition of this book appeared in 1950. The advent of molecular genetics, sophisticated new imaging techniques, robotics, and advances in bioinformatics and information technology have contributed to an explosion of scientific information that has changed fundamentally the way physicians define, diagnose, treat, and attempt to prevent disease. This growth of scientific knowledge is ongoing and accelerating.

The widespread use of electronic medical records and the Internet have altered the way physicians access and exchange information as a routine part of medical practice **(Fig. 1-1)**. As today's physicians strive to integrate copious amounts of scientific knowledge into everyday practice, it is critically important to remember two things: first, the ultimate goal of medicine is to prevent disease and, when it occurs, to diagnose it early and provide effective treatment; and second, despite nearly 70 years of scientific advances since the first edition of this text, a trusting relationship between physician and patient still lies at the heart of successful patient care.

THE SCIENCE AND ART OF MEDICINE

Deductive reasoning and applied technology form the foundation for the solution to many clinical problems. Spectacular advances in biochemistry, cell biology, and genomics, coupled with newly developed imaging techniques, allow access to the innermost parts of the cell and provide a window into the most remote recesses of the body. Revelations about the nature of genes and single cells have opened a portal for formulating a new molecular basis for the physiology of systems. Increasingly, physicians are learning how subtle changes in many different genes can affect the function of cells and organisms. Researchers are deciphering the complex mechanisms by which genes are regulated. Clinicians have developed a new appreciation of the role of stem cells in normal tissue function, in the development of cancer and other disorders, and in the treatment of certain diseases. Entirely new areas of research, including studies of chronobiology, the human microbiome, and epigenetics, have become important for understanding both health and disease. Information technology enables the interrogation of medical records from millions of individuals, yielding new insights into the etiology, characteristics, and stratification of many diseases. The knowledge gleaned from the ***science of medicine*** continues to enhance the understanding by physicians of complex pathologic processes and to provide new approaches to disease prevention, diagnosis, and treatment. Yet skill in the most sophisticated applications of laboratory technology and in the use of the latest therapeutic modality alone does not make a good physician.

When a patient poses challenging clinical problems, an effective physician must be able to identify the crucial elements in a complex history and physical examination; order the appropriate laboratory, imaging, and diagnostic tests; and extract the key results from densely populated computer screens to determine whether to treat or to "watch." As the number of tests increases, so does the likelihood that some incidental finding, completely unrelated to the clinical problem at hand, will be uncovered. Deciding whether a clinical clue is worth pursuing or should be dismissed as a "red herring" and weighing whether a proposed test, preventive measure, or treatment entails a greater risk than the disease itself are essential judgments that a skilled clinician must make many times each day. This combination of medical knowledge, intuition, experience, and judgment defines the ***art of medicine***, which is as necessary to the practice of medicine as is a sound scientific base.

CLINICAL SKILLS

History-Taking The recorded history of an illness should include all the facts of medical significance in the life of the patient. Recent events should be given the most attention. Patients should, at some early point, have the opportunity to tell their own story of the illness without frequent interruption and, when appropriate, should receive expressions of interest, encouragement, and empathy from the physician. Any event related by a patient, however trivial or seemingly irrelevant, may provide the key to solving the medical problem. A methodical review of systems is important to elicit features of an underlying disease that might not be mentioned in the patient's narrative. In general, patients who feel comfortable with the physician will offer more complete information; thus, putting the patient at ease contributes substantially to obtaining an adequate history.

An informative history is more than an orderly listing of symptoms. By listening to patients and noting the way in which they describe their symptoms, physicians can gain valuable insight. Inflections of voice, facial expression, gestures, and attitude (i.e., "body language") may offer important clues to patients' perception of their symptoms. Because patients vary considerably in their medical sophistication and ability to recall facts, the reported medical history should be corroborated whenever possible. The social history also can provide important insights into the types of diseases that should be considered and can identify practical considerations for subsequent management. The family history not only identifies rare Mendelian disorders but often reveals risk factors for common disorders, such as coronary heart disease, hypertension, autoimmunity, and asthma. A thorough family history may require input from multiple relatives to ensure completeness and accuracy. An experienced clinician can usually formulate a relevant differential diagnosis from the history alone, using the physical examination and diagnostic tests to narrow the list or reveal unexpected findings that lead to more focused inquiry.

The very act of eliciting the history provides the physician with an opportunity to establish or enhance a unique bond that forms the basis for a good patient–physician relationship. This process helps the physician develop an appreciation of the patient's view of the illness, the patient's expectations of the physician and the health care system, and the financial and social implications of the illness for the patient. Although current health care settings may impose time constraints on patient visits, it is important not to rush the encounter. A hurried approach may lead patients to believe that what they are relating is not of importance to the physician, and thus they may withhold relevant information. The confidentiality of the patient–physician relationship cannot be overemphasized.

Physical Examination The purpose of the physical examination is to identify physical signs of disease. The significance of these objective indications of disease is enhanced when they confirm a functional or structural change already suggested by the patient's history. At times, however, physical signs may be the only evidence of disease and may not have been suggested by the history.

The physical examination should be methodical and thorough, with consideration given to the patient's comfort and modesty. Although

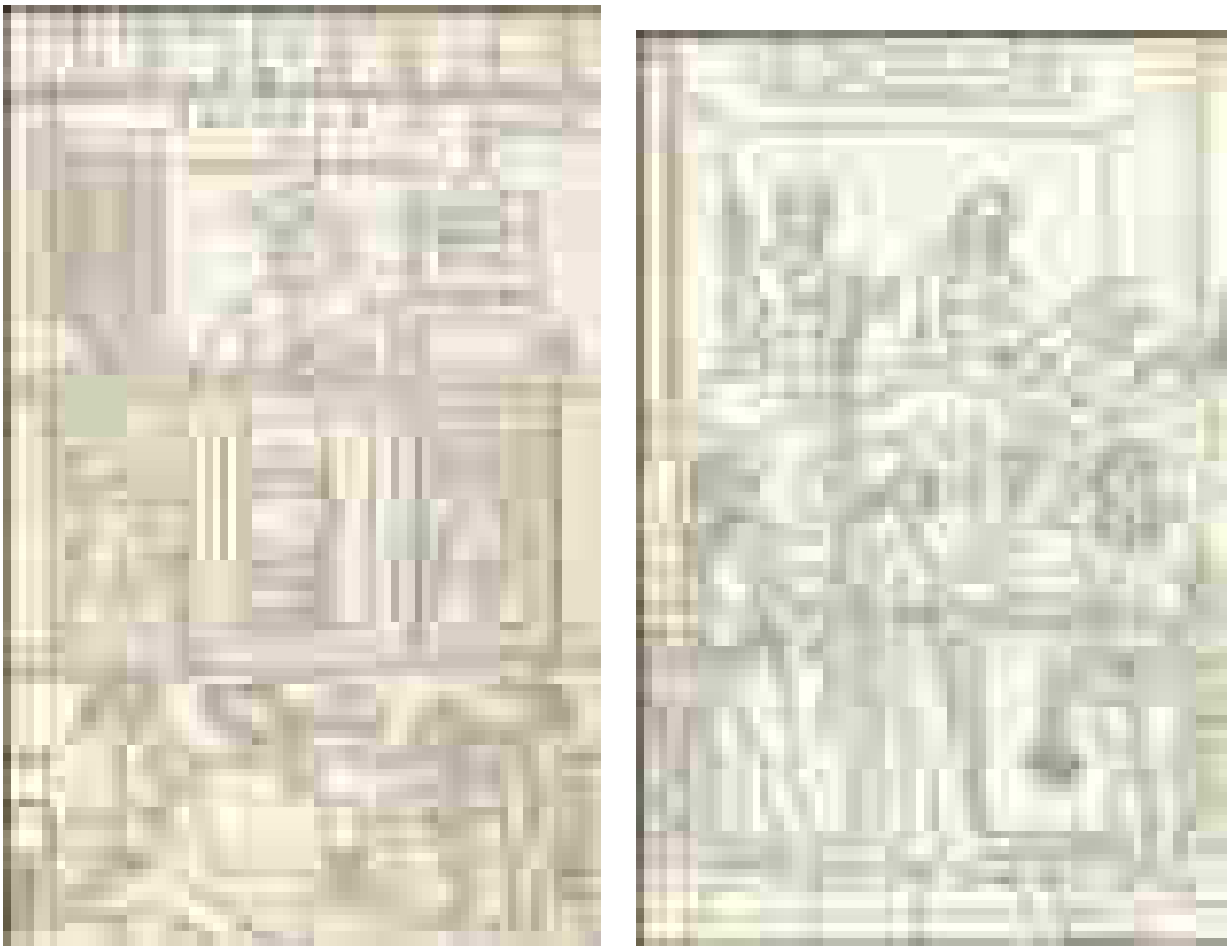

FIGURE 1-1 Woodcuts from Johannes de Ketham's *Fasciculus Medicinae*, the first illustrated medical text ever printed, show methods of information access and exchange in medical practice during the early Renaissance. Initially published in 1491 for use by medical students and practitioners, *Fasciculus Medicinae* appeared in six editions over the next 25 years. *Left:* Petrus de Montagnana, a well-known physician and teacher at the University of Padua and author of an anthology of instructive case studies, consults medical texts dating from antiquity up to the early Renaissance. *Right:* A patient with plague is attended by a physician and his attendants. *(Courtesy, U.S. National Library of Medicine.)*

attention is often directed by the history to the diseased organ or part of the body, the examination of a new patient must extend from head to toe in an objective search for abnormalities. The results of the examination, like the details of the history, should be recorded at the time they are elicited—not hours later, when they are subject to the distortions of memory. Physical examination skills should be learned under direct observation of experienced clinicians. Even highly experienced clinicians can benefit from ongoing coaching and feedback. Simulation laboratories and standardized patients play an increasingly important role in the development of clinical skills. Although the skills of physical diagnosis are acquired with experience, it is not merely technique that determines success in identifying signs of disease. The detection of a few scattered petechiae, a faint diastolic murmur, or a small mass in the abdomen is not a question of keener eyes and ears or more sensitive fingers, but of a mind alert to those findings. Because physical findings can change with time, the physical examination should be repeated as frequently as the clinical situation warrants.

Given the many highly sensitive diagnostic tests now available (particularly imaging techniques), it may be tempting to place less emphasis on the physical examination. Indeed, many patients are seen by consultants after a series of diagnostic tests have been performed and the results are known. This fact should not deter the physician from performing a thorough physical examination since important clinical findings may have escaped detection. The act of examining (touching) the patient also offers an opportunity for communication and may have reassuring effects that foster the patient–physician relationship.

Diagnostic Studies Physicians rely increasingly on a wide array of laboratory and imaging tests to make diagnoses and ultimately to solve clinical problems. However, accumulated results do not relieve the physician from the responsibility of carefully observing and examining the patient. It is also essential to appreciate the limitations of diagnostic tests. By virtue of their apparent precision, these tests often gain an aura of certainty regardless of the fallibility of the tests themselves, the instruments used in the tests, and the individuals performing or interpreting the tests. Physicians must weigh the expense involved in laboratory procedures against the value of the information these procedures are likely to provide.

Single laboratory tests are rarely ordered. Instead, physicians generally request "batteries" of multiple tests, which often prove useful and can be performed with a single specimen at relatively low cost. For example, abnormalities of hepatic function may provide the clue to nonspecific symptoms such as generalized weakness and increased fatigability, suggesting a diagnosis of chronic liver disease. Sometimes a single abnormality, such as an elevated serum calcium level, points to a particular disease, such as hyperparathyroidism or an underlying malignancy.

The thoughtful use of screening tests (e.g., measurement of low-density lipoprotein cholesterol) may allow early intervention to prevent disease **(Chap. 4)**. Screening tests are most informative when they are directed toward common diseases and when their results indicate whether other useful—but often costly—tests or interventions are needed. On the one hand, biochemical measurements, together with simple laboratory determinations such as routine serum chemistries, blood counts, and urinalysis, often provide a major clue to the presence of a pathologic process. On the other hand, the physician must learn to evaluate occasional screening-test abnormalities that do not necessarily connote significant disease. An in-depth workup after the report

of an isolated laboratory abnormality in a person who is otherwise well is often wasteful and unproductive. Because so many tests are performed routinely for screening purposes, it is not unusual for one or two values to be slightly abnormal. Nevertheless, even if there is no reason to suspect an underlying illness, tests yielding abnormal results ordinarily are repeated to rule out laboratory error. If an abnormality is confirmed, it is important to consider its potential significance in the context of the patient's condition and other test results.

There is almost continual development of technically improved imaging studies with greater sensitivity and specificity. These tests provide remarkably detailed anatomic information that can be pivotal in informing medical decision-making. Ultrasonography, CT, MRI, a variety of isotopic scans, and positron emission tomography (PET) have supplanted older, more invasive approaches and opened new diagnostic vistas. In light of their capabilities and the rapidity with which they can lead to a diagnosis, it is tempting to order a battery of imaging studies. All physicians have had experiences in which imaging studies revealed findings that led to an unexpected diagnosis. Nonetheless, patients must endure each of these tests, and the added cost of unnecessary testing is substantial. Furthermore, investigation of an unexpected abnormal finding may be associated with risk and/or expense and may lead to the diagnosis of an irrelevant or incidental problem. A skilled physician must learn to use these powerful diagnostic tools judiciously, always considering whether the results will alter management and benefit the patient.

MANAGEMENT OF PATIENT CARE

Team-Based Care Medical practice has long involved teams, particularly physicians working with nurses. Advances in medicine have increased our ability to manage very complex clinical situations (e.g., intensive care units [ICUs], bone marrow transplantation) and have shifted the burden of disease toward chronic illnesses. Because an individual patient may have multiple chronic diseases, he or she may be cared for by different specialists as well as a primary care physician. In the inpatient setting, care may involve multiple consultants along with the primary admitting physician. Communication through the medical record is necessary but not sufficient, particularly when patients have complex medical problems or when difficult decisions need to be made about the optimal management plan. Physicians should willingly meet face-to-face or by phone to ensure clear communication and thoughtful planning. It is important to note that patients often receive or perceive different messages from various care providers; attempts should be made to provide consistency among these messages to the patient. Management plans and treatment options should be outlined succinctly and clearly for the patient.

Another dimension of team-based care involves allied health professions. It is not unusual for a hospitalized patient to encounter physical therapists, pharmacists, respiratory therapists, radiology technicians, social workers, dieticians, and transport personnel (among others) in addition to physicians and nurses. Each of these individuals contributes to clinical care as well as to the patient's experience with the health care system. In the outpatient setting, disease screening and chronic disease management are often carried out by nurses, physician assistants, or other allied health professionals.

The growth of team-based care has important implications for medical culture, student and resident training, and the organization of health care systems. Despite diversity in training, skills, and responsibilities among health care professionals, common values need to be espoused and reinforced. Many medical schools have incorporated interprofessional teamwork into their curricula. Effective communication is inevitably the most challenging aspect of implementing team-based care. While communication can be aided by electronic devices, including medical records, apps, or text messages, it is vitally important to balance efficiency with taking the necessary time to speak directly with colleagues.

The Dichotomy of Inpatient and Outpatient Internal Medicine The hospital environment has experienced sweeping changes over the last few decades. Emergency departments and critical care units have evolved to manage critically ill patients, allowing them to survive formerly fatal conditions. In parallel, there is increasing pressure to reduce the length of stay in the hospital and to manage complex disorders in the outpatient setting. This transition has been driven not only by efforts to reduce costs but also by the availability of new outpatient technologies, such as imaging and percutaneous infusion catheters for long-term antibiotics or nutrition, minimally invasive surgical procedures, and evidence that outcomes often are improved by reducing inpatient hospitalization.

In addition to traditional medical beds, hospitals now encompass multiple distinct levels of care, such as the emergency department, procedure rooms, overnight observation units, critical care units, and palliative care units. A consequence of this differentiation has been the emergence of new specialties (e.g., emergency medicine and end-of-life care) and the provision of in-hospital care by hospitalists and intensivists. Most *hospitalists* are board-certified internists who bear primary responsibility for the care of hospitalized patients and whose work is limited entirely to the hospital setting. The shortened length of hospital stay means that most patients receive only acute care while hospitalized; the increased complexities of inpatient medicine make the presence of an internist with specific training, skills, and experience in the hospital environment extremely beneficial. *Intensivists* are board-certified physicians who are further certified in critical care medicine and who direct and provide care for very ill patients in critical care units. Clearly, an important challenge in internal medicine today is to ensure the continuity of communication and information flow between a patient's primary care physician and those who are in charge of the patient's hospital care. Maintaining these channels of communication is frequently complicated by patient "handoffs"—i.e., transitions from the outpatient to the inpatient environment, from the critical care unit to a general medicine floor, from a medical to a surgical service and vice versa, and from the hospital to the outpatient environment.

The involvement of many care providers in conjunction with these transitions can threaten the traditional one-to-one relationship between patient and primary care physician. Of course, patients can benefit greatly from effective collaboration among a number of health care professionals; however, *it is the duty of the patient's principal or primary physician to provide cohesive guidance through an illness*. To meet this challenge, primary care physicians must be familiar with the techniques, skills, and objectives of specialist physicians and allied health professionals who care for their patients in the hospital. In addition, primary care physicians must ensure that their patients benefit from scientific advances and the expertise of specialists, both in and out of the hospital. Primary care physicians should explain the role of these specialists to reassure patients that they are in the hands of physicians best trained to manage an acute illness. However, the primary care physician should assure patients and their families that decisions are being made in consultation with these specialists. The evolving concept of the "medical home" incorporates team-based primary care with subspecialty care in a cohesive environment that ensures smooth transitions of care.

Mitigating the Stress of Acute Illness Few people are prepared for a new diagnosis of cancer or anticipate the occurrence of a myocardial infarction, stroke, or major accident. The care of a frightened or distraught patient is confounded by these understandable responses to life-threatening events. The physician and other health providers can reduce the shock of life-changing events by providing information in a clear, calm, consistent, and reassuring manner. Often, information and reassurance need to be repeated. Caregivers should also recognize that, for outsiders, hospital emergency rooms, operating rooms, ICUs, and general medical floors represent an intimidating environment. Hospitalized patients find themselves surrounded by air jets, buttons, and glaring lights; invaded by tubes and wires; and beset by the numerous members of the health care team—hospitalists, specialists, nurses, nurses' aides, physicians' assistants, social workers, technologists, physical therapists, medical students, house officers, attending and consulting physicians, and many others. They may be

transported to special laboratories and imaging facilities replete with blinking lights, strange sounds, and unfamiliar personnel; they may be left unattended at times; and they may be obligated to share a room with other patients who have their own health problems. It is little wonder that patients may be stressed by this environment. Physicians who appreciate the hospital experience from the patient's perspective and who make an effort to guide the patient through this experience may make a stressful situation more tolerable and enhance the patient's chances for an optimal recovery.

Medical Decision-Making Medical decision-making is a fundamental responsibility of the physician and occurs at each stage of the diagnostic and therapeutic process. The decision-making process involves the ordering of additional tests, requests for consultations, decisions about treatment, and predictions concerning prognosis. This process requires an in-depth understanding of the pathophysiology and natural history of disease. Formulating a differential diagnosis requires not only a broad knowledge base but also the ability to assess the relative probabilities of various diseases for a given patient. Application of the scientific method, including hypothesis formulation and data collection, is essential to the process of accepting or rejecting a particular diagnosis. Analysis of the differential diagnosis is an iterative process. As new information or test results are acquired, the group of disease processes being considered can be contracted or expanded appropriately. Whenever possible, decisions should be evidence-based, taking advantage of rigorously designed clinical trials or objective comparisons of different diagnostic tests. *Evidence-based medicine* is in sharp contrast to anecdotal experience, which is often biased. Unless attuned to the importance of using larger, objective studies for making decisions, even the most experienced physicians can be influenced to an undue extent by recent encounters with selected patients. Evidence-based medicine has become an increasingly important part of routine medical practice and has led to the publication of many useful practice guidelines.

Despite the importance of evidence-based medicine, much medical decision-making still relies on good clinical judgment, an attribute that is difficult to quantify or even to assess qualitatively. Physicians must use their knowledge and experience as a basis for weighing known factors, along with the inevitable uncertainties, and then making a sound judgment; this synthesis of information is particularly important when a relevant evidence base is not available. Several quantitative tools may be invaluable in synthesizing the available information, including diagnostic tests, Bayes' theorem, and multivariate statistical models. Diagnostic tests serve to reduce uncertainty about an individual's diagnosis or prognosis and help the physician decide how best to manage that individual's condition. The battery of diagnostic tests complements the history and the physical examination. The accuracy of a particular test is ascertained by determining its sensitivity (true-positive rate) and specificity (true-negative rate) as well as the predictive value of a positive and a negative result. **See Chap. 3 for a more thorough discussion of decision-making in clinical medicine.**

Practice Guidelines Many professional organizations and government agencies have developed formal clinical-practice guidelines to aid physicians and other caregivers in making diagnostic and therapeutic decisions that are evidence-based, cost-effective, and most appropriate to a particular patient and clinical situation. As the evidence base of medicine increases, guidelines can provide a useful framework for managing patients with particular diagnoses or symptoms. Clinical guidelines can protect patients—particularly those with inadequate health care benefits—from receiving substandard care. These guidelines also can protect conscientious caregivers from inappropriate charges of malpractice and society from the excessive costs associated with the overuse of medical resources. There are, however, caveats associated with clinical-practice guidelines since they tend to oversimplify the complexities of medicine. Furthermore, groups with different perspectives may develop divergent recommendations regarding issues as basic as the need for screening of women by mammography or of men by serum prostate-specific antigen (PSA). Finally, guidelines, as the term implies, do not—and cannot be expected to—account for the uniqueness of each individual and his or her illness. The physician's challenge is to integrate into clinical practice the useful recommendations offered by experts without accepting them blindly or being inappropriately constrained by them.

Precision Medicine The concept of *precision* or *personalized medicine* reflects the growing recognition that diseases once lumped together can be further stratified on the basis of genetic, biomarker, phenotypic, and/or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations. Inherent in this concept is the goal of targeting therapies in a more specific way to improve clinical outcomes for the individual patient and minimize unnecessary side effects for those less likely to respond to a particular treatment. In some respects, precision medicine represents the evolution of clinical practice guidelines, which are usually developed for populations of patients or a particular diagnosis (e.g., hypertension, thyroid nodule). As the pathophysiology, prognosis, and treatment responses of subgroups within these diagnoses become better understood, the relevant clinical guidelines incorporate progressively more refined recommendations for individuals within these subgroups. The role of precision medicine is particularly important for cancers in which genetic testing is able to predict responses (or the lack thereof) to targeted therapies **(Chap. 69)**. One can anticipate similar applications of precision medicine in pharmacogenomics, immunologic disorders, and diseases in which biomarkers better predict treatment responses.

Evaluation of Outcomes Clinicians generally use *objective* and readily measurable parameters to judge the outcome of a therapeutic intervention. These measures may oversimplify the complexity of a clinical condition as patients often present with a major clinical problem in the context of multiple complicating background illnesses. For example, a patient may present with chest pain and cardiac ischemia, but with a background of chronic obstructive pulmonary disease and renal insufficiency. For this reason, outcome measures such as mortality, length of hospital stay, or readmission rates are typically risk-adjusted. An important point to remember is that patients usually seek medical attention for *subjective* reasons; they wish to obtain relief from pain, to preserve or regain function, and to enjoy life. The components of a patient's health status or quality of life can include bodily comfort, capacity for physical activity, personal and professional function, sexual function, cognitive function, and overall perception of health. Each of these important domains can be assessed through structured interviews or specially designed questionnaires. Such assessments provide useful parameters by which a physician can judge patients' subjective views of their disabilities and responses to treatment, particularly in chronic illness. The practice of medicine requires consideration and integration of both objective and subjective outcomes.

Many health systems use survey and patient feedback data to assess qualitative features such as patient satisfaction, access to care, and communication with nurses and physicians. In the United States, HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) surveys are used by many systems and are publically reported. Social media is also being used to assess feedback in real time as well as to share patient experiences with health care systems.

Errors in the Delivery of Health Care A series of reports from the Institute of Medicine (now the National Academy of Medicine [NAM]) called for an ambitious agenda to reduce medical error rates and improve patient safety by designing and implementing fundamental changes in health care systems. It is the responsibility of hospitals and health care organizations to develop systems to reduce risk and ensure patient safety. Medication errors can be reduced through the use of ordering systems that rely on electronic processes or, when electronic options are not available, that eliminate misreading of handwriting. Whatever the clinical situation, it is the physician's responsibility to use powerful therapeutic measures wisely, with due regard for their beneficial actions, potential dangers, and cost. Implementation of infection

control systems, enforcement of hand-washing protocols, and careful oversight of antibiotic use can minimize the complications of nosocomial infections. Central-line infection rates have been dramatically reduced at many centers by careful adherence of trained personnel to standardized protocols for introducing and maintaining central lines. Rates of surgical infection and wrong-site surgery can likewise be reduced by the use of standardized protocols and checklists. Falls by patients can be minimized by judicious use of sedatives and appropriate assistance with bed-to-chair and bed-to-bathroom transitions. Taken together, these and other measures are saving thousands of lives each year.

Electronic Medical Records Both the growing reliance on computers and the strength of information technology now play central roles in medicine, including efforts to reduce medical errors. Laboratory data are accessed almost universally through computers. Many medical centers now have electronic medical records (EMRs), computerized order entry, and bar-coded tracking of medications. Some of these systems are interactive, sending reminders or warning of potential medical errors.

EMRs offer rapid access to information that is invaluable in enhancing health care quality and patient safety, including relevant data, historical and clinical information, imaging studies, laboratory results, and medication records. These data can be used to monitor and reduce unnecessary variations in care and to provide real-time information about processes of care and clinical outcomes. Ideally, patient records are easily transferred across the health care system. However, technological limitations and concerns about privacy and cost continue to limit broad-based use of EMRs in many clinical settings.

For all of the advantages of EMRs, they can create distance between the physician and patient if care is not taken to preserve face-to-face contact. EMRs also require training and time for data entry. Many providers spend significant time entering information to generate structured data and to meet billing requirements. They may feel pressured to take short cuts, such as "cutting and pasting" parts of earlier notes into the daily record, thereby increasing the risk of errors. EMRs also structure information in a manner that disrupts the traditional narrative flow across time and among providers. These features, which may be frustrating for some providers, must be weighed against the advantages of ready access to past medical history, imaging, laboratory data, and consultant notes.

It is important to emphasize that information technology is merely a tool and can never replace the clinical decisions that are best made by the physician. Clinical knowledge and an understanding of a patient's needs, supplemented by quantitative tools, still represent the best approach to decision-making in the practice of medicine.

THE PATIENT–PHYSICIAN RELATIONSHIP

The significance of the intimate personal relationship between physician and patient cannot be too strongly emphasized, for in an extraordinarily large number of cases both the diagnosis and treatment are directly dependent on it. One of the essential qualities of the clinician is interest in humanity, ***for the secret of the care of the patient is in caring for the patient****.*

—Francis W. Peabody, October 21, 1925,
Lecture at Harvard Medical School

Physicians must never forget that patients are individuals with problems that all too often transcend their physical complaints. They are not "cases" or "admissions" or "diseases." Patients do not fail treatments; treatments fail to benefit patients. This point is particularly important in this era of high technology in clinical medicine. Most patients are anxious and fearful. Physicians should instill confidence and offer reassurance, but they must never come across as arrogant or patronizing. A professional attitude, coupled with warmth and openness, can do much to alleviate anxiety and to encourage patients to share all aspects of their medical history. Empathy and compassion are the essential features of a caring physician. The physician needs to consider the setting in which an illness occurs—in terms not only of patients themselves but also of their familial, social, and cultural backgrounds. The ideal patient–physician relationship is based on thorough knowledge of the patient, mutual trust, and the ability to communicate.

Informed Consent The fundamental principles of medical ethics require physicians to act in the patient's best interest and to respect the patient's autonomy. These requirements are particularly relevant to the issue of informed consent. Patients are required to sign consent forms for most diagnostic or therapeutic procedures. Many patients possess limited medical knowledge and must rely on their physicians for advice. Communicating in a clear and understandable manner, physicians must fully discuss the alternatives for care and explain the risks, benefits, and likely consequences of each alternative. The physician is responsible for ensuring that the patient thoroughly understands these risks and benefits; encouraging questions is an important part of this process. It may be necessary to go over certain issues with the patient more than once. This is the very definition of *informed consent*. Complete, clear explanation and discussion of the proposed procedures and treatment can greatly mitigate the fear of the unknown that commonly accompanies hospitalization. Often the patient's understanding is enhanced by repeatedly discussing the issues in an unthreatening and supportive way, answering new questions that occur to the patient as they arise. Clear communication can also help alleviate misunderstandings in situations where complications of intervention occur.

Special care should be taken to ensure that a physician seeking a patient's informed consent has no real or apparent conflict of interest.

Approach to Grave Prognoses and Death No circumstance is more distressing than the diagnosis of an incurable disease, particularly when premature death is inevitable. What should the patient and family be told? What measures should be taken to maintain life? What can be done to optimize quality of life?

Transparency of information, delivered in an appropriate manner, is essential in the face of a terminal illness. Even patients who seem unaware of their medical circumstances, or whose family members have protected them from diagnoses or prognoses, often have keen insights into their condition. They may also have misunderstandings that can lead to additional anxiety. The patient must be given an opportunity to talk with the physician and ask questions. A wise and insightful physician uses such open communication as the basis for assessing what the patient wants to know and when he or she wants to know it. On the basis of the patient's responses, the physician can assess the right tempo for sharing information. Ultimately, the patient must understand the expected course of the disease so that appropriate plans and preparations can be made. The patient should participate in decision-making with an understanding of the goal of treatment (palliation) and its likely effects. The patient's religious beliefs should be taken into consideration. Some patients may find it easier to share their feelings about death with their physician, nurses, or members of the clergy than with family members or friends.

The physician should provide or arrange for emotional, physical, and spiritual support and must be compassionate, unhurried, and open. In many instances, there is much to be gained by the laying on of hands. Pain should be controlled adequately, human dignity maintained, and isolation from family and close friends avoided. These aspects of care tend to be overlooked in hospitals, where the intrusion of life-sustaining equipment can detract from attention to the whole person and encourage concentration instead on the life-threatening disease, against which the battle ultimately will be lost in any case. In the face of terminal illness, the goal of medicine must shift from *cure* to *care* in the broadest sense of the term. *Primum succurrere*, first hasten to help, is a guiding principle. In offering care to a dying patient, a physician should be prepared to provide information to family members and deal with their grief and sometimes their feelings of guilt or even anger. It is important for the physician to assure the family that everything reasonable is being done. A substantial challenge in these discussions is that the physician often does not know how to gauge the prognosis. In addition, various members of the health care team may offer different opinions. Good communication among providers is

essential so that consistent information is provided to patients. This is especially important when the best path forward is uncertain. Advice from experts in palliative and terminal care should be sought whenever appropriate to ensure that clinicians are not providing patients with unrealistic expectations. **For a more complete discussion of end-of-life care, see Chap. 9.**

Maintaining Humanism and Professionalism Many trends in the delivery of health care tend to make medical care impersonal. These trends, some of which have been mentioned already, include (1) vigorous efforts to reduce the escalating costs of health care; (2) the growing number of managed-care programs, which are intended to reduce costs but in which the patient may have little choice in selecting a physician; (3) increasing reliance on technological advances and computerization; and (4) the need for numerous physicians and other health professionals to be involved in the care of most patients who are seriously ill.

In light of these changes in the medical care system, it is a major challenge for physicians to maintain the *humane* aspects of medical care. The American Board of Internal Medicine, working together with the American College of Physicians–American Society of Internal Medicine and the European Federation of Internal Medicine, has published a *Charter on Medical Professionalism* that underscores three main principles in physicians' contract with society: (1) the primacy of patient welfare, (2) patient autonomy, and (3) social justice. While medical schools appropriately place substantial emphasis on professionalism, a physician's personal attributes, including integrity, respect, and compassion, also are extremely important. In the United States, the Gold Humanism Society recognizes individuals who are exemplars of humanistic patient care and serve as role models for medical education and training.

Availability to the patient, expression of sincere concern, willingness to take the time to explain all aspects of the illness, and a nonjudgmental attitude when dealing with patients whose cultures, lifestyles, attitudes, and values differ from those of the physician are just a few of the characteristics of a humane physician. Every physician will, at times, be challenged by patients who evoke strongly negative or positive emotional responses. Physicians should be alert to their own reactions to such situations and should consciously monitor and control their behavior so that the patient's best interest remains the principal motivation for their actions at all times.

Another important aspect of patient care involves an appreciation of the patient's "quality of life," a subjective assessment of what each patient values most. This assessment requires detailed, sometimes intimate knowledge of the patient, which usually can be obtained only through deliberate, unhurried, and often repeated conversations. Time pressures will always threaten these interactions, but they should not diminish the importance of understanding and seeking to fulfill the priorities of the patient.

EXPANDING FRONTIERS IN MEDICAL PRACTICE

The Era of "Omics" In the spring of 2003, announcement of the complete sequencing of the human genome officially ushered in the genomic era. However, even before that landmark accomplishment, the practice of medicine had been evolving as a result of insights into both the human genome and the genomes of a wide variety of microbes. The clinical implications of these insights are illustrated by the complete genome sequencing of H1N1 influenza virus in 2009 and the rapid identification of H1N1 influenza as a potentially fatal pandemic illness, leading to the swift development and dissemination of an effective protective vaccine. Today, gene expression profiles are being used to guide therapy and inform prognosis for a number of diseases, and genotyping is providing a new means to assess the risk of certain diseases as well as variations in response to a number of drugs. Despite these advances, the use of complex genomics in the diagnosis, prevention, and treatment of disease is still in its early stages. The task of physicians is complicated by the fact that phenotypes generally are determined not by genes alone but by the interplay of genetic and environmental factors.

Rapid progress is also being made in other areas of molecular medicine. *Epigenetics* is the study of alterations in chromatin and histone proteins and methylation of DNA sequences that influence gene expression **(Chap. 471)**. Every cell of the body has identical DNA sequences; the diverse phenotypes a person's cells manifest are the result of epigenetic regulation of gene expression. Epigenetic alterations are associated with a number of cancers and other diseases. *Proteomics*, the study of the entire library of proteins made in a cell or organ and the complex relationship of these proteins to disease, is enhancing the repertoire of the 23,000 genes in the human genome through alternate splicing, posttranslational processing, and posttranslational modifications that often have unique functional consequences. The presence or absence of particular proteins in the circulation or in cells is being explored for diagnostic and disease-screening applications. *Microbiomics* is the study of the resident microbes in humans and other mammals, which together compose the microbiome. The human haploid genome has ~23,000 genes, whereas the microbes residing on and in the human body encompass more than 3–4 million genes; these resident microbes are likely to be of great significance with regard to health status. Ongoing research is demonstrating that the microbes inhabiting human mucosal and skin surfaces play a critical role in maturation of the immune system, in metabolic balance, and in disease susceptibility. A variety of environmental factors, including the use and overuse of antibiotics, have been tied experimentally to substantial increases in disorders such as obesity, metabolic syndrome, atherosclerosis, and immune-mediated diseases in both adults and children. *Metagenomics*, of which microbiomics is a part, is the genomic study of environmental species that have the potential to influence human biology directly or indirectly. An example is the study of exposures to microorganisms in farm environments that may be responsible for the lower incidence of asthma among children raised on farms. *Metabolomics* is the study of the range of metabolites in cells or organs and the ways they are altered in disease states. The aging process itself may leave telltale metabolic footprints that allow the prediction (and possibly the prevention) of organ dysfunction and disease. It seems likely that disease-associated patterns will be found in lipids, carbohydrates, membranes, mitochondria, and other vital components of cells and tissues. *Exposomics* is the study of the exposome—i.e., the environmental exposures such as smoking, sunlight, diet, exercise, education, and violence that together have an enormous impact on health. All of this new information represents a challenge to the traditional reductionist approach to medical thinking. The variability of results in different patients, together with the large number of variables that can be assessed, creates challenges in identifying preclinical disease and defining disease states unequivocally. Accordingly, the tools of *systems biology* and *network medicine* are being applied to the enormous body of information now obtainable for every patient and may eventually provide new approaches to classifying disease. **For a more complete discussion of a complex systems approach to human disease, see Chap. 476.**

The rapidity of these advances may seem overwhelming to practicing physicians. However, physicians have an important role to play in ensuring that these powerful technologies and sources of new information are applied judiciously to patient care. Since "omics" are evolving so rapidly, physicians and other health care professionals must engage in continuous learning so that they can apply this new knowledge to the benefit of their patients' health and well-being. Genetic testing requires wise counsel based on an understanding of the value and limitations of the tests as well as the implications of their results for specific individuals. **For a more complete discussion of genetic testing, see Chap. 457.**

The Globalization of Medicine Physicians should be cognizant of diseases and health care services beyond local boundaries. Global travel has implications for disease spread, and it is not uncommon for diseases endemic to certain regions to be seen in other regions after a patient has traveled to and returned from those regions. The outbreak of Zika virus infections in the Americas is a cogent example of this phenomenon. In addition, factors such as wars, the migration of refugees, and climate change are contributing to changing disease

profiles worldwide. Patients have broader access to unique expertise or clinical trials at distant medical centers, and the cost of travel may be offset by the quality of care at those distant locations. As much as any other factor influencing global aspects of medicine, the Internet has transformed the transfer of medical information throughout the world. This change has been accompanied by the transfer of technological skills through telemedicine and international consultation—for example, interpretation of radiologic images and pathologic specimens. **For a complete discussion of global issues, see Chap. 460.**

Medicine on the Internet On the whole, the Internet has had a positive effect on the practice of medicine; through personal computers, a wide range of information is available to physicians and patients almost instantaneously at any time and from anywhere in the world. This medium holds enormous potential for the delivery of current information, practice guidelines, state-of-the-art conferences, journal content, textbooks (including this text), and direct communications with other physicians and specialists, expanding the depth and breadth of information available to the physician regarding the diagnosis and care of patients. Medical journals are now accessible online, providing rapid sources of new information. By bringing them into direct and timely contact with the latest developments in medical care, this medium also serves to lessen the information gap that has hampered physicians and health care providers in remote areas.

Patients, too, are turning to the Internet in increasing numbers to acquire information about their illnesses and therapies and to join Internet-based support groups. Patients often arrive at a clinic visit with sophisticated information about their illnesses. In this regard, physicians are challenged in a positive way to keep abreast of the latest relevant information while serving as an "editor" as patients navigate this seemingly endless source of information, the accuracy and validity of which are not uniform.

A critically important caveat is that virtually anything can be published on the Internet, with easy circumvention of the peer-review process that is an essential feature of academic publications. Both physicians and patients who search the Internet for medical information must be aware of this danger. Notwithstanding this limitation, appropriate use of the Internet is revolutionizing information access for physicians and patients and in this regard represents a remarkable resource that was not available to practitioners a generation ago.

Public Expectations and Accountability The general public's level of knowledge and sophistication regarding health issues has grown rapidly over the last few decades. As a result, expectations of the health care system in general and of physicians in particular have risen. Physicians are expected to master rapidly advancing fields (the *science* of medicine) while considering their patients' unique needs (the *art* of medicine). Thus, physicians are held accountable not only for the technical aspects of the care they provide but also for their patients' satisfaction with the delivery and costs of care.

In many parts of the world, physicians increasingly are expected to account for the way in which they practice medicine by meeting certain standards prescribed by federal and local governments. The hospitalization of patients whose health care costs are reimbursed by the government and other third parties is subjected to utilization review. Thus, a physician must defend the cause for and duration of a patient's hospitalization if it falls outside certain "average" standards. Authorization for reimbursement increasingly is based on documentation of the nature and complexity of an illness, as reflected by recorded elements of the history and physical examination. A growing "pay-for-performance" movement seeks to link reimbursement to quality of care. The goal of this movement is to improve standards of health care and contain spiraling health care costs. In many parts of the United States, managed (capitated) care contracts with insurers have replaced traditional fee-for-service care, placing the onus of managing the cost of all care directly on the providers and increasing the emphasis on preventive strategies. In addition, physicians are expected to give evidence of their current competence through mandatory continuing education, patient record audits, maintenance of certification, and relicensing.

Medical Ethics and New Technologies The rapid pace of technological advances has profound implications for medical applications that go far beyond the traditional goals of disease prevention, treatment, and cure. Cloning, genetic engineering, gene therapy, human–computer interfaces, nanotechnology, and use of targeted therapies have the potential to modify inherited predispositions to disease, select desired characteristics in embryos, augment "normal" human performance, replace failing tissues, and substantially prolong life span. Given their unique training, physicians have a responsibility to help shape the debate on the appropriate uses of and limits placed on these new techniques and to consider carefully the ethical issues associated with the implementation of such interventions. As medicine becomes more complex, shared decision-making is increasingly important, particularly in areas such as genetic counseling and end-of-life care, but also in most instances of considering diagnostic and treatment options.

Learning Medicine More than a century has passed since the publication of the Flexner Report, a seminal study that transformed medical education and emphasized the scientific foundations of medicine as well as the acquisition of clinical skills. In an era of burgeoning information and access to medical simulation and informatics, many schools are implementing new curricula that emphasize lifelong learning and the acquisition of competencies in teamwork, communication skills, system-based practice, and professionalism. The tools of medicine also change continuously, necessitating formal training in the use of EMRs, large datasets, ultrasound, robotics, and new imaging techniques. These and other features of the medical school curriculum provide the foundation for many of the themes highlighted in this chapter and are expected to allow physicians to progress, with experience and learning over time, from competency to proficiency to mastery.

At a time when the amount of information that must be mastered to practice medicine continues to expand, increasing pressures both within and outside of medicine have led to the implementation of restrictions on the amount of time a physician-in-training can spend in the hospital and in clinics. Because the benefits associated with continuity of medical care and observation of a patient's progress over time were thought to be outstripped by the stresses imposed on trainees by long hours and by fatigue-related errors, strict limits were set on the number of patients that trainees could be responsible for at one time, the number of new patients they could evaluate in a day on call, and the number of hours they could spend in the hospital. In 1980, residents in medicine worked in the hospital more than 90 hours per week on average. In 1989, their hours were restricted to no more than 80 per week. Resident physicians' hours further decreased by ~10% between 1996 and 2008, and in 2010 the Accreditation Council for Graduate Medical Education further restricted (i.e., to 16 hours per shift) consecutive in-hospital duty hours for first-year residents. The impact of these changes is still being assessed, but the evidence that medical errors have decreased as a consequence is sparse. An unavoidable by-product of fewer hours at the bedside is an increase in the number of "handoffs" of patient responsibility from one physician to another. These transfers often involve a transition from a physician who knows the patient well, having evaluated that individual on admission, to a physician who knows the patient less well. It is imperative that these transitions of responsibility be handled with care and thoroughness, with all relevant information exchanged and acknowledged.

The Physician as Perpetual Student From the time physicians graduate from medical school, it becomes all too apparent that this milestone is symbolic and that they must embrace the role of a "perpetual student." This realization is at the same time exhilarating and anxiety-provoking. It is exhilarating because physicians can apply constantly expanding knowledge to the treatment of their patients; it is anxiety-provoking because physicians realize that they will never know as much as they want or need to know. Ideally, physicians will translate the latter feeling into energy through which they can continue to improve and reach their potential. It is the physician's responsibility to pursue new knowledge continually by reading, attending

conferences and courses, and consulting colleagues and the Internet. This is often a difficult task for a busy practitioner; however, a commitment to continued learning is an integral part of being a physician and must be given the highest priority.

The Physician as Citizen Being a physician is a privilege. The capacity to apply one's skills for the benefit of fellow human beings is a noble calling. The physician–patient relationship is inherently unbalanced in the distribution of power. In light of their influence, physicians must always be aware of the potential impact of what they do and say and must always strive to strip away individual biases and preferences to find what is best for their patients. To the extent possible, physicians should also act within their communities to promote health and alleviate suffering. Meeting these goals begins by setting a healthy example and continues in taking action to deliver needed care even when personal financial compensation may not be available.

Research, Teaching, and the Practice of Medicine The word *doctor* is derived from the Latin *docere*, "to teach." As teachers, physicians should share information and medical knowledge with colleagues, students of medicine and related professions, and their patients. The practice of medicine is dependent on the sum total of medical knowledge, which in turn is based on an unending chain of scientific discovery, clinical observation, analysis, and interpretation. Advances in medicine depend on the acquisition of new information through research, and improved medical care requires the transmission of that information. As part of their broader societal responsibilities, physicians should encourage patients to participate in ethical and properly approved clinical investigations if these studies do not impose undue hazard, discomfort, or inconvenience. Physicians engaged in clinical research must be alert to potential conflicts of interest between their research goals and their obligations to individual patients. The best interests of the patient must always take priority.

To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease—these are our ambitions.

—William Osler, 1849–1919

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2 Promoting Good Health

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GOALS AND APPROACHES TO PREVENTION

Prevention of acute and chronic diseases before their onset has been recognized as one of the hallmarks of excellent medical practice for centuries, and is now used as a metric for highly functioning healthcare systems. The ultimate goal of preventive strategies is to avoid premature death. However, as longevity has increased dramatically worldwide over the last century (largely as a result of public health practices), increasing emphasis is placed on prevention for the purpose of preserving quality of life and extending the healthspan, not just the lifespan. Given that all patients will eventually die, the goal of prevention ultimately becomes compression of morbidity toward the end of the lifespan; that is, reduction of the amount of burden and time spent with disease prior to dying. As shown in Fig. 2-1, normative aging tends to involve a steady decline in the stock of health, with accelerating decline over time. Successful prevention offers the opportunity both to extend life and to extend healthy life, thus "squaring the curve" of health loss during aging.

Prevention strategies have been characterized as tertiary, secondary, primary, and primordial. *Tertiary prevention* requires rapid action to prevent imminent death in the setting of acute illness, such as through percutaneous coronary intervention in the setting of ST-segment elevation myocardial infarction. *Secondary prevention* strategies focus on avoiding the recurrence of disease and death in an individual who is already affected. For example, tamoxifen is recommended for women with surgically treated early-stage, estrogen-receptor-positive breast cancer, because it reduces the risk of recurrent breast cancer (including in the contralateral breast) and death. *Primary prevention* attempts to reduce the risk of incident disease among individuals with a risk factor. Treatment of elevated blood pressure in individuals who have not yet experienced cardiovascular disease represents one example of primary prevention that has proven effective in reducing the incidence of stroke, heart failure, and coronary heart disease.

Primordial prevention is a more recent concept (first introduced in 1979) which focuses on prevention of the development of *risk factors* for disease, not just prevention of disease. Primordial prevention strategies emphasize upstream determinants of risk for chronic diseases, such as eating patterns, physical activity, and environmental and social determinants of health. It therefore encompasses medical treatment strategies for individuals as well as a strong reliance on public health and social policy. It is increasingly clear that primordial prevention represents the ultimate means for reducing the burden of chronic diseases of aging. Once risk factors develop, it is difficult

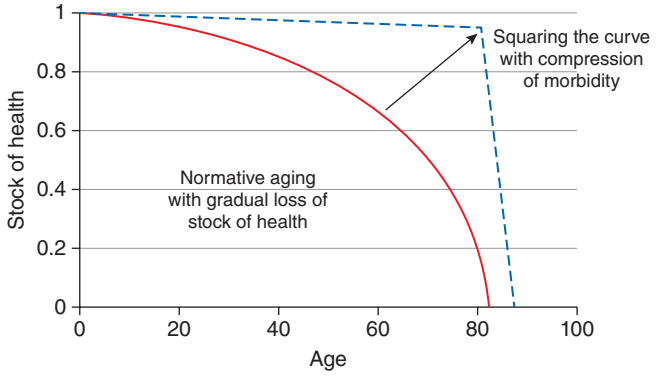

FIGURE 2-1 Loss of health with aging. Representation of normative aging with loss of the full stock of health with which individuals are born (indicating gain of morbidity), contrasted with a squared curve with greater longevity and fuller stock of health (less morbidity) until shortly before death. The "squared curve" represents the likely ideal situation for most patients.

to restore risk to the low level of someone who never developed the risk factor. The time spent with adverse levels of the risk factor often causes irreversible damage that precludes complete restoration of low risk. For example, individuals with hypertension who are treated back to optimal levels (<120/<80 mmHg) do have a lower risk compared with untreated patients with hypertension, but they still have twice the risk of cardiovascular events as those who maintained optimal blood pressure without medications. Patients with elevated blood pressure that is subsequently treated have greater left ventricular mass index, worse renal function, and more evidence of atherosclerosis and other target organ damage as a result of the time spent with elevated blood pressure; such damage cannot be fully reversed despite efficacious therapy with antihypertensive medications. Conversely, as described below in greater detail, individuals who maintain optimal levels of all major cardiovascular risk factors into middle age through primordial prevention essentially abolish their lifetime risk of developing cardiovascular disease while also living substantially longer and having a lower burden of other comorbid illnesses (compression of morbidity).

Prevention strategies should be distinguished from disease screening strategies. Screening attempts to detect evidence of disease at its earliest stages, when treatment is likely to be more efficacious than for advanced disease **(Chap. 4)**. Screening can be performed in service of prevention, especially if it aids in identifying pre-clinical markers associated with elevated disease risk.

HEALTH PROMOTION

In recent decades, medical practice has increasingly focused on public health approaches to promote health, and not just prevent disease. Prevention of disease is a worthy individual and societal goal in and of itself, but it does not necessarily guarantee health. Health is a broader construct encompassing more than just absence of disease. It includes biological, physiological, and psychological domains (among others) in a continuum, rather than occurring as a dichotomous trait. Health is therefore somewhat subjective, but attempts have been made to use more objective criteria to define health in order to raise awareness, prevent disease, and promote healthy longevity.

For example, in 2010 the American Heart Association (AHA) defined a new construct of "cardiovascular health" based on evidence of associations with longevity, disease avoidance, healthy longevity, and quality of life. The definition of cardiovascular health is based on seven health behaviors and health factors (eating pattern, physical activity, body mass, smoking status, and levels of blood pressure, blood cholesterol, and blood glucose) and includes a spectrum from poor to ideal. Individuals with optimal levels of all seven metrics simultaneously are considered to have ideal cardiovascular health. The state of cardiovascular health for an individual or a population can be assessed with simple scoring by counting the number of ideal metrics (out of 7) or applying 0 points for each poor metric, 1 point for each intermediate metric, and 2 points for each ideal metric, thus creating a composite cardiovascular health score ranging from 0 to 14 points. Higher cardiovascular health scores in younger and middle ages have been associated with greater longevity, lower incidence of cardiovascular disease, lower incidence of other chronic diseases of aging (including dementia, cancer, and more), compression of morbidity, greater quality of life, and lower healthcare costs, achieving both individual and societal goals for healthy aging, and further establishing the critical importance of primordial prevention and cardiovascular health promotion.

Focusing on health promotion, rather than just disease prevention, may also provide greater motivation for patients to pursue lifestyle changes or adhere to clinician recommendations. Extensive literature suggests that providing patients solely with information regarding disease risk, or risk reduction with treatment, is unlikely to motivate desired behavior change. Empowering patients with strategies to achieve positive health goals after discussing risks can provide more effective adherence and better long-term outcomes. In the case of smoking cessation, enumerating only the risks of smoking can lead to patient inertia and therapeutic nihilism, and has proven an ineffective approach, whereas strategies that incorporate positive health messaging, support and feedback, with appropriate use of evidence-based therapies, have proven far more effective.

PRIORITIZING PREVENTION STRATEGIES

In secondary prevention, the patient already has manifest clinical disease, and is therefore at high risk for progression. The approach should be to work with the patient to implement all evidence-based strategies that will help to prevent recurrence or progression. This will typically include drug therapy as well as therapeutic lifestyle changes to control ongoing risk factors which may have caused disease in the first place. Juggling priorities can be difficult, and barriers to implementation are many, including costs, time, patient health literacy, and patient and caregiver capacity to organize the regimen. Addressing these potential barriers with the patient can help to forge a therapeutic bond and may improve adherence; ignoring them will likely lead to therapeutic failure. Numerous studies demonstrate that, even in high-functioning health systems, only ~50% of patients are taking recommended, evidence-based secondary prevention medications, such as statins, by 1 year after a myocardial infarction.

In patients who are eligible for primary prevention strategies, it is important to frame the discussion around the overall evidence base as well as an individual patient's likelihood of benefit from a given preventive intervention. A first step is to understand the patient's estimated absolute risk for disease in the foreseeable future, or during their remaining lifespan. However, absolute risk estimation and presentation of those risks is generally insufficient to motivate behavior change. It is critical to assess the patient's understanding and tolerance of the risk, their readiness to implement lifestyle changes or adhere to drug therapy, and their overall preferences regarding use of drug therapy to prevent an event (e.g., cancer, myocardial infarction, stroke). The clinician can help the patient by informing them of the risks for disease and potential for absolute benefits (and harms) from the available evidence-based choices. This may take more than one conversation, but given that diseases, such as cancer and cardiovascular disease, are the leading causes of premature death and disability, the time is well spent.

Partnering with the patient through motivational interviewing may assist in the process of selecting initial approaches to prevention. Selecting an area that the patient feels they are ready to change can lead to better adherence and greater achievement of success in the short and longer term. If the patient is uncertain what course to choose, prudence would dictate focusing on control of risk factors that may lead to the most rapid reduction in risk for acute events. For example, blood pressure is both a chronic risk factor and an acute trigger for cardiovascular events. Thus, if a patient has both significant elevations in blood pressure and dyslipidemia, it would be appropriate to focus initial efforts on blood pressure control. Likewise, focus on smoking cessation can lead to more rapid reductions in risk for acute events than some other lifestyle interventions.

PREVENTION AND HEALTH PROMOTION ACROSS THE LIFE COURSE

Periodic Health Evaluations The "routine annual physical" has in many ways become an expected part of the patient-physician relationship in primary care practice. However, evidence for the efficacy of the periodic health evaluation in asymptomatic adults unselected for risk factors or disease is mixed, and depends on the outcome. Systematic reviews and meta-analyses of published trials have consistently observed lack of benefit (and also lack of harm) in terms of total mortality in association with periodic health evaluations. Data are more heterogeneous but overall suggest no benefit for cancer- or cardiovascular-specific mortality, with the potential for either benefit or harm depending on number of evaluations and patient-level factors. Well-designed studies on non-fatal clinical events and morbidity have been sparsely reported but there appear to be no large effects.

Periodic health evaluations do appear to lead to greater diagnosis of certain conditions such as hypertension and dyslipidemia, as expected. Likewise, periodic health examinations also improve the delivery of recommended preventive services, such as gynecologic examinations

and Papanicolaou smears, fecal occult blood testing, and cholesterol screening. The benefits and risks associated with screening tests are discussed in detail in Chap. 4. Risks of routine evaluations include inappropriate or over-testing, or false-positive findings that require follow-up and induce patients to worry. Periodic health examinations appear to be associated with less patient worry. On balance, given the lack of convincing evidence of harm and the potential for better delivery of appropriate screening, counseling, and preventive services, periodic health evaluations appear reasonable for general populations at average risk for chronic conditions.

It is important to note that routine annual comprehensive physical examinations of asymptomatic adult patients have very low yield and may take an inordinate amount of time in a wellness visit. Such time may be better spent on assessing and counseling the patient on other aspects of their health, as discussed below. Evidence-based components that should be included in periodic evaluations focused on health and prevention include a number of age-appropriate screening tests for chronic disease and risk factors, preventive interventions including immunizations and chemoprevention for at-risk individuals, and preventive counseling. The United States Preventive Services Task Force publishes its *Guide to Clinical Preventive Services,* which contains evidence-based recommendations from the Task Force on preventive services for which there is a high degree of certainty that the service provides at least moderate net clinical benefit (i.e., benefits outweigh harms significantly and to a reasonable magnitude).

Healthy Behaviors and Lifestyles Owing to the paucity of evidence, the heterogeneity of study designs and the diverse nature of interventions studied, many clinicians are uncertain as to how to deliver advice regarding healthy behaviors and lifestyles. Nevertheless, adverse behaviors and lifestyles contribute to more than 75% of premature, preventable deaths and disability. Estimates from the US National Health and Nutrition Survey indicate that fewer than 1% of Americans achieve an optimal heart-healthy eating pattern. Thus, whereas there are many demands on time during a typical patient-clinician encounter, few things may have more impact on longevity, health and quality of life for asymptomatic patients than an efficient approach to assessing, documenting, and improving patients' health behaviors. Indeed, the mere act of assessing health behaviors has been shown to affect patient's health behaviors. Facility with tools for assessment of lifestyle and with strategies for counseling are therefore of paramount importance.

Healthy Eating Patterns (see Chap. 325) Despite the existence of numerous "fad" diets, and seemingly inconsistent recommendations on dietary composition, there is remarkable agreement about what should constitute a healthy eating pattern for the broad population to avoid nutritional deficits (i.e., vitamin deficiency) and excesses (i.e., excessive caloric intake) and to maximize potential health (Table 2-1). Optimal eating patterns consist of whole fruits and vegetables, whole grains, lean proteins, healthy oils, and allow for non-fat or low-fat dairy intake. They tend to exclude frequent ingestion of foods high in refined sugars and starches, saturated fat, and sodium. Since sodium and refined sugars and starches are the hallmark of much of the processed/packaged food supply, a simple rule of thumb is to provide/cook the majority of one's own meals starting from whole foods and emphasizing fruits and vegetables. Likewise, foods prepared outside of the home tend to have higher fat and sodium content, so special attention to menu choices focused on fruits, vegetables, lean proteins, and whole grains, while minimizing sauces and dressings can help most individuals follow healthier eating patterns. In all cases, sugar-sweetened beverages and non-nutritious snack foods should be minimized. If snacks are included, small amounts of healthy nuts and seeds, or more fruits and vegetables, should be encouraged.

Specific conditions and diseases, such as diabetes, other metabolic disorders, allergies, and gastrointestinal disorders, may require tailored approaches to diet. In counseling most patients, the general approach should focus on whole foods, eating patterns and appropriate calorie balance, rather than on specific micronutrients such as electrolytes or selected vitamins. It should be remembered that most patients have

TABLE 2-1 Guidelines and Key Recommendations from the *Dietary Guidelines for Americans*, 2015–2020

GUIDELINES	KEY RECOMMENDATIONS
1. Follow a healthy eating pattern across the lifespan. All food and beverage choices matter. Choose a healthy eating pattern at an appropriate calorie level to help achieve and maintain a healthy body weight, support nutrient adequacy, and reduce the risk of chronic disease.	The Dietary Guidelines' Key Recommendations for healthy eating patterns should be applied in their entirety, given the interconnected relationship that each dietary component can have with others. **Consume a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.** **A healthy eating pattern includes:** • A variety of vegetables from all of the subgroups—dark green, red and orange, legumes (beans and peas), starchy, and other • Fruits, especially whole fruits • Grains, at least half of which are whole grains • Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages • A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products • Oils **A healthy eating pattern limits:** • Saturated fats and trans fats, added sugars, and sodium Key Recommendations that are quantitative are provided for several components of the diet that should be limited. These components are of particular public health concern in the United States, and the specified limits can help individuals achieve healthy eating patterns within calorie limits: • Consume <10% of calories per day from added sugars • Consume <10% of calories per day from saturated fats • Consume <2300 milligrams (mg) per day of sodium • If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and up to two drinks per day for men—and only by adults of legal drinking age. In tandem with the recommendations above, Americans of all ages—children, adolescents, adults, and older adults—should meet the *Physical Activity Guidelines for Americans* to help promote health and reduce the risk of chronic disease. Americans should aim to achieve and maintain a healthy body weight. The relationship between diet and physical activity contributes to calorie balance and managing body weight. As such, the Dietary Guidelines includes a Key Recommendation to: **Meet the US Department of Health and Human Services' *Physical Activity Guidelines for Americans*** **2. Focus on variety, nutrient density, and amount.** To meet nutrient needs within calorie limits, choose a variety of nutrient-dense foods across and within all food groups in recommended amounts. **3. Limit calories from added sugars and saturated fats and reduce sodium intake.** Consume an eating pattern low in added sugars, saturated fats, and sodium. Cut back on foods and beverages higher in these components to amounts that fit within healthy eating patterns. **4. Shift to healthier food and beverage choices.** Choose nutrient-dense foods and beverages across and within all food groups in place of less healthy choices. Consider cultural and personal preferences to make these shifts easier to accomplish and maintain. **5. Support healthy eating patterns for all.** Everyone has a role in helping to create and support healthy eating patterns in multiple settings nationwide, from home to school to work to communities.

Source: Adapted from the *Dietary Guidelines for Americans, 2015–2020.* Washington, DC: US Department of Agriculture and US Department of Health and Human Services; 2015. Available at *https://health.gov/dietaryguidelines/2015/guidelines/*.

difficulty understanding nutritional labels on packaged foods, with the attendant demands on numeracy and health literacy.

Dietary guidelines are published by the US Department of Agriculture (USDA) and US Department of Health and Human Services every 5 years, and these guidelines have undergone substantial evolution over time. The current US Dietary Guidelines and Key Recommendations for 2015–2020 are summarized in Table 2-1 and emphasize eating patterns with nutrient-dense (rather than calorie-dense) whole foods, and appropriate caloric intake to achieve and maintain healthy weight. The USDA Guidelines focus on the concept of a healthy plate (rather than the prior food pyramid) for ease of counseling and adoption. Fifty percent of the plate should consist of fruits and vegetables, with remaining portions for whole grains and lean protein foods. When using fat for cooking, it should be done by sauteing in healthier oils (e.g., canola oil), and addition of judicious amounts of healthy raw oils (e.g., olive oil) to dishes is appropriate.

The USDA Guidelines focus on specific healthy eating patterns that adhere to these broad recommendations, and are appropriate for ~97% of the general population. They identify a "Healthy US-Style Eating Pattern" that adheres closely to the evidence-based Dietary Approaches to Stop Hypertension (DASH) eating pattern. Alternative patterns, which vary more in emphasis than in content, include a "Healthy Mediterranean-Style Eating Pattern" and a "Healthy Vegetarian Eating Pattern."

AGE- AND SEX-SPECIFIC RECOMMENDATIONS Current dietary recommendations are generally similar for all life stages from ages ≥2 years, but recommended levels of caloric intake (and hence amounts of foods) differ by age, sex, and physical activity level. For example, recommended caloric intake ranges from 1000 calories/d for sedentary 2-year-old children to as high as 3200 calories/d for active 16- to 18-year-old young men. Recommended caloric intakes peak in the early twenties for men and women and gradually decrease over ensuing decades.

As with all lifestyle counseling aimed at behavior change, dietary approaches that partner with the patient and utilize motivational interviewing strategies and shared goals and commitments tend to work best, as described below (see Approach to the Patient).

Physical Activity Similar to the approach to counseling regarding healthy eating patterns, recommendations on participation in physical activity emphasize the point that any physical activity is better than none. A simple rule of thumb for patients is: "If you are doing nothing, do something; and if you are doing something, do more, every day." The evidence base for physical activity indicates that the marginal benefits from physical activity are greatest in advancing from no activity to low levels of moderate activity. With increasing duration and intensity of activity, there is a continued curvilinear increase in health benefits, but the marginal gains for each additional minute of moderate-to-vigorous activity slowly diminish. Thus, for adults, the optimal amount of physical activity recommended is 150 min of moderate-intensity or 75 min of vigorous intensity aerobic activity per week, performed in episodes of at least 10 min, and preferably spread throughout the week. Additional health benefits can be realized by engaging in physical activity beyond this amount, and/or by adding muscle-strengthening activities that involve all major muscle groups 2 or more days per week.

In counseling patients regarding physical activity, it is important to note that sedentary time (e.g., seated at work, or at home in front of electronic screens) has adverse health consequences independent of the lack of physical activity during these episodes. Therefore, even modest efforts like standing at the desk and doing gentle stretching for periods during the day may be beneficial. It is also important to emphasize that participating in a variety of aerobic activities (biking, swimming, walking, jogging, rowing, elliptical training, stair-climbing, etc.) can be beneficial and may help to avoid overuse injuries and boredom with the exercise regimen. If patients choose to participate in muscle-strengthening activities for health improvement, emphasis should be placed on weights that allow more repetitions (e.g., 3 sets of 15–20 repetitions that can be performed comfortably, with a rest period in between) and on avoiding breath-holding and straining against a closed glottis.

SUDDEN CARDIAC DEATH RISK Patients may express concerns regarding the risk of sudden cardiac death during exercise. Whereas the risk of sudden death during exercise does increase directly with the amount of time spent exercising, this association is substantially mitigated by training effects. Thus, patients embarking on an exercise program should be encouraged to increase the duration of aerobic exercise gradually as tolerated, aiming for episodes of at least 30 min 5 times a week as an ideal. Once a comfortable duration is reached, incorporating interval training periods of more intensive activity interspersed during the exercise can provide greater fitness gains.

EXTREME ENDURANCE ACTIVITIES As with other forms of exercise, extreme endurance activities such as triathlons and marathons should be undertaken only with appropriate and graded training. Such activities tend to take a greater toll on the musculoskeletal system over time than less extreme activities, and they are also associated with measurable damage to the myocardium and greater risks for other organ damage. Athletes participating in endurance activities routinely have elevations in cardiac troponin (a specific circulating marker of myocardial cell damage and death) at the end of the race, although elevations are lower in those who are well trained. Patients and clinicians should consider the patient's overall health, specific limitations, potential for injury, and ability to train in decision-making regarding participation in endurance events.

AGE-SPECIFIC RECOMMENDATIONS The US Department of Health and Human Services' *Physical Activity Guidelines for Americans* **(Table 2-2)** recommend that children and adolescents aged 6–17 years should participate in ≥60 min of physical activity daily, most of which should be moderate- or vigorous-intensity aerobic activity, including vigorous activity at least 3 days a week. As noted above, adults aged 18–64 years are recommended to pursue at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity per week (or equivalent combinations). Adults aged ≥65 years should follow the adult guidelines, or be as active as possible as abilities and conditions allow. Special emphasis is also placed on exercises to improve balance in those at risk for falling.

Sleep Hygiene Sleeping between 7 and 9 h per night appears to be optimal for health in adults aged ≥18 years. Sleeping <7 h is associated with adverse outcomes, including obesity, diabetes, elevated blood pressure, cardiovascular disease, depression, and all-cause mortality, as well as physiologic disturbances such as impaired immune function, increased pain sensitivity, and impaired cognitive performance. Conversely, achieving appropriate levels of sleep is associated with more success in weight loss, better blood pressure control among patients with hypertension, and improved mental health and performance. Regular sleep more than 9 h per night is appropriate for children and adolescents, or individuals recovering from sleep deprivation or illness, but for most individuals the effects on health are uncertain.

Patients often express concerns about the quantity and quality of their sleep. With aging, both aspects of sleep tend to decline, even without overt sleep disorders. Documentation of sleep using a sleep log may assist in understanding different types of insomnia and sleep disorders. Encouraging daily activity to promote fatigue, avoidance of eating and drinking alcohol too close to bedtime, and regular daily sleep habits may help patients achieve better sleep. Regular use of sedative medications should generally be discouraged given the high potential for dependence, addiction, and altered sleep quality.

DISORDERS OF SLEEP The prevalence of sleep-related breathing disorders, including obstructive sleep apnea (OSA), is poorly documented. Based on data from the 1990s, the prevalence of diagnosed mild OSA in the US population was ~10%, and of moderate to severe apnea was ~5%. However, the increasing prevalence of obesity, a major risk factor for OSA, suggests that the prevalence may have increased. The prevalence of asymptomatic or undiagnosed sleep apnea is unknown. Patients with persistent complaints of poor sleep quality, excessive daytime somnolence, or with witnessed apneic spells may benefit from screening for sleep disorders, prior to consideration of a formal sleep study. A number of clinical tools have been developed to screen

TABLE 2-2 Recommendations from *Physical Activity Guidelines for Americans*

AGE	RECOMMENDATIONS
6–17 years	Children and adolescents should do 60 min (1 h) or more of physical activity daily. • Aerobic: Most of the ≥60 min a day should be either moderate[a] or vigorous-intensity[b] aerobic physical activity, and should include vigorous-intensity physical activity at least 3 days a week. • Muscle-strengthening:[c] As part of their ≥60 min of daily physical activity, children and adolescents should include muscle-strengthening physical activity on at least 3 days of the week. • Bone-strengthening:[d] As part of their ≥60 min of daily physical activity, children and adolescents should include bone-strengthening physical activity on at least 3 days of the week. • It is important to encourage young people to participate in physical activities that are appropriate for their age, that are enjoyable, and that offer variety.
18–64 years	• All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits. • For substantial health benefits, adults should do at least 150 min (2 h and 30 min) a week of moderate-intensity, or 75 min (1 h and 15 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 min, and preferably, it should be spread throughout the week. • For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 min (5 h) a week of moderate-intensity, or 150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount. • Adults should also include muscle-strengthening activities that involve all major muscle groups on ≥2 days a week.
≥65 years	• Older adults should follow the adult guidelines. When older adults cannot meet the adult guidelines, they should be as physically active as their abilities and conditions will allow. • Older adults should do exercises that maintain or improve balance if they are at risk of falling. • Older adults should determine their level of effort for physical activity relative to their level of fitness. • Older adults with chronic conditions should understand whether and how their conditions affect their ability to do regular physical activity safely.

[a]Moderate-intensity physical activity: Aerobic activity that increases a person's heart rate and breathing to some extent. On a scale relative to a person's capacity, moderate-intensity activity is usually a 5 or 6 on a 0 to 10 scale. Brisk walking, dancing, swimming, or bicycling on a level terrain are examples. [b]Vigorous-intensity physical activity: Aerobic activity that greatly increases a person's heart rate and breathing. On a scale relative to a person's capacity, vigorous-intensity activity is usually a 7 or 8 on a 0 to 10 scale. Jogging, singles tennis, swimming continuous laps, or bicycling uphill are examples. [c]Muscle-strengthening activity: Physical activity, including exercise that increases skeletal muscle strength, power, endurance, and mass. It includes strength training, resistance training, and muscular strength and endurance exercises. [d]Bone-strengthening activity: Physical activity that produces an impact or tension force on bones, which promotes bone growth and strength. Running, jumping rope, and lifting weights are examples.

Source: Adapted from U.S. Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans.* Washington, DC: U.S. Department of Health and Human Services; 2008. Available at *http://www.health.gov/paguidelines.*

for sleep apnea, including the Epworth Sleepiness Scale, the STOP (Snoring, Tiredness, Observed apnea, high blood Pressure) Questionnaire, and the STOP-Bang Questionnaire (STOP plus assessment of body mass index, age, neck circumference, and gender), among others. The US Preventive Services Task Force found that current evidence is insufficient to assess the balance of benefits and harms of screening for OSA in asymptomatic adults owing to a lack of validation data in primary care settings. Nonetheless, the high prevalence and significant health consequences of sleep apnea suggest that clinicians should be alert for its potential presence, particularly in patients who are obese with symptoms of excessive daytime somnolence or witnessed apnea episodes. Other sleep disorders, such as restless leg syndrome, may be identified with simple history.

Weight Management Overweight and obesity are prevalent in epidemic proportions in the US and other industrialized nations **(Chaps. 394, 395)**. Since 1985, the prevalence of obesity in the United States has increased from ~10% to almost 35%, and the prevalence of overweight is now ~40%. Overweight and obesity disproportionately affect individuals in lower socio-economic strata, and in many underserved minority populations, including African Americans, Latino Americans, and American Indians. In all race-ethnic groups, both overweight and obesity are associated with adverse health consequences, including diabetes, certain cancers, cardiovascular diseases, and degenerative joint disease. Eating disorders such as anorexia and bulimia are much less common but pose major health consequences for affected patients, and should be suspected particularly in younger women with history of rapid weight shifts or underweight status.

Weight loss is one of the most difficult preventive interventions to achieve and sustain over time. However, several key factors can assist the patient and clinician, and early referral to a dietician can be very helpful. The first therapeutic goal is to aim for weight stabilization. Many of the risks of overweight and obesity are driven more strongly by continued weight gain, rather than overweight/obese status per se. Working with the patient to find initial strategies for weight maintenance can be a successful initial step with success for many patients. For those who can progress to considering weight loss, it is critical to help the patient understand that there is no standard solution. Experimentation and documentation are key. Tools to assist patients can include food and weight logs, activity logs, and smart phone apps. Some patients respond best to structured commercial dietary programs where meals are provided to them. Any of these approaches can be tried with or without social group supports.

The key construct for weight loss is, of course, negative calorie balance. This is achieved through a combination of reduced caloric intake and increased physical activity. Patients may already understand, from prior weight loss attempts, what combination works best for them to achieve this. Some patients find that they cannot lose weight without increasing their exercise. For many, reduction of caloric intake is most efficient. Encouraging the patient to find what works for them is most important. The same principle holds for dietary content. Well done feeding studies indicate that weigh loss is dependent far more on the reduction of caloric intake than on the relative composition of fat, protein and carbohydrate in the diet. There may be other medical reasons to choose one approach over another, but if not, encouraging the patient to pick one approach and document the results is an important start.

Tobacco Cessation (see Chap. 448) Escaping nicotine dependence is another major, but critical, challenge to prevention and wellness efforts. The addictive effects of nicotine have been well documented, with effects that can last for years after successful cessation. Assessing a patient's past history of cessation attempts and current readiness for change are key first steps in forging a successful approach. Frequent follow-up and reinforcement, as well as use of nicotine replacement therapy and other cessation-promoting medications are additional critical elements. Recidivism is the rule, and patients should expect to resume smoking and attempt again as they journey to tobacco cessation.

MENTAL HEALTH AND ADDICTION

Assessment for depression and cognitive impairment are important to address when patients exhibit symptoms, or they or their family members express concerns. Both of these common conditions play a major role in reducing quality of life and are high on patients' lists of concerns, even if not clearly expressed. Screening tools for depression are reviewed in **Chap. 444**. Cognitive function decline with aging or comorbid illness, including depression, should be anticipated. Assessment tools such as the General Practitioner Assessment of Cognition or the Mini-Cog™ test are widely available and effective rapid assessment tools.

Alcohol and Opioids (see Chaps. 445, 446) Alcohol dependence and abuse are common and underdiagnosed. Rapid screening tools have proven efficacy for identifying patients with alcohol problems. In a systematic review, the CAGE (cut down, guilty, annoyed, eye opener) questionnaire was most effective at identifying alcohol abuse and dependence, with reasonable sensitivity and high specificity. The present opioid epidemic in the United States presents a new and substantial public health challenge given the high potential for dependency and abuse of these drugs. Rapid screening tools are being developed and validated to assist clinicians in screening for opioid dependence.

ACCIDENTS AND SUICIDE

Regular assessment of patient safety through simple questions about seat belt use, domestic violence, and gun safety in the home continue to be important parts of health promotion and wellness. Longstanding recommendations for assessment of suicidal ideation among patients with depression or a history of suicide attempts also continue to be relevant.

APPROACH TO THE PATIENT

In the context of a clinical visit focused on health assessment, health promotion, and prevention, the basic skills of history taking are of paramount importance. Much of the evaluation, counseling, and management that focus on health promotion and prevention also require engagement and buy-in from the patient in order to assist with recognition of contributing behaviors and to promote adherence to therapeutic plans. Therefore, in addition to standard history-taking, additional skills such as motivational interviewing and eliciting patient commitments and contracting may prove of significant value. The availability of additional tools to assist with screening and chronic management, both online and through mobile health technologies, is rapidly expanding, with uncertain implications for the future. Major research gaps exist in our understanding of how best to employ these newer technologies to improve health outcomes. Concepts of behavioral economics are being explored to better understand the psychology of decision-making and incentives as a means to improve lifestyle choices and adherence to treatment plans **(Chap. 468)**.

The limited time available to clinicians and patients during a wellness visit or periodic health examination (not driven by specific patient issues) makes it important to prioritize assessment and counseling for factors that affect longevity, healthspan, and quality of life over approaches that may have low yield, such as the annual comprehensive physical examination in an asymptomatic patient. Setting clear expectations for the content of a wellness visit may be a first step, and scheduling follow-up visits for findings or to continue indicated counseling are important steps to achieving better health outcomes.

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3 Decision-Making in Clinical Medicine

Daniel B. Mark, John B. Wong

Sir William Osler's familiar quote "Medicine is a science of uncertainty and an art of probability" captures well the complex nature of clinical medicine. Although the science of medicine is often taught as if the mechanisms of the human body operate with Newtonian predictability, every aspect of medical practice is infused with an element of irreducible uncertainty that the clinician ignores at her peril. Clinical medicine has deep roots in science, but it is an imprecise science. More than 100 years after the practice of medicine took its modern form, it remains at its core a craft, to which individual doctors bring varying levels of skill and understanding. With the exponential growth in medical literature and other technical information and an ever increasing number of testing and treatment options, twenty-first century physicians who seek excellence in their craft must master a more diverse and complex set of skills than any of the generations that preceded them. This chapter provides an introduction to three of the pillars upon which the craft of modern medicine rests: (1) expertise in clinical reasoning (what it is and how it can be developed); (2) rational diagnostic tests, use and interpretation; and (3) integration of the best available research evidence with clinical judgment in the care of individual patients (*evidence-based medicine* or *EBM* and the tools of EBM).

BRIEF INTRODUCTION TO CLINICAL REASONING

Clinical Expertise Defining "clinical expertise" remains surprisingly difficult. Chess has an objective ranking system based on skill and performance criteria. Athletics, similarly, have ranking systems to distinguish novices from Olympians. But in medicine, after physicians complete training and pass the boards (or get recertified), no tests or benchmarks are used to identify those who have attained the highest levels of clinical performance. Physicians often consult a few "elite" clinicians for their "special problem-solving prowess" when particularly difficult or obscure cases have baffled everyone else. Yet despite their skill, even such master clinicians typically cannot explain their exact processes and methods, thereby limiting the acquisition and dissemination of the expertise used to achieve their impressive results. Furthermore, clinical virtuosity appears not to be generalizable, e.g., an expert on hypertrophic cardiomyopathy may be no better (and possibly worse) than a first-year medical resident at diagnosing and managing a patient with neutropenia, fever, and hypotension.

Broadly construed, clinical expertise includes not only cognitive dimensions involving the integration of disease knowledge with verbal and visual cues and test interpretation but also potentially the complex fine-motor skills necessary for invasive procedures and tests. In addition, "the complete package" of expertise in medicine requires effective communication and care coordination with patients and members of the medical team. Research on medical expertise remains sparse overall

and mostly centered on diagnostic reasoning, so in this chapter, we focus primarily on the cognitive elements of clinical reasoning.

Because clinical reasoning occurs in the heads of clinicians, objective study of the process is difficult. One research method used for this area asks clinicians to "think out loud" as they receive increments of clinical information in a manner meant to simulate a clinical encounter. Another research approach focuses on how doctors should reason diagnostically to identify remediable "errors" rather than on how they actually do reason. Much of what is known about clinical reasoning comes from empirical studies of nonmedical problem-solving behavior. Because of the diverse perspectives contributing to this area, with important contributions from cognitive psychology, medical education, behavioral economics, sociology, informatics, and decision sciences, no single integrated model of clinical reasoning exists, and not infrequently, different terms and reasoning models describe similar phenomena.

Intuitive Versus Analytic Reasoning A useful contemporary model of reasoning, dual-process theory distinguishes two general systems of cognitive processes. *Intuition* (System 1) provides rapid effortless judgments from memorized associations using pattern recognition and other simplifying "rules of thumb" (i.e., heuristics). For example, a very simple pattern that could be useful in certain situations is "African-American women plus hilar adenopathy equals sarcoid." Because no effort is involved in recalling the pattern, typically, the clinician is unable to say how those judgments were formulated. In contrast, *Analysis* (System 2), the other form of reasoning in the dual-process model, is slow, methodical, deliberative, and effortful. A student might read about lymph nodes in the lung and from that list (e.g., **Chap. 62**), identify diseases more common in African-American women or examine the patient for skin or eye findings that may occur with sarcoid. These dual processes, of course, represent two exemplars taken from the cognitive continuum. They provide helpful descriptive insights but very little guidance in how to develop expertise in clinical reasoning. How these idealized systems interact in different decision problems, how experts use them differently from novices, and when their use can lead to errors in judgment remain the subject of study and considerable debate.

Pattern recognition, an important part of System 1 reasoning, is a complex cognitive process that appears largely effortless. One can recognize people's faces, the breed of a dog, an automobile model, or a piece of music from just a few notes within milliseconds without necessarily being able to articulate the specific features that prompted the recognition. Analogously, experienced clinicians often recognize familiar diagnosis patterns very quickly. The key here is having a large library of stored patterns that can be rapidly accessed. In the absence of an extensive stored repertoire of diagnostic patterns, students (as well as more experienced clinicians operating outside their area of expertise and familiarity) often must use the more laborious System 2 analytic approach along with more intensive and comprehensive data collection to reach the diagnosis.

The following three brief scenarios of a patient with hemoptysis illustrate three distinct patterns that experienced clinicians recognize without effort:

- A 46-year-old man presents to his internist with a chief complaint of hemoptysis. An otherwise healthy, nonsmoker, he is recovering from an apparent viral bronchitis. This presentation pattern suggests that the small amount of blood-streaked sputum is due to acute bronchitis, so that a chest x-ray provides sufficient reassurance that a more serious disorder is absent.
- In the second scenario, a 46-year-old patient who has the same chief complaint but with a 100-pack-year smoking history, a productive morning cough, with blood-streaked sputum, and weight loss fits the pattern of carcinoma of the lung. Consequently, along with the chest x-ray, the clinician obtains a sputum cytology examination and refers this patient for a chest CT scan.
- In the third scenario, the clinician hears a soft diastolic rumbling murmur at the apex on cardiac auscultation in a 46-year-old patient with hemoptysis who immigrated from a developing country and orders an echocardiogram as well, because of possible pulmonary hypertension from suspected rheumatic mitral stenosis.

Pattern recognition by itself is not, however, sufficient for secure diagnosis. Without deliberative systematic reflection, pattern recognition can result in premature closure: mistakenly jumping to the conclusion that one has correct diagnosis before all the relevant data are in. A critical second step, even when the diagnosis seems obvious, is *diagnostic verification*: considering whether the diagnosis adequately accounts for the presenting symptoms and signs and can explain all the ancillary findings. An example of premature closure is contained in the following case, modified from a real clinical encounter. A 45-year-old man presents with a 3-week history of a "flulike" upper respiratory infection (URI) including dyspnea and a productive cough. The Emergency Department (ED) clinician pulled out a "URI assessment form" which defines and standardizes the information gathered. After quickly acquiring the requisite structured examination components and noting in particular the absence of fever and a clear chest examination, the physician prescribed a cough suppressant for acute bronchitis and reassured the patient that his illness was not serious. Following a sleepless night at home with significant dyspnea, the patient developed nausea and vomiting and collapsed. He was brought back to the ED in cardiac arrest and was unable to be resuscitated. His autopsy showed a posterior wall myocardial infarction (MI) and a fresh thrombus in an atherosclerotic right coronary artery. What went wrong? Presumably, the ED clinician felt that the patient was basically healthy (one can be misled by the way the patient appears on examination—a patient that does not "appear sick" may be incorrectly assumed to have an innocuous illness). So in this case, the physician, upon hearing the overview of the patient from the triage nurse, elected to use the URI assessment protocol even before starting the history, closing consideration of the broader range of possibilities and associated tests required to confirm or refute these possibilities. In particular, by concentrating on the abbreviated and focused URI protocol, the clinician failed to elicit the full dyspnea history, which was precipitated by exertion and accompanied by chest heaviness and relieved by rest, suggesting a far more serious disorder.

Heuristics or rules of thumb are a part of the intuitive system. These cognitive shortcuts provide a quick and easy path to reaching conclusions and making choices, but when used improperly they can lead to errors. Two major research programs have studied heuristics in a mostly non-medical context and have reached very different conclusions about the value of these cognitive tools. The "heuristics and biases" program focuses on how relying on heuristics can lead to cognitive biases and incorrect judgments. Over 100 different cognitive biases have been described. So far, however, there is little evidence that educating physicians and other decision makers to watch for these cognitive biases has any effect on the rate of diagnostic errors. In contrast, the "fast and frugal heuristics" research program explores how and when relying on simple heuristics can produce good decisions. Although many heuristics have relevance to clinical reasoning, only four will be mentioned here.

When diagnosing patients, clinicians usually develop diagnostic hypotheses based on the similarity of that patient's symptoms, signs and other data to their mental representations (memorized patterns) of the disease possibilities. In other words, clinicians pattern match to identify the diagnoses which share the most similar findings to the patient at hand. This cognitive shortcut is called the representativeness heuristic. Consider a patient with hypertension and headache, palpitations, and diaphoresis. Based on the representativeness heuristic, clinicians might judge pheochromocytoma to be quite likely given this classic presenting symptom triad suggesting pheochromocytoma. Doing so however, would be incorrect given that other causes of hypertension are much more common than pheochromocytoma and this triad of symptoms can occur in patients who do not have it. Thus, clinicians using the representativeness heuristic may overestimate the likelihood of a particular disease based on its representativeness by failing to recognize the low underlying prevalence (i.e., the prior, or

pretest, probabilities). Conversely, atypical presentations of common diseases may lead to underestimating the likelihood of a particular disease. Thus, inexperience with a specific disease and with the breadth of its presentations may also lead to diagnostic delays or errors, e.g., diseases that affect multiple organ systems, such as sarcoid or tuberculosis, may be particularly challenging to diagnose because of the many different patterns they may manifest.

A second commonly used cognitive shortcut, the availability heuristic, involves judgments based on how easily prior similar cases or outcomes can be brought to mind. For example, a clinician may recall a case from a morbidity and mortality conference in which an elderly patient presented with painless dyspnea of acute onset and was evaluated for a pulmonary cause, but eventually found to have acute MI with the diagnostic delay likely contributing to the development of ischemic cardiomyopathy. If the case was associated with a malpractice accusation, such examples may be even more memorable. Errors with the availability heuristic arise from several sources of recall bias. Rare catastrophes are likely to be remembered with a clarity and force disproportionate to their likelihood for future diagnosis—for example, a patient with a sore throat eventually found to have leukemia or a young athlete with leg pain subsequently found to have a sarcoma—and those publicized in the media or recent experience are, of course, easier to recall and therefore more influential on clinical judgments.

The third commonly used cognitive shortcut, the anchoring heuristic (also called conservatism or stickiness), involves insufficiently adjusting the initial probability of disease up (or down) following a positive (or negative test) when compared with Bayes' theorem, i.e., sticking to the initial diagnosis. For example, a clinician may still judge the probability of coronary artery disease (CAD) to be high despite a negative exercise perfusion test and go on to cardiac catheterization (see "Measures of Disease Probability and Bayes' Rule," below).

The fourth heuristic states that clinicians should use the simplest explanation possible that will adequately account for the patient's symptoms and findings (Occam's razor or alternatively the simplicity heuristic). Although this is an attractive and often used principle, it is important to remember that no biologic basis for it exists. Errors from the simplicity heuristic include premature closure leading to the neglect of unexplained significant symptoms or findings.

For complex or unfamiliar diagnostic problems, clinicians typically resort to analytic reasoning processes (System 2) and proceed methodically using the *hypothetico-deductive model of reasoning*. Based on the stated reasons for seeking medical attention, clinicians develop an initial list of diagnostic possibilities in *hypothesis generation*. During the history of the present illness, the initial hypotheses evolve in *diagnostic refinement* as emerging information is tested against the mental models of the diseases being considered with diagnoses increasing and decreasing in likelihood or even being dropped from consideration as the working hypotheses of the moment. These mental models often generate additional questions that distinguish the diagnostic possibilities from one another. The focused physical examination contributes further distinguishing the working hypotheses. Is the spleen enlarged? How big is the liver? Is it tender? Are there any palpable masses or nodules? *Diagnostic verification* involves testing the adequacy (whether the diagnosis accounts for all symptoms and signs) and coherency (whether the signs and symptoms are consistent with the underlying pathophysiological causal mechanism) of the diagnosis. For example, if the enlarged and quite tender liver felt on physical examination is due to acute hepatitis (the hypothesis), then certain specific liver function tests will be markedly elevated (the prediction). Should the tests come back normal, the hypothesis may have to be discarded or substantially modified.

Although often neglected, negative findings are as important as positive ones because they reduce the likelihood of the diagnostic hypotheses under consideration. Chest discomfort that is not provoked or worsened by exertion and not relieved by rest in an active patient reduces the likelihood that chronic ischemic heart disease is the underlying cause. The absence of a resting tachycardia and thyroid gland enlargement reduces the likelihood of hyperthyroidism in a patient with paroxysmal atrial fibrillation.

The acuity of a patient's illness may override considerations of prevalence and the other issues described above. "Diagnostic imperatives" recognize the significance of relatively rare but potentially catastrophic diagnoses if undiagnosed and untreated. For example, clinicians should consider aortic dissection routinely as a possible cause of acute severe chest discomfort. Although the typical presenting symptoms of dissection differ from that of MI, dissection may mimic MI, and because it is far less prevalent and potentially fatal if mistreated, diagnosing dissection remains a challenging diagnostic imperative **(Chap. 274)**. Clinicians taking care of acute, severe chest pain patients should explicitly and routinely inquire about symptoms suggestive of dissection, measure blood pressures in both arms for discrepancies, and examine for pulse deficits. When these are all negative, clinicians may feel sufficiently reassured to discard the aortic dissection hypothesis. If, however, the chest x-ray shows a possible widened mediastinum, the hypothesis should be reinstated and an appropriate imaging test ordered (e.g., thoracic computed tomography [CT] scan or transesophageal echocardiogram). In non-acute situations, the prevalence of potential alternative diagnoses should play a much more prominent role in diagnostic hypothesis generation.

Cognitive scientists studying the thought processes of expert clinicians have observed that clinicians group data into packets, or "chunks," that are stored in short-term or "working memory" and manipulated to generate diagnostic hypotheses. Because short-term memory is limited (classically humans can accurately repeat a list of 7±2 numbers read to them), the number of diagnoses that can be actively considered in hypothesis-generating activities is similarly limited. For this reason, cognitive shortcuts discussed above play a key role in the generation of diagnostic hypotheses, many of which are discarded as rapidly as they are formed, thereby demonstrating that the distinction between analytic and intuitive reasoning is an arbitrary and simplistic, but nonetheless useful, representation of cognition.

Research into the hypothetico-deductive model of reasoning has had difficulty identifying the elements of the reasoning process that distinguish experts from novices. This has led to a shift from examining the problem-solving process of experts to analyzing the organization of their knowledge for pattern matching as exemplars, prototypes, and illness scripts. For example, diagnosis may be based on the resemblance of a new case to patients seen previously (exemplars). As abstract mental models of disease, prototypes incorporate the likelihood of various disease features. Illness scripts include risk factors, pathophysiology, and symptoms and signs. Experts have a much larger store of exemplar and prototype cases, an example of which is the visual long-term memory of experienced radiologists. However, clinicians do not simply rely on literal recall of specific cases but have constructed elaborate conceptual networks of memorized information or models of disease to aid in arriving at their conclusions (illness scripts). That is, expertise involves an enhanced ability to connect symptoms, signs, and risk factors to one another in meaningful ways; relate those findings to possible diagnoses; and identify the additional information necessary to confirm the diagnosis.

No single theory accounts for all the key features of expertise in medical diagnosis. Experts have more knowledge about presenting symptoms of diseases and a larger repertoire of cognitive tools to employ in problem solving than non-experts. One definition of expertise highlights the ability to make powerful distinctions. In this sense, expertise involves a working knowledge of the diagnostic possibilities and those features that distinguish one disease from another. Memorization alone is insufficient, e.g., photographic memory of a medical textbook would not make one an expert. But having access to detailed case-specific relevant information is critically important. In the past, clinicians primarily acquired clinical knowledge through their patient experiences, but now clinicians have access to a plethora of information sources (see Evidence-Based Medicine [EBM] below). Clinicians of the future will be able to leverage the experiences of large numbers of other clinicians using electronic tools, but, as with the memorized textbook, the data alone will be insufficient for becoming an expert. Nonetheless, availability of these data removes one barrier for acquiring experience with connecting symptoms, signs, and risk factors to the possible

diagnoses and identifying the additional distinguishing information necessary to confirm the diagnosis, thereby potentially facilitating the development of the working knowledge necessary for becoming an expert.

Despite all of the research seeking to understand expertise in medicine and other disciplines, it remains uncertain whether any didactic program can actually accelerate the progression from novice to expert or from experienced clinician to master clinician. Deliberate effortful practice (over an extended period of time, sometimes said to be 10 years or 10,000 practice hours) and personal coaching are two strategies that are often used outside medicine (e.g., music, athletics, chess) to promote expertise. Their use in developing medical expertise and maintaining or enhancing it has not yet been adequately explored. Some studies in medicine suggest that didactic education exposing students to both the signs and symptoms of specific diseases and, in addition, the diseases that may present with specific symptoms and signs may be beneficial. Developing a personal learning system (e.g., metacognition) through for example EBM processes below and follow-up to identify diagnoses and treatments for patients that you have cared for provide active learning opportunities.

DIAGNOSTIC VERSUS THERAPEUTIC DECISION-MAKING

The modern ideal of medical therapeutic decision making is to "personalize" treatment recommendations. In the abstract, personalizing treatment involves combining the best available evidence about what works with an individual patient's unique features (e.g., risk factors, genomics and co-morbidities) and his or her preferences and health goals to craft an optimal treatment recommendation with the patient. Operationally, two different and complementary levels of personalization are possible: individualizing the risk of harm and benefit for the options being considered based on the specific patient characteristics (precision medicine), and personalizing the therapeutic decision process by incorporating the patient's preferences and values for the possible health outcomes. This latter process is sometimes referred to as shared decision-making, and typically involves clinicians sharing their knowledge about the options and the associated consequences and tradeoffs, and patients sharing their health goals, e.g., avoiding a short-term risk of dying from coronary artery bypass grafting to see their grandchild get married in a few months.

Individualizing the evidence about therapy **does not** mean relying on physician impressions of benefit and harm from their personal experience. Because of small sample sizes and rare events, the chance of drawing erroneous causal inferences from one's own clinical experience is very high. For most chronic diseases, therapeutic effectiveness is only demonstrable statistically in large patient populations. It would be incorrect to infer with any certainty, for example, that treating a hypertensive patient with angiotensin-converting enzyme (ACE) inhibitors necessarily prevented a stroke from occurring during treatment, or that an untreated patient would definitely have avoided their stroke had they been treated. For many chronic diseases, a majority of patients will remain event free regardless of treatment choices; some will have events regardless of which treatment is selected; and those who avoided having an event through treatment cannot be individually identified. Blood pressure lowering, a readily observable surrogate endpoint, does not have a tightly coupled relationship with strokes prevented. Consequently, in most situations demonstrating therapeutic effectiveness cannot rely simply on observing the outcome of an individual patient but should instead be based on large groups of patients carefully studied and properly analyzed.

Therapeutic decision-making, therefore, should be based on the best available evidence from clinical trials and well done outcome studies. Trustworthy clinical practice guidelines that synthesize such evidence offer normative guidance for many testing and treatment decisions. However, all guidelines recognize that "one size fits all" recommendations may not apply to individual patients. Increased research into the heterogeneity of treatment effects seeks to understand how best to adjust group level clinical evidence of treatment harms and benefits to account for the absolute level of risks faced by subgroups and even by individual patients, using, for example, validated clinical risk scores.

NON-CLINICAL INFLUENCES ON CLINICAL DECISION-MAKING

More than three decades of research on variations in clinician practice patterns has identified important non-clinical forces that shape clinical decisions. These factors can be grouped conceptually into three overlapping categories: (1) factors related to individual physicians practice, (2) factors related to practice setting, and (3) factors related to payment systems.

Factors Related to Practice Style To ensure that necessary care is provided at a high level of quality, physicians fulfill a key role in medical care by serving as the patient's advocate. Factors that influence performance in this role include the physician's knowledge, training, and experience. Clearly, physicians cannot practice evidence-based medicine if they are unfamiliar with the evidence. As would be expected, specialists generally know the evidence in their field better than do generalists. Beyond published evidence and practice guidelines, a major set of influences on physician practice can be subsumed under the general concept of "practice style." The practice style serves to define norms of clinical behavior. Beliefs about effectiveness of different therapies and preferred patterns of diagnostic test use are examples of different facets of a practice style. The physician beliefs that drive these different practice styles may be based on training, personal experience, and medical evidence. For example, in heart failure patients, heart failure specialists have more familiarity than general internists with the target doses of ACE inhibitor therapy as defined by large clinical trials and the specific drugs (including adverse effects), and are less likely to overreact to foreseeable problems in therapy such as a rise in creatinine levels or asymptomatic hypotension. Not surprisingly, the specialists are much more likely than generalists to achieve target doses of ACE inhibitor therapy. By contrast, perhaps due to specialization, cardiologists may overestimate the benefit and underestimate the harm of coronary revascularization relative to general internists.

Beyond the patient's welfare, physician perceptions about the risk of a malpractice suit resulting from either an erroneous decision or a bad outcome may drive clinical decisions and create a practice referred to as defensive medicine. This practice involves using tests and therapies with very small marginal benefits, ostensibly to preclude future criticism should an adverse outcome occur. With conscious or unconscious awareness of a connection to the risk of litigation or to payment, however, over time such patterns of care may become accepted as part of the practice norm, thereby perpetuating their overuse, e.g., annual cardiac exercise testing in asymptomatic patients.

Practice Setting Factors Factors in this category relate to work systems including tasks and workflow (interruptions, inefficiencies, workload), technology (poor design or implementation, errors in use, failure, misuse), organizational characteristics (e.g., culture, leadership, staffing, scheduling), and the physical environment (e.g., noise, lighting, layout). Physician-induced demand is a term that refers to the repeated observation that once medical facilities and technologies become available to physicians, they will use them. Other environmental factors that can influence decision-making include the local availability of specialists for consultations and procedures; "high-tech" advanced imaging or procedure facilities such as MRI machines and proton beam therapy centers; and fragmentation of care.

Payment Systems Economic incentives are closely related to the other two categories of practice-modifying factors. Financial issues can exert both stimulatory and inhibitory influences on clinical practice. Historically, physicians are paid on a fee-for-service, capitation, or salary basis. In fee-for-service, physicians who do more get paid more, thereby encouraging overuse, consciously or unconsciously. When fees are reduced (discounted reimbursement), clinicians tend to increase the number of services provided to maintain revenue. Capitation, in contrast, provides a fixed payment per patient per year to encourage

physicians to consider a global population budget in managing individual patients and ideally reducing the use of interventions with small marginal benefit. To discourage volume-based excessive utilization, fixed salary compensation plans pay physicians the same regardless of the clinical effort expended, but may provide an incentive to see fewer patients. In recognition of the non-sustainability of continued growth in medical expenditures and the opportunity costs associated with that (funds that might be more beneficially applied to education, energy, social welfare or defense), current efforts seek to transition to a value-based payment system to reduce overuse and to reflect benefit. Work to define how to actually tie payment to value has mostly focused so far on "pay for performance" models. High quality clinical trial evidence for the effectiveness of these models is still mostly lacking.

INTERPRETATION OF DIAGNOSTIC TESTS

Despite impressive technological advances in medicine over the last century, uncertainty still abounds and challenges all aspects of medical decision-making. Compounding this challenge, massive information overload characterizes modern medicine. Clinicians on average subscribe to seven journals, presenting them with over 2500 new articles each year, and need access to 2 million pieces of information to practice medicine. Of course, to be useful, this information must be sifted for quality and examined for applicability for integration into patient-specific care. Although computers appear to offer an obvious solution both for information management and for quantification of medical care uncertainties, many practical problems must be solved before computerized decision support can be routinely incorporated into the clinical reasoning process in a way that demonstrably improves the quality of care. For the present, understanding the nature of diagnostic test information can help clinicians become more efficient users of such data. The next section reviews concepts related to diagnostic testing.

DIAGNOSTIC TESTING: MEASURES OF TEST ACCURACY

The purpose of performing a test on a patient is to reduce uncertainty about the patient's diagnosis or prognosis in order to facilitate appropriate management. Although diagnostic tests commonly refer to laboratory (e.g., blood count) or imaging tests or procedures (e.g., colonoscopy or bronchoscopy), any information that changes a provider's understanding of the patient's problem qualifies as a diagnostic test. Thus, even the history and physical examination should be considered as diagnostic tests. In clinical medicine, it is common to reduce the results of a test to a dichotomous outcome, such as positive or negative, normal or abnormal. Although this simplification ignores useful information (such as the degree of abnormality), it facilitates illustrating some important principles of test interpretation which are described below.

The accuracy of any diagnostic test is assessed relative to a "gold standard," where a positive gold standard test defines the patients who have disease and a negative test rules out disease **(Table 3-1)**. Characterizing the diagnostic performance of a new test requires identifying an appropriate population (ideally, patients representative of those in whom the new test would be used) and applying both the new and the gold standard tests to all subjects. Biased estimates of test performance occur when diagnostic accuracy is defined using an inappropriate population or one in which gold standard determination of disease status is incomplete. The accuracy of the new test in distinguishing disease from health is determined relative to the gold standard results and summarized in four estimates. The sensitivity or true-positive rate of the new test reflects how well the new test identifies patients with disease. It is the proportion of patients with disease (defined by the gold standard) who have a positive test. The proportion of patients with disease who have a negative test is the false-negative rate, calculated as 1 – sensitivity. The specificity, or true-negative rate reflects how well the new test correctly identifies patients without disease. It is the proportion of patients without disease (defined by the gold standard) who have a negative test. The proportion of patients without disease who have positive test is the false-positive rate, calculated as 1 – specificity. In theory, a perfect test would be one with a sensitivity of 100% and a specificity of 100% and would completely distinguish patients with disease from those without it. A useful mnemonic is the following: a *negative* high sensitivity (*Sn*) test helps rule *out* disease (Negative SnOut), and a *positive* high specificity (*Sp*) test helps rule *in* disease (Positive SpIn).

Calculating sensitivity and specificity requires selection of a threshold value or cut point above which the test is considered "positive." Making the cut point "stricter" (e.g., raising it) lowers sensitivity but improves specificity, while making it "laxer" (e.g., lowering it) raises sensitivity but lowers specificity. This dynamic trade-off between more accurate identification of subjects with disease versus those without disease is often displayed graphically as a receiver operating characteristic (ROC) curve **(Fig. 3-1)** by plotting sensitivity (*y* axis) versus 1 – specificity (*x* axis). Each point on the curve represents a potential cut point with an associated sensitivity and specificity value. The area under the ROC curve often is used as a quantitative measure of the information content of a test. Values range from 0.5 (no diagnostic information from testing at all; the test is equivalent to flipping a coin) to 1.0 (perfect test). The choice of cut point should in theory reflect the relative harms and benefits of treatment for those without versus those with disease. For example, if treatment was safe with substantial benefit, then choosing a high sensitivity cut point (upper right of the ROC curve) for a low risk test may be appropriate (e.g., phenylketonuria in newborns), but if treatment had substantial risk for harm, then

TABLE 3-1 Measures of Diagnostic Test Accuracy

	DISEASE STATUS	
TEST RESULT	**PRESENT**	**ABSENT**
Positive	True positives (TP)	False positives (FP)
Negative	False negatives (FN)	True Negatives (TN)
Test Characteristics in Patients with Disease		
True-positive rate (sensitivity) = TP/(TP + FN)		
False-negative rate = FN/(TP + FN) = 1 – true positive rate		
Test Characteristics in Patients without Disease		
True-negative rate (specificity) = TN/(TN + FP)		
False-positive rate = FP/(TN + FP) = 1 – true-negative rate		

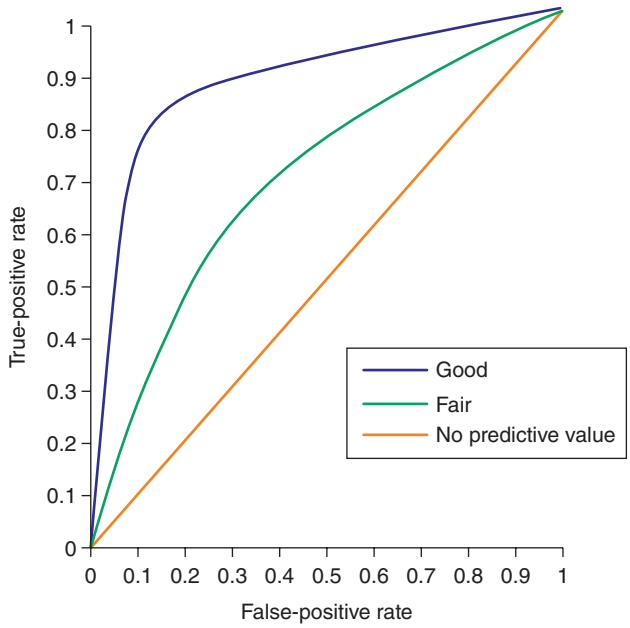

FIGURE 3-1 Each receiver operating characteristic (ROC curve) illustrates a trade-off that occurs between improved test sensitivity (accurate detection of patients with disease) and improved test specificity (accurate detection of patients without disease), as the test value defining when the test turns from "negative" to "positive" is varied. A 45° line would indicate a test with no predictive value (sensitivity = specificity at every test value). The area under each ROC curve is a measure of the information content of the test. Thus, a larger ROC area signifies increased diagnostic accuracy.

choosing a high specificity cut point (lower left of the ROC curve) may be appropriate (e.g., chemotherapy for cancer). The choice of cut point may also depend on the likelihood of disease with low likelihoods placing a greater emphasis on the harms of false positive tests (e.g., HIV testing in marriage applicants) or the harms of false-negative tests (e.g., HIV testing in blood donors).

MEASURES OF DISEASE PROBABILITY AND BAYES' RULE

In the absence of perfect tests, the true disease state of the patient remains uncertain after every test. Bayes' rule provides a way to quantify the revised uncertainty using simple probability mathematics (and thereby avoid anchoring bias). It calculates the *posttest probability* or likelihood of disease after a test result, from three parameters: the pretest probability of disease, the test sensitivity, and the test specificity. The *pretest probability* is a quantitative estimate of the likelihood of the diagnosis before the test is performed and is usually estimated from the prevalence of the disease in the underlying population (if known) or clinical context (e.g., age, sex and type of chest pain). For some common conditions, such as CAD, existing nomograms and statistical models generate estimates of pretest probability that account for history, physical examination, and test findings. The posttest probability (also called the predictive value of the test, see below) is a recalibrated statement of the likelihood of the diagnosis, accounting for both pretest probability and test results. For the likelihood of disease following a positive test (i.e., positive predictive value), Bayes' rule is calculated as:

$$\text{Posttest probability} = \frac{\text{Pretest probability} \times \text{test sensitivity}}{\text{Pretest probability} \times \text{test sensitivity} + (1 - \text{Pretest probability}) \times \text{test false-positive rate}}$$

For example, consider a 64-year-old woman with atypical chest pain who has a pretest probability of 0.50 and a "positive" diagnostic test result (assuming test sensitivity = 0.90 and specificity = 0.90).

$$\text{Posttest probability} = \frac{(0.50)(0.90)}{(0.50)(0.90) + (0.50)(0.10)} = 0.90$$

The term predictive value has often been used as a synonym for the posttest probability. Unfortunately, clinicians commonly misinterpret reported predictive values as intrinsic measures of test accuracy rather than calculated probabilities. Studies of diagnostic test performance compound the confusion by calculating predictive values from the same sample used to measure sensitivity and specificity. Such calculations are misleading unless the test is applied subsequently to populations with exactly the same disease prevalence. For these reasons, the term predictive value is best avoided in favor of the more descriptive posttest probability following a positive or a negative test result.

The nomogram version of Bayes' rule **(Fig. 3-2)** helps us to understand at a conceptual level how it estimates the posttest probability of disease. In this nomogram, the impact of the diagnostic test result is summarized by the likelihood ratio, which is defined as the ratio of the probability of a given test result (e.g., "positive" or "negative") in a patient with disease to the probability of that result in a patient without disease, thereby providing a measure of how well the test distinguishes those with from those without disease.

The *likelihood ratio for a positive test* is calculated as the ratio of the true-positive rate to the false-positive rate (or sensitivity/[1 – specificity]). For example, a test with a sensitivity of 0.90 and a specificity of 0.90 has a likelihood ratio of 0.90/(1 – 0.90), or 9. Thus, for this hypothetical test, a "positive" result is 9 times more likely in a patient with the disease than in a patient without it. Most tests in medicine have likelihood ratios for a positive result between 1.5 and 20. Higher values are associated with tests that more substantially increase the posttest likelihood of disease. A very high likelihood ratio positive (>10) usually implies high specificity, so a positive high specificity test helps "rule in" disease. If sensitivity is excellent but specificity is less so, the likelihood ratio will be reduced substantially (e.g., with a 90% sensitivity but a 55% specificity, the likelihood ratio positive is 2.0).

The corresponding *likelihood ratio for a negative test* is the ratio of the false-negative rate to the true-negative rate (or [1 – sensitivity]/specificity). Lower likelihood ratio negative values more substantially lower the posttest likelihood of disease. A very low likelihood ratio negative (falling below 0.10) usually implies high sensitivity, so a negative high sensitivity test helps "rule out" disease. The hypothetical test considered above with a sensitivity of 0.9 and a specificity of 0.9 would have a likelihood ratio for a negative test result of (1 – 0.9)/0.9, or 0.11, meaning that a negative result is about one-tenth as likely in patients with disease than in those without disease (or about ten times more likely in those without disease than in those with disease).

APPLICATIONS TO DIAGNOSTIC TESTING IN CAD

Consider two tests commonly used in the diagnosis of CAD: an exercise treadmill and an exercise single-photon emission CT (SPECT) myocardial perfusion imaging test **(Chap. 236)**. Meta-analysis has shown that a positive treadmill ST-segment response has an average sensitivity of 60% and an average specificity of 75%, yielding a likelihood ratio positive of 2.4 (0.60/[1 – 0.75]) (consistent with modest discriminatory ability because it falls between 2 and 5). For a 41-year-old man with nonanginal pain and a 10% pretest probability of CAD, the posttest probability of disease after a positive result rises to only about 30%. For a 60-year-old woman with typical angina and a pretest probability of CAD of 80%, a positive test result raises the posttest probability of disease to about 95%.

In contrast, exercise SPECT myocardial perfusion test is more accurate for diagnosis of CAD. For simplicity, assume that the finding of a reversible exercise-induced perfusion defect has both a sensitivity and a specificity of 90% (a bit higher than reported), yielding a likelihood ratio for a positive test of 9.0 (0.90/[1 – 0.90]) (consistent with intermediate discriminatory ability because it falls between 5 and 10). For the same 10% pretest probability patient, a positive test raises the probability of CAD to 50% (Fig. 3-2). However, despite the differences in posttest probabilities between these two tests (30 versus 50%), the more accurate test may not improve diagnostic likelihood enough to change patient management (e.g., decision to refer to cardiac catheterization) because the more accurate test has only moved the physician from being fairly certain that the patient did not have CAD to a 50:50 chance of disease. In a patient with a pretest probability of 80%, exercise SPECT test raises the posttest probability to 97% (compared with 95% for the exercise treadmill). Again, the more accurate test does not provide enough improvement in posttest confidence to alter management, and neither test has improved much on what was known from clinical data alone.

In general, positive results with an accurate test (e.g., likelihood ratio positive 10) when the pretest probability is low (e.g., 20%) do not move the posttest probability to a range high enough to rule in disease (e.g., 80%). In screening situations, pretest probabilities are often particularly low because patients are asymptomatic. In such cases, specificity becomes particularly important. For example, in screening first-time female blood donors without risk factors for HIV, a positive test raised the likelihood of HIV to only 67% despite a specificity of 99.995% because the prevalence was 0.01%. Conversely, with a high pretest probability, a negative test may not rule out disease adequately if it is not sufficiently sensitive. Thus, the largest change in diagnostic likelihood following a test result occurs when the clinician is most uncertain (i.e., pretest probability between 30 and 70%). For example, if a patient has a pretest probability for CAD of 50%, a positive exercise treadmill test will move the posttest probability to 80% and a positive exercise SPECT perfusion test will move it to 90% (Fig. 3-2).

As presented above, Bayes' rule employs a number of important simplifications that should be considered. First, few tests provide only "positive" or "negative" results. Many tests have multi-dimensional outcomes (e.g., extent of ST-segment depression, exercise duration, and exercise-induced symptoms with exercise testing). Although Bayes'

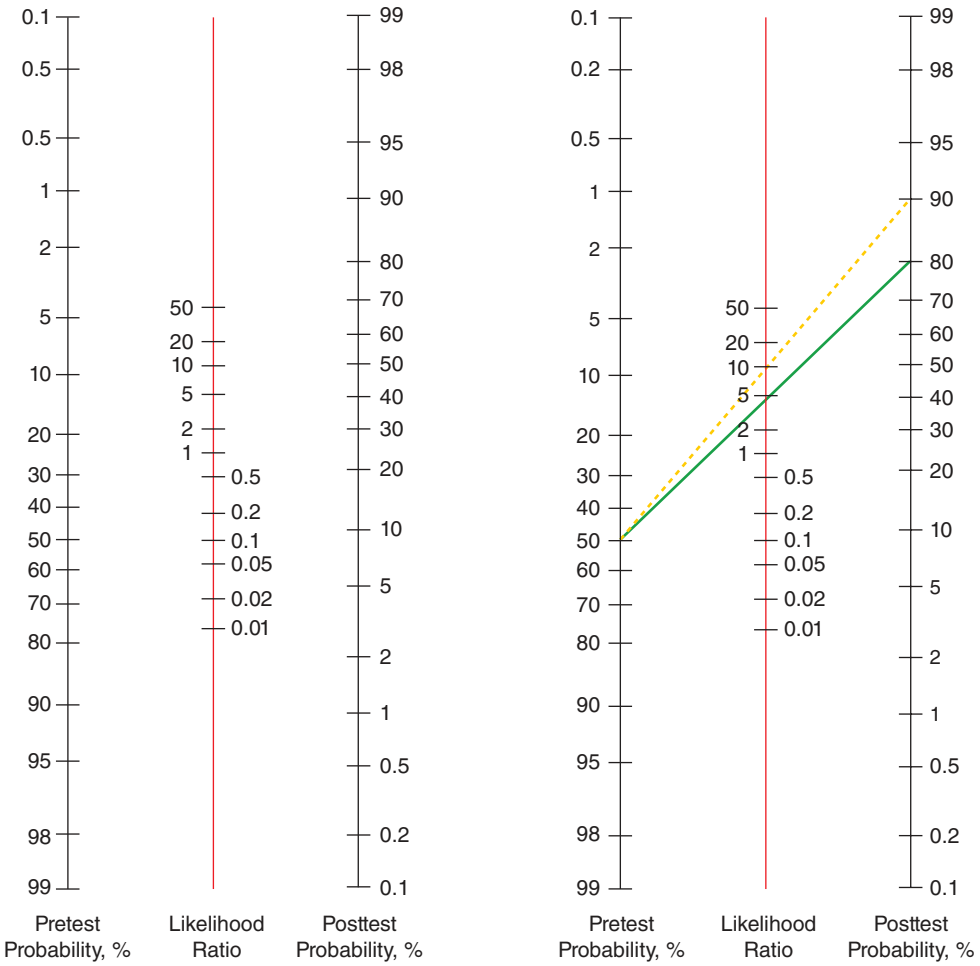

FIGURE 3-2 Nomogram version of Bayes' theorem used to predict the posttest probability of disease (right-hand scale) using the pretest probability of disease (left-hand scale) and the likelihood ratio for a positive test (middle scale). See text for information on calculation of likelihood ratios. To use, place a straightedge connecting the pretest probability and the likelihood ratio and read off the posttest probability. The right-hand part of the figure illustrates the value of a positive exercise treadmill test (likelihood ratio 4, *green line*) and a positive exercise thallium single-photon emission CT perfusion study (likelihood ratio 9, broken *yellow line*) in a patient with a pretest probability of coronary artery disease of 50%. *(Adapted from Centre for Evidence-Based Medicine: Likelihood ratios. Available at http://www.cebm.net/likelihood-ratios/.)*

theorem can be adapted to this more detailed test result format, it is computationally more complex to do so. Similarly, when multiple sequential tests are performed, the posttest probability may be used as the pretest probability to interpret the second test. However, this simplification assumes conditional independence—that is, that the results of the first test do not affect the likelihood of the second test result—and this is often not true.

Finally, many texts assert that sensitivity and specificity are prevalence-independent parameters of test accuracy. This statistically useful assumption, however, is clinically simplistic. A treadmill exercise test, for example, has a sensitivity of ~30% in a population of patients with 1-vessel CAD, whereas its sensitivity in patients with severe 3-vessel CAD approaches 80%. Thus, the best estimate of sensitivity to use in a particular decision may vary, depending on the severity of disease in the local population. A hospitalized, symptomatic, or referral population typically has a higher prevalence of disease and, in particular, a higher prevalence of more advanced disease than does an outpatient population. Consequently, test sensitivity will likely be higher in hospitalized patients, and test specificity higher in outpatients.

STATISTICAL PREDICTION MODELS

Bayes' rule, when used as presented above, is useful in studying diagnostic testing concepts but may prove too simplistic for use in actual patient care decisions. Predictions based on multivariable statistical models can more accurately address these more complex problems by simultaneously accounting for additional relevant patient characteristics. In particular, these models explicitly account for multiple, even possibly overlapping, pieces of patient-specific information and assign a relative weight to each on the basis of its unique independent contribution to the prediction in question. For example, a logistic regression model to predict the probability of CAD ideally considers all the relevant independent factors from the clinical examination and diagnostic testing and their relative importance instead of the limited data that clinicians can manage in their heads or with Bayes' rule. However, despite this strength, prediction models are usually too complex computationally to use without a calculator or computer. Guideline-driven treatment recommendations based on statistical prediction models available online, e.g., the ACC/AHA risk calculator for primary prevention with statins and the CHA_2DS_2-VASC calculator for anticoagulation for atrial fibrillation have generated more widespread usage. Whether the adoption of electronic health records will promote more use of predictive models in clinical practice and increase their impact on clinical encounters and outcomes remains unclear.

One reason for limited clinical use is that, to date, only a handful of prediction models have been validated properly (for example, Wells' criteria for pulmonary embolism, see Table 3-2). The importance of independent validation in a population separate from the one used to develop the model cannot be overstated. An unvalidated prediction model should be viewed with the skepticism appropriate for any new drug or medical device that has not had rigorous clinical trial testing.

When statistical survival models in cancer and heart disease have been compared directly with clinicians' predictions, the survival models have been found to be more consistent, as would be expected but not always more accurate. On the other hand, comparison of clinicians with websites and apps that generate lists of possible diagnoses to help patients with self-diagnosis found that physicians outperformed the currently available programs. For students and less-experienced

TABLE 3-2 Wells Clinical Prediction Rule for Pulmonary Embolism

CLINICAL FEATURE	POINTS
Clinical signs of deep-vein thrombosis	3
Alternative diagnosis is less likely than PE	3
Heart rate >100 beats per min	1.5
Immobilization ≥3 d or surgery in previous 4 weeks	1.5
History of deep-vein thrombosis or pulmonary embolism	1.5
Hemoptysis	1
Malignancy (with treatment within 6 months) or palliative	1
INTERPRETATION	
Score >6.0	High
Score 2.0–6.0	Intermediate
Score <2.0	Low

clinicians, the biggest value of diagnostic decision support may be in extending diagnostic possibilities and triggering "rational override" but their impact on knowledge, information-seeking, and problem-solving needs additional research.

FORMAL DECISION SUPPORT TOOLS

DECISION SUPPORT SYSTEMS

Over the last 40 years, many attempts have been made to develop computer systems to aid clinical decision-making and patient management. Conceptually, computers offer several levels of potentially useful support for clinicians. At the most basic level, they provide ready access to vast reservoirs of information, which may, however, be quite difficult to sort through to find what is needed. At higher levels, computers can support care management decisions by making accurate predictions of outcome, or can simulate the whole decision process, and provide algorithmic guidance. Computer-based predictions using Bayesian or statistical regression models inform a clinical decision but do not actually reach a "conclusion" or "recommendation." Machine learning methods are being applied to pattern recognition tasks such as the examination of skin lesions and the interpretation of x-rays. Artificial intelligence systems attempt to simulate or replace human reasoning with a computer-based analogue. To date, such approaches have achieved only limited success. Reminder or protocol-directed systems do not make predictions but use existing algorithms, such as guidelines or appropriate utilization criteria, to direct clinical practice. In general, however, decision support systems have had little impact on practice. Reminder systems built into electronic health records have shown the most promise, particularly in correcting drug dosing and promoting adherence to guidelines. Checklists may also help avoid or reduce errors.

DECISION ANALYSIS

Compared with the decision support methods above, decision analysis represents a normative prescriptive approach to decision-making in the face of uncertainty. Its principal application is in complex decisions. For example, public health policy decisions often involve *trade-offs* in length versus quality of life, benefits versus resource use, population versus individual health, and *uncertainty* regarding efficacy, effectiveness, and adverse events as well as *values* or preferences regarding mortality and morbidity outcomes.

One recent analysis using this approach involved the optimal screening strategy for breast cancer, which has remained controversial, in part because a randomized controlled trial to determine when to begin screening and how often to repeat screening mammography is impractical. In 2016, the National Cancer Institute sponsored Cancer Intervention and Surveillance Network (CISNET) examined eight strategies differing by whether to initiate mammography screening at age 40, 45, or 50 years and whether to screen annually, biennially, or annually for women in their forties and biennially thereafter (hybrid). The six simulation models found biennial strategies to be the most efficient for average-risk women. Biennial screening for 1000 women from age 50 to 74 years versus no screening avoided seven breast cancer deaths. Screening annually from age 40 to 74 years avoided three additional deaths but required 20,000 additional mammograms and yielded 1988 more false-positive results. Factors that influenced the results included patients with a 2–4-fold higher risk for developing breast cancer in whom annual screening from 40 to 74 yielded similar benefits as biennial screening from age 50 to 74. For average-risk patients with moderate or severe co-morbidities, screening could be stopped earlier at ages 66–68 years.

This analysis involved six models that reproduced epidemiologic trends and a screening trial result, accounted for digital technology and treatments advances, and considered quality of life, risk factors, breast density, and comorbidity. It provided novel insights into a public health problem in the absence of a randomized clinical trial and helped weigh the pros and cons of such a health policy recommendation. Although such models have been developed for selected clinical problems, their benefit and application to individual real-time clinical management has yet to be demonstrated.

DIAGNOSIS AS AN ELEMENT OF QUALITY OF CARE

High quality medical care begins with accurate diagnosis. The incidence of diagnostic errors has been estimated by a variety of methods including postmortem examinations, medical record reviews, and medical malpractice claims, with each yielding complementary but different estimates of this quality of care patient-safety problem. In the past, diagnostic errors tended to be viewed as a failure of individual clinicians. The modern view is that they are mostly system of care deficiencies. Current estimates suggest that nearly everyone will experience at least one diagnostic error in their lifetime, leading to mortality, morbidity, unnecessary tests and procedures, costs, and anxiety.

Solutions to the "diagnostic errors as a system of care problem" have focused on system-level approaches, such as decision support and other tools integrated into electronic medical records. The use of checklists has been proposed as a means of reducing some of the cognitive errors discussed earlier in the chapter, such as premature closure. While checklists have been shown useful in certain medical contexts, such as the ORs and ICUs, their value in preventing diagnostic errors that lead to patient adverse events remains to be shown.

EVIDENCE-BASED MEDICINE

Clinical medicine is defined traditionally as a practice combining medical knowledge (including scientific evidence), intuition, and judgment in the care of patients **(Chap. 1)**. Evidence-based medicine (EBM) updates this construct by placing much greater emphasis on the processes by which clinicians gain knowledge of the most up-to-date and relevant clinical research to determine for themselves whether medical interventions alter the disease course and improve the length or quality of life. The meaning of practicing EBM becomes clearer through an examination of its four key steps:

1. Formulating the management question to be answered
2. Searching the literature and online databases for applicable research data
3. Appraising the evidence gathered with regard to its validity and relevance
4. Integrating this appraisal with knowledge about the unique aspects of the patient (including the patient's preferences about the possible outcomes)

The process of searching the world's research literature and appraising the quality and relevance of studies can be time-consuming and requires skills and training that most clinicians do not possess. Thus, identifying recent systematic overviews of the problem in question **(Table 3-3)** may offer the best starting point for most EBM searches. However, the medical literature is now being flooded with systematic reviews of varying quality and clinical utility. Therefore, systematic reviews should be used in conjunction with selective reading of some of the best empirical studies.

Generally, the EBM tools listed in Table 3-3 provide access to research information in one of two forms. The first, primary research reports, is the original peer-reviewed research work that is published in medical journals and accessible through MEDLINE in abstract form. However, without training in using MEDLINE, locating reports quickly and efficiently that are on point in a sea of irrelevant or unhelpful citations remains difficult, and important studies are easily missed. Systematic reviews, the second form, are regarded by some as the highest level of evidence in the hierarchy because they are intended to comprehensively summarize the available evidence on a particular topic. To avoid the potential biases found in review articles, predefined reproducible explicit search strategies and inclusion and exclusion criteria seek to find all of the relevant scientific research and grade its quality. The prototype for this kind of resource is the Cochrane Database of Systematic Reviews. When appropriate, a meta-analysis is used to quantitatively summarize the systematic review findings. The next two sections explicate the major types of clinical research reports available in the literature and the process of aggregating those data into meta-analyses.

TABLE 3-3 Selected Tools for Finding the Evidence in Evidence-Based Medicine

NAME	DESCRIPTION	WEB ADDRESS	AVAILABILITY
Evidence-Based Medicine Reviews	Comprehensive electronic database that combines and integrates: 1. The Cochrane Database of Systematic Reviews 2. ACP Journal Club 3. The Database of Abstracts of Reviews of Effectiveness	*www.ovid.com*	Subscription required. Available through medical center libraries and other institutions.
Cochrane Library	Collection of EBM databases, including the Cochrane Database of Systematic Reviews—full text articles reviewing specific health care topics	*www.cochrane.org*	Subscription required. Abstracts of systematic reviews available free online. Some countries have funding to provide free access to all residents.
ACP Journal Club	Collection of summaries of original studies and systematic reviews. Published bimonthly. All data since 1991 available on website, updated yearly.	*www.acpjc.org*	Subscription required.
Clinical Evidence	Monthly updated directory of concise overviews of common clinical interventions.	*www.clinicalevidence.com*	Subscription required. Free access for United Kingdom and developing countries.
MEDLINE	National Library of Medicine database with citations back to 1966.	*www.nlm.nih.gov*	Free via Internet.

SOURCES OF EVIDENCE: CLINICAL TRIALS AND REGISTRIES

The notion of learning from observation of patients is as old as medicine itself. Over the last 50 years, physicians' understanding of how best to turn raw observation into useful evidence has evolved considerably. Case reports, personal anecdotal experience, and small single-center case series are now recognized as having severe limitations in validity and generalizability, and although they may generate hypotheses or be the first reports of adverse events or therapeutic benefit, they have no role in formulating modern standards of practice. The major tools used to develop reliable evidence consist of the randomized clinical trial and the large observational registry. A registry or database typically is focused on a disease or syndrome (e.g., different types of cancer, acute or chronic CAD, pacemaker capture or chronic heart failure), a clinical procedure (e.g., bone marrow transplantation, coronary revascularization), or an administrative process (e.g., claims data used for billing and reimbursement).

By definition, in observational data, the investigator does not control patient care. Carefully collected prospective observational data, however, can at times achieve a level of evidence quality approaching that of major clinical trial data. At the other end of the spectrum, data collected retrospectively (e.g., chart review) are limited in form and content to what previous observers recorded and may not include the specific research data being sought (e.g., claims data). Advantages of observational data include the inclusion of a broader population as encountered in practice than is typically represented in clinical trials because of their restrictive inclusion and exclusion criteria. In addition, observational data provide primary evidence for research questions when a randomized trial cannot be performed. For example, it would be difficult to randomize patients to test diagnostic or therapeutic strategies that are unproven but widely accepted in practice, and it would be unethical to randomize based on sex, racial/ethnic group, socioeconomic status, or country of residence or to randomize patients to a potentially harmful intervention, such as smoking or deliberately overeating to develop obesity.

A well-done prospective observational study of a particular management strategy differs from a well-done randomized clinical trial most importantly by its lack of protection from treatment selection bias. The use of observational data to compare diagnostic or therapeutic strategies assumes that sufficient uncertainty and heterogeneity exists in clinical practice to ensure that similar patients will be managed differently by diverse physicians. In short, the analysis assumes that a sufficient element of randomness (in the sense of disorder rather than in the formal statistical sense) exists in clinical management. In such cases, statistical models attempt to adjust for important imbalances to "level the playing field" so that a fair comparison among treatment options can be made. When management is clearly not random (e.g., all eligible left main CAD patients are referred for coronary bypass surgery), the problem may be too confounded (biased) for statistical correction, and observational data may not provide reliable evidence.

In general, the use of concurrent controls is vastly preferable to that of historical controls. For example, comparison of current surgical management of left main CAD with medically treated patients with left main CAD during the 1970s (the last time these patients were routinely treated with medicine alone) would be extremely misleading because "medical therapy" has substantially improved in the interim.

Randomized controlled clinical trials include the careful prospective design features of the best observational data studies but also include the use of random allocation of treatment. This design provides the best protection against measured and unmeasured confounding due to treatment selection bias (a major aspect of internal validity). However, the randomized trial may not have good external validity (generalizability) if the process of recruitment into the trial resulted in the exclusion of many potentially eligible subjects or if the nominal eligibility for the trial describe a very heterogeneous population.

Consumers of medical evidence need to be aware that randomized trials vary widely in their quality and applicability to practice. The process of designing such a trial often involves many compromises. For example, trials designed to gain U.S. Food and Drug Administration (FDA) approval for an investigational drug or device must fulfill regulatory requirements (such as the use of a placebo control) that may result in a trial population and design that differs substantially from what practicing clinicians would find most useful.

META-ANALYSIS

The Greek prefix *meta* signifies something at a later or higher stage of development. Meta-analysis is research that combines and summarizes the available evidence quantitatively. Although it is used to examine nonrandomized studies, meta-analysis is most useful for summarizing all randomized trials examining a particular therapy. Ideally, unpublished trials should be identified and included to avoid publication bias (i.e., missing "negative" trials which may not be published). Furthermore, the best meta-analyses obtain and analyze individual patient-level data from all trials rather than using only the summary data from published reports. Nonetheless, not all published meta-analyses yield reliable evidence for a particular problem, so their methodology should be scrutinized carefully to ensure proper study design and analysis. The results of a well-done meta-analysis are likely to be most persuasive if they include at least several large-scale, properly performed randomized trials. Meta-analysis can especially help detect benefits when individual trials are inadequately powered (e.g., the benefits of streptokinase thrombolytic therapy in acute MI demonstrated by ISIS-2 in 1988 were evident by the early 1970s through meta-analysis). However, in cases in which the available trials are small or poorly done, meta-analysis should not be viewed as a remedy for deficiencies in primary trial data or trial design.

Meta-analyses typically focus on summary measures of relative treatment benefit, such as odds ratios or relative risks. Clinicians also should examine what absolute risk reduction (ARR) can be expected from the therapy. A summary metric of absolute treatment benefit is the number needed to treat (NNT) to prevent one adverse outcome event (e.g., death, stroke). NNT is simply 1/ARR. For example, if a hypothetical therapy reduced mortality rates over a 5-year follow-up by 33% (the relative treatment benefit) from 12% (control arm) to 8% (treatment arm), the absolute risk reduction would be 12% – 8% = 4% and the NNT would be 1/.04, or 25. Thus, it would be necessary to treat 25 patients for 5 years to prevent 1 death. If the hypothetical treatment was applied to a lower-risk population, say, with a 6% 5-year mortality, the 33% relative treatment benefit would reduce absolute mortality by 2% (from 6 to 4%), and the NNT for the same therapy in this lower-risk group of patients would be 50. Although not always made explicit, comparisons of NNT estimates from different studies should account for the duration of follow-up used to create each estimate. In addition, the NNT concept assumes a homogeneity in response to treatment that may not be accurate. The NNT is simply another way of summarizing the absolute treatment difference and does not provide any unique information.

CLINICAL PRACTICE GUIDELINES

According to the 1990 Institute of Medicine definition, clinical practice guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." This definition emphasizes several crucial features of modern guideline development. First, guidelines are created by using the tools of EBM. In particular, the core of the development process is a systematic literature search followed by a review of the relevant peer-reviewed literature. Second, guidelines usually are focused on a clinical disorder (e.g., diabetes mellitus, stable angina pectoris) or a health care intervention (e.g., cancer screening). Third, the primary objective of guidelines is to improve the quality of medical care by identifying care practices which should be routinely implemented, based on high quality evidence and high benefit to harm ratios for the interventions. Guidelines are intended to "assist" decision-making, not to define explicitly what decisions should be made in a particular situation, in part because guideline level evidence alone is never sufficient for clinical decision-making (e.g., deciding whether to intubate and administer antibiotics for pneumonia in a terminally ill individual, in an individual with dementia, or in an otherwise healthy 30-year-old mother).

Guidelines are narrative documents constructed by expert panels whose composition often is determined by interested professional organizations. These panels vary in expertise and in the degree to which they represent all relevant stakeholders. The guideline documents consist of a series of specific management recommendations, a summary indication of the quantity and quality of evidence supporting each recommendation, an assessment of the benefit to harm ratio for the recommendation, and a narrative discussion of the recommendations. Many recommendations simply reflect the expert consensus of the guideline panel because literature-based evidence is insufficient or absent. The final step in guideline construction is peer review, followed by a final revision in response to the critiques provided. To improve the reliability and trustworthiness of guidelines, the National Academy of Medicine (formerly Institute of Medicine) has made methodological recommendations for guideline development.

Guidelines are closely tied to the process of quality improvement in medicine through their identification of evidence-based best practices. Such practices can be used as quality indicators. Examples include the proportion of acute MI patients who receive aspirin upon admission to a hospital and the proportion of heart failure patients with a depressed ejection fraction treated with an ACE inhibitor.

CONCLUSIONS

In this era of EBM, it is tempting to think that all the difficult decisions practitioners face have been or soon will be solved and digested into practice guidelines and computerized reminders. However, EBM provides practitioners with an ideal rather than a finished set of tools with which to manage patients. Moreover, even with such evidence, it is always worth remembering that the response to therapy of the "average" patient represented by the summary clinical trial outcomes may not be what can be expected for the specific patient sitting in front of a provider in the clinic or hospital. In addition, meta-analyses cannot generate evidence when there are no adequate randomized trials, and most of what clinicians confront in practice will never be thoroughly tested in a randomized trial. For the foreseeable future, excellent clinical reasoning skills and experience supplemented by well-designed quantitative tools and a keen appreciation for the role of individual patient preferences in their health care will continue to be of paramount importance in the practice of clinical medicine.

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4 Screening and Prevention of Disease

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A primary goal of health care is to prevent disease or detect it early enough that intervention will be more effective. Tremendous progress has been made toward this goal over the last 50 years. Screening tests are available for many common diseases and encompass biochemical (e.g., cholesterol, glucose), physiologic (e.g., blood pressure, growth curves), radiologic (e.g., mammogram, bone densitometry), and cytologic (e.g., Pap smear) approaches. Effective preventive interventions have resulted in dramatic declines in mortality from many diseases, particularly infections. Preventive interventions include counseling about risk behaviors, vaccinations, medications, and, in some relatively uncommon settings, surgery. Preventive services (including screening tests, preventive interventions, and counseling) are different than other medical interventions because they are proactively administered to healthy individuals instead of in response to a symptom, sign, or diagnosis. Thus, the decision to recommend a screening test or preventive intervention requires a particularly high bar of evidence that testing and intervention are both practical and effective.

Because population-based screening and prevention strategies must be extremely low risk to have an acceptable benefit-to-harm ratio, the ability to target individuals who are more likely to

develop disease could enable the application of a wider set of potential approaches and increase efficiency. Currently, there are many types of data that can predict disease incidence in an asymptomatic individual. Genomic data have received the most attention to date, at least in part because mutations in high-penetrance genes have clear implications for preventive care **(Chap. 457)**. Women with mutations in either *BRCA1* or *BRCA2*, the two major breast cancer susceptibility genes identified to date, have a markedly increased risk (five- to twentyfold) of breast and ovarian cancer. Screening and prevention recommendations include prophylactic oophorectomy and breast magnetic resonance imaging (MRI), both of which are considered to incur too much harm for women at average cancer risk. Some women opt for prophylactic mastectomy to dramatically reduce their breast cancer risk. Although the proportion of common disease explained by high-penetrance genes appears to be relatively small (5–10% of most diseases), mutations in rare, moderate-penetrance genes, and variants in low-penetrance genes, also contribute to the prediction of disease risk. The advent of affordable whole exome/whole genome sequencing is likely to speed the dissemination of these tests into clinical practice and may transform the delivery of preventive care.

Other forms of "omic" data also have the potential to provide important predictive information, including proteomics and metabolomics. These fields are earlier in development and have yet to move into clinical practice. Imaging and other clinical data may also be integrated into a risk-stratified paradigm as evidence grows about the predictive ability of these data and the feasibility of their collection. Of course, all of these data may also be helpful in predicting the risk of harms from screening or prevention, such as the risk of a false-positive mammogram. To the degree that this information can be incorporated into personalized screening and prevention strategies, it could also improve delivery and efficiency.

In addition to advances in risk prediction, there are several other factors that are likely to promote the importance of screening and prevention in the near term. New imaging modalities are being developed that promise to detect changes at the cellular and subcellular levels, greatly increasing the probability that early detection improves outcomes. The rapidly growing understanding of the biologic pathways underlying initiation and progression of many common diseases has the potential to transform the development of preventive interventions, including chemoprevention. Furthermore, screening and prevention offer the promise of both improving health and sparing the costs of disease treatment, an issue that has gained national attention with the relatively high proportion of Gross Domestic Product spent on health care in the United States.

This chapter will review the basic principles of screening and prevention in the primary care setting. Recommendations for specific disorders such as cardiovascular disease, diabetes, and cancer are provided in the chapters dedicated to those topics.

BASIC PRINCIPLES OF SCREENING

The basic principles of screening populations for disease were published by the World Health Organization in 1968 **(Table 4-1)**.

In general, screening is most effective when applied to relatively common disorders that carry a large disease burden **(Table 4-2)**. The five leading causes of mortality in the United States are heart diseases, malignant neoplasms, chronic obstructive pulmonary disease, accidents, and cerebrovascular diseases. Thus, many screening strategies are targeted at these conditions. From a global health perspective, these conditions are priorities, but malaria, malnutrition, AIDS, tuberculosis, and violence also carry a heavy disease burden **(Chap. 460)**.

TABLE 4-1 Principles of Screening

The condition should be an important health problem.
There should be a treatment for the condition.
Facilities for diagnosis and treatment should be available.
There should be a latent stage of the disease.
There should be a test or examination for the condition.
The test should be acceptable to the population.
The natural history of the disease should be adequately understood.
There should be an agreed policy on whom to treat.
The cost of finding a case should be balanced in relation to overall medical expenditure.

TABLE 4-2 Lifetime Cumulative Risk

Breast cancer for women	10%
Colon cancer	6%
Cervical cancer for women[a]	2%
Domestic violence for women	Up to 15%
Hip fracture for white women	16%

[a]Assuming an unscreened population.

Having an effective treatment for early disease has proven challenging for some common diseases. For example, although Alzheimer's disease is the sixth leading cause of death in the United States, there are no curative treatments and no evidence that early treatment improves outcomes. Lack of facilities for diagnosis and treatment is a particular challenge for developing countries and may change screening strategies, including the development of "see and treat" approaches such as those currently used for cervical cancer screening in some countries. A long latent or preclinical phase where early treatment increases the chance of cure is a hallmark of many cancers; for example, polypectomy prevents progression to colon cancer. Similarly, early identification of hypertension or hyperlipidemia allows therapeutic interventions that reduce the long-term risk of cardiovascular or cerebrovascular events. In contrast, lung cancer screening has historically proven more challenging because most tumors are not curable by the time they can be detected on a chest x-ray. However, the length of the preclinical phase also depends on the level of resolution of the screening test, and this situation changed with the development of chest computed tomography (CT). Low-dose chest CT scanning can detect tumors earlier and has been demonstrated to reduce lung cancer mortality by 20% in individuals who had at least a 30-pack-year history of smoking. The short interval between the ability to detect disease on a screening test and the development of incurable disease also contributes to the limited effectiveness of mammography screening in reducing deaths from some forms of breast cancer. Similarly, the early detection of prostate cancer may not lead to a difference in the mortality rate because the disease is often indolent and competing morbidities, such as coronary artery disease, may ultimately cause mortality **(Chap. 66)**. This uncertainty about the natural history is also reflected in the controversy about treatment of prostate cancer, further contributing to the challenge of screening in this disease. Finally, screening programs can incur significant economic costs that must be considered in the context of the available resources and alternative strategies for improving health outcomes.

METHODS OF MEASURING HEALTH BENEFITS

Because screening and preventive interventions are recommended to asymptomatic individuals, they are held to a high standard for demonstrating a favorable risk-benefit ratio before implementation. In general, the principles of evidence-based medicine apply to demonstrating the efficacy of screening tests and preventive interventions, where randomized controlled trials (RCTs) with mortality outcomes are the gold standard. However, because RCTs are often not feasible, observational studies, such as case-control designs, have been used to assess the effectiveness of some interventions such as colorectal cancer screening. For some strategies, such as Pap smear screening for cervical cancer, the only data available are ecologic data demonstrating dramatic declines in mortality.

Irrespective of the study design used to assess the effectiveness of screening, it is critical that disease incidence or mortality is the primary endpoint rather than length of disease survival. This is important because lead time bias and length time bias can create the appearance of an improvement in disease survival from a screening test when there is no actual effect. Lead time bias occurs because screening identifies a case before it would have presented clinically, thereby creating the

TABLE 4-3 Estimated Average Increase in Life Expectancy for a Population

SCREENING OR PREVENTIVE INTERVENTION	AVERAGE INCREASE
Mammography:	
Women, 40–50 years	0–5 days
Women, 50–70 years	1 month
Pap smears, age 18–65	2–3 months
Getting a 35-year-old smoker to quit	3–5 years
Beginning regular exercise for a 40-year-old man (30 min, 3 times a week)	9 months–2 years

perception that a patient lived longer after diagnosis simply by moving the date of diagnosis earlier rather than the date of death later. Length time bias occurs because screening is more likely to identify slowly progressive disease than rapidly progressive disease. Thus, within a fixed period of time, a screened population will have a greater proportion of these slowly progressive cases and will appear to have better disease survival than an unscreened population.

A variety of endpoints are used to assess the potential gain from screening and preventive interventions.

1. *The absolute and relative impact of screening on disease incidence or mortality*. The absolute difference in disease incidence or mortality between a screened and nonscreened group allows the comparison of size of the benefit across preventive services. A meta-analysis of Swedish mammography trials (ages 40–70) found that ~1.2 fewer women per 1000 would die from breast cancer if they were screened over a 12-year period. By comparison, ~3 lives per 1000 would be saved from colon cancer in a population (aged 50–75) screened with annual fecal occult blood testing (FOBT) over a 13-year period. Based on this analysis, colon cancer screening may actually save more women's lives than does mammography. However, the relative impact of FOBT (30% reduction in colon cancer death) is similar to the relative impact of mammography (14–32% reduction in breast cancer death), emphasizing the importance of both relative and absolute comparisons.
2. *The number of subjects screened to prevent disease or death in one individual*. The inverse of the absolute difference in mortality is the number of subjects who would need to be screened or receive a preventive intervention to prevent one death. For example, 731 women aged 65–69 would need to be screened by dual-energy x-ray absorptiometry (DEXA) (and treated appropriately) to prevent one hip fracture from osteoporosis.
3. *Increase in average life expectancy for a population*. Predicted increases in life expectancy for various screening and preventive interventions are listed in **Table 4-3**. It should be noted, however, that the increase in life expectancy is an average that applies to a population, not to an individual. In reality, the vast majority of the population does not derive any benefit from a screening test or preventive intervention. A small subset of patients, however, will benefit greatly. For example, Pap smears do not benefit the 98% of women who never develop cancer of the cervix. However, for the 2% who would have developed cervical cancer, Pap smears may add as much as 25 years to their lives. Some studies suggest that a 1-month gain of life expectancy is a reasonable goal for a population-based screening or prevention strategy.

ASSESSING THE HARMS OF SCREENING AND PREVENTION

Just as with most aspects of medical care, screening and preventive interventions also incur the possibility of adverse outcomes. These adverse outcomes include side effects from preventive medications and vaccinations, false-positive screening tests, overdiagnosis of disease from screening tests, anxiety, radiation exposure from some screening tests, and discomfort from some interventions and screening tests. The risk of side effects from preventive medications is analogous to the use of medications in therapeutic settings and is considered in the U.S. Food and Drug Administration (FDA) approval process. Side effects from currently recommended vaccinations are primarily limited to discomfort and minor immune reactions. However, the concern about associations between vaccinations and serious adverse outcomes continues to limit the acceptance of many vaccinations despite the lack of data supporting the causal nature of these associations.

The possibility of a false-positive test occurs with nearly all screening tests, although the definition of what constitutes a false-positive result often varies across settings. For some tests such as screening mammography and screening chest CT, a false-positive result occurs when an abnormality is identified that is not malignant, requiring either a biopsy diagnosis or short-term follow-up. For other tests such as Pap smears, a false-positive result occurs because the test identifies a wide range of potentially premalignant states, only a small percentage of which would ever progress to an invasive cancer. This risk is closely tied to the risk of overdiagnosis in which the screening test identifies disease that would not have presented clinically in the patient's lifetime. Assessing the degree of overdiagnosis from a screening test is very difficult given the need for long-term follow-up of an unscreened population to determine the true incidence of disease over time. Recent estimates suggest that as much as 15–40% of breast cancers identified by mammography screening and 15–37% of prostate cancers identified by prostate-specific antigen testing may never have presented clinically. Screening tests also have the potential to create unwarranted anxiety, particularly in conjunction with false-positive findings. Although multiple studies have documented increased anxiety through the screening process, there are few data suggesting this anxiety has long-term adverse consequences, including subsequent screening behavior. Screening tests that involve radiation (e.g., mammography, chest CT) add to the cumulative radiation exposure for the screened individual. The absolute amount of radiation is very small from any of these tests, but the overall impact of repeated exposure from multiple sources is still being determined. Some preventive interventions (e.g., vaccinations) and screening tests (e.g., mammography) may lead to discomfort at the time of administration, but again, there is little evidence of long-term adverse consequences.

WEIGHING THE BENEFITS AND HARMS

The decision to implement a population-based screening and prevention strategy requires weighing the benefits and harms, including the economic impact of the strategy. The costs include not only the expense of the intervention but also time away from work, downstream costs from false-positive results or adverse events, and other potential harms. Cost-effectiveness is typically assessed by calculating the cost per year of life saved, with adjustment for the quality of life impact of different interventions and disease states (i.e., quality-adjusted life-year). Typically, strategies that cost $50,000–100,000 per quality-adjusted year of life saved are considered "cost-effective" **(Chap. 3)**.

The U.S. Preventive Services Task Force (USPSTF) is an independent panel of experts in preventive care that provides evidence-based recommendations for screening and preventive strategies based on an assessment of the benefit-to-harm ratio **(Tables 4-4 and 4-5)**. Because there are multiple advisory organizations providing recommendations for preventive services, the agreement among the organizations varies across the different services. For example, all advisory groups support screening for hyperlipidemia and colorectal cancer, whereas consensus is lower for breast cancer screening among women in their forties and for prostate cancer screening. Because the guidelines are only updated periodically, differences across advisory organizations may also reflect the data that were available when the guideline was issued. For example, the recommendations about lung cancer screening among heavy smokers varied across organizations after the results of the National Lung Screening Trial (NLST) were published in 2011 based upon how quickly the screening guidelines were updated.

For many screening tests and preventive interventions, the balance of benefits and harms may be uncertain for the average-risk population but more favorable for individuals at higher risk for disease. Although

TABLE 4-4 Screening Tests Recommended by the U.S. Preventive Services Task Force for Average-Risk Adults

DISEASE	TEST	POPULATION	FREQUENCY	CHAPTER
Abdominal aortic aneurysm	Ultrasound	Men 65–75 who have ever smoked	Once	
Alcohol misuse	Alcohol Use Disorders Identification Test	All adults	Unknown	445
Breast cancer	Mammography with or without clinical breast examination	Women 50–75	Every 2 years	
Cervical cancer	Pap smear	Women 21–65	Every 3 years	66
	Pap smear and HPV testing	Women 30–65	Every 5 years if HPV negative	
Chlamydia/gonorrhea	Nucleic acid amplification test on urine or cervical swab	Sexually active women <25	Unknown	184
Colorectal cancer	Fecal occult blood testing	50–75	Every year	66, 77
	Sigmoidoscopy	50–75	Every 5 years	
	Colonoscopy (or occult blood testing combined with sigmoidoscopy)	50–75	Every 10 years	
Depression	Screening questions	All adults	Periodically	
Diabetes	Fasting blood glucose or HgbA1c	Adults overweight, obese or with hypertension	Every 3 years	396
Hepatitis C	Anti-HCV antibody followed by confirmatory PCR	Adults born between 1945 and 1965	Once	
HIV	Reactive immunoassay or rapid HIV followed by confirmatory test	15–65	At least once	
Hyperlipidemia	Cholesterol	40–75	Unknown	400
Hypertension	Blood pressure	All adults	Periodically	271
Intimate partner violence	Screening questions	Women of childbearing age	Unknown	
Obesity	Body mass index	All adults	Unknown	
Osteoporosis	DEXA	Women >65 or >60 with risk factors	Unknown	404

Abbreviations: DEXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; HPV, human papillomavirus; PCR, polymerase chain reaction.

Source: Adapted from the U.S. Preventive Services Task Force 2017. *www.uspreventiveservicestaskforce.org/Page/Name/uspstf-a-and-b-recommendations/.*

age is the most commonly used risk factor for determining screening and prevention recommendations, the USPSTF also recommends some screening tests in populations based upon the presence of other risk factors for the disease. In addition, being at increased risk for the disease often supports initiating screening at an earlier age than that recommended for the average-risk population. For example, when there is a significant family history of colon cancer, it is prudent to initiate screening 10 years before the age at which the youngest family member was diagnosed with cancer.

Although informed consent is important for all aspects of medical care, shared decision-making may be a particularly important approach to decisions about preventive services when the benefit-to-harm ratio is uncertain for a specific population. For example, many expert groups, including the American Cancer Society, recommend an individualized discussion about prostate cancer screening, because the decision-making process is complex and relies heavily on personal issues. Some men may decline screening, whereas others may be more willing to accept the risks of an early detection strategy. Recent analysis suggests that many men may be better off not screening for prostate cancer because watchful waiting was the preferred strategy when quality-adjusted life-years were considered. Another example of shared decision-making involves the choice of techniques for colon cancer screening (Chap. 66). In controlled studies, the use of annual FOBT reduces colon cancer deaths by 15–30%. Flexible sigmoidoscopy reduces colon cancer deaths by ~40–60%. Colonoscopy appears to offer a greater benefit than flexible sigmoidoscopy with a reduction in risk of ~70%, but its use incurs additional costs and risks. These screening procedures have not been compared directly in the same population, but

TABLE 4-5 Preventive Interventions Recommended for Average-Risk Adults

INTERVENTION	DISEASE	POPULATION	FREQUENCY	CHAPTER
Adult immunization				118, 119
Tetanus-diphtheria		>18	Every 10 years	
Varicella		Susceptibles only, >18	Two doses	
Measles-mumps-rubella		Women, childbearing age	One dose	
Pneumococcal		>64	13 followed by 23 valent	
Influenza		>18	Yearly	
Human papillomavirus		Up to age 27	If not done prior	
Zoster		>60	Once	
Chemoprevention				
Aspirin	Cardiovascular disease	Aged 50 to 59 years with a ≥10% 10-year CVD risk		
Folic acid	Neural tube defects in baby	Women planning or capable of pregnancy		
Tamoxifen/raloxifene	Breast cancer	Women at high risk for breast cancer		
Vitamin D	Fracture/falls	>64 at increased risk for falls		

TABLE 4-6 Preventive Counseling Recommended by the U.S. Preventive Services Task Force (USPSTF)

TOPIC	CHAPTER REFERENCE
Alcohol and drug use	445–447
Genetic counseling for *BRCA1/2* testing among women at increased risk for deleterious mutations	75, 457
Nutrition and diet	325, 326
Sexually transmitted infections	131, 197
Sun exposure	57
Tobacco use	448

models suggest that appropriate frequencies of each technique may be associated with similar numbers of lives saved and cost to society per life saved ($10,000–25,000). Thus, although one patient may prefer the ease of preparation, less time disruption, and the lower risk of flexible sigmoidoscopy, others may prefer the sedation, thoroughness and time interval of colonoscopy.

COUNSELING ON HEALTHY BEHAVIORS

In considering the impact of preventive services, it is important to recognize that tobacco and alcohol use, diet, and exercise constitute the vast majority of factors that influence preventable deaths in developed countries. Perhaps the single greatest preventive health care measure is to help patients quit smoking (Chap. 448). However, efforts in these areas frequently require behavior changes (e.g., weight loss, exercise) or the management of addictive conditions (e.g., tobacco and alcohol use) that are often recalcitrant to intervention. Although these are challenging problems, evidence strongly supports the role of counseling by health care providers (Table 4-6) in effecting health behavior change. Educational campaigns, public policy changes, and community-based interventions have also proven to be important parts of a strategy for addressing these factors in some settings. Although the USPSTF found that the evidence was conclusive to recommend a relatively small set of counseling activities, counseling in areas such as physical activity and injury prevention (including seat belts and bicycle and motorcycle helmets) has become a routine part of primary care practice.

IMPLEMENTING DISEASE PREVENTION AND SCREENING

The implementation of disease prevention and screening strategies in practice is challenging. A number of techniques can assist physicians with the delivery of these services. An appropriately configured electronic health record can provide reminder systems that make it easier for physicians to track and meet guidelines. Some systems give patients secure access to their medical records, providing an additional means to enhance adherence to routine screening. Systems that provide nurses and other staff with standing orders are effective for immunizations. The USPSTF has developed flow sheets and electronic tools to assist clinicians (*https://www.uspreventiveservicestaskforce.org/Page/Name/tools-and-resources-for-better-preventive-care*). Many of these tools use age categories to help guide implementation. Age-specific recommendations for screening and counseling are summarized in Table 4-7.

Many patients see a physician for ongoing care of chronic illnesses, and this visit provides an opportunity to include a "measure of prevention"

TABLE 4-7 Age-Specific Causes of Mortality and Corresponding Preventive Options

AGE GROUP	LEADING CAUSES OF AGE-SPECIFIC MORTALITY	SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION
15–24	1. Accident 2. Homicide 3. Suicide 4. Malignancy 5. Heart disease	• Counseling on routine seat belt use, bicycle/motorcycle/ATV helmets (1) • Counseling on diet and exercise (5) • Discuss dangers of alcohol use while driving, swimming, boating (1) • Assess and update vaccination status (tetanus, diphtheria, hepatitis B, MMR, rubella, varicella, meningitis, HPV) • Ask about gun use and/or gun possession (2,3) • Assess for substance abuse history including alcohol (2,3) • Screen for domestic violence (2,3) • Screen for depression and/or suicidal/homicidal ideation (2,3) • Pap smear for cervical cancer screening after age 21 (4) • Discuss skin, breast awareness, and testicular self-examinations (4) • Recommend UV light avoidance and regular sunscreen use (4) • Measurement of blood pressure, height, weight, and body mass index (5) • Discuss health risks of tobacco use, consider emphasis on cosmetic and economic issues to improve quit rates for younger smokers (4,5) • Chlamydia and gonorrhea screening and contraceptive counseling for sexually active females, discuss STD prevention • Hepatitis B, and syphilis testing if there is high-risk sexual behavior(s) or any prior history of sexually transmitted disease • HIV testing • Continue annual influenza vaccination
25–44	1. Accident 2. Malignancy 3. Heart disease 4. Suicide 5. Homicide 6. HIV	*As above plus consider the following:* • Readdress smoking status, encourage cessation at every visit (2,3) • Obtain detailed family history of malignancies and begin early screening/prevention program if patient is at significant increased risk (2) • Assess all cardiac risk factors (including screening for diabetes and hyperlipidemia) and consider primary prevention with aspirin for patients at >3% 5-year risk of a vascular event (3) • Assess for chronic alcohol abuse, risk factors for viral hepatitis, or other risks for development of chronic liver disease • Consider individualized breast cancer screening with mammography at age 40 (2)

(*Continued*)

TABLE 4-7 Age-Specific Causes of Mortality and Corresponding Preventive Options (Continued)

AGE GROUP	LEADING CAUSES OF AGE-SPECIFIC MORTALITY	SCREENING PREVENTION INTERVENTIONS TO CONSIDER FOR EACH SPECIFIC POPULATION
45–64	1. Malignancy 2. Heart disease 3. Accident 4. Diabetes mellitus 5. Cerebrovascular disease 6. Chronic lower respiratory disease 7. Chronic liver disease and cirrhosis 8. Suicide	• Consider prostate cancer screen with annual PSA and digital rectal examination at age 50 (or possibly earlier in African Americans or patients with family history) (1) • Begin colorectal cancer screening at age 50 with fecal occult blood testing, flexible sigmoidoscopy, or colonoscopy (1) • Reassess and update vaccination status at age 50 and vaccinate all smokers against *S. pneumoniae* at age 50 (6) • Consider screening for coronary disease in higher-risk patients (2,5) • Consider screening for hepatitis C in adults born between 1945 and 1965 (7) • Zoster vaccination at age 60 • Begin mammography screening by age 50
≥65	1. Heart disease 2. Malignancy 3. Cerebrovascular disease 4. Chronic lower respiratory disease 5. Alzheimer's disease 6. Influenza and pneumonia 7. Diabetes mellitus 8. Kidney disease 9. Accidents 10. Septicemia	*As above plus consider the following:* • Readdress smoking status, encourage cessation at every visit (1,2,3,4) • One-time ultrasound for AAA in men 65–75 who have ever smoked • Consider pulmonary function testing for all long-term smokers to assess for development of chronic obstructive pulmonary disease (4,6) • Screen all postmenopausal women (and all men with risk factors) for osteoporosis • Continue annual influenza vaccination and vaccinate against *S. pneumoniae* at age 65 (4,6) • Screen for visual and hearing problems, home safety issues, and elder abuse (9)

Note: The numbers in parentheses refer to areas of risk in the mortality column affected by the specified intervention.

Abbreviations: AAA, abdominal aortic aneurysm; ATV, all-terrain vehicle; HPV, human papillomavirus; MMR, measles-mumps-rubella; PSA, prostate-specific antigen; STD, sexually transmitted disease; UV, ultraviolet.

for other health problems. For example, a patient seen for management of hypertension or diabetes can have breast cancer screening incorporated into one visit and a discussion about colon cancer screening at the next visit. Other patients may respond more favorably to a clearly defined visit that addresses all relevant screening and prevention interventions. Because of age or comorbidities, it may be appropriate with some patients to abandon certain screening and prevention activities, although there are fewer data about when to "sunset" these services. For many screening tests, the benefit of screening does not accrue until 5–10 years of follow-up, and there are generally few data to support continuing screening for most diseases past age 75. In addition, for patients with advanced diseases and limited life expectancy, there is considerable benefit from shifting the focus from screening procedures to the conditions and interventions more likely to affect quality and length of life.

FURTHER READING

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5 Health Care Systems in Developed Countries

Richard B. Saltman

Health care systems are highly complex organizations, with many interdependent components. Traditionally, health systems in the developed world have been classified by their type of financing—i.e., either predominantly tax-funded (such as the National Health Service in England and publicly operated regional care systems in the four European Nordic countries) or predominantly statutory social health insurance (SHI)-funded (such as in Germany, the Netherlands, and France). Over the last decade, however, there has been structural convergence in the technical characteristics of both funding arrangements, and also in the associated delivery systems, making analytic observations about the differences across national systems more difficult.

A second confounding factor has been that former Soviet Bloc countries have, since 1991, replaced their former Soviet-style Semashko models (a top-down, national government–controlled structure with a parallel Communist Party apparatus) with various hybrid arrangements built on government-run SHI financing. Distinctions across health systems, especially in Europe, have been further compressed by the continuing negative impact of the 2008 global financial crisis on public revenues in many countries.

This chapter focuses on the individual patient care system: on the financing and delivery of individual clinical and preventive services. The individual patient care system is composed of the financing and delivery of necessary services to prevent death or serious harm ("rule of rescue"); to maintain quality of life; and to manage, reduce, and/or prevent the burden of illness on individual patients. While the

technical dimensions of most clinical services are similar across countries, their organizational, social, and economic characteristics differ markedly. Health systems in different countries exhibit substantial differences, for example, in access to care; in the design and reliance on quality assurance and provider payment mechanisms; in the relationship of primary care to hospital services; in the coordination of health care with home care and nursing home services; in the design and use of provider management strategies; in the way physicians work and are paid; in the decision-making roles of politically elected officials and of national, regional and municipal governments; and in participation of both citizens and patients. These differences reflect differing country contexts (geographical, social, economic and political), differences in national culture (consisting of prioritized norms and values), and substantial variation in how health sector institutions are structured.

FINANCING INDIVIDUAL PATIENT CARE SERVICES

Funding for individual care services in developed countries comes from the particular national mix among four possible sources of revenue: national, regional and/or municipal taxes; mandatory social health insurance; private health insurance; and out-of-pocket payments. Most countries have one preponderant payer, which then defines its funding arrangements and serves to frame the structure of its delivery system as well.

The Organization for Economic Co-operation and Development (OECD) data from 2015 (adjusted for purchasing power parities) show that total health care expenditures in developed countries vary across a considerable range, tied to health system structure as well as national history and culture. Total health expenditures in tax-funded health systems in Western Europe ranged from a low of 9.0% of GDP in Spain and 9.6% in Finland to a high of 10.6% in Denmark and 11.1% in Sweden. In SHI-funded systems in Western Europe, the range was about 1% higher, running from 10.4% in Belgium and 10.8% in the Netherlands to a high of 11.1% in Germany and 11.5% in Switzerland. Central European health care systems, reflecting the economic and health system consequences of their pre-1991 Soviet Bloc history, spend considerably lower percentages of their GDP on health care: from a low of 5.6% in Latvia and 6.1% in Estonia to 7.7% in the Czech Republic and 8.4% in Slovenia. In Asia, total health expenditures ranged widely from 4.9% in 2014 in Singapore to 7.1% in 2015 in South Korea to 11.4% in 2015 in Japan. Total health expenditures in the United States in 2015 were 16.9% of GDP.

Tax-Funded Systems In the United Kingdom, 79% of all health care funding was furnished through general tax revenues allocated by the national government in its annual budget process (all figures from OECD 2016). In Sweden, all public taxes combined raised 83.7% of total health care spending in 2015. Sweden's 21 regional level elected governments provide approximately 70% of that 83.7%, with the remaining 13.7% of total health spending raised by national and municipal taxes. In Canada, 71% of total health spending was raised by tax revenues, with 66% of that 71% coming from provincial or territorial taxes, while 5% came from national and local government taxes.

Social Insurance–Funded Systems In Western Europe, SHI funds have traditionally been organized on a private not-for-profit basis, but with statutory responsibilities under national law. When former Soviet Bloc countries in Eastern Europe regained their independence in 1991, they returned to pre-WWII SHI models, but since there was no remaining organizational infrastructure, these post-1991 arrangements typically became a single SHI fund, run as an arm of the national government. In the United States, the Medicare social insurance system for citizens over age 65, enacted in 1965, is organized as a single fund tied to the national Social Security (public pension) Administration, an independent agency within the national government, with reimbursement arrangements supervised by the Centers for Medicare & Medicaid Services inside the Department of Health and Human Services. Medicare covers inpatient hospital care plus limited post-hospital nursing home services (Medicare Part A). Supplemental private insurance policies are bought by covered individuals to help pay for outpatient physician visits (Medicare Part B) and for outpatient pharmaceuticals (Medicare Part D).

In Germany, 85% of the population is enrolled in 132 not-for-profit private social health insurance funds (in addition, 11% of the population are enrolled in private health insurance, and 4% in sector-specific public programs such as the military). Since 2009, all SHI members pay a flat tax on gross monthly income as a contribution (8.2% in 2013), which is sent by their SHI fund to a national pool. In addition, employers send 7.3% of each employee's salary to the same national pool. Special arrangements exist for payments from self-employed, retired, and unemployed workers. Since 1995 there has been a separate mandatory social insurance fund for long-term care (LTC), with an annual premium of 1.95% of each adult's gross monthly income, split 50%–50% with their employer. Pensioners since 2004 are required to pay the full amount from their pensions. Childless SHI enrollees pay a surcharge of 0.25% of monthly gross income. Overall, 85% of all health care expenditures in Germany were paid from public and/or mandatory private SHI sources.

In the Netherlands since 2006, all adult citizens pay a fixed premium (about 1290 euros in 2015) to their choice among 35 private health insurers (not-for-profit and for-profit). In addition, employers pay 6.95% of salary below 51,400 euro for each employee into a national health insurance fund. Self-employed individuals pay 4.85% into the national fund for taxable income up to the same limit. Retired and unemployed individuals also make payments. In addition to the individual premiums paid to their choice of private insurance fund, payments from the national health insurance fund, adjusted by individual age, sex, and health characteristics, also are made to the individual's chosen insurer. The Netherlands also has a separate mandatory social insurance fund for LTC (the ABWZ, since 2015 the WLZ, and now only for residential nursing home care) to which each employee pays 9.5% of taxable income beneath 33,600 euros every year. Self-employed, unemployed, and retired individuals also are required to pay premiums to the WLZ. Overall, including SHI revenues, public spending provided 87% of total health expenditures in 2014.

In Estonia, a former Soviet Republic that re-established a social health insurance system in 1991 upon regaining its independence, there is one national social health insurance fund that is an arm of the national government. This fund collects mandatory payments of 13% from salaried workers and 20% from self-employed individuals, covering both health care and retirement pensions. Overall, including SHI revenues, public spending accounted for 78.8% of total health expenditures.

Singapore, Japan, South Korea, and Taiwan have predominantly SHI systems of funding for individual care services. In these Asian countries (except Japan) there is one SHI fund that typically is operated as an arm of the national government.

In Singapore, starting in 1983, all employees up to age 50 have been required to place 20% of their income (employers add 16% more) into a health savings account to pay for direct health care costs, managed in their name by the Singapore government, called a Medisave account. Medisave accounts have a maximum amount, are tax-exempt, and receive interest payments (currently set at 4%). Consistent with a Confucian emphasis on family, the funds that accumulate in the Medisave account can be spent on health care for family members as well. If the accumulated funds are not spent on health care during the insured's life, they become part of the individual's personal estate and are distributed as an inheritance to his/her designated heirs. In addition, Singaporean citizens are also automatically enrolled into a second government-run health insurance plan called MediShield that pays for supplemental catastrophic, chronic, and long-term care. While citizens can opt out, 90% of citizens remain in the program. The Singapore government also operates a third, wholly tax-funded payer called Medifund that, with approval of a local neighborhood committee, will pay hospital costs for 3–4% of the population who are recognized as indigent. In part reflecting the high level of mandatory individual saving, tax funds provided only 41.7% of total health expenditures in 2014.

In South Korea, a state-run social health insurance system was established in 1977, which in 1990 covered 30.9% of total health care costs.

This percentage paid by the SHI system rose to 43.6% of total costs in 2011, leaving out-of-pocket costs at 35.2% of total costs. In 2000, three types of public SHI funds were merged into a single national state-run fund. As of 2011, 5.64% of an employee's salary must be paid as a social insurance contribution into this fund, with employees and employers each paying 50% of that amount. In 2008, an additional SHI fund was introduced to pay for LTC, operated by the main state-run SHI fund to reduce administrative costs. Contributions to the LTC fund are set at 6.55% of the individual's regular SHI contribution, coupled with 20% copayments for institutional care and 15% copayments for home care services.

There is no single preponderant source of health care spending in the United States. The source of health care revenues is fairly evenly divided among (1) national, state, county, and municipal taxes at 20% of all health spending in 2011 (for Medicaid, Children's Health Insurance Program [CHIP], the Veteran's Administration Hospitals, the Public Health Service, and the Indian Health Service); (2) mandatory social health insurance (for Medicare for all citizens over 65) at 23% of all spending; and (3) private health insurance (company and individual) at 35% of all spending. Out-of-pocket payments make up the remaining 14%. The World Bank, combining tax and social insurance funding, sets public funding in the United States at 48.3% of total health expenditures in 2014.

In 2010, the passage of the Affordable Care Act (ACA) extended privately provided but heavily regulated and federally subsidized health insurance to a number of low- and middle-income uninsured individuals and families. Since the same act reduced the availability of existing individually purchased private health insurance, the total increase in the number of newly covered individuals was less than expected. Insurance premium increases for 2017 have risen from 20% to over 100%, depending on the particular state, with additional increases in up-front deductible requirements, raising serious questions about the long-term sustainability of the ACA initiative. The current Republican administration has sought to repeal major financial and tax elements of the ACA (using congressional budget reconciliation rules) and to replace existing subsidy arrangements with a system of refundable tax credits toward the establishment of individual health savings accounts and/or purchase of private health insurance on open cross-state markets.

DELIVERING INDIVIDUAL PATIENT CARE SERVICES

Hospital Services In Europe, hospitals in both tax-funded and SHI-funded health systems are mostly publicly owned and operated by regional or municipal governments. In tax-funded health systems, most hospital-based physicians are civil servants, employed on a negotiated salary basis (often by a physician labor union), and subject to most of the usual advantages and disadvantages of being a public sector employee. There are somewhat more private hospitals in SHI-funded health systems. However, most larger hospitals are public institutions operated by local governments, and most hospital physicians (with the notable exception of the Netherlands, where they are private contractors organized in private group practices) are, like those in tax-funded systems, public sector employees. In most tax-funded European countries (but not continental SHI-funded countries), few specialist physicians have office-based practices, and in both tax- and SHI-funded systems, office-based specialists do not have admitting privileges to publicly operated hospitals.

Most public hospitals in both tax-funded and SHI-funded health systems are single free-standing institutions that can be classified into three broad categories by complexity of patients admitted and number of specialties available: (1) district hospitals (four specialties: internal medicine, general surgery, obstetrics, and psychiatry); (2) regional hospitals (20 specialties); and (3) university hospitals (>40 specialties). In addition, many countries have a number of small, 15- to 20-bed, freestanding, private (typically for-profit) clinics. Recently, some countries have begun to merge district and regional hospitals in an effort to improve the quality of care and create financial efficiencies (for example, Norway; planned for Finland starting in 2019). Institutional mergers can be difficult to negotiate among publicly operated hospitals, due to the role that these large institutions play as important care providers and as large employers in smaller cities and towns, especially given political and union concerns about maintaining current employment levels. In the United States, financial and reimbursement pressures triggered by the implementation of the 2010 ACA have generated a number of private sector hospital mergers into larger hospital groups.

In tax-funded health systems, publicly funded patients who are admitted for an elective procedure cannot choose their specialist physician (except private-pay patients in "pay beds" in NHS hospitals in England). Specialists are assigned by the clinic to a patient based on availability, with both junior and senior doctors placed in rotation.

Capital costs (buildings, large medical equipment) are publicly funded in all tax-funded systems and in most traditional SHI systems. For example, in Germany capital costs for all public hospitals are paid for by the regional governments. As a result, new capital investment is often allocated politically, according to location and political priorities. In Finland, local politicians in the 1980s would say that it "takes 10 years to build a hospital," meaning that it took that long to become a political priority for the regional government that controlled capital expenditures. As a result, local politicians would regularly overbuild when they got their one opportunity to obtain new capital. Because capital was not depreciated on the operating budget, such investment was perceived to be "free." As a result, new equipment often was not properly serviced or kept in use, as maintenance costs came from the operating budget, which was held by a different level political organization (municipalities in Finland).

Recently, efforts have been made to make public hospitals more responsible for their use of capital. In the Netherlands, public hospitals were shifted into private not-for-profit entities that are expected either to fund new capital from operating surplus or to borrow the funds from a bank with a viable business plan. In England, more than 100 hospitals have been built using the Public Finance Initiative (PFI) program, in which private developers build turn-key facilities (thus taking capital costs off the public borrowing limit), and then rent these facilities back to the NHS and/or the relevant NHS Foundation Trust.

In Singapore or South Korea, both of which are SHI funded, larger hospitals are publicly operated. However, there are a substantial number of smaller private clinics typically owned by specialist physicians. In the United States, the passage of the 2010 ACA has triggered the selling of many private specialist group practices to hospital groups, transforming previously independent practicing physicians into hospital employees.

Primary Care Services Most primary health care in SHI-funded health systems, and also in an increasing number of tax-funded health systems (except in low-income areas of some large cities), is delivered by independent private general practitioners (GPs), working either individually or in small privately owned group practices. Recent changes in tax-funded health systems include Norway, where most primary care moved from municipally employed physicians to private-practice GPs in 2003, and Sweden, where, following a 2010 change in national reimbursement requirements, new privately owned not-for-profit and for-profit GP practices were established and now deliver 50% of all primary care visits. In Finland, where public primary health care centers used to provide most primary care visits, delays in getting public health center appointments have pushed up to 40% of all visits to a parallel occupational health system, as well as to publicly employed primary care physicians working privately in the afternoons, seeing patients who are partly reimbursed by Finland's separate Social Insurance Institution (known as KELA).

In England, most primary care physicians are private GPs who are contractors to the NHS, working either independently or in small group practices. These private GPs own their own practices, which they can sell when they retire. However, as part of the original agreement establishing the NHS in 1948 (which most physicians strongly opposed), private GPs also receive a national government pension upon retirement. In the inner cities in England, there are some larger primary health clinics.

In 2001, England's private primary care doctors were organized into geographically based Primary Care Trusts (PCTs). These PCTs were allocated 80% of the total NHS budget to contract for elective hospital services required by their patients with both NHS hospital trusts as well as private hospitals. In 2013, PCTs were restructured into Clinical Commissioning Groups with similar contracting responsibilities.

In 2004, the Quality Outcomes Framework (QOF) was introduced as a quality of care–tied approach to providing additional income for NHS GPs. This regulatory mechanism in 2010 set 134 different standards for best practice primary care in four main domains: 86 clinical, 36 organizational, 4 preventive service, and 3 patient experience. GPs income grew on average by 25% through the introduction of the QOF, with general practices averaging 96% of possible QOF points. Total spending on QOF in 2014 in England consumed 15% of all primary care expenditures.

In Central European countries like Poland and Estonia that were formerly within the Soviet Bloc, primary care provision had to be newly established after independence was regained in 1991, since first-line care in the former Semashko model was provided in specialist polyclinics. Primary care doctors rapidly emerged as almost entirely private for-profit GPs working on contract from the national SHI fund. Private GPs in most Central European countries now are paid on a per-visit basis, in an amount set by the national SHI fund. This arrangement was heavily influenced by the structure of primary care in Germany's SHI-based health system.

In Asian countries such as Singapore, South Korea, and Japan, most primary care is provided by private for-profit GPs working independently or in small group practices. Private GPs are reimbursed at a set per-service fee by the national SHI fund(s).

Developed countries have varying policies regarding access to individual preventive services. Health systems in most countries provide vaccinations and mammography as part of funded health care services. In the United States, most insured individuals—and in Canada, most covered residents—automatically receive an annual physical exam including full blood profiles. In Norway and Denmark, adult physical exams are provided only upon special request by the individual, and in Sweden adult physical exams are provided only to pregnant women. In Sweden, adults who wish to know their cholesterol or PSA levels have begun to purchase blood tests out-of-pocket from private laboratories. Lack of physical exams and accompanying blood profiles may contribute to lower health care expenditures in the Nordic region.

Access to Elective Specialist Care Approximately half of all European health care systems have a gatekeeping system that requires referrals from primary care physicians to book specialist visits (for publicly paid visits). In most tax-funded health systems (although not in most SHI systems), there are substantial waiting times, typically several months or more, for elective specialist appointments and high-tech diagnostic procedures, especially for cancer and other elective surgical or high-demand services. In England, a patient who requires a further consultation with a second specialist typically has to return to their primary care physician for a second referral, and then has to wait in the regular patient queue for that second appointment. In Finland, middle class families purchase separate private health insurance for their children to enable them to skip the long waiting times for primary and secondary pediatric health care services. More than 400,000 Finnish children have privately purchased policies.

There is also substantial waiting time for radiologic imaging services in most tax-funded systems. In Malta, the tax-funded health system's recent efforts to prioritize elective MRI investigations have succeeded in reducing waiting times from 18 months to 4 months. In both Alberta and British Columbia Provinces in Canada, waiting time in 2016 for a publicly funded elective MRI is approximately 6 months, whereas privately paid MRIs are available in both provinces within 1 week.

This issue of waiting times in tax-funded health systems reflects a combination of growing demand (including increasing clinical indications), financial constraints, and insufficient capacity, including inadequate physician working hours. In the 1980s, when several surgical procedures for the elderly became more routine practice (e.g., hip replacement, coronary artery bypass graft, corneal lens implantation), the waiting list problem worsened. It had been mitigated somewhat by the early 2000s, only to return as a growing policy challenge once public sector financial resources became constrained after 2008. Timely cancer diagnosis and care have been a particularly sensitive issue, with tax-funded systems often taking several months for a patient to see an oncologist and then months more to begin treatment. In Sweden, a newspaper journalist set off a political storm in 2013 when he wrote extensively about women patients in one large county council (Malmo) who had to wait 47 days to receive the results from their breast cancer biopsy.

In response to patient anger in the early 2000s, a number of tax-funded health care systems introduced maximum waiting times for elective hospital procedures. (Most Western European SHI systems do not have long waiting times or treatment guarantees.) These maximum waiting times typically include initial primary care visits as well as specialist evaluations and treatment. In Denmark, a patient has the right to go to a different Danish public hospital for care after waiting 30 days without treatment. In Sweden, under the 2005 "waiting time guarantee," an untreated patient's local county council is required to pay for care in another county's hospital after 180 days. Beginning in 1997, the European Union Court of Justice has slowly expanded the right of all EU citizens to travel to another EU country to receive "timely" care, with their home country health system required to pay for that care.

Long-Term Care Services LTC (consisting of residential and home-based services) consumes a relatively small but increasing proportion of gross domestic product (GDP) in developed countries. In Sweden, LTC consumes 3.6% of GDP, mostly from public funds, whereas in Switzerland LTC services consume 2.1% of GDP, with only 0.8% of GDP coming from public funding. In the United States, total LTC expenditures represent 1.0% of total GDP, with 0.6% of GDP representing public funds, mostly from state-based Medicaid programs, which typically spend about 40% of their total funding on nursing home services. (Note that these figures do not include emergency, inpatient, or outpatient hospital costs generated by elderly patients.)

Since nursing home care is far more expensive than home care (nursing home care requiring the provision of housing, food, and around-the-clock care providers), government policymakers seek to keep the elderly and the chronically ill out of nursing homes for as long as feasible. Moreover, in developed countries like Sweden and Norway, some 70% of all home care services come from informal caregivers: spouses, children (typically daughters), neighbors, and friends. While some SHI systems (e.g., Germany) make available cash payments for LTC that can be used to compensate informal caregivers, most policymakers work hard to not monetize what is a large amount of essentially free care. Indeed, they actively seek to encourage those providing these services to continue to do so as long as possible, trying to postpone caregiver burnout by providing support services such as free respite care, special call-in lines for caregiving advice, pension points toward retirement for the informal caregiver (Nordic countries), and free day-care center services.

In most tax-funded and SHI-funded European countries, home care services are organized at the municipal government level. In tax-funded systems, these services are also delivered mostly by municipal employees, working according to union-negotiated protocols. In some European SHI systems, and recently in tax-funded Sweden and Finland, private companies also provide home care services on contract to municipal governments. In combination with national legislation, these municipal systems also provide important support for informal caregivers, since the financial costs of caring for adults in their own home are substantially less than providing housing, food, and caregiver support in publicly funded homes for the aged or in nursing homes.

A high proportion of nursing homes in European tax-funded and SHI-funded health systems are publicly owned facilities operated by municipal governments; in some instances in SHI-funded systems (Israel, Netherlands), they are operated by private not-for-profit organizations. Recently, in some tax-funded systems (e.g., Sweden), private for-profit chains have begun to open nursing homes that are funded on

a contract basis with local municipal governments. Costs for nursing home care can be expensive: in Norway, the cost per patient is often over $100,000 per year in a publicly funded home, with the patient responsible for paying up to 80% depending on the family's economic status. In Sweden, patients living in publicly funded nursing homes in Stockholm County pay a relatively small official fee, but they also pay room rent and up to 2706 Swedish Krona (SEK) per month (about $350 USD) for food out of their pensions.

In 2012, in an effort to reduce demand for expensive hospital and nursing home services, Norway and Denmark both began a number of elderly care reforms that shifted service delivery as well as funding responsibilities to municipal governments. Among innovations in Norway, municipalities are required to establish a municipal acute bed unit (MAU) to treat stable elderly patients and provide observation beds for evaluation. Partial funding for these units is provided by the four regional health care administrations. Some municipalities have also embedded primary care units inside their regional hospital to arrange discharge and to coordinate care for the chronically ill elderly. Norwegian municipalities are also responsible through their contracted (mostly private) primary care physicians to implement the National Pathways Program, which established treatment protocols for cross-sector conditions such as diabetes and cardiovascular conditions.

A differently configured structural innovation to better integrate LTC for the chronically ill elderly with clinical individual health services has been to consolidate both social and health care services within the same public administrative organization. In proposed 2019 health reforms in Finland, as well as a pilot decentralization program in England for 2.8 million people in Greater Manchester, social and health care programs are to be administered by a single responsible agency.

In the SHI-funded system in the Netherlands, almost 7% of the population live in a residential home. National government legislation revised the structure of nursing home funding and care in 2015. Three acts restructured the separate public LTC SHI fund, which requires mandatory payments by 100% of Dutch adults, and introduced delivery-related reforms that reduced the number and overall cost of nursing home patients paid for by the fund. Determination of eligibility for public payment for nursing home care is now made by an independent national assessment body (the Centre for Needs Assessment). Moreover, municipal governments now play a stronger role in funding and delivering home care services. The reforms created social care teams that hold "kitchen table talks" to steer the elderly first toward seeking care from family, neighbors, churches, and other local community organizations before they qualify for publicly paid in-home care. In 2012, some 1.5 million people (12% of total population) provided informal care to ill or disabled persons, averaging 22 hours per week of care per person.

Home care recipients in the Netherlands can choose to set up a "personal budget," using their public funding allocation to select their preferred individual care personnel (either publicly employed or publicly approved private providers). This arrangement also enables these home care recipients to determine the particular mix of services they want, as well as to augment the allocated public funds with personal funds. A number of innovative not-for-profit nursing homes have been created to provide additional services to elderly living in their neighborhood (primary care home visits), as well as terminal hospice care (e.g., the Saffier De Residentie Groep residences in The Haag).

In the United States, nursing home and home care are funded and delivered in a variety of different ways. For individuals who have minimal financial assets, nursing home costs are paid by a joint federal-regional (state) welfare program called Medicaid. Most state government Medicaid programs pay out more than 40% of their total budget for nursing home care. In the past, Medicaid did not pay for home care services. However, some states have programs with private for-profit and not-for-profit providers that provide home care as a way to forestall the need for the more expensive nursing home care.

Many private individuals take out private LTC insurance, typically from commercial insurance companies. These policies require individuals to make premium payments for years in advance (often 20 or more) before the individual learns whether they will, in fact, require home or nursing home care. Some private insurers have also raised premiums after individuals have paid in for many years and canceled policies if the new higher rate is not affordable. The 2010 ACA contained a new public LTC insurance program. However, the program was designed to be voluntary, and U.S. Department of Health and Human Services administrators decided not to implement that portion of the law.

In addition to the tax-funded Medicaid program, and privately purchased LTC insurance, many middle-class families pay for care from savings, by selling the elderly person's home, or by direct contribution from children and other family members. Expenses can reach more than $60,000 per year depending on the location of a facility and who operates it.

Nursing home care in the United States is provided by a wide mix of private not-for-profit and for-profit providers, ranging from church-owned single-site homes to large stock market–listed companies. Many of these homes are purpose-built as assisted-living residences. There also are special units and facilities designed to care for the memory impaired. Home care services are delivered by a mix of private and not-for-profit and for-profit providers.

In Japan, a national LTC insurance fund was introduced in 2000. Although the new fund applies uniformly across the country, the program is administered by municipal governments and the premium level differs across municipalities, with an average monthly premium of 3000 yen (about $30 USD). In South Korea, an SHI fund for LTC is funded by mandatory contributions of 4.78% of a person's regular national health insurance contribution, with an additional 20% of total LTC expenditures provided by national government funds. The client copayment for home care is set at 15% of expenses and at 20% for residential care.

PHARMACEUTICALS

Pharmaceutical expenditures in developed countries (inpatient and outpatient combined) vary widely across different health system types, as well as between different countries within those different institutional types. OECD figures for 2014 show drug expenditures in tax-funded countries in Western Europe ranging from 6.7% of total health expenditures (THE) in Denmark to 12.2% of THE in the United Kingdom and 17.9% of THE in Spain. In SHI-funded Western European systems, pharmaceuticals absorbed 7.6% of THE in the Netherlands, while in Germany that figure was 14.5%. In the hybrid tax-funded SHI systems of Central Europe, pharmaceuticals were much higher: 18% of THE in Estonia to 30.2% of THE in Hungary. In Asian SHI systems, pharmaceuticals consumed 20.6% of THE in South Korea and 21% of THE (in 2012) in Japan. The OECD's 2014 figures for pharmaceutical spending in North America are 12.3% of THE in the United States and 17.2% in Canada.

Contributing factors to this wide-ranging variation are (1) the ratio problem (relatively fixed level of pharmaceutical costs due to international prices—the numerator—divided by a greatly varying per-capita health expenditure cost in different developed country health systems); (2) the range and type of pharmaceutical price controls in each country; and (3) the degree of limitation placed on pharmaceutical supply, tied to formularies and/or explicit forms of drug rationing.

Most European health systems have tight national controls on the cost and, in some tax-based countries, on the availability of pharmaceuticals. Most European countries also use a number of different regulatory measures to limit prices and/or availability of both inpatient and outpatient drugs, including mandatory generic prescribing, reference pricing, patient copays (sometimes with an annual ceiling, after which copayments are no longer required), and (particularly in tax-funded systems) national formularies tied to clinical effectiveness. (Norway, for example, allows only about 2300 different preparations—including dosage, delivery method, and box size—to be stocked by pharmacies.) Prices for drugs can vary considerably across different European countries, tied to economic development and domestic pricing patterns. One consequence of these differential national pricing controls has been the development of a parallel import market, in which drug wholesalers and pharmacists in the more expensive countries purchase supplies from a cheaper market elsewhere in Europe.

Access to expensive drugs has also been intentionally limited in some tax-funded health systems in Europe. One basis for rationing, as noted above, has been rationing tied to QALYs (quality-adjusted life-years). Rationing also reflects a clash between strained public drug budgets and public pressure. For example, in the case of cancer drugs in England, the recommendation of NICE against funding the breast cancer drug trastuzumab (Herceptin) was subsequently overturned by the Minister of Health. Expensive cancer drugs continue to be rationed in England where the NHS Cancer Drug Fund, established to provide access on a case-by-case basis, ran out of funds and was forced to close down for 3 months to restructure its operations.

As part of the medical tradition in Asian countries, office-based physicians fill prescriptions as well as prescribing drugs to patients. These sales serve to supplement their income in the setting of relatively low per-visit payments from state-run SHI funds. Korea has now implemented restrictions on these office-based sales. Japan has attempted to reduce physician sale of pharmaceuticals by various changes in reimbursement rates, reducing the total percentage of physician-sold pharmaceuticals to 42.8% of all outpatient prescriptions.

GOVERNANCE AND REGULATION

Health care services in developed countries are steered, constrained, monitored, and (to varying degrees) assessed by governments and governmentally established and/or empowered bodies. Although these measures apply particularly to the financial efficiency of government-funded services, they also seek to promote patient and community safety, equity of access, and high-quality clinical outcomes. This oversight is often strongly focused on privately operated and contracted providers and insurers, although in principle it applies to publicly operated organizations as well.

Governance consists of macro national-level policy, meso institutional-level management, and micro clinic-level care decisions. This complex mix of governance decisions is often shared among different national, regional, and local governments, depending on the degree of centralization, decentralization, or, recently, recentralization (e.g., Norway). While most systems officially prioritize "good governance," governance activities frequently comingle with political objectives as core policy concepts are developed and transformed into concrete organizational targets.

In Sweden, health system governance is shared among national, regional (county), and local municipal governments. The national government has responsibility to pass "frame" legislation, which establishes the basic structure of the system. To cite one example, until recently, the national government had limited an adult patient's total copayments for outpatient physician (specialist and primary care) and pharmaceuticals to 2800 SEK (about $350 USD) for a 12-month period. The 20 regional governments, in turn, made policy decisions within that legislation, deciding how to apportion the specific copayments for each primary care and specialist outpatient visit. Since Swedes can self-refer to specialists, some counties double the copayment to hospital-based doctors to discourage unnecessary appointments. Similarly, fiscal policy normally is shared between the regional government, which raises about 70% of total health expenditures through its own county-set flat income tax, and the national government, which provides additional purpose-tied funds for national objectives such as consolidating open-heart surgery across county lines and balancing lower tax receipts in rural counties with smaller working populations. However, this normal funding relationship across governments can change. In the early 1990s, the national government placed a "stop" on raising county taxes prior to Sweden's admission in 1995 to the European Union. In 2016, each of the 20 counties could set their own ceilings, which were almost all at 3300 SEK (about $370 USD).

In Spain's tax-funded health system (70.9% publicly funded), 17 regional "autonomous communities" were given full managerial responsibility for the provision of health services in a decentralization process, along with ownership of all publicly owned hospitals. The national government generates a substantial proportion of health care resources, which are included in the broad block grants it allocates to the regional governments, which then add regional tax revenue to make up the full public-sector budget. In a mechanism to further influence operating policy, the national Spanish government established a joint federal-regional council to review quality and performance data (through the 2003 Health System Cohesion and Quality Act). Italy's tax-funded health system (75.6% publicly funded) is similarly operated by 20 regional governments, which pay for the publicly operated system through a complicated mix of national, and nationally stipulated but regionally collected, taxes. Again like Spain, the national government established a federal-regional government council, which seeks to coordinate care standards and information among the regions and with national government agencies.

In Germany, where funding for the health system is formally the responsibility of 132 private not-for-profit sickness funds, governance decisions are shared among these private sector sickness funds and public-sector national, regional, and municipal governments. The sickness funds receive a risk-adjusted premium payment for each enrolled individual, determined by a national government–determined formula, and from a national government–run health insurance pool. Most hospitals are owned and operated by municipal governments, while investment capital for structural renovations and new building comes from the 16 regional Länder taken from their tax revenues. Payment frameworks and amounts for public hospitals are negotiated between associations of these municipally owned hospitals and associations of the private sickness funds, without formal government participation.

Regulation is an essential element of an effective health care system and a key component of overall health system governance. Regulation incorporates both broad standard requirements that affect all organizations that operate in a country (e.g., hiring, firing, and wage decisions) as well as specific health sector–related regulations (e.g., proper handling, use, and disposal of low-grade nuclear waste from radiation treatments). Recent examples of health sector regulation in England, for example, include the following:

1. Requiring all cancer drugs adopted for use in the NHS to cost no more than £30,000/QALY;
2. Requiring in their employment contract that junior doctors in hospitals work a specific number of Sundays; and
3. Requiring that all emergency department patients receive care within 4 h of their arrival.

A powerful tool that has the force of law, regulation can have substantial negative as well as positive effects. A well-known political science corollary of regulatory power is that "the right to regulate is also the right to destroy." For example, in the United States, the federal Environmental Protection Agency, as part of its pursuit of cleaner air, issued wide-ranging regulatory orders setting performance standards that resulted in the closing of many West Virginia coal mines, resulting in the loss of tens of millions of dollars of productive capacity and thousands of high-paying jobs. Similarly, in some tax-funded European systems, such as those in Sweden and England, there is growing pressure from public health advocates to prohibit the making of a profit from publicly paid funds. In Sweden, the national government's Reepalu report honored a pledge made by the Social Democratic government to its Left (socialist) Party ally by calling for a legislated ban on profit-making in the provision of publicly funded health care services. The Report's publication resulted in substantial divestment of existing investor-owned primary care, nursing home, and home care companies.

FUTURE CHALLENGES

Health systems in developed countries face serious challenges in the coming years. These include financial, organizational, and policy dilemmas for which institutionally viable, financially sustainable, and politically supportable solutions will be complicated to develop and difficult to implement. On the delivery side, a key question is whether privately structured GP-based primary care is more efficient and effective than various clinic-based forms of primary care services. Recent movement in Northern and Central Europe toward more private GPs, along with continued private office–based primary care in much of

Canada, the United States, and economically developed countries in Asia, raises complex policy issues for international organizations like the World Health Organization (WHO), as well as national policymakers. In the hospital sector, existing levels of clinical quality and patient responsiveness in publicly operated command-and-control institutions will increasingly have to compete with those of semi-autonomous public hospitals, as well as various types of private, sometimes very innovative providers. In the financing arena, continued pressure on publicly raised health system revenues is likely to erode longtime commitments in some tax-funded health systems to minimal patient copayments and low out-of-pocket funding.

An additional set of challenges will arise from recent commitments by international organizations like WHO to restructure health systems in developed countries to better address the social determinants of health. This new, incomplete strategy calls for a dramatic expansion of health sector responsibility to include a wide range of existing institutional arrangements in housing, education, work-life, and social and political decision-making. The influential 2010 Strategic Review of Health Inequalities in England entitled "Fair Society, Healthy Lives," led by Sir Michael Marmot, a British epidemiologist, called for the elimination of all "inequities in power, money, and resources." Separate from the political dimensions of this proposed new paradigm, how such fundamental societal change will be funded has yet to be addressed.

Looking forward, among the most essential challenges to national decision-makers in the coming period will be four specific health system imperatives:

1. **Finding a more sustainable balance between ethics and funding.** Policymakers in publicly funded health systems face a growing gap between patient expectations of high-quality clinical care, staff expectations of better compensation, and the economic imperative of no new taxes. While the present solidaristic foundation for raising collective revenues is insufficient, available non-solidaristic tools (copayments, supplemental insurance, private pay) inevitably contribute to overall inequality. But what then are the realistic policy alternatives? The minimalist new policy goal necessarily will have to become one of raising new revenues while doing the least economic and social harm.
2. **Developing better strategies to steer provider diversity.** Health systems in developed countries are becoming more diverse with more and different types of public owners: hospital trusts, state enterprises, and mixed public-private hospital owners/managers. There also are more and different types of private providers: not-for-profit community groups, foundations, and cooperatives, as well as for-profit small local entrepreneurs, large international companies, and risk capital funds (venture capital). Furthermore, new innovative delivery models are reorganizing traditional service boundaries: not-for-profit private nursing homes in the Netherlands also provide outpatient primary care to neighborhood elderly patients, as well as hospice care; Israeli technology companies combine high-tech home-based patient monitoring with standard medical and custodial home care services. Public pressure from citizens for more choice and better outcomes will pressure policymakers toward new, more accommodative health system arrangements.
3. **Ensuring better coordination between social and health services.** Tax-funded and SHI-funded systems alike are under intense policy pressure to develop better strategies to integrate services for the chronically ill elderly, as a way to improve the quality of services that these patients receive and to keep them at home healthier and longer, reducing expensive acute visits to hospitals and emergency departments. The clear delivery system goal will increasingly be to keep the elderly out of nursing homes and acute care facilities for as long as possible.
4. **Building labor unions into provider innovation.** In many developed countries, health sector staff, including hospital physicians, are members of labor unions. Effective policymaking will require finding mechanisms to build these personnel unions into accelerated health system restructuring processes. This process will necessarily involve integrating unions into more innovative, flexible, fiscally sustainable organizational arrangements with contracts that reward active participation in organizational change, contracts that pay incentives to more productive employees, quicker reassignment and redundancy procedures (firing health sector workers can take a year or longer in some European health systems), and establishing profit-sharing payments to teams/unions, also in public sector organizations.

While the structure and complexity of resolving these specific organizational challenges will vary depending on a country's cultural and institutional context, the commonality of these problems suggests that health systems in the developed world will require a new, broader range of targeted policy strategies and solutions.

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6 The Safety and Quality of Health Care

David W. Bates

Safety and quality are two of the central dimensions of health care. In recent years it has become easier to measure safety and quality, and it is increasingly clear that performance in both dimensions could be much better. The public is—with good justification—demanding measurement and accountability, and payment for services will increasingly be based on performance in these areas. Thus, physicians must learn about these two domains, how they can be improved, and the relative strengths and limitations of the current ability to measure them.

Safety and quality are closely related but do not completely overlap. The Institute of Medicine has suggested in a seminal series of reports that safety is the first part of quality and that the health care system must first and foremost guarantee that it will deliver safe care, although quality is also pivotal. In the end, it is likely that more net clinical benefit will be derived from improving quality than from improving safety, though both are important and safety is in many ways more tangible to the public. The first section of this chapter will address issues relating to the safety of care and the second will cover quality of care.

SAFETY IN HEALTH CARE

Safety Theory and Systems Theory *Safety theory* clearly points out that individuals make errors all the time. Think of driving home from the hospital: you intend to stop and pick up a quart of milk on the way home but find yourself entering your driveway without realizing how you got there. Everybody uses low-level, semiautomatic behavior for many activities in daily life; this kind of error is called a *slip*. Slips

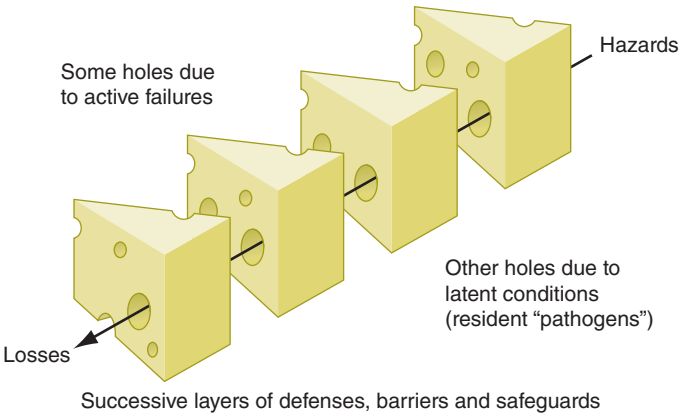

FIGURE 6-1 "Swiss cheese" diagram. Reason argues that most accidents occur when a series of "latent failures" are present in a system and happen to line up in a given instance, resulting in an accident. Examples of latent failures in the case of a fall might be that the unit is unusually busy and the floor happens to be wet. *(Adapted from J Reason: BMJ 320:768, 2000; with permission.)*

occur often during care delivery—e.g., when people intend to write an order but forget because they have to complete another action first. *Mistakes*, by contrast, are errors of a higher level; they occur in new or nonstereotypic situations in which conscious decisions are being made. An example would be dosing of a medication with which a physician is not familiar. The strategies used to prevent slips and mistakes are often different.

Systems theory suggests that most accidents occur as the result of a series of small failures that happen to line up in an individual instance so that an accident can occur **(Fig. 6-1)**. It also suggests that most individuals in an industry such as health care are trying to do the right thing (e.g., deliver safe care) and that most accidents thus can be seen as resulting from defects in systems. Systems should be designed both to make errors less likely and to identify those that do inevitably occur.

Factors that Increase the Likelihood of Errors Many factors ubiquitous in health care systems can increase the likelihood of errors, including fatigue, stress, interruptions, complexity, and transitions. The effects of fatigue in other industries are clear, but its effects in health care have been more controversial until recently. For example, the accident rate among truck drivers increases dramatically if they work over a certain number of hours in a week, especially with prolonged shifts. A recent study of house officers in the intensive care unit demonstrated that they were about one-third more likely to make errors when they were on a 24-h shift than when they were on a schedule that allowed them to sleep 8 h the previous night. The American College of Graduate Medical Education has moved to address this issue by putting in place the 80-h workweek. Although this stipulation is a step forward, it does not address the most important cause of fatigue-related errors: extended-duty shifts. High levels of stress and heavy workloads also can increase error rates. Thus, in extremely high-pressure situations, such as cardiac arrests, errors are more likely to occur. Strategies such as using protocols in these settings can be helpful, as can simple recognition that the situation is stressful.

Interruptions also increase the likelihood of error and occur frequently in health care delivery. It is common to forget to complete an action when one is interrupted partway through it by a page, for example. Approaches that may be helpful in this area include minimizing interruptions and setting up tools that help define the urgency of an interruption.

Complexity represents a key issue that contributes to errors. Providers are confronted by streams of data (e.g., laboratory tests and vital signs), many of which provide little useful information but some of which are important and require action or suggest a specific diagnosis. Tools that emphasize specific abnormalities or combinations of abnormalities may be helpful in this area.

Transitions between providers and settings are also common in health care, especially with the advent of the 80-h workweek, and generally represent points of vulnerability. Tools that provide structure in exchanging information—for example, when transferring care between providers—may be helpful.

The Frequency of Adverse Events in Health Care Most large studies focusing on the frequency and consequences of adverse events have been performed in the inpatient setting; some data are available for nursing homes, but much less information is available about the outpatient setting. The Harvard Medical Practice Study, one of the largest studies to address this issue, was performed with hospitalized patients in New York. The primary outcome was the adverse event: an injury caused by medical management rather than by the patient's underlying disease. In this study, an event either resulted in death or disability at discharge or prolonged the length of hospital stay by at least 2 days. Key findings were that the adverse event rate was 3.7% and that 58% of the adverse events were considered preventable. Although New York is not representative of the United States as a whole, the study was replicated later in Colorado and Utah, where the rates were essentially similar. Since then, other studies using analogous methodologies have been performed in various developed nations, and the rates of adverse events in these countries appear to be ~10%. Rates of safety issues appear to be even higher in developing and transitional countries; thus, this is clearly an issue of global proportions. The World Health Organization has focused on this area, forming the World Alliance for Patient Safety.

In the Harvard Medical Practice Study, adverse drug events (ADEs) were most common, accounting for 19% of all adverse events, and were followed in frequency by wound infections (14%) and technical complications (13%). Almost half of adverse events were associated with a surgical procedure. Among nonoperative events, 37% were ADEs, 15% were diagnostic mishaps, 14% were therapeutic mishaps, 13% were procedure-related mishaps, and 5% were falls.

ADEs have been studied more than any other error category. Studies focusing specifically on ADEs have found that they appear to be much more common than was suggested by the Harvard Medical Practice Study, although most other studies use more inclusive criteria. Detection approaches in the research setting include chart review and the use of a computerized ADE monitor, a tool that explores the database and identifies signals that suggest an ADE may have occurred. Studies that use multiple approaches find more ADEs than does any individual approach, and this discrepancy suggests that the true underlying rate in the population is higher than would be identified by a single approach. About 6–10% of patients admitted to U.S. hospitals experience an ADE.

Injuries caused by drugs are also common in the outpatient setting. One study found a rate of 21 ADEs per every 100 patients per year when patients were called to assess whether they had had a problem with one of their medications. The severity level was lower than in the inpatient setting, but approximately one-third of these ADEs were preventable.

The period immediately after a patient is discharged from the hospital appears to be very risky. A recent study of patients hospitalized on a medical service found an adverse event rate of 19%; about one-third of those events were preventable, and another one-third were ameliorable (i.e., they could have been made less severe). ADEs were the single leading error category.

Prevention Strategies Most work on strategies to prevent adverse events has targeted specific types of events in the inpatient setting, with nosocomial infections and ADEs having received the most attention. Nosocomial infection rates have been reduced greatly in intensive care settings, especially through the use of checklists. For ADEs, several strategies have been found to reduce the medication error rate, although it has been harder to demonstrate that they reduce the ADE rate overall, and no studies with adequate power to show a clinically meaningful reduction have been published.

Implementation of checklists to ensure that specific actions are carried out has had a major impact on rates of catheter-associated bloodstream infection and ventilator-associated pneumonia, two of the most serious complications occurring in intensive care units. The checklist

concept is based on the premise that several specific actions can reduce the frequency of these issues; when these actions are all taken for every patient, the result has been an extreme reduction in the frequency of the associated complication. These practices have been disseminated across wide areas, in particular in the state of Michigan.

Computerized physician order entry (CPOE) linked with clinical decision support reduces the rate of serious medication errors, defined as those that harm someone or have the potential to do so. In one study, CPOE, even with limited decision support, decreased the serious medication error rate by 55%. CPOE can prevent medication errors by suggesting a default dose, ensuring that all orders are complete (e.g., that they include dose, route, and frequency), and checking orders for allergies, drug–drug interactions, and drug–laboratory issues. In addition, clinical decision support can suggest the right dose for a patient, tailoring it to level of renal function and age. In one study, patients with renal insufficiency received the appropriate dose only one-third of the time without decision support, whereas that fraction increased to approximately two-thirds with decision support; moreover, with such support, patients with renal insufficiency were discharged from the hospital half a day earlier. As of 2017, over 90% of U.S. hospitals have implemented CPOE, though the decision support often is still limited.

Another technology that can improve medication safety is bar coding linked with an electronic medication administration record. Bar coding can help ensure that the right patient gets the right medication at the right time. Electronic medication administration records can make it much easier to determine what medications a patient has received. Studies to assess the impact of bar coding on medication safety are under way, and the early results are promising. Another technology to improve medication safety is "smart pumps." These pumps can be set according to which medication is being given and at what dose; the health care professional will receive a warning if too high a dose is about to be administered.

The National Safety Picture Several organizations, including the National Quality Forum and the Joint Commission, have made recommendations for improving safety. In particular, the National Quality Forum has released recommendations to U.S. hospitals about what practices will most improve the safety of care, and all hospitals are expected to implement these recommendations. Many of these practices arise frequently in routine care. One example is "readback," the practice of recording all verbal orders and immediately reading them back to the physician to verify the accuracy of what was heard. Another is the consistent use of standard abbreviations and dose designations; some abbreviations and dose designations are particularly prone to error (e.g., 7U may be read as 70).

Measurement of Safety Measuring the safety of care is difficult and expensive, since adverse events are, fortunately, rare. Most hospitals rely on spontaneous reporting to identify errors and adverse events, but the sensitivity of this approach is very low, with only ~1 in 20 ADEs reported. Promising research techniques involve searching the electronic record for signals suggesting that an adverse event has occurred. These methods are not yet in wide use but will probably be used routinely in the future. Claims data have been used to identify the frequency of adverse events; this approach works much better for surgical care than for medical care and requires additional validation. The net result is that, except for a few specific types of events (e.g., falls and nosocomial infections), hospitals have little idea about the true frequency of safety issues.

Nonetheless, all providers have the responsibility to report problems with safety as they are identified. All hospitals have spontaneous reporting systems, and, if providers report events as they occur, those events can serve as lessons for subsequent improvement.

Conclusions about Safety It is abundantly clear that the safety of health care can be improved substantially. As more areas are studied closely, more problems are identified. Much more is known about the epidemiology of safety in the inpatient setting than in outpatient settings. A number of effective strategies for improving inpatient safety have been identified and are increasingly being applied. Some effective strategies are also available for the outpatient setting. Transitions appear to be especially risky. The solutions to improving care often entails the consistent use of systematic techniques such as checklists and often involves leveraging of information technology. Nevertheless, solutions will also include many other domains, such human factors techniques, team training, and a culture of safety.

QUALITY IN HEALTH CARE

Assessment of quality of care has remained somewhat elusive, although the tools for this purpose have increasingly improved. Selection of health care and measurement of its quality are components of a complex process.

Quality Theory Donabedian has suggested that quality of care can be categorized by type of measurement into structure, process, and outcome. *Structure* refers to whether a particular characteristic is applicable in a particular setting—e.g., whether a hospital has a catheterization laboratory or whether a clinic uses an electronic health record. *Process* refers to the way care is delivered; examples of process measures are whether a Pap smear was performed at the recommended interval or whether an aspirin was given to a patient with a suspected myocardial infarction. *Outcome* refers to what actually happens—e.g., the mortality rate in myocardial infarction. It is important to note that good structure and process do not always result in a good outcome. For instance, a patient may present with a suspected myocardial infarction to an institution with a catheterization laboratory and receive recommended care, including aspirin, but still die because of the infarction.

Quality theory also suggests that overall quality will be improved more in the aggregate if the performance level of all providers is raised rather than if a few poor performers are identified and punished. This view suggests that systems changes are especially likely to be helpful in improving quality, since large numbers of providers may be affected simultaneously.

The theory of *continuous quality improvement* suggests that organizations should be evaluating the care they deliver on an ongoing basis and continually making small changes to improve their individual processes. This approach can be very powerful if embraced over time.

A number of specific tools have been developed to help improve process performance. One of the most important is the Plan-Do-Check-Act cycle **(Fig. 6-2)**. This approach can be used for "rapid cycle" improvement of a process—e.g., the time that elapses between a diagnosis of pneumonia and administration of antibiotics to the patient. Specific statistical tools, such as control charts, are often used in conjunction to determine whether progress is being made. Because most medical care includes one or many processes, this tool is especially important for improvement.

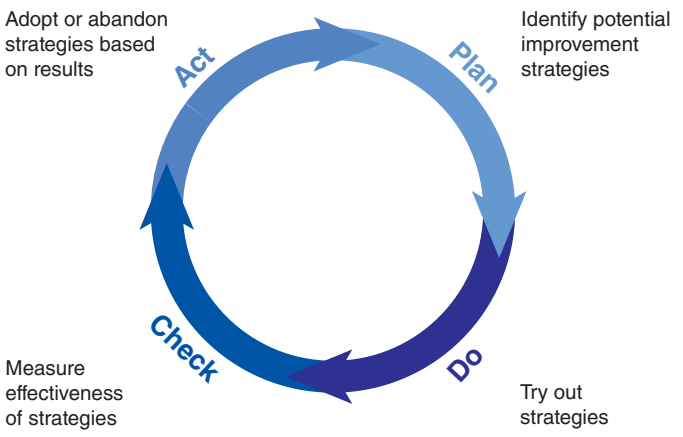

FIGURE 6-2 Plan-Do-Check-Act cycle. This approach can be used to improve a specific process rapidly. First, planning is undertaken, and several potential improvement strategies are identified. Next, these strategies are evaluated in small "tests of change." "Checking" entails measuring whether the strategies have appeared to make a difference, and "acting" refers to acting on the results.

Factors Relating to Quality Many factors can decrease the level of quality, including stress to providers, high or low levels of production pressure, and poor systems. Stress can have an adverse effect on quality because it can lead providers to omit important steps, as can a high level of production pressure. Low levels of production pressure sometimes can result in worse quality, as providers may be bored or have little experience with a specific problem. Poor systems can have a tremendous impact on quality, and even extremely dedicated providers typically cannot achieve high levels of performance if they are operating within a poor system.

Data about the Current State of Quality A study published by the RAND Corporation in 2006 provided the most complete picture of quality of care delivered in the United States to date. The results were sobering. The authors found that, across a wide range of quality parameters, patients in the United States received only 55% of recommended care overall; there was little variation by subtype, with scores of 54% for preventive care, 54% for acute care, and 56% for care of chronic conditions. The authors concluded that, in broad terms, the chances of getting high-quality care in the United States were little better than those of winning a coin flip.

Work from the Dartmouth Atlas of Health Care evaluating geographic variation in use and quality of care demonstrates that, despite large variations in utilization, there is no positive correlation between the two variables at the regional level. An array of data demonstrate, however, that providers with larger volumes for specific conditions, especially for surgical conditions, do have better outcomes.

Strategies for Improving Quality and Performance A number of specific strategies can be used to improve quality at the individual level, including rationing, education, feedback, incentives, and penalties. *Rationing* has been effective in some specific areas, such as persuading physicians to prescribe within a formulary, but it generally has been resisted. *Education* is effective in the short run and is necessary for changing opinions, but its effect decays fairly rapidly with time. *Feedback* on performance can be given at either the group or the individual level. Feedback is most effective if it is individualized and is given in close temporal proximity to the original events. *Incentives* can be effective, and many believe that they will prove to be a key to improving quality, especially if pay-for-performance with sufficient incentives is broadly implemented (see below). *Penalties* produce provider resentment and are rarely used in health care.

Another set of strategies for improving quality involves changing the systems of care. An example would be introducing reminders about which specific actions needed to be taken at a visit for a specific patient—a strategy that has been demonstrated to improve performance in certain situations, such as the delivery of preventive services. Another approach that has been effective is the development of "bundles" or groups of quality measures that can be implemented together with a high degree of fidelity. A number of hospitals have implemented a bundle for ventilator-associated pneumonia in the intensive care unit that includes five measures (e.g., ensuring that the head of the bed is elevated). These hospitals have been able to improve performance substantially.

Perhaps the most pressing need is to improve the quality of care for chronic diseases. The Chronic Care Model has been developed by Wagner and colleagues **(Fig. 6-3)**; it suggests that a combination of strategies is necessary (including self-management support, changes in delivery system design, decision support, and information systems) and that these strategies must be delivered by a practice team composed of several providers, not just a physician.

Available evidence about the relative efficacy of strategies in reducing hemoglobin A1c (HbA1c) in outpatient diabetes care supports this general premise. It is especially notable that the outcome was the HbA1c level, as it has generally been much more difficult to improve outcome measures than process measures (such as whether HbA1c was measured). In this meta-analysis, a variety of strategies were effective, but the most effective ones were the use of team changes and the use of a case manager. When cost-effectiveness is considered in addition, it appears likely that an amalgam of strategies will be needed. However, the more expensive strategies, such as the use of case managers, probably will be implemented widely only if pay-for-performance takes hold.

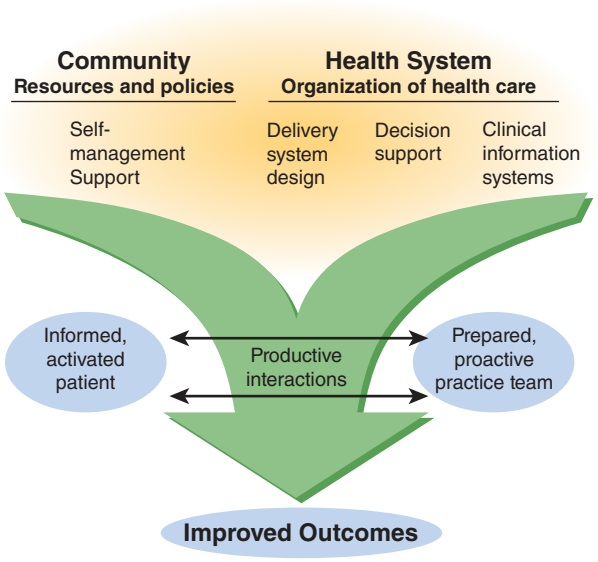

FIGURE 6-3 The Chronic Care Model, which focuses on improving care for chronic diseases, suggests that (1) delivery of high-quality care requires a range of strategies that must closely involve and engage the patient and (2) team care is essential. *(From EH Wagner et al: Eff Clin Pract 1:2, 1998.)*

National State of Quality Measurement In the inpatient setting, quality measurement is now being performed by a very large proportion of hospitals for several conditions, including myocardial infarction, congestive heart failure, pneumonia, and surgical infection prevention; 20 measures are included in all. This is the result of the Hospital Quality Initiative, which represents a collaboration among many entities, including the Hospital Quality Alliance, the Joint Commission, the National Quality Forum, and the Agency for Healthcare Research and Quality. The data are housed at the Center for Medicare and Medicaid Services, which publicly releases performance data on the measures on a website called *Hospital Compare* (*www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/HospitalCompare.html*). These data are reported voluntarily and are available for a very high proportion of the nation's hospitals. Analyses demonstrate substantial regional variation in quality and important differences among hospitals. Analyses by the Joint Commission for similar indicators reveal that performance on measures by hospitals has improved over time and that, as might be hoped, lower performers have improved more than higher performers.

Public Reporting Overall, public reporting of quality data is becoming increasingly common. There are now commercial websites that have quality-related data for most regions of the United States, and these data can be accessed for a fee. Similarly, national data for hospitals are available. The evidence to date indicates that patients have not made much use of such data, but that the data have had an important effect on provider and organization behavior. Instead, patients have relied on provider reputation to make choices, partly because little information was available until very recently and the information that was available was not necessarily presented in ways that were easy for patients to access. Many authorities think that, as more information about quality becomes available, it will become increasingly central to patients' choices about where to access care.

Pay-for-Performance Currently, providers in the United States get paid exactly the same amount for a specific service, regardless of the quality of care delivered. The pay-for-performance theory suggests that, if providers are paid more for higher-quality care, they will invest in strategies that enable them to deliver that care. The current key issues in the pay-for-performance debate relate to (1) how effective it is, (2) what levels of incentives are needed, and (3) what perverse

consequences are produced. The evidence on effectiveness is fairly limited, although a number of studies are ongoing. With respect to incentive levels, most quality-based performance incentives have accounted for merely 1–2% of total payment in the United States to date. In the United Kingdom, however, 40% of general practitioners' salaries have been placed at risk according to performance across a wide array of parameters; this approach has been associated with substantial improvements in reported quality performance, although it is still unclear to what extent this change represents better performance versus better reporting. The potential for perverse consequences exists with any incentive scheme. One problem is that, if incentives are tied to outcomes, there may be a tendency to transfer the sickest patients to other providers and systems. Another concern is that providers will pay too much attention to quality measures with incentives and ignore the rest of the quality picture. The validity of these concerns remains to be determined. Nonetheless, it appears likely that, under health care reform, the use of various pay-for-performance schemes is likely to increase.

CONCLUSIONS

The safety and quality of care in the United States could be improved substantially. A number of available interventions have been shown to improve the safety of care and should be used more widely; others are undergoing evaluation or soon will be. Quality also could be dramatically better, and the science of quality improvement continues to mature. Implementation of value-based approaches such as accountable care which include pay-for-performance related to safety and quality should make it much easier for organizations to justify investments in improving safety and quality parameters, including health information technology. However, many improvements will also require changing the structure of care—e.g., moving to a more team-oriented approach and ensuring that patients are more involved in their own care. Payment reform focusing on value seems very likely to progress and will likely include both positive incentives and penalties related to safety and quality performance. Measures of safety are still relatively immature and could be made much more robust; it would be particularly useful if organizations had measures they could use in routine operations to assess safety at a reasonable cost, and substantial research is addressing this. Although the quality measures available are more robust than those for safety, they still cover a relatively small proportion of the entire domain of quality, and more measures need to be developed. The public and payers are demanding better information about safety and quality as well as better performance in these areas. The clear implication is that these domains will have to be addressed directly by providers.

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7 Racial and Ethnic Disparities in Health Care

Joseph R. Betancourt, Alexander R. Green

Over the course of its history, the United States has experienced dramatic improvements in overall health and life expectancy, largely as a result of initiatives in public health, health promotion, disease prevention, and chronic care management. Our ability to prevent, detect, and treat diseases in their early stages has allowed us to target and reduce rates of morbidity and mortality. Despite interventions that have improved the overall health of the majority of Americans, racial and ethnic minorities (blacks, Hispanics/Latinos, Native Americans/Alaskan Natives, Asian/Pacific Islanders) have benefited less from these advances than whites and have suffered poorer health outcomes from many major diseases, including cardiovascular disease, cancer, and diabetes. These disparities highlight the importance of recognizing and addressing the *social determinants of health*, which contribute enormously to health outcomes. Research has revealed that minorities may receive less care and lower-quality care than whites, even when confounders such as stage of presentation, comorbidities, and health insurance are controlled. These differences in quality are called *racial and ethnic disparities in health care*. These health care disparities have taken on greater importance with the significant transformation of the U.S. health care system and value-based purchasing. The shift toward creating financial incentives and disincentives to achieve quality goals makes focusing on those who receive lower-quality care more important than ever before. This chapter will provide an overview of racial and ethnic disparities in health and health care, identify root causes, and provide key recommendations to address these disparities at both the clinical and health system levels.

NATURE AND EXTENT OF DISPARITIES

Minority Americans have poorer health outcomes than whites from preventable and treatable conditions such as cardiovascular disease, diabetes, asthma, cancer, and HIV/AIDS **(Fig. 7-1)**. Multiple factors contribute to these racial and ethnic disparities in health. First and foremost, social determinants—such as lower socioeconomic status (SES; e.g., lower income, less wealth, and lower educational attainment), inadequate and unsafe housing, and racism—are strongly linked to poor health outcomes. These factors disproportionately impact minority populations. In fact, SES has consistently been found to be one of the strongest predictors of health outcomes. While the mechanisms are complex (i.e., does poverty cause poor health, or does poor health cause poverty?), it is clear that low-SES populations experience disparities in health and that low SES is a major factor in racial/ethnic disparities.

Racial/ethnic disparities are documented globally, although their assessment has centered more on the comparison of individuals by SES in other countries than in the United States. Similar to the U.S. pattern, low-SES residents of other nations tend to have poorer health outcomes. It is noteworthy that results are mixed when the health status of nations is compared by SES. High-SES nations such as the United States do not necessarily have health outcomes that correlate with their high expenditures for health care. For example, as of 2016, the United States ranks 27th in the world—just behind Serbia—on basic public health measures such as infant mortality. This ranking may be due in

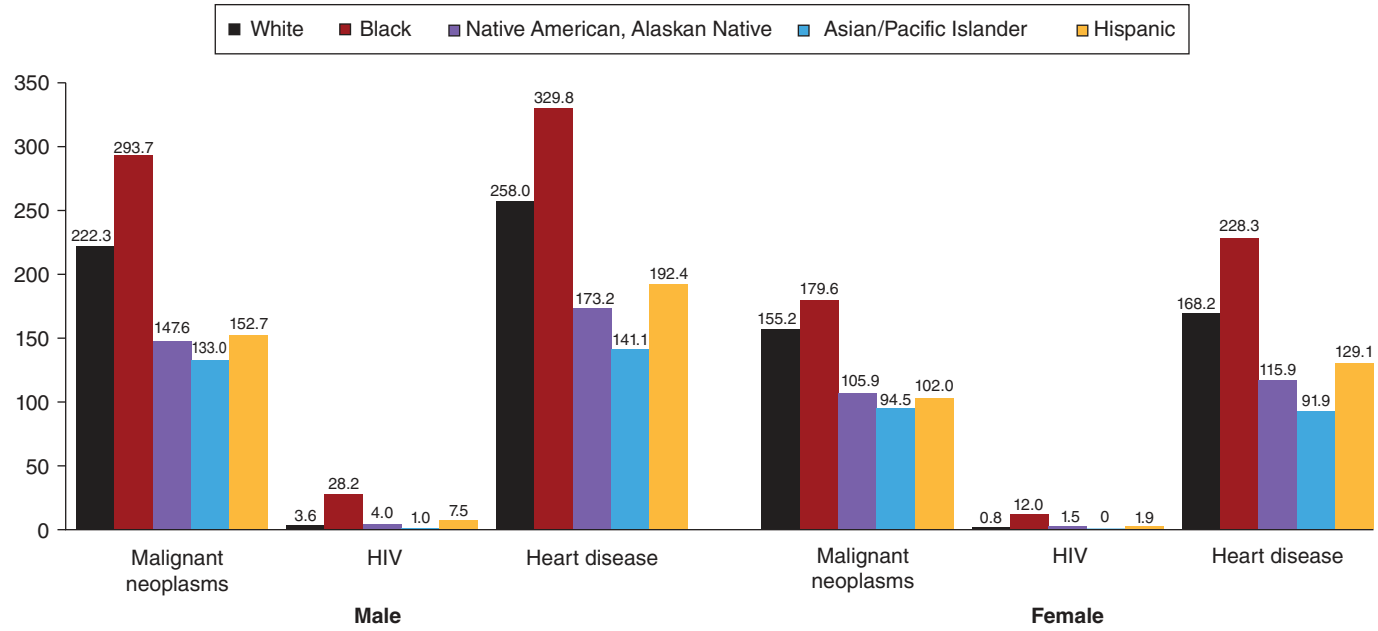


FIGURE 7-1 Age-adjusted death rates for selected causes by race and ethnic origin, 2005. *(From the U.S. Census Bureau, 2009.)*

part to the correlation between wealth distribution and SES rather than just absolute SES. This area of active research is outside the scope of this chapter.

Racism has more recently been shown to predict poorer health outcomes. The physiologic impact of the stress imposed by racism (and poverty), including increased cortisol levels, can lead to chronic adverse effects on health. Lack of access to care also takes a significant toll. Uninsured individuals are less likely to have a regular source of care and are more likely to delay seeking care and to go without needed care; this limited access results in avoidable hospitalizations, emergency hospital care, and adverse health outcomes.

In addition to racial and ethnic disparities in *health*, there are racial and ethnic disparities in the *quality of care* for persons with access to the health care system. For instance, disparities have been found in the treatment of pneumonia **(Fig. 7-2)** and congestive heart failure, with blacks receiving less optimal care than whites when hospitalized for these conditions. Moreover, blacks with end-stage renal disease are referred less often to the transplant list than are their white counterparts **(Fig. 7-3)**. Disparities have been found, for example, in the use of cardiac diagnostic and therapeutic procedures (with blacks being referred less often than whites for cardiac catheterization and bypass grafting), prescription of analgesia for pain control (with blacks and Latinos receiving less pain medication than whites for long-bone fractures and cancer), and surgical treatment of lung cancer (with blacks receiving less curative surgery than whites for non-small-cell lung cancer). Again, many of these disparities have occurred even when variations in factors such as insurance status, income, age, comorbid conditions, and symptom expression are taken into account. However, one additional factor—disparities in the quality of care provided at the sites where minorities tend to receive care—has been shown to be an important contributor to overall disparities.

Little progress has been made in addressing racial/ethnic disparities in cardiovascular procedures and other advanced surgical procedures, whereas some progress has been made in eliminating disparities in primary-care process measures. Data from the National Registry of Myocardial Infarction found evidence of continued disparities in guideline-based admission, procedural, and discharge therapy use from 1994 to 2006. Black patients were less likely than white patients

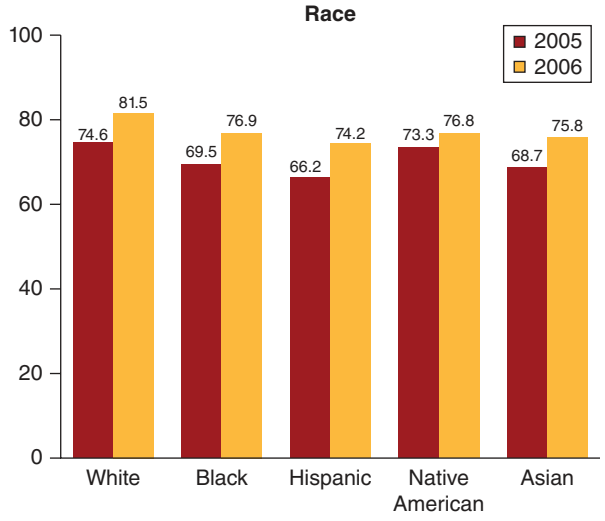


FIGURE 7-2 Recommended hospital care received by Medicare patients with pneumonia, by race/ethnicity, 2006. The reference population consisted of Medicare beneficiaries with pneumonia who were hospitalized. The composite was calculated by averaging the percentage of the population that received each of the five incorporated components of care. *(Adapted from Agency for Healthcare Research and Quality: The 2008 National Health Care Disparities Report.)*

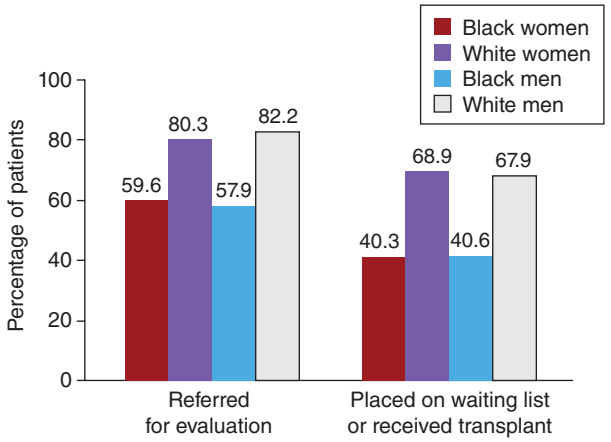


FIGURE 7-3 Referral for evaluation at a transplantation center or placement on a waiting list/receipt of a renal transplant within 18 months after the start of dialysis among patients who wanted a transplant, according to race and sex. The reference population consisted of 239 black women, 280 white women, 271 black men, and 271 white men. Racial differences were statistically significant among both the women and the men ($p<.0001$ for each comparison). *(From JZ Ayanian et al: N Engl J Med 341:1661, 1999.)*

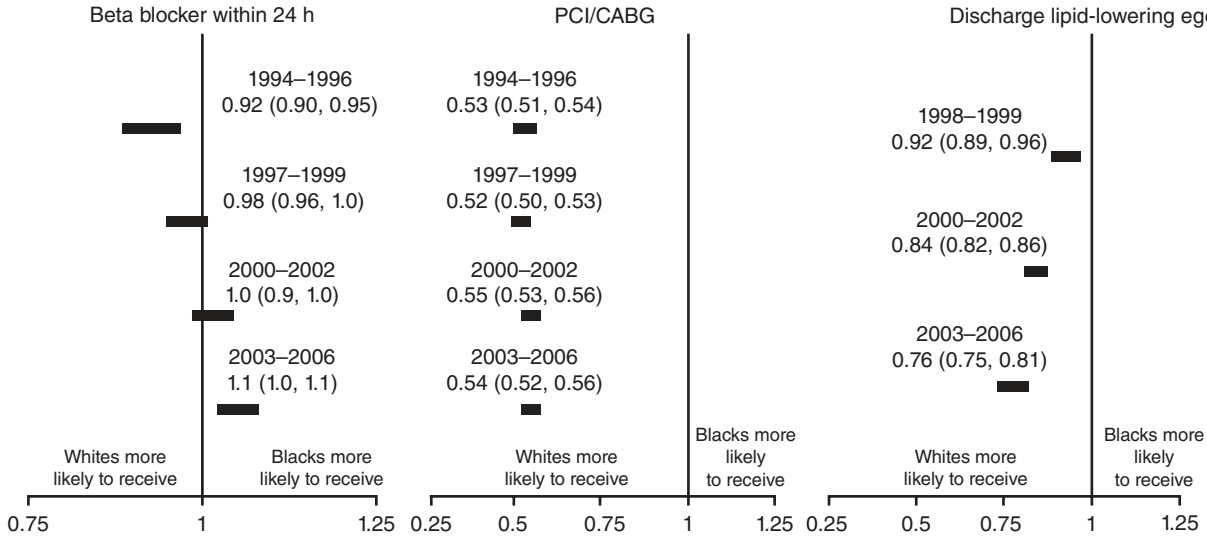


FIGURE 7-4 Racial differences in guideline-based treatments for acute myocardial infarction (AMI). The reference population consisted of 2,515,106 patients with AMI admitted to U.S. hospitals between July 1990 and December 2006. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention. *(From ED Peterson et al: Am Heart J 156:1045, 2008.)*

to receive percutaneous coronary intervention/coronary artery bypass grafting (PCI/CABG), a disparity that has improved little since 1994. Further, compared with whites, black patients were less likely to receive lipid-lowering medications at discharge, with a gap that has widened since 1998 **(Fig. 7-4)**. A 2009 study showed that blacks had worse post–myocardial infarction outcomes than whites, but that the difference could be explained by site of care and patient factors (such as socioeconomic status and comorbid conditions).

The Centers for Disease Control and Prevention (CDC) analyzed national and state rates of total knee replacement (TKR) for Medicare enrollees for the period 2000–2006, with patients stratified by sex, age, and black or white race. TKR rates overall in the United States increased 58%, with similar increases among whites (61%) and blacks (56%). However, the TKR rate for blacks was 37% lower than the rate for whites in 2000 and 39% lower in 2006; i.e., the disparity not only did not improve but even worsened slightly **(Fig. 7-5)**. More recent data (up to 2010) show no apparent change in these figures. Data for enrollees in Medicare managed-care plans provide evidence for a narrowing in racial disparities between 2006 and 2011 in several "report card" preventive care measures, such as mammography and glucose and cholesterol testing. However, racial disparities in more complex measures, such as glucose control in diabetic patients and cholesterol levels in patients after a heart attack, did not improve during that interval.

The 2015 National Healthcare Quality and Disparities Report, released by the Agency for Healthcare Research and Quality, found few improvements in disparities for a wide range of quality measures between 2001 and 2013. In fact, for minority groups and poor people, disparities in the vast majority of core quality measures either stayed the same or got worse, including measures of effectiveness, patient safety, and timeliness of care. For example, for black vs white individuals, disparities in quality worsened for 102 measures and persisted for 116 measures out of 248 total measures, and disparities were eliminated in no measured area. This annual report is particularly important, given that most studies of disparities have not been repeated with the same methodology used to document possible trends. Some studies have tracked disparities using specific disease and treatment registries. For example, by 2008, the use of acute and discharge medications for myocardial infarction had largely been equalized among racial and ethnic groups; however, African American and Hispanic patients still experienced longer delays before reperfusion, with door-to-balloon times of <90 min for 83% of white patients as opposed to 75 and 76% of black and Hispanic patients, respectively. A recent review of disparities for kidney transplant recipients over two decades showed similar mixed findings with trends for some measures improving while others worsened.

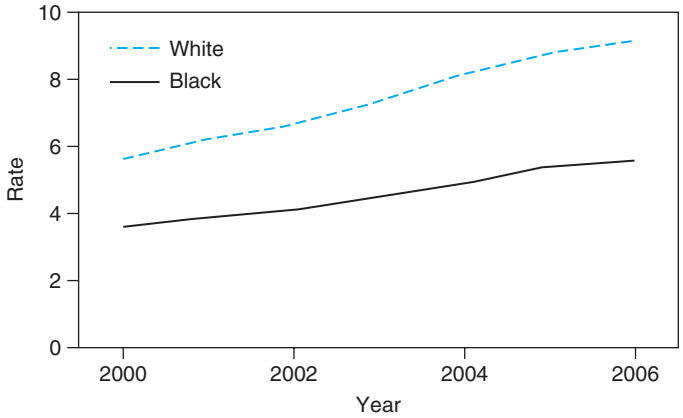


FIGURE 7-5 Racial trends in age-adjusted total knee replacement in Medicaid enrollees from 2000 to 2006. The reference population consisted of Medicaid part A enrollees ≥65 years of age who were not members of a managed-care plan. *(From the Centers for Disease Control and Prevention, 2009.)*

ROOT CAUSES OF DISPARITIES

The National Academy of Medicine (formerly, the Institute of Medicine, IOM) report *Unequal Treatment*, released in March 2002, remains the preeminent study of racial and ethnic disparities in health care in the United States. The IOM was charged with assessing the extent of racial/ethnic differences in health care that are not otherwise attributable to known factors, such as access to care. To provide recommendations regarding interventions aimed at eliminating health care disparities, the IOM studied health system, provider, and patient factors. The study found the following:

- Racial and ethnic disparities in health care exist and, because they are associated with worse health outcomes, are unacceptable.
- Racial and ethnic disparities in health care occur in the context of (1) broader historic and contemporary social and economic inequality and (2) evidence of persistent racial and ethnic discrimination in many sectors of American life.
- Many sources—including health systems, health care providers, patients, and utilization managers—may contribute to racial and ethnic disparities in health care.
- Bias, stereotyping, prejudice, and clinical uncertainty on the part of health care providers may contribute to racial and ethnic disparities in health care.
- A small number of studies suggest that minority patients may be more likely to refuse treatments, yet these refusal rates are generally small and do not fully explain health care disparities.

Unequal Treatment went on to identify a set of root causes that included the following:

- *Health system factors:* These include issues related to the complexity of the health care system, the difficulty that minority patients may have in navigating this complex system, and the lack of availability of interpreter services to assist patients with limited English proficiency. In addition, health care systems are generally ill prepared to identify and address disparities.
- *Provider-level factors:* These include issues related to the health care provider, including stereotyping, the impact of race/ethnicity on clinical decision-making, and clinical uncertainty due to poor communication.
- *Patient-level factors:* These include patients' mistrust of the health care system leading to refusal of services, poor adherence to treatment, and delay in seeking care.

A more detailed analysis of these root causes is presented below.

Health System Factors • **HEALTH SYSTEM COMPLEXITY** Even among persons who are insured and educated and who have a high degree of health literacy, navigating the U.S. health care system can be complicated and confusing. Some individuals may be at higher risk for receiving substandard care because of their difficulty navigating the system's complexities. These individuals may include those from cultures unfamiliar with the Western model of health care delivery, those with limited English proficiency, those with low health literacy, and those who are mistrustful of the health care system. These individuals may have difficulty knowing how and where to go for a referral to a specialist; how to prepare for a procedure such as a colonoscopy; or how to follow up on an abnormal test result such as a mammogram. Since people of color in the United States tend to be overrepresented among the groups listed above, the inherent complexity of navigating the health care system has been seen as a root cause for racial/ethnic disparities in health care.

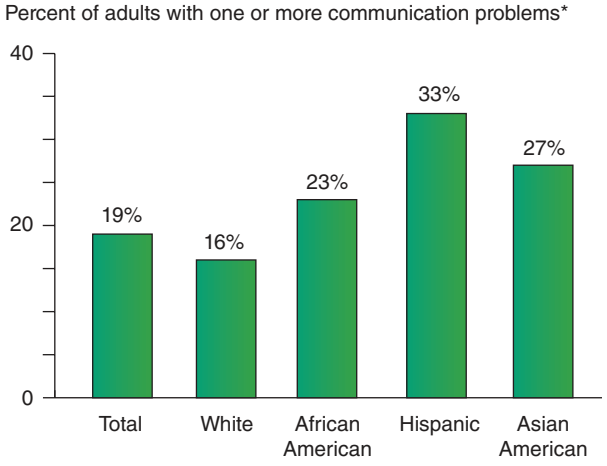
OTHER HEALTH SYSTEM FACTORS Racial/ethnic disparities are due not only to differences in care provided within hospitals but also to where and from whom minorities receive their care; i.e., certain specific providers, geographic regions, or hospitals are lower-performing on certain aspects of quality. For example, one study showed that 25% of hospitals cared for 90% of black Medicare patients in the United States and that these hospitals tended to have lower performance scores on certain quality measures than other hospitals. That said, health systems generally are not well prepared to measure, report, and intervene to reduce disparities in care. Few hospitals or health plans stratify their quality data by race/ethnicity or language to measure disparities, and even fewer use data of this type to develop disparity-targeted interventions. Similarly, despite regulations concerning the need for professional interpreters, research demonstrates that many health care organizations and providers fail to routinely provide this service for patients with limited English proficiency. Despite the link between limited English proficiency and health-care quality and safety, few providers or institutions monitor performance for patients in these areas.

Provider-Level Factors • **PROVIDER–PATIENT COMMUNICATION** Significant evidence highlights the impact of sociocultural factors, race, ethnicity, and limited English proficiency on health and clinical care. Health care professionals frequently care for diverse populations with varied perspectives, values, beliefs, and behaviors regarding health and well-being. The differences include variations in the recognition of symptoms, thresholds for seeking care, comprehension of management strategies, expectations of care (including preferences for or against diagnostic and therapeutic procedures), and adherence to preventive measures and medications. In addition, sociocultural differences between patient and provider influence communication and clinical decision-making and are especially pertinent: evidence clearly links provider–patient communication to improved patient satisfaction, regimen adherence, and better health outcomes (Fig. 7-6). Thus, when sociocultural differences between patient and provider are not appreciated, explored, understood, or communicated effectively during the medical encounter, patient dissatisfaction, poor adherence, poorer health outcomes, and racial/ethnic disparities in care may result.

FIGURE 7-6 The link between effective communication and patient satisfaction, adherence, and health outcomes. *(From the Institute of Medicine: Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. Washington, DC, National Academy Press, 2002.)*

A survey of 6722 Americans ≥18 years of age is particularly relevant to this important link between provider–patient communication and health outcomes. Whites, African Americans, Hispanics/Latinos, and Asian Americans who had made a medical visit in the past 2 years were asked whether they had trouble understanding their doctors; whether they felt the doctors did not listen; and whether they had medical questions they were afraid to ask. The survey found that 19% of all patients experienced one or more of these problems, yet whites experienced them 16% of the time as opposed to 23% of the time for African Americans, 33% for Hispanics/Latinos, and 27% for Asian Americans (Fig. 7-7).

In addition, in the setting of even a minimal language barrier, provider–patient communication without an interpreter is recognized as a major challenge to effective health care delivery. These communication barriers for patients with limited English proficiency lead to frequent misunderstanding of diagnosis, treatment, and follow-up plans; inappropriate use of medications; lack of informed consent for surgical procedures; high rates of adverse events with more serious clinical consequences; and a lower-quality health care experience than is provided to patients who speak fluent English. Physicians who have access to trained interpreters report a significantly higher quality of patient–physician communication than physicians who use other methods. Communication issues related to discordant language disproportionately affect minorities and likely contribute to racial/ethnic disparities in health care.



Base: Adults with health care visit in past two years
*Problems include understanding doctor, feeling doctor listened, had questions but did not ask.

FIGURE 7-7 Communication difficulties with physicians, by race/ethnicity. The reference population consisted of 6722 Americans ≥18 years of age who had made a medical visit in the previous 2 years and were asked whether they had had trouble understanding their doctors, whether they felt that the doctors had not listened, and whether they had had medical questions they were afraid to ask. *(From the Commonwealth Fund Health Care Quality Survey, 2001.)*

CLINICAL DECISION-MAKING Theory and research suggest that variations in clinical decision-making may contribute to racial and ethnic disparities in health care. Two factors are central to this process: clinical uncertainty and stereotyping.

First, a doctor's decision-making process is nested in *clinical uncertainty*. Doctors depend on inferences about severity based on what they understand about illness and the information obtained from the patient. A doctor caring for a patient whose symptoms he or she has difficulty understanding and whose "signals"—the set of clues and indications that physicians rely on to make clinical decisions—are hard to read may make a decision different from the one that would be made for another patient who presents with exactly the same clinical condition. Given that the expression of symptoms may differ among cultural and racial groups, doctors—the overwhelming majority of whom are white—may understand symptoms best when expressed by patients of their own racial/ethnic groups. The consequence is that white patients may be treated differently from minority patients. Differences in clinical decisions can arise from this mechanism even when the doctor has the same regard for each patient (i.e., is not prejudiced).

Second, the literature on social cognitive theory highlights how natural tendencies to stereotype may influence clinical decision-making. *Stereotyping* can be defined as the way in which people use social categories (e.g., race, gender, age) in acquiring, processing, and recalling information about others. Faced with enormous information loads and the need to make many decisions, people often subconsciously simplify the decision-making process and lessen cognitive effort by using "categories" or "stereotypes" that bundle information into groups or types that can be processed more quickly. Although functional, stereotyping can be systematically biased, as people are automatically classified into social categories based on dimensions such as *race*, *gender*, and *age*. Many people may not be aware of their attitudes, may not consciously endorse specific stereotypes, and paradoxically may consider themselves egalitarian and not prejudiced.

Stereotypes may be strongly influenced by the messages presented consciously and unconsciously in society. For instance, if the media and our social/professional contacts tend to present images of minorities as being less educated, more violent, and nonadherent to health care recommendations, these impressions may generate stereotypes that unnaturally and unjustly impact clinical decision-making. As signs of racism, classism, gender bias, and ageism are experienced (consciously or unconsciously) in our society, stereotypes may be created that impact the way doctors manage patients from these groups. On the basis of training or practice location, doctors may develop certain perceptions about race/ethnicity, culture, and class that may evolve into stereotypes. For example, many medical students and residents are trained—and minorities cared for—in academic health centers or public hospitals located in socioeconomically disadvantaged areas. As a result, doctors may begin to equate certain races and ethnicities with specific health beliefs and behaviors (e.g., "these patients" engage in risky behaviors, "those patients" tend to be noncompliant) that are more associated with the social environment (e.g., poverty) than with a patient's racial/ethnic background or cultural traditions. This "conditioning" phenomenon may also be operative if doctors are faced with certain racial/ethnic patient groups who frequently do not choose aggressive forms of diagnostic or therapeutic intervention. The result over time may be that doctors begin to believe that "these patients" do not like invasive procedures; thus they may not offer these procedures as options. A wide range of studies have documented the potential for provider biases to contribute to racial/ethnic disparities in health care. For example, one study measured physicians' unconscious (or implicit) biases and showed that these were related to differences in decisions to provide thrombolysis for a hypothetical black or white patient with a myocardial infarction.

It is important to differentiate stereotyping from prejudice and discrimination. *Prejudice* is a conscious prejudgment of individuals that may lead to disparate treatment, and *discrimination* is conscious and intentional disparate treatment. All individuals *stereotype* subconsciously, yet, if left unquestioned, these subconscious assumptions may lead to lower-quality care for certain groups because of differences in clinical decision-making or differences in communication and patient-centeredness. For example, one study tested physicians' unconscious racial/ethnic biases and showed that patients perceived more biased physicians as being less patient-centered in their communication. What is particularly salient is that stereotypes tend to be activated most in environments where the individual is stressed, multitasking, and under time pressure—the hallmarks of the clinical encounter. In fact, in a survey of close to 16,000 physicians, 42% admitted that bias—including by race and ethnicity—impacted their clinical decision-making. Interestingly, emergency medicine physicians, who worked in environments of stress, time pressure, risk, and where they are multitasking, topped the list by discipline at 62%.

Patient-Level Factors Lack of trust has become a major concern for many health care institutions today. For example, an IOM report, *To Err Is Human: Building a Safer Health System*, documented alarming rates of medical errors that made patients feel vulnerable and less trustful of the U.S. health care system. The increased media and academic attention to problems related to quality of care (and of disparities themselves) has clearly diminished trust in doctors and nurses.

Trust is a crucial element in the therapeutic alliance between patient and health care provider. It facilitates open communication and is directly correlated with adherence to the physician's recommendations and the patient's satisfaction. In other words, patients who mistrust their health care providers are less satisfied with the care they receive, and mistrust of the health care system greatly affects patients' use of services. Mistrust can also result in inconsistent care, "doctor-shopping," self-medication, and an increased demand by patients for referrals and diagnostic tests.

On the basis of historic factors such as discrimination, segregation, and medical experimentation, blacks may be especially mistrustful of providers. The exploitation of blacks by the U.S. Public Health Service during the Tuskegee syphilis study from 1932 to 1972 left a legacy of mistrust that persists even today among this population. Other populations, including Native Americans/Alaskan Natives, Hispanics/Latinos, and Asian Americans, also harbor significant mistrust of the health care system. A national survey conducted by the Kaiser Family Foundation found that there is significant mistrust for the health care system among minority populations. Of the 3884 individuals surveyed, 36% of Hispanics and 35% of blacks (compared to 15% of whites) felt they were treated unfairly in the health care system in the past based on their race and ethnicity. Perhaps even more alarming—65% of blacks and 58% of Hispanics (compared to 22% of whites) were afraid of being treated unfairly in the future based on their race/ethnicity **(Fig. 7-8)**.

This mistrust may contribute to wariness in accepting or following recommendations, undergoing invasive procedures, or participating in

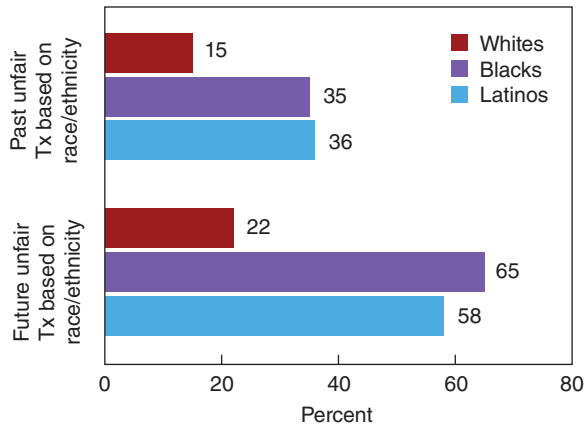


FIGURE 7-8 Patient perspectives regarding unfair treatment (Tx) based on race/ethnicity. The reference population consisted of 3884 individuals surveyed about how fairly they had been treated in the health care system in the past and how fairly they felt they would be treated in the future on the basis of their race/ethnicity. *(From Race, Ethnicity & Medical Care: A Survey of Public Perceptions and Experiences. Kaiser Family Foundation, 2005.)*

clinical research, and these choices, in turn, may lead to misunderstanding and the perpetuation of stereotypes among health professionals.

KEY RECOMMENDATIONS TO ADDRESS RACIAL/ETHNIC DISPARITIES IN HEALTH CARE

The publication *Unequal Treatment* provides a series of recommendations to address racial and ethnic disparities in health care, focusing on a broad set of stakeholders. These recommendations include *health system interventions*, *provider interventions*, *patient interventions*, and *general recommendations*, which are described in more detail below.

Health System Interventions • **COLLECTION AND REPORTING OF DATA ON HEALTH CARE ACCESS AND USE, BY PATIENTS' RACE/ETHNICITY** *Unequal Treatment* found that the appropriate systems to track and monitor racial and ethnic disparities in health care are lacking and that less is known about the disparities affecting minority groups other than African Americans (Hispanics, Asian Americans, Pacific Islanders, Native Americans, and Alaskan Natives). For instance, only in the mid-1980s did the Medicare database begin to collect data on patient groups outside the standard categories of "white," "black," and "other." Federal, private, and state-supported data-collection efforts are scattered and unsystematic, and many health care systems and hospitals still do not collect data on the race, ethnicity, or primary language of enrollees or patients. A survey by the Institute for Diversity in Health Management and the Health Research and Educational Trust in 2015 found that 98% of 1083 U.S. hospitals collected information on race, 95% collected data on ethnicity, and 94% collected data on primary language. However, only 45% collected data on race, 40% collected data on ethnicity, and 38% collected data on primary language to benchmark gaps in care. A survey by America's Health Insurance Plans Foundation in 2008 and 2010 showed that the proportion of enrollees in plans that collected race/ethnicity data of some type increased from 75 to 79%; however, the total percentage of plan enrollees whose race/ethnicity and language are recorded is still much lower than these figures.

ENCOURAGEMENT OF THE USE OF EVIDENCE-BASED GUIDELINES AND QUALITY IMPROVEMENT *Unequal Treatment* highlights the subjectivity of clinical decision-making as a potential cause of racial and ethnic disparities in health care by describing how clinicians—despite the existence of well-delineated practice guidelines—may offer (consciously or unconsciously) different diagnostic and therapeutic options to different patients on the basis of their race or ethnicity. Therefore, the widespread adoption and implementation of evidence-based guidelines is a key recommendation in eliminating disparities. For instance, evidence-based guidelines are now available for the management of diabetes, HIV/AIDS, cardiovascular diseases, cancer screening and management, and asthma—all areas where significant disparities exist. As part of ongoing quality-improvement efforts, particular attention should be paid to the implementation of evidence-based guidelines for all patients, regardless of their race and ethnicity.

SUPPORT FOR THE USE OF LANGUAGE INTERPRETATION SERVICES IN THE CLINICAL SETTING As described previously, a lack of efficient and effective interpreter services in a health care system can lead to patient dissatisfaction, to poor comprehension and adherence, and thus to ineffective/lower-quality care for patients with limited English proficiency. *Unequal Treatment*'s recommendation to support the use of interpretation services has clear implications for delivery of quality health care by improving doctors' ability to communicate effectively with these patients.

INCREASES IN THE PROPORTION OF UNDERREPRESENTED MINORITIES IN THE HEALTH CARE WORKFORCE Data for 2014 from the Association of American Medical Colleges indicate that, of the 72.4% of U.S. physicians whose race and ethnicity are known, Hispanics make up 4.1%, blacks 4.1%, and Native American and Alaskan Natives 0.4%. Furthermore, U.S. national data show that minorities (excluding Asians) compose just 7.1 % of full-time medical school faculty. In addition, minority faculty in 2007 were more likely to be at or below the rank of assistant professor, while whites composed the highest proportion of full professors. Similarly, a 2012 study found that both Hispanic and Black faculty were promoted at lower rates than their white counterparts. Despite representing ~26% of the U.S. population (a number projected to almost double by 2050), minority students are still underrepresented in medical schools. In 2016, matriculates to U.S. medical schools were 6.1% Latino, 6.6% African American, 0.1% Native Hawaiian or Other Pacific Islander, and 0.3% Native American or Alaskan Native. These percentages have decreased or remained the same since 2007. It will be difficult to develop a diverse health-care workforce that can meet the needs of an increasingly diverse population without dramatic changes in the racial and ethnic composition of medical student bodies.

Provider Interventions • **INTEGRATION OF CROSS-CULTURAL EDUCATION INTO THE TRAINING OF ALL HEALTH CARE PROFESSIONALS** The goal of cross-cultural education is to improve providers' ability to understand, communicate with, and care for patients from diverse backgrounds. Such education focuses on enhancing awareness of sociocultural influences on health beliefs and behaviors and on building skills to facilitate understanding and management of these factors in the medical encounter. Cross-cultural education includes curricula on health care disparities, use of interpreters, and effective communication and negotiation across cultures. These curricula can be incorporated into health-professions training in medical schools, residency programs, nursing schools, and other health professions programs, and can be offered as a component of continuing education. Despite the importance of this area of education and the attention it has attracted from medical education accreditation bodies, a national survey of senior resident physicians by Weissman and colleagues found that up to 28% felt unprepared to deal with cross-cultural issues, including caring for patients who have religious beliefs that may affect treatment, patients who use complementary medicine, patients who have health beliefs at odds with Western medicine, patients who mistrust the health care system, and new immigrants. In a study at one medical school, 70% of fourth-year students felt inadequately prepared to care for patients with limited English proficiency. Efforts to incorporate cross-cultural education into medical education will contribute to improving communication and to providing a better quality of care for all patients.

INCORPORATION OF TEACHING ON THE IMPACT OF RACE, ETHNICITY, AND CULTURE ON CLINICAL DECISION-MAKING *Unequal Treatment* and more recent studies found that stereotyping by health care providers can lead to disparate treatment based on a patient's race or ethnicity. The Liaison Committee on Medical Education, which accredits medical schools, issued a directive that medical education should include instruction on how a patient's race, ethnicity, and culture might unconsciously impact communication and clinical decision-making.

Patient Interventions Difficulty navigating the health care system and obtaining access to care can be a hindrance to all populations, particularly to minorities. Similarly, lack of empowerment or involvement in the medical encounter by minorities can be a barrier to care. Patients need to be educated on how to navigate the health care system and how best to access care. Interventions should be used to increase patients' participation in treatment decisions.

General Recommendations • **INCREASE AWARENESS OF RACIAL/ETHNIC DISPARITIES IN HEALTH CARE** Efforts to raise awareness of racial/ethnic health care disparities have done little for the general public but have been fairly successful among physicians, according to a Kaiser Family Foundation report. In 2006, nearly 6 in 10 people surveyed believed that blacks received the same quality of care as whites, and 5 in 10 believed that Latinos received the same quality of care as whites. These estimates are similar to findings in a 1999 survey. Despite this lack of awareness, most people believed that all Americans deserve quality care, regardless of their background. In contrast, the level of awareness among physicians has risen sharply. In 2002, the majority (69%) of physicians said that the health care system "rarely or never" treated people unfairly on the basis of their racial/ethnic background. In 2005, less than one-quarter (24%) of physicians disagreed with the statement that "minority patients generally receive lower-quality care than white patients." More recently, a survey by WedMD showed that 42% of 16,000 physicians admitted that their own personal biases

impact their clinical decision-making, including on characteristics such as race and ethnicity. Increasing awareness of racial and ethnic health disparities, and their root causes, among health care professionals and the public is an important first step in addressing these disparities. The ultimate goals are to generate discourse and to mobilize action to address disparities at multiple levels, including health policy makers, health systems, and the community.

CONDUCT FURTHER RESEARCH TO IDENTIFY SOURCES OF DISPARITIES AND PROMISING INTERVENTIONS While the literature that formed the basis for the findings reported and recommendations made in *Unequal Treatment* provided significant evidence for racial and ethnic disparities, additional research is needed in several areas. First, most of the literature on disparities focuses on black-versus-white differences; much less is known about the experiences of other minority groups. Improving the ability to collect racial and ethnic patient data should facilitate this process. However, in instances where the necessary systems are not yet in place, racial and ethnic patient data may be collected prospectively in the setting of clinical or health services research to more fully elucidate disparities for other populations. Second, much of the literature on disparities to date has focused on defining areas in which these disparities exist, but less has been done to identify the multiple factors that contribute to the disparities or to test interventions to address these factors. There is clearly a need for research that identifies promising practices and solutions to disparities.

IMPLICATIONS FOR CLINICAL PRACTICE

Individual health care providers can do several things in the clinical encounter to address racial and ethnic disparities in health care.

Be Aware that Disparities Exist Increasing awareness of racial and ethnic disparities among health care professionals is an important first step in addressing disparities in health care. Only with greater awareness can care providers be attuned to their behavior in clinical practice and thus monitor that behavior and ensure that all patients receive the highest quality of care, regardless of race, ethnicity, or culture.

Practice Culturally Competent Care Previous efforts have been made to teach clinicians about the attitudes, values, beliefs, and behaviors of certain cultural groups—the key practice "dos and don'ts" in caring for "the Hispanic patient" or the "Asian patient," for example. In certain situations, learning about a particular local community or cultural group, with a goal of following the principles of community-oriented primary care, can be helpful; when broadly and uncritically applied, however, this approach can actually lead to stereotyping and oversimplification of culture, without respect for its complexity.

Cultural competence has thus evolved from merely learning information and making assumptions about patients on the basis of their backgrounds to focusing on the development of skills that follow the principles of patient-centered care. *Patient-centeredness* encompasses the qualities of compassion, empathy, and responsiveness to the needs, values, and expressed preferences of the individual patient. *Cultural competence* aims to take things a step further by expanding the repertoire of knowledge and skills classically defined as "patient-centered" to include those that are especially useful in cross-cultural interactions (and that, in fact, are vital in all clinical encounters). This repertoire includes effectively using interpreter services, eliciting the patient's understanding of his or her condition, assessing decision-making preferences and the role of family, determining the patient's views about biomedicine versus complementary and alternative medicine, recognizing sexual and gender issues, and building trust. For example, while it is important to understand all patients' beliefs about health, it may be particularly crucial to understand the health beliefs of patients who come from a different culture or have a different health care experience. With the individual patient as teacher, the physician can adjust his or her practice style to meet the patient's specific needs.

Avoid Stereotyping Several strategies can allow health care providers to counteract, both systemically and individually, the normal tendency to stereotype. For example, when racially/ethnically/culturally/socially diverse teams in which each member is given equal power are assembled and are tasked to achieve a common goal, a sense of camaraderie develops and prevents the development of stereotypes based on race/ethnicity, gender, culture, or class. Thus, health care providers should aim to gain experiences working with and learning from a diverse set of colleagues. In addition, simply being aware of the operation of social cognitive factors allows providers to actively check up on or monitor their behavior. Physicians can constantly reevaluate to ensure that they are offering the same things, in the same ways, to all patients. Understanding one's own susceptibility to stereotyping—and how disparities may result—is essential in providing equitable, high-quality care to all patients.

Work to Build Trust Patients' mistrust of the health care system and of health care providers impacts multiple facets of the medical encounter, with effects ranging from decreased patient satisfaction to delayed care. Although the historic legacy of discrimination can never be erased, several steps can be taken to build trust with patients and to address disparities. First, providers must be aware that mistrust exists and is more prevalent among minority populations, given the history of discrimination in the United States and other countries. Second, providers must reassure patients that they come first, that everything possible will be done to ensure that they always get the best care available, and that their caregivers will serve as their advocates. Third, interpersonal skills and communication techniques that demonstrate honesty, openness, compassion, and respect on the part of the health care provider are essential tools in dismantling mistrust. Finally, patients indicate that trust is built when there is shared, participatory decision-making and the provider makes a concerted effort to understand the patient's background. When the doctor–patient relationship is reframed as one of solidarity, the patient's sense of vulnerability can be transformed into one of trust. The successful elimination of disparities requires trust-building interventions and strengthening of this relationship.

CONCLUSION

The issue of racial and ethnic disparities in health care has gained national prominence, both with the release of the IOM report *Unequal Treatment* and with more recent articles that have confirmed their persistence and explored their root causes. Furthermore, another influential IOM report, *Crossing the Quality Chasm*, has highlighted the importance of equity—i.e., no variations in quality of care due to personal characteristics, including race and ethnicity—as a central principle of quality. Current efforts in health care reform and transformation, including a greater focus on value (high-quality care and cost-control), will sharpen the nation's focus on the care of populations who experience low-quality, costly care. Addressing disparities will become a major focus, and there will be many obvious opportunities for interventions to eliminate them. Greater attention to addressing the root causes of disparities will improve the care provided to all patients, not just those who belong to racial and ethnic minorities.

Acknowledgments

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8 Ethical Issues in Clinical Medicine

Bernard Lo, Christine Grady

Twenty-first-century physicians face novel ethical dilemmas that can be perplexing and emotionally draining. For example, electronic medical records, handheld personal devices, and provision of care by interdisciplinary teams all hold the promise of more coordinated and comprehensive care, but also raise new concerns about confidentiality, appropriate boundaries of the doctor–patient relationship, and responsibility. **Chapter 1** puts the practice of medicine into a professional and historical context. The current chapter presents approaches and principles that physicians can use to address the ethical issues they encounter in their work. Physicians make ethical judgments about clinical situations every day. Traditional professional codes and ethical principles provide instructive guidance for physicians but need to be interpreted and applied to each situation. Physicians need to be prepared for lifelong learning about ethical issues and dilemmas as well as about new scientific and clinical developments. When struggling with difficult ethical issues, physicians may need to reevaluate their basic convictions, tolerate uncertainty, and maintain their integrity while respecting the opinions of others. Discussing perplexing ethical issues with other members of the health care team, ethics consultation services, or the hospital ethics committee can clarify issues and reveal strategies for resolution, including improving communication and dealing with strong or conflicting emotions.

APPROACHES TO ETHICAL PROBLEMS

Several approaches may be useful for resolving ethical issues. Among these approaches are those based on ethical principles, virtue ethics, professional oaths, and personal values. These various sources of guidance encompass precepts that may conflict in a particular case, leaving the physician in a quandary. In a diverse society, different individuals may turn to different sources of moral guidance. In addition, general moral precepts often need to be interpreted and applied in the context of a particular clinical situation. When facing an ethical challenge, physicians should articulate their concerns and reasoning, discuss and listen to the views of others involved in the case, and call on available resources as needed. Through these efforts, physicians can gain deeper insight into the ethical issues they face and often can reach mutually acceptable resolutions to complex problems.

ETHICAL PRINCIPLES

Ethical principles can serve as general guidelines to help physicians determine the right thing to do.

Respecting Patients Physicians should always treat patients with respect, which entails understanding patients' goals, communicating effectively, obtaining informed and voluntary consent, respecting informed refusals, and protecting confidentiality. Different clinical goals and approaches are often feasible, and interventions result in both benefit and harm. Individuals differ in how they value health and medical care and how they weigh the benefits and risks of medical interventions. Generally, the values and informed choices of patients should be respected.

GOALS AND TREATMENT DECISIONS Physicians should discuss the goals of care with patients, as well as relevant and accurate information about diagnosis, current clinical circumstances, likely trajectory and prognosis, and treatment options. Physicians may be tempted to withhold a serious diagnosis, misrepresent it by using ambiguous terms, or limit discussions of prognosis or risks for fear that patients will become anxious or depressed. Providing honest information about clinical situations preserves patients' autonomy and trust and promotes sound communication with patients and colleagues. To help patients cope with bad news, doctors can adjust the pace of disclosure, offer empathy and hope, provide emotional support, and call on other resources such as spiritual care or social work. However, patients may choose not to receive such information or ask surrogates to make decisions on their behalf, as is common with serious diagnoses in some traditional cultures.

OBTAINING INFORMED CONSENT Physicians should discuss with patients the nature of proposed care, alternatives, and the risks, benefits, and likely consequences of each option. Informed consent involves more than obtaining signatures on consent forms. Physicians should promote shared decision-making by educating patients, answering their questions, checking that they understand key issues, making recommendations, and helping them to deliberate. Patients can be overwhelmed by medical jargon, needlessly complicated explanations, or the provision of too much information at once. Patients can make informed decisions only if they receive honest and understandable information. Competent, informed patients may refuse recommended interventions and choose among reasonable alternatives. If patients cannot give consent in an emergency and if delay of treatment while surrogates are contacted will place their lives or health in peril, treatment can be given without informed consent. People are presumed to want such emergency care unless they have previously indicated otherwise.

Respect for patients does not entitle patients to insist on any care they want. Physicians are not obligated to provide interventions that have no physiologic rationale, that have already failed, or that are contrary to evidence-based practice recommendations or good clinical judgment. Public policies and laws also dictate certain decisions—e.g., allocation of cadaveric organs for transplantation and physician aid-in-dying.

CARING FOR PATIENTS WHO LACK DECISION-MAKING CAPACITY Many patients are not able to make informed decisions because of unconsciousness, dementia, delirium, or other medical conditions. Although only courts have the legal authority to determine that a patient is legally incompetent, in practice, physicians determine when patients lack the capacity to make particular health care decisions and arrange for authorized surrogates to make decisions for them, without involving the courts. Patients with decision-making capacity can express a choice and appreciate their medical situation, the nature of proposed care, alternatives, and the risks, benefits, and consequences of each alternative. Patient choices should be consistent with their values and not the result of delusions or hallucinations. Physicians should use available assessment tools, other resources such as psychiatry consultation, and clinical judgment to ascertain whether individuals have the capacity to consent and make decisions for themselves. It should not be automatically assumed that a patient who disagrees with a recommendation or refuses treatment lacks capacity, but such decisions should be probed to be sure the patient has the capacity for an informed decision and that there are no misunderstandings. When impairments are fluctuating or reversible, decisions should be postponed if possible until the patient recovers decision-making capacity.

If a patient lacks decision-making capacity, physicians should seek the appropriate surrogate, and ask what the patient would have wanted done. Patients may designate a health care proxy or a durable power of attorney for health care in advance; such choices should be respected. (See **Chap. 9** for further details about advance care planning.) If a patient without decision-making capacity has not previously

designated a health care proxy, physicians usually ask family members to serve as surrogates. Many patients want family members as surrogates, and family members generally have the patient's best interests at heart. Statutes in most U.S. states delineate a prioritized list of relatives who may serve as surrogates if the patient has not designated a proxy. Surrogates' decisions should be guided by the patient's values, goals, and previously expressed preferences. However, it may be appropriate to override previous preferences in favor of the patient's current best interests if an intervention is likely to provide a significant benefit, if previous statements do not fit the situation well, or if the patient indicated that the surrogate should have leeway in decisions.

MAINTAINING CONFIDENTIALITY Maintaining confidentiality is essential in respecting patients' autonomy and privacy; it encourages them to seek treatment and to discuss problems candidly, and helps to prevent discrimination. However, confidentiality may be overridden to prevent serious harm to third parties or to the patient. Exceptions to confidentiality are justified if the risk is serious and probable, there are no less restrictive measures by which to avert risk, and the adverse effects of overriding confidentiality are minimized and deemed acceptable by society. For example, laws require physicians to report cases of tuberculosis, sexually transmitted infection, elder or child abuse, and domestic violence.

Beneficence or Acting in Patients' Best Interests The principle of *beneficence* requires physicians to act for the patient's benefit. Patients typically lack medical expertise, and illness may make them vulnerable. They rely on and trust physicians to treat them with compassion, provide sound recommendations and promote their well-being. Physicians encourage such trust and have a fiduciary duty to act in the best interests of the patient, which should prevail over physicians' self-interest or the interests of third parties such as hospitals or insurers. Physicians' fiduciary obligations contrast sharply with business relationships, which are characterized by "buyer beware," and not by reliance and trust. A related principle, "first do no harm," obliges physicians to prevent unnecessary harm by recommending interventions that maximize benefit and minimize harm, and forbids physicians from providing known ineffective interventions or acting without due care. Although often cited, this precept alone provides limited guidance because many beneficial interventions pose serious risks.

Physicians increasingly provide care with a multidisciplinary team. Team members contribute different types of expertise to the provision of comprehensive, high-quality care for patients. Physicians should collaborate with and respect the contributions of the various members of the multidisciplinary team. Physicians should also initiate and participate in regular communication and planning to avoid diffusion of responsibility and ensure accountability for quality patient care.

INFLUENCES ON PATIENTS' BEST INTERESTS Conflicts can arise when patients' refusal or request of interventions thwarts their own goals for care, causes serious harm, or conflicts with their best medical interests. For example, simply accepting refusal of mechanical ventilation for reversible respiratory failure by a young adult with asthma, in the name of respecting autonomy, is morally constricted. Physicians should elicit patients' expectations and concerns, correct their misunderstandings, and try to persuade them to accept beneficial therapies. If disagreements persist after such efforts, patients' informed choices and views of their own best interests should prevail.

Physicians should appreciate that patients, who face increasing co-payments and out-of-pocket expenses, may not be able to afford tests and interventions that are ordered. Physicians should follow up with patients who don't fill prescriptions or skip doses, discuss alternative drugs, and when possible, prescribe medications that are affordable to the patient.

Organizational policies may sometimes conflict with patients' best interests. For example, limitations on work-hours could lead to a shift-worker mentality that undermines physician's dedication to patient's well-being and sense of responsibility for decisions. Forced handoffs might actually tend to increase the risk of errors unless other measures are taken. Patients' best interests may be served by flexibility in work-hour limits in some cases, especially if there is rapport with the patient or family that is not easily transferred to another provider. For example, a resident may want to discuss decisions about life-sustaining interventions or comfort a family member over a patient's death (Chap. 9). Physicians, residents, and medical students should take responsibility for helping to design and improve work-hour schedules based on empirical evidence.

Patients' interests are also served by improvements in overall quality of care resulting from the increasing use of evidence-based practice guidelines and performance benchmarking. However, practice guideline recommendations may not serve the interests of each individual patient, especially when another plan of care may provide substantially greater benefits. In such situations, physicians should prioritize their duty to act in the patient's best interests. Physicians should be familiar with relevant practice guidelines, be able to recognize situations in which exceptions might be reasonable, and be prepared to justify an exception.

Acting Justly The principle of *justice* provides guidance to physicians about how to ethically treat patients and make decisions about allocating important resources, including their own time. *Justice* in a general sense means fairness: people should receive what they deserve. In addition, it is important to act consistently in cases that are similar in ethically relevant ways, in order to avoid arbitrary, biased, and unfair decisions. Justice forbids discrimination in health care based on race, religion, gender, sexual orientation, or other personal characteristics (Chap. 7).

ALLOCATION OF RESOURCES Justice also requires that limited health care resources be allocated fairly. Universal access to medically needed health care remains an unrealized moral aspiration in the United States and much of the rest of the world. Patients without health insurance often cannot afford health care and lack access to safety-net services. Even among insured patients, insurers may deny coverage for interventions recommended by the physician. In this situation, physicians should advocate for patients and try to help them obtain needed care. Doctors might consider—or patients might request—the use of lies or deception to obtain such benefits. For example, a physician might sign a disability form for a patient who does not meet disability criteria. Although motivated by a desire to help the patient, such deception breaches a basic ethical guideline and undermines physicians' credibility and trustworthiness.

Allocation of health care resources is unavoidable because resources are limited. Many allocation decisions are made at the level of public policy, with physician input. For example, the United Network for Organ Sharing (*www.unos.org*) provides criteria for allocating scarce organs. *Ad hoc* resource allocation by the physician at the bedside is problematic because it may be inconsistent, unfair, and ineffective. Physicians do have an important role, however, in avoiding unnecessary interventions. Evidence-based lists of tests and procedures that physicians and patients should question and discuss are available through *Choosing Wisely* (*http://www.choosingwisely.org/*). At the bedside, physicians should act as patient advocates within constraints set by society, reasonable insurance coverage, and evidence-based practice. For example, if a patient's insurer has a higher copayment for nonformulary drugs, it still may be reasonable for physicians to advocate for nonformulary products for good reasons (e.g., when the formulary drugs are less effective or not tolerated).

VIRTUE ETHICS

Virtue ethics focuses on physicians' character and qualities, with the expectation that doctors will cultivate such virtues as compassion, trustworthiness, intellectual honesty, humility, and integrity. Proponents argue that, if such characteristics become ingrained, they help guide physicians in unforeseen situations. Moreover, following ethical precepts or principles without any of these virtues could lead to uncaring doctor–patient relationships.

PROFESSIONAL OATHS AND CODES

Professional oaths and codes are useful guides for physicians. Most physicians take oaths at medical school white-coat ceremonies and

graduations, and many are members of professional societies that have professional codes. Physicians pledge to the public and to their patients that they will be guided by the principles and values in these oaths or codes. Oaths and codes—including the Hippocratic tradition—focus on ethical ideals rather than on daily pragmatic concerns, and have been criticized for lack of patient or public input and the limited role given to patients in making decisions.

PERSONAL VALUES

Personal values, cultural traditions, and religious beliefs are important sources of personal morality that help physicians address ethical issues and cope with the moral distress they may experience in practice. While essential, personal morality alone is a limited ethical guide in clinical practice. Physicians have role-specific ethical obligations that go beyond their obligations as good people, including the duties to obtain informed consent and maintain confidentiality discussed earlier. Furthermore, in a culturally and religiously diverse world, it is not uncommon for patients and colleagues to have personal moral beliefs that differ from those of their physicians.

ETHICALLY COMPLEX PROFESSIONAL ISSUES FOR PHYSICIANS

CLAIMS OF CONSCIENCE

Some physicians have conscientious objections to providing, or referring patients for, certain treatments such as contraception. Although physicians should not be asked to violate deeply held moral beliefs or religious convictions, patients need medically appropriate, timely care. Institutions such as clinics and hospitals have a collective duty to provide care that patients need while making reasonable attempts to accommodate health care workers' conscientious objections—for example, when possible by arranging for another professional to provide the service in question. Patients seeking a relationship with a doctor or health care institution should be notified in advance of any conscientious objections to the provision of specific interventions. Since patients commonly must select providers for insurance purposes, switching providers for a specific service can be burdensome. There are also important limits on claims of conscience. Health care workers may not insist that patients receive unwanted medical interventions and may not refuse to treat patients because of their race, ethnicity, national origin, gender, or religion. Such discrimination is illegal and violates the physician's duty to respect patients. While legally more controversial, refusal to treat patients because of their sexual orientation or gender identity is ethically inappropriate because it falls short of helping patients in need and respecting them as persons.

OCCUPATIONAL RISKS

Some health care workers, fearing fatal occupational infections, have refused to care for certain patients, such as those with HIV infection, Ebola virus disease, or severe acute respiratory syndrome (SARS). Such fears about personal safety need to be acknowledged. Health care institutions should reduce occupational risk by providing proper training, protective equipment, and supervision. To fulfill their mission of helping patients, physicians should provide appropriate care within their clinical expertise, despite sometimes considerable personal risk.

MORAL DISTRESS

Health care providers, including residents and medical students, may experience moral distress when they feel that the ethically appropriate action to take in a particular situation is hindered by institutional policies, limited resources, decision-making hierarchies, or other reasons. Moral distress can lead to anger, anxiety, frustration, fatigue, and work dissatisfaction. Discussing complex or unfamiliar clinical situations with colleagues and seeking assistance with difficult decisions helps to alleviate moral distress, as does a healthy work environment characterized by open communication and mutual respect. In addition, physicians should take good care of their own well-being, and be aware of the personal and system factors associated with stress, burnout, and depression. A physician's health can affect how he or she cares for patients.

CONFLICTS OF INTEREST

Acting in patients' best interests may sometimes conflict with the physician's self-interest or the interests of third parties such as insurers or hospitals. From an ethical viewpoint, patients' interests are paramount. Even the appearance of a conflict of interest may undermine trust in the profession.

FINANCIAL INCENTIVES

Health care providers may be offered financial incentives to improve the quality or efficiency of care. Such pay-for-performance incentives, however, could lead physicians to avoid sicker patients with more complicated cases or to focus on benchmarked outcomes even when such a focus is not in the best interests of an individual patient. In contrast, fee-for-service payments might encourage physicians to order more interventions than may be necessary or to refer patients to laboratory or imaging facilities in which they have a financial stake. Regardless of financial incentives, physicians should recommend available care that is in the patient's best interests—no more and no less.

RELATIONSHIPS WITH PHARMACEUTICAL COMPANIES

Financial relationships between physicians and industry are increasingly scrutinized. Gifts from drug and device companies may create an inappropriate risk of undue influence, induce subconscious feelings of reciprocity, impair public trust, and increase the cost of health care. Many academic medical centers have banned drug-company gifts of branded pens and notepads and meals to physicians. The federal Open Payments website provides public information on the payments and amounts that drug and device companies give to individual physicians by name. The challenge is to distinguish payments for scientific consulting and research contracts—which are consistent with professional and academic missions and should be encouraged—from those for promotional speaking and consulting whose goal is to increase sales of company products.

LEARNING CLINICAL SKILLS

Not all conflicts of interest are financial. Medical students, residents, and physicians' interests in learning, which fosters the long-term goal of benefiting future patients, may conflict with the short-term goal of providing optimal care to current patients. When trainees are learning procedures on patients, they lack the proficiency of experienced physicians, and patients may experience inconvenience, discomfort, longer procedures, or increased risk. Seeking patients' consent for trainee participation in their care is always important, and particularly important for intimate examinations, such as pelvic, rectal, breast, and testicular examinations, and for invasive procedures. Patients should be told who is providing care and how trainees are supervised. Failing to introduce students or not telling patients that trainees will be performing procedures undermines trust, may lead to more elaborate deception, and makes it difficult for patients to make informed choices about their care. Most patients, when informed, allow trainees to play an active role in their care.

RESPONSE TO MEDICAL ERRORS

Errors are inevitable in clinical medicine, and some errors cause serious adverse events that harm patients. Most errors are caused by lapses of attention or flaws in the system of delivering health care; only a small number result from blameworthy individual behavior **(Chaps. 3 and 6)**. Physicians and students may fear that disclosing errors will damage their careers. However, patients are owed an explanation, and appreciate being told when an error occurs, receiving an apology, and being informed about efforts to prevent similar errors in the future. Physicians and health care institutions show respect for patients by disclosing errors, offering appropriate compensation for harm done, and using errors as opportunities to improve the quality of care. Overall, patient safety is more likely to be improved through a quality improvement rather than a punitive approach to errors, except in cases of gross incompetence, physician impairment, boundary violations, or repeated violations of standard procedures.

PHYSICIAN IMPAIRMENT

Physicians may hesitate to intervene when colleagues impaired by alcohol abuse, drug abuse, or psychiatric or medical illness place patients at risk. However, society relies on physicians to regulate themselves. If colleagues of an impaired physician do not take steps to protect patients, no one else may be in a position to do so.

USE OF SOCIAL MEDIA

Increasingly, physicians use social and electronic media to share information with patients and other providers. Social networking may be especially useful in reaching young or otherwise hard-to-access patients. However, the use of social media, including blogs, social networks, and websites, raises ethical challenges and should be approached prudently to avoid harmful consequences for patients. Injudicious use of social media can pose risks to patient confidentiality, cross professional boundaries, and jeopardize therapeutic relationships. Internet and social networking postings are usually permanent and may be accessible to the public, physicians' employers, and their patients. Unprofessional posts can lead to adverse consequences for a provider's reputation, safety, or even employment, especially if they express frustration or anger over work incidents, disparage patients or colleagues, use offensive or discriminatory language, reveal highly personal information, or picture a physician intoxicated, using illegal drugs, or in sexually suggestive poses. Physicians should separate professional from personal websites, social networking accounts and blogs, and should follow guidelines developed by institutions and professional societies on using social media to communicate with patients.

ETHICAL ISSUES IN CLINICAL RESEARCH

Clinical research is essential to translate scientific discoveries into beneficial tests and therapies for patients. However, clinical research raises ethical concerns because participants face inconvenience and risks in research, which is not designed specifically to benefit them but rather to advance scientific knowledge. Ethical guidelines for researchers require them to rigorously design research, minimize risk to participants, and obtain informed and voluntary consent from participants and approval from an institutional review board (IRB). IRBs determine that risks to participants are acceptable and have been minimized, and recommend appropriate additional protections when research includes vulnerable participants. Physicians may be involved as clinical research investigators or may be in a position to refer or recommend clinical trial participation to their patients. Physician-investigators may feel an inherent tension between conducting research and providing health care. Awareness of this tension, familiarity with the ethics of research, collaboration with others on the research and clinical teams, and utilizing research ethics consultation can help to mitigate the tension. Before starting clinical research, investigators should receive training in the ethics of clinical research. Courses and guidance on the ethics of clinical research are widely available.

Physicians should be critical consumers of clinical research results and keep up with the expanding scope of research and advances that change standards of practice. Precision medicine initiatives aim to individualize clinical care by sometimes combining clinical information from electronic health records, genomic sequencing of leftover biomaterials originally obtained for clinical care, and data from personal mobile devices. Furthermore, physicians and health care institutions are analyzing data routinely collected and available in electronic health records in order to improve the quality of care in real-world clinical settings; these efforts may be through quality improvement, comparative effectiveness research, or learning health care systems. These new types of research raise important issues about informed consent, privacy, and risk.

GLOBAL CONSIDERATIONS

International Research Clinical research is increasingly conducted at multiple sites and across national borders. Societal, legal, and cultural norms and perspectives about research may vary and there are many ethical challenges. Physician-investigators involved in international research should be familiar with international guidelines, such as the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS) guidelines, and the International Council on Harmonisation Good Clinical Practice guidelines, as well as national and local laws where the research is taking place. Partnering with local researchers and communities is essential not only to demonstrate respect but also to facilitate successful clinical research.

Global Health Field Experiences Many physicians and trainees choose to gain valuable experience by providing patient care in international settings. Such arrangements, however, raise ethical challenges—for example, as a result of differences in beliefs about health and illness, expectations regarding health care and the physician's role, standards of clinical practice, resource limitations, and norms for disclosure of serious diagnoses. Additional dilemmas arise if visiting physicians and trainees take on responsibilities beyond their expertise or if donated drugs and equipment are not appropriate to local needs. Visiting physicians and trainees should receive training and mentoring and seek information regarding cultural and clinical practices in the host community, respect local customs and values, work closely with local professionals and team members, and be explicit about their skills, knowledge, and limits. Leaders of global health field experiences should ensure that participating physicians receive training on ethical and cultural issues, mentoring, backup, and debriefing and that plans for evacuation are in place in case they are needed.

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9 Palliative and End-of-Life Care

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EPIDEMIOLOGY

CAUSES OF DEATH

In 2015, 2,712,630 individuals died in the United States **(Table 9-1)**. Approximately 73% of these deaths occurred in those aged >65 years. The epidemiology of death has changed significantly since 1900 and even since 1980. In 1900, heart disease caused ~8% of all deaths and cancer accounted for <4% of all deaths. In 1980, heart disease accounted for 38.2% of all deaths, cancer 20.9%, and cerebrovascular disease 8.6% of all deaths. By 2014, there had been a dramatic drop in deaths from cardiovascular and cerebrovascular diseases. In 2014, 23.4% of all deaths were from cardiovascular disease and just 5.1% from cerebrovascular disease. Deaths attributable to cancer, however, had increased to 22.5%. The proportions of deaths due to chronic lower respiratory disease, diabetes, Alzheimer's, and suicides have also increased. Interestingly, in 2014, HIV/AIDS accounted for <0.26% of all U.S. deaths.

This change in the epidemiology of death is also reflected in the costs of illness. In the United States, ~84% of all health care spending goes to patients with chronic illnesses, and ~12% of total personal

TABLE 9-1 Ten Leading Causes of Death in the United States and Britain

CAUSE OF DEATH	UNITED STATES (2014)		ENGLAND AND WALES (2015)	
	NUMBER OF DEATHS, ALL AGES (%)	NUMBER OF DEATHS, PEOPLE ≥65 YEARS OF AGE	NUMBER OF DEATHS, ALL AGES (%)	NUMBER OF DEATHS, PEOPLE ≥65 YEARS OF AGE
All deaths	2,626,418	1,922,271	529,655	449,409
Heart disease	614,348 (23.4)	489,722 (25.5)	114,345 (21.6)	99,029 (22.0)
Malignant neoplasms	591,699 (22.5)	413,885 (21.5)	144,330 (27.2)	115,302 (25.7)
Chronic lower respiratory diseases	147,101 (5.6)	124,693 (6.5)	30,368 (5.7)	27,674 (6.2)
Accidents	136,053 (5.2)	48,295 (2.5)	13,871 (2.6)	8,214 (1.8)
Cerebrovascular diseases	133,103 (5.1)	113,308 (5.9)	34,883 (6.6)	32,212 (7.2)
Alzheimer's disease	93,541 (3.6)	92,604 (4.8)	14,323 (2.7)	14,222 (3.2)
Diabetes mellitus	76,488 (2.9)	54,161 (2.8)	5,582 (1.1)	4,843 (1.1)
Influenza and pneumonia	55,227 (2.1)	44,836 (2.3)	29,885 (5.6)	27,982 (6.2)
Nephritis, nephritic syndrome, nephrosis	48,146 (1.8)	39,957 (2.1)	3,537 (0.7)	3,312 (0.7)
Intentional self-harm	42,773 (1.6)	-	4,150 (0.8)	727 (0.2)

Source: National Center for Health Statistics (United States, 2014), *http://www.cdc.gov/nchs;* National Statistics (Great Britain, 2015), *http://www.statistics.gov.uk*.

health care spending—slightly <$400 billion in 2015—goes to the 0.83% of the population in the last year of their lives.

In developed countries, an estimated ~70% of all deaths are preceded by a disease or condition, making it reasonable to plan for dying in the foreseeable future. Cancer has served as the paradigm for terminal care, but it is not the only type of illness with a recognizable and predictable terminal phase. Since heart failure, chronic obstructive pulmonary disease (COPD), chronic liver failure, dementia, and many other conditions have recognizable terminal phases, a systematic approach to end-of-life care should be part of all medical specialties. Many patients with illness-related suffering also can benefit from palliative care regardless of prognosis. Ideally, palliative care should be considered part of comprehensive care for all chronically ill patients. Reviews of the recent literature have found strong evidence that palliative care can be improved by coordination between caregivers, doctors, and patients for advance care planning, as well as dedicated teams of physicians, nurses, and other providers.

SITE OF DEATH

Where patients die varies by country **(Table 9-2)**. In Belgium and Canada, for instance, over half of all cancer patients still die in the hospital. The last few decades have seen a steady shift, both in the United States and other countries like the Netherlands, out of the hospital, as patients and their families list their own homes as the preferred site of death. In the early 1980s, about 70% of American cancer patients died in the hospital. Today that percentage is ~20% **(Fig. 9-1)**. A recent report shows that even since 2000, there has been a shift in the United States from inpatient to home deaths, especially for patients with cancer, COPD, and dementia. For instance, 30.1% of deaths due to cancer in 2000 occurred in acute care hospitals; by 2009, this figure had dropped to 22.1%.

Paradoxically, while deaths in acute care hospitals have declined in the United States since 2000, both hospitalizations in the last 90 days of life and—even more troublingly—admission to the ICU in the last 30 days have actually increased. Recent data show that >40% of cancer patients in the United States are admitted to the ICU in their last 6 months of life, and >25% of cancer patients are admitted to the hospital in the last 30 days.

The shift in deaths out of the hospital has been accompanied by an increase in the use of hospice in the United States. In 2000, 21.6% of all decedents used hospice at the time of death; by 2009, 42.2% were using hospice. Among cancer patients, ~60% were using hospice at the time of death. Hospice is also increasingly being used by non-cancer patients. Today, cancer patients constitute <40% of hospice users. About 79% of patients receiving hospice care die out of the hospital, and around 41% of those receiving hospice care die in a private residence.

In 2008, for the first time, the American Board of Medical Specialties (ABMS) offered certification in hospice and palliative medicine. With the shortening of hospital stays, many serious conditions are now being treated at home or on an outpatient basis. Consequently, providing optimal palliative and end-of-life care requires ensuring that appropriate services are available in a variety of settings, including non-institutional settings.

HOSPICE AND THE PALLIATIVE CARE FRAMEWORK

Central to this type of care is an interdisciplinary team approach that typically encompasses pain and symptom management, spiritual and psychological care for the patient, and support for family caregivers during the patient's illness and the bereavement period.

One of the more important changes in this field is beginning palliative care many months before death in order to focus on symptom relief, and then switching to hospice in the patient's last few months. This approach avoids leaving hospice until the very end by introducing palliative care earlier, thereby allowing patients and families time to transition. Phasing palliative care into end-of-life care means that patients will often receive palliative interventions long before they are formally diagnosed as terminally ill, or likely to die within 6 months.

Fundamental to ensuring quality palliative and end-of-life care is a focus on four broad domains: (1) physical symptoms; (2) psychological symptoms; (3) social needs that include interpersonal relationships, caregiving, and economic concerns; and (4) existential or spiritual needs.

ASSESSMENT AND CARE PLANNING

Comprehensive Assessment Standardized methods for conducting a comprehensive assessment focus on evaluating the patient's condition in all four domains affected by the illness: physical, psychological, social, and spiritual.

A comprehensive assessment should follow a modified version of the traditional medical history and physical examination, and should emphasize both physical and mental symptoms. Questions should aim to elucidate symptoms, discern sources of suffering, and gauge how much those symptoms interfere with the patient's quality of life. Standardized and repeated assessments to evaluate the effectiveness of interventions are critical. Thus, clinicians should use shorter, validated instruments, such as: (1) The revised Edmonton Symptom Assessment Scale; (2) Condensed Memorial Symptom Assessment Scale (MSAS); (3) MD Anderson Brief Symptom Inventory; (4) Rotterdam Symptom Checklist; (5) Symptom Distress Scale; (6) Patient-Reported Outcomes Measurement Information System; and (7) The Interactive Symptom Assessment and Collection (ISAAC) tool.

Mental Health: With respect to mental health, many practices use the Patient Health Questionnaire-9 (PHQ-9) to screen for depression and the Generalized Anxiety Disorder-7 (GAD-7) to screen for anxiety. Using such tools ensures that the assessment is comprehensive and does not focus excessively on only pain.

TABLE 9-2 Elements of Communicating Bad News—The P-SPIKES Approach

ACRONYM	STEPS	AIM OF THE INTERACTION	PREPARATIONS, QUESTIONS, OR PHRASES
P	Preparation	Mentally prepare for the interaction with the patient and/or family.	Review what information needs to be communicated. Plan how you will provide emotional support. Rehearse key steps and phrases in the interaction.
S	Setting of the interaction	Ensure the appropriate setting for a serious and potentially emotionally charged discussion.	Ensure that patient, family, and appropriate social supports are present. Devote sufficient time. Ensure privacy and prevent interruptions by people or beeper. Bring a box of tissues.
P	Patient's perception and preparation	Begin the discussion by establishing the baseline and whether the patient and family can grasp the information. Ease tension by having the patient and family contribute.	Start with open-ended questions to encourage participation. Possible phrases to use: *What do you understand about your illness?* *When you first had symptom X, what did you think it might be?* *What did Dr. X tell you when he or she sent you here?* *What do you think is going to happen?*
I	Invitation and information needs	Discover what information needs the patient and/or family have and what limits they want regarding the bad information.	Possible phrases to use: *If this condition turns out to be something serious, do you want to know?* *Would you like me to tell you all the details of your condition? If not, who would you like me to talk to?*
K	Knowledge of the condition	Provide the bad news or other information to the patient and/or family sensitively.	Do not just dump the information on the patient and family. Check for patient and family understanding. Possible phrases to use: *I feel badly to have to tell you this, but…* *Unfortunately, the tests showed…* *I'm afraid the news is not good…*
E	Empathy and exploration	Identify the cause of the emotions—e.g., poor prognosis. Empathize with the patient and/or family's feelings. Explore by asking open-ended questions.	Strong feelings in reaction to bad news are normal. Acknowledge what the patient and family are feeling. Remind them such feelings are normal, even if frightening. Give them time to respond. Remind patient and family you won't abandon them. Possible phrases to use: *I imagine this is very hard for you to hear.* *You look very upset. Tell me how you are feeling.* *I wish the news were different.* *We'll do whatever we can to help you.*
S	Summary and planning	Delineate for the patient and the family the next steps, including additional tests or interventions.	It is the unknown and uncertain that can increase anxiety. Recommend a schedule with goals and landmarks. Provide your rationale for the patient and/or family to accept (or reject). If the patient and/or family are not ready to discuss the next steps, schedule a follow-up visit.

Source: Adapted from R Buckman: *How to Break Bad News: A Guide for Health Care Professionals.* Baltimore, Johns Hopkins University Press, 1992.

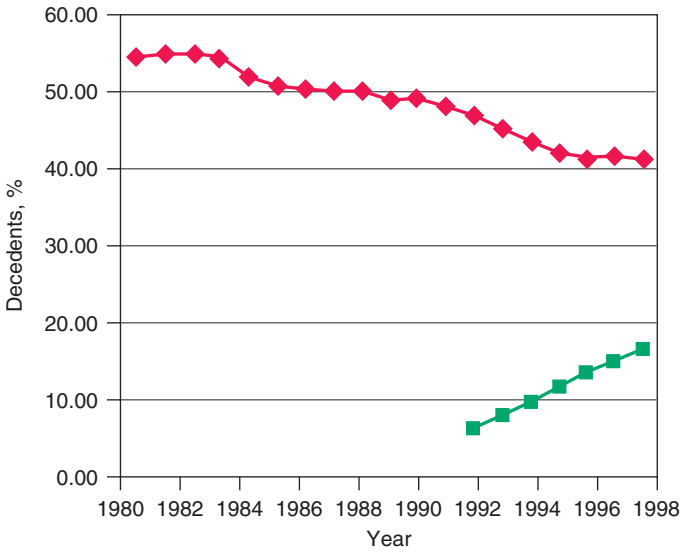

FIGURE 9-1 Graph showing trends in the site of death in the last two decades. ◆, percentage of hospital inpatient deaths; ■, percentage of decedents enrolled in a hospice.

Invasive Tests: Invasive tests are best avoided in end-of-life care, and even minimally invasive tests should be evaluated carefully for their benefit-to-burden ratio for the patient. Aspects of the physical examination that are uncomfortable and unlikely to yield useful information should be omitted.

Social Needs: Health care providers should also assess the status of important relationships, financial burdens, caregiving needs, and access to medical care. Relevant questions will include the following: *How often is there someone to feel close to? How has this illness been for your family? How has it affected your relationships? How much help do you need with things like getting meals and getting around? How much trouble do you have getting the medical care you need?*

Existential Needs: To determine a patient's existential needs, providers should assess distress, the patient's sense of emotional and existential well-being, and whether the patient believes he or she has found purpose or meaning. Helpful assessment questions can include the following: *How much are you able to find meaning since your illness began? What things are most important to you at this stage?*

Perception of Care: In addition, it can be helpful to ask how the patient perceives his or her care: *How much do you feel your doctors and nurses respect you? How clear is the information from us about what to expect regarding your illness? How much do you feel that the medical care you are*

getting fits with your goals? If concern is detected in any of these areas, deeper evaluative questions are warranted.

Communication Particularly when an illness is life-threatening, there exists the potential for many emotionally charged and potentially conflict-creating moments—collectively called "bad news" situations—in which empathic and effective communication skills are essential. Those moments include the sharing of a terminal diagnosis with the patient and/or family, the discussion of patient's prognosis and any treatment failures, the consideration of deemphasizing efforts to cure and prolong life while focusing more on symptom management and palliation, advance care planning, and the patient's actual death. Although these conversations can be difficult, research indicates that end-of-life discussions can lead to earlier hospice referrals, rather than overly aggressive treatment, ultimately benefiting quality of life for patients and improving the bereavement process for families.

Just as surgeons prepare for major operations and investigators rehearse a presentation of research results, physicians and health care providers caring for patients with significant or advanced illnesses should develop a standardized approach for sharing important information and planning interventions. In addition, physicians must be aware that families often care not only about how prepared the physician was to deliver bad news, but also the setting in which it was delivered. For instance, one study found that 27% of families making critical decisions for patients in an intensive care unit (ICU) desired better and more private physical space to communicate with physicians.

One structured seven-step procedure for communicating bad news goes by the acronym P-SPIKES: (1) ***p***repare for the discussion, (2) ***s***et up a suitable environment, (3) begin the discussion by finding out what the ***p***atient and/or family understand, (4) determine how they will comprehend new ***i***nformation best and how much they want to know, (5) provide needed new ***k***nowledge accordingly, (6) allow for ***e***motional responses, and (7) ***s***hare plans for the next steps in care. Table 9-2 provides a summary of these steps, along with suggested phrases and underlying rationales for each one.

Continuous Goal Assessment Major barriers to providing high-quality palliative and end-of-life care include the difficulty in determining both an accurate prognosis, and the emotional resistance of patients and their families to accepting the implications of a poor prognosis. A practical solution to these barriers is to integrate palliative care interventions or home visits from a palliative care visiting nurse months before the estimated final 6 months of life. Under this approach, palliative care no longer conveys the message of failure, having no more treatments, or "giving up hope." The transition from palliative to end-of-life care or hospice also feels less hasty and unexpected to the family. Fundamental to integrating palliative care with curative therapy is the inclusion of a continuous goal assessment as part of the routine patient reassessments that occur at most patient-physician encounters.

Goals for care are numerous, ranging from curing a specific disease, to prolonging life, to relieving a particular symptom, to adapting to a progressive disability without disrupting the family, to finding peace of mind or personal meaning, to dying in a manner that leaves loved ones with positive memories. Discerning a patient's goals for care can be approached through a seven-step protocol: (1) ensure that medical and other information is as complete as reasonably possible and is understood by all relevant parties (see above); (2) explore what the patient and/or family is hoping for, while also identifying relevant and realistic goals; (3) share all the options with the patient and family; (4) respond with empathy as they adjust to changing expectations; (5) make a plan that emphasizes what can be done to achieve the realistic goals; (6) follow through with the plan; and (7) periodically review the plan and consider at every encounter whether the goals of care should be revised with the patient and/or family. Each of these steps need not be followed in rote order, but together they provide a helpful framework for interactions with patients and their families regarding their goals for care. Such interactions can be especially challenging if a patient or family member has difficulty letting go of an unrealistic goal. In such cases, the provider should help them refocus on more realistic goals, and should also suggest that while it is fine to hope for the best, it is still prudent to plan for other outcomes as well.

Advance Care Planning • PRACTICES Advance care planning is the process of planning for future medical care in case the patient becomes incapable of making medical decisions. A 2010 study of adults aged ≥60 who died between 2000 and 2006 found that while 42% of adults were required to make treatment decisions in their final days of life, 70% lacked decision-making capacity. Among those lacking decision-making capacity, approximately one-third did not have advance planning directives. Ideally, such planning would occur before a health care crisis or the terminal phase of an illness. Unfortunately, diverse barriers prevent this. Approximately 80% of Americans endorse advance care planning and living wills. However, according to a Pew survey only 35% of adults have written down their end-of-life wishes. Other studies report even fewer Americans—with some estimates as low as 26% of adults—having filled out advance care directives. Larger numbers of adults, between 50 and 70%, claim to have talked with someone about their treatment wishes.

Effective advance care planning should follow six key steps: (1) introducing the topic, (2) structuring a discussion, (3) reviewing plans that have been discussed by the patient and family, (4) documenting the plans, (5) updating them periodically, and (6) implementing the advance care directives **(Table 9-3)**. Two of the main barriers to advance care planning are problems in raising the topic and difficulty in structuring a succinct discussion. Raising the topic can be done efficiently as a routine matter, noting that it is recommended for all patients, analogous to purchasing insurance or estate planning. Many of the most difficult cases have involved unexpected, acute episodes of brain damage in young individuals.

Structuring a focused discussion is an important communication skill. To do so, a provider must first identify the health care proxy and recommend his or her involvement in the advance care planning process. Next, a worksheet must be selected that has been demonstrated to produce reliable and valid expressions of patient preferences, and the patient and proxy must be oriented to it. Such worksheets exist for both general and disease-specific situations. The provider should then discuss with the patient and proxy one example scenario to demonstrate how to think about the issues. It is often helpful to begin with a scenario in which the patient is likely to have settled preferences for care, such as being in a persistent vegetative state. Once the patient's preferences for interventions in this scenario are determined, the provider should suggest that the patient and proxy discuss and complete the worksheet for each other. If appropriate, the patient and proxy should consider involving other family members in the discussion. During a subsequent return visit, the provider should go over the patient's preferences, checking and resolving any inconsistencies. After having the patient and proxy sign the document, the provider should place the document in the patient's medical chart and make sure that copies are provided to relevant family members and care sites. Since patients' preferences can change, these documents must be reviewed periodically.

TYPES OF DOCUMENTS There are two broad types of advance care planning documents. The first includes living wills, also known as instructional directives; these are advisory documents that describe the types of decisions that should direct a patient's care. Some are more specific, delineating different scenarios and interventions for the patient to choose from. Among these, some are for general use and others are designed for use by patients with a specific type of disease, such as cancer, renal failure, or HIV. Less specific directives can be general statements, such as not wanting life-sustaining interventions, or forms that describe the values that should guide specific discussions about terminal care. The second type of advance directive allows the designation of a health care proxy (sometimes also referred to as a durable attorney for health care), an individual selected by the patient to make decisions. The choice is not either/or; a combined directive that includes a living will and designates a proxy is often used, and the directive should indicate clearly whether the specified patient

TABLE 9-3 Steps in Advance Care Planning

STEP	GOALS TO BE ACHIEVED AND MEASURES TO COVER	USEFUL PHRASES OR POINTS TO MAKE
Introducing advance care planning	Ask the patient what he or she knows about advance care planning and if he or she has already completed an advance care directive.	*I'd like to talk with you about something I try to discuss with all my patients. It's called advance care planning. In fact, I feel that this is such an important topic that I have done this myself. Are you familiar with advance care planning or living wills?*
	Indicate that you as a physician have completed advance care planning.	*Have you thought about the type of care you would want if you ever became too sick to speak for yourself? That is the purpose of advance care planning.*
	Indicate that you try to perform advance care planning with all patients regardless of prognosis.	*There is no change in health that we have not discussed. I am bringing this up now because it is sensible for everyone, no matter how well or ill, old or young.*
	Explain the goals of the process as empowering the patient and ensuring that you and the proxy understand the patient's preferences.	*Have many copies of advance care directives available, including in the waiting room, for patients and families.*
	Provide the patient relevant literature, including the advance care directive that you prefer to use.	*Know resources for state-specific forms (available at www .nhpco.org).*
	Recommend the patient identify a proxy decision-maker who should attend the next meeting.	
Structured discussion of scenarios and patient	Affirm that the goal of the process is to follow the patient's wishes if the patient loses decision-making capacity.	*Use a structured worksheet with typical scenarios.*
	Elicit the patient's overall goals related to health care. Elicit the patient's preferences for specific interventions in a few salient and common scenarios. Help the patient define the threshold for withdrawing and withholding interventions. Define the patient's preference for the role of the proxy.	*Begin the discussion with persistent vegetative state and consider other scenarios, such as recovery from an acute event with serious disability, asking the patient about his or her preferences regarding specific interventions, such as ventilators, artificial nutrition, and CPR, and then proceeding to less invasive interventions, such as blood transfusions and antibiotics.*
Review the patient's preferences	After the patient has made choices of interventions, review them to ensure they are consistent and the proxy is aware of them.	
Document the patient's preferences	Formally complete the advance care directive and have a witness sign it.	
	Provide a copy for the patient and the proxy.	
	Insert a copy into the patient's medical record and summarize in a progress note.	
Update the directive	Periodically, and with major changes in health status, review the directive with the patient and make any modifications.	
Apply the directive	The directive goes into effect only when the patient becomes unable to make medical decisions for himself or herself.	
	Reread the directive to be sure about its content.	
	Discuss your proposed actions based on the directive with the proxy.	

Abbreviation: CPR, cardiopulmonary resuscitation.

preferences or the proxy's choice takes precedence if they conflict. Some states have begun to put into practice a "Physician Orders for Life-Sustaining Treatment (POLST)" directive, which builds on communication between providers and patients by including guidance for end-of-life care in a color-coordinated form that follows the patient across treatment settings. The procedures for completing advance care planning documents vary according to state law.

A potentially misleading distinction relates to statutory, as opposed to advisory, documents. Statutory documents are drafted to fulfill relevant state laws. Advisory documents are drafted to reflect the patient's wishes. Both are legal, the first under state law and the latter under common or constitutional law.

LEGAL ASPECTS As of 2017, 48 states and the District of Columbia had enacted living will legislation. Massachusetts and Michigan are the two states without living will legislation. Indiana has a life-prolonging procedures declaration. States differ in the requirements for advanced directives, whether they need to be witnessed, by how many witnesses, or notarized. Importantly, in 26 states, the laws state that the living will is not valid if a woman is pregnant. All states except Alaska have enacted durable power of attorney for health care laws that permits patients to designate a proxy decision-maker with authority to terminate life-sustaining treatments. Only in Alaska does the law prohibit proxies from terminating life-sustaining treatments for pregnant women.

The U.S. Supreme Court has ruled that patients have a constitutional right to decide any issues related to refusing or terminating medical interventions, including life-sustaining interventions, and that mentally incompetent patients can exercise this right by providing "clear and convincing evidence" of their preferences. Since advance care directives permit patients to provide such evidence, commentators agree that they are constitutionally protected. Most commentators believe that a state is required to honor any clear advance care directive, regardless of whether it is written on an "official" form. Many states have enacted laws for the explicit purpose of honoring out-of-state directives. If a patient is not using a statutory form, it may be advisable to attach a statutory form to the advance care directive being used. State-specific forms are readily available free of charge for health care providers, patients, and families through the website of the National Hospice and Palliative Care Organization (*http://www.nhpco.org*).

Reimbursement: As of January 1, 2016, the Center for Medicare and Medicaid Services amended the physician fee schedule to reimburse discussions of advance care planning (ACP) under CPT codes 99497 and 99498. The session must be voluntary and include an explanation of advance care planning, but need not include a completed advance care document. There can be multiple bills for the discussion if it extends over several encounters.

INTERVENTIONS

PHYSICAL SYMPTOMS AND THEIR MANAGEMENT

Great emphasis has been placed on addressing dying patients' pain. In order to emphasize its importance, pain assessment has frequently been included as the fifth vital sign. Heightened consideration of pain has been advocated by large health care systems such as the Veterans' Administration and accrediting bodies such as the Joint Commission on the Accreditation of Health Care Organizations (JCAHO). Although

TABLE 9-4 Common Physical and Psychological Symptoms of Terminally Ill Patients

PHYSICAL SYMPTOMS	PSYCHOLOGICAL SYMPTOMS
Pain	Anxiety
Fatigue and weakness	Depression
Dyspnea	Hopelessness
Insomnia	Meaninglessness
Dry mouth	Irritability
Anorexia	Impaired concentration
Nausea and vomiting	Confusion
Constipation	Delirium
Cough	Loss of libido
Swelling of arms or legs	
Itching	
Diarrhea	
Dysphagia	
Dizziness	
Fecal and urinary incontinence	
Numbness/tingling in hands/feet	

this embrace of pain has been symbolically important, available data suggests that making pain the fifth vital sign does not lead to improved pain management practices. In light of the growing opioid crisis in the United States, the emphasis on pain management has begun to be re-examined. For instance, in 2017 draft standards, the JCAHO recommends nonpharmacological pain treatment as well as identification of psychosocial risk factors for addiction. Importantly, good palliative care requires much more than good pain management. The frequency of symptoms varies by disease and other factors. The most common physical and psychological symptoms among all terminally ill patients include pain, fatigue, insomnia, anorexia, dyspnea, depression, anxiety, nausea, and vomiting. In the last days of life, terminal delirium is also common. Assessments of patients with advanced cancer have shown that patients experienced an average of 11.5 different physical and psychological symptoms **(Table 9-4)**.

In the vast majority of cases, evaluations to determine the etiology of these symptoms should be limited to the history and physical examination. In some cases, radiologic or other diagnostic examinations will provide sufficient benefit in directing optimal palliative care to warrant the risks, potential discomfort, and inconvenience, especially to a seriously ill patient. Only a few of the common symptoms that present difficult management issues will be addressed in this chapter. **Additional information on the management of other symptoms, such as nausea and vomiting, insomnia, and diarrhea, can be found in Chaps. 41, 65, 27, and 42, respectively.**

Pain • FREQUENCY The frequency of pain among terminally ill patients varies significantly. Cancer (~85%), CHF (~75%), and AIDS have been associated with a higher prevalence of pain compared to other advanced illnesses, such as COPD (~45%), CKD (~40%), and dementia (~40%). One meta-analysis of adults with advanced or terminal illness found pain prevalence of 30–94% in patients with cancer, compared to 21–77% for COPD, 14–78% for CHF, 11–83% for ESRD, 14–63% for dementia, and 30–98% for AIDS.

ETIOLOGY There are two types of pain: nociceptive and neuropathic. Nociceptive pain is further divided into somatic or visceral pain. *Somatic pain* is the result of direct mechanical or chemical stimulation of nociceptors and normal neural signaling to the brain. It tends to be localized, aching, throbbing, and cramping. The classic example is bone metastases. *Visceral pain* is caused by nociceptors in gastrointestinal (GI), respiratory, and other organ systems. It is a deep or colicky type of pain classically associated with pancreatitis, myocardial infarction, or tumor invasion of viscera. *Neuropathic pain* arises from disordered nerve signals. It is described by patients as burning, electrical, or shock-like pain. Classic examples are post-stroke pain, tumor invasion of the brachial plexus, and herpetic neuralgia.

ASSESSMENT Pain is a subjective experience. Depending on the patient's circumstances, perspective, and physiologic condition, the same physical lesion or disease state can produce different levels of reported pain and need for pain relief. Systematic assessment includes eliciting the following: (1) type: throbbing, cramping, burning, etc.; (2) periodicity: continuous, with or without exacerbations, or incident; (3) location; (4) intensity; (5) modifying factors; (6) effects of treatments; (7) functional impact; and (8) impact on patient. Several validated pain assessment measures may be used, including the Visual Analogue Scale (VAS), the Brief Pain Inventory (BPI), or the Numerical Pain Rating Scale (NRS-11). Other scales have been developed for neuropathic pain, such as the Neuropathic Pain Scale and the DN4 Questionnaire. Frequent reassessments on a consistent scale are essential to assess the impact of and need to readjust interventions.

INTERVENTIONS Interventions for pain must be tailored to each individual, with the goal of preempting chronic pain and relieving breakthrough pain. At the end of life, there is rarely reason to doubt a patient's report of pain. With the opioid crisis in the United States there is more emphasis on making opioids one component of multimodal analgesia. Nevertheless, at the end of life, pain medications, especially opioids, remain the cornerstone of management. If they are failing and nonpharmacologic interventions—including radiotherapy and anesthetic or neurosurgical procedures such as peripheral nerve blocks or epidural medications—are required, a pain consultation is appropriate.

Pharmacologic interventions still largely follow the World Health Organization three-step, "analgesic ladder" approach, which involves non-opioid analgesics, "mild" opioids, and "strong" opioids, with or without adjuvants **(Chap. 10)**. Nonopioid analgesics, especially nonsteroidal anti-inflammatory drugs (NSAIDs), are the initial treatments for mild pain. They work primarily by inhibiting peripheral prostaglandins and reducing inflammation, but may also have central nervous system (CNS) effects. Additionally, NSAIDs have a ceiling effect. Ibuprofen, up to 2400 mg/d qid, has a minimal risk of causing bleeding and renal impairment and is a good initial choice. In patients with a history of severe GI or other bleeding, however, ibuprofen should be avoided. In patients with a history of mild gastritis or gastroesophageal reflux disease (GERD), acid-lowering therapy, such as a proton pump inhibitor, should be used. Acetaminophen is an alternative in patients with a history of GI bleeding and can be used safely at up to 4 g/d qid. In patients with liver dysfunction due to metastases or other causes, and in patients with heavy alcohol use, doses should be reduced.

If nonopioid analgesics are insufficient, opioids should be introduced. Opioids primarily work by interacting with μ opioid receptors to activate pain-inhibitory neurons in the CNS, although they also interact variably with δ and κ receptors. Receptor agonists, such as morphine, codeine, and fentanyl, produce analgesia by activating pain-inhibitory neurons in the CNS. Partial agonists, such as buprenorphine, have a ceiling effect for analgesia and a lower potential for abuse. They are useful for post-acute pain, but should not be used for chronic pain in end-of-life care. Pure antagonists, such as naloxone and methylnaltrexone, are used for reversal of opioid effects.

Traditionally, "weak" opioids such as codeine were used first. If they failed to relieve pain after dose escalation, "strong" opioids like morphine were used in doses of 5–10 mg every 4 h. However, this breakdown between "weak" and "strong" opioids is no longer commonly accepted, with smaller doses of "stronger" opioids frequently being preferred over similar or larger doses of "weaker" opioids, and different pain syndromes having different preferred therapies. Regardless, nonopioid analgesics should be combined with opioids, as they potentiate the effect of opioids.

For continuous pain, opioids should be administered on a regular, around-the-clock basis consistent with their duration of analgesia. They should not be provided only when the patient experiences pain; the goal is to prevent patients from experiencing pain. Patients should also be provided rescue medication, such as liquid morphine, for breakthrough pain, generally at 20% of the baseline dose. Patients should be informed that using the rescue medication does not obviate the need to take the

next standard dose of pain medication. If the patient's pain remains uncontrolled after 24 h and recurs before the next dose, requiring the patient to utilize the rescue medication, the daily opioid dose can be increased by the total dose of rescue medications used by the patient, or by 50% of the standing opioid daily dose for moderate pain and 100% for severe pain.

It is inappropriate to start with extended-release preparations. Instead, an initial focus on using short-acting preparations to determine how much is required in the first 24–48 h will allow clinicians to determine opioid needs. Once pain relief is obtained using short-acting preparations, the switch should be made to extended-release preparations. Even with a stable extended-release preparation regimen, the patient may experience incident pain, such as during movement or dressing changes. Short-acting preparations should be taken before such predictable episodes. Although less common, patients may have "end-of-dose failure" with long-acting opioids, meaning that they develop pain after 8 h in the case of an every-12-h medication. In these cases, a trial of giving an every-12-h medication every 8 h is appropriate.

Due to differences in opioid receptors, cross-tolerance among opioids is incomplete, and patients may experience different side effects with different opioids. Therefore, if a patient is not experiencing pain relief or is experiencing too many side effects, a change to another opioid preparation is appropriate. When switching, one should begin with 50–75% of the published equianalgesic dose of the new opioid.

Unlike NSAIDs, opioids have no ceiling effect; therefore, there is no maximum dose, no matter how many milligrams the patient is receiving. The appropriate dose is the dose needed to achieve pain relief. This is an important point for clinicians to explain to patients and families. Addiction or excessive respiratory depression is extremely unlikely in the terminally ill; fear of these side effects should neither prevent escalating opioid medications when the patient is experiencing insufficient pain relief, nor justify using opioid antagonists.

Opioid side effects should be anticipated and treated preemptively. Nearly all patients experience constipation that can be debilitating (see below). Failure to prevent constipation often results in noncompliance with opioid therapy. The preferred treatment is prevention. Cathartics (senna 2 tables qHS), stool softeners (docusate 100 mg PO qd), and/or laxatives (laxtulose 30 mL qd) are considered first-line. For refractory cases, opioid antagonists or other therapies, such as lubiprostone, should be considered.

Methylnaltrexone is the best-studied opioid antagonist for use in refractory opioid-induced constipation. It reverses opioid-induced constipation by blocking peripheral opioid receptors, but not central receptors, for analgesia. In placebo-controlled trials, it has been shown to cause laxation within 24 h of administration. As with the use of opioids, about a third of patients using methylnaltrexone experience nausea and vomiting, but unlike with opioid usage, tolerance usually develops within a week. Therefore, when one is beginning opioids, an antiemetic such as metoclopramide or a serotonin antagonist is often prescribed prophylactically and stopped after 1 week. Olanzapine has also been shown to have anti-nausea properties and can be effective in countering delirium or anxiety, with the advantage of some weight gain.

Drowsiness, a common side effect of opioids, also usually abates within a week. For refractory or severe cases, pharmacologic therapy should be considered. The best-studied agents are the psychostimulants dextroamphetamine, methylphenidate, and modafinil, although evidence regarding their efficacy is weak. Modafinil has the advantage of once-a-day dosing compared to methyphenidate's twice daily dosing.

Seriously ill patients who require chronic pain relief rarely become addicted. Suspicion of addiction should not be a reason to withhold pain medications from terminally ill patients. Nonetheless, patients and families may withhold prescribed opioids for fear of addiction or dependence. Physicians and health care providers should reassure patients and families that the patient will not become addicted to opioids if they are used as prescribed for pain relief; this fear should not prevent the patient from taking the medications around the clock. However, diversion of drugs for use by other family members or illicit sale may occur. It may be necessary to advise the patient and caregiver about secure storage of opioids. Contract writing with the patient and family can help. If that fails, transfer to a safe facility may be necessary.

Tolerance describes the need to increase medication dosage for the same pain relief without a concurrent change in disease. In the case of patients with advanced disease, the need for increasing opioid dosage for pain relief usually is caused by disease progression rather than tolerance. Physical dependence is indicated by symptoms resulting from the abrupt withdrawal of opioids and should not be confused with addiction.

In recent years, the potential dangers of opioid drugs have become increasingly apparent. To help mitigate the risk of these powerful drugs, several strategies should be used to reduce the risk of aberrant drug use. To start, all patients should be assessed for their individual levels of risk. While there are multiple surveys available, including the Opioid Risk Tool, none have gained wide-spread use or validation. In general, however, it is important to screen for prior substance abuse and major psychiatric disorders.

For patients deemed to be high-risk, a multidisciplinary effort should be pursued to reduce the risk of adverse consequences, such as addiction and diversion. Prescribing strategies include selecting opioids with longer durations of action and lower street values, such as methadone, and prescribing smaller quantities with more frequent follow-up. Monitoring options include periodic urine screening and referral to pain specialists. In some cases, it may also be reasonable to consider not offering short-acting opioids for breakthrough pain. In no situation, however, should adequate pain-relief be withheld due to risk.

Adjuvant analgesic medications are nonopioids that potentiate the analgesic effects of opioids. They are especially important in the management of neuropathic pain. Gabapentin, an anticonvulsant initially studied in the setting of herpetic neuralgia, is now the first-line treatment for neuropathic pain resulting from a variety of causes. It is begun at 100–300 mg bid or tid, with 50–100% dose increments every 3 days. Usually 900–3600 mg/d in two or three doses is effective. The combination of gabapentin and nortriptyline may be more effective than gabapentin alone. One potential side effect of gabapentin to be aware of is confusion and drowsiness, especially in the elderly. Other effective adjuvant medications include pregabalin, which has the same mechanism of action as gabapentin, but is absorbed more efficiently from the GI tract. Lamotrigine is a novel agent whose mechanism of action is unknown, but has been shown to be effective. It is recommended to begin at 25–50 mg/d, increasing to 100 mg/d. Carbamazepine, a first-generation agent, has been proven effective in randomized trials for neuropathic pain. Other potentially effective anticonvulsant adjuvants include topiramate (25–50 mg qd or bid, rising to 100–300 mg/d) and oxcarbazepine (75–300 mg bid, rising to 1200 mg bid).

Glucocorticoids, preferably dexamethasone given once a day, can be useful in reducing inflammation that causes pain, while also elevating mood, energy, and appetite. Its main side effects include confusion, sleep difficulties, and fluid retention. Glucocorticoids are especially effective for bone pain and abdominal pain from distention of the GI tract or liver. Other drugs, including clonidine and baclofen, can be effective in providing pain relief. These drugs are adjuvants and generally should be used in conjunction with—not instead of—opioids. Methadone, carefully dosed because of its unpredictable half-life in many patients, has activity at the *N*-methyl-D-aspartamate (NMDA) receptor and is useful for complex pain syndromes and neuropathic pain. It is generally reserved for cases in which first-line opioids (morphine, oxycodone, hydromorphone) are either ineffective or unavailable.

Radiation therapy can treat bone pain from single metastatic lesions. Bone pain from multiple metastases can be amenable to radiopharmaceuticals such as strontium 89 and samarium 153. Bisphosphonates, such as pamidronate (90 mg every 4 weeks) and calcitonin (200 IU intranasally once or twice a day), also provide relief from bone pain, but have multi-day onsets of action.

Constipation • **FREQUENCY** Constipation is reported in up to 70–100% of patients requiring palliative care.

ETIOLOGY Although hypercalcemia and other factors can cause constipation, it is most frequently a predictable consequence of the use of opioids for pain and dyspnea relief, and of the anticholinergic effects of tricyclic anti-depressants, as well as due to the inactivity and poor diets common among seriously ill patients. If left untreated, constipation can cause substantial pain and vomiting, and also is associated with confusion and delirium. Whenever opioids and other medications known to cause constipation are used, preemptive treatment for constipation should be instituted.

ASSESSMENT Assessing constipation can be difficult, because people describe it differently. Four commonly used assessment scales are the Bristol Stool Form Scale, the Constipation Assessment Scale, the Constipation Visual Analogue Scale, and the Eton Scale Risk Assessment for Constipation. The Bowel Function Index can be used to quantify opioid induced constipation. The physician should establish the patient's previous bowel habits, as well as any changes in subjective and objective qualities such as bloating or decreased frequency. Abdominal and rectal examinations should be performed to exclude impaction or an acute abdomen. Radiographic assessments beyond a simple flat plate of the abdomen in cases in which obstruction is suspected are rarely necessary.

INTERVENTION Any measure to address constipation during end-of-life care should include interventions to reestablish comfortable bowel habits and to relieve pain or discomfort. Although physical activity, adequate hydration, and dietary treatments with fiber can be helpful, each is limited in its effectiveness for most seriously ill patients, and fiber may exacerbate problems in the setting of dehydration or if impaired motility is the etiology. Fiber is contraindicated in the presence of opioid use. Stimulant and osmotic laxatives, stool softeners, fluids, and enemas are the mainstays of therapy (Table 9-5). To prevent constipation from opioids and other medications, a combination of a laxative and a stool softener (such as senna and docusate) should be used. If after several days of treatment a bowel movement has not occurred, a rectal examination to remove impacted stool and place a suppository is necessary. For patients with impending bowel obstruction or gastric stasis, octreotide to reduce secretions can be helpful. For patients in whom the suspected mechanism is dysmotility, metoclopramide can be helpful.

TABLE 9-5 Medications for the Management of Constipation

INTERVENTION	DOSE	COMMENT
Stimulant laxatives		These agents directly stimulate peristalsis and may reduce colonic absorption of water.
Prune juice	120–240 mL/d	Work in 6–12 h.
Senna (Senokot)	2–8 tablets PO bid	
Bisacodyl	5–15 mg/d PO, PR	
Osmotic laxatives		These agents are not absorbed. They attract and retain water in the gastrointestinal tract.
Lactulose	15–30 mL PO q4–8h	Lactulose may cause flatulence and bloating.
Magnesium hydroxide (Milk of Magnesia)	15–30 mL/d PO	Lactulose works in 1 day, magnesium products in 6 h.
Magnesium citrate	125–250 mL/d PO	
Stool softeners		These agents work by increasing water secretion and as detergents, increasing water penetration into the stool.
Sodium docusate (Colace)	300–600 mg/d PO	Work in 1–3 days.
Calcium docusate	300–600 mg/d PO	
Suppositories and enemas		
Bisacodyl	10–15 PR qd	
Sodium phosphate enema	PR qd	Fixed dose, 4.5 oz, Fleet's.

Nausea • **FREQUENCY** Up to 70% of patients with advanced cancer have nausea, defined as the subjective sensation of wanting to vomit.

ETIOLOGY Nausea and vomiting are both caused by stimulation at one of four sites: the GI tract, the vestibular system, the chemoreceptor trigger zone (CTZ), and the cerebral cortex. Medical treatments for nausea are aimed at receptors at each of these sites: The GI tract contains mechanoreceptors, chemoreceptors, and 5-hydroxytryptamine type 3 (5-HT3) receptors; the vestibular system probably contains histamine and acetylcholine receptors; and the CTZ contains chemoreceptors, dopamine type 2 receptors, and 5-HT3 receptors. An example of nausea that most likely is mediated by the cortex is anticipatory nausea before a dose of chemotherapy or other noxious stimuli.

Specific causes of nausea include metabolic changes (liver failure, uremia from renal failure, hypercalcemia), bowel obstruction, constipation, infection, GERD, vestibular disease, brain metastases, medications (including antibiotics, NSAIDs, proton pump inhibitors, opioids, and chemotherapy), and radiation therapy. Anxiety can also contribute to nausea.

INTERVENTION Medical treatment of nausea is directed at the anatomic and receptor-mediated cause revealed by a careful history and physical examination. When no specific cause of nausea is identified, many advocate beginning treatment with either metoclopramide, a serotonin type 3 (5-HT3) receptor antagonist like ondansetron, granisetron, palonosetron, dolasetron, tropisetron, or ramosetron, or a dopamine antagonist such as chlorpromazine, haloperidol or prochlorperazine. When decreased motility is suspected, metoclopramide can be an effective treatment. When inflammation of the GI tract is suspected, glucocorticoids, such as dexamethasone, are an appropriate treatment. For nausea that follows chemotherapy and radiation therapy, one of the 5-HT3 receptor antagonists or neurokinin-1 antagonists, such as aprepitant or fosaprepitant, is recommended. Clinicians should attempt prevention of post-chemotherapy nausea, rather than simply providing treatment after the fact. Current clinical guidelines recommend tailoring the strength of treatments to the specific emetic risk posed by a specific chemotherapy drug. When a vestibular cause (such as "motion sickness" or labyrinthitis) is suspected, antihistamines, such as meclizine (whose primary side effect is drowsiness), or anticholinergics, such as scopolamine, can be effective. In anticipatory nausea, patients can benefit from non-pharmacological interventions, such as biofeedback and hypnosis. The most common pharmacological intervention for anticipatory nausea is a benzodiazepine, such as lorazepam. As with antihistamines, drowsiness and confusion are the main side effects.

The use of medical marijuana or oral cannabinoids for palliative treatment of nausea is controversial, as there are no controlled trials showing its effectiveness for patients at the end of life. A 2015 meta-analysis showed "low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy," and such treatments are not as good as 5-HT3 receptor antagonists and can sometimes even cause cannabis hyperemesis syndrome. Older patients—the vast majority of dying patients— seem to tolerate cannabinoids poorly.

Dyspnea • **FREQUENCY** Dyspnea is the subjective experience of being short of breath. Over 50%, and as many as 75%, of dying patients, especially those with lung cancer, congestive heart failure and COPD, experience dyspnea at some point near the end of life. Dyspnea is among the most distressing of physical symptoms and can be even more distressing than pain.

ASSESSMENT As with pain, dyspnea is a subjective experience that may not correlate with objective measures of P_{O2}, P_{CO2}, or respiratory rate. Consequently, measurements of oxygen saturation through

pulse oximetry or blood gases are rarely helpful in guiding therapy. Despite the limitations of existing assessment methods, physicians should regularly assess and document patients' experience of dyspnea and its intensity. Guidelines recommend visual analogue dyspnea scales to assess the severity of symptoms and the effects of treatment. Potentially reversible or treatable causes of dyspnea include infection, pleural effusions, pulmonary emboli, pulmonary edema, asthma, and tumor encroachment on the airway. However, the risk-versus-benefit ratio of the diagnostic and therapeutic interventions for patients with little time left to live must be considered carefully before undertaking diagnostic steps. Frequently, the specific etiology cannot be identified, and dyspnea is the consequence of progression of the underlying disease that cannot be treated. The anxiety caused by dyspnea and the choking sensation can significantly exacerbate the underlying dyspnea in a negatively reinforcing cycle.

INTERVENTIONS When reversible or treatable etiologies are diagnosed, they should be treated as long as the side effects of treatment, such as repeated drainage of effusions or anticoagulants, are less burdensome than the dyspnea itself. More aggressive treatments such as stenting a bronchial lesion may be warranted if it is clear that the dyspnea is due to tumor invasion at that site and if the patient and family understand the risks of such a procedure.

Usually, treatment will be symptomatic **(Table 9-6)**. Supplemental oxygen does not appear to be effective. "A systematic review of the literature failed to demonstrate a consistent beneficial effect of oxygen inhalation over air inhalation for study participants with dyspnea due to end-stage cancer or cardiac failure." Therefore, oxygen may be no more than an expensive placebo. Low-dose opioids reduce the sensitivity of the central respiratory center and relieve the sensation of dyspnea. If patients are not receiving opioids, weak opioids can be initiated; if patients are already receiving opioids, morphine or other stronger opioids should be used. Controlled trials do not support the use of nebulized opioids for dyspnea at the end of life. Phenothiazines and chlorpromazine may be helpful when combined with opioids. Benzodiazepines can be helpful in treating dyspnea, but only if anxiety is present. Benzodiazepines should neither be used as first-line therapy nor if there is no anxiety. If the patient has a history of COPD or asthma, inhaled bronchodilators and glucocorticoids may be helpful. If the patient has pulmonary edema due to heart failure, diuresis with a medication such as furosemide is indicated. Excess secretions can be transdermally or intravenously dried with scopolamine. More general interventions that medical staff can perform include sitting the patient upright, removing smoke or other irritants like perfume, ensuring a supply of fresh air with sufficient humidity, and minimizing other factors that can increase anxiety.

TABLE 9-6 Medications for the Management of Dyspnea

INTERVENTION	DOSE	COMMENTS
Weak opioids		For patients with mild dyspnea
Codeine (or codeine with 325 mg acetaminophen)	30 mg PO q4h	For opioid-naïve patients
Hydrocodone	5 mg PO q4h	
Strong opioids		For opioid-naïve patients with moderate to severe dyspnea
Morphine	5–10 mg PO q4h	For patients already taking opioids for pain or other symptoms
	30–50% of baseline opioid dose q4h	
Oxycodone	5–10 mg PO q4h	
Hydromorphone	1–2 mg PO q4h	
Anxiolytics		Give a dose every hour until the patient is relaxed, then provide a dose for maintenance
Lorazepam	0.5–2.0 mg PO/SL/IV qh then q4–6h	
Clonazepam	0.25–2.0 mg PO q12h	
Midazolam	0.5 mg IV q15min	

Fatigue • FREQUENCY Fatigue is one of the most commonly reported symptoms of not only cancer treatment, but also of the palliative care of multiple sclerosis, COPD, heart failure, and HIV. More than 90% of terminally ill patients experience fatigue and/or weakness. Fatigue is frequently cited among the most distressing symptoms.

ETIOLOGY The multiple causes of fatigue in the terminally ill can be categorized as resulting from the underlying disease; from disease-induced factors such as tumor necrosis factor and other cytokines; and from secondary factors such as dehydration, anemia, infection, hypothyroidism, and drug side effects. In addition to low caloric intake, loss of muscle mass and changes in muscle enzymes may play an important role in fatigue during terminal illness. The importance of changes in the CNS, especially the reticular activating system, have been hypothesized based on reports of fatigue in patients receiving cranial radiation, experiencing depression, or having chronic pain in the absence of cachexia or other physiologic changes. Finally, depression and other causes of psychological distress can contribute to fatigue.

ASSESSMENT Like pain and dyspnea, fatigue is subjective, as it represents a patient's sense of tiredness and decreased capacity for physical work. Objective changes, even in body mass, may be absent. Consequently, assessment must rely on patient self-reporting. Scales used to measure fatigue, such as the Edmonton Functional Assessment Tool, the Fatigue Self-Report Scales, and the Rhoten Fatigue Scale, are usually appropriate for research, but not clinical purposes. In clinical practice, a simple performance assessment such as the Karnofsky Performance Status or the Eastern Cooperative Oncology Group's question "How much of the day does the patient spend in bed?" may be the best measure. In this 0–4 performance status assessment, 0 = normal activity; 1 = symptomatic without being bedridden; 2 = requiring some, but <50%, bed time; 3 = bedbound more than half the day; and 4 = bedbound all the time. Such a scale allows for assessment over time and correlates with overall disease severity and prognosis. A 2008 review by the European Association of Palliative Care also described several longer assessment tools that contained 9–20 items, including the Piper Fatigue Inventory, the Multidimensional Fatigue Inventory, and the Brief Fatigue Inventory (BFI).

INTERVENTIONS Reversible causes of fatigue, such as anemia and infection, should be treated. However, at the end of life, it must be realistically acknowledged that fatigue will not be "cured." The goal is to ameliorate fatigue and help patients and families adjust expectations. Behavioral interventions should be utilized to avoid blaming the patient for inactivity and to educate both the family and the patient that the underlying disease causes physiologic changes that produce low energy levels. Understanding that the problem is physiologic and not psychological can help alter expectations regarding the patient's level of physical activity. Practically, this may mean reducing routine activities such as housework, cooking, and social events outside the house, and making it acceptable to receive guests while lying on a couch. At the same time, the implementation of exercise regimens and physical therapy can raise endorphins, reduce muscle wasting, and decrease the risk of depression. In addition, ensuring good hydration without worsening edema may help reduce fatigue. Discontinuing medications that worsen fatigue may help, including cardiac medications, benzodiazepines, certain antidepressants, or opioids if the pain is well-controlled. As end-of-life care proceeds into its final stages, fatigue may protect patients from further suffering, and continued treatment could be detrimental.

Only a few pharmacologic interventions target fatigue and weakness. Randomized controlled trials suggest glucocorticoids can increase energy and enhance mood. Dexamethasone (8 mg per d) is preferred for its once-a-day dosing and minimal mineralocorticoid activity. Benefit, if any, is usually seen within the first month. For fatigue related to anorexia, megestrol (480–800 mg) can be helpful. Psychostimulants

such as dextroamphetamine (5–10 mg PO) and methylphenidate (2.5–5 mg PO) may enhance energy levels, although controlled trials have not shown these drugs to be effective for fatigue induced by mild to moderate cancer. Doses should be given in the morning and at noon to minimize the risk of counterproductive insomnia. Modafinil and armodafinil, developed for narcolepsy, have shown promise in the treatment of fatigue and have the advantage of once-daily dosing. Their precise role in fatigue at the end of life has not been documented, but may be worth trying if other interventions are not beneficial. Anecdotal evidence suggests that L-carnitine may improve fatigue, depression, and sleep disruption.

PALLIATIVE SEDATION

When patients experience severe symptoms, such as pain or dyspnea, that cannot be relieved by conventional interventions or experience acute catastrophic symptoms, such as uncontrolled seizures, then palliative sedation should be considered as an intervention of last resort. Palliative sedation is used in distressing situations that cannot be addressed in other ways. It can be abused if done to hasten death (which it usually does not), when at the request of the family, rather than the patient's wishes, or when there are other interventions that could still be tried. The use of palliative sedation in cases of extreme existential or spiritual distress remains controversial. Typically, palliative sedation should be introduced only after the patient and family have been assured that all other interventions have been tried, and after the patient and their loved ones have been able to "say goodbye."

Palliative sedation can be achieved by significantly increasing opioid doses until patients become unconscious, then putting them on a continuous infusion. Another commonly used medication for palliative sedation is midazolam at 1–5 mg IV every 5–15 min to calm the patient, followed by a continuous IV or subcutaneous infusion of 1 mg per h. In hospital settings, a continuous propofol infusion of 5 μg/kg per min can be used. There are also other, less commonly used medications for palliative sedation that include levomepromazine, chlorpromazine, and phenobarbital.

PSYCHOLOGICAL SYMPTOMS AND THEIR MANAGEMENT

Depression • **FREQUENCY AND IMPACT** Depression at the end of life presents an apparently paradoxical situation. Many people believe that depression is normal among seriously ill patients, because they are dying. People frequently say, "Wouldn't you be depressed?" Although sadness, anxiety, anger, and irritability are normal responses to a serious condition, they are typically of modest intensity and transient. Persistent sadness and anxiety and the physically disabling symptoms that they can lead to are abnormal and suggestive of major depression. The precise number of terminally ill patients who are depressed is uncertain, primarily due to a lack of consistent diagnostic criteria and screening. Careful follow-up of patients suggests that while as many as 75% of terminally ill patients experience depressive symptoms, ~25% of terminally ill patients have major depression. Depression at the end of life is concerning, because it can decrease the quality of life, interfere with closure in relationships and other separation work, obstruct adherence to medical interventions, and amplify the suffering associated with pain and other symptoms.

ETIOLOGY Previous history of depression, family history of depression or bipolar disorder, and prior suicide attempts are associated with increased risk for depression among terminally ill patients. Other symptoms, such as pain and fatigue, are associated with higher rates of depression; uncontrolled pain can exacerbate depression, and depression can cause patients to be more distressed by pain. Many medications used in the terminal stages, including glucocorticoids, and some anticancer agents, such as tamoxifen, interleukin 2, interferon α, and vincristine, also are associated with depression. Some terminal conditions, such as pancreatic cancer, certain strokes, and heart failure, have been reported to be associated with higher rates of depression, although this is controversial. Finally, depression may be attributable to grief over the loss of a role or function, social isolation, or loneliness.

ASSESSMENT Unfortunately, most studies suggest that depressed patients at the end of life are neither diagnosed, nor even properly treated if diagnosed. Diagnosing depression among seriously ill patients is complicated, as many of the vegetative symptoms in the DSM-V (*Diagnostic and Statistical Manual of Mental Disorders*) criteria for clinical depression—insomnia, anorexia and weight loss, fatigue, decreased libido, and difficulty concentrating—are associated with the process of dying itself. The assessment of depression in seriously ill patients therefore should focus on the dysphoric mood, helplessness, hopelessness, and lack of interest, enjoyment, and concentration in normal activities. It is now recommended that patients near the end of life should be screened either with the Patient Health Questionnarie-9 (PHQ-9) or the PHQ-2 which asks "Over the past two weeks, how often have you been bothered by any of the following problems? (1) Little interest or pleasure in doing things and (2) feeling down, depressed or hopeless." The answer categories are: Not at all, Several days, More than half the days, Nearly every day. There are other possible diagnostic tools such as the short form of the Beck Depression Index or a visual analog scale.

Certain conditions may be confused with depression. Endocrinopathies, such as hypothyroidism and Cushing's syndrome, electrolyte abnormalities, such as hypercalcemia, and akathisia, especially from dopamine-blocking antiemetics such as metoclopramide and prochlorperazine, can mimic depression and should be excluded.

INTERVENTIONS Under-treatment of depressed, terminally ill patients is common. Physicians must treat any physical symptom, such as pain, that may be causing or exacerbating depression. Fostering adaptation to the many losses that the patient is experiencing can also be helpful. Unfortunately, there are few randomized trials to guide such interventions. Thus, treatment typically follows the treatment used for non-terminally ill depressed patients.

While there are no randomized controlled trials, nonpharmacologic interventions, including group or individual psychological counseling, and behavioral therapies such as relaxation and imagery can be helpful, especially in combination with drug therapy.

Pharmacologic interventions remain at the core of therapy. The same medications are used to treat depression in terminally ill as in non-terminally ill patients. Psychostimulants may be preferred for patients with a poor prognosis, or for those with fatigue or opioid-induced somnolence. Psychostimulants are comparatively fast-acting, working within a few days instead of the weeks required for selective serotonin reuptake inhibitors (SSRIs). Dextroamphetamine or methylphenidate should be started at 2.5–5.0 mg in the morning and at noon, the same starting doses used for treating fatigue. The doses can eventually be escalated up to 15 mg bid. Modafinil is started at 100 mg qd and can be increased to 200 mg if there is no effect at the lower dose. Pemoline is a nonamphetamine psychostimulant with minimal abuse potential. It is also effective as an antidepressant beginning at 18.75 mg in the morning and at noon. Because it can be absorbed through the buccal mucosa, it is preferred for patients with intestinal obstruction or dysphagia. If it is used for prolonged periods, liver function must be monitored. The psychostimulants can also be combined with more traditional antidepressants while waiting for the antidepressants to become effective, then tapered down after a few weeks if necessary. Psychostimulants have side effects, particularly initial anxiety, insomnia, and very rarely paranoia, which may necessitate lowering the dose or discontinuing treatment.

Mirtazapine, an antagonist at the postsynaptic serotonin receptors, is a promising psychostimulant. It should be started at 7.5 mg before bed and titrated up no more than once every 1–2 weeks to a maximal dose of 45 mg per d. It has sedating, antiemetic, and anxiolytic properties, with few drug interactions. Its side effect of weight gain may be beneficial for seriously ill patients; it is available in orally disintegrating tablets.

For patients with a prognosis of several months or longer, SSRIs, including fluoxetine, sertraline, paroxetine, escitalopram, and citalopram, and serotonin-noradrenaline reuptake inhibitors, such as venlafaxine and duloxetine, are the preferred treatments, due to their

efficacy and comparatively few side effects. Because low doses of these medications may be effective for seriously ill patients, one should use half the usual starting dose as for healthy adults. The starting dose for fluoxetine is 10 mg once a day. In most cases, once-a-day dosing is possible. The choice of which SSRI to use should be driven by (1) the patient's past success or failure with the specific medication and (2) the most favorable side-effect profile for that specific agent. For instance, for a patient in whom fatigue is a major symptom, a more activating SSRI (fluoxetine) would be appropriate. For a patient in whom anxiety and sleeplessness are major symptoms, a more sedating SSRI (paroxetine) would be appropriate. Importantly, it can take up to 4 weeks for these drugs to have an effect.

Atypical antidepressants are recommended only in select circumstances, usually with the assistance of a specialty consultation. Trazodone can be an effective antidepressant, but is sedating and can cause orthostatic hypotension and, occasionally, priapism. Therefore, it should be used before bed and only when a sedating effect is desired, and is often used for patients with insomnia, at a dose starting at 25 mg. Bupropion can also be used. In addition to its antidepressant effects, bupropion is energizing, making it useful for depressed patients who experience fatigue. However, it can cause seizures, preventing its use for patients with a risk of CNS neoplasms or terminal delirium. Finally, alprazolam, a benzodiazepine, starting at 0.25–1.0 mg tid, can be effective in seriously ill patients who have a combination of anxiety and depression. Although it is potent and works quickly, it has many drug interactions and may cause delirium, especially among very ill patients, because of its strong binding to the benzodiazepine–γ-aminobutyric acid (GABA) receptor complex.

Unless used as adjuvants for the treatment of pain, tricyclic antidepressants are not recommended. While they can be effective, their therapeutic window and serious side effects typically limit their utility. Similarly, monoamine oxidase (MAO) inhibitors are not recommended because of their side effects and dangerous drug interactions.

Delirium **(See Chap. 24)** • **FREQUENCY** In the weeks or months before death, delirium is uncommon, although it may be significantly underdiagnosed. However, delirium becomes relatively common in the days and hours immediately before death. Up to 85% of patients dying from cancer may experience terminal delirium.

ETIOLOGY Delirium is a global cerebral dysfunction characterized by alterations in cognition and consciousness. It is frequently preceded by anxiety, changes in sleep patterns (especially reversal of day and night), and decreased attention. In contrast to dementia, delirium has an acute onset, is characterized by fluctuating consciousness and inattention, and is reversible, although reversibility may be more theoretical than real for patients near death. Delirium may occur in a patient with dementia; indeed, patients with dementia are more vulnerable to delirium.

Causes of delirium include metabolic encephalopathy arising from liver or renal failure, hypoxemia, or infection; electrolyte imbalances such as hypercalcemia; paraneoplastic syndromes; dehydration; and primary brain tumors, brain metastases, or leptomeningeal spread of tumor. Among dying patients, delirium is commonly caused by side effects of treatments, including radiation for brain metastases and medications, such as opioids, glucocorticoids, anticholinergic drugs, antihistamines, antiemetics, benzodiazepines, and chemotherapeutic agents. The etiology may be multifactorial; e.g., dehydration may exacerbate opioid-induced delirium.

ASSESSMENT Delirium should be recognized in any terminally ill patient exhibiting new onset of disorientation, impaired cognition, somnolence, fluctuating levels of consciousness, or delusions with or without agitation. Delirium must be distinguished from acute anxiety, depression, and dementia. The central distinguishing feature is altered consciousness, which usually is not noted in anxiety, depression, or dementia. Although "hyperactive" delirium, characterized by overt confusion and agitation, is probably more common, patients should also be assessed for "hypoactive" delirium, which is characterized by sleep-wake reversal and decreased alertness.

In some cases, use of formal assessment tools such as the Mini-Mental Status Examination (which does not distinguish delirium from dementia) and the Delirium Rating Scale (which does distinguish delirium from dementia) may be helpful in distinguishing delirium from other processes. The patient's list of medications must be evaluated carefully. Nonetheless, a reversible etiologic factor for delirium is found in fewer than half of all terminally ill patients. Given that most terminally ill patients experiencing delirium are very close to death and often at home, extensive diagnostic evaluations such as lumbar punctures and neuroradiologic examinations are inappropriate.

INTERVENTIONS One of the most important objectives of terminal care is to provide terminally ill patients the lucidity to say goodbye to the people they love. Delirium, especially when in combination with agitation during the final days, is distressing to family and caregivers. A strong determinant of bereavement difficulties is witnessing a difficult death. Thus, terminal delirium should be treated aggressively.

At the first sign of delirium, such as day-night reversal with slight changes in mentation, the physician should let the family members know that it is time to be sure that everything they want to say has been said. The family should be informed that delirium is common just before death.

If medications are suspected of being a cause of the delirium, unnecessary agents should be discontinued. Other potentially reversible causes, such as constipation, urinary retention, and metabolic abnormalities, should be treated. Supportive measures aimed at providing a familiar environment should be instituted, including restricting visits only to individuals with whom the patient is familiar and eliminating new experiences; orienting the patient, if possible, by providing a clock and calendar; and gently correcting the patient's hallucinations or cognitive mistakes.

Pharmacologic management focuses on the use of neuroleptics and, in extreme cases, anesthetics **(Table 9-7)**. Haloperidol remains the first-line therapy. Usually, patients can be controlled with a low dose (1–3 mg/d), given every 6 h, although some may require as much as 20 mg/d. Haloperidol can be administered PO, SC, or IV. IM injections should not be used, except when this is the only way to address a patient's delirium. Olanzapine, an atypical neuroleptic, has shown significant effectiveness in completely resolving delirium in cancer patients. It also has other beneficial effects for terminally ill patients, including anti-nausea, antianxiety, and weight gain. Olanzapine is useful for patients with longer anticipated life expectancies, because it is less likely to cause dysphoria and has a lower risk of dystonic reactions. Additionally, because olanzapine is metabolized through multiple pathways, it can be used in patients with hepatic and renal dysfunction. Olanzapine has the disadvantage that it is only available orally and takes a week to reach steady state. The usual dose is 2.5–5 mg PO bid. Chlorpromazine (10–25 mg every 4–6 h) can be useful if sedation is desired and can be administered IV or PR in addition to PO. Dystonic reactions resulting from dopamine blockade are a side effect of neuroleptics, although they are reported to be rare when these

TABLE 9-7 Medications for the Management of Delirium

INTERVENTIONS	DOSE
Neuroleptics	
Haloperidol	0.5–5 mg q2–12h, PO/IV/SC/IM
Thioridazine	10–75 mg q4–8h, PO
Chlorpromazine	12.5–50 mg q4–12h, PO/IV/IM
Atypical neuroleptics	
Olanzapine	2.5–5 mg qd or bid, PO
Risperidone	1–3 mg q12h, PO
Anxiolytics	
Lorazepam	0.5–2 mg q1–4h, PO/IV/IM
Midazolam	1–5 mg/h continuous infusion, IV/SC
Anesthetics	
Propofol	0.3–2.0 mg/h continuous infusion, IV

drugs are used to treat terminal delirium. If patients develop dystonic reactions, benztropine should be administered. Neuroleptics may be combined with lorazepam to reduce agitation when the delirium is the result of alcohol or sedative withdrawal.

If no response to first-line therapy is observed, a specialty consultation should be obtained with a goal to change to a different medication. If the patient fails to improve after a second neuroleptic, sedation with either an anesthetic such as propofol or continuous-infusion midazolam may be necessary. By some estimates, as many as 25% of patients at the very end of life who experience delirium, especially restless delirium with myoclonus or convulsions, may require sedation.

Physical restraints should be used with great reluctance and only when the patient's violence is threatening to himself or others. If restraints are used, their appropriateness should be frequently reevaluated.

Insomnia • **FREQUENCY** Sleep disorders, defined as difficulty initiating sleep or maintaining sleep, sleep difficulty at least 3 nights a week, or sleep difficulty that causes impairment of daytime functioning, occurs in 19–63% of patients with advanced cancer. Some 30–74% of patients with other end-stage conditions, including AIDS, heart disease, COPD, and renal disease, experience insomnia.

ETIOLOGY Patients with cancer may experience changes in sleep efficiency, such as an increase in stage I sleep. Insomnia may also coexist with both physical illnesses, like thyroid disease, and psychological illnesses, like depression and anxiety. Medications, including antidepressants, psychostimulants, steroids, and β agonists, are significant contributors to sleep disorders, as are caffeine and alcohol. Multiple over-the-counter medications contain caffeine and antihistamines, which can contribute to sleep disorders.

ASSESSMENT Assessments should include specific questions concerning sleep onset, sleep maintenance, and early-morning wakening, as these will provide clues to both the causative agents and management of insomnia. Patients should be asked about previous sleep problems, screened for depression and anxiety, and asked about symptoms of thyroid disease. Caffeine and alcohol are prominent causes of sleep problems, and a careful history of the use of these substances should be obtained. Both excessive use and withdrawal from alcohol can be causes of sleep problems.

INTERVENTIONS The mainstays of any intervention include improvement of sleep hygiene (encouragement of regular time for sleep, decreased nighttime distractions, elimination of caffeine and other stimulants and alcohol), interventions to treat anxiety and depression, and treatment for the insomnia itself. For patients with depression who have insomnia and anxiety, a sedating antidepressant such as mirtazapine can be helpful. In the elderly, trazodone, beginning at 25 mg at nighttime, is an effective sleep aid at doses lower than those which cause its antidepressant effect. Zolpidem may have a decreased incidence of delirium in patients compared with traditional benzodiazepines, but this has not been clearly established. When benzodiazepines are prescribed, short-acting ones (such as lorazepam) are favored over longer-acting ones (such as diazepam). Patients who receive these medications should be observed for signs of increased confusion and delirium.

SOCIAL NEEDS AND THEIR MANAGEMENT

Financial Burdens • **FREQUENCY** Dying can impose substantial economic strains on patients and families, potentially causing distress. In the United States, which has one of the least comprehensive health insurance systems among developed countries, a quarter of families coping with end-stage cancer report that care was a major financial burden and a third used up most of their savings. Among Medicare beneficiaries, average out-of-pocket costs were >$8,000. Between 10 and 30% of families are forced to sell assets, use savings, or take out a mortgage to pay for the patient's health care costs.

The patient is likely to reduce hours worked, and eventually stop working altogether. In 20% of cases, a family member of the terminally ill patient also must stop working to provide care. The major underlying causes of economic burden are related to poor physical functioning and care needs, such as the need for housekeeping, nursing, and personal care. More debilitated patients and poor patients experience greater economic burdens.

INTERVENTION The economic burden of end-of-life care should not be ignored as a private matter. It has been associated with a number of adverse health outcomes, including preferring comfort care over life-prolonging care, as well as consideration of euthanasia or physician-assisted suicide (PAS). Economic burdens increase the psychological distress of the families and caregivers of terminally ill patients, and poverty is associated with many adverse health outcomes. Importantly, recent studies have found that "patients with advanced cancer who reported having end-of-life conversations with physicians had significantly lower health care costs in their final week of life. Higher costs were associated with worse quality of death." Assistance from a social worker, early on if possible, to ensure access to all available benefits may be helpful. Many patients, families, and health care providers are unaware of options for long-term care insurance, respite care, the Family Medical Leave Act (FMLA), and other sources of assistance. Some of these options (such as respite care) may be part of a formal hospice program, but others (such as the FMLA) do not require enrollment in a hospice program.

Relationships • **FREQUENCY** Settling personal issues and closing the narrative of lived relationships are universal needs. When asked if sudden death or death after an illness is preferable, respondents often initially select the former, but soon change to the latter as they reflect on the importance of saying goodbye. Bereaved family members who have not had the chance to say goodbye often have a more difficult grief process.

INTERVENTIONS Care of seriously ill patients requires efforts to facilitate the types of encounters and time spent with family and friends that are necessary to meet those needs. Family and close friends may need to be accommodated in hospitals and other facilities with unrestricted visiting hours, which may include sleeping near the patient, even in otherwise regimented institutional settings. Physicians and other health care providers may be able to facilitate and resolve strained interactions between the patient and other family members. Assistance for patients and family members who are unsure about how to create or help preserve memories, whether by providing materials such as a scrapbook or memory box, or by offering them suggestions and informational resources, can be deeply appreciated. Taking photographs and creating videos can be especially helpful to terminally ill patients who have younger children or grandchildren.

Family Caregivers • **FREQUENCY** Caring for seriously ill patients places a heavy burden on families. Families are frequently required to provide transportation and homemaking, as well as other services. Typically, paid professionals, such as home health nurses and hospice workers, supplement family care; only about a quarter of all caregiving consists of exclusively paid professional assistance. Over the last 40 years, there has been a significant decline in the United States of deaths occurring in hospitals, with a simultaneous increase in deaths in other facilities and at home. Over a third of deaths occur in patients' home. This increase in out-of-hospital deaths increases reliance on families for end-of-life care. Increasingly, family members are being called upon to provide physical care (such as moving and bathing patients) and medical care (such as assessing symptoms and giving medications) in addition to emotional care and support.

Three-quarters of family caregivers of terminally ill patients are women—wives, daughters, sisters, and even daughters-in-law. Since many are widowed, women tend to be able to rely less on family for caregiving assistance and may need more paid assistance. About 20% of terminally ill patients report substantial unmet needs for nursing and personal care. The impact of caregiving on family caregivers is substantial: both bereaved and current caregivers have a higher mortality rate than that of non-caregiving controls.

INTERVENTIONS It is imperative to inquire about unmet needs and to try to ensure that those needs are met either through the family or

by paid professional services when possible. Community assistance through houses of worship or other community groups often can be mobilized by telephone calls from the medical team to someone the patient or family identifies. Sources of support specifically for family caregivers should be identified through local sources or nationally through groups such as the National Family Caregivers Association (*www.nfcacares.org*), the American Cancer Society (*www.cancer.org*), and the Alzheimer's Association (*www.alz.org*).

EXISTENTIAL NEEDS AND THEIR MANAGEMENT

Frequency Religion and spirituality are often important to dying patients. Nearly 70% of patients report becoming more religious or spiritual when they became terminally ill, and many find comfort in religious or spiritual practices such as prayer. However, ~20% of terminally ill patients become less religious, frequently feeling cheated or betrayed by becoming terminally ill. For other patients, the need is for existential meaning and purpose that is distinct from, and may even be antithetical to, religion or spirituality. When asked, patients and family caregivers frequently report wanting their professional caregivers to be more attentive to religion and spirituality.

ASSESSMENT Health care providers are often hesitant about involving themselves in the religious, spiritual, and existential experiences of their patients because it may seem private or not relevant to the current illness. But physicians and other members of the care team should be able at least to detect spiritual and existential needs. Screening questions have been developed for a physician's spiritual history taking. Spiritual distress can amplify other types of suffering and even masquerade as intractable physical pain, anxiety, or depression. The screening questions in the comprehensive assessment are usually sufficient. Deeper evaluation and intervention are rarely appropriate for the physician unless no other member of a care team is available or suitable. Pastoral care providers may be helpful, whether from the medical institution or from the patient's own community.

INTERVENTIONS Precisely how religious practices, spirituality, and existential explorations can be facilitated and improve end-of-life care is not well established. What is clear is that for physicians, one main intervention is to inquire about the role and importance of spirituality and religion in a patient's life. This will help a patient feel heard and help physicians identify specific needs. In one study, only 36% of respondents indicated that a clergy member would be comforting. Nevertheless, the increase in religious and spiritual interest among a substantial fraction of dying patients suggests inquiring of individual patients how this need can be addressed. Some evidence supports specific methods of addressing existential needs in patients, ranging from establishing a supportive group environment for terminal patients to individual treatments emphasizing a patient's dignity and sources of meaning.

MANAGING THE LAST STAGES

PALLIATIVE CARE SERVICES: HOW AND WHERE

Determining the best approach to providing palliative care to patients will depend on patient preferences, the availability of caregivers and specialized services in close proximity, institutional resources, and reimbursement. Hospice is a leading, but not the only, model of palliative care services. In the United States, slightly more than a third—35.7%—of hospice care is provided in private residential homes. In 2014, 14.5% of hospice care was provided in nursing homes. In the United States, Medicare pays for hospice services under Part A, the hospital insurance part of reimbursement. Two physicians must certify that the patient has a prognosis of ≤6 months if the disease runs its usual course. Prognoses are probabilistic by their nature; patients are not required to die within 6 months but rather to have a condition from which half the individuals with it would not be alive within 6 months. Patients sign a hospice enrollment form that states their intent to forgo curative services related to their terminal illness, but can still receive medical services for other comorbid conditions. Patients also can withdraw enrollment and reenroll later; the hospice Medicare benefit can be revoked later to secure traditional Medicare benefits. Payments to the hospice are per diem (or capitated), not fee-for-service. Payments are intended to cover physician services for the medical direction of the care team; regular home care visits by registered nurses and licensed practical nurses; home health aide and homemaker services; chaplain services; social work services; bereavement counseling; and medical equipment, supplies, and medications. No specific therapy is excluded, and the goal is for each therapy to be considered for its symptomatic (as opposed to disease-modifying) effect. Additional clinical care, including services of the primary physician, is covered by Medicare Part B even while the hospice Medicare benefit is in place.

The Affordable Care Act directs the Secretary of Health and Human Services to gather data on Medicare hospice reimbursement with the goal of reforming payment rates to account for resource use over an entire episode of care. The legislation also requires additional evaluations and reviews of eligibility for hospice care by hospice physicians or nurses. Finally, the Center for Medicare and Medicaid Innovation (CMMI) is testing concurrent hospice and palliative care services with curative treatment with ~120 providers.

By 2014, the mean length of enrollment in a hospice was 71 days, with the median being 17 days. Such short stays create barriers to establishing high-quality palliative services in patients' homes and also place financial strains on hospice providers since the initial assessments are resource intensive. Physicians should initiate early referrals to the hospice to allow more time for patients to receive palliative care.

In the United States, hospice care has been the main method for securing palliative services for terminally ill patients. However, as leading physicians have increasingly emphasized the need to introduce palliative care much earlier in patients' illness, efforts are being made to develop palliative care services that can be provided before the last 6 months of life and across a variety of settings. For instance, some companies and home health agencies are offering non-hospice palliative care services in patients' homes in an effort to increase quality of life and forestall hospitalizations. Similarly, palliative care services are increasingly available via consultation, rather than present only in hospital, day care, outpatient, and nursing home settings. Palliative care consultations for non-hospice patients can be billed as for other consultations under Medicare Part B. It is argued that using palliative care earlier in patients' illness allows patients and family members to become more acculturated to avoiding life-sustaining treatments, facilitating a smoother transition to hospice care closer to death.

WITHDRAWING AND WITHHOLDING LIFE-SUSTAINING TREATMENT

LEGAL ASPECTS For centuries, it has been deemed ethical to withhold or withdraw life-sustaining interventions. The current legal consensus in the United States and most developed countries is that patients have a moral as well as constitutional or common law right to refuse medical interventions. American courts also have held that incompetent patients have a right to refuse medical interventions. For patients who are incompetent and terminally ill and who have not completed an advance care directive, next of kin can exercise that right, although this may be restricted in some states, depending on how clear and convincing the evidence is of the patient's preferences. Courts have limited families' ability to terminate life-sustaining treatments in patients who are conscious and incompetent, but not terminally ill. In theory, patients' right to refuse medical therapy can be limited by four countervailing interests: (1) preservation of life, (2) prevention of suicide, (3) protection of third parties such as children, and (4) preservation of the integrity of the medical profession. In practice, these interests almost never override the right of competent patients and incompetent patients who have left explicit wishes or advance care directives.

For incompetent patients who either appointed a proxy without specific indications of their wishes or never completed an advance care directive, three criteria have been suggested to guide the decision to terminate medical interventions. First, some commentators suggest

that ordinary care should be administered but extraordinary care could be terminated. Because the ordinary/extraordinary distinction is too vague, courts and commentators widely agree that it should not be used to justify decisions about stopping treatment. Second, many courts have advocated the use of the substituted-judgment criterion, which holds that the proxy decision-makers should try to imagine what the incompetent patient would do if he or she were competent. However, multiple studies indicate that many proxies, even close family members, cannot accurately predict what the patient would have wanted. Therefore, substituted judgment becomes more of a guessing game than a way of fulfilling the patient's wishes. Finally, the best-interests criterion holds that proxies should evaluate treatments by balancing their benefits and risks and select those treatments in which the benefits maximally outweigh the burdens of treatment. Clinicians have a clear and crucial role in this by carefully and dispassionately explaining the known benefits and burdens of specific treatments. Yet even when that information is as clear as possible, different individuals can have very different views of what is in the patient's best interests, and families may have disagreements or even overt conflicts. This criterion has been criticized because there is no single way to determine the balance between benefits and burdens; it depends on a patient's personal values. For instance, for some people being alive even if mentally incapacitated is a benefit, whereas for others it may be the worst possible existence. As a matter of practice, physicians rely on family members to make decisions that they feel are best and object only if those decisions seem to demand treatments that the physicians consider not beneficial.

PRACTICES Withholding and withdrawing acutely life-sustaining medical interventions from terminally ill patients are now standard practice. More than 90% of American patients die without cardiopulmonary resuscitation (CPR), and just as many forgo other potentially life-sustaining interventions. For instance, in ICUs in the period 1987–1988, CPR was performed 49% of the time, but it was performed only 10% of the time in 1992–1993 and on just 1.8% of admissions from 2001 to 2008. On average, 3.8 interventions, such as vasopressors and transfusions, were stopped for each dying ICU patient. However, up to 19% of decedents in hospitals received interventions such as extubation, ventilation, and surgery in the 48 h preceding death. There is wide variation in practices among hospitals and ICUs, suggesting an important element of physician preferences rather than consistent adherence to professional society recommendations.

Mechanical ventilation may be the most challenging intervention to withdraw. The two approaches are *terminal extubation*, which is the removal of the endotracheal tube, and *terminal weaning*, which is the gradual reduction of the FIo_2 or ventilator rate. One-third of ICU physicians prefer to use the terminal weaning technique, and 13% extubate; the majority of physicians utilize both techniques. The American Thoracic Society's 2008 clinical policy guidelines note that there is no single correct process of ventilator withdrawal and that physicians use and should be proficient in both methods but that the chosen approach should carefully balance benefits and burdens as well as patient and caregiver preferences. Some recommend terminal weaning because patients do not develop upper airway obstruction and the distress caused by secretions or stridor; however, terminal weaning can prolong the dying process and not allow a patient's family to be with the patient unencumbered by an endotracheal tube. To ensure comfort for conscious or semiconscious patients before withdrawal of the ventilator, neuromuscular blocking agents should be terminated and sedatives and analgesics administered. Removing the neuromuscular blocking agents permits patients to show discomfort, facilitating the titration of sedatives and analgesics; it also permits interactions between patients and their families. A common practice is to inject a bolus of midazolam (2–4 mg) or lorazepam (2–4 mg) before withdrawal, followed by a bolus of 5–10 mg of morphine and continuous infusion of morphine (50% of the bolus dose per hour) during weaning. In patients who have significant upper airway secretions, IV scopolamine at a rate of 100 μg/h can be administered. Additional boluses of morphine or increases in the infusion rate should be administered for respiratory distress or signs of pain. Higher doses will be needed for patients already receiving sedatives and opioids.

The median time to death after stopping of the ventilator is ~1 h. However, up to 10% of patients unexpectedly survive for 1 day or more after mechanical ventilation is stopped. Women and older patients tend to survive longer after extubation. Families need to be reassured about both the continuations of treatments for common symptoms, such as dyspnea and agitation, after withdrawal of ventilatory support and the uncertainty of length of survival after withdrawal of ventilatory support.

FUTILE CARE

Beginning in the late 1980s, some commentators argued that physicians could terminate futile treatments demanded by the families of terminally ill patients. Although no objective definition or standard of futility exists, several categories have been proposed. Physiologic futility means that an intervention will have no physiologic effect. Some have defined qualitative futility as applying to procedures that "fail to end a patient's total dependence on intensive medical care." Quantitative futility occurs "when physicians conclude (through personal experience, experiences shared with colleagues, or consideration of reported empiric data) that in the last 100 cases, a medical treatment has been useless." The term conceals subjective value judgments about when a treatment is "not beneficial." Deciding whether a treatment that obtains an additional 6 weeks of life or a 1% survival advantage confers benefit depends on patients' preferences and goals. Furthermore, physicians' predictions of when treatments are futile deviate markedly from the quantitative definition. When residents thought CPR was quantitatively futile, more than one in five patients had a >10% chance of survival to hospital discharge. Most studies that purport to guide determinations of futility are based on insufficient data and therefore cannot provide statistical confidence for clinical decision-making. Quantitative futility rarely applies in ICU settings.

Many commentators reject using futility as a criterion for withdrawing care, preferring instead to consider futility situations as ones that represent conflict that calls for careful negotiation between families and health care providers. The AMA and other professional societies have developed process-based approaches to resolving cases clinicians feel are futile. These process-based measures mainly suggest involving consultants and/or ethics committees when there are seemingly irresolvable differences. Some hospitals have enacted "unilateral DNR" policies to allow clinicians to provide a do-not-resuscitate order in cases in which consensus cannot be reached with families and medical opinion is that resuscitation would be futile if attempted. This type of a policy is not a replacement for careful and patient communication and negotiation but recognizes that agreement cannot always be reached.

In 1999 Texas enacted the so-called Futile Care Act. Other states, such as Virginia, Maryland, and California, have also enacted such laws that provide physicians a "safe harbor" from liability if they refuse a patient or family's request for life-sustaining interventions. For instance, in Texas when a disagreement about terminating interventions between the medical team and the family has not been resolved by an ethics consultation, the physician is tasked with trying to facilitate transfer of the patient to an institution willing to provide treatment. If this fails after 10 days, the hospital and physician may unilaterally withdraw treatments determined to be futile. The family may appeal to a state court. Early data suggest that the law increases futility consultations for the ethics committee and that although most families concur with withdrawal, about 10–15% of families refuse to withdraw treatment. As of 2007, there had been 974 ethics committee consultations on medical futility cases and 65 in which committees ruled against families and gave notice that treatment would be terminated. In 2007 a survey of Texas hospitals showed that 30% of hospitals had used the futility law in 213 adult cases and 42 pediatric cases. Treatment was withdrawn for 27 of those patients, and the remainder transferred to other facilities or died while awaiting transfer.

TABLE 9-8 Definitions of Physician-Assisted Suicide and Euthanasia

TERM	DEFINITION	LEGAL STATUS
Voluntary active euthanasia	Intentionally administering medications or other interventions to cause the patient's death with the patient's informed consent	Netherlands, Belgium, Luxembourg, Canada, Colombia
Involuntary active euthanasia	Intentionally administering medications or other interventions to cause the patient's death when the patient was competent to consent but did not—e.g., the patient may not have been asked	Nowhere
Passive euthanasia	Withholding or withdrawing life-sustaining medical treatments from a patient to let him or her die (terminating life-sustaining treatments)	Everywhere
Physician-assisted suicide	A physician provides medications or other interventions to a patient with the understanding that the patient can use them to commit suicide	Netherlands, Belgium, Luxembourg, Canada, Colombia, Switzerland, Oregon, Washington, Montana, Vermont, California

EUTHANASIA AND PHYSICIAN-ASSISTED SUICIDE

Euthanasia and PAS are defined in Table 9-8. Terminating life-sustaining care and providing opioid medications to manage symptoms such as pain or dyspnea have long been considered ethical by the medical profession and legal by courts and should not be conflated with euthanasia or PAS.

LEGAL ASPECTS Euthanasia and PAS are legal in the Netherlands, Belgium, Luxembourg, Colombia, and Canada. Euthanasia was legalized in the Northern Territory of Australia in 1996, but that legislation was repealed 9 months later in 1997. Under certain conditions, a layperson in Switzerland can legally elect assisted suicide. In the United States, PAS is legal in five states: Oregon, Washington State, Montana, Vermont, and California. No state in the United States has legalized euthanasia. In the United States, multiple criteria must be met for PAS: the patient must have a terminal condition of <6 months, and must be determined eligible through a process that includes a 15-day waiting period. In 2009, the state supreme court of Montana ruled that state law permits PAS for terminally ill patients. Many other countries, such as Australia, are actively debating the legalization of euthanasia and/or PAS.

PRACTICES Fewer than 10–20% of terminally ill patients actually consider euthanasia and/or PAS for themselves. Use of euthanasia and PAS is relatively rare. In all countries, even the Netherlands and Belgium where these practices have been tolerated and legal for many years, fewer than 5% of death occur by euthanasia or PAS. As of the most recent data, the share of deaths attributable to euthanasia or PAS was 2.9% in the Netherlands (2010) and 4.6% in Belgium (2013). In 2015, 0.39% of all deaths in Oregon and 0.31% of all deaths in Washington State were reported to be by PAS, although these may be underestimates.

In the Netherlands, Belgium, Oregon, and Washington >70% of patients utilizing these interventions are dying of cancer; <10% of deaths by euthanasia or PAS involve patients with AIDS or amyotrophic lateral sclerosis.

Pain is not the primary motivator for patients' requests for or interest in euthanasia and/or PAS. Among the first patients to receive PAS in Oregon, only 1 of the 15 patients had inadequate pain control, compared with 15 of the 43 patients in a control group who experienced inadequate pain relief. Only 25% of patients in Oregon seeking PAS currently cite pain or fear of pain as their main reason for doing so. Conversely, depression and hopelessness are strongly associated with patient interest in euthanasia and PAS. Concerns about loss of dignity or autonomy or being a burden on family members appear to be more important factors motivating a desire for euthanasia or PAS. Losing autonomy (91% Oregon, 90% Washington), not being able to enjoy activities (89% OR, 89% WA), or fear of losing dignity (68% OR, 76% WA) are the most cited end of life concerns in both states. Over a third of patients seeking PAS note being a burden on family (41% OR, 53% WA). A study from the Netherlands showed that depressed terminally ill cancer patients were four times more likely to request euthanasia and confirmed that uncontrolled pain was not associated with greater interest in euthanasia.

Euthanasia and PAS are no guarantee of a painless, quick death. Data from the Netherlands indicate that in as many as 20% of euthanasia and PAS cases technical and other problems arose, including patients waking from coma, not becoming comatose, regurgitating medications, and experiencing a prolonged time to death. Data from Oregon indicate that between 1998 and 2015, 53% of cases had no complications, 44% of patients had no data on complications, and 2.4% of cases had regurgitation after taking the prescribed medicine as the only complication. In addition, six patients awakened and the reported range of time to death extended to 104 h. In Washington State between 2014 and 2015, 1.4% of cases had regurgitation, 1 patient had a seizure, and the reported range of time to death extended to 30 h. In the Netherlands, problems were significantly more common in PAS, sometimes requiring the physician to intervene and provide euthanasia.

Regardless of whether they practice in a setting where euthanasia is legal or not, many physicians over the course of their careers will receive a patient request for euthanasia or PAS. In the United States, 18% of physicians have received a request for PAS and 11% have received a request for euthanasia. Three percent complied with a request for PAS, while 5% complied with a request for euthanasia. In the Netherlands, where the practices are legal, 77% of physicians have received a request for PAS or euthanasia and 60% have performed these interventions.

Competency in dealing with such a request is crucial. Although challenging, the request can also provide a chance to address intense suffering. After receiving a request for euthanasia and/or PAS, health care providers should carefully clarify the request with empathic, open-ended questions to help elucidate the underlying cause for the request, such as: "What makes you want to consider this option?" Endorsing either moral opposition or moral support for the act tends to be counterproductive, giving an impression of being judgmental or of endorsing the idea that the patient's life is worthless. Health care providers must reassure the patient of continued care and commitment. The patient should be educated about alternative, less controversial options, such as symptom management and withdrawing any unwanted treatments and the reality of euthanasia and/or PAS, since the patient may have misconceptions about their effectiveness as well as the legal implications of the choice. Depression, hopelessness, and other symptoms of psychological distress as well as physical suffering and economic burdens are likely factors motivating the request, and such factors should be assessed and treated aggressively. After these interventions and clarification of options, most patients proceed with another approach, declining life-sustaining interventions, possibly including refusal of nutrition and hydration.

CARE DURING THE LAST HOURS

Most laypersons have limited experiences with the actual dying process and death. They frequently do not know what to expect of the final hours and afterward. The family and other caregivers must be prepared, especially if the plan is for the patient to die at home.

Patients in the last days of life typically experience extreme weakness and fatigue and become bedbound; this can lead to pressure sores. The issue of turning patients who are near the end of life, however, must be balanced against the potential discomfort that movement may cause. Patients stop eating and drinking with drying of mucosal membranes and dysphagia. Careful attention to oral swabbing, lubricants for lips, and use of artificial tears can provide a form of care to substitute for attempts at feeding the patient. With loss of the gag reflex and

dysphagia, patients may also experience accumulation of oral secretions, producing noises during respiration sometimes called "the death rattle." Scopolamine can reduce the secretions. Patients also experience changes in respiration with periods of apnea or Cheyne-Stokes breathing. Decreased intravascular volume and cardiac output cause tachycardia, hypotension, peripheral coolness, and livedo reticularis (skin mottling). Patients can have urinary and, less frequently, fecal incontinence. Changes in consciousness and neurologic function generally lead to two different paths to death.

Each of these terminal changes can cause patients and families distress, requiring reassurance and targeted interventions **(Table 9-9)**. Informing families that these changes might occur and providing them with an information sheet can help preempt problems and minimize distress. Understanding that patients stop eating because they are dying, not dying because they have stopped eating, can reduce family and caregiver anxiety. Similarly, informing the family and caregivers that the "death rattle" may occur and that it is not indicative of suffocation, choking, or pain can reduce their worry from the breathing sounds.

Families and caregivers may also feel guilty about stopping treatments, fearing that they are "killing" the patient. This may lead to demands for interventions, such as feeding tubes, that may be ineffective. In such cases, the physician should remind the family and caregivers about the inevitability of events and the palliative goals. Interventions may prolong the dying process and cause discomfort. Physicians also should emphasize that withholding treatments is both legal and ethical and that the family members are not the cause of the patient's death. This reassurance may have to be provided multiple times.

Hearing and touch are said to be the last senses to stop functioning. Whether this is the case or not, families and caregivers can be encouraged to communicate with the dying patient. Encouraging them to talk directly to the patient, even if he or she is unconscious, and hold the patient's hand or demonstrate affection in other ways can be an effective way to channel their urge "to do something" for the patient.

When the plan is for the patient to die at home, the physician must inform the family and caregivers how to determine that the patient has died. The cardinal signs are cessation of cardiac function and respiration; the pupils become fixed; the body becomes cool; muscles relax; and incontinence may occur. Remind the family and caregivers that the eyes may remain open even after the patient has died.

The physician should establish a plan for who the family or caregivers will contact when the patient is dying or has died. Without a plan, family members may panic and call 911, unleashing a cascade of unwanted events, from arrival of emergency personnel and resuscitation to hospital admission. The family and caregivers should be instructed to contact the hospice (if one is involved), the covering physician, or the on-call member of the palliative care team. They should also be told that the medical examiner need not be called unless the state requires it for all deaths. Unless foul play is suspected, the health care team need not contact the medical examiner either.

Just after the patient dies, even the best-prepared family may experience shock and loss and be emotionally distraught. They need time to assimilate the event and be comforted. Health care providers are likely to find it meaningful to write a bereavement card or letter to the family. The purpose is to communicate about the patient, perhaps emphasizing the patient's virtues and the honor it was to care for the patient, and to express concern for the family's hardship. Some physicians attend the funerals of their patients. Although this is beyond any medical obligation, the presence of the physician can be a source of support to the grieving family and provides an opportunity for closure for the physician.

Death of a spouse is a strong predictor of poor health, and even mortality, for the surviving spouse. It may be important to alert the spouse's physician about the death so that he or she is aware of symptoms that might require professional attention.

TABLE 9-9 Managing Changes in the Patient's Condition during the Final Days and Hours

CHANGES IN THE PATIENT'S CONDITION	POTENTIAL COMPLICATION	FAMILY'S POSSIBLE REACTION AND CONCERN	ADVICE AND INTERVENTION
Profound fatigue	Bedbound with development of pressure ulcers that are prone to infection, malodor, and pain, and joint pain	Patient is lazy and giving up.	Reassure family and caregivers that terminal fatigue will not respond to interventions and should not be resisted. Use an air mattress if necessary.
Anorexia	None	Patient is giving up; patient will suffer from hunger and will starve to death.	Reassure family and caregivers that the patient is not eating because he or she is dying; not eating at the end of life does not cause suffering or death. Forced feeding, whether oral, parenteral, or enteral, does not reduce symptoms or prolong life.
Dehydration	Dry mucosal membranes (see below)	Patient will suffer from thirst and die of dehydration.	Reassure family and caregivers that dehydration at the end of life does not cause suffering because patients lose consciousness before any symptom distress. Intravenous hydration can worsen symptoms of dyspnea by pulmonary edema and peripheral edema as well as prolong dying process.
Dysphagia	Inability to swallow oral medications needed for palliative care		Do not force oral intake. Discontinue unnecessary medications that may have been continued, including antibiotics, diuretics, antidepressants, and laxatives. If swallowing pills is difficult, convert essential medications (analgesics, antiemetics, anxiolytics, and psychotropics) to oral solutions, buccal, sublingual, or rectal administration.
"Death rattle"—noisy breathing		Patient is choking and suffocating.	Reassure the family and caregivers that this is caused by secretions in the oropharynx and the patient is not choking. Reduce secretions with scopolamine (0.2–0.4 mg SC q4h or 1–3 patches q3d). Reposition patient to permit drainage of secretions. Do not suction. Suction can cause patient and family discomfort and is usually ineffective.

(*Continued*)

TABLE 9-9 Managing Changes in the Patient's Condition during the Final Days and Hours (Continued)

CHANGES IN THE PATIENT'S CONDITION	POTENTIAL COMPLICATION	FAMILY'S POSSIBLE REACTION AND CONCERN	ADVICE AND INTERVENTION
Apnea, Cheyne-Stokes respirations, dyspnea		Patient is suffocating.	Reassure family and caregivers that unconscious patients do not experience suffocation or air hunger. Apneic episodes are frequently a premorbid change. Opioids or anxiolytics may be used for dyspnea. Oxygen is unlikely to relieve dyspneic symptoms and may prolong the dying process.
Urinary or fecal incontinence	Skin breakdown if days until death Potential transmission of infectious agents to caregivers	Patient is dirty, malodorous, and physically repellent.	Remind family and caregivers to use universal precautions. Frequent changes of bedclothes and bedding. Use diapers, urinary catheter, or rectal tube if diarrhea or high urine output.
Agitation or delirium	Day/night reversal Hurt self or caregivers	Patient is in horrible pain and going to have a horrible death.	Reassure family and caregivers that agitation and delirium do not necessarily connote physical pain. Depending on the prognosis and goals of treatment, consider evaluating for causes of delirium and modify medications. Manage symptoms with haloperidol, chlorpromazine, diazepam, or midazolam.
Dry mucosal membranes	Cracked lips, mouth sores, and candidiasis can also cause pain. Odor	Patient may be malodorous, physically repellent.	Use baking soda mouthwash or saliva preparation q15–30 min. Use topical nystatin for candidiasis. Coat lips and nasal mucosa with petroleum jelly q60–90 min. Use ophthalmic lubricants q4h or artificial tears q30 min.

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Education in Palliative and End of Life Care (EPEC): *http://www.epec.net*
End of Life—Palliative Education Resource Center: *http://www.eperc.mcw.edu*
Family Caregiver Alliance: *http://www.caregiver.org*
The Medical Directive: *http://www.medicaldirective.org*
National Family Caregivers Association: *http://www.nfcacares.org/*
National Hospice and Palliative Care Organization (including state-specific advance directives): *http://www.nhpco.org*
NCCN: The National Comprehensive Cancer Network palliative care guidelines: *http://www.nccn.org*

Section 1 Pain

10 Pain: Pathophysiology and Management

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The province of medicine is to preserve and restore health and to relieve suffering. Understanding pain is essential to both of these goals. Because pain is universally understood as a signal of disease, it is the most common symptom that brings a patient to a physician's attention. The function of the pain sensory system is to protect the body and maintain homeostasis. It does this by detecting, localizing, and identifying potential or actual tissue-damaging processes. Because different diseases produce characteristic patterns of tissue damage, the quality, time course, and location of a patient's pain lend important diagnostic clues. It is the physician's responsibility to assess each patient promptly for any remediable cause underlying the pain and to provide rapid and effective pain relief whenever possible.

THE PAIN SENSORY SYSTEM

Pain is an unpleasant sensation localized to a part of the body. It is often described in terms of a penetrating or tissue-destructive process (e.g., stabbing, burning, twisting, tearing, squeezing) and/or of a bodily or emotional reaction (e.g., terrifying, nauseating, sickening). Furthermore, any pain of moderate or higher intensity is accompanied by anxiety and the urge to escape or terminate the feeling. These properties illustrate the duality of pain: it is both sensation and emotion. When it is acute, pain is characteristically associated with behavioral arousal and a stress response consisting of increased blood pressure, heart rate, pupil diameter, and plasma cortisol levels. In addition, local muscle contraction (e.g., limb flexion, abdominal wall rigidity) is often present.

PERIPHERAL MECHANISMS

The Primary Afferent Nociceptor A peripheral nerve consists of the axons of three different types of neurons: primary sensory afferents, motor neurons, and sympathetic postganglionic neurons (Fig. 10-1). The cell bodies of primary sensory afferents are located in the dorsal root ganglia within the vertebral foramina. The primary afferent axon has two branches: one projects centrally into the spinal cord and the other projects peripherally to innervate tissues. Primary afferents are classified by their diameter, degree of myelination, and conduction velocity. The largest diameter afferent fibers, A-beta (Aβ), respond maximally to light touch and/or moving stimuli; they are present primarily in nerves that innervate the skin. In normal individuals, the activity of these fibers does not produce pain. There are two other classes of primary afferent nerve fibers: the small diameter myelinated A-delta (Aδ) and the unmyelinated (C) axons (Fig. 10-1). These fibers are present in nerves to the skin and to deep somatic and visceral structures. Some tissues, such as the cornea, are innervated only by Aδ and C fiber afferents. Most Aδ and C fiber afferents respond maximally only to intense (painful) stimuli and produce the subjective experience of pain when they are electrically stimulated; this defines them as *primary afferent nociceptors* (*pain receptors*). The ability to detect painful stimuli is completely abolished when conduction in Aδ and C fiber axons is blocked.

Individual primary afferent nociceptors can respond to several different types of noxious stimuli. For example, most nociceptors respond to heat; intense cold; intense mechanical distortion, such as a pinch; changes in pH, particularly an acidic environment; and application of chemical irritants including adenosine triphosphate (ATP), serotonin, bradykinin (BK), and histamine. The transient receptor potential cation channel subfamily V member 1 (TrpV1), also known as the vanilloid receptor, mediates perception of some noxious stimuli, especially heat sensations, by nociceptive neurons; it is activated by acidic pH, endogenous mediators and by capsaicin, a component of hot chili peppers.

Sensitization When intense, repeated, or prolonged stimuli are applied to damaged or inflamed tissues, the threshold for activating primary afferent nociceptors is lowered, and the frequency of firing is higher for all stimulus intensities. Inflammatory mediators such as BK, nerve-growth factor, some prostaglandins (PGs), and leukotrienes contribute to this process, which is called *sensitization*. Sensitization occurs at the level of the peripheral nerve terminal (*peripheral sensitization*) as well as at the level of the dorsal horn of the spinal cord (*central sensitization*). Peripheral sensitization occurs in damaged or inflamed tissues, when inflammatory mediators activate intracellular signal transduction in nociceptors, prompting an increase in the production, transport, and membrane insertion of chemically gated and voltage-gated ion channels. These changes increase the excitability of nociceptor terminals and lower their threshold for activation by mechanical, thermal, and chemical stimuli. Central sensitization occurs when activity, generated by nociceptors during inflammation, enhances the excitability of nerve cells in the dorsal horn of the spinal cord. Following injury and resultant sensitization, normally innocuous stimuli can produce pain (termed *allodynia*). Sensitization is a clinically important process that contributes to tenderness, soreness, and *hyperalgesia* (increased pain intensity in response to the same noxious stimulus; e.g., pinprick causes severe pain). A striking example of sensitization is sunburned skin, in which severe pain can be produced by a gentle slap on the back or a warm shower.

Sensitization is of particular importance for pain and tenderness in deep tissues. Viscera are normally relatively insensitive to noxious mechanical and thermal stimuli, although hollow viscera do generate significant discomfort when distended. In contrast, when affected by

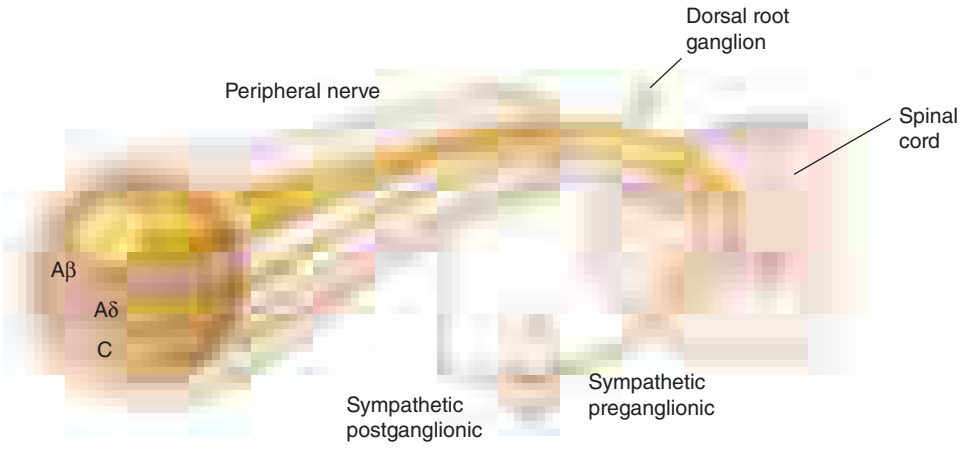


FIGURE 10-1 Components of a typical cutaneous nerve. There are two distinct functional categories of axons: primary afferents with cell bodies in the dorsal root ganglion and sympathetic postganglionic fibers with cell bodies in the sympathetic ganglion. Primary afferents include those with large-diameter myelinated (Aβ), small-diameter myelinated (Aδ), and unmyelinated (C) axons. All sympathetic postganglionic fibers are unmyelinated.

a disease process with an inflammatory component, deep structures such as joints or hollow viscera characteristically become exquisitely sensitive to mechanical stimulation.

A large proportion of Aδ and C fiber afferents innervating viscera are completely insensitive in normal noninjured, noninflamed tissue. That is, they cannot be activated by known mechanical or thermal stimuli and are not spontaneously active. However, in the presence of inflammatory mediators, these afferents become sensitive to mechanical stimuli. Such afferents have been termed *silent nociceptors*, and their characteristic properties may explain how, under pathologic conditions, the relatively insensitive deep structures can become the source of severe and debilitating pain and tenderness. Low pH, PGs, leukotrienes, and other inflammatory mediators such as BK play a significant role in sensitization.

Nociceptor-Induced Inflammation Primary afferent nociceptors also have a neuroeffector function. Most nociceptors contain polypeptide mediators that are released from their peripheral terminals when they are activated (Fig. 10-2). An example is substance P, an 11-amino-acid peptide. Substance P is released from primary afferent nociceptors and has multiple biologic activities. It is a potent vasodilator, causes mast cell degranulation, is a chemoattractant for leukocytes, and increases the production and release of inflammatory mediators. Interestingly, depletion of substance P from joints reduces the severity of experimental arthritis. Primary afferent nociceptors are not simply passive messengers of threats to tissue injury but also play an active role in tissue protection through these neuroeffector functions.

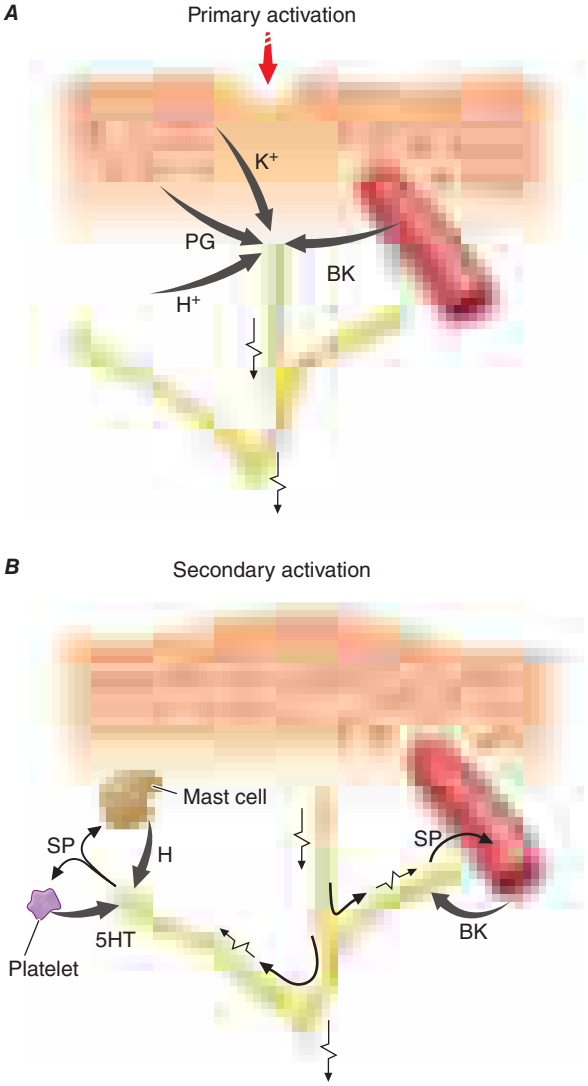


FIGURE 10-2 Events leading to activation, sensitization, and spread of sensitization of primary afferent nociceptor terminals. ***A***. Direct activation by intense pressure and consequent cell damage. Cell damage induces lower pH (H^+) and leads to release of potassium (K^+) and to synthesis of prostaglandins (PGs) and bradykinin (BK). PGs increase the sensitivity of the terminal to BK and other pain-producing substances. ***B***. Secondary activation. Impulses generated in the stimulated terminal propagate not only to the spinal cord but also into other terminal branches where they induce the release of peptides, including substance P (SP). Substance P causes vasodilation and neurogenic edema with further accumulation of BK. Substance P also causes the release of histamine (H) from mast cells and serotonin (5HT) from platelets.

CENTRAL MECHANISMS

The Spinal Cord and Referred Pain The axons of primary afferent nociceptors enter the spinal cord via the dorsal root. They terminate in the dorsal horn of the spinal gray matter (Fig. 10-3). The terminals of primary afferent axons contact spinal neurons that transmit the pain signal to brain sites involved in pain perception. When primary afferents are activated by noxious stimuli, they release neurotransmitters from their terminals that excite the spinal cord neurons. The major neurotransmitter released is glutamate, which rapidly excites the second-order dorsal horn neurons. Primary afferent nociceptor terminals also release peptides, including substance P and calcitonin gene-related peptide, which produce a slower and longer-lasting excitation of the dorsal horn neurons. The axon of each primary afferent contacts many spinal neurons, and each spinal neuron receives convergent inputs from many primary afferents.

The convergence of sensory inputs to a single spinal pain-transmission neuron is of great importance because it underlies the phenomenon of referred pain. All spinal neurons that receive input from the viscera and deep musculoskeletal structures also receive input from the skin. The convergence patterns are determined by the spinal segment of the dorsal root ganglion that supplies the afferent innervation of a structure. For example, the afferents that supply the central diaphragm are derived from the third and fourth cervical dorsal root ganglia. Primary afferents with cell bodies in these same ganglia supply the skin of the shoulder and lower neck. Thus, sensory inputs from both the shoulder skin and the central diaphragm converge on pain-transmission neurons in the third and fourth cervical spinal segments. *Because of this convergence and the fact that the spinal neurons are most often activated by inputs from the skin, activity evoked in spinal neurons by input from deep structures is mislocalized by the patient to a place that roughly corresponds with the region of skin innervated by the same spinal segment*. Thus, inflammation near the central diaphragm is often reported as shoulder discomfort. This spatial displacement of pain sensation from the site of the injury that produces it is known as *referred pain*.

Ascending Pathways for Pain A majority of spinal neurons contacted by primary afferent nociceptors send their axons to the

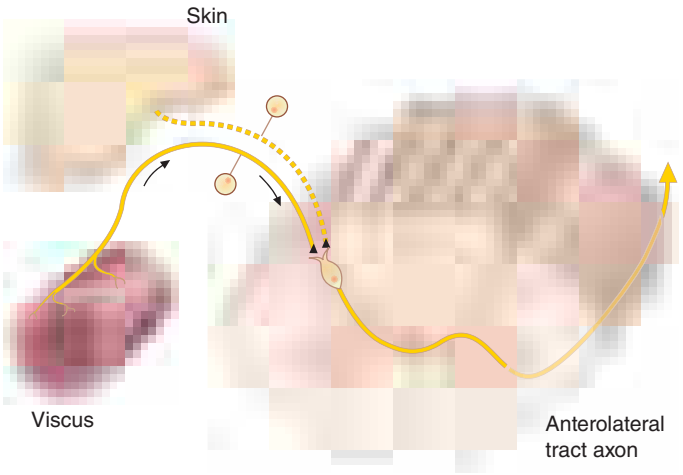


FIGURE 10-3 The convergence-projection hypothesis of referred pain. According to this hypothesis, visceral afferent nociceptors converge on the same pain-projection neurons as the afferents from the somatic structures in which the pain is perceived. The brain has no way of knowing the actual source of input and mistakenly "projects" the sensation to the somatic structure.

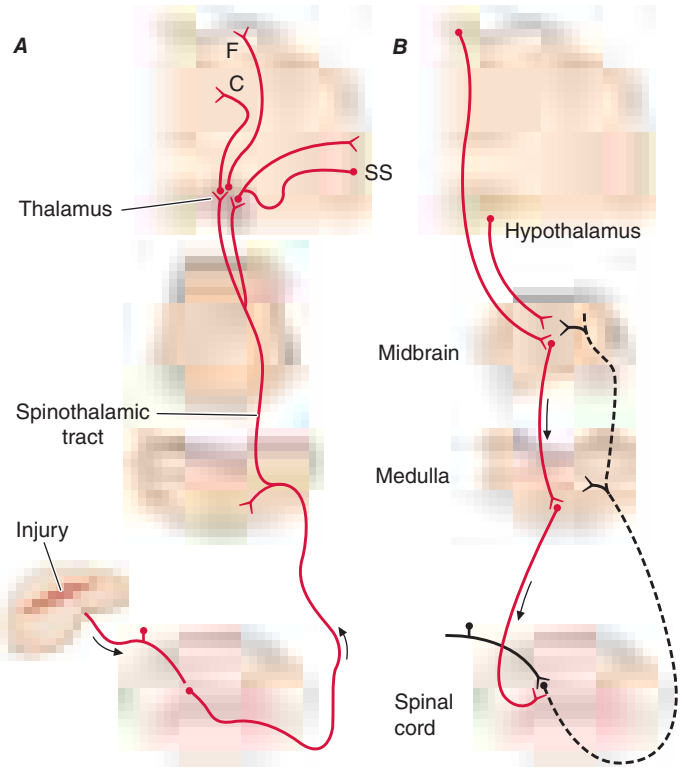


FIGURE 10-4 Pain-transmission and modulatory pathways. ***A***. Transmission system for nociceptive messages. Noxious stimuli activate the sensitive peripheral ending of the primary afferent nociceptor by the process of transduction. The message is then transmitted over the peripheral nerve to the spinal cord, where it synapses with cells of origin of the major ascending pain pathway, the spinothalamic tract. The message is relayed in the thalamus to the anterior cingulate (C), frontal insular (F), and somatosensory cortex (SS). ***B***. Pain-modulation network. Inputs from frontal cortex and hypothalamus activate cells in the midbrain that control spinal pain-transmission cells via cells in the medulla.

contralateral thalamus. These axons form the contralateral spinothalamic tract, which lies in the anterolateral white matter of the spinal cord, the lateral edge of the medulla, and the lateral pons and midbrain. The spinothalamic pathway is crucial for pain sensation in humans. Interruption of this pathway produces permanent deficits in pain and temperature discrimination.

Spinothalamic tract axons ascend to several regions of the thalamus. There is tremendous divergence of the pain signal from these thalamic sites to several distinct areas of the cerebral cortex that subserve different aspects of the pain experience **(Fig. 10-4)**. One of the thalamic projections is to the somatosensory cortex. This projection mediates the purely sensory aspects of pain, i.e., its location, intensity, and quality. Other thalamic neurons project to cortical regions that are linked to emotional responses, such as the cingulate gyrus and other areas of the frontal lobes, including the insular cortex. These pathways to the frontal cortex subserve the affective or unpleasant emotional dimension of pain. This affective dimension of pain produces suffering and exerts potent control of behavior. Because of this dimension, fear is a constant companion of pain. As a consequence, injury or surgical lesions to areas of the frontal cortex activated by painful stimuli can diminish the emotional impact of pain while largely preserving the individual's ability to recognize noxious stimuli as painful.

PAIN MODULATION

The pain produced by injuries of similar magnitude is remarkably variable in different situations and in different individuals. For example, athletes have been known to sustain serious fractures with only minor pain, and Beecher's classic World War II survey revealed that many soldiers in battle were unbothered by injuries that would have produced agonizing pain in civilian patients. Furthermore, even the suggestion that a treatment will relieve pain can have a significant analgesic effect (the *placebo effect*). On the other hand, many patients find even minor injuries such as venipuncture frightening and unbearable, and the expectation of pain can induce pain even without a noxious stimulus. The suggestion that pain will worsen following administration of an inert substance can increase its perceived intensity (the *nocebo effect*).

The powerful effect of expectation and other psychological variables on the perceived intensity of pain is explained by brain circuits that modulate the activity of the pain-transmission pathways. One of these circuits has links to the hypothalamus, midbrain, and medulla, and it selectively controls spinal pain-transmission neurons through a descending pathway (Fig. 10-4).

Human brain-imaging studies have implicated this pain-modulating circuit in the pain-relieving effect of attention, suggestion, and opioid analgesic medications **(Fig. 10-5)**. Furthermore, each of the component structures of the pathway contains opioid receptors and is sensitive to the direct application of opioid drugs. In animals, lesions of this descending modulatory system reduce the analgesic effect of systemically administered opioids such as morphine. Along with the opioid receptor, the component nuclei of this pain-modulating circuit contain endogenous opioid peptides such as the enkephalins and β-endorphin.

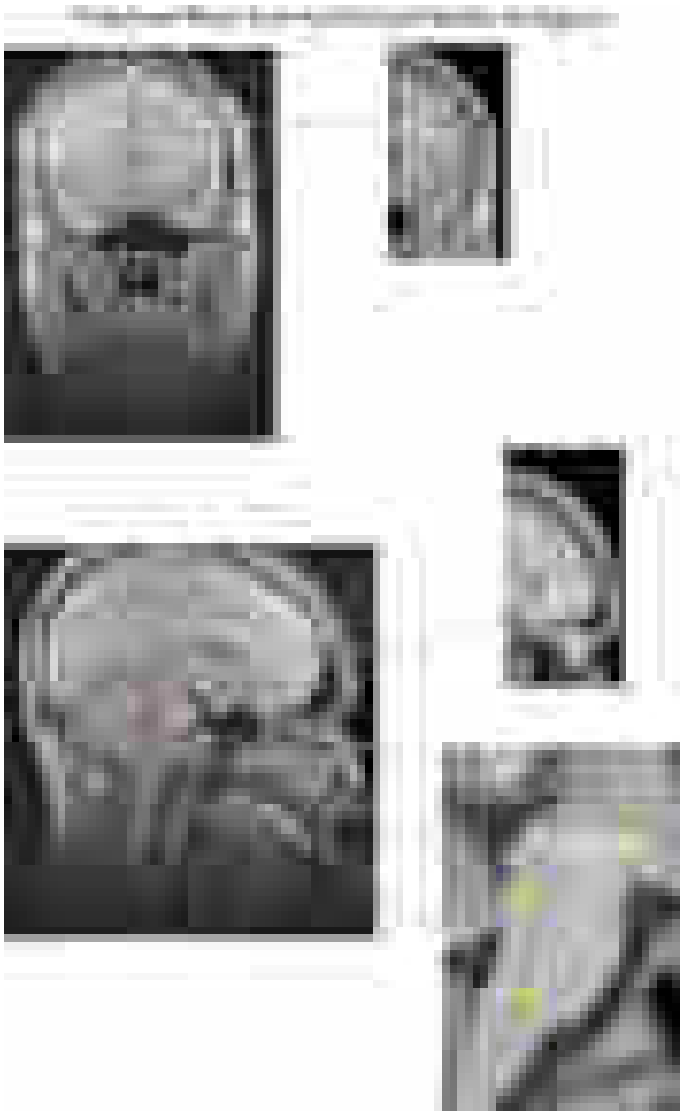


FIGURE 10-5 Functional magnetic resonance imaging (fMRI) demonstrates placebo-enhanced brain activity in anatomic regions correlating with the opioidergic descending pain control system. *Top panel:* Frontal fMRI image shows placebo-enhanced brain activity in the dorsal lateral prefrontal cortex (DLPFC). *Bottom panel:* Sagittal fMRI images show placebo-enhanced responses in the rostral anterior cingulate cortex (rACC), the rostral ventral medullae (RVM), the periaqueductal gray (PAG) area, and the hypothalamus. The placebo-enhanced activity in all areas was reduced by naloxone, demonstrating the link between the descending opioidergic system and the placebo analgesic response. *(Adapted with permission from F Eippert et al: Neuron 63:533, 2009.)*

The most reliable way to activate this endogenous opioid-mediated modulating system is by suggestion of pain relief or by intense emotion directed away from the pain-causing injury (e.g., during severe threat or an athletic competition). In fact, pain-relieving endogenous opioids are released following surgical procedures and in patients given a placebo for pain relief.

Pain-modulating circuits can enhance as well as suppress pain. Both pain-inhibiting and pain-facilitating neurons in the medulla project to and control spinal pain-transmission neurons. Because pain-transmission neurons can be activated by modulatory neurons, it is theoretically possible to generate a pain signal with no peripheral noxious stimulus. In fact, human functional imaging studies have demonstrated increased activity in this circuit during migraine headaches. A central circuit that facilitates pain could account for the finding that pain can be induced by suggestion or enhanced by expectation and provides a framework for understanding how psychological factors can contribute to chronic pain.

NEUROPATHIC PAIN

Lesions of the peripheral or central nociceptive pathways typically result in a loss or impairment of pain sensation. Paradoxically, damage to or dysfunction of these pathways can also produce pain. For example, damage to peripheral nerves, as occurs in diabetic neuropathy, or to primary afferents, as in herpes zoster infection, can result in pain that is referred to the body region innervated by the damaged nerves. Pain may also be produced by damage to the central nervous system (CNS), for example, in some patients following trauma or vascular injury to the spinal cord, brainstem, or thalamic areas that contain central nociceptive pathways. Such pains are termed *neuropathic* and are often severe and are typically resistant to standard treatments for pain.

Neuropathic pain typically has an unusual burning, tingling, or electric shock-like quality and may occur spontaneously, without any stimulus, or be triggered by very light touch. These features are rare in other types of pain. On examination, a sensory deficit is characteristically present in the area of the patient's pain. *Hyperpathia*, a greatly exaggerated pain response to innocuous or mild nociceptive stimuli, especially when applied repeatedly, is also characteristic of neuropathic pain; patients often complain that the very lightest moving stimulus evokes exquisite pain (allodynia). In this regard, it is of clinical interest that a topical preparation of 5% lidocaine in patch form is effective for patients with postherpetic neuralgia who have prominent allodynia.

A variety of mechanisms contribute to neuropathic pain. As with sensitized primary afferent nociceptors, damaged primary afferents, including nociceptors, become highly sensitive to mechanical stimulation and may generate impulses in the absence of stimulation. Increased sensitivity and spontaneous activity are due, in part, to an increased density of sodium channels in the damaged nerve fiber. Damaged primary afferents may also develop sensitivity to norepinephrine. Interestingly, spinal cord pain-transmission neurons cut off from their normal input may also become spontaneously active. Thus, both central and peripheral nervous system hyperactivity contribute to neuropathic pain.

Sympathetically Maintained Pain Patients with peripheral nerve injury occasionally develop spontaneous pain in the region innervated by the nerve. This pain is often described as having a burning quality. The pain typically begins after a delay of hours to days or even weeks and is accompanied by swelling of the extremity, periarticular bone loss, and arthritic changes in the distal joints. The pain may be relieved by a local anesthetic block of the sympathetic innervation to the affected extremity. Damaged primary afferent nociceptors acquire adrenergic sensitivity and can be activated by stimulation of the sympathetic outflow. This constellation of spontaneous pain and signs of sympathetic dysfunction following injury has been termed *complex regional pain syndrome* (CRPS). When this occurs after an identifiable nerve injury, it is termed CRPS type II (also known as posttraumatic neuralgia or, if severe, *causalgia*). When a similar clinical picture appears without obvious nerve injury, it is termed CRPS type I (also known as *reflex sympathetic dystrophy*). CRPS can be produced by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke. CRPS type I typically resolves with symptomatic treatment; however, when it persists, detailed examination often reveals evidence of peripheral nerve injury. Although the pathophysiology of CRPS is poorly understood, the pain and the signs of inflammation, when acute, can be rapidly relieved by blocking the sympathetic nervous system. This implies that sympathetic activity can activate undamaged nociceptors when inflammation is present. Signs of sympathetic hyperactivity should be sought in patients with posttraumatic pain and inflammation and no other obvious explanation.

TREATMENT

Acute Pain

The ideal treatment for any pain is to remove the cause; thus, while treatment can be initiated immediately, efforts to establish the underlying etiology should always proceed as treatment begins. Sometimes, treating the underlying condition does not immediately relieve pain. Furthermore, some conditions are so painful that rapid and effective analgesia is essential (e.g., the postoperative state, burns, trauma, cancer, or sickle cell crisis). Analgesic medications are a first line of treatment in these cases, and all practitioners should be familiar with their use.

ASPIRIN, ACETAMINOPHEN, AND NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)

These drugs are considered together because they are used for similar problems and may have a similar mechanism of action **(Table 10-1)**. All these compounds inhibit cyclooxygenase (COX), and, except for acetaminophen, all have anti-inflammatory actions, especially at higher dosages. They are particularly effective for mild to moderate headache and for pain of musculoskeletal origin.

Because they are effective for these common types of pain and are available without prescription, COX inhibitors are by far the most commonly used analgesics. They are absorbed well from the gastrointestinal tract and, with occasional use, have only minimal side effects. With chronic use, gastric irritation is a common side effect of aspirin and NSAIDs and is the problem that most frequently limits the dose that can be given. Gastric irritation is most severe with aspirin, which may cause erosion and ulceration of the gastric mucosa leading to bleeding or perforation. Because aspirin irreversibly acetylates platelet COX and thereby interferes with coagulation of the blood, gastrointestinal bleeding is a particular risk. Older age and history of gastrointestinal disease increase the risks of aspirin and NSAIDs. In addition to the well-known gastrointestinal toxicity of NSAIDs, nephrotoxicity is a significant problem for patients using these drugs on a chronic basis. Patients at risk for renal insufficiency, particularly those with significant contraction of their intravascular volume as occurs with chronic diuretic use or acute hypovolemia, should avoid NSAIDs. NSAIDs can also increase blood pressure in some individuals. Long-term treatment with NSAIDs requires regular blood pressure monitoring and treatment if necessary. Although toxic to the liver when taken in high doses, acetaminophen rarely produces gastric irritation and does not interfere with platelet function.

The introduction of parenteral forms of NSAIDs, ketorolac and diclofenac, extends the usefulness of this class of compounds in the management of acute severe pain. Both agents are sufficiently potent and rapid in onset to supplant opioids for many patients with acute severe headache and musculoskeletal pain.

There are two major classes of COX: COX-1 is constitutively expressed, and COX-2 is induced in the inflammatory state. COX-2-selective drugs have similar analgesic potency and produce less gastric irritation than the nonselective COX inhibitors. The use of COX-2-selective drugs does not appear to lower the risk of nephrotoxicity compared to nonselective NSAIDs. On the other hand, COX-2-selective drugs offer a significant benefit in the management of acute postoperative pain because they do not affect blood

TABLE 10-1 Drugs for Relief of Pain

GENERIC NAME	DOSE, mg	INTERVAL	COMMENTS
Nonnarcotic Analgesics: Usual Doses and Intervals			
Acetylsalicylic acid	650 PO	q4h	Enteric-coated preparations available
Acetaminophen	650 PO	q4h	Side effects uncommon
Ibuprofen	400 PO	q4–6h	Available without prescription
Naproxen	250–500 PO	q12h	Naproxen is the common NSAID that poses the least cardiovascular risk; but it has a somewhat higher incidence of gastrointestinal bleeding
Fenoprofen	200 PO	q4–6h	Contraindicated in renal disease
Indomethacin	25–50 PO	q8h	Gastrointestinal side effects common
Ketorolac	15–60 IM/IV	q4–6h	Available for parenteral use
Celecoxib	100–200 PO	q12–24h	Useful for arthritis
Valdecoxib	10–20 PO	q12–24h	Removed from U.S. market in 2005
GENERIC NAME	**PARENTERAL DOSE, mg**	**PO DOSE, mg**	**COMMENTS**
Narcotic Analgesics: Usual Doses and Intervals			
Codeine	30–60 q4h	30–60 q4h	Nausea common
Oxycodone	—	5–10 q4–6h	Usually available with acetaminophen or aspirin
Morphine	5 q4h	30 q4h	
Morphine sustained release	—	15–60 bid to tid	Oral slow-release preparation
Hydromorphone	1–2 q4h	2–4 q4h	Shorter acting than morphine sulfate
Levorphanol	2 q6–8h	4 q6–8h	Longer acting than morphine sulfate; absorbed well PO
Methadone	5–10 q6–8h	5–20 q6–8h	Due to long half-life, respiratory depression and sedation may persist after analgesic effect subsides; therapy should not be initiated with >40 mg/d, and dose escalation should be made no more frequently than every 3 days
Meperidine	50–100 q3–4h	300 q4h	Poorly absorbed PO; normeperidine is a toxic metabolite; routine use of this agent is not recommended
Butorphanol	—	1–2 q4h	Intranasal spray
Fentanyl	25–100 μg/h	—	72-h transdermal patch
Buprenorphine	5–20 μg/h		7-day transdermal patch
Buprenorphine	0.3 q6–8h		Parenteral administration
Tramadol	—	50–100 q4–6h	Mixed opioid/adrenergic action

GENERIC NAME	UPTAKE BLOCKADE 5-HT	UPTAKE BLOCKADE NE	SEDATIVE POTENCY	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC ARRHYTHMIA	AVE. DOSE, mg/d	RANGE, mg/d
Antidepressants[a]								
Doxepin	++	+	High	Moderate	Moderate	Less	200	75–400
Amitriptyline	++++	++	High	Highest	Moderate	Yes	150	25–300
Imipramine	++++	++	Moderate	Moderate	High	Yes	200	75–400
Nortriptyline	+++	++	Moderate	Moderate	Low	Yes	100	40–150
Desipramine	+++	++++	Low	Low	Low	Yes	150	50–300
Venlafaxine	+++	++	Low	None	None	No	150	75–400
Duloxetine	+++	+++	Low	None	None	No	40	30–60

GENERIC NAME	PO DOSE, mg	INTERVAL	GENERIC NAME	PO DOSE, mg	INTERVAL
Anticonvulsants and Antiarrhythmics[a]					
Phenytoin	300	daily/qhs	Clonazepam	1	q6h
Carbamazepine	200–300	q6h	Gabapentin[b]	600–1200	q8h
Oxcarbazepine	300	bid	Pregabalin	150–600	bid

[a]Antidepressants, anticonvulsants, and antiarrhythmics have not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of pain. [b]Gabapentin in doses up to 1800 mg/d is FDA approved for postherpetic neuralgia.

Abbreviations: 5-HT, serotonin; NE, norepinephrine; NSAID, nonsteroidal anti-inflammatory agent.

coagulation. Nonselective COX inhibitors are usually contraindicated postoperatively because they impair platelet-mediated blood clotting and are thus associated with increased bleeding at the operative site. COX-2 inhibitors, including celecoxib (Celebrex), are associated with increased cardiovascular risk, including cardiovascular death, myocardial infarction, stroke, heart failure, or a thromboembolic event. It appears that this is a class effect of NSAIDs, excluding aspirin. These drugs are contraindicated in patients in the immediate period after coronary artery bypass surgery and should be used with caution in elderly patients and those with a history of or significant risk factors for cardiovascular disease.

OPIOID ANALGESICS

Opioids are the most potent pain-relieving drugs currently available. Of all analgesics, they have the broadest range of efficacy and provide the most reliable and effective method for rapid pain relief. Although side effects are common, most are reversible: nausea, vomiting, pruritus, and constipation are the most frequent and bothersome side effects. Respiratory depression is uncommon at standard analgesic doses, but can be life-threatening. Opioid-related side effects can be reversed rapidly with the narcotic antagonist naloxone. Many physicians, nurses, and patients have a certain trepidation about using opioids that is based on a fear of initiating

addiction in their patients. In fact, there is a very small chance of patients becoming addicted to narcotics as a result of their appropriate medical use. For chronic pain, particularly chronic noncancer pain, the risk of addiction in patients taking opioids on a chronic basis remains small, but the risk does appear to increase with dose escalation. The physician should not hesitate to use opioid analgesics in patients with acute severe pain. Table 10-1 lists the most commonly used opioid analgesics.

Opioids produce analgesia by actions in the CNS. They activate pain-inhibitory neurons and directly inhibit pain-transmission neurons. Most of the commercially available opioid analgesics act at the same opioid receptor (μ-receptor), differing mainly in potency, speed of onset, duration of action, and optimal route of administration. Some side effects are due to accumulation of nonopioid metabolites that are unique to individual drugs. One striking example of this is normeperidine, a metabolite of meperidine. At higher doses of meperidine, typically >1 g/d, accumulation of normeperidine can produce hyperexcitability and seizures that are not reversible with naloxone. Normeperidine accumulation is increased in patients with renal failure.

The most rapid pain relief is obtained by intravenous administration of opioids; relief with oral administration is significantly slower. Because of the potential for respiratory depression, patients with any form of respiratory compromise must be kept under close observation following opioid administration; an oxygen-saturation monitor may be useful, but only in a setting where the monitor is under constant surveillance. Opioid-induced respiratory depression is typically accompanied by sedation and a reduction in respiratory rate. A fall in oxygen saturation represents a critical level of respiratory depression and the need for immediate intervention to prevent life-threatening hypoxemia. Newer monitoring devices that incorporate capnography or pharyngeal air flow can detect apnea at the point of onset and should be used in hospitalized patients. Ventilatory assistance should be maintained until the opioid-induced respiratory depression has resolved. The opioid antagonist naloxone should be readily available whenever opioids are used at high doses or in patients with compromised pulmonary function. Opioid effects are dose-related, and there is great variability among patients in the doses that relieve pain and produce side effects. Synergistic respiratory depression is common when opioids are administered with other CNS depressants, most commonly the benzodiazepines. Because of this, initiation of therapy requires titration to optimal dose and interval. The most important principle is to provide adequate pain relief. This requires determining whether the drug has adequately relieved the pain and frequent reassessment to determine the optimal interval for dosing. *The most common error made by physicians in managing severe pain with opioids is to prescribe an inadequate dose. Because many patients are reluctant to complain, this practice leads to needless suffering*. In the absence of sedation at the expected time of peak effect, a physician should not hesitate to repeat the initial dose to achieve satisfactory pain relief.

A now standard approach to the problem of achieving adequate pain relief is the use of patient-controlled analgesia (PCA). PCA uses a microprocessor-controlled infusion device that can deliver a baseline continuous dose of an opioid drug as well as preprogrammed additional doses whenever the patient pushes a button. The patient can then titrate the dose to the optimal level. This approach is used most extensively for the management of postoperative pain, but there is no reason why it should not be used for any hospitalized patient with persistent severe pain. PCA is also used for short-term home care of patients with intractable pain, such as that caused by metastatic cancer.

It is important to understand that the PCA device delivers small, repeated doses to maintain pain relief; in patients with severe pain, the pain must first be brought under control with a loading dose before transitioning to the PCA device. The bolus dose of the drug (typically 1 mg of morphine, 0.2 mg of hydromorphone, or 10 μg of fentanyl) can then be delivered repeatedly as needed. To prevent overdosing, PCA devices are programmed with a lockout period after each demand dose is delivered (typically starting at 10 min) and a limit on the total dose delivered per hour. Although some have advocated the use of a simultaneous continuous or basal infusion of the PCA drug, this may increase the risk of respiratory depression and has not been shown to increase the overall efficacy of the technique.

The availability of new routes of administration has extended the usefulness of opioid analgesics. Most important is the availability of spinal administration. Opioids can be infused through a spinal catheter placed either intrathecally or epidurally. By applying opioids directly to the spinal or epidural space adjacent to the spinal cord, regional analgesia can be obtained using relatively low total doses. Indeed, the dose required to produce effective analgesia when using morphine intrathecally (0.1–0.3 mg) is a fraction of that required to produce similar analgesia when administered intravenously (5–10 mg). In this way, side effects such as sedation, nausea, and respiratory depression can be minimized. This approach has been used extensively during labor and delivery and for postoperative pain relief following surgical procedures. Continuous intrathecal delivery via implanted spinal drug-delivery systems is now commonly used, particularly for the treatment of cancer-related pain that would require sedating doses for adequate pain control if given systemically. Opioids can also be given intranasally (butorphanol), rectally, and transdermally (fentanyl and buprenorphine), or through the oral mucosa (fentanyl), thus avoiding the discomfort of frequent injections in patients who cannot be given oral medication. The fentanyl and buprenorphine transdermal patches have the advantage of providing fairly steady plasma levels, which may improve patient comfort.

Recent additions to the armamentarium for treating opioid-induced side effects are the peripherally acting opioid antagonists alvimopan (Entereg) and methylnaltrexone (Rellistor). Alvimopan is available as an orally administered agent that is restricted to the intestinal lumen by limited absorption; methylnaltrexone is available in a subcutaneously administered form that has virtually no penetration into the CNS. Both agents act by binding to peripheral μ-receptors, thereby inhibiting or reversing the effects of opioids at these peripheral sites. The action of both agents is restricted to receptor sites outside of the CNS; thus, these drugs can reverse the adverse effects of opioid analgesics that are mediated through their peripheral receptors without reversing their analgesic effects. Alvimopan has proven effective in lowering the duration of persistent ileus following abdominal surgery in patients receiving opioid analgesics for postoperative pain control. Methylnaltrexone has proven effective for relief of opioid-induced constipation in patients taking opioid analgesics on a chronic basis.

Opioid and COX Inhibitor Combinations When used in combination, opioids and COX inhibitors have additive effects. Because a lower dose of each can be used to achieve the same degree of pain relief and their side effects are nonadditive, such combinations are used to lower the severity of dose-related side effects. However, fixed-ratio combinations of an opioid with acetaminophen carry an important risk. Dose escalation as a result of increased severity of pain or decreased opioid effect as a result of tolerance may lead to ingestion of levels of acetaminophen that are toxic to the liver. Although acetaminophen-related hepatotoxicity is uncommon, it remains a significant cause for liver failure. Thus, many practitioners have moved away from the use of opioid-acetaminophen combination analgesics to avoid the risk of excessive acetaminophen exposure as the dose of the analgesic is escalated.

CHRONIC PAIN

Managing patients with chronic pain is intellectually and emotionally challenging. Sensitization of the nervous system can occur without an obvious precipitating cause, e.g., fibromyalgia, or chronic headache. In many patients, chronic pain becomes a distinct disease unto itself. The pain-generating mechanism is often difficult or impossible to determine with certainty; such patients are demanding of the physician's

time and often appear emotionally distraught. The traditional medical approach of seeking an obscure organic pathology is usually unhelpful. On the other hand, psychological evaluation and behaviorally based treatment paradigms are frequently helpful, particularly in the setting of a multidisciplinary pain-management center. Unfortunately, this approach, while effective, remains largely underused in current medical practice.

There are several factors that can cause, perpetuate, or exacerbate chronic pain. First, of course, the patient may simply have a disease that is characteristically painful for which there is presently no cure. Arthritis, cancer, chronic daily headaches, fibromyalgia, and diabetic neuropathy are examples of this. Second, there may be secondary perpetuating factors that are initiated by disease and persist after that disease has resolved. Examples include damaged sensory nerves, sympathetic efferent activity, and painful reflex muscle contraction (spasm). Finally, a variety of psychological conditions can exacerbate or even cause pain.

There are certain areas to which special attention should be paid in a patient's medical history. Because depression is the most common emotional disturbance in patients with chronic pain, patients should be questioned about their mood, appetite, sleep patterns, and daily activity. A simple standardized questionnaire, such as the Beck Depression Inventory, can be a useful screening device. It is important to remember that major depression is a common, treatable, and potentially fatal illness.

Other clues that a significant emotional disturbance is contributing to a patient's chronic pain complaint include pain that occurs in multiple, unrelated sites; a pattern of recurrent, but separate, pain problems beginning in childhood or adolescence; pain beginning at a time of emotional trauma, such as the loss of a parent or spouse; a history of physical or sexual abuse; and past or present substance abuse.

On examination, special attention should be paid to whether the patient guards the painful area and whether certain movements or postures are avoided because of pain. Discovering a mechanical component to the pain can be useful both diagnostically and therapeutically. Painful areas should be examined for deep tenderness, noting whether this is localized to muscle, ligamentous structures, or joints. Chronic myofascial pain is very common, and, in these patients, deep palpation may reveal highly localized trigger points that are firm bands or knots in muscle. Relief of the pain following injection of local anesthetic into these trigger points supports the diagnosis. A neuropathic component to the pain is indicated by evidence of nerve damage, such as sensory impairment, exquisitely sensitive skin (allodynia), weakness, and muscle atrophy, or loss of deep tendon reflexes. Evidence suggesting sympathetic nervous system involvement includes the presence of diffuse swelling, changes in skin color and temperature, and hypersensitive skin and joint tenderness compared with the normal side. Relief of the pain with a sympathetic block supports the diagnosis, but once the condition becomes chronic, the response to sympathetic blockade is of variable magnitude and duration; the role for repeated sympathetic blocks in the overall management of CRPS is unclear.

A guiding principle in evaluating patients with chronic pain is to assess both emotional and organic factors before initiating therapy. Addressing these issues together, rather than waiting to address emotional issues after organic causes of pain have been ruled out, improves compliance in part because it assures patients that a psychological evaluation does not mean that the physician is questioning the validity of their complaint. Even when an organic cause for a patient's pain can be found, it is still wise to look for other factors. For example, a cancer patient with painful bony metastases may have additional pain due to nerve damage and may also be depressed. Optimal therapy requires that each of these factors be looked for and treated.

TREATMENT

Chronic Pain

Once the evaluation process has been completed and the likely causative and exacerbating factors identified, an explicit treatment plan should be developed. An important part of this process is to identify specific and realistic functional goals for therapy, such as getting a good night's sleep, being able to go shopping, or returning to work. A multidisciplinary approach that uses medications, counseling, physical therapy, nerve blocks, and even surgery may be required to improve the patient's quality of life. There are also some newer, minimally invasive procedures that can be helpful for some patients with intractable pain. These include image-guided interventions such as epidural injection of glucocorticoids for acute radicular pain and radiofrequency treatment of the facet joints for chronic facet-related back and neck pain. For patients with severe and persistent pain that is unresponsive to more conservative treatment, placement of electrodes within the spinal canal overlying the dorsal columns of the spinal cord (spinal cord stimulation) or implantation of intrathecal drug-delivery systems has shown significant benefit. The criteria for predicting which patients will respond to these procedures continue to evolve. They are generally reserved for patients who have not responded to conventional pharmacologic approaches. Referral to a multidisciplinary pain clinic for a full evaluation should precede any invasive procedure. Such referrals are clearly not necessary for all chronic pain patients. For some, pharmacologic management alone can provide adequate relief.

ANTIDEPRESSANT MEDICATIONS

The tricyclic antidepressants (TCAs), particularly nortriptyline and desipramine (Table 10-1), are useful for the management of chronic pain. Although developed for the treatment of depression, the TCAs have a spectrum of dose-related biologic activities that include analgesia in a variety of chronic clinical conditions. Although the mechanism is unknown, the analgesic effect of TCAs has a more rapid onset and occurs at a lower dose than is typically required for the treatment of depression. Furthermore, patients with chronic pain who are not depressed obtain pain relief with antidepressants. There is evidence that TCAs potentiate opioid analgesia, so they may be useful adjuncts for the treatment of severe persistent pain such as occurs with malignant tumors. **Table 10-2** lists some of the painful conditions that respond to TCAs. TCAs are of particular value in the management of neuropathic pain such as occurs in diabetic neuropathy and postherpetic neuralgia, for which there are few other therapeutic options.

The TCAs that have been shown to relieve pain have significant side effects (Table 10-1; **Chap. 444**). Some of these side effects, such as orthostatic hypotension, drowsiness, cardiac conduction delay, memory impairment, constipation, and urinary retention, are particularly problematic in elderly patients, and several are additive to the side effects of opioid analgesics. The selective serotonin reuptake inhibitors such as fluoxetine (Prozac) have fewer and less serious side effects than TCAs, but they are much less effective for relieving pain. It is of interest that venlafaxine (Effexor) and duloxetine (Cymbalta), which are nontricyclic antidepressants that block both serotonin and norepinephrine reuptake, appear to retain most of the pain-relieving effect of TCAs with a side effect profile more like that of the selective serotonin reuptake inhibitors. These drugs may be particularly useful in patients who cannot tolerate the side effects of TCAs.

TABLE 10-2 Painful Conditions That Respond to Tricyclic Antidepressants

Postherpetic neuralgia[a]
Diabetic neuropathy[a]
Fibromyalgia[a]
Tension headache[a]
Migraine headache[a]
Rheumatoid arthritis[a,b]
Chronic low back pain[b]
Cancer
Central poststroke pain

[a]Controlled trials demonstrate analgesia. [b]Controlled studies indicate benefit but not analgesia.

ANTICONVULSANTS AND ANTIARRHYTHMICS

These drugs are useful primarily for patients with neuropathic pain. Phenytoin (Dilantin) and carbamazepine (Tegretol) were first shown to relieve the pain of trigeminal neuralgia **(Chap. 433)**. This pain has a characteristic brief, shooting, electric shock-like quality. In fact, anticonvulsants seem to be particularly helpful for pains that have such a lancinating quality. Newer anticonvulsants, the calcium channel alpha-2-delta subunit ligands gabapentin (Neurontin) and pregabalin (Lyrica), are effective for a broad range of neuropathic pains. Furthermore, because of their favorable side effect profile, these newer anticonvulsants are often used as first-line agents.

CHRONIC OPIOID MEDICATION

The long-term use of opioids is accepted for patients with pain due to malignant disease. Although opioid use for chronic pain of nonmalignant origin is controversial, it is clear that, for many patients, opioids are the only option that produces meaningful pain relief. This is understandable because opioids are the most potent and have the broadest range of efficacy of any analgesic medications. Although addiction is rare in patients who first use opioids for pain relief, some degree of tolerance and physical dependence is likely with long-term use. Furthermore, studies suggest that long-term opioid therapy may worsen pain in some individuals, termed *opioid-induced hyperalgesia*. Therefore, before embarking on opioid therapy, other options should be explored, and the limitations and risks of opioids should be explained to the patient. It is also important to point out that some opioid analgesic medications have mixed agonist-antagonist properties (e.g., butorphanol and buprenorphine). From a practical standpoint, this means that they may worsen pain by inducing an abstinence syndrome in patients who are physically dependent on other opioid analgesics.

With long-term outpatient use of orally administered opioids, it may be desirable to use long-acting compounds such as levorphanol, methadone, sustained-release morphine, or transdermal fentanyl (Table 10-1). The pharmacokinetic profiles of these drug preparations enable the maintenance of sustained analgesic blood levels, potentially minimizing side effects such as sedation that are associated with high peak plasma levels, and reducing the likelihood of rebound pain associated with a rapid fall in plasma opioid concentration. Although long-acting opioid preparations may provide superior pain relief in patients with a continuous pattern of ongoing pain, others suffer from intermittent severe episodic pain and experience superior pain control and fewer side effects with the periodic use of short-acting opioid analgesics. Constipation is a virtually universal side effect of opioid use and should be treated expectantly. As noted above in the discussion of acute pain treatment, a recent advance for patients is the development of peripherally acting opioid antagonists that can reverse the constipation associated with opioid use without interfering with analgesia.

Soon after the introduction of a controlled-release oxycodone formulation (OxyContin) in the late 1990s, a dramatic rise in emergency department visits and deaths associated with oxycodone ingestion appeared, focusing public attention on misuse of prescription pain medications. The magnitude of prescription opioid abuse has grown over the last decade, leading the Centers for Disease Control and Prevention to classify prescription opioid analgesic abuse as an epidemic. This appears to be due in large part to individuals using a prescription drug nonmedically, most often an opioid analgesic. Drug-induced deaths have rapidly risen and are now the second leading cause of death in Americans, just behind motor vehicle fatalities. In 2011, the Office of National Drug Control Policy established a multifaceted approach to address prescription drug abuse, including Prescription Drug Monitoring Programs (PDMPs) that allow practitioners to determine if patients are receiving prescriptions from multiple providers and use of law enforcement to eliminate improper prescribing practices. In 2016, the Centers for Disease Control (CDC) released the *CDC Guideline for Prescribing Opioids for Chronic Pain*, with recommendations for primary care clinicians who are prescribing opioids for chronic noncancer. The guideline is based on the best available scientific evidence and addresses (1) when to initiate or continue opioids for chronic pain; (2) opioid selection, dosage, duration, follow-up, and discontinuation; and (3) assessing risk and addressing harms of opioid use. The recent increase in scrutiny leaves many practitioners hesitant to prescribe opioid analgesics, other than for brief periods to control pain associated with illness or injury. For now, the choice to begin chronic opioid therapy for a given patient is left to the individual practitioner. Pragmatic guidelines for properly selecting and monitoring patients receiving chronic opioid therapy are shown in **Table 10-3**; a checklist for primary care clinicians prescribing opioids for noncancer pain is shown in **Table 10-4**.

TABLE 10-3 Guidelines for Selecting and Monitoring Patients Receiving Chronic Opioid Therapy (COT) for the Treatment of Chronic, Noncancer Pain

Patient Selection
• Conduct a history, physical examination, and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction.
• Consider a trial of COT if pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh potential harms.
• A benefit-to-harm evaluation, including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during COT.
Informed Consent and Use of Management Plans
• Informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT.
• Consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education.
Initiation and Titration
• Initial treatment with opioids should be considered as a therapeutic trial to determine whether COT is appropriate.
• Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms.
Monitoring
• Reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies.
• In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care.
• In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care.

Source: Adapted with permission from R Chou et al: J Pain 10:113, 2009.

TREATMENT OF NEUROPATHIC PAIN

It is important to individualize treatment for patients with neuropathic pain. Several general principles should guide therapy: the first is to move quickly to provide relief and the second is to minimize drug side effects. For example, in patients with postherpetic neuralgia and significant cutaneous hypersensitivity, topical lidocaine (Lidoderm patches) can provide immediate relief without side effects. Anticonvulsants (gabapentin or pregabalin; see above) or antidepressants (nortriptyline, desipramine, duloxetine, or venlafaxine) can be used as first-line drugs for patients with neuropathic pain. Systemically administered antiarrhythmic drugs such as lidocaine and mexiletine are less likely to be effective; although intravenous infusion of lidocaine can provide analgesia for patients with different types of neuropathic pain, the relief is usually transient, typically lasting just hours after the cessation of the infusion. The oral lidocaine congener mexiletine is poorly tolerated, producing

TABLE 10-4 Centers for Disease Control Checklist for Prescribing Opioids for Chronic Pain

For Primary Care Providers Treating Adults (18+) with Chronic Pain ≥3 months, Excluding Cancer, Palliative, and End-of-Life Care

CHECKLIST

WHEN CONSIDERING LONG-TERM OPIOID THERAPY

- Set realistic goals for pain and function based on diagnosis (e.g., walk around the block).
- Check that nonopioid therapies tried and optimized.
- Discuss benefits and risks (e.g., addiction, overdose) with patient.
- Evaluate risk of harm or misuse.
  - Discuss risk factors with patient.
  - Check prescription drug monitoring program (PDMP) data.
  - Check urine drug screen.
- Set criteria for stopping or continuing opioids.
- Assess baseline pain and function (e.g., Pain, Enjoyment, General Activity [PEG] scale).
- Schedule initial reassessment within 1–4 weeks.
- Prescribe short-acting opioids using lowest dosage on product labeling; match duration to scheduled reassessment.

IF RENEWING WITHOUT A PATIENT VISIT

- Check that return visit is scheduled ≤3 months from last visit.

WHEN REASSESSING AT A PATIENT VISIT

- Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm.
- Assess pain and function (e.g., PEG); compare results to baseline.
- Evaluate risk of harm or misuse:
  - Observe patient for signs of oversedation or overdose risk. If yes: Taper dose.
  - Check PDMP.
  - Check for opioid use disorder if indicated (e.g., difficulty controlling use). If yes: Refer for treatment.
- Check that nonopioid therapies optimized. Determine whether to continue, adjust, taper, or stop opioids.
- Calculate opioid dosage morphine milligram equivalent (MME).
  - If ≥50 MME/day total (≥50 mg hydrocodone; ≥33 mg oxycodone), increase frequency of follow-up; consider offering naloxone.
  - Avoid ≥90 MME/day total (≥90 mg hydrocodone; ≥60 mg oxycodone), or carefully justify; consider specialist referral.
- Schedule reassessment at regular intervals (≤3 months).

Source: Centers for Disease Control, Available at: https://stacks.cdc.gov/view/cdc/38025, accessed May 25, 2017 (Public Domain).

frequent gastrointestinal adverse effects. There is no consensus on which class of drug should be used as a first-line treatment for any chronically painful condition. However, because relatively high doses of anticonvulsants are required for pain relief, sedation is very common. Sedation is also a problem with TCAs but is much less of a problem with serotonin/norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine and duloxetine). Thus, in the elderly or in patients whose daily activities require high-level mental activity, these drugs should be considered the first line. In contrast, opioid medications should be used as a second- or third-line drug class. Although highly effective for many painful conditions, opioids are sedating, and their effect tends to lessen over time, leading to dose escalation and, occasionally, a worsening of pain. Drugs of different classes can be used in combination to optimize pain control. Repeated injection of botulinum toxin is an emerging approach that is showing some promise in treating focal neuropathic pain, particularly post-herpetic, trigeminal, and post-traumatic neuralgias.

It is worth emphasizing that many patients, especially those with chronic pain, seek medical attention primarily because they are suffering and because only physicians can provide the medications required for pain relief. A primary responsibility of all physicians is to minimize the physical and emotional discomfort of their patients. Familiarity with pain mechanisms and analgesic medications is an important step toward accomplishing this aim.

FURTHER READING

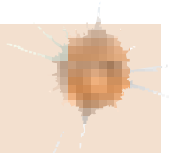
Dowell D et al: CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 315:1624, 2016.

Finnerup NB et al: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 14:162, 2015.

Sun EC et al: Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med 176:1286, 2016.

11 Chest Discomfort

David A. Morrow



Chest discomfort is among the most common reasons for which patients present for medical attention at either an emergency department (ED) or an outpatient clinic. The evaluation of nontraumatic chest discomfort is inherently challenging owing to the broad variety of possible causes, a minority of which are life-threatening conditions that should not be missed. It is helpful to frame the initial diagnostic assessment and triage of patients with acute chest discomfort around three categories: (1) myocardial ischemia; (2) other cardiopulmonary causes (pericardial disease, aortic emergencies, and pulmonary conditions); and (3) non-cardiopulmonary causes. Although rapid identification of high-risk conditions is a priority of the initial assessment, strategies that incorporate routine liberal use of testing carry the potential for adverse effects of unnecessary investigations.

EPIDEMIOLOGY AND NATURAL HISTORY

Chest discomfort is the third most common reason for visits to the ED in the United States, resulting in 6 to 7 million emergency visits each year. More than 60% of patients with this presentation are hospitalized for further testing, and the remainder undergo additional investigation in the ED. As few as 15% of evaluated patients are eventually diagnosed with acute coronary syndrome (ACS), with rates of 10–20% in most series of unselected populations, and a rate as low as 5% in some studies. The most common diagnoses are gastrointestinal causes **(Fig. 11-1)**, and fewer than 10% are other life-threatening cardiopulmonary conditions. In a large proportion of patients with transient acute chest discomfort, ACS or another acute cardiopulmonary cause is excluded but the cause is not determined. Therefore, the resources and time devoted to the evaluation of chest discomfort *in the absence of a severe cause* are substantial. Nevertheless, a disconcerting 2% to 6% of patients with chest discomfort of presumed non-ischemic etiology who are discharged from the ED are later deemed to have had a missed myocardial infarction (MI). Patients with a missed diagnosis of MI have a 30-day risk of death that is double that of their counterparts who are hospitalized.

The natural histories of ACS, acute pericardial diseases, pulmonary embolism, and aortic emergencies are discussed in **Chaps. 265, 268, 269, 273, and 274,** respectively. In a study of >350,000 patients with unspecified presumed non-cardiopulmonary chest discomfort, the mortality rate 1 year after discharge was <2% and did not differ significantly from age-adjusted mortality in the general population. The estimated rate of major cardiovascular events through 30 days in patients with acute chest pain who had been stratified as low risk was 2.5% in a large population-based study that excluded patients with ST-segment elevation or definite noncardiac chest pain.

CAUSES OF CHEST DISCOMFORT

The major etiologies of chest discomfort are discussed in this section and summarized in **Table 11-1**. Additional elements of the history, physical examination, and diagnostic testing that aid in distinguishing these causes are discussed in a later section (see "Approach to the Patient").

FIGURE 11-1 Distribution of final discharge diagnoses in patients with nontraumatic acute chest pain. *(Figure prepared from data in P Fruergaard et al: Eur Heart J 17:1028, 1996.)*

TABLE 11-1 Typical Clinical Features of Major Causes of Acute Chest Discomfort

SYSTEM	CONDITION	ONSET/DURATION	QUALITY	LOCATION	ASSOCIATED FEATURES
Cardiopulmonary					
Cardiac	Myocardial ischemia	*Stable angina:* Precipitated by exertion, cold, or stress; 2–10 min *Unstable angina:* Increasing pattern or at rest *Myocardial infarction:* Usually >30 min	Pressure, tightness, squeezing, heaviness, burning	Retrosternal; often radiation to neck, jaw, shoulders, or arms; sometimes epigastric	S_4 gallop or mitral regurgitation murmur (rare) during pain; S_3 or rales if severe ischemia or complication of myocardial infarction
	Pericarditis	Variable; hours to days; may be episodic	Pleuritic, sharp	Retrosternal or toward cardiac apex; may radiate to left shoulder	May be relieved by sitting up and leaning forward; pericardial friction rub
Vascular	Acute aortic syndrome	Sudden onset of unrelenting pain	Tearing or ripping; knifelike	Anterior chest, often radiating to back, between shoulder blades	Associated with hypertension and/or underlying connective tissue disorder; murmur of aortic insufficiency; loss of peripheral pulses
	Pulmonary embolism	Sudden onset	Pleuritic; may manifest as heaviness with massive pulmonary embolism	Often lateral, on the side of the embolism	Dyspnea, tachypnea, tachycardia, and hypotension
	Pulmonary hypertension	Variable; often exertional	Pressure	Substernal	Dyspnea, signs of increased venous pressure
Pulmonary	Pneumonia or pleuritis	Variable	Pleuritic	Unilateral, often localized	Dyspnea, cough, fever, rales, occasional rub
	Spontaneous pneumothorax	Sudden onset	Pleuritic	Lateral to side of pneumothorax	Dyspnea, decreased breath sounds on side of pneumothorax
Non-cardiopulmonary					
Gastrointenstinal	Esophageal reflux	10–60 min	Burning	Substernal, epigastric	Worsened by postprandial recumbency; relieved by antacids
	Esophageal spasm	2–30 min	Pressure, tightness, burning	Retrosternal	Can closely mimic angina
	Peptic ulcer	Prolonged; 60–90 min after meals	Burning	Epigastric, substernal	Relieved with food or antacids
	Gallbladder disease	Prolonged	Aching or colicky	Epigastric, right upper quadrant; sometimes to the back	May follow meal
Neuromuscular	Costochondritis	Variable	Aching	Sternal	Sometimes swollen, tender, warm over joint; may be reproduced by localized pressure on examination
	Cervical disk disease	Variable; may be sudden	Aching; may include numbness	Arms and shoulders	May be exacerbated by movement of neck
	Trauma or strain	Usually constant	Aching	Localized to area of strain	Reproduced by movement or palpation
	Herpes zoster	Usually prolonged	Sharp or burning	Dermatomal distribution	Vesicular rash in area of discomfort
Psychological	Emotional and psychiatric conditions	Variable; may be fleeting or prolonged	Variable; often manifests as tightness and dyspnea with feeling of panic or doom	Variable; may be retrosternal	Situational factors may precipitate symptoms; history of panic attacks, depression

MYOCARDIAL ISCHEMIA/INJURY

Myocardial ischemia causing chest discomfort, termed *angina pectoris*, is a primary clinical concern in patients presenting with chest symptoms. Myocardial ischemia is precipitated by an imbalance between myocardial oxygen requirements and myocardial oxygen supply, resulting in insufficient delivery of oxygen to meet the heart's metabolic demands. Myocardial oxygen consumption may be elevated by increases in heart rate, ventricular wall stress, and myocardial contractility, whereas myocardial oxygen supply is determined by coronary blood flow and coronary arterial oxygen content. When myocardial ischemia is sufficiently severe and prolonged in duration (as little as 20 min), irreversible cellular injury occurs, resulting in MI.

Ischemic heart disease is most commonly caused by atheromatous plaque that obstructs one or more of the epicardial coronary arteries. Stable ischemic heart disease **(Chap. 267)** usually results from the gradual atherosclerotic narrowing of the coronary arteries. *Stable angina* is characterized by ischemic episodes that are typically precipitated by a superimposed increase in oxygen demand during physical exertion and relieved upon resting. Ischemic heart disease becomes unstable most commonly when rupture or erosion of one or more atherosclerotic lesions triggers coronary thrombosis. Unstable ischemic heart disease is classified clinically by the presence or absence of detectable myocardial injury and the presence or absence of ST-segment elevation on the patient's electrocardiogram (ECG). When acute coronary atherothrombosis occurs, the intracoronary thrombus may be partially obstructive, generally leading to myocardial ischemia in the absence of ST-segment elevation. Marked by ischemic symptoms at rest, with minimal activity, or in an accelerating pattern, unstable ischemic heart disease is classified as *unstable angina* when there is no detectable myocardial injury and as *non–ST elevation MI* (NSTEMI) when there is evidence of myocardial necrosis **(Chap. 268)**. When the coronary thrombus is acutely and completely occlusive, transmural myocardial ischemia usually ensues, with ST-segment elevation on the ECG and myocardial necrosis leading to a diagnosis of *ST elevation MI* (STEMI, see **Chap. 269**).

Clinicians should be aware that unstable ischemic symptoms may also occur predominantly because of increased myocardial oxygen demand (e.g., during intense psychological stress or fever) or because of decreased oxygen delivery due to anemia, hypoxia, or hypotension. However, the term *acute coronary syndrome*, which encompasses unstable angina, NSTEMI, and STEMI, is in general reserved for ischemia precipitated by acute coronary atherothrombosis. In order to guide therapeutic strategies, a standardized system for classification of MI has been expanded to discriminate MI resulting from acute coronary thrombosis (type 1) from MI occurring secondary to other imbalances of myocardial oxygen supply and demand (type 2; see **Chap. 268**).

Other contributors to stable and unstable ischemic heart disease, such as endothelial dysfunction, microvascular disease, and vasospasm, may exist alone or in combination with coronary atherosclerosis and may be the dominant cause of myocardial ischemia in some patients. Moreover, non-atherosclerotic processes, including congenital abnormalities of the coronary vessels, myocardial bridging, coronary arteritis, and radiation-induced coronary disease, can lead to coronary obstruction. In addition, conditions associated with extreme myocardial oxygen demand and impaired endocardial blood flow, such as aortic valve disease **(Chap. 274)**, hypertrophic cardiomyopathy, or idiopathic dilated cardiomyopathy **(Chap. 254)**, can precipitate myocardial ischemia in patients with or without underlying obstructive atherosclerosis.

Characteristics of Ischemic Chest Discomfort The clinical characteristics of angina pectoris, often referred to simply as "angina," are highly similar whether the ischemic discomfort is a manifestation of stable ischemic heart disease, unstable angina, or MI; the exceptions are differences in the pattern and duration of symptoms associated with these syndromes (Table 11-1). Heberden initially described angina as a sense of "strangling and anxiety." Chest discomfort characteristic of myocardial ischemia is typically described as aching, heavy, squeezing, crushing, or constricting. However, in a substantial minority of patients, the quality of discomfort is extremely vague and may be described as a mild tightness, or merely an uncomfortable feeling, that sometimes is experienced as numbness or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and generally occurs down the ulnar surface of the left arm; the right arm, both arms, neck, jaw, or shoulders may also be involved. These and other characteristics of ischemic chest discomfort pertinent to discrimination from other causes of chest pain are discussed later in this chapter (see "Approach to the Patient").

Stable angina usually begins gradually and reaches its maximal intensity over a period of minutes before dissipating within several minutes with rest or with nitroglycerin. The discomfort typically occurs predictably at a characteristic level of exertion or psychological stress. By definition, unstable angina is manifest by anginal chest discomfort that occurs with progressively lower intensity of physical activity or even at rest. Chest discomfort associated with MI is typically more severe, is prolonged (usually lasting ≥30 min), and is not relieved by rest.

Mechanisms of Cardiac Pain The neural pathways involved in ischemic cardiac pain are poorly understood. Ischemic episodes are thought to excite local chemosensitive and mechanoreceptive receptors that, in turn, stimulate release of adenosine, bradykinin, and other substances that activate the sensory ends of sympathetic and vagal afferent fibers. The afferent fibers traverse the nerves that connect to the upper five thoracic sympathetic ganglia and upper five distal thoracic roots of the spinal cord. From there, impulses are transmitted to the thalamus. Within the spinal cord, cardiac sympathetic afferent impulses may converge with impulses from somatic thoracic structures, and this convergence may be the basis for referred cardiac pain. In addition, cardiac vagal afferent fibers synapse in the nucleus tractus solitarius of the medulla and then descend to the upper cervical spinothalamic tract, and this route may contribute to anginal pain experienced in the neck and jaw.

OTHER CARDIOPULMONARY CAUSES

Pericardial and Other Myocardial Diseases (See also Chap. 265) Inflammation of the pericardium due to infectious or noninfectious causes can be responsible for acute or chronic chest discomfort. The visceral surface and most of the parietal surface of the pericardium are insensitive to pain. Therefore, the pain of pericarditis is thought to arise principally from associated pleural inflammation. Because of this pleural association, the discomfort of pericarditis is usually pleuritic pain that is exacerbated by breathing, coughing, or changes in position. Moreover, owing to the overlapping sensory supply of the central diaphragm via the phrenic nerve with somatic sensory fibers originating in the third to fifth cervical segments, the pain of pleural pericarditis is often referred to the shoulder and neck. Involvement of the pleural surface of the lateral diaphragm can lead to pain in the upper abdomen.

Acute inflammatory and other non-ischemic myocardial diseases can also produce chest discomfort. The symptoms of *Takotsubo (stress-related) cardiomyopathy* often start abruptly with chest pain and shortness of breath. This form of cardiomyopathy, in its most recognizable form, is triggered by an emotionally or physically stressful event and may mimic acute MI because of its commonly associated ECG abnormalities, including ST-segment elevation, and elevated biomarkers of myocardial injury. Observational studies support a predilection for women >50 years of age. The symptoms of acute myocarditis are highly varied. Chest discomfort may either originate with inflammatory injury of the myocardium or be due to severe increases in wall stress related to poor ventricular performance.

Diseases of the Aorta (See also Chap. 274) Acute aortic dissection (Fig. 11-1) is a less common cause of chest discomfort but is important because of the catastrophic natural history of certain subsets of cases when recognized late or left untreated. Acute aortic syndromes encompass a spectrum of acute aortic diseases related to disruption of the media of the aortic wall. *Aortic dissection* involves a tear in the aortic intima, resulting in separation of the media and creation of a separate "false" lumen. A *penetrating ulcer* has been described as ulceration of an aortic atheromatous plaque that extends through the intima and

into the aortic media, with the potential to initiate an intramedial dissection or rupture into the adventitia. *Intramural hematoma* is an aortic wall hematoma with no demonstrable intimal flap, no radiologically apparent intimal tear, and no false lumen. Intramural hematoma can occur due to either rupture of the vasa vasorum or, less commonly, a penetrating ulcer.

Each of these subtypes of acute aortic syndrome typically presents with chest discomfort that is often severe, sudden in onset, and sometimes described as "tearing" in quality. Acute aortic syndromes involving the *ascending* aorta tend to cause pain in the midline of the anterior chest, whereas *descending* aortic syndromes most often present with pain in the back. Therefore, dissections that begin in the ascending aorta and extend to the descending aorta tend to cause pain in the front of the chest that extends toward the back, between the shoulder blades. Proximal aortic dissections that involve the ascending aorta (type A in the Stanford nomenclature) are at high risk for major complications that may influence the clinical presentation, including (1) compromise of the aortic ostia of the coronary arteries, resulting in MI; (2) disruption of the aortic valve, causing acute aortic insufficiency; and (3) rupture of the hematoma into the pericardial space, leading to pericardial tamponade.

Knowledge of the epidemiology of acute aortic syndromes can be helpful in maintaining awareness of this relatively uncommon group of disorders (estimated annual incidence, 3 cases per 100,000 population). Nontraumatic aortic dissections are very rare in the absence of hypertension or conditions associated with deterioration of the elastic or muscular components of the aortic media, including pregnancy, bicuspid aortic disease, or inherited connective tissue diseases, such as Marfan and Ehlers-Danlos syndromes.

Although aortic aneurysms are most often asymptomatic, thoracic aortic aneurysms can cause chest pain and other symptoms by compressing adjacent structures. This pain tends to be steady, deep, and occasionally severe. Aortitis, whether of noninfectious or infectious etiology, in the absence of aortic dissection is a rare cause of chest or back discomfort.

Pulmonary Conditions Pulmonary and pulmonary-vascular conditions that cause chest discomfort usually do so in conjunction with dyspnea and often produce symptoms that have a pleuritic nature.

PULMONARY EMBOLISM (SEE ALSO CHAP. 273) Pulmonary emboli (annual incidence, ~1 per 1000) can produce dyspnea and chest discomfort that is sudden in onset. Typically pleuritic in pattern, the chest discomfort associated with pulmonary embolism may result from (1) involvement of the pleural surface of the lung adjacent to a resultant pulmonary infarction; (2) distention of the pulmonary artery; or (3) possibly, right ventricular wall stress and/or subendocardial ischemia related to acute pulmonary hypertension. The pain associated with small pulmonary emboli is often lateral and pleuritic and is believed to be related to the first of these three possible mechanisms. In contrast, massive pulmonary emboli may cause severe substernal pain that may mimic an MI and that is plausibly attributed to the second and third of these potential mechanisms. Massive or submassive pulmonary embolism may also be associated with syncope, hypotension, and signs of right heart failure. Other typical characteristics that aid in the recognition of pulmonary embolism are discussed later in this chapter (see "Approach to the Patient").

PNEUMOTHORAX (SEE ALSO CHAP. 289) *Primary spontaneous pneumothorax* is a rare cause of chest discomfort, with an estimated annual incidence in the United States of 7 per 100,000 among men and <2 per 100,000 among women. Risk factors include male sex, smoking, family history, and Marfan syndrome. The symptoms are usually sudden in onset, and dyspnea may be mild; thus, presentation to medical attention is sometimes delayed. *Secondary spontaneous pneumothorax* may occur in patients with underlying lung disorders, such as chronic obstructive pulmonary disease, asthma, or cystic fibrosis, and usually produces symptoms that are more severe. Tension pneumothorax is a medical emergency caused by trapped intrathoracic air that precipitates hemodynamic collapse.

Other Pulmonary Parenchymal, Pleural, or Vascular Disease (See also Chaps. 277, 278, and 288) Most pulmonary diseases that produce chest pain, including pneumonia and malignancy, do so because of involvement of the pleura or surrounding structures. Pleurisy is typically described as a knifelike pain that is worsened by inspiration or coughing. In contrast, chronic pulmonary hypertension can manifest as chest pain that may be very similar to angina in its characteristics, suggesting right ventricular myocardial ischemia in some cases. Reactive airways diseases similarly can cause chest tightness associated with breathlessness rather than pleurisy.

NON-CARDIOPULMONARY CAUSES

Gastrointestinal Conditions (See also Chap. 314) Gastrointestinal disorders are the most common cause of nontraumatic chest discomfort and often produce symptoms that are difficult to discern from more serious causes of chest pain, including myocardial ischemia. Esophageal disorders, in particular, may simulate angina in the character and location of the pain. Gastroesophageal reflux and disorders of esophageal motility are common and should be considered in the differential diagnosis of chest pain (Fig. 11-1 and Table 11-1). Acid reflux often causes a burning discomfort. The pain of esophageal spasm, in contrast, is commonly an intense, squeezing discomfort that is retrosternal in location and, like angina, may be relieved by nitroglycerin or dihydropyridine calcium channel antagonists. Chest pain can also result from injury to the esophagus, such as a Mallory-Weiss tear or even an esophageal rupture (Boerhaave syndrome) caused by severe vomiting. Peptic ulcer disease is most commonly epigastric in location but can radiate into the chest (Table 11-1).

Hepatobiliary disorders, including cholecystitis and biliary colic, may mimic acute cardiopulmonary diseases. Although the pain arising from these disorders usually localizes to the right upper quadrant of the abdomen, it is variable and may be felt in the epigastrium and radiate to the back and lower chest. This discomfort is sometimes referred to the scapula or may in rare cases be felt in the shoulder, suggesting diaphragmatic irritation. The pain is steady, usually lasts several hours, and subsides spontaneously, without symptoms between attacks. Pain resulting from pancreatitis is typically aching epigastric pain that radiates to the back.

Musculoskeletal and Other Causes (See also Chap. 363) Chest discomfort can be produced by any musculoskeletal disorder involving the chest wall or the nerves of the chest wall, neck, or upper limbs. Costochondritis causing tenderness of the costochondral junctions (*Tietze's syndrome*) is relatively common. Cervical radiculitis may manifest as a prolonged or constant aching discomfort in the upper chest and limbs. The pain may be exacerbated by motion of the neck. Occasionally, chest pain can be caused by compression of the brachial plexus by the cervical ribs, and tendinitis or bursitis involving the left shoulder may mimic the radiation of angina. Pain in a dermatomal distribution can also be caused by cramping of intercostal muscles or by herpes zoster (Chap. 188).

Emotional and Psychiatric Conditions As many as 10% of patients who present to EDs with acute chest discomfort have a panic disorder or related condition (Table 11-1). The symptoms may include chest tightness or aching that is associated with a sense of anxiety and difficulty in breathing. The symptoms may be prolonged or fleeting.

APPROACH TO THE PATIENT

Chest Discomfort

Given the broad set of potential causes and the heterogeneous risk of serious complications in patients who present with acute nontraumatic chest discomfort, the priorities of the initial clinical encounter include assessment of (1) the patient's clinical stability and (2) the probability that the patient has an underlying cause of the discomfort that may be life-threatening. The high-risk conditions of principal concern are acute cardiopulmonary processes, including ACS, acute aortic syndrome, pulmonary embolism, tension pneumothorax, and pericarditis with tamponade. Among non-cardiopulmonary causes

TABLE 11-2 Considerations in the Assessment of the Patient with Chest Discomfort

1. Could the chest discomfort be due to an acute, potentially life-threatening condition that warrants urgent evaluation and management?			
Unstable ischemic heart disease	Aortic dissection	Pneumothorax	Pulmonary embolism
2. If not, could the discomfort be due to a chronic condition likely to lead to serious complications?			
Stable angina	Aortic stenosis	Pulmonary hypertension	
3. If not, could the discomfort be due to an acute condition that warrants specific treatment?			
Pericarditis	Pneumonia/ pleuritis	Herpes zoster	
4. If not, could the discomfort be due to another treatable chronic condition?			
Esophageal reflux		Cervical disk disease	
Esophageal spasm		Arthritis of the shoulder or spine	
Peptic ulcer disease		Costochondritis	
Gallbladder disease		Other musculoskeletal disorders	
Other gastrointestinal conditions		Anxiety state	

Source: Developed by Dr. Thomas H. Lee for the 18th edition of *Harrison's Principles of Internal Medicine.*

of chest pain, esophageal rupture likely holds the greatest urgency for diagnosis. Patients with these conditions may deteriorate rapidly despite initially appearing well. The remaining population with non-cardiopulmonary conditions has a more favorable prognosis during completion of the diagnostic work-up. A rapid targeted assessment for a serious cardiopulmonary cause is of particular relevance for patients with acute ongoing pain who have presented for emergency evaluation. Among patients presenting in the outpatient setting with chronic pain or pain that has resolved, a general diagnostic assessment is reasonably undertaken (see "Outpatient Evaluation of Chest Discomfort," below). A series of questions that can be used to structure the clinical evaluation of patients with chest discomfort is shown in **Table 11-2**.

HISTORY

The evaluation of nontraumatic chest discomfort relies heavily on the clinical history and physical examination to direct subsequent diagnostic testing. The evaluating clinician should assess the quality, location (including radiation), and pattern (including onset and duration) of the pain as well as any provoking or alleviating factors. The presence of associated symptoms may also be useful in establishing a diagnosis.

Quality of Pain The quality of chest discomfort alone is never sufficient to establish a diagnosis. However, the characteristics of the pain are pivotal in formulating an initial clinical impression and assessing the likelihood of a serious cardiopulmonary process (Table 11-1), including ACS in particular **(Fig. 11-2)**. Pressure or tightness is consistent with a typical presentation of myocardial ischemic pain. Nevertheless, the clinician must remember that some patients with ischemic chest symptoms deny any "pain" but rather complain of dyspnea or a vague sense of anxiety. The severity of the discomfort has poor diagnostic accuracy. It is often helpful to ask about the similarity of the discomfort to previous definite ischemic symptoms. It is unusual for angina to be sharp, as in knifelike, stabbing, or pleuritic; however, patients sometimes use the word "sharp" to convey the intensity of discomfort rather than the quality. Pleuritic discomfort is suggestive of a process involving the pleura, including pericarditis, pulmonary embolism, or pulmonary parenchymal processes. Less frequently, the pain of pericarditis or massive pulmonary embolism is a steady severe pressure or aching that can be difficult to discriminate from myocardial ischemia. "Tearing" or "ripping" pain is often described by patients with acute aortic dissection. However, acute aortic emergencies also present commonly with severe, knifelike pain. A burning quality can suggest acid reflux or peptic ulcer disease but may also occur with myocardial ischemia. Esophageal pain, particularly with spasm, can be a severe squeezing discomfort identical to angina.

Location of Discomfort A substernal location with radiation to the neck, jaw, shoulder, or arms is typical of myocardial ischemic discomfort. Radiation to both arms has a particularly high association with MI as the etiology. Some patients present with aching in sites of radiated pain as their only symptoms of ischemia. However, pain that is highly localized—for example, that which can be demarcated by the tip of one finger—is highly unusual for angina. A retrosternal location should prompt consideration of esophageal pain; however, other gastrointestinal conditions usually present with pain that is most intense in the abdomen or epigastrium, with possible radiation into the chest. Angina may also occur in an epigastric location. However, pain that occurs solely above the mandible or below the epigastrium is rarely angina. Severe pain radiating to the back, particularly between the shoulder blades, should prompt consideration of an acute aortic syndrome. Radiation to the trapezius ridge is characteristic of pericardial pain and does not usually occur with angina.

Pattern Myocardial ischemic discomfort usually builds over minutes and is exacerbated by activity and mitigated by rest. In contrast, pain that reaches its peak intensity immediately is more suggestive of aortic dissection, pulmonary embolism, or spontaneous pneumothorax. Pain that is fleeting (lasting only a few seconds) is rarely ischemic in origin. Similarly, pain that is constant in intensity for a prolonged period (many hours to days) is unlikely to represent myocardial ischemia if it occurs in the absence of other clinical consequences, such as abnormalities of the ECG, elevation of cardiac biomarkers, or clinical sequelae (e.g., heart failure or hypotension). Both myocardial ischemia and acid reflux may have their onset in the morning.

Provoking and Alleviating Factors Patients with myocardial ischemic pain usually prefer to rest, sit, or stop walking. However, clinicians should be aware of the phenomenon of "warm-up angina" in which some patients experience relief from angina as they continue at the same or even a greater level of exertion **(Chap. 267)**. Alterations in the intensity of pain with changes in position or movement of the upper extremities and neck are less likely with myocardial ischemia and suggest a musculoskeletal etiology. The pain of pericarditis, however, often is worse in the supine position and relieved by sitting upright and leaning forward. Gastroesophageal reflux may be exacerbated by alcohol, some foods, or by a reclined position. Relief can occur with sitting.

Exacerbation by eating suggests a gastrointestinal etiology such as peptic ulcer disease, cholecystitis, or pancreatitis. Peptic ulcer disease tends to become symptomatic 60–90 min after meals. However, in the setting of severe coronary atherosclerosis, redistribution of blood flow to the splanchnic vasculature after eating can trigger postprandial angina. The discomfort of acid reflux and peptic ulcer disease is usually diminished promptly by acid-reducing therapies. In contrast with its impact in some patients with angina, physical exertion is very unlikely to alter symptoms from gastrointestinal causes of chest pain. Relief of chest discomfort within minutes after administration of nitroglycerin is suggestive of but not sufficiently sensitive or specific for a definitive diagnosis of myocardial ischemia. Esophageal spasm may also be relieved promptly with nitroglycerin. A delay of >10 min before relief is obtained after nitroglycerin suggests that the symptoms either are not caused by ischemia or are caused by severe ischemia, such as during acute MI.

Associated Symptoms Symptoms that accompany myocardial ischemia may include diaphoresis, dyspnea, nausea, fatigue, faintness, and eructations. In addition, these symptoms may exist in isolation as anginal equivalents (i.e., symptoms of myocardial ischemia

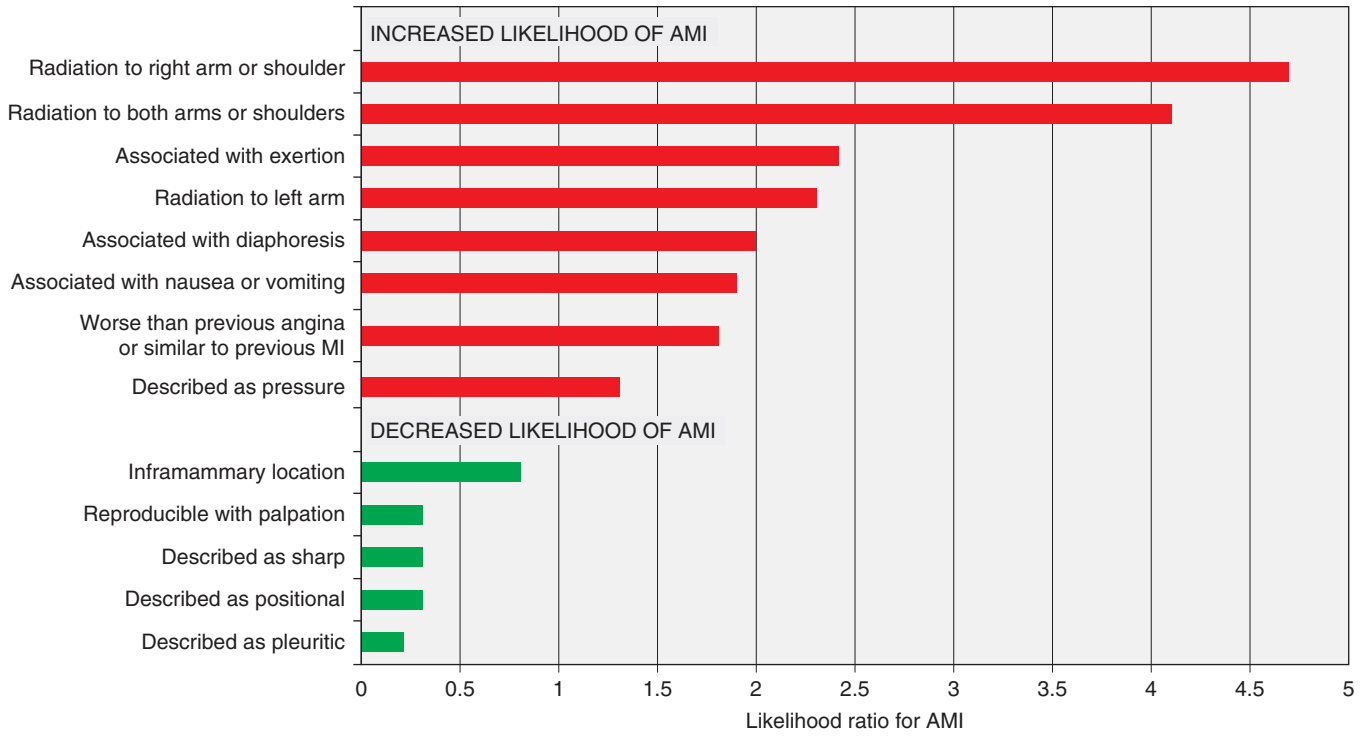


FIGURE 11-2 Association of chest pain characteristics with the probability of acute myocardial infarction (AMI). Note that a subsequent larger study showed a non-significant association with radiation to the right arm. *(Figure prepared from data in CJ Swap, JT Nagurney: JAMA 294:2623, 2005.)*

other than typical angina), particularly in women and the elderly. Dyspnea may occur with multiple conditions considered in the differential diagnosis of chest pain and thus is not discriminative, but the presence of dyspnea is important because it suggests a cardiopulmonary etiology. Sudden onset of significant respiratory distress should lead to consideration of pulmonary embolism and spontaneous pneumothorax. Hemoptysis may occur with pulmonary embolism, or as blood-tinged frothy sputum in severe heart failure but usually points toward a pulmonary parenchymal etiology of chest symptoms. Presentation with syncope or pre-syncope should prompt consideration of hemodynamically significant pulmonary embolism or aortic dissection as well as ischemic arrhythmias. Although nausea and vomiting suggest a gastrointestinal disorder, these symptoms may occur in the setting of MI (more commonly inferior MI), presumably because of activation of the vagal reflex or stimulation of left ventricular receptors as part of the Bezold-Jarisch reflex.

Past Medical History The past medical history is useful in assessing the patient for risk factors for coronary atherosclerosis and venous thromboembolism **(Chap. 273)** as well as for conditions that may predispose the patient to specific disorders. For example, a history of connective tissue diseases such as Marfan syndrome should heighten the clinician's suspicion of an acute aortic syndrome or spontaneous pneumothorax. A careful history may elicit clues about depression or prior panic attacks.

PHYSICAL EXAMINATION

In addition to providing an initial assessment of the patient's clinical stability, the physical examination of patients with chest discomfort can provide direct evidence of specific etiologies of chest pain (e.g., unilateral absence of lung sounds) and can identify potential precipitants of acute cardiopulmonary causes of chest pain (e.g., uncontrolled hypertension), relevant comorbid conditions (e.g., obstructive pulmonary disease), and complications of the presenting syndrome (e.g., heart failure). However, because the findings on physical examination may be normal in patients with unstable ischemic heart disease, an unremarkable physical examination is not definitively reassuring.

General The patient's general appearance is helpful in establishing an initial impression of the severity of illness. Patients with acute MI or other acute cardiopulmonary disorders often appear anxious, uncomfortable, pale, cyanotic, or diaphoretic. Patients who are massaging or clutching their chests may describe their pain with a clenched fist held against the sternum (*Levine's sign*). Occasionally, body habitus is helpful—for example, in patients with Marfan syndrome or the prototypical young, tall, thin man with spontaneous pneumothorax.

Vital Signs Significant tachycardia and hypotension are indicative of important hemodynamic consequences of the underlying cause of chest discomfort and should prompt a rapid survey for the most severe conditions, such as acute MI with cardiogenic shock, massive pulmonary embolism, pericarditis with tamponade, or tension pneumothorax. Acute aortic emergencies usually present with severe hypertension but may be associated with profound hypotension when there is coronary arterial compromise or dissection into the pericardium. Sinus tachycardia is an important manifestation of submassive pulmonary embolism. Tachypnea and hypoxemia point toward a pulmonary cause. The presence of low-grade fever is nonspecific because it may occur with MI and with thromboembolism in addition to infection.

Pulmonary Examination of the lungs may localize a primary pulmonary cause of chest discomfort, as in cases of pneumonia, asthma, or pneumothorax. Left ventricular dysfunction from severe ischemia/infarction as well as acute valvular complications of MI or aortic dissection can lead to pulmonary edema, which is an indicator of high risk.

Cardiac The jugular venous pulse is often normal in patients with acute myocardial ischemia but may reveal characteristic patterns with pericardial tamponade or acute right ventricular dysfunction **(Chaps. 234 and 265)**. Cardiac auscultation may reveal a third or, more commonly, a fourth heart sound, reflecting myocardial systolic or diastolic dysfunction. Murmurs of mitral regurgitation or a ventricular-septal defect may indicate mechanical complications of STEMI. A murmur of aortic insufficiency may be a complication of proximal aortic dissection. Other murmurs may reveal underlying

cardiac disorders contributory to ischemia (e.g., aortic stenosis or hypertrophic cardiomyopathy). Pericardial friction rubs reflect pericardial inflammation.

Abdominal Localizing tenderness on the abdominal examination is useful in identifying a gastrointestinal cause of the presenting syndrome. Abdominal findings are infrequent with purely acute cardiopulmonary problems, except in the case of underlying chronic cardiopulmonary disease or severe right ventricular dysfunction leading to hepatic congestion.

Vascular pulse deficits may reflect underlying chronic atherosclerosis, which increases the likelihood of coronary artery disease. However, evidence of acute limb ischemia with loss of the pulse and pallor, particularly in the upper extremities, can indicate catastrophic consequences of aortic dissection. Unilateral lower-extremity swelling should raise suspicion about venous thromboembolism.

Musculoskeletal Pain arising from the costochondral and chondrosternal articulations may be associated with localized swelling, redness, or marked localized tenderness. Pain on palpation of these joints is usually well localized and is a useful clinical sign, though deep palpation may elicit pain in the absence of costochondritis. Although palpation of the chest wall often elicits pain in patients with various musculoskeletal conditions, it should be appreciated that chest wall tenderness does not exclude myocardial ischemia. Sensory deficits in the upper extremities may be indicative of cervical disk disease.

ELECTROCARDIOGRAPHY

Electrocardiography is crucial in the evaluation of nontraumatic chest discomfort. The ECG is pivotal for identifying patients with ongoing ischemia as the principal reason for their presentation as well as secondary cardiac complications of other disorders. Professional society guidelines recommend that an ECG be obtained within 10 min of presentation, with the primary goal of identifying patients with ST-segment elevation diagnostic of MI who are candidates for immediate interventions to restore flow in the occluded coronary artery. ST-segment depression and symmetric T-wave inversions at least 0.2 mV in depth are useful for detecting myocardial ischemia in the absence of STEMI and are also indicative of higher risk of death or recurrent ischemia. Serial performance of ECGs (every 30–60 min) is recommended in the ED evaluation of suspected ACS. In addition, an ECG with right-sided lead placement should be considered in patients with clinically suspected ischemia and a nondiagnostic standard 12-lead ECG. Despite the value of the resting ECG, its sensitivity for ischemia is poor—as low as 20% in some studies.

Abnormalities of the ST segment and T wave may occur in a variety of conditions, including pulmonary embolism, ventricular hypertrophy, acute and chronic pericarditis, myocarditis, electrolyte imbalance, and metabolic disorders. Notably, hyperventilation associated with panic disorder can also lead to nonspecific ST and T-wave abnormalities. Pulmonary embolism is most often associated with sinus tachycardia but can also lead to rightward shift of the ECG axis, manifesting as an S-wave in lead I, with a Q-wave and T-wave in lead III **(Chaps. 235 and 273)**. In patients with ST-segment elevation, the presence of diffuse lead involvement not corresponding to a specific coronary anatomic distribution and PR-segment depression can aid in distinguishing pericarditis from acute MI.

CHEST RADIOGRAPHY

(See Chap. A12) Plain radiography of the chest is performed routinely when patients present with acute chest discomfort and selectively when individuals who are being evaluated as outpatients have subacute or chronic pain. The chest radiograph is most useful for identifying pulmonary processes, such as pneumonia or pneumothorax. Findings are often unremarkable in patients with ACS, but pulmonary edema may be evident. Other specific findings include widening of the mediastinum in some patients with aortic dissection, Hampton's hump or Westermark's sign in patients with pulmonary embolism **(Chaps. 273 and A12)**, or pericardial calcification in chronic pericarditis.

CARDIAC BIOMARKERS

Laboratory testing in patients with acute chest pain is focused on the detection of myocardial injury. Such injury can be detected by the presence of circulating proteins released from damaged myocardial cells. Owing to the time necessary for this release, initial biomarkers of injury may be in the normal range, even in patients with STEMI. Because of superior cardiac tissue-specificity compared with creatine kinase MB, cardiac troponin is the preferred biomarker for the diagnosis of MI and should be measured in all patients with suspected ACS at presentation and repeated in 3–6 h. Testing after 6 h is required only when there is uncertainty regarding the onset of pain or when stuttering symptoms have occurred. It is not necessary or advisable to measure troponin in patients without suspicion of ACS unless this test is being used specifically for risk stratification (e.g., in pulmonary embolism or heart failure).

The development of cardiac troponin assays with progressively greater analytical sensitivity has facilitated detection of substantially lower blood concentrations of troponin than was previously possible. This evolution permits earlier detection of myocardial injury, enhances the overall accuracy of a diagnosis of MI, and improves risk stratification in suspected ACS. The greater negative predictive value of a negative troponin result with current-generation assays is an advantage in the evaluation of chest pain in the ED. Rapid rule-out protocols that use serial testing and changes in troponin concentration over as short a period as 1–2 h appear promising and have been adopted in some centers where high-sensitivity assays for troponin are used routinely. In patients presenting >2 h after symptom onset, a concentration of cardiac troponin below the limit of detection using a high-sensitivity assay may be sufficient to exclude MI with a negative predictive value >99% at the time of hospital presentation. However, with these advantages has come a trade-off: myocardial injury is detected in a larger proportion of patients who have non-ACS cardiopulmonary conditions than with previous, less sensitive assays. This evolution in testing for myocardial necrosis has rendered other aspects of the clinical evaluation critical to the practitioner's determination of the probability that the symptoms represent ACS. In addition, observation of a change in cardiac troponin concentration between serial samples is useful in discriminating acute causes of myocardial injury from chronic elevation due to underlying structural heart disease, end-stage renal disease, or interfering antibodies. The diagnosis of MI is reserved for acute myocardial injury that is marked by a rising and/or falling pattern—with at least one value exceeding the 99th percentile reference limit—and that is caused by ischemia. Other non-ischemic insults, such as myocarditis, may result in myocardial injury but should not be labeled MI.

Other laboratory assessments may include the D-dimer test to aid in exclusion of pulmonary embolism **(Chap. 273)**. Measurement of a B-type natriuretic peptide is useful when considered in conjunction with the clinical history and examination for the diagnosis of heart failure. B-type natriuretic peptides also provide prognostic information among patients with ACS and those with pulmonary embolism.

INTEGRATIVE DECISION-AIDS

Multiple clinical algorithms have been developed to aid in decision-making during the evaluation and disposition of patients with acute nontraumatic chest pain. Such decision-aids estimate either of two closely related but not identical probabilities: (1) the probability of a final diagnosis of ACS and (2) the probability of major cardiac events during short-term follow-up. Such decision-aids are used most commonly to identify patients with a low clinical probability of ACS who are candidates either for early provocative testing for ischemia or for discharge from the ED. Goldman and Lee developed one of the first such decision-aids, using only the ECG and risk indicators—hypotension, pulmonary rales, and known ischemic heart disease—to categorize patients into four risk categories

HEART Score		
History	Highly suspicious Moderately suspicious Slightly suspicious	2 1 0
ECG	Significant ST-depression Non-specific abnormality Normal	2 1 0
Age	≥65 y 45–<65 y <45 y	2 1 0
Risk factors	≥3 risk factors 1–2 risk factors None	2 1 0
Troponin (serial)	≥3 × 99th percentile 1–<3 × 99th percentile ≤99th percentile	2 1 0
	TOTAL	
	Low-risk: 0–3 **Not low risk:** ≥4	

North American Chest Pain Rule	
High Risk Criteria	**Y/N**
Typical symptoms for ischemia	
ECG: acute ischemic changes	
Age ≥50 y	
Known coronary artery disease	
Troponin (serial) >99th percentile	
Low-risk: All No **Not Low-risk:** Any Yes	

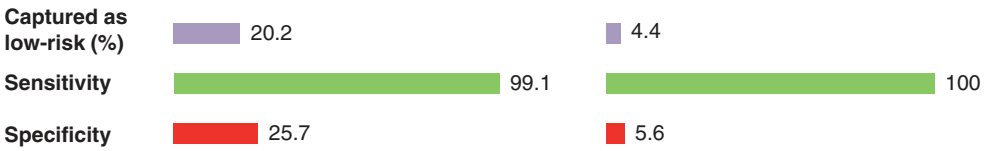


FIGURE 11-3 Examples of decision-aids used in conjunction with serial measurement of cardiac troponin for evaluation of acute chest pain. *(Figure prepared from data in SA Mahler et al: Int J Cardiol 168:795, 2013.)*

ranging from a <1% to a >16% probability of a major cardiovascular complication. The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) combines age, sex, chest pain presence, and ST-segment abnormalities to define a probability of ACS. More recently developed decision-aids are shown in **Fig. 11-3**. Elements common to each of these tools are (1) symptoms typical for ACS; (2) older age; (3) risk factors for or known atherosclerosis; (4) ischemic ECG abnormalities; and (5) elevated cardiac troponin levels. Although, because of very low specificity, the overall diagnostic performance of such decision-aids is poor (area under the receiver operating curve, 0.55–0.65), they can help identify patients with a very low probability of ACS (e.g., <1%). Nevertheless, no such decision-aid (or single clinical factor) is sufficiently sensitive and well validated to use as a sole tool for clinical decision-making.

Clinicians should differentiate between the algorithms discussed above and risk scores derived for stratification of prognosis (e.g., the TIMI and GRACE risk scores, **Chap. 269**) in patients *who already have an established diagnosis of ACS*. The latter risk scores were not designed to be used for *diagnostic* assessment.

PROVOCATIVE TESTING FOR ISCHEMIA

Exercise electrocardiography ("stress testing") is commonly employed for completion of risk stratification of patients who have undergone an initial evaluation that has not revealed a specific cause of chest discomfort and has identified them as being at low or selectively intermediate risk of ACS. Early exercise testing is safe in patients without high-risk findings after 8–12 h of observation and can assist in refining their prognostic assessment. For example, of low-risk patients who underwent exercise testing in the first 48 h after presentation, those without evidence of ischemia had a 2% rate of cardiac events through 6 months, whereas the rate was 15% among patients with either clear evidence of ischemia or an equivocal result. Patients who are unable to exercise may undergo pharmacological stress testing with either nuclear perfusion imaging or echocardiography. Notably, some experts have deemed the routine use of stress testing for low-risk patients unsupported by direct clinical evidence and a potentially unnecessary source of cost.

Professional society guidelines identify ongoing chest pain as a contraindication to stress testing. In selected patients with persistent pain and nondiagnostic ECG and biomarker data, resting myocardial perfusion images can be obtained; the absence of any perfusion abnormality substantially reduces the likelihood of coronary artery disease. In some centers, early myocardial perfusion imaging is performed as part of a routine strategy for evaluating patients at low or intermediate risk of ACS in parallel with other testing. Management of patients with normal perfusion images can be expedited with earlier discharge and outpatient stress testing, if indicated. Those with abnormal rest perfusion imaging, which cannot discriminate between old or new myocardial defects, usually warrant additional in-hospital evaluation.

OTHER NONINVASIVE STUDIES

Other noninvasive imaging studies of the chest can be used selectively to provide additional diagnostic and prognostic information on patients with chest discomfort.

Echocardiography Echocardiography is not necessarily routine in patients with chest discomfort. However, in patients with an uncertain diagnosis, particularly those with nondiagnostic ST elevation, ongoing symptoms, or hemodynamic instability, detection of abnormal regional wall motion provides evidence of possible ischemic dysfunction. Echocardiography is diagnostic in patients with mechanical complications of MI or in patients with pericardial tamponade. Transthoracic echocardiography is poorly sensitive for aortic dissection, although an intimal flap may sometimes be detected in the ascending aorta.

CT Angiography (See Chap. 236) CT angiography is emerging as a modality for the evaluation of patients with acute chest discomfort. Coronary CT angiography is a sensitive technique for detection of obstructive coronary disease, particularly in the proximal third of the major epicardial coronary arteries. CT appears to enhance the speed to disposition of patients with a low-intermediate probability for ACS; its major strength being the negative predictive value of a finding of no significant disease. In addition, contrast-enhanced CT can detect focal areas of myocardial injury in the acute setting. At the same time, CT angiography can exclude aortic dissection, pericardial effusion, and pulmonary embolism. Balancing factors in the consideration of the emerging role of coronary CT angiography in low-risk patients are radiation exposure and additional testing prompted by nondiagnostic abnormal results.

MRI (See Chap. 236) Cardiac magnetic resonance (CMR) imaging is an evolving, versatile technique for structural and functional evaluation of the heart and the vasculature of the chest. CMR can be performed as a modality for pharmacologic stress perfusion imaging. Gadolinium-enhanced CMR can provide early detection of MI, defining areas of myocardial necrosis accurately, and can delineate patterns of myocardial disease that are often useful in discriminating ischemic from non-ischemic myocardial injury. Although usually not practical for the urgent evaluation of acute chest discomfort, CMR can be a useful modality for cardiac structural evaluation of patients with elevated cardiac troponin levels in the absence of definite coronary artery disease. CMR coronary angiography is in its early stages. MRI also permits highly accurate assessment for aortic dissection but is infrequently used as the first test because CT and transesophageal echocardiography are usually more practical.

CRITICAL PATHWAYS FOR ACUTE CHEST DISCOMFORT

Because of the challenges inherent in reliably identifying the small proportion of patients with serious causes of acute chest discomfort while not exposing the larger number of low-risk patients to unnecessary testing and extended ED or hospital evaluations, many medical centers have adopted critical pathways to expedite the assessment and management of patients with nontraumatic chest pain, often in dedicated chest pain units. Such pathways are generally aimed at (1) rapid identification, triage, and treatment of high-risk cardiopulmonary conditions (e.g., STEMI); (2) accurate identification of low-risk patients who can be safely observed in units with less intensive monitoring, undergo early exercise testing, or be discharged home; and (3) through more efficient and systematic accelerated diagnostic protocols, safe reduction in costs associated with overuse of testing and unnecessary hospitalizations. In some studies, provision of protocol-driven care in chest pain units has decreased costs and overall duration of hospital evaluation with no detectable excess of adverse clinical outcomes.

OUTPATIENT EVALUATION OF CHEST DISCOMFORT

Chest pain is common in outpatient practice, with a lifetime prevalence of 20–40% in the general population. More than 25% of patients with MI have had a related visit with a primary care physician in the previous month. The diagnostic principles are the same as in the ED. However, the pretest probability of an acute cardiopulmonary cause is significantly lower. Therefore, testing paradigms are less intense, with an emphasis on the history, physical examination, and ECG. Moreover, decision-aids developed for settings with a high prevalence of significant cardiopulmonary disease have lower positive predictive value when applied in the practitioner's office. However, in general, if the level of clinical suspicion of ACS is sufficiently high to consider troponin testing, the patient should be referred to the ED for evaluation.

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12 Abdominal Pain

Danny O. Jacobs

Correctly interpreting acute abdominal pain can be quite challenging. Few clinical situations require greater judgment, because the most catastrophic of events may be forecast by the subtlest of symptoms and signs. In every instance, the clinician must distinguish those conditions that require urgent intervention from those that do not and can best be managed nonoperatively. A meticulously executed, detailed history and physical examination are critically important for focusing the differential diagnosis and allowing the diagnostic evaluation to proceed expeditiously **(Table 12-1)**.

The etiologic classification in **Table 12-2**, although not complete, provides a useful framework for evaluating patients with abdominal pain.

Any patient with abdominal pain of recent onset requires an early and thorough evaluation. The most common causes of abdominal pain on admission are nonspecific abdominal pain, acute appendicitis, pain of urologic origin, and intestinal obstruction. A diagnosis of "acute or surgical abdomen" is not acceptable because of its often misleading and erroneous connotations. Most patients who present with acute abdominal pain will have self-limited disease processes. However, it is important to remember that pain severity does not necessarily correlate with the severity of the underlying condition. And, the presence or absence of various degrees of "hunger" is unreliable as a sole indicator of the severity of intra-abdominal disease. The most obvious of "acute abdomens" may not require operative intervention, and the mildest of abdominal pains may herald an urgently correctable disease.

SOME MECHANISMS OF PAIN ORIGINATING IN THE ABDOMEN

Inflammation of the Parietal Peritoneum The pain of parietal peritoneal inflammation is steady and aching in character and is located directly over the inflamed area, its exact reference being possible because it is transmitted by somatic nerves supplying the parietal peritoneum. The intensity of the pain is dependent on the type and amount of material to which the peritoneal surfaces are exposed in a given time period. For example, the sudden release of a

TABLE 12-1 Some Key Components of the Patient's History

Age
Time and mode of onset of the pain
Pain characteristics
Duration of symptoms
Location of pain and sites of radiation
Associated symptoms and their relationship to the pain
Nausea, emesis, and anorexia
Diarrhea, constipation, or other changes in bowel habits
Menstrual history

TABLE 12-2 Some Important Causes of Abdominal Pain

Pain Originating in the Abdomen	
Parietal peritoneal inflammation	Vascular disturbances
Bacterial contamination	Embolism or thrombosis
Perforated appendix or other perforated viscus	Vascular rupture
Pelvic inflammatory disease	Pressure or torsional occlusion
Chemical irritation	Sickle cell anemia
Perforated ulcer	Abdominal wall
Pancreatitis	Distortion or traction of mesentery
Mittelschmerz	Trauma or infection of muscles
Mechanical obstruction of hollow viscera	Distension of visceral surfaces, e.g., by hemorrhage
Obstruction of the small or large intestine	Hepatic or renal capsules
Obstruction of the biliary tree	Inflammation
Obstruction of the ureter	Appendicitis
	Typhoid fever
	Neutropenic enterocolitis or "typhlitis"
Pain Referred from Extraabdominal Source	
Cardiothoracic	Pleurodynia
Acute myocardial infarction	Pneumothorax
Myocarditis, endocarditis, pericarditis	Empyema
Congestive heart failure	Esophageal disease, including spasm, rupture, or inflammation
Pneumonia (especially lower lobes)	Genitalia
Pulmonary embolus	Torsion of the testis
Metabolic Causes	
Diabetes	Acute adrenal insufficiency
Uremia	Familial Mediterranean fever
Hyperlipidemia	Porphyria
Hyperparathyroidism	C1 esterase inhibitor deficiency (angioneurotic edema)
Neurologic/Psychiatric Causes	
Herpes zoster	Spinal cord or nerve root compression
Tabes dorsalis	Functional disorders
Causalgia	Psychiatric disorders
Radiculitis from infection or arthritis	
Toxic Causes	
Lead poisoning	
Insect or animal envenomation	
Black widow spider bites	
Snake bites	
Uncertain Mechanisms	
Narcotic withdrawal	
Heat stroke	

small quantity of *sterile* acidic gastric juice into the peritoneal cavity causes much more pain than the same amount of grossly contaminated neutral feces. Enzymatically active pancreatic juice incites more pain and inflammation than does the same amount of sterile bile containing no potent enzymes. Blood is normally only a mild irritant and the response to urine is also typically bland, so exposure of blood and urine to the peritoneal cavity may go unnoticed unless it is sudden and massive. Bacterial contamination, such as may occur with pelvic inflammatory disease or perforated distal intestine, causes low-intensity pain until multiplication causes a significant amount of inflammatory mediators to be released. Patients with perforated upper gastrointestinal ulcers may present entirely differently depending on how quickly gastric juices enter the peritoneal cavity, and its pH. Thus, the rate at which any inflammatory material irritates the peritoneum is important.

The pain of peritoneal inflammation is invariably accentuated by pressure or changes in tension of the peritoneum, whether produced by palpation or by movement such as with coughing or sneezing. The patient with peritonitis characteristically lies quietly in bed, preferring to avoid motion, in contrast to the patient with colic, who may be thrashing in discomfort.

Another characteristic feature of peritoneal irritation is tonic reflex spasm of the abdominal musculature, localized to the involved body segment. Its intensity depends on the integrity of the nervous system, the location of the inflammatory process, and the rate at which it develops. Spasm over a perforated retrocecal appendix or perforation into the lesser peritoneal sac may be minimal or absent because of the protective effect of overlying viscera. Catastrophic abdominal emergencies may be associated with minimal or no detectable pain or muscle spasm in obtunded, seriously ill, debilitated, immunosuppressed, or psychotic patients. A slowly developing process also often greatly attenuates the degree of muscle spasm.

Obstruction of Hollow Viscera Intraluminal obstruction classically elicits intermittent or colicky abdominal pain that is not as well localized as the pain of parietal peritoneal irritation. However, the absence of cramping discomfort can be misleading because distention of a hollow viscus may also produce steady pain with only rare paroxysms.

Small-bowel obstruction often presents as poorly localized, intermittent periumbilical, or supraumbilical pain. As the intestine progressively dilates and loses muscular tone, the colicky nature of the pain may diminish. With superimposed strangulating obstruction, pain may spread to the lower lumbar region if there is traction on the root of the mesentery. The colicky pain of colonic obstruction is of lesser intensity, is commonly located in the infraumbilical area, and may often radiate to the lumbar region.

Sudden distention of the biliary tree produces a steady rather than colicky type of pain; hence, the term *biliary colic* is misleading. Acute distention of the gallbladder typically causes pain in the right upper quadrant with radiation to the right posterior region of the thorax or to the tip of the right scapula, but discomfort is also not uncommonly found near the midline. Distention of the common bile duct often causes epigastric pain that may radiate to the upper lumbar region. Considerable variation is common, however, so that differentiation between gallbladder or common ductal disease may be impossible.

Gradual dilatation of the biliary tree, as can occur with carcinoma of the head of the pancreas, may cause no pain or only a mild aching sensation in the epigastrium or right upper quadrant. The pain of distention of the pancreatic ducts is similar to that described for distention of the common bile duct but, in addition, is very frequently accentuated by recumbency and relieved by the upright position.

Obstruction of the urinary bladder usually causes dull, low-intensity pain in the suprapubic region. Restlessness, without specific complaint of pain, may be the only sign of a distended bladder in an obtunded patient. In contrast, acute obstruction of the intravesicular portion of the ureter is characterized by severe suprapubic and flank pain that radiates to the penis, scrotum, or inner aspect of the upper thigh. Obstruction of the ureteropelvic junction manifests as pain near the costovertebral angle, whereas obstruction of the remainder of the ureter is associated with flank pain that often extends into the same side of the abdomen.

Vascular Disturbances A frequent misconception is that pain due to intraabdominal vascular disturbances is sudden and catastrophic in nature. Certain disease processes, such as embolism or thrombosis of the superior mesenteric artery or impending rupture of an abdominal aortic aneurysm, can certainly be associated with diffuse, severe pain. Yet, just as frequently, the patient with occlusion of the superior mesenteric artery only has mild continuous or cramping diffuse pain for 2 or 3 days before vascular collapse or findings of peritoneal inflammation appear. The early, seemingly insignificant discomfort is caused by hyperperistalsis rather than peritoneal inflammation. Indeed, absence of tenderness and rigidity in the presence of continuous, diffuse pain (e.g., "pain out of proportion to physical findings") in a patient likely to have vascular disease is quite characteristic of occlusion of the superior

mesenteric artery. Abdominal pain with radiation to the sacral region, flank, or genitalia should always signal the possible presence of a rupturing abdominal aortic aneurysm. This pain may persist over a period of several days before rupture and collapse occur.

Abdominal Wall Pain arising from the abdominal wall is usually constant and aching. Movement, prolonged standing, and pressure accentuate the discomfort and associated muscle spasm. In the relatively rare case of hematoma of the rectus sheath, now most frequently encountered in association with anticoagulant therapy, a mass may be present in the lower quadrants of the abdomen. Simultaneous involvement of muscles in other parts of the body usually serves to differentiate myositis of the abdominal wall from other processes that might cause pain in the same region.

REFERRED PAIN IN ABDOMINAL DISEASE

Pain referred to the abdomen from the thorax, spine, or genitalia may present a diagnostic challenge because diseases of the upper part of the abdominal cavity such as acute cholecystitis or perforated ulcer may be associated with intrathoracic complications. A most important, yet often forgotten, dictum is that the possibility of intrathoracic disease must be considered in every patient with abdominal pain, especially if the pain is in the upper abdomen.

Systematic questioning and examination directed toward detecting myocardial or pulmonary infarction, pneumonia, pericarditis, or esophageal disease (the intrathoracic diseases that most often masquerade as abdominal emergencies) will often provide sufficient clues to establish the proper diagnosis. Diaphragmatic pleuritis resulting from pneumonia or pulmonary infarction may cause pain in the right upper quadrant and pain in the supraclavicular area, the latter radiation to be distinguished from the referred subscapular pain caused by acute distention of the extrahepatic biliary tree. The ultimate decision as to the origin of abdominal pain may require deliberate and planned observation over a period of several hours, during which repeated questioning and examination will provide the diagnosis or suggest the appropriate studies.

Referred pain of thoracic origin is often accompanied by splinting of the involved hemithorax with respiratory lag and a decrease in excursion more marked than that seen in the presence of intraabdominal disease. In addition, apparent abdominal muscle spasm caused by referred pain will diminish during the inspiratory phase of respiration, whereas it persists throughout both respiratory phases if it is of abdominal origin. Palpation over the area of referred pain in the abdomen also does not usually accentuate the pain and, in many instances, actually seems to relieve it.

Thoracic disease and abdominal disease frequently coexist and may be difficult or impossible to differentiate. For example, the patient with known biliary tract disease often has epigastric pain during myocardial infarction, or biliary colic may be referred to the precordium or left shoulder in a patient who has suffered previously from angina pectoris. **For an explanation of the radiation of pain to a previously diseased area, see Chap. 10.**

Referred pain from the spine, which usually involves compression or irritation of nerve roots, is characteristically intensified by certain motions such as cough, sneeze, or strain and is associated with hyperesthesia over the involved dermatomes. Pain referred to the abdomen from the testes or seminal vesicles is generally accentuated by the slightest pressure on either of these organs. The abdominal discomfort experienced is of dull, aching character and is poorly localized.

METABOLIC ABDOMINAL CRISES

Pain of metabolic origin may simulate almost any other type of intraabdominal disease. Several mechanisms may be at work. In certain instances, such as hyperlipidemia, the metabolic disease itself may be accompanied by an intraabdominal process such as pancreatitis, which can lead to unnecessary laparotomy unless recognized. C1 esterase deficiency associated with angioneurotic edema is often associated with episodes of severe abdominal pain. Whenever the cause of abdominal pain is obscure, a metabolic origin always must be considered. Abdominal pain is also the hallmark of familial Mediterranean fever **(Chap. 362)**.

The pain of porphyria and of lead colic is usually difficult to distinguish from that of intestinal obstruction, because severe hyperperistalsis is a prominent feature of both. The pain of uremia or diabetes is nonspecific, and the pain and tenderness frequently shift in location and intensity. Diabetic acidosis may be precipitated by acute appendicitis or intestinal obstruction, so if prompt resolution of the abdominal pain does not result from correction of the metabolic abnormalities, an underlying organic problem should be suspected. Black widow spider bites produce intense pain and rigidity of the abdominal muscles and back, an area infrequently involved in intraabdominal disease.

IMMUNOCOMPROMISE

Evaluating and diagnosing causes of abdominal pain in immunosuppressed or otherwise immunocompromised patients is very difficult. This includes those who have undergone organ transplantation; who are receiving immunosuppressive treatments for autoimmune diseases, chemotherapy, or glucocorticoids; who have AIDS; and who are very old. In these circumstances, normal physiologic responses may be absent or masked. In addition, unusual infections may cause abdominal pain where the etiologic agents include cytomegalovirus, mycobacteria, protozoa, and fungi. These pathogens may affect all gastrointestinal organs, including the gallbladder, liver, and pancreas, as well as the gastrointestinal tract, causing occult or overtly symptomatic perforations of the latter. Splenic abscesses due to *Candida* or *Salmonella* infection should also be considered, especially when evaluating patients with left upper quadrant or left flank pain. Acalculous cholecystitis may be observed in immunocompromised patients or those with AIDS, where it is often associated with cryptosporidiosis or cytomegalovirus infection.

Neutropenic enterocolitis (typhlitis) is often identified as a cause of abdominal pain and fever in some patients with bone marrow suppression due to chemotherapy. Acute graft-versus-host disease should be considered in this circumstance. Optimal management of these patients requires meticulous follow-up including serial examinations to assess the need for more surgical intervention, for example, to address perforation.

NEUROGENIC CAUSES

Diseases that injure sensory nerves may cause causalgic pain. It has a burning character and is usually limited to the distribution of a given peripheral nerve. Stimuli that are normally not painful such as touch or a change in temperature may be causalgic and are often present even at rest. The demonstration of irregularly spaced cutaneous "pain spots" may be the only indication that an old nerve injury exists. Even though the pain may be precipitated by gentle palpation, rigidity of the abdominal muscles is absent, and the respirations are not usually disturbed. Distention of the abdomen is uncommon, and the pain has no relationship to food intake.

Pain arising from spinal nerves or roots comes and goes suddenly and is of a lancinating type **(Chap. 14)**. It may be caused by herpes zoster, impingement by arthritis, tumors, a herniated nucleus pulposus, diabetes, or syphilis. It is not associated with food intake, abdominal distention, or changes in respiration. Severe muscle spasms, when present, are either relieved but are certainly not accentuated by abdominal palpation. The pain is made worse by movement of the spine and is usually confined to a few dermatomes. Hyperesthesia is very common.

Pain due to functional causes conforms to none of the aforementioned patterns. Mechanisms of disease are not clearly established. Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habits. The diagnosis is made on the basis of clinical criteria **(Chap. 320)** and after exclusion of demonstrable structural abnormalities. The episodes of abdominal pain may be brought on by stress, and the pain varies considerably in type and location. Nausea and vomiting are rare. Localized tenderness and muscle spasm are inconsistent or absent. The causes of IBS or related functional disorders are not yet fully understood.

APPROACH TO THE PATIENT

Abdominal Pain

Few abdominal conditions require such urgent operative intervention that an orderly approach needs to be abandoned, no matter how ill the patient is. Only patients with exsanguinating intraabdominal hemorrhage (e.g., ruptured aneurysm) must be rushed to the operating room immediately, but in such instances, only a few minutes are required to assess the critical nature of the problem. Under these circumstances, all obstacles must be swept aside, adequate venous access for fluid replacement obtained, and the operation begun. Unfortunately, many of these patients may die in the radiology department or the emergency room while awaiting unnecessary examinations. *There are no absolute contraindications to operation when massive intraabdominal hemorrhage is present.* Fortunately, this situation is relatively rare. This statement does not necessarily apply to patients with intraluminal gastrointestinal hemorrhage, who can often be managed by other means **(Chap. 44)**. In these patients, obtaining a *detailed history when possible* can be extremely helpful even though it can be laborious and time-consuming. Decision-making regarding next steps is facilitated and a reasonably accurate diagnosis can be made before any further diagnostic testing is undertaken.

In cases of *acute* abdominal pain, a diagnosis can be readily established in most instances, whereas success is not so frequent in patients with *chronic* pain. IBS is one of the most common causes of abdominal pain and must always be kept in mind **(Chap. 320)**. The location of the pain can assist in narrowing the differential diagnosis **(Table 12-3)**; however, the *chronological sequence of events* in the patient's history is often more important than the pain's location. Careful attention should be paid to the extraabdominal regions. Narcotics or analgesics should *not* be withheld until a definitive diagnosis or a definitive plan has been formulated; obfuscation of the diagnosis by adequate analgesia is unlikely.

TABLE 12-3 Differential Diagnoses of Abdominal Pain by Location

Right Upper Quadrant	Epigastric	Left Upper Quadrant
Cholecystitis	Peptic ulcer disease	Splenic infarct
Cholangitis	Gastritis	Splenic rupture
Pancreatitis	GERD	Splenic abscess
Pneumonia/empyema	Pancreatitis	Gastritis
Pleurisy/pleurodynia	Myocardial infarction	Gastric ulcer
Subdiaphragmatic abscess	Pericarditis	Pancreatitis
Hepatitis	Ruptured aortic aneurysm	Subdiaphragmatic abscess
Budd-Chiari syndrome	Esophagitis	
Right Lower Quadrant	**Periumbilical**	**Left Lower Quadrant**
Appendicitis	Early appendicitis	Diverticulitis
Salpingitis	Gastroenteritis	Salpingitis
Inguinal hernia	Bowel obstruction	Inguinal hernia
Ectopic pregnancy	Ruptured aortic aneurysm	Ectopic pregnancy
Nephrolithiasis		Nephrolithiasis
Inflammatory bowel disease		Irritable bowel syndrome
Mesenteric lymphadenitis		Inflammatory bowel disease
Typhlitis		
Diffuse Nonlocalized Pain		
Gastroenteritis	Malaria	
Mesenteric ischemia	Familial Mediterranean fever	
Bowel obstruction	Metabolic diseases	
Irritable bowel syndrome	Psychiatric disease	
Peritonitis		
Diabetes		

Abbreviation: GERD, gastroesophageal reflux disease.

An accurate menstrual history in a female patient is essential. It is important to remember that normal anatomic relationships can be significantly altered by the gravid uterus. Abdominal and pelvic pain may occur during pregnancy due to conditions that do not require operation. Lastly, some otherwise noteworthy laboratory values (e.g., leukocytosis) may represent the normal physiologic changes of pregnancy.

In the examination, simple critical inspection of the patient, for example, of facies, position in bed, and respiratory activity, provides valuable clues. The amount of information to be gleaned is directly proportional to the *gentleness* and thoroughness of the examiner. Once a patient with peritoneal inflammation has been examined brusquely, accurate assessment by the next examiner becomes almost impossible. Eliciting rebound tenderness by sudden release of a deeply palpating hand in a patient with suspected peritonitis is cruel and unnecessary. The same information can be obtained by gentle percussion of the abdomen (rebound tenderness on a miniature scale), a maneuver that can be far more precise and localizing. Asking the patient to cough will elicit true rebound tenderness without the need for placing a hand on the abdomen. Furthermore, the forceful demonstration of rebound tenderness will startle and induce protective spasm in a nervous or worried patient in whom true rebound tenderness is not present. A palpable gallbladder will be missed if palpation is so aggressive that voluntary muscle spasm becomes superimposed on involuntary muscular rigidity.

As with history-taking, sufficient time should be spent in the examination. Abdominal signs may be minimal but nevertheless, if accompanied by consistent symptoms, may be exceptionally meaningful. Abdominal signs may be virtually or totally absent in cases of pelvic peritonitis, so careful *pelvic and rectal examinations are mandatory in every patient with abdominal pain.* Tenderness on pelvic or rectal examination in the absence of other abdominal signs can be caused by operative indications such as perforated appendicitis, diverticulitis, twisted ovarian cyst, and many others. Much attention has been paid to the presence or absence of peristaltic sounds, their quality, and their frequency. Auscultation of the abdomen is one of the least revealing aspects of the physical examination of a patient with abdominal pain. Catastrophes such as a strangulating small-intestinal obstruction or perforated appendicitis may occur in the presence of normal peristaltic sounds. Conversely, when the proximal part of the intestine above obstruction becomes markedly distended and edematous, peristaltic sounds may lose the characteristics of borborygmi and become weak or absent, even when peritonitis is not present. It is usually the severe chemical peritonitis of sudden onset that is associated with the truly silent abdomen.

Laboratory examinations may be valuable in assessing the patient with abdominal pain, yet, with few exceptions, they rarely establish a diagnosis. Leukocytosis should never be the single deciding factor as to whether or not operation is indicated. A white blood cell count >20,000/μL may be observed with perforation of a viscus, but pancreatitis, acute cholecystitis, pelvic inflammatory disease, and intestinal infarction may also be associated with marked leukocytosis. A normal white blood cell count is not rare in cases of perforation of abdominal viscera. A diagnosis of anemia may be more helpful than the white blood cell count, especially when combined with the history.

The urinalysis may reveal the state of hydration or rule out severe renal disease, diabetes, or urinary infection. Blood urea nitrogen, glucose, and serum bilirubin levels and liver function tests may be helpful. Serum amylase levels may be increased by many diseases other than pancreatitis, for example, perforated ulcer, strangulating intestinal obstruction, and acute cholecystitis; thus, elevations of serum amylase do not rule in or rule out the need for an operation.

Plain and upright or lateral decubitus radiographs of the abdomen have limited utility and may be unnecessary in some patients who have substantial evidence of some diseases such as acute appendicitis or strangulated external hernia. Where the indications for surgical or medical intervention are not clear, low dose

computed tomography is preferred to abdominal radiography when evaluating non-traumatic acute abdominal pain.

Very rarely, barium or water-soluble contrast study of the upper part of the gastrointestinal tract are appropriate radiographic investigations and may demonstrate partial intestinal obstruction that may elude diagnosis by other means. If there is any question of obstruction of the colon, oral administration of barium sulfate should be avoided. On the other hand, in cases of suspected colonic obstruction (without perforation), a contrast enema may be diagnostic.

In the absence of trauma, peritoneal lavage has been replaced as a diagnostic tool by CT scanning and laparoscopy. Ultrasonography has proved to be useful in detecting an enlarged gallbladder or pancreas, the presence of gallstones, an enlarged ovary, or a tubal pregnancy. Laparoscopy is especially helpful in diagnosing pelvic conditions, such as ovarian cysts, tubal pregnancies, salpingitis, and acute appendicitis and other disease processes. Laparoscopy has a particular advantage over imaging in that the underlying etiologic condition can often be definitively addressed.

Radioisotopic hepatobiliary iminodiacetic acid scans (HIDAs) may help differentiate acute cholecystitis or biliary colic from acute pancreatitis. A CT scan may demonstrate an enlarged pancreas, ruptured spleen, or thickened colonic or appendiceal wall and streaking of the mesocolon or mesoappendix characteristic of diverticulitis or appendicitis.

Sometimes, even under the best circumstances with all available aids and with the greatest of clinical skill, a definitive diagnosis cannot be established at the time of the initial examination. And, in some cases, operation may be indicated based on clinical grounds alone. Should that decision be questionable, watchful waiting with repeated questioning and examination will often elucidate the true nature of the illness and indicate the proper course of action.

Acknowledgment

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13 Headache

Peter J. Goadsby

Headache is among the most common reasons patients seek medical attention, on a global basis being responsible for more disability than any other neurologic problem. Diagnosis and management are based on a careful clinical approach augmented by an understanding of the anatomy, physiology, and pharmacology of the nervous system pathways mediating the various headache syndromes. This chapter will focus on the general approach to a patient with headache; migraine and other primary headache disorders are discussed in **Chap. 422**.

TABLE 13-1 Common Causes of Headache

PRIMARY HEADACHE		SECONDARY HEADACHE	
TYPE	%	TYPE	%
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: After J Olesen et al: *The Headaches*. Philadelphia, Lippincott Williams & Wilkins, 2005.

GENERAL PRINCIPLES

A classification system developed by the International Headache Society (*www.ihs-headache.org/ichd-guidelines*) characterizes headache as primary or secondary **(Table 13-1)**. *Primary headaches* are those in which headache and its associated features are the disorder itself, whereas *secondary headaches* are those caused by exogenous disorders (Headache Classification Committee of the International Headache Society, 2018). Primary headache often results in considerable disability and a decrease in the patient's quality of life. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but rarely worrisome. Life-threatening headache is relatively uncommon, but vigilance is required in order to recognize and appropriately treat such patients.

ANATOMY AND PHYSIOLOGY OF HEADACHE

Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors **(Chap. 10)**. In such situations, pain perception is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain-producing pathways of the peripheral or central nervous system (CNS) are damaged or activated inappropriately. Headache may originate from either or both mechanisms. Relatively few cranial structures are pain-producing; these include the scalp, meningeal arteries, dural sinuses, falx cerebri, and proximal segments of the large pial arteries. The ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are not pain-producing.

The key structures involved in primary headache appear to be the following:

- The large intracranial vessels and dura mater and the peripheral terminals of the trigeminal nerve that innervate these structures
- The caudal portion of the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex)
- Rostral pain-processing regions, such as the ventroposteromedial thalamus and the cortex
- The pain-modulatory systems in the brain that modulate input from trigeminal nociceptors at all levels of the pain-processing pathways and influence vegetative functions, such as hypothalamus and brainstem structures

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the *trigeminovascular system*. Cranial autonomic symptoms, such as *lacrimation, conjunctival injection, nasal congestion, rhinorrhea, periorbital swelling, aural fullness*, and *ptosis*, are prominent in the trigeminal autonomic cephalalgias (TACs), including cluster headache and paroxysmal hemicrania, and may also be seen in migraine, even in children. These autonomic symptoms reflect activation of cranial parasympathetic pathways, and functional imaging studies indicate that vascular changes in migraine and cluster headache, when present, are similarly driven by these cranial autonomic systems. Moreover, they can often be mistaken for symptoms or signs of cranial sinus inflammation, which is thus overdiagnosed and inappropriately managed. Migraine and other primary headache types are

TABLE 13-2 Headache Symptoms That Suggest a Serious Underlying Disorder

Sudden-onset headache
First severe headache
"Worst" headache ever
Vomiting that precedes headache
Subacute worsening over days or weeks
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness
Onset after age 55
Fever or unexplained systemic signs
Abnormal neurologic examination
Pain associated with local tenderness, e.g., region of temporal artery

not "vascular headaches"; these disorders do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects. Migraine is a brain disorder and is best understood and managed as such.

CLINICAL EVALUATION OF ACUTE, NEW-ONSET HEADACHE

The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache. Patients with recent onset of pain require prompt evaluation and appropriate treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumor, and purulent sinusitis. When worrisome symptoms and signs are present **(Table 13-2)**, rapid diagnosis and management are critical.

A careful neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a computed tomography (CT) or magnetic resonance imaging (MRI) study of the brain. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. In some circumstances, a lumbar puncture (LP) is also required, unless a benign etiology can be otherwise established. A general evaluation of acute headache might include cranial arteries by palpation; cervical spine by the effect of passive movement of the head and by imaging; the investigation of cardiovascular and renal status by blood pressure monitoring and urine examination; and eyes by funduscopy, intraocular pressure measurement, and refraction.

The psychological state of the patient should also be evaluated because a relationship exists between head pain, depression, and anxiety. This is intended to identify comorbidity rather than provide an explanation for the headache, because troublesome headache is seldom simply caused by mood change. Although it is notable that medicines with antidepressant actions are also effective in the preventive treatment of both tension-type headache and migraine, each symptom must be treated optimally.

Underlying recurrent headache disorders may be activated by pain that follows otologic or endodontic surgical procedures. Thus, pain about the head as the result of diseased tissue or trauma may reawaken an otherwise quiescent migraine syndrome. Treatment of the headache is largely ineffective until the cause of the primary problem is addressed.

Serious underlying conditions that are associated with headache are described below. Brain tumor is a rare cause of headache and even less commonly a cause of severe pain. The vast majority of patients presenting with severe headache have a benign cause.

SECONDARY HEADACHE

The management of secondary headache focuses on diagnosis and treatment of the underlying condition.

MENINGITIS

Acute, severe headache with stiff neck and fever suggests meningitis. LP is mandatory. Often there is striking accentuation of pain with eye movement. Meningitis can be easily mistaken for migraine in that the cardinal symptoms of pounding headache, photophobia, nausea, and vomiting are frequently present, perhaps reflecting the underlying biology of some of the patients.

Meningitis is discussed in Chaps. 133 and 134.

INTRACRANIAL HEMORRHAGE

Acute, maximal in <5 min, severe headache lasting >5 min with stiff neck but without fever suggests subarachnoid hemorrhage. A ruptured aneurysm, arteriovenous malformation, or intraparenchymal hemorrhage may also present with headache alone. Rarely, if the hemorrhage is small or below the foramen magnum, the head CT scan can be normal. Therefore, LP may be required to diagnose definitively subarachnoid hemorrhage.

Subarachnoid hemorrhage is discussed in Chap. 302, and intracranial hemorrhage in Chap. 421.

BRAIN TUMOR

Approximately 30% of patients with brain tumors consider headache to be their chief complaint. The head pain is usually nondescript—an intermittent deep, dull aching of moderate intensity, which may worsen with exertion or change in position and may be associated with nausea and vomiting. This pattern of symptoms results from migraine far more often than from brain tumor. The headache of brain tumor disturbs sleep in about 10% of patients. Vomiting that precedes the appearance of headache by weeks is highly characteristic of posterior fossa brain tumors. A history of amenorrhea or galactorrhea should lead one to question whether a prolactin-secreting pituitary adenoma (or the polycystic ovary syndrome) is the source of headache. Headache arising de novo in a patient with known malignancy suggests either cerebral metastases or carcinomatous meningitis, or both. Head pain appearing abruptly after bending, lifting, or coughing can be due to a posterior fossa mass, a Chiari malformation, or low cerebrospinal fluid (CSF) volume.

Brain tumors are discussed in Chap. 86.

TEMPORAL ARTERITIS

(See also Chaps. 28 and 356) Temporal (giant cell) arteritis is an inflammatory disorder of arteries that frequently involves the extracranial carotid circulation. It is a common disorder of the elderly; its annual incidence is 77 per 100,000 individuals aged ≥50. The average age of onset is 70 years, and women account for 65% of cases. About half of patients with untreated temporal arteritis develop blindness due to involvement of the ophthalmic artery and its branches; indeed, the ischemic optic neuropathy induced by giant cell arteritis is the major cause of rapidly developing bilateral blindness in patients >60 years. Because treatment with glucocorticoids is effective in preventing this complication, prompt recognition of the disorder is important.

Typical presenting symptoms include headache, polymyalgia rheumatica **(Chap. 356)**, jaw claudication, fever, and weight loss. Headache is the dominant symptom and often appears in association with malaise and muscle aches. Head pain may be unilateral or bilateral and is located temporally in 50% of patients but may involve any and all aspects of the cranium. Pain usually appears gradually over a few hours before peak intensity is reached; occasionally, it is explosive in onset. The quality of pain is infrequently throbbing; it is almost invariably described as dull and boring, with superimposed episodic stabbing pains similar to the sharp pains that appear in migraine. Most patients can recognize that the origin of their head pain is superficial, external to the skull, rather than originating deep within the cranium (the pain site usually identified migraineurs). Scalp tenderness is present, often to a marked degree; brushing the hair or resting the head on a pillow may be impossible because of pain. Headache is usually worse at night and often aggravated by exposure to cold. Additional findings may include reddened, tender nodules or red streaking of the skin overlying the temporal arteries, and tenderness of the temporal or, less commonly, the occipital arteries.

The erythrocyte sedimentation rate (ESR) is often, although not always, elevated; a normal ESR does not exclude giant cell arteritis. A temporal artery biopsy followed by immediate treatment with prednisone 80 mg daily for the first 4–6 weeks should be initiated when clinical suspicion is high. The prevalence of migraine among the elderly is substantial, considerably higher than that of giant cell arteritis. Migraineurs often report amelioration of their headaches with prednisone; thus, caution must be used when interpreting the therapeutic response.

GLAUCOMA

Glaucoma may present with a prostrating headache associated with nausea and vomiting. The headache often starts with severe eye pain. On physical examination, the eye is often red with a fixed, moderately dilated pupil.

Glaucoma is discussed in Chap. 28.

PRIMARY HEADACHE DISORDERS

Primary headaches are disorders in which headache and associated features occur in the absence of any exogenous cause. The most common are migraine, tension-type headache, and the TACs, notably cluster headache. These entities are discussed in detail in **Chap. 422**.

CHRONIC DAILY OR NEAR-DAILY HEADACHE

The broad description of chronic daily headache (CDH) can be applied when a patient experiences headache on 15 days or more per month. CDH is not a single entity; it encompasses a number of different headache syndromes, both primary and secondary **(Table 13-3)**. In aggregate, this group presents considerable disability and is thus specially dealt with here. Population-based estimates suggest that about 4% of adults have daily or near-daily headache.

APPROACH TO THE PATIENT

Chronic Daily Headache

The first step in the management of patients with CDH is to diagnose any secondary headache and treat that problem (Table 13-3). This can sometimes be a challenge where the underlying cause triggers a worsening of a primary headache. For patients with primary headaches, diagnosis of the headache type will guide therapy. Preventive treatments such as tricyclics, either amitriptyline or nortriptyline at doses up to 1 mg/kg, are very useful in patients with CDH arising from migraine or tension-type headache or where the secondary cause has activated the underlying primary headache. Tricyclics are started in low doses (10–25 mg) daily and may be given 12 h before the expected time of awakening in order to avoid excess morning sleepiness. Medicines including topiramate, valproate, propranolol, flunarizine (not available in the United States), and candesartan are also useful in migraine.

TABLE 13-3 Classification of Daily or Near-Daily Headache

Primary		
>4 H DAILY	**<4 H DAILY**	**SECONDARY**
Chronic migraine[a]	Chronic cluster headache[b]	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache[a]	Chronic paroxysmal hemicrania	Inflammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua[a] New daily persistent headache[a]	SUNCT/SUNA Hypnic headache	Chronic CNS infection Medication-overuse headache[a]

[a]May be complicated by medication overuse. [b]Some patients may have headache >4 h/d.

Abbreviations: CNS, central nervous system; SUNA, short-lasting *u*nilateral *n*euralgiform headache *a*ttacks with cranial autonomic symptoms; SUNCT, short-lasting *u*nilateral *n*euralgiform headache attacks with conjunctival injection and *t*earing.

MANAGEMENT OF MEDICALLY INTRACTABLE DISABLING PRIMARY CHRONIC DAILY HEADACHE

The management of medically intractable headache is difficult, although developments in therapy are at hand. Monoclonal antibodies to calcitonin gene-related peptide (CGRP) or its receptor have been reported to be effective and well-tolerated in chronic migraine in phase II/III randomized placebo-controlled trials. Non-invasive neuromodulatory approaches, such as single pulse transcranial magnetic stimulation and non-invasive vagal nerve stimulation, which appear to modulate thalamic processing or brainstem mechanisms, respectively, in migraine have, or are, entering clinical practice, respectively. Non-invasive vagal nerve stimulation has also shown promise in chronic cluster headache, chronic paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua **(Chap. 422)**. Other modalities are discussed in **Chap. 422**.

MEDICATION-OVERUSE HEADACHE

Overuse of analgesic medication for headache can aggravate headache frequency, markedly impair the effect of preventive medicines, and induce a state of refractory daily or near-daily headache called *medication-overuse headache*. A proportion of patients who stop taking analgesics will experience substantial improvement in the severity and frequency of their headache. However, even after cessation of analgesic use, many patients continue to have headache, although they may feel clinically improved in some way, especially if they have been using opioids or barbiturates regularly. The residual symptoms probably represent the underlying primary headache disorder, and most commonly, this issue occurs in patients prone to migraine.

Management of Medication Overuse: Outpatients For patients who overuse medications, it is often helpful that analgesic use be reduced and eliminated. One approach is to reduce the medication dose by 10% every 1–2 weeks. Immediate cessation of analgesic use is possible for some patients, provided there is no contraindication. Both approaches are facilitated by the use of a medication diary maintained during the month or two before cessation; this helps to identify the scope of the problem. A small dose of a nonsteroidal anti-inflammatory drug (NSAID) such as naproxen, 500 mg bid, if tolerated, will help relieve residual pain as analgesic use is reduced. NSAID overuse is not usually a problem for patients with daily headache when a NSAID with a longer half-life is taken once or twice daily; however, overuse problems may develop with more frequent dosing schedules or shorter acting NSAIDS. Once the patient has substantially reduced analgesic use, a preventive medication should be introduced, although another equally widely used approach is to commence the preventive at the same time as the analgesic reduction is started. It must be emphasized that *preventives often do not work in the presence of analgesic overuse*. The most common cause of unresponsiveness to treatment is the use of a preventive when analgesics continue to be used regularly. For some patients, discontinuing analgesics is very difficult; often the best approach is to inform the patient that some degree of pain is inevitable during this initial period.

Management of Medication Overuse: Inpatients Some patients will require hospitalization for detoxification. Such patients have typically failed efforts at outpatient withdrawal or have a significant medical condition, such as diabetes mellitus or epilepsy, which would complicate withdrawal as an outpatient. Following admission to the hospital, acute medications are withdrawn completely on the first day, in the absence of a contraindication. Antiemetics and fluids are administered as required; clonidine is used for

opioid withdrawal symptoms. For acute intolerable pain during the waking hours, aspirin, 1 g IV (not approved in United States), is useful. IM chlorpromazine can be helpful at night; patients must be adequately hydrated. Three to five days into the admission, as the effect of the withdrawn substance wears off, a course of IV dihydroergotamine (DHE) can be used. DHE, administered every 8 h for 5 consecutive days, can induce a significant remission that allows a preventive treatment to be established. Serotonin 5-HT_3 receptor antagonists, such as ondansetron or granisetron, or the neurokinin receptor antagonist, aprepitant, may be required with DHE to prevent significant nausea, and domperidone (not approved in the United States) orally or by suppository can be very helpful. Avoiding sedating or otherwise side effect–prone antiemetics is helpful.

NEW DAILY PERSISTENT HEADACHE

New daily persistent headache (NDPH) is a clinically distinct syndrome with important secondary causes; these are listed in **Table 13-4**.

Clinical Presentation The patient with NDPH presents with headache on most if not all days, and the patient can clearly, and often vividly, recall the moment of onset. The headache usually begins abruptly, but onset may be more gradual; evolution over 3 days has been proposed as the upper limit for this syndrome. Patients typically recall the exact day and circumstances of the onset of headache; the new, persistent head pain does not remit. The first priority is to distinguish between a primary and a secondary cause of this syndrome. Subarachnoid hemorrhage is the most serious of the secondary causes and must be excluded either by history or appropriate investigation **(Chap. 302)**.

Secondary NDPH • **Low CSF Volume Headache** In these syndromes, head pain is positional: it begins when the patient sits or stands upright and resolves upon reclining. The pain, which is occipitofrontal, is usually a dull ache but may be throbbing. Patients with chronic low CSF volume headache typically present with a history of headache from 1 day to the next that is generally not present on waking but worsens during the day. Recumbency usually improves the headache within minutes, and it can take only minutes to an hour for the pain to return when the patient resumes an upright position.

The most common cause of headache due to persistent low CSF volume is CSF leak following LP. Post-LP headache usually begins within 48 h but may be delayed for up to 12 days. Its incidence is between 10 and 30%. Beverages with caffeine may provide temporary relief. Besides LP, index events may include epidural injection or a vigorous Valsalva maneuver, such as from lifting, straining, coughing, clearing the eustachian tubes in an airplane, or multiple orgasms. Spontaneous CSF leaks are well recognized, and the diagnosis should be considered whenever the headache history is typical, even when there is no obvious index event. As time passes from the index event, the postural nature may become less apparent; cases in which the index event occurred several years before the eventual diagnosis have been recognized. Symptoms appear to result from low volume rather than low pressure: although low CSF pressures, typically 0–50 mm CSF, are usually identified, a pressure as high as 140 mm CSF has been noted with a documented leak.

Postural orthostatic tachycardia syndrome (POTS; **Chap. 432**) can present with orthostatic headache similar to low CSF volume headache and is a diagnosis that needs consideration in this setting.

TABLE 13-4 Differential Diagnosis of New Daily Persistent Headache

PRIMARY	SECONDARY
Migrainous-type	Subarachnoid hemorrhage
Featureless (tension-type)	Low cerebrospinal fluid (CSF) volume headache
	Raised CSF pressure headache
	Posttraumatic headache[a]
	Chronic meningitis

[a]Includes postinfectious forms.

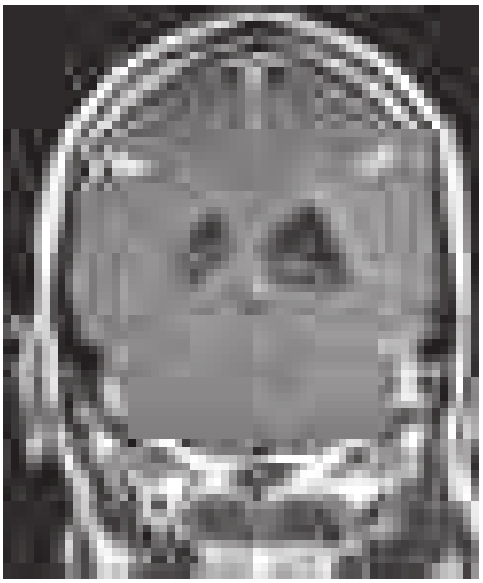

FIGURE 13-1 Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low cerebrospinal fluid (CSF) volume headache.

When imaging is indicated to identify the source of a presumed leak, an MRI with gadolinium is the initial study of choice **(Fig. 13-1)**. A striking pattern of diffuse meningeal enhancement is so typical that in the appropriate clinical context the diagnosis is established. Chiari malformations may sometimes be noted on MRI; in such cases, surgery to decompress the posterior fossa is *not* indicated and usually worsens the headache. Spinal MRI with T2 weighting may reveal a leak, and spinal MRI may demonstrate spinal meningeal cysts whose role in these syndromes is yet to be elucidated. The source of CSF leakage may be identified by spinal MRI with appropriate sequences, by CT, or increasingly by MR myelography. Less used now, ^{111}In-DTPA CSF studies in the absence of a directly identified site of leakage, may demonstrate early emptying of ^{111}In-DTPA tracer into the bladder or slow progress of tracer across the brain suggesting a CSF leak.

Initial treatment for low CSF volume headache is bed rest. For patients with persistent pain, IV caffeine (500 mg in 500 mL of saline administered over 2 h) can be very effective. An electrocardiogram (ECG) to screen for arrhythmia should be performed before administration. It is reasonable to administer at least two infusions of caffeine before embarking on additional tests to identify the source of the CSF leak. Because IV caffeine is safe and can be curative, it spares many patients the need for further investigations. If unsuccessful, an abdominal binder may be helpful. If a leak can be identified, an autologous blood patch is usually curative. A blood patch is also effective for post-LP headache; in this setting, the location is empirically determined to be the site of the LP. In patients with intractable headache, oral theophylline is a useful alternative; however, its effect is less rapid than caffeine.

Raised CSF Pressure Headache Raised CSF pressure is well recognized as a cause of headache. Brain imaging can often reveal the cause, such as a space-occupying lesion. NDPH due to raised CSF pressure can be the presenting symptom for patients with idiopathic intracranial hypertension (pseudotumor cerebri) without visual problems, particularly when the fundi are normal. Persistently raised intracranial pressure can trigger chronic migraine. These patients typically present with a history of generalized headache that is present on waking and improves as the day goes on. It is generally worse with recumbency. Visual obscurations are frequent. The diagnosis is relatively straightforward when papilledema is present, but the possibility must be considered even in patients without funduscopic changes. Formal visual field testing should

be performed even in the absence of overt ophthalmic involvement. Headache on rising in the morning or nocturnal headache is also characteristic of obstructive sleep apnea or poorly controlled hypertension.

Evaluation of patients suspected to have raised CSF pressure requires brain imaging. It is most efficient to obtain an MRI, including an MR venogram, as the initial study. If there are no contraindications, the CSF pressure should be measured by LP; this should be done when the patient is symptomatic so that both the pressure and the response to removal of 20–30 mL of CSF can be determined. An elevated opening pressure and improvement in headache following removal of CSF are diagnostic in the absence of fundal changes.

Initial treatment is with acetazolamide (250–500 mg bid); the headache may improve within weeks. If ineffective, topiramate is the next treatment of choice; it has many actions that may be useful in this setting, including carbonic anhydrase inhibition, weight loss, and neuronal membrane stabilization, likely mediated via effects on phosphorylation pathways. Severely disabled patients who do not respond to medical treatment require intracranial pressure monitoring and may require shunting.

Posttraumatic Headache A traumatic event can trigger a headache process that lasts for many months or years after the event. The term *trauma* is used here in a very broad sense: headache can develop following an injury to the head, but it can also develop after an infectious episode, typically viral meningitis, a flulike illness, or a parasitic infection. Complaints of dizziness, vertigo, and impaired memory can accompany the headache. Symptoms may remit after several weeks or persist for months and even years after the injury. Typically the neurologic examination is normal and CT or MRI studies are unrevealing. Chronic subdural hematoma may on occasion mimic this disorder. Posttraumatic headache may also be seen after carotid dissection and subarachnoid hemorrhage and after intracranial surgery. The underlying theme appears to be that a traumatic event involving the pain-producing meninges can trigger a headache process that lasts for many years.

Other Causes In one series, one-third of patients with NDPH reported headache beginning after a transient flulike illness characterized by fever, neck stiffness, photophobia, and marked malaise. Evaluation typically reveals no apparent cause for the headache. There is no convincing evidence that persistent Epstein-Barr virus infection plays a role in NDPH. A complicating factor is that many patients undergo LP during the acute illness; iatrogenic low CSF volume headache must be considered in these cases.

Treatment Treatment is largely empirical and directed at the headache phenotype. Tricyclic antidepressants, notably amitriptyline, and anticonvulsants, such as topiramate, valproate, and gabapentin, have been used with reported benefit. The monoamine oxidase inhibitor phenelzine may also be useful in carefully selected patients. The headache usually resolves within 3–5 years, but it can be quite disabling.

PRIMARY CARE AND HEADACHE MANAGEMENT

Most patients with headache will be seen first in a primary care setting. The task of the primary care physician is to identify the very few worrisome secondary headaches from the very great majority of primary and less troublesome secondary headaches (Table 13-2).

Absent any warning signs, a reasonable approach is to treat when a diagnosis is established. As a general rule, the investigation should focus on identifying worrisome causes of headache or on gaining confidence if no primary headache diagnosis can be made.

After treatment has been initiated, follow-up care is essential to identify whether progress has been made against the headache complaint. Not all headaches will respond to treatment, but, in general, worrisome headaches will progress and will be easier to identify.

When a primary care physician feels the diagnosis is a primary headache disorder, it is worth noting that >90% of patients who present to primary care with a complaint of headache will have migraine **(Chap. 422)**.

In general, patients who do not have a clear diagnosis, have a primary headache disorder other than migraine or tension-type headache, or are unresponsive to two or more standard therapies for the considered headache type should be considered for referral to a specialist. In a practical sense, the threshold for referral is also determined by the experience of the primary care physician in headache medicine and the availability of secondary care options.

ACKNOWLEDGMENT

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14 Back and Neck Pain

John W. Engstrom

The importance of back and neck pain in our society is underscored by the following: (1) the cost of chronic back pain in the United States is estimated at $177 billion annually; approximately one-third of this cost is due to direct health care expenses and two-thirds are indirect costs resulting from loss of wages and productivity; (2) back symptoms are the most common cause of disability in individuals <45 years of age; (3) low back pain (LBP) is the second most common reason for visiting a physician in the United States; and (4) more than four out of five people will experience significant back pain at some point in their lives.

ANATOMY OF THE SPINE

The anterior spine consists of cylindrical vertebral bodies separated by intervertebral disks and held together by the anterior and posterior longitudinal ligaments. The intervertebral disks are composed of a central gelatinous nucleus pulposus surrounded by a tough cartilaginous ring, the annulus fibrosis. Disks are responsible for 25% of spinal column length and allow the bony vertebrae to move easily upon each other **(Figs. 14-1 and 14-2)**. Desiccation of the nucleus pulposus and degeneration of the annulus fibrosus increase with age, resulting in loss of disk height. The disks are largest in the cervical and lumbar regions where movements of the spine are greatest. The anterior spine absorbs the shock of bodily movements such as walking and running and, with the posterior spine, protects the spinal cord and nerve roots in the spinal canal.

The posterior spine consists of the vertebral arches and processes. Each arch consists of paired cylindrical pedicles anteriorly and paired lamina posteriorly. The vertebral arch also gives rise to two transverse processes laterally, one spinous process posteriorly, plus two superior and two inferior articular facets. The apposition of a superior and inferior facet constitutes a *facet joint*. The posterior spine provides an anchor for the attachment of muscles and ligaments. The contraction of muscles attached to the spinous and transverse processes and lamina works like a system of pulleys and levers that results in flexion, extension, and lateral bending movements of the spine.

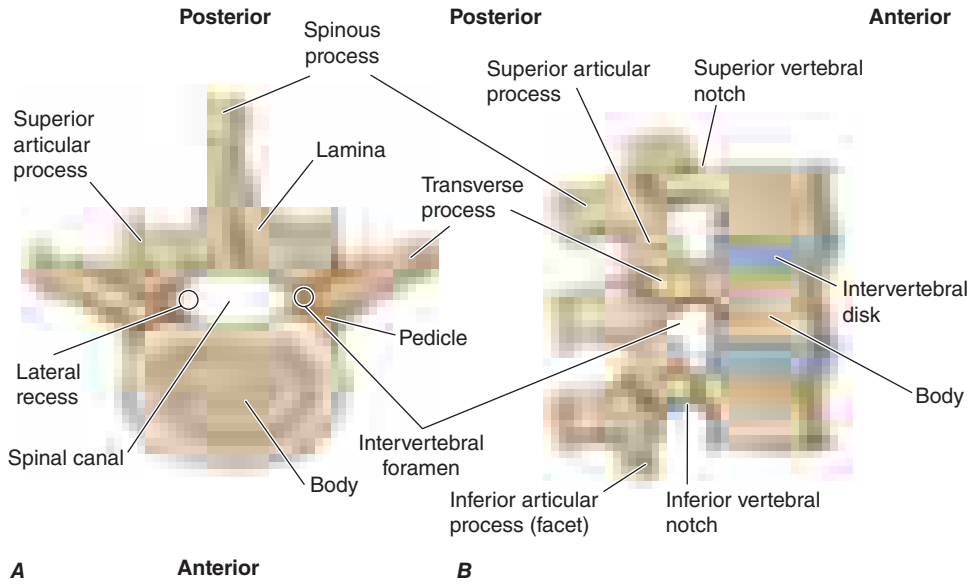


FIGURE 14-1 Vertebral anatomy. *(From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.)*

Nerve root injury (*radiculopathy*) is a common cause of neck and arm, or low back and buttock or leg, pain **(see dermatomes in Figs. 22-2 and 22-3)**. The nerve roots exit at a level above their respective vertebral bodies in the cervical region (e.g., the C7 nerve root exits at the C6-C7 level) and below their respective vertebral bodies in the thoracic and lumbar regions (e.g., the T1 nerve root exits at the T1-T2 level). The cervical nerve roots follow a short intraspinal course before exiting. By contrast, because the spinal cord ends at the vertebral L1 or L2 level, the lumbar nerve roots follow a long intraspinal course and can be injured anywhere from the upper lumbar spine to the intervertebral foramen or extraforaminal space. For example, disk herniation at the L4-L5 level can produce L4 root compression laterally, but more often compression of the traversing L5 nerve root **(Fig. 14-3)**. The lumbar nerve roots are mobile in the spinal canal, but eventually pass through the narrow *lateral recess* of the spinal canal and *intervertebral foramen* (Figs. 14-2 and 14-3). Neuroimaging of the spine must include both sagittal and axial views to assess possible compression in either the lateral recess or intervertebral foramen.

Beginning at the C3 level, each cervical (and the first thoracic) vertebral body projects a lateral bony process upward—the uncinate process. The uncinate process articulates with the cervical vertebral body above via the uncovertebral joint. The uncovertebral joint can hypertrophy with age and contribute to neural foraminal narrowing and radiculopathy in the cervical spine.

Pain-sensitive structures of the spine include the periosteum of the vertebrae, dura, facet joints, annulus fibrosus of the intervertebral disk, epidural veins and arteries, and the longitudinal ligaments. Disease of these diverse structures may explain many cases of back pain without nerve root compression. Under normal circumstances, the nucleus pulposus of the intervertebral disk is not pain sensitive.

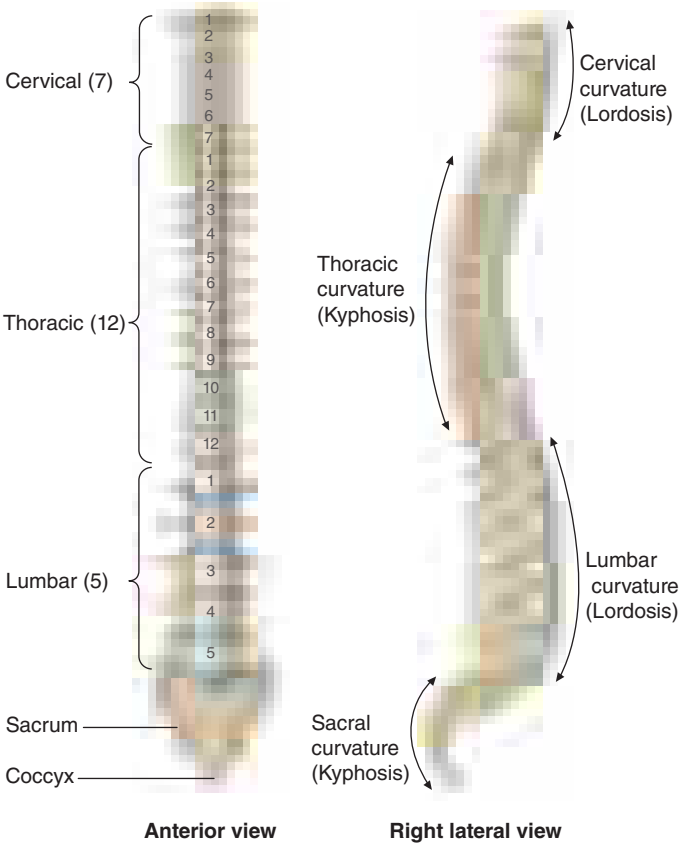


FIGURE 14-2 Spinal column. *(From A Gauthier Cornuelle, DH Gronefeld: Radiographic Anatomy Positioning. New York, McGraw-Hill, 1998; with permission.)*

APPROACH TO THE PATIENT

Back Pain

TYPES OF BACK PAIN

Delineating the type of pain reported by the patient is the essential first step. Attention is also focused on identification of risk factors for a serious underlying etiology. The most frequent serious causes of back pain are radiculopathy, fracture, tumor, infection, or referred pain from visceral structures **(Table 14-1)**.

Local pain is caused by injury to pain-sensitive structures that compress or irritate sensory nerve endings. The site of the pain is near the affected part of the back.

Pain referred to the back may arise from abdominal or pelvic viscera. The pain is usually described as primarily abdominal or pelvic, accompanied by back pain and usually unaffected by posture. The patient may occasionally complain of back pain only.

Pain of spine origin may be located in the back or referred to the buttocks or legs. Diseases affecting the upper lumbar spine tend to refer pain to the lumbar region, groin, or anterior thighs. Diseases affecting the lower lumbar spine tend to produce pain referred to the buttocks, posterior thighs, calves, or feet. Referred pain can explain pain syndromes that cross multiple dermatomes without evidence of nerve or nerve root injury.

Radicular pain is typically sharp and radiates from the low back to a leg within the territory of a nerve root (see "Lumbar Disk Disease,"

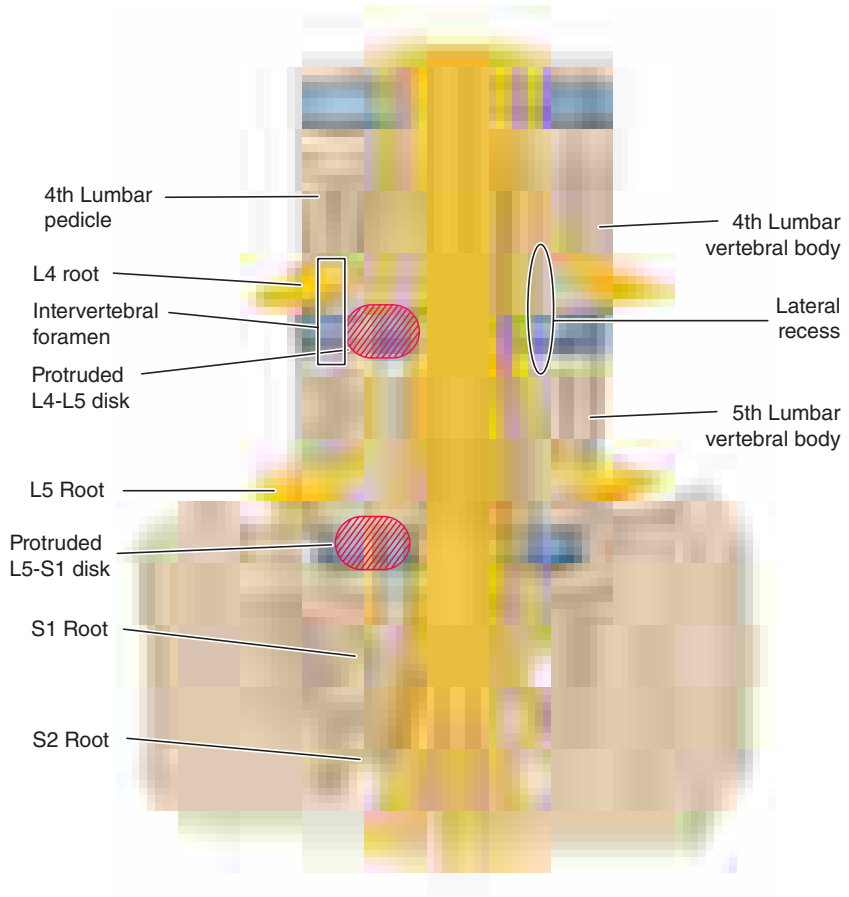


FIGURE 14-3 Compression of L5 and S1 roots by herniated disks. *(From AH Ropper, MA Samuels: Adams and Victor's Principles of Neurology, 9th ed. New York, McGraw-Hill, 2009; with permission.)*

below). Coughing, sneezing or voluntary contraction of abdominal muscles (lifting heavy objects or straining at stool) may elicit or worsen the radiating pain. The pain may increase in postures that stretch the nerves and nerve roots. Sitting with the leg outstretched places traction on the sciatic nerve and L5 and S1 roots because the sciatic nerve passes posterior to the hip. The femoral nerve (L2, L3, and L4 roots) passes anterior to the hip and is not stretched by sitting. The description of the pain alone often fails to distinguish between referred pain and radiculopathy, although a burning or electric quality favors radiculopathy.

Pain associated with muscle spasm is commonly associated with many spine disorders. The spasms may be accompanied by an abnormal posture, tense paraspinal muscles, and dull or achy pain in the paraspinal region.

Knowledge of the circumstances associated with the onset of back pain is important when weighing possible serious underlying causes for the pain. Some patients involved in accidents or work-related injuries may exaggerate their pain for the purpose of compensation or for psychological reasons.

TABLE 14-1 Acute Low Back Pain: Risk Factors for an Important Structural Cause

History
Pain worse at rest or at night
Prior history of cancer
History of chronic infection (especially lung, urinary tract, skin)
History of trauma
Incontinence
Age >70 years
Intravenous drug use
Glucocorticoid use
History of a rapidly progressive neurologic deficit
Examination
Unexplained fever
Unexplained weight loss
Palpation/percussion tenderness over the midline spine
Abdominal, rectal, or pelvic mass
Internal/external rotation of the leg at the hip; heel percussion sign
Straight leg- or reverse straight leg-raising signs
Progressive focal neurologic deficit

EXAMINATION

A physical examination that includes the abdomen and rectum is advisable. Back pain referred from visceral organs may be reproduced during palpation of the abdomen (pancreatitis, abdominal aortic aneurysm [AAA]) or percussion over the costovertebral angles (pyelonephritis).

The normal spine has a cervical and lumbar lordosis and a thoracic kyphosis. Exaggeration of these normal alignments may result in hyperkyphosis of the thoracic spine or hyperlordosis of the lumbar spine. Inspection may reveal a lateral curvature of the spine (scoliosis). An asymmetry in the prominence of the paraspinal muscles suggests muscle spasm. Spine pain reproduced by palpation over the spinous process reflects injury of the affected vertebrae or adjacent pain-sensitive structures.

Forward bending is often limited by paraspinal muscle spasm; the latter may flatten the usual lumbar lordosis. Flexion at the hips is normal in patients with lumbar spine disease, but flexion of the lumbar spine is limited and sometimes painful. Lateral bending to the side opposite the injured spinal element may stretch the damaged tissues, worsen pain, and limit motion. Hyperextension of the spine (with the patient prone or standing) is limited when nerve

root compression, facet joint pathology, or other bony spine disease is present.

Pain from hip disease may mimic the pain of lumbar spine disease. Hip pain can be reproduced by passive internal and external rotation at the hip with the knee and hip in flexion or by percussing the heel with the examiner's palm with the leg extended (heel percussion sign).

The *straight leg-raising (SLR)* maneuver is a simple bedside test for nerve root disease. With the patient supine, passive straight leg flexion at the hip stretches the L5 and S1 nerve roots and the sciatic nerve; dorsiflexion of the foot during the maneuver adds to the stretch. In healthy individuals, flexion to at least 80° is normally possible without causing pain, although a tight, stretching sensation in the hamstring muscles is common. The SLR test is positive if the maneuver reproduces the patient's usual back or limb pain. Eliciting the SLR sign in both the supine and sitting positions can help determine if the finding is reproducible. The patient may describe pain in the low back, buttocks, posterior thigh, or lower leg, but the *key feature is reproduction of the patient's usual pain*. The *crossed SLR sign* is present when flexion of one leg reproduces the usual pain in the opposite leg or buttocks. In disk herniation, the crossed SLR sign is less sensitive but more specific than the SLR sign. The *reverse SLR sign* is elicited by standing the patient next to the examination table and passively extending each leg with the knee fully extended. This maneuver, which stretches the L2-L4 nerve roots, lumbosacral plexus, and femoral nerve, is considered positive if the patient's usual back or limb pain is reproduced. For all of these tests, the nerve or nerve root lesion is always on the side of the pain.

The neurologic examination includes a search for focal weakness or muscle atrophy, focal reflex changes, diminished sensation in the legs, or signs of spinal cord injury. The examiner should be alert to the possibility of breakaway weakness, defined as fluctuations in the maximum power generated during muscle testing. Breakaway weakness may be due to pain, inattention, or a combination of pain and underlying true weakness. Breakaway weakness without pain is usually due to a lack of effort. In uncertain cases, electromyography (EMG) can determine if true weakness due to nerve tissue injury is present. Findings with specific lumbosacral nerve root lesions are shown in **Table 14-2** and are discussed below.

LABORATORY, IMAGING, AND EMG STUDIES

Laboratory studies are rarely needed for the initial evaluation of nonspecific acute (<3 months in duration) low back pain (ALBP). Risk factors for a serious underlying cause and for infection, tumor, or fracture, in particular, should be sought by history and examination. If risk factors are present (Table 14-1), then laboratory studies (complete blood count [CBC], erythrocyte sedimentation rate [ESR], urinalysis) are indicated. If risk factors are absent, then management is conservative (see "Treatment," below).

Computed tomography (CT) scanning is superior to x-rays for detection of fractures involving posterior spine structures, craniocervical and cervicothoracic junctions, C1 and C2 vertebrae, bone fragments in the spinal canal, or misalignment. CT scans are increasingly used as a primary screening modality for moderate to severe acute trauma. Magnetic resonance imaging (MRI) or CT myelography is the radiologic test of choice for evaluation of most serious diseases involving the spine. MRI is superior for the definition of soft tissue structures, whereas CT myelography provides optimal imaging of the lateral recess of the spinal canal, defines bony abnormalities, and is tolerated by claustrophobic patients.

Population surveys in the United States suggest that patients with back pain report greater functional limitations in recent years, despite rapid increases in spine imaging, opioid prescribing, injections, and spine surgery. This suggests that more selective use of diagnostic and treatment modalities may be reasonable for many patients.

Spine imaging often reveals abnormalities of dubious clinical relevance that may alarm clinicians and patients alike and prompt further testing and unnecessary therapy. When imaging tests are reported, it is important to remember that degenerative findings are common in normal, pain-free individuals. Randomized trials and observational studies have suggested that imaging can have a "cascade effect", creating a gateway to other unnecessary care. Based in part on such evidence, the American College of Physicians and the North American Spine Society have partnered to make parsimonious use of spine imaging a high priority in the "Choosing Wisely" campaign, aimed at reducing unnecessary spine care. Successful efforts to reduce unnecessary imaging have typically been multifaceted. Some include physician education and computerized decision support to identify prior imaging examinations and to require specific indications for approval of imaging tests. Other strategies have included audit and feedback of individual practitioners' rates of ordering, and more rapid access to physical therapy or expert consultation for patients without imaging indications.

For example, educational tools for patients and the public have included "Five Things Physicians and Patients Should Question": (1) Do not recommend advanced imaging (e.g., MRI) of the spine within the first 6 weeks in patients with nonspecific ALBP in the absence of red flags. (2) Do not perform elective spinal injections without imaging guidance, unless contraindicated. (3) Do not use bone morphogenetic protein (BMP) for routine anterior cervical

TABLE 14-2 Lumbosacral Radiculopathy: Neurologic Features

LUMBOSACRAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
L2[a]	—	Upper anterior thigh	Psoas (hip flexors)	Anterior thigh
L3[a]	—	Lower anterior thigh Anterior knee	Psoas (hip flexors) Quadriceps (knee extensors) Thigh adductors	Anterior thigh, knee
L4[a]	Quadriceps (knee)	Medial calf	Quadriceps (knee extensors)[b] Thigh adductors	Knee, medial calf Anterolateral thigh
L5[c]	—	Dorsal surface—foot Lateral calf	Peronei (foot evertors)[b] Tibialis anterior (foot dorsiflexors) Gluteus medius (leg abductors) Toe dorsiflexors	Lateral calf, dorsal foot, posterolateral thigh, buttocks
S1[c]	Gastrocnemius/soleus (ankle)	Plantar surface—foot Lateral aspect—foot	Gastrocnemius/soleus (foot plantar flexors)[b] Abductor hallucis (toe flexors)[b] Gluteus maximus (leg extensors)	Bottom foot, posterior calf, posterior thigh, buttocks

[a]Reverse straight leg-raising sign present—see "Examination of the Back." [b]These muscles receive the majority of innervation from this root. [c]Straight leg-raising sign present—see "Examination of the Back."

spine fusion surgery. (4) Do not use EMG and nerve conduction studies (NCSs) to determine the cause of axial lumbar, thoracic or cervical spine pain. (5) Do not recommend bed rest for >48 h when treating LBP. In an observational study, application of this strategy was associated with lower rates of repeat imaging, opioid use, and referrals for physical therapy.

Electrodiagnostic studies can be used to assess the functional integrity of the peripheral nervous system (Chap. 438). Sensory NCSs are normal when focal sensory loss confirmed by examination is due to nerve root damage because the nerve roots are proximal to the nerve cell bodies in the dorsal root ganglia. Injury to nerve tissue distal to the dorsal root ganglion (e.g., plexus or peripheral nerve) results in reduced sensory nerve signals. Needle EMG complements NCSs by detecting denervation or reinnervation changes in a myotomal (segmental) distribution. Multiple muscles supplied by different nerve roots and nerves are sampled; the pattern of muscle involvement indicates the nerve root(s) responsible for the injury. Needle EMG provides objective information about motor nerve fiber injury when clinical evaluation of weakness is limited by pain or poor effort. EMG and NCSs will be normal when sensory nerve root injury or irritation is the pain source.

CAUSES OF BACK PAIN (TABLE 14-3)

LUMBAR DISK DISEASE

This is a common cause of acute, chronic, or recurrent low back and leg pain (Figs. 14-3 and 14-4). Disk disease is most likely to occur at the L4-L5 or L5-S1 levels, but upper lumbar levels can also be involved. The cause is often unknown, but the risk is increased in overweight individuals. Disk herniation is unusual prior to age 20 years and is rare in the fibrotic disks of the elderly. Complex genetic factors may play a role in predisposition. The pain may be located in the low back only or referred to a leg, buttock, or hip. A sneeze, cough, or trivial movement may cause the nucleus pulposus to prolapse, pushing the frayed and weakened annulus posteriorly. With severe disk disease, the nucleus can protrude through the annulus (herniation) or become extruded to lie as a free fragment in the spinal canal.

The mechanism by which intervertebral disk injury causes back pain is uncertain. The inner annulus fibrosus and nucleus pulposus are normally devoid of innervation. Inflammation and production of proinflammatory cytokines within a ruptured nucleus pulposus may trigger or perpetuate back pain. Ingrowth of nociceptive (pain) nerve fibers into the nucleus pulposus of a diseased disk may be responsible for some cases of chronic "diskogenic" pain. Nerve root injury (radiculopathy) from disk herniation is usually due to inflammation, but lateral herniation may produce compression in the lateral recess or at the intervertebral foramen.

A ruptured disk may be asymptomatic or cause back pain, limited spine motion (particularly flexion), a focal neurologic deficit, or radicular pain. A dermatomal pattern of sensory loss or a reduced or absent deep tendon reflex is more suggestive of a specific root lesion than is the pattern of pain. Motor findings (focal weakness, muscle atrophy, or fasciculations) occur less frequently than focal sensory or reflex changes. Symptoms and signs are usually unilateral, but bilateral involvement does occur with large central disk herniations that compress multiple roots or cause inflammation of nerve roots within the spinal canal. Clinical manifestations of specific nerve root lesions are summarized in Table 14-2.

The differential diagnosis covers a variety of serious and treatable conditions, including epidural abscess, hematoma, fracture, or tumor. Fever, constant pain uninfluenced by position, sphincter abnormalities, or signs of spinal cord disease suggest an etiology other than lumbar disk disease. Absence of ankle reflexes can be a normal finding in persons >60 years or a sign of bilateral S1 radiculopathy. An absent deep tendon reflex or focal sensory loss may indicate injury to a nerve root, but other sites of injury along the nerve must also be considered. For example, an absent knee reflex may be due to a femoral neuropathy or an L4 nerve root injury, and a loss of sensation over the foot and lateral lower calf may result from a peroneal or lateral sciatic neuropathy or an L5 nerve root injury. Focal muscle atrophy may reflect injury to the anterior horn cells of the spinal cord, a nerve root, peripheral nerve, or disuse.

A lumbar spine MRI scan or CT myelogram can often confirm the location and type of pathology. Spine MRIs yield exquisite views of intraspinal and adjacent soft tissue anatomy, whereas bony lesions of the lateral recess or intervertebral foramen are optimally visualized by CT myelography. The correlation of neuroradiologic findings to clinical symptoms, particularly pain, is not simple. Contrast-enhancing tears in the annulus fibrosus or disk protrusions are widely accepted as common sources of back pain; however, studies have found that many asymptomatic adults have similar findings. Entirely asymptomatic disk protrusions are also common, occurring in up to one-third of adults, and these may also enhance with contrast. Furthermore, in patients with known disk herniation treated either medically or surgically, persistence of the herniation 10 years later had no relationship to the clinical outcome. In summary, MRI findings of disk protrusion, tears in the annulus fibrosus, or hypertrophic facet joints are common incidental findings that, by themselves, should not dictate management decisions for patients with back pain.

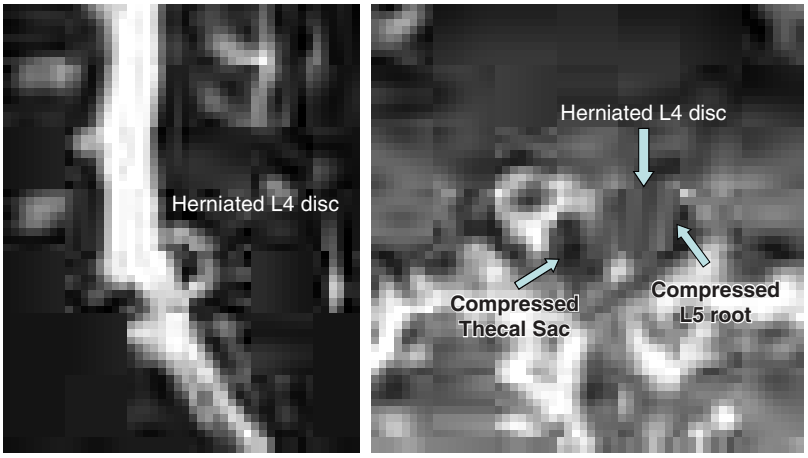
The diagnosis of nerve root injury is most secure when the history, examination, results of imaging studies, and the EMG are concordant. There is often good correlation between CT and EMG for localization of nerve root injury.

Management of lumbar disk disease is discussed below.

Cauda equina syndrome (CES) signifies an injury of multiple lumbosacral nerve roots within the spinal canal distal to the termination

TABLE 14-3 Causes of Back or Neck Pain

Lumbar or Cervical Disk Disease
Degenerative Spine Disease
Lumbar spinal stenosis without or with neurogenic claudication
Intervertebral foraminal or lateral recess narrowing
Disk-osteophyte complex
Facet or uncovertebral joint hypertrophy
Lateral disk protrusion
Spondylosis (osteoarthritis) and spondylolisthesis
Spine Infection
Vertebral osteomyelitis
Spinal epidural abscess
Septic disk (diskitis)
Meningitis
Lumbar arachnoiditis
Neoplasms—Metastatic, Hematologic, Primary Bone Tumors, Fractures
Trauma/falls, motor vehicle accidents
Atraumatic fractures: osteoporosis, neoplastic infiltration, osteomyelitis
Minor Trauma
Strain or sprain
Whiplash injury
Metabolic Spine Disease
Osteoporosis—hyperparathyroidism, immobility
Osteosclerosis (e.g., Paget's disease)
Congenital/Developmental
Spondylolysis
Kyphoscoliosis
Spina bifida occulta
Tethered spinal cord
Autoimmune Inflammatory Arthritis
Other Causes of Back Pain
Referred pain from visceral disease (e.g., abdominal aortic aneurysm)
Postural
Psychiatric, malingering, chronic pain syndromes



A B

FIGURE 14-4 Left L5 radiculopathy. ***A***. Sagittal T2-weighted image on the left reveals disk herniation at the L4-L5 level. ***B***. Axial T1-weighted image shows paracentral disk herniation with displacement of the thecal sac medially and the left L5 nerve root posteriorly in the left lateral recess.

of the spinal cord at L1-L2. LBP, weakness and areflexia in the legs, saddle anesthesia, or loss of bladder function may occur. The problem must be distinguished from disorders of the lower spinal cord (conus medullaris syndrome), acute transverse myelitis **(Chap. 434)**, and Guillain-Barré syndrome **(Chap. 439)**. Combined involvement of the conus medullaris and cauda equina can occur. CES is most commonly due to a large ruptured lumbosacral intervertebral disk, but other causes include lumbosacral spine fracture, hematoma within the spinal canal (sometimes following lumbar puncture in patients with coagulopathy), and tumor or other compressive mass lesions. Treatment is surgical decompression, sometimes on an urgent basis in an attempt to restore or preserve motor or sphincter function, or radiotherapy for metastatic tumors **(Chap. 86)**.

DEGENERATIVE CONDITIONS

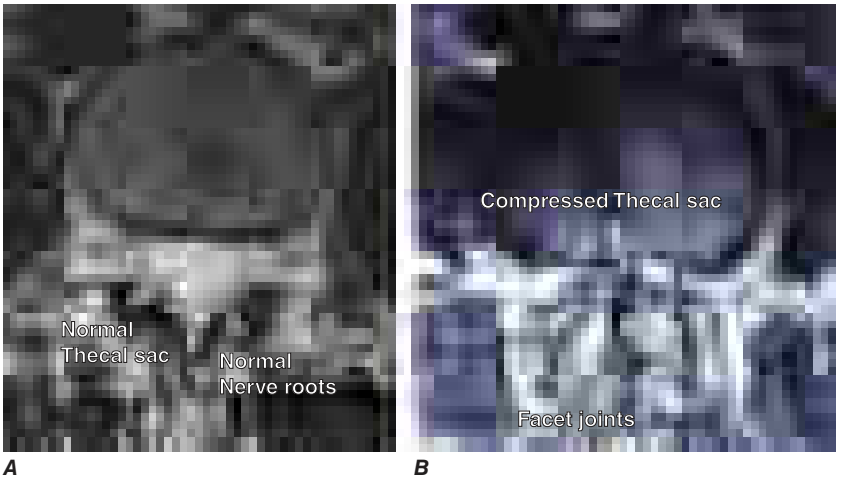
Lumbar spinal stenosis (*LSS*) describes a narrowed lumbar spinal canal. *Neurogenic claudication* consists of pain, typically in the back and buttock or leg, that is brought on by walking or standing and relieved by sitting. Symptoms in the legs are usually bilateral. Unlike vascular claudication, symptoms are often provoked by standing without walking. Unlike lumbar disk disease, symptoms are usually relieved by sitting. Patients with neurogenic claudication can often walk much farther when leaning over a shopping cart and can pedal a stationary bike with ease while sitting. These flexed positions increase the anteroposterior spinal canal diameter and reduce intraspinal venous hypertension, producing pain relief. Focal weakness, sensory loss, or reflex changes may occur when spinal stenosis is associated with neural foraminal narrowing and radiculopathy. Severe neurologic deficits, including paralysis and urinary incontinence, occur only rarely.

LSS by itself is common (6–7% of adults) and is frequently asymptomatic. The correlation between the severity of symptoms and the degree of spinal canal stenosis is variable. LSS is most often acquired (75%), but can also be congenital or due to a mixture of both. Congenital forms (achondroplasia and idiopathic) are characterized by short, thick pedicles that produce both spinal canal and lateral recess stenosis. Acquired factors that contribute to spinal stenosis include degenerative diseases (spondylosis, spondylolisthesis, and scoliosis), trauma, spine surgery, metabolic or endocrine disorders (epidural lipomatosis, osteoporosis, acromegaly, renal osteodystrophy, and hypoparathyroidism), and Paget's disease. MRI provides the best definition of the abnormal anatomy **(Fig. 14-5)**.

LSS accompanied by neurogenic claudication responds to surgical decompression of the stenotic segments. The same processes leading to LSS may cause lumbar foraminal or lateral recess narrowing resulting in coincident lumbar radiculopathy that may require treatment as well. A recent trial for LSS accompanied by leg pain did not show an overall benefit for epidural glucocorticoids plus lidocaine, but subgroup analysis showed a small improvement in disability scores at 6 weeks of uncertain clinical significance.

Conservative treatment of symptomatic LSS can include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, exercise programs, and symptomatic treatment of acute pain episodes. There is insufficient evidence to support the routine use of epidural glucocorticoid injections. Surgical therapy is considered when medical therapy does not relieve symptoms sufficiently to allow for resumption of activities of daily living or when focal neurologic signs are present. Most patients with neurogenic claudication who are treated medically do not improve over time. Surgical management with laminectomy can produce significant relief of exertional back and leg pain, leading to less disability and improved functional outcome at 4 years. Laminectomy and fusion is usually reserved for patients with LSS and spondylolisthesis. Predictors of a poor surgical outcome include impaired walking preoperatively, depression, cardiovascular disease, and scoliosis. Up to one-quarter of surgically treated patients develop recurrent stenosis at the same spinal level or at an adjacent level within 7–10 years; recurrent symptoms usually respond to a second surgical decompression.

Neural foraminal narrowing with radiculopathy is a common consequence of osteoarthritic processes that cause LSS (**Figs.** 14-1 and **14-6**), including osteophytes, lateral disk protrusion, calcified disk-osteophytes, facet joint hypertrophy, uncovertebral joint hypertrophy (in the cervical spine), congenitally shortened pedicles, or, frequently, a combination of these processes. Neoplasms (primary or metastatic), fractures, infections (epidural abscess), or hematomas are other less common causes. Most common is bony foraminal narrowing leading to nerve root ischemia and persistent symptoms, in contrast to the inflammation associated with a herniated disk and radiculopathy. These conditions can produce unilateral nerve root symptoms or signs due to compression at the intervertebral foramen or in the lateral recess; symptoms are indistinguishable from disk-related radiculopathy, but treatment may differ depending on the specific etiology. The history and neurologic examination alone cannot distinguish between these possibilities. Neuroimaging (CT or MRI) is required to identify the anatomic cause. Neurologic findings from the examination and EMG



A B

FIGURE 14-5 Axial T2-weighted images of the lumbar spine. ***A***. The image shows a normal thecal sac within the lumbar spinal canal. The thecal sac is bright. The lumbar roots are dark punctate dots in the posterior thecal sac with the patient supine. ***B***. The thecal sac is not well visualized due to severe lumbar spinal canal stenosis, partially the result of hypertrophic facet joints.

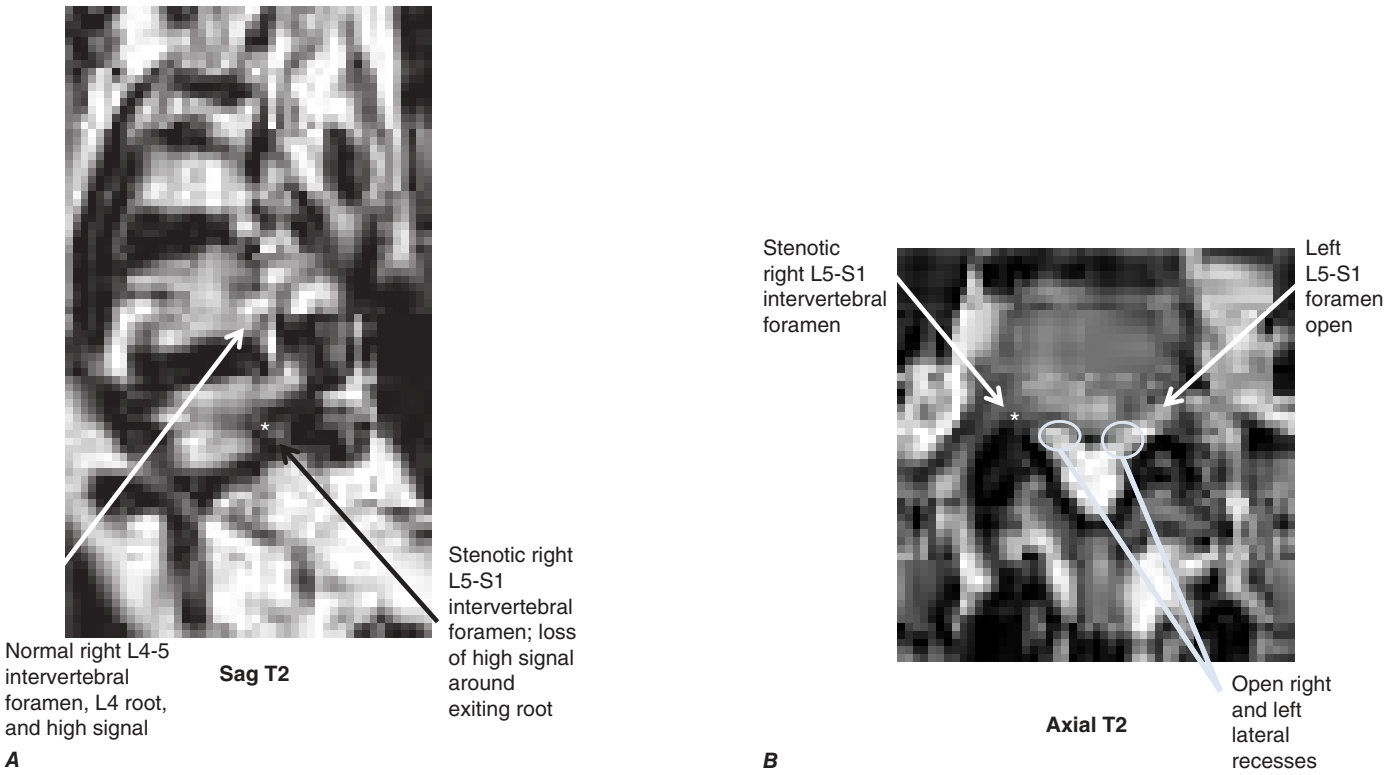


FIGURE 14-6 Right L5 radiculopathy. ***A***. Sagittal T2-weighted image. There is normal high signal around the exiting right L4 nerve root in the right neural foramen at L4-L5; effacement of the high signal in the right L5-S1 foramen is present one level caudal on the right at L5-S1. ***B***. Axial T2-weighted image. The lateral recesses are normal bilaterally; the intervertebral foramen is normal on the left, but severely stenotic on the right. *Severe right L5-S1 foraminal stenosis.

can help direct the attention of the radiologist to specific nerve roots, especially on axial images. For *facet joint hypertrophy*, surgical foraminotomy produces long-term relief of leg and back pain in 80–90% of patients. Facet joint blocks for back or neck pain are sometimes used to help determine the anatomic origin of back pain or for treatment, but there is a lack of clinical data to support their utility. Medical causes of lumbar or cervical radiculopathy unrelated to anatomic spine disease include infections (e.g., herpes zoster and Lyme disease), carcinomatous meningitis, and root avulsion or traction (trauma).

SPONDYLOSIS AND SPONDYLOLISTHESIS

Spondylosis, or osteoarthritic spine disease, typically occurs in later life and primarily involves the cervical and lumbosacral spine. Patients often complain of back pain that increases with movement, is associated with stiffness, and is better with inactivity. The relationship between clinical symptoms and radiologic findings is usually not straightforward. Pain may be prominent when x-ray, CT, or MRI findings are minimal, and prominent degenerative spine disease can be seen in asymptomatic patients. Osteophytes, combined disk-osteophytes, or thickened ligamentum flavum may cause or contribute to central spinal canal stenosis, lateral recess stenosis, or neural foraminal narrowing.

Spondylolisthesis is the anterior slippage of the vertebral body, pedicles, and superior articular facets, leaving the posterior elements behind. Spondylolisthesis can be associated with spondylolysis, congenital anomalies, degenerative spine disease, or other causes of mechanical weakness of the pars interarticularis (e.g., infection, osteoporosis, tumor, trauma, prior surgery). The slippage may be asymptomatic or may cause LBP and hamstring tightness, nerve root injury (the L5 root most frequently), symptomatic spinal stenosis, or CES in severe cases. A "step-off" on palpation or tenderness may be elicited near the segment that has "slipped" forward (most often L4 on L5 or occasionally L5 on S1). Focal anterolisthesis or retrolisthesis can occur at any cervical or lumbar level and be the source of neck or LBP. Plain x-rays of the neck or low back in flexion and extension will reveal movement at the abnormal spinal segment. Surgery is performed for spinal instability (slippage 5–8 mm) and considered for pain symptoms that do not respond to conservative measures (e.g., rest, physical therapy), cases with progressive neurologic deficit, or scoliosis.

NEOPLASMS

Back pain is the most common neurologic symptom in patients with systemic cancer and is the presenting symptom in 20%. The cause is usually vertebral body metastasis (85–90%) but can also result from spread of cancer through the intervertebral foramen (especially with lymphoma), carcinomatous meningitis, or metastasis to the spinal cord. The thoracic spine is most often affected. Cancer-related back pain tends to be constant, dull, unrelieved by rest, and worse at night. By contrast, mechanical causes of LBP usually improve with rest. MRI, CT, and CT myelography are the studies of choice when spinal metastasis is suspected. Once a metastasis is found, imaging of the entire spine is essential, as it reveals additional tumor deposits in one-third of patients. MRI is preferred for soft tissue definition, but the most rapidly available imaging modality is best because the patient's condition may worsen quickly without intervention. Early diagnosis is crucial. A strong predictor of outcome is the baseline neurologic function prior to diagnosis. Half to three quarters of patients are nonambulatory at the time of diagnosis and few regain the ability to walk. **The management of spinal metastasis is discussed in detail in Chap. 86.**

INFECTIONS/INFLAMMATION

Vertebral osteomyelitis is most often caused by hematogenous seeding of staphylococci, but other bacteria or tuberculosis (Pott's disease) may be responsible. The primary source of infection is usually the skin or urinary tract; IV drug use, poor dentition, endocarditis, pulmonary disease, IV catheters, or post-operative wound sites may also be responsible. Back pain at rest, tenderness over the involved vertebra, and an elevated ESR or CRP are the most common findings in vertebral osteomyelitis. Fever or an elevated white blood cell count is found in a minority of patients. MRI and CT are sensitive and specific for early detection of osteomyelitis. The intervertebral disk can also be affected by infection (diskitis) and almost never by tumor. Extension of the infection posteriorly from the vertebra can produce a spinal epidural abscess.

Spinal epidural abscess **(Chap. 434)** presents with back pain (aggravated by movement or spinous process palpation), fever, radiculopathy,

or signs of spinal cord compression. The subacute development of two or more of these findings should increase the index of suspicion for spinal epidural abscess. The abscess is best delineated by spine MRI and may track over multiple spinal levels.

Lumbar adhesive arachnoiditis with radiculopathy is due to fibrosis following inflammation within the subarachnoid space. The fibrosis results in nerve root adhesions and presents as back and leg pain associated with multifocal motor, sensory, or reflex changes. Causes of arachnoiditis include multiple lumbar operations (most common in the United States), chronic spinal infections (especially tuberculosis in the developing world), spinal cord injury, intrathecal hemorrhage, myelography (rare), intrathecal injections (glucocorticoids, anesthetics, or other agents), and foreign bodies. The MRI shows clumped nerve roots on axial views or loculations of cerebrospinal fluid within the thecal sac. Clumped nerve roots alone are not diagnostic and may also occur with demyelinating polyneuropathy or neoplastic infiltration. Treatment is usually unsatisfactory. Microsurgical lysis of adhesions, dorsal rhizotomy, dorsal root ganglionectomy, and epidural glucocorticoids have been tried, but outcomes have been poor. Dorsal column stimulation for pain relief has produced varying results.

TRAUMA

A patient complaining of back pain and an inability to move the legs may have a spine fracture or dislocation; with fractures above L1 the spinal cord is at risk for compression. Care must be taken to avoid further damage to the spinal cord or nerve roots by immobilizing the back or neck pending the results of radiologic studies. Vertebral fractures frequently occur in the absence of trauma in association with osteoporosis, glucocorticoid use, osteomyelitis, or neoplastic infiltration.

Sprains and Strains The terms *low back sprain*, *strain*, and *mechanically induced muscle spasm* refer to minor, self-limited injuries associated with lifting a heavy object, a fall, or a sudden deceleration such as in an automobile accident. These terms are used loosely and do not clearly describe a specific anatomic lesion. The pain is usually confined to the lower back. Patients with paraspinal muscle spasm often assume unusual postures.

Traumatic Vertebral Fractures Most traumatic fractures of the lumbar vertebral bodies result from injuries producing anterior wedging or compression. With severe trauma, the patient may sustain a fracture-dislocation or a "burst" fracture involving the vertebral body and posterior elements. Traumatic vertebral fractures are caused by falls from a height, sudden deceleration in an automobile accident, or direct injury. Neurologic impairment is common, and early surgical treatment is indicated. In victims of blunt trauma, CT scans of the chest, abdomen, or pelvis can be reformatted to detect associated vertebral fractures. Rules have been developed to avoid unnecessary spine imaging associated with low risk trauma, but these studies excluded patients aged >65—a group that can sustain fractures with minor trauma.

METABOLIC CAUSES

Osteoporosis and Osteosclerosis Immobilization, osteomalacia, the postmenopausal state, renal disease, multiple myeloma, hyperparathyroidism, hyperthyroidism, metastatic carcinoma, or glucocorticoid use may accelerate osteoporosis and weaken the vertebral body, leading to compression fractures and pain. Up to two-thirds of compression fractures seen on radiologic imaging are asymptomatic. The most common nontraumatic vertebral body fractures are due to postmenopausal or senile osteoporosis **(Chap. 404)**. The risk of an additional vertebral fracture 1 year following a first vertebral fracture is 20%. The presence of fever, weight loss, fracture at a level above T4, any fracture in a young adult, or the predisposing conditions described above should increase suspicion for a cause other than senile osteoporosis. The sole manifestations of a compression fracture may be localized back or radicular pain exacerbated by movement and often reproduced by palpation over the spinous process of the affected vertebra.

Relief of acute pain can often be achieved with acetaminophen, NSAIDs, opioids, or a combination of these medications. Both pain and disability are improved with bracing. Antiresorptive drugs are not recommended in the setting of acute pain, but are the preferred treatment to prevent additional fractures. Less than one-third of patients with prior compression fractures are adequately treated for osteoporosis despite the increased risk for future fractures; even fewer at-risk patients without a history of fracture are adequately treated. The literature for percutaneous vertebroplasty (PVP) or kyphoplasty for osteoporotic compression fractures associated with debilitating pain is mixed, but meta-analyses do not support their utility.

Osteosclerosis, an abnormally increased bone density often due to Paget's disease, is readily identifiable on routine x-ray studies and can sometimes be a source of back pain. It may be associated with an isolated increase in alkaline phosphatase in an otherwise healthy older person. Spinal cord or nerve root compression can result from bony encroachment. The diagnosis of Paget's disease as the cause of a patient's back pain is a diagnosis of exclusion.

For further discussion of these bone disorders, see Chaps. 403, 404, and 405.

AUTOIMMUNE INFLAMMATORY ARTHRITIS

Autoimmune inflammatory disease of the spine can present with the insidious onset of low back, buttock, or neck pain. Examples include rheumatoid arthritis (RA) **(Chap. 351)**, ankylosing spondylitis, reactive arthritis, psoriatic arthritis, or inflammatory bowel disease **(Chaps. 319 and 355)**.

CONGENITAL ANOMALIES OF THE LUMBAR SPINE

Spondylolysis is a bony defect in the vertebral pars interarticularis (a segment near the junction of the pedicle with the lamina); the cause is usually a stress microfracture in a congenitally abnormal segment. It occurs in up to 6% of adolescents. The defect (usually bilateral) is best visualized on plain x-rays or CT scan and is frequently asymptomatic. Symptoms may occur in the setting of a single injury, repeated minor injuries, or during a growth spurt. Spondylolysis is the most common cause of persistent LBP in adolescents and is often associated with sports-related activities.

Scoliosis refers to an abnormal curvature in the coronal (lateral) plane of the spine. With *kyphoscoliosis*, there is, in addition, a forward curvature of the spine. The abnormal curvature may be congenital, due to abnormal spine development, acquired in adulthood due to degenerative spine disease, or occasionally progressive due to neuromuscular disease. The deformity can progress until ambulation or pulmonary function is compromised.

Spina bifida occulta (closed spinal dysraphism) is a failure of closure of one or several vertebral arches posteriorly; the meninges and spinal cord are normal. A dimple or small lipoma may overlie the defect, but the skin is intact. Most cases are asymptomatic and discovered incidentally during an evaluation for back pain.

Tethered cord syndrome usually presents as a progressive cauda equina disorder (see below), although myelopathy may also be the initial manifestation. The patient is often a child or young adult who complains of perineal or perianal pain, sometimes following minor trauma. MRI studies typically reveal a low-lying conus (below L1 and L2) and a short and thickened filum terminale.

REFERRED PAIN FROM VISCERAL DISEASE

Diseases of the thorax, abdomen, or pelvis may refer pain to the spinal segment that innervates the diseased organ. Occasionally, back pain may be the first and only manifestation. Upper abdominal diseases generally refer pain to the lower thoracic or upper lumbar region (eighth thoracic to the first and second lumbar vertebrae), lower abdominal diseases to the midlumbar region (second to fourth lumbar vertebrae), and pelvic diseases to the sacral region. Local signs (pain with spine palpation, paraspinal muscle spasm) are absent, and little or no pain accompanies routine movements.

Low Thoracic or Lumbar Pain with Abdominal Disease Tumors of the posterior wall of the stomach or duodenum typically produce epigastric pain **(Chaps. 76 and 317)**, but back pain may occur if retroperitoneal extension is present. Fatty foods occasionally induce back pain associated with biliary or pancreatic disease. Pathology in retroperitoneal structures (hemorrhage, tumors, and pyelonephritis) can produce paraspinal pain that radiates to the lower abdomen, groin,

or anterior thighs. A mass in the iliopsoas region can produce unilateral lumbar pain with radiation toward the groin, labia, or testicle. The sudden appearance of lumbar pain in a patient receiving anticoagulants suggests retroperitoneal hemorrhage.

Isolated LBP occurs in some patients with a contained rupture of an AAA. The classic clinical triad of abdominal pain, shock, and back pain occurs in <20% of patients. The diagnosis may be missed because the symptoms and signs can be nonspecific. Misdiagnoses include nonspecific back pain, diverticulitis, renal colic, sepsis, and myocardial infarction. A careful abdominal examination revealing a pulsatile mass (present in 50–75% of patients) is an important physical finding. Patients with suspected AAA should be evaluated with abdominal ultrasound, CT, or MRI **(Chap. 274)**.

Sacral Pain with Gynecologic and Urologic Disease Pelvic organs rarely cause LBP. Uterine malposition (retroversion, descensus, and prolapse) may cause traction on the uterosacral ligament. The pain is referred to the sacral region, sometimes appearing after prolonged standing. Endometriosis or uterine cancers can invade the uterosacral ligaments. Pain associated with endometriosis is typically premenstrual and often continues until it merges with menstrual pain.

Menstrual pain with poorly localized, cramping pain can radiate down the legs. LBP that radiates into one or both thighs is common in the last weeks of pregnancy. Continuous and worsening pain unrelieved by rest or at night may be due to neoplastic infiltration of nerves or nerve roots.

Urologic sources of lumbosacral back pain include chronic prostatitis, prostate cancer with spinal metastasis **(Chap. 83)**, and diseases of the kidney or ureter. Infectious, inflammatory, or neoplastic renal diseases may produce ipsilateral lumbosacral pain, as can renal artery or vein thrombosis. Paraspinal lumbar pain may be a symptom of ureteral obstruction due to nephrolithiasis.

OTHER CAUSES OF BACK PAIN

Postural Back Pain There is a group of patients with nonspecific chronic low back pain (CLBP) in whom no specific anatomic lesion can be found despite exhaustive investigation. Exercises to strengthen the paraspinal and abdominal muscles are sometimes helpful.

Psychiatric Disease CLBP may be encountered in patients who seek financial compensation; in malingerers; or in those with concurrent substance abuse. Many patients with CLBP have a history of psychiatric illness (depression, anxiety states) or childhood trauma (physical or sexual abuse) that antedates the onset of back pain. Preoperative psychological assessment has been used to exclude patients with marked psychological impairments that predict a poor surgical outcome from spine surgery.

IDIOPATHIC

The cause of low back pain occasionally remains unclear. Some patients have had multiple operations for disk disease. The original indications for surgery may have been questionable, with back pain only, no definite neurologic signs, or a minor disk bulge noted on CT or MRI. Scoring systems based on neurologic signs, psychological factors, physiologic studies, and imaging studies have been devised to minimize the likelihood of unsuccessful surgery.

GLOBAL CONSIDERATIONS

While many of the history and examination features described in this chapter apply to all patients, information regarding the global epidemiology and prevalence of LBP is limited. The Global Burden of Diseases Study 2010 reported that LBP ranked #6 overall as a cause of disability-related life years (DALYs), and was the #1 cause overall for total years lived with disability (YLD). These numbers increased substantially from 1990 estimates, and with the aging of the population worldwide, the numbers of individuals suffering from low back pain are expected to increase further in the future. Although rankings for low back pain generally were higher in developed regions of the world, this was not uniformly the case; for example, in North Africa and the Middle East low back pain ranked #2 for DALYs. Another area of uncertainty is the extent to which regional differences exist in terms of the specific etiologies of LBP and how these are managed. For example, the most common cause of arachnoiditis in developing countries is prior spine infection, but in developed countries is multiple lumbar spine surgeries. The longstanding history and acceptance of acupuncture in China may also explain the large number of studies from China regarding the efficacy of acupuncture in many pain settings.

TREATMENT

Back Pain

Mounting evidence of morbidity from long-term opioid therapy (including overdose, dependency, addiction, falls, fractures, accident risk, and sexual dysfunction) has prompted efforts to reduce its use for chronic pain, including back pain **(Chap. 10)**. Safety may be improved with automated notices for high doses, early refills, prescriptions from multiple pharmacies, and overlapping opioid and benzodiazepine prescriptions. Greater access to alternative treatments for chronic pain, such as tailored exercise programs and cognitive-behavioral therapy (CBT), may also reduce opioid prescribing. Public concern in the United States resulted in passage of the Comprehensive Addiction and Recovery Act of 2016.

The high cost, wide geographic variations, and rapidly increasing rates of spinal fusion surgery have prompted scrutiny regarding the lack of standardization of appropriate indications. Some insurance carriers have begun to limit coverage for the most controversial indications, such as low back pain without radiculopathy. Finally, educating patients and the public about the risks of overtreatment may be necessary.

ALBP WITHOUT RADICULOPATHY

ALBP is defined as pain of <3 months in duration. Full recovery can be expected in >85% of adults with ALBP without leg pain. Most have purely "mechanical" symptoms (i.e., pain that is aggravated by motion and relieved by rest).

The initial assessment excludes serious causes of spine pathology that require urgent intervention, including infection, cancer, or trauma. Risk factors for a serious cause of ALBP are shown in Table 14-1. Laboratory and imaging studies are unnecessary if risk factors are absent. CT, MRI, or plain spine films are rarely indicated in the first month of symptoms unless a spine fracture, tumor, or infection is suspected.

The prognosis of ALBP is generally excellent, however episodes tend to recur, and as many as two-thirds of patients will experience a second episode within 1 year. Most patients do not seek medical care and improve on their own. Even among those seen in primary care, two-thirds report being substantially improved after 7 weeks. Spontaneous improvement can mislead clinicians and patients alike about the efficacy of treatment interventions unless subjected to rigorous prospective trials. Many treatments commonly used in the past are now known to be ineffective, including bed rest and lumbar traction.

Clinicians should reassure and educate patients that improvement is very likely and instruct them in self-care. Satisfaction and the likelihood of follow-up increase when patients are educated about prognosis, treatment methods, activity modifications, and strategies to prevent future exacerbations. Patients who report that they did not receive an adequate explanation for their symptoms are likely to request further diagnostic tests. In general, bed rest should be avoided for relief of severe symptoms or kept to a day or two at most. Several randomized trials suggest that bed rest does not hasten the pace of recovery. In general, the best activity recommendation is for early resumption of normal physical activity, avoiding only strenuous manual labor. Possible advantages of early ambulation for ALBP include maintenance of cardiovascular conditioning, improved bone, cartilage, and muscle strength, and increased endorphin levels. Specific back exercises or early vigorous exercise have not shown benefits for acute back pain. Use of heating pads or blankets is sometimes helpful.

Evidence-based guidelines recommend over-the-counter medicines such as NSAIDs and acetaminophen as first-line options for treatment of ALBP. In otherwise healthy patients, a trial of NSAIDs can be followed by acetaminophen for time-limited periods. In

theory, the anti-inflammatory effects of NSAIDs might provide an advantage over acetaminophen to suppress inflammation that accompany many causes of ALBP, but in practice there is no clinical evidence to support the superiority of NSAIDs. The risk of renal and gastrointestinal toxicity with NSAIDs is increased in patients with preexisting medical comorbidities (e.g., renal insufficiency, cirrhosis, prior gastrointestinal hemorrhage, use of anticoagulants or glucocorticoids, heart failure). Some patients elect to take acetaminophen and a NSAID together in hopes of a more rapid benefit. Skeletal muscle relaxants, such as cyclobenzaprine or methocarbamol, may be useful, but sedation is a common side effect. Limiting the use of muscle relaxants to nighttime only may be an option for patients with back pain that interferes with sleep.

There is no good evidence to support the use of opioid analgesics or tramadol as first-line therapy for ALBP. Their use is best reserved for patients who cannot tolerate acetaminophen or NSAIDs and for those with severe refractory pain. As with muscle relaxants, these drugs are often sedating, so it may be useful to prescribe them at nighttime only. Side effects of short-term opioid use include nausea, constipation, and pruritus; risks of long-term opioid use include hypersensitivity to pain, hypogonadism, and dependency. Falls, fractures, driving accidents, and fecal impaction are other risks. Clinical efficacy of opioids for chronic pain beyond 16 weeks of use is unproven.

There is no evidence to support use of oral or injected glucocorticoids, antiepileptics, antidepressants, therapies for neuropathic pain such as gabapentin or herbal therapies. Commonly used nonpharmacologic treatments for ALBP are also of unproven benefit, including spinal manipulation, physical therapy, massage, acupuncture, laser therapy, therapeutic ultrasound, corsets, transcutaneous electrical nerve stimulation (TENS), special mattresses, or lumbar traction. Although important for chronic pain, back exercises for ALBP are generally not supported by clinical evidence. There is no convincing evidence regarding the value of ice or heat applications for ABLP; however, many patients report temporary symptomatic relief from ice or frozen gel packs, and heat may produce a short-term reduction in pain after the first week. Patients often report improved satisfaction with the care that they receive when they actively participate in the selection of symptomatic approaches.

CLBP WITHOUT RADICULOPATHY

CLBP is defined as pain lasting >12 weeks; it accounts for 50% of total back pain costs. Risk factors include obesity, female gender, older age, prior history of back pain, restricted spinal mobility, pain radiating into a leg, high levels of psychological distress, poor self-rated health, minimal physical activity, smoking, job dissatisfaction, and widespread pain. In general, the same treatments that are recommended for ALBP can be useful for patients with CLBP. In this setting, however, the benefit of opioid therapy or muscle relaxants is less clear. In general, activity tolerance is the primary goal, while pain relief is secondary.

Evidence supports the use of exercise therapy to alleviate pain symptoms and improve function. Exercise can be one of the mainstays of treatment for CLBP. Effective regimens have generally included a combination of core strengthening exercises, stretching, and gradually increasing aerobic exercise. A program of supervised exercise can improve compliance. Supervised intensive physical exercise or "work hardening" regimens have been effective in returning some patients to work, improving walking distance, and reducing pain. In addition, some forms of yoga have been evaluated in randomized trials and may be helpful for patients who are interested. A long-term benefit of spinal manipulation or massage for CLBP is unproven.

Medications for CLBP may include short courses of NSAIDs or acetaminophen. Tricyclic antidepressants can provide modest pain relief for some patients without evidence of depression. Trials do not support the efficacy of selective serotonin reuptake inhibitors (SSRIs) for CLBP. However, depression is common among patients with chronic pain and should be appropriately treated.

CBT is based on evidence that psychological and social factors, as well as somatic pathology, are important in the genesis of chronic pain and disability; CBT focuses on efforts to identify and modify patients' thinking about their condition. In one randomized trial, CBT reduced disability and pain in patients with CLBP. Such behavioral treatments appear to provide benefits similar in magnitude to exercise therapy.

Back pain is the most frequent reason for seeking complementary and alternative treatments, most commonly spinal manipulation, acupuncture, and massage. The value of these approaches remains unclear, however. Biofeedback has not been studied rigorously. There is no convincing evidence that either spinal manipulation, TENS, laser therapy, or ultrasound are effective in treating CLBP. Rigorous trials of acupuncture suggest that true acupuncture is not superior to sham acupuncture, but that both may offer an advantage over routine care. Whether this is due entirely to placebo effects provided even by sham acupuncture is uncertain. Some trials of massage therapy have been encouraging for short-term relief only.

Various injections, including epidural glucocorticoid injections, facet joint injections, and trigger point injections, have been used for treating CLBP. However, in the absence of radiculopathy, there is no clear evidence that these approaches are effective.

Injection studies are sometimes used diagnostically to help determine the anatomic source of back pain. Pain relief following a glucocorticoid and anesthetic injection into a facet is commonly used as evidence that the facet joint is the pain source; however, the possibility that the response was a placebo effect or due to systemic absorption of the glucocorticoids is difficult to exclude.

Another category of intervention for CLBP is electrothermal and radiofrequency therapy. Intradiskal therapy has been proposed using both types of energy to thermocoagulate and destroy nerves in the intervertebral disk, using specially designed catheters or electrodes. Current evidence does not support the use of discography to identify a specific disk as the pain source, or the use of intradiskal therapy for CLBP.

Radiofrequency denervation is sometimes used to destroy nerves that are thought to mediate pain, and this technique has been used for facet joint pain (with the target nerve being the medial branch of the primary dorsal ramus), for back pain thought to arise from the intervertebral disk (ramus communicans), and radicular back pain (dorsal root ganglia). A few small trials have produced conflicting results for facet joint and diskogenic pain. A trial in patients with chronic radicular pain found no difference between radiofrequency denervation of the dorsal root ganglia and sham treatment. These interventional therapies have not been studied in sufficient detail to draw firm conclusions regarding their value for CLBP.

Surgical intervention for CLBP without radiculopathy has been evaluated in a number of randomized trials. The case for fusion surgery for CLBP without radiculopathy is weak. While some studies have shown modest benefit, there has been no benefit when compared to an active medical treatment arm, often including highly structured, rigorous rehabilitation combined with CBT. The use of BMP instead of iliac crest graft for the fusion was shown to increase hospital costs and length of stay, but not improve clinical outcomes. Guidelines suggest that referral for an opinion on spinal fusion be considered for people who have completed an optimal nonsurgical treatment program (including combined physical and psychological treatment) and who have persistent severe back pain for which they would consider surgery.

Lumbar disk replacement with prosthetic disks is U.S. Food and Drug Administration approved for uncomplicated patients needing single-level surgery at the L3-S1 levels. The disks are generally designed as metal plates with a polyethylene cushion sandwiched in between. The trials that led to approval of these devices were not blinded. When compared to spinal fusion, the artificial disks were "not inferior." Serious complications are somewhat more likely with the artificial disk. This treatment remains controversial for CLBP.

Intensive multidisciplinary rehabilitation programs can include daily or frequent physical therapy, exercise, CBT, a workplace evaluation, and other interventions. For patients who have not responded to other approaches, such programs appear to offer some benefit. Systematic reviews suggest that the evidence is limited and benefits are limited.

Some observers have raised concerns that CLBP may often be overtreated. For CLBP without radiculopathy, multiple guidelines explicitly recommend against use of SSRIs, any type of injection, TENS, lumbar supports, traction, ulrtaradiofrequency facet joint denervation, intradiskal electrothermal therapy, or intradiskal radiofrequency thermocoagulation. On the other hand, exercise therapy and treatment of depression appear to be useful and underused.

LOW BACK PAIN WITH RADICULOPATHY

A common cause of back pain with radiculopathy is a herniated disk affecting the nerve root and producing back pain with radiation down the leg. The term sciatica is used when the leg pain radiates posteriorly in a sciatic or L5/S1 distribution. The prognosis for acute low back and leg pain with radiculopathy due to disk herniation is generally favorable, with most patients showing substantial improvement over months. Serial imaging studies suggest spontaneous regression of the herniated portion of the disk in two-thirds of patients over 6 months. Nonetheless, there are several important treatment options that provide symptomatic relief while the healing process unfolds.

Resumption of normal activity is recommended. Randomized trial evidence suggests that bed rest is ineffective for treating sciatica as well as back pain alone. Acetaminophen and NSAIDs are useful for pain relief, although severe pain may require short courses of opioid analgesics. Opioids are superior for acute pain relief in the emergency room.

Epidural glucocorticoid injections have a role in providing symptom relief for acute lumbar radiculopathy due to a herniated disk. However, there does not appear to be a benefit in terms of reducing subsequent surgical interventions. A brief course of high dose oral glucocorticoids for 5 days followed by a rapid taper >5 days can be helpful for some patients with acute disk-related radiculopathy, although this specific regimen has not been studied rigorously.

Diagnostic nerve root blocks have been advocated to determine if pain originates from a specific nerve root. However, improvement may result even when the nerve root is not responsible for the pain; this may occur as a placebo effect, from a pain-generating lesion located distally along the peripheral nerve, or from effects of systemic absorption.

Urgent surgery is recommended for patients who have evidence of CES or spinal cord compression, generally manifest as combinations of bowel or bladder dysfunction, diminished sensation in a saddle distribution, a sensory level on the trunk, and bilateral leg weakness or spasticity. Surgical intervention is also indicated for patients with progressive motor weakness due to nerve root injury demonstrated on clinical examination or EMG.

Surgery is also an important option for patients who have disabling radicular pain despite optimal conservative treatment. Because patients with a herniated disk and sciatica generally experience rapid improvement over weeks, most experts do not recommend considering surgery unless the patient has failed to respond to a minimum of 6–8 weeks of nonsurgical management. For patients who have not improved, randomized trials indicate that, compared to nonsurgical treatment, surgery results in more rapid pain relief. However, after 2 years of follow-up, patients appear to have similar pain relief and functional improvement with or without surgery. Thus, both treatment approaches are reasonable, and patient preferences and needs (e.g., rapid return to employment) strongly influence decision making. Some patients will want the fastest possible relief and find surgical risks acceptable. Others will be more risk-averse, more tolerant of symptoms and will choose watchful waiting, especially if they understand that improvement is likely in the end.

The usual surgical procedure is a partial hemilaminectomy with excision of the prolapsed disk (diskectomy). Minimally invasive techniques have gained in popularity in recent years, but preliminary evidence suggests they may be less effective than standard surgical techniques, with more residual back pain, leg pain, and higher rates of rehospitalization. Fusion of the involved lumbar segments should be considered only if significant spinal instability is present (i.e., degenerative spondylolisthesis). The costs associated with lumbar interbody fusion have increased dramatically in recent years. There are no large prospective, randomized trials comparing fusion to other types of surgical intervention. In one study, patients with persistent low back pain despite an initial diskectomy fared no better with spine fusion than with a conservative regimen of cognitive intervention and exercise. Artificial disks are used in Europe; their utility remains controversial in the United States.

PAIN IN THE NECK AND SHOULDER

Neck pain, which usually arises from diseases of the cervical spine and soft tissues of the neck, is common. Neck pain arising from the cervical spine is typically precipitated by movement and may be accompanied by focal tenderness and limitation of motion. Many of the prior comments made regarding causes of low back pain also apply to disorders of the cervical spine. The text below will emphasize differences. Pain arising from the brachial plexus, shoulder, or peripheral nerves can be confused with cervical spine disease **(Table 14-4)**, but the history and examination usually identify a more distal origin for the pain. When the site of nerve tissue injury is unclear, EMG studies can localize the lesion. Cervical spine trauma, disk disease, or spondylosis with intervertebral foraminal narrowing may be asymptomatic or painful and can produce a myelopathy, radiculopathy, or both. The same risk factors for serious causes of low back pain also apply to neck pain with the additional feature that neurologic signs of myelopathy (incontinence, sensory level, spastic legs) may also occur. Lhermitte's sign, an electrical shock down the spine with neck flexion, suggests involvement of the cervical spinal cord.

TRAUMA TO THE CERVICAL SPINE

Trauma to the cervical spine (fractures, subluxation) places the spinal cord at risk for compression. Motor vehicle accidents, violent crimes, or falls account for 87% of cervical spinal cord injuries **(Chap. 434)**. Immediate immobilization of the neck is essential to minimize further spinal cord injury from movement of unstable cervical spine segments. The decision to obtain imaging should be based on the nature of the injury. The National Emergency X-Radiography Utilization Study (NEXUS) low-risk criteria established that normally alert patients without palpation tenderness in the midline; intoxication; neurologic deficits; or painful distracting injuries were very unlikely to have sustained a clinically significant traumatic injury to the cervical spine. The Canadian C-spine rule recommends that imaging should be obtained following neck region trauma if the patient is >65 years old or has limb paresthesias or if there was a dangerous mechanism for the injury (e.g., bicycle collision with tree or parked car, fall from height >3 feet or five stairs, diving accident). These guidelines are helpful but must be tailored to individual circumstances; for example, patients with advanced osteoporosis, glucocorticoid use, or cancer may warrant imaging after even mild trauma. A CT scan is the diagnostic procedure of choice for detection of acute fractures following severe trauma; plain x-rays can be used for lesser degrees of trauma. When traumatic injury to the vertebral arteries or cervical spinal cord is suspected, visualization by MRI with magnetic resonance angiography is preferred.

Whiplash injury is due to rapid flexion and extension of the neck, usually from automobile accidents. The exact mechanism of injury is unclear. This diagnosis should not be applied to patients with fractures, disk herniation, head injury, focal neurologic findings, or altered consciousness. Up to 50% of persons reporting whiplash injury acutely have persistent neck pain 1 year later. When personal compensation for pain and suffering was removed from the Australian health care system, the prognosis for recovery at 1 year improved. Imaging of the cervical spine is not cost-effective acutely but is useful to detect disk herniations when symptoms persist for >6 weeks following the injury. Severe initial symptoms have been associated with a poor long-term outcome.

CERVICAL DISK DISEASE

Degenerative cervical disk disease is very common and usually asymptomatic. Herniation of a lower cervical disk is a common cause of pain or tingling in the neck, shoulder, arm, or hand. Neck pain, stiffness, and a range of motion limited by pain are the usual manifestations.

TABLE 14-4 Cervical Radiculopathy: Neurologic Features

CERVICAL NERVE ROOTS	EXAMINATION FINDINGS			PAIN DISTRIBUTION
	REFLEX	SENSORY	MOTOR	
C5	Biceps	Lateral deltoid	Rhomboids[a] (elbow extends backward with hand on hip) Infraspinatus[a] (arm rotates externally with elbow flexed at the side) Deltoid[a] (arm raised laterally 30–45° from the side)	Lateral arm, medial scapula
C6	Biceps	Thumb/index finger; Dorsal hand/lateral forearm	Biceps[a] (arm flexed at the elbow in supination) Pronator teres (forearm pronated)	Lateral forearm, thumb/index fingers
C7	Triceps	Middle fingers Dorsal forearm	Triceps[a] (forearm extension, flexed at elbow) Wrist/finger extensors[a]	Posterior arm, dorsal forearm, dorsal hand
C8	Finger flexors	Palmar surface of little finger Medial hand and forearm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Fourth and fifth fingers, medial hand and forearm
T1	Finger flexors	Axilla and medial arm	Abductor pollicis brevis (abduction of thumb) First dorsal interosseous (abduction of index finger) Abductor digiti minimi (abduction of little finger)	Medial arm, axilla

[a]These muscles receive the majority of innervation from this root.

Herniated cervical disks are responsible for ~25% of cervical radiculopathies. Extension and lateral rotation of the neck narrow the ipsilateral intervertebral foramen and may reproduce radicular symptoms (Spurling's sign). In young adults, acute nerve root compression from a ruptured cervical disk is often due to trauma. Cervical disk herniations are usually posterolateral near the lateral recess. Typical patterns of reflex, sensory, and motor changes that accompany cervical nerve root lesions are summarized in Table 14-4. Although the classic patterns are clinically helpful, there are numerous exceptions because (1) there is overlap in sensory function between adjacent nerve roots, (2) symptoms and signs may be evident in only part of the injured nerve root territory, and (3) the location of pain is the most variable of the clinical features.

CERVICAL SPONDYLOSIS

Osteoarthritis of the cervical spine may produce neck pain that radiates into the back of the head, shoulders, or arms, or may be the source of headaches in the posterior occipital region (supplied by the C2-C4 nerve roots). Osteophytes, disk protrusions, or hypertrophic facet or uncovertebral joints may alone or in combination compress one or several nerve roots at the intervertebral foramina; these causes together account for 75% of cervical radiculopathies. The roots most commonly affected are C7 and C6. Narrowing of the spinal canal by osteophytes, ossification of the posterior longitudinal ligament (OPLL), or a large central disk may compress the cervical spinal cord and produce signs of myelopathy alone or radiculopathy with myelopathy (myeloradiculopathy). When little or no neck pain accompanies cervical cord involvement, other diagnoses to be considered include amyotrophic lateral sclerosis **(Chap. 429)**, multiple sclerosis **(Chap. 436)**, spinal cord tumors, or syringomyelia **(Chap. 434)**. Cervical spondylotic myelopathy should be considered even when the patient presents with symptoms or spinal cord signs in the legs only. MRI is the study of choice to define soft tissues in the cervical region including the spinal cord, whereas plain CT is optimal to identify bone pathology including foraminal, lateral recess, or spinal canal stenosis. With spondylotic myelopathy focal enhancement by MRI, sometimes in a characteristic "pancake pattern", may be present at the site of maximal cord compression.

There is no evidence to support prophylactic surgery for asymptomatic cervical spinal stenosis unaccompanied by myelopathic signs or abnormal spinal cord findings on MR imaging, except in the setting of *dynamic instability* (see spondylolisthesis above). If the patient has postural neck pain, a prior history of whiplash or other spine/head injury, a Lhermitte sign, or preexisting listhesis at the stenotic segment on cervical MRI, or CT, then cervical spine flexion-extension x-rays are indicated to look for dynamic instability. Surgical intervention is not recommended for patients with listhesis alone, unaccompanied by dynamic instability.

OTHER CAUSES OF NECK PAIN

RA **(Chap. 351)** of the cervical facet joints produces neck pain, stiffness, and limitation of motion. Synovitis of the atlantoaxial joint (C1-C2; Fig. 14-2) may damage the transverse ligament of the atlas, producing forward displacement of the atlas on the axis (atlantoaxial subluxation). Radiologic evidence of atlantoaxial subluxation occurs in up to 30% of patients with RA and plain x-ray films of the neck should be routinely performed preoperatively to assess the risk of neck hyperextension in patients requiring intubation. The degree of subluxation correlates with the severity of erosive disease. When subluxation is present, careful assessment is important to identify early signs of myelopathy that could be a harbinger of life-threatening spinal cord compression. Surgery should be considered when myelopathy or spinal instability is present. *Ankylosing spondylitis* is another cause of neck pain and less commonly atlantoaxial subluxation.

Acute *herpes zoster* can present as acute posterior occipital or neck pain prior to the outbreak of vesicles. *Neoplasms* metastatic to the cervical spine, *infections* (osteomyelitis and epidural abscess), and *metabolic bone diseases* may be the cause of neck pain, as discussed above. Neck pain may also be referred from the heart with coronary artery ischemia (cervical angina syndrome).

THORACIC OUTLET SYNDROMES

The thoracic outlet contains the first rib, the subclavian artery and vein, the brachial plexus, the clavicle, and the lung apex. Injury to these structures may result in postural or movement-induced pain around the shoulder and supraclavicular region, classified as follows.

True neurogenic thoracic outlet syndrome (*TOS*) is an uncommon disorder resulting from compression of the lower trunk of the brachial plexus or ventral rami of the C8 or T1 nerve roots, caused most often by an anomalous band of tissue connecting an elongate transverse process at C7 with the first rib. Pain is mild or may be absent. Signs include weakness and wasting of intrinsic muscles of the hand and diminished sensation on the palmar aspect of the fifth digit. An anteroposterior cervical spine x-ray will show an elongate C7 transverse process (an anatomic marker for the anomalous cartilaginous band), and EMG and NCSs confirm the diagnosis. Treatment consists of surgical resection of the anomalous band. The weakness and wasting of intrinsic hand muscles typically does not improve, but surgery halts the insidious progression of weakness.

Arterial TOS results from compression of the subclavian artery by a cervical rib, resulting in poststenotic dilatation of the artery and in some cases secondary thrombus formation. Blood pressure is reduced

in the affected limb, and signs of emboli may be present in the hand. Neurologic signs are absent. Ultrasound can confirm the diagnosis noninvasively. Treatment is with thrombolysis or anticoagulation (with or without embolectomy) and surgical excision of the cervical rib compressing the subclavian artery.

Venous TOS is due to subclavian vein thrombosis resulting in swelling of the arm and pain. The vein may be compressed by a cervical rib or anomalous scalene muscle. Venography is the diagnostic test of choice.

Disputed TOS accounts for 95% of patients diagnosed with TOS; chronic arm and shoulder pain are prominent and of unclear cause. The lack of sensitive and specific findings on physical examination or specific markers for this condition results in diagnostic uncertainty. The role of surgery in disputed TOS is controversial. Major depression, chronic symptoms, work-related injury, and diffuse arm symptoms predict poor surgical outcomes. Multidisciplinary pain management is a conservative approach, although treatment is often unsuccessful.

BRACHIAL PLEXUS AND NERVES

Pain from injury to the brachial plexus or peripheral nerves of the arm can occasionally mimic referred pain of cervical spine origin including cervical radiculopathy. Neoplastic infiltration of the lower trunk of the brachial plexus may produce shoulder or supraclavicular pain radiating down the arm, numbness of the fourth and fifth fingers or medial forearm, and weakness of intrinsic hand muscles innervated by the lower trunk and medial cord of the brachial plexus. Delayed radiation injury may produce weakness in the upper arm or numbness of the lateral forearm or arm due to involvement of the upper trunk and lateral cord of the plexus. Pain is less common and less severe than with neoplastic infiltration. A Pancoast tumor of the lung **(Chap. 74)** is another cause and should be considered, especially when a concurrent Horner's syndrome is present. *Suprascapular neuropathy* may produce severe shoulder pain, weakness, and wasting of the supraspinatus and infraspinatus muscles. *Acute brachial neuritis* is often confused with radiculopathy; the acute onset of severe shoulder or scapular pain is followed typically over days by weakness of the proximal arm and shoulder girdle muscles innervated by the upper brachial plexus. The onset may be preceded by an infection, vaccination, or minor surgical procedure. The long thoracic nerve may be affected, resulting in a winged scapula. Brachial neuritis may also present as an isolated paralysis of the diaphragm with or without involvement of other nerves of the upper limb. Recovery may take up to 3 years, and full functional recovery can be expected in the majority of patients.

Occasional cases of carpal tunnel syndrome produce pain and paresthesias extending into the forearm, arm, and shoulder resembling a C5 or C6 root lesion. Lesions of the radial or ulnar nerve can also mimic radiculopathy, at C7 or C8, respectively. EMG and NCSs can accurately localize lesions to the nerve roots, brachial plexus, or peripheral nerves.

For further discussion of peripheral nerve disorders, see Chap. 438.

SHOULDER

Pain arising from the shoulder can on occasion mimic pain from the spine. If symptoms and signs of radiculopathy are absent, then the differential diagnosis includes mechanical shoulder pain (tendonitis, bursitis, rotator cuff tear, dislocation, adhesive capsulitis, or rotator cuff impingement under the acromion) and referred pain (subdiaphragmatic irritation, angina, Pancoast tumor). Mechanical pain is often worse at night, associated with local shoulder tenderness and aggravated by passive abduction, internal rotation, or extension of the arm. Demonstrating normal passive full range of motion of the arm at the shoulder without worsening the usual pain can help exclude mechanical shoulder pathology as a cause of neck region pain. Pain from shoulder disease may radiate into the arm or hand, but focal neurologic signs (sensory, motor, or reflex changes) are absent.

GLOBAL CONSIDERATIONS

Many of the considerations described above for LBP also apply to neck pain. Neck pain was ranked #21 as a cause of DALYs in the Global Burden of Diseases Study 2010, accounting for ~40% of the total global DALYs due to LBP. In general, neck pain rankings were also higher in developed regions of the world.

TREATMENT

Neck Pain without Radiculopathy

The evidence regarding treatment for neck pain is less comprehensive than that for low back pain, but the approach is remarkably similar in many respects. As with low back pain, spontaneous improvement is the norm for acute neck pain. The usual goals of therapy are to promote a rapid return to normal function and provide pain relief while healing proceeds.

Acute neck pain is often treated with a combination of NSAIDs, acetaminophen, cold packs, or heat while awaiting spontaneous recovery. For patients kept awake by symptoms, cyclobenzaprine (5–10 mg) at night can help relieve muscle spasm and promote drowsiness. For patients with neck pain unassociated with trauma, supervised exercise with or without mobilization appears to be effective. Exercises often include shoulder rolls and neck stretches. The evidence in support of nonsurgical treatments for whiplash-associated disorders is generally of limited quality and neither supports nor refutes the common treatments used for symptom relief. Gentle mobilization of the cervical spine combined with exercise programs may be beneficial. Evidence is insufficient to recommend the use of cervical traction, TENS, ultrasound, electromagnetic therapy, trigger point injections, botulinum toxin injections, tricyclic antidepressants, and SSRIs for acute or chronic neck pain. Some patients obtain modest pain relief using a soft neck collar; there is little risk or cost. Massage can produce temporary pain relief.

For patients with chronic neck pain, supervised exercise programs can provide symptom relief and improve function. Acupuncture provided short-term benefit for some patients when compared to a sham procedure and is an option. Spinal manipulation alone has not been shown to be effective and carries a risk for injury. Surgical treatment for chronic neck pain without radiculopathy or spine instability is not recommended.

TREATMENT

Neck Pain with Radiculopathy

The natural history of neck pain with acute radiculopathy due to disk disease is favorable, and many patients will improve without specific therapy. Although there are no randomized trials of NSAIDs for neck pain, a course of NSAIDs, acetaminophen, or both, with or without muscle relaxants, and avoidance of activities that trigger symptoms are reasonable as initial therapy. Gentle supervised exercise and avoidance of inactivity are reasonable as well. A short course of high dose oral glucocorticoids with a rapid taper, or epidural steroids administered under imaging guidance can be effective for acute or subacute disk-related cervical radiculopathy, but have not been subjected to rigorous trials. The risk of injection complications is higher in the neck than the low back; vertebral artery dissection, dural puncture, and embolism from injection particles in the vertebral arteries have all been reported. Opioid analgesics can be used in the emergency room and for short courses as an outpatient. Soft cervical collars can be modestly helpful by limiting spontaneous and reflex neck movements that exacerbate pain; hard collars are in general poorly tolerated.

If cervical radiculopathy is due to bony compression from cervical spondylosis with foraminal narrowing, periodic follow-up to assess for progression is indicated and consideration of surgical decompression is reasonable. Surgical treatment can produce rapid pain relief, although it is unclear whether long-term outcomes are improved over nonsurgical therapy. Indications for cervical disk surgery include a progressive motor deficit due to nerve root compression, functionally limiting pain that fails to respond to conservative management, or spinal cord compression.

Surgical treatments include anterior cervical diskectomy alone, laminectomy with diskectomy, or diskectomy with fusion. The risk of subsequent radiculopathy or myelopathy at cervical segments adjacent to a fusion is ~3% per year and 26% per decade. Although this risk is sometimes portrayed as a late complication of surgery, it may also reflect the natural history of degenerative cervical disk disease.

FURTHER READING

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Section 2 Alterations in Body Temperature

15 Fever

Charles A. Dinarello, Reuven Porat

Body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals: one from peripheral nerves that transmit information from warmth/cold receptors in the skin and the other from the temperature of the blood bathing the region. These two types of signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral temperature environment, the human metabolic rate produces more heat than is necessary to maintain the core body temperature in the range of 36.5–37.5°C (97.7–99.5°F).

A normal body temperature is ordinarily maintained despite environmental variations because the hypothalamic thermoregulatory center balances the excess heat production derived from metabolic activity in muscle and the liver with heat dissipation from the skin and lungs. According to studies of healthy individuals 18–40 years of age, the mean oral temperature is 36.8° ± 0.4°C (98.2° ± 0.7°F), with low levels at 6 A.M. and higher levels at 4–6 P.M. The maximal normal oral temperature is 37.2°C (98.9°F) at 6 A.M. and 37.7°C (99.9°F) at 4 P.M.; these values define the 99th percentile for healthy individuals. In light of these studies, *an A.M. temperature of >37.2°C (>98.9°F) or a P.M. temperature of >37.7°C (>99.9°F) would define a fever.* The normal daily temperature variation, also called the *circadian rhythm*, is typically 0.5°C (0.9°F). However, in some individuals recovering from a febrile illness, this daily variation can be as great as 1.0°C. During a febrile illness, the diurnal variation is usually maintained, but at higher, febrile levels. The daily temperature variation appears to be fixed in early childhood; in contrast, elderly individuals can exhibit a reduced ability to develop fever, with only a modest fever even in severe infections.

Rectal temperatures are generally 0.4°C (0.7°F) higher than oral readings. The lower oral readings are probably attributable to mouth breathing, which is a factor in patients with respiratory infections and rapid breathing. Lower-esophageal temperatures closely reflect core temperature. Tympanic membrane thermometers measure radiant heat from the tympanic membrane and nearby ear canal and display that absolute value (*unadjusted mode*) or a value automatically calculated from the absolute reading on the basis of nomograms relating the radiant temperature measured to actual core temperatures obtained in clinical studies (*adjusted mode*). These measurements, although convenient, may be more variable than directly determined oral or rectal values. Studies in adults show that readings are lower with unadjusted-mode than with adjusted-mode tympanic membrane thermometers and that unadjusted-mode tympanic membrane values are 0.8°C (1.6°F) lower than rectal temperatures.

In women who menstruate, the A.M. temperature is generally lower during the 2 weeks before ovulation; it then rises by ~0.6°C (1°F) with ovulation and stays at that level until menses occur. During the luteal phase, the amplitude of the circadian rhythm remains the same.

FEVER VERSUS HYPERTHERMIA

Fever is an elevation of body temperature that exceeds the normal daily variation and occurs *in conjunction with an increase in the hypothalamic set point* (e.g., from 37°C to 39°C). This shift of the set point from "normothermic" to febrile levels very much resembles the resetting of the home thermostat to a higher level in order to raise the ambient temperature in a room. Once the hypothalamic set point is raised, neurons in the vasomotor center are activated and vasoconstriction commences. The individual first notices vasoconstriction in the hands and feet. Shunting of blood away from the periphery to the internal organs essentially decreases heat loss from the skin, and the person feels cold. For most fevers, body temperature increases by 1–2°C. Shivering, which increases heat production from the muscles, may begin at this time; however, shivering is not required if mechanisms of heat conservation raise blood temperature sufficiently. Nonshivering heat production from the liver also contributes to increasing core temperature. Behavioral adjustments (e.g., putting on more clothing or bedding) help raise body temperature by decreasing heat loss.

The processes of heat conservation (vasoconstriction) and heat production (shivering and increased nonshivering thermogenesis) continue until the temperature of the blood bathing the hypothalamic neurons matches the new "thermostat setting." Once that point is reached, the hypothalamus maintains the temperature at the febrile level by the same mechanisms of heat balance that function in the afebrile state. When the hypothalamic set point is again reset downward (in response to either a reduction in the concentration of pyrogens or the use of antipyretics), the processes of heat loss through vasodilation and sweating are initiated. Loss of heat by sweating and vasodilation continues until the blood temperature at the hypothalamic level matches the lower setting. Behavioral changes (e.g., removal of clothing) facilitate heat loss.

A fever of >41.5°C (>106.7°F) is called *hyperpyrexia*. This extraordinarily high fever can develop in patients with severe infections but most commonly occurs in patients with central nervous system (CNS) hemorrhages. In the preantibiotic era, fever due to a variety of infectious diseases rarely exceeded 106°F, and there has been speculation that this natural "thermal ceiling" is mediated by neuropeptides functioning as central antipyretics.

In rare cases, the hypothalamic set point is elevated as a result of local trauma, hemorrhage, tumor, or intrinsic hypothalamic malfunction. The term *hypothalamic fever* is sometimes used to describe elevated

temperature caused by abnormal hypothalamic function. However, most patients with hypothalamic damage have *sub*normal, not *supra*-normal, body temperatures.

Although most patients with elevated body temperature have fever, there are circumstances in which elevated temperature represents not fever but *hyperthermia* (*heat stroke*). Hyperthermia is characterized by an uncontrolled increase in body temperature that exceeds the body's ability to lose heat. The setting of the hypothalamic thermoregulatory center is unchanged. In contrast to fever in infections, hyperthermia does not involve pyrogenic molecules. Exogenous heat exposure and endogenous heat production are two mechanisms by which hyperthermia can result in dangerously high internal temperatures. Excessive heat production can easily cause hyperthermia despite physiologic and behavioral control of body temperature. For example, work or exercise in hot environments can produce heat faster than peripheral mechanisms can lose it. **For a detailed discussion of hyperthermia, see Chap. 455.**

It is important to distinguish between fever and hyperthermia since hyperthermia can be rapidly fatal and characteristically does not respond to antipyretics. In an emergency situation, however, making this distinction can be difficult. For example, in systemic sepsis, fever (hyperpyrexia) can be rapid in onset, and temperatures can exceed 40.5°C (104.9°F). Hyperthermia is often diagnosed on the basis of the events immediately preceding the elevation of core temperature—e.g., heat exposure or treatment with drugs that interfere with thermoregulation. In patients with heat stroke syndromes and in those taking drugs that block sweating, the skin is hot but dry, whereas in fever the skin can be cold as a consequence of vasoconstriction. Antipyretics do not reduce the elevated temperature in hyperthermia, whereas in fever—and even in hyperpyrexia—adequate doses of either aspirin or acetaminophen usually result in some decrease in body temperature.

PATHOGENESIS OF FEVER

PYROGENS

The term *pyrogen* (Greek *pyro*, "fire") is used to describe any substance that causes fever. *Exogenous* pyrogens are derived from outside the patient; most are microbial products, microbial toxins, or whole microorganisms (including viruses). The classic example of an exogenous pyrogen is the lipopolysaccharide (endotoxin) produced by all gram-negative bacteria. Pyrogenic products of gram-positive organisms include the enterotoxins of *Staphylococcus aureus* and the groups A and B streptococcal toxins, also called *superantigens*. One staphylococcal toxin of clinical importance is that associated with isolates of *S. aureus* from patients with toxic shock syndrome. These products of staphylococci and streptococci cause fever in experimental animals when injected intravenously at concentrations of 1–10 μg/kg. Endotoxin is a highly pyrogenic molecule in humans: when injected intravenously into volunteers, a dose of 2–3 ng/kg produces fever, leukocytosis, acute-phase proteins, and generalized symptoms of malaise.

PYROGENIC CYTOKINES

Cytokines are small proteins (molecular mass, 10,000–20,000 Da) that regulate immune, inflammatory, and hematopoietic processes. For example, the elevated leukocytosis seen in several infections with an absolute neutrophilia is attributable to the cytokines interleukin (IL) 1 and IL-6. Some cytokines also cause fever; formerly referred to as *endogenous pyrogens*, they are now called *pyrogenic cytokines*. The pyrogenic cytokines include IL-1, IL-6, tumor necrosis factor (TNF), and ciliary neurotropic factor, a member of the IL-6 family. Fever is a prominent side effect of interferon α therapy. Each pyrogenic cytokine is encoded by a separate gene, and each has been shown to cause fever in laboratory animals and in humans. When injected into humans at low doses (10–100 ng/kg), IL-1 and TNF produce fever; in contrast, for IL-6, a dose of 1–10 μg/kg is required for fever production.

A wide spectrum of bacterial and fungal products induce the synthesis and release of pyrogenic cytokines. However, fever can be a manifestation of disease in the absence of microbial infection. For example, inflammatory processes such as pericarditis, trauma, stroke, and routine immunizations induce the production of IL-1, TNF, and/or IL-6; individually or in combination, these cytokines trigger the hypothalamus to raise the set point to febrile levels.

ELEVATION OF THE HYPOTHALAMIC SET POINT BY CYTOKINES

During fever, levels of prostaglandin E_2 (PGE_2) are elevated in hypothalamic tissue and the third cerebral ventricle. The concentrations of PGE_2 are highest near the circumventricular vascular organs (organum vasculosum of lamina terminalis)—networks of enlarged capillaries surrounding the hypothalamic regulatory centers. Destruction of these organs reduces the ability of pyrogens to produce fever. Most studies in animals have failed to show, however, that pyrogenic cytokines pass from the circulation into the brain itself. Thus, it appears that both exogenous pyrogens and pyrogenic cytokines interact with the endothelium of these capillaries and that this interaction is the first step in initiating fever—i.e., in raising the set point to febrile levels.

The key events in the production of fever are illustrated in **Fig. 15-1**. Myeloid and endothelial cells are the primary cell types that produce pyrogenic cytokines. Pyrogenic cytokines such as IL-1, IL-6, and TNF are released from these cells and enter the systemic circulation. Although these circulating cytokines lead to fever by inducing the synthesis of PGE_2, they also induce PGE_2 in peripheral tissues. The increase in PGE_2 in the periphery accounts for the nonspecific myalgias and arthralgias that often accompany fever. It is thought that some systemic PGE_2 escapes destruction by the lung and gains access to the hypothalamus via the internal carotid. However, it is the elevation of PGE_2 in the brain that starts the process of raising the hypothalamic set point for core temperature.

There are four receptors for PGE_2, and each signals the cell in different ways. Of the four receptors, the third (EP-3) is essential for fever: when the gene for this receptor is deleted in mice, no fever follows the injection of IL-1 or endotoxin. Deletion of the other PGE_2 receptor genes leaves the fever mechanism intact. Although PGE_2 is essential for fever, it is not a neurotransmitter. Rather, the release of PGE_2 from the brain side of the hypothalamic endothelium triggers the PGE_2 receptor on glial cells, and this stimulation results in the rapid release of cyclic adenosine 5′-monophosphate (cAMP), which is a neurotransmitter. As shown in Fig. 15-1, the release of cAMP from glial cells activates neuronal endings from the thermoregulatory center that extend into the area. The elevation of cAMP is thought to account for changes in the hypothalamic set point either directly or indirectly (by inducing the release of neurotransmitters). Distinct receptors for microbial products are located on the hypothalamic endothelium. These receptors are called *Toll-like receptors* and are similar in many ways to IL-1 receptors. IL-1 receptors and Toll-like receptors share the same signal-transducing mechanism. Thus, the direct activation of Toll-like receptors or IL-1 receptors results in PGE_2 production and fever.

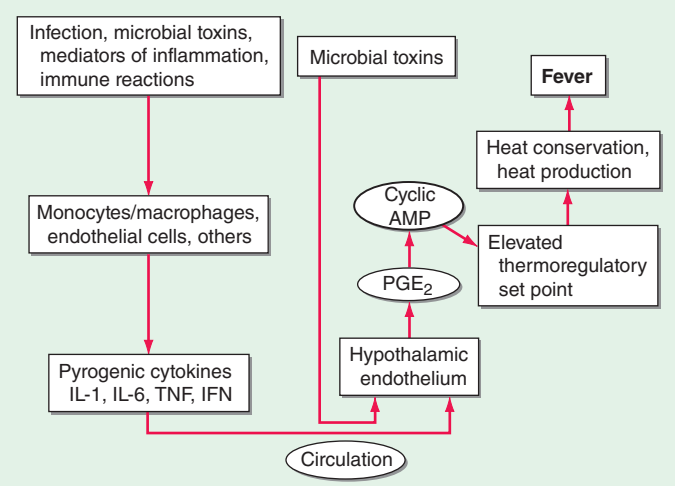

FIGURE 15-1 Chronology of events required for the induction of fever. AMP, adenosine 5′-monophosphate; IFN, interferon; IL, interleukin; PGE_2, prostaglandin E_2; TNF, tumor necrosis factor.

PRODUCTION OF CYTOKINES IN THE CNS

Cytokines produced in the brain may account for the hyperpyrexia of CNS hemorrhage, trauma, or infection. Viral infections of the CNS induce microglial and possibly neuronal production of IL-1, TNF, and IL-6. In experimental animals, the concentration of a cytokine required to cause fever is several orders of magnitude lower with direct injection into the brain substance or brain ventricles than with systemic injection. Therefore, cytokines produced in the CNS can raise the hypothalamic set point, bypassing the circumventricular organs. CNS cytokines likely account for the hyperpyrexia of CNS hemorrhage, trauma, or infection.

APPROACH TO THE PATIENT

Fever

PHYSICAL EXAMINATION

The chronology of events preceding fever, including exposure to other infected individuals or to vectors of disease, should be ascertained. Electronic devices for measuring oral, tympanic membrane, or rectal temperatures are reliable, but the same site should be used consistently to monitor a febrile disease. Moreover, physicians should be aware that newborns, elderly patients, patients with chronic hepatic or renal failure, and patients taking glucocorticoids or being treated with an anticytokine may have active infection in the absence of fever because of a blunted febrile response.

LABORATORY TESTS

The workup should include a complete blood count; a differential count should be performed manually or with an instrument sensitive to the identification of juvenile or band forms, toxic granulations, and Döhle bodies, which are suggestive of bacterial infection. Neutropenia may be present with some viral infections.

Measurement of circulating cytokines in patients with fever is not helpful since levels of cytokines such as IL-1 and TNF in the circulation often are below the detection limit of the assay or do not coincide with fever. However, in patients with low-grade fevers or with suspected occult disease, the most valuable measurements are the C-reactive protein (CRP) level and the erythrocyte sedimentation rate. These markers of inflammatory processes are particularly helpful in detecting occult disease. Measurement of circulating IL-6, which induces CRP, can be useful. However, whereas IL-6 levels may vary during a febrile disease, CRP levels remain elevated. **Acute-phase reactants are discussed in Chap. 297**.

FEVER IN PATIENTS RECEIVING ANTICYTOKINE THERAPY

Patients receiving long-term treatment with anticytokine-based regimens are at increased risk of infection because of lowered host defenses. For example, latent *Mycobacterium tuberculosis* infection can disseminate in patients receiving anti-TNF therapy. With the increasing use of anticytokines to reduce the activity of IL-1, IL-6, IL-12, IL-17, or TNF in patients with Crohn's disease, rheumatoid arthritis, or psoriasis, the possibility that these therapies blunt the febrile response should be kept in mind.

The blocking of cytokine activity has the distinct clinical drawback of lowering the level of host defenses against both routine bacterial and opportunistic infections such as *M. tuberculosis* and fungal infections. The use of monoclonal antibodies to reduce IL-17 in psoriasis increases the risk of systemic candidiasis.

In nearly all reported cases of infection associated with anticytokine therapy, fever is among the presenting signs. However, the extent to which the febrile response is blunted in these patients remains unknown. Therefore, low-grade fever in patients receiving anticytokine therapies is of considerable concern. The physician should conduct an early and rigorous diagnostic evaluation in these cases. The febrile response is also blunted in patients receiving chronic glucocorticoid therapy or anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs).

TREATMENT

Fever

THE DECISION TO TREAT FEVER

Most fevers are associated with self-limited infections, such as common viral diseases. The use of antipyretics is not contraindicated in these infections: no significant clinical evidence indicates either that antipyretics delay the resolution of viral or bacterial infections or that fever facilitates recovery from infection or acts as an adjuvant to the immune system. In short, treatment of fever and its symptoms with routine antipyretics does no harm and does not slow the resolution of common viral and bacterial infections.

However, in bacterial infections, the withholding of antipyretic therapy can be helpful in evaluating the effectiveness of a particular antibiotic, especially in the absence of positive cultures of the infecting organism, and the routine use of antipyretics can mask an inadequately treated bacterial infection. Withholding antipyretics in some cases may facilitate the diagnosis of an unusual febrile disease. Temperature–pulse dissociation (*relative bradycardia*) occurs in typhoid fever, brucellosis, leptospirosis, some drug-induced fevers, and factitious fever. As stated earlier, in newborns, elderly patients, patients with chronic liver or kidney failure, and patients taking glucocorticoids, fever may not be present despite infection. Hypothermia can develop in patients with septic shock.

Some infections have characteristic patterns in which febrile episodes are separated by intervals of normal temperature. For example, *Plasmodium vivax* causes fever every third day, whereas fever occurs every fourth day with *Plasmodium malariae*. Another relapsing fever is related to *Borrelia* infection, with days of fever followed by a several-day afebrile period and then a relapse into additional days of fever. In the Pel-Ebstein pattern, fever lasting 3–10 days is followed by afebrile periods of 3–10 days; this pattern can be classic for Hodgkin's disease and other lymphomas. In cyclic neutropenia, fevers occur every 21 days and accompany the neutropenia. There is no periodicity of fever in patients with familial Mediterranean fever. However, these patterns have limited or no diagnostic value compared with specific and rapid laboratory tests.

ANTICYTOKINE THERAPY TO REDUCE FEVER IN AUTOIMMUNE AND AUTOINFLAMMATORY DISEASES

Recurrent fever is documented at some point in most autoimmune diseases and nearly all autoinflammatory diseases. Although fever can be a manifestation of autoimmune diseases, recurrent fevers are characteristic of autoinflammatory diseases **(Table 15-1)**, including uncommon diseases such as adult and juvenile Still's disease, familial Mediterranean fever, and hyper-IgD syndrome but also common diseases such as idiopathic pericarditis and gout. In addition to recurrent fevers, neutrophilia and serosal inflammation characterize autoinflammatory diseases. The fevers associated with these illnesses are dramatically reduced by blocking of IL-1 activity with anakinra or canakinumab. Anticytokines therefore reduce fever in

TABLE 15-1 Autoinflammatory Diseases in Which Fever Is Characteristic

Adult and juvenile Still's disease
Cryopyrin-associated periodic syndromes (CAPS)
Familial Mediterranean fever
Hyper-IgD syndrome
Behçet's syndrome
Macrophage activation syndrome
Normocomplementemic urticarial vasculitis
Antisynthetase myositis
PAPA[a] syndrome
Blau syndrome
Gouty arthritis

[a]Pyogenic arthritis, pyoderma gangrenosum, and acne.

autoimmune and autoinflammatory diseases. Although fevers in autoinflammatory diseases are mediated by IL-1β, patients also respond to antipyretics.

MECHANISMS OF ANTIPYRETIC AGENTS

The reduction of fever by lowering of the elevated hypothalamic set point is a direct function of reduction of the PGE_2 level in the thermoregulatory center. The synthesis of PGE_2 depends on the constitutively expressed enzyme cyclooxygenase. The substrate for cyclooxygenase is arachidonic acid released from the cell membrane, and this release is the rate-limiting step in the synthesis of PGE_2. Therefore, inhibitors of cyclooxygenase are potent antipyretics. The antipyretic potency of various drugs is directly correlated with the inhibition of brain cyclooxygenase. Acetaminophen is a poor cyclooxygenase inhibitor in peripheral tissue and lacks noteworthy anti-inflammatory activity; in the brain, however, acetaminophen is oxidized by the p450 cytochrome system, and the oxidized form inhibits cyclooxygenase activity. Moreover, in the brain, the inhibition of another enzyme, COX-3, by acetaminophen may account for the antipyretic effect of this agent. However, COX-3 is not found outside the CNS.

Oral aspirin and acetaminophen are equally effective in reducing fever in humans. NSAIDs such as ibuprofen and specific inhibitors of COX-2 also are excellent antipyretics. Chronic, high-dose therapy with antipyretics such as aspirin or any NSAID does not reduce normal core body temperature. Thus, PGE_2 appears to play no role in normal thermoregulation.

As effective antipyretics, glucocorticoids act at two levels. First, similar to the cyclooxygenase inhibitors, glucocorticoids reduce PGE_2 synthesis by inhibiting the activity of phospholipase A_2, which is needed to release arachidonic acid from the cell membrane. Second, glucocorticoids block the transcription of the mRNA for the pyrogenic cytokines. Limited experimental evidence indicates that ibuprofen and COX-2 inhibitors reduce IL-1-induced IL-6 production and may contribute to the antipyretic activity of NSAIDs.

REGIMENS FOR THE TREATMENT OF FEVER

The objectives in treating fever are first to reduce the elevated hypothalamic set point and second to facilitate heat loss. Reducing fever with antipyretics also reduces systemic symptoms of headache, myalgias, and arthralgias.

Oral aspirin and NSAIDs effectively reduce fever but can adversely affect platelets and the gastrointestinal tract. Therefore, acetaminophen is preferred as an antipyretic. In children, acetaminophen or oral ibuprofen must be used because aspirin increases the risk of Reye's syndrome. If the patient cannot take oral antipyretics, parenteral preparations of NSAIDs and rectal suppositories of various antipyretics can be used.

Treatment of fever in some patients is highly recommended. Fever increases the demand for oxygen (i.e., for every increase of 1°C over 37°C, there is a 13% increase in oxygen consumption) and can aggravate the condition of patients with preexisting impairment of cardiac, pulmonary, or CNS function. Children with a history of febrile or nonfebrile seizure should be aggressively treated to reduce fever. However, it is unclear what triggers the febrile seizure, and there is no correlation between absolute temperature elevation and onset of a febrile seizure in susceptible children.

In hyperpyrexia, the use of cooling blankets facilitates the reduction of temperature; however, cooling blankets should not be used without oral antipyretics. In hyperpyretic patients with CNS disease or trauma (CNS bleeding), reducing core temperature mitigates the detrimental effects of high temperature on the brain.

For a discussion of treatment for hyperthermia, see Chap. 455.

FURTHER READING

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16 Fever and Rash

Elaine T. Kaye, Kenneth M. Kaye

The acutely ill patient with fever and rash often presents a diagnostic challenge for physicians, yet the distinctive appearance of an eruption in concert with a clinical syndrome can facilitate a prompt diagnosis and the institution of life-saving therapy or critical infection-control interventions. **Representative images of many of the rashes discussed in this chapter are included in Chap. A1.**

APPROACH TO THE PATIENT

Fever and Rash

A thorough history of patients with fever and rash includes the following relevant information: immune status, medications taken within the previous month, specific travel history, immunization status, exposure to domestic pets and other animals, history of animal (including arthropod) bites, recent dietary exposures, existence of cardiac abnormalities, presence of prosthetic material, recent exposure to ill individuals, and sexual exposures. The history should also include the site of onset of the rash and its direction and rate of spread.

A thorough physical examination entails close attention to the rash, with an assessment and precise definition of its salient features. First, it is critical to determine what *type* of lesions make up the eruption. *Macules* are flat lesions defined by an area of changed color (i.e., a blanchable erythema). *Papules* are raised, solid lesions <5 mm in diameter; *plaques* are lesions >5 mm in diameter with a flat, plateau-like surface; and *nodules* are lesions >5 mm in diameter with a more rounded configuration. *Wheals* (urticaria, hives) are papules or plaques that are pale pink and may appear annular (ringlike) as they enlarge; classic (nonvasculitic) wheals are transient, lasting only 24 h in any defined area. *Vesicles* (<5 mm) and *bullae* (>5 mm) are circumscribed, elevated lesions containing fluid. *Pustules* are raised lesions containing purulent exudate; vesicular processes such as varicella or herpes simplex may evolve to pustules. *Nonpalpable purpura* is a flat lesion that is due to bleeding into the skin. If <3 mm in diameter, the purpuric lesions are termed *petechiae*; if >3 mm, they are termed *ecchymoses*. *Palpable purpura* is a raised lesion that is due to inflammation of the vessel wall (vasculitis) with subsequent hemorrhage. An *ulcer* is a defect in the skin extending at least into the upper layer of the dermis, and an *eschar* (tâche noire) is a necrotic lesion covered with a black crust.

Other pertinent features of rashes include their *configuration* (i.e., annular or target), the *arrangement* of their lesions, and their *distribution* (i.e., central or peripheral).

For further discussion, see Chaps. 52, 54, 117, and 124.

CLASSIFICATION OF RASH

This chapter reviews rashes that reflect systemic disease, but it does not include localized skin eruptions (i.e., cellulitis, impetigo) that may also be associated with fever **(Chap. 124)**. The chapter is not intended to be all-inclusive, but it covers the most important and most common diseases associated with fever and rash. Rashes are classified herein on the basis of lesion morphology and distribution. For practical purposes, this classification system is based on the most typical disease presentations. However, morphology may vary as rashes evolve, and the presentation of diseases with rashes is subject to many variations **(Chap. 54)**. For instance, the classic petechial rash of Rocky Mountain spotted fever **(Chap. 182)** may initially consist of blanchable erythematous macules distributed peripherally; at times, however, the rash associated with this disease may not be predominantly acral, or no rash may develop at all.

Diseases with fever and rash may be classified by type of eruption: centrally distributed maculopapular, peripheral, confluent desquamative erythematous, vesiculobullous, urticaria-like, nodular, purpuric, ulcerated, or with eschars. Diseases are listed by these categories in Table 16-1, and many are highlighted in the text. However, for a more detailed discussion of each disease associated with a rash, the reader is referred to the chapter dealing with that specific disease. **(Reference chapters are cited in the text and listed in Table 16-1.)**

CENTRALLY DISTRIBUTED MACULOPAPULAR ERUPTIONS

Centrally distributed rashes, in which lesions are primarily truncal, are the most common type of eruption. The rash of *rubeola* (measles) starts at the hairline 2–3 days into the illness and moves down the body, typically sparing the palms and soles **(Chap. 200)**. It begins as discrete erythematous lesions, which become confluent as the rash spreads. Koplik's spots (1- to 2-mm white or bluish lesions with an erythematous halo on the buccal mucosa) are pathognomonic for measles and are generally seen during the first 2 days of symptoms. They should not be confused with Fordyce's spots (ectopic sebaceous glands), which have no erythematous halos and are found in the mouth of healthy individuals. Koplik's spots may briefly overlap with the measles exanthem.

Rubella (German measles) also spreads from the hairline downward; unlike that of measles, however, the rash of rubella tends to clear from originally affected areas as it migrates, and it may be pruritic **(Chap. 201)**. Forchheimer spots (palatal petechiae) may develop but are nonspecific because they also develop in *infectious mononucleosis* **(Chap. 189)**, *scarlet fever* **(Chap. 143)**, and *Zika virus infection* **(Chap. 204)**. Postauricular and suboccipital adenopathy and arthritis are common among adults with rubella. Exposure of pregnant women to ill individuals should be avoided, as rubella causes severe congenital abnormalities. Numerous strains of *enteroviruses* **(Chap. 199)**, primarily echoviruses and coxsackieviruses, cause nonspecific syndromes of fever and eruptions that may mimic rubella or measles. Patients with *infectious mononucleosis* caused by Epstein-Barr virus **(Chap. 189)** or with *primary HIV infection* **(Chap. 197)** may exhibit pharyngitis, lymphadenopathy, and a nonspecific maculopapular exanthem.

The rash of *erythema infectiosum* (fifth disease), which is caused by human parvovirus B19, primarily affects children 3–12 years old; it develops after fever has resolved as a bright blanchable erythema on the cheeks ("slapped cheeks") with perioral pallor **(Chap. 192)**. A more diffuse rash (often pruritic) appears the next day on the trunk and extremities and then rapidly develops into a lacy reticular eruption that may wax and wane (especially with temperature change) over 3 weeks. Adults with fifth disease often have arthritis, and fetal hydrops can develop in association with this condition in pregnant women.

Exanthem subitum (roseola) is caused by human herpesvirus 6 and is most common among children <3 years of age **(Chap. 190)**. As in erythema infectiosum, the rash usually appears after fever has subsided. It consists of 2- to 3-mm rose-pink macules and papules that coalesce only rarely, occur initially on the trunk and sometimes on the extremities (sparing the face), and fade within 2 days.

Although drug reactions have many manifestations, including urticaria, exanthematous *drug-induced eruptions* **(Chap. 56)** are most common and are often difficult to distinguish from viral exanthems. Eruptions elicited by drugs are usually more intensely erythematous and pruritic than viral exanthems, but this distinction is not reliable. A history of new medications and an absence of prostration may help to distinguish a drug-related rash from an eruption of another etiology. Rashes may persist for up to 2 weeks after administration of the offending agent is discontinued. Certain populations are more prone than others to drug rashes. Of HIV-infected patients, 50–60% develop a rash in response to sulfa drugs; 30–90% of patients with mononucleosis due to Epstein-Barr virus develop a rash when given ampicillin.

Rickettsial illnesses **(Chap. 182)** should be considered in the evaluation of individuals with centrally distributed maculopapular eruptions. The usual setting for *epidemic typhus* is a site of war or natural disaster in which people are exposed to body lice. Endemic typhus or *leptospirosis* (the latter caused by a spirochete) **(Chap. 179)** may be seen in urban environments where rodents proliferate. Outside the United States, other rickettsial diseases cause a spotted-fever syndrome and should be considered in residents of or travelers to endemic areas. Similarly, *typhoid fever*, a nonrickettsial disease caused by *Salmonella typhi* **(Chap. 160)**, is usually acquired during travel outside the United States. *Dengue fever*, caused by a mosquito-transmitted flavivirus, occurs in tropical and subtropical regions of the world **(Chap. 204)**.

Some centrally distributed maculopapular eruptions have distinctive features. Erythema migrans, the rash of *Lyme disease* **(Chap. 181)**, typically manifests as single or multiple annular lesions. Untreated erythema migrans lesions usually fade within a month but may persist for more than a year. *Southern tick-associated rash illness* (STARI) **(Chap. 181)** has an erythema migrans–like rash, but is less severe than Lyme disease and often occurs in regions where Lyme is not endemic. Erythema marginatum, the rash of *acute rheumatic fever* **(Chap. 352)**, has a distinctive pattern of enlarging and shifting transient annular lesions.

Collagen vascular diseases may cause fever and rash. Patients with *systemic lupus erythematosus* **(Chap. 349)** typically develop a sharply defined, erythematous eruption in a butterfly distribution on the cheeks (malar rash) as well as many other skin manifestations. *Still's disease* presents as an evanescent, salmon-colored rash on the trunk and proximal extremities that coincides with fever spikes.

Zika virus is a mosquito-transmitted flavivirus that is associated with severe birth defects **(Chap. 204)**. Zika is rapidly spreading among tropical and subtropical regions of the world. The eruption of Zika virus infection is typically pruritic and often accompanied by conjunctival injection.

PERIPHERAL ERUPTIONS

These rashes are alike in that they are most prominent peripherally or begin in peripheral (acral) areas before spreading centripetally. Early diagnosis and therapy are critical in *Rocky Mountain spotted fever* **(Chap. 182)** because of its grave prognosis if untreated. Lesions evolve from macular to petechial, start on the wrists and ankles, spread centripetally, and appear on the palms and soles only later in the disease. The rash of *secondary syphilis* **(Chap. 177)**, which may be generalized but is prominent on the palms and soles, should be considered in the differential diagnosis of pityriasis rosea, especially in sexually active patients. *Chikungunya fever* **(Chap. 204)**, which is transmitted by mosquito bite in tropical and subtropical regions, is associated with a maculopapular eruption and severe polyarticular small-joint arthralgias. *Hand-foot-and-mouth disease* **(Chap. 199)**, most commonly caused by coxsackievirus A16 or enterovirus 71, is distinguished by tender vesicles distributed on the hands and feet and in the mouth; coxsackievirus A6 causes an atypical syndrome with more extensive lesions. The classic target lesions of *erythema multiforme* appear symmetrically on the elbows, knees, palms, soles, and face. In severe cases, these lesions spread diffusely and involve mucosal surfaces. Lesions may develop on the hands and feet in *endocarditis* **(Chap. 123)**.

CONFLUENT DESQUAMATIVE ERYTHEMAS

These eruptions consist of diffuse erythema frequently followed by desquamation. The eruptions caused by group A *Streptococcus* or *Staphylococcus aureus* are toxin-mediated. *Scarlet fever* **(Chap. 143)** usually follows pharyngitis; patients have a facial flush, a "strawberry" tongue, and accentuated petechiae in body folds (Pastia's lines). *Kawasaki disease* **(Chaps. 54 and 356)** presents in the pediatric population as fissuring of the lips, a strawberry tongue, conjunctivitis, adenopathy, and sometimes cardiac abnormalities. *Streptococcal toxic shock syndrome* **(Chap. 143)** manifests with hypotension, multiorgan failure, and, often, a severe group A streptococcal infection (e.g., necrotizing fasciitis). *Staphylococcal toxic shock syndrome* **(Chap. 142)** also presents with hypotension and multiorgan failure, but usually only *S. aureus* colonization—not a severe *S. aureus* infection—is documented. *Staphylococcal scalded-skin syndrome* **(Chap. 142)** is seen primarily in children and in immunocompromised adults. Generalized erythema is often evident during the prodrome of fever and malaise; profound tenderness of the skin is distinctive. In the exfoliative stage, the skin can be

TABLE 16-1 Diseases Associated with Fever and Rash

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Centrally Distributed Maculopapular Eruptions					
Acute meningococcemia[a]	—	—	—	—	150
Drug reaction with eosinophilia and systemic symptoms (DRESS); also termed drug-induced hypersensitivity syndrome (DIHS)[b]	—	—	—	—	56
Rubeola (measles, first disease)	Paramyxovirus	Discrete lesions that become confluent as rash spreads from hairline downward, usually sparing palms and soles; lasts ≥3 days; Koplik's spots	Nonimmune individuals	Cough, conjunctivitis, coryza, severe prostration	200
Rubella (German measles, third disease)	Togavirus	Spreads from hairline downward, clearing as it spreads; Forschheimer spots	Nonimmune individuals	Adenopathy, arthritis	201
Erythema infectiosum (fifth disease)	Human parvovirus B19	Bright-red "slapped-cheeks" appearance followed by lacy reticular rash that waxes and wanes over 3 weeks; rarely, papular-purpuric "gloves-and-socks" syndrome on hands and feet	Most common among children 3–12 years old; occurs in winter and spring	Mild fever; arthritis in adults; rash following resolution of fever	192
Exanthem subitum (roseola, sixth disease)	Human herpesvirus 6	Diffuse maculopapular eruption over trunk and neck; resolves within 2 days	Usually affects children <3 years old	Rash following resolution of fever; similar to Boston exanthem (echovirus 16); febrile seizures may occur	190
Primary HIV infection	HIV	Nonspecific diffuse macules and papules; less commonly, urticarial or vesicular oral or genital ulcers	Individuals recently infected with HIV	Pharyngitis, adenopathy, arthralgias	197
Infectious mononucleosis	Epstein-Barr virus	Diffuse maculopapular eruption (5% of cases; 30–90% if ampicillin is given); urticaria, petechiae in some cases; periorbital edema (50%); palatal petechiae (25%)	Adolescents, young adults	Hepatosplenomegaly, pharyngitis, cervical lymphadenopathy, atypical lymphocytosis, heterophile antibody	189
Other viral exanthems	Echoviruses 2, 4, 9, 11, 16, 19, 25; coxsackieviruses A9, B1, B5; etc.	Wide range of skin findings that may mimic rubella or measles	Affect children more commonly than adults	Nonspecific viral syndromes	199
Exanthematous drug-induced eruption	Drugs (antibiotics, anticonvulsants, diuretics, etc.)	Intensely pruritic, bright-red macules and papules, symmetric on trunk and extremities; may become confluent	Occurs 2–3 days after exposure in previously sensitized individuals; otherwise, after 2–3 weeks (but can occur anytime, even shortly after drug is discontinued)	Variable findings: fever and eosinophilia	56
Epidemic typhus	*Rickettsia prowazekii*	Maculopapular eruption appearing in axillae, spreading to trunk and later to extremities; usually spares face, palms, soles; evolves from blanchable macules to confluent eruption with petechiae; rash evanescent in recrudescent typhus (Brill-Zinsser disease)	Exposure to body lice; occurrence of recrudescent typhus as relapse after 30–50 years	Headache, myalgias; mortality rates 10–40% if untreated; milder clinical presentation in recrudescent form	182
Endemic (murine) typhus	*Rickettsia typhi*	Maculopapular eruption, usually sparing palms, soles	Exposure to rat or cat fleas	Headache, myalgias	182
Scrub typhus	*Orientia tsutsugamushi*	Diffuse macular rash starting on trunk; eschar at site of mite bite	Endemic in South Pacific, Australia, Asia; transmitted by mites	Headache, myalgias, regional adenopathy; mortality rates up to 30% if untreated	182
Rickettsial spotted fevers	*Rickettsia conorii* (boutonneuse fever), *Rickettsia australis* (North Queensland tick typhus), *Rickettsia sibirica* (Siberian tick typhus), and others	Eschar common at bite site; maculopapular (rarely, vesicular and petechial) eruption on proximal extremities, spreading to trunk and face	Exposure to ticks; *R. conorii* in Mediterranean region, India, Africa; *R. australis* in Australia; *R. sibirica* in Siberia, Mongolia	Headache, myalgias, regional adenopathy	182

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Human monocytotropic ehrlichiosis[c]	*Ehrlichia chaffeensis*	Maculopapular eruption (40% of cases), involves trunk and extremities; may be petechial	Tick-borne; most common in U.S. Southeast, southern Midwest, and mid-Atlantic regions	Headache, myalgias, leukopenia	182
Leptospirosis	*Leptospira interrogans* and other *Leptospira* species	Maculopapular eruption; conjunctivitis; scleral hemorrhage in some cases	Exposure to water contaminated with animal urine	Myalgias; aseptic meningitis; *fulminant form*: icterohemorrhagic fever (Weil's disease)	179
Lyme disease	*Borrelia burgdorferi* (sole cause in U.S.), *Borrelia afzelii, Borrelia garinii*	Papule expanding to erythematous annular lesion with central clearing (erythema migrans; average diameter, 15 cm), sometimes with concentric rings, sometimes with indurated or vesicular center; multiple secondary erythema migrans lesions in some cases	Bite of *Ixodes* tick vector	Headache, myalgias, chills, photophobia occurring acutely; CNS disease, myocardial disease, arthritis weeks to months later in some cases	181
Southern tick-associated rash illness (STARI, Master's disease)	Unknown (possibly *Borrelia lonestari* or other *Borrelia* spirochetes)	Similar to erythema migrans of Lyme disease with several differences, including: multiple secondary lesions less likely; lesions tending to be smaller (average diameter, ~8 cm); central clearing more likely	Bite of tick vector *Amblyomma americanum* (Lone Star tick); often found in regions where Lyme disease is uncommon, including southern United States	Compared with Lyme disease: fewer constitutional symptoms, tick bite more likely to be recalled; other Lyme disease sequelae lacking	181
Typhoid fever	*Salmonella typhi*	Transient, blanchable erythematous macules and papules, 2–4 mm, usually on trunk (rose spots)	Ingestion of contaminated food or water (rare in U.S.)	Variable abdominal pain and diarrhea; headache, myalgias, hepatosplenomegaly	160
Dengue fever[d]	Dengue virus (4 serotypes; flaviviruses)	Rash in 50% of cases; initially diffuse flushing; midway through illness, onset of maculopapular rash, which begins on trunk and spreads centrifugally to extremities and face; pruritus, hyperesthesia in some cases; after defervescence, petechiae on extremities may occur	Occurs in tropics and subtropics; transmitted by mosquito	Headache; musculoskeletal pain ("breakbone fever"); leukopenia; occasionally biphasic ("saddleback") fever	204
Rat-bite fever (sodoku)	*Spirillum minus*	Eschar at bite site; then blotchy violaceous or red-brown rash involving trunk and extremities	Rat bite; primarily found in Asia; rare in U.S.	Regional adenopathy; recurrent fevers if untreated	136
Relapsing fever	*Borrelia* species	Central rash at end of febrile episode; petechiae in some cases	Exposure to ticks or body lice	Recurrent fever, headache, myalgias, hepatosplenomegaly	180
Erythema marginatum (rheumatic fever)	Group A *Streptococcus*	Erythematous annular papules and plaques occurring as polycyclic lesions in waves over trunk, proximal extremities; evolving and resolving within hours	Patients with rheumatic fever	Pharyngitis preceding polyarthritis, carditis, subcutaneous nodules, chorea	381
Systemic lupus erythematosus (SLE)	Autoimmune disease	Macular and papular erythema, often in sun-exposed areas; discoid lupus lesions (local atrophy, scale, pigmentary changes); periungual telangiectasis; malar rash; vasculitis sometimes causing urticaria, palpable purpura; oral erosions in some cases	Most common in young to middle-aged women; flares precipitated by sun exposure	Arthritis; cardiac, pulmonary, renal, hematologic, and vasculitic disease	352
Still's disease	Autoimmune disease	Transient 2- to 5-mm erythematous papules appearing at height of fever on trunk, proximal extremities; lesions evanescent	Children and young adults	High spiking fever, polyarthritis, splenomegaly; erythrocyte sedimentation rate, >100 mm/h	—
African trypanosomiasis	*Trypanosoma brucei rhodesiense/gambiense*	Blotchy or annular erythematous macular and papular rash (trypanid), primarily on trunk; pruritus; chancre at site of tsetse fly bite may precede rash by several weeks	Tsetse fly bite in eastern *(T. brucei rhodesiense)* or western *(T. brucei gambiense)* Africa	Hemolymphatic disease followed by meningoencephalitis; Winterbottom's sign (posterior cervical lymphadenopathy) *(T. brucei gambiense)*	222

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Arcanobacterial pharyngitis	*Arcanobacterium (Corynebacterium) haemolyticum*	Diffuse, erythematous, maculopapular eruption involving trunk and proximal extremities; may desquamate	Children and young adults	Exudative pharyngitis, lymphadenopathy	145
West Nile fever	West Nile virus	Maculopapular eruption involving the trunk, extremities, and head or neck; rash in 20–50% of cases	Mosquito bite; rarely, blood transfusion or transplanted organ	Headache, weakness, malaise, myalgia, neuroinvasive disease (encephalitis, meningitis, flaccid paralysis)	204
Zika virus infection	Zika virus	Pruritic macular and papular erythema; rash may begin on trunk and descend to lower body; conjunctival injection; palatal petechiae may occur	Mosquito bite; sexual transmission or blood transfusion less common	Arthralgia (especially of small joints), myalgia, lymphadenopathy, headache, low-grade fever; illness in pregnancy may cause severe birth defects, including microcephaly; neurologic complications, including Guillain-Barré, may occur	204
Peripheral Eruptions					
Chronic meningococcemia, disseminated gonococcal infection,[a] human parvovirus B19 infection[e]	—	—	—	—	150, 151, 192
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Rash beginning on wrists and ankles and spreading centripetally; appears on palms and soles later in disease; lesion evolution from blanchable macules to petechiae	Tick vector; widespread but more common in southeastern and southwest-central U.S.	Headache, myalgias, abdominal pain; mortality rates up to 40% if untreated	182
Secondary syphilis	*Treponema pallidum*	Coincident primary chancre in 10% of cases; copper-colored, scaly papular eruption, diffuse but prominent on palms and soles; rash never vesicular in adults; condyloma latum, mucous patches, and alopecia in some cases	Sexually transmitted	Fever, constitutional symptoms	177
Chikungunya fever	Chikungunya virus	Maculopapular eruption; typically occurs on trunk, but also occurs on extremities and face	*Aedes aegypti* and *A. albopictus* mosquito bites; tropical and subtropical regions	Severe polyarticular, migratory arthralgias, especially involving small joints (e.g., hands, wrists, ankles)	204
Hand-foot-and-mouth disease	Coxsackievirus A16 and enterovirus 71 most common causes; coxsackievirus A6 associated with atypical syndrome	Tender vesicles, erosions in mouth; 0.25-cm papules on hands and feet with rim of erythema evolving into tender vesicles; shedding of nails can occur 1–2 months after acute illness; coxsackievirus A6 lesions extend to perioral area, extremities, trunk, buttocks, genitals, and areas affected by eczema	Summer and fall; primarily children <10 years old; multiple family members; coxsackievirus A6 infection also occurs in young adults	Transient fever; enterovirus 71 can be associated with brain stem encephalitis, flaccid paralysis resembling polio, or aseptic meningitis	199
Erythema multiforme (EM)	Infection, drugs, idiopathic causes	Target lesions (central erythema surrounded by area of clearing and another rim of erythema) up to 2 cm; symmetric on knees, elbows, palms, soles; spreads centripetally; papular, sometimes vesicular; when extensive and involving mucous membranes, termed *EM major*	Herpes simplex virus or *Mycoplasma pneumoniae* infection; drug intake (i.e., sulfa, phenytoin, penicillin)	50% of patients <20 years old; fever more common in most severe form, EM major, which can be confused with Stevens-Johnson syndrome (but EM major lacks prominent skin sloughing)	—[f]
Rat-bite fever (Haverhill fever)	*Streptobacillus moniliformis*	Maculopapular eruption over palms, soles, and extremities; tends to be more severe at joints; eruption sometimes becoming generalized; may be purpuric; may desquamate	Rat bite, ingestion of contaminated food	Myalgias; arthritis (50%); fever recurrence in some cases	136

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Peripheral Eruptions (Continued)					
Bacterial endocarditis	*Streptococcus*, *Staphylococcus*, etc.	*Subacute course* (e.g., viridans streptococci): Osler's nodes (tender pink nodules on finger or toe pads); petechiae on skin and mucosa; splinter hemorrhages. *Acute course* (e.g., *Staphylococcus aureus*): Janeway lesions (painless erythematous or hemorrhagic macules, usually on palms and soles)	Abnormal heart valve (e.g., viridans streptococci), intravenous drug use	New or changing heart murmur	**123**
Confluent Desquamative Erythemas					
Scarlet fever (second disease)	Group A *Streptococcus* (pyrogenic exotoxins A, B, C)	Diffuse blanchable erythema beginning on face and spreading to trunk and extremities; circumoral pallor; "sandpaper" texture to skin; accentuation of linear erythema in skin folds (Pastia's lines); enanthem of white evolving into red "strawberry" tongue; desquamation in second week	Most common among children 2–10 years old; usually follows group A streptococcal pharyngitis	Fever, pharyngitis, headache	**143**
Kawasaki disease	Idiopathic causes	Rash similar to scarlet fever (scarlatiniform) or EM; fissuring of lips, strawberry tongue; conjunctivitis; edema of hands, feet; desquamation later in disease	Children <8 years old	Cervical adenopathy, pharyngitis, coronary artery vasculitis	**54, 356**
Streptococcal toxic shock syndrome	Group A *Streptococcus* (associated with pyrogenic exotoxin A and/or B or certain M types)	When present, rash often scarlatiniform	May occur in setting of severe group A streptococcal infections (e.g., necrotizing fasciitis, bacteremia, pneumonia)	Multiorgan failure, hypotension; mortality rate 30%	**143**
Staphylococcal toxic shock syndrome	*S. aureus* (toxic shock syndrome toxin 1, enterotoxins B and others)	Diffuse erythema involving palms; pronounced erythema of mucosal surfaces; conjunctivitis; desquamation 7–10 days into illness	Colonization with toxin-producing *S. aureus*	Fever >39°C (>102°F), hypotension, multiorgan dysfunction	**142**
Staphylococcal scalded-skin syndrome	*S. aureus*, phage group II	Diffuse tender erythema, often with bullae and desquamation; Nikolsky's sign	Colonization with toxin-producing *S. aureus*; occurs in children <10 years old (termed *Ritter's disease* in neonates) or adults with renal dysfunction	Irritability; nasal or conjunctival secretions	**142**
Exfoliative erythroderma syndrome	Underlying psoriasis, eczema, drug eruption, mycosis fungoides	Diffuse erythema (often scaling) interspersed with lesions of underlying condition	Usually occurs in adults over age 50; more common among men	Fever, chills (i.e., difficulty with thermoregulation); lymphadenopathy	**54, 56**
DRESS [drug-induced hypersensitivity syndrome (DIHS)]	Aromatic anticonvulsants; other drugs, including sulfonamides, minocycline	Maculopapular eruption (mimicking exanthematous drug rash), sometimes progressing to exfoliative erythroderma; profound edema, especially facial; pustules may occur	Individuals genetically unable to detoxify arene oxides (anticonvulsant metabolites), patients with slow *N*-acetylating capacity (sulfonamides)	Lymphadenopathy, multiorgan failure (especially hepatic), eosinophilia, atypical lymphocytes; mimics sepsis	**56**
Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	Drugs (80% of cases; often allopurinol, anticonvulsants, antibiotics), infection, idiopathic factors	Erythematous and purpuric macules, sometimes targetoid, or diffuse erythema progressing to bullae, with sloughing and necrosis of entire epidermis; Nikolsky's sign; involves mucosal surfaces; TEN (>30% epidermal necrosis) is maximal form; SJS involves <10% of epidermis; SJS/TEN overlap involves 10–30% of epidermis	Uncommon among children; more common among patients with HIV infection, systemic lupus erythematosus, certain HLA types, or slow acetylators	Dehydration, sepsis sometimes resulting from lack of normal skin integrity; mortality rates up to 30%	**56**
Vesiculobullous or Pustular Eruptions					
Hand-foot-and-mouth syndrome[g]; staphylococcal scalded-skin syndrome; TEN[b];DRESS[b]	—	—	—	—	—[f]

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Varicella (chickenpox)	VZV	Macules (2–3 mm) evolving into papules, then vesicles (sometimes umbilicated), on an erythematous base ("dewdrops on a rose petal"); pustules then forming and crusting; lesions appearing in crops; may involve scalp, mouth; intensely pruritic	Usually affects children; 10% of adults susceptible; most common in late winter and spring; incidence down by 90% in U.S. as a result of varicella vaccination	Malaise; generally mild disease in healthy children; more severe disease with complications in adults and immunocompromised children	188
Pseudomonas "hot-tub" folliculitis	*Pseudomonas aeruginosa*	Pruritic erythematous follicular, papular, vesicular, or pustular lesions that may involve axillae, buttocks, abdomen, and especially areas occluded by bathing suits; can manifest as tender isolated nodules on palmar or plantar surfaces (the latter designated "*Pseudomonas* hot-foot syndrome")	Bathers in hot tubs or swimming pools; occurs in outbreaks	Earache, sore eyes and/ or throat; fever may be absent; generally self-limited	159
Variola (smallpox)	Variola major virus	Red macules on tongue and palate evolving to papules and vesicles; skin macules evolving to papules, then vesicles, then pustules over 1 week, with subsequent lesion crusting; lesions initially appearing on face and spreading centrifugally from trunk to extremities; differs from varicella in that (1) skin lesions in any given area are at same stage of development and (2) there is a prominent distribution of lesions on face and extremities (including palms, soles)	Nonimmune individuals exposed to smallpox	Prodrome of fever, headache, backache, myalgias; vomiting in 50% of cases	S2
Primary herpes simplex virus (HSV) infection	HSV	Erythema rapidly followed by hallmark painful *grouped vesicles* that may evolve into pustules that ulcerate, especially on mucosal surfaces; lesions at site of inoculation: commonly gingivostomatitis for HSV-1 and genital lesions for HSV-2; recurrent disease milder (e.g., herpes labialis does not involve oral mucosa)	Primary infection most common among children and young adults for HSV-1 and among sexually active young adults for HSV-2; no fever in recurrent infection	Regional lymphadenopathy	187
Disseminated herpesvirus infection	Varicella-zoster virus (VZV) or HSV	Generalized vesicles that can evolve to pustules and ulcerations; individual lesions similar for VZV and HSV. *Zoster cutaneous dissemination*: >25 lesions extending outside involved dermatome. *HSV*: extensive, progressive mucocutaneous lesions that may occur in absence of dissemination, sometimes disseminate in eczematous skin (eczema herpeticum); HSV visceral dissemination may occur with only localized mucocutaneous disease; in disseminated neonatal disease, skin lesions diagnostically helpful when present, but rash absent in a substantial minority of cases	Patients with immunosuppression, eczema; neonates	Visceral organ involvement (e.g., liver, lungs) in some cases; neonatal disease particularly severe	133, 187, 188
Rickettsialpox	*Rickettsia akari*	Eschar found at site of mite bite; generalized rash involving face, trunk, extremities; may involve palms and soles; <100 papules and plaques (2–10 mm); tops of lesions developing vesicles that may evolve into pustules	Seen in urban settings; transmitted by mouse mites	Headache, myalgias, regional adenopathy; mild disease	182

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Vesiculobullous or Pustular Eruptions (Continued)					
Acute generalized exanthematous pustulosis	Drugs (mostly anticonvulsants or antimicrobials); also viral	Tiny sterile nonfollicular pustules on erythematous, edematous skin; begins on face and in body folds, then becomes generalized	Appears 2–21 days after start of drug therapy, depending on whether patient has been sensitized	Acute fever, pruritus, leukocytosis	56
Disseminated *Vibrio vulnificus* infection	*V. vulnificus*	Erythematous lesions evolving into hemorrhagic bullae and then into necrotic ulcers	Patients with cirrhosis, diabetes, renal failure; exposure by ingestion of contaminated saltwater, seafood	Hypotension; mortality rate 50%	163
Ecthyma gangrenosum	*P. aeruginosa*, other gram-negative rods, fungi	Indurated plaque evolving into hemorrhagic bulla or pustule that sloughs, resulting in eschar formation; erythematous halo; most common in axillary, groin, perianal regions	Usually affects neutropenic patients; occurs in up to 28% of individuals with *Pseudomonas* bacteremia	Clinical signs of sepsis	159
Urticaria-Like Eruptions					
Urticarial vasculitis	Serum sickness, often due to infection (including hepatitis B viral, enteroviral, parasitic), drugs; connective tissue disease	Erythematous, edematous "urticaria-like" plaques, pruritic or burning; unlike urticaria: typical lesion duration >24 h (up to 5 days) and lack of complete lesion blanching with compression due to hemorrhage	Patients with serum sickness (including hepatitis B), connective tissue disease	Fever variable; arthralgias/ arthritis	356[f]
Nodular Eruptions					
Disseminated infection	Fungal infections (e.g., candidiasis, histoplasmosis, cryptococcosis, sporotrichosis, coccidioidomycosis); mycobacteria	Subcutaneous nodules (up to 3 cm); fluctuance, draining common with mycobacteria; necrotic nodules (extremities, periorbital or nasal regions) common with *Aspergillus*, *Mucor*	Immunocompromised hosts (e.g., bone marrow transplant recipients, patients undergoing chemotherapy, HIV-infected patients)	Features vary with organism	—[f]
Erythema nodosum (septal panniculitis)	Infections (e.g., streptococcal, fungal, mycobacterial, yersinial); drugs (e.g., sulfas, penicillins, oral contraceptives); sarcoidosis; idiopathic causes	Large, violaceous, nonulcerative, subcutaneous nodules; exquisitely tender; usually on lower legs but also on upper extremities	More common among girls and women 15–30 years old	Arthralgias (50%); features vary with associated condition	—[f]
Sweet syndrome (acute febrile neutrophilic dermatosis)	*Yersinia* infection; upper respiratory infection; inflammatory bowel disease; pregnancy; malignancy (usually hematologic); drugs (G-CSF)	Tender red or blue edematous nodules giving impression of vesiculation; usually on face, neck, upper extremities; when on lower extremities, may mimic erythema nodosum	More common among women and among persons 30–60 years old; 20% of cases associated with malignancy (men and women equally affected in this group)	Headache, arthralgias, leukocytosis	54
Bacillary angiomatosis	*Bartonella henselae*, *B. quintana*	Many forms, including erythematous, smooth vascular nodules; friable, exophytic lesions; erythematous plaques (may be dry, scaly); subcutaneous nodules (may be erythematous)	Immunosuppressed individuals, especially those with advanced HIV infection	Peliosis of liver and spleen in some cases; lesions sometimes involving multiple organs; bacteremia	167
Purpuric Eruptions					
Rocky Mountain spotted fever, rat-bite fever, endocarditis[g]; epidemic typhus[e]; dengue fever[d,e]; human parvovirus B19 infection[e]	—	—	—	—	—[f]
Acute meningococcemia	*Neisseria meningitidis*	Initially pink maculopapular lesions evolving into petechiae; petechiae rapidly becoming numerous, sometimes enlarging and becoming vesicular; trunk, extremities most commonly involved; may appear on face, hands, feet; may include purpura fulminans (see below) reflecting DIC	Most common among children, individuals with asplenia or terminal complement component deficiency (C5–C8)	Hypotension, meningitis (sometimes preceded by upper respiratory infection)	150

(*Continued*)

TABLE 16-1 Diseases Associated with Fever and Rash (Continued)

DISEASE	ETIOLOGY	DESCRIPTION	GROUP AFFECTED/ EPIDEMIOLOGIC FACTORS	CLINICAL SYNDROME	CHAPTER
Purpura fulminans	Severe DIC	Large ecchymoses with sharply irregular shapes evolving into hemorrhagic bullae and then into black necrotic lesions	Individuals with sepsis (e.g., involving *N. meningitidis*), malignancy, or massive trauma; asplenic patients at high risk for sepsis	Hypotension	150, 297
Chronic meningococcemia	*N. meningitidis*	Variety of recurrent eruptions, including pink maculopapular; nodular (usually on lower extremities); petechial (sometimes developing vesicular centers); purpuric areas with pale blue-gray centers	Individuals with complement deficiencies	Fevers, sometimes intermittent; arthritis, myalgias, headache	150
Disseminated gonococcal infection	*Neisseria gonorrhoeae*	Papules (1–5 mm) evolving over 1–2 days into hemorrhagic pustules with gray necrotic centers; hemorrhagic bullae occurring rarely; lesions (usually <40) distributed peripherally near joints (more commonly on upper extremities)	Sexually active individuals (more often females), some with complement deficiency	Low-grade fever, tenosynovitis, arthritis	151
Enteroviral petechial rash	Usually echovirus 9 or coxsackievirus A9	Disseminated petechial lesions (may also be maculopapular, vesicular, or urticarial)	Often occurs in outbreaks	Pharyngitis, headache; aseptic meningitis with echovirus 9	199
Viral hemorrhagic fever	Arboviruses (including dengue) and arenaviruses	Petechial rash	Residence in or travel to endemic areas, other virus exposure	Triad of fever, shock, hemorrhage from mucosa or gastrointestinal tract	204, 205
Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome	Idiopathic, bloody diarrhea caused by Shiga toxin–generating bacteria (e.g., *Escherichia coli* O157:H7), deficiency in ADAMTS13 (cleaves von Willebrand factor), drugs (e.g., quinine, chemotherapy, immunosuppression)	Petechiae	Individuals with *E. coli* O157:H7 gastroenteritis (especially children), cancer chemotherapy, HIV infection, autoimmune diseases, pregnant/postpartum women	Fever (not always present), microangiopathic hemolytic anemia, thrombocytopenia, renal dysfunction, neurologic dysfunction; coagulation studies normal	54, 96, 111, 156, 161
Cutaneous small-vessel vasculitis (leukocytoclastic vasculitis)	Infections (including group A streptococcal infection, hepatitis B or C), drugs, idiopathic factors	Palpable purpuric lesions appearing in crops on legs or other dependent areas; may become vesicular or ulcerative	Occurs in a wide spectrum of diseases, including connective tissue disease, cryoglobulinemia, malignancy, Henoch-Schönlein purpura (HSP); more common among children	Fever (not always present), malaise, arthralgias, myalgias; systemic vasculitis in some cases; renal, joint, and gastrointestinal involvement common in HSP	54
Eruptions with Ulcers and/or Eschars					
Scrub typhus, rickettsial spotted fevers, rat-bite fever[e]; rickettsialpox, ecthyma gangrenosum[h]	—	—	—	—	—[f]
Tularemia	*Francisella tularensis*	Ulceroglandular form: erythematous, tender papule evolves into necrotic, tender ulcer with raised borders; in 35% of cases, eruptions (maculopapular, vesiculopapular, acneiform, or urticarial; erythema nodosum; or EM) may occur	Exposure to ticks, biting flies, infected animals	Fever, headache, lymphadenopathy	165
Anthrax	*Bacillus anthracis*	Pruritic papule enlarging and evolving into a 1- by 3-cm painless ulcer surrounded by vesicles and then developing a central eschar with edema; residual scar	Exposure to infected animals or animal products, other exposure to anthrax spores	Lymphadenopathy, headache	S2

[a]See "Purpuric Eruptions." [b]See "Confluent Desquamative Erythemas." [c]Rash is rare in human granulocytotropic ehrlichiosis or anaplasmosis (caused by *Anaplasma phagocytophila*; most common in the upper midwestern and northeastern United States). [d]See "Viral hemorrhagic fever" under "Purpuric Eruptions" for dengue hemorrhagic fever/dengue shock syndrome. [e]See "Centrally Distributed Maculopapular Eruptions." [f]See etiology-specific chapters. [g]See "Peripheral Eruptions." [h]See "Vesiculobullous or Pustular Eruptions."

Abbreviations: CNS, central nervous system; DIC, disseminated intravascular coagulation; G-CSF, granulocyte colony-stimulating factor; HLA, human leukocyte antigen.

induced to form bullae with light lateral pressure (Nikolsky's sign). In a mild form, a scarlatiniform eruption mimics scarlet fever, but the patient does not exhibit a strawberry tongue or circumoral pallor. In contrast to the staphylococcal scalded-skin syndrome, in which the cleavage plane is superficial in the epidermis, *toxic epidermal necrolysis* **(Chap. 56)**, a maximal variant of *Stevens-Johnson syndrome*, involves sloughing of the entire epidermis, resulting in severe disease. *Exfoliative erythroderma syndrome* **(Chaps. 54 and 56)** is a serious reaction associated with systemic toxicity that is often due to eczema, psoriasis, a drug reaction, or mycosis fungoides. *Drug rash with eosinophilia and systemic symptoms (DRESS)*, often due to antiepileptic and antibiotic agents **(Chap. 56)**, initially appears similar to an exanthematous drug reaction but may progress to exfoliative erythroderma; it is accompanied by multiorgan failure and has an associated mortality rate of ~10%.

VESICULOBULLOUS OR PUSTULAR ERUPTIONS

Varicella **(Chap. 188)** is highly contagious, often occurring in winter or spring, and is characterized by pruritic lesions that, within a given region of the body, are in different stages of development at any point in time. In immunocompromised hosts, varicella vesicles may lack the characteristic erythematous base or may appear hemorrhagic. Lesions of *Pseudomonas"hot-tub" folliculitis* **(Chap. 159)** are also pruritic and may appear similar to those of varicella. However, hot-tub folliculitis generally occurs in outbreaks after bathing in hot tubs or swimming pools, and lesions occur in regions occluded by bathing suits. Lesions of *variola (smallpox)* **(Chap. S2)** also appear similar to those of varicella but are all at the same stage of development in a given region of the body. Variola lesions are most prominent on the face and extremities, while varicella lesions are most prominent on the trunk. *Herpes simplex virus infection* **(Chap. 187)** is characterized by hallmark grouped vesicles on an erythematous base. Primary herpes infection is accompanied by fever and toxicity, while recurrent disease is milder. *Rickettsialpox* **(Chap. 182)** is often documented in urban settings and is characterized by vesicles followed by pustules. It can be distinguished from varicella by an eschar at the site of the mouse-mite bite and the papule/plaque base of each vesicle. *Acute generalized exanthematous pustulosis* should be considered in individuals who are acutely febrile and are taking new medications, especially anticonvulsant or antimicrobial agents **(Chap. 56)**. Disseminated *Vibrio vulnificus* infection **(Chap. 163)** or *ecthyma gangrenosum* due to *Pseudomonas aeruginosa* **(Chap. 159)** should be considered in immunosuppressed individuals with sepsis and hemorrhagic bullae.

URTICARIA-LIKE ERUPTIONS

Individuals with classic urticaria ("hives") usually have a hypersensitivity reaction without associated fever. In the presence of fever, urticaria-like eruptions are most often due to *urticarial vasculitis* **(Chap. 356)**. Unlike individual lesions of classic urticaria, which last up to 24 h, these lesions may last 3–5 days. Etiologies include serum sickness (often induced by drugs such as penicillins, sulfas, salicylates, or barbiturates), connective-tissue disease (e.g., systemic lupus erythematosus or Sjögren's syndrome), and infection (e.g., with hepatitis B virus, enteroviruses, or parasites). Malignancy, especially lymphoma, may be associated with fever and chronic urticaria **(Chap. 54)**.

NODULAR ERUPTIONS

In immunocompromised hosts, nodular lesions often represent disseminated infection. Patients with disseminated *candidiasis* (often due to *Candida tropicalis*) may have a triad of fever, myalgias, and eruptive nodules **(Chap. 211)**. Disseminated *cryptococcosis* lesions **(Chap. 210)** may resemble molluscum contagiosum **(Chap. 191)**. Necrosis of nodules should raise the suspicion of *aspergillosis* **(Chap. 212)** or *mucormycosis* **(Chap. 213)**. *Erythema nodosum* presents with exquisitely tender nodules on the lower extremities. *Sweet syndrome* **(Chap. 54)** should be considered in individuals with multiple nodules and plaques, often so edematous that they give the appearance of vesicles or bullae. Sweet syndrome may occur in individuals with infection, inflammatory bowel disease, or malignancy and can also be induced by drugs.

PURPURIC ERUPTIONS

Acute meningococcemia **(Chap. 150)** classically presents in children as a petechial eruption, but initial lesions may appear as blanchable macules or urticaria. Rocky Mountain spotted fever should be considered in the differential diagnosis of acute meningococcemia. *Echovirus 9 infection* **(Chap. 199)** may mimic acute meningococcemia; patients should be treated as if they have bacterial sepsis because prompt differentiation of these conditions may be impossible. Large ecchymotic areas of *purpura fulminans* **(Chaps. 150 and 297)** reflect severe underlying disseminated intravascular coagulation, which may be due to infectious or noninfectious causes. The lesions of *chronic meningococcemia* **(Chap. 150)** may have a variety of morphologies, including petechial. Purpuric nodules may develop on the legs and resemble erythema nodosum but lack its exquisite tenderness. Lesions of *disseminated gonococcemia* **(Chap. 151)** are distinctive, sparse, countable hemorrhagic pustules, usually located near joints. The lesions of chronic meningococcemia and those of gonococcemia may be indistinguishable in terms of appearance and distribution. *Viral hemorrhagic fever* **(Chaps. 204 and 205)** should be considered in patients with an appropriate travel history and a petechial rash. *Thrombotic thrombocytopenic purpura* **(Chaps. 54, 96, and 111)** and *hemolytic-uremic syndrome* **(Chaps. 111, 156, and 161)** are closely related and are noninfectious causes of fever and petechiae. *Cutaneous small-vessel vasculitis* (*leukocytoclastic vasculitis*) typically manifests as palpable purpura and has a wide variety of causes **(Chap. 54)**.

ERUPTIONS WITH ULCERS OR ESCHARS

The presence of an ulcer or eschar in the setting of a more widespread eruption can provide an important diagnostic clue. For example, an eschar may suggest the diagnosis of *scrub typhus* or *rickettsialpox* **(Chap. 182)** in the appropriate setting. In other illnesses (e.g., anthrax) **(Chap. S2)**, an ulcer or eschar may be the only skin manifestation.

FURTHER READING

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17 Fever of Unknown Origin

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DEFINITION

Clinicians commonly refer to any febrile illness without an initially obvious etiology as *fever of unknown origin* (FUO). Most febrile illnesses either resolve before a diagnosis can be made or develop distinguishing characteristics that lead to a diagnosis. The term *FUO* should be reserved for prolonged febrile illnesses without an established etiology despite intensive evaluation and diagnostic testing. This chapter focuses on classic FUO in the adult patient.

FUO was originally defined by Petersdorf and Beeson in 1961 as an illness of >3 weeks' duration with fever of ≥38.3°C (≥101°F) on two occasions and an uncertain diagnosis despite 1 week of inpatient evaluation. Nowadays, most patients with FUO are hospitalized only if their clinical condition requires it, and not for diagnostic purposes alone; thus the in-hospital evaluation requirement has been eliminated from the definition. The definition of FUO has been further modified by the exclusion of immunocompromised patients, whose workup requires

an entirely different diagnostic and therapeutic approach. For optimal comparison of patients with FUO in different geographic areas, it has been proposed that the quantitative criterion (diagnosis uncertain after 1 week of evaluation) be changed to a qualitative criterion that requires the performance of a specific list of investigations. Accordingly, FUO is now defined as follows:

1. Fever ≥38.3°C (≥101°F) on at least two occasions
2. Illness duration of ≥3 weeks
3. No known immunocompromised state
4. Diagnosis that remains uncertain after a thorough history-taking, physical examination, and the following obligatory investigations: determination of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level; platelet count; leukocyte count and differential; measurement of levels of hemoglobin, electrolytes, creatinine, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine kinase, ferritin, antinuclear antibodies, and rheumatoid factor; protein electrophoresis; urinalysis; blood cultures (n = 3); urine culture; chest x-ray; abdominal ultrasonography; and tuberculin skin test (TST) or interferon γ release assay (IGRA).

ETIOLOGY AND EPIDEMIOLOGY

The range of FUO etiologies has evolved over time as a result of changes in the spectrum of diseases causing FUO, the widespread use of antibiotics, and especially the availability of new diagnostic techniques. The proportion of cases caused by intraabdominal abscesses and tumors, for example, has decreased because of earlier detection by CT and ultrasound. In addition, infective endocarditis is a less frequent cause because blood culture and echocardiographic techniques have improved. Conversely, some diagnoses, such as acute HIV infection, were unknown four decades ago.

Table 17-1 summarizes the findings of large studies on FUO conducted over the past 25 years. In general, infection accounts for about one-fifth of cases of FUO in Western countries; next in frequency are noninfectious inflammatory diseases (NIIDs, which include "collagen or rheumatic diseases," vasculitis syndromes, granulomatous disorders, and autoinflammatory syndromes) and neoplasms. In geographic areas outside the West, infections are a much more common cause of FUO (43% vs 17%), while the proportions of cases due to NIIDs and neoplasms are similar. Up to 50% of cases caused by infections in patients with FUO outside Western nations are due to tuberculosis, which is a less common cause in the United States and Western Europe. The number of FUO patients diagnosed with NIIDs probably will not decrease in the near future, as fever may precede more typical manifestations or serologic evidence of these diseases by months. Moreover, many NIIDs can be diagnosed only after prolonged observation and exclusion of other diseases.

In the West, the proportion of patients who remain undiagnosed is higher than in non-Western populations and has been increasing over figures reported in studies before the 1990s. An important factor contributing to the seemingly high diagnostic failure rate is that a diagnosis is more often being established before 3 weeks have elapsed, given that patients with fever tend to seek medical advice earlier and that better diagnostic techniques, such as CT and MRI, are available; therefore, only the cases that are most difficult to diagnose continue to

TABLE 17-1 Etiology of Fever of Unknown Origin (FUO) Over the Past 25 Years: Findings from Large FUO Studies

FIRST AUTHOR (COUNTRY, YEAR OF PUBLICATION)	NO. OF PATIENTS (RECRUITMENT PERIOD)	PERCENTAGE OF CASES DUE TO INDICATED CAUSE				
		INFECTIONS	NONINFECTIOUS INFLAMMATORY DISEASES	NEOPLASMS	MISCELLANEOUS	UNKNOWN
Western Countries						
De Kleijn et al. (Netherlands, 1997)	167 (1992–1994)	26	24	13	8	30
Vanderschueren et al. (Belgium, 2003)	185 (1990–1999)	11	18	10	8	53
Hot et al. (France, 2005)	280 (1995–2005)	11	20	27	9	33
Zenone et al. (France, 2006)	144 (1999–2005)	23	26	10	15	26
Bleeker-Rovers (Netherlands, 2007)	73 (2003–2005)	16	22	7	4	51
Mansueto et al. (Italy, 2008)	91 (1991–2002)	32	12	14	10	32
Vanderschueren et al. (Belgium, 2009)	114 (2003–2007)	15	22	13	10	40
Efstathiou et al. (Greece, 2010)	112 (2001–2007)	30	33	11	5	21
Pedersen et al. (Denmark, 2012)	52 (2005–2010)	19	33	8	0	40
Robine et al. (France, 2014)	103 (2002–2012)	12	30	3	5	51
Vanderschueren et al. (Belgium, 2014)	436 (2000–2010)	17	24	11	10	39
Total	**1757**	**19**	**24**	**12**	**8**	**38**
Other Geographic Locations						
Tabak et al. (Turkey, 2003)	117 (1984–2001)	34	29	19	4	14
Saltoglu et al. (Turkey, 2004)	87 (1994–2002)	59	18	14	2	7

(Continued)

TABLE 17-1 Etiology of Fever of Unknown Origin (FUO) Over the Past 25 Years: Findings from Large FUO Studies (Continued)

FIRST AUTHOR (COUNTRY, YEAR OF PUBLICATION)	NO. OF PATIENTS (RECRUITMENT PERIOD)	PERCENTAGE OF CASES DUE TO INDICATED CAUSE				
		INFECTIONS	NONINFECTIOUS INFLAMMATORY DISEASES	NEOPLASMS	MISCELLANEOUS	UNKNOWN
Ergonul et al. (Turkey, 2005)	80 (1993–1999)	52	16	18	3	11
Brahim et al. (Turkey, 2005)	97 (1990–2005)	36	8	16	5	35
Chin et al. (Taiwan, 2006)	94 (2001–2002)	57	7	9	9	18
Colpan et al. (Turkey, 2007)	71 (2001–2004)	45	27	14	6	9
Hu et al. (China, 2008)	142 (2002–2003)	36	32	13	5	14
Kucukardali et al. (Turkey, 2008)	154 (2003–2004)	34	31	14	5	16
Ali-Eldin et al. (Egypt, 2011)	93 (2009–2010)	42	15	30	0	12
Bandyopadhya et al. (India, 2011)	164 (2008–2009)	55	11	22	0	12
Mete et al. (Turkey, 2012)	100 (2001–2009)	26	38	14	2	20
Ma et al. (China, 2012)	397 (2000–2009)	49	18	16	7	10
Ryuko et al. (Japan, 2013)	174 (2004–2010)	41	27	7	6	19
Mahmood et al. (Pakistan, 2013)	205 (2006–2011)	49	20	13	2	17
Alvi et al. (Iran, 2013)	106 (2007–2011)	44	18	12	10	15
Naito et al. (Japan, 2013)	121 (2011)	23	31	11	12	23
Yamanouchi et al. (Japan, 2014)	256 (1994–2012)	28	18	10	15	29
Moawad et al. (Turkey, 2014)	98 (1995–2008)	33	14	18	18	17
Yu et al. (China, 2014)	107 (2010–2011)	30	17	18	14	22
Mir et al. (India, 2014)	91 (2010–2012)	44	12	12	4	27
Kabapy et al. (Egypt, 2015)	979 (2009–2010)	79	17	1	1	2
Montasser et al. (Egypt, 2015)	217 (unknown)	66	7	7	12	8
Popovsa-Jovicic et al. (Serbia, 2016)	74	38	26	15	18	4
Total	**4024**	**43**	**20**	**14**	**7**	**16**

meet the criteria for FUO. Furthermore, most patients who have FUO without a diagnosis currently do well, and thus a less aggressive diagnostic approach may be used in clinically stable patients once diseases with immediate therapeutic or prognostic consequences have been ruled out to a reasonable extent. This factor may be especially relevant to patients with recurrent fever who are asymptomatic between febrile episodes. In patients with recurrent fever (defined as repeated episodes of fever interspersed with fever-free intervals of at least 2 weeks and apparent remission of the underlying disease), the chance of attaining an etiologic diagnosis is <50%.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for FUO is extensive. It is important to remember that FUO is far more often caused by an atypical presentation of a rather common disease than by a very rare disease. Table 17-2 presents an overview of possible causes of FUO. Atypical presentations of endocarditis, diverticulitis, vertebral osteomyelitis, and extrapulmonary tuberculosis are the more common infectious disease diagnoses. Q fever and Whipple's disease are quite rare but should always be kept in mind as a cause of FUO since the presenting symptoms can be nonspecific. Serologic testing for Q fever, which results from exposure to animals or animal products, should be performed when the patient lives in a rural area or has a history of heart valve disease, an aortic aneurysm, or a vascular prosthesis. In patients with unexplained symptoms localized to the central nervous system, gastrointestinal tract, or joints, polymerase chain reaction testing for *Tropheryma whipplei* should be performed. Travel to or (former) residence in tropical countries or the American Southwest should lead

TABLE 17-2 All Reported Causes of FUO[a]

Infections	
Bacterial, nonspecific	Abdominal abscess, adnexitis, apical granuloma, appendicitis, cholangitis, cholecystitis, diverticulitis, endocarditis, endometritis, epidural abscess, infected joint prosthesis, infected vascular catheter, infected vascular prosthesis, infectious arthritis, infective myonecrosis, intracranial abscess, liver abscess, lung abscess, malakoplakia, mastoiditis, mediastinitis, mycotic aneurysm, osteomyelitis, pelvic inflammatory disease, prostatitis, pyelonephritis, pylephlebitis, renal abscess, septic phlebitis, sinusitis, spondylodiscitis, xanthogranulomatous urinary tract infection
Bacterial, specific	Actinomycosis, atypical mycobacterial infection, bartonellosis, brucellosis, *Campylobacter* infection, *Chlamydia pneumoniae* infection, chronic meningococcemia, ehrlichiosis, gonococcemia, legionellosis, leptospirosis, listeriosis, louse-borne relapsing fever (*Borrelia recurrentis*), Lyme disease, melioidosis (*Pseudomonas pseudomallei*), *Mycoplasma* infection, nocardiosis, psittacosis, Q fever (*Coxiella burnetii),* rickettsiosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tuberculosis, tularemia, typhoid fever and other salmonelloses, Whipple's disease (*Tropheryma whipplei*), yersiniosis
Fungal	Aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, *Malassezia furfur* infection, paracoccidioidomycosis, *Pneumocystis jirovecii* pneumonia, sporotrichosis, zygomycosis
Parasitic	Amebiasis, babesiosis, echinococcosis, fascioliasis, malaria, schistosomiasis, strongyloidiasis, toxocariasis, toxoplasmosis, trichinellosis, trypanosomiasis, visceral leishmaniasis
Viral	Colorado tick fever, coxsackievirus infection, cytomegalovirus infection, dengue, Epstein-Barr virus infection, hantavirus infection, hepatitis (A, B, C, D, E), herpes simplex, HIV infection, human herpesvirus 6 infection, parvovirus infection, West Nile virus infection
Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, dermatomyositis, Felty syndrome, gout, mixed connective-tissue disease, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, rheumatic fever, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Vogt-Koyanagi-Harada syndrome
Vasculitis	Allergic vasculitis, eosinophilic granulomatosis with polyangiitis, giant cell vasculitis/polymyalgia rheumatica, granulomatosis with polyangiitis, hypersensitivity vasculitis, Kawasaki disease, polyarteritis nodosa, Takayasu arteritis, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CAPS[b] (cryopyrin-associated periodic syndromes), Crohn's disease, DIRA (deficiency of the interleukin 1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), Schnitzler syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)
Neoplasms	
Hematologic malignancies	Amyloidosis, angioimmunoblastic lymphoma, Castleman's disease, Hodgkin's disease, hypereosinophilic syndrome, leukemia, lymphomatoid granulomatosis, malignant histiocytosis, multiple myeloma, myelodysplastic syndrome, myelofibrosis, non-Hodgkin's lymphoma, plasmacytoma, systemic mastocytosis, vaso-occlusive crisis in sickle cell disease
Solid tumors	Most solid tumors and metastases can cause fever. Those most commonly causing FUO are breast, colon, hepatocellular, lung, pancreatic, and renal cell carcinomas.
Benign tumors	Angiomyolipoma, cavernous hemangioma of the liver, craniopharyngioma, necrosis of dermoid tumor in Gardner's syndrome
Miscellaneous Causes	
	ADEM (acute disseminated encephalomyelitis), adrenal insufficiency, aneurysms, anomalous thoracic duct, aortic dissection, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, Caroli disease, cholesterol emboli, cirrhosis, complex partial status epilepticus, cyclic neutropenia, drug fever, Erdheim-Chester disease, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fire-eater's lung, fraudulent fever, Gaucher disease, Hamman-Rich syndrome (acute interstitial pneumonia), Hashimoto's encephalopathy, hematoma, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, idiopathic normal-pressure hydrocephalus, inflammatory pseudotumor, Kikuchi's disease, linear IgA dermatosis, mesenteric fibromatosis, metal fume fever, milk protein allergy, myotonic dystrophy, nonbacterial osteitis, organic dust toxic syndrome, panniculitis, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), polymer fume fever, post–cardiac injury syndrome, primary biliary cirrhosis, primary hyperparathyroidism, pulmonary embolism, pyoderma gangrenosum, retroperitoneal fibrosis, Rosai-Dorfman disease, sclerosing mesenteritis, silicone embolization, subacute thyroiditis (de Quervain's), Sweet syndrome (acute febrile neutrophilic dermatosis), thrombosis, tubulointerstitial nephritis and uveitis syndrome (TINU), ulcerative colitis
Thermoregulatory Disorders	
Central	Brain tumor, cerebrovascular accident, encephalitis, hypothalamic dysfunction
Peripheral	Anhidrotic ectodermal dysplasia, exercise-induced hyperthermia, hyperthyroidism, pheochromocytoma

[a]This table includes all causes of FUO that have been described in the literature. [b]CAPS includes chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease, or NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome.

to consideration of infectious diseases such as malaria, leishmaniasis, histoplasmosis, or coccidioidomycosis. Fever with signs of endocarditis and negative blood culture results poses a special problem. Culture-negative endocarditis may be due to difficult-to-culture bacteria such as nutritionally variant bacteria, HACEK organisms (including *Haemophilus parainfluenzae*, *H. paraphrophilus*, *Aggregatibacter actinomycetemcomitans*, *A. aphrophilus*, *A. paraphrophilus*, *Cardiobacterium hominis*, *C. valvarum*, *Eikenella corrodens*, and *Kingella kingae*; discussed below), *Coxiella burnetii*, *T. whipplei*, and *Bartonella* species. Marantic endocarditis is a sterile thrombotic disease that occurs as a paraneoplastic phenomenon, especially with adenocarcinomas. Sterile endocarditis is also seen in the context of systemic lupus erythematosus and antiphospholipid syndrome.

Of the NIIDs, large-vessel vasculitis, polymyalgia rheumatica, sarcoidosis, familial Mediterranean fever, and adult-onset Still's disease are rather common diagnoses in patients with FUO. The hereditary autoinflammatory syndromes are very rare and usually present in young patients. Schnitzler syndrome, which can present at any age, is uncommon but can often be diagnosed easily in a patient with FUO who presents with urticaria, bone pain, and monoclonal gammopathy.

Although most tumors can present with fever, malignant lymphoma is by far the most common diagnosis of FUO among the neoplasms. Sometimes the fever even precedes lymphadenopathy detectable by physical examination.

Apart from drug-induced fever and exercise-induced hyperthermia, none of the miscellaneous causes of fever is found very frequently

in patients with FUO. Virtually all drugs can cause fever, even that commencing after long-term use. *Drug-induced fever*, including DRESS (drug reaction with eosinophilia and systemic symptoms; **Fig. A1-48**), is often accompanied by eosinophilia and also by lymphadenopathy, which can be extensive. More common causes of drug-induced fever are allopurinol, carbamazepine, lamotrigine, phenytoin, sulfasalazine, furosemide, antimicrobial drugs (especially sulfonamides, minocycline, vancomycin, β-lactam antibiotics, and isoniazid), some cardiovascular drugs (e.g., quinidine), and some antiretroviral drugs (e.g., nevirapine). *Exercise-induced hyperthermia* **(Chaps. 15 and 455)** is characterized by an elevated body temperature that is associated with moderate to strenuous exercise lasting from half an hour up to several hours without an increase in CRP level or ESR; typically these patients sweat during the temperature elevation. *Factitious fever* (fever artificially induced by the patient—for example, by IV injection of contaminated water) should be considered in all patients but is more common among young women in health care professions. In *fraudulent fever*, the patient is normothermic but manipulates the thermometer. Simultaneous measurements at different body sites (rectum, ear, mouth) should rapidly identify this diagnosis. Another clue to fraudulent fever is a dissociation between pulse rate and temperature.

Previous studies of FUO have shown that a diagnosis is more likely in elderly patients than in younger age groups. In many cases, FUO in the elderly results from an atypical manifestation of a common disease, among which giant cell arteritis and polymyalgia rheumatica are most frequently involved. Tuberculosis is the most common infectious disease associated with FUO in elderly patients, occurring much more often than in younger patients. As many of these diseases are treatable, it is well worth pursuing the cause of fever in elderly patients.

APPROACH TO THE PATIENT

Fever of Unknown Origin

FIRST-STAGE DIAGNOSTIC TESTS

Figure 17-1 shows a structured approach to patients presenting with FUO. The most important step in the diagnostic workup is the search for potentially diagnostic clues (PDCs) through complete and repeated history-taking and physical examination and the obligatory investigations listed above and in the figure. *PDCs* are defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis. Although PDCs are often misleading, only with their help can a concise list of probable diagnoses be made. The history should include information about the fever pattern (continuous or recurrent) and duration, previous medical history, present and recent drug use, family history, sexual history, country of origin, recent and remote travel, unusual environmental exposures associated with travel or hobbies, and animal contacts. A complete physical examination should be performed, with special attention to the eyes, lymph nodes, temporal arteries, liver, spleen, sites of previous surgery, entire skin surface, and mucous membranes. Before further diagnostic tests are initiated, antibiotic and glucocorticoid treatment, which can mask many diseases, should be stopped. For example, blood and other cultures are not reliable when samples are obtained during antibiotic treatment, and the size of enlarged lymph nodes usually decreases during glucocorticoid treatment, regardless of the cause of lymphadenopathy. Despite the high percentage of false-positive ultrasounds and the relatively low sensitivity of chest x-rays, the performance of these simple, low-cost diagnostic tests remains obligatory in all patients with FUO in order to separate cases that are caused by easily diagnosed diseases from those that are not. Abdominal ultrasound is preferred to abdominal CT as an obligatory test because of relatively low cost, lack of radiation burden, and absence of side effects.

Only rarely do biochemical tests (beyond the obligatory tests needed to classify a patient's fever as FUO) lead directly to a definitive diagnosis in the absence of PDCs. The diagnostic yield of immunologic serology other than that included in the obligatory tests is relatively low. These tests more often yield false-positive rather than true-positive results and are of little use without PDCs pointing to specific immunologic disorders. Given the absence of specific symptoms in many patients and the relatively low cost of the test, investigation of cryoglobulins appears to be a valuable screening test in patients with FUO.

Multiple blood samples should be cultured in the laboratory long enough to ensure ample growth time for any fastidious organisms, such as HACEK organisms. It is critical to inform the laboratory of the intent to test for unusual organisms. Specialized media should be used when the history suggests uncommon microorganisms, such as *Histoplasma* or *Legionella*. Performing more than three blood cultures or more than one urine culture is useless in patients with FUO in the absence of PDCs (e.g., a high level of clinical suspicion of endocarditis). Repeating blood or urine cultures is useful only when previously cultured samples were collected during antibiotic treatment or within 1 week after its discontinuation. FUO with headache should prompt microbiologic examination of cerebrospinal fluid (CSF) for organisms including herpes simplex virus (especially type 2), *Cryptococcus neoformans*, and *Mycobacterium tuberculosis*. In central nervous system tuberculosis, the CSF typically has elevated protein and lowered glucose concentrations, with a mononuclear pleocytosis. CSF protein levels range from 100 to 500 mg/dL in most patients, the CSF glucose concentration is <45 mg/dL in 80% of cases, and the usual CSF cell count is between 100 and 500 cells/μL.

Microbiologic serology should not be included in the diagnostic workup of patients without PDCs for specific infections. A TST is included in the obligatory investigations, but it may yield false-negative results in patients with miliary tuberculosis, malnutrition, or immunosuppression. Although the IGRA is less influenced by prior vaccination with bacille Calmette-Guérin or by infection with nontuberculous mycobacteria, its sensitivity is similar to that of the TST; a negative TST or IGRA therefore does not exclude a diagnosis of tuberculosis. Miliary tuberculosis is especially difficult to diagnose. Granulomatous disease in liver or bone marrow biopsy samples, for example, should always lead to a (re)consideration of this diagnosis. If miliary tuberculosis is suspected, liver biopsy for acid-fast smear, culture, and polymerase chain reaction probably still has the highest diagnostic yield; however, biopsies of bone marrow, lymph nodes, or other involved organs also can be considered.

The diagnostic yield of echocardiography, sinus radiography, radiologic or endoscopic evaluation of the gastrointestinal tract, and bronchoscopy is very low in the absence of PDCs. Therefore, these tests should not be used as screening procedures.

After identification of all PDCs retrieved from the history, physical examination, and obligatory tests, a limited list of the most probable diagnoses should be made. Since most investigations are helpful only for patients who have PDCs for the diagnoses sought, further diagnostic procedures should be limited to specific investigations aimed at confirming or excluding diseases on this list. In FUO, the diagnostic pointers are numerous and diverse but may be missed on initial examination, often being detected only by a very careful examination performed subsequently. In the absence of PDCs, the history and physical examination should therefore be repeated regularly. One of the first steps should be to rule out factitious or fraudulent fever, particularly in patients without signs of inflammation in laboratory tests. All medications, including nonprescription drugs and nutritional supplements, should be discontinued early in the evaluation to exclude drug fever. If fever persists beyond 72 h after discontinuation of the suspected drug, it is unlikely that this drug is the cause. In patients without PDCs or with only misleading PDCs, funduscopy by an ophthalmologist may be useful in the early stage of the diagnostic workup. When the first-stage diagnostic tests do not lead to a diagnosis, scintigraphy should be performed, especially when the ESR or the CRP level is elevated.

Recurrent Fever In patients with recurrent fever, the diagnostic workup should consist of thorough history-taking, physical

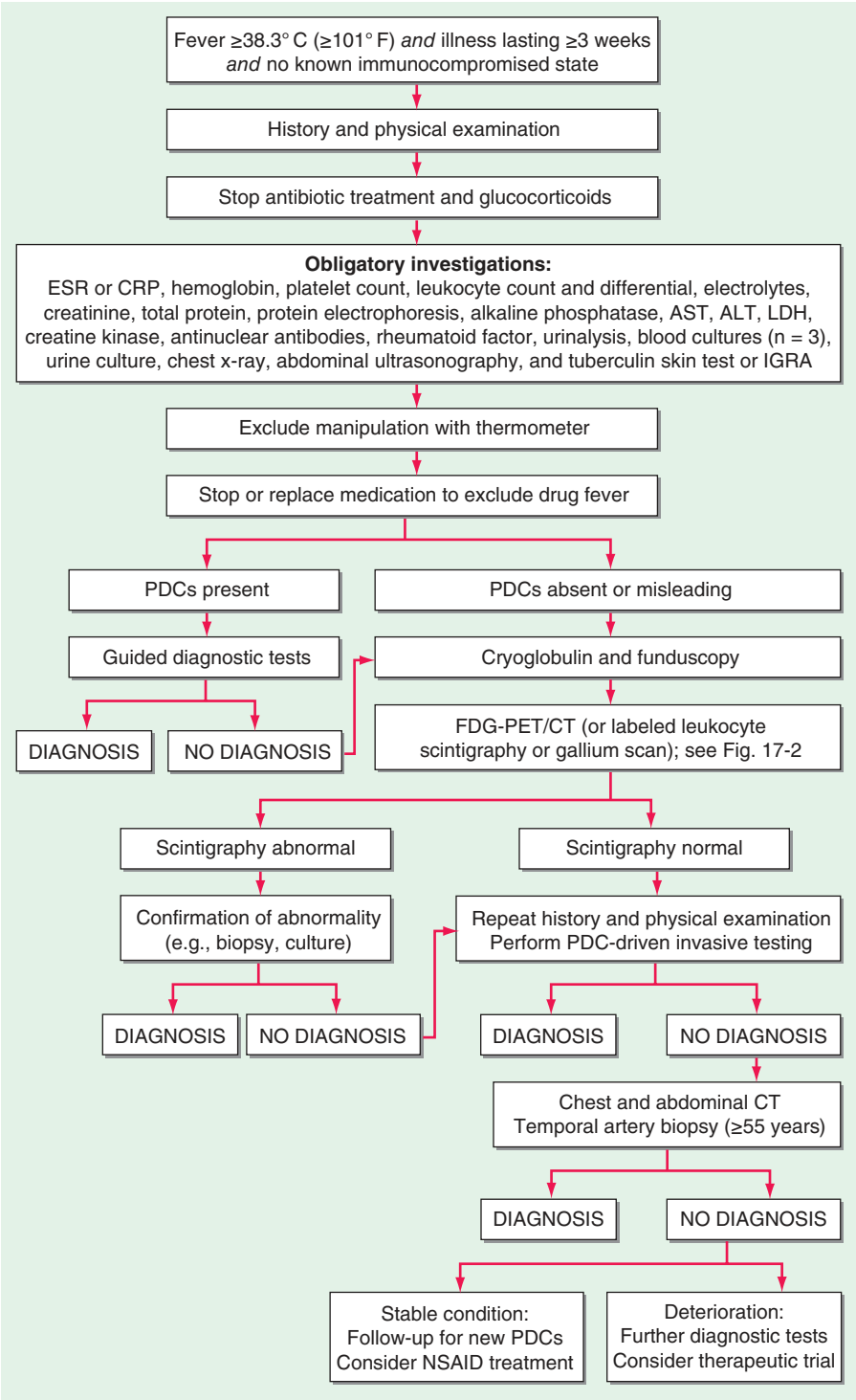

FIGURE 17-1 Structured approach to patients with FUO. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography combined with low-dose CT; IGRA, interferon γ release assay; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; PDCs, potentially diagnostic clues (all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis).

examination, and obligatory tests. The search for PDCs should be directed toward clues matching known recurrent syndromes (Table 17-3). Patients should be asked to return during a febrile episode so that the history, physical examination, and laboratory tests can be repeated during a symptomatic phase. Further diagnostic tests, such as scintigraphic imaging (see below), should be performed only during a febrile episode because abnormalities may be absent between episodes. In patients with recurrent fever lasting >2 years, it is very unlikely that the fever is caused by infection or malignancy. Further diagnostic tests in that direction should be considered only when PDCs for infections, vasculitis syndromes, or malignancy are present or when the patient's clinical condition is deteriorating.

Scintigraphy Scintigraphic imaging is a noninvasive method allowing delineation of foci in all parts of the body on the basis of functional changes in tissues. This procedure plays an important role in the diagnosis of patients with FUO in clinical practice. Conventional scintigraphic methods used in clinical practice are ^{67}Ga-citrate scintigraphy and ^{111}In- or ^{99m}Tc-labeled leukocyte scintigraphy. Focal infectious and inflammatory processes can also be

TABLE 17-3 All Reported Causes of Recurrent Fever[a]

Infections	
Bacterial, nonspecific	Apical granuloma, diverticulitis, prostatitis, recurrent bacteremia caused by colonic neoplasia or persistent focal infection, recurrent cellulitis, recurrent cholangitis or cholecystitis, recurrent pneumonia, recurrent sinusitis, recurrent urinary tract infection
Bacterial, specific	Bartonellosis, brucellosis, chronic gonococcemia, chronic meningococcemia, louse-borne relapsing fever (*Borrelia recurrentis*), melioidosis (*Pseudomonas pseudomallei*), Q fever (*Coxiella burnetii*), salmonellosis, *Spirillum minor* infection, *Streptobacillus moniliformis* infection, syphilis, tick-borne relapsing fever (*Borrelia duttonii*), tularemia, Whipple's disease (*Tropheryma whipplei*), yersiniosis
Fungal	Coccidioidomycosis, histoplasmosis, paracoccidioidomycosis
Parasitic	Babesiosis, malaria, toxoplasmosis, trypanosomiasis, visceral leishmaniasis
Viral	Cytomegalovirus infection, Epstein-Barr virus infection, herpes simplex
Noninfectious Inflammatory Diseases	
Systemic rheumatic and autoimmune diseases	Ankylosing spondylitis, antiphospholipid syndrome, autoimmune hemolytic anemia, autoimmune hepatitis, Behçet's disease, cryoglobulinemia, gout, polymyositis, pseudogout, reactive arthritis, relapsing polychondritis, systemic lupus erythematosus
Vasculitis	Churg-Strauss syndrome, giant cell vasculitis/polymyalgia rheumatica, hypersensitivity vasculitis, polyarteritis nodosa, urticarial vasculitis
Granulomatous diseases	Idiopathic granulomatous hepatitis, sarcoidosis
Autoinflammatory syndromes	Adult-onset Still's disease, Blau syndrome, CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome), CAPS[b] (cryopyrin-associated periodic syndrome), CRMO (chronic recurrent multifocal osteomyelitis), Crohn's disease, DIRA (deficiency of the interleukin 1 receptor antagonist), familial Mediterranean fever, hemophagocytic syndrome, hyper-IgD syndrome (HIDS, also known as mevalonate kinase deficiency), juvenile idiopathic arthritis, NLRC4-activating mutations, PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne), PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, adenitis), recurrent idiopathic pericarditis, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteomyelitis), SAVI (stimulator of interferon genes [STING]–associated vasculopathy with onset in infancy), Schnitzler syndrome, TRAPS (tumor necrosis factor receptor–associated periodic syndrome)
Neoplasms	
	Angioimmunoblastic lymphoma, Castleman's disease, colon carcinoma, craniopharyngioma, Hodgkin's disease, malignant histiocytosis, mesothelioma, non-Hodgkin's lymphoma
Miscellaneous Causes	
	Adrenal insufficiency, aortic-enteral fistula, aseptic meningitis (Mollaret's syndrome), atrial myxoma, brewer's yeast ingestion, cholesterol emboli, cyclic neutropenia, drug fever, extrinsic allergic alveolitis, Fabry's disease, factitious disease, fraudulent fever, Gaucher disease, hypersensitivity pneumonitis, hypertriglyceridemia, hypothalamic hypopituitarism, inflammatory pseudotumor, metal fume fever, milk protein allergy, polymer fume fever, pulmonary embolism, sclerosing mesenteritis
Thermoregulatory Disorders	
Central	Hypothalamic dysfunction
Peripheral	Anhidrotic ectodermal dysplasia, exercise-induced hyperthermia, pheochromocytoma

[a]This table includes all causes of recurrent fever that have been described in the literature. [b]CAPS includes chronic infantile neurologic cutaneous and articular syndrome (CINCA, also known as neonatal-onset multisystem inflammatory disease, or NOMID), familial cold autoinflammatory syndrome (FCAS), and Muckle-Wells syndrome.

detected by several radiologic techniques, such as CT, MRI, and ultrasound. However, because of the lack of substantial pathologic changes in the early phase, infectious and inflammatory foci cannot be detected at this time. Furthermore, distinguishing active infectious or inflammatory lesions from residual changes due to cured processes or surgery remains critical. Finally, CT and MRI routinely provide information on only part of the body, while scintigraphy readily allows whole-body imaging.

Fluorodeoxyglucose Positron Emission Tomography ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with CT has become an established imaging procedure in FUO. FDG accumulates in tissues with a high rate of glycolysis, which occurs not only in malignant cells but also in activated leukocytes and thus permits the imaging of acute and chronic inflammatory processes. Normal uptake may obscure pathologic foci in the brain, heart, bowel, kidneys, and bladder. FDG uptake in the heart, which obscures endocarditis, may be prevented by consumption of a low-carbohydrate diet before the PET investigation. In patients with fever, bone marrow uptake is frequently increased in a nonspecific way due to cytokine activation, which upregulates glucose transporters in bone marrow cells. Compared with conventional scintigraphy, FDG-PET/CT offers the advantages of higher resolution, greater sensitivity in chronic low-grade infections, and a high degree of accuracy in the central skeleton. Furthermore, vascular uptake of FDG is increased in patients with vasculitis **(Fig. 17-2)**. The mechanisms responsible for FDG uptake do not allow differentiation among infection, sterile inflammation, and malignancy. However, since all of these disorders are causes of FUO, FDG-PET/CT can be used to guide additional diagnostic tests (e.g., targeted biopsies) that may yield the final diagnosis.

In recent years, many cohort studies and several meta-analyses have focused on the diagnostic yield of PET and PET/CT in FUO. Although these studies are highly variable in terms of the selection of patients, follow-up, and the selection of a gold-standard reference point, all meta-analyses report a high diagnostic yield for PET and PET/CT in the workup of FUO patients, with pooled sensitivity and specificity figures of ~85% and ~50%, respectively, and a total diagnostic yield of ~50% for PET/CT and ~40% for PET. In one study, FDG-PET was never helpful in diagnosing FUO in patients who had a normal CRP level and a normal ESR. In a meta-analysis on the performance, diagnostic yield, and management decision impact of nuclear imaging tests in patients with FUO, the diagnostic yield of gallium scintigraphy ranged from 21% to 54%, and, on average, the location of a source of fever was correctly localized in approximately one-third of patients. Moreover, in gallium scintigraphy, results do not become available for days, whereas FDG-PET/CT yields results within hours. In this meta-analysis, estimates of the diagnostic yield of labeled leukocyte scintigraphy ranged from 8% to 31%, and overall the cause of FUO was correctly identified on the basis of the scan results in only one-fifth of patients. Indirect comparisons of test performance suggested that FDG-PET/CT outperformed standalone FDG-PET, gallium scintigraphy, and leukocyte scintigraphy. Similarly, indirect comparisons of diagnostic yield suggested that

FIGURE 17-2 FDG-PET/CT in a patient with FUO. This 72-year-old woman presented with a low-grade fever and severe fatigue of almost 3 months' duration. An extensive history was taken, but the patient had no specific complaints and had not traveled recently. Her previous history was unremarkable, and she did not use any drugs. Physical examination, including palpation of the temporal arteries, yielded completely normal results. Laboratory examination showed normocytic anemia, a C-reactive protein level of 43 mg/L, an erythrocyte sedimentation rate of 87 mm/h, and mild hypoalbuminemia. Results of the other obligatory tests were all normal. Since there were no potentially diagnostic clues, FDG-PET/CT was performed. This test showed increased FDG uptake in all major arteries (carotid, jugular, and subclavian arteries; thoracic and abdominal aorta; iliac, femoral, and popliteal arteries) and in the soft tissue around the shoulders, hips, and knees—findings compatible with large-vessel vasculitis and polymyalgia rheumatica. Within 1 week after the initiation of treatment with prednisone (60 mg once daily), the patient completely recovered. After 1 month, the prednisone dose was slowly tapered.

FDG-PET/CT was more likely than alternative tests to correctly identify the cause of FUO.

Although scintigraphic techniques do not directly provide a definitive diagnosis, they often identify the anatomic location of a particular ongoing metabolic process and, with the help of other techniques such as biopsy and culture, facilitate timely diagnosis and treatment. Pathologic FDG uptake is quickly eradicated by treatment with glucocorticoids in many diseases, including vasculitis and lymphoma; therefore, glucocorticoid use should be stopped or postponed until after FDG-PET/CT is performed. Results reported in the literature and the advantages offered by FDG-PET/CT indicate that conventional scintigraphic techniques should be replaced by FDG-PET/CT in the investigation of patients with FUO at institutions where this technique is available. FDG-PET/CT is a relatively expensive procedure whose availability is still limited compared with that of CT and conventional scintigraphy. Nevertheless, FDG-PET/CT can be cost-effective in the FUO diagnostic workup if used at an early stage, helping to establish an early diagnosis, reducing days of hospitalization for diagnostic purposes, and obviating unnecessary and unhelpful tests.

LATER-STAGE DIAGNOSTIC TESTS

In some cases, more invasive tests are appropriate. Abnormalities found with scintigraphic techniques often need to be confirmed by pathology and/or culture of biopsy specimens. If lymphadenopathy is found, lymph node biopsy is necessary, even when the affected lymph nodes are hard to reach or when previous biopsies were inconclusive. In the case of skin lesions, skin biopsy should be undertaken. In one study, pulmonary wedge excision, histologic examination of an excised tonsil, and biopsy of the peritoneum were performed in light of PDCs or abnormal FDG-PET results and yielded a diagnosis.

If no diagnosis is reached despite scintigraphic and PDC-driven histologic investigations or culture, second-stage screening diagnostic tests should be considered (Fig. 17-1). In three studies, the diagnostic yield of screening chest and abdominal CT in patients with FUO was ~20%. The specificity of chest CT was ~80%, but that of abdominal CT varied between 63% and 80%. Despite the relatively limited specificity of abdominal CT and the probably limited additional value of chest CT after normal FDG-PET/CT, chest and abdominal CT may be used as screening procedures at a later stage of the diagnostic protocol because of their noninvasive nature and high sensitivity. Bone marrow aspiration is seldom useful in the absence of PDCs for bone marrow disorders. With addition of FDG-PET/CT, which is highly sensitive in detecting lymphoma, carcinoma, and osteomyelitis, the value of bone marrow biopsy as a screening procedure is probably further reduced. Several studies have shown a high prevalence of giant cell arteritis among patients with FUO, with rates up to 17% among elderly patients. Giant cell arteritis often involves large arteries and in most cases can be diagnosed by FDG-PET/CT. However, temporal artery biopsy is still recommended for patients ≥55 years of age in a later stage of the diagnostic protocol: FDG-PET/CT will not be useful in vasculitis limited to the temporal arteries because of the small diameter of these vessels and the high levels of FDG uptake in the brain. In the past, liver biopsies have often been performed as a screening procedure in patients with FUO. In each of two recent studies, liver biopsy as part of the later stage of a screening diagnostic protocol was helpful in only one patient. Moreover, abnormal liver tests are not predictive of a diagnostic liver biopsy in FUO. Liver biopsy is an invasive procedure that carries the possibility of complications and even death. Therefore, it should not be used for screening purposes in patients with FUO except in those with PDCs for liver disease or miliary tuberculosis.

In patients with unexplained fever after all of the above procedures, the last steps in the diagnostic workup—with only a marginal diagnostic yield—come at an extraordinarily high cost in terms of both expense and discomfort for the patient. Repetition of a thorough history-taking and physical examination and review of laboratory results and imaging studies (including those from other

hospitals) are recommended. Diagnostic delay often results from a failure to recognize PDCs in the available information. In these patients with persisting FUO, waiting for new PDCs to appear probably is better than ordering more screening investigations. Only when a patient's condition deteriorates without providing new PDCs should a further diagnostic workup be performed.

TREATMENT

Fever of Unknown Origin

Empirical therapeutic trials with antibiotics, glucocorticoids, or antituberculous agents should be avoided in FUO except when a patient's condition is rapidly deteriorating after the aforementioned diagnostic tests have failed to provide a definite diagnosis.

ANTIBIOTICS AND ANTITUBERCULOUS THERAPY

Antibiotic or antituberculous therapy may irrevocably diminish the ability to culture fastidious bacteria or mycobacteria. However, hemodynamic instability or neutropenia is a good indication for empirical antibiotic therapy. If the TST or IGRA is positive or if granulomatous disease is present with anergy and sarcoidosis seems unlikely, a trial of therapy for tuberculosis should be started. Especially in miliary tuberculosis, it may be very difficult to obtain a rapid diagnosis. If the fever does not respond after 6 weeks of empirical antituberculous treatment, another diagnosis should be considered.

COLCHICINE, NONSTEROIDAL ANTI-INFLAMMATORY DRUGS, AND GLUCOCORTICOIDS

Colchicine is highly effective in preventing attacks of familial Mediterranean fever but is not always effective once an attack is well under way. When familial Mediterranean fever is suspected, the response to colchicine is not a completely reliable diagnostic tool in the acute phase, but with colchicine treatment most patients show remarkable improvements in the frequency and severity of subsequent febrile episodes within weeks to months. Therefore, colchicine may be tried in patients with features compatible with familial Mediterranean fever, especially when these patients originate from a high-prevalence region. If the fever persists and the source remains elusive after completion of the later-stage investigations, supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful. The response of adult-onset Still's disease to NSAIDs is dramatic in some cases. The effects of glucocorticoids on giant cell arteritis and polymyalgia rheumatica are equally impressive. Early empirical trials with glucocorticoids, however, decrease the chances of reaching a diagnosis for which more specific and sometimes life-saving treatment might be more appropriate, such as malignant lymphoma. The ability of NSAIDs and glucocorticoids to mask fever while permitting the spread of infection or lymphoma dictates that their use should be avoided unless infectious diseases and malignant lymphoma have been largely ruled out and inflammatory disease is probable and is likely to be debilitating or threatening.

ANAKINRA

Interleukin (IL) 1 is a key cytokine in local and systemic inflammation and the febrile response. The availability of specific IL-1-targeting agents has revealed a pathologic role of IL-1-mediated inflammation in a growing list of diseases. Anakinra, a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra), blocks the activity of both IL-1α and IL-1β. Anakinra is extremely effective in the treatment of many autoinflammatory syndromes, such as familial Mediterranean fever, cryopyrin-associated periodic syndrome, tumor necrosis factor receptor–associated periodic syndrome, mevalonate kinase deficiency (hyper IgD syndrome), and Schnitzler syndrome. There are many other chronic inflammatory disorders in which anti-IL-1 therapy is highly effective. A therapeutic trial with anakinra can be considered in patients whose FUO has not been diagnosed after later-stage diagnostic tests. Although most chronic inflammatory conditions without a known basis can be controlled with glucocorticoids, monotherapy with IL-1 blockade can provide improved control without the metabolic, immunologic, and gastrointestinal side effects of glucocorticoid administration.

PROGNOSIS

FUO-related mortality rates have continuously declined over recent decades. The majority of fevers are caused by treatable diseases, and the risk of death related to FUO is, of course, dependent on the underlying disease. In a study by our group (Table 17-1), none of 37 FUO patients without a diagnosis died during a follow-up period of at least 6 months; 4 of 36 patients with a diagnosis died during follow-up as a result of infection ($n = 1$) or malignancy ($n = 3$). A large study on the prognosis of FUO (Vanderschueren et al, 2014; Table 17-1) included 436 patients and documented a mortality rate of 10%, of which 68% was related to the febrile illness—malignancy in most cases. In this study, only 4 of 168 patients in whom no diagnosis could be made died, all during their first admission. In two of these patients, diagnosis (lymphoma and pneumonia) was made during autopsy. Other studies have also shown that malignancy accounts for most FUO-related deaths. Non-Hodgkin's lymphoma carries a disproportionately high death toll. In nonmalignant FUO, fatality rates are very low. The good outcome in patients without a diagnosis confirms that potentially lethal occult diseases are very unusual and that empirical therapy with antibiotics, antituberculous agents, or glucocorticoids is rarely required in stable patients. In less affluent regions, infectious diseases are still a major cause of FUO, and outcomes may be different.

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Section 3 Nervous System Dysfunction

18 Syncope

Roy Freeman

Syncope is a transient, self-limited loss of consciousness due to acute global impairment of cerebral blood flow. The onset is rapid, duration brief, and recovery spontaneous and complete. Other causes of transient loss of consciousness need to be distinguished from syncope; these include seizures, vertebrobasilar ischemia, hypoxemia, and hypoglycemia. A syncopal prodrome (*presyncope*) is common, although loss of consciousness may occur without any warning symptoms. Typical presyncopal symptoms include dizziness, lightheadedness or faintness, weakness, fatigue, and visual and auditory disturbances. The causes of syncope can be divided into three general categories: (1) neurally mediated syncope (also called *reflex or vasovagal syncope*), (2) orthostatic hypotension, and (3) cardiac syncope.

Neurally mediated syncope comprises a heterogeneous group of functional disorders that are characterized by a transient change in the reflexes responsible for maintaining cardiovascular homeostasis. Episodic vasodilation (or loss of vasoconstrictor tone) and bradycardia occur in varying combinations, resulting in temporary failure of blood

pressure control. In contrast, in patients with orthostatic hypotension due to autonomic failure, these cardiovascular homeostatic reflexes are chronically impaired. Cardiac syncope may be due to arrhythmias or structural cardiac diseases that cause a decrease in cardiac output. The clinical features, underlying pathophysiologic mechanisms, therapeutic interventions, and prognoses differ markedly among these three causes.

EPIDEMIOLOGY AND NATURAL HISTORY

Syncope is a common presenting problem, accounting for ~3% of all emergency room visits and 1% of all hospital admissions. The annual cost for syncope-related hospitalization in the United States is ~$2.4 billion. Syncope has a lifetime cumulative incidence of up to 35% in the general population. The peak incidence in the young occurs between ages 10 and 30 years, with a median peak around 15 years. Neurally mediated syncope is the etiology in the vast majority of these cases. In elderly adults, there is a sharp rise in the incidence of syncope after 70 years.

In population-based studies, neurally mediated syncope is the most common cause of syncope. The incidence is slightly higher in females than males. In young subjects, there is often a family history in first-degree relatives. Cardiovascular disease due to structural disease or arrhythmias is the next most common cause in most series, particularly in emergency room settings and in older patients. Orthostatic hypotension also increases in prevalence with age because of the reduced baroreflex responsiveness, decreased cardiac compliance, and attenuation of the vestibulosympathetic reflex associated with aging. In the elderly, orthostatic hypotension is substantially more common in institutionalized (54–68%) than community-dwelling (6%) individuals, an observation most likely explained by the greater prevalence of predisposing neurologic disorders, physiologic impairment, and vasoactive medication use among institutionalized patients.

The prognosis after a single syncopal event for all age groups is generally benign. In particular, syncope of noncardiac and unexplained origin in younger individuals has an excellent prognosis; life expectancy is unaffected. By contrast, syncope due to a cardiac cause, either structural heart disease or primary arrhythmic disease, is associated with an increased risk of sudden cardiac death and mortality from other causes. Similarly, mortality rate is increased in individuals with syncope due to orthostatic hypotension related to age and the associated comorbid conditions **(Table 18-1)**.

PATHOPHYSIOLOGY

The upright posture imposes a unique physiologic stress upon humans; most, although not all, syncopal episodes occur from a standing position. Standing results in pooling of 500–1000 mL of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and reduced ventricular filling that result in diminished cardiac output and blood pressure. These hemodynamic changes provoke a compensatory reflex response, initiated by the baroreceptors in the carotid sinus and aortic arch, resulting in increased sympathetic outflow and decreased vagal nerve activity **(Fig. 18-1)**. The reflex increases peripheral resistance, venous return to the heart, and cardiac output and thus limits the fall in blood pressure. If this response fails, as is the case chronically in orthostatic hypotension and transiently in neurally mediated syncope, cerebral hypoperfusion occurs.

Syncope is a consequence of global cerebral hypoperfusion and thus represents a failure of cerebral blood flow autoregulatory mechanisms. Myogenic factors, local metabolites, and to a lesser extent autonomic neurovascular control are responsible for the autoregulation of cerebral blood flow **(Chap. 301)**. The latency of the autoregulatory response is 5–10 s. Typically cerebral blood flow ranges from 50 to 60 mL/min per 100 g brain tissue and remains relatively constant over perfusion pressures ranging from 50 to 150 mmHg. Cessation of blood flow for 6–8 s will result in loss of consciousness, while impairment of consciousness ensues when blood flow decreases to 25 mL/min per 100 g brain tissue.

From the clinical standpoint, a fall in systemic systolic blood pressure to ~50 mmHg or lower will result in syncope. A decrease in cardiac output and/or systemic vascular resistance—the determinants of blood pressure—thus underlies the pathophysiology of syncope. Common causes of impaired cardiac output include decreased effective circulating blood volume; increased thoracic pressure; massive pulmonary embolus; cardiac brady- and tachyarrhythmias; valvular heart disease; and myocardial dysfunction. Systemic vascular resistance may be decreased by central and peripheral autonomic nervous system diseases, sympatholytic medications, and transiently during neurally mediated syncope. Increased cerebral vascular resistance, most frequently due to hypocarbia induced by hyperventilation, may also contribute to the pathophysiology of syncope.

Two patterns of electroencephalographic (EEG) changes occur in syncopal subjects. The first is a "slow-flat-slow" pattern **(Fig. 18-2)** in which normal background activity is replaced with high-amplitude slow delta waves. This is followed by sudden flattening of the EEG—a cessation or attenuation of cortical activity—followed by the return of slow waves, and then normal activity. A second pattern, the "slow pattern," is characterized by increasing and decreasing slow wave activity only. The EEG flattening that occurs in the slow-flat-slow pattern is a marker of more severe cerebral hypoperfusion. Despite the presence of myoclonic movements and other motor activity during some syncopal events, EEG seizure discharges are not detected.

TABLE 18-1 High-Risk Features Indicating Hospitalization or Intensive Evaluation of Syncope

Chest pain suggesting coronary ischemia
Features of congestive heart failure
Moderate or severe valvular disease
Moderate or severe structural cardiac disease
Electrocardiographic features of ischemia
History of ventricular arrhythmias
Prolonged QT interval (>500 ms)
Repetitive sinoatrial block or sinus pauses
Persistent sinus bradycardia
Bi- or trifascicular block or intraventricular conduction delay with QRS duration ≥120 ms
Atrial fibrillation
Nonsustained ventricular tachycardia
Family history of sudden death
Preexcitation syndromes
Brugada pattern on ECG
Palpitations at time of syncope
Syncope at rest or during exercise

CLASSIFICATION

NEURALLY MEDIATED SYNCOPE

Neurally mediated (reflex; vasovagal) syncope is the final pathway of a complex central and peripheral nervous system reflex arc. There is a sudden, transient change in autonomic efferent activity with increased parasympathetic outflow, plus sympathoinhibition (the vasodepressor response), resulting in bradycardia, vasodilation, and/or reduced vasoconstrictor tone. The resulting fall in systemic blood pressure can then reduce cerebral blood flow to below the compensatory limits of autoregulation **(Fig. 18-3)**. In order to elicit neurally mediated syncope, a functioning autonomic nervous system is necessary, in contrast to syncope resulting from autonomic failure (discussed below).

Multiple triggers of the afferent limb of the reflex arc can result in neurally mediated syncope. In some situations, these can be clearly defined, e.g., the carotid sinus, the gastrointestinal tract, or the bladder. Often, however, the trigger is less easily recognized and the cause is multifactorial. Under these circumstances, it is likely that different afferent pathways converge on the central autonomic network within the medulla that integrates the neural impulses and mediates the vasodepressor-bradycardic response.

Classification of Neurally Mediated Syncope Neurally mediated syncope may be subdivided based on the afferent pathway

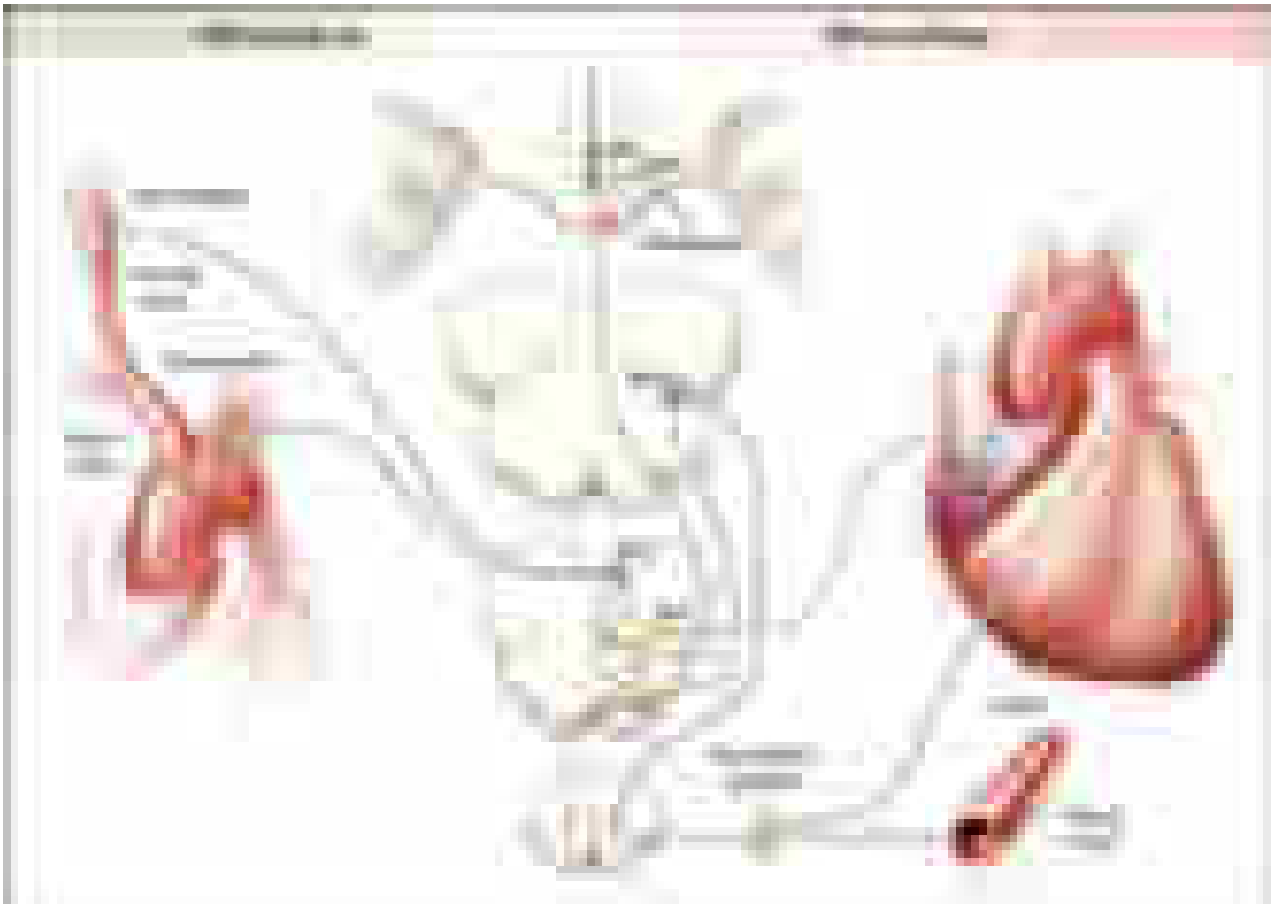

FIGURE 18-1 The baroreflex. A decrease in arterial pressure unloads the baroreceptors—the terminals of afferent fibers of the glossopharyngeal and vagus nerves—that are situated in the carotid sinus and aortic arch. This leads to a reduction in the afferent impulses that are relayed from these mechanoreceptors through the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. The reduced baroreceptor afferent activity produces a decrease in vagal nerve input to the sinus node that is mediated via connections of the NTS to the nucleus ambiguus (NA). There is an increase in sympathetic efferent activity that is mediated by the NTS projections to the caudal ventrolateral medulla (CVLM) (an excitatory pathway) and from there to the rostral ventrolateral medulla (RVLM) (an inhibitory pathway). The activation of RVLM presympathetic neurons in response to hypotension is thus predominantly due to disinhibition. In response to a sustained fall in blood pressure, vasopressin release is mediated by projections from the A1 noradrenergic cell group in the ventrolateral medulla. This projection activates vasopressin-synthesizing neurons in the magnocellular portion of the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus. *Blue* denotes sympathetic neurons, and *green* denotes parasympathetic neurons. *(From R Freeman: N Engl J Med 358:615, 2008.)*

and provocative trigger. Vasovagal syncope (the common faint) is provoked by intense emotion, pain, and/or orthostatic stress, whereas the situational reflex syncopes have specific localized stimuli that provoke the reflex vasodilation and bradycardia that leads to syncope. The underlying mechanisms have been identified and pathophysiology delineated for most of these situational reflex syncopes. The afferent trigger may originate in the pulmonary system, gastrointestinal system, urogenital system, heart, and carotid artery **(Table 18-2)**. Hyperventilation leading to hypocarbia and cerebral vasoconstriction, and raised intrathoracic pressure that impairs venous return to the heart, play a central role in many of the situational reflex syncopes. The afferent pathway of the reflex arc differs among these disorders, but the efferent response via the vagus and sympathetic pathways is similar.

Alternately, neurally mediated syncope may be subdivided based on the predominant efferent pathway. Vasodepressor syncope describes syncope predominantly due to efferent, sympathetic, vasoconstrictor failure; cardioinhibitory syncope describes syncope predominantly associated with bradycardia or asystole due to increased vagal outflow; and mixed syncope describes syncope in which there are both vagal and sympathetic reflex changes.

Features of Neurally Mediated Syncope In addition to symptoms of orthostatic intolerance such as dizziness, lightheadedness, and fatigue, premonitory features of autonomic activation may be present in patients with neurally mediated syncope. These include diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. During the syncopal event, proximal and distal myoclonus (typically arrhythmic and multifocal) may occur, raising the possibility of epilepsy. The eyes typically remain open and usually deviate upward. Pupils are usually dilated. Roving eye movements may occur. Grunting, moaning, snorting, and stertorous breathing may be present. Urinary incontinence may occur. Fecal incontinence is very rare. Postictal confusion is also rare, although visual and auditory hallucinations and near death and out-of-body experiences are sometimes reported.

Although some predisposing factors and provocative stimuli are well established (for example, motionless upright posture, warm ambient temperature, intravascular volume depletion, alcohol ingestion, hypoxemia, anemia, pain, the sight of blood, venipuncture, and intense emotion), the underlying basis for the widely different thresholds for syncope among individuals exposed to the same provocative stimulus is not known. A genetic basis for neurally mediated syncope may exist; several studies have reported an increased incidence of syncope in first-degree relatives of fainters, but no gene or genetic marker has been identified, and environmental, social, and cultural factors have not been excluded by these studies.

TREATMENT

Neurally Mediated Syncope

Reassurance, avoidance of provocative stimuli, and plasma volume expansion with fluid and salt are the cornerstones of the management of neurally mediated syncope. Isometric counterpressure maneuvers of the limbs (leg crossing or handgrip and arm tensing)

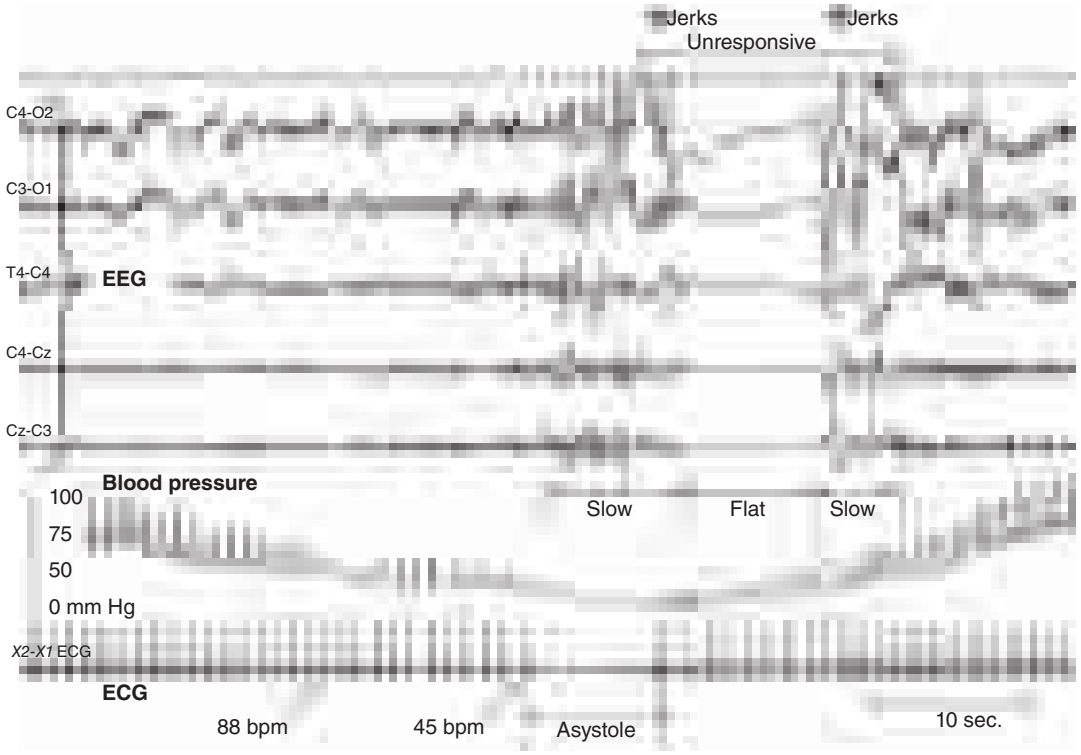

FIGURE 18-2 The electroencephalogram (EEG) in vasovagal syncope. A 1-min segment of a tilt-table test with typical vasovagal syncope demonstrating the "slow-flat-slow" EEG pattern. Finger beat-to-beat blood pressure, electrocardiogram (ECG), and selected EEG channels are shown. EEG slowing starts when systolic blood pressure drops to ~50 mmHg; heart rate is then ~45 beats/min (bpm). Asystole occurred, lasting about 8 s. The EEG flattens for a similar period, but with a delay. A transient loss of consciousness, lasting 14 s, was observed. There were muscle jerks just before and just after the flat period of the EEG. *(Figure reproduced with permission from W Wieling et al: Brain 132:2630, 2009.)*

may raise blood pressure by increasing central blood volume and cardiac output. By maintaining pressure in the autoregulatory zone, these maneuvers avoid or delay the onset of syncope. Randomized controlled trials support this intervention.

Fludrocortisone, vasoconstricting agents, and β-adrenoreceptor antagonists are widely used by experts to treat refractory patients, although there is no consistent evidence from randomized controlled trials for any pharmacotherapy to treat neurally mediated syncope. Because vasodilation is the dominant pathophysiologic syncopal mechanism in most patients, use of a cardiac pacemaker is rarely beneficial. Possible exceptions are older patients (>40 years) in whom syncope is associated with asystole or severe bradycardia and patients with prominent cardioinhibition due to carotid sinus syndrome. In these patients, dual-chamber pacing may be helpful although this continues to be an area of uncertainty.

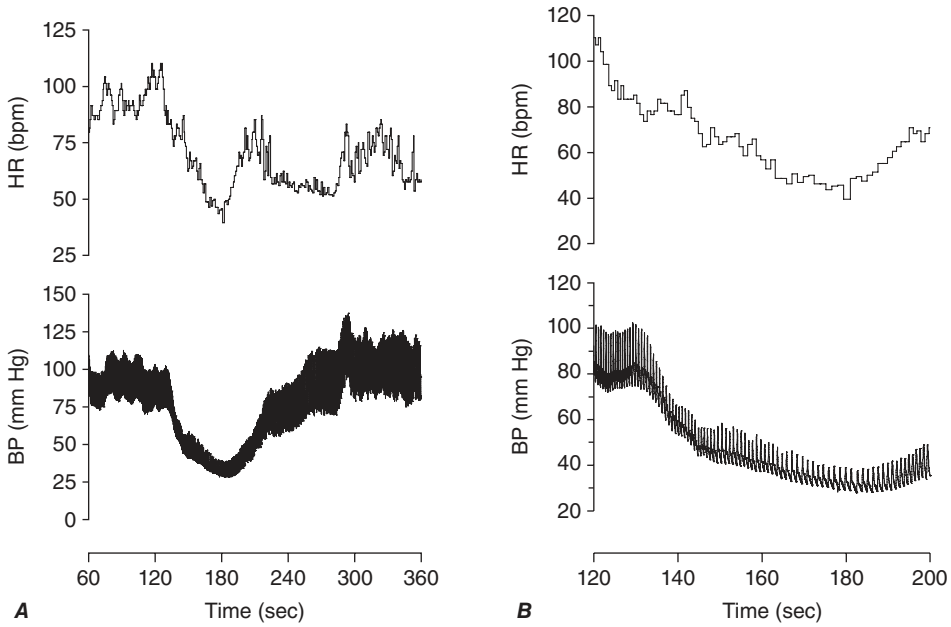

FIGURE 18-3 ***A.*** The paroxysmal hypotensive-bradycardic response that is characteristic of neurally mediated syncope. Noninvasive beat-to-beat blood pressure and heart rate are shown >5 min (from 60 to 360 s) of an upright tilt on a tilt table. ***B.*** The same tracing expanded to show 80 s of the episode (from 80 to 200 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

TABLE 18-2 Causes of Syncope

A. Neurally Mediated Syncope
Vasovagal syncope
Provoked fear, pain, anxiety, intense emotion, sight of blood, unpleasant sights and odors, orthostatic stress
Situational reflex syncope
Pulmonary
Cough syncope, wind instrument player's syncope, weightlifter's syncope, "mess trick"[a] and "fainting lark,"[b] sneeze syncope, airway instrumentation
Urogenital
Postmicturition syncope, urogenital tract instrumentation, prostatic massage
Gastrointestinal
Swallow syncope, glossopharyngeal neuralgia, esophageal stimulation, gastrointestinal tract instrumentation, rectal examination, defecation syncope
Cardiac
Bezold-Jarisch reflex, cardiac outflow obstruction
Carotid sinus
Carotid sinus sensitivity, carotid sinus massage
Ocular
Ocular pressure, ocular examination, ocular surgery
B. Orthostatic Hypotension
Primary autonomic failure due to idiopathic central and peripheral neurodegenerative diseases—the "synucleinopathies"
Lewy body diseases
Parkinson's disease
Lewy body dementia
Pure autonomic failure
Multiple system atrophy (Shy-Drager syndrome)
Secondary autonomic failure due to autonomic peripheral neuropathies
Diabetes
Hereditary amyloidosis (familial amyloid polyneuropathy)
Primary amyloidosis (AL amyloidosis; immunoglobulin light chain associated)
Hereditary sensory and autonomic neuropathies (HSAN) (especially type III—familial dysautonomia)
Idiopathic immune-mediated autonomic neuropathy
Autoimmune autonomic ganglionopathy
Sjögren's syndrome
Paraneoplastic autonomic neuropathy
HIV neuropathy
Postprandial hypotension
Iatrogenic (drug-induced)
Volume depletion
C. Cardiac Syncope
Arrhythmias
Sinus node dysfunction
Atrioventricular dysfunction
Supraventricular tachycardias
Ventricular tachycardias
Inherited channelopathies
Cardiac structural disease
Valvular disease
Myocardial ischemia
Obstructive and other cardiomyopathies
Atrial myxoma
Pericardial effusions and tamponade

[a]Hyperventilation for ~1 min, followed by sudden chest compression. [b]Hyperventilation (~20 breaths) in a squatting position, rapid rise to standing, then Valsalva.

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension, defined as a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 min of standing or head-up tilt on a tilt table, is a manifestation of sympathetic vasoconstrictor (autonomic) failure **(Fig. 18-4)**. In many (but not all) cases, there is no compensatory increase in heart rate despite hypotension; with partial autonomic failure, heart rate may increase to some degree but is insufficient to maintain cardiac output. A variant of orthostatic hypotension is "delayed" orthostatic hypotension, which occurs beyond 3 min of standing; this may reflect a mild or early form of sympathetic adrenergic dysfunction. In some cases, orthostatic hypotension occurs within 15 s of standing (so-called "initial" orthostatic hypotension), a finding that may reflect a transient mismatch between cardiac output and peripheral vascular resistance and does not represent autonomic failure.

Characteristic symptoms of orthostatic hypotension include light-headedness, dizziness, and presyncope (near-faintness) occurring in response to sudden postural change. However, symptoms may be absent or nonspecific, such as generalized weakness, fatigue, cognitive slowing, leg buckling, or headache. Visual blurring may occur, likely due to retinal or occipital lobe ischemia. Neck pain, typically in the suboccipital, posterior cervical, and shoulder region (the "coat-hanger headache"), most likely due to neck muscle ischemia, may be the only symptom. Patients may report orthostatic dyspnea (thought to reflect ventilation-perfusion mismatch due to inadequate perfusion of ventilated lung apices) or angina (attributed to impaired myocardial perfusion even with normal coronary arteries). Symptoms may be exacerbated by exertion, prolonged standing, increased ambient temperature, or meals. Syncope is usually preceded by warning symptoms, but may occur suddenly, suggesting the possibility of a seizure or cardiac cause.

Supine hypertension is common in patients with orthostatic hypotension due to autonomic failure, affecting >50% of patients in some series. Orthostatic hypotension may present after initiation of therapy for hypertension, and supine hypertension may follow treatment of orthostatic hypotension. However, in other cases, the association of the two conditions is unrelated to therapy; it may in part be explained by baroreflex dysfunction in the presence of residual sympathetic outflow, particularly in patients with central autonomic degeneration.

Causes of Neurogenic Orthostatic Hypotension Causes of neurogenic orthostatic hypotension include central and peripheral autonomic nervous system dysfunction **(Chap. 432)**. Autonomic dysfunction of other organ systems (including the bladder, bowels, sexual organs, and sudomotor system) of varying severity frequently accompanies orthostatic hypotension in these disorders (Table 18-2).

The primary autonomic degenerative disorders are multiple system atrophy (Shy-Drager syndrome; **Chap. 432**), Parkinson's disease **(Chap. 427)**, dementia with Lewy bodies **(Chap. 426)**, and pure autonomic failure **(Chap. 432)**. These are often grouped together as "synucleinopathies" due to the presence of α-synuclein, a small protein that aggregates predominantly in the cytoplasm of neurons in the Lewy body disorders (Parkinson's disease, dementia with Lewy bodies, and pure autonomic failure) and in the glia in multiple system atrophy.

Peripheral autonomic dysfunction may also accompany small-fiber peripheral neuropathies such as those seen in diabetes mellitus, amyloid, immune-mediated neuropathies, hereditary sensory and autonomic neuropathies (HSAN; particularly HSAN type III, familial dysautonomia) **(Chaps. 438 and 439)**. Less frequently, orthostatic hypotension is associated with the peripheral neuropathies that accompany vitamin B_{12} deficiency, neurotoxic exposure, HIV and other infections, and porphyria.

Patients with autonomic failure and the elderly are susceptible to falls in blood pressure associated with meals. The magnitude of the blood pressure fall is exacerbated by large meals, meals high in carbohydrate, and alcohol intake. The mechanism of postprandial syncope is not fully elucidated.

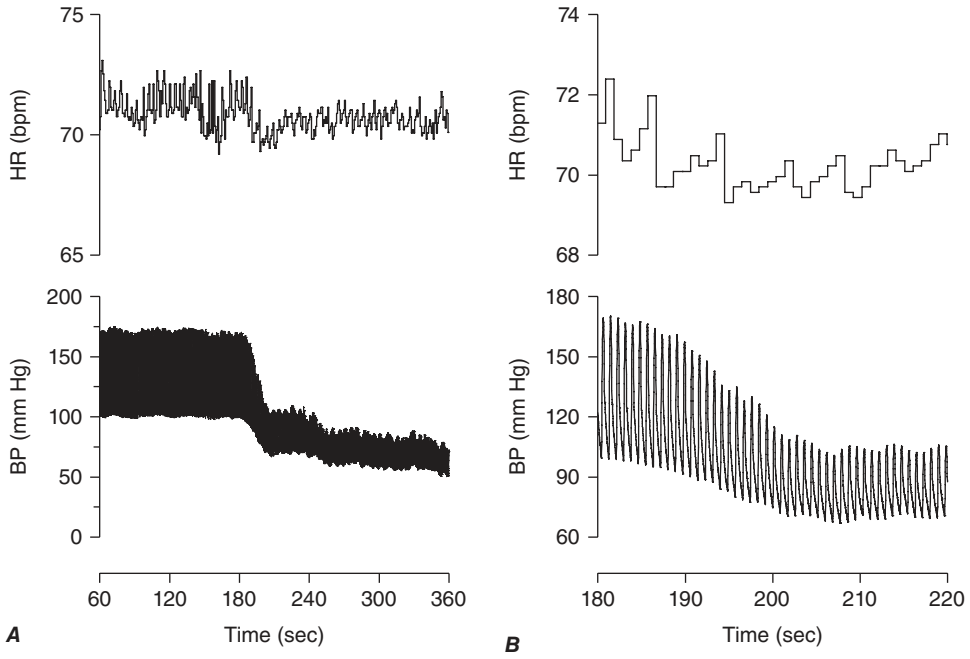

FIGURE 18-4 ***A.*** The gradual fall in blood pressure without a compensatory heart rate increase that is characteristic of orthostatic hypotension due to autonomic failure. Blood pressure and heart rate are shown >5 min (from 60 to 360 s) of an upright tilt on a tilt table. ***B.*** The same tracing expanded to show 40 s of the episode (from 180 to 220 s). BP, blood pressure; bpm, beats per minute; HR, heart rate.

Orthostatic hypotension is often iatrogenic. Drugs from several classes may lower peripheral resistance (e.g., α-adrenoreceptor antagonists used to treat hypertension and prostatic hypertrophy; antihypertensive agents of several classes; nitrates and other vasodilators; tricyclic agents and phenothiazines). Iatrogenic volume depletion due to diuresis and volume depletion due to medical causes (hemorrhage, vomiting, diarrhea, or decreased fluid intake) may also result in decreased effective circulatory volume, orthostatic hypotension, and syncope.

TREATMENT

Orthostatic Hypotension

The first step is to remove reversible causes—usually vasoactive medications **(Table 432-6)**. Next, nonpharmacologic interventions should be introduced. These interventions include patient education regarding staged moves from supine to upright; warnings about the hypotensive effects of large meals; instructions about the isometric counterpressure maneuvers that increase intravascular pressure (see above); and raising the head of the bed to reduce supine hypertension. Intravascular volume should be expanded by increasing dietary fluid and salt. If these nonpharmacologic measures fail, pharmacologic intervention with fludrocortisone acetate and vasoconstricting agents such as midodrine, L-dihydroxyphenylserine, and pseudoephedrine should be introduced. Some patients with intractable symptoms require additional therapy with supplementary agents that include pyridostigmine, atomoxetine, yohimbine, desmopressin acetate (DDAVP), and erythropoietin **(Chap. 432)**.

CARDIAC SYNCOPE

Cardiac (or cardiovascular) syncope is caused by arrhythmias and structural heart disease. These may occur in combination because structural disease renders the heart more vulnerable to abnormal electrical activity.

Arrhythmias Bradyarrhythmias that cause syncope include those due to severe sinus node dysfunction (e.g., sinus arrest or sinoatrial block) and atrioventricular (AV) block (e.g., Mobitz type II, high-grade, and complete AV block). The bradyarrhythmias due to sinus node dysfunction are often associated with an atrial tachyarrhythmia, a disorder known as the tachycardia-bradycardia syndrome. A prolonged pause following the termination of a tachycardic episode is a frequent cause of syncope in patients with the tachycardia-bradycardia syndrome. Medications of several classes may also cause bradyarrhythmias of sufficient severity to cause syncope. Syncope due to bradycardia or asystole is referred to as a Stokes-Adams attack.

Ventricular tachyarrhythmias frequently cause syncope. The likelihood of syncope with ventricular tachycardia is in part dependent on the ventricular rate; rates <200 beats/min are less likely to cause syncope. The compromised hemodynamic function during ventricular tachycardia is caused by ineffective ventricular contraction, reduced diastolic filling due to abbreviated filling periods, loss of AV synchrony, and concurrent myocardial ischemia.

Several disorders associated with cardiac electrophysiologic instability and arrhythmogenesis are due to mutations in ion channel subunit genes. These include the long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. The long QT syndrome is a genetically heterogeneous disorder associated with prolonged cardiac repolarization and a predisposition to ventricular arrhythmias. Syncope and sudden death in patients with long QT syndrome result from a unique polymorphic ventricular tachycardia called *torsades des pointes* that degenerates into ventricular fibrillation. The long QT syndrome has been linked to genes encoding K^+ channel α-subunits, K^+ channel β-subunits, voltage-gated Na^+ channel, and a scaffolding protein, ankyrin B (ANK2). Brugada syndrome is characterized by idiopathic ventricular fibrillation in association with right ventricular electrocardiogram (ECG) abnormalities without structural heart disease. This disorder is also genetically heterogeneous, although it is most frequently linked to mutations in the Na^+ channel α-subunit, SCN5A. Catecholaminergic polymorphic tachycardia is an inherited, genetically heterogeneous disorder associated with exercise- or stress-induced ventricular arrhythmias, syncope, or sudden death. Acquired QT interval prolongation, most commonly due to drugs, may also result in ventricular arrhythmias and syncope. **These disorders are discussed in detail in Chap. 249.**

Structural Disease Structural heart disease (e.g., valvular disease, myocardial ischemia, hypertrophic and other cardiomyopathies, cardiac masses such as atrial myxoma, and pericardial effusions) may lead to syncope by compromising cardiac output. Structural disease may also contribute to other pathophysiologic mechanisms of syncope. For example, cardiac structural disease may predispose to arrhythmogenesis; aggressive treatment of cardiac failure with diuretics and/or vasodilators may lead to orthostatic hypotension; and inappropriate reflex vasodilation may occur with structural disorders such as aortic stenosis and hypertrophic cardiomyopathy, possibly provoked by increased ventricular contractility.

TREATMENT

Cardiac Syncope

Treatment of cardiac disease depends on the underlying disorder. Therapies for arrhythmias include cardiac pacing for sinus node disease and AV block, and ablation, antiarrhythmic drugs, and cardioverter-defibrillators for atrial and ventricular tachyarrhythmias. These disorders are best managed by physicians with specialized skills in this area.

APPROACH TO THE PATIENT

Syncope

DIFFERENTIAL DIAGNOSIS

Syncope is easily diagnosed when the characteristic features are present; however, several disorders with transient real or apparent loss of consciousness may create diagnostic confusion.

Generalized and partial seizures may be confused with syncope; however, there are a number of differentiating features. Whereas tonic-clonic movements are the hallmark of a generalized seizure, myoclonic and other movements also may occur in up to 90% of syncopal episodes. Myoclonic jerks associated with syncope may be multifocal or generalized. They are typically arrhythmic and of short duration (<30 s). Mild flexor and extensor posturing also may occur. Partial or partial-complex seizures with secondary generalization are usually preceded by an aura, commonly an unpleasant smell; fear; anxiety; abdominal discomfort; or other visceral sensations. These phenomena should be differentiated from the premonitory features of syncope.

Autonomic manifestations of seizures (autonomic epilepsy) may provide a more difficult diagnostic challenge. Autonomic seizures have cardiovascular, gastrointestinal, pulmonary, urogenital, pupillary, and cutaneous manifestations that are similar to the premonitory features of syncope. Furthermore, the cardiovascular manifestations of autonomic epilepsy include clinically significant tachycardias and bradycardias that may be of sufficient magnitude to cause loss of consciousness. The presence of accompanying nonautonomic auras may help differentiate these episodes from syncope.

Loss of consciousness associated with a seizure usually lasts >5 min and is associated with prolonged postictal drowsiness and disorientation, whereas reorientation occurs almost immediately after a syncopal event. Muscle aches may occur after both syncope and seizures, although they tend to last longer and be more severe following a seizure. Seizures, unlike syncope, are rarely provoked by emotions or pain. Incontinence of urine may occur with both seizures and syncope; however, fecal incontinence occurs very rarely with syncope.

Hypoglycemia may cause transient loss of consciousness, typically in individuals with type 1 or type 2 diabetes treated with insulin. The clinical features associated with impending or actual hypoglycemia include tremor, palpitations, anxiety, diaphoresis, hunger, and paresthesias. These symptoms are due to autonomic activation to counter the falling blood glucose. Hunger, in particular, is not a typical premonitory feature of syncope. Hypoglycemia also impairs neuronal function, leading to fatigue, weakness, dizziness, and cognitive and behavioral symptoms. Diagnostic difficulties may occur in individuals in strict glycemic control; repeated hypoglycemia impairs the counterregulatory response and leads to a loss of the characteristic warning symptoms that are the hallmark of hypoglycemia.

Patients with cataplexy experience an abrupt partial or complete loss of muscular tone triggered by strong emotions, typically anger or laughter. Unlike syncope, consciousness is maintained throughout the attacks, which typically last between 30 s and 2 min. There are no premonitory symptoms. Cataplexy occurs in 60–75% of patients with narcolepsy.

The clinical interview and interrogation of eyewitnesses usually allow differentiation of syncope from falls due to vestibular dysfunction, cerebellar disease, extrapyramidal system dysfunction, and other gait disorders. A diagnosis of syncope can be particularly challenging in patients with dementia who experience repeated falls and are unable to provide a clear history of the episodes. If the fall is accompanied by head trauma, a postconcussive syndrome, amnesia for the precipitating events, and/or the presence of loss of consciousness may also contribute to diagnostic difficulty.

Apparent loss of consciousness can be a manifestation of psychiatric disorders such as generalized anxiety, panic disorders, major depression, and somatization disorder. These possibilities should be considered in individuals who faint frequently without prodromal symptoms. Such patients are rarely injured despite numerous falls. There are no clinically significant hemodynamic changes concurrent with these episodes. In contrast, transient loss of consciousness due to vasovagal syncope precipitated by fear, stress, anxiety, and emotional distress is accompanied by hypotension, bradycardia, or both.

INITIAL EVALUATION

The goals of the initial evaluation are to determine whether the transient loss of consciousness was due to syncope; to identify the cause; and to assess risk for future episodes and serious harm (Table 18-1). The initial evaluation should include a detailed history, thorough questioning of eyewitnesses, and a complete physical and neurologic examination. Blood pressure and heart rate should be measured in the supine position and after 3 min of standing to determine whether orthostatic hypotension is present. An ECG should be performed if there is suspicion of syncope due to an arrhythmia or underlying cardiac disease. Relevant electrocardiographic abnormalities include bradyarrhythmias or tachyarrhythmias, AV block, ischemia, old myocardial infarction, long QT syndrome, and bundle branch block. This initial assessment will lead to the identification of a cause of syncope in ~50% of patients and also allows stratification of patients at risk for cardiac mortality.

Laboratory Tests Baseline laboratory blood tests are rarely helpful in identifying the cause of syncope. Blood tests should be performed when specific disorders, e.g., myocardial infarction, anemia, and secondary autonomic failure, are suspected (Table 18-2).

Autonomic Nervous System Testing (Chap. 432) Autonomic testing, including tilt-table testing, can be performed in specialized centers. Autonomic testing is helpful to uncover objective evidence of autonomic failure and also to demonstrate a predisposition to neurally mediated syncope. Autonomic testing includes assessments of parasympathetic autonomic nervous system function (e.g., heart rate variability to deep respiration and a Valsalva maneuver), sympathetic cholinergic function (e.g., thermoregulatory sweat response and quantitative sudomotor axon reflex test), and sympathetic adrenergic function (e.g., blood pressure response to a Valsalva maneuver and a tilt-table test with beat-to-beat blood pressure measurement). The hemodynamic abnormalities demonstrated on the tilt-table test (Figs. 18-3 and 18-4) may be useful in distinguishing orthostatic hypotension due to autonomic failure from the hypotensive bradycardic response of neurally mediated syncope. Similarly, the tilt-table test may help identify patients with syncope due to immediate or delayed orthostatic hypotension.

Carotid sinus massage should be considered in patients with symptoms suggestive of carotid sinus syncope and in patients >50 years with recurrent syncope of unknown etiology. This test should only be carried out under continuous ECG and blood pressure monitoring and should be avoided in patients with carotid bruits, plaques, or stenosis.

Cardiac Evaluation ECG monitoring is indicated for patients with a high pretest probability of arrhythmia causing syncope. Patients should be monitored in hospital if the likelihood of a life-threatening arrhythmia is high, e.g., patients with severe structural or coronary artery disease, nonsustained ventricular tachycardia, trifascicular heart block, prolonged QT interval, Brugada syndrome ECG pattern, or family history of sudden cardiac death (Table 18-1). Outpatient Holter monitoring is recommended for patients who experience frequent syncopal episodes (one or more per week), whereas loop recorders, which continually record and erase cardiac rhythm, are indicated for patients with suspected arrhythmias with low risk of sudden cardiac death. Loop recorders may be external (recommended for evaluation of episodes that occur at a frequency of >1 per month) or implantable (if syncope occurs less frequently).

Echocardiography should be performed in patients with a history of cardiac disease or if abnormalities are found on physical

examination or the ECG. Echocardiographic diagnoses that may be responsible for syncope include aortic stenosis, hypertrophic cardiomyopathy, cardiac tumors, aortic dissection, and pericardial tamponade. Echocardiography also has a role in risk stratification based on the left ventricular ejection fraction.

Treadmill exercise testing with ECG and blood pressure monitoring should be performed in patients who have experienced syncope during or shortly after exercise. Treadmill testing may help identify exercise-induced arrhythmias (e.g., tachycardia-related AV block) and exercise-induced exaggerated vasodilation.

Electrophysiologic studies are indicated in patients with structural heart disease and ECG abnormalities in whom noninvasive investigations have failed to yield a diagnosis. Electrophysiologic studies have low sensitivity and specificity and should only be performed when a high pretest probability exists. Currently, this test is rarely performed to evaluate patients with syncope.

Psychiatric Evaluation Screening for psychiatric disorders may be appropriate in patients with recurrent unexplained syncope episodes. Tilt-table testing, with demonstration of symptoms in the absence of hemodynamic change, may be useful in reproducing syncope in patients with suspected psychogenic syncope.

FURTHER READING

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19 Dizziness and Vertigo

Mark F. Walker, Robert B. Daroff

Dizziness is an imprecise symptom used to describe a variety of common sensations that include vertigo, light-headedness, faintness, and imbalance. *Vertigo* refers to a sense of spinning or other motion that may be physiological, occurring during or after a sustained head rotation, or pathological, due to vestibular dysfunction. The term *light-headedness* is classically applied to presyncopal sensations resulting from brain hypoperfusion but as used by patients has little specificity, as it may also refer to other symptoms such as disequilibrium and imbalance. A challenge to diagnosis is that patients often have difficulty distinguishing among these various symptoms, and the words they choose do not reliably indicate the underlying etiology.

There are many causes of dizziness. Vestibular dizziness (vertigo or imbalance) may be due to peripheral disorders that affect the labyrinths or vestibular nerves, or it may result from disruption of central vestibular pathways. It may be paroxysmal or due to a fixed unilateral or bilateral vestibular deficit. Acute unilateral lesions cause vertigo due to a sudden imbalance in vestibular inputs from the two labyrinths. Bilateral lesions cause imbalance and instability of vision when the head moves (*oscillopsia*) due to loss of normal vestibular reflexes.

Presyncopal dizziness occurs when cardiac dysrhythmia, orthostatic hypotension, medication effects, or another cause leads to brain hypoperfusion. Such presyncopal sensations vary in duration; they may increase in severity until loss of consciousness occurs, or they may resolve before loss of consciousness if the cerebral ischemia is corrected. Faintness and syncope, which are discussed in detail in **Chap. 18**, should always be considered when one is evaluating patients with brief episodes of dizziness or dizziness that occurs with upright posture. Other causes of dizziness include non-vestibular imbalance and gait disorders (e.g., loss of proprioception from sensory neuropathy, parkinsonism), and anxiety.

When evaluating patients with dizziness, questions to consider include the following: (1) Is it dangerous (e.g., arrhythmia, transient ischemic attack/stroke)? (2) Is it vestibular? (3) If vestibular, is it peripheral or central? A careful history and examination often provide sufficient information to answer these questions and determine whether additional studies or referral to a specialist is necessary.

APPROACH TO THE PATIENT

Dizziness

HISTORY

When a patient presents with dizziness, the first step is to delineate more precisely the nature of the symptom. In the case of vestibular disorders, the physical symptoms depend on whether the lesion is unilateral or bilateral, and whether it is acute or chronic. Vertigo, an illusion of self or environmental motion, implies asymmetry of vestibular inputs from the two labyrinths or in their central pathway that is usually acute. Symmetric bilateral vestibular hypofunction causes imbalance but no vertigo. Because of the ambiguity in patients' descriptions of their symptoms, diagnosis based simply on symptom characteristics is typically unreliable. Thus, the history should focus closely on other features, including whether this is the first attack, the duration of this and any prior episodes, provoking factors, and accompanying symptoms.

Dizziness can be divided into episodes that last for seconds, minutes, hours, or days. Common causes of brief dizziness (seconds) include benign paroxysmal positional vertigo (BPPV) and orthostatic hypotension, both of which typically are provoked by changes in head and body position. Attacks of vestibular migraine and Ménière's disease often last hours. When episodes are of intermediate duration (minutes), transient ischemic attacks of the posterior circulation should be considered, although migraine and a number of other causes are also possible.

Symptoms that accompany vertigo may be helpful in distinguishing peripheral vestibular lesions from central causes. Unilateral hearing loss and other aural symptoms (ear pain, pressure, fullness) typically point to a peripheral cause. Because the auditory pathways quickly become bilateral upon entering the brainstem, central lesions are unlikely to cause unilateral hearing loss, unless the lesion lies near the root entry zone of the auditory nerve. Symptoms such as double vision, numbness, and limb ataxia suggest a brainstem or cerebellar lesion.

EXAMINATION

Because dizziness and imbalance can be a manifestation of a variety of neurologic disorders, the neurologic examination is important in the evaluation of these patients. Particular focus should be given to assessment of eye movements, vestibular function, and hearing.

The range of eye movements and whether they are equal in each eye should be observed. Peripheral eye movement disorders (e.g., cranial neuropathies, eye muscle weakness) are usually disconjugate (different in the two eyes). One should check pursuit (the ability to follow a smoothly moving target) and saccades (the ability to look back and forth accurately between two targets). Poor pursuit or inaccurate (dysmetric) saccades usually indicate central pathology, often involving the cerebellum. Alignment of the two eyes can be checked with a cover test: while the patient is looking at a target, alternately cover the eyes and observe for corrective saccades. A vertical misalignment may indicate a brainstem or cerebellar lesion. Finally, one should look for spontaneous nystagmus, an involuntary back-and-forth movement of the eyes. Nystagmus is most often of the jerk type, in which a slow drift (slow phase) in one direction alternates with a rapid saccadic movement (quick phase or fast phase) in the opposite direction that resets the position of the eyes in the orbits. Except in the case of acute vestibulopathy (e.g., vestibular neuritis), if primary position nystagmus is easily seen in the light, it is probably due to a central cause. Two forms of nystagmus that are characteristic of lesions of the cerebellar pathways are vertical nystagmus with downward fast phases (downbeat nystagmus) and horizontal nystagmus that changes direction with gaze (gaze-evoked nystagmus). By contrast, peripheral lesions typically cause unidirectional horizontal nystagmus. Use of Frenzel eyeglasses (self-illuminated goggles with convex lenses that blur the patient's vision but allow the examiner to see the eyes greatly magnified) can aid in the detection of peripheral vestibular nystagmus, because they reduce the patient's ability to use visual fixation to suppress nystagmus. **Table 19-1** outlines key findings that help distinguish peripheral from central causes of vertigo.

The most useful bedside test of peripheral vestibular function is the head impulse test, in which the vestibuloocular reflex (VOR) is assessed with small-amplitude (~20 degrees) rapid head rotations. While the patient fixates on a target, the head is rotated to the left or right. If the VOR is deficient, the rotation is followed by a catch-up saccade in the opposite direction (e.g., a leftward saccade after a rightward rotation). The head impulse test can identify both unilateral (catch-up saccades after rotations toward the weak side) and bilateral vestibular hypofunction (catch-up saccades after rotations in both directions).

All patients with episodic dizziness, especially if provoked by positional change, should be tested with the Dix-Hallpike maneuver. The patient begins in a sitting position with the head turned 45 degrees; holding the back of the head, the examiner then lowers the patient into a supine position with the head extended backward by about 20 degrees while watching the eyes. Posterior canal BPPV can be diagnosed confidently if transient upbeating-torsional nystagmus is seen. If no nystagmus is observed after 15–20 s, the patient is raised to the sitting position, and the procedure is repeated with the head turned to the other side. Again, Frenzel goggles may improve the sensitivity of the test.

Dynamic visual acuity is a functional test that can be useful in assessing vestibular function. Visual acuity is measured with the head still and when the head is rotated back and forth by the examiner (about 1–2 Hz). A drop in visual acuity during head motion of more than one line on a near card or Snellen chart is abnormal and indicates vestibular dysfunction.

ANCILLARY TESTING

The choice of ancillary tests should be guided by the history and examination findings. Audiometry should be performed whenever a vestibular disorder is suspected. Unilateral sensorineural hearing loss supports a peripheral disorder (e.g., vestibular schwannoma). Predominantly low-frequency hearing loss is characteristic of Ménière's disease. Electronystagmography or videonystagmography includes recordings of spontaneous nystagmus (if present) and measurement of positional nystagmus. Caloric testing assesses the responses of the two horizontal semicircular canals. The test battery often includes recording of saccades and pursuit to assess central ocular motor function. Neuroimaging is important if a central vestibular disorder is suspected. In addition, patients with unexplained unilateral hearing loss or vestibular hypofunction should undergo magnetic resonance imaging (MRI) of the internal auditory canals, including administration of gadolinium, to rule out a schwannoma.

TABLE 19-1 Features of Peripheral and Central Vertigo

- Nystagmus from an acute peripheral lesion is unidirectional, with fast phases beating away from the ear with the lesion. Nystagmus that changes direction with gaze is due to a central lesion.
- Transient mixed vertical-torsional nystagmus occurs in benign paroxysmal positional vertigo (BPPV), but pure vertical or pure torsional nystagmus is a central sign.
- Nystagmus from a peripheral lesion may be inhibited by visual fixation, whereas central nystagmus is not suppressed.
- Absence of a head impulse sign in a patient with acute prolonged vertigo should suggest a central cause.
- Unilateral hearing loss suggests peripheral vertigo. Findings such as diplopia, dysarthria, and limb ataxia suggest a central disorder.

DIFFERENTIAL DIAGNOSIS AND TREATMENT

Treatment of vestibular symptoms should be driven by the underlying diagnosis. Simply treating dizziness with vestibular suppressant medications is often not helpful and may make the symptoms worse and prolong recovery. The diagnostic and specific treatment approaches for the most commonly encountered vestibular disorders are discussed below.

ACUTE PROLONGED VERTIGO (VESTIBULAR NEURITIS)

An acute unilateral vestibular lesion causes constant vertigo, nausea, vomiting, oscillopsia (motion of the visual scene), and imbalance. These symptoms are due to a sudden asymmetry of inputs from the two labyrinths or in their central connections, simulating a continuous rotation of the head. Unlike BPPV, continuous vertigo persists even when the head remains still.

When a patient presents with an acute vestibular syndrome, the most important question is whether the lesion is central (e.g., a cerebellar or brainstem infarct or hemorrhage), which may be life-threatening, or peripheral, affecting the vestibular nerve or labyrinth (vestibular neuritis). Attention should be given to any symptoms or signs that point to central dysfunction (diplopia, weakness or numbness, dysarthria). The pattern of spontaneous nystagmus, if present, may be helpful (Table 19-1). If the head impulse test is normal, an acute peripheral vestibular lesion is unlikely. A central lesion cannot always be excluded with certainty based on symptoms and examination alone; thus, older patients with vascular risk factors who present with an acute vestibular syndrome should be evaluated for the possibility of stroke even when there are no specific findings that indicate a central lesion.

Most patients with vestibular neuritis recover spontaneously, but glucocorticoids can improve outcome if administered within 3 days of symptom onset. Antiviral medications are of no proven benefit and are not typically given unless there is evidence to suggest herpes zoster oticus (Ramsay Hunt syndrome). Vestibular suppressant medications may reduce acute symptoms but should be avoided after the first several days because they may impede central compensation and recovery. Patients should be encouraged to resume a normal level of activity as soon as possible, and directed vestibular rehabilitation therapy may accelerate improvement.

BENIGN PAROXYSMAL POSITIONAL VERTIGO

BPPV is a common cause of recurrent vertigo. Episodes are brief (<1 min and typically 15–20 s) and are always provoked by changes in head position relative to gravity, such as lying down, rolling over in bed, rising from a supine position, and extending the head to look upward. The attacks are caused by free-floating otoconia (calcium carbonate crystals) that have been dislodged from the utricular macula and have moved into one of the semicircular canals, usually the

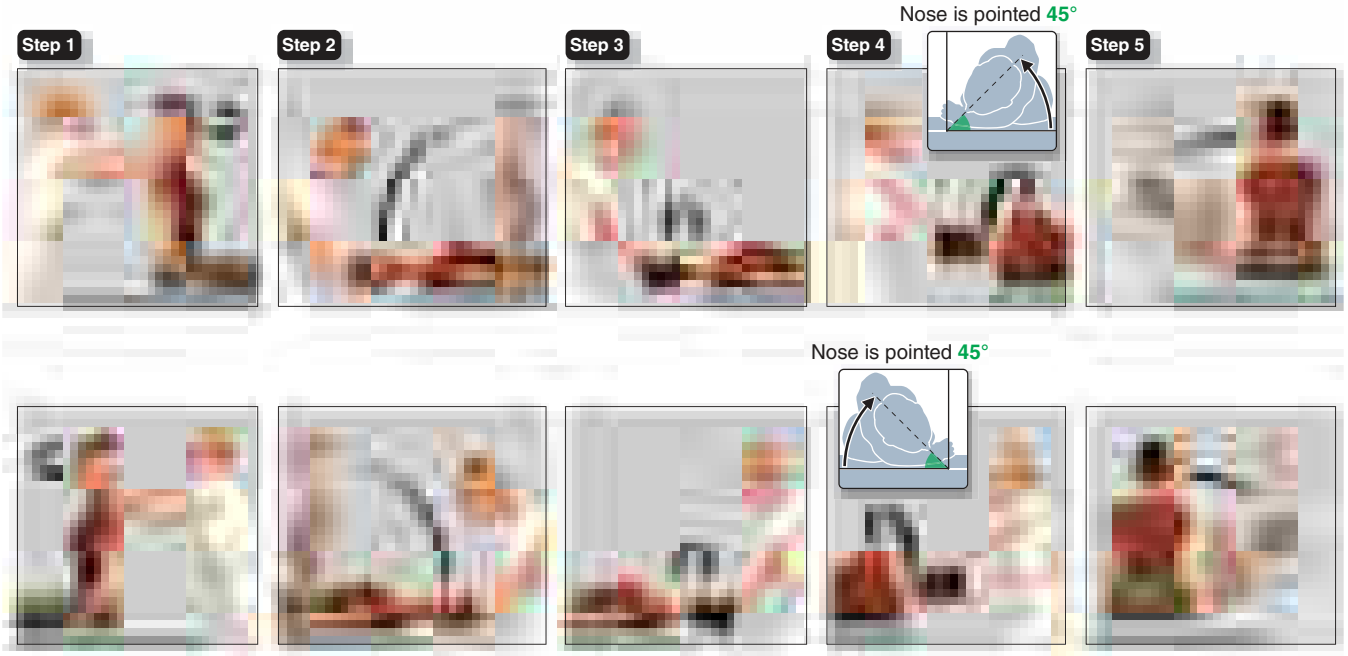

FIGURE 19-1 Modified Epley maneuver for treatment of benign paroxysmal positional vertigo of the right (*top panels*) and left (*bottom panels*) posterior semicircular canals. **Step 1.** With the patient seated, turn the head 45 degrees toward the affected ear. **Step 2.** Keeping the head turned, lower the patient to the head-hanging position and hold for at least 30 s and until nystagmus disappears. **Step 3.** Without lifting the head, turn it 90 degrees toward the other side. Hold for another 30 s. **Step 4.** Rotate the patient onto her side while turning the head another 90 degrees, so that the nose is pointed down 45 degrees. Hold again for 30 s. **Step 5.** Have the patient sit up on the side of the table. After a brief rest, the maneuver should be repeated to confirm successful treatment. *(Figure adapted from http://www.dizziness-and-balance.com/disorders/bppv/movies/Epley-480x640.avi.)*

posterior canal. When head position changes, gravity causes the otoconia to move within the canal, producing vertigo and nystagmus. With posterior canal BPPV, the nystagmus beats upward and torsionally (the upper poles of the eyes beat toward the affected lower ear). Less commonly, the otoconia enter the horizontal canal, resulting in a horizontal nystagmus when the patient is lying with either ear down. Superior (also called anterior) canal involvement is rare. BPPV is treated with repositioning maneuvers that use gravity to remove the otoconia from the semicircular canal. For posterior canal BPPV, the Epley maneuver **(Fig. 19-1)** is the most commonly used procedure. For more refractory cases of BPPV, patients can be taught a variant of this maneuver that they can perform alone at home. A demonstration of the Epley maneuver is available online (*http://www.dizziness-and-balance.com/disorders/bppv/bppv.html*).

VESTIBULAR MIGRAINE

Vestibular migraine is a very common yet underdiagnosed cause of episodic vertigo. Vertigo sometimes precedes a typical migraine headache but more often occurs without headache or with only a mild headache. Some patients who have had frequent migraine headaches in the past present later in life with vestibular migraine as the predominant problem. In vestibular migraine, the duration of vertigo may be from minutes to hours, and some migraineurs also experience more prolonged periods of disequilibrium (lasting days to weeks). Motion sensitivity and sensitivity to visual motion (e.g., movies) are common. Even in the absence of headache, other migraine features may be present, such as photophobia, phonophobia, or a visual aura. Although data from controlled studies are generally lacking, vestibular migraine typically is treated with medications that are used for prophylaxis of migraine headaches **(Chap. 422)**. Antiemetics may be helpful to relieve symptoms at the time of an attack.

MÉNIÈRE'S DISEASE

Attacks of Ménière's disease consist of vertigo and hearing loss, as well as pain, pressure, and/or fullness in the affected ear. The low-frequency hearing loss and aural symptoms are key features that distinguish Ménière's disease from other peripheral vestibulopathies and from vestibular migraine. Audiometry at the time of an attack shows a characteristic asymmetric low-frequency hearing loss; hearing commonly improves between attacks, although permanent hearing loss may eventually occur. Ménière's disease is thought to be due to excess fluid (endolymph) in the inner ear; hence the term *endolymphatic hydrops*. Patients suspected of having Ménière's disease should be referred to an otolaryngologist for further evaluation. Diuretics and sodium restriction are typically the initial treatments. If attacks persist, injections of glucocorticoids or gentamicin into the middle ear may be considered. Non-ablative surgical options include decompression and shunting of the endolymphatic sac. Full ablative procedures (vestibular nerve section, labyrinthectomy) are seldom required.

VESTIBULAR SCHWANNOMA

Vestibular schwannomas (sometimes termed *acoustic neuromas*) and other tumors at the cerebellopontine angle cause slowly progressive unilateral sensorineural hearing loss and vestibular hypofunction. These patients typically do not have vertigo, because the gradual vestibular deficit is compensated centrally as it develops. The diagnosis often is not made until there is sufficient hearing loss to be noticed. The vestibular examination will show a deficient response to the head impulse test when the head is rotated toward the affected side, but nystagmus will not be prominent. As noted above, patients with unexplained unilateral sensorineural hearing loss or vestibular hypofunction require MRI of the internal auditory canals to look for a schwannoma.

BILATERAL VESTIBULAR HYPOFUNCTION

Patients with bilateral loss of vestibular function also typically do not have vertigo, because vestibular function is lost on both sides simultaneously, and there is no asymmetry of vestibular input. Symptoms include loss of balance, particularly in the dark, where vestibular input is most critical, and oscillopsia during head movement, such as while walking or riding in a car. Bilateral vestibular hypofunction may be (1) idiopathic and progressive, (2) part of a neurodegenerative disorder, or (3) iatrogenic, due to medication ototoxicity (most commonly gentamicin or other aminoglycoside antibiotics). Other causes include bilateral vestibular schwannomas (neurofibromatosis type 2), autoimmune disease, superficial siderosis, and meningeal-based infection or

tumor. It also may occur in patients with peripheral polyneuropathy; in these patients, both vestibular loss and impaired proprioception may contribute to poor balance. Finally, unilateral processes such as vestibular neuritis and Ménière's disease may involve both ears sequentially, resulting in bilateral vestibulopathy.

Examination findings include diminished *dynamic visual acuity* (see above) due to loss of stable vision when the head is moving, abnormal head impulse responses in both directions, and a Romberg sign. Responses to caloric testing are reduced. Patients with bilateral vestibular hypofunction should be referred for vestibular rehabilitation therapy. Vestibular suppressant medications should not be used, as they will increase the imbalance. Evaluation by a neurologist is important not only to confirm the diagnosis but also to consider any other associated neurologic abnormalities that may clarify the etiology.

CENTRAL VESTIBULAR DISORDERS

Central lesions causing vertigo typically involve vestibular pathways in the brainstem and/or cerebellum. They may be due to discrete lesions, such as from ischemic or hemorrhagic stroke **(Chaps. 419–421)**, demyelination **(Chap. 436)**, or tumors **(Chap. 86)**, or they may be due to neurodegenerative conditions that include the vestibulocerebellum **(Chaps. 423-426)**. Subacute cerebellar degeneration may be due to immune, including paraneoplastic, processes **(Chaps. 90 and 431)**. Table 19-1 outlines important features of the history and examination that help to identify central vestibular disorders. Acute central vertigo is a medical emergency, due to the possibility of life-threatening stroke or hemorrhage. All patients with suspected central vestibular disorders should undergo brain MRI, and the patient should be referred for full neurologic evaluation.

PSYCHOSOMATIC AND FUNCTIONAL DIZZINESS

Psychological factors play an important role in chronic dizziness. First, dizziness may be a somatic manifestation of a psychiatric condition such as major depression, anxiety, or panic disorder **(Chap. 443)**. Second, patients may develop anxiety and autonomic symptoms as a consequence or comorbidity of an independent vestibular disorder. One particular form of this has been termed variously *phobic postural vertigo*, *psychophysiologic vertigo*, or *chronic subjective dizziness*, but is now referred to as *persistent postural-perceptual dizziness (PPPD)*. These patients have a chronic feeling (3 months or longer) of fluctuating dizziness and disequilibrium that is present at rest but worse while standing. There is an increased sensitivity to self-motion and visual motion (e.g., watching movies), and a particular intensification of symptoms when moving through complex visual environments such as supermarkets. Although there may be a past history of an acute vestibular disorder (e.g., vestibular neuritis), the neurootologic examination and vestibular testing are normal or indicative of a compensated vestibular deficit, indicating that the ongoing subjective dizziness cannot be explained by a primary vestibular pathology. Anxiety disorders are particularly common in patients with chronic dizziness; when present, they contribute substantially to the morbidity. Treatment approaches for PPPD include pharmacological therapy with selective serotonin reuptake inhibitors (SSRIs), cognitive-behavioral psychotherapy, and vestibular rehabilitation. Vestibular suppressant medications generally should be avoided.

TREATMENT

Vertigo

Table 19-2 provides a list of commonly used medications for suppression of vertigo. As noted, these medications should be reserved for short-term control of active vertigo, such as during the first few days of acute vestibular neuritis, or for acute attacks of Ménière's disease. They are less helpful for chronic dizziness and, as previously stated, may hinder central compensation. An exception is that benzodiazepines may attenuate psychosomatic dizziness and the associated anxiety, although SSRIs are generally preferable in such patients.

TABLE 19-2 Treatment of Vertigo

AGENT[a]	DOSE[b]
Antihistamines	
Meclizine	25–50 mg 3 times daily
Dimenhydrinate	50 mg 1–2 times daily
Promethazine	25 mg 2–3 times daily (also can be given rectally and IM)
Benzodiazepines	
Diazepam	2.5 mg 1–3 times daily
Clonazepam	0.25 mg 1–3 times daily
Anticholinergic	
Scopolamine transdermal[c]	Patch
Physical therapy	
Repositioning maneuvers[d]	
Vestibular rehabilitation	
Other	
Diuretics and/or low-sodium (1000 mg/d) diet[e]	
Antimigrainous drugs[f]	
Methylprednisolone[g]	100 mg daily days 1–3; 80 mg daily days 4–6; 60 mg daily days 7–9; 40 mg daily days 10–12; 20 mg daily days 13–15; 10 mg daily days 16–18, 20, 22
Selective serotonin reuptake inhibitors[h]	

[a]All listed drugs are approved by the U.S. Food and Drug Administration, but most are not approved for the treatment of vertigo. [b]Usual oral (unless otherwise stated) starting dose in adults; a higher maintenance dose can be reached by a gradual increase. [c]For motion sickness only. [d]For benign paroxysmal positional vertigo. [e]For Ménière's disease. [f]For vestibular migraine. [g]For acute vestibular neuritis (started within 3 days of onset). [h]For persistent postural-perceptual vertigo and anxiety.

Vestibular rehabilitation therapy promotes central adaptation processes that compensate for vestibular loss and also may help habituate motion sensitivity and other symptoms of psychosomatic dizziness. The general approach is to use a graded series of exercises that progressively challenge gaze stabilization and balance.

FURTHER READING

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20 Fatigue

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Fatigue is one of the most common symptoms in clinical medicine. It is a prominent manifestation of a number of systemic, neurologic, and psychiatric syndromes, although a precise cause will not be identified in a substantial minority of patients. Fatigue refers to the subjective human experience of physical and mental weariness, sluggishness, low energy, and exhaustion. In the context of clinical medicine, fatigue is most typically and practically defined as difficulty initiating or maintaining voluntary mental or physical activity. Nearly everyone who has ever been ill with a self-limited infection has experienced this near-universal symptom, and fatigue is usually brought to medical attention only when it is either of unclear cause, fails to remit, or the

severity is out of proportion with what would be expected for the associated trigger.

Fatigue should be distinguished from *muscle weakness*, a reduction of neuromuscular power **(Chap. 21)**; most patients complaining of fatigue are not truly weak when direct muscle power is tested. Fatigue is also distinct from *somnolence*, which refers to sleepiness in the context of disturbed sleep-wake physiology **(Chap. 27)**, and from *dyspnea on exertion*, although patients may use the word fatigue to describe those symptoms. The task facing clinicians when a patient presents with fatigue is to identify the underlying cause and to develop a therapeutic alliance, the goal of which is to spare patients expensive and fruitless diagnostic workups and steer them toward effective therapy.

EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS

Variability in the definitions of fatigue and the survey instruments used in different studies makes it difficult to arrive at precise figures about the global burden of fatigue. The point prevalence of fatigue was 6.7% and the lifetime prevalence was 25% in a large National Institute of Mental Health survey of the U.S. general population. In primary care clinics in Europe and the United States, between 10 and 25% of patients surveyed endorsed symptoms of prolonged (present for >1 month) or chronic (present for >6 months) fatigue, but in only a minority was fatigue the primary reason for seeking medical attention. In a community survey of women in India, 12% reported chronic fatigue. By contrast, the prevalence of chronic fatigue syndrome, as defined by the U.S. Centers for Disease Control and Prevention, is low **(Chap. 442)**.

DIFFERENTIAL DIAGNOSIS

Psychiatric Disease Fatigue is a common somatic manifestation of many major psychiatric syndromes, including depression, anxiety, and somatoform disorders. Psychiatric symptoms are reported in more than three-quarters of patients with unexplained chronic fatigue. Even in patients with systemic or neurologic syndromes in which fatigue is independently recognized as a manifestation of disease, comorbid psychiatric symptoms or disease may still be an important source of interaction.

Neurologic Disease Patients complaining of fatigue often say they feel weak, but upon careful examination objective muscle weakness is rarely discernible. If found, muscle weakness must then be localized to the central nervous system, peripheral nervous system, neuromuscular junction, or muscle and appropriate follow-up studies obtained **(Chap. 21)**. *Fatigability* of muscle power is a cardinal manifestation of some neuromuscular disorders such as myasthenia gravis and is distinguished from *fatigue* by finding clinically apparent diminution of the amount of force that a muscle generates upon repeated contraction **(Chap. 440)**. Fatigue is one of the most common and bothersome symptoms reported in multiple sclerosis (MS) **(Chap. 436)**, affecting nearly 90% of patients; fatigue in MS can persist between MS attacks and does not necessarily correlate with magnetic resonance imaging (MRI) disease activity. Fatigue is also increasingly identified as a troublesome feature of many neurodegenerative diseases, including Parkinson's disease, central dysautonomias, and amyotrophic lateral sclerosis. Fatigue after stroke is a well-described but poorly understood entity with a widely varying prevalence. Episodic fatigue can be a premonitory symptom of migraine. Fatigue is also a frequent result of traumatic brain injury, often occurring in association with depression and sleep disorders.

Sleep Disorders Obstructive sleep apnea is an important cause of excessive daytime sleepiness in association with fatigue and should be investigated using overnight polysomnography, particularly in those with prominent snoring, obesity, or other predictors of obstructive sleep apnea **(Chap. 291)**. Whether the cumulative sleep deprivation that is common in modern society contributes to clinically apparent fatigue is not known **(Chap. 27)**.

Endocrine Disorders Fatigue, sometimes in association with true muscle weakness, can be a heralding symptom of hypothyroidism, particularly in the context of hair loss, dry skin, cold intolerance, constipation, and weight gain. Fatigue associated with heat intolerance, sweating, and palpitations is typical of hyperthyroidism. Adrenal insufficiency can also manifest with unexplained fatigue as a primary or prominent symptom, often with anorexia, weight loss, nausea, myalgias, and arthralgias; hyponatremia, hyperkalemia, and hyperpigmentation may be present at time of diagnosis. Mild hypercalcemia can cause fatigue, which may be relatively vague, whereas severe hypercalcemia can lead to lethargy, stupor, and coma. Both hypoglycemia and hyperglycemia can cause lethargy, often in association with confusion; diabetes mellitus, and in particular type 1 diabetes, is also associated with fatigue independent of glucose levels. Fatigue may also accompany Cushing's disease, hypoaldosteronism, and hypogonadism. Low vitamin D status has also been associated with fatigue.

Liver and Kidney Disease Both chronic liver failure and chronic kidney disease can cause fatigue. Over 80% of hemodialysis patients complain of fatigue, which makes it one of the most common symptoms reported by patients in chronic kidney disease.

Obesity Obesity is associated with fatigue and sleepiness independent of the presence of obstructive sleep apnea. Obese patients undergoing bariatric surgery experience improvement in daytime sleepiness sooner than would be expected if the improvement were solely the result of weight loss and resolution of sleep apnea. A number of other factors common in obese patients are likely contributors as well, including physical inactivity, diabetes, and depression.

Physical Inactivity Physical inactivity is associated with fatigue, and increasing physical activity can improve fatigue in some patients.

Malnutrition Although fatigue can be a presenting feature of malnutrition, nutritional status may also be an important comorbidity and contributor to fatigue in other chronic illnesses, including cancer-associated fatigue.

Infection Both acute and chronic infections commonly lead to fatigue as part of the broader infectious syndrome. Evaluation for undiagnosed infection as the cause of unexplained fatigue, and particularly prolonged or chronic fatigue, should be guided by the history, physical examination, and infectious risk factors, with particular attention to risk for tuberculosis, HIV, chronic hepatitis, and endocarditis. Infectious mononucleosis may cause prolonged fatigue that persists for weeks to months following the acute illness, but infection with the Epstein-Barr virus is only very rarely the cause of unexplained chronic fatigue.

Drugs Many medications, drugs, drug withdrawal, and chronic alcohol use can all lead to fatigue. Medications that are more likely to be causative include antidepressants, antipsychotics, anxiolytics, opiates, antispasticity agents, antiseizure agents, and beta blockers.

Cardiovascular and Pulmonary Fatigue is one of the most taxing symptoms reported by patients with congestive heart failure and chronic obstructive pulmonary disease and negatively affects quality of life.

Malignancy Fatigue, particularly in association with unexplained weight loss, can be a sign of occult malignancy, but cancer is rarely identified in patients with unexplained chronic fatigue in the absence of other telltale signs or symptoms. Cancer-related fatigue is experienced by 40% of patients at the time of diagnosis and by >80% at some time in the disease course.

Hematologic Chronic or progressive anemia may present with fatigue, sometimes in association with exertional tachycardia and breathlessness. Anemia may also contribute to fatigue in chronic illness. Low serum ferritin in the absence of anemia may also cause fatigue that is reversible with iron replacement.

Systemic Inflammatory/Rheumatologic Disorders Fatigue is a prominent complaint in many chronic inflammatory disorders, including systemic lupus erythematosus, polymyalgia

rheumatica, rheumatoid arthritis, inflammatory bowel disease, antineutrophil cytoplasmic antibody (ANCA)—associated vasculitis, sarcoidosis, and Sjögren's syndrome, but is not usually an isolated symptom. Fatigue is also associated with primary immunodeficiency diseases.

Pregnancy Fatigue is very commonly reported by women during all stages of pregnancy and postpartum.

Disorders of Unclear Cause Chronic fatigue syndrome (Chap. 442) and fibromyalgia (Chap. 366) incorporate chronic fatigue as part of the syndromic definition when present in association with a number of other inclusion and exclusion criteria, as discussed in the respective chapters. Chronic multisymptom illness, also known as Gulf-War syndrome, is another symptom complex with prominent fatigue; it is most commonly, although not exclusively, observed in veterans of the 1991 Gulf war conflict (Chap. S6). Idiopathic chronic fatigue is used to describe the syndrome of unexplained chronic fatigue in the absence of enough additional clinical features to meet the diagnostic criteria for chronic fatigue syndrome.

APPROACH TO THE PATIENT

Fatigue

A detailed history focusing on the quality, pattern, time-course, associated symptoms, and alleviating factors of fatigue is critical to define the syndrome and help direct further evaluation and treatment. It is important to determine if fatigue is the appropriate designation, whether symptoms are acute or chronic, and if the impairment is primarily mental, physical, or a combination of the two. The review of systems should attempt to distinguish fatigue from excessive sleepiness, dyspnea on exertion, exercise intolerance, and muscle weakness. The presence of fever, chills, night sweats, or weight loss should raise suspicion for an occult infection or malignancy. A careful review of prescription, over-the-counter, herbal, and recreational drug and alcohol use is required. Circumstances surrounding the onset of symptoms and potential triggers should be investigated. The social history is important, with attention paid to life stressors, workhours, the social support network, and domestic affairs including a screen for intimate partner violence. Sleep habits and sleep hygiene should be questioned. The impact of fatigue on daily functioning is important to understand the patient's experience and gauge recovery and the success of treatment.

The physical examination of patients with fatigue is guided by the history and differential diagnosis. A detailed mental status examination should be performed with particular attention to symptoms of depression and anxiety. A formal neurologic examination is required to determine whether objective muscle weakness is present. This is usually a straightforward exercise, although occasionally patients with fatigue have difficulty sustaining effort against resistance and sometimes report that generating full power requires substantial mental effort. On confrontational testing, full power can be generated for only a brief period before the patient suddenly gives way to the examiner. This type of weakness is often referred to as *breakaway weakness* and may or may not be associated with pain. This is contrasted with weakness due to lesions in the motor tracts or lower motor unit, in which the patient's resistance can be overcome in a smooth and steady fashion and full power can never be generated. Occasionally, a patient may demonstrate fatigable weakness, in which power is full when first tested but becomes weak upon repeat evaluation without interval rest. Fatigable weakness, which usually indicates a problem of neuromuscular transmission, never has the sudden breakaway quality that one occasionally observes in patients with fatigue. If the presence or absence of muscle weakness cannot be determined with the physical examination, electromyography with nerve conductions studies can be a helpful ancillary test.

The general physical examination should screen for signs of cardiopulmonary disease, malignancy, lymphadenopathy, organomegaly, infection, liver failure, kidney disease, malnutrition, endocrine abnormalities, and connective tissue disease. In patients with associated widespread musculoskeletal pain, assessment of tender points may help to reveal fibromyalgia. Although the diagnostic yield of the general physical examination may be relatively low in the context of evaluation of unexplained chronic fatigue, elucidating the cause of only 2% of cases in one prospective analysis, the yield of a detailed neuropsychiatric and mental status evaluation is likely to be much higher, revealing a potential explanation for fatigue in up to 75–80% of patients in some series. Furthermore, a complete physical examination demonstrates a serious and systematic approach to the patient's complaint and helps build trust and a therapeutic alliance.

Laboratory testing is likely to identify the cause of chronic fatigue in only about 5% of cases. Beyond a few standard screening tests, laboratory evaluation should be guided by the history and physical examination; extensive testing is more likely to lead to false-positive results that require explanation and unnecessary follow-up investigation, and should be avoided in lieu of frequent clinical follow-up. A reasonable approach to screening includes a complete blood count with differential (to screen for anemia, infection, and malignancy), electrolytes (including sodium, potassium, and calcium), glucose, renal function, liver function, and thyroid function. Testing for HIV and adrenal function can also be considered. Published guidelines for chronic fatigue syndrome also recommend an erythrocyte sedimentation rate (ESR) as part of the evaluation for mimics, but unless the value is very high such nonspecific testing in the absence of other features is unlikely to clarify the situation. Routine screening with an antinuclear antibody (ANA) test is also unlikely to be informative in isolation and is frequently positive at low titers in otherwise healthy adults. Additional unfocused studies, such as whole-body imaging scans, are usually not indicated; in addition to their inconvenience, potential risk, and cost, they often reveal unrelated incidental findings that can prolong the workup unnecessarily.

TREATMENT

Fatigue

The first priority of treatment is to address the underlying disorder or disorders that account for fatigue, because this can be curative in select contexts and palliative in others. Unfortunately, in many chronic illnesses fatigue may be refractory to traditional disease-modifying therapies, but it is nevertheless important in such cases to evaluate for other potential contributors, because the cause may be multifactorial. Antidepressant treatment (Chap. 444) may be helpful for treatment of chronic fatigue when symptoms of depression are present and may be most effective as part of a multimodal approach. However, antidepressants can also cause fatigue and should be discontinued if they are not clearly effective. Cognitive-behavioral therapy has also been demonstrated to be helpful in the context of chronic fatigue syndrome as well as cancer-associated fatigue. Both cognitive behavioral therapy and graded exercise therapy, in which physical exercise, most typically walking, is gradually increased with attention to target heart rates to avoid overexertion, were shown to modestly improve walking times and self-reported fatigue measures when compared to standard medical care in patients in the United Kingdom with chronic fatigue. These benefits were maintained after a median follow-up of 2.5 years. Psychostimulants such as amphetamines, modafinil, and armodafinil can help increase alertness and concentration and reduce excessive daytime sleepiness in certain clinical contexts, which may in turn help with symptoms of fatigue in a minority of patients, but they have generally proven to be unhelpful in randomized trials for treating fatigue in posttraumatic brain injury, Parkinson's disease, cancer, and MS. In patients with low vitamin D status, vitamin D replacement may lead to improvement in fatigue.

Development of more effective therapy for fatigue is hampered by limited knowledge of the biologic basis of this symptom, including how fatigue is detected and registered in the nervous system. Proinflammatory cytokines, such as interleukin 1α and 1β, and

tumor necrosis factor α, might mediate fatigue in some patients. Preliminary data suggests that biological therapies that inhibit IL-1 or other cytokines can help to ameliorate fatigue in some patients with inflammatory conditions in addition to, or as part of, their disease modifying effect; thus, cytokine antagonists represent one possible future approach.

PROGNOSIS

Acute fatigue significant enough to require medical evaluation is more likely to lead to an identifiable medical, neurologic, or psychiatric cause than unexplained chronic fatigue. Evaluation of unexplained chronic fatigue most commonly leads to diagnosis of a psychiatric condition or remains unexplained. Identification of a previously undiagnosed serious or life-threatening culprit etiology is rare on longitudinal follow-up in patients with unexplained chronic fatigue. Complete resolution of unexplained chronic fatigue is uncommon, at least over the short term, but multidisciplinary treatment approaches can lead to symptomatic improvements that can substantially improve quality of life.

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21 Neurologic Causes of Weakness and Paralysis

Michael J. Aminoff

Normal motor function involves integrated muscle activity that is modulated by the activity of the cerebral cortex, basal ganglia, cerebellum, red nucleus, brainstem reticular formation, lateral vestibular nucleus, and spinal cord. Motor system dysfunction leads to weakness or paralysis, discussed in this chapter, or to ataxia **(Chap. 431)** or abnormal movements **(Chap. 428)**. *Weakness* is a reduction in the power that can be exerted by one or more muscles. It must be distinguished from increased *fatigability* (i.e., the inability to sustain the performance of an activity that should be normal for a person of the same age, sex, and size), limitation in function due to pain or articular stiffness, or impaired motor activity because severe *proprioceptive sensory loss* prevents adequate feedback information about the direction and power of movements. It is also distinct from *bradykinesia* (in which increased time is required for full power to be exerted) and *apraxia*, a disorder of planning and initiating a skilled or learned movement unrelated to a significant motor or sensory deficit **(Chap. 26)**.

Paralysis or the suffix "-plegia" indicates weakness so severe that a muscle cannot be contracted at all, whereas *paresis* refers to less severe weakness. The prefix "hemi-" refers to one-half of the body, "para-" to both legs, and "quadri-" to all four limbs.

The *distribution* of weakness helps to localize the underlying lesion. Weakness from involvement of upper motor neurons occurs particularly in the extensors and abductors of the upper limb and the flexors of the lower limb. Lower motor neuron weakness depends on whether involvement is at the level of the anterior horn cells, nerve root, limb plexus, or peripheral nerve—only muscles supplied by the affected structure are weak. Myopathic weakness is generally most marked in proximal muscles. Weakness from impaired neuromuscular transmission has no specific pattern of involvement.

Weakness often is accompanied by other neurologic abnormalities that help indicate the site of the responsible lesion **(Table 21-1)**.

Tone is the resistance of a muscle to passive stretch. Increased tone may be of several types. *Spasticity* is the increase in tone associated with disease of upper motor neurons. It is velocity-dependent, has a sudden release after reaching a maximum (the "clasp-knife" phenomenon), and predominantly affects the antigravity muscles (i.e., upper-limb flexors and lower-limb extensors). *Rigidity* is hypertonia that is present throughout the range of motion (a "lead pipe" or "plastic" stiffness) and affects flexors and extensors equally; it sometimes has a cogwheel quality that is enhanced by voluntary movement of the contralateral limb (reinforcement). Rigidity occurs with certain extrapyramidal disorders, such as Parkinson's disease. *Paratonia* (or *gegenhalten*) is increased tone that varies irregularly in a manner seemingly related to the degree of relaxation, is present throughout the range of motion, and affects flexors and extensors equally; it usually results from disease of the frontal lobes. Weakness with *decreased tone* (*flaccidity*) or normal tone occurs with disorders of *motor units*. A motor unit consists of a single lower motor neuron and all the muscle fibers that it innervates.

Muscle bulk generally is not affected by upper motor neuron lesions, although mild disuse atrophy eventually may occur. By contrast, atrophy is often conspicuous when a lower motor neuron lesion is responsible for weakness and also may occur with advanced muscle disease.

Muscle stretch (tendon) reflexes are usually increased with upper motor neuron lesions, but may be decreased or absent for a variable period immediately after onset of an acute lesion. Hyperreflexia is usually—but not invariably—accompanied by loss of *cutaneous reflexes* (such as superficial abdominals; **Chap. 415**) and, in particular, by an extensor plantar (Babinski) response. The muscle stretch reflexes are depressed with lower motor neuron lesions directly involving specific reflex arcs. They generally are preserved in patients with myopathic weakness except in advanced stages, when they sometimes are attenuated. In disorders of the neuromuscular junction, reflex responses may be affected by preceding voluntary activity of affected muscles; such activity may lead to enhancement of initially depressed reflexes in Lambert-Eaton myasthenic syndrome and, conversely, to depression of initially normal reflexes in myasthenia gravis **(Chap. 440)**.

The distinction of *neuropathic* (lower motor neuron) from *myopathic* weakness is sometimes difficult clinically, although distal weakness is likely to be neuropathic, and symmetric proximal weakness myopathic. *Fasciculations* (visible or palpable twitch within a muscle due to the

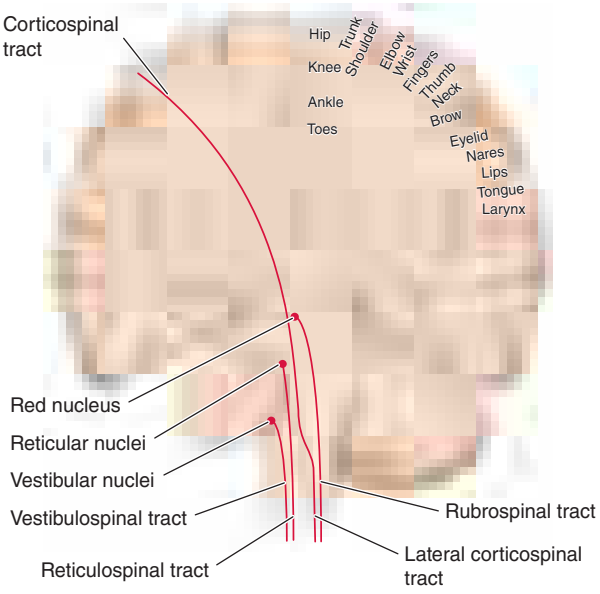
TABLE 21-1 Signs That Distinguish the Origin of Weakness

SIGN	UPPER MOTOR NEURON	LOWER MOTOR NEURON	MYOPATHIC	PSYCHOGENIC
Atrophy	None	Severe	Mild	None
Fasciculations	None	Common	None	None
Tone	Spastic	Decreased	Normal/decreased	Variable/paratonia
Distribution of weakness	Pyramidal/regional	Distal/segmental	Proximal	Variable/inconsistent with daily activities
Muscle stretch reflexes	Hyperactive	Hypoactive/absent	Normal/hypoactive	Normal
Babinski sign	Present	Absent	Absent	Absent

spontaneous discharge of a motor unit) and early atrophy indicate that weakness is neuropathic.

PATHOGENESIS

Upper Motor Neuron Weakness Lesions of the upper motor neurons or their descending axons to the spinal cord (Fig. 21-1) produce weakness through decreased activation of lower motor neurons.



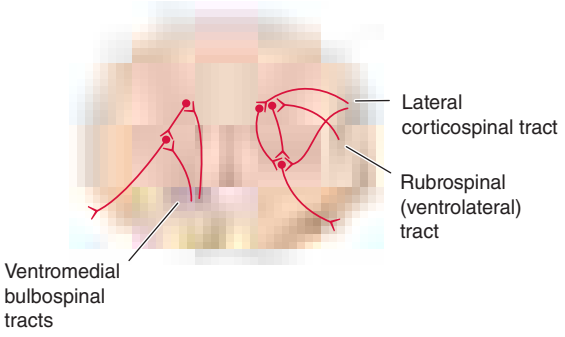


FIGURE 21-1 The corticospinal and bulbospinal upper motor neuron pathways. Upper motor neurons have their cell bodies in layer V of the primary motor cortex (the precentral gyrus, or Brodmann's area 4) and in the premotor and supplemental motor cortex (area 6). The upper motor neurons in the primary motor cortex are somatotopically organized (right side of figure). Axons of the upper motor neurons descend through the subcortical white matter and the posterior limb of the internal capsule. Axons of the *pyramidal* or *corticospinal system* descend through the brainstem in the cerebral peduncle of the midbrain, the basis pontis, and the medullary pyramids. At the cervicomedullary junction, most corticospinal axons decussate into the contralateral corticospinal tract of the lateral spinal cord, but 10–30% remain ipsilateral in the anterior spinal cord. Corticospinal neurons synapse on premotor interneurons, but some—especially in the cervical enlargement and those connecting with motor neurons to distal limb muscles—make direct monosynaptic connections with lower motor neurons. They innervate most densely the lower motor neurons of hand muscles and are involved in the execution of learned, fine movements. Corticobulbar neurons are similar to corticospinal neurons but innervate brainstem motor nuclei. *Bulbospinal upper motor neurons* influence strength and tone but are not part of the pyramidal system. The descending *ventromedial bulbospinal pathways* originate in the tectum of the midbrain (tectospinal pathway), the vestibular nuclei (vestibulospinal pathway), and the reticular formation (reticulospinal pathway). These pathways influence axial and proximal muscles and are involved in the maintenance of posture and integrated movements of the limbs and trunk. The descending *ventrolateral bulbospinal pathways*, which originate predominantly in the red nucleus (rubrospinal pathway), facilitate distal limb muscles. The bulbospinal system sometimes is referred to as the *extrapyramidal upper motor neuron system*. In all figures, nerve cell bodies and axon terminals are shown, respectively, as closed circles and forks.

In general, distal muscle groups are affected more severely than proximal ones, and axial movements are spared unless the lesion is severe and bilateral. Spasticity is typical but may not be present acutely. Rapid repetitive movements are slowed and coarse, but normal rhythmicity is maintained. With corticobulbar involvement, weakness occurs in the lower face and tongue; extraocular, upper facial, pharyngeal, and jaw muscles are typically spared. Bilateral corticobulbar lesions produce a *pseudobulbar palsy*: dysarthria, dysphagia, dysphonia, and emotional lability accompany bilateral facial weakness and a brisk jaw jerk. Electromyogram (EMG) (Chap. 438) shows that with weakness of the upper motor neuron type, motor units have a diminished maximal discharge frequency.

Lower Motor Neuron Weakness This pattern results from disorders of lower motor neurons in the brainstem motor nuclei and the anterior horn of the spinal cord or from dysfunction of the axons of these neurons as they pass to skeletal muscle (Fig. 21-2). Weakness is due to a decrease in the number of muscle fibers that can be activated through a loss of α motor neurons or disruption of their connections to muscle. Loss of γ motor neurons does not cause weakness but decreases tension on the muscle spindles, which decreases muscle tone and attenuates the stretch reflexes. An absent stretch reflex suggests involvement of spindle afferent fibers.

When a motor unit becomes diseased, especially in anterior horn cell diseases, it may discharge spontaneously, producing *fasciculations*. When α motor neurons or their axons degenerate, the denervated muscle fibers also may discharge spontaneously. These single muscle fiber discharges, or *fibrillation potentials*, cannot be seen but can be recorded with EMG. Weakness leads to delayed or reduced recruitment of motor units, with fewer than normal activated at a particular discharge frequency.

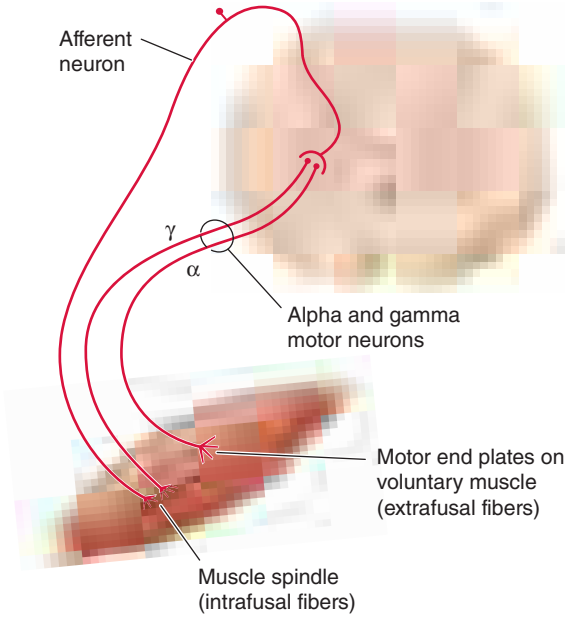


FIGURE 21-2 Lower motor neurons are divided into α and γ types. The larger α motor neurons are more numerous and innervate the extrafusal muscle fibers of the motor unit. Loss of α motor neurons or disruption of their axons produces lower motor neuron weakness. The smaller, less numerous γ motor neurons innervate the intrafusal muscle fibers of the muscle spindle and contribute to normal tone and stretch reflexes. The α motor neuron receives direct excitatory input from corticomotoneurons and primary muscle spindle afferents. The α and γ motor neurons also receive excitatory input from other descending upper motor neuron pathways, segmental sensory inputs, and interneurons. The α motor neurons receive direct inhibition from Renshaw cell interneurons, and other interneurons indirectly inhibit the α and γ motor neurons. A muscle stretch (tendon) reflex requires the function of all the illustrated structures. A tap on a tendon stretches muscle spindles (which are tonically activated by γ motor neurons) and activates the primary spindle afferent neurons. These neurons stimulate the α motor neurons in the spinal cord, producing a brief muscle contraction, which is the familiar tendon reflex.

Neuromuscular Junction Weakness Disorders of the neuromuscular junctions produce weakness of variable degree and distribution. The number of muscle fibers that are activated varies over time, depending on the state of rest of the neuromuscular junctions. Strength is influenced by preceding activity of the affected muscle. In myasthenia gravis, for example, sustained or repeated contractions of affected muscle decline in strength despite continuing effort (Chap. 440). Thus, fatigable weakness is suggestive of disorders of the neuromuscular junction, which cause functional loss of muscle fibers due to failure of their activation.

Myopathic Weakness Myopathic weakness is produced by a decrease in the number or contractile force of muscle fibers activated within motor units. With muscular dystrophies, inflammatory myopathies, or myopathies with muscle fiber necrosis, the number of muscle fibers is reduced within many motor units. On EMG, the size of each motor unit action potential is decreased, and motor units must be recruited more rapidly than normal to produce the desired power. Some myopathies produce weakness through loss of contractile force of muscle fibers or through relatively selective involvement of type II (fast) fibers. These myopathies may not affect the size of individual motor unit action potentials and are detected by a discrepancy between the electrical activity and force of a muscle.

Psychogenic Weakness Weakness may occur without a recognizable organic basis. It tends to be variable, inconsistent, and with a pattern of distribution that cannot be explained on a neuroanatomic basis. On formal testing, antagonists may contract when the patient is supposedly activating the agonist muscle. The severity of weakness is out of keeping with the patient's daily activities.

DISTRIBUTION OF WEAKNESS

Hemiparesis Hemiparesis results from an upper motor neuron lesion above the midcervical spinal cord; most such lesions are above the foramen magnum. The presence of other neurologic deficits helps localize the lesion. Thus, language disorders, for example, point to a cortical lesion. Homonymous visual field defects reflect either a cortical or a subcortical hemispheric lesion. A "pure motor" hemiparesis of the face, arm, and leg often is due to a small, discrete lesion in the posterior limb of the internal capsule, cerebral peduncle in the midbrain, or upper pons. Some brainstem lesions produce "crossed paralyses," consisting of ipsilateral cranial nerve signs and contralateral hemiparesis (Chap. 419). The absence of cranial nerve signs or facial weakness suggests that a hemiparesis is due to a lesion in the high cervical spinal cord, especially if associated with the Brown-Séquard syndrome (Chap. 434).

Acute or episodic hemiparesis usually results from focal structural lesions, particularly rapidly expanding lesions, or an inflammatory process. *Subacute hemiparesis* that evolves over days or weeks may relate to subdural hematoma, infectious or inflammatory disorders (e.g., cerebral abscess, fungal granuloma or meningitis, parasitic infection, multiple sclerosis, sarcoidosis), or primary or metastatic neoplasms. AIDS may present with subacute hemiparesis due to toxoplasmosis or primary central nervous system (CNS) lymphoma. *Chronic hemiparesis* that evolves over months usually is due to a neoplasm or vascular malformation, a chronic subdural hematoma, or a degenerative disease.

Investigation of hemiparesis (Fig. 21-3) of acute origin starts with a computed tomography (CT) scan of the brain and laboratory studies. If the CT is normal, or in subacute or chronic cases of hemiparesis, magnetic resonance imaging (MRI) of the brain and/or cervical spine (including the foramen magnum) is performed, depending on the clinical accompaniments.

Paraparesis *Acute paraparesis* is caused most commonly by an intraspinal lesion, but its spinal origin may not be recognized initially if the legs are flaccid and areflexic. Usually, however, there is sensory loss in the legs with an upper level on the trunk, a dissociated sensory loss suggestive of a central cord syndrome (Chap. 434), or hyperreflexia in the legs with normal reflexes in the arms. Imaging the spinal cord (Fig. 21-3) may reveal compressive lesions, infarction (proprioception usually is spared), arteriovenous fistulas or other vascular anomalies, or transverse myelitis (Chap. 434).

Diseases of the cerebral hemispheres that produce acute paraparesis include anterior cerebral artery ischemia (shoulder shrug also is affected), superior sagittal sinus or cortical venous thrombosis, and acute hydrocephalus.

Paraparesis may result from a cauda equina syndrome, for example, after trauma to the low back, a midline disk herniation, or an intraspinal tumor. The sphincters are commonly affected, whereas hip flexion often is spared, as is sensation over the anterolateral thighs. Rarely, paraparesis is caused by a rapidly evolving anterior horn cell disease (such as poliovirus or West Nile virus infection), peripheral neuropathy (such as Guillain-Barré syndrome; Chap. 439), or myopathy (Chap. 441).

Subacute or chronic spastic paraparesis is caused by upper motor neuron disease. When associated with lower-limb sensory loss and sphincter involvement, a chronic spinal cord disorder should be considered (Chap. 434). If hemispheric signs are present, a parasagittal meningioma or chronic hydrocephalus is likely. The absence of spasticity in a long-standing paraparesis suggests a lower motor neuron or myopathic etiology.

Investigations typically begin with spinal MRI, but when upper motor neuron signs are associated with drowsiness, confusion, seizures, or other hemispheric

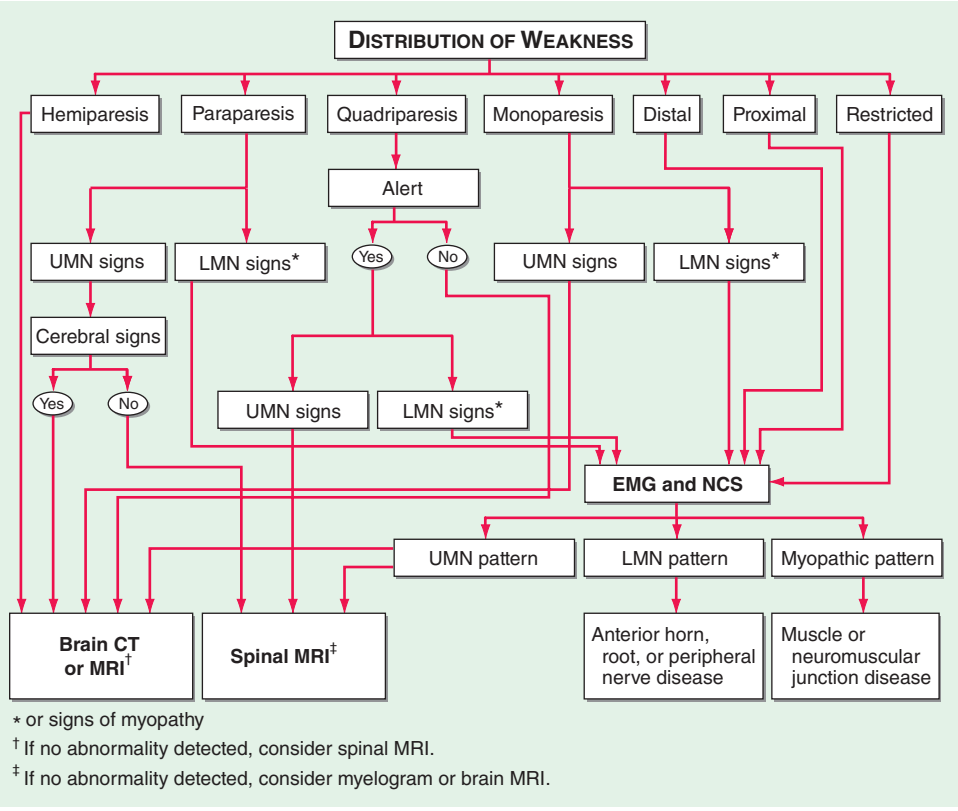


FIGURE 21-3 An algorithm for the initial workup of a patient with weakness. CT, computed tomography; EMG, electromyography; LMN, lower motor neuron; MRI, magnetic resonance imaging; NCS, nerve conduction studies; UMN, upper motor neuron.

TABLE 21-2 Causes of Episodic Generalized Weakness

1. Electrolyte disturbances, e.g., hypokalemia, hyperkalemia, hypercalcemia, hypernatremia, hyponatremia, hypophosphatemia, hypermagnesemia
2. Muscle disorders
   a. Channelopathies (periodic paralyses)
   b. Metabolic defects of muscle (impaired carbohydrate or fatty acid utilization; abnormal mitochondrial function)
3. Neuromuscular junction disorders
   a. Myasthenia gravis
   b. Lambert-Eaton myasthenic syndrome
4. Central nervous system disorders
   a. Transient ischemic attacks of the brainstem
   b. Transient global cerebral ischemia
   c. Multiple sclerosis
5. Lack of voluntary effort
   a. Anxiety
   b. Pain or discomfort
   c. Somatization disorder

signs, brain MRI should also be performed, sometimes as the initial investigation. Electrophysiologic studies are diagnostically helpful when clinical findings suggest an underlying neuromuscular disorder.

Quadriparesis or Generalized Weakness Generalized weakness may be due to disorders of the CNS or the motor unit. Although the terms often are used interchangeably, *quadriparesis* is commonly used when an upper motor neuron cause is suspected, and *generalized weakness* is used when a disease of the motor units is likely. Weakness from CNS disorders usually is associated with changes in consciousness or cognition and accompanied by spasticity, hyperreflexia, and sensory disturbances. Most neuromuscular causes of generalized weakness are associated with normal mental function, hypotonia, and hypoactive muscle stretch reflexes. The major causes of intermittent weakness are listed in Table 21-2. A patient with generalized fatigability without objective weakness may have the chronic fatigue syndrome (Chap. 442).

ACUTE QUADRIPARESIS Quadriparesis with onset over minutes may result from disorders of upper motor neurons (such as from anoxia, hypotension, brainstem or cervical cord ischemia, trauma, and systemic metabolic abnormalities) or muscle (electrolyte disturbances, certain inborn errors of muscle energy metabolism, toxins, and periodic paralyses). Onset over hours to weeks may, in addition to these disorders, be due to lower motor neuron disorders such as Guillain-Barré syndrome (Chap. 439).

In obtunded patients, evaluation begins with a CT scan of the brain. If upper motor neuron signs are present but the patient is alert, the initial test is usually an MRI of the cervical cord. If weakness is lower motor neuron, myopathic, or uncertain in origin, the clinical approach begins with blood studies to determine the level of muscle enzymes and electrolytes and with EMG and nerve conduction studies.

SUBACUTE OR CHRONIC QUADRIPARESIS Quadriparesis due to upper motor neuron disease may develop over weeks to years from chronic myelopathies, multiple sclerosis, brain or spinal tumors, chronic subdural hematomas, and various metabolic, toxic, and infectious disorders. It may also result from lower motor neuron disease, a chronic neuropathy (in which weakness is often most profound distally), or myopathic weakness (typically proximal).

When *quadriparesis* develops acutely in obtunded patients, evaluation begins with a CT scan of the brain. If upper motor neuron signs have developed acutely but the patient is alert, the initial test is usually an MRI of the cervical cord. When onset has been gradual, disorders of the cerebral hemispheres, brainstem, and cervical spinal cord can usually be distinguished clinically, and imaging is directed first at the clinically suspected site of pathology. If weakness is lower motor neuron, myopathic, or uncertain in origin, laboratory studies to determine the levels of muscle enzymes and electrolytes, and EMG and nerve conduction studies help to localize the pathologic process.

Monoparesis Monoparesis usually is due to lower motor neuron disease, with or without associated sensory involvement. Upper motor neuron weakness occasionally presents as a monoparesis of distal and nonantigravity muscles. Myopathic weakness rarely is limited to one limb.

ACUTE MONOPARESIS If weakness is predominantly distal and of upper motor neuron type and is not associated with sensory impairment or pain, focal cortical ischemia is likely (Chap. 420); diagnostic possibilities are similar to those for acute hemiparesis. Sensory loss and pain usually accompany acute lower motor neuron weakness; the weakness commonly localizes to a single nerve root or peripheral nerve, but occasionally reflects plexus involvement. If lower motor neuron weakness is likely, evaluation begins with EMG and nerve conduction studies.

SUBACUTE OR CHRONIC MONOPARESIS Weakness and atrophy that develop over weeks or months are usually of lower motor neuron origin. When associated with sensory symptoms, a peripheral cause (nerve, root, or plexus) is likely; otherwise, anterior horn cell disease should be considered. In either case, an electrodiagnostic study is indicated. If weakness is of the upper motor neuron type, a discrete cortical (precentral gyrus) or cord lesion may be responsible, and appropriate imaging is performed.

Distal Weakness Involvement of two or more limbs distally suggests lower motor neuron or peripheral nerve disease. Acute distal lower-limb weakness results occasionally from an acute toxic polyneuropathy or cauda equina syndrome. Distal symmetric weakness usually develops over weeks, months, or years and, when associated with numbness, is due to peripheral neuropathy (Chap. 438). Anterior horn cell disease may begin distally but is typically asymmetric and without accompanying numbness (Chap. 429). Rarely, myopathies present with distal weakness (Chap. 441). Electrodiagnostic studies help localize the disorder (Fig. 21-3).

Proximal Weakness Myopathy often produces symmetric weakness of the pelvic or shoulder girdle muscles (Chap. 441). Diseases of the neuromuscular junction, such as myasthenia gravis (Chap. 440), may present with symmetric proximal weakness often associated with ptosis, diplopia, or bulbar weakness and fluctuating in severity during the day. In anterior horn cell disease, proximal weakness is usually asymmetric, but it may be symmetric if familial. Numbness does not occur with any of these diseases. The evaluation usually begins with determination of the serum creatine kinase level and electrophysiologic studies.

Weakness in a Restricted Distribution Weakness may not fit any of these patterns, being limited, for example, to the extraocular, hemifacial, bulbar, or respiratory muscles. If it is unilateral, restricted weakness usually is due to lower motor neuron or peripheral nerve disease, such as in a facial palsy. Weakness of part of a limb is commonly due to a peripheral nerve lesion such as an entrapment neuropathy. Relatively symmetric weakness of extraocular or bulbar muscles frequently is due to a myopathy (Chap. 441) or neuromuscular junction disorder (Chap. 440). Bilateral facial palsy with areflexia suggests Guillain-Barré syndrome (Chap. 439). Worsening of relatively symmetric weakness with fatigue is characteristic of neuromuscular junction disorders. Asymmetric bulbar weakness usually is due to motor neuron disease. Weakness limited to respiratory muscles is uncommon and usually is due to motor neuron disease, myasthenia gravis, or polymyositis/dermatomyositis (Chap. 358).

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22 Numbness, Tingling, and Sensory Loss

Michael J. Aminoff

Normal somatic sensation reflects a continuous monitoring process, little of which reaches consciousness under ordinary conditions. By contrast, disordered sensation, particularly when experienced as painful, is alarming and dominates the patient's attention. Physicians should be able to recognize abnormal sensations by how they are described, know their type and likely site of origin, and understand their implications. **Pain is considered separately in Chap. 10.**

POSITIVE AND NEGATIVE SYMPTOMS

Abnormal sensory symptoms can be divided into two categories: positive and negative. The prototypical positive symptom is tingling (pins and needles); other positive sensory phenomena include itch and altered sensations that are described as pricking, bandlike, lightning-like shooting feelings (lancinations), aching, knifelike, twisting, drawing, pulling, tightening, burning, searing, electrical, or raw feelings. Such symptoms are often painful.

Positive phenomena usually result from trains of impulses generated at sites of lowered threshold or heightened excitability along a peripheral or central sensory pathway. The nature and severity of the abnormal sensation depend on the number, rate, timing, and distribution of ectopic impulses and the type and function of nervous tissue in which they arise. Because positive phenomena represent excessive activity in sensory pathways, they are not necessarily associated with a sensory deficit (loss) on examination.

Negative phenomena represent loss of sensory function and are characterized by diminished or absent feeling that often is experienced as numbness and by abnormal findings on sensory examination. In disorders affecting peripheral sensation, at least one-half the afferent axons innervating a particular site are probably lost or functionless before a sensory deficit can be demonstrated by clinical examination. If the rate of loss is slow, however, lack of cutaneous feeling may be unnoticed by the patient and difficult to demonstrate on examination, even though few sensory fibers are functioning; if it is rapid, both positive and negative phenomena are usually conspicuous. Subclinical degrees of sensory dysfunction may be revealed by sensory nerve conduction studies or somatosensory-evoked potentials.

Whereas sensory symptoms may be either positive or negative, sensory signs on examination are always a measure of negative phenomena.

TERMINOLOGY

Paresthesias and dysesthesias are general terms used to denote positive sensory symptoms. The term *paresthesias* typically refers to tingling or pins-and-needles sensations but may include a wide variety of other abnormal sensations, except pain; it sometimes implies that the abnormal sensations are perceived spontaneously. The more general term *dysesthesias* denotes all types of abnormal sensations, including painful ones, regardless of whether a stimulus is evident.

Another set of terms refers to sensory abnormalities found on examination. *Hypesthesia* or *hypoesthesia* refers to a reduction of cutaneous sensation to a specific type of testing such as pressure, light touch, and warm or cold stimuli; *anesthesia,* to a complete absence of skin sensation to the same stimuli plus pinprick; and *hypalgesia* or *analgesia,* to reduced or absent pain perception (nociception). *Hyperesthesia* means pain or increased sensitivity in response to touch. Similarly, *allodynia* describes the situation in which a nonpainful stimulus, once perceived, is experienced as painful, even excruciating. An example is elicitation of a painful sensation by application of a vibrating tuning fork. *Hyperalgesia* denotes severe pain in response to a mildly noxious stimulus, and *hyperpathia*, a broad term, encompasses all the phenomena described by hyperesthesia, allodynia, and hyperalgesia. With hyperpathia, the threshold for a sensory stimulus is increased and perception is delayed, but once felt, it is unduly painful.

Disorders of deep sensation arising from muscle spindles, tendons, and joints affect proprioception (position sense). Manifestations include imbalance (particularly with eyes closed or in the dark), clumsiness of precision movements, and unsteadiness of gait, which are referred to collectively as *sensory ataxia*. Other findings on examination usually, but not invariably, include reduced or absent joint position and vibratory sensibility and absent deep tendon reflexes in the affected limbs. The Romberg sign is positive, which means that the patient sways markedly or topples when asked to stand with feet close together and eyes closed. In severe states of deafferentation involving deep sensation, the patient cannot walk or stand unaided or even sit unsupported. Continuous involuntary movements (*pseudoathetosis*) of the outstretched hands and fingers occur, particularly with eyes closed.

ANATOMY OF SENSATION

Cutaneous receptors are classified by the type of stimulus that optimally excites them. They consist of naked nerve endings (nociceptors, which respond to tissue-damaging stimuli, and thermoreceptors, which respond to noninjurious thermal stimuli) and encapsulated terminals (several types of mechanoreceptor, activated by physical deformation of the skin). Each type of receptor has its own set of sensitivities to specific stimuli, size and distinctness of receptive fields, and adaptational qualities.

Afferent fibers in peripheral nerve trunks traverse the dorsal roots and enter the dorsal horn of the spinal cord **(Fig. 22-1)**. From there, the polysynaptic projections of the smaller fibers (unmyelinated and small myelinated), which subserve mainly nociception, itch, temperature sensibility, and touch, cross and ascend in the opposite anterior and lateral columns of the spinal cord, through the brainstem, to the ventral posterolateral (VPL) nucleus of the thalamus and ultimately project to the postcentral gyrus of the parietal cortex and other cortical areas **(Chap. 10)**. This is the *spinothalamic pathway* or *anterolateral system*. The larger fibers, which subserve tactile and position sense and kinesthesia, project rostrally in the posterior and posterolateral columns on the same side of the spinal cord and make their first synapse in the gracile or cuneate nucleus of the lower medulla. Axons of second-order neurons decussate and ascend in the medial lemniscus located medially in the medulla and in the tegmentum of the pons and midbrain and synapse in the VPL nucleus; third-order neurons project to parietal cortex as well as to other cortical areas. This large-fiber system is referred to as the *posterior column–medial lemniscal pathway* (lemniscal, for short). Although the fiber types and functions that make up the spinothalamic and lemniscal systems are relatively well known, many other fibers, particularly those associated with touch, pressure, and position sense, ascend in a diffusely distributed pattern both ipsilaterally and contralaterally in the anterolateral quadrants of the spinal cord. This explains why a complete lesion of the posterior columns of the spinal cord may be associated with little sensory deficit on examination.

Nerve conduction studies and nerve biopsy are important means of investigating the peripheral nervous system, but they do not evaluate the function or structure of cutaneous receptors and free nerve endings or of unmyelinated or thinly myelinated nerve fibers in the nerve trunks. Skin biopsy can be used to evaluate these structures in the dermis and epidermis.

CLINICAL EXAMINATION OF SENSATION

The main components of the sensory examination are tests of primary sensation (pain, touch, vibration, joint position, and thermal sensation) **(Table 22-1)**. The examiner must depend on patient responses, and this complicates interpretation. Further, examination may be limited in some patients. In a stuporous patient, for example, sensory examination is reduced to observing the briskness of withdrawal in response to a pinch or another noxious stimulus. Comparison of responses on the two sides of the body is essential. In an alert but uncooperative patient, it may not be possible to examine cutaneous sensation, but some idea of proprioceptive function may be gained by noting the patient's best performance of movements requiring balance and precision.

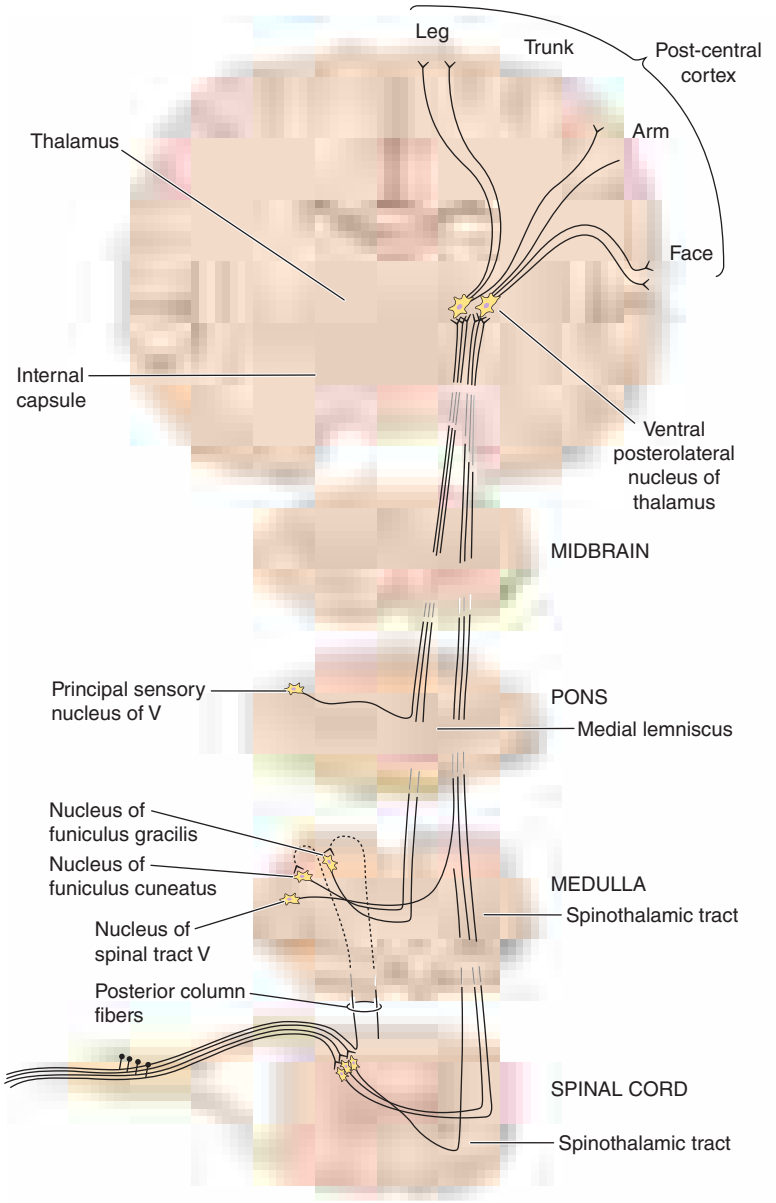

FIGURE 22-1 The main somatosensory pathways. The spinothalamic tract (pain, thermal sense) and the posterior column–lemniscal system (touch, pressure, joint position) are shown. Offshoots from the ascending anterolateral fasciculus (spinothalamic tract) to nuclei in the medulla, pons, and mesencephalon and nuclear terminations of the tract are indicated. *(From AH Ropper, MA Samuels: Adams and Victor's Principles of Neurology, 9th ed. New York, McGraw-Hill, 2009.)*

In patients with sensory complaints, testing should begin in the center of the affected region and proceed radially until sensation is perceived as normal. The distribution of any abnormality is defined and compared to root and peripheral nerve territories **(Figs. 22-2 and 22-3)**.

Some patients present with sensory symptoms that do not fit an anatomic localization and are accompanied by either no abnormalities or gross inconsistencies on examination. The examiner should consider whether the sensory symptoms are a disguised request for help with psychologic or situational problems. Sensory examination of a patient who has no neurologic complaints can be brief and consist of pinprick, touch, and vibration testing in the hands and feet plus evaluation of stance and gait, including the Romberg maneuver **(Chap. V6)**. Evaluation of stance and gait also tests the integrity of motor and cerebellar systems.

Primary Sensation The sense of pain usually is tested with a clean pin, which is then discarded. The patient is asked to close the eyes and focus on the pricking or unpleasant quality of the stimulus, not just the pressure or touch sensation elicited. Areas of hypalgesia should be mapped by proceeding radially from the most hypalgesic site. Temperature sensation to both hot and cold is best tested with small containers filled with water of the desired temperature. An alternative way to test cold sensation is to touch a metal object, such as a tuning fork at room temperature, to the skin. For testing warm temperatures, the tuning fork or another metal object may be held under warm water of the desired temperature and then used. The appreciation of both cold and warmth should be tested because different receptors respond to each. Touch usually is tested with a wisp of cotton or a fine camel hair brush, minimizing pressure on the skin. In general, it is better to avoid testing touch on hairy skin because of the profusion of the sensory endings that surround each hair follicle. The patient is tested with the eyes closed and should indicate as soon as the stimulus is perceived, indicating its location.

Joint position testing is a measure of proprioception. With the patient's eyes closed, joint position is tested in the distal interphalangeal joint of the great toe and fingers. The digit is held by its sides, distal to the joint being tested, and moved passively while more proximal joints are stabilized—the patient indicates the change in position or direction of movement. If errors are made, more proximal joints are tested. A test of proximal joint position sense, primarily at the shoulder, is performed by asking the patient to bring the two index fingers together with arms extended and eyes closed. Normal individuals can do this accurately, with errors of 1 cm or less.

The sense of vibration is tested with an oscillating tuning fork that vibrates at 128 Hz. Vibration is tested over bony points, beginning distally; in the feet, it is tested over the dorsal surface of the distal phalanx of the big toes and at the malleoli of the ankles, and in the hands, it is tested dorsally at the distal phalanx of the fingers. If abnormalities are found, more proximal sites should be examined. Vibratory thresholds at the same site in the patient and the examiner may be compared for control purposes.

TABLE 22-1 Testing Primary Sensation

SENSE	TEST DEVICE	ENDINGS ACTIVATED	FIBER SIZE MEDIATING	CENTRAL PATHWAY
Pain	Pinprick	Cutaneous nociceptors	Small	SpTh, also D
Temperature, heat	Warm metal object	Cutaneous thermoreceptors for hot	Small	SpTh
Temperature, cold	Cold metal object	Cutaneous thermoreceptors for cold	Small	SpTh
Touch	Cotton wisp, fine brush	Cutaneous mechanoreceptors, also naked endings	Large and small	Lem, also D and SpTh
Vibration	Tuning fork, 128 Hz	Mechanoreceptors, especially pacinian corpuscles	Large	Lem, also D
Joint position	Passive movement of specific joints	Joint capsule and tendon endings, muscle spindles	Large	Lem, also D

Abbreviations: D, diffuse ascending projections in ipsilateral and contralateral anterolateral columns; Lem, posterior column and lemniscal projection, ipsilateral; SpTh, spinothalamic projection, contralateral.

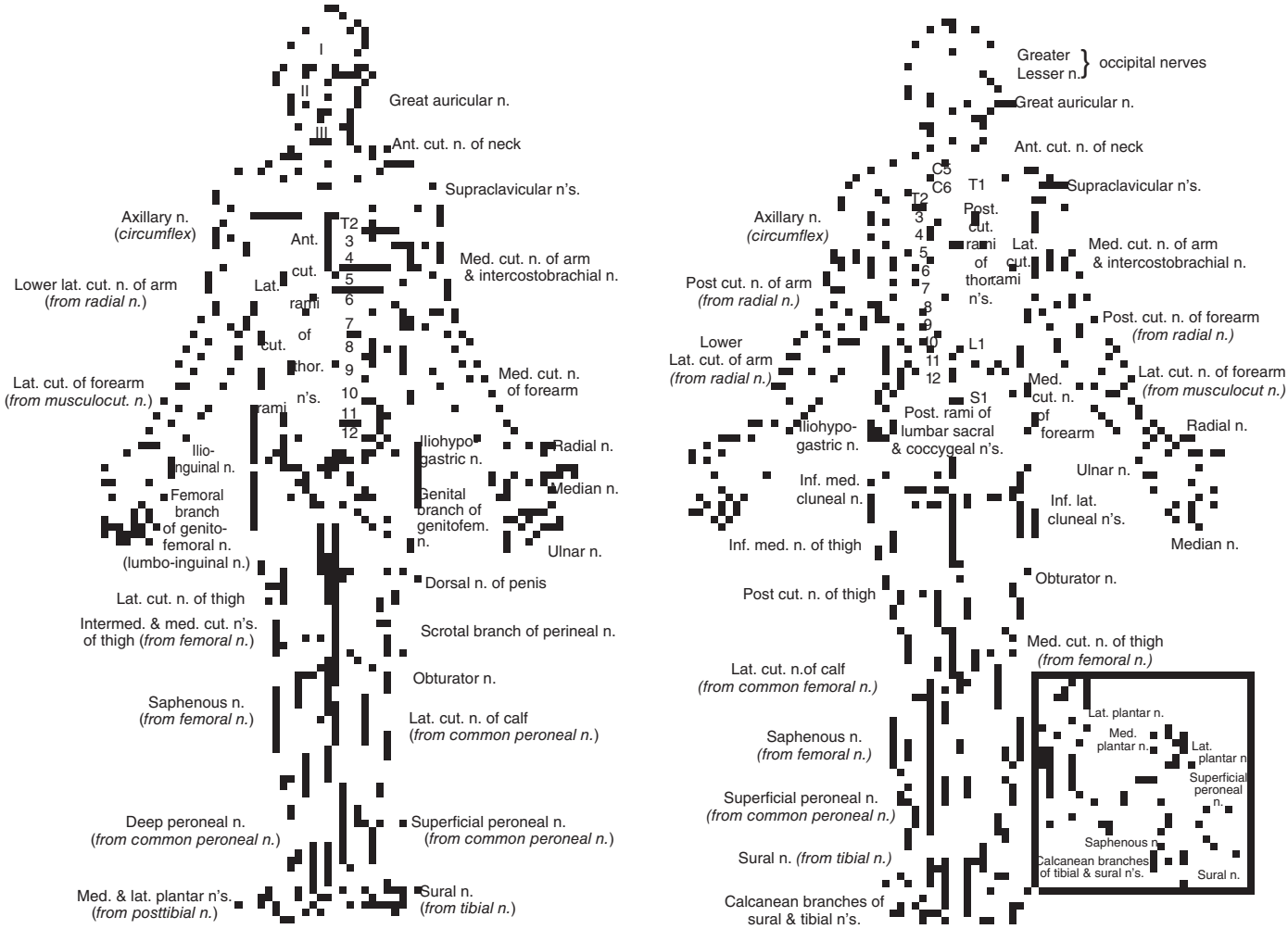

FIGURE 22-2 The cutaneous fields of peripheral nerves. *(Reproduced by permission from W Haymaker, B Woodhall: Peripheral Nerve Injuries, 2nd ed. Philadelphia, Saunders, 1953.)*

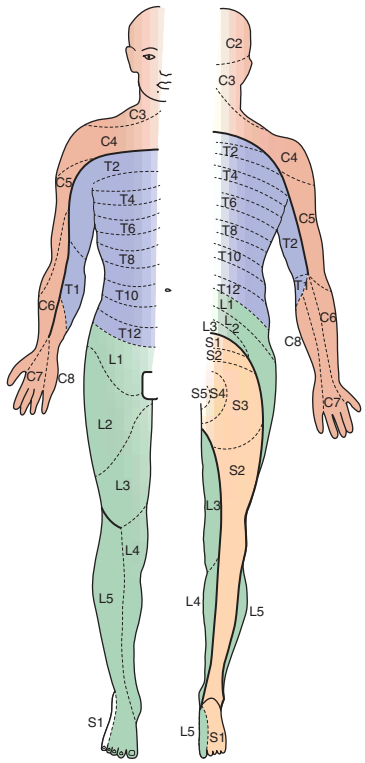

FIGURE 22-3 Distribution of the sensory spinal roots on the surface of the body (dermatomes). *(From D Sinclair: Mechanisms of Cutaneous Sensation. Oxford, UK, Oxford University Press, 1981; with permission from Dr. David Sinclair.)*

Quantitative Sensory Testing Effective sensory testing devices are commercially available. Quantitative sensory testing is particularly useful for serial evaluation of cutaneous sensation in clinical trials. Threshold testing for touch and vibratory and thermal sensation is the most widely used application.

Cortical Sensation The most commonly used tests of cortical function are two-point discrimination, touch localization, and bilateral simultaneous stimulation and tests for graphesthesia and stereognosis. Abnormalities of these sensory tests, in the presence of normal primary sensation in an alert cooperative patient, signify a lesion of the parietal cortex or thalamocortical projections. If primary sensation is altered, these cortical discriminative functions usually will be abnormal also. Comparisons should always be made between analogous sites on the two sides of the body because the deficit with a specific parietal lesion is likely to be unilateral.

Two-point discrimination is tested with special calipers, the points of which may be set from 2 mm to several centimeters apart and then applied simultaneously to the test site. On the fingertips, a normal individual can distinguish about a 3-mm separation of points.

Touch localization is performed by light pressure for an instant with the examiner's fingertip or a wisp of cotton wool; the patient, whose eyes are closed, is required to identify the site of touch. *Bilateral simultaneous stimulation* at analogous sites (e.g., the dorsum of both hands) can be carried out to determine whether the perception of touch is extinguished consistently on one side (*extinction* or *neglect*). *Graphesthesia* refers to the capacity to recognize, with eyes closed, letters or numbers drawn by the examiner's fingertip on the palm of the hand. Once again, interside comparison is of prime importance. Inability to recognize numbers or letters is termed *agraphesthesia*.

Stereognosis refers to the ability to identify common objects by palpation, recognizing their shape, texture, and size. Common standard objects such as keys, paper clips, and coins are best used. Patients with normal stereognosis should be able to distinguish a dime from a penny and a nickel from a quarter without looking. Patients should feel the object with only one hand at a time. If they are unable to identify it in one hand, it should be placed in the other for comparison. Individuals who are unable to identify common objects and coins in one hand but can do so in the other are said to have *astereognosis* of the abnormal hand.

LOCALIZATION OF SENSORY ABNORMALITIES

Sensory symptoms and signs can result from lesions at many different levels of the nervous system from the parietal cortex to the peripheral sensory receptor. Noting their distribution and nature is the most important way to localize their source. Their extent, configuration, symmetry, quality, and severity are the key observations.

Dysesthesias without sensory findings by examination may be difficult to interpret. To illustrate, tingling dysesthesias in an acral distribution (hands and feet) can be systemic in origin, for example, secondary to hyperventilation, or induced by a medication such as acetazolamide. Distal dysesthesias can also be an early event in an evolving polyneuropathy or may herald a myelopathy, such as from vitamin B_{12} deficiency. Sometimes, distal dysesthesias have no definable basis. In contrast, dysesthesias that correspond in distribution to that of a particular peripheral nerve structure denote a lesion at that site. For instance, dysesthesias restricted to the fifth digit and the adjacent one-half of the fourth finger on one hand reliably point to disorder of the ulnar nerve, most commonly at the elbow.

Nerve and Root In focal nerve trunk lesions, sensory abnormalities are readily mapped and generally have discrete boundaries (Figs. 22-2 and 22-3). Root ("radicular") lesions frequently are accompanied by deep, aching pain along the course of the related nerve trunk. With compression of a fifth lumbar (L5) or first sacral (S1) root, as from a ruptured intervertebral disk, sciatica (radicular pain relating to the sciatic nerve trunk) is a common manifestation **(Chap. 14)**. With a lesion affecting a single root, sensory deficits may be minimal or absent because adjacent root territories overlap extensively.

Isolated mononeuropathies may cause symptoms beyond the territory supplied by the affected nerve, but abnormalities on examination typically are confined to appropriate anatomic boundaries. In multiple mononeuropathies, symptoms and signs occur in discrete territories supplied by different individual nerves and—as more nerves are affected—may simulate a polyneuropathy if deficits become confluent. With polyneuropathies, sensory deficits are generally graded, distal, and symmetric in distribution **(Chap. 438)**. Dysesthesias, followed by numbness, begin in the toes and ascend symmetrically. When dysesthesias reach the knees, they usually also have appeared in the fingertips. The process is nerve length–dependent, and the deficit is often described as "stocking-glove" in type. Involvement of both hands and feet also occurs with lesions of the upper cervical cord or the brainstem, but an upper level of the sensory disturbance may then be found on the trunk and other evidence of a central lesion may be present, such as sphincter involvement or signs of an upper motor neuron lesion **(Chap. 21)**. Although most polyneuropathies are pansensory and affect all modalities of sensation, selective sensory dysfunction according to nerve fiber size may occur. Small-fiber polyneuropathies are characterized by burning, painful dysesthesias with reduced pinprick and thermal sensation but with sparing of proprioception, motor function, and deep tendon reflexes. Touch is involved variably; when it is spared, the sensory pattern is referred to as exhibiting *sensory dissociation*. Sensory dissociation may occur also with spinal cord lesions. Large-fiber polyneuropathies are characterized by vibration and position sense deficits, imbalance, absent tendon reflexes, and variable motor dysfunction but preservation of most cutaneous sensation. Dysesthesias, if present at all, tend to be tingling or bandlike in quality.

Sensory neuronopathy (or ganglionopathy) is characterized by widespread but asymmetric sensory loss occurring in a non-length-dependent manner so that it may occur proximally or distally and in the arms, legs, or both. Pain and numbness progress to sensory ataxia and impairment of all sensory modalities with time. This condition is usually paraneoplastic or idiopathic in origin **(Chaps. 90 and 438)** or related to an autoimmune disease, particularly Sjögren's syndrome.

Spinal Cord **(See also Chap. 434)** If the spinal cord is transected, all sensation is lost below the level of transection. Bladder and bowel function also are lost, as is motor function. Lateral hemisection of the spinal cord produces the Brown-Séquard syndrome, with absent pain and temperature sensation contralaterally and loss of proprioceptive sensation and power ipsilaterally below the lesion (see **Figs.** 22-1 and **434-1**); ipsilateral pain or hyperesthesia may also occur.

Numbness or paresthesias in both feet may arise from a spinal cord lesion; this is especially likely when the upper level of the sensory loss extends to the trunk. When all extremities are affected, the lesion is probably in the cervical region or brainstem unless a peripheral neuropathy is responsible. The presence of upper motor neuron signs **(Chap. 21)** supports a central lesion; a hyperesthetic band on the trunk may suggest the level of involvement.

A dissociated sensory loss can reflect spinothalamic tract involvement in the spinal cord, especially if the deficit is unilateral and has an upper level on the torso. Bilateral spinothalamic tract involvement occurs with lesions affecting the center of the spinal cord, such as in syringomyelia. There is a dissociated sensory loss with impairment of pinprick and temperature appreciation but relative preservation of light touch, position sense, and vibration appreciation.

Dysfunction of the posterior columns in the spinal cord or of the posterior root entry zone may lead to a bandlike sensation around the trunk or a feeling of tight pressure in one or more limbs. Flexion of the neck sometimes leads to an electric shock–like sensation that radiates down the back and into the legs (Lhermitte's sign) in patients with a cervical lesion affecting the posterior columns, such as from multiple sclerosis, cervical spondylosis, or recent irradiation to the cervical region.

Brainstem Crossed patterns of sensory disturbance, in which one side of the face and the opposite side of the body are affected, localize to the lateral medulla. Here a small lesion may damage both the ipsilateral descending trigeminal tract and the ascending spinothalamic fibers subserving the opposite arm, leg, and hemitorso (see "Lateral medullary syndrome" in **Fig. 419-7**). A lesion in the tegmentum of the pons and midbrain, where the lemniscal and spinothalamic tracts merge, causes pansensory loss contralaterally.

Thalamus Hemisensory disturbance with tingling numbness from head to foot is often thalamic in origin but also can arise from the anterior parietal region. If abrupt in onset, the lesion is likely to be due to a small stroke (lacunar infarction), particularly if localized to the thalamus. Occasionally, with lesions affecting the VPL nucleus or adjacent white matter, a syndrome of thalamic pain, also called *Déjerine-Roussy syndrome*, may ensue. The persistent, unrelenting unilateral pain often is described in dramatic terms.

Cortex With lesions of the parietal lobe involving either the cortex or the subjacent white matter, the most prominent symptoms are contralateral hemineglect, hemi-inattention, and a tendency not to use the affected hand and arm. On cortical sensory testing (e.g., two-point discrimination, graphesthesia), abnormalities are often found but primary sensation is usually intact. Anterior parietal infarction may present as a pseudothalamic syndrome with contralateral loss of primary sensation from head to toe. Dysesthesias or a sense of numbness and, rarely, a painful state may also occur.

Focal Sensory Seizures These seizures generally are due to lesions in the area of the postcentral or precentral gyrus. The principal symptom of focal sensory seizures is tingling, but additional, more complex sensations may occur, such as a rushing feeling, a sense of warmth, or a sense of movement without detectable motion. Symptoms typically are unilateral; commonly begin in the arm or hand, face, or foot; and often spread in a manner that reflects the cortical

representation of different bodily parts, as in a Jacksonian march. Their duration is variable; seizures may be transient, lasting only for seconds, or persist for an hour or more. Focal motor features may supervene, often becoming generalized with loss of consciousness and tonic-clonic jerking.

Psychogenic Symptoms Sensory symptoms may have a psychogenic basis. Such symptoms may be generalized or have an anatomic boundary that is difficult to explain neurologically, for example, circumferentially at the groin or shoulder or around a specific joint. Pain is common, but the nature and intensity of any sensory disturbances are variable. The diagnosis should not be one of exclusion but based on suggestive findings that are otherwise difficult to explain, such as midline splitting of impaired vibration, pinprick, or light touch appreciation; variability or poor reproducibility of sensory deficits; or normal performance of tasks requiring sensory input that is seemingly abnormal on formal testing, such as good performance with eyes closed of the finger-to-nose test despite an apparent loss of position sense in the upper limb. The side with abnormal sensation may be confused when the limbs are placed in an unusual position, such as crossed behind the back. Sensory complaints should not be regarded as psychogenic simply because they are unusual.

FURTHER READING

Brazis P, Masdeu JC, Biller J: *Localization in Clinical Neurology*, 7th ed. Philadelphia, Lippincott William & Wilkins, 2016.

Campbell WW: *DeJong's The Neurological Examination*, 7th ed. Philadelphia, Lippincott William & Wilkins, 2012.

23 Gait Disorders, Imbalance, and Falls

Jessica M. Baker, Lewis R. Sudarsky

PREVALENCE, MORBIDITY, AND MORTALITY

Gait and balance problems are common in the elderly and contribute to the risk of falls and injury. Gait disorders have been described in 15% of individuals aged >65. By age 80 one person in four will use a mechanical aid to assist with ambulation. Among those aged ≥85, the prevalence of gait abnormality approaches 40%. In epidemiologic studies, gait disorders are consistently identified as a major risk factor for falls and injury.

ANATOMY AND PHYSIOLOGY

An upright bipedal gait depends on the successful integration of postural control and locomotion. These functions are widely distributed in the central nervous system. The biomechanics of bipedal walking are complex, and the performance is easily compromised by a neurologic deficit at any level. Command and control centers in the brainstem, cerebellum, and forebrain modify the action of spinal pattern generators to promote stepping. While a form of "fictive locomotion" can be elicited from quadrupedal animals after spinal transection, this capacity is limited in primates. Step generation in primates is dependent on locomotor centers in the pontine tegmentum, midbrain, and subthalamic region. Locomotor synergies are executed through the reticular formation and descending pathways in the ventromedial spinal cord. Cerebral control provides a goal and purpose for walking and is involved in avoidance of obstacles and adaptation of locomotor programs to context and terrain.

Postural control requires the maintenance of the center of mass over the base of support through the gait cycle. Unconscious postural adjustments maintain standing balance: long latency responses are measurable in the leg muscles, beginning 110 milliseconds after a perturbation. Forward motion of the center of mass provides propulsive force for stepping, but failure to maintain the center of mass within stability limits results in falls. The anatomic substrate for dynamic balance has not been well defined, but the vestibular nucleus and midline cerebellum contribute to balance control in animals. Patients with damage to these structures have impaired balance while standing and walking.

Standing balance depends on good-quality sensory information about the position of the body center with respect to the environment, support surface, and gravitational forces. Sensory information for postural control is primarily generated by the visual system, the vestibular system, and proprioceptive receptors in the muscle spindles and joints. A healthy redundancy of sensory afferent information is generally available, but loss of two of the three pathways is sufficient to compromise standing balance. Balance disorders in older individuals sometimes result from multiple insults in the peripheral sensory systems (e.g., visual loss, vestibular deficit, peripheral neuropathy) that critically degrade the quality of afferent information needed for balance stability.

Older patients with cognitive impairment appear to be particularly prone to falls and injury. There is a growing body of literature on the use of attentional resources to manage gait and balance. Walking is generally considered to be unconscious and automatic, but the ability to walk while attending to a cognitive task (*dual-task walking*) may be compromised in the elderly. Older patients with deficits in executive function may have particular difficulty in managing the attentional resources needed for dynamic balance when distracted.

DISORDERS OF GAIT

Disorders of gait may be attributed to neurological and non-neurological causes, though significant overlap often exists. The *antalgic gait* results from avoidance of pain associated with weight-bearing and is commonly seen in osteoarthritis. Asymmetry is a common feature of gait disorders due to contractures and other orthopedic deformities. Impaired vision rounds out the list of common non-neurological causes of gait disorders.

Neurologic gait disorders are disabling and equally important to address. The heterogeneity of gait disorders observed in clinical practice reflects the large network of neural systems involved in the task. Walking is vulnerable to neurologic disease at every level. Gait disorders have been classified descriptively on the basis of abnormal physiology and biomechanics. One problem with this approach is that many failing gaits look fundamentally similar. This overlap reflects common patterns of adaptation to threatened balance stability and declining performance. *The gait disorder observed clinically must be viewed as the product of a neurologic deficit and a functional adaptation*. Unique features of the failing gait are often overwhelmed by the adaptive response. Some common patterns of abnormal gait are summarized next. Gait disorders can also be classified by etiology **(Table 23-1)**.

TABLE 23-1 Etiology of Gait Disorders

ETIOLOGY	NO. OF CASES	PERCENT
Sensory deficits	22	18.3
Myelopathy	20	16.7
Multiple infarcts	18	15.0
Parkinsonism	14	11.7
Cerebellar degeneration	8	6.7
Hydrocephalus	8	6.7
Toxic/metabolic causes	3	2.5
Psychogenic causes	4	3.3
Other	6	5.0
Unknown causes	17	14.2
Total	120	100

Source: Reproduced with permission from J Masdeu et al: *Gait Disorders of Aging*. Lippincott Raven, 1997.

CAUTIOUS GAIT

The term *cautious gait* is used to describe the patient who walks with an abbreviated stride, widened base and lowered center of mass, as if walking on a slippery surface. This disorder is both common and nonspecific. It is, in essence, an adaptation to a perceived postural threat. There may be an associated fear of falling. This disorder can be observed in more than one-third of older patients with gait impairment. Physical therapy often improves walking to the degree that follow-up observation may reveal a more specific underlying disorder.

STIFF-LEGGED GAIT

Spastic gait is characterized by stiffness in the legs, an imbalance of muscle tone, and a tendency to circumduct and scuff the feet. The disorder reflects compromise of corticospinal command and overactivity of spinal reflexes. The patient may walk on the toes. In extreme instances, the legs cross due to increased tone in the adductors ("scissoring" gait). Upper motor neuron signs are present on physical examination. The disorder may be cerebral or spinal in origin.

Myelopathy from cervical spondylosis is a common cause of spastic or spastic-ataxic gait in the elderly. Demyelinating disease and trauma are the leading causes of myelopathy in younger patients. In chronic progressive myelopathy of unknown cause, a workup with laboratory and imaging tests may establish a diagnosis. A structural lesion, such as a tumor or a spinal vascular malformation, should be excluded with appropriate testing. **Spinal cord disorders are discussed in detail in Chap. 434.**

With cerebral spasticity, asymmetry is common, the upper extremities are usually involved, and dysarthria is often an associated feature. Common causes include vascular disease (stroke), multiple sclerosis, motor neuron disease, and perinatal nervous system injury (cerebral palsy).

Other stiff-legged gaits include dystonia **(Chap. 428)** and stiff-person syndrome **(Chap. 90)**. Dystonia is a disorder characterized by sustained muscle contractions resulting in repetitive twisting movements and abnormal posture. It often has a genetic basis. Dystonic spasms can produce plantar flexion and inversion of the feet, sometimes with torsion of the trunk. In autoimmune stiff-person syndrome, exaggerated lordosis of the lumbar spine and overactivation of antagonist muscles restrict trunk and lower-limb movement and result in a wooden or fixed posture.

PARKINSONISM, FREEZING GAIT, AND OTHER MOVEMENT DISORDERSS

Parkinson's disease **(Chap. 427)** is common, affecting 1% of the population >55 years of age. The stooped posture and shuffling gait are characteristic and distinctive features. Patients sometimes accelerate (festinate) with walking, display retropulsion, or exhibit a tendency to turn en bloc. The step-to-step variability of the parkinsonian gait also contributes to fall risk. Dopamine replacement improves step length, arm swing, turning speed, and gait initiation. There is increasing evidence that deficits in cholinergic circuits in the pedunculopontine nucleus and cortex contribute to the gait disorder of Parkinson's disease. Cholinesterase inhibitors such as donepezil and rivastigmine have been shown in early studies to significantly decrease gait variability, instability, and fall frequency, even in the absence of cognitive impairment, perhaps through improvement in attention.

Freezing is defined as a brief, episodic absence of forward progression of the feet, despite the intention to walk. Freezing may be triggered by approaching a narrow doorway or crowd, may be overcome by visual cueing, and contributes to fall risk. Gait freezing is present in approximately one-quarter of Parkinson's patients within 5 years of onset, and its frequency increases further over time. In treated patients, an end-of-dose gait freezing is a common problem that may improve with more frequent administration of dopaminergic drugs, or with use of monoamine oxidase type B inhibitors such as rasagiline or selegiline **(Chap. 427)**.

Freezing of gait is also common in other neurodegenerative disorders associated with parkinsonism, including progressive supranuclear palsy (PSP), multiple-system atrophy, and corticobasal degeneration. Patients with these disorders frequently present with axial stiffness, postural instability, and a shuffling, freezing gait while lacking the characteristic pill-rolling tremor of Parkinson's disease. The gait of PSP is typically more erect compared with the stooped posture of typical Parkinson's disease, and falls within the first year also suggest the possibility of, PSP.

Hyperkinetic movement disorders also produce characteristic and recognizable disturbances in gait. In Huntington's disease **(Chap. 428)**, the unpredictable occurrence of choreic movements gives the gait a dancing quality. Tardive dyskinesia is the cause of many odd, stereotypic gait disorders seen in patients chronically exposed to antipsychotics and other drugs that block the D_2 dopamine receptor. *Orthostatic tremor* is a high frequency, low amplitude tremor predominantly involving the lower extremities. Patients often report shakiness or unsteadiness on standing, and improvement with sitting or walking. Falls are common. The tremor is often only appreciable by palpating the legs while standing.

FRONTAL GAIT DISORDER

Frontal gait disorder, also known as higher level gait disorder, is common in the elderly and has a variety of causes. The term is used to describe a shuffling, freezing gait with imbalance, and other signs of higher cerebral dysfunction. Typical features include a wide base of support, a short stride, shuffling along the floor, and difficulty with starts and turns. Many patients exhibit a difficulty with gait initiation that is descriptively characterized as the "slipping clutch" syndrome or gait ignition failure. The term *lower-body parkinsonism* is also used to describe such patients. Strength is generally preserved, and patients are able to make stepping movements when not standing and maintaining their balance at the same time. This disorder is best considered a higher-level motor control disorder, as opposed to an apraxia **(Chap. 26)**, though the term *gait apraxia* persists in the literature.

The most common cause of frontal gait disorder is vascular disease, particularly subcortical small-vessel disease in the deep frontal white matter and centrum ovale. Over three-quarters of patients with subcortical vascular dementia demonstrate gait abnormalities; decreased arm swing and a stooped posture are particularly prevalent features. The clinical syndrome also includes dysarthria, pseudobulbar affect (emotional disinhibition), increased tone, and hyperreflexia in the lower limbs.

Normal pressure (communicating) hydrocephalus (NPH) in adults also presents with a similar gait disorder. Other features of the diagnostic triad (mental changes, incontinence) may be absent in a substantial number of patients. MRI demonstrates ventricular enlargement, an enlarged flow void about the aqueduct, periventricular white-matter change, and high-convexity tightness (disproportionate widening of the sylvian fissures versus the cortical sulci). A lumbar puncture or dynamic test is necessary to confirm a diagnosis of NPH. Neurodegenerative dementias and mass lesions of the frontal lobes cause a similar clinical picture and can be differentiated from vascular disease and hydrocephalus by neuroimaging.

CEREBELLAR GAIT ATAXIA

Disorders of the cerebellum have a dramatic impact on gait and balance. Cerebellar gait ataxia is characterized by a wide base of support, lateral instability of the trunk, erratic foot placement, and decompensation of balance when attempting to walk on a narrow base. Difficulty maintaining balance when turning is often an early feature. Patients are unable to walk tandem heel to toe and display truncal sway in narrow-based or tandem stance. They show considerable variation in their tendency to fall in daily life.

Causes of cerebellar ataxia in older patients include stroke, trauma, tumor, and neurodegenerative disease such as multiple-system atrophy **(Chap. 432)** and various forms of hereditary cerebellar degeneration **(Chap. 431)**. A short expansion at the site of the fragile X mutation (*fragile X pre-mutation*) has been associated with gait ataxia in older men. Alcohol causes an acute and chronic cerebellar ataxia. In patients with ataxia due to cerebellar degeneration, MRI demonstrates the extent and topography of cerebellar atrophy.

TABLE 23-2 Features of Cerebellar Ataxia, Sensory Ataxia, and Frontal Gait Disorders

FEATURE	CEREBELLAR ATAXIA	SENSORY ATAXIA	FRONTAL GAIT
Base of support	Wide-based	Narrow base, looks down	Wide-based
Velocity	Variable	Slow	Very slow
Stride	Irregular, lurching	Regular with path deviation	Short, shuffling
Romberg test	+/−	Unsteady, falls	+/−
Heel → shin	Abnormal	+/−	Normal
Initiation	Normal	Normal	Hesitant
Turns	Unsteady	+/−	Hesitant, multistep
Postural instability	+	+++	++++ Poor postural synergies rising from a chair
Falls	Late event	Frequent	Frequent

SENSORY ATAXIA

As reviewed earlier in this chapter, balance depends on high-quality afferent information from the visual and the vestibular systems and proprioception. When this information is lost or degraded, balance during locomotion is impaired and instability results. The sensory ataxia of tabetic neurosyphilis is a classic example. The contemporary equivalent is the patient with neuropathy affecting large fibers. Vitamin B_{12} deficiency is a treatable cause of large-fiber sensory loss in the spinal cord and peripheral nervous system. Joint position and vibration sense are diminished in the lower limbs. The stance in such patients is destabilized by eye closure; they often look down at their feet when walking and do poorly in the dark. Table 23-2 compares sensory ataxia with cerebellar ataxia and frontal gait disorder.

NEUROMUSCULAR DISEASE

Patients with neuromuscular disease often have an abnormal gait, occasionally as a presenting feature. With distal weakness (peripheral neuropathy), the step height is increased to compensate for foot drop, and the sole of the foot may slap on the floor during weight acceptance, termed the *steppage gait*. Patients with myopathy or muscular dystrophy more typically exhibit proximal weakness. Weakness of the hip girdle may result in some degree of excess pelvic sway during locomotion. The stooped posture of lumbar spinal stenosis ameliorates pain from the compression of the cauda equina occurring with a more upright posture while walking, and may mimic early parkinsonism.

TOXIC AND METABOLIC DISORDERS

Chronic toxicity from medications and metabolic disturbances can impair motor function and gait. Examination may reveal mental status changes, asterixis or myoclonus. Static equilibrium is disturbed, and such patients are easily thrown off balance. Disequilibrium is particularly evident in patients with chronic renal disease and those with hepatic failure, in whom asterixis may impair postural support. Sedative drugs, especially neuroleptics and long-acting benzodiazepines, affect postural control and increase the risk for falls. These disorders are especially important to recognize because they are often treatable.

FUNCTIONAL GAIT DISORDER

Functional disorders (formerly "psychogenic") are common in neurologic practice, and the presentation often involves gait. The hallmark of a functional gait disorder is an internal inconsistency of deficits that may be incompatible with a neurological deficit. For example, odd gyrations of posture with wastage of muscular energy (astasia–abasia) appear superficially unsteady, yet in reality require significant postural control. Falls are rare, and there are often discrepancies between examination findings and the patient's functional status. Extreme slow motion, an inappropriately overcautious gait, and dramatic fluctuations over time may improve with distraction, keeping in mind that numerous organic neurological diseases are also paroxysmal in nature. Preceding stress or trauma is variably present, and its absence no longer precludes the diagnosis of a functional neurological disorder. Functional gait disorders are among the most dramatic encountered, and should be differentiated from the slowness and psychomotor retardation seen in certain patients with major depression.

APPROACH TO THE PATIENT

Slowly Progressive Disorder of Gait

When reviewing the history, it is helpful to inquire about the onset and progression of disability. Initial awareness of an unsteady gait often follows a fall. Stepwise evolution or sudden progression suggests vascular disease. Gait disorder may be associated with urinary urgency and incontinence, particularly in patients with cervical spine disease or hydrocephalus. It is always important to review the use of alcohol and medications that affect gait and balance. Information on localization derived from the neurologic examination can be helpful in narrowing the list of possible diagnoses.

Gait observation provides an immediate sense of the patient's degree of disability. Arthritic and antalgic gaits are recognized by observation, though neurologic and orthopedic problems may coexist. Characteristic patterns of abnormality are sometimes seen, though, as stated previously, failing gaits often look fundamentally similar. Cadence (steps per minute), velocity, and stride length can be recorded by timing a patient over a fixed distance. Watching the patient rise from a chair provides a good functional assessment of balance.

Brain imaging studies may be informative in patients with an undiagnosed disorder of gait. MRI is sensitive for cerebral lesions of vascular or demyelinating disease and is a good screening test for occult hydrocephalus. Patients with recurrent falls are at risk for subdural hematoma. As mentioned earlier, many elderly patients with gait and balance difficulty have white matter abnormalities in the periventricular region and centrum semiovale. While these lesions may be an incidental finding, a substantial burden of white matter disease will ultimately impact cerebral control of locomotion.

DISORDERS OF BALANCE

DEFINITION, ETIOLOGY, AND MANIFESTATIONS

Balance is the ability to maintain equilibrium—a dynamic state in which one's center of mass is controlled with respect to the lower extremities, gravity and the support surface despite external perturbations. The reflexes required to maintain upright posture require input from cerebellar, vestibular, and somatosensory systems; the premotor cortex, corticospinal and reticulospinal tracts mediate output to axial and proximal limb muscles. These responses are physiologically complex, and the anatomic representation they entail is not well understood. Failure can occur at any level and presents as difficulty maintaining posture while standing and walking.

The history and physical examination may differentiate underlying causes of imbalance. Patients with *cerebellar* ataxia do not generally complain of dizziness, though balance is visibly impaired. Neurologic examination reveals a variety of cerebellar signs. Postural compensation may prevent falls early on, but falls are inevitable with disease progression. The progression of neurodegenerative ataxia is often measured by the number of years to loss of stable ambulation.

Vestibular disorders (Chap. 19) have symptoms and signs that fall into three categories: (1) vertigo (the subjective inappropriate perception or illusion of movement); (2) nystagmus (involuntary eye

movements); and (3) impaired standing balance. Not every patient has all manifestations. Patients with vestibular deficits related to ototoxic drugs may lack vertigo or obvious nystagmus, but their balance is impaired on standing and walking, and they cannot navigate in the dark. Laboratory testing is available to investigate vestibular deficits.

Somatosensory deficits also produce imbalance and falls. There is often a subjective sense of insecure balance and fear of falling. Postural control is compromised by eye closure (*Romberg's sign*); these patients also have difficulty navigating in the dark. A dramatic example is provided by the patient with autoimmune subacute sensory neuropathy, which is sometimes a paraneoplastic disorder **(Chap. 90)**. Compensatory strategies enable such patients to walk in the virtual absence of proprioception, but the task requires active visual monitoring.

Patients with *higher-level disorders of equilibrium* have difficulty maintaining balance in daily life and may present with falls. Their awareness of balance impairment may be reduced. Patients taking sedating medications are in this category.

FALLS

Falls are common in the elderly; over one-third of people aged >65 who are living in the community fall each year. This number is even higher in nursing homes and hospitals. Elderly people are not only at higher risk for falls, but are more likely to suffer serious complications due to medical comorbidities such as osteoporosis. Hip fractures result in hospitalization, can lead to nursing home admission, and are associated with an increased mortality risk in the subsequent year. Falls may result in brain or spinal injury, the history of which may be difficult for the patient to provide. The proportion of spinal cord injuries due to falls in individuals aged >65 years has doubled in the last decade, perhaps due to increasing activity in this age group. Some falls result in a prolonged time lying on the ground; fractures and CNS injury are a particular concern in this context.

For each person who is physically disabled, there are others whose functional independence is limited by anxiety and fear of falling. Nearly one in five elderly individuals voluntarily restricts his or her activity because of fear of falling. With loss of ambulation, the quality of life diminishes, and rates of morbidity and mortality increase.

RISK FACTORS FOR FALLS

Risk factors for falls may be *intrinsic* (e.g., gait and balance disorders) or *extrinsic* (e.g., polypharmacy, and environmental factors); some risk factors are modifiable. The presence of multiple risk factors is associated with a substantially increased risk of falls. **(Table 23-3)** summarizes a meta-analysis of studies establishing the principal risk factors for falls. Polypharmacy (use of four or more prescription medications) has also been identified as an important risk factor.

ASSESSMENT OF THE PATIENT WITH FALLS

The most productive approach is to identify the high-risk patient prospectively, before there is a serious injury. All community-dwelling adults should be asked about falls at least annually. The Timed Up and Go ("TUG") test involves timing a patient as they stand up from a chair, walk 10 ft, turn, then sit down. Patients with a history of falls, or those requiring >12 s to complete the TUG test, are high risk for falls and should undergo further assessment.

TABLE 23-3 Meta-Analysis of Risk Factors for Falls in Older Persons

RISK FACTOR	MEAN RR (OR)	RANGE
Muscle weakness	4.4	1.5–10.3
History of falls	3.0	1.7–7.0
Gait deficit	2.9	1.3–5.6
Balance deficit	2.9	1.6–5.4
Use assistive device	2.6	1.2–4.6
Visual deficit	2.5	1.6–3.5
Arthritis	2.4	1.9–2.9
Impaired ADL	2.3	1.5–3.1
Depression	2.2	1.7–2.5
Cognitive impairment	1.8	1.0–2.3
Age >80 years	1.7	1.1–2.5

Abbreviations: ADL, activity of daily living; OR, odds ratio from retrospective studies; RR, relative risk from prospective studies.

Source: Reproduced with permission from Guideline for the Prevention of Falls in Older Persons. J Am Geriatr Soc 49:664, 2001.

History The history surrounding a fall is often problematic or incomplete, and the underlying mechanism or cause may be difficult to establish in retrospect. Patients should be queried about any provoking factors (including head turn, standing) or prodromal symptoms, such as dizziness, vertigo, pre-syncopal symptoms or focal weakness. A history of baseline mobility and medical comorbidities should be elicited. Patients at particular risk include those with mental status changes or dementia. Medications should be reviewed, with particular attention to neuroleptics, benzodiazepines, anti-depressants, anti-arrhythmics, and diuretics, all of which are associated with an increased risk of falls. It is equally important to distinguish *mechanical falls* (those caused by tripping or slipping) due to purely extrinsic or environmental factors from those in which a modifiable intrinsic factor contributes. *Recurrent falls* may indicate an underlying gait or balance disorder. Falls associated with loss of consciousness (syncope, seizure) may require appropriate cardiac or neurological evaluation and intervention **(Chaps. 18 and 418)**, though a patient's report of change in consciousness may be unreliable.

Physical Examination Examination of the patient with falls should include a basic cardiac examination, including orthostatic blood pressure if indicated by history, and observation of any orthopedic abnormalities. Mental status is easily assessed while obtaining a history from the patient; the remainder of the neurological examination should include visual acuity, strength and sensation in the lower extremities, muscle tone, and cerebellar function, with particular attention to gait and balance as described earlier in this chapter.

Fall Patterns The description of a fall event may provide further clues to the underlying etiology. While there is no standard nosology of falls, some common clinical patterns may emerge and provide a clue.

DROP ATTACKS AND COLLAPSING FALLS Drop attacks and collapsing falls are associated with a sudden loss of postural tone. Patients may report that their legs just "gave out" underneath them, or that they "collapsed in a heap." Syncope or orthostatic hypotension may be a factor in some such falls. Neurological causes are relatively rare, but include atonic seizures, myoclonus and intermittent obstruction of the foramen of Monro by a colloid cyst of the third ventricle causing acute obstructive hydrocephalus. An emotional trigger suggests cataplexy. While collapsing falls are more common among older patients with vascular risk factors, drop attacks should not be confused with vertebrobasilar ischemic attacks.

TOPPLING FALLS Some patients maintain tone in antigravity muscles but fall over like a tree trunk, as if postural defenses had disengaged. Causes include cerebellar pathology and lesions of the vestibular system. There may be a consistent direction to such falls. Toppling falls are an early feature of PSP, and a late feature of Parkinson's disease, once postural instability has developed. Thalamic lesions causing truncal instability (*thalamic astasia*) may also contribute to this type of fall.

FALLS DUE TO GAIT FREEZING Freezing of gait is seen in Parkinson's disease and related disorders. The feet stick to the floor and the center of mass keeps moving, resulting in a disequilibrium from which the patient has difficulty recovering, resulting in a forward fall. Similarly, patients with Parkinson's disease and festinating gait may find their feet unable to keep up and may thus fall forward.

FALLS RELATED TO SENSORY LOSS Patients with somatosensory, visual, or vestibular deficits are prone to falls. These patients have particular difficulty dealing with poor illumination or walking on uneven ground. They often report subjective imbalance, apprehension, and fear of falling. These patients may be especially responsive to a rehabilitation-based intervention.

FALLS RELATED TO WEAKNESS Patients who lack strength in antigravity muscles have difficulty rising from a chair or maintaining their balance

after a perturbation. These patients are often unable to get up after a fall and may have to remain on the floor for a prolonged period until help arrives. If due to deconditioning, this is often treatable. Resistance strength training can increase muscle mass and leg strength, even for people in their eighties and nineties.

TREATMENT

Interventions to Reduce the Risk of Falls and Injury

Efforts should be made to define the etiology of the gait disorder and the mechanism underlying the falls by a given patient. Orthostatic changes in blood pressure and pulse should be recorded. Rising from a chair and walking should be evaluated for safety. Specific treatment may be possible once a diagnosis is established. Therapeutic intervention is often recommended for older patients at substantial risk for falls, even if no neurologic disease is identified. A home visit to look for environmental hazards can be helpful. A variety of modifications may be recommended to improve safety, including improved lighting and the installation of grab bars and nonslip surfaces.

Rehabilitative interventions aim to improve muscle strength and balance stability and to make the patient more resistant to injury. High-intensity resistance strength training with weights and machines is useful to improve muscle mass, even in frail older patients. Improvements realized in posture and gait should translate to reduced risk of falls and injury. Sensory balance training is another approach to improving balance stability. Measurable gains can be made in a few weeks of training, and benefits can be maintained over 6 months by a 10- to 20-min home exercise program. This strategy is particularly successful in patients with vestibular and somatosensory balance disorders. A Tai Chi exercise program has been demonstrated to reduce the risk of falls and injury in patients with Parkinson's disease.

FURTHER READING

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24 Confusion and Delirium

S. Andrew Josephson, Bruce L. Miller

Confusion, a mental and behavioral state of reduced comprehension, coherence, and capacity to reason, is one of the most common problems encountered in medicine, accounting for a large number of emergency department visits, hospital admissions, and inpatient consultations. *Delirium*, a term used to describe an acute confusional state, remains a major cause of morbidity and mortality, costing billions of dollars yearly in health care costs in the United States alone. Despite increased efforts targeting awareness of this condition, delirium often goes unrecognized in the face of evidence that it is usually the cognitive manifestation of serious underlying medical or neurologic illness.

CLINICAL FEATURES OF DELIRIUM

A multitude of terms are used to describe patients with delirium, including *encephalopathy, acute brain failure, acute confusional state*, and *postoperative* or *intensive care unit (ICU) psychosis*. Delirium has many clinical manifestations, but it is defined as a relatively acute decline in cognition that fluctuates over hours or days. The hallmark of delirium is a deficit of attention, although all cognitive domains—including memory, executive function, visuospatial tasks, and language—are variably involved. Associated symptoms that may be present in some cases include altered sleep-wake cycles, perceptual disturbances such as hallucinations or delusions, affect changes, and autonomic findings that include heart rate and blood pressure instability.

Delirium is a clinical diagnosis that is made only at the bedside. Two subtypes have been described—hyperactive and hypoactive—based on differential psychomotor features. The cognitive syndrome associated with severe alcohol withdrawal (i.e., "delirium tremens") remains the classic example of the hyperactive subtype, featuring prominent hallucinations, agitation, and hyperarousal, often accompanied by life-threatening autonomic instability. In striking contrast is the hypoactive subtype, exemplified by benzodiazepine intoxication, in which patients are withdrawn and quiet, with prominent apathy and psychomotor slowing.

This dichotomy between subtypes of delirium is a useful construct, but patients often fall somewhere along a spectrum between the hyperactive and hypoactive extremes, sometimes fluctuating from one to the other. Therefore, clinicians must recognize this broad range of presentations of delirium to identify all patients with this potentially reversible cognitive disturbance. Hyperactive patients are often easily recognized by their characteristic severe agitation, tremor, hallucinations, and autonomic instability. Patients who are quietly hypoactive are more often overlooked on the medical wards and in the ICU.

The reversibility of delirium is emphasized because many etiologies, such as infection and medication effects, can be treated easily. The long-term cognitive consequences of delirium remain largely unknown. Some episodes of delirium continue for weeks, months, or even years. The persistence of delirium in some patients and its high recurrence rate may be due to inadequate initial treatment of the underlying etiology. In other instances, delirium appears to cause permanent neuronal damage and cognitive decline; therefore prevention strategies are important to implement. Even if an episode of delirium completely resolves, there may be lingering effects of the disorder; a patient's recall of events after delirium varies widely, ranging from complete amnesia to repeated re-experiencing of the frightening period of confusion, similar to what is seen in patients with posttraumatic stress disorder.

RISK FACTORS

An effective primary prevention strategy for delirium begins with identification of high-risk patients, including those preparing for elective surgery or being admitted to the hospital. Multiple validated scoring systems have been developed as a screen for asymptomatic patients, many of which emphasize well-established risk factors for delirium.

The two most consistently identified risk factors are older age and baseline cognitive dysfunction. Individuals who are aged >65 or exhibit low scores on standardized tests of cognition develop delirium upon hospitalization at a rate approaching 50%. Whether age and baseline cognitive dysfunction are truly independent risk factors is uncertain. Other predisposing factors include sensory deprivation, such as preexisting hearing and visual impairment, as well as indices for poor overall health, including baseline immobility, malnutrition, and underlying medical or neurologic illness.

In-hospital risks for delirium include the use of bladder catheterization, physical restraints, sleep and sensory deprivation, and the addition of three or more new medications. Avoiding such risks remains a key component of delirium prevention as well as treatment. Surgical and anesthetic risk factors for the development of postoperative delirium include procedures such as those involving cardiopulmonary bypass, inadequate or excessive treatment of pain in the immediate postoperative period, and perhaps specific agents such as inhalational anesthetics.

The relationship between delirium and dementia (Chap. 25) is complicated by significant overlap between the two conditions, and it is not always simple to distinguish between them. Dementia and preexisting cognitive dysfunction serve as major risk factors for delirium, and at

least two-thirds of cases of delirium occur in patients with coexisting underlying dementia. A form of dementia with parkinsonism, *dementia with Lewy bodies*, is characterized by a fluctuating course, prominent visual hallucinations, parkinsonism, and an attentional deficit that clinically resembles hyperactive delirium; patients with this condition are particularly vulnerable to delirium. Delirium in the elderly often reflects an insult to a brain that is vulnerable due to an underlying neurodegenerative condition. Therefore, the development of delirium sometimes heralds the onset of a previously unrecognized brain disorder, and after the acute delirious episode has cleared, careful screening for an underlying condition should occur in the outpatient setting.

EPIDEMIOLOGY

Delirium is common, but its reported incidence has varied widely with the criteria used to define this disorder. Estimates of delirium in hospitalized patients range from 10 to >50%, with higher rates reported for elderly patients and patients undergoing hip surgery. Older patients in the ICU have especially high rates of delirium that approach 75%. The condition is not recognized in up to one-third of delirious inpatients, and the diagnosis is especially problematic in the ICU environment, where cognitive dysfunction is often difficult to appreciate in the setting of serious systemic illness and sedation. Delirium in the ICU should be viewed as an important manifestation of organ dysfunction not unlike liver, kidney, or heart failure. Outside the acute hospital setting, delirium occurs in nearly one-quarter of patients in nursing homes and in 50–80% of those at the end of life. These estimates emphasize the remarkably high frequency of this cognitive syndrome in older patients, a population that continues to grow.

An episode of delirium was previously viewed as a transient condition that carried a benign prognosis. It is now recognized as a disorder with substantial morbidity and mortality, and that often represents the first manifestation of a serious underlying illness. Estimates of in-hospital mortality rates among delirious patients range from 25 to 33%, similar to mortality rates due to sepsis. Patients with an in-hospital episode of delirium have a fivefold higher mortality rate in the months after their illness compared with age-matched nondelirious hospitalized patients. Delirious hospitalized patients also have a longer length of stay, are more likely to be discharged to a nursing home, and are more likely to experience subsequent episodes of delirium and cognitive decline; as a result, this condition has an enormous economic cost.

PATHOGENESIS

The pathogenesis and anatomy of delirium are incompletely understood. The attentional deficit that serves as the neuropsychological hallmark of delirium has a diffuse localization within the brainstem, thalamus, prefrontal cortex, and parietal lobes. Rarely, focal lesions such as ischemic strokes have led to delirium in otherwise healthy persons; right parietal and medial dorsal thalamic lesions have been reported most commonly, pointing to the importance of these areas in delirium pathogenesis. In most cases, however, delirium results from widespread disturbances in cortical and subcortical regions of the brain. Electroencephalogram (EEG) usually reveals symmetric slowing, a nonspecific finding that supports diffuse cerebral dysfunction.

Multiple neurotransmitter abnormalities, proinflammatory factors, and specific genes likely play a role in the pathogenesis of delirium. Deficiency of acetylcholine may play a key role, and medications with anticholinergic properties can commonly precipitate delirium. As noted above, patients with preexisting dementia are particularly susceptible to episodes of delirium. Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease dementia are all associated with cholinergic deficiency due to degeneration of acetylcholine-producing neurons in the basal forebrain. In addition, other neurotransmitters are also likely to be involved in this diffuse cerebral disorder. For example, increases in dopamine can lead to delirium, and patients with Parkinson's disease treated with dopaminergic medications can develop a delirium-like state that features visual hallucinations, fluctuations, and confusion.

Not all individuals exposed to the same insult will develop signs of delirium. A low dose of an anticholinergic medication may have no cognitive effects on a healthy young adult but produce a florid delirium in an elderly person with known underlying dementia, although even healthy young persons develop delirium with very high doses of anticholinergic medications. This concept of delirium developing as the result of an insult in predisposed individuals is currently the most widely accepted pathogenic construct. Therefore, if a previously healthy individual with no known history of cognitive illness develops delirium in the setting of a relatively minor insult such as elective surgery or hospitalization, an unrecognized underlying neurologic illness such as a neurodegenerative disease, multiple previous strokes, or another diffuse cerebral cause should be considered. In this context, delirium can be viewed as a "stress test for the brain" whereby exposure to known inciting factors such as systemic infection and offending drugs can unmask a decreased cerebral reserve and herald a serious underlying and potentially treatable illness.

APPROACH TO THE PATIENT

Delirium

Because the diagnosis of delirium is clinical and is made at the bedside, a careful history and physical examination are necessary in evaluating patients with possible confusional states. Screening tools can aid physicians and nurses in identifying patients with delirium, including the Confusion Assessment Method (CAM); the Nursing Delirium Screening Scale (NuDESC); the Organic Brain Syndrome Scale; the Delirium Rating Scale; and, in the ICU, the ICU version of the CAM and the Delirium Detection Score. Using the well-validated CAM, a diagnosis of delirium is made if there is (1) an acute onset and fluctuating course and (2) inattention accompanied by either (3) disorganized thinking or (4) an altered level of consciousness (Table 24-1). These scales may not identify the full spectrum of patients with delirium, and all patients who are acutely confused should be presumed delirious regardless of their presentation due to the wide variety of possible clinical features. A course that fluctuates over hours or days and may worsen at night (termed *sundowning*) is typical but not essential for the diagnosis. Observation will usually reveal an altered level of consciousness or a deficit of attention. Other features that are sometimes present include

TABLE 24-1 The Confusion Assessment Method (CAM) Diagnostic Algorithm[a]

The diagnosis of delirium requires the presence of features 1 and 2 **and** *either* feature 3 or 4.
Feature 1. Acute Onset and Fluctuating Course
This feature is satisfied by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or did it increase and decrease in severity?
Feature 2. Inattention
This feature is satisfied by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or have difficulty keeping track of what was being said?
Feature 3. Disorganized Thinking
This feature is satisfied by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
Feature 4. Altered Level of Consciousness
This feature is satisfied by any answer other than "alert" to the following question: Overall, how would you rate the patient's level of consciousness: alert (normal), vigilant (hyperalert), lethargic (drowsy, easily aroused), stupor (difficult to arouse), or coma (unarousable)?

[a]Information is usually obtained from a reliable reporter, such as a family member, caregiver, or nurse.

Source: Modified from SK Inouye et al: Clarifying confusion: The Confusion Assessment Method. A new method for detection of delirium. Ann Intern Med 113:941, 1990.

alteration of sleep-wake cycles, thought disturbances such as hallucinations or delusions, autonomic instability, and changes in affect.

HISTORY

It may be difficult to elicit an accurate history in delirious patients who have altered levels of consciousness or impaired attention. Information from a collateral source such as a spouse or another family member is therefore invaluable. The three most important pieces of history are the patient's baseline cognitive function, the time course of the present illness, and current medications.

Premorbid cognitive function can be assessed through the collateral source or, if needed, via a review of outpatient records. Delirium by definition represents a change that is relatively acute and usually developing over hours to days, from a cognitive baseline. An acute confusional state is nearly impossible to diagnose without some knowledge of baseline cognitive function. Without this information, many patients with dementia or longstanding depression may be mistaken as delirious during a single initial evaluation. Patients with a more hypoactive, apathetic presentation with psychomotor slowing may be identified as being different from baseline only through conversations with family members. A number of validated instruments have been shown to diagnose cognitive dysfunction accurately using a collateral source, including the modified Blessed Dementia Rating Scale and the Clinical Dementia Rating (CDR). Baseline cognitive impairment is common in patients with delirium. Even when no such history of cognitive impairment is elicited, there should still be a high suspicion for a previously unrecognized underlying neurologic disorder.

Establishing the time course of cognitive change is important not only to make a diagnosis of delirium but also to correlate the onset of the illness with potentially treatable etiologies such as recent medication changes or symptoms of systemic infection.

Medications remain a common cause of delirium, especially compounds with anticholinergic or sedative properties. It is estimated that nearly one-third of all cases of delirium are secondary to medications, especially in the elderly. Medication histories should include all prescription as well as over-the-counter and herbal substances taken by the patient and any recent changes in dosing or formulation, including substitution of generics for brand-name medications.

Other important elements of the history include screening for symptoms of organ failure or systemic infection, which often contributes to delirium in the elderly. A history of illicit drug use, alcoholism, or toxin exposure is common in younger delirious patients. Finally, asking the patient and collateral source about other symptoms that may accompany delirium, such as depression, may help identify potential therapeutic targets.

PHYSICAL EXAMINATION

The general physical examination in a delirious patient should include careful screening for signs of infection such as fever, tachypnea, pulmonary consolidation, heart murmur, and meningismus. The patient's fluid status should be assessed; both dehydration and fluid overload with resultant hypoxemia have been associated with delirium, and each is usually easily rectified. The appearance of the skin can be helpful, showing jaundice in hepatic encephalopathy, cyanosis in hypoxemia, or needle tracks in patients using intravenous drugs.

The neurologic examination requires a careful assessment of mental status. Patients with delirium often present with a fluctuating course; therefore, the diagnosis can be missed when one relies on a single time point of evaluation. For patients who worsen in the evening (sundowning), assessment only during morning rounds may be falsely reassuring.

An altered level of consciousness ranging from hyperarousal to lethargy to coma is present in most patients with delirium and can be assessed easily at the bedside. In a patient with a relatively normal level of consciousness, a screen for an attentional deficit is in order, because this deficit is the classic neuropsychological hallmark of delirium. Attention can be assessed while taking a history from the patient. Tangential speech, a fragmentary flow of ideas, or inability to follow complex commands often signifies an attentional problem. There are formal neuropsychological tests to assess attention, but a simple bedside test of digit span forward is quick and fairly sensitive. In this task, patients are asked to repeat successively longer random strings of digits beginning with two digits in a row, said to the patient at one per second intervals. Healthy adults can repeat a string of five to seven digits before faltering; a digit span of four or less usually indicates an attentional deficit unless hearing or language barriers are present, and many patients with delirium have digit spans of three or fewer digits.

More formal neuropsychological testing can be helpful in assessing a delirious patient, but it is usually too cumbersome and time-consuming in the inpatient setting. A Mini-Mental State Examination (MMSE) provides information regarding orientation, language, and visuospatial skills **(Chap. 25)**; however, performance of many tasks on the MMSE, including the spelling of "world" backward and serial subtraction of digits, will be impaired by delirious patients' attentional deficits, rendering the test unreliable.

The remainder of the screening neurologic examination should focus on identifying new focal neurologic deficits. Focal strokes or mass lesions in isolation are rarely the cause of delirium, but patients with underlying extensive cerebrovascular disease or neurodegenerative conditions may not be able to cognitively tolerate even relatively small new insults. Patients should be screened for other signs of neurodegenerative conditions such as parkinsonism, which is seen not only in idiopathic Parkinson's disease but also in other dementing conditions including Alzheimer's disease, dementia with Lewy bodies, and progressive supranuclear palsy. The presence of multifocal myoclonus or asterixis on the motor examination is nonspecific but usually indicates a metabolic or toxic etiology of the delirium.

ETIOLOGY

Some etiologies can be easily discerned through a careful history and physical examination, whereas others require confirmation with laboratory studies, imaging, or other ancillary tests. A large, diverse group of insults can lead to delirium, and the cause in many patients is multifactorial. Common etiologies are listed in **Table 24-2**.

Prescribed, over-the-counter, and herbal medications all can precipitate delirium. Drugs with anticholinergic properties, narcotics, and benzodiazepines are particularly common offenders, but nearly any compound can lead to cognitive dysfunction in a predisposed patient. Whereas an elderly patient with baseline dementia may become delirious upon exposure to a relatively low dose of a medication, in less susceptible individuals delirium occurs only with very high doses of the same medication. This observation emphasizes the importance of correlating the timing of recent medication changes, including dose and formulation, with the onset of cognitive dysfunction.

In younger patients, illicit drugs and toxins are common causes of delirium. In addition to more classic drugs of abuse, the recent rise in availability of "bath salts," synthetic cannabis, methylenedioxymethamphetamine (MDMA, ecstasy), γ-hydroxybutyrate (GHB), and the phencyclidine (PCP)-like agent ketamine has led to an increase in delirious young persons presenting to acute care settings **(Chap. 447)**. Many common prescription drugs such as oral narcotics and benzodiazepines are often abused and readily available on the street. Alcohol abuse leading to high serum levels causes confusion, but more commonly, it is withdrawal from alcohol that leads to a hyperactive delirium **(Chap. 445)**. Alcohol and benzodiazepine withdrawal should be considered in all cases of delirium because even patients who drink only a few servings of alcohol every day can experience relatively severe withdrawal symptoms upon hospitalization.

Metabolic abnormalities such as electrolyte disturbances of sodium, calcium, magnesium, or glucose can cause delirium, and

TABLE 24-2 Common Etiologies of Delirium

Toxins
Prescription medications: especially those with anticholinergic properties, narcotics, and benzodiazepines
Drugs of abuse: alcohol intoxication and alcohol withdrawal, opiates, ecstasy, LSD, GHB, PCP, ketamine, cocaine, "bath salts," marijuana and its synthetic forms
Poisons: inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic Conditions
Electrolyte disturbances: hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypercalcemia, hypocalcemia, hypomagnesemia
Hypothermia and hyperthermia
Pulmonary failure: hypoxemia and hypercarbia
Liver failure/hepatic encephalopathy
Renal failure/uremia
Cardiac failure
Vitamin deficiencies: B_{12}, thiamine, folate, niacin
Dehydration and malnutrition
Anemia
Infections
Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis
CNS infections: meningitis, encephalitis, brain abscess
Endocrine Conditions
Hyperthyroidism, hypothyroidism
Hyperparathyroidism
Adrenal insufficiency
Cerebrovascular Disorders
Global hypoperfusion states
Hypertensive encephalopathy
Focal ischemic strokes and hemorrhages (rare): especially nondominant parietal and thalamic lesions
Autoimmune Disorders
CNS vasculitis
Cerebral lupus
Neurologic paraneoplastic and autoimmune encephalitis
Seizure-Related Disorders
Nonconvulsive status epilepticus
Intermittent seizures with prolonged postictal states
Neoplastic Disorders
Diffuse metastases to the brain
Gliomatosis cerebri
Carcinomatous meningitis
CNS lymphoma
Hospitalization
Terminal end-of-life delirium

Abbreviations: CNS, central nervous system; GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; PCP, phencyclidine.

mild derangements can lead to substantial cognitive disturbances in susceptible individuals. Other common metabolic etiologies include liver and renal failure, hypercarbia and hypoxemia, vitamin deficiencies of thiamine and B_{12}, autoimmune disorders including central nervous system (CNS) vasculitis, and endocrinopathies such as thyroid and adrenal disorders.

Systemic infections often cause delirium, especially in the elderly. A common scenario involves the development of an acute cognitive decline in the setting of a urinary tract infection in a patient with baseline dementia. Pneumonia, skin infections such as cellulitis, and frank sepsis also lead to delirium. This so-called septic encephalopathy, often seen in the ICU, is probably due to the release of proinflammatory cytokines and their diffuse cerebral effects. CNS infections such as meningitis, encephalitis, and abscess are less common etiologies of delirium as are cases of autoimmune or paraneoplastic encephalitis; however, in light of the high morbidity and mortality rates associated with these conditions when they are not treated, clinicians must always maintain a high index of suspicion.

In some susceptible individuals, exposure to the unfamiliar environment of a hospital itself can lead to delirium. This etiology usually occurs as part of a multifactorial delirium and should be considered a diagnosis of exclusion after all other causes have been thoroughly investigated. Many primary prevention and treatment strategies for delirium involve relatively simple methods to address the aspects of the inpatient setting that are most confusing.

Cerebrovascular etiologies of delirium are usually due to global hypoperfusion in the setting of systemic hypotension from heart failure, septic shock, dehydration, or anemia. Focal strokes in the right parietal lobe and medial dorsal thalamus rarely can lead to a delirious state. A more common scenario involves a new focal stroke or hemorrhage causing confusion in a patient who has decreased cerebral reserve. In these individuals, it is sometimes difficult to distinguish between cognitive dysfunction resulting from the new neurovascular insult itself and delirium due to the infectious, metabolic, and pharmacologic complications that can accompany hospitalization after stroke.

Because a fluctuating course often is seen in delirium, intermittent seizures may be overlooked when one is considering potential etiologies. Both nonconvulsive status epilepticus and recurrent focal or generalized seizures followed by postictal confusion can cause delirium; EEG remains essential for this diagnosis and should be considered whenever the etiology of delirium remains unclear following initial workup. Seizure activity spreading from an electrical focus in a mass or infarct can explain global cognitive dysfunction caused by relatively small lesions.

It is extremely common for patients to experience delirium at the end of life in palliative care settings. This condition, sometimes described as *terminal restlessness*, must be identified and treated aggressively because it is an important cause of patient and family discomfort at the end of life. It should be remembered that these patients also may be suffering from more common etiologies of delirium such as systemic infection.

LABORATORY AND DIAGNOSTIC EVALUATION

A cost-effective approach allows the history and physical examination to guide further tests. No single algorithm will fit all delirious patients due to the staggering number of potential etiologies, but one stepwise approach is detailed in **Table 24-3**. If a clear precipitant such as an offending medication is identified, further testing may not be required. If, however, no likely etiology is uncovered with initial evaluation, an aggressive search for an underlying cause should be initiated.

Basic screening labs, including a complete blood count, electrolyte panel, and tests of liver and renal function, should be obtained in all patients with delirium. In elderly patients, screening for systemic infection, including chest radiography, urinalysis and culture, and possibly blood cultures, is important. In younger individuals, serum and urine drug and toxicology screening may be appropriate earlier in the workup. Additional laboratory tests addressing other autoimmune, endocrinologic, metabolic, and infectious etiologies should be reserved for patients in whom the diagnosis remains unclear after initial testing.

Multiple studies have demonstrated that brain imaging in patients with delirium is often unhelpful. If, however, the initial workup is unrevealing, most clinicians quickly move toward imaging of the brain to exclude structural causes. A noncontrast computed tomography (CT) scan can identify large masses and hemorrhages but is otherwise unlikely to help determine an etiology of delirium. The ability of magnetic resonance imaging (MRI) to identify most acute ischemic strokes as well as to provide neuroanatomic detail that gives clues to possible infectious, inflammatory, neurodegenerative, and neoplastic conditions makes it the test of choice. Because MRI

TABLE 24-3 Stepwise Evaluation of a Patient with Delirium

Initial Evaluation
History with special attention to medications (including over-the-counter and herbals)
General physical examination and neurologic examination
Complete blood count
Electrolyte panel including calcium, magnesium, phosphorus
Liver function tests, including albumin
Renal function tests
First-tier Further Evaluation Guided by Initial Evaluation
Systemic infection screen
Urinalysis and culture
Chest radiograph
Blood cultures
Electrocardiogram
Arterial blood gas
Serum and/or urine toxicology screen (perform earlier in young persons)
Brain imaging with MRI with diffusion and gadolinium (preferred) or CT
Suspected CNS infection or other inflammatory disorder: lumbar puncture after brain imaging
Suspected seizure-related etiology: electroencephalogram (EEG) (if high suspicion, should be performed immediately)
Second-tier Further Evaluation
Vitamin levels: B_{12}, folate, thiamine
Endocrinologic laboratories: thyroid-stimulating hormone (TSH) and free T_4; cortisol
Serum ammonia
Sedimentation rate
Autoimmune serologies: antinuclear antibodies (ANA), complement levels; p-ANCA, c-ANCA, consider paraneoplastic/autoimmune encephalitis serologies
Infectious serologies: rapid plasmin reagin (RPR); fungal and viral serologies if high suspicion; HIV antibody
Lumbar puncture (if not already performed)
Brain MRI with and without gadolinium (if not already performed)

Abbreviations: c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.

techniques are limited by availability, speed of imaging, patient's cooperation, and contraindications, many clinicians begin with CT scanning and proceed to MRI if the etiology of delirium remains elusive.

Lumbar puncture (LP) must be obtained immediately after neuroimaging for all patients in whom CNS infection is suspected. Spinal fluid examination can also be useful in identifying inflammatory and neoplastic conditions. As a result, LP should be considered in any delirious patient with a negative workup. EEG remains invaluable if seizures are considered or if there is no cause readily identified.

TREATMENT

Delirium

Management of delirium begins with treatment of the underlying inciting factor (e.g., patients with systemic infections should be given appropriate antibiotics, and underlying electrolyte disturbances judiciously corrected). These treatments often lead to prompt resolution of delirium. Blindly targeting the symptoms of delirium pharmacologically only serves to prolong the time patients remain in the confused state and may mask important diagnostic information.

Relatively simple methods of supportive care can be highly effective. Reorientation by the nursing staff and family combined with visible clocks, calendars, and outside-facing windows can reduce confusion. Sensory isolation should be prevented by providing glasses and hearing aids to patients who need them. Sundowning can be addressed to a large extent through vigilance to appropriate sleep-wake cycles. During the day, a well-lit room should be accompanied by activities or exercises to prevent napping. At night, a quiet, dark environment with limited interruptions by staff can assure proper rest. These sleep-wake cycle interventions are especially important in the ICU setting as the usual constant 24-h activity commonly provokes delirium. Attempting to mimic the home environment as much as possible also has been shown to help treat and even prevent delirium. Visits from friends and family throughout the day minimize the anxiety associated with the constant flow of new faces of staff and physicians. Allowing hospitalized patients to have access to home bedding, clothing, and nightstand objects makes the hospital environment less foreign and therefore less confusing. Simple standard nursing practices such as maintaining proper nutrition and volume status as well as managing pain, incontinence and skin breakdown also help alleviate discomfort and resulting confusion.

In some instances, patients pose a threat to their own safety or to the safety of staff members, and acute management is required. Bed alarms and personal sitters are more effective and much less disorienting than physical restraints. Chemical restraints should be avoided, but when necessary, very-low-dose typical or atypical antipsychotic medications administered on an as-needed basis can be used; however, there is little evidence that these medications are effective in delirium, and therefore they should be reserved for patients who display severe agitation and significant potential to harm themselves or staff. The recent association of antipsychotic use in the elderly with increased mortality rates underscores the importance of using these medications judiciously and only as a last resort. Benzodiazepines often worsen confusion through their sedative properties. Although many clinicians still use benzodiazepines to treat acute confusion, their use should be limited to cases in which delirium is caused by alcohol or benzodiazepine withdrawal.

PREVENTION

In light of the high morbidity associated with delirium and the tremendously increased health care costs that accompany it, development of an effective strategy to prevent delirium in hospitalized patients is extremely important. Successful identification of high-risk patients is the first step, followed by initiation of appropriate interventions. Increasingly, hospitals are using nursing or physician-administered tools to screen for high-risk individuals, triggering simple standardized protocols used to manage risk factors for delirium, including sleep-wake cycle reversal, immobility, visual impairment, hearing impairment, sleep deprivation, and dehydration. No specific medications have been definitively shown to be effective for delirium prevention, including trials of cholinesterase inhibitors and antipsychotic agents. Melatonin and its agonist ramelteon have shown some promising results in small preliminary trials. Recent studies in the ICU have focused both on identifying sedatives, such as dexmedetomidine, that are less likely to lead to delirium in critically ill patients and on developing protocols for daily awakenings in which infusions of sedative medications are interrupted and the patient is reorientated by the staff. All hospitals and health care systems should work toward decreasing the incidence of delirium and promptly recognizing and treating the disorder when it occurs.

FURTHER READING

Constantin JM et al: Efficacy and safety of sedation with dexmedetomidine in critical care patients: A meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med 35:7, 2016.

Hatta K et al: Preventive effects of ramelteon on delirium: A randomized placebo-controlled trial. JAMA Psychiatry 71:397, 2014.

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25 Dementia

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Dementia, a syndrome with many causes, affects >5 million people in the United States and results in a total annual health care cost in excess of $250 billion. Dementia is defined as an acquired deterioration in cognitive abilities that impairs the successful performance of activities of daily living. Episodic memory, the ability to recall events specific in time and place, is the cognitive function most commonly lost; 10% of persons aged >70 years and 20–40% of individuals aged >85 years have clinically identifiable memory loss. In addition to memory, dementia may erode other mental faculties, including language, visuospatial, praxis, calculation, judgment, and problem-solving abilities. Neuropsychiatric and social deficits also arise in many dementia syndromes, manifesting as depression, apathy, anxiety, hallucinations, delusions, agitation, insomnia, sleep disturbances, compulsions, or disinhibition. The clinical course may be slowly progressive, as in *Alzheimer's disease* (*AD*); static, as in anoxic encephalopathy; or may fluctuate from day to day or minute to minute, as in *dementia with Lewy bodies* (*DLB*). Most patients with AD, the most prevalent form of dementia, begin with episodic memory impairment, although in other dementias, such as *frontotemporal dementia* (*FTD*), memory loss is not typically a presenting feature. **Focal cerebral disorders are discussed in Chap. 26 and illustrated in a video library in Chap. V2; detailed discussions of AD can be found in Chap. 423; FTD and related disorders in Chap. 424; vascular dementia in Chap. 425; DLB in Chap. 426; Huntington's disease (HD) in Chap. 428; and prion diseases in Chap. 430.**

FUNCTIONAL ANATOMY OF THE DEMENTIAS

Dementia syndromes result from the disruption of specific large-scale neuronal networks; the location and severity of synaptic and neuronal loss combine to produce the clinical features **(Chap. 26)**. Behavior, mood, and attention are modulated by ascending noradrenergic, serotonergic, and dopaminergic pathways, whereas cholinergic signaling is critical for attention and memory functions. The dementias differ in the relative neurotransmitter deficit profiles; accordingly, accurate diagnosis guides effective pharmacologic therapy.

AD begins in the entorhinal region of the medial temporal lobe, spreads to the hippocampus, and then moves to lateral and posterior temporal and parietal neocortex, eventually causing a more widespread degeneration. *Vascular dementia* is associated with focal damage in a variable patchwork of cortical and subcortical regions or white matter tracts that disconnect nodes within distributed networks. In keeping with its anatomy, AD typically presents with episodic memory loss accompanied later by aphasia, executive dysfunction, or navigational problems. In contrast, dementias that begin in frontal or subcortical regions, such as FTD or HD, are less likely to begin with memory problems and more likely to present with difficulties with judgment, mood, executive control, movement, and behavior.

Lesions of frontal-striatal[1] pathways produce specific and predictable effects on behavior. The dorsolateral prefrontal cortex has connections with a central band of the caudate nucleus. Lesions of either the caudate or dorsolateral prefrontal cortex, or their connecting white matter pathways, may result in executive dysfunction, manifesting as poor organization and planning, decreased cognitive flexibility, and impaired working memory. The lateral orbital frontal cortex connects with the ventromedial caudate, and lesions of this system cause impulsiveness, distractibility, and disinhibition. The anterior cingulate cortex and adjacent medial prefrontal cortex project to the nucleus accumbens, and interruption of this system produces apathy, poverty of speech, emotional blunting, or even akinetic mutism. All corticostriatal systems also include topographically organized projections through the globus pallidus and thalamus, and damage to these nodes can likewise reproduce the clinical syndrome associated with the corresponding cortical or striatal injuries.

[1]The striatum comprises the caudate/putamen/nucleus accumbens.

THE CAUSES OF DEMENTIA

The single strongest risk factor for dementia is increasing age. The prevalence of disabling memory loss increases with each decade for those aged >50 and is usually associated with the microscopic changes of AD at autopsy. Yet some centenarians have intact memory function and no evidence of clinically significant dementia. Whether dementia is an inevitable consequence of normal human aging remains controversial.

The many causes of dementia are listed in **Table 25-1**. The frequency of each condition depends on the age group under study, access of the group to medical care, country of origin, and perhaps racial or ethnic

TABLE 25-1 Differential Diagnosis of Dementia

Most Common Causes of Dementia	
Alzheimer's disease	Alcoholism[a]
Vascular dementia	PDD/LBD spectrum
Multi-infarct	Drug/medication intoxication[a]
Diffuse white matter disease (Binswanger's)	
Less Common Causes of Dementia	
Vitamin deficiencies	Toxic disorders
Thiamine (B_1): Wernicke's encephalopathy[a]	Drug, medication, and narcotic poisoning[a]
B_{12} (subacute combined degeneration)[a]	Heavy metal intoxication[a]
Nicotinic acid (pellagra)[a]	Organic toxins
Endocrine and other organ failure	Psychiatric
Hypothyroidism[a]	Depression (pseudodementia)[a]
Adrenal insufficiency and Cushing's syndrome[a]	Schizophrenia[a]
Hypo- and hyperparathyroidism[a]	Conversion disorder[a]
Renal failure[a]	Degenerative disorders
Liver failure[a]	Huntington's disease
Pulmonary failure[a]	Multisystem atrophy
Chronic infections	Hereditary ataxias (some forms)
HIV	Frontotemporal lobar degeneration spectrum
Neurosyphilis[a]	Multiple sclerosis
Papovavirus (JC virus) (progressive multifocal leukoencephalopathy)	Adult Down's syndrome with Alzheimer's disease
Tuberculosis, fungal, and protozoal[a]	ALS-parkinsonism-dementia complex of Guam
Whipple's disease[a]	Prion (Creutzfeldt-Jakob and Gerstmann-Sträussler-Scheinker diseases)
Head trauma and diffuse brain damage	Miscellaneous
Chronic traumatic encephalopathy	Sarcoidosis[a]
Chronic subdural hematoma[a]	Vasculitis[a]
Postanoxia	CADASIL, etc.
Postencephalitis	Acute intermittent porphyria[a]
Normal-pressure hydrocephalus[a]	Recurrent nonconvulsive seizures[a]
Intracranial hypotension	Additional conditions in children or adolescents
Neoplastic	Pantothenate kinase–associated neurodegeneration
Primary brain tumor[a]	Subacute sclerosing panencephalitis
Metastatic brain tumor[a]	Metabolic disorders (e.g., Wilson's and Leigh's diseases, leukodystrophies, lipid storage diseases, mitochondrial mutations)
Paraneoplastic/autoimmune limbic encephalitis[a]	

[a]Potentially reversible dementia.

Abbreviations: ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LBD, Lewy body disease; PDD, Parkinson's disease dementia.

background. AD is the most common cause of dementia in Western countries, accounting for more than half of all patients. Vascular disease is considered the second most frequent cause for dementia and is particularly common in elderly patients or populations with limited access to medical care, where vascular risk factors are undertreated. Often, vascular brain injury is mixed with neurodegenerative disorders, making it difficult, even for the neuropathologist, to estimate the contribution of cerebrovascular disease to the cognitive disorder in an individual patient. Dementias associated with Parkinson's disease (PD) are common and may develop years after onset of a parkinsonian disorder, as seen with PD-related dementia (PDD), or can occur concurrently with or preceding the motor syndrome, as in DLB. A mixed pathology is common, especially in very old individuals. In patients aged <65, FTD rivals AD as the most common cause of dementia. Chronic intoxications, including those resulting from alcohol and prescription drugs, are an important and often treatable cause of dementia. Other disorders listed in Table 25-1 are uncommon but important because many are reversible. The classification of dementing illnesses into reversible and irreversible disorders is a useful approach to differential diagnosis. When effective treatments for the neurodegenerative conditions emerge, this dichotomy will become obsolete.

In a study of 1000 persons attending a memory disorders clinic, 19% had a potentially reversible cause of the cognitive impairment and 23% had a potentially reversible concomitant condition that may have contributed to the patient's impairment. The three most common potentially reversible diagnoses were depression, normal pressure hydrocephalus (NPH), and alcohol dependence; medication side effects are also common and should be considered in every patient (Table 25-1).

Subtle cumulative decline in episodic memory is a common part of aging. This frustrating experience, often the source of jokes and humor, is often referred to as *benign forgetfulness of the elderly*. *Benign* means that it is not so progressive or serious that it impairs reasonably successful and productive daily functioning, although the distinction between benign and more significant memory loss can be difficult to make. At age 85, the average person is able to learn and recall approximately one-half of the items (e.g., words on a list) that he or she could at age 18. A measurable cognitive problem that does not seriously disrupt daily activities is often referred to as *mild cognitive impairment* (MCI). Factors that predict progression from MCI to an AD dementia include a prominent memory deficit, family history of dementia, presence of an apolipoprotein ε4 (Apo ε4) allele, small hippocampal volumes, an AD-like signature of cortical atrophy, low cerebrospinal fluid Aβ, and elevated tau or evidence of brain amyloid deposition on positron emission tomography (PET) imaging.

The major degenerative dementias include AD, DLB, FTD and related disorders, HD, and prion diseases, including Creutzfeldt-Jakob disease (CJD). These disorders are all associated with the abnormal aggregation of a specific protein: $A\beta_{42}$ and tau in AD; α-synuclein in DLB; tau, TAR DNA-binding protein of 43 kDa (TDP-43), or *fu*sed in *s*arcoma (FUS) in FTD; huntingtin in HD; and misfolded prion protein (PrP^{sc}) in CJD **(Table 25-2)**.

APPROACH TO THE PATIENT

Dementias

Three major issues should be kept at the forefront: (1) What is the best fit for a clinical diagnosis? (2) What component of the dementia syndrome is treatable or reversible? (3) Can the physician help to alleviate the burden on caregivers? A broad overview of the approach to dementia is shown in **Table 25-3**. The major degenerative dementias can usually be distinguished by the initial symptoms; neuropsychological, neuropsychiatric, and neurologic findings; and neuroimaging features **(Table 25-4)**.

HISTORY

The history should concentrate on the onset, duration, and tempo of progression. An acute or subacute onset of confusion may be due to delirium **(Chap. 24)** and should trigger the search for intoxication, infection, or metabolic derangement. An elderly person with slowly progressive memory loss over several years is likely to suffer from AD. Nearly 75% of patients with AD begin with memory symptoms, but other early symptoms include difficulty with managing money, driving, shopping, following instructions, finding words, or navigating. Personality change, disinhibition, and weight gain or compulsive eating suggest FTD, not AD. FTD is also suggested by prominent apathy, compulsivity, loss of empathy for others, or progressive loss of speech fluency or single-word comprehension and by a relative sparing of memory and visuospatial abilities. The diagnosis of DLB is suggested by early visual hallucinations; parkinsonism; proneness to delirium or sensitivity to psychoactive medications; rapid eye movement (REM) behavior disorder (RBD; the loss of skeletal muscle paralysis during dreaming); or Capgras syndrome, the delusion that a familiar person has been replaced by an impostor.

A history of stroke with irregular stepwise progression suggests vascular dementia. Vascular dementia is also commonly seen in the setting of hypertension, atrial fibrillation, peripheral vascular disease, and diabetes. In patients suffering from cerebrovascular disease, it can be difficult to determine whether the dementia is due to AD, vascular disease, or a mixture of the two because many of the risk factors for vascular dementia, including diabetes, high cholesterol, elevated homocysteine, and low exercise, are also putative risk factors for AD. Moreover, many patients with a major vascular contribution to their dementia lack a history of stepwise decline. Rapid progression with motor rigidity and myoclonus suggests CJD **(Chap. 430)**. Seizures may indicate strokes or neoplasm but also occur in AD, particularly early-age-of-onset AD. Gait disturbance is common in vascular dementia, PD/DLB, or NPH. A history of high-risk sexual behaviors or intravenous drug use should trigger a search for central nervous system (CNS) infection, especially HIV or syphilis. A history of recurrent head trauma could indicate chronic subdural hematoma, chronic traumatic encephalopathy (a progressive dementia best characterized in contact sport athletes such as

TABLE 25-2 The Molecular Basis for Degenerative Dementia

DEMENTIA	MOLECULAR BASIS	CAUSAL GENES (CHROMOSOME)	SUSCEPTIBILITY GENES	PATHOLOGIC FINDINGS
AD	Aβ/tau	*APP* (21), *PS-1* (14), *PS-2* (1) (<2% carry these mutations, most often in *PS-1*)	*Apo ε4* (19)	Amyloid plaques, neurofibrillary tangles, and neuropil threads
FTD	Tau	*MAPT* exon and intron mutations (17) (about 10% of familial cases)	H1 *MAPT* haplotype	Tau neuronal and glial inclusions varying in morphology and distribution
	TDP-43	*GRN* (10% of familial cases), *C9ORF72* (20–30% of familial cases), rare *VCP*, very rare *TARDBP, TBK1, TIA1*		TDP-43 neuronal and glial inclusions varying in morphology and distribution
	FUS	Very rare *FUS*		FUS neuronal and glial inclusions varying in morphology and distribution
DLB	α-Synuclein	Very rare *SNCA* (4)	Unknown	α-Synuclein neuronal inclusions (Lewy bodies)
CJD	PrP^{SC}	*PRNP* (20) (up to 15% of patients carry these dominant mutations)	Codon 129 homozygosity for methionine or valine	PrP^{SC} deposition, panlaminar spongiosis

Abbreviations: AD, Alzheimer's disease; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia.

TABLE 25-3 Evaluation of the Patient with Dementia

ROUTINE EVALUATION	OPTIONAL FOCUSED TESTS	OCCASIONALLY HELPFUL TESTS
History	Psychometric testing	EEG
Physical examination	Chest x-ray	Parathyroid function
Laboratory tests	Lumbar puncture	Adrenal function
Thyroid function (TSH)	Liver function	Urine heavy metals
Vitamin B_{12}	Renal function	RBC sedimentation rate
Complete blood count	Urine toxin screen	Angiogram
Electrolytes	HIV	Brain biopsy
CT/MRI	Apolipoprotein E	SPECT
	RPR or VDRL	PET
		Lab screen for autoantibodies
Diagnostic Categories		
REVERSIBLE CAUSES	**IRREVERSIBLE/ DEGENERATIVE DEMENTIAS**	**PSYCHIATRIC DISORDERS**
Examples	Examples	Depression
Hypothyroidism	Alzheimer's	Schizophrenia
Thiamine deficiency	Frontotemporal dementia	Conversion reaction
Vitamin B_{12} deficiency	Huntington's	
Normal-pressure hydrocephalus	Dementia with Lewy bodies	
Subdural hematoma	Vascular	
Chronic infection	Leukoencephalopathies	
Brain tumor	Parkinson's	
Drug intoxication		
Autoimmune encephalopathy		
Associated Treatable Conditions		
	Depression	Agitation
	Seizures	Caregiver "burnout"
	Insomnia	Drug side effects

Abbreviations: CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; RBC, red blood cell; RPR, rapid plasma reagin (test); SPECT, single-photon emission computed tomography; TSH, thyroid-stimulating hormone; VDRL, Venereal Disease Research Laboratory (test for syphilis).

boxers and American football players), intracranial hypotension, or NPH. Subacute onset of severe amnesia and psychosis with mesial temporal T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities on magnetic resonance imaging (MRI) should raise concern for paraneoplastic limbic encephalitis, especially in a long-term smoker or other patients at risk for cancer. Related autoimmune conditions, such as voltage-gated potassium channel (VGKC)- or N-methyl-D-aspartate (NMDA)-receptor antibody-mediated encephalopathy, can present with a similar tempo and imaging signature with or without characteristic motor manifestations such as myokymia (anti-VGKC) and faciobrachial dystonic seizures (anti-NMDA) **(Chap. 90)**. Alcohol abuse creates risk for malnutrition and thiamine deficiency. Veganism, bowel irradiation, an autoimmune diathesis, a remote history of gastric surgery, and chronic antihistamine therapy for dyspepsia or gastroesophageal reflux predispose to B_{12} deficiency. Certain occupations, such as working in a battery or chemical factory, might indicate heavy metal intoxication. Careful review of medication intake, especially for sedatives and analgesics, may raise the issue of chronic drug intoxication. An autosomal dominant family history is found in HD and in familial forms of AD, FTD, DLB, or prion disorders. A history of mood disorders, the recent death of a loved one, or depressive signs, such as insomnia or weight loss, raise the possibility of depression-related cognitive impairments.

PHYSICAL AND NEUROLOGIC EXAMINATION

A thorough general and neurologic examination is essential to document dementia, to look for other signs of nervous system involvement, and to search for clues suggesting a systemic disease that might be responsible for the cognitive disorder. Typical AD spares motor systems until later in the course. In contrast, FTD patients often develop axial rigidity, supranuclear gaze palsy, or a motor neuron disease reminiscent of amyotrophic lateral sclerosis (ALS). In DLB, the initial symptoms may include the new onset of a parkinsonian syndrome (resting tremor, cogwheel rigidity, bradykinesia, festinating gait), but DLB often starts with visual hallucinations or dementia. Symptoms referable to the lower brainstem (RBD, gastrointestinal or autonomic problems) may arise years or even decades before parkinsonism or dementia. Corticobasal syndrome (CBS) features asymmetric akinesia and rigidity, dystonia, myoclonus, alien limb phenomena, pyramidal signs, and prefrontal deficits such as nonfluent aphasia with or without motor speech impairment, executive dysfunction, apraxia, or a behavioral disorder. Progressive supranuclear palsy (PSP) is associated with unexplained falls, axial rigidity, dysphagia, and vertical gaze deficits. CJD is suggested by the presence of diffuse rigidity, an akinetic-mute state, and prominent, often startle-sensitive myoclonus.

Hemiparesis or other focal neurologic deficits suggest vascular dementia or brain tumor. Dementia with a myelopathy and peripheral neuropathy suggests vitamin B_{12} deficiency. Peripheral neuropathy could also indicate another vitamin deficiency, heavy metal

TABLE 25-4 Clinical Differentiation of the Major Dementias

DISEASE	FIRST SYMPTOM	MENTAL STATUS	NEUROPSYCHIATRY	NEUROLOGY	IMAGING
AD	Memory loss	Episodic memory loss	Irritability, anxiety, depression	Initially normal	Entorhinal cortex and hippocampal atrophy
FTD	Apathy; poor judgment/ insight, speech/language; hyperorality	Frontal/executive and/or language; spares drawing	Apathy, disinhibition, overeating, compulsivity	May have vertical gaze palsy, axial rigidity, dystonia, alien hand, or MND	Frontal, insular, and/or temporal atrophy; usually spares posterior parietal lobe
DLB	Visual hallucinations, REM sleep behavior disorder, delirium, Capgras syndrome, parkinsonism	Drawing and frontal/ executive; spares memory; delirium-prone	Visual hallucinations, depression, sleep disorder, delusions	Parkinsonism	Posterior parietal atrophy; hippocampi larger than in AD
CJD	Dementia, mood, anxiety, movement disorders	Variable, frontal/ executive, focal cortical, memory	Depression, anxiety, psychosis in some	Myoclonus, rigidity, parkinsonism	Cortical ribboning and basal ganglia or thalamus hyperintensity on diffusion/ FLAIR MRI
Vascular	Often but not always sudden; variable; apathy, falls, focal weakness	Frontal/executive, cognitive slowing; can spare memory	Apathy, delusions, anxiety	Usually motor slowing, spasticity; can be normal	Cortical and/or subcortical infarctions, confluent white matter disease

Abbreviations: AD, Alzheimer's disease; CBD, cortical basal degeneration; CJD, Creutzfeldt-Jakob disease; DLB, dementia with Lewy bodies; FLAIR, fluid-attenuated inversion recovery; FTD, frontotemporal dementia; MND, motor neuron disease; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy; REM, rapid eye movement.

intoxication, thyroid dysfunction, Lyme disease, or vasculitis. Dry, cool skin, hair loss, and bradycardia suggest hypothyroidism. Fluctuating confusion associated with repetitive stereotyped movements may indicate ongoing limbic, temporal, or frontal seizures. In the elderly, hearing impairment or visual loss may produce confusion and disorientation misinterpreted as dementia. Profound bilateral sensorineural hearing loss in a younger patient with short stature or myopathy, however, should raise concern for a mitochondrial disorder.

COGNITIVE AND NEUROPSYCHIATRIC EXAMINATION

Brief screening tools such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MOCA), and Cognistat can be used to capture dementia and follow progression. None of these tests is highly sensitive to early-stage dementia or discriminates between dementia syndromes. The MMSE is a 30-point test of cognitive function, with each correct answer being scored as 1 point. It includes tests in the areas of: orientation (e.g., identify season/date/month/year/floor/hospital/town/state/country); registration (e.g., name and restate 3 objects); recall (e.g., remember the same three objects 5 min later); and language (e.g., name pencil and watch; repeat "no ifs ands or buts"; follow a 3-step command; obey a written command; and write a sentence and copy a design). In most patients with MCI and some with clinically apparent AD, bedside screening tests may be normal, and a more challenging and comprehensive set of neuropsychological tests will be required. When the etiology for the dementia syndrome remains in doubt, a specially tailored evaluation should be performed that includes tasks of working and episodic memory, executive function, language, and visuospatial and perceptual abilities. In AD, the early deficits involve episodic memory, category generation ("name as many animals as you can in 1 minute"), and visuoconstructive ability. Usually deficits in verbal or visual episodic memory are the first neuropsychological abnormalities detected, and tasks that require the patient to recall a long list of words or a series of pictures after a predetermined delay will demonstrate deficits in most patients. In FTD, the earliest deficits on cognitive testing involve executive control or language (speech or naming) function, but some patients lack either finding despite profound social-emotional deficits. PDD or DLB patients have more severe deficits in visuospatial function but do better on episodic memory tasks than patients with AD. Patients with vascular dementia often demonstrate a mixture of executive control and visuospatial deficits, with prominent psychomotor slowing. In delirium, the most prominent deficits involve attention, working memory, and executive function, making the assessment of other cognitive domains challenging and often uninformative.

A functional assessment should also be performed to help the physician determine the day-to-day impact of the disorder on the patient's memory, community affairs, hobbies, judgment, dressing, and eating. Knowledge of the patient's functional abilities will help the clinician and the family to organize a therapeutic approach.

Neuropsychiatric assessment is important for diagnosis, prognosis, and treatment. In the early stages of AD, mild depressive features, social withdrawal, and irritability or anxiety are the most prominent psychiatric changes, but patients often maintain core social graces into the middle or late stages, when delusions, agitation, and sleep disturbance may emerge. In FTD, dramatic personality change with apathy, overeating, compulsions, disinhibition, euphoria, and loss of empathy are early and common. DLB is associated with visual hallucinations, delusions related to person or place identity, RBD, and excessive daytime sleepiness. Dramatic fluctuations occur not only in cognition but also in arousal. Vascular dementia can present with psychiatric symptoms such as depression, anxiety, delusions, disinhibition, or apathy.

LABORATORY TESTS

The choice of laboratory tests in the evaluation of dementia is complex and should be tailored to the individual patient. The physician must take measures to avoid missing a reversible or treatable cause, yet no single treatable etiology is common; thus, a screen must use multiple tests, each of which has a low yield. Cost/benefit ratios are difficult to assess, and many laboratory screening algorithms for dementia discourage multiple tests. Nevertheless, even a test with only a 1–2% positive rate is worth undertaking if the alternative is missing a treatable cause of dementia. Table 25-3 lists most screening tests for dementia. The American Academy of Neurology recommends the routine measurement of a complete blood count, electrolytes, renal and thyroid function, a vitamin B_{12} level, and a neuroimaging study (computed tomography [CT] or MRI).

Neuroimaging studies, especially MRI, help to rule out primary and metastatic neoplasms, locate areas of infarction or inflammation, detect subdural hematomas, and suggest NPH or diffuse white matter disease. They also help to establish a regional pattern of atrophy. Support for the diagnosis of AD includes hippocampal atrophy in addition to posterior-predominant cortical atrophy **(Fig. 25-1)**. Focal frontal, insular, and/or anterior temporal atrophy suggests FTD **(Chap. 424)**. DLB often features less prominent atrophy, with greater involvement of amygdala than hippocampus. In CJD, magnetic resonance (MR) diffusion-weighted imaging reveals restricted diffusion within the cortical ribbon and/or basal ganglia in most patients. Extensive multifocal white matter abnormalities suggest a vascular etiology **(Fig. 25-2)**. Communicating hydrocephalus with

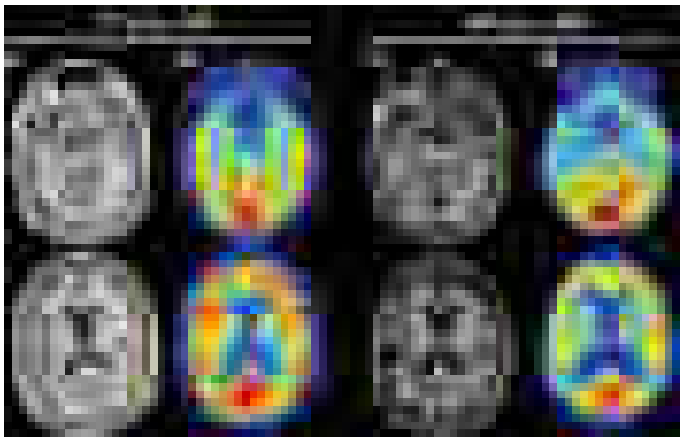


FIGURE 25-1 Alzheimer's disease (AD). Axial T1-weighted magnetic resonance images of a healthy 71-year-old (***A***) and a 64-year-old with AD (***C***). Note the reduction in medial temporal lobe volume in the patient with AD. Fluorodeoxyglucose positron emission tomography scans of the same individuals (***B*** and ***D***) demonstrate reduced glucose metabolism in the posterior temporoparietal regions bilaterally in AD, a typical finding in this condition. HC, healthy control. *(Images courtesy of Gil Rabinovici, University of California, San Francisco and William Jagust, University of California, Berkeley.)*

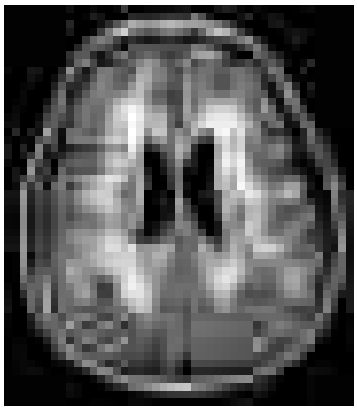


FIGURE 25-2 Diffuse white matter disease. Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance image through the lateral ventricles reveals multiple areas of hyperintensity (*arrows*) involving the periventricular white matter as well as the corona radiata and striatum. Although seen in some individuals with normal cognition, this appearance is more pronounced in patients with dementia of a vascular etiology.

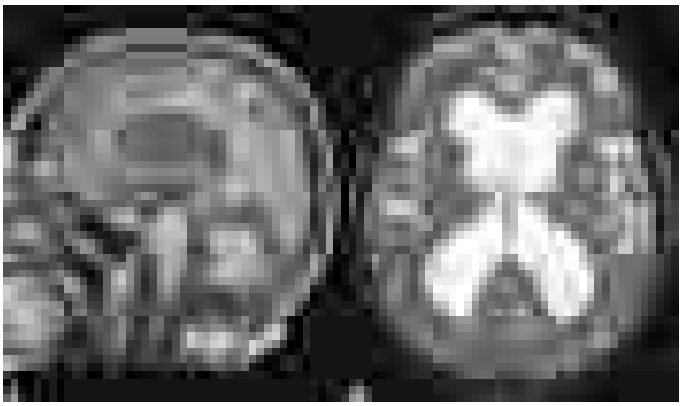


FIGURE 25-3 Normal-pressure hydrocephalus. *A.* Sagittal T1-weighted magnetic resonance image (MRI) demonstrates dilation of the lateral ventricle and stretching of the corpus callosum (*arrows*), depression of the floor of the third ventricle (*single arrowhead*), and enlargement of the aqueduct (*double arrowheads*). Note the diffuse dilation of the lateral, third, and fourth ventricles with a patent aqueduct, typical of communicating hydrocephalus. ***B.*** Axial T2-weighted MRIs demonstrate dilation of the lateral ventricles. This patient underwent successful ventriculoperitoneal shunting.

vertex effacement (crowding of dorsal convexity gyri/sulci), gaping Sylvian fissures despite minimal cortical atrophy, and additional features shown in Fig. 25-3 suggest NPH. Single-photon emission computed tomography (SPECT) and PET scanning show temporal-parietal hypoperfusion or hypometabolism in AD and frontotemporal deficits in FTD, but these changes often reflect atrophy and can therefore be detected with MRI alone in many patients. Recently, amyloid imaging has shown promise for the diagnosis of AD, and Pittsburgh Compound-B (PiB) (not available outside of research settings) and ^{18}F-AV-45 (florbetapir; approved by the U.S. Food and Drug Administration in 2013) are reliable radioligands for detecting brain amyloid associated with amyloid angiopathy or neuritic plaques of AD (Fig. 25-4). Because these abnormalities can be seen in cognitively normal older persons (~25% of individuals at age 65), however, amyloid imaging may also detect preclinical or incidental AD in patients lacking an AD-like dementia syndrome. Currently, the main clinical value of amyloid imaging is to exclude AD as the likely cause of dementia in patients who have negative scans. Once disease-modifying therapies become available, use of these biomarkers may help to identify treatment candidates before irreversible brain injury has occurred. In the meantime, the prognostic value of detecting brain amyloid in an asymptomatic elder remains a topic of vigorous investigation. Similarly, MRI perfusion and structural/functional connectivity methods are being explored as potential treatment-monitoring strategies.

Lumbar puncture need not be done routinely in the evaluation of dementia, but it is indicated when CNS infection or inflammation are credible diagnostic possibilities. Cerebrospinal fluid (CSF) levels of $A\beta_{42}$ and tau proteins show differing patterns with the various dementias, and the presence of low $A\beta_{42}$ and mildly elevated CSF tau is highly suggestive of AD. The routine use of lumbar puncture in the diagnosis of dementia is debated, but the sensitivity and specificity of AD diagnostic measures are not yet high enough to warrant routine use. Formal psychometric testing helps to document the severity of cognitive disturbance, suggest psychogenic causes, and provide a more formal method for following the disease course. Electroencephalogram (EEG) is not routinely used but can help to suggest CJD (repetitive bursts of diffuse high-amplitude sharp waves, or "periodic complexes") or an underlying nonconvulsive seizure disorder (epileptiform discharges). Brain biopsy (including meninges) is not advised except to diagnose vasculitis, potentially treatable neoplasms, or unusual infections when the diagnosis is uncertain. Systemic disorders with CNS manifestations, such as sarcoidosis, can usually be confirmed through biopsy of lymph node or solid organ rather than brain. MR angiography should be considered when cerebral vasculitis or cerebral venous thrombosis is a possible cause of the dementia.

GLOBAL CONSIDERATIONS

Vascular dementia (Chap. 425) is more common in Asian countries, due to the higher prevalence of intracranial atherosclerosis. Rates of vascular dementia are also on the rise in developing countries as vascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus become more widespread. CNS infections, particularly with HIV (and associated opportunistic infections), syphilis, and tuberculosis, likewise represent major contributors to dementia in the developing world. Isolated populations have also contributed to our understanding of neurodegenerative dementia. Kuru, the cannibalism-associated rapidly progressive dementia seen in tribal New Guinea, played a role in the discovery of human prion disease. Amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam (or, Lytico-Bodig disease) is a poly-proteinopathy, often with tau, TDP-43, and alpha-synuclein aggregation. The root cause of the disease remains uncertain, but its incidence has declined sharply over the past 60 years.

TREATMENT

Dementia

The major goals of dementia management are to treat reversible causes and to provide comfort and support to the patient and caregivers. Treatment of underlying causes includes thyroid replacement for hypothyroidism; vitamin therapy for thiamine or B_{12} deficiency or for elevated serum homocysteine; antimicrobials for opportunistic infections or antiretrovirals for HIV; ventricular shunting for NPH; or appropriate surgical, radiation, and/or chemotherapeutic treatment for CNS neoplasms. Removal of cognition-impairing

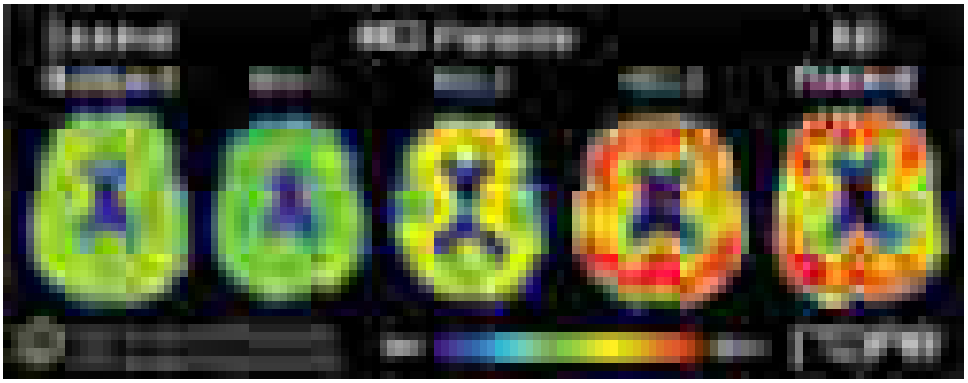


FIGURE 25-4 Positron emission tomography (PET) images obtained with the amyloid-imaging agent Pittsburgh Compound-B ([^{11}C]PIB) in a normal control (*left*); three different patients with mild cognitive impairment (MCI; *center*); and a patient with mild Alzheimer's disease (AD; *right*). Some MCI patients have control-like levels of amyloid, some have AD-like levels of amyloid, and some have intermediate levels. *(Images courtesy of William Klunk and Chester Mathis, University of Pittsburgh.)*

drugs or medications is frequently useful. If the patient's cognitive complaints stem from a psychiatric disorder, vigorous treatment of this condition should seek to eliminate the cognitive complaint or confirm that it persists despite adequate resolution of the mood or anxiety symptoms. Patients with degenerative diseases may also be depressed or anxious, and those aspects of their condition often respond to therapy. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) **(Chap. 443)**, which feature anxiolytic properties but few cognitive side effects, provide the mainstay of treatment when necessary. Anticonvulsants are used to control seizures. Levetiracetam may be particularly useful, but there have as yet been no randomized trials for treatment of AD-associated seizures.

Agitation, hallucinations, delusions, and confusion are difficult to treat. These behavioral problems represent major causes for nursing home placement and institutionalization. Before treating these behaviors with medications, the clinician should aggressively seek out modifiable environmental or metabolic factors. Hunger, lack of exercise, toothache, constipation, urinary tract or respiratory infection, electrolyte imbalance, and drug toxicity all represent easily correctable causes that can be remedied without psychoactive drugs. Drugs such as phenothiazines and benzodiazepines may ameliorate the behavior problems but have untoward side effects such as sedation, rigidity, dyskinesia, and occasionally paradoxical disinhibition (benzodiazepines). Despite their unfavorable side effect profile, second-generation antipsychotics such as quetiapine (starting dose, 12.5–25 mg daily) can be used for patients with agitation, aggression, and psychosis, although the risk profile for these compounds is significant. When patients do not respond to treatment, it is usually a mistake to advance to higher doses or to use anticholinergic drugs or sedatives (such as barbiturates or benzodiazepines). It is important to recognize and treat depression; treatment can begin with a low dose of an SSRI (e.g., escitalopram, starting dose 5 mg daily, target dose 5–10 mg daily) while monitoring for efficacy and toxicity. Sometimes apathy, visual hallucinations, depression, and other psychiatric symptoms respond to the cholinesterase inhibitors, especially in DLB, obviating the need for other more toxic therapies.

Cholinesterase inhibitors are being used to treat AD (donepezil, rivastigmine, galantamine) and PDD (rivastigmine). Recent work has focused on developing antibodies against $A\beta_{42}$ as a treatment for AD. Although the initial randomized controlled trials failed, there was some evidence for efficacy in the mildest patient groups. Therefore, researchers have begun to focus on patients with very mild disease and asymptomatic individuals at risk for AD, such as those who carry autosomal dominantly inherited genetic mutations or healthy elders with CSF or amyloid imaging biomarker evidence supporting presymptomatic AD. Memantine proves useful when treating some patients with moderate to severe AD; its major benefit relates to decreasing caregiver burden, most likely by decreasing resistance to dressing and grooming support. In moderate to severe AD, the combination of memantine and a cholinesterase inhibitor delayed nursing home placement in several studies, although other studies have not supported the efficacy of adding memantine to the regimen.

A proactive strategy has been shown to reduce the occurrence of delirium in hospitalized patients. This strategy includes frequent orientation, cognitive activities, sleep-enhancement measures, vision and hearing aids, and correction of dehydration.

Nondrug behavior therapy has an important place in dementia management. The primary goals are to make the patient's life comfortable, uncomplicated, and safe. Preparing lists, schedules, calendars, and labels can be helpful in the early stages. It is also useful to stress familiar routines, walks, and simple physical exercises. For many demented patients, memory for events is worse than their ability to carry out routine activities, and they may still be able to take part in activities such as walking, bowling, dancing, singing, bingo, and golf. Demented patients often object to losing control over familiar tasks such as driving, cooking, and handling finances. Attempts to help or take over may be greeted with complaints, depression, or anger. Hostile responses on the part of the caregiver are counterproductive and sometimes even harmful. Reassurance, distraction, and calm positive statements are more productive in this setting. Eventually, tasks such as finances and driving must be assumed by others, and the patient will conform and adjust. Safety is an important issue that includes not only driving but controlling the kitchen, bathroom, and sleeping area environments, as well as stairways. These areas need to be monitored, supervised, and made as safe as possible. A move to a retirement complex, assisted-living center, or nursing home can initially increase confusion and agitation. Repeated reassurance, reorientation, and careful introduction to the new personnel will help to smooth the process. Providing activities that are known to be enjoyable to the patient can be of considerable benefit.

The clinician must pay special attention to frustration and depression among family members and caregivers. Caregiver guilt and burnout are common. Family members often feel overwhelmed and helpless and may vent their frustrations on the patient, each other, and health care providers. Caregivers should be encouraged to take advantage of day-care facilities and respite services. Education and counseling about dementia are important. Local and national support groups, such as the Alzheimer's Association (*www.alz.org*), can provide considerable help.

FURTHER READING

Barton C et al: Non-pharmacological management of behavioral symptoms in frontotemporal and other dementias. Curr Neurol Neurosci Rep 16:14, 2016.

Griem J et al: Psychologic/functional forms of memory disorder. Handb Clin Neurol 139:407, 2017.

26 Aphasia, Memory Loss, Hemispatial Neglect, Frontal Syndromes, and Other Cerebral Disorders

M.-Marsel Mesulam

The cerebral cortex of the human brain contains ~20 billion neurons spread over an area of 2.5 m^2. The primary sensory and motor areas constitute 10% of the cerebral cortex. The rest is subsumed by modality-selective, heteromodal, paralimbic, and limbic areas collectively known as the *association cortex* **(Fig. 26-1)**. The association cortex mediates the integrative processes that subserve cognition, emotion, and comportment. A systematic testing of these mental functions is necessary for the effective clinical assessment of the association cortex and its diseases. According to current thinking, there are no centers for "hearing words," "perceiving space," or "storing memories." Cognitive and behavioral functions (domains) are coordinated by intersecting *large-scale neural networks* that contain interconnected cortical and subcortical components. Five anatomically defined *large-scale networks* are most relevant to clinical practice: (1) a left-dominant perisylvian network for language, (2) a right-dominant parietofrontal network for spatial orientation, (3) an occipitotemporal network for face and object recognition, (4) a limbic network for explicit episodic memory, and (5) a prefrontal network for the executive control of cognition and comportment. Investigations based on functional imaging have also identified a *default mode network*, which becomes activated when the person is not engaged in a specific task requiring attention to external events. The clinical consequences of damage to this network are not yet fully defined.

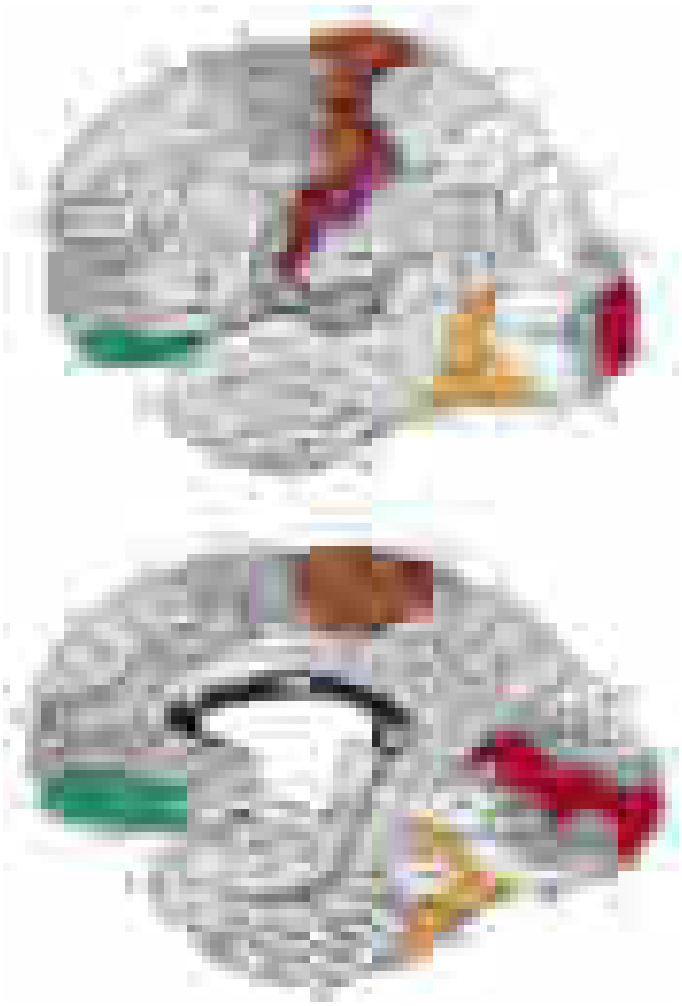


FIGURE 26-1 Lateral (*top*) and medial (*bottom*) views of the cerebral hemispheres. The numbers refer to the Brodmann cyto-architectonic designations. Area 17 corresponds to the primary visual cortex, 41–42 to the primary auditory cortex, 1–3 to the primary somatosensory cortex, and 4 to the primary motor cortex. The rest of the cerebral cortex contains association areas. AG, angular gyrus; B, Broca's area; CC, corpus callosum; CG, cingulate gyrus; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye fields (premotor cortex); FG, fusiform gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LG, lingual gyrus; MPFC, medial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PPC, posterior parietal cortex; PSC, peristriate cortex; SC, striate cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; TP, temporopolar cortex; W, Wernicke's area.

THE LEFT PERISYLVIAN NETWORK FOR LANGUAGE AND APHASIAS

The production and comprehension of words and sentences is dependent on the integrity of a distributed network located along the perisylvian region of the language-dominant (usually left) hemisphere. One hub, situated in the inferior frontal gyrus, is known as *Broca's area*. Damage to this region impairs fluency of verbal output and the grammatical structure of sentences. The location of a second hub, critical for language comprehension, is less clearly settled. Accounts of patients with focal cerebrovascular lesions identified *Wernicke's area*, located at the parietotemporal junction, as a critical hub for word and sentence comprehension. Occlusive or embolic strokes involving this area interfere with the ability to understand spoken or written language as well as the ability to express thoughts through meaningful words and statements. However, investigations of patients with the neurodegenerative syndrome of primary progressive aphasia (PPA) have shown that sentence comprehension is a widely distributed faculty jointly subserved by Broca's and Wernicke's areas, and that the areas critical for word comprehension are more closely associated with the anterior temporal lobe rather than Wernicke's area. All components of the language network are interconnected with each other and with surrounding parts of the frontal, parietal, and temporal lobes. Damage to this network gives rise to language impairments known as aphasia. Aphasia should be diagnosed only when there are deficits in the formal aspects of language, such as word finding, word choice, comprehension, spelling, or grammar. Dysarthria, apraxia of speech and mutism do not by themselves lead to a diagnosis of aphasia. In ~90% of right-handers and 60% of left-handers, aphasia occurs only after lesions of the left hemisphere.

CLINICAL EXAMINATION

The clinical examination of language should include the assessment of naming, spontaneous speech, comprehension, repetition, reading, and writing. A deficit of naming (*anomia*) is the single most common finding in aphasic patients. When asked to name a common object, the patient may fail to come up with the appropriate word, may provide a circumlocutious description of the object ("the thing for writing"), or may come up with the wrong word (*paraphasia*). If the patient offers an incorrect but related word ("pen" for "pencil"), the naming error is known as a *semantic paraphasia*; if the word approximates the correct answer but is phonetically inaccurate ("plentil" for "pencil"), it is known as a *phonemic paraphasia*. In most anomias, the patient cannot retrieve the appropriate name when shown an object but can point to the appropriate object when the name is provided by the examiner. This is known as a one-way (or retrieval-based) naming deficit. A two-way (comprehension-based or semantic) naming deficit exists if the patient can neither provide nor recognize the correct name. *Spontaneous speech* is described as "fluent" if it maintains appropriate output volume, phrase length, and melody or as "nonfluent" if it is sparse and halting and average utterance length is below four words. The examiner also should note the integrity of *grammar* as manifested by word order (syntax), tenses, suffixes, prefixes, plurals, and possessives. *Comprehension* can be tested by assessing the patient's ability to follow conversation, asking yes-no questions ("Can a dog fly?" "Does it snow in summer?"), asking the patient to point to appropriate objects ("Where is the source of illumination in this room?"), or asking for verbal definitions of single words. *Repetition* is assessed by asking the patient to repeat single words, short sentences, or strings of words such as "No ifs, ands, or buts." The testing of repetition with tongue twisters such as "hippopotamus" and "Irish constabulary" provides a better assessment of dysarthria and palilalia than of aphasia. It is important to make sure that the number of words does not exceed the patient's attention span. Otherwise, the failure of repetition becomes a reflection of the narrowed attention span (auditory working memory) rather than an indication of an aphasic deficit caused by dysfunction of a hypothetical *phonological loop* in the language network. *Reading* should be assessed for deficits in reading aloud as well as comprehension. *Alexia* describes an inability to either read aloud or comprehend written words and sentences; *agraphia* (or dysgraphia) is used to describe an acquired deficit in spelling.

Aphasias can arise acutely in cerebrovascular accidents (CVAs) or gradually in neurodegenerative diseases. In CVAs damage encompasses cerebral cortex as well as deep white matter pathways interconnecting otherwise unaffected cortical areas. The syndromes listed in **Table 26-1** are most applicable to this group, where gray matter and white matter at the lesion site are abruptly and jointly destroyed. Progressive neurodegenerative diseases can have cellular, laminar, and regional specificity for the cerebral cortex, giving rise to a different set of aphasias that will be described separately.

Wernicke's Aphasia Comprehension is impaired for spoken and written words and sentences. Language output is fluent but is highly paraphasic and circumlocutious. Paraphasic errors may lead to strings of neologisms, which lead to "jargon aphasia." Speech contains few substantive nouns. The output is therefore voluminous but uninformative. For example, a patient attempts to describe how his wife accidentally threw away something important, perhaps his dentures: "We don't need it anymore, she says. And with it when that was downstairs was my teeth-tick … a … den … dentith … my dentist. And they

TABLE 26-1 Clinical Features of Aphasias and Related Conditions Commonly Seen in Cerebrovascular Accidents

	COMPREHENSION	REPETITION OF SPOKEN LANGUAGE	NAMING	FLUENCY
Wernicke's	Impaired	Impaired	Impaired	Preserved or increased
Broca's	Preserved (except grammar)	Impaired	Impaired	Decreased
Global	Impaired	Impaired	Impaired	Decreased
Conduction	Preserved	Impaired	Impaired	Preserved
Nonfluent (anterior) transcortical	Preserved	Preserved	Impaired	Impaired
Fluent (posterior) transcortical	Impaired	Preserved	Impaired	Preserved
Isolation	Impaired	Echolalia	Impaired	No purposeful speech
Anomic	Preserved	Preserved	Impaired	Preserved except for word-finding pauses
Pure word deafness	Impaired only for spoken language	Impaired	Preserved	Preserved
Pure alexia	Impaired only for reading	Preserved	Preserved	Preserved

happened to be in that bag … see? …Where my two … two little pieces of dentist that I use … that I … all gone. If she throws the whole thing away … visit some friends of hers and she can't throw them away."

Gestures and pantomime do not improve communication. The patient may not realize that his or her language is incomprehensible and may appear angry and impatient when the examiner fails to decipher the meaning of a severely paraphasic statement. In some patients this type of aphasia can be associated with severe agitation and paranoia. The ability to follow commands aimed at axial musculature may be preserved. The dissociation between the failure to understand simple questions ("What is your name?") in a patient who rapidly closes his or her eyes, sits up, or rolls over when asked to do so is characteristic of Wernicke's aphasia and helps differentiate it from deafness, psychiatric disease, or malingering. Patients with Wernicke's aphasia cannot express their thoughts in meaning-appropriate words and cannot decode the meaning of words in any modality of input. This aphasia therefore has expressive as well as receptive components. Repetition, naming, reading, and writing also are impaired.

The lesion site most commonly associated with Wernicke's aphasia caused by CVAs is the posterior portion of the language network. An embolus to the inferior division of the middle cerebral artery (MCA), to the posterior temporal or angular branches in particular, is the most common etiology **(Chap. 419)**. Intracerebral hemorrhage, head trauma, and neoplasm are other causes of Wernicke's aphasia. A coexisting right hemianopia or superior quadrantanopia is common, and mild right nasolabial flattening may be found, but otherwise, the examination is often unrevealing. The paraphasic, neologistic speech in an agitated patient with an otherwise unremarkable neurologic examination may lead to the suspicion of a primary psychiatric disorder such as schizophrenia or mania, but the other components characteristic of acquired aphasia and the absence of prior psychiatric disease usually settle the issue. Prognosis for recovery of language function is guarded.

Broca's Aphasia Speech is nonfluent, labored, interrupted by many word-finding pauses, and usually dysarthric. It is impoverished in function words but enriched in meaning-appropriate nouns. Abnormal word order and the inappropriate deployment of *bound morphemes* (word endings used to denote tenses, possessives, or plurals) lead to a characteristic agrammatism. Speech is telegraphic and pithy but quite informative. In the following passage, a patient with Broca's aphasia describes his medical history: "I see … the dotor, dotor sent me … Bosson. Go to hospital. Dotor … kept me beside. Two, tee days, doctor send me home."

Output may be reduced to a grunt or single word ("yes" or "no"), which is emitted with different intonations in an attempt to express approval or disapproval. In addition to fluency, naming and repetition are impaired. Comprehension of spoken language is intact except for syntactically difficult sentences with a passive voice structure or embedded clauses, indicating that Broca's aphasia is not just an "expressive" or "motor" disorder and that it also may involve a comprehension deficit in decoding syntax. Patients with Broca's aphasia can be tearful, easily frustrated, and profoundly depressed. Insight into their condition is preserved, in contrast to Wernicke's aphasia. Even when spontaneous speech is severely dysarthric, the patient may be able to display a relatively normal articulation of words when singing. This dissociation has been used to develop specific therapeutic approaches (melodic intonation therapy) for Broca's aphasia. Additional neurologic deficits include right facial weakness, hemiparesis or hemiplegia, and a buccofacial apraxia characterized by an inability to carry out motor commands involving oropharyngeal and facial musculature (e.g., patients are unable to demonstrate how to blow out a match or suck through a straw). The cause is most often infarction of Broca's area (the inferior frontal convolution; "B" in Fig. 26-1) and surrounding anterior perisylvian and insular cortex due to occlusion of the superior division of the MCA **(Chap. 419)**. Mass lesions, including tumor, intracerebral hemorrhage, and abscess, also may be responsible. When the cause of Broca's aphasia is stroke, recovery of language function generally peaks within 2–6 months, after which time further progress is limited. Speech therapy is more successful than in Wernicke's aphasia.

Conduction Aphasia Speech output is fluent but contains many phonemic paraphasias, comprehension of spoken language is intact, and repetition is severely impaired. Naming elicits phonemic paraphasias, and spelling is impaired. Reading aloud is impaired, but reading comprehension is preserved. The responsible lesion, usually a CVA in the temporoparietal or dorsal perisylvian region, interferes with the function of the phonological loop interconnecting Broca's area with Wernicke's area. Occasionally, a transient Wernicke's aphasia may rapidly resolve into a conduction aphasia. The paraphasic output in conduction aphasia interferes with the ability to express meaning, but this deficit is not nearly as severe as the one displayed by patients with Wernicke's aphasia. Associated neurologic signs in conduction aphasia vary according to the primary lesion site.

Transcortical Aphasias: Fluent and Nonfluent Clinical features of *fluent (posterior) transcortical aphasia* are similar to those of Wernicke's aphasia, but repetition is intact. The lesion site disconnects the intact core of the language network from other temporoparietal association areas. Associated neurologic findings may include hemianopia. Cerebrovascular lesions (e.g., infarctions in the posterior watershed zone) and neoplasms that involve the temporoparietal cortex posterior to Wernicke's area are common causes. The features of *nonfluent (anterior) transcortical aphasia* are similar to those of Broca's aphasia, but repetition is intact and agrammatism is less pronounced. The neurologic examination may be otherwise intact, but a right hemiparesis also can exist. The lesion site disconnects the intact language network from prefrontal areas of the brain and usually involves the anterior watershed zone between anterior and MCA territories or the supplementary motor cortex in the territory of the anterior cerebral artery.

Global and Isolation Aphasias *Global aphasia* represents the combined dysfunction of Broca's and Wernicke's areas and usually results from strokes that involve the entire MCA distribution in the left hemisphere. Speech output is nonfluent, and comprehension of

language is severely impaired. Related signs include right hemiplegia, hemisensory loss, and homonymous hemianopia. *Isolation aphasia* represents a combination of the two transcortical aphasias. Comprehension is severely impaired, and there is no purposeful speech output. The patient may parrot fragments of heard conversations (*echolalia*), indicating that the neural mechanisms for repetition are at least partially intact. This condition represents the pathologic function of the language network when it is isolated from other regions of the brain. Broca's and Wernicke's areas tend to be spared, but there is damage to the surrounding frontal, parietal, and temporal cortex. Lesions are patchy and can be associated with anoxia, carbon monoxide poisoning, or complete watershed zone infarctions.

Anomic Aphasia This form of aphasia may be considered the "minimal dysfunction" syndrome of the language network. Articulation, comprehension, and repetition are intact, but confrontation naming, word finding, and spelling are impaired. Word-finding pauses are uncommon, so language output is fluent but paraphasic, circumlocutious, and uninformative. The lesion sites can be anywhere within the left hemisphere language network, including the middle and inferior temporal gyri. *Anomic aphasia is the single most common language disturbance seen in head trauma, metabolic encephalopathy, and Alzheimer's disease*.

Pure Word Deafness The most common causes are either bilateral or left-sided MCA strokes affecting the superior temporal gyrus. The net effect of the underlying lesion is to interrupt the flow of information from the auditory association cortex to the language network. Patients have no difficulty understanding written language and can express themselves well in spoken or written language. They have no difficulty interpreting and reacting to environmental sounds if the primary auditory cortex and auditory association areas of the right hemisphere are spared. Because auditory information cannot be conveyed to the language network, however, it cannot be decoded into neural word representations, and the patient reacts to speech as if it were in an alien tongue that cannot be deciphered. Patients cannot repeat spoken language but have no difficulty naming objects. In time, patients with pure word deafness teach themselves lipreading and may appear to have improved. There may be no additional neurologic findings, but agitated paranoid reactions are common in the acute stages. Cerebrovascular lesions are the most common cause.

Pure Alexia Without Agraphia This is the visual equivalent of pure word deafness. The lesions (usually a combination of damage to the left occipital cortex and to a posterior sector of the corpus callosum—the splenium) interrupt the flow of visual input into the language network. There is usually a right hemianopia, but the core language network remains unaffected. The patient can understand and produce spoken language, name objects in the left visual hemifield, repeat, and write. However, the patient acts as if illiterate when asked to read even the simplest sentence because the visual information from the written words (presented to the intact left visual hemifield) cannot reach the language network. Objects in the left hemifield may be named accurately because they activate nonvisual associations in the right hemisphere, which in turn can access the language network through transcallosal pathways anterior to the splenium. Patients with this syndrome also may lose the ability to name colors, although they can match colors. This is known as a *color anomia*. The most common etiology of pure alexia is a vascular lesion in the territory of the posterior cerebral artery or an infiltrating neoplasm in the left occipital cortex that involves the optic radiations as well as the crossing fibers of the splenium. Because the posterior cerebral artery also supplies medial temporal components of the limbic system, a patient with pure alexia also may experience an amnesia, but this is usually transient because the limbic lesion is unilateral.

Apraxia and Aphemia *Apraxia* designates a complex motor deficit that cannot be attributed to pyramidal, extrapyramidal, cerebellar, or sensory dysfunction and that does not arise from the patient's failure to understand the nature of the task. *Apraxia of speech* is used to designate articulatory abnormalities in the duration, fluidity, and stress of syllables that make up words. It can arise with CVAs in the posterior part of Broca's area or in the course of frontotemporal lobar degeneration (FTLD) with tauopathy. *Aphemia* is a severe form of acute speech apraxia that presents with severely impaired fluency (often mutism). Recovery is the rule and involves an intermediate stage of hoarse whispering. Writing, reading, and comprehension are intact, and so this is not a true aphasic syndrome. CVAs in parts of Broca's area or subcortical lesions that undercut its connections with other parts of the brain may be present. Occasionally, the lesion site is on the medial aspects of the frontal lobes and may involve the supplementary motor cortex of the left hemisphere. *Ideomotor apraxia* is diagnosed when commands to perform a specific motor act ("cough," "blow out a match") or pantomime the use of a common tool (a comb, hammer, straw, or toothbrush) in the absence of the real object cannot be followed. The patient's ability to comprehend the command is ascertained by demonstrating multiple movements and establishing that the correct one can be recognized. Some patients with this type of apraxia can imitate the appropriate movement when it is demonstrated by the examiner and show no impairment when handed the real object, indicating that the sensorimotor mechanisms necessary for the movement are intact. Some forms of ideomotor apraxia represent a disconnection of the language network from pyramidal motor systems so that commands to execute complex movements are understood but cannot be conveyed to the appropriate motor areas. *Buccofacial apraxia* involves apraxic deficits in movements of the face and mouth. Ideomotor *limb apraxia* encompasses apraxic deficits in movements of the arms and legs. Ideomotor apraxia almost always is caused by lesions in the left hemisphere and is commonly associated with aphasic syndromes, especially Broca's aphasia and conduction aphasia. Because the handling of real objects is not impaired, ideomotor apraxia by itself causes no major limitation of daily living activities. Patients with lesions of the anterior corpus callosum can display ideomotor apraxia confined to the left side of the body, a sign known as *sympathetic dyspraxia*. A severe form of sympathetic dyspraxia, known as the *alien hand* syndrome, is characterized by additional features of motor disinhibition on the left hand. *Ideational apraxia* refers to a deficit in the sequencing of goal-directed movements in patients who have no difficulty executing the individual components of the sequence. For example, when the patient is asked to pick up a pen and write, the sequence of uncapping the pen, placing the cap at the opposite end, turning the point toward the writing surface, and writing may be disrupted, and the patient may be seen trying to write with the wrong end of the pen or even with the removed cap. These motor sequencing problems usually are seen in the context of confusional states and dementias rather than focal lesions associated with aphasic conditions. *Limb-kinetic apraxia* involves clumsiness in the use of tools or objects that cannot be attributed to sensory, pyramidal, extrapyramidal, or cerebellar dysfunction. This condition can emerge in the context of focal premotor cortex lesions or *corticobasal degeneration* and can interfere with the use of tools and utensils.

Gerstmann's Syndrome The combination of *acalculia* (impairment of simple arithmetic), *dysgraphia* (impaired writing), *finger anomia* (an inability to name individual fingers such as the index and thumb), and *right-left confusion* (an inability to tell whether a hand, foot, or arm of the patient or examiner is on the right or left side of the body) is known as Gerstmann's syndrome. In making this diagnosis, it is important to establish that the finger and left-right naming deficits are not part of a more generalized anomia and that the patient is not otherwise aphasic. When Gerstmann's syndrome arises acutely and in isolation, it is commonly associated with damage to the inferior parietal lobule (especially the angular gyrus) in the left hemisphere.

Pragmatics and Prosody *Pragmatics* refers to aspects of language that communicate attitude, affect, and the figurative rather than literal aspects of a message (e.g., "green thumb" does not refer to the actual color of the finger). One component of pragmatics, *prosody,* refers to variations of melodic stress and intonation that influence attitude and the inferential aspect of verbal messages. For example, the two

statements "He *is* clever." and "He is *clever*?" contain an identical word choice and syntax but convey vastly different messages because of differences in the intonation with which the statements are uttered. Damage to right hemisphere regions corresponding to Broca's area impairs the ability to introduce meaning-appropriate prosody into spoken language. The patient produces grammatically correct language with accurate word choice, but the statements are uttered in a monotone that interferes with the ability to convey the intended stress and effect. Patients with this type of *aprosodia* give the mistaken impression of being depressed or indifferent. Other aspects of pragmatics, especially the ability to infer the figurative aspect of a message, become impaired by damage to the right hemisphere or frontal lobes.

Subcortical Aphasia Damage to subcortical components of the language network (e.g., the striatum and thalamus of the left hemisphere) also can lead to aphasia. The resulting syndromes contain combinations of deficits in the various aspects of language but rarely fit the specific patterns described in Table 26-1. In a patient with a CVA, an anomic aphasia accompanied by dysarthria or a fluent aphasia with hemiparesis should raise the suspicion of a subcortical lesion site.

CLINICAL PRESENTATION AND DIAGNOSIS OF PPA Aphasias caused by CVAs start suddenly and display maximal deficits at the onset. These are the "classic" aphasias described above. Aphasias caused by neurodegenerative diseases have an insidious onset and relentless progression. The neuropathology can be selective not only for gray matter but also for specific layers and cell types. The clinico-anatomic patterns are therefore different from those described in Table 26-1.

Several neurodegenerative syndromes, such as typical Alzheimer-type (amnestic; **Chap. 423**) and frontotemporal (behavioral; **Chap. 424**) dementias, can also include language impairments as the disease progresses. In these cases, the aphasia is an ancillary component of the overall syndrome. A diagnosis of PPA is justified only if the language disorder (i.e., aphasia) arises in relative isolation, becomes the primary concern that brings the patient to medical attention, and remains the most salient deficit for 1–2 years. PPA can be caused by either FTLD or Alzheimer's disease (AD) pathology. Rarely, an identical syndrome can be caused by Creutzfeldt-Jacob disease (CJD) but with a more rapid progression **(Chap. 430)**.

LANGUAGE IN PPA The impairments of language in PPA have slightly different patterns from those seen in CVA-caused aphasias. For example, the full syndrome of Wernicke's aphasia is almost never seen in PPA, confirming the view that sentence comprehension and word comprehension are controlled by different regions of the language network. Three major subtypes of PPA can be recognized.

Agrammatic PPA The *agrammatic variant* is characterized by consistently low fluency and impaired grammar but intact word comprehension. It most closely resembles Broca's aphasia or anterior transcortical aphasia but usually lacks the right hemiparesis or dysarthria and may have more profound impairments of grammar. Peak sites of neuronal loss (gray matter atrophy) include the left inferior frontal gyrus where Broca's area is located. The neuropathology is usually a FTLD with tauopathy but can also be an atypical form of AD pathology.

Semantic PPA The *semantic variant* is characterized by preserved fluency and syntax but poor single-word comprehension and profound two-way naming impairments. This kind of aphasia is not seen with CVAs. It differs from Wernicke's aphasia or posterior transcortical aphasia because speech is usually informative and repetition is intact. Comprehension of sentences is relatively preserved if the meaning is not too dependent on words that fail to be understood allowing the patient to surmise the gist of the conversation through contextual cues. Such patients may appear unimpaired in the course of casual small talk but become puzzled upon encountering an undecipherable word such as "pumpkin" or "umbrella." Peak atrophy sites are located in the left anterior temporal lobe, indicating that this part of the brain plays a critical role in the comprehension of words, especially words that denote concrete objects. This is a part of the brain that was not included within the classic language network, probably because it is not a common site for focal CVAs. The neuropathology is frequently an FTLD with abnormal precipitates of the 43-kDa transactive response DNA-binding protein TDP-43 of type C.

Logopenic PPA The *logopenic variant* is characterized by preserved syntax and comprehension but frequent and severe word-finding pauses, anomia, circumlocutions, and simplifications during spontaneous speech. Repetition is usually impaired. Peak atrophy sites are located in the temporoparietal junction and posterior temporal lobe, partially overlapping with traditional location of Wernicke's area. However, the comprehension impairment of *Wernicke's aphasia* is absent probably because the underlying deep white matter, frequently damaged by CVAs, remains relatively intact in PPA. The repetition impairment suggests that parts of Wernicke's area are critical for phonological loop functionality. In contrast to Broca's aphasia or agrammatic PPA, the interruption of fluency is variable so that speech may appear entirely normal if the patient is allowed to engage in small talk. Logopenic PPA resembles the anomic aphasia of Table 26-1 but usually has longer and more frequent word-finding pauses. When repetition is impaired the aphasia resembles the *conduction aphasia* in Table 26-1. Of all PPA subtypes, this is the one most commonly associated with the pathology of AD, but FTLD can also be the cause. In addition to these three major subtypes, there is also a *mixed* type of PPA where grammar, fluency and word comprehension are jointly impaired. This is most like the global aphasia of Table 26-1. Rarely, PPA can present with patterns reminiscent of *pure word deafness* or *Gerstmann's syndrome*.

THE PARIETOFRONTAL NETWORK FOR SPATIAL ORIENTATION

Adaptive spatial orientation is subserved by a large-scale network containing three major cortical components. The *cingulate cortex* provides access to a motivational mapping of the extrapersonal space, the *posterior parietal cortex* to a sensorimotor representation of salient extrapersonal events, and the *frontal eye fields* to motor strategies for attentional behaviors **(Fig. 26-2)**. Subcortical components of this network include the striatum and the thalamus. Damage to this network can undermine the distribution of attention within the extrapersonal space, giving rise to hemispatial neglect, simultanagnosia and object finding failures. The integration of egocentric (self-centered) with allocentric (object-centered) coordinates can also be disrupted, giving rise to impairments in route finding, the ability to avoid obstacles, and the ability to dress.

HEMISPATIAL NEGLECT

Contralesional hemispatial neglect represents one outcome of damage to the cortical or subcortical components of this network. *The traditional view that hemispatial neglect always denotes a parietal lobe lesion is inaccurate*. According to one model of spatial cognition, the right hemisphere directs attention within the *entire* extrapersonal space, whereas the left hemisphere directs attention mostly within the contralateral right hemispace. Consequently, left hemisphere lesions do not give rise to much contralesional neglect because the global attentional mechanisms of the right hemisphere can compensate for the loss of the *contralaterally* directed attentional functions of the left hemisphere. Right hemisphere lesions, however, give rise to severe contralesional left hemispatial neglect because the unaffected left hemisphere does not contain ipsilateral attentional mechanisms. This model is consistent with clinical experience, which shows that contralesional neglect is more common, more severe, and longer lasting after damage to the right hemisphere than after damage to the left hemisphere. Severe neglect for the right hemispace is rare, even in left-handers with left hemisphere lesions.

Clinical Examination Patients with severe neglect may fail to dress, shave, or groom the left side of the body; fail to eat food placed on the left side of the tray; and fail to read the left half of sentences. When asked to copy a simple line drawing, the patient fails to copy detail on the left, and when the patient is asked to write, there is a tendency to leave an unusually wide margin on the left. Two bedside tests that are useful in assessing neglect are *simultaneous bilateral stimulation* and *visual target cancellation*. In the former, the examiner provides either unilateral or simultaneous bilateral stimulation in the visual, auditory,

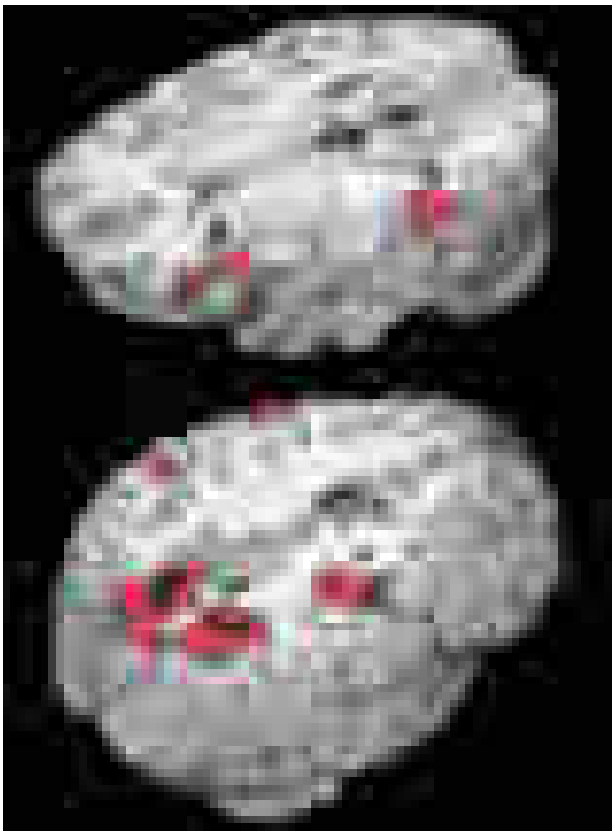


FIGURE 26-2 Functional magnetic resonance imaging of language and spatial attention in neurologically intact subjects. The red and black areas show regions of task-related significant activation. (*Top*) The subjects were asked to determine if two words were synonymous. This language task led to the simultaneous activation of the two components of the language network, Broca's area (B) and Wernicke's area (W). The activations are exclusively in the left hemisphere. (*Bottom*) The subjects were asked to shift spatial attention to a peripheral target. This task led to the simultaneous activation of the three epicenters of the attentional network: the posterior parietal cortex (P), the frontal eye fields (F), and the cingulate gyrus (CG). The activations are predominantly in the right hemisphere. *(Courtesy of Darren Gitelman, MD; with permission.)*

and tactile modalities. After right hemisphere injury, patients who have no difficulty detecting unilateral stimuli on either side experience the bilaterally presented stimulus as coming only from the right. This phenomenon is known as *extinction* and is a manifestation of the sensory-representational aspect of hemispatial neglect. In the target detection task, targets (e.g., A's) are interspersed with foils (e.g., other letters of the alphabet) on a 21.5- to 28.0-cm (8.5–11 in.) sheet of paper, and the patient is asked to circle all the targets. A failure to detect targets on the left is a manifestation of the exploratory (motor) deficit in hemispatial neglect **(Fig. 26-3*A*)**. Hemianopia is not by itself sufficient to cause the target detection failure because the patient is free to turn the head and eyes to the left. Target detection failures therefore reflect a distortion of spatial attention, not just of sensory input. Some patients with neglect also may deny the existence of hemiparesis and may even deny ownership of the paralyzed limb, a condition known as *anosognosia*.

BÁLINT'S SYNDROME, SIMULTANAGNOSIA, DRESSING APRAXIA, CONSTRUCTION APRAXIA, AND ROUTE FINDING IMPAIRMENTS

Bilateral involvement of the network for spatial attention, especially its parietal components, leads to a state of severe spatial disorientation known as *Bálint's syndrome*. Bálint's syndrome involves deficits in the orderly visuomotor scanning of the environment (*oculomotor apraxia*), accurate manual reaching toward visual targets (*optic ataxia*), and the ability to integrate visual information in the center of gaze with more peripheral information (*simultanagnosia*). A patient with simultanagnosia "misses the forest for the trees." For example, a patient who is shown a table lamp and asked to name the object may look at its circular base and call it an ashtray. Some patients with simultanagnosia report that objects they look at may vanish suddenly, probably indicating an inability to compute the oculomotor return to the original point of gaze after brief saccadic displacements. Movement and distracting stimuli greatly exacerbate the difficulties of visual perception. Simultanagnosia can occur without the other two components of Bálint's syndrome especially in association with Alzheimer's disease.

A modification of the letter cancellation task described above can be used for the bedside diagnosis of simultanagnosia. In this modification, some of the targets (e.g., A's) are made to be much larger than the others (7.5–10 cm vs 2.5 cm [3–4 in. vs 1 in.] in height), and all targets are embedded among foils. Patients with simultanagnosia display a counterintuitive but characteristic tendency to miss the larger targets **(Fig. 26-3*B*)**. This occurs because the information needed for the identification of the larger targets cannot be confined to the immediate line of gaze and requires the integration of visual information across multiple fixation points. The greater difficulty in the detection of the larger targets also indicates that poor acuity is not responsible for the impairment of visual function and that the problem is central rather than peripheral. The test shown in Fig. 26-3*B* is not by itself sufficient to diagnose simultanagnosia because some patients with a frontal network syndrome may omit the strange looking large letters, perhaps because they lack the mental flexibility needed to realize that the two types of targets are symbolically identical despite being superficially different.

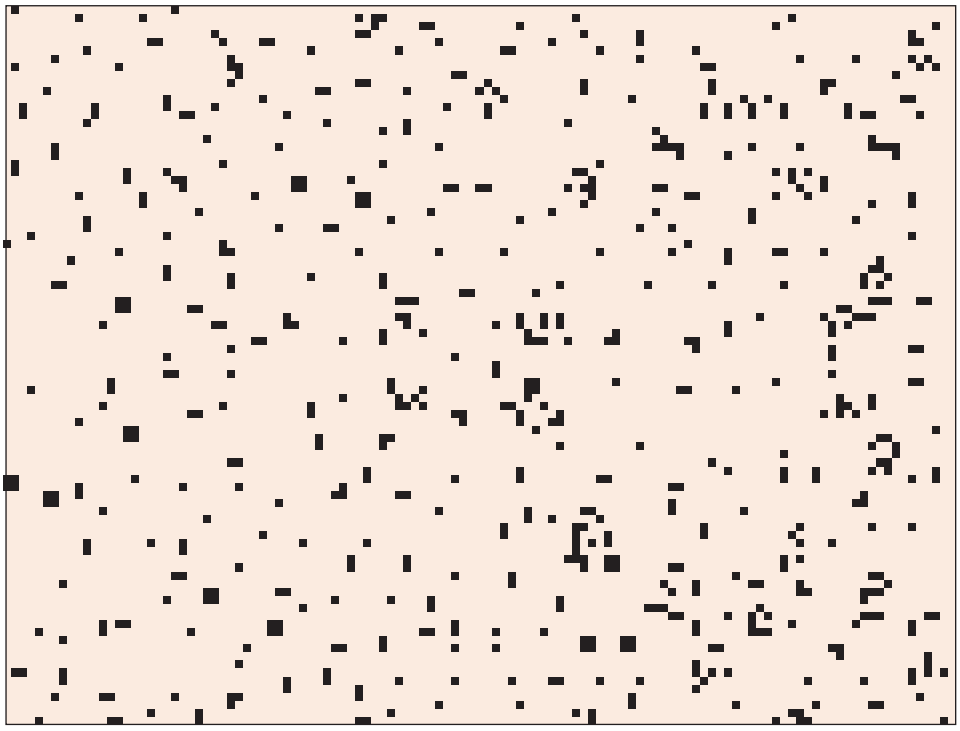
Bilateral parietal lesions can impair the integration of egocentric with allocentric spatial coordinates. One manifestation is *dressing apraxia*. A patient with this condition is unable to align the body axis with the axis of the garment and can be seen struggling as he or she holds a coat from its bottom or extends his or her arm into a fold of the garment rather than into its sleeve. Lesions that involve the posterior parietal cortex also lead to severe difficulties in copying simple line drawings. This is known as a *construction apraxia* and is much more severe if the lesion is in the right hemisphere. In some patients with right hemisphere lesions, the drawing difficulties are confined to the left side of the figure and represent a manifestation of hemispatial neglect; in others, there is a more universal deficit in reproducing contours and three-dimensional perspective. Impairments of route finding can be included in this group of disorders, which reflect an inability to orient the self with respect to external objects and landmarks.

Causes of Spatial Disorientation and the Posterior Cortical Atrophy Syndrome Cerebrovascular lesions and neoplasms in the right hemisphere are common causes of hemispatial neglect. Depending on the site of the lesion, a patient with neglect also may have hemiparesis, hemihypesthesia, and hemianopia on the left, but these are not invariant findings. The majority of these patients display considerable improvement of hemispatial neglect, usually within the first several weeks. Bálint's syndrome, dressing apraxia, and route finding impairments are more likely to result from bilateral dorsal parietal lesions; common settings for acute onset include watershed infarction between the middle and posterior cerebral artery territories, hypoglycemia, and sagittal sinus thrombosis.

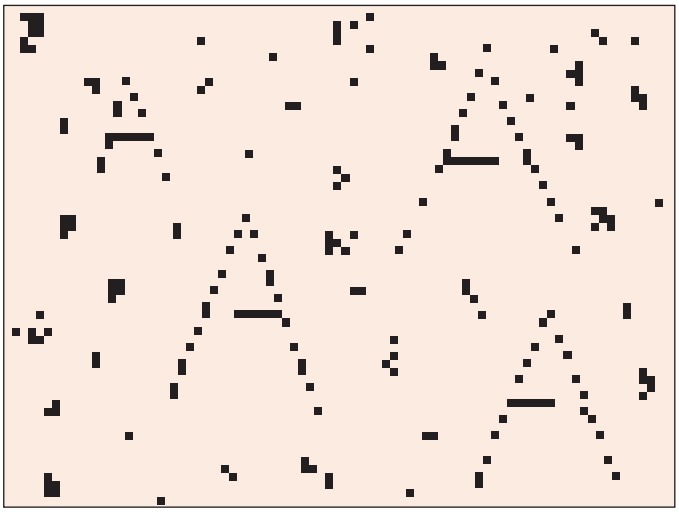
A progressive form of spatial disorientation, known as the *posterior cortical atrophy* (PCA) syndrome, most commonly represents a variant of AD with unusual concentrations of neurofibrillary degeneration in the parieto-occipital cortex and the superior colliculus **(Fig. 26-4)**. Lewy body disease (LBD), CJD, and FTLD (corticobasal degeneration type) are other possible causes. The patient displays progressive hemispatial neglect, Bálint's syndrome, and route finding impairments, usually accompanied by dressing and construction apraxia.

THE OCCIPITOTEMPORAL NETWORK FOR FACE AND OBJECT RECOGNITION

A patient with *prosopagnosia* cannot recognize familiar faces, including, sometimes, the reflection of his or her own face in the mirror. This is not a perceptual deficit because prosopagnosic patients easily can tell whether two faces are identical. Furthermore, a prosopagnosic patient who cannot recognize a familiar face by visual inspection alone can use auditory cues to reach appropriate recognition if allowed to



A



B

FIGURE 26-3 ***A.*** A 47-year-old man with a large frontoparietal lesion in the right hemisphere was asked to circle all the 'A's. Only targets on the right are circled. This is a manifestation of left hemispatial neglect. ***B.*** A 70-year-old woman with a 2-year history of degenerative dementia was able to circle most of the small targets but ignored the larger ones. This is a manifestation of simultanagnosia.

listen to the person's voice. The deficit in prosopagnosia is therefore modality-specific and reflects the existence of a lesion that prevents the activation of otherwise intact multimodal associative templates by relevant visual input. Prosopagnosic patients characteristically have no difficulty with the generic identification of a face as a face or a car as a car, but may not recognize the identity of an individual face or the make of an individual car. This reflects a visual recognition deficit for proprietary features that characterize individual members of an object class. When recognition problems become more generalized and extend to the generic identification of common objects, the condition is known as *visual object agnosia*. A patient with anomia cannot name the object but can describe its use. In contrast, a patient with visual agnosia is unable either to name a visually presented object or to describe its use. Face and object recognition disorders also can result from the simultanagnosia of Bálint's syndrome, in which case they are known as *apperceptive* agnosias as opposed to the *associative* agnosias that result from inferior temporal lobe lesions.

CAUSES AND RELATION TO SEMANTIC DEMENTIA

The characteristic lesions in prosopagnosia and visual object agnosia of acute onset consist of bilateral infarctions in the territory of the posterior cerebral arteries that involve the fusiform gyrus. Associated deficits can include visual field defects (especially superior quadrantanopias) and a centrally based color blindness known as achromatopsia. Rarely, the responsible lesion is unilateral. In such cases, prosopagnosia is associated with lesions in the right hemisphere, and object agnosia with lesions in the left. Degenerative diseases of anterior and inferior temporal cortex can cause progressive associative prosopagnosia and object agnosia. The combination of progressive associative agnosia and a fluent aphasia with word comprehension impairment is known as *semantic dementia*. Patients with semantic dementia fail to recognize faces and objects and cannot understand the meaning of words denoting objects. This needs to be differentiated from the semantic type of PPA where there is severe impairment in understanding words that denote objects and in naming faces and objects but a relative preservation of face

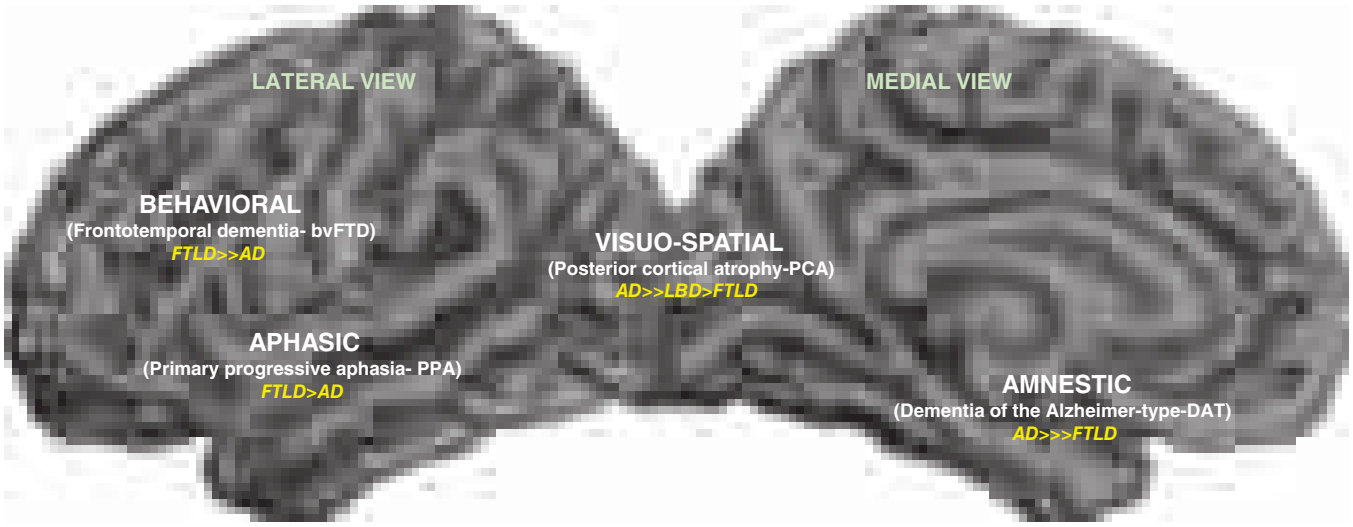


FIGURE 26-4 Four focal dementia syndromes and their most likely neuropathologic correlates. AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; DAT, amnestic dementia of the Alzheimer-type; FTLD, frontotemporal lobar degeneration (tau or TDP-43 type); LBD, Lewy body disease; PCA, posterior cortical atrophy syndrome; PPA, primary progressive aphasia.

and object recognition. The anterior temporal lobe atrophy is usually bilateral in semantic dementia whereas it tends to affect mostly the left hemisphere in semantic PPA. Acute onset of the semantic dementia syndrome can be associated with herpes simplex encephalitis.

LIMBIC NETWORK FOR EXPLICIT MEMORY AND AMNESIA

Limbic and paralimbic areas (such as the hippocampus, amygdala, and entorhinal cortex), the anterior and medial nuclei of the thalamus, the medial and basal parts of the striatum, and the hypothalamus collectively constitute a distributed network known as the *limbic system*. The behavioral affiliations of this network include the coordination of emotion, motivation, autonomic tone, and endocrine function. An additional area of specialization for the limbic network and the one that is of most relevance to clinical practice is that of declarative (explicit) memory for recent episodes and experiences. A disturbance in this function is known as an *amnestic state*. In the absence of deficits in motivation, attention, language, or visuospatial function, the clinical diagnosis of a persistent global amnestic state is always associated with bilateral damage to the limbic network, usually within the hippocampo-entorhinal complex or the thalamus. Damage to the limbic network does not necessarily destroy memories but interferes with their conscious recall in coherent form. The individual fragments of information remain preserved despite the limbic lesions and can sustain what is known as *implicit memory*. For example, patients with amnestic states can acquire new motor or perceptual skills even though they may have no conscious knowledge of the experiences that led to the acquisition of these skills.

The memory disturbance in the amnestic state is multimodal and includes retrograde and anterograde components. The *retrograde amnesia* involves an inability to recall experiences that occurred before the onset of the amnestic state. Relatively recent events are more vulnerable to retrograde amnesia than are more remote and more extensively consolidated events. A patient who comes to the emergency room complaining that he cannot remember his or her identity but can remember the events of the previous day almost certainly does not have a neurologic cause of memory disturbance. The second and most important component of the amnestic state is the *anterograde amnesia*, which indicates an inability to store, retain, and recall new knowledge. Patients with amnestic states cannot remember what they ate a few hours ago or the details of an important event they may have experienced in the recent past. In the acute stages, there also may be a tendency to fill in memory gaps with inaccurate, fabricated, and often implausible information. This is known as *confabulation*. Patients with the amnestic syndrome forget that they forget and tend to deny the existence of a memory problem when questioned. Confabulation is more common in cases where the underlying lesion also interferes with parts of the frontal network, as in the case of the Wernicke-Korsakoff syndrome or traumatic head injury.

CLINICAL EXAMINATION

A patient with an amnestic state is almost always disoriented, especially to time, and has little knowledge of current news. The anterograde component of an amnestic state can be tested with a list of four to five words read aloud by the examiner up to five times or until the patient can immediately repeat the entire list without an intervening delay. The next phase of the recall occurs after a period of 5–10 min during which the patient is engaged in other tasks. Amnestic patients fail this phase of the task and may even forget that they were given a list of words to remember. Accurate recognition of the words by multiple choice in a patient who cannot recall them indicates a less severe memory disturbance that affects mostly the retrieval stage of memory. The retrograde component of an amnesia can be assessed with questions related to autobiographical or historic events. The anterograde component of amnestic states is usually much more prominent than the retrograde component. In rare instances, occasionally associated with temporal lobe epilepsy or herpes simplex encephalitis, the retrograde component may dominate. Confusional states caused by toxic-metabolic encephalopathies and some types of frontal lobe damage lead to secondary memory impairments, especially at the stages of encoding and retrieval, even in the absence of limbic lesions. This sort of memory impairment can be differentiated from the amnestic state by the presence of additional impairments in the attention-related tasks described below in the section on the frontal lobes.

CAUSES, INCLUDING ALZHEIMER'S DISEASE

Neurologic diseases that give rise to an amnestic state include tumors (of the sphenoid wing, posterior corpus callosum, thalamus, or medial temporal lobe), infarctions (in the territories of the anterior or posterior cerebral arteries), head trauma, herpes simplex encephalitis, Wernicke-Korsakoff encephalopathy, autoimmune limbic encephalitis, and degenerative dementias such as AD and Pick's disease. The one common denominator of all these diseases is the presence of bilateral lesions within one or more components in the limbic network. Occasionally, unilateral left-sided hippocampal lesions can give rise to an amnestic state, but the memory disorder tends to be transient. Depending on the nature and distribution of the underlying neurologic disease, the patient also may have visual field deficits, eye movement limitations, or cerebellar findings.

The most common cause of progressive memory impairments in the elderly is AD. This is why a predominantly amnestic dementia is also known as a dementia of the Alzheimer-type (DAT). A prodromal stage

of DAT, when daily living activities are generally preserved, is known as amnestic mild cognitive impairment (MCI). The predilection of the entorhinal cortex and hippocampus for early neurofibrillary degeneration by typical AD pathology is responsible for the initially selective impairment of episodic memory. In time, additional impairments in language, attention, and visuospatial skills emerge as the neurofibrillary degeneration spreads to additional neocortical areas. Less frequently, amnestic dementias can also be caused by FTLD.

Transient global amnesia is a distinctive syndrome usually seen in late middle age. Patients become acutely disoriented and repeatedly ask who they are, where they are, and what they are doing. The spell is characterized by anterograde amnesia (inability to retain new information) and a retrograde amnesia for relatively recent events that occurred before the onset. The syndrome usually resolves within 24–48 h and is followed by the filling in of the period affected by the retrograde amnesia, although there is persistent loss of memory for the events that occurred during the ictus. Recurrences are noted in ~20% of patients. Migraine, temporal lobe seizures, and perfusion abnormalities in the posterior cerebral territory have been postulated as causes of transient global amnesia. The absence of associated neurologic findings occasionally may lead to the incorrect diagnosis of a psychiatric disorder.

THE PREFRONTAL NETWORK FOR EXECUTIVE FUNCTION AND BEHAVIOR

The frontal lobes can be subdivided into motor-premotor, dorsolateral prefrontal, medial prefrontal, and orbitofrontal components. The terms *frontal lobe syndrome* and *prefrontal cortex* refer only to the last three of these four components. These are the parts of the cerebral cortex that show the greatest phylogenetic expansion in primates, especially in humans. The dorsolateral prefrontal, medial prefrontal, and orbitofrontal areas, along with the subcortical structures with which they are interconnected (i.e., the head of the caudate and the dorsomedial nucleus of the thalamus), collectively make up a large-scale network that coordinates exceedingly complex aspects of human cognition and behavior. The term *salience network* has been introduced to designate parts of the frontal network and their interactions with adjacent paralimbic cortices of the insula and cingulate gyrus. Impairments of social conduct and empathy seen in neurodegenerative frontal dementias are attributed to pathology of the salience network.

The prefrontal network plays an important role in behaviors that require multitasking and the integration of thought with emotion. Cognitive operations impaired by prefrontal cortex lesions often are referred to as "executive functions." The most common clinical manifestations of damage to the prefrontal network take the form of two relatively distinct syndromes. In the *frontal abulic syndrome*, the patient shows a loss of initiative, creativity, and curiosity and displays a pervasive emotional blandness, apathy, and lack of empathy. In the *frontal disinhibition syndrome*, the patient becomes socially disinhibited and shows severe impairments of judgment, insight, foresight, and the ability to mind rules of conduct. The dissociation between intact intellectual function and a total lack of even rudimentary common sense is striking. Despite the preservation of all essential memory functions, the patient cannot learn from experience and continues to display inappropriate behaviors without appearing to feel emotional pain, guilt, or regret when those behaviors repeatedly lead to disastrous consequences. The impairments may emerge only in real-life situations when behavior is under minimal external control and may not be apparent within the structured environment of the medical office. Testing judgment by asking patients what they would do if they detected a fire in a theater or found a stamped and addressed envelope on the road is not very informative because patients who answer these questions wisely in the office may still act very foolishly in real-life settings. The physician must therefore be prepared to make a diagnosis of frontal lobe disease based on historic information alone even when the mental state is quite intact in the office examination.

CLINICAL EXAMINATION

The emergence of developmentally primitive reflexes, also known as frontal release signs, such as grasping (elicited by stroking the palm) and sucking (elicited by stroking the lips) are seen primarily in patients with large structural lesions that extend into the premotor components of the frontal lobes or in the context of metabolic encephalopathies. The vast majority of patients with prefrontal lesions and frontal lobe behavioral syndromes do not display these reflexes. Damage to the frontal lobe disrupts a variety of attention-related functions, including working memory (the transient online holding and manipulation of information), concentration span, the effortful scanning and retrieval of stored information, the inhibition of immediate but inappropriate responses, and mental flexibility. Digit span (which should be seven forward and five reverse) is decreased, reflecting poor working memory; the recitation of the months of the year in reverse order (which should take <15 s) is slowed as another indication of poor working memory; and the fluency in producing words starting with the letter a, f, or s that can be generated in 1 min (normally ≥12 per letter) is diminished even in nonaphasic patients, indicating an impairment in the ability to search and retrieve information from long-term stores. In "go–no go" tasks (where the instruction is to raise the finger upon hearing one tap but keep it still upon hearing two taps), the patient shows a characteristic inability to inhibit the response to the "no go" stimulus. Mental flexibility (tested by the ability to shift from one criterion to another in sorting or matching tasks) is impoverished; distractibility by irrelevant stimuli is increased; and there is a pronounced tendency for impersistence and perseveration. The ability for abstracting similarities and interpreting proverbs is also undermined.

The attentional deficits disrupt the orderly registration and retrieval of new information and lead to *secondary* deficits of explicit memory. The distinction of the underlying neural mechanisms is illustrated by the observation that severely amnestic patients who cannot remember events that occurred a few minutes ago may have intact if not superior working memory capacity as shown in tests of digit span. The use of the term "memory" to designate two completely different mental faculties is confusing. Working memory depends on the on-line holding of information for brief periods of time whereas explicit memory depends on the off-line storage and subsequent retrieval of the information.

CAUSES: TRAUMA, NEOPLASM, AND FRONTOTEMPORAL DEMENTIA

The abulic syndrome tends to be associated with damage in dorsolateral or dorsomedial prefrontal cortex, and the disinhibition syndrome with damage in orbitofrontal or ventromedial cortex. These syndromes tend to arise almost exclusively after bilateral lesions. Unilateral lesions confined to the prefrontal cortex may remain silent until the pathology spreads to the other side; this explains why thromboembolic CVA is an unusual cause of the frontal lobe syndrome. When behavioral syndromes of the frontal network arise in conjunction with asymmetric disease, the lesion tends to be predominantly on the right side of the brain. Common settings for frontal lobe syndromes include head trauma, ruptured aneurysms, hydrocephalus, tumors (including metastases, glioblastoma, and falx or olfactory groove meningiomas), and focal degenerative diseases, especially FTLD. The most prominent neurodegenerative frontal syndrome is known as the behavioral variant of frontotemporal dementia (bvFTD). In many patients with bvFTD the atrophy extends into the anterior temporal lobes. Occasionally, atrophy prodominantly in the right anterior temporal lobe presents with the bvFTD syndrome. The behavioral changes in these patients can range from apathy to shoplifting, compulsive gambling, sexual indiscretions, remarkable lack of common sense, new ritualistic behaviors, and alterations in dietary preferences, usually leading to increased taste for sweets or rigid attachment to specific food items. In many patients with AD, neurofibrillary degeneration eventually spreads to prefrontal cortex and gives rise to components of the frontal lobe syndrome, but almost always on a background of severe memory impairment. Rarely, the bvFTD syndrome can arise in isolation in the context of an atypical form of AD pathology.

Lesions in the caudate nucleus or in the dorsomedial nucleus of the thalamus (subcortical components of the prefrontal network) also can produce a frontal lobe syndrome affecting mostly executive functions. This is one reason why the changes in mental state associated with

degenerative basal ganglia diseases such as Parkinson's disease and Huntington's disease display components of the frontal lobe syndrome. Bilateral multifocal lesions of the cerebral hemispheres, none of which are individually large enough to cause specific cognitive deficits such as aphasia and neglect, can collectively interfere with the connectivity and therefore integrating (executive) function of the prefrontal cortex. A frontal lobe syndrome, usually of the abulic form, is therefore the single most common behavioral profile associated with a variety of bilateral multifocal brain diseases, including metabolic encephalopathy, multiple sclerosis, and vitamin B_{12} deficiency, among others. Many patients with the clinical diagnosis of a frontal lobe syndrome tend to have lesions that do not involve prefrontal cortex but involve either the subcortical components of the prefrontal network or its connections with other parts of the brain. To avoid making a diagnosis of "frontal lobe syndrome" in a patient with no evidence of frontal cortex disease, it is advisable to use the diagnostic term *frontal network syndrome*, with the understanding that the responsible lesions can lie anywhere within this distributed network. A patient with frontal lobe disease raises potential dilemmas in differential diagnosis: the abulia and blandness may be misinterpreted as depression, and the disinhibition as idiopathic mania or acting out. Appropriate intervention may be delayed while a treatable tumor keeps expanding.

CARING FOR PATIENTS WITH DEFICITS OF HIGHER CEREBRAL FUNCTION

Spontaneous improvement of cognitive deficits following stroke or trauma is common. It is most rapid in the first few weeks but may continue for up to 2 years, especially in young individuals with single brain lesions. Some of the initial deficits in such cases appear to arise from remote dysfunction (diaschisis) in brain regions that are interconnected with the site of initial injury. Improvement in these patients may reflect, at least in part, a normalization of the remote dysfunction. Other mechanisms may involve functional reorganization in surviving neurons adjacent to the injury or the compensatory use of homologous structures, e.g., the right superior temporal gyrus with recovery from Wernicke's aphasia. In contrast, neurodegenerative diseases show a progression of impairment but at rates that vary greatly from patient to patient.

Pharmacologic and Non-pharmacologic Interventions

Some of the deficits described in this chapter are so complex that they may bewilder not only the patient and family but also the physician. The care of patients with such deficits requires a careful evaluation of the history, cognitive test results and diagnostic procedures. Each piece of information needs to be interpreted cautiously and placed in context. A complaint of "poor memory," for example, may reflect an anomia; poor scores on a learning task may reflect a weakness of attention rather than explicit memory; a report of depression or indifference may reflect impaired prosody rather than a change in mood or empathy; jocularity may arise from poor insight rather than good mood. Although there are few well-controlled studies, several non-pharmacologic interventions have been used to treat higher cortical deficits. These include speech therapy for aphasias, behavioral modification for comportmental disorders, and cognitive training for visuospatial disorientation and amnestic syndromes. More practical interventions, usually delivered through occupational therapy, aim to improve daily living activities through assistive devices and modifications of the home environment. Determining driving competence is challenging, especially in the early stages of dementing diseases. An on-the-road driving test and reports from family members may help time decisions related to this very important activity. In neurodegenerative conditions such as PPA, transcranial magnetic (or direct current) stimulation has had mixed success in eliciting symptomatic improvement. The goal is to activate remaining neurons at sites of atrophy or in unaffected regions of the contralateral hemisphere. Depression and sleep disorders can intensify the cognitive disorders and should be treated with appropriate modalities. If neuroleptics become absolutely necessary for the control of agitation, atypical neuroleptics are preferable because of their lower extrapyramidal side effects. Treatment with neuroleptics in elderly patients with dementia requires weighing the potential benefits against the potentially serious side effects. This is especially relevant to the case of patients with Lewy body dementia, who can be unusually sensitive to side effects.

As in all other branches of medicine, a crucial step in patient care is to identify the underlying cause of the impairment. This is easily done in cases of CVA, head trauma or encephalitis but becomes particularly challenging in the dementias because the same progressive clinical syndrome can be caused by one of several neuropathologic entities. The advent of imaging, blood, and CSF biomarkers now makes it possible to address this question with reasonable success and to make specific diagnoses of AD, LBD, CJD, FTLD. A specific etiological diagnosis allows the physician to recommend medications or clinical trials that are the most appropriate for the underlying disease process. A clinical assessment that identifies the principal domain of behavioral and cognitive impairment followed by the judicious use of biomarker information to surmise the nature of the underlying disease allows a personalized approach to patients with higher cognitive impairment.

FURTHER READING

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27 Sleep Disorders

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Disturbed sleep is one of the most common health complaints that physicians encounter. More than one-half of adults in the United States experience at least intermittent sleep disturbance, and only 30% of adult Americans report consistently obtaining a sufficient amount of sleep. The National Academy of Medicine has estimated that 50–70 million Americans suffer from a chronic disorder of sleep and wakefulness, which can adversely affect daytime functioning as well as physical and mental health. A high prevalence of sleep disorders across all cultures is also now increasingly recognized, and these problems are expected to further increase in the years ahead as the global population ages. Over the last 20 years, the field of sleep medicine has emerged as a distinct specialty in response to the impact of sleep disorders and sleep deficiency on overall health. Nonetheless, over 80% of patients with sleep disorders remain undiagnosed and untreated—costing the U.S. economy over $400 billion annually in increased health care costs, lost productivity, accidents and injuries, and leading to the development of workplace-based sleep health education and sleep disorders screening programs designed to address this unmet medical need.

PHYSIOLOGY OF SLEEP AND WAKEFULNESS

Adults need at least 7 h of sleep per night to promote optimal health, although the timing, duration, and internal structure of sleep vary among individuals. In the United States, adults tend to have one consolidated sleep episode each night, although in some cultures sleep may be divided into a mid-afternoon nap and a shortened night sleep. This pattern changes considerably over the life span, as infants and young children sleep considerably more than older people.

The stages of human sleep are defined on the basis of characteristic patterns in the electroencephalogram (EEG), the electrooculogram (EOG—a measure of eye-movement activity), and the surface electromyogram (EMG) measured on the chin, neck, and legs. The continuous recording of these electrophysiologic parameters to define sleep and wakefulness is termed *polysomnography*.

Polysomnographic profiles define two basic states of sleep: (1) rapid eye movement (REM) sleep and (2) non–rapid eye movement (NREM) sleep. NREM sleep is further subdivided into three stages: N1, N2, and N3, characterized by increasing arousal threshold and slowing of the cortical EEG. REM sleep is characterized by a low-amplitude, mixed-frequency EEG similar to that of NREM stage N1 sleep, and the EOG shows REMs which tend to occur in flurries or bursts. EMG activity is absent in nearly all skeletal muscles except those involved in respiration, reflecting the brainstem-mediated muscle paralysis that is characteristic of REM sleep.

ORGANIZATION OF HUMAN SLEEP

Normal nocturnal sleep in adults displays a consistent organization from night to night **(Fig. 27-1)**. After sleep onset, sleep usually progresses through NREM stages N1–N3 sleep within 45–60 min. NREM stage N3 sleep (also known as slow-wave sleep) predominates in the first third of the night and comprises 15–25% of total nocturnal sleep time in young adults. Sleep deprivation increases the rapidity of sleep onset and both the intensity and amount of slow-wave sleep.

The first REM sleep episode usually occurs in the second hour of sleep. NREM and REM sleep alternate through the night with an average period of 90–110 min (the "ultradian" sleep cycle). Overall, in a healthy young adult, REM sleep constitutes 20–25% of total sleep, and NREM stages N1 and N2 constitute 50–60%.

Age has a profound impact on sleep state organization (Fig. 27-1). N3 sleep is most intense and prominent during childhood, decreasing with puberty and across the second and third decades of life. N3 sleep declines during adulthood to the point where it may be completely absent in older adults. The remaining NREM sleep becomes more fragmented, with many more frequent awakenings from NREM sleep. It is the increased frequency of awakenings, rather than a decreased ability to fall back asleep, that accounts for the increased wakefulness during the sleep episode in older people. While REM sleep may account for 50% of total sleep time in infancy, the percentage falls off sharply over the first postnatal year as a mature REM-NREM cycle develops; thereafter, REM sleep occupies about 25% of total sleep time.

Sleep deprivation degrades cognitive performance, particularly on tests that require continual vigilance. Paradoxically, older people are less vulnerable to the neurobehavioral performance impairment induced by acute sleep deprivation than young adults, maintaining their reaction time and sustaining vigilance with fewer lapses of attention. However, it is more difficult for older adults to obtain recovery sleep after staying awake all night, as the ability to sleep during the daytime declines with age.

After sleep deprivation, NREM sleep is generally recovered first, followed by REM sleep. However, because REM sleep tends to be most prominent in the second half of the night, sleep truncation (e.g., by an alarm clock) results in selective REM sleep deprivation. This may increase REM sleep pressure to the point where the first REM sleep may occur much earlier in the nightly sleep episode. Because several disorders (see below) also cause sleep fragmentation, it is important that the patient have sufficient sleep opportunity (at least 8 h per night) for several nights prior to a diagnostic polysomnogram.

There is growing evidence that inadequate sleep in humans is associated with glucose intolerance that may contribute to the development of diabetes, obesity, and the metabolic syndrome, plus impaired immune responses, accelerated atherosclerosis, and increased risk of cardiac disease, cognitive impairment, Alzheimer's disease, and stroke. For these reasons, the National Academy of Medicine declared sleep deficiency and sleep disorders "an unmet public health problem."

WAKE AND SLEEP ARE REGULATED BY BRAIN CIRCUITS

Two principal neural systems govern the expression of sleep and wakefulness. The ascending arousal system, illustrated in green in **Fig. 27-2**, consists of clusters of nerve cells extending from the upper pons to the hypothalamus and basal forebrain that activate the cerebral cortex, thalamus (which is necessary to relay sensory information to the cortex), and other forebrain regions. The ascending arousal neurons use monoamines (norepinephrine, dopamine, serotonin, and histamine), glutamate, or acetylcholine as neurotransmitters to activate their target neurons. Some basal forebrain neurons use GABA to disinhibit cortical inhibitory interneurons, thus promoting arousal. Additional wake-promoting neurons in the hypothalamus use the peptide neurotransmitter orexin (also known as hypocretin, shown in blue) to reinforce activity in the other arousal cell groups.

Damage to the arousal system at the level of the rostral pons and lower midbrain causes coma, indicating that the ascending arousal influence from this level is critical in maintaining wakefulness. Injury to the hypothalamic branch of the arousal system causes profound sleepiness, but usually not coma. Specific loss of the orexin neurons produces the sleep disorder narcolepsy (see below). Damage to the thalamus causes loss of the content of wakefulness, but wake-sleep cycles are largely preserved.

The arousal system is turned off during sleep by inhibitory inputs from cell groups in the sleep-promoting system, shown in Fig. 27-2 in red. These neurons in the preoptic area and pons use γ-aminobutyric acid (GABA) to inhibit the arousal system. Additional neurons in the lateral hypothalamus containing the peptide melanin-concentrating hormone promote REM sleep. Many sleep-promoting neurons are themselves inhibited by inputs from the arousal system. This mutual inhibition between the arousal- and sleep-promoting systems forms a neural circuit akin to what electrical engineers call a "flip-flop switch." A switch of this type tends to promote rapid transitions between the on (wake) and off (sleep) states, while avoiding intermediate states. The relatively rapid transitions between waking and sleeping states, as seen in the EEG of humans and animals, is consistent with this model.

Neurons in the ventrolateral preoptic nucleus, one of the key sleep-promoting sites, are lost during normal human aging, correlating with reduced ability to maintain sleep (sleep fragmentation). The ventrolateral preoptic neurons are also injured in Alzheimer's disease, which may in part account for the poor sleep quality in those patients.

Transitions between NREM and REM sleep appear to be governed by a similar switch in the brainstem. GABAergic REM-Off neurons have been identified in the lower midbrain that inhibit REM-On neurons in the upper pons. The REM-On group contains both GABAergic neurons that inhibit the REM-Off group (thus satisfying the conditions

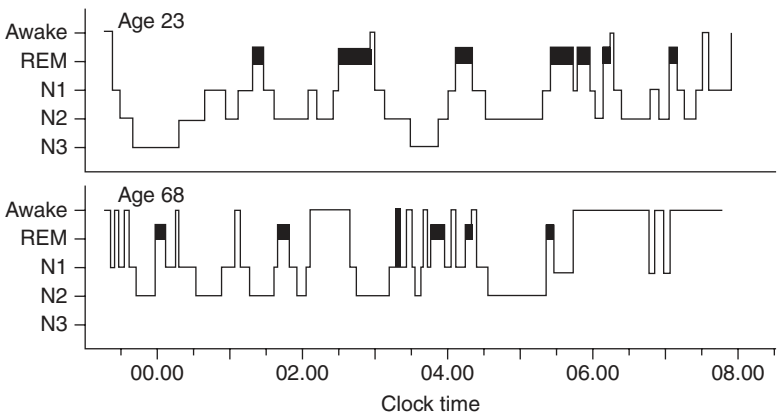

FIGURE 27-1 Wake-sleep architecture. Alternating stages of wakefulness, the three stages of non–rapid eye movement sleep (N1–N3), and rapid eye movement (REM) sleep (*solid bars*) occur over the course of the night for representative young and older adult men. Characteristic features of sleep in older people include reduction of N3 slow-wave sleep, frequent spontaneous awakenings, early sleep onset, and early morning awakening.

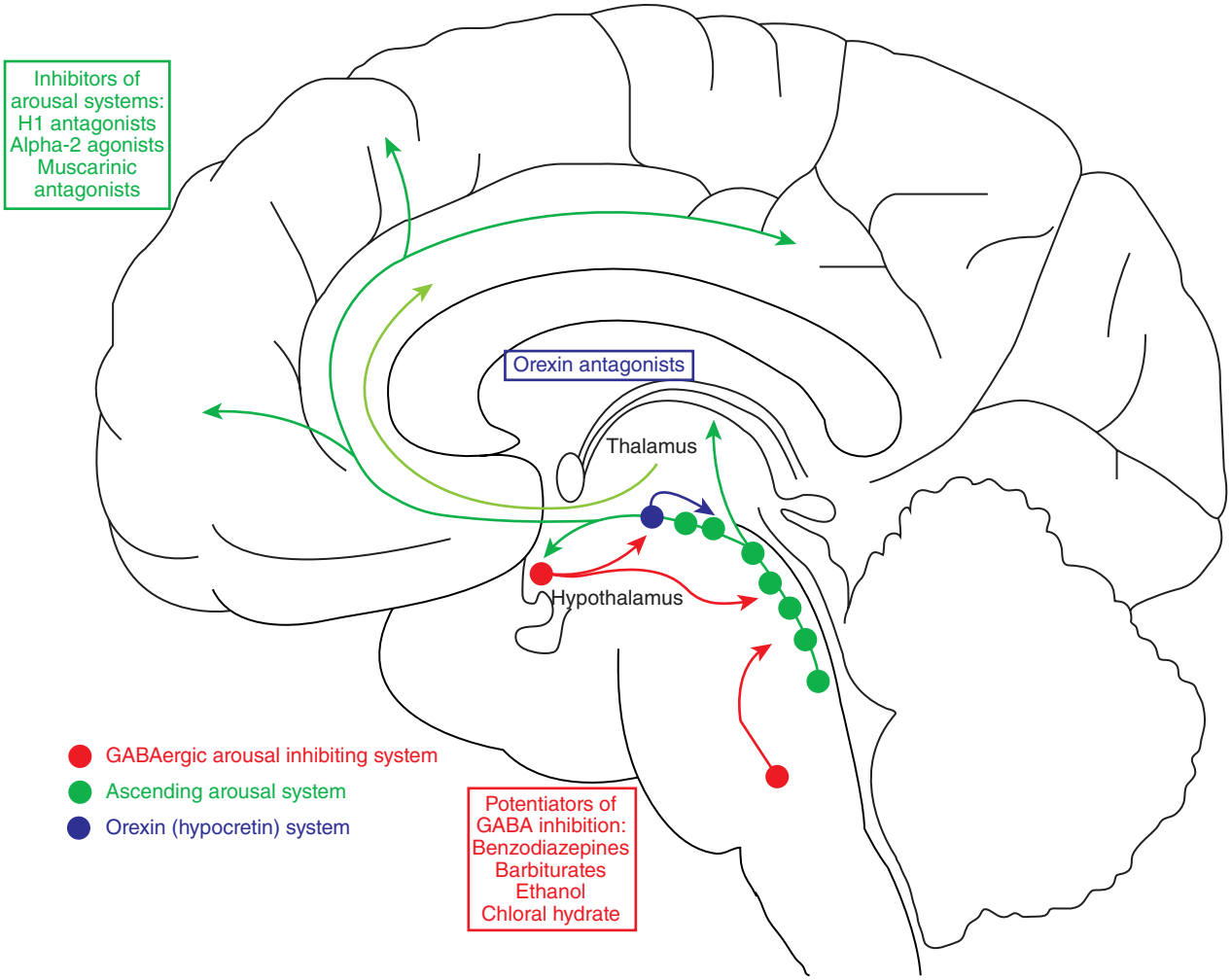

FIGURE 27-2 Relationship of drugs for insomnia with wake-sleep systems. The arousal system in the brain (*green*) includes monoaminergic, glutamatergic, and cholinergic neurons in the brainstem that activate neurons in the hypothalamus, thalamus, basal forebrain, and cerebral cortex. Orexin neurons (*blue*) in the hypothalamus, which are lost in narcolepsy, reinforce and stabilize arousal by activating other components of the arousal system. The sleep-promoting system (*red*) consists of GABAergic neurons in the preoptic area and brainstem that inhibit the components of the arousal system, thus allowing sleep to occur. Drugs used to treat insomnia include those that block the effects of arousal system neurotransmitters (*green and blue*) and those that enhance the effects of γ-aminobutyric acid (GABA) produced by the sleep system (*red*).

for a REM sleep flip-flop switch) as well as glutamatergic neurons that project widely in the central nervous system (CNS) to cause the key phenomena associated with REM sleep. REM-On neurons that project to the medulla and spinal cord activate inhibitory (GABA and glycine-containing) interneurons, which in turn hyperpolarize the motor neurons, producing the paralysis of REM sleep. REM-On neurons that project to the forebrain may be important in producing dreams.

The REM sleep switch receives cholinergic input, which favors transitions to REM sleep, and monoaminergic (norepinephrine and serotonin) input that prevents REM sleep. As a result, drugs that increase monoamine tone (e.g., serotonin or norepinephrine reuptake inhibitors) tend to reduce the amount of REM sleep. Damage to the neurons that promote REM sleep paralysis can produce REM sleep behavior disorder, a condition in which patients act out their dreams (see below).

SLEEP-WAKE CYCLES ARE DRIVEN BY HOMEOSTATIC, ALLOSTATIC, AND CIRCADIAN INPUTS

The gradual increase in sleep drive with prolonged wakefulness, followed by deeper slow-wave sleep and prolonged sleep episodes, demonstrates that there is a *homeostatic* mechanism that regulates sleep. The neurochemistry of sleep homeostasis is only partially understood, but with prolonged wakefulness, adenosine levels rise in parts of the brain. Adenosine may act through A1 receptors to directly inhibit many arousal-promoting brain regions. In addition, adenosine promotes sleep through A2a receptors; blockade of these receptors by caffeine is one of the chief ways in which people fight sleepiness. Other humoral factors, such as prostaglandin D_2, have also been implicated in this process. Both adenosine and prostaglandin D_2 activate the sleep-promoting neurons in the ventrolateral preoptic nucleus.

Allostasis is the physiologic response to a challenge such as physical danger or psychological threat that cannot be managed by homeostatic mechanisms. These stress responses can severely impact the need for and ability to sleep. For example, insomnia is very common in patients with anxiety and other psychiatric disorders. Stress-induced insomnia is even more common, affecting most people at some time in their lives. Positron emission tomography (PET) studies in patients with chronic insomnia show hyperactivation of components of the ascending arousal system, as well as their targets in the limbic system in the forebrain (e.g., cingulate cortex and amygdala). The limbic areas are not only targets for the arousal system, but they also send excitatory outputs back to the arousal system, which contributes to a vicious cycle of anxiety about insomnia that makes it more difficult to sleep. Approaches to treating insomnia may employ drugs that either inhibit the output of the ascending arousal system (green and blue in Fig. 27-2) or potentiate the output of the sleep-promoting system (red in Fig. 27-2). However, behavioral approaches (cognitive behavioral therapy [CBT] and sleep hygiene) that may reduce forebrain limbic activity at bedtime are often the best long term treatment.

Sleep is also regulated by a strong *circadian* timing signal, driven by the suprachiasmatic nuclei (SCN) of the hypothalamus, as described below. The SCN sends outputs to key sites in the hypothalamus, which impose 24-h rhythms on a wide range of behaviors and body systems, including the wake-sleep cycle.

PHYSIOLOGY OF CIRCADIAN RHYTHMICITY

The wake-sleep cycle is the most evident of many 24-h rhythms in humans. Prominent daily variations also occur in endocrine, thermoregulatory, cardiac, pulmonary, renal, immune, gastrointestinal, and neurobehavioral functions. At the molecular level, endogenous circadian rhythmicity is driven by self-sustaining transcriptional/translational feedback loops. In evaluating daily rhythms in humans, it is important to distinguish between diurnal components passively evoked by periodic environmental or behavioral changes (e.g., the increase in blood pressure and heart rate that occurs upon assumption of the upright posture) and circadian rhythms actively driven by an endogenous oscillatory process (e.g., the circadian variations in adrenal cortisol and pineal melatonin secretion that persist across a variety of environmental and behavioral conditions).

While it is now recognized that most cells in the body have circadian clocks that regulate diverse physiologic processes, most of these disparate clocks when placed in isolation in a tissue explant are unable to maintain the long-term synchronization with each other that is required to produce useful 24-h rhythms aligned with the external light-dark cycle. The neurons in the SCN are interconnected with one another in such a way as to produce a near-24-h synchronous rhythm of neural activity even in prolonged slice culture. They also receive visual input to synchronize them with the external world and have outputs to transmit that signal to the rest of the body. Bilateral destruction of the SCN results in a loss of most endogenous circadian rhythms including wake-sleep behavior and rhythms in endocrine and metabolic systems. The genetically determined period of this endogenous neural oscillator, which averages ~24.15 h in humans, is normally synchronized to the 24-h period of the environmental light-dark cycle through direct input from intrinsically photosensitive ganglion cells in the retina to the SCN. Humans are exquisitely sensitive to the resetting effects of light, particularly the shorter wavelengths (~460–500 nm) in the blue part of the visible spectrum. Small differences in circadian period contribute to variations in diurnal preference. For example, young adults typically have long intrinsic circadian periods and consequently go to bed late and rise late, whereas others have short periods and go to bed and rise earlier. Changes in homeostatic sleep regulation may underlie age-related changes in sleep-wake timing.

The timing and internal architecture of sleep are directly coupled to the output of the endogenous circadian pacemaker. Paradoxically, the endogenous circadian rhythm for wake propensity peaks just before the habitual bedtime, whereas that of sleep propensity peaks near the habitual wake time. These rhythms are thus timed to oppose the rise of sleep tendency throughout the usual waking day and the decline of sleep propensity during the habitual sleep episode, respectively. Misalignment of the endogenous circadian pacemaker with the desired wake-sleep cycle can, therefore, induce insomnia, decrease alertness, and impair performance, posing health problems for night-shift workers and airline travelers.

BEHAVIORAL AND PHYSIOLOGIC CORRELATES OF SLEEP STATES AND STAGES

Polysomnographic staging of sleep correlates with behavioral changes during specific states and stages. During the transitional state (stage N1) between wakefulness and deeper sleep, individuals may respond to faint auditory or visual signals. Formation of short-term memories is inhibited at the onset of NREM stage N1 sleep, which may explain why individuals aroused from that transitional sleep stage frequently lack situational awareness. After sleep deprivation, such transitions may intrude upon behavioral wakefulness notwithstanding attempts to remain continuously awake (see "Shift-Work Disorder," below).

Subjects woken from REM sleep recall vivid dream imagery >80% of the time, especially later in the night. Less vivid imagery may also be reported after NREM sleep interruptions. Certain disorders may occur during specific sleep stages and are described below under "Parasomnias." These include sleepwalking, night terrors, and enuresis (bed wetting), which occur most commonly in children during deep (N3) NREM sleep, and REM sleep behavior disorder, which occurs mainly among older men who fail to maintain full paralysis during REM sleep, and often call out, thrash around, or even act out fragments of dreams.

All major physiologic systems are influenced by sleep. Blood pressure and heart rate decrease during NREM sleep, particularly during N3 sleep. During REM sleep, bursts of eye movements are associated with large variations in both blood pressure and heart rate mediated by the autonomic nervous system. Cardiac dysrhythmias may occur selectively during REM sleep. Respiratory function also changes. In comparison to relaxed wakefulness, respiratory rate becomes slower but more regular during NREM sleep (especially N3 sleep) and becomes irregular during bursts of eye movements in REM sleep. Decreases in minute ventilation during NREM sleep are out of proportion to the decrease in metabolic rate, resulting in a slightly higher P_{CO_2}.

Within the brain itself, neurotransmission is supported by ion gradients across the cell membranes of neurons and astrocytes. These ion flows are accompanied by increases in intracellular volume, so that during wake, there is very little extracellular space in the brain. During sleep, intracellular volume is reduced, resulting in increased extracellular space, which has higher calcium and lower potassium concentrations, supporting hyperpolarization and reduced firing of neurons. This expansion of the extracellular space during sleep increases diffusion of substances that accumulate extracellularly, like β-amyloid peptide, enhancing their clearance from the brain via cerebrospinal fluid flow. Recent evidence suggests that lack of adequate sleep may contribute to extracellular accumulation of β-amyloid peptide, a key step in the pathogenesis of Alzheimer's disease.

Endocrine function also varies with sleep. N3 sleep is associated with secretion of growth hormone in men, while sleep in general is associated with augmented secretion of prolactin in both men and women. Sleep has a complex effect on the secretion of luteinizing hormone (LH): during puberty, sleep is associated with increased LH secretion, whereas sleep in postpubertal women inhibits LH secretion in the early follicular phase of the menstrual cycle. Sleep onset (and probably N3 sleep) is associated with inhibition of thyroid-stimulating hormone and of the adrenocorticotropic hormone–cortisol axis, an effect that is superimposed on the prominent circadian rhythms in the two systems.

The pineal hormone melatonin is secreted predominantly at night in both day- and night-active species, reflecting the direct modulation of pineal activity by the SCN via the sympathetic nervous system which innervates the pineal gland. Melatonin secretion does not require sleep, but melatonin secretion is inhibited by ambient light, an effect mediated by the neural connection from the retina to the pineal gland via the SCN. Sleep efficiency is highest when sleep coincides with endogenous melatonin secretion. When endogenous melatonin levels are low, such as during the biological day or at the desired bedtime in patients with delayed sleep-wake phase disorder (DSWPD), administration of exogenous melatonin can hasten sleep onset and increase sleep efficiency, but it does not increase sleep efficiency if administered when endogenous melatonin levels are elevated. This may explain why melatonin is often ineffective in the treatment of patients with primary insomnia. On the other hand, patients with sympathetic denervation of the pineal gland, such as occurs in cervical spinal cord injury or in patients with Parkinson's disease, often have low melatonin levels, and administration of melatonin (3 mg 30 min before bedtime) may help them sleep.

Sleep is accompanied by alterations of thermoregulatory function. NREM sleep is associated with an increase in the firing of warm-responsive neurons in the preoptic area and a fall in body temperature; conversely, skin warming without increasing core body temperature has been found to increase NREM sleep. REM sleep is associated with reduced thermoregulatory responsiveness.

APPROACH TO THE PATIENT

Sleep Disorders

Patients may seek help from a physician because of: (1) sleepiness or tiredness during the day; (2) difficulty initiating or maintaining sleep at night (insomnia); or (3) unusual behaviors during sleep itself (parasomnias).

Obtaining a careful history is essential. In particular, the duration, severity, and consistency of the symptoms are important, along with the patient's estimate of the consequences of the sleep disorder on waking function. Information from a bed partner or family member is often helpful because some patients may be unaware of symptoms such as heavy snoring or may underreport symptoms such as falling asleep at work or while driving. Physicians should inquire about when the patient typically goes to bed, when they fall asleep and wake up, whether they awaken during sleep, whether they feel rested in the morning, and whether they nap during the day. Depending on the primary complaint, it may be useful to ask about snoring, witnessed apneas, restless sensations in the legs, movements during sleep, depression, anxiety, and behaviors around the sleep episode. The physical examination may provide evidence of a small airway, large tonsils, or a neurologic or medical disorder that contributes to the main complaint.

It is important to remember that, rarely, seizures may occur exclusively during sleep, mimicking a primary sleep disorder; such sleep-related seizures typically occur during episodes of NREM sleep and may take the form of generalized tonic-clonic movements (sometimes with urinary incontinence or tongue biting) or stereotyped movements in partial complex epilepsy **(Chap. 418)**.

It is often helpful for the patient to complete a daily sleep log for 1–2 weeks to define the timing and amounts of sleep. When relevant, the log can also include information on levels of alertness, work times, and drug and alcohol use, including caffeine and hypnotics.

Polysomnography is necessary for the diagnosis of several disorders such as sleep apnea, narcolepsy, and periodic limb movement disorder (PLMD). A conventional polysomnogram performed in a clinical sleep laboratory allows measurement of sleep stages, respiratory effort and airflow, oxygen saturation, limb movements, heart rhythm, and additional parameters. A home sleep test usually focuses on just respiratory measures and is helpful in patients with a moderate to high likelihood of having obstructive sleep apnea. The multiple sleep latency test (MSLT) is used to measure a patient's propensity to sleep during the day and can provide crucial evidence for diagnosing narcolepsy and some other causes of sleepiness. The maintenance of wakefulness test is used to measure a patient's ability to sustain wakefulness during the daytime and can provide important evidence for evaluating the efficacy of therapies for improving sleepiness in conditions such as narcolepsy and obstructive sleep apnea.

EVALUATION OF DAYTIME SLEEPINESS

Up to 25% of the adult population has persistent daytime sleepiness that impairs an individual's ability to perform optimally in school, at work, while driving, and in other conditions that require alertness. Sleepy students often have trouble staying alert and performing well in school, and sleepy adults struggle to stay awake and focused on their work. More than half of Americans have fallen asleep while driving. An estimated 1.2 million motor vehicle crashes per year are due to drowsy drivers, causing about 20% of all serious crash injuries and deaths. One needn't fall asleep to have an accident, as the inattention and slowed responses of drowsy drivers are a major contributor. Twenty-four hours of continuous wakefulness impairs reaction time as much as a blood alcohol concentration of 0.10 g/dL (which is legally drunk in all 50 states).

Identifying and quantifying sleepiness can be challenging. First, patients may describe themselves as "sleepy," "fatigued," or "tired," and the meanings of these words may differ between patients. For clinical purposes, it is best to use the term "sleepiness" to describe a propensity to fall asleep; whereas "fatigue" is best used to describe a feeling of low physical or mental energy but without a tendency to actually sleep. Sleepiness is usually most evident when the patient is sedentary, whereas fatigue may interfere with more active pursuits. Sleepiness generally occurs with disorders that reduce the quality or quantity of sleep or that interfere with the neural mechanisms of arousal, whereas fatigue is more common in inflammatory disorders such as cancer, multiple sclerosis **(Chap. 436)**, fibromyalgia **(Chap. 366)**, chronic fatigue syndrome **(Chap. 442)**, or endocrine deficiencies such as hypothyroidism **(Chap. 376)** or Addison's disease **(Chap. 379)**. Second, sleepiness can affect judgment in a manner analogous to ethanol, such that patients may have limited insight into the condition and the extent of their functional impairment. Finally, patients may be reluctant to admit that sleepiness is a problem because they may have become unfamiliar with feeling fully alert and because sleepiness is sometimes viewed pejoratively as reflecting poor motivation or bad sleep habits.

Table 27-1 outlines the diagnostic and therapeutic approach to the patient with a complaint of excessive daytime sleepiness.

To determine the extent and impact of sleepiness on daytime function, it is helpful to ask patients about the occurrence of sleep episodes during normal waking hours, both intentional and unintentional. Specific areas to be addressed include the occurrence of inadvertent sleep

TABLE 27-1 Evaluation of the Patient with Excessive Daytime Sleepiness

FINDINGS ON HISTORY AND PHYSICAL EXAMINATION	DIAGNOSTIC EVALUATION	DIAGNOSIS	THERAPY
Difficulty waking in the morning, rebound sleep on weekends and vacations with improvement in sleepiness	Sleep log	Insufficient sleep	Sleep education and behavioral modification to increase amount of sleep
Obesity, snoring, hypertension	Polysomnogram or home sleep test	Obstructive sleep apnea **(Chap. 291)**	Continuous positive airway pressure; upper airway surgery (e.g., uvulopalatopharyngoplasty); dental appliance; weight loss
Cataplexy, hypnogogic hallucinations, sleep paralysis	Polysomnogram and multiple sleep latency test	Narcolepsy	Stimulants (e.g., modafinil, methylphenidate); REM sleep-suppressing antidepressants (e.g., venlafaxine); sodium oxybate
Restless legs, kicking movements during sleep	Assessment for predisposing medical conditions (e.g., iron deficiency or renal failure)	Restless legs syndrome with or without periodic limb movements	Treatment of predisposing condition; dopamine agonists (e.g., pramipexole, ropinirole); gabapentin; opiates
Sedating medications, stimulant withdrawal, head trauma, systemic inflammation, Parkinson's disease and other neurodegenerative disorders, hypothyroidism, encephalopathy	Thorough medical history and examination including detailed neurologic examination	Sleepiness due to a drug or medical condition	Change medications, treat underlying condition, consider stimulants

episodes while driving or in other safety-related settings, sleepiness while at work or school (and the relationship of sleepiness to work and school performance), and the effect of sleepiness on social and family life. Standardized questionnaires such as the Epworth Sleepiness Scale are often used clinically to measure sleepiness.

Eliciting a history of daytime sleepiness is usually adequate, but objective quantification is sometimes necessary. The MSLT measures a patient's propensity to sleep under quiet conditions. An overnight polysomnogram should precede the MSLT to establish that the patient has had an adequate amount of good-quality nighttime sleep. The MSLT consists of five 20-min nap opportunities every 2 h across the day. The patient is instructed to try to fall asleep, and the major endpoints are the average latency to sleep and the occurrence of REM sleep during the naps. An average sleep latency across the naps of <8 min is considered objective evidence of excessive daytime sleepiness. REM sleep normally occurs only during the nighttime sleep episode, and the occurrence of REM sleep in two or more of the MSLT naps provides support for the diagnosis of narcolepsy.

For the safety of the individual and the general public, physicians have a responsibility to help manage issues around driving in patients with sleepiness. Legal reporting requirements vary from state to state, but at a minimum, physicians should inform sleepy patients about their increased risk of having an accident and advise such patients not to drive a motor vehicle until the sleepiness has been treated effectively. This discussion is especially important for commercial drivers, and it should be documented in the patient's medical record.

INSUFFICIENT SLEEP

Insufficient sleep is probably the most common cause of excessive daytime sleepiness. The average adult needs 7.5–8 h of sleep, but on weeknights, the average U.S. adult gets only 6.75 h of sleep. Only 30% of the U.S. adult population reports consistently obtaining sufficient sleep. Insufficient sleep is especially common among shift workers, individuals working multiple jobs, and people in lower socioeconomic groups. Most teenagers need ≥9 h of sleep, but many fail to get enough sleep because of circadian phase delay, plus social pressures to stay up late coupled with early school start times. Late evening light exposure, television viewing, video-gaming, social media, texting, and smartphone use often delay bedtimes despite the fixed, early wake times required for work or school. As is typical with any disorder that causes sleepiness, individuals with chronically insufficient sleep may feel inattentive, irritable, unmotivated, and depressed, and have difficulty with school, work, and driving. Individuals differ in their optimal amount of sleep, and it can be helpful to ask how much sleep the patient obtains on a quiet vacation when he or she can sleep without restrictions. Some patients may think that a short amount of sleep is normal or advantageous, and they may not appreciate their biological need for more sleep, especially if coffee and other stimulants mask the sleepiness. A 2-week sleep log documenting the timing of sleep and daily level of alertness is diagnostically useful and provides helpful feedback for the patient. Extending sleep to the optimal amount on a regular basis can resolve the sleepiness and other symptoms. As with any lifestyle change, extending sleep requires commitment and adjustments, but the improvements in daytime alertness make this change worthwhile.

SLEEP APNEA SYNDROMES

Respiratory dysfunction during sleep is a common, serious cause of excessive daytime sleepiness as well as of disturbed nocturnal sleep. At least 24% of middle-aged men and 9% of middle-aged women in the United States have a reduction or cessation of breathing dozens or more times each night during sleep, with 9% of men and 4% of women doing so more than a hundred times per night. These episodes may be due to an occlusion of the airway (*obstructive sleep apnea*), absence of respiratory effort (*central sleep apnea*), or a combination of these factors. Failure to recognize and treat these conditions appropriately may lead to impairment of daytime alertness, increased risk of sleep-related motor vehicle crashes, depression, hypertension, myocardial infarction, diabetes, stroke, and increased mortality. Sleep apnea is particularly prevalent in overweight men and in the elderly, yet it is estimated to go undiagnosed in most affected individuals. This is unfortunate because several effective treatments are available. **Readers are referred to Chap. 291 for a comprehensive review of the diagnosis and treatment of patients with sleep apnea.**

NARCOLEPSY

Narcolepsy is characterized by difficulty sustaining wakefulness, poor regulation of REM sleep, and disturbed nocturnal sleep. All patients with narcolepsy have excessive daytime sleepiness. This sleepiness is usually moderate to severe, and in contrast to patients with disrupted sleep (e.g., sleep apnea), people with narcolepsy usually feel well rested upon awakening and then feel tired throughout much of the day. In addition, they often experience symptoms related to an intrusion of REM sleep characteristics. REM sleep is characterized by dreaming and muscle paralysis, and people with narcolepsy can have: (1) sudden muscle weakness without a loss of consciousness, which is usually triggered by strong emotions (cataplexy; **Video 27-1**); (2) dream-like hallucinations at sleep onset (hypnagogic hallucinations) or upon awakening (hypnopompic hallucinations); and (3) muscle paralysis upon awakening (sleep paralysis). With severe cataplexy, an individual may be laughing at a joke and then suddenly collapse to the ground, immobile but awake for 1–2 min. With milder episodes, patients may have partial weakness of the face or neck. Narcolepsy is one of the more common causes of chronic sleepiness and affects about 1 in 2000 people in the United States. Narcolepsy typically begins between age 10 and 20; once established, the disease persists for life.

Narcolepsy is caused by loss of the hypothalamic neurons that produce the orexin neuropeptides (also known as hypocretins). Research in mice and dogs first demonstrated that a loss of orexin signaling due to null mutations of either the orexin neuropeptides or one of the orexin receptors causes sleepiness and cataplexy nearly identical to that seen in people with narcolepsy. Although genetic mutations rarely cause human narcolepsy, researchers soon discovered that patients with narcolepsy with cataplexy (now called type 1 narcolepsy) have very low or undetectable levels of orexins in their cerebrospinal fluid, and autopsy studies showed a nearly complete loss of the orexin-producing neurons in the hypothalamus. The orexins normally promote long episodes of wakefulness and suppress REM sleep, and thus, loss of orexin signaling results in frequent intrusions of sleep during the usual waking episode, with REM sleep and fragments of REM sleep at any time of day **(Fig. 27-3)**. Patients with narcolepsy but no cataplexy

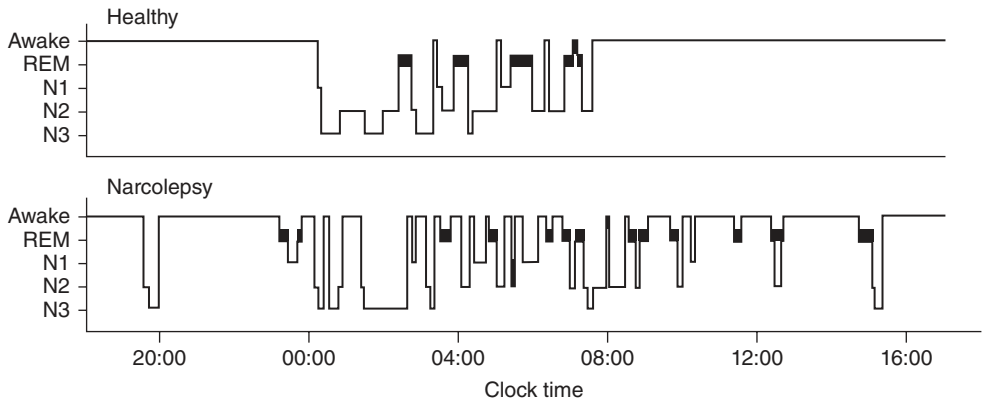

FIGURE 27-3 Polysomnographic recordings of a healthy individual and a patient with narcolepsy. The healthy individual has a long period or NREM sleep before entering REM sleep, but the individual with narcolepsy enters rapid eye movement (REM) sleep quickly at night and has moderately fragmented sleep. During the day, the healthy subject stays awake from 8:00 AM until midnight, but the patient with narcolepsy dozes off frequently, with many daytime naps that include REM sleep.

(type 2 narcolepsy) usually have normal orexin levels and may have other yet uncharacterized causes of their excessive daytime sleepiness.

Extensive evidence suggests that an autoimmune process likely causes this selective loss of the orexin-producing neurons. Certain human leukocyte antigens (HLAs) can increase the risk of autoimmune disorders **(Chap. 343)**, and narcolepsy has the strongest known HLA association. HLA DQB1*06:02 is found in >90% of people with type 1 narcolepsy, whereas it occurs in only 12–25% of the general population. Researchers now hypothesize that in people with DQB1*06:02, an immune response against influenza, *Streptococcus*, or other infections may also damage the orexin-producing neurons through a process of molecular mimicry. This mechanism may account for the eight- to twelvefold increase in new cases of narcolepsy among children in Europe who received a particular brand of H1N1 influenza A vaccine (Pandemrix). Traumatic brain injury can also damage orexin-containing neurons, inducing type 2 narcolepsy.

On rare occasions, narcolepsy can occur with neurologic disorders such as tumors or strokes that directly damage the orexin-producing neurons in the hypothalamus or their projections.

Diagnosis Narcolepsy is most commonly diagnosed by the history of chronic sleepiness plus cataplexy or other symptoms. Many disorders can cause feelings of weakness, but with true cataplexy, patients will describe definite functional weakness (e.g., slurred speech, dropping a cup, slumping into a chair) that has consistent emotional triggers such as heartfelt mirth when laughing at a great joke, happy surprise at unexpectedly seeing a friend, or intense anger. Cataplexy occurs in about half of all narcolepsy patients and is diagnostically very helpful because it occurs in almost no other disorder. In contrast, occasional hypnagogic hallucinations and sleep paralysis occur in about 20% of the general population, and these symptoms are not as diagnostically specific.

When narcolepsy is suspected, the diagnosis should be firmly established with a polysomnogram followed the next day by an MSLT. The polysomnogram helps rule out other possible causes of sleepiness such as sleep apnea and establishes that the patient was not sleep deprived the night before, and the MSLT provides essential, objective evidence of sleepiness plus REM sleep dysregulation. Across the five naps of the MSLT, most patients with narcolepsy will fall asleep in <8 min on average, and they will have episodes of REM sleep in at least two of the naps. Abnormal regulation of REM sleep is also manifested by the appearance of REM sleep within 15 min of sleep onset at night, which is rare in healthy individuals sleeping at their habitual bedtime. Stimulants should be stopped 1 week before the MSLT and antidepressants should be stopped 3 weeks prior, because these medications can affect the MSLT. In addition, patients should be encouraged to obtain a fully adequate amount of sleep each night for the week prior to the test to eliminate any effects of insufficient sleep.

TREATMENT

Narcolepsy

The treatment of narcolepsy is symptomatic. Most patients with narcolepsy feel more alert after sleep, and they should be encouraged to get adequate sleep each night and to take a 15- to 20-min nap in the afternoon. This nap may be sufficient for some patients with mild narcolepsy, but most also require treatment with wake-promoting medications. Modafinil is used quite often because it has fewer side effects than amphetamines and a relatively long half-life; for most patients, 200–400 mg each morning is very effective. Methylphenidate (10–20 mg bid) or dextroamphetamine (10 mg bid) are often effective, but sympathomimetic side effects, anxiety, and the potential for abuse can be concerns. These medications are available in slow-release formulations, extending their duration of action and allowing easier dosing. Sodium oxybate (gamma hydroxybutyrate) is given twice each night and is often very valuable in improving alertness, but it can produce excessive sedation, nausea, and confusion.

Cataplexy is usually much improved with antidepressants that increase noradrenergic or serotonergic tone because these neurotransmitters strongly suppress REM sleep and cataplexy. Venlafaxine (37.5–150 mg each morning) and fluoxetine (10–40 mg each morning) are often quite effective. The tricyclic antidepressants, such as protriptyline (10–40 mg/d) or clomipramine (25–50 mg/d) are potent suppressors of cataplexy, but their anticholinergic effects, including sedation and dry mouth, make them less attractive.[1] Sodium oxybate, given at bedtime and 3–4 h later, is also very helpful in reducing cataplexy.

[1]No antidepressant has been approved by the U.S. Food and Drug Administration (FDA) for treating narcolepsy.

EVALUATION OF INSOMNIA

Insomnia is the complaint of poor sleep and usually presents as difficulty initiating or maintaining sleep. People with insomnia are dissatisfied with their sleep and feel that it impairs their ability to function well in work, school, and social situations. Affected individuals often experience fatigue, decreased mood, irritability, malaise, and cognitive impairment.

Chronic insomnia, lasting >3 months, occurs in about 10% of adults and is more common in women, older adults, people of lower socioeconomic status, and individuals with medical, psychiatric, and substance abuse disorders. Acute or short-term insomnia affects over 30% of adults and is often precipitated by stressful life events such as a major illness or loss, change of occupation, medications, and substance abuse. If the acute insomnia triggers maladaptive behaviors such as increased nocturnal light exposure, frequently checking the clock, or attempting to sleep more by napping, it can lead to chronic insomnia.

Most insomnia begins in adulthood, but many patients may be predisposed and report easily disturbed sleep predating the insomnia, suggesting that their sleep is lighter than usual. Clinical studies and animal models indicate that insomnia is associated with activation during sleep of brain areas normally active only during wakefulness. The polysomnogram is rarely used in the evaluation of insomnia, as it typically confirms the patient's subjective report of long latency to sleep and numerous awakenings but usually adds little new information. Many patients with insomnia have increased fast (beta) activity in the EEG during sleep; this fast activity is normally present only during wakefulness, which may explain why some patients report feeling awake for much of the night. The MSLT is rarely used in the evaluation of insomnia because, despite their feelings of low energy, most people with insomnia do not easily fall asleep during the day, and on the MSLT, their average sleep latencies are usually longer than normal.

Many factors can contribute to insomnia, and obtaining a careful history is essential so one can select therapies targeting the underlying factors. The assessment should focus on identifying predisposing, precipitating, and perpetuating factors.

Psychophysiologic Factors Many patients with insomnia have negative expectations and conditioned arousal that interfere with sleep. These individuals may worry about their insomnia during the day and have increasing anxiety as bedtime approaches if they anticipate a poor night of sleep. While attempting to sleep, they may frequently check the clock, which only heightens anxiety and frustration. They may find it easier to sleep in a new environment rather than their bedroom, as it lacks the negative associations.

Inadequate Sleep Hygiene Patients with insomnia sometimes develop counterproductive behaviors that contribute to their insomnia. These can include daytime napping that reduces sleep drive at night; an irregular sleep-wake schedule that disrupts their circadian rhythms; use of wake-promoting substances (e.g., caffeine, tobacco) too close to bedtime; engaging in alerting or stressful activities close to bedtime (e.g., arguing with a partner, work-related emailing and texting while in bed, sleeping with a smartphone or tablet at the bedside); and routinely using the bedroom for activities other than sleep or sex (e.g., TV, work), so the bedroom becomes associated with arousing or stressful feelings.

Psychiatric Conditions About 80% of patients with psychiatric disorders have sleep complaints, and about half of all chronic insomnia occurs in association with a psychiatric disorder. Depression is classically associated with early morning awakening, but it can also interfere with the onset and maintenance of sleep. Mania and hypomania can disrupt sleep and often are associated with substantial reductions in the total amount of sleep. Anxiety disorders can lead to racing thoughts and rumination that interfere with sleep and can be very problematic if the patient's mind becomes active midway through the night. Panic attacks can arise from sleep and need to be distinguished from other parasomnias. Insomnia is common in schizophrenia and other psychoses, often resulting in fragmented sleep, less deep NREM sleep, and sometimes reversal of the day-night sleep pattern.

Medications and Drugs of Abuse A wide variety of psychoactive drugs can interfere with sleep. Caffeine, which has a half-life of 6–9 h, can disrupt sleep for up to 8–14 h, depending on the dose, variations in metabolism, and an individual's caffeine sensitivity. Insomnia can also result from use of prescription medications too close to bedtime (e.g., antidepressants, stimulants, glucocorticoids, theophylline). Conversely, withdrawal of sedating medications such as alcohol, narcotics, or benzodiazepines can cause insomnia. Alcohol taken just before bed can shorten sleep latency, but it often produces rebound insomnia 2–3 h later as it wears off. This same problem with sleep maintenance can occur with short-acting benzodiazepines such as alprazolam.

Medical Conditions A large number of medical conditions disrupt sleep. Pain from rheumatologic disorders or a painful neuropathy commonly disrupts sleep. Some patients may sleep poorly because of respiratory conditions such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, congestive heart failure, or restrictive lung disease, and some of these disorders are worse at night in bed due to circadian variations in airway resistance and postural changes that can result in nocturnal dyspnea. Many women experience poor sleep with the hormonal changes of menopause. Gastroesophageal reflux is also a common cause of difficulty sleeping.

Neurologic Disorders Dementia **(Chap. 25)** is often associated with poor sleep, probably due to a variety of factors, including napping during the day, altered circadian rhythms, and perhaps a weakened output of the brain's sleep-promoting mechanisms. In fact, insomnia and nighttime wandering are some of the most common causes for institutionalization of patients with dementia, because they place a larger burden on caregivers. Conversely, in cognitively intact elderly men, fragmented sleep and poor sleep quality are associated with subsequent cognitive decline. Patients with Parkinson's disease may sleep poorly due to rigidity, dementia, and other factors. Fatal familial insomnia is a very rare neurodegenerative condition caused by mutations in the prion protein gene, and although insomnia is a common early symptom, most patients present with other obvious neurologic signs such dementia, myoclonus, dysarthria, or autonomic dysfunction.

TREATMENT

Insomnia

Treatment of insomnia improves quality of life and can promote long-term health. With improved sleep, patients often report less daytime fatigue, improved cognition, and more energy. Treating the insomnia can also improve the comorbid disease. For example, management of insomnia at the time of diagnosis of major depression often improves the response to antidepressants and reduces the risk of relapse. Sleep loss can heighten the perception of pain, so a similar approach is warranted in acute and chronic pain management.

The treatment plan should target all putative contributing factors: establish good sleep hygiene, treat medical disorders, use behavioral therapies for anxiety and negative conditioning, and use pharmacotherapy and/or psychotherapy for psychiatric disorders. Behavioral therapies should be the first-line treatment, followed by judicious use of sleep-promoting medications if needed.

TREATMENT OF MEDICAL AND PSYCHIATRIC DISEASE

If the history suggests that a medical or psychiatric disease contributes to the insomnia, then it should be addressed by, for example, treating the pain, improving breathing, and switching or adjusting the timing of medications.

IMPROVE SLEEP HYGIENE

Attention should be paid to improving sleep hygiene and avoiding counterproductive, arousing behaviors before bedtime. Patients should establish a regular bedtime and wake time, even on weekends, to help synchronize their circadian rhythms and sleep patterns. The amount of time allocated for sleep should not be more than their actual total amount of sleep. In the 30 min before bedtime, patients should establish a relaxing "wind-down" routine that can include a warm bath, listening to music, meditation, or other relaxation techniques. The bedroom should be off-limits to computers, televisions, radios, smartphones, videogames, and tablets. Once in bed, patients should try to avoid thinking about anything stressful or arousing such as problems with relationships or work. If they cannot fall asleep within 20 min, it often helps to get out of bed and read or listen to relaxing music in dim light as a form of distraction from any anxiety, but artificial light, including light from a television, cell phone, or computer, should be avoided, because light itself suppresses melatonin secretion and is arousing.

Table 27-2 outlines some of the key aspects of good sleep hygiene to improve insomnia.

COGNITIVE BEHAVIORAL THERAPY

CBT uses a combination of the techniques above plus additional methods to improve insomnia. A trained therapist may use cognitive psychology techniques to reduce excessive worrying about sleep and to reframe faulty beliefs about the insomnia and its daytime consequences. The therapist may also teach the patient relaxation techniques, such as progressive muscle relaxation or meditation, to reduce autonomic arousal, intrusive thoughts, and anxiety.

MEDICATIONS FOR INSOMNIA

If insomnia persists after treatment of these contributing factors, pharmacotherapy is often used on a nightly or intermittent basis. A variety of sedatives can improve sleep.

Antihistamines, such as diphenhydramine, are the primary active ingredient in most over-the-counter sleep aids. These may be of benefit when used intermittently, but can produce tolerance and anticholinergic side effects such as dry mouth and constipation, which limit their use, particularly in the elderly.

Benzodiazepine receptor agonists (BzRAs) are an effective and well-tolerated class of medications for insomnia. BzRAs bind to the $GABA_A$ receptor and potentiate the postsynaptic response to GABA. $GABA_A$ receptors are found throughout the brain, and BzRAs may

TABLE 27-2 Methods to Improve Sleep Hygiene in Insomnia Patients

HELPFUL BEHAVIORS	BEHAVIORS TO AVOID
Use the bed only for sleep and sex • If you cannot sleep within 20 min, get out of bed and read or do other relaxing activities in dim light before returning to bed	Avoid behaviors that interfere with sleep physiology, including: • Napping, especially after 3:00 PM • Attempting to sleep too early • Caffeine after lunchtime
Make quality sleep a priority • Go to bed and get up at the same time each day • Ensure a restful environment (comfortable bed, bedroom quiet and dark)	In the 2–3 h before bedtime, avoid: • Heavy eating • Smoking or alcohol • Vigorous exercise
Develop a consistent bedtime routine. For example: • Prepare for sleep with 20–30 min of relaxation (e.g., soft music, meditation, yoga, pleasant reading) • Take a warm bath	When trying to fall asleep, avoid: • Solving problems • Thinking about life issues • Reviewing events of the day

globally reduce neural activity and may enhance the activity of specific sleep-promoting GABAergic pathways. Classic BzRAs include lorazepam, triazolam, and clonazepam, whereas newer agents such as zolpidem and zaleplon have more selective affinity for the α_1 subunit of the $GABA_A$ receptor.

Specific BzRAs are often chosen based on the desired duration of action. The most commonly prescribed agents in this family are zaleplon (5–20 mg), with a half-life of 1–2 h; zolpidem (5–10 mg) and triazolam (0.125–0.25 mg), with half-lives of 2–4 h; eszopiclone (1–3 mg), with a half-life of 5–8 h; and temazepam (15–30 mg), with a half-life of 8–20 h. Generally, side effects are minimal when the dose is kept low and the serum concentration is minimized during the waking hours (by using the shortest-acting effective agent). For chronic insomnia, intermittent use is recommended, unless the consequences of untreated insomnia outweigh concerns regarding chronic use.

The heterocyclic *antidepressants* (trazodone, amitriptyline,[2] and doxepin) are the most commonly prescribed alternatives to BzRAs due to their lack of abuse potential and lower cost. Trazodone (25–100 mg) is used more commonly than the tricyclic antidepressants, because it has a much shorter half-life (5–9 h) and less anticholinergic activity.

The orexin receptor antagonist suvorexant (10–20 mg) can also improve insomnia by blocking the wake-promoting effects of the orexin neuropeptides. It has a long half-life and can produce morning sedation, and as it reduces orexin signaling, it can rarely produce hypnagogic hallucinations and sleep paralysis (see narcolepsy section above).

Medications for insomnia are now among the most commonly prescribed medications, but they should be used cautiously. All sedatives increase the risk of injurious falls and confusion in the elderly, and therefore if needed, these medications should be used at the lowest effective dose. Morning sedation can interfere with driving and judgment, and when selecting a medication, one should consider the duration of action. Benzodiazepines carry a risk of addiction and abuse, especially in patients with a history of alcohol or sedative abuse. In patients with depression, all sedatives can worsen the depression. Like alcohol, some sleep-promoting medications can worsen sleep apnea. Sedatives can also produce complex behaviors during sleep, such as sleep walking and sleep eating, although this seems more likely at higher doses.

[2]Trazodone and amitriptyline have not been approved by the FDA for treating insomnia.

RESTLESS LEGS SYNDROME

Patients with restless legs syndrome (RLS) report an irresistible urge to move the legs. Many patients report a creepy-crawly or unpleasant deep ache within the thighs or calves, and those with more severe RLS may have discomfort in the arms as well. For most patients with RLS, these dysesthesias and restlessness are much worse in the evening and first half of the night. The symptoms appear with inactivity and can make sitting still in an airplane or when watching a movie a miserable experience. The sensations are temporarily relieved by movement, stretching, or massage. This nocturnal discomfort usually interferes with sleep, and patients may report daytime sleepiness as a consequence. RLS is very common, affecting 5–10% of adults and is more common in women and older adults.

A variety of factors can cause RLS. Iron deficiency is the most common treatable cause, and iron replacement should be considered if the ferritin level is <75 ng/mL. RLS can also occur with peripheral neuropathies and uremia and can be worsened by pregnancy, caffeine, alcohol, antidepressants, lithium, neuroleptics, and antihistamines. Genetic factors contribute to RLS, and polymorphisms in a variety of genes (*BTBD9, MEIS1, MAP2K5/LBXCOR*, and *PTPRD*) have been linked to RLS, although as yet, the mechanism through which they cause RLS remains unknown. Roughly one-third of patients (particularly those with an early age of onset) have multiple affected family members.

RLS is treated by addressing the underlying cause such as iron deficiency if present. Otherwise, treatment is symptomatic, and dopamine agonists or alpha-2-delta calcium channel ligands are used most frequently. Agonists of dopamine $D_{2/3}$ receptors such as pramipexole (0.25–0.5 mg q7PM) or ropinirole (0.5–4 mg q7PM) are usually quite effective, but about 25% of patients taking dopamine agonists develop augmentation, a worsening of RLS such that symptoms begin earlier in the day and can spread to other body regions. Other possible side effects of dopamine agonists include nausea, morning sedation, and increases in rewarding behavior such as gambling and sex. Alpha-2-delta calcium channel ligands such as gabapentin (300–600 mg q7PM) and pregabalin (150–450 mg q7PM) can also be quite effective; these do not cause augmentation and they can be especially helpful in patients with concomitant pain, neuropathy or anxiety. Opioids and benzodiazepines may also be of therapeutic value. Most patients with restless legs also experience PLMD, although the reverse is not the case.

PERIODIC LIMB MOVEMENT DISORDER

PLMD involves rhythmic twitches of the legs that disrupt sleep. The movements resemble a triple flexion reflex with extensions of the great toe and dorsiflexion of the foot for 0.5–5.0 s, which recur every 20–40 s during NREM sleep, in episodes lasting from minutes to hours. PLMD is diagnosed by a polysomnogram that includes recordings of the anterior tibialis and sometimes other muscles. The EEG shows that the movements of PLMD frequently cause brief arousals that disrupt sleep and can cause insomnia and daytime sleepiness. PLMD can be caused by the same factors that cause RLS (see above), and the frequency of leg movements improves with the same medications as used for RLS, including dopamine agonists. Recent genetic studies identified polymorphisms associated with both RLS and PLMD, suggesting that they may have a common pathophysiology.

PARASOMNIAS

Parasomnias are abnormal behaviors or experiences that arise from or occur during sleep. A variety of parasomnias can occur during NREM sleep, from brief confusional arousals to sleepwalking and night terrors. The presenting complaint is usually related to the behavior itself, but the parasomnias can disturb sleep continuity or lead to mild impairments in daytime alertness. Two main parasomnias occur in REM sleep: REM sleep behavior disorder (RBD) and nightmares.

Sleepwalking (Somnambulism) Patients affected by this disorder carry out automatic motor activities that range from simple to complex. Individuals may walk, urinate inappropriately, eat, exit the house, or drive a car with minimal awareness. It may be difficult to arouse the patient to wakefulness, and occasional individuals may respond to attempted awakening with agitation or violence. In general it is safest to lead the patient back to bed, at which point he or she will often fall back asleep. Sleepwalking arises from NREM stage N3 sleep, usually in the first few hours of the night, and the EEG initially shows the slow cortical activity of deep NREM sleep even when the patient is moving about. Sleepwalking is most common in children and adolescents, when deep NREM sleep is most abundant. About 15% of children have occasional sleepwalking, and it persists in about 1% of adults. Episodes are usually isolated but may be recurrent in 1–6% of patients. The cause is unknown, although it has a familial basis in roughly one-third of cases. Sleepwalking can be worsened by insufficient sleep, which subsequently causes an increase in deep NREM sleep; alcohol; and stress. These should be addressed if present. Small studies have shown some efficacy of antidepressants and benzodiazepines; relaxation techniques and hypnosis can also be helpful. Patients and their families should improve home safety (e.g., replace glass doors, remove low tables to avoid tripping) to minimize the chance of injury if sleepwalking occurs.

Sleep Terrors This disorder occurs primarily in young children during the first few hours of sleep during NREM stage N3 sleep. The child often sits up during sleep and screams, exhibiting autonomic arousal with sweating, tachycardia, large pupils, and hyperventilation. The individual may be difficult to arouse and rarely recalls the episode on awakening in the morning. Treatment usually consists of reassuring

the parents that the condition is self-limited and benign, and like sleepwalking, it may improve by avoiding insufficient sleep.

Sleep Enuresis Bedwetting, like sleepwalking and night terrors, is another parasomnia that occurs during sleep in the young. Before age 5 or 6 years, nocturnal enuresis should be considered a normal feature of development. The condition usually improves spontaneously by puberty, persists in 1–3% of adolescents, and is rare in adulthood. Treatment consists of bladder training exercises and behavioral therapy. Symptomatic pharmacotherapy is usually accomplished in adults with desmopressin (0.2 mg qhs), oxybutynin chloride (5 mg qhs), or imipramine (10–25 mg qhs). Important causes of nocturnal enuresis in patients who were previously continent for 6–12 months include urinary tract infections or malformations, cauda equina lesions, emotional disturbances, epilepsy, sleep apnea, and certain medications.

Sleep Bruxism Bruxism is an involuntary, forceful grinding of teeth during sleep that affects 10–20% of the population. The patient is usually unaware of the problem. The typical age of onset is 17–20 years, and spontaneous remission usually occurs by age 40. In many cases, the diagnosis is made during dental examination, damage is minor, and no treatment is indicated. In more severe cases, treatment with a mouth guard is necessary to prevent tooth injury. Stress management, benzodiazepines, and biofeedback can be useful when bruxism is a manifestation of psychological stress.

REM Sleep Behavior Disorder (RBD) RBD **(Video 27-2)** is distinct from other parasomnias in that it occurs during REM sleep. The patient or the bed partner usually reports agitated or violent behavior during sleep, and upon awakening, the patient can often report a dream that matches the accompanying movements. During normal REM sleep, nearly all non-respiratory skeletal muscles are paralyzed, but in patients with RBD, dramatic limb movements such as punching or kicking lasting seconds to minutes occur during REM sleep, and it is not uncommon for the patient or the bed partner to be injured.

The prevalence of RBD increases with age, afflicting about 2% of adults aged >70, and is about twice as common in men. Most already have or will develop a neurodegenerative disorder. Within 12 years of disease onset, half of RBD patients develop a synucleinopathy such as Parkinson's disease **(Chap. 427)** or dementia with Lewy bodies **(Chap. 426)**, or occasionally multiple system atrophy **(Chap. 432)**, and over 90% develop a synucleinopathy by 25 years. RBD can occur in patients taking antidepressants, and in some, these medications may unmask this early indicator of neurodegeneration. Synucleinopathies probably cause neuronal loss in brainstem regions that regulate muscle paralysis during REM sleep, and loss of these neurons permits movements to break through during REM sleep. RBD also occurs in about 30% of patients with narcolepsy, but the underlying cause is probably different, as they seem to be at no increased risk of a neurodegenerative disorder.

Many patients with RBD have sustained improvement with clonazepam (0.5–2.0 mg qhs).[3] Melatonin at doses up to 9 mg nightly may also prevent attacks.

CIRCADIAN RHYTHM SLEEP DISORDERS

A subset of patients presenting with either insomnia or hypersomnia may have a disorder of sleep *timing* rather than sleep *generation*. Disorders of sleep timing can be either organic (i.e., due to an abnormality of circadian pacemaker[s]) or environmental/behavioral (i.e., due to a disruption of environmental synchronizers). Effective therapies aim to entrain the circadian rhythm of sleep propensity to an appropriate phase.

Delayed Sleep-Wake Phase Disorder DSWPD is characterized by: (1) reported sleep onset and wake times persistently later than desired; (2) actual sleep times at nearly the same clock hours daily; and (3) if conducted at the habitual delayed sleep time, essentially normal sleep on polysomnography (except for delayed sleep onset). Patients with DSWPD exhibit an abnormally delayed endogenous circadian phase, which can be assessed by measuring the onset of secretion of melatonin in either the blood or saliva; this is best done in a dimly lit environment as light suppresses melatonin secretion. Dim-light melatonin onset (DLMO) in DSWPD patients occurs later in the evening than normal, which is about 8:00–9:00 P.M. (i.e., about 1–2 h before habitual bedtime). Patients tend to be young adults. The delayed circadian phase could be due to: (1) an abnormally long, genetically determined intrinsic period of the endogenous circadian pacemaker; (2) reduced phase-advancing capacity of the pacemaker; (3) slower rate of buildup of homeostatic sleep drive during wakefulness; or (4) an irregular prior sleep-wake schedule, characterized by frequent nights when the patient chooses to remain awake while exposed to artificial light well past midnight (for personal, social, school, or work reasons). In most cases, it is difficult to distinguish among these factors, as patients with either a behaviorally induced or biologically driven circadian phase delay may both exhibit a similar circadian phase delay in DLMO, and both factors make it difficult to fall asleep at the desired hour. Late onset of dim-light melatonin secretion can help distinguish DSWD from other forms of sleep-onset insomnia. DSWPD is a chronic condition that can persist for years and may not respond to attempts to reestablish normal bedtime hours. Treatment methods involving phototherapy with blue-enriched light during the morning hours and/or melatonin administration in the evening hours show promise in these patients, although the relapse rate is high.

Advanced Sleep-Wake Phase Disorder Advanced sleep-wake phase disorder (ASWPD) is the converse of DSWPD. Most commonly, this syndrome occurs in older people, 15% of whom report that they cannot sleep past 5:00 A.M., with twice that number complaining that they wake up too early at least several times per week. Patients with ASWPD are sleepy during the evening hours, even in social settings. Sleep-wake timing in ASWPD patients can interfere with a normal social life. Patients with this circadian rhythm sleep disorder can be distinguished from those who have early wakening due to insomnia because ASWPD patients show early onset of dim-light melatonin secretion.

In addition to age-related ASWPD, an early-onset familial variant of this condition has also been reported. In two families in which ASWPD was inherited in an autosomal dominant pattern, the syndrome was due to missense mutations in a circadian clock component (in the casein kinase binding domain of *PER2* in one family, and in casein kinase I delta in the other) that shortens the circadian period. Patients with ASWPD may benefit from bright light and/or blue enriched phototherapy during the evening hours to reset the circadian pacemaker to a later hour.

Non-24-h Sleep-Wake Rhythm Disorder Non-24-h sleep-wake rhythm disorder (N24SWRD) most commonly occurs when the primary synchronizing input (i.e., the light-dark cycle) from the environment to the circadian pacemaker is lost (as occurs in many blind people with no light perception), and the maximal phase-advancing capacity of the circadian pacemaker in response to non-photic cues cannot accommodate the difference between the 24-h geophysical day and the intrinsic period of the patient's circadian pacemaker, resulting in loss of entrainment to the 24-h day. The sleep of most blind patients with N24SWRD is restricted to the nighttime hours due to social or occupational demands. Despite this regular sleep-wake schedule, affected patients with N24SWRD are nonetheless unable to maintain a stable phase relationship between the output of the non-entrained circadian pacemaker and the 24-h day. Therefore, most blind patients present with intermittent bouts of insomnia. When the blind patient's endogenous circadian rhythms are out of phase with the local environment, nighttime insomnia coexists with excessive daytime sleepiness. Conversely, when the endogenous circadian rhythms of those same patients are in phase with the local environment, symptoms remit. The interval between symptomatic phases may last several weeks to several months in blind patients with N24SWRD, depending on the period of the underlying nonentrained rhythm and the 24-h day. Nightly low-dose (0.5 mg) melatonin administration may improve sleep and,

[3]No medications have been approved by the FDA for the treatment of RBD.

in some cases, induce synchronization of the circadian pacemaker. In sighted patients, N24SWRD is usually caused by self-selected exposure to artificial light that inadvertently entrains the circadian pacemaker to a >24-h schedule, and these individuals present with an incremental pattern of successive delays in sleep timing, progressing in and out of phase with local time—a clinical presentation that is seldom seen in blind patients with N24SWRD.

Shift-Work Disorder More than 7 million workers in the United States regularly work at night, either on a permanent or rotating schedule. Many more begin the commute to work or school between 4:00 A.M. and 7:00 A.M., requiring them to commute and then work during a time of day that they would otherwise be asleep. In addition, each week, millions of "day" workers and students elect to remain awake at night or awaken very early in the morning to work or study to meet work or school deadlines, drive long distances, compete in sporting events, or participate in recreational activities. Such schedules can result in both sleep loss and misalignment of circadian rhythms with respect to the sleep-wake cycle.

The circadian timing system usually fails to adapt successfully to the inverted schedules required by overnight work or the phase advance required by early morning (4:00 A.M. to 7:00 A.M.) start times. This leads to a misalignment between the desired work-rest schedule and the output of the pacemaker and to disturbed daytime sleep in most such individuals. Excessive work hours (per day or per week), insufficient time off between consecutive days of work or school, and frequent travel across time zones may be contributing factors. Sleep deficiency, increased length of time awake prior to work, and misalignment of circadian phase produce decreased alertness and performance, increased reaction time, and increased risk of performance lapses, thereby resulting in greater safety hazards among night workers and other sleep-deprived individuals. Sleep disturbance nearly doubles the risk of a fatal work accident. In addition, long-term night shift workers have higher rates of breast, colorectal, and prostate cancer and of cardiac, gastrointestinal, metabolic, and reproductive disorders. The World Health Organization has added night-shift work to its list of probable carcinogens.

Sleep onset begins in local brain regions before gradually sweeping over the entire brain as sensory thresholds rise and consciousness is lost. A sleepy individual struggling to remain awake may attempt to continue performing routine and familiar motor tasks during the transition state between wakefulness and stage N1 sleep, while unable to adequately process sensory input from the environment. Such sleep-related attentional failures typically last only seconds but are known on occasion to persist for longer durations. Motor vehicle operators who fail to heed the warning signs of sleepiness are especially vulnerable to sleep-related accidents, as sleep processes can slow reaction times, induce automatic behavior, and intrude involuntarily upon the waking brain, causing catastrophic consequences—including 6400 fatalities and 50,000 debilitating injuries in the United States annually. For this reason, an expert consensus panel has concluded that individuals who have slept <2 h in the prior 24 h are unfit to drive a motor vehicle. There is a significant increase in the risk of sleep-related, fatal-to-the-driver highway crashes in the early morning and late afternoon hours, coincident with bimodal peaks in the daily rhythm of sleep tendency.

Physicians who work prolonged shifts, especially intermittent overnight shifts, constitute another group of workers at greater risk for accidents and other adverse consequences of lack of sleep and misalignment of the circadian rhythm. Recurrent scheduling of resident physicians to work shifts of ≥24 consecutive hours impairs psychomotor performance to a degree that is comparable to alcohol intoxication, doubles the risk of attentional failures among intensive care unit resident physicians working at night, and significantly increases the risk of serious medical errors in intensive care units, including a fivefold increase in the risk of serious diagnostic mistakes. Some 20% of hospital resident physicians report making a fatigue-related mistake that injured a patient, and 5% admit making a fatigue-related mistake that resulted in the death of a patient. Moreover, working for >24 consecutive hours increases the risk of percutaneous injuries and more than doubles the risk of motor vehicle crashes during the commute home. For these reasons, in 2008, the National Academy of Medicine concluded that the practice of scheduling resident physicians to work for >16 consecutive hours without sleep is hazardous for both resident physicians and their patients.

From 5 to 15% of individuals scheduled to work at night or in the early morning hours have much greater-than-average difficulties remaining awake during night work and sleeping during the day; these individuals are diagnosed with chronic and severe shift-work disorder (SWD). Patients with this disorder have a level of excessive sleepiness during work at night or in the early morning and insomnia during day sleep that the physician judges to be clinically significant; the condition is associated with an increased risk of sleep-related accidents and with some of the illnesses associated with night-shift work. Patients with chronic and severe SWD are profoundly sleepy at work. In fact, their sleep latencies during night work average just 2 min, comparable to mean daytime sleep latency durations of patients with narcolepsy or severe sleep apnea.

TREATMENT

Shift-Work Disorder

Caffeine is frequently used by night workers to promote wakefulness. However, it cannot forestall sleep indefinitely, and it does not shield users from sleep-related performance lapses. Postural changes, exercise, and strategic placement of nap opportunities can sometimes temporarily reduce the risk of fatigue-related performance lapses. Properly timed exposure to blue-enriched light or bright white light can directly enhance alertness and facilitate more rapid adaptation to night-shift work.

Modafinil (200 mg) or armodafinil (150 mg) 30–60 min before the start of an 8-h overnight shift is an effective treatment for the excessive sleepiness during night work in patients with SWD. Although treatment with modafinil or armodafinil significantly improves performance and reduces sleep propensity and the risk of lapses of attention during night work, affected patients remain excessively sleepy.

Fatigue risk management programs for night shift workers should promote education about sleep, increase awareness of the hazards associated with sleep deficiency and night work, and screen for common sleep disorders. Work schedules should be designed to minimize: (1) exposure to night work; (2) the frequency of shift rotations; (3) the number of consecutive night shifts; and (4) the duration of night shifts.

Jet Lag Disorder Each year, >60 million people fly from one time zone to another, often resulting in excessive daytime sleepiness, sleep-onset insomnia, and frequent arousals from sleep, particularly in the latter half of the night. The syndrome is transient, typically lasting 2–14 d depending on the number of time zones crossed, the direction of travel, and the traveler's age and phase-shifting capacity. Travelers who spend more time outdoors at their destination reportedly adapt more quickly than those who remain in hotel or seminar rooms, presumably due to brighter (outdoor) light exposure. Avoidance of antecedent sleep loss or napping on the afternoon prior to overnight travel can reduce the difficulties associated with extended wakefulness. Laboratory studies suggest that low doses of melatonin can enhance sleep efficiency, but only if taken when endogenous melatonin concentrations are low (i.e., during the biologic daytime).

In addition to jet lag associated with travel across time zones, many patients report a behavioral pattern that has been termed *social jet lag*, in which bedtimes and wake times on weekends or days off occur 4–8 h later than during the week. Such recurrent displacement of the timing of the sleep-wake cycle is common in adolescents and young adults and is associated with delayed circadian phase, sleep-onset insomnia, excessive daytime sleepiness, poorer academic performance, and increased risk of both obesity and depressive symptoms.

MEDICAL IMPLICATIONS OF CIRCADIAN RHYTHMICITY

Prominent circadian variations have been reported in the incidence of acute myocardial infarction, sudden cardiac death, and stroke, the leading causes of death in the United States. Platelet aggregability is increased in the early morning hours, coincident with the peak incidence of these cardiovascular events. Recurrent circadian disruption combined with chronic sleep deficiency, such as occurs during night-shift work, is associated with increased plasma glucose concentrations after a meal due to inadequate pancreatic insulin secretion. Night shift workers with elevated fasting glucose have an increased risk of progressing to diabetes. Blood pressure of night workers with sleep apnea is higher than that of day workers. A better understanding of the possible role of circadian rhythmicity in the acute destabilization of a chronic condition such as atherosclerotic disease could improve the understanding of its pathophysiology.

Diagnostic and therapeutic procedures may also be affected by the time of day at which data are collected. Examples include blood pressure, body temperature, the dexamethasone suppression test, and plasma cortisol levels. The timing of chemotherapy administration has been reported to have an effect on the outcome of treatment. In addition, both the toxicity and effectiveness of drugs can vary with time of day. For example, more than a fivefold difference has been observed in mortality rates following administration of toxic agents to experimental animals at different times of day. Anesthetic agents are particularly sensitive to time-of-day effects. Finally, the physician must be aware of the public health risks associated with the ever-increasing demands made by the 24/7 schedules in our round-the-clock society.

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John W. Winkelman, MD, PhD and Gary S. Richardson, MD contributed to this chapter in prior editions, and some material from their work has been retained here.

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VIDEO 27-1 A typical episode of severe cataplexy. The patient is joking and then falls to the ground with an abrupt loss of muscle tone. The electromyogram recordings (four lower traces on the right) show reductions in muscle activity during the period of paralysis. The electroencephalogram (top two traces) shows wakefulness throughout the episode. *(Video courtesy of Giuseppe Plazzi, University of Bologna.)*

VIDEO 27-2 Typical aggressive movements in rapid eye movement (REM) sleep behavior disorder. *(Video courtesy of Dr. Carlos Schenck, University of Minnesota Medical School.)*

Section 4 Disorders of Eyes, Ears, Nose, and Throat

28 Disorders of the Eye

Jonathan C. Horton

THE HUMAN VISUAL SYSTEM

The visual system provides a supremely efficient means for the rapid assimilation of information from the environment to aid in the guidance of behavior. The act of seeing begins with the capture of images focused by the cornea and lens on a light-sensitive membrane in the back of the eye called the *retina*. The retina is actually part of the brain, banished to the periphery to serve as a transducer for the conversion of patterns of light energy into neuronal signals. Light is absorbed by pigment in two types of photoreceptors: rods and cones. In the human retina there are 100 million rods and 5 million cones. The rods operate in dim (scotopic) illumination. The cones function under daylight (photopic) conditions. The cone system is specialized for color perception and high spatial resolution. The majority of cones are within the macula, the portion of the retina that serves the central 10° of vision. In the middle of the macula a small pit termed the *fovea*, packed exclusively with cones, provides the best visual acuity.

Photoreceptors hyperpolarize in response to light, activating bipolar, amacrine, and horizontal cells in the inner nuclear layer. After processing of photoreceptor responses by this complex retinal circuit, the flow of sensory information ultimately converges on a final common pathway: the ganglion cells. These cells translate the visual image impinging on the retina into a continuously varying barrage of action potentials that propagates along the primary optic pathway to visual centers within the brain. There are a million ganglion cells in each retina and hence a million fibers in each optic nerve.

Ganglion cell axons sweep along the inner surface of the retina in the nerve fiber layer, exit the eye at the optic disc, and travel through the optic nerve, optic chiasm, and optic tract to reach targets in the brain. The majority of fibers synapse on cells in the lateral geniculate body, a thalamic relay station. Cells in the lateral geniculate body project in turn to the primary visual cortex. This afferent retinogeniculocortical sensory pathway provides the neural substrate for visual perception. Although the lateral geniculate body is the main target of the retina, separate classes of ganglion cells project to other subcortical visual nuclei involved in different functions. Ganglion cells that mediate pupillary constriction and circadian rhythms are light sensitive owing to a novel visual pigment, melanopsin. Pupil responses are mediated by input to the pretectal olivary nuclei in the midbrain. The pretectal nuclei send their output to the Edinger-Westphal nuclei, which in turn provide parasympathetic innervation to the iris sphincter via an interneuron in the ciliary ganglion. Circadian rhythms are timed by a retinal projection to the suprachiasmatic nucleus. Visual orientation and eye movements are served by retinal input to the superior colliculus. Gaze stabilization and optokinetic reflexes are governed by a group of small retinal targets known collectively as the *brainstem accessory optic system*.

The eyes must be rotated constantly within their orbits to place and maintain targets of visual interest on the fovea. This activity, called *foveation*, or looking, is governed by an elaborate efferent motor system. Each eye is moved by six extraocular muscles that are supplied by cranial nerves from the oculomotor (III), trochlear (IV), and abducens (VI) nuclei. Activity in these ocular motor nuclei is coordinated by pontine and midbrain mechanisms for smooth pursuit, saccades, and gaze stabilization during head and body movements. Large regions of the frontal and parietooccipital cortex control these brainstem eye movement centers by providing descending supranuclear input.

REFRACTIVE STATE

In approaching a patient with reduced vision, the first step is to decide whether refractive error is responsible. In *emmetropia*, parallel rays from infinity are focused perfectly on the retina. Sadly, this condition is enjoyed by only a minority of the population. In *myopia*, the globe is too long, and light rays come to a focal point in front of the retina. Near objects can be seen clearly, but distant objects require a diverging lens in front of the eye. In *hyperopia*, the globe is too short, and hence a converging lens is used to supplement the refractive power of the eye. In *astigmatism*, the corneal surface is not perfectly spherical, necessitating a cylindrical corrective lens. Most patients elect to wear eyeglasses or contact lenses to neutralize refractive error. An alternative is to permanently alter the refractive properties of the cornea by performing laser in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK).

With the onset of middle age, *presbyopia* develops as the lens within the eye becomes unable to increase its refractive power to accommodate on near objects. To compensate for presbyopia an emmetropic patient must use reading glasses. A patient already wearing glasses for distance correction usually switches to bifocals. The only exception is a myopic patient, who may achieve clear vision at near simply by removing glasses containing the distance prescription.

Refractive errors usually develop slowly and remain stable after adolescence, except in unusual circumstances. For example, the acute onset of diabetes mellitus can produce sudden myopia because of lens edema induced by hyperglycemia. Testing vision through a pinhole aperture is a useful way to screen quickly for refractive error. If visual acuity is better through a pinhole than it is with the unaided eye, the patient needs refraction to obtain best corrected visual acuity.

VISUAL ACUITY

The Snellen chart is used to test acuity at a distance of 6 m (20 ft). For convenience, a scale version of the Snellen chart called the Rosenbaum card is held at 36 cm (14 in.) from the patient **(Fig. 28-1)**. All subjects should be able to read the 6/6 m (20/20 ft) line with each eye using their refractive correction, if any. Patients who need reading glasses because of presbyopia must wear them for accurate testing with the Rosenbaum card. If 6/6 (20/20) acuity is not present in each eye, the deficiency in vision must be explained. If it is worse than 6/240 (20/800), acuity should be recorded in terms of counting fingers, hand motions, light perception, or no light perception. Legal blindness is defined by the Internal Revenue Service as a best corrected acuity of 6/60 (20/200) or less in the better eye or a binocular visual field subtending 20° or less. Loss of vision in one eye only does not constitute legal blindness. For driving the laws vary by state, but most require a corrected acuity of 6/12 (20/40) in at least one eye for unrestricted privileges. Patients who develop a homonymous hemianopia should not drive.

FIGURE 28-1 The Rosenbaum card is a miniature, scale version of the Snellen chart for testing visual acuity at near. When the visual acuity is recorded, the Snellen distance equivalent should bear a notation indicating that vision was tested at near, not at 6 m (20 ft), or else the Jaeger number system should be used to report the acuity.

PUPILS

The pupils should be tested individually in dim light with the patient fixating on a distant target. There is no need to check the near response if the pupils respond briskly to light, because isolated loss of constriction (miosis) to accommodation does not occur. For this reason, the ubiquitous abbreviation PERRLA (pupils equal, round, and reactive to light and accommodation) implies a wasted effort with the last step. However, it is important to test the near response if the light response is poor or absent. Light-near dissociation occurs with neurosyphilis (Argyll Robertson pupil), with lesions of the dorsal midbrain (*Parinaud's syndrome*), and after aberrant regeneration (oculomotor nerve palsy, Adie's tonic pupil).

An eye with no light perception has no pupillary response to direct light stimulation. If the retina or optic nerve is only partially injured, the direct pupillary response will be weaker than the consensual pupillary response evoked by shining a light into the healthy fellow eye. A *relative afferent pupillary defect* (Marcus Gunn pupil) is elicited with the swinging flashlight test **(Fig. 28-2)**. It is an extremely useful sign in retrobulbar optic neuritis and other optic nerve diseases, in which it may be the sole objective evidence for disease. In bilateral optic neuropathy, no afferent pupil defect is present if the optic nerves are affected equally.

Subtle inequality in pupil size, up to 0.5 mm, is a fairly common finding in normal persons. The diagnosis of essential or physiologic anisocoria is secure as long as the relative pupil asymmetry remains constant as ambient lighting varies. Anisocoria that increases in dim light indicates a sympathetic paresis of the iris dilator muscle. The triad of miosis with ipsilateral ptosis and anhidrosis constitutes *Horner's syndrome*, although anhidrosis is an inconstant feature. Brainstem stroke, carotid dissection, and neoplasm impinging on the sympathetic chain occasionally are identified as the cause of Horner's syndrome, but most cases are idiopathic.

Anisocoria that increases in bright light suggests a parasympathetic palsy. The first concern is an oculomotor nerve paresis. This possibility is excluded if the eye movements are full and the patient has no ptosis or diplopia. Acute pupillary dilation (mydriasis) can result from damage to the ciliary ganglion in the orbit. Common mechanisms are infection (herpes zoster, influenza), trauma (blunt, penetrating, surgical), and ischemia (diabetes, temporal arteritis). After denervation of the iris sphincter the pupil does not respond well to light, but the response to near is often relatively intact. When the near stimulus is removed, the pupil redilates very slowly compared with the normal pupil, hence the term *tonic pupil*. In *Adie's syndrome* a tonic pupil is present, sometimes in conjunction with weak or absent tendon reflexes in the lower extremities. This benign disorder, which occurs predominantly in healthy

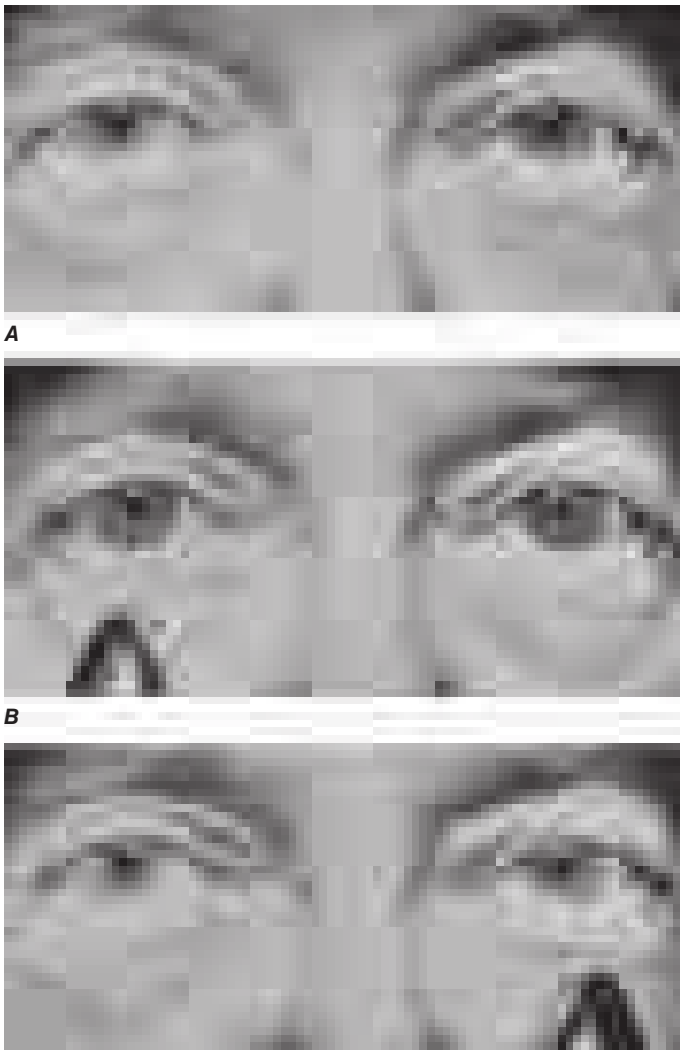


FIGURE 28-2 Demonstration of a relative afferent pupil defect (Marcus Gunn pupil) in the left eye, done with the patient fixating on a distant target. ***A.*** With dim background lighting, the pupils are equal and relatively large. ***B.*** Shining a flashlight into the right eye evokes equal, strong constriction of both pupils. ***C.*** Swinging the flashlight over to the damaged left eye causes dilation of both pupils, although they remain smaller than in ***A***. Swinging the flashlight back over to the healthy right eye would result in symmetric constriction back to the appearance shown in ***B***. Note that the pupils always remain equal; the damage to the left retina/optic nerve is revealed by weaker bilateral pupil constriction to a flashlight in the left eye compared with the right eye. *(From P Levatin: Arch Ophthalmol 62:768, 1959. Copyright © 1959 American Medical Association. All rights reserved.)*

young women, is assumed to represent a mild dysautonomia. Tonic pupils are also associated with multiple system atrophy, segmental hypohidrosis, diabetes, and amyloidosis. Occasionally, a tonic pupil is discovered incidentally in an otherwise completely normal, asymptomatic individual. The diagnosis is confirmed by placing a drop of dilute (0.125%) pilocarpine into each eye. Denervation hypersensitivity produces pupillary constriction in a tonic pupil, whereas the normal pupil shows no response. Pharmacologic dilatation from accidental or deliberate instillation of anticholinergic (atropine, scopolamine) drops can produce pupillary mydriasis. Gardener's pupil refers to mydriasis induced by exposure to tropane alkaloids, contained in plants such as deadly nightshade, jimsonweed, or angel's trumpet. When an anticholinergic agent is responsible for pupil dilation, 1% pilocarpine causes no constriction.

Both pupils are affected equally by systemic medications. They are small with narcotic use (morphine, oxycodone) and large with anticholinergics (scopolamine). Parasympathetic agents (pilocarpine) used to treat glaucoma produce miosis. In any patient with an unexplained pupillary abnormality, a slit-lamp examination is helpful to exclude surgical trauma to the iris, an occult foreign body, perforating injury, intraocular inflammation, adhesions (synechia), angle-closure glaucoma, and iris sphincter rupture from blunt trauma.

EYE MOVEMENTS AND ALIGNMENT

Eye movements are tested by asking the patient, with both eyes open, to pursue a small target such as a pen tip into the cardinal fields of gaze. Normal ocular versions are smooth, symmetric, full, and maintained in all directions without nystagmus. Saccades, or quick refixation eye movements, are assessed by having the patient look back and forth between two stationary targets. The eyes should move rapidly and accurately in a single jump to their target. Ocular alignment can be judged by holding a penlight directly in front of the patient at about 1 m. If the eyes are straight, the corneal light reflex will be centered in the middle of each pupil. To test eye alignment more precisely, the cover test is useful. The patient is instructed to look at a small fixation target in the distance. One eye is occluded with a paddle or hand, while the other eye is observed. If the viewing eye shifts position to take up fixation on the target, it was misaligned. If it remains motionless, the first eye is uncovered and the test is repeated on the second eye. If neither eye moves the eyes are aligned orthotropically. If the eyes are orthotropic in primary gaze but the patient complains of diplopia, the cover test should be performed with the head tilted or turned in whatever direction elicits diplopia. With practice, the examiner can detect an ocular deviation (heterotropia) as small as 1–2° with the cover test. In a patient with vertical diplopia, a small deviation can be difficult to detect and easy to dismiss. The magnitude of the deviation can be measured by placing a prism in front of the misaligned eye to determine the power required to neutralize the fixation shift evoked by covering the other eye. Temporary press-on plastic Fresnel prisms, prism eyeglasses, or eye muscle surgery can be used to restore binocular alignment.

STEREOPSIS

Stereoacuity is determined by presenting targets with retinal disparity separately to each eye by using polarized images. The most popular office tests measure a range of thresholds from 800 to 40 s of arc. Normal stereoacuity is 40 s of arc. If a patient achieves this level of stereoacuity, one is assured that the eyes are aligned orthotropically and that vision is intact in each eye. Random dot stereograms have no monocular depth cues and provide an excellent screening test for strabismus.

COLOR VISION

The retina contains three classes of cones, with visual pigments of differing peak spectral sensitivity: red (560 nm), green (530 nm), and blue (430 nm). The red and green cone pigments are encoded on the X chromosome, and the blue cone pigment on chromosome 7. Mutations of the blue cone pigment are exceedingly rare. Mutations of the red and green pigments cause congenital X-linked color blindness in 8% of males. Affected individuals are not truly color blind; rather, they differ from normal subjects in the way they perceive color and how they combine primary monochromatic lights to match a particular color. Anomalous trichromats have three cone types, but a mutation in one cone pigment (usually red or green) causes a shift in peak spectral sensitivity, altering the proportion of primary colors required to achieve a color match. Dichromats have only two cone types and therefore will accept a color match based on only two primary colors. Anomalous trichromats and dichromats have 6/6 (20/20) visual acuity, but their hue discrimination is impaired. Ishihara color plates can be used to detect red-green color blindness. The test plates contain a hidden number that is visible only to subjects with color confusion from red-green color blindness. Because color blindness is almost exclusively X-linked, it is worth screening only male children.

The Ishihara plates often are used to detect acquired defects in color vision, although they are intended as a screening test for congenital color blindness. Acquired defects in color vision frequently result from disease of the macula or optic nerve. For example, patients with a history of optic neuritis often complain of color desaturation long after their visual acuity has returned to normal. Color blindness also

can result from bilateral strokes involving the ventral portion of the occipital lobe (cerebral achromatopsia). Such patients can perceive only shades of gray and also may have difficulty recognizing faces (prosopagnosia). Infarcts of the dominant occipital lobe sometimes give rise to color anomia. Affected patients can discriminate colors but cannot name them.

VISUAL FIELDS

Vision can be impaired by damage to the visual system anywhere from the eyes to the occipital lobes. One can localize the site of the lesion with considerable accuracy by mapping the visual field deficit by finger confrontation and then correlating it with the topographic anatomy of the visual pathway (Fig. 28-3). Quantitative visual field mapping is performed by computer-driven perimeters that present a target of variable intensity at fixed positions in the visual field (Fig. 28-3*A*). By generating an automated printout of light thresholds, these static perimeters provide a sensitive means of detecting scotomas in the visual field. They are exceedingly useful for serial assessment of visual function in chronic diseases such as glaucoma and pseudotumor cerebri.

The crux of visual field analysis is to decide whether a lesion is before, at, or behind the optic chiasm. If a scotoma is confined to one

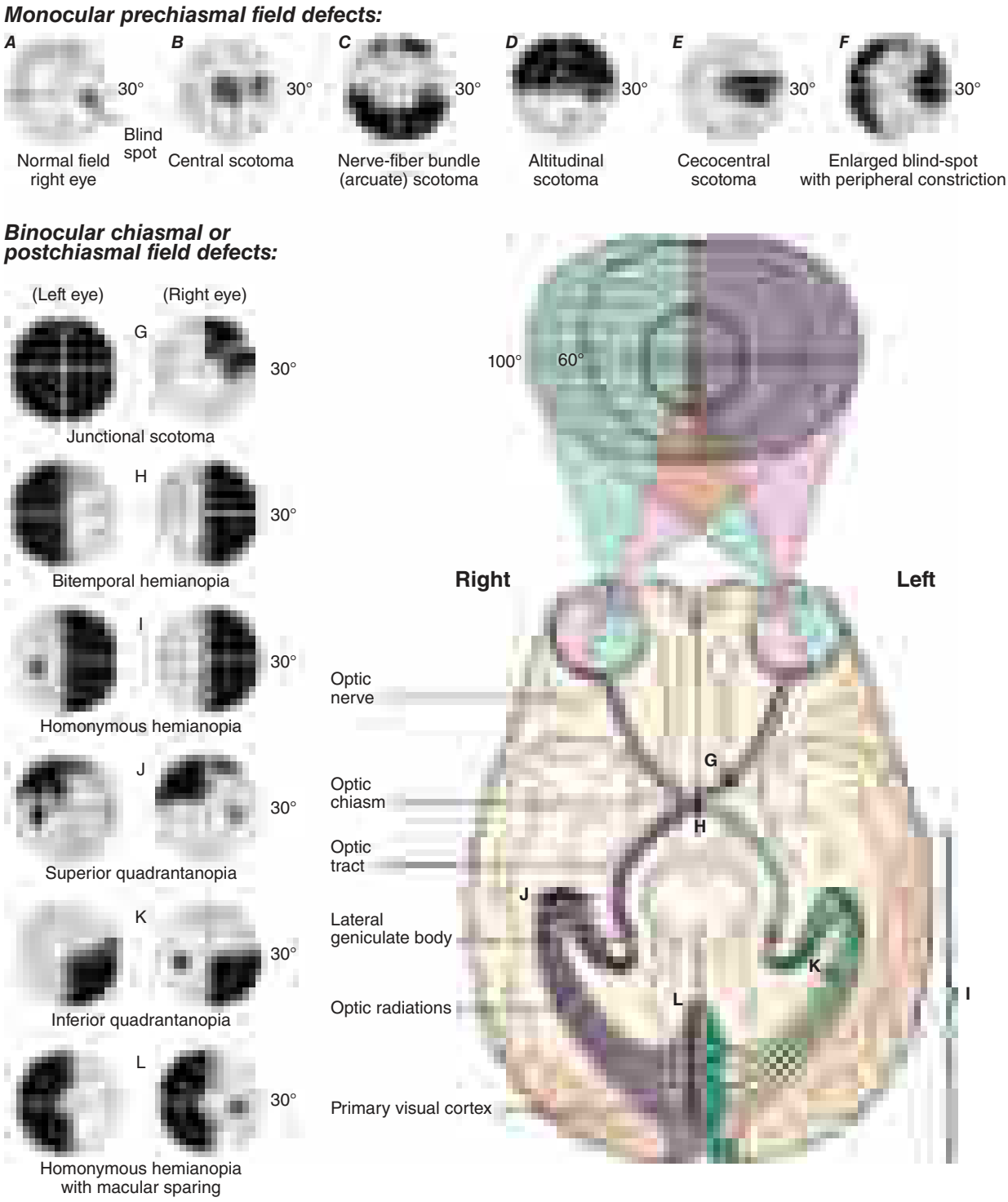


FIGURE 28-3 Ventral view of the brain, correlating patterns of visual field loss with the sites of lesions in the visual pathway. The visual fields overlap partially, creating 120° of central binocular field flanked by a 40° monocular crescent on either side. The visual field maps in this figure were done with a computer-driven perimeter (Humphrey Instruments, Carl Zeiss, Inc.). It plots the retinal sensitivity to light in the central 30° by using a gray scale format. Areas of visual field loss are shown in black. The examples of common monocular, prechiasmal field defects are all shown for the right eye. By convention, the visual fields are always recorded with the left eye's field on the left and the right eye's field on the right, just as the patient sees the world.

eye, it must be due to a lesion anterior to the chiasm, involving either the optic nerve or the retina. Retinal lesions produce scotomas that correspond optically to their location in the fundus. For example, a superior-nasal retinal detachment results in an inferior-temporal field cut. Damage to the macula causes a central scotoma **(Fig. 28-3*B*)**.

Optic nerve disease produces characteristic patterns of visual field loss. Glaucoma selectively destroys axons that enter the superotemporal or inferotemporal poles of the optic disc, resulting in arcuate scotomas shaped like a Turkish scimitar, which emanate from the blind spot and curve around fixation to end flat against the horizontal meridian **(Fig. 28-3*C*)**. This type of field defect mirrors the arrangement of the nerve fiber layer in the temporal retina. Arcuate or nerve fiber layer scotomas also result from optic neuritis, ischemic optic neuropathy, optic disc drusen, and branch retinal artery or vein occlusion.

Damage to the entire upper or lower pole of the optic disc causes an altitudinal field cut that follows the horizontal meridian **(Fig. 28-3*D*)**. This pattern of visual field loss is typical of ischemic optic neuropathy but also results from retinal vascular occlusion, advanced glaucoma, and optic neuritis.

About half the fibers in the optic nerve originate from ganglion cells serving the macula. Damage to papillomacular fibers causes a cecocentral scotoma that encompasses the blind spot and macula **(Fig. 28-3*E*)**. If the damage is irreversible, pallor eventually appears in the temporal portion of the optic disc. Temporal pallor from a cecocentral scotoma may develop in optic neuritis, nutritional optic neuropathy, toxic optic neuropathy, Leber's hereditary optic neuropathy, Kjer's dominant optic atrophy, and compressive optic neuropathy. It is worth mentioning that the temporal side of the optic disc is slightly paler than the nasal side in most normal individuals. Therefore, it sometimes can be difficult to decide whether the temporal pallor visible on fundus examination represents a pathologic change. Pallor of the nasal rim of the optic disc is a less equivocal sign of optic atrophy.

At the optic chiasm, fibers from nasal ganglion cells decussate into the contralateral optic tract. Crossed fibers are damaged more by compression than are uncrossed fibers. As a result, mass lesions of the sellar region cause a temporal hemianopia in each eye. Tumors anterior to the optic chiasm, such as meningiomas of the tuberculum sella, produce a junctional scotoma characterized by an optic neuropathy in one eye and a superior-temporal field cut in the other eye **(Fig. 28-3*G*)**. More symmetric compression of the optic chiasm by a pituitary adenoma **(see Fig. 373-1)**, meningioma, craniopharyngioma, glioma, or aneurysm results in a bitemporal hemianopia **(Fig. 28-3*H*)**. The insidious development of a bitemporal hemianopia often goes unnoticed by the patient and will escape detection by the physician unless each eye is tested separately.

It is difficult to localize a postchiasmal lesion accurately, because injury anywhere in the optic tract, lateral geniculate body, optic radiations, or visual cortex can produce a homonymous hemianopia (i.e., a temporal hemifield defect in the contralateral eye and a matching nasal hemifield defect in the ipsilateral eye) **(Fig. 28-3*I*)**. A unilateral postchiasmal lesion leaves the visual acuity in each eye unaffected, although the patient may read the letters on only the left or right half of the eye chart. Lesions of the optic radiations tend to cause poorly matched or incongruous field defects in each eye. Damage to the optic radiations in the temporal lobe (Meyer's loop) produces a superior quadrantic homonymous hemianopia **(Fig. 28-3*J*)**, whereas injury to the optic radiations in the parietal lobe results in an inferior quadrantic homonymous hemianopia **(Fig. 28-3*K*)**. Lesions of the primary visual cortex give rise to dense, congruous hemianopic field defects. Occlusion of the posterior cerebral artery supplying the occipital lobe is a common cause of total homonymous hemianopia. Some patients with hemianopia after occipital stroke have macular sparing, because the macular representation at the tip of the occipital lobe is supplied by collaterals from the middle cerebral artery **(Fig. 28-3*L*)**. Destruction of both occipital lobes produces cortical blindness. This condition can be distinguished from bilateral prechiasmal visual loss by noting that the pupil responses and optic fundi remain normal.

Partial recovery of homonymous hemianopia has been reported through computer-based rehabilitation therapy. During daily training sessions, patients fixate a central target while visual stimuli are presented within the blind region. The premise of vision restoration programs is that extra stimulation can promote recovery of partially damaged tissue located at the fringe of a cortical lesion. When fixation is controlled rigorously, however, no real improvement of the visual fields can be demonstrated. No effective treatment has been devised for homonymous hemianopia caused by loss of visual cortex.

DISORDERS

RED OR PAINFUL EYE

Corneal Abrasions Corneal abrasions are seen best by placing a drop of fluorescein in the eye and looking with the slit lamp, using a cobalt-blue light. A penlight with a blue filter will suffice if a slit lamp is not available. Damage to the corneal epithelium is revealed by yellow fluorescence of the exposed basement membrane underlying the epithelium. It is important to check for foreign bodies. To search the conjunctival fornices, the lower lid should be pulled down and the upper lid everted. A foreign body can be removed with a moistened cotton-tipped applicator after a drop of a topical anesthetic such as proparacaine has been placed in the eye. Alternatively, it may be possible to flush the foreign body from the eye by irrigating copiously with saline or artificial tears. If the corneal epithelium has been abraded, antibiotic ointment and a patch should be applied to the eye. A drop of an intermediate-acting cycloplegic such as cyclopentolate hydrochloride 1% helps reduce pain by relaxing the ciliary body. The eye should be reexamined the next day. Minor abrasions may not require patching, antibiotics, or cycloplegia.

Subconjunctival Hemorrhage This results from rupture of small vessels bridging the potential space between the episclera and the conjunctiva. Blood dissecting into this space can produce a spectacular red eye, but vision is not affected and the hemorrhage resolves without treatment. Subconjunctival hemorrhage is usually spontaneous but can result from blunt trauma, eye rubbing, or vigorous coughing. Occasionally it is a clue to an underlying bleeding disorder.

Pinguecula Pinguecula is a small, raised conjunctival nodule, usually at the nasal limbus. In adults such lesions are extremely common and have little significance unless they become inflamed (pingueculitis). They are more apt to occur in workers with frequent outdoor exposure. A *pterygium* resembles a pinguecula but has crossed the limbus to encroach on the corneal surface. Removal is justified when symptoms of irritation or blurring develop, but recurrence is a common problem.

Blepharitis This refers to inflammation of the eyelids. The most common form occurs in association with acne rosacea or seborrheic dermatitis. The eyelid margins usually are colonized heavily by staphylococci. Upon close inspection, they appear greasy, ulcerated, and crusted with scaling debris that clings to the lashes. Treatment consists of strict eyelid hygiene, using warm compresses and eyelash scrubs with baby shampoo. An external *hordeolum* (sty) is caused by staphylococcal infection of the superficial accessory glands of Zeis or Moll located in the eyelid margins. An internal hordeolum occurs after suppurative infection of the oil-secreting meibomian glands within the tarsal plate of the eyelid. Topical antibiotics such as bacitracin/polymyxin B ophthalmic ointment can be applied. Systemic antibiotics, usually tetracyclines or azithromycin, sometimes are necessary for treatment of meibomian gland inflammation (meibomitis) or chronic, severe blepharitis. A *chalazion* is a painless, chronic granulomatous inflammation of a meibomian gland that produces a pealike nodule within the eyelid. It can be incised and drained, but injection with glucocorticoids is equally effective. Basal cell, squamous cell, or meibomian gland carcinoma should be suspected with any nonhealing ulcerative lesion of the eyelids.

Dacryocystitis An inflammation of the lacrimal drainage system, dacryocystitis can produce epiphora (tearing) and ocular injection. Gentle pressure over the lacrimal sac evokes pain and reflux of mucus or pus from the tear puncta. Dacryocystitis usually occurs

after obstruction of the lacrimal system. It is treated with topical and systemic antibiotics, followed by probing, silicone stent intubation, or surgery to reestablish patency. *Entropion* (inversion of the eyelid) or *ectropion* (sagging or eversion of the eyelid) can also lead to epiphora and ocular irritation.

Conjunctivitis Conjunctivitis is the most common cause of a red, irritated eye. Pain is minimal, and visual acuity is reduced only slightly. The most common viral etiology is adenovirus infection. It causes a watery discharge, a mild foreign-body sensation, and photophobia. Bacterial infection tends to produce a more mucopurulent exudate. Mild cases of infectious conjunctivitis usually are treated empirically with broad-spectrum topical ocular antibiotics such as sulfacetamide 10%, polymyxin-bacitracin, or a trimethoprim-polymyxin combination. Smears and cultures usually are reserved for severe, resistant, or recurrent cases of conjunctivitis. To prevent contagion, patients should be admonished to wash their hands frequently, not to touch their eyes, and to avoid direct contact with others.

Allergic Conjunctivitis This condition is extremely common and often is mistaken for infectious conjunctivitis. Itching, redness, and epiphora are typical. The palpebral conjunctiva may become hypertropic with giant excrescences called cobblestone papillae. Irritation from contact lenses or any chronic foreign body also can induce formation of cobblestone papillae. *Atopic conjunctivitis* occurs in subjects with atopic dermatitis or asthma. Symptoms caused by allergic conjunctivitis can be alleviated with cold compresses, topical vasoconstrictors, antihistamines (olopatadine), and mast cell stabilizers (cromolyn). Topical glucocorticoid solutions provide dramatic relief of immune-mediated forms of conjunctivitis, but their long-term use is ill advised because of the complications of glaucoma, cataract, and secondary infection. Topical nonsteroidal anti-inflammatory drugs (ketorolac) are better alternatives.

Keratoconjunctivitis Sicca Also known as dry eye, this produces a burning foreign-body sensation, injection, and photophobia. In mild cases the eye appears surprisingly normal, but tear production measured by wetting of a filter paper (Schirmer strip) is deficient. A variety of systemic drugs, including antihistaminic, anticholinergic, and psychotropic medications, result in dry eye by reducing lacrimal secretion. Disorders that involve the lacrimal gland directly, such as sarcoidosis and Sjögren's syndrome, also cause dry eye. Patients may develop dry eye after radiation therapy if the treatment field includes the orbits. Problems with ocular drying are also common after lesions affecting cranial nerve V or VII. Corneal anesthesia is particularly dangerous, because the absence of a normal blink reflex exposes the cornea to injury without pain to warn the patient. Dry eye is managed by frequent and liberal application of artificial tears and ocular lubricants. In severe cases the tear puncta can be plugged or cauterized to reduce lacrimal outflow.

Keratitis Keratitis is a threat to vision because of the risk of corneal clouding, scarring, and perforation. Worldwide, the two leading causes of blindness from keratitis are trachoma from chlamydial infection and vitamin A deficiency related to malnutrition. In the United States, contact lenses play a major role in corneal infection and ulceration. They should not be worn by anyone with an active eye infection. In evaluating the cornea, it is important to differentiate between a superficial infection (*keratoconjunctivitis*) and a deeper, more serious ulcerative process. The latter is accompanied by greater visual loss, pain, photophobia, redness, and discharge. Slit-lamp examination shows disruption of the corneal epithelium, a cloudy infiltrate or abscess in the stroma, and an inflammatory cellular reaction in the anterior chamber. In severe cases, pus settles at the bottom of the anterior chamber, giving rise to a hypopyon. Immediate empirical antibiotic therapy should be initiated after corneal scrapings are obtained for Gram's stain, Giemsa stain, and cultures. Fortified topical antibiotics are most effective, supplemented with subconjunctival antibiotics as required. A fungal etiology should always be considered in a patient with keratitis. Fungal infection is common in warm humid climates, especially after penetration of the cornea by plant or vegetable material. Acanthamoeba keratitis is associated with improper disinfection of contact lenses.

Herpes Simplex The *herpesviruses* are a major cause of blindness from keratitis. Most adults in the United States have serum antibodies to herpes simplex, indicating prior viral infection (Chap. 187). Primary ocular infection generally is caused by herpes simplex type 1 rather than type 2. It manifests as a unilateral follicular blepharoconjunctivitis that is easily confused with adenoviral conjunctivitis, unless telltale vesicles are present on the eyelids or conjunctiva. A dendritic pattern of corneal epithelial ulceration revealed by fluorescein staining is pathognomonic for herpes infection but is seen in only a minority of primary infections. Recurrent ocular infection arises from reactivation of the latent herpesvirus. Viral eruption in the corneal epithelium may result in the characteristic herpes dendrite. Involvement of the corneal stroma produces edema, vascularization, and iridocyclitis. Herpes keratitis is treated with cycloplegia, and either a topical antiviral (trifluridine, ganciclovir) or an oral antiviral (acyclovir, ganciclovir) agent. Topical glucocorticoids are effective in mitigating corneal scarring but are generally reserved for cases involving stromal damage, because of the danger of corneal melting and perforation. Topical glucocorticoids also carry the risk of prolonging infection and inducing glaucoma.

Herpes Zoster Herpes zoster from reactivation of latent varicella (chickenpox) virus causes a dermatomal pattern of painful vesicular dermatitis (Chap. 188). Ocular symptoms can occur after zoster eruption in any branch of the trigeminal nerve but are particularly common when vesicles form on the nose, reflecting nasociliary (V1) nerve involvement (Hutchinson's sign). Herpes zoster ophthalmicus produces corneal dendrites, which can be difficult to distinguish from those seen in herpes simplex. Stromal keratitis, anterior uveitis, raised intraocular pressure, ocular motor nerve palsies, acute retinal necrosis, and postherpetic scarring and neuralgia are other common sequelae. Herpes zoster ophthalmicus is treated with antiviral agents and cycloplegics. In severe cases, glucocorticoids may be added to prevent permanent visual loss from corneal scarring.

Episcleritis This is an inflammation of the episclera, a thin layer of connective tissue between the conjunctiva and the sclera. Episcleritis resembles conjunctivitis, but it is a more localized process and discharge is absent. Most cases of episcleritis are idiopathic, but some occur in the setting of an autoimmune disease. *Scleritis* refers to a deeper, more severe inflammatory process that frequently is associated with a connective tissue disease such as rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, granulomatosis with polyangiitis, or relapsing polychondritis. The inflammation and thickening of the sclera can be diffuse or nodular. In anterior forms of scleritis, the globe assumes a violet hue and the patient complains of severe ocular tenderness and pain. With posterior scleritis, the pain and redness may be less marked, but there is often proptosis, choroidal effusion, reduced motility, and visual loss. Episcleritis and scleritis should be treated with NSAIDs. If these agents fail, topical or even systemic glucocorticoid therapy may be necessary, especially if an underlying autoimmune process is active.

Uveitis Involving the anterior structures of the eye, uveitis also is called *iritis* or *iridocyclitis*. The diagnosis requires slit-lamp examination to identify inflammatory cells floating in the aqueous humor or deposited on the corneal endothelium (keratic precipitates). Anterior uveitis develops in sarcoidosis, ankylosing spondylitis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, reactive arthritis, and Behçet's disease. It also is associated with herpes infections, syphilis, Lyme disease, onchocerciasis, tuberculosis, and leprosy. Although anterior uveitis can occur in conjunction with many diseases, no cause is found to explain the majority of cases. For this reason, laboratory evaluation usually is reserved for patients with recurrent or severe anterior uveitis. Treatment is aimed at reducing inflammation and scarring by judicious use of topical glucocorticoids. Dilatation of the pupil reduces pain and prevents the formation of synechiae.

Posterior Uveitis This is diagnosed by observing inflammation of the vitreous, retina, or choroid on fundus examination. It is more likely than anterior uveitis to be associated with an identifiable systemic disease. Some patients have panuveitis, or inflammation of both the anterior and posterior segments of the eye. Posterior uveitis is a manifestation of autoimmune diseases such as sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome, and inflammatory bowel disease. It also accompanies diseases such as toxoplasmosis, onchocerciasis, cysticercosis, coccidioidomycosis, toxocariasis, and histoplasmosis; infections caused by organisms such as *Candida*, *Pneumocystis carinii*, *Cryptococcus*, *Aspergillus*, herpes, and cytomegalovirus **(see Fig. 190-1)**; and other diseases, such as syphilis, Lyme disease, tuberculosis, cat-scratch disease, Whipple's disease, and brucellosis. In multiple sclerosis, chronic inflammatory changes can develop in the extreme periphery of the retina (pars planitis or intermediate uveitis). Glucocorticoids have been the mainstay of treatment for noninfectious uveitis. Monoclonal antibodies which target proinflammatory cytokines, such as the tumor necrosis factor alpha (TNF-α) inhibitor adalimumab, are effective at preventing vision loss in chronic uveitis.

Acute Angle-Closure Glaucoma This is an unusual but frequently misdiagnosed cause of a red, painful eye. Asian populations have a particularly high risk of angle-closure glaucoma. Susceptible eyes have a shallow anterior chamber because the eye has either a short axial length (hyperopia) or a lens enlarged by the gradual development of cataract. When the pupil becomes mid-dilated, the peripheral iris blocks aqueous outflow via the anterior chamber angle and the intraocular pressure rises abruptly, producing pain, injection, corneal edema, obscurations, and blurred vision. In some patients, ocular symptoms are overshadowed by nausea, vomiting, or headache, prompting a fruitless workup for abdominal or neurologic disease. The diagnosis is made by measuring the intraocular pressure during an acute attack or by performing gonioscopy, a procedure that allows one to observe a narrow chamber angle with a mirrored contact lens. Acute angle closure is treated with acetazolamide (PO or IV), topical beta blockers, prostaglandin analogues, α_2-adrenergic agonists, and pilocarpine to induce miosis. If these measures fail, a laser can be used to create a hole in the peripheral iris to relieve pupillary block. Many physicians are reluctant to dilate patients routinely for fundus examination because they fear precipitating an angle-closure glaucoma. The risk is actually remote and more than outweighed by the potential benefit to patients of discovering a hidden fundus lesion visible only through a fully dilated pupil. Moreover, a single attack of angle closure after pharmacologic dilatation rarely causes any permanent damage to the eye and serves as an inadvertent provocative test to identify patients with narrow angles who would benefit from prophylactic laser iridectomy.

Endophthalmitis This results from bacterial, viral, fungal, or parasitic infection of the internal structures of the eye. It usually is acquired by hematogenous seeding from a remote site. Chronically ill, diabetic, or immunosuppressed patients, especially those with a history of indwelling IV catheters or positive blood cultures, are at greatest risk for endogenous endophthalmitis. Although most patients have ocular pain and injection, visual loss is sometimes the only symptom. Septic emboli from a diseased heart valve or a dental abscess that lodge in the retinal circulation can give rise to endophthalmitis. White-centered retinal hemorrhages known as Roth's spots **(Fig. 28-4)** are considered pathognomonic for subacute bacterial endocarditis, but they also appear in leukemia, diabetes, and many other conditions. Endophthalmitis also occurs as a complication of ocular surgery, especially glaucoma filtering, occasionally months or even years after the operation. An occult penetrating foreign body or unrecognized trauma to the globe should be considered in any patient with unexplained intraocular infection or inflammation.

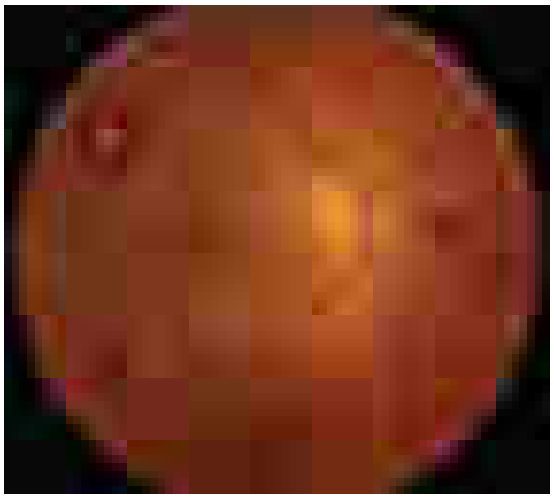


FIGURE 28-4 Roth's spot, cotton-wool spot, and retinal hemorrhages in a 48-year-old liver transplant patient with candidemia from immunosuppression.

TRANSIENT OR SUDDEN VISUAL LOSS

Amaurosis Fugax This term refers to a transient ischemic attack of the retina **(Chap. 420)**. Because neural tissue has a high rate of metabolism, interruption of blood flow to the retina for more than a few seconds results in *transient monocular blindness*, a term used interchangeably with amaurosis fugax. Patients describe a rapid fading of vision like a curtain descending, sometimes affecting only a portion of the visual field. Amaurosis fugax usually results from an embolus that becomes stuck within a retinal arteriole **(Fig. 28-5)**. If the embolus breaks up or passes, flow is restored and vision returns quickly to normal without permanent damage. With prolonged interruption of blood flow, the inner retina suffers infarction. Ophthalmoscopy reveals zones of whitened, edematous retina following the distribution of branch retinal arterioles. Complete occlusion of the central retinal artery produces arrest of blood flow and a milky retina with a cherry-red fovea **(Fig. 28-6)**. Emboli are composed of cholesterol (Hollenhorst plaque), calcium, or platelet-fibrin debris. The most common source is an atherosclerotic plaque in the carotid artery or aorta, although emboli also can arise from the heart, especially in patients with diseased valves, atrial fibrillation, or wall motion abnormalities.

In rare instances, amaurosis fugax results from low central retinal artery perfusion pressure in a patient with a critical stenosis of the ipsilateral carotid artery and poor collateral flow via the circle of Willis. In this situation, amaurosis fugax develops when there is a dip in systemic blood pressure or a slight worsening of the carotid stenosis. Sometimes there is contralateral motor or sensory loss, indicating concomitant hemispheric cerebral ischemia.

Retinal arterial occlusion also occurs rarely in association with retinal migraine, lupus erythematosus, anticardiolipin antibodies,

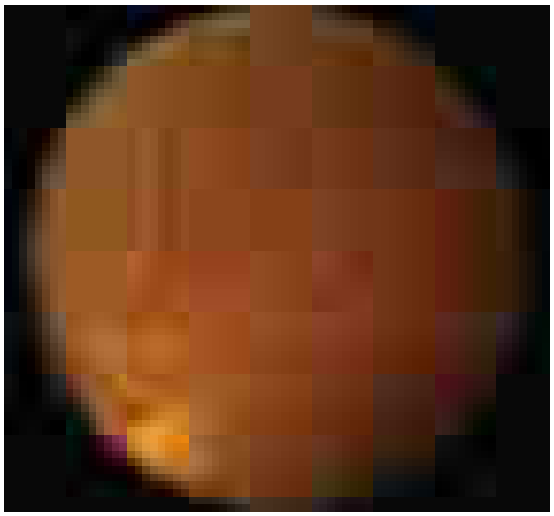


FIGURE 28-5 Hollenhorst plaque lodged at the bifurcation of a retinal arteriole proves that a patient is shedding emboli from the carotid artery, great vessels, or heart.

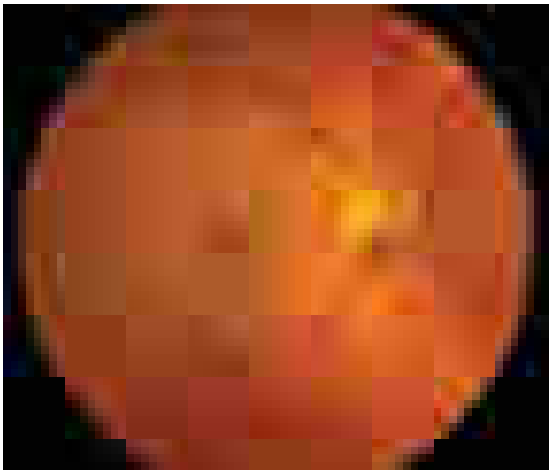


FIGURE 28-6 Central retinal artery occlusion in a 78-year-old man reducing acuity to counting fingers in the right eye. Note the splinter hemorrhage on the optic disc and the slightly milky appearance to the macula with a cherry-red fovea.

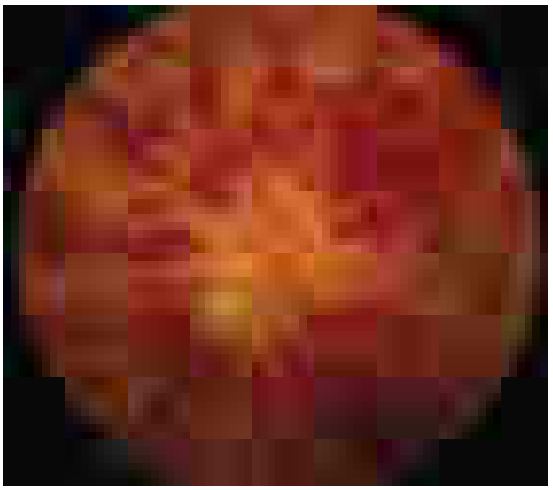


FIGURE 28-8 Central retinal vein occlusion can produce massive retinal hemorrhage ("blood and thunder"), ischemia, and vision loss.

anticoagulant deficiency states (protein S, protein C, and antithrombin deficiency), Susac's syndrome, pregnancy, IV drug abuse, blood dyscrasias, dysproteinemias, and temporal arteritis.

Marked *systemic hypertension* causes sclerosis of retinal arterioles, splinter hemorrhages, focal infarcts of the nerve fiber layer (cotton-wool spots), and leakage of lipid and fluid (hard exudate) into the macula **(Fig. 28-7)**. In hypertensive crisis, sudden visual loss can result from vasospasm of retinal arterioles and retinal ischemia. In addition, acute hypertension may produce visual loss from ischemic swelling of the optic disc. Patients with acute hypertensive retinopathy should be treated by lowering the blood pressure. However, the blood pressure should not be reduced precipitously, because there is a danger of optic disc infarction from sudden hypoperfusion.

Impending *branch* or *central retinal vein occlusion* can produce prolonged visual obscurations that resemble those described by patients with amaurosis fugax. The veins appear engorged and phlebitic, with numerous retinal hemorrhages **(Fig. 28-8)**. In some patients, venous blood flow recovers spontaneously, whereas others evolve a frank obstruction with extensive retinal bleeding ("blood and thunder" appearance), infarction, and visual loss. Venous occlusion of the retina is often idiopathic, but hypertension, diabetes, and glaucoma are prominent risk factors. Polycythemia, thrombocythemia, or other factors leading to an underlying hypercoagulable state should be corrected; aspirin treatment may be beneficial.

Anterior Ischemic Optic Neuropathy (AION) This is caused by insufficient blood flow through the posterior ciliary arteries that supply the optic disc. It produces painless monocular visual loss that is sudden in onset, followed sometimes by stuttering progression. The optic disc is edematous and usually bordered by nerve fiber layer splinter hemorrhages **(Fig. 28-9)**. AION is divided into two forms: arteritic and nonarteritic. The nonarteritic form is most common. No specific cause is known, although diabetes, renal failure, and hypertension are common risk factors. Case reports have linked erectile dysfunction drugs to AION, but a causal association is doubtful. Evidence is strong that a crowded disc architecture and small optic cup predispose to the development of nonarteritic AION. In patients with a "disc-at-risk," the advent of AION in one eye increases the likelihood of the same event occurring in the other eye. No treatment is available for nonarteritic AION; glucocorticoids should not be prescribed.

About 5% of patients, especially Caucasian females aged >60, develop the arteritic form of AION in conjunction with giant-cell (temporal) arteritis **(Chap. 356)**. It is urgent to recognize arteritic AION so that high doses of glucocorticoids can be instituted immediately to prevent blindness in the second eye. Tocilizumab is an effective alternative to glucocorticoids for sustained suppression of symptoms of giant cell arteritis. Symptoms of polymyalgia rheumatica may be present; the sedimentation rate and C-reactive protein level are usually elevated. In a patient with visual loss from suspected arteritic AION, temporal artery biopsy is mandatory to confirm the diagnosis. Administer glucocorticoids immediately, without waiting for the biopsy to be completed. The biopsy should be obtained as soon as practical, because prolonged glucocorticoid treatment can hide inflammatory changes. It is important to harvest an arterial segment at least 3 cm long and to

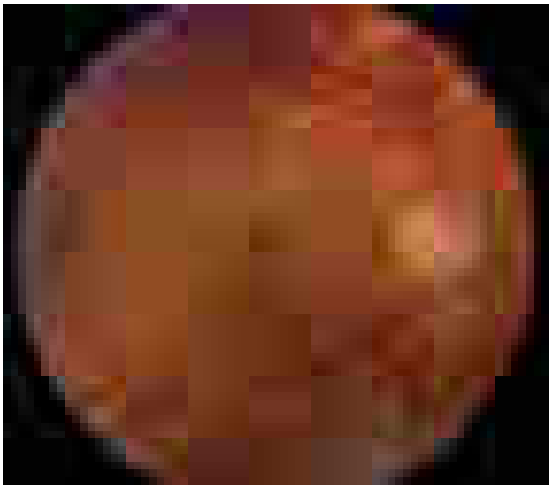


FIGURE 28-7 Hypertensive retinopathy with blurred optic disc, scattered hemorrhages, cotton-wool spots (nerve fiber layer infarcts), and foveal exudate in a 62-year-old man with chronic renal failure and a systolic blood pressure of 220.

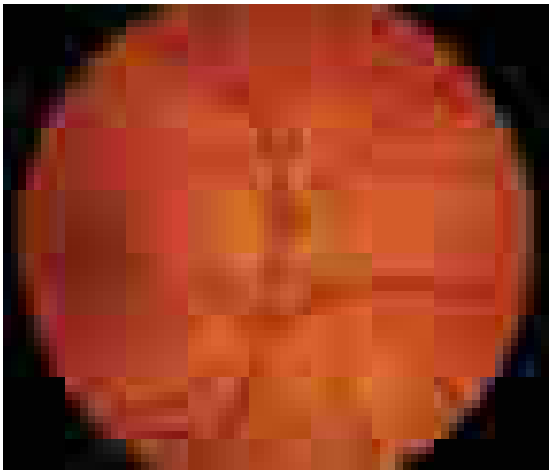


FIGURE 28-9 Anterior ischemic optic neuropathy from temporal arteritis in a 64-year-old woman with acute disc swelling, splinter hemorrhages, visual loss, and an erythrocyte sedimentation rate of 60 mm/h.

examine a sufficient number of tissue sections. The histological features of granulomatous inflammation are often quite subtle in temporal artery specimens. If the biopsy is declared negative by an experienced pathologist, the diagnosis of arteritic AION is highly unlikely and glucocorticoids should usually be discontinued.

Posterior Ischemic Optic Neuropathy This is an uncommon cause of acute visual loss, induced by the combination of severe anemia and hypotension. Cases have been reported after major blood loss during surgery (especially in patients undergoing cardiac or lumbar spine operations), shock, gastrointestinal bleeding, and renal dialysis. The fundus usually appears normal, although optic disc swelling develops if the process extends anteriorly far enough to reach the globe. Vision can be salvaged in some patients by immediate blood transfusion and reversal of hypotension.

Optic Neuritis This is a common inflammatory disease of the optic nerve. In the Optic Neuritis Treatment Trial (ONTT), the mean age of patients was 32 years, 77% were female, 92% had ocular pain (especially with eye movements), and 35% had optic disc swelling. In most patients, the demyelinating event was retrobulbar and the ocular fundus appeared normal on initial examination **(Fig. 28-10)**, although optic disc pallor slowly developed over subsequent months.

Virtually all patients experience a gradual recovery of vision after a single episode of optic neuritis, even without treatment. This rule is so reliable that failure of vision to improve after a first attack of optic neuritis casts doubt on the original diagnosis. Treatment with high-dose IV methylprednisolone (250 mg every 6 h for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days) makes no difference in ultimate acuity 6 months after the attack, but the recovery of visual function occurs more rapidly. Therefore, when visual loss is severe (worse than 20/100), IV followed by PO glucocorticoids are often recommended.

For some patients, optic neuritis remains an isolated event. However, the ONTT showed that the 15-year cumulative probability of developing clinically definite multiple sclerosis after optic neuritis is 50%. A brain magnetic resonance (MR) scan is advisable in every patient with a first attack of optic neuritis. If two or more plaques are present on initial imaging, treatment should be considered to prevent the development of additional demyelinating lesions **(Chap. 436)**.

A particularly severe form of optic neuritis occurs in neuromyelitis optica (NMO); it is typically longitudinally extensive, and may be bilateral or associated with myelitis. NMO can occur as a primary disorder, in the setting of systemic autoimmune disease or rarely as a paraneoplastic condition. Detection of circulating antibodies directed against aquaporin-4 is diagnostic. Treatment for acute episodes consists of glucocorticoids and, in resistant cases, plasma exchange. **Neuromyelitis optica is discussed in detail in Chap. 437.**

LEBER'S HEREDITARY OPTIC NEUROPATHY

This disease usually affects young men, causing gradual, painless, severe central visual loss in one eye, followed weeks to years later by the same process in the other eye. Acutely, the optic disc appears mildly plethoric with surface capillary telangiectasias but no vascular leakage on fluorescein angiography. Eventually optic atrophy ensues. Leber's optic neuropathy is caused by a point mutation at codon 11778 in the mitochondrial gene encoding nicotinamide adenine dinucleotide dehydrogenase (NADH) subunit 4. Additional mutations responsible for the disease have been identified, most in mitochondrial genes that encode proteins involved in electron transport. Mitochondrial mutations that cause Leber's neuropathy are inherited from the mother by all her children, but for unknown reasons, daughters are rarely affected. Early stage clinical trials of gene therapy for this condition are in progress.

Toxic Optic Neuropathy This can result in acute visual loss with bilateral optic disc swelling and cecocentral scotomas. Cases have been reported from exposure to ethambutol, methyl alcohol (moonshine), ethylene glycol (antifreeze), or carbon monoxide. In toxic optic neuropathy, visual loss also can develop gradually and produce optic atrophy **(Fig. 28-11)** without a phase of acute optic disc edema. Many agents have been implicated in toxic optic neuropathy, but evidence supporting the association is often weak. The following is a partial list of potential offending drugs or toxins: disulfiram, ethchlorvynol, chloramphenicol, amiodarone, monoclonal anti-CD3 antibody, ciprofloxacin, digitalis, streptomycin, lead, arsenic, thallium, D-penicillamine, isoniazid, emetine, and sulfonamides. Metallosis (chromium, cobalt, nickel) from hip implant failure is a rare cause of toxic optic neuropathy. Deficiency states induced by starvation, malabsorption, or alcoholism can lead to insidious visual loss. Thiamine, vitamin B_{12}, and folate levels should be checked in any patient with unexplained bilateral central scotomas and optic pallor.

Papilledema This connotes bilateral optic disc swelling from raised intracranial pressure **(Fig. 28-12)**. Headache is a common but not invariable accompaniment. All other forms of optic disc swelling (e.g., from optic neuritis or ischemic optic neuropathy) should be called "optic disc edema." This convention is arbitrary but serves to avoid confusion. Often it is difficult to differentiate papilledema from other forms of optic disc edema by fundus examination alone. Transient visual obscurations are a classic symptom of papilledema. They can occur in only one eye or simultaneously in both eyes. They usually last seconds but can persist longer. Obscurations follow abrupt shifts in posture or happen spontaneously. When obscurations are prolonged or spontaneous, the papilledema is more threatening. Visual acuity is not affected by papilledema unless the papilledema is severe, longstanding, or accompanied by macular edema and hemorrhage. Visual field testing shows enlarged blind spots and peripheral constriction (Fig. 28-3*F*). With unremitting papilledema, peripheral visual field loss

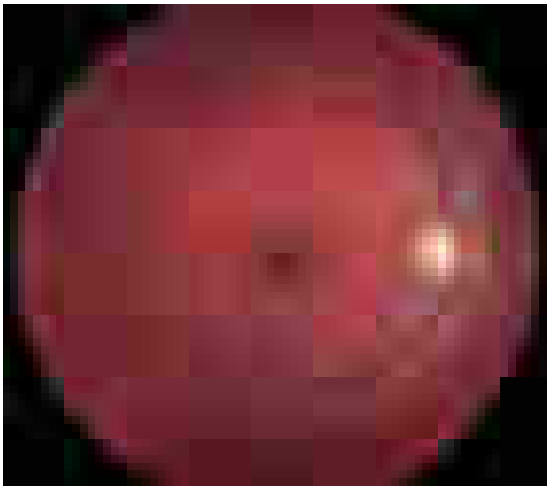


FIGURE 28-10 Retrobulbar optic neuritis is characterized by a normal fundus examination initially, hence the rubric "the doctor sees nothing, and the patient sees nothing." Optic atrophy develops after severe or repeated attacks.

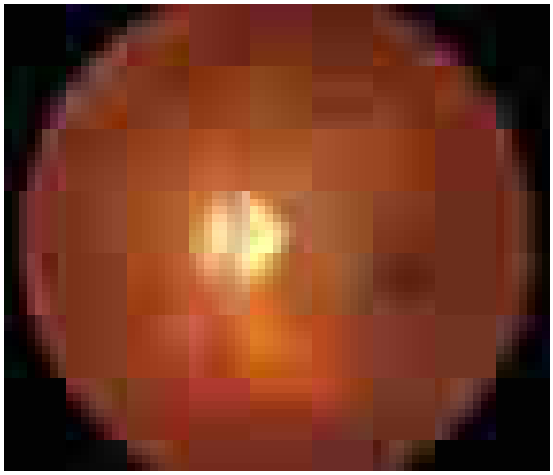


FIGURE 28-11 Optic atrophy is not a specific diagnosis but refers to the combination of optic disc pallor, arteriolar narrowing, and nerve fiber layer destruction produced by a host of eye diseases, especially optic neuropathies.

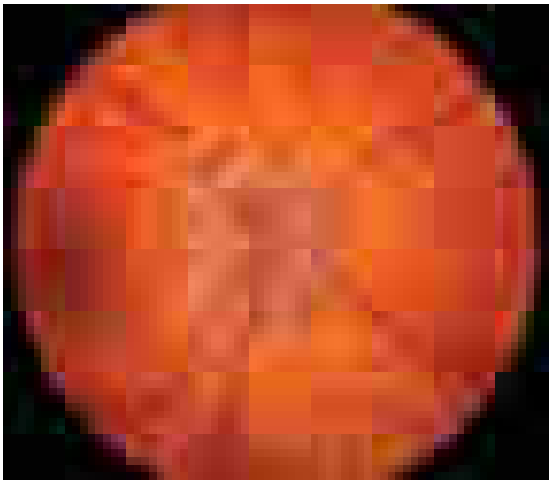


FIGURE 28-12 Papilledema means optic disc edema from raised intracranial pressure. This young woman developed acute papilledema, with hemorrhages and cotton-wool spots, as a rare side effect of treatment with tetracycline for acne.

progresses in an insidious fashion while the optic nerve develops atrophy. In this setting, reduction of optic disc swelling is an ominous sign of a dying nerve rather than an encouraging indication of resolving papilledema.

Evaluation of papilledema requires neuroimaging to exclude an intracranial lesion. MR angiography is appropriate in selected cases to search for a dural venous sinus occlusion or an arteriovenous shunt. If neuroradiologic studies are negative, the subarachnoid opening pressure should be measured in the lateral decubitus position by lumbar puncture. Inaccurate pressure readings are a common pitfall. An elevated pressure, with normal cerebrospinal fluid, points by exclusion to the diagnosis of *pseudotumor cerebri* (idiopathic intracranial hypertension). Almost all patients are female, and most are obese. Treatment with a carbonic anhydrase inhibitor such as acetazolamide lowers intracranial pressure by reducing the production of cerebrospinal fluid and improves the visual fields. Weight reduction is vital: bariatric surgery should be considered in patients who cannot lose weight by diet control. If vision loss is severe or progressive, a shunt should be performed without delay to prevent blindness. Optic nerve sheath fenestration is less efficacious, and does not address other neurological symptoms. Occasionally, fulminant papilledema produces rapid onset of blindness. In such patients, emergency surgery should be performed to install a shunt without delay.

Optic Disc Drusen These are refractile deposits within the substance of the optic nerve head **(Fig. 28-13)**. They are unrelated to drusen of the retina, which occur in age-related macular degeneration. Optic disc drusen are most common in people of northern European descent. Their diagnosis is obvious when they are visible as glittering particles on the surface of the optic disc. However, in many patients they are hidden beneath the surface, producing pseudopapilledema. It is important to recognize optic disc drusen to avoid an unnecessary evaluation for papilledema. When optic disc drusen are buried, B-ultrasound is the most sensitive way to detect them. They appear hyperechoic because they contain calcium. They are also visible on computed tomography (CT) or optical coherence tomography (OCT), a technique for acquiring cross-section images of the retina. In most patients, optic disc drusen are an incidental, innocuous finding, but they can produce visual obscurations. On perimetry they give rise to enlarged blind spots and arcuate scotomas from damage to the optic disc. With increasing age, drusen tend to become more exposed on the disc surface as optic atrophy develops. Hemorrhage, choroidal neovascular membrane, and AION are more likely to occur in patients with optic disc drusen. No treatment is available.

Vitreous Degeneration This occurs in all individuals with advancing age, leading to visual symptoms. Opacities develop in the vitreous, casting annoying shadows on the retina. As the eye moves, these distracting "floaters" move synchronously, with a slight lag caused by inertia of the vitreous gel. Vitreous traction on the retina causes mechanical stimulation, resulting in perception of flashing lights. This photopsia is brief and is confined to one eye, in contrast to the bilateral, prolonged scintillations of cortical migraine. Contraction of the vitreous can result in sudden separation from the retina, heralded by an alarming shower of floaters and photopsia. This process, known as *vitreous detachment*, is a common involutional event in the elderly. It is not harmful unless it damages the retina. A careful examination of the dilated fundus is important in any patient complaining of floaters or photopsia to search for peripheral tears or holes. If such a lesion is found, laser application can forestall a retinal detachment. Occasionally a tear ruptures a retinal blood vessel, causing vitreous hemorrhage and sudden loss of vision. On attempted ophthalmoscopy the fundus is hidden by a dark haze of blood. Ultrasound is required to examine the interior of the eye for a retinal tear or detachment. If the hemorrhage does not resolve spontaneously, the vitreous can be removed surgically. Vitreous hemorrhage also results from the fragile neovascular vessels that proliferate on the surface of the retina in diabetes, sickle cell anemia, and other ischemic ocular diseases.

Retinal Detachment This produces symptoms of floaters, flashing lights, and a scotoma in the peripheral visual field corresponding to the detachment **(Fig. 28-14)**. If the detachment includes the fovea, there is an afferent pupil defect and the visual acuity is reduced. In most eyes, retinal detachment starts with a hole, flap, or tear in the peripheral

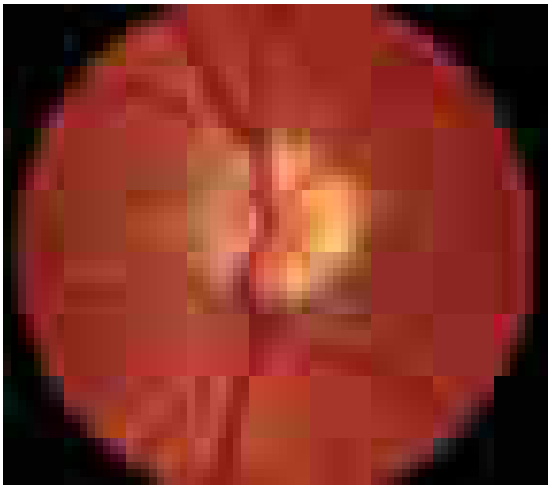


FIGURE 28-13 Optic disc drusen are calcified, mulberry-like deposits of unknown etiology within the optic disc, giving rise to "pseudopapilledema."

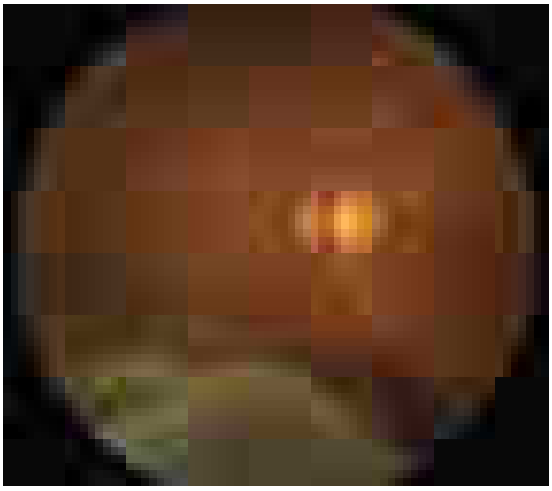


FIGURE 28-14 Retinal detachment appears as an elevated sheet of retinal tissue with folds. In this patient, the fovea was spared, so acuity was normal, but an inferior detachment produced a superior scotoma.

retina (rhegmatogenous retinal detachment). Patients with peripheral retinal thinning (lattice degeneration) are particularly vulnerable to this process. Once a break has developed in the retina, liquefied vitreous is free to enter the subretinal space, separating the retina from the pigment epithelium. The combination of vitreous traction on the retinal surface and passage of fluid behind the retina leads inexorably to detachment. Patients with a history of myopia, trauma, or prior cataract extraction are at greatest risk for retinal detachment. The diagnosis is confirmed by ophthalmoscopic examination of the dilated eye.

Classic Migraine (See also Chap. 422) This usually occurs with a visual aura lasting about 20 min. In a typical attack, a small central disturbance in the field of vision marches toward the periphery, leaving a transient scotoma in its wake. The expanding border of migraine scotoma has a scintillating, dancing, or zigzag edge, resembling the bastions of a fortified city, hence the term *fortification spectra*. Patients' descriptions of fortification spectra vary widely and can be confused with amaurosis fugax. Migraine patterns usually last longer and are perceived in both eyes, whereas amaurosis fugax is briefer and occurs in only one eye. Migraine phenomena also remain visible in the dark or with the eyes closed. Generally they are confined to either the right or the left visual hemifield, but sometimes both fields are involved simultaneously. Patients often have a long history of stereotypic attacks. After the visual symptoms recede, headache develops in most patients.

Transient Ischemic Attacks Vertebrobasilar insufficiency may result in acute homonymous visual symptoms. Many patients mistakenly describe symptoms in the left or right eye when in fact the symptoms are occurring in the left or right hemifield of both eyes. Interruption of blood supply to the visual cortex causes a sudden fogging or graying of vision, occasionally with flashing lights or other positive phenomena that mimic migraine. Cortical ischemic attacks are briefer in duration than migraine, occur in older patients, and are not followed by headache. There may be associated signs of brainstem ischemia, such as diplopia, vertigo, numbness, weakness, and dysarthria.

Stroke Stroke occurs when interruption of blood supply from the posterior cerebral artery to the visual cortex is prolonged. The only finding on examination is a homonymous visual field defect that stops abruptly at the vertical meridian. Occipital lobe stroke usually is due to thrombotic occlusion of the vertebrobasilar system, embolus, or dissection. Lobar hemorrhage, tumor, abscess, and arteriovenous malformation are other common causes of hemianopic cortical visual loss.

Factitious (Functional, Nonorganic) Visual Loss This is claimed by hysterics or malingerers. The latter account for the vast majority, seeking sympathy, special treatment, or financial gain by feigning loss of sight. The diagnosis is suspected when the history is atypical, physical findings are lacking or contradictory, inconsistencies emerge on testing, and a secondary motive can be identified. In our litigious society, the fraudulent pursuit of recompense has spawned an epidemic of factitious visual loss.

CHRONIC VISUAL LOSS

Cataract Cataract is a clouding of the lens sufficient to reduce vision. Most cataracts develop slowly as a result of aging, leading to gradual impairment of vision. The formation of cataract occurs more rapidly in patients with a history of uveitis, diabetes mellitus, ocular trauma or vitrectomy. Cataracts are acquired in a variety of genetic diseases, such as myotonic dystrophy, neurofibromatosis type 2, and galactosemia. Radiation therapy and glucocorticoid treatment can induce cataract as a side effect. The cataracts associated with radiation or glucocorticoids have a typical posterior subcapsular location. Cataract can be detected by noting an impaired red reflex when viewing light reflected from the fundus with an ophthalmoscope or by examining the dilated eye with the slit lamp.

The only treatment for cataract is surgical extraction of the opacified lens. Millions of cataract operations are performed each year around the globe. The operation generally is done under local anesthesia on an outpatient basis. A plastic or silicone intraocular lens is placed within the empty lens capsule in the posterior chamber, substituting for the natural lens and leading to rapid recovery of sight. More than 95% of patients who undergo cataract extraction can expect an improvement in vision. In some patients, the lens capsule remaining in the eye after cataract extraction eventually turns cloudy, causing secondary loss of vision. A small opening, called a posterior capsulotomy, is made in the lens capsule with a laser to restore clarity.

Glaucoma Glaucoma is a slowly progressive, insidious optic neuropathy that usually is associated with chronic elevation of intraocular pressure. After cataract, it is the most common cause of blindness in the world. It is especially prevalent in people of African descent. The mechanism by which raised intraocular pressure injures the optic nerve is not understood. Axons entering the inferotemporal and superotemporal aspects of the optic disc are damaged first, producing typical nerve fiber bundle or arcuate scotomas on perimetric testing. As fibers are destroyed, the neural rim of the optic disc shrinks and the physiologic cup within the optic disc enlarges (Fig. 28-15). This process is referred to as pathologic "cupping." The cup-to-disc diameter is expressed as a fraction (e.g., 0.2). The cup-to-disc ratio ranges widely in normal individuals, making it difficult to diagnose glaucoma reliably simply by observing an unusually large or deep optic cup. Careful documentation of serial examinations is helpful. In a patient with physiologic cupping the large cup remains stable, whereas in a patient with glaucoma it expands relentlessly over the years. Observation of progressive cupping and detection of an arcuate scotoma or a nasal step on computerized visual field testing is sufficient to establish the diagnosis of glaucoma. OCT reveals corresponding loss of fibers along the arcuate pathways in the nerve fiber layer.

The preponderance of patients with glaucoma have open anterior chamber angles. In most affected individuals the intraocular pressure is elevated. The cause of elevated intraocular pressure is unknown, but it is associated with gene mutations in the heritable forms. Surprisingly, a third of patients with open-angle glaucoma have an intraocular pressure within the normal range of 10–20 mmHg. For this so-called normal or low-tension form of glaucoma, high myopia is a risk factor.

Chronic angle-closure glaucoma and chronic open-angle glaucoma are usually asymptomatic. Only acute angle-closure glaucoma causes a red or painful eye, from abrupt elevation of intraocular pressure. In all forms of glaucoma, foveal acuity is spared until end-stage disease is reached. For these reasons, severe and irreversible damage can occur before either the patient or the physician recognizes the diagnosis. Screening of patients for glaucoma by noting the cup-to-disc ratio on ophthalmoscopy and by measuring intraocular pressure is vital. Glaucoma is treated with topical adrenergic agonists, cholinergic agonists, beta blockers, prostaglandin analogues, and carbonic anhydrase inhibitors. Occasionally, systemic absorption of beta blocker from eyedrops

FIGURE 28-15 Glaucoma results in "cupping" as the neural rim is destroyed and the central cup becomes enlarged and excavated. The cup-to-disc ratio is about 0.8 in this patient.

can be sufficient to cause side effects of bradycardia, hypotension, heart block, bronchospasm, or depression. Laser treatment of the trabecular meshwork in the anterior chamber angle improves aqueous outflow from the eye. If medical or laser treatments fail to halt optic nerve damage from glaucoma, a filter must be constructed surgically (trabeculectomy) or a drainage device placed to release aqueous from the eye in a controlled fashion.

Macular Degeneration This is a major cause of gradual, painless, bilateral central visual loss in the elderly. It occurs in a nonexudative (dry) form and an exudative (wet) form. Inflammation may be important in both forms of macular degeneration; susceptibility is associated with variants in the gene for complement factor H, an inhibitor of the alternative complement pathway. The nonexudative process begins with the accumulation of extracellular deposits called drusen underneath the retinal pigment epithelium. On ophthalmoscopy, they are pleomorphic but generally appear as small discrete yellow lesions clustered in the macula **(Fig. 28-16)**. With time they become larger, more numerous, and confluent. The retinal pigment epithelium becomes focally detached and atrophic, causing visual loss by interfering with photoreceptor function. Treatment with vitamins C and E, beta-carotene, and zinc may retard dry macular degeneration.

Exudative macular degeneration, which develops in only a minority of patients, occurs when neovascular vessels from the choroid grow through defects in Bruch's membrane and proliferate underneath the retinal pigment epithelium or the retina. Leakage from these vessels produces elevation of the retina, with distortion (metamorphopsia) and blurring of vision. Although the onset of these symptoms is usually gradual, bleeding from a subretinal choroidal neovascular membrane sometimes causes acute visual loss. Neovascular membranes can be difficult to see on fundus examination because they are located beneath the retina. Fluorescein angiography and OCT are extremely useful for their detection. Major or repeated hemorrhage under the retina from neovascular membranes results in fibrosis, development of a round (disciform) macular scar, and permanent loss of central vision.

A major therapeutic advance has occurred with the discovery that exudative macular degeneration can be treated with intraocular injection of antagonists to vascular endothelial growth factor. Bevacizumab, ranibizumab, or aflibercept is administered by direct injection into the vitreous cavity, beginning on a monthly basis. These antibodies cause the regression of neovascular membranes by blocking the action of vascular endothelial growth factor, thereby improving visual acuity.

Central Serous Chorioretinopathy This primarily affects males between the ages of 20 and 50 years. Leakage of serous fluid from the choroid causes small, localized detachment of the retinal pigment epithelium and the neurosensory retina. These detachments produce acute or chronic symptoms of metamorphopsia and blurred vision when the macula is involved. They are difficult to visualize with a direct ophthalmoscope because the detached retina is transparent and only slightly elevated. OCT shows fluid beneath the retina, and fluorescein angiography shows dye streaming into the subretinal space. The cause of central serous chorioretinopathy is unknown. Symptoms may resolve spontaneously if the retina reattaches, but recurrent detachment is common. Laser photocoagulation has benefited some patients with this condition.

Diabetic Retinopathy A rare disease until 1921, when the discovery of insulin resulted in a dramatic improvement in life expectancy for patients with diabetes mellitus, diabetic retinopathy is now a leading cause of blindness in the United States. The retinopathy takes years to develop but eventually appears in nearly all cases. Regular surveillance of the dilated fundus is crucial for any patient with diabetes. In advanced diabetic retinopathy, the proliferation of neovascular vessels leads to blindness from vitreous hemorrhage, retinal detachment, and glaucoma **(Fig. 28-17)**. These complications can be avoided in most patients by administration of panretinal laser photocoagulation at the appropriate point in the evolution of the disease. Anti-vascular endothelial growth factor antibody treatment is equally effective, but intraocular injections must be given repeatedly. **For further discussion of the manifestations and management of diabetic retinopathy, see Chaps. 396–398.**

Retinitis Pigmentosa This is a general term for a disparate group of rod-cone dystrophies characterized by progressive night blindness, visual field constriction with a ring scotoma, loss of acuity, and an abnormal electroretinogram (ERG). It occurs sporadically or in an autosomal recessive, dominant, or X-linked pattern. Irregular black deposits of clumped pigment in the peripheral retina, called *bone spicules* because of their vague resemblance to the spicules of cancellous bone, give the disease its name **(Fig. 28-18)**. The name is actually a misnomer because retinitis pigmentosa is not an inflammatory process. Most cases are due to a mutation in the gene for rhodopsin, the rod photopigment, or in the gene for peripherin, a glycoprotein located in photoreceptor outer segments. Vitamin A (15,000 IU/d) slightly retards the deterioration of the ERG in patients with retinitis pigmentosa but has no beneficial effect on visual acuity or fields.

Leber's congenital amaurosis, a rare cone dystrophy, has been treated by replacement of the missing RPE65 protein through gene therapy, resulting in slight improvement in visual function. Some forms of retinitis pigmentosa occur in association with rare, hereditary systemic diseases (olivopontocerebellar degeneration, Bassen-Kornzweig disease, Kearns-Sayre syndrome, Refsum's disease). Chronic treatment with chloroquine, hydroxychloroquine, and phenothiazines (especially thioridazine) can produce visual loss from a toxic retinopathy that

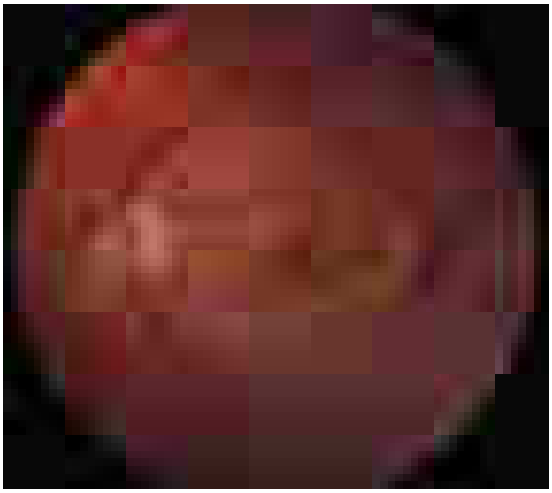


FIGURE 28-16 Age-related macular degeneration consisting of scattered yellow drusen in the macula (dry form) and a crescent of fresh hemorrhage temporal to the fovea from a subretinal neovascular membrane (wet form).

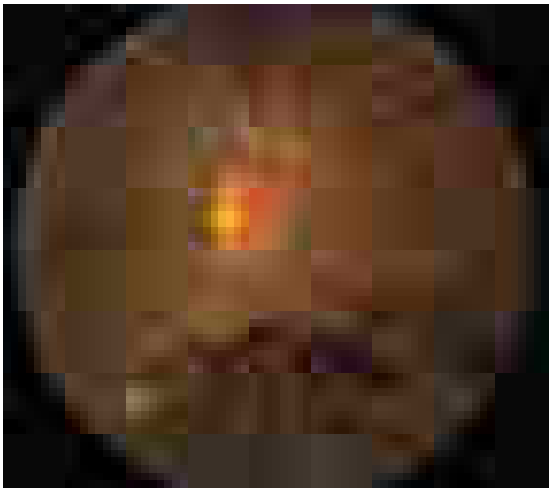


FIGURE 28-17 Proliferative diabetic retinopathy in a 25-year-old man with an 18-year history of diabetes, showing neovascular vessels emanating from the optic disc, retinal and vitreous hemorrhage, cotton-wool spots, and macular exudate. Round spots in the periphery represent recently applied panretinal photocoagulation.

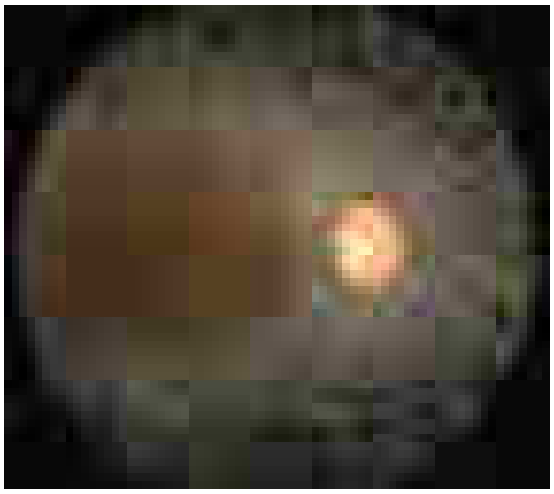


FIGURE 28-18 Retinitis pigmentosa with black clumps of pigment known as "bone spicules." The patient had peripheral visual field loss with sparing of central (macular) vision.

resembles retinitis pigmentosa. Patients receiving long-term treatment with hydroxychloroquine require regular eye examinations to monitor for potential development of a bull's eye maculopathy.

Epiretinal Membrane This is a fibrocellular tissue that grows across the inner surface of the retina, causing metamorphopsia and reduced visual acuity from distortion of the macula. A crinkled, cellophane-like membrane is visible on the retinal examination. Epiretinal membrane is most common in patients aged >50 years and is usually unilateral. Most cases are idiopathic, but some occur as a result of hypertensive retinopathy, diabetes, retinal detachment, or trauma. When visual acuity is reduced to the level of about 6/24 (20/80), vitrectomy and surgical peeling of the membrane to relieve macular puckering are recommended. Contraction of an epiretinal membrane sometimes gives rise to a *macular hole*. Most macular holes, however, are caused by local vitreous traction within the fovea. Vitrectomy can improve acuity in selected cases.

Melanoma and Other Tumors Melanoma is the most common primary tumor of the eye **(Fig. 28-19)**. It causes photopsia, an enlarging scotoma, and loss of vision. A small melanoma is often difficult to differentiate from a benign choroidal nevus. Serial examinations are required to document a malignant pattern of growth. Treatment of

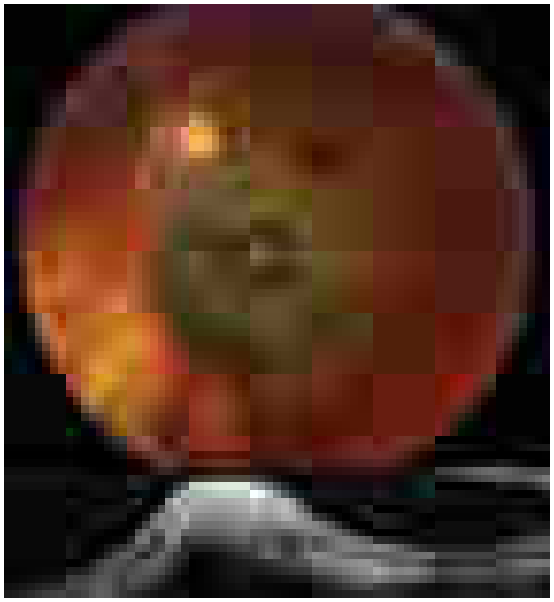


FIGURE 28-19 Melanoma of the choroid, appearing as an elevated dark mass in the inferior fundus, with overlying hemorrhage. The black line denotes the plane of the optical coherence tomography scan (*below*) showing the subretinal tumor.

melanoma is controversial. Options include enucleation, local resection, and irradiation. *Metastatic tumors* to the eye outnumber primary tumors. Breast and lung carcinomas have a special propensity to spread to the choroid or iris. Leukemia and lymphoma also commonly invade ocular tissues. Sometimes their only sign on eye examination is cellular debris in the vitreous, which can masquerade as a chronic posterior uveitis.

In a patient with vision loss, CT or MR scanning should be considered if the cause remains unknown after careful review of the history, visual fields, and thorough examination of the eye. Optic nerve sheath meningioma is a common retrobulbar tumor. It produces the classic triad of opto-ciliary shunt vessels, optic atrophy, and progressive visual loss. Optic disc swelling and proptosis are also frequent signs. Optic nerve glioma in young patients is usually a pilocytic astrocytoma and has a good prognosis for preservation of vision, especially in neurofibromatosis type 1 **(Chap. 118)**. In adults, optic nerve glioma is rare and highly malignant. Chiasmal tumors (pituitary adenoma, meningioma, craniopharyngioma) produce visual loss with few objective findings except for optic disc pallor. Loss of the temporal visual field in each eye is typically described, but in fact, patients complain of vision loss in just one eye. A high degree of vigilance is necessary to avoid missing chiasmal tumors. Although symptoms progress gradually, in rare instances the sudden expansion of a pituitary adenoma from infarction and bleeding (*pituitary apoplexy*) causes acute retrobulbar visual loss, with headache, nausea, and ocular motor nerve palsies.

PROPTOSIS

When the globes appear asymmetric, the clinician must first decide which eye is abnormal. Is one eye recessed within the orbit (*enophthalmos*), or is the other eye protuberant (*exophthalmos*, or *proptosis*)? A small globe or a Horner's syndrome can give the appearance of enophthalmos. True enophthalmos occurs commonly after trauma, from atrophy of retrobulbar fat, or from fracture of the orbital floor. The position of the eyes within the orbits is measured by using a Hertel exophthalmometer, a handheld instrument that records the position of the anterior corneal surface relative to the lateral orbital rim. If this instrument is not available, relative eye position can be judged by bending the patient's head forward and looking down upon the orbits. A proptosis of only 2 mm in one eye is detectable from this perspective. The development of proptosis implies a space-occupying lesion in the orbit and usually warrants CT or MR imaging.

Graves' Ophthalmopathy This is the leading cause of proptosis in adults **(Chap. 375)**. The proptosis is often asymmetric and can even appear to be unilateral. Orbital inflammation and engorgement of the extraocular muscles, particularly the medial rectus and the inferior rectus, account for the protrusion of the globe. Corneal exposure, lid retraction, lid lag on downgaze, conjunctival injection, restriction of gaze, diplopia, and visual loss from optic nerve compression are cardinal symptoms. Graves' eye disease is a clinical diagnosis, but laboratory testing can be useful. The serum level of thyroid-stimulating immunoglobulins is often elevated. Orbital imaging usually reveals enlarged extraocular eye muscles, but not always. Graves' ophthalmopathy can be treated with oral prednisone (60 mg/d) for 1 month, followed by a taper over several months. Worsening of symptoms upon glucocorticoid withdrawal is common. Topical lubricants, taping the eyelids closed at night, moisture chambers, and eyelid surgery are helpful to limit exposure of ocular tissues. Radiation therapy is not effective. Orbital decompression should be performed for severe, symptomatic exophthalmos or if visual function is reduced by optic nerve compression. In patients with diplopia, prisms or eye muscle surgery can be used to restore ocular alignment in primary gaze.

Orbital Pseudotumor This is an idiopathic, inflammatory orbital syndrome that is distinguished from Graves' ophthalmopathy by the prominent complaint of pain. Other symptoms include diplopia, ptosis, proptosis, and orbital congestion. Evaluation for sarcoidosis, granulomatosis with polyangiitis, and other types of orbital vasculitis or collagen-vascular disease is negative. Imaging often shows swollen eye muscles (orbital myositis) with enlarged tendons. By contrast, in

Graves' ophthalmopathy, the tendons of the eye muscles usually are spared. The Tolosa-Hunt syndrome (Chap. 433) may be regarded as an extension of orbital pseudotumor through the superior orbital fissure into the cavernous sinus. The diagnosis of orbital pseudotumor is difficult. Biopsy of the orbit frequently yields nonspecific evidence of fat infiltration by lymphocytes, plasma cells, and eosinophils. A dramatic response to a therapeutic trial of systemic glucocorticoids indirectly provides the best confirmation of the diagnosis.

Orbital Cellulitis This causes pain, lid erythema, proptosis, conjunctival chemosis, restricted motility, decreased acuity, afferent pupillary defect, fever, and leukocytosis. It often arises from the paranasal sinuses, especially by contiguous spread of infection from the ethmoid sinus through the lamina papyracea of the medial orbit. A history of recent upper respiratory tract infection, chronic sinusitis, thick mucus secretions, or dental disease is significant in any patient with suspected orbital cellulitis. Blood cultures should be obtained, but they are usually negative. Most patients respond to empirical therapy with broad-spectrum IV antibiotics. Occasionally, orbital cellulitis follows an overwhelming course, with massive proptosis, blindness, septic cavernous sinus thrombosis, and meningitis. To avert this disaster, orbital cellulitis should be managed aggressively in the early stages, with immediate imaging of the orbits and antibiotic therapy that includes coverage of methicillin-resistant *Staphylococcus aureus* (MRSA). Prompt surgical drainage of an orbital abscess or paranasal sinusitis is indicated if optic nerve function deteriorates despite antibiotics.

Tumors Tumors of the orbit cause painless, progressive proptosis. The most common primary tumors are cavernous hemangioma, lymphangioma, neurofibroma, schwannoma, dermoid cyst, adenoid cystic carcinoma, optic nerve glioma, optic nerve meningioma, and benign mixed tumor of the lacrimal gland. Metastatic tumor to the orbit occurs frequently in breast carcinoma, lung carcinoma, and lymphoma. Diagnosis by fine-needle aspiration followed by urgent radiation therapy sometimes can preserve vision.

Carotid Cavernous Fistulas With anterior drainage through the orbit, these fistulas produce proptosis, diplopia, glaucoma, and corkscrew, arterialized conjunctival vessels. Direct fistulas usually result from trauma. They are easily diagnosed because of the prominent signs produced by high-flow, high-pressure shunting. Indirect fistulas, or dural arteriovenous malformations, are more likely to occur spontaneously, especially in older women. The signs are more subtle, and the diagnosis frequently is missed. The combination of slight proptosis, diplopia, enlarged muscles, and an injected eye often is mistaken for thyroid ophthalmopathy. A bruit heard upon auscultation of the head or reported by the patient is a valuable diagnostic clue. Imaging shows an enlarged superior ophthalmic vein in the orbits. Carotid cavernous shunts can be eliminated by intravascular embolization.

PTOSIS

Blepharoptosis This is an abnormal drooping of the eyelid. Unilateral or bilateral ptosis can be congenital, from dysgenesis of the levator palpebrae superioris, or from abnormal insertion of its aponeurosis into the eyelid. Acquired ptosis can develop so gradually that the patient is unaware of the problem. Inspection of old photographs is helpful in dating the onset. A history of prior trauma, eye surgery, contact lens use, diplopia, systemic symptoms (e.g., dysphagia or peripheral muscle weakness), or a family history of ptosis should be sought. Fluctuating ptosis that worsens late in the day is typical of myasthenia gravis. Ptosis evaluation should focus on evidence for proptosis, eyelid masses or deformities, inflammation, pupil inequality, or limitation of motility. The width of the palpebral fissures is measured in primary gaze to determine the degree of ptosis. The ptosis will be underestimated if the patient compensates by lifting the brow with the frontalis muscle.

Mechanical Ptosis This occurs in many elderly patients from stretching and redundancy of eyelid skin and subcutaneous fat (dermatochalasis). The extra weight of these sagging tissues causes the lid to droop. Enlargement or deformation of the eyelid from infection, tumor, trauma, or inflammation also results in ptosis on a purely mechanical basis.

Aponeurotic Ptosis This is an acquired dehiscence or stretching of the aponeurotic tendon, which connects the levator muscle to the tarsal plate of the eyelid. It occurs commonly in older patients, presumably from loss of connective tissue elasticity. Aponeurotic ptosis is also a common sequela of eyelid swelling from infection or blunt trauma to the orbit, cataract surgery, or contact lens use.

Myogenic Ptosis The causes of *myogenic ptosis* include myasthenia gravis (Chap. 440) and a number of rare myopathies that manifest with ptosis. The term *chronic progressive external ophthalmoplegia* refers to a spectrum of systemic diseases caused by mutations of mitochondrial DNA. As the name implies, the most prominent findings are symmetric, slowly progressive ptosis and limitation of eye movements. In general, diplopia is a late symptom because all eye movements are reduced equally. In the *Kearns-Sayre* variant, retinal pigmentary changes and abnormalities of cardiac conduction develop. Peripheral muscle biopsy shows characteristic "ragged-red fibers." *Oculopharyngeal dystrophy* is a distinct autosomal dominant disease with onset in middle age, characterized by ptosis, limited eye movements, and trouble swallowing. *Myotonic dystrophy*, another autosomal dominant disorder, causes ptosis, ophthalmoparesis, cataract, and pigmentary retinopathy. Patients have muscle wasting, myotonia, frontal balding, and cardiac abnormalities.

Neurogenic Ptosis This results from a lesion affecting the innervation to either of the two muscles that open the eyelid: Müller's muscle or the levator palpebrae superioris. Examination of the pupil helps distinguish between these two possibilities. In Horner's syndrome, the eye with ptosis has a smaller pupil and the eye movements are full. In an oculomotor nerve palsy, the eye with the ptosis has a larger or a normal pupil. If the pupil is normal but there is limitation of adduction, elevation, and depression, a pupil-sparing oculomotor nerve palsy is likely (see next section). Rarely, a lesion affecting the small, central subnucleus of the oculomotor complex will cause bilateral ptosis with normal eye movements and pupils.

DOUBLE VISION (DIPLOPIA)

The first point to clarify is whether diplopia persists in either eye after the opposite eye is covered. If it does, the diagnosis is monocular diplopia. The cause is usually intrinsic to the eye and therefore has no dire implications for the patient. Corneal aberrations (e.g., keratoconus, pterygium), uncorrected refractive error, cataract, or foveal traction may give rise to monocular diplopia. Occasionally it is a symptom of malingering or psychiatric disease. Diplopia alleviated by covering one eye is binocular diplopia and is caused by disruption of ocular alignment. Inquiry should be made into the nature of the double vision (purely side-by-side versus partial vertical displacement of images), mode of onset, duration, intermittency, diurnal variation, and associated neurologic or systemic symptoms. If the patient has diplopia while being examined, motility testing should reveal a deficiency corresponding to the patient's symptoms. However, subtle limitation of ocular excursions is often difficult to detect. For example, a patient with a slight left abducens nerve paresis may appear to have full eye movements despite a complaint of horizontal diplopia upon looking to the left. In this situation, the cover test provides a more sensitive method for demonstrating the ocular misalignment. It should be conducted in primary gaze and then with the head turned and tilted in each direction. In the above example, a cover test with the head turned to the right will maximize the fixation shift evoked by the cover test.

Occasionally, a cover test performed in an asymptomatic patient during a routine examination will reveal an ocular deviation. If the eye movements are full and the ocular misalignment is equal in all directions of gaze (comitant deviation), the diagnosis is strabismus. In this condition, which affects about 1% of the population, fusion is disrupted in infancy or early childhood. To avoid diplopia, retinal input from the

nonfixating eye may be partially suppressed. In some children, this leads to impaired vision (amblyopia, or "lazy" eye) in the deviated eye.

Binocular diplopia results from a wide range of processes: infectious, neoplastic, metabolic, degenerative, inflammatory, and vascular. One must decide whether the diplopia is neurogenic in origin or is due to restriction of globe rotation by local disease in the orbit. Orbital pseudotumor, myositis, infection, tumor, thyroid disease, and muscle entrapment (e.g., from a blowout fracture) cause restrictive diplopia. The diagnosis of restriction is usually made by recognizing other associated signs and symptoms of local orbital disease. Dedicated, high-resolution orbital imaging is helpful when the cause of diplopia is not evident.

Myasthenia Gravis (See also Chap. 440) This is a major cause of painless diplopia. The diplopia is often intermittent, variable, and not confined to any single ocular motor nerve distribution. The pupils are always normal. Serial measurements of a variable, fatigable ptosis, often accompanied by diplopia, are helpful to establish the diagnosis. Many patients have a purely ocular form of the disease, with no evidence of systemic muscular weakness. The diagnosis can be confirmed by an IV edrophonium injection, which produces a transient reversal of eyelid or eye muscle weakness. Blood tests for antibodies against the acetylcholine receptor or the MuSK protein are frequently negative in the purely ocular form of myasthenia gravis. *Botulism* from food or wound poisoning can mimic ocular myasthenia.

If restrictive orbital disease and myasthenia gravis are excluded, a lesion of a cranial nerve supplying innervation to the extraocular muscles is the most likely cause of binocular diplopia.

Oculomotor Nerve The third cranial nerve innervates the medial, inferior, and superior recti; inferior oblique; levator palpebrae superioris; and the iris sphincter. Total palsy of the oculomotor nerve causes ptosis, a dilated pupil, and leaves the eye "down and out" because of the unopposed action of the lateral rectus and superior oblique. This combination of findings is obvious. More challenging is the diagnosis of early or partial oculomotor nerve palsy. In this setting any combination of ptosis, pupil dilation, and weakness of the eye muscles supplied by the oculomotor nerve may be encountered. Frequent serial examinations during the rapidly evolving phase of the palsy help ensure that the diagnosis is not missed. The advent of an oculomotor nerve palsy with a pupil involvement, especially when accompanied by pain, suggests a compressive lesion, such as a tumor or circle of Willis aneurysm. Urgent neuroimaging should be obtained, along with a CT or MR angiogram. With improvement in the resolution of these non-invasive techniques, catheter angiography is rarely necessary to exclude an aneurysm.

A lesion of the oculomotor nucleus in the rostral midbrain produces signs that differ from those caused by a lesion of the nerve itself. There is bilateral ptosis because the levator muscle is innervated by a single central subnucleus. There is also weakness of the contralateral superior rectus, because it is supplied by the oculomotor nucleus on the other side. Occasionally both superior recti are weak. Isolated nuclear oculomotor palsy is rare. Usually neurologic examination reveals additional signs that suggest brainstem damage from infarction, hemorrhage, tumor, or infection.

Injury to structures surrounding fascicles of the oculomotor nerve descending through the midbrain has given rise to a number of classic eponymic designations. In *Nothnagel's syndrome*, injury to the superior cerebellar peduncle causes ipsilateral oculomotor palsy and contralateral cerebellar ataxia. In *Benedikt's syndrome*, injury to the red nucleus results in ipsilateral oculomotor palsy and contralateral tremor, chorea, and athetosis. *Claude's syndrome* incorporates features of both of these syndromes, by injury to both the red nucleus and the superior cerebellar peduncle. Finally, in *Weber's syndrome*, injury to the cerebral peduncle causes ipsilateral oculomotor palsy with contralateral hemiparesis.

In the subarachnoid space the oculomotor nerve is vulnerable to aneurysm, meningitis, tumor, infarction, and compression. In cerebral herniation, the nerve becomes trapped between the edge of the tentorium and the uncus of the temporal lobe. Oculomotor palsy also can result from midbrain torsion and hemorrhage during herniation. In the cavernous sinus, oculomotor palsy arises from carotid aneurysm, carotid cavernous fistula, cavernous sinus thrombosis, tumor (pituitary adenoma, meningioma, metastasis), herpes zoster infection, and the Tolosa-Hunt syndrome.

The etiology of an isolated, pupil-sparing oculomotor palsy often remains an enigma even after neuroimaging and extensive laboratory testing. Most cases are thought to result from microvascular infarction of the nerve somewhere along its course from the brainstem to the orbit. Usually the patient complains of pain. Diabetes, hypertension, and vascular disease are major risk factors. Spontaneous recovery over a period of months is the rule. If this fails to occur or if new findings develop, the diagnosis of microvascular oculomotor nerve palsy should be reconsidered. Aberrant regeneration is common when the oculomotor nerve is injured by trauma or compression (tumor, aneurysm). Miswiring of sprouting fibers to the levator muscle and the rectus muscles results in elevation of the eyelid upon downgaze or adduction. The pupil also constricts upon attempted adduction, elevation, or depression of the globe. Aberrant regeneration is not seen after oculomotor palsy from microvascular infarct and hence vitiates that diagnosis.

Trochlear Nerve The fourth cranial nerve originates in the midbrain, just caudal to the oculomotor nerve complex. Fibers exit the brainstem dorsally and cross to innervate the contralateral superior oblique. The principal actions of this muscle are to depress and intort the globe. A palsy therefore results in hypertropia and excyclotorsion. The cyclotorsion seldom is noticed by patients. Instead, they complain of vertical diplopia, especially upon reading or looking down. The vertical diplopia also is exacerbated by tilting the head toward the side with the muscle palsy and alleviated by tilting it away. This "head tilt test" is a cardinal diagnostic feature.

Isolated trochlear nerve palsy results from all the causes listed above for the oculomotor nerve except aneurysm. The trochlear nerve is particularly apt to suffer injury after closed head trauma. The free edge of the tentorium is thought to impinge on the nerve during a concussive blow. Most isolated trochlear nerve palsies are idiopathic and hence are diagnosed by exclusion as "microvascular." Spontaneous improvement occurs over a period of months in most patients. A base-down prism (conveniently applied to the patient's glasses as a stick-on Fresnel lens) may serve as a temporary measure to alleviate diplopia. If the palsy does not resolve, the eyes can be realigned by weakening the inferior oblique muscle.

Abducens Nerve The sixth cranial nerve innervates the lateral rectus muscle. A palsy produces horizontal diplopia, worse on gaze to the side of the lesion. A nuclear lesion has different consequences, because the abducens nucleus contains interneurons that project via the medial longitudinal fasciculus to the medial rectus subnucleus of the contralateral oculomotor complex. Therefore, an abducens nuclear lesion produces a complete lateral gaze palsy from weakness of both the ipsilateral lateral rectus and the contralateral medial rectus. *Foville's syndrome* after dorsal pontine injury includes lateral gaze palsy, ipsilateral facial palsy, and contralateral hemiparesis incurred by damage to descending corticospinal fibers. *Millard-Gubler syndrome* from ventral pontine injury is similar except for the eye findings. There is lateral rectus weakness only, instead of gaze palsy, because the abducens fascicle is injured rather than the nucleus. Infarct, tumor, hemorrhage, vascular malformation, and multiple sclerosis are the most common etiologies of brainstem abducens palsy.

After leaving the ventral pons, the abducens nerve runs forward along the clivus to pierce the dura at the petrous apex, where it enters the cavernous sinus. Along its subarachnoid course it is susceptible to meningitis, tumor (meningioma, chordoma, carcinomatous meningitis), subarachnoid hemorrhage, trauma, and compression by aneurysm or dolichoectatic vessels. At the petrous apex, mastoiditis can produce deafness, pain, and ipsilateral abducens palsy (*Gradenigo's*

syndrome). In the cavernous sinus, the nerve can be affected by carotid aneurysm, carotid cavernous fistula, tumor (pituitary adenoma, meningioma, nasopharyngeal carcinoma), herpes infection, and Tolosa-Hunt syndrome.

Unilateral or bilateral abducens palsy is a classic sign of raised intracranial pressure. The diagnosis can be confirmed if papilledema is observed on fundus examination. The mechanism is still debated but probably is related to rostral-caudal displacement of the brainstem. The same phenomenon accounts for abducens palsy from Chiari malformation or low intracranial pressure (e.g., after lumbar puncture, spinal anesthesia, or spontaneous dural cerebrospinal fluid leak).

Treatment of abducens palsy is aimed at prompt correction of the underlying cause. However, the cause remains obscure in many instances despite diligent evaluation. As was mentioned above for isolated trochlear or oculomotor palsy, most cases are assumed to represent microvascular infarcts because they often occur in the setting of diabetes or other vascular risk factors. Some cases may develop as a postinfectious mononeuritis (e.g., after a viral flu). Patching one eye, occluding one eyeglass lens with tape, or applying a temporary prism will provide relief of diplopia until the palsy resolves. If recovery is incomplete, eye muscle surgery nearly always can realign the eyes, at least in primary position. A patient with an abducens palsy that fails to improve should be reevaluated for an occult etiology (e.g., chordoma, carcinomatous meningitis, carotid cavernous fistula, myasthenia gravis). Skull base tumors are easily missed even on contrast-enhanced neuroimaging studies.

Multiple Ocular Motor Nerve Palsies These should not be attributed to spontaneous microvascular events affecting more than one cranial nerve at a time. This remarkable coincidence does occur, especially in diabetic patients, but the diagnosis is made only in retrospect after all other diagnostic alternatives have been exhausted. Neuroimaging should focus on the cavernous sinus, superior orbital fissure, and orbital apex, where all three ocular motor nerves are in close proximity. In a diabetic or immunocompromised host, fungal infection (*Aspergillus*, Mucorales, *Cryptococcus*) is a common cause of multiple nerve palsies. In a patient with systemic malignancy, carcinomatous meningitis is a likely diagnosis. Cytologic examination may be negative despite repeated sampling of the cerebrospinal fluid. The cancer-associated Lambert-Eaton myasthenic syndrome also can produce ophthalmoplegia. Giant cell (temporal) arteritis occasionally manifests as diplopia from ischemic palsies of extraocular muscles. Fisher's syndrome, an ocular variant of Guillain-Barré, produces ophthalmoplegia with areflexia and ataxia. Often the ataxia is mild, and the reflexes are normal. Antiganglioside antibodies (GQ1b) can be detected in about 50% of cases.

Supranuclear Disorders of Gaze These are often mistaken for multiple ocular motor nerve palsies. For example, Wernicke's encephalopathy can produce nystagmus and a partial deficit of horizontal and vertical gaze that mimics a combined abducens and oculomotor nerve palsy. The disorder occurs in patients who are malnourished, alcoholic, or following bariatric surgery, and can be reversed by thiamine. Infarct, hemorrhage, tumor, multiple sclerosis, encephalitis, vasculitis, and Whipple's disease are other important causes of supranuclear gaze palsy. Disorders of vertical gaze, especially downward saccades, are an early feature of progressive supranuclear palsy. Smooth pursuit is affected later in the course of the disease. Parkinson's disease, Huntington's disease, and olivopontocerebellar degeneration also can affect vertical gaze.

The *frontal eye field* of the cerebral cortex is involved in generation of saccades to the contralateral side. After hemispheric stroke, the eyes usually deviate toward the lesioned side because of the unopposed action of the frontal eye field in the normal hemisphere. With time, this deficit resolves. Seizures generally have the opposite effect: the eyes deviate conjugately away from the irritative focus. *Parietal lesions* disrupt smooth pursuit of targets moving toward the side of the lesion. Bilateral parietal lesions produce *Bálint's syndrome*, which is characterized by impaired eye-hand coordination (optic ataxia), difficulty initiating voluntary eye movements (ocular apraxia), and visuospatial disorientation (simultanagnosia).

Horizontal Gaze Descending cortical inputs mediating horizontal gaze ultimately converge at the level of the pons. Neurons in the paramedian pontine reticular formation are responsible for controlling conjugate gaze toward the same side. They project directly to the ipsilateral abducens nucleus. A lesion of either the paramedian pontine reticular formation or the abducens nucleus causes an ipsilateral conjugate gaze palsy. Lesions at either locus produce nearly identical clinical syndromes, with the following exception: vestibular stimulation (oculocephalic maneuver or caloric irrigation) will succeed in driving the eyes conjugately to the side in a patient with a lesion of the paramedian pontine reticular formation but not in a patient with a lesion of the abducens nucleus.

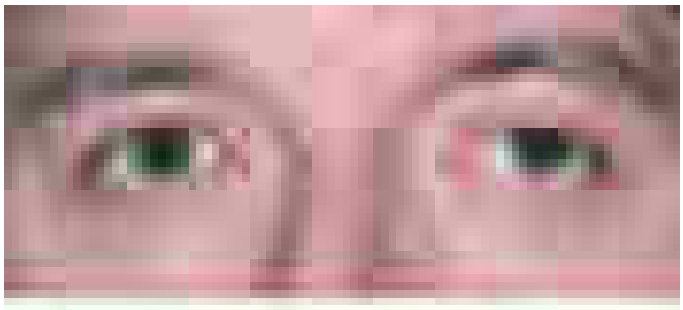
INTERNUCLEAR OPHTHALMOPLEGIA This results from damage to the medial longitudinal fasciculus ascending from the abducens nucleus in the pons to the oculomotor nucleus in the midbrain (hence, "internuclear"). Damage to fibers carrying the conjugate signal from abducens interneurons to the contralateral medial rectus motoneurons results in a failure of adduction on attempted lateral gaze. For example, a patient with a left internuclear ophthalmoplegia (INO) will have slowed or absent adducting movements of the left eye **(Fig. 28-20)**. A patient with bilateral injury to the medial longitudinal fasciculus will have bilateral INO. Multiple sclerosis is the most common cause, although tumor, stroke, trauma, or any brainstem process may be responsible. *One-and-a-half syndrome* is due to a lesion of the medial longitudinal fasciculus combined with a lesion of either the abducens nucleus or the paramedian pontine reticular formation on the same side. The patient's only horizontal eye movement is abduction of the eye on the other side.

Vertical Gaze This is controlled at the level of the midbrain. The neuronal circuits affected in disorders of vertical gaze are not fully elucidated, but lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal cause supranuclear paresis of upgaze, downgaze, or all vertical eye movements. Distal basilar artery ischemia is the most common etiology. *Skew deviation* refers to a vertical misalignment of the eyes, usually constant in all positions of gaze. The finding has poor localizing value because skew deviation has been reported after lesions in widespread regions of the brainstem and cerebellum.

PARINAUD'S SYNDROME Also known as dorsal midbrain syndrome, this is a distinct supranuclear vertical gaze disorder caused by damage to the posterior commissure. It is a classic sign of hydrocephalus from aqueductal stenosis. Pineal region or midbrain tumors, cysticercosis, and stroke also cause Parinaud's syndrome. Features include loss of upgaze (and sometimes downgaze), convergence-retraction nystagmus on attempted upgaze, downward ocular deviation ("setting sun" sign), lid retraction (Collier's sign), skew deviation, pseudoabducens palsy, and light-near dissociation of the pupils.

Nystagmus This is a rhythmic oscillation of the eyes, occurring physiologically from vestibular and optokinetic stimulation or pathologically in a wide variety of diseases **(Chap. 19)**. Abnormalities of the eyes or optic nerves, present at birth or acquired in childhood, can produce a complex, searching nystagmus with irregular pendular (sinusoidal) and jerk features. Examples are albinism, Leber's congenital amaurosis, and bilateral cataract. This nystagmus is commonly referred to as *congenital sensory nystagmus*. This is a poor term because even in children with congenital lesions, the nystagmus does not appear until weeks after birth. *Congenital motor nystagmus*, which looks similar to congenital sensory nystagmus, develops in the absence of any abnormality of the sensory visual system. Visual acuity also is reduced in congenital motor nystagmus, probably by the nystagmus itself, but seldom below a level of 20/200.

JERK NYSTAGMUS This is characterized by a slow drift off the target, followed by a fast corrective saccade. By convention, the nystagmus



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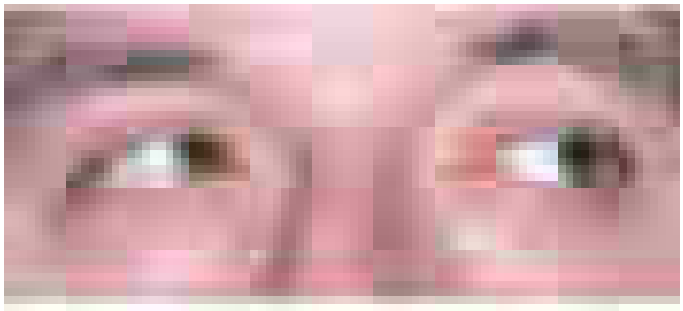

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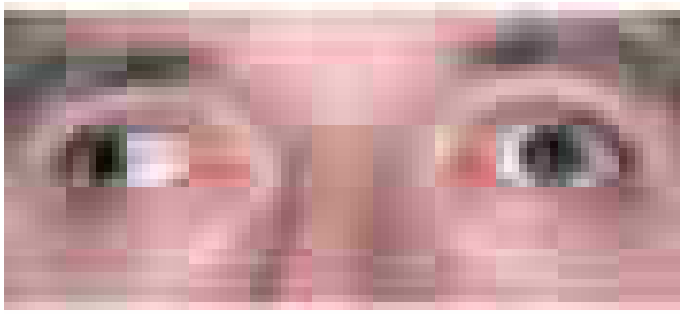

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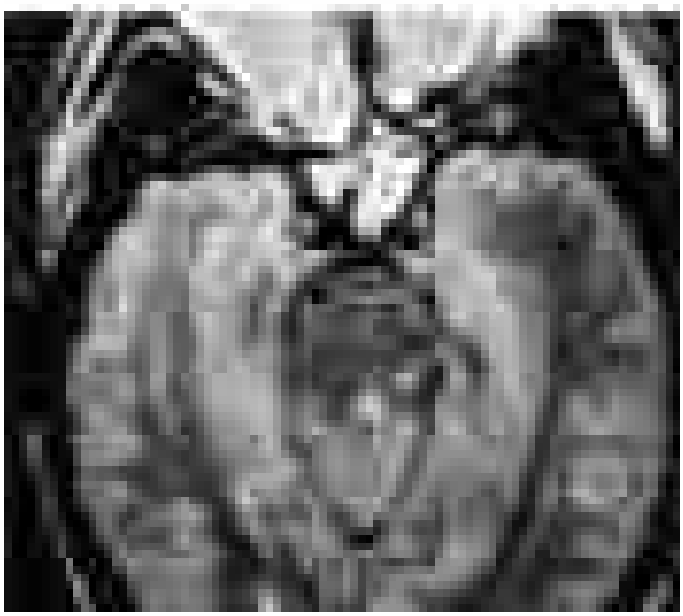

D

FIGURE 28-20 Left internuclear ophthalmoplegia (INO). *A.* In primary position of gaze, the eyes appear normal. ***B.*** Horizontal gaze to the left is intact. ***C.*** On attempted horizontal gaze to the right, the left eye fails to adduct. In mildly affected patients, the eye may adduct partially or more slowly than normal. Nystagmus is usually present in the abducted eye. ***D.*** T2-weighted axial magnetic resonance image through the pons showing a demyelinating plaque in the left medial longitudinal fasciculus (*arrow*).

is named after the quick phase. Jerk nystagmus can be downbeat, upbeat, horizontal (left or right), and torsional. The pattern of nystagmus may vary with gaze position. Some patients will be oblivious to their nystagmus. Others will complain of blurred vision or a subjective to-and-fro movement of the environment (oscillopsia) corresponding to the nystagmus. Fine nystagmus may be difficult to see on gross examination of the eyes. Observation of nystagmoid movements of the optic disc on ophthalmoscopy is a sensitive way to detect subtle nystagmus.

GAZE-EVOKED NYSTAGMUS This is the most common form of jerk nystagmus. When the eyes are held eccentrically in the orbits, they have a natural tendency to drift back to primary position. The subject compensates by making a corrective saccade to maintain the deviated eye position. Many normal patients have mild gaze-evoked nystagmus. Exaggerated gaze-evoked nystagmus can be induced by drugs (sedatives, anticonvulsants, alcohol); muscle paresis; myasthenia gravis; demyelinating disease; and cerebellopontine angle, brainstem, and cerebellar lesions.

VESTIBULAR NYSTAGMUS *Vestibular nystagmus* results from dysfunction of the labyrinth (Ménière's disease), vestibular nerve, or vestibular nucleus in the brainstem. Peripheral vestibular nystagmus often occurs in discrete attacks, with symptoms of nausea and vertigo. There may be associated tinnitus and hearing loss. Sudden shifts in head position may provoke or exacerbate symptoms.

DOWNBEAT NYSTAGMUS *Downbeat nystagmus* results from lesions near the craniocervical junction (Chiari malformation, basilar invagination). It also has been reported in brainstem or cerebellar stroke, lithium or anticonvulsant intoxication, alcoholism, and multiple sclerosis. *Upbeat nystagmus* is associated with damage to the pontine tegmentum from stroke, demyelination, or tumor.

Opsoclonus This rare, dramatic disorder of eye movements consists of bursts of consecutive saccades (saccadomania). When the saccades are confined to the horizontal plane, the term *ocular flutter* is preferred. It can result from viral encephalitis, trauma, or a paraneoplastic effect of neuroblastoma, breast carcinoma, and other malignancies. It has also been reported as a benign, transient phenomenon in otherwise healthy patients.

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29 Disorders of Smell and Taste

Richard L. Doty, Steven M. Bromley

All environmental chemicals necessary for life enter the body by the nose and mouth. The senses of smell (olfaction) and taste (gustation) monitor such chemicals, determine the flavor and palatability of foods and beverages, and warn of dangerous environmental conditions, including fire, air pollution, leaking natural gas, and bacteria-laden foodstuffs. These senses contribute significantly to quality of life and, when dysfunctional, can have untoward physical and psychological consequences. Indeed, a recent longitudinal study of 1162 non-demented elderly persons found, even after controlling for confounders, that those with the lowest baseline olfactory test scores had a 45% mortality rate over a 4-year period, compared to an 18% mortality rate for those with the highest olfactory test scores. A basic understanding of these senses in health and disease is critical for the physician, because thousands of patients present to doctors' offices each year with complaints of chemosensory dysfunction. Among the more important recent developments in neurology is the discovery that decreased smell function is among the first signs, if not the first sign, of such neurodegenerative diseases as Parkinson's disease (PD) and Alzheimer's disease (AD), signifying their "presymptomatic" phase.

ANATOMY AND PHYSIOLOGY

Olfactory System Odorous chemicals enter the front of nose during inhalation and active sniffing, as well as the back of the nose (nasopharynx) during deglutition. After reaching the highest recesses of the nasal cavity, they dissolve in the olfactory mucus and diffuse or are actively transported by specialized proteins to receptors located on the cilia of olfactory receptor cells. The cilia, dendrites, cell bodies, and proximal axonal segments of these bipolar cells are located within a unique neuroepithelium covering the cribriform plate, the superior nasal septum, superior turbinate, and sectors of the middle turbinate (Fig. 29-1). Nearly 400 types of G-protein-coupled odor receptors (GPCRs) are expressed on the cilia of the receptor cells, with only one type of GPCR receptor being expressed on a given cell. Other receptors, including trace amine-associated receptors and members of the non-GPCR membrane-spanning 4-domain family, subfamily A (MS4A) protein family, are also present on some receptor cells. Such a plethora of receptor cell types does not exist in any other sensory system. Importantly, when damaged, the receptor cells can be replaced by stem cells near the basement membrane, although such replacement is often incomplete.

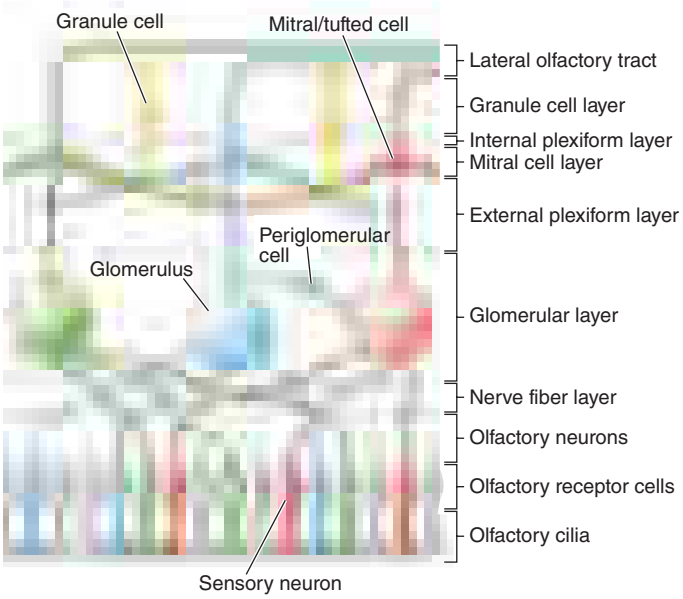

FIGURE 29-2 Schematic of the layers and wiring of the olfactory bulb. Each receptor type (red, green, blue) projects to a common glomerulus. The neural activity within each glomerulus is modulated by periglomerular cells. The activity of the primary projection cells, the mitral and tufted cells, is modulated by granule cells, periglomerular cells, and secondary dendrites from adjacent mitral and tufted cells. *(From www.med.yale.edu/neurosurg/treloar/index.html.)*

After coalescing into bundles surrounded by glia-like ensheathing cells (termed fila), the receptor cell axons pass through the cribriform plate to the olfactory bulbs, where they synapse with dendrites of other cell types within the glomeruli (Fig. 29-2). These spherical structures, which make up a distinct layer of the olfactory bulb, are a site of convergence of information, because many more fibers enter than leave them. Receptor cells that express the same type of receptor project to the same glomeruli, effectively making each glomerulus a functional unit. The major projection neurons of the olfactory system—the mitral and tufted cells—send primary dendrites into the glomeruli, connecting not only with the incoming receptor cell axons, but with dendrites of periglomerular cells. The activity of the mitral/tufted cells is modulated by the periglomerular cells, secondary dendrites from other mitral/tufted cells, and granule cells, the most numerous cells of the bulb. The latter cells, which are largely GABAergic, receive inputs from central brain structures and modulate the output of the mitral/

FIGURE 29-1 Anatomy of the nose, showing the distribution of olfactory receptors in the roof of the nasal cavity. *(Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center; used with permission.)*

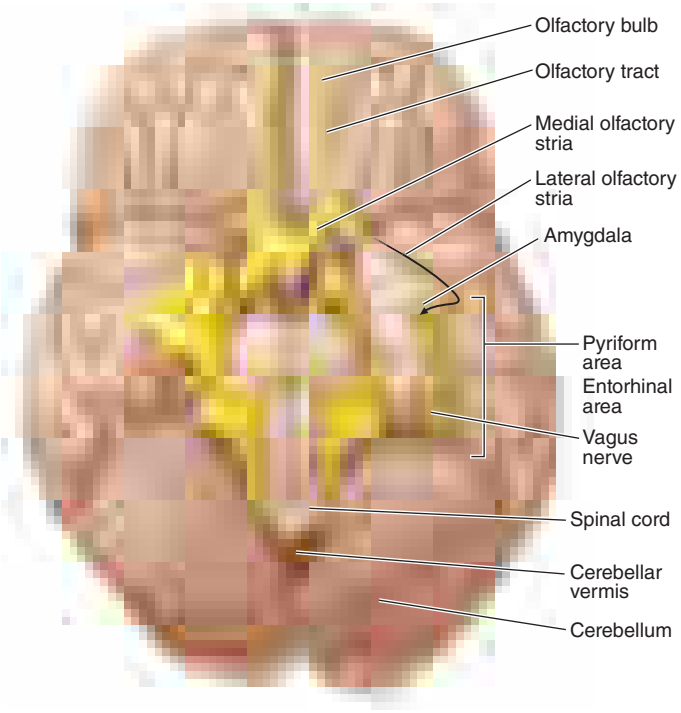

FIGURE 29-3 Anatomy of the base of the brain showing the primary olfactory cortex.

tufted cells. Interestingly, like the olfactory receptor cells, some cells within the bulb undergo replacement. Thus, neuroblasts formed within the anterior subventricular zone of the brain migrate along the rostral migratory stream, ultimately becoming granule and periglomerular cells.

The axons of the mitral and tufted cells synapse within secondary olfactory structures which largely comprise the primary olfactory cortex (POC) **(Fig. 29-3)**. The POC is defined as those cortical structures that receive direct projections from the olfactory bulb, most notably the piriform and entorhinal cortices. Although olfaction is unique in that its initial afferent projections bypass the thalamus, persons with damage to the thalamus can exhibit olfactory deficits, particularly ones of odor identification. Such deficits likely reflect the involvement of thalamic connections between the POC and the orbitofrontal cortex (OFC), where odor identification largely occurs. The close anatomic ties between the olfactory system and the amygdala, hippocampus, and hypothalamus help to explain the intimate associations between odor perception and cognitive functions such as memory, motivation, arousal, autonomic activity, digestion, and sex.

Taste System Tastants are sensed by specialized receptor cells present within taste buds—small grapefruit-like segmented structures located on the lateral margins and dorsum of the tongue, roof of the mouth, pharynx, larynx, and superior esophagus **(Fig. 29-4)**. Lingual taste buds are embedded in well-defined protuberances, termed fungiform, foliate, and circumvallate papillae. After dissolving in a liquid, tastants enter the opening of the taste bud—the taste pore—and bind to receptors on microvilli, small extensions of receptor cells within each taste bud. Such binding changes the electrical potential across the taste cell, resulting in neurotransmitter release onto the first-order taste neurons. Although humans have ~7500 taste buds, not all harbor taste-sensitive cells; some contain only one class of receptor (e.g., cells responsive only to sugars), whereas others contain cells sensitive to more than one class. The number of taste receptor cells per taste bud ranges from zero to well over 100. A small family of three G-protein-coupled receptors (GPCRs), namely T1R1, T1R2, and T1R3, mediate sweet and umami taste sensations. Bitter sensations, on the other hand, depend on T2R receptors, a family of ~30 GPCRs expressed on cells different from those that express the sweet and umami receptors. T2Rs sense a wide range of bitter substances but do not distinguish among them. Sour tastants are sensed by the PKD2L1 receptor, a member of the transient receptor potential protein (TRP) family. Perception of salty sensations, such as induced by sodium chloride, arises from the entry of Na^+ ions into the cells via specialized membrane channels, such as the amiloride-sensitive Na^+ channel.

It is now well established that both bitter and sweet taste-related receptors are also present elsewhere in the body, most notably in the alimentary and respiratory tracts. This important discovery generalizes the concept of taste-related chemoreception to areas of the body

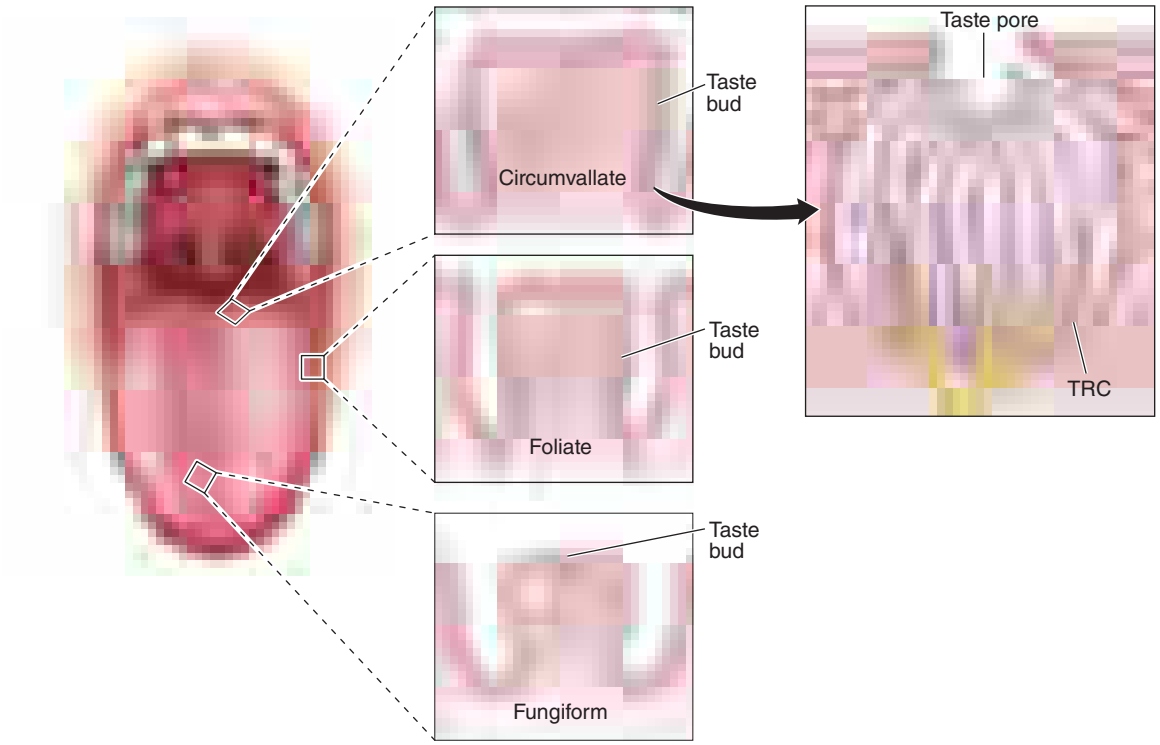

FIGURE 29-4 Schematic of the taste bud and its opening (pore), as well as the location of buds on the three major types of papillae: Fungiform (anterior), foliate (lateral), and circumvallate (posterior).

beyond the mouth and throat, with α-gustducin, the taste-specific G-protein α-subunit, expressed in so-called brush cells found specifically within the human trachea, lung, pancreas, and gallbladder. These brush cells are rich in nitric oxide (NO) synthase, known to defend against xenobiotic organisms, protect the mucosa from acid-induced lesions, and, in the case of the gastrointestinal tract, stimulate vagal and splanchnic afferent neurons. NO further acts on nearby cells, including enteroendocrine cells, absorptive or secretory epithelial cells, mucosal blood vessels, and cells of the immune system. Members of the T2R family of bitter receptors and the sweet receptors of the T1R family have been identified within the gastrointestinal tract and in enteroendocrine cell lines. In some cases, these receptors are important for metabolism, with the T1R3 receptors and gustducin playing decisive roles in the sensing and transport of dietary sugars from the intestinal lumen into absorptive enterocytes via a sodium-dependent glucose transporter and in regulation of hormone release from gut enteroendocrine cells. In other cases, these receptors may be important for airway protection, with a number of T2R bitter receptors in the motile cilia of the human airway that responded to bitter compounds by increasing their beat frequency. One specific T2R38 taste receptor is expressed in human upper respiratory epithelia and responds to acyl-monoserine lactone quorum-sensing molecules secreted by *Pseudomonas aeruginosa* and other gram-negative bacteria. Differences in T2R38 functionality, as related to TAS2R38 genotype, correlate with susceptibility to upper respiratory infections in humans.

Taste information is sent to the brain via three cranial nerves (CNs): CN VII (the *facial nerve*, which involves the intermediate nerve with its branches, the greater petrosal and chorda tympani nerves), CN IX (the *glossopharyngeal nerve*), and CN X (the *vagus nerve*) **(Fig. 29-5)**. CN VII innervates the anterior tongue and all of the soft palate, CN IX innervates the posterior tongue, and CN X innervates the laryngeal surface of the epiglottis, larynx, and proximal portion of the esophagus. The mandibular branch of CN V (V_3) conveys somatosensory information (e.g., touch, burning, cooling, irritation) to the brain. Although not technically a gustatory nerve, CN V shares primary nerve routes with many of the gustatory nerve fibers and adds temperature, texture, pungency, and spiciness to the taste experience. The chorda tympani nerve is famous for taking a recurrent course through the facial canal in the petrosal portion of the temporal bone, passing through the middle ear, and then exiting the skull via the petrotympanic fissure, where it joins the lingual nerve (a division of CN V) near the tongue. This nerve also carries parasympathetic fibers to the submandibular and sublingual glands, whereas the greater petrosal nerve supplies the palatine glands, thereby influencing saliva production.

The axons of the projection cells, which synapse with taste buds, enter the rostral portion of the nucleus of the solitary tract (NTS) within the medulla of the brainstem (Fig. 29-5). From the NTS, neurons then project to a division of the ventroposteromedial thalamic nucleus (VPM) via the medial lemniscus. From here, projections are made to the rostral part of the frontal operculum and adjoining insula, a brain region considered the *primary taste cortex* (PTC). Projections from the PTC then go to the *secondary taste cortex*, namely the caudolateral OFC. This brain region is involved in the conscious recognition of taste qualities. Moreover, because it contains cells that are activated by several sensory modalities, it is likely a center for establishing "flavor."

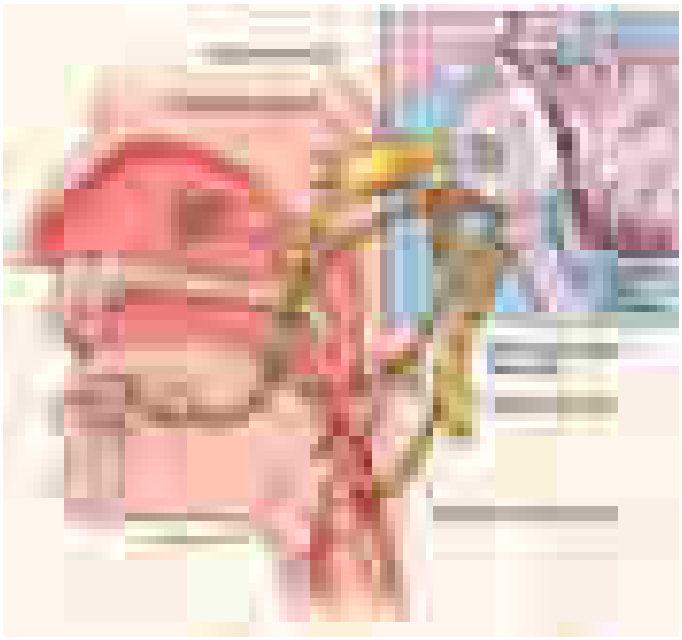

FIGURE 29-5 Schematic of the cranial nerves (CNs) that mediate taste function, including the chorda tympani nerve (CN VII), the glossopharyngeal nerve (CN IX), and the vagus nerve (CN X). *(Copyright David Klemm, Faculty and Curriculum Support [FACS], Georgetown University Medical Center; used with permission.)*

DISORDERS OF OLFACTION

The ability to smell is influenced, in everyday life, by such factors as age, gender, general health, nutrition, smoking, and reproductive state. Women typically outperform men on tests of olfactory function and retain normal smell function to a later age than do men.

Estimates of the prevalence of olfactory dysfunction in the general population vary; a recent cross-sectional analysis from the National Health and Nutrition Examination Survey (NHANES 2013–2014) found an overall prevalence of 13.5%. However, it is apparent that significant decrements in the ability to smell are present in >50% of the population between 65 and 80 years of age and in 75% of those aged ≥80 years **(Fig. 29-6)**. Such presbyosmia helps to explain why many elderly report that food has little flavor, a problem that can result in nutritional disturbances. This also helps to explain why a disproportionate number of elderly die in accidental gas poisonings. A relatively complete listing of conditions and disorders that have been associated with olfactory dysfunction is presented in **Table 29-1**.

Aside from aging, the three most common identifiable causes of long-lasting or permanent smell loss seen in the clinic are, in order of frequency, severe upper respiratory infections, head trauma, and chronic rhinosinusitis. The physiologic basis for most head trauma–related losses is the shearing and subsequent scarring of the olfactory fila as they pass from the nasal cavity into the brain cavity. The cribriform plate does not have to be fractured or show pathology for smell loss to be present. Severity of trauma, as indexed by a poor Glasgow Coma Scale score on presentation and the length of posttraumatic amnesia, is associated with higher risk of olfactory impairment. Less than 10% of posttraumatic anosmic patients will recover age-related normal function over time. This increases to nearly 25% of those with less-than-total loss. Upper respiratory infections, such as those

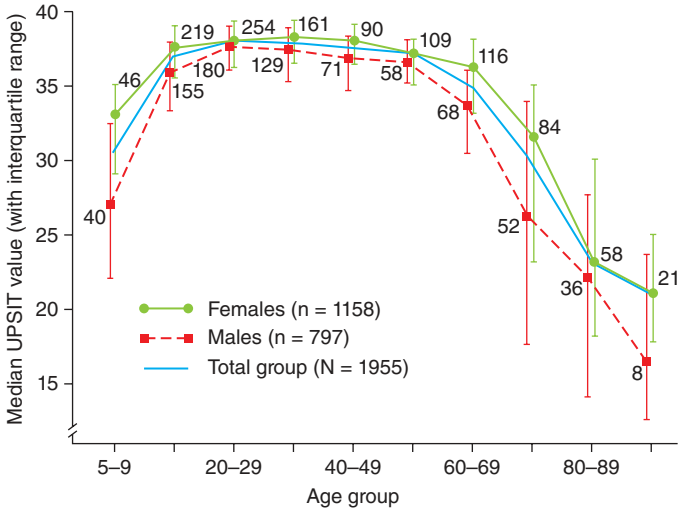

FIGURE 29-6 Scores on the University of Pennsylvania Smell Identification Test (UPSIT) as a function of subject age and sex. Numbers by each data point indicate sample sizes. Note that women identify odorants better than men at all ages. *(From RL Doty et al: Science 226:1421, 1984. Copyright © 1984 American Association for the Advancement of Science.)*

TABLE 29-1 Disorders and Conditions Associated with Compromised Olfactory Function, as Measured by Olfactory Testing

22q11 deletion syndrome	Korsakoff's psychosis
AIDS/HIV infection	Laryngopharyngeal reflux disease
Adenoid hypertrophy	Legionnaires' disease
Adrenal cortical insufficiency	Leprosy
Age	Liver disease
Alcoholism	Lubag disease
Allergies	Medications
Alzheimer's disease	Migraine
Amyotrophic lateral sclerosis (ALS)	Multiple sclerosis
Anorexia nervosa	Multi-infarct dementia
Asperger's syndrome	Myasthenia gravis
Ataxias	Narcolepsy with cataplexy
Attention deficit/hyperactivity disorder	Neoplasms, cranial/nasal
Behcet's disease	Nutritional deficiencies
Bardet-Biedl syndrome	Obstructive pulmonary disease
Chagas' disease	Obesity
Chemical exposure	Obsessive compulsive disorder
Chronic obstructive pulmonary disease	Orthostatic tremor
Congenital	Panic disorder
Cushing's syndrome	Parkinson's disease (PD)
Cystic fibrosis	Pick's disease
Degenerative ataxias	Posttraumatic stress disorder
Depression	Pregnancy
Diabetes	Pseudohypoparathyroidism
Down's syndrome	Psychopathy
Epilepsy	Radiation (therapeutic, cranial)
Facial paralysis	REM behavior disorder
Fibromyalgia	Refsum's disease
Frontotemporal lobe degeneration	Renal failure/end-stage kidney disease
Gonadal dysgenesis (Turner's syndrome)	Restless leg syndrome
Granulomatosis with Polyangiitis (Wegener's)	Rhinosinusitis/polyposis
Guamanian ALS/PD/dementia syndrome	Schizophrenia
Head trauma	Seasonal affective disorder
Herpes simplex encephalitis	Sjögren's syndrome
Hypothyroidism	Stroke
Huntington's disease	Systemic sclerosis
Iatrogenesis	Tobacco smoking
Idiopathic inflammatory myopathies	Toxic chemical exposure
Kallmann's syndrome	Upper respiratory infections
	Usher syndrome
	Vitamin B_{12} deficiency

associated with the common cold, influenza, pneumonia, or HIV, can directly and permanently harm the olfactory epithelium by decreasing receptor cell number, damaging cilia on remaining receptor cells, and inducing the replacement of sensory epithelium with respiratory epithelium. The smell loss associated with chronic rhinosinusitis is related to disease severity, with most loss occurring in cases where rhinosinusitis and polyposis are both present. Although systemic glucocorticoid therapy can usually induce short-term functional improvement, it does not, on average, return smell test scores to normal, implying that chronic permanent neural loss is present and/or that short-term administration of systemic glucocorticoids does not completely mitigate the inflammation. It is well established that microinflammation in an otherwise seemingly normal epithelium can influence smell function.

A number of neurodegenerative diseases are accompanied by olfactory impairment, including PD, AD, Huntington's disease, parkinsonism-dementia complex of Guam, dementia with Lewy bodies (DLB), multiple system atrophy, corticobasal degeneration, frontotemporal dementia, and Down's syndrome; smell loss can also occur in idiopathic rapid eye movement (REM) behavioral sleep disorder (iRBD), as well as in multiple sclerosis (MS) related to lesions within olfaction-related structures. Olfactory impairment in PD often predates the clinical diagnosis by a number of years. In staged cases, studies of the sequence of formation of abnormal α-synuclein aggregates and Lewy bodies suggest that the olfactory bulbs may be, along with the dorsomotor nucleus of the vagus, the first site of neural damage in PD. In postmortem studies of patients with very mild "presymptomatic" signs of AD, poorer smell function has been associated with higher levels of AD-related pathology. Smell loss is more marked in patients with early clinical manifestations of DLB than in those with mild AD. Interestingly, smell loss is minimal or nonexistent in progressive supranuclear palsy and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism. The relative contributions of disease-specific pathology or differential damage to forebrain neuromodulator/neurotransmitter systems in explaining different degrees of olfactory dysfunction among the various neurodegenerative diseases are presently unknown.

The smell loss seen in iRBD is of the same magnitude as that found in PD. This is of particular interest because patients with iRBD frequently develop PD and hyposmia. REM behavior disorder is not only seen in its idiopathic form, but can also be associated with narcolepsy **(Chap. 27)**. A study of narcoleptic patients with and without REM behavior disorder demonstrated that narcolepsy, independent of REM behavior disorder, was associated with impairments in olfactory function. Loss of hypothalamic neurons expressing orexin (also known as hypocretin) neuropeptides is believed to be responsible for narcolepsy and cataplexy. Orexin-containing neurons project throughout the entire olfactory system (from the olfactory epithelium to the olfactory cortex), and damage to these projections may be one underlying mechanism for impaired olfactory performance in narcoleptic patients. Administration of intranasal orexin A (hypocretin-1) improved olfactory function, supporting the notion that mild olfactory impairment is not only a primary feature of narcolepsy with cataplexy, but that orexin deficiency may be directly responsible for the loss of smell in this condition.

DISORDERS OF TASTE

The majority of patients who present with taste dysfunction exhibit olfactory, not taste, loss. This is because most flavors attributed to taste actually depend on retronasal stimulation of the olfactory receptors during deglutition. As noted earlier, taste buds only mediate basic tastes such as sweet, sour, bitter, salty, and umami. Significant impairment of whole-mouth gustatory function is rare outside of generalized metabolic disturbances or systemic use of some medications, because taste bud regeneration occurs and peripheral damage alone would require the involvement of multiple CN pathways. Taste function can be influenced by age, diet, smoking behavior, use of medications, and other subject-related factors including (1) the release of foul-tasting materials from the oral cavity from oral medical conditions (e.g., gingivitis, purulent sialadenitis) or appliances; (2) transport problems of tastants to the taste buds (e.g., drying, infections, or inflammatory conditions of the orolingual mucosa), (3) damage to the taste buds themselves (e.g., local trauma, invasive carcinomas), (4) damage to the neural pathways innervating the taste buds (e.g., middle ear infections), (5) damage to central structures (e.g., multiple sclerosis, tumor, epilepsy, stroke), and (6) systemic disturbances of metabolism (e.g., diabetes, thyroid disease, medications). Unlike CN VII, CN IX is relatively protected along its path, although iatrogenic interventions such as tonsillectomy, bronchoscopy, laryngoscopy, endotracheal intubation, and radiation therapy can result in selective injury. CN VII damage commonly results from mastoidectomy, tympanoplasty, and stapedectomy, in some cases inducing persistent metallic sensations. Bell's palsy **(Chap. 433)** is one of the most common causes of CN VII injury that results in taste disturbance. On rare occasions, migraine **(Chap. 422)** is associated with a gustatory prodrome or aura, and in some cases tastants can trigger a migraine attack. Interestingly, dysgeusia occurs in some cases of *burning mouth syndrome* (also termed *glossodynia* or *glossalgia*), as does dry mouth and thirst. Burning mouth syndrome is likely associated with dysfunction of the trigeminal nerve (CN V).

Some of the etiologies suggested for this poorly understood syndrome are amenable to treatment, including (1) nutritional deficiencies (e.g., iron, folic acid, B vitamins, zinc), (2) diabetes mellitus (possibly predisposing to oral candidiasis), (3) denture allergy, (4) mechanical irritation from dentures or oral devices, (5) repetitive movements of the mouth (e.g., tongue thrusting, teeth grinding, jaw clenching), (6) tongue ischemia as a result of temporal arteritis, (7) periodontal disease, (8) reflux esophagitis, and (9) geographic tongue.

Although both taste and smell can be adversely influenced by drugs, taste alterations are more common. Indeed, over 250 medications have been reported to alter the ability to taste. Major offenders include antineoplastic agents, antirheumatic drugs, antibiotics, and blood pressure medications. Terbinafine, a commonly used antifungal, has been linked to taste disturbance lasting up to 3 years. In a recent controlled trial, nearly two-thirds of individuals taking eszopiclone (Lunesta) experienced a bitter dysgeusia that was stronger in women, systematically related to the time since drug administration, and positively correlated with both blood and saliva levels of the drug. Intranasal use of nasal gels and sprays containing zinc, which are common over-the-counter prophylactics for upper respiratory viral infections, has been implicated in loss of smell function. Whether their efficacy in preventing such infections, which are the most common cause of anosmia and hyposmia, outweighs their potential detriment to smell function requires study. Dysgeusia occurs commonly in the context of drugs used to treat or minimize symptoms of cancer, with a weighted prevalence from 56 to 76% depending on the type of cancer treatment. Attempts to prevent taste problems from such drugs using prophylactic zinc sulfate or amifostine have proven to be minimally beneficial. Although antiepileptic medications are occasionally used to treat smell or taste disturbances, the use of topiramate has been reported to result in a reversible loss of an ability to detect and recognize tastes and odors during treatment.

As with olfaction, a number of systemic disorders can affect taste. These include, but are not limited to, chronic renal failure, end-stage liver disease, vitamin and mineral deficiencies, diabetes mellitus, and hypothyroidism. In diabetes, there appears to be a progressive loss of taste beginning with glucose and then extending to other sweeteners, salty stimuli, and then all stimuli. Psychiatric conditions can be associated with chemosensory alterations (e.g., depression, schizophrenia, bulimia). A recent review of tactile, gustatory, and olfactory hallucinations demonstrated that no one type of hallucinatory experience is pathognomonic to any given diagnosis.

Pregnancy is a unique condition with regard to taste function. There appears to be an increase in dislike and intensity of bitter tastes during the first trimester that may help to ensure that pregnant women avoid poisons during a critical phase of fetal development. Similarly, a relative increase in the preference for salt and bitter in the second and third trimesters may support the ingestion of much needed electrolytes to expand fluid volume and support a varied diet.

CLINICAL EVALUATION

In most cases, a careful clinical history will establish the probable etiology of a chemosensory problem, including questions about its nature, onset, duration, and pattern of fluctuations. *Sudden loss* suggests the possibility of head trauma, ischemia, infection, or a psychiatric condition. *Gradual loss* can reflect the development of a progressive obstructive lesion, although gradual loss can also follow head trauma. *Intermittent loss* suggests the likelihood of an inflammatory process. The patient should be asked about potential precipitating events, such as cold or flu infections prior to symptom onset, because these often go underappreciated. Information regarding head trauma, smoking habits, drug and alcohol abuse (e.g., intranasal cocaine, chronic alcoholism), exposures to pesticides and other toxic agents, and medical interventions is also informative. A determination of all the medications that the patient was taking before and at the time of symptom onset is important, because many can cause chemosensory disturbances. Comorbid medical conditions associated with smell impairment, such as renal failure, liver disease, hypothyroidism, diabetes, or dementia, should be assessed. Delayed puberty in association with anosmia (with or without midline craniofacial abnormalities, deafness, and renal anomalies) suggests the possibility of Kallmann's syndrome. Recollection of epistaxis, discharge (clear, purulent, or bloody), nasal obstruction, allergies, and somatic symptoms, including headache or irritation, may have localizing value. Questions related to memory, parkinsonian symptoms, and seizure activity (e.g., automatisms, blackouts, auras, déjà vu) should be posed. Pending litigation and the possibility of malingering should be considered. Modern forced-choice olfactory tests can detect malingering from improbable responses.

Neurologic and otorhinolaryngologic (ORL) examinations, along with appropriate brain and nasosinus imaging, aid in the evaluation of patients with olfactory or gustatory complaints. The neural evaluation should focus on CN function, with particular attention to possible skull base and intracranial lesions. Visual acuity, field, and optic disc examinations aid in the detection of intracranial mass lesions that produce raised intracranial pressure (papilledema) and optic atrophy. Foster Kennedy syndrome refers to raised intracranial pressure plus a compressive optic neuropathy; typical causes are olfactory groove meningiomas or other frontal lobe tumors. The ORL examination should thoroughly assess the intranasal architecture and mucosal surfaces. Polyps, masses, and adhesions of the turbinates to the septum may compromise the flow of air to the olfactory receptors, because less than a fifth of the inspired air traverses the olfactory cleft in the unobstructed state. Blood tests may be helpful to identify such conditions as diabetes, infection, heavy metal exposure, nutritional deficiency (e.g., vitamin B_6 or B_{12}), allergy, and thyroid, liver, and kidney disease.

As with other sensory disorders, quantitative sensory testing is advised. Self-reports of patients can be misleading, and a number of patients who complain of chemosensory dysfunction have normal function for their age and gender. Quantitative smell and taste testing provides objective information for worker's compensation and other legal claims, as well as a way to accurately assess the effects of treatment interventions. A number of standardized olfactory and taste tests are commercially available. The most widely used of these tests, the 40-item University of Pennsylvania Smell Identification Test (UPSIT), uses norms based on nearly 4000 normal subjects. A determination is made of both absolute dysfunction (i.e., mild loss, moderate loss, severe loss, total loss, probable malingering) and relative dysfunction (percentile rank for age and gender). Although electrophysiologic testing is available at some smell and taste centers (e.g., odor event-related potentials), they require complex stimulus presentation and recording equipment and rarely provide additional diagnostic information. With the exception of electrogustometers, commercially available taste tests have only recently become available. Most use filter paper strips impregnated with tastants, so no stimulus preparation is required.

TREATMENT AND MANAGEMENT

Given the various mechanisms by which olfactory and gustatory disturbance can occur, management of patients tends to be condition-specific. For example, patients with hypothyroidism, diabetes, or infections often benefit from specific treatments to correct the underlying disease process that is adversely influencing chemoreception. For most patients who present primarily with obstructive/transport loss affecting the nasal and paranasal regions (e.g., allergic rhinitis, polyposis, intranasal neoplasms, nasal deviations), medical and/or surgical intervention is often beneficial. Antifungal and antibiotic treatments may reverse taste problems secondary to candidiasis or other oral infections. Chlorhexidine mouthwash mitigates some salty or bitter dysgeusias, conceivably as a result of its strong positive charge. Excessive dryness of the oral mucosa is a problem with many medications and conditions, and artificial saliva (e.g., Xerolube) or oral pilocarpine treatments may prove beneficial. Other methods to improve salivary flow include the use of mints, lozenges, or sugarless gum. Flavor enhancers may make food more palatable (e.g., monosodium glutamate), but caution is advised to avoid overusing ingredients containing sodium or sugar, particularly in circumstances when a patient also has underlying hypertension or diabetes. Medications that induce distortions of taste can often be discontinued and replaced with other types of medications or modes of therapy. As mentioned earlier, pharmacologic agents result

in taste disturbances much more frequently than smell disturbances. It is important to note, however, that many drug-related effects are long lasting and not reversed by short-term drug discontinuance.

A recent study of endoscopic sinus surgery in patients with chronic rhinosinusitis and hyposmia revealed that patients with severe olfactory dysfunction prior to the surgery had a more dramatic and sustained improvement over time compared to patients with more mild olfactory dysfunction prior to intervention. In the case of intranasal and sinus-related inflammatory conditions, such as seen with allergy, viruses, and traumas, the use of intranasal or systemic glucocorticoids may also be helpful. One common approach is to use a tapering course of oral prednisone. Topical intranasal administration of glucocorticoids was found to be less effective in general than systemic administration, however the effects of different nasal administration techniques were not analyzed; for example, intranasal glucocorticoids are more effective if administered in the Moffett's position (head in the inverted position such as over the edge of the bed with the bridge of the nose perpendicular to the floor). After head trauma, an initial trial of glucocorticoids may help to reduce local edema and the potential deleterious deposition of scar tissue around olfactory fila at the level of the cribriform plate.

Treatments are limited for patients with chemosensory loss or primary injury to neural pathways. Nonetheless, spontaneous recovery can occur. In a follow-up study of 542 patients presenting to our center with smell loss from a variety of causes, modest improvement occurred over an average time period of 4 years in about half of the participants. However, only 11% of the anosmic and 23% of the hyposmic patients regained normal age-related function. Interestingly, the amount of dysfunction present at the time of presentation, not etiology, was the best predictor of prognosis. Other predictors were age and the duration of dysfunction prior to initial testing.

Several studies have reported that patients with hyposmia may benefit from repeated smelling of odors over the course of weeks or months. The usual paradigm is to smell odors such as eucalyptol, citronella, eugenol, and phyenyl ethyl alcohol before going to bed and immediately upon awakening each day. The rationale for such an approach comes from animal studies demonstrating that prolonged exposure to odorants can induce increased neural activity within the olfactory bulb. There is also limited evidence that α-lipoic acid (400 mg/d), an essential cofactor for many enzyme complexes with possible antioxidant effects, may be beneficial in mitigating smell loss following viral infection of the upper respiratory tract. However, double-blind studies are needed to confirm this observation. α-lipoic acid has also been suggested to be useful in some cases of hypogeusia and burning mouth syndrome.

The use of zinc and vitamin A in treating olfactory disturbances is controversial, and there does not appear to be much benefit beyond replenishing established deficiencies. However, zinc has been shown to improve taste function secondary to hepatic deficiencies, and retinoids (bioactive vitamin A derivatives) are known to play an essential role in the survival of olfactory neurons. One protocol in which zinc was infused with chemotherapy treatments suggested a possible protective effect against developing taste impairment. Diseases of the alimentary tract can not only influence chemoreceptive function, but also occasionally influence vitamin B_{12} absorption. This can result in a relative deficiency of vitamin B_{12}, theoretically contributing to olfactory nerve disturbance. Vitamin B_2 (riboflavin) and magnesium supplements are reported in the alternative literature to aid in the management of migraine that, in turn, may be associated with smell dysfunction. Because vitamin D deficiency is a cofactor of chemotherapy-induced mucocutaneous toxicity and dysgeusia, adding vitamin D_3, 1000–2000 units per day, may benefit some patients with smell and taste complaints during or following chemotherapy.

A number of medications have reportedly been used with success in ameliorating olfactory symptoms, although strong scientific evidence for efficacy is generally lacking. A report that theophylline improved smell function was uncontrolled and failed to account for the fact that some meaningful improvement occurs without treatment; indeed, the percentage of responders was about the same (~50%) as that noted by others to show spontaneous improvement over a similar time period. Antiepileptics and some antidepressants (e.g., amitriptyline) have been used to treat dysosmias and smell distortions, particularly following head trauma. Ironically, amitriptyline is also frequently on the list of medications that can ultimately distort smell and taste function, possibly from its anticholinergic effects. One study suggested that the centrally acting acetylcholinesterase inhibitor donepezil in AD resulted in improvements on smell identification measures that correlated with overall clinician-based impressions of change in dementia severity scores.

Alternative therapies, such as acupuncture, meditation, cognitive-behavioral therapy, and yoga, can help patients manage uncomfortable experiences associated with chemosensory disturbance and oral pain syndromes and to cope with the psychosocial stressors surrounding the impairment. Additionally, modification of diet and eating habits is also important. By accentuating the other sensory experiences of a meal, such as food texture, aroma, temperature, and color, one can optimize the overall eating experience for a patient. In some cases, a flavor enhancer like monosodium glutamate (MSG) can be added to foods to increase palatability and encourage intake.

Proper oral and nasal hygiene and routine dental care are extremely important ways for patients to protect themselves from disorders of the mouth and nose that can ultimately result in chemosensory disturbance. Patients should be warned not to overcompensate for their taste loss by adding excessive amounts of sugar or salt. Smoking cessation and the discontinuance of oral tobacco use are essential in the management of any patient with smell and/or taste disturbance and should be repeatedly emphasized.

A major and often overlooked element of therapy comes from chemosensory testing itself. Confirmation or lack of conformation of loss is beneficial to patients who come to believe, in light of unsupportive family members and medical providers, that they may be "crazy." In cases where the loss is minor, patients can be informed of the likelihood of a more positive prognosis. Importantly, quantitative testing places the patient's problem into overall perspective. Thus, it is often therapeutic for an older person to know that, while his or her smell function is not what it used to be, it still falls above the average of his or her peer group. Without testing, many such patients are simply told that they are getting old and nothing can be done for them, leading in some cases to depression and decreased self-esteem.

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30 Disorders of Hearing

Anil K. Lalwani

Hearing loss can present at any age and is one of the most common sensory disorders in humans. Nearly 10% of the adult population has some hearing loss, and one-third of individuals age >65 years have a hearing loss of sufficient magnitude to require a hearing aid.

PHYSIOLOGY OF HEARING

The function of the external and middle ear is to amplify sound to facilitate conversion of the mechanical energy of the sound wave into an electrical signal by the inner ear hair cells, a process called mechanotransduction (Fig. 30-1). Sound waves enter the external auditory canal and set the tympanic membrane (eardrum) in motion, which in turn moves the malleus, incus, and stapes of the middle ear. Movement of the footplate of the stapes causes pressure changes in the fluid-filled inner ear, eliciting a traveling wave in the basilar membrane of the cochlea. The tympanic membrane and the ossicular chain in the middle ear serve as an impedance-matching mechanism, improving the efficiency of energy transfer from air to the fluid-filled inner ear. In its absence, nearly 99.9% of the acoustical energy would be reflected and thus not heard. Instead, the ear drum and the ossicles boost the sound energy nearly 200-fold by the time it reaches the inner ear.

Within the cochlea of the inner ear, there are two types of hair cells that aid in hearing: inner and outer. The inner and outer hair cells of the organ of Corti have different innervation patterns, but both are mechanoreceptors; they detect the mechanical energy of the acoustical signal and aid its conversion to an electrical signal that travels by the auditory nerve. The afferent innervation relates principally to the inner hair cells while the efferent innervation relates principally to the outer hair cells. The outer hair cells outnumber the inner hair cells by nearly 6:1 (20,000 vs 3500). The motility of the outer hair cells alters the micromechanics of the inner hair cells, creating a cochlear amplifier, which explains the exquisite sensitivity and frequency selectivity of the cochlea.

Stereocilia of the hair cells of the organ of Corti, which rests on the basilar membrane, are in contact with the tectorial membrane and are deformed by the traveling wave. The deformation stretches tiny filamentous connections (tip links) between stereocilia, leading to opening of ion channels, influx of potassium, and hair cell depolarization and subsequent neurotransmission. A point of maximal displacement of the basilar membrane is determined by the frequency of the stimulating tone. High-frequency tones cause maximal displacement of the basilar membrane near the base of the cochlea, whereas for low-frequency sounds, the point of maximal displacement is toward the apex of the cochlea.

Beginning in the cochlea, the frequency specificity is maintained at each point of the central auditory pathway: dorsal and ventral cochlear nuclei, trapezoid body, superior olivary complex, lateral lemniscus, inferior colliculus, medial geniculate body, and auditory cortex. At low frequencies, individual auditory nerve fibers can respond more or less synchronously with the stimulating tone. At higher frequencies, phase-locking occurs so that neurons alternate in response to particular phases of the cycle of the sound wave. Intensity is encoded by the amount of neural activity in individual neurons, the number of neurons that are active, and the specific neurons that are activated.

There is evidence that the right and left ears as well as the central nervous system may process speech asymmetrically. Generally, a sound is processed symmetrically from the peripheral to the central auditory system. However, a "right ear advantage" exists for dichotic listening tasks, in which subjects are asked to report on competing sounds presented to each ear. In most individuals, a perceptual right ear advantage for consonant-vowel syllables, stop consonants, and words also exists. Similarly, whereas central auditory processing for sounds is symmetric with minimal lateral specialization for the most part, speech processing is lateralized. There is specialization of the left auditory cortex for speech recognition and production, and of the right hemisphere for emotional and tonal aspects of speech. Left hemisphere dominance for speech is found in 95–98% of right-handed persons and 70–80% of left-handed persons.

DISORDERS OF THE SENSE OF HEARING

Hearing loss can result from disorders of the auricle, external auditory canal, middle ear, inner ear, or central auditory pathways (Fig. 30-2). In general, lesions in the auricle, external auditory canal, or middle ear that impede the transmission of sound from the external environment to the inner ear cause conductive hearing loss, whereas lesions that impair mechanotransduction in the inner ear or transmission of the electrical signal along the eighth nerve to the brain cause sensorineural hearing loss.

Conductive Hearing Loss The external ear, the external auditory canal, and the middle ear apparatus are designed to collect and amplify sound and efficiently transfer the mechanical energy of the sound wave to the fluid-filled cochlea. Factors that obstruct the transmission of sound or dampen the acoustical energy result in conductive hearing loss. Conductive hearing loss can occur from obstruction of the external auditory canal by cerumen, debris, and foreign bodies; swelling of the lining of the canal; atresia or neoplasms of the canal; perforations of the tympanic membrane; disruption of the ossicular chain, as occurs with necrosis of the long process of the incus in trauma or infection; otosclerosis; or fluid, scarring, or neoplasms in the middle ear. Rarely, inner

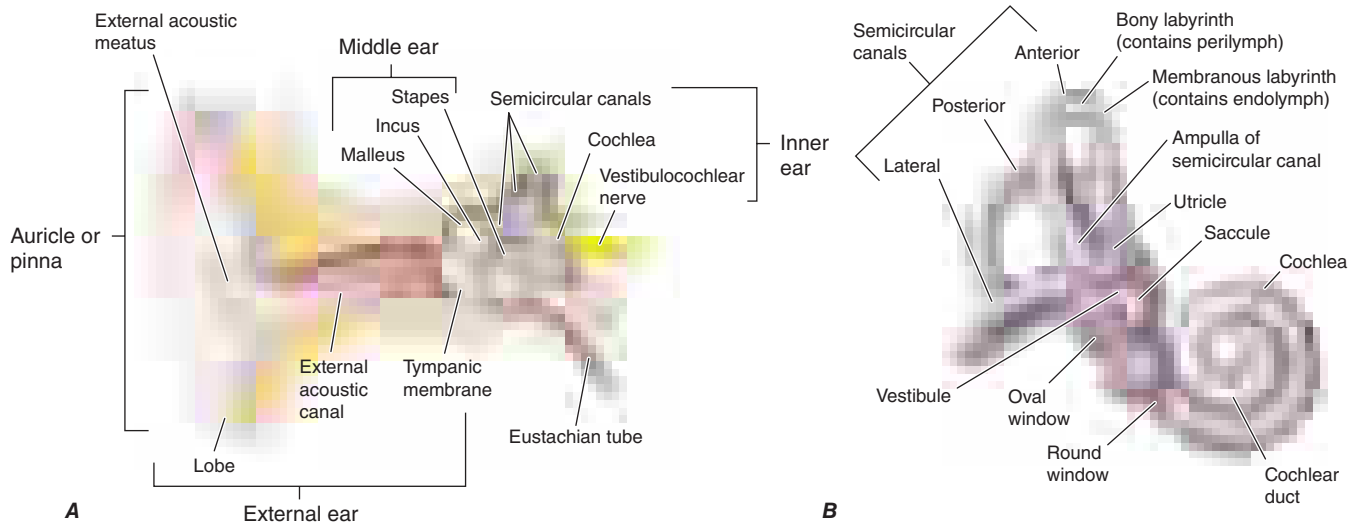

FIGURE 30-1 Ear anatomy. ***A.*** Drawing of modified coronal section through external ear and temporal bone, with structures of the middle and inner ear demonstrated. ***B.*** High-resolution view of inner ear.

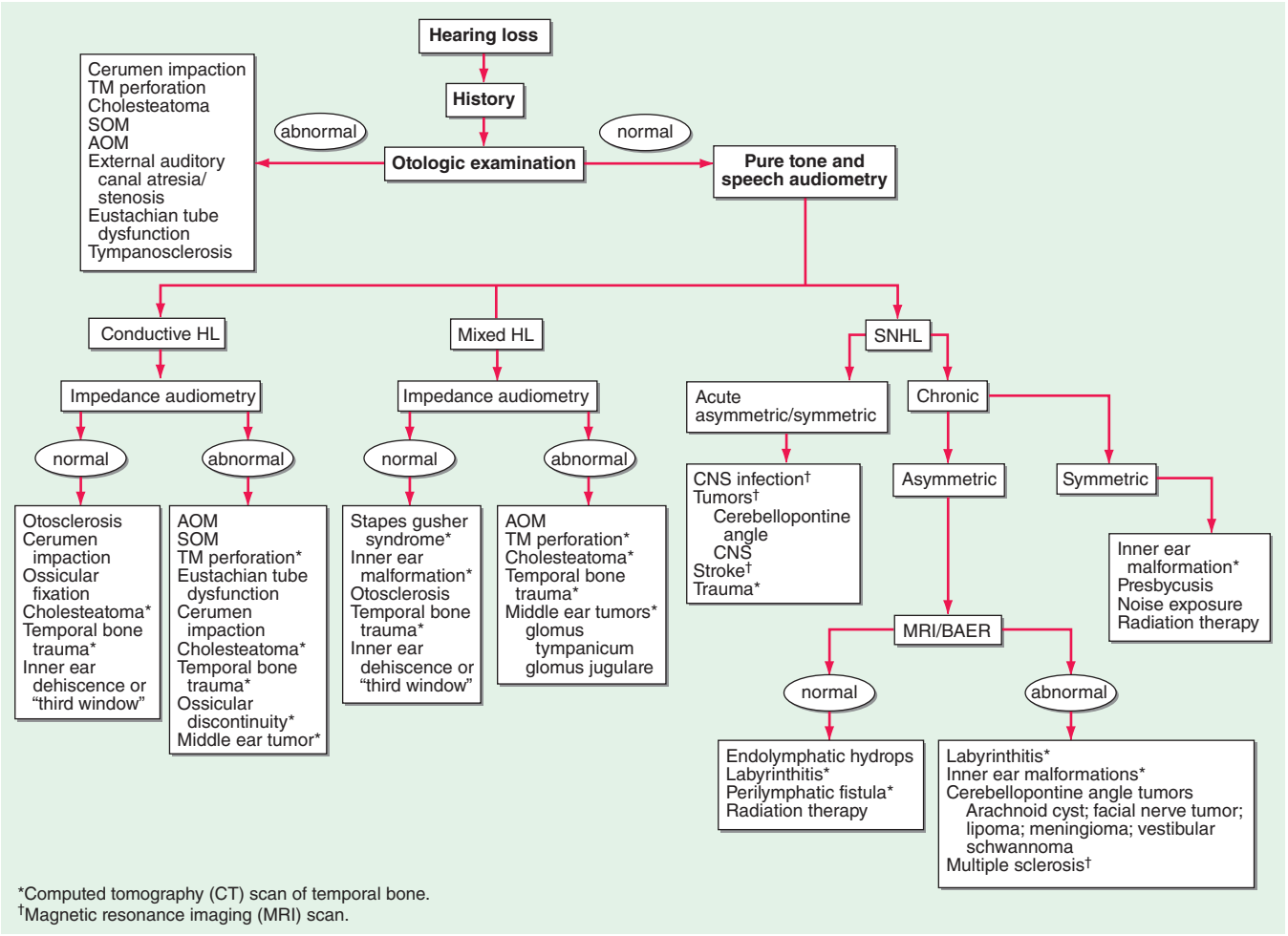

FIGURE 30-2 An algorithm for the approach to hearing loss. AOM, acute otitis media; BAER, brainstem auditory-evoked response; CNS, central nervous system; HL, hearing loss; SNHL, sensorineural hearing loss; SOM, serous otitis media; TM, tympanic membrane.

ear malformations or pathologies, such as superior semicircular canal dehiscence, lateral semicircular canal dysplasia, incomplete partition of the inner ear, and large vestibular aqueduct, are also associated with conductive hearing loss.

Eustachian tube dysfunction is extremely common in adults and may predispose to acute otitis media (AOM) or serous otitis media (SOM). Trauma, AOM, and chronic otitis media are the usual factors responsible for tympanic membrane perforation. While small perforations often heal spontaneously, larger defects usually require surgical intervention. Tympanoplasty is highly effective (>90%) in the repair of tympanic membrane perforations. Otoscopy is usually sufficient to diagnose AOM, SOM, chronic otitis media, cerumen impaction, tympanic membrane perforation, and eustachian tube dysfunction; tympanometry can be useful to confirm the clinical suspicion of these conditions.

Cholesteatoma, a benign tumor composed of stratified squamous epithelium in the middle ear or mastoid, occurs frequently in adults. This is a slowly growing lesion that destroys bone and normal ear tissue. Theories of pathogenesis include traumatic immigration and invasion of squamous epithelium through a retraction pocket of the tympanic membrane, implantation of squamous epithelia in the middle ear through a perforation or surgery, and metaplasia following chronic infection and irritation. A chronically draining ear that fails to respond to appropriate antibiotic therapy should raise suspicion of a cholesteatoma. On examination, there is often a perforation of the tympanic membrane filled with cheesy white squamous debris. The presence of an aural polyp obscuring the tympanic membrane is also highly suggestive of an underlying cholesteatoma. Conductive hearing loss secondary to ossicular erosion is common. Bony destruction visualized on computerized tomography (CT) of the temporal bone is highly suggestive of cholesteatoma. Surgery is required to remove this destructive process and reconstruct the ossicles.

Conductive hearing loss with a normal ear canal and intact tympanic membrane suggests either ossicular pathology or the presence of "third window" in the inner ear (see below). Fixation of the stapes from *otosclerosis* is a common cause of low-frequency conductive hearing loss. It occurs equally in men and women and is inherited as an autosomal dominant trait with incomplete penetrance; in some cases, it may be a manifestation of osteogenesis imperfecta. Hearing impairment usually presents between the late teens and the forties. In women, the otosclerotic process is accelerated during pregnancy, and the hearing loss is often first noticeable at this time. A hearing aid or a simple outpatient surgical procedure (stapedectomy) can provide excellent auditory rehabilitation. Extension of otosclerosis beyond the stapes footplate to involve the cochlea (cochlear otosclerosis) can lead to mixed or sensorineural hearing loss. Fluoride therapy to prevent hearing loss from cochlear otosclerosis is of uncertain value.

Disorders that lead to the formation of a pathologic "third window" in the inner ear can be associated with conductive hearing loss. There are normally two major openings, or windows, that connect the inner ear with the middle ear and serve as conduits for transmission of sound; these are, respectively, the oval and round windows. A third window is formed where the normally hard otic bone surrounding the inner ear is eroded; dissipation of the acoustic energy at the third window is responsible for the "inner ear conductive hearing loss." The superior semicircular canal dehiscence syndrome resulting from erosion of the otic bone over the superior circular canal can present with conductive hearing loss that mimics otosclerosis. A common symptom is vertigo evoked by loud sounds (Tullio phenomenon), by Valsalva maneuvers that change middle ear pressure, or by applying positive

pressure on the tragus (the cartilage anterior to the external opening of the ear canal). Patients with this syndrome also complain of fullness of the ear, pulsatile tinnitus, and being able to hear the movement of their eyes and neck. A large jugular bulb or jugular bulb diverticulum can create a "third window" by eroding into the vestibular aqueduct or posterior semicircular canal; the symptoms are similar to those of the superior semicircular canal dehiscence syndrome. Low activation threshold on the vestibular-evoked myogenic potential test (VEMP test, see below) and inner ear erosion on CT are diagnostic. Recalcitrant vertigo and dizziness may respond to surgical repair of the dehiscence.

Sensorineural Hearing Loss Sensorineural hearing loss results from either damage to the mechanotransduction apparatus of the cochlea or disruption of the electrical conduction pathway from the inner ear to the brain. Thus, injury to hair cells, supporting cells, auditory neurons, or the central auditory pathway can cause sensorineural hearing loss. Damage to the hair cells of the organ of Corti may be caused by intense noise, viral infections, ototoxic drugs (e.g., salicylates, quinine and its synthetic analogues, aminoglycoside antibiotics, loop diuretics such as furosemide and ethacrynic acid, and cancer chemotherapeutic agents such as cisplatin), fractures of the temporal bone, meningitis, cochlear otosclerosis (see above), Ménière's disease, and aging. Congenital malformations of the inner ear may be the cause of hearing loss in some adults. Genetic predisposition alone or in concert with environmental exposures may also be responsible (see below).

Exposure to loud noise, either a short burst or over a more prolonged period of time, can lead to noise-induced hearing loss. Acute exposure to noise can lead to either temporary or permanent threshold shifts, depending on the intensity and duration of sound, due to hair cell injury and/or death. Typically, with permanent hearing loss there is a "noise notch" with elevated hearing thresholds at 3000–4000 Hz. More recently, loud noise exposure has also been associated with "hidden hearing loss"—hidden, because routine audiometry shows the pure tone hearing to be normal. Patients usually complains of not being able to hear clearly and are more bothered by the presence of background noise. In contrast to hair cell loss, hidden hearing loss is thought to be due to loss of auditory synapses on hair cells following noise exposure. In an increasingly noisy world, avoiding acoustic trauma with ear plugs or earmuffs is highly recommended to prevent noise-induced or hidden hearing loss.

Presbycusis (age-associated hearing loss) is the most common cause of sensorineural hearing loss in adults. It is estimated to affect over half of the adults aged >75 in the United States, a population that is expected to double in size over the next 40 years. In the early stages, it is characterized by symmetric, gentle to sharply sloping, high-frequency hearing loss **(Fig. 30-3)**. With progression, the hearing loss involves all frequencies. More importantly, the hearing impairment is associated with significant loss in clarity. There is a loss of discrimination for phonemes, recruitment (abnormal growth of loudness), and particular difficulty in understanding speech in noisy environments such as at restaurants and social events. Poor hearing is also associated with an increased incidence of cognitive impairment and rate of cognitive decline. In the elderly, left untreated, hearing loss leads to diminished quality of life, and has been shown to increase overall morbidity and mortality through falls and accidents. Hearing aids are helpful in enhancing the signal-to-noise ratio by amplifying sounds that are close to the listener. Hearing aid use has been shown to reduce cognitive decline. Although hearing aids are able to amplify sounds, they cannot restore the clarity of hearing. Thus, amplification with hearing aids may provide only limited rehabilitation once the word recognition score deteriorates below 50%. Cochlear implants are the treatment of choice when hearing aids prove inadequate, even when hearing loss is incomplete (see below).

Ménière's disease is characterized by episodic vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness. Tinnitus and/or deafness may be absent during the initial attacks of vertigo, but it invariably appears as the disease progresses and increases in severity during acute attacks. The annual incidence of Ménière's disease is 0.5–7.5 per 1000; onset is most frequently in the fifth decade of life but may also occur in young adults or the elderly. Histologically, there

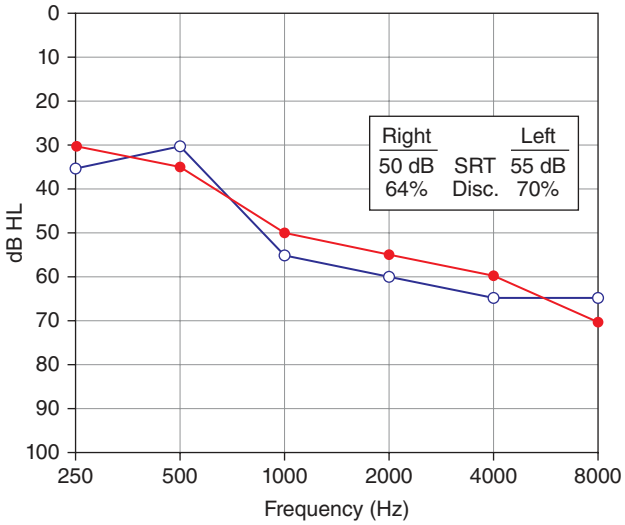

FIGURE 30-3 Presbyacusis or age-related hearing loss. The audiogram shows a moderate to severe downsloping sensorineural hearing loss typical of presbyacusis. The loss of high-frequency hearing is associated with a decreased speech discrimination score; consequently, patients complain of lack of clarity of hearing, especially in a noisy background. HL, hearing threshold level; SRT, speech reception threshold.

is distention of the endolymphatic system (endolymphatic hydrops) leading to degeneration of vestibular and cochlear hair cells. This may result from endolymphatic sac dysfunction secondary to infection, trauma, autoimmune disease, inflammatory causes, or tumor; an idiopathic etiology constitutes the largest category and is most accurately referred to as Ménière's disease. Although any pattern of hearing loss can be observed, typically, low-frequency, unilateral sensorineural hearing impairment is present. An abnormal VEMP test may be helpful in detecting Ménière's disease in a clinically unaffected contralateral ear. Magnetic resonance imaging (MRI) should be obtained to exclude retrocochlear pathology such as a cerebellopontine angle tumor or demyelinating disorder. Therapy is directed toward the control of vertigo. A 2-g/d low-salt diet is the mainstay of treatment for control of rotatory vertigo. Diuretics, a short course of oral glucocorticoids, intratympanic glucocorticoids, or intratympanic gentamicin may also be useful adjuncts in recalcitrant cases. Surgical therapy of vertigo is reserved for unresponsive cases and includes endolymphatic sac decompression, labyrinthectomy, and vestibular nerve section. Both labyrinthectomy and vestibular nerve section abolish rotatory vertigo in >90% of cases. Unfortunately, there is no effective therapy for hearing loss, tinnitus, or aural fullness from Ménière's disease.

Sensorineural hearing loss may also result from any neoplastic, vascular, demyelinating, infectious, or degenerative disease or trauma affecting the central auditory pathways. Characteristically, a reduction in clarity of hearing and speech comprehension is much greater than the loss of the ability to hear pure tone. Auditory testing is consistent with an auditory neuropathy; normal otoacoustic emissions (OAEs) and an abnormal auditory brainstem response (ABR) is typical (see below). Hearing loss can accompany hereditary sensorimotor neuropathies and inherited disorders of myelin. Tumors of the cerebellopontine angle such as vestibular schwannoma and meningioma **(Chap. 86)** usually present with asymmetric sensorineural hearing loss with greater deterioration of speech understanding than pure tone hearing. Multiple sclerosis **(Chap. 436)** may present with acute unilateral or bilateral hearing loss; typically, pure tone testing remains relatively stable while speech understanding fluctuates. Isolated labyrinthine infarction can present with acute hearing loss and vertigo due to a cerebrovascular accident involving the posterior circulation, usually the anterior inferior cerebellar artery; it may also be the heralding sign of impending catastrophic basilar artery infarction **(Chap. 419)**. HIV **(Chap. 197)**, which can produce both peripheral and central auditory system pathology, is another consideration in the evaluation of sensorineural hearing impairment.

A finding of conductive and sensorineural hearing loss in combination is termed *mixed hearing loss*. Mixed hearing losses can result

from pathology of both the middle and inner ear, as can occur in otosclerosis involving the ossicles and the cochlea, head trauma, chronic otitis media, cholesteatoma, middle ear tumors, and some inner ear malformations.

Trauma resulting in temporal bone fractures may be associated with conductive, sensorineural, or mixed hearing loss. If the fracture spares the inner ear, there may simply be conductive hearing loss due to rupture of the tympanic membrane or disruption of the ossicular chain. These abnormalities can be surgically corrected. Profound hearing loss and severe vertigo are associated with temporal bone fractures involving the inner ear. A perilymphatic fistula associated with leakage of inner ear fluid into the middle ear can occur and may require surgical repair. An associated facial nerve injury is not uncommon. CT is best suited to assess fracture of the traumatized temporal bone, evaluate the ear canal, and determine the integrity of the ossicular chain and involvement of the inner ear. Cerebrospinal fluid leaks that accompany temporal bone fractures are usually self-limited; the value of prophylactic antibiotics is uncertain.

Tinnitus is defined as the perception of a sound when there is no sound in the environment. It can have a buzzing, roaring, or ringing quality and may be pulsatile (synchronous with the heartbeat). Tinnitus is often associated with either a conductive or sensorineural hearing loss. The pathophysiology of tinnitus is not well understood. The cause of the tinnitus can usually be determined by finding the cause of the associated hearing loss. Tinnitus may be the first symptom of a serious condition such as a vestibular schwannoma. Pulsatile tinnitus requires evaluation of the vascular system of the head to exclude vascular tumors such as glomus jugulare tumors, aneurysms, dural arteriovenous fistulas, and stenotic arterial lesions; it may also occur with SOM, superior semicircular dehiscence, and inner ear dehiscence. It is most commonly associated with some abnormality of the jugular bulb such as a large jugular bulb or jugular bulb diverticulum.

GENETIC CAUSES OF HEARING LOSS

More than half of childhood hearing impairment is thought to be hereditary; hereditary hearing impairment (HHI) can also manifest later in life. HHI may be classified as either nonsyndromic, when hearing loss is the only clinical abnormality, or syndromic, when hearing loss is associated with anomalies in other organ systems. Nearly two-thirds of HHIs are nonsyndromic. Between 70 and 80% of nonsyndromic HHI is inherited in an autosomal recessive manner and designated DFNB; another 15–20% is autosomal dominant (DFNA). Less than 5% is X-linked (DFNX) or maternally inherited via the mitochondria.

More than 150 loci harboring genes for nonsyndromic HHI have been mapped, with recessive loci outnumbering dominant ones; numerous genes have now been identified **(Table 30-1)**. The hearing genes fall into the categories of structural proteins (*MYH9, MYO7A, MYO15, TECTA, DIAPH1*), transcription factors (*POU3F4, POU4F3*), ion channels (*KCNQ4, SLC26A4*), and gap junction proteins (*GJB2, GJB3, GJB6*). Several of these genes, including *GJB2, TECTA*, and *TMC1*, cause both autosomal dominant and recessive forms of nonsyndromic HHI. In general, the hearing loss associated with dominant genes has its onset in adolescence or adulthood, varies in severity, and progresses with age, whereas the hearing loss associated with recessive inheritance is congenital and profound. Connexin 26, product of the *GJB2* gene, is particularly important because it is responsible for nearly 20% of all cases of childhood deafness; half of genetic deafness in children is *GJB2*-related. Two frameshift mutations, 35delG and 167delT, account for >50% of the cases; however, screening for these two mutations alone is insufficient, and sequencing of the entire gene is required to fully capture *GJB2*-related recessive deafness. The 167delT mutation is highly prevalent in Ashkenazi Jews; ~1 in 1765 individuals in this population are homozygous and affected. *GJB2* hearing loss can also vary among the members of the same family, suggesting that other genes or factors influence the auditory phenotype. A single mutation in *GJB2* in combination with a single mutation in *GJB6* (connexin 30) can also lead to hearing loss and is an example of digenic inheritance of hearing loss.

In addition to *GJB2*, several other nonsyndromic genes are associated with hearing loss that progresses with age. The contribution of genetics to presbycusis is also becoming better understood. Sensitivity to aminoglycoside ototoxicity can be maternally transmitted through a mitochondrial mutation. Susceptibility to noise-induced hearing loss may also be genetically determined.

There are >400 syndromic forms of hearing loss. These include Usher's syndrome (retinitis pigmentosa and hearing loss), Waardenburg's syndrome (pigmentary abnormality and hearing loss), Pendred's syndrome (thyroid organification defect and hearing loss), Alport's syndrome (renal disease and hearing loss), Jervell and Lange-Nielsen syndrome (prolonged QT interval and hearing loss), neurofibromatosis type 2 (bilateral acoustic schwannoma), and mitochondrial disorders (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; myoclonic epilepsy and ragged red fibers [MERRF]; and progressive external ophthalmoplegia [PEO]) **(Table 30-2)**.

APPROACH TO THE PATIENT

Disorders of the Sense of Hearing

The goal in the evaluation of a patient with auditory complaints is to determine (1) the nature of the hearing impairment (conductive vs sensorineural vs mixed), (2) the severity of the impairment (mild, moderate, severe, or profound), (3) the anatomy of the impairment (external ear, middle ear, inner ear, or central auditory pathway), and (4) the etiology. The presence of signs and symptoms associated with hearing loss should be ascertained **(Table 30-3)**. The history should elicit characteristics of the hearing loss, including the duration of deafness, unilateral versus bilateral involvement, nature of onset (sudden vs insidious), and rate of progression (rapid vs slow). Symptoms of tinnitus, vertigo, imbalance, aural fullness, otorrhea, headache, facial nerve dysfunction, and head and neck paresthesias should be noted. Information regarding head trauma, exposure to ototoxins, occupational or recreational noise exposure, and family history of hearing impairment may also be important. A sudden onset of unilateral hearing loss, with or without tinnitus, may represent a viral infection of the inner ear, vestibular schwannoma, or a stroke. Patients with unilateral hearing loss (sensory or conductive) usually complain of reduced hearing, poor sound localization, and difficulty hearing clearly in the presence of background noise. Gradual progression of a hearing deficit is common with otosclerosis, noise-induced hearing loss, vestibular schwannoma, or Ménière's disease. Small vestibular schwannomas typically present with asymmetric hearing impairment, tinnitus, and imbalance (rarely vertigo); cranial neuropathy, in particular of the trigeminal or facial nerve, may accompany larger tumors. In addition to hearing loss, Ménière's disease may be associated with episodic vertigo, tinnitus, and aural fullness. Hearing loss with otorrhea is most likely due to chronic otitis media or cholesteatoma.

Examination should include the auricle, external ear canal, and tympanic membrane. In the elderly, the external ear canal is often dry and fragile; it is preferable to clean cerumen with wall-mounted suction or cerumen loops and to avoid irrigation. In examining the eardrum, the topography of the tympanic membrane is more important than the presence or absence of the light reflex. In addition to the pars tensa (the lower two-thirds of the tympanic membrane), the pars flaccida (upper one-third of the tympanic membrane) above the short process of the malleus should also be examined for retraction pockets that may be evidence of chronic eustachian tube dysfunction or cholesteatoma. Insufflation of the ear canal is necessary to assess tympanic membrane mobility and compliance. Careful inspection of the nose, nasopharynx, and upper respiratory tract is important. Unilateral serous effusion or unexplained otalgia should prompt a fiberoptic examination of the nasopharynx and larynx to exclude neoplasms. Cranial nerves should be evaluated with special attention to facial and trigeminal nerves, which are commonly affected with tumors involving the cerebellopontine angle.

The Rinne and Weber tuning fork tests, with a 512-Hz tuning fork, are used to screen for hearing loss, differentiate conductive from sensorineural hearing losses, and confirm the findings of

TABLE 30-1 Hereditary Hearing Impairment Genes

DESIGNATION	GENE	FUNCTION
Autosomal Dominant		
	CRYM	Thyroid hormone–binding protein
DFNA1	*DIAPH1*	Cytoskeletal protein
DFNA2A	*KCNQ4*	Potassium channel
DFNA2B	*GJB3 (Cx31)*	Gap junction
DFNA3A	*GJB2 (Cx26)*	Gap junction
DFNA3B	*GJB6 (Cx30)*	Gap junction
DFNA4	*MYH14*	Class II nonmuscle myosin
	CEACAM16	Cell adhesion molecule
DFNA5	*DFNA5*	Unknown
DFNA6/14/38	*WFS1*	Transmembrane protein
DFNA8/12	*TECTA*	Tectorial membrane protein
DFNA9	*COCH*	Unknown
DFNA10	*EYA4*	Developmental gene
DFNA11	*MYO7A*	Cytoskeletal protein
DFNA13	*COL11A2*	Cytoskeletal protein
DFNA15	*POU4F3*	Transcription factor
DFNA17	*MYH9*	Cytoskeletal protein
DFNA20/26	*ACTG1*	Cytoskeletal protein
DFNA22	*MYO6*	Unconventional myosin
DFNA23	*SIX1*	Developmental gene
DFNA25	*SLC17A8*	Vesicular glutamate transporter
DFNA28	*GRHL2*	Transcription factor
DFNA36	*TMC1*	Transmembrane protein
DFNA41	*P2RX2*	Purinergic receptor
DFNA44	*CCDC50*	Effector of epidermal growth factor–mediated signaling
DFNA50	*MIRN96*	MicroRNA
DFNA51	*TJP2*	Tight junction protein
DFNA56	*TNC*	Extracellular matrix protein
DFNA64	*SMAC/DIABLO*	Mitochondrial proapoptotic protein
DFNA65	*TBC1D24*	ARF6-interacting protein
DFNA66	*CD164*	Sialomucin
DFNA67	*OSBPL2*	Intracellular lipid receptor
DFNA68	*HOMER2*	Stereociliary scaffolding protein
DFNA69	*KITLG*	Ligand for KIT receptor
DFNA70	*MCM2*	Initiation and elongation during DNA replication
DFNA71	*DMXL2*	Regulator of Notch signaling
Autosomal Recessive		
DFNB1A	*GJB2 (CX26)*	Gap junction
DFNB1B	*GJB6 (CX30)*	Gap junction
DFNB2	*MYO7A*	Cytoskeletal protein
DFNB3	*MYO15*	Cytoskeletal protein
DFNB4	*PDS (SLC26A4)*	Chloride/iodide transporter
DFNB6	*TMIE*	Transmembrane protein
DFNB7/B11	*TMC1*	Transmembrane protein
DFNB9	*OTOF*	Trafficking of membrane vesicles
DFNB8/10	*TMPRSS3*	Transmembrane serine protease
DFNB12	*CDH23*	Intercellular adherence protein
DFNB15/72/95	*GIPC3*	PDZ domain–containing protein
DFNB16	*STRC*	Stereocilia protein
DFNB18	*USH1C*	Unknown
DFNB18B	*OTOG*	Tectorial membrane protein
DFNB21	*TECTA*	Tectorial membrane protein
DFNB22	*OTOA*	Gel attachment to nonsensory cell
DFNB23	*PCDH15*	Morphogenesis and cohesion
DFNB24	*RDX*	Cytoskeletal protein
DFNB25	*GRXCR1*	Reversible *S*-glutathionylation of proteins
DFNB28	*TRIOBP*	Cytoskeletal-organizing protein
DFNB29	*CLDN14*	Tight junctions
DFNB30	*MYO3A*	Hybrid motor-signaling myosin
DFNB31	*WHRN*	PDZ domain–containing protein
DFNB35	*ESRRB*	Estrogen-related receptor beta protein
DFNB36	*ESPN*	Ca-insensitive actin-bundling protein
DFNB37	*MYO6*	Unconventional myosin
DFNB39	*HFG*	Hepatocyte growth factor
DFNB42	*ILDR1*	Ig-like domain–containing receptor
DFNB44	*ADCY1*	Adenylate cyclase
DFNB48	*CIB2*	Calcium and integrin binding protein
DFNB49	*BDP1*	Subunit of RNA polymerase
DFNB49	*MARVELD2*	Tight junction protein
DFNB53	*COL11A2*	Collagen protein
DFNB59	*PJVK*	Zn-binding protein
DFNB60	*SLC22A4*	Prestin, motor protein of cochlear outer hair cell
DFNB61	*SLC26A5*	Motor protein
DFNB63	*LRTOMT/COMT2*	Putative methyltransferase
DFNB66	*DCDC2*	Ciliary protein
DFNB66/67	*LHFPL5*	Tetraspan protein
DFNB68	*S1PR2*	Tetraspan membrane protein of hair cell stereocilia
DFNB70	*PNPT1*	Mitochondrial–RNA–import protein
DFNB73	*BSND*	Beta subunit of chloride channel
DFNB74	*MSRB3*	Methionine sulfoxide reductase
DFNB76	*SYNE4*	Part of *LINC* tethering complex
DFNB77	*LOXHD1*	Stereociliary protein
DFNB79	*TPRN*	Unknown
DFNB82	*GPSM2*	G protein signaling modulator
DFNB84	*PTPRQ*	Type III receptor-like protein-tyrosine phosphatase family
DFNB84	*OTOGL*	Otogelin-like protein
DFNB86	*TBC1D24*	GTPase-activating protein
DFNB88	*ELMOD3*	GTPase-activating protein
DFNB89	*KARS*	Lysyl-tRNA synthetase
DFNB91	*SERPINB6*	Protease inhibitor
DFNB93	*CABP2*	Calcium-binding protein
DFNA97	*MET*	Oncogene/hepatocyte growth factor receptor
DFNB98	*TSPEAR*	Epilepsy-associated repeats containing protein
DFNB99	*TMEM132E*	Transmembrane protein
DFNB101	*GRXCR2*	Maintaining stereocilia bundles
DFNB102	*EPS8*	Epidermal growth factor receptor
DFNB103	*CLIC5*	Chloride ion transport
DFNB105	*CDC14A*	Protein phosphatase involved in hair cell ciliogenesis
	FAM65B	Membrane-associated protein in stereocilia
	EPS8L2	Actin remodeling in response to *EGF* stimulation
	ROR1	Receptor tyrosine kinase-like orphan receptor

TABLE 30-2 Syndromic Hereditary Hearing Impairment Genes

SYNDROME	GENE	FUNCTION
Alport's syndrome	*COL4A3-5*	Cytoskeletal protein
BOR syndrome	*EYA1*	Developmental gene
	SIX5	Developmental gene
	SIX1	Developmental gene
Jervell and Lange-Nielsen syndrome	*KCNQ1*	Delayed rectifier K^+ channel
	KCNE1	Delayed rectifier K^+ channel
Norrie's disease	*NDP*	Cell–cell interactions
Pendred's syndrome	*SLC26A4*	Chloride/iodide transporter
	FOXI1	Transcriptional activator of *SLC26A4*
	KCNJ10	Inwardly rectifying K^+ channel
Treacher Collins syndrome	*TCOF1*	Nucleolar-cytoplasmic transport
	POLR1D	Subunit of RNA polymerases I and III
	POLR1C	Subunit of RNA polymerases I and III
Usher's syndrome	*MYO7A*	Cytoskeletal protein
	USH1C	Unknown
	CDH23	Intercellular adherence protein
	PCDH15	Cell adhesion molecule
	SANS	Harmonin-associated protein
	CIB2	Calcium- and integrin-binding protein
	USH2A	Cell adhesion molecule
	VLGR1	G protein–coupled receptor
	WHRN	PDZ domain–containing protein
	CLRN1	Cellular synapse protein
	HARS	Histidyl-tRNA synthetase
	PDZD7	PDZ domain–containing protein
WS type I, III	*PAX3*	Transcription factor
WS type II	*MITF*	Transcription factor
	SNAI2	Transcription factor
WS type IV	*EDNRB*	Endothelin B receptor
	EDN3	Endothelin B receptor ligand
	SOX10	Transcription factor

Abbreviations: BOR, branchio-oto-renal syndrome; WS, Waardenburg's syndrome.

audiologic evaluation. The Rinne test compares the ability to hear by air conduction with the ability to hear by bone conduction. The tines of a vibrating tuning fork are held near the opening of the external auditory canal, and then the stem is placed on the mastoid process; for direct contact, it may be placed on teeth or dentures. The patient is asked to indicate whether the tone is louder by air conduction or bone conduction. Normally, and in the presence of sensorineural hearing loss, a tone is heard louder by air conduction than by bone conduction; however, with conductive hearing loss of ≥30 dB (see "Audiologic Assessment," below), the bone-conduction stimulus is perceived as louder than the air-conduction stimulus. For the Weber test, the stem of a vibrating tuning fork is placed on the head in the midline and the patient is asked whether the tone is heard in both ears or better in one ear than in the other. With a unilateral conductive hearing loss, the tone is perceived in the affected ear. With a unilateral sensorineural hearing loss, the tone is perceived in the unaffected ear. A 5-dB difference in hearing between the two ears is required for lateralization.

TABLE 30-3 Signs and Symptoms Suggestive of Hearing Loss

Saying "huh" a great deal
Reduced clarity of hearing
Difficulty understanding conversations in background noise
Family complaining of hearing loss
Tinnitus
Turning the volume up on radio or television
Sensitivity to noises
Fullness in the ear
Avoiding social settings

LABORATORY ASSESSMENT OF HEARING

Audiologic Assessment The minimum audiologic assessment for hearing loss should include the measurement of pure tone air-conduction and bone-conduction thresholds, speech reception threshold, word recognition score, tympanometry, acoustic reflexes, and acoustic-reflex decay. This test battery provides a screening evaluation of the entire auditory system and allows one to determine whether further differentiation of a sensory (cochlear) from a neural (retrocochlear) hearing loss is indicated.

Pure tone audiometry assesses hearing acuity for pure tones. The test is administered by an audiologist and is performed in a sound-attenuated chamber. The pure tone stimulus is delivered with an audiometer, an electronic device that allows the presentation of specific frequencies (generally between 250 and 8000 Hz) at specific intensities. Air- and bone-conduction thresholds are established for each ear. Air-conduction thresholds are determined by presenting the stimulus in air with the use of headphones. Bone-conduction thresholds are determined by placing the stem of a vibrating tuning fork or an oscillator of an audiometer in contact with the head. In the presence of a hearing loss, broad-spectrum noise is presented to the nontest ear for *masking* purposes so that responses are based on perception from the ear under test.

The responses are measured in decibels (dBs). An *audiogram* is a plot of intensity in dBs of hearing threshold versus frequency. A dB is equal to 20 times the logarithm of the ratio of the sound pressure required to achieve threshold in the patient to the sound pressure required to achieve threshold in a normal-hearing person. Therefore, a change of 6 dB represents doubling of sound pressure, and a change of 20 dB represents a tenfold change in sound pressure. Loudness, which depends on the frequency, intensity, and duration of a sound, doubles with approximately each 10-dB increase in sound pressure level. Pitch, on the other hand, does not directly correlate with frequency. The perception of pitch changes slowly in the low and high frequencies. In the middle tones, which are important for human speech, pitch varies more rapidly with changes in frequency.

Pure tone audiometry establishes the presence and severity of hearing impairment, unilateral versus bilateral involvement, and the type of hearing loss. Conductive hearing losses with a large mass component, as is often seen in middle ear effusions, produce elevation of thresholds that predominate in the higher frequencies. Conductive hearing losses with a large stiffness component, as in fixation of the footplate of the stapes in early otosclerosis, produce threshold elevations in the lower frequencies. Often, the conductive hearing loss involves all frequencies, suggesting involvement of both stiffness and mass. In general, sensorineural hearing losses such as presbycusis affect higher frequencies more than lower frequencies (Fig. 30-3). An exception is Ménière's disease, which is characteristically associated with low-frequency sensorineural hearing loss (though any frequency can be affected). Noise-induced hearing loss has an unusual pattern of hearing impairment in which the loss at 4000 Hz is greater than at higher frequencies. Vestibular schwannomas characteristically affect the higher frequencies, but any pattern of hearing loss can be observed.

Speech recognition requires greater synchronous neural firing than is necessary for appreciation of pure tones. *Speech audiometry* tests the clarity with which one hears. The *speech reception threshold* (SRT) is defined as the intensity at which speech is recognized as a meaningful symbol and is obtained by presenting two-syllable words with an equal accent on each syllable. The intensity at which the patient can repeat 50% of the words correctly is the SRT. Once the SRT is determined, discrimination or word recognition ability is tested by presenting one-syllable words at 25–40 dB above the SRT. The words are phonetically balanced in that the phonemes (speech sounds) occur in the list of words at the same frequency that they occur in ordinary conversational

English. An individual with normal hearing or conductive hearing loss can repeat 88–100% of the phonetically balanced words correctly. Patients with a sensorineural hearing loss have variable loss of discrimination. As a general rule, neural lesions produce greater deficits in discrimination than do cochlear lesions. For example, in a patient with mild asymmetric sensorineural hearing loss, a clue to the diagnosis of vestibular schwannoma is the presence of greater than expected deterioration in discrimination ability. Deterioration in discrimination ability at higher intensities above the SRT also suggests a lesion in the eighth nerve or central auditory pathways.

Tympanometry measures the impedance of the middle ear to sound and is useful in diagnosis of middle ear effusions. A *tympanogram* is the graphic representation of change in impedance or compliance as the pressure in the ear canal is changed. Normally, the middle ear is most compliant at atmospheric pressure, and the compliance decreases as the pressure is increased or decreased (type A); this pattern is seen with normal hearing or in the presence of sensorineural hearing loss. Compliance that does not change with change in pressure suggests middle ear effusion (type B). With a negative pressure in the middle ear, as with eustachian tube obstruction, the point of maximal compliance occurs with negative pressure in the ear canal (type C). A tympanogram in which no point of maximal compliance can be obtained is most commonly seen with discontinuity of the ossicular chain (type A_d). A reduction in the maximal compliance peak can be seen in otosclerosis (type A_s).

During tympanometry, an intense tone elicits contraction of the stapedius muscle. The change in compliance of the middle ear with contraction of the stapedius muscle can be detected. The presence or absence of this *acoustic reflex* is important in determining the etiology of hearing loss as well as in the anatomic localization of facial nerve paralysis. The acoustic reflex can help differentiate between conductive hearing loss due to otosclerosis and that caused by an inner ear "third window": it is absent in otosclerosis and present in inner ear conductive hearing loss. Normal or elevated acoustic reflex thresholds in an individual with sensorineural hearing impairment suggest a cochlear hearing loss. An absent acoustic reflex in the setting of sensorineural hearing loss is not helpful in localizing the site of lesion. Assessment of *acoustic reflex decay* helps differentiate sensory from neural hearing losses. In neural hearing loss, such as with vestibular schwannoma, the reflex adapts or decays with time.

OAEs generated by outer hair cells only can be measured with microphones inserted into the external auditory canal. The emissions may be spontaneous or evoked with sound stimulation. The presence of OAEs indicates that the outer hair cells of the organ of Corti are intact and can be used to assess auditory thresholds and to distinguish sensory from neural hearing losses.

Evoked Responses *Electrocochleography* measures the earliest evoked potentials generated in the cochlea and the auditory nerve. Receptor potentials recorded include the cochlear microphonic, generated by the outer hair cells of the organ of Corti, and the summating potential, generated by the inner hair cells in response to sound. The whole nerve action potential representing the composite firing of the first-order neurons can also be recorded during electrocochleography. Clinically, the test is useful in the diagnosis of Ménière's disease, in which an elevation of the ratio of summating potential to action potential is seen.

Brainstem auditory-evoked responses (BAERs), also known as (ABRs), are useful in differentiating the site of sensorineural hearing loss. In response to sound, five distinct electrical potentials arising from different stations along the peripheral and central auditory pathway (eighth nerve, cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus) can be identified using computer averaging from scalp surface electrodes. BAERs are valuable in situations in which patients cannot or will not give reliable voluntary thresholds. They are also used to assess the integrity of the auditory nerve and brainstem in various clinical situations, including intraoperative monitoring, and in determination of brain death.

The *VEMP test* investigates otolith and vestibular nerve function by presenting a high-level acoustic stimuli and evoking a short-latency electromyographic potential; cVEMP (or cervical VEMP) and oVEMP (or ocular VEMP) have been described. The cVEMP elicits a vestibulocollic reflex whose afferent limb arises from acoustically sensitive cells in the saccule, with signals conducted via the inferior vestibular nerve. cVEMP is a biphasic, short-latency response recorded from the tonically contracted sternocleidomastoid muscle in response to loud auditory clicks or tones. cVEMPs may be diminished or absent in patients with early and late Ménière's disease, vestibular neuritis, benign paroxysmal positional vertigo, and vestibular schwannoma. On the other hand, the threshold for VEMPs may be lower in cases of superior canal dehiscence, other inner ear dehiscence, and perilymphatic fistula. The oVEMP, in contrast, is a response involving the utricle primarily and superior vestibular nerve. The oVEMP excitatory response is recorded from the extraocular muscle. The oVEMP is abnormal in superior vestibular neuritis.

Imaging Studies The choice of radiologic tests is largely determined by whether the goal is to evaluate the bony anatomy of the external, middle, and inner ear or to image the auditory nerve and brain. Axial and coronal CT of the temporal bone with fine 0.3-mm cuts is ideal for determining the caliber of the external auditory canal, integrity of the ossicular chain, and presence of middle ear or mastoid disease; it can also detect inner ear malformations. CT is also ideal for the detection of bone erosion with chronic otitis media and cholesteatoma. Pöschl reformatting in the plane of the superior semicircular canal is required for the identification of dehiscence or absence of bone over the superior semicircular canal. MRI is superior to CT for imaging of retrocochlear pathology such as vestibular schwannoma, meningioma, other lesions of the cerebellopontine angle, demyelinating lesions of the brainstem, and brain tumors. Both CT and MRI are equally capable of identifying inner ear malformations and assessing cochlear patency for preoperative evaluation of patients for cochlear implantation.

TREATMENT

Disorders of the Sense of Hearing

In general, conductive hearing losses are amenable to surgical correction, whereas sensorineural hearing losses are usually managed medically. Atresia of the ear canal can be surgically repaired, often with significant improvement in hearing. Alternatively, the conductive hearing loss associated with atresia can be addressed with a bone-anchored hearing aid (BAHA). Tympanic membrane perforations due to chronic otitis media or trauma can be repaired with an outpatient tympanoplasty. Likewise, conductive hearing loss associated with otosclerosis can be treated by stapedectomy, which is successful in >95% of cases. Tympanostomy tubes allow the prompt return of normal hearing in individuals with middle ear effusions. Hearing aids are effective and well tolerated in patients with conductive hearing losses.

Patients with mild, moderate, and severe sensorineural hearing losses are regularly rehabilitated with hearing aids of varying configuration and strength. Hearing aids have been improved to provide greater fidelity and have been miniaturized. The current generation of hearing aids can be placed entirely within the ear canal, thus reducing any stigma associated with their use. In general, the more severe the hearing impairment, the larger the hearing aid required for auditory rehabilitation. Digital hearing aids lend themselves to individual programming, and multiple and directional microphones at the ear level may be helpful in noisy surroundings. Because all hearing aids amplify noise as well as speech, the only absolute solution to the problem of noise is to place the microphone closer to the speaker than the noise source. This arrangement is not possible with a self-contained, cosmetically acceptable device. A significant limitation of rehabilitation with a hearing aid is that although it is able to enhance detection of sound with amplification, it cannot restore clarity of hearing that is lost with presbycusis.

The cost of a single hearing aid (~$2300 US) is a significant obstacle for many hearing-impaired individuals and usually bilateral amplification is recommended. To reduce cost and spur innovation, efforts are underway to create a new category for "basic" hearing

aids that could be sold over-the-counter, similar to some eyeglasses and contact lenses. By reducing the cost of hearing aids to consumers, promoting innovation, and increasing competition, this new class of devices could fundamentally change the way hearing rehabilitation is delivered.

Patients with unilateral deafness have difficulty with sound localization and reduced clarity of hearing in background noise. They may benefit from a contralateral routing of signal (CROS) hearing aid in which a microphone is placed on the hearing-impaired side, and the sound is transmitted to the receiver placed on the contralateral ear. The same result may be obtained with a BAHA, in which a hearing aid clamps to a screw integrated into the skull on the hearing-impaired side. Like the CROS hearing aid, the BAHA transfers the acoustic signal to the contralateral hearing ear, but it does so by vibrating the skull. Patients with profound deafness on one side and some hearing loss in the better ear are candidates for a BICROS hearing aid; it differs from the CROS hearing aid in that the patient wears a hearing aid, and not simply a receiver, in the better ear. Unfortunately, while CROS and BAHA devices provide benefit, they do not restore hearing in the deaf ear. Only cochlear implants can restore hearing (see below). Increasingly, cochlear implants are being investigated for the treatment of patients with single-sided deafness; early reports show great promise in not only restoring hearing and reducing tinnitus, but also improving sound localization and performance in background noise.

In many situations, including lectures and the theater, hearing-impaired persons benefit from assistive devices that are based on the principle of having the speaker closer to the microphone than any source of noise. Assistive devices include infrared and frequency-modulated (FM) transmission as well as an electromagnetic loop around the room for transmission to the individual's hearing aid. Hearing aids with telecoils can also be used with properly equipped telephones in the same way.

In the event that the hearing aid provides inadequate rehabilitation, cochlear implants may be appropriate **(Fig. 30-4)**. Criteria for implantation include severe to profound hearing loss with open-set sentence cognition of ≤40% under best-aided conditions. Worldwide, >600,000 hearing-impaired individuals have received cochlear implants. Cochlear implants are neural prostheses that convert sound energy to electrical energy and can be used to stimulate the auditory division of the eighth nerve directly. In most cases of profound hearing impairment, the auditory hair cells are lost but the ganglionic cells of the auditory division of the eighth nerve are preserved. Cochlear implants consist of electrodes that are inserted into the cochlea through the round window, speech processors that extract acoustical elements of speech for conversion to electrical currents, and a means of transmitting the electrical energy through the skin. Patients with implants experience sound that helps with speech reading, allows open-set word recognition, and helps in modulating the person's own voice. Usually, within the first 3–6 months after implantation, adult patients can understand speech without visual cues. With the current generation of multichannel cochlear implants, nearly 75% of patients are able to converse on the telephone. Bilateral cochlear implantations are increasingly being performed, especially in children; these patients perform better in background noise, have better sound localization, and are less fatigued by the "work" compared to monaural hearing.

The first hybrid cochlear implant for the treatment of high-frequency hearing loss has now been approved by the U.S. Food and Drug Administration. Patients with presbyacusis typically have normal low-frequency hearing, while suffering from high-frequency hearing loss associated with loss of clarity that cannot always be adequately rehabilitated with a hearing aid. However, these patients are not candidates for conventional cochlear implants because they have too much residual hearing. The hybrid implant has been specifically designed for this patient population; it has a shorter electrode than a conventional cochlear implant and can be introduced into the cochlea atraumatically, thus preserving low-frequency hearing. Individuals with a hybrid implant use their own natural low-frequency

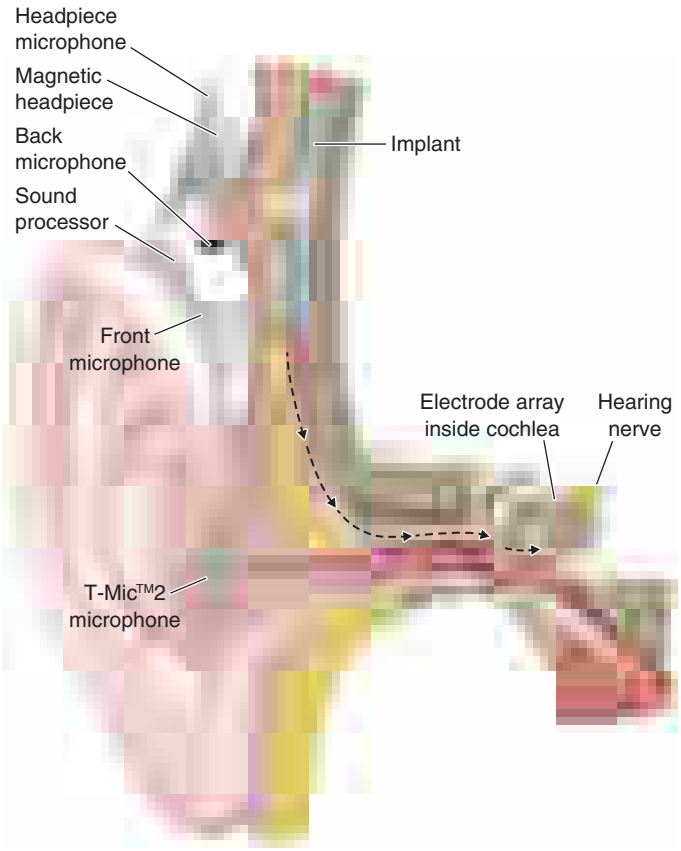

FIGURE 30-4 A cochlear implant is composed of an external microphone and speech processor worn on the ear and a receiver implanted underneath the temporalis muscle. The internal receiver is attached to an electrode that is placed surgically in the cochlea.

"acoustic" hearing and rely on the implant for providing "electrical" high-frequency hearing. Patients who have received the hybrid implant perform better on speech discrimination tests in both quiet and noisy backgrounds.

For individuals who have had both eighth nerves destroyed by trauma or bilateral vestibular schwannomas (e.g., neurofibromatosis type 2), brainstem auditory implants placed near the cochlear nucleus may provide auditory rehabilitation. Currently, brainstem implants provide sound awareness but unfortunately speech understanding remains elusive.

Tinnitus often accompanies hearing loss. As for background noise, tinnitus can degrade speech comprehension in individuals with hearing impairment. Patients with tinnitus should be advised to minimize caffeine ingestion, avoid high dosage of nonsteroidal anti-inflammatory drugs (NSAIDs), and reduce stress. Therapy for tinnitus is usually directed toward minimizing the appreciation of tinnitus. Relief of the tinnitus may be obtained by masking it with background music. Hearing aids are also helpful in tinnitus suppression, as are tinnitus maskers, devices that present a sound to the affected ear that is more pleasant to listen to than the tinnitus. The use of a tinnitus masker is often followed by several hours of inhibition of the tinnitus. Antidepressants have also been shown to be beneficial in helping patients cope with tinnitus.

Hard-of-hearing individuals often benefit from a reduction in unnecessary noise in the environment (e.g., radio or television) to enhance the signal-to-noise ratio. Speech comprehension is aided by lip reading; therefore, the impaired listener should be seated so that the face of the speaker is well illuminated and easily seen. Although speech should be in a loud, clear voice, one should be aware that in sensorineural hearing losses in general and in hard-of-hearing elderly in particular, recruitment (abnormal perception of loud sounds) may be troublesome. Above all, optimal communication cannot take place without both parties giving it their full and undivided attention.

TABLE 30-4 Decibel (Loudness) Level of Common Environmental Noise

SOURCE	DECIBEL (dB)
Weakest sound heard	0
Whisper	30
Normal conversation	55–65
City traffic inside car	85
OSHA Monitoring Requirement Begins	**90**
Jackhammer	95
Subway train at 200 ft	95
Power mower	107
Power saw	110
Painful Sound	**125**
Jet engine at 100 feet	140
12-gauge shotgun blast	165
Loudest sound that can occur	194

Abbreviation: OSHA, Occupational Safety and Health Administration.

PREVENTION

Conductive hearing losses may be prevented by prompt antibiotic therapy of adequate duration for AOM and by ventilation of the middle ear with tympanostomy tubes in middle ear effusions lasting ≥12 weeks. Loss of vestibular function and deafness due to aminoglycoside antibiotics can largely be prevented by careful monitoring of serum peak and trough levels.

Some 10 million Americans have noise-induced hearing loss, and 20 million are exposed to hazardous noise in their employment. Noise-induced hearing loss can be prevented by avoidance of exposure to loud noise or by regular use of ear plugs or fluid-filled ear muffs to attenuate intense sound. Table 30-4 lists loudness levels for a variety of environmental sounds. High-risk activities for noise-induced hearing loss include use of electrical equipment for wood and metal working and target practice or hunting with small firearms. All internal-combustion and electric engines, including snow and leaf blowers, snowmobiles, outboard motors, and chainsaws, require protection of the user with hearing protectors. Virtually all noise-induced hearing loss is preventable through education, which should begin before the teenage years. Programs for conservation of hearing in the workplace are required by the Occupational Safety and Health Administration (OSHA) whenever the exposure over an 8-h period averages 85 dB. OSHA mandates that workers in such noisy environments have hearing monitoring and protection programs that include a preemployment screen, an annual audiologic assessment, and the mandatory use of hearing protectors. Exposure to loud sounds above 85 dB in the work environment is restricted by OSHA, with halving of allowed exposure time for each increment of 5 dB above this threshold; for example, exposure to 90 dB is permitted for 8 h; 95 dB for 4 h, and 100 dB for 2 h (Table 30-5).

TABLE 30-5 OSHA Daily Permissible Noise Level Exposure

SOUND LEVEL (dB)	DURATION PER DAY (h)
90	8
92	6
95	4
97	3
100	2
102	1.5
105	1
110	0.5
115	≤0.25

Note: Exposure to impulsive or impact noise should not exceed 140-dB peak sound pressure level.

Source: From *https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=9735*.

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31 Sore Throat, Earache, and Upper Respiratory Symptoms

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Infections of the upper respiratory tract (URIs) have a tremendous impact on public health. They are among the most common reasons for visits to primary care providers, and although the illnesses are typically mild, their high incidence and transmission rates place them among the leading causes of time lost from work or school. Even though a minority (~25%) of cases are caused by bacteria, URIs are the leading diagnoses for which antibiotics are prescribed on an outpatient basis in the United States, often inappropriately. Antibiotics are more often misprescribed in adults than in pediatric populations. The enormous consumption of antibiotics for these illnesses has contributed to the rise in antibiotic resistance among common community-acquired pathogens such as *Streptococcus pneumoniae*—a trend that in itself has an enormous influence on public health and on the individual patient.

Although most URIs are caused by viruses, distinguishing patients with primary viral infection from those with primary bacterial infection is difficult. Signs and symptoms of bacterial and viral URIs are typically indistinguishable. Until consistent, inexpensive, and rapid testing becomes available and is used widely, acute infections will be diagnosed largely on clinical grounds. The judicious use and potential for misuse of antibiotics in this setting pose ongoing challenges.

NONSPECIFIC INFECTIONS OF THE UPPER RESPIRATORY TRACT

Nonspecific URIs are a broadly defined group of disorders that collectively constitute the leading cause of ambulatory care visits in the United States. By definition, nonspecific URIs have no prominent localizing features. They are identified by a variety of descriptive names, including *acute infective rhinitis*, *acute rhinopharyngitis/nasopharyngitis*, *acute coryza*, and *acute nasal catarrh*, as well as by the inclusive label *common cold*.

ETIOLOGY

The large assortment of URI classifications reflects the wide variety of causative infectious agents and the varied manifestations of common pathogens. Nearly all nonspecific URIs are caused by viruses spanning multiple virus families and many antigenic types. For instance, there are at least 100 immunotypes of rhinovirus (Chap. 194), the most common cause of URI (~30–40% of cases); other causes include influenza virus (three immunotypes; Chap. 195) as well as parainfluenza virus (four immunotypes), coronavirus (at least three immunotypes), and adenovirus (47 immunotypes) (Chap. 194). Respiratory syncytial virus (RSV), a well-established pathogen in pediatric populations, is also a recognized cause of significant disease in elderly and immunocompromised individuals. A host of additional viruses, including some viruses not typically associated with URIs (e.g., enteroviruses, rubella virus,

and varicella-zoster virus), account for a small percentage of cases in adults each year. Although new diagnostic modalities (e.g., nasopharyngeal swab for polymerase chain reaction) can assign a viral etiology, there are few specific treatment options, and no pathogen is identified in a substantial proportion of cases. A specific diagnostic workup beyond a clinical diagnosis is generally unnecessary in an otherwise healthy adult.

CLINICAL MANIFESTATIONS

The signs and symptoms of nonspecific URI are similar to those of other URIs but lack a pronounced localization to one particular anatomic location, such as the sinuses, pharynx, or lower airway. Nonspecific URI commonly presents as an acute, mild, and self-limited catarrhal syndrome with a median duration of ~1 week (range, 2–10 days). Signs and symptoms are diverse and frequently variable across patients, even when caused by the same virus. The principal signs and symptoms of nonspecific URI include rhinorrhea (with or without purulence), nasal congestion, cough, and sore throat. Other manifestations, such as fever, malaise, sneezing, lymphadenopathy, and hoarseness, are more variable, with fever more common among infants and young children. This varying presentation may reflect differences in host response as well as in infecting organisms; myalgias and fatigue, for example, sometimes are seen with influenza and parainfluenza infections, whereas conjunctivitis may suggest infection with adenovirus or enterovirus. Cough secondary to upper respiratory inflammation after such an illness frequently lasts 2–3 weeks and can be misinterpreted as an indication of a process that necessitates antibiotic therapy. Findings on physical examination are frequently nonspecific and unimpressive. Between 0.5 and 2% of colds are complicated by secondary bacterial infections (e.g., rhinosinusitis, otitis media, and pneumonia), particularly in higher-risk populations such as infants, elderly persons, and chronically ill or immunosuppressed individuals. Secondary bacterial infections usually are associated with a prolonged course of illness, increased severity of illness, and localization of signs and symptoms, often as a rebound after initial clinical improvement (the "double-dip" sign). Purulent secretions from the nares or throat often are misinterpreted as an indication of bacterial sinusitis or pharyngitis. These secretions, however, can be seen in nonspecific URI and, in the absence of other clinical features, are poor predictors of bacterial infection.

TREATMENT

Nonspecific Upper Respiratory Infections

Antibiotics have no role in the treatment of uncomplicated nonspecific URI, and their misuse facilitates the emergence of antimicrobial resistance; in healthy volunteers, a single course of a commonly prescribed antibiotic like azithromycin can result in macrolide resistance in oral streptococci many months later. In the absence of clinical evidence of bacterial infection, treatment remains entirely symptom based, with use of decongestants and nonsteroidal anti-inflammatory drugs. Clinical trials of zinc, vitamin C, echinacea, and other alternative remedies have revealed no consistent benefit in the treatment of nonspecific URI.

INFECTIONS OF THE SINUS

Rhinosinusitis refers to an inflammatory condition involving the nasal sinuses. Although most cases of sinusitis involve more than one sinus, the maxillary sinus is most commonly involved; next, in order of frequency, are the ethmoid, frontal, and sphenoid sinuses. Each sinus is lined with a respiratory epithelium that produces mucus, which is transported out by ciliary action through the sinus ostium and into the nasal cavity. Normally, mucus does not accumulate in the sinuses, which remain mostly sterile despite their adjacency to the bacterium-filled nasal passages. When the sinus ostia are obstructed or when ciliary clearance is impaired or absent, the secretions can be retained, producing the typical signs and symptoms of sinusitis. As these secretions accumulate with obstruction, they become more susceptible to infection with a variety of pathogens, including viruses, bacteria, and, rarely, fungi. Sinusitis affects a tremendous proportion of the population, accounts for millions of visits to primary care physicians each year, and is the fifth leading diagnosis for which antibiotics are prescribed. It typically is classified by duration of illness (acute vs. chronic); by etiology (infectious vs. noninfectious); and, when infectious, by the offending pathogen type (viral, bacterial, or fungal).

ACUTE RHINOSINUSITIS

Acute rhinosinusitis—defined as sinusitis of <4 weeks' duration—constitutes the vast majority of sinusitis cases. Most cases are diagnosed in the ambulatory care setting and occur primarily as a consequence of a preceding viral URI. Differentiating acute bacterial from viral sinusitis on clinical grounds is difficult. Therefore, it is perhaps not surprising that antibiotics are prescribed frequently (in 85–98% of all cases) for this condition.

Etiology The ostial obstruction in rhinosinusitis can arise from both infectious and noninfectious causes. Noninfectious etiologies include allergic rhinitis (with either mucosal edema or polyp obstruction), barotrauma (e.g., from deep-sea diving or air travel), and exposure to chemical irritants. Obstruction can also occur with nasal and sinus tumors (e.g., squamous cell carcinoma) or granulomatous diseases (e.g., granulomatosis with polyangiitis, rhinoscleroma), and conditions leading to altered mucus content (e.g., cystic fibrosis) can cause sinusitis through impaired mucus clearance. In intensive care units, nasotracheal intubation and nasogastric tubes are major risk factors for nosocomial sinusitis.

Viral rhinosinusitis is far more common than bacterial sinusitis, although relatively few studies have sampled sinus aspirates for the presence of different viruses. In the studies that have done so, the viruses most commonly isolated—both alone and with bacteria—have been rhinovirus, parainfluenza virus, and influenza virus. Bacterial causes of sinusitis have been better described. Among community-acquired cases, *S. pneumoniae* and nontypable *Haemophilus influenzae* are the most common pathogens, accounting for 50–60% of cases. *Moraxella catarrhalis* causes disease in a significant percentage (20%) of children but a lesser percentage of adults. Other streptococcal species and *Staphylococcus aureus* cause only a small percentage of cases, although there is increasing concern about methicillin-resistant *S. aureus* (MRSA) as an emerging cause. It is difficult to assess whether a cultured bacterium represents a true infecting organism, an insufficiently deep sample (which would not be expected to be sterile), or—especially in the case of previous sinus surgeries—a colonizing organism. Anaerobes occasionally are found in association with infections of the roots of premolar teeth that spread to the adjacent maxillary sinuses. The role of atypical organisms like *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in the pathogenesis of acute sinusitis is unclear. Nosocomial cases commonly are associated with bacteria prevalent in the hospital environment, including *S. aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Klebsiella pneumoniae*, and *Enterobacter* species. Often, these infections are polymicrobial and can involve organisms that are highly resistant to numerous antibiotics. Fungi also are established causes of sinusitis, although most acute cases affect immunocompromised patients and represent invasive, life-threatening infections. The best-known example is rhinocerebral mucormycosis caused by fungi of the order Mucorales, which includes *Rhizopus*, *Rhizomucor*, *Mucor*, *Lichtheimia* (formerly *Mycocladus*, formerly *Absidia*), and *Cunninghamella* **(Chap. 213)**. These infections classically occur in diabetic patients with ketoacidosis but can also develop in transplant recipients, patients with hematologic malignancies, and patients receiving chronic glucocorticoid or deferoxamine therapy. Other hyaline molds, such as *Aspergillus* and *Fusarium* species, also are occasional causes of this disease.

Clinical Manifestations Most cases of acute sinusitis present after or in conjunction with a viral URI, and it can be difficult to discriminate the clinical features of one from the other, with timing becoming important in diagnosis (see below). A large proportion of patients with colds have sinus inflammation, although true bacterial sinusitis complicates only 0.2–2% of these viral infections. Common presenting

symptoms of sinusitis include nasal drainage and congestion, facial pain or pressure, and headache. Thick, purulent or discolored nasal discharge is often thought to indicate bacterial sinusitis but also occurs early in viral infections such as the common cold and is not specific to bacterial infection. Other nonspecific manifestations include cough, sneezing, and fever. Tooth pain, most often involving the upper molars, as well as halitosis are occasionally associated with bacterial sinusitis.

In acute sinusitis, sinus pain or pressure often localizes to the involved sinus (particularly the maxillary sinus) and can be worse when the patient bends over or is supine. Although rare, manifestations of advanced sphenoid or ethmoid sinus infection can be profound, including severe frontal or retroorbital pain radiating to the occiput, thrombosis of the cavernous sinus, and signs of orbital cellulitis. Acute focal sinusitis is uncommon but should be considered with severe symptoms involving the maxillary sinus and fever, regardless of illness duration. This condition is typically associated with red, hot, and swollen sinuses that are extremely tender to palpation; is of staphylococcal etiology; and requires emergent debridement and initial IV administration of antibiotics. Similarly, patients with advanced frontal sinusitis can present with a condition known as *Pott's puffy tumor*, with soft-tissue swelling and pitting edema over the frontal bone from a communicating subperiosteal abscess. Life-threatening complications of sinusitis are rare but include meningitis, epidural abscess, and cerebral abscess.

Patients with acute fungal rhinosinusitis (such as mucormycosis; Chap. 213) often present with symptoms related to pressure effects, particularly when the infection has spread to the orbits and cavernous sinus. Signs such as orbital swelling and cellulitis, proptosis, ptosis, and decreased extraocular movement are common, as is retro- or periorbital pain. Nasopharyngeal ulcerations, epistaxis, and headaches are also common, and involvement of cranial nerves V and VII has been described in more advanced cases. Bony erosion may be evident on examination or endoscopy. Often the patient does not appear to be seriously ill despite the rapidly progressive nature of these infections.

Patients with acute nosocomial sinusitis are often critically ill and thus do not manifest the typical clinical features of sinus disease. This diagnosis should be suspected, however, when hospitalized patients with appropriate risk factors (e.g., nasotracheal intubation) develop fever without another apparent cause.

Diagnosis Distinguishing viral from bacterial rhinosinusitis in the ambulatory setting is usually difficult because of the relatively low sensitivity and specificity of the common clinical features. One clinical feature that has been used to help guide diagnostic and therapeutic decision-making is illness duration. Because acute bacterial sinusitis is uncommon in patients whose symptoms have lasted <10 days, expert panels now recommend reserving this diagnosis for patients with "persistent" symptoms (i.e., symptoms lasting >10 days in adults or >10–14 days in children) accompanied by the three cardinal signs of purulent nasal discharge, nasal obstruction, and facial pain (Table 31-1). The fact that, even among patients who meet these criteria, only 40–50% have true bacterial sinusitis prompts some authorities to favor 14 days of symptoms before considering treatment. The use of CT or sinus radiography is not recommended for acute disease, particularly early in the course of illness (i.e., at <10 days) in light of the high prevalence of similar findings among patients with acute viral rhinosinusitis. In the evaluation of persistent, recurrent, or chronic sinusitis, CT of the sinuses becomes the radiographic study of choice.

The clinical history and/or setting often can identify cases of acute anaerobic bacterial sinusitis, acute fungal sinusitis, or sinusitis from noninfectious causes (e.g., allergic rhinosinusitis). In the case of an immunocompromised patient with acute fungal sinus infection, immediate examination by an otolaryngologist is required. In addition to cultures, biopsy specimens from involved areas should be examined by a pathologist for evidence of fungal hyphal elements and tissue invasion. Cases of suspected acute nosocomial sinusitis should be confirmed by sinus CT. Because therapy should target the offending organism, a sinus aspirate for culture and susceptibility testing should be obtained, whenever possible, before the initiation of antimicrobial therapy. As the ability to isolate the sometimes-myriad components of the sinus microbiome is augmented by molecular techniques, the hope is for an even more tailored treatment regimen.

TABLE 31-1 Guidelines for the Diagnosis and Treatment of Acute Bacterial Sinusitis in Adults

DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS[a]
Moderate symptoms (e.g., nasal purulence/congestion or cough) for >10 d ***or*** Severe symptoms of any duration, including unilateral/focal facial swelling or tooth pain	*Initial therapy:* Amoxicillin/clavulanate, 500/125 mg PO tid or 875/125 mg PO bid[b] *Penicillin allergy:* Doxycycline, 100 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg/d PO daily)[c] *Exposure to antibiotics within 30 d or >30% prevalence of penicillin-resistant Streptococcus pneumoniae:* Amoxicillin/clavulanate (extended release), 2000/125 mg PO bid; ***or*** Doxycycline, 100 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)[c] *Recent treatment failure:* Amoxicillin/clavulanate (extended release), 2000 mg PO bid; ***or*** An antipneumococcal fluoroquinolone (e.g., moxifloxacin, 400 mg PO daily)[c]

[a]The duration of therapy is 5–7 days if symptoms improve within the first few days of treatment but can be up to 7–10 days, with appropriate follow-up. Severe disease may warrant IV antibiotics and consideration of hospital admission.
[b]In areas where the prevalence of antibiotic resistance is low, amoxicillin can be considered as initial therapy in patients without recent antibiotic exposure.
[c]Fluoroquinolones carry a risk of tendinitis and neuropathy and should be used only if other options are not reasonable, with consideration of risks and benefits.

TREATMENT

Acute Rhinosinusitis

Most patients with a clinical diagnosis of acute rhinosinusitis improve without antibiotic therapy. The preferred initial approach in patients with mild to moderate symptoms of short duration is therapy aimed at symptom relief and facilitation of sinus drainage, such as with oral and topical decongestants, nasal saline lavage, and—at least in patients with a history of chronic sinusitis or allergies—nasal glucocorticoids. Newer studies have cast doubt on the role of antibiotics and nasal glucocorticoids in acute rhinosinusitis. In one notable double-blind, randomized, placebo-controlled trial, neither antibiotics nor topical glucocorticoids had a significant impact on cure in the study population of patients, the majority of whom had had symptoms for <7 days. Similarly, another high-profile randomized trial comparing antibiotics to placebo in patients with acute rhinosinusitis demonstrated no significant improvement in symptoms by the third day of therapy. Still, antibiotic therapy can be considered for adult patients whose condition does not improve after 10–14 days, and patients with more severe symptoms (regardless of duration) should be treated with antibiotics (Table 31-1). However, watchful waiting remains a viable option in many cases.

Empirical antibiotic therapy for community-acquired sinusitis in adults should consist of the narrowest-spectrum agent active against the most common bacterial pathogens, including *S. pneumoniae* and *H. influenzae*—e.g., amoxicillin/clavulanate (with the decision guided by local rates of β-lactamase-producing *H. influenzae*). No clinical trials support the use of broader-spectrum agents for routine cases of bacterial sinusitis, even in the current era of drug-resistant *S. pneumoniae*. For those patients who do not respond to initial antimicrobial therapy, sinus aspiration and/or lavage by an otolaryngologist should be considered. Antibiotic prophylaxis to prevent episodes of recurrent acute bacterial sinusitis is not recommended.

Surgical intervention and IV antibiotic administration usually are reserved for patients with severe disease or those with intracranial

complications such as abscess and orbital involvement. Immunocompromised patients with acute invasive fungal sinusitis usually require extensive surgical debridement and treatment with IV antifungal agents active against fungal hyphal forms, such as amphotericin B. Specific therapy should be individualized according to the fungal species and its susceptibilities as well as the individual patient's characteristics.

Treatment of nosocomial sinusitis should begin with broad-spectrum antibiotics to cover common and often resistant pathogens such as *S. aureus* and gram-negative bacilli. Therapy then should be tailored to the results of culture and susceptibility testing of sinus aspirates.

CHRONIC SINUSITIS

Chronic sinusitis is characterized by symptoms of sinus inflammation lasting >12 weeks. This illness is most commonly associated with either bacteria or fungi, and clinical cure in most cases is very difficult. Many patients have undergone treatment with repeated courses of antibacterial agents and multiple sinus surgeries, increasing their risk of colonization with antibiotic-resistant pathogens and of surgical complications. These patients often have high rates of morbidity, sometimes over many years.

In *chronic bacterial sinusitis*, infection is thought to be due to the impairment of mucociliary clearance from repeated infections rather than to persistent bacterial infection. The pathogenesis of this condition, however, is poorly understood. The role of biofilms in such chronic infections continues to be explored, including the contribution that low-virulence pathogens may play in this complex, interacting milieu. Although certain conditions (e.g., cystic fibrosis) can predispose patients to chronic bacterial sinusitis, most patients with chronic rhinosinusitis do not have obvious underlying conditions that result in the obstruction of sinus drainage, the impairment of ciliary action, or immune dysfunction. Patients experience constant nasal congestion and sinus pressure, with intermittent periods of greater severity, which may persist for years. CT can be helpful in determining the extent of disease, detecting an underlying anatomic defect or obstructing process (e.g., a polyp), and assessing the response to therapy. Management should involve an otolaryngologist to conduct endoscopic examinations and obtain tissue samples for histologic examination and culture. An endoscopy-derived culture not only has a higher yield but also allows direct visualization for abnormal anatomy.

Chronic fungal sinusitis is a disease of immunocompetent hosts and is usually noninvasive, although slowly progressive invasive disease is sometimes seen. Noninvasive disease, which typically is associated with hyaline molds such as *Aspergillus* species and dematiaceous molds such as *Curvularia* or *Bipolaris* species, can present as a number of different scenarios. In mild, indolent disease, which usually occurs in the setting of repeated failures of antibacterial therapy, only nonspecific mucosal changes may be seen on sinus CT. Although there is some controversy on this point, endoscopic surgery is usually curative in these cases, with no need for antifungal therapy. Another form of disease presents as long-standing, often unilateral symptoms and opacification of a single sinus on imaging studies as a result of a mycetoma (fungus ball) within the sinus. Treatment for this condition also is surgical, although systemic antifungal therapy may be warranted in the rare case in which bony erosion occurs. A third form of disease, known as *allergic fungal sinusitis*, is seen in patients with a history of nasal polyposis and asthma, who often have had multiple sinus surgeries. Patients with this condition produce a thick, eosinophil-laden mucus with the consistency of peanut butter that contains sparse fungal hyphae on histologic examination. These patients often present with pansinusitis.

TREATMENT

Chronic Sinusitis

Treatment of chronic bacterial sinusitis can be challenging and consists primarily of repeated culture-guided courses of antibiotics, sometimes for 3–4 weeks or longer at a time; administration of intranasal glucocorticoids; and mechanical irrigation of the sinus with sterile saline solution. When this management approach fails, sinus surgery may be indicated and sometimes provides significant, albeit short-term, alleviation. Treatment of chronic fungal sinusitis consists of surgical removal of impacted mucus. Recurrence, unfortunately, is common.

INFECTIONS OF THE EAR AND MASTOID

Infections of the ear and associated structures can involve both the middle and the external ear, including the skin, cartilage, periosteum, ear canal, and tympanic and mastoid cavities. Both viruses and bacteria are known causes of these infections, some of which result in significant morbidity if not treated appropriately.

INFECTIONS OF EXTERNAL EAR STRUCTURES

Infections involving the structures of the external ear are often difficult to differentiate from noninfectious inflammatory conditions with similar clinical manifestations. Clinicians should consider inflammatory disorders as possible causes of external ear irritation, particularly in the absence of local or regional adenopathy. Aside from the more salient causes of inflammation, such as trauma, insect bite, and overexposure to sunlight or extreme cold, the differential diagnosis should include less common conditions such as autoimmune disorders (e.g., lupus or relapsing polychondritis) and vasculitides (e.g., granulomatosis with polyangiitis).

Auricular Cellulitis Auricular cellulitis is an infection of the skin overlying the external ear and typically follows minor local trauma. It presents as the typical signs and symptoms of cellulitis, with tenderness, erythema, swelling, and warmth of the external ear (particularly the lobule) but without apparent involvement of the ear canal or inner structures. Treatment consists of warm compresses and oral antibiotics such as cephalexin or dicloxacillin that are active against typical skin and soft-tissue pathogens (specifically, *S. aureus* and streptococci). IV antibiotics such as a first-generation cephalosporin (e.g., cefazolin) or a penicillinase-resistant penicillin (e.g., nafcillin) occasionally are needed for more severe cases, with consideration of MRSA if either risk factors or failure of therapy point to this organism.

Perichondritis Perichondritis, an infection of the perichondrium of the auricular cartilage, typically follows local trauma (e.g., piercings, burns, or lacerations). Occasionally, when the infection spreads down to the cartilage of the pinna itself, patients may develop chondritis. The infection may closely resemble auricular cellulitis, with erythema, swelling, and extreme tenderness of the pinna, although the lobule is less often involved in perichondritis. The most common pathogens are *P. aeruginosa* and *S. aureus*, although other gram-negative and gram-positive organisms occasionally are involved. Treatment consists of systemic antibiotics active against both *P. aeruginosa* and *S. aureus*. An antipseudomonal penicillin (e.g., piperacillin) or a combination of a penicillinase-resistant penicillin and an antipseudomonal quinolone (e.g., nafcillin plus ciprofloxacin) is typically used. Incision and drainage may be helpful for culture and for resolution of infection, which often takes weeks. When perichondritis fails to respond to adequate antimicrobial therapy, clinicians should consider a noninfectious inflammatory etiology such as relapsing polychondritis.

Otitis Externa The term *otitis externa* refers to a collection of diseases involving primarily the auditory meatus. Otitis externa usually results from a combination of heat and retained moisture, with desquamation and maceration of the epithelium of the outer ear canal. The disease exists in several forms: localized, diffuse, chronic, and invasive. All forms are predominantly bacterial in origin, with *P. aeruginosa* and *S. aureus* the most common pathogens.

Acute localized otitis externa (*furunculosis*) can develop in the outer third of the ear canal, where skin overlies cartilage and hair follicles are numerous. As in furunculosis elsewhere on the body, *S. aureus* is the usual pathogen, and treatment typically consists of an oral antistaphylococcal penicillin (e.g., dicloxacillin or cephalexin), with incision and drainage in cases of abscess formation.

Acute diffuse otitis externa is also known as *swimmer's ear*, although it can develop in patients who have not recently been swimming. Heat, humidity, and the loss of protective cerumen lead to excessive moisture and elevation of the pH in the ear canal, which in turn lead to skin maceration and irritation. Infection may then follow; the predominant pathogen is *P. aeruginosa*, although other bacteria—and rarely yeasts—have been recovered from patients with this condition. The illness often starts with itching and progresses to severe pain, which is usually elicited by manipulation of the pinna or tragus. The onset of pain is generally accompanied by the development of an erythematous, swollen ear canal, often with scant white, clumpy discharge. Treatment consists of cleansing the canal to remove debris and enhance the activity of topical therapeutic agents—usually hypertonic saline or mixtures of alcohol and acetic acid. Inflammation can also be decreased by adding glucocorticoids to the treatment regimen or by using Burow's solution (aluminum acetate in water). Antibiotics are most effective when given topically. Otic mixtures provide adequate pathogen coverage; these preparations usually combine neomycin with polymyxin, with or without glucocorticoids. Systemic antimicrobial agents typically are reserved for severe disease or infections in immunocompromised hosts.

Chronic otitis externa is caused primarily by repeated local irritation, most commonly arising from persistent drainage from a chronic middle-ear infection. Other causes of repeated irritation, such as insertion of cotton swabs or other foreign objects into the ear canal, can lead to this condition, as can rare chronic infections such as syphilis, tuberculosis, and leprosy. Chronic otitis externa typically presents as erythematous, scaling dermatitis in which the predominant symptom is pruritus rather than pain; this condition must be differentiated from several others that produce a similar clinical picture, such as atopic dermatitis, seborrheic dermatitis, psoriasis, and dermatomycosis. Therapy consists of identifying and treating or removing the offending process, although successful resolution is frequently difficult.

Invasive otitis externa, also known as *malignant* or *necrotizing* otitis externa, is an aggressive and potentially life-threatening disease that occurs predominantly in elderly diabetic patients and other immunocompromised persons. The disease begins in the external canal as a soft-tissue infection that progresses slowly over weeks to months and often is difficult to distinguish from a severe case of chronic otitis externa because of the presence of purulent otorrhea and an erythematous swollen ear and external canal. Severe, deep-seated otalgia, frequently out of proportion to findings on examination, is often noted and can help differentiate invasive from chronic otitis externa. The characteristic finding on examination is granulation tissue in the posteroinferior wall of the external canal, near the junction of bone and cartilage. If left unchecked, the infection can migrate to the base of the skull (resulting in skull-base osteomyelitis) and onward to the meninges and brain, with a high mortality rate. Cranial nerve involvement is seen occasionally, with the facial nerve usually affected first and most often. Thrombosis of the sigmoid sinus can occur if the infection extends to the area. CT, which can reveal osseous erosion of the temporal bone and skull base, can be used to help determine the extent of disease, as can gallium and technetium-99 scintigraphy studies. *P. aeruginosa* is by far the most common offender, although *S. aureus*, *Staphylococcus epidermidis*, *Aspergillus*, *Actinomyces*, and some gram-negative bacteria also have been associated with this disease. In all cases, the external ear canal should be cleansed and a biopsy specimen of the granulation tissue within the canal (or of deeper tissues) obtained for culture of the offending organism. IV antibiotic therapy should be given for a prolonged course (6–8 weeks) and directed specifically toward the recovered pathogen. For *P. aeruginosa*, the regimen typically includes an antipseudomonal penicillin or cephalosporin (e.g., piperacillin or cefepime), sometimes with an aminoglycoside or a fluoroquinolone, the latter of which can even be administered orally given its excellent bioavailability. In addition, antibiotic drops containing an agent active against *Pseudomonas* (e.g., ciprofloxacin) are usually prescribed and are combined with glucocorticoids to reduce inflammation. Cases of invasive *Pseudomonas* otitis externa recognized in the early stages can sometimes be treated with oral and otic fluoroquinolones alone, albeit with close follow-up. Extensive surgical debridement, once an important component of the treatment approach, is now rarely indicated.

In *necrotizing otitis externa*, recurrence is documented up to 20% of the time. Aggressive glycemic control in diabetics is important not only for effective treatment but also for prevention of recurrence. The role of hyperbaric oxygen has not been clearly established.

INFECTIONS OF MIDDLE-EAR STRUCTURES

Otitis media is an inflammatory condition of the middle ear that results from dysfunction of the eustachian tube in association with a number of illnesses, including URIs and chronic rhinosinusitis. The inflammatory response in these conditions leads to the development of a sterile transudate within the middle-ear and mastoid cavities. Infection may occur if bacteria or viruses from the nasopharynx contaminate this fluid, producing an acute (or sometimes chronic) illness.

Acute Otitis Media Acute otitis media results when pathogens from the nasopharynx are introduced into the inflammatory fluid collected in the middle ear (e.g., by nose blowing during a URI). Pathogenic proliferation in this space leads to the development of the typical signs and symptoms of acute middle-ear infection. The diagnosis of acute otitis media requires the demonstration of fluid in the middle ear (with tympanic membrane [TM] immobility) and the accompanying signs or symptoms of local or systemic illness **(Table 31-2)**.

ETIOLOGY Acute otitis media typically follows a viral URI. The causative viruses (most commonly RSV, influenza virus, rhinovirus, and enterovirus) can themselves cause subsequent acute otitis media; more often, they predispose the patient to bacterial otitis media. Studies using tympanocentesis have consistently found *S. pneumoniae* to be the most important bacterial cause, isolated in up to 35% of cases. *H. influenzae* (nontypable strains) and *M. catarrhalis* also are common bacterial causes of acute otitis media, and concern is increasing with MRSA as an emerging etiologic agent. Viruses, such as those mentioned above, have been recovered either alone or with bacteria in 17–40% of cases.

CLINICAL MANIFESTATIONS Fluid in the middle ear is typically demonstrated or confirmed with pneumatic otoscopy. In the absence of fluid, the TM moves visibly with the application of positive and negative pressure, but this movement is dampened when fluid is present. With bacterial infection, the TM can also be erythematous, bulging, or retracted and occasionally can perforate spontaneously. The signs and symptoms accompanying infection can be local or systemic, including otalgia, otorrhea, diminished hearing, and fever. Erythema of the TM is often evident but is nonspecific as it frequently is seen in association with inflammation of the upper respiratory mucosa. Other signs and symptoms occasionally reported include vertigo, nystagmus, and tinnitus.

TREATMENT

Acute Otitis Media

There has been considerable debate on the usefulness of antibiotics for the treatment of acute otitis media. A higher proportion of treated than untreated patients are free of illness 3–5 days after diagnosis. The difficulty of predicting which patients will benefit from antibiotic therapy has led to different approaches. In the Netherlands, for instance, physicians typically manage acute otitis media with initial observation, administering anti-inflammatory agents for aggressive pain management and reserving antibiotics for high-risk patients, patients with complicated disease, or patients whose condition does not improve after 48–72 h. In contrast, many experts in the United States continue to recommend antibiotic therapy for children <6 months old in light of the higher frequency of secondary complications in this young and functionally immunocompromised population. However, observation without antimicrobial therapy is now the recommended option in the United States for acute otitis media in children >2 years of age and for mild to moderate disease without middle-ear effusion in children 6 months to 2 years of age. Treatment

TABLE 31-2 Guidelines for the Diagnosis and Treatment of Acute Otitis Media

ILLNESS SEVERITY	DIAGNOSTIC CRITERIA	TREATMENT RECOMMENDATIONS
Mild to moderate	>2 yrs *or* 6 mo to 2 yrs without middle-ear effusion	*Observation alone* (deferring antibiotic therapy for 48–72 h and limiting management to symptom relief)
	<6 mo; ***or*** 6 mo to 2 yrs with middle-ear effusion (fluid in the middle ear, evidenced by decreased TM mobility, air/fluid level behind TM, bulging TM, purulent otorrhea) *and* acute onset of signs and symptoms of middle-ear inflammation, including fever, otalgia, decreased hearing, tinnitus, vertigo, erythematous TM; ***or*** >2 yrs with bilateral disease, TM perforation, high fever, immunocompromise, emesis	*Initial therapy*[a]: Amoxicillin, 80–90 mg/kg qd (up to 2 g) PO in divided doses (bid or tid); ***or*** Cefdinir, 14 mg/kg qd PO in 1 dose or divided doses (bid); ***or*** Cefuroxime, 30 mg/kg qd PO in divided doses (bid); ***or*** Azithromycin, 10 mg/kg qd PO on day 1 followed by 5 mg/kg qd PO for 4 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b]: Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); ***or*** Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; ***or*** Clindamycin, 30–40 mg/kg qd PO in divided doses (tid)
Severe	As above, with temperature ≥39.0°C (≥102°F); ***or*** Moderate to severe otalgia	*Initial therapy*[a]: Amoxicillin, 90 mg/kg qd (up to 2 g) PO in divided doses (bid), plus clavulanate, 6.4 mg/kg qd PO in divided doses (bid); ***or*** Ceftriaxone, 50 mg/kg IV/IM qd for 3 d *Exposure to antibiotics within 30 d or recent treatment failure*[a,b]: Ceftriaxone, 50 mg/kg IV/IM qd for 3 d; ***or*** Clindamycin, 30–40 mg/kg qd PO in divided doses (tid); ***or*** Consider tympanocentesis with culture

[a]Duration (unless otherwise specified): 10 days for patients <6 years old and patients with severe disease; 5–7 days (with consideration of observation only in previously healthy individuals with mild disease) for patients ≥6 years old. [b]Failure to improve and/or clinical worsening after 48–72 h of observation or treatment.

Abbreviation: TM, tympanic membrane.

Source: American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media, 2004.

is typically indicated for patients <6 months old; for children 6 months to 2 years old who have middle-ear effusion and signs/symptoms of middle-ear inflammation; for all patients >2 years old who have bilateral disease, TM perforation, immunocompromise, or emesis; and for any patient who has severe symptoms, including a fever ≥39°C or moderate to severe otalgia (Table 31-2).

Because most studies of the etiologic agents of acute otitis media consistently document similar pathogen profiles, therapy is generally empirical except in those few cases in which tympanocentesis is warranted—e.g., cases refractory to therapy and cases in patients who are severely ill or immunodeficient. Despite resistance to penicillin and amoxicillin in roughly one-quarter of *S. pneumoniae* isolates, one-third of *H. influenzae* isolates, and nearly all *M. catarrhalis* isolates, outcome studies continue to find that amoxicillin is as successful as any other agent, and it remains the drug of first choice in recommendations from multiple sources (Table 31-2). Therapy for uncomplicated acute otitis media typically is administered for 5–7 days to patients aged ≥6 years; longer courses (e.g., 10 days) should be reserved for immunocompromised patients or patients with severe disease, in whom short-course therapy may be inadequate.

A switch in regimen is recommended if there is no clinical improvement by the third day of therapy, given the possibility of infection with a β-lactamase-producing strain of *H. influenzae* or *M. catarrhalis* or with a strain of penicillin-resistant *S. pneumoniae*. Decongestants and antihistamines are frequently used as adjunctive agents to reduce congestion and relieve obstruction of the eustachian tube, but clinical trials have yielded no significant evidence of benefit with either class of agents.

Recurrent Acute Otitis Media Recurrent acute otitis media (more than three episodes within 6 months or four episodes within 12 months) generally is due to relapse or reinfection, although data indicate that the majority of early recurrences are new infections. In general, the same pathogens responsible for acute otitis media cause recurrent disease; even so, the recommended treatment consists of antibiotics active against β-lactamase-producing organisms. Antibiotic prophylaxis (e.g., with amoxicillin) can reduce recurrences in patients with recurrent acute otitis media by an average of one episode per year, which benefit is small compared with the high likelihood of colonization with antibiotic-resistant pathogens. Other approaches, including placement of tympanostomy tubes, adenoidectomy, and tonsillectomy plus adenoidectomy, are of questionable overall value in light of the relatively small benefit compared with the potential for complications.

Serous Otitis Media In serous otitis media (otitis media with effusion), fluid is present in the middle ear for an extended period in the absence of signs and symptoms of infection. In general, acute effusions are self-limited; most resolve in 2–4 weeks. In some cases, however (in particular after an episode of acute otitis media), effusions can persist for months. These chronic effusions are often associated with significant hearing loss in the affected ear. The great majority of cases of otitis media with effusion resolve spontaneously within 3 months without antibiotic therapy. Antibiotic therapy or myringotomy with insertion of tympanostomy tubes typically is reserved for patients in whom bilateral effusion (1) has persisted for at least 3 months and (2) is associated with significant bilateral hearing loss. With this conservative approach and the application of strict diagnostic criteria for acute otitis media and otitis media with effusion, an estimated 6–8 million courses of antibiotics could be avoided each year in the United States.

Chronic Otitis Media Chronic suppurative otitis media is characterized by persistent or recurrent purulent otorrhea in the setting of TM perforation. Usually, there is also some degree of conductive hearing loss. This condition can be categorized as active or inactive. Inactive disease is characterized by a central perforation of the TM, which allows drainage of purulent fluid from the middle ear. When the perforation is more peripheral, squamous epithelium from the auditory canal may invade the middle ear through the perforation, forming a mass of keratinaceous debris (*cholesteatoma*) at the site of invasion. This mass can enlarge and has the potential to erode bone and promote further infection, which can lead to meningitis, brain abscess, or paralysis of cranial nerve VII. Treatment of chronic active otitis media is surgical; mastoidectomy, myringoplasty, and tympanoplasty can be performed as outpatient surgical procedures, with an overall success rate of ~80%. Chronic inactive otitis media is more difficult to cure, usually requiring repeated courses of topical antibiotic drops during periods of drainage. Systemic antibiotics may offer better cure rates, but their role in the treatment of this condition remains unclear.

Mastoiditis Acute mastoiditis was relatively common among children before the introduction of antibiotics. Because the mastoid air

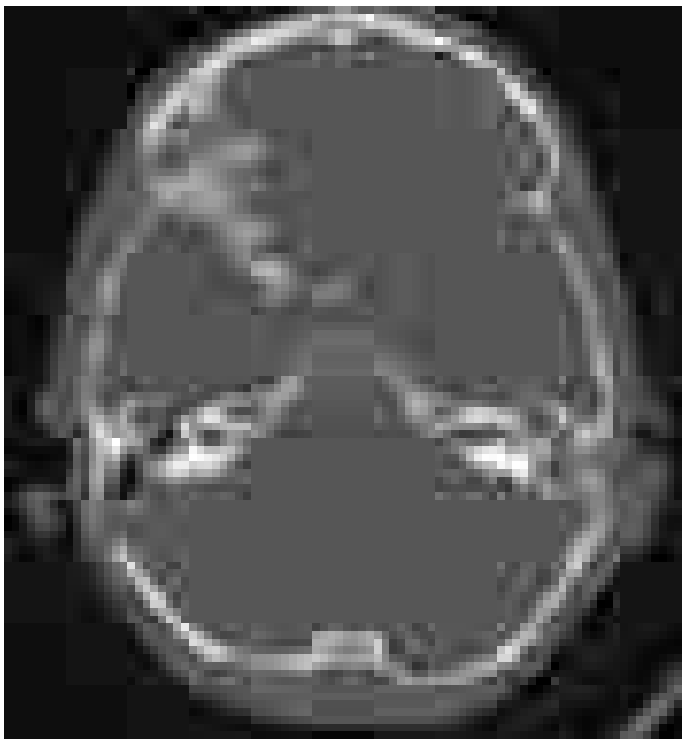


FIGURE 31-1 Acute mastoiditis. Axial CT image shows an acute fluid collection within the mastoid air cells on the left.

cells connect with the middle ear, the process of fluid collection and infection is usually the same in the mastoid as in the middle ear. Early and frequent treatment of acute otitis media is most likely the reason that the incidence of acute mastoiditis has declined to only 1.2–2.0 cases per 100,000 person-years in countries with high prescribing rates for acute otitis media.

In countries such as the Netherlands, where antibiotics are used sparingly for acute otitis media, the incidence rate of acute mastoiditis is roughly twice that in countries like the United States. However, neighboring Denmark has a rate of acute mastoiditis similar to that in the Netherlands but an antibiotic-prescribing rate for acute otitis media more similar to that in the United States.

In typical acute mastoiditis, purulent exudate collects in the mastoid air cells **(Fig. 31-1)**, producing pressure that may result in erosion of the surrounding bone and formation of abscess-like cavities that are usually evident on CT. Patients typically present with pain, erythema, and swelling of the mastoid process along with displacement of the pinna, usually in conjunction with the typical signs and symptoms of acute middle-ear infection. Rarely, patients can develop severe complications if the infection tracks under the periosteum of the temporal bone to cause a subperiosteal abscess, erodes through the mastoid tip to cause a deep neck abscess, or extends posteriorly to cause septic thrombosis of the lateral sinus.

Purulent fluid should be cultured whenever possible to help guide antimicrobial therapy. Initial empirical therapy usually is directed against the typical organisms associated with acute otitis media, such as *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Patients with more severe or prolonged courses of illness should be treated for infection with *S. aureus* and gram-negative bacilli (including *Pseudomonas*). Broad-spectrum empirical therapy should be narrowed once culture results become available. Most patients can be treated conservatively with IV antibiotics; surgery (cortical mastoidectomy) is reserved for complicated cases and those in which conservative treatment has failed.

INFECTIONS OF THE PHARYNX AND ORAL CAVITY

Oropharyngeal infections range from mild, self-limited viral illnesses to serious, life-threatening bacterial infections. The most common presenting symptom is sore throat—one of the most common reasons for ambulatory care visits by both adults and children. Although sore throat is a symptom in many noninfectious illnesses as well, the overwhelming majority of patients with a new sore throat have acute pharyngitis of viral or bacterial etiology.

ACUTE PHARYNGITIS

Millions of visits to primary care providers each year are for sore throat; the majority of cases of acute pharyngitis are caused by typical respiratory viruses. The most important source of concern is infection with group A β-hemolytic *Streptococcus* (*S. pyogenes*), which is associated with acute glomerulonephritis and acute rheumatic fever. The risk of rheumatic fever can be reduced by timely penicillin therapy.

Etiology A wide variety of organisms cause acute pharyngitis. The relative importance of the different pathogens can only be estimated, since a significant proportion of cases (~30%) have no identified cause. Together, respiratory viruses are the most common identifiable cause of acute pharyngitis, with rhinoviruses and coronaviruses accounting for large proportions of cases (~20% and at least 5%, respectively). Influenza virus, parainfluenza virus, and adenovirus also account for a measurable share of cases, with the former two more seasonal and the latter as part of the more clinically severe syndrome of pharyngoconjunctival fever. Other important but less common viral causes include herpes simplex virus (HSV) types 1 and 2, coxsackievirus A, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Acute HIV infection can present as acute pharyngitis and should always be considered in at-risk populations.

Acute bacterial pharyngitis is typically caused by *S. pyogenes*, which accounts for ~5–15% of all cases of acute pharyngitis in adults; rates vary with the season and with utilization of the health care system. Group A streptococcal pharyngitis is primarily a disease of children aged 5–15 years; it is uncommon among children <3 years old, as is rheumatic fever. Streptococci of groups C and G account for a minority of cases, although these serogroups are nonrheumatogenic. *Fusobacterium necrophorum* has been increasingly recognized as a cause of pharyngitis in adolescents and young adults and, when sought, is isolated nearly as often as group A streptococci. This organism is important because of the rare but life-threatening *Lemierre disease*, which is generally associated with *F. necrophorum* and is usually preceded by pharyngitis (see "Oral Infections," below). The remaining bacterial causes of acute pharyngitis are seen infrequently (<1% of cases each) but should be considered in appropriate exposure groups because of the severity of illness if left untreated; these etiologic agents include *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Yersinia enterocolitica*, and *Treponema pallidum* (in secondary syphilis). Anaerobic bacteria also can cause acute pharyngitis (*Vincent angina*) and can contribute to more serious polymicrobial infections, such as peritonsillar or retropharyngeal abscesses (see below). Atypical organisms such as *M. pneumoniae* and *C. pneumoniae* have been recovered from patients with acute pharyngitis; whether these agents are commensals or causes of acute infection is debatable.

Clinical Manifestations Although the signs and symptoms accompanying acute pharyngitis are not reliable predictors of the etiologic agent, the clinical presentation occasionally suggests one etiology over another. Acute pharyngitis due to respiratory viruses such as rhinovirus or coronavirus usually is not severe and typically is associated with a constellation of coryzal symptoms better characterized as nonspecific URI. Findings on physical examination are uncommon; fever is rare, and tender cervical adenopathy and pharyngeal exudates are not seen. In contrast, acute pharyngitis from influenza virus can be severe and is much more likely to be associated with fever as well as with myalgias, headache, and cough. The presentation of pharyngoconjunctival fever due to adenovirus infection is similar. Since pharyngeal exudate may be present on examination, this condition can be difficult to differentiate from streptococcal pharyngitis. However, adenoviral pharyngitis is distinguished by the presence of conjunctivitis in one-third to one-half of patients. Acute pharyngitis from primary HSV infection can also mimic streptococcal pharyngitis in some cases, with

pharyngeal inflammation and exudate, but the presence of vesicles and shallow ulcers on the palate can help differentiate the two diseases. This HSV syndrome is distinct from pharyngitis caused by coxsackievirus (*herpangina*), which is associated with small vesicles that develop on the soft palate and uvula and then rupture to form shallow white ulcers. Acute pharyngitis coupled with fever, fatigue, generalized lymphadenopathy, and (on occasion) splenomegaly is characteristic of infectious mononucleosis due to EBV or CMV. Acute primary infection with HIV is frequently associated with fever and acute pharyngitis as well as with myalgias, arthralgias, malaise, and occasionally a nonpruritic maculopapular rash, which may be followed by lymphadenopathy and mucosal ulcerations without exudate.

The clinical features of acute pharyngitis caused by streptococci of groups A, C, and G are similar, ranging from a relatively mild illness without many accompanying symptoms to clinically severe cases with profound pharyngeal pain, fever, chills, and abdominal pain. A hyperemic pharyngeal membrane with tonsillar hypertrophy and exudate is usually seen, along with tender anterior cervical adenopathy. Coryzal manifestations, including cough, are typically absent; when present, they suggest a viral etiology. Strains of *S. pyogenes* that generate erythrogenic toxin can also produce scarlet fever characterized by an erythematous rash and strawberry tongue. The other types of acute bacterial pharyngitis (e.g., gonococcal, diphtherial, and yersinial) often present as exudative pharyngitis with or without other clinical features. Their etiologies are often suggested only by the clinical history.

Diagnosis The primary goal of diagnostic testing is to separate acute streptococcal pharyngitis from pharyngitis of other etiologies (particularly viral) so that antibiotics can be prescribed more efficiently for patients in whom they may be beneficial. The most appropriate standard for the diagnosis of streptococcal pharyngitis, however, has not been established definitively. Throat swab culture is generally regarded as the most appropriate but cannot distinguish between infection and colonization and requires 24–48 h to yield results that vary with technique and culture conditions. Rapid antigen-detection tests offer good specificity (>90%) but lower sensitivity when implemented in routine practice. Sensitivity has also been shown to vary across the clinical spectrum of disease (65–90%). Several clinical prediction systems **(Fig. 31-2)** can increase the sensitivity of rapid antigen-detection tests to >90% in controlled settings. Since the sensitivities achieved in routine clinical practice are often lower, several medical and professional societies continue to recommend that all negative rapid antigen-detection tests in children be confirmed by a throat culture to limit transmission and complications of illness caused by group A streptococci. The Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the American Academy of Family Physicians do not recommend backup culture when adults have negative results from a highly sensitive rapid antigen-detection test, however, because of the lower prevalence and smaller benefit in this age group.

Cultures and rapid diagnostic tests for other causes of acute pharyngitis, such as influenza virus, adenovirus, HSV, EBV, CMV, and *M. pneumoniae*, are available in many locations and can be used when these pathogens are suspected. The diagnosis of acute EBV infection depends primarily on the detection of antibodies to the virus with a heterophile agglutination assay (monospot slide test) or enzyme-linked immunosorbent assay. Testing for HIV, ideally through a combination antigen/antibody method, should be performed when acute primary HIV infection is suspected. If other bacterial causes are suspected (particularly *N. gonorrhoeae*, *C. diphtheriae*, or *Y. enterocolitica*), specific cultures should be requested since these organisms may be missed on routine throat swab culture.

TREATMENT

Pharyngitis

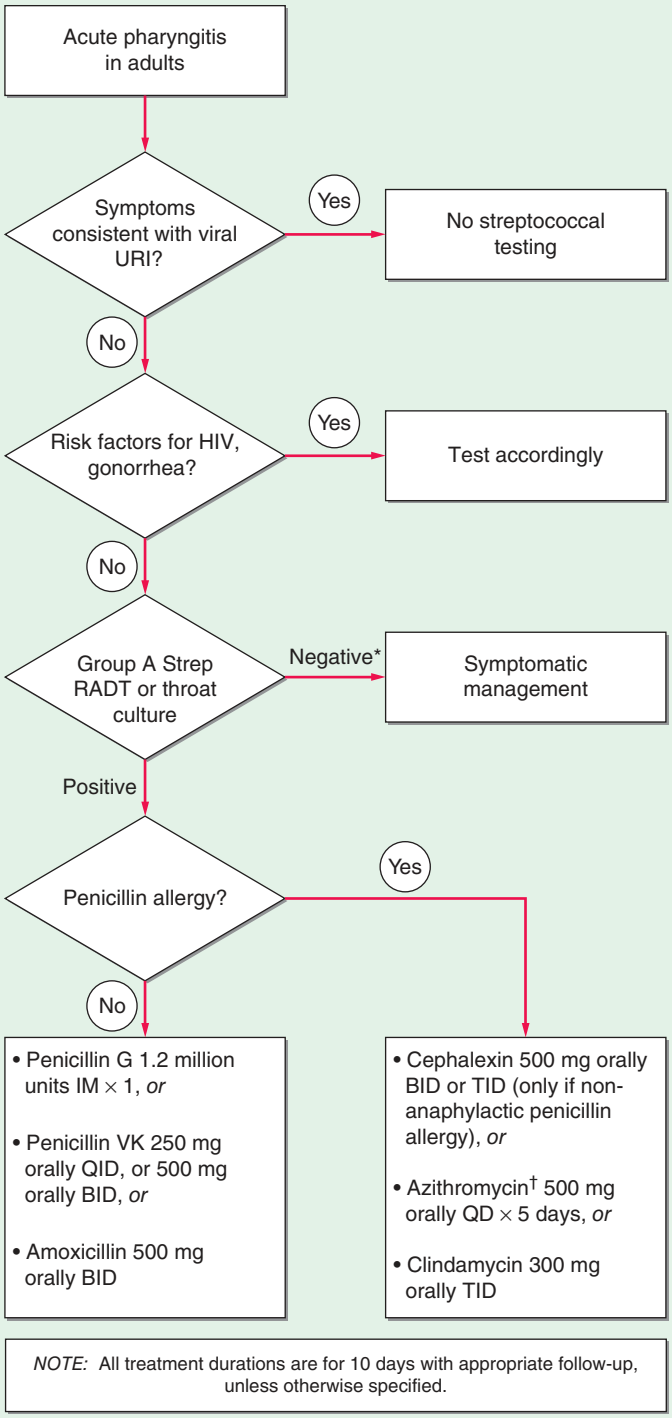
Antibiotic treatment of pharyngitis due to *S. pyogenes* confers numerous benefits, including a decrease in the risk of rheumatic fever—the primary focus of treatment. The magnitude of this benefit is fairly small, since rheumatic fever is now a rare disease, even among untreated patients. Nevertheless, when therapy is started within 48 h of illness onset, symptom duration is decreased modestly. An additional benefit of therapy is the potential to reduce the transmission of streptococcal pharyngitis, particularly in areas of overcrowding or close contact. Antibiotic therapy for acute pharyngitis is therefore recommended in cases in which *S. pyogenes* is confirmed as the etiologic agent by rapid antigen-detection test or throat swab culture. Otherwise, antibiotics should be given in routine cases only when another bacterial cause has been identified. Effective therapy for streptococcal pharyngitis consists of either a single dose of IM benzathine penicillin or a full 10-day course of oral penicillin (Fig. 31-2).

Azithromycin can be used in place of penicillin, although its potential utility is waning and its use in some parts of the world (particularly Europe) is prohibited as a result of resistance among *S. pyogenes* strains. Broader-spectrum (and often more expensive) antibiotics also are active against streptococci but offer no greater efficacy than the agents mentioned above. Testing for cure is unnecessary and may reveal only chronic colonization. There is no evidence to support antibiotic treatment of group C or G streptococcal pharyngitis or pharyngitis in which mycoplasmas or chlamydiae have been recovered. Cultures can be of benefit because *F. necrophorum*, an increasingly common cause of bacterial pharyngitis in young adults, is not covered by macrolide therapy. Long-term penicillin prophylaxis (benzathine penicillin G, 1.2 million units IM every 3–4 weeks; or penicillin VK, 250 mg PO twice daily) is indicated for patients at risk of recurrent rheumatic fever in order to prevent what could be catastrophic sequelae of recurrent streptococcal pharyngitis.

Antibiotic shortages, sometimes the result of manufacturing difficulties or delays, natural disasters, and regulatory or other issues, can preclude the use of the optimal antibiotic. These shortages can be regional, national, or international. Communication with pharmacists and the use of antibiotic stewardship teams can help mitigate the effects of shortages, yield recommendations for the use of alternative agents, and prevent delays in treatment that can affect patients' access to antibiotics.

Treatment of viral pharyngitis is entirely symptom-based except in infection with influenza virus or HSV. For influenza, the armamentarium includes the adamantanes amantadine and rimantadine and the neuraminidase inhibitors oseltamivir and zanamivir. Administration of all these agents needs to be started within 48 h of symptom onset to reduce illness duration meaningfully. Among these agents, only oseltamivir and zanamivir are active against both influenza A and influenza B and therefore can be used when local patterns of infection and antiviral resistance are unknown. Oropharyngeal HSV infection sometimes responds to treatment with antiviral agents such as acyclovir, although these drugs are often reserved for immunosuppressed patients.

Complications Although rheumatic fever is the best-known complication of acute streptococcal pharyngitis, the risk of its following acute infection remains quite low. Other complications include acute glomerulonephritis and numerous suppurative conditions, such as peritonsillar abscess (*quinsy*), otitis media, mastoiditis, sinusitis, bacteremia, and pneumonia—all of which occur at low rates. Although antibiotic treatment of acute streptococcal pharyngitis can prevent the development of rheumatic fever, there is no evidence that it can prevent acute glomerulonephritis. Some evidence supports antibiotic use to prevent the suppurative complications of streptococcal pharyngitis, particularly peritonsillar abscess, which can also involve oral anaerobes such as *Fusobacterium*. Abscesses usually are accompanied by severe pharyngeal pain, dysphagia, fever, and dehydration; in addition, medial displacement of the tonsil and lateral displacement of the uvula are often evident on examination. Although early use of IV antibiotics (e.g., clindamycin, penicillin G with metronidazole) may eliminate the need for surgical drainage in some cases, treatment typically involves needle aspiration or incision and drainage.



*Confirmation of a negative rapid antigen-detection test by a throat culture is not required in adults.
†Macrolides do not treat *F. necrophorum*, a cause of pharyngitis in young adults (see text).
Abbreviations: URI, upper respiratory infection; RADT, rapid antigen detection test

FIGURE 31-2 Algorithm for the diagnosis and treatment of acute pharyngitis.

ORAL INFECTIONS

Aside from periodontal diseases such as gingivitis, infections of the oral cavity most commonly involve HSV or *Candida* species. In addition to causing painful cold sores on the lips, HSV can infect the tongue and buccal mucosa, causing the formation of irritating vesicles. Although topical antiviral agents (e.g., acyclovir and penciclovir) can be used externally for cold sores, with possible benefit, oral or IV acyclovir is often needed for primary infections, extensive oral infections, and infections in immunocompromised patients. Oropharyngeal candidiasis (*thrush*) is caused by a variety of *Candida* species, most often *C. albicans*. Thrush occurs predominantly in neonates, immunocompromised patients (especially those with AIDS), and recipients of prolonged antibiotic or glucocorticoid therapy. In addition to sore throat, patients often report a burning tongue or abnormal taste, and physical examination reveals friable white or gray plaques on the gingiva, tongue, and oral mucosa, often with underlying erythema. Treatment, which usually consists of a topical antifungal (nystatin or clotrimazole) or oral fluconazole, is typically successful. In the uncommon cases of fluconazole-refractory thrush that are seen in some patients with HIV/AIDS or in patients with resistant organisms that can sometimes complicate the treatment of recurrent oral candidiasis, other therapeutic options include oral voriconazole, an IV echinocandin (caspofungin, micafungin, or anidulafungin), or amphotericin B deoxycholate, if needed. In these cases, therapy based on culture and susceptibility test results is ideal.

Vincent angina, also known as *acute necrotizing ulcerative gingivitis* or *trench mouth*, is a unique and dramatic form of gingivitis characterized by painful, inflamed gingiva with ulcerations of the interdental papillae that bleed easily. Since oral anaerobes are the cause, patients typically have halitosis and frequently present with fever, malaise, and lymphadenopathy. Treatment consists of debridement and oral administration of penicillin plus metronidazole, with clindamycin or doxycycline alone as an alternative.

Ludwig angina is a rapidly progressive, potentially fulminant form of cellulitis that involves the bilateral sublingual and submandibular spaces and that typically originates from an infected or recently extracted tooth, most commonly a lower second or third molar. Improved dental care has reduced the incidence of this disorder substantially. Infection in these areas leads to dysphagia, odynophagia, and "woody" edema in the sublingual region, forcing the tongue up and back with the potential for airway obstruction. Fever, dysarthria, and drooling also may occur, and patients may speak in a "hot potato" voice. Intubation or tracheostomy may be necessary to secure the airway, as asphyxiation is the most common cause of death. Patients should be admitted to the hospital and closely monitored during treatment with IV antibiotics directed against streptococci and oral anaerobes. Recommended agents include ampicillin/sulbactam, clindamycin, or high-dose penicillin plus metronidazole.

Septic thrombophlebitis of the internal jugular vein (*Lemierre disease*) is a rare anaerobic oropharyngeal infection caused predominantly by *F. necrophorum*. The illness typically starts as a sore throat (most commonly in adolescents and young adults), which may present as exudative tonsillitis or peritonsillar abscess. Infection of the deep pharyngeal tissue allows organisms to drain into the lateral pharyngeal space,

which contains the carotid artery and internal jugular vein. Septic thrombophlebitis of the internal jugular vein can result, with associated pain, dysphagia, and unilateral neck swelling and stiffness. Sepsis usually occurs 3–10 days after the onset of sore throat and is often coupled with metastatic infection to the lung and other distant sites, with pulmonary abscess or empyema. Occasionally, the infection can extend along the carotid sheath and into the posterior mediastinum, resulting in mediastinitis, or it can erode into the carotid artery, with the early sign of repeated small bleeds into the mouth. The mortality rate from these invasive infections can be as high as 50%. Treatment consists of IV antibiotics (clindamycin or ampicillin/sulbactam) and surgical drainage of any purulent collections. The concomitant use of anticoagulants to prevent embolization remains controversial and is not typically advised; both the risks and the benefits of their use must be carefully considered.

INFECTIONS OF THE LARYNX AND EPIGLOTTIS

LARYNGITIS

Laryngitis is defined as any inflammatory process involving the larynx and can be caused by a variety of infectious and noninfectious processes. The vast majority of laryngitis cases seen in clinical practice in developed countries are acute. Acute laryngitis is a common syndrome caused predominantly by the same viruses responsible for many other URIs. In fact, most cases of acute laryngitis occur in the setting of a viral URI.

Etiology Nearly all major respiratory viruses have been implicated in acute viral laryngitis, including rhinovirus, influenza virus, parainfluenza virus, adenovirus, coxsackievirus, coronavirus, and RSV. Acute laryngitis can also be associated with acute bacterial respiratory infections such as those caused by group A *Streptococcus* or *C. diphtheriae* (although diphtheria has been virtually eliminated in the United States). Another bacterial pathogen thought to play a role (albeit unclear) in the pathogenesis of acute laryngitis is *M. catarrhalis*, which has been recovered from nasopharyngeal cultures in a significant percentage of cases.

Chronic laryngitis of infectious etiology is much less common in developed than in developing countries. Laryngitis due to *Mycobacterium tuberculosis* is often difficult to distinguish from laryngeal cancer, in part because of the frequent absence of signs, symptoms, and radiographic findings typical of pulmonary disease. *Histoplasma* and *Blastomyces* may cause laryngitis, often as a complication of systemic infection. *Candida* species can cause laryngitis as well, often in association with thrush or esophagitis and particularly in immunosuppressed patients. Rare cases of chronic laryngitis are due to *Coccidioides* and *Cryptococcus*.

Clinical Manifestations Laryngitis is characterized by hoarseness and also can be associated with reduced vocal pitch or aphonia. As acute laryngitis is caused primarily by respiratory viruses, these symptoms usually occur in association with other symptoms and signs of URI, including rhinorrhea, nasal congestion, cough, and sore throat. Direct laryngoscopy often reveals diffuse laryngeal erythema and edema, along with vascular engorgement of the vocal folds. In addition, chronic disease (e.g., tuberculous laryngitis) often includes mucosal nodules and ulcerations visible on laryngoscopy; these lesions are sometimes mistaken for laryngeal cancer.

TREATMENT

Laryngitis

Acute laryngitis is usually treated with humidification and voice rest alone. Antibiotics are not recommended except when group A *Streptococcus* is cultured, in which case penicillin is the drug of choice. The choice of therapy for chronic laryngitis depends on the pathogen, whose identification usually requires biopsy with culture.

Patients with laryngeal tuberculosis are highly contagious because of the large number of organisms that are easily aerosolized. These patients should be managed in the same way as patients with active pulmonary disease.

CROUP

The term *croup* actually denotes a group of diseases collectively referred to as "croup syndrome," all of which are acute and predominantly viral respiratory illnesses characterized by marked swelling of the subglottic region of the larynx. Croup primarily affects children <6 years old. For a detailed discussion of this entity, the reader should consult a textbook of pediatric medicine.

EPIGLOTTITIS

Acute epiglottitis (supraglottitis) is an acute, rapidly progressive form of cellulitis of the epiglottis and adjacent structures that can result in complete—and potentially fatal—airway obstruction in both children and adults. Before the widespread use of *H. influenzae* type b (Hib) vaccine, this entity was much more common among children, with a peak incidence at ~3.5 years of age. In some countries, mass vaccination against Hib has reduced the annual incidence of acute epiglottitis in children by >90%; in contrast, the annual incidence in adults has changed little since the introduction of Hib vaccine. Because of the danger of airway obstruction, acute epiglottitis constitutes a medical emergency, particularly in children, and prompt diagnosis and airway protection are of the utmost importance.

Etiology After the introduction of the Hib vaccine in the mid-1980s, disease incidence among children in the United States declined dramatically. Nevertheless, lack of vaccination or vaccine failure has meant that many pediatric cases seen today are still due to Hib. In adults and (more recently) in children, a variety of other bacterial pathogens have been associated with epiglottitis, the most common being group A *Streptococcus*. Other pathogens—seen less frequently— include *S. pneumoniae*, *Haemophilus parainfluenzae*, and *S. aureus* (including MRSA). Viruses have not been established as causes of acute epiglottitis.

Clinical Manifestations and Diagnosis Epiglottitis typically presents more acutely in young children than in adolescents or adults. On presentation, most children have had symptoms for <24 h, including high fever, severe sore throat, tachycardia, systemic toxicity, and (in many cases) drooling while sitting forward. Symptoms and signs of respiratory obstruction also may be present and may progress rapidly. The somewhat milder illness in adolescents and adults often follows 1–2 days of severe sore throat and is commonly accompanied by dyspnea, drooling, and stridor. Physical examination of patients with acute epiglottitis may reveal moderate or severe respiratory distress, with inspiratory stridor and retractions of the chest wall. These findings *diminish* as the disease progresses and the patient tires. Conversely, oropharyngeal examination reveals infection that is much less severe than would be predicted from the symptoms—a finding that should alert the clinician to a cause of symptoms and obstruction that lies beyond the tonsils. The diagnosis often is made on clinical grounds, although direct fiberoptic laryngoscopy is frequently performed in a controlled environment (e.g., an operating room) to visualize and culture the typical edematous "cherry-red" epiglottis and facilitate placement of an endotracheal tube. Direct visualization in an examination room (i.e., with a tongue blade and indirect laryngoscopy) is not recommended because of the risk of immediate laryngospasm and complete airway obstruction. Lateral neck radiographs and laboratory tests can assist in the diagnosis but may delay the critical securing of the airway and cause the patient to be moved or repositioned more than is necessary, thereby increasing the risk of further airway compromise. Neck radiographs typically reveal an enlarged edematous epiglottis (the "thumbprint sign," Fig. 31-3), usually with a dilated hypopharynx and normal subglottic structures. Laboratory tests characteristically document mild to moderate leukocytosis with a predominance of neutrophils. Blood cultures are positive in a significant proportion of cases.

FIGURE 31-3 Acute epiglottitis. In this lateral soft-tissue radiograph of the neck, the arrow indicates the enlarged edematous epiglottis (the "thumbprint sign").

TREATMENT

Epiglottitis

Security of the airway is always of primary concern in acute epiglottitis, even if the diagnosis is only suspected. Mere observation for signs of impending airway obstruction is not routinely recommended, particularly in children. Many adults have been managed with observation only since the illness is perceived to be milder in this age group, but some data suggest that this approach may be risky and probably should be reserved only for adult patients who have yet to develop dyspnea or stridor. Once the airway has been secured and specimens of blood and epiglottis tissue have been obtained for culture, treatment with IV antibiotics should be given to cover the most likely organisms, particularly *H. influenzae*. Because rates of ampicillin resistance in this organism have risen significantly in recent years, therapy with a β-lactam/β-lactamase inhibitor combination or a third-generation cephalosporin is recommended. Typically, ampicillin/sulbactam, cefotaxime, or ceftriaxone is given, with clindamycin and trimethoprim-sulfamethoxazole reserved for patients allergic to β-lactams. Antibiotic therapy should be continued for 7–10 days and should be tailored to the organism recovered in culture. If the household contacts of a patient with *H. influenzae* epiglottitis include an unvaccinated child aged <4 years, all members of the household (including the patient) should receive prophylactic rifampin for 4 days to eradicate carriage of *H. influenzae*.

INFECTIONS OF DEEP NECK STRUCTURES

Deep neck infections are usually extensions of infection from other primary sites, most often within the pharynx or oral cavity. Many of these infections are life-threatening but are difficult to detect at early stages, when they may be more easily managed. Three of the most clinically relevant spaces in the neck are the submandibular (and sublingual) space, the lateral pharyngeal (or parapharyngeal) space, and the retropharyngeal space. These spaces communicate with one another and with other important structures in the head, neck, and thorax, providing pathogens with easy access to areas that include the mediastinum, carotid sheath, skull base, and meninges. Once infection reaches these sensitive areas, mortality rates can be as high as 20–50%.

Infection of the submandibular and/or sublingual space typically originates from an infected or recently extracted lower tooth. The result is the severe, life-threatening infection referred to as Ludwig angina (see "Oral Infections," above). Infection of the lateral pharyngeal (or parapharyngeal) space is most often a complication of common infections of the oral cavity and upper respiratory tract, including tonsillitis, peritonsillar abscess, pharyngitis, mastoiditis, and periodontal infection. This space, situated deep in the lateral wall of the pharynx, contains a number of sensitive structures, including the carotid artery, internal jugular vein, cervical sympathetic chain, and portions of cranial nerves IX through XII; at its distal end, it opens into the posterior mediastinum. Involvement of this space with infection can therefore be rapidly fatal. Examination may reveal some tonsillar displacement, trismus, and neck rigidity, but swelling of the lateral pharyngeal wall can easily be missed. The diagnosis can be confirmed by CT. Treatment consists of airway management, operative drainage of fluid collections, and at least 10 days of IV therapy with an antibiotic active against streptococci and oral anaerobes (e.g., ampicillin/sulbactam). A particularly severe form of this infection involving the components of the carotid sheath (postanginal septicemia, Lemierre disease) is described above (see "Oral Infections"). Infection of the retropharyngeal space also can be extremely dangerous, as this space runs posterior to the pharynx from the skull base to the superior mediastinum. Infections in this space are more common among children <5 years old because of the presence of several small retropharyngeal lymph nodes that typically atrophy by age 4 years. Infection is usually a consequence of extension from another site of infection—most commonly, acute pharyngitis. Other sources include otitis media, tonsillitis, dental infections, Ludwig angina, and anterior extension of vertebral osteomyelitis. Retropharyngeal space infection also can follow penetrating trauma to the posterior pharynx (e.g., from an endoscopic procedure). Infections are commonly polymicrobial, involving a mixture of aerobes and anaerobes; group A β-hemolytic streptococci and *S. aureus* are the most common pathogens. *M. tuberculosis* was a common cause in the past but now is rarely involved in the United States.

Patients with retropharyngeal abscess typically present with sore throat, fever, dysphagia, and neck pain and are often drooling because of difficulty and pain with swallowing. Examination may reveal tender cervical adenopathy, neck swelling, and diffuse erythema and edema of the posterior pharynx as well as a bulge in the posterior pharyngeal wall that may not be obvious on routine inspection. A soft-tissue mass is usually demonstrable by lateral neck radiography or CT. Because of the risk of airway obstruction, treatment begins with securing of the airway, which is followed by a combination of surgical drainage and IV antibiotic administration. Initial empirical therapy should cover streptococci, oral anaerobes, and *S. aureus*; ampicillin/sulbactam, clindamycin plus ceftriaxone, or meropenem is usually effective. Complications result primarily from extension to other areas (e.g., rupture into the posterior pharynx may lead to aspiration pneumonia and empyema). Extension may also occur to the lateral pharyngeal space and mediastinum, resulting in mediastinitis and pericarditis, or into nearby major blood vessels. All these events are associated with a high mortality rate.

FURTHER READING

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32 Oral Manifestations of Disease

Samuel C. Durso

As primary care physicians and consultants, internists are often asked to evaluate patients with disease of the oral soft tissues, teeth, and pharynx. Knowledge of the oral milieu and its unique structures is necessary to guide preventive services and recognize oral manifestations of local or systemic disease **(Chap. A2)**. Furthermore, internists frequently collaborate with dentists in the care of patients who have a variety of medical conditions that affect oral health or who undergo dental procedures that increase their risk of medical complications.

DISEASES OF THE TEETH AND PERIODONTAL STRUCTURES

Tooth formation begins during the sixth week of embryonic life and continues through 17 years of age. Teeth start to develop in utero and continue to develop until after the tooth erupts. Normally, all 20 deciduous teeth have erupted by age 3 and have been shed by age 13. Permanent teeth, eventually totaling 32, begin to erupt by age 6 and have completely erupted by age 14, though third molars ("wisdom teeth") may erupt later.

The erupted tooth consists of the visible *crown* covered with enamel and the root submerged below the gum line and covered with bonelike *cementum*. *Dentin*, a material that is denser than bone and exquisitely sensitive to pain, forms the majority of the tooth substance, surrounding a core of myxomatous *pulp* containing the vascular and nerve supply. The tooth is held firmly in the alveolar socket by the *periodontium*, supporting structures that consist of the gingivae, alveolar bone, cementum, and periodontal ligament. The periodontal ligament tenaciously binds the tooth's cementum to the alveolar bone. Above this ligament is a collar of attached gingiva just below the crown. A few millimeters of unattached or free gingiva (1–3 mm) overlap the base of the crown, forming a shallow sulcus along the gum-tooth margin.

Dental Caries, Pulpal and Periapical Disease, and Complications Dental caries usually begin asymptomatically as a destructive infectious process of the enamel. Bacteria—principally *Streptococcus mutans*—colonize the organic buffering biofilm (*plaque*) on the tooth surface. If not removed by brushing or by the natural cleansing and antibacterial action of saliva, bacterial acids can demineralize the enamel. Fissures and pits on the occlusal surfaces are the most frequent sites of early decay. Surfaces between the teeth, adjacent to tooth restorations and exposed roots, are also vulnerable, particularly as individuals age. Over time, dental caries extend to the underlying dentin, leading to cavitation of the enamel. Without management, the caries will penetrate to the tooth pulp, producing *acute pulpitis*. At this stage, when the pulp infection is limited, the tooth may become sensitive to percussion and to hot or cold, and pain resolves immediately when the irritating stimulus is removed. Should the infection spread throughout the pulp, *irreversible pulpitis* occurs, leading to *pulp necrosis*. At this later stage, pain can be severe and has a sharp or throbbing visceral quality that may be worse when the patient lies down. Once pulp necrosis is complete, pain may be constant or intermittent, but cold sensitivity is lost.

Treatment of caries involves removal of the softened and infected hard tissue and restoration of the tooth structure with silver amalgam, glass ionomer, composite resin, or gold. Once irreversible pulpitis occurs, root canal therapy becomes necessary; removal of the contents of the pulp chamber and root canal is followed by thorough cleaning and filling with an inert material. Alternatively, the tooth may be extracted.

Pulpal infection leads to *periapical abscess* formation, which can produce pain on chewing. If the infection is mild and chronic, a *periapical granuloma* or eventually a *periapical cyst* forms, either of which produces radiolucency at the root apex. When unchecked, a periapical abscess can erode into the alveolar bone, producing osteomyelitis; penetrate and drain through the gingivae, producing a parulis (gumboil); or track along deep fascial planes, producing virulent cellulitis (Ludwig's angina) involving the submandibular space and floor of the mouth **(Chap. 172)**. Elderly patients, patients with diabetes mellitus, and patients taking glucocorticoids may experience little or no pain or fever as these complications develop.

Periodontal Disease Periodontal disease and dental caries are the primary causes of tooth loss. Like dental caries, chronic infection of the gingiva and anchoring structures of the tooth begins with formation of bacterial plaque. The process begins at the gum line. Plaque and *calculus* (calcified plaque) are preventable by appropriate daily oral hygiene, including periodic professional cleaning. Left undisturbed, chronic inflammation can ensue and produce hyperemia of the free and attached gingivae (*gingivitis*), which then typically bleed with brushing. If this issue is ignored, severe *periodontitis* can develop, leading to deepening of the physiologic sulcus and destruction of the periodontal ligament. Gingival pockets develop around the teeth. As the periodontium (including the supporting bone) is destroyed, the teeth loosen. A role for chronic inflammation due to chronic periodontal disease in promoting coronary heart disease and stroke has been proposed. Epidemiologic studies have demonstrated a moderate but significant association between chronic periodontal inflammation and atherogenesis, though a causal role remains unproven.

Acute and aggressive forms of periodontal disease are less common than the chronic forms described above. However, if the host is stressed or exposed to a new pathogen, rapidly progressive and destructive disease of the periodontal tissue can occur. A virulent example is *acute necrotizing ulcerative gingivitis*. Stress and poor oral hygiene are risk factors. The presentation includes sudden gingival inflammation, ulceration, bleeding, interdental gingival necrosis, and fetid halitosis. *Localized juvenile periodontitis*, which is seen in adolescents, is particularly destructive and appears to be associated with impaired neutrophil chemotaxis. *AIDS-related periodontitis* resembles acute necrotizing ulcerative gingivitis in some patients and a more destructive form of adult chronic periodontitis in others. It may also produce a gangrene-like destructive process of the oral soft tissues and bone that resembles *noma*, an infectious condition seen in severely malnourished children in developing nations.

Prevention of Tooth Decay and Periodontal Infection Despite the reduced prevalences of dental caries and periodontal disease in the United States (due in large part to water fluoridation and improved dental care, respectively), both diseases constitute a major public health problem worldwide, particularly in certain groups. The internist should promote preventive dental care and hygiene as part of health maintenance. Populations at high risk for dental caries and periodontal disease include those with hyposalivation and/or xerostomia, diabetics, alcoholics, tobacco users, persons with Down syndrome, and those with gingival hyperplasia. Furthermore, patients lacking access to dental care (e.g., as a result of low socioeconomic status) and patients with a reduced ability to provide self-care (e.g., individuals with disabilities, nursing home residents, and persons with dementia or upper-extremity disability) suffer at a disproportionate rate. It is important to provide counseling regarding regular dental hygiene and professional cleaning, use of fluoride-containing toothpaste, professional fluoride treatments, and (for patients with limited dexterity) use of electric toothbrushes and also to instruct persons caring for those who are not capable of self-care. Cost, fear of dental care, and differences in language and culture create barriers that prevent some people from seeking preventive dental services.

Developmental and Systemic Disease Affecting the Teeth and Periodontium In addition to posing cosmetic issues, *malocclusion*, the most common developmental oral problem, can interfere with mastication unless corrected through orthodontic and surgical techniques. Impacted third molars are common and can become infected or erupt into an insufficient space. Acquired prognathism

due to *acromegaly* may also lead to malocclusion, as may deformity of the maxilla and mandible due to *Paget's disease* of the bone. Delayed tooth eruption, a receding chin, and a protruding tongue are occasional features of *cretinism* and *hypopituitarism*. Congenital syphilis produces tapering, notched (*Hutchinson's*) incisors and finely nodular (*mulberry*) molar crowns. *Enamel hypoplasia* results in crown defects ranging from pits to deep fissures of primary or permanent teeth. Intrauterine infection (syphilis, rubella), vitamin deficiency (A, C, or D), disorders of calcium metabolism (malabsorption, vitamin D–resistant rickets, hypoparathyroidism), prematurity, high fever, and rare inherited defects (*amelogenesis imperfecta*) are all causes. Tetracycline, given in sufficiently high doses during the first 8 years of life, may produce enamel hypoplasia and discoloration. Exposure to endogenous pigments can discolor developing teeth; etiologies include *erythroblastosis fetalis* (green or bluish-black), congenital liver disease (green or yellow-brown), and porphyria (red or brown that fluoresces with ultraviolet light). *Mottled enamel* occurs if excessive fluoride is ingested during development. Worn enamel is seen with age, bruxism, or excessive acid exposure (e.g., chronic gastric reflux or bulimia). Celiac disease is associated with nonspecific enamel defects in children but not in adults.

Total or partial tooth loss resulting from periodontitis is seen with cyclic neutropenia, Papillon-Lefévre syndrome, Chédiak-Higashi syndrome, and leukemia. Rapid focal tooth loosening is most often due to infection, but rarer causes include Langerhans cell histiocytosis, Ewing's sarcoma, osteosarcoma, and Burkitt's lymphoma. Early loss of primary teeth is a feature of *hypophosphatasia*, a rare congenital error of metabolism.

Pregnancy may produce gingivitis and localized *pyogenic granulomas*. Severe periodontal disease occurs in uncontrolled diabetes mellitus. *Gingival hyperplasia* may be caused by phenytoin, calcium channel blockers (e.g., nifedipine), and cyclosporine, though excellent daily oral care can prevent or reduce its occurrence. *Idiopathic familial gingival fibromatosis* and several syndrome-related disorders cause similar conditions. Discontinuation of the medication may reverse the drug-induced form, though surgery may be needed to control both of the latter entities. *Linear gingival erythema* is variably seen in patients with advanced HIV infection and probably represents immune deficiency and decreased neutrophil activity. Diffuse or focal gingival swelling may be a feature of early or late acute myelomonocytic leukemia as well as of other lymphoproliferative disorders. A rare but pathognomonic sign of granulomatosis with polyangiitis is a red-purplish, granular gingivitis (*strawberry gums*).

DISEASES OF THE ORAL MUCOSA

Infections Most oral mucosal diseases involve microorganisms **(Table 32-1)**.

Pigmented Lesions See **Table 32-2**.

Dermatologic Diseases See Tables 32-1, 32-2, and **32-3** and **Chaps. 52–57**.

Diseases of the Tongue See **Table 32-4**.

HIV Disease and AIDS See Tables 32-1, 32-2, 32-3, and **32-5**; **Chap. 197**; and **Fig. 189-3**.

Ulcers Ulceration is the most common oral mucosal lesion. Although there are many causes, the host and the pattern of lesions, including the presence of organ system features, narrow the differential diagnosis (Table 32-1). Most acute ulcers are painful and self-limited. Recurrent aphthous ulcers and herpes simplex account for the majority. Persistent and deep aphthous ulcers can be idiopathic or can accompany HIV/AIDS. Aphthous lesions are often the presenting symptom in *Behçet's syndrome* **(Chap. 357)**. Similar-appearing, though less painful, lesions may occur in reactive arthritis, and aphthous ulcers are occasionally present during phases of *discoid* or *systemic lupus erythematosus* **(Chap. 353)**. Aphthous-like ulcers are seen in *Crohn's disease* **(Chap. 319)**, but, unlike the common aphthous variety, they may exhibit granulomatous inflammation on histologic examination. Recurrent aphthae are more prevalent in patients with *celiac disease* and have been reported to remit with elimination of gluten.

Of major concern are chronic, relatively painless ulcers and mixed red/white patches (erythroplakia and leukoplakia) of >2 weeks' duration. Squamous cell carcinoma and premalignant dysplasia should be considered early and a diagnostic biopsy performed. This awareness and this procedure are critically important because early-stage malignancy is vastly more treatable than late-stage disease. High-risk sites include the lower lip, floor of the mouth, ventral and lateral tongue, and soft palate–tonsillar pillar complex. Significant risk factors for oral cancer in Western countries include sun exposure (lower lip), tobacco and alcohol use, and human papillomavirus infection. In India and some other Asian countries, smokeless tobacco mixed with betel nut, slaked lime, and spices is a common cause of oral cancer. Rarer causes of chronic oral ulcer, such as tuberculosis, fungal infection, granulomatosis with polyangiitis, and midline granuloma may look identical to carcinoma. Making the correct diagnosis depends on recognizing other clinical features and performing a biopsy of the lesion. The syphilitic chancre is typically painless and therefore easily missed. Regional lymphadenopathy is invariably present. The syphilitic etiology is confirmed with appropriate bacterial and serologic tests.

Disorders of mucosal fragility often produce painful oral ulcers that fail to heal within 2 weeks. *Mucous membrane pemphigoid* and *pemphigus vulgaris* are the major acquired disorders. While their clinical features are often distinctive, a biopsy or immunohistochemical examination should be performed to diagnose these entities and to distinguish them from *lichen planus* and drug reactions.

Hematologic and Nutritional Disease Internists are more likely to encounter patients with acquired, rather than congenital, bleeding disorders. Bleeding should stop 15 min after minor trauma and within an hour after tooth extraction if local pressure is applied. More prolonged bleeding, if not due to continued injury or rupture of a large vessel, should lead to investigation for a clotting abnormality. In addition to bleeding, petechiae and ecchymoses are prone to occur at the vibrating line between the soft and hard palates in patients with platelet dysfunction or thrombocytopenia.

All forms of leukemia, but particularly *acute myelomonocytic leukemia*, can produce gingival bleeding, ulcers, and gingival enlargement. Oral ulcers are a feature of agranulocytosis, and ulcers and mucositis are often severe complications of chemotherapy and radiation therapy for hematologic and other malignancies. *Plummer-Vinson syndrome* (iron deficiency, angular stomatitis, glossitis, and dysphagia) raises the risk of oral squamous cell cancer and esophageal cancer at the postcricoidal tissue web. Atrophic papillae and a red, burning tongue may occur with pernicious anemia. Deficiencies in B-group vitamins produce many of these same symptoms as well as oral ulceration and cheilosis. Consequences of *scurvy* include swollen, bleeding gums; ulcers; and loosening of the teeth.

NONDENTAL CAUSES OF ORAL PAIN

Most, but not all, oral pain emanates from inflamed or injured tooth pulp or periodontal tissues. Nonodontogenic causes are often overlooked. In most instances, toothache is predictable and proportional to the stimulus applied, and an identifiable condition (e.g., caries, abscess) is found. Local anesthesia eliminates pain originating from dental or periodontal structures, but not referred pains. The most common nondental source of pain is myofascial pain referred from muscles of mastication, which become tender and ache with increased use. Many sufferers exhibit *bruxism* (grinding of the teeth) secondary to stress and anxiety. *Temporomandibular joint disorder* is closely related. It affects both sexes, with a higher prevalence among women. Features include pain, limited mandibular movement, and temporomandibular joint sounds. The etiologies are complex; malocclusion does not play the primary role once attributed to it. *Osteoarthritis* is a common cause of masticatory pain. Anti-inflammatory medication, jaw rest, soft foods, and heat provide relief. The temporomandibular joint is involved in 50% of patients with *rheumatoid arthritis*, and its involvement is usually a late feature of severe disease. Bilateral preauricular pain, particularly in the morning, limits range of motion.

TABLE 32-1 Vesicular, Bullous, or Ulcerative Lesions of the Oral Mucosa

CONDITION	USUAL LOCATION	CLINICAL FEATURES	COURSE
Viral Diseases			
Primary acute herpetic gingivostomatitis (HSV type 1; rarely type 2)	Lip and oral mucosa (buccal, gingival, lingual mucosa)	Labial vesicles that rupture and crust, and intraoral vesicles that quickly ulcerate; extremely painful; acute gingivitis, fever, malaise, foul odor, and cervical lymphadenopathy; occurs primarily in infants, children, and young adults	Heals spontaneously in 10–14 days; unless secondarily infected, lesions lasting >3 weeks are not due to primary HSV infection
Recurrent herpes labialis	Mucocutaneous junction of lip, perioral skin	Eruption of groups of vesicles that may coalesce, then rupture and crust; painful to pressure or spicy foods	Lasts ~1 week, but condition may be prolonged if secondarily infected; if severe, topical or oral antiviral treatment may reduce healing time
Recurrent intraoral herpes simplex	Palate and gingiva	Small vesicles on keratinized epithelium that rupture and coalesce; painful	Heals spontaneously in ~1 week; if severe, topical, or oral antiviral treatment may reduce healing time
Chickenpox (VZV)	Gingiva and oral mucosa	Skin lesions may be accompanied by small vesicles on oral mucosa that rupture to form shallow ulcers; may coalesce to form large bullous lesions that ulcerate; mucosa may have generalized erythema	Lesions heal spontaneously within 2 weeks
Herpes zoster (VZV reactivation)	Cheek, tongue, gingiva, or palate	Unilateral vesicular eruptions and ulceration in linear pattern following sensory distribution of trigeminal nerve or one of its branches	Gradual healing without scarring unless secondarily infected; postherpetic neuralgia is common; oral acyclovir, famciclovir, or valacyclovir reduces healing time and postherpetic neuralgia
Infectious mononucleosis (Epstein-Barr virus)	Oral mucosa	Fatigue, sore throat, malaise, fever, and cervical lymphadenopathy; numerous small ulcers usually appear several days before lymphadenopathy; gingival bleeding and multiple petechiae at junction of hard and soft palates	Oral lesions disappear during convalescence; no treatment is given, though glucocorticoids are indicated if tonsillar swelling compromises the airway
Herpangina (coxsackievirus A; also possibly coxsackievirus B and echovirus)	Oral mucosa, pharynx, tongue	Sudden onset of fever, sore throat, and oropharyngeal vesicles, usually in children <4 years old, during summer months; diffuse pharyngeal congestion and vesicles (1–2 mm), grayish-white surrounded by red areola; vesicles enlarge and ulcerate	Incubation period of 2–9 days; fever for 1–4 days; recovery uneventful
Hand-foot-and-mouth disease (most commonly coxsackievirus A16)	Oral mucosa, pharynx, palms, and soles	Fever, malaise, headache with oropharyngeal vesicles that become painful, shallow ulcers; highly infectious; usually affects children under age 10	Incubation period 2–18 days; lesions heal spontaneously in 2–4 weeks
Primary HIV infection	Gingiva, palate, and pharynx	Acute gingivitis and oropharyngeal ulceration, associated with febrile illness resembling mononucleosis and including lymphadenopathy	Followed by HIV seroconversion, asymptomatic HIV infection, and usually ultimately by HIV disease
Bacterial or Fungal Diseases			
Acute necrotizing ulcerative gingivitis ("trench mouth")	Gingiva	Painful, bleeding gingiva characterized by necrosis and ulceration of gingival papillae and margins plus lymphadenopathy and foul breath	Debridement and diluted (1:3) peroxide lavage provide relief within 24 h; antibiotics in acutely ill patients; relapse may occur
Prenatal (congenital) syphilis	Palate, jaws, tongue, and teeth	Gummatous involvement of palate, jaws, and facial bones; Hutchinson's incisors, mulberry molars, glossitis, mucous patches, and fissures at corner of mouth	Tooth deformities in permanent dentition irreversible
Primary syphilis (chancre)	Lesion appearing where organism enters body; may occur on lips, tongue, or tonsillar area	Small papule developing rapidly into a large, painless ulcer with indurated border; unilateral lymphadenopathy; chancre and lymph nodes containing spirochetes; serologic tests positive by third to fourth weeks	Healing of chancre in 1–2 months, followed by secondary syphilis in 6–8 weeks
Secondary syphilis	Oral mucosa frequently involved with mucous patches, which occur primarily on palate and also at commissures of mouth	Maculopapular lesions of oral mucosa, 5–10 mm in diameter with central ulceration covered by grayish membrane; eruptions occurring on various mucosal surfaces and skin, accompanied by fever, malaise, and sore throat	Lesions may persist from several weeks to a year
Tertiary syphilis	Palate and tongue	Gummatous infiltration of palate or tongue followed by ulceration and fibrosis; atrophy of tongue papillae produces characteristic bald tongue and glossitis	Gumma may destroy palate, causing complete perforation
Gonorrhea	Lesions may occur in mouth at site of inoculation or secondarily by hematogenous spread from a primary focus	Most pharyngeal infection is asymptomatic; may produce burning or itching sensation; oropharynx and tonsils may be ulcerated and erythematous; saliva viscous and fetid	More difficult to eradicate than urogenital infection, though pharyngitis usually resolves with appropriate antimicrobial treatment
Tuberculosis	Tongue, tonsillar area, soft palate	Painless, solitary, 1- to 5-cm, irregular ulcer covered with persistent exudate; ulcer has firm undermined border	Autoinoculation from pulmonary infection is usual; lesions resolve with appropriate antimicrobial therapy
Cervicofacial actinomycosis	Swellings in region of face, neck, and floor of mouth	Infection may be associated with extraction, jaw fracture, or eruption of molar tooth; in acute form, resembles acute pyogenic abscess, but contains yellow "sulfur granules" (gram-positive mycelia and their hyphae)	Typically, swelling is hard and grows painlessly; multiple abscesses with draining tracts develop; penicillin first choice; surgery usually necessary

(*Continued*)

TABLE 32-1 Vesicular, Bullous, or Ulcerative Lesions of the Oral Mucosa (Continued)

CONDITION	USUAL LOCATION	CLINICAL FEATURES	COURSE
Bacterial or Fungal Diseases (Continued)			
Histoplasmosis	Any area of the mouth, particularly tongue, gingiva, or palate	Nodular, verrucous, or granulomatous lesions; ulcers are indurated and painful; usual source hematogenous or pulmonary, but may be primary	Systemic antifungal therapy necessary
Candidiasis[a]			
Dermatologic Diseases			
Mucous membrane pemphigoid	Typically produces marked gingival erythema and ulceration; other areas of oral cavity, esophagus, and vagina may be affected	Painful, grayish-white collapsed vesicles or bullae of full-thickness epithelium with peripheral erythematous zone; gingival lesions desquamate, leaving ulcerated area	Protracted course with remissions and exacerbations; involvement of different sites develops slowly; glucocorticoids may temporarily reduce symptoms but do not control disease
EM minor and EM major (Stevens-Johnson syndrome)	Primarily oral mucosa and skin of hands and feet	Intraoral ruptured bullae surrounded by inflammatory area; lips may show hemorrhagic crusts; "iris" or "target" lesion on skin is pathognomonic; patient may have severe signs of toxicity	Onset very rapid; usually idiopathic, but may be associated with trigger such as drug reaction; condition may last 3–6 weeks; mortality rate for untreated EM major is 5–15%
Pemphigus vulgaris	Oral mucosa and skin; sites of mechanical trauma (soft/hard palate, frenulum, lips, buccal mucosa)	Usually (>70%) presents with oral lesions; fragile, ruptured bullae and ulcerated oral areas; mostly in older adults	With repeated occurrence of bullae, toxicity may lead to cachexia, infection, and death within 2 years; often controllable with oral glucocorticoids
Lichen planus	Oral mucosa and skin	White striae in mouth; purplish nodules on skin at sites of friction; occasionally causes oral mucosal ulcers and erosive gingivitis	White striae alone usually asymptomatic; erosive lesions often difficult to treat, but may respond to glucocorticoids
Other Conditions			
Recurrent aphthous ulcers	Usually on nonkeratinized oral mucosa (buccal and labial mucosa, floor of mouth, soft palate, lateral and ventral tongue)	Single or clustered painful ulcers with surrounding erythematous border; lesions may be 1–2 mm in diameter in crops (herpetiform), 1–5 mm (minor), or 5–15 mm (major)	Lesions heal in 1–2 weeks but may recur monthly or several times a year; protective barrier with benzocaine and topical glucocorticoids relieve symptoms; systemic glucocorticoids may be needed in severe cases
Behçet's syndrome	Oral mucosa, eyes, genitalia, gut, and CNS	Multiple aphthous ulcers in mouth; inflammatory ocular changes, ulcerative lesions on genitalia; inflammatory bowel disease and CNS disease	Oral lesions often first manifestation; persist several weeks and heal without scarring
Traumatic ulcers	Anywhere on oral mucosa; dentures frequently responsible for ulcers in vestibule	Localized, discrete ulcerated lesions with red border; produced by accidental biting of mucosa, penetration by foreign object, or chronic irritation by dentures	Lesions usually heal in 7–10 days when irritant is removed, unless secondarily infected
Squamous cell carcinoma	Any area of mouth, most commonly on lower lip, lateral borders of tongue, and floor of mouth	Red, white, or red and white ulcer with elevated or indurated border; failure to heal; pain not prominent in early lesions	Invades and destroys underlying tissues; frequently metastasizes to regional lymph nodes
Acute myeloid leukemia (usually monocytic)	Gingiva	Gingival swelling and superficial ulceration followed by hyperplasia of gingiva with extensive necrosis and hemorrhage; deep ulcers may occur elsewhere on mucosa, complicated by secondary infection	Usually responds to systemic treatment of leukemia; occasionally requires local irradiation
Lymphoma	Gingiva, tongue, palate, and tonsillar area	Elevated, ulcerated area that may proliferate rapidly, giving appearance of traumatic inflammation	Fatal if untreated; may indicate underlying HIV infection
Chemical or thermal burns	Any area in mouth	White slough due to contact with corrosive agents (e.g., aspirin, hot cheese) applied locally; removal of slough leaves raw, painful surface	Lesion heals in several weeks if not secondarily infected

[a]See Table 32-3.

Abbreviations: CNS, central nervous system; EM, erythema multiforme; HSV, herpes simplex virus; VZV, varicella-zoster virus.

Migrainous neuralgia may be localized to the mouth. Episodes of pain and remission without an identifiable cause and a lack of relief with local anesthesia are important clues. *Trigeminal neuralgia* (*tic douloureux*) can involve the entire branch or part of the mandibular or maxillary branch of the fifth cranial nerve and can produce pain in one or a few teeth. Pain may occur spontaneously or may be triggered by touching the lip or gingiva, brushing the teeth, or chewing. *Glossopharyngeal neuralgia* produces similar acute neuropathic symptoms in the distribution of the ninth cranial nerve. Swallowing, sneezing, coughing, or pressure on the tragus of the ear triggers pain that is felt in the base of the tongue, pharynx, and soft palate and may be referred to the temporomandibular joint. *Neuritis* involving the maxillary and mandibular divisions of the trigeminal nerve (e.g., maxillary sinusitis, neuroma, and leukemic infiltrate) is distinguished from ordinary toothache by the neuropathic quality of the pain. Occasionally, *phantom pain* follows tooth extraction. Pain and hyperalgesia behind the ear and on the side of the face in the day or so before facial weakness develops often constitute the earliest symptom of *Bell's palsy*. Likewise, similar symptoms may precede visible lesions of herpes zoster infecting the seventh nerve (*Ramsey-Hunt syndrome*) or trigeminal nerve. *Postherpetic neuralgia* may follow either condition. *Coronary ischemia* may produce pain exclusively in the face and jaw; as in typical angina pectoris, this pain is usually reproducible with increased myocardial demand. Aching in several upper molar or premolar teeth that is unrelieved by anesthetizing the teeth may point to *maxillary sinusitis*.

Giant cell arteritis is notorious for producing headache, but it may also produce facial pain or sore throat without headache. Jaw and tongue claudication with chewing or talking is relatively common. Tongue infarction is rare. Patients with subacute thyroiditis often experience pain referred to the face or jaw before the tenderness of the thyroid gland and transient hyperthyroidism are appreciated.

"Burning mouth syndrome" (*glossodynia*) occurs in the absence of an identifiable cause (e.g., vitamin B_{12} deficiency, iron deficiency, diabetes

TABLE 32-2 Pigmented Lesions of the Oral Mucosa

CONDITION	USUAL LOCATION	CLINICAL FEATURES	COURSE
Oral melanotic macule	Any area of mouth	Discrete or diffuse, localized, brown to black macule	Remains indefinitely; no growth
Diffuse melanin pigmentation	Any area of mouth	Diffuse pale to dark-brown pigmentation; may be physiologic ("racial") or due to smoking	Remains indefinitely
Nevi	Any area of mouth	Discrete, localized, brown to black pigmentation	Remains indefinitely
Malignant melanoma	Any area of mouth	Can be flat and diffuse, painless, brown to black; or can be raised and nodular	Expands and invades early; metastasis leads to death
Addison's disease	Any area of mouth, but mostly buccal mucosa	Blotches or spots of bluish-black to dark-brown pigmentation occurring early in disease, accompanied by diffuse pigmentation of skin; other symptoms of adrenal insufficiency	Condition controlled by adrenal steroid replacement
Peutz-Jeghers syndrome	Any area of mouth	Dark-brown spots on lips, buccal mucosa, with characteristic distribution of pigment around lips, nose, and eyes and on hands; concomitant intestinal polyposis	Oral pigmented lesions remain indefinitely; gastrointestinal polyps may become malignant
Drug ingestion (neuroleptics, oral contraceptives, minocycline, zidovudine, quinine derivatives)	Any area of mouth	Brown, black, or gray areas of pigmentation	Gradually disappears following cessation of drug intake
Amalgam tattoo	Gingiva and alveolar mucosa	Small blue-black pigmented areas associated with embedded amalgam particles in soft tissues; may show up on radiographs as radiopaque particles in some cases	Remains indefinitely
Heavy metal pigmentation (bismuth, mercury, lead)	Gingival margin	Thin blue-black pigmented line along gingival margin; rarely seen except in children exposed to lead-based paint	Indicative of systemic absorption; no significance for oral health
Black hairy tongue	Dorsum of tongue	Elongation of filiform papillae of tongue, which become stained by coffee, tea, tobacco, or pigmented bacteria	Improves within 1–2 weeks with gentle brushing of tongue or (if due to bacterial overgrowth) discontinuation of antibiotic
Fordyce spots	Buccal and labial mucosa	Numerous small yellowish spots just beneath mucosal surface; no symptoms; due to hyperplasia of sebaceous glands	Benign; remains without apparent change
Kaposi's sarcoma	Palate most common, but may occur at any other site	Red or blue plaques of variable size and shape; often enlarge, become nodular, and may ulcerate	Usually indicative of HIV infection or non-Hodgkin's lymphoma; rarely fatal, but may require treatment for comfort or cosmesis
Mucous retention cysts	Buccal and labial mucosa	Bluish, clear fluid–filled cyst due to extravasated mucus from injured minor salivary gland	Benign; painless unless traumatized; may be removed surgically

TABLE 32-3 White Lesions of Oral Mucosa

CONDITION	USUAL LOCATION	CLINICAL FEATURES	COURSE
Lichen planus	Buccal mucosa, tongue, gingiva, and lips; skin	Striae, white plaques, red areas, ulcers in mouth; purplish papules on skin; may be asymptomatic, sore, or painful; lichenoid drug reactions may look similar	Protracted; responds to topical glucocorticoids
White sponge nevus	Oral mucosa, vagina, anal mucosa	Painless white thickening of epithelium; adolescence/early adulthood onset; familial	Benign and permanent
Smoker's leukoplakia and smokeless tobacco lesions	Any area of oral mucosa, sometimes related to location of habit	White patch that may become firm, rough, or red-fissured and ulcerated; may become sore and painful but is usually painless	May or may not resolve with cessation of habit; 2% of patients develop squamous cell carcinoma; early biopsy essential
Erythroplakia with or without white patches	Floor of mouth commonly affected in men; tongue and buccal mucosa in women	Velvety, reddish plaque; occasionally mixed with white patches or smooth red areas	High risk of squamous cell cancer; early biopsy essential
Candidiasis	Any area in mouth	*Pseudomembranous type* ("thrush"): creamy white curdlike patches that reveal a raw, bleeding surface when scraped; found in sick infants, debilitated elderly patients receiving high-dose glucocorticoids or broad-spectrum antibiotics, and patients with AIDS	Responds favorably to antifungal therapy and correction of predisposing causes where possible
		Erythematous type: flat, red, sometimes sore areas in same groups of patients	Course same as for pseudomembranous type
		Candidal leukoplakia: nonremovable white thickening of epithelium due to *Candida*	Responds to prolonged antifungal therapy
		Angular cheilitis: sore fissures at corner of mouth	Responds to topical antifungal therapy
Hairy leukoplakia	Usually on lateral tongue, rarely elsewhere on oral mucosa	White areas ranging from small and flat to extensive accentuation of vertical folds; found in HIV carriers (all risk groups for AIDS)	Due to Epstein-Barr virus; responds to high-dose acyclovir but recurs; rarely causes discomfort unless secondarily infected with *Candida*
Warts (human papillomavirus)	Anywhere on skin and oral mucosa	Single or multiple papillary lesions with thick, white, keratinized surfaces containing many pointed projections; cauliflower lesions covered with normal-colored mucosa or multiple pink or pale bumps (focal epithelial hyperplasia)	Lesions grow rapidly and spread; squamous cell carcinoma must be ruled out with biopsy; excision or laser therapy; may regress in HIV-infected patients receiving antiretroviral therapy

TABLE 32-4 Alterations of the Tongue

TYPE OF CHANGE	CLINICAL FEATURES
Size or Morphology	
Macroglossia	Enlarged tongue that may be part of a syndrome found in developmental conditions such as Down syndrome, Simpson-Golabi-Behmel syndrome, or Beckwith-Wiedemann syndrome; may be due to tumor (hemangioma or lymphangioma), metabolic disease (e.g., primary amyloidosis), or endocrine disturbance (e.g., acromegaly or cretinism); may occur when all teeth are removed
Fissured ("scrotal") tongue	Dorsal surface and sides of tongue covered by painless shallow or deep fissures that may collect debris and become irritated
Median rhomboid glossitis	Congenital abnormality with ovoid, denuded area in median posterior portion of tongue; may be associated with candidiasis and may respond to antifungal treatment
Color	
"Geographic" tongue (benign migratory glossitis)	Asymptomatic inflammatory condition of tongue, with rapid loss and regrowth of filiform papillae leading to appearance of denuded red patches "wandering" across surface
Hairy tongue	Elongation of filiform papillae of medial dorsal surface area due to failure of keratin layer of papillae to desquamate normally; brownish-black coloration may be due to staining by tobacco, food, or chromogenic organisms
"Strawberry" and "raspberry" tongue	Appearance of tongue during scarlet fever due to hypertrophy of fungiform papillae as well as changes in filiform papillae
"Bald" tongue	Atrophy may be associated with xerostomia, pernicious anemia, iron-deficiency anemia, pellagra, or syphilis; may be accompanied by painful burning sensation; may be an expression of erythematous candidiasis and respond to antifungal treatment

TABLE 32-5 Oral Lesions Associated with HIV Infection

LESION MORPHOLOGY	ETIOLOGIES
Papules, nodules, plaques	Candidiasis (hyperplastic and pseudomembranous)[a] Condyloma acuminatum (human papillomavirus infection) Squamous cell carcinoma (preinvasive and invasive) Non-Hodgkin's lymphoma[a] Hairy leukoplakia[a]
Ulcers	Recurrent aphthous ulcers[a] Angular cheilitis Squamous cell carcinoma Acute necrotizing ulcerative gingivitis[a] Necrotizing ulcerative periodontitis[a] Necrotizing ulcerative stomatitis Non-Hodgkin's lymphoma[a] Viral infection (herpes simplex, herpes zoster, cytomegalovirus infection) Infection caused by *Mycobacterium tuberculosis* or *Mycobacterium avium-intracellulare* Fungal infection (histoplasmosis, cryptococcosis, candidiasis, geotrichosis, aspergillosis) Bacterial infection (*Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Pseudomonas aeruginosa*) Drug reactions (single or multiple ulcers)
Pigmented lesions	Kaposi's sarcoma[a] Bacillary angiomatosis (skin and visceral lesions more common than oral) Zidovudine pigmentation (skin, nails, and occasionally oral mucosa) Addison's disease
Miscellaneous	Linear gingival erythema[a]

[a]Strongly associated with HIV infection.

mellitus, low-grade *Candida* infection, food sensitivity, or subtle xerostomia) and predominantly affects postmenopausal women. The etiology may be neuropathic. Clonazepam, α-lipoic acid, and cognitive behavioral therapy have benefited some patients. Some cases associated with an angiotensin-converting enzyme inhibitor have remitted when treatment with the drug was discontinued.

DISEASES OF THE SALIVARY GLANDS

Saliva is essential to oral health. Its absence leads to dental caries, periodontal disease, and difficulties in wearing dental prostheses, masticating, and speaking. Its major components, water and mucin, serve as a cleansing solvent and lubricating fluid. In addition, saliva contains antimicrobial factors (e.g., lysozyme, lactoperoxidase, secretory IgA), epidermal growth factor, minerals, and buffering systems. The major salivary glands secrete intermittently in response to autonomic stimulation, which is high during a meal but low otherwise. Hundreds of minor glands in the lips and cheeks secrete mucus continuously throughout the day and night. Consequently, oral function becomes impaired when salivary function is reduced. The sensation of a dry mouth (*xerostomia*) is perceived when salivary flow is reduced by 50%. The most common etiology is medication, especially drugs with anticholinergic properties but also alpha and beta blockers, calcium channel blockers, and diuretics. Other causes include Sjögren's syndrome, chronic parotitis, salivary duct obstruction, diabetes mellitus, HIV/AIDS, and radiation therapy that includes the salivary glands in the field (e.g., for Hodgkin's lymphoma and for head and neck cancer). Management involves the elimination or limitation of drying medications, preventive dental care, and supplementation with oral liquid or salivary substitutes. Sugarless mints or chewing gum may stimulate salivary secretion if dysfunction is mild. When sufficient exocrine tissue remains, pilocarpine or cevimeline has been shown to increase secretions. Commercial saliva substitutes or gels relieve dryness. Fluoride supplementation is critical to prevent caries.

Sialolithiasis presents most often as painful swelling but in some instances as only swelling or only pain. Conservative therapy consists of local heat, massage, and hydration. Promotion of salivary secretion with mints or lemon drops may flush out small stones. Antibiotic treatment is necessary when bacterial infection in suspected. In adults, *acute bacterial parotitis* is typically unilateral and most commonly affects postoperative, dehydrated, and debilitated patients. *Staphylococcus aureus* (including methicillin-resistant strains) and anaerobic bacteria are the most common pathogens. Chronic bacterial *sialadenitis* results from lowered salivary secretion and recurrent bacterial infection. When suspected bacterial infection is not responsive to therapy, the differential diagnosis should be expanded to include benign and malignant neoplasms, lymphoproliferative disorders, Sjögren's syndrome, sarcoidosis, tuberculosis, lymphadenitis, actinomycosis, and granulomatosis with polyangiitis. Bilateral nontender parotid enlargement occurs with diabetes mellitus, cirrhosis, bulimia, HIV/AIDS, and drugs (e.g., iodide, propylthiouracil).

Pleomorphic adenoma comprises two-thirds of all salivary neoplasms. The parotid is the principal salivary gland affected, and the tumor presents as a firm, slow-growing mass. Although this tumor is benign, its recurrence is common if resection is incomplete. Malignant tumors such as mucoepidermoid carcinoma, adenoid cystic carcinoma, and adenocarcinoma tend to grow relatively fast, depending upon grade. They may ulcerate and invade nerves, producing numbness and facial paralysis. Surgical resection is the primary treatment. Radiation therapy (particularly neutron-beam therapy) is used when surgery is not feasible and as post-resection for certain histologic types with a high risk of recurrence. Malignant salivary gland tumors have a 5-year survival rate of ~68%.

Dental Care for Medically Complex Patients Routine dental care (e.g., uncomplicated extraction, scaling and cleaning, tooth restoration, and root canal) is remarkably safe. The most common

concerns regarding care of dental patients with medical disease are excessive bleeding for patients taking anticoagulants, infection of the heart valves and prosthetic devices from hematogenous seeding by the oral flora, and cardiovascular complications resulting from vasopressors used with local anesthetics during dental treatment. Experience confirms that the risk of any of these complications is very low.

Patients undergoing tooth extraction or alveolar and gingival surgery rarely experience uncontrolled bleeding when warfarin anticoagulation is maintained within the therapeutic range currently recommended for prevention of venous thrombosis, atrial fibrillation, or mechanical heart valve. Embolic complications and death, however, have been reported during subtherapeutic anticoagulation. Therapeutic anticoagulation should be confirmed before and continued through the procedure. Likewise, low-dose aspirin (e.g., 81–325 mg) can safely be continued. For patients taking aspirin and another antiplatelet medication (e.g., clopidogrel), the decision to continue the second antiplatelet medication should be based on individual consideration of the risks of thrombosis and bleeding. The newer target-specific oral anticoagulants (dabigatran, apixaban, rivaroxaban, and edoxaban) are in increasingly common use. Simple extractions of 1–3 teeth, periodontal surgery, abscess drainage, and implant positioning do not typically require interruption of therapy. More extensive surgery may necessitate delaying or holding a dose of the anticoagulant or more elaborate measures to manage the risk of thrombosis and bleeding.

Patients at risk for bacterial endocarditis **(Chap. 123)** should maintain optimal oral hygiene, including flossing, and have regular professional cleanings. Currently, guidelines recommend that prophylactic antibiotics be restricted to those patients at high risk for bacterial endocarditis who undergo dental and oral procedures involving significant manipulation of gingival or periapical tissue or penetration of the oral mucosa. If unexpected bleeding occurs, antibiotics given within 2 h after the procedure provide effective prophylaxis.

Hematogenous bacterial seeding from oral infection can undoubtedly produce late prosthetic-joint infection and therefore requires removal of the infected tissue (e.g., drainage, extraction, root canal) and appropriate antibiotic therapy. However, evidence that late prosthetic-joint infection follows routine dental procedures is lacking. For this reason, antibiotic prophylaxis is generally not recommended before oral surgery or oral mucosal manipulation for patients who have undergone joint replacement surgery. Exceptions to this may be considered for patients who have experienced joint replacement complications.

Concern often arises regarding the use of vasoconstrictors to treat patients with hypertension and heart disease. Vasoconstrictors enhance the depth and duration of local anesthesia, thus reducing the anesthetic dose and potential toxicity. If intravascular injection is avoided, 2% lidocaine with 1:100,000 epinephrine (limited to a total of 0.036 mg of epinephrine) can be used safely in patients with controlled hypertension and stable coronary heart disease, arrhythmia, or congestive heart failure. Precautions should be taken with patients taking tricyclic antidepressants and nonselective beta blockers because these drugs may potentiate the effect of epinephrine.

Elective dental treatments should be postponed for at least 1 month and preferably for 6 months after myocardial infarction, after which the risk of reinfarction is low provided the patient is medically stable (e.g., stable rhythm, stable angina, and no heart failure). Patients who have suffered a stroke should have elective dental care deferred for 9 months. In both situations, effective stress reduction requires good pain control, including the use of the minimal amount of vasoconstrictor necessary to provide good hemostasis and local anesthesia.

Bisphosphonate therapy is associated with *osteonecrosis* of the jaw. However, the risk with oral bisphosphonate therapy is very low. Most patients affected have received high-dose aminobisphosphonate therapy for multiple myeloma or metastatic breast cancer and have undergone tooth extraction or dental surgery. Intraoral lesions, of which two-thirds are painful, appear as exposed yellow-white hard bone involving the mandible or maxilla. Screening tests for determining risk of osteonecrosis are unreliable. Patients slated for aminobisphosphonate therapy should receive preventive dental care that reduces the risk of infection and the need for future dentoalveolar surgery.

Halitosis Halitosis typically emanates from the oral cavity or nasal passages. Volatile sulfur compounds resulting from bacterial decay of food and cellular debris account for the malodor. Periodontal disease, caries, acute forms of gingivitis, poorly fitting dentures, oral abscess, and tongue coating are common causes. Treatment includes correcting poor hygiene, treating infection, and tongue brushing. Hyposalivation can produce and exacerbate halitosis. Pockets of decay in the tonsillar crypts, esophageal diverticulum, esophageal stasis (e.g., achalasia, stricture), sinusitis, and lung abscess account for some instances. A few systemic diseases produce distinctive odors: renal failure (ammoniacal), hepatic (fishy), and ketoacidosis (fruity). *Helicobacter pylori* gastritis can also produce ammoniacal breath. If a patient presents because of concern about halitosis but no odor is detectable, then pseudohalitosis or halitophobia must be considered.

Aging and Oral Health While tooth loss and dental disease are not normal consequences of aging, a complex array of structural and functional changes that occur with age can affect oral health. Subtle changes in tooth structure (e.g., diminished pulp space and volume, sclerosis of dentinal tubules, and altered proportions of nerve and vascular pulp content) result in the elimination or diminution of pain sensitivity and a reduction in the reparative capacity of the teeth. In addition, age-associated fatty replacement of salivary acini may reduce physiologic reserve, thus increasing the risk of hyposalivation. In healthy older adults, there is minimal, if any, reduction in salivary flow.

Poor oral hygiene often results when general health fails or when patients lose manual dexterity and upper-extremity flexibility. This situation is particularly common among frail older adults and nursing home residents and must be emphasized because regular oral cleaning and dental care reduce the incidence of pneumonia and oral disease as well as the mortality risk in this population. Other risks for dental decay include limited lifetime fluoride exposure. Without assiduous care, decay can become quite advanced yet remain asymptomatic. Consequently, much of a tooth—or the entire tooth—can be destroyed before the patient is aware of the process.

Periodontal disease, a leading cause of tooth loss, is indicated by loss of alveolar bone height. More than 90% of the U.S. population has some degree of periodontal disease by age 50. Healthy adults who have not had significant alveolar bone loss by the sixth decade of life do not typically experience significant worsening with advancing age.

With the passing of those born in the first half of the twentieth century, complete edentulousness in the United States is becoming increasingly restricted to impoverished populations. When it is present, speech, mastication, and facial contours are dramatically affected. Edentulousness may also exacerbate obstructive sleep apnea, particularly in asymptomatic individuals who wear dentures. Dentures can improve verbal articulation and restore diminished facial contours. Mastication can also be restored; however, patients expecting dentures to facilitate oral intake are often disappointed. Accommodation to dentures requires a period of adjustment. Pain can result from friction or traumatic lesions produced by loose dentures. Poor fit and poor oral hygiene may permit the development of candidiasis. This fungal infection may be either asymptomatic or painful and is suggested by erythematous smooth or granular tissue conforming to an area covered by the appliance. Individuals with dentures and no natural teeth need regular (annual) professional oral examinations.

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33 Dyspnea

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DYSPNEA

Definition: The American Thoracic Society consensus statement defines *dyspnea* as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors and may induce secondary physiological and behavioral responses." Dyspnea, a symptom, can be perceived only by the person experiencing it and, therefore, must be self-reported. In contrast, signs of increased work of breathing, such as tachypnea, accessory muscle use, and intercostal retraction, can be measured and reported by clinicians.

Epidemiology: Dyspnea is a common, and it has been reported that up to one half of inpatients and one quarter of ambulatory patients experience dyspnea, with a prevalence of 9–13% in the community that increases to as high as 37% for adults aged ≥70 years. Dyspnea is a frequent cause for emergency room visits, accounting for as many as 3–4 million visits per year. Furthermore, it is increasingly appreciated that the degree of dyspnea may better predict outcomes in chronic obstructive pulmonary disease (COPD) than does the forced expiratory volume in 1 s (FEV1), and formal measures of dyspnea have been incorporated into the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 COPD severity assessment guidelines. Dyspnea may also predict outcomes in other chronic heart and lung diseases as well. Dyspnea can arise from a diverse array of pulmonary, cardiac, and neurologic underlying causes, and elucidation of particular symptoms may point toward a specific etiology and/or mechanism driving dyspnea (although additional diagnostic testing is often required as will be further discussed below).

MECHANISMS UNDERLYING DYSPNEA

The mechanisms underlying dyspnea are complex, as it can arise from different contributory respiratory sensations. While a large body of research has increased our understanding of mechanisms underlying particular respiratory sensations such as "chest tightness" or "air hunger" it is likely that a given disease state might produce the sensation of dyspnea via more than one underlying mechanism. Dyspnea can arise from a variety of pathways, including generation of *afferent* signals from the respiratory system to the central nervous system (CNS), *efferent* signals from the CNS to the respiratory muscles, and particularly when there is a mismatch in the integrative signaling between these two pathways, termed "efferent-reafferent mismatch" **(Fig. 33-1)**.

Afferent signals trigger the CNS (brainstem and/or cortex) and include primarily: (a) peripheral chemoreceptors in the carotid body and aortic arch and central chemoreceptors in the medulla that are activated by hypoxemia, hypercapnia, or academia, and might produce a sense of "air hunger"; and (b) mechanoreceptors in the upper airways, lungs (including stretch receptors, irritant receptors, and J receptors), and chest wall (including muscle spindles as stretch receptors and tendon organs that monitor force generation) that are activated in the setting of an increased work load from a disease state producing an increase in airway resistance that may be associated with symptoms of chest tightness (e.g., asthma or COPD) or decreased lung or chest wall compliance (e.g., pulmonary fibrosis). Other afferent signals that trigger dyspnea within the respiratory system can arise from pulmonary vascular receptor responses to changes in pulmonary artery pressure and skeletal muscle (termed metaboreceptors) that are believed to sense changes in the biochemical environment.

Efferent signals are sent from the CNS (motor cortex and brainstem) to the respiratory muscles, and are also transmitted by corollary discharge to the sensory cortex that are believed to underlie sensations of respiratory effort (or "work of breathing") and perhaps contribute to sensations of "air hunger," especially in response to an increased ventilatory load in a disease state such as COPD. In addition, fear or anxiety may heighten the sense of dyspnea through exacerbating the underlying physiologic disturbance in response to an increased respiratory rate or disordered breathing pattern.

ASSESSING DYSPNEA

While it is well appreciated that dyspnea is a difficult quality to reliably measure due to multiple relevant possible domains that can be measured (e.g., sensory-perceptual experience, affective distress, and symptom impact or burden), and there exist no uniformly agreed upon tools for dyspnea assessment, consensus opinion is that dyspnea should be formally assessed in a context most relevant and beneficial for patient management; furthermore, that the specific domains being measured are adequately described. There are a number of emerging tools that have been developed for formal dyspnea assessment. As an example, the GOLD 2017 criteria advocate use of a dyspnea assessment tool such as the Modified Medical Research Council Dyspnea Scale (MMRC, **Table 33-1**) to assess symptom/impact burden in COPD.

DIFFERENTIAL DIAGNOSIS

This chapter focuses largely on chronic dyspnea, which is defined as symptoms lasting longer than 1 month and can arise from a broad array of different underlying conditions, most commonly attributable to pulmonary or cardiac conditions that account for as many as 85% of the underlying causes of dyspnea. However, as many as one-third of patients may have multifactorial reasons underlying dyspnea. Examples of a wide array of conditions that underlie dyspnea with possible mechanisms underlying the presenting symptoms are described in **Table 33-2**.

Respiratory system causes include diseases of the airways (e.g., asthma and COPD), diseases of the parenchyma (more commonly interstitial lung diseases are seen in the setting of chronic dyspnea, but alveolar filling processes, such as hypersensitivity pneumonitis or bronchiolitis obliterans organizing pneumonia [BOOP], can also present with similar symptoms), diseases affecting the chest wall (e.g., bony abnormalities such as kyphoscoliosis, or neuromuscular weakness conditions such as amyotrophic lateral sclerosis), and diseases affecting the pulmonary vasculature (e.g., pulmonary hypertension that can arise from a variety of underlying causes, or chronic thromboemolic disease). Diseases affecting the cardiovascular system that can present with dyspnea include processes affecting left heart function, such as coronary artery disease and cardiomyopathy, as well as disease processes affecting the pericardium, including restrictive pericarditis and cardiac tamponade. Other conditions underyling dyspnea that might not directly emanate from the pulmonary or cardiovascular systems include anemia (thereby potentially affecting oxygen-carrying capacity), deconditioning, and psychological processes such as anxiety. Distinguishing between the myriad of underlying processes that might present with dyspnea can be challenging. A graded approach that begins with a history and physical examination, followed by selected laboratory testing that might then advance to additional diagnostics and potentially subspecialty referral may help elucidate the underlying cause of dyspnea. However, a substantial proportion of patients may have persistent dyspnea despite treatment for an underlying process, or may not have a specific underlying process identified that is driving the dyspnea.

APPROACH TO THE PATIENT

Dyspnea (See Fig. 33-2)

OVERALL

For patients with a known prior pulmonary, cardiac, or neuromuscular condition and worsening dyspnea, the initial focus of the evaluation will usually address determining whether the known condition has progressed or whether a new process has developed

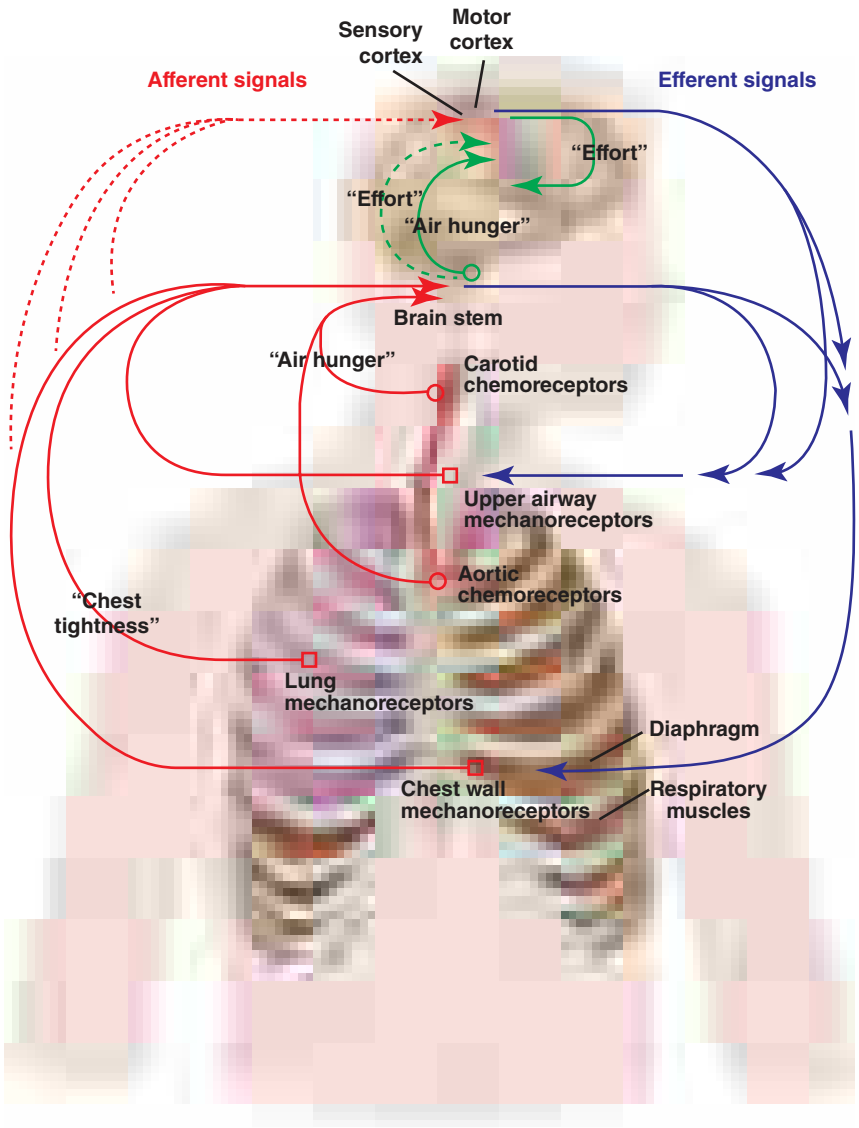

FIGURE 33-1 Signalling pathways underlying dyspnea. Dyspnea arises from a range of sensory inputs, many of which lead to distinct descriptive phrases used by patients (shown in quotes in the figure). The sensation of respiratory effort likely arises from signals transmitted from the motor cortex to the sensory cortex (*green arrow*) when outgoing motor commands are sent to the ventilatory muscles (*efferent signals, blue arrow*). Motor output from the brain stem (*blue arrow*) may also be accompanied by signals transmitted to the sensory cortex and contribute to the sensation of effort (*dotted green arrow*). The sensation of air hunger probably derives from a combination of stimuli that increase the drive to breathe such as hypoxemia or hypercapnia (mediated by signals from chemoreceptors in the carotid body and aortic arch, indicated by afferent signals in red), acute hypercapnia or acidemia (mediated by signals from the peripheral and central chemoreceptors, indicated by afferent signals in red), airway and interstitial inflammation (mediated by pulmonary afferents, indicated by afferent signals in red), and pulmonary vascular receptors. Dyspnea arises in part from a perceived mismatch between the outgoing efferent messages to the ventilatory muscles and incoming afferent signals from the lungs and chest wall. Chest tightness, often associated with bronchospasm, is largely mediated by stimulation of vagal-irritant receptors. Afferent signals (*red arrows*) from airway, lung, and chest wall mechanoreceptors most likely pass through the brain stem before being transmitted to sensory cortex, although it is also possible that some afferent information bypasses the brain stem and goes directly to sensory cortex (*dotted arrow*).

Red arrows and text: afferent signals; Blue arrows and text: efferent signals; Green arrows: signals within the central nervous system; Dotted lines: hypothetical pathways; Hollow Red Circles: chemoreceptors; Hollow Red Squares: mechanoreceptors. *(Adapted from UpToDate 2017.)*

that is causing dyspnea. For patients without a prior known potential cause of dyspnea, the initial evaluation will focus on determining an underlying etiology. Determining the underlying cause, if possible, is extremely important, as the treatment may vary dramatically based upon the predisposing condition. An initial history and physical examination remain fundamental to the evaluation followed by initial diagnostic testing as indicated that might prompt subspecialty referral (e.g., pulmonary, cardiology, neurology, sleep, and/or specialized dyspnea clinic) if the cause of dyspnea remains elusive (Fig. 33-2). As many as two-thirds of patients will require diagnostic testing beyond the initial clinical presentation.

HISTORY

The patient should be asked to describe in his/her own words what the discomfort feels like as well as the effect of position, infections, and environmental stimuli on the dyspnea, as descriptors may be helpful in pointing toward an etiology. For example, symptoms of chest tightness might suggest the possibility of bronchoconstriction, and the sensation of inability to take a deep breath may correlate with dynamic hyperinflation from COPD. Orthopnea is a common indicator of congestive heart failure (CHF), mechanical impairment of the diaphragm associated with obesity, or asthma triggered by esophageal reflux. Nocturnal dyspnea suggests CHF or asthma. Acute, intermittent episodes of dyspnea are more likely to reflect episodes of myocardial ischemia, bronchospasm, or pulmonary embolism, while chronic persistent dyspnea is more typical of COPD, interstitial lung disease, and chronic thromboembolic disease. Information on risk factors for drug-induced or occupational lung disease and for coronary artery disease should be elicited. Left atrial myxoma or hepatopulmonary syndrome should be considered

TABLE 33-1 An Example of a Clinical Method for Rating Dyspnea: The Modified Medical Research Council Dyspnea Scale[a]

GRADE OF DYSPNEA	DESCRIPTION
0	Not troubled by breathlessness, except with strenuous exercise
1	Shortness of breath walking on level ground or with walking up a slight hill
2	Walks slower than people of similar age on level ground due to breathlessness, or has to stop to rest when walking at own pace on level ground
3	Stops to rest after walking 100 m or after walking a few minutes on level ground
4	Too breathless to leave the house, or breathless with activities of daily living (e.g., dressing/undressing)

[a]Which has been incorporated into the GOLD 2017 guidelines as a possible tool for rating dyspnea in COPD.

Source: Modified from DA Mahler, CK Wells: Evaluation of clinical methods for rating dyspnea. Chest 93:580, 1988.

when the patient complains of *platypnea*—i.e., dyspnea in the upright position with relief in the supine position.

PHYSICAL EXAMINATION

Initial vital signs might be helpful in pointing toward an underlying etiology in the context of the remainder of the evaluation. For example, the presence of fever might point toward an underlying infectious or inflammatory process; the presence of hypertension in the setting of a heart failure might point toward diastolic dysfunction; the presence of tachycardia might be associated with many different underlying processes including fever, cardiac dysfunction, and deconditioning; and the presence of resting hypoxemia suggests processes involving hypercapnia, ventilation-perfusion mismatch, shunt, or impairment in diffusion capacity might be involved. An exertional oxygen saturation should also be obtained as described below. The physical examination should begin during the interview of the patient. Inability of the patient to speak in full sentences before stopping to get a deep breath suggests a condition that leads to stimulation of the controller or impairment of the ventilatory pump with reduced vital capacity. Evidence of increased work of breathing (supraclavicular retractions; use of accessory muscles of ventilation; and the tripod position, characterized by sitting with the hands braced on the knees) is indicative of increased airway resistance or stiffness of the lungs and the chest wall. When measuring the vital signs, the physician should accurately assess the respiratory rate and measure the pulsus paradoxus (Chap. 265); if the systolic pressure decreases by >10 mmHg, the presence of COPD, acute asthma, or pericardial disease should be considered. During the general examination, signs of anemia (pale conjunctivae), cyanosis, and cirrhosis (spider angiomata, gynecomastia) should be sought. Examination of the chest should focus on symmetry of movement; percussion (dullness is indicative of pleural effusion; hyperresonance is a sign of

TABLE 33-2 Differential Diagnosis of Disease Processes Underlying Dyspnea

SYSTEM	TYPE OF PROCESS	EXAMPLE OF DISEASE PROCESS	POSSIBLE PRESENTING DYSPNEA SYMPTOMS	POSSIBLE PHYSICAL FINDINGS	POSSIBLE MECHANISMS UNDERLYING DYSPNEA	INITIAL DIAGNOSTIC STUDIES (AND POSSIBLE FINDINGS)
Pulmonary	Airways disease	Asthma, COPD	Chest tightness, tachypnea, increased WOB, air hunger, inability to get a deep breath	Wheezing, accessory muscle use, exertional hypoxemia (especially with COPD)	Increased WOB, hypoxemia, hypercapnia, stimulation of pulmonary receptors	Peak flow (reduced); Spirometry (OVD); CXR (hyper-inflation; loss of lung parenchyma in COPD)
	Parenchymal disease	Interstitial lung disease[a]	Air hunger, inability to get a deep breath	Dry end-inspiratory crackles, clubbing, exertional hypoxemia	Increased WOB, increased respiratory drive, hypoxemia, hypercapnia, stimulation of pulmonary receptors	Spirometry and lung volumes (RVD); CXR and chest CT (interstitial lung disease)
	Chest wall disease	Kyphoscoliosis, Neuromuscular (NM) weakness	Increased WOB, inability to get a deep breath	Decreased diaphragm excursion; atelectasis	Increased WOB; stimulation ofpulmonary receptors (if atelectasis is present)	Spirometry and lung volumes (RVD); MIP and MEPs (reduced in NM weakness)
Pulmonary and cardiac	Pulmonary vasculature	Pulmonary Hypertension	Tachypnea	Elevated R heart pressures, exertional hypoxemia	Increased respiratory drive, hypoxemia, stimulation of vascular receptors	Diffusion capacity (reduced); ECG; ECHO (to evaluate PA pressures)[b]
Cardiac	Left heart failure ——— Pericardial disease	Coronary artery disease, cardio-myopathy[c] ——— Restrictive pericarditis; Cardiac tamponade	Chest tightness, air hunger	Elevated L heart pressures; wet crackles on lung examination; pulsus paradoxus (pericardial disease)	Increased WOB and drive, hypoxemia, stimulation of vascular and pulmonary receptors^	Consider BNP testing in the acute setting; ECG, ECHO, may need stress testing and/or LHC
Other	Variable	Anemia Deconditioning Psychological	Exertional breathlessness Poor fitness Anxiety	Variable	Metabo-receptors (anemia, poor fitness); chemoreceptors (anaerobic metabolism from poor fitness); some subjects may have increased sensitivity to hypercapnia	Hematocrit for anemia; exclude other causes

[a]Differential diagnosis of interstitial lung disease includes idiopathic pulmonary fibrosis, collagen vascular disease, drug or occupation-induced pneumonitis, lymphangitic spread of malignancy; processes that are more alveolar rather than interstitial in nature can also less commonly contribute to parenchymal lung disease underlying chronic dyspnea and include entities such as hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, etc. [b]Would additionally consider these patients for CT angiography to evaluate for presence of thromboemboli, ventilation/perfusion scanning to evaluate for the presence of chronic thromboembolic disease, and right heart catheterization (RHC) to further evaluate pulmonary hypertension. [c]Diastolic dysfunction in the setting of a stiff left ventricle is often seen and contributes significantly to insidious dyspnea that can be difficult to treat. ^May stimulate metaboreceptors if cardiac output is sufficiently reduced to a result in a lactic acidosis.

Abbreviations: BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CT angio, CT angiography; CXR, chest x-ray; ECHO, echocardiogram; ECG, electrocardiogram; LHC, left heart catheterization; MIP/MEP, maximal inspiratory and maximal expiratory pressures (obtained in the PFT laboratory); OVD, obstructive ventilatory defect; RVD, restrictive ventilatory defect; WOB, work of breathing.

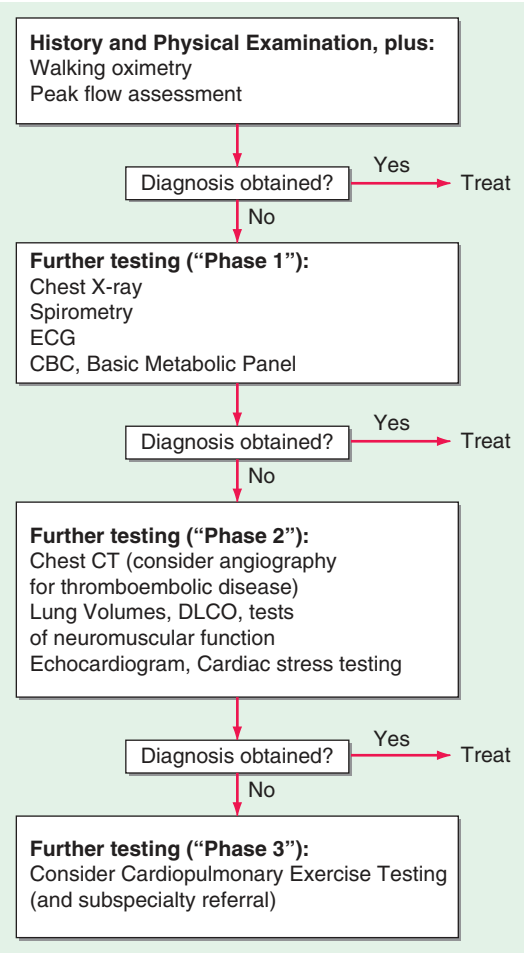

FIGURE 33-2 Possible algorithm for the evaluation of the patient with dyspnea. As described in the text, the approach should begin with a detailed history and physical examination, followed by progressive testing and ultimately more invasive testing and subspecialty referral as is indicated to determine the underlying cause of dyspnea. *(Adapted from NG Karnani et al: Am Fam Physician 71:1529, 2005.)*

emphysema); and auscultation (wheezes, rhonchi, prolonged expiratory phase, and diminished breath sounds are clues to disorders of the airways; rales suggest interstitial edema or fibrosis). The cardiac examination should focus on signs of elevated right heart pressures (jugular venous distention, edema, accentuated pulmonic component to the second heart sound); left ventricular dysfunction (S3 and S4 gallops); and valvular disease (murmurs). When examining the abdomen with the patient in the supine position, the physician should note whether there is paradoxical movement of the abdomen as well as the presence of increased respiratory distress in the supine position: inward motion during inspiration is a sign of diaphragmatic weakness, and rounding of the abdomen during exhalation is suggestive of pulmonary edema. Clubbing of the digits may be an indication of interstitial pulmonary fibrosis or bronchiectasis, and joint swelling or deformation as well as changes consistent with Raynaud's disease may be indicative of a collagen-vascular process that can be associated with pulmonary disease.

Patients should be asked to walk under observation with oximetry in order to reproduce the symptoms. The patient should be examined during and at the end of exercise for new findings that were not present at rest (e.g., presence of wheezing), and for changes in oxygen saturation.

CHEST IMAGING

After the history elicitation and the physical examination, a chest radiograph should be obtained if the diagnosis remains elusive. The lung volumes should be assessed: hyperinflation is consistent with obstructive lung disease, whereas low lung volumes suggest interstitial edema or fibrosis, diaphragmatic dysfunction, or impaired chest wall motion. The pulmonary parenchyma should be examined for evidence of interstitial disease, infiltrates, and emphysema. Prominent pulmonary vasculature in the upper zones indicates pulmonary venous hypertension, while enlarged central pulmonary arteries may suggest pulmonary arterial hypertension. An enlarged cardiac silhouette can point toward dilated cardiomyopathy or valvular disease. Bilateral pleural effusions are typical of CHF and some forms of collagen-vascular disease. Unilateral effusions raise the specter of carcinoma and pulmonary embolism but may also occur in heart failure or in the case of a parapneumonic effusion. CT of the chest is generally reserved for further evaluation of the lung parenchyma (interstitial lung disease) and possible pulmonary embolism if there remains diagnostic uncertainty.

LABORATORY STUDIES

Initial laboratory testing should include a hematocrit to exclude occult anemia as an underlying cause of reduced oxygen-carrying capacity contributing to dyspnea, and a basic metabolic panel may be helpful to exclude a significant underlying metabolic acidosis (and conversely, an elevated bicarbonate might point toward the possibility of carbon dioxide retention that might be seen in chronic respiratory failure—in such a setting, an arterial blood gas may provide useful additional information). Additional laboratory studies should include electrocardiography to seek evidence of ventricular hypertrophy and prior myocardial infarction and spirometry that can be diagnostic of the presence of an obstructive ventilatory defect, and suggest the possibility of a restrictive ventilatory defect (that then might prompt additional pulmonary function laboratory testing, including lung volumes, diffusion capacity, and possible tests of neuromuscular function). Echocardiography is indicated when systolic dysfunction, pulmonary hypertension, or valvular heart disease is suspected. Bronchoprovocation testing and/or home peak-flow monitoring may be useful in patients with intermittent symptoms suggestive of asthma who have a normal physical examination and spirometry; up to one-third of patients with the clinical diagnosis of asthma do not have reactive airways disease when formally tested. Measurement of brain natriuretic peptide levels in serum is increasingly used to assess for CHF in patients presenting with acute dyspnea but may be elevated in the presence of right ventricular strain as well.

DISTINGUISHING CARDIOVASCULAR FROM RESPIRATORY SYSTEM DYSPNEA

If a patient has evidence of both pulmonary and cardiac disease that is either not responsive to treatment, or it remains unclear what factors are primarily driving dyspnea, a cardiopulmonary exercise test (CPET) can be carried out to determine which system is responsible for the exercise limitation. CPET includes incremental symptom-limited exercise (cycling or treadmill) with measurements of ventilation and pulmonary gas exchange, and in some cases includes non-invasive and invasive measures of pulmonary vascular pressures and cardiac output. If, at peak exercise, the patient achieves predicted maximal ventilation, demonstrates an increase in dead space or hypoxemia, or develops bronchospasm, the respiratory system may be the cause of the problem. Alternatively, if the heart rate is >85% of the predicted maximum, if the anaerobic threshold occurs early, if the blood pressure becomes excessively high or decreases during exercise, if the O_2 pulse (O_2 consumption/heart rate, an indicator of stroke volume) falls, or if there are ischemic changes on the electrocardiogram, an abnormality of the cardiovascular system is likely the explanation for the breathing discomfort. Additionally, a CPET may also help point toward a peripheral extraction deficit, or metabolic/neuromuscular disease as potential underlying processes driving dyspnea.

TREATMENT

Dyspnea

The first goal is to correct the underlying condition(s) driving dyspnea and address potentially reversible causes with appropriate treatment for the particular condition. Multiple different interventions may be necessary, given that dyspnea often arises from multifactorial causes. If relief of dyspnea with treatment of the underlying condition(s) is not fully possible, an effort is made to lessen the intensity of the symptom and its effect on the patient's quality of life. Despite an increased understanding of the mechanisms underlying dyspnea, there has been limited progress in treatment strategies for dyspnea. Supplemental O_2 should be administered if the resting O_2 saturation is ≤88% or if the patient's saturation drops to these levels with activity or sleep. In particular, for patients with COPD, supplemental oxygen for those with hypoxemia has been shown to improve mortality, and pulmonary rehabilitation programs have demonstrated positive effects on dyspnea, exercise capacity, and rates of hospitalization. Opioids have been shown to reduce symptoms of dyspnea, largely through reducing air hunger, thus, likely suppressing respiratory drive and influencing cortical activity. However, opioids should be considered for each patient individually based upon the risk-benefit profile as regards the effects of respiratory depression. Studies of anxiolytics for dyspnea have not demonstrated consistent benefit. Additional approaches are under study for dyspnea, including inhaled furosemide that might alter afferent sensory information.

ACKNOWLEDGMENT

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34 Cough

Christopher H. Fanta

COUGH

Cough performs an essential protective function for human airways and lungs. Without an effective cough reflex, we are at risk for retained airway secretions and aspirated material predisposing to infection, atelectasis, and respiratory compromise. At the other extreme, excessive coughing can be exhausting; can be complicated by emesis, syncope, muscular pain, or rib fractures; can aggravate low back pain, abdominal or inguinal hernias, and urinary incontinence; and can be a major impediment to social interactions. Cough is often a clue to the presence of respiratory disease. In many instances, cough is an expected and accepted manifestation of disease, as in acute respiratory tract infection. However, persistent cough in the absence of other respiratory symptoms commonly causes patients to seek medical attention.

COUGH MECHANISM

Spontaneous cough is triggered by stimulation of sensory nerve endings that are thought to be primarily rapidly adapting receptors and C fibers. Both chemical (e.g., capsaicin) and mechanical (e.g., particulates in air pollution) stimuli may initiate the cough reflex. A cationic ion channel—the transient receptor potential vanilloid 1 (TRPV1)—found on rapidly adapting receptors and C fibers is the receptor for capsaicin, and its expression is increased in patients with chronic cough. Afferent nerve endings richly innervate the pharynx, larynx, and airways to the level of the terminal bronchioles and extend into the lung parenchyma. They may also be located in the external auditory meatus (the auricular branch of the vagus nerve, or Arnold's nerve) and in the esophagus. Sensory signals travel via the vagus and superior laryngeal nerves to a region of the brainstem in the nucleus tractus solitarius vaguely identified as the "cough center." The cough reflex involves a highly orchestrated series of involuntary muscular actions, with the potential for input from cortical pathways as well. The vocal cords adduct, leading to transient upper-airway occlusion. Expiratory muscles contract, generating positive intrathoracic pressures as high as 300 mmHg. With sudden release of the laryngeal contraction, rapid expiratory flows are generated, exceeding the normal "envelope" of maximal expiratory flow seen on the flow-volume curve (Fig. 34-1). Bronchial smooth-muscle contraction together with dynamic compression of airways narrows airway lumens and maximizes the velocity of exhalation. The kinetic energy available to dislodge mucus from the inside of airway walls is directly proportional to the square of the velocity of expiratory airflow. A deep breath preceding a cough optimizes the function of the expiratory muscles; a series of repetitive coughs at successively lower lung volumes sweeps the point of maximal expiratory velocity progressively further into the lung periphery.

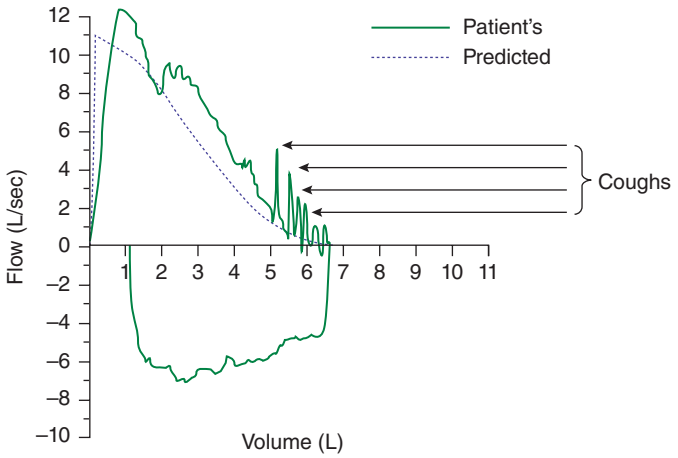

FIGURE 34-1 Flow-volume curve shows spikes of high expiratory flow achieved with cough.

IMPAIRED COUGH

Weak or ineffective cough compromises the ability to clear lower respiratory tract secretions, predisposing to more serious infections and their sequelae. Weakness or paralysis of the expiratory (abdominal and intercostal) muscles and pain in the chest wall or abdomen are foremost on the list of causes of impaired cough (Table 34-1). Cough strength is generally assessed qualitatively; peak expiratory flow or maximal expiratory pressure at the mouth can be used as a surrogate marker for cough strength. A variety of assistive devices and techniques have been developed to improve cough strength, running the gamut from

TABLE 34-1 Causes of Impaired Cough

Decreased respiratory muscle strength
Chest wall or abdominal pain
Chest wall deformity (e.g., severe kyphoscoliosis)
Impaired glottic closure or tracheostomy
Tracheobronchomalacia
Abnormal airway secretions
Central respiratory depression (e.g., anesthesia, sedation, or coma)

simple (splinting of the abdominal muscles with a tightly held pillow to reduce postoperative pain while coughing) to complex (a mechanical cough-assist device supplied via face mask or tracheal tube that applies a cycle of positive pressure followed rapidly by negative pressure). Cough may fail to clear secretions despite a preserved ability to generate normal expiratory velocities; such failure may be due to either abnormal airway secretions (e.g., bronchiectasis due to cystic fibrosis) or structural abnormalities of the airways (e.g., tracheomalacia with excessive expiratory collapse of the trachea during cough).

SYMPTOMATIC COUGH

Cough may occur in the context of other respiratory symptoms that together point to a diagnosis; for example, cough accompanied by wheezing, shortness of breath, and chest tightness after exposure to a cat or other sources of allergens suggests asthma. At times, however, cough is the dominant or sole symptom of disease, and it may be of sufficient duration and severity that relief is sought. The duration of cough is a clue to its etiology, at least retrospectively. Acute cough (<3 weeks) is most commonly due to a respiratory tract infection, aspiration, or inhalation of noxious chemicals or smoke. Subacute cough (3–8 weeks in duration) is a common residuum of tracheobronchitis, as in pertussis or "postviral tussive syndrome." Chronic cough (>8 weeks) may be caused by a wide variety of cardiopulmonary diseases, including those of inflammatory, infectious, neoplastic, and cardiovascular etiologies. When initial assessment with chest examination and radiography is normal, cough-variant asthma, gastroesophageal reflux, nasopharyngeal drainage, and medications (angiotensin-converting enzyme [ACE] inhibitors) are the most common identifiable causes of chronic cough. In a long-time cigarette smoker, an early-morning, productive cough suggests chronic bronchitis. A dry, irritative cough that lingers for >2 months following one or more respiratory tract infections ("post-bronchitic cough") is a very common cause of chronic cough, especially in the winter months.

ASSESSMENT OF CHRONIC COUGH

Except for our ability to detect the sound of excess airway secretions, details as to the resonance of the cough, its time of occurrence during the day, and the pattern of coughing (e.g., occurring in paroxysms) infrequently provide useful etiologic clues. Regardless of cause, cough often worsens upon first lying down at night, with talking, or with the hyperpnea of exercise; it frequently improves with sleep. An exception may involve the cough that occurs only with certain allergic exposures or exercise in cold air, as in asthma. Useful historical questions include what circumstances surrounded the onset of cough, what makes the cough better or worse, and does the cough produce sputum.

The physical examination seeks clues suggesting the presence of cardiopulmonary disease, including findings such as wheezing or crackles on chest examination. Examination of the auditory canals and tympanic membranes (for irritation of the latter resulting in stimulation of Arnold's nerve), the nasal passageways (for rhinitis or polyps), and the nails (for clubbing) may also provide etiologic clues. Because cough can be a manifestation of a systemic disease such as sarcoidosis or vasculitis, a thorough general examination is likewise important.

In virtually all instances, evaluation of chronic cough merits a chest radiograph. The list of diseases that can cause persistent cough without other symptoms and without detectable abnormalities on physical examination is long. It includes serious illnesses such as sarcoidosis or Hodgkin's disease in young adults, lung cancer in older patients, and (worldwide) pulmonary tuberculosis. An abnormal chest film prompts an evaluation aimed at explaining the radiographic abnormality. In a patient with chronic productive cough, examination of expectorated sputum is warranted, because determining the cause of mucus hypersecretion is critically important. Purulent-appearing sputum should be sent for routine bacterial culture and, in certain circumstances, mycobacterial culture as well. Cytologic examination of mucoid sputum may be useful to assess for malignancy and oropharyngeal aspiration and to distinguish neutrophilic from eosinophilic bronchitis. Expectoration of blood—whether streaks of blood, blood mixed with airway secretions, or pure blood—deserves a special approach to assessment and management.

CHRONIC COUGH WITH A NORMAL CHEST RADIOGRAPH

It is commonly held that (alone or in combination) the use of an ACE inhibitor; postnasal drainage; gastroesophageal reflux; and asthma account for >90% of cases of chronic cough with a normal or noncontributory chest radiograph. However, clinical experience does not support this contention, and strict adherence to this concept discourages the search for alternative explanations by both clinicians and researchers. In recent years, the concept of a distinct "cough hypersensitivity syndrome" has emerged, emphasizing the putative role of sensitized sensory nerve endings and afferent neural pathways in causing chronic refractory cough, akin to chronic neuropathic pain. It presents with a dry or minimally productive cough and a tickle or sensitivity in the throat, made worse with talking, laughing, or exertion. It is more common in women than men and can last for years. Specific diagnostic criteria are lacking; the diagnosis is suspected when alternative etiologies are excluded by diagnostic testing or failed therapeutic trials. It is uncertain whether persistent daily coughing elicits an inflammatory response and is thereby self-perpetuating.

ACE inhibitor–induced cough occurs in 5–30% of patients taking these agents and is not dose-dependent. ACE metabolizes bradykinin and other tachykinins, such as substance P. The mechanism of ACE inhibitor–associated cough may involve sensitization of sensory nerve endings due to accumulation of bradykinin. Any patient with chronic unexplained cough who is taking an ACE inhibitor should have a trial period off the medication, regardless of the timing of the onset of cough relative to the initiation of ACE inhibitor therapy. In most instances, a safe alternative is available; angiotensin-receptor blockers do not cause cough. Failure to observe a decrease in cough after 1 month off medication argues strongly against this etiology. Postnasal drainage of any etiology can cause cough as a response to stimulation of sensory receptors of the cough-reflex pathway in the hypopharynx or aspiration of draining secretions into the trachea. Clues suggesting this etiology include postnasal drip, frequent throat clearing, and sneezing and rhinorrhea. On speculum examination of the nose, excess mucoid or purulent secretions, inflamed and edematous nasal mucosa, and/or polyps may be seen; in addition, secretions or a cobblestoned appearance of the mucosa along the posterior pharyngeal wall may be noted. Unfortunately, there is no means by which to quantitate postnasal drainage. In many instances, this diagnosis must rely on subjective information provided by the patient. This assessment must also be counterbalanced by the fact that many people who have chronic postnasal drainage do not experience cough.

Linking gastroesophageal reflux to chronic cough poses similar challenges. It is thought that reflux of gastric contents into the lower esophagus may trigger cough via reflex pathways initiated in the esophageal mucosa. Reflux to the level of the pharynx (laryngopharyngeal reflux), with consequent aspiration of gastric contents, causes a chemical bronchitis and possibly pneumonitis that can elicit cough for days afterward, but it is a rare finding among persons with chronic cough. Retrosternal burning after meals or on recumbency, frequent eructation, hoarseness, and throat pain may be indicative of gastroesophageal reflux. Nevertheless, reflux may also elicit minimal or no symptoms. Glottic inflammation detected on laryngoscopy may be a manifestation of recurrent reflux to the level of the throat, but it is a nonspecific finding. Quantification of the frequency and level of reflux requires a somewhat invasive procedure to measure esophageal pH (either nasopharyngeal placement of a catheter with a pH probe into the esophagus for 24 h or endoscopic placement of a radiotransmitter capsule into the esophagus) and, with newer techniques, non-acid reflux. The precise interpretation of test results that permits an etiologic linking of reflux events and cough remains debated. Again, assigning the cause of cough to gastroesophageal reflux must be weighed against the observation that many people with symptomatic reflux do not experience chronic cough.

Cough alone as a manifestation of asthma is common among children but not among adults. Cough due to asthma in the absence of wheezing, shortness of breath, and chest tightness is referred to as "cough-variant asthma." A history suggestive of cough-variant asthma

ties the onset of cough to exposure to typical triggers for asthma and the resolution of cough to discontinuation of exposure. Objective testing can establish the diagnosis of asthma (airflow obstruction on spirometry that varies over time or reverses in response to a bronchodilator) or exclude it with certainty (a negative response to a bronchoprovocation challenge—e.g., with methacholine). In a patient capable of taking reliable measurements, home expiratory peak flow monitoring can be a cost-effective method to support or discount a diagnosis of asthma.

Chronic eosinophilic bronchitis causes chronic cough with a normal chest radiograph. This condition is characterized by sputum eosinophilia in excess of 3% without airflow obstruction or bronchial hyperresponsiveness and is successfully treated with inhaled glucocorticoids.

Treatment of chronic cough in a patient with a normal chest radiograph is often empirical and is targeted at the most likely cause(s) of cough as determined by history, physical examination, and possibly pulmonary-function testing. Therapy for postnasal drainage depends on the presumed etiology (infection, allergy, or vasomotor rhinitis) and may include systemic antihistamines; decongestants; antibiotics; nasal saline irrigation; and nasal pump sprays with glucocorticoids, antihistamines, or anticholinergics. Antacids, histamine type 2 (H2) receptor antagonists, and proton-pump inhibitors are used to neutralize or decrease the production of gastric acid in gastroesophageal reflux disease; dietary changes, elevation of the head and torso during sleep, and medications to improve gastric emptying are additional therapeutic measures. Cough-variant asthma typically responds well to inhaled glucocorticoids and intermittent use of inhaled β-agonist bronchodilators.

Patients who fail to respond to treatment targeting the common causes of chronic cough or who have had these causes excluded by appropriate diagnostic testing should undergo chest CT. Diseases causing cough that may be missed on chest x-ray include tumors, early interstitial lung disease, bronchiectasis, and atypical mycobacterial pulmonary infection. On the other hand, patients with chronic cough who have normal findings on chest examination, lung function testing, oxygenation assessment, and chest CT can be reassured as to the absence of serious pulmonary pathology.

GLOBAL CONSIDERATIONS

Regular exposure to air pollution can cause chronic cough and throat clearing, as well as lower respiratory tract disease. Smoke from cooking and heating fuels in poorly ventilated homes; toxic exposures in work settings lacking implementation of occupational safety standards; and ambient chemicals and particulates in highly polluted outdoor air are all forms of air pollution causing cough. Limited therapeutic options are available; treatment focuses on improving environmental air quality (e.g., use of a stove chimney in the home), removal from the exposure, and use of an appropriate face mask.

SYMPTOM-BASED TREATMENT OF COUGH

Empiric treatment of chronic idiopathic cough with inhaled corticosteroids, inhaled anticholinergic bronchodilators, and macrolide antibiotics has been tried without consistent success. Currently available cough suppressants are only modestly effective. Most potent are narcotic cough suppressants, such as codeine or hydrocodone, which are thought to act in the "cough center" in the brainstem. The tendency of narcotic cough suppressants to cause drowsiness and constipation and their potential for addictive dependence limit their appeal for long-term use. *Dextromethorphan* is an over-the-counter, centrally acting cough suppressant with fewer side effects and less efficacy than the narcotic cough suppressants. Dextromethorphan is thought to have a different site of action than narcotic cough suppressants and can be used in combination with them if necessary. *Benzonatate* is thought to inhibit neural activity of sensory nerves in the cough-reflex pathway. It is generally free of side effects; however, its effectiveness in suppressing cough is variable and unpredictable. Attempts to treat cough hypersensitivity syndrome have focused on inhibition of neural pathways. Small case series and randomized clinical trials have indicated benefit from off-label use of gabapentin, pregabalin, or amitriptyline. Recent studies suggest a role for behavioral modification using specialized speech therapy techniques, but widespread application of this modality is currently not practical. Novel cough suppressants without the limitations of currently available agents are greatly needed. Approaches that are being explored include the development of neurokinin receptor antagonists, TRPV1 ion channel antagonists, and novel opioid and opioid-like receptor agonists.

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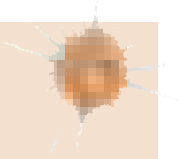
35 Hemoptysis

Anna K. Brady, Patricia A. Kritek



Hemoptysis is the expectoration of blood from the respiratory tract. The first step in evaluation is to ascertain whether the bleeding is coming from the respiratory tree or instead originating from the nasal cavities (i.e., epistaxis) or the gastrointestinal tract (i.e., hematemesis) as the therapies for these etiologies will be significantly different. Once established as hemoptysis, the exact nature of the expectoration is important as the term can be applied to blood-tinged phlegm, the pink frothy sputum of pulmonary edema, or frank blood. Next steps include identifying the source and etiology of bleeding.

ANATOMY AND PHYSIOLOGY OF HEMOPTYSIS

Hemoptysis can arise from anywhere in the respiratory tract; from the glottis to the alveolus. Most commonly, bleeding arises from the bronchi or medium sized airways, but a thorough evaluation of the entire respiratory tree is often necessary.

A unique feature of the lung that predisposes to hemoptysis of varied severity is its dual blood supply—the pulmonary and bronchial circulations. The former is a low-pressure system that is essential to gas exchange at the alveolar level; in contrast, the bronchial arteries originate from the aorta and are under systemic pressure. The bronchial arteries supply the airways and have the ability to neovascularize tumors, dilate airways of bronchiectasis, and cavitary lesions. Most hemoptysis is due to vessels in the bronchial circulation and is, therefore, under systemic pressure, making it more challenging to arrest the bleeding.

ETIOLOGY

Hemoptysis commonly results from infection, malignancy, or vascular disease; however, the differential for bleeding from the respiratory tree is varied and broad.

Infections Most blood-tinged sputum and small-volume hemoptysis is due to viral bronchitis. Patients with chronic bronchitis are at risk for bacterial superinfection with organisms such as *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis,* increasing airway inflammation and potential for bleeding. Similarly, patients

with bronchiectasis are prone to hemoptysis with exacerbations of disease. Due to recurrent bacterial infection, bronchiectatic airways are dilated, inflamed, and highly vascular, supplied by the bronchial circulation. In several case series, bronchiectasis is the leading cause of massive hemoptysis and subsequent death.

Tuberculosis had long been the most common cause of hemoptysis worldwide, but it is now surpassed in industrialized countries by bronchitis and bronchiectasis. In patients with tuberculosis, development of cavitary disease is frequently the source of bleeding but rarer complications such as the erosion of a pulmonary artery aneurysm into a preexisting cavity (i.e., Rasmussen's aneurysm) can also be the source.

Other infectious agents such as endemic fungi, *Nocardia,* and nontuberculous mycobacteria can present as cavitary lung disease complicated by hemoptysis. In addition, *Aspergillus* species can develop into mycetomas within preexisting cavities, with neovascularization to these inflamed spaces leading to bleeding. Pulmonary abscesses and necrotizing pneumonia can cause bleeding by devitalizing lung parenchyma. Common responsible organisms include *Staphylococcus aureus, Klebsiella pneumoniae*, and oral anaerobes.

Paragonimiasis can mimic tuberculosis and is another significant cause of hemoptysis seen globally; it is common in Southeast Asia and China, although cases have been reported in North America from raw crayfish ingestion. It should be considered as a cause of hemoptysis in recent immigrants from endemic areas.

Vascular Hemoptysis commonly results from pulmonary edema due to elevated left ventricular end-diastolic pressure. While the classic description of the sputum expectorated in pulmonary edema is "pink and frothy," a spectrum of hemoptysis including frank blood can be seen.

A pulmonary embolism with parenchymal infarction can present with hemoptysis, although most pulmonary emboli do not cause hemoptysis and will present with other signs and symptoms. An ectatic vessel in an airway or a pulmonary arteriovenous malformation can be a source of bleeding. While rare, rupture of an aortobronchial fistula can result in massive bleeding and sudden death; these fistulae arise in the setting of aortic pathology such as aneurysm or pseudoaneurysm and can cause small bleeding episodes that herald massive hemoptysis.

Diffuse alveolar hemorrhage (DAH), despite causing significant bleeding into the lung parenchyma, uncommonly results in hemoptysis. A range of insults cause DAH, including immune-mediated capillaritis from diseases such as systemic lupus erythematosus, toxicity from cocaine and other inhalants, and stem cell transplantation. The so-called "pulmonary-renal" syndromes, including granulomatosis with polyangiitis and anti-glomerular basement membrane disease, may lead to both hemoptysis and hematuria (though one manifestation may be present without the other). DAH more commonly presents with diffuse ground glass opacities on imaging and anemia, so the absence of hemoptysis should not exclude the diagnosis.

Malignancy Bronchogenic carcinoma of any histology is a common cause of hemoptysis (both massive and non-massive) in modern published series. Hemoptysis often indicates airway involvement of the tumor and can be a presenting symptom of carcinoid tumors, vascular lesions that frequently arise in the proximal airways. Small cell and squamous cell carcinomas are frequently central in nature and more likely to erode into major pulmonary vessels, resulting in massive hemoptysis. Pulmonary metastases from distant tumors (e.g., melanoma, sarcoma, adenocarcinomas of the breast and colon) can also cause bleeding. Kaposi's sarcoma, seen in advanced acquired immunodeficiency syndrome, is very vascular and can develop anywhere along the respiratory tract, from the bronchi to the oral cavity.

Mechanical and Other Causes In addition to infection, vascular disease, and malignancy, other insults to the pulmonary system can cause hemoptysis. Pulmonary endometriosis causes cyclical bleeding known as catamenial hemoptysis. Foreign body aspiration can lead to airway irritation and bleeding. Diagnostic and therapeutic procedures are also potential offenders: pulmonary vein stenosis can result from left atrial procedures, such as pulmonary vein isolation, and pulmonary artery catheters can lead to rupture of the pulmonary artery if the distal balloon is kept inflated. Finally, in the setting of thrombocytopenia, coagulopathy, anticoagulation, or antiplatelet therapy, even minor insults can cause hemoptysis.

EVALUATION AND MANAGEMENT

History The first step in evaluating hemoptysis is to determine the amount or severity of bleeding. A patient's description of the sputum (e.g., flecks of blood, pink-tinged, or frank blood or clot) is helpful if you cannot examine it. An approach to management of hemoptysis is outlined in Fig. 35-1.

It is crucial to determine whether the amount of blood expectorated is *massive*; while there is no agreed-upon volume, blood loss of 400 mL in 24 hours or 100–150 mL expectorated at one time are considered *massive hemoptysis*. These numbers derive from the volume of the tracheobronchial tree (generally 100–200 mL). This determination is clinically important as patients rarely die of exsanguination and, instead, are at risk of death due to asphyxiation from blood filling the airways and airspaces. Most patients cannot describe the volume of their hemoptysis in mL, so using referents like cups (one U.S. cup is 236 mL) can be helpful. Fortunately, massive hemoptysis only accounts for 5–15% of cases of hemoptysis.

Careful history may point to the cause of hemoptysis. Fever, chills, or antecedent cough may suggest infection. A history of smoking or unintentional weight loss makes malignancy more likely. Patients should be asked about inhalational exposures. A thorough medical history with careful attention to chronic pulmonary disease should

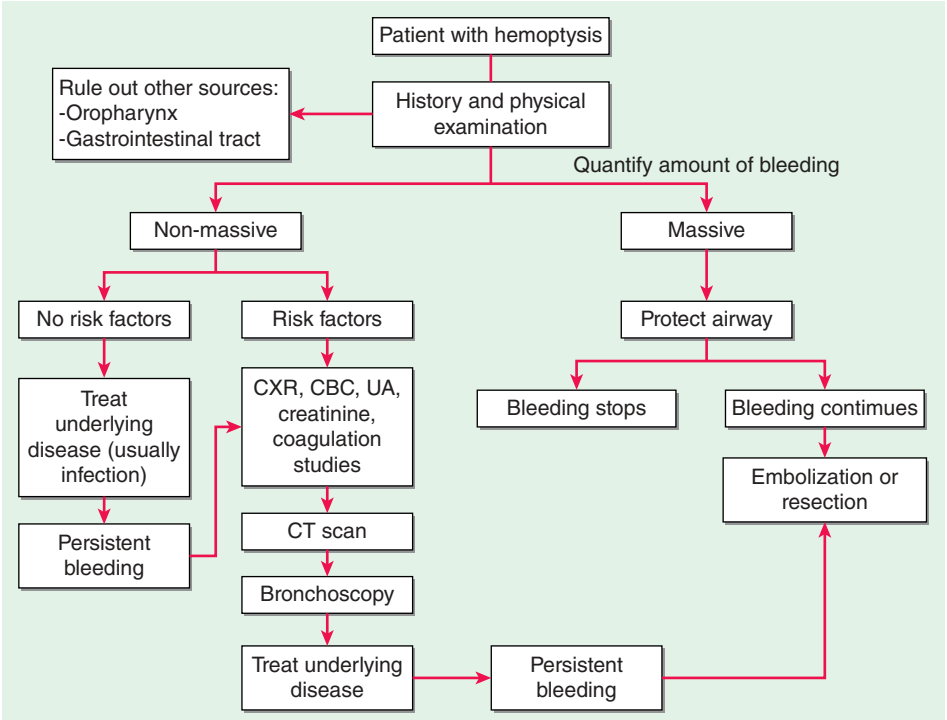


FIGURE 35-1 Approach to the management of hemoptysis. CBC, complete blood count; CT, computed tomography; CXR, chest x-ray; UA, urinalysis.

be obtained, and the clinician should determine risk factors for malignancy and bronchiectatic lung disease (e.g., cystic fibrosis, sarcoidosis).

Physical Examination Reviewing the vital signs is an important first step. The presence of hypoxemia, tachypnea, and tachycardia should raise concern. Clinicians should examine the nasal and oral cavities; observe the patient's breathing pattern, with careful attention to any respiratory distress; and auscultate the lungs. Clubbing can suggest underlying lung disease such as lung cancer or cystic fibrosis. Signs of bleeding diathesis (e.g., skin or mucosal ecchymoses and petechiae) or teleangectasias may suggest other predispositions to hemoptysis.

Diagnostic Studies Initial studies should include measurement of a complete blood count to assess for infection, anemia, or thrombocytopenia, coagulation parameters, measurement of electrolytes and renal function, as well as urinalysis to exclude pulmonary-renal disease.

In patients with small, non-massive hemoptysis, outpatient evaluation can be pursued. All patients with hemoptysis need chest imaging. A chest radiograph is usually obtained first, though it frequently does not localize bleeding and can appear normal. In patients without risk factors for malignancy and with a normal chest radiograph, treating for bronchitis and ensuring close follow-up is a reasonable strategy, with further diagnostic workup if bleeding persists.

In contrast, patients with risk factors for malignancy (i.e., age >40 or a smoking history) should undergo additional testing. First, chest computed tomography (CT) should be obtained to better identify masses, bronchiectasis, and parenchymal lesions. Following CT, a flexible bronchoscopy should be performed to exclude bronchogenic carcinoma unless imaging reveals a lesion that can be sampled without bronchoscopy. Small case series show that patients with hemoptysis and unrevealing bronchoscopies have good outcomes.

Interventions When the amount of hemoptysis is massive, there are three simultaneous goals: first, protect the non-bleeding lung; second, locate the site of bleeding; and third, control the bleeding.

Protecting the airway and non-bleeding lung is paramount in the management of massive hemoptysis, since asphyxiation can happen quickly. If the side of bleeding is known, the patient should be positioned with the bleeding side down, to use gravitational advantage to keep blood out of the non-bleeding lung. Endotracheal intubation should be avoided unless truly necessary, since suctioning through an endotracheal tube is a less effective means of removing blood and clot than the cough reflex. If intubation is required, take steps to protect the non-bleeding lung either by selective intubation of one lung (i.e., the non-bleeding lung) or insertion of a double-lumen endotracheal tube.

Locating the bleeding site is sometimes obvious, but frequently it can be difficult to determine the source of hemoptysis. A chest radiograph, if it shows new opacities, can be helpful in localizing the side or site of bleeding, though this test is not adequate by itself. CT angiography helps by localizing active extravasation. Flexible bronchoscopy may be useful to identify the side of bleeding (although it has only a 50% chance of locating the site). Experts do not agree on the timing of bronchoscopy, though in some cases—cystic fibrosis, for instance—bronchoscopy is *not* recommended because it may delay definitive management. Finally, proceeding directly to angiography is also a reasonable strategy given that it has both diagnostic and therapeutic capabilities.

Controlling the bleeding during an episode of massive hemoptysis can be accomplished in one of three ways: from the airway lumen, from the involved blood vessel, or by surgical resection of both airway and vessel involved. Bronchoscopic measures are generally only temporizing: a flexible bronchoscope can be used to suction clot and insert a balloon catheter that occludes the involved airway. Rigid bronchoscopy, done by an interventional pulmonologist or thoracic surgeon, may allow therapeutic interventions of bleeding airway lesions such as photocoagulation and cautery. Because most massive hemoptysis arises from the bronchial circulation, bronchial artery embolization is the procedure of choice for control of massive hemoptysis. It is not without risk—embolization of the anterior spinal artery is a known complication—but is generally successful in the short term, with >80% success rate at controlling bleeding immediately, though bleeding can recur if the underlying disease (e.g., a mycetoma) is not treated. Surgical resection has a high mortality rate (up to 15–40%) and should not be pursued unless initial measures have failed and bleeding is ongoing. Ideal candidates for surgery have localized disease but otherwise normal lung parenchyma.

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36 Hypoxia and Cyanosis

Joseph Loscalzo

HYPOXIA

The fundamental purpose of the cardiorespiratory system is to deliver O_2 and nutrients to cells and to remove CO_2 and other metabolic products from them. Proper maintenance of this function depends not only on intact cardiovascular and respiratory systems, but also on an adequate number of red blood cells and hemoglobin, and a supply of inspired gas containing adequate O_2.

RESPONSES TO HYPOXIA

Decreased O_2 availability to cells results in an inhibition of oxidative phosphorylation and increased anaerobic glycolysis. This switch from aerobic to anaerobic metabolism, the Pasteur effect, reduces the rate of adenosine 5′-triphosphate (ATP) production. In severe hypoxia, when ATP production is inadequate to meet the energy requirements of ionic and osmotic equilibrium, cell membrane depolarization leads to uncontrolled Ca^{2+} influx and activation of Ca^{2+}-dependent phospholipases and proteases. These events, in turn, cause cell swelling, activation of apoptotic pathways, and, ultimately, cell death.

The adaptations to hypoxia are mediated, in part, by the upregulation of genes encoding a variety of proteins, including glycolytic enzymes, such as phosphoglycerate kinase and phosphofructokinase, as well as the glucose transporters Glut-1 and Glut-2; and by growth factors, such as vascular endothelial growth factor (VEGF) and erythropoietin, which enhance erythrocyte production. The hypoxia-induced increase in expression of these key proteins is governed by the hypoxia-sensitive transcription factor, hypoxia-inducible factor-1 (HIF-1).

During hypoxia, systemic arterioles dilate, at least in part, by opening of K_{ATP} channels in vascular smooth-muscle cells due to the hypoxia-induced reduction in ATP concentration. By contrast, in pulmonary vascular smooth-muscle cells, inhibition of K^+ channels causes depolarization which, in turn, activates voltage-gated Ca^{2+} channels raising the cytosolic $[Ca^{2+}]$ and causing smooth-muscle cell contraction. Hypoxia-induced pulmonary arterial constriction shunts blood away from poorly ventilated portions toward better ventilated portions of

the lung; however, it also increases pulmonary vascular resistance and right ventricular afterload.

Effects on the Central Nervous System Changes in the central nervous system (CNS), particularly the higher centers, are especially important consequences of hypoxia. Acute hypoxia causes impaired judgment, motor incoordination, and a clinical picture resembling acute alcohol intoxication. High-altitude illness is characterized by headache secondary to cerebral vasodilation, gastrointestinal symptoms, dizziness, insomnia, fatigue, or somnolence. Pulmonary arterial and sometimes venous constriction causes capillary leakage and high-altitude pulmonary edema (HAPE) (Chap. 33), which intensifies hypoxia, further promoting vasoconstriction. Rarely, high-altitude cerebral edema (HACE) develops, which is manifest by severe headache and papilledema and can cause coma. As hypoxia becomes more severe, the regulatory centers of the brainstem are affected, and death usually results from respiratory failure.

Effects on the Cardiovascular System Acute hypoxia stimulates the chemoreceptor reflex arc to induce venoconstriction and systemic arterial vasodilation. These acute changes are accompanied by transiently increased myocardial contractility, which is followed by depressed myocardial contractility with prolonged hypoxia.

CAUSES OF HYPOXIA

Respiratory Hypoxia When hypoxia occurs from respiratory failure, Pa_{O_2} declines, and when respiratory failure is persistent, the hemoglobin-oxygen (Hb-O_2) dissociation curve (see Fig. 94-2) is displaced to the right, with greater quantities of O_2 released at any level of tissue P_{O_2}. Arterial hypoxemia, that is, a reduction of O_2 saturation of arterial blood (Sa_{O_2}), and consequent cyanosis are likely to be more marked when such depression of Pa_{O_2} results from pulmonary disease than when the depression occurs as the result of a decline in the fraction of oxygen in inspired air (F_{IO_2}). In this latter situation, Pa_{CO_2} falls secondary to anoxia-induced hyperventilation and the Hb-O_2 dissociation curve is displaced to the left, limiting the decline in Sa_{O_2} at any level of Pa_{O_2}.

The most common cause of respiratory hypoxia is *ventilation-perfusion mismatch* resulting from perfusion of poorly ventilated alveoli. Respiratory hypoxemia may also be caused by *hypoventilation*, in which case it is associated with an elevation of Pa_{CO_2} (Chap. 279). These two forms of respiratory hypoxia are usually correctable by inspiring 100% O_2 for several minutes. A third cause of respiratory hypoxia is shunting of blood across the lung from the pulmonary arterial to the venous bed (*intrapulmonary right-to-left shunting*) by perfusion of nonventilated portions of the lung, as in pulmonary atelectasis or through pulmonary arteriovenous connections. The low Pa_{O_2} in this situation is only partially corrected by an F_{IO_2} of 100%.

Hypoxia Secondary to High Altitude As one ascends rapidly to 3000 m (~10,000 ft), the reduction of the O_2 content of inspired air (F_{IO_2}) leads to a decrease in alveolar P_{O_2} to ~60 mmHg, and a condition termed *high-altitude illness* develops (see above). At higher altitudes, arterial saturation declines rapidly and symptoms become more serious; and at 5000 m, unacclimated individuals usually cease to be able to function normally owing to the changes in CNS function described above.

Hypoxia Secondary to Right-to-Left Extrapulmonary Shunting From a physiologic viewpoint, this cause of hypoxia resembles intrapulmonary right-to-left shunting but is caused by congenital cardiac malformations, such as tetralogy of Fallot, transposition of the great arteries, and Eisenmenger's syndrome (Chap. 264). As in pulmonary right-to-left shunting, the Pa_{O_2} cannot be restored to normal with inspiration of 100% O_2.

Anemic Hypoxia A reduction in hemoglobin concentration of the blood is accompanied by a corresponding decline in the O_2-carrying capacity of the blood. Although the Pa_{O_2} is normal in anemic hypoxia, the absolute quantity of O_2 transported per unit volume of blood is diminished. As the anemic blood passes through the capillaries and the usual quantity of O_2 is removed from it, the P_{O_2} and saturation in the venous blood decline to a greater extent than normal.

Carbon Monoxide (CO) Intoxication (See also Chap. S11) Hemoglobin that binds with CO (carboxy-hemoglobin, COHb) is unavailable for O_2 transport. In addition, the presence of COHb shifts the Hb-O_2 dissociation curve to the left (see Fig. 94-2) so that O_2 is unloaded only at lower tensions, further contributing to tissue hypoxia.

Circulatory Hypoxia As in anemic hypoxia, the Pa_{O_2} is usually normal, but venous and tissue P_{O_2} values are reduced as a consequence of reduced tissue perfusion and greater tissue O_2 extraction. This pathophysiology leads to an increased arterial-mixed venous O_2 difference (a-v-O_2 difference), or gradient. Generalized circulatory hypoxia occurs in heart failure (Chap. 252) and in most forms of shock (Chap. 296).

Specific Organ Hypoxia Localized circulatory hypoxia may occur as a result of decreased perfusion secondary to arterial obstruction, as in localized atherosclerosis in any vascular bed, or as a consequence of vasoconstriction, as observed in Raynaud's phenomenon (Chap. 275). Localized hypoxia may also result from venous obstruction and the resultant expansion of interstitial fluid causing arteriolar compression and, thereby, reduction of arterial inflow. Edema, which increases the distance through which O_2 must diffuse before it reaches cells, can also cause localized hypoxia. In an attempt to maintain adequate perfusion to more vital organs in patients with reduced cardiac output secondary to heart failure or hypovolemic shock, vasoconstriction may reduce perfusion in the limbs and skin, causing hypoxia of these regions.

Increased O_2 Requirements If the O_2 consumption of tissues is elevated without a corresponding increase in perfusion, tissue hypoxia ensues and the P_{O_2} in venous blood declines. Ordinarily, the clinical picture of patients with hypoxia due to an elevated metabolic rate, as in fever or thyrotoxicosis, is quite different from that in other types of hypoxia: the skin is warm and flushed owing to increased cutaneous blood flow that dissipates the excessive heat produced, and cyanosis is usually absent.

Exercise is a classic example of increased tissue O_2 requirements. These increased demands are normally met by several mechanisms operating simultaneously: (1) increase in the cardiac output and ventilation and, thus, O_2 delivery to the tissues; (2) a preferential shift in blood flow to the exercising muscles by changing vascular resistances in the circulatory beds of exercising tissues, directly and/or reflexly; (3) an increase in O_2 extraction from the delivered blood and a widening of the arteriovenous O_2 difference; and (4) a reduction in the pH of the tissues and capillary blood, shifting the Hb-O_2 curve to the right (see Fig. 94-2), and unloading more O_2 from hemoglobin. If the capacity of these mechanisms is exceeded, then hypoxia, especially of the exercising muscles, will result.

Improper Oxygen Utilization Cyanide (Chap. 450) and several other similarly acting poisons cause cellular hypoxia. The tissues are unable to use O_2, and, as a consequence, the venous blood tends to have a high O_2 tension. This condition has been termed *histotoxic hypoxia*.

ADAPTATION TO HYPOXIA

An important component of the respiratory response to hypoxia originates in special chemosensitive cells in the carotid and aortic bodies and in the respiratory center in the brainstem. The stimulation of these cells by hypoxia increases ventilation, with a loss of CO_2, and can lead to respiratory alkalosis. When combined with the metabolic acidosis resulting from the production of lactic acid, the serum bicarbonate level declines (Chap. 51).

With the reduction of Pa_{O_2}, cerebrovascular resistance decreases and cerebral blood flow increases in an attempt to maintain O_2 delivery to the brain. However, when the reduction of Pa_{O_2} is accompanied by hyperventilation and a reduction of Pa_{CO_2}, cerebrovascular resistance rises, cerebral blood flow falls, and tissue hypoxia intensifies.

The diffuse, systemic vasodilation that occurs in generalized hypoxia increases the cardiac output. In patients with underlying heart disease,

the requirements of peripheral tissues for an increase of cardiac output with hypoxia may precipitate congestive heart failure. In patients with ischemic heart disease, a reduced Pao_2 may intensify myocardial ischemia and further impair left ventricular function.

One of the important compensatory mechanisms for chronic hypoxia is an increase in the hemoglobin concentration and in the number of red blood cells in the circulating blood, that is, the development of polycythemia secondary to erythropoietin production **(Chap. 99)**. In persons with chronic hypoxemia secondary to prolonged residence at a high altitude (>13,000 ft, 4200 m), a condition termed *chronic mountain sickness* develops. This disorder is characterized by a blunted respiratory drive, reduced ventilation, erythrocytosis, cyanosis, weakness, right ventricular enlargement secondary to pulmonary hypertension, and even stupor.

CYANOSIS

Cyanosis refers to a bluish color of the skin and mucous membranes resulting from an increased quantity of reduced hemoglobin (i.e., deoxygenated hemoglobin) or of hemoglobin derivatives (e.g., methemoglobin or sulfhemoglobin) in the small blood vessels of those tissues. It is usually most marked in the lips, nail beds, ears, and malar eminences. Cyanosis, especially if developed recently, is more commonly detected by a family member than the patient. The florid skin characteristic of polycythemia vera **(Chap. 99)** must be distinguished from the true cyanosis discussed here. A cherry-colored flush, rather than cyanosis, is caused by COHb **(Chap. 450)**.

The degree of cyanosis is modified by the color of the cutaneous pigment and the thickness of the skin, as well as by the state of the cutaneous capillaries. The accurate clinical detection of the presence and degree of cyanosis is difficult, as proved by oximetric studies. In some instances, central cyanosis can be detected reliably when the Sao_2 has fallen to 85%; in others, particularly in dark-skinned persons, it may not be detected until it has declined to 75%. In the latter case, examination of the mucous membranes in the oral cavity and the conjunctivae rather than examination of the skin is more helpful in the detection of cyanosis.

The increase in the quantity of reduced hemoglobin in the mucocutaneous vessels that produces cyanosis may be brought about either by an increase in the quantity of venous blood as a result of dilation of the venules (including precapillary venules) or by a reduction in the Sao_2 in the capillary blood. In general, cyanosis becomes apparent when the concentration of reduced hemoglobin in capillary blood exceeds 40 g/L (4 g/dL).

It is the *absolute*, rather than the *relative*, quantity of reduced hemoglobin that is important in producing cyanosis. Thus, in a patient with severe anemia, the *relative* quantity of reduced hemoglobin in the venous blood may be very large when considered in relation to the total quantity of hemoglobin in the blood. However, since the concentration of the latter is markedly reduced, the *absolute* quantity of reduced hemoglobin may still be low, and, therefore, patients with severe anemia and even *marked* arterial desaturation may not display cyanosis. Conversely, the higher the total hemoglobin content, the greater the tendency toward cyanosis; thus, patients with marked polycythemia tend to be cyanotic at higher levels of Sao_2 than patients with normal hematocrit values. Likewise, local passive congestion, which causes an increase in the total quantity of reduced hemoglobin in the vessels in a given area, may cause cyanosis. Cyanosis is also observed when nonfunctional hemoglobin, such as methemoglobin (consequential or acquired) or sulfhemoglobin **(Chap. 94)**, is present in blood.

Cyanosis may be subdivided into central and peripheral types. In *central* cyanosis, the Sao_2 is reduced or an abnormal hemoglobin derivative is present, and the mucous membranes and skin are both affected. *Peripheral* cyanosis is due to a slowing of blood flow and abnormally great extraction of O_2 from normally saturated arterial blood; it results from vasoconstriction and diminished peripheral blood flow, such as occurs in cold exposure, shock, congestive failure, and peripheral vascular disease. Often in these conditions, the mucous membranes of the oral cavity or those beneath the tongue may be spared. Clinical differentiation between central and peripheral cyanosis may not always be straightforward, and in conditions such as cardiogenic shock with pulmonary edema, there may be a mixture of both types.

DIFFERENTIAL DIAGNOSIS

Central Cyanosis **(Table 36-1)** Decreased Sao_2 results from a marked reduction in the Pao_2. This reduction may be brought about by a decline in the FIo_2 without sufficient compensatory alveolar hyperventilation to maintain alveolar Po_2. Cyanosis usually becomes manifest in an ascent to an altitude of 4000 m (13,000 ft).

Seriously *impaired pulmonary function*, through perfusion of unventilated or poorly ventilated areas of the lung or alveolar hypoventilation, is a common cause of central cyanosis **(Chap. 279)**. This condition may occur acutely, as in extensive pneumonia or pulmonary edema, or chronically, with chronic pulmonary diseases (e.g., emphysema). In the latter situation, secondary polycythemia is generally present and clubbing of the fingers (see below) may occur. Another cause of reduced Sao_2 is *shunting of systemic venous blood into the arterial circuit*. Certain forms of congenital heart disease are associated with cyanosis on this basis (see above and **Chap. 264**).

Pulmonary arteriovenous fistulae may be congenital or acquired, solitary or multiple, microscopic or massive. The severity of cyanosis produced by these fistulae depends on their size and number. They occur with some frequency in hereditary hemorrhagic telangiectasia. Sao_2 reduction and cyanosis may also occur in some patients with cirrhosis, presumably as a consequence of pulmonary arteriovenous fistulae or portal vein–pulmonary vein anastomoses.

In patients with cardiac or pulmonary right-to-left shunts, the presence and severity of cyanosis depend on the size of the shunt relative to the systemic flow and on the Hb-O_2 saturation of the venous blood. With increased extraction of O_2 from the blood by the exercising muscles, the venous blood returning to the right side of the heart is more unsaturated than at rest, and shunting of this blood intensifies the cyanosis. Secondary polycythemia occurs frequently in patients in this setting and contributes to the cyanosis.

Cyanosis can be caused by small quantities of circulating methemoglobin (Hb Fe^{3+}) and by even smaller quantities of sulfhemoglobin **(Chap. 94)**; both of these hemoglobin derivatives impair oxygen delivery to the tissues. Although they are uncommon causes of cyanosis, these abnormal hemoglobin species should be sought by spectroscopy when cyanosis is not readily explained by malfunction of the

TABLE 36-1 Causes of Cyanosis

Central Cyanosis
Decreased arterial oxygen saturation
Decreased atmospheric pressure—high altitude
Impaired pulmonary function
Alveolar hypoventilation
Inhomogeneity in pulmonary ventilation and perfusion (perfusion of hypoventilated alveoli)
Impaired oxygen diffusion
Anatomic shunts
Certain types of congenital heart disease
Pulmonary arteriovenous fistulas
Multiple small intrapulmonary shunts
Hemoglobin with low affinity for oxygen
Hemoglobin abnormalities
Methemoglobinemia—hereditary, acquired
Sulfhemoglobinemia—acquired
Carboxyhemoglobinemia (not true cyanosis)
Peripheral Cyanosis
Reduced cardiac output
Cold exposure
Redistribution of blood flow from extremities
Arterial obstruction
Venous obstruction

circulatory or respiratory systems. Generally, digital clubbing does not occur with them.

Peripheral Cyanosis Probably the most common cause of peripheral cyanosis is the normal vasoconstriction resulting from exposure to cold air or water. When cardiac output is reduced, cutaneous vasoconstriction occurs as a compensatory mechanism so that blood is diverted from the skin to more vital areas such as the CNS and heart, and cyanosis of the extremities may result even though the arterial blood is normally saturated.

Arterial obstruction to an extremity, as with an embolus, or arteriolar constriction, as in cold-induced vasospasm (Raynaud's phenomenon) **(Chap. 275)**, generally results in pallor and coldness, and there may be associated cyanosis. Venous obstruction, as in thrombophlebitis or deep venous thrombosis, dilates the subpapillary venous plexuses and thereby intensifies cyanosis.

APPROACH TO THE PATIENT

Cyanosis

Certain features are important in arriving at the cause of cyanosis:

1. It is important to ascertain the time of onset of cyanosis. Cyanosis present since birth or infancy is usually due to congenital heart disease.
2. Central and peripheral cyanosis must be differentiated. Evidence of disorders of the respiratory or cardiovascular systems is helpful. Massage or gentle warming of a cyanotic extremity will increase peripheral blood flow and abolish peripheral, but not central, cyanosis.
3. The presence or absence of clubbing of the digits (see below) should be ascertained. The combination of cyanosis and clubbing is frequent in patients with congenital heart disease and right-to-left shunting and is seen occasionally in patients with pulmonary disease, such as lung abscess or pulmonary arteriovenous fistulae. In contrast, peripheral cyanosis or acutely developing central cyanosis is *not* associated with clubbed digits.
4. Pao_2 and Sao_2 should be determined, and, in patients with cyanosis in whom the mechanism is obscure, spectroscopic examination of the blood should be performed to look for abnormal types of hemoglobin (critical in the differential diagnosis of cyanosis).

CLUBBING

The selective bulbous enlargement of the distal segments of the fingers and toes due to proliferation of connective tissue, particularly on the dorsal surface, is termed *clubbing*; there is also increased sponginess of the soft tissue at the base of the clubbed nail. Clubbing may be hereditary, idiopathic, or acquired and associated with a variety of disorders, including cyanotic congenital heart disease (see above), infective endocarditis, and a variety of pulmonary conditions (among them primary and metastatic lung cancer, bronchiectasis, asbestosis, sarcoidosis, lung abscess, cystic fibrosis, tuberculosis, and mesothelioma), as well as with some gastrointestinal diseases (including inflammatory bowel disease and hepatic cirrhosis). In some instances, it is occupational, for example, in jackhammer operators.

Clubbing in patients with primary and metastatic lung cancer, mesothelioma, bronchiectasis, or hepatic cirrhosis may be associated with *hypertrophic osteoarthropathy*. In this condition, the subperiosteal formation of new bone in the distal diaphyses of the long bones of the extremities causes pain and symmetric arthritis-like changes in the shoulders, knees, ankles, wrists, and elbows. The diagnosis of hypertrophic osteoarthropathy may be confirmed by bone radiograph or magnetic resonance imaging (MRI). Although the mechanism of clubbing is unclear, it appears to be secondary to humoral substances that cause dilation of the vessels of the distal digits as well as growth factors released from platelet precursors in the digital circulation. In certain circumstances, clubbing is reversible, such as following lung transplantation for cystic fibrosis.

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37 Edema

Eugene Braunwald, Joseph Loscalzo

PLASMA AND INTERSTITIAL FLUID EXCHANGE

About two-thirds of total body water is intracellular and one-third is extracellular. Approximately one-fourth of the latter is in the plasma and the remainder comprises the interstitial fluid. Edema represents an excess of interstitial fluid that has become evident clinically.

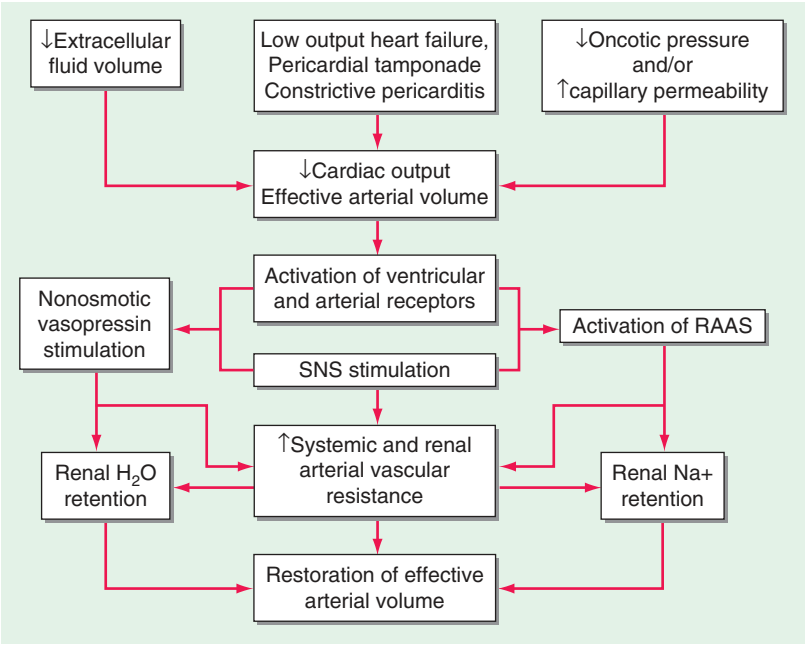
There is constant interchange of fluid between the two compartments of the extracellular fluid. The hydrostatic pressure within the capillaries and the colloid oncotic pressure in the interstitial fluid promote the movement of water and diffusible solutes from plasma to the interstitium. This movement is most prominent at the arterial origin of the capillary and falls progressively with the decline in intracapillary pressure and the rise in oncotic pressure toward the venular end. Fluid is returned from the interstitial space into the vascular system largely through the lymphatic system. These interchanges of fluids are normally balanced so that the volumes of the intravascular and interstitial compartments remain constant. However, a net movement of fluid from the intravascular to the interstitial spaces takes place and may be responsible for the development of edema under the following conditions: (1) an increase in intracapillary hydrostatic pressure; (2) inadequate lymphatic drainage; (3) reductions in the oncotic pressure in the plasma; (4) damage to the capillary endothelial barrier; and (5) increases in the oncotic pressure in the interstitial space.

REDUCTION OF EFFECTIVE ARTERIAL VOLUME

In many forms of edema, the effective arterial blood volume, a parameter that represents the filling of the arterial tree and that effectively perfuses the tissues, is reduced. Underfilling of the arterial tree may be caused by a reduction of cardiac output and/or systemic vascular resistance, by the pooling of blood in the splanchnic veins (as in cirrhosis), and by hypoalbuminemia **(Fig. 37-1*A*)**. As a consequence of this underfilling, a series of physiologic responses designed to restore the effective arterial volume to normal are set into motion. A key element of these responses is the renal retention of sodium and, therefore, water, thereby restoring effective arterial volume, but sometimes also leading to the development or intensification of edema.

RENAL FACTORS AND THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The diminished renal blood flow characteristic of states in which the effective arterial blood volume is reduced is translated by the renal juxtaglomerular cells (specialized myoepithelial cells surrounding the afferent arteriole) into a signal for increased renin release. Renin is an enzyme with a molecular mass of about 40,000 Da that acts on its substrate, angiotensinogen, an α_2-globulin synthesized by the liver, to release angiotensin I, a decapeptide, which in turn is converted to angiotensin II (AII), an octapeptide. AII has generalized vasoconstrictor properties, particularly on the renal efferent arterioles. This action reduces the hydrostatic pressure in the peritubular capillaries, whereas the increased filtration fraction raises the colloid osmotic pressure in these vessels, thereby enhancing salt and water reabsorption in the proximal tubule as well as in the ascending limb of the loop of Henle.



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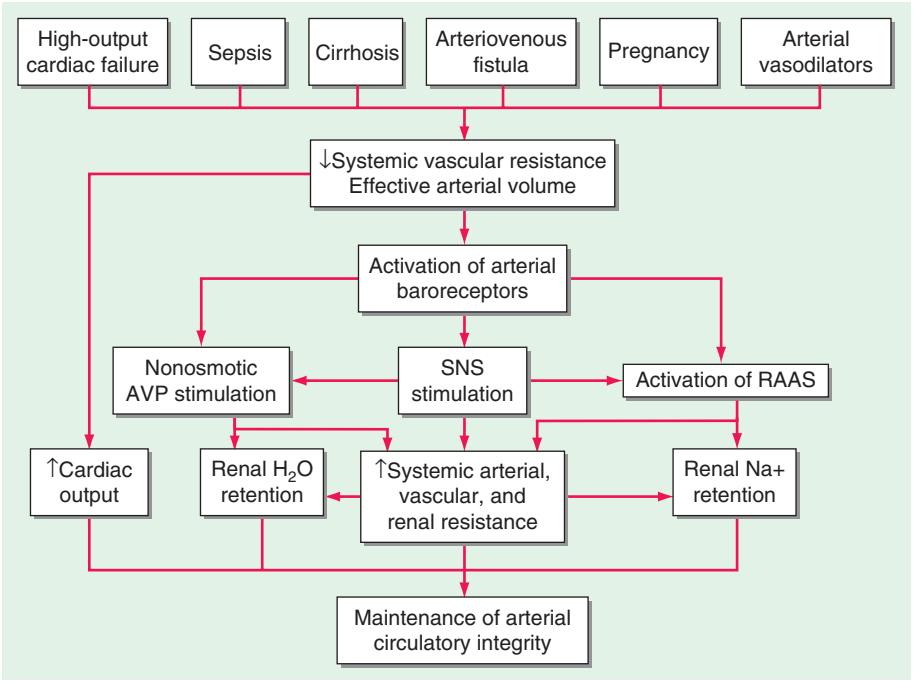

B

FIGURE 37-1 Clinical conditions in which a decrease in cardiac output (*A*) and systemic vascular resistance (*B*) cause arterial underfilling with resulting neurohumoral activation and renal sodium and water retention. In addition to activating the neurohumoral axis, adrenergic stimulation causes renal vasoconstriction and enhances sodium and fluid transport by the proximal tubule epithelium. RAAS, renin-angiotensin aldosterone system; SNS, sympathetic nervous system. *(Modified from RW Schrier: Ann Intern Med 113:155, 1990.)*

The renin-angiotensin-aldosterone system (RAAS) operates as both a hormonal and paracrine system. Its activation causes sodium and water retention and thereby contributes to edema formation. Blockade of the conversion of angiotensin I to AII and blockade of the AII receptors enhance sodium and water excretion and reduce many forms of edema. AII that enters the systemic circulation stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone in turn enhances sodium reabsorption (and potassium excretion) by the collecting tubule, further favoring edema formation. Blockade of the action of aldosterone by spironolactone or eplerenone (aldosterone antagonists) or by amiloride (a blocker of epithelial sodium channels) often induces a moderate diuresis in edematous states.

ARGININE VASOPRESSIN

(See also Chap. 374) The secretion of arginine vasopressin (AVP) by the posterior pituitary gland occurs in response to increased intracellular osmolar concentration; by stimulating V_2 receptors, AVP increases the reabsorption of free water in the distal tubules and collecting ducts of the kidneys, thereby increasing total-body water. Circulating AVP is elevated in many patients with heart failure secondary to a nonosmotic stimulus associated with decreased effective arterial volume and reduced compliance of the left atrium. Such patients fail to show the normal reduction of AVP with a reduction of osmolality, contributing to edema formation and hyponatremia.

ENDOTHELIN-1

This potent peptide vasoconstrictor is released by endothelial cells. Its concentration in the plasma is elevated in patients with severe heart failure and contributes to renal vasoconstriction, sodium retention, and edema.

NATRIURETIC PEPTIDES

Atrial distention causes release into the circulation of atrial natriuretic peptide (ANP), a polypeptide. A high-molecular-weight precursor of ANP is stored in secretory granules within atrial myocytes. A closely related natriuretic peptide (pre-prohormone brain natriuretic peptide) is stored primarily in ventricular myocytes and is released when ventricular diastolic pressure rises. Released ANP and BNP (which is derived from its precursor) bind to the natriuretic receptor-A, which causes: (1) excretion of sodium and water by augmenting glomerular filtration rate, inhibiting sodium reabsorption in the proximal tubule, and inhibiting release of renin and aldosterone; and (2) dilation of arterioles and venules by antagonizing the vasoconstrictor actions of AII, AVP, and sympathetic stimulation. Thus, elevated levels of natriuretic peptides have the capacity to oppose sodium retention in hypervolemic and edematous states.

Although circulating levels of ANP and BNP are elevated in heart failure and in cirrhosis with ascites, these natriuretic peptides are not sufficiently potent to prevent edema formation. Indeed, in edematous states, resistance to the actions of natriuretic peptides may be increased, further reducing their effectiveness.

Further discussion of the control of sodium and water balance is found in **Chap. S1**.

CLINICAL CAUSES OF EDEMA

A weight gain of several kilograms usually precedes overt manifestations of generalized edema. *Anasarca* refers to gross, generalized edema. *Ascites* **(Chap. 46)** and *hydrothorax* refer to accumulation of excess fluid in the peritoneal and pleural cavities, respectively, and are considered special forms of edema.

Edema is recognized by the persistence of an indentation of the skin after pressure known as "pitting" edema. In its more subtle form, edema may be detected by noting that after the stethoscope is removed from the chest wall, the rim of the bell leaves an indentation on the skin of the chest for a few minutes. Edema may be present when the ring on a finger fits more snugly than in the past or when a patient complains

of difficulty putting on shoes, particularly in the evening. Edema may also be recognized by puffiness of the face, which is most readily apparent in the periorbital areas.

GENERALIZED EDEMA

The differences among the major causes of generalized edema are shown in Table 37-1. Cardiac, renal, hepatic, or nutritional disorders are responsible for a large majority of patients with generalized edema. Consequently, the differential diagnosis of generalized edema should be directed toward identifying or excluding these several conditions.

Heart Failure (See also Chap. 252) In heart failure, the impaired systolic emptying of the ventricle(s) and/or the impairment of ventricular relaxation promotes an accumulation of blood in the venous circulation at the expense of the effective arterial volume. In addition, the activation of the sympathetic nervous system and the RAAS (see above) acts in concert to cause renal vasoconstriction and reduction of glomerular filtration and salt and water retention. Sodium and water retention continue, and the increment in blood volume accumulates in the venous circulation, raising venous and intracapillary pressure resulting in edema (Fig. 37-1).

The presence of overt cardiac disease, as manifested by cardiac enlargement and/or ventricular hypertrophy, together with clinical evidence of cardiac failure, such as dyspnea, basilar rales, venous distention, and hepatomegaly, usually indicates that edema results from heart failure. Noninvasive tests such as electrocardiography, echocardiography, and measurements of BNP (or NTproBNP) are helpful in establishing the diagnosis of heart disease. The edema of heart failure typically occurs in the dependent portions of the body.

Edema of Renal Disease (See also Chap. 308) The edema that occurs during the acute phase of glomerulonephritis is characteristically associated with hematuria, proteinuria, and hypertension. In most instances, the edema results from primary retention of sodium and water by the kidneys owing to renal dysfunction. This state differs from most forms of heart failure in that it is characterized by a normal (or sometimes even increased) cardiac output. Patients with *chronic* renal failure may also develop edema due to primary renal retention of sodium and water.

Nephrotic Syndrome and Other Hypoalbuminemic States The primary alteration in the nephrotic syndrome is a diminished colloid oncotic pressure due to losses of large quantities (≥3.5 g/d) of protein into the urine, and hypoalbuminemia (<3.0 g/dL). As a result of the reduced colloid osmotic pressure, the sodium and water that are retained cannot be confined within the vascular compartment, and total and effective arterial blood volumes decline. This process initiates the edema-forming sequence of events described above, including activation of the RAAS. The nephrotic syndrome may occur during the course of a variety of kidney diseases, including glomerulonephritis, diabetic glomerulosclerosis, and hypersensitivity reactions. The edema is diffuse, symmetric, and most prominent in the dependent areas; periorbital edema is most prominent in the morning.

Hepatic Cirrhosis (See also Chap. 337) This condition is characterized in part by hepatic venous outflow obstruction, which in turn expands the splanchnic blood volume, and hepatic lymph formation. Intrahepatic hypertension acts as a stimulus for renal sodium retention and causes a reduction of effective arterial blood volume. These alterations are frequently complicated by hypoalbuminemia secondary to reduced hepatic synthesis of albumin, as well as peripheral arterial vasodilation. These effects reduce the effective arterial blood volume, leading to activation of the sodium- and water-retaining mechanisms described above (Fig. 37-1*B*). The concentration of circulating aldosterone often is elevated by the failure of the liver to metabolize this hormone. Initially, the excess interstitial fluid is localized preferentially proximal (upstream) to the congested portal venous system, causing ascites (Chap. 46). In later stages, particularly when there is severe hypoalbuminemia, peripheral edema may develop. A sizable accumulation of ascitic fluid may increase intraabdominal pressure and impede venous return from the lower extremities and contribute to the accumulation of the edema.

Drug-Induced Edema A large number of widely used drugs can cause edema (Table 37-2). Mechanisms include renal vasoconstriction (NSAIDs and cyclosporine), arteriolar dilation (vasodilators), augmented renal sodium reabsorption (steroid hormones), and capillary damage.

Edema of Nutritional Origin A diet grossly deficient in calories and particularly in protein over a prolonged period may produce hypoproteinemia and edema. The latter may be intensified by the development of beriberi heart disease, which also is of nutritional origin, in which multiple peripheral arteriovenous fistulae result in

TABLE 37-1 Principal Causes of Generalized Edema: History, Physical Examination, and Laboratory Findings

ORGAN SYSTEM	HISTORY	PHYSICAL EXAMINATION	LABORATORY FINDINGS
Cardiac	Dyspnea with exertion prominent—often associated with orthopnea—or paroxysmal nocturnal dyspnea	Elevated jugular venous pressure, ventricular (S_3) gallop; occasionally with displaced or dyskinetic apical pulse; peripheral cyanosis, cool extremities, small pulse pressure when severe	Elevated urea nitrogen-to-creatinine ratio common; serum sodium often diminished; elevated natriuretic peptides
Hepatic	Dyspnea uncommon, except if associated with significant degree of ascites; most often a history of ethanol abuse	Frequently associated with ascites; jugular venous pressure normal or low; blood pressure lower than in renal or cardiac disease; one or more additional signs of chronic liver disease (jaundice, palmar erythema, Dupuytren's contracture, spider angiomata, male gynecomastia; asterixis and other signs of encephalopathy) may be present	If severe, reductions in serum albumin, cholesterol, other hepatic proteins (transferrin, fibrinogen); liver enzymes elevated, depending on the cause and acuity of liver injury; tendency toward hypokalemia, respiratory alkalosis; macrocytosis from folate deficiency
Renal (CRF)	Usually chronic: may be associated with uremic signs and symptoms, including decreased appetite, altered (metallic or fishy) taste, altered sleep pattern, difficulty concentrating, restless legs, or myoclonus; dyspnea can be present, but generally less prominent than in heart failure	Elevated blood pressure; hypertensive retinopathy; nitrogenous fetor; pericardial friction rub in advanced cases with uremia	Elevation of serum creatinine and cystatin C; albuminuria; hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, anemia (usually normocytic)
Renal (NS)	Childhood diabetes mellitus; plasma cell dyscrasias	Periorbital edema; hypertension	Proteinuria (≥3.5 g/d); hypoalbuminemia; hypercholesterolemia; microscopic hematuria

Abbreviations: CRF, chronic renal failure; NS, nephrotic syndrome.

Source: Modified from GM Chertow: Approach to the patient with edema, in *Primary Cardiology*, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

TABLE 37-2 Drugs Associated with Edema Formation

Nonsteroidal anti-inflammatory drugs
Antihypertensive agents
Direct arterial/arteriolar vasodilators
Hydralazine
Clonidine
Methyldopa
Guanethidine
Minoxidil
Calcium channel antagonists
α-Adrenergic antagonists
Thiazolidinediones
Steroid hormones
Glucocorticoids
Anabolic steroids
Estrogens
Progestins
Cyclosporine
Growth hormone
Immunotherapies
Interleukin 2
OKT3 monoclonal antibody

Source: Modified from GM Chertow: Approach to the patient with edema, in *Primary Cardiology*, 2nd ed, E Braunwald, L Goldman (eds). Philadelphia, Saunders, 2003, pp 117–128.

reduced effective systemic perfusion and effective arterial blood volume, thereby enhancing edema formation **(Chap. 326)** (Fig. 37-1*B*). Edema develops or becomes intensified when famished subjects are first provided with an adequate diet. The ingestion of more food may increase the quantity of sodium ingested, which is then retained along with water. So-called refeeding edema also may be linked to increased release of insulin, which directly increases tubular sodium reabsorption. In addition to hypoalbuminemia, hypokalemia and caloric deficits may be involved in the edema of starvation.

LOCALIZED EDEMA

In thrombophlebitis, varicose veins, and in primary venous valve failure, the hydrostatic pressure in the capillary bed upstream (proximal) of the obstruction increases so that an abnormal quantity of fluid is transferred from the vascular to the interstitial space, which may give rise to localized edema. The latter may also occur in lymphatic obstruction caused by chronic lymphangitis, resection of regional lymph nodes, filariasis, and genetic (frequently called primary) lymphedema. The latter is particularly intractable because restriction of lymphatic flow results in both an increase in intracapillary pressure and increased protein concentration in the interstitial fluid, which act in concert to aggravate fluid retention.

Other Causes of Edema These causes include hypothyroidism (myxedema) due to deposition of hyaluronic acid, and hyperthyroidism (pretibial myxedema secondary to Graves' disease), in which edema is typically nonpitting and, in Graves' disease, exogenous hyperadrenocortism; pregnancy; and administration of estrogens and vasodilators, particularly dihydropyridines such as nifedipine.

DISTRIBUTION OF EDEMA

The distribution of edema is an important guide to its cause. Edema associated with heart failure tends to be more extensive in the legs and to be accentuated in the evening, a feature also determined largely by posture. When patients with heart failure are confined to bed, edema may be most prominent in the presacral region.

Edema resulting from hypoproteinemia, as occurs in the nephrotic syndrome, characteristically is generalized, but it is especially evident in the very soft tissues of the eyelids and face and tends to be most pronounced in the morning owing to the recumbent posture assumed during the night. Less common causes of facial edema include trichinosis, allergic reactions, and myxedema. Edema limited to one leg or to one or both arms is usually the result of venous and/or lymphatic obstruction. Unilateral paralysis reduces lymphatic and venous drainage on the affected side and may also be responsible for unilateral edema. In patients with obstruction of the superior vena cava, edema is confined to the face, neck, and upper extremities in which the venous pressure is elevated compared with that in the lower extremities.

APPROACH TO THE PATIENT

Edema

An important first question is whether the edema is localized or generalized. If it is localized, the local phenomena that may be responsible should be identified. If the edema is generalized, one should determine if there is serious hypoalbuminemia, e.g., serum albumin <3.0 g/dl. If so, the history, physical examination, urinalysis, and other laboratory data will help evaluate the question of cirrhosis, severe malnutrition, or the nephrotic syndrome as the underlying disorder. If hypoalbuminemia is not present, it should be determined if there is evidence of heart failure severe enough to promote generalized edema. Finally, it should be ascertained as to whether or not the patient has an adequate urine output or if there is significant oliguria or anuria. **These abnormalities are discussed in Chaps. 48, 304, and 305.**

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38 Approach to the Patient with a Heart Murmur

Patrick T. O'Gara, Joseph Loscalzo

The differential diagnosis of a heart murmur begins with a careful assessment of its major attributes and response to bedside maneuvers. The history, clinical context, and associated physical examination findings provide additional clues to help establish the significance of a heart murmur. Accurate bedside identification of a heart murmur can inform decisions regarding the indications for noninvasive testing and the need for referral to a cardiovascular specialist. Preliminary discussions can be held with the patient regarding antibiotic or rheumatic fever prophylaxis, the need to restrict various forms of physical activity, and the potential role for family screening.

Heart murmurs are caused by audible vibrations that are due to increased turbulence from accelerated blood flow through normal or abnormal orifices; flow through a narrowed or irregular orifice into a dilated vessel or chamber; or backward flow through an incompetent valve, ventricular septal defect, or patent ductus arteriosus. They traditionally are defined by their timing within the cardiac cycle **(Fig. 38-1)**. *Systolic murmurs* begin with or after the first heart sound (S_1) and terminate at or before the component (A_2 or P_2) of the second heart

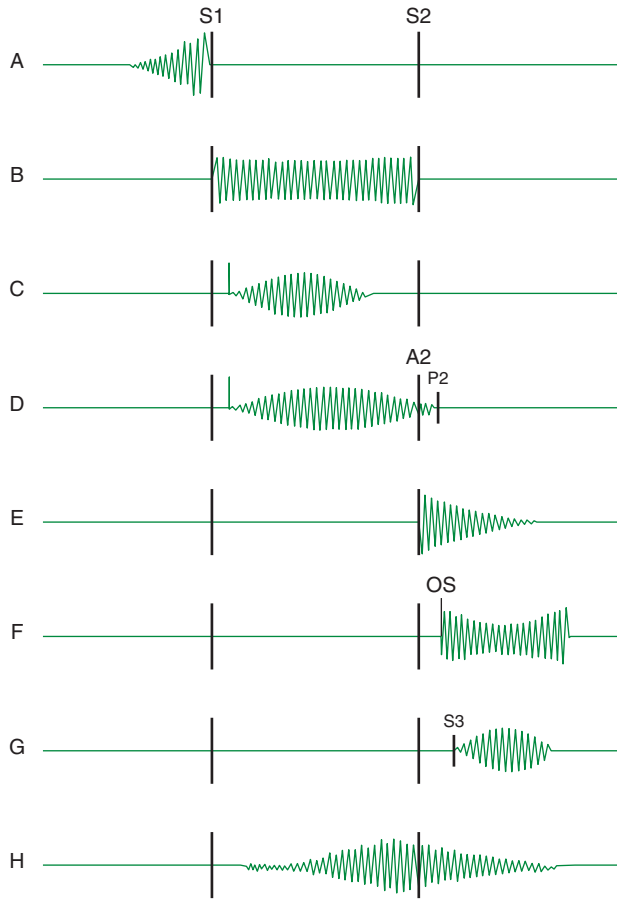

FIGURE 38-1 Diagram depicting principal heart murmurs. ***A.*** Presystolic murmur of mitral or tricuspid stenosis. ***B.*** Holosystolic (pansystolic) murmur of mitral or tricuspid regurgitation or of ventricular septal defect. ***C.*** Aortic ejection murmur beginning with an ejection click and fading before the second heart sound. ***D.*** Systolic murmur in pulmonic stenosis spilling through the aortic second sound, pulmonic valve closure being delayed. ***E.*** Aortic or pulmonary diastolic murmur. ***F.*** Long diastolic murmur of mitral stenosis after the opening snap (OS). ***G.*** Short mid-diastolic inflow murmur after a third heart sound. ***H.*** Continuous murmur of patent ductus arteriosus. *(Adapted from P Wood: Diseases of the Heart and Circulation, London, Eyre & Spottiswood, 1968. Permission granted courtesy of Antony and Julie Wood.)*

sound (S_2) that corresponds to their site of origin (left or right, respectively). *Diastolic murmurs* begin with or after the associated component of S_2 and end at or before the subsequent S_1. *Continuous murmurs* are not confined to either phase of the cardiac cycle but instead begin in early systole and proceed through S_2 into all or part of diastole. The accurate timing of heart murmurs is the first step in their identification. The distinction between S_1 and S_2, and therefore systole and diastole is usually a straightforward process but can be difficult in the setting of a tachyarrhythmia, in which case the heart sounds can be distinguished by simultaneous palpation of the carotid upstroke, which should closely follow S_1.

Duration and Character The duration of a heart murmur depends on the length of time over which a pressure difference exists between two cardiac chambers, the left ventricle and the aorta, the right ventricle and the pulmonary artery, or the great vessels. The magnitude and variability of this pressure difference, coupled with the geometry and compliance of the involved chambers or vessels, dictate the velocity of flow; the degree of turbulence; and the resulting frequency, configuration, and intensity of the murmur. The diastolic murmur of chronic aortic regurgitation (AR) is a blowing, high-frequency event, whereas the murmur of mitral stenosis (MS), indicative of the left atrial–left ventricular diastolic pressure gradient, is a low-frequency event, heard as a rumbling sound with the bell of the stethoscope. The frequency components of a heart murmur may vary at different sites of auscultation. The coarse systolic murmur of aortic stenosis (AS) may sound higher pitched and more acoustically pure at the apex, a phenomenon eponymously referred to as the *Gallavardin effect*. Some murmurs may have a distinct or unusual quality, such as the "honking" sound appreciated in some patients with mitral regurgitation (MR) due to mitral valve prolapse (MVP).

The configuration of a heart murmur may be described as crescendo, decrescendo, crescendo-decrescendo, or plateau. The decrescendo configuration of the murmur of chronic AR **(Fig. 38-1*E*)** can be understood in terms of the progressive decline in the diastolic pressure gradient between the aorta and the left ventricle. The crescendo-decrescendo configuration of the murmur of AS reflects the changes in the systolic pressure gradient between the left ventricle and the aorta as ejection occurs, whereas the plateau configuration of the murmur of chronic MR **(Fig. 38-1*B*)** is consistent with the large and nearly constant pressure difference between the left ventricle and the left atrium.

Intensity The intensity of a heart murmur is graded on a scale of 1–6 (or I–VI). A grade 1 murmur is very soft and is heard only with great effort. A grade 2 murmur is easily heard but not particularly loud. A grade 3 murmur is loud but is not accompanied by a palpable thrill over the site of maximal intensity. A grade 4 murmur is very loud and accompanied by a thrill. A grade 5 murmur is loud enough to be heard with only the edge of the stethoscope touching the chest, whereas a grade 6 murmur is loud enough to be heard with the stethoscope slightly off the chest. Murmurs of grade 3 or greater intensity usually signify important structural heart disease and indicate high blood flow velocity at the site of murmur production. Small ventricular septal defects (VSDs), for example, are accompanied by loud, usually grade 4 or greater, systolic murmurs as blood is ejected at high velocity from the left ventricle to the right ventricle. Low-velocity events, such as left-to-right shunting across an atrial septal defect (ASD), are usually silent. The intensity of a heart murmur may be diminished by any process that increases the distance between the intracardiac source and the stethoscope on the chest wall, such as obesity, obstructive lung disease, or a large pericardial effusion. The intensity of a murmur also may be misleadingly soft when cardiac output is reduced significantly or when the pressure gradient between the involved cardiac structures is low.

Location and Radiation Recognition of the location and radiation of the murmur help facilitate its accurate identification **(Fig. 38-2)**. Adventitious sounds, such as a systolic click or diastolic snap, or abnormalities of S_1 or S_2 may provide additional clues. Careful attention to the characteristics of the murmur and other heart sounds during the respiratory cycle and the performance of simple bedside maneuvers complete the auscultatory examination. These features, along with recommendations for further testing, are discussed below in the context of specific systolic, diastolic, and continuous heart murmurs **(Table 38-1)**.

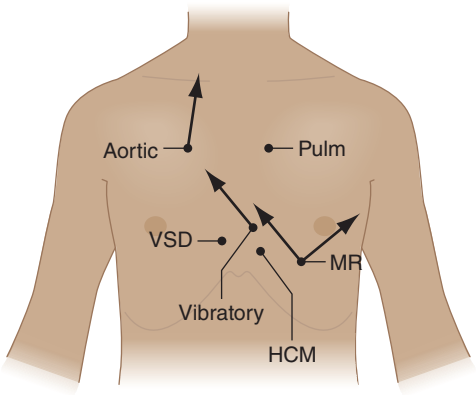

FIGURE 38-2 Maximal intensity and radiation of six isolated systolic murmurs. Aortic, aortic stenosis; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; Pulm, pulmonary stenosis; VSD, ventricular septal defect. *(From JB Barlow: Perspectives on the Mitral Valve. Philadelphia, FA Davis, 1987, p 140.)*

TABLE 38-1 Principal Causes of Heart Murmurs

Systolic Murmurs
Early systolic
Mitral
Acute MR
VSD
Muscular
Nonrestrictive with pulmonary hypertension
Tricuspid
TR with normal pulmonary artery pressure
Midsystolic
Aortic
Obstructive
Supravalvular–supravalvular AS, coarctation of the aorta
Valvular–AS and aortic sclerosis
Subvalvular–discrete, tunnel or HOCM
Increased flow, hyperkinetic states, AR, complete heart block
Dilation of ascending aorta, atheroma, aortitis
Pulmonary
Obstructive
Supravalvular–pulmonary artery stenosis
Valvular–pulmonic valve stenosis
Subvalvular–infundibular stenosis (dynamic)
Increased flow, hyperkinetic states, left-to-right shunt (e.g., ASD)
Dilation of pulmonary artery
Late systolic
Mitral
MVP, acute myocardial ischemia
Tricuspid
TVP
Holosystolic
Atrioventricular valve regurgitation (MR, TR)
Left-to-right shunt at ventricular level (VSD)
Early Diastolic Murmurs
AR
Valvular: congenital (bicuspid valve), rheumatic deformity, endocarditis, prolapse, trauma, post-valvulotomy
Dilation of valve ring: aorta dissection, annuloaortic ectasia, cystic medial degeneration, hypertension, ankylosing spondylitis
Widening of commissures: syphilis
Pulmonic regurgitation
Valvular: post-valvulotomy, endocarditis, rheumatic fever, carcinoid
Dilation of valve ring: pulmonary hypertension; Marfan syndrome
Congenital: isolated or associated with tetralogy of Fallot, VSD, pulmonic stenosis
Mid-Diastolic Murmurs
Mitral
MS
Carey-Coombs murmur (mid-diastolic apical murmur in acute rheumatic fever)
Increased flow across nonstenotic mitral valve (e.g., MR, VSD, PDA, high-output states, and complete heart block)
Tricuspid
Tricuspid stenosis
Increased flow across nonstenotic tricuspid valve (e.g., TR, ASD, and anomalous pulmonary venous return)
Left and right atrial tumors (myxoma)
Severe AR (Austin Flint murmur)

Continuous Murmurs	
Patent ductus arteriosus	Proximal coronary artery stenosis
Coronary AV fistula	Mammary souffle of pregnancy
Ruptured sinus of Valsalva aneurysm	Pulmonary artery branch stenosis
Aortic septal defect	Bronchial collateral circulation
Cervical venous hum	Small (restrictive) ASD with MS
Anomalous left coronary artery	Intercostal AV fistula

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; AV, arteriovenous; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; TR, tricuspid regurgitation; TVP, tricuspid valve prolapse; VSD, ventricular septal defect.

Source: E Braunwald, JK Perloff, in D Zipes et al (eds): *Braunwald's Heart Disease*, 7th ed. Philadelphia, Elsevier, 2005; PJ Norton, RA O'Rourke, in E Braunwald, L Goldman (eds): *Primary Cardiology*, 2nd ed. Philadelphia, Elsevier, 2003.

SYSTOLIC HEART MURMURS

Early Systolic Murmurs Early systolic murmurs begin with S_1 and extend for a variable period, ending well before S_2. Their causes are relatively few in number. *Acute, severe MR* into a normal-sized, relatively noncompliant left atrium results in an early, decrescendo systolic murmur best heard at or just medial to the apical impulse. These characteristics reflect the progressive attenuation of the pressure gradient between the left ventricle and the left atrium during systole owing to the rapid rise in left atrial pressure caused by the sudden volume load into an unprepared, noncompliant chamber and contrast sharply with the auscultatory features of chronic MR. Clinical settings in which acute, severe MR occur include (1) papillary muscle rupture complicating acute myocardial infarction (MI) **(Chap. 269)**, (2) rupture of chordae tendineae in the setting of myxomatous mitral valve disease (MVP, **Chap. 260**), (3) infective endocarditis **(Chap. 123)**, and (4) blunt chest wall trauma.

Acute, severe MR from papillary muscle rupture usually accompanies an inferior, posterior, or lateral MI, and occurs 2–7 days after presentation. It often is signaled by chest pain, hypotension, and pulmonary edema, but a murmur may be absent in up to 50% of cases. The posteromedial papillary muscle is involved 6 to 10 times more frequently than the anterolateral papillary muscle. The murmur is to be distinguished from that associated with post-MI ventricular septal rupture, which is accompanied by a systolic thrill at the left sternal border in nearly all patients and is holosystolic in duration. A new heart murmur after an MI is an indication for transthoracic echocardiography (TTE) **(Chap. 236)**, which allows bedside delineation of its etiology and pathophysiologic significance. The distinction between acute MR and ventricular septal rupture also can be achieved with right-sided heart catheterization, sequential determination of oxygen saturations, and analysis of the pressure waveforms (tall *v* wave in the pulmonary artery wedge pressure in MR). Post-MI mechanical complications of this nature mandate aggressive medical stabilization and prompt referral for surgical repair.

Spontaneous chordal rupture can complicate the course of myxomatous mitral valve disease (MVP) and result in new-onset or "acute on chronic" severe MR. MVP may occur as an isolated phenomenon, or the lesion may be part of a more generalized connective tissue disorder as seen, for example, in patients with Marfan syndrome. Acute, severe MR as a consequence of infective endocarditis results from destruction of leaflet tissue, chordal rupture, or both. Blunt chest wall trauma is usually self-evident but may be disarmingly trivial; it can result in papillary muscle contusion and rupture, chordal detachment, or leaflet avulsion. TTE is indicated in all cases of suspected acute, severe MR to define its mechanism and severity, delineate left ventricular size and systolic function, and provide an assessment of suitability for primary valve repair.

A congenital, small muscular VSD **(Chap. 264)** may be associated with an early systolic murmur. The defect closes progressively during septal contraction, and thus the murmur is confined to early systole. It is localized to the left sternal border (Fig. 38-2) and is usually of grade 4 or 5 intensity. Signs of pulmonary hypertension or left ventricular volume overload are absent. Anatomically large and uncorrected VSDs, which usually involve the membranous portion of the septum, may lead to pulmonary hypertension. The murmur associated with the left-to-right shunt, which earlier may have been holosystolic, becomes limited to the first portion of systole as the elevated pulmonary vascular resistance leads to an abrupt rise in right ventricular pressure and an attenuation of the interventricular pressure gradient during the remainder of the cardiac cycle. In such instances, signs of pulmonary hypertension (right ventricular lift, loud and single or closely split S_2) may predominate. The murmur is best heard along the left sternal border but is softer. Suspicion of a VSD is an indication for TTE.

Tricuspid regurgitation (TR) with normal pulmonary artery pressures, as may occur with infective endocarditis, may produce an early systolic murmur. The murmur is soft (grade 1 or 2), is best heard at the lower left sternal border and may increase in intensity with inspiration

(Carvallo's sign). Regurgitant *c-v* waves may be visible in the jugular venous pulse. TR in this setting is not associated with signs of right heart failure.

Midsystolic Murmurs Midsystolic murmurs begin at a short interval after S_1, end before S_2 **(Fig. 38-1*C*)** and are usually crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. The murmur of AS is usually loudest to the right of the sternum in the second intercostal space (aortic area, Fig. 38-2) and radiates into the carotids. Transmission of the midsystolic murmur to the apex, where it becomes higher-pitched, is common (Gallavardin effect; see above).

Differentiation of this apical systolic murmur from MR can be difficult. The murmur of AS will increase in intensity or become louder, in the beat after a premature beat, whereas the murmur of MR will have constant intensity from beat to beat. The intensity of the AS murmur also varies directly with the cardiac output. With a normal cardiac output, a systolic thrill and a grade 4 or higher murmur suggest severe AS. The murmur is softer in the setting of heart failure and low cardiac output. Other auscultatory findings of severe AS include a soft or absent A_2, paradoxical splitting of S_2, an apical S_4, and a late-peaking systolic murmur. In children, adolescents, and young adults with congenital valvular AS, an early ejection sound (click) is usually audible, more often along the left sternal border than at the base. Its presence signifies a flexible, noncalcified bicuspid valve (or one of its variants) and localizes the left ventricular outflow obstruction to the valvular (rather than sub- or supravalvular) level.

Assessment of the volume and rate of rise of the carotid pulse can provide additional information. A small and delayed upstroke (*parvus et tardus*) is consistent with severe AS. The carotid pulse examination is less discriminatory, however, in older patients with stiffened arteries. The electrocardiogram (ECG) shows signs of left ventricular hypertrophy (LVH) as the severity of the stenosis increases. TTE is indicated to assess the anatomic features of the aortic valve, the severity of the stenosis, left ventricular size, wall thickness and function, and the size and contour of the aortic root and proximal ascending aorta.

The obstructive form of hypertrophic cardiomyopathy (HOCM) is associated with a midsystolic murmur that is usually loudest along the left sternal border or between the left lower sternal border and the apex (**Chap. 254**, Fig. 38-2). The murmur is produced by both dynamic left ventricular outflow tract obstruction and MR, and thus, its configuration is a hybrid between ejection and regurgitant phenomena. The intensity of the murmur may vary from beat to beat and after provocative maneuvers but usually does not exceed grade 3. The murmur classically will increase in intensity with maneuvers that result in increasing degrees of outflow tract obstruction, such as a reduction in preload or afterload (Valsalva, standing, vasodilators), or with an augmentation of contractility (inotropic stimulation). Maneuvers that increase preload (squatting, passive leg raising, volume administration) or afterload (squatting, vasopressors) or that reduce contractility (β-adrenoreceptor blockers) decrease the intensity of the murmur. In rare patients, there may be reversed splitting of S_2. A sustained left ventricular apical impulse and an S_4 may be appreciated. In contrast to AS, the carotid upstroke is rapid and of normal volume. Rarely, it is bisferiens or bifid in contour **(see Fig. 234-2*D*)** due to midsystolic closure of the aortic valve. LVH is present on the ECG, and the diagnosis is confirmed by TTE. Although the systolic murmur associated with MVP behaves similarly to that due to HOCM in response to the Valsalva maneuver and to standing/squatting **(Fig. 38-3)**, these two lesions can be distinguished on the basis of their associated findings, such as the presence of LVH in HOCM or a nonejection click in MVP.

The midsystolic, crescendo-decrescendo murmur of congenital pulmonic stenosis (PS, **Chap. 264**) is best appreciated in the second and third left intercostal spaces (pulmonic area) **(Figs.** 38-2 and **38-4)**. The duration of the murmur lengthens and the intensity of P_2 diminishes with increasing degrees of valvular stenosis **(Fig. 38-1*D*)**. An early ejection sound, the intensity of which decreases with inspiration, is heard in younger patients. A parasternal lift and ECG evidence of right ventricular hypertrophy indicate severe pressure overload. If obtained, the chest x-ray may show poststenotic dilation of the main pulmonary artery. TTE is recommended for complete characterization.

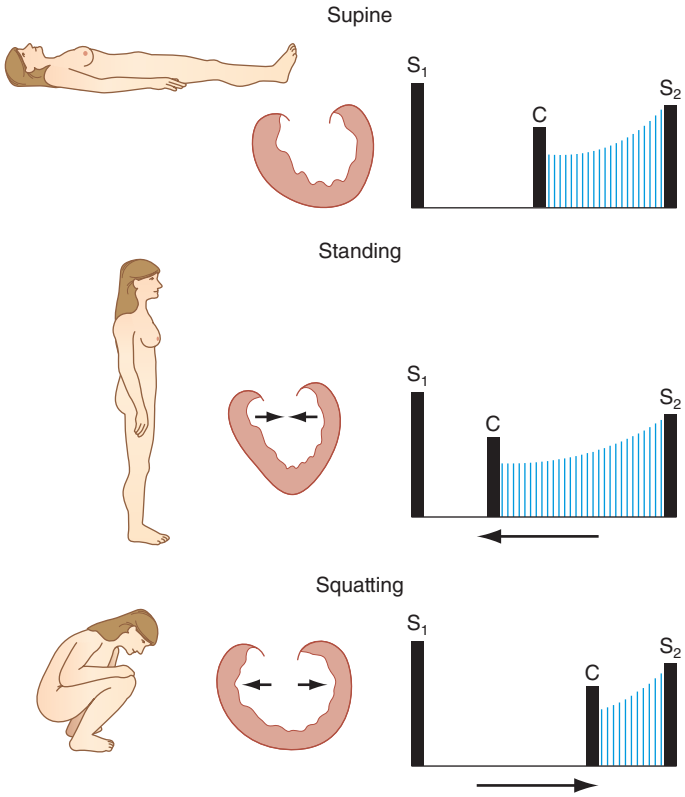

FIGURE 38-3 A midsystolic nonejection sound (C) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to the second heart sound (S_2). Standing decreases venous return; the heart becomes smaller; C moves closer to the first heart sound (S_1), and the mitral regurgitant murmur has an earlier onset. With prompt squatting, venous return and afterload increase; the heart becomes larger; C moves toward S_2; and the duration of the murmur shortens. The systolic murmur of hypertrophic obstructive cardiomyopathy behaves similarly. *(From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 13. Copyright, American Heart Association.)*

Significant left-to-right intracardiac shunting due to an ASD **(Chap. 264)** leads to an increase in pulmonary blood flow and a grades 2–3 midsystolic murmur at the middle to upper left sternal border attributed to increased flow rates across the pulmonic valve with fixed splitting of S_2. Ostium secundum ASDs are the most common cause of these shunts in adults. Features suggestive of a primum ASD include the coexistence of MR due to a cleft anterior mitral valve leaflet and left axis deviation of the QRS complex on the ECG. With sinus venosus ASDs, the left-to-right shunt is usually not large enough to result in a systolic murmur, although the ECG may show abnormalities of sinus node function. A grade 2 or 3 midsystolic murmur may also be heard best at the upper left sternal border in patients with idiopathic dilation of the pulmonary artery; a pulmonary ejection sound is also present in these patients. TTE is indicated to evaluate a grade 2 or 3 midsystolic murmur when there are other signs of cardiac disease.

An isolated grade 1 or 2 midsystolic murmur, heard in the absence of symptoms or signs of heart disease, is most often a benign finding for which no further evaluation, including TTE, is necessary. The most common example of a murmur of this type in an older adult patient is the crescendo-decrescendo murmur of aortic valve sclerosis, heard at the second right interspace (Fig. 38-2). Aortic sclerosis is defined as focal thickening and calcification of the aortic valve to a degree that does not interfere with leaflet opening. The carotid upstrokes are normal, and electrocardiographic LVH is not present. A grade 1 or 2 midsystolic murmur often can be heard at the left sternal border with pregnancy, hyperthyroidism, or anemia, physiologic states that are associated with accelerated blood flow. *Still's murmur* refers to a benign

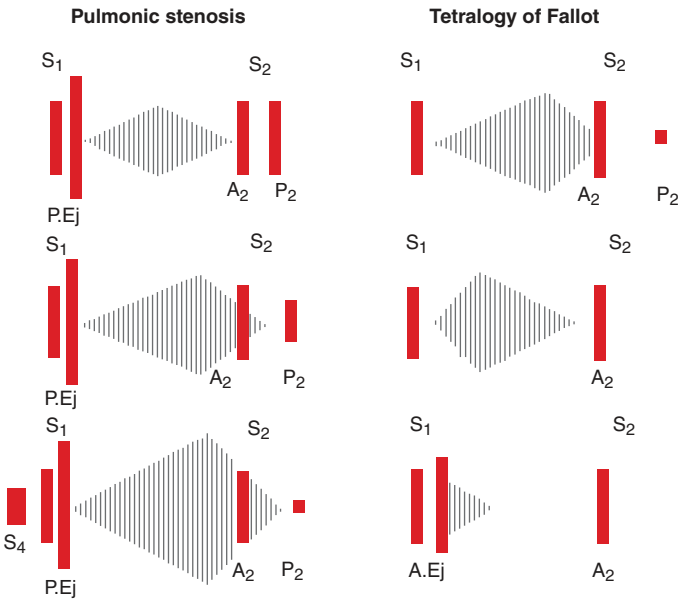

FIGURE 38-4 ***Left.*** In valvular pulmonic stenosis with intact ventricular septum, right ventricular systolic ejection becomes progressively longer, with increasing obstruction to flow. As a result, the murmur becomes longer and louder, enveloping the aortic component of the second heart sound (A_2). The pulmonic component (P_2) occurs later, and splitting becomes wider but more difficult to hear because A_2 is lost in the murmur and P_2 becomes progressively fainter and lower pitched. As the pulmonic gradient increases, the isometric contraction phase shortens until the pulmonic valve ejection sound fuses with the first heart sound (S_1). In severe pulmonic stenosis with concentric hypertrophy and decreasing right ventricular compliance, a fourth heart sound appears. ***Right.*** In tetralogy of Fallot with increasing obstruction at the pulmonic infundibular area, an increasing amount of right ventricular blood is shunted across the silent ventricular septal defect and flow across the obstructed outflow tract decreases. Therefore, with increasing obstruction the murmur becomes shorter, earlier, and fainter. P_2 is absent in severe tetralogy of Fallot. A large aortic root receives almost all cardiac output from both ventricular chambers, and the aorta dilates and is accompanied by a root ejection sound that does not vary with respiration. *(From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 45. Copyright, American Heart Association.)*

grade 2, vibratory or musical midsystolic murmur at the mid or lower left sternal border in normal children and adolescents, best heard in the supine position (Fig. 38-2).

Late Systolic Murmurs A late systolic murmur that is best heard at the left ventricular apex is usually due to MVP **(Chap. 260)**. Often, this murmur is introduced by one or more nonejection clicks. The radiation of the murmur can help identify the specific mitral leaflet involved in the process of prolapse or flail. The term *flail* refers to the movement made by an unsupported portion of the leaflet (usually the tip) after loss of its chordal attachment(s). With posterior leaflet prolapse or flail, the resultant jet of MR is directed anteriorly and medially, as a result of which the murmur radiates to the base of the heart and masquerades as AS. Anterior leaflet prolapse or flail results in a posteriorly directed MR jet that radiates to the axilla or left infrascapular region. Leaflet flail is associated with a murmur of grade 3 or 4 intensity that can be heard throughout the precordium in thin-chested patients. The presence of an S_3 or a short, rumbling mid-diastolic murmur due to enhanced flow signifies severe MR.

Bedside maneuvers that decrease left ventricular preload, such as standing, will cause the click and murmur of MVP to move closer to the first heart sound, as leaflet prolapse occurs earlier in systole. Standing also causes the murmur to become louder and longer. With squatting, left ventricular preload and afterload are increased abruptly, leading to an increase in left ventricular volume, and the click and murmur move away from the first heart sound as leaflet prolapse is delayed; the murmur becomes softer and shorter in duration (Fig. 38–3). As noted above, these responses to standing and squatting are directionally similar to those observed in patients with HOCM.

A late, apical systolic murmur indicative of MR may be heard transiently in the setting of acute myocardial ischemia; it is due to apical tethering and malcoaptation of the leaflets in response to structural and functional changes of the ventricle and mitral annulus. The intensity of the murmur varies as a function of left ventricular afterload and will increase in the setting of hypertension. TTE is recommended for assessment of late systolic murmurs.

Holosystolic Murmurs **(Figs. 38-1*B* and 38-5)** Holosystolic murmurs begin with S_1 and continue through systole to S_2. They are usually indicative of chronic mitral or tricuspid valve regurgitation or a VSD and warrant TTE for further characterization. The holosystolic murmur of chronic MR is best heard at the left ventricular apex and radiates to the axilla (Fig. 38-2); it is usually high-pitched and plateau in configuration because of the wide difference between left ventricular and left atrial pressure throughout systole. In contrast to acute MR, left atrial compliance is normal or even increased in chronic MR. As a result, there is only a small increase in left atrial pressure for any increase in regurgitant volume.

Several conditions are associated with chronic MR and an apical holosystolic murmur, including rheumatic scarring of the leaflets, mitral annular calcification, postinfarction left ventricular remodeling, and severe left ventricular chamber enlargement. The circumference of the mitral annulus increases as the left ventricle enlarges and leads to failure of leaflet coaptation with central MR in patients with dilated cardiomyopathy **(Chap. 254)**. The severity of the MR is worsened by any contribution from apical displacement of the papillary muscles and leaflet tethering (remodeling). Because the mitral annulus is contiguous with the left atrial endocardium, gradual enlargement of the left atrium from chronic MR will result in further stretching of the annulus and more MR; thus, "MR begets MR." Chronic severe MR results in enlargement and leftward displacement of the left ventricular apex beat and, in some patients, a diastolic filling complex, as described previously **(Fig. 38-1*G*)**.

The holosystolic murmur of chronic TR is generally softer than that of MR, is loudest at the left lower sternal border, and usually increases in intensity with inspiration (Carvallo's sign). Associated signs include *c-v* waves in the jugular venous pulse, an enlarged and pulsatile liver, ascites, and peripheral edema. The abnormal jugular venous waveforms are the predominant finding and seen very often in the absence of an audible murmur despite Doppler echocardiographic verification of TR. Causes of *primary* TR include myxomatous disease (prolapse), endocarditis, rheumatic disease, radiation, carcinoid, Ebstein's anomaly, and chordal detachment as a complication of right ventricular endomyocardial biopsy. TR is much more commonly a passive process that results secondarily from annular enlargement due to right ventricular dilation in the face of volume or pressure overload or adverse right ventricular remodeling.

The holosystolic murmur of a VSD is loudest at the mid- to lower-left sternal border (Fig. 38-2) and radiates widely. A thrill is present at the site of maximal intensity in the majority of patients. There is no change in the intensity of the murmur with inspiration. The intensity of the murmur varies as a function of the anatomic size of the defect. Small, restrictive VSDs, as exemplified by the *maladie de Roger*, create a very loud murmur due to the significant and sustained systolic pressure gradient between the left and right ventricles. With large defects, the ventricular pressures tend to equalize, shunt flow is balanced, and a murmur is not appreciated. The distinction between post-MI ventricular septal rupture and MR has been reviewed previously.

DIASTOLIC HEART MURMURS

Early Diastolic Murmurs (Fig. 38-1*E*) Chronic AR results in a high-pitched, blowing, decrescendo, early- to mid-diastolic murmur that begins after the aortic component of S_2 (A_2), and is best heard at the second right interspace. The murmur may be soft and difficult to hear unless auscultation is performed with the patient leaning forward at end expiration. This maneuver brings the aortic root closer to the

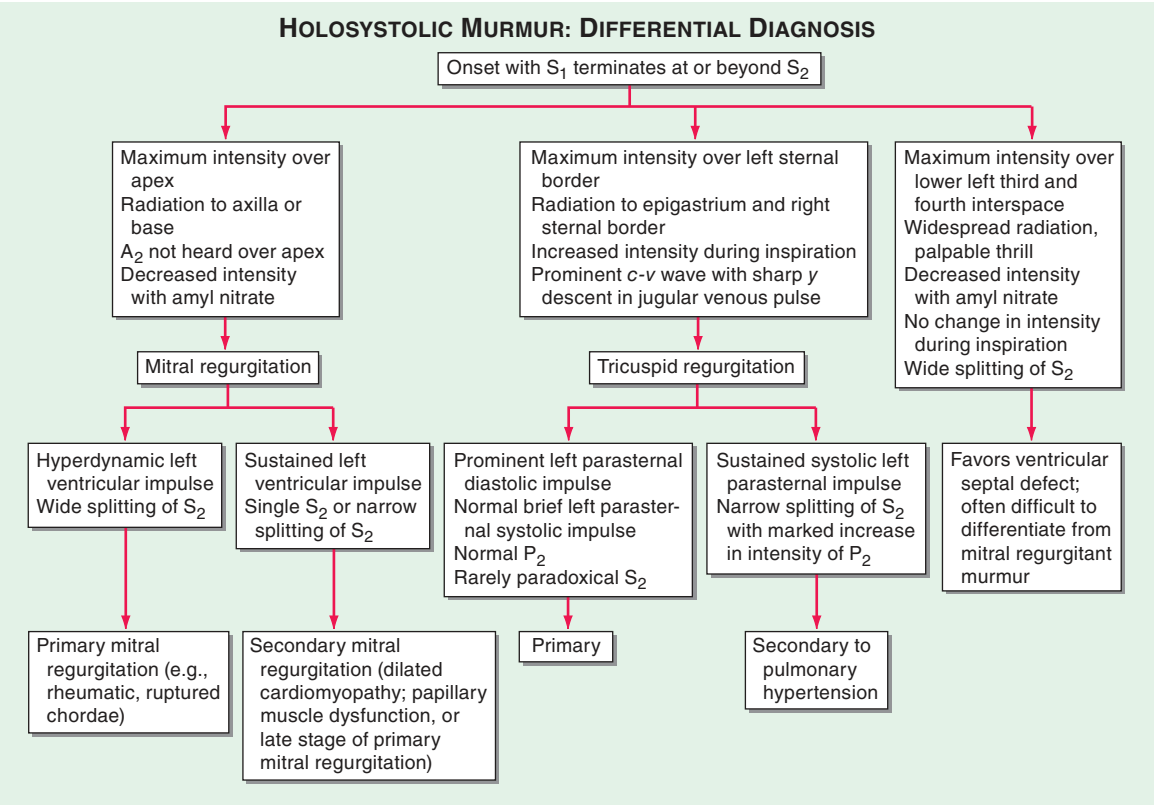

FIGURE 38-5 Differential diagnosis of a holosystolic murmur.

anterior chest wall. Radiation of the murmur may provide a clue to the cause of the AR. With primary valve disease, such as that due to congenital bicuspid disease, prolapse, or endocarditis, the diastolic murmur tends to radiate along the left sternal border, where it is often louder than appreciated in the second right interspace. When AR is caused by aortic root disease, the diastolic murmur may radiate along the right sternal border. Diseases of the aortic root cause dilation or distortion of the aortic annulus and failure of leaflet coaptation. Causes include Marfan syndrome with aneurysm formation, annuloaortic ectasia, ankylosing spondylitis, and aortic dissection.

Chronic, severe AR also may produce a lower-pitched mid to late, grade 1 or 2 diastolic murmur at the apex (Austin Flint murmur), which is thought to reflect turbulence at the mitral inflow area from the admixture of regurgitant (aortic) and forward (mitral) blood flow. This lower-pitched, apical diastolic murmur can be distinguished from that due to MS by the absence of an opening snap and the response of the murmur to a vasodilator challenge. Lowering afterload with an agent such as amyl nitrite will decrease the duration and magnitude of the aortic–left ventricular diastolic pressure gradient, and thus the Austin Flint murmur of severe AR will become shorter and softer. The intensity of the diastolic murmur of MS **(Fig. 38-6)** may either remain constant or increase with afterload reduction because of the reflex increase in cardiac output and mitral valve flow.

Although AS and AR may coexist, a grade 2 or 3 crescendo-decrescendo midsystolic murmur frequently is heard at the base of the heart in patients with isolated, severe AR and is due to an increased volume and rate of systolic flow. Accurate bedside identification of coexistent AS can be difficult unless the carotid pulse examination is abnormal or the midsystolic murmur is of grade 4 or greater intensity. In the absence of heart failure, chronic severe AR is accompanied by several peripheral signs of significant diastolic runoff, including a wide pulse pressure, a "water-hammer" carotid upstroke (Corrigan's pulse), and Quincke's pulsations of the nail beds. The diastolic murmur of *acute, severe AR* is notably shorter in duration and lower pitched than the murmur of chronic AR. It can be very difficult to appreciate in the presence of a rapid heart rate. These attributes reflect the abrupt rate of rise of diastolic pressure within the unprepared and noncompliant left ventricle and the correspondingly rapid decline in the aortic–left ventricular diastolic pressure gradient. Left ventricular diastolic pressure may increase sufficiently to result in premature closure of the mitral valve and a soft first heart sound. Peripheral signs of significant diastolic runoff are not present.

Pulmonic regurgitation (PR) results in a decrescendo, early to mid-diastolic murmur (*Graham Steell murmur*) that begins after the pulmonic component of S_2 (P_2), is best heard at the second left interspace, and radiates along the left sternal border. The intensity of the murmur may increase with inspiration. PR is most commonly due to dilation of the valve annulus from chronic elevation of the pulmonary

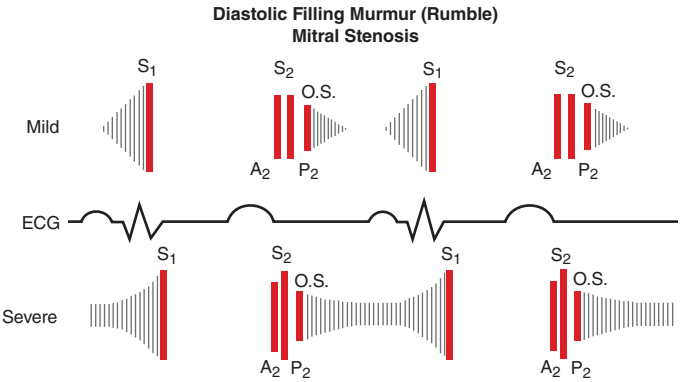

FIGURE 38-6 Diastolic filling murmur (rumble) in mitral stenosis. In mild mitral stenosis, the diastolic gradient across the valve is limited to the phases of rapid ventricular filling in early diastole and presystole. The rumble may occur during either or both periods. As the stenotic process becomes severe, a large pressure gradient exists across the valve during the entire diastolic filling period, and the rumble persists throughout diastole. As the left atrial pressure becomes greater, the interval between A_2 (or P_2) and the opening snap (O.S.) shortens. In severe mitral stenosis, secondary pulmonary hypertension develops and results in a loud P_2 and the splitting interval usually narrows. ECG, electrocardiogram. *(From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright, American Heart Association.)*

artery pressure. Signs of pulmonary hypertension, including a right ventricular lift and a loud, single or narrowly split S_2, are present. These features also help distinguish PR from AR as the cause of a decrescendo diastolic murmur heard along the left sternal border. PR in the absence of pulmonary hypertension can occur with endocarditis or a congenitally deformed valve. It is usually present after repair of tetralogy of Fallot in childhood. When pulmonary hypertension is not present, the diastolic murmur is softer and lower pitched than the classic Graham Steell murmur, and the severity of the PR can be difficult to appreciate.

TTE is indicated for the further evaluation of a patient with an early to mid-diastolic murmur. Longitudinal assessment of lesion severity, ventricular size, and of systolic function helps guide a potential decision for surgical management. TTE also can provide anatomic information regarding the root and proximal ascending aorta, although computed tomographic or magnetic resonance angiography may be indicated for more precise characterization **(Chap. 236)**.

Mid-Diastolic Murmurs (**Figs. 38-1*F*** and 38-1*G*) Mid-diastolic murmurs result from obstruction and/or augmented flow at the level of the mitral or tricuspid valve. Rheumatic fever is the most common cause of MS (Fig. 38-6). In younger patients with pliable valves, S_1 is loud and the murmur begins after an opening snap, which is a high-pitched sound that occurs shortly after S_2. The interval between the pulmonic component of the second heart sound (P_2) and the opening snap is inversely related to the magnitude of the left atrial–left ventricular pressure gradient. The murmur of MS is low-pitched and thus is best heard with the bell of the stethoscope. It is loudest at the left ventricular apex and often is appreciated only when the patient is turned in the left lateral decubitus position. It is usually of grade 1 or 2 intensity but may be absent when the cardiac output is severely reduced despite significant obstruction. The intensity of the murmur increases during maneuvers that increase cardiac output and mitral valve flow, such as exercise. The duration of the murmur reflects the length of time over which left atrial pressure exceeds left ventricular diastolic pressure. An increase in the intensity of the murmur just before S_1, a phenomenon known as *presystolic accentuation* (Figs. 38-1*A* and 38-6), occurs in patients in sinus rhythm and is due to a late increase in transmitral flow with atrial contraction. Presystolic accentuation does not occur in patients with atrial fibrillation.

The mid-diastolic murmur associated with tricuspid stenosis is best heard at the lower left sternal border and increases in intensity with inspiration. A prolonged *y* descent may be visible in the jugular venous waveform. This murmur is very difficult to hear and often is obscured by left-sided acoustical events.

There are several other causes of mid-diastolic murmurs. Large left atrial myxomas may prolapse across the mitral valve and cause variable degrees of obstruction to left ventricular inflow **(Chap. 266)**. The murmur associated with an atrial myxoma may change in duration and intensity with changes in body position. An opening snap is not present, and there is no presystolic accentuation. Augmented mitral diastolic flow can occur with isolated severe MR or with a large left-to-right shunt at the ventricular or great vessel level and produce a soft, rapid filling sound (S_3) followed by a short, low-pitched mid-diastolic apical murmur (Fig. 38-1*G*). The Austin Flint murmur of severe, chronic AR has already been described.

A short, mid-diastolic murmur is rarely heard during an episode of acute rheumatic fever (Carey-Coombs murmur) and probably is due to flow through an edematous mitral valve. An opening snap is not present in the acute phase, and the murmur dissipates with resolution of the acute attack. Complete heart block with dyssynchronous atrial and ventricular activation may be associated with intermittent mid- to late diastolic murmurs if atrial contraction occurs when the mitral valve is partially closed. Mid-diastolic murmurs indicative of increased tricuspid valve flow can occur with severe, isolated TR and with large ASDs and significant left-to-right shunting. Other signs of an ASD are present **(Chap. 264)**, including fixed splitting of S_2 and a midsystolic murmur at the mid- to upper left sternal border. TTE is indicated for evaluation of a patient with a mid- to late diastolic murmur. Findings specific to the diseases discussed above will help guide management.

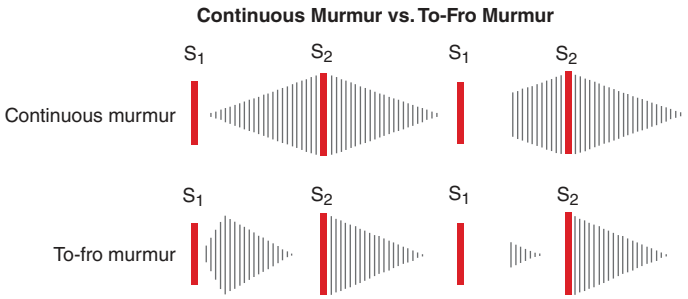

FIGURE 38-7 Comparison of the continuous murmur and the to-fro murmur. During abnormal communication between high-pressure and low-pressure systems, a large pressure gradient exists throughout the cardiac cycle, producing a continuous murmur. A classic example is patent ductus arteriosus. At times, this type of murmur can be confused with a to-fro murmur, which is a combination of systolic ejection murmur and a murmur of semilunar valve incompetence. A classic example of a to-fro murmur is aortic stenosis and regurgitation. A continuous murmur crescendos to near the second heart sound (S_2), whereas a to-fro murmur has two components. The midsystolic ejection component decrescendos and disappears as it approaches S_2. *(From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright, American Heart Association.)*

CONTINUOUS MURMURS

(Figs. 38-1*H* and 38-7) Continuous murmurs begin in systole, peak near the second heart sound, and continue into all or part of diastole. Their presence throughout the cardiac cycle implies a pressure gradient between two chambers or vessels during both systole and diastole. The continuous murmur associated with a patent ductus arteriosus is best heard at the upper left sternal border. Large, uncorrected shunts may lead to pulmonary hypertension, attenuation or obliteration of the diastolic component of the murmur, reversal of shunt flow, and differential cyanosis of the lower extremities. A ruptured sinus of Valsalva aneurysm creates a continuous murmur of abrupt onset at the upper right sternal border. Rupture typically occurs into a right heart chamber, and the murmur is indicative of a continuous pressure difference between the aorta and either the right ventricle or the right atrium. A continuous murmur also may be audible along the left sternal border with a coronary arteriovenous fistula and at the site of an arteriovenous fistula used for hemodialysis access. Enhanced flow through enlarged intercostal collateral arteries in patients with aortic coarctation may produce a continuous murmur along the course of one or more ribs. A cervical bruit with both systolic and diastolic components (a to-fro murmur, Fig. 38-7) usually indicates a high-grade carotid artery stenosis.

Not all continuous murmurs are pathologic. A continuous venous hum can be heard in healthy children and young adults, especially during pregnancy; it is best appreciated in the right supraclavicular fossa and can be obliterated by pressure over the right internal jugular vein or by having the patient turn his or her head toward the examiner. The continuous mammary souffle of pregnancy is created by enhanced arterial flow through engorged breasts and usually appears during the late third trimester or early puerperium. The murmur is louder in systole. Firm pressure with the diaphragm of the stethoscope can eliminate the diastolic portion of the murmur.

DYNAMIC AUSCULTATION

(Table 38-2; see Table 234-1) Careful attention to the behavior of heart murmurs during simple maneuvers that alter cardiac hemodynamics can provide important clues to their cause and significance.

Respiration Auscultation should be performed during quiet respiration or with a modest increase in inspiratory effort, as more forceful movement of the chest tends to obscure the heart sounds. Left-sided murmurs may be best heard at end expiration, when lung volumes are minimized and the heart and great vessels are brought closer to the chest wall. This phenomenon is characteristic of the murmur of AR. Murmurs of right-sided origin, such as tricuspid or pulmonic regurgitation, increase in intensity during inspiration. The intensity of left-sided murmurs either remains constant or decreases with inspiration.

TABLE 38-2 Dynamic Auscultation: Bedside Maneuvers That Can Be Used to Change the Intensity of Cardiac Murmurs (See Text)

1. Respiration
2. Isometric exercise (handgrip)
3. Transient arterial occlusion
4. Pharmacologic manipulation of preload and/or afterload
5. Valsalva maneuver
6. Rapid standing/squatting
7. Passive leg raising
8. Post-premature beat

Bedside assessment also should evaluate the behavior of S_2 with respiration and the dynamic relationship between the aortic and pulmonic components (Fig. 38-8). Reversed splitting can be a feature of severe AS, HOCM, left bundle branch block, right ventricular pacing, or acute myocardial ischemia. Fixed splitting of S_2 in the presence of a grade 2 or 3 midsystolic murmur at the mid- or upper left sternal border indicates an ASD. Physiologic but wide splitting during the respiratory cycle implies either premature aortic valve closure, as can occur with severe MR, or delayed pulmonic valve closure due to PS or right bundle branch block.

Alterations of Systemic Vascular Resistance Murmurs can change characteristics after maneuvers that alter systemic vascular resistance and left ventricular afterload. The systolic murmurs of MR and VSD become louder during sustained handgrip, simultaneous inflation of blood pressure cuffs on both upper extremities to pressures 20–40 mmHg above systolic pressure for 20 s, or infusion of a vasopressor agent. The murmurs associated with AS or HOCM will become softer or remain unchanged with these maneuvers. The diastolic murmur of AR becomes louder in response to interventions that raise systemic vascular resistance.

Opposite changes in systolic and diastolic murmurs may occur with the use of pharmacologic agents that lower systemic vascular resistance. Inhaled amyl nitrite is now rarely used for this purpose but can help distinguish the murmur of AS or HOCM from that of either MR or VSD, if necessary. The former two murmurs increase in intensity, whereas the latter two become softer after exposure to amyl nitrite. As noted previously, the Austin Flint murmur of severe AR becomes softer, but the mid-diastolic rumble of MS becomes louder, in response to the abrupt lowering of systemic vascular resistance with amyl nitrite.

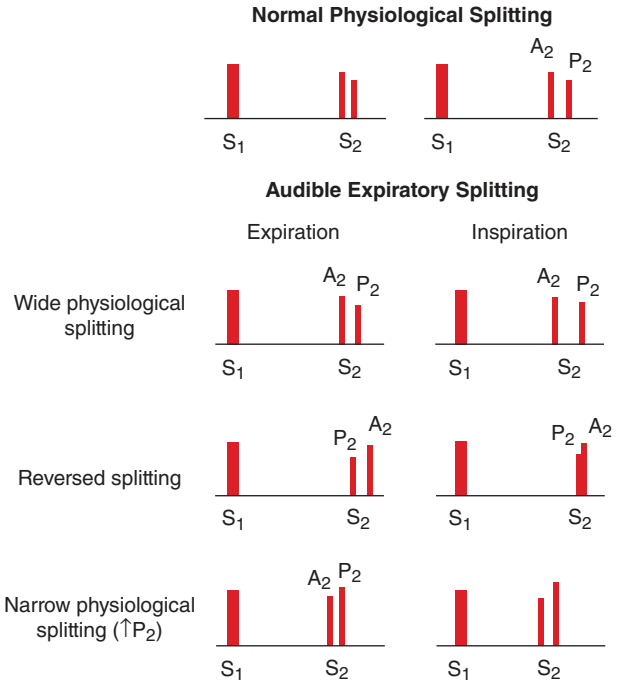

FIGURE 38-8 ***Top.*** Normal physiologic splitting. During expiration, the aortic (A_2) and pulmonic (P_2) components of the second heart sound are separated by <30 ms and are appreciated as a single sound. During inspiration, the splitting interval widens, and A_2 and P_2 are clearly separated into two distinct sounds. ***Bottom.*** Audible expiratory splitting. Wide physiologic splitting is caused by a delay in P_2 (as, for example, with right bundle branch block) or by early closure of the aortic valve (A_2, as for example with severe mitral regurgitation). Reversed splitting is caused by a delay in A_2, resulting in paradoxical movement; i.e., with inspiration P_2 moves toward A_2, and the splitting interval narrows. Narrow physiologic splitting occurs in pulmonary hypertension, and both A_2 and P_2 are heard during expiration at a narrow splitting interval because of the increased intensity and high-frequency composition of P_2. *(From JA Shaver, JJ Leonard, DF Leon: Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 17. Copyright, American Heart Association.)*

Changes in Venous Return The Valsalva maneuver results in an increase in intrathoracic pressure, followed by a decrease in venous return, ventricular filling, and cardiac output. The majority of murmurs decrease in intensity during the strain phase of the maneuver. Two notable exceptions are the murmurs associated with MVP and obstructive HOCM, both of which become louder during the Valsalva maneuver. The murmur of MVP may also become longer as leaflet prolapse occurs earlier in systole at smaller ventricular volumes. These murmurs behave in a similar and parallel fashion with standing. Both the click and the murmur of MVP move closer in timing to S_1 on rapid standing from a squatting position (Fig. 38-3). The increase in the intensity of the murmur of HOCM is predicated on the augmentation of the dynamic left ventricular outflow tract gradient that occurs with reduced ventricular filling. Squatting results in abrupt increases in both venous return (preload) and left ventricular afterload that increase ventricular volume, changes that predictably cause a decrease in the intensity and duration of the murmurs associated with MVP and HOCM; the click and murmur of MVP move away from S_1 with squatting. Passive leg raising can be used to increase venous return in patients who are unable to squat and stand. This maneuver may lead to a decrease in the intensity of the murmur associated with HOCM but has less effect in patients with MVP.

Post-premature Ventricular Contraction A change in the intensity of a systolic murmur in the first beat after a premature beat, or in the beat after a long cycle length in patients with atrial fibrillation, can help distinguish AS from MR, particularly in an older patient in whom the murmur of AS is well transmitted to the apex. Systolic murmurs due to left ventricular outflow obstruction, including that due to AS, increase in intensity in the beat after a premature beat because of the combined effects of enhanced left ventricular filling and post-extrasystolic potentiation of contractile function. Forward flow accelerates, causing an increase in the gradient and a louder murmur. The intensity of the murmur of MR does not change in the post-premature beat as there is relatively little further increase in mitral valve flow or change in the left ventricular–left atrial gradient.

THE CLINICAL CONTEXT

Additional clues to the etiology and importance of a heart murmur can be gleaned from the history and other physical examination findings. Symptoms suggestive of cardiovascular, neurologic, or pulmonary disease help focus the differential diagnosis, as do findings relevant to the jugular venous pressure and waveforms, the arterial pulses, other heart sounds, the lungs, the abdomen, the skin, and the extremities. In many instances, laboratory studies, an ECG, and/or a chest x-ray may have been obtained earlier and may contain valuable information. A patient with suspected infective endocarditis, for example, may have a murmur in the setting of fever, chills, anorexia, fatigue, dyspnea, splenomegaly, petechiae, and positive blood cultures. A new systolic murmur in a patient with a marked fall in blood pressure after a recent MI suggests myocardial rupture. By contrast, an isolated grade 1 or 2 midsystolic murmur at the left sternal border in a healthy, active, and asymptomatic young adult is most likely a benign finding for which no further evaluation is indicated. The context in which the murmur is appreciated often dictates the need for further testing and the pace of the evaluation.

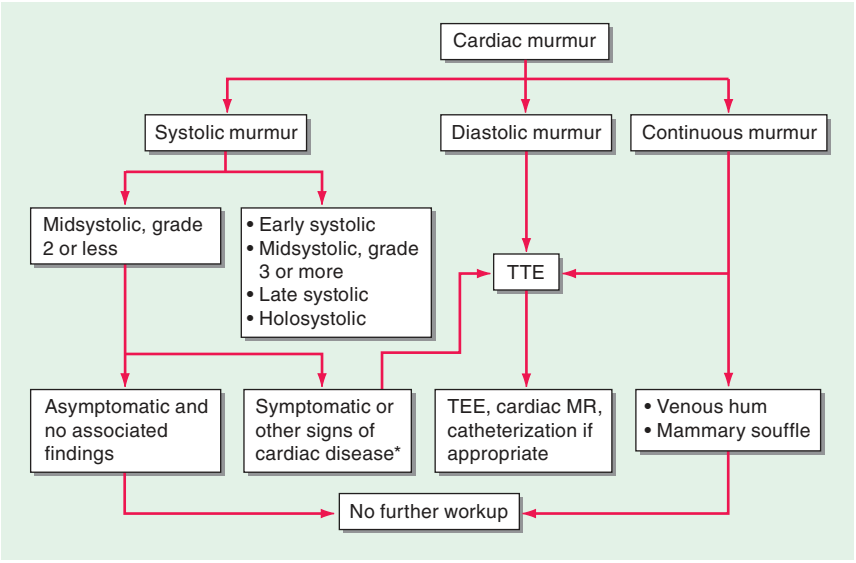

FIGURE 38-9 Strategy for evaluating heart murmurs. *If an electrocardiogram or chest x-ray has been obtained and is abnormal, echocardiography is indicated. TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; MR, magnetic resonance. *(Adapted from RO Bonow et al: J Am Coll Cardiol 32:1486, 1998.)*

ECHOCARDIOGRAPHY

(Fig. 38–9; Chaps. 234 and 236) Echocardiography with color flow and spectral Doppler is a valuable tool for the assessment of cardiac murmurs. Information regarding valve structure and function, chamber size, wall thickness, ventricular function, estimated pulmonary artery pressures, intracardiac shunt flow, pulmonary and hepatic vein flow, and aortic flow can be ascertained readily. It is important to note that Doppler signals of trace or mild valvular regurgitation of no clinical consequence can be detected with structurally normal tricuspid, pulmonic, and mitral valves. Such signals are not likely to generate enough turbulence to create an audible murmur.

Echocardiography is indicated for the evaluation of patients with early, late, or holosystolic murmurs and patients with grade 3 or louder midsystolic murmurs. Patients with grade 1 or 2 midsystolic murmurs but other symptoms or signs of cardiovascular disease, including those from ECG or chest x-ray, should also undergo echocardiography. Echocardiography is also indicated for the evaluation of any patient with a diastolic murmur and for patients with continuous murmurs not due to a venous hum or mammary souffle. Echocardiography should be considered when there is a clinical need to verify normal cardiac structure and function in a patient whose symptoms and signs are probably noncardiac in origin. The performance of serial echocardiography to follow the course of asymptomatic individuals with valvular heart disease is a central feature of their longitudinal assessment, and it provides valuable information that may have an impact on decisions regarding the timing of surgery. Routine echocardiography is *not* recommended for asymptomatic patients with a grade 1 or 2 midsystolic murmur without other signs of heart disease. For this category of patients, referral to a cardiovascular specialist should be considered if there is doubt about the significance of the murmur after the initial examination.

The selective use of echocardiography outlined above has not been subjected to rigorous analysis of its cost-effectiveness. For some clinicians, handheld or miniaturized cardiac ultrasound devices have replaced the stethoscope. Although several reports attest to the improved sensitivity of such devices for the detection of valvular heart disease (e.g., rheumatic heart disease in susceptible populations), accuracy is highly operator-dependent, and incremental cost considerations and outcomes have not been addressed adequately for most patient scenarios. The use of electronic or digital stethoscopes with spectral display capabilities has also been proposed as a method to improve the characterization of heart murmurs and the mentored teaching of cardiac auscultation.

OTHER CARDIAC TESTING

(Chap. 236, Fig. 38-9) In relatively few patients, clinical assessment and TTE do not adequately characterize the origin and significance of a heart murmur. Transesophageal echocardiography (TEE) can be considered for further evaluation, especially when the TTE windows are limited by body size, chest configuration, or intrathoracic pathology. TEE offers enhanced sensitivity for the detection of a wide range of structural cardiac disorders. Electrocardiographically gated cardiac magnetic resonance (CMR) imaging, although limited in its ability to display valvular morphology, can provide quantitative information regarding valvular function, stenosis severity, regurgitant fraction, regurgitant volume, shunt flow, chamber and great vessel size, ventricular function, and myocardial perfusion. CMR has largely supplanted the need for cardiac catheterization and invasive hemodynamic assessment when there is a discrepancy between the clinical and echocardiographic findings. Invasive coronary angiography is performed routinely in most adult patients before valve surgery, especially when there is a suspicion of coronary artery disease predicated on symptoms, risk factors, and/or age. The use of computed tomography coronary angiography (CTCA) to exclude coronary artery disease in selected patients with a low pretest probability of disease before valve surgery has gained wider acceptance.

INTEGRATED APPROACH

The accurate identification of a heart murmur begins with a systematic approach to cardiac auscultation. Characterization of its major attributes, as reviewed above, allows the examiner to construct a preliminary differential diagnosis, which is then refined by integration of information available from the history, associated cardiac findings, the general physical examination, and the clinical context. The need for and urgency of further testing follow sequentially. Correlation of the findings on auscultation with the noninvasive data provides an educational feedback loop and an opportunity for improving physical examination skills. Cost constraints mandate that noninvasive imaging be justified on the basis of its incremental contribution to diagnosis, treatment, and outcome. Cardiac auscultation using a stethoscope remains a time-honored tradition in medicine, the benefits of which extend beyond accurate recognition of heart sounds. Selective augmentation with, rather than wholesale replacement by, handheld ultrasound and newer technologies may improve diagnostic accuracy and better guide therapeutic decisions.

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39 Palpitations

Joseph Loscalzo

Palpitations are extremely common among patients who present to their internists and can best be defined as a "thumping," "pounding," or "fluttering" sensation in the chest. This sensation can be either intermittent or sustained and either regular or irregular. Most patients interpret palpitations as an unusual awareness of the heartbeat and become especially concerned when they sense that they have had "skipped" or "missing" heartbeats. Palpitations are often noted when the patient is quietly resting, during which time other stimuli are minimal. Palpitations that are positional generally reflect a structural process within (e.g., atrial myxoma) or adjacent to (e.g., mediastinal mass) the heart.

Palpitations are brought about by cardiac (43%), psychiatric (31%), miscellaneous (10%), and unknown (16%) causes, according to one large series. Among the cardiovascular causes are premature atrial and ventricular contractions, supraventricular and ventricular arrhythmias, mitral valve prolapse (with or without associated arrhythmias), aortic insufficiency, atrial myxoma, myocarditis, and pulmonary embolism. Intermittent palpitations are commonly caused by premature atrial or ventricular contractions: the post-extrasystolic beat is sensed by the patient owing to the increase in ventricular end-diastolic dimension following the pause in the cardiac cycle and the increased strength of contraction (post-extrasystolic potentiation) of that beat. Regular, sustained palpitations can be caused by regular supraventricular and ventricular tachycardias. Irregular, sustained palpitations can be caused by atrial fibrillation. It is important to note that most arrhythmias are not associated with palpitations. In those that are, it is often useful either to ask the patient to "tap out" the rhythm of the palpitations or to take his/her pulse during palpitations. In general, hyperdynamic cardiovascular states caused by catecholaminergic stimulation from exercise, stress, or pheochromocytoma can lead to palpitations. Palpitations are common among athletes, especially older endurance athletes. In addition, the enlarged ventricle of aortic regurgitation and accompanying hyperdynamic precordium frequently lead to the sensation of palpitations. Other factors that enhance the strength of myocardial contraction, including tobacco, caffeine, aminophylline, atropine, thyroxine, cocaine, and amphetamines, can cause palpitations.

Psychiatric causes of palpitations include panic attacks or disorders, anxiety states, and somatization, alone or in combination. Patients with psychiatric causes for palpitations more commonly report a longer duration of the sensation (>15 min) and other accompanying symptoms than do patients with other causes. Among the miscellaneous causes of palpitations are thyrotoxicosis, drugs (see above) and ethanol, spontaneous skeletal muscle contractions of the chest wall, pheochromocytoma, and systemic mastocytosis.

APPROACH TO THE PATIENT

Palpitations

The principal goal in assessing patients with palpitations is to determine whether the symptom is caused by a life-threatening arrhythmia. Patients with preexisting coronary artery disease (CAD) or risk factors for CAD are at greatest risk for ventricular arrhythmias **(Chap. 241)** as a cause for palpitations. In addition, the association of palpitations with other symptoms suggesting hemodynamic compromise, including syncope or lightheadedness, supports this diagnosis. Palpitations caused by sustained tachyarrhythmias in patients with CAD can be accompanied by angina pectoris or dyspnea, and, in patients with ventricular dysfunction (systolic or diastolic), aortic stenosis, hypertrophic cardiomyopathy, or mitral stenosis (with or without CAD), can be accompanied by dyspnea from increased left atrial and pulmonary venous pressure.

Key features of the physical examination that will help confirm or refute the presence of an arrhythmia as a cause for palpitations (as well as its adverse hemodynamic consequences) include measurement of the vital signs, assessment of the jugular venous pressure and pulse, and auscultation of the chest and precordium. A resting electrocardiogram can be used to document the arrhythmia. If exertion is known to induce the arrhythmia and accompanying palpitations, exercise electrocardiography can be used to make the diagnosis. If the arrhythmia is sufficiently infrequent, other methods must be used, including continuous electrocardiographic (Holter) monitoring; telephonic monitoring, through which the patient can transmit an electrocardiographic tracing during a sensed episode; loop recordings (external or implantable), which can capture the electrocardiographic event for later review; and mobile cardiac outpatient telemetry. Data suggest that Holter monitoring is of limited clinical utility, while the implantable loop recorder and mobile cardiac outpatient telemetry are safe and possibly more cost-effective in the assessment of patients with (infrequent) recurrent, unexplained palpitations.

Most patients with palpitations do not have serious arrhythmias or underlying structural heart disease. If sufficiently troubling to the patient, occasional benign atrial or ventricular premature contractions can often be managed with beta-blocker therapy. Palpitations incited by alcohol, tobacco, or illicit drugs need to be managed by abstention, while those caused by pharmacologic agents should be addressed by considering alternative therapies when appropriate or possible. Psychiatric causes of palpitations may benefit from cognitive therapy or pharmacotherapy. The physician should note that palpitations are at the very least bothersome and, on occasion, frightening to the patient. Once serious causes for the symptom have been excluded, the patient should be reassured that the palpitations will not adversely affect prognosis.

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Section 6 Alterations in Gastrointestinal Function

40 Dysphagia

Ikuo Hirano, Peter J. Kahrilas

Dysphagia—difficulty with swallowing—refers to problems with the transit of food or liquid from the mouth to the hypopharynx or through the esophagus. Severe dysphagia can compromise nutrition, cause aspiration, and reduce quality of life. Additional terminology pertaining to swallowing dysfunction is as follows. *Aphagia* (inability to swallow) typically denotes complete esophageal obstruction, most commonly encountered in the acute setting of a food bolus or foreign body impaction. *Odynophagia* refers to painful swallowing, typically resulting from mucosal ulceration within the oropharynx or esophagus.

It commonly is accompanied by dysphagia, but the converse is not true. *Globus pharyngeus* is a foreign body sensation localized in the neck that does not interfere with swallowing and sometimes is relieved by swallowing. *Transfer dysphagia* frequently results in nasal regurgitation and pulmonary aspiration during swallowing and is characteristic of oropharyngeal dysphagia. *Phagophobia* (fear of swallowing) and *refusal to swallow* may be psychogenic or related to anticipatory anxiety about food bolus obstruction, odynophagia, or aspiration.

PHYSIOLOGY OF SWALLOWING

Swallowing begins with a voluntary (oral) phase that includes preparation during which food is masticated and mixed with saliva. This is followed by a transfer phase during which the bolus is pushed into the pharynx by the tongue. Bolus entry into the hypopharynx initiates the pharyngeal swallow response, which is centrally mediated and involves a complex series of actions, the net result of which is to propel food through the pharynx into the esophagus while preventing its entry into the airway. To accomplish this, the larynx is elevated and pulled forward, actions that also facilitate upper esophageal sphincter (UES) opening. Tongue pulsion then propels the bolus through the UES, followed by a peristaltic contraction that clears residue from the pharynx and through the esophagus. The lower esophageal sphincter (LES) relaxes as the food enters the esophagus and remains relaxed until the peristaltic contraction has delivered the bolus into the stomach. Peristaltic contractions elicited in response to a swallow are called *primary peristalsis* and involve sequenced inhibition followed by contraction of the musculature along the entire length of the esophagus. The inhibition that precedes the peristaltic contraction is called *deglutitive inhibition*. Local distention of the esophagus anywhere along its length, as may occur with gastroesophageal reflux, activates *secondary peristalsis* that begins at the point of distention and proceeds distally. Tertiary esophageal contractions are nonperistaltic, disordered esophageal contractions that may be observed to occur spontaneously during fluoroscopic observation.

The musculature of the oral cavity, pharynx, UES, and cervical esophagus is striated and directly innervated by lower motor neurons carried in cranial nerves **(Fig. 40-1)**. Oral cavity muscles are innervated by the fifth (trigeminal) and seventh (facial) cranial nerves; the tongue, by the twelfth (hypoglossal) cranial nerve. Pharyngeal muscles are innervated by the ninth (glossopharyngeal) and tenth (vagus) cranial nerves.

Physiologically, the UES consists of the cricopharyngeus muscle, the adjacent inferior pharyngeal constrictor, and the proximal portion of the cervical esophagus. UES innervation is derived from the vagus nerve, whereas the innervation to the musculature acting on the UES to facilitate its opening during swallowing comes from the fifth, seventh, and twelfth cranial nerves. The UES remains closed at rest owing to both its inherent elastic properties and neurogenically mediated contraction of the cricopharyngeus muscle. UES opening during swallowing involves both cessation of vagal excitation to the cricopharyngeus and simultaneous contraction of the suprahyoid and geniohyoid muscles that pull open the UES in conjunction with the upward and forward displacement of the larynx.

The neuromuscular apparatus for peristalsis is distinct in proximal and distal parts of the esophagus. The cervical esophagus, like the pharyngeal musculature, consists of striated muscle and is directly innervated by lower motor neurons of the vagus nerve. Peristalsis in the proximal esophagus is governed by the sequential activation of the vagal motor neurons in the nucleus ambiguus. In contrast, the distal esophagus and LES are composed of smooth muscle and are controlled by excitatory and inhibitory neurons within the esophageal myenteric plexus. Medullary preganglionic neurons from the dorsal motor nucleus of the vagus trigger peristalsis via these ganglionic neurons during primary peristalsis. Neurotransmitters of the excitatory ganglionic neurons are acetylcholine and substance P; those of the inhibitory neurons are vasoactive intestinal peptide and nitric oxide. Peristalsis results from the patterned activation of inhibitory followed by excitatory ganglionic neurons, with progressive dominance of the inhibitory neurons distally. Similarly, LES relaxation occurs with the onset of deglutitive inhibition and persists until the peristaltic sequence is complete. At rest, the LES is contracted because of excitatory ganglionic stimulation and its intrinsic myogenic tone, a property that distinguishes it from the adjacent esophagus. The function of the LES is supplemented by the surrounding muscle of the right diaphragmatic crus, which acts as an external sphincter during inspiration, cough, or abdominal straining.

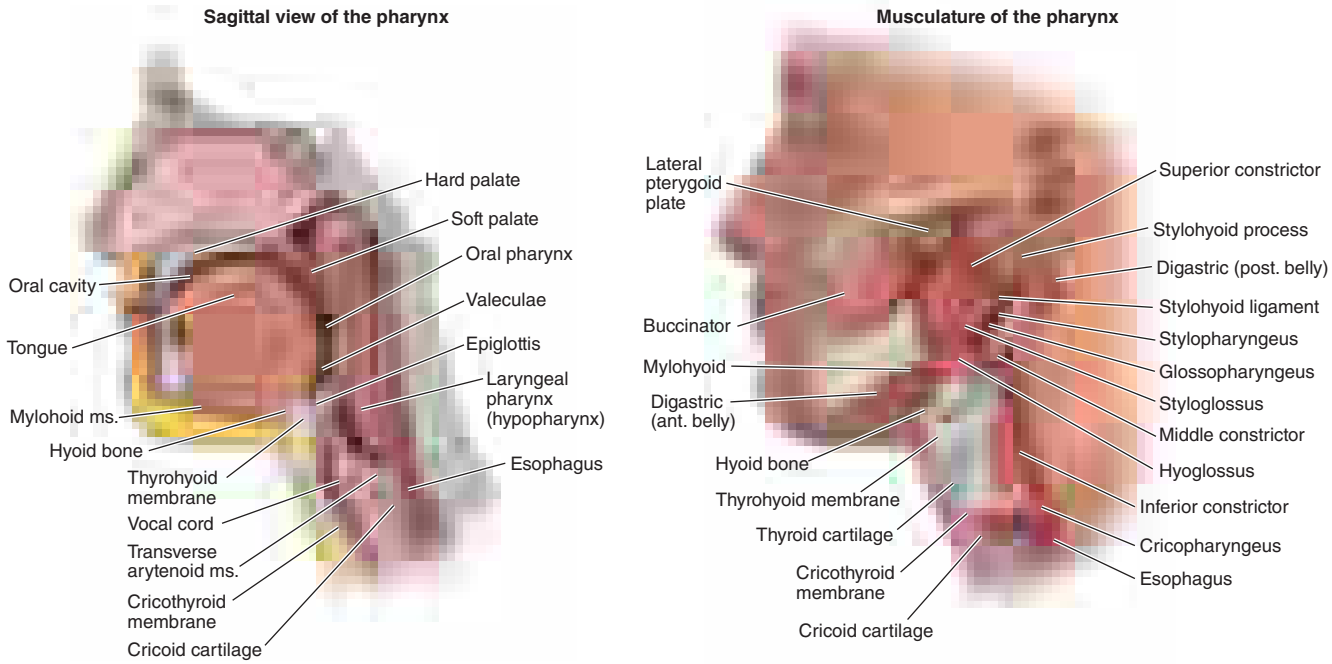

FIGURE 40-1 Sagittal and diagrammatic views of the musculature involved in enacting oropharyngeal swallowing. Note the dominance of the tongue in the sagittal view and the intimate relationship between the entrance to the larynx (airway) and the esophagus. In the resting configuration illustrated, the esophageal inlet is closed. This is transiently reconfigured such that the esophageal inlet is open and the laryngeal inlet closed during swallowing. *(Adapted from PJ Kahrilas, in DW Gelfand and JE Richter [eds]: Dysphagia: Diagnosis and Treatment. New York: Igaku-Shoin Medical Publishers, 1989, pp. 11–28.)*

PATHOPHYSIOLOGY OF DYSPHAGIA

Dysphagia can be subclassified both by location and by the circumstances in which it occurs. With respect to location, distinct considerations apply to oral, pharyngeal, or esophageal dysphagia. Normal transport of an ingested bolus depends on the consistency and size of the bolus, the caliber of the lumen, the integrity of peristaltic contraction, and deglutitive inhibition of both the UES and the LES. Dysphagia caused by an oversized bolus or a narrow lumen is called *structural dysphagia*, whereas dysphagia due to abnormalities of peristalsis or impaired sphincter relaxation after swallowing is called *propulsive* or *motor dysphagia*. More than one mechanism may be operative in a patient with dysphagia. Scleroderma commonly presents with absent peristalsis as well as a weakened LES that predisposes patients to peptic stricture formation. Likewise, radiation therapy for head and neck cancer may compound the functional deficits in the oropharyngeal swallow attributable to the tumor and cause cervical esophageal stenosis. It is worth noting that in addition to bolus transit, symptom reporting of dysphagia is dependent upon intact sensory innervation and central nervous system perception.

Oral and Pharyngeal (Oropharyngeal) Dysphagia Oral-phase dysphagia is associated with poor bolus formation and control so that food has prolonged retention within the oral cavity and may seep out of the mouth. Drooling and difficulty in initiating swallowing are other characteristic signs. Poor bolus control also may lead to premature spillage of food into the hypopharynx with resultant aspiration into the trachea or regurgitation into the nasal cavity. Pharyngeal-phase dysphagia is associated with retention of food in the pharynx due to poor tongue or pharyngeal propulsion or obstruction at the UES. Signs and symptoms of concomitant hoarseness or cranial nerve dysfunction may be associated with oropharyngeal dysphagia.

Oropharyngeal dysphagia may be due to neurologic, muscular, structural, iatrogenic, infectious, and metabolic causes. Iatrogenic, neurologic, and structural pathologies are most common. Iatrogenic causes include surgery and radiation, often in the setting of head and neck cancer. Neurogenic dysphagia resulting from cerebrovascular accidents, Parkinson's disease, and amyotrophic lateral sclerosis is a major source of morbidity related to aspiration and malnutrition. Medullary nuclei directly innervate the oropharynx. Lateralization of pharyngeal dysphagia implies either a structural pharyngeal lesion or a neurologic process that selectively targeted the ipsilateral brainstem nuclei or cranial nerve. Advances in functional brain imaging have elucidated an important role of the cerebral cortex in swallow function and dysphagia. Asymmetry in the cortical representation of the pharynx provides an explanation for the dysphagia that occurs as a consequence of unilateral cortical cerebrovascular accidents.

Oropharyngeal structural lesions causing dysphagia include Zenker's diverticulum, cricopharyngeal bar, and neoplasia. Zenker's diverticulum typically is encountered in elderly patients. In addition to dysphagia, patients may present with regurgitation of particulate food debris, aspiration, and halitosis. The pathogenesis is related to stenosis of the cricopharyngeus that causes diminished opening of the UES and results in increased hypopharyngeal pressure during swallowing with development of a pulsion diverticulum immediately above the cricopharyngeus in a region of potential weakness known as Killian's dehiscence. A cricopharyngeal bar, appearing as a prominent indentation behind the lower third of the cricoid cartilage, is related to Zenker's diverticulum in that it involves limited distensibility of the cricopharyngeus and can lead to the formation of a Zenker's diverticulum. However, a cricopharyngeal bar is a common radiographic finding, and most patients with transient cricopharyngeal bars are asymptomatic, making it important to rule out alternative etiologies of dysphagia before treatment. Furthermore, cricopharyngeal bars may be secondary to other neuromuscular disorders that impair opening of the UES.

Since the pharyngeal phase of swallowing occurs in less than a second, rapid-sequence fluoroscopy is necessary to evaluate for functional abnormalities. Adequate fluoroscopic examination requires that the patient be conscious and cooperative. The study incorporates recordings of swallow sequences during ingestion of food and liquids of varying consistencies. The pharynx is examined to detect bolus retention, regurgitation into the nose, or aspiration into the trachea. Timing and integrity of pharyngeal contraction and opening of the UES with a swallow are analyzed to assess both aspiration risk and the potential for swallow therapy. Structural abnormalities of the oropharynx, especially those which may require biopsies, also should be assessed by direct laryngoscopic examination.

Esophageal Dysphagia The adult esophagus measures 18–26 cm in length and is anatomically divided into the cervical esophagus, extending from the pharyngoesophageal junction to the suprasternal notch, and the thoracic esophagus, which continues to the diaphragmatic hiatus. When distended, the esophageal lumen has internal dimensions of about 2 cm in the anteroposterior plane and 3 cm in the lateral plane. Solid food dysphagia becomes common when the lumen is narrowed to <13 mm, but also can occur with larger diameters in the setting of poorly masticated food or motor dysfunction. Circumferential lesions are more likely to cause dysphagia than are lesions that involve only a partial circumference of the esophageal wall. The most common structural causes of dysphagia are Schatzki's rings, eosinophilic esophagitis, and peptic strictures. Dysphagia also occurs in the setting of gastroesophageal reflux disease without a stricture, perhaps on the basis of altered esophageal sensation, reduced esophageal mural distensibility, or motor dysfunction.

Propulsive disorders leading to esophageal dysphagia result from abnormalities of peristalsis and/or deglutitive inhibition, potentially affecting the cervical or thoracic esophagus. Since striated muscle pathology usually involves both the oropharynx and the cervical esophagus, the clinical manifestations usually are dominated by oropharyngeal dysphagia. Diseases affecting smooth muscle involve both the thoracic esophagus and the LES. A dominant manifestation of this, absent peristalsis, refers to either the complete absence of swallow-induced contraction (absent contractility) or the presence of non-peristaltic, disordered contractions. Absent peristalsis and failure of deglutitive LES relaxation are the defining features of achalasia. In diffuse esophageal spasm (DES), LES function is normal, with the disordered motility restricted to the esophageal body. Absent contractility combined with severe weakness of the LES is a nonspecific pattern commonly found in patients with scleroderma.

APPROACH TO THE PATIENT

Dysphagia

Figure 40-2 shows an algorithm for the approach to a patient with dysphagia.

HISTORY

The patient history is extremely valuable in making a presumptive diagnosis or at least substantially restricting the differential diagnoses in most patients. Key elements of the history are the localization of dysphagia, the circumstances in which dysphagia is experienced, other symptoms associated with dysphagia, and progression. Dysphagia that localizes to the suprasternal notch may indicate either an oropharyngeal or an esophageal etiology as distal dysphagia is referred proximally about 30% of the time. Dysphagia that localizes to the chest is esophageal in origin. Nasal regurgitation and tracheobronchial aspiration manifest by coughing with swallowing are hallmarks of oropharyngeal dysphagia. Severe cough with swallowing may also be a sign of a tracheoesophageal fistula. The presence of hoarseness may be another important diagnostic clue. When hoarseness precedes dysphagia, the primary lesion is usually laryngeal; hoarseness that occurs after the development of dysphagia may result from compromise of the recurrent laryngeal nerve by a malignancy. The type of food causing dysphagia is a crucial detail. Intermittent dysphagia that occurs only with solid food implies

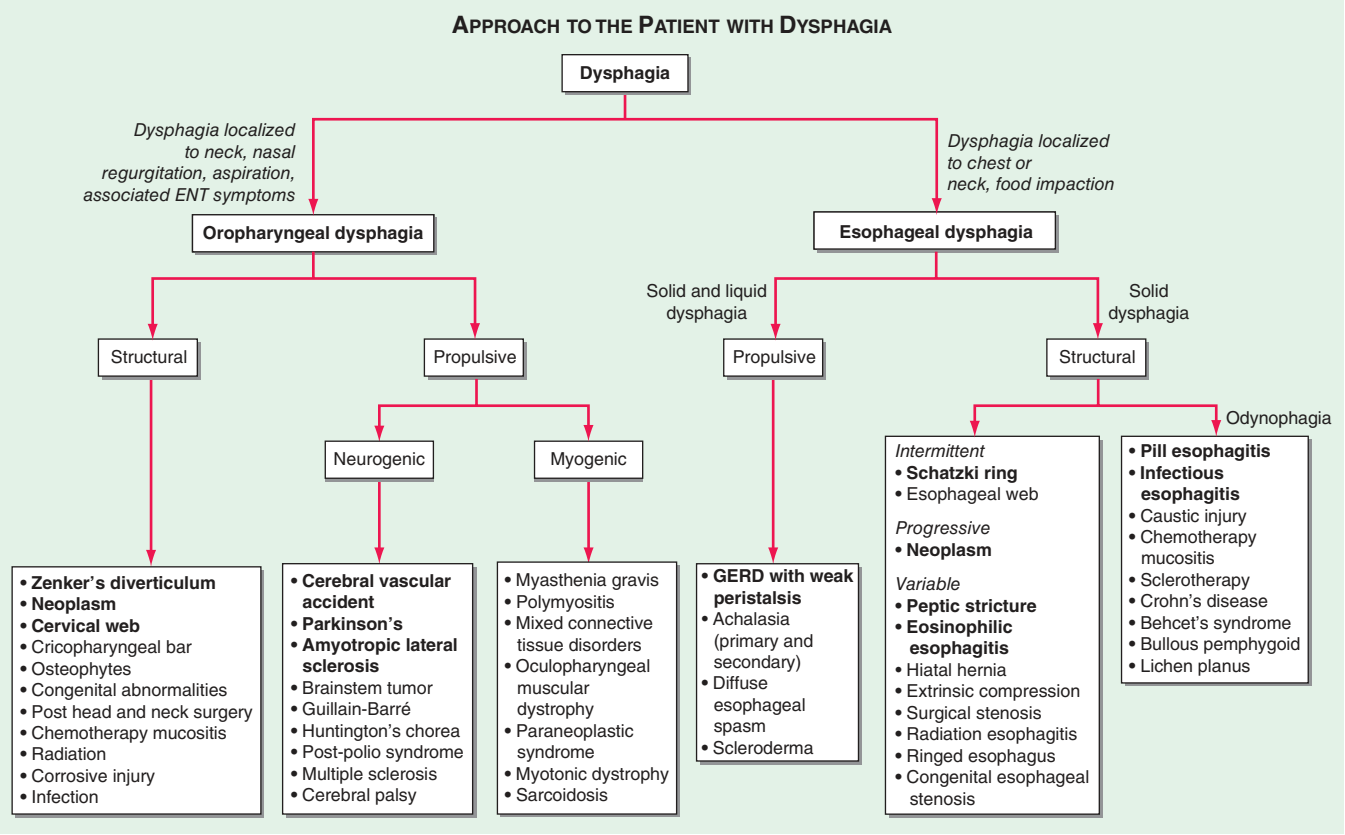

FIGURE 40-2 Approach to the patient with dysphagia. Etiologies in bold print are the most common. ENT, ear, nose, and throat; GERD, gastroesophageal reflux disease.

structural dysphagia, whereas constant dysphagia with both liquids and solids strongly suggests a motor abnormality. Two caveats to this pattern are that despite having a motor abnormality, patients with scleroderma generally develop mild dysphagia for solids only and, somewhat paradoxically, that patients with oropharyngeal dysphagia often have greater difficulty managing liquids than solids. Dysphagia that is progressive over the course of weeks to months raises concern for neoplasia. Episodic dysphagia to solids that is unchanged or slowly progressive over years indicates a benign disease process such as a Schatzki ring or eosinophilic esophagitis. Food impaction with a prolonged inability to pass an ingested bolus even with ingestion of liquid is typical of a structural dysphagia. Chest pain frequently accompanies dysphagia whether it is related to motor disorders, structural disorders, or reflux disease. A prolonged history of heartburn preceding the onset of dysphagia is suggestive of peptic stricture and, infrequently, esophageal adenocarcinoma. A history of prolonged nasogastric intubation, esophageal or head and neck surgery, ingestion of caustic agents or pills, previous radiation or chemotherapy, or associated mucocutaneous diseases may help isolate the cause of dysphagia. With accompanying odynophagia, which usually is indicative of ulceration, infectious or pill-induced esophagitis should be suspected. In patients with AIDS or other immunocompromised states, esophagitis due to opportunistic infections such as *Candida*, herpes simplex virus, or cytomegalovirus and to tumors such as Kaposi's sarcoma and lymphoma should be considered. A strong history of atopy increases concerns for eosinophilic esophagitis, especially in younger Caucasian male patients.

PHYSICAL EXAMINATION

Physical examination is important in the evaluation of oral and pharyngeal dysphagia because dysphagia is usually only one of many manifestations of a more global disease process. Signs of bulbar or pseudobulbar palsy, including dysarthria, dysphonia, ptosis, tongue atrophy, and hyperactive jaw jerk, in addition to evidence of generalized neuromuscular disease, should be elicited. The neck should be examined for thyromegaly. A careful inspection of the mouth and pharynx should disclose lesions that may interfere with passage of food. Missing dentition can interfere with mastication and exacerbate an existing cause of dysphagia. Physical examination is less helpful in the evaluation of esophageal dysphagia as most relevant pathology is restricted to the esophagus. The notable exception is skin disease. Changes in the skin may suggest a diagnosis of scleroderma or mucocutaneous diseases such as pemphigoid, lichen planus, and epidermolysis bullosa, all of which can involve the esophagus.

DIAGNOSTIC PROCEDURES

Although most instances of dysphagia are attributable to benign disease processes, dysphagia is also a cardinal symptom of several malignancies, making it an important symptom to evaluate. Cancer may result in dysphagia due to intraluminal obstruction (esophageal or proximal gastric cancer, metastatic deposits), extrinsic compression (lymphoma, lung cancer), or paraneoplastic syndromes. Even when not attributable to malignancy, dysphagia is usually a manifestation of an identifiable and treatable disease entity, making its evaluation beneficial to the patient and gratifying to the practitioner. The specific diagnostic algorithm to pursue is guided by the details of the history (Fig. 40-2). If oral or pharyngeal dysphagia is suspected, a fluoroscopic swallow study, usually done by a swallow therapist, is the procedure of choice. Otolaryngoscopic and neurologic evaluation also can be important, depending on the circumstances. For suspected esophageal dysphagia, upper endoscopy is the single most useful test. Endoscopy allows better visualization of mucosal lesions than does barium radiography and also allows one to obtain mucosal biopsies. Endoscopic or histologic abnormalities are evident in the leading causes of esophageal dysphagia: Schatzki's ring, gastroesophageal reflux disease, and eosinophilic esophagitis. Furthermore, therapeutic intervention with esophageal

dilation can be done as part of the procedure if it is deemed necessary. The emergence of eosinophilic esophagitis as a leading cause of dysphagia in both children and adults has led to the recommendation that esophageal mucosal biopsies be obtained routinely in the evaluation of unexplained dysphagia even if characteristic, endoscopically identified esophageal mucosal features are absent. For cases of suspected esophageal motility disorders, endoscopy is still the appropriate initial evaluation as neoplastic and inflammatory conditions can secondarily produce patterns of either achalasia or esophageal spasm. Esophageal manometry is done if dysphagia is not adequately explained by endoscopy or to confirm the diagnosis of a suspected esophageal motor disorder. Barium radiography can provide useful adjunctive information in cases of subtle or complex esophageal strictures, prior esophageal surgery, esophageal diverticula, or paraesophageal herniation. In specific cases, computed tomography (CT) examination and endoscopic ultrasonography may be useful.

TREATMENT

Treatment of dysphagia depends on both the locus and the specific etiology. Oropharyngeal dysphagia most commonly results from functional deficits caused by neurologic disorders. In such circumstances, the treatment focuses on utilizing postures or maneuvers devised to reduce pharyngeal residue and enhance airway protection learned under the direction of a trained swallow therapist. Aspiration risk may be reduced by altering the consistency of ingested food and liquid. Dysphagia resulting from a cerebrovascular accident usually, but not always, spontaneously improves within the first few weeks after the event. More severe and persistent cases may require gastrostomy and enteral feeding. Patients with myasthenia gravis **(Chap. 440)** and polymyositis **(Chap. 358)** may respond to medical treatment of the primary neuromuscular disease. Surgical intervention with cricopharyngeal myotomy is usually not helpful, with the exception of specific disorders such as the idiopathic cricopharyngeal bar, Zenker's diverticulum, and oculopharyngeal muscular dystrophy. Chronic neurologic disorders such as Parkinson's disease and amyotrophic lateral sclerosis may manifest with severe oropharyngeal dysphagia. Feeding by a nasogastric tube or an endoscopically placed gastrostomy tube may be considered for nutritional support; however, these maneuvers do not provide protection against aspiration of salivary secretions or refluxed gastric contents.

Treatment of esophageal dysphagia is covered in detail in **Chap. 316**. The majority of causes of esophageal dysphagia are effectively managed by means of esophageal dilatation using bougie or balloon dilators. Cancer and achalasia are often managed surgically, although endoscopic techniques are available for both palliation and primary therapy, respectively. Infectious etiologies respond to antimicrobial medications or treatment of the underlying immunosuppressive state. Finally, eosinophilic esophagitis has emerged as an important cause of dysphagia that is amenable to treatment by elimination of dietary allergens or administration of swallowed, topically acting glucocorticoids.

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41 Nausea, Vomiting, and Indigestion

William L. Hasler

Nausea is the subjective feeling of a need to vomit. *Vomiting* (emesis) is the oral expulsion of gastrointestinal contents due to gut and thoracoabdominal wall contractions. Vomiting is contrasted with *regurgitation*, the effortless passage of gastric contents into the mouth. *Rumination* is the repeated regurgitation of food residue, which may be rechewed and reswallowed. In contrast to emesis, these phenomena exhibit volitional control. *Indigestion* is a term encompassing a range of complaints including nausea, vomiting, heartburn, regurgitation, and dyspepsia (symptoms thought to originate in the gastroduodenal region). Some individuals with dyspepsia experience postprandial fullness, early satiety (an inability to complete a meal due to premature fullness), bloating, eructation (belching), and anorexia. Others report predominantly epigastric burning or pain.

NAUSEA AND VOMITING

MECHANISMS

Vomiting is coordinated by the brainstem and is effected by responses in the gut, pharynx, and somatic musculature. Mechanisms underlying nausea are poorly understood but likely involve the cerebral cortex, as nausea requires conscious perception. This is supported by functional brain imaging studies showing activation of cerebral cortical regions during nausea.

Coordination of Emesis Brainstem nuclei—including the nucleus tractus solitarius; dorsal vagal and phrenic nuclei; medullary nuclei regulating respiration; and nuclei that control pharyngeal, facial, and tongue movements—coordinate initiation of emesis involving neurokinin NK_1, serotonin 5-HT_3, and vasopressin pathways.

Somatic and visceral muscles respond stereotypically during emesis. Inspiratory thoracic and abdominal wall muscles contract, producing high intrathoracic and intraabdominal pressures that evacuate the stomach. The gastric cardia herniates above the diaphragm, and the larynx moves upward to propel the vomitus. Distally migrating gut contractions are normally regulated by an electrical phenomenon, the slow wave, which cycles at 3 cycles/min in the stomach and 11 cycles/min in the duodenum. During emesis, the slow wave is abolished and replaced by orally propagating spikes that evoke retrograde contractions that assist in expulsion of gut contents.

Activators of Emesis Emetic stimuli act at several sites. Emesis evoked by unpleasant thoughts or smells originates in the brain, whereas cranial nerves mediate vomiting after gag reflex activation. Motion sickness and inner ear disorders act on labyrinthine pathways. Gastric irritants and cytotoxic agents like cisplatin stimulate gastroduodenal vagal afferent nerves. Nongastric afferents are activated by bowel obstruction and mesenteric ischemia. The area postrema, in the medulla, responds to bloodborne stimuli (emetogenic drugs, bacterial toxins, uremia, hypoxia, ketoacidosis) and is termed the *chemoreceptor trigger zone*.

Neurotransmitters mediating vomiting are selective for different sites. Labyrinthine disorders stimulate vestibular muscarinic M_1 and histaminergic H_1 receptors. Vagal afferent stimuli activate 5-HT_3 receptors. The area postrema is served by nerves acting on 5-HT_3, M_1, H_1, and dopamine D_2 subtypes. Central NK_1 receptors mediate both nausea and vomiting. Cannabinoid CB_1 pathways may participate in the cerebral cortex and brainstem. Optimal pharmacologic therapy of vomiting requires understanding these pathways.

DIFFERENTIAL DIAGNOSIS

Nausea and vomiting are caused by conditions within and outside the gut, by drugs, and by circulating toxins **(Table 41-1)**. Unexplained causes of chronic nausea and vomiting are relatively rare, being reported by 2–3% of the population.

TABLE 41-1 Causes of Nausea and Vomiting

INTRAPERITONEAL	EXTRAPERITONEAL	MEDICATIONS/METABOLIC DISORDERS
Obstructing disorders	Cardiopulmonary disease	Drugs
Pyloric obstruction	Cardiomyopathy	Cancer chemotherapy
Small-bowel obstruction	Myocardial infarction	Antibiotics
Colonic obstruction	Labyrinthine disease	Cardiac antiarrhythmics
Superior mesenteric artery syndrome	Motion sickness	Digoxin
Enteric infections	Labyrinthitis	Oral hypoglycemics
Viral	Malignancy	Oral contraceptives
Bacterial	Intracerebral disorders	Antidepressants
Inflammatory diseases	Malignancy	Restless legs/Parkinson's therapies
Cholecystitis	Hemorrhage	Smoking cessation agents
Pancreatitis	Abscess	Endocrine/metabolic disease
Appendicitis	Hydrocephalus	Pregnancy
Hepatitis	Psychiatric illness	Uremia
Altered sensorimotor function	Anorexia and bulimia nervosa	Ketoacidosis
Gastroparesis	Depression	Thyroid and parathyroid disease
Intestinal pseudoobstruction	Postoperative vomiting	Adrenal insufficiency
Gastroesophageal reflux		Toxins
Chronic nausea vomiting syndrome		Liver failure
Cyclic vomiting syndrome		Ethanol
Cannabinoid hyperemesis syndrome		
Rumination syndrome		
Biliary colic		
Abdominal irradiation		

Intraperitoneal Disorders Visceral obstruction and inflammation of hollow and solid viscera may elicit vomiting. Gastric obstruction results from ulcers and malignancy. Small-bowel and colon blockage occur because of adhesions, benign or malignant tumors, volvulus, intussusception, or inflammatory diseases like Crohn's disease. The superior mesenteric artery syndrome, occurring after weight loss or prolonged bed rest, results when the duodenum is compressed by the overlying superior mesenteric artery. Abdominal irradiation impairs intestinal motor function and induces strictures. Biliary colic causes nausea by acting on local afferent nerves. Vomiting with pancreatitis, cholecystitis, and appendicitis result from visceral irritation and induction of ileus. Enteric infections with viruses like norovirus or rotavirus or bacteria like *Staphylococcus aureus* and *Bacillus cereus* cause vomiting, especially in children. Opportunistic infections like cytomegalovirus or herpes simplex virus induce emesis in immunocompromised individuals.

Gut sensorimotor dysfunction often causes nausea and vomiting. *Gastroparesis* presents with symptoms of gastric retention with evidence of delayed gastric emptying and occurs after vagotomy or with pancreatic carcinoma, mesenteric vascular insufficiency, or organic diseases like diabetes, scleroderma, and amyloidosis. Idiopathic gastroparesis is the most common etiology. It occurs in the absence of systemic illness and follows a viral illness in ~15–20% of cases, suggesting an infectious trigger. *Intestinal pseudoobstruction* is characterized by disrupted intestinal and colonic motor activity with retention of food residue and secretions; bacterial overgrowth; nutrient malabsorption; and symptoms of nausea, vomiting, bloating, pain, and altered defecation. Intestinal pseudoobstruction may be idiopathic, inherited as a familial visceral myopathy or neuropathy, result from systemic disease like scleroderma or an infiltrative process like amyloidosis, or occur as a paraneoplastic consequence of malignancy (e.g., small-cell lung carcinoma). Patients with gastroesophageal reflux report nausea and vomiting, as do some with irritable bowel syndrome (IBS) or chronic constipation.

Other functional gastroduodenal disorders without organic abnormalities have been characterized. *Chronic nausea vomiting syndrome* is defined as bothersome nausea at least one day and/or one or more vomiting episodes weekly in the absence of an eating disorder or psychiatric disease. *Cyclic vomiting syndrome* causes 3–14% of cases of unexplained nausea and vomiting and presents with periodic discrete episodes of relentless vomiting in children and adults and shows an association with migraine headaches, suggesting that some cases may be migraine variants. Some adult cases have been associated with rapid gastric emptying. A related condition, *cannabinoid hyperemesis syndrome*, presents with cyclical vomiting with intervening well periods in individuals (mostly men) who use large quantities of cannabis over many years and resolves with its discontinuation. Pathologic behaviors such as taking prolonged hot baths or showers are associated with the syndrome. *Rumination syndrome*, characterized by repetitive regurgitation of recently ingested food, is often misdiagnosed as refractory vomiting.

Extraperitoneal Disorders Myocardial infarction and congestive heart failure may cause nausea and vomiting. Postoperative emesis occurs after 25% of surgeries, most commonly abdominal and orthopedic surgery. Increased intracranial pressure from tumors, bleeding, abscess, or blockage of cerebrospinal fluid outflow produces vomiting with or without nausea. Patients with psychiatric illnesses including anorexia nervosa, bulimia nervosa, anxiety, and depression often report significant nausea that may be associated with delayed gastric emptying.

Medications and Metabolic Disorders Drugs evoke vomiting by action on the stomach (analgesics, erythromycin) or area postrema (opiates, anti-parkinsonian drugs). Other emetogenic agents include antibiotics, cardiac antiarrhythmics, antihypertensives, oral hypoglycemics, antidepressants (selective serotonin and serotonin norepinephrine reuptake inhibitors), smoking cessation drugs (varenicline, nicotine), and contraceptives. Cancer chemotherapy causes vomiting that is acute (within hours of administration), delayed (after 1 or more days), or anticipatory. Acute emesis from highly emetogenic agents (e.g., cisplatin) is mediated by 5-HT_3 pathways. Delayed emesis is less dependent on 5-HT_3 pathways with greater mediation by NK_1 mechanisms. Anticipatory nausea may respond to anxiolytic therapy rather than antiemetics.

Metabolic disorders elicit nausea and vomiting. Pregnancy is the most prevalent endocrinologic cause, and nausea affects 70% of women in the first trimester. Hyperemesis gravidarum is a severe form of nausea of pregnancy that produces significant dehydration and electrolyte disturbances. Uremia, ketoacidosis, adrenal insufficiency, and parathyroid and thyroid disease are other metabolic etiologies.

Circulating toxins evoke emesis via effects on the area postrema. Endogenous toxins are generated in fulminant liver failure, whereas exogenous enterotoxins may be produced by enteric bacterial infection. Ethanol intoxication is a common toxic etiology of nausea and vomiting.

APPROACH TO THE PATIENT

Nausea and Vomiting

HISTORY AND PHYSICAL EXAMINATION

The history helps define the etiology of nausea and vomiting. Drugs, toxins, and infections often cause acute symptoms, whereas established illnesses evoke chronic complaints. Gastroparesis and pyloric

obstruction elicit vomiting within an hour of eating. Emesis from intestinal blockage occurs later. Vomiting occurring minutes after meal consumption prompts consideration of rumination syndrome. With severe gastric emptying delays, the vomitus may contain food residue ingested days before. Hematemesis raises suspicion of an ulcer, malignancy, or Mallory-Weiss tear. Feculent emesis is noted with distal intestinal or colonic obstruction. Bilious vomiting excludes gastric obstruction, whereas emesis of undigested food is consistent with a Zenker's diverticulum or achalasia. Vomiting can relieve abdominal pain from a bowel obstruction, but has no effect in pancreatitis or cholecystitis. Profound weight loss raises concern about malignancy or obstruction. Fevers suggest inflammation. An intracranial source is considered if there are headaches or visual field changes. Vertigo or tinnitus indicates labyrinthine disease.

The physical examination complements the history. Orthostatic hypotension and reduced skin turgor indicate intravascular fluid loss. Pulmonary abnormalities raise concern for aspiration of vomitus. Bowel sounds may be absent with ileus. High-pitched rushes suggest bowel obstruction, whereas a succussion splash upon abrupt lateral movement of the patient is found with gastroparesis or pyloric obstruction. Tenderness or involuntary guarding raises suspicion of inflammation. Fecal blood suggests mucosal injury from ulcer, ischemia, or tumor. Neurologic disease presents with papilledema, visual field loss, or focal neural abnormalities. Neoplasm is suggested by palpable masses or adenopathy.

DIAGNOSTIC TESTING

For intractable symptoms or an elusive diagnosis, selected screening tests can direct clinical care. Electrolyte replacement is indicated for hypokalemia or metabolic alkalosis. Iron-deficiency anemia mandates a search for mucosal injury. Pancreaticobiliary disease is indicated by abnormal pancreatic or liver biochemistries. Endocrinologic, rheumatologic, or paraneoplastic etiologies are suggested by hormone or serologic abnormalities. If obstruction is suspected, supine and upright abdominal radiographs may show intestinal air-fluid levels with reduced colonic air. Ileus is characterized by diffusely dilated air-filled bowel loops.

Anatomic studies may be indicated if initial testing is nondiagnostic. Upper endoscopy detects ulcers, malignancy, and retained food residue in gastroparesis. Small-bowel barium radiography or computed tomography (CT) diagnoses partial bowel obstruction. Colonoscopy or contrast enema radiography detects colonic obstruction. Ultrasound or CT defines intraperitoneal inflammation; CT and magnetic resonance imaging (MRI) enterography provide define inflammation in Crohn's disease. Brain CT or MRI can delineate intracranial disease. Mesenteric angiography, CT, or MRI is useful for suspected ischemia.

Gastrointestinal motility testing may detect an underlying motor disorder. Gastroparesis commonly is diagnosed by gastric scintigraphy, by which measures emptying of a radiolabeled meal. A non-radioactive ^{13}C-labelled gastric emptying breath test was FDA-approved in 2015 and may be a cost-effective alternative to scintigtraphy. Intestinal pseudoobstruction is suggested by abnormal barium transit and luminal dilation on small-bowel contrast radiography. Wireless motility capsule methods measure transit in the stomach, small bowel, and colon by detecting pH changes between regions and also can diagnose gastroparesis and small bowel dysmotility. Small-intestinal manometry can confirm the diagnosis of pseudoobstruction and characterize the motor abnormality as neuropathic or myopathic based on contractile patterns. Manometry can obviate the need for surgical intestinal biopsy to detect smooth muscle or neuronal degeneration. Combined ambulatory esophageal pH/impedance testing and high-resolution manometry facilitates diagnosis of rumination syndrome.

TREATMENT

Nausea and Vomiting

GENERAL PRINCIPLES

Therapy of vomiting is tailored to correcting remediable abnormalities if possible. Hospitalization is considered for severe dehydration, especially if oral fluid replenishment cannot be sustained. Once oral intake is tolerated, nutrients are restarted with low-fat liquids, because lipids delay gastric emptying. A low residue, small particle diet has shown efficacy in gastroparesis in a controlled study. Controlling blood glucose in poorly controlled diabetics can reduce hospitalizations in gastroparesis and may improve nausea and vomiting.

ANTIEMETIC MEDICATIONS

The most commonly used antiemetic agents act on central nervous system sites **(Table 41-2)**. Antihistamines like dimenhydrinate and meclizine and anticholinergics like scopolamine act on labyrinthine pathways to treat motion sickness and labyrinthine disorders. D_2 antagonists treat emesis evoked by area postrema stimuli and are used for medication, toxic, and metabolic etiologies. Dopamine antagonists cross the blood-brain barrier and cause anxiety,

TABLE 41-2 Treatment of Nausea and Vomiting

TREATMENT	MECHANISM	EXAMPLES	CLINICAL INDICATIONS
Antiemetic agents	Antihistaminergic	Dimenhydrinate, meclizine	Motion sickness, inner ear disease
	Anticholinergic	Scopolamine	Motion sickness, inner ear disease
	Antidopaminergic	Prochlorperazine, thiethylperazine	Medication-, toxin-, or metabolic-induced emesis
	5-HT_3 antagonist	Ondansetron, granisetron	Chemotherapy- and radiation-induced emesis, postoperative emesis
	NK_1 antagonist	Aprepitant	Chemotherapy-induced nausea and vomiting
	Tricyclic antidepressant	Amitriptyline, nortriptyline	Chronic nausea vomiting syndrome, cyclic vomiting syndrome, ?gastroparesis
	Other antidepressant	Mirtazapine, olanzapine	?Chronic nausea vomiting syndrome, ?gastroparesis
Prokinetic agents	5-HT_4 agonist and antidopaminergic	Metoclopramide	Gastroparesis
	Motilin agonist	Erythromycin	Gastroparesis, ?intestinal pseudoobstruction
	Peripheral antidopaminergic	Domperidone	Gastroparesis
	Somatostatin analogue	Octreotide	Intestinal pseudoobstruction
	Acetylcholinesterase inhibitor	Pyridostigmine	?Small-intestinal dysmotility/pseudoobstruction
Special settings	Benzodiazepines	Lorazepam	Anticipatory nausea and vomiting with chemotherapy
	Glucocorticoids	Methylprednisolone, dexamethasone	Chemotherapy-induced emesis
	Cannabinoids	Tetrahydrocannabinol	Chemotherapy-induced emesis

Note: ?, indication is uncertain.

movement disorders, and hyperprolactinemic effects (galactorrhea, sexual dysfunction).

Other classes exhibit antiemetic properties. 5-HT_3 antagonists like ondansetron and granisetron prevent postoperative vomiting, radiation therapy–induced symptoms, and cancer chemotherapy–induced emesis, but also are used for other causes of emesis. NK_1 antagonists like aprepitant are approved for chemotherapy-induced vomiting and also reduce gastroparesis symptoms. Tricyclic antidepressants reduce symptoms in some patients with functional causes of vomiting, but did not show benefits in a controlled trial in gastroparesis. Other antidepressants such as mirtazapine and olanzapine and the pain-modulating agent gabapentin also may exhibit antiemetic effects.

GASTROINTESTINAL MOTOR STIMULANTS

Drugs that stimulate gastric emptying are used for gastroparesis (Table 41-2). Metoclopramide, a combined 5-HT_4 agonist and D_2 antagonist, is effective in gastroparesis, but antidopaminergic side effects, including dystonias and mood disturbances, limit use in ~25% of cases. Erythromycin increases gastroduodenal motility by action on receptors for motilin, an endogenous fasting motor stimulant. Intravenous erythromycin is useful for inpatients with refractory gastroparesis. Utility of oral forms is limited by development of tolerance. Domperidone, a D_2 antagonist not available in the United States, exhibits prokinetic and antiemetic effects but does not cross into most brain regions; thus, dystonic reactions are rare. Domperidone can induce hyperprolactinemic side effects via effects on pituitary regions served by a porous blood-brain barrier. Prucalopride, a 5-HT_4 agonist available in Canada and Europe, has shown efficacy in a preliminary gastroparesis trial.

Refractory motility disorders pose challenges. Intestinal pseudoobstruction may respond to the somatostatin analogue octreotide, which induces propagative small-intestinal motor complexes. Acetylcholinesterase inhibitors like pyridostigmine may benefit some patients with small-bowel dysmotility. Pyloric botulinum toxin injections are reported in uncontrolled studies to reduce gastroparesis symptoms, but small controlled trials observe benefits no greater than sham treatments. Surgical pyloroplasty and peroral endoscopic myotomy (POEM) of the pylorus has improved symptoms in case series. Placing a feeding jejunostomy reduces hospitalizations and improves overall health in some patients with refractory gastroparesis. Postvagotomy gastroparesis may improve with near-total gastric resection; similar operations are being tried for other gastroparesis etiologies. Implanted gastric electrical stimulators may reduce symptoms, enhance nutrition, improve quality of life, and decrease health care expenditures in medication-refractory gastroparesis, but small controlled trials do not report convincing benefits.

SAFETY CONSIDERATIONS

Safety concerns have been raised about selected antiemetics. Centrally acting antidopaminergics, especially metoclopramide, can cause irreversible movement disorders like tardive dyskinesia, particularly in older patients. This complication should be explained and documented in the medical record. Domperidone, erythromycin, tricyclic antidepressants, and 5-HT_3 antagonists can induce dangerous cardiac arrhythmias, especially in those with QTc interval prolongation on electrocardiography (ECG). Surveillance ECG testing has been advocated for some of these agents.

SELECTED CLINICAL SETTINGS

Some cancer chemotherapies are intensely emetogenic **(Chap. 69)**. Combining a 5-HT_3 antagonist, an NK_1 antagonist, and a glucocorticoid can control both acute and delayed vomiting after highly emetogenic chemotherapy. Unlike other drugs in the same class, the 5-HT_3 antagonist palonosetron can prevent delayed chemotherapy-induced vomiting. Benzodiazepines like lorazepam reduce anticipatory nausea and vomiting. Miscellaneous therapies with benefit in chemotherapy-induced emesis include cannabinoids, olanzapine, and alternative therapies like ginger. Most antiemetic regimens produce greater reductions in vomiting than nausea.

Clinicians should exercise caution in managing pregnant patients with nausea. Studies of the teratogenic effects of antiemetic agents provide conflicting results. Few controlled trials have been performed in nausea of pregnancy. Antihistamines like meclizine and doxylamine, antidopaminergics like prochlorperazine, and antiserotonergics like ondansetron demonstrate limited efficacy. Some obstetricians offer alternative therapies including pyridoxine, acupressure, or ginger.

Managing cyclic vomiting syndrome is challenging. Prophylaxis with tricyclic antidepressants, cyproheptadine, or β-adrenoceptor antagonists can reduce the severity and frequency of attacks. Intravenous 5-HT_3 antagonists combined with the sedating effects of a benzodiazepine like lorazepam are a mainstay for treating acute flares. Small studies report benefits with antimigraine agents, including the 5-HT_1 agonist sumatriptan, and selected anticonvulsants like topiramate, zonisamide, and levetiracetam.

INDIGESTION

MECHANISMS

The most common causes of indigestion are gastroesophageal reflux and functional dyspepsia. Other cases are a consequence of organic illness.

Gastroesophageal Reflux Gastroesophageal reflux results from many physiologic defects. Reduced lower esophageal sphincter (LES) tone contributes to reflux in scleroderma and pregnancy and may be a factor in some patients without systemic illness. Others exhibit frequent transient LES relaxations (TLESRs) that permit bathing of the esophagus by acid or nonacidic fluid. Reductions in esophageal body motility or salivary secretion prolong fluid exposure. Increased intragastric pressure promotes gastroesophageal reflux in obese patients. The role of hiatal hernias is controversial—most reflux patients have hiatal hernias, but most with hiatal hernias do not report excess heartburn.

Gastric Motor Dysfunction Disturbed gastric motility may contribute to gastroesophageal reflux in up to one-third of cases. Delayed gastric emptying is also found in ~30% of functional dyspeptics, while rapid gastric emptying affects 5%. The relation of these defects to symptom induction is uncertain; studies show poor correlation between symptom severity and degrees of motor dysfunction. Impaired gastric fundus relaxation after eating (i.e., accommodation) may underlie selected dyspeptic symptoms like bloating, nausea, and early satiety in ~40% of patients and may predispose to TLESRs and acid reflux.

Visceral Afferent Hypersensitivity Disturbed gastric sensation is another pathogenic factor in functional dyspepsia. Approximately 35% of dyspeptic patients note discomfort with fundic distention to lower pressures than in healthy controls. Others with dyspepsia exhibit hypersensitivity to chemical stimulation with capsaicin or with acid or lipid perfusion of the duodenum. Some individuals with functional heartburn without increased acid or nonacid reflux may have heightened perception of normal esophageal acidity.

Other Factors *Helicobacter pylori* has a clear etiologic role in peptic ulcer disease, but ulcers cause a minority of dyspepsia cases. *H. pylori* is a minor factor in the genesis of functional dyspepsia. Anxiety and depression may play contributing roles in some functional dyspepsia cases. Functional MRI studies show increased activation of several brain regions, emphasizing contributions from central nervous system pathways. Inflammatory factors like duodenal eosinophilia (and possibly increased duodenal mast cells) may contribute to early satiety and pain in functional dyspepsia. Up to 20% of functional dyspepsia patients report symptom onset after a viral illness, suggestive of an infectious cause. Analgesics cause dyspepsia, whereas nitrates, calcium channel blockers, theophylline, and progesterone promote

gastroesophageal reflux. Other stimuli that induce reflux include ethanol, tobacco, and caffeine via LES relaxation. Genetic factors predispose to development of reflux and dyspepsia.

DIFFERENTIAL DIAGNOSIS

Gastroesophageal Reflux Disease Gastroesophageal reflux disease (GERD) is prevalent. Heartburn or regurgitation are reported weekly by 18–28%. Most cases of heartburn result from excess acid reflux, but reflux of nonacidic fluid produces similar symptoms. Alkaline reflux esophagitis produces GERD-like symptoms most often in patients who have had surgery for peptic ulcer disease. Ten percent of patients with heartburn exhibit no increase in acid or nonacidic esophageal reflux (functional heartburn).

Functional Dyspepsia Nearly 25% of the populace has dyspepsia at least six times yearly, but only 10–20% present to clinicians. Functional dyspepsia, the cause of symptoms in >70% of dyspeptic patients, is defined as bothersome postprandial fullness, early satiety, or epigastric pain or burning with symptom onset at least 6 months before diagnosis in the absence of organic cause. Functional dyspepsia is subdivided into postprandial distress syndrome, characterized by meal-induced fullness and early satiety, and epigastric pain syndrome, which presents with epigastric pain or burning which may or may not be meal-related. Most cases follow a benign course, but some with *H. pylori* infection or on nonsteroidal anti-inflammatory drugs (NSAIDs) develop ulcers.

Ulcer Disease In most GERD patients, there is no injury to the esophagus. However, 5% develop esophageal ulcers, and some form strictures. Symptoms cannot distinguish nonerosive from erosive or ulcerative esophagitis. A minority of cases of dyspepsia stem from gastric or duodenal ulcers. The most common causes of ulcers are *H. pylori* infection and NSAID use. Other rare causes of gastroduodenal ulcers include Crohn's disease **(Chap. 319)** and Zollinger-Ellison syndrome **(Chap. 317)**, resulting from gastrin overproduction by an endocrine tumor.

Malignancy Dyspeptic patients often seek care because of fear of cancer, but few cases result from malignancy. Esophageal squamous cell carcinoma occurs most often with long-standing tobacco or ethanol intake. Other risks include prior caustic ingestion, achalasia, and the hereditary disorder tylosis. Esophageal adenocarcinoma usually complicates prolonged acid reflux. Eight to 20% of GERD patients exhibit esophageal intestinal metaplasia, termed *Barrett's metaplasia*, which predisposes to esophageal adenocarcinoma **(Chap. 76)**. Gastric malignancies include adenocarcinoma, which is prevalent in certain Asian societies, and lymphoma.

Other Causes Opportunistic fungal or viral esophageal infections may produce heartburn but more often cause odynophagia. Other causes of esophageal inflammation include eosinophilic esophagitis and pill esophagitis. Biliary colic is in the differential diagnosis of unexplained upper abdominal pain, but most patients with biliary colic report discrete acute episodes of right upper quadrant or epigastric pain rather than the chronic burning or fullness of dyspepsia. Twenty percent of gastroparesis patients report a predominance of pain rather than nausea and vomiting. Intestinal lactase deficiency as a cause of gas, bloating, and discomfort occurs in 15–25% of whites of northern European descent but is more common in blacks and Asians. Intolerance of other carbohydrates (e.g., fructose, sorbitol) produces similar symptoms. Small-intestinal bacterial overgrowth may cause dyspepsia, often associated with bowel dysfunction, distention, and malabsorption. Celiac disease, pancreatic disease (chronic pancreatitis, malignancy), hepatocellular carcinoma, Ménétrier's disease, infiltrative diseases (sarcoidosis, eosinophilic gastroenteritis), mesenteric ischemia, thyroid and parathyroid disease, and abdominal wall strain cause dyspepsia. Gluten sensitivity in the absence of celiac disease can elicit unexplained upper abdominal symptoms. Extraperitoneal etiologies of indigestion include congestive heart failure and tuberculosis.

APPROACH TO THE PATIENT

Indigestion

HISTORY AND PHYSICAL EXAMINATION

Management of indigestion requires a thorough interview. GERD classically produces heartburn, a substernal warmth that moves toward the neck. Heartburn often is exacerbated by meals and may awaken the patient. Associated symptoms include regurgitation of acid or nonacidic fluid and water brash, the reflex release of salty salivary secretions into the mouth. Atypical symptoms include pharyngitis, asthma, cough, bronchitis, hoarseness, and chest pain that mimics angina. Some patients with acid reflux on esophageal pH testing do not report heartburn, but note abdominal pain or other symptoms.

Dyspeptic patients typically report symptoms referable to the upper abdomen that may be meal-related, as with postprandial distress syndrome, or possibly independent of food ingestion in epigastric pain syndrome. Functional dyspepsia overlaps with other disorders including GERD, IBS, and idiopathic gastroparesis.

The physical examination with GERD and functional dyspepsia usually is normal. In atypical GERD, pharyngeal erythema and wheezing may be noted. Recurrent acid regurgitation may cause poor dentition. Dyspeptics may exhibit epigastric tenderness or distention.

Discriminating functional from organic causes of indigestion mandates excluding certain historic and examination features. Odynophagia suggests esophageal infection. Dysphagia is concerning for a benign or malignant esophageal blockage. Other alarm features include unexplained weight loss, recurrent vomiting, occult or gross bleeding, jaundice, palpable mass or adenopathy, and a family history of gastrointestinal neoplasm.

DIAGNOSTIC TESTING

Because indigestion is prevalent and most cases result from GERD or functional dyspepsia, a general principle is to perform only limited and directed diagnostic testing in selected individuals.

Once alarm factors are excluded **(Table 41-3)**, patients with typical GERD do not need further evaluation and are treated empirically. Upper endoscopy is indicated to exclude mucosal injury in cases with atypical symptoms or alarm factors. For heartburn >5 years in duration, especially in patients >50 years old, endoscopy is advocated to screen for Barrett's metaplasia. Endoscopy is not needed in low risk patients who exhibit a therapeutic response to acid suppressants. Ambulatory esophageal pH testing using a catheter method or a wireless capsule endoscopically attached to the esophageal wall is considered for drug-refractory symptoms and atypical symptoms like unexplained chest pain. High-resolution esophageal manometry is ordered when surgical treatment of GERD is considered. A low LES pressure predicts failure of drug therapy and provides a rationale to proceed to surgery. Poor esophageal body peristalsis raises concern about postoperative dysphagia and directs the choice of surgical technique. Nonacidic reflux may be detected by combined esophageal impedance-pH testing in medication-unresponsive patients.

Upper endoscopy is recommended as the initial test in patients with unexplained dyspepsia who are >55 years old or who have

TABLE 41-3 Alarm Symptoms in Gastroesophageal Reflux Disease

Odynophagia or dysphagia
Unexplained weight loss
Recurrent vomiting
Occult or gross gastrointestinal bleeding
Jaundice
Palpable mass or adenopathy
Family history of gastroesophageal malignancy

alarm factors because of the purported elevated risks of malignancy and ulcer in these groups. However, findings of endoscopy performed for uninvestigated dyspepsia include erosive esophagitis in 13%, peptic ulcer in 8%, and gastric or esophageal malignancy in only 0.3%. Management of patients <55 years old without alarm factors depends on the local prevalence of *H. pylori* infection. In regions with low *H. pylori* prevalence (<10%), a 4-week trial of an acid-suppressing medication such as a proton pump inhibitor (PPI) is recommended. If this fails, a "test and treat" approach is most commonly applied. *H. pylori* status is determined with urea breath testing or stool antigen measurement. Those who are *H. pylori* positive are given therapy to eradicate the infection. If symptoms resolve on either regimen, no further intervention is required. For patients in areas with high *H. pylori* prevalence (>10%), an initial test and treat approach is advocated, with a subsequent trial of an acid-suppressing regimen offered for those in whom *H. pylori* treatment fails or for those who are negative for the infection. In each of these patient subsets, upper endoscopy is reserved for those whose symptoms fail to respond to therapy.

Further testing is indicated in some settings. If bleeding is noted, a blood count can exclude anemia. Thyroid chemistries or calcium levels screen for metabolic disease, whereas specific serologies may suggest celiac disease. Pancreatic and liver chemistries are obtained for possible pancreaticobiliary causes which are further investigated with ultrasound, CT, or MRI. Gastric emptying testing is considered to exclude gastroparesis for dyspeptic symptoms that resemble postprandial distress when drug therapy fails and in some GERD patients, especially if surgical intervention is an option. Breath testing after carbohydrate ingestion detects lactase deficiency, intolerance to other carbohydrates, or small-intestinal bacterial overgrowth.

TREATMENT

Indigestion

GENERAL PRINCIPLES

For mild indigestion, reassurance that a careful evaluation revealed no serious organic disease may be the only intervention needed. Drugs that cause gastroesophageal reflux or dyspepsia should be stopped, if possible. Patients with GERD should limit ethanol, caffeine, chocolate, and tobacco use due to their effects on the LES. Other measures in GERD include ingesting a low-fat diet, avoiding snacks before bedtime, and elevating the head of the bed. Patients with functional dyspepsia also may be advised to reduce intake of fat, spicy foods, caffeine, and alcohol.

Specific therapies for organic disease should be offered when possible. Surgery is appropriate for biliary colic. Diet changes are indicated for lactase deficiency or celiac disease. Peptic ulcers may be cured by specific medical regimens. However, because most indigestion is caused by GERD or functional dyspepsia, medications that reduce gastric acid, modulate motility, or blunt gastric sensitivity are used.

ACID-SUPPRESSING OR NEUTRALIZING MEDICATIONS

Drugs that reduce or neutralize gastric acid are often prescribed for GERD. Histamine H_2 antagonists like cimetidine, ranitidine, famotidine, and nizatidine are useful in mild to moderate GERD. For severe symptoms or for many cases of erosive or ulcerative esophagitis, PPIs like omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, or dexlansoprazole are needed. These drugs inhibit gastric H^+, K^+-ATPase and are more potent than H_2 antagonists. Up to one-third of GERD patients do not respond to standard PPI doses; one-third of these patients have nonacidic reflux, whereas 10% have persistent acid-related disease. Heartburn typically responds better to PPI therapy than regurgitation or atypical GERD symptoms. Some individuals respond to doubling of the PPI dose or adding an H_2 antagonist at bedtime. Infrequent complications of long-term PPI therapy include diarrhea (from *Clostridium difficile* infection or microscopic colitis), small-intestinal bacterial overgrowth, nutrient deficiency (vitamin B_{12}, iron, calcium), hypomagnesemia, bone demineralization, interstitial nephritis, and impaired medication absorption (e.g., clopidogrel). Many patients started on a PPI can be stepped down to an H_2 antagonist or switched to an on-demand schedule.

Acid-suppressing drugs are also effective in selected patients with functional dyspepsia. A meta-analysis of 10 controlled trials calculated a risk ratio of 0.87, with a 95% confidence interval of 0.80–0.96, favoring PPI therapy over placebo. H_2 antagonists also reportedly improve symptoms in functional dyspepsia; however, findings of trials of this drug class likely are influenced by inclusion of large numbers of GERD patients.

Antacids are useful for short-term control of mild GERD but have less benefit in severe cases unless given at high doses that cause side effects (diarrhea and constipation with magnesium- and aluminum-containing agents, respectively). Alginic acid combined with antacids forms a floating barrier to reflux in patients with upright symptoms. Sucralfate, a salt of aluminum hydroxide and sucrose octasulfate that buffers acid and binds pepsin and bile salts, shows efficacy in GERD similar to H_2 antagonists.

HELICOBACTER PYLORI ERADICATION

H. pylori eradication is definitively indicated only for peptic ulcer and mucosa-associated lymphoid tissue gastric lymphoma. The benefits of eradication therapy in functional dyspepsia are limited but are statistically significant. A systematic review of 25 controlled trials calculated a pooled risk ratio of 1.24, with a 95% confidence interval of 1.12–1.37, favoring *H. pylori* eradication over placebo. Most drug combinations **(Chaps. 158 and 317)** include 10–14 days of a PPI or bismuth subsalicylate with two antibiotics. *H. pylori* infection is associated with reduced prevalence of GERD, especially in the elderly. However, eradication of the infection does not worsen GERD symptoms. No consensus recommendations regarding *H. pylori* eradication in GERD patients have been offered.

AGENTS THAT MODIFY GASTROINTESTINAL MOTOR ACTIVITY

Prokinetics like metoclopramide, erythromycin, and domperidone have limited utility in GERD. The γ-aminobutyric acid B (GABA-B) agonist baclofen reduces esophageal exposure to acid and nonacidic fluids by reducing TLESRs by 40%; this drug is proposed as adjunctive therapy for refractory acid and nonacid reflux. Several studies have promoted the efficacy of motor-stimulating drugs in functional dyspepsia with 33% relative risk reductions, but publication bias and small sample sizes raise questions about reported benefits of these agents. Some clinicians suggest that patients with the postprandial distress subtype may respond preferentially to prokinetic drugs. The 5-HT_{1A} agonists buspirone and tandospirone may improve some functional dyspepsia symptoms by enhancing meal-induced gastric accommodation. Acotiamide promotes gastric emptying and augments accommodation by enhancing acetylcholine release via muscarinic receptor antagonism and acetylcholinesterase inhibition. This agent is approved for functional dyspepsia in Japan.

ANTIDEPRESSANTS

Some patients with refractory functional heartburn may respond to antidepressants in tricyclic and selective serotonin reuptake inhibitor (SSRI) classes, although studies are limited. Their mechanism of action may involve blunting of visceral pain processing in the brain. In a recent controlled trial in functional dyspepsia, the tricyclic drug amitriptyline produced symptom reductions while the SSRI escitalopram had no benefit in a 3-way comparison with placebo. In another controlled trial in functional dyspepsia, the antidepressant mirtazapine produced superior symptom reductions versus placebo.

OTHER OPTIONS

Antireflux surgery (fundoplication) to increase LES pressure may be offered to GERD patients who are young and require lifelong therapy, have typical heartburn and regurgitation, are responsive to

PPIs, and show acid reflux on pH monitoring. Surgery also is effective for some cases of nonacidic reflux. Individuals who respond less well to fundoplication include those with atypical symptoms or who have esophageal body motor disturbances. Dysphagia, gas-bloat syndrome, and gastroparesis are long-term complications of fundoplication; ~60% develop recurrent GERD symptoms over time. Studies assessing the utility and safety of gastroesophageal junction endoscopic therapies (radiofrequency therapy, transoral fundoplication, endoscopic stapling, antireflux mucosectomy) and laparoscopic magnetic sphincter augmentation to enhance gastroesophageal barrier function in GERD are ongoing.

Gas and bloating can be troubling symptoms in some patients with indigestion that are difficult to treat. Dietary exclusion of gas-producing foods such as legumes and use of simethicone or activated charcoal provide benefits in some cases. Low FODMAP (fermentable oligosaccharide, disaccharide, monosaccharide, and polyol) diets and therapies to modify gut flora (nonabsorbable antibiotics, probiotics) reduce gaseous symptoms in some IBS patients. The utility of low-FODMAP diets, antibiotics, and probiotics in functional dyspepsia is unproven. Herbal remedies such as STW 5 (Iberogast, a mixture of nine herbal agents) are useful in some dyspeptic patients. Psychological treatments (e.g., behavioral therapy, psychotherapy, hypnotherapy) may be offered for refractory functional dyspepsia, but no convincing data confirm their efficacy.

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42 Diarrhea and Constipation

Michael Camilleri, Joseph A. Murray

Diarrhea and constipation are exceedingly common and, together, exact an enormous toll in terms of mortality, morbidity, social inconvenience, loss of work productivity, and consumption of medical resources. Worldwide, >1 billion individuals suffer one or more episodes of acute diarrhea each year. Among the 100 million persons affected annually by acute diarrhea in the United States, nearly half must restrict activities, 10% consult physicians, ~250,000 require hospitalization, and ~5000 die (primarily the elderly). The annual economic burden to society may exceed $20 billion. Acute infectious diarrhea remains one of the most common causes of mortality in developing countries, particularly among impoverished infants, accounting for 1.8 million deaths per year. Recurrent, acute diarrhea in children in tropical countries results in environmental enteropathy with long-term impacts on physical and intellectual development.

Constipation, by contrast, is rarely associated with mortality and is exceedingly common in developed countries, leading to frequent self-medication and, in a third of those, to medical consultation. Population statistics on chronic diarrhea and constipation are more uncertain, perhaps due to variable definitions and reporting, but the frequency of these conditions is also high. U.S. population surveys put prevalence rates for chronic diarrhea at 2–7% and for chronic constipation at 12–19%, with women being affected twice as often as men. Diarrhea and constipation are among the most common patient complaints presenting to internists and primary care physicians, and they account for nearly 50% of referrals to gastroenterologists.

Although diarrhea and constipation may present as mere nuisance symptoms at one extreme, they can be severe or life threatening at the other. Even mild symptoms may signal a serious underlying gastrointestinal (GI) lesion, such as colorectal cancer, or systemic disorder, such as thyroid disease. Given the heterogeneous causes and potential severity of these common complaints, it is imperative for clinicians to appreciate the pathophysiology, etiologic classification, diagnostic strategies, and principles of management of diarrhea and constipation, so that rational and cost-effective care can be delivered.

NORMAL PHYSIOLOGY

While the primary function of the small intestine is the digestion and assimilation of nutrients from food, the small intestine and colon together perform important functions that regulate the secretion and absorption of water and electrolytes, the storage and subsequent transport of intraluminal contents aborally, and the salvage of some nutrients that are not absorbed in the small intestine after bacterial metabolism of carbohydrate allows salvage of short-chain fatty acids. The main motor functions are summarized in Table 42-1. Alterations in fluid and electrolyte handling contribute significantly to diarrhea. Alterations in motor and sensory functions of the colon result in highly prevalent syndromes such as irritable bowel syndrome (IBS), chronic diarrhea, and chronic constipation.

NEURAL CONTROL

The small intestine and colon have intrinsic and extrinsic innervation. The *intrinsic innervation*, also called the enteric nervous system, comprises myenteric, submucosal, and mucosal neuronal layers. The function of these layers is modulated by interneurons through the actions of neurotransmitter amines or peptides, including acetylcholine, vasoactive intestinal peptide (VIP), opioids, norepinephrine, serotonin, adenosine triphosphate (ATP), and nitric oxide (NO). The myenteric plexus regulates smooth-muscle function through intermediary pacemaker-like cells called the interstitial cells of Cajal, and the submucosal plexus affects secretion, absorption, and mucosal blood flow. The enteric nervous system receives input from the extrinsic nerves, but it is capable of independent control of these functions.

The *extrinsic innervations* of the small intestine and colon are part of the autonomic nervous system and also modulate motor and secretory functions. The parasympathetic nerves convey visceral sensory pathways from and excitatory pathways to the small intestine and colon. Parasympathetic fibers via the vagus nerve reach the small intestine and proximal colon along the branches of the superior mesenteric artery. The distal colon is supplied by sacral parasympathetic nerves (S_{2-4}) via the pelvic plexus; these fibers course through the wall of the colon as ascending intracolonic fibers as far as, and in some instances including, the proximal colon. The chief excitatory neurotransmitters controlling motor function are acetylcholine and the tachykinins, such as substance P. The sympathetic nerve supply modulates motor functions and reaches the small intestine and colon alongside their

TABLE 42-1 Normal Gastrointestinal Motility: Functions at Different Anatomic Levels

Stomach and Small Bowel
Synchronized MMC in fasting
Accommodation, trituration, mixing, transit
Stomach ~3 h
Small bowel ~3 h
Ileal reservoir empties boluses
Colon: Irregular Mixing, Fermentation, Absorption, Transit
Ascending, transverse: reservoirs
Descending: conduit
Sigmoid/rectum: volitional reservoir

Abbreviation: MMC, migrating motor complex.

arterial vessels. Sympathetic input to the gut is generally excitatory to sphincters and inhibitory to non-sphincteric muscle. Visceral afferents convey sensation from the gut to the central nervous system (CNS). Some afferent fibers synapse in the prevertebral ganglia and reflexly modulate intestinal motility, blood flow, and secretion.

INTESTINAL FLUID ABSORPTION AND SECRETION

On an average day, 9 L of fluid enter the GI tract, ~1 L of residual fluid reaches the colon, and the stool excretion of fluid constitutes about 0.2 L/d. The colon has a large capacitance and functional reserve and may recover up to four times its usual volume of 0.8 L/d, provided the rate of flow permits reabsorption to occur. Thus, the colon can partially compensate for excess fluid delivery to the colon that may result from intestinal absorptive or secretory disorders.

In the small intestine and colon, sodium absorption is predominantly electrogenic (i.e., it can be measured as an ionic current across the membrane because there is not an equivalent loss of a cation from the cell), and uptake takes place at the apical membrane; it is compensated for by the export functions of the basolateral sodium pump. There are several active transport proteins at the apical membrane, especially in the small intestine, whereby sodium ion entry is coupled to monosaccharides (e.g., glucose through the transporter SGLT1, or fructose through GLUT-5). Glucose then exits the basal membrane through a specific transport protein, GLUT-5, creating a glucose concentration and osmotic gradient between the lumen and the intercellular space, drawing water and electrolytes passively from the lumen. A variety of neural and nonneural mediators regulate colonic fluid and electrolyte balance, including cholinergic, adrenergic, and serotonergic mediators. Angiotensin and aldosterone also influence colonic absorption, reflecting the common embryologic development of the distal colonic epithelium and the renal tubules.

SMALL-INTESTINAL MOTILITY

During the fasting period, the motility of the small intestine is characterized by a cyclical event called the migrating motor complex (MMC), which serves to clear nondigestible residue from the small intestine (the intestinal "housekeeper"). This organized, propagated series of contractions lasts, on average, 4 min, occurs every 60–90 min, and usually involves the entire small intestine. After food ingestion, the small intestine produces irregular, mixing contractions of relatively low amplitude, except in the distal ileum where more powerful contractions occur intermittently and empty the ileum by bolus transfers.

ILEOCOLONIC STORAGE AND SALVAGE

The distal ileum acts as a reservoir, emptying intermittently by bolus movements. This action allows time for salvage of fluids, electrolytes, and nutrients. Segmentation by haustra compartmentalizes the colon and facilitates mixing, retention of residue, and formation of solid stools. There is increased appreciation of the intimate interaction between the colonic function and the luminal ecology. The resident microorganisms, predominantly anaerobic bacteria, in the colon are necessary for the digestion of unabsorbed carbohydrates that reach the colon even in health, thereby providing a vital source of nutrients to the mucosa. Normal intestinal flora also keeps pathogens at bay by a variety of mechanisms including a crucial role in the development and maintenance of a potent but well-regulated immune response capacity to pathogens and tolerance to normal ingesta. In health, the ascending and transverse regions of colon function as reservoirs (average transit time, 15 h), and the descending colon acts as a conduit (average transit time, 3 h). The colon is efficient at conserving sodium and water, a function that is particularly important in sodium-depleted patients in whom the small intestine alone is unable to maintain sodium balance. Diarrhea or constipation may result from alteration in the reservoir function of the proximal colon or the propulsive function of the left colon. Constipation may also result from disturbances of the rectal or sigmoid reservoir, typically as a result of dysfunction of the pelvic floor, the anal sphincters, the coordination of defecation, or dehydration.

COLONIC MOTILITY AND TONE

The small-intestinal MMC only rarely continues into the colon. However, short duration or phasic contractions mix colonic contents and high-amplitude (>75 mmHg) propagated contractions (HAPCs) are sometimes associated with mass movements through the colon and normally occur approximately five times per day, usually on awakening in the morning and postprandially. Increased frequency of HAPCs may result in diarrhea or urgency. The predominant phasic contractions in the colon are irregular and nonpropagated and serve a "mixing" function.

Colonic tone refers to the background contractility upon which phasic contractile activity (typically contractions lasting <15 s) is superimposed. It is an important cofactor in the colon's capacitance (volume accommodation) and sensation.

COLONIC MOTILITY AFTER MEAL INGESTION

After meal ingestion, colonic phasic and tonic contractility increases for a period of ~2 h. The initial phase (~10 min) is mediated by the vagus nerve in response to mechanical distention of the stomach. The subsequent response of the colon requires caloric stimulation (e.g., intake of at least 500 kcal) and is mediated, at least in part, by hormones (e.g., gastrin and serotonin).

DEFECATION

Tonic contraction of the puborectalis muscle, which forms a sling around the rectoanal junction, is important to maintain continence; during defecation, sacral parasympathetic nerves relax this muscle, facilitating the straightening of the rectoanal angle **(Fig. 42-1)**. Distention of the rectum results in transient relaxation of the internal anal sphincter via intrinsic and reflex sympathetic innervation. As sigmoid and rectal contractions, as well as straining (Valsalva maneuver), which increases intraabdominal pressure, increase the pressure within the rectum, the rectosigmoid angle opens by >15°. Voluntary relaxation of the external anal sphincter (striated muscle innervated by the pudendal nerve) in response to the sensation produced by distention permits the evacuation of feces. Defecation can also be delayed voluntarily by contraction of the external anal sphincter.

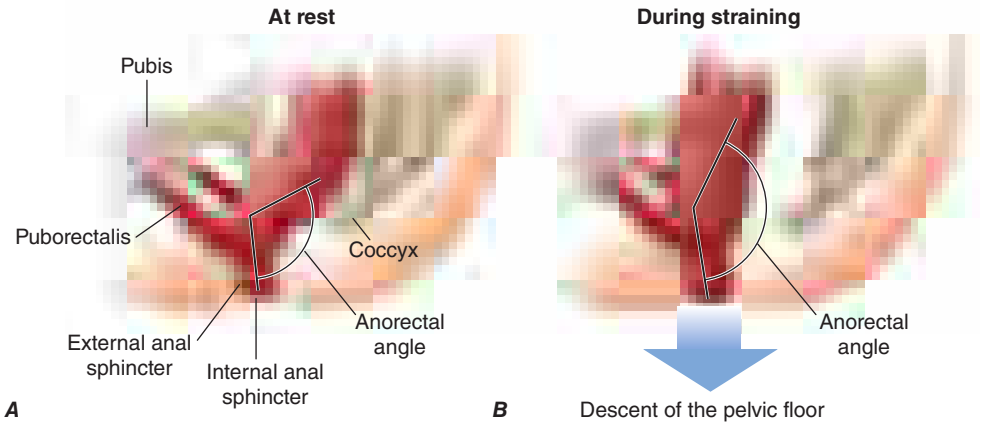

FIGURE 42-1 Sagittal view of the anorectum (*A*) at rest and (*B*) during straining to defecate. Continence is maintained by normal rectal sensation and tonic contraction of the internal anal sphincter and the puborectalis muscle, which wraps around the anorectum, maintaining an anorectal angle between 80° and 110°. During defecation, the pelvic floor muscles (including the puborectalis) relax, allowing the anorectal angle to straighten by at least 15°, and the perineum descends by 1–3.5 cm. The external anal sphincter also relaxes and reduces pressure on the anal canal. *(Reproduced with permission from A Lembo, M Camilleri: N Engl J Med 349:1360, 2003.)*

DIARRHEA

DEFINITION

Diarrhea is loosely defined as passage of abnormally liquid or unformed stools at an increased frequency. For adults on a typical Western diet, stool weight >200 g/d can generally be considered diarrheal. Diarrhea may be further defined as *acute* if <2 weeks, *persistent* if 2–4 weeks, and *chronic* if >4 weeks in duration.

Two common conditions, usually associated with the passage of stool totaling <200 g/d, must be distinguished from diarrhea, because diagnostic and therapeutic algorithms differ. *Pseudodiarrhea*, or the frequent passage of small volumes of stool, is often associated with rectal urgency, tenesmus, or a feeling of incomplete evacuation, and accompanies IBS or proctitis. *Fecal incontinence* is the involuntary discharge of rectal contents and is most often caused by neuromuscular disorders or structural anorectal problems. Diarrhea and urgency, especially if severe, may aggravate or cause incontinence. Pseudodiarrhea and fecal incontinence occur at prevalence rates comparable to or higher than that of chronic diarrhea and should always be considered in patients complaining of "diarrhea." Overflow diarrhea may occur in nursing home patients due to fecal impaction that is readily detectable by rectal examination. A careful history and physical examination generally allow these conditions to be discriminated from true diarrhea.

ACUTE DIARRHEA

More than 90% of cases of acute diarrhea are caused by infectious agents; these cases are often accompanied by vomiting, fever, and abdominal pain. The remaining 10% or so are caused by medications, toxic ingestions, ischemia, food indiscretions, and other conditions.

Infectious Agents Most infectious diarrheas are acquired by fecal-oral transmission or, more commonly, via ingestion of food or water contaminated with pathogens from human or animal feces. In the immunocompetent person, the resident fecal microflora, containing >500 taxonomically distinct species, are rarely the source of diarrhea and may actually play a role in suppressing the growth of ingested pathogens. Disturbances of flora by antibiotics can lead to diarrhea by reducing the digestive function or by allowing the overgrowth of pathogens, such as *Clostridium difficile* **(Chap. 129)**. Acute infection or injury occurs when the ingested agent overwhelms or bypasses the host's mucosal immune and nonimmune (gastric acid, digestive enzymes, mucus secretion, peristalsis, and suppressive resident flora) defenses. Established clinical associations with specific enteropathogens may offer diagnostic clues.

In the United States, five high-risk groups are recognized:

1. *Travelers*. Nearly 40% of tourists to endemic regions of Latin America, Africa, and Asia develop so-called traveler's diarrhea, most commonly due to enterotoxigenic or enteroaggregative *Escherichia coli* as well as to *Campylobacter*, *Shigella*, *Aeromonas*, norovirus, *Coronavirus*, and *Salmonella*. Visitors to Russia (especially St. Petersburg) may have increased risk of *Giardia*-associated diarrhea; visitors to Nepal may acquire *Cyclospora*. Campers, backpackers, and swimmers in wilderness areas may become infected with *Giardia*. Cruise ships may be affected by outbreaks of gastroenteritis caused by agents such as norovirus.
2. *Consumers of certain foods*. Diarrhea closely following food consumption at a picnic, banquet, or restaurant may suggest infection with *Salmonella*, *Campylobacter*, or *Shigella* from chicken; enterohemorrhagic *E. coli* (O157:H7) from undercooked hamburger; *Bacillus cereus* from fried rice or other reheated food; *Staphylococcus aureus* or *Salmonella* from mayonnaise or creams; *Salmonella* from eggs; *Listeria* from fresh or frozen uncooked foods or soft cheeses; and *Vibrio* species, *Salmonella*, or acute hepatitis A from seafood, especially if raw. State departments of public health issue communications regarding food-related illnesses, which may have originated domestically or been imported, but ultimately cause epidemics in the United States (e.g., the *Cyclospora* epidemic of 2013 in midwestern states that resulted from bagged salads).
3. *Immunodeficient persons*. Individuals at risk for diarrhea include those with either primary immunodeficiency (e.g., IgA deficiency, common variable hypogammaglobulinemia, chronic granulomatous disease) or the much more common secondary immunodeficiency states (e.g., AIDS, senescence, pharmacologic suppression). Common enteric pathogens often cause a more severe and protracted diarrheal illness, and, particularly in persons with AIDS, opportunistic infections, such as by *Mycobacterium* species, certain viruses (cytomegalovirus, adenovirus, and herpes simplex), and protozoa (*Cryptosporidium*, *Isospora belli*, Microsporida, and *Blastocystis hominis*) may also play a role **(Chap. 197)**. In patients with AIDS, agents transmitted venereally per rectum or by extension from vaginal infection (e.g., *Neisseria gonorrhoeae*, *Treponema pallidum*, *Chlamydia*) may contribute to proctocolitis. Symptoms suggesting anorectal disease, particularly pain, may result from constipation occurring coincidentally in a person with immunodeficiency. Persons with hemochromatosis are especially prone to invasive, even fatal, enteric infections with *Vibrio* species and *Yersinia* infections and should avoid raw fish.
4. *Daycare attendees and their family members*. Infections with *Shigella*, *Giardia*, *Cryptosporidium*, rotavirus, and other agents are very common and should be considered.
5. *Institutionalized persons*. Infectious diarrhea is one of the most frequent categories of nosocomial infections in many hospitals and long-term care facilities; the causes are a variety of microorganisms but most commonly *C. difficile*. *C. difficile* can affect those with no history of antibiotic use and may be acquired in the community.

The pathophysiology underlying acute diarrhea by infectious agents produces specific clinical features that may also be helpful in diagnosis **(Table 42-2)**. Profuse, watery diarrhea secondary to small-bowel hypersecretion occurs with ingestion of preformed bacterial toxins, enterotoxin-producing bacteria, and enteroadherent pathogens. Diarrhea associated with marked vomiting and minimal or no fever may occur abruptly within a few hours after ingestion of the former two types; vomiting is usually less, abdominal cramping or bloating is greater, and fever is higher with the latter. Cytotoxin-producing and invasive microorganisms all cause high fever and abdominal pain. Invasive bacteria and *Entamoeba histolytica* often cause bloody diarrhea (referred to as *dysentery*). *Yersinia* invades the terminal ileal and proximal colon mucosa and may cause especially severe abdominal pain with tenderness mimicking acute appendicitis.

Finally, infectious diarrhea may be associated with systemic manifestations. Reactive arthritis (formerly known as Reiter's syndrome), arthritis, urethritis, and conjunctivitis may accompany or follow infections by *Salmonella*, *Campylobacter*, *Shigella*, and *Yersinia*. Yersiniosis may also lead to an autoimmune-type thyroiditis, pericarditis, and glomerulonephritis. Both enterohemorrhagic *E. coli* (O157:H7) and *Shigella* can lead to the *hemolytic-uremic syndrome* with an attendant high mortality rate. The syndrome of postinfectious IBS has now been recognized as a complication of infectious diarrhea. Similarly, acute gastroenteritis may precede the diagnosis of celiac disease or Crohn's disease. Acute diarrhea can also be a major symptom of several systemic infections including *viral hepatitis*, *listeriosis*, *legionellosis*, and *toxic shock syndrome*.

Other Causes Side effects from medications are probably the most common noninfectious causes of acute diarrhea, and etiology may be suggested by a temporal association between use and symptom onset. Although innumerable medications may produce diarrhea, some of the more frequently incriminated include antibiotics, cardiac antidysrhythmics, antihypertensives, nonsteroidal anti-inflammatory drugs (NSAIDs), certain antidepressants, chemotherapeutic agents, bronchodilators, antacids, and laxatives. Occlusive or nonocclusive ischemic colitis typically occurs in persons aged >50 years; often presents as acute lower abdominal pain preceding watery, then bloody diarrhea; and generally results in acute inflammatory changes in the sigmoid or left colon while sparing the rectum. Acute diarrhea may accompany colonic diverticulitis and graft-versus-host disease. Acute diarrhea, often associated with systemic compromise, can follow ingestion of toxins including organophosphate insecticides, amanita and other

TABLE 42-2 Association Between Pathobiology of Causative Agents and Clinical Features in Acute Infectious Diarrhea

PATHOBIOLOGY/AGENTS	INCUBATION PERIOD	VOMITING	ABDOMINAL PAIN	FEVER	DIARRHEA
Toxin producers					
Preformed toxin					
Bacillus cereus, *Staphylococcus aureus*, *Clostridium perfringens*	1–8 h 8–24 h	3–4+	1–2+	0–1+	3–4+, watery
Enterotoxin					
Vibrio cholerae, enterotoxigenic *Escherichia coli*, *Klebsiella pneumoniae*, *Aeromonas* species	8–72 h	2–4+	1–2+	0–1+	3–4+, watery
Enteroadherent					
Enteropathogenic and enteroadherent *E. coli*, *Giardia* organisms, cryptosporidiosis, helminths	1–8 d	0–1+	1–3+	0–2+	1–2+, watery, mushy
Cytotoxin producers					
Clostridium difficile	1–3 d	0–1+	3–4+	1–2+	1–3+, usually watery, occasionally bloody
Hemorrhagic *E. coli*	12–72 h	0–1+	3–4+	1–2+	1–3+, initially watery, quickly bloody
Invasive organisms					
Minimal inflammation					
Rotavirus and norovirus	1–3 d	1–3+	2–3+	3–4+	1–3+, watery
Variable inflammation					
Salmonella, *Campylobacter*, and *Aeromonas* species, *Vibrio parahaemolyticus*, *Yersinia*	12 h–11 d	0–3+	2–4+	3–4+	1–4+, watery or bloody
Severe inflammation					
Shigella species, enteroinvasive *E. coli*, *Entamoeba histolytica*	12 h–8 d	0–1+	3–4+	3–4+	1–2+, bloody

Source: Adapted from DW Powell, in T Yamada (ed): *Textbook of Gastroenterology and Hepatology*, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2003.

mushrooms, arsenic, and preformed toxins in seafood such as ciguatera (from algae that the fish eat) and scombroid (an excess of histamine due to inadequate refrigeration). Acute anaphylaxis to food ingestion can have a similar presentation. Conditions causing chronic diarrhea can also be confused with acute diarrhea early in their course. This confusion may occur with inflammatory bowel disease (IBD) and some of the other inflammatory chronic diarrheas that may have an abrupt rather than insidious onset and exhibit features that mimic infection.

APPROACH TO THE PATIENT

Acute Diarrhea

The decision to evaluate acute diarrhea depends on its severity and duration and on various host factors **(Fig. 42-2)**. Most episodes of acute diarrhea are mild and self-limited and do not justify the cost and potential morbidity rate of diagnostic or pharmacologic interventions. Indications for evaluation include profuse diarrhea with dehydration, grossly bloody stools, fever ≥38.5°C (≥101°F), duration >48 h without improvement, recent antibiotic use, new community outbreaks, associated severe abdominal pain in patients aged >50 years, and elderly (≥70 years) or immunocompromised patients. In some cases of moderately severe febrile diarrhea associated with fecal leukocytes (or increased fecal levels of the leukocyte proteins, such as calprotectin) or with gross blood, a diagnostic evaluation might be avoided in favor of an empirical antibiotic trial (see below).

The cornerstone of diagnosis in those suspected of severe acute infectious diarrhea is microbiologic analysis of the stool. Workup includes cultures for bacterial and viral pathogens; direct inspection for ova and parasites; and immunoassays for certain bacterial toxins (*C. difficile*), viral antigens (rotavirus), and protozoal antigens (*Giardia*, *E. histolytica*). The aforementioned clinical and epidemiologic associations may assist in focusing the evaluation. If a particular pathogen or set of possible pathogens is so implicated, either the whole panel of routine studies may not be necessary or, in some instances, special cultures may be appropriate as for enterohemorrhagic and other types of *E. coli*, *Vibrio* species, and *Yersinia*. Molecular diagnosis of

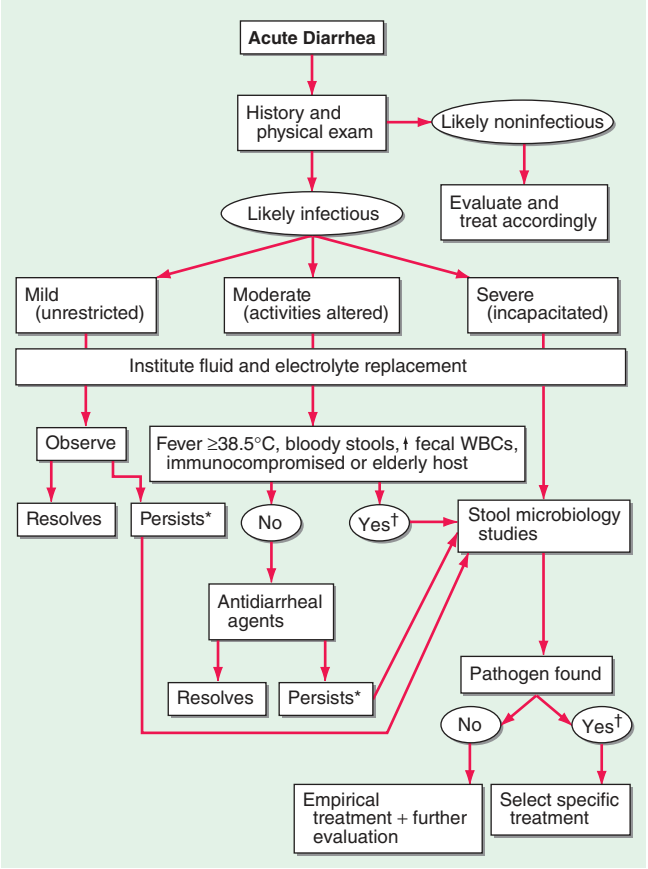

FIGURE 42-2 Algorithm for the management of acute diarrhea. Consider empirical treatment before evaluation with (*) metronidazole and with (†) quinolone. WBCs, white blood cells.

pathogens in stool can be made by identification of unique DNA sequences, and evolving microarray technologies have led to more rapid, sensitive, specific, and cost-effective diagnosis.

Persistent diarrhea is commonly due to *Giardia* **(Chap. 218)**, but additional causative organisms that should be considered include *C. difficile* (especially if antibiotics had been administered), *E. histolytica*, *Cryptosporidium*, *Campylobacter*, and others. If stool studies are unrevealing, flexible sigmoidoscopy with biopsies and upper endoscopy with duodenal aspirates and biopsies may be indicated. Brainerd diarrhea is an increasingly recognized entity characterized by an abrupt-onset diarrhea that persists for at least 4 weeks, but may last 1–3 years, and is thought to be of infectious origin. It may be associated with subtle inflammation of the distal small intestine or proximal colon.

Structural examination by sigmoidoscopy, colonoscopy, or abdominal computed tomography (CT) scanning (or other imaging approaches) may be appropriate in patients with uncharacterized persistent diarrhea to exclude IBD or as an initial approach in patients with suspected noninfectious acute diarrhea such as might be caused by ischemic colitis, diverticulitis, or partial bowel obstruction.

TREATMENT

Acute Diarrhea

Fluid and electrolyte replacement are of central importance to all forms of acute diarrhea. Fluid replacement alone may suffice for mild cases. Oral sugar-electrolyte solutions (iso-osmolar sport drinks or designed formulations) should be instituted promptly with severe diarrhea to limit dehydration, which is the major cause of death. Profoundly dehydrated patients, especially infants and the elderly, require IV rehydration.

In moderately severe nonfebrile and nonbloody diarrhea, antimotility and antisecretory agents such as loperamide can be useful adjuncts to control symptoms. Such agents should be avoided with febrile dysentery, which may be exacerbated or prolonged by them. Bismuth subsalicylate may reduce symptoms of vomiting and diarrhea but should not be used to treat immunocompromised patients or those with renal impairment because of the risk of bismuth encephalopathy.

Judicious use of antibiotics is appropriate in selected instances of acute diarrhea and may reduce its severity and duration (Fig. 42-2). Many physicians treat moderately to severely ill patients with febrile dysentery empirically without diagnostic evaluation using a quinolone, such as ciprofloxacin (500 mg bid for 3–5 d). Empirical treatment can also be considered for suspected giardiasis with metronidazole (250 mg qid for 7 d). Selection of antibiotics and dosage regimens are otherwise dictated by specific pathogens, geographic patterns of resistance, and conditions found **(Chaps. 128, 156, and 160–166)**. Because of resistance to first-line treatments, newer agents such as nitazoxanide may be required for *Giardia* and *Cryptosporidium* infections. Antibiotic coverage is indicated, whether or not a causative organism is discovered, in patients who are immunocompromised, have mechanical heart valves or recent vascular grafts, or are elderly. Bismuth subsalicylate may reduce the frequency of traveler's diarrhea. Antibiotic prophylaxis is only indicated for certain patients traveling to high-risk countries in whom the likelihood or seriousness of acquired diarrhea would be especially high, including those with immunocompromise, IBD, hemochromatosis, or gastric achlorhydria. Use of ciprofloxacin, azithromycin, or rifaximin may reduce bacterial diarrhea in such travelers by 90%, though rifaximin is not suitable for invasive disease but rather as treatment for uncomplicated traveler's diarrhea. There is little role for endoscopic evaluation in most circumstances except in immunocompromised patients. Finally, physicians should be vigilant to identify if an outbreak of diarrheal illness is occurring and to alert the public health authorities promptly. This may reduce the ultimate size of the affected population.

CHRONIC DIARRHEA

Diarrhea lasting >4 weeks warrants evaluation to exclude serious underlying pathology. In contrast to acute diarrhea, most of the causes of chronic diarrhea are noninfectious. The classification of chronic diarrhea by pathophysiologic mechanism facilitates a rational approach to management, although many diseases cause diarrhea by more than one mechanism **(Table 42-3)**.

Secretory Causes Secretory diarrheas are due to derangements in fluid and electrolyte transport across the enterocolonic mucosa. They are characterized clinically by watery, large-volume fecal outputs that are typically painless and persist with fasting. Because there is

TABLE 42-3 Major Causes of Chronic Diarrhea According to Predominant Pathophysiologic Mechanism

Secretory Causes
Exogenous stimulant laxatives
Chronic ethanol ingestion
Other drugs and toxins
Endogenous laxatives (dihydroxy bile acids)
Idiopathic secretory diarrhea or bile acid diarrhea
Certain bacterial infections
Bowel resection, disease, or fistula (↓ absorption)
Partial bowel obstruction or fecal impaction
Hormone-producing tumors (carcinoid, VIPoma, medullary cancer of thyroid, mastocytosis, gastrinoma, colorectal villous adenoma)
Addison's disease
Congenital electrolyte absorption defects
Osmotic Causes
Osmotic laxatives (Mg^{2+}, PO_4^{-3}, SO_4^{-2})
Lactase and other disaccharide deficiencies
Nonabsorbable carbohydrates (sorbitol, lactulose, polyethylene glycol)
Gluten and FODMAP intolerance
Steatorrheal Causes
Intraluminal maldigestion (pancreatic exocrine insufficiency, bacterial overgrowth, bariatric surgery, liver disease)
Mucosal malabsorption (celiac sprue, Whipple's disease, infections, abetalipoproteinemia, ischemia, drug-induced enteropathy)
Postmucosal obstruction (1° or 2° lymphatic obstruction)
Inflammatory Causes
Idiopathic inflammatory bowel disease (Crohn's, chronic ulcerative colitis)
Lymphocytic and collagenous colitis
Immune-related mucosal disease (1° or 2° immunodeficiencies, food allergy, eosinophilic gastroenteritis, graft-versus-host disease)
Infections (invasive bacteria, viruses, and parasites, Brainerd diarrhea)
Radiation injury
Gastrointestinal malignancies
Dysmotile Causes
Irritable bowel syndrome (including postinfectious IBS)
Visceral neuromyopathies
Hyperthyroidism
Drugs (prokinetic agents)
Postvagotomy
Factitial Causes
Munchausen
Eating disorders
Iatrogenic Causes
Cholecystectomy
Ileal resection
Bariatric surgery
Vagotomy, fundoplication

Abbreviation: FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

no malabsorbed solute, stool osmolality is accounted for by normal endogenous electrolytes with no fecal osmotic gap.

MEDICATIONS Side effects from regular ingestion of drugs and toxins are the most common secretory causes of chronic diarrhea. Hundreds of prescription and over-the-counter medications (see earlier section, "Acute Diarrhea, Other Causes") may produce diarrhea. Surreptitious or habitual use of stimulant laxatives (e.g., senna, cascara, bisacodyl, ricinoleic acid [castor oil]) must also be considered. Chronic ethanol consumption may cause a secretory-type diarrhea due to enterocyte injury with impaired sodium and water absorption as well as rapid transit and other alterations. Inadvertent ingestion of certain environmental toxins (e.g., arsenic) may lead to chronic rather than acute forms of diarrhea. Certain bacterial infections may occasionally persist and be associated with a secretory-type diarrhea. The oral angiotensin-receptor blocker, olmesartan, is associated with diarrhea due to sprue-like enteropathy.

BOWEL RESECTION, MUCOSAL DISEASE, OR ENTEROCOLIC FISTULA These conditions may result in a secretory-type diarrhea because of inadequate surface for reabsorption of secreted fluids and electrolytes. Unlike other secretory diarrheas, this subset of conditions tends to worsen with eating. With disease (e.g., Crohn's ileitis) or resection of <100 cm of terminal ileum, dihydroxy bile acids may escape absorption and stimulate colonic secretion (cholerheic diarrhea). This mechanism may contribute to so-called *idiopathic secretory diarrhea or bile acid diarrhea (BAD)*, in which bile acids are functionally malabsorbed from a normal-appearing terminal ileum. This *idiopathic bile acid malabsorption (BAM)* may account for an average of 40% of unexplained chronic diarrhea. Reduced negative feedback regulation of bile acid synthesis in hepatocytes by fibroblast growth factor 19 (FGF-19) produced by ileal enterocytes results in a degree of bile-acid synthesis that exceeds the normal capacity for ileal reabsorption, producing BAD. An alternative cause of BAD is a genetic variation in the receptor proteins (β-klotho and fibroblast growth factor 4) on the hepatocyte that normally mediate the effect of FGF-19. Dysfunction of these proteins prevents FGF-19 inhibition of hepatocyte bile acid synthesis. Another mechanism is based on genetic variation in the bile acid receptor (TGR5) in the colon, resulting in accelerated colonic transit.

Partial bowel obstruction, ostomy stricture, or fecal impaction may paradoxically lead to increased fecal output due to fluid hypersecretion.

HORMONES Although uncommon, the classic examples of secretory diarrhea are those mediated by hormones. *Metastatic gastrointestinal carcinoid tumors* or, rarely, *primary bronchial carcinoids* may produce watery diarrhea alone or as part of the carcinoid syndrome that comprises episodic flushing, wheezing, dyspnea, and right-sided valvular heart disease. Diarrhea is due to the release into the circulation of potent intestinal secretagogues including serotonin, histamine, prostaglandins, and various kinins. Pellagra-like skin lesions may rarely occur as the result of serotonin overproduction with niacin depletion. *Gastrinoma*, one of the most common neuroendocrine tumors, most typically presents with refractory peptic ulcers, but diarrhea occurs in up to one-third of cases and may be the only clinical manifestation in 10%. While other secretagogues released with gastrin may play a role, the diarrhea most often results from fat maldigestion owing to pancreatic enzyme inactivation by low intraduodenal pH. The watery diarrhea hypokalemia achlorhydria syndrome, also called *pancreatic cholera*, is due to a non-β cell pancreatic adenoma, referred to as a *VIPoma*, that secretes VIP and a host of other peptide hormones including pancreatic polypeptide, secretin, gastrin, gastrin-inhibitory polypeptide (also called glucose-dependent insulinotropic peptide), neurotensin, calcitonin, and prostaglandins. The secretory diarrhea is often massive with stool volumes >3 L/d; daily volumes as high as 20 L have been reported. Life-threatening dehydration; neuromuscular dysfunction from associated hypokalemia, hypomagnesemia, or hypercalcemia; flushing; and hyperglycemia may accompany a VIPoma. *Medullary carcinoma of the thyroid* may present with watery diarrhea caused by calcitonin, other secretory peptides, or prostaglandins. Prominent diarrhea is often associated with metastatic disease and poor prognosis. *Systemic mastocytosis*, which may be associated with the skin lesion urticaria pigmentosa, may cause diarrhea that is either secretory and mediated by histamine or inflammatory due to intestinal infiltration by mast cells. Large *colorectal villous adenomas* may rarely be associated with a secretory diarrhea that may cause hypokalemia, can be inhibited by NSAIDs, and are apparently mediated by prostaglandins.

CONGENITAL DEFECTS IN ION ABSORPTION Rarely, defects in specific carriers associated with ion absorption cause watery diarrhea from birth. These disorders include defective Cl^-/HCO_3^- exchange (*congenital chloridorrhea*) with alkalosis (which results from a mutated *DRA* [down-regulated in adenoma] gene) and defective Na^+/H^+ exchange (*congenital sodium diarrhea*), which results from a mutation in the *NHE3* (sodium-hydrogen exchanger) gene and results in acidosis.

Some hormone deficiencies may be associated with watery diarrhea, such as occurs with adrenocortical insufficiency (Addison's disease) that may be accompanied by skin hyperpigmentation.

Osmotic Causes

Osmotic diarrhea occurs when ingested, poorly absorbable, osmotically active solutes draw enough fluid into the lumen to exceed the reabsorptive capacity of the colon. Fecal water output increases in proportion to such a solute load. Osmotic diarrhea characteristically ceases with fasting or with discontinuation of the causative agent.

OSMOTIC LAXATIVES Ingestion of magnesium-containing antacids, health supplements, or laxatives may induce osmotic diarrhea typified by a stool osmotic gap (>50 mosmol/L): serum osmolarity (typically 290 mosmol/kg) − (2 × [fecal sodium + potassium concentration]). Measurement of fecal osmolarity is no longer recommended because, even when measured immediately after evacuation, it may be erroneous because carbohydrates are metabolized by colonic bacteria, causing an increase in osmolarity.

CARBOHYDRATE MALABSORPTION Carbohydrate malabsorption due to acquired or congenital defects in brush-border disaccharidases and other enzymes leads to osmotic diarrhea with a low pH. One of the most common causes of chronic diarrhea in adults is *lactase deficiency*, which affects three-fourths of nonwhites worldwide and 5–30% of persons in the United States; the total lactose load at any one time influences the symptoms experienced. Most patients learn to avoid milk products without requiring treatment with enzyme supplements. Some sugars, such as sorbitol, lactulose, or fructose, are frequently malabsorbed, and diarrhea ensues with ingestion of medications, gum, or candies sweetened with these poorly or incompletely absorbed sugars.

WHEAT AND FODMAP INTOLERANCE Chronic diarrhea, bloating, and abdominal pain are recognized as symptoms of non-celiac gluten intolerance (which is associated with impaired intestinal or colonic barrier function) and intolerance of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). The latter's effects represent the interaction between the GI microbiome and the nutrients.

Steatorrheal Causes

Fat malabsorption may lead to greasy, foul-smelling, difficult-to-flush diarrhea often associated with weight loss and nutritional deficiencies due to concomitant malabsorption of amino acids and vitamins. Increased fecal output is caused by the osmotic effects of fatty acids, especially after bacterial hydroxylation, and, to a lesser extent, by the neutral fat. Quantitatively, steatorrhea is defined as stool fat exceeding the normal 7 g/d; rapid-transit diarrhea may result in fecal fat up to 14 g/d; daily fecal fat averages 15–25 g with small-intestinal diseases and is often >32 g with pancreatic exocrine insufficiency. Intraluminal maldigestion, mucosal malabsorption, or lymphatic obstruction may produce steatorrhea.

INTRALUMINAL MALDIGESTION This condition most commonly results from pancreatic exocrine insufficiency, which occurs when >90% of pancreatic secretory function is lost. *Chronic pancreatitis*, usually a sequel of ethanol abuse, most frequently causes pancreatic insufficiency. Other causes include *cystic fibrosis*, *pancreatic duct obstruction*, and, rarely, *somatostatinoma*. Bacterial overgrowth in the small intestine may deconjugate bile acids and alter micelle formation, impairing fat digestion; it occurs with stasis from a blind-loop, small-bowel diverticulum or dysmotility and is especially likely in the elderly. Finally,

cirrhosis or biliary obstruction may lead to mild steatorrhea due to deficient intraluminal bile acid concentration.

MUCOSAL MALABSORPTION Mucosal malabsorption occurs from a variety of enteropathies, but it most commonly occurs from *celiac disease*. This gluten-sensitive enteropathy affects all ages and is characterized by villous atrophy and crypt hyperplasia in the proximal small bowel and can present with fatty diarrhea associated with multiple nutritional deficiencies of varying severity. Celiac disease is much more frequent than previously thought; it affects ~1% of the population, frequently presents without steatorrhea, can mimic IBS, and has many other GI and extraintestinal manifestations. *Tropical sprue* may produce a similar histologic and clinical syndrome but occurs in residents of or travelers to tropical climates; abrupt onset and response to antibiotics suggest an infectious etiology. *Whipple's disease*, due to the bacillus *Tropheryma whipplei* and histiocytic infiltration of the small-bowel mucosa, is a less common cause of steatorrhea that most typically occurs in young or middle-aged men; it is frequently associated with arthralgias, fever, lymphadenopathy, and extreme fatigue, and it may affect the CNS and endocardium. A similar clinical and histologic picture results from *Mycobacterium avium-intracellulare* infection in patients with AIDS. *Abetalipoproteinemia* is a rare defect of chylomicron formation and fat malabsorption in children, associated with acanthocytic erythrocytes, ataxia, and retinitis pigmentosa. Several other conditions may cause mucosal malabsorption including infections, especially with protozoa such as *Giardia*, numerous medications (e.g., olmesartan, mycophenolate mofetil, colchicine, cholestyramine, neomycin), amyloidosis, and chronic ischemia.

POSTMUCOSAL LYMPHATIC OBSTRUCTION The pathophysiology of this condition, which is due to the rare *congenital intestinal lymphangiectasia* or to *acquired lymphatic obstruction* secondary to trauma, tumor, cardiac disease or infection, leads to the unique constellation of fat malabsorption with enteric losses of protein (often causing edema) and lymphocytopenia. Carbohydrate and amino acid absorption are preserved.

Inflammatory Causes Inflammatory diarrheas are generally accompanied by pain, fever, bleeding, or other manifestations of inflammation. The mechanism of diarrhea may not only be exudation but, depending on lesion site, may include fat malabsorption, disrupted fluid/electrolyte absorption, and hypersecretion or hypermotility from release of cytokines and other inflammatory mediators. The unifying feature on stool analysis is the presence of leukocytes or leukocyte-derived proteins such as calprotectin. With severe inflammation, exudative protein loss can lead to anasarca (generalized edema). Any middle-aged or older person with chronic inflammatory-type diarrhea, especially with blood, should be carefully evaluated to exclude a colorectal tumor.

IDIOPATHIC INFLAMMATORY BOWEL DISEASE The illnesses in this category, which include *Crohn's disease* and *chronic ulcerative colitis*, are among the most common organic causes of chronic diarrhea in adults and range in severity from mild to fulminant and life-threatening. They may be associated with uveitis, polyarthralgias, cholestatic liver disease (primary sclerosing cholangitis), and skin lesions (erythema nodosum, pyoderma gangrenosum). *Microscopic colitis*, including both lymphocytic and *collagenous colitis*, is an increasingly recognized cause of chronic watery diarrhea, especially in middle-aged women and those on NSAIDs, statins, proton pump inhibitors (PPIs), and selective serotonin reuptake inhibitors (SSRIs); biopsy of a normal-appearing colon is required for histologic diagnosis. It may coexist with symptoms suggesting IBS or with celiac sprue or drug-induced enteropathy. It typically responds well to anti-inflammatory drugs (e.g., bismuth), the opioid agonist loperamide, or to budesonide.

PRIMARY OR SECONDARY FORMS OF IMMUNODEFICIENCY Immunodeficiency may lead to prolonged infectious diarrhea. With selective IgA deficiency or common variable *hypogammaglobulinemia*, diarrhea is particularly prevalent and often the result of giardiasis, bacterial overgrowth, or sprue.

EOSINOPHILIC GASTROENTERITIS Eosinophil infiltration of the mucosa, muscularis, or serosa at any level of the GI tract may cause diarrhea, pain, vomiting, or ascites. Affected patients often have an atopic history, Charcot-Leyden crystals due to extruded eosinophil contents may be seen on microscopic inspection of stool, and peripheral eosinophilia is present in 50–75% of patients. While hypersensitivity to certain foods occurs in adults, true food allergy causing chronic diarrhea is rare.

OTHER CAUSES Chronic inflammatory diarrhea may be caused by *radiation enterocolitis*, *chronic graft-versus-host disease*, *Behçet's syndrome*, and *Cronkhite-Canada syndrome*, among others.

Dysmotility Causes Rapid transit may accompany many diarrheas as a secondary or contributing phenomenon, but primary dysmotility is an unusual etiology of true diarrhea. Stool features often suggest a secretory diarrhea, but mild steatorrhea of up to 14 g of fat per day can be produced by maldigestion from rapid transit alone. *Hyperthyroidism*, *carcinoid syndrome*, and certain drugs (e.g., prostaglandins, prokinetic agents) may produce hypermotility with resultant diarrhea. Primary visceral neuromyopathies or idiopathic acquired intestinal pseudoobstruction may lead to stasis with secondary bacterial overgrowth causing diarrhea. *Diabetic diarrhea*, often accompanied by peripheral and generalized autonomic neuropathies, may occur in part because of intestinal dysmotility.

The exceedingly common IBS (10% point prevalence, 1–2% per year incidence) is characterized by disturbed intestinal and colonic motor and sensory responses to various stimuli. Symptoms of stool frequency typically cease at night, alternate with periods of constipation, are accompanied by abdominal pain relieved with defecation, and rarely result in weight loss.

Factitial Causes Factitial diarrhea accounts for up to 15% of unexplained diarrheas referred to tertiary care centers. Either as a form of *Munchausen syndrome* (deception or self-injury for secondary gain) or *eating disorders*, some patients covertly self-administer laxatives alone or in combination with other medications (e.g., diuretics) or surreptitiously add water or urine to stool sent for analysis. Such patients are typically women, often with histories of psychiatric illness, and disproportionately from careers in health care. Hypotension and hypokalemia are common co-presenting features. The evaluation of such patients may be difficult: contamination of the stool with water or urine is suggested by very low or high stool osmolarity, respectively. Such patients often deny this possibility when confronted, but they do benefit from psychiatric counseling when they acknowledge their behavior.

APPROACH TO THE PATIENT

Chronic Diarrhea

The laboratory tools available to evaluate the very common problem of chronic diarrhea are extensive, and many are costly and invasive. As such, the diagnostic evaluation must be rationally directed by a careful history, including medications, and physical examination **(Fig. 42-3)**. When this strategy is unrevealing, simple triage tests are often warranted to direct the choice of more complex investigations (Fig. 42-3). The history, physical examination **(Table 42-4)**, and routine blood studies should attempt to characterize the mechanism of diarrhea, identify diagnostically helpful associations, and assess the patient's fluid/electrolyte and nutritional status. Patients should be questioned about the onset, duration, pattern, aggravating (especially diet) and relieving factors, and stool characteristics of their diarrhea. The presence or absence of fecal incontinence, fever, weight loss, pain, certain exposures (travel, medications, contacts with diarrhea), and common extraintestinal manifestations (skin changes, arthralgias, oral aphthous ulcers) should be noted. A family history of inflammatory bowel disease (IBD) or sprue may indicate those possibilities. Physical findings may offer clues such as a thyroid mass, wheezing, heart murmurs, edema, hepatomegaly, abdominal masses, lymphadenopathy, mucocutaneous abnormalities, perianal fistulas, or anal sphincter laxity. Peripheral blood leukocytosis, elevated sedimentation rate, or C-reactive protein suggests inflammation; anemia reflects blood loss or nutritional deficiencies; or eosinophilia may

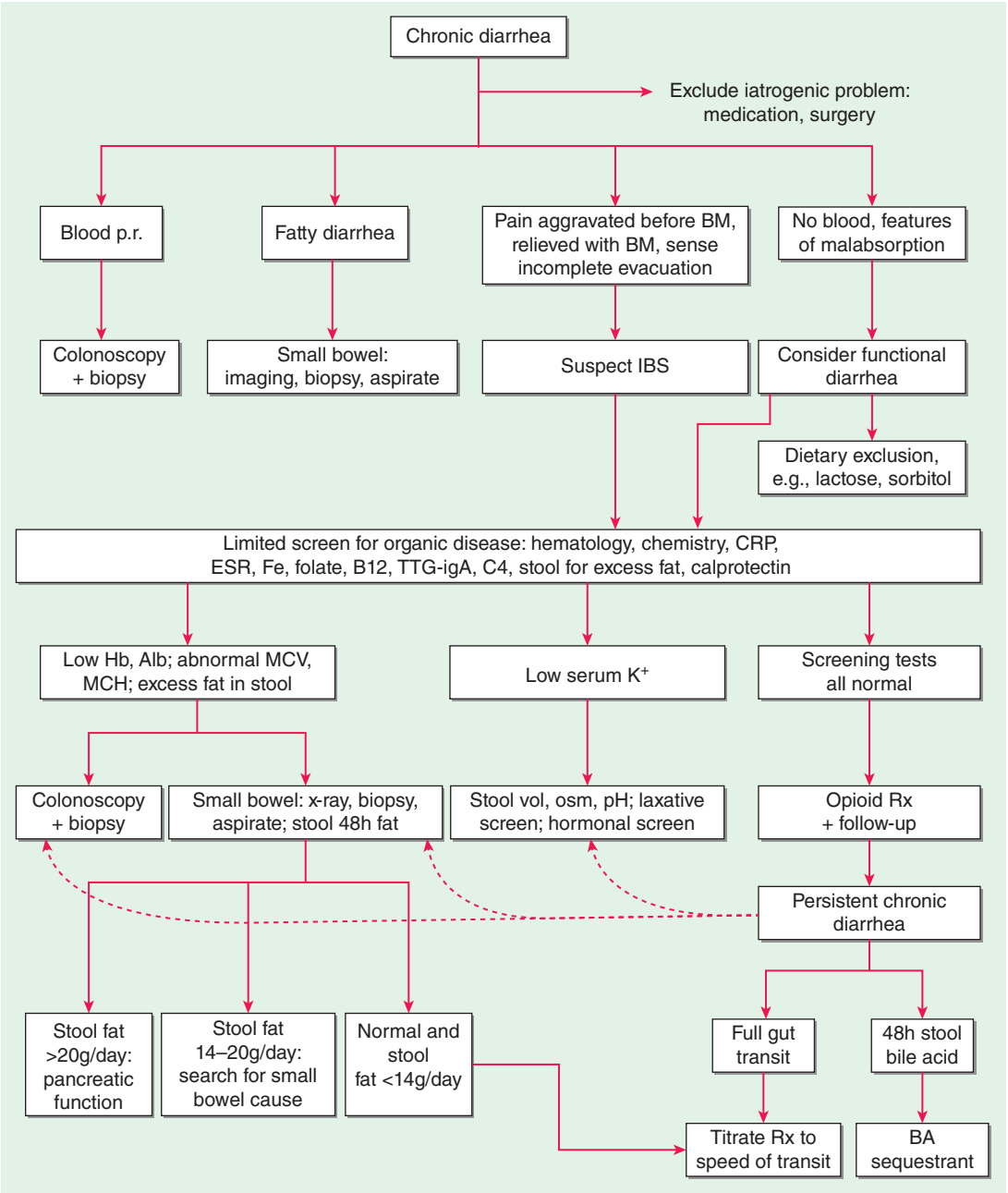

FIGURE 42-3 Algorithm for management of chronic diarrhea. Patients undergo an initial evaluation based on different symptom presentations, leading to selection of patients for imaging, biopsy analysis, and limited screens for organic diseases. Alb, albumin; BA, bile acid; BM, bowel movement; C4, 7 α-hydroxy-4-cholesten-3-one; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hx, history; IBS, irritable bowel syndrome; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; osm, osmolality; p.r., per rectum; Rx, treatment. *(Reprinted from M Camilleri, JH Sellin, KE Barrett: Pathophysiology, evaluation, and management of chronic watery diarrhea. Gastroenterology 152:515, 2017.)*

TABLE 42-4 Physical Examination in Patients with Chronic Diarrhea

1. Are there general features to suggest malabsorption or inflammatory bowel disease (IBD) such as anemia, dermatitis herpetiformis, edema, or clubbing?
2. Are there features to suggest underlying autonomic neuropathy or collagen-vascular disease in the pupils, orthostasis, skin, hands, or joints?
3. Is there an abdominal mass or tenderness?
4. Are there any abnormalities of rectal mucosa, rectal defects, or altered anal sphincter functions?
5. Are there any mucocutaneous manifestations of systemic disease such as dermatitis herpetiformis (celiac disease), erythema nodosum (ulcerative colitis), flushing (carcinoid), or oral ulcers for IBD or celiac disease?

occur with parasitoses, neoplasia, collagen-vascular disease, allergy, or eosinophilic gastroenteritis. Blood chemistries may demonstrate electrolyte, hepatic, or other metabolic disturbances. Measuring IgA tissue transglutaminase antibodies may help detect celiac disease. Bile acid diarrhea is confirmed by a scintigraphic radiolabeled bile acid retention test; however, this is not available in many countries. Alternative approaches are a screening blood test (serum C4 or FGF-19), measurement of fecal bile acids, or a therapeutic trial with a bile acid sequestrant (e.g., cholestyramine or colesevelam).

A therapeutic trial is often appropriate, definitive, and highly cost-effective when a specific diagnosis is suggested on the initial physician encounter. For example, chronic watery diarrhea, which ceases with fasting in an otherwise healthy young adult, may justify

a trial of a lactose-restricted diet; bloating and diarrhea persisting since a mountain backpacking trip may warrant a trial of metronidazole for likely giardiasis; and postprandial diarrhea persisting following resection of terminal ileum might be due to bile acid malabsorption and be treated with cholestyramine or colesevelam before further evaluation. Persistent symptoms require additional investigation.

Certain diagnoses may be suggested on the initial encounter (e.g., idiopathic IBD); however, additional focused evaluations may be necessary to confirm the diagnosis and characterize the severity or extent of disease so that treatment can be best guided. Patients suspected of having IBS should be initially evaluated with flexible sigmoidoscopy with colorectal biopsies to exclude IBD, or particularly microscopic colitis, which is clinically indistinguishable from IBS with diarrhea or functional diarrhea; those with normal findings might be reassured and, as indicated, treated empirically with antispasmodics, antidiarrheals, or antidepressants (e.g., tricyclic agents). Any patient who presents with chronic diarrhea and hematochezia should be evaluated with stool microbiologic studies and colonoscopy.

In an estimated two-thirds of cases, the cause for chronic diarrhea remains unclear after the initial encounter, and further testing is required. Quantitative stool collection and analyses can yield important objective data that may establish a diagnosis or characterize the type of diarrhea as a triage for focused additional studies (Fig. 42-3). If stool weight is >200 g/d, additional stool analyses should be performed that might include electrolyte concentration, pH, occult blood testing, leukocyte inspection (or leukocyte protein assay), fat quantitation, and laxative screens.

For secretory diarrheas (watery, normal osmotic gap), possible medication-related side effects or surreptitious laxative use should be reconsidered. Microbiologic studies should be done including fecal bacterial cultures (including media for *Aeromonas* and *Plesiomonas*), inspection for ova and parasites, and *Giardia* antigen assay (the most sensitive test for giardiasis). Small-bowel bacterial overgrowth can be excluded by intestinal aspirates with quantitative cultures or with glucose or lactulose breath tests involving measurement of breath hydrogen, methane, or other metabolite. However, interpretation of these breath tests may be confounded by disturbances of intestinal transit. Upper endoscopy and colonoscopy with biopsies and small-bowel x-rays (formerly barium, but increasingly CT with enterography or magnetic resonance with enteroclysis) are helpful to rule out structural or occult inflammatory disease. When suggested by history or other findings, screens for peptide hormones should be pursued (e.g., serum gastrin, VIP, calcitonin, and thyroid hormone/thyroid-stimulating hormone, urinary 5-hydroxyindolacetic acid, histamine).

Further evaluation of osmotic diarrhea should include tests for lactose intolerance and magnesium ingestion, the two most common causes. Low fecal pH suggests carbohydrate malabsorption; lactose malabsorption can be confirmed by lactose breath testing or by a therapeutic trial with lactose exclusion and observation of the effect of lactose challenge (e.g., a liter of milk). Lactase determination on small-bowel biopsy is not generally available. If fecal magnesium or laxative levels are elevated, inadvertent or surreptitious ingestion should be considered and psychiatric help should be sought.

For those with proven fatty diarrhea, endoscopy with small-bowel biopsy (including aspiration for *Giardia* and quantitative cultures) should be performed; if this procedure is unrevealing, a small-bowel radiograph is often an appropriate next step. If small-bowel studies are negative or if pancreatic disease is suspected, pancreatic exocrine insufficiency should be excluded with direct tests, such as the secretin-cholecystokinin stimulation test or a variation that could be performed endoscopically. In general, indirect tests such as assay of fecal elastase or chymotrypsin activity or a bentiromide test have fallen out of favor because of low sensitivity and specificity.

Chronic inflammatory-type diarrheas should be suspected by the presence of blood or leukocytes in the stool. Such findings warrant stool cultures; inspection for ova and parasites; *C. difficile* toxin assay; colonoscopy with biopsies; and, if indicated, small-bowel contrast studies.

TREATMENT

Chronic Diarrhea

Treatment of chronic diarrhea depends on the specific etiology and may be curative, suppressive, or empirical. If the cause can be eradicated, treatment is curative as with resection of a colorectal cancer, antibiotic administration for Whipple's disease or tropical sprue, or discontinuation of a drug. For many chronic conditions, diarrhea can be controlled by suppression of the underlying mechanism. Examples include elimination of dietary lactose for lactase deficiency or gluten for celiac sprue, use of glucocorticoids or other anti-inflammatory agents for idiopathic IBDs, bile acid sequestrants for bile acid malabsorption, PPIs for the gastric hypersecretion of gastrinomas, somatostatin analogues such as octreotide for malignant carcinoid syndrome, prostaglandin inhibitors such as indomethacin for medullary carcinoma of the thyroid, and pancreatic enzyme replacement for pancreatic insufficiency. When the specific cause or mechanism of chronic diarrhea evades diagnosis, empirical therapy may be beneficial. Mild opiates, such as diphenoxylate or loperamide, are often helpful in mild or moderate watery diarrhea. For those with more severe diarrhea, codeine or tincture of opium may be beneficial. Such antimotility agents should be avoided with severe IBD, because toxic megacolon may be precipitated. Clonidine, an α_2-adrenergic agonist, may allow control of diabetic diarrhea, although the medication may be poorly tolerated because it causes postural hypotension. The 5-HT_3 receptor antagonists (e.g., alosetron, ondansetron) may relieve diarrhea and urgency in patients with IBS diarrhea. Other medications approved for the treatment of diarrhea associated with IBS are the nonabsorbed antibiotic, rifaximin, and the mixed μ-opioid receptor (OR) and κ-OR agonist and δ-OR antagonist, eluxadoline. The latter may induce sphincter of Oddi spasm and subsequent acute pancreatitis, usually in patients with prior cholecystectomy. For all patients with chronic diarrhea, fluid and electrolyte repletion is an important component of management (see "Acute Diarrhea," earlier). Replacement of fat-soluble vitamins may also be necessary in patients with chronic steatorrhea.

CONSTIPATION

DEFINITION

Constipation is a common complaint in clinical practice and usually refers to persistent, difficult, infrequent, or seemingly incomplete defecation. Because of the wide range of normal bowel habits, constipation is difficult to define precisely. Most persons have at least three bowel movements per week; however, low stool frequency alone is not the sole criterion for the diagnosis of constipation. Many constipated patients have a normal frequency of defecation but complain of excessive straining, hard stools, lower abdominal fullness, or a sense of incomplete evacuation. The individual patient's symptoms must be analyzed in detail to ascertain what is meant by "constipation" or "difficulty" with defecation.

Stool form and consistency are well correlated with the time elapsed from the preceding defecation. Hard, pellety stools occur with slow transit, whereas loose, watery stools are associated with rapid transit. Both small pellety or very large stools are more difficult to expel than normal stools.

The perception of hard stools or excessive straining is more difficult to assess objectively, and the need for enemas or digital disimpaction is a clinically useful way to corroborate the patient's perceptions of difficult defecation.

Psychosocial or cultural factors may also be important. A person whose parents attached great importance to daily defecation will

TABLE 42-5 Causes of Constipation in Adults

TYPES OF CONSTIPATION AND CAUSES	EXAMPLES
Recent Onset	
Colonic obstruction	Neoplasm; stricture: ischemic, diverticular, inflammatory
Anal sphincter spasm	Anal fissure, painful hemorrhoids
Medications	
Chronic	
Irritable bowel syndrome	Constipation-predominant, alternating
Medications	Ca^{2+} blockers, antidepressants
Colonic pseudoobstruction	Slow-transit constipation, megacolon (rare Hirschsprung's, Chagas' diseases)
Disorders of rectal evacuation	Pelvic floor dysfunction; anismus; descending perineum syndrome; rectal mucosal prolapse; rectocele
Endocrinopathies	Hypothyroidism, hypercalcemia, pregnancy
Psychiatric disorders	Depression, eating disorders, drugs
Neurologic disease	Parkinsonism, multiple sclerosis, spinal cord injury
Generalized muscle disease	Progressive systemic sclerosis

become greatly concerned when he or she misses a daily bowel movement; some children withhold stool to gain attention or because of fear of pain from anal irritation; and some adults habitually ignore or delay the call to have a bowel movement.

CAUSES

Pathophysiologically, chronic constipation generally results from inadequate fiber or fluid intake or from disordered colonic transit or anorectal function. These result from neurogastroenterologic disturbance, certain drugs, advancing age, or in association with a large number of systemic diseases that affect the GI tract **(Table 42-5)**. Constipation of recent onset may be a symptom of significant organic disease such as tumor, anorectal irritation, or stricture. In *idiopathic constipation*, a subset of patients exhibits delayed emptying of the ascending and transverse colon with prolongation of transit (often in the proximal colon) and a reduced frequency of propulsive HAPCs. *Outlet obstruction to defecation* (also called *evacuation disorders*) accounts for about a quarter of cases presenting with constipation in tertiary care and may cause delayed colonic transit, which is usually corrected by biofeedback retraining of the disordered defecation. Constipation of any cause may be exacerbated by hospitalization or chronic illnesses that lead to physical or mental impairment and result in inactivity or physical immobility.

APPROACH TO THE PATIENT

Constipation

A careful history should explore the patient's symptoms and confirm whether he or she is indeed constipated based on frequency (e.g., fewer than three bowel movements per week), consistency (lumpy/hard), excessive straining, prolonged defecation time, or need to support the perineum or digitate the anorectum to facilitate stool evacuation. In the vast majority of cases (probably >90%), there is no underlying cause (e.g., cancer, depression, or hypothyroidism), and constipation responds to ample hydration, exercise, and supplementation of dietary fiber (15–25 g/d). A good diet and medication history and attention to psychosocial issues are key. Physical examination and, particularly, a rectal examination should exclude fecal impaction and most of the important diseases that present with constipation and possibly indicate features suggesting an evacuation disorder (e.g., high anal sphincter tone, failure of perineal descent, or paradoxical puborectalis contraction during straining to simulate stool evacuation).

The presence of weight loss, rectal bleeding, or anemia with constipation mandates either flexible sigmoidoscopy plus barium enema or colonoscopy alone, particularly in patients aged >40 years, to exclude structural diseases such as cancer or strictures. Colonoscopy alone is most cost-effective in this setting because it provides an opportunity to biopsy mucosal lesions, perform polypectomy, or dilate strictures. Barium enema has advantages over colonoscopy in the patient with isolated constipation because it is less costly and identifies colonic dilation and all significant mucosal lesions or strictures that are likely to present with constipation. Melanosis coli, or pigmentation of the colon mucosa, indicates the use of anthraquinone laxatives such as cascara or senna; however, this is usually apparent from a careful history. An unexpected disorder such as megacolon or cathartic colon may also be detected by colonic radiographs. Measurement of serum calcium, potassium, and thyroid-stimulating hormone levels will identify rare patients with metabolic disorders.

Patients with more troublesome constipation may not respond to fiber alone and may be helped by a bowel-training regimen, which involves taking an osmotic laxative (e.g., magnesium salts, lactulose, sorbitol, polyethylene glycol) and evacuating with enema or suppository (e.g., glycerin or bisacodyl) as needed. After breakfast, a distraction-free 15–20 min on the toilet without straining is encouraged. Excessive straining may lead to development of hemorrhoids and, if there is weakness of the pelvic floor or injury to the pudendal nerve, may result in obstructed defecation from descending perineum syndrome several years later. Those few who do not benefit from the simple measures delineated above or require long-term treatment or fail to respond to potent laxatives should undergo further investigation **(Fig. 42-4)**. Novel agents that induce secretion (e.g., lubiprostone, a chloride channel activator, or linaclotide, a guanylate cyclase C agonist that activates chloride secretion) are also available.

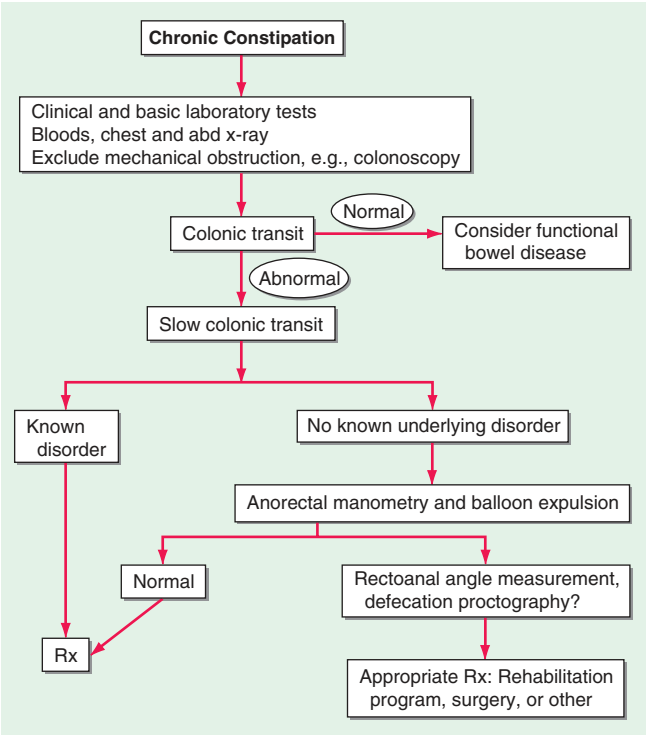

FIGURE 42-4 Algorithm for the management of constipation. abd, abdominal.

INVESTIGATION OF SEVERE CONSTIPATION

A small minority (probably <5%) of patients have severe or "intractable" constipation; about 25% have evacuation disorders. These are the patients most likely to require evaluation by gastroenterologists or in referral centers. Further observation of the patient may occasionally reveal a previously unrecognized cause, such as an evacuation

disorder, laxative abuse, malingering, or psychological disorder. In these patients, evaluations of the physiologic function of the colon and pelvic floor and of psychological status aid in the rational choice of treatment. Even among these highly selected patients with severe constipation, a cause can be identified in only about one-third of tertiary referral patients, with the others being diagnosed with normal transit constipation.

Measurement of Colonic Transit Radiopaque marker transit tests are easy, repeatable, generally safe, inexpensive, reliable, and highly applicable in evaluating constipated patients in clinical practice. Several validated methods are very simple. For example, radiopaque markers are ingested; an abdominal flat film taken 5 days later should indicate passage of 80% of the markers out of the colon without the use of laxatives or enemas. This test does not provide useful information about the transit profile of the stomach and small bowel. An alternative approach involves ingestion of 24 radiopaque markers on 3 successive days and an abdominal radiograph on the fourth day. The number of markers counted in the radiograph is an estimate of the colonic transit in hours. The collection of gas in the rectum between the level of the ischial spines and the lower border of the sacroiliac joints may suggest the presence of a rectal evacuation disorder as the cause of constipation.

Radioscintigraphy with a delayed-release capsule containing radiolabeled particles has been used to noninvasively characterize normal, accelerated, or delayed colonic function over 24–48 h with low radiation exposure. This approach simultaneously assesses gastric, small bowel (which may be important in ~20% of patients with delayed colonic transit because they reflect a more generalized GI motility disorder), and colonic transit. The disadvantages are the greater cost and the need for specific materials prepared in a nuclear medicine laboratory.

Anorectal and Pelvic Floor Tests Pelvic floor dysfunction is suggested by the inability to evacuate the rectum, a feeling of persistent rectal fullness, rectal pain, the need to extract stool from the rectum digitally, application of pressure on the posterior wall of the vagina, support of the perineum during straining, and excessive straining. These significant symptoms should be contrasted with the simple sense of incomplete rectal evacuation, which is common in IBS.

Formal psychological evaluation may identify eating disorders, "control issues," depression, or posttraumatic stress disorders that may respond to cognitive or other intervention and may be important in restoring quality of life to patients who might present with chronic constipation.

A simple clinical test in the office to document a nonrelaxing puborectalis muscle is to have the patient strain to expel the index finger during a digital rectal examination. Motion of the puborectalis posteriorly during straining indicates proper coordination of the pelvic floor muscles. Motion anteriorly with paradoxical contraction or limited perineal descent (<1.5 cm) during simulated evacuation indicates pelvic floor dysfunction.

Measurement of perineal descent is relatively easy to gauge clinically by placing the patient in the left decubitus position and watching the perineum to detect inadequate descent (<1.5 cm, a sign of pelvic floor dysfunction) or perineal ballooning during straining relative to bony landmarks (>4 cm, suggesting excessive perineal descent).

A useful overall test of evacuation is the balloon expulsion test. A balloon-tipped urinary catheter is placed and inflated with 50 mL of water. Normally, a patient can expel it while seated on a toilet or in the left lateral decubitus position. In the lateral position, the weight needed to facilitate expulsion of the balloon is determined; normally, expulsion occurs with <200 g added or unaided within 1 minute.

Anorectal manometry, when used in the evaluation of patients with severe constipation, may find an excessively high resting (>80 mmHg) or squeeze anal sphincter tone, suggesting anismus (anal sphincter spasm). This test also identifies rare syndromes, such as adult Hirschsprung's disease, by the absence of the rectoanal inhibitory reflex.

Defecography (a dynamic barium enema including lateral views obtained during barium expulsion or a magnetic resonance defecogram) reveals "soft abnormalities" in many patients; the most relevant findings are the measured changes in rectoanal angle, anatomic defects of the rectum such as internal mucosal prolapse, and enteroceles or rectoceles. Surgically remediable conditions are identified in only a few patients. These include severe, whole-thickness intussusception with complete outlet obstruction due to funnel-shaped plugging at the anal canal or an extremely large rectocele that fills preferentially during attempts at defecation instead of expulsion of the barium through the anus. In summary, defecography requires an interested and experienced radiologist, and abnormalities are not pathognomonic for pelvic floor dysfunction. The most common cause of outlet obstruction is failure of the puborectalis muscle to relax; this is not identified by barium defecography but can be demonstrated by magnetic resonance defecography, which provides more information about the structure and function of the pelvic floor, distal colorectum, and anal sphincters.

Neurologic testing (electromyography) is more helpful in the evaluation of patients with incontinence than of those with symptoms suggesting obstructed defecation. The absence of neurologic signs in the lower extremities suggests that any documented denervation of the puborectalis results from pelvic (e.g., obstetric) injury or from stretching of the pudendal nerve by chronic, long-standing straining. Constipation is common among patients with spinal cord injuries, neurologic diseases such as Parkinson's disease, multiple sclerosis, and diabetic neuropathy.

Spinal-evoked responses during electrical rectal stimulation or stimulation of external anal sphincter contraction by applying magnetic stimulation over the lumbosacral cord identify patients with limited sacral neuropathies with sufficient residual nerve conduction to attempt biofeedback training.

In summary, a balloon expulsion test is an important screening test for anorectal dysfunction. Rarely, an anatomic evaluation of the rectum or anal sphincters and an assessment of pelvic floor relaxation are the tools for evaluating patients in whom obstructed defecation is suspected and is associated with symptoms of rectal mucosal prolapse, pressure of the posterior wall of the vagina to facilitate defecation (suggestive of anterior rectocele), or prior pelvic surgery that may be complicated by enterocele.

TREATMENT

Constipation

After the cause of constipation is characterized, a treatment decision can be made. Slow-transit constipation requires aggressive medical or surgical treatment; anismus or pelvic floor dysfunction usually responds to biofeedback management (Fig. 42-4). The remaining ~60% of patients with constipation has normal colonic transit and can be treated symptomatically. Patients with spinal cord injuries or other neurologic disorders require a dedicated bowel regimen that often includes rectal stimulation, enema therapy, and carefully timed laxative therapy.

Patients with constipation are treated with bulk, osmotic, prokinetic, secretory, and stimulant laxatives including fiber, psyllium, milk of magnesia, lactulose, polyethylene glycol (colonic lavage solution), lubiprostone, linaclotide, and bisacodyl, or, in some countries, prucalopride, a 5-HT_4 agonist. If a 3- to 6-month trial of medical therapy fails, unassociated with obstructed defecation, the patients should be considered for laparoscopic colectomy with ileorectostomy; however, this should not be undertaken if there is continued evidence of an evacuation disorder or a generalized GI dysmotility. Referral to a specialized center for further tests of colonic motor function is warranted. The decision to resort to surgery is facilitated in the presence of megacolon and megarectum. The complications after surgery include small-bowel obstruction (11%) and fecal soiling, particularly at night during the first postoperative year. Frequency of defecation is 3–8 per day during the first year, dropping to 1–3 per day from the second year after surgery.

Patients who have a combined (evacuation and transit/motility) disorder should first pursue pelvic floor retraining (biofeedback and

muscle relaxation), psychological counseling, and dietetic advice. If symptoms are intractable despite biofeedback and optimized medical therapy, colectomy and ileorectostomy could be considered as long as the evacuation disorder is resolved and optimized medical therapy is unsuccessful. In patients with pelvic floor dysfunction alone, biofeedback training has a 70–80% success rate, measured by the acquisition of comfortable stool habits. Attempts to manage pelvic floor dysfunction with operations (internal anal sphincter or puborectalis muscle division) or injections with botulinum toxin have achieved only mediocre success and have been largely abandoned.

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43 Unintentional Weight Loss

J. Larry Jameson

Unintentional weight loss (UWL) is frequently insidious and can have important implications, often serving as a harbinger of serious underlying disease. Clinically important weight loss is defined as the loss of 10 pounds (4.5 kg) or >5% of one's body weight over a period of 6–12 months. UWL is encountered in up to 8% of all adult outpatients and 27% of frail persons aged ≥65 years. There is no identifiable cause in up to one-quarter of patients despite extensive investigation. Conversely, up to half of people who claim to have lost weight have no documented evidence of weight loss. People with no known cause of weight loss generally have a better prognosis than do those with known causes, particularly when the source is neoplastic. Weight loss in older persons is associated with a variety of deleterious effects, including falls and fractures, pressure ulcers, impaired immune function, and decreased functional status. Not surprisingly, significant weight loss is associated with increased mortality, which can range from 9% to as high as 38% within 1–2.5 years in the absence of clinical awareness and attention.

PHYSIOLOGY OF WEIGHT REGULATION WITH AGING

(See also Chaps. 463 and 394) Among healthy aging people, total body weight peaks in the sixth decade of life and generally remains stable until the ninth decade, after which it gradually falls. In contrast, lean body mass (fat-free mass) begins to decline at a rate of 0.3 kg per year in the third decade, and the rate of decline increases further beginning at age 60 in men and age 65 in women. These changes in lean body mass largely reflect the age-dependent decline in growth hormone secretion and, consequently, circulating levels of insulin-like growth factor type I (IGF-I) that occur with normal aging. Loss of sex steroids, at menopause in women and more gradually with aging in men, also contributes to these changes in body composition. In the healthy elderly, an increase in fat tissue balances the loss in lean body mass until very old age, when loss of both fat and skeletal muscle occurs. Age-dependent changes also occur at the cellular level. Telomeres shorten, and body cell mass—the fat-free portion of cells—declines steadily with aging.

Between ages 20 and 80, mean energy intake is reduced by up to 1200 kcal/d in men and 800 kcal/d in women. Decreased hunger is a reflection of reduced physical activity and loss of lean body mass, producing lower demand for calories and food intake. Several important age-associated physiologic changes also predispose elderly persons to weight loss, such as declining chemosensory function (smell and taste), reduced efficiency of chewing, slowed gastric emptying, and alterations in the neuroendocrine axis, including changes in levels of leptin, cholecystokinin, neuropeptide Y, and other hormones and peptides. These changes are associated with early satiety and a decline in both appetite and the hedonistic appreciation of food. Collectively, they contribute to the "anorexia of aging." As noted below, these physiologic changes with aging may be accompanied by social isolation and/or poverty, further contributing to undernutrition.

CAUSES OF UNINTENTIONAL WEIGHT LOSS

Most causes of UWL belong to one of four categories: (1) malignant neoplasms, (2) chronic inflammatory or infectious diseases, (3) metabolic disorders (e.g., hyperthyroidism and diabetes), or (4) psychiatric disorders **(Table 43-1)**. Not infrequently, more than one of these causes can be responsible for UWL. In most series, UWL is caused by malignant disease in a quarter of patients and by organic disease in one-third, with the remainder due to psychiatric disease, medications, or uncertain causes.

The most common malignant causes of UWL are gastrointestinal, hepatobiliary, hematologic, lung, breast, genitourinary, ovarian, and prostate. Half of all patients with cancer lose some body weight; one-third lose more than 5% of their original body weight, and up to 20% of all cancer deaths are caused directly by cachexia (through immobility and/or cardiac/respiratory failure). The greatest incidence of weight loss is seen among patients with solid tumors. Malignancy that reveals itself through significant weight loss usually has a very poor prognosis.

In addition to malignancies, gastrointestinal causes are among the most prominent causes of UWL. Peptic ulcer disease, inflammatory bowel disease, dysmotility syndromes, chronic pancreatitis, celiac disease, constipation, and atrophic gastritis are some of the more common entities. Oral and dental problems are easily overlooked and may manifest with halitosis, poor oral hygiene, xerostomia, inability to chew, reduced masticatory force, nonocclusion, temporomandibular joint syndrome, edentulousness, and pain due to caries or abscesses.

Tuberculosis, fungal diseases, parasites, subacute bacterial endocarditis, and HIV are well-documented causes of UWL. Cardiovascular and pulmonary diseases cause UWL through increased metabolic demand and decreased appetite and caloric intake. Repeated surgeries may lead to weight loss because of reduced caloric intake and increased metabolic demands resulting from a systemic inflammatory response. Uremia produces nausea, anorexia, and vomiting. Connective tissue diseases may increase metabolic demand and disrupt nutritional balance. As the incidence of diabetes mellitus increases with aging, the associated glucosuria can contribute to weight loss. Hyperthyroidism in the elderly may have less prominent sympathomimetic

TABLE 43-1 Causes of Involuntary Weight Loss

- **Cancer**
  - Colon
  - Hepatobiliary
  - Hematologic
  - Lung
  - Breast
  - Genitourinary
  - Ovarian
  - Prostate
- **Gastrointestinal disorders**
  - Malabsorption
  - Peptic ulcer
  - Inflammatory bowel disease
  - Pancreatitis
  - Obstruction/constipation
  - Pernicious anemia
- **Endocrine and metabolic**
  - Hyperthyroidism
  - Diabetes mellitus
  - Pheochromocytoma
  - Adrenal insufficiency
- **Cardiac disorders**
  - Chronic ischemia
  - Chronic congestive heart failure
- **Respiratory disorders**
  - Emphysema
  - Chronic obstructive pulmonary disease
- **Renal insufficiency**
- **Rheumatologic disease**
- **Infections**
  - HIV
  - Tuberculosis
  - Parasitic infection
  - Subacute bacterial endocarditis
- **Medications**
  - Sedatives
  - Antibiotics
  - Nonsteroidal anti-inflammatory drugs
  - Serotonin reuptake inhibitors
  - Metformin
  - Levodopa
  - Angiotensin-converting enzyme inhibitors
  - Other drugs
- **Disorders of the mouth and teeth**
  - Caries
  - Dysgeusia
- **Age-related factors**
  - Physiologic changes
  - Visual impairment
  - Decreased taste and smell
  - Functional disabilities
- **Neurologic**
  - Stroke
  - Parkinson's disease
  - Neuromuscular disorders
  - Dementia
- **Social**
  - Isolation
  - Economic hardship
- **Psychiatric and behavioral**
  - Depression
  - Anxiety
  - Paranoia
  - Bereavement
  - Alcoholism
  - Eating disorders
  - Increased activity or exercise
- **Idiopathic**

features and may present as "apathetic hyperthyroidism" or T_3 toxicosis **(Chap. 375)**.

Neurologic injuries such as stroke, quadriplegia, and multiple sclerosis may lead to visceral and autonomic dysfunction that can impair caloric intake. Dysphagia from these neurologic insults is a common mechanism. Functional disability that compromises activities of daily living (ADLs) is a common cause of undernutrition in the elderly. Visual impairment from ophthalmic or central nervous system disorders such as a tremor can limit the ability of people to prepare and eat meals. UWL may be one of the earliest manifestations of Alzheimer's dementia.

Isolation and depression are significant causes of UWL that may manifest as an inability to care for oneself, including nutritional needs. A cytokine-mediated inflammatory metabolic cascade can be both a cause of and a manifestation of depression. Bereavement can be a cause of UWL and, when present, is often more pronounced in men. More intense forms of mental illness such as paranoid disorders may lead to delusions about food and cause weight loss. Alcoholism can be a significant source of weight loss and malnutrition.

Elderly persons living in poverty may have to choose whether to purchase food or use the money for other expenses, including medications. Institutionalization is an independent risk factor, as up to 30–50% of nursing home patients have inadequate food intake.

Medications can cause anorexia, nausea, vomiting, gastrointestinal distress, diarrhea, dry mouth, and changes in taste. This is particularly an issue in the elderly, many of whom take five or more medications.

ASSESSMENT

The four major manifestations of UWL are (1) anorexia (loss of appetite), (2) sarcopenia (loss of muscle mass), (3) cachexia (a syndrome that combines weight loss, loss of muscle and adipose tissue, anorexia, and weakness), and (4) dehydration. The current obesity epidemic adds complexity, as excess adipose tissue can mask the development of sarcopenia and delay awareness of the development of cachexia. If it is not possible to measure weight directly, a change in clothing size, corroboration of weight loss by a relative or friend, and a numeric estimate of weight loss provided by the patient are suggestive of true weight loss.

Initial assessment includes a comprehensive history and physical, a complete blood count, tests of liver enzyme levels, C-reactive protein, erythrocyte sedimentation rate, renal function studies, thyroid function tests, chest radiography, and an abdominal ultrasound **(Table 43-2)**. Age, sex, and risk factor–specific cancer screening tests, such as mammography and colonoscopy, should be performed **(Chap. 66)**. Patients at risk should have HIV testing. All elderly patients with weight loss should undergo screening for dementia and depression by using instruments such as the Mini-Mental State Examination and the Geriatric Depression Scale, respectively **(Chap. 464)**. The Mini Nutritional Assessment (*www.mna-elderly.com*) and the Nutrition Screening Initiative (*http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1694757/*) are also available for the nutritional assessment of elderly patients. Almost all patients with a malignancy and >90% of those with other organic diseases have at least one laboratory abnormality. In patients presenting with substantial UWL, major organic and malignant diseases are unlikely when a baseline evaluation is completely normal. Careful follow-up rather than undirected testing is advised since the prognosis of weight loss of undetermined cause is generally favorable.

TREATMENT

Unintentional Weight Loss

The first priority in managing weight loss is to identify and treat the underlying causes. Treatment of underlying metabolic, psychiatric, infectious, or other systemic disorders may be sufficient to restore weight and functional status gradually. Medications that cause nausea or anorexia should be withdrawn or changed, if possible.

TABLE 43-2 Assessment and Testing for Involuntary Weight Loss

Indications	Laboratory
5% weight loss in 30 d	Complete blood count
10% weight loss in 180 d	Comprehensive electrolyte and metabolic panel, including liver and renal function tests
Body mass index <21	Thyroid function tests
25% of food left uneaten after 7 d	Erythrocyte sedimentation rate
Change in fit of clothing	C-reactive protein
Change in appetite, smell, or taste	Ferritin
Abdominal pain, nausea, vomiting, diarrhea, constipation, dysphagia	HIV testing, if indicated
Assessment	**Radiology**
Complete physical examination, including dental evaluation	Chest x-ray Abdominal ultrasound
Medication review	
Recommended cancer screening	
Mini-Mental State Examination[a]	
Mini-Nutritional Assessment[a]	
Nutrition Screening Initiative[a]	
Simplified Nutritional Assessment Questionnaire[a]	
Observation of eating[a]	
Activities of daily living[a]	
Instrumental activities of daily living[a]	

[a]May be more specific to assess weight loss in the elderly.

For those with unexplained UWL, oral nutritional supplements such as high-energy drinks sometimes reverse weight loss. Advising patients to consume supplements between meals rather than with a meal may help minimize appetite suppression and facilitate increased overall intake. Orexigenic, anabolic, and anticytokine agents are under investigation. In selected patients, the antidepressant mirtazapine results in a significant increase in body weight, body fat mass, and leptin concentration. Patients with wasting conditions who can comply with an appropriate exercise program gain muscle protein mass, strength, and endurance and may be more capable of performing ADLs.

Acknowledgment

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44 Gastrointestinal Bleeding

Loren Laine

Gastrointestinal bleeding (GIB) is the most common gastrointestinal condition leading to hospitalization in the United States, accounting for over 507,000 admissions and $4.85 billion in direct costs annually. Upper GIB (UGIB) incidence has decreased in recent decades, primarily due to decreases in GIB from ulcers. The ratio of UGIB to lower GIB (LGIB) among GIB admissions from U.S. emergency rooms is ~1.3. The case fatality of patients hospitalized with GIB has also decreased and is <3% in the United States. Patients generally die from decompensation of other underlying illnesses rather than exsanguination.

GIB presents as either overt or occult bleeding. *Overt GIB* is manifested by *hematemesis*, vomitus of red blood or "coffee-grounds" material; *melena*, black, tarry stool; and/or *hematochezia*, passage of red or maroon blood from the rectum. In the absence of overt bleeding, *occult GIB* may present with *symptoms of blood loss or anemia* such as lightheadedness, syncope, angina, or dyspnea; or with iron-deficiency anemia or a positive fecal occult blood test on routine testing. GIB is also categorized by the site of bleeding as UGIB (esophagus, stomach, duodenum), LGIB (colonic), small intestinal, or obscure GIB (if the source is unclear).

SOURCES OF GASTROINTESTINAL BLEEDING

Upper Gastrointestinal Sources of Bleeding

PEPTIC ULCERS Peptic ulcers are the most common cause of UGIB, accounting for ~50% of UGIB hospitalizations. Features of an ulcer at endoscopy provide important prognostic information that guides subsequent management decisions as outlined in **Figs. 315-3 and 315-4**. Approximately 20% of patients with bleeding ulcers have the highest risk findings of active bleeding or a nonbleeding visible vessel: one-third of such patients have further bleeding that requires urgent surgery if they are treated conservatively. These patients benefit from endoscopic therapy with bipolar electrocoagulation, heater probe, injection therapy (e.g., absolute alcohol, 1:10,000 epinephrine), and/or clips with reductions in bleeding, hospital stay, mortality, and costs. In contrast, patients with clean-based ulcers have rates of serious recurrent bleeding approaching zero. If stable with no other reason for hospitalization, such patients may be discharged home after endoscopy.

Randomized controlled trials document that high-dose, constant-infusion IV proton pump inhibitor (PPI) (80-mg bolus and 8-mg/h infusion), designed to sustain intragastric pH >6 and enhance clot stability, decreases further bleeding and mortality in patients with high-risk ulcers (active bleeding, nonbleeding visible vessel, adherent clot) when given after endoscopic therapy. Recent meta-analysis of randomized trials documents that high-dose intermittent PPIs are non-inferior to constant-infusion PPI therapy and thus may be substituted in this population. Patients with lower-risk findings (flat pigmented spot or clean base) do not require endoscopic therapy and receive standard doses of oral PPI.

Approximately 10–50% of patients with bleeding ulcers will rebleed within the next year if no preventive strategies are employed. Prevention of recurrent bleeding focuses on the three main factors in ulcer pathogenesis, *Helicobacter pylori*, nonsteroidal anti-inflammatory drugs (NSAIDs), and acid. Eradication of *H. pylori* in patients with bleeding ulcers decreases rebleeding rates to <5%. If a bleeding ulcer develops in a patient taking NSAIDs, the NSAIDs should be discontinued. If NSAIDs must be given, a cyclooxygenase (COX)-2 selective NSAID plus a PPI is recommended, based on results of a randomized trial. Patients with established cardiovascular disease who develop bleeding ulcers while taking low-dose aspirin for secondary prevention should restart aspirin as soon as possible after their bleeding episode (1–7 days). A randomized trial showed that failure to restart aspirin was associated with no significant difference in rebleeding (5% vs 10%) at 30 days but a significant increase in mortality (9% vs 1%) compared with immediate reinstitution of aspirin. In contrast, aspirin probably should be discontinued in most patients taking aspirin for primary prevention of cardiovascular events who develop UGIB. Patients with bleeding ulcers unrelated to *H. pylori* or NSAIDs should remain on PPI therapy indefinitely given a 42% incidence of rebleeding at 7 years without protective therapy. **Peptic ulcers are discussed in Chap. 317.**

MALLORY-WEISS TEARS Mallory-Weiss tears account for ~2–10% of UGIB hospitalizations. The classic history is vomiting, retching, or coughing preceding hematemesis, especially in an alcoholic patient. Bleeding from these tears, which are usually on the gastric side of the gastroesophageal junction, stops spontaneously in 80–90% of patients and recurs in only 0–10%. Endoscopic therapy is indicated for actively bleeding Mallory-Weiss tears. **Mallory-Weiss tears are discussed in Chap. 316.**

ESOPHAGEAL VARICES The proportion of UGIB hospitalizations due to varices varies widely, from ~2–40%, depending on the population. Patients with variceal hemorrhage have poorer outcomes than patients with other sources of UGIB. Urgent endoscopy within 12 h is recommended in cirrhotics with UGIB, and if esophageal varices are present, endoscopic ligation is performed and an IV vasoactive medication (octreotide, somatostatin, vapreotide, terlipressin) is given for 2–5 days. Combination of endoscopic and medical therapy is superior to either therapy alone in decreasing rebleeding. Over the long term, treatment with nonselective beta blockers plus endoscopic ligation is recommended because the combination is more effective than either alone in reduction of recurrent esophageal variceal bleeding. Transjugular intrahepatic portosystemic shunt (TIPS) is recommended in patients who have persistent or recurrent bleeding despite endoscopic and medical therapy. TIPS should also be considered in the first 1–2 days of hospitalization for acute variceal bleeding in patients with advanced liver disease (e.g., Child-Pugh class C with Child-Pugh score 10–13), because randomized trials show significant decreases in rebleeding and mortality compared with standard endoscopic and medical therapy.

Portal hypertension is also responsible for bleeding from gastric varices, varices in the small and large intestine, and portal hypertensive gastropathy and enterocolopathy. Bleeding gastric varices due to cirrhosis are treated with endoscopic injection of tissue adhesive (e.g., *n*-butyl cyanoacrylate), if available; if not, TIPS is performed.

EROSIVE DISEASE Erosions are endoscopically visualized breaks which are confined to the mucosa and do not cause major bleeding due to the absence of arteries and veins in the mucosa. Erosions in the esophagus, stomach, or duodenum commonly cause mild UGIB, with erosive gastritis and duodenitis accounting for perhaps ~10–15% and erosive esophagitis (primarily due to gastroesophageal reflux disease) ~1–10% of UGIB hospitalizations. The most important cause of gastric and duodenal erosions is NSAID use: ~50% of patients who chronically ingest NSAIDs may have gastric erosions. Other potential causes of gastric erosions include alcohol intake, *H. pylori* infection, and stress-related mucosal injury.

Stress-related gastric mucosal injury occurs only in extremely sick patients, such as those who have experienced serious trauma, major surgery, burns covering more than one-third of the body surface area, major intracranial disease, or severe medical illness (i.e., ventilator dependence, coagulopathy). Severe bleeding should not develop unless ulceration occurs. The mortality rate in these patients is high because of their serious underlying illnesses.

The incidence of bleeding from stress-related gastric mucosal injury has decreased dramatically in recent years, most likely due to better care of critically ill patients. Pharmacologic prophylaxis for bleeding may be considered in the high-risk patients mentioned above. Meta-analyses of randomized trials indicate that PPIs are more effective than H_2-receptor antagonists in reduction of overt and clinically important UGIB without differences in mortality or nosocomial pneumonia.

OTHER CAUSES Less common causes of UGIB include neoplasms, vascular ectasias (including hereditary hemorrhagic telangiectasias [Osler-Weber-Rendu] and gastric antral vascular ectasia ["watermelon stomach"]), Dieulafoy's lesion (in which an aberrant vessel in the mucosa bleeds from a pinpoint mucosal defect), prolapse gastropathy (prolapse of proximal stomach into esophagus with retching, especially in alcoholics), aortoenteric fistulas, and hemobilia or hemosuccus pancreaticus (bleeding from the bile duct or pancreatic duct).

Small-Intestinal Sources of Bleeding Patients without a source of GIB identified on upper endoscopy and colonoscopy were previously labeled as having obscure GIB. With the advent of improved diagnostic modalities, ~75% of GIB previously labeled obscure is now estimated to originate in the small intestine beyond the extent of a standard upper endoscopic exam. Small-intestinal GIB may account for up to ~5–10% of GIB cases. The most common causes in adults >40 years are vascular ectasias, neoplasm (e.g., GI stromal tumor, carcinoid, adenocarcinoma, lymphoma, metastases), and NSAID-induced erosions and ulcers. Meckel's diverticulum is the most common cause of significant small-intestinal GIB in children, decreasing in frequency as a cause of bleeding with age. Other causes in patients <40 years include Crohn's disease, polyposis syndromes, or neoplasm. Less common causes of small-intestinal GIB include infection, ischemia, vasculitis, small-bowel varices, diverticula, intussusception, Dieulafoy's lesions, aortoenteric fistulas, and duplication cysts.

Small-intestinal vascular ectasias are treated with endoscopic therapy if possible based on observational studies suggesting initial efficacy. However, rebleeding is common: 45% over a mean follow-up of 26 months in a recent systematic review. Estrogen/progesterone compounds are not recommended because a multicenter double-blind trial found no benefit in prevention of recurrent bleeding. Octreotide is used, based on positive results from case series but no randomized trials. A randomized trial reported significant benefit of thalidomide and awaits further confirmation. Other isolated lesions, such as tumors, generally require surgical resection.

Colonic Sources of Bleeding Hemorrhoids are probably the most common cause of LGIB; anal fissures also cause minor bleeding and pain. If these local anal processes, which rarely require hospitalization, are excluded, the most common cause of LGIB in adults is diverticulosis, followed by vascular ectasias (especially in the proximal colon of patients >70 years), neoplasms (primarily adenocarcinoma), colitis (ischemic, infectious, Crohn's or ulcerative colitis, NSAID-induced colitis or ulcers), postpolypectomy bleeding, and radiation proctopathy. Rarer causes include solitary rectal ulcer syndrome, trauma, varices (most commonly rectal), lymphoid nodular hyperplasia, vasculitis, and aortocolic fistulas. In children and adolescents, the most common colonic causes of significant GIB are inflammatory bowel disease and juvenile polyps.

Diverticular bleeding is abrupt in onset, usually painless, sometimes massive, and often from the right colon; chronic or occult bleeding is not characteristic. Colonic diverticula stop bleeding spontaneously in ~80–90% of patients and, on long-term follow-up, rebleed in ~15–40% of patients. Case series suggest endoscopic therapy may decrease recurrent bleeding in the uncommon case when colonoscopy identifies the specific bleeding diverticulum. When diverticular bleeding is found at angiography, transcatheter arterial embolization by superselective technique stops bleeding in a majority of patients. Segmental surgical resection is recommended for persistent or refractory diverticular bleeding.

Bleeding from colonic vascular ectasias may be overt or occult; it tends to be chronic and only occasionally is hemodynamically significant. Endoscopic hemostatic therapy may be used in the treatment of vascular ectasias, as well as discrete bleeding ulcers and postpolypectomy bleeding. Transcatheter arterial embolization also may be attempted for persistent bleeding from vascular ectasias and other discrete lesions. Surgical therapy is generally required for major persistent or recurrent bleeding from colonic sources that cannot be treated medically, endoscopically, or angiographically. Patients with Heyde's syndrome (bleeding vascular ectasias and aortic stenosis) appear to benefit from aortic valve replacement.

APPROACH TO THE PATIENT

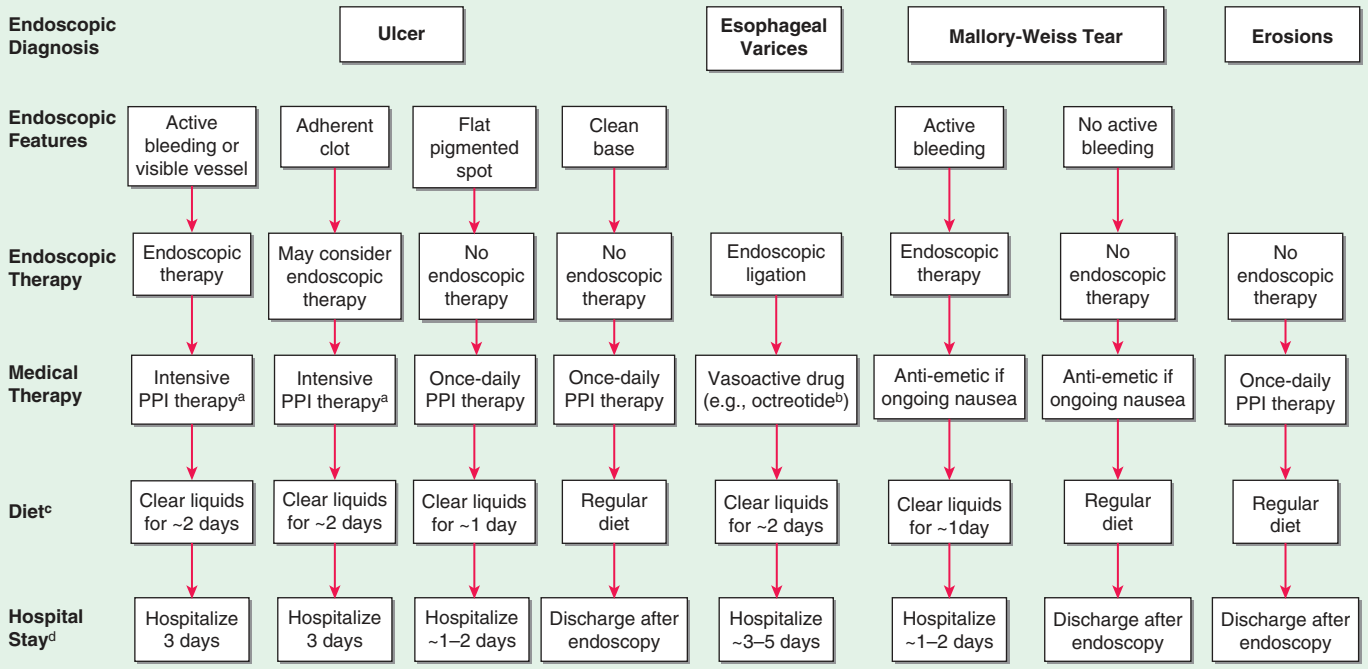
Gastrointestinal Bleeding

INITIAL ASSESSMENT

Measurement of the heart rate and blood pressure is the best way to initially assess a patient with GIB. Clinically significant bleeding leads to postural changes in heart rate or blood pressure, tachycardia, and, finally, recumbent hypotension. In contrast, hemoglobin does not fall immediately with acute GIB, due to proportionate reductions in plasma and red cell volumes (people bleed whole blood). Thus, hemoglobin may be normal or only minimally decreased at the initial presentation of a severe bleeding episode. As extravascular fluid enters the vascular space to restore volume, the hemoglobin falls, but this process may take up to 72 h. Transfusion is recommended when the hemoglobin drops below 7 g/dL, based on a large randomized trial showing this restrictive transfusion strategy decreases rebleeding and death in acute UGIB compared with a transfusion threshold of 9 g/dL. Patients with slow, chronic GIB may have very low hemoglobin values despite normal blood pressure and heart rate. With the development of iron-deficiency anemia, the mean corpuscular volume is low and red blood cell distribution width is increased.

DIFFERENTIATION OF UGIB FROM LGIB

Hematemesis indicates an UGIB source. Melena indicates blood has been present in the GI tract for ≥14 h, and as long as 3–5 days. The more proximal the bleeding site, the more likely melena will occur. Hematochezia usually represents a lower GI source of bleeding, although an upper GI lesion may bleed so briskly that blood transits the bowel before melena develops. When hematochezia is the presenting symptom of UGIB, it is associated with hemodynamic instability and dropping hemoglobin. Bleeding lesions of the small bowel may present as melena or hematochezia. Other clues to UGIB include hyperactive bowel sounds and an elevated blood urea nitrogen (due to volume depletion and blood proteins absorbed in the small intestine).



[a]Intravenous bolus (80 mg) followed by infusion (8 mg/h) for 3 days; or oral or intravenous bolus (e.g., 80 mg) followed by intermittent high doses (e.g., 40–80 mg bid or 40 mg tid) for 3 days.Then twice-daily PPI on days 4–14 followed by once-daily PPI.
[b]Intravenous 50 µg bolus followed by 50 µg/h infusion for 2–5 days.
[c]Diet after endoscopy, assuming no nausea or vomiting.
[d]Duration after endoscopy assuming patient stable without further bleeding or concurrent medical conditions requiring hospitalization; PPI, proton pump inhibitor.

FIGURE 44-1 Suggested algorithm for patients with acute upper gastrointestinal bleeding based on endoscopic findings.

A nonbloody nasogastric aspirate may be seen in ~15% of patients with UGIB who present with clinically serious hematochezia. A bile-stained appearance does not exclude UGIB because reports of bile in the aspirate are incorrect in ~50% of cases. Testing of aspirates that are not grossly bloody for occult blood is not useful.

EVALUATION AND MANAGEMENT OF UGIB (FIG. 44-1)

Baseline characteristics predictive of rebleeding and death include hemodynamic compromise (tachycardia or hypotension), increasing age, and comorbidities. Risk assessment tools may be used to identify patients with very low risk. Discharge from the emergency room with outpatient management has been suggested for patients with a Glasgow-Blatchford score (possible range 0–23, Table 44-1) of 0–1 or 0–2 among patients <70 years because when hospitalized <1% of such patients require intervention and <0.5% die.

PPI infusion may be considered at presentation: it decreases high-risk ulcer stigmata (e.g., active bleeding) and need for endoscopic therapy but does not improve clinical outcomes such as further bleeding, surgery, or death. The promotility agent erythromycin, 250 mg intravenously ~30 min before endoscopy, also may be considered to improve visualization at endoscopy: it provides a small but significant increase in diagnostic yield and decrease in red cell transfusions. Cirrhotic patients presenting with UGIB should be given an antibiotic (quinolone or ceftriaxone) and IV vasoactive medication upon presentation, even before endoscopy. Antibiotics decrease bacterial infections, rebleeding, and mortality, and vasoactive medications may improve control of bleeding in the first 12 h after presentation.

Upper endoscopy should be performed within 24 h in most patients with UGIB. Patients at higher risk (e.g., hemodynamic instability, cirrhosis) may benefit from more urgent endoscopy within 12 h. Early endoscopy is also beneficial in low-risk patients for management decisions (e.g., discharge). Patients with major bleeding and high-risk endoscopic findings (e.g., varices, ulcers with active bleeding or a visible vessel) benefit from endoscopic hemostatic therapy, whereas patients with low-risk lesions (e.g., clean-based ulcers, erosions, nonbleeding Mallory-Weiss tears) who have stable vital signs and hemoglobin and no other medical problems may be discharged home.

EVALUATION AND MANAGEMENT OF LGIB (FIG. 44-2)

Patients with hematochezia and hemodynamic instability should have upper endoscopy to rule out an upper GI source before evaluation of the lower GI tract.

TABLE 44-1 Glasgow-Blatchford Score

ADMISSION MARKER	SCORE
Blood urea nitrogen (mg/dL)	
18.2 to <22.4	2
22.4 to <28.0	3
28.0 to <70.0	4
≥70.0	6
Hemoglobin (g/dL)	
12.0 to <13.0 (men); 10.0 to <12.0 (women)	1
10.0 to <12.0 (men)	3
<10.0	6
Systolic blood pressure (mmHg)	
100–109	1
90–99	2
<90	3
Heart rate (beats per minute)	
≥100	1
Other markers	
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

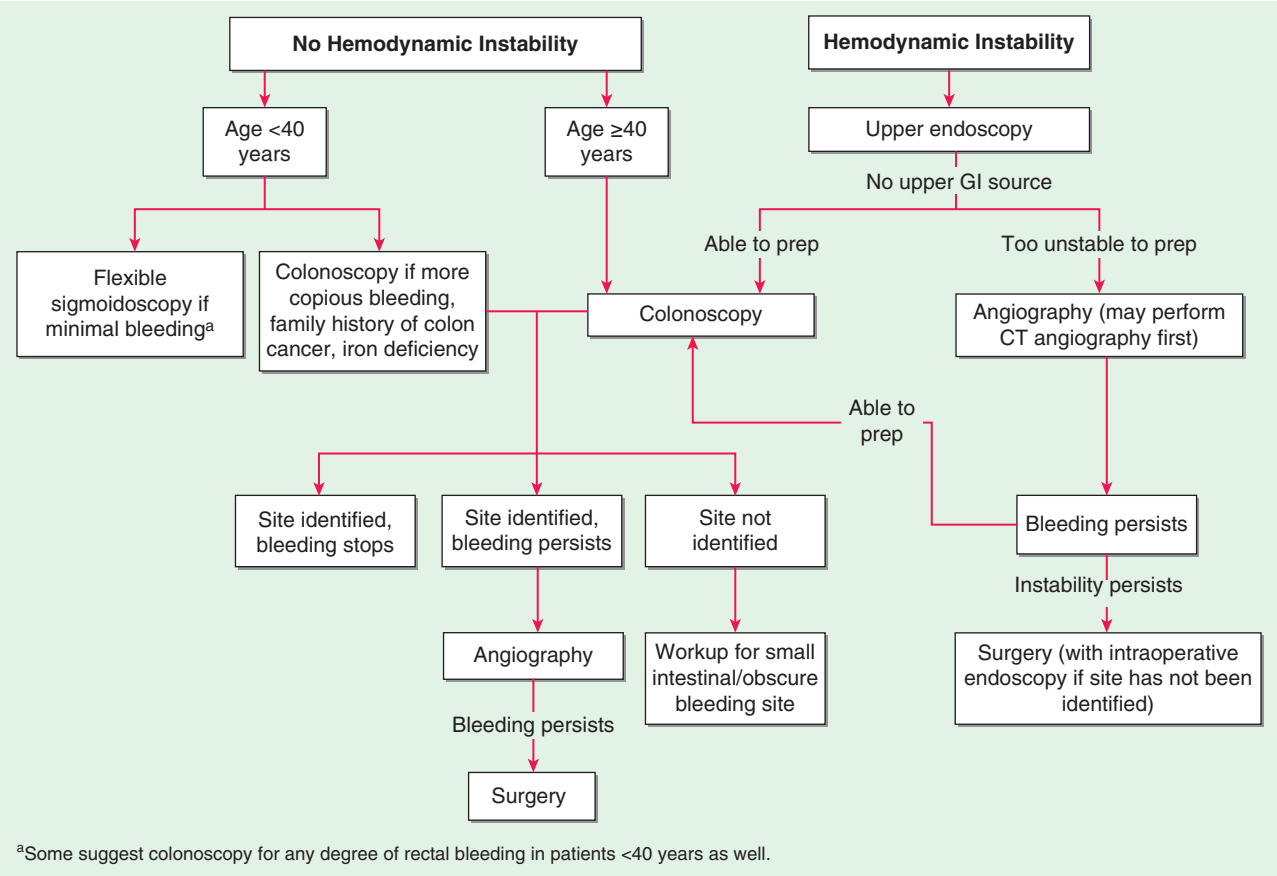


FIGURE 44-2 Suggested algorithm for patients with acute lower gastrointestinal bleeding.

Colonoscopy after an oral lavage solution is the procedure of choice in most patients admitted with LGIB unless bleeding is too massive, in which case angiography is recommended. Computed tomography (CT) angiography is often suggested prior to angiography to document evidence and location of active bleeding. Sigmoidoscopy is used primarily in patients <40 years old with minor bleeding. In patients with no source identified on colonoscopy, imaging studies may be employed. ^{99m}Tc-labeled red cell scan allows repeated imaging for up to 24 h and may identify the general location of bleeding. However, radionuclide scans should be interpreted with caution because results, especially from later images, are highly variable. Multidetector CT angiography is likely superior to nuclear scintigraphy and increasingly used in its place. In active LGIB, angiography can detect the site of bleeding (extravasation of contrast into the gut) and permits treatment with embolization.

EVALUATION AND MANAGEMENT OF SMALL-INTESTINAL OR OBSCURE GIB

In patients with massive bleeding suspected to be from the small intestine, current guidelines suggest angiography as the initial test, with CT angiography or ^{99m}Tc-labeled red cell scan prior to angiography if the patient's clinical status permits. For others, repeat upper and lower endoscopy may be considered as the initial evaluation because second-look procedures identify a source in up to ~25% of upper endoscopies and colonoscopies; a push enteroscopy, usually performed with a pediatric colonoscope to inspect the entire duodenum and proximal jejunum, may be substituted for a repeat standard upper endoscopy. If second-look procedures are negative, evaluation of the entire small intestine is performed, usually with video capsule endoscopy. A systematic review of comparative studies showed the yield of "clinically significant findings" greater with capsule than push enteroscopy (56% vs 26%) or small bowel barium radiography (42% vs 6%). However, capsule endoscopy does not allow full visualization of the small intestine, tissue sampling, or application of therapy.

CT enterography may be used initially instead of video capsule in patients with possible small bowel narrowing (e.g., stricture, prior surgery or radiation, Crohn's disease) and may follow a negative video capsule for suspected small-intestinal GIB, given its higher sensitivity for small-intestinal masses.

If capsule endoscopy is positive, management is dictated by the finding. If capsule endoscopy is negative, current recommendations suggest patients may either be observed or, if their clinical course mandates (e.g., need for transfusions), undergo further testing. "Deep" enteroscopy (double-balloon, single-balloon, or spiral enteroscopy) is commonly the next test undertaken for clinically important GIB documented or suspected to be from the small intestine because it allows the endoscopist to examine, obtain specimens from, and provide therapy to much or all of the small intestine. Other imaging techniques sometimes used in evaluation of obscure GIB include ^{99m}Tc-labeled red blood cell scintigraphy, CT angiography, angiography, and ^{99m}Tc-pertechnetate scintigraphy for Meckel's diverticulum (especially in young patients). If all tests are unrevealing, intraoperative endoscopy is indicated in patients with severe recurrent or persistent bleeding requiring repeated transfusions.

POSITIVE FECAL OCCULT BLOOD TEST

Fecal occult blood testing is recommended only for colorectal cancer screening, beginning at age 50 in average-risk adults. A positive test necessitates colonoscopy. If evaluation of the colon is negative, further workup is not recommended unless iron-deficiency anemia or GI symptoms are present.

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45 Jaundice

Savio John, Daniel S. Pratt

Jaundice is a yellowish discoloration of body tissues resulting from the deposition of bilirubin. Tissue deposition of bilirubin occurs only in the presence of serum hyperbilirubinemia and is a sign of either liver disease or, less often, a hemolytic disorder or disorder of bilirubin metabolism. The degree of serum bilirubin elevation can be estimated by physical examination. Slight increases in serum bilirubin level are best detected by examining the sclerae for icterus. Sclerae have a particular affinity for bilirubin due to their high elastin content, and the presence of scleral icterus indicates a serum bilirubin level of at least 51 μmol/L (3 mg/dL). The ability to detect scleral icterus is made more difficult if the examining room has fluorescent lighting. If the examiner suspects scleral icterus, a second site to examine is underneath the tongue. As serum bilirubin levels rise, the skin will eventually become yellow in light-skinned patients and even green if the process is long-standing; the green color is produced by oxidation of bilirubin to biliverdin.

The differential diagnosis for yellowing of the skin is limited. In addition to jaundice, it includes carotenoderma, the use of the drug quinacrine, and excessive exposure to phenols. Carotenoderma is the yellow color imparted to the skin of healthy individuals who ingest excessive amounts of vegetables and fruits that contain carotene, such as carrots, leafy vegetables, squash, peaches, and oranges. In jaundice the yellow coloration of the skin is uniformly distributed over the body, whereas in carotenoderma the pigment is concentrated on the palms, soles, forehead, and nasolabial folds. Carotenoderma can be distinguished from jaundice by the sparing of the sclerae. Quinacrine causes a yellow discoloration of the skin in 4–37% of patients treated with it.

Another sensitive indicator of increased serum bilirubin is darkening of the urine, which is due to the renal excretion of conjugated bilirubin. Patients often describe their urine as tea- or cola-colored. Bilirubinuria indicates an elevation of the direct serum bilirubin fraction and, therefore, the presence of liver or biliary disease.

Serum bilirubin levels increase when an imbalance exists between bilirubin production and clearance. A logical evaluation of the patient who is jaundiced requires an understanding of bilirubin production and metabolism.

PRODUCTION AND METABOLISM OF BILIRUBIN

(See Chap. 331) Bilirubin, a tetrapyrrole pigment, is a breakdown product of heme (ferroprotoporphyrin IX). About 80–85% of the 4 mg/kg body weight of bilirubin produced each day is derived from the breakdown of hemoglobin in senescent red blood cells. The remainder comes from prematurely destroyed erythroid cells in bone marrow and from the turnover of hemoproteins such as myoglobin and cytochromes found in tissues throughout the body.

The formation of bilirubin occurs in reticuloendothelial cells, primarily in the spleen and liver. The first reaction, catalyzed by the microsomal enzyme heme oxygenase, oxidatively cleaves the α bridge of the porphyrin group and opens the heme ring. The end products of this reaction are biliverdin, carbon monoxide, and iron. The second reaction, catalyzed by the cytosolic enzyme biliverdin reductase, reduces the central methylene bridge of biliverdin and converts it to bilirubin. Bilirubin formed in the reticuloendothelial cells is virtually insoluble in water due to tight internal hydrogen bonding between the water-soluble moieties of bilirubin—that is, the bonding of the propionic acid carboxyl groups of one dipyrrolic half of the molecule with the imino and lactam groups of the opposite half. This configuration blocks solvent access to the polar residues of bilirubin and places the hydrophobic residues on the outside. To be transported in blood, bilirubin must be solubilized. Solubilization is accomplished by the reversible, noncovalent binding of bilirubin to albumin. Unconjugated bilirubin bound to albumin is transported to the liver. There, the bilirubin—but not the albumin—is taken up by hepatocytes via a process that at least partly involves carrier-mediated membrane transport. No specific bilirubin transporter has yet been identified (Chap. 331, Fig. 331-1).

After entering the hepatocyte, unconjugated bilirubin is bound in the cytosol to a number of proteins including proteins in the glutathione-S-transferase superfamily. These proteins serve both to reduce efflux of bilirubin back into the serum and to present the bilirubin for conjugation. In the endoplasmic reticulum, bilirubin is made aqueous soluble by conjugation to glucuronic acid, a process that disrupts the hydrophobic internal hydrogen bonds and yields bilirubin monoglucuronide and diglucuronide. The conjugation of glucuronic acid to bilirubin is catalyzed by bilirubin uridine diphosphate-glucuronosyl transferase (UDPGT). The now-hydrophilic bilirubin conjugates diffuse from the endoplasmic reticulum to the canalicular membrane, where bilirubin monoglucuronide and diglucuronide are actively transported into canalicular bile by an energy-dependent mechanism involving the multidrug resistance–associated protein 2 (MRP2). A portion of bilirubin glucuronides is transported into the sinusoids and portal circulation by MRP3 and is subjected to reuptake into the hepatocyte by the sinusoidal organic anion transport protein 1B1 (OATP1B1) and OATP1B3. The conjugated bilirubin excreted into bile drains into the duodenum and passes unchanged through the proximal small bowel. Conjugated bilirubin is not reabsorbed by the intestinal mucosa due to its hydrophilicity and increased molecular size. When the conjugated bilirubin reaches the distal ileum and colon, it is hydrolyzed to unconjugated bilirubin by bacterial β-glucuronidases. The unconjugated bilirubin is reduced by normal gut bacteria to form a group of colorless tetrapyrroles called *urobilinogens* and other products, the nature and relative amounts of which depend on the bacterial flora. About 80–90% of these products are excreted in feces, either unchanged or oxidized to orange derivatives called *urobilins*. The remaining 10–20% of the urobilinogens undergo enterohepatic cycling. A small fraction (usually <3 mg/dL) escapes hepatic uptake, filters across the renal glomerulus, and is excreted in urine. Increased urinary excretion of urobilinogen can be due to increased bilirubin production, increased hepatic reabsorption of urobilinogen from the colon, or decreased hepatic clearance of urobilinogen.

MEASUREMENT OF SERUM BILIRUBIN

The terms *direct* and *indirect* bilirubin—that is, conjugated and unconjugated bilirubin, respectively—are based on the original van den Bergh reaction. This assay, or a variation of it, is still used in most clinical chemistry laboratories to determine the serum bilirubin level. In this assay, bilirubin is exposed to diazotized sulfanilic acid and splits into two relatively stable dipyrrylmethene azopigments that absorb maximally at 540 nm, allowing photometric analysis. The direct fraction is that which reacts with diazotized sulfanilic acid in the absence of an accelerator substance such as alcohol. The direct fraction provides an approximation of the conjugated bilirubin level in serum. The *total* serum bilirubin is the amount that reacts after the addition of alcohol. The indirect fraction is the difference between the total and the direct bilirubin levels and provides an estimate of the unconjugated bilirubin in serum. Unconjugated bilirubin also reacts with diazo reagents,

albeit slowly, even when the accelerator is absent. Thus the calculated indirect bilirubin may underestimate the true amount of unconjugated bilirubin in circulation.

With the van den Bergh method, the normal serum bilirubin concentration usually is between 17 and 26 µmol/L (1 and 1.5 mg/dL). Total serum bilirubin concentrations are between 3.4 and 15.4 µmol/L (0.2 and 0.9 mg/dL) in 95% of a normal population. Unconjugated hyperbilirubinemia is present when the direct fraction is <15% of the total serum bilirubin. The presence of even limited amounts of true conjugated bilirubin in serum suggests significant hepatobiliary pathology. As conjugated hyperbilirubinemia is always associated with bilirubinuria (except in the presence of delta bilirubin in prolonged cholestasis when jaundice is overt), detection of bilirubin in urine via dipstick test is extremely helpful to confirm the presence of conjugated hyperbilirubinemia in a patient with mildly elevated direct fraction.

Several new techniques, although less convenient to perform, have added considerably to our understanding of bilirubin metabolism. First, studies using these methods demonstrate that, in normal persons or those with Gilbert's syndrome, almost 100% of the serum bilirubin is unconjugated; <3% is monoconjugated bilirubin. Second, in jaundiced patients with hepatobiliary disease, the total serum bilirubin concentration measured by these new, more accurate methods is lower than the values found with diazo methods. This finding suggests that there are diazo-positive compounds distinct from bilirubin in the serum of patients with hepatobiliary disease. Third, these studies indicate that, in jaundiced patients with hepatobiliary disease, monoglucuronides of bilirubin predominate over diglucuronides. Fourth, part of the direct-reacting bilirubin fraction includes conjugated bilirubin that is covalently linked to albumin. This albumin-linked fraction of conjugated bilirubin (*delta fraction, delta bilirubin*, or *biliprotein*) represents an important fraction of total serum bilirubin in patients with cholestasis and hepatobiliary disorders. The delta bilirubin is formed in serum when hepatic excretion of bilirubin glucuronides is impaired and the glucuronides accumulate in serum. By virtue of its tight binding to albumin, the clearance rate of delta bilirubin from serum approximates the half-life of albumin (12–14 days) rather than the short half-life of bilirubin (about 4 h).

The prolonged half-life of albumin-bound conjugated bilirubin accounts for two previously unexplained enigmas in jaundiced patients with liver disease: (1) that some patients with conjugated hyperbilirubinemia do not exhibit bilirubinuria during the recovery phase of their disease because the delta bilirubin, although conjugated, is covalently bound to albumin and therefore not filtered by the renal glomeruli, and (2) that the elevated serum bilirubin level declines more slowly than expected in some patients who otherwise appear to be recovering satisfactorily. Late in the recovery phase of hepatobiliary disorders, all the conjugated bilirubin may be in the albumin-linked form.

MEASUREMENT OF URINE BILIRUBIN

Unconjugated bilirubin is always bound to albumin in the serum, is not filtered by the kidney, and is not found in the urine. Conjugated bilirubin is filtered at the glomerulus, and the majority is reabsorbed by the proximal tubules; a small fraction is excreted in the urine. Any bilirubin found in the urine is conjugated bilirubin. The presence of bilirubinuria on urine dipstick test (Ictotest) indicates an elevation of the conjugated bilirubin fraction that cannot be excreted from the liver, and implies the presence of hepatobiliary disease. A false-negative result is possible in patients with prolonged cholestasis due to the predominance of delta bilirubin, which is covalently bound to albumin and therefore not filtered by the renal glomeruli.

APPROACH TO THE PATIENT

Jaundice

The goal of this chapter is not to provide an encyclopedic review of all of the conditions that can cause jaundice. Rather, the chapter is intended to offer a framework that helps a physician to evaluate the patient with jaundice in a logical way **(Fig. 45-1)**.

Simply stated, the initial step is to perform appropriate blood tests in order to determine whether the patient has an isolated elevation of serum bilirubin. If so, is the bilirubin elevation due to an increased unconjugated or conjugated fraction? If the hyperbilirubinemia is accompanied by other liver test abnormalities, is the disorder hepatocellular or cholestatic? If cholestatic, is it intra- or extrahepatic? All of these questions can be answered with a thoughtful history, physical examination, and interpretation of laboratory and radiologic tests and procedures.

The bilirubin present in serum represents a balance between input from the production of bilirubin and hepatic/biliary removal of the pigment. Hyperbilirubinemia may result from (1) overproduction of bilirubin; (2) impaired uptake, conjugation, or excretion of bilirubin; or (3) regurgitation of unconjugated or conjugated bilirubin from damaged hepatocytes or bile ducts. An increase in unconjugated bilirubin in serum results from overproduction, impaired uptake, or conjugation of bilirubin. An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or backward leakage of the pigment. The initial steps in evaluating the patient with jaundice are to determine (1) whether the hyperbilirubinemia is predominantly conjugated or unconjugated in nature and (2) whether other biochemical liver tests are abnormal. The thoughtful interpretation of limited data permits a rational evaluation of the patient (Fig. 45-1). The following discussion will focus solely on the evaluation of the adult patient with jaundice.

ISOLATED ELEVATION OF SERUM BILIRUBIN

Unconjugated Hyperbilirubinemia The differential diagnosis of isolated unconjugated hyperbilirubinemia is limited **(Table 45-1)**. The critical determination is whether the patient is suffering from a hemolytic process resulting in an overproduction of bilirubin (hemolytic disorders and ineffective erythropoiesis) or from impaired hepatic uptake/conjugation of bilirubin (drug effect or genetic disorders).

Hemolytic disorders that cause excessive heme production may be either inherited or acquired. Inherited disorders include spherocytosis, sickle cell anemia, thalassemia, and deficiency of red cell enzymes such as pyruvate kinase and glucose-6-phosphate dehydrogenase. In these conditions, the serum bilirubin level rarely exceeds 86 µmol/L (5 mg/dL). Higher levels may occur when there is coexistent renal or hepatocellular dysfunction or in acute hemolysis, such as a sickle cell crisis. In evaluating jaundice in patients with chronic hemolysis, it is important to remember the high incidence of pigmented (calcium bilirubinate) gallstones found in these patients, which increases the likelihood of choledocholithiasis as an alternative explanation for hyperbilirubinemia.

Acquired hemolytic disorders include microangiopathic hemolytic anemia (e.g., hemolytic-uremic syndrome), paroxysmal nocturnal hemoglobinuria, spur cell anemia, immune hemolysis, and parasitic infections (e.g., malaria and babesiosis). Ineffective erythropoiesis occurs in cobalamin, folate, and iron deficiencies. Resorption of hematomas and massive blood transfusions both can result in increased hemoglobin release and overproduction of bilirubin.

In the absence of hemolysis, the physician should consider a problem with the hepatic uptake or conjugation of bilirubin. Certain drugs, including rifampin and probenecid, may cause unconjugated hyperbilirubinemia by diminishing hepatic uptake of bilirubin. Impaired bilirubin conjugation occurs in three genetic conditions: Crigler-Najjar syndrome types I and II and Gilbert's syndrome. *Crigler-Najjar type I* is an exceptionally rare condition found in neonates and characterized by severe jaundice (bilirubin >342 µmol/L [>20 mg/dL]) and neurologic impairment due to kernicterus, frequently leading to death in infancy or childhood. These patients have a complete absence of bilirubin UDPGT activity; are totally unable to conjugate bilirubin; and hence cannot excrete it.

Crigler-Najjar type II is somewhat more common than type I. Patients live into adulthood with serum bilirubin levels of 103–428 µmol/L (6–25 mg/dL). In these patients, mutations in the bilirubin

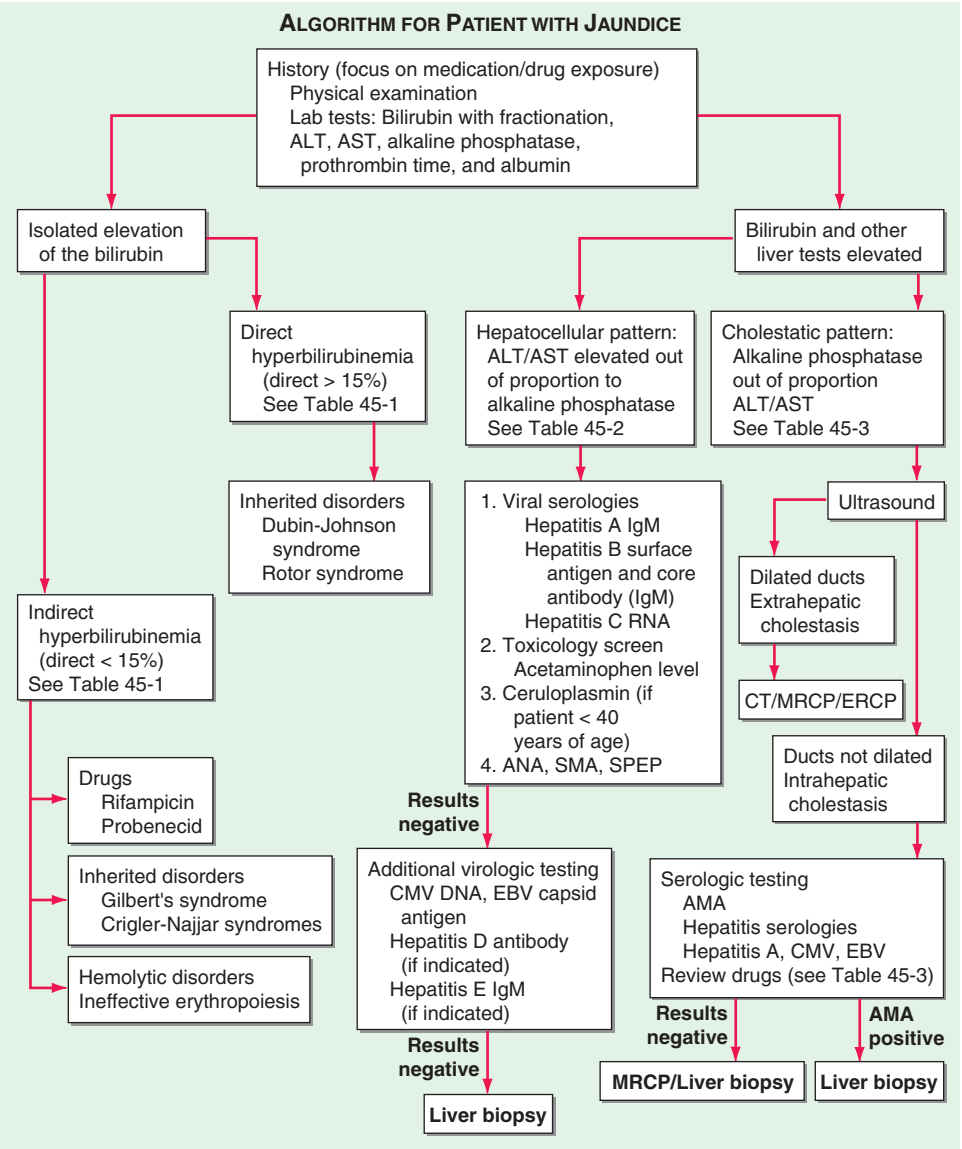

FIGURE 45-1 Evaluation of the patient with jaundice. ALT, alanine aminotransferase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; LKM, liver-kidney microsomal antibody; MRCP, magnetic resonance cholangiopancreatography; SMA, smooth-muscle antibody; SPEP, serum protein electrophoresis.

TABLE 45-1 Causes of Isolated Hyperbilirubinemia

I. Indirect hyperbilirubinemia
- A. Hemolytic disorders
- B. Ineffective erythropoiesis
- C. Increased bilirubin production
  1. Massive blood transfusion
  2. Resorption of hematoma
- D. Drugs
  1. Rifampin
  2. Probenecid
  3. Ribavirin
  4. Protease inhibitors (Atazanavir, Indinavir)
- E. Inherited conditions
  1. Crigler-Najjar types I and II
  2. Gilbert's syndrome

II. Direct hyperbilirubinemia (inherited conditions)
- A. Dubin-Johnson syndrome
- B. Rotor syndrome

UDPGT gene cause the reduction—typically ≤10%—of the enzyme's activity. Bilirubin UDPGT activity can be induced by the administration of phenobarbital, which can reduce serum bilirubin levels in these patients. Despite marked jaundice, these patients usually survive into adulthood, although they may be susceptible to kernicterus under the stress of concurrent illness or surgery.

Gilbert's syndrome is also marked by the impaired conjugation of bilirubin due to reduced bilirubin UDPGT activity (typically 10–35% of normal). Patients with Gilbert's syndrome have mild unconjugated hyperbilirubinemia, with serum levels almost always <103 μmol/L (6 mg/dL). The serum levels may fluctuate, and jaundice is often identified only during periods of stress, concurrent illness, alcohol use, or fasting. Unlike both Crigler-Najjar syndromes, Gilbert's syndrome is very common. The reported incidence is 3–7% of the population, with males predominating over females by a ratio of 1.5–7:1.

Conjugated Hyperbilirubinemia Elevated conjugated hyperbilirubinemia is found in two rare inherited conditions: *Dubin-Johnson syndrome* and *Rotor syndrome* (Table 45-1). Patients with either condition present with asymptomatic jaundice. The defect in Dubin-Johnson syndrome is the presence of mutations in the gene for MRP2. These patients have altered excretion of bilirubin into the

bile ducts. Rotor syndrome may represent a deficiency of the major hepatic drug reuptake transporters OATP1B1 and OATP1B3. Differentiating between these syndromes is possible but is clinically unnecessary due to their benign nature.

ELEVATION OF SERUM BILIRUBIN WITH OTHER LIVER TEST ABNORMALITIES

The remainder of this chapter will focus on the evaluation of patients with conjugated hyperbilirubinemia in the setting of other liver test abnormalities. This group of patients can be divided into those with a primary hepatocellular process and those with intra- or extrahepatic cholestasis. This distinction, which is based on the history and physical examination as well as the pattern of liver test abnormalities, guides the clinician's evaluation (Fig. 45-1).

History A complete medical history is perhaps the single most important part of the evaluation of the patient with unexplained jaundice. Important considerations include the use of or exposure to any chemical or medication, whether physician-prescribed, over-the-counter, complementary, or alternative medicines (e.g., herbal and vitamin preparations) or other drugs such as anabolic steroids. The patient should be carefully questioned about possible parenteral exposures, including transfusions, intravenous and intranasal drug use, tattooing, and sexual activity. Other important points include recent travel history; exposure to people with jaundice; exposure to possibly contaminated foods; occupational exposure to hepatotoxins; alcohol consumption; the duration of jaundice; and the presence of any accompanying signs and symptoms, such as arthralgias, myalgias, rash, anorexia, weight loss, abdominal pain, fever, pruritus, and changes in the urine and stool. While none of the latter manifestations is specific for any one condition, any of them can suggest a particular diagnosis. A history of arthralgias and myalgias predating jaundice suggests hepatitis, either viral or drug-related. Jaundice associated with the sudden onset of severe right-upper-quadrant pain and shaking chills suggests choledocholithiasis and ascending cholangitis.

Physical Examination The general assessment should include evaluation of the patient's nutritional status. Temporal and proximal muscle wasting suggests long-standing disease such as pancreatic cancer or cirrhosis. Stigmata of chronic liver disease, including spider nevi, palmar erythema, gynecomastia, caput medusae, Dupuytren's contractures, parotid gland enlargement, and testicular atrophy, are commonly seen in advanced alcoholic (Laennec's) cirrhosis and occasionally in other types of cirrhosis. An enlarged left supraclavicular node (Virchow's node) or a periumbilical nodule (Sister Mary Joseph's nodule) suggests an abdominal malignancy. Jugular venous distention, a sign of right-sided heart failure, suggests hepatic congestion. Right pleural effusion even in the absence of clinically apparent ascites may be seen in advanced cirrhosis.

The abdominal examination should focus on the size and consistency of the liver, on whether the spleen is palpable and hence enlarged, and on whether ascites is present. Patients with cirrhosis may have an enlarged left lobe of the liver, which is felt below the xiphoid, and an enlarged spleen. A grossly enlarged nodular liver or an obvious abdominal mass suggests malignancy. An enlarged tender liver could signify viral or alcoholic hepatitis; an infiltrative process such as amyloidosis; or, less often, an acutely congested liver secondary to right-sided heart failure. Severe right-upper-quadrant tenderness with respiratory arrest on inspiration (Murphy's sign) suggests cholecystitis. Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

Laboratory Tests A battery of tests are helpful in the initial evaluation of a patient with unexplained jaundice. These include total and direct serum bilirubin measurement with fractionation; determination of serum aminotransferase, alkaline phosphatase, and albumin concentrations; and prothrombin time tests. Enzyme tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) are helpful in differentiating between a hepatocellular process and a cholestatic process (**Table 330-1**; Fig. 45-1)—a critical step in determining what additional workup is indicated. Patients with a hepatocellular process generally have a rise in the aminotransferases that is disproportionate to that in ALP, whereas patients with a cholestatic process have a rise in ALP that is disproportionate to that of the aminotransferases. The serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two.

In addition to enzyme tests, all jaundiced patients should have additional blood tests—specifically, an albumin level and a prothrombin time—to assess liver function. A low albumin level suggests a chronic process such as cirrhosis or cancer. A normal albumin level is suggestive of a more acute process such as viral hepatitis or choledocholithiasis. An elevated prothrombin time indicates either vitamin K deficiency due to prolonged jaundice and malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to correct with parenteral administration of vitamin K indicates severe hepatocellular injury.

The results of the bilirubin, enzyme, albumin, and prothrombin time tests will usually indicate whether a jaundiced patient has a hepatocellular or a cholestatic disease and offer some indication of the duration and severity of the disease. The causes and evaluations of hepatocellular and cholestatic diseases are quite different.

Hepatocellular Conditions Hepatocellular diseases that can cause jaundice include viral hepatitis, drug or environmental toxicity, alcohol, and end-stage cirrhosis from any cause (**Table 45-2**). Wilson's disease occurs primarily in young adults. Autoimmune hepatitis is typically seen in young to middle-aged women, but may affect men and women of any age. Alcoholic hepatitis can be differentiated from viral and toxin-related hepatitis by the pattern of the aminotransferases: patients with alcoholic hepatitis typically have an AST-to-ALT ratio of at least 2:1, and the AST level rarely exceeds 300 U/L. Patients with acute viral hepatitis and toxin-related injury severe enough to produce jaundice typically have aminotransferase levels >500 U/L, with the ALT greater than or equal to the AST. While ALT and AST values <8 times normal may be seen in either hepatocellular or cholestatic liver disease, values 25 times normal or higher are seen primarily in acute hepatocellular diseases. Patients with jaundice from cirrhosis can have normal or only slightly elevated aminotransferase levels.

When the clinician determines that a patient has a hepatocellular disease, appropriate testing for acute viral hepatitis includes a hepatitis A IgM antibody assay, a hepatitis B surface antigen and core IgM antibody assay, a hepatitis C viral RNA test, and, depending on the circumstances, a hepatitis E IgM antibody assay. Because it can take

TABLE 45-2 Hepatocellular Conditions That May Produce Jaundice

Viral hepatitis
Hepatitis A, B, C, D, and E
Epstein-Barr virus
Cytomegalovirus
Herpes simplex virus
Alcoholic hepatitis
Chronic liver disease and cirrhosis
Drug toxicity
Predictable, dose-dependent (e.g., acetaminophen)
Unpredictable, idiosyncratic (e.g., isoniazid)
Environmental toxins
Vinyl chloride
Jamaica bush tea—pyrrolizidine alkaloids
Kava Kava
Wild mushrooms—*Amanita phalloides, A. verna*
Wilson's disease
Autoimmune hepatitis

many weeks for hepatitis C antibody to become detectable, its assay is an unreliable test if acute hepatitis C is suspected. Studies for hepatitis D and E viruses, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) may also be indicated. Ceruloplasmin is the initial screening test for Wilson's disease. Testing for autoimmune hepatitis usually includes an antinuclear antibody assay and measurement of specific immunoglobulins.

Drug-induced hepatocellular injury can be classified as either predictable or unpredictable. Predictable drug reactions are dose-dependent and affect all patients who ingest a toxic dose of the drug in question. The classic example is acetaminophen hepatotoxicity. Unpredictable or idiosyncratic drug reactions are not dose-dependent and occur in a minority of patients. A great number of drugs can cause idiosyncratic hepatic injury. Environmental toxins are also an important cause of hepatocellular injury. Examples include industrial chemicals such as vinyl chloride, herbal preparations containing pyrrolizidine alkaloids (Jamaica bush tea) or Kava, and the mushrooms *Amanita phalloides* and *A. verna*, which contain highly hepatotoxic amatoxins.

Cholestatic Conditions When the pattern of the liver tests suggests a cholestatic disorder, the next step is to determine whether it is intra- or extrahepatic cholestasis (Fig. 45-1). Distinguishing intrahepatic from extrahepatic cholestasis may be difficult. History, physical examination, and laboratory tests often are not helpful. The next appropriate test is an ultrasound. The ultrasound is inexpensive, does not expose the patient to ionizing radiation, and can detect dilation of the intra- and extrahepatic biliary tree with a high degree of sensitivity and specificity. The absence of biliary dilation suggests intrahepatic cholestasis, while its presence indicates extrahepatic cholestasis. False-negative results occur in patients with partial obstruction of the common bile duct or in patients with cirrhosis or primary sclerosing cholangitis (PSC), in which scarring prevents the intrahepatic ducts from dilating.

Although ultrasonography may indicate extrahepatic cholestasis, it rarely identifies the site or cause of obstruction. The distal common bile duct is a particularly difficult area to visualize by ultrasound because of overlying bowel gas. Appropriate next tests include CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasound (EUS). CT scanning and MRCP are better than ultrasonography for assessing the head of the pancreas and for identifying choledocholithiasis in the distal common bile duct, particularly when the ducts are not dilated. ERCP is the "gold standard" for identifying choledocholithiasis. Beyond its diagnostic capabilities, ERCP allows therapeutic interventions, including the removal of common bile duct stones and the placement of stents. PTC can provide the same information as ERCP and it also allows for intervention in patients in whom ERCP is unsuccessful due to proximal biliary obstruction or altered gastrointestinal anatomy. MRCP has replaced ERCP as the initial diagnostic test in cases where the need for intervention is thought to be small. EUS displays sensitivity and specificity comparable to that of MRCP in the detection of bile duct obstruction. EUS also allows biopsy of suspected malignant lesions, but is invasive and requires sedation.

In patients with apparent *intrahepatic cholestasis*, the diagnosis is often made by serologic testing in combination with percutaneous liver biopsy. The list of possible causes of intrahepatic cholestasis is long and varied **(Table 45-3)**. A number of conditions that typically cause a hepatocellular pattern of injury can also present as a cholestatic variant. Both hepatitis B and C viruses can cause cholestatic hepatitis (fibrosing cholestatic hepatitis). This disease variant has been reported in patients who have undergone solid organ transplantation. Hepatitis A and E, alcoholic hepatitis, and EBV or CMV infections may also present as cholestatic liver disease.

Drugs may cause intrahepatic cholestasis that is usually reversible after discontinuation of the offending agent, although it may take many months for cholestasis to resolve. Drugs most commonly associated with cholestasis are the anabolic and contraceptive steroids. Cholestatic hepatitis has been reported with chlorpromazine, imipramine, tolbutamide, sulindac, cimetidine, and erythromycin estolate. It also occurs in patients taking trimethoprim; sulfamethoxazole; and penicillin-based antibiotics such as ampicillin, dicloxacillin, and clavulanic acid. Rarely, cholestasis may be chronic and associated with progressive fibrosis despite early discontinuation of the offending drug. Chronic cholestasis has been associated with chlorpromazine and prochlorperazine.

Primary biliary cholangitis is an autoimmune disease predominantly affecting middle-aged women and characterized by

TABLE 45-3 Cholestatic Conditions That May Produce Jaundice

I. Intrahepatic
- A. Viral hepatitis
  1. Fibrosing cholestatic hepatitis—hepatitis B and C
  2. Hepatitis A, Epstein-Barr virus infection, cytomegalovirus infection
- B. Alcoholic hepatitis
- C. Drug toxicity
  1. Pure cholestasis—anabolic and contraceptive steroids
  2. Cholestatic hepatitis—chlorpromazine, erythromycin estolate
  3. Chronic cholestasis—chlorpromazine and prochlorperazine
- D. Primary biliary cholangitis
- E. Primary sclerosing cholangitis
- F. Vanishing bile duct syndrome
  1. Chronic rejection of liver transplants
  2. Sarcoidosis
  3. Drugs
- G. Congestive hepatopathy and ischemic hepatitis
- H. Inherited conditions
  1. Progressive familial intrahepatic cholestasis
  2. Benign recurrent intrahepatic cholestasis
- I. Cholestasis of pregnancy
- J. Total parenteral nutrition
- K. Nonhepatobiliary sepsis
- L. Benign postoperative cholestasis
- M. Paraneoplastic syndrome
- N. Veno-occlusive disease
- O. Graft-versus-host disease
- P. Infiltrative disease
  1. Tuberculosis
  2. Lymphoma
  3. Amyloidosis
- Q. Infections
  1. Malaria
  2. Leptospirosis

II. Extrahepatic
- A. Malignant
  1. Cholangiocarcinoma
  2. Pancreatic cancer
  3. Gallbladder cancer
  4. Ampullary cancer
  5. Malignant involvement of the porta hepatis lymph nodes
- B. Benign
  1. Choledocholithiasis
  2. Postoperative biliary strictures
  3. Primary sclerosing cholangitis
  4. Chronic pancreatitis
  5. AIDS cholangiopathy
  6. Mirizzi's syndrome
  7. Parasitic disease (ascariasis)

progressive destruction of interlobular bile ducts. The diagnosis is made by the detection of antimitochondrial antibody, which is found in 95% of patients. *Primary sclerosing cholangitis* is characterized by the destruction and fibrosis of larger bile ducts. The diagnosis of PSC is made with cholangiography (either MRCP or ERCP), which demonstrates the pathognomonic segmental strictures. Approximately 75% of patients with PSC have inflammatory bowel disease.

The *vanishing bile duct syndrome* and *adult bile ductopenia* are rare conditions in which a decreased number of bile ducts are seen in liver biopsy specimens. The histologic picture is similar to that in primary biliary cholangitis. This picture is seen in patients who develop chronic rejection after liver transplantation and in those who develop graft-versus-host disease after bone marrow transplantation. Vanishing bile duct syndrome also occurs in rare cases of sarcoidosis, in patients taking certain drugs (including chlorpromazine), and idiopathically.

There are also familial forms of intrahepatic cholestasis. The familial intrahepatic cholestatic syndromes include *progressive familial intrahepatic cholestasis* (PFIC) *types 1–3* and *benign recurrent intrahepatic cholestasis* (BRIC) types 1 and 2. BRIC is characterized by episodic attacks of pruritus, cholestasis, and jaundice beginning at any age, which can be debilitating but does not lead to chronic liver disease. Serum bile acids are elevated during episodes, but serum γ-glutamyltransferase (γ-GT) activity is normal. PFIC disorders begin at childhood and are progressive in nature. All three types of PFIC are associated with progressive cholestasis, elevated levels of serum bile acids, similar phenotypes but different genetic mutations. Only type 3 PFIC is associated with high levels of γ-GT. *Cholestasis of pregnancy* occurs in the second and third trimesters and resolves after delivery. Its cause is unknown, but the condition is probably inherited, and cholestasis can be triggered by estrogen administration.

Other causes of intrahepatic cholestasis include total parenteral nutrition (TPN); nonhepatobiliary sepsis; benign postoperative cholestasis; and a paraneoplastic syndrome associated with a number of different malignancies, including Hodgkin's disease, medullary thyroid cancer, renal cell cancer, renal sarcoma, T cell lymphoma, prostate cancer, and several gastrointestinal malignancies. The term *Stauffer's syndrome* has been used for intrahepatic cholestasis specifically associated with renal cell cancer. In patients developing cholestasis in the intensive care unit, the major considerations should be sepsis, ischemic hepatitis ("shock liver"), and TPN jaundice. Jaundice occurring after bone marrow transplantation is most likely due to veno-occlusive disease or graft-versus-host disease. In addition to hemolysis, sickle cell disease may cause intrahepatic and extrahepatic cholestasis. Jaundice is a late finding in heart failure caused by hepatic congestion and hepatocellular hypoxia. Ischemic hepatitis is a distinct entity of acute hypoperfusion characterized by an acute and dramatic elevation in the serum aminotransferases followed by a gradual peak in serum bilirubin.

Jaundice with associated liver dysfunction can be seen in severe cases of *Plasmodium falciparum* malaria. The jaundice in these cases is due to a combination of indirect hyperbilirubinemia from hemolysis and both cholestatic and hepatocellular jaundice. Weil's disease, a severe presentation of leptospirosis, is marked by jaundice with renal failure, fever, headache, and muscle pain.

Causes of *extrahepatic cholestasis* can be split into malignant and benign (Table 45-3). Malignant causes include pancreatic, gallbladder, and ampullary cancers as well as cholangiocarcinoma. This last malignancy is most commonly associated with PSC and is exceptionally difficult to diagnose because its appearance is often identical to that of PSC. Pancreatic and gallbladder tumors as well as cholangiocarcinoma are rarely resectable and have poor prognoses. Ampullary carcinoma has the highest surgical cure rate of all the tumors that present as painless jaundice. Hilar lymphadenopathy due to metastases from other cancers may cause obstruction of the extrahepatic biliary tree.

Choledocholithiasis is the most common cause of extrahepatic cholestasis. The clinical presentation can range from mild right-upper-quadrant discomfort with only minimal elevations of enzyme test values to ascending cholangitis with jaundice, sepsis, and circulatory collapse. PSC may occur with clinically important strictures limited to the extrahepatic biliary tree. IgG4-associated cholangitis is marked by stricturing of the biliary tree. It is critical that the clinician differentiate this condition from PSC as it is responsive to glucocorticoid therapy. In rare instances, chronic pancreatitis causes strictures of the distal common bile duct, where it passes through the head of the pancreas. AIDS cholangiopathy is a condition that is usually due to infection of the bile duct epithelium with CMV or cryptosporidia and has a cholangiographic appearance similar to that of PSC. The affected patients usually present with greatly elevated serum alkaline phosphatase levels (mean, 800 IU/L), but the bilirubin level is often near normal. These patients do not typically present with jaundice.

GLOBAL CONSIDERATIONS

While extrahepatic biliary obstruction and drugs are common causes of new-onset jaundice in developed countries, infections remain the leading cause in developing countries. Liver involvement and jaundice are observed with numerous infections, particularly malaria, babesiosis, severe leptospirosis, infections due to *Mycobacterium tuberculosis* and the *Mycobacterium avium* complex, typhoid fever, infection with hepatitis viruses A–E, EBV, CMV, Ebola virus, late phases of yellow fever, dengue hemorrhagic fever, schistosomiasis, fascioliasis, clonorchiasis, opisthorchiasis, ascariasis, echinococcosis, hepatosplenic candidiasis, disseminated histoplasmosis, cryptococcosis, coccidioimycosis, ehrlichiosis, chronic Q fever, yersiniosis, brucellosis, syphilis, and leprosy. Bacterial infections that do not necessarily involve the liver and bile ducts may also lead to jaundice, as in cholestasis of sepsis. The presence of fever or abdominal pain suggests concurrent infection, sepsis, or complications from gallstones. The development of encephalopathy and coagulopathy in a jaundiced patient with no preexisting liver disease signifies acute liver failure, which warrants urgent liver transplant evaluation.

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This chapter is a revised version of chapters that have appeared in prior editions of Harrison's in which Marshall M. Kaplan was a co-author together with Daniel Pratt.

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46 Abdominal Swelling and Ascites

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ABDOMINAL SWELLING

Abdominal swelling is a manifestation of numerous diseases. Patients may complain of bloating or abdominal fullness and may note increasing abdominal girth on the basis of increased clothing or belt size. Abdominal discomfort is often reported, but pain is less frequent. When abdominal pain does accompany swelling, it is frequently the result of an intraabdominal infection, peritonitis, or pancreatitis. Patients with abdominal distention from *ascites* (fluid in the abdomen)

may report the new onset of an inguinal or umbilical hernia. Dyspnea may result from pressure against the diaphragm and the inability to expand the lungs fully.

CAUSES

The causes of abdominal swelling can be remembered conveniently as the *six Fs*: flatus, fat, fluid, fetus, feces, or a "fatal growth" (often a neoplasm).

Flatus Abdominal swelling may be the result of increased intestinal gas. The normal small intestine contains ~200 mL of gas made up of nitrogen, oxygen, carbon dioxide, hydrogen, and methane. Nitrogen and oxygen are consumed (swallowed), whereas carbon dioxide, hydrogen, and methane are produced intraluminally by bacterial fermentation. Increased intestinal gas can occur in a number of conditions. *Aerophagia*, the swallowing of air, can result in increased amounts of oxygen and nitrogen in the small intestine and lead to abdominal swelling. Aerophagia typically results from gulping food; chewing gum; smoking; or as a response to anxiety, which can lead to repetitive belching. In some cases, increased intestinal gas is the consequence of bacterial metabolism of excess fermentable substances such as lactose and other oligosaccharides, which can lead to production of hydrogen, carbon dioxide, or methane. In many cases, the precise cause of abdominal distention cannot be determined. In some persons, particularly those with irritable bowel syndrome and bloating, the subjective sense of abdominal pressure is attributable to impaired intestinal transit of gas rather than increased gas volume. Abdominal distention—an objective increase in girth—is the result of a lack of coordination between diaphragmatic contraction and anterior abdominal wall relaxation, a response in some cases to an increase in intraabdominal volume loads. Occasionally, increased lumbar lordosis accounts for apparent abdominal distention.

Fat Weight gain with an increase in abdominal fat can result in an increase in abdominal girth and can be perceived as abdominal swelling. Abdominal fat may be caused by an imbalance between caloric intake and energy expenditure associated with a poor diet and sedentary lifestyle; it also can be a manifestation of certain diseases, such as Cushing's syndrome. Excess abdominal fat has been associated with an increased risk of insulin resistance and cardiovascular disease.

Fluid The accumulation of fluid within the abdominal cavity (ascites) often results in abdominal distention and is discussed in detail below.

Fetus Pregnancy results in increased abdominal girth. Typically, an increase in abdominal size is first noted at 12–14 weeks of gestation, when the uterus moves from the pelvis into the abdomen. Abdominal distention may be seen before this point as a result of fluid retention and relaxation of the abdominal muscles.

Feces In the setting of severe constipation or intestinal obstruction, increased stool in the colon leads to increased abdominal girth. These conditions are often accompanied by abdominal discomfort or pain, nausea, and vomiting and can be diagnosed by imaging studies.

Fatal Growth An abdominal mass can result in abdominal swelling. Neoplasms, abscesses, or cysts can grow to sizes that lead to increased abdominal girth. Enlargement of the intraabdominal organs, specifically the liver (hepatomegaly) or spleen (splenomegaly), or an abdominal aortic aneurysm can result in abdominal distention. Bladder distention also may result in abdominal swelling.

APPROACH TO THE PATIENT

Abdominal Swelling

HISTORY

Determining the etiology of abdominal swelling begins with history-taking and a physical examination. Patients should be questioned regarding symptoms suggestive of malignancy, including weight loss, night sweats, and anorexia. Inability to pass stool or flatus together with nausea or vomiting suggests bowel obstruction, severe constipation, or an ileus (lack of peristalsis). Increased eructation and flatus may point toward aerophagia or increased intestinal production of gas. Patients should be questioned about risk factors for or symptoms of chronic liver disease, including excessive alcohol use and jaundice, which suggest ascites. Patients should also be asked about symptoms of other medical conditions, including heart failure and tuberculosis, which may cause ascites.

PHYSICAL EXAMINATION

Physical examination should include an assessment for signs of systemic disease. The presence of lymphadenopathy, especially supraclavicular lymphadenopathy (*Virchow's node*), suggests metastatic abdominal malignancy. Care should be taken during the cardiac examination to evaluate for elevation of jugular venous pressure (JVP); *Kussmaul's sign* (elevation of the JVP during inspiration); a pericardial knock, which may be seen in heart failure or constrictive pericarditis; or a murmur of tricuspid regurgitation. Spider angiomas, palmar erythema, dilated superficial veins around the umbilicus (*caput medusae*), and gynecomastia suggest chronic liver disease.

The abdominal examination should begin with inspection for the presence of uneven distention or an obvious mass. Auscultation should follow. The absence of bowel sounds or the presence of high-pitched localized bowel sounds points toward an ileus or intestinal obstruction. An umbilical venous hum may suggest the presence of portal hypertension, and a harsh bruit over the liver is heard rarely in patients with hepatocellular carcinoma or alcoholic hepatitis. Abdominal swelling caused by intestinal gas can be differentiated from swelling caused by fluid or a solid mass by percussion; an abdomen filled with gas is tympanic, whereas an abdomen containing a mass or fluid is dull to percussion. The absence of abdominal dullness, however, does not exclude ascites, because a minimum of 1500 mL of ascitic fluid is required for detection on physical examination. Finally, the abdomen should be palpated to assess for tenderness, a mass, enlargement of the spleen or liver, or presence of a nodular liver suggesting cirrhosis or tumor. Light palpation of the liver may detect pulsations suggesting retrograde vascular flow from the heart in patients with right-sided heart failure, particularly tricuspid regurgitation.

IMAGING AND LABORATORY EVALUATION

Abdominal x-rays can be used to detect dilated loops of bowel suggesting intestinal obstruction or ileus. Abdominal ultrasonography can detect as little as 100 mL of ascitic fluid, hepatosplenomegaly, a nodular liver, or a mass. Ultrasonography is often inadequate to detect retroperitoneal lymphadenopathy or a pancreatic lesion because of overlying bowel gas. If malignancy or pancreatic disease is suspected, CT can be performed. CT may also detect changes associated with advanced cirrhosis and portal hypertension **(Fig. 46-1)**.

Laboratory evaluation should include liver biochemical testing, serum albumin level measurement, and prothrombin time determination (international normalized ratio) to assess hepatic function as well as a complete blood count to evaluate for the presence of cytopenias that may result from portal hypertension or of leukocytosis, anemia, and thrombocytosis that may result from systemic infection. Serum amylase and lipase levels should be checked to evaluate the patient for acute pancreatitis. Urinary protein quantitation is indicated when nephrotic syndrome, which may cause ascites, is suspected.

In selected cases, the hepatic venous pressure gradient (pressure across the liver between the portal and hepatic veins) can be measured via cannulation of the hepatic vein to confirm that ascites is caused by cirrhosis **(Chap. 337)**. In some cases, a liver biopsy may be necessary to confirm cirrhosis.

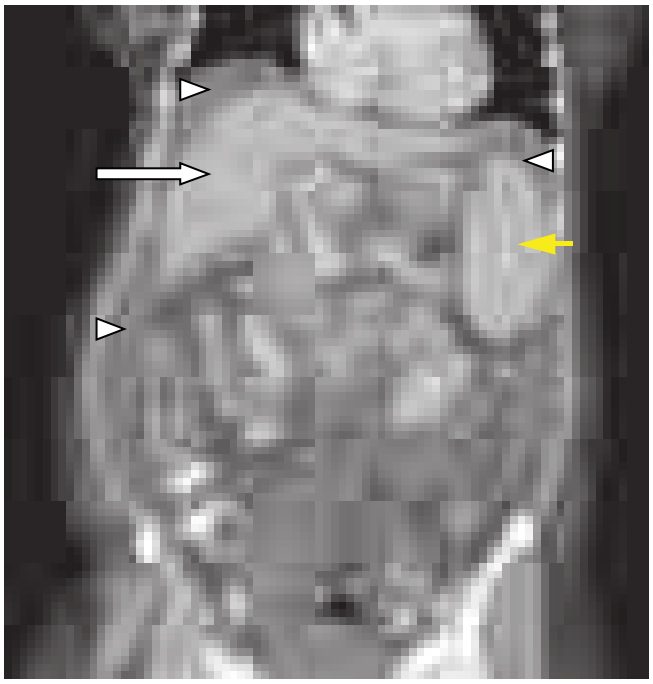

FIGURE 46-1 CT of a patient with a cirrhotic, nodular liver (*white arrow*), splenomegaly (*yellow arrow*), and ascites (*arrowheads*).

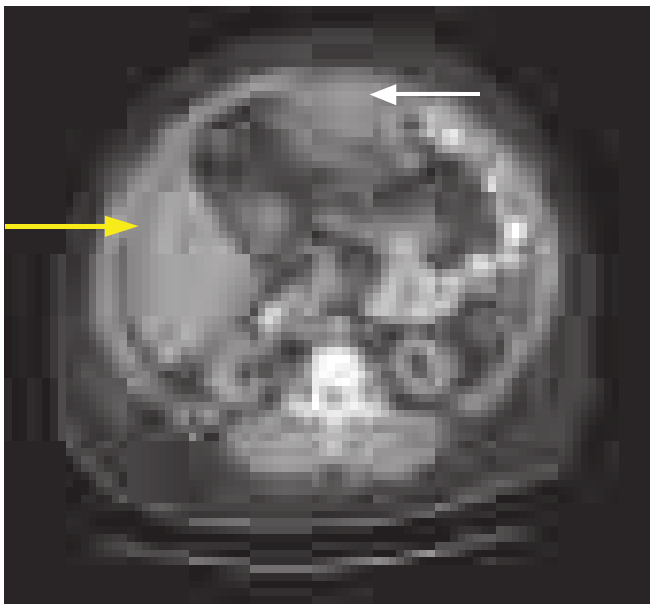

FIGURE 46-2 CT of a patient with peritoneal carcinomatosis (*white arrow*) and ascites (*yellow arrow*).

ASCITES

PATHOGENESIS IN THE PRESENCE OF CIRRHOSIS

Ascites in patients with cirrhosis is the result of portal hypertension and renal salt and water retention. Similar mechanisms contribute to ascites formation in heart failure. Portal hypertension signifies elevation of the pressure within the portal vein. According to Ohm's law, pressure is the product of resistance and flow. Increased hepatic resistance occurs by several mechanisms. First, the development of hepatic fibrosis, which defines cirrhosis, disrupts the normal architecture of the hepatic sinusoids and impedes normal blood flow through the liver. Second, activation of hepatic stellate cells, which mediate fibrogenesis, leads to smooth-muscle contraction and fibrosis. Finally, cirrhosis is associated with a decrease in endothelial nitric oxide synthetase (eNOS) production, which results in decreased nitric oxide production and increased intrahepatic vasoconstriction.

The development of cirrhosis is also associated with increased systemic circulating levels of nitric oxide (contrary to the decrease seen intrahepatically) as well as increased levels of vascular endothelial growth factor and tumor necrosis factor that result in splanchnic arterial vasodilation. Vasodilation of the splanchnic circulation results in pooling of blood and a decrease in the effective circulating volume, which is perceived by the kidneys as hypovolemia. Compensatory vasoconstriction via release of antidiuretic hormone ensues; the consequences are free water retention and activation of the sympathetic nervous system and the renin angiotensin aldosterone system, which lead in turn to renal sodium and water retention.

PATHOGENESIS IN THE ABSENCE OF CIRRHOSIS

Ascites in the absence of cirrhosis generally results from peritoneal carcinomatosis, peritoneal infection, or pancreatic disease. Peritoneal carcinomatosis can result from primary peritoneal malignancies such as mesothelioma or sarcoma, abdominal malignancies such as gastric or colonic adenocarcinoma, or metastatic disease from breast or lung carcinoma or melanoma **(Fig. 46-2)**. The tumor cells lining the peritoneum produce a protein-rich fluid that contributes to the development of ascites. Fluid from the extracellular space is drawn into the peritoneum, further contributing to the development of ascites. Tuberculous peritonitis causes ascites via a similar mechanism; tubercles deposited on the peritoneum exude a proteinaceous fluid. Pancreatic ascites results from leakage of pancreatic enzymes into the peritoneum.

CAUSES

Cirrhosis accounts for 84% of cases of ascites. Cardiac ascites, peritoneal carcinomatosis, and "mixed" ascites resulting from cirrhosis and a second disease account for 10–15% of cases. Less common causes of ascites include massive hepatic metastasis, infection (tuberculosis, *Chlamydia* infection), pancreatitis, and renal disease (nephrotic syndrome). Rare causes of ascites include hypothyroidism and familial Mediterranean fever.

EVALUATION

Once the presence of ascites has been confirmed, the etiology of the ascites is best determined by *paracentesis*, a bedside procedure in which a needle or small catheter is passed transcutaneously to extract ascitic fluid from the peritoneum. The lower quadrants are the most frequent sites for paracentesis. The left lower quadrant is preferred because of the greater depth of ascites and the thinner abdominal wall. Paracentesis is a safe procedure even in patients with coagulopathy; complications, including abdominal wall hematomas, hypotension, hepatorenal syndrome, and infection, are infrequent.

Once ascitic fluid has been extracted, its gross appearance should be examined. Turbid fluid can result from the presence of infection or tumor cells. White, milky fluid indicates a triglyceride level >200 mg/dL (and often >1000 mg/dL), which is the hallmark of *chylous ascites*. Chylous ascites results from lymphatic disruption that may occur with trauma, cirrhosis, tumor, tuberculosis, or certain congenital abnormalities. Dark brown fluid can reflect a high bilirubin concentration and indicates biliary tract perforation. Black fluid may indicate the presence of pancreatic necrosis or metastatic melanoma.

The ascitic fluid should be sent for measurement of albumin and total protein levels, cell and differential counts, and, if infection is suspected, Gram's stain and culture, with inoculation into blood culture bottles at the patient's bedside to maximize the yield. A serum albumin level should be measured simultaneously to permit calculation of the *serum-ascites albumin gradient* (SAAG).

The SAAG is useful for distinguishing ascites caused by portal hypertension from nonportal hypertensive ascites **(Fig. 46-3)**. The SAAG reflects the pressure within the hepatic sinusoids and correlates with the hepatic venous pressure gradient. The SAAG is calculated by subtracting the ascitic albumin concentration from the serum albumin

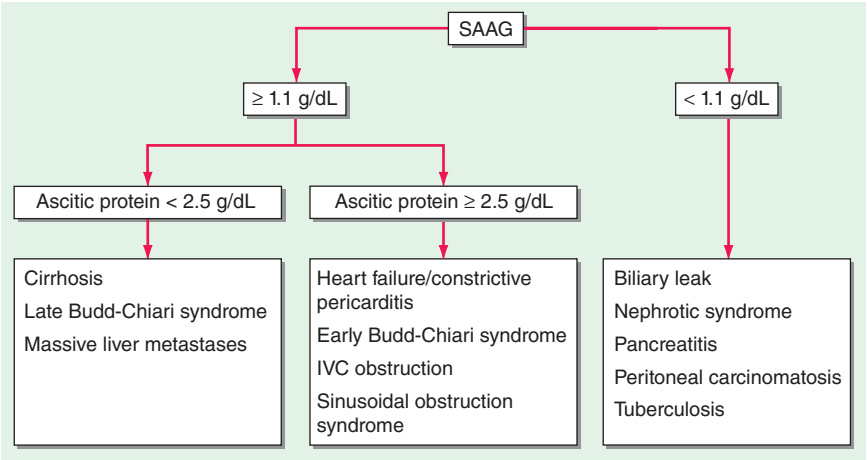

FIGURE 46-3 Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG). IVC, inferior vena cava.

level and does not change with diuresis. A SAAG ≥1.1 g/dL reflects the presence of portal hypertension and indicates that the ascites is due to increased pressure in the hepatic sinusoids. According to Starling's law, a high SAAG reflects the oncotic pressure that counterbalances the portal pressure. Possible causes include cirrhosis, cardiac ascites, hepatic vein thrombosis (Budd-Chiari syndrome), sinusoidal obstruction syndrome (veno-occlusive disease), or massive liver metastases. A SAAG <1.1 g/dL indicates that the ascites is not related to portal hypertension, as in tuberculous peritonitis, peritoneal carcinomatosis, or pancreatic ascites.

For high-SAAG (≥1.1) ascites, the ascitic protein level can provide further clues to the etiology (Fig. 46-3). An ascitic protein level of ≥2.5 g/dL indicates that the hepatic sinusoids are normal and are allowing passage of protein into the ascites, as occurs in cardiac ascites, early Budd-Chiari syndrome, or sinusoidal obstruction syndrome. An ascitic protein level <2.5 g/dL indicates that the hepatic sinusoids have been damaged and scarred and no longer allow passage of protein, as occurs with cirrhosis, late Budd-Chiari syndrome, or massive liver metastases. Pro-brain-type natriuretic peptide (BNP) is a natriuretic hormone released by the heart as a result of increased volume and ventricular wall stretch. High levels of BNP in serum occur in heart failure and may be useful in identifying heart failure as the cause of high-SAAG ascites.

Further tests are indicated only in specific clinical circumstances. When secondary peritonitis resulting from a perforated hollow viscus is suspected, ascitic glucose and lactate dehydrogenase (LDH) levels can be measured. In contrast to "spontaneous" bacterial peritonitis, which may complicate cirrhotic ascites (see "Complications," below), secondary peritonitis is suggested by an ascitic glucose level <50 mg/dL, an ascitic LDH level higher than the serum LDH level, and the detection of multiple pathogens on ascitic fluid culture. When pancreatic ascites is suspected, the ascitic amylase level should be measured and is typically >1000 mg/dL. Cytology can be useful in the diagnosis of peritoneal carcinomatosis. At least 50 mL of fluid should be obtained and sent for immediate processing. Tuberculous peritonitis is typically associated with ascitic fluid lymphocytosis but can be difficult to diagnose by paracentesis. A smear for acid-fast bacilli has a diagnostic sensitivity of only 0 to 3%; a culture increases the sensitivity to 35–50%. In patients without cirrhosis, an elevated ascitic adenosine deaminase level has a sensitivity of >90% when a cut-off value of 30–45 U/L is used. When the cause of ascites remains uncertain, laparotomy or laparoscopy with peritoneal biopsies for histology and culture remains the gold standard.

TREATMENT

Ascites

The initial treatment for cirrhotic ascites is restriction of sodium intake to 2 g/d. When sodium restriction alone is inadequate to control ascites, oral diuretics—typically the combination of spironolactone and furosemide—are used. Spironolactone is an aldosterone antagonist that inhibits sodium resorption in the distal convoluted tubule of the kidney. Use of spironolactone may be limited by hyponatremia, hyperkalemia, and painful gynecomastia. If the gynecomastia is distressing, amiloride (5–40 mg/d) may be substituted for spironolactone. Furosemide is a loop diuretic that is generally combined with spironolactone in a ratio of 40:100; maximal daily doses of spironolactone and furosemide are 400 mg and 160 mg, respectively. Fluid intake may be restricted in patients with hyponatremia.

Refractory cirrhotic ascites is defined by the persistence of ascites despite sodium restriction and maximal (or maximally tolerated) diuretic use. Pharmacologic therapy for refractory ascites includes the addition of midodrine, an α_1-adrenergic agonist, or clonidine, an α_2-adrenergic agonist, to diuretic therapy. These agents act as vasoconstrictors, counteracting splanchnic vasodilation. Midodrine alone or in combination with clonidine improves systemic hemodynamics and control of ascites over that obtained with diuretics alone. Although β-adrenergic blocking agents (beta blockers) are often prescribed to prevent variceal hemorrhage in patients with cirrhosis, the use of beta blockers in patients with refractory ascites may be associated with decreased survival rates.

When medical therapy alone is insufficient, refractory ascites can be managed by repeated large-volume paracentesis (LVP) or a transjugular intrahepatic peritoneal shunt (TIPS)—a radiologically placed portosystemic shunt that decompresses the hepatic sinusoids. Intravenous infusion of albumin accompanying LVP decreases the risk of "post-paracentesis circulatory dysfunction" and death. Patients undergoing LVP should receive IV albumin infusions of 6–8 g/L of ascitic fluid removed. TIPS placement is superior to LVP in reducing the reaccumulation of ascites but is associated with an increased frequency of hepatic encephalopathy, with no difference in mortality rates.

Malignant ascites does not respond to sodium restriction or diuretics. Patients must undergo serial LVPs, transcutaneous drainage catheter placement, or, rarely, creation of a peritoneovenous shunt (a shunt from the abdominal cavity to the vena cava).

Ascites caused by tuberculous peritonitis is treated with standard antituberculosis therapy. Noncirrhotic ascites of other causes is treated by correction of the precipitating condition.

COMPLICATIONS

Spontaneous bacterial peritonitis (SBP; **Chap. 127**) is a common and potentially lethal complication of cirrhotic ascites. Occasionally, SBP also complicates ascites caused by nephrotic syndrome, heart failure, acute hepatitis, and acute liver failure but is rare in malignant ascites.

Patients with SBP generally note an increase in abdominal girth; however, abdominal tenderness is found in only 40% of patients, and rebound tenderness is uncommon. Patients may present with fever, nausea, vomiting, or the new onset of or exacerbation of preexisting hepatic encephalopathy.

In hospitalized patients with ascites, paracentesis within 12 hours of admission reduces mortality because of early detection of SBP. SBP is defined by a polymorphonuclear neutrophil (PMN) count of ≥250/μL in the ascitic fluid. Cultures of ascitic fluid typically reveal one bacterial pathogen. The presence of multiple pathogens in the setting of an elevated ascitic PMN count suggests *secondary peritonitis* from a ruptured viscus or abscess **(Chap. 127)**. The presence of multiple pathogens without an elevated PMN count suggests bowel perforation from the paracentesis needle. SBP is generally the result of enteric bacteria that have translocated across an edematous bowel wall. The most common pathogens are gram-negative rods, including *Escherichia coli* and *Klebsiella*, as well as streptococci and enterococci.

Treatment of SBP with an antibiotic such as IV cefotaxime is effective against gram-negative and gram-positive aerobes. A 5-day course of treatment is sufficient if the patient improves clinically. Nosocomial or health care–acquired SBP is frequently caused by multidrug-resistant bacteria, and initial antibiotic therapy should be guided by the local bacterial epidemiology.

Cirrhotic patients with a history of SBP, an ascitic fluid total protein concentration <1 g/dL, or active gastrointestinal bleeding should receive prophylactic antibiotics to prevent SBP; oral daily norfloxacin is commonly used. Diuresis increases the activity of ascitic fluid protein opsonins and may decrease the risk of SBP.

Hepatic hydrothorax occurs when ascites, often caused by cirrhosis, migrates via fenestrae in the diaphragm into the pleural space. This condition can result in shortness of breath, hypoxia, and infection. Treatment is similar to that for cirrhotic ascites and includes sodium restriction, diuretics, and, if needed, thoracentesis or TIPS placement. Chest tube placement should be avoided.

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47 Dysuria, Bladder Pain, and the Interstitial Cystitis/Bladder Pain Syndrome

John W. Warren

Dysuria and bladder pain are two symptoms that commonly call attention to the lower urinary tract.

DYSURIA

Dysuria, or pain that occurs during urination, is commonly perceived as burning or stinging in the urethra and is a symptom of several syndromes. The presence or absence of *other* symptoms is often helpful in distinguishing among these conditions. Some of these syndromes differ between men and women.

Women Approximately 50% of women experience dysuria at some time in their lives; ~20% report having had dysuria within the past year. Most dysuria syndromes in women can be categorized into two broad groups: bacterial cystitis and lower genital tract infections.

Bacterial cystitis is usually caused by *Escherichia coli*; a few other gram-negative rods and *Staphylococcus saprophyticus* also can be responsible. Bacterial cystitis is acute in onset and manifests not only as dysuria but also as urinary frequency, urinary urgency, suprapubic pain, and/or hematuria.

The lower genital tract infections include vaginitis, urethritis, and ulcerative lesions; many of these infections are caused by sexually transmitted organisms and should be considered particularly in young women who have new or multiple sexual partners or whose partners do not use condoms. The onset of dysuria associated with these syndromes is more gradual than in bacterial cystitis and is thought (but not proven) to result from the flow of urine over damaged epithelium. Frequency, urgency, suprapubic pain, and hematuria are reported less frequently than in bacterial cystitis. Vaginitis, caused by *Candida albicans* or *Trichomonas vaginalis*, presents as vaginal discharge or irritation. Urethritis is a consequence of infection by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Ulcerative genital lesions may be caused by herpes simplex virus and several other specific organisms.

Among women presenting with dysuria, the probability of bacterial cystitis is ~50%. This figure rises to >90% if four criteria are met: dysuria and frequency without vaginal discharge or irritation. Present standards suggest that women meeting these four criteria, if they are otherwise healthy, are not pregnant, and have an apparently normal urinary tract, can be diagnosed with uncomplicated bacterial cystitis and treated empirically with appropriate antibiotics. Other women with dysuria should be further evaluated by urine dipstick, urine culture, and a pelvic examination.

Men Dysuria is less common among men. The syndromes presenting as dysuria are similar to those in women but with some important distinctions.

In the majority of men with dysuria, frequency, urgency, and/or suprapubic, penile, and/or perineal pain, the prostate is involved, either as the source of infection or as an obstruction to urine flow. Bacterial prostatitis is usually caused by *E. coli* or another gram-negative rod, with one of two presentations. *Acute bacterial prostatitis* presents with fever and chills; prostate examination should be gentle or not performed at all, as massage may result in a wave of bacteremia. *Chronic bacterial prostatitis* presents as recurrent episodes of bacterial cystitis; prostate examination with massage demonstrates prostatic bacteria

and leukocytes. *Benign prostatic hyperplasia* (BPH) can obstruct urine flow, with consequent symptoms of weak stream, hesitancy, and dribbling. If a bacterial infection develops behind the obstructing prostate, dysuria and other symptoms of cystitis will occur. Men whose symptoms are consistent with bacterial cystitis should be evaluated with urinalysis and urine culture.

Several sexually transmitted infections can manifest as dysuria. Urethritis (usually without urinary frequency) presents as a urethral discharge and can be caused by *C. trachomatis*, *N. gonorrhoeae*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, or *T. vaginalis*. Herpes simplex, chancroid, and other ulcerous lesions may present as dysuria, again without urinary frequency.

For further discussion, see Chaps. 130 and 131.

Either Women or Men Other causes of dysuria may be found in patients of either sex. Some cases are acute and include lower urinary tract stones, trauma, and urethral exposure to topical chemicals. Others may be relatively chronic and attributable to lower urinary tract cancers, certain medications, Behçet's syndrome, reactive arthritis, a poorly understood entity known as *chronic urethral syndrome*, or interstitial cystitis/bladder pain syndrome (see below).

BLADDER PAIN

Studies indicate that patients perceive pain as coming from the urinary bladder if it is suprapubic in location, alters with bladder filling or emptying, and/or is associated with urinary symptoms such as urgency and frequency. Bladder pain occurring acutely (i.e., over hours or a day or two) is helpful in distinguishing bacterial cystitis from urethritis, vaginitis, and other genital infections. Chronic or recurrent bladder pain may accompany lower urinary tract stones; bladder, uterine, cervical, vaginal, urethral, or prostate cancer; urethral diverticulum; cystitis induced by radiation or certain medications; tuberculous cystitis; bladder neck obstruction; neurogenic bladder; urogenital prolapse; or BPH. In the absence of these conditions, the diagnosis of interstitial cystitis/bladder pain syndrome (IC/BPS) should be considered.

INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Most clinicians with outpatient practices see undiagnosed cases of IC/BPS. This chronic condition is characterized by pain perceived to be from the urinary bladder, urinary urgency and frequency, and nocturia. As currently diagnosed, the majority of cases occur in women. Symptoms wax and wane for months or years or possibly even for the rest of the patient's life. The spectrum of symptom intensity is broad. The pain can be excruciating, urgency can be distressing, frequency can be up to 60 times per 24 h, and nocturia can cause sleep deprivation. These symptoms can disrupt daily activities, work schedules, and personal relationships; patients with IC/BPS report less life satisfaction than do those with end-stage renal disease.

IC/BPS is not a new disease, having first been described in the late nineteenth century in a patient with the symptoms described above and a single ulcer visible on cystoscopy (now called a *Hunner lesion* after the urologist who first reported it). Over the ensuing decades, it became clear that many patients with similar symptoms had no ulcer. It is now appreciated that ≤10% of patients with IC/BPS have a Hunner lesion. The definition of IC/BPS, its diagnostic features, and even its name continue to evolve. The American Urological Association has defined IC/BPS as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks' duration, in the absence of infection or other identifiable causes."

Many patients with IC/BPS also have other syndromes, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. These syndromes collectively are known as *functional somatic syndromes* (FSSs): chronic conditions in which pain and fatigue are prominent features but laboratory tests and histologic findings are normal. Like IC/BPS, the FSSs often are associated with depression and anxiety. The majority of FSSs affect more women than men, and more than one FSS can affect a single patient. Because of its similar features and comorbidity, IC/BPS sometimes is considered an FSS.

Epidemiology Contemporary population studies of IC/BPS in the United States indicate a prevalence of 3–6% among women and 2–4% among men. For decades, it was thought that IC/BPS occurred mostly in women. These prevalence findings, however, have generated research aimed at determining the proportion of men who have symptoms usually diagnosed as chronic prostatitis (now known as *chronic prostatitis/chronic pelvic pain syndrome*) but who actually have IC/BPS.

Among women, the average age at onset of IC/BPS symptoms is the early forties, but the range is from childhood through the early sixties. Risk factors (antecedent features that distinguish cases from controls) primarily have been FSSs. Indeed, the odds of IC/BPS increase with the number of such syndromes present. Surgery was long thought to be a risk factor for IC/BPS, but analyses adjusting for FSSs refuted that association. About one-third of patients appear to have bacterial cystitis at the onset of IC/BPS.

The natural history of IC/BPS is not known. Although studies from urology and urogynecology practices have been interpreted as showing that IC/BPS lasts for the lifetime of the patient, population studies suggest that some individuals with IC/BPS do not consult specialists and may not seek medical care at all, and most prevalence studies do not show an upward trend with age—a pattern that would be expected with incident cases throughout adulthood followed by lifetime persistence of a nonfatal disease. It may be reasonable to conclude that patients in a urology practice represent those with the most severe and recalcitrant IC/BPS.

Pathology For the ≤10% of IC/BPS patients who have a Hunner lesion, the term *interstitial cystitis* may indeed describe the histopathologic picture. Most of these patients have substantive inflammation, mast cells, and granulation tissue. However, in the 90% of patients without such lesions, the bladder mucosa and interstitium are relatively normal, with scant inflammation.

Etiology Numerous hypotheses about the pathogenesis of IC/BPS have been put forward. It is not surprising that most early theories focused on the bladder. For instance, IC/BPS has been investigated as a chronic bladder infection. Sophisticated technologies have not identified a causative organism in urine or in bladder tissue; however, the patients studied by these methods had IC/BPS of long duration, and the results do not preclude the possibility that infection may trigger the syndrome or may be a feature of early IC/BPS. Other inflammatory factors, including a role for mast cells, have been postulated, but (as noted above) the 90% of patients who do not have a Hunner ulcer have little bladder inflammation and do not have a prominence of mast cells in urine or in bladder tissue. Autoimmunity has been considered, but autoantibodies are low in titer, nonspecific, and thought to be a result rather than a cause of IC/BPS. Increased permeability of the bladder mucosa due to defective epithelium or glycosaminoglycan (the bladder's mucous coating) has been studied frequently, but the findings have been inconclusive.

Investigations of causes outside the bladder have been prompted by the presence of comorbid FSSs. Many patients with FSSs have abnormal pain sensitivity as evidenced by (1) low pain thresholds in body areas unrelated to the diagnosed syndrome, (2) dysfunctional descending neurologic control of tactile signals, and (3) enhanced brain responses to touch in functional neuroimaging studies. Moreover, in patients with IC/BPS, body surfaces remote from the bladder are more sensitive to pain than is the case in individuals without IC/BPS. All these findings are consistent with upregulation of sensory processing in the brain. Indeed, a prevailing theory is that these concomitantly occurring syndromes have in common an abnormality of brain processing of sensory input. However, antecedence is a critical criterion for causality, and no study has demonstrated that abnormal pain sensitivity precedes either IC/BPS or the FSSs.

Clinical Presentation In some patients, IC/BPS has a gradual onset and/or the cardinal symptoms of pain, urgency, frequency, and nocturia appear sequentially in no consistent order. Other patients can identify the exact date of onset of IC/BPS symptoms. More than half of the latter patients describe dysuria beginning on that date.

Only a minority of IC/BPS patients who obtain medical care soon after symptom onset have uropathogenic bacteria or leukocytes in the urine. These patients—and many others with new-onset IC/BPS—are treated with antibiotics for presumptive bacterial cystitis or, if male, chronic bacterial prostatitis. Persistent or recurring symptoms without bacteriuria eventually prompt a differential diagnosis, and IC/BPS is considered. Traditionally, the diagnosis of IC/BPS has been delayed for years, but recent interest in the disease appears to have shortened this interval.

Two-thirds of women with IC/BPS report two or more sites of pain. The most common site (involved in 80% of women) and generally the one with the most severe pain is the suprapubic area. About 35% of female patients have pain in the urethra, 25% in other parts of the vulva, and 30% in non-urogenital areas, mostly the low back and also the anterior or posterior thighs or the buttocks. The pain of IC/BPS is most commonly described as aching, pressing, throbbing, tender, and/or piercing. What may distinguish IC/BPS from other pelvic pain is that, in 95% of patients, bladder filling exacerbates the pain and/or bladder emptying relieves it. Almost as many patients report a puzzling pattern in which certain dietary substances worsen the pain of IC/BPS. Smaller majorities report that their IC/BPS pain is worsened by menstruation, stress, tight clothing, exercise, and riding in a car as well as during or after vaginal intercourse.

The urethral and vulvar pains of IC/BPS merit special mention. In addition to the descriptive adjectives for IC/BPS mentioned above, these pains commonly are described as burning, stinging, and sharp and as being worsened by touch, tampons, and vaginal intercourse. Patients report that urethral pain increases during urination and generally lessens afterward. These characteristics have commonly resulted in the diagnosis of the urethral pain of IC/BPS as chronic urethral syndrome and of the vulvar pain as vulvodynia.

In many patients with IC/BPS, there is a link between pain and urinary urgency; that is, two-thirds of patients describe the urge to urinate as a desire to relieve their bladder pain. Only 20% report that the urge stems from a desire to prevent incontinence; indeed, very few patients with IC/BPS are incontinent. As mentioned above, urinary frequency can be severe, with ~85% of patients voiding more than 10 times per 24 h and some as often as 60 times. Voiding continues through the night, and nocturia is common, frequent, and often associated with sleep deprivation.

Beyond these common symptoms of IC/BPS, additional urinary and other symptoms may be present. Among the urinary symptoms are difficulty in starting urine flow, perceptions of difficulty in emptying the bladder, and bladder spasms. Among the non-urinary symptoms are the manifestations of comorbid FSSs as well as symptoms that do not constitute recognized syndromes, such as numbness, muscle spasms, dizziness, ringing in the ears, and blurred vision.

The pain, urgency, and frequency of IC/BPS can be debilitating. Proximity to a bathroom is a continual focus, and patients report difficulties in the workplace, leisure activities, travel, and simply leaving home. Familial and sexual relationships can be strained.

Diagnosis Traditionally, IC/BPS has been considered a rare condition that is diagnosed by urologists at cystoscopy. However, this disorder is much more common than once was thought; it is now being considered earlier in its course and is being diagnosed and managed more often by primary care clinicians. Results of physical examination, urinalysis, and urologic procedures are insensitive and/or nonspecific. Thus, diagnosis is based on the presence of appropriate symptoms and the exclusion of diseases with a similar presentation.

Three categories of disorders can be considered in the differential diagnosis of IC/BPS. The first comprises diseases that manifest as bladder pain or urinary symptoms. Among the latter diseases is *overactive bladder*, a chronic condition of women and men that presents as urgency and frequency and can be distinguished from IC/BPS by the patient's history: pain is not a feature of overactive bladder, and its urgency arises from the need to avoid incontinence. Endometriosis is a special case: it can be asymptomatic or can cause pelvic pain, dysmenorrhea, and dyspareunia—i.e., types of pain that mimic IC/BPS. Endometrial implants on the bladder (although uncommon) can cause urinary symptoms, and the resulting syndrome can mimic IC/BPS. Even if endometriosis is identified, it is difficult in the absence of bladder implants to determine whether it is causative of or incidental to the symptoms of IC/BPS in a specific woman.

The second category of disorders encompasses the FSSs that can accompany IC/BPS. IC/BPS can be misdiagnosed as gynecologic chronic pelvic pain, irritable bowel syndrome, or fibromyalgia. The correct diagnosis may be entertained only when either changes of pain with altered bladder volume or urinary symptoms become more prominent.

The third category involves syndromes that IC/BPS mimics by way of its referred pain, such as vulvodynia and chronic urethral syndrome. Therefore, IC/BPS should be considered in the differential diagnosis of persistent or recurrent "urinary tract infection" (UTI) with sterile urine cultures; "overactive bladder" with pain; chronic pelvic pain, endometriosis, vulvodynia, or FSSs with urinary symptoms; and "chronic prostatitis." Important clues to the diagnosis of IC/BPS are changes of pain with bladder volume or with certain foods or drinks.

Cystoscopy under anesthesia formerly was thought to be necessary for the diagnosis of IC/BPS because of its capacity to reveal a Hunner lesion or—in the 90% of patients without an ulcer—petechial hemorrhages after bladder distention. However, because Hunner lesions are uncommon in IC/BPS and petechiae are nonspecific, cystoscopy is no longer necessary for diagnosis. Accordingly, the indications for urologic referral have evolved toward the need to rule out other diseases or to administer more advanced treatment.

A typical patient presents to the primary clinician after days, weeks, or months of pain, urgency, frequency, and/or nocturia. The presence of urinary nitrites, leukocytes, or uropathogenic bacteria should prompt treatment for UTI in women and for chronic bacterial prostatitis in men. Persistence or recurrence of symptoms in the absence of bacteriuria should prompt a pelvic examination for women, an assay for serum prostate-specific antigen for men, and urine cytology and inclusion of IC/BPS in the differential diagnosis for both sexes.

In the diagnosis of IC/BPS, inquiries about pain, pressure, and discomfort are useful; IC/BPS should be considered if any of these sensations are noted in one or more anterior or posterior sites between the umbilicus and the upper thighs. Nondirective questions about the effect of bladder volume changes include "As your next urination approaches, does this pain get better, get worse, or stay the same?" and "After you urinate, does this pain get better, get worse, or stay the same?" Establishing that the pain is exacerbated by the consumption of certain foods and drinks not only supports the diagnosis of IC/BPS but also serves as the basis for one of the first steps in managing this syndrome. A nondirective way to ask about urgency is to describe it to the patient as a compelling urge to urinate that is difficult to postpone; follow-up questions can determine whether this urge is intended to relieve pain or prevent incontinence. To assess severity and provide quantitative baseline measures, pain and urgency should be estimated by the patient on a scale of 0–10, with 0 being none and 10 the worst imaginable. Frequency per 24-h period should be determined and nocturia assessed as the number of times per night the patient is awakened by the need to urinate.

About half of patients with IC/BPS have intermittent or persistent microscopic hematuria; this manifestation and the need to exclude bladder stones or cancer require urologic or urogynecologic referral. Initiation of therapy for IC/BPS does not hamper subsequent urologic evaluation.

TREATMENT

Interstitial Cystitis/Bladder Pain Syndrome

The goal of therapy is to relieve the symptoms of IC/BPS; the challenge lies in the fact that no treatment is uniformly successful. However, most patients eventually obtain relief, generally with a multifaceted approach. The American Urological Association's guidelines for management of IC/BPS are an excellent resource.

The correct strategy is to begin with conservative therapies and proceed to riskier measures only if necessary and under the supervision of a urologist or urogynecologist. Conservative tactics include education, stress reduction, dietary changes, medications, pelvic-floor physical therapy, and treatment of associated FSSs.

Months or even years may have passed since the onset of symptoms, and the patient's life may have been disrupted continually, with repeated medical visits provoking frustration and dismay in both the patient and the physician. In this circumstance, simply giving a name to the syndrome is beneficial. The physician should discuss the disease, the diagnostic and therapeutic strategies, and the prognosis with the patient and with the spouse and/or other pertinent family members, who may need to be made aware that although IC/BPS has no visible manifestations, the patient is undergoing substantial pain and suffering. This information is particularly important for sexual partners, as exacerbation of pain during and after intercourse is a common feature of IC/BPS. Because stress can worsen IC/BPS symptoms, stress reduction and active measures such as yoga or meditation exercises may be suggested. The Interstitial Cystitis Association (*www.ichelp.com*) and the Interstitial Cystitis Network (*www.ic-network.com*) can be useful in this educational process.

Over time, many patients identify particular foods and drinks that exacerbate their symptoms. Common among these are chilies, chocolate, citrus fruits, tomatoes, alcohol, caffeinated drinks, and carbonated beverages; full lists of common trigger foods are available at the websites cited above. In constructing a benign diet, some patients find it useful to exclude all possible offenders and add items back into the diet one at a time to identify those that worsen their symptoms. Patients also should experiment with fluid volumes; some find relief with less fluid, others with more.

The pelvic floor is often tender in IC/BPS patients. Two randomized controlled trials showed that weekly physical therapy directed at relaxation of the pelvic muscles yielded significantly more relief than a similar schedule of general body massage. This intervention can be initiated under the direction of a knowledgeable physical therapist who recognizes that the objective is to relax the pelvic floor, not to strengthen it.

Among oral medications, nonsteroidal anti-inflammatory drugs are commonly used but are controversial and often unsuccessful. Two randomized controlled trials showed that amitriptyline can diminish IC/BPS symptoms if an adequate dose (≥50 mg per night) can be given. This drug is used not for its antidepressant activity but because of its proven effects on neuropathic pain; however, it is not approved by the U.S. Food and Drug Administration for treatment of IC/BPS. An initial dose of 10 mg at bedtime is increased weekly up to 75 mg (or less if a lower dose adequately relieves symptoms). Side effects can be expected and include dry mouth, weight gain, sedation, and constipation. If this regimen does not control symptoms adequately, pentosan polysulfate, a semisynthetic polysaccharide, can be added at a dose of 100 mg three times a day. Its theoretical effect is to replenish a possibly defective glycosaminoglycan layer over the bladder mucosa; randomized controlled trials suggest only a modest benefit over placebo. Adverse reactions are uncommon and include gastrointestinal symptoms, headache, and alopecia. Pentosan polysulfate has weak anticoagulant effects and probably should be avoided by patients with coagulation abnormalities.

Anecdotal reports suggest that successful therapy for one FSS is accompanied by diminished symptoms of other FSSs. As has been noted here, IC/BPS often is associated with one or several FSSs. Thus, it seems reasonable to hope that, to the extent that accompanying FSSs are treated successfully, the symptoms of IC/BPS will be relieved as well.

If several months of these therapies in combination do not relieve symptoms adequately, the patient should be referred to a urologist or urogynecologist who has access to additional modalities. Cystoscopy under anesthesia allows distention of the bladder with water, a procedure that provides ~40% of patients with several months of relief and can be repeated. For those few patients with a Hunner lesion, fulguration may offer relief. Solutions containing lidocaine, hyaluronic acid, or dimethyl sulfoxide can be instilled into the bladder, or botulinum toxin can be injected into the bladder wall. Physicians experienced in the care of IC/BPS patients have used anticonvulsants, narcotics, and cyclosporine as components of therapy. Pain specialists can be of assistance. Sacral neuromodulation can be tested with a temporary percutaneous electrode and, if effective, can be administered with an implanted device. In a very small number of patients with recalcitrant symptoms, surgeries, including cystoplasty, partial or total cystectomy, and urinary diversion, may provide relief.

FURTHER READING

Fitzgerald MP et al: Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. J Urol 187:2113, 2012.

Hanno PM et al: AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol 185:2162, 2011.

Hanno PM et al: Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol 193:1545, 2015.

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48 Azotemia and Urinary Abnormalities

David B. Mount

Normal kidney functions occur through numerous cellular processes to maintain body homeostasis. Disturbances in any of these functions can lead to abnormalities that may be detrimental to survival. Clinical manifestations of these disorders depend on the pathophysiology of renal injury and often are identified as a complex of symptoms, abnormal physical findings, and laboratory changes that constitute specific syndromes. These renal syndromes **(Table 48-1)** may arise from systemic illness or as primary renal disease. Nephrologic syndromes usually consist of several elements that reflect the underlying pathologic processes, typically including one or more of the following: (1) reduction in glomerular filtration rate (GFR), (2) abnormalities of urine sediment (red blood cells [RBCs], white blood cells [WBCs], casts, and crystals), (3) abnormal excretion of serum proteins (proteinuria), (4) disturbances in urine volume (oliguria, anuria, polyuria), (5) presence of hypertension and/or expanded total body fluid volume (edema), (6) electrolyte abnormalities, and (7) in some syndromes, fever/pain. The specific combination of these findings should permit identification of one of the major nephrologic syndromes (Table 48-1) and allow differential diagnoses to be narrowed so that the appropriate diagnostic and therapeutic course can be determined. All these syndromes and their associated diseases are discussed in more detail in subsequent chapters. This chapter focuses on several aspects of renal abnormalities that are critically important for distinguishing among those processes: (1) reduction in GFR, (2) alterations of the urinary sediment and/or protein excretion, and (3) abnormalities of urinary volume.

AZOTEMIA

ASSESSMENT OF GFR

Monitoring the GFR is important in both hospital and outpatient settings, and several different methodologies are available. GFR is the primary metric for kidney "function," and its direct measurement involves administration of a radioactive isotope (such as inulin or

TABLE 48-1 Initial Clinical and Laboratory Database for Defining Major Syndromes in Nephrology

SYNDROME	IMPORTANT CLUES TO DIAGNOSIS	COMMON FINDINGS	CHAP(S). DISCUSSING DISEASE-CAUSING SYNDROME
Acute or rapidly progressive renal failure	Anuria	Hypertension, hematuria	304, 308, 310, 313
	Oliguria	Proteinuria, pyuria	
	Documented recent decline in GFR	Casts, edema	
Acute nephritis	Hematuria, RBC casts	Proteinuria	308
	Azotemia, reduced GFR, oliguria	Pyuria	
	Edema, hypertension	Circulatory congestion	
Chronic renal failure	Azotemia for >3 months	Proteinuria, casts	305
	Symptoms or signs of uremia, (late manifestation), casts	Hypocalcemia, hyperphosphatemia, hyperparathyroidism	
	Symptoms or signs of renal osteodystrophy	Polyuria, nocturia	
	Kidneys reduced in size bilaterally	Edema, hypertension	
	Broad casts in urinary sediment	Hyperkalemia, metabolic acidosis	
Nephrotic syndrome	Proteinuria, with >3.5 g/24 h per 1.73 m^2	Casts	308
	Hypoalbuminemia	Lipiduria	
	Edema	Hypercoagulable state	
	Hyperlipidemia		
Asymptomatic urinary abnormalities	Hematuria		308
	Proteinuria (below nephrotic range)		
	Sterile pyuria, casts		
Urinary tract infection/ pyelonephritis	Bacteriuria, with >10^5 cfu/mL	Hematuria	130
	Other infectious agent documented in urine	Mild azotemia and reduced GFR	
	Pyuria, leukocyte casts	Mild proteinuria	
	Frequency, urgency	Fever	
	Bladder tenderness, flank tenderness		
Renal tubular defects	Electrolyte disorders	Hematuria	309, 310
	Polyuria, nocturia	"Tubular" proteinuria (<1 g/24 h)	
	Renal calcification	Enuresis	
	Large kidneys	Electrolyte and/or acid-base abnormalities	
	Renal transport defects	Other electrolyte issues, e.g. hypomagnesemia	
Hypertension	Systolic/diastolic hypertension	Proteinuria	271, 311
		Casts	
		Azotemia	
Nephrolithiasis	Previous history of stone passage or removal	Hematuria	312
	Previous history of stone seen by x-ray	Pyuria	
	Renal colic	Frequency, urgency	
Urinary tract obstruction	Azotemia, oliguria, anuria	Hematuria	313
	Polyuria, nocturia, urinary retention	Pyuria	
	Slowing of urinary stream	Enuresis, dysuria	
	Large prostate, large kidneys		
	Flank tenderness, full bladder after voiding		

Abbreviations: cfu, colony-forming units; GFR; glomerular filtration rate; RBC, red blood cell.

iothalamate) that is filtered at the glomerulus into the urinary space but is neither reabsorbed nor secreted throughout the tubule. GFR—i.e., the clearance of inulin or iothalamate in milliliters per minute—is calculated from the rate of appearance of the isotope in the urine over several hours. In most clinical circumstances, direct GFR measurement is not feasible, and the plasma creatinine level is used as a surrogate to estimate GFR. Plasma creatinine (P_{Cr}) is the most widely used marker for GFR, which is related directly to urine creatinine (U_{Cr}) excretion and inversely to P_{Cr}. On the basis of this relationship (with some important caveats, as discussed below), GFR will fall in roughly inverse proportion to the rise in P_{Cr}. Failure to account for GFR reductions in drug dosing can lead to significant morbidity and death from drug toxicities (e.g., digoxin, imipenem). In the outpatient setting, P_{Cr} serves as an estimate for GFR (although much less accurate; see below). In patients with chronic progressive renal disease, there is an approximately linear relationship between $1/P_{Cr}$ (y axis) and time (x axis). The slope of that line will remain constant for an individual; when values deviate, an investigation for a superimposed acute process (e.g., volume depletion, drug reaction) should be initiated. Signs and symptoms of uremia, the clinical symptom complex associated with renal failure, develop at significantly different levels of P_{Cr}, depending on the patient (size, age, and sex), underlying renal disease, existence of concurrent diseases, and true GFR. Generally, patients do not develop symptomatic uremia until renal insufficiency is severe (GFR <15 mL/min).

A significantly reduced GFR (either acute or chronic) is usually reflected in a rise in P_{Cr}, leading to retention of nitrogenous waste products (defined as azotemia) such as urea. Azotemia may result from reduced renal perfusion, intrinsic renal disease, or postrenal processes (ureteral obstruction; see below and Fig. 48-1). Precise determination of GFR is problematic, as both commonly measured indices (urea and creatinine) have characteristics that affect their accuracy as markers of clearance. Urea clearance may underestimate GFR significantly

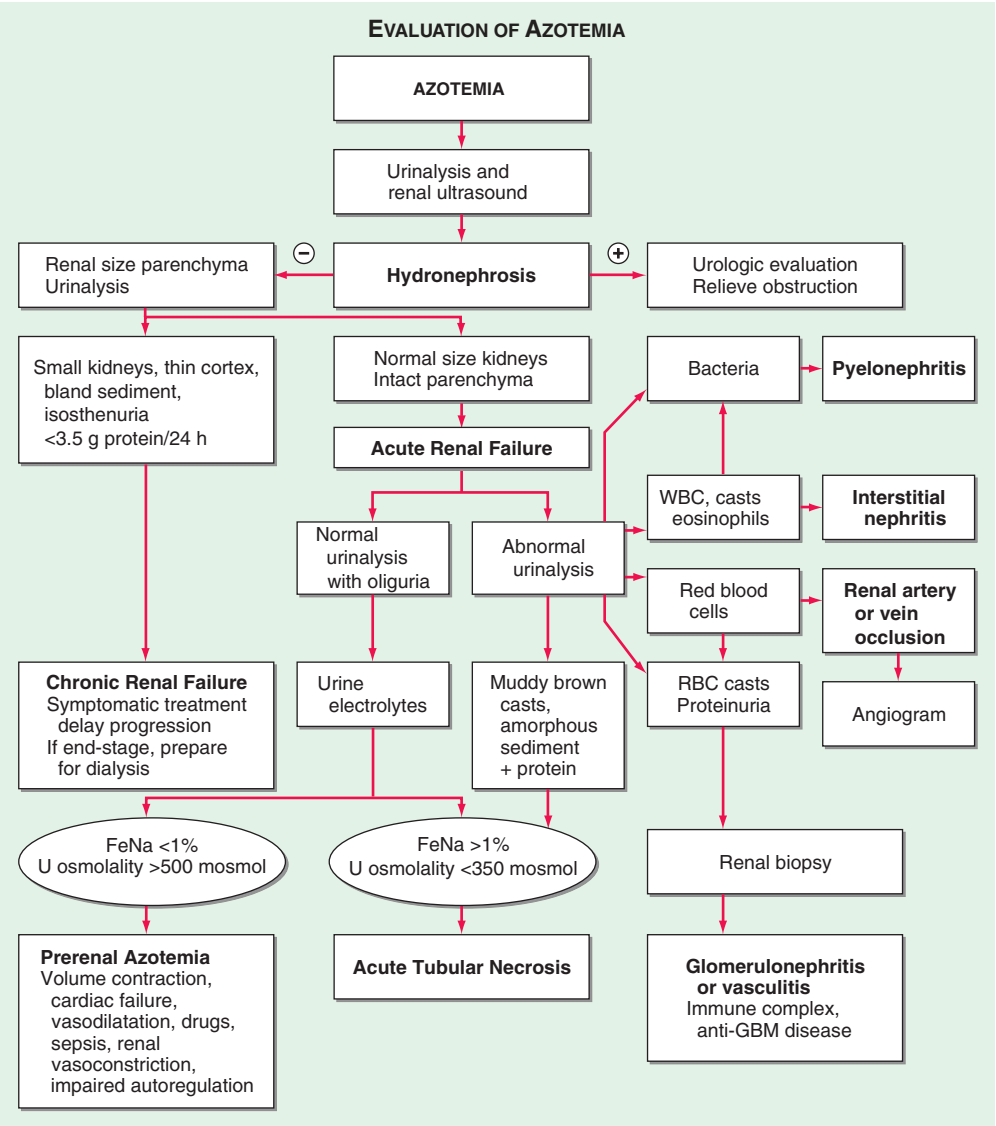

FIGURE 48-1 Approach to the patient with azotemia. FeNa, fractional excretion of sodium; GBM, glomerular basement membrane; RBC, red blood cell; WBC, white blood cell.

because of urea reabsorption by the tubule. In contrast, creatinine is derived from muscle metabolism of creatine, and its generation varies little from day to day.

Creatinine clearance (CrCl), an approximation of GFR, is measured from plasma and urinary creatinine excretion rates for a defined period (usually 24 h) and is expressed in milliliters per minute: $CrCl = (U_{vol} \times U_{Cr})/(P_{Cr} \times T_{min})$. The "adequacy" or "completeness" of the urinary collection is estimated by the urinary volume and creatinine content; creatinine is produced from muscle and excreted at a relatively constant rate. For a 20- to 50-year-old man, creatinine excretion should be 18.5–25.0 mg/kg body weight; for a woman of the same age, it should be 16.5–22.4 mg/kg body weight. For example, an 80-kg man should excrete between ~1500 and 2000 mg of creatinine in an "adequate" collection. Creatinine is useful for estimating GFR because it is a small, freely filtered solute that is not reabsorbed by the tubules. P_{Cr} levels can increase acutely from dietary ingestion of cooked meat, however, and creatinine can be secreted into the proximal tubule through an organic cation pathway (especially in advanced progressive chronic kidney disease), leading to overestimation of GFR. When a timed collection for CrCl is not available, decisions about drug dosing must be based on P_{Cr} alone. Two formulas are used widely to estimate kidney function from P_{Cr}: (1) Cockcroft-Gault and (2) four-variable MDRD (Modification of Diet in Renal Disease).

$$\text{Cockcroft-Gault: CrCl (mL/min)} = (140 - \text{age (years)}) \times \text{weight (kg)} \times [0.85 \text{ if female}])/(72 \times P_{Cr}\ (\text{mg/dL}).$$

$$\text{MDRD: eGFR (mL/min per 1.73 m}^2) = 186.3 \times P_{Cr}^{(-1.154)} \times \text{age}^{(-0.203)} \times (0.742 \text{ if female}) \times (1.21 \text{ if black}).$$

Numerous websites are available to assist with these calculations (*www.kidney.org/professionals/kdoqi/gfr_calculator.cfm*). A newer CKD-EPI eGFR, which was developed by pooling several cohorts with and without kidney disease who had data on directly measured GFR, appears to be more accurate:

$$\text{CKD-EPI: eGFR} = 141 \times \min(P_{Cr}/k, 1)^{a} \times \max(P_{Cr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]},$$

where P_{Cr} is plasma creatinine, *k* is 0.7 for females and 0.9 for males, *a* is –0.329 for females and –0.411 for males, *min* indicates the minimum of P_{Cr}/k or 1, and *max* indicates the maximum of P_{Cr}/k or 1 (*http://www.qxmd.com/renal/Calculate-CKD-EPI-GFR.php*).

There are limitations to all creatinine-based estimates of GFR. Each equation, along with 24-h urine collection for measurement of creatinine clearance, is based on the assumption that the patient is in *steady state*, without daily increases or decreases in P_{Cr} as a result of rapidly changing GFR. The MDRD equation is better correlated with true GFR when the GFR is <60 mL/min per 1.73 m^2. The gradual loss of muscle from chronic illness, chronic use of glucocorticoids, or malnutrition can mask significant changes in GFR with small or imperceptible changes in P_{Cr}. Cystatin C, a member of the cystatin superfamily of cysteine protease inhibitors, is produced at a relatively constant rate from all nucleated cells. Serum cystatin C has been proposed to be a more sensitive

marker of early GFR decline than is P_{Cr}; however, like serum creatinine, cystatin C is influenced by the patient's age, race, and sex and also is associated with diabetes, smoking, and markers of inflammation.

APPROACH TO THE PATIENT

Azotemia

Once GFR reduction has been established, the physician must decide if it represents acute or chronic renal injury. The clinical situation, history, and laboratory data often make this an easy distinction. However, the laboratory abnormalities characteristic of chronic renal failure, including anemia, hypocalcemia, and hyperphosphatemia, are also often present in patients presenting with acute renal failure. Radiographic evidence of renal osteodystrophy **(Chap. 305)** can be seen only in chronic renal failure but is a very late finding, typically in patients with end-stage renal disease (ESRD) maintained on dialysis. The urinalysis and renal ultrasound can facilitate distinguishing acute from chronic renal failure. An approach to the evaluation of azotemic patients is shown in Fig. 48-1. Patients with advanced chronic renal insufficiency often have some proteinuria, nonconcentrated urine (isosthenuria; isosmotic with plasma), and small kidneys on ultrasound, characterized by increased echogenicity and cortical thinning. Treatment should be directed toward slowing the progression of renal disease and providing symptomatic relief for edema, acidosis, anemia, and hyperphosphatemia, as discussed in **Chap. 305**. Acute renal failure **(Chap. 304)** can result from processes that affect and blood flow and glomerular perfusion (prerenal azotemia), intrinsic renal diseases (affecting small vessels, glomeruli, or tubules), or postrenal processes (obstruction of urine flow in ureters, bladder, or urethra) **(Chap. 313)**.

PRERENAL FAILURE

Decreased renal perfusion accounts for 40–80% of cases of acute renal failure and, if appropriately treated, is readily reversible. The etiologies of prerenal azotemia include any cause of decreased circulating blood volume (gastrointestinal hemorrhage, burns, diarrhea, diuretics), volume sequestration (pancreatitis, peritonitis, rhabdomyolysis), or decreased effective arterial volume (cardiogenic shock, sepsis). Renal and glomerular perfusion also can be affected by reductions in cardiac output from peripheral vasodilation (sepsis, drugs) or profound renal vasoconstriction (severe heart failure, hepatorenal syndrome, agents such as nonsteroidal anti-inflammatory drugs [NSAIDs]). True or "effective" arterial hypovolemia leads to a fall in mean arterial pressure, which in turn triggers a series of neural and humoral responses, including activation of the sympathetic nervous and renin-angiotensin-aldosterone systems and vasopressin (AVP) release. GFR is maintained by prostaglandin-mediated dilatation of afferent arterioles and angiotensin II–mediated constriction of efferent arterioles. Once the mean arterial pressure falls below 80 mmHg, GFR declines steeply.

Blockade of prostaglandin production by NSAIDs can result in severe vasoconstriction and acute renal failure. Blocking angiotensin action with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) decreases efferent arteriolar tone and in turn decreases glomerular capillary perfusion pressure. Patients taking NSAIDs and/or ACE inhibitors/ARBs are most susceptible to hemodynamically mediated acute renal failure when blood volume or arterial perfusion pressure is reduced for any reason; under these circumstances, preservation of GFR is dependent on afferent vasodilation due to prostaglandins and efferent vasoconstriction due to angiotensin-II. Patients with bilateral renal artery stenosis (or stenosis in a solitary kidney) can also be dependent on efferent arteriolar vasoconstriction for maintenance of glomerular filtration pressure and are particularly susceptible to a precipitous decline in GFR when given ACE inhibitors or ARBs.

Prolonged renal hypoperfusion may lead to acute tubular necrosis (ATN), an intrinsic renal disease that is discussed below. The urinalysis and urinary electrolyte measurements can be useful in distinguishing prerenal azotemia from ATN **(Table 48-2)**. The urine Na and osmolality of patients with prerenal azotemia can be predicted from the stimulatory actions of norepinephrine, angiotensin II, AVP, aldosterone, and low tubule fluid flow rate. In prerenal conditions, the tubules are intact, leading to a concentrated urine (>500 mosmol), avid Na retention (urine Na concentration, <20 mmol/L; fractional excretion of Na, <1%), and U_{Cr}/P_{Cr} >40 (Table 48-2). The FE_{Na} is typically >1% in ATN, but may be <1% in patients with milder, nonoliguric ATN (e.g., from rhabdomyolysis) and in pts with underlying "prerenal" disorders, such as congestive heart failure (CHF) or cirrhosis or hepatorenal syndrome. The prerenal urine sediment is usually normal or has hyaline and granular casts, whereas the sediment of ATN usually is filled with cellular debris, tubular epithelial casts, and dark (muddy brown) granular casts. The measurement of urinary biomarkers associated with tubular injury is a promising technique to detect subclinical ATN and/or help further diagnose the exact cause of acute renal failure.

TABLE 48-2 Laboratory Findings in Acute Renal Failure

INDEX	PRERENAL AZOTEMIA	OLIGURIC ACUTE RENAL FAILURE
BUN/P_{Cr} ratio	>20:1	10–15:1
Urine sodium U_{Na}, meq/L	<20	>40
Urine osmolality, mosmol/L H_2O	>500	<350
Fractional excretion of sodium[a]	<1%	>2%
Urine/plasma creatinine U_{Cr}/P_{Cr}	>40	<20
Urinalysis (casts)	None or hyaline/granular	Muddy brown

$$^{a}FE_{Na} = \frac{U_{Na} \times P_{Cr} \times 100}{P_{Na} \times U_{Cr}}$$

Abbreviations: BUN, blood urea nitrogen; P_{Cr}, plasma creatinine concentration; P_{Na}, plasma sodium concentration; U_{Cr}, urine creatinine concentration; U_{Na}, urine sodium concentration.

POSTRENAL AZOTEMIA

Urinary tract obstruction accounts for <5% of cases of acute renal failure but is usually reversible and must be ruled out early in the evaluation (Fig. 48-1). Since a single kidney is capable of adequate clearance, complete obstructive acute renal failure requires obstruction at the urethra or bladder outlet, bilateral ureteral obstruction, or unilateral obstruction in a patient with a single functioning kidney. Obstruction is usually diagnosed by the presence of ureteral and renal pelvic dilation on renal ultrasound. However, early in the course of obstruction or if the ureters are unable to dilate (e.g., encasement by pelvic or periureteral tumors or by retroperitoneal fibrosis), the ultrasound examination may be negative. Other imaging, such as a furosemide renogram (MAG3 nuclear medicine study), may be required to better define the presence or absence of obstructive uropathy. **The specific urologic conditions that cause obstruction are discussed in Chap. 313.**

INTRINSIC RENAL DISEASE

When prerenal and postrenal azotemia have been excluded as etiologies of renal failure, an intrinsic parenchymal renal disease is present. Intrinsic renal disease can arise from processes involving large renal vessels, intrarenal microvasculature and glomeruli, or the tubulointerstitium. Ischemic and toxic ATN account for ~90% of cases of acute intrinsic renal failure. As outlined in Fig. 48-1, the clinical setting and urinalysis are helpful in separating the possible etiologies. Prerenal azotemia and ATN are part of a spectrum of renal hypoperfusion; evidence of structural tubule injury is present in ATN, whereas prompt reversibility occurs with prerenal azotemia upon restoration of adequate renal perfusion. Thus, ATN often can be distinguished from prerenal azotemia by urinalysis and urine electrolyte composition (Table 48-2 and Fig. 48-1). Ischemic ATN is

observed most frequently in patients who have undergone major surgery, trauma, severe hypovolemia, overwhelming sepsis, or extensive burns. Nephrotoxic ATN complicates the administration of many common medications, usually by inducing a combination of intrarenal vasoconstriction, direct tubule toxicity, and/or tubular obstruction. The kidney is vulnerable to toxic injury by virtue of its rich blood supply (25% of cardiac output) and its ability to concentrate and metabolize toxins. A diligent search for hypotension and nephrotoxins usually uncovers the specific etiology of ATN. Discontinuation of nephrotoxins and stabilization of blood pressure often suffice without the need for dialysis, with ongoing regeneration of tubular cells. **An extensive list of potential drugs and toxins implicated in ATN is found in Chap. 304.**

Processes involving the tubules and interstitium can lead to acute kidney injury (AKI), a subtype of acute renal failure. These processes include drug-induced interstitial nephritis (especially by antibiotics, NSAIDs, and diuretics), severe infections (both bacterial and viral), systemic diseases (e.g., systemic lupus erythematosus), and systemic disorders (e.g., sarcoidosis, Sjögren's syndrome, lymphoma, or leukemia). A list of drugs associated with allergic interstitial nephritis is found in **Chap. 310**. Urinalysis usually shows mild to moderate proteinuria, hematuria, and pyuria (~75% of cases) and occasionally WBC casts. The finding of RBC casts in interstitial nephritis has been reported but should prompt a search for glomerular diseases (Fig. 48-1). Occasionally, renal biopsy will be needed to distinguish among these possibilities. The classic sediment finding in allergic interstitial nephritis is a predominance (>10%) of urinary eosinophils with Wright's or Hansel's stain; however, urinary eosinophils can be increased in several other causes of AKI, such that measurement of urine eosinophils has no diagnostic utility in renal disease.

Occlusion of large renal vessels, including arteries and veins, is an uncommon cause of acute renal failure. A significant reduction in GFR by this mechanism suggests bilateral processes or, in a patient with a single functioning kidney, a unilateral process. In patients with preexisting renal artery stenosis, a substantial renal collateral circulation can develop over time and sustain renal perfusion—typically not enough to sustain glomerular filtration—in the event of total renal artery occlusion. Renal arteries can be occluded with atheroemboli, thromboemboli, in situ thrombosis, aortic dissection, or vasculitis. Atheroembolic renal failure can occur spontaneously but most often is associated with recent aortic instrumentation. The emboli are cholesterol-rich and lodge in medium and small renal arteries, with a consequent eosinophil-rich inflammatory reaction. Patients with atheroembolic acute renal failure often have a normal urinalysis, but the urine may contain eosinophils and casts. The diagnosis can be confirmed by renal biopsy, but this procedure is often unnecessary when other stigmata of atheroemboli are present (livedo reticularis, distal peripheral infarcts, eosinophilia). Renal artery thrombosis may lead to mild proteinuria and hematuria, whereas renal vein thrombosis typically occurs in the context of heavy proteinuria and hematuria. **These vascular complications often require angiography for confirmation and are discussed in Chap. 311.**

Diseases of the glomeruli (glomerulonephritis and vasculitis) and the renal microvasculature (hemolytic-uremic syndromes, thrombotic thrombocytopenic purpura, and malignant hypertension) usually present with various combinations of glomerular injury: proteinuria, hematuria, reduced GFR, and alterations of sodium excretion that lead to hypertension, edema, and circulatory congestion (acute nephritic syndrome). These findings may occur as primary renal diseases or as renal manifestations of systemic diseases. The clinical setting and other laboratory data help distinguish primary renal diseases from systemic diseases. The finding of RBC casts in the urine is an indication for early renal biopsy (Fig. 48-1), as the pathologic pattern has important implications for diagnosis, prognosis, and treatment. Hematuria without RBC casts can also be an indication of glomerular disease, since RBC casts are highly specific but very insensitive for glomerulonephritis. The specificity of urine microscopy can be enhanced by examining urine with a phase contrast microscope capable of detecting dysmorphic red cells ("acanthocytes") that are associated with glomerular disease. This evaluation is summarized in **Fig. 48-2. A detailed discussion of glomerulonephritis and diseases of the microvasculature is found in Chap. 310.**

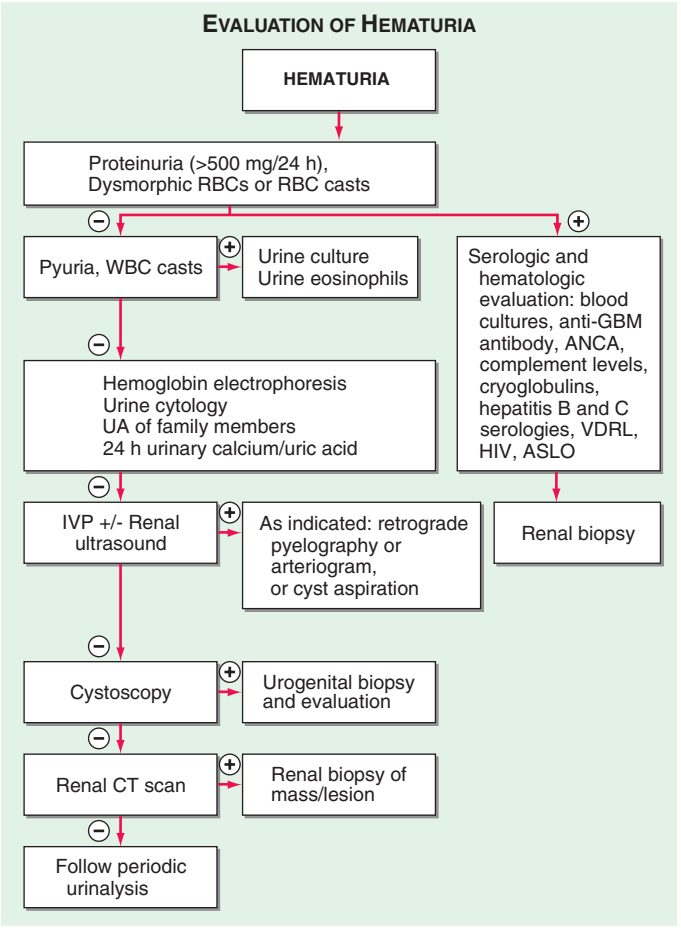

FIGURE 48-2 Approach to the patient with hematuria. ANCA, antineutrophil cytoplasmic antibody; ASLO, antistreptolysin O; CT, computed tomography; GBM, glomerular basement membrane; IVP, intravenous pyelography; RBC, red blood cell; UA, urinalysis; VDRL, Venereal Disease Research Laboratory; WBC, white blood cell.

OLIGURIA AND ANURIA

Oliguria refers to a 24-h urine output <400 mL, and *anuria* is the complete absence of urine formation (<100 mL). Anuria can be caused by complete bilateral urinary tract obstruction; a vascular catastrophe (dissection or arterial occlusion); renal vein thrombosis; acute cast nephropathy in myeloma; renal cortical necrosis; severe ATN; combined therapy with nonsteroidal anti-inflammatory drugs, ACE inhibitors, and/or ARBs; and hypovolemic, cardiogenic, or septic shock. Oliguria is never normal, since at least 400 mL of maximally concentrated urine must be produced to excrete the obligate daily osmolar load. *Nonoliguria* refers to urine output >400 mL/d in patients with acute or chronic azotemia. With nonoliguric ATN, disturbances of potassium and hydrogen balance are less severe than in oliguric patients, and recovery to normal renal function is usually more rapid.

ABNORMALITIES OF THE URINE

PROTEINURIA

The evaluation of proteinuria is shown schematically in **Fig. 48-3** and typically is initiated after detection of proteinuria by dipstick examination. The dipstick measurement detects only albumin and gives

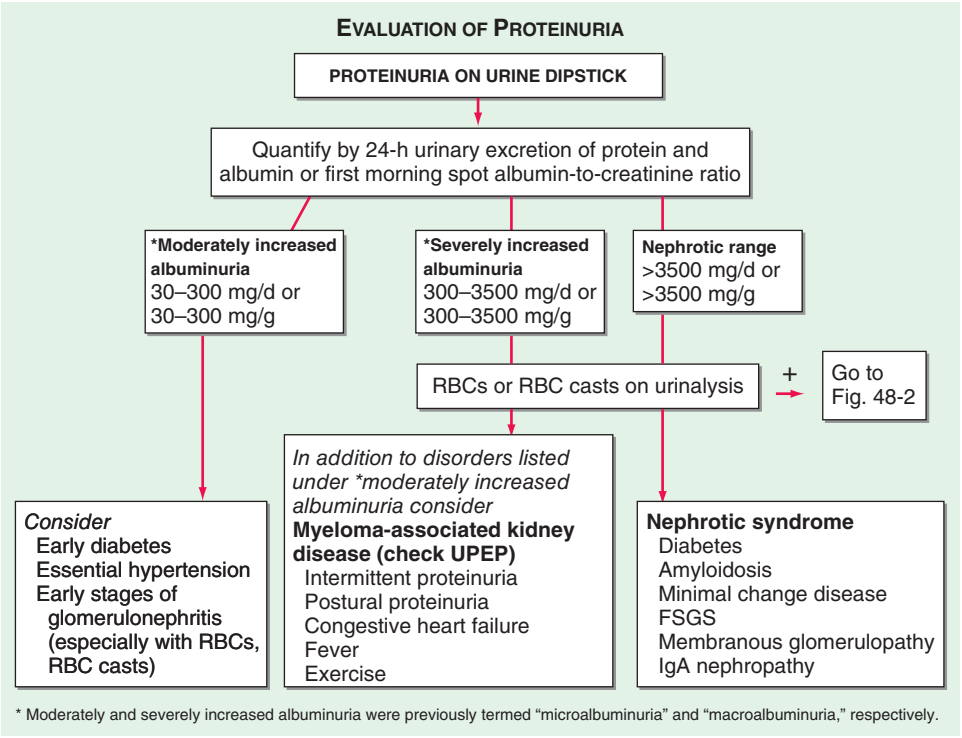

FIGURE 48-3 Approach to the patient with proteinuria. Investigation of proteinuria is often initiated by a positive dipstick on routine urinalysis. Conventional dipsticks detect predominantly albumin and provide a semiquantitative assessment (trace, 1+, 2+, or 3+), which is influenced by urinary concentration as reflected by urine specific gravity (minimum, <1.005; maximum, 1.030). However, more exact determination of proteinuria should employ a spot morning protein/creatinine ratio (mg/g) or a 24-h urine collection (mg/24 h). FSGS, focal segmental glomerulosclerosis; RBC, red blood cell; UPEP, urine protein electrophoresis.

false-positive results at pH >7.0 or when the urine is very concentrated or contaminated with blood. Because the dipstick relies on urinary albumin concentration, a very dilute urine may obscure significant proteinuria on dipstick examination. Quantification of urinary albumin on a spot urine sample (ideally from a first morning void) by measurement of an albumin-to-creatinine ratio (ACR) is helpful in approximating a 24-h albumin excretion rate (AER), where ACR (mg/g) ≈AER (mg/24 h). Furthermore, proteinuria that is not predominantly due to albumin will be missed by dipstick screening. This information is particularly important for the detection of Bence-Jones proteins in the urine of patients with multiple myeloma. Tests to measure total urine protein concentration accurately rely on precipitation with sulfosalicylic or trichloracetic acid (Fig. 48-3). As with albuminuria, the ratio of protein to creatinine in a random, "spot" urine can also provide a rough estimate of protein excretion; for example, a protein/creatinine ratio of 3.0 correlates to ~3.0 g of proteinuria per day. Formal assessment of urinary protein excretion requires a 24-h urine protein collection (see "Measurement of GFR," above).

The magnitude of proteinuria and its composition in the urine depend on the mechanism of renal injury that leads to protein losses. Both charge and size selectivity normally prevent virtually all plasma albumin, globulins, and other high-molecular-weight proteins from crossing the glomerular wall; however, if this barrier is disrupted, plasma proteins may leak into the urine (glomerular proteinuria; Fig. 48-3). Smaller proteins (<20 kDa) are freely filtered but are readily reabsorbed by the proximal tubule. Typically, healthy individuals excrete <150 mg/d of total protein and <30 mg/d of albumin. However, even at albuminuria levels <30 mg/d, risk for progression to overt nephropathy or subsequent cardiovascular disease is increased. The remainder of the protein in the urine is secreted by the tubules (Tamm-Horsfall, IgA, and urokinase) or represents small amounts of filtered β_2-microglobulin, apoproteins, enzymes, and peptide hormones. Another mechanism of proteinuria entails excessive production of an abnormal protein that exceeds the capacity of the tubule for reabsorption. This situation most commonly occurs with plasma cell dyscrasias, such as multiple myeloma, amyloidosis, and lymphomas, that are associated with monoclonal production of immunoglobulin light chains.

The normal glomerular endothelial cell forms a barrier composed of pores of ~100 nm that retain blood cells but offer little impediment to passage of most proteins. The glomerular basement membrane traps most large proteins (>100 kDa), and the foot processes of epithelial cells (podocytes) cover the urinary side of the glomerular basement membrane and produce a series of narrow channels (slit diaphragms) to allow molecular passage of small solutes and water but not proteins. Some glomerular diseases, such as minimal change disease, cause fusion of glomerular epithelial cell foot processes, resulting in predominantly "selective" (Fig. 48-3) loss of albumin. Other glomerular diseases can present with disruption of the basement membrane and slit diaphragms (e.g., by immune complex deposition), resulting in losses of albumin and other plasma proteins. The fusion of foot processes causes increased pressure across the capillary basement membrane, resulting in areas with larger pore sizes (and more severe "nonselective" proteinuria (Fig. 48-3).

When the total daily urinary excretion of protein is >3.5 g, hypoalbuminemia, hyperlipidemia, and edema (nephrotic syndrome; Fig. 48-3) are often present as well. However, total daily urinary protein excretion >3.5 g can occur without the other features of the nephrotic syndrome in a variety of other renal diseases, including diabetes (Fig. 48-3). Plasma cell dyscrasias (multiple myeloma) can be associated with large amounts of excreted light chains in the urine, which may not be detected by dipstick. The light chains are filtered by the glomerulus and overwhelm the reabsorptive capacity of the proximal tubule. Renal failure from these disorders occurs through a variety of mechanisms, including but not limited to proximal tubule injury, tubule obstruction (cast nephropathy), amyloid deposition, and light chain deposition (Chap. 310). The specific renal lesion is dictated by the sequence and structural characteristics of the monoclonal light chain; however, not all excreted light chains are nephrotoxic.

Hypoalbuminemia in nephrotic syndrome occurs through excessive urinary losses and increased proximal tubule catabolism of filtered albumin. Edema results from renal sodium retention and reduced plasma oncotic pressure, which favors fluid movement from capillaries to interstitium. To compensate for the perceived decrease in effective intravascular volume, activation of the renin-angiotensin system, stimulation of AVP, and activation of the sympathetic nervous system take place, promoting continued renal salt and water reabsorption and progressive edema. Filtered proteases, normally retained by the glomerular filtration barrier, can also directly activate sodium reabsorption by the epithelial Na channels in principal cells (ENaC) in nephrotic syndrome. Despite these changes, hypertension is uncommon in primary kidney diseases resulting in the nephrotic syndrome (Fig. 48-3 and Chap. 308). The urinary loss of regulatory proteins and changes in hepatic synthesis contribute to the other manifestations of the nephrotic syndrome. A hypercoagulable state may arise from urinary losses of antithrombin III, reduced serum levels of proteins S and C, hyperfibrinogenemia, and enhanced platelet aggregation. Hypercholesterolemia may be severe and results from increased hepatic lipoprotein synthesis. Loss of immunoglobulins contributes to an increased risk of infection. Many diseases (some listed in Fig. 48-3) and drugs can cause the nephrotic syndrome; a complete list is found in Chap. 308.

HEMATURIA, PYURIA, AND CASTS

Isolated hematuria without proteinuria, other cells, or casts is often indicative of bleeding from the urinary tract. Hematuria is defined as two to five RBCs per high-power field (HPF) and can be detected by dipstick. A false-positive dipstick for hematuria (where no RBCs are seen on urine microscopy) may occur when myoglobinuria is present, often in the setting of rhabdomyolysis. Common causes of isolated hematuria include stones, neoplasms, tuberculosis, trauma, and prostatitis. Gross hematuria with blood clots usually is not an intrinsic renal process; rather, it suggests a postrenal source in the urinary collecting system. Evaluation of patients presenting with microscopic hematuria is outlined in Fig. 48-2. A single urinalysis with hematuria is common and can result from menstruation, viral illness, allergy, exercise, or mild trauma. Persistent or significant hematuria (>3 RBCs/HPF on three urinalyses, a single urinalysis with >100 RBCs, or gross hematuria) is associated with significant renal or urologic lesions in 9.1% of cases. The level of suspicion for urogenital neoplasms in patients with isolated painless hematuria and nondysmorphic RBCs increases with age. Neoplasms are rare in the pediatric population, and isolated hematuria is more likely to be "idiopathic" or associated with a congenital anomaly. Hematuria with pyuria and bacteriuria is typical of infection and should be treated with antibiotics after appropriate cultures. Acute cystitis or urethritis in women can cause gross hematuria. Hypercalciuria and hyperuricosuria are also risk factors for unexplained isolated hematuria in both children and adults. In some of these patients (50–60%), reducing calcium and uric acid excretion through dietary interventions can eliminate the microscopic hematuria.

Isolated microscopic hematuria can be a manifestation of glomerular diseases. The RBCs of glomerular origin are often dysmorphic when examined by phase-contrast microscopy. Irregular shapes of RBCs may also result from pH and osmolarity changes produced along the distal nephron. Observer variability in detecting dysmorphic RBCs is common. The most common etiologies of isolated glomerular hematuria are IgA nephropathy, hereditary nephritis, and thin basement membrane disease. IgA nephropathy and hereditary nephritis can lead to episodic gross hematuria. A family history of renal failure is often present in hereditary nephritis, and patients with thin basement membrane disease often have family members with microscopic hematuria. A renal biopsy is needed for the definitive diagnosis of these disorders, which are discussed in more detail in Chap. 308. Hematuria with dysmorphic RBCs, RBC casts, and protein excretion >500 mg/d is virtually diagnostic of glomerulonephritis. RBC casts form as RBCs that enter the tubule fluid and become trapped in a cylindrical mold of gelled Tamm-Horsfall protein. Even in the absence of azotemia, these patients should undergo serologic evaluation and renal biopsy as outlined in Fig. 48-2.

Isolated pyuria is unusual since inflammatory reactions in the kidney or collecting system also are associated with hematuria. The presence of bacteria suggests infection, and WBC casts with bacteria are indicative of pyelonephritis. WBCs and/or WBC casts also may be seen in acute glomerulonephritis as well as in tubulointerstitial processes such as interstitial nephritis and transplant rejection.

Casts can be seen in chronic renal diseases. Degenerated cellular casts called *waxy casts* or *broad casts* (arising in the dilated tubules that have undergone compensatory hypertrophy in response to reduced renal mass) may be seen in the urine.

ABNORMALITIES OF URINE VOLUME

POLYURIA

By history, it is often difficult for patients to distinguish urinary frequency (often of small volumes) from true polyuria (>3 L/d), and a quantification of volume by 24-h urine collection may be needed (Fig. 48-4). Polyuria results from two potential mechanisms: (1) excretion of nonabsorbable solutes (such as glucose) or (2) excretion of water (usually from a defect in AVP production or renal responsiveness). To distinguish a solute diuresis from a water diuresis and to determine whether the diuresis is appropriate for the clinical circumstances, urine osmolality is measured. The average person excretes between 600 and

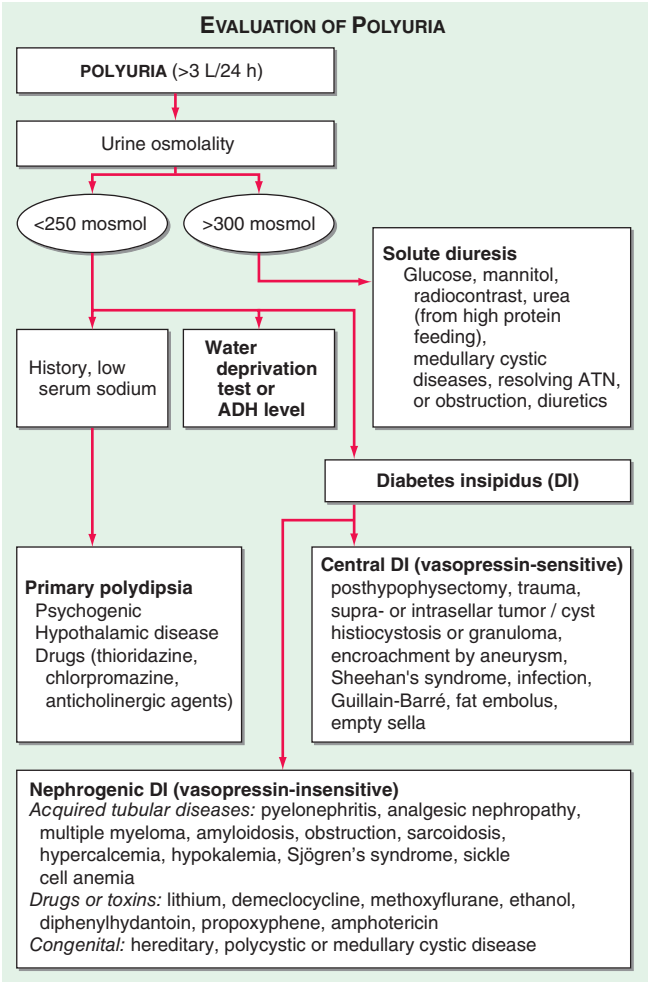

FIGURE 48-4 Approach to the patient with polyuria. AVP, antidiuretic hormone; ATN, acute tubular necrosis.

800 mosmol of solutes per day, primarily as urea and electrolytes. If the urine output is >3 L/d and the urine is dilute (<250 mosmol/L), total osmolar excretion is normal and a water diuresis is present. This circumstance could arise from polydipsia, inadequate secretion of vasopressin (*central diabetes insipidus*), or failure of renal tubules to respond to vasopressin (*nephrogenic diabetes insipidus*). If the urine volume is >3 L/d and urine osmolality is >300 mosmol/L, a solute diuresis is clearly present and a search for the responsible solute(s) is mandatory.

Excessive filtration of a poorly reabsorbed solute such as glucose or mannitol can depress reabsorption of NaCl and water in the proximal tubule and lead to enhanced excretion in the urine. Poorly controlled diabetes mellitus with glucosuria is the most common cause of a solute diuresis, leading to volume depletion and serum hypertonicity. Since the urine sodium concentration is less than that of blood, more water than sodium is lost, causing hypernatremia and hypertonicity. Common iatrogenic solute diuresis occurs in association with mannitol administration, radiocontrast media, and high-protein feedings (enteral or parenteral), leading to increased urea production and excretion. Less commonly, excessive sodium loss may result from cystic renal diseases or Bartter's syndrome or may develop during a tubulointerstitial process (such as resolving ATN). In these so-called salt-wasting disorders, the tubule damage results in direct impairment of sodium reabsorption and indirectly reduces the responsiveness of the tubule to aldosterone. Usually, the sodium losses are mild, and the obligatory urine output is <2 L/d; resolving ATN and postobstructive diuresis are exceptions and may be associated with significant natriuresis and polyuria.

Formation of large volumes of dilute urine is usually due to polydipsic states or diabetes insipidus. Primary polydipsia can result from habit, psychiatric disorders, neurological lesions, or medications. During deliberate polydipsia, extracellular fluid volume is normal or

expanded and plasma AVP levels are reduced because serum osmolality tends to be near the lower limits of normal. Urine osmolality is also maximally dilute at 50 mosmol/L.

Central diabetes insipidus may be idiopathic in origin or secondary to a variety of conditions, including hypophysectomy, trauma, neoplastic, inflammatory, vascular, or infectious hypothalamic diseases. Idiopathic central diabetes insipidus is associated with selective destruction of the vasopressin-secreting neurons in the supraoptic and paraventricular nuclei and can either be inherited as an autosomal dominant trait or occur spontaneously. Nephrogenic diabetes insipidus can occur in a variety of clinical situations, as summarized in Fig. 48-4.

A plasma AVP level is recommended as the best method for distinguishing between central and nephrogenic diabetes insipidus. Alternatively, a water deprivation test plus exogenous vasopressin may distinguish primary polydipsia from central and nephrogenic diabetes insipidus. **For a detailed discussion, see Chap. 374.**

Acknowledgment

This chapter was adapted and updated from the prior version written by Julie Lin and Bradley Denker.

FURTHER READING

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49 Fluid and Electrolyte Disturbances

David B. Mount

SODIUM AND WATER

COMPOSITION OF BODY FLUIDS

Water is the most abundant constituent in the body, comprising ~50% of body weight in women and 60% in men. Total-body water is distributed in two major compartments: 55–75% is intracellular (intracellular fluid [ICF]), and 25–45% is extracellular (extracellular fluid [ECF]). The ECF is further subdivided into intravascular (plasma water) and extravascular (interstitial) spaces in a ratio of 1:3. Fluid movement between the intravascular and interstitial spaces occurs across the capillary wall and is determined by Starling forces, i.e., capillary hydraulic pressure and colloid osmotic pressure. The transcapillary hydraulic pressure gradient exceeds the corresponding oncotic pressure gradient, thereby favoring the movement of plasma ultrafiltrate into the extravascular space. The return of fluid into the intravascular compartment occurs via lymphatic flow.

The solute or particle concentration of a fluid is known as its osmolality, expressed as milliosmoles per kilogram of water (mOsm/kg). Water easily diffuses across most cell membranes to achieve osmotic equilibrium (ECF osmolality = ICF osmolality). Notably, the extracellular and intracellular solute compositions differ considerably owing to the activity of various transporters, channels, and ATP-driven membrane pumps. The major ECF particles are Na^+ and its accompanying anions Cl^- and HCO_3^-, whereas K^+ and organic phosphate esters (ATP, creatine phosphate, and phospholipids) are the predominant ICF osmoles. Solutes that are restricted to the ECF or the ICF determine the "tonicity" or effective osmolality of that compartment. Certain solutes, particularly urea, do not contribute to water shifts across most membranes and are thus known as *ineffective osmoles*.

Water Balance Vasopressin secretion, water ingestion, and renal water transport collaborate to maintain human body fluid osmolality between 280 and 295 mOsm/kg. Vasopressin (AVP) is synthesized in magnocellular neurons within the hypothalamus; the distal axons of these neurons project to the posterior pituitary or neurohypophysis, from which AVP is released into the circulation. A network of central "osmoreceptor" neurons, which includes the AVP-expressing magnocellular neurons themselves, sense circulating osmolality via nonselective, stretch-activated cation channels. These osmoreceptor neurons are activated or inhibited by modest increases and decreases in circulating osmolality, respectively; activation leads to AVP release and thirst.

AVP secretion is stimulated as systemic osmolality increases above a threshold level of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP **(Fig. 49-1)**. Thirst and thus water ingestion are also activated at ~285 mOsm/kg, beyond which there is an equivalent linear increase in the perceived intensity of thirst as a function of circulating osmolality. Changes in blood volume and blood pressure are also direct stimuli for AVP release and thirst, albeit with a less sensitive response profile. Of perhaps greater clinical relevance to the pathophysiology of water homeostasis, ECF volume strongly modulates the relationship between circulating osmolality and AVP release, such that hypovolemia reduces the osmotic threshold and increases the slope of the response curve to osmolality; *hypervolemia* has an opposite effect, increasing the osmotic threshold and reducing the slope of the response curve (Fig. 49-1). Notably, AVP has a half-life in the circulation of only 10–20 min; thus, changes in ECF volume and/or circulating osmolality can rapidly affect water homeostasis. In addition to volume status, a number of other "nonosmotic" stimuli have potent activating effects on osmosensitive neurons and AVP release, including nausea, intracerebral angiotensin II, serotonin, and multiple drugs.

The excretion or retention of electrolyte-free water by the kidney is modulated by circulating AVP. AVP acts on renal, V_2-type receptors in the thick ascending limb of Henle and principal cells of the collecting duct (CD), increasing intracellular levels of cyclic AMP and activating protein kinase A (PKA)–dependent phosphorylation of multiple transport proteins. The AVP- and PKA-dependent activation of Na^+-Cl^- and K^+ transport by the thick ascending limb of the loop of Henle (TALH) is a key participant in the countercurrent mechanism **(Fig. 49-2)**. The countercurrent mechanism ultimately increases the interstitial osmolality in the inner medulla of the kidney, driving water absorption

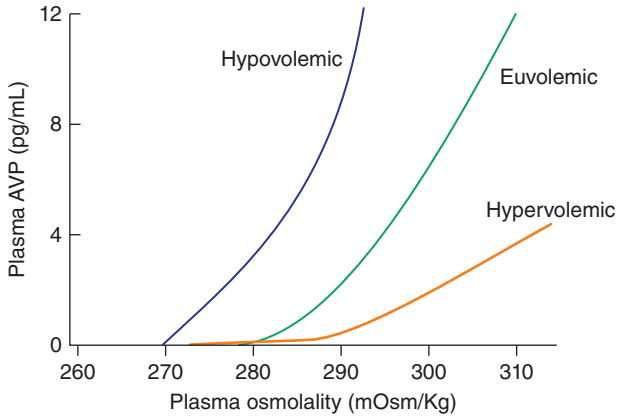

FIGURE 49-1 Circulating levels of vasopressin (AVP) in response to changes in osmolality. Plasma AVP becomes detectable in euvolemic, healthy individuals at a threshold of ~285 mOsm/kg, above which there is a linear relationship between osmolality and circulating AVP. The vasopressin response to osmolality is modulated strongly by volume status. The osmotic threshold is thus slightly lower in hypovolemia, with a steeper response curve; hypervolemia reduces the sensitivity of circulating AVP levels to osmolality.

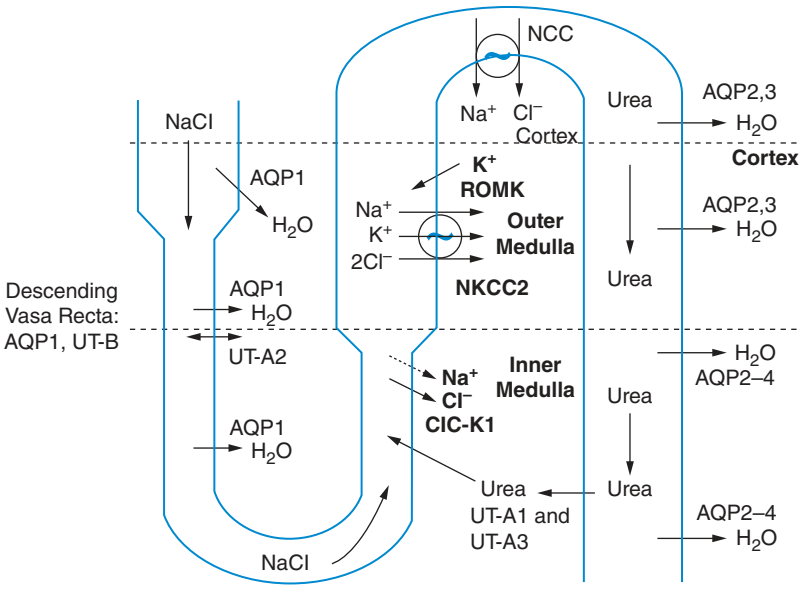

FIGURE 49-2 The renal concentrating mechanism. Water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (see text for details). Diagram showing the location of the major transport proteins involved; a loop of Henle is depicted on the *left*, collecting duct on the *right*. AQP, aquaporin; CLC-K1, chloride channel; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary K^+ channel; UT, urea transporter. *(Used with permission from JM Sands: Molecular approaches to urea transporters. J Am Soc Nephrol 13:2795, 2002.)*

across the renal CD. However, water, salt, and solute transport by both proximal and distal nephron segments participates in the renal concentrating mechanism (Fig. 49-2). Water transport across apical and basolateral aquaporin-1 water channels in the descending thin limb of the loop of Henle is thus involved, as is passive absorption of Na^+-Cl^- by the thin ascending limb, via apical and basolateral CLC-K1 chloride channels and paracellular Na^+ transport. Renal urea transport in turn plays important roles in the generation of the medullary osmotic gradient and the ability to excrete solute-free water under conditions of both high and low protein intake (Fig. 49-2).

AVP-induced, PKA-dependent phosphorylation of the aquaporin-2 water channel in principal cells stimulates the insertion of active water channels into the lumen of the CD, resulting in transepithelial water absorption down the medullary osmotic gradient **(Fig. 49-3)**. Under "antidiuretic" conditions, with increased circulating AVP, the kidney reabsorbs water filtered by the glomerulus, equilibrating the osmolality across the CD epithelium to excrete a hypertonic, "concentrated" urine (osmolality of up to 1200 mOsm/kg). In the absence of circulating AVP, insertion of aquaporin-2 channels and water absorption across the CD is essentially abolished, resulting in secretion of a hypotonic, dilute urine (osmolality as low as 30–50 mOsm/kg). Abnormalities in this "final common pathway" are involved in most disorders of water homeostasis, e.g., a reduced or absent insertion of active aquaporin-2 water channels into the membrane of principal cells in diabetes insipidus (DI).

Maintenance of Arterial Circulatory Integrity Sodium is actively pumped out of cells by the Na^+/K^+-ATPase membrane pump. In consequence, 85–90% of body Na^+ is extracellular, and the ECF volume (ECFV) is a function of total-body Na^+ content. Arterial perfusion and circulatory integrity are, in turn, determined by renal Na^+ retention or excretion, in addition to the modulation of systemic arterial resistance. Within the kidney, Na^+ is filtered by the glomeruli and then sequentially reabsorbed by the renal tubules. The Na^+ cation is typically reabsorbed with the chloride anion (Cl^-), and, thus, chloride homeostasis also affects the ECFV. On a quantitative level, at a glomerular filtration rate (GFR) of 180 L/d and serum Na^+ of ~140 m*M*, the kidney filters some 25,200 mmol/d of Na^+. This is equivalent to ~1.5 kg of salt, which would occupy roughly 10 times the extracellular space; 99.6% of filtered Na^+-Cl^- must be reabsorbed to excrete 100 m*M* per day. Minute changes in renal Na^+-Cl^- excretion will thus have significant effects on the ECFV, leading to edema syndromes or hypovolemia.

Approximately two-thirds of filtered Na^+-Cl^- is reabsorbed by the renal proximal tubule, via both paracellular and transcellular mechanisms. The TALH subsequently reabsorbs another 25–30% of filtered Na^+-Cl^- via the apical, furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter. The adjacent aldosterone-sensitive distal nephron, comprising the distal convoluted tubule (DCT), connecting tubule (CNT), and CD, accomplishes the "fine-tuning" of renal Na^+-Cl^- excretion. The thiazide-sensitive apical Na^+-Cl^- cotransporter (NCC) reabsorbs 5–10% of filtered Na^+-Cl^- in the DCT. Principal cells in the CNT and CD reabsorb Na^+ via electrogenic, amiloride-sensitive epithelial Na^+ channels (ENaC); Cl^- ions are primarily reabsorbed by adjacent intercalated cells, via apical Cl^- exchange (Cl^--OH^- and Cl^--HCO_3^- exchange, mediated by the SLC26A4 anion exchanger) **(Fig. 49-4)**.

Renal tubular reabsorption of filtered Na^+-Cl^- is regulated by multiple circulating and paracrine hormones, in addition to the activity of renal nerves. Angiotensin II activates proximal Na^+-Cl^- reabsorption, as do adrenergic receptors under the influence of renal sympathetic innervation; locally generated dopamine, in contrast, has a *natriuretic* effect. Aldosterone primarily activates Na^+-Cl^- reabsorption within the aldosterone-sensitive distal nephron. In particular, aldosterone activates the ENaC channel in principal cells, inducing Na^+ absorption and promoting K^+ excretion (Fig. 49-4).

Circulatory integrity is critical for the perfusion and function of vital organs. "Underfilling" of the arterial circulation is sensed by ventricular and vascular pressure receptors, resulting in a neurohumoral activation (increased sympathetic tone, activation of the renin-angiotensin-aldosterone axis, and increased circulating AVP) that synergistically increases renal Na^+-Cl^- reabsorption, vascular resistance, and renal water reabsorption. This occurs in the context of decreased cardiac

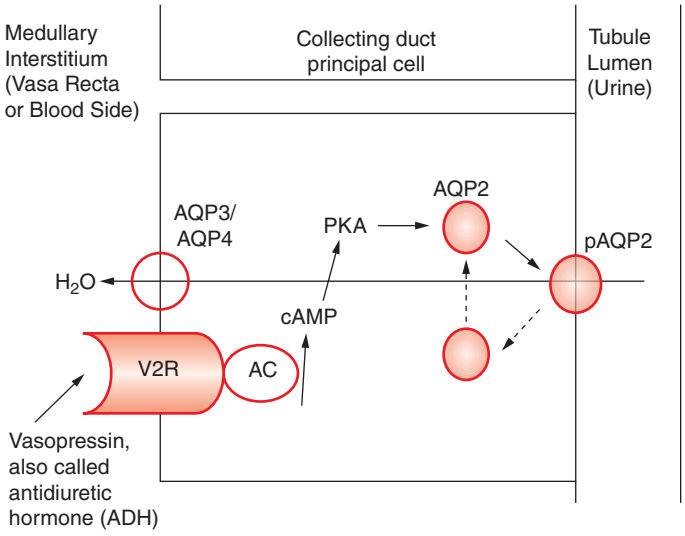

FIGURE 49-3 Vasopressin and the regulation of water permeability in the renal collecting duct. Vasopressin binds to the type 2 vasopressin receptor (V2R) on the basolateral membrane of principal cells, activates adenylyl cyclase (AC), increases intracellular cyclic adenosine monophosphatase (cAMP), and stimulates protein kinase A (PKA) activity. Cytoplasmic vesicles carrying aquaporin-2 (AQP) water channel proteins are inserted into the luminal membrane in response to vasopressin, thereby increasing the water permeability of this membrane. When vasopressin stimulation ends, water channels are retrieved by an endocytic process and water permeability returns to its low basal rate. The AQP3 and AQP4 water channels are expressed on the basolateral membrane and complete the transcellular pathway for water reabsorption. pAQP2, phosphorylated aquaporin-2. *(From JM Sands, DG Bichet: Nephrogenic diabetes insipidus. Ann Intern Med 144:186, 2006, with permission.)*

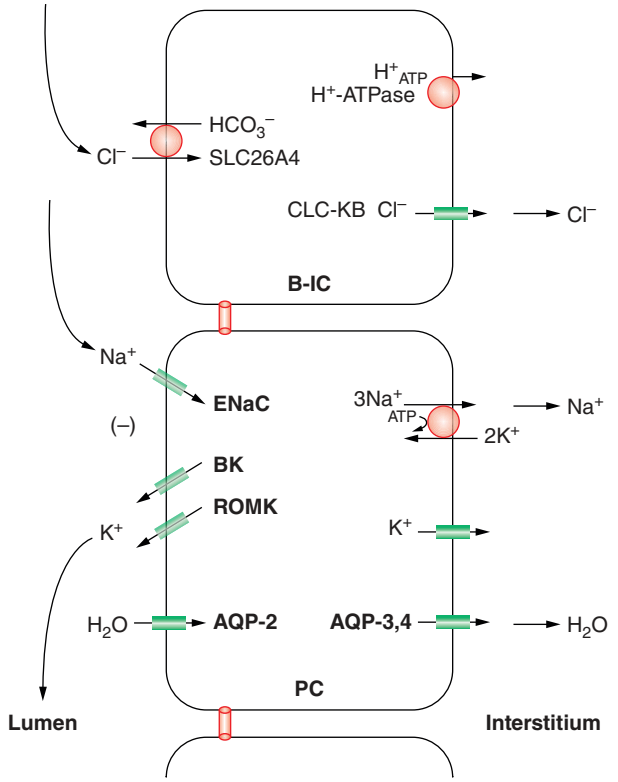

FIGURE 49-4 Sodium, water, and potassium transport in principal cells (PC) and adjacent β-intercalated cells (B-IC). The absorption of Na^+ via the amiloride-sensitive epithelial sodium channel (ENaC) generates a lumen-negative potential difference, which drives K^+ excretion through the apical secretory K^+ channel ROMK (renal outer medullary K^+ channel) and/or the flow-dependent BK channel. Transepithelial Cl^- transport occurs in adjacent β-intercalated cells, via apical Cl^--HCO_3^- and Cl^--OH^- exchange (SLC26A4 anion exchanger, also known as pendrin) basolateral CLC chloride channels. Water is absorbed down the osmotic gradient by principal cells, through the apical aquaporin-2 (AQP-2) and basolateral aquaporin-3 and aquaporin-4 (Fig. 49-3).

output, as occurs in hypovolemic states, low-output cardiac failure, decreased oncotic pressure, and/or increased capillary permeability. Alternatively, excessive arterial vasodilation results in *relative* arterial underfilling, leading to neurohumoral activation in the defense of tissue perfusion. These physiologic responses play important roles in many of the disorders discussed in this chapter. In particular, it is important to appreciate that AVP functions in the defense of circulatory integrity, inducing vasoconstriction, increasing sympathetic nervous system tone, increasing renal retention of both water and Na^+-Cl^-, and modulating the arterial baroreceptor reflex. Most of these responses involve activation of systemic V_{1A} AVP receptors, but concomitant activation of V_2 receptors in the kidney can result in renal water retention and hyponatremia.

HYPOVOLEMIA

Etiology True volume depletion, or hypovolemia, generally refers to a state of combined salt and water loss, leading to contraction of the ECFV. The loss of salt and water may be renal or nonrenal in origin.

RENAL CAUSES Excessive urinary Na^+-Cl^- and water loss is a feature of several conditions. A high filtered load of endogenous solutes, such as glucose and urea, can impair tubular reabsorption of Na^+-Cl^- and water, leading to an osmotic diuresis. Exogenous mannitol, often used to decrease intracerebral pressure, is filtered by glomeruli but not reabsorbed by the proximal tubule, thus causing an osmotic diuresis. Pharmacologic diuretics selectively impair Na^+-Cl^- reabsorption at specific sites along the nephron, leading to increased urinary Na^+-Cl^- excretion. Other drugs can induce natriuresis as a side effect. For example, acetazolamide can inhibit proximal tubular Na^+-Cl^- absorption via its inhibition of carbonic anhydrase; other drugs, such as the antibiotics trimethoprim (TMP) and pentamidine, inhibit distal tubular Na^+ reabsorption through the amiloride-sensitive ENaC channel, leading to urinary Na^+-Cl^- loss. Hereditary defects in renal transport proteins are also associated with reduced reabsorption of filtered Na^+-Cl^- and/or water. Alternatively, mineralocorticoid deficiency, mineralocorticoid resistance, or inhibition of the mineralocorticoid receptor (MLR) can reduce Na^+-Cl^- reabsorption by the aldosterone-sensitive distal nephron. Finally, tubulointerstitial injury, as occurs in interstitial nephritis, acute tubular injury, or obstructive uropathy, can reduce distal tubular Na^+-Cl^- and/or water absorption.

Excessive excretion of free water, i.e., water without electrolytes, can also lead to hypovolemia. However, the effect on ECFV is usually less marked, given that two-thirds of the water volume is lost from the ICF. Excessive renal water excretion occurs in the setting of decreased circulating AVP or renal resistance to AVP (central and nephrogenic DI, respectively).

EXTRARENAL CAUSES Nonrenal causes of hypovolemia include fluid loss from the gastrointestinal tract, skin, and respiratory system. Accumulations of fluid within specific tissue compartments, typically the interstitium, peritoneum, or gastrointestinal tract, can also cause hypovolemia.

Approximately 9 L of fluid enter the gastrointestinal tract daily, 2 L by ingestion and 7 L by secretion; almost 98% of this volume is absorbed, such that daily fecal fluid loss is only 100–200 mL. Impaired gastrointestinal reabsorption or enhanced secretion of fluid can cause hypovolemia. Because gastric secretions have a low pH (high H^+ concentration), whereas biliary, pancreatic, and intestinal secretions are alkaline (high HCO_3^- concentration), vomiting and diarrhea are often accompanied by metabolic alkalosis and acidosis, respectively.

Evaporation of water from the skin and respiratory tract (so-called "insensible losses") constitutes the major route for loss of solute-free water, which is typically 500–650 mL/d in healthy adults. This evaporative loss can increase during febrile illness or prolonged heat exposure. Hyperventilation can also increase insensible losses via the respiratory tract, particularly in ventilated patients; the humidity of inspired air is another determining factor. In addition, increased exertion and/or ambient temperature will increase insensible losses via sweat, which is hypotonic to plasma. Profuse sweating without adequate repletion of water and Na^+-Cl^- can thus lead to both hypovolemia and hypertonicity. Alternatively, replacement of these insensible losses with a surfeit of free water, without adequate replacement of electrolytes, may lead to hypovolemic hyponatremia.

Excessive fluid accumulation in interstitial and/or peritoneal spaces can also cause intravascular hypovolemia. Increases in vascular permeability and/or a reduction in oncotic pressure (hypoalbuminemia) alter Starling forces, resulting in excessive "third spacing" of the ECFV. This occurs in sepsis syndrome, burns, pancreatitis, nutritional hypoalbuminemia, and peritonitis. Alternatively, distributive hypovolemia can occur due to accumulation of fluid within specific compartments, for example within the bowel lumen in gastrointestinal obstruction or ileus. Hypovolemia can also occur after extracorporeal hemorrhage or after significant hemorrhage into an expandable space, for example, the retroperitoneum.

Diagnostic Evaluation A careful history will usually determine the etiologic cause of hypovolemia. Symptoms of hypovolemia are nonspecific and include fatigue, weakness, thirst, and postural dizziness; more severe symptoms and signs include oliguria, cyanosis, abdominal and chest pain, and confusion or obtundation. Associated electrolyte disorders may cause additional symptoms, for example, muscle weakness in patients with hypokalemia. On examination, diminished skin turgor and dry oral mucous membranes are less than ideal markers of a decreased ECFV in adult patients; more reliable signs of hypovolemia include a decreased jugular venous pressure (JVP), orthostatic tachycardia (an increase of >15–20 beats/min upon standing), and orthostatic hypotension (a >10–20 mmHg drop in blood pressure on standing). More severe fluid loss leads to hypovolemic shock, with hypotension, tachycardia, peripheral vasoconstriction, and peripheral hypoperfusion; these patients may exhibit peripheral cyanosis, cold extremities, oliguria, and altered mental status.

Routine chemistries may reveal an increase in blood urea nitrogen (BUN) and creatinine, reflective of a decrease in GFR. Creatinine is the more dependable measure of GFR, because BUN levels may be influenced by an increase in tubular reabsorption ("prerenal azotemia"), an increase in urea generation in catabolic states, hyperalimentation, or gastrointestinal bleeding, and/or a decreased urea generation in decreased protein intake. In hypovolemic shock, liver function tests and cardiac biomarkers may show evidence of hepatic and cardiac ischemia, respectively. Routine chemistries and/or blood gases may reveal evidence of acid-base disorders. For example, bicarbonate loss due to diarrheal illness is a very common cause of metabolic acidosis; alternatively, patients with severe hypovolemic shock may develop lactic acidosis with an elevated anion gap.

The neurohumoral response to hypovolemia stimulates an increase in renal tubular Na^+ and water reabsorption. Therefore, the urine Na^+ concentration is typically <20 m*M* in nonrenal causes of hypovolemia, with a urine osmolality of >450 mOsm/kg. The reduction in both GFR and distal tubular Na^+ delivery may cause a defect in renal potassium excretion, with an increase in plasma K^+ concentration. Of note, patients with hypovolemia and a hypochloremic alkalosis due to vomiting, diarrhea, or diuretics will typically have a urine Na^+ concentration >20 m*M* and urine pH of >7.0, due to the increase in filtered HCO_3^-; the urine Cl^- concentration in this setting is a more accurate indicator of volume status, with a level <25 m*M* suggestive of hypovolemia. The urine Na^+ concentration is often >20 m*M* in patients with *renal* causes of hypovolemia, such as acute tubular necrosis; similarly, patients with DI will have an inappropriately dilute urine.

TREATMENT

Hypovolemia

The therapeutic goals in hypovolemia are to restore normovolemia and replace ongoing fluid losses. Mild hypovolemia can usually be treated with oral hydration and resumption of a normal maintenance diet. More severe hypovolemia requires intravenous hydration, tailoring the choice of solution to the underlying pathophysiology. Isotonic, "normal" saline (0.9% NaCl, 154 m*M* Na^+) is the most appropriate resuscitation fluid for normonatremic or hyponatremic patients with severe hypovolemia; colloid solutions such as intravenous albumin are not demonstrably superior for this purpose. Hypernatremic patients should receive a hypotonic solution, 5% dextrose if there has only been water loss (as in DI), or hypotonic saline (1/2 or 1/4 normal saline) if there has been water and Na^+-Cl^- loss; changes in free water administration should be made if necessary, based on frequent measuring of serum chemistries. Patients with bicarbonate loss and metabolic acidosis, as occur frequently in diarrhea, should receive intravenous bicarbonate, either an isotonic solution (150 meq of Na^+-HCO_3^- in 5% dextrose) or a more hypotonic bicarbonate solution in dextrose or dilute saline. Patients with severe hemorrhage or anemia should receive red cell transfusions, without increasing the hematocrit beyond 35%.

SODIUM DISORDERS

Disorders of serum Na^+ concentration are caused by abnormalities in water homeostasis, leading to changes in the relative ratio of Na^+ to body water. Water intake and circulating AVP constitute the two key effectors in the defense of serum osmolality; defects in one or both of these two defense mechanisms cause most cases of hyponatremia and hypernatremia. In contrast, abnormalities in sodium homeostasis *per se* lead to a deficit or surplus of whole-body Na^+-Cl^- content, a key determinant of the ECFV and circulatory integrity. Notably, volume status also modulates the release of AVP by the posterior pituitary, such that hypovolemia is associated with higher circulating levels of the hormone at each level of serum osmolality. Similarly, in "hypervolemic" causes of arterial underfilling, e.g., heart failure and cirrhosis, the associated neurohumoral activation encompasses an increase in circulating AVP, leading to water retention and hyponatremia. Therefore, a key concept in sodium disorders is that the absolute plasma Na^+ concentration tells one nothing about the volume status of a given patient, which furthermore must be taken into account in the diagnostic and therapeutic approach.

HYPONATREMIA

Hyponatremia, which is defined as a plasma Na^+ concentration <135 m*M*, is a very common disorder, occurring in up to 22% of hospitalized patients. This disorder is almost always the result of an increase in circulating AVP and/or increased renal sensitivity to AVP, combined with an intake of free water; a notable exception is hyponatremia due to low solute intake (see below). The underlying pathophysiology for the exaggerated or "inappropriate" AVP response differs in patients with hyponatremia as a function of their ECFV. Hyponatremia is thus subdivided diagnostically into three groups, depending on clinical history and volume status, i.e., "hypovolemic," "euvolemic," and "hypervolemic" **(Fig. 49-5)**.

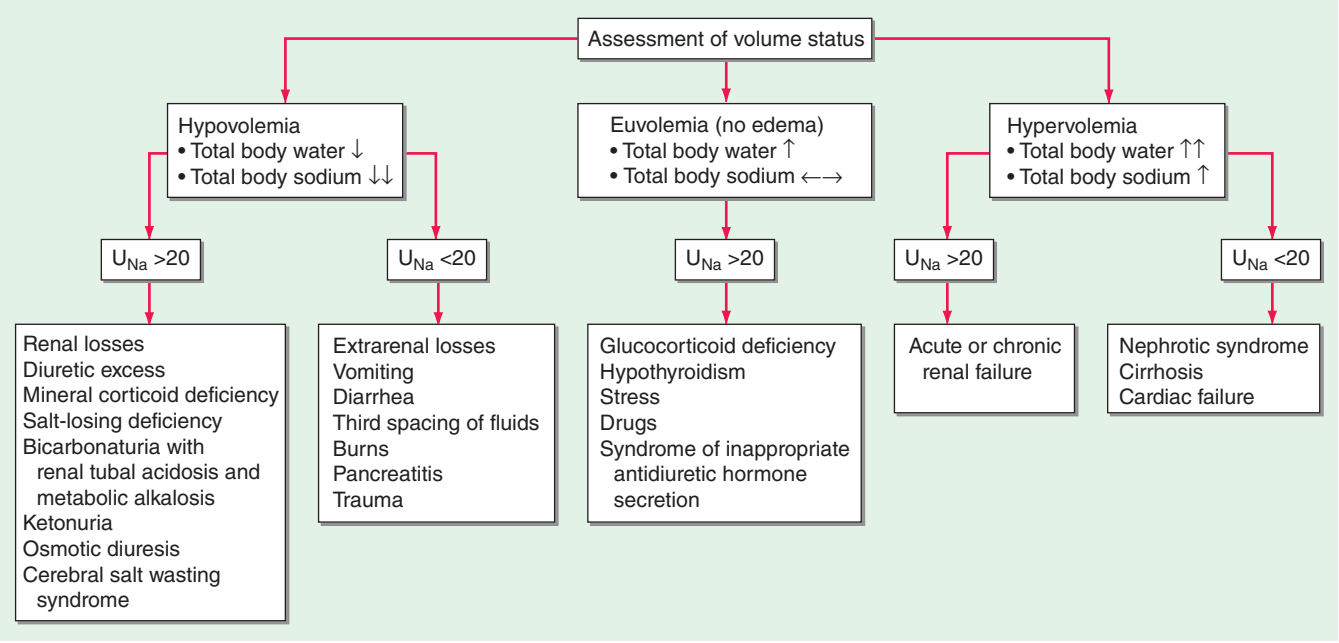

FIGURE 49-5 The diagnostic approach to hyponatremia. *(From S Kumar, T Berl: Diseases of water metabolism, in Atlas of Diseases of the Kidney, RW Schrier [ed]. Philadelphia, Current Medicine, Inc, 1999; with permission.)*

Hypovolemic Hyponatremia Hypovolemia causes a marked neurohumoral activation, increasing circulating levels of AVP. The increase in circulating AVP helps preserve blood pressure via vascular and baroreceptor V_{1A} receptors and increases water reabsorption via renal V_2 receptors; activation of V_2 receptors can lead to hyponatremia in the setting of increased free water intake. Nonrenal causes of hypovolemic hyponatremia include GI loss (e.g., vomiting, diarrhea, tube drainage) and insensible loss (sweating, burns) of Na^+-Cl^- and water, in the absence of adequate oral replacement; urine Na^+ concentration is typically <20 m*M*. Notably, these patients may be clinically classified as euvolemic, with only the reduced urinary Na^+ concentration to indicate the cause of their hyponatremia. Indeed, a urine Na^+ concentration <20 m*M*, in the absence of a cause of hypervolemic hyponatremia, predicts a rapid increase in plasma Na^+ concentration in response to intravenous normal saline; saline therapy thus induces a water diuresis in this setting, as circulating AVP levels plummet.

The *renal* causes of hypovolemic hyponatremia share an inappropriate loss of Na^+-Cl^- in the urine, leading to volume depletion and an increase in circulating AVP; urine Na^+ concentration is typically >20 m*M* (Fig. 49-5). A deficiency in circulating aldosterone and/or its renal effects can lead to hyponatremia in primary adrenal insufficiency and other causes of hypoaldosteronism; hyperkalemia and hyponatremia in a hypotensive and/or hypovolemic patient with high urine Na^+ concentration (much greater than 20 m*M*) should strongly suggest this diagnosis. Salt-losing nephropathies may lead to hyponatremia when sodium intake is reduced, due to impaired renal tubular function; typical causes include reflux nephropathy, interstitial nephropathies, postobstructive uropathy, medullary cystic disease, and the recovery phase of acute tubular necrosis. Thiazide diuretics cause hyponatremia via a number of mechanisms, including polydipsia and diuretic-induced volume depletion. Notably, thiazides do not inhibit the renal concentrating mechanism, such that circulating AVP retains a full effect on renal water retention. In contrast, loop diuretics, which are less frequently associated with hyponatremia, inhibit Na^+-Cl^- and K^+ absorption by the TALH, blunting the countercurrent mechanism and reducing the ability to concentrate the urine. Increased excretion of an osmotically active nonreabsorbable or poorly reabsorbable solute can also lead to volume depletion and hyponatremia; important causes include glycosuria, ketonuria (e.g., in starvation or in diabetic or alcoholic ketoacidosis), and bicarbonaturia (e.g., in renal tubular acidosis or metabolic alkalosis, where the associated bicarbonaturia leads to loss of Na^+).

Finally, the syndrome of "cerebral salt wasting" is a rare cause of hypovolemic hyponatremia, encompassing hyponatremia with clinical hypovolemia and inappropriate natriuresis in association with intracranial disease; associated disorders include subarachnoid hemorrhage, traumatic brain injury, craniotomy, encephalitis, and meningitis. Distinction from the more common syndrome of inappropriate antidiuresis (SIAD) is critical because cerebral salt wasting will typically respond to aggressive Na^+-Cl^- repletion.

Hypervolemic Hyponatremia Patients with hypervolemic hyponatremia develop an increase in total-body Na^+-Cl^- that is accompanied by a proportionately *greater* increase in total-body water, leading to a reduced plasma Na^+ concentration. As in hypovolemic hyponatremia, the causative disorders can be separated by the effect on urine Na^+ concentration, with acute or chronic renal failure uniquely associated with an increase in urine Na^+ concentration (Fig. 49-5). The pathophysiology of hyponatremia in the sodium-avid edematous disorders (congestive heart failure [CHF], cirrhosis, and nephrotic syndrome) is similar to that in hypovolemic hyponatremia, except that arterial filling and circulatory integrity is decreased due to the specific etiologic factors (e.g., cardiac dysfunction in CHF, peripheral vasodilation in cirrhosis). Urine Na^+ concentration is typically very low, i.e., <10 m*M*, even after hydration with normal saline; this Na^+-avid state may be obscured by diuretic therapy. The degree of hyponatremia provides an indirect index of the associated neurohumoral activation and is an important prognostic indicator in hypervolemic hyponatremia.

Euvolemic Hyponatremia Euvolemic hyponatremia can occur in moderate to severe hypothyroidism, with correction after achieving a euthyroid state. Severe hyponatremia can also be a consequence of secondary adrenal insufficiency due to pituitary disease; whereas the deficit in circulating aldosterone in primary adrenal insufficiency causes *hypovolemic* hyponatremia, the predominant glucocorticoid deficiency in secondary adrenal failure is associated with *euvolemic* hyponatremia. Glucocorticoids exert a negative feedback on AVP release by the posterior pituitary such that hydrocortisone replacement in these patients can rapidly normalize the AVP response to osmolality, reducing circulating AVP.

The SIAD is the most frequent cause of euvolemic hyponatremia (Table 49-1). The generation of hyponatremia in SIAD requires an intake of free water, with persistent intake at serum osmolalities that are lower than the usual threshold for thirst; as one would expect,

TABLE 49-1 Causes of the Syndrome of Inappropriate Antidiuresis (SIAD)

MALIGNANT DISEASES	PULMONARY DISORDERS	DISORDERS OF THE CENTRAL NERVOUS SYSTEM	DRUGS	OTHER CAUSES
Carcinoma	Infections	Infection	Drugs that stimulate release of AVP or enhance its action	Hereditary (gain-of-function mutations in the vasopressin V_2 receptor)
Lung	Bacterial pneumonia	Encephalitis	Chlorpropamide	Idiopathic
Small cell	Viral pneumonia	Meningitis	SSRIs	Transient
Mesothelioma	Pulmonary abscess	Brain abscess	Tricyclic antidepressants	Endurance exercise
Oropharynx	Tuberculosis	Rocky Mountain spotted fever	Clofibrate	General anesthesia
Gastrointestinal tract	Aspergillosis	AIDS	Carbamazepine	Nausea
Stomach	Asthma	Bleeding and masses	Vincristine	Pain
Duodenum	Cystic fibrosis	Subdural hematoma	Nicotine	Stress
Pancreas	Respiratory failure associated with positive-pressure breathing	Subarachnoid hemorrhage	Narcotics	
Genitourinary tract		Cerebrovascular accident	Antipsychotic drugs	
Ureter		Brain tumors	Ifosfamide	
Bladder		Head trauma	Cyclophosphamide	
Prostate		Hydrocephalus	Nonsteroidal anti-inflammatory drugs	
Endometrium		Cavernous sinus thrombosis	MDMA ("ecstasy")	
Endocrine thymoma		Other	AVP analogues	
Lymphomas		Multiple sclerosis	Desmopressin	
Sarcomas		Guillain-Barré syndrome	Oxytocin	
Ewing's sarcoma		Shy-Drager syndrome	Vasopressin	
		Delirium tremens		
		Acute intermittent porphyria		

Abbreviations: AVP, vasopressin; MDMA; 3,4-methylenedioxymethamphetamine; SSRI, selective serotonin reuptake inhibitor.

Source: From DH Ellison, T Berl: Syndrome of inappropriate antidiuresis. N Engl J Med 356:2064, 2007.

the osmotic threshold and osmotic response curves for the sensation of thirst are shifted downward in patients with SIAD. Four distinct patterns of AVP secretion have been recognized in patients with SIAD, independent for the most part of the underlying cause. Unregulated, erratic AVP secretion is seen in about a third of patients, with no obvious correlation between serum osmolality and circulating AVP levels. Other patients fail to suppress AVP secretion at lower serum osmolalities, with a normal response curve to hyperosmolar conditions; others have a "reset osmostat," with a lower threshold osmolality and a left-shifted osmotic response curve. Finally, the fourth subset of patients have essentially no detectable circulating AVP, suggesting either a gain in function in renal water reabsorption or a circulating antidiuretic substance that is distinct from AVP. Gain-in-function mutations of a single specific residue in the V_2 AVP receptor have been described in some of these patients, leading to constitutive activation of the receptor in the absence of AVP and "nephrogenic" SIAD.

Strictly speaking, patients with SIAD are not euvolemic but are subclinically volume-expanded, due to AVP-induced water and Na^+-Cl^- retention; "AVP escape" mechanisms invoked by sustained increases in AVP serve to limit distal renal tubular transport, preserving a modestly hypervolemic steady state. Serum uric acid is often low (<4 mg/dL) in patients with SIAD, consistent with suppressed proximal tubular transport in the setting of increased distal tubular Na^+-Cl^- and water transport; in contrast, patients with hypovolemic hyponatremia will often be hyperuricemic, due to a shared activation of proximal tubular Na^+-Cl^- and urate transport.

Common causes of SIAD include pulmonary disease (e.g., pneumonia, tuberculosis, pleural effusion) and central nervous system (CNS) diseases (e.g., tumor, subarachnoid hemorrhage, meningitis). SIAD also occurs with malignancies, most commonly with small-cell lung carcinoma (75% of malignancy-associated SIAD); ~10% of patients with this tumor will have a plasma Na^+ concentration of <130 m*M* at presentation. SIAD is also a frequent complication of certain drugs, most commonly the selective serotonin reuptake inhibitors (SSRIs). Other drugs can potentiate the renal effect of AVP, without exerting direct effects on circulating AVP levels (Table 49-1).

Low Solute Intake and Hyponatremia Hyponatremia can occasionally occur in patients with a very low intake of dietary solutes. Classically, this occurs in alcoholics whose sole nutrient is beer, hence the diagnostic label of *beer potomania*; beer is very low in protein and salt content, containing only 1–2 m*M* of Na^+. The syndrome has also been described in nonalcoholic patients with highly restricted solute intake due to nutrient-restricted diets, e.g., extreme vegetarian diets. Patients with hyponatremia due to low solute intake typically present with a very low urine osmolality (<100–200 mOsm/kg) with a urine Na^+ concentration that is <10–20 m*M*. The fundamental abnormality is the inadequate dietary intake of solutes; the reduced urinary solute excretion limits water excretion such that hyponatremia ensues after relatively modest polydipsia. AVP levels have not been reported in patients with beer potomania but are expected to be suppressed or rapidly suppressible with saline hydration; this fits with the overly rapid correction in plasma Na^+ concentration that can be seen with saline hydration. Resumption of a normal diet and/or saline hydration will also correct the causative deficit in urinary solute excretion, such that patients with beer potomania typically correct their plasma Na^+ concentration promptly after admission to the hospital.

Clinical Features of Hyponatremia Hyponatremia induces generalized cellular swelling, a consequence of water movement down the osmotic gradient from the hypotonic ECF to the ICF. The symptoms of hyponatremia are primarily neurologic, reflecting the development of cerebral edema within a rigid skull. The initial CNS response to acute hyponatremia is an increase in interstitial pressure, leading to shunting of ECF and solutes from the interstitial space into the cerebrospinal fluid and then on into the systemic circulation. This is accompanied by an efflux of the major intracellular ions, Na^+, K^+, and Cl^-, from brain cells. Acute hyponatremic encephalopathy ensues when these volume regulatory mechanisms are overwhelmed by a rapid decrease in tonicity, resulting in acute cerebral edema. Early symptoms can include nausea, headache, and vomiting. However, severe complications can rapidly evolve, including seizure activity, brainstem herniation, coma, and death. A key complication of acute hyponatremia is normocapneic or hypercapneic respiratory failure; the associated hypoxia may amplify the neurologic injury. Normocapneic respiratory failure in this setting is typically due to noncardiogenic, "neurogenic" pulmonary edema, with a normal pulmonary capillary wedge pressure.

TABLE 49-2 Causes of Acute Hyponatremia

Iatrogenic
Postoperative: premenopausal women
Hypotonic fluids with cause of ↑ vasopressin
Glycine irrigation: TURP, uterine surgery
Colonoscopy preparation
Recent institution of thiazides
Polydipsia
MDMA ("ecstasy," "Molly") ingestion
Exercise induced
Multifactorial, e.g., thiazide and polydipsia

Abbreviations: MDMA, 3,4-methylenedioxymethamphetamine; TURP, transurethral resection of the prostate.

Acute symptomatic hyponatremia is a medical emergency, occurring in a number of specific settings **(Table 49-2)**. Women, particularly before menopause, are much more likely than men to develop encephalopathy and severe neurologic sequelae. Acute hyponatremia often has an iatrogenic component, e.g., when hypotonic intravenous fluids are given to postoperative patients with an increase in circulating AVP. Exercise-associated hyponatremia, an important clinical issue at marathons and other endurance events, has similarly been linked to both a "nonosmotic" increase in circulating AVP and excessive free water intake. The recreational drugs Molly and ecstasy, which share an active ingredient (MDMA, 3,4-methylenedioxymethamphetamine), cause a rapid and potent induction of both thirst and AVP, leading to severe acute hyponatremia.

Persistent, chronic hyponatremia results in an efflux of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine) from brain cells; this response reduces intracellular osmolality and the osmotic gradient favoring water entry. This reduction in intracellular osmolytes is largely complete within 48 h, the time period that clinically defines chronic hyponatremia; this temporal definition has considerable relevance for the treatment of hyponatremia (see below). The cellular response to chronic hyponatremia does not fully protect patients from symptoms, which can include vomiting, nausea, confusion, and seizures, usually at plasma Na^+ concentration <125 m*M*. Even patients who are judged "asymptomatic" can manifest subtle gait and cognitive defects that reverse with correction of hyponatremia; notably, chronic "asymptomatic" hyponatremia increases the risk of falls. Chronic hyponatremia also increases the risk of bony fractures owing to the associated neurologic dysfunction and to a hyponatremia-associated reduction in bone density. Therefore, every attempt should be made to safely correct the plasma Na^+ concentration in patients with chronic hyponatremia, even in the absence of overt symptoms (see the section on treatment of hyponatremia below).

The management of chronic hyponatremia is complicated significantly by the asymmetry of the cellular response to correction of plasma Na^+ concentration. Specifically, the *reaccumulation* of organic osmolytes by brain cells is attenuated and delayed as osmolality increases after correction of hyponatremia, sometimes resulting in degenerative loss of oligodendrocytes and an osmotic demyelination syndrome (ODS). Overly rapid correction of hyponatremia (>8–10 m*M* in 24 h or 18 m*M* in 48 h) is also associated with a disruption in integrity of the blood-brain barrier, allowing the entry of immune mediators that may contribute to demyelination. The lesions of ODS classically affect the pons, a neuroanatomic structure wherein the delay in the reaccumulation of osmotic osmolytes is particularly pronounced; clinically, patients with central pontine myelinolysis can present 1 or more days after overcorrection of hyponatremia with paraparesis or quadriparesis,

dysphagia, dysarthria, diplopia, a "locked-in syndrome," and/or loss of consciousness. Other regions of the brain can also be involved in ODS, most commonly in association with lesions of the pons but occasionally in isolation; in order of frequency, the lesions of extrapontine myelinolysis can occur in the cerebellum, lateral geniculate body, thalamus, putamen, and cerebral cortex or subcortex. Clinical presentation of ODS can, therefore, vary as a function of the extent and localization of extrapontine myelinolysis, with the reported development of ataxia, mutism, parkinsonism, dystonia, and catatonia. Relowering of plasma Na^+ concentration after overly rapid correction can prevent or attenuate ODS (see the section on treatment of hyponatremia below). However, even appropriately slow correction can be associated with ODS, particularly in patients with additional risk factors; these include alcoholism, malnutrition, hypokalemia, and liver transplantation.

Diagnostic Evaluation of Hyponatremia Clinical assessment of hyponatremic patients should focus on the underlying cause; a detailed drug history is particularly crucial (Table 49-1). A careful clinical assessment of volume status is obligatory for the classical diagnostic approach to hyponatremia (Fig. 49-5). Hyponatremia is frequently multifactorial, particularly when severe; clinical evaluation should consider *all* the possible causes for excessive circulating AVP, including volume status, drugs, and the presence of nausea and/or pain. Radiologic imaging may also be appropriate to assess whether patients have a pulmonary or CNS cause for hyponatremia. A screening chest x-ray may fail to detect a small-cell carcinoma of the lung; computed tomography (CT) scanning of the thorax should be considered in patients at high risk for this tumor (e.g., patients with a smoking history).

Laboratory investigation should include a measurement of serum osmolality to exclude pseudohyponatremia, which is defined as the coexistence of hyponatremia with a normal or increased plasma tonicity. Most clinical laboratories measure plasma Na^+ concentration by testing diluted samples with automated ion-sensitive electrodes, correcting for this dilution by assuming that plasma is 93% water. This correction factor can be inaccurate in patients with pseudohyponatremia due to extreme hyperlipidemia and/or hyperproteinemia, in whom serum lipid or protein makes up a greater percentage of plasma volume. The measured osmolality should also be converted to the effective osmolality (tonicity) by subtracting the measured concentration of urea (divided by 2.8, if in mg/dL); patients with hyponatremia have an effective osmolality of <275 mOsm/kg.

Elevated BUN and creatinine in routine chemistries can also indicate renal dysfunction as a potential cause of hyponatremia, whereas hyperkalemia may suggest adrenal insufficiency or hypoaldosteronism. Serum glucose should also be measured; plasma Na^+ concentration falls by ~1.6–2.4 m*M* for every 100-mg/dL increase in glucose, due to glucose-induced water efflux from cells; this "true" hyponatremia resolves after correction of hyperglycemia. Measurement of serum uric acid should also be performed; whereas patients with SIAD-type physiology will typically be hypouricemic (serum uric acid <4 mg/dL), volume-depleted patients will often be hyperuricemic. In the appropriate clinical setting, thyroid, adrenal, and pituitary function should also be tested; hypothyroidism and secondary adrenal failure due to pituitary insufficiency are important causes of euvolemic hyponatremia, whereas primary adrenal failure causes hypovolemic hyponatremia. A cosyntropin stimulation test is necessary to assess for primary adrenal insufficiency.

Urine electrolytes and osmolality are crucial tests in the initial evaluation of hyponatremia. A urine Na^+ concentration <20–30 m*M* is consistent with hypovolemic hyponatremia, in the clinical absence of a hypervolemic, Na^+-avid syndrome such as CHF (Fig. 49-5). In contrast, patients with SIAD will typically excrete urine with an Na^+ concentration that is >30 m*M*. However, there can be substantial overlap in urine Na^+ concentration values in patients with SIAD and hypovolemic hyponatremia, particularly in the elderly; the ultimate "gold standard" for the diagnosis of hypovolemic hyponatremia is the demonstration that plasma Na^+ concentration corrects after hydration with normal saline. Patients with thiazide-associated hyponatremia may also present with higher than expected urine Na^+ concentration and other findings suggestive of SIAD; one should defer making a diagnosis of SIAD in these patients until 1–2 weeks after discontinuing the thiazide. A urine osmolality <100 mOsm/kg is suggestive of polydipsia; urine osmolality >400 mOsm/kg indicates that AVP excess is playing a more dominant role, whereas intermediate values are more consistent with multifactorial pathophysiology (e.g., AVP excess with a significant component of polydipsia). Patients with hyponatremia due to decreased solute intake (beer potomania) typically have urine Na^+ concentration <20 m*M* and urine osmolality in the range of <100 to the low 200s. Finally, the measurement of urine K^+ concentration is required to calculate the urine-to-plasma electrolyte ratio, which is useful to predict the response to fluid restriction (see the section on treatment of hyponatremia below).

TREATMENT

Hyponatremia

Three major considerations guide the therapy of hyponatremia. First, the presence and/or severity of symptoms determine the urgency and goals of therapy. Patients with acute hyponatremia (Table 49-2) present with symptoms that can range from headache, nausea, and/or vomiting, to seizures, obtundation, and central herniation; patients with chronic hyponatremia, present for >48 h, are less likely to have severe symptoms. Second, patients with chronic hyponatremia are at risk for ODS if plasma Na^+ concentration is corrected by >8–10 m*M* within the first 24 h and/or by >18 m*M* within the first 48 h. Third, the response to interventions such as hypertonic saline, isotonic saline, or AVP antagonists can be highly unpredictable, such that frequent monitoring of plasma Na^+ concentration during corrective therapy is imperative.

Once the urgency in correcting the plasma Na^+ concentration has been established and appropriate therapy instituted, the focus should be on treatment or withdrawal of the underlying cause. Patients with euvolemic hyponatremia due to SIAD, hypothyroidism, or secondary adrenal failure will respond to successful treatment of the underlying cause, with an increase in plasma Na^+ concentration. However, not all causes of SIAD are immediately reversible, necessitating pharmacologic therapy to increase the plasma Na^+ concentration (see below). Hypovolemic hyponatremia will respond to intravenous hydration with isotonic normal saline, with a rapid reduction in circulating AVP and a brisk water diuresis; it may be necessary to reduce the rate of correction if the history suggests that hyponatremia has been chronic, i.e., present for more than 48 h (see below). Hypervolemic hyponatremia due to CHF will often respond to improved therapy of the underlying cardiomyopathy, e.g., following the institution or intensification of angiotensin-converting enzyme (ACE) inhibition. Finally, patients with hyponatremia due to beer potomania and low solute intake will respond very rapidly to intravenous saline and the resumption of a normal diet. Notably, patients with beer potomania have a very high risk of developing ODS, due to the associated hypokalemia, alcoholism, malnutrition, and high risk of overcorrecting the plasma Na^+ concentration.

Water deprivation has long been a cornerstone of the therapy of chronic hyponatremia. However, patients who are excreting minimal electrolyte-free water will require aggressive fluid restriction; this can be very difficult for patients with SIAD to tolerate, given that their thirst is also inappropriately stimulated. The urine-to-plasma electrolyte ratio (urinary $[Na^+] + [K^+]$/plasma $[Na^+]$) can be exploited as a quick indicator of electrolyte-free water excretion **(Table 49-3)**; patients with a ratio of >1 should be more aggressively restricted (<500 mL/d), those with a ratio of ~1 should be restricted to 500–700 mL/d, and those with a ratio <1 should be restricted to <1 L/d. In hypokalemic patients, potassium replacement will serve to increase plasma Na^+ concentration, given that the plasma Na^+ concentration is a functional of both exchangeable Na^+ and exchangeable K^+ divided by total-body water; a corollary is that aggressive repletion of K^+ has the potential to overcorrect the plasma

TABLE 49-3 Management of Hypernatremia

Water Deficit
1. Estimate total-body water (TBW): 50% of body weight in women and 60% in men
2. Calculate free-water deficit: $[(Na^+ - 140)/140] \times TBW$
3. Administer deficit over 48–72 h, without decrease in plasma Na^+ concentration by >10 m*M*/24 h
Ongoing Water Losses
4. Calculate free-water clearance, C_eH_2O: $$C_eH_2O = V \times \left(1 - \frac{U_{Na} + U_K}{P_{Na}}\right)$$ where V is urinary volume, U_{Na} is urinary $[Na^+]$, U_K is urinary $[K^+]$, and P_{Na} is plasma $[Na^+]$
Insensible Losses
5. ~10 mL/kg per day: less if ventilated, more if febrile
Total
6. Add components to determine water deficit and ongoing water loss; correct the water deficit over 48–72 h and replace daily water loss. Avoid correction of plasma $[Na^+]$ by >10 m*M*/d.

Na^+ concentration even in the absence of hypertonic saline. Plasma Na^+ concentration will also tend to respond to an increase in dietary solute intake, which increases the ability to excrete free water; this can be accomplished with oral salt tablets and with newly available, palatable preparations of oral urea.

Patients in whom therapy with fluid restriction, potassium replacement, and/or increased solute intake fails may merit pharmacologic therapy to increase their plasma Na^+ concentration. Many patients with SIAD respond to combined therapy with oral furosemide, 20 mg twice a day (higher doses may be necessary in renal insufficiency), and oral salt tablets; furosemide serves to inhibit the renal countercurrent mechanism and blunt urinary concentrating ability, whereas the salt tablets counteract diuretic-associated natriuresis. Demeclocycline is a potent inhibitor of principal cells and can be used in patients whose Na levels do not increase in response to furosemide and salt tablets. However, this agent can be associated with a reduction in GFR, due to excessive natriuresis and/or direct renal toxicity; it should be avoided in cirrhotic patients in particular, who are at higher risk of nephrotoxicity due to drug accumulation. If available, palatable preparations of oral urea can also be used to manage SIAD; the increase in solute excretion with oral urea ingestion increases free water excretion, thus reducing the plasma Na^+.

AVP antagonists (vaptans) are highly effective in SIAD and in hypervolemic hyponatremia due to heart failure or cirrhosis, reliably increasing plasma Na^+ concentration due to their "aquaretic" effects (augmentation of free water clearance). Most of these agents specifically antagonize the V_2 AVP receptor; tolvaptan is currently the only oral V_2 antagonist to be approved by the U.S. Food and Drug Administration. Conivaptan, the only available intravenous vaptan, is a mixed V_{1A}/V_2 antagonist, with a modest risk of hypotension due to V_{1A} receptor inhibition. Therapy with vaptans must be initiated in a hospital setting, with a liberalization of fluid restriction (>2 L/d) and close monitoring of plasma Na^+ concentration. Although approved for the management of all but hypovolemic hyponatremia and acute hyponatremia, the clinical indications are limited. Oral tolvaptan is perhaps most appropriate for the management of significant and persistent SIAD (e.g., in small-cell lung carcinoma) that has not responded to water restriction and/or oral furosemide and salt tablets. Abnormalities in liver function tests have been reported with chronic tolvaptan therapy; hence, the use of this agent should be restricted to <1–2 months.

Treatment of acute symptomatic hyponatremia should include hypertonic 3% saline (513 m*M*) to acutely increase plasma Na^+ concentration by 1–2 m*M*/h to a total of 4–6 m*M*; this modest increase is typically sufficient to alleviate severe acute symptoms, after which corrective guidelines for chronic hyponatremia are appropriate (see below). A number of equations have been developed to estimate the required rate of hypertonic saline, which has an Na^+-Cl^- concentration of 513 m*M*. The traditional approach is to calculate an Na^+ deficit, where the Na^+ deficit = 0.6 × body weight × (target plasma Na^+ concentration − starting plasma Na^+ concentration), followed by a calculation of the required rate. Regardless of the method used to determine the rate of administration, the increase in plasma Na^+ concentration can be highly unpredictable during treatment with hypertonic saline, due to rapid changes in the underlying physiology; plasma Na^+ concentration should be monitored every 2–4 h during treatment, with appropriate changes in therapy based on the observed rate of change. The administration of supplemental oxygen and ventilatory support is also critical in acute hyponatremia, in the event that patients develop acute pulmonary edema or hypercapneic respiratory failure. Intravenous loop diuretics will help treat acute pulmonary edema and will also increase free water excretion, by interfering with the renal countercurrent multiplication system. AVP antagonists do *not* have an approved role in the management of acute hyponatremia.

The rate of correction should be comparatively slow in *chronic* hyponatremia (<8–10 m*M* in the first 24 h and <18 m*M* in the first 48 h), so as to avoid ODS; lower target rates are appropriate in patients at particular risk for ODS, such as alcoholics or hypokalemic patients. Overcorrection of the plasma Na^+ concentration can occur when AVP levels rapidly normalize, for example following the treatment of patients with chronic hypovolemic hyponatremia with intravenous saline or following glucocorticoid replacement of patients with hypopituitarism and secondary adrenal failure. Approximately 10% of patients treated with vaptans will overcorrect; the risk is increased if water intake is not liberalized. In the event that the plasma Na^+ concentration overcorrects following therapy, be it with hypertonic saline, isotonic saline, or a vaptan, hyponatremia can be safely reinduced or stabilized by the administration of the AVP *agonist* desmopressin acetate (DDAVP) and/or the administration of free water, typically intravenous D_5W; the goal is to prevent or reverse the development of ODS. Alternatively, the treatment of patients with marked hyponatremia can be initiated with the twice-daily administration of DDAVP to maintain constant AVP bioactivity, combined with the administration of hypertonic saline to slowly correct the serum sodium in a more controlled fashion, thus reducing upfront the risk of overcorrection.

HYPERNATREMIA

Etiology Hypernatremia is defined as an increase in the plasma Na^+ concentration to >145 m*M*. Considerably less common than hyponatremia, hypernatremia is nonetheless associated with mortality rates of as high as 40–60%, mostly due to the severity of the associated underlying disease processes. Hypernatremia is usually the result of a combined water and electrolyte deficit, with losses of H_2O in excess of Na^+. Less frequently, the ingestion or iatrogenic administration of excess Na^+ can be causative, for example after IV administration of excessive hypertonic Na^+-Cl^- or Na^+-HCO_3^- **(Fig. 49-6)**.

Elderly individuals with reduced thirst and/or diminished access to fluids are at the highest risk of developing hypernatremia. Patients with hypernatremia may rarely have a central defect in hypothalamic osmoreceptor function, with a mixture of both decreased thirst and reduced AVP secretion. Causes of this adipsic DI include primary or metastatic tumor, occlusion or ligation of the anterior communicating artery, trauma, hydrocephalus, and inflammation.

Hypernatremia can develop following the loss of water via both renal and nonrenal routes. Insensible losses of water may increase in the setting of fever, exercise, heat exposure, severe burns, or mechanical ventilation. Diarrhea is, in turn, the most common gastrointestinal cause of hypernatremia. Notably, osmotic diarrhea and viral gastroenteritides typically generate stools with Na^+ and K^+ <100 m*M*, thus leading to water loss and hypernatremia; in contrast, secretory diarrhea

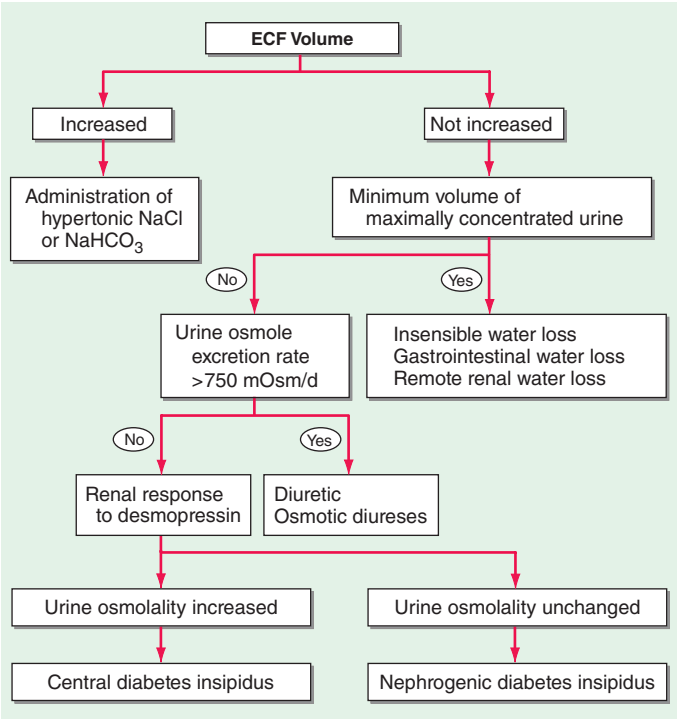

FIGURE 49-6 The diagnostic approach to hypernatremia. ECF, extracellular fluid.

typically results in isotonic stool and thus hypovolemia with or without hypovolemic hyponatremia.

Common causes of renal water loss include osmotic diuresis secondary to hyperglycemia, excess urea, postobstructive diuresis, or mannitol; these disorders share an increase in urinary solute excretion and urinary osmolality (see "Diagnostic Approach," below). Hypernatremia due to a water diuresis occurs in central or nephrogenic DI (NDI).

NDI is characterized by renal resistance to AVP, which can be partial or complete (see "Diagnostic Approach," below). Genetic causes include loss-of-function mutations in the X-linked V_2 receptor; mutations in the AVP-responsive aquaporin-2 water channel can cause autosomal recessive and autosomal dominant NDI, whereas recessive deficiency of the aquaporin-1 water channel causes a more modest concentrating defect (Fig. 49-2). Hypercalcemia can also cause polyuria and NDI; calcium signals directly through the calcium-sensing receptor to downregulate Na^+, K^+, and Cl^- transport by the TALH and water transport in principal cells, thus reducing renal concentrating ability in hypercalcemia. Another common acquired cause of NDI is hypokalemia, which inhibits the renal response to AVP and downregulates aquaporin-2 expression. Several drugs can cause acquired NDI, in particular lithium, ifosfamide, and several antiviral agents. Lithium causes NDI by multiple mechanisms, including direct inhibition of renal glycogen synthase kinase-3 (GSK3), a kinase thought to be the pharmacologic target of lithium in bipolar disease; GSK3 is required for the response of principal cells to AVP. The entry of lithium through the amiloride-sensitive Na^+ channel ENaC (Fig. 49-4) is required for the effect of the drug on principal cells, such that combined therapy within lithium and amiloride can mitigate lithium-associated NDI. However, lithium causes chronic tubulointerstitial scarring and chronic kidney disease after prolonged therapy, such that patients may have a persistent NDI long after stopping the drug, with a reduced therapeutic benefit from amiloride.

Finally, gestational DI is a rare complication of late-term pregnancy wherein increased activity of a circulating placental protease with "vasopressinase" activity leads to reduced circulating AVP and polyuria, often accompanied by hypernatremia. DDAVP is an effective therapy for this syndrome, given its resistance to the vasopressinase enzyme.

Clinical Features Hypernatremia increases osmolality of the ECF, generating an osmotic gradient between the ECF and ICF, an efflux of intracellular water, and cellular shrinkage. As in hyponatremia, the symptoms of hypernatremia are predominantly neurologic. Altered mental status is the most frequent manifestation, ranging from mild confusion and lethargy to deep coma. The sudden shrinkage of brain cells in acute hypernatremia may lead to parenchymal or subarachnoid hemorrhages and/or subdural hematomas; however, these vascular complications are primarily encountered in pediatric and neonatal patients. Osmotic damage to muscle membranes can also lead to hypernatremic rhabdomyolysis. Brain cells accommodate to a chronic increase in ECF osmolality (>48 h) by activating membrane transporters that mediate influx and intracellular accumulation of organic osmolytes (creatine, betaine, glutamate, myoinositol, and taurine); this results in an increase in ICF water and normalization of brain parenchymal volume. In consequence, patients with *chronic* hypernatremia are less likely to develop severe neurologic compromise. However, the cellular response to chronic hypernatremia predisposes these patients to the development of cerebral edema and seizures during overly rapid hydration (overcorrection of plasma Na^+ concentration by >10 m*M*/d).

Diagnostic Approach The history should focus on the presence or absence of thirst, polyuria, and/or an extrarenal source for water loss, such as diarrhea. The physical examination should include a detailed neurologic exam and an assessment of the ECFV; patients with a particularly large water deficit and/or a combined deficit in electrolytes and water may be hypovolemic, with reduced JVP and orthostasis. Accurate documentation of daily fluid intake and daily urine output is also critical for the diagnosis and management of hypernatremia.

Laboratory investigation should include a measurement of serum and urine osmolality, in addition to urine electrolytes. The appropriate response to hypernatremia and a serum osmolality >295 mOsm/kg is an increase in circulating AVP and the excretion of low volumes (<500 mL/d) of maximally concentrated urine, i.e., urine with osmolality >800 mOsm/kg; should this be the case, then an extrarenal source of water loss is primarily responsible for the generation of hypernatremia. Many patients with hypernatremia are polyuric; should an osmotic diuresis be responsible, with excessive excretion of Na^+-Cl^-, glucose, and/or urea, then daily solute excretion will be >750–1000 mOsm/d (>15 mOsm/kg body water per day) (Fig. 49-6). More commonly, patients with hypernatremia and polyuria will have a predominant water diuresis, with excessive excretion of hypotonic, dilute urine.

Adequate differentiation between nephrogenic and central causes of DI requires the measurement of the response in urinary osmolality to DDAVP, combined with measurement of circulating AVP in the setting of hypertonicity. By definition, patients with baseline hypernatremia are hypertonic, with an adequate stimulus for AVP by the posterior pituitary. Therefore, in contrast to polyuric patients with a normal or reduced baseline plasma Na^+ concentration and osmolality, a water deprivation test **(Chap. 48)** is unnecessary in hypernatremia; indeed, water deprivation is absolutely contraindicated in this setting, given the risk for worsening the hypernatremia. Patients with NDI will fail to respond to DDAVP, with a urine osmolality that increases by <50% or <150 mOsm/kg from baseline, in combination with a normal or high circulating AVP level; patients with central DI will respond to DDAVP, with a reduced circulating AVP. Patients may exhibit a partial response to DDAVP, with a >50% rise in urine osmolality that nonetheless fails to reach 800 mOsm/kg; the level of circulating AVP will help differentiate the underlying cause, i.e., NDI versus central DI. In pregnant patients, AVP assays should be drawn in tubes containing the protease inhibitor 1,10-phenanthroline, to prevent in vitro degradation of AVP by placental vasopressinase.

For patients with hypernatremia due to renal loss of water, it is critical to quantify *ongoing* daily losses using the calculated electrolyte-free water clearance, in addition to calculation of the baseline water deficit (the relevant formulas are discussed in Table 49-3). This requires daily measurement of urine electrolytes, combined with accurate measurement of daily urine volume.

TREATMENT

Hypernatremia

The underlying cause of hypernatremia should be withdrawn or corrected, be it drugs, hyperglycemia, hypercalcemia, hypokalemia, or diarrhea. The approach to the correction of hypernatremia is outlined in Table 49-3. It is imperative to correct hypernatremia slowly to avoid cerebral edema, typically replacing the calculated free water deficit over 48 h. Notably, the plasma Na^+ concentration should be corrected by no >10 m*M*/d, which may take longer than 48 h in patients with severe hypernatremia (>160 m*M*). A rare exception is patients with acute hypernatremia (<48 h) due to sodium loading, who can safely be corrected rapidly at a rate of 1 m*M*/h.

Water should ideally be administered by mouth or by nasogastric tube, as the most direct way to provide free water, i.e., water without electrolytes. Alternatively, patients can receive free water in dextrose-containing IV solutions, such as 5% dextrose (D_5W); blood glucose should be monitored in case hyperglycemia occurs. Depending on the history, blood pressure, or clinical volume status, it may be appropriate to initially treat with hypotonic saline solutions (1/4 or 1/2 normal saline); normal saline is usually inappropriate in the absence of very severe hypernatremia, where normal saline is proportionally more hypotonic relative to plasma, or frank hypotension. Calculation of urinary electrolyte-free water clearance (Table 49-3) is required to estimate daily, ongoing loss of free water in patients with NDI or central DI, which should be replenished daily.

Additional therapy may be feasible in specific cases. Patients with central DI should respond to the administration of intravenous, intranasal, or oral DDAVP. Patients with NDI due to lithium may reduce their polyuria with amiloride (2.5–10 mg/d), which decreases entry of lithium into principal cells by inhibiting ENaC (see above); in practice, however, most patients with lithium-associated DI are able to compensate for their polyuria by simply increasing their daily water intake. Thiazides may reduce polyuria due to NDI, ostensibly by inducing hypovolemia and increasing proximal tubular water reabsorption. Occasionally, nonsteroidal anti-inflammatory drugs (NSAIDs) have been used to treat polyuria associated with NDI, reducing the negative effect of intrarenal prostaglandins on urinary concentrating mechanisms; however, this assumes the risks of NSAID-associated gastric and/or renal toxicity. Furthermore, it must be emphasized that thiazides, amiloride, and NSAIDs are only appropriate for *chronic* management of polyuria from NDI and have *no* role in the acute management of associated hypernatremia, where the focus is on replacing free water deficits and ongoing free water loss.

POTASSIUM DISORDERS

Homeostatic mechanisms maintain plasma K^+ concentration between 3.5 and 5.0 m*M*, despite marked variation in dietary K^+ intake. In a healthy individual at steady state, the entire daily intake of potassium is excreted, ~90% in the urine and 10% in the stool; thus, the kidney plays a dominant role in potassium homeostasis. However, >98% of total-body potassium is intracellular, chiefly in muscle; buffering of extracellular K^+ by this large intracellular pool plays a crucial role in the regulation of plasma K^+ concentration. Changes in the exchange and distribution of intra- and extracellular K^+ can thus lead to marked hypo- or hyperkalemia. A corollary is that massive necrosis and the attendant release of tissue K^+ can cause severe hyperkalemia, particularly in the setting of acute kidney injury and reduced excretion of K^+.

Changes in whole-body K^+ content are primarily mediated by the kidney, which *reabsorbs* filtered K^+ in hypokalemic, K^+-deficient states and *secretes* K^+ in hyperkalemic, K^+-replete states. Although K^+ is transported along the entire nephron, it is the principal cells of the connecting segment (CNT) and cortical CD that play a dominant role in renal K^+ secretion, whereas alpha-intercalated cells of the outer medullary CD function in renal tubular reabsorption of filtered K^+ in K^+-deficient states. In principal cells, apical Na^+ entry via the amiloride-sensitive ENaC generates a lumen-negative potential difference, which drives passive K^+ exit through apical K^+ channels (Fig. 49-4). Two major K^+ channels mediate distal tubular K^+ secretion: the secretory K^+ channel ROMK (renal outer medullary K^+ channel; also known as Kir1.1 or KcnJ1) and the flow-sensitive "big potassium" (BK) or maxi-K K^+ channel. ROMK is thought to mediate the bulk of constitutive K^+ secretion, whereas increases in distal flow rate and/or genetic absence of ROMK activate K^+ secretion via the BK channel.

An appreciation of the relationship between ENaC-dependent Na^+ entry and distal K^+ secretion (Fig. 49-4) is required for the bedside interpretation of potassium disorders. For example, decreased distal delivery of Na^+, as occurs in hypovolemic, prerenal states, tends to blunt the ability to excrete K^+, leading to hyperkalemia; on the other hand, an *increase* in distal delivery of Na^+ and distal flow rate, as occurs after treatment with thiazide and loop diuretics, can enhance K^+ secretion and lead to hypokalemia. Hyperkalemia is also a predictable consequence of drugs that directly inhibit ENaC, due to the role of this Na^+ channel in generating a lumen-negative potential difference. Aldosterone in turn has a major influence on potassium excretion, increasing the activity of ENaC channels and thus amplifying the driving force for K^+ secretion across the luminal membrane of principal cells. Abnormalities in the renin-angiotensin-aldosterone system can thus cause both hypokalemia and hyperkalemia. Notably, however, potassium excess and potassium restriction have opposing, aldosterone-independent effects on the density and activity of apical K^+ channels in the distal nephron, i.e., factors other than aldosterone modulate the renal capacity to secrete K^+. In addition, potassium restriction and hypokalemia activates aldosterone-independent distal *reabsorption* of filtered K^+, activating apical H^+/K^+-ATPase activity in intercalated cells within the outer medullary CD. Reflective perhaps of this physiology, changes in plasma K^+ concentration are not universal in disorders associated with changes in aldosterone activity.

HYPOKALEMIA

Hypokalemia, defined as a plasma K^+ concentration of <3.5 m*M*, occurs in up to 20% of hospitalized patients. Hypokalemia is associated with a tenfold increase in in-hospital mortality, due to adverse effects on cardiac rhythm, blood pressure, and cardiovascular morbidity. Mechanistically, hypokalemia can be caused by redistribution of K^+ between tissues and the ECF or by renal and nonrenal loss of K^+ **(Table 49-4)**. Systemic hypomagnesemia can also cause treatment-resistant hypokalemia, due to a combination of reduced cellular uptake of K^+ and exaggerated renal secretion. Spurious hypokalemia or "pseudohypokalemia" can occasionally result from in vitro cellular uptake of K^+ after venipuncture, for example, due to profound leukocytosis in acute leukemia.

Redistribution and Hypokalemia Insulin, β_2-adrenergic activity, thyroid hormone, and alkalosis promote Na^+/K^+-ATPase-mediated cellular uptake of K^+, leading to hypokalemia. Inhibition of the passive *efflux* of K^+ can also cause hypokalemia, albeit rarely; this typically occurs in the setting of systemic inhibition of K^+ channels by toxic barium ions. Exogenous insulin can cause iatrogenic hypokalemia, particularly during the management of K^+-deficient states such as diabetic ketoacidosis. Alternatively, the stimulation of *endogenous* insulin can provoke hypokalemia, hypomagnesemia, and/or hypophosphatemia in malnourished patients given a carbohydrate load. Alterations in the activity of the endogenous sympathetic nervous system can cause hypokalemia in several settings, including alcohol withdrawal, hyperthyroidism, acute myocardial infarction, and severe head injury. β_2 agonists, including both bronchodilators and tocolytics (ritodrine), are powerful activators of cellular K^+ uptake; "hidden" sympathomimetics, such as pseudoephedrine and ephedrine in cough syrup or dieting agents, may also cause unexpected hypokalemia. Finally, xanthine-dependent activation of cAMP-dependent signaling, downstream of the β_2 receptor, can lead to hypokalemia, usually in the setting of overdose (theophylline) or marked overingestion (dietary caffeine).

Redistributive hypokalemia can also occur in the setting of hyperthyroidism, with periodic attacks of hypokalemic paralysis (thyrotoxic periodic paralysis [TPP]). Similar episodes of hypokalemic weakness in the absence of thyroid abnormalities occur in *familial* hypokalemic

TABLE 49-4 Causes of Hypokalemia

I. Decreased intake
  A. Starvation
  B. Clay ingestion
II. Redistribution into cells
  A. Acid-base
    1. Metabolic alkalosis
  B. Hormonal
    1. Insulin
    2. Increased β_2-adrenergic sympathetic activity: post–myocardial infarction, head injury
    3. β_2-Adrenergic agonists—bronchodilators, tocolytics
    4. α-Adrenergic antagonists
    5. Thyrotoxic periodic paralysis
    6. Downstream stimulation of Na^+/K^+-ATPase: theophylline, caffeine
  C. Anabolic state
    1. Vitamin B_{12} or folic acid administration (red blood cell production)
    2. Granulocyte-macrophage colony-stimulating factor (white blood cell production)
    3. Total parenteral nutrition
  D. Other
    1. Pseudohypokalemia
    2. Hypothermia
    3. Familial hypokalemic periodic paralysis
    4. Barium toxicity: systemic inhibition of "leak" K^+ channels
III. Increased loss
  A. Nonrenal
    1. Gastrointestinal loss (diarrhea)
    2. Integumentary loss (sweat)
  B. Renal
    1. Increased distal flow and distal Na+ delivery: diuretics, osmotic diuresis, salt-wasting nephropathies
    2. Increased secretion of potassium
      a. Mineralocorticoid excess: primary hyperaldosteronism (aldosterone-producing adenomas, primary or unilateral adrenal hyperplasia, idiopathic hyperaldosteronism due to bilateral adrenal hyperplasia, and adrenal carcinoma), genetic hyperaldosteronism (familial hyperaldosteronism types I/II/III, congenital adrenal hyperplasias), secondary hyperaldosteronism (malignant hypertension, renin-secreting tumors, renal artery stenosis, hypovolemia), Cushing's syndrome, Bartter's syndrome, Gitelman's syndrome
      b. Apparent mineralocorticoid excess: genetic deficiency of 11β-dehydrogenase-2 (syndrome of apparent mineralocorticoid excess), inhibition of 11β-dehydrogenase-2 (glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone; licorice, food products, drugs), Liddle's syndrome (genetic activation of epithelial Na^+ channels)
      c. Distal delivery of nonreabsorbed anions: vomiting, nasogastric suction, proximal renal tubular acidosis, diabetic ketoacidosis, glue-sniffing (toluene abuse), penicillin derivatives (penicillin, nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin)
    3. Magnesium deficiency

periodic paralysis, usually caused by missense mutations of voltage sensor domains within the α_1 subunit of L-type calcium channels or the skeletal Na^+ channel; these mutations generate an abnormal gating pore current activated by hyperpolarization. TPP develops more frequently in patients of Asian or Hispanic origin; this shared predisposition has been linked to genetic variation in Kir2.6, a muscle-specific, thyroid hormone–responsive K^+ channel. Patients with TPP typically present with weakness of the extremities and limb girdles, with paralytic episodes that occur most frequently between 1 and 6 A.M. Signs and symptoms of hyperthyroidism are not invariably present. Hypokalemia is usually profound and almost invariably accompanied by hypophosphatemia and hypomagnesemia. The hypokalemia in TPP is also attributed to both direct and indirect activation of the Na^+/K^+-ATPase, resulting in increased uptake of K^+ by muscle and other tissues. Increases in β-adrenergic activity play an important role in that high-dose propranolol (3 mg/kg) rapidly reverses the associated hypokalemia, hypophosphatemia, and paralysis.

Nonrenal Loss of Potassium The loss of K^+ in sweat is typically low, except under extremes of physical exertion. Direct gastric losses of K^+ due to vomiting or nasogastric suctioning are also minimal; however, the ensuing hypochloremic alkalosis results in persistent kaliuresis due to secondary hyperaldosteronism and bicarbonaturia, i.e., a *renal* loss of K^+. Diarrhea is a globally important cause of hypokalemia, given the worldwide prevalence of infectious diarrheal disease. Noninfectious gastrointestinal processes such as celiac disease, ileostomy, villous adenomas, inflammatory bowel disease, colonic pseudo-obstruction (Ogilvie's syndrome), VIPomas, and chronic laxative abuse can also cause significant hypokalemia; an exaggerated intestinal secretion of potassium by upregulated colonic BK channels has been directly implicated in the pathogenesis of hypokalemia in many of these disorders.

Renal Loss of Potassium Drugs can increase renal K^+ excretion by a variety of different mechanisms. Diuretics are a particularly common cause, due to associated increases in distal tubular Na^+ delivery and distal tubular flow rate, in addition to secondary hyperaldosteronism. Thiazides have a greater effect on plasma K^+ concentration than loop diuretics, despite their lesser natriuretic effect. The diuretic effect of thiazides is largely due to inhibition of the Na^+-Cl^- cotransporter NCC in DCT cells. This leads to a direct increase in the delivery of luminal Na^+ to the principal cells immediately downstream in the CNT and cortical CD, which augments Na^+ entry via ENaC, increases the lumen-negative potential difference, and amplifies K^+ secretion. The higher propensity of thiazides to cause hypokalemia may also be secondary to thiazide-associated hypocalciuria, versus the *hypercalciuria* seen with loop diuretics; the increases in downstream luminal calcium in response to loop diuretics inhibit ENaC in principal cells, thus reducing the lumen-negative potential difference and attenuating distal K^+ excretion. High doses of penicillin-related antibiotics (nafcillin, dicloxacillin, ticarcillin, oxacillin, and carbenicillin) can increase obligatory K^+ excretion by acting as nonreabsorbable anions in the distal nephron. Finally, several renal tubular toxins cause renal K^+ and magnesium wasting, leading to hypokalemia and hypomagnesemia; these drugs include aminoglycosides, amphotericin, foscarnet, cisplatin, and ifosfamide (see also "Magnesium Deficiency and Hypokalemia," below).

Aldosterone activates the ENaC channel in principal cells via multiple synergistic mechanisms, thus increasing the driving force for K^+ excretion. In consequence, increases in aldosterone bioactivity and/or gains in function of aldosterone-dependent signaling pathways are associated with hypokalemia. Increases in circulating aldosterone (hyperaldosteronism) may be primary or secondary. Increased levels of circulating renin in secondary forms of hyperaldosteronism lead to increased angiotensin II and thus aldosterone; renal artery stenosis is perhaps the most frequent cause (Table 49-4). Primary hyperaldosteronism may be genetic or acquired. Hypertension and hypokalemia, due to increases in circulating 11-deoxycorticosterone, occur in patients with congenital adrenal hyperplasia caused by defects in either steroid 11β-hydroxylase or steroid 17α-hydroxylase; deficient 11β-hydroxylase results in associated virilization and other signs of androgen excess, whereas reduced sex steroids in 17α-hydroxylase deficiency lead to hypogonadism.

The major forms of *isolated* primary genetic hyperaldosteronism are familial hyperaldosteronism type I (FH-I, also known as glucocorticoid-remediable hyperaldosteronism [GRA]) and familial hyperaldosteronism types II and III (FH-II and FH-III), in which aldosterone production is not repressible by exogenous glucocorticoids. FH-I is caused by a chimeric gene duplication between the homologous 11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*) genes, fusing the adrenocorticotropic hormone (ACTH)–responsive 11β-hydroxylase promoter to the coding region of aldosterone synthase; this chimeric gene is under the control of ACTH and thus repressible by glucocorticoids. FH-III is caused by mutations in the *KCNJ5* gene, which encodes

the G-protein-activated inward rectifier K^+ channel 4 (GIRK4); these mutations lead to the acquisition of sodium permeability in the mutant GIRK4 channels, causing an exaggerated membrane depolarization in adrenal glomerulosa cells and the activation of voltage-gated calcium channels. The resulting calcium influx is sufficient to produce aldosterone secretion and cell proliferation, leading to adrenal adenomas and hyperaldosteronism.

Acquired causes of primary hyperaldosteronism include aldosterone-producing adenomas (APAs), primary or unilateral adrenal hyperplasia (PAH), idiopathic hyperaldosteronism (IHA) due to bilateral adrenal hyperplasia, and adrenal carcinoma; APA and IHA account for close to 60 and 40%, respectively, of diagnosed hyperaldosteronism. Acquired somatic mutations in *KCNJ5* or less frequently in the *ATP1A1* (an Na^+/K^+ ATPase α subunit) and *ATP2B3* (a Ca^{2+} ATPase) genes can be detected in APAs; as in FH-III (see above), the exaggerated depolarization of adrenal glomerulosa cells caused by these mutations is implicated in the excessive adrenal proliferation and the exaggerated release of aldosterone.

Random testing of plasma renin activity (PRA) and aldosterone is a helpful screening tool in hypokalemic and/or hypertensive patients, with an aldosterone:PRA ratio of >50 suggestive of primary hyperaldosteronism. Hypokalemia and multiple antihypertensive drugs may alter the aldosterone:PRA ratio by suppressing aldosterone or increasing PRA, leading to a ratio of <50 in patients who do in fact have primary hyperaldosteronism; therefore, the clinical context should always be considered when interpreting these results.

The glucocorticoid cortisol has equal affinity for the MLR to that of aldosterone, with resultant "mineralocorticoid-like" activity. However, cells in the aldosterone-sensitive distal nephron are protected from this "illicit" activation by the enzyme 11β-hydroxysteroid dehydrogenase-2 (11βHSD-2), which converts cortisol to cortisone; cortisone has minimal affinity for the MLR. Recessive loss-of-function mutations in the *11βHSD-2* gene are thus associated with cortisol-dependent activation of the MLR and the syndrome of apparent mineralocorticoid excess (SAME), encompassing hypertension, hypokalemia, hypercalciuria, and metabolic alkalosis, with suppressed PRA and suppressed aldosterone. A similar syndrome is caused by biochemical inhibition of 11βHSD-2 by glycyrrhetinic/glycyrrhizinic acid and/or carbenoxolone. Glycyrrhizinic acid is a natural sweetener found in licorice root, typically encountered in licorice and its many guises or as a flavoring agent in tobacco and food products.

Finally, hypokalemia may also occur with systemic increases in glucocorticoids. In Cushing's syndrome caused by increases in pituitary ACTH **(Chap. 379)**, the incidence of hypokalemia is only 10%, whereas it is 60–100% in patients with ectopic secretion of ACTH, despite a similar incidence of hypertension. Indirect evidence suggests that the activity of renal 11βHSD-2 is reduced in patients with ectopic ACTH compared with Cushing's syndrome, resulting in SAME.

Finally, defects in multiple renal tubular transport pathways are associated with hypokalemia. For example, loss-of-function mutations in subunits of the acidifying H^+-ATPase in alpha-intercalated cells cause hypokalemic distal renal tubular acidosis, as do many acquired disorders of the distal nephron. Liddle's syndrome is caused by autosomal dominant gain-in-function mutations of ENaC subunits. Disease-associated mutations either activate the channel directly or abrogate aldosterone-inhibited retrieval of ENaC subunits from the plasma membrane; the end result is increased expression of activated ENaC channels at the plasma membrane of principal cells. Patients with Liddle's syndrome classically manifest severe hypertension with hypokalemia, unresponsive to spironolactone yet sensitive to amiloride. Hypertension and hypokalemia are, however, variable aspects of the Liddle's phenotype; more consistent features include a blunted aldosterone response to ACTH and reduced urinary aldosterone excretion.

Loss of the transport functions of the TALH and DCT nephron segments causes hereditary hypokalemic alkalosis, Bartter's syndrome (BS) and Gitelman's syndrome (GS), respectively. Patients with classic BS typically suffer from polyuria and polydipsia, due to the reduction in renal concentrating ability. They may have an increase in urinary calcium excretion, and 20% are hypomagnesemic. Other features include marked activation of the renin-angiotensin-aldosterone axis. Patients with antenatal BS suffer from a severe systemic disorder characterized by marked electrolyte wasting, polyhydramnios, and hypercalciuria with nephrocalcinosis; renal prostaglandin synthesis and excretion are significantly increased, accounting for much of the systemic symptoms. There are five disease genes for BS, all of them functioning in some aspect of regulated Na^+, K^+, and Cl^- transport by the TALH. In contrast, GS is genetically homogeneous, caused almost exclusively by loss-of-function mutations in the thiazide-sensitive Na^+-Cl^- cotransporter of the DCT. Patients with GS are uniformly hypomagnesemic and exhibit marked hypocalciuria, rather than the hypercalciuria typically seen in BS; urinary calcium excretion is thus a critical diagnostic test in GS. GS is a milder phenotype than BS; however, patients with GS may suffer from chondrocalcinosis, an abnormal deposition of calcium pyrophosphate dihydrate (CPPD) in joint cartilage **(Chap. 309)**.

Magnesium Deficiency and Hypokalemia Magnesium depletion has inhibitory effects on muscle Na^+/K^+-ATPase activity, reducing influx into muscle cells and causing a secondary kaliuresis. In addition, magnesium depletion causes exaggerated K^+ secretion by the distal nephron; this effect is attributed to a reduction in the magnesium-dependent, intracellular block of K^+ efflux through the secretory K^+ channel of principal cells (ROMK; Fig. 49-4). In consequence, hypomagnesemic patients are clinically refractory to K^+ replacement in the absence of Mg^{2+} repletion. Notably, magnesium deficiency is also a common concomitant of hypokalemia because many disorders of the distal nephron may cause both potassium and magnesium wasting **(Chap. 309)**.

Clinical Features Hypokalemia has prominent effects on cardiac, skeletal, and intestinal muscle cells. In particular, hypokalemia is a major risk factor for both ventricular and atrial arrhythmias. Hypokalemia predisposes to digoxin toxicity by a number of mechanisms, including reduced competition between K^+ and digoxin for shared binding sites on cardiac Na^+/K^+-ATPase subunits. Electrocardiographic changes in hypokalemia include broad flat T waves, ST depression, and QT prolongation; these are most marked when serum K^+ is <2.7 mmol/L. Hypokalemia can thus be an important precipitant of arrhythmia in patients with additional genetic or acquired causes of QT prolongation. Hypokalemia also results in hyperpolarization of skeletal muscle, thus impairing the capacity to depolarize and contract; weakness and even paralysis may ensue. It also causes a skeletal myopathy and predisposes to rhabdomyolysis. Finally, the paralytic effects of hypokalemia on intestinal smooth muscle may cause intestinal ileus.

The functional effects of hypokalemia on the kidney can include Na^+-Cl^- and HCO_3^- retention, polyuria, phosphaturia, hypocitraturia, and an activation of renal ammoniagenesis. Bicarbonate retention and other acid-base effects of hypokalemia can contribute to the generation of metabolic alkalosis. Hypokalemic polyuria is due to a combination of central polydipsia and an AVP-resistant renal concentrating defect. Structural changes in the kidney due to hypokalemia include a relatively specific vacuolizing injury to proximal tubular cells, interstitial nephritis, and renal cysts. Hypokalemia also predisposes to acute kidney injury and can lead to end-stage renal disease (ESRD) in patients with long-standing hypokalemia due to eating disorders and/or laxative abuse.

Hypokalemia and/or reduced dietary K^+ are implicated in the pathophysiology and progression of hypertension, heart failure, and stroke. For example, short-term K^+ restriction in healthy humans and patients with essential hypertension induces Na^+-Cl^- retention and hypertension. Correction of hypokalemia is particularly important in hypertensive patients treated with diuretics, in whom blood pressure improves with potassium supplementation and the establishment of normokalemia.

Diagnostic Approach The cause of hypokalemia is usually evident from history, physical examination, and/or basic laboratory tests. The history should focus on medications (e.g., laxatives, diuretics,

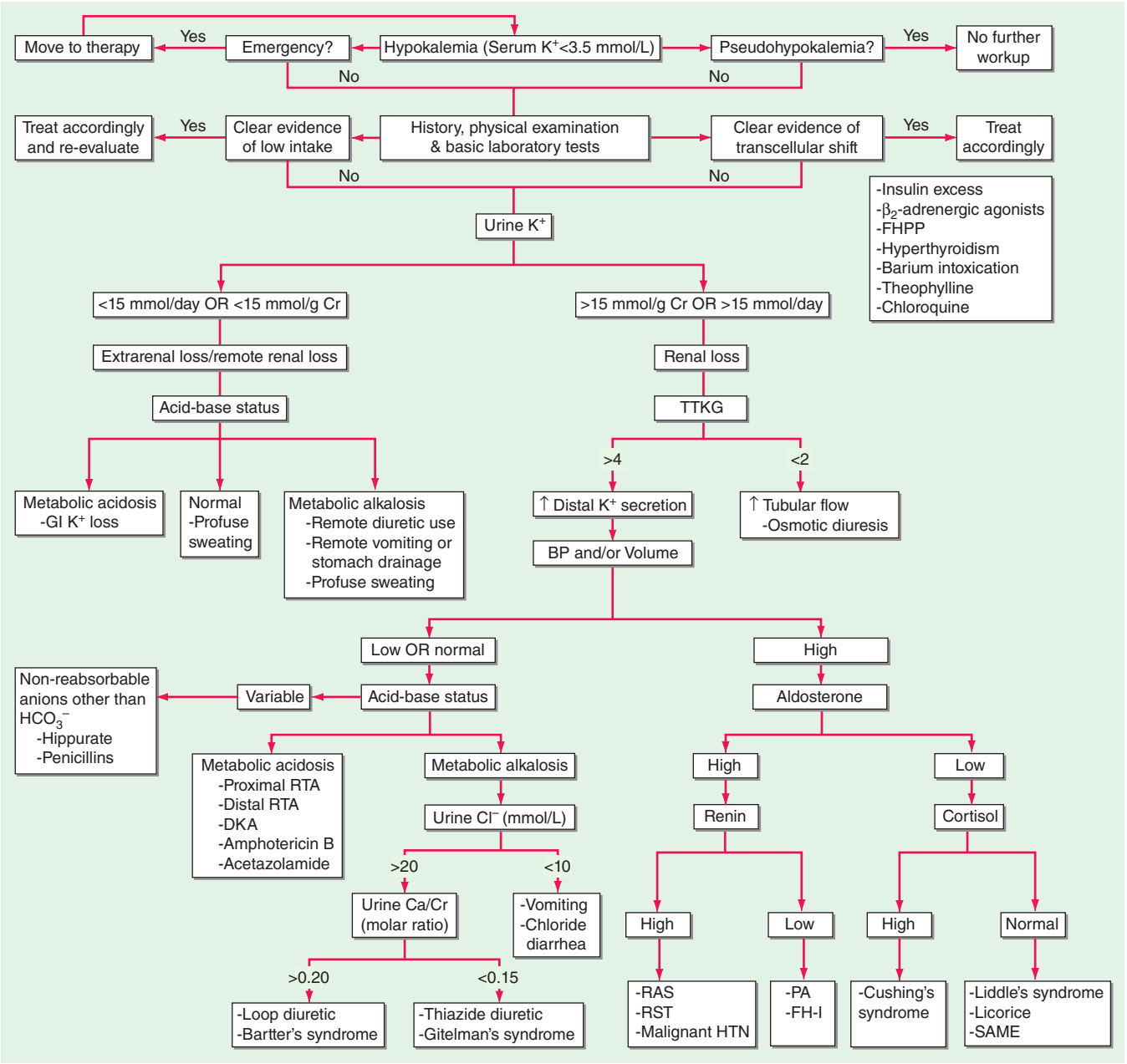

FIGURE 49-7 The diagnostic approach to hypokalemia. See text for details. AME, apparent mineralocorticoid excess; BP, blood pressure; CCD, cortical collecting duct; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; GI, gastrointestinal; GRA, glucocorticoid remediable aldosteronism; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. *(Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders & Company, 2008, pp 547–587.)*

antibiotics), diet and dietary habits (e.g., licorice), and/or symptoms that suggest a particular cause (e.g., periodic weakness, diarrhea). The physical examination should pay particular attention to blood pressure, volume status, and signs suggestive of specific hypokalemic disorders, e.g., hyperthyroidism and Cushing's syndrome. Initial laboratory evaluation should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+}, Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes **(Fig. 49-7)**. The presence of a non–anion gap acidosis suggests a distal, hypokalemic renal tubular acidosis or diarrhea; calculation of the urinary anion gap can help differentiate these two diagnoses. Renal K^+ excretion can be assessed with a 24-h urine collection; a 24-h K^+ excretion of <15 mmol is indicative of an extrarenal cause of hypokalemia (Fig. 49-7). If only a random, spot urine sample is available, serum and urine osmolality can be used to calculate the transtubular K^+ gradient (TTKG), which should be <3 in the presence of hypokalemia (see also "Hyperkalemia"). Alternatively, a urinary K^+-to-creatinine ratio of >13 mmol/g creatinine (>1.5 mmol/mmol creatinine) is compatible with excessive renal K^+ excretion. Urine Cl^- is usually decreased in patients with hypokalemia from a nonreabsorbable anion, such as antibiotics or HCO_3^-. The most common causes of chronic hypokalemic alkalosis are surreptitious vomiting, diuretic abuse, and GS; these can be distinguished by the pattern of urinary electrolytes. Hypokalemic patients with vomiting due to bulimia will thus typically have a urinary Cl^- <10 mmol/L; urine Na^+, K^+, and Cl^- are persistently elevated in GS, due to loss of function in the thiazide-sensitive Na^+-Cl^- cotransporter, but less elevated in diuretic abuse and with greater variability. Urine diuretic screens for loop diuretics and thiazides may be necessary to further exclude diuretic abuse.

Other tests, such as urinary Ca^{2+}, thyroid function tests, and/or PRA and aldosterone levels, may also be appropriate in specific cases. A plasma aldosterone:PRA ratio of >50, due to suppression of circulating renin and an elevation of circulating aldosterone, is suggestive of hyperaldosteronism. Patients with hyperaldosteronism or apparent mineralocorticoid excess may require further testing, for example

adrenal vein sampling **(Chap. 379)** or the clinically available testing for specific genetic causes (e.g., FH-I, SAME, Liddle's syndrome). Patients with primary aldosteronism should thus be tested for the chimeric FH-I/GRA gene (see above) if they are younger than 20 years of age or have a family history of primary aldosteronism or stroke at a young age (<40 years). Preliminary differentiation of Liddle's syndrome due to mutant ENaC channels from SAME due to mutant 11βHSD-2 (see above), both of which cause hypokalemia and hypertension with aldosterone suppression, can be made on a clinical basis and then confirmed by genetic analysis; patients with Liddle's syndrome should respond to amiloride (ENaC inhibition) but not spironolactone, whereas patients with SAME will respond to spironolactone.

TREATMENT

Hypokalemia

The goals of therapy in hypokalemia are to prevent life-threatening and/or serious chronic consequences, to replace the associated K^+ deficit, and to correct the underlying cause and/or mitigate future hypokalemia. The urgency of therapy depends on the severity of hypokalemia, associated clinical factors (e.g., cardiac disease, digoxin therapy), and the rate of decline in serum K^+. Patients with a prolonged QT interval and/or other risk factors for arrhythmia should be monitored by continuous cardiac telemetry during repletion. Urgent but cautious K^+ replacement should be considered in patients with severe redistributive hypokalemia (plasma K^+ concentration <2.5 m*M*) and/or when serious complications ensue; however, this approach has a risk of rebound hyperkalemia following acute resolution of the underlying cause. When excessive activity of the sympathetic nervous system is thought to play a dominant role in redistributive hypokalemia, as in TPP, theophylline overdose, and acute head injury, high-dose propranolol (3 mg/kg) should be considered; this nonspecific b-adrenergic blocker will correct hypokalemia without the risk of rebound hyperkalemia.

Oral replacement with K^+-Cl^- is the mainstay of therapy in hypokalemia. Potassium phosphate, oral or IV, may be appropriate in patients with combined hypokalemia and hypophosphatemia. Potassium bicarbonate or potassium citrate should be considered in patients with concomitant metabolic acidosis. Notably, hypomagnesemic patients are refractory to K^+ replacement alone, such that concomitant Mg^{2+} deficiency should *always* be corrected with oral or intravenous repletion. The deficit of K^+ and the rate of correction should be estimated as accurately as possible; renal function, medications, and comorbid conditions such as diabetes should also be considered, so as to gauge the risk of overcorrection. In the absence of abnormal K^+ redistribution, the total deficit correlates with serum K^+, such that serum K^+ drops by ~0.27 m*M* for every 100-mmol reduction in total-body stores; loss of 400–800 mmol of total-body K^+ results in a reduction in serum K^+ by ~2.0 m*M*. Notably, given the delay in redistributing potassium into intracellular compartments, this deficit must be replaced gradually over 24–48 h, with frequent monitoring of plasma K^+ concentration to avoid transient overrepletion and transient hyperkalemia.

The use of intravenous administration should be limited to patients unable to use the enteral route or in the setting of severe complications (e.g., paralysis, arrhythmia). Intravenous K^+-Cl^- should always be administered in saline solutions, rather than dextrose, because the dextrose-induced increase in insulin can acutely exacerbate hypokalemia. The peripheral intravenous dose is usually 20–40 mmol of K^+-Cl^- per liter; higher concentrations can cause localized pain from chemical phlebitis, irritation, and sclerosis. If hypokalemia is severe (<2.5 mmol/L) and/or critically symptomatic, intravenous K^+-Cl^- can be administered through a central vein with cardiac monitoring in an intensive care setting, at rates of 10–20 mmol/h; higher rates should be reserved for acutely life-threatening complications. The absolute amount of administered K^+ should be restricted (e.g., 20 mmol in 100 mL of saline solution) to prevent inadvertent infusion of a large dose. Femoral veins are preferable, because infusion through internal jugular or subclavian central lines can acutely increase the local concentration of K^+ and affect cardiac conduction.

Strategies to minimize K^+ losses should also be considered. These measures may include minimizing the dose of non-K^+-sparing diuretics, restricting Na^+ intake, and using clinically appropriate combinations of non-K^+-sparing and K^+-sparing medications (e.g., loop diuretics with ACE inhibitors).

HYPERKALEMIA

Hyperkalemia is defined as a plasma potassium level of 5.5 m*M*, occurring in up to 10% of hospitalized patients; severe hyperkalemia (>6.0 m*M*) occurs in ~1%, with a significantly increased risk of mortality. Although redistribution and reduced tissue uptake can acutely cause hyperkalemia, a decrease in renal K^+ excretion is the most frequent underlying cause **(Table 49-5)**. Excessive intake of K^+ is a rare cause, given the adaptive capacity to increase renal secretion; however, dietary intake can have a major effect in susceptible patients, e.g., diabetics with hyporeninemic hypoaldosteronism and chronic kidney disease. Drugs that impact on the renin-angiotensin-aldosterone axis are also a major cause of hyperkalemia.

Pseudohyperkalemia Hyperkalemia should be distinguished from factitious hyperkalemia or "pseudohyperkalemia," an artifactual increase in serum K^+ due to the release of K^+ during or after venipuncture. Pseudohyperkalemia can occur in the setting of excessive muscle activity during venipuncture (e.g., fist clenching), a marked increase in cellular elements (thrombocytosis, leukocytosis, and/or erythrocytosis) with in vitro efflux of K^+, and acute anxiety during venipuncture with respiratory alkalosis and redistributive hyperkalemia. Cooling of blood following venipuncture is another cause, due to reduced cellular uptake; the converse is the increased uptake of K^+ by cells at high ambient temperatures, leading to normal values for hyperkalemic patients and/or to spurious hypokalemia in normokalemic patients. Finally, there are multiple genetic subtypes of hereditary pseudohyperkalemia, caused by increases in the passive K^+ permeability of erythrocytes. For example, causative mutations have been described in the red cell anion exchanger (AE1, encoded by the *SLC4A1* gene), leading to reduced red cell anion transport, hemolytic anemia, the acquisition of a novel AE1-mediated K^+ leak, and pseudohyperkalemia.

Redistribution and Hyperkalemia Several different mechanisms can induce an efflux of intracellular K^+ and hyperkalemia. Acidemia is associated with cellular uptake of H^+ and an associated efflux of K^+; it is thought that this effective K^+-H^+ exchange serves to help maintain extracellular pH. Notably, this effect of acidosis is limited to non–anion gap causes of metabolic acidosis and, to a lesser extent, respiratory causes of acidosis; hyperkalemia due to an acidosis-induced shift of potassium from the cells into the ECF does *not* occur in the anion gap acidoses lactic acidosis and ketoacidosis. Hyperkalemia due to hypertonic mannitol, hypertonic saline, and intravenous immune globulin is generally attributed to a "solvent drag" effect, as water moves out of cells along the osmotic gradient. Diabetics are also prone to osmotic hyperkalemia in response to intravenous hypertonic glucose, when given without adequate insulin. Cationic amino acids, specifically lysine, arginine, and the structurally related drug epsilon-aminocaproic acid, cause efflux of K^+ and hyperkalemia, through an effective cation-K^+ exchange of unknown identity and mechanism. Digoxin inhibits Na^+/K^+-ATPase and impairs the uptake of K^+ by skeletal muscle, such that digoxin overdose predictably results in hyperkalemia. Structurally related glycosides are found in specific plants (e.g., yellow oleander, foxglove) and in the cane toad, *Bufo marinus* (bufadienolide); ingestion of these substances and extracts thereof can also cause hyperkalemia. Finally, fluoride ions also inhibit Na^+/K^+-ATPase, such that fluoride poisoning is typically associated with hyperkalemia.

Succinylcholine depolarizes muscle cells, causing an efflux of K^+ through acetylcholine receptors (AChRs). The use of this agent is contraindicated in patients who have sustained thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization.

TABLE 49-5 Causes of Hyperkalemia

I. Pseudohyperkalemia
  A. Cellular efflux; thrombocytosis, erythrocytosis, leukocytosis, in vitro hemolysis
  B. Hereditary defects in red cell membrane transport
II. Intra- to extracellular shift
  A. Acidosis
  B. Hyperosmolality; radiocontrast, hypertonic dextrose, mannitol
  C. β_2-Adrenergic antagonists (noncardioselective agents)
  D. Digoxin and related glycosides (yellow oleander, foxglove, bufadienolide)
  E. Hyperkalemic periodic paralysis
  F. Lysine, arginine, and ε-aminocaproic acid (structurally similar, positively charged)
  G. Succinylcholine; thermal trauma, neuromuscular injury, disuse atrophy, mucositis, or prolonged immobilization
  H. Rapid tumor lysis
III. Inadequate excretion
  A. Inhibition of the renin-angiotensin-aldosterone axis; ↑ risk of hyperkalemia when used in combination
    1. Angiotensin-converting enzyme (ACE) inhibitors
    2. Renin inhibitors; aliskiren (in combination with ACE inhibitors or angiotensin receptor blockers [ARBs])
    3. Angiotensin receptor blockers (ARBs)
    4. Blockade of the mineralocorticoid receptor: spironolactone, eplerenone, drospirenone
    5. Blockade of the epithelial sodium channel (ENaC): amiloride, triamterene, trimethoprim, pentamidine, nafamostat
  B. Decreased distal delivery
    1. Congestive heart failure
    2. Volume depletion
  C. Hyporeninemic hypoaldosteronism
    1. Tubulointerstitial diseases: systemic lupus erythematosus (SLE), sickle cell anemia, obstructive uropathy
    2. Diabetes, diabetic nephropathy
    3. Drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX2) inhibitors, β-blockers, cyclosporine, tacrolimus
    4. Chronic kidney disease, advanced age
    5. Pseudohypoaldosteronism type II: defects in WNK1 or WNK4 kinases, Kelch-like 3 (KLHL3), or Cullin 3 (CUL3)
  D. Renal resistance to mineralocorticoid
    1. Tubulointerstitial diseases: SLE, amyloidosis, sickle cell anemia, obstructive uropathy, post–acute tubular necrosis
    2. Hereditary: pseudohypoaldosteronism type I; defects in the mineralocorticoid receptor *or* the epithelial sodium channel (ENaC)
  E. Advanced renal insufficiency
    1. Chronic kidney disease
    2. End-stage renal disease
    3. Acute oliguric kidney injury
  F. Primary adrenal insufficiency
    1. Autoimmune: Addison's disease, polyglandular endocrinopathy
    2. Infectious: HIV, cytomegalovirus, tuberculosis, disseminated fungal infection
    3. Infiltrative: amyloidosis, malignancy, metastatic cancer
    4. Drug-associated: heparin, low-molecular-weight heparin
    5. Hereditary: adrenal hypoplasia congenita, congenital lipoid adrenal hyperplasia, aldosterone synthase deficiency
    6. Adrenal hemorrhage or infarction, including in antiphospholipid syndrome

These disorders share a marked increase and redistribution of AChRs at the plasma membrane of muscle cells; depolarization of these upregulated AChRs by succinylcholine leads to an exaggerated efflux of K^+ through the receptor-associated cation channels, resulting in acute hyperkalemia.

Hyperkalemia Caused by Excess Intake or Tissue Necrosis Increased intake of even small amounts of K^+ may provoke severe hyperkalemia in patients with predisposing factors; hence, an assessment of dietary intake is crucial. Foods rich in potassium include tomatoes, bananas, and citrus fruits; occult sources of K^+, particularly K^+-containing salt substitutes, may also contribute significantly. Iatrogenic causes include simple overreplacement with K^+-Cl^- or the administration of a potassium-containing medication (e.g., K^+-penicillin) to a susceptible patient. Red cell transfusion is a well-described cause of hyperkalemia, typically in the setting of massive transfusions. Finally, severe tissue necrosis, as in acute tumor lysis syndrome and rhabdomyolysis, will predictably cause hyperkalemia from the release of intracellular K^+.

Hypoaldosteronism and Hyperkalemia Aldosterone release from the adrenal gland may be reduced by hyporeninemic hypoaldosteronism, medications, primary hypoaldosteronism, or isolated deficiency of ACTH (secondary hypoaldosteronism). Primary hypoaldosteronism may be genetic or acquired (Chap. 379) but is commonly caused by autoimmunity, either in Addison's disease or in the context of a polyglandular endocrinopathy. HIV has surpassed tuberculosis as the most important infectious cause of adrenal insufficiency. The adrenal involvement in HIV disease is usually subclinical; however, adrenal insufficiency may be precipitated by stress, drugs such as ketoconazole that inhibit steroidogenesis, or the acute withdrawal of steroid agents such as megestrol.

Hyporeninemic hypoaldosteronism is a very common predisposing factor in several overlapping subsets of hyperkalemic patients: diabetics, the elderly, and patients with renal insufficiency. Classically, patients should have suppressed PRA and aldosterone; ~50% have an associated acidosis, with a reduced renal excretion of NH_4^+, a positive urinary anion gap, and urine pH <5.5. Most patients are volume expanded, with secondary increases in circulating atrial natriuretic peptide (ANP) that inhibit both renal renin release and adrenal aldosterone release.

Renal Disease and Hyperkalemia Chronic kidney disease and end-stage kidney disease are very common causes of hyperkalemia, due to the associated deficit or absence of functioning nephrons. Hyperkalemia is more common in oliguric acute kidney injury; distal tubular flow rate and Na^+ delivery are less limiting factors in nonoliguric patients. Hyperkalemia out of proportion to GFR can also be seen in the context of tubulointerstitial disease that affects the distal nephron, such as amyloidosis, sickle cell anemia, interstitial nephritis, and obstructive uropathy.

Hereditary renal causes of hyperkalemia have overlapping clinical features with hypoaldosteronism, hence the diagnostic label *pseudohypoaldosteronism* (PHA). PHA type I (PHA-I) has both an autosomal recessive and an autosomal dominant form. The autosomal dominant form is due to loss-of-function mutations in the MLR; the recessive form is caused by various combinations of mutations in the three subunits of ENaC, resulting in impaired Na^+ channel activity in principal cells and other tissues. Patients with recessive PHA-I suffer from lifelong salt wasting, hypotension, and hyperkalemia, whereas the phenotype of autosomal dominant PHA-I due to MLR dysfunction improves in adulthood. PHA type II (PHA-II; also known as *hereditary hypertension with hyperkalemia*) is in every respect the mirror image of GS caused by loss of function in NCC, the thiazide-sensitive Na^+-Cl^- cotransporter (see above); the clinical phenotype includes hypertension, hyperkalemia, hyperchloremic metabolic acidosis, suppressed PRA and aldosterone, hypercalciuria, and reduced bone density. PHA-II thus behaves like a gain of function in NCC, and treatment with thiazides results in resolution of the entire clinical phenotype. However, the NCC gene is not directly involved in PHA-II, which is caused by mutations in the WNK1 and WNK4 serine-threonine kinases or the upstream Kelch-like 3 (KLHL3) and Cullin 3 (CUL3) proteins, two components of an E3 ubiquitin ligase complex that regulates these kinases; these proteins collectively regulate NCC activity, with PHA-II-associated activation of the transporter.

Medication-Associated Hyperkalemia Most medications associated with hyperkalemia cause inhibition of some component of the renin-angiotensin-aldosterone axis. ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and MLRs are predictable and common causes of hyperkalemia, particularly when prescribed in combination. The oral contraceptive agent Yasmin-28 contains the progestin drospirenone, which inhibits the MLR and can cause hyperkalemia in susceptible patients. Cyclosporine, tacrolimus, NSAIDs, and cyclooxygenase 2 (COX2) inhibitors cause hyperkalemia by multiple mechanisms, but share the ability to cause hyporeninemic hypoaldosteronism. Notably, most drugs that affect the renin-angiotensin-aldosterone axis also block the local adrenal response to hyperkalemia, thus attenuating the *direct* stimulation of aldosterone release by increased plasma K^+ concentration.

Inhibition of apical ENaC activity in the distal nephron by amiloride and other K^+-sparing diuretics results in hyperkalemia, often with a voltage-dependent hyperchloremic acidosis and/or hypovolemic hyponatremia. Amiloride is structurally similar to the antibiotics TMP and pentamidine, which also block ENaC; risk factors for TMP-associated hyperkalemia include the administered dose, renal insufficiency, and hyporeninemic hypoaldosteronism. Indirect inhibition of ENaC at the plasma membrane is also a cause of drug-associated hyperkalemia; nafamostat, a protease inhibitor used in some countries for anticoagulation and for the management of pancreatitis, inhibits aldosterone-induced renal proteases that activate ENaC by proteolytic cleavage.

Clinical Features Hyperkalemia is a medical emergency due to its effects on the heart. Cardiac arrhythmias associated with hyperkalemia include sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. Mild increases in extracellular K^+ affect the repolarization phase of the cardiac action potential, resulting in changes in T-wave morphology; further increase in plasma K^+ concentration depresses intracardiac conduction, with progressive prolongation of the PR and QRS intervals. Severe hyperkalemia results in loss of the P wave and a progressive widening of the QRS complex; development of a sine-wave sinoventricular rhythm suggests impending ventricular fibrillation or asystole. Hyperkalemia can also cause a type I Brugada pattern in the electrocardiogram (ECG), with a pseudo–right bundle branch block and persistent coved ST segment elevation in at least two precordial leads. This hyperkalemic Brugada's sign occurs in critically ill patients with severe hyperkalemia and can be differentiated from genetic Brugada's syndrome by an absence of P waves, marked QRS widening, and an abnormal QRS axis. Classically, the electrocardiographic manifestations in hyperkalemia progress from tall peaked T waves (5.5–6.5 m*M*), to a loss of P waves (6.5–7.5 m*M*) to a widened QRS complex (7.0–8.0 m*M*), and, ultimately, a to a sine wave pattern (>8.0 m*M*). However, these changes are notoriously insensitive, particularly in patients with chronic kidney disease or ESRD.

Hyperkalemia from a variety of causes can also present with ascending paralysis, denoted *secondary hyperkalemic paralysis* to differentiate it from familial hyperkalemic periodic paralysis (HYPP). The presentation may include diaphragmatic paralysis and respiratory failure. Patients with familial HYPP develop myopathic weakness during hyperkalemia induced by increased K^+ intake or rest after heavy exercise. Depolarization of skeletal muscle by hyperkalemia unmasks an inactivation defect in skeletal Na^+ channel; autosomal dominant mutations in the *SCN4A* gene encoding this channel are the predominant cause.

Within the kidney, hyperkalemia has negative effects on the ability to excrete an acid load, such that hyperkalemia per se can contribute to metabolic acidosis. This defect appears to be due in part to competition between K^+ and NH_4^+ for reabsorption by the TALH and subsequent countercurrent multiplication, ultimately reducing the medullary gradient for NH_3/NH_4 excretion by the distal nephron. Regardless of the underlying mechanism, restoration of normokalemia can, in many instances, correct hyperkalemic metabolic acidosis.

Diagnostic Approach The first priority in the management of hyperkalemia is to assess the need for emergency treatment, followed by a comprehensive workup to determine the cause **(Fig. 49-8)**. History and physical examination should focus on medications, diet and dietary supplements, risk factors for kidney failure, reduction in urine output, blood pressure, and volume status. Initial laboratory tests should include electrolytes, BUN, creatinine, serum osmolality, Mg^{2+} and Ca^{2+}, a complete blood count, and urinary pH, osmolality, creatinine, and electrolytes. A urine Na^+ concentration of <20 m*M* indicates that distal Na^+ delivery is a limiting factor in K^+ excretion; volume repletion with 0.9% saline or treatment with furosemide may be effective in reducing plasma K^+ concentration. Serum and urine osmolality are required for calculation of the transtubular K^+ gradient (TTKG) (Fig. 49-8). The expected values of the TTKG are largely based on historical data, and are <3 in the presence of hypokalemia and >7–8 in the presence of hyperkalemia.

$$\text{TTKG} = \frac{[K^+]_{\text{urine}} \times \text{Osm}_{\text{serum}}}{[K^+]_{\text{serum}} \times \text{Osm}_{\text{urine}}}$$

TREATMENT

Hyperkalemia

Electrocardiographic manifestations of hyperkalemia should be considered a medical emergency and treated urgently. However, patients with significant hyperkalemia (plasma K^+ concentration ≥6.5 m*M*) in the absence of ECG changes should also be aggressively managed, given the limitations of ECG changes as a predictor of cardiac toxicity. Urgent management of hyperkalemia includes admission to the hospital, continuous cardiac monitoring, and immediate treatment. The treatment of hyperkalemia is divided into three stages:

1. *Immediate antagonism of the cardiac effects of hyperkalemia.* Intravenous calcium serves to protect the heart, whereas other measures are taken to correct hyperkalemia. Calcium raises the action potential threshold and reduces excitability, without changing the resting membrane potential. By restoring the difference between resting and threshold potentials, calcium reverses the depolarization blockade due to hyperkalemia. The recommended dose is 10 mL of 10% calcium gluconate (3–4 mL of calcium chloride), infused intravenously over 2–3 min with cardiac monitoring. The effect of the infusion starts in 1–3 min and lasts 30–60 min; the dose should be repeated if there is no change in ECG findings or if they recur after initial improvement. Hypercalcemia potentiates the cardiac toxicity of digoxin; hence, intravenous calcium should be used with extreme caution in patients taking this medication; if judged necessary, 10 mL of 10% calcium gluconate can be added to 100 mL of 5% dextrose in water and infused over 20–30 min to avoid acute hypercalcemia.
2. *Rapid reduction in plasma K^+ concentration by redistribution into cells.* Insulin lowers plasma K^+ concentration by shifting K^+ into cells. The recommended dose is 10 units of intravenous regular insulin followed immediately by 50 mL of 50% dextrose ($D_{50}W$, 25 g of glucose total); the effect begins in 10–20 min, peaks at 30–60 min, and lasts for 4–6 h. Bolus $D_{50}W$ without insulin is *never* appropriate, given the risk of acutely worsening hyperkalemia due to the osmotic effect of hypertonic glucose. Hypoglycemia is common with insulin plus glucose; hence, this should be followed by an infusion of 10% dextrose at 50–75 mL/h, with close monitoring of plasma glucose concentration. In hyperkalemic patients with glucose concentrations of ≥200–250 mg/dL, insulin should be administered *without* glucose, again with close monitoring of glucose concentrations.

   β_2-agonists, most commonly albuterol, are effective but underused agents for the acute management of hyperkalemia. Albuterol and insulin with glucose have an additive effect on plasma K^+ concentration; however, ~20% of patients with ESRD are resistant to the effect of β_2-agonists; hence, these drugs should not be used without insulin. The recommended dose for inhaled

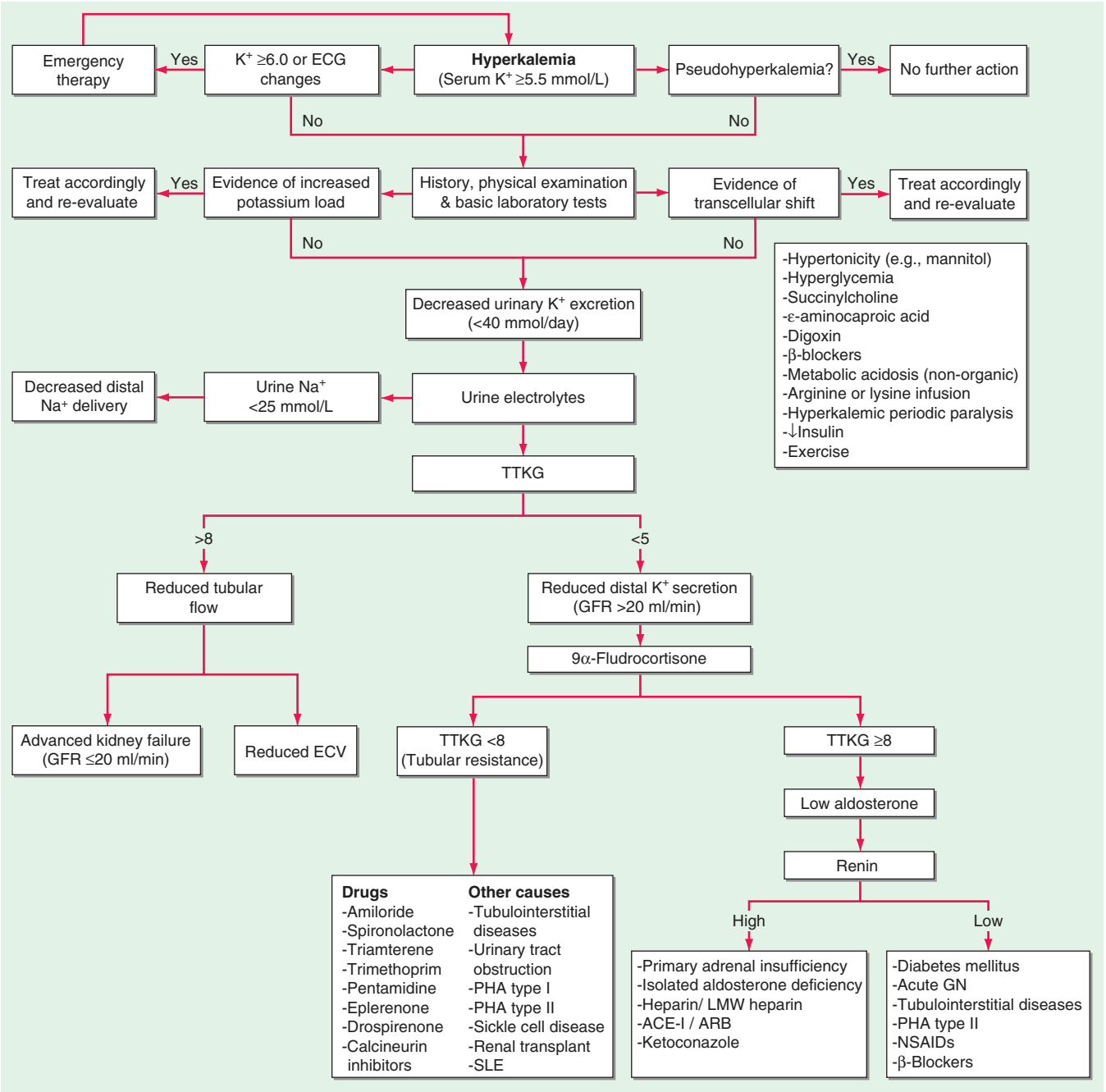

FIGURE 49-8 The diagnostic approach to hyperkalemia. See text for details. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCD, cortical collecting duct; ECG, electrocardiogram; ECV, effective circulatory volume; GFR, glomerular filtration rate; GN, glomerulonephritis; HIV, human immunodeficiency virus; LMW heparin, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; PHA, pseudohypoaldosteronism; SLE, systemic lupus erythematosus; TTKG, transtubular potassium gradient. *(Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner [ed]. Philadelphia, W.B. Saunders & Company, 2008, pp 547–587.)*

albuterol is 10–20 mg of nebulized albuterol in 4 mL of normal saline, inhaled over 10 min; the effect starts at about 30 min, reaches its peak at about 90 min, and lasts for 2–6 h. Hyperglycemia is a side effect, along with tachycardia. β_2-Agonists should be used with caution in hyperkalemic patients with known cardiac disease.

Intravenous bicarbonate has no role in the acute treatment of hyperkalemia, but may slowly attenuate hyperkalemia with sustained administration over several hours. It should not be given repeatedly as a hypertonic intravenous bolus of undiluted ampules, given the risk of associated hypernatremia, but should instead be infused in an isotonic or hypotonic fluid (e.g., 150 mEqu in 1 L of D_5W). In patients with metabolic acidosis, a delayed drop in plasma K^+ concentration can be seen after 4–6 h of isotonic bicarbonate infusion.

3. *Removal of potassium.* This is typically accomplished using cation exchange resins, diuretics, and/or dialysis. The cation exchange resin sodium polystyrene sulfonate (SPS) exchanges Na^+ for K^+ in the gastrointestinal tract and increases the fecal excretion of K^+; alternative calcium-based resins, when available, may be more appropriate in patients with an increased ECFV. The recommended dose of SPS is 15–30 g of powder, almost always given in a premade suspension with 33% sorbitol. The effect of SPS on plasma K^+ concentration is slow; the full effect may take up to 24 h and usually requires repeated doses every 4–6 h. Intestinal necrosis, typically of the colon or ileum, is a rare but usually fatal complication of SPS. Intestinal necrosis is more common in patients administered SPS via enema and/or in patients with reduced intestinal motility (e.g., in the postoperative state or after treatment with opioids). The coadministration of SPS with

sorbitol appears to increase the risk of intestinal necrosis; however, this complication can also occur with SPS alone. The low but real risk of intestinal necrosis with SPS, which can sometimes be the only available or appropriate therapy for the removal of potassium, must be weighed against the delayed onset of efficacy. Whenever possible, alternative therapies for the acute management of hyperkalemia (i.e., aggressive redistributive therapy, isotonic bicarbonate infusion, diuretics, and/or hemodialysis) should be used instead of SPS.

Novel intestinal potassium binders have recently become available for the management of hyperkalemia. These agents appear to lack the intestinal toxicity of SPS. Patiromer is a nonabsorbed polymer provided as a powder for suspension, which binds K^+ in exchange for Ca^{2+}. In healthy adults, patiromer causes a decrease in urinary potassium, magnesium, and sodium excretion, suggesting the binding of the polymer to these cations in the intestine; notably, a side-effect of the medication is hypomagnesemia. ZS-9 is an inorganic, nonabsorbable crystalline compound that exchanges both Na^+ and H^+ ions in exchange for K^+ and NH_4^+ in the intestine. These agents promise to revolutionize the management of both chronic and acute hyperkalemia. In particular, the availability of safe, well-tolerated potassium binders is expected to allow for greater intensity of RAAS inhibition in both renal and cardiac disease.

Therapy with intravenous saline may be beneficial in hypovolemic patients with oliguria and decreased distal delivery of Na^+, with the associated reductions in renal K^+ excretion. Loop and thiazide diuretics can be used to reduce plasma K^+ concentration in volume-replete or hypervolemic patients with sufficient renal function for a diuretic response; this may need to be combined with intravenous saline or isotonic bicarbonate to achieve or maintain euvolemia.

Hemodialysis is the most effective and reliable method to reduce plasma K^+ concentration; peritoneal dialysis is considerably less effective. Patients with acute kidney injury require temporary, urgent venous access for hemodialysis, with the attendant risks; in contrast, patients with ESRD or advanced chronic kidney disease may have a preexisting venous access. The amount of K^+ removed during hemodialysis depends on the relative distribution of K^+ between ICF and ECF (potentially affected by prior therapy for hyperkalemia), the type and surface area of the dialyzer used, dialysate and blood flow rates, dialysate flow rate, dialysis duration, and the plasma-to-dialysate K^+ gradient.

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50 Hypercalcemia and Hypocalcemia

Sundeep Khosla

The calcium ion plays a critical role in normal cellular function and signaling, regulating diverse physiologic processes such as neuromuscular signaling, cardiac contractility, hormone secretion, and blood coagulation. Thus, extracellular calcium concentrations are maintained within an exquisitely narrow range through a series of feedback mechanisms that involve parathyroid hormone (PTH) and the active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. These feedback mechanisms are orchestrated by integrating signals between the parathyroid glands, kidney, intestine, and bone **(Fig. 50-1; Chap. 402)**. Disorders of serum calcium concentration are relatively common and often serve as a harbinger of underlying disease. This chapter provides a brief summary of the approach to patients with altered serum calcium levels. **See Chap. 403 for a detailed discussion of this topic.**

HYPERCALCEMIA

ETIOLOGY

The causes of hypercalcemia can be understood and classified based on derangements in the normal feedback mechanisms that regulate serum calcium **(Table 50-1)**. Excess PTH production, which is not appropriately suppressed by increased serum calcium concentrations, occurs in primary neoplastic disorders of the parathyroid glands (parathyroid adenomas; hyperplasia; or, rarely, carcinoma) that are associated with increased parathyroid cell mass and impaired feedback inhibition by calcium. Inappropriate PTH secretion for the ambient level of serum

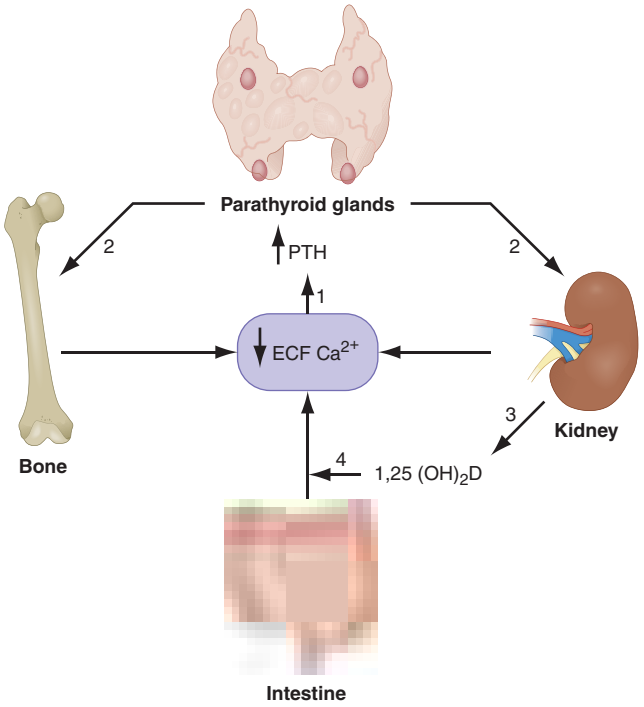

FIGURE 50-1 Feedback mechanisms maintaining extracellular calcium concentrations within a narrow, physiologic range (8.9–10.1 mg/dL [2.2–2.5 m*M*]). A decrease in extracellular (ECF) calcium (Ca^{2+}) triggers an increase in parathyroid hormone (PTH) secretion (1) via the calcium sensor receptor on parathyroid cells. PTH, in turn, results in increased tubular reabsorption of calcium by the kidney (2) and resorption of calcium from bone (2) and also stimulates renal 1,25$(OH)_2$D production (3). 1,25$(OH)_2$D, in turn, acts principally on the intestine to increase calcium absorption (4). Collectively, these homeostatic mechanisms serve to restore serum calcium levels to normal.

TABLE 50-1 Causes of Hypercalcemia

Excessive PTH production
Primary hyperparathyroidism (adenoma, hyperplasia, rarely carcinoma)
Tertiary hyperparathyroidism (long-term stimulation of PTH secretion in renal insufficiency)
Ectopic PTH secretion (very rare)
FHH
Alterations in CaSR function (lithium therapy)
Hypercalcemia of malignancy
Overproduction of PTHrP (many solid tumors)
Lytic skeletal metastases (breast, myeloma)
Excessive 1,25$(OH)_2$D production
Granulomatous diseases (sarcoidosis, tuberculosis, silicosis)
Lymphomas
Vitamin D intoxication
Primary increase in bone resorption
Hyperthyroidism
Immobilization
Excessive calcium intake
Milk-alkali syndrome
Total parenteral nutrition
Other causes
Endocrine disorders (adrenal insufficiency, pheochromocytoma, VIPoma)
Medications (thiazides, vitamin A, antiestrogens)

Abbreviations: CaSR, calcium sensor receptor; FHH, familial hypocalciuric hypercalcemia; PTH, parathyroid hormone; PTHrP, PTH-related peptide.

calcium also occurs in familial hypocalciuric hypercalcemia (FHH), which is an autosomal dominant syndrome most commonly involving inactivating mutations in the calcium sensor receptor (*CaSR;* FHH type 1), with rare families having mutations in the $G\alpha_{11}$ protein (*GNA11;* FHH type 2) or the adaptor-related protein complex 2, σ-2 subunit (*AP2S1;* FHH type 3); all of these mutations impair extracellular calcium sensing by the parathyroid glands and the kidneys, leading to inappropriate PTH secretion and increased renal tubular calcium reabsorption. Although PTH secretion by tumors is extremely rare, many solid tumors produce PTH-related peptide (PTHrP), which shares homology with PTH in the first 13 amino acids and binds the PTH receptor, thus mimicking effects of PTH on bone and the kidney. In PTHrP-mediated hypercalcemia of malignancy, PTH levels are suppressed by the high serum calcium levels. Hypercalcemia associated with granulomatous disease (e.g., sarcoidosis) or lymphomas is caused by enhanced conversion of 25(OH)D to the potent 1,25$(OH)_2$D. In these disorders, 1,25$(OH)_2$D enhances intestinal calcium absorption, resulting in hypercalcemia and suppressed PTH. Disorders that directly increase calcium mobilization from bone, such as hyperthyroidism or osteolytic metastases, also lead to hypercalcemia with suppressed PTH secretion as does exogenous calcium overload, as in milk-alkali syndrome, or total parenteral nutrition with excessive calcium supplementation.

CLINICAL MANIFESTATIONS

Mild hypercalcemia (up to 11–11.5 mg/dL) is usually asymptomatic and recognized only on routine calcium measurements. Some patients may complain of vague neuropsychiatric symptoms, including trouble concentrating, personality changes, or depression. Other presenting symptoms may include peptic ulcer disease or nephrolithiasis, and fracture risk may be increased. More severe hypercalcemia (>12–13 mg/dL), particularly if it develops acutely, may result in lethargy, stupor, or coma, as well as gastrointestinal symptoms (nausea, anorexia, constipation, or pancreatitis). Hypercalcemia decreases renal concentrating ability, which may cause polyuria and polydipsia. With long-standing hyperparathyroidism, patients may present with bone pain or pathologic fractures. Finally, hypercalcemia can result in significant electrocardiographic changes, including bradycardia, AV block, and short QT interval; changes in serum calcium can be monitored by following the QT interval.

DIAGNOSTIC APPROACH

The first step in the diagnostic evaluation of hyper- or hypocalcemia is to ensure that the alteration in serum calcium levels is not due to abnormal albumin concentrations. About 50% of total calcium is ionized, and the rest is bound principally to albumin. Although direct measurements of ionized calcium are possible, they are easily influenced by collection methods and other artifacts; thus, it is generally preferable to measure total calcium and albumin to "correct" the serum calcium. When serum albumin concentrations are reduced, a corrected calcium concentration is calculated by adding 0.2 m*M* (0.8 mg/dL) to the total calcium level for every decrement in serum albumin of 1.0 g/dL below the reference value of 4.1 g/dL for albumin, and, conversely, for elevations in serum albumin.

A detailed history may provide important clues regarding the etiology of the hypercalcemia (Table 50-1). Chronic hypercalcemia is most commonly caused by primary hyperparathyroidism, as opposed to the second most common etiology of hypercalcemia, an underlying malignancy. The history should include medication use, previous neck surgery, and systemic symptoms suggestive of sarcoidosis or lymphoma.

Once true hypercalcemia is established, the second most important laboratory test in the diagnostic evaluation is a PTH level using a two-site assay for the intact hormone. Increases in PTH are often accompanied by hypophosphatemia. In addition, serum creatinine should be measured to assess renal function; hypercalcemia may impair renal function, and renal clearance of PTH may be altered depending on the fragments detected by the assay. If the PTH level is increased (or "inappropriately normal") in the setting of elevated calcium and low phosphorus, the diagnosis is almost always primary hyperparathyroidism. Because individuals with FHH may also present with mildly elevated PTH levels and hypercalcemia, this diagnosis should be considered and excluded because parathyroid surgery is ineffective in this condition. A calcium/creatinine clearance ratio (calculated as urine calcium/serum calcium divided by urine creatinine/serum creatinine) of <0.01 is suggestive of FHH, particularly when there is a family history of mild, asymptomatic hypercalcemia. In addition, sequence analysis of the *CASR* gene is now commonly performed for the definitive diagnosis of FHH, although as noted above, in rare families FHH may be caused by mutations in the *GNA11* or *AP2S1* genes. Ectopic PTH secretion is extremely rare.

A suppressed PTH level in the face of hypercalcemia is consistent with non-parathyroid-mediated hypercalcemia, most often due to underlying malignancy. Although a tumor that causes hypercalcemia is generally overt, a PTHrP level may be needed to establish the diagnosis of hypercalcemia of malignancy. Serum 1,25$(OH)_2$D levels are increased in granulomatous disorders, and clinical evaluation in combination with laboratory testing will generally provide a diagnosis for the various disorders listed in Table 50-1.

TREATMENT

Hypercalcemia

Mild, asymptomatic hypercalcemia does not require immediate therapy, and management should be dictated by the underlying diagnosis. By contrast, significant, symptomatic hypercalcemia usually requires therapeutic intervention independent of the etiology of hypercalcemia. Initial therapy of significant hypercalcemia begins with volume expansion because hypercalcemia invariably leads to dehydration; 4–6 L of intravenous saline may be required over the first 24 h, keeping in mind that underlying comorbidities (e.g., congestive heart failure) may require the use of loop diuretics to enhance sodium and calcium excretion. However, loop diuretics should not be initiated until the volume status has been restored to normal. If there is increased calcium mobilization from bone (as in malignancy or severe hyperparathyroidism), drugs that inhibit bone resorption should be considered. Zoledronic acid (e.g., 4 mg intravenously over ~30 min), pamidronate (e.g., 60–90 mg intravenously over 2–4 h), and ibandronate (2 mg intravenously over 2 h) are bisphosphonates that are commonly used for the treatment of hypercalcemia of

malignancy in adults. Onset of action is within 1–3 days, with normalization of serum calcium levels occurring in 60–90% of patients. Bisphosphonate infusions may need to be repeated if hypercalcemia relapses. An alternative to the bisphosphonates is gallium nitrate (200 mg/m^2 intravenously daily for 5 days), which is also effective, but has potential nephrotoxicity. More recently, the potent inhibitor of bone resorption, denosumab (120 mg sc on days 1, 8, 15, and 29, and then every 4 weeks), has also been shown to be effective in treating hypercalcemia refractory to bisphosphonates. In rare instances, dialysis may be necessary. Finally, although intravenous phosphate chelates calcium and decreases serum calcium levels, this therapy can be toxic because calcium-phosphate complexes may deposit in tissues and cause extensive organ damage.

In patients with 1,25(OH)$_2$D-mediated hypercalcemia, glucocorticoids are the preferred therapy, as they decrease 1,25(OH)$_2$D production. Intravenous hydrocortisone (100–300 mg daily) or oral prednisone (40–60 mg daily) for 3–7 days is used most often. Other drugs, such as ketoconazole, chloroquine, and hydroxychloroquine, may also decrease 1,25(OH)$_2$D production and are used occasionally.

HYPOCALCEMIA

ETIOLOGY

The causes of hypocalcemia can be differentiated according to whether serum PTH levels are low (hypoparathyroidism) or high (secondary hyperparathyroidism). Although there are many potential causes of hypocalcemia, impaired PTH production and impaired vitamin D production are the most common etiologies **(Table 50-2)** **(Chap. 403)**. Because PTH is the main defense against hypocalcemia, disorders associated with deficient PTH production or secretion may be associated with profound, life-threatening hypocalcemia. In adults, hypoparathyroidism most commonly results from inadvertent damage to all four glands during thyroid or parathyroid gland surgery. Hypoparathyroidism is a cardinal feature of autoimmune endocrinopathies **(Chap. 381)**; rarely, it may be associated with infiltrative diseases such as sarcoidosis. Impaired PTH secretion may be secondary to magnesium deficiency or to activating mutations in the CaSR or in the G proteins that mediate CaSR signaling (autosomal dominant hypocalcemia), which suppress PTH, leading to effects that are opposite to those that occur in FHH.

Vitamin D deficiency, impaired 1,25(OH)$_2$D production (primarily secondary to renal insufficiency), or vitamin D resistance also cause hypocalcemia. However, the degree of hypocalcemia in these disorders is generally not as severe as that seen with hypoparathyroidism because the parathyroids are capable of mounting a compensatory increase in PTH secretion. Hypocalcemia may also occur in conditions associated with severe tissue injury such as burns, rhabdomyolysis, tumor lysis, or pancreatitis. The cause of hypocalcemia in these settings may include a combination of low albumin, hyperphosphatemia, tissue deposition of calcium, and impaired PTH secretion.

TABLE 50-2 Causes of Hypocalcemia

Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated
DiGeorge's syndrome
Parathyroid destruction
Surgical
Radiation
Infiltration by metastases or systemic diseases
Autoimmune
Reduced parathyroid function
Hypomagnesemia
Autosomal dominant hypocalcemia
High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)
Vitamin D deficiency or impaired 1,25(OH)$_2$D production/action
Nutritional vitamin D deficiency (poor intake or absorption)
Renal insufficiency with impaired 1,25(OH)$_2$D production
Vitamin D resistance, including receptor defects
Parathyroid hormone resistance syndromes
PTH receptor mutations
Pseudohypoparathyroidism (G protein mutations)
Drugs
Calcium chelators
Inhibitors of bone resorption (bisphosphonates, plicamycin)
Altered vitamin D metabolism (phenytoin, ketoconazole)
Miscellaneous causes
Acute pancreatitis
Acute rhabdomyolysis
Hungry bone syndrome after parathyroidectomy
Osteoblastic metastases with marked stimulation of bone formation (prostate cancer)

Abbreviations: CaSR, calcium sensor receptor; PTH, parathyroid hormone.

CLINICAL MANIFESTATIONS

Patients with hypocalcemia may be asymptomatic if the decreases in serum calcium are relatively mild and chronic, or they may present with life-threatening complications. Moderate to severe hypocalcemia is associated with paresthesias, usually of the fingers, toes, and circumoral regions, and is caused by increased neuromuscular irritability. On physical examination, a Chvostek's sign (twitching of the circumoral muscles in response to gentle tapping of the facial nerve just anterior to the ear) may be elicited, although it is also present in ~10% of normal individuals. Carpal spasm may be induced by inflation of a blood pressure cuff to 20 mmHg above the patient's systolic blood pressure for 3 min (Trousseau's sign). Severe hypocalcemia can induce seizures, carpopedal spasm, bronchospasm, laryngospasm, and prolongation of the QT interval.

DIAGNOSTIC APPROACH

In addition to measuring serum calcium, it is useful to determine albumin, phosphorus, and magnesium levels. As for the evaluation of hypercalcemia, determining the PTH level is central to the evaluation of hypocalcemia. A suppressed (or "inappropriately low") PTH level in the setting of hypocalcemia establishes absent or reduced PTH secretion (hypoparathyroidism) as the cause of the hypocalcemia. Further history will often elicit the underlying cause (i.e., parathyroid agenesis vs. destruction). By contrast, an elevated PTH level (secondary hyperparathyroidism) should direct attention to the vitamin D axis as the cause of the hypocalcemia. Nutritional vitamin D deficiency is best assessed by obtaining serum 25-hydroxyvitamin D levels, which reflect vitamin D stores. In the setting of renal insufficiency or suspected vitamin D resistance, serum 1,25(OH)$_2$D levels are informative.

TREATMENT

Hypocalcemia

The approach to treatment depends on the severity of the hypocalcemia, the rapidity with which it develops, and the accompanying complications (e.g., seizures, laryngospasm). Acute, symptomatic hypocalcemia is initially managed with calcium gluconate, 10 mL 10% wt/vol (90 mg or 2.2 mmol) intravenously, diluted in 50 mL of 5% dextrose or 0.9% sodium chloride, given intravenously over 5 min. Continuing hypocalcemia often requires a constant intravenous infusion (typically 10 ampules of calcium gluconate or 900 mg of calcium in 1 L of 5% dextrose or 0.9% sodium chloride administered over 24 h). Accompanying hypomagnesemia, if present, should be treated with appropriate magnesium supplementation.

Chronic hypocalcemia due to hypoparathyroidism is treated with calcium supplements (1000–1500 mg/d elemental calcium in divided doses) and either vitamin D$_2$ or D$_3$ (25,000–100,000 U daily) or calcitriol [1,25(OH)$_2$D, 0.25–2 μg/d]. Other vitamin D metabolites (dihydrotachysterol, alfacalcidiol) are now used less frequently.

Importantly, PTH (1-84) (Natpara) has recently been approved by the FDA for the treatment of refractory hypoparathyroidism, representing an important advance in treatment of these patients. Vitamin D deficiency is best treated using vitamin D supplementation, with the dose depending on the severity of the deficit and the underlying cause. Thus, nutritional vitamin D deficiency generally responds to relatively low doses of vitamin D (50,000 U, 2–3 times per week for several months), whereas vitamin D deficiency due to malabsorption may require much higher doses (100,000 U/d or more). The treatment goal is to bring serum calcium into the low normal range and to avoid hypercalciuria, which may lead to nephrolithiasis.

GLOBAL CONSIDERATIONS

In countries with more limited access to health care or screening laboratory testing of serum calcium levels, primary hyperparathyroidism often presents in its severe form with skeletal complications (osteitis fibrosa cystica) in contrast to the asymptomatic form that is common in developed countries. In addition, vitamin D deficiency is paradoxically common in some countries despite extensive sunlight (e.g., India) due to avoidance of sun exposure and poor dietary vitamin D intake.

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51 Acidosis and Alkalosis

Thomas D. DuBose, Jr.

NORMAL ACID-BASE HOMEOSTASIS

Systemic arterial pH is maintained between 7.35 and 7.45 by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of arterial CO_2 tension ($Paco_2$) by the central nervous system (CNS) and respiratory system and the control of plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali. The metabolic and respiratory components that regulate systemic pH are described by the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log \frac{HCO_3^-}{PaCO_2 \times 0.03001}$$

Under most circumstances, CO_2 production and excretion are matched, and the usual steady-state $Paco_2$ is maintained at 40 mmHg. Underexcretion of CO_2 produces hypercapnia, and overexcretion causes hypocapnia. Nevertheless, production and excretion are again matched at a new steady-state $Paco_2$. Therefore, the $Paco_2$ is regulated primarily by neural respiratory factors and is not subject to regulation by the rate of CO_2 production. Hypercapnia is usually the result of hypoventilation rather than of increased CO_2 production. Increases or decreases in $Paco_2$ represent derangements of neural respiratory control or are due to compensatory changes in response to a primary alteration in the plasma $[HCO_3^-]$.

DIAGNOSIS OF GENERAL TYPES OF DISTURBANCES

The most common clinical disturbances are simple acid-base disorders, that is, metabolic acidosis or alkalosis or respiratory acidosis or alkalosis.

SIMPLE ACID-BASE DISORDERS

Primary respiratory disturbances (primary changes in $Paco_2$) invoke compensatory metabolic responses (secondary changes in $[HCO_3^-]$), and primary metabolic disturbances elicit predictable compensatory respiratory responses (secondary changes in $Paco_2$). Physiologic compensation can be predicted from the relationships displayed in Table 51-1. In general, with one exception, compensatory responses return the pH toward, but not to, the normal value. Chronic respiratory alkalosis when prolonged is an exception to this rule and may return the pH to a normal value. Metabolic acidosis due to an increase in endogenous acid production (e.g., ketoacidosis) lowers extracellular fluid $[HCO_3^-]$ and decreases extracellular pH. This stimulates the medullary chemoreceptors to increase ventilation and to return the ratio of $[HCO_3^-]$ to $Paco_2$, and thus pH, toward, but not to, normal. The degree of respiratory compensation expected in a metabolic acidosis can be predicted from the relationship: $Paco_2 = (1.5 \times [HCO_3^-]) + 8 \pm 2$. Thus, a patient with metabolic acidosis and $[HCO_3^-]$ of 12 mmol/L would be expected to have a $Paco_2$ of ~26 mmHg. Values for $Paco_2$ <24 or >28 mmHg define a mixed disturbance (metabolic acidosis and respiratory alkalosis or metabolic acidosis and respiratory acidosis, respectively). Compensatory responses for primary metabolic disorders move the $Paco_2$ in the same direction as the change in $[HCO_3^-]$, whereas, conversely, compensation for primary respiratory disorders moves the $[HCO_3^-]$ in the same direction as the primary change in $Paco_2$ (Table 51-1). Therefore, changes in $Paco_2$ and $[HCO_3^-]$ in **opposite directions** (i.e., $Paco_2$ or $[HCO_3^-]$ is increased, whereas the other value is decreased) indicate a **mixed acid-base disturbance**. Another way to judge the appropriateness of the response in $[HCO_3^-]$ or $Paco_2$ is to use an acid-base nomogram (Fig. 51-1). While the shaded areas of the

TABLE 51-1 Prediction of Compensatory Responses to Simple Acid-Base Disturbances and Pattern of Changes

DISORDER	PREDICTION OF COMPENSATION	RANGE OF VALUES		
		pH	HCO_3^-	$Paco_2$
Metabolic acidosis	$Paco_2 = (1.5 \times HCO_3^-) + 8 \pm 2$ *or* $Paco_2$ will ↓ 1.25 mmHg per mmol/L ↓ in $[HCO_3^-]$ *or* $Paco_2 = [HCO_3^-] + 15$	Low	Low	Low
Metabolic alkalosis	$Paco_2$ will ↑ 0.75 mmHg per mmol/L ↑ in $[HCO_3^-]$ *or* $Paco_2$ will ↑ 6 mmHg per 10 mmol/L ↑ in $[HCO_3^-]$ *or* $Paco_2 = [HCO_3^-] + 15$	High	High	High
Respiratory alkalosis		High	Low	Low
Acute	$[HCO_3^-]$ will ↓ 0.2 mmol/L per mmHg ↓ in $Paco_2$			
Chronic	$[HCO_3^-]$ will ↓ 0.4 mmol/L per mmHg ↓ in $Paco_2$			
Respiratory acidosis		Low	High	High
Acute	$[HCO_3^-]$ will ↑ 0.1 mmol/L per mmHg ↑ in $Paco_2$			
Chronic	$[HCO_3^-]$ will ↑ 0.4 mmol/L per mmHg ↑ in $Paco_2$			

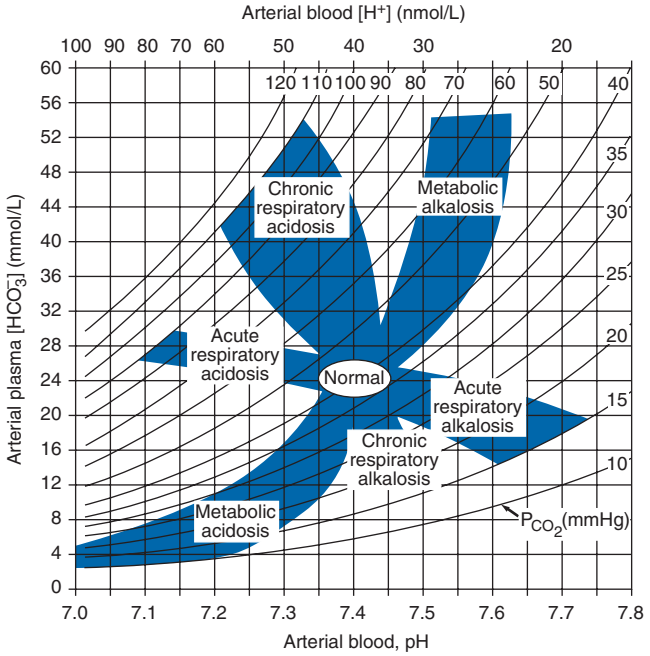

FIGURE 51-1 Acid-base nomogram. Shown are the 90% confidence limits (range of values) of the normal respiratory and metabolic compensations for primary acid-base disturbances. *(From TD DuBose Jr: Acid-Base Disorders, in Brenner and Rector's The Kidney, 10th ed, K Skorecki, GM Chertow, PA Marsden, MW Taal, and Alan SL Yu [eds]. Philadelphia, Saunders, 2016, p. 522; with permission.)*

nomogram show the 95% confidence limits for physiologic compensation in simple disturbances, finding acid-base values within the shaded area does not necessarily rule out a mixed disturbance. Imposition of one disorder over another may result in values lying within the area of a third. Thus, the nomogram, while convenient, is not a substitute for the equations in Table 51-1.

MIXED ACID-BASE DISORDERS

Mixed acid-base disorders—defined as independently coexisting disorders, not merely compensatory responses—are often seen in patients in critical care units and can lead to dangerous extremes of pH (Table 51-2). The diagnosis of mixed acid-base disorders requires consideration of the anion gap (AG), and requires the presence of or correction to a normal serum albumin of 4.5 g/dL. A patient with diabetic ketoacidosis (metabolic acidosis) may develop an independent respiratory problem (e.g., pneumonia) leading to a superimposed respiratory acidosis or alkalosis. Patients with underlying pulmonary disease (e.g., chronic obstructive pulmonary disease) may not respond to metabolic acidosis with an appropriate ventilatory response because of insufficient respiratory reserve. Such imposition of respiratory acidosis on metabolic acidosis can lead to severe acidemia. When metabolic acidosis and metabolic alkalosis coexist in the same patient, the pH may be in the normal range. In this circumstance, it is the presence of an elevated AG (see below) that denotes the presence of a metabolic acidosis. Assuming a normal value for the AG of 10 mmol/L, an incongruity in the ΔAG (prevailing minus normal AG) and the ΔHCO_3^- (normal value of 25 mmol/L minus abnormal HCO_3^- in the patient) indicates the presence of a mixed high-gap acidosis—metabolic alkalosis (see example below). A diabetic patient with ketoacidosis may have renal dysfunction resulting in simultaneous metabolic acidosis. Patients who have ingested an overdose of drug combinations such as sedatives and salicylates may have mixed disturbances as a result of the acid-base response to the individual drugs (metabolic acidosis mixed with respiratory acidosis or respiratory alkalosis, respectively). Triple acid-base disturbances are more complex. For example, patients with metabolic acidosis due to alcoholic ketoacidosis may develop metabolic alkalosis due to vomiting and superimposed respiratory alkalosis due to the hyperventilation of hepatic dysfunction or alcohol withdrawal.

TABLE 51-2 Examples of Mixed Acid-Base Disorders

Mixed Metabolic and Respiratory
Metabolic acidosis—respiratory alkalosis
Key: High- or normal-AG metabolic acidosis; prevailing $Paco_2$ *below* predicted value (Table 51-1)
Example: Na^+, 140; K^+, 4.0; Cl^-, 106; HCO_3^-, 14; AG, 20; $Paco_2$, 24; pH, 7.39 (lactic acidosis, sepsis in ICU)
Metabolic acidosis—respiratory acidosis
Key: High- or normal-AG metabolic acidosis; prevailing $Paco_2$ *above* predicted value (Table 51-1)
Example: Na^+, 140; K^+, 4.0; Cl^-, 102; HCO_3^-, 18; AG, 20; $Paco_2$, 38; pH, 7.30 (severe pneumonia, pulmonary edema)
Metabolic alkalosis—respiratory alkalosis
Key: $Paco_2$ does not increase as predicted; pH higher than expected
Example: Na^+, 140; K^+, 4.0; Cl^-, 91; HCO_3^-, 33; AG, 16; $Paco_2$, 38; pH, 7.55 (liver disease and diuretics)
Metabolic alkalosis—respiratory acidosis
Key: $Paco_2$ higher than predicted; pH normal
Example: Na^+, 140; K^+, 3.5; Cl^-, 88; HCO_3^-, 42; AG, 10; $Paco_2$, 67; pH, 7.42 (COPD on diuretics)
Mixed Metabolic Disorders
Metabolic acidosis—metabolic alkalosis
Key: Only detectable with high-AG acidosis; $\Delta AG >> \Delta HCO_3^-$
Example: Na^+, 140; K^+, 3.0; Cl^-, 95; HCO_3^-, 25; AG, 20; $Paco_2$, 40; pH, 7.42 (uremia with vomiting)
Metabolic acidosis—metabolic acidosis
Key: Mixed high-AG—normal-AG acidosis; ΔHCO_3^- accounted for by combined change in ΔAG and ΔCl^-
Example: Na^+, 135; K^+, 3.0; Cl^-, 110; HCO_3^-, 10; AG, 15; $Paco_2$, 25; pH, 7.20 (diarrhea and lactic acidosis, toluene toxicity, treatment of diabetic ketoacidosis)

Abbreviations: AG, anion gap; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

APPROACH TO THE PATIENT

Acid-Base Disorders

A stepwise approach to the diagnosis of acid-base disorders follows (Table 51-3). Blood for electrolytes and arterial blood gases should be drawn simultaneously prior to therapy. An increase in $[HCO_3^-]$ occurs with either metabolic alkalosis or respiratory acidosis. Conversely, a decrease in $[HCO_3^-]$ occurs with either metabolic acidosis or respiratory alkalosis. In the determination of arterial blood gases by the clinical laboratory, both pH and $Paco_2$ are measured, and the $[HCO_3^-]$ is calculated from the Henderson-Hasselbalch equation. This calculated value should be compared with the measured $[HCO_3^-]$ (total CO_2) on the electrolyte panel. These two values should agree within 2 mmol/L. If they do not, the values may not have been drawn simultaneously, or a laboratory error may be present. After verifying the blood acid-base values, the precise acid-base disorder can then be identified.

TABLE 51-3 Steps in Acid-Base Diagnosis

1. Obtain arterial blood gas (ABG) and electrolytes simultaneously.
2. Compare $[HCO_3^-]$ on ABG and electrolytes to verify accuracy.
3. Calculate anion gap (AG), but correct to a normal albumin concentration of 4.5 g/dL.
4. Know four causes of high-AG acidosis (ketoacidosis, lactic acid acidosis, renal failure, and toxins).
5. Know two causes of hyperchloremic or nongap acidosis (bicarbonate loss from gastrointestinal tract, renal tubular acidosis).
6. Estimate compensatory response (Table 51-1).
7. Compare ΔAG and ΔHCO_3^-.
8. Compare change in $[Cl^-]$ with change in $[Na^+]$.

CALCULATE THE ANION GAP

All evaluations of acid-base disorders should include a simple calculation of the AG. The AG is calculated as follows: AG = $Na^+ - (Cl^- + HCO_3^-)$. In the United States, the value for plasma $[K^+]$ is typically omitted from the calculation of the AG. The "normal" value for the AG reported by clinical laboratories has declined with improved methodology for measuring plasma electrolytes, and ranges from 6 to 12 mmol/L, with an average of ~10 mmol/L. The clinician is encouraged to be aware of the normal value for the AG in their clinical chemistry laboratory. The unmeasured anions normally present in plasma include anionic proteins (e.g., albumin), phosphate, sulfate, and organic anions. When acid anions, such as acetoacetate and lactate, accumulate in extracellular fluid, the AG increases, causing a **high-AG acidosis**. An increase in the AG is most often due to an increase in unmeasured anions and, less commonly, may be due to a decrease in unmeasured cations (calcium, magnesium, potassium). In addition, the AG may increase with an increase in anionic albumin. A decrease in the AG can be due to (1) an increase in unmeasured cations; (2) the addition to the blood of abnormal cations, such as lithium (lithium intoxication) or cationic immunoglobulins (plasma cell dyscrasias); (3) a reduction in the plasma anion albumin concentration (nephrotic syndrome, liver disease or malabsorption); or (4) hyperviscosity and severe hyperlipidemia, which can lead to an underestimation of sodium and chloride concentrations. Because the normal AG of 10 mmol/L assumes that the serum albumin is normal, if hypoalbuminemia is present, the value for the AG must be corrected. For example, for each g/dL of serum albumin below the normal value (4.5 g/dL), 2.5 mmol/L should be added to the reported (uncorrected) AG. Thus, in a patient with a serum albumin of 2.5 g/dL (2 g/dL below the normal value), and an uncorrected AG of 15, the corrected AG is calculated by adding 5 mmol/L (2.5 × 2 = 5; 5 + 15 = corrected AG of 20 mmol/L). The clinical disorders that cause a high-AG acidosis are displayed in Table 51-3.

A high AG is usually due to accumulation of non–chloride-containing acids that contain inorganic (phosphate, sulfate), organic (ketoacids, lactate, uremic organic anions), exogenous (salicylate or ingested toxins with organic acid production), or unidentified anions. The high AG is significant clinically even if the $[HCO_3^-]$ or pH is normal. Simultaneous metabolic acidosis of the high-AG variety plus either chronic respiratory acidosis or metabolic alkalosis represents such a situation in which $[HCO_3^-]$ may be normal or even high (Table 51-3). In cases of high-AG metabolic acidosis it is valuable to compare the decline in $[HCO_3^-]$ (ΔHCO_3^-: 25 – patient's $[HCO_3^-]$) with the increase in the AG (ΔAG: patient's AG – 10).

Similarly, normal values for $[HCO_3^-]$, $Paco_2$, and pH do not ensure the absence of an acid-base disturbance. For instance, an alcoholic who has been vomiting may develop a metabolic alkalosis with a pH of 7.55, $Paco_2$ of 47 mmHg, $[HCO_3^-]$ of 40 mmol/L, $[Na^+]$ of 135, $[Cl^-]$ of 80, and $[K^+]$ of 2.8. If such a patient were then to develop a superimposed alcoholic ketoacidosis with a β-hydroxybutyrate concentration of 15 mmol/L, arterial pH would fall to 7.40, the $[HCO_3^-]$ to 25 mmol/L, and the $Paco_2$ to 40 mmHg. Although these blood gases are normal, the AG is elevated at 30 mmol/L, indicating a mixed metabolic alkalosis and metabolic acidosis. A mixture of high-gap acidosis and metabolic alkalosis is recognized easily by comparing the differences (Δ values) in the normal to prevailing patient values. In this example, the ΔHCO_3^- is 0 (25 – 25 mmol/L), but the ΔAG is 20 (30 – 10 mmol/L). Therefore, 20 mmol/L is unaccounted for in the Δ/Δ value (ΔAG to ΔHCO_3^-).

METABOLIC ACIDOSIS

Metabolic acidosis can occur because of an increase in endogenous acid production (such as lactate and ketoacids), loss of bicarbonate (as in diarrhea), or accumulation of endogenous acids because of inappropriately low excretion of net acid by the kidney (as in chronic kidney disease [CKD]). Metabolic acidosis has profound effects on the respiratory, cardiac, and nervous systems. The fall in blood pH is accompanied by a characteristic increase in ventilation, especially the tidal volume (Kussmaul respiration). Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release. Both peripheral arterial vasodilation and central venoconstriction can be present; the decrease in central and pulmonary vascular compliance predisposes to pulmonary edema with even minimal volume overload. CNS function is depressed, with headache, lethargy, stupor, and, in some cases, even coma. Glucose intolerance may also occur.

There are two major categories of clinical metabolic acidosis: high-AG and non-AG acidosis (Table 51-3 and **Table 51-4**). The presence of metabolic acidosis, a normal AG, and hyperchloremia denotes the presence of a normal AG metabolic acidosis.

TABLE 51-4 Causes of High-Anion Gap Metabolic Acidosis

Lactic acidosis	Toxins
Ketoacidosis	Ethylene glycol
Diabetic	Methanol
Alcoholic	Salicylates
Starvation	Propylene glycol
	Pyroglutamic acid (5-oxoproline)
	Renal failure (acute and chronic)

TREATMENT

Metabolic Acidosis

Treatment of metabolic acidosis with alkali should be reserved for severe acidemia except when the patient has no "potential HCO_3^-" in plasma. The potential $[HCO_3^-]$ can be estimated from the increment (Δ) in the AG (ΔAG = patient's AG – 10), only if the acid anion that has accumulated in plasma is metabolizable (i.e., β-hydroxybutyrate, acetoacetate, and lactate). Conversely nonmetabolizable anions that may accumulate in advanced stage CKD or after toxin ingestion are not metabolizable and do not represent "potential" HCO_3^-. With acute CKD improvement in kidney function to replenish the $[HCO_3^-]$ deficit is a slow and often unpredictable process. Consequently, patients with a normal AG acidosis (hyperchloremic acidosis) or an AG attributable to a nonmetabolizable anion due to advanced kidney failure should receive alkali therapy, either PO ($NaHCO_3$ or Shohl's solution) or IV ($NaHCO_3$), in an amount necessary to slowly increase the plasma $[HCO_3^-]$ to a target value of 22 mmol/L. Nevertheless, overcorrection should be avoided.

Controversy exists in regard to the use of alkali in patients with a pure AG acidosis owing to accumulation of a metabolizable organic acid anion (ketoacidosis or lactic acidosis). In general, severe acidemia (pH <7.10) in an adult patient (especially the elderly and patients with severe heart disease) warrants the IV administration of 50 meq of $NaHCO_3$ diluted in 300 mL of sterile water over 30–45 min, during the initial 1–2 h of therapy. Provision of such modest quantities of alkali in this situation seems to provide an added measure of safety. Administration of alkali requires careful monitoring of plasma electrolytes, especially the plasma $[K^+]$, during the course of therapy. A reasonable initial goal is to increase the $[HCO_3^-]$ to 10–12 mmol/L and the pH to ~7.20, but clearly not to increase these values to normal. Estimation of the "bicarbonate deficit" by calculation of the volume of distribution of bicarbonate is often taught but is unnecessary and may result in administration of excessive amounts of alkali.

HIGH-ANION GAP ACIDOSES

APPROACH TO THE PATIENT

There are four principal causes of a high-AG acidosis: (1) lactic acidosis, (2) ketoacidosis, (3) ingested toxins, and (4) acute and chronic renal failure (Table 51-4). Initial screening to differentiate

the high-AG acidoses should include (1) a probe of the history for evidence of drug and toxin ingestion and measurement of arterial blood gas to detect coexistent respiratory alkalosis (salicylates); (2) determination of whether diabetes mellitus is present (diabetic ketoacidosis); (3) a search for evidence of alcoholism or increased levels of β-hydroxybutyrate (alcoholic ketoacidosis); (4) observation for clinical signs of uremia and determination of the blood urea nitrogen (BUN) and creatinine (uremic acidosis); (5) inspection of the urine for oxalate crystals (ethylene glycol); and (6) recognition of the numerous clinical settings in which lactate levels may be increased (hypotension, shock, cardiac failure, leukemia, cancer, and drug or toxin ingestion).

Lactic Acidosis An increase in plasma l-lactate may be secondary to poor tissue perfusion (type A)—circulatory insufficiency (shock, cardiac failure), severe anemia, mitochondrial enzyme defects, and inhibitors (carbon monoxide, cyanide)—or to aerobic disorders (type B)—malignancies, nucleoside analogue reverse transcriptase inhibitors in HIV, diabetes mellitus, renal or hepatic failure, thiamine deficiency, severe infections (cholera, malaria), seizures, or drugs/toxins (biguanides, ethanol, and the toxic alcohols: ethylene glycol (EG), methanol, or propylene glycol). Unrecognized bowel ischemia or infarction in a patient with severe atherosclerosis or cardiac decompensation receiving vasopressors is a common cause of lactic acidosis in elderly patients. Pyroglutamic acidemia may occur in critically ill patients receiving acetaminophen, which causes depletion of glutathione and accumulation of 5-oxyprolene. D-Lactic acid acidosis, which may be associated with jejunoileal bypass, short bowel syndrome, or intestinal obstruction, is due to formation of D-lactate by gut bacteria.

APPROACH TO THE PATIENT

L-Lactic Acid Acidosis

The underlying condition that disrupts lactate metabolism should be corrected preemptively, if possible; tissue perfusion must be restored when inadequate, but vasoconstrictors should be avoided, if possible, because they may worsen tissue perfusion. Alkali therapy is generally advocated for acute, severe acidemia (pH <7.00) to improve cardiovascular function. However, $NaHCO_3$ therapy may paradoxically depress cardiac performance and exacerbate acidosis by enhancing lactate production (HCO_3^- stimulates phosphofructokinase). While the use of alkali in moderate lactic acidosis is controversial, it is generally agreed that attempts to return the pH or [HCO_3^-] to normal by administration of exogenous $NaHCO_3$ are deleterious. A reasonable approach is to infuse sufficient $NaHCO_3$ to raise the arterial pH to no more than 7.2 or the [HCO_3^-] to no more than 12, over 30–40 min.

$NaHCO_3$ therapy can cause fluid overload and hypertension because the amount required can be massive when accumulation of lactic acid is relentless. Fluid administration is poorly tolerated, especially in the oliguric patient, when central venoconstriction coexists. When the underlying cause of the lactic acidosis can be remedied, blood lactate will be converted to HCO_3^- and may result in an overshoot alkalosis if excess $NaHCO_3$ has been administered excessively.

Ketoacidosis • **DIABETIC KETOACIDOSIS (DKA)** This condition is caused by increased fatty acid metabolism and the accumulation of ketoacids (acetoacetate and β-hydroxybutyrate). DKA usually occurs in insulin-dependent diabetes mellitus in association with cessation of insulin or an intercurrent illness such as an infection, gastroenteritis, pancreatitis, or myocardial infarction, which increases insulin requirements temporarily and acutely. The accumulation of ketoacids accounts for the increment in the AG and is accompanied most often by hyperglycemia (glucose >17 mmol/L [300 mg/dL]). The relationship between the ΔAG and ΔHCO_3^- is usually 1:1 in DKA. It should be noted that because insulin prevents production of ketones, bicarbonate therapy is rarely needed except with extreme acidemia (pH < 7.10), and then in only limited amounts. Patients with DKA are typically volume depleted and require fluid resuscitation with isotonic saline. Volume overexpansion with IV isotonic fluid administration is not uncommon, however, and contributes to the development of a hyperchloremic acidosis during treatment of DKA. The mainstay for treatment of this condition is IV regular insulin and is described in Chap. 396 in more detail.

ALCOHOLIC KETOACIDOSIS (AKA) Chronic alcoholics can develop ketoacidosis when alcohol consumption is abruptly curtailed and nutrition is poor. AKA is usually associated with binge drinking, vomiting, abdominal pain, starvation, and volume depletion. The glucose concentration is variable, and acidosis may be severe because of elevated ketones, predominantly β-hydroxybutyrate. Hypoperfusion may enhance lactic acid production, chronic respiratory alkalosis may accompany liver disease, and metabolic alkalosis can result from vomiting (refer to the relationship between ΔAG and ΔHCO_3^-). Thus, mixed acid-base disorders are common in AKA. As the circulation is restored by administration of isotonic saline, the preferential accumulation of β-hydroxybutyrate is then shifted to acetoacetate. This explains the common clinical observation of an increasingly positive nitroprusside reaction (ketones) as the patient improves. The nitroprusside ketone reaction (Acetest) can detect acetoacetic acid but not β-hydroxybutyrate, so that the degree of ketosis and ketonuria can not only change with therapy, but can be underestimated initially. Patients with AKA usually present with relatively normal renal function, as opposed to DKA, where renal function is often compromised because of volume depletion (osmotic diuresis) or diabetic nephropathy. The AKA patient with normal renal function may excrete relatively large quantities of ketoacids in the urine and, therefore, may have a relatively normal AG and a discrepancy in the $\Delta AG/\Delta HCO_3^-$ relationship.

TREATMENT

Alcoholic Ketoacidosis

Extracellular fluid deficits almost always accompany AKA and should be repleted by IV administration of saline and glucose (5% dextrose in 0.9% NaCl). Hypophosphatemia, hypokalemia, and hypomagnesemia may coexist and should be monitored carefully and corrected when indicated. Hypophosphatemia typically emerges 12–24 h after admission, may be exacerbated by glucose infusion, and, if severe, may induce rhabdomyolysis or even respiratory arrest. Upper gastrointestinal hemorrhage, pancreatitis, and pneumonia may accompany this disorder.

DRUG- AND TOXIN-INDUCED ACIDOSIS

Salicylates **(See also Chap. 449)** Salicylate intoxication in adults usually causes respiratory alkalosis or a mixture of high-AG metabolic acidosis and respiratory alkalosis. Only a portion of the AG is due to salicylates. Lactic acid production is also often increased.

TREATMENT

Salicylate-Induced Acidosis

Vigorous gastric lavage with isotonic saline (not $NaHCO_3$) should be initiated immediately. All patients should receive at least one round of activated charcoal per nasogastric tube (1 g/kg up to 50 g). In the acidotic patient, to facilitate removal of salicylate, IV $NaHCO_3$ is administered in amounts adequate to alkalinize the urine and to maintain urine output (urine pH >7.5), because raising the urine pH from 6.5 to 7.5 increases salicylate clearance fivefold. Patients with coexisting respiratory alkalosis should also receive $NaHCO_3$, but with caution to avoid excessive alkalemia. Acetazolamide may be administered in the face of alkalemia, when an alkaline diuresis cannot be achieved, or to ameliorate volume overload associated with $NaHCO_3$ administration, but this drug can cause systemic metabolic acidosis if the excreted HCO_3^- is not replaced, a circumstance that can markedly reduce salicylate clearance.

Hypokalemia should be anticipated with vigorous bicarbonate therapy and should be treated promptly and aggressively. Glucose-containing fluids should be administered because of the danger of hypoglycemia. Excessive insensible fluid losses may cause severe volume depletion and hypernatremia. If renal failure prevents rapid clearance of salicylate, hemodialysis can be performed against a bicarbonate–containing dialysate.

ALCOHOLS Under most physiologic conditions, sodium, urea, and glucose generate the osmotic pressure of blood. Plasma osmolality is calculated according to the following expression: $P_{osm} = 2Na^+ + Glu + BUN$ (all in mmol/L), or, using conventional laboratory values in which glucose and BUN are expressed in milligrams per deciliter: $P_{osm} = 2Na^+ + Glu/18 + BUN/2.8$. The calculated and determined osmolality should agree within 10–15 mmol/kg H_2O. When the measured osmolality exceeds the calculated osmolality by >10–15 mmol/kg H_2O, one of two circumstances prevails. Either the serum sodium is spuriously low, as with hyperlipidemia or hyperproteinemia (pseudohyponatremia), or osmolytes other than sodium salts, glucose, or urea have accumulated in plasma. Examples of such osmolytes include mannitol, radiocontrast media, ethanol, isopropyl alcohol, EG, propylene glycol, methanol, and acetone. In this situation, the difference between the calculated osmolality and the measured osmolality (*osmolar gap*) is proportional to the concentration of the unmeasured solute. With an appropriate clinical history and index of suspicion, identification of an osmolar gap is helpful in identifying the presence of toxic alcohol-associated AG acidosis. Three alcohols may cause fatal intoxications: EG, methanol, and isopropyl alcohol. All cause an elevated osmolal gap, but only the first two cause a high-AG acidosis. Isopropyl alcohol ingestion does not typically elevate the AG unless extreme overdose causes hypotension and lactic acid acidosis.

ETHYLENE GLYCOL (See also Chap. 449) Ingestion of EG (commonly used in antifreeze) leads to a metabolic acidosis and severe damage to the CNS, heart, lungs, and kidneys. The combination of a high AG and high osmolar gap is highly suspicious for EG or methanol intoxication. The increased AG and osmolar gap in EG intoxication are attributable to EG and its metabolites, oxalic acid, glycolic acid, and other organic acids. Lactic acid production increases secondary to inhibition of the tricarboxylic acid cycle and altered intracellular redox state. In addition to the presence of elevated osmolar and AGs, the diagnosis is further enabled by recognition of oxalate crystals in the urine. Use of a Wood's lamp to visualize the fluorescent additive to commercial antifreeze in the urine of patients with EG ingestion, has been reported, but is not reliable. The combination of a high AG and high osmolar gap in a patient suspected of EG ingestion should be taken as evidence of EG toxicity. Treatment should not be delayed while awaiting measurement of EG levels in this setting.

TREATMENT

Ethylene Glycol-Induced Acidosis

This includes the prompt institution of a saline or osmotic diuresis, thiamine and pyridoxine supplements, fomepizole, and usually, hemodialysis. The IV administration of the alcohol dehydrogenase inhibitor fomepizole (4-methylpyrazole; 15 mg/kg as a loading dose) is the agent of choice and offers the advantages of a predictable decline in EG levels without excessive obtundation as seen during ethyl alcohol infusion. If used, ethanol IV should be infused to achieve a blood level of 22 mmol/L (100 mg/dL). Both fomepizole and ethanol reduce toxicity because they compete with EG for metabolism by alcohol dehydrogenase. Hemodialysis is indicated when the arterial pH is <7.3 or the osmolar gap exceeds 20 mOsm/kg.

METHANOL (See also Chap. 449) The ingestion of methanol (wood alcohol) causes metabolic acidosis, and its metabolites formaldehyde and formic acid cause severe optic nerve and CNS damage. Lactic acid, ketoacids, and other unidentified organic acids may contribute to the acidosis. Due to its low molecular mass (32 Da), an osmolar gap is usually present.

TREATMENT

Methanol-Induced Acidosis

This is similar to that for EG intoxication, including general supportive measures, fomepizole, and hemodialysis (as above).

PROPYLENE GLYCOL Propylene glycol is the vehicle used in IV administration of diazepam, lorazepam, phenobarbital, nitroglycerine, etomidate, enoximone, and phenytoin. Propylene glycol is generally safe for limited use in these IV preparations, but toxicity has been reported, most often in the setting of the intensive care unit in patients receiving frequent or continuous therapy. This form of high-gap acidosis should be considered in patients with unexplained high-gap acidosis, hyperosmolality, and clinical deterioration, especially in the setting of treatment for alcohol withdrawal. Propylene glycol, like EG and methanol, is metabolized by alcohol dehydrogenase. With intoxication by propylene glycol, the first response is to stop the offending infusion. Additionally, fomepizole should also be administered in acidotic patients.

ISOPROPYL ALCOHOL Ingested isopropanol is absorbed rapidly and may be fatal when as little as 150 mL of rubbing alcohol, solvent, or deicer is consumed. A plasma level >400 mg/dL is life-threatening. Isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone. The characteristic features differ significantly from EG and methanol intoxication in that the parent compound, not the metabolites, causes toxicity, and a high AG acidosis is ***not*** present because acetone is rapidly excreted. Both isopropyl alcohol and acetone increase the osmolar gap, and hypoglycemia is common. Alternative diagnoses should be considered if the patient does not improve significantly within a few hours. Patients with hemodynamic instability with plasma levels above 400 mg/dL should be considered for hemodialysis.

TREATMENT

Isopropyl Alcohol Toxicity

Isopropanol alcohol toxicity is treated by supportive therapy, IV fluids, pressors, ventilatory support if needed, and occasionally hemodialysis for prolonged coma, hemodynamic instability, or levels >400 mg/dL.

PYROGLUTAMIC ACID Acetaminophen-induced high-AG metabolic acidosis is uncommon but is being recognized more often in either patients with acetaminophen overdose or malnourished or critically ill patients receiving acetaminophen in typical dosage. 5-Oxoproline accumulation after acetaminophen should be suspected in the setting of an unexplained high-AG acidosis without elevation of the osmolar gap in patients receiving acetaminophen. The first step in treatment is to immediately discontinue the drug. Additionally, sodium bicarbonate IV should be given. Although *N*-acetylcysteine has been suggested, it is not known if it hastens the metabolism of 5-oxoproline by increasing intracellular glutathione concentrations in this setting.

Chronic Kidney Disease (See also Chap. 305) The hyperchloremic acidosis of moderate CKD (Stage 3) is eventually converted to the high-AG acidosis of advanced renal failure (Stages 4 and 5 CKD). Poor filtration and reabsorption of organic anions contribute to the pathogenesis. As renal disease progresses, the number of functioning nephrons eventually becomes insufficient to keep pace with net acid production. Uremic acidosis in advanced CKD is characterized, therefore, by a reduced rate of NH_4^+ production and excretion. Alkaline salts from bone buffer the acid retained in chronic kidney disease. Despite significant retention of acid (up to 20 mmol/d), the serum [HCO_3^-] does not typically decrease further, indicating participation of buffers outside the extracellular compartment. Therefore, the trade-off in untreated chronic metabolic acidosis of CKD stages 3

and 4 is significant loss of bone mass due to reduction in bone calcium carbonate. Chronic acidosis also increases urinary calcium excretion, proportional to cumulative acid retention, and contributes significantly to muscle wasting.

TREATMENT

Metabolic Acidosis of Chronic Kidney Disease

Because of the association of metabolic acidosis in advanced CKD with muscle catabolism, bone disease and more rapid progression of CKD, both the "uremic acidosis" of ESRD and the non-AG metabolic acidosis of stages 3 and 4 CKD require oral alkali replacement to maintain the [HCO_3^-] to approximately the normal value (25 mmol/L). This can be accomplished with relatively modest amounts of alkali (1.0–1.5 mmol/kg body weight per day). Either $NaHCO_3$ tablets (650-mg tablets contain 7.8 meq) or sodium citrate (Shohl's solution) is effective.

NON–ANION GAP METABOLIC ACIDOSES

Alkali can be lost from the gastrointestinal tract as a result of diarrhea or from the kidneys due to renal tubular abnormalities (e.g., renal tubular acidosis [RTA]). In these disorders **(Table 51-5)**, reciprocal changes in [Cl^-] and [HCO_3^-] result in a normal AG. In pure non–AG acidosis, therefore, the increase in [Cl^-] above the normal value approximates the decrease in [HCO_3^-]. The absence of such a relationship suggests a mixed disturbance.

Stool contains a higher concentration of HCO_3^- and decomposed HCO_3^- than plasma so that metabolic acidosis develops in diarrhea. Instead of an acid urine pH (as anticipated with systemic acidosis), urine pH is usually >6 because metabolic acidosis and hypokalemia increase renal synthesis and excretion of NH_4^+, thus providing a urinary buffer that increases urine pH. Metabolic acidosis due to gastrointestinal losses with a high urine pH can be differentiated from RTA because urinary NH_4^+ excretion is typically low in RTA and high with diarrhea. Urinary NH_4^+ levels can be estimated by calculating the urine AG (UAG): $UAG = [Na^+ + K^+]_u - [Cl^-]_u$. When $[Cl^-]_u > [Na^+ + K^+]_u$, the UAG is negative by definition. This indicates that the urine ammonium level is appropriately increased, suggesting an extrarenal cause of the acidosis. Conversely, when the UAG is positive, the urine ammonium level is low, suggesting a renal cause of the acidosis.

Proximal RTA (type 2 RTA) **(Chap. 309)** is most often due to generalized proximal tubular dysfunction manifested by glycosuria, generalized aminoaciduria, and phosphaturia (Fanconi syndrome). When the plasma [HCO_3^-] is low the urine pH is acid (pH <5.5), but exceeds 5.5 with alkali therapy. The fractional excretion of [HCO_3^-] may exceed 10–15% when the serum HCO_3^- is >20 mmol/L. Because HCO_3^- is not reabsorbed normally in the proximal tubule, therapy with $NaHCO_3$ will enhance delivery of HCO_3^- to the distal nephron and enhance renal potassium secretion, thereby, causing hypokalemia.

The typical findings in acquired or inherited forms of **classic distal RTA** (type 1 RTA) include hypokalemia, a non-AG metabolic acidosis, low urinary NH_4^+ excretion (positive UAG, low urine [NH_4^+]), and inappropriately high urine pH (pH > 5.5). Most patients have hypocitraturia and hypercalciuria, so nephrolithiasis, nephrocalcinosis, and bone disease are common. In **generalized distal RTA** (type 4 RTA), hyperkalemia is disproportionate to the reduction in glomerular filtration rate (GFR) because of coexisting dysfunction of potassium and acid secretion. Urinary ammonium excretion is invariably depressed, and kidney function may be compromised, for example, due to diabetic nephropathy, obstructive uropathy, or chronic tubulointerstitial disease.

Hyporeninemic hypoaldosteronism typically causes non-AG metabolic acidosis, most commonly in older adults with diabetes mellitus or tubulointerstitial disease and CKD. Patients usually have mild to moderate CKD (GFR, 20–50 mL/min) and acidosis, with elevation in serum [K^+] (5.2–6.0 mmol/L), concurrent hypertension, and congestive heart failure. Both the metabolic acidosis and the hyperkalemia are out of proportion to impairment in GFR. Nonsteroidal anti-inflammatory drugs, trimethoprim, pentamidine, angiotensin-converting enzyme (ACE) inhibitors, and aldosterone receptor blockers (ARBs), can also increase the risk for a hyperkalemia and a non-AG metabolic acidosis in patients with CKD (Table 51-5).

TABLE 51-5 Causes of Non–Anion Gap Acidosis

I. Gastrointestinal bicarbonate loss
- A. Diarrhea
- B. External pancreatic or small-bowel drainage
- C. Ureterosigmoidostomy, jejunal loop, ileal loop
- D. Drugs
  1. Calcium chloride (acidifying agent)
  2. Magnesium sulfate (diarrhea)
  3. Cholestyramine (bile acid diarrhea)

II. Renal acidosis
- A. Hypokalemia
  1. Proximal RTA (type 2)
     Drug-induced: acetazolamide, topiramate
  2. Distal (classic) RTA (type 1)
     Drug-induced: amphotericin B, ifosfamide
- B. Hyperkalemia
  1. Generalized distal nephron dysfunction (type 4 RTA)
     a. Mineralocorticoid deficiency
     b. Mineralocorticoid resistance (PHA I, autosomal dominant)
     c. Voltage defect (PHA I, autosomal recessive, and PHA II)
     d. Tubulointerstitial disease
- C. Normokalemia
  1. Chronic progressive kidney disease

III. Drug-induced hyperkalemia (with renal insufficiency)
- A. Potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone)
- B. Trimethoprim
- C. Pentamidine
- D. ACE-Is and ARBs
- E. Nonsteroidal anti-inflammatory drugs
- F. Calcineurin inhibitors
- G. Heparin in critically ill patients

IV. Other
- A. Acid loads (ammonium chloride, hyperalimentation)
- B. Loss of potential bicarbonate: ketosis with ketone excretion
- C. Expansion acidosis (rapid saline administration)
- D. Hippurate
- E. Cation exchange resins

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PHA, pseudohypoaldosteronism; RTA, renal tubular acidosis.

TREATMENT

Non–Anion Gap Metabolic Acidoses

For non-renal causes of non-AG acidosis due to gastrointestinal losses of bicarbonate, $NaHCO_3$ may be administered intravenously or orally, as determined by the severity of both the acidosis and the accompanying volume depletion. Proximal RTA is the most challenging of the RTAs to treat if the goal is to restore the serum [HCO_3^-] to normal, because administration of oral alkali increases urinary excretion of potassium. In patients with proximal RTA (type 1), potassium administration is typically required. An oral solution of a combination of sodium and potassium citrate (citric acid 334 mg, sodium citrate 500 mg, and potassium citrate 550 mg per 5 mL) may be prescribed for this purpose and is available commercially as Virtrate-3. The syrup preparation is not recommended for chronic administration. In classical distal RTA (type 2), potassium should be administered in the acutely acidotic patient

with hypokalemia. For chronic therapy, most patients respond to replacement with either sodium citrate (Shohl's solution) or $NaHCO_3$ tablets (650-mg tablets contain 7.8 meq) with the goal of correcting the serum [HCO_3^-] to normal. These patients typically respond to chronic alkali therapy readily and the benefits of adequate alkali therapy include a decrease in the frequency of nephrolithiasis, improvement in bone density, resumption of normal growth patterns in children, and preservation of kidney function in both adults and children. For type 4 RTA, attention must be paid to the dual goals of correction of the metabolic acidosis, using the same approach as for cDRTA, but in addition, effort toward correcting the plasma [K^+] is necessary. This latter goal deserves emphasis because restoration of normokalemia increases urinary net acid excretion and in that way can greatly improve the metabolic acidosis. Chronic administration of oral sodium polystyrene solfonate (15 g of power prepared as an oral solution, and without sorbitol, once daily 2–3 times per week) is sometimes used. Additionally, the diet should be low in potassium-containing foods, all potassium-retaining medications should be discontinued, and a loop diuretic may be administered. The recent release of a new a non-absorbed, calcium-potassium cation exchange polymer, patiromer, may prove to be very useful for type 4 RTA patients with significant hyperkalemia. However, patiromer has not yet been investigated in this population of patients. Finally, patients with demonstrated adrenal insufficiency should also receive fludocortisone, but the dose varies with the cause of the hormone deficiency, and should be assiduously avoided in patients with hyporeninemic-hypoaldosteronism.

METABOLIC ALKALOSIS

Metabolic alkalosis is established by an elevated arterial pH, an increase in the serum [HCO_3^-], and an increase in $Paco_2$ as a result of compensatory alveolar hypoventilation (Table 51-1). It is often accompanied by hypochloremia and hypokalemia. The arterial pH establishes the diagnosis, because it is increased in metabolic alkalosis and decreased in respiratory acidosis. Metabolic alkalosis frequently occurs as a mixed acid base disorder in association with either respiratory acidosis, respiratory alkalosis, or metabolic acidosis.

PATHOGENESIS

Metabolic alkalosis occurs as a result of net gain of [HCO_3^-] or loss of nonvolatile acid (usually HCl by vomiting) from the extracellular fluid. When vomiting causes loss of HCl from the stomach, HCO_3^- secretion cannot be initiated in the small bowel and thus HCO_3 is added to the extracellular fluid. Thus, vomiting or nasogastric (NG) suction is an example of the *generation stage*, in which the loss of acid typically causes alkalosis. Upon cessation of vomiting, the *maintenance stage*, typically ensues because secondary factors prevent the kidneys from compensating by excreting HCO_3^-.

Maintenance of metabolic alkalosis, therefore, represents a failure of the kidneys to eliminate excess HCO_3^- from the extracellular compartment. The kidneys will retain, rather than excrete, the excess alkali and maintain the alkalosis if (1) volume deficiency, chloride deficiency, and K^+ deficiency exist in combination with a reduced GFR; or (2) hypokalemia exists because of autonomous hyperaldosteronism. In the first example, alkalosis is corrected by administration of NaCl and KCl, whereas, in the latter, it may be necessary to repair the alkalosis by pharmacologic or surgical intervention, not with saline administration.

DIFFERENTIAL DIAGNOSIS

To establish the cause of metabolic alkalosis **(Table 51-6)**, it is necessary to assess the status of the extracellular fluid volume (ECFV), the recumbent and upright blood pressure (to determine if orthostasis is present), the serum [K^+], and in some circumstances, an assessment of the renin-aldosterone system. For example, the presence of chronic hypertension and chronic hypokalemia in an alkalotic patient suggests either mineralocorticoid excess or that the hypertensive patient is receiving diuretics. Low plasma renin activity and normal values for both the urine [Na^+] and [Cl^-], in a patient who is not taking diuretics, suggest primary mineralocorticoid excess. The combination of hypokalemia and alkalosis in a normotensive, nonedematous patient can be due to Bartter's or Gitelman's syndrome, magnesium deficiency, vomiting, exogenous alkali, or diuretic ingestion. Measurement of urine electrolytes (especially the urine [Cl^-]) and screening of the urine for diuretics is recommended. If the urine is alkaline, with an elevated $[Na^+]_u$ and $[K^+]_u$ but low $[Cl^-]_u$, the diagnosis is usually either vomiting (overt or surreptitious) or alkali ingestion. If the urine is relatively acid and has low concentrations of Na^+, K^+, and Cl^-, the most likely possibilities are prior vomiting, the posthypercapnic state, or prior diuretic ingestion. If, on the other hand, neither the urine sodium, potassium, nor chloride concentrations are depressed, magnesium deficiency, Bartter's or Gitelman's syndrome, or current diuretic ingestion should be considered. Bartter's syndrome is distinguished from Gitelman's syndrome because of hypocalciuria in the latter disorder.

TABLE 51-6 Causes of Metabolic Alkalosis

I. Exogenous HCO_3^- loads
  A. Acute alkali administration
  B. Milk-alkali syndrome
II. Effective ECFV contraction, normotension, K^+ deficiency, and secondary hyperreninemic hyperaldosteronism
  A. Gastrointestinal origin
    1. Vomiting
    2. Gastric aspiration
    3. Congenital chloridorrhea
    4. Gastrocystoplasty
    5. Villous adenoma
  B. Renal origin
    1. Diuretics
    2. Posthypercapnic state
    3. Hypercalcemia/hypoparathyroidism
    4. Recovery from lactic acidosis or ketoacidosis
    5. Nonreabsorbable anions including penicillin, carbenicillin
    6. Mg^{2+} deficiency
    7. K^+ depletion
    8. Bartter's syndrome (loss of function mutations of transporters and ion channels in TALH)
    9. Gitelman's syndrome (loss of function mutation of Na^+-Cl^- cotransporter in DCT)
III. ECFV expansion, hypertension, K^+ deficiency, and mineralocorticoid excess
  A. High renin
    1. Renal artery stenosis
    2. Accelerated hypertension
    3. Renin-secreting tumor
    4. Estrogen therapy
  B. Low renin
    1. Primary aldosteronism
      a. Adenoma
      b. Hyperplasia
      c. Carcinoma
    2. Adrenal enzyme defects
      a. 11β-Hydroxylase deficiency
      b. 17α-Hydroxylase deficiency
    3. Cushing's syndrome or disease
    4. Other
      a. Licorice
      b. Carbenoxolone
      c. Chewer's tobacco
IV. Gain-of-function mutation of sodium channel in DCT with ECFV expansion, hypertension, K^+ deficiency, and hyporeninemic-hypoaldosteronism
  A. Liddle's syndrome

Abbreviations: DCT, distal convoluted tubule; ECFV, extracellular fluid volume; TALH, thick ascending limb of Henle's loop.

Alkali Administration Chronic administration of alkali to individuals with normal renal function rarely causes alkalosis. However,

in patients with coexistent hemodynamic disturbances associated with effective ECF volume depletion, alkalosis can develop because the normal capacity to excrete HCO_3^- is diminished or there may be enhanced reabsorption of HCO_3^-. Such patients include those who receive $NaHCO_3$ (PO or IV), citrate loads (transfusions of whole blood, or therapeutic apheresis), or antacids plus cation-exchange resins (aluminum hydroxide and sodium polystyrene sulfonate). Nursing home patients receiving enteral tube feedings (an often overlooked source of alkali loads) have a higher incidence of metabolic alkalosis than nursing home patients receiving regular diets.

METABOLIC ALKALOSIS ASSOCIATED WITH ECFV CONTRACTION, K^+ DEPLETION, AND SECONDARY HYPERRENINEMIC HYPERALDOSTERONISM

Gastrointestinal Origin Gastrointestinal loss of H^+ from vomiting or gastric aspiration causes simultaneous addition of HCO_3^- into the extracellular fluid. During active vomiting, the filtered load of bicarbonate reaching the kidneys is acutely increased and will exceed the reabsorptive capacity of the proximal tubule for HCO_3^- absorption. Subsequently, enhanced delivery of HCO_3 to the distal nephron will cause excretion of alkaline urine that is high in potassium. When vomiting ceases, the persistence of volume, potassium, and chloride depletion triggers maintenance of the alkalosis because these conditions promote HCO_3^- reabsorption. Correction of the contracted ECFV with NaCl and repair of K^+ deficits with KCl corrects the acid-base disorder by restoring the ability of the kidney to excrete the excess bicarbonate.

Renal Origin • **DIURETICS** (See also Chap. 252) Diuretics such as thiazides and loop diuretics (furosemide, bumetanide, torsemide) increase excretion of salt and acutely diminish the ECFV without altering the total body bicarbonate content. The serum $[HCO_3^-]$ increases because the reduced ECFV "contracts" around the $[HCO_3^-]$ in the plasma (contraction alkalosis). The chronic administration of diuretics tends to generate an alkalosis by increasing distal salt delivery, so that both K^+ and H^+ secretion are stimulated. The alkalosis is maintained by persistence of the contraction of the ECFV, secondary hyperaldosteronism, K^+ deficiency, and the direct effect of the diuretic (as long as diuretic administration continues). Discontinuing the diuretic and providing isotonic saline to correct the ECFV deficit will repair the alkalosis.

SOLUTE LOSING DISORDERS: BARTTER'S SYNDROME AND GITELMAN'S SYNDROME See Chap. 309.

NONREABSORBABLE ANIONS AND MAGNESIUM DEFICIENCY Administration of large quantities of the penicillin derivatives carbenicillin or ticarcillin cause their nonreabsorbable anions to appear in the urine. This increases the transepithelial potential difference in the collecting tubule, and thereby enhances H^+ and K^+ secretion. Mg^{2+} deficiency, may occur with chronic administration of thiazide diuretics, alcoholism, and malnutrition, and in Gitelman's syndrome potentiates the development of hypokalemic alkalosis by enhancing distal acidification through stimulation of renin and hence aldosterone secretion.

POTASSIUM DEPLETION Chronic K^+ depletion may cause metabolic alkalosis by increasing urinary acid excretion. The renal generation of NH_4^+ (ammoniagenesis) is upregulated directly by hypokalemia. Chronic K^+ deficiency also upregulates the renal H^+, K^+-ATPase to increase K^+ absorption at the expense of enhanced H^+ secretion. Alkalosis associated with severe K^+ depletion is resistant to salt administration, but repair of the K^+ deficiency corrects the alkalosis. Potassium depletion often occurs concomitant with magnesium deficiency in alcoholics with malnutrition.

AFTER TREATMENT OF LACTIC ACIDOSIS OR KETOACIDOSIS When an underlying stimulus for the generation of lactic acid or ketoacid is corrected by treatment of the underlying disorder, such as correction shock or severe volume depletion by volume restoration, or with insulin therapy, respectively, the lactate or ketones are metabolized to yield an equivalent amount of HCO_3^-. Exogenous sources of HCO_3^- will be additive with that amount generated by organic anion metabolism to create a surfeit of HCO_3^-. Acidosis-induced contraction of the ECFV and K^+ deficiency act in concert to sustain the alkalosis.

POSTHYPERCAPNIA Prolonged CO_2 retention with chronic respiratory acidosis enhances renal HCO_3^- absorption and the generation of new HCO_3^- (increased net acid excretion). Metabolic alkalosis results from the effect of the persistently elevated $[HCO_3^-]$ when the elevated $Paco_2$ is abruptly returned toward normal.

METABOLIC ALKALOSIS ASSOCIATED WITH ECFV EXPANSION, HYPERTENSION, AND HYPERALDOSTERONISM

Increased aldosterone levels may be the result of autonomous primary adrenal overproduction or of secondary aldosterone release due to renal overproduction of renin. Mineralocorticoid excess increases net acid excretion and may result in metabolic alkalosis, which is typically exacerbated by associated K^+ deficiency. Salt retention is due to upregulation of the epithelial Na^+ channels in the collecting tubule to aldosterone, as a result of the associated ECFV expansion, causes hypertension. The kaliuresis persists because of mineralocorticoid excess and distal Na^+ absorption causing enhanced K^+ excretion, continued K^+ depletion with polydipsia, inability to concentrate the urine, and polyuria.

Liddle's syndrome (Chap. 309) results from an inherited gain of function mutation of genes that regulate the collecting duct Na^+ channel (ENaC). Liddle's is a rare monogenic form of hypertension due to volume expansion manifested as hypokalemic alkalosis and normal aldosterone levels.

Symptoms With metabolic alkalosis, changes in CNS and peripheral nervous system function are similar to those of hypocalcemia (Chap. 402); symptoms include mental confusion; obtundation; and a predisposition to seizures, paresthesia, muscular cramping, tetany, aggravation of arrhythmias, and hypoxemia in chronic obstructive pulmonary disease. Related electrolyte abnormalities include hypokalemia and hypophosphatemia.

TREATMENT

Metabolic Alkalosis

This is primarily directed at correcting the underlying stimulus for HCO_3^- generation. If primary aldosteronism or Cushing's syndrome is present, correction of the underlying cause, when successful, will reverse the hypokalemia and alkalosis. $[H^+]$ loss by the stomach or kidneys can be mitigated by the use of proton pump inhibitors or the discontinuation of diuretics. The second aspect of treatment is to remove the factors that sustain the inappropriate increase in HCO_3^- reabsorption, such as ECFV contraction or K^+ deficiency. K^+ deficits should always be repaired. Isotonic saline is recommended to reverse the alkalosis when ECFV contraction is present. If associated conditions preclude infusion of saline, renal HCO_3^- loss can be accelerated by administration of acetazolamide, a carbonic anhydrase inhibitor (125–250 mg IV), which is usually effective in patients with adequate renal function but can worsen K^+ losses. Dilute hydrochloric acid (0.1 *N* HCl) has been advocated historically in extreme cases, but can cause hemolysis, and must be delivered slowly in a central vein. This preparation is not available generally and must be mixed by the pharmacist. Because serious errors or harm may occur, its use is not recommended.

RESPIRATORY ACIDOSIS

Respiratory acidosis can be due to severe pulmonary disease, respiratory muscle fatigue, or abnormalities in ventilatory control and is recognized by an increase in $Paco_2$ and decrease in pH (Table 51-7). In acute respiratory acidosis, there is a compensatory elevation (due to cellular buffering mechanisms) in HCO_3^-, which increases 1 mmol/L for every 10-mmHg increase in $Paco_2$. In chronic respiratory acidosis (>24 h), renal adaptation increases the $[HCO_3^-]$ by 4 mmol/L for every 10-mmHg increase in $Paco_2$. The serum HCO_3^- usually does not increase above 38 mmol/L.

TABLE 51-7 Respiratory Acid-Base Disorders

I. Alkalosis
- A. Central nervous system stimulation
  1. Pain
  2. Anxiety, psychosis
  3. Fever
  4. Cerebrovascular accident
  5. Meningitis, encephalitis
  6. Tumor
  7. Trauma
- B. Hypoxemia or tissue hypoxia
  1. High altitude
  2. Pneumonia, pulmonary edema
  3. Aspiration
  4. Severe anemia
- C. Drugs or hormones
  1. Pregnancy, progesterone
  2. Salicylates
  3. Cardiac failure
- D. Stimulation of chest receptors
  1. Hemothorax
  2. Flail chest
  3. Cardiac failure
  4. Pulmonary embolism
- E. Miscellaneous
  1. Septicemia
  2. Hepatic failure
  3. Mechanical hyperventilation
  4. Heat exposure
  5. Recovery from metabolic acidosis

II. Acidosis
- A. Central
  1. Drugs (anesthetics, morphine, sedatives)
  2. Stroke
  3. Infection
- B. Airway
  1. Obstruction
  2. Asthma
- C. Parenchyma
  1. Emphysema
  2. Pneumoconiosis
  3. Bronchitis
  4. Adult respiratory distress syndrome
  5. Barotrauma
- D. Neuromuscular
  1. Poliomyelitis
  2. Kyphoscoliosis
  3. Myasthenia
  4. Muscular dystrophies
- E. Miscellaneous
  1. Obesity
  2. Hypoventilation
  3. Permissive hypercapnia

The clinical features vary according to the severity and duration of the respiratory acidosis, the underlying disease, and whether there is accompanying hypoxemia. A rapid increase in $Paco_2$ may cause anxiety, dyspnea, confusion, psychosis, and hallucinations and may progress to coma. Lesser degrees of dysfunction in chronic hypercapnia include sleep disturbances; loss of memory; daytime somnolence; personality changes; impairment of coordination; and motor disturbances such as tremor, myoclonic jerks, and asterixis. Headaches and other signs that mimic raised intracranial pressure, such as papilledema, abnormal reflexes, and focal muscle weakness, are due to vasoconstriction secondary to loss of the vasodilator effects of CO_2.

Depression of the respiratory center by a variety of drugs, injury, or disease can produce respiratory acidosis. This may occur acutely with general anesthetics, sedatives, and head trauma or chronically with sedatives, alcohol, intracranial tumors, and the syndromes of sleep-disordered breathing including the primary alveolar and obesity-hypoventilation syndromes **(Chaps. 290 and 291)**. Abnormalities or disease in the motor neurons, neuromuscular junction, and skeletal muscle can cause hypoventilation via respiratory muscle fatigue. Mechanical ventilation, when not properly adjusted and supervised, may result in respiratory acidosis, particularly if CO_2 production suddenly rises (because of fever, agitation, sepsis, or overfeeding) or alveolar ventilation falls because of worsening pulmonary function. High levels of positive end-expiratory pressure in the presence of reduced cardiac output may cause hypercapnia as a result of large increases in alveolar dead space **(Chap. 279)**. Permissive hypercapnia may be used to minimize intrinsic positive end-expiratory pressure in acute lung injury/acute respiratory distress syndrome and severe obstructive lung disease. The respiratory acidosis associated with permissive hypercapnia may require administration of $NaHCO_3$ to increase the arterial pH to ~7.15–7.20, but correction of the acidemia to a normal arterial pH is deleterious.

Acute hypercapnia follows sudden occlusion of the upper airway or generalized bronchospasm as in severe asthma, anaphylaxis, inhalational burn, or toxin injury. Chronic hypercapnia and respiratory acidosis occur in end-stage obstructive lung disease. Restrictive disorders involving both the chest wall and the lungs can cause respiratory acidosis because the high metabolic cost of respiration causes ventilatory muscle fatigue. Advanced stages of intrapulmonary and extrapulmonary restrictive defects present as chronic respiratory acidosis.

The diagnosis of respiratory acidosis requires the measurement of $Paco_2$ and arterial pH. A detailed history and physical examination often indicate the cause. Pulmonary function studies **(Chap. 279)**, including spirometry, diffusion capacity for carbon monoxide, lung volumes, and arterial $Paco_2$ and O_2 saturation, usually make it possible to determine if respiratory acidosis is secondary to lung disease. The workup for nonpulmonary causes should include a detailed drug history, measurement of hematocrit, and assessment of upper airway, chest wall, pleura, and neuromuscular function.

TREATMENT

Respiratory Acidosis

The management of respiratory acidosis depends on its severity and rate of onset. Acute respiratory acidosis can be life-threatening, and measures to reverse the underlying cause should be undertaken simultaneously with restoration of adequate alveolar ventilation. This may necessitate tracheal intubation and assisted mechanical ventilation. Oxygen administration should be titrated carefully in patients with severe obstructive pulmonary disease and chronic CO_2 retention who are breathing spontaneously **(Chap. 286)**. When oxygen is used injudiciously, these patients may experience progression of the respiratory acidosis causing severe acidemia. Aggressive and rapid correction of hypercapnia should be avoided, because the falling $Paco_2$ may provoke the same complications noted with acute respiratory alkalosis (i.e., cardiac arrhythmias, reduced cerebral perfusion, and seizures). The $Paco_2$ should be lowered gradually in chronic respiratory acidosis, aiming to restore the $Paco_2$ to baseline levels and to provide sufficient Cl^- and K^+ to enhance the renal excretion of HCO_3^-.

Chronic respiratory acidosis is frequently difficult to correct, but measures aimed at improving lung function **(Chap. 286)** should be the primary focus of treatment.

RESPIRATORY ALKALOSIS

Alveolar hyperventilation decreases $Paco_2$ and increases the $HCO_3^-/Paco_2$ ratio, thus increasing pH (Table 51-7). Nonbicarbonate cellular buffers respond by consuming HCO_3^-. Hypocapnia develops when

a sufficiently strong ventilatory stimulus causes CO_2 output in the lungs to exceed its metabolic production by tissues. Plasma pH and $[HCO_3^-]$ appear to vary proportionately with $Paco_2$ over a range from 40–15 mmHg. The relationship between arterial $[H^+]$ concentration and $Paco_2$ is ~0.7 mmol/L per mmHg (or 0.01 pH unit/mmHg), and that for plasma $[HCO_3^-]$ is 0.2 mmol/L per mmHg. Hypocapnia sustained for >2–6 h is further compensated by a decrease in renal ammonium and titratable acid excretion and a reduction in filtered HCO_3^- reabsorption. Full renal adaptation to respiratory alkalosis may take several days and requires normal volume status and renal function. The kidneys appear to respond directly to the lowered $Paco_2$ rather than to alkalosis per se. In chronic respiratory alkalosis a 1-mmHg decrease in $Paco_2$ causes a 0.4- to 0.5-mmol/L drop in $[HCO_3^-]$ and a 0.3-mmol/L decrease (or 0.003 increase in pH) in $[H^+]$.

The effects of respiratory alkalosis vary according to duration and severity but are primarily those of the underlying disease. Reduced cerebral blood flow as a consequence of a rapid decline in $Paco_2$ may cause dizziness, mental confusion, and seizures, even in the absence of hypoxemia. The cardiovascular effects of acute hypocapnia in the conscious human are generally minimal, but in the anesthetized or mechanically ventilated patient, cardiac output and blood pressure may fall because of the depressant effects of anesthesia and positive-pressure ventilation on heart rate, systemic resistance, and venous return. Cardiac arrhythmias may occur in patients with heart disease as a result of changes in oxygen unloading by blood from a left shift in the hemoglobin-oxygen dissociation curve (Bohr effect). Acute respiratory alkalosis causes intracellular shifts of Na^+, K^+, and PO_4^{2-} and reduces free $[Ca^{2+}]$ by increasing the protein-bound fraction. Hypocapnia-induced hypokalemia is usually minor.

Chronic respiratory alkalosis is the most common acid-base disturbance in critically ill patients and, when severe, portends a poor prognosis. Many cardiopulmonary disorders manifest respiratory alkalosis in their early to intermediate stages, and the finding of normocapnia and hypoxemia in a patient with hyperventilation may herald the onset of rapid respiratory failure and should prompt an assessment to determine if the patient is becoming fatigued. Respiratory alkalosis is common during mechanical ventilation.

The hyperventilation syndrome may be disabling. Paresthesia; circumoral numbness; chest wall tightness or pain; dizziness; inability to take an adequate breath; and, rarely, tetany may be sufficiently stressful to perpetuate the disorder. Arterial blood-gas analysis demonstrates an acute or chronic respiratory alkalosis, often with hypocapnia in the range of 15–30 mmHg and no hypoxemia. CNS diseases or injury can produce several patterns of hyperventilation and sustained $Paco_2$ levels of 20–30 mmHg. Hyperthyroidism, high caloric loads, and exercise raise the basal metabolic rate, but ventilation usually rises in proportion so that arterial blood gases are unchanged and respiratory alkalosis does not develop. Salicylates are the most common cause of drug-induced respiratory alkalosis as a result of direct stimulation of the medullary chemoreceptor **(Chap. 449)**. The methylxanthines, theophylline, and aminophylline stimulate ventilation and increase the ventilatory response to CO_2. Progesterone increases ventilation and lowers arterial $Paco_2$ by as much as 5–10 mmHg. Therefore, chronic respiratory alkalosis is a common feature of pregnancy. Respiratory alkalosis is also prominent in liver failure, and the severity correlates with the degree of hepatic insufficiency. Respiratory alkalosis is often an early finding in gram-negative septicemia, before fever, hypoxemia, or hypotension develops.

The diagnosis of respiratory alkalosis depends on measurement of arterial pH and $Paco_2$. The plasma $[K^+]$ is often reduced and the $[Cl^-]$ increased. In the acute phase, respiratory alkalosis is not associated with increased renal HCO_3^- excretion, but within hours net acid excretion is reduced. In general, the HCO_3^- concentration falls by 2.0 mmol/L for each 10-mmHg decrease in $Paco_2$. If the hypocapnia persists for >3–5 days, chronic respiratory alkalosis is present, and the decline in $Paco_2$ reduces the serum $[HCO_3^-]$ by 4–5 mmol/L for each 10-mmHg decrease in $Paco_2$. It is unusual to observe a plasma HCO_3^- <12 mmol/L as a result of a pure respiratory alkalosis. Moreover, the compensatory reduction in the plasma HCO_3^- concentration is so effective in chronic respiratory alkalosis that the pH does not decline significantly from the normal value. In this regard, chronic respiratory alkalosis is the only acid-base disorder that may return the pH to the normal value.

When a diagnosis of respiratory alkalosis is made, its cause should be investigated. The diagnosis of hyperventilation syndrome is made by exclusion. In difficult cases, it may be important to rule out other conditions such as pulmonary embolism, coronary artery disease, and hyperthyroidism.

TREATMENT

Respiratory Alkalosis

The management of respiratory alkalosis is directed toward alleviation of the underlying disorder. If respiratory alkalosis complicates ventilator management, changes in dead space, tidal volume, and frequency can minimize the hypocapnia. Patients with the hyperventilation syndrome may benefit from reassurance, rebreathing from a paper bag during symptomatic attacks, and attention to underlying psychological stress. Antidepressants and sedatives are not recommended. β-adrenergic blockers may ameliorate peripheral manifestations of the hyperadrenergic state.

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Section 8 Alterations in the Skin

52 Approach to the Patient with a Skin Disorder

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The challenge of examining the skin lies in distinguishing normal from abnormal findings, distinguishing significant findings from trivial ones, and integrating pertinent signs and symptoms into an appropriate differential diagnosis. The fact that the largest organ in the body is visible is both an advantage and a disadvantage to those who examine it. It is advantageous because no special instrumentation is necessary and because the skin can be biopsied with little morbidity. However, the casual observer can be misled by a variety of stimuli and overlook important, subtle signs of skin or systemic disease. For instance, the sometimes minor differences in color and shape that distinguish a melanoma **(Fig. 52-1)** from a benign nevomelanocytic nevus **(Fig. 52-2)** can be difficult to recognize. A variety of descriptive terms have been developed that characterize cutaneous lesions **(Tables 52-1, 52-2, and 52-3; Fig. 52-3)**, thereby aiding in their interpretation and in

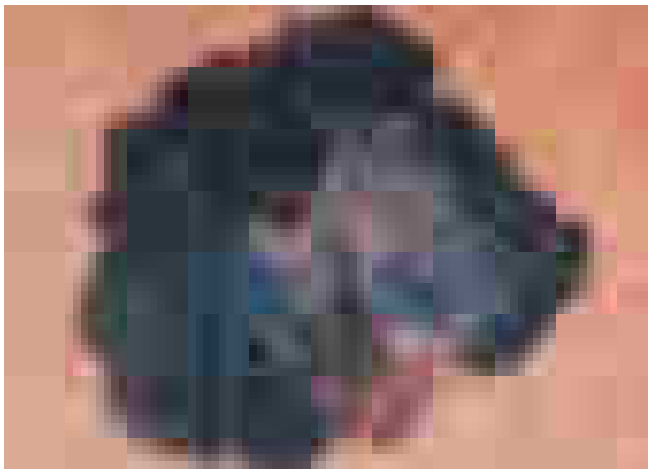

FIGURE 52-1 Superficial spreading melanoma. This is the most common type of melanoma. Such lesions usually demonstrate asymmetry, border irregularity, color variegation (black, blue, brown, pink, and white), a diameter >6 mm, and a history of change (e.g., an increase in size or development of associated symptoms such as pruritus or pain).

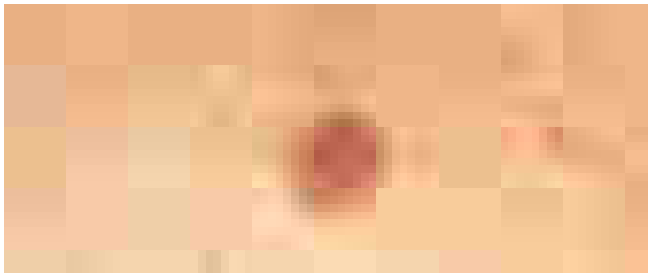

FIGURE 52-2 Nevomelanocytic nevus. Nevi are benign proliferations of nevomelanocytes characterized by regularly shaped hyperpigmented macules or papules of a uniform color.

TABLE 52-1 Description of Primary Skin Lesions

Macule: A flat, colored lesion, <2 cm in diameter, not raised above the surface of the surrounding skin. A "freckle," or ephelid, is a prototypical pigmented macule.
Patch: A large (>2 cm) flat lesion with a color different from the surrounding skin. This differs from a macule only in size.
Papule: A small, solid lesion, <0.5 cm in diameter, raised above the surface of the surrounding skin and thus palpable (e.g., a closed comedone, or whitehead, in acne).
Nodule: A larger (0.5 to 5.0 cm), firm lesion raised above the surface of the surrounding skin. This differs from a papule only in size (e.g., a large dermal nevomelanocytic nevus).
Tumor: A solid, raised growth >5 cm in diameter.
Plaque: A large (>1 cm), flat-topped, raised lesion; edges may either be distinct (e.g., in psoriasis) or gradually blend with surrounding skin (e.g., in eczematous dermatitis).
Vesicle: A small, fluid-filled lesion, <0.5 cm in diameter, raised above the plane of surrounding skin. Fluid is often visible, and the lesions are translucent (e.g., vesicles in allergic contact dermatitis caused by *Toxicodendron* [poison ivy]).
Pustule: A vesicle filled with leukocytes. Note: The presence of pustules does not necessarily signify the existence of an infection.
Bulla: A fluid-filled, raised, often translucent lesion >0.5 cm in diameter.
Wheal: A raised, erythematous, edematous papule or plaque, usually representing short-lived vasodilation and vasopermeability.
Telangiectasia: A dilated, superficial blood vessel.

TABLE 52-2 Description of Secondary Skin Lesions

Lichenification: A distinctive thickening of the skin that is characterized by accentuated skin-fold markings.
Scale: Excessive accumulation of stratum corneum.
Crust: Dried exudate of body fluids that may be either yellow (i.e., serous crust) or red (i.e., hemorrhagic crust).
Erosion: Loss of epidermis without an associated loss of dermis.
Ulcer: Loss of epidermis and at least a portion of the underlying dermis.
Excoriation: Linear, angular erosions that may be covered by crust and are caused by scratching.
Atrophy: An acquired loss of substance. In the skin, this may appear as a depression with intact epidermis (i.e., loss of dermal or subcutaneous tissue) or as sites of shiny, delicate, wrinkled lesions (i.e., epidermal atrophy).
Scar: A change in the skin secondary to trauma or inflammation. Sites may be erythematous, hypopigmented, or hyperpigmented depending on their age or character. Sites on hair-bearing areas may be characterized by destruction of hair follicles.

TABLE 52-3 Common Dermatologic Terms

Alopecia: Hair loss, partial or complete.
Annular: Ring-shaped.
Cyst: A soft, raised, encapsulated lesion filled with semisolid or liquid contents.
Herpetiform: In a grouped configuration.
Lichenoid eruption: Violaceous to purple, polygonal lesions that resemble those seen in lichen planus.
Milia: Small, firm, white papules filled with keratin.
Morbilliform rash: Generalized, small erythematous macules and/or papules that resemble lesions seen in measles.
Nummular: Coin-shaped.
Poikiloderma: Skin that displays variegated pigmentation, atrophy, and telangiectases.
Polycyclic lesions: A configuration of skin lesions formed from coalescing rings or incomplete rings.
Pruritus: A sensation that elicits the desire to scratch. Pruritus is often the predominant symptom of inflammatory skin diseases (e.g., atopic dermatitis, allergic contact dermatitis); it is also commonly associated with xerosis and aged skin. Systemic conditions that can be associated with pruritus include chronic renal disease, cholestasis, pregnancy, malignancy, thyroid disease, polycythemia vera, and delusions of parasitosis.

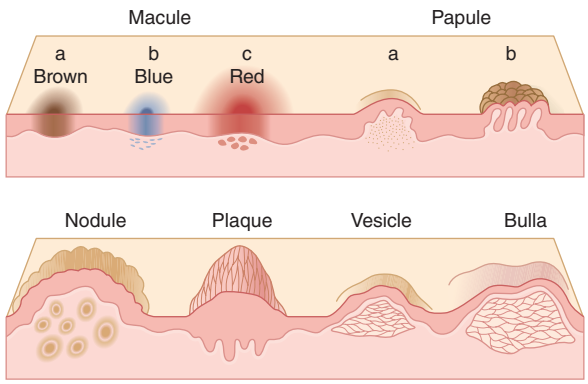

FIGURE 52-3 A schematic representation of several common primary skin lesions (see Table 52-1).

TABLE 52-4 Selected Common Dermatologic Conditions

DIAGNOSIS	COMMON DISTRIBUTION	USUAL MORPHOLOGY	DIAGNOSIS	COMMON DISTRIBUTION	USUAL MORPHOLOGY
Acne vulgaris	Face, upper back, chest	Open and closed comedones, erythematous papules, pustules, cysts	Seborrheic keratosis	Trunk, face, extremities	Brown plaques with adherent, greasy scale; "stuck on" appearance
Rosacea	Blush area of cheeks, nose, forehead, chin	Erythema, telangiectases, papules, pustules	Folliculitis Impetigo	Any hair-bearing area Anywhere	Follicular pustules Papules, vesicles, pustules, often with honey-colored crusts
Seborrheic dermatitis	Scalp, eyebrows, perinasal areas	Erythema with greasy yellow-brown scale	Herpes simplex	Lips, genitalia	Grouped vesicles progressing to crusted erosions
Atopic dermatitis	Antecubital and popliteal fossae; may be widespread	Patches and plaques of erythema, scaling, and lichenification; pruritus	Herpes zoster	Dermatomal, usually trunk but may be anywhere	Vesicles limited to a dermatome (often painful)
Stasis dermatitis	Ankles, lower legs over medial malleoli	Patches of erythema and scaling on background of hyperpigmentation associated with signs of venous insufficiency	Varicella	Face, trunk, relative sparing of extremities	Lesions arise in crops and quickly progress from erythematous macules, to papules, to vesicles, to pustules, to crusted sites.
Dyshidrotic eczema	Palms, soles, sides of fingers and toes	Deep vesicles	Pityriasis rosea	Trunk (Christmas tree pattern); herald patch followed by multiple smaller lesions	Symmetric erythematous papules and plaques with a collarette of scale
Allergic contact dermatitis	Anywhere	Localized erythema, vesicles, scale, and pruritus (e.g., fingers, earlobes—nickel; dorsal aspect of foot—shoe; exposed surfaces—poison ivy)	Tinea versicolor	Chest, back, abdomen, proximal extremities	Scaly hyper- or hypopigmented macules
Psoriasis	Elbows, knees, scalp, lower back, fingernails (may be generalized)	Papules and plaques covered with silvery scale; nails have pits	Candidiasis	Groin, beneath breasts, vagina, oral cavity	Erythematous macerated areas with satellite pustules; white, friable patches on mucous membranes
Lichen planus	Wrists, ankles, mouth (may be widespread)	Violaceous flat-topped papules and plaques	Dermatophytosis	Feet, groin, beard, or scalp	Varies with site (e.g., tinea corporis—scaly annular plaque)
Keratosis pilaris	Extensor surfaces of arms and thighs, buttocks	Keratotic follicular papules with surrounding erythema	Scabies	Groin, axillae, between fingers and toes, beneath breasts	Excoriated papules, burrows, pruritus
Melasma	Forehead, cheeks, temples, upper lip	Tan to brown patches	Insect bites	Anywhere	Erythematous papules with central puncta
Vitiligo	Periorificial, trunk, extensor surfaces of extremities, flexor wrists, axillae	Chalk-white macules	Cherry angioma Keloid Dermatofibroma	Trunk Anywhere (site of previous injury) Anywhere	Red, blood-filled papules Firm tumor, pink, purple, or brown Firm red to brown nodule that shows dimpling of overlying skin with lateral compression
Actinic keratosis	Sun-exposed areas	Skin-colored or red-brown macule or papule with dry, rough, adherent scale	Acrochordons (skin tags)	Groin, axilla, neck	Fleshy papules
Basal cell carcinoma	Face	Papule with pearly, telangiectatic border on sun-damaged skin	Urticaria	Anywhere	Wheals, sometimes with surrounding flare; pruritus
Squamous cell carcinoma	Face, especially lower lip, ears	Indurated and possibly hyperkeratotic lesions often showing ulceration and/or crusting	Transient acantholytic dermatosis Xerosis	Trunk, especially anterior chest Extensor extremities, especially legs	Erythematous papules Dry, erythematous, scaling patches; pruritus

the formulation of a differential diagnosis (Table 52-4). For example, the finding of scaling papules, which are present in psoriasis or atopic dermatitis, places the patient in a different diagnostic category than would hemorrhagic papules, which may indicate vasculitis or sepsis (Figs. 52-4 and 52-5, respectively). It is also important to differentiate primary from secondary skin lesions. If the examiner focuses on linear erosions overlying an area of erythema and scaling, he or she may incorrectly assume that the erosion is the primary lesion and that the redness and scale are secondary, whereas the correct interpretation would be that the patient has a pruritic eczematous dermatitis with erosions caused by scratching.

APPROACH TO THE PATIENT

Skin Disorder

In examining the skin it is usually advisable to assess the patient before taking an extensive history. This approach ensures that the entire cutaneous surface will be evaluated, and objective findings can be integrated with relevant historical data. Four basic features of a skin lesion must be noted and considered during a physical examination: the *distribution* of the eruption, the *types* of primary and secondary lesions, the *shape* of individual lesions, and the *arrangement* of the lesions. An ideal skin examination includes evaluation

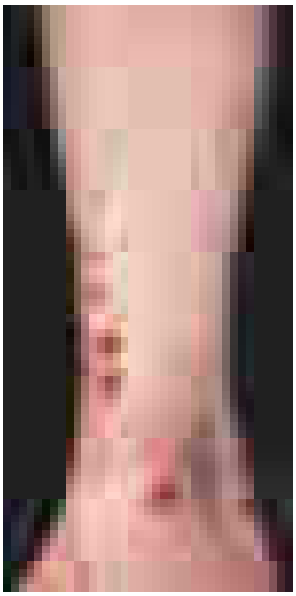

FIGURE 52-4 Necrotizing vasculitis. Palpable purpuric papules on the lower legs are seen in this patient with cutaneous small-vessel vasculitis. *(Courtesy of Robert Swerlick, MD; with permission.)*

of the skin, hair, and nails as well as the mucous membranes of the mouth, eyes, nose, nasopharynx, and anogenital region. In the initial examination, it is important that the patient be disrobed as completely as possible to minimize chances of missing important individual skin lesions and permit accurate assessment of the distribution of the eruption. The patient should first be viewed from a distance of about 1.5–2 m (4–6 ft) so that the general character of the skin and the distribution of lesions can be evaluated. Indeed, the distribution of lesions often correlates highly with diagnosis **(Fig. 52-6)**. For example, a hospitalized patient with a generalized erythematous exanthem is more likely to have a drug eruption than is a patient with a similar rash limited to the sun-exposed portions of the face. Once the distribution of the lesions has been established, the nature of the primary lesion must be determined. Thus, when lesions are distributed on elbows, knees, and scalp, the most likely possibility based solely on distribution is psoriasis or dermatitis herpetiformis **(Figs. 52-7 and 52-8, respectively)**. The primary lesion in psoriasis is a scaly papule that soon forms erythematous plaques covered with a white scale, whereas that of dermatitis herpetiformis is an urticarial papule that quickly becomes a small vesicle. In this manner, identification of the primary lesion directs the examiner toward the proper diagnosis. Secondary changes in skin can also be quite helpful. For example, scale represents excessive epidermis, while crust is the result of a discontinuous epithelial cell layer. Palpation of skin lesions can yield insight into the character of an eruption. Thus, red papules on the lower extremities that blanch with pressure can be a manifestation of many different diseases, but hemorrhagic red papules that do not blanch with pressure indicate palpable purpura characteristic of necrotizing vasculitis (Fig. 52-4).

The shape of lesions is also an important feature. Flat, round, erythematous papules and plaques are common in many cutaneous diseases. However, target-shaped lesions that consist in part of erythematous plaques are specific for erythema multiforme **(Fig. 52-9)**. Likewise, the arrangement of individual lesions is important. Erythematous papules and vesicles can occur in many conditions, but their arrangement in a specific linear array suggests an external etiology such as allergic contact dermatitis **(Fig. 52-10)** or primary irritant dermatitis. In contrast, lesions with a generalized arrangement are common and suggest a systemic etiology.

As in other branches of medicine, a complete history should be obtained to emphasize the following features:

1. Evolution of lesions
   a. Site of onset
   b. Manner in which the eruption progressed or spread
   c. Duration
   d. Periods of resolution or improvement in chronic eruptions
2. Symptoms associated with the eruption
   a. Itching, burning, pain, numbness
   b. What, if anything, has relieved symptoms
   c. Time of day when symptoms are most severe
3. Current or recent medications (prescribed as well as over-the-counter)
4. Associated systemic symptoms (e.g., malaise, fever, arthralgias)
5. Ongoing or previous illnesses
6. History of allergies
7. Presence of photosensitivity
8. Review of systems
9. Family history (particularly relevant for patients with melanoma, atopy, psoriasis, or acne)
10. Social, sexual, or travel history

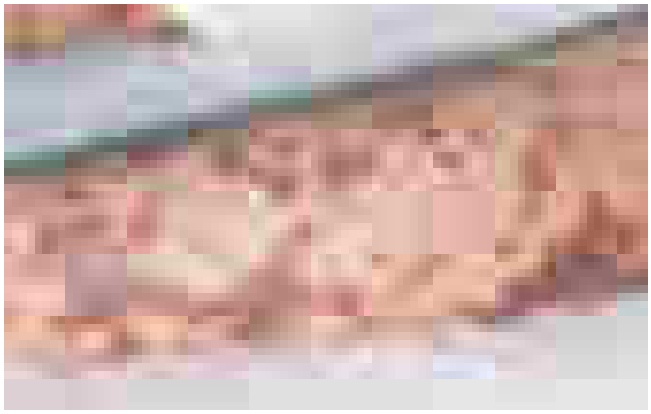

FIGURE 52-5 Meningococcemia. An example of fulminant meningococcemia with extensive angular purpuric patches. *(Courtesy of Stephen E. Gellis, MD; with permission.)*

DIAGNOSTIC TECHNIQUES

Many skin diseases can be diagnosed on the basis of gross clinical appearance, but sometimes relatively simple diagnostic procedures can yield valuable information. In most instances, they can be performed at the bedside with a minimum of equipment.

Skin Biopsy A skin biopsy is a straightforward minor surgical procedure; however, it is important to biopsy a lesion that is most likely to yield diagnostic findings. This decision may require expertise in skin diseases and knowledge of superficial anatomic structures in selected areas of the body. In this procedure, a small area of skin is anesthetized with 1% lidocaine with or without epinephrine. The skin lesion in question can be excised or saucerized with a scalpel or removed by punch biopsy. In the latter technique, a punch is pressed against the surface of the skin and rotated with downward pressure until it penetrates to the subcutaneous tissue. The circular biopsy is then lifted with forceps, and the bottom is cut with iris scissors. Biopsy sites may or may not need suture closure, depending on size and location.

KOH Preparation A potassium hydroxide (KOH) preparation is performed on scaling skin lesions where a fungal infection is suspected. The edge of such a lesion is scraped gently with a no. 15 scalpel blade. The removed scale is collected on a glass microscope slide and then treated with 1 or 2 drops of a solution of 10–20% KOH. KOH dissolves keratin and allows easier visualization of fungal elements. Brief heating of the slide accelerates dissolution of keratin. When the preparation is viewed under the microscope, the refractile hyphae are seen more easily when the light intensity is reduced and the condenser is lowered. This technique can be used to identify hyphae in dermatophyte infections, pseudohyphae and budding yeasts in *Candida* infections,

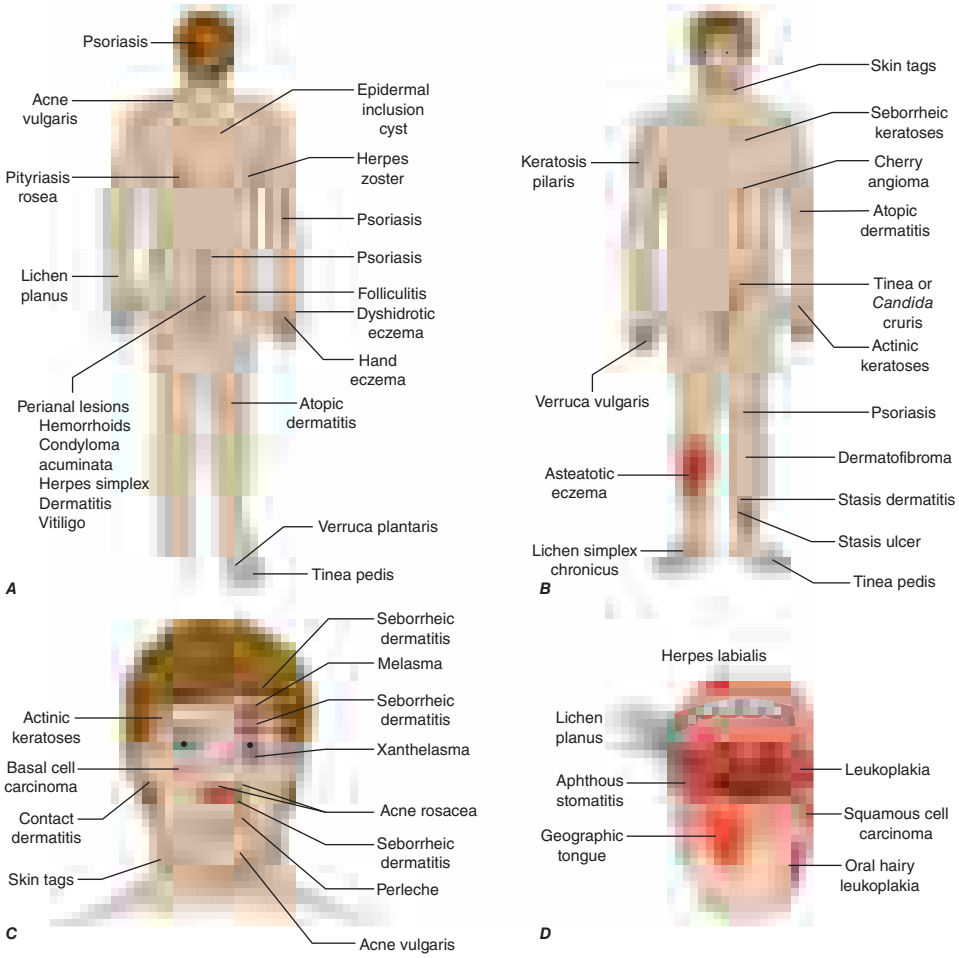

FIGURE 52-6 Distribution of some common dermatologic diseases and lesions.

and "spaghetti and meatballs" yeast forms in tinea versicolor. The same sampling technique can be used to obtain scale for culture of selected pathogenic organisms.

Tzanck Smear A Tzanck smear is a cytologic technique most often used in the diagnosis of herpesvirus infections (herpes simplex virus [HSV] or varicella zoster virus [VZV]) **(see Figs. 188-1 and 188-3)**. An early vesicle, not a pustule or crusted lesion, is unroofed, and the base of the lesion is scraped gently with a scalpel blade. The material is placed on a glass slide, air-dried, and stained with Giemsa or Wright's stain. Multinucleated epithelial giant cells suggest the presence of HSV or VZV; culture, immunofluorescence microscopy, or genetic testing must be performed to identify the specific virus.

Diascopy Diascopy is designed to assess whether a skin lesion will blanch with pressure as, for example, in determining whether a red lesion is hemorrhagic or simply blood-filled. Urticaria **(Fig. 52-11)** will blanch with pressure, whereas a purpuric lesion caused by necrotizing vasculitis (Fig. 52-4) will not. Diascopy is performed by pressing a microscope slide or magnifying lens against a lesion and noting the amount of blanching that occurs. Granulomas often have an opaque to transparent, brown-pink "apple jelly" appearance on diascopy.

Wood's Light A Wood's lamp generates 360-nm ultraviolet ("black") light that can be used to aid the evaluation of certain skin disorders. For example, a Wood's lamp will cause erythrasma (a superficial, intertriginous infection caused by *Corynebacterium minutissimum*)

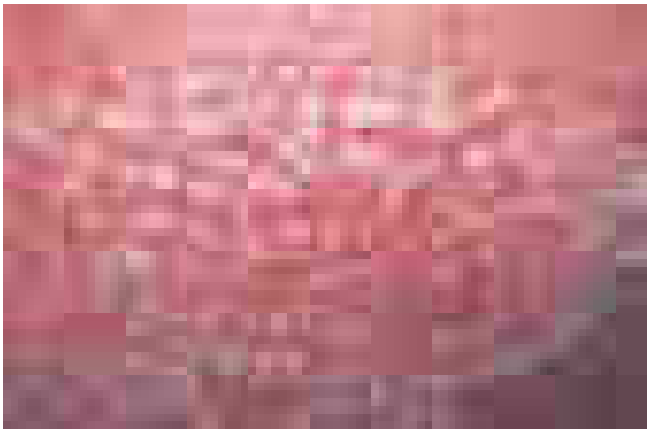

FIGURE 52-7 Psoriasis. This papulosquamous skin disease is characterized by small and large erythematous papules and plaques with overlying adherent silvery scale.

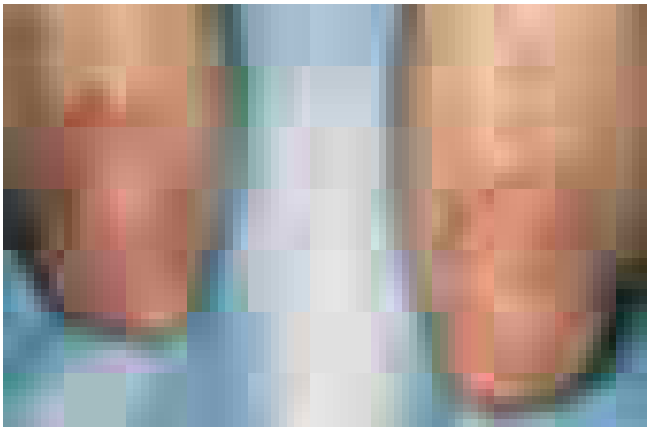

FIGURE 52-8 Dermatitis herpetiformis. This disorder typically displays pruritic, grouped papulovesicles on elbows, knees, buttocks, and posterior scalp. Vesicles are often excoriated due to associated pruritus.

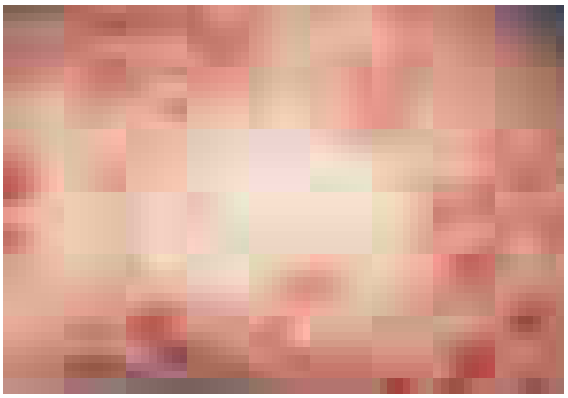

FIGURE 52-9 Erythema multiforme. This eruption is characterized by multiple erythematous plaques with a target or iris morphology. It usually represents a hypersensitivity reaction to drugs (e.g., sulfonamides) or infections (e.g., HSV). *(Courtesy of the Yale Resident's Slide Collection; with permission.)*

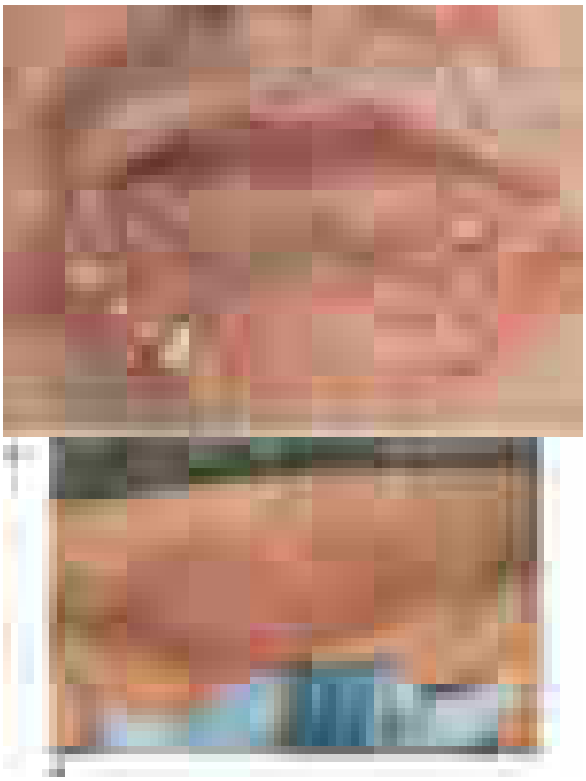

FIGURE 52-10 Allergic contact dermatitis (ACD). *A.* An example of ACD in its acute phase, with sharply demarcated, weeping, eczematous plaques in a perioral distribution. ***B.*** ACD in its chronic phase, with an erythematous, lichenified, weeping plaque on skin chronically exposed to nickel in a metal snap. *(B, Courtesy of Robert Swerlick, MD; with permission.)*

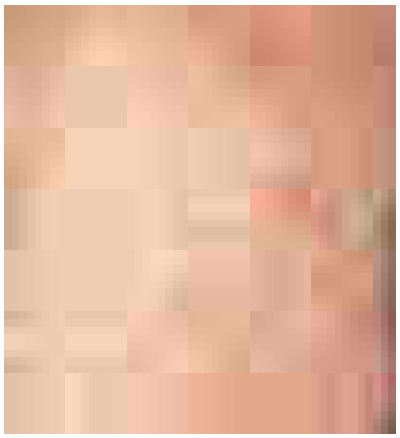

FIGURE 52-11 Urticaria. Discrete and confluent, edematous, erythematous papules and plaques are characteristic of this whealing eruption.

FIGURE 52-12 Vitiligo. Characteristic lesions display an acral distribution and striking depigmentation as a result of loss of melanocytes.

to show a characteristic coral pink color, and wounds colonized by *Pseudomonas* will appear pale blue. Tinea capitis caused by certain dermatophytes (e.g., *Microsporum canis* or *M. audouinii*) exhibits a yellow fluorescence. Pigmented lesions of the epidermis such as freckles are accentuated, while dermal pigment such as postinflammatory hyperpigmentation fades under a Wood's light. Vitiligo (Fig. 52-12) appears totally white under a Wood's lamp, and previously unsuspected areas of involvement often become apparent. A Wood's lamp may also aid in the demonstration of tinea versicolor, sites of depigmentation within and/or surrounding melanomas, and in recognition of ash leaf spots in patients with tuberous sclerosis.

Patch Tests Patch testing is designed to document sensitivity to a specific antigen. In this procedure, a battery of suspected allergens is applied to the patient's back under occlusive dressings and allowed to remain in contact with the skin for 48 h. The dressings are removed, and the area is examined for evidence of delayed hypersensitivity reactions (e.g., erythema, edema, or papulovesicles). This test is best performed by physicians with special expertise in patch testing and is often helpful in the evaluation of patients with chronic dermatitis.

FURTHER READING

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Goldsmith LA et al (eds): *Fitzpatrick's Dermatology in General Medicine*, 8th ed. New York, McGraw-Hill, 2012.

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53 Eczema, Psoriasis, Cutaneous Infections, Acne, and Other Common Skin Disorders

Leslie P. Lawley, Calvin O. McCall, Thomas J. Lawley

ECZEMA AND DERMATITIS

Eczema is a type of dermatitis, and these terms are often used synonymously (e.g., atopic eczema or atopic dermatitis [AD]). Eczema is a reaction pattern that presents with variable clinical findings and the common histologic finding of *spongiosis* (intercellular edema of the epidermis). Eczema is the final common expression for a number of disorders, including those discussed in the following sections.

TABLE 53-1 Clinical Features of Atopic Dermatitis

1. Pruritus and scratching
2. Course marked by exacerbations and remissions
3. Lesions typical of eczematous dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, food allergies, or eczema)
5. Clinical course lasting >6 weeks
6. Lichenification of skin
7. Presence of dry skin

Primary lesions may include erythematous macules, papules, and vesicles, which can coalesce to form patches and plaques. In severe eczema, secondary lesions from infection or excoriation, marked by weeping and crusting, may predominate. In chronic eczematous conditions, *lichenification* (cutaneous hypertrophy and accentuation of normal skin markings) may alter the characteristic appearance of eczema.

ATOPIC DERMATITIS

AD is the cutaneous expression of the atopic state, characterized by a family history of asthma, allergic rhinitis, or eczema. The prevalence of AD is increasing worldwide. Some of its features are shown in **Table 53-1**.

The etiology of AD is only partially defined, but there is a clear genetic predisposition. When both parents are affected by AD, >80% of their children manifest the disease. When only one parent is affected, the prevalence drops to slightly >50%. A characteristic defect in AD that contributes to the pathophysiology is an impaired epidermal barrier. In many patients, a mutation in the gene encoding filaggrin, a structural protein in the stratum corneum, is responsible. Patients with AD may display a variety of immunoregulatory abnormalities, including increased IgE synthesis; increased serum IgE levels; and impaired, delayed-type hypersensitivity reactions.

The clinical presentation often varies with age. Half of patients with AD present within the first year of life, and 80% present by 5 years of age. About 80% ultimately coexpress allergic rhinitis or asthma. The infantile pattern is characterized by weeping inflammatory patches and crusted plaques on the face, neck, and extensor surfaces. The childhood and adolescent pattern is typified by dermatitis of flexural skin, particularly in the antecubital and popliteal fossae **(Fig. 53-1)**. AD may resolve spontaneously, but approximately 40% of all individuals affected as children will have dermatitis in adult life. The distribution of lesions in adults may be similar to those seen in childhood; however, adults frequently have localized disease manifesting as lichen simplex chronicus or hand eczema (see below). In patients with localized disease, AD may be suspected because of a typical personal or family history or the presence of cutaneous stigmata of AD such as perioral pallor, an extra fold of skin beneath the lower eyelid (Dennie-Morgan folds), increased palmar skin markings, and an increased incidence of cutaneous infections, particularly with *Staphylococcus aureus*. Regardless of other manifestations, pruritus is a prominent characteristic of AD in all age groups and is exacerbated by dry skin. Many of the cutaneous findings in affected patients, such as lichenification, are secondary to rubbing and scratching.

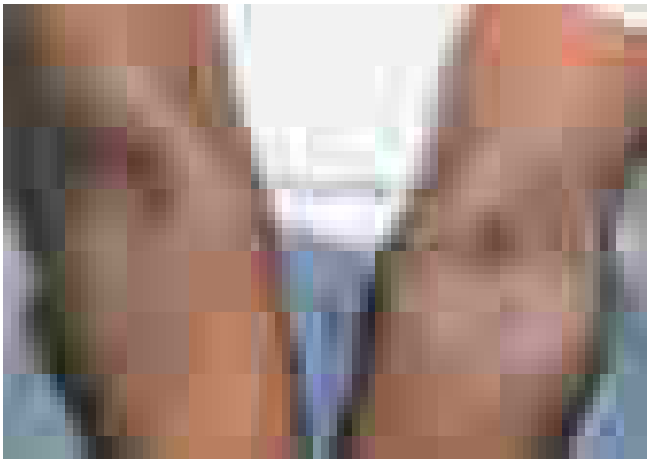

FIGURE 53-1 Atopic dermatitis. Hyperpigmentation, lichenification, and scaling in the antecubital fossae are seen in this patient with atopic dermatitis. *(Courtesy of Robert Swerlick, MD; with permission.)*

TREATMENT

Atopic Dermatitis

Therapy for AD should include avoidance of cutaneous irritants, adequate moisturizing through the application of emollients, judicious use of topical anti-inflammatory agents, and prompt treatment of secondary infection. Patients should be instructed to bathe no more often than daily, using warm or cool water, and to use only mild bath soap. Immediately after bathing, while the skin is still moist, a topical anti-inflammatory agent in a cream or ointment base should be applied to areas of dermatitis, and all other skin areas should be lubricated with a moisturizer. Approximately 30 g of a topical agent is required to cover the entire body surface of an average adult.

Low- to mid-potency topical glucocorticoids are employed in most treatment regimens for AD. Skin atrophy and the potential for systemic absorption are constant concerns, especially with more potent agents. Low-potency topical glucocorticoids or nonglucocorticoid anti-inflammatory agents should be selected for use on the face and in intertriginous areas to minimize the risk of skin atrophy. Two nonglucocorticoid anti-inflammatory agents are available: tacrolimus ointment and pimecrolimus cream. These agents are macrolide immunosuppressants that are approved by the U.S. Food and Drug Administration (FDA) for topical use in AD. Reports of broader effectiveness appear in the literature. These agents do not cause skin atrophy, nor do they suppress the hypothalamic-pituitary-adrenal axis. However, concerns have emerged regarding the potential for lymphomas in patients treated with these agents. Thus, caution should be exercised when these agents are considered. Currently, they are also more costly than topical glucocorticoids. Barrier-repair products that attempt to restore the impaired epidermal barrier are also nonglucocorticoid agents and are gaining popularity in the treatment of AD.

Secondary infection of eczematous skin may lead to exacerbation of AD. Crusted and weeping skin lesions may be infected with *S. aureus*. When secondary infection is suspected, eczematous lesions should be cultured and patients treated with systemic antibiotics active against *S. aureus*. The initial use of penicillinase-resistant penicillins or cephalosporins is preferable. Dicloxacillin or cephalexin (250 mg qid for 7–10 days) is generally adequate for adults; however, antibiotic selection must be directed by culture results and clinical response. More than 50% of *S. aureus* isolates are now methicillin resistant in some communities. Current recommendations for the treatment of infection with these community-acquired methicillin-resistant *S. aureus* (CA-MRSA) strains in adults include trimethoprim-sulfamethoxazole (one double-strength tablet bid), minocycline (100 mg bid), doxycycline (100 mg bid), or clindamycin (300–450 mg qid). Duration of therapy should be 7–10 days. Inducible resistance may limit clindamycin's usefulness. Such resistance can be detected by the double-disk diffusion test, which should be ordered if the isolate is erythromycin resistant and clindamycin sensitive. As an adjunct, antibacterial washes or dilute sodium hypochlorite baths (0.005% bleach) and intermittent nasal mupirocin may be useful.

Control of pruritus is essential for treatment, because AD often represents "an itch that rashes." Antihistamines are most often used to control pruritus. Diphenhydramine (25 mg every 4–6 h), hydroxyzine (10–25 mg every 6 h), or doxepin (10–25 mg at bedtime) are useful primarily due to their sedating action. Higher doses of these agents may be required, but sedation can become bothersome. Patients need to be counseled about driving or operating heavy equipment after taking these medications. When used at bedtime, sedating antihistamines may improve the patient's sleep. Although they are effective in urticaria, nonsedating antihistamines and selective H_2 blockers are of little use in controlling the pruritus of AD.

Treatment with systemic glucocorticoids should be limited to severe exacerbations unresponsive to topical therapy. In the patient with chronic AD, therapy with systemic glucocorticoids will generally clear the skin only briefly, and cessation of the systemic therapy will invariably be accompanied by a return, if not a worsening, of the dermatitis. Patients who do not respond to conventional therapies should be considered for patch testing to rule out allergic contact dermatitis (ACD). The role of dietary allergens in AD is controversial, and there is little evidence that they play any role outside of infancy, during which a small percentage of patients with AD may be affected by food allergens.

LICHEN SIMPLEX CHRONICUS

Lichen simplex chronicus may represent the end stage of a variety of pruritic and eczematous disorders, including AD. It consists of a circumscribed plaque or plaques of lichenified skin due to chronic scratching or rubbing. Common areas involved include the posterior nuchal region, dorsum of the feet, and ankles. Treatment of lichen simplex chronicus centers on breaking the cycle of chronic itching and scratching. High-potency topical glucocorticoids are helpful in most cases, but, in recalcitrant cases, application of topical glucocorticoids under occlusion or intralesional injection of glucocorticoids may be required.

CONTACT DERMATITIS

Contact dermatitis is an inflammatory skin process caused by an exogenous agent or agents that directly or indirectly injure the skin. In *irritant* contact dermatitis (ICD), this injury is caused by an inherent characteristic of a compound—for example, a concentrated acid or base. Agents that cause *allergic* contact dermatitis (ACD) induce an antigen-specific immune response (e.g., poison ivy dermatitis). The clinical lesions of contact dermatitis may be acute (wet and edematous) or chronic (dry, thickened, and scaly), depending on the persistence of the insult **(see Chap. 52, Fig. 52-10)**.

Irritant Contact Dermatitis ICD is generally well demarcated and often localized to areas of thin skin (eyelids, intertriginous areas) or areas where the irritant was occluded. Lesions may range from minimal skin erythema to areas of marked edema, vesicles, and ulcers. Prior exposure to the offending agent is not necessary, and the reaction develops in minutes to a few hours. Chronic low-grade irritant dermatitis is the most common type of ICD, and the most common area of involvement is the hands (see below). The most common irritants encountered are chronic wet work, soaps, and detergents. Treatment should be directed toward the avoidance of irritants and the use of protective gloves or clothing.

Allergic Contact Dermatitis ACD is a manifestation of delayed-type hypersensitivity mediated by memory T lymphocytes in the skin. Prior exposure to the offending agent is necessary to develop the hypersensitivity reaction, which may take as little as 12 h or as much as 72 h to develop. The most common cause of ACD is exposure to plants, especially to members of the family Anacardiaceae, including the genus *Toxicodendron*. Poison ivy, poison oak, and poison sumac are members of this genus and cause an allergic reaction marked by erythema, vesiculation, and severe pruritus. The eruption is often linear or angular, corresponding to areas where plants have touched the skin. The sensitizing antigen common to these plants is urushiol, an oleoresin containing the active ingredient pentadecylcatechol. The oleoresin may adhere to skin, clothing, tools, and pets, and contaminated articles may cause dermatitis even after prolonged storage. Blister fluid does not contain urushiol and is not capable of inducing skin eruption in exposed subjects.

TREATMENT

Contact Dermatitis

If contact dermatitis is suspected and an offending agent is identified and removed, the eruption will resolve. Usually, treatment with high-potency topical glucocorticoids is enough to relieve symptoms while the dermatitis runs its course. For those patients who require systemic therapy, daily oral prednisone—beginning at 1 mg/kg, but usually ≤60 mg/d—is sufficient. The dose should be tapered over 2–3 weeks, and each daily dose should be taken in the morning with food.

Identification of a contact allergen can be a difficult and time-consuming task. Allergic contact dermatitis should be suspected in patients with dermatitis unresponsive to conventional therapy or with an unusual and patterned distribution. Patients should be questioned carefully regarding occupational exposures and topical medications. Common sensitizers include preservatives in topical preparations, nickel sulfate, potassium dichromate, thimerosal, neomycin sulfate, fragrances, formaldehyde, and rubber-curing agents. Patch testing is helpful in identifying these agents but should not be attempted when patients have widespread active dermatitis or are taking systemic glucocorticoids.

HAND ECZEMA

Hand eczema is a very common, chronic skin disorder in which both exogenous and endogenous factors play important roles. It may be associated with other cutaneous disorders such as AD, and contact with various agents may be involved. Hand eczema represents a large proportion of cases of occupation-associated skin disease. Chronic, excessive exposure to water and detergents, harsh chemicals, or allergens may initiate or aggravate this disorder. It may present with dryness and cracking of the skin of the hands as well as with variable amounts of erythema and edema. Often, the dermatitis will begin under rings, where water and irritants are trapped. *Dyshidrotic* eczema, a variant of hand eczema, presents with multiple, intensely pruritic, small papules and vesicles on the thenar and hypothenar eminences and the sides of the fingers **(Fig. 53-2)**. Lesions tend to occur in crops that slowly form crusts and then heal.

The evaluation of a patient with hand eczema should include an assessment of potential occupation-associated exposures. The history should be directed to identifying possible irritant or allergen exposures.

TREATMENT

Hand Eczema

Therapy for hand eczema is directed toward avoidance of irritants, identification of possible contact allergens, treatment of coexistent infection, and application of topical glucocorticoids. Whenever possible, the hands should be protected by gloves, preferably vinyl.

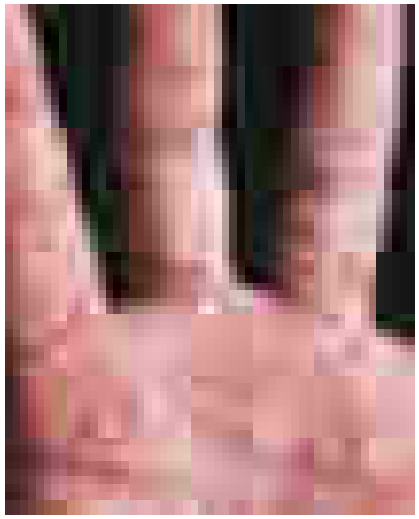

FIGURE 53-2 Dyshidrotic eczema. This example is characterized by deep-seated vesicles and scaling on palms and lateral fingers, and the disease is often associated with an atopic diathesis.

The use of rubber gloves (latex) to protect dermatitic skin is sometimes associated with the development of hypersensitivity reactions to components of the gloves, which could be a type I hypersensitivity reaction to the latex manifested by the development of hives, itching, angioedema, and possibly anaphylaxis within minutes to hours of exposure or a type IV hypersensitivity reaction to rubber accelerators with worsening of eczematous eruptions days after exposure. Patients can be treated with cool moist compresses followed by application of a mid- to high-potency topical glucocorticoid in a cream or ointment base. As in AD, treatment of secondary infection is essential for good control. In addition, patients with hand eczema should be examined for dermatophyte infection by potassium hydroxide (KOH) preparation and culture (see below).

NUMMULAR ECZEMA

Nummular eczema is characterized by circular or oval "coinlike" lesions, beginning as small edematous papules that become crusted and scaly. The etiology of nummular eczema is unknown, but dry skin is a contributing factor. Common locations are the trunk or the extensor surfaces of the extremities, particularly on the pretibial areas or dorsum of the hands. Nummular eczema occurs more frequently in men and is most common in middle age. The treatment of nummular eczema is similar to that for AD.

ASTEATOTIC ECZEMA

Asteatotic eczema, also known as *xerotic eczema* or "winter itch," is a mildly inflammatory dermatitis that develops in areas of extremely dry skin, especially during the dry winter months. Clinically, there may be considerable overlap with nummular eczema. This form of eczema accounts for a large number of physician visits because of the associated pruritus. Fine cracks and scale, with or without erythema, characteristically develop in areas of dry skin, especially on the anterior surfaces of the lower extremities in elderly patients. Asteatotic eczema responds well to topical moisturizers and the avoidance of cutaneous irritants. Overbathing and the use of harsh soaps exacerbate asteatotic eczema.

STASIS DERMATITIS AND STASIS ULCERATION

Stasis dermatitis develops on the lower extremities secondary to venous incompetence and chronic edema. Patients may give a history of deep venous thrombosis and may have evidence of vein removal or varicose veins. Early findings in stasis dermatitis consist of mild erythema and scaling associated with pruritus. The typical initial site of involvement is the medial aspect of the ankle, often over a distended vein **(Fig. 53-3)**.

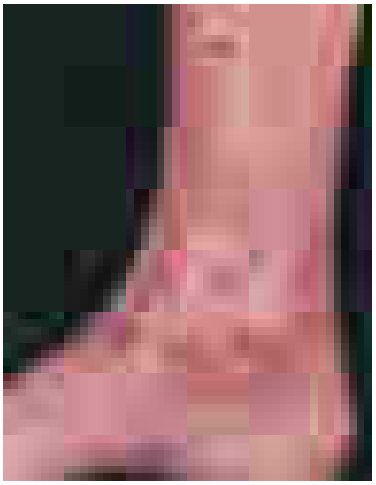

FIGURE 53-3 Stasis dermatitis. An example of stasis dermatitis showing erythematous, scaly, and oozing patches over the lower leg. Several stasis ulcers are also seen in this patient.

Stasis dermatitis may become acutely inflamed, with crusting and exudate. In this state, it is easily confused with cellulitis. Of note, symmetrical and bilateral involvement is more likely stasis dermatitis whereas unilateral involvement may represent cellulitis. Chronic stasis dermatitis is often associated with dermal fibrosis that is recognized clinically as brawny edema of the skin. As the disorder progresses, the dermatitis becomes progressively pigmented due to chronic erythrocyte extravasation leading to cutaneous hemosiderin deposition. Stasis dermatitis may be complicated by secondary infection and contact dermatitis. Severe stasis dermatitis may precede the development of stasis ulcers.

TREATMENT

Stasis Dermatitis and Stasis Ulceration

Patients with stasis dermatitis and stasis ulceration benefit greatly from leg elevation and the routine use of compression stockings with a gradient of at least 30–40 mmHg. Stockings providing less compression, such as antiembolism hose, are poor substitutes. Use of emollients and/or mid-potency topical glucocorticoids and avoidance of irritants are also helpful in treating stasis dermatitis. Protection of the legs from injury, including scratching, and control of chronic edema are essential to prevent ulcers. Diuretics may be required to adequately control chronic edema.

Stasis ulcers are difficult to treat, and resolution is slow. It is extremely important to elevate the affected limb as much as possible. The ulcer should be kept clear of necrotic material by gentle debridement and covered with a semipermeable dressing and a compression dressing or compression stocking. Glucocorticoids should not be applied to ulcers, because they may retard healing; however, they may be applied to the surrounding skin to control itching, scratching, and additional trauma. Secondarily infected lesions should be treated with appropriate oral antibiotics, but it should be noted that all ulcers will become colonized with bacteria, and the purpose of antibiotic therapy should not be to clear all bacterial growth. Care must be taken to exclude treatable causes of leg ulcers (hypercoagulation, vasculitis) before beginning the chronic management outlined above.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common, chronic disorder characterized by greasy scales overlying erythematous patches or plaques. Induration and scale are generally less prominent than in psoriasis, but clinical overlap exists between these diseases ("sebopsoriasis"). The most common location is in the scalp, where it may be recognized as severe dandruff. On the face, seborrheic dermatitis affects the eyebrows, eyelids, glabella, and nasolabial folds **(Fig. 53-4)**. Scaling of the external auditory canal is common in seborrheic dermatitis. In addition, the postauricular areas often become macerated and tender. Seborrheic dermatitis may also develop in the central chest, axilla, groin, submammary folds, and gluteal cleft. Rarely, it may cause widespread generalized dermatitis. Pruritus is variable.

Seborrheic dermatitis may be evident within the first few weeks of life, and within this context it typically occurs in the scalp ("cradle cap"), face, or groin. It is rarely seen in children beyond infancy but becomes evident again during adolescent and adult life. Although it is frequently seen in patients with Parkinson's disease, in those who have had cerebrovascular accidents, and in those with HIV infection, the overwhelming majority of individuals with seborrheic dermatitis have no underlying disorder.

TREATMENT

Seborrheic Dermatitis

Treatment with low-potency topical glucocorticoids in conjunction with a topical antifungal agent, such as ketoconazole cream or ciclopirox cream, is often effective. The scalp and beard areas

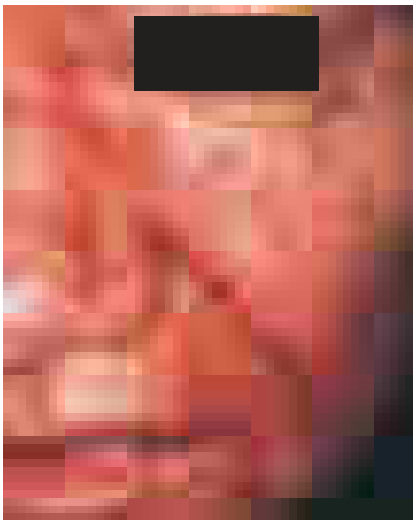

FIGURE 53-4 Seborrheic dermatitis. Central facial erythema with overlying greasy, yellowish scale is seen in this patient. *(Courtesy of Jean Bolognia, MD; with permission.)*

may benefit from antidandruff shampoos, which should be left in place 3–5 min before rinsing. High-potency topical glucocorticoid solutions (betamethasone or clobetasol) are effective for control of severe scalp involvement. High-potency glucocorticoids should not be used on the face because this treatment is often associated with steroid-induced rosacea or atrophy.

PAPULOSQUAMOUS DISORDERS (TABLE 53-2)

PSORIASIS

Psoriasis is one of the most common dermatologic diseases, affecting up to 2% of the world's population. It is an immune-mediated disease clinically characterized by erythematous, sharply demarcated papules and rounded plaques covered by silvery micaceous scale. The skin lesions of psoriasis are variably pruritic. Traumatized areas often develop lesions of psoriasis (the *Koebner* or isomorphic phenomenon). In addition, other external factors may exacerbate psoriasis, including infections, stress, and medications (lithium, beta blockers, and antimalarial drugs).

The most common variety of psoriasis is called *plaque-type*. Patients with plaque-type psoriasis have stable, slowly enlarging plaques, which remain basically unchanged for long periods of time. The most commonly involved areas are the elbows, knees, gluteal cleft, and scalp. Involvement tends to be symmetric. Plaque psoriasis generally develops slowly and runs an indolent course. It rarely remits spontaneously.

Inverse psoriasis affects the intertriginous regions, including the axilla, groin, submammary region, and navel; it also tends to affect the scalp, palms, and soles. The individual lesions are sharply demarcated plaques **(see Chap. 52, Fig. 52-7)**, but they may be moist and without scale due to their locations.

Guttate psoriasis (eruptive psoriasis) is most common in children and young adults. It develops acutely in individuals without psoriasis or in those with chronic plaque psoriasis. Patients present with many small erythematous, scaling papules, frequently after upper respiratory tract infection with β-hemolytic streptococci. The differential diagnosis should include pityriasis rosea and secondary syphilis.

In *pustular psoriasis*, patients may have disease localized to the palms and soles, or the disease may be generalized. Regardless of the extent of disease, the skin is erythematous, with pustules and variable scale. Localized to the palms and soles, it is easily confused with eczema. When it is generalized, episodes are characterized by fever (39°–40°C [102.2°–104.0°F]) lasting several days, an accompanying generalized eruption of sterile pustules, and a background of intense erythema; patients may become erythrodermic. Episodes of fever and pustules are recurrent. Local irritants, pregnancy, medications, infections, and systemic glucocorticoid withdrawal can precipitate this form of psoriasis. Oral retinoids are the treatment of choice in nonpregnant patients.

Fingernail involvement, appearing as punctate pitting, onycholysis, nail thickening, or subungual hyperkeratosis, may be a clue to the diagnosis of psoriasis when the clinical presentation is not classic.

According to the National Psoriasis Foundation, up to 30% of patients with psoriasis have psoriatic arthritis (PsA). It develops most commonly between the ages of 30 and 50 years. There are five subtypes of PsA: symmetric PsA, asymmetric PsA, distal PsA, spondylitis, and arthritis mutilans. Approximately 50% of PsA is classified as symmetric, which may resemble rheumatoid arthritis. Asymmetric arthritis comprises about 35% of cases. It can involve any joint and may present as "sausage digits." Distal PsA is the classic form; however, it occurs in only about 5% of patients with PsA. It can involve fingers and toes; fingernails and toenails are often dystrophic, including nail pitting. Spondylitis also occurs in ~5% of patients with PsA. Arthritis mutilans is severe and deforming, and affects primarily the small joints of the hands and feet. It accounts for fewer than 5% of PsA cases.

An increased risk of metabolic syndrome, including increased morbidity and mortality from cardiovascular events, has been demonstrated in psoriasis patients. Appropriate screening tests should be performed. The etiology of psoriasis is still poorly understood, but there is clearly a genetic component to the disease. In various studies, 30–50% of patients with psoriasis report a positive family history. Psoriatic lesions contain infiltrates of activated T cells that are thought to elaborate cytokines responsible for keratinocyte hyperproliferation, which results in the characteristic clinical findings. Agents inhibiting T cell activation, clonal expansion, or release of proinflammatory cytokines are often effective for the treatment of severe psoriasis (see below).

TABLE 53-2 Papulosquamous Disorders

	CLINICAL FEATURES	OTHER NOTABLE FEATURES	HISTOLOGIC FEATURES
Psoriasis	Sharply demarcated, erythematous plaques with mica-like scale; predominantly on elbows, knees, and scalp; atypical forms may localize to intertriginous areas; eruptive forms may be associated with infection	May be aggravated by certain drugs, infection; severe forms seen in association with HIV	Acanthosis, vascular proliferation
Lichen planus	Purple polygonal papules marked by severe pruritus; lacy white markings, especially associated with mucous membrane lesions	Certain drugs may induce: thiazides, antimalarial drugs	Interface dermatitis
Pityriasis rosea	Rash often preceded by herald patch; oval to round plaques with trailing scale; most often affects trunk; eruption lines up in skinfolds giving a "fir tree–like" appearance; generally spares palms and soles	Variable pruritus; self-limited, resolving in 2–8 weeks; may be imitated by secondary syphilis	Pathologic features often nonspecific
Dermatophytosis	Polymorphous appearance depending on dermatophyte, body site, and host response; sharply defined to ill-demarcated scaly plaques with or without inflammation; may be associated with hair loss	KOH preparation may show branching hyphae; culture helpful	Hyphae and neutrophils in stratum corneum

Abbreviations: HIV, human immunodeficiency virus; KOH, potassium hydroxide.

TREATMENT

Psoriasis

Treatment of psoriasis depends on the type, location, and extent of disease. All patients should be instructed to avoid excess drying or irritation of their skin and to maintain adequate cutaneous hydration. Most cases of localized, plaque-type psoriasis can be managed with mid-potency topical glucocorticoids, although their long-term use is often accompanied by loss of effectiveness (tachyphylaxis) and atrophy of the skin. A topical vitamin D analogue (calcipotriene) and a retinoid (tazarotene) are also efficacious in the treatment of limited psoriasis and have largely replaced other topical agents such as coal tar, salicylic acid, and anthralin.

Ultraviolet (UV) light, natural or artificial, is an effective therapy for many patients with widespread psoriasis. Ultraviolet B (UVB), narrowband UVB, and ultraviolet A (UVA) light with either oral or topical psoralens (PUVA) are used clinically. UV light's immunosuppressive properties are thought to be responsible for its therapeutic activity in psoriasis. It is also mutagenic, potentially leading to an increased incidence of nonmelanoma and melanoma skin cancer. UV-light therapy is contraindicated in patients receiving cyclosporine and should be used with great care in all immunocompromised patients due to the increased risk of skin cancer.

Various systemic agents can be used for severe, widespread psoriatic disease **(Table 53-3)**. Oral glucocorticoids should not be used for the treatment of psoriasis due to the potential for development of life-threatening pustular psoriasis when therapy is discontinued. Methotrexate is an effective agent, especially in patients with PsA. The synthetic retinoid acitretin is useful, especially when immunosuppression must be avoided; however, teratogenicity limits its use. Apremilast is a new oral agent that inhibits phosphodiesterase type 4. It is approved for both psoriasis and PsA. It must be used cautiously in the presence of renal failure or depression.

The evidence implicating psoriasis as a T cell–mediated disorder has directed therapeutic efforts to immunoregulation. Cyclosporine and other immunosuppressive agents can be very effective in the treatment of psoriasis, and much attention is currently directed toward the development of biologic agents with more selective immunosuppressive properties and better safety profiles **(Table 53-4)**. Experience with some of these biologic agents is limited, and information regarding combination therapy and adverse events continues to emerge. These biologic agents appear to be quite efficacious in treatment of psoriasis and are well tolerated; however, caution with certain patient comorbidities must be exercised. Use of tumor necrosis factor-α (TNF-α) inhibitors may worsen congestive heart failure (CHF), and they should be used with caution in patients at risk for or known to have CHF. Further, none of the immunosuppressive agents used in the treatment of psoriasis should be initiated if the patient has a severe infection (including TB, HIV, hepatitis B or C); patients on such therapy should be routinely screened for tuberculosis. There have been reports of progressive multifocal leukoencephalopathy and lupus erythematosus in association with treatment with the TNF-α inhibitors. Malignancies, including a risk or history of certain malignancies, may limit the use of these systemic agents. In general, immunosuppressive agents have also been linked to an increase risk of skin cancer and patients receiving these agents should be monitored for the development of skin cancer.

LICHEN PLANUS

Lichen planus (LP) is a papulosquamous disorder that may affect the skin, scalp, nails, and mucous membranes. The primary cutaneous lesions are pruritic, polygonal, flat-topped, violaceous papules. Close examination of the surface of these papules often reveals a network of gray lines (*Wickham's striae*). The skin lesions may occur anywhere but have a predilection for the wrists, shins, lower back, and genitalia **(Fig. 53-5)**. Involvement of the scalp (*lichen planopilaris*) may lead to scarring alopecia, and nail involvement may lead to permanent deformity or loss of fingernails and toenails. LP commonly involves mucous membranes, particularly the buccal mucosa, where it can present on a spectrum ranging from a mild, white, reticulate eruption of the mucosa to a severe, erosive stomatitis. Erosive stomatitis may persist for years and may be linked to an increased risk of oral squamous cell carcinoma. Cutaneous eruptions clinically resembling LP have been observed after administration of numerous drugs, including thiazide diuretics, gold, antimalarial agents, penicillamine, and phenothiazines, and in patients with skin lesions of chronic graft-versus-host disease. In addition, LP may be associated with hepatitis C infection. The course of LP is variable, but most patients have spontaneous remissions 6 months to 2 years after the onset of disease. Topical glucocorticoids are the mainstay of therapy.

PITYRIASIS ROSEA

Pityriasis rosea (PR) is a papulosquamous eruption of unknown etiology occurring more commonly in the spring and fall. Its first manifestation is the development of a 2- to 6-cm annular lesion (the herald patch). This is followed in a few days to a few weeks by the appearance of many smaller annular or papular lesions with a predilection to occur on the trunk **(Fig. 53-6)**. The lesions are generally oval, with their long axis parallel to the skinfold lines. Individual lesions may range in color from red to brown and have a trailing scale. PR shares many clinical features with the eruption of secondary syphilis, but palm and sole lesions are extremely rare in PR and common in secondary syphilis. The eruption tends to be moderately pruritic and lasts 3–8 weeks. Treatment is directed at alleviating pruritus and consists of oral antihistamines; mid-potency topical glucocorticoids; and, in some cases, UVB phototherapy.

CUTANEOUS INFECTIONS (TABLE 53-5)

IMPETIGO, ECTHYMA, AND FURUNCULOSIS

Impetigo is a common superficial bacterial infection of skin caused most often by *S. aureus* **(Chap. 142)** and in some cases by group A β-hemolytic streptococci **(Chap. 143)**. The primary lesion is a superficial pustule that ruptures and forms a characteristic yellow-brown honey-colored crust **(see Chap. 143, Fig. 143-3)**. Lesions may occur on normal skin (primary infection) or in areas already affected by another

TABLE 53-3 FDA-Approved Systemic Therapy for Psoriasis

		ADMINISTRATION		
AGENT	MEDICATION CLASS	ROUTE	FREQUENCY	ADVERSE EVENTS (SELECTED)
Methotrexate	Antimetabolite	Oral	Weekly[a]	Hepatotoxicity, pulmonary toxicity, pancytopenia, potential for increased malignancies, ulcerative stomatitis, nausea, diarrhea, teratogenicity
Acitretin	Retinoid	Oral	Daily	Teratogenicity, hepatotoxicity, hyperostosis, hyperlipidemia/pancreatitis, depression, ophthalmologic effects, pseudotumor cerebri
Cyclosporine	Calcineurin inhibitor	Oral	Twice daily	Renal dysfunction, hypertension, hyperkalemia, hyperuricemia, hypomagnesemia, hyperlipidemia, increased risk of malignancies
Apremilast	Phosphodiesterase type 4 inhibitor	Oral	Twice daily[b]	Hypersensitivity reaction, depression, nausea, diarrhea, vomiting, dyspepsia, weight loss, headache, fatigue

Abbreviation: FDA, Food and Drug Administration.

[a]Initial test dose is required. [b]Initial dose escalation is required.

TABLE 53-4 FDA-Approved Biologics for Psoriasis or Psoriatic Arthritis

		ADMINISTRATION			
AGENT	MECHANISM OF ACTION	INDICATION	ROUTE	FREQUENCY	WARNINGS, SELECTED
Etanercept	Anti-TNF-α	Ps, PsA	SC	Once or twice weekly[a]	Serious infections, hepatotoxicity, CHF, hematologic events, hypersensitivity reactions, neurologic events, potential for increased malignancies
Adalimumab	Anti-TNF-α	Ps, PsA	SC	Every other week[a]	Serious infections, hepatotoxicity, CHF, hematologic events, hypersensitivity reactions, neurologic events, potential for increased malignancies
Infliximab	Anti-TNF-α	Ps, PsA	IV	Every 8 weeks[a]	Serious infections, hepatotoxicity, CHF, hematologic events, hypersensitivity reactions, neurologic events, potential for increased malignancies
Golimumab	Anti-TNF-α	PsA	SC	Every 4 or 8 weeks	Serious infections, hepatotoxicity, CHF, hypersensitivity reactions, neurologic events, potential for increased malignancies
Ustekinumab	Anti-IL-12 and anti-IL-23	Ps, PsA	SC	Every 12 weeks[a]	Serious infections, neurologic events, potential for increased malignancies
Certolizumab pegol	Anti-TNF-α	PsA	SC	Every 2 or 4 weeks[a]	Serious infections, CHF, hematologic events, hypersensitivity reactions, neurologic events, potential for increased malignancies, hepatotoxicity
Secukinumab	Anti-IL-17	Ps, PsA	SC	Every 4 weeks[a]	Serious infections, hypersensitivity reaction, inflammatory bowel disease
Ixekizumab	Anti-IL-17	Ps	SC	Every 4 weeks[a]	Serious infections, hypersensitivity reaction, inflammatory bowel disease

[a]Initial dose modifications required.

Abbreviations: CHF, congestive heart failure; IL, interleukin; IV, intravenous; Ps, psoriasis; PsA, psoriatic arthritis; SC, subcutaneous; TNF-α, tumor necrosis factor-α.

skin disease (secondary infection). Lesions caused by staphylococci may be tense, clear bullae, and this less common form of the disease is called *bullous impetigo*. Blisters are caused by the production of exfoliative toxin by *S. aureus* phage type II. This is the same toxin responsible for staphylococcal scalded-skin syndrome, often resulting in dramatic loss of the superficial epidermis due to blistering. The latter syndrome is much more common in children than in adults; however, it should be considered along with toxic epidermal necrolysis and severe drug eruptions in patients with widespread blistering of the skin. *Ecthyma* is a deep nonbullous variant of impetigo that causes punched-out ulcerative lesions. It is more often caused by a primary or secondary infection with *Streptococcus pyogenes*. Ecthyma is a deeper infection than typical impetigo and resolves with scars. Treatment of both ecthyma and impetigo involves gentle debridement of adherent crusts, which is facilitated by the use of soaks and topical antibiotics in conjunction with appropriate oral antibiotics.

Furunculosis is also caused by *S. aureus*, and this disorder has gained prominence in the last decade because of CA-MRSA. A furuncle, or boil, is a painful, erythematous nodule that can occur on any cutaneous surface. The lesions may be solitary but are most often multiple. Patients frequently believe they have been bitten by spiders or insects. Family members or close contacts may also be affected. Furuncles can rupture and drain spontaneously or may need incision and drainage, which may be adequate therapy for small solitary furuncles without cellulitis or systemic symptoms. Whenever possible, lesional material should be sent for culture. Current recommendations for methicillin-sensitive infections are β-lactam antibiotics. Therapy for CA-MRSA is discussed previously (see "Atopic Dermatitis"). Warm compresses and nasal mupirocin are helpful therapeutic additions. Severe infections may require IV antibiotics.

ERYSIPELAS AND CELLULITIS

See Chap. 124.

DERMATOPHYTOSIS

Dermatophytes are fungi that infect skin, hair, and nails and include members of the genera *Trichophyton*, *Microsporum*, and *Epidermophyton* (Chap. 214). *Tinea corporis*, or infection of the relatively hairless skin of the body (glabrous skin), may have a variable appearance depending

FIGURE 53-5 Lichen planus. An example of lichen planus showing multiple flat-topped, violaceous papules and plaques. Nail dystrophy, as seen in this patient's thumbnail, may also be a feature. *(Courtesy of Robert Swerlick, MD; with permission.)*

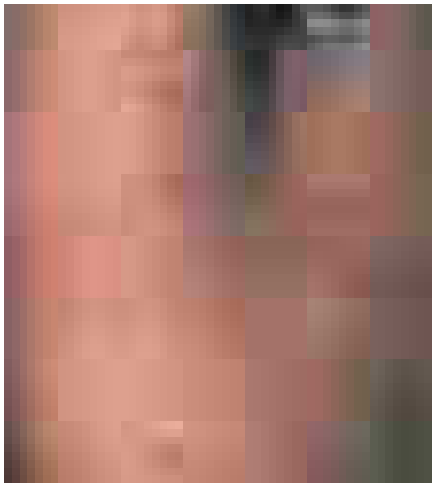

FIGURE 53-6 Pityriasis rosea. In this patient with pityriasis rosea, multiple round to oval erythematous patches with fine central scale are distributed along the skin tension lines on the trunk.

TABLE 53-5 Common Skin Infections

	CLINICAL FEATURES	ETIOLOGIC AGENT	TREATMENT
Impetigo	Honey-colored crusted papules, plaques, or bullae	Group A *Streptococcus* and *Staphylococcus aureus*	Systemic or topical antistaphylococcal and antistreptococcal antibiotics
Dermatophytosis	Inflammatory or noninflammatory annular scaly plaques; may involve hair loss; groin involvement spares scrotum; hyphae on KOH preparation	*Trichophyton*, *Epidermophyton*, or *Microsporum* spp.	Topical azoles, systemic griseofulvin, terbinafine, or azoles
Candidiasis	Inflammatory papules and plaques with satellite pustules, frequently in intertriginous areas; may involve scrotum; pseudohyphae on KOH preparation	*Candida albicans* and other *Candida* spp.	Topical nystatin or azoles; systemic azoles for resistant disease
Tinea versicolor	Hyper- or hypopigmented scaly patches on trunk; characteristic mixture of hyphae and spores ("spaghetti and meatballs") on KOH preparation	*Malassezia furfur*	Topical selenium sulfide lotion or azoles

Abbreviation: KOH, potassium hydroxide.

on the extent of the associated inflammatory reaction. Typical infections consist of erythematous, scaly plaques, with an annular appearance that accounts for the common name "ringworm." Deep inflammatory nodules or granulomas occur in some infections, most often those inappropriately treated with mid- to high-potency topical glucocorticoids. Involvement of the groin (*tinea cruris*) is more common in males than in females. It presents as a scaling, erythematous eruption sparing the scrotum. Infection of the foot (*tinea pedis*) is the most common dermatophyte infection and is often chronic; it is characterized by variable erythema, edema, scaling, pruritus, and occasionally vesiculation. The infection may be widespread or localized but generally involves the web space between the fourth and fifth toes. Infection of the nails (*tinea unguium* or *onychomycosis*) occurs in many patients with tinea pedis and is characterized by opacified, thickened nails and subungual debris. The distal-lateral variant is most common. Proximal subungual onychomycosis may be a marker for HIV infection or other immunocompromised states. Dermatophyte infection of the scalp (*tinea capitis*) continues to be common, particularly affecting inner-city children but also affecting adults. The predominant organism is *Trichophyton tonsurans*, which can produce a relatively noninflammatory infection with mild scale and hair loss that is diffuse or localized. *T. tonsurans* and *Microsporum canis* can also cause a markedly inflammatory dermatosis with edema and nodules. This latter presentation is a *kerion*.

The diagnosis of tinea can be made from skin scrapings, nail scrapings, or hair by culture or direct microscopic examination with KOH. Nail clippings may be sent for histologic examination with periodic acid–Schiff (PAS) stain.

TREATMENT

Dermatophytosis

Both topical and systemic therapies may be used in dermatophyte infections. Treatment depends on the site involved and the type of infection. Topical therapy is generally effective for uncomplicated tinea corporis, tinea cruris, and limited tinea pedis. Topical agents are not effective as monotherapy for tinea capitis or onychomycosis (see below), and nystatin is not active against dermatophytes. Topicals are generally applied twice daily, and treatment should continue for 1 week beyond clinical resolution of the infection. Tinea pedis often requires longer treatment courses and frequently relapses. Oral antifungal agents may be required for recalcitrant tinea pedis or tinea corporis.

For dermatophyte infections involving the hair and nails and for other infections unresponsive to topical therapy, oral antifungal agents are often used. Markedly inflammatory tinea capitis may result in scarring and hair loss, and a systemic antifungal agent plus systemic or topical glucocorticoids may be helpful in preventing these sequelae. A fungal etiology should be confirmed by direct microscopic examination or by culture before oral antifungal agents are prescribed for any infection. All of the oral agents may cause hepatotoxicity. They should not be used in women who are pregnant or breast-feeding.

Griseofulvin is approved in the United States for dermatophyte infections involving the skin, hair, or nails. Common side effects of griseofulvin include gastrointestinal distress, headache, and urticaria.

Two newer oral antifungal agents, itraconazole and terbinafine, are sometimes prescribed "off-label" for superficial fungal infections. Oral itraconazole is approved for onychomycosis. Itraconazole has the potential for serious interactions with other drugs requiring the P450 enzyme system for metabolism. Itraconazole should not be administered to patients with evidence of ventricular dysfunction or patients with known CHF.

Terbinafine is also approved for onychomycosis, and the granule version is approved for treatment of tinea capitis. Terbinafine has fewer interactions with other drugs than itraconazole; however, caution should be used with patients who are on multiple medications. The risk/benefit ratio should be considered when an asymptomatic toenail infection is treated with systemic agents.

The FDA has limited the use of a third oral agent due to potential hepatotoxicity and published the following: "Nizoral [ketoconazole] oral tablets should not be a first-line treatment for any fungal infection." The topical form of ketoconazole is not affected by this action.

TINEA (PITYRIASIS) VERSICOLOR

Tinea versicolor is caused by a nondermatophytic, dimorphic fungus, *Malassezia furfur*, a normal inhabitant of the skin. The expression of infection is promoted by heat and humidity. The typical lesions consist of oval scaly macules, papules, and patches concentrated on the chest, shoulders, and back but only rarely on the face or distal extremities. On dark skin the lesions often appear as hypopigmented areas, whereas on light skin they are slightly erythematous or hyperpigmented. A KOH preparation from scaling lesions will demonstrate a confluence of short hyphae and round spores ("spaghetti and meatballs"). Lotions or shampoos containing sulfur, salicylic acid, or selenium sulfide are the treatments of choice and will clear the infection if used daily for 1–2 weeks and then weekly thereafter. These preparations are irritating if left on the skin for >10 min; thus, they should be washed off completely. Treatment with some oral antifungal agents is also effective, but they do not provide lasting results and are not FDA approved for this indication.

CANDIDIASIS

Candidiasis is a fungal infection caused by a related group of yeasts whose manifestations may be localized to the skin and mucous membranes or, rarely, may be systemic and life-threatening **(Chap. 211)**. The causative organism is usually *Candida albicans*. These organisms are normal saprophytic inhabitants of the gastrointestinal tract but may overgrow due to broad-spectrum antibiotic therapy, diabetes mellitus, or immunosuppression and cause disease. Candidiasis is a very common infection in HIV-infected individuals **(Chap. 197)**. The oral cavity is commonly involved. Lesions may occur on the tongue or buccal mucosa (*thrush*) and appear as white plaques. Fissured, macerated lesions at the corners of the mouth (*perlèche*) are often seen in individuals with poorly fitting dentures and may also be associated with candidal infection. In addition, candidal infections have an affinity for sites

that are chronically wet and macerated, including the skin around nails (onycholysis and paronychia), and in intertriginous areas. Intertriginous lesions are characteristically edematous, erythematous, and scaly, with scattered "satellite pustules." In males, there is often involvement of the penis and scrotum as well as the inner aspect of the thighs. In contrast to dermatophyte infections, candidal infections are frequently painful and accompanied by a marked inflammatory response. Diagnosis of candidal infection is based on the clinical pattern and demonstration of yeast on KOH preparation or culture.

TREATMENT

Candidiasis

Treatment involves removal of any predisposing factors such as antibiotic therapy or chronic wetness and the use of appropriate topical or systemic antifungal agents. Effective topicals include nystatin or azoles (miconazole, clotrimazole, econazole, or ketoconazole). The associated inflammatory response accompanying candidal infection on glabrous skin can be treated with a mild glucocorticoid lotion or cream (2.5% hydrocortisone). Systemic therapy is usually reserved for immunosuppressed patients or individuals with chronic or recurrent disease who fail to respond to appropriate topical therapy. Oral fluconazole is most commonly prescribed for cutaneous candidiasis. Oral nystatin is effective only for candidiasis of the gastrointestinal tract.

WARTS

Warts are cutaneous neoplasms caused by papillomaviruses. More than 100 different human papillomaviruses (HPVs) have been described. A typical wart, *verruca vulgaris*, is sessile, dome-shaped, and usually about a centimeter in diameter. Its surface is hyperkeratotic, consisting of many small filamentous projections. HPV also causes typical plantar warts, flat warts (*verruca plana*), and filiform warts. Plantar warts are endophytic and are covered by thick keratin. Paring of the wart will generally reveal a central core of keratinized debris and punctate bleeding points. Filiform warts are most commonly seen on the face, neck, and skinfolds, and present as papillomatous lesions on a narrow base. Flat warts are only slightly elevated and have a velvety, nonverrucous surface. They have a propensity for the face, arms, and legs, and are often spread by shaving.

Genital warts begin as small papillomas that may grow to form large, fungating lesions. In women, they may involve the labia, perineum, or perianal skin. In addition, the mucosa of the vagina, urethra, and anus can be involved as well as the cervical epithelium. In men, the lesions often occur initially in the coronal sulcus but may be seen on the shaft of the penis, the scrotum, or the perianal skin or in the urethra.

Appreciable evidence has accumulated indicating that HPV plays a role in the development of neoplasia of the uterine cervix and anogenital skin **(Chap. 85)**. HPV types 16 and 18 have been most intensely studied and are the major risk factors for intraepithelial neoplasia and squamous cell carcinoma of the cervix, anus, vulva, and penis. The risk is higher among patients immunosuppressed after solid organ transplantation and among those infected with HIV. Recent evidence also implicates other HPV types. Histologic examination of biopsied samples from affected sites may reveal changes associated with typical warts and/or features typical of intraepidermal carcinoma (Bowen's disease). Squamous cell carcinomas associated with HPV infections have also been observed in extragenital skin **(Chap. 72)**, most commonly in patients immunosuppressed after organ transplantation. Patients on long-term immunosuppression should be monitored for the development of squamous cell carcinoma and other cutaneous malignancies.

TREATMENT

Warts

Treatment of warts, other than anogenital warts, should be tempered by the observation that a majority of warts in normal individuals resolve spontaneously within 1–2 years. There are many modalities available to treat warts, but no single therapy is universally effective. Factors that influence the choice of therapy include the location of the wart, the extent of disease, the age and immunologic status of the patient, and the patient's desire for therapy. Perhaps the most useful and convenient method for treating warts in almost any location is cryotherapy with liquid nitrogen. Equally effective for nongenital warts, but requiring much more patient compliance, is the use of keratolytic agents such as salicylic acid plasters or solutions. For genital warts, in-office application of a podophyllin solution is moderately effective but may be associated with marked local reactions. Prescription preparations of dilute, purified podophyllin are available for home use. Topical imiquimod, a potent inducer of local cytokine release, has been approved for treatment of genital warts. A new topical compound composed of green tea extracts (sinecatechins) is also available. Conventional and laser surgical procedures may be required for recalcitrant warts. Recurrence of warts appears to be common with all these modalities. A highly effective vaccine for selected types of HPV has been approved by the FDA, and its use is reported to reduce the incidence of anogenital and cervical carcinoma.

HERPES SIMPLEX

See Chap. 187.

HERPES ZOSTER

See Chap. 188.

ACNE

ACNE VULGARIS

Acne vulgaris is a self-limited disorder primarily of teenagers and young adults, although perhaps 10–20% of adults may continue to experience some form of the disorder. The permissive factor for the expression of the disease in adolescence is the increase in sebum production by sebaceous glands after puberty. Small cysts, called *comedones*, form in hair follicles due to blockage of the follicular orifice by retention of keratinous material and sebum. The activity of bacteria (*Propionibacterium acnes*) within the comedones releases free fatty acids from sebum, causes inflammation within the cyst, and results in rupture of the cyst wall. An inflammatory foreign-body reaction develops as result of extrusion of oily and keratinous debris from the cyst.

The clinical hallmark of acne vulgaris is the comedone, which may be closed (*whitehead*) or open (*blackhead*). Closed comedones appear as 1- to 2-mm pebbly white papules, which are accentuated when the skin is stretched. They are the precursors of inflammatory lesions of acne vulgaris. The contents of closed comedones are not easily expressed. Open comedones, which rarely result in inflammatory acne lesions, have a large dilated follicular orifice and are filled with easily expressible oxidized, darkened, oily debris. Comedones are usually accompanied by inflammatory lesions: papules, pustules, or nodules.

The earliest lesions seen in adolescence are generally mildly inflamed or noninflammatory comedones on the forehead. Subsequently, more typical inflammatory lesions develop on the cheeks, nose, and chin **(Fig. 53-7)**. The most common location for acne is the face, but involvement of the chest and back is common. Most disease remains mild and does not lead to scarring. A small number of patients develop large inflammatory cysts and nodules, which may drain and result in significant scarring. Regardless of the severity, acne may affect a patient's quality of life. With adequate treatment, this effect may be transient. In the case of severe, scarring acne, the effects can be permanent and profound. Early therapeutic intervention in severe acne is essential.

Exogenous and endogenous factors can alter the expression of acne vulgaris. Friction and trauma (from headbands or chin straps of athletic helmets), application of comedogenic topical agents (cosmetics or hair preparations), or chronic topical exposure to certain industrial compounds may elicit or aggravate acne. Glucocorticoids, topical or systemic, may also elicit acne. Other systemic medications such as oral

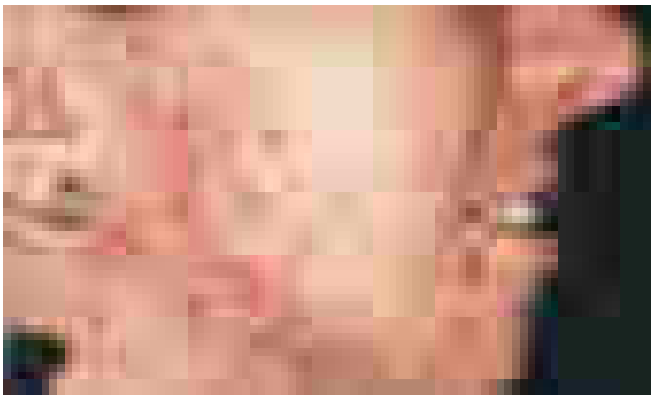

FIGURE 53-7 Acne vulgaris. An example of acne vulgaris with inflammatory papules, pustules, and comedones. *(Courtesy of Kalman Watsky, MD; with permission.)*

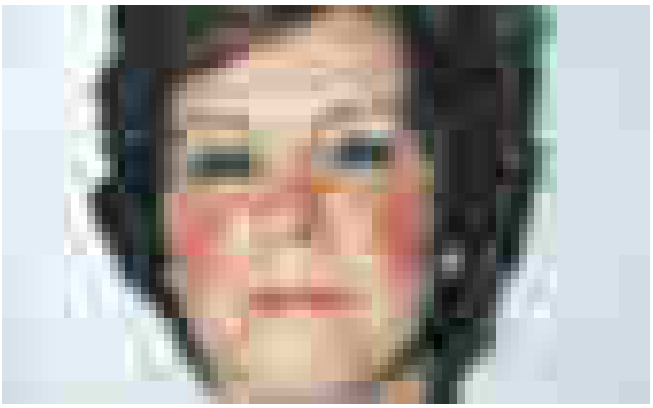

FIGURE 53-8 Acne rosacea. Prominent facial erythema, telangiectasia, scattered papules, and small pustules are seen in this patient with acne rosacea. *(Courtesy of Robert Swerlick, MD; with permission.)*

contraceptive pills, lithium, isoniazid, androgenic steroids, halogens, phenytoin, and phenobarbital may produce acneiform eruptions or aggravate preexisting acne. Genetic factors and polycystic ovary disease may also play a role.

TREATMENT

Acne Vulgaris

Treatment of acne vulgaris is directed toward elimination of comedones by normalizing follicular keratinization and decreasing sebaceous gland activity, the population of *P. acnes*, and inflammation. Minimal to moderate pauci-inflammatory disease may respond adequately to local therapy alone. Although areas affected with acne should be kept clean, overly vigorous scrubbing may aggravate acne due to mechanical rupture of comedones. Topical agents such as retinoic acid, benzoyl peroxide, or salicylic acid may alter the pattern of epidermal desquamation, preventing the formation of comedones and aiding in the resolution of preexisting cysts. Topical antibacterial agents (such as azelaic acid, erythromycin, clindamycin, or dapsone) are also useful adjuncts to therapy. Benzoyl peroxide products should be used in combination with topical antibiotics (erythromycin and clindamycin) to prevent development of bacterial resistance.

Patients with moderate to severe acne with a prominent inflammatory component will benefit from the addition of systemic therapy, such as tetracycline in doses of 250–500 mg bid or doxycycline in doses of 100 mg bid. Minocycline is also useful. Such antibiotics appear to have anti-inflammatory effects independent of their antibacterial effects. If the patient is not showing appropriate response within 3 months, changes in the plan should be considered. Female patients who do not respond to oral antibiotics may benefit from hormonal therapy. Several oral contraceptives are now approved by the FDA for use in the treatment of acne vulgaris.

Patients with severe nodulocystic acne unresponsive to the therapies discussed above may benefit from treatment with the synthetic retinoid isotretinoin. Its dose is based on the patient's weight, and it is given once daily for 5 months. Results are excellent in appropriately selected patients. Its use is highly regulated due to its potential for severe adverse events, primarily teratogenicity and depression. In addition, patients receiving this medication develop extremely dry skin and cheilitis and must be followed for development of hypertriglyceridemia.

At present, prescribers must enroll in a program designed to prevent pregnancy and adverse events while patients are taking isotretinoin. These measures are imposed to ensure that all prescribers are familiar with the risks of isotretinoin, that all female patients have two negative pregnancy tests prior to initiation of therapy and a negative pregnancy test prior to each refill, and that all patients have been warned about the risks associated with isotretinoin.

ACNE ROSACEA

Acne rosacea, commonly referred to simply as *rosacea*, is an inflammatory disorder predominantly affecting the central face. Persons most often affected are Caucasians of northern European background, but rosacea also occurs in patients with dark skin. Rosacea is seen almost exclusively in adults, only rarely affecting patients <30 years old. Rosacea is more common in women, but those most severely affected are men. It is characterized by the presence of erythema, telangiectases, and superficial pustules **(Fig. 53-8)** but is not associated with the presence of comedones. Rosacea rarely involves the chest or back.

There is a relationship between the tendency for facial flushing and the subsequent development of acne rosacea. Often, individuals with rosacea initially demonstrate a pronounced flushing reaction. This may be in response to heat, emotional stimuli, alcohol, hot drinks, or spicy foods. As the disease progresses, the flush persists longer and longer and may eventually become permanent. Papules, pustules, and telangiectases can become superimposed on the persistent flush. Rosacea of very long standing may lead to connective tissue overgrowth, particularly of the nose (*rhinophyma*). Rosacea may also be complicated by various inflammatory disorders of the eye, including keratitis, blepharitis, iritis, and recurrent chalazion. These ocular problems are potentially sight-threatening and warrant ophthalmologic evaluation.

TREATMENT

Acne Rosacea

Acne rosacea can be treated topically or systemically. Mild disease often responds to topical metronidazole, sodium sulfacetamide, azelaic acid, topical ivermectin, or topical brimonidine. More severe disease requires oral tetracyclines: tetracycline, 250–500 mg bid; doxycycline, 100 mg bid; or minocycline, 50–100 mg bid. Residual telangiectasia may respond to laser therapy. Topical glucocorticoids, especially potent agents, should be avoided because chronic use of these preparations may elicit rosacea. Application of topical agents to the skin is not effective treatment for ocular disease.

SKIN DISEASES AND SMALLPOX VACCINATION

Although smallpox vaccinations were discontinued several decades ago for the general population, they are still required for certain military personnel and first responders. In the absence of a bioterrorism attack and a real or potential exposure to smallpox, such vaccination is contraindicated in persons with a history of skin diseases such as AD, eczema, and psoriasis, who have a higher incidence of adverse events associated with smallpox vaccination. In the case of such exposure, the risk of smallpox infection outweighs that of adverse events from the vaccine **(Chap. S2)**.

FURTHER READING

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54 Skin Manifestations of Internal Disease

Jean L. Bolognia, Irwin M. Braverman

It is a generally accepted concept in medicine that the skin can develop signs of internal disease. Therefore, in textbooks of medicine, one finds a chapter describing in detail the major systemic disorders that can be identified by cutaneous signs. The underlying assumption of such a chapter is that the clinician has been able to identify the specific disorder in the patient and needs only to read about it in the textbook. In reality, concise differential diagnoses and the identification of these disorders are actually difficult for the nondermatologist because he or she is not well-versed in the recognition of cutaneous lesions or their spectrum of presentations. Therefore, this chapter covers this particular topic of cutaneous medicine not by simply focusing on individual diseases, but by describing the various presenting clinical signs and symptoms that point to specific disorders. Concise differential diagnoses will be generated in which the significant diseases will be distinguished from the more common cutaneous disorders that have minimal or no significance with regard to associated internal disease. The latter disorders are reviewed in table form and always need to be excluded when considering the former. For a detailed description of individual diseases, the reader should consult a dermatologic text.

PAPULOSQUAMOUS SKIN LESIONS

(Table 54-1) When an eruption is characterized by elevated lesions, either papules (<1 cm) or plaques (>1 cm), in association with scale, it is referred to as *papulosquamous*. The most common papulosquamous diseases—*tinea*, *psoriasis*, *pityriasis rosea*, and *lichen planus*—are primary cutaneous disorders **(Chap. 53)**. When psoriatic lesions are accompanied by arthritis, the possibility of psoriatic arthritis or reactive arthritis should be considered. A history of oral ulcers, conjunctivitis, uveitis, and/or urethritis points to the latter diagnosis. Lithium, beta blockers, HIV or streptococcal infections, and a rapid taper of systemic glucocorticoids are known to exacerbate psoriasis; despite being used to treat psoriasis, TNF-α inhibitors can also induce psoriatic lesions. Comorbidities in patients with psoriasis include cardiovascular disease and metabolic syndrome.

Whenever the diagnosis of pityriasis rosea or lichen planus is made, it is important to review the patient's medications because the eruption may resolve by simply discontinuing the offending agent. Pityriasis rosea–like drug eruptions are seen most commonly with beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and metronidazole, whereas the drugs that can produce a lichenoid eruption include thiazides, antimalarials, quinidine, beta blockers, TNF-α inhibitors, anti-PD-1/PD-L1 Ab, and ACE inhibitors. In some populations, there is a higher prevalence of hepatitis C viral infection in patients with oral lichen planus. Lichen planus–like lesions are also observed in chronic graft-versus-host disease.

In its early stages, the mycosis fungoides (MF) form of *cutaneous T cell lymphoma* (CTCL) may be confused with eczema or psoriasis, but it often fails to respond to appropriate therapy for those inflammatory diseases. MF can develop within lesions of large-plaque parapsoriasis and is suggested by an increase in the thickness of the lesions. The diagnosis of MF is established by skin biopsy in which collections of atypical T lymphocytes are found in the epidermis and dermis. As the disease progresses, cutaneous tumors and lymph node involvement may appear.

In *secondary syphilis*, there are scattered red-brown papules with thin scale. The eruption often involves the palms and soles and can resemble pityriasis rosea. Associated findings are helpful in making the diagnosis and include annular plaques on the face, nonscarring alopecia, condyloma lata (broad-based and moist), and mucous patches as well as lymphadenopathy, malaise, fever, headache, and myalgias. The interval between the primary chancre and the secondary stage is usually 4–8 weeks, and spontaneous resolution without appropriate therapy occurs.

TABLE 54-1 Selected Causes of Papulosquamous Skin Lesions

1. Primary cutaneous disorders
   a. Tinea[a]—widespread disease may be sign of immunosuppression
   b. Psoriasis[a]—widespread or resistant disease may be sign of HIV infection
   c. Pityriasis rosea[a]
   d. Lichen planus[a]
   e. Parapsoriasis, small plaque and large plaque
   f. Bowen's disease (squamous cell carcinoma in situ)[b]
2. Drugs
3. Systemic diseases
   a. Lupus erythematosus, primarily subacute or chronic (discoid) lesions[c]
   b. Cutaneous T cell lymphoma, in particular, mycosis fungoides[d]
   c. Secondary syphilis
   d. Reactive arthritis
   e. Sarcoidosis[e]—with scale less common than without scale

[a]Discussed in detail in **Chap. 53**; cardiovascular disease and the metabolic syndrome are comorbidities in psoriasis; primarily in Europe, hepatitis C virus is associated with oral lichen planus. [b]Associated with chronic sun exposure more often than exposure to arsenic; usually one or a few lesions. [c]See also Red Lesions in "Papulonodular Skin Lesions." [d]Also cutaneous lesions of HTLV-1-associated adult T cell leukemia/lymphoma. [e]See also Red-Brown Lesions in "Papulonodular Skin Lesions."

Abbreviation: HIV, human immunodeficiency virus.

ERYTHRODERMA

(Table 54-2) *Erythroderma* is the term used when the majority of the skin surface is erythematous (red in color). There may be associated scale, erosions, or pustules as well as shedding of the hair and nails. Potential systemic manifestations include fever, chills, hypothermia, reactive lymphadenopathy, peripheral edema, hypoalbuminemia, and high-output cardiac failure. The major etiologies of erythroderma are (1) cutaneous diseases such as psoriasis and dermatitis **(Table 54-3)**; (2) drugs; (3) systemic diseases, most commonly CTCL; and (4) idiopathic. In the first three groups, the location and description of the initial lesions, prior to the development of the erythroderma, aid in the diagnosis. For example, a history of red scaly plaques on the elbows and knees would point to psoriasis. It is also important to examine the skin carefully for a migration of the erythema and associated secondary

TABLE 54-2 Causes of Erythroderma

1. Primary cutaneous disorders
   a. Psoriasis[a]
   b. Dermatitis (atopic > contact >> stasis [with autosensitization] or seborrheic [primarily infants])[a]
   c. Pityriasis rubra pilaris
2. Drugs
3. Systemic diseases
   a. Cutaneous T cell lymphoma (Sézary syndrome, erythrodermic mycosis fungoides)
   b. Other lymphomas
4. Idiopathic (usually older men)

[a]Discussed in detail in **Chap. 53**.

TABLE 54-3 Erythroderma (Primary Cutaneous Disorders)

	INITIAL LESIONS	LOCATION OF INITIAL LESIONS	OTHER FINDINGS	DIAGNOSTIC AIDS	TREATMENT
Psoriasis[a]	Pink-red, silvery scale, sharply demarcated	Elbows, knees, scalp, presacral area, intergluteal fold	Nail dystrophy, arthritis, pustules, SAPHO syndrome[b]	Skin biopsy	Topical glucocorticoids, vitamin D; UV-B (narrowband) > PUVA; oral retinoid; MTX, cyclosporine, anti-TNF agents, apremilast, anti-IL-12/23 Ab, anti-IL-17A or -IL-17 receptor Ab
Dermatitis[a]					
Atopic	Acute: Erythema, fine scale, crust, indistinct borders, excoriations Chronic: Lichenification (increased skin markings), excoriations	Antecubital and popliteal fossae, neck, hands, eyelids	Pruritus Personal and/or family history of atopy, including asthma, allergic rhinitis or conjunctivitis, and atopic dermatitis Exclude secondary infection with *Staphylococcus aureus* or HSV Exclude superimposed irritant or allergic contact dermatitis	Skin biopsy	Topical glucocorticoids, tacrolimus, pimecrolimus, tar, and antipruritics; oral antihistamines; open wet dressings; UV-B ± UV-A > PUVA; oral/IM glucocorticoids (short-term); MTX; mycophenolate mofetil; azathioprine; cyclosporine; anti-IL-4/13 Ab Topical or oral antibiotics
Contact	Local: Erythema, crusting, vesicles, and bullae Systemic: Erythema, fine scale, crust	Depends on offending agent Generalized vs major intertriginous zones (especially groin)	Irritant—onset often within hours Allergic—delayed-type hypersensitivity; lag time of 48 h with re-challenge Patient has history of allergic contact dermatitis to topical agent and then receives systemic medication that is structurally related, e.g., formaldehyde (skin), aspartame (oral)	Patch testing; repeat open application test Patch testing	Remove irritant or allergen; topical glucocorticoids; oral antihistamines; oral/IM glucocorticoids (short-term) Same as local
Seborrheic (rare in adults)	Pink-red to pink-orange, greasy scale	Scalp, nasolabial folds, eyebrows, intertriginous zones	Flares with stress, HIV infection Associated with Parkinson's disease	Skin biopsy	Topical glucocorticoids and imidazoles
Stasis (with autosensitization)	Erythema, crusting, excoriations	Lower extremities	Pruritus, lower extremity edema, varicosities, hemosiderin deposits, lipodermatosclerosis History of venous ulcers, thrombophlebitis, and/or cellulitis Exclude cellulitis Exclude superimposed contact dermatitis, e.g., topical neomycin	Skin biopsy	Topical glucocorticoids; open wet dressings; leg elevation; pressure stockings; pressure wraps if associated ulcers
Pityriasis rubra pilaris	Orange-red (salmon-colored), perifollicular papules	Generalized, but characteristic "skip" areas of normal skin	Wax-like palmoplantar keratoderma Exclude cutaneous T cell lymphoma	Skin biopsy	Isotretinoin or acitretin; MTX; perhaps anti-IL-12/23 Ab, anti-TNF agents, anti-IL-17 Ab

[a]Discussed in detail in **Chap. 53**. [b]SAPHO syndrome occurs more commonly in patients with palmoplantar pustulosis than in those with erythrodermic psoriasis.

Abbreviations: Ab, antibody; HSV, herpes simplex virus; IL, interleukin; IM, intramuscular; MTX, methotrexate; PUVA, psoralens + ultraviolet A irradiation; SAPHO, synovitis, *a*cne, *p*ustulosis, *h*yperostosis, and *o*steitis (a subtype is chronic recurrent multifocal osteomyelitis); TNF, tumor necrosis factor; UV-A, ultraviolet A irradiation; UV-B, ultraviolet B irradiation.

changes such as pustules or erosions. Migratory waves of erythema studded with superficial pustules are seen in *pustular psoriasis*.

Drug-induced erythroderma (exfoliative dermatitis) may begin as an exanthematous (morbilliform) eruption **(Chap. 56)** or may arise as diffuse erythema. A number of drugs can produce an erythroderma, including penicillins, sulfonamides, carbamazepine, phenytoin, and allopurinol. Fever and peripheral eosinophilia often accompany the eruption, and there may also be facial swelling, hepatitis, myocarditis, thyroiditis, and allergic interstitial nephritis; this constellation is frequently referred to as *drug reaction with eosinophilia and systemic symptoms* (DRESS) or *drug-induced hypersensitivity reaction* (DIHS). In addition, these reactions, especially to aromatic anticonvulsants, can lead to a pseudolymphoma syndrome (with adenopathy and circulating atypical lymphocytes), while reactions to allopurinol may be accompanied by gastrointestinal bleeding.

The most common malignancy that is associated with erythroderma is CTCL; in some series, up to 25% of the cases of erythroderma were due to CTCL. The patient may progress from isolated plaques and tumors, but more commonly, the erythroderma is present throughout the course of the disease (Sézary syndrome). In Sézary syndrome, there are circulating clonal atypical T lymphocytes, pruritus, and lymphadenopathy. In cases of erythroderma where there is no apparent cause (idiopathic), longitudinal evaluation is mandatory to monitor for the possible development of CTCL. There have been isolated case reports of erythroderma secondary to some solid tumors—lung, liver, prostate, thyroid, and colon—but it is primarily during a late stage of the disease.

ALOPECIA

(Table 54-4) The two major forms of alopecia are scarring and nonscarring. *Scarring alopecia* is associated with fibrosis, inflammation, and loss of hair follicles. A smooth scalp with a decreased number of follicular openings is usually observed clinically, but in some patients, the changes are seen only in biopsy specimens from affected areas.

TABLE 54-4 Causes of Alopecia

I. Nonscarring alopecia
  A. Primary cutaneous disorders
    1. Androgenetic alopecia
    2. Telogen effluvium
    3. Alopecia areata
    4. Tinea capitis
    5. Traumatic alopecia[a]
    6. Psoriasiform alopecia, including TNF-α inhibitor-induced
  B. Drugs
  C. Systemic diseases
    1. Systemic lupus erythematosus
    2. Secondary syphilis
    3. Hypothyroidism
    4. Hyperthyroidism
    5. Hypopituitarism
    6. Deficiencies of protein, biotin, zinc, and perhaps iron
II. Scarring alopecia
  A. Primary cutaneous disorders
    1. Cutaneous lupus (chronic discoid lesions)[b]
    2. Lichen planus, including frontal fibrosing alopecia
    3. Central centrifugal cicatricial alopecia
    4. Folliculitis decalvans
    5. Linear morphea (linear scleroderma)[c]
  B. Systemic diseases
    1. Discoid lesions in the setting of systemic lupus erythematosus[b]
    2. Sarcoidosis
    3. Cutaneous metastases

[a]Most patients with trichotillomania or early stages of traction alopecia and some patients with pressure-induced alopecia. [b]While the majority of patients with discoid lesions have only cutaneous disease, these lesions do represent one of the 11 American College of Rheumatology criteria (1982) for systemic lupus erythematosus. [c]Can involve underlying muscles and osseous structures and rarely in linear morphea of the frontal scalp (*en coup de sabre*), there is involvement of the meninges and brain.

In *nonscarring alopecia*, the hair shafts are absent or miniaturized, but the hair follicles are preserved, explaining the reversible nature of nonscarring alopecia.

The most common causes of nonscarring alopecia include *androgenetic alopecia*, *telogen effluvium*, *alopecia areata*, *tinea capitis*, and the early phase of *traumatic alopecia* **(Table 54-5)**. In women with androgenetic alopecia, an elevation in circulating levels of androgens may be seen as a result of ovarian or adrenal gland dysfunction or neoplasm. When there are signs of virilization, such as a deepened voice and enlarged clitoris, the possibility of an ovarian or adrenal gland tumor should be considered.

Exposure to various drugs can also cause diffuse hair loss, usually by inducing a telogen effluvium. An exception is the anagen effluvium observed with antimitotic agents such as daunorubicin. Alopecia is a side effect of the following drugs: warfarin, heparin, propylthiouracil, carbimazole, isotretinoin, acitretin, lithium, beta blockers, interferons, colchicine, and amphetamines. Fortunately, spontaneous regrowth usually follows discontinuation of the offending agent.

Less commonly, nonscarring alopecia is associated with *lupus erythematosus* and *secondary syphilis*. In systemic lupus there are two forms of alopecia—one is scarring secondary to discoid lesions (see below), and the other is nonscarring. The latter form coincides with flares of systemic disease and may involve the entire scalp or just the frontal scalp, with the appearance of multiple short hairs ("lupus hairs") as a sign of initial regrowth. Scattered, poorly circumscribed patches of alopecia with a "moth-eaten" appearance are a manifestation of the secondary stage of syphilis. Diffuse thinning of the hair is also associated with hypothyroidism and hyperthyroidism (Table 54-4).

Scarring alopecia is more frequently the result of a primary cutaneous disorder such as *lichen planus*, *chronic cutaneous (discoid) lupus*, *central centrifugal cicatricial alopecia*, *folliculitis decalvans*, or *linear scleroderma* (*morphea*) than it is a sign of systemic disease. Although the scarring lesions of *discoid lupus* can be seen in patients with systemic lupus, in the majority of patients, the disease process is limited to the skin. Less common causes of scarring alopecia include *sarcoidosis* (see "Papulonodular Skin Lesions," below) and *cutaneous metastases*.

In the early phases of discoid lupus, lichen planus, and folliculitis decalvans, there are circumscribed areas of alopecia. Fibrosis and

TABLE 54-5 Nonscarring Alopecia (Primary Cutaneous Disorders)

	CLINICAL CHARACTERISTICS	PATHOGENESIS	TREATMENT
Telogen effluvium	Diffuse shedding of normal hairs Follows major stress (high fever, severe infection) or change in hormone levels (postpartum) Reversible without treatment	Stress causes more of the asynchronous growth cycles of individual hairs to become synchronous; therefore, larger numbers of growing (anagen) hairs simultaneously enter the dying (telogen) phase	Observation; discontinue any drugs that have alopecia as a side effect; must exclude underlying metabolic causes, e.g., hypothyroidism, hyperthyroidism
Androgenetic alopecia (male pattern; female pattern)	Miniaturization of hairs along the midline of the scalp Recession of the anterior scalp line in men and some women	Increased sensitivity of affected hairs to the effects of androgens Increased levels of circulating androgens (ovarian or adrenal source in women)	If no evidence of hyperandrogenemia, then topical minoxidil; finasteride[a]; spironolactone (women); hair transplant
Alopecia areata	Well-circumscribed, circular areas of hair loss, 2–5 cm in diameter In extensive cases, coalescence of lesions and/or involvement of other hair-bearing surfaces of the body Pitting or sandpapered appearance of the nails	The germinative zones of the hair follicles are surrounded by T lymphocytes Occasional associated diseases: hyperthyroidism, hypothyroidism, vitiligo, Down syndrome	Topical anthralin or tazarotene; intralesional glucocorticoids; topical contact sensitizers; JAK inhibitors
Tinea capitis	Varies from scaling with minimal hair loss to discrete patches with "black dots" (sites of broken infected hairs) to boggy plaque with pustules (kerion)[b]	Invasion of hairs by dermatophytes, most commonly *Trichophyton tonsurans*	Oral griseofulvin or terbinafine plus 2.5% selenium sulfide or ketoconazole shampoo; examine family members
Traumatic alopecia[c]	Broken hairs, often of varying lengths Irregular outline in trichotillomania and traction alopecia	Traction with curlers, rubber bands, tight braiding Exposure to heat or chemicals (e.g., hair straighteners) Mechanical pulling (trichotillomania)	Discontinuation of offending hair style or chemical treatments; diagnosis of trichotillomania may require observation of shaved hairs (for growth) or biopsy, possibly followed by psychotherapy

[a]To date, Food and Drug Administration–approved for men. [b]Scarring alopecia can occur at sites of kerions. [c]May also be scarring, especially late-stage traction alopecia.

subsequent loss of hair follicles are observed primarily in the center of these alopecic patches, whereas the inflammatory process is most prominent at the periphery. The areas of active inflammation in discoid lupus are erythematous with scale, whereas the areas of previous inflammation are often hypopigmented with a rim of hyperpigmentation. In lichen planus, perifollicular macules at the periphery are usually violet-colored. A complete examination of the skin and oral mucosa combined with a biopsy and direct immunofluorescence microscopy of inflamed skin will aid in distinguishing these two entities. The peripheral active lesions in folliculitis decalvans are follicular pustules; these patients can develop a reactive arthritis.

FIGURATE SKIN LESIONS

(Table 54-6) In *figurate eruptions*, the lesions form rings and arcs that are usually erythematous but can be skin-colored to brown. Most commonly, they are due to primary cutaneous diseases such as *tinea*, *urticaria*, *granuloma annulare*, and *erythema annulare centrifugum* **(Chaps. 53 and 55)**. An underlying systemic illness is found in a second, less common group of migratory annular erythemas. It includes *erythema migrans*, *erythema gyratum repens*, *erythema marginatum*, and *necrolytic migratory erythema*.

In erythema gyratum repens, one sees numerous mobile concentric arcs and wavefronts that resemble the grain in wood. A search for an underlying malignancy is mandatory in a patient with this eruption. Erythema migrans is the cutaneous manifestation of Lyme disease, which is caused by the spirochete *Borrelia burgdorferi*. In the initial stage (3–30 days after tick bite), a single annular lesion is usually seen, which can expand to ≥10 cm in diameter. Within several days, up to half of the patients develop multiple smaller erythematous lesions at sites distant from the bite. Associated symptoms include fever, headache, photophobia, myalgias, arthralgias, and malar rash. Erythema marginatum is seen in patients with rheumatic fever, primarily on the trunk. Lesions are pink-red in color, flat to minimally elevated, and transient.

There are additional cutaneous diseases that present as annular eruptions but lack an obvious migratory component. Examples include *CTCL*, *subacute cutaneous lupus*, *secondary syphilis*, and *sarcoidosis* (see "Papulonodular Skin Lesions," below).

TABLE 54-6 Causes of Figurate Skin Lesions

I. Primary cutaneous disorders
  A. Tinea
  B. Urticaria (primary in ≥90% of patients)
  C. Granuloma annulare
  D. Erythema annulare centrifugum
  E. Psoriasis, annular pustular psoriasis
  F. Interstitial granulomatous drug reaction
II. Systemic diseases
  A. Migratory
    1. Erythema migrans (CDC case definition is ≥5 cm in diameter)
    2. Urticaria (≤10% of patients)
    3. Erythema gyratum repens
    4. Erythema marginatum
    5. Pustular psoriasis (generalized and annular forms)
    6. Necrolytic migratory erythema (glucagonoma syndrome)[a]
  B. Nonmigratory
    1. Sarcoidosis
    2. Subacute cutaneous lupus erythematosus, LE tumidus
    3. Annular erythema of Sjögren's syndrome
    4. Secondary syphilis (especially the face)
    5. Cutaneous T cell lymphoma (especially mycosis fungoides)
    6. Interstitial granulomatous dermatitis[b]

[a]Migratory erythema with erosions; favors lower extremities and girdle area.
[b]Underlying diseases include rheumatoid arthritis, LE, and granulomatosis with polyangiitis.

Abbreviations: CDC, Centers for Disease Control and Prevention; LE, lupus erythematosus.

TABLE 54-7 Causes of Acneiform Eruptions

I. Primary cutaneous disorders
  A. Acne vulgaris
  B. Acne rosacea
II. Drugs, e.g., anabolic steroids, glucocorticoids, lithium, EGFR inhibitors, MEK inhibitors iodides
III. Systemic diseases
  A. Increased androgen production
    1. Adrenal origin, e.g., Cushing's disease, 21-hydroxylase deficiency
    2. Ovarian origin, e.g., polycystic ovary syndrome, ovarian hyperthecosis
  B. Cryptococcosis, disseminated
  C. Dimorphic fungal infections
  D. Behçet's disease

Abbreviation: EGFR, epidermal growth factor receptor; MEK, MAP (mitogen activated protein) kinase.

ACNE

(Table 54-7) In addition to *acne vulgaris* and *acne rosacea*, the two major forms of acne **(Chap. 53)**, there are drugs and systemic diseases that can lead to acneiform eruptions.

Patients with the *carcinoid syndrome* have episodes of flushing of the head, neck, and sometimes the trunk. Resultant skin changes of the face, in particular telangiectasias, may mimic the clinical appearance of erythematotelangiectatic acne rosacea.

PUSTULAR LESIONS

Acneiform eruptions (see "Acne," above) and *folliculitis* represent the most common pustular dermatoses. An important consideration in the evaluation of follicular pustules is a determination of the associated pathogen, for example, normal flora (culture-negative), *Staphylococcus aureus*, *Pseudomonas aeruginosa* ("hot tub" folliculitis), *Malassezia*, dermatophytes (Majocchi's granuloma), and *Demodex* spp. Noninfectious forms of folliculitis include HIV- or immunosuppression-associated eosinophilic folliculitis and folliculitis secondary to drugs such as glucocorticoids, lithium, and epidermal growth factor receptor (EGFR) or MEK inhibitors. Administration of high-dose systemic glucocorticoids can result in a widespread eruption of follicular pustules on the trunk, characterized by lesions in the same stage of development. With regard to underlying systemic diseases, nonfollicular-based pustules are a characteristic component of pustular psoriasis (sterile) and can be seen in septic emboli of bacterial or fungal origin (see "Purpura," below). In patients with acute generalized exanthematous pustulosis (AGEP) due primarily to medications (e.g., cephalosporins), there are large areas of erythema studded with multiple sterile pustules in addition to neutrophilia.

TELANGIECTASIAS

(Table 54-8) To distinguish the various types of telangiectasias, it is important to examine the shape and configuration of the dilated blood vessels. *Linear telangiectasias* are seen on the face of patients with *actinically damaged skin* and *acne rosacea,* and they are found on the legs of patients with *venous hypertension* and first appear on the legs in *generalized essential telangiectasia*. Patients with an unusual form of *mastocytosis* (telangiectasia macularis eruptiva perstans) and the *carcinoid syndrome* (see "Acne," above) also have linear telangiectasias. Lastly, linear telangiectasias are found in areas of cutaneous inflammation. For example, longstanding lesions of discoid lupus frequently have telangiectasias within them.

Poikiloderma is a term used to describe a patch of skin with: (1) reticulated hypo- and hyperpigmentation, (2) wrinkling secondary to epidermal atrophy, and (3) telangiectasias. Poikiloderma does not imply a single disease entity—although it is becoming less common, it is seen in skin damaged by *ionizing radiation* as well as in patients with autoimmune connective tissue diseases, primarily *dermatomyositis* (DM), and rare genodermatoses (e.g., Kindler syndrome).

In *systemic sclerosis (scleroderma)* the dilated blood vessels have a unique configuration and are known as *mat telangiectasias*. The lesions

TABLE 54-8 Causes of Telangiectasias

I. Primary cutaneous disorders
- A. Linear/branching
  - 1. Acne rosacea (face)
  - 2. Actinically damaged skin (face, neck, V of chest)
  - 3. Venous hypertension (legs)
  - 4. Generalized essential telangiectasia
  - 5. Cutaneous collagenous vasculopathy
  - 6. Within basal cell carcinomas or cutaneous lymphoma
- B. Poikiloderma
  - 1. Ionizing radiation[a]
- C. Spider angioma
  - 1. Idiopathic
  - 2. Pregnancy

II. Systemic diseases
- A. Linear/branching
  - 1. Carcinoid (head, neck, upper trunk)
  - 2. Ataxia-telangiectasia (bulbar conjunctivae, head and neck)
  - 3. Mastocytosis (within lesions)
- B. Poikiloderma
  - 1. Dermatomyositis, lupus erythematosus
  - 2. Mycosis fungoides, patch stage
  - 3. Genodermatoses, e.g., xeroderma pigmentosum, Kindler syndrome
- C. Mat
  - 1. Systemic sclerosis (scleroderma)
- D. Cuticular/periungual
  - 1. Lupus erythematosus
  - 2. Systemic sclerosis (scleroderma)
  - 3. Dermatomyositis
  - 4. Hereditary hemorrhagic telangiectasia
- E. Papular
  - 1. Hereditary hemorrhagic telangiectasia
- F. Spider angioma
  - 1. Cirrhosis

[a]Becoming less common.

are broad macules that usually measure 2–7 mm in diameter but occasionally are larger. Mats have a polygonal or oval shape, and their erythematous color may appear uniform, but, upon closer inspection, the erythema is the result of delicate telangiectasias. The most common locations for mat telangiectasias are the face, oral mucosa, and hands—peripheral sites that are prone to intermittent ischemia. The limited form of systemic sclerosis, often referred to as the CREST (*c*alcinosis cutis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasia) variant **(Chap. 353)**, is associated with a chronic course and anticentromere antibodies. Mat telangiectasias are an important clue to the diagnosis of this variant as well as the diffuse form of systemic sclerosis because they may be the only cutaneous finding.

Cuticular telangiectasias are pathognomonic signs of the three major autoimmune connective tissue diseases: *lupus erythematosus*, *systemic sclerosis*, and *DM*. They are easily visualized by the naked eye and occur in at least two-thirds of these patients. In both DM and lupus, there is associated nailfold erythema, and in DM, the erythema is often accompanied by "ragged" cuticles and fingertip tenderness. Under 10× magnification, the blood vessels in the nailfolds of lupus patients are tortuous and resemble "glomeruli," whereas in systemic sclerosis and DM, there is a loss of capillary loops and those that remain are markedly dilated.

In *hereditary hemorrhagic telangiectasia* (Osler-Rendu-Weber disease), the lesions usually appear during adolescence (mucosal) and adulthood (cutaneous) and are most commonly seen on the mucous membranes (nasal, orolabial), face, and distal extremities, including under the nails. They represent arteriovenous (AV) malformations of the dermal microvasculature, are dark red in color, and are usually slightly elevated. When the skin is stretched over an individual lesion, an eccentric punctum with radiating legs is seen. Although the degree of systemic involvement varies in this autosomal dominant disease (due primarily to mutations in either the endoglin or activin receptor–like kinase gene), the major symptoms are recurrent epistaxis and gastrointestinal bleeding. The fact that these mucosal telangiectasias are actually AV communications helps to explain their tendency to bleed.

HYPOPIGMENTATION

(Table 54-9) Disorders of hypopigmentation are often classified as either diffuse or localized. The classic example of *diffuse hypopigmentation* is *oculocutaneous albinism* (OCA). The most common forms are due to mutations in the tyrosinase gene (type I) or the *P* gene (type II); patients with type IA OCA have a total lack of enzyme activity. At birth, different forms of OCA can appear similar—white hair, gray-blue eyes, and pink-white skin. However, the patients with no tyrosinase activity maintain this phenotype, whereas those with decreased activity will acquire some pigmentation of the eyes, hair, and skin as they age. The degree of pigment formation is also a function of racial background, and the pigmentary dilution is more readily apparent when patients are compared to their first-degree relatives. The ocular findings in OCA correlate with the degree of hypopigmentation and include decreased visual acuity, nystagmus, photophobia, strabismus, and a lack of normal binocular vision.

The differential diagnosis of *localized hypomelanosis* includes the following primary cutaneous disorders: *idiopathic guttate hypomelanosis*, *postinflammatory hypopigmentation*, *pityriasis* (*tinea*) *versicolor*, *vitiligo*, *chemical- or drug-induced leukoderma*, *nevus depigmentosus* (see below),

TABLE 54-9 Causes of Hypopigmentation

I. Primary cutaneous disorders
- A. Diffuse
  - 1. Generalized vitiligo[a]
- B. Localized
  - 1. Idiopathic guttate hypomelanosis
  - 2. Postinflammatory
  - 3. Pityriasis (tinea) versicolor
  - 4. Vitiligo[a]
  - 5. Chemical- or drug-induced leukoderma, e.g., topical imiquimod, oral imatinib
  - 6. Nevus depigmentosus
  - 7. Piebaldism[a]

II. Systemic diseases
- A. Diffuse
  - 1. Oculocutaneous albinism[b]
  - 2. Hermansky-Pudlak syndrome[b,c]
  - 3. Chédiak-Higashi syndrome[b,d]
  - 4. Phenylketonuria
- B. Localized
  - 1. Systemic sclerosis (scleroderma)
  - 2. Melanoma-associated leukoderma, spontaneous or immunotherapy-induced
  - 3. Vogt-Koyanagi-Harada syndrome
  - 4. Onchocerciasis
  - 5. Sarcoidosis
  - 6. Cutaneous T cell lymphoma (especially mycosis fungoides)
  - 7. Tuberculoid and indeterminate leprosy
  - 8. Linear nevoid hypopigmentation (hypomelanosis of Ito)[e]
  - 9. Incontinentia pigmenti (stage IV)
  - 10. Tuberous sclerosis
  - 11. Waardenburg syndrome and Shah-Waardenburg syndrome

[a]Absence of melanocytes in areas of leukoderma. [b]Normal number of melanocytes. [c]Platelet storage defect and restrictive lung disease secondary to deposits of ceroid-like material or immunodeficiency; due to mutations in β or δ subunit of adaptor-related protein complex 3 as well as subunits of *b*iogenesis of *l*ysosome-related *o*rganelles *c*omplex (BLOC)-1, 2, and 3. [d]Giant lysosomal granules and recurrent infections. [e]Minority of patients in a nonreferral setting have systemic abnormalities (musculoskeletal, central nervous system, ocular).

TABLE 54-10 Hypopigmentation (Primary Cutaneous Disorders, Localized)

	CLINICAL CHARACTERISTICS	WOOD'S LAMP EXAMINATION (UV-A; PEAK = 365 NM)	SKIN BIOPSY SPECIMEN	PATHOGENESIS	TREATMENT
Idiopathic guttate hypomelanosis	Common; acquired; usually 2–4 mm in diameter Shins and extensor forearms	Less enhancement than vitiligo	Abrupt decrease in epidermal melanin content	Possible somatic mutations as a reflection of aging or UV exposure	None
Postinflammatory hypopigmentation	Can develop within active lesions, as in subacute cutaneous lupus, or after the lesion fades, as in atopic dermatitis	Depends on particular disease Usually less enhancement than in vitiligo	Type of inflammatory infiltrate depends on specific disease	Block in transfer of melanin from melanocytes to keratinocytes could be secondary to edema or decrease in contact time Destruction of melanocytes if inflammatory cells attack basal layer of epidermis	Treat underlying inflammatory disease
Pityriasis (tinea) versicolor	Common disorder Upper trunk and neck (shawl-like distribution), groin Young adults Macules have fine white scale when scratched	Golden fluorescence	Hyphal forms and budding yeast in stratum corneum	Invasion of stratum corneum by the yeast *Malassezia* Yeast is lipophilic and produces C_9 and C_{11} dicarboxylic acids, which *in vitro* inhibit tyrosinase	Selenium sulfide 2.5% shampoo; topical imidazoles; oral triazoles
Vitiligo	Acquired; progressive Symmetric areas of complete pigment loss Periorificial—around mouth, nose, eyes, nipples, umbilicus, anus Other areas—flexor wrists, extensor distal extremities Segmental form is less common—unilateral, dermatomal-like	More apparent Chalk-white	Absence of melanocytes in well-developed lesions Mild inflammation	Autoimmune phenomenon that results in destruction of melanocytes—primarily cellular (circulating skin-homing autoreactive T cells)	Topical glucocorticoids; topical calcineurin inhibitors; UV-B (narrowband); PUVA; JAK inhibitors transplants, if stable; depigmentation (topical MBEH), if widespread and treatment-resistant
Chemical- or drug-induced leukoderma	Similar appearance to vitiligo Often begins on hands when associated with chemical exposure Satellite lesions in areas not exposed to chemicals	More apparent Chalk-white	Decreased number or absence of melanocytes	Exposure to chemicals that selectively destroy melanocytes, in particular phenols and catechols (germicides; rubber products) or ingestion of drugs such as imatinib Release of cellular antigens and activation of circulating lymphocytes may explain satellite phenomenon Possible inhibition of KIT receptor	Avoid exposure to offending agent, then treat as vitiligo Drug-induced variant may undergo repigmentation when medication is discontinued
Piebaldism	Autosomal dominant Congenital, stable White forelock Areas of amelanosis contain normally pigmented and hyperpigmented macules of various sizes Symmetric involvement of central forehead, ventral trunk, and mid regions of upper and lower extremities	Enhancement of leukoderma and hyperpigmented macules	Amelanotic areas—few to no melanocytes	Defect in migration of melanoblasts from neural crest to involved skin or failure of melanoblasts to survive or differentiate in these areas Mutations within the *KIT* protooncogene that encodes the tyrosine kinase receptor for stem cell growth factor (kit ligand)	None; occasionally transplants

Abbreviations: MBEH, monobenzylether of hydroquinone; UV-B, ultraviolet B irradiation; PUVA, psoralens + ultraviolet A irradiation.

and *piebaldism* **(Table 54-10)**. In this group of diseases, the areas of involvement are macules or patches with a decrease or absence of pigmentation. Patients with vitiligo also have an increased incidence of several autoimmune disorders, including Hashimoto's thyroiditis, Graves' disease, pernicious anemia, Addison's disease, uveitis, alopecia areata, chronic mucocutaneous candidiasis, and the autoimmune polyendocrine syndromes (types I and II). Diseases of the thyroid gland are the most frequently associated disorders, occurring in up to 30% of patients with vitiligo. Circulating autoantibodies are often found, and the most common ones are antithyroglobulin, antimicrosomal, and antithyroid-stimulating hormone receptor antibodies.

There are four systemic diseases that should be considered in a patient with skin findings suggestive of vitiligo—*Vogt-Koyanagi-Harada syndrome*, *systemic sclerosis*, *onchocerciasis*, and *melanoma-associated leukoderma*. A history of aseptic meningitis, nontraumatic uveitis, tinnitus, hearing loss, and/or dysacousia points to the diagnosis of the Vogt-Koyanagi-Harada syndrome. In these patients, the face and scalp are the most common locations of pigment loss. The vitiligo-like leukoderma seen in patients with systemic sclerosis has a clinical resemblance to idiopathic vitiligo that has begun to repigment as a result of treatment; that is, perifollicular macules of normal pigmentation are seen within areas of depigmentation. The basis of this leukoderma is unknown; there is no evidence of inflammation in areas of involvement, but it can resolve if the underlying connective tissue disease becomes inactive. In contrast to idiopathic vitiligo, melanoma-associated leukoderma often begins on the trunk, and its appearance,

if spontaneous, should prompt a search for metastatic disease. It is also seen in patients undergoing immunotherapy for melanoma, including ipilimumab, with cytotoxic T lymphocytes presumably recognizing cell surface antigens common to melanoma cells and melanocytes, and is associated with a greater likelihood of a clinical response.

There are two systemic disorders (neurocristopathies) that may have the cutaneous findings of piebaldism (Table 54-9). They are *Shah-Waardenburg syndrome* and *Waardenburg syndrome*. A possible explanation for both disorders is an abnormal embryonic migration or survival of two neural crest–derived elements, one of them being melanocytes and the other myenteric ganglion cells (leading to Hirschsprung disease in Shah-Waardenburg syndrome) or auditory nerve cells (Waardenburg syndrome). The latter syndrome is characterized by congenital sensorineural hearing loss, dystopia canthorum (lateral displacement of the inner canthi but normal interpupillary distance), heterochromic irises, and a broad nasal root, in addition to the piebaldism. The facial dysmorphism can be explained by the neural crest origin of the connective tissues of the head and neck. Patients with Waardenburg syndrome have been shown to have mutations in four genes, including *PAX-3* and *MITF*, all of which encode transcription factors, whereas patients with Hirschsprung disease plus white spotting have mutations in one of three genes—endothelin 3, endothelin B receptor, and *SOX-10*.

In *tuberous sclerosis*, the earliest cutaneous sign is macular hypomelanosis, referred to as an ash leaf spot. These lesions are often present at birth and are usually multiple; however, detection may require Wood's lamp examination, especially in fair-skinned individuals. The pigment within them is reduced, but not absent. The average size is 1–3 cm, and the common shapes are polygonal and lance-ovate. Examination of the patient for additional cutaneous signs such as multiple angiofibromas of the face (adenoma sebaceum), ungual and intraoral fibromas, fibrous cephalic plaques, and connective tissue nevi (shagreen patches) is recommended. It is important to remember that an ash leaf spot on the scalp will result in a circumscribed patch of lightly pigmented hair. Internal manifestations include seizures, intellectual disability, central nervous system (CNS) and retinal hamartomas, pulmonary lymphangioleiomyomatosis (women), renal angiomyolipomas, and cardiac rhabdomyomas. The latter can be detected in up to 60% of children (<18 years) with tuberous sclerosis by echocardiography.

Nevus depigmentosus is a stable, well-circumscribed hypomelanosis that is present at birth. There is usually a single oval or rectangular lesion, but when there are multiple lesions, the possibility of tuberous sclerosis needs to be considered. In *linear nevoid hypopigmentation*, a term that is replacing hypomelanosis of Ito and segmental or systematized nevus depigmentosus, streaks and swirls of hypopigmentation are observed. Up to one-third of patients in a tertiary care setting had associated abnormalities involving the musculoskeletal system (asymmetry), the CNS (seizures and intellectual disability), and the eyes (strabismus and hypertelorism). Chromosomal mosaicism has been detected in these patients, lending support to the hypothesis that the cutaneous pattern is the result of the migration of two clones of primordial melanocytes, each with a different pigment potential.

Localized areas of decreased pigmentation are commonly seen as a result of cutaneous inflammation (Table 54-10) and have been observed in the skin overlying active lesions of sarcoidosis (see "Papulonodular Skin Lesions," below) as well as in CTCL. Cutaneous infections also present as disorders of hypopigmentation, and in *tuberculoid leprosy*, there are a few asymmetric patches of hypomelanosis that have associated anesthesia, anhidrosis, and alopecia. Biopsy specimens of the palpable border show dermal granulomas that contain rare, if any, *Mycobacterium leprae* organisms.

HYPERPIGMENTATION

(Table 54-11) Disorders of hyperpigmentation are also divided into two major groups—localized and diffuse. The localized forms are due to an epidermal alteration, a proliferation of melanocytes, or an increase in pigment production. Both seborrheic keratoses and acanthosis nigricans belong to the first group. *Seborrheic keratoses* are common lesions, but in one rare clinical setting, they are a sign of systemic disease, and that setting is the sudden appearance of multiple lesions, often with an

TABLE 54-11 Causes of Hyperpigmentation

- I. Primary cutaneous disorders
  - A. Localized
    - 1. Epidermal alteration
      - a. Seborrheic keratosis
      - b. Pigmented actinic keratosis
    - 2. Proliferation of melanocytes
      - a. Lentigo
      - b. Melanocytic nevus (mole)
      - c. Melanoma
    - 3. Increased pigment production
      - a. Ephelide (freckle)
      - b. Café au lait macule
      - c. Postinflammatory hyperpigmentation
      - d. Melasma
    - 4. Dermal pigmentation
      - a. Fixed drug eruption
  - B. Localized and diffuse
    - 1. Drugs (e.g., minocycline, hydroxychloroquine, bleomycin)
- II. Systemic diseases
  - A. Localized
    - 1. Epidermal alteration
      - a. Seborrheic keratoses (sign of Leser-Trélat)
      - b. Acanthosis nigricans (insulin resistance, other endocrine disorders, paraneoplastic)
    - 2. Proliferation of melanocytes
      - a. Lentigines (Peutz-Jeghers and LEOPARD/Noonan with multiple lentigines syndromes; xeroderma pigmentosum)
      - b. Melanocytic nevi (Carney complex [LAMB and NAME syndromes])[a]
    - 3. Increased pigment production
      - a. Café au lait macules (neurofibromatosis, McCune-Albright syndrome[b])
      - b. Urticaria pigmentosa[c]
    - 4. Dermal pigmentation
      - a. Incontinentia pigmenti (stage III)
      - b. Dyskeratosis congenita
  - B. Diffuse
    - 1. Endocrinopathies
      - a. Addison's disease
      - b. Nelson syndrome
      - c. Ectopic ACTH syndrome
      - d. Hyperthyroidism
    - 2. Metabolic
      - a. Porphyria cutanea tarda
      - b. Hemochromatosis
      - c. Vitamin B_{12}, folate deficiency
      - d. Pellagra
      - e. Malabsorption, including Whipple's disease
    - 3. Melanosis secondary to metastatic melanoma
    - 4. Autoimmune
      - a. Biliary cirrhosis
      - b. Systemic sclerosis (scleroderma)
      - c. POEMS syndrome
      - d. Eosinophilia-myalgia syndrome[d]
    - 5. Drugs (e.g. cyclophosphamide) and metals (e.g. silver)

[a]Also lentigines. [b]Polyostotic fibrous dysplasia. [c]See also "Papulonodular Skin Lesions." [d]Late 1980s.

Abbreviations: LAMB, *l*entigines, *a*trial *m*yxomas, *m*ucocutaneous myxomas, and *b*lue nevi; LEOPARD, *l*entigines, *E*CG abnormalities, ocular hypertelorism, *p*ulmonary stenosis and subaortic valvular stenosis, *a*bnormal genitalia, *r*etardation of growth, and *d*eafness (sensorineural); NAME, *n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and ephelides (freckles); POEMS, *p*olyneuropathy, organomegaly, endocrinopathies, *M*-protein, and skin changes.

inflammatory base and in association with acrochordons (skin tags) and acanthosis nigricans. This is termed the *sign of Leser-Trélat* and alerts the clinician to search for an internal malignancy. *Acanthosis nigricans* can also be a reflection of an internal malignancy, most commonly of the gastrointestinal tract, and it appears as velvety hyperpigmentation, primarily in flexural areas. However, in the majority of patients, acanthosis nigricans is associated with obesity and insulin resistance, although it may be a reflection of an endocrinopathy such as acromegaly, Cushing's syndrome, polycystic ovary syndrome, or insulin-resistant diabetes mellitus (type A, type B, and lipodystrophic forms).

A proliferation of melanocytes results in the following pigmented lesions: *lentigo*, *melanocytic nevus*, and *melanoma* **(Chap. 72)**. In an adult, the majority of lentigines are related to sun exposure, which explains their distribution. However, in the Peutz-Jeghers and LEOPARD (*l*entigines; *E*CG abnormalities, primarily conduction defects; *o*cular hypertelorism; *p*ulmonary stenosis and subaortic valvular stenosis; *a*bnormal genitalia [cryptorchidism, hypospadias]; *r*etardation of growth; and *d*eafness [sensorineural]) syndromes, lentigines do serve as a clue to systemic disease. In *LEOPARD/Noonan with multiple lentigines syndrome*, hundreds of lentigines develop during childhood and are scattered over the entire surface of the body. The lentigines in patients with *Peutz-Jeghers syndrome* are located primarily around the nose and mouth, on the hands and feet, and within the oral cavity. While the pigmented macules on the face may fade with age, the oral lesions persist. However, similar intraoral lesions are also seen in Addison's disease, in Laugier-Hunziker syndrome (no internal manifestations), and as a normal finding in darkly pigmented individuals. Patients with this autosomal dominant syndrome (due to mutations in a novel serine threonine kinase gene) have multiple benign polyps of the gastrointestinal tract, testicular or ovarian tumors, and an increased risk of developing gastrointestinal (primarily colon) and pancreatic cancers.

In the *Carney complex,* numerous lentigines are also seen, but they are in association with cardiac myxomas. This autosomal dominant disorder is also known as the *LAMB* (*l*entigines, *a*trial myxomas, *m*ucocutaneous myxomas, and *b*lue nevi) *syndrome* or *NAME* (*n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and *e*phelides [freckles]) *syndrome*. These patients can also have evidence of endocrine overactivity in the form of Cushing's syndrome (pigmented nodular adrenocortical disease) and acromegaly.

The third type of localized hyperpigmentation is due to a local increase in pigment production, and it includes *ephelides* and *café au lait macules* (CALMs). While a single CALM can be seen in up to 10% of the normal population, the presence of multiple or large-sized CALMs raises the possibility of an associated genodermatosis, for example, neurofibromatosis (NF) or McCune-Albright syndrome. *CALMs* are flat, uniformly brown in color (usually two shades darker than uninvolved skin), and can vary in size from 0.5 to 12+ cm. More than 90% of adult patients with *type I NF* will have six or more CALMs measuring ≥1.5 cm in diameter. Additional findings are discussed in the section on neurofibromas (see "Papulonodular Skin Lesions," below). In comparison with NF, the CALMs in patients with *McCune-Albright syndrome* (polyostotic fibrous dysplasia with precocious puberty in females due to mosaicism for an activating mutation in a G protein [$G_s\alpha$] gene) are usually larger, are more irregular in outline, and tend to respect the midline.

In incontinentia pigmenti, dyskeratosis congenita, and bleomycin pigmentation, the areas of localized hyperpigmentation form a pattern—swirled in the first, reticulated in the second, and flagellate in the third. In *dyskeratosis congenita*, atrophic reticulated hyperpigmentation is seen on the neck, trunk, and thighs and is accompanied by nail dystrophy, pancytopenia, and leukoplakia of the oral and anal mucosae. The latter often develops into squamous cell carcinoma. In addition to the flagellate pigmentation (linear streaks) on the trunk, patients receiving bleomycin often have hyperpigmentation overlying the elbows, knees, and small joints of the hand.

Localized hyperpigmentation is seen as a side effect of several other *systemic medications*, including those that produce fixed drug reactions (nonsteroidal anti-inflammatory drugs [NSAIDs], sulfonamides, barbiturates, and tetracyclines) and those that can complex with melanin or iron (antimalarials and minocycline). Fixed drug eruptions recur in the exact same location as circular areas of erythema that can become bullous and then resolve as brown macules. The eruption usually appears within hours of re-administration of the offending agent, and common locations include the genitalia, distal extremities, and perioral region. Chloroquine and hydroxychloroquine produce gray-brown to blue-black discoloration of the shins, hard palate, and face, while blue macules (often misdiagnosed as bruises) can be seen on the lower extremities and in sites of inflammation with prolonged minocycline administration. Estrogen in oral contraceptives can induce melasma—symmetric brown patches on the face, especially the cheeks, upper lip, and forehead. Similar changes are seen in pregnancy and in patients receiving phenytoin.

In the diffuse forms of hyperpigmentation, the darkening of the skin may be of equal intensity over the entire body or may be accentuated in sun-exposed areas. The causes of diffuse hyperpigmentation can be divided into four major groups—endocrine, metabolic, autoimmune, and drugs. The endocrinopathies that frequently have associated hyperpigmentation include *Addison's disease*, *Nelson's syndrome*, and *ectopic ACTH syndrome*. In these diseases, the increased pigmentation is diffuse but is accentuated in sun-exposed areas, as well as in the palmar creases, sites of friction, and scars. An overproduction of the pituitary hormones α-MSH (melanocyte-stimulating hormone) and ACTH can lead to an increase in melanocyte activity. These peptides are products of the proopiomelanocortin gene and exhibit homology, for example, α-MSH and ACTH share 13 amino acids. A minority of patients with Cushing's disease or hyperthyroidism have generalized hyperpigmentation.

The metabolic causes of hyperpigmentation include *porphyria cutanea tarda* (PCT), *hemochromatosis*, *vitamin B_{12} deficiency*, *folic acid deficiency*, *pellagra*, and *malabsorption*, including *Whipple's disease*. In patients with PCT (see "Vesicles/Bullae," below), the skin darkening is seen in sun-exposed areas and is a reflection of the photoreactive properties of porphyrins. The increased level of iron in the skin of patients with type 1 hemochromatosis stimulates melanin pigment production and leads to the classic bronze color. Patients with pellagra have a brown discoloration of the skin, especially in sun-exposed areas, as a result of nicotinic acid (niacin) deficiency. In the areas of increased pigmentation, there is a thin, varnish-like scale. These changes are also seen in patients who are vitamin B_6 deficient, have functioning carcinoid tumors (increased consumption of niacin), or take isoniazid. Approximately 50% of the patients with Whipple's disease have an associated generalized hyperpigmentation in association with diarrhea, weight loss, arthritis, and lymphadenopathy. A diffuse, slate-blue to gray-brown color is seen in patients with *melanosis secondary to metastatic melanoma*. The color reflects widespread deposition of melanin within the dermis as a result of the high concentration of circulating melanin precursors.

Of the autoimmune diseases associated with diffuse hyperpigmentation, *biliary cirrhosis* and *systemic sclerosis* are the most common, and occasionally, both disorders are seen in the same patient. The skin is dark brown in color, especially in sun-exposed areas. In biliary cirrhosis, the hyperpigmentation is accompanied by pruritus, jaundice, and xanthomas, whereas in systemic sclerosis, it is accompanied by sclerosis of the extremities, face, and, less commonly, the trunk. Additional clues to the diagnosis of systemic sclerosis are mat and cuticular telangiectasias, calcinosis cutis, Raynaud's phenomenon, and distal ulcerations (see "Telangiectasias," above). The differential diagnosis of cutaneous sclerosis with hyperpigmentation includes POEMS (*p*olyneuropathy; *o*rganomegaly [liver, spleen, lymph nodes]; *e*ndocrinopathies [impotence, gynecomastia]; *M*-protein; and *s*kin changes) syndrome. The skin changes include hyperpigmentation, induration, hypertrichosis, angiomas, clubbing, and facial lipoatrophy.

Diffuse hyperpigmentation that is due to drugs or metals can result from one of several mechanisms—induction of melanin pigment formation, complexing of the drug or its metabolites to melanin, and deposits of the drug in the dermis. Busulfan, cyclophosphamide, 5-fluorouracil, and inorganic arsenic induce pigment production. Complexes containing melanin or iron plus the drug or its metabolites are seen in patients receiving minocycline, and a diffuse, brown-gray,

muddy appearance within sun-exposed areas may develop, in addition to pigmentation of the mucous membranes, teeth, nails, bones, and thyroid. Administration of amiodarone can result in both a phototoxic eruption (exaggerated sunburn) and/or a slate-gray to violaceous discoloration of sun-exposed skin. Biopsy specimens of the latter show yellow-brown granules in dermal macrophages, which represent intralysosomal accumulations of lipids, amiodarone, and its metabolites. Actual deposits of a particular drug or metal in the skin are seen with silver (argyria), where the skin appears blue-gray in color; gold (chrysiasis), where the skin has a brown to blue-gray color; and clofazimine, where the skin appears reddish brown. The associated pigmentation is accentuated in sun-exposed areas, and discoloration of the eye is seen with gold (sclerae) and clofazimine (conjunctivae).

VESICLES/BULLAE

(Table 54-12) Depending on their size, cutaneous blisters are referred to as *vesicles* (<1 cm) or *bullae* (>1 cm). The primary autoimmune blistering disorders include *pemphigus vulgaris*, *pemphigus foliaceus*, *paraneoplastic pemphigus*, *bullous pemphigoid*, *gestational pemphigoid*, *cicatricial pemphigoid*, *epidermolysis bullosa acquisita*, *linear IgA bullous dermatosis* (*LABD*), and *dermatitis herpetiformis* **(Chap. 55)**.

Vesicles and bullae are also seen in *contact dermatitis*, both allergic and irritant forms **(Chap. 53)**. When there is a linear arrangement of vesicular lesions, an exogenous cause or herpes zoster should be suspected. Bullous disease secondary to the ingestion of drugs can take one of several forms, including phototoxic eruptions, isolated bullae, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) **(Chap. 56)**. Clinically, phototoxic eruptions resemble an exaggerated sunburn with diffuse erythema and bullae in sun-exposed areas. The most commonly associated drugs are doxycycline, quinolones, thiazides, NSAIDs, voriconazole, and psoralens. The development of a phototoxic eruption is dependent on the doses of both the drug and ultraviolet (UV)-A irradiation.

Toxic epidermal necrolysis is characterized by bullae that arise on widespread areas of tender erythema and then slough. This results in large areas of denuded skin. The associated morbidity, such as sepsis, and mortality rates are relatively high and are a function of the extent of epidermal necrosis. In addition, these patients may also have involvement of the mucous membranes and respiratory and intestinal tracts. Drugs are the primary cause of TEN, and the most common offenders are aromatic anticonvulsants (phenytoin, barbiturates, carbamazepine), sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Severe acute graft-versus-host disease (grade 4), vancomycin-induced LABD, and flares of lupus can also resemble TEN.

In *erythema multiforme* (EM), the primary lesions are pink-red macules and edematous papules, the centers of which may become vesicular. In contrast to a morbilliform exanthem, the clue to the diagnosis of EM, and especially SJS, is the development of a "dusky" violet color in the center of the lesions. Target lesions are also characteristic of EM and arise as a result of active centers and borders in combination with centrifugal spread. However, target lesions need not be present to make the diagnosis of EM.

EM has been subdivided into two major groups: (1) EM minor due to herpes simplex virus (HSV); and (2) EM major due to HSV, *Mycoplasma pneumonia*, or, occasionally, drugs. Involvement of the mucous membranes (ocular, nasal, oral, and genital) is seen more commonly in the latter form. Hemorrhagic crusts of the lips are characteristic of EM major and SJS as well as herpes simplex, pemphigus vulgaris, and paraneoplastic pemphigus. Fever, malaise, myalgias, sore throat, and cough may precede or accompany the eruption. The lesions of EM usually resolve over 2–4 weeks but may be recurrent, especially when due to HSV. In addition to HSV (in which lesions usually appear 7–12 days after the viral eruption), EM can also follow vaccinations, radiation therapy, and exposure to environmental toxins, including the oleoresin in poison ivy.

Induction of SJS is most often due to drugs, especially sulfonamides, phenytoin, barbiturates, lamotrigine, aminopenicillins, nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine), and carbamazepine. Widespread dusky macules and significant mucosal involvement are characteristic of SJS, and the cutaneous lesions may or may not develop epidermal detachment. If the latter occurs, by definition, it is limited to <10% of the body surface area (BSA). Greater involvement leads to the diagnosis of SJS/TEN overlap (10–30% BSA) or TEN (>30% BSA).

In addition to primary blistering disorders and hypersensitivity reactions, bacterial and viral infections can lead to vesicles and bullae. The most common infectious agents are HSV **(Chap. 187)**, varicella-zoster virus **(Chap. 188)**, and *S. aureus* **(Chap. 142)**.

Staphylococcal scalded-skin syndrome (SSSS) and *bullous impetigo* are two blistering disorders associated with staphylococcal (phage group II) infection. In SSSS, the initial findings are redness and tenderness of the central face, neck, trunk, and intertriginous zones. This is followed by short-lived flaccid bullae and a slough or exfoliation of the superficial epidermis. Crusted areas then develop, characteristically around the mouth in a radial pattern. SSSS is distinguished from TEN by the following features: younger age group (primarily infants), more superficial site of blister formation, no oral lesions, shorter course, lower morbidity and mortality rates, and an association with staphylococcal exfoliative toxin ("exfoliatin"), not drugs. A rapid diagnosis of SSSS versus TEN can be made by a frozen section of the blister roof or exfoliative cytology of the blister contents. In SSSS, the site of staphylococcal infection is usually extracutaneous (conjunctivitis, rhinorrhea, otitis media, pharyngitis, tonsillitis), and the cutaneous lesions are sterile,

TABLE 54-12 Causes of Vesicles/Bullae

I. Primary mucocutaneous diseases
  A. Primary blistering diseases (autoimmune)
    1. Pemphigus, foliaceus and vulgaris[a]
    2. Bullous pemphigoid[b]
    3. Gestational pemphigoid[b]
    4. Cicatricial pemphigoid[b]
    5. Dermatitis herpetiformis[b,c]
    6. Linear IgA bullous dermatosis[b]
    7. Epidermolysis bullosa acquisita[b,d]
  B. Secondary blistering diseases
    1. Contact dermatitis[a,b]
    2. Erythema multiforme[e]
    3. Stevens-Johnson syndrome[e]
    4. Toxic epidermal necrolysis[e]
  C. Infections
    1. Varicella-zoster virus[a,f]
    2. Herpes simplex virus[a,f]
    3. Enteroviruses, e.g., hand-foot-and-mouth disease[f]
    4. Staphylococcal scalded-skin syndrome[a,g]
    5. Bullous impetigo[a]
II. Systemic diseases
  A. Autoimmune
    1. Paraneoplastic pemphigus[a]
  B. Infections
    1. Cutaneous emboli[b]
  C. Metabolic
    1. Diabetic bullae[a,b]
    2. Porphyria cutanea tarda[b]
    3. Porphyria variegata[b]
    4. Pseudoporphyria[b]
    5. Bullous dermatosis of hemodialysis[b]
  D. Ischemia
    1. Coma bullae
  E. Secondary blistering diseases
    1. Toxic epidermal necrolysis[e] (respiratory and GI tracts can be involved)

[a]Intraepidermal. [b]Subepidermal. [c]Associated with gluten enteropathy. [d]Associated with inflammatory bowel disease. [e]Degeneration of cells within the basal layer of the epidermis can give impression split is subepidermal. [f]Also systemic. [g]In adults, associated with renal failure and immunocompromised state.

whereas in bullous impetigo, the skin lesions are the site of infection. Impetigo is more localized than SSSS and usually presents with honey-colored crusts. Occasionally, superficial purulent blisters also form. *Cutaneous emboli* from gram-negative infections may present as isolated bullae, but the base of the lesion is purpuric or necrotic, and it may develop into an ulcer (see "Purpura," below).

Several metabolic disorders are associated with blister formation, including diabetes mellitus, renal failure, and porphyria. Local hypoxemia secondary to decreased cutaneous blood flow can also produce blisters, which explains the presence of bullae over pressure points in comatose patients (coma bullae). In *diabetes mellitus*, tense bullae with clear sterile viscous fluid arise on normal skin. The lesions can be as large as 6 cm in diameter and are located on the distal extremities. There are several types of porphyria, but the most common form with cutaneous findings is *porphyria cutanea tarda* (PCT). In sun-exposed areas (primarily the hands), the skin is very fragile, with trauma leading to erosions mixed with tense vesicles. These lesions then heal with scarring and formation of milia; the latter are firm, 1- to 2-mm white or yellow papules that represent epidermoid inclusion cysts. Associated findings can include hypertrichosis of the lateral malar region (men) or face (women) and, in sun-exposed areas, hyperpigmentation and firm sclerotic plaques. An elevated level of urinary uroporphyrins confirms the diagnosis and is due to a decrease in uroporphyrinogen decarboxylase activity. PCT can be exacerbated by alcohol, hemochromatosis and other forms of iron overload, chlorinated hydrocarbons, hepatitis C virus and HIV infections, and hepatomas.

The differential diagnosis of PCT includes (1) *porphyria variegata*—the skin signs of PCT plus the systemic findings of acute intermittent porphyria; it has a diagnostic plasma porphyrin fluorescence emission at 626 nm; (2) *drug-induced pseudoporphyria*—the clinical and histologic findings are similar to PCT, but porphyrins are normal; etiologic agents include naproxen and other NSAIDs, furosemide, tetracycline, and voriconazole; (3) *bullous dermatosis of hemodialysis*—the same appearance as PCT, but porphyrins are usually normal or occasionally borderline elevated; patients have chronic renal failure and are on hemodialysis; (4) *PCT associated with hepatomas and hemodialysis;* and (5) *epidermolysis bullosa acquisita* **(Chap. 55)**.

EXANTHEMS

(Table 54-13) Exanthems are characterized by an acute generalized eruption. The most common presentation is erythematous macules and papules (morbilliform) and less often confluent blanching erythema (scarlatiniform). *Morbilliform* eruptions are usually due to either drugs or viral infections. For example, up to 5% of patients receiving penicillins, sulfonamides, phenytoin, or nevirapine will develop a maculopapular eruption. Accompanying signs may include pruritus, fever, eosinophilia, and transient lymphadenopathy. Similar maculopapular eruptions are seen in the classic childhood viral exanthems, including (1) *rubeola* (measles)—a prodrome of coryza, cough, and conjunctivitis followed by Koplik's spots on the buccal mucosa; the eruption begins behind the ears, at the hairline, and on the forehead and then spreads down the body, often becoming confluent; (2) *rubella*—the eruption begins on the forehead and face and then spreads down the body; it resolves in the same order and is associated with retroauricular and suboccipital lymphadenopathy; and (3) *erythema infectiosum* (fifth disease)—erythema of the cheeks is followed by a reticulated pattern on the extremities; it is secondary to a parvovirus B19 infection, and an associated arthritis is seen in adults.

Both measles and rubella can occur in unvaccinated adults, and an atypical form of measles is seen in adults immunized with either killed measles vaccine or killed vaccine followed in time by live vaccine. In contrast to classic measles, the eruption of atypical measles begins on the palms, soles, wrists, and ankles, and the lesions may become purpuric. The patient with atypical measles can have pulmonary involvement and be quite ill. Rubelliform and roseoliform eruptions are also associated with *Epstein-Barr virus* (5–15% of patients), *echovirus*, *coxsackievirus*, *cytomegalovirus*, *adenovirus*, *dengue virus*, *Zika virus*, and *West Nile virus* infections. Detection of specific IgM antibodies or fourfold elevations in IgG antibodies often allows the proper diagnosis, but polymerase chain reaction (PCR) is gradually replacing serologic assays. Occasionally, a maculopapular drug eruption is a reflection of an underlying viral infection. For example, ~95% of the patients with infectious mononucleosis who are given ampicillin will develop a rash.

TABLE 54-13 Causes of Exanthems

I. Morbilliform
- A. Drugs
- B. Viral
  1. Rubeola (measles)
  2. Rubella
  3. Erythema infectiosum (erythema of cheeks; reticulated on extremities)
  4. Epstein-Barr virus, echovirus, coxsackievirus, CMV, adenovirus, HHV-6/HHV-7[a], dengue virus, Zika virus, Chikungunya, and West Nile virus infections
  5. HIV seroconversion exanthem (plus mucosal ulcerations)
- C. Bacterial
  1. Typhoid fever
  2. Early secondary syphilis
  3. Early *Rickettsia* infections
  4. Early meningococcemia
  5. Ehrlichiosis
- D. Acute graft-versus-host disease
- E. Kawasaki disease

II. Scarlatiniform
- A. Scarlet fever
- B. Toxic shock syndrome
- C. Kawasaki disease
- D. Early staphylococcal scalded-skin syndrome

[a]Primary infection in infants and reactivation in the setting of immunosuppression.

Abbreviations: CMV, cytomegalovirus; HHV, human herpesvirus; HIV, human immunodeficiency virus.

Of note, early in the course of infections with *Rickettsia* and meningococcus, prior to the development of petechiae and purpura, the lesions may be erythematous macules and papules. This is also the case in chickenpox prior to the development of vesicles. Maculopapular eruptions are associated with early *HIV infection*, early secondary *syphilis*, *typhoid fever*, and *acute graft-versus-host disease*. In the last, lesions frequently begin on the dorsal hands and forearms; the macular rose spots of typhoid fever involve primarily the anterior trunk.

The prototypic *scarlatiniform* eruption is seen in *scarlet fever* and is due to an erythrogenic toxin produced by bacteriophage-containing group A β-hemolytic streptococci, most commonly in the setting of pharyngitis. This eruption is characterized by diffuse erythema, which begins on the neck and upper trunk, and red follicular puncta. Additional findings include a white strawberry tongue (white coating with red papillae) followed by a red strawberry tongue (red tongue with red papillae); petechiae of the palate; a facial flush with circumoral pallor; linear petechiae in the antecubital fossae; and desquamation of the involved skin, palms, and soles 5–20 days after onset of the eruption. A similar desquamation of the palms and soles is seen in toxic shock syndrome (TSS), in Kawasaki disease, and after severe febrile illnesses. Certain strains of staphylococci also produce an erythrotoxin that leads to the same clinical findings as in streptococcal scarlet fever, except that the anti-streptolysin O or DNase B titers are not elevated.

In *toxic shock syndrome*, staphylococcal (phage group I) infections produce an exotoxin (TSST-1) that causes the fever and rash as well as enterotoxins. Initially, the majority of cases were reported in menstruating women who were using tampons. However, other sites of infection, including wounds and nasal packing, can lead to TSS. The diagnosis of TSS is based on clinical criteria **(Chap. 142)**, and three of these involve mucocutaneous sites (diffuse erythema of the skin, desquamation of the palms and soles 1–2 weeks after onset of illness, and involvement of the mucous membranes). The latter is characterized as hyperemia of the vagina, oropharynx, or conjunctivae. Similar systemic findings

have been described in *streptococcal toxic shock syndrome* **(Chap. 143)**, and although an exanthem is seen less often than in TSS due to a staphylococcal infection, the underlying infection is often in the soft tissue (e.g., cellulitis).

The cutaneous eruption in *Kawasaki disease* **(Chap. 356)** is polymorphous, but the two most common forms are morbilliform and scarlatiniform. Additional mucocutaneous findings include bilateral conjunctival injection; erythema and edema of the hands and feet followed by desquamation; and diffuse erythema of the oropharynx, red strawberry tongue, and dry fissured lips. This clinical picture can resemble TSS and scarlet fever, but clues to the diagnosis of Kawasaki disease are cervical lymphadenopathy, cheilitis, and thrombocytosis. The most serious associated systemic finding in this disease is coronary aneurysms secondary to arteritis. Scarlatiniform eruptions are also seen in the early phase of SSSS (see "Vesicles/Bullae," above), in young adults with *Arcanobacterium haemolyticum* infection, and as reactions to drugs.

URTICARIA

(Table 54-14) *Urticaria* (hives) are transient lesions that are composed of a central wheal surrounded by an erythematous halo or flare. Individual lesions are round, oval, or figurate and are often pruritic. Acute and chronic urticarias have a wide variety of allergic etiologies and reflect edema in the dermis. Urticarial lesions can also be seen in patients with mastocytosis (urticaria pigmentosa), hypo- or hyperthyroidism, Schnitzler's syndrome, and systemic-onset juvenile idiopathic arthritis (Still's disease). In both juvenile- and adult-onset Still's disease, the lesions coincide with the fever spike, are transient, and are due to dermal infiltrates of neutrophils.

The common *physical urticarias* include dermographism, solar urticaria, cold urticaria, and cholinergic urticaria. Patients with *dermographism* exhibit linear wheals following minor pressure or scratching of the skin. It is a common disorder, affecting ~5% of the population. *Solar urticaria* characteristically occurs within minutes of sun exposure and is a skin sign of one systemic disease—erythropoietic protoporphyria. In addition to the urticaria, these patients have subtle pitted scarring of the nose and hands. *Cold urticaria* is precipitated by exposure to the cold, and therefore exposed areas are usually affected. In occasional patients, the disease is associated with abnormal circulating proteins—more commonly cryoglobulins and less commonly cryofibrinogens. Additional systemic symptoms include wheezing and syncope, thus explaining the need for these patients to avoid swimming in cold water. Autosomal dominantly inherited cold urticaria is associated with dysfunction of cryopyrin. *Cholinergic urticaria* is precipitated by heat, exercise, or emotion and is characterized by small wheals with relatively large flares. It is occasionally associated with wheezing.

Whereas urticarias are the result of dermal edema, subcutaneous edema leads to the clinical picture of *angioedema*. Sites of involvement include the eyelids, lips, tongue, larynx, and gastrointestinal tract as well as the subcutaneous tissue. Angioedema occurs alone or in combination with urticaria, including urticarial vasculitis and the physical urticarias. Both acquired and hereditary (autosomal dominant) forms of angioedema occur **(Chap. 347)**, and in the latter, urticaria is rarely, if ever, seen.

Urticarial vasculitis is an immune complex disease that may be confused with simple urticaria. In contrast to simple urticaria, individual lesions tend to last longer than 24 h and usually develop central petechiae that can be observed even after the urticarial phase has resolved. The patient may also complain of burning rather than pruritus. On biopsy, there is a leukocytoclastic vasculitis of the small dermal blood vessels. Although urticarial vasculitis may be idiopathic in origin, it can be a reflection of an underlying systemic illness such as lupus erythematosus, Sjögren's syndrome, or hereditary complement deficiency. There is a spectrum of urticarial vasculitis that ranges from purely cutaneous to multisystem involvement. The most common systemic signs and symptoms are arthralgias and/or arthritis, nephritis, and crampy abdominal pain, with asthma and chronic obstructive lung disease seen less often. Hypocomplementemia occurs in one- to two-thirds of patients, even in the idiopathic cases. Urticarial vasculitis can also be seen in patients with *hepatitis B* and *hepatitis C* infections, *serum sickness*, and *serum sickness–like illnesses* (e.g., due to cefaclor, minocycline).

TABLE 54-14 Causes of Urticaria and Angioedema

I. Primary cutaneous disorders
A. Acute and chronic urticaria[a]
B. Physical urticaria
1. Dermographism
2. Solar urticaria[b]
3. Cold urticaria[b]
4. Cholinergic urticaria[b]
C. Angioedema (hereditary and acquired)[b,c]
II. Systemic diseases
A. Urticarial vasculitis
B. Hepatitis B or C viral infection
C. Serum sickness
D. Angioedema (hereditary and acquired)

[a]A small minority develop anaphylaxis. [b]Also systemic. [c]Acquired angioedema can be idiopathic, associated with a lymphoproliferative disorder, or due to a drug, e.g., angiotensin-converting enzyme (ACE) inhibitors.

PAPULONODULAR SKIN LESIONS

(Table 54-15) In the *papulonodular diseases*, the lesions are elevated above the surface of the skin and may coalesce to form larger plaques. The location, consistency, and color of the lesions are the keys to their diagnosis; this section is organized on the basis of color.

WHITE LESIONS

In *calcinosis cutis*, there are firm white to white-yellow papules with an irregular surface. When the contents are expressed, a chalky white material is seen. *Dystrophic calcification* is seen at sites of previous inflammation or damage to the skin. It develops in acne scars as well as on the distal extremities of patients with systemic sclerosis and in the subcutaneous tissue and intermuscular fascial planes in DM. The latter is more extensive and is more commonly seen in children. An elevated calcium phosphate product, most commonly due to secondary hyperparathyroidism in the setting of renal failure, can lead to nodules of *metastatic calcinosis cutis*, which tend to be subcutaneous and periarticular. These patients can also develop calcification of muscular arteries and subsequent ischemic necrosis (calciphylaxis). *Osteoma cutis*, in the form of small papules, most commonly occurs on the face of individuals with a history of acne vulgaris, whereas plate-like lesions occur in rare genetic syndromes.

SKIN-COLORED LESIONS

There are several types of skin-colored lesions, including epidermoid inclusion cysts, lipomas, rheumatoid nodules, neurofibromas, angiofibromas, neuromas, and adnexal tumors such as tricholemmomas. Both *epidermoid inclusion cysts* and *lipomas* are very common mobile subcutaneous nodules—the former are rubbery and drain cheeselike material (sebum and keratin) if incised. Lipomas are firm and somewhat lobulated on palpation. When extensive facial epidermoid inclusion cysts develop during childhood or there is a family history of such lesions, the patient should be examined for other signs of Gardner syndrome, including osteomas and desmoid tumors. *Rheumatoid nodules* are firm 0.5- to 4-cm nodules that favor the extensor aspect of joints, especially the elbows. They are seen in ~20% of patients with rheumatoid arthritis and 6% of patients with Still's disease. Biopsies of the nodules show palisading granulomas. Similar lesions that are smaller and shorter-lived are seen in rheumatic fever.

Neurofibromas (benign Schwann cell tumors) are soft papules or nodules that exhibit the "button-hole" sign; that is, they invaginate into the skin with pressure in a manner similar to a hernia. Single lesions are seen in normal individuals, but multiple neurofibromas, usually in combination with six or more CALMs measuring >1.5 cm (see "Hyperpigmentation," above), axillary freckling, and multiple Lisch nodules, are seen in von Recklinghausen's disease (NF type I) **(Chap. 86)**.

TABLE 54-15 Papulonodular Skin Lesions According to Color Groups

- I. White
  - A. Calcinosis cutis
  - B. Osteoma cutis (also skin-colored or blue)
- II. Skin-colored
  - A. Rheumatoid nodules
  - B. Neurofibromas (von Recklinghausen's disease [NF1])
  - C. Angiofibromas (tuberous sclerosis, MEN syndrome, type 1)
  - D. Neuromas (MEN syndrome, type 2b)
  - E. Adnexal tumors
    1. Basal cell carcinomas (basal cell nevus syndrome)
    2. Tricholemmomas (Cowden disease)
  - F. Osteomas (arise in skull and jaw in Gardner syndrome)
  - G. Primary cutaneous disorders
    1. Epidermal inclusion cysts[a]
    2. Lipomas
- III. Pink/translucent[b]
  - A. Amyloidosis, primary systemic
  - B. Papular mucinosis/scleromyxedema
  - C. Multicentric reticulohistiocytosis
- IV. Yellow
  - A. Xanthomas
  - B. Tophi
  - C. Necrobiosis lipoidica
  - D. Pseudoxanthoma elasticum
  - E. Sebaceous adenomas (Muir-Torre syndrome)
- V. Red[b]
  - A. Papules
    1. Angiokeratomas (Fabry disease)
    2. Bacillary angiomatosis (primarily in AIDS)
  - B. Papules/plaques
    1. Cutaneous lupus
    2. Lymphoma cutis
    3. Leukemia cutis
    4. Sweet syndrome
  - C. Nodules
    1. Panniculitis
    2. Medium-sized vessel vasculitis (e.g., cutaneous polyarteritis nodosa)
  - D. Primary cutaneous disorders
    1. Arthropod bites
    2. Cherry hemangiomas
    3. Infections, e.g., streptococcal cellulitis, sporotrichosis
    4. Polymorphous light eruption
    5. Cutaneous lymphoid hyperplasia (lymphocytoma cutis, pseudolymphoma)
- VI. Red-brown[b]
  - A. Sarcoidosis
  - B. Urticaria pigmentosa
  - C. Erythema elevatum diutinum (chronic leukocytoclastic vasculitis)
  - D. Lupus vulgaris
- VII. Blue[b]
  - A. Venous malformations (e.g., blue rubber bleb syndrome)
  - B. Primary cutaneous disorders
    1. Venous lake
    2. Blue nevus
- VIII. Violaceous
  - A. Lupus pernio (sarcoidosis)
  - B. Lymphoma cutis
  - C. Cutaneous lupus
- IX. Purple
  - A. Kaposi's sarcoma
  - B. Angiosarcoma
  - C. Palpable purpura (see Table 54-16)
- X. Brown-black[c]
- XI. Any color
  - A. Metastases

[a]If multiple with childhood onset, consider Gardner syndrome. [b]May have darker hue in more darkly pigmented individuals. [c]See also "Hyperpigmentation."

Abbreviation: MEN, multiple endocrine neoplasia.

In some patients, the neurofibromas are localized and unilateral due to somatic mosaicism.

Angiofibromas are firm pink to skin-colored papules that measure from 3 mm to 1.5 cm in diameter. When multiple lesions are located on the central cheeks (adenoma sebaceum), the patient has tuberous sclerosis or multiple endocrine neoplasia (MEN) syndrome, type 1. The former is an autosomal disorder due to mutations in two different genes, and the associated findings are discussed in the section on ash leaf spots as well as in **Chap. 86**.

Neuromas (benign proliferations of nerve fibers) are also firm, skin-colored papules. They are more commonly found at sites of amputations and in rudimentary polydacyly. However, when there are multiple neuromas on the eyelids, lips, distal tongue, and/or oral mucosa, the patient should be investigated for other signs of MEN syndrome, type 2b. Associated findings include marfanoid habitus, protuberant lips, intestinal ganglioneuromas, and medullary thyroid carcinoma (>75% of patients; **Chap. 381**).

Adnexal tumors are derived from pluripotent cells of the epidermis that can differentiate toward hair, sebaceous, apocrine or eccrine glands, or remain undifferentiated. *Basal cell carcinomas* (BCCs) are examples of adnexal tumors that have little or no evidence of differentiation. Clinically, they are translucent papules with rolled borders, telangiectasias, and central erosion. BCCs commonly arise in sun-damaged skin of the head and neck as well as the upper trunk. When a patient has multiple BCCs, especially prior to age 30, the possibility of the basal cell nevus syndrome should be raised. It is inherited as an autosomal dominant trait and is associated with jaw cysts, palmar and plantar pits, frontal bossing, medulloblastomas, and calcification of the falx cerebri and diaphragma sellae. *Tricholemmomas* are also skin-colored adnexal tumors but differentiate toward hair follicles and can have a wartlike appearance. The presence of multiple tricholemmomas on the face and cobblestoning of the oral mucosa points to the diagnosis of Cowden disease (multiple hamartoma syndrome) due to mutations in the phosphatase and tensin homolog (*PTEN*) gene. Internal organ involvement (in decreasing order of frequency) includes fibrocystic disease and carcinoma of the breast, adenomas and carcinomas of the thyroid, and gastrointestinal polyposis. Keratoses of the palms, soles, and dorsal aspect of the hands are also seen.

PINK LESIONS

The cutaneous lesions associated with primary systemic *amyloidosis* are often pink to pink-orange in color and translucent. Common locations are the face, especially the periorbital and perioral regions, and flexural areas. On biopsy, homogeneous deposits of amyloid are seen in the dermis and in the walls of blood vessels; the latter lead to an increase in vessel wall fragility. As a result, petechiae and purpura develop in clinically normal skin as well as in lesional skin following minor trauma, hence the term *pinch purpura*. Amyloid deposits are also seen in the striated muscle of the tongue and result in macroglossia.

Even though specific mucocutaneous lesions are present in only ~30% of the patients with primary systemic (AL) amyloidosis, the diagnosis can be made via histologic examination of abdominal subcutaneous fat, in conjunction with a serum free light chain assay. By special staining, amyloid deposits are seen around blood vessels or individual fat cells in 40–50% of patients. There are also three forms of amyloidosis that are limited to the skin and that should not be construed as cutaneous lesions of systemic amyloidosis. They are macular amyloidosis (upper back), lichen amyloidosis (usually lower extremities), and nodular amyloidosis. In macular and lichen amyloidosis, the deposits are composed of altered epidermal keratin. Early-onset macular and lichen amyloidosis have been associated with MEN syndrome, type 2a.

Patients with *multicentric reticulohistiocytosis* also have pink-colored papules and nodules on the face and mucous membranes as well as on the extensor surface of the hands and forearms. They have a polyarthritis that can mimic rheumatoid arthritis clinically. On histologic examination, the papules have characteristic giant cells that are not seen in biopsies of rheumatoid nodules. Pink to skin-colored papules that are firm, 2–5 mm in diameter, and often in a linear arrangement are seen in patients with *papular mucinosis*. This disease is also referred to as

scleromyxedema. The latter name comes from the induration of the face and extremities that may accompany the papular eruption. Biopsy specimens of the papules show localized mucin deposition, and serum protein electrophoresis plus immunofixation electrophoresis demonstrates a monoclonal spike of IgG, usually with a λ light chain.

YELLOW LESIONS

Several systemic disorders are characterized by yellow-colored cutaneous papules or plaques—hyperlipidemia (xanthomas), gout (tophi), diabetes (necrobiosis lipoidica), pseudoxanthoma elasticum, and Muir-Torre syndrome (sebaceous tumors). Eruptive xanthomas are the most common form of *xanthomas* and are associated with hypertriglyceridemia (primarily hyperlipoproteinemia types I, IV, and V). Crops of yellow papules with erythematous halos occur primarily on the extensor surfaces of the extremities and the buttocks, and they spontaneously involute with a fall in serum triglycerides. Types II and III result in one or more of the following types of xanthoma: xanthelasma, tendon xanthomas, and plane xanthomas. Xanthelasma are found on the eyelids, whereas tendon xanthomas are frequently associated with the Achilles and extensor finger tendons; plane xanthomas are flat and favor the palmar creases and flexural folds. Tuberous xanthomas are frequently associated with hypercholesterolemia; however, they are also seen in patients with hypertriglyceridemia and are found most frequently over the large joints or hand. Biopsy specimens of xanthomas show collections of lipid-containing macrophages (foam cells).

Patients with several disorders, including biliary cirrhosis, can have a secondary form of hyperlipidemia with associated tuberous and plane xanthomas. However, patients with plasma cell dyscrasias have *normolipemic plane xanthomas*. This latter form of xanthoma may be ≥12 cm in diameter and is most frequently seen on the neck, upper trunk, and flexural folds. It is important to note that the most common setting for eruptive xanthomas is uncontrolled diabetes mellitus. The least specific sign for hyperlipidemia is xanthelasma, because at least 50% of the patients with this finding have normal lipid profiles.

In *tophaceous gout*, there are deposits of monosodium urate in the skin around the joints, particularly those of the hands and feet. Additional sites of *tophi* formation include the helix of the ear and the olecranon and prepatellar bursae. The lesions are firm, yellow to yellow-white in color, and occasionally discharge a chalky material. Their size varies from 1 mm to 7 cm, and the diagnosis can be established by polarized light microscopy of the aspirated contents of a tophus. Lesions of *necrobiosis lipoidica* are found primarily on the shins (90%), and patients can have diabetes mellitus or develop it subsequently. Characteristic findings include a central yellow color, atrophy (transparency), telangiectasias, and a red to red-brown border. Ulcerations can also develop within the plaques. Biopsy specimens show necrobiosis of collagen and granulomatous inflammation.

In *pseudoxanthoma elasticum* (PXE), due to mutations in the gene *ABCC6*, there is an abnormal deposition of calcium on the elastic fibers of the skin, eye, and blood vessels. In the skin, the flexural areas such as the neck, axillae, antecubital fossae, and inguinal area are the primary sites of involvement. Yellow papules coalesce to form reticulated plaques that have an appearance similar to that of plucked chicken skin. In severely affected skin, hanging, redundant folds develop. Biopsy specimens of involved skin show swollen and irregularly clumped elastic fibers with deposits of calcium. In the eye, the calcium deposits in Bruch's membrane lead to angioid streaks and choroiditis; in the arteries of the heart, kidney, gastrointestinal tract, and extremities, the deposits lead to angina, hypertension, gastrointestinal bleeding, and claudication, respectively.

Adnexal tumors that have differentiated toward sebaceous glands include sebaceous adenoma, sebaceous carcinoma, and sebaceous hyperplasia. Except for sebaceous hyperplasia, which is commonly seen on the face, these tumors are fairly rare. Patients with Muir-Torre syndrome have one or more *sebaceous adenoma(s)*, and they can also have sebaceous carcinomas and sebaceous hyperplasia as well as keratoacanthomas. The internal manifestations of Muir-Torre syndrome include *multiple* carcinomas of the gastrointestinal tract (primarily colon) as well as cancers of the genitourinary tract.

RED LESIONS

Cutaneous lesions that are red in color have a wide variety of etiologies; in an attempt to simplify their identification, they will be subdivided into papules, papules/plaques, and subcutaneous nodules. Common red papules include *arthropod bites* and *cherry hemangiomas*; the latter are small, bright-red, dome-shaped papules that represent a benign proliferation of capillaries. In patients with AIDS **(Chap. 197)**, the development of multiple red hemangioma-like lesions points to bacillary angiomatosis, and biopsy specimens show clusters of bacilli that stain positively with the Warthin-Starry stain; the pathogens have been identified as *Bartonella henselae* and *Bartonella quintana*. Disseminated visceral disease is seen primarily in immunocompromised hosts but can occur in immunocompetent individuals.

Multiple *angiokeratomas* are seen in Fabry disease, an X-linked recessive lysosomal storage disease that is due to a deficiency of α-galactosidase A. The lesions are red to red-blue in color and can be quite small in size (1–3 mm), with the most common location being the lower trunk. Associated findings include chronic renal disease, peripheral neuropathy, and corneal opacities (cornea verticillata). Electron photomicrographs of angiokeratomas and clinically normal skin demonstrate lamellar lipid deposits in fibroblasts, pericytes, and endothelial cells that are diagnostic of this disease. Widespread acute eruptions of erythematous papules are discussed in the section on exanthems.

There are several infectious diseases that present as erythematous papules or nodules in a lymphocutaneous or sporotrichoid pattern, that is, in a linear arrangement along the lymphatic channels. The two most common etiologies are *Sporothrix schenckii* (sporotrichosis) and the atypical mycobacterium *Mycobacterium marinum*. The organisms are introduced as a result of trauma, and a primary inoculation site is often seen in addition to the lymphatic nodules. Additional causes include *Nocardia*, *Leishmania*, and other atypical mycobacteria and dimorphic fungi; culture or PCR of lesional tissue will aid in the diagnosis.

The diseases that are characterized by erythematous plaques with scale are reviewed in the papulosquamous section, and the various forms of dermatitis are discussed in the section on erythroderma. Additional disorders in the differential diagnosis of red papules/plaques include *cellulitis*, *polymorphous light eruption* (PMLE), *cutaneous lymphoid hyperplasia* (lymphocytoma cutis), *cutaneous lupus*, *lymphoma cutis*, and *leukemia cutis*. The first three diseases represent primary cutaneous disorders, although cellulitis may be accompanied by a bacteremia. PMLE is characterized by erythematous papules and plaques in a primarily sun-exposed distribution—dorsum of the hand, extensor forearm, and upper trunk. Lesions follow exposure to UV-B and/or UV-A, and in higher latitudes, PMLE is most severe in the late spring and early summer. A process referred to as "hardening" occurs with continued UV exposure, and the eruption fades, but in temperate climates, it recurs the next spring. PMLE must be differentiated from cutaneous lupus, and this is accomplished by observation of the natural history, histologic examination, and sometimes direct immunofluorescence of the lesions. Cutaneous lymphoid hyperplasia (pseudolymphoma) is a *benign* polyclonal proliferation of lymphocytes within the skin that presents as infiltrated pink-red to red-purple papules and plaques; it must be distinguished from lymphoma cutis.

Several types of red plaques are seen in patients with systemic *lupus*, including (1) erythematous urticarial plaques across the cheeks and nose in the classic butterfly rash; (2) erythematous discoid lesions with fine or "carpet-tack" scale, telangiectasias, central hypopigmentation, peripheral hyperpigmentation, follicular plugging, and atrophy located on the scalp, face, external ears, arms, and upper trunk; and (3) psoriasiform or annular lesions of subacute cutaneous lupus with hypopigmented centers located primarily on the extensor arms and upper trunk. Additional mucocutaneous findings include (1) a violaceous flush on the face and V of the neck; (2) photosensitivity; (3) urticarial vasculitis (see "Urticaria," above); (4) lupus panniculitis (see below); (5) diffuse alopecia; (6) alopecia secondary to discoid lesions; (7) cuticular telangiectasias and erythema; (8) EM- or TEN-like lesions that may become bullous; (9) oral or nasal ulcers; (10) livedo reticularis; and (11) distal ulcerations secondary to Raynaud's phenomenon, vasculitis, or livedoid vasculopathy. Patients with only discoid lesions

usually have the form of lupus that is limited to the skin. However, up to 10–15% of these patients eventually develop systemic lupus. Direct immunofluorescence of involved skin, in particular discoid lesions, shows deposits of IgG or IgM and C3 in a granular distribution along the dermal-epidermal junction.

In *lymphoma cutis*, there is a clonal proliferation of malignant lymphocytes within the skin, and the clinical appearance resembles that of cutaneous lymphoid hyperplasia—infiltrated pink-red to red-purple papules and plaques. Lymphoma cutis can occur anywhere on the surface of the skin, whereas the sites of predilection for lymphocytomas include the malar ridge, tip of the nose, and earlobes. Patients with non-Hodgkin's lymphomas have specific cutaneous lesions more often than those with Hodgkin's disease, and, occasionally, the skin nodules precede the development of extracutaneous non-Hodgkin's lymphoma or represent the only site of involvement (e.g., primary cutaneous B cell lymphoma). Arcuate lesions are sometimes seen in lymphoma and lymphocytoma cutis as well as in CTCL. *Adult T cell leukemia/lymphoma* that develops in association with HTLV-1 infection is characterized by cutaneous plaques, hypercalcemia, and circulating CD25+ lymphocytes. *Leukemia cutis* has the same appearance as lymphoma cutis, and specific lesions are seen more commonly in monocytic leukemias than in lymphocytic or granulocytic leukemias. Cutaneous chloromas (granulocytic sarcomas) may precede the appearance of circulating blasts in acute myelogenous leukemia and, as such, represent a form of aleukemic leukemia cutis.

Sweet syndrome is characterized by pink-red to red-brown edematous plaques that are frequently painful and occur primarily on the head, neck, and upper extremities. The patients also have fever, neutrophilia, and a dense dermal infiltrate of neutrophils in the lesions. In ~10% of the patients, there is an associated malignancy, most commonly acute myelogenous leukemia. Sweet syndrome has also been reported with inflammatory bowel disease, systemic lupus erythematosus, and solid tumors (primarily of the genitourinary tract) as well as drugs (e.g., all-*trans*-retinoic acid, granulocyte colony-stimulating factor [G-CSF]). The differential diagnosis includes neutrophilic eccrine hidradenitis; bullous forms of pyoderma gangrenosum; and, occasionally, cellulitis. Extracutaneous sites of involvement include joints, muscles, eyes, kidneys (proteinuria, occasionally glomerulonephritis), and lungs (neutrophilic infiltrates). The idiopathic form of Sweet syndrome is seen more often in women, following a respiratory tract infection.

Common causes of erythematous subcutaneous nodules include inflamed epidermoid inclusion cysts, acne cysts, and furuncles. *Panniculitis*, an inflammation of the fat, also presents as subcutaneous nodules and is frequently a sign of systemic disease. There are several forms of panniculitis, including erythema nodosum, erythema induratum/nodular vasculitis, lupus panniculitis, lipodermatosclerosis, α_1-antitrypsin deficiency, factitial, and fat necrosis secondary to pancreatic disease. Except for erythema nodosum, these lesions may break down and ulcerate or heal with a scar. The shin is the most common location for the nodules of erythema nodosum, whereas the calf is the most common location for lesions of erythema induratum. In erythema nodosum, the nodules are initially red but then develop a blue color as they resolve. Patients with erythema nodosum but no underlying systemic illness can still have fever, malaise, leukocytosis, arthralgias, and/or arthritis. However, the possibility of an underlying illness should be excluded, and the most common associations are streptococcal infections, upper respiratory viral infections, sarcoidosis, and inflammatory bowel disease, in addition to drugs (oral contraceptives, sulfonamides, penicillins, bromides, iodides, BRAF inhibitors). Less common associations include bacterial gastroenteritis (*Yersinia*, *Salmonella*) and coccidioidomycosis followed by tuberculosis, histoplasmosis, brucellosis, and infections with *Chlamydophila pneumoniae*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, or hepatitis B virus.

Erythema induratum and nodular vasculitis have overlapping features clinically and histologically, and whether they represent two separate entities or the ends of a single disease spectrum is a point of debate; in general, the latter is usually idiopathic and the former is associated with the presence of *Mycobacterium tuberculosis* DNA by PCR within skin lesions. The lesions of lupus panniculitis are found primarily on the cheeks, upper arms, and buttocks (sites of abundant fat) and are seen in both the cutaneous and systemic forms of lupus. The overlying skin may be normal, erythematous, or have the changes of discoid lupus. The subcutaneous fat necrosis that is associated with pancreatic disease is presumably secondary to circulating lipases and is seen in patients with pancreatic carcinoma as well as in patients with acute and chronic pancreatitis. In this disorder, there may be an associated arthritis, fever, and inflammation of visceral fat. Histologic examination of deep incisional biopsy specimens will aid in the diagnosis of the particular type of panniculitis.

Subcutaneous erythematous nodules are also seen in cutaneous polyarteritis nodosa and as a manifestation of *systemic vasculitis* when there is involvement of medium-sized vessels, for example, systemic polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis, or granulomatosis with polyangiitis **(Chap. 356)**. Cutaneous polyarteritis nodosa presents with painful subcutaneous nodules and ulcers within a red-purple, netlike pattern of livedo reticularis. The latter is due to slowed blood flow through the superficial horizontal venous plexus. The majority of lesions are found on the lower extremities, and while arthralgias and myalgias may accompany cutaneous polyarteritis nodosa, there is no evidence of systemic involvement. In both the cutaneous and systemic forms of vasculitis, skin biopsy specimens of the associated nodules will show the changes characteristic of a necrotizing vasculitis and/or granulomatous inflammation.

RED-BROWN LESIONS

The cutaneous lesions in *sarcoidosis* **(Chap. 360)** are classically red to red-brown in color, and with diascopy (pressure with a glass slide), a yellow-brown residual color is observed that is secondary to the granulomatous infiltrate. The waxy papules and plaques may be found anywhere on the skin, but the face is the most common location. Usually there are no surface changes, but occasionally the lesions will have scale. Biopsy specimens of the papules show "naked" granulomas in the dermis, that is, granulomas surrounded by a minimal number of lymphocytes. Other cutaneous findings in sarcoidosis include annular lesions with an atrophic or scaly center, papules within scars, hypopigmented papules and patches, alopecia, acquired ichthyosis, erythema nodosum, and lupus pernio (see below).

The differential diagnosis of sarcoidosis includes foreign-body granulomas produced by chemicals such as beryllium and zirconium, late secondary syphilis, and *lupus vulgaris*. Lupus vulgaris is a form of cutaneous tuberculosis that is seen in previously infected and sensitized individuals. There is often underlying active tuberculosis elsewhere, usually in the lungs or lymph nodes. Lesions occur primarily in the head and neck region and are red-brown plaques with a yellow-brown color on diascopy. Secondary scarring can develop within the central portion of the plaques. Cultures or PCR analysis of the lesions should be performed, along with an interferon γ release assay of peripheral blood, because it is rare for the acid-fast stain to show bacilli within the dermal granulomas.

A generalized distribution of red-brown macules and papules is seen in the form of mastocytosis known as *urticaria pigmentosa* **(Chap. 347)**. Each lesion represents a collection of mast cells in the dermis, with hyperpigmentation of the overlying epidermis. Stimuli such as rubbing cause these mast cells to degranulate, and this leads to the formation of localized urticaria (Darier's sign). Additional symptoms can result from mast cell degranulation and include headache, flushing, diarrhea, and pruritus. Mast cells also infiltrate various organs such as the liver, spleen, and gastrointestinal tract, and accumulations of mast cells in the bones may produce either osteosclerotic or osteolytic lesions on radiographs. In the majority of these patients, however, the internal involvement remains indolent. A subtype of chronic cutaneous small-vessel vasculitis, *erythema elevatum diutinum* (EED), also presents with papules that are red-brown in color. The papules coalesce into plaques on the extensor surfaces of knees, elbows, and the small joints of the hand. Flares of EED have been associated with streptococcal infections.

BLUE LESIONS

Lesions that are blue in color are the result of vascular ectasias, hyperplasias and tumors or melanin pigment within the dermis. *Venous lakes* (ectasias) are compressible dark-blue lesions that are found commonly in the head and neck region. *Venous malformations* are also compressible blue papulonodules and plaques that can occur anywhere on the body, including the oral mucosa. When there are multiple papulonodules rather than a single congenital lesion, the patient may have the blue rubber bleb syndrome or Maffucci's syndrome. Patients with the blue rubber bleb syndrome also have vascular anomalies of the gastrointestinal tract that may bleed, whereas patients with Maffucci's syndrome have associated osteochondromas. *Blue nevi* (moles) are seen when there are collections of pigment-producing nevus cells in the dermis. These benign papular lesions are dome-shaped and occur most commonly on the dorsum of the hand or foot or in the head and neck region.

VIOLACEOUS LESIONS

Violaceous papules and plaques are seen in *lupus pernio*, *lymphoma cutis*, and *cutaneous lupus*. Lupus pernio is a particular type of sarcoidosis that involves the tip and alar rim of the nose as well as the earlobes, with lesions that are violaceous in color rather than red-brown. This form of sarcoidosis is associated with involvement of the upper respiratory tract. The plaques of lymphoma cutis and cutaneous lupus may be red or violaceous in color and were discussed above.

PURPLE LESIONS

Purple-colored papules and plaques are seen in vascular tumors, such as *Kaposi's sarcoma* **(Chap. 197)** and *angiosarcoma*, and when there is extravasation of red blood cells into the skin in association with inflammation, as in *palpable purpura* (see "Purpura," below). Patients with congenital or acquired AV fistulas and venous hypertension can develop purple papules on the lower extremities that can resemble Kaposi's sarcoma clinically and histologically; this condition is referred to as pseudo-Kaposi's sarcoma (acral angiodermatitis). Angiosarcoma is found most commonly on the scalp and face of elderly patients or within areas of chronic lymphedema and presents as purple papules and plaques. In the head and neck region, the tumor often extends beyond the clinically defined borders and may be accompanied by facial edema.

BROWN AND BLACK LESIONS

Brown- and black-colored papules are reviewed in "Hyperpigmentation," above.

CUTANEOUS METASTASES

These are discussed last because they can have a wide range of colors. Most commonly, they present as either firm, skin-colored subcutaneous nodules or firm, red to red-brown papulonodules while metastatic melanoma can be pink, blue, or black in color. Cutaneous metastases develop from hematogenous or lymphatic spread and are most often due to the following primary carcinomas: in men, melanoma, oropharynx, lung, and colon; and in women, breast, melanoma, and ovary. These metastatic lesions may be the initial presentation of the carcinoma, especially when the primary site is the lung.

PURPURA

(Table 54-16) *Purpura* are seen when there is an extravasation of red blood cells into the dermis and, as a result, the lesions do not blanch with pressure. This is in contrast to those erythematous or violet-colored lesions that are due to localized vasodilatation—they do blanch with pressure. Purpura (≥3 mm) and petechiae (≤2 mm) are divided into two major groups: palpable and nonpalpable. The most frequent causes of *nonpalpable* petechiae and purpura are primary cutaneous disorders such as *trauma*, *solar* (*actinic*) *purpura*, and *capillaritis*. Less common causes are *steroid purpura* and *livedoid vasculopathy* (see "Ulcers," below). Solar purpura are seen primarily on the extensor forearms, whereas steroid purpura secondary to potent topical glucocorticoids or endogenous or exogenous Cushing's syndrome can be more widespread. In both cases, there is alteration of the supporting connective tissue that surrounds the dermal blood vessels. In contrast, the petechiae that result from capillaritis are found primarily on the lower extremities. In capillaritis, there is an extravasation of erythrocytes as a result of perivascular lymphocytic inflammation. The petechiae are bright red, 1–2 mm in size, and scattered within yellow-brown patches. The yellow-brown color is caused by hemosiderin deposits within the dermis.

Systemic causes of nonpalpable purpura fall into several categories, and those secondary to clotting disturbances and vascular fragility will be discussed first. The former group includes *thrombocytopenia* **(Chap. 111)**, *abnormal platelet function* as is seen in uremia, and *clotting factor defects*. The initial site of presentation for thrombocytopenia-induced petechiae is the distal lower extremity. Capillary fragility leads to nonpalpable purpura in patients with systemic *amyloidosis*

TABLE 54-16 Causes of Purpura

- I. Primary cutaneous disorders
  - A. Nonpalpable
    1. Trauma
    2. Solar (actinic, senile) purpura
    3. Steroid purpura
    4. Capillaritis
    5. Livedoid vasculopathy in the setting of venous hypertension[a]
- II. Drugs (e.g. anti-platelet agents, anti-coagulants)
- III. Systemic diseases
  - A. Nonpalpable
    1. Clotting disturbances
       a. Thrombocytopenia (including ITP)
       b. Abnormal platelet function
       c. Clotting factor defects
    2. Vascular fragility
       a. Amyloidosis (within normal-appearing skin)
       b. Ehlers-Danlos syndrome
       c. Scurvy
    3. Thrombi
       a. Disseminated intravascular coagulation
       b. Warfarin (Coumadin®)-induced necrosis
       c. Heparin-induced thrombocytopenia and thrombosis
       d. Antiphospholipid antibody syndrome
       e. Monoclonal cryoglobulinemia
       f. Vasculopathy induced by levamisole-adulterated cocaine
       g. Thrombotic thrombocytopenic purpura
       h. Thrombocytosis
       i. Homozygous protein C or protein S deficiency
    4. Emboli
       a. Cholesterol
       b. Fat
    5. Possible immune complex
       a. Gardner-Diamond syndrome (autoerythrocyte sensitivity)
       b. Waldenström's hypergammaglobulinemic purpura
  - B. Palpable
    1. Vasculitis
       a. Cutaneous small-vessel vasculitis, including in the setting of systemic vasculitides
    2. Emboli[b]
       a. Acute meningococcemia
       b. Disseminated gonococcal infection
       c. Rocky Mountain spotted fever
       d. Ecthyma gangrenosum

[a]Also associated with underlying disorders that lead to hypercoagulability/thrombophilia, e.g., factor V Leiden, protein C dysfunction/deficiency. [b]Bacterial (including rickettsial), fungal, or parasitic.

Abbreviation: ITP, idiopathic thrombocytopenic purpura.

(see "Papulonodular Skin Lesions," above), disorders of collagen production such as *Ehlers-Danlos syndrome*, and *scurvy*. In scurvy, there are flattened corkscrew hairs with surrounding hemorrhage on the lower extremities, in addition to gingivitis. Vitamin C is a cofactor for lysyl hydroxylase, an enzyme involved in the posttranslational modification of procollagen that is necessary for cross-link formation.

In contrast to the previous group of disorders, the noninflammatory purpura seen in the following group of diseases are associated with thrombi formation within vessels and have a retiform configuration. It is important to note that these thrombi are demonstrable in skin biopsy specimens. This group of disorders includes disseminated intravascular coagulation (DIC), monoclonal cryoglobulinemia, thrombocytosis, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome, and reactions to warfarin and heparin (heparin-induced thrombocytopenia and thrombosis). DIC is triggered by several types of infection (gram-negative, gram-positive, viral, and rickettsial) as well as by tissue injury and neoplasms. Widespread purpura and hemorrhagic infarcts of the distal extremities are seen. Similar lesions are found in purpura fulminans, which is a form of DIC associated with fever and hypotension that occurs more commonly in children following an infectious illness such as varicella, scarlet fever, or an upper respiratory tract infection. In both disorders, hemorrhagic bullae can develop in involved skin.

Monoclonal cryoglobulinemia is associated with plasma cell dyscrasias, chronic lymphocytic leukemia, and lymphoma. Purpura, primarily of the lower extremities, and hemorrhagic infarcts of the fingers, toes, and ears are seen in these patients. Exacerbations of disease activity can follow cold exposure or an increase in serum viscosity. Biopsy specimens show precipitates of the cryoglobulin within dermal vessels. Similar deposits have been found in the lung, brain, and renal glomeruli. Patients with *thrombotic thrombocytopenic purpura* can also have hemorrhagic infarcts as a result of intravascular thromboses. Additional signs include microangiopathic hemolytic anemia and fluctuating neurologic abnormalities, especially headaches and confusion.

Administration of *warfarin* can result in painful areas of erythema that become purpuric and then necrotic with an adherent black eschar; the condition is referred to as warfarin-induced necrosis. This reaction is seen more often in women and in areas with abundant subcutaneous fat—breasts, abdomen, buttocks, thighs, and calves. The erythema and purpura develop between the third and tenth day of therapy, most likely as a result of a transient imbalance in the levels of anticoagulant and procoagulant vitamin K–dependent factors. Continued therapy does not exacerbate preexisting lesions, and patients with an inherited or acquired deficiency of protein C are at increased risk for this particular reaction as well as for purpura fulminans and calciphylaxis.

Purpura secondary to *cholesterol emboli* are usually seen on the lower extremities of patients with atherosclerotic vascular disease. They often follow anticoagulant therapy or an invasive vascular procedure such as an arteriogram but also occur spontaneously from disintegration of atheromatous plaques. Associated findings include livedo reticularis, gangrene, cyanosis, and ischemic ulcerations. Multiple step sections of the biopsy specimen may be necessary to demonstrate the cholesterol clefts within the vessels. Petechiae are also an important sign of *fat embolism* and occur primarily on the upper body 2–3 days after a major injury. By using special fixatives, the emboli can be demonstrated in biopsy specimens of the petechiae. Emboli of tumor or thrombus are seen in patients with atrial myxomas and marantic endocarditis.

In the *Gardner-Diamond syndrome* (autoerythrocyte sensitivity), female patients develop large ecchymoses within areas of painful, warm erythema. Intradermal injections of autologous erythrocytes or phosphatidyl serine derived from the red cell membrane can reproduce the lesions in some patients; however, there are instances where a reaction is seen at an injection site of the forearm but not in the midback region. The latter has led some observers to view Gardner-Diamond syndrome as a cutaneous manifestation of severe emotional stress. More recently, the possibility of platelet dysfunction (as assessed via aggregation studies) has been raised. *Waldenström's hypergammaglobulinemic purpura* is a chronic disorder characterized by recurrent crops of petechiae and larger purpuric macules on the lower extremities. There are circulating complexes of IgG–anti-IgG molecules, and exacerbations are associated with prolonged standing or walking.

Palpable purpura are further subdivided into vasculitic and embolic. In the group of vasculitic disorders, cutaneous small-vessel vasculitis, also known as *leukocytoclastic vasculitis* (LCV), is the one most commonly associated with palpable purpura **(Chap. 356)**. Underlying etiologies include drugs (e.g., antibiotics), infections (e.g., hepatitis C virus), and autoimmune connective tissue diseases (e.g., rheumatoid arthritis, Sjögren's syndrome, lupus). *Henoch-Schönlein purpura* (HSP) is a subtype of acute LCV that is seen more commonly in children and adolescents following an upper respiratory infection. The majority of lesions are found on the lower extremities and buttocks. Systemic manifestations include fever, arthralgias (primarily of the knees and ankles), abdominal pain, gastrointestinal bleeding, and nephritis. Direct immunofluorescence examination shows deposits of IgA within dermal blood vessel walls. Renal disease is of particular concern in adults with HSP.

Several types of infectious emboli can give rise to palpable purpura. These embolic lesions are usually *irregular* in outline as opposed to the lesions of LCV, which are *circular* in outline. The irregular outline is indicative of a cutaneous infarct, and the size corresponds to the area of skin that received its blood supply from that particular arteriole or artery. The palpable purpura in LCV are circular because the erythrocytes simply diffuse out evenly from the postcapillary venules as a result of inflammation. Infectious emboli are most commonly due to gram-negative cocci (meningococcus, gonococcus), gram-negative rods (Enterobacteriaceae), and gram-positive cocci (*Staphylococcus*). Additional causes include *Rickettsia* and, in immunocompromised patients, *Aspergillus* and other opportunistic fungi.

The embolic lesions in *acute meningococcemia* are found primarily on the trunk, lower extremities, and sites of pressure, and a gunmetal-gray color often develops within them. Their size varies from a few millimeters to several centimeters, and the organisms can be cultured from the lesions. Associated findings include a preceding upper respiratory tract infection; fever; meningitis; DIC; and, in some patients, a deficiency of the terminal components of complement. In *disseminated gonococcal infection* (arthritis-dermatitis syndrome), a small number of inflammatory papules and vesicopustules, often with central purpura or hemorrhagic necrosis, are found on the distal extremities. Additional symptoms include arthralgias, tenosynovitis, and fever. To establish the diagnosis, a Gram stain of these lesions should be performed. *Rocky Mountain spotted fever* is a tick-borne disease that is caused by *Rickettsia rickettsii*. A several-day history of fever, chills, severe headache, and photophobia precedes the onset of the cutaneous eruption. The initial lesions are erythematous macules and papules on the wrists, ankles, palms, and soles. With time, the lesions spread centripetally and become purpuric.

Lesions of *ecthyma gangrenosum* begin as edematous, erythematous papules or plaques and then develop central purpura and necrosis. Bullae formation also occurs in these lesions, and they are frequently found in the girdle region. The organism that is classically associated with ecthyma gangrenosum is *Pseudomonas aeruginosa*, but other gram-negative rods such as *Klebsiella*, *Escherichia coli*, and *Serratia* can produce similar lesions. In immunocompromised hosts, the list of potential pathogens is expanded to include *Candida* and other opportunistic fungi (e.g., *Aspergillus*, *Fusarium)*.

ULCERS

The approach to the patient with a cutaneous ulcer is outlined in **Table 54-17**. Peripheral vascular diseases of the extremities are reviewed in **Chap. 275**, as is Raynaud's phenomenon.

Livedoid vasculopathy (livedoid vasculitis; atrophie blanche) represents a combination of a vasculopathy plus intravascular thrombosis. Purpuric lesions and livedo reticularis are found in association with *painful* ulcerations of the lower extremities. These ulcers are often slow to heal, but when they do, irregularly shaped white scars form. The majority of cases are secondary to venous hypertension, but possible underlying illnesses include disorders of hypercoagulability, for example, antiphospholipid syndrome, factor V Leiden **(Chaps. 113 and 350)**.

TABLE 54-17 Causes of Mucocutaneous Ulcers

I. Primary cutaneous disorders
  A. Peripheral vascular disease **(Chap. 275)**
    1. Venous
    2. Arterial[a]
  B. Livedoid vasculopathy in the setting of venous hypertension[b]
  C. Squamous cell carcinoma (e.g., within scars), basal cell carcinomas
  D. Infections, e.g., ecthyma caused by *Streptococcus* **(Chap. 143)**
  E. Physical, e.g., trauma, pressure
  F. Drugs, e.g., hydroxyurea
II. Systemic diseases
  A. Lower legs
    1. Small-vessel and medium-vessel vasculitis[c]
    2. Hemoglobinopathies **(Chap. 94)**
    3. Cryoglobulinemia,[c] cryofibrinogenemia
    4. Cholesterol emboli[a,c]
    5. Necrobiosis lipoidica[d]
    6. Antiphospholipid syndrome **(Chap. 112)**
    7. Neuropathic[e] **(Chap. 396)**
    8. Panniculitis
    9. Kaposi's sarcoma, acral angiodermatitis
    10. Diffuse dermal angiomatosis
  B. Hands and feet
    1. Raynaud's phenomenon **(Chap. 275)**
    2. Buerger disease
  C. Generalized
    1. Pyoderma gangrenosum, but most commonly legs
    2. Calciphylaxis **(Chap. 403)**
    3. Infections, e.g., dimorphic fungi, leishmaniasis
    4. Lymphoma
  D. Face, especially perioral, and anogenital
    1. Chronic herpes simplex[f]
III. Mucosal
  A. Behçet's syndrome **(Chap. 357)**
  B. Erythema multiforme major, Stevens-Johnson syndrome, TEN
  C. Primary blistering disorders **(Chap. 55)**
  D. Lupus erythematosus, lichen planus
  E. Inflammatory bowel disease
  F. Acute HIV infection
  G. Reactive arthritis

[a]Underlying atherosclerosis. [b]Also associated with underlying disorders that lead to hypercoagulability/thrombophilia, e.g., factor V Leiden, protein C dysfunction/deficiency, antiphospholipid antibodies. [c]Reviewed in section on Purpura. [d]Reviewed in section on Papulonodular Skin Lesions. [e]Favors plantar surface of the foot. [f]Sign of immunosuppression.

Abbreviations: HIV, human immunodeficiency virus; TEN, toxic epidermal necrolysis.

In *pyoderma gangrenosum*, the border of untreated active ulcers has a characteristic appearance consisting of an undermined necrotic violaceous edge and a peripheral erythematous halo. The ulcers often begin as pustules that then expand rather rapidly to a size as large as 20 cm. Although these lesions are most commonly found on the lower extremities, they can arise anywhere on the surface of the body, including at sites of trauma (pathergy). An estimated 30–50% of cases are idiopathic, and the most common associated disorders are ulcerative colitis and Crohn's disease. Less commonly, pyoderma gangrenosum is associated with seropositive rheumatoid arthritis, acute and chronic myelogenous leukemia, hairy cell leukemia, myelofibrosis, or a monoclonal gammopathy, usually IgA. Because the histology of pyoderma gangrenosum may be nonspecific (dermal infiltrate of neutrophils when in untreated state), the diagnosis requires clinicopathologic correlation, in particular, the exclusion of similar-appearing ulcers such as necrotizing vasculitis, Meleney's ulcer (synergistic infection at a site of trauma or surgery), dimorphic fungi, cutaneous amebiasis, spider bites, and factitial. In the myeloproliferative disorders, the ulcers may be more superficial with a pustulobullous border, and these lesions provide a connection between classic pyoderma gangrenosum and acute febrile neutrophilic dermatosis (Sweet syndrome).

FEVER AND RASH

The major considerations in a patient with a fever and a rash are inflammatory diseases versus infectious diseases. In the hospital setting, the most common scenario is a patient who has a drug rash plus a fever secondary to an underlying infection. However, it should be emphasized that a drug reaction can lead to both a cutaneous eruption and a fever ("drug fever"), especially in the setting of DRESS, AGEP, or serum sickness–like reaction. Additional inflammatory diseases that are often associated with a fever include pustular psoriasis, erythroderma, and Sweet syndrome. Lyme disease, secondary syphilis, and viral and bacterial exanthems (see "Exanthems," above) are examples of infectious diseases that produce a rash and a fever. Lastly, it is important to determine whether or not the cutaneous lesions represent septic emboli (see "Purpura," above). Such lesions usually have evidence of ischemia in the form of purpura, necrosis, or impending necrosis (gunmetal-gray color). In the patient with thrombocytopenia, however, purpura can be seen in inflammatory reactions such as morbilliform drug eruptions and infectious lesions.

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55 Immunologically Mediated Skin Diseases

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A number of immunologically mediated skin diseases and immunologically mediated systemic disorders with cutaneous manifestations are now recognized as distinct entities with consistent clinical, histologic, and immunopathologic findings. Clinically, these disorders are characterized by morbidity (pain, pruritus, disfigurement) and, in some instances, result in death (largely due to loss of epidermal barrier function and/or secondary infection). The major features of the more common immunologically mediated skin diseases are summarized in this chapter **(Table 55-1)**, as are autoimmune systemic disorders with cutaneous manifestations.

AUTOIMMUNE CUTANEOUS DISEASES

PEMPHIGUS VULGARIS

Pemphigus refers to a group of autoantibody-mediated intraepidermal blistering diseases characterized by loss of cohesion between epidermal cells (a process termed *acantholysis*). Manual pressure to the skin of these patients may elicit the separation of the epidermis (*Nikolsky's sign*). This finding, while characteristic of pemphigus, is not specific to this group of disorders and is also seen in toxic epidermal necrolysis, Stevens-Johnson syndrome, and a few other skin diseases.

Pemphigus vulgaris (PV) is a mucocutaneous blistering disease that predominantly occurs in patients >40 years of age. PV typically begins on mucosal surfaces and often progresses to involve the skin.

TABLE 55-1 Immunologically Mediated Blistering Diseases

DISEASE	CLINICAL MANIFESTATIONS	HISTOLOGY	IMMUNOPATHOLOGY	AUTOANTIGENS[a]
Pemphigus vulgaris	Flaccid blisters, denuded skin, oromucosal lesions	Acantholytic blister formed in suprabasal layer of epidermis	Cell surface deposits of IgG on keratinocytes	Dsg3 (plus Dsg1 in patients with skin involvement)
Pemphigus foliaceus	Crusts and shallow erosions on scalp, central face, upper chest, and back	Acantholytic blister formed in superficial layer of epidermis	Cell surface deposits of IgG on keratinocytes	Dsg1
Paraneoplastic pemphigus	Painful stomatitis with papulosquamous or lichenoid eruptions that may progress to blisters	Acantholysis, keratinocyte necrosis, and vacuolar interface dermatitis	Cell surface deposits of IgG and C3 on keratinocytes and (variably) similar immunoreactants in epidermal BMZ	Plakin protein family members and desmosomal cadherins (see text for details)
Bullous pemphigoid	Large tense blisters on flexor surfaces and trunk	Subepidermal blister with eosinophil-rich infiltrate	Linear band of IgG and/or C3 in epidermal BMZ	BPAG1, BPAG2
Pemphigoid gestationis	Pruritic, urticarial plaques rimmed by vesicles and bullae on the trunk and extremities	Teardrop-shaped, subepidermal blisters in dermal papillae; eosinophil-rich infiltrate	Linear band of C3 in epidermal BMZ	BPAG2 (plus BPAG1 in some patients)
Dermatitis herpetiformis	Extremely pruritic small papules and vesicles on elbows, knees, buttocks, and posterior neck	Subepidermal blister with neutrophils in dermal papillae	Granular deposits of IgA in dermal papillae	Epidermal transglutaminase
Linear IgA disease	Pruritic small papules on extensor surfaces; occasionally larger, arciform blisters	Subepidermal blister with neutrophil-rich infiltrate	Linear band of IgA in epidermal BMZ	BPAG2 (see text for specific details)
Epidermolysis bullosa acquisita	Blisters, erosions, scars, and milia on sites exposed to trauma; widespread, inflammatory, tense blisters may be seen initially	Subepidermal blister that may or may not include a leukocytic infiltrate	Linear band of IgG and/or C3 in epidermal BMZ	Type VII collagen
Mucous membrane pemphigoid	Erosive and/or blistering lesions of mucous membranes and possibly the skin; scarring of some sites	Subepidermal blister that may or may not include a leukocytic infiltrate	Linear band of IgG, IgA, and/or C3 in epidermal BMZ	BPAG2, laminin-332, or others

[a]Autoantigens bound by these patients' autoantibodies are defined as follows: Dsg1, desmoglein 1; Dsg3, desmoglein 3; BPAG1, bullous pemphigoid antigen 1; BPAG2, bullous pemphigoid antigen 2.

Abbreviation: BMZ, basement membrane zone.

This disease is characterized by fragile, flaccid blisters that rupture to produce extensive denudation of mucous membranes and skin **(Fig. 55-1)**. The mouth, scalp, face, neck, axilla, groin, and trunk are typically involved. PV may be associated with severe skin pain; some patients experience pruritus as well. Lesions usually heal without scarring except at sites complicated by secondary infection or mechanically induced dermal wounds. Postinflammatory hyperpigmentation is usually present for some time at sites of healed lesions.

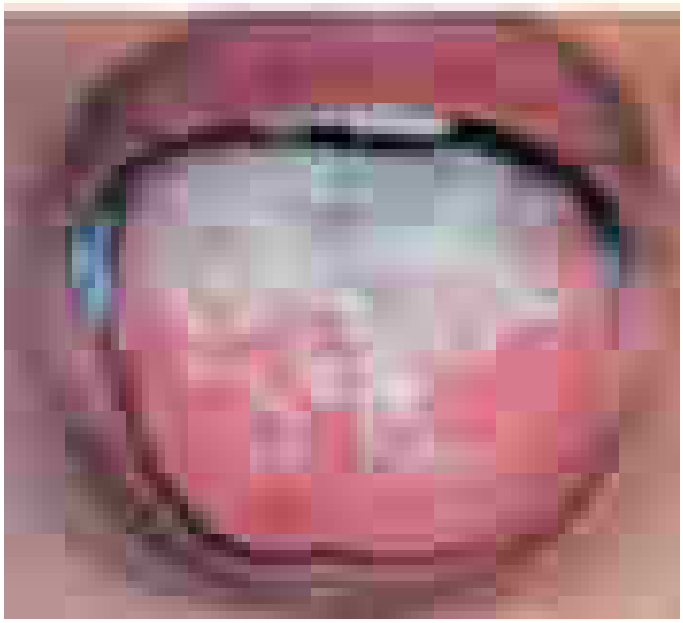
Biopsies of early lesions demonstrate intraepidermal vesicle formation secondary to loss of cohesion between epidermal cells (i.e., acantholytic blisters). Blister cavities contain acantholytic epidermal cells, which appear as round homogeneous cells containing hyperchromatic nuclei. Basal keratinocytes remain attached to the epidermal basement membrane; hence, blister formation takes place within the suprabasal portion of the epidermis. Lesional skin may contain focal collections of intraepidermal eosinophils within blister cavities; dermal alterations are slight, often limited to an eosinophil-predominant leukocytic infiltrate. Direct immunofluorescence microscopy of lesional or intact patient skin shows deposits of IgG on the surface of keratinocytes; deposits of complement components are typically found in lesional but not in uninvolved skin. Deposits of IgG on keratinocytes are derived from circulating autoantibodies to cell-surface autoantigens. Such circulating autoantibodies can be demonstrated in 80–90% of PV patients by indirect immunofluorescence microscopy; monkey esophagus is the optimal substrate for these studies. Patients with PV have IgG autoantibodies to *desmogleins* (Dsgs), transmembrane desmosomal glycoproteins that belong to the cadherin family of calcium-dependent adhesion molecules. Such autoantibodies can be precisely quantitated by enzyme-linked immunosorbent assay (ELISA). Patients with early PV (i.e., mucosal disease) have IgG autoantibodies to Dsg3; patients with advanced PV (i.e., mucocutaneous disease) have IgG autoantibodies to both Dsg3 and Dsg1. Experimental studies have shown that autoantibodies from patients with PV are pathogenic (i.e., responsible for blister formation) and that their titer correlates with disease activity. Recent studies have shown that the anti-Dsg autoantibody profile in these patients' sera as well as the tissue distribution of Dsg3 and Dsg1 determine the site of blister formation in patients with PV. Coexpression of Dsg3 and Dsg1 by epidermal cells protects against pathogenic IgG antibodies to either of these cadherins but not against pathogenic autoantibodies to both.

PV can be life-threatening. Prior to the availability of glucocorticoids, mortality rates ranged from 60% to 90%; the current figure is ~5%. Common causes of morbidity and death are infection and complications of treatment. Bad prognostic factors include advanced age, widespread involvement, and the requirement for high doses of glucocorticoids (with or without other immunosuppressive agents) for control of disease. The course of PV in individual patients is variable and difficult to predict. Some patients experience remission, while others may require long-term treatment or succumb to complications of their disease or its treatment. The mainstay of treatment is systemic glucocorticoids. Patients with moderate to severe PV are usually started on prednisone at 1 mg/kg per day. If new lesions continue to appear after 1–2 weeks of treatment, the dose may need to be increased and/or prednisone may need to be combined with other immunosuppressive agents such as azathioprine (2–2.5 mg/kg per day), mycophenolate mofetil (20–35 mg/kg per day), rituximab (375 mg/m^2 per week × 4, or 1000 mg on days 1 and 15), or cyclophosphamide (1–2 mg/kg per day). Patients with severe, treatment-resistant disease may derive benefit from plasmapheresis (six high-volume exchanges [i.e., 2–3 L per exchange] over ~2 weeks) and/or IV immunoglobulin (IVIg) (2 g/kg over 3–5 days every 6–8 weeks). It is important to bring severe or progressive disease under control quickly in order to lessen the severity and/or duration of this disorder. Increasingly, rituximab and daily glucocorticoids are used early in PV patients to avert the development of advanced and/or treatment-resistant disease.

PEMPHIGUS FOLIACEUS

Pemphigus foliaceus (PF) is distinguished from PV by several features. In PF, acantholytic blisters are located high within the epidermis, usually just beneath the stratum corneum. Hence, PF is a more superficial

A



B

FIGURE 55-1 Pemphigus vulgaris. ***A.*** Flaccid bullae are easily ruptured, resulting in multiple erosions and crusted plaques. ***B.*** Involvement of the oral mucosa, which is almost invariable, may present with erosions on the gingiva, buccal mucosa, palate, posterior pharynx, or tongue. *(B, Courtesy of Robert Swerlick, MD; with permission.)*

blistering disease than PV. The distribution of lesions in the two disorders is much the same, except that in PF mucous membranes are almost always spared. Patients with PF rarely have intact blisters but rather exhibit shallow erosions associated with erythema, scale, and crust formation. Mild cases of PF can resemble severe seborrheic dermatitis; severe PF may cause extensive exfoliation. Sun exposure (ultraviolet irradiation) may be an aggravating factor.

PF has immunopathologic features in common with PV. Specifically, direct immunofluorescence microscopy of perilesional skin demonstrates IgG on the surface of keratinocytes. Similarly, patients with PF have circulating IgG autoantibodies directed against the surface of keratinocytes. In PF, autoantibodies are directed against Dsg1, a 160-kDa desmosomal cadherin. These autoantibodies can be quantitated by ELISA. As noted for PV, the autoantibody profile in patients with PF (i.e., anti-Dsg1 IgG) and the tissue distribution of this autoantigen (i.e., expression in oral mucosa that is compensated by coexpression of Dsg3) are thought to account for the distribution of lesions in this disease.

Endemic forms of PF are found in south-central rural Brazil, where the disease is known as *fogo salvagem* (FS), as well as in selected sites in Latin America and Tunisia. Endemic PF, like other forms of this disease, is mediated by IgG autoantibodies to Dsg1. Clusters of FS overlap with those of leishmaniasis, a disease transmitted by bites of the sand fly *Lutzomyia longipalis*. Recent studies have shown that sand-fly salivary antigens (specifically, the LJM11 salivary protein) are recognized by IgG autoantibodies from FS patients (as well as by monoclonal antibodies to Dsg1 derived from these patients). Moreover, mice immunized with LJM11 produce antibodies to Dsg1. Thus, these findings suggest that insect bites may deliver salivary antigens that initiate a cross-reactive humoral immune response, which may lead to FS in genetically susceptible individuals.

Although pemphigus has been associated with several autoimmune diseases, its association with thymoma and/or myasthenia gravis is particularly notable. To date, >30 cases of thymoma and/or myasthenia gravis have been reported in association with pemphigus, usually with PF. Patients may also develop pemphigus as a consequence of drug exposure; drug-induced pemphigus usually resembles PF rather than PV. Drugs containing a thiol group in their chemical structure (e.g., penicillamine, captopril, enalapril) are most commonly associated with drug-induced pemphigus. Nonthiol drugs linked to pemphigus include penicillins, cephalosporins, and piroxicam. Some cases of drug-induced pemphigus are durable and require treatment with systemic glucocorticoids and/or immunosuppressive agents.

PF is generally a less severe disease than PV and usually carries a better prognosis. Localized disease can sometimes be treated with topical or intralesional glucocorticoids; more active cases can usually be controlled with systemic glucocorticoids either alone or in combination with other immunosuppressive agents. Patients with severe, treatment-resistant disease may require more aggressive interventions, as described above for patients with PV.

PARANEOPLASTIC PEMPHIGUS

Paraneoplastic pemphigus (PNP) is an autoimmune acantholytic mucocutaneous disease associated with an occult or confirmed neoplasm. Patients with PNP typically have painful stomatitis in association with papulosquamous and/or lichenoid eruptions that often progress to blisters. Palm and sole involvement are common in these patients and raise the possibility that prior reports of neoplasia-associated erythema multiforme actually may have represented unrecognized cases of PNP. Biopsies of lesional skin from these patients show varying combinations of acantholysis, keratinocyte necrosis, and vacuolar-interface dermatitis. Direct immunofluorescence microscopy of a patient's skin shows deposits of IgG and complement on the surface of keratinocytes and (variably) similar immunoreactants in the epidermal basement membrane zone. Patients with PNP have IgG autoantibodies to cytoplasmic proteins that are members of the plakin family (e.g., desmoplakins I and II, bullous pemphigoid antigen [BPAG]1, envoplakin, periplakin, and plectin) and to cell-surface proteins that are members of the cadherin family (e.g., Dsg1 and Dsg3). Passive transfer studies have shown that autoantibodies from patients with PNP are pathogenic in animal models.

The predominant neoplasms associated with PNP are non-Hodgkin's lymphoma, chronic lymphocytic leukemia, thymoma, spindle cell tumors, Waldenström's macroglobulinemia, and Castleman's disease; the last-mentioned neoplasm is particularly common among children with PNP. Rare cases of seronegative PNP have been reported in patients with B cell malignancies previously treated with rituximab. In addition to severe skin lesions, many patients with PNP develop life-threatening bronchiolitis obliterans. PNP is generally resistant to conventional therapies (i.e., those used to treat PV); rarely, a patient's disease may ameliorate or even remit following ablation or removal of underlying neoplasms.

BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is a polymorphic autoimmune subepidermal blistering disease usually seen in the elderly. Initial lesions may consist of urticarial plaques; most patients eventually display tense blisters on

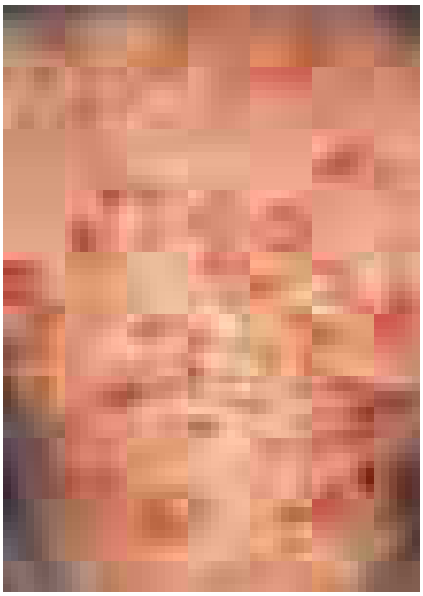


FIGURE 55-2 Bullous pemphigoid with tense vesicles and bullae on erythematous, urticarial bases. *(Courtesy of the Yale Resident's Slide Collection; with permission.)*

either normal-appearing or erythematous skin **(Fig. 55-2)**. The lesions are usually distributed over the lower abdomen, groin, and flexor surface of the extremities; oral mucosal lesions are found in some patients. Pruritus may be nonexistent or severe. As lesions evolve, tense blisters tend to rupture and be replaced by erosions with or without surmounting crust. Nontraumatized blisters heal without scarring. The major histocompatibility complex class II allele HLA-DQβ1*0301 is prevalent in patients with BP. Despite isolated reports, several studies have shown that patients with BP do not have a higher incidence of malignancy than appropriately age- and gender-matched controls.

Biopsies of early lesional skin demonstrate subepidermal blisters and histologic features that roughly correlate with the clinical character of the particular lesion under study. Lesions on normal-appearing skin generally contain a sparse perivascular leukocytic infiltrate with some eosinophils; conversely, biopsies of inflammatory lesions typically show an eosinophil-rich infiltrate at sites of vesicle formation and in perivascular areas. In addition to eosinophils, cell-rich lesions also contain mononuclear cells and neutrophils. It is not possible to distinguish BP from other subepidermal blistering diseases by routine histologic studies alone.

Direct immunofluorescence microscopy of normal-appearing perilesional skin from patients with BP shows linear deposits of IgG and/or C3 in the epidermal basement membrane. The sera of ~70% of these patients contain circulating IgG autoantibodies that bind the epidermal basement membrane of normal human skin in indirect immunofluorescence microscopy. IgG from an even higher percentage of patients reacts with the epidermal side of 1 *M* NaCl split skin (an alternative immunofluorescence microscopy test substrate used to distinguish circulating IgG autoantibodies to the basement membrane in patients with BP from those in patients with similar, yet different, subepidermal blistering diseases; see below). In BP, circulating autoantibodies recognize 230- and 180-kDa hemidesmosome-associated proteins in basal keratinocytes (i.e., BPAG1 and BPAG2, respectively). Autoantibodies to BPAG2 are thought to deposit in situ, activate complement, produce dermal mast-cell degranulation, and generate granulocyte-rich infiltrates that cause tissue damage and blister formation.

BP may persist for months to years, with exacerbations or remissions. Extensive involvement may result in widespread erosions and compromise cutaneous integrity; elderly and/or debilitated patients may die. The mainstay of treatment is systemic glucocorticoids. Local or minimal disease can sometimes be controlled with topical glucocorticoids alone; more extensive lesions generally respond to systemic glucocorticoids either alone or in combination with other immunosuppressive agents. Patients usually respond to prednisone (0.75–1 mg/kg per day). In some instances, azathioprine (2–2.5 mg/kg per day), mycophenolate mofetil (20–35 mg/kg per day), or rituximab (375 mg/m^2 per week x 4, or 1000 mg on days 1 and 15) are necessary adjuncts.

PEMPHIGOID GESTATIONIS

Pemphigoid gestationis (PG), also known as *herpes gestationis*, is a rare, nonviral, subepidermal blistering disease of pregnancy and the puerperium. PG may begin during any trimester of pregnancy or present shortly after delivery. Lesions are usually distributed over the abdomen, trunk, and extremities; mucous membrane lesions are rare. Skin lesions in these patients may be quite polymorphic and consist of erythematous urticarial papules and plaques, vesiculopapules, and/or frank bullae. Lesions are almost always extremely pruritic. Severe exacerbations of PG frequently follow delivery, typically within 24–48 h. PG tends to recur in subsequent pregnancies, often beginning earlier during such gestations. Brief flare-ups of disease may occur with resumption of menses and may develop in patients later exposed to oral contraceptives. Occasionally, infants of affected mothers have transient skin lesions.

Biopsies of early lesional skin show teardrop-shaped subepidermal vesicles forming in dermal papillae in association with an eosinophil-rich leukocytic infiltrate. Differentiation of PG from other subepidermal bullous diseases by light microscopy is difficult. However, direct immunofluorescence microscopy of perilesional skin from PG patients reveals the immunopathologic hallmark of this disorder: linear deposits of C3 in the epidermal basement membrane. These deposits develop as a consequence of complement activation produced by low-titer IgG anti–basement membrane autoantibodies directed against BPAG2, the same hemidesmosome-associated protein that is targeted by autoantibodies in patients with BP—a subepidermal bullous disease that resembles PG clinically, histologically, and immunopathologically.

The goals of therapy in patients with PG are to prevent the development of new lesions, relieve intense pruritus, and care for erosions at sites of blister formation. Many patients require treatment with moderate doses of daily glucocorticoids (i.e., 20–40 mg of prednisone) at some point in their course. Mild cases (or brief flare-ups) may be controlled by vigorous use of potent topical glucocorticoids. Infants born of mothers with PG appear to be at increased risk of being born slightly premature or "small for dates." Current evidence suggests that there is no difference in the incidence of uncomplicated live births between PG patients treated with systemic glucocorticoids and those managed more conservatively. If systemic glucocorticoids are administered, newborns are at risk for development of reversible adrenal insufficiency.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is an intensely pruritic, papulovesicular skin disease characterized by lesions symmetrically distributed over extensor surfaces (i.e., elbows, knees, buttocks, back, scalp, and posterior neck) **(see Fig. 52-8)**. Primary lesions in this disorder consist of papules, papulovesicles, or urticarial plaques. Because pruritus is prominent, patients may present with excoriations and crusted papules but no observable primary lesions. Patients sometimes report that their pruritus has a distinctive burning or stinging component; the onset of such local symptoms reliably heralds the development of distinct clinical lesions 12–24 h later. Almost all DH patients have associated, usually subclinical, gluten-sensitive enteropathy **(Chap. 318)**, and >90% express the HLA-B8/DRw3 and HLA-DQw2 haplotypes. DH may present at any age, including in childhood; onset in the second to fourth decades is most common. The disease is typically chronic.

Biopsy of early lesional skin reveals neutrophil-rich infiltrates within dermal papillae. Neutrophils, fibrin, edema, and microvesicle formation at these sites are characteristic of early disease. Older lesions may demonstrate nonspecific features of a subepidermal bulla or an excoriated papule. Because the clinical and histologic features of this disease can be variable and resemble those of other subepidermal blistering disorders, the diagnosis is confirmed by direct immunofluorescence microscopy of normal-appearing perilesional skin. Such studies demonstrate granular deposits of IgA (with or without complement

components) in the papillary dermis and along the epidermal basement membrane zone. IgA deposits in the skin are unaffected by control of disease with medication; however, these immunoreactants diminish in intensity or disappear in patients maintained for long periods on a strict gluten-free diet (see below). Patients with DH have granular deposits of IgA in their epidermal basement membrane zone and should be distinguished from individuals with linear IgA deposits at this site (see below).

Although most DH patients do not report overt gastrointestinal symptoms or have laboratory evidence of malabsorption, biopsies of the small bowel usually reveal blunting of intestinal villi and a lymphocytic infiltrate in the lamina propria. As is true for patients with celiac disease, this gastrointestinal abnormality can be reversed by a gluten-free diet. Moreover, if maintained, this diet alone may control the skin disease and eventuate in clearance of IgA deposits from these patients' epidermal basement membrane zones. Subsequent gluten exposure in such patients alters the morphology of their small bowel, elicits a flare-up of their skin disease, and is associated with the reappearance of IgA in their epidermal basement membrane zones. As in patients with celiac disease, dietary gluten sensitivity in patients with DH is associated with IgA anti-endomysial autoantibodies that target tissue transglutaminase. Studies indicate that patients with DH also have high-avidity IgA autoantibodies to epidermal transglutaminase and that the latter is co-localized with granular deposits of IgA in the papillary dermis of DH patients. Patients with DH also have an increased incidence of thyroid abnormalities, achlorhydria, atrophic gastritis, and autoantibodies to gastric parietal cells. These associations likely relate to the high frequency of the HLA-B8/DRw3 haplotype in these patients, since this marker is commonly linked to autoimmune disorders. The mainstay of treatment of DH is dapsone, a sulfone. Patients respond rapidly (24–48 h) to dapsone (50–200 mg/d), but require careful pretreatment evaluation and close follow-up to ensure that complications are avoided or controlled. All patients taking dapsone at >100 mg/d will have some hemolysis and methemoglobinemia, which are expected pharmacologic side effects of this agent. Gluten restriction can control DH and lessen dapsone requirements; this diet must rigidly exclude gluten to be of maximal benefit. Many months of dietary restriction may be necessary before a beneficial result is achieved. Good dietary counseling by a trained dietitian is essential.

LINEAR IgA DISEASE

Linear IgA disease, once considered a variant form of DH, is actually a separate and distinct entity. Clinically, patients with linear IgA disease may resemble individuals with DH, BP, or other subepidermal blistering diseases. Lesions typically consist of papulovesicles, bullae, and/or urticarial plaques that develop predominantly on central or flexural sites. Oral mucosal involvement occurs in some patients. Severe pruritus resembles that is seen in patients with DH. Patients with linear IgA disease do not have an increased frequency of the HLA-B8/DRw3 haplotype or an associated enteropathy and therefore are not candidates for treatment with a gluten-free diet.

Histologic alterations in early lesions may be virtually indistinguishable from those in DH. However, direct immunofluorescence microscopy of normal-appearing perilesional skin reveals a linear band of IgA (and often C3) in the epidermal basement membrane zone. Most patients with linear IgA disease have circulating IgA anti-basement membrane autoantibodies directed against neoepitopes in the proteolytically processed extracellular domain of BPAG2. These patients generally respond to treatment with dapsone (50–200 mg/d).

EPIDERMOLYSIS BULLOSA ACQUISITA

Epidermolysis bullosa acquisita (EBA) is a rare, noninherited, polymorphic, chronic, subepidermal blistering disease. **(The inherited form is discussed in Chap. 406.)** Patients with classic or noninflammatory EBA have blisters on noninflamed skin, atrophic scars, milia, nail dystrophy, and oral lesions. Because lesions generally occur at sites exposed to minor trauma, classic EBA is considered a mechanobullous disease. Other patients with EBA have widespread inflammatory scarring and bullous lesions that resemble severe BP. Inflammatory EBA may evolve into the classic, noninflammatory form of this disease. Rarely, patients present with lesions that predominate on mucous membranes. The HLA-DR2 haplotype is found with increased frequency in EBA patients. Studies suggest that EBA is sometimes associated with inflammatory bowel disease (especially Crohn's disease).

The histology of lesional skin varies with the character of the lesion being studied. Noninflammatory bullae are subepidermal, feature a sparse leukocytic infiltrate, and resemble the lesions in patients with porphyria cutanea tarda. Inflammatory lesions consist of neutrophil-rich subepidermal blisters. EBA patients have continuous deposits of IgG (and frequently C3) in a linear pattern within the epidermal basement membrane zone. Ultrastructurally, these immunoreactants are found in the sublamina densa region in association with anchoring fibrils. Approximately 50% of EBA patients have demonstrable circulating IgG anti-basement membrane autoantibodies directed against type VII collagen—the collagen species that makes up anchoring fibrils. Such IgG autoantibodies bind the dermal side of 1 *M* NaCl split skin (in contrast to IgG autoantibodies in patients with BP). Studies have shown that passive transfer of experimental or patient IgG against type VII collagen can produce lesions in mice that clinically, histologically, and immunopathologically resemble those in patients with EBA.

Treatment of EBA is generally unsatisfactory. Some patients with inflammatory EBA may respond to systemic glucocorticoids, either alone or in combination with immunosuppressive agents. Other patients (especially those with neutrophil-rich inflammatory lesions) may respond to dapsone. The chronic, noninflammatory form of EBA is largely resistant to treatment, although some patients may respond to cyclosporine, azathioprine, IVIg, or rituximab.

MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (MMP) is a rare, acquired, subepithelial immunobullous disease characterized by erosive lesions of mucous membranes and skin that result in scarring of at least some sites of involvement. Common sites include the oral mucosa (especially the gingiva) and conjunctiva; other sites that may be affected include the nasopharyngeal, laryngeal, esophageal, and anogenital mucosa. Skin lesions (present in about one-third of patients) tend to predominate on the scalp, face, and upper trunk and generally consist of a few scattered erosions or tense blisters on an erythematous or urticarial base. MMP is typically a chronic and progressive disorder. Serious complications may arise as a consequence of ocular, laryngeal, esophageal, or anogenital lesions. Erosive conjunctivitis may result in shortened fornices, symblepharon, ankyloblepharon, entropion, corneal opacities, and (in severe cases) blindness. Similarly, erosive lesions of the larynx may cause hoarseness, pain, and tissue loss that, if unrecognized and untreated, may eventuate in complete destruction of the airway. Esophageal lesions may result in stenosis and/or strictures that could place patients at risk for aspiration. Strictures may also complicate anogenital involvement.

Biopsies of lesional tissue generally show subepithelial vesiculobullae and a mononuclear leukocytic infiltrate. Neutrophils and eosinophils may be seen in biopsies of early lesions; older lesions may demonstrate a scant leukocytic infiltrate and fibrosis. Direct immunofluorescence microscopy of perilesional tissue typically reveals deposits of IgG, IgA, and/or C3 in the epidermal basement membrane. Because many patients with MMP exhibit no evidence of circulating anti-basement membrane autoantibodies, testing of perilesional skin is important diagnostically. Although MMP was once thought to be a single nosologic entity, it is now largely regarded as a disease phenotype that may develop as a consequence of an autoimmune reaction to a variety of molecules in the epidermal basement membrane (e.g., BPAG2, laminin-332, type VII collagen, $\alpha_6\beta_4$ integrin) and other antigens yet to be completely defined. Studies suggest that MMP patients with autoantibodies to laminin-332 have an increased relative risk for cancer. Treatment of MMP is largely dependent upon the sites of involvement. Due to potentially severe complications, patients with ocular, laryngeal, esophageal, and/or anogenital involvement require aggressive systemic treatment with dapsone, prednisone, or the latter

in combination with another immunosuppressive agent (e.g., azathioprine, mycophenolate mofetil, cyclophosphamide, or rituximab), or IVIg. Less threatening forms of the disease may be managed with topical or intralesional glucocorticoids.

AUTOIMMUNE SYSTEMIC DISEASES WITH PROMINENT CUTANEOUS FEATURES

DERMATOMYOSITIS

The cutaneous manifestations of dermatomyositis **(Chap. 358)** are often distinctive but at times may resemble those of systemic lupus erythematosus (SLE) **(Chap. 349)**, scleroderma **(Chap. 353)**, or other overlapping connective tissue diseases **(Chap. 353)**. The extent and severity of cutaneous disease may or may not correlate with the extent and severity of the myositis. The cutaneous manifestations of dermatomyositis are similar, whether the disease appears in children or in the elderly, except that calcification of subcutaneous tissue is a common late sequela in childhood dermatomyositis.

The cutaneous signs of dermatomyositis may precede or follow the development of myositis by weeks to years. Cases lacking muscle involvement (i.e., *dermatomyositis sine myositis* or *amyopathic dermatomyositis*) have also been reported. The most common manifestation is a purple-red discoloration of the upper eyelids, sometimes associated with scaling ("heliotrope" erythema; **Fig. 55-3**) and periorbital edema. Erythema on the cheeks and nose in a "butterfly" distribution may resemble the malar eruption of SLE. Erythematous or violaceous scaling patches are common on the upper anterior chest, posterior neck, scalp, and the extensor surfaces of the arms, legs, and hands. Erythema and scaling may be particularly prominent over the elbows, knees, and dorsal interphalangeal joints. Approximately one-third of patients have violaceous, flat-topped papules over the dorsal interphalangeal joints that are pathognomonic of dermatomyositis (Gottron's papules) **(Fig. 55-4)**. Thin violaceous papules and plaques on the elbows and knees of patients with dermatomyositis are referred to as *Gottron's sign* (Fig. 55-4). These lesions can be contrasted with the erythema and scaling on the dorsum of the fingers that spares the skin over the interphalangeal joints of some SLE patients. Periungual telangiectases and edema may be prominent in patients with dermatomyositis. Lacy or reticulated erythema may be associated with fine scaling on the extensor and lateral surfaces of the thighs and upper arms. Other patients, particularly those with long-standing disease, develop areas of hypopigmentation, hyperpigmentation, mild atrophy, and telangiectasia known as *poikiloderma*. Poikiloderma is rare in both SLE and scleroderma and thus can serve as a clinical sign that distinguishes dermatomyositis from these two diseases. Cutaneous changes may be similar in dermatomyositis and various overlap syndromes where

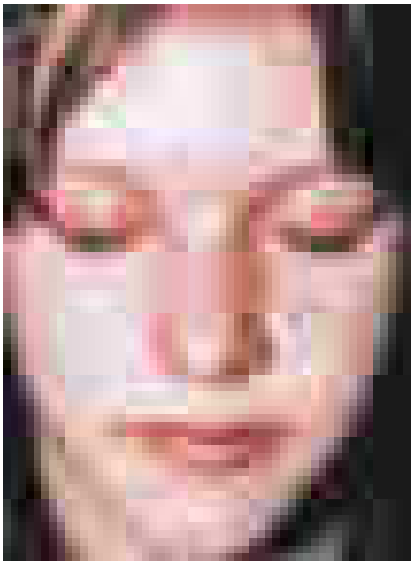


FIGURE 55-3 Dermatomyositis. Periorbital violaceous erythema characterizes the classic heliotrope rash. *(Courtesy of James Krell, MD; with permission.)*

FIGURE 55-4 Gottron's papules. Dermatomyositis often involves the hands as erythematous flat-topped papules over the knuckles. Periungual telangiectases are also evident.

thickening and binding down of the skin of the hands (*sclerodactyly*) as well as Raynaud's phenomenon can be seen. However, the presence of severe muscle disease, Gottron's papules, heliotrope erythema, and poikiloderma serve to distinguish patients with dermatomyositis. Skin biopsy of the erythematous, scaling lesions of dermatomyositis may reveal only mild nonspecific inflammation, but sometimes may show changes indistinguishable from those found in cutaneous lupus erythematosus (LE), including epidermal atrophy, hydropic degeneration of basal keratinocytes, and dermal changes consisting of edema of the upper dermis, interstitial mucin deposition, and a mild mononuclear cell infiltrate. Direct immunofluorescence microscopy of lesional skin is usually negative, although granular deposits of immunoglobulin(s) and complement in the epidermal basement membrane zone have been described in some patients. Treatment should be directed at the systemic disease. Topical glucocorticoids are sometimes useful; patients should avoid exposure to ultraviolet irradiation and aggressively use photoprotective measures, including broad-spectrum sunscreens.

LUPUS ERYTHEMATOSUS

The cutaneous manifestations of LE **(Chap. 349)** can be divided into acute, subacute, and chronic or discoid types. *Acute cutaneous LE* is characterized by erythema of the nose and malar eminences in a "butterfly" distribution **(Fig. 55-5*A*)**. The erythema is often sudden in onset, accompanied by edema and fine scale, and correlated with systemic involvement. Patients may have widespread involvement of the face as well as erythema and scaling of the extensor surfaces of the extremities and upper chest **(Fig. 55-5*B*)**. These acute lesions, while sometimes evanescent, usually last for days and are often associated with exacerbations of systemic disease. Skin biopsy of acute lesions typically shows hydropic degeneration of basal keratinocytes, dermal edema, and (in some cases) a sparse infiltrate of mononuclear cells in the upper dermis as well as dermal mucin. Direct immunofluorescence microscopy of lesional skin frequently reveals deposits of immunoglobulin(s) and complement in the epidermal basement membrane zone. Treatment is aimed at control of systemic disease. Photoprotection is very important in this as well as in other forms of LE.

Subacute cutaneous lupus erythematosus (SCLE) is characterized by a widespread photosensitive, nonscarring eruption. In most patients, renal and central nervous system involvement is mild or absent. SCLE may present as a papulosquamous eruption that resembles psoriasis or as annular polycyclic lesions. In the papulosquamous form, discrete erythematous papules arise on the back, chest, shoulders, extensor surfaces of the arms, and dorsum of the hands; lesions are uncommon on the central face and the flexor surfaces of the arms as well as below the waist. These slightly scaling papules tend to merge into large plaques, some with a reticulate appearance. The annular form involves the same areas and presents with erythematous papules that evolve into oval, circular, or polycyclic lesions. The lesions of SCLE are more widespread but have less tendency for scarring than lesions of discoid LE. In many

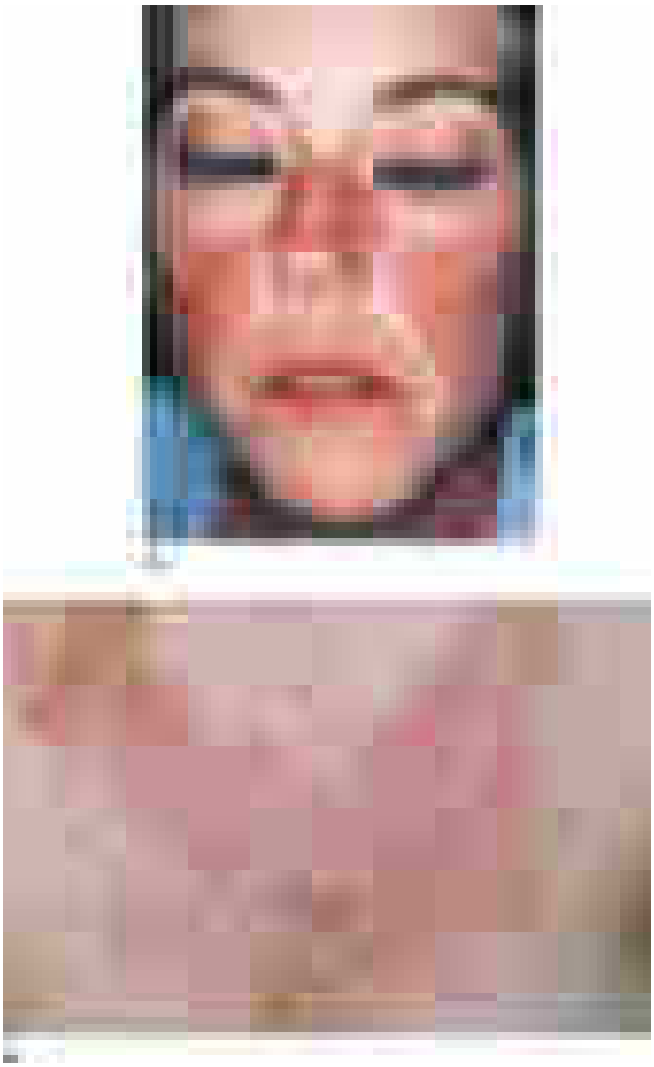


FIGURE 55-5 Acute cutaneous lupus erythematosus (LE). ***A.*** Acute cutaneous LE on the face, showing prominent, scaly, malar erythema. Involvement of other sun-exposed sites is also common. ***B.*** Acute cutaneous LE on the upper chest, demonstrating brightly erythematous and slightly edematous papules and plaques. *(B, Courtesy of Robert Swerlick, MD; with permission.)*

patients with SCLE, drugs (e.g., hydrochlorothiazide, calcium channel blockers, proton pump inhibitors) may induce or exacerbate disease. Skin biopsy typically reveals epidermal changes that include atrophy, hydropic degeneration of basal keratinocytes, and apoptosis accompanied by an infiltrate of mononuclear cells in the upper dermis. Direct immunofluorescence microscopy of lesional skin reveals deposits of immunoglobulin(s) in the epidermal basement membrane zone in about one-half of these cases. A particulate pattern of IgG deposition throughout the epidermis has been associated with SCLE. Most SCLE patients have anti-Ro autoantibodies. Local therapy alone is usually unsuccessful. Most patients require treatment with aminoquinoline antimalarial drugs. Low-dose therapy with oral glucocorticoids is sometimes necessary. Photoprotective measures against both ultraviolet B and ultraviolet A wavelengths are very important.

Discoid lupus erythematosus (DLE, also called *chronic cutaneous LE*) is characterized by discrete lesions, most often found on the face, scalp, and/or external ears. The lesions are erythematous papules or plaques with a thick, adherent scale that occludes hair follicles (follicular plugging). When the scale is removed, its underside shows small excrescences that correlate with the openings of hair follicles (so-called "carpet tacking"), a finding relatively specific for DLE. Longstanding lesions develop central atrophy, scarring, and hypopigmentation but frequently have erythematous, sometimes raised borders **(Fig. 55-6)**. These lesions persist for years and tend to expand slowly. Up to 15% of patients with DLE eventually meet the American College

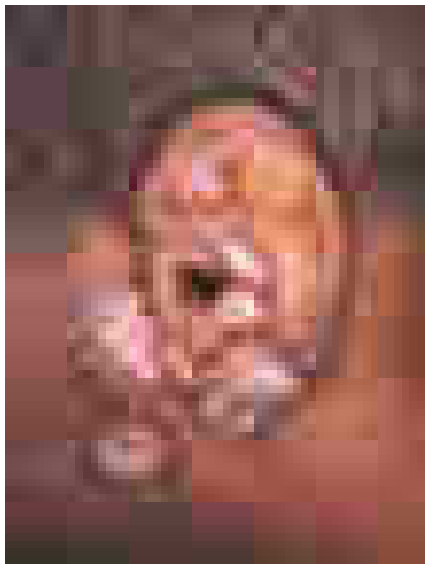


FIGURE 55-6 Discoid (chronic cutaneous) lupus erythematosus (LE). Violaceous, hyperpigmented, atrophic plaques, follicular plugging, and scarring are typical features of chronic cutaneous LE.

of Rheumatology criteria for SLE. Typical discoid lesions are frequently seen in patients with SLE. Biopsy of DLE lesions shows hyperkeratosis, follicular plugging, atrophy of the epidermis, hydropic degeneration of basal keratinocytes, thickening of the epidermal basement membrane zone, and a mononuclear cell infiltrate adjacent to epidermal, adnexal, and microvascular basement membranes. Direct immunofluorescence microscopy demonstrates immunoglobulin(s) and complement deposits at the basement membrane zone in ~90% of cases. Treatment is focused on control of local cutaneous disease and consists mainly of photoprotection and topical or intralesional glucocorticoids. If local therapy is ineffective, use of aminoquinoline antimalarial agents may be indicated.

SCLERODERMA AND MORPHEA

The skin changes of scleroderma **(Chap. 353)** usually begin on the fingers, hands, toes, feet, and face, with episodes of recurrent nonpitting edema. Sclerosis of the skin commences distally on the fingers (sclerodactyly) and spreads proximally, usually accompanied by resorption of bone of the fingertips, which may have punched out ulcers, stellate scars, or areas of hemorrhage **(Fig. 55-7)**. The fingers may actually shrink and become sausage-shaped, and, because the fingernails are usually unaffected, they may curve over the end of the fingertips. Periungual telangiectases are usually present, but periungual erythema is rare. In advanced cases, the extremities show contractures and calcinosis cutis. Facial involvement includes a smooth, unwrinkled brow, taut skin over the nose, shrinkage of tissue around the mouth, and perioral

FIGURE 55-7 Scleroderma showing acral sclerosis and focal digital ulcers.

FIGURE 55-8 Scleroderma often eventuates in development of an expressionless, masklike facies.

radial furrowing **(Fig. 55-8)**. Matlike telangiectases are often present, particularly on the face and hands. Involved skin feels indurated, smooth, and bound to underlying structures; hyper- and hypopigmentation are common as well. *Raynaud's phenomenon* (i.e., cold-induced blanching, cyanosis, and reactive hyperemia) is documented in almost all patients and can precede development of scleroderma by many years. *Linear scleroderma* is a limited form of disease that presents in a linear, bandlike distribution and tends to involve deep as well as superficial layers of skin. The combination of calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectases has been termed as the *CREST syndrome*. Anti-centromere autoantibodies have been reported in a very high percentage of patients with CREST syndrome but in only a small minority of patients with scleroderma. Skin biopsy reveals thickening of the dermis, homogenization of collagen bundles, atrophic pilosebaceous and eccrine glands, and a sparse mononuclear cell infiltrate in the dermis and subcutaneous fat. Direct immunofluorescence microscopy of lesional skin is usually negative.

Morphea is characterized by localized thickening and sclerosis of skin; it dominates on the trunk. This disorder may affect children or adults. Morphea begins as erythematous or flesh-colored plaques that become sclerotic, develop central hypopigmentation, and have an erythematous border. In most cases, patients have one or a few lesions, and the disease is termed *localized morphea*. In some patients, widespread cutaneous lesions may occur without systemic involvement (*generalized morphea*). Many adults with generalized morphea have concomitant rheumatic or other autoimmune disorders. Skin biopsy of morphea is generally indistinguishable from that of scleroderma. Scleroderma and morphea are usually quite resistant to therapy. For this reason, physical therapy to prevent joint contractures and to maintain function is employed and is often helpful. Treatment options for early, rapidly progressive disease include phototherapy (UVA1 [ultraviolet A1 irradiation] or PUVA [psoralens + ultraviolet A irradiation]) or methotrexate (15–20 mg/week) alone or in combination with daily glucocorticoids.

Diffuse fasciitis with eosinophilia is a clinical entity that can sometimes be confused with scleroderma. There is usually a sudden onset of swelling, induration, and erythema of the extremities, frequently following significant physical exertion. The proximal portions of the extremities (upper arms, forearms, thighs, calves) are more often involved than are the hands and feet. While the skin is indurated, it usually displays a woody, dimpled, or "pseudocellulite" appearance rather than being bound down as in scleroderma; contractures may occur early secondary to fascial involvement. The latter may also cause muscle groups to be separated and veins to appear depressed (i.e., the "groove sign"). These skin findings are accompanied by peripheral-blood eosinophilia, increased erythrocyte sedimentation rate, and sometimes hypergammaglobulinemia. Deep biopsy of affected areas of skin reveals inflammation and thickening of the deep fascia overlying muscle. An inflammatory infiltrate composed of eosinophils and mononuclear cells is usually found. Patients with eosinophilic fasciitis appear to be at increased risk for developing bone marrow failure or other hematologic abnormalities. While the ultimate course of eosinophilic fasciitis is uncertain, many patients respond favorably to treatment with prednisone in doses of 40–60 mg/d.

The *eosinophilia-myalgia syndrome*, a disorder with epidemic numbers of cases reported in 1989 and linked to ingestion of L-tryptophan manufactured by a single company in Japan, is a multisystem disorder characterized by debilitating myalgias and absolute eosinophilia in association with varying combinations of arthralgias, pulmonary symptoms, and peripheral edema. In a later phase (3–6 months after initial symptoms), these patients often develop localized sclerodermatous skin changes, weight loss, and/or neuropathy **(Chap. 353)**. The precise cause of this syndrome, which may resemble other sclerotic skin conditions, is unknown. However, the implicated lots of L-tryptophan contained the contaminant 1,1-ethylidene bis[tryptophan]. This contaminant may be pathogenic or may be a marker for another substance that provokes the disorder.

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56 Cutaneous Drug Reactions

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Cutaneous reactions are among the most frequent adverse reactions to drugs. Most are benign, but a few can be life threatening. Prompt recognition of severe reactions, drug withdrawal, and appropriate therapeutic interventions can minimize toxicity. This chapter focuses on adverse cutaneous reactions to systemic medications; it covers their incidence, patterns, and pathogenesis, and provides some practical guidelines on treatment, assessment of causality, and future use of drugs.

USE OF PRESCRIPTION DRUGS IN THE UNITED STATES

In the United States, more than 3 billion prescriptions for >60,000 drug products, which include >2000 different active agents, are dispensed annually. Hospital inpatients alone annually receive about 120 million courses of drug therapy, and half of adult Americans receive prescription drugs on a regular outpatient basis. Adverse effects of a prescription medication may result in 4.5 million urgent or emergency care visits each year in the United States. Many patients use over-the-counter medicines that may cause adverse cutaneous reactions.

INCIDENCE OF CUTANEOUS REACTIONS

Several large cohort studies established that acute cutaneous reactions to drugs affect about 3% of hospitalized patients. Reactions usually occur a few days to 4 weeks after initiation of therapy.

Many drugs of common use are associated with a 1–2% rate of rashes during premarketing clinical trials. The risk is often higher when medications are used in general, unselected populations. The rate may reach 3–7% for amoxicillin, sulfamethoxazole, many anticonvulsants, and anti-HIV agents.

In addition to acute eruptions, a variety of skin diseases can be induced or exacerbated by prolonged use of drugs (e.g., pruritus, pigmentation, nail or hair disorders, psoriasis, bullous pemphigoid, photosensitivity, and even cutaneous neoplasms). These drug reactions are not frequent, but neither their incidence nor their impact on public health has been evaluated.

In a series of 48,005 inpatients over a 20-year period, morbilliform rash (91%) and urticaria (6%) were the most frequent skin reactions. Severe reactions are too rare to be detected in such cohorts. Although rare, severe cutaneous reactions to drugs have an important impact on health because of significant sequelae, including mortality. Adverse drug rashes are responsible for hospitalization, increase the duration of hospital stay, and can be life threatening. Some populations are at increased risk of drug reactions, including elderly patients, patients with autoimmune disease, hematopoietic stem cell transplant recipients, and those with acute Epstein-Barr virus (EBV) or human immunodeficiency virus (HIV) infection. The pathophysiology underlying this association is unknown but may be related to immunocompromise or immune dysregulation. Individuals with advanced HIV disease (e.g., CD4 T lymphocyte count <200 cells/μL) have a 40- to 50-fold increased risk of adverse reactions to sulfamethoxazole (Chap. 197) and increased risk of severe hypersensitivity reactions.

PATHOGENESIS OF DRUG REACTIONS

Adverse cutaneous responses to drugs can arise as a result of immunologic or nonimmunologic mechanisms.

NONIMMUNOLOGIC DRUG REACTIONS

Examples of nonimmunologic drug reactions are pigmentary changes due to dermal accumulation of medications or their metabolites, alteration of hair follicles by antimetabolites and signaling inhibitors, and lipodystrophy associated with metabolic effects of anti-HIV medications. These side effects are predictable and sometimes can be prevented.

IMMUNOLOGIC DRUG REACTIONS

Evidence suggests an immunologic basis for most acute drug eruptions. Drug reactions may result from immediate release of preformed mediators (e.g., urticaria, anaphylaxis), antibody-mediated reactions, immune complex deposition, and antigen-specific responses. Drug-specific T cell clones can be derived from the blood or from skin lesions of patients with a variety of drug allergies, strongly suggesting that these T cells mediate drug allergy in an antigen-specific manner. Specific clones are generated by medications that are frequently a cause of drug eruptions: penicillin G, amoxicillin, cephalosporins, sulfamethoxazole, phenobarbital, carbamazepine, and lamotrigine. Both CD4 and CD8 clones have been obtained; however, their specific roles in drug allergy have not been elucidated. Drug presentation to T cells is major histocompatibility complex (MHC)-restricted and likely involves drug-peptide complex recognition by specific T cell receptors (TCRs).

Once a drug has induced an immune response, the final phenotype of the reaction is determined by the nature of effectors: cytotoxic (CD8+) T cells in blistering and certain hypersensitivity reactions, chemokines for reactions mediated by neutrophils or eosinophils, and B cell collaboration for production of specific antibodies for urticarial reactions. Immunologic reactions have recently been classified into further subtypes that provide a useful framework for designating adverse drug reactions based on involvement of specific immune pathways (Table 56-1).

TABLE 56-1 Classification of Adverse Drug Reactions Based on Immune Pathway

TYPE	KEY PATHWAY	KEY IMMUNE MEDIATORS	ADVERSE DRUG REACTION TYPE
Type I	IgE	IgE	Urticaria, angioedema, anaphylaxis
Type II	IgG-mediated cytotoxicity	IgG	Drug-induced hemolysis, thrombocytopenia (e.g., penicillin)
Type III	Immune complex	IgG + antigen	Vasculitis, serum sickness, drug-induced lupus
Type IVa	T lymphocyte–mediated macrophage inflammation	IFN-γ, TNF-α T_H1 cells	Tuberculin skin test, contact dermatitis
Type IVb	T lymphocyte–mediated eosinophil inflammation	IL-4, IL-5, IL-13 T_H2 cells Eosinophils	DIHS Morbilliform eruption
Type IVc	T lymphocyte–mediated cytotoxic T lymphocyte inflammation	Cytotoxic T lymphocytes Granzyme Perforin Granulysin (SJS/TEN only)	SJS/TEN Morbilliform eruption
Type IVd	T lymphocyte–mediated neutrophil inflammation	CXCL8, IL-17, GM-CSF Neutrophils	AGEP

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DIHS, drug-induced hypersensitivity syndrome; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor.

Immediate Reactions Immediate reactions depend on the release of mediators of inflammation by tissue mast cells or circulating basophils. These mediators include histamine, leukotrienes, prostaglandins, bradykinins, platelet-activating factor, enzymes, and proteoglycans. Drugs can trigger mediator release either directly ("anaphylactoid" reaction) or through IgE-specific antibodies. These reactions usually manifest in the skin and gastrointestinal, respiratory, and cardiovascular systems (Chap. 346). Primary symptoms and signs include pruritus, urticaria, nausea, vomiting, abdominal cramps, bronchospasm, laryngeal edema, and, occasionally, anaphylactic shock with hypotension and death. They occur within minutes of drug exposure. Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, and radiocontrast media are frequent causes of direct mast cell degranulation or anaphylactoid reactions, which can occur on first exposure. Penicillins and muscle relaxants used in general anesthesia are the most frequent causes of IgE-dependent reactions to drugs, which require prior sensitization. Release of mediators is triggered when polyvalent drug protein conjugates cross-link IgE molecules fixed to sensitized cells. Certain routes of administration favor different clinical patterns (e.g., gastrointestinal effects from oral route, circulatory effects from intravenous route).

Immune Complex–Dependent Reactions Serum sickness is produced by tissue deposition of circulating immune complexes with consumption of complement. It is characterized by fever, arthritis, nephritis, neuritis, edema, and an urticarial, papular, or purpuric rash (Chap. 356). First described following administration of nonhuman sera, it currently occurs in the setting of monoclonal antibodies and similar medications. In classic serum sickness, symptoms develop 6 or more days after drug exposure, the latent period representing the time needed to synthesize antibody. Vasculitis, a relatively rare complication of drugs, may also be a result of immune complex deposition (Chap. 356). Cephalosporin and other medications, including monoclonal antibodies such as infliximab, rituximab, and omalizumab, may be associated with clinically similar "serum sickness–like" reactions. The mechanism of this reaction is unknown but is unrelated to immune complex formation and complement activation.

Delayed Hypersensitivity While not completely understood, delayed hypersensitivity directed by drug-specific T cells is an important mechanism underlying the most common drug eruptions, that is, morbilliform eruptions, and also rare and severe forms such as drug-induced hypersensitivity syndrome (DIHS) (also known as drug rash with eosinophilia and systemic symptoms [DRESS]), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (Table 56-1). Drug-specific T cells have been detected in these types of drug eruptions. In TEN, skin

lesions contain T lymphocytes reactive to autologous lymphocytes and keratinocytes in a drug-specific, human leukocyte antigen (HLA)-restricted, and perforin/granzyme-mediated pathway.

The mechanism(s) by which medications result in T cell activation is unknown. Two hypotheses prevail: first, that the antigens driving these reactions may be the native drug itself or components of the drug covalently complexed with endogenous proteins, presented in association with HLA molecules to T cells through the classic antigen presentation pathway or, alternatively, through direct interaction of the drug/metabolite with the TCR or peptide-loaded HLA (e.g., the pharmacologic interaction of drugs with immune receptors, or p-i hypothesis). Recent x-ray crystallography data characterizing binding between specific HLA molecules to particular drugs known to cause hypersensitivity reactions demonstrate unique alterations to the MHC peptide-binding groove, suggesting a molecular basis for T cell activation in the development of hypersensitivity reactions.

GENETIC FACTORS AND CUTANEOUS DRUG REACTIONS

Genetic determinants may predispose individuals to severe drug reactions by affecting either drug metabolism or immune responses to drugs. Polymorphisms in cytochrome P450 enzymes, drug acetylation, methylation (such as thiopurine methyltransferase activity and azathioprine), and other forms of metabolism (such as glucose-6-phosphate dehydrogenase and dapsone) may increase susceptibility to drug toxicity or underdosing, highlighting a role for differential pharmacokinetic or pharmacodynamic effects. The value of routine screening of P450 enzymes has not been determined, though its cost-effectiveness in certain populations (e.g., patients with seizure disorder) has been suggested.

Associations between drug hypersensitivities and HLA haplotypes suggest a key role for immune mechanisms. Hypersensitivity to the anti-HIV medication abacavir is strongly associated with HLA-B*57:01 (Chap. 197). In Taiwan, within a homogeneous Han Chinese population, a 100% association was observed between SJS/TEN (but not DIHS) related to carbamazepine and HLA-B*15:02. In the same population, another 100% association was found between HLA-B*58:01 and SJS, TEN, or DIHS related to allopurinol. These associations are drug and phenotype specific; that is, HLA-specific T cell stimulation by medications leads to distinct reactions. However, the strong associations found in Taiwan have not been observed in other countries with more heterogeneous populations.

GLOBAL CONSIDERATIONS

Recognition of HLA associations with drug hypersensitivity has resulted in recommendations to screen high-risk populations. Genetic screening for HLA-B*57:01 to prevent abacavir hypersensitivity, which carries a 100% negative predictive value when patch test confirmed and 55% positive predictive value generalizable across races, is becoming the clinical standard of care worldwide (number needed to treat = 13). The U.S. Food and Drug Administration has recommended HLA-B*15:02 screening of Asian individuals prior to a new prescription of carbamazepine. The American College of Rheumatology has recommended HLA-B*58:01 screening of Han Chinese patients prescribed allopurinol. To date, screening for a single HLA (but not multiple HLA haplotypes) in specific populations has been determined to be cost-effective.

Several investigators have proposed that specific HLA haplotypes associated with drug hypersensitivity indeed play a pathogenic role; stimulation of carbamazepine-specific cytotoxic T lymphocytes (CTLs) in the context of HLA-B*15:02 results in production of a putative mediator of keratinocyte necrosis in TEN. Other studies have identified CTLs reactive to carbamazepine that use highly restricted V-alpha and V-beta TCR repertoires in patients with carbamazepine hypersensitivity that are not found in carbamazepine-tolerant individuals. Genetic testing for specific HLA haplotypes and functional screening for TCR repertoire to identify patients at risk is becoming more widely available and heralds the era of personalized medicine and pharmacogenomics.

CLINICAL PRESENTATION OF CUTANEOUS DRUG REACTIONS

NONIMMUNE CUTANEOUS REACTIONS

Exacerbation or Induction of Dermatologic Diseases A variety of drugs can exacerbate preexisting diseases or induce—or unmask—a disease that may or may not disappear after withdrawal of the inducing medication. For example, NSAIDs, lithium, beta blockers, tumor necrosis factor (TNF) antagonists, interferon (IFN) α, and angiotensin-converting enzyme (ACE) inhibitors can exacerbate plaque psoriasis, whereas antimalarials and withdrawal of systemic glucocorticoids can worsen pustular psoriasis. The situation of TNF-α inhibitors is unusual, as this class of medications is used to treat psoriasis; however, they may induce psoriasis (especially palmoplantar) in patients being treated for other conditions. Acne may be induced by glucocorticoids, androgens, lithium, and antidepressants. Follicular papular or pustular eruptions of the face and trunk resembling acne frequently occur with epidermal growth factor receptor (EGFR) antagonists. The severity of the eruption correlates with a better anticancer effect. This rash is typically responsive to and prevented by tetracycline antibiotics.

Several medications induce or exacerbate autoimmune disease. Interleukin (IL) 2, IFN-α, and anti-TNF-α are associated with new-onset systemic lupus erythematosus (SLE). Drug-induced lupus is classically marked by antinuclear and antihistone antibodies and, in some cases, anti-double-stranded DNA (D-penicillamine, anti-TNF-α) or perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) (minocycline) antibodies. Subacute lupus erythematosus (SCLE) can be induced by a growing list of drugs, including thiazide diuretics, TNF-inhibitors, terbinafine, and minocycline. IFN and TNF-inhibitors can induce granulomatous disease and sarcoidosis. Autoimmune blistering diseases may be drug induced as well: pemphigus by D-penicillamine and ACE inhibitors, bullous pemphigoid by furosemide and PD-1 inhibitors, and linear IgA bullous dermatosis by vancomycin. Other medications may cause highly specific cutaneous reactions. Gadolinium contrast has been associated with nephrogenic systemic fibrosis, a condition of sclerosing skin with rare internal organ involvement; advanced renal compromise may be an important risk factor. Granulocyte colony-stimulating factor, azacitidine, all-trans retinoic acid, and the *FLT3*-inhibitor class of drugs may induce neutrophilic dermatoses. In this setting, the hypothesis that a drug may be responsible should always be considered, even after the treatment is complete. In addition, reactions may develop in cases of long-term medication therapy due to small changes in dosing or host metabolism. Resolution of the cutaneous reaction may be delayed upon discontinuation of the medication.

Photosensitivity Eruptions Photosensitivity eruptions are usually most marked in sun-exposed areas, but they may extend to sun-protected areas. The mechanism is almost always phototoxicity. Phototoxic reactions resemble sunburn and can occur with first exposure to a drug. Blistering may occur in drug-related pseudoporphyria, most commonly with NSAIDs. The severity of the reaction depends on the tissue level of the drug, its efficiency as a photosensitizer, and the extent of exposure to the activating wavelengths of ultraviolet (UV) light (Chap. 57).

Common orally administered photosensitizing drugs include fluoroquinolones, tetracycline antibiotics, and trimethoprim/sulfamethoxazole. Other drugs less frequently implicated are chlorpromazine, thiazides, NSAIDs, and BRAF inhibitors. Voriconazole may result in severe photosensitivity, accelerated photoaging, and cutaneous carcinogenesis.

Because UV-A and visible light, which trigger these reactions, are not easily absorbed by nonopaque sunscreens and are transmitted through window glass, photosensitivity reactions may be difficult to block. Photosensitivity reactions abate with removal of either the drug or UV radiation, use of sunscreens that block UV-A light, and treatment of the reaction as one would a sunburn. Rarely, individuals develop persistent reactivity to light, necessitating long-term avoidance of sun exposure. Some chemotherapeutic agents, such as methotrexate, can

induce a UV-recall reaction characterized by an erythematous, slightly scaly eruption at sites of prior severe sun exposure.

Pigmentation Changes Drugs, either systemic or topical, may cause a variety of pigmentary changes in the skin by triggering melanocyte production of melanin (as in the case of oral contraceptives causing melasma) or due to deposition of drug or drug metabolites. Long-term minocycline and amiodarone may cause blue-gray pigmentation. Phenothiazine, gold, and bismuth result in gray-brown pigmentation of sun-exposed areas. Numerous cancer chemotherapeutic agents may be associated with characteristic patterns of pigmentation (e.g., bleomycin, busulfan, daunorubicin, cyclophosphamide, hydroxyurea, fluorouracil, and methotrexate). Clofazimine causes a drug-induced lipofuscinosis with characteristic red-brown coloration. Hyperpigmentation of the face, mucous membranes, and pretibial and subungual areas occurs with antimalarials. Quinacrine causes generalized yellow discoloration. Pigmentation changes may also occur in mucous membranes (busulfan, bismuth), conjunctiva (chlorpromazine, thioridazine, imipramine, clomipramine), nails (zidovudine, doxorubicin, cyclophosphamide, bleomycin, fluorouracil, hydroxyurea), hair, and teeth (tetracyclines).

Warfarin Necrosis of Skin This rare reaction (0.01–0.1%) usually occurs between the third and tenth days of therapy with warfarin, usually in women. Common sites are breasts, thighs, and buttocks (Fig. 56-1). Lesions are sharply demarcated, erythematous, or purpuric, and may progress to form large, hemorrhagic bullae with necrosis and eschar formation.

Warfarin anticoagulation in protein C or S deficiency causes an additional reduction in already low circulating levels of endogenous anticoagulants, permitting hypercoagulability and thrombosis in the cutaneous microvasculature, with consequent areas of necrosis. Heparin-induced necrosis may have clinically similar features but is probably due to heparin-induced platelet aggregation with subsequent occlusion of blood vessels; it can affect areas adjacent to the injection site or more distant sites if infused.

Warfarin-induced cutaneous necrosis is treated with vitamin K, heparin, surgical debridement, and intensive wound care. Treatment with protein C concentrates may also be helpful. Newer anticoagulants such as dabigatran etexilate may avoid warfarin necrosis in high-risk patients.

Drug-Induced Hair Disorders • **DRUG-INDUCED HAIR LOSS** Medications may affect hair follicles at two different phases of their growth cycle: anagen (growth) or telogen (resting). *Anagen effluvium* occurs within days of drug administration, especially with antimetabolite or other chemotherapeutic drugs. In contrast, in *telogen effluvium*, the delay is 2–4 months following initiation of a new medication. Both present as diffuse, nonscarring alopecia most often reversible after discontinuation of the responsible agent.

A considerable number of drugs have been associated with hair loss. These include antineoplastic agents (alkylating agents, bleomycin, vinca alkaloids, platinum compounds), anticonvulsants (carbamazepine, valproate), beta blockers, antidepressants, antithyroid drugs, IFNs, oral contraceptives, and cholesterol-lowering agents.

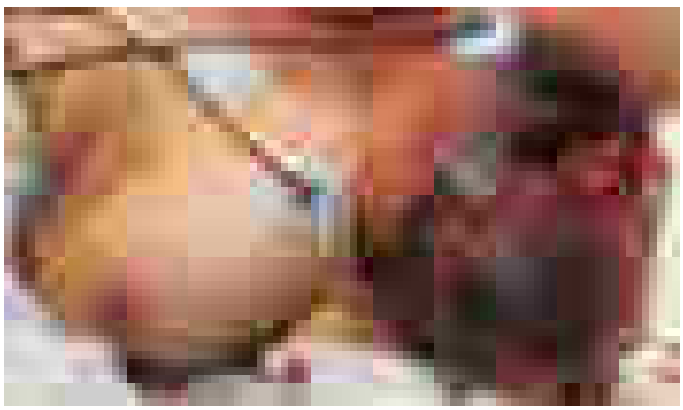

FIGURE 56-1 **Warfarin necrosis** involving the breasts.

DRUG-INDUCED HAIR GROWTH Medications may also cause hair growth. Hirsutism is an excessive growth of terminal hair with masculine hair growth pattern in a female, most often on the face and trunk, due to androgenic stimulation of hormone-sensitive hair follicles (anabolic steroids, oral contraceptives, testosterone, corticotropin). Hypertrichosis is a distinct pattern of hair growth, not in a masculine pattern, typically located on the forehead and temporal regions of the face. Drugs responsible for hypertrichosis include anti-inflammatory drugs, glucocorticoids, vasodilators (diazoxide, minoxidil), diuretics (acetazolamide), anticonvulsants (phenytoin), immunosuppressive agents (cyclosporine A), psoralens, and zidovudine.

Changes in hair color or structure are uncommon adverse effects from medications. Hair discoloration may occur with chloroquine, IFN-α, chemotherapeutic agents, and tyrosine kinase inhibitors. Changes in hair structure have been observed in patients given EGFR inhibitors, BRAF inhibitors, tyrosine kinase inhibitors, and acitretin.

Drug-Induced Nail Disorders Drug-related nail disorders usually involve all 20 nails and need months to resolve after withdrawal of the medication. The pathogenesis is most often toxic. Drug-induced nail changes include Beau's line (transverse depression of the nail plate), onycholysis (detachment of the distal part of the nail plate), onychomadesis (detachment of the proximal part of the nail plate), pigmentation, and paronychia (inflammation of periungual skin).

ONYCHOLYSIS Onycholysis occurs with tetracyclines, fluoroquinolones, retinoids, NSAIDs, and others, including many chemotherapeutic agents, and may be triggered by exposure to sunlight.

ONYCHOMADESIS Onychomadesis is caused by temporary arrest of nail matrix mitotic activity. Common drugs reported to induce onychomadesis include carbamazepine, lithium, retinoids, and chemotherapeutic agents.

PARONYCHIA Paronychia and multiple pyogenic granuloma with progressive and painful periungual abscess of fingers and toes are side effects of systemic retinoids, lamivudine, indinavir, and anti-EGFR monoclonal antibodies.

NAIL DISCOLORATION Some drugs—including anthracyclines, taxanes, fluorouracil, psoralens, and zidovudine—may induce nail bed hyperpigmentation through melanocyte stimulation. It appears to be reversible and dose dependent.

Toxic Erythema of Chemotherapy and Other Chemotherapy Reactions Because many agents used in cancer chemotherapy inhibit cell division, rapidly proliferating elements of the skin, including hair, mucous membranes, and appendages, are sensitive to their effects. A broad spectrum of chemotherapy-related skin toxicities have been reported, including neutrophilic eccrine hidradenitis, sterile cellulitis, exfoliative dermatitis, and flexural erythema; recent nomenclature classifies these under the unifying diagnosis of toxic erythema of chemotherapy (TEC) (Fig. 56-2). Acral erythema is marked by dysesthesia and an erythematous, edematous eruption of the palms and soles. Common causes include cytarabine, doxorubicin, methotrexate, hydroxyurea, fluorouracil, and capecitabine.

The recent introduction of many new monoclonal antibody and small molecular signaling inhibitors for the treatment of cancer has been accompanied by numerous reports of skin and hair toxicity; only the most common of these are mentioned here. EGFR antagonists induce follicular eruptions and nail toxicity after a mean interval of 10 days in a majority of patients. Xerosis, eczematous eruptions, acneiform eruptions, and pruritus are common. Erlotinib is associated with marked hair textural changes. Sorafenib, a tyrosine kinase inhibitor, may result in follicular eruptions and focal bullous eruptions at palmoplantar, flexural sites or areas of frictional pressure. BRAF inhibitors are associated with photosensitivity, palmoplantar hyperkeratosis, hair curling, dyskeratotic (Grover's-like) rash, hyperkeratotic benign cutaneous neoplasms, and keratoacanthoma-like squamous cell carcinomas. Rash, pruritus, and vitiliginous depigmentation have been

FIGURE 56-2 Toxic erythema of chemotherapy.

reported in association with ipilimumab (anti-CTLA4) treatment. Up to 50% of patients experience immune-mediated skin eruptions, including granulomatous reactions, dermatomyositis, panniculitis, and vasculitis.

IMMUNE CUTANEOUS REACTIONS: COMMON

Maculopapular Eruptions Morbilliform or maculopapular eruptions (Fig. 56-3) are the most common of all drug-induced reactions, often start on the trunk or intertriginous areas, and consist of blanching erythematous macules and papules that are symmetric and confluent. Nonblanching, dusky, or bright-red macules should raise concern for a more severe reaction. Involvement of mucous membranes is rare and should prompt consideration of SJS. Facial involvement in morbilliform eruptions is also uncommon, and the presence of extensive facial lesions with facial edema suggests DIHS. Diagnosis of morbilliform eruptions is rarely assisted by laboratory testing. Skin biopsy often shows nonspecific inflammatory changes.

Morbilliform eruptions may be associated with moderate to severe pruritus and fever. A viral exanthem is another differential diagnostic consideration, especially in children, and graft-versus-host disease is also a consideration in the proper clinical setting. Absence of enanthems; absence of ear, nose, throat, and upper respiratory tract symptoms; and polymorphism of the skin lesions support a drug rather than a viral eruption. Common offenders include aminopenicillins, cephalosporins, antibacterial sulfonamides, allopurinol, and antiepileptic drugs. Beta blockers, calcium channel blockers, and ACE inhibitors are rarely the culprit; however, any drug can cause a morbilliform exanthem. Certain medications carry very high rates of morbilliform eruption, including nevirapine and lamotrigine, even in the absence of DIHS reactions. Lamotrigine morbilliform rash is associated with higher starting doses, rapid dose escalation, concomitant use of valproate (which increases lamotrigine levels and half-life), and use in children.

Maculopapular reactions usually develop within 1 week of initiation of therapy and last less than 2 weeks. Occasionally, these eruptions resolve despite continued use of the responsible drug. Because the eruption may also worsen, the suspect drug should be discontinued unless it is essential. It is important to note that the rash may continue to progress for a few days up to 1 week following medication discontinuation. Oral antihistamines and emollients may help relieve pruritus. Short courses of potent topical glucocorticoids can reduce inflammation and symptoms. Systemic glucocorticoid treatment is rarely indicated.

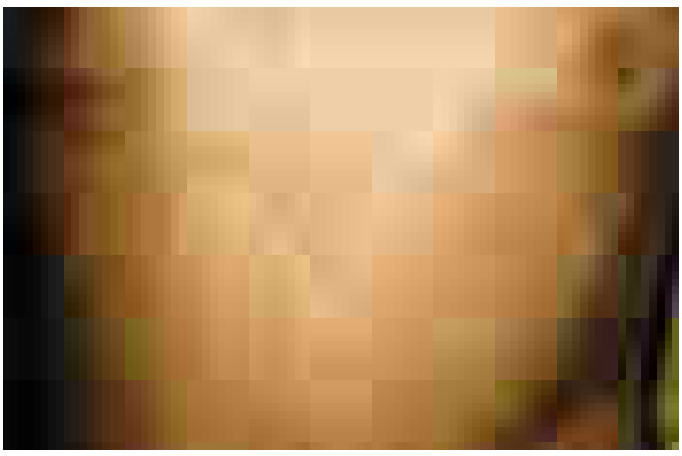

FIGURE 56-3 Morbilliform drug eruption.

Pruritus Pruritus is associated with almost all drug eruptions and, in some cases, may represent the only symptom of the adverse cutaneous reaction. It may be alleviated by antihistamines such as hydroxyzine or diphenhydramine. Pruritus stemming from specific medications may require distinct treatment, such as selective opiate antagonists for opiate-related pruritus.

Urticaria/Angioedema/Anaphylaxis Urticaria, the second most frequent type of cutaneous reaction to drugs, is characterized by pruritic, red wheals of varying size rarely lasting more than 24 hours. It has been observed in association with nearly all drugs, most frequently ACE inhibitors, aspirin, NSAIDs, penicillin, and blood products. However, medications account for no more than 10–20% of acute urticaria cases. Deep edema within dermal and subcutaneous tissues is known as angioedema and may involve respiratory and gastrointestinal mucous membranes. Urticaria and angioedema may be part of a life-threatening anaphylactic reaction.

Drug-induced urticaria may be caused by three mechanisms: an IgE-dependent mechanism, circulating immune complexes (serum sickness), and nonimmunologic activation of effector pathways. IgE-dependent urticarial reactions usually occur within 36 hours of drug exposure, but can occur within minutes. Immune complex–induced urticaria associated with serum sickness–like reactions usually occur 6–12 days after first exposure. In this syndrome, the urticarial eruption (typically polycyclic plaques over distal joints) may be accompanied by fever, hematuria, arthralgias, hepatic dysfunction, and neurologic symptoms. Certain drugs, such as NSAIDs, ACE inhibitors, angiotensin II antagonists, radiographic dye, and opiates, may induce urticarial reactions, angioedema, and anaphylaxis in the absence of drug-specific antibodies through direct mast-cell degranulation.

Radiocontrast agents are a common cause of urticaria and, in rare cases, can cause anaphylaxis. High-osmolality radiocontrast media are about five times more likely to induce urticaria (1%) or anaphylaxis than are newer low-osmolality media. About one-third of those with mild reactions to previous exposure react on reexposure. Pretreatment with prednisone and diphenhydramine reduces reaction rates.

The treatment of urticaria or angioedema depends on the severity of the reaction. In severe cases with respiratory or cardiovascular compromise, epinephrine and intravenous glucocorticoids are the mainstay of therapy. For patients with urticaria without symptoms of angioedema or anaphylaxis, drug withdrawal and oral antihistamines are usually sufficient. Future drug avoidance is recommended; rechallenge,

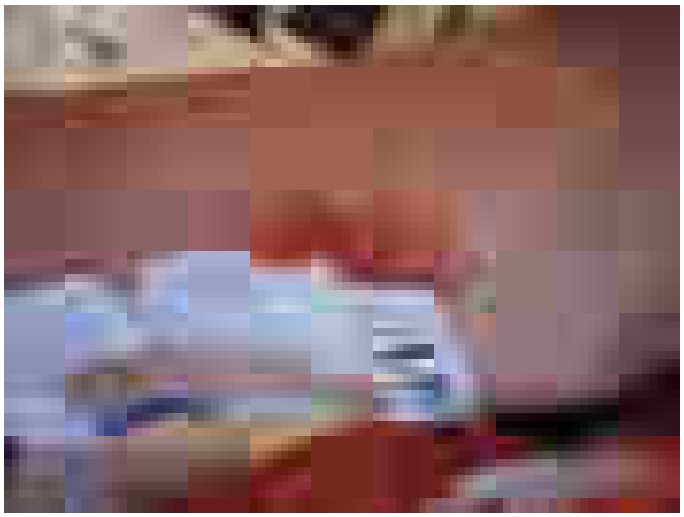

FIGURE 56-4 Allergic contact dermatitis (bullous) due to adhesive tape.

especially in individuals with severe reactions, should only occur in an intensive care setting.

Anaphylactoid Reactions Vancomycin is associated with red man syndrome, a histamine-related anaphylactoid reaction characterized by flushing, diffuse maculopapular eruption, and hypotension. In rare cases, cardiac arrest may be associated with rapid IV infusion of the medication.

Irritant/Allergic Contact Dermatitis Patients using topical medications may develop an irritant or allergic contact dermatitis to the medication itself or to a preservative or other component of the formulation. Reactions to neomycin sulfate, bacitracin, and polymyxin B are common. Contact dermatitis may be seen to adhesive tapes, leading to irritation or blisters around ports and IV sites **(Fig. 56-4)**. Harsh disinfectant skin cleansers may lead to localized irritant dermatitis.

Fixed Drug Eruptions These less common reactions are characterized by one or more sharply demarcated, dull red to brown lesions, sometimes with central dusky violaceous erythema and central bulla **(Fig. 56-5)**. Hyperpigmentation often results after resolution of the acute inflammation. With rechallenge, the process recurs in the same (fixed) location but may spread to new areas as well. Lesions often involve the lips, hands, legs, face, genitalia, and oral mucosa, and cause a burning sensation. Most patients have multiple lesions. Fixed drug eruptions have been associated with pseudoephedrine (frequently a nonpigmenting reaction), phenolphthalein (in laxatives), sulfonamides, tetracyclines, NSAIDs, barbiturates, and others.

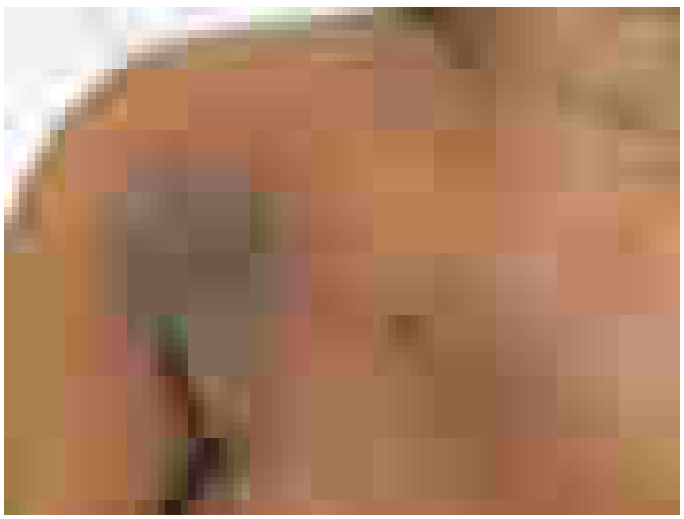

FIGURE 56-5 Fixed drug eruption.

IMMUNE CUTANEOUS REACTIONS: RARE AND SEVERE

Drug-Induced Hypersensitivity Syndrome DIHS is a systemic drug reaction also known as DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome; since eosinophilia is not always present, the term *DIHS* is now preferred. Clinically, DIHS presents with a prodrome of fever and flu-like symptoms for several days, followed by the appearance of a diffuse morbilliform eruption usually involving the face **(Fig. 56-6)**. Facial swelling and hand/foot swelling are often present. Systemic manifestations include lymphadenopathy, fever, and leukocytosis (often with eosinophilia or atypical lymphocytosis), as well as hepatitis, nephritis, pneumonitis, myositis, and gastroenteritis, in descending order. Distinct patterns of timing of onset and organ involvement may exist; for example allopurinol classically induces DIHS with renal involvement, cardiac and lung involvements are more common with minocycline, gastrointestinal involvement is almost exclusively seen with abacavir, and some medications typically lack eosinophilia (abacavir, dapsone, lamotrigine). The cutaneous reaction usually begins 2–8 weeks after the drug is started and persists after drug cessation. Signs and symptoms may continue for several weeks, especially those associated with hepatitis. The eruption recurs with rechallenge, and cross-reactions among aromatic anticonvulsants, including phenytoin, carbamazepine, and phenobarbital, are common. Other drugs causing DIHS include antibacterial sulfonamides and other antibiotics. Hypersensitivity to reactive drug metabolites, hydroxylamine for sulfamethoxazole and arene oxide for aromatic anticonvulsants, may be involved in the pathogenesis of DIHS. Reactivation of herpes viruses, in particular human herpesviruses 6 and 7, EBV, and cytomegalovirus (CMV), has been frequently reported in this syndrome, although the causal role of viral infection has been debated. Recent research suggests that inciting drugs may reactivate quiescent herpes viruses, resulting in expansion of viral-specific CD8+ T lymphocytes and subsequent end-organ damage.

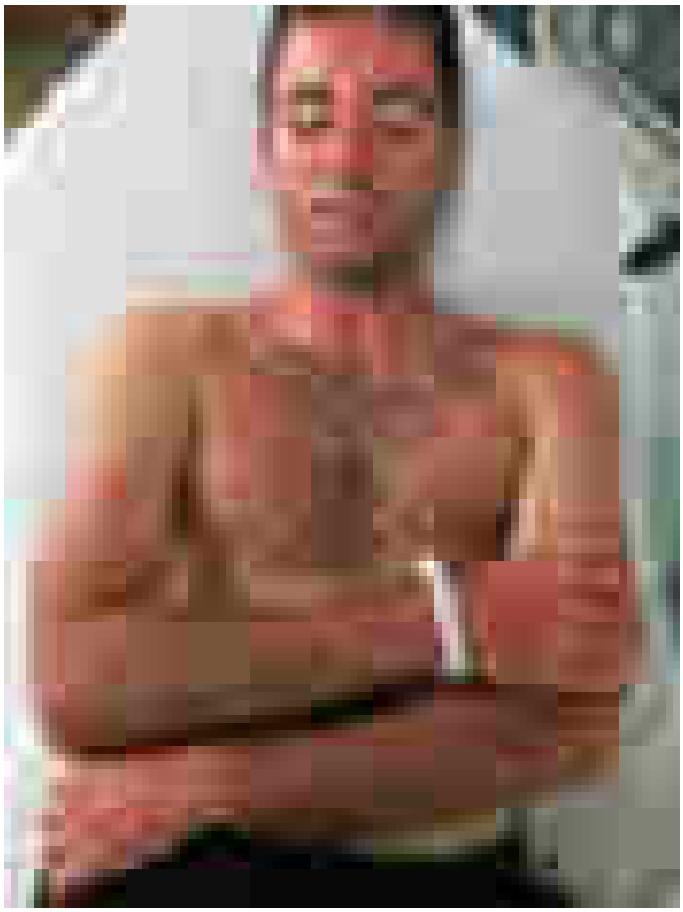

FIGURE 56-6 Drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (DIHS/DRESS).

Viral reactivation may be associated with a worse clinical prognosis. Mortality rates as high as 10% have been reported, with most fatalities resulting from liver failure. Systemic glucocorticoids (1.5–2 mg/kg/d prednisone equivalent) should be started and tapered slowly over 8–12 weeks, during which time clinical symptoms and labs (including complete blood count with differential, basic metabolic panel, and liver function tests) should be followed carefully. A steroid-sparing agent such as mycophenolate mofetil may be indicated in cases of rapid recurrence upon steroid taper. In all cases, immediate withdrawal of the suspected culprit drug is required. Given the severe long-term complications of myocarditis, patients should undergo cardiac evaluation in cases of severe DIHS or if heart involvement is suspected due to hypotension or arrhythmia. Patients should be closely monitored for resolution of organ dysfunction and for development of late-onset autoimmune thyroiditis and diabetes (up to 6 months).

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and *TEN* are characterized by blisters and mucosal/epidermal detachment resulting from full-thickness epidermal necrosis in the absence of substantial dermal inflammation. The term *Stevens-Johnson syndrome* (SJS) describes cases in which the total body surface area of blistering and eventual detachment is <10% **(Fig. 56-7)**. The term *Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap* is used to describe cases with 10–30% epidermal detachment **(Fig. 56-8)**, and *TEN* is used to describe cases with >30% detachment **(Figs. 56-9 and 56-10)**.

Other blistering eruptions with concomitant mucositis may be confused with SJS/TEN. Erythema multiforme (EM) associated with herpes simplex virus is characterized by painful mucosal erosions and target lesions, typically with an acral distribution and limited skin detachment. *Mycoplasma* infection in children causes a clinically distinct presentation with prominent mucositis and limited cutaneous involvement. The name *Mycoplasma*-induced rash and mucositis has been proposed to help differentiate this clinical entity, which some believe may be the syndrome originally described by Stevens and Johnson.

Patients with SJS/TEN initially present with fever >39°C (102.2°F); sore throat; conjunctivitis; and acute onset of painful dusky, atypical, target-like lesions **(Fig. 56-11)**. Intestinal and upper respiratory tract involvement are associated with a poor prognosis, as are older age and greater extent of epidermal detachment. At least 10% of those with SJS and 30% of those with TEN die from the disease. Drugs that most commonly cause SJS/TEN are sulfonamides, allopurinol, antiepileptics (e.g., lamotrigine, phenytoin, carbamazepine), oxicam NSAIDs, β-lactam and other antibiotics, and nevirapine. Frozen-section skin biopsy may aid in rapid diagnosis. At this time, there is no consensus on the most effective treatment for SJS/TEN. The best outcomes stem from early diagnosis, immediate discontinuation of the suspected drug, and meticulous supportive therapy in an intensive care or burn unit. Issues such as fluid management, atraumatic wound care, infection prevention and treatment, and ophthalmologic and respiratory support are critical. Systemic glucocorticoid therapy (prednisone 1–2 mg/kg) may be useful early in disease evolution; however, long-term or late systemic glucocorticoid use has been associated with increased mortality. After initial enthusiasm for the use of intravenous immunoglobulin (IVIG) in the treatment of SJS/TEN, more recent data question whether it is beneficial. There are emerging data to support treatment with cyclosporine and etanercept. Randomized studies to evaluate potential therapies are lacking and difficult to perform.

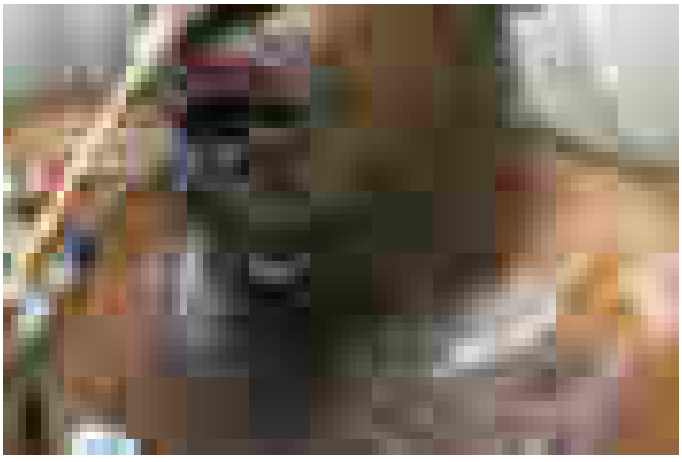

FIGURE 56-7 Stevens-Johnson syndrome (SJS).

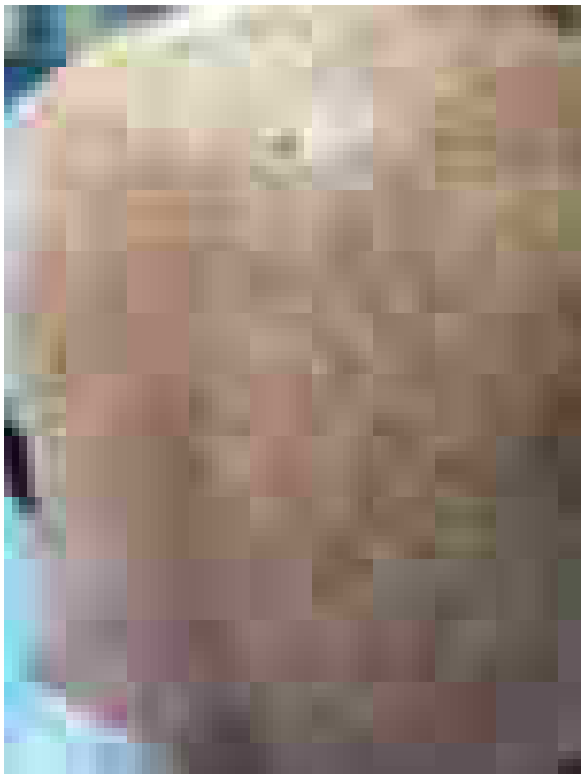

FIGURE 56-8 SJS-TEN overlap.

Pustular Eruptions AGEP is a rare reaction pattern affecting 3–5 people per million per year. It is thought to be secondary to medication exposure in >90% of cases **(Fig. 56-12)**. Patients typically present with diffuse erythema or erythroderma, as well as high spiking fevers, and

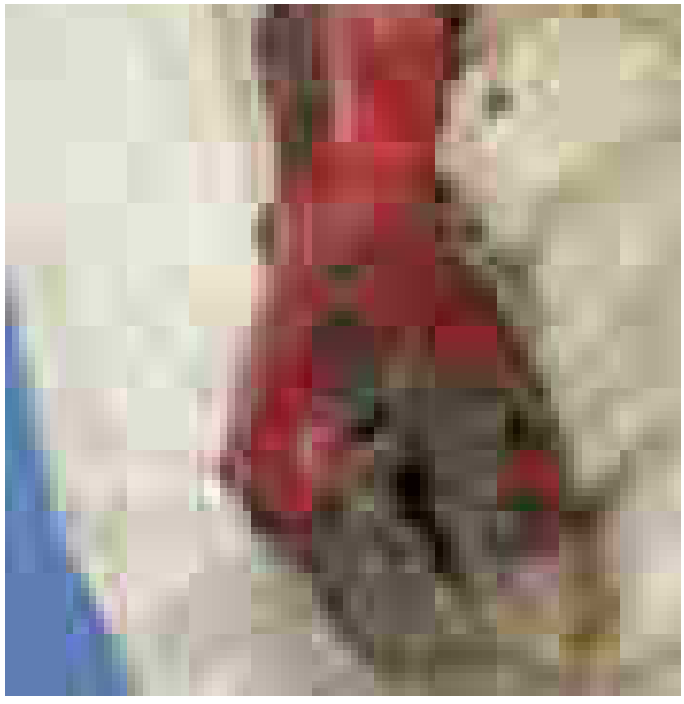

FIGURE 56-9 Toxic epidermal necrolysis, hand.

FIGURE 56-10 Toxic epidermal necrolysis.

leukocytosis. One to two days later, innumerable pinpoint pustules develop overlying the erythema. The pustules are most pronounced in body fold areas; however, they may become generalized and, when coalescent, can lead to superficial erosion. In such cases, differentiating the eruption from SJS in its initial stages may be difficult; in AGEP, any erosions tend to be more superficial, and prominent mucosal involvement is lacking. Skin biopsy shows collections of neutrophils and sparse necrotic keratinocytes in the upper part of the epidermis, unlike the full-thickness epidermal necrosis that characterizes SJS. Before the pustules appear, AGEP may also mimic DIHS due to the prominent fever and erythroderma.

The principal differential diagnosis for AGEP is acute pustular psoriasis, which has an identical clinical and histologic appearance. Many patients with AGEP have a personal or family history of psoriasis. AGEP classically begins within 24–48 hours of drug exposure, though it may occur as much as 1–2 weeks later. β-Lactam antibiotics, calcium channel blockers, macrolide antibiotics, and other inciting agents (including radiocontrast and dialysates) have been reported. Patch testing with the responsible drug often results in a localized pustular eruption.

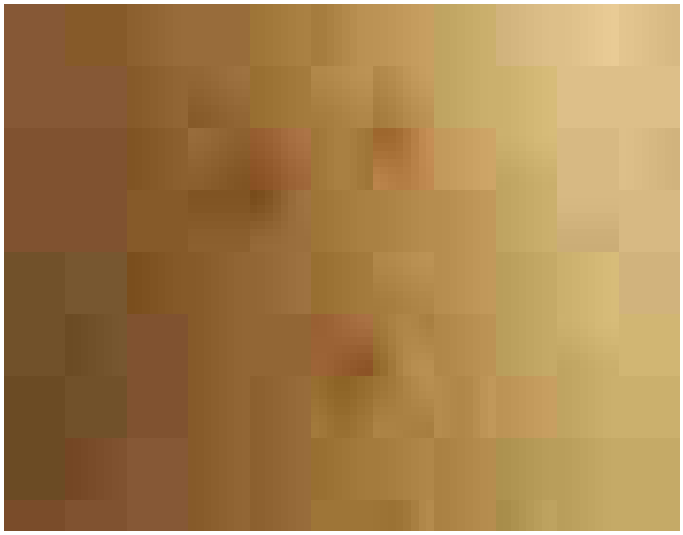

FIGURE 56-11 Target-like lesion in SJS.

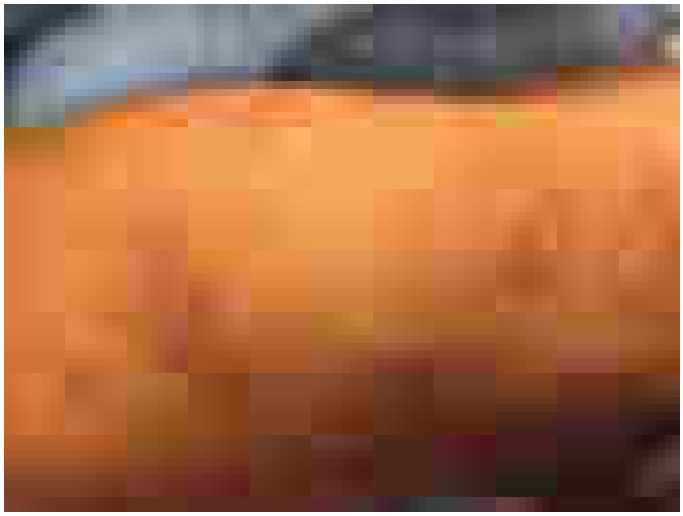

FIGURE 56-12 Acute generalized exanthematous pustulosis.

Overlap Hypersensitivity Syndromes An important concept in the clinical approach to severe drug eruptions is the presence of overlap syndromes, most notably DIHS with TEN-like features, DIHS with pustular eruption (AGEP-like), and AGEP with TEN-like features. In several case series of AGEP, 50% of cases had TEN-like or DRESS-like features, and 20% of cases had mucosal involvement resembling SJS/TEN. In one study, up to 20% of all severe drug eruptions had overlap features, suggesting that AGEP, DIHS, and SJS/TEN represent a clinical spectrum with some common pathophysiologic mechanisms. Designation of a single diagnosis based on cutaneous and extracutaneous involvement may not always be possible in cases of hypersensitivity; in such instances, treatment should be geared toward addressing the dominant clinical features. The timing of rash onset with respect to drug administration, which is usually much more delayed in DIHS, and the presence of systemic manifestations such as hepatitis are helpful clues to that diagnosis.

Vasculitis Cutaneous small-vessel vasculitis (CSVV) typically presents with purpuric papules and macules involving the lower extremities and other dependent areas **(Fig. 56-13) (Chap. 356)**. Pustular and hemorrhagic vesicles as well as rounded ulcers also occur. Importantly, vasculitis may involve other organs, including the kidneys, joints, gastrointestinal tract, and lungs, necessitating a thorough clinical evaluation for systemic involvement. Drugs are implicated as a cause of roughly 15% of all cases of small vessel vasculitis. Antibiotics, particularly β-lactams, are commonly implicated; however, almost any drug can cause vasculitis. Vasculitis may also be idiopathic or due to underlying infection, connective tissue disease, or (rarely) malignancy.

Rare but important types of drug-induced vasculitis include drug-induced ANCA vasculitis. Such patients commonly present with cutaneous manifestations but can develop the full range of symptoms associated with ANCA vasculitis, including crescentic glomerulonephritis and alveolar hemorrhage. Propylthiouracil, methimazole, and hydralazine are common culprits. Drug-induced polyarteritis nodosa has been associated with long-term exposure to minocycline. The presence of perivascular eosinophils on skin biopsy can be a clue to possible drug etiology.

MANAGEMENT OF THE PATIENT WITH SUSPECTED DRUG ERUPTION

There are four main questions to answer regarding a suspected drug eruption:

1. Is the observed rash caused by a medication?
2. Is the reaction severe or evolving?
3. Which drug or drugs are suspected, and should they be withdrawn?
4. What recommendation can be made for future medication use?

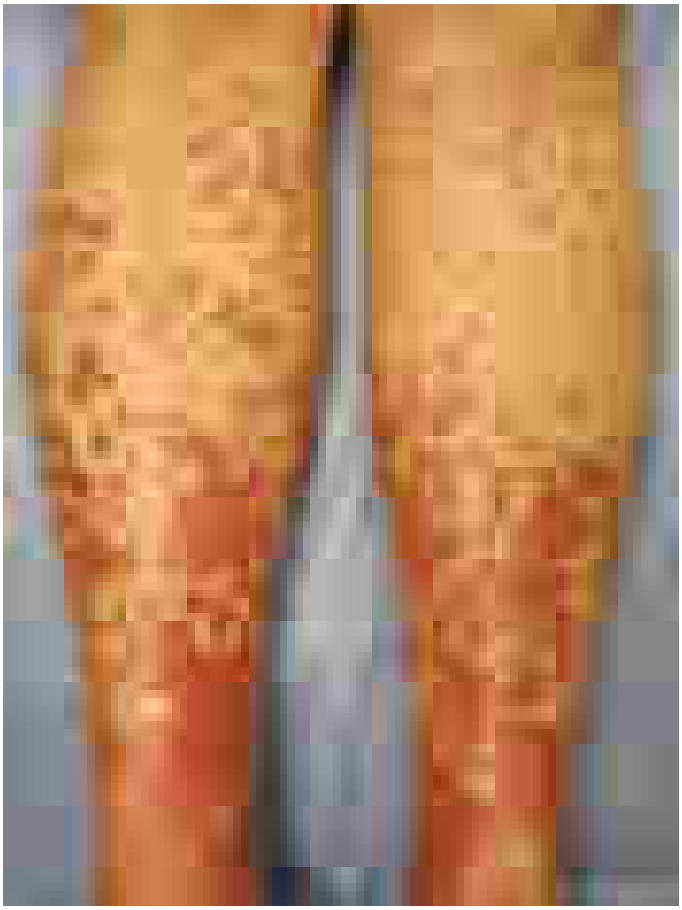

FIGURE 56-13 Cutaneous small-vessel vasculitis (CSVV, leukocytoclastic vasculitis).

EARLY DIAGNOSIS OF SEVERE ERUPTIONS

Rapid recognition of potentially serious or life-threatening reactions is paramount. In this regard, a suspected drug eruption is best defined initially by what it is not (e.g., SJS/TEN, DIHS). Table 56-2 lists clinical and laboratory features that, if present, suggest the presence of a severe reaction. Table 56-3 lists the most important of these reactions, along with their key features and commonly associated medications. Any concern for a serious reaction should prompt immediate consultation with a dermatologist and/or referral of the patient to a specialized center.

TABLE 56-2 Clinical and Laboratory Findings Suggestive of Severe Cutaneous Adverse Drug Reaction

Cutaneous
Generalized erythema
Facial edema
Skin pain
Palpable purpura
Dusky or target-like lesions
Skin necrosis
Blisters or epidermal detachment
Positive Nikolsky sign
Mucous membrane erosions
Swelling of lips or tongue
General
High fever
Enlarged lymph nodes
Arthralgias or arthritis
Shortness of breath, hoarseness, wheezing, hypotension
Laboratory Results
Eosinophil count >1000/μL
Lymphocytosis with atypical lymphocytes
Abnormal liver or kidney function tests

Source: Adapted from JC Roujeau, RS Stern: Severe adverse cutaneous reactions to drugs. N Engl J Med 331:1272, 1994.

CONFIRMATION OF DRUG REACTION

The probability of drug etiology varies with the pattern of the reaction. Only fixed drug eruptions are always drug-induced. Morbilliform eruptions are usually viral in children and drug-induced in adults. Among severe reactions, drugs account for 10–20% of anaphylaxis and vasculitis and between 70% and 90% of AGEP, DIHS, SJS, and TEN. Skin biopsy helps characterize the reaction but does not indicate drug causality. Blood counts and liver and renal function tests are important for evaluating organ involvement. The association of mild elevation of liver enzymes and high eosinophil count is frequent but not specific for a drug reaction. Blood tests that could identify an alternative cause, serologic tests (to rule out drug-induced lupus), and serology or polymerase chain reaction for infections may be of great importance to determine a cause.

WHAT DRUG(S) TO SUSPECT AND WITHDRAW

Most cases of drug eruptions occur during the first course of treatment with a new medication. A notable exception is IgE-mediated urticaria and anaphylaxis that need presensitization and develop a few minutes to a few hours after rechallenge. Characteristic timing of onset following drug administration is as follows: 4–14 days for morbilliform eruption, 2–4 days for AGEP, 5–28 days for SJS/TEN, and 14–48 days for DIHS. A drug chart, compiling information of all current and past medications/supplements and the timing of administration relative to the rash, is a key diagnostic tool for identifying the inciting drug. Medications introduced for the first time in the relevant time frame are prime suspects. Two other important elements to suspect causality at this stage are (1) previous experience with the drug in the population and (2) alternative etiologic candidates.

The decision to continue or discontinue any medication depends on the severity of the reaction, the severity of the primary disease undergoing treatment, the degree of suspicion of causality, and the feasibility of finding an alternative safer treatment. In any potentially fatal drug reaction, elimination of all possible suspect drugs or unnecessary medications should be immediately attempted. Some rashes may resolve when "treating through" a benign drug-related eruption. The decision to treat through an eruption should, however, remain the exception and withdrawal of every suspect drug the general rule. On the other hand, drugs that are not suspected and are important for the patient (e.g., antihypertensive agents) generally should not be quickly withdrawn. This approach may permit judicious use of these agents in the future.

RECOMMENDATION FOR FUTURE USE OF DRUGS

The aims are to (1) prevent the recurrence of the drug eruption and (2) avoid compromising future treatment by inaccurately excluding otherwise useful medications.

A thorough assessment of drug causality is based on timing of the reaction, evaluation of other possible causes, and effect of drug withdrawal or continuation. The RegiSCAR group has proposed the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) to rank likelihood of drug causality in SJS/TEN; validation of this and other instruments, such as the Naranjo adverse drug reaction probability scale, is limited. Medication(s) with a "definite" or "probable" causality should be contraindicated, a warning card or medical alert tag (e.g., wristband) should be given to the patient, and the drugs should be listed in the patient's medical chart as allergies.

CROSS-SENSITIVITY

Because of possible cross-sensitivity among chemically related drugs, many physicians recommend avoidance of not only the medication that induced the reaction but also all drugs of the same pharmacologic class.

There are two types of cross-sensitivity. Reactions that depend on a pharmacologic interaction may occur with all drugs that target the same pathway, whether the drugs are structurally similar or not. This is the case with angioedema caused by NSAIDs and ACE inhibitors. In this situation, the risk of recurrence varies from drug to drug in a

TABLE 56-3 Clinical Features of Severe Cutaneous Drug Reactions

DIAGNOSIS	MUCOSAL LESIONS	TYPICAL SKIN LESIONS	FREQUENT SIGNS AND SYMPTOMS	MOST COMMON CULPRIT DRUGS
Stevens-Johnson syndrome (SJS)	Erosions usually at two or more sites	Small blisters form from dusky macules or atypical targets; rare areas of confluence; detachment ≤10% body surface area	Most cases involve fever	Sulfonamides, anticonvulsants, allopurinol, nonsteroidal anti-inflammatory drugs (NSAIDs)
Toxic epidermal necrolysis (TEN)[a]	Erosions usually at two or more sites	Individual lesions like those seen in SJS; confluent dusky erythema; large sheets of necrotic epidermis; total detachment of >30% body surface area	Nearly all cases involve fever, "acute skin failure," leukopenia	Same as for SJS
Drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (DIHS/DRESS)	Mucositis reported in as many as 30%	Diffuse, deep red morbilliform eruption with facial involvement; facial and acral swelling	Fever, lymphadenopathy, hepatitis, nephritis, myocarditis, eosinophilia, atypical lymphocytosis	Anticonvulsants, sulfonamides, allopurinol, minocycline
Acute generalized exanthematous pustulosis (AGEP)	Oral erosions in perhaps 20%	Innumerable pinpoint pustules overlying a diffuse erythematous eruption; may develop superficial erosions	High fever, leukocytosis (neutrophilia), hypocalcemia	β-Lactam antibiotics, calcium channel blockers, macrolide antibiotics
Serum sickness or serum sickness-like reaction	Absent	Urticarial serpiginous or polycyclic rash; purpuric eruption along the sides of the feet and hands is characteristic	Fever, arthralgias	Antithymocyte globulin, cephalosporins, monoclonal antibodies
Anticoagulant-induced necrosis	Infrequent	Purpura and necrosis, especially of central, fatty areas	Pain in affected areas	Warfarin, heparin
Angioedema	Often involved	Urticaria or swelling of the central face, other areas	Respiratory distress, cardiovascular collapse	Angiotensin-converting enzyme (ACE) inhibitors, NSAIDs, contrast dye

[a]Overlap of SJS and TEN have features of both, and attachment of 10–30% of body surface area may occur.

Source: Adapted from JC Roujeau, RS Stern: Severe adverse cutaneous reactions to drugs. N Engl J Med 331:1272, 1994.

particular class; however, avoidance of all drugs in the class is usually recommended. Immune recognition of structurally related drugs is the second mechanism by which cross-sensitivity occurs. A classic example is hypersensitivity to aromatic antiepileptics (barbiturates, phenytoin, carbamazepine) with up to 50% reaction to a second drug in patients who reacted to one. For other drugs, in vitro and in vivo data have suggested that cross-reactivity exists only between compounds with very similar chemical structures. Sulfamethoxazole-specific lymphocytes may be activated by other antibacterial sulfonamides but not diuretics, antidiabetic drugs, or anti-COX2 NSAIDs with a sulfonamide group. Approximately 10% of patients with penicillin allergies will also develop allergic reactions to cephalosporin class antibiotics.

Recent data suggest that although the risk of developing a drug eruption to another drug is increased in persons with a prior reaction, "cross-sensitivity" is probably not the explanation. As an example, those with a history of an allergic-like reaction to penicillin are at greater risk of developing a reaction to antibacterial sulfonamides than to cephalosporins.

These data suggest that the list of drugs to avoid after a drug reaction should be limited to the causative one(s) and to a few very similar medications.

Because of growing evidence that some severe cutaneous reactions to drugs are associated with HLA genes, it is recommended that first-degree family members of patients with severe cutaneous reactions also should avoid causative agents. This may be most relevant for sulfonamides and antiepileptic medications.

ROLE OF TESTING FOR CAUSALITY AND DRUG RECHALLENGE

The usefulness of laboratory tests, skin-prick, or patch testing to determine causality is debated. Many in vitro immunologic assays have been developed for research purposes; however, the predictive value of these tests has not been validated in large series of affected patients. In some cases, diagnostic rechallenge may be appropriate, even for drugs with high rates of adverse reactions.

Skin-prick testing has clinical value in limited settings. In patients with a history suggesting immediate IgE-mediated reactions to penicillin, skin-prick testing with penicillins or cephalosporins has proven useful for identifying patients at risk of anaphylactic reactions to these agents. Negative skin tests do not totally rule out IgE-mediated reactivity; however, the risk of anaphylaxis in response to penicillin administration in patients with negative skin tests is about 1%. In contrast, two-thirds of patients with a positive skin test experience an allergic response upon rechallenge. The skin tests themselves carry a small risk of anaphylaxis.

For patients with delayed-type hypersensitivity, the clinical utility of skin tests remains questionable. At least one of a combination of several tests (prick, patch, and intradermal) is positive in 50–70% of patients with a reaction "definitely" attributed to a single medication. This low sensitivity corresponds to the observation that readministration of drugs with negative skin testing results in eruptions in 17% of cases.

Desensitization can be considered in those with a history of reaction to a medication that must be used again. Efficacy of such procedures has been demonstrated in cases of immediate reaction to penicillin and positive skin tests, anaphylactic reactions to platinum chemotherapy, and delayed reactions to sulfonamides in patients with AIDS. Desensitization is often successful in HIV-infected patients with morbilliform eruptions to sulfonamides but is not recommended in HIV-infected patients who developed erythroderma or a bullous reaction in response to prior sulfonamide exposure. Various protocols are available, including oral and parenteral approaches. Oral desensitization appears to have a lower risk of serious anaphylactic reaction. Desensitization carries the risk of anaphylaxis regardless of how it is performed and should be performed in monitored clinical settings such as an intensive care unit. After desensitization, many patients experience non-life-threatening reactions during therapy with the culprit drug.

REPORTING

Any severe reaction to drugs should be reported to a regulatory agency or to pharmaceutical companies. Because severe reactions are too rare to be detected in premarketing clinical trials, spontaneous reports are of critical importance for early detection of unexpected life-threatening events. To be useful, the report should contain enough details to permit ascertainment of severity and drug causality.

ACKNOWLEDGMENTS

We acknowledge the contribution of Drs. Jean-Claude Roujeau and Robert S. Stern to this chapter in previous editions.

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57 Photosensitivity and Other Reactions to Light

Alexander G. Marneros, David R. Bickers

SOLAR RADIATION

Sunlight is the most visible and obvious source of comfort in the environment. The sun provides the beneficial effects of warmth and vitamin D synthesis. However, acute and chronic sun exposure also has pathologic consequences. Cutaneous exposure to sunlight is a major cause of human skin cancer and can have immunosuppressive effects as well.

The sun's energy reaching the earth's surface is limited to components of the ultraviolet (UV) spectrum, the visible spectrum, and portions of the infrared spectrum. The cutoff at the short end of the UV spectrum at ~290 nm is due primarily to stratospheric ozone—formed by highly energetic ionizing radiation—that prevents penetration to the earth's surface of the shorter, more energetic, potentially more harmful wavelengths of solar radiation. Indeed, concern about destruction of the ozone layer by chlorofluorocarbons released into the atmosphere has led to international agreements to reduce production of those chemicals.

Measurements of solar flux showed a 20-fold regional variation in the amount of energy at 300 nm that reaches the earth's surface. This variability relates to seasonal effects, the path that sunlight traverses through ozone and air, the altitude (a 4% increase for each 300 m of elevation), the latitude (increasing intensity with decreasing latitude), and the amount of cloud cover, fog, and pollution.

The major components of the photobiologic action spectrum that are capable of affecting human skin include the UV and visible wavelengths between 290 and 700 nm. In addition, the wavelengths beyond 700 nm in the infrared spectrum primarily emit heat and in certain circumstances may exacerbate the pathologic effects of energy in the UV and visible spectra.

The UV spectrum reaching the Earth represents <10% of total incident solar energy and is arbitrarily divided into two major segments, UV-B and UV-A, which constitute the wavelengths from 290 to 400 nm. UV-B consists of wavelengths between 290 and 320 nm. This portion of the photobiologic action spectrum is the most efficient in producing redness or erythema in human skin and thus is sometimes known as the "sunburn spectrum." UV-A includes wavelengths between 320 and 400 nm and is ~1000-fold less efficient in producing skin redness than is UV-B.

The wavelengths between 400 and 700 nm are visible to the human eye. The photon energy in the visible spectrum is not capable of damaging human skin in the absence of a photosensitizing chemical. Without the absorption of energy by a molecule, there can be no photosensitivity. Thus, the *absorption spectrum* of a molecule is defined as the range of wavelengths it absorbs, whereas the *action spectrum* for an effect of incident radiation is defined as the range of wavelengths that evoke the response.

Photosensitivity occurs when a photon-absorbing chemical (*chromophore*) present in the skin absorbs incident energy, becomes excited, and transfers the absorbed energy to various structures or to molecular oxygen.

UV RADIATION (UVR) AND SKIN STRUCTURE AND FUNCTION

Human skin consists of two major compartments: the outer epidermis, which is a stratified squamous epithelium, and the underlying dermis, which is rich in matrix proteins such as collagens and elastin. Both compartments are susceptible to damage from sun exposure. The epidermis and the dermis contain several chromophores capable of absorbing incident solar energy, including nucleic acids, proteins, and lipids. The outermost epidermal layer, the stratum corneum, is a major absorber of UV-B, and <10% of incident UV-B wavelengths penetrate through the epidermis to the dermis. Approximately 3% of radiation below 300 nm, 20% of radiation below 360 nm, and 33% of short visible radiation reach the basal cell layer in untanned human skin. UV-A readily penetrates to the dermis and is capable of altering structural and matrix proteins that contribute to photoaging of chronically sun-exposed skin, particularly in individuals of light complexion. Thus, longer wavelengths can penetrate more deeply into the skin.

Molecular Targets for UVR-Induced Skin Effects Epidermal DNA—predominantly in keratinocytes and in Langerhans cells, which are dendritic antigen-presenting cells—absorbs UV-B and undergoes structural changes between adjacent pyrimidine bases (thymine or cytosine), including the formation of cyclobutane dimers and 6,4-photoproducts. These structural changes are potentially mutagenic and are found in most basal cell and squamous cell carcinomas (BCCs and SCCs, respectively). They can be repaired by cellular mechanisms that result in their recognition and excision and the restoration of normal base sequences. The efficient repair of these structural aberrations is crucial, since individuals with defective DNA repair are at high risk for the development of cutaneous cancer. For example, patients with xeroderma pigmentosum, an autosomal recessive disorder, have a variably deficient repair of UV-induced photoproducts. The skin of these patients often shows the dry, leathery appearance of prematurely photoaged skin, and these patients have an increased frequency of skin cancer already in the first two decades of life. Studies in transgenic mice have verified the importance of functional genes that regulate these repair pathways in preventing the development of UV-induced skin cancer. DNA damage to Langerhans cells may also contribute to the known immunosuppressive effects of UV-B (see "Photoimmunology," later).

In addition to DNA, molecular oxygen is a target for incident solar UVR, leading to the generation of reactive oxygen species (ROS). These

ROS can damage skin components through oxidative damage to DNA, oxidation of polyunsaturated fatty acids in lipids (lipid peroxidation), oxidation of amino acids in proteins, or they can lead to oxidative deactivation of specific enzymes. UVR can also promote increased cross-linking and degradation of dermal matrix proteins and accumulation of abnormal dermal elastin leading to photoaging changes known as *solar elastosis*.

Cutaneous Optics and Chromophores *Chromophores* are endogenous or exogenous chemical components that can absorb physical energy. Endogenous chromophores are of two types: (1) normal components of skin, including nucleic acids, proteins, lipids, and 7-dehydrocholesterol (the precursor of vitamin D); and (2) components that are synthesized elsewhere in the body and that circulate in the bloodstream and diffuse into the skin, such as porphyrins. Normally, only trace amounts of porphyrins are present in the skin, but, in selected diseases known as the *porphyrias* **(Chap. 409)**, porphyrins are released into the circulation in increased amounts from the bone marrow and the liver and are transported to the skin, where they absorb incident energy both in the Soret band (~400 nm; short visible) and, to a lesser extent, in the red portion of the visible spectrum (580–660 nm). This energy absorption results in the generation of ROS that can mediate structural damage to the skin, manifested as erythema, edema, urticaria, or blister formation. It is of interest that photoexcited porphyrins are currently used in the treatment of BCCs and SCCs and their precursor lesions, actinic keratoses. Known as *photodynamic therapy* (PDT), this modality generates ROS in the skin, leading to cell death. Topical photosensitizers used in PDT are the porphyrin precursors 5-aminolevulinic acid and methyl aminolevulinate, which are converted to porphyrins in the skin. It is believed that PDT targets tumor cells for destruction more selectively than it targets adjacent nonneoplastic cells. The efficacy of such therapy requires appropriate timing of the application of methyl aminolevulinate or 5-aminolevulinic acid to the affected skin followed by exposure to artificial sources of visible light. High-intensity blue light has been used successfully for the treatment of thin actinic keratoses. Red light has a longer wavelength, penetrates more deeply into the skin, and is more beneficial in the treatment of superficial BCCs.

Acute Effects of Sun Exposure The acute effects of skin exposure to sunlight include sunburn and vitamin D synthesis.

SUNBURN This painful skin condition is an acute inflammatory response of the skin, predominantly to UV-B. Generally, an individual's ability to tolerate sunlight is inversely proportional to that individual's degree of melanin pigmentation. Melanin, a complex polymer of tyrosine derivatives, is synthesized in specialized epidermal dendritic cells known as *melanocytes* and is packaged into *melanosomes* that are transferred via dendritic processes into *keratinocytes*, thereby providing photoprotection (dissipating the vast majority of absorbed UVR in the skin) and simultaneously darkening the skin. Sun-induced melanogenesis is a consequence of increased tyrosinase activity in melanocytes. Central to the suntan response is the melanocortin-1 receptor (*MC1R*), and mutations in this gene contribute to the wide variation in human skin and hair color; individuals with red hair and fair skin typically have low MC1R activity. In the skin there are two main types of melanin: eumelanin (providing brown and black pigmentation associated with high MC1R activity) and pheomelanin (providing red pigmentation associated with low MC1R activity). Pheomelanin is a cysteine-containing red polymer of benzothiazine units and has much weaker shielding capacity against UVR compared to eumelanin. This may explain why individuals with a higher proportion of pheomelanin (red hair/fair skin appearance) have an increased risk of melanoma formation. In addition, pheomelanin may also promote melanoma formation through induction of oxidative damage by amplifying UV-A-induced ROS but also through UVR-independent mechanisms.

Genetic studies have revealed additional genes that influence skin color variation in humans, such as the gene for tyrosinase (*TYR*) and the genes *APBA2[OCA2]*, *SLC45A2*, and *SLC24A5*. The human *MC1R* gene encodes a G protein–coupled receptor that binds α-melanocyte-stimulating hormone (α-MSH), which is secreted in the skin mainly by keratinocytes in response to UVR. The UV-induced expression of this hormone is controlled by the tumor suppressor p53, and absence of functional p53 attenuates the tanning response. Activation of the melanocortin receptor leads to increased intracellular cyclic adenosine 5′-monophosphate (cAMP) and protein kinase A activation, resulting in an increased transcription of the microphthalmia-associated transcription factor (MITF), which stimulates melanogenesis. Since the precursor of α-MSH, proopiomelanocortin produced by keratinocytes, is also the precursor of β-endorphins, UVR may result in not only increased pigmentation but also in increased β-endorphin production in the skin, an effect that has been hypothesized to promote sun-seeking behaviors and even mediate addiction to tanning.

TABLE 57-1 Skin Type and Sunburn Sensitivity (Fitzpatrick Classification)

TYPE	DESCRIPTION
I	Always burn, never tan
II	Always burn, sometimes tan
III	Sometimes burn, sometimes tan
IV	Sometimes burn, always tan
V	Never burn, sometimes tan
VI	Never burn, always tan

The Fitzpatrick classification of human skin phototypes is based on the efficiency of the epidermal-melanin unit, which usually can be ascertained by asking an individual two questions: (1) Do you burn after sun exposure? (2) Do you tan after sun exposure? The answers to these questions permit division of the population into six skin types, varying from type I (always burn, never tan) to type VI (never burn, always tan) **(Table 57-1)**.

Sunburn erythema is due to vasodilation of dermal blood vessels. There is a lag time (usually 4–12 h) between skin exposure to sunlight and the development of visible redness. The action spectrum for sunburn erythema includes UV-B and UV-A, although UV-B is much more efficient than UV-A in evoking the response. However, UV-A may contribute to sunburn erythema at midday, when much more UV-A than UV-B is present in the solar spectrum. The erythema that accompanies the inflammatory response induced by UVR results from the orchestrated release of cytokines along with growth factors and the generation of ROS. Furthermore, UV-induced activation of nuclear factor κB–dependent gene transcription can augment release of several proinflammatory cytokines and vasoactive mediators. These cytokines and mediators accumulate locally in sunburned skin, providing chemotactic factors that attract neutrophils, macrophages, and T lymphocytes, which promote the inflammatory response. UVR also stimulates infiltration of inflammatory cells through induced expression of adhesion molecules such as E-selectin and intercellular adhesion molecule 1 on endothelial cells and keratinocytes. UVR also has been shown to activate phospholipase A_2, resulting in increases in eicosanoids such as prostaglandin E_2, which is known to be a potent inducer of sunburn erythema. The role of eicosanoids in this reaction has been verified by studies showing that nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce sunburn erythema.

Epidermal changes in sunburn include the induction of "sunburn cells," which are keratinocytes undergoing p53-dependent apoptosis as a defense, with elimination of cells that harbor UV-B-induced structural DNA damage.

VITAMIN D SYNTHESIS AND PHOTOCHEMISTRY Cutaneous exposure to UV-B causes photolysis of epidermal 7-dehydrocholesterol, converting it to pre–vitamin D_3, which then undergoes temperature-dependent isomerization to form the stable hormone vitamin D_3. This compound diffuses to the dermal vasculature and circulates to the liver and kidney, where it is converted to the dihydroxylated functional hormone 1,25-dihydroxyvitamin D_3. Vitamin D metabolites from the circulation and those produced in the skin itself can augment epidermal differentiation signaling and inhibit keratinocyte proliferation. These effects are exploited therapeutically in psoriasis with the topical application

of synthetic vitamin D analogues. In addition, vitamin D is increasingly thought to have beneficial effects in several other inflammatory conditions, and some evidence suggests that—besides its classic physiologic effects on calcium metabolism and bone homeostasis—it is associated with a reduced risk of various internal malignancies. There is controversy regarding the risk-to-benefit ratio of sun exposure for vitamin D homeostasis. At present, it is important to emphasize that no clear-cut evidence suggests that the use of sunscreens substantially diminishes vitamin D levels. Since aging also substantially decreases the ability of human skin to photocatalytically produce vitamin D_3, the widespread use of sunscreens that filter out UV-B has led to concerns that the elderly might be unduly susceptible to vitamin D deficiency. However, the amount of sunlight needed to produce sufficient vitamin D is small and does not justify the risks of skin cancer and other types of photodamage linked to increased sun exposure or tanning behavior. Nutritional supplementation of vitamin D is a preferable strategy for patients with vitamin D deficiency.

Chronic Effects of Sun Exposure: Nonmalignant The clinical features of photoaging (*dermatoheliosis*) consist of wrinkling, blotchiness, and telangiectasia, as well as a roughened, irregular, "weather-beaten" leathery appearance.

UVR is important in the pathogenesis of photoaging in human skin, and ROS are likely involved. The dermis and its connective tissue matrix are major targets for sun-associated chronic damage that manifests as solar elastosis, a massive increase in thickened irregular masses of abnormal-appearing elastic fibers. Collagen fibers are also abnormally clumped in the deeper dermis of sun-damaged skin. The chromophores, the action spectra, and the specific biochemical events orchestrating these changes are only partially understood, although more deeply penetrating UV-A seems to be primarily involved. Chronologically aged sun-protected skin and photoaged skin share important molecular features, including connective tissue damage and elevated levels of matrix metalloproteinases (MMPs). MMPs are enzymes involved in the degradation of the extracellular matrix. UV-A induces expression of some MMPs, including MMP-1 and MMP-3, leading to increased collagen breakdown. In addition, UV-A reduces type I procollagen messenger RNA (mRNA) expression. Thus, chronic UVR alters the structure and function of dermal collagen both by inhibiting its synthesis and enhancing its breakdown. On the basis of these observations, it is not surprising that high-dose UV-A phototherapy may have beneficial effects in some patients with localized fibrotic diseases of the skin, such as localized scleroderma.

Chronic Effects of Sun Exposure: Malignant One of the major known consequences of chronic excessive skin exposure to sunlight is nonmelanoma skin cancer (NMSC). The two most common types of NMSC are BCC and SCC **(Chap. 72)**. A model for skin cancer induction involves three major steps: initiation, promotion, and progression. Exposure of human skin to sunlight results in *initiation*, a step by which structural (mutagenic) changes in DNA evoke an irreversible alteration in the target cell (keratinocyte) that begins the tumorigenic process. Exposure to a tumor initiator such as UV-B is believed to be a necessary but not a sufficient step in the malignant process, since initiated skin cells not exposed to tumor promoters generally do not develop into tumors. The second stage in tumor development is *promotion*, a multistep process by which chronic exposure to sunlight evokes further changes that culminate in the clonal expansion of initiated cells and cause the development of premalignant growths known as *actinic keratoses*, which may progress to form SCCs. As a result of extensive studies, it seems clear that UV-B is a *complete carcinogen*, meaning that it can act as both a tumor initiator and a tumor promoter. The third and final step in the malignant process is *malignant conversion* of benign precursors into malignant lesions, a process thought to require additional genetic alterations.

On a molecular level, skin carcinogenesis results from the accumulation of gene mutations that cause inactivation of tumor suppressors, activation of oncogenes, or reactivation of cellular signaling pathways that normally are expressed only during embryologic epidermal development. Interestingly, a large number of UV-induced oncogenic driver mutations that are present in SCCs can already be found in aged sun-exposed normal skin, leading to a growth advantage and innumerable precancerous clones carrying cancer-causing mutations. These mutations occur particularly often in genes that affect proliferation of epidermal stem cells (e.g., NOTCH receptor genes). The pattern of oncogenic gene mutations in aged sun-exposed skin shows considerable overlap with the mutations identified in SCCs, while there is little overlap with the mutations identified in BCCs or melanomas. For example, ~20% of normal aged sun-exposed skin cells and ~60% of SCCs carry driver mutations in *NOTCH1*. Additionally, the accumulation of mutations in the tumor-suppressor gene *p53* can also promote skin carcinogenesis. Indeed, the majority of both human and murine UV-induced skin cancers have characteristic UVR-induced *p53* mutations (C → T and CC → TT transitions). Studies in mice have shown that sunscreens can substantially reduce the frequency of these signature mutations in *p53* and inhibit the induction of tumors. The comparison of UVR-induced gene mutations between aged sun-exposed normal skin and SCCs supports the hypothesis of a progressive accumulation of additional oncogenic mutations that eventually lead to the transition from precancerous cell clones to SCCs. It has been estimated that SCCs harbor ~10 times more oncogenic driver mutations per cell than cells in aged sun-exposed normal skin. Furthermore, while aged sun-exposed skin and SCCs carry similar UVR-induced mutations in *p53* or NOTCH receptors, oncogenic mutations in other genes (e.g., *CDKN2A*) were mainly found in SCCs and not in aged sun-exposed skin, which are thus likely to play a critical role in malignant progression.

Compared to SCCs, BCCs carry a distinct mutational profile in specific genes that are critical for their formation. BCCs harbor inactivating mutations particularly in the tumor-suppressor gene *patched* or activating mutations in the oncogene *smoothened*, which results in the constitutive activation of the sonic hedgehog signaling pathway and increased cell proliferation. New evidence links alterations in the Wnt/β-catenin signaling pathway, which is known to be critical for hair follicle development, to skin cancer as well. Thus, interactions between this pathway and the hedgehog signaling pathway appear to be involved in both skin carcinogenesis and embryologic development of the skin and hair follicles.

Clonal analysis in mouse models of BCC revealed that tumor cells arise from stem cells of the interfollicular epidermis and the upper infundibulum of the hair follicle. These BCC-initiating cells are reprogrammed to resemble embryonic hair follicle progenitors, whose tumor-initiating ability depends on activation of the Wnt/β-catenin signaling pathway.

SCC initiation occurs both in the interfollicular epidermis and in the hair follicle bulge stem cell populations. In mouse models, the combination of mutant K-Ras and p53 is sufficient to induce invasive SCCs from these cell populations.

The transcription factor Myc is important for stem cell maintenance in the skin, and oncogenic activation of Myc has been implicated in the development of BCCs and SCCs. Thus, NMSC involves mutations and alterations in multiple genes and pathways that occur as a result of their chronic accumulation driven by exposure to environmental factors such as solar UVR.

Epidemiologic studies have linked excessive sun exposure to an increased risk of NMSCs and melanoma of the skin; the evidence is far more direct for NMSCs (BCCs and SCCs) than for melanoma. Approximately 80% of NMSCs develop on sun-exposed body areas, including the face, neck, and hands. Major risk factors include male sex, childhood sun exposures, older age, fair skin, and residence at latitudes relatively close to the equator. Individuals with darker-pigmented skin have a lower risk of skin cancer than do fair-skinned individuals. More than 2 million individuals in the United States develop NMSC annually, and the lifetime risk that a fair-skinned individual will develop such a neoplasm is estimated at ~15%. The incidence of NMSC in the population is increasing at a rate of 2–3% per year.

The relationship of sun exposure to melanoma development is less direct, but strong evidence supports an association. Clear-cut risk factors include a positive family or personal history of melanoma and multiple dysplastic nevi. Melanomas can occur during adolescence;

the implication is that the latent period for tumor growth is shorter than that for NMSC. For reasons that are only partially understood, melanomas are among the most rapidly increasing human malignancies (Chap. 72). One potential explanation is the widespread use of indoor tanning. It is estimated that 30 million people tan indoors in the United States annually, including >2 million adolescents. Furthermore, epidemiologic studies suggest that life in a sunny climate from birth or early childhood may increase the risk of melanoma development. In general, risk does not correlate with cumulative sun exposure but may be related to the duration and extent of exposure in childhood.

However, in contrast to NMSCs, melanoma frequently develops in non–sun-exposed skin, and oncogenic mutations in melanoma may also not be UVR-signature mutations. These observations suggest that UVR-independent factors may contribute to melanomagenesis, which is consistent with findings in mouse models showing that pheomelanin can promote melanoma formation through UVR-independent mechanisms.

Importantly, mutations in BRAF and NRAS that lead to activation of a growth-promoting signaling cascade are frequently found in melanoma (but not in SCCs or BCCs), which has led to the development of specific inhibitors of this pathway for the treatment of BRAF-mutant melanoma. However, a high mutational load in melanoma may not be equated with a more unfavorable prognosis. Tumor-specific missense mutations in melanomas can result in neoantigens that facilitate an immune response to the tumor cell. A novel therapeutic approach for melanoma, termed immune checkpoint blockade, targets inhibitors of T cell activation (such as CTLA-4 or PD-1) that in a subset of patients has resulted in a durable and potent immune destruction of melanoma cells, resulting in prolonged survival of patients with metastatic melanoma. It has recently been shown that a high mutational load in melanomas correlated indeed with improved therapeutic outcome to immune checkpoint blockade, consistent with the hypothesis that acquired missense mutations in the tumor cells lead to neoantigens that increase the vulnerability of these melanoma cells to attack by activated T cells.

GLOBAL CONSIDERATIONS The frequency of skin cancer shows strong geographic variation, depending on the skin phototype of the majority of the population in these geographic areas, but also depending on the intensity of UVR. For example, both melanoma and NMSCs are particularly common in Australia.

Photoimmunology Exposure to solar radiation causes both local immunosuppression (inhibition of immune responses to antigens applied at the irradiated site) and systemic immunosuppression (inhibition of immune responses to antigens applied at remote, unirradiated sites). For example, human skin exposure to modest doses of UV-B can deplete the epidermal antigen-presenting cells known as Langerhans cells, thereby reducing the degree of allergic sensitization to application of the potent contact allergen dinitrochlorobenzene at the irradiated skin site.

An example of the systemic immunosuppressive effects of higher doses of UVR is the diminished immunologic response to antigens introduced either epicutaneously or intracutaneously at sites distant from the irradiated site. Various immunomodulatory factors and immune cells have been implicated in UVR-induced systemic immunosuppression, including tumor necrosis factor α, interleukin 4, interleukin 10, *cis*-urocanic acid, and eicosanoids. Experimental evidence suggests that prostaglandin E_2 signaling through prostaglandin E receptor subtype 4 mediates UVR-induced systemic immunosuppression by elevating the number of regulatory T cells, and this effect can be inhibited with NSAIDs.

The major chromophores in the upper epidermis that are known to initiate UV-mediated immunosuppression include DNA, *trans*-urocanic acid, and membrane components. The action spectrum for UV-induced immunosuppression closely mimics the absorption spectrum of DNA. Pyrimidine dimers in Langerhans cells may inhibit antigen presentation. The absorption spectrum of epidermal urocanic acid closely mimics the action spectrum for UV-B-induced immunosuppression. Urocanic acid is a metabolic product of the essential amino acid histidine and accumulates in the upper epidermis through breakdown of the histidine-rich protein filaggrin due to the absence of its catabolizing enzyme in keratinocytes. Urocanic acid is synthesized as a *trans*-isomer, and UV-induced *trans-cis* isomerization of urocanic acid in the stratum corneum drives immunosuppression. *Cis*-urocanic acid may exert its immunosuppressive effects through a variety of mechanisms, including inhibition of antigen presentation by Langerhans cells.

One important consequence of chronic sun exposure and associated immunosuppression is an enhanced risk of skin cancer. In part, UV-B activates regulatory T cells that suppress antitumor immune responses via interleukin 10 expression, whereas in the absence of high UV-B exposure, epidermal Langerhans cells present tumor-associated antigens and induce protective immunity, thereby inhibiting skin tumorigenesis. UV-induced DNA damage is a major molecular trigger of this immunosuppressive effect.

Perhaps the most graphic demonstration of the role of immunosuppression in enhancing the risk of NMSC comes from studies of organ transplant recipients who require lifelong immunosuppressive/antirejection drug regimens. More than 50% of organ transplant recipients develop BCCs and SCCs, and these cancers are the most common types of malignancies arising in these patients. Rates of BCC and SCC increase with the duration and degree of immunosuppression. These patients ideally should be screened prior to organ transplantation, be monitored closely thereafter, and adhere to rigorous photoprotection measures, including the use of sunscreens and protective clothing as well as sun avoidance. Notably, immunosuppressive drugs that target the mTOR pathway, such as sirolimus and everolimus, may reduce the risk of NMSC in organ transplant recipients compared to that associated with the use of calcineurin inhibitors (cyclosporine and tacrolimus). The latter may contribute to NMSC formation not only through their immunosuppressive effects but also through suppression of p53-dependent cancer cell senescence pathways independent of host immunity.

PHOTOSENSITIVITY DISEASES

The diagnosis of photosensitivity requires elicitation of a careful history to define the duration of signs and symptoms, the length of time between exposure to sunlight and the development of subjective symptoms, and visible changes in the skin. The age of onset can also be a helpful diagnostic clue. For example, the acute photosensitivity of erythropoietic protoporphyria (EPP) almost always begins in infancy or early childhood, whereas the chronic photosensitivity of porphyria cutanea tarda (PCT) typically begins in the fourth and fifth decades of life. A patient's history of exposure to topical and systemic drugs and chemicals may provide important diagnostic clues. Many classes of drugs can cause photosensitivity on the basis of either phototoxicity or photoallergy. Fragrances such as musk ambrette that were previously present in numerous cosmetic products are also potent photosensitizers.

Examination of the skin may offer important clues. Anatomic areas that are naturally protected from direct sunlight, such as the hairy scalp, the upper eyelids, the retroauricular areas, and the infranasal and submental regions, may be spared, whereas exposed areas show characteristic features of the pathologic process. These anatomic localization patterns are often helpful, but not infallible, in making the diagnosis. For example, airborne contact sensitizers that are blown onto the skin may produce dermatitis that can be difficult to distinguish from photosensitivity despite the fact that such material may trigger skin reactivity in areas shielded from direct sunlight.

Many dermatologic conditions may be caused or aggravated by sunlight (Table 57-2). The role of light in evoking these responses may be dependent on genetic abnormalities ranging from well-described defects in DNA repair that occur in xeroderma pigmentosum to the inherited abnormalities in heme synthesis that characterize the porphyrias.

Polymorphous Light Eruption The most common type of photosensitivity disease is *polymorphous light eruption* (PMLE). Many affected individuals never seek medical attention because the condition

TABLE 57-2 Classification of Photosensitivity Diseases

TYPE	DISEASE
Genetic	Erythropoietic porphyria
	Erythropoietic protoporphyria
	Porphyria cutanea tarda—familial
	Variegate porphyria
	Hepatoerythropoietic porphyria
	Albinism
	Xeroderma pigmentosum
	Rothmund-Thomson syndrome
	Bloom syndrome
	Cockayne syndrome
	Kindler syndrome
	Phenylketonuria
Metabolic	Porphyria cutanea tarda—sporadic
	Hartnup disease
	Kwashiorkor
	Pellagra
	Carcinoid syndrome
Phototoxic	
Internal	Drugs
External	Drugs, plants, food
Photoallergic	
Immediate	Solar urticaria
Delayed	Drug photoallergy
	Persistent light reaction/chronic actinic dermatitis
Neoplastic and degenerative	Photoaging
	Actinic keratosis
	Melanoma and nonmelanoma skin cancer
Idiopathic	Polymorphous light eruption
	Hydroa aestivale
	Actinic prurigo
Photoaggravated	Lupus erythematosus
	Systemic
	Subacute cutaneous
	Discoid
	Dermatomyositis
	Herpes simplex
	Lichen planus actinicus
	Acne vulgaris (aestivale)

is often transient, becoming manifest in the spring with initial sun exposure but then subsiding spontaneously with continuing exposure, a phenomenon known as "hardening." The major manifestations of PMLE include (often intensely) pruritic erythematous papules that may coalesce into plaques in a patchy distribution on exposed areas of the trunk and forearms. The face is usually less seriously involved. Whereas the morphologic skin findings remain similar for each patient with subsequent recurrences, significant interindividual variations in skin findings are characteristic (hence the term "polymorphous").

A skin biopsy and phototest procedures in which skin is exposed to multiple erythemal doses of UV-A and UV-B may aid in the diagnosis. The action spectrum for PMLE is usually within these portions of the solar spectrum.

Whereas the treatment of an acute flare of PMLE may require topical or systemic glucocorticoids, approaches to preventing PMLE are important and include the use of high-SPF broad-spectrum sunscreens as well as the induction of "hardening" by the cautious administration of artificial UV-B (broad-band or narrow-band) and/or UV-A radiation or the use of psoralen plus UV-A (PUVA) photochemotherapy for ~4 weeks before initial sun exposure. Such prophylactic phototherapy or photochemotherapy at the beginning of spring may prevent the occurrence of PMLE throughout the summer.

TABLE 57-3 Drugs That May Cause a Phototoxic Reaction

DRUG	TOPICAL	SYSTEMIC
Amiodarone		+
Dacarbazine		+
Fluoroquinolones		+
5-Fluorouracil	+	+
Furosemide		+
Nalidixic acid		+
Phenothiazines		+
Psoralens	+	+
Retinoids	+/−	+
Sulfonamides		+
Sulfonylureas		+
Tetracyclines		+
Thiazides		+
Vinblastine		+

Phototoxicity and Photoallergy These photosensitivity disorders are related to the topical or systemic administration of drugs and other chemicals that can act as chromophores. Both reactions require the absorption of energy by a drug or chemical with consequent production of an excited-state photosensitizer that can transfer its absorbed energy to a bystander molecule or to molecular oxygen, thereby generating tissue-destructive chemical species, including ROS.

Phototoxicity is a nonimmunologic reaction that can be caused by a broad range of drugs and chemicals, a few of which are listed in Table 57-3. The usual clinical manifestations include erythema resembling a sunburn reaction that quickly desquamates, or "peels," within several days. In addition, edema, vesicles, and bullae may occur.

Photoallergy is much less common and is distinct in that it is an immunopathologic process. The excited-state photosensitizer may create highly unstable haptenic free radicals that bind covalently to macromolecules to form a functional antigen capable of evoking a delayed-type hypersensitivity response. Some drugs and chemicals that can produce photoallergy are listed in Table 57-4. The clinical manifestations typically differ from those of phototoxicity in that an intensely pruritic eczematous dermatitis tends to predominate and evolves into lichenified, thickened, "leathery" changes in sun-exposed areas. A small subset (perhaps 5–10%) of patients with photoallergy may develop a persistent exquisite hypersensitivity to light even when the offending drug or chemical is identified and eliminated, a condition known as *persistent light reaction*.

A very uncommon type of persistent photosensitivity is known as *chronic actinic dermatitis*. The affected patients are typically elderly men with a long history of preexisting allergic contact dermatitis or photosensitivity. These individuals are usually exquisitely sensitive to UV-B, UV-A, and visible wavelengths.

Phototoxicity and photoallergy often can be diagnostically confirmed by phototest procedures. In patients with suspected phototoxicity,

TABLE 57-4 Drugs That May Cause a Photoallergic Reaction

DRUG	TOPICAL	SYSTEMIC
6-Methylcoumarin	+	
Aminobenzoic acid and esters	+	
Bithionol	+	
Chlorpromazine		+
Diclofenac		+
Fluoroquinolones		+
Halogenated salicylanilides	+	
Hypericin (St. John's wort)	+	+
Musk ambrette	+	
Piroxicam		+
Promethazine		+
Sulfonamides		+
Sulfonylureas		+

determining the minimal erythemal dose (MED) while the patient is exposed to a suspected agent and then repeating the MED after discontinuation of the agent may provide a clue to the causative drug or chemical. Photopatch testing can be performed to confirm the diagnosis of photoallergy. In this simple variant of ordinary patch testing, a series of known photoallergens is applied to the skin in duplicate, and one set is irradiated with a suberythemal dose of UV-A. The development of eczematous changes at sites exposed to sensitizer and light is a positive result. The characteristic abnormality in patients with persistent light reaction is a diminished threshold to erythema evoked by UV-B. Patients with chronic actinic dermatitis usually manifest a broad spectrum of UV hyperresponsiveness and require meticulous photoprotection, including avoidance of sun exposure, use of high-SPF (>30) sunscreens, and, in severe cases, systemic immunosuppression, such as with azathioprine.

The management of drug photosensitivity involves first and foremost the elimination of exposure to the chemical agents responsible for the reaction and the minimization of sun exposure. The acute symptoms of phototoxicity may be ameliorated by cool moist compresses, topical glucocorticoids, and systemically administered NSAIDs. In severely affected individuals, a tapered course of systemic glucocorticoids may be useful. Judicious use of analgesics may be necessary.

Photoallergic reactions require a similar management approach. Furthermore, patients with persistent light reaction and chronic actinic dermatitis must be meticulously protected against light exposure. In selected patients to whom chronic systemic high-dose glucocorticoids pose unacceptable risks, it may be necessary to employ an immunosuppressive drug such as azathioprine, cyclophosphamide, cyclosporine, or mycophenolate mofetil.

Porphyria The porphyrias **(Chap. 409)** are a group of diseases that have in common inherited or acquired derangements in the synthesis of heme. Heme is an iron-chelated tetrapyrrole or porphyrin, and the nonmetal chelated porphyrins are potent photosensitizers that absorb light intensely in both the short (400–410 nm) and the long (580–650 nm) portions of the visible spectrum.

Heme cannot be reutilized and must be synthesized continuously. The two body compartments with the largest capacity for its production are the bone marrow and the liver. Accordingly, the porphyrias originate in one or the other of these organs, with an end result of excessive endogenous production of potent photosensitizing porphyrins. The porphyrins circulate in the bloodstream and diffuse into the skin, where they absorb solar energy, become photoexcited, generate ROS, and evoke cutaneous photosensitivity. The mechanism of porphyrin photosensitization is known to be photodynamic, or oxygen-dependent, and is mediated by ROS such as singlet oxygen and superoxide anions.

The group of cutaneous porphyrias can be classified as either causing (1) chronic blistering photosensitivity or (2) acute nonblistering photosensitivity. Chronic cutaneous porphyrias include porphyria cutanea tarda (PCT), congenital erythropoietic porphyria (CEP), hepatoerythropoietic porphyria (HEP), hereditary coproporphyria (HCP), and variegate porphyria (VP). CEP, HEP, and PCT manifest only with cutaneous symptoms, while HCP and VP have acute neurovisceral symptoms in addition to the skin photosensitivity. Acute cutaneous nonblistering porphyrias include EPP and X-linked protoporphyria (XLP). Representative examples of chronic and acute cutaneous porphyrias are discussed below.

Porphyria cutanea tarda (PCT) is the most common type of porphyria and is associated with decreased activity of the heme pathway enzyme uroporphyrinogen decarboxylase (UROD) to <20% of normal. Increased iron and various acquired factors (e.g., alcohol consumption, estrogens, smoking, hepatitis C or HIV infection) can reduce UROD activity. There are two basic types of PCT: (1) the sporadic or acquired type, generally seen in individuals ingesting ethanol or receiving estrogens; and (2) the inherited type, in which there is autosomal dominant transmission of deficient enzyme activity (resulting in heterozygosity for UROD with a reduction to 50% of UROD enzymatic activity and thus predisposing the individual to PCT). Both forms are associated with increased hepatic iron stores.

In both types of PCT, the predominant feature is chronic photosensitivity characterized by increased fragility of sun-exposed skin, particularly areas subject to repeated trauma such as the dorsa of the hands, the forearms, the face, and the ears. The predominant skin lesions are vesicles and bullae that rupture, producing moist erosions (often with a hemorrhagic base) that heal slowly, with crusting and purplish discoloration of the affected skin. Hypertrichosis, mottled pigmentary change, and scleroderma-like induration are associated features. The diagnosis can be confirmed biochemically by measurement of urinary porphyrin excretion, plasma porphyrin assay, and assay of erythrocyte and/or hepatic UROD. Multiple mutations of the *UROD* gene have been identified in human populations. Some patients with PCT have associated mutations in the *HFE* gene, which is linked to hemochromatosis and leads to increased iron absorption by reducing hepcidin expression; these mutations could contribute to the iron overload precipitating PCT, although iron status as measured by serum ferritin, iron levels, and transferrin saturation is no different from that in PCT patients without *HFE* mutations.

Treatment of PCT consists of repeated phlebotomies to diminish the excessive hepatic iron stores and/or intermittent (twice weekly) low doses of orally administered hydroxychloroquine. This treatment is highly effective for PCT but not suited for treatment of other porphyrias. Long-term remission of the disease can often be achieved if the patient eliminates exposure to porphyrinogenic agents such as ethanol or estrogens and avoids sun exposure.

Erythropoietic protoporphyria (EPP) is an acute nonblistering cutaneous porphyria, originates in the bone marrow, and is due to genetic mutations that in most cases decrease the activity of the mitochondrial enzyme ferrochelatase. The major clinical features include acute photosensitivity characterized by painful burning and stinging of exposed skin that often develops during or just after sun exposure. There may be associated skin swelling and, after repeated episodes, a waxlike scarring.

The diagnosis is confirmed by demonstration of elevated levels of free erythrocyte protoporphyrin. Detection of increased plasma protoporphyrin helps distinguish EPP from lead poisoning and iron-deficiency anemia, in both of which erythrocyte protoporphyrin levels are elevated in the absence of cutaneous photosensitivity and elevated plasma protoporphyrin levels.

Rigorous sunlight protection is essential in the management of EPP. Therapies that may increase sunlight tolerance in patients with EPP may be helpful as well, such as oral administration of β-carotene, which is an effective scavenger of free radicals. Notably, a recent clinical trial showed that a synthetic peptide analogue of α-MSH, afamelanotide, increased skin pigmentation through melanogenesis and thereby enhanced tolerance to sunlight in patients with EPP. Patients treated with afamelanotide tolerated sun exposure without pain for longer periods of time and had an improved quality of life as compared to untreated patients. Interestingly, initial studies suggest that afamelanotide may also be beneficial when combined with NB-UVB in the treatment of patients with vitiligo (in patients with skin phototypes IV–VI).

An algorithm for managing patients with photosensitivity is presented in **Fig. 57-1**.

PHOTOPROTECTION

Since photosensitivity of the skin results from exposure to sunlight, it follows that absolute avoidance of sunlight will eliminate these disorders. However, contemporary lifestyles make this approach impractical for most individuals. Thus, better approaches to photoprotection have been sought.

Natural photoprotection is provided by structural proteins in the epidermis, particularly keratins and melanin. The amount of melanin and its distribution in cells are genetically regulated, and individuals of darker complexion (skin types IV–VI) are at decreased risk for the development of acute sunburn and cutaneous malignancy.

Other forms of photoprotection include clothing and sunscreens. Clothing constructed of tightly woven sun-protective fabrics, irrespective of color, affords substantial protection. Wide-brimmed hats, long

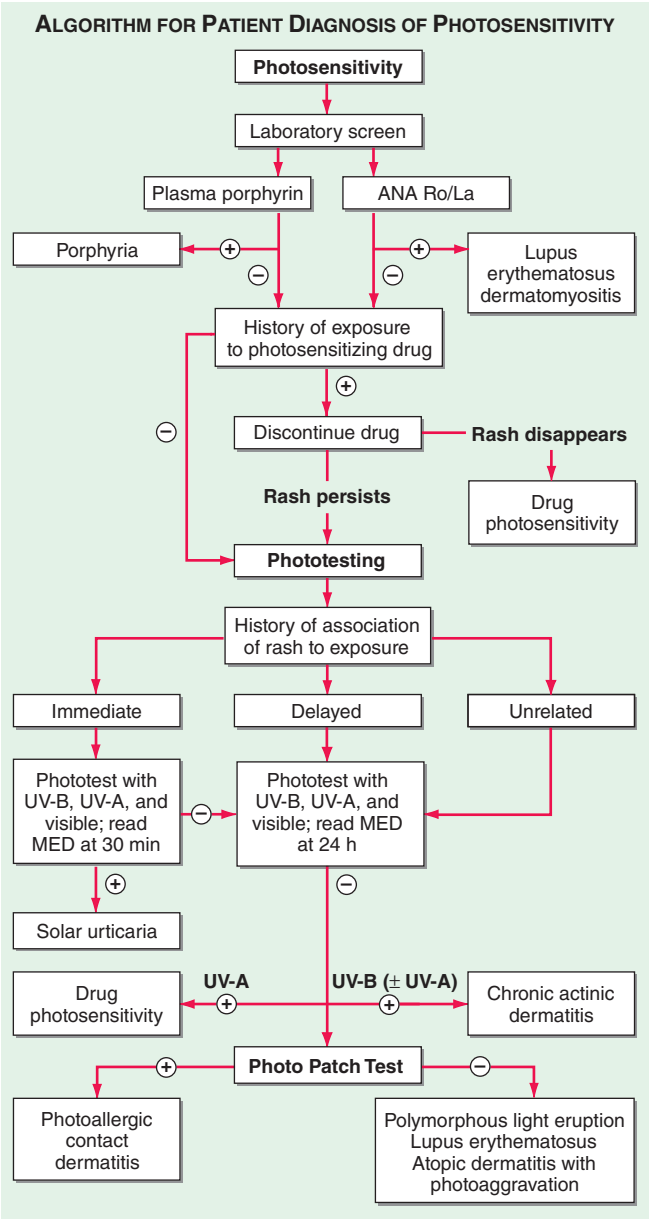

FIGURE 57-1 Algorithm for the diagnosis of a patient with photosensitivity. ANA, antinuclear antibody; MED, minimal erythemal dose; UV-A and UV-B, ultraviolet spectrum segments including wavelengths of 320–400 nm and 290–320 nm, respectively.

sleeves, and trousers all reduce direct exposure. Sunscreens are now considered over-the-counter drugs, and a monograph from the U.S. Food and Drug Administration (FDA) has recognized category I ingredients as safe and effective. Those ingredients are listed in Table 57-5. Sunscreens are rated for their photoprotective effect by their sun protection factor (SPF). The SPF is simply a ratio of the time required to produce sunburn erythema with and without sunscreen application. The SPF of most sunscreens reflects protection from UV-B but not from UV-A. The FDA monograph stipulates that sunscreens must be rated on a scale ranging from minimal (SPF ≥2 and <12) to moderate (SPF ≥12 and <30) to high (SPF ≥30, labeled as 30+).

Broad-spectrum sunscreens contain both UV-B-absorbing and UV-A-absorbing chemicals, the latter including avobenzone and ecamsule (terephthalylidene dicamphor sulfonic acid). These chemicals absorb UVR and transfer the absorbed energy to surrounding cells. In contrast, physical UV blockers (zinc oxide and titanium dioxide) scatter or reflect UVR.

In addition to light absorption, a critical determinant of the sustained photoprotective effect of sunscreens is their water resistance. The FDA monograph has defined strict testing criteria for sunscreens

TABLE 57-5 FDA Category I Monographed Sunscreen Ingredients

INGREDIENTS	MAXIMUM CONCENTRATION, %
p-Aminobenzoic acid (PABA)	15
Avobenzone	3
Cinoxate	3
Dioxybenzone (benzophenone-8)	3
Ecamsule	15
Homosalate	15
Methyl anthranilate	5
Octocrylene	10
Octyl methoxycinnamate	7.5
Octyl salicylate	5
Oxybenzone (benzophenone-3)	6
Padimate O (octyl dimethyl PABA)	8
Phenylbenzimidazole sulfonic acid	4
Sulisobenzone (benzophenone-4)	10
Titanium dioxide	25
Trolamine salicylate	12
Zinc oxide	25

Abbreviation: FDA, U.S. Food and Drug Administration.

that claim to possess a high degree of water resistance. Some degree of photoprotection can be achieved by limiting the time of sun exposure during the day. Since a large part of an individual's total lifetime sun exposure may occur by age 18, it is important to educate parents and young children about the hazards of sunlight. Eliminating exposure at midday will substantially reduce lifetime UVR exposure.

PHOTOTHERAPY AND PHOTOCHEMOTHERAPY

UVR can be used therapeutically. The administration of UV-B alone or in combination with topically applied agents can induce remissions of many dermatologic diseases, including psoriasis and atopic dermatitis. In particular, narrow-band UV-B treatments (with fluorescent bulbs emitting radiation at ~311 nm) have enhanced efficacy over that obtained with broad-band UV-B in the treatment of psoriasis.

Photochemotherapy in which topically applied or systemically administered psoralens are combined with UV-A (PUVA) is effective in treating psoriasis and the early stages of cutaneous T cell lymphoma and vitiligo. Psoralens are tricyclic furocoumarins that, when intercalated into DNA and exposed to UV-A, form adducts with pyrimidine bases and eventually form DNA cross-links. These structural changes are thought to decrease DNA synthesis and to be related to the amelioration of psoriasis. Why PUVA photochemotherapy is effective in cutaneous T cell lymphoma is only partially understood, but it has been shown to induce apoptosis of atypical T lymphocyte populations in the skin. Consequently, direct treatment of circulating atypical lymphocytes by extracorporeal photochemotherapy (photopheresis) has been used in Sézary syndrome as well as in other severe systemic diseases with circulating atypical lymphocytes, such as graft-versus-host disease.

In addition to its effects on DNA, PUVA photochemotherapy stimulates epidermal thickening and melanin synthesis; the latter property, together with its anti-inflammatory effects, provides the rationale for use of PUVA in the depigmenting disease vitiligo. Oral 8-methoxypsoralen and UV-A appear to be most effective in this regard, but as many as 100 treatments extending over 12–18 months may be required for satisfactory repigmentation.

Not surprisingly, the major side effects of long-term UV-B phototherapy and PUVA photochemotherapy mimic those seen in individuals with chronic sun exposure. Despite these risks, the therapeutic index of these modalities continues to be excellent. It is important to choose the most appropriate phototherapeutic approach for a specific dermatologic disease. For example, narrow-band UV-B has been reported in several studies to be as effective as PUVA photochemotherapy in the treatment of psoriasis but to pose a lower risk of skin cancer development than PUVA.

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58 Interpreting Peripheral Blood Smears

Dan L. Longo

Some of the relevant findings in peripheral blood, enlarged lymph nodes, and bone marrow are illustrated in this chapter. Systematic histologic examination of the bone marrow and lymph nodes is beyond the scope of a general medicine textbook. However, every internist should know how to examine a peripheral blood smear.

The examination of a peripheral blood smear is one of the most informative exercises a physician can perform. Although advances in automated technology have made the examination of a peripheral blood smear by a physician seem less important, the technology is not a completely satisfactory replacement for a blood smear interpretation by a trained medical professional who also knows the patient's clinical history, family history, social history, and physical findings. It is useful to ask the laboratory to generate a Wright's-stained peripheral blood smear and examine it.

The best place to examine blood cell morphology is the feathered edge of the blood smear where red cells lie in a single layer, side by side, just barely touching one another but not overlapping. The author's approach is to look at the smallest cellular elements, the platelets, first and work his way up in size to red cells and then white cells.

Using an oil immersion lens that magnifies the cells 100-fold, one counts the platelets in five to six fields, averages the number per field, and multiplies by 20,000 to get a rough estimate of the platelet count. The platelets are usually 1–2 μm in diameter and have a blue granulated appearance. There is usually 1 platelet for every 20 or so red cells. Of course, the automated counter is much more accurate, but gross disparities between the automated and manual counts should be assessed. Large platelets may be a sign of rapid platelet turnover, as young platelets are often larger than old ones; alternatively, certain rare inherited syndromes can produce large platelets. If the platelet count is low, the absence of large (young) platelets may be an indicator of marrow production problems. Platelet clumping visible on the smear can be associated with falsely low automated platelet counts. Clumping may be caused by the anticoagulant into which the blood is drawn. Similarly, neutrophil fragmentation can be a source of falsely elevated automated platelet counts. The absence of platelet granules may be an artifact of the handling of the blood or may indicate marrow disease or a rare congenital anomaly, gray platelet syndrome. Elevated platelet counts usually signify a myeloproliferative disorder or a reaction to systemic inflammation.

Next one examines the red blood cells. One can gauge their size by comparing the red cell to the nucleus of a small lymphocyte. Both are normally about 8-μm wide. Red cells that are smaller than the small lymphocyte nucleus may be microcytic; those larger than the small lymphocyte nucleus may be macrocytic. Macrocytic cells also tend to be more oval than spherical in shape and are sometimes called macroovalocytes. The automated mean corpuscular volume (MCV) can assist in making a classification. However, some patients may have both iron and vitamin B_{12} deficiency, which will produce an MCV in the normal range but wide variation in red cell size. When the red cells vary greatly in size, *anisocytosis* is said to be present. When the red cells vary greatly in shape, *poikilocytosis* is said to be present. The electronic cell counter provides an independent assessment of variability in red cell size. It measures the range of red cell volumes and reports the results as "red cell distribution width" (RDW). This value is calculated from the MCV; thus, cell width is not being measured but cell volume is. The term is derived from the curve displaying the frequency of cells at each volume, also called the distribution. The width of red cell volume distribution curve is what determines the RDW. The RDW is calculated as follows: RDW = (standard deviation of MCV ÷ mean MCV) × 100. In the presence of morphologic anisocytosis, RDW (normally 11–14%) increases to 15–18%. The RDW is useful in at least two clinical settings. In patients with microcytic anemia, the differential diagnosis is generally between iron deficiency and thalassemia. In thalassemia, the small red cells are generally of uniform size with a normal small RDW. In iron deficiency, the size variability and the RDW are large. In addition, a large RDW can suggest a dimorphic anemia when a chronic atrophic gastritis can produce both vitamin B_{12} malabsorption to produce macrocytic anemia and blood loss to produce iron deficiency. In such settings, RDW is also large. An elevated RDW also has been reported as a risk factor for all-cause mortality in population-based studies, a finding that is unexplained currently.

After red cell size is assessed, one examines the hemoglobin content of the cells. They are either normal in color (*normochromic*) or pale in color (*hypochromic*). They are never "hyperchromic." If more than the normal amount of hemoglobin is made, the cells get larger—they do not become darker. In addition to hemoglobin content, the red cells are examined for inclusions. Red cell inclusions are the following:

1. *Basophilic stippling*—diffuse fine or coarse blue dots in the red cell usually representing RNA residue—especially common in lead poisoning
2. *Howell-Jolly bodies*—dense blue circular inclusions that represent nuclear remnants—their presence implies defective splenic function
3. *Nuclei*—red cells may be released or pushed out of the marrow prematurely before nuclear extrusion—often implies a myelophthisic process or a vigorous narrow response to anemia, usually hemolytic anemia
4. *Parasites*—red cell parasites include malaria and babesia **(Chap. A6)**
5. *Polychromatophilia*—the red cell cytoplasm has a bluish hue, reflecting the persistence of ribosomes still actively making hemoglobin in a young red cell

Vital stains are necessary to see precipitated hemoglobin called *Heinz bodies*.

Red cells can take on a variety of different shapes. All abnormally shaped red cells are *poikilocytes*. Small red cells without the central pallor are *spherocytes*; they can be seen in hereditary spherocytosis, hemolytic anemias of other causes, and clostridial sepsis. *Dacrocytes* are teardrop-shaped cells that can be seen in hemolytic anemias, severe iron deficiency, thalassemias, myelofibrosis, and myelodysplastic syndromes. *Schistocytes* are helmet-shaped cells that reflect microangiopathic hemolytic anemia or fragmentation on an artificial heart valve. *Echinocytes* are spiculated red cells with the spikes evenly spaced; they can represent an artifact of abnormal drying of the blood smear or reflect changes in stored blood. They also can be seen in renal failure and malnutrition and are often reversible. *Acanthocytes* are spiculated red cells with the spikes irregularly distributed. This process tends to be irreversible and reflects underlying renal disease, abetalipoproteinemia, or splenectomy. *Elliptocytes* are elliptical-shaped red cells that can reflect an inherited defect in the red cell membrane, but they also are seen in iron deficiency, myelodysplastic syndromes, megaloblastic anemia, and thalassemias. *Stomatocytes* are red cells in which the area

of central pallor takes on the morphology of a slit instead of the usual round shape. Stomatocytes can indicate an inherited red cell membrane defect and also can be seen in alcoholism. *Target cells* have an area of central pallor that contains a dense center, or bull's-eye. These cells are seen classically in thalassemia, but they are also present in iron deficiency, cholestatic liver disease, and some hemoglobinopathies. They also can be generated artifactually by improper slide making.

One last feature of the red cells to assess before moving to the white blood cells is the distribution of the red cells on the smear. In most individuals, the cells lie side by side in a single layer. Some patients have red cell clumping (called *agglutination*) in which the red cells pile upon one another; it is seen in certain paraproteinemias and autoimmune hemolytic anemias. Another abnormal distribution involves red cells lying in single cell rows on top of one another like stacks of coins. This is called *rouleaux formation* and reflects abnormal serum protein levels.

Finally, one examines the white blood cells. Three types of granulocytes are usually present: neutrophils, eosinophils, and basophils, in decreasing frequency. Neutrophils are generally the most abundant white cell. They are round, are 10–14 μm wide, and contain a lobulated nucleus with two to five lobes connected by a thin chromatin thread. Bands are immature neutrophils that have not completed nuclear condensation and have a U-shaped nucleus. Bands reflect a left shift in neutrophil maturation in an effort to make more cells more rapidly. Neutrophils can provide clues to a variety of conditions. Vacuolated neutrophils may be a sign of bacterial sepsis. The presence of 1- to 2-μm blue cytoplasmic inclusions, called *Döhle bodies*, can reflect infections, burns, or other inflammatory states. If the neutrophil granules are larger than normal and stain a darker blue, "toxic granulations" are said to be present, and they also suggest a systemic inflammation. The presence of neutrophils with more than five nuclear lobes suggests megaloblastic anemia. Large misshapen granules may reflect the inherited Chédiak-Higashi syndrome.

Eosinophils are slightly larger than neutrophils, have bilobed nuclei, and contain large red granules. Diseases of eosinophils are associated with too many of them rather than any morphologic or qualitative change. They normally total less than one-thirtieth the number of neutrophils. Basophils are even more rare than eosinophils in the blood. They have large dark blue granules and may be increased as part of chronic myeloid leukemia.

Lymphocytes can be present in several morphologic forms. Most common in healthy individuals are small lymphocytes with a small dark nucleus and scarce cytoplasm. In the presence of viral infections, more of the lymphocytes are larger, about the size of neutrophils, with abundant cytoplasm and a less condensed nuclear chromatin. These cells are called *reactive lymphocytes*. About 1% of lymphocytes are larger and contain blue granules in a light blue cytoplasm; they are called *large granular lymphocytes*. In chronic lymphoid leukemia, the small lymphocytes are increased in number, and many of them are ruptured

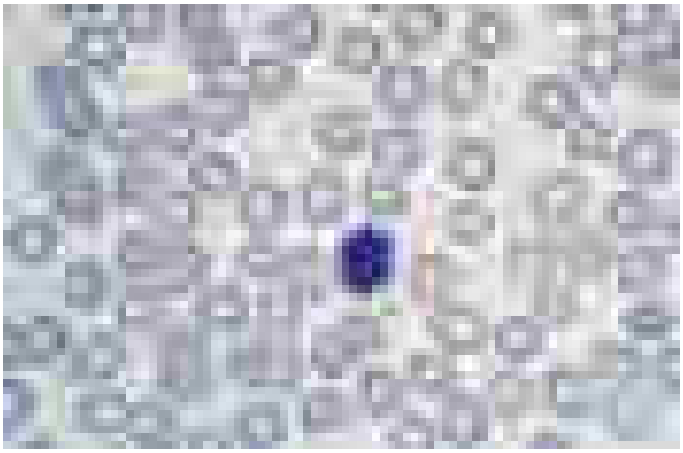

FIGURE 58-1 Normal peripheral blood smear. Small lymphocyte in center of field. Note that the diameter of the red blood cell is similar to the diameter of the small lymphocyte nucleus.

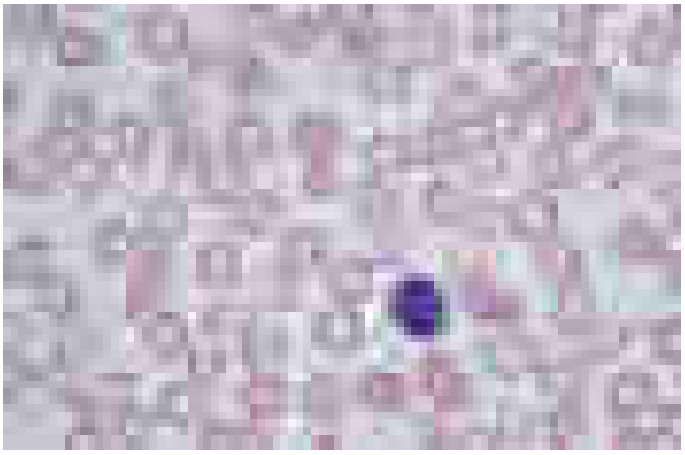

FIGURE 58-3 Hypochromic microcytic anemia of iron deficiency. Small lymphocyte in field helps assess the red blood cell size.

FIGURE 58-2 Reticulocyte count preparation. This new methylene blue–stained blood smear shows large numbers of heavily stained reticulocytes (the cells containing the dark blue–staining RNA precipitates).

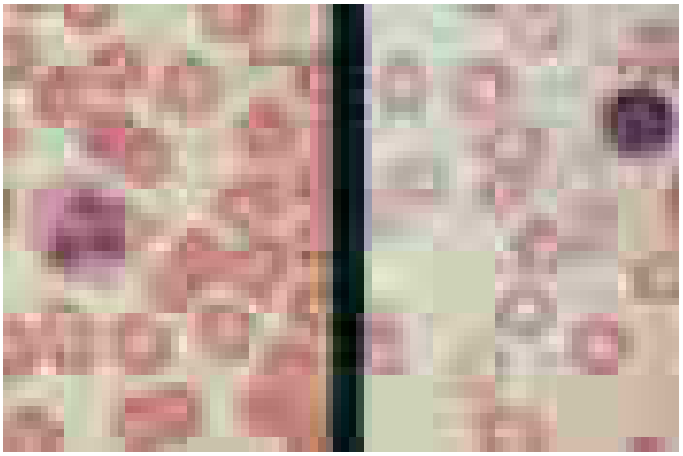

FIGURE 58-4 Iron deficiency anemia next to normal red blood cells. Microcytes (*right panel*) are smaller than normal red blood cells (cell diameter <7 μm) and may or may not be poorly hemoglobinized (hypochromic).

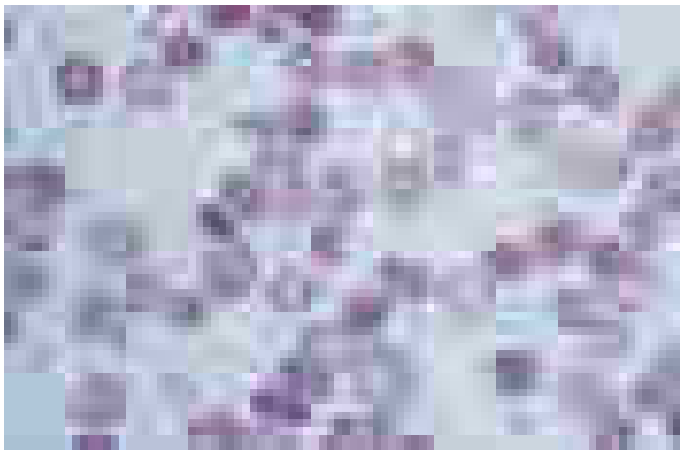

FIGURE 58-5 Polychromatophilia. Note large red cells with light purple coloring.

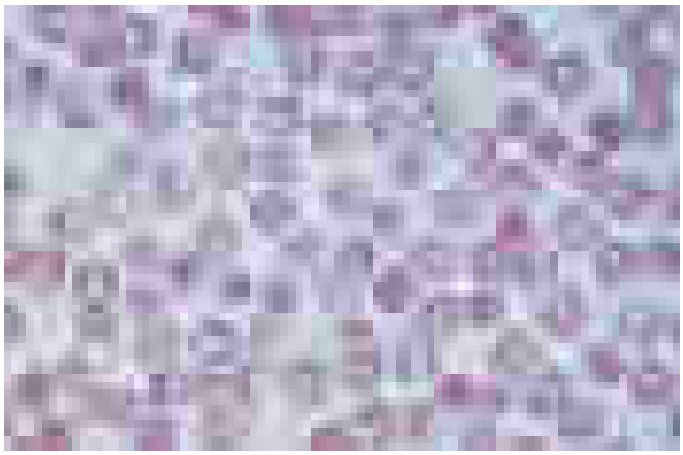

FIGURE 58-8 Spherocytosis. Note small hyperchromatic cells without the usual clear area in the center.

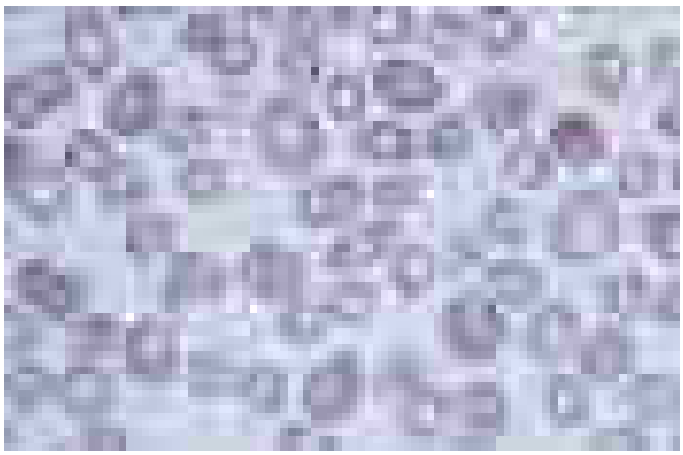

FIGURE 58-6 Macrocytosis. These cells are both larger than normal (mean corpuscular volume >100) and somewhat oval in shape. Some morphologists call these cells macroovalocytes.

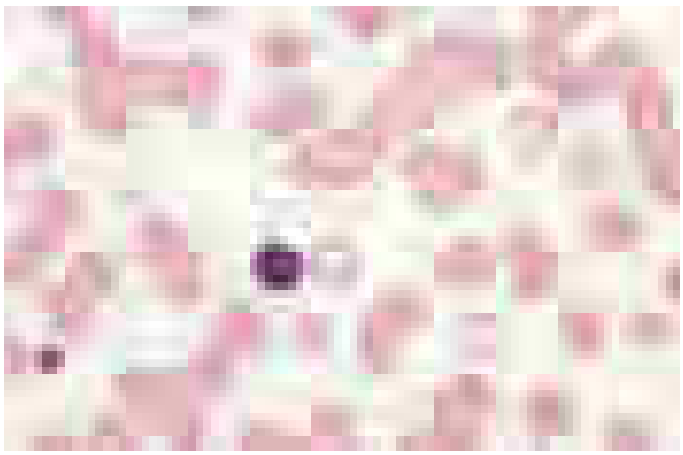

FIGURE 58-9 Rouleaux formation. Small lymphocyte in center of field. These red cells align themselves in stacks and are related to increased serum protein levels.

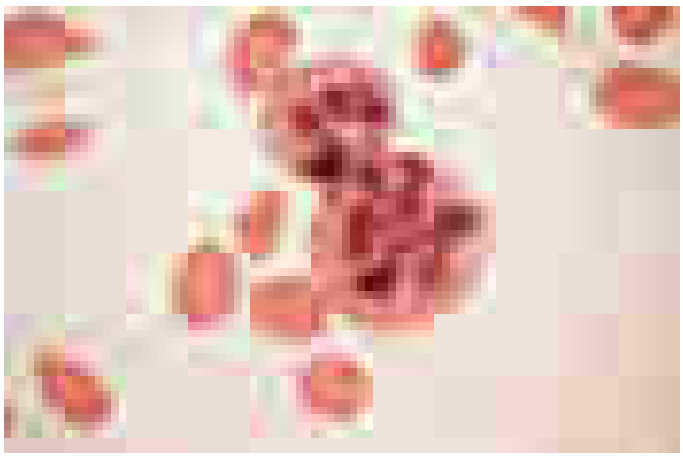

FIGURE 58-7 Hypersegmented neutrophils. Hypersegmented neutrophils (multilobed polymorphonuclear leukocytes) are larger than normal neutrophils with five or more segmented nuclear lobes. They are commonly seen with folic acid or vitamin B_{12} deficiency.

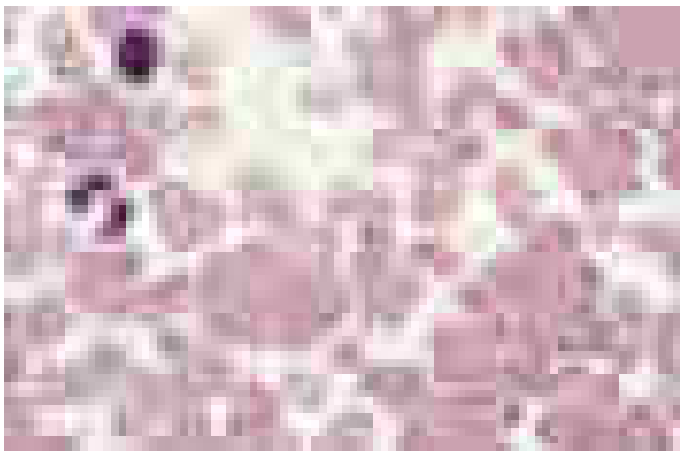

FIGURE 58-10 Red cell agglutination. Small lymphocyte and segmented neutrophil in upper left center. Note irregular collections of aggregated red cells.

FIGURE 58-11 Fragmented red cells. Heart valve hemolysis.

FIGURE 58-12 Sickle cells. Homozygous sickle cell disease. A nucleated red cell and neutrophil are also in the field.

FIGURE 58-13 Target cells. Target cells are recognized by the bull's-eye appearance of the cell. Small numbers of target cells are seen with liver disease and thalassemia. Larger numbers are typical of hemoglobin C disease.

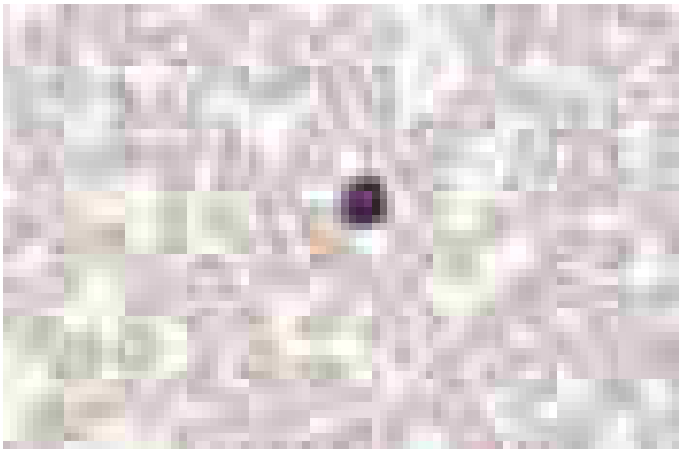

FIGURE 58-14 Elliptocytosis. Small lymphocyte in center of field. Elliptical shape of red cells related to weakened membrane structure, usually due to mutations in spectrin.

FIGURE 58-15 Stomatocytosis. Red cells characterized by a wide transverse slit or stoma. This often is seen as an artifact in a dehydrated blood smear. These cells can be seen in hemolytic anemias and in conditions in which the red cell is overhydrated or dehydrated.

FIGURE 58-16 Acanthocytosis. Spiculated red cells are of two types: *acanthocytes* are contracted dense cells with irregular membrane projections that vary in length and width; *echinocytes* have small, uniform, and evenly spaced membrane projections. Acanthocytes are present in severe liver disease, in patients with abetalipoproteinemia, and in rare patients with McLeod blood group. Echinocytes are found in patients with severe uremia, in glycolytic red cell enzyme defects, and in microangiopathic hemolytic anemia.

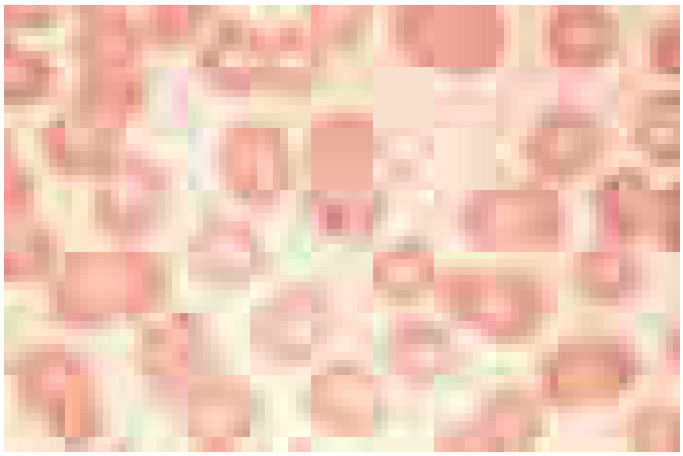

FIGURE 58-17 Howell-Jolly bodies. Howell-Jolly bodies are tiny nuclear remnants that normally are removed by the spleen. They appear in the blood after splenectomy (defect in removal) and with maturation/dysplastic disorders (excess production).

FIGURE 58-20 Reticulin stain of marrow myelofibrosis. Silver stain of a myelofibrotic marrow showing an increase in reticulin fibers (black-staining threads).

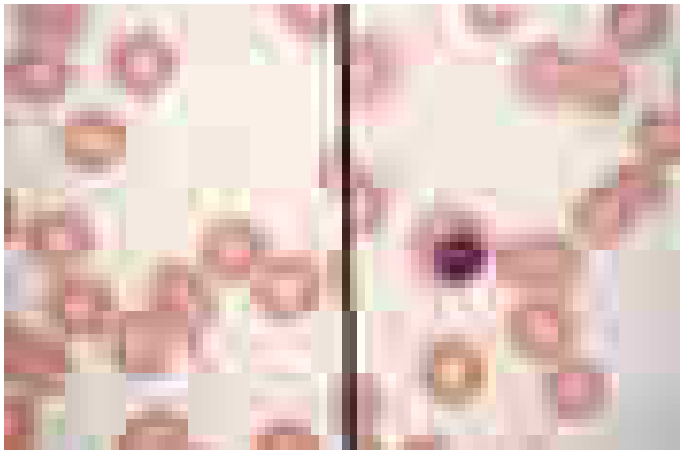

FIGURE 58-18 Teardrop cells and nucleated red blood cells characteristic of myelofibrosis. A teardrop-shaped red blood cell (*left panel*) and a nucleated red blood cell (*right panel*) as typically seen with myelofibrosis and extramedullary hematopoiesis.

FIGURE 58-21 Stippled red cell in lead poisoning. Mild hypochromia. Coarsely stippled red cell.

FIGURE 58-19 Myelofibrosis of the bone marrow. Total replacement of marrow precursors and fat cells by a dense infiltrate of reticulin fibers and collagen (H&E stain).

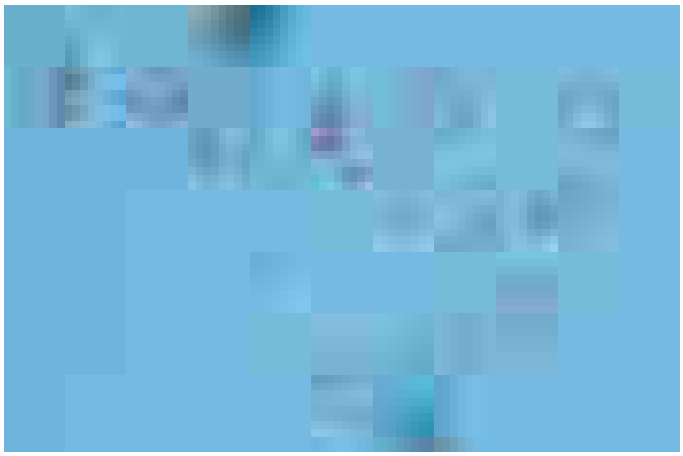

FIGURE 58-22 Heinz bodies. Blood mixed with hypotonic solution of crystal violet. The stained material is precipitates of denatured hemoglobin within cells.

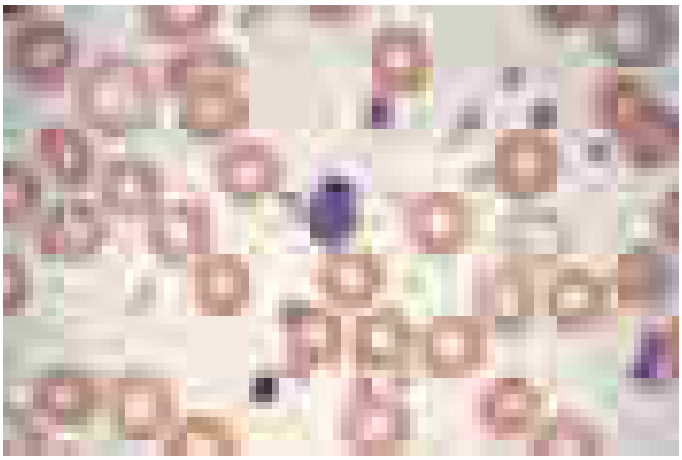

FIGURE 58-23 Giant platelets. Giant platelets, together with a marked increase in the platelet count, are seen in myeloproliferative disorders, especially primary thrombocythemia.

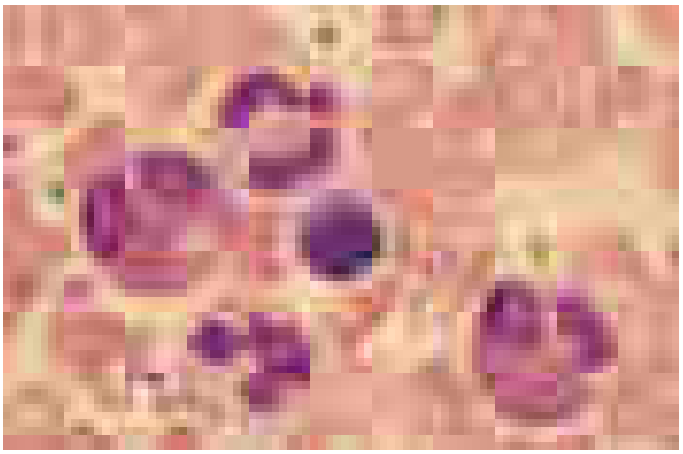

FIGURE 58-26 Normal eosinophils. The film was prepared from the buffy coat of the blood from a normal donor. E, eosinophil; L, lymphocyte; N, neutrophil.

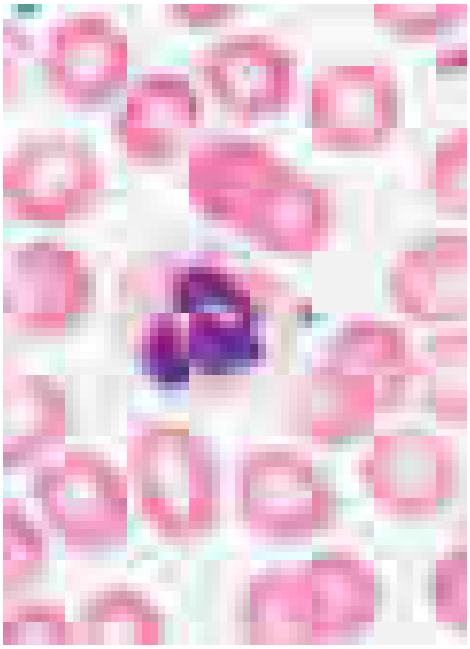

FIGURE 58-24 Normal granulocytes. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

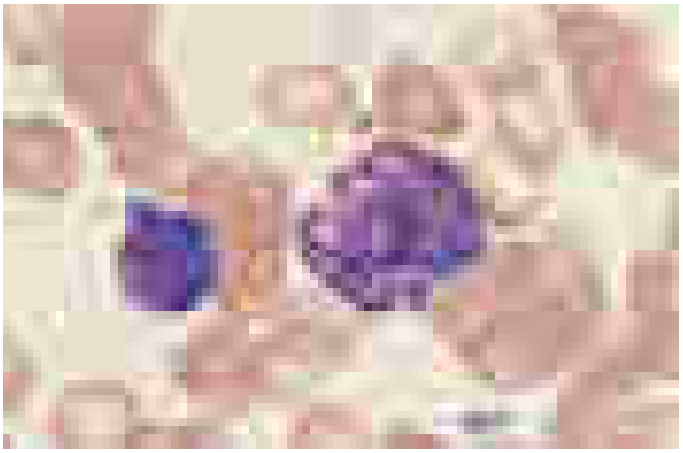

FIGURE 58-27 Normal basophil. The film was prepared from the buffy coat of the blood from a normal donor. B, basophil; L, lymphocyte.

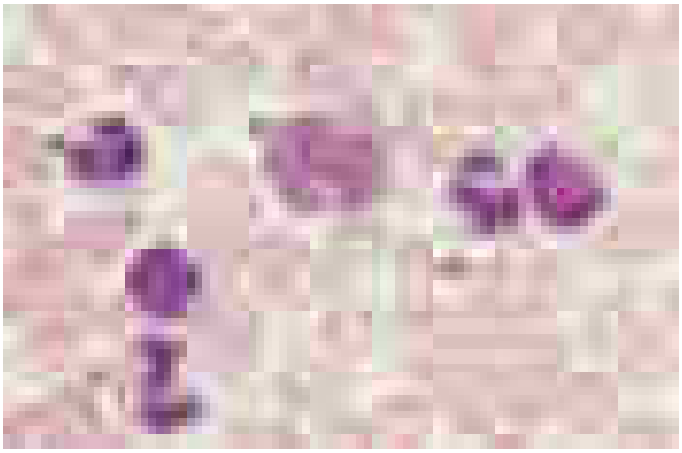

FIGURE 58-25 Normal monocytes. The film was prepared from the buffy coat of the blood from a normal donor. L, lymphocyte; M, monocyte; N, neutrophil.

FIGURE 58-28 Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration.

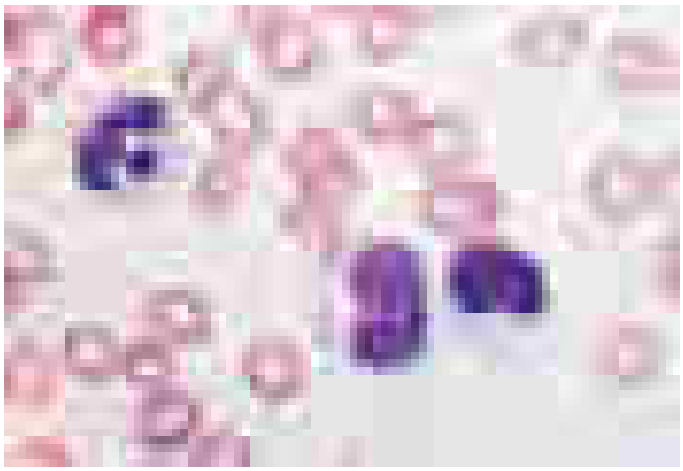

FIGURE 58-29 Döhle body. Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum.

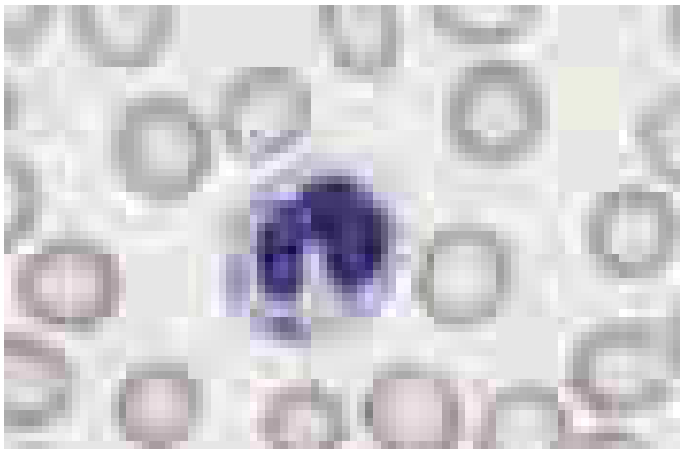

FIGURE 58-30 Chédiak-Higashi disease. Note giant granules in neutrophil.

in making the blood smear, leaving a smudge of nuclear material without a surrounding cytoplasm or cell membrane; they are called *smudge cells* and are rare in the absence of chronic lymphoid leukemia.

Monocytes are the largest white blood cells, ranging from 15 to 22 μm in diameter. The nucleus can take on a variety of shapes but usually appears to be folded; the cytoplasm is gray.

Abnormal cells may appear in the blood. Most often the abnormal cells originate from neoplasms of bone marrow–derived cells, including lymphoid cells, myeloid cells, and occasionally red cells. More rarely, other types of tumors can get access to the bloodstream, and rare epithelial malignant cells may be identified. The chances of seeing such abnormal cells are increased by examining blood smears made from buffy coats, the layer of cells that is visible on top of sedimenting red cells when blood is left in the test tube for an hour. Smears made from finger sticks may include rare endothelial cells.

Acknowledgment

Figures in this chapter were borrowed from Williams Hematology, 7th edition, M Lichtman et al (eds). New York, McGraw-Hill, 2005; Hematology in General Practice, 4th edition, RS Hillman, KA Ault, New York, McGraw-Hill, 2005.

59 Anemia and Polycythemia

John W. Adamson, Dan L. Longo

HEMATOPOIESIS AND THE PHYSIOLOGIC BASIS OF RED CELL PRODUCTION

Hematopoiesis is the process by which the formed elements of blood are produced. The process is regulated through a series of steps beginning with the hematopoietic stem cell. Stem cells are capable of producing red cells, all classes of granulocytes, monocytes, platelets, and the cells of the immune system. The precise molecular mechanism by which the stem cell becomes committed to a given lineage is not fully defined. However, experiments in mice suggest that erythroid cells come from a common erythroid/megakaryocyte progenitor that does not develop in the absence of expression of the GATA-1 and FOG-1 (friend of GATA-1) transcription factors **(Chap. 92)**. Following lineage commitment, hematopoietic progenitor and precursor cells come increasingly under the regulatory influence of growth factors and hormones. For red cell production, erythropoietin (EPO) is the primary regulatory hormone. EPO is required for the maintenance of committed erythroid progenitor cells that, in the absence of the hormone, undergo programmed cell death (*apoptosis*). The regulated process of red cell production is *erythropoiesis*, and its key elements are illustrated in **Fig. 59-1**.

In the bone marrow, the first morphologically recognizable erythroid precursor is the pronormoblast. This cell can undergo four to five cell divisions, which result in the production of 16–32 mature red cells. With increased EPO production, or the administration of EPO as a drug, early progenitor cell numbers are amplified and, in turn, give rise to increased numbers of erythrocytes. The regulation of EPO production itself is linked to tissue oxygenation.

In mammals, O_2 is transported to tissues bound to the hemoglobin contained within circulating red cells. The mature red cell is 8 μm in diameter, anucleate, discoid in shape, and extremely pliable in order to traverse the microcirculation successfully; its membrane integrity is maintained by the intracellular generation of ATP. Normal red cell production results in the daily replacement of 0.8–1% of all circulating red cells in the body, since the average red cell lives 100–120 days. The organ responsible for red cell production is called the *erythron*. The erythron is a dynamic organ made up of a rapidly proliferating pool of marrow erythroid precursor cells and a large mass of mature circulating red blood cells. The size of the red cell mass reflects the balance of red cell production and destruction. The physiologic basis of red cell production and destruction provides an understanding of the mechanisms that can lead to anemia.

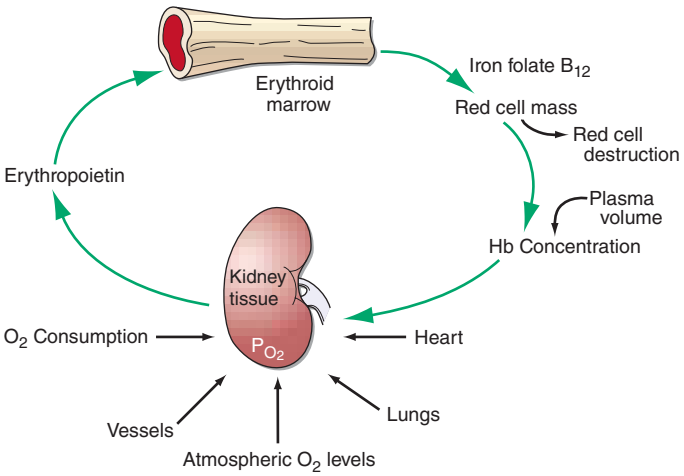

FIGURE 59-1 The physiologic regulation of red cell production by tissue oxygen tension. Hb, hemoglobin.

The physiologic regulator of red cell production, the glycoprotein hormone EPO, is produced and released by peritubular capillary lining cells within the kidney. These cells are highly specialized epithelial-like cells. A small amount of EPO is produced by hepatocytes. The fundamental stimulus for EPO production is the availability of O_2 for tissue metabolic needs. Key to EPO gene regulation is hypoxia-inducible factor (HIF)-1α. In the presence of O_2, HIF-1α is hydroxylated at a key proline, allowing HIF-1α to be ubiquitinated and degraded via the proteasome pathway. If O_2 becomes limiting, this critical hydroxylation step does not occur, allowing HIF-1α to partner with other proteins, translocate to the nucleus, and upregulate the expression of the EPO gene, among others.

Impaired O_2 delivery to the kidney can result from a decreased red cell mass (*anemia*), impaired O_2 loading of the hemoglobin molecule or a high O_2 affinity mutant hemoglobin (*hypoxemia*), or, rarely, impaired blood flow to the kidney (renal artery stenosis). EPO governs the day-to-day production of red cells, and ambient levels of the hormone can be measured in the plasma by sensitive immunoassays—the normal level being 10–25 U/L. When the hemoglobin concentration falls below 100–120 g/L (10–12 g/dL), plasma EPO levels increase in proportion to the severity of the anemia **(Fig. 59-2)**. In circulation, EPO has a half-clearance time of 6–9 h. EPO acts by binding to specific receptors on the surface of marrow erythroid precursors, inducing them to proliferate and to mature. With EPO stimulation, red cell production can increase four- to fivefold within a 1- to 2-week period, but only in the presence of adequate nutrients, especially iron. The functional capacity of the erythron, therefore, requires normal renal production of EPO, a functioning erythroid marrow, and an adequate supply of substrates for hemoglobin synthesis. A defect in any of these key components can lead to anemia. Generally, anemia is recognized in the laboratory when a patient's hemoglobin level or hematocrit is reduced below an expected value (the normal range). The likelihood and severity of anemia are defined based on the deviation of the patient's hemoglobin/hematocrit from values expected for age- and sex-matched normal subjects. The hemoglobin concentration in adults has a Gaussian distribution. The mean hematocrit value for adult males is 47% (standard deviation, ±7%) and that for adult females is 42% (±5%). Any single hematocrit or hemoglobin value carries with it a likelihood of associated anemia. Thus, a hematocrit of <39% in an adult male or <35% in an adult female has only about a 25% chance of being normal. Hematocrit levels are less useful than hemoglobin levels in assessing anemia because they are calculated rather than measured directly. Suspected low hemoglobin or hematocrit values are more easily interpreted if previous values for the same patient are known for comparison. The World Health Organization (WHO) defines anemia as a hemoglobin level <130 g/L (13 g/dL) in men and <120 g/L (12 g/dL) in women.

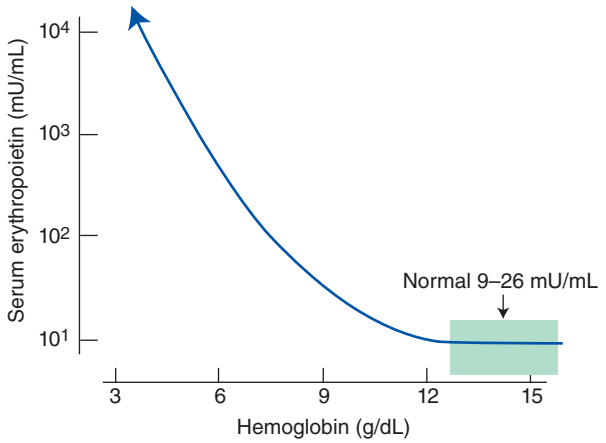

FIGURE 59-2 Erythropoietin (EPO) levels in response to anemia. When the hemoglobin level falls to 120 g/L (12 g/dL), plasma EPO levels increase logarithmically. In the presence of chronic kidney disease or chronic inflammation, EPO levels are typically lower than expected for the degree of anemia. As individuals age, the level of EPO needed to sustain normal hemoglobin levels appears to increase. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

The critical elements of erythropoiesis—EPO production, iron availability, the proliferative capacity of the bone marrow, and effective maturation of red cell precursors—are used for the initial classification of anemia (see below).

ANEMIA

CLINICAL PRESENTATION OF ANEMIA

Signs and Symptoms Anemia is most often recognized by abnormal screening laboratory tests. Patients less commonly present with advanced anemia and its attendant signs and symptoms. Acute anemia is due to blood loss or hemolysis. If blood loss is mild, enhanced O_2 delivery is achieved through changes in the O_2–hemoglobin dissociation curve mediated by a decreased pH or increased CO_2 (*Bohr effect*). With acute blood loss, hypovolemia dominates the clinical picture, and the hematocrit and hemoglobin levels do not reflect the volume of blood lost. Signs of vascular instability appear with acute losses of 10–15% of the total blood volume. In such patients, the issue is not anemia but hypotension and decreased organ perfusion. When >30% of the blood volume is lost suddenly, patients are unable to compensate with the usual mechanisms of vascular contraction and changes in regional blood flow. The patient prefers to remain supine and will show postural hypotension and tachycardia. If the volume of blood lost is >40% (i.e., >2 L in the average-sized adult), signs of hypovolemic shock including confusion, dyspnea, diaphoresis, hypotension, and tachycardia appear **(Chap. 97)**. Such patients have significant deficits in vital organ perfusion and require immediate volume replacement.

With acute hemolysis, the signs and symptoms depend on the mechanism that leads to red cell destruction. Intravascular hemolysis with release of free hemoglobin may be associated with acute back pain, free hemoglobin in the plasma and urine, and renal failure. Symptoms associated with more chronic or progressive anemia depend on the age of the patient and the adequacy of blood supply to critical organs. Symptoms associated with moderate anemia include fatigue, loss of stamina, breathlessness, and tachycardia (particularly with physical exertion). However, because of the intrinsic compensatory mechanisms that govern the O_2–hemoglobin dissociation curve, the gradual onset of anemia—particularly in young patients—may not be associated with signs or symptoms until the anemia is severe (hemoglobin <70–80 g/L [7–8 g/dL]). When anemia develops over a period of days or weeks, the total blood volume is normal to slightly increased, and changes in cardiac output and regional blood flow help compensate for the overall loss in O_2-carrying capacity. Changes in the position of the O_2–hemoglobin dissociation curve account for some of the compensatory response to anemia. With chronic anemia, intracellular levels of 2,3-bisphosphoglycerate rise, shifting the dissociation curve to the right and facilitating O_2 unloading. This compensatory mechanism can only maintain normal tissue O_2 delivery in the face of a 20–30 g/L (2–3 g/dL) deficit in hemoglobin concentration. Finally, further protection of O_2 delivery to vital organs is achieved by the shunting of blood away from organs that are relatively rich in blood supply, particularly the kidney, gut, and skin.

Certain disorders are commonly associated with anemia. Chronic inflammatory states (e.g., infection, rheumatoid arthritis, cancer) are associated with mild to moderate anemia, whereas lymphoproliferative disorders, such as chronic lymphocytic leukemia and certain other B cell neoplasms, may be associated with autoimmune hemolysis.

APPROACH TO THE PATIENT

Anemia

The evaluation of the patient with anemia requires a careful history and physical examination. Nutritional history related to drugs or alcohol intake and family history of anemia should always be assessed. Certain geographic backgrounds and ethnic origins are associated with an increased likelihood of an inherited disorder of the hemoglobin molecule or intermediary metabolism. Glucose-6-phosphate

dehydrogenase (G6PD) deficiency and certain hemoglobinopathies are seen more commonly in those of Middle Eastern or African origin, including African Americans who have a high frequency of G6PD deficiency. Other information that may be useful includes exposure to certain toxic agents or drugs and symptoms related to other disorders commonly associated with anemia. These include symptoms and signs such as bleeding, fatigue, malaise, fever, weight loss, night sweats, and other systemic symptoms. Clues to the mechanisms of anemia may be provided on physical examination by findings of infection, blood in the stool, lymphadenopathy, splenomegaly, or petechiae. Splenomegaly and lymphadenopathy suggest an underlying lymphoproliferative disease, whereas petechiae suggest platelet dysfunction. Past laboratory measurements are helpful to determine a time of onset.

In the anemic patient, physical examination may demonstrate a forceful heartbeat, strong peripheral pulses, and a systolic "flow" murmur. The skin and mucous membranes may be pale if the hemoglobin is <80–100 g/L (8–10 g/dL). This part of the physical examination should focus on areas where vessels are close to the surface such as the mucous membranes, nail beds, and palmar creases. If the palmar creases are lighter in color than the surrounding skin when the hand is hyperextended, the hemoglobin level is usually <80 g/L (8 g/dL).

LABORATORY EVALUATION

Table 59-1 lists the tests used in the initial workup of anemia. A routine complete blood count (CBC) is required as part of the evaluation and includes the hemoglobin, hematocrit, and red cell indices: the mean cell volume (MCV) in femtoliters, mean cell hemoglobin (MCH) in picograms per cell, and mean concentration of hemoglobin per volume of red cells (MCHC) in grams per liter (non-SI: grams per deciliter). The MCH is the least useful of the indices; it tends to track with the MCV. The red cell indices are calculated as shown in **Table 59-2**, and the normal variations in the hemoglobin and hematocrit with age are shown in **Table 59-3**. A number of physiologic factors affect the CBC, including age, sex, pregnancy, smoking, and altitude. High-normal hemoglobin values may be seen in men and women who live at altitude or smoke heavily. Hemoglobin elevations due to smoking reflect normal compensation due to the displacement of O_2 by CO in hemoglobin binding. Other important information is provided by the reticulocyte count and measurements of iron supply including *serum iron*, *total iron-binding capacity* (TIBC; an indirect measure of serum transferrin), and *serum ferritin*. Marked alterations in the red cell indices usually reflect disorders of maturation or iron deficiency. A careful evaluation of the peripheral blood smear is important, and clinical laboratories often provide a description of both the red and white cells, a white cell differential count, and the platelet count. In patients with severe anemia and abnormalities in red blood cell morphology and/or low reticulocyte counts, a bone marrow aspirate or biopsy can assist in the diagnosis. Other tests of value in the diagnosis of specific anemias are discussed in chapters on specific disease states.

The components of the CBC also help in the classification of anemia. *Microcytosis* is reflected by a lower than normal MCV (<80), whereas high values (>100) reflect *macrocytosis*. The MCHC reflect defects in hemoglobin synthesis (*hypochromia*). Automated cell counters describe the red cell volume distribution width (RDW). The MCV (representing the peak of the distribution curve) is insensitive to the appearance of small populations of macrocytes or microcytes. An experienced laboratory technician will be able to identify minor populations of large or small cells or hypochromic cells before the red cell indices change.

Peripheral Blood Smear The peripheral blood smear provides important information about defects in red cell production **(Chap. 58)**. As a complement to the red cell indices, the blood smear also reveals variations in cell size (*anisocytosis*) and shape (*poikilocytosis*). The degree of anisocytosis usually correlates with increases in the RDW or the range of cell sizes. Poikilocytosis suggests a defect in the maturation of red cell precursors in the bone marrow or fragmentation of circulating red cells. The blood smear may also reveal *polychromasia*—red cells that are slightly larger than normal and grayish blue in color on the Wright-Giemsa stain. These cells

TABLE 59-1 Laboratory Tests in Anemia Diagnosis

- I. Complete blood count (CBC)
  - A. Red blood cell count
    1. Hemoglobin
    2. Hematocrit
    3. Reticulocyte count
  - B. Red blood cell indices
    1. Mean cell volume (MCV)
    2. Mean cell hemoglobin (MCH)
    3. Mean cell hemoglobin concentration (MCHC)
    4. Red cell distribution width (RDW)
  - C. White blood cell count
    1. Cell differential
    2. Nuclear segmentation of neutrophils
  - D. Platelet count
  - E. Cell morphology
    1. Cell size
    2. Hemoglobin content
    3. Anisocytosis
    4. Poikilocytosis
    5. Polychromasia
- II. Iron supply studies
  - A. Serum iron
  - B. Total iron-binding capacity
  - C. Serum ferritin
- III. Marrow examination
  - A. Aspirate
    1. M/E ratio[a]
    2. Cell morphology
    3. Iron stain
  - B. Biopsy
    1. Cellularity
    2. Morphology

[a]M/E ratio, ratio of myeloid to erythroid precursors.

TABLE 59-2 Red Blood Cell Indices

INDEX	NORMAL VALUE
Mean cell volume (MCV) = (hematocrit × 10)/(red cell count × 10^6)	90 ± 8 fL
Mean cell hemoglobin (MCH) = (hemoglobin × 10)/(red cell count × 10^6)	30 ± 3 pg
Mean cell hemoglobin concentration = (hemoglobin × 10)/hematocrit, or MCH/MCV	33 ± 2%

TABLE 59-3 Changes in Normal Hemoglobin/Hematocrit Values with Age, Sex, and Pregnancy

AGE/SEX	HEMOGLOBIN, g/dL	HEMATOCRIT, %
At birth	17	52
Childhood	12	36
Adolescence	13	40
Adult man	16 (±2)	47 (±6)
Adult woman (menstruating)	13 (±2)	40 (±6)
Adult woman (postmenopausal)	14 (±2)	42 (±6)
During pregnancy	12 (±2)	37 (±6)

Source: From RS Hillman et al: *Hematology in Clinical Practice*, 5th ed. New York, McGraw-Hill, 2010.

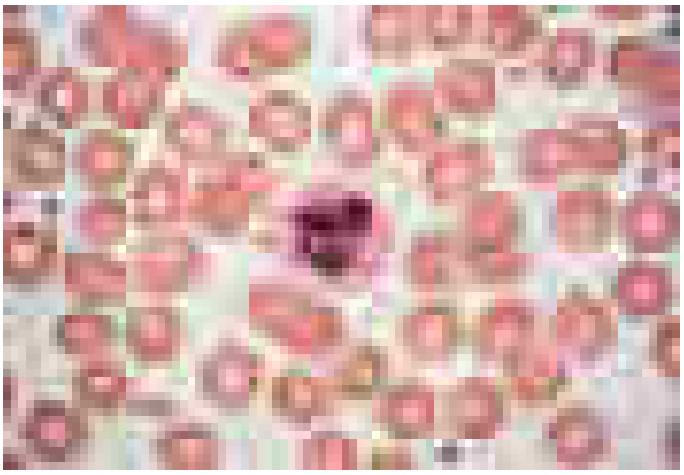

FIGURE 59-3 Normal blood smear (Wright stain). High-power field showing normal red cells, a neutrophil, and a few platelets. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

FIGURE 59-5 Macrocytosis. Red cells are larger than a small lymphocyte and well hemoglobinized. Often macrocytes are oval shaped (macro-ovalocytes).

are reticulocytes that have been prematurely released from the bone marrow, and their color represents residual amounts of ribosomal RNA. These cells appear in circulation in response to EPO stimulation or to architectural damage of the bone marrow (fibrosis, infiltration of the marrow by malignant cells, etc.) that results in their disordered release from the marrow. The appearance of nucleated red cells, Howell-Jolly bodies, target cells, sickle cells, and others may provide clues to specific disorders **(Figs. 59-3 to 59-11)**.

Reticulocyte Count An accurate reticulocyte count is key to the initial classification of anemia. Reticulocytes are red cells that have been recently released from the bone marrow. They are identified by staining with a supravital dye that precipitates the ribosomal RNA **(Fig. 59-12)**. These precipitates appear as blue or black punctate spots and can be counted manually or, currently, by fluorescent emission of dyes that bind to RNA. This residual RNA is metabolized over the first 24–36 h of the reticulocyte's life span in circulation. Normally, the reticulocyte count ranges from 1 to 2% and reflects the daily replacement of 0.8–1.0% of the circulating red cell population. A corrected reticulocyte percentage or the absolute number of reticulocytes provides a reliable measure of effective red cell production.

In the initial classification of anemia, the patient's reticulocyte count is compared with the expected reticulocyte response. In general, if the EPO and erythroid marrow responses to moderate anemia [hemoglobin <100 g/L (10 g/dL)] are intact, the red cell production

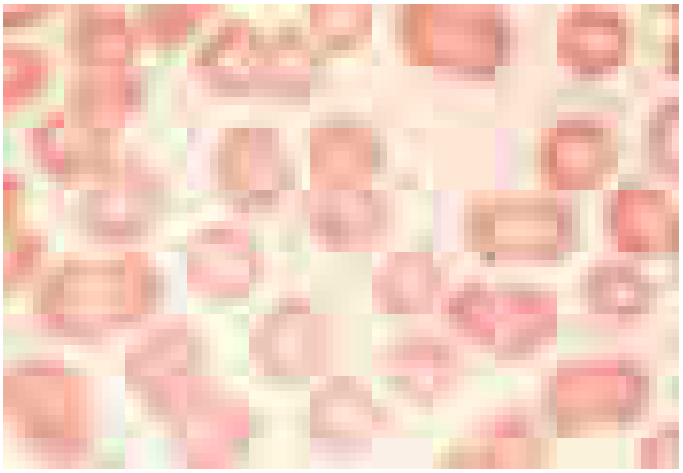

FIGURE 59-6 Howell-Jolly bodies. In the absence of a functional spleen, nuclear remnants are not culled from the red cells and remain as small homogeneously staining blue inclusions on Wright stain. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

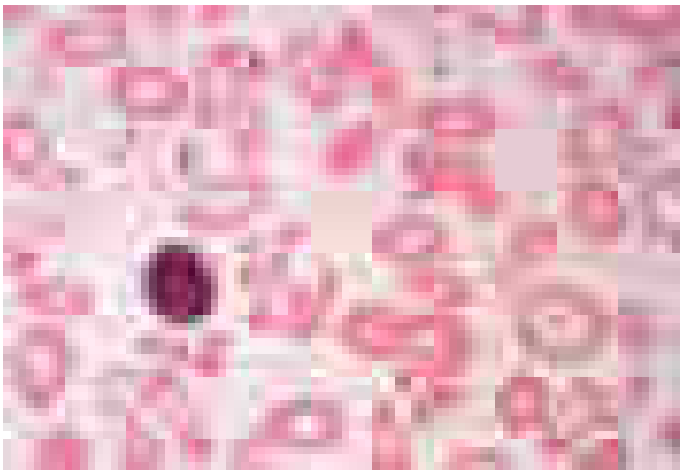

FIGURE 59-4 Severe iron-deficiency anemia. Microcytic and hypochromic red cells smaller than the nucleus of a lymphocyte associated with marked variation in size (anisocytosis) and shape (poikilocytosis). *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

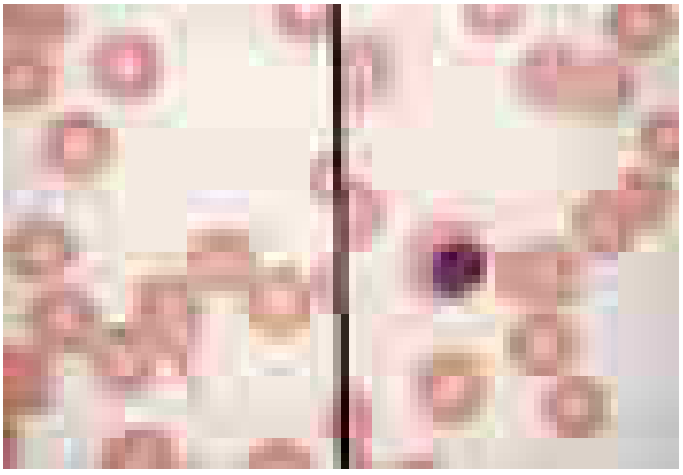

FIGURE 59-7 Red cell changes in myelofibrosis. The left panel shows a teardrop-shaped cell. The right panel shows a nucleated red cell. These forms can be seen in myelofibrosis. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

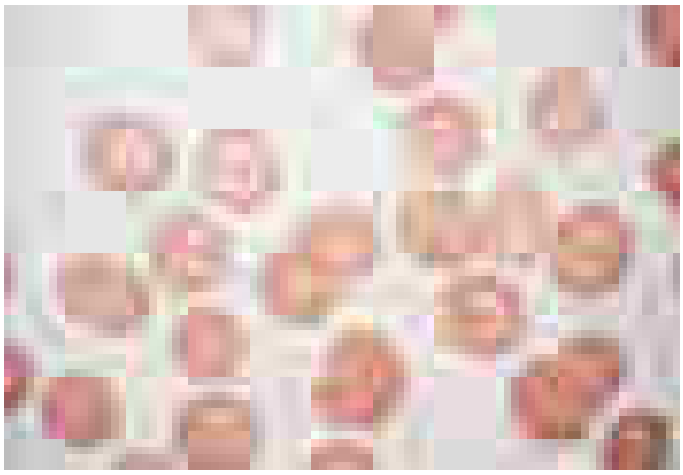

FIGURE 59-8 Target cells. Target cells have a bull's-eye appearance and are seen in thalassemia and in liver disease. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

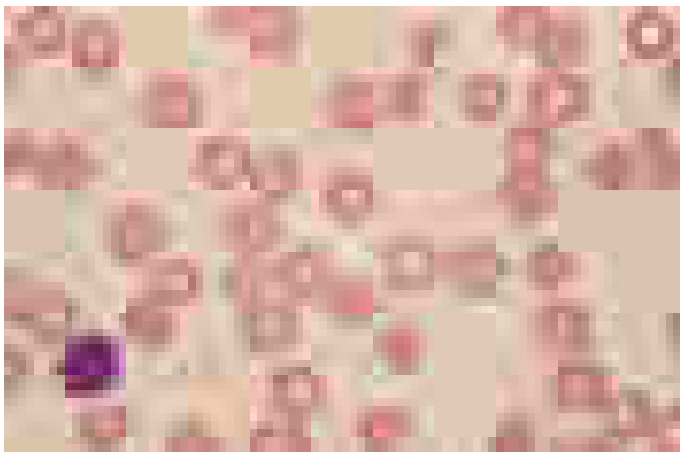

FIGURE 59-11 Spur cells. Spur cells are recognized as distorted red cells containing several irregularly distributed thorn-like projections. Cells with this morphologic abnormality are also called acanthocytes. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

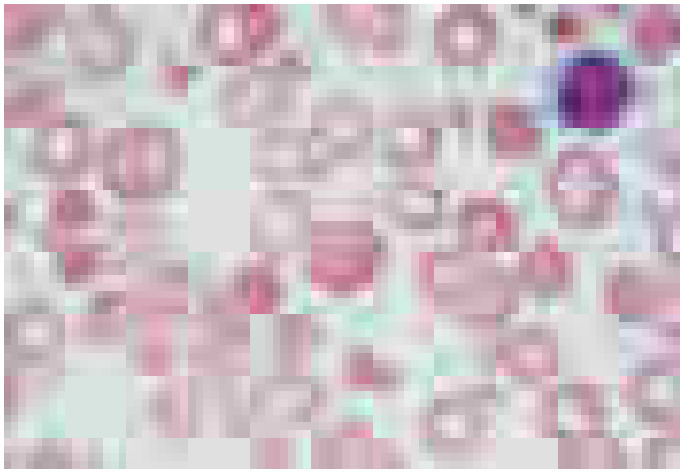

FIGURE 59-9 Red cell fragmentation. Red cells may become fragmented in the presence of foreign bodies in the circulation, such as mechanical heart valves, or in the setting of thermal injury. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

rate increases to two to three times normal within 10 days following the onset of anemia. In the face of established anemia, a reticulocyte response less than two to three times normal indicates an inadequate marrow response.

To use the reticulocyte count to estimate marrow response, two corrections are necessary. The first correction adjusts the reticulocyte count based on the reduced number of circulating red cells. With anemia, the percentage of reticulocytes may be increased while the absolute number is unchanged. To correct for this effect, the reticulocyte percentage is multiplied by the ratio of the patient's hemoglobin or hematocrit to the expected hemoglobin/hematocrit for the age and sex of the patient **(Table 59-4)**. This provides an estimate of the reticulocyte count corrected for anemia. To convert the corrected reticulocyte count to an index of marrow production, a further correction is required, depending on whether some of the reticulocytes in circulation have been released from the marrow prematurely. For this second correction, the peripheral blood smear is examined to see if there are polychromatophilic macrocytes present.

These cells, representing prematurely released reticulocytes, are referred to as "shift" cells, and the relationship between the degree of shift and the necessary shift correction factor is shown in **Fig. 59-13**. The correction is necessary because these prematurely released cells survive as reticulocytes in circulation for >1 day, thereby providing a falsely high estimate of daily red cell production. If polychromasia is increased, the reticulocyte count, already corrected for anemia,

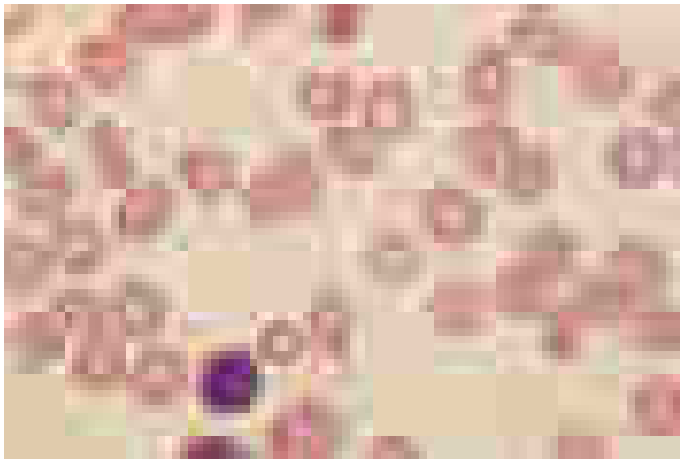

FIGURE 59-10 Uremia. The red cells in uremia may acquire numerous regularly spaced, small, spiny projections. Such cells, called burr cells or echinocytes, are readily distinguishable from irregularly spiculated acanthocytes shown in Fig. 59-11.

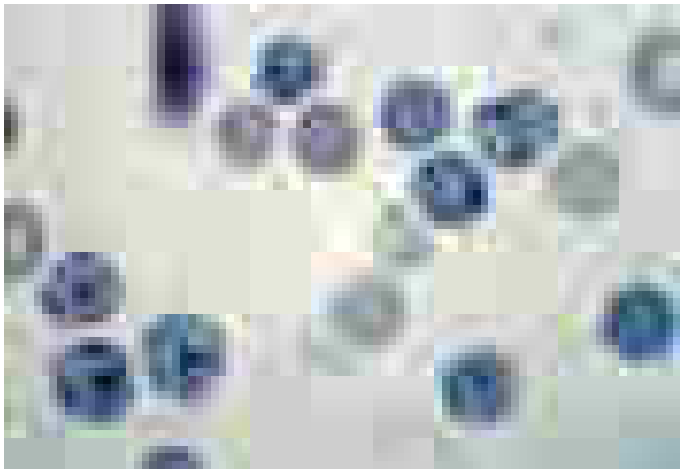

FIGURE 59-12 Reticulocytes. Methylene blue stain demonstrates residual RNA in newly made red cells. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

TABLE 59-4 Calculation of Reticulocyte Production Index

Correction #1 for Anemia:

This correction produces the corrected reticulocyte count.

In a person whose reticulocyte count is 9%, hemoglobin 7.5 g/dL, and hematocrit 23%, the absolute reticulocyte count = 9 × (7.5/15) [or × (23/45)] = 4.5%

Note. This correction is not done if the reticulocyte count is reported in absolute numbers (e.g., 50,000/μL of blood)

Correction #2 for Longer Life of Prematurely Released Reticulocytes in the Blood:

This correction produces the reticulocyte production index.

In a person whose reticulocyte count is 9%, hemoglobin 7.5 gm/dL, and hematocrit 23%, the reticulocyte production index

$$= 9 \times \frac{(7.5/15)(\text{hemoglobin correction})}{2(\text{maturation time correction})} = 2.25$$

should be corrected again by 2 to account for the prolonged reticulocyte maturation time. The second correction factor varies from 1 to 3 depending on the severity of anemia. In general, a correction of 2 is simply used. An appropriate correction is shown in Table 59-4. If polychromatophilic cells are not seen on the blood smear, the second correction is not indicated. The now doubly corrected reticulocyte count is the *reticulocyte production index*, and it provides an estimate of marrow production relative to normal. In many hospital laboratories, the reticulocyte count is reported not only as a percentage but also in absolute numbers. If so, no correction for dilution is required. A summary of the appropriate marrow response to varying degrees of anemia is shown in Table 59-5.

Premature release of reticulocytes is normally due to increased EPO stimulation. However, if the integrity of the bone marrow release process is lost through tumor infiltration, fibrosis, or other disorders, the appearance of nucleated red cells or polychromatophilic macrocytes should still invoke the second reticulocyte correction. The shift correction should always be applied to a patient with anemia and a very high reticulocyte count to provide a true index of effective red cell production. Patients with severe chronic hemolytic anemia may increase red cell production as much as six- to sevenfold. This measure alone confirms the fact that the patient has an appropriate EPO response, a normally functioning bone marrow, and sufficient iron available to meet the demands for new red cell formation. If the reticulocyte production index is <2 in the face of established anemia, a defect in erythroid marrow proliferation or maturation must be present.

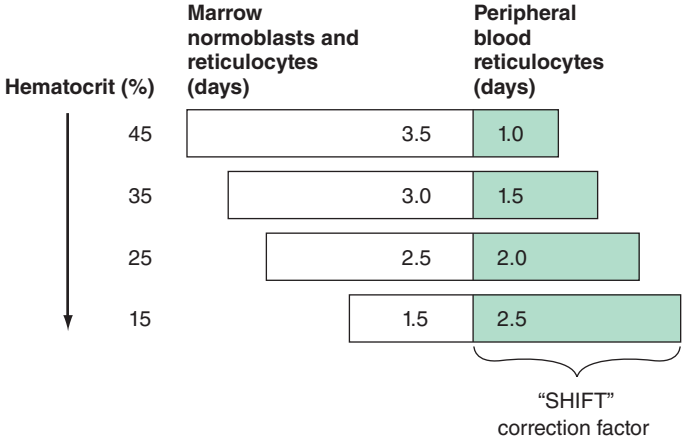

FIGURE 59-13 Correction of the reticulocyte count. To use the reticulocyte count as an indicator of effective red cell production, the reticulocyte number must be corrected based on the level of anemia and the circulating life span of the reticulocytes. Erythroid cells take ~4.5 days to mature. At a normal hemoglobin, reticulocytes are released to the circulation with ~1 day left as reticulocytes. However, with different levels of anemia, reticulocytes (and even earlier erythroid cells) may be released from the marrow prematurely. Most patients come to clinical attention with hematocrits in the mid-20s, and thus a correction factor of 2 is commonly used because the observed reticulocytes will live for 2 days in the circulation before losing their RNA.

TABLE 59-5 Normal Marrow Response to Anemia

HEMOGLOBIN	PRODUCTION INDEX	RETICULOCYTE COUNT
15 g/dL	1	50,000/μL
11 g/dL	2.0–2.5	100–150,000/μL
8 g/dL	3.0–4.0	300–400,000/μL

Tests of Iron Supply and Storage The laboratory measurements that reflect the availability of iron for hemoglobin synthesis include the serum iron, the TIBC, and the percent transferrin saturation. The percent transferrin saturation is derived by dividing the serum iron level (× 100) by the TIBC. The normal serum iron ranges from 9 to 27 μmol/L (50–150 μg/dL), whereas the normal TIBC is 54–64 μmol/L (300–360 μg/dL); the normal transferrin saturation ranges from 25 to 50%. A diurnal variation in the serum iron leads to a variation in the percent transferrin saturation. The serum ferritin is used to evaluate total body iron stores. Adult males have serum ferritin levels that average ~100 μg/L, corresponding to iron stores of ~1 g. Adult females have lower serum ferritin levels averaging 30 μg/L, reflecting lower iron stores (~300 mg). A serum ferritin level of 10–15 μg/L indicates depletion of body iron stores. However, ferritin is also an acute-phase reactant and, in the presence of acute or chronic inflammation, may rise several-fold above baseline levels. As a rule, a serum ferritin >200 μg/L means there is at least some iron in tissue stores.

Bone Marrow Examination A bone marrow aspirate and smear or a needle biopsy can be useful in the evaluation of some patients with anemia. In patients with hypoproliferative anemia and normal iron status, a bone marrow is indicated. Marrow examination can diagnose primary marrow disorders such as myelofibrosis, a red cell maturation defect, or an infiltrative disease (Figs. 59-14 to 59-16). The increase or decrease of one cell lineage (myeloid vs erythroid) compared to another is obtained by a differential count of nucleated cells in a bone marrow smear (the myeloid/erythroid [M/E] ratio). A patient with a hypoproliferative anemia (see below) and a reticulocyte production index <2 will demonstrate an M/E ratio of 2 or 3:1. In contrast, patients with hemolytic disease and a production index >3 will have an M/E ratio of at least 1:1. Maturation disorders are identified from the discrepancy between the M/E ratio and the reticulocyte production index (see below). Either the marrow smear or biopsy can be stained for the presence of iron stores or iron in developing red cells. The storage iron is in the form of ferritin or

FIGURE 59-14 Normal bone marrow. This is a low-power view of a section of a normal bone marrow biopsy stained with hematoxylin and eosin (H&E). Note that the nucleated cellular elements account for ~40–50% and the fat (clear areas) accounts for ~50–60% of the area. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

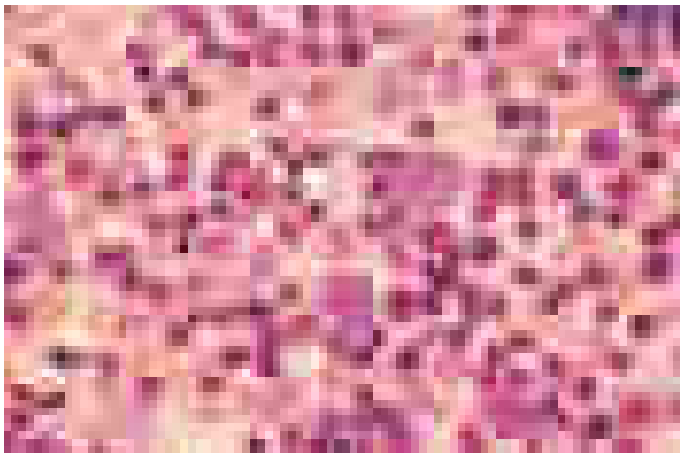

FIGURE 59-15 Erythroid hyperplasia. This marrow shows an increase in the fraction of cells in the erythroid lineage as might be seen when a normal marrow compensates for acute blood loss or hemolysis. The myeloid/erythroid (M/E) ratio is about 1:1. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

hemosiderin. On carefully prepared bone marrow smears, small ferritin granules can normally be seen under oil immersion in 20–40% of developing erythroblasts. Such cells are called *sideroblasts*.

OTHER LABORATORY MEASUREMENTS

Additional laboratory tests may be of value in confirming specific diagnoses. **For details of these tests and how they are applied in individual disorders, see Chaps. 93 to 97.**

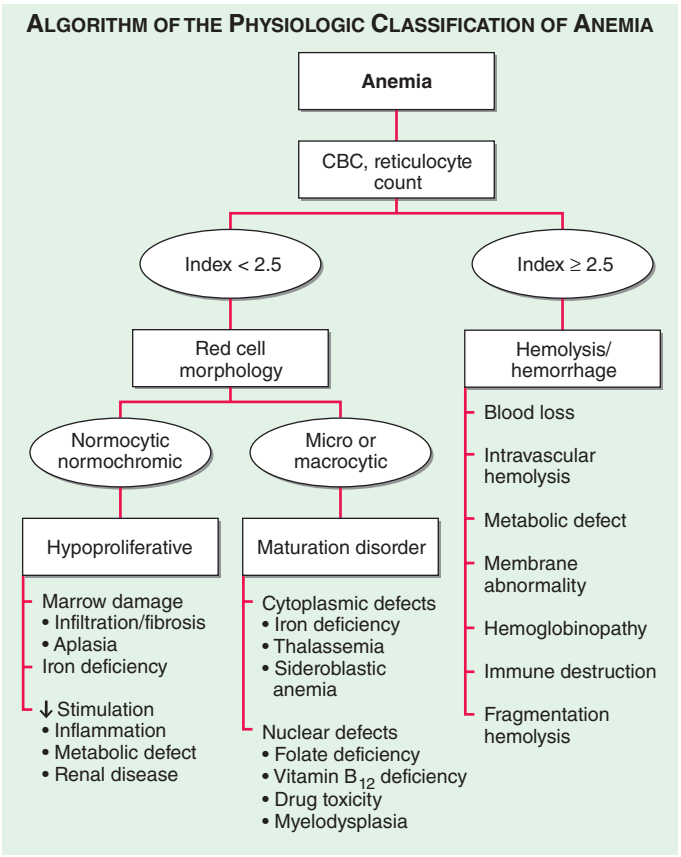

FIGURE 59-17 The physiologic classification of anemia. CBC, complete blood count.

DEFINITION AND CLASSIFICATION OF ANEMIA

Initial Classification of Anemia The functional classification of anemia has three major categories. These are (1) marrow production defects (*hypoproliferation*), (2) red cell maturation defects (*ineffective erythropoiesis*), and (3) decreased red cell survival (*blood loss/hemolysis*). The classification is shown in **Fig. 59-17**. A hypoproliferative anemia is typically seen with a low reticulocyte production index together with little or no change in red cell morphology (a normocytic, normochromic anemia) **(Chap. 93)**. Maturation disorders typically have a slight to moderately elevated reticulocyte production index that is accompanied by either macrocytic **(Chap. 95)** or microcytic **(Chaps. 93, 94)** red cell indices. Increased red blood cell destruction secondary to hemolysis results in an increase in the reticulocyte production index to at least three times normal **(Chap. 96)**, provided sufficient iron is available. Hemorrhagic anemia does not typically result in production indices of more than 2.0–2.5 times normal because of the limitations placed on expansion of the erythroid marrow by iron availability **(Chap. 97)**.

In the first branch point of the classification of anemia, a reticulocyte production index >2.5 indicates that hemolysis is most likely. A reticulocyte production index <2 indicates either a hypoproliferative anemia or maturation disorder. The latter two possibilities can often be distinguished by the red cell indices, by examination of the peripheral blood smear, or by a marrow examination. If the red cell indices are normal, the anemia is almost certainly hypoproliferative in nature. Maturation disorders are characterized by ineffective red cell production and a low reticulocyte production index. Bizarre red cell shapes—macrocytes or hypochromic microcytes—are seen on the peripheral blood smear. With a hypoproliferative anemia, no erythroid hyperplasia is noted in the marrow, whereas patients with ineffective red cell production have erythroid hyperplasia and an M/E ratio <1:1.

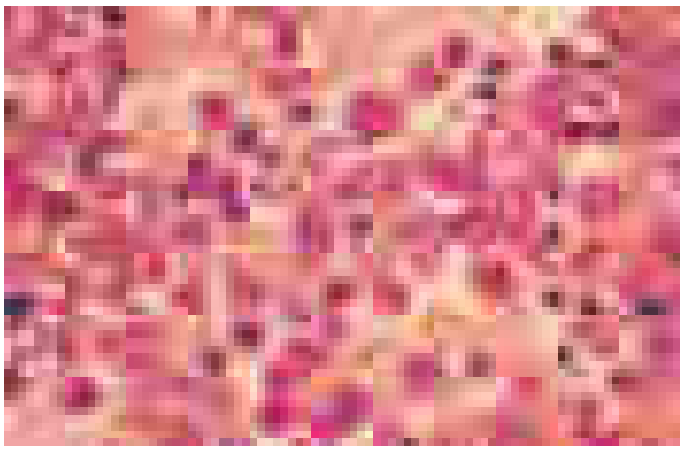

FIGURE 59-16 Myeloid hyperplasia. This marrow shows an increase in the fraction of cells in the myeloid or granulocytic lineage as might be seen in a normal marrow responding to infection. The myeloid/erythroid (M/E) ratio is >3:1. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2010.)*

Hypoproliferative Anemias At least 75% of all cases of anemia are hypoproliferative in nature. A hypoproliferative anemia reflects absolute or relative marrow failure in which the erythroid marrow has not proliferated appropriately for the degree of anemia. The majority of hypoproliferative anemias are due to mild to moderate iron deficiency or inflammation. A hypoproliferative anemia can result from marrow damage, iron deficiency, or inadequate EPO stimulation. The last may reflect impaired renal function, suppression of EPO production by inflammatory cytokines such as interleukin 1, or reduced tissue needs for O_2 from metabolic disease such as hypothyroidism. Only occasionally is the marrow unable to produce red cells at a normal rate, and this is most prevalent in patients with renal failure. With diabetes mellitus or myeloma, the EPO deficiency may be more marked than would be predicted by the degree of renal insufficiency. In general, hypoproliferative anemias are characterized by normocytic, normochromic red cells, although microcytic, hypochromic cells may be observed with mild iron deficiency or long-standing chronic inflammatory disease.

The key laboratory tests in distinguishing between the various forms of hypoproliferative anemia include the serum iron and iron-binding capacity, evaluation of renal and thyroid function, a marrow biopsy or aspirate to detect marrow damage or infiltrative disease, and serum ferritin to assess iron stores. An iron stain of the marrow will determine the pattern of iron distribution. Patients with the anemia of acute or chronic inflammation show a distinctive pattern of serum iron (low), TIBC (normal or low), percent transferrin saturation (low), and serum ferritin (normal or high). These changes in iron values are brought about by hepcidin, the iron regulatory hormone that is produced by the liver and is increased in inflammation **(Chap. 93)**. A distinct pattern of results is noted in mild to moderate iron deficiency (low serum iron, high TIBC, low percent transferrin saturation, low serum ferritin) **(Chap. 93)**. Marrow damage by drugs, infiltrative disease such as leukemia or lymphoma, or marrow aplasia is diagnosed from the peripheral blood and bone marrow morphology. With infiltrative disease or fibrosis, a marrow biopsy is required.

Maturation Disorders The presence of anemia with an inappropriately low reticulocyte production index, macro- or microcytosis on smear, and abnormal red cell indices suggests a maturation disorder. Maturation disorders are divided into two categories: nuclear maturation defects, associated with macrocytosis, and cytoplasmic maturation defects, associated with microcytosis and hypochromia usually from defects in hemoglobin synthesis. The inappropriately low reticulocyte production index is a reflection of the ineffective erythropoiesis that results from the destruction within the marrow of developing erythroblasts. Bone marrow examination shows erythroid hyperplasia.

Nuclear maturation defects result from vitamin B_{12} or folic acid deficiency, drug damage, or myelodysplasia. Drugs that interfere with cellular DNA synthesis, such as methotrexate or alkylating agents, can produce a nuclear maturation defect. Alcohol, alone, is also capable of producing macrocytosis and a variable degree of anemia, but this is usually associated with folic acid deficiency. Measurements of folic acid and vitamin B_{12} are critical not only in identifying the specific vitamin deficiency but also because they reflect different pathogenetic mechanisms **(Chap. 95)**.

Cytoplasmic maturation defects result from severe iron deficiency or abnormalities in globin or heme synthesis. Iron deficiency occupies an unusual position in the classification of anemia. If the iron-deficiency anemia is mild to moderate, erythroid marrow proliferation is blunted and the anemia is classified as hypoproliferative. However, if the anemia is severe and prolonged, the erythroid marrow will become hyperplastic despite the inadequate iron supply, and the anemia will be classified as ineffective erythropoiesis with a cytoplasmic maturation defect. In either case, an inappropriately low reticulocyte production index, microcytosis, and a classic pattern of iron values make the diagnosis clear and easily distinguish iron deficiency from other cytoplasmic maturation defects such as the thalassemias. Defects in heme synthesis, in contrast to globin synthesis, are less common and may be acquired or inherited **(Chap. 409)**. Acquired abnormalities are usually associated with myelodysplasia, may lead to either a macro- or microcytic anemia, and are frequently associated with mitochondrial iron loading. In these cases, iron is taken up by the mitochondria of the developing erythroid cell but not incorporated into heme. The iron-encrusted mitochondria surround the nucleus of the erythroid cell, forming a ring. Based on the distinctive finding of so-called ringed sideroblasts on the marrow iron stain, patients are diagnosed as having a sideroblastic anemia—almost always reflecting myelodysplasia. Again, studies of iron parameters are helpful in the differential diagnosis of these patients.

Blood Loss/Hemolytic Anemia In contrast to anemias associated with an inappropriately low reticulocyte production index, hemolysis is associated with red cell production indices ≥2.5 times normal. The stimulated erythropoiesis is reflected in the blood smear by the appearance of increased numbers of polychromatophilic macrocytes. A marrow examination is rarely indicated if the reticulocyte production index is increased appropriately. The red cell indices are typically normocytic or slightly macrocytic, reflecting the increased number of reticulocytes. Acute blood loss is not associated with an increased reticulocyte production index because of the time required to increase EPO production and, subsequently, marrow proliferation **(Chap. 97)**. Subacute blood loss may be associated with modest reticulocytosis. Anemia from chronic blood loss presents more often as iron deficiency than with the picture of increased red cell production.

The evaluation of blood loss anemia is usually not difficult. Most problems arise when a patient presents with an increased red cell production index from an episode of acute blood loss that went unrecognized. The cause of the anemia and increased red cell production may not be obvious. The confirmation of a recovering state may require observations over a period of 2–3 weeks, during which the hemoglobin concentration will rise and the reticulocyte production index fall **(Chap. 97)**.

Hemolytic disease, while dramatic, is among the least common forms of anemia. The ability to sustain a high reticulocyte production index reflects the ability of the erythroid marrow to compensate for hemolysis and, in the case of extravascular hemolysis, the efficient recycling of iron from the destroyed red cells to support red cell production. With intravascular hemolysis, such as paroxysmal nocturnal hemoglobinuria, the loss of iron may limit the marrow response. The level of response depends on the severity of the anemia and the nature of the underlying disease process.

Hemoglobinopathies, such as sickle cell disease and the thalassemias, present a mixed picture. The reticulocyte index may be high but is inappropriately low for the degree of marrow erythroid hyperplasia **(Chap. 94)**.

Hemolytic anemias present in different ways. Some appear suddenly as an acute, self-limited episode of intravascular or extravascular hemolysis, a presentation pattern often seen in patients with autoimmune hemolysis or with inherited defects of the Embden-Meyerhof pathway or the glutathione reductase pathway. Patients with inherited disorders of the hemoglobin molecule or red cell membrane generally have a lifelong clinical history typical of the disease process. Those with chronic hemolytic disease, such as hereditary spherocytosis, may actually present not with anemia but with a complication stemming from the prolonged increase in red cell destruction such as symptomatic bilirubin gallstones or splenomegaly. Patients with chronic hemolysis are also susceptible to aplastic crises if an infectious process interrupts red cell production.

The differential diagnosis of an acute or chronic hemolytic event requires the careful integration of family history, the pattern of clinical presentation, and—whether the disease is congenital or acquired—careful examination of the peripheral blood smear. Precise diagnosis may require more specialized laboratory tests, such as hemoglobin electrophoresis or a screen for red cell enzymes. Acquired defects in red cell survival are often immunologically mediated and require a direct or indirect antiglobulin test or a cold agglutinin titer to detect the presence of hemolytic antibodies or complement-mediated red cell destruction **(Chap. 96)**.

TREATMENT

Anemia

An overriding principle is to initiate treatment of mild to moderate anemia only when a specific diagnosis is made. Rarely, in the acute setting, anemia may be so severe that red cell transfusions are required before a specific diagnosis is available. Whether the anemia is of acute or gradual onset, the selection of the appropriate treatment is determined by the documented cause(s) of the anemia. Often, the cause of the anemia is multifactorial. For example, a patient with severe rheumatoid arthritis who has been taking anti-inflammatory drugs may have a hypoproliferative anemia associated with chronic inflammation as well as chronic blood loss associated with intermittent gastrointestinal bleeding. In every circumstance, it is important to evaluate the patient's iron status fully before and during the treatment of any anemia. **Transfusion is discussed in Chap. 109; iron therapy is discussed in Chap. 93;**

treatment of megaloblastic anemia is discussed in Chap. 95; treatment of other entities is discussed in their respective chapters (sickle cell anemia, Chap. 94; hemolytic anemias, Chap. 96; aplastic anemia and myelodysplasia, Chap. 98).

Therapeutic options for the treatment of anemias have expanded dramatically during the past 30 years. Blood component therapy is available and safe. Recombinant EPO as an adjunct to anemia management has transformed the lives of patients with chronic renal failure on dialysis and reduced transfusion needs of anemic cancer patients receiving chemotherapy. Eventually, patients with inherited disorders of globin synthesis or mutations in the globin gene, such as sickle cell disease, may benefit from the successful introduction of targeted genetic therapy **(Chap. 458)**.

POLYCYTHEMIA

Polycythemia is defined as an increase in the hemoglobin above normal. This increase may be real or only apparent because of a decrease in plasma volume (spurious or relative polycythemia). The term *erythrocytosis* may be used interchangeably with polycythemia, but some draw a distinction between them: erythrocytosis implies documentation of increased red cell mass, whereas polycythemia refers to any increase in red cells. Often patients with polycythemia are detected through an incidental finding of elevated hemoglobin or hematocrit levels. Concern that the hemoglobin level may be abnormally high is usually triggered at 170 g/L (17 g/dL) for men and 150 g/L (15 g/dL) for women. Hematocrit levels >50% in men or >45% in women may be abnormal. Hematocrits >60% in men and >55% in women are almost invariably associated with an increased red cell mass. Given that the machine that quantitates red cell parameters actually measures hemoglobin concentrations and calculates hematocrits, hemoglobin levels may be a better index.

Features of the clinical history that are useful in the differential diagnosis include smoking history; current living at high altitude; or a history of diuretic use, congenital heart disease, sleep apnea, or chronic lung disease.

Patients with polycythemia may be asymptomatic or experience symptoms related to the increased red cell mass or the underlying disease process that leads to the increased red cell mass. The dominant symptoms from an increased red cell mass are related to hyperviscosity and thrombosis (both venous and arterial), because the blood viscosity increases logarithmically at hematocrits >55%. Manifestations include neurologic symptoms such as vertigo, tinnitus, headache, and visual disturbances. Hypertension is often present. Patients with *polycythemia vera* may have aquagenic pruritus, symptoms related to hepatosplenomegaly, easy bruising, epistaxis, or bleeding from the gastrointestinal tract. Peptic ulcer disease is common. Such patients also may present with digital ischemia, Budd–Chiari syndrome, hepatic or splenic/mesenteric vein thrombosis. Patients with hypoxemia may develop cyanosis on minimal exertion or have headache, impaired mental acuity, and fatigue.

The physical examination usually reveals a ruddy complexion. Splenomegaly favors polycythemia vera as the diagnosis **(Chap. 99)**. The presence of cyanosis or evidence of a right-to-left shunt suggests congenital heart disease presenting in the adult, particularly tetralogy of Fallot or Eisenmenger's syndrome **(Chap. 264)**. Increased blood viscosity raises pulmonary artery pressure; hypoxemia can lead to increased pulmonary vascular resistance. Together, these factors can produce cor pulmonale.

Polycythemia can be spurious (related to a decrease in plasma volume; Gaisbock's syndrome), primary, or secondary in origin. The secondary causes are all mediated by EPO: either a physiologically adapted appropriate level based on tissue hypoxia (lung disease, high altitude, CO poisoning, high-affinity hemoglobinopathy) or an abnormal overproduction (renal cysts, renal artery stenosis, tumors with ectopic EPO production). A rare familial form of polycythemia is associated with normal EPO levels but hyperresponsive EPO receptors due to mutations.

APPROACH TO THE PATIENT

Polycythemia

As shown in **Fig. 59-18**, the first step is to document the presence of an increased red cell mass using the principle of isotope dilution by administering ^{51}Cr-labeled autologous red blood cells to the patient and sampling blood radioactivity over a 2-h period. If the red cell mass is normal (<36 mL/kg in men, <32 mL/kg in women), the patient has spurious or relative polycythemia. If the red cell mass is increased (>36 mL/kg in men, >32 mL/kg in women), serum EPO levels should be measured. If EPO levels are low or unmeasurable, the patient most likely has polycythemia vera. A mutation in *JAK2* (Val617Phe), a key member of the cytokine intracellular signaling pathway, can be found in 90–95% of patients with polycythemia vera. Many of those without this particular *JAK2* mutation have mutations in exon 12. As a practical matter, few centers assess red cell mass in the setting of an increased hemoglobin level. The alternative workup is to measure EPO levels, check for *JAK2* mutation(s), and perform an abdominal ultrasound to assess spleen size. Tests that support the diagnosis of polycythemia vera include elevated white blood cell count, increased absolute basophil count, and thrombocytosis.

If serum EPO levels are elevated, one needs to distinguish whether the elevation is a physiologic response to hypoxia or related to autonomous EPO production. Patients with low arterial O_2 saturation (<92%) should be further evaluated for the presence of heart or lung disease, if they are not living at high altitude. Patients with normal O_2 saturation who are smokers may have elevated EPO levels because of CO displacement of O_2. If carboxyhemoglobin (COHb) levels are high, the diagnosis is "smoker's polycythemia." Such patients should be urged to stop smoking. Those who cannot stop smoking require phlebotomy to control their polycythemia. Patients with normal O_2 saturation who do not smoke either have an

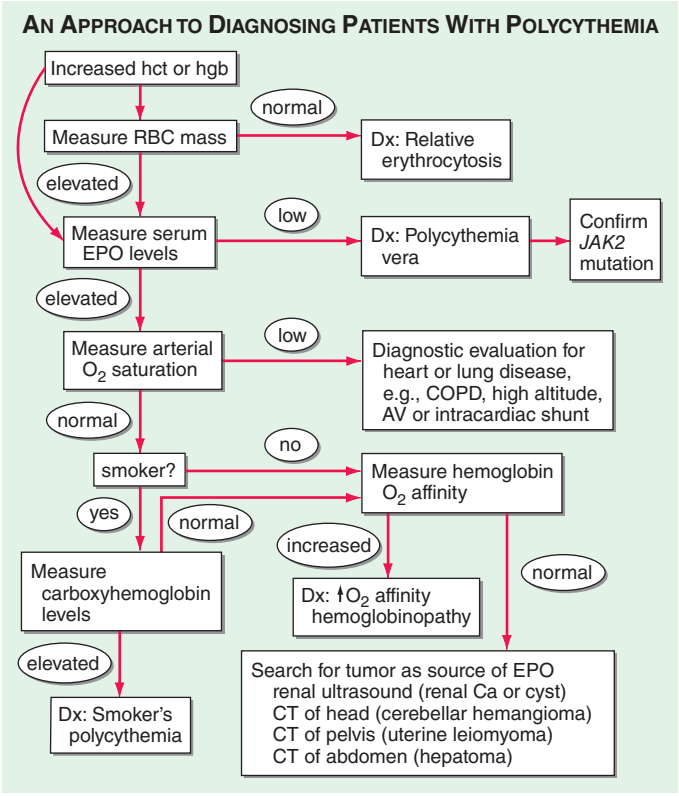

FIGURE 59-18 An approach to the differential diagnosis of patients with an elevated hemoglobin (possible polycythemia). AV, atrioventricular; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EPO, erythropoietin; hct, hematocrit; hgb, hemoglobin; IVP, intravenous pyelogram; RBC, red blood cell.

abnormal hemoglobin that does not deliver O_2 to the tissues (evaluated by finding elevated O_2–hemoglobin affinity) or have a source of EPO production that is not responding to the normal feedback inhibition. Further workup is dictated by the differential diagnosis of EPO-producing neoplasms. Hepatoma, uterine leiomyoma, and renal cancer or cysts are all detectable with abdominopelvic computed tomography scans. Cerebellar hemangiomas may produce EPO, but they present with localizing neurologic signs and symptoms rather than polycythemia-related symptoms.

FURTHER READING

HILLMAN RS et al: *Hematology in Clinical Practice*, 5th ed. New York, McGraw-Hill, 2010.

MCMULLIN MF et al: Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. Br J Haematol 130:174, 2005.

SANKARAN VG, WEISS MJ: Anemia: Progress in molecular mechanisms and therapies. Nat Med 21:221, 2015.

60 Disorders of Granulocytes and Monocytes

Steven M. Holland, John I. Gallin

Leukocytes, the major cells comprising inflammatory and immune responses, include neutrophils, T and B lymphocytes, natural killer (NK) cells, monocytes, eosinophils, and basophils. These cells have specific functions, such as antibody production by B lymphocytes or destruction of bacteria by neutrophils, but in no single infectious disease is the exact role of the cell types completely established. Thus, whereas neutrophils are classically thought to be critical to host defense against bacteria, they may also play important roles in defense against viral infections.

The blood delivers leukocytes to the various tissues from the bone marrow, where they are produced. Normal blood leukocyte counts are $4.3–10.8 \times 10^9$/L, with neutrophils representing 45–74% of the cells, bands 0–4%, lymphocytes 16–45%, monocytes 4–10%, eosinophils 0–7%, and basophils 0–2%. Variation among individuals and among different ethnic groups can be substantial, with lower leukocyte numbers for certain African-American ethnic groups. The various leukocytes are derived from a common stem cell in the bone marrow. Three-fourths of the nucleated cells of bone marrow are committed to the production of leukocytes. Leukocyte maturation in the marrow is under the regulatory control of a number of different factors, known as colony-stimulating factors (CSFs) and interleukins (ILs). Because an alteration in the number and type of leukocytes is often associated with disease processes, total white blood cell (WBC) count (cells per μL) and differential counts are informative. This chapter focuses on neutrophils, monocytes, and eosinophils. **Lymphocytes and basophils are discussed in Chaps. 342 and 346, respectively.**

NEUTROPHILS

MATURATION

Important events in neutrophil life are summarized in **Fig. 60-1**. In normal humans, neutrophils are produced only in the bone marrow. The minimum number of stem cells necessary to support hematopoiesis is estimated to be 400–500 at any one time. Human blood monocytes, tissue macrophages, and stromal cells produce CSFs, hormones required for the growth of monocytes and neutrophils in the bone marrow. The hematopoietic system not only produces enough neutrophils (~1.3×10^{11} cells per 80-kg person per day) to carry out physiologic functions but also has a large reserve stored in the marrow, which can be mobilized in response to inflammation or infection. An increase in the number of blood neutrophils is called *neutrophilia*, and the presence of immature cells is termed a *shift to the left*. A decrease in the number of blood neutrophils is called *neutropenia*.

Neutrophils and monocytes evolve from pluripotent stem cells under the influence of cytokines and CSFs **(Fig. 60-2)**. The proliferation phase through the metamyelocyte takes about 1 week, while the maturation phase from metamyelocyte to mature neutrophil takes another week. The myeloblast is the first recognizable precursor cell and is followed by the *promyelocyte*. The promyelocyte evolves

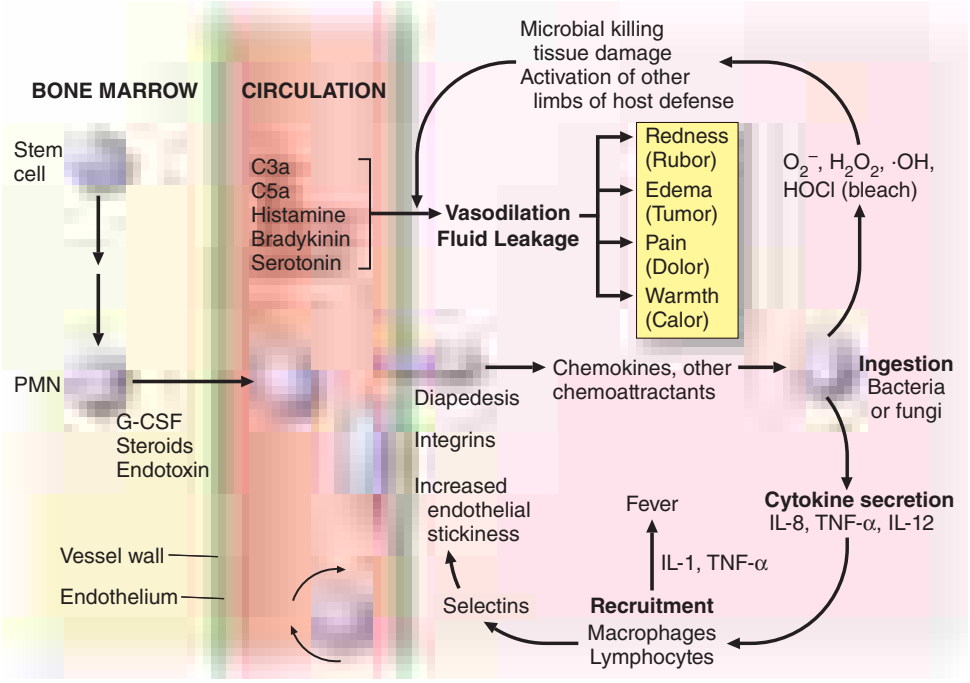

FIGURE 60-1 Schematic events in neutrophil production, recruitment, and inflammation. The four cardinal signs of inflammation (rubor, tumor, calor, dolor) are indicated, as are the interactions of neutrophils with other cells and cytokines. G-CSF, granulocyte colony-stimulating factor; IL, interleukin; PMN, polymorphonuclear leukocyte; TNF-α, tumor necrosis factor α.

Cell	Stage	Surface Markers[a]	Characteristics
	MYELOBLAST	CD33, CD13, CD15	Prominent nucleoli
	PROMYELOCYTE	CD33, CD13, CD15	Large cell Primary granules appear
	MYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Secondary granules appear
	METAMYELOCYTE	CD33, CD13, CD15, CD14, CD11b	Kidney bean–shaped nucleus
	BAND FORM	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, band–shaped nucleus
	NEUTROPHIL	CD33, CD13, CD15, CD14, CD11b CD10, CD16	Condensed, multilobed nucleus

[a]CD = Cluster Determinant; ● Nucleolus; ● Primary granule; ● Secondary granule.

FIGURE 60-2 Stages of neutrophil development shown schematically. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are critical to this process. Identifying cellular characteristics and specific cell-surface markers are listed for each maturational stage.

when the classic lysosomal granules, called the *primary*, or *azurophil, granules* are produced. The primary granules contain hydrolases, elastase, myeloperoxidase, cathepsin G, cationic proteins, and bactericidal/permeability-increasing protein, which is important for killing gram-negative bacteria. Azurophil granules also contain *defensins*, a family of cysteine-rich polypeptides with broad antimicrobial activity against bacteria, fungi and certain enveloped viruses. The promyelocyte divides to produce the *myelocyte*, a cell responsible for the synthesis of the *specific*, or *secondary, granules*, which contain unique (specific) constituents such as lactoferrin, vitamin B_{12}–binding protein, membrane components of the reduced nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase required for hydrogen peroxide production, histaminase, and receptors for certain chemoattractants and adherence-promoting factors (CR3) as well as receptors for the basement membrane component, laminin. The secondary granules do not contain acid hydrolases and therefore are not classic lysosomes. Packaging of secondary granule contents during myelopoiesis is controlled by CCAAT/enhancer binding protein-ε. Secondary granule contents are readily released extracellularly, and their mobilization is important in modulating inflammation. During the final stages of maturation, no cell division occurs, and the cell passes through the metamyelocyte stage and then to the band neutrophil with a sausage-shaped nucleus (Fig. 60-3). As the band cell matures, the nucleus assumes a lobulated configuration. The nucleus of neutrophils normally contains up to four segments (Fig. 60-4). Excessive segmentation (>5 nuclear lobes) may be a manifestation of folate or vitamin B_{12} deficiency or the congenital neutropenia syndrome of warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) described below. The Pelger-Hüet anomaly (Fig. 60-5), an infrequent dominant benign inherited trait, results in neutrophils with distinctive bilobed nuclei that must be distinguished from band forms. Acquired bilobed nuclei, pseudo Pelger-Hüet anomaly, can occur with acute infections or in myelodysplastic syndromes. The physiologic role of the normal multilobed nucleus of neutrophils is unknown, but it may allow great deformation of neutrophils during migration into tissues at sites of inflammation.

In severe acute bacterial infection, prominent neutrophil cytoplasmic granules, called *toxic granulations*, are occasionally seen. Toxic granulations are immature or abnormally staining azurophil granules. Cytoplasmic inclusions, also called *Döhle bodies* (Fig. 60-3), can be seen during infection and are fragments of ribosome-rich endoplasmic reticulum. Large neutrophil vacuoles are often present in acute bacterial infection and probably represent pinocytosed (internalized) membrane.

Neutrophils are heterogeneous in function. Monoclonal antibodies have been developed that recognize only a subset of mature neutrophils. The meaning of neutrophil heterogeneity is not known.

The morphology of eosinophils and basophils is shown in Fig. 60-6.

MARROW RELEASE AND CIRCULATING COMPARTMENTS

Specific signals, including IL-1, tumor necrosis factor α (TNF-α), the CSFs, complement fragments, and chemokines, mobilize leukocytes from the bone marrow and deliver them to the blood in an unstimulated state. Under normal conditions, ~90% of the neutrophil pool is in the bone marrow, 2–3% in the circulation, and the remainder in the tissues (Fig. 60-7).

The circulating pool exists in two dynamic compartments: one freely flowing and one marginated. The freely flowing pool is about one-half the neutrophils in the basal state and is composed of those cells that are in the blood and not in contact with the endothelium. Marginated leukocytes are those that are in close physical contact with the endothelium (Fig. 60-8). In the pulmonary circulation, where an extensive capillary bed (~1000 capillaries per alveolus) exists, margination occurs because the capillaries are about the same size as a mature neutrophil. Therefore, neutrophil fluidity and deformability are necessary to make the transit through the pulmonary bed. Increased neutrophil rigidity and decreased

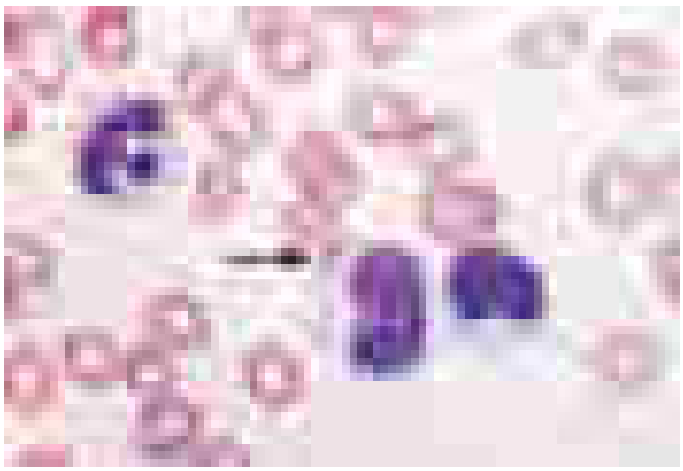

FIGURE 60-3 Neutrophil band with Döhle body. The neutrophil with a sausage-shaped nucleus in the center of the field is a band form. Döhle bodies are discrete, blue-staining, nongranular areas found in the periphery of the cytoplasm of the neutrophil in infections and other toxic states. They represent aggregates of rough endoplasmic reticulum.

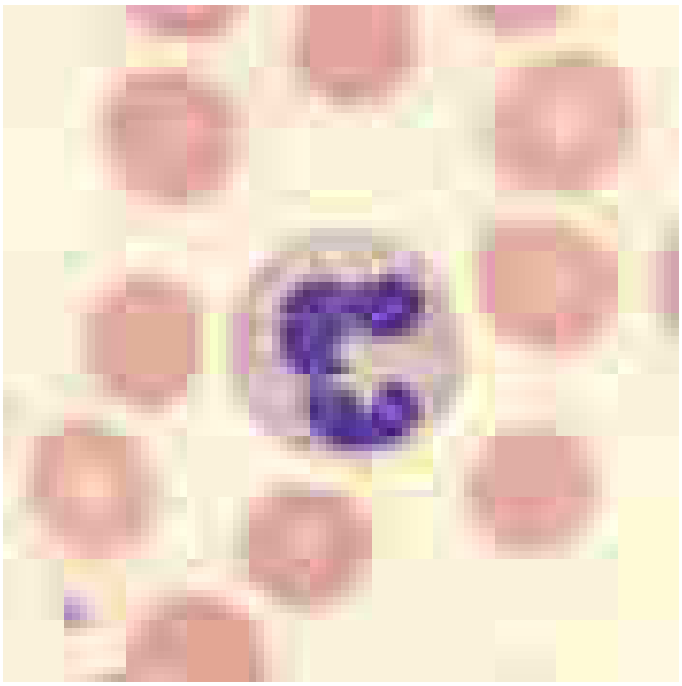

FIGURE 60-4 Normal granulocyte. The normal granulocyte has a segmented nucleus with heavy, clumped chromatin; fine neutrophilic granules are dispersed throughout the cytoplasm.

deformability lead to augmented neutrophil trapping and margination in the lung. In contrast, in the systemic postcapillary venules, margination is mediated by the interaction of specific cell-surface molecules called *selectins*. Selectins are glycoproteins expressed on neutrophils and endothelial cells, among others, that cause a low-affinity interaction, resulting in "rolling" of the neutrophil along the endothelial surface. On neutrophils, the molecule L-selectin (cluster determinant [CD] 62L) binds to glycosylated proteins on endothelial cells (e.g., glycosylation-dependent cell adhesion molecule [GlyCAM1] and CD34). Glycoproteins on neutrophils, most importantly sialyl-Lewis^x (SLe^x, CD15s), are targets for binding of selectins expressed on endothelial cells (E-selectin [CD62E] and P-selectin [CD62P]) and other leukocytes. In response to chemotactic stimuli from injured tissues (e.g., complement product C5a, leukotriene B_4, IL-8) or bacterial products (e.g., *N*-formylmethionylleucylphenylalanine [f-met-leu-phe]), neutrophil adhesiveness increases through mobilization of intracellular adhesion proteins stored in specific granules to the cell surface, and the cells "stick" to the endothelium through *integrins*. The integrins are leukocyte glycoproteins that exist as complexes of a common

FIGURE 60-5 Pelger-Hüet anomaly. In this benign disorder, the majority of granulocytes are bilobed. The nucleus frequently has a spectacle-like, or "pince-nez," configuration.

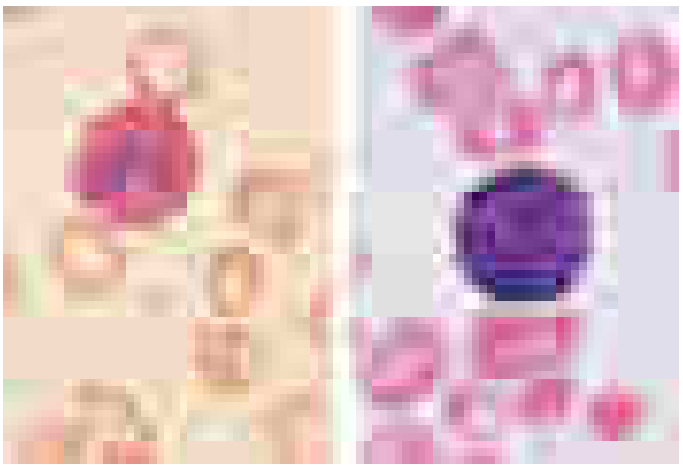

FIGURE 60-6 Normal eosinophil (*left*) and basophil (*right*). The eosinophil contains large, bright orange granules and usually a bilobed nucleus. The basophil contains large purple-black granules that fill the cell and obscure the nucleus.

CD18 β chain with CD11a (LFA-1), CD11b (called Mac-1, CR3, or the C3bi receptor), and CD11c (called p150,95 or CR4). CD11a/CD18 and CD11b/CD18 bind to specific endothelial receptors (intercellular adhesion molecules [ICAM] 1 and 2).

On cell stimulation, L-selectin is shed from neutrophils, and E-selectin increases in the blood, presumably because it is shed from endothelial cells; receptors for chemoattractants and opsonins are mobilized; and the phagocytes orient toward the chemoattractant source in the extravascular space, increase their motile activity (chemokinesis), and migrate directionally (chemotaxis) into tissues. The process of migration into tissues is called *diapedesis* and involves the crawling of neutrophils between postcapillary endothelial cells that open junctions between adjacent cells to permit leukocyte passage. Diapedesis involves platelet/endothelial cell adhesion molecule (PECAM) 1 (CD31), which is expressed on both the emigrating leukocyte and the endothelial cells. The endothelial responses (increased blood flow from increased vasodilation and permeability) are mediated by anaphylatoxins (e.g., C3a and C5a) as well as vasodilators such as histamine,

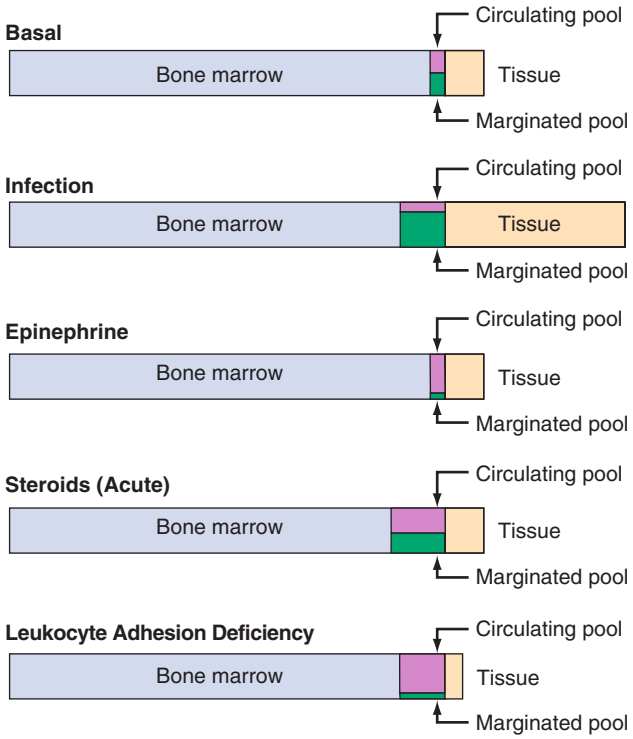

FIGURE 60-7 Schematic neutrophil distribution and kinetics between the different anatomic and functional pools.

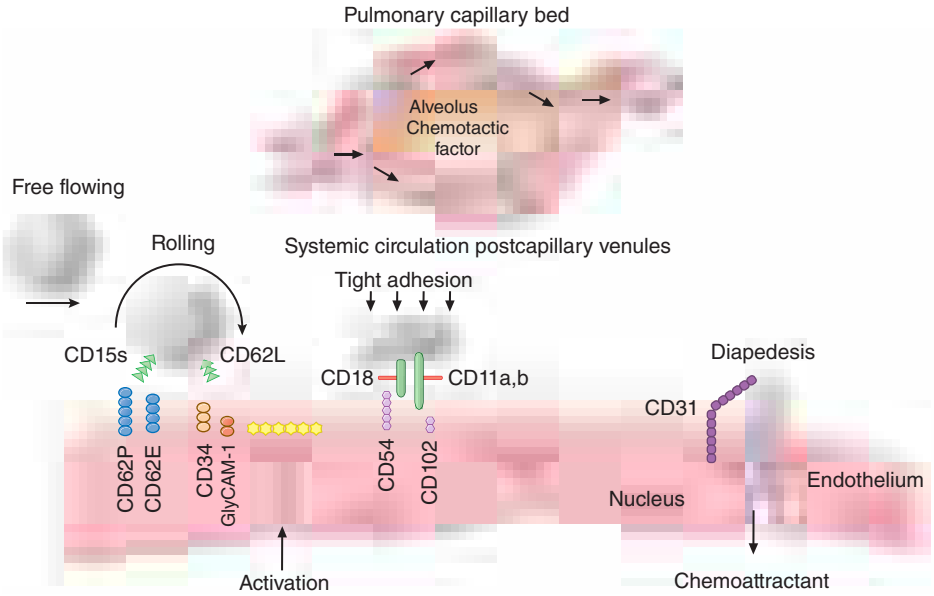

FIGURE 60-8 Neutrophil travel through the pulmonary capillaries is dependent on neutrophil deformability. Neutrophil rigidity (e.g., caused by C5a) enhances pulmonary trapping and response to pulmonary pathogens in a way that is not so dependent on cell-surface receptors. Intraalveolar chemotactic factors, such as those caused by certain bacteria (e.g., *Streptococcus pneumoniae*), lead to diapedesis of neutrophils from the pulmonary capillaries into the alveolar space. Neutrophil interaction with the endothelium of the systemic postcapillary venules is dependent on molecules of attachment. The neutrophil "rolls" along the endothelium using selectins: neutrophil CD15s (sialyl-Lewis^x) binds to CD62E (E-selectin) and CD62P (P-selectin) on endothelial cells; CD62L (L-selectin) on neutrophils binds to CD34 and other molecules (e.g., GlyCAM-1) expressed on endothelium. Chemokines or other activation factors stimulate integrin-mediated "tight adhesion": CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1, CR3) bind to CD54 (ICAM-1) and CD102 (ICAM-2) on the endothelium. Diapedesis occurs between endothelial cells: CD31 (PECAM-1) expressed by the emigrating neutrophil interacts with CD31 expressed at the endothelial cell-cell junction. CD, cluster determinant; GlyCAM, glycosylation-dependent cell adhesion molecule; ICAM, intercellular adhesion molecule; PECAM, platelet/endothelial cell adhesion molecule.

bradykinin, serotonin, nitric oxide, vascular endothelial growth factor (VEGF), and prostaglandins E and I. Cytokines regulate some of these processes (e.g., TNF-α induction of VEGF, interferon [IFN] γ inhibition of prostaglandin E).

In the healthy adult, most neutrophils leave the body by migration through the mucous membrane of the gastrointestinal tract. Normally, neutrophils spend a short time in the circulation (half-life, 6–7 h). Senescent neutrophils are cleared from the circulation by macrophages in the lung and spleen. Once in the tissues, neutrophils release enzymes, such as collagenase and elastase, which may help establish abscess cavities. Neutrophils ingest pathogenic materials that have been opsonized by IgG and C3b. Fibronectin and the tetrapeptide tuftsin also facilitate phagocytosis.

With phagocytosis comes a burst of oxygen consumption and activation of the hexose-monophosphate shunt. A membrane-associated NADPH oxidase, consisting of membrane and cytosolic components, is assembled and catalyzes the univalent reduction of oxygen to superoxide anion, which is then converted by superoxide dismutase to hydrogen peroxide and other toxic oxygen products (e.g., hydroxyl radical). Hydrogen peroxide + chloride + neutrophil myeloperoxidase generate hypochlorous acid (bleach), hypochlorite, and chlorine. These products oxidize and halogenate microorganisms and tumor cells and, when uncontrolled, can damage host tissue. Strongly cationic proteins, defensins, elastase, cathepsins, and probably nitric oxide also participate in microbial killing. Lactoferrin chelates iron, an important growth factor for microorganisms, especially fungi. Other enzymes, such as lysozyme and acid proteases, help digest microbial debris. After 1–4 days in tissues, neutrophils die. The apoptosis of neutrophils is also cytokine-regulated; granulocyte colony-stimulating factor (G-CSF) and IFN-γ prolong their life span. Under certain conditions, such as in delayed-type hypersensitivity, monocyte accumulation occurs within 6–12 h of initiation of inflammation. Neutrophils, monocytes, microorganisms in various states of digestion, and altered local tissue cells make up the inflammatory exudate, pus. Myeloperoxidase confers the characteristic green color to pus and may participate in turning off the inflammatory process by inactivating chemoattractants and immobilizing phagocytic cells.

Neutrophils respond to certain cytokines (IFN-γ, granulocyte-macrophage colony-stimulating factor [GM-CSF], IL-8) and produce cytokines and chemotactic signals (TNF-α, IL-8, macrophage inflammatory protein [MIP] 1) that modulate the inflammatory response. In the presence of fibrinogen, f-met-leu-phe or leukotriene B_4 induce IL-8 production by neutrophils, providing autocrine amplification of inflammation. *Chemokines* (*chemo*attractant cyto*kines*) are small proteins produced by many different cell types, including endothelial cells, fibroblasts, epithelial cells, neutrophils, and monocytes, that regulate neutrophil, monocyte, eosinophil, and lymphocyte recruitment and activation. Chemokines transduce their signals through heterotrimeric G protein–linked receptors that have seven cell membrane–spanning domains, the same type of cell-surface receptor that mediates the response to the classic chemoattractants f-met-leu-phe and C5a. Four major groups of chemokines are recognized based on the cysteine structure near the N terminus: C, CC, CXC, and CXXXC. The CXC cytokines such as IL-8 mainly attract neutrophils; CC chemokines such as MIP-1 attract lymphocytes, monocytes, eosinophils, and basophils; the C chemokine lymphotactin is T-cell tropic; the CXXXC chemokine fractalkine attracts neutrophils, monocytes, and T cells. These molecules and their receptors not only regulate the trafficking and activation of inflammatory cells, but specific chemokine receptors also serve as co-receptors for HIV infection (Chap. 197) and have a role in other viral infections such as West Nile infection and atherogenesis.

NEUTROPHIL ABNORMALITIES

Defects in the neutrophil life cycle can lead to dysfunction and compromised host defenses. Inflammation is often depressed, and the clinical result is often recurrent, severe bacterial and fungal infections. Aphthous ulcers of mucous membranes (gray ulcers without pus) and gingivitis and periodontal disease suggest a phagocytic cell disorder. Patients with congenital phagocyte defects can have infections within the first few days of life. Skin, ear, upper and lower respiratory tract, and bone infections are common. Sepsis and meningitis are rare. In some disorders, the frequency of infection is variable, and patients can go for months or even years without major infection. Aggressive management of these congenital diseases, including hematopoietic stem cell transplantation and gene therapy, has extended the life span of patients well into adulthood.

Neutropenia The consequences of absent neutrophils are dramatic. Susceptibility to infectious diseases increases sharply when neutrophil counts fall to <1000 cells/μL. When the absolute neutrophil count (ANC; band forms and mature neutrophils combined) falls to <500 cells/μL, control of endogenous microbial flora (e.g., mouth, gut) is impaired; when the ANC is <200/μL, the local inflammatory process is absent. Neutropenia can be due to depressed production, increased peripheral destruction, or excessive peripheral pooling. A falling neutrophil count or a significant decrease in the number of neutrophils below steady-state levels, together with a failure to increase neutrophil counts in the setting of infection or other challenge, requires investigation. Acute neutropenia, such as that caused by cancer chemotherapy,

TABLE 60-1 Causes of Neutropenia

Decreased Production
Drug-induced—alkylating agents (nitrogen mustard, busulfan, chlorambucil, cyclophosphamide); antimetabolites (methotrexate, 6-mercaptopurine, 5-flucytosine); noncytotoxic agents (antibiotics [chloramphenicol, penicillins, sulfonamides], phenothiazines, tranquilizers [meprobamate], anticonvulsants [carbamazepine], antipsychotics [clozapine], certain diuretics, anti-inflammatory agents, antithyroid drugs, many others)
Hematologic diseases—idiopathic, cyclic neutropenia, Chédiak-Higashi syndrome, aplastic anemia, infantile genetic disorders (see text)
Tumor invasion, myelofibrosis
Nutritional deficiency—vitamin B_{12}, folate (especially alcoholics)
Infection—tuberculosis, typhoid fever, brucellosis, tularemia, measles, infectious mononucleosis, malaria, viral hepatitis, leishmaniasis, AIDS
Peripheral Destruction
Antineutrophil antibodies and/or splenic or lung trapping
Autoimmune disorders—Felty's syndrome, rheumatoid arthritis, lupus erythematosus
Drugs as haptens—aminopyrine, α-methyldopa, phenylbutazone, mercurial diuretics, some phenothiazines
Granulomatosis with polyangiitis (Wegener's)
Peripheral Pooling (Transient Neutropenia)
Overwhelming bacterial infection (acute endotoxemia)
Hemodialysis
Cardiopulmonary bypass

is more likely to be associated with increased risk of infection than neutropenia of long duration (months to years) that reverses in response to infection or carefully controlled administration of endotoxin (see "Laboratory Diagnosis and Management," below).

Some causes of inherited and acquired neutropenia are listed in Table 60-1. The most common neutropenias are iatrogenic, resulting from the use of cytotoxic or immunosuppressive therapies for malignancy or control of autoimmune disorders. These drugs cause neutropenia because they result in decreased production of rapidly growing progenitor (stem) cells of the marrow. Certain antibiotics such as chloramphenicol, trimethoprim-sulfamethoxazole, flucytosine, vidarabine, and the antiretroviral drug zidovudine may cause neutropenia by inhibiting proliferation of myeloid precursors. Azathioprine and 6-mercaptopurine are metabolized by the enzyme thiopurine methyltransferase (TMPT), hypofunctional polymorphisms that are found in 11% of whites and can lead to accumulation of 6-thioguanine and profound marrow toxicity. The marrow suppression is generally dose-related and dependent on continued administration of the drug. Cessation of the offending agent and recombinant human G-CSF usually reverse these forms of neutropenia.

Another important mechanism for iatrogenic neutropenia is the effect of drugs that serve as immune haptens and sensitize neutrophils or neutrophil precursors to immune-mediated peripheral destruction. This form of drug-induced neutropenia can be seen within 7 days of exposure to the drug; with previous drug exposure, resulting in preexisting antibodies, neutropenia may occur a few hours after administration of the drug. Although any drug can cause this form of neutropenia, the most frequent causes are commonly used antibiotics, such as sulfa-containing compounds, penicillins, and cephalosporins. Fever and eosinophilia may also be associated with drug reactions, but often these signs are not present. Drug-induced neutropenia can be severe, but discontinuation of the sensitizing drug is sufficient for recovery, which is usually seen within 5–7 days and is complete by 10 days. Readministration of the sensitizing drug should be avoided, because abrupt neutropenia will often result. For this reason, diagnostic challenge should be avoided.

Autoimmune neutropenias caused by circulating antineutrophil antibodies are another form of acquired neutropenia that results in increased destruction of neutrophils. Acquired neutropenia may also be seen with viral infections, including acute infection with HIV. Acquired neutropenia may be cyclic in nature, occurring at intervals of several weeks. Acquired cyclic or stable neutropenia may be associated with an expansion of large granular lymphocytes (LGLs), which may be T cells, NK cells, or NK-like cells. Patients with large granular lymphocytosis may have moderate blood and bone marrow lymphocytosis, neutropenia, polyclonal hypergammaglobulinemia, splenomegaly, rheumatoid arthritis, and absence of lymphadenopathy. Such patients may have a chronic and relatively stable course. Recurrent bacterial infections are frequent. Benign and malignant forms of this syndrome occur. In some patients, a spontaneous regression has occurred even after 11 years, suggesting an immunoregulatory defect as the basis for at least one form of the disorder. Glucocorticoids, cyclosporine, and methotrexate are commonly used to manage these cytopenias.

Hereditary Neutropenias Hereditary neutropenias are rare and may manifest in early childhood as a profound constant neutropenia or agranulocytosis. Congenital forms of neutropenia include Kostmann's syndrome (neutrophil count <100/μL), which is often fatal and due to mutations in the antiapoptosis gene *HAX-1*; severe chronic neutropenia (neutrophil count of 300–1500/μL) due to mutations in neutrophil elastase (*ELANE*); hereditary cyclic neutropenia, or, more appropriately, cyclic hematopoiesis, also due to mutations in neutrophil elastase (*ELANE*); the cartilage-hair hypoplasia syndrome due to mutations in the mitochondrial RNA-processing endoribonuclease *RMRP*; Shwachman-Diamond syndrome associated with pancreatic insufficiency due to mutations in the Shwachman-Bodian-Diamond syndrome gene *SBDS*; the WHIM (*w*arts, *h*ypogammaglobulinemia, *i*nfections, *m*yelokathexis [retention of WBCs in the marrow]) syndrome, characterized by neutrophil hypersegmentation and bone marrow myeloid arrest due to mutations in the chemokine receptor *CXCR4*; and neutropenias associated with other immune defects, such as X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and CD40 ligand deficiency. Mutations in the G-CSF receptor can develop in severe congenital neutropenia and are linked to leukemia. Absence of both myeloid and lymphoid cells is seen in reticular dysgenesis, due to mutations in the nuclear genome-encoded mitochondrial enzyme adenylate kinase-2 (*AK2*).

Maternal factors can be associated with neutropenia in the newborn. Transplacental transfer of IgG directed against antigens on fetal neutrophils can result in peripheral destruction. Drugs (e.g., thiazides) ingested during pregnancy can cause neutropenia in the newborn by either depressed production or peripheral destruction.

In Felty's syndrome—the triad of rheumatoid arthritis, splenomegaly, and neutropenia (Chap. 351)—spleen-produced antibodies can shorten neutrophil life span, while large granular lymphocytes can attack marrow neutrophil precursors. Splenectomy may increase the neutrophil count in Felty's syndrome and lower serum neutrophil-binding IgG. Some Felty's syndrome patients also have neutropenia associated with an increased number of LGLs. Splenomegaly with peripheral trapping and destruction of neutrophils is also seen in lysosomal storage diseases and in portal hypertension.

Neutrophilia Neutrophilia results from increased neutrophil production, increased marrow release, or defective margination (Table 60-2). The most important acute cause of neutrophilia is infection. Neutrophilia from acute infection represents both increased production and increased marrow release. Increased production is also associated with chronic inflammation and certain myeloproliferative diseases. Increased marrow release and mobilization of the marginated leukocyte pool are induced by glucocorticoids. Release of epinephrine, as with vigorous exercise, excitement, or stress, will demarginate neutrophils in the spleen and lungs and double the neutrophil count in minutes. Cigarette smoking can elevate neutrophil counts above the normal range. Leukocytosis with cell counts of 10,000–25,000/μL occurs in response to infection and other forms of acute inflammation and results from both release of the marginated pool and mobilization of marrow reserves. Persistent neutrophilia with cell counts of ≥30,000–50,000/μL is called a *leukemoid reaction*, a term often used to distinguish this degree of neutrophilia from leukemia. In a leukemoid reaction, the circulating neutrophils are usually mature and not clonally derived.

TABLE 60-2 Causes of Neutrophilia
Increased Production
Idiopathic
Drug-induced—glucocorticoids, G-CSF
Infection—bacterial, fungal, sometimes viral
Inflammation—thermal injury, tissue necrosis, myocardial and pulmonary infarction, hypersensitivity states, collagen vascular diseases
Myeloproliferative diseases—myelocytic leukemia, myeloid metaplasia, polycythemia vera
Increased Marrow Release
Glucocorticoids
Acute infection (endotoxin)
Inflammation—thermal injury
Decreased or Defective Margination
Drugs—epinephrine, glucocorticoids, nonsteroidal anti-inflammatory agents
Stress, excitement, vigorous exercise
Leukocyte adhesion deficiency type 1 (CD18); leukocyte adhesion deficiency type 2 (selectin ligand, CD15s); leukocyte adhesion deficiency type 3 (FERMT3)
Miscellaneous
Metabolic disorders—ketoacidosis, acute renal failure, eclampsia, acute poisoning
Drugs—lithium
Other—metastatic carcinoma, acute hemorrhage or hemolysis

Abbreviation: G-CSF, granulocyte colony-stimulating factor.

Abnormal Neutrophil Function Inherited and acquired abnormalities of phagocyte function are listed in Table 60-3. The resulting diseases are best considered in terms of the functional defects of adherence, chemotaxis, and microbicidal activity. The distinguishing features of the important inherited disorders of phagocyte function are shown in Table 60-4.

DISORDERS OF ADHESION Three main types of leukocyte adhesion deficiency (LAD) have been described. All are autosomal recessive and result in the inability of neutrophils to exit the circulation to sites of infection, leading to leukocytosis and increased susceptibility to infection (Fig. 60-8). Patients with LAD 1 have mutations in *CD18*, the common component of the integrins LFA-1, Mac-1, and p150,95, leading to a defect in tight adhesion between neutrophils and the endothelium. The heterodimer formed by CD18/CD11b (Mac-1) is also the receptor for the complement-derived opsonin C3bi (CR3). The *CD18* gene is located on distal chromosome 21q. The severity of the defect determines the severity of clinical disease. Complete lack of expression of the leukocyte integrins results in a severe phenotype in which inflammatory stimuli do not increase the expression of leukocyte integrins on neutrophils or activated T and B cells. Neutrophils (and monocytes) from patients with LAD 1 adhere poorly to endothelial cells and protein-coated surfaces and exhibit defective spreading, aggregation, and chemotaxis. The inability of neutrophils to exit the vasculature to the tissue deprives the tissue macrophage of its expected neutrophil ingestion, leading to macrophage production of IL-23, which induces T- cell production of IL-17, a potent proinflammatory cytokine. These processes conspire to drive inflammation in LAD1. Patients with LAD 1 have recurrent bacterial infections involving the skin, oral and genital mucosa, and respiratory and intestinal tracts; persistent leukocytosis (resting neutrophil counts of 15,000–20,000/μL) because cells do not marginate; and, in severe cases, a history of delayed separation of the umbilical stump. Infections, especially of the skin, may become necrotic with progressively enlarging borders, slow healing, and development of dysplastic scars. The most common bacteria are *Staphylococcus aureus* and enteric gram-negative bacteria. LAD 2 is caused by an abnormality of fucosylation of SLe^x (CD15s), the ligand on neutrophils that interacts with selectins on endothelial cells and is responsible for neutrophil rolling along the endothelium. Infection susceptibility in LAD 2 appears to be less severe than in LAD 1. LAD 2 is also known as *congenital disorder of glycosylation IIc* (CDGIIc) due to mutation in a GDP-fucose transporter (*SLC35C1*). LAD 3 is characterized by infection susceptibility, leukocytosis, and petechial hemorrhage due to impaired integrin activation caused by mutations in the gene *FERMT3*.

DISORDERS OF NEUTROPHIL GRANULES The most common neutrophil defect is myeloperoxidase deficiency, a primary granule defect inherited as an autosomal recessive trait; the incidence is ~1 in 2000 persons. Isolated myeloperoxidase deficiency is not associated with clinically compromised defenses, presumably because other defense systems such as hydrogen peroxide generation are amplified. Microbicidal activity of neutrophils is delayed but not absent. Myeloperoxidase deficiency may make other acquired host defense defects more serious, and patients with myeloperoxidase deficiency and diabetes are more susceptible to *Candida* infections. An acquired form of myeloperoxidase deficiency occurs in myelomonocytic leukemia and acute myeloid leukemia.

Chédiak-Higashi syndrome (CHS) is a rare disease with autosomal recessive inheritance due to defects in the lysosomal transport protein LYST, encoded by the gene *CHS1* at 1q42. This protein is required for normal packaging and disbursement of granules. Neutrophils (and all cells containing lysosomes) from patients with CHS characteristically have large granules (Fig. 60-9), making it a systemic disease. Patients with CHS have nystagmus, partial oculocutaneous albinism, and an increased number of infections resulting from many bacterial agents. Some CHS patients develop an "accelerated phase" in childhood with a hemophagocytic syndrome and an aggressive lymphoma requiring bone marrow transplantation. CHS neutrophils and monocytes have impaired chemotaxis and abnormal rates of microbial killing due to slow rates of fusion of the lysosomal granules with phagosomes.

TABLE 60-3 Types of Granulocyte and Monocyte Disorders

	CAUSE OF INDICATED DYSFUNCTION		
FUNCTION	**DRUG-INDUCED**	**ACQUIRED**	**INHERITED**
Adherence-aggregation	Aspirin, colchicine, alcohol, glucocorticoids, ibuprofen, piroxicam	Neonatal state, hemodialysis	Leukocyte adhesion deficiency types 1, 2, and 3
Deformability		Leukemia, neonatal state, diabetes mellitus, immature neutrophils	
Chemokinesis-chemotaxis	Glucocorticoids (high dose), auranofin, colchicine (weak effect), phenylbutazone, naproxen, indomethacin, interleukin 2	Thermal injury, malignancy, malnutrition, periodontal disease, neonatal state, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, sepsis, influenza virus infection, herpes simplex virus infection, acrodermatitis enteropathica, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, hyper IgE–recurrent infection (Job's) syndrome (in some patients), Down's syndrome, α-mannosidase deficiency, leukocyte adhesion deficiencies, Wiskott-Aldrich syndrome
Microbicidal activity	Colchicine, cyclophosphamide, glucocorticoids (high dose), TNF-α-blocking antibodies	Leukemia, aplastic anemia, certain neutropenias, tuftsin deficiency, thermal injury, sepsis, neonatal state, diabetes mellitus, malnutrition, AIDS	Chédiak-Higashi syndrome, neutrophil-specific granule deficiency, chronic granulomatous disease, defects in IFNγ/IL-12 axis

Abbreviations: IFNγ, interferon γ; IL, interleukin; TNF-α, tumor necrosis factor alpha.

TABLE 60-4 Inherited Disorders of Phagocyte Function: Differential Features

CLINICAL MANIFESTATIONS	CELLULAR OR MOLECULAR DEFECTS	DIAGNOSIS
Chronic Granulomatous Diseases (70% X-Linked, 30% Autosomal Recessive)		
Severe infections of skin, ears, lungs, liver, and bone with catalase-positive microorganisms such as *Staphylococcus aureus, Burkholderia cepacia* complex, *Aspergillus* spp., *Chromobacterium violaceum*; often hard to culture organism; excessive inflammation with granulomas, frequent lymph node suppuration; granulomas can obstruct GI or GU tracts; gingivitis, aphthous ulcers, seborrheic dermatitis	No respiratory burst due to the lack of one of five NADPH oxidase subunits in neutrophils, monocytes, and eosinophils	DHR or NBT test; no superoxide and H_2O_2 production by neutrophils; immunoblot for NADPH oxidase components; genetic detection
Chédiak-Higashi Syndrome (Autosomal Recessive)		
Recurrent pyogenic infections, especially with *S. aureus*; many patients get lymphoma-like illness during adolescence; periodontal disease; partial oculocutaneous albinism, nystagmus, progressive peripheral neuropathy, mental retardation in some patients	Reduced chemotaxis and phagolysosome fusion, increased respiratory burst activity, defective egress from marrow, abnormal skin window; defect in *CHS1*	Giant primary granules in neutrophils and other granule-bearing cells (Wright's stain); genetic detection
Specific Granule Deficiency (Autosomal Recessive and Dominant)		
Recurrent infections of skin, ears, and sinopulmonary tract; delayed wound healing; decreased inflammation; bleeding diathesis	Abnormal chemotaxis, impaired respiratory burst and bacterial killing, failure to upregulate chemotactic and adhesion receptors with stimulation, defect in transcription of granule proteins; defect in *CEBPE*	Lack of secondary (specific) granules in neutrophils (Wright's stain), no neutrophil-specific granule contents (i.e., lactoferrin), no defensins, platelet α granule abnormality; genetic detection
Myeloperoxidase Deficiency (Autosomal Recessive)		
Clinically normal except in patients with underlying disease such as diabetes mellitus; then candidiasis or other fungal infections	No myeloperoxidase due to pre- and posttranslational defects in myeloperoxidase deficiency	No peroxidase in neutrophils; genetic detection
Leukocyte Adhesion Deficiency		
Type 1: Delayed separation of umbilical cord, sustained neutrophilia, recurrent infections of skin and mucosa, gingivitis, periodontal disease	Impaired phagocyte adherence, aggregation, spreading, chemotaxis, phagocytosis of C3bi-coated particles; defective production of CD18 subunit common to leukocyte integrins	Reduced phagocyte surface expression of the CD18-containing integrins with monoclonal antibodies against LFA-1 (CD18/CD11a), Mac-1 or CR3 (CD18/CD11b), p150,95 (CD18/CD11c); genetic detection
Type 2: Mental retardation, short stature, Bombay (hh) blood phenotype, recurrent infections, neutrophilia	Impaired phagocyte rolling along endothelium; due to defects in fucose transporter	Reduced phagocyte surface expression of Sialyl-Lewis^x, with monoclonal antibodies against CD15s; genetic detection
Type 3: Petechial hemorrhage, recurrent infections	Impaired signaling for integrin activation resulting in impaired adhesion due to mutation in *FERMT3*	Reduced signaling for adhesion through integrins; genetic detection
Phagocyte Activation Defects (X-Linked and Autosomal Recessive)		
NEMO deficiency: mild hypohidrotic ectodermal dysplasia; broad-based immune defect: pyogenic and encapsulated bacteria, viruses, *Pneumocystis*, mycobacteria; X-linked	Impaired phagocyte activation by IL-1, IL-18, TLR, CD40L, TNF-α leading to problems with inflammation and antibody production	Poor in vitro response to endotoxin; impaired NF-κB activation; genetic detection
IRAK4 and MyD88 deficiency: susceptibility to pyogenic bacteria such as staphylococci, streptococci, clostridia; resistant to *Candida*; autosomal recessive	Impaired phagocyte activation by endotoxin through TLR and other pathways; TNF-α signaling preserved	Poor in vitro response to endotoxin; lack of NF-κB activation by endotoxin; genetic detection
Hyper IgE–Recurrent Infection Syndrome (Autosomal Dominant) (Job's Syndrome)		
Eczematoid or pruritic dermatitis, "cold" skin abscesses, recurrent pneumonias with *S. aureus* with bronchopleural fistulae and cyst formation, mild eosinophilia, mucocutaneous candidiasis, characteristic facies, restrictive lung disease, scoliosis, delayed primary dental deciduation	Reduced chemotaxis in some patients, reduced memory T and B cells; mutation in *STAT3*	Somatic and immune features involving lungs, skeleton, and immune system; serum IgE >2000 IU/mL; genetic testing
DOCK8 deficiency (autosomal recessive), severe eczema, atopic dermatitis, cutaneous abscesses, HSV, HPV, and molluscum infections, severe allergies, cancer	Impaired T-cell proliferation to mitogens; mutation in *DOCK8*	Severe allergies, viral infections, high IgE, eosinophilia, low IgM, progressive lymphopenia, genetic detection
Mycobacteria Susceptibility (Autosomal Dominant and Recessive Forms)		
Severe extrapulmonary or disseminated infections with bacille Calmette-Guérin (BCG), nontuberculous mycobacteria, salmonella, histoplasmosis, coccidioidomycosis, poor granuloma formation	Inability to kill intracellular organisms due to low IFN-γ production or response; mutations in IFN-γ receptors, IL-12 receptors, IL-12 p40, *STAT1*, *NEMO*, *ISG15*, *GATA2*	Abnormally low or very high levels of IFN-γ receptor 1; functional assays of cytokine production and response; genetic detection
GATA2 Deficiency (Autosomal Dominant)		
Persistent or disseminated warts, disseminated mycobacterial disease, low monocytes, NK cells, B cells; hypoplastic myelodysplasia, leukemia, cytogenetic abnormalities, pulmonary alveolar proteinosis	Impaired macrophage activity, cytopenias; mutations in *GATA2*	Profound circulating monocytopenia, NK and B-cell cytopenias; genetic detection

Abbreviations: C/EBPε, CCAAT/enhancer binding protein-ε; DHR, dihydrorhodamine (oxidation test); DOCK8, dedicator of cytokinesis 8; GI, gastrointestinal; GU, genitourinary; HPV, human papilloma virus; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; IRAK4, IL-1 receptor–associated kinase 4; LFA-1, leukocyte function–associated antigen 1; MyD88, myeloid differentiation primary response gene 88; NADPH, nicotinamide–adenine dinueleotide phosphate; NBT, nitroblue tetrazolium (dye test); NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; NK, natural killer; STAT1–3, signal transducer and activator of transcription 1–3; TLR, Toll-like receptor; TNF, tumor necrosis factor.

FIGURE 60-9 Chédiak-Higashi syndrome. The granulocytes contain huge cytoplasmic granules formed from aggregation and fusion of azurophilic and specific granules. Large abnormal granules are found in other granule-containing cells throughout the body.

NK cell function is also impaired. CHS patients may develop a severe disabling peripheral neuropathy in adulthood.

Specific granule deficiency is a rare autosomal recessive disease in which the production of secondary granules and their contents, as well as the primary granule component defensins, is defective. The defect in killing leads to severe bacterial infections. One type of specific granule deficiency is due to a mutation in the CCAAT/enhancer binding protein-ε, a regulator of expression of granule components. A dominant mutation in *C/EBP-ε* has also been described.

CHRONIC GRANULOMATOUS DISEASE Chronic granulomatous disease (CGD) is a group of disorders of granulocyte and monocyte oxidative metabolism. Although CGD is rare, with an incidence of ~1 in 200,000 individuals, it is an important model of defective neutrophil oxidative metabolism. In about two-thirds of patients, CGD is inherited as an X-linked recessive trait; the remainder patients inherit the disease in an autosomal recessive pattern. Mutations in the genes for the five proteins that assemble at the plasma membrane account for all patients with CGD. Two proteins (a 91-kDa protein, abnormal in X-linked CGD, and a 22-kDa protein, absent in one form of autosomal recessive CGD) form the heterodimer cytochrome b-558 in the plasma membrane. Three other proteins (40, 47, and 67 kDa, abnormal in the other autosomal recessive forms of CGD) are cytoplasmic in origin and interact with the cytochrome after cell activation to form the NADPH oxidase, required for hydrogen peroxide production. Leukocytes from patients with CGD have severely diminished hydrogen peroxide production. The genes involved in each of the defects have been cloned and sequenced and the chromosome locations identified. Patients with CGD characteristically have increased numbers of infections due to catalase-positive microorganisms (organisms that destroy their own hydrogen peroxide) such as *S. aureus*, *Burkholderia cepacia* complex, and *Aspergillus* species. When patients with CGD become infected, they often have extensive inflammatory reactions, and lymph node suppuration is common despite the administration of appropriate antibiotics. Aphthous ulcers and chronic inflammation of the nares are often present. Granulomas are frequent and can obstruct the gastrointestinal or genitourinary tracts. The excessive inflammation is due to failure to downregulate inflammation, reflecting a failure to inhibit the synthesis of, degradation of, or response to ILs or chemoattractants, leading to persistent myeloid reaction. Impaired killing of intracellular microorganisms by macrophages may lead to persistent cell-mediated immune activation and granuloma formation. Autoimmune complications such as immune thrombocytopenic purpura and juvenile rheumatoid arthritis are also increased in CGD. In addition, for unexplained reasons, discoid lupus is more common in X-linked carriers. Late complications, including nodular regenerative hyperplasia and portal hypertension, are increasingly recognized in older patients with CGD.

DISORDERS OF PHAGOCYTE ACTIVATION Phagocytes depend on cell-surface stimulation to induce signals that evoke multiple levels of the inflammatory response, including cytokine synthesis, chemotaxis, and antigen presentation. Mutations affecting the major pathway that signals through NF-κB have been noted in patients with a variety of infection susceptibility syndromes. If the defects are at a very late stage of signal transduction, in the protein critical for NF-κB activation known as the NF-κB essential modulator (NEMO), then affected males develop ectodermal dysplasia and severe immune deficiency with susceptibility to bacteria, fungi, mycobacteria, and viruses. If the defects in NF-κB activation are closer to the cell-surface receptors, in the proteins transducing Toll-like receptor signals, IL-1 receptor–associated kinase 4 (IRAK4), and myeloid differentiation primary response gene 88 (MyD88), then children have a marked susceptibility to pyogenic infections early in life but develop resistance to infection later.

MONONUCLEAR PHAGOCYTES

The mononuclear phagocyte system is composed of monoblasts, promonocytes, and monocytes, in addition to the structurally diverse tissue macrophages that make up what was previously referred to as the reticuloendothelial system. Macrophages are long-lived phagocytic cells capable of many of the functions of neutrophils. They are also secretory cells that participate in many immunologic and inflammatory processes distinct from neutrophils. Monocytes leave the circulation by diapedesis more slowly than neutrophils and have a half-life in the blood of 12–24 h.

After blood monocytes arrive in the tissues, they differentiate into macrophages ("big eaters") with specialized functions suited for specific anatomic locations. Macrophages are particularly abundant in capillary walls of the lung, spleen, liver, and bone marrow, where they function to remove microorganisms and other noxious elements from the blood. Alveolar macrophages, liver Kupffer cells, splenic macrophages, peritoneal macrophages, bone marrow macrophages, lymphatic macrophages, brain microglial cells, and dendritic macrophages all have specialized functions. Macrophage-secreted products include lysozyme, neutral proteases, acid hydrolases, arginase, complement components, enzyme inhibitors (plasmin, α_2-macroglobulin), binding proteins (transferrin, fibronectin, transcobalamin II), nucleosides, and cytokines (TNF-α; IL-1, 8, 12, 18). IL-1 **(Chaps. 15 and 342)** has many functions, including initiating fever in the hypothalamus, mobilizing leukocytes from the bone marrow, and activating lymphocytes and neutrophils. TNF-α is a pyrogen that duplicates many of the actions of IL-1 and plays an important role in the pathogenesis of gram-negative shock **(Chap. 297)**. TNF-α stimulates production of hydrogen peroxide and related toxic oxygen species by macrophages and neutrophils. In addition, TNF-α induces catabolic changes that contribute to the profound wasting (cachexia) associated with many chronic diseases.

Other macrophage-secreted products include reactive oxygen and nitrogen metabolites, bioactive lipids (arachidonic acid metabolites and platelet-activating factors), chemokines, CSFs, and factors stimulating fibroblast and vessel proliferation. Macrophages help regulate the replication of lymphocytes and participate in the killing of tumors, viruses, and certain bacteria (*Mycobacterium tuberculosis* and *Listeria monocytogenes*). Macrophages are key effector cells in the elimination of intracellular microorganisms. Their ability to fuse to form giant cells that coalesce into granulomas in response to some inflammatory stimuli is important in the elimination of intracellular microbes and is under the control of IFN-γ. Nitric oxide induced by IFN-γ is an important effector against intracellular parasites, including tuberculosis and *Leishmania*.

Macrophages play an important role in the immune response **(Chap. 342)**. They process and present antigen to lymphocytes and secrete cytokines that modulate and direct lymphocyte development

and function. Macrophages participate in autoimmune phenomena by removing immune complexes and other substances from the circulation. Polymorphisms in macrophage receptors for immunoglobulin (FcγRII) determine susceptibility to some infections and autoimmune diseases. In wound healing, they dispose of senescent cells, and they contribute to atheroma development. Macrophage elastase mediates development of emphysema from cigarette smoking.

DISORDERS OF THE MONONUCLEAR PHAGOCYTE SYSTEM

Many disorders of neutrophils extend to mononuclear phagocytes. Monocytosis is associated with tuberculosis, brucellosis, subacute bacterial endocarditis, Rocky Mountain spotted fever, malaria, and visceral leishmaniasis (kala azar). Monocytosis also occurs with malignancies, leukemias, myeloproliferative syndromes, hemolytic anemias, chronic idiopathic neutropenias, and granulomatous diseases such as sarcoidosis, regional enteritis, and some collagen vascular diseases. Patients with LAD, hyperimmunoglobulin E–recurrent infection (Job's) syndrome, CHS, and CGD all have defects in the mononuclear phagocyte system.

Monocyte cytokine production or response is impaired in some patients with disseminated nontuberculous mycobacterial infection who are not infected with HIV. Genetic defects in the pathways regulated by IFN-γ and IL-12 lead to impaired killing of intracellular bacteria, mycobacteria, salmonellae, and certain viruses **(Fig. 60-10)**.

Certain viral infections impair mononuclear phagocyte function. For example, influenza virus infection causes abnormal monocyte chemotaxis. Mononuclear phagocytes can be infected by HIV using CCR5, the chemokine receptor that acts as a co-receptor with CD4 for HIV. T lymphocytes produce IFN-γ, which induces FcR expression and phagocytosis and stimulates hydrogen peroxide production by mononuclear phagocytes and neutrophils. In certain diseases, such as AIDS, IFN-γ production may be deficient, whereas in other diseases, such as T-cell lymphomas, excessive release of IFN-γ may be associated with erythrophagocytosis by splenic macrophages.

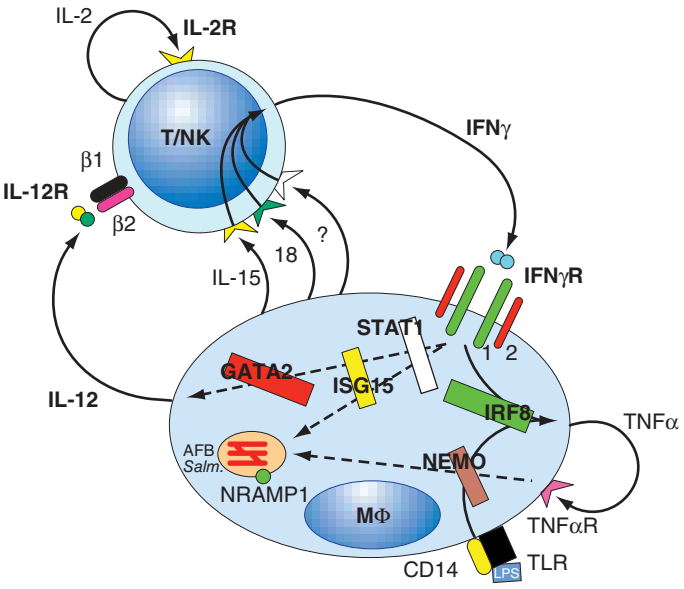

FIGURE 60-10 Lymphocyte-macrophage interactions underlying resistance to mycobacteria and other intracellular pathogens such as *Salmonella*, *Histoplasma*, and *Coccidioides*. Mycobacteria (and others) infect macrophages, leading to the production of IL-12, which activates T or NK cells through its receptor, leading to production of IL-2 and IFN-γ. IFN-γ acts through its receptor on macrophages to upregulate TNF-γ and IL-12 and kill intracellular pathogens. Other critical interacting molecules include signal transducer and activator of transcription 1 (STAT1), interferon regulatory factor 8 (IRF8), GATA2, and ISG15. Mutant forms of the cytokines and receptors shown in *bold type* have been found in severe cases of nontuberculous mycobacterial infection, salmonellosis and other intracellular pathogens. AFB, acid-fast bacilli; IFN, interferon; IL, interleukin; NEMO, nuclear factor-κB essential modulator; NK, natural killer; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Autoinflammatory diseases are characterized by abnormal cytokine regulation, leading to excess inflammation in the absence of infection. These diseases can mimic infectious or immunodeficient syndromes. Gain-of-function mutations in the TNF-α receptor cause TNF-α receptor–associated periodic syndrome (TRAPS), which is characterized by recurrent fever in the absence of infection, due to persistent stimulation of the TNF-α receptor **(Chap. 362)**. Diseases with abnormal IL-1 regulation leading to fever include familial Mediterranean fever due to mutations in *PYRIN*. Mutations in *cold-induced autoinflammatory syndrome 1* (*CIAS1*) lead to neonatal-onset multisystem autoinflammatory disease, familial cold urticaria, and Muckle-Wells syndrome. The syndrome of *p*yoderma gangrenosum, *a*cne, and sterile *p*yogenic *a*rthritis (PAPA syndrome) is caused by mutations in *PSTPIP1*. In contrast to these syndromes of overexpression of proinflammatory cytokines, blockade of TNF-α by the antagonists infliximab, adalimumab, certolizumab, golimumab, or etanercept has been associated with severe infections due to tuberculosis, nontuberculous mycobacteria, and fungi **(Chap. 362)**.

Monocytopenia occurs with acute infections, with stress, and after treatment with glucocorticoids. Drugs that suppress neutrophil production in the bone marrow can cause monocytopenia. Persistent severe circulating monocytopenia is seen in GATA2 deficiency, even though macrophages are found at the sites of inflammation. Monocytopenia also occurs in aplastic anemia, hairy cell leukemia, acute myeloid leukemia, and as a direct result of myelotoxic drugs.

EOSINOPHILS

Eosinophils and neutrophils share similar morphology, many lysosomal constituents, phagocytic capacity, and oxidative metabolism. Eosinophils express a specific chemoattractant receptor and respond to a specific chemokine, eotaxin, but little is known about their required role. Eosinophils are much longer lived than neutrophils, and unlike neutrophils, tissue eosinophils can recirculate. During most infections, eosinophils appear unimportant. However, in invasive helminthic infections, such as hookworm, schistosomiasis, strongyloidiasis, toxocariasis, trichinosis, filariasis, echinococcosis, and cysticercosis, the eosinophil plays a central role in host defense. Eosinophils are associated with bronchial asthma, cutaneous allergic reactions, and other hypersensitivity states.

The distinctive feature of the red-staining (Wright's stain) eosinophil granule is its crystalline core consisting of an arginine-rich protein (major basic protein) with histaminase activity, important in host defense against parasites. Eosinophil granules also contain a unique eosinophil peroxidase that catalyzes the oxidation of many substances by hydrogen peroxide and may facilitate killing of microorganisms.

Eosinophil peroxidase, in the presence of hydrogen peroxide and halide, initiates mast cell secretion in vitro and thereby promotes inflammation. Eosinophils contain cationic proteins, some of which bind to heparin and reduce its anticoagulant activity. Eosinophil-derived neurotoxin and eosinophil cationic protein are ribonucleases that can kill respiratory syncytial virus. Eosinophil cytoplasm contains Charcot-Leyden crystal protein, a hexagonal bipyramidal crystal first observed in a patient with leukemia and then in sputum of patients with asthma; this protein is lysophospholipase and may function to detoxify certain lysophospholipids.

Several factors enhance the eosinophil's function in host defense. T cell–derived factors enhance the ability of eosinophils to kill parasites. Mast cell–derived eosinophil chemotactic factor of anaphylaxis (ECFa) increases the number of eosinophil complement receptors and enhances eosinophil killing of parasites. Eosinophil CSFs (e.g., IL-5) produced by macrophages increase eosinophil production in the bone marrow and activate eosinophils to kill parasites.

EOSINOPHILIA

Eosinophilia is the presence of >500 eosinophils per μL of blood and is common in many settings besides parasite infection. Significant tissue eosinophilia can occur without an elevated blood count. A common cause of eosinophilia is allergic reaction to drugs (iodides, aspirin, sulfonamides, nitrofurantoin, penicillins, and cephalosporins). Allergies such as hay fever, asthma, eczema, serum sickness,

allergic vasculitis, and pemphigus are associated with eosinophilia. Eosinophilia also occurs in collagen vascular diseases (e.g., rheumatoid arthritis, eosinophilic fasciitis, allergic angiitis, and periarteritis nodosa) and malignancies (e.g., Hodgkin's disease; mycosis fungoides; chronic myeloid leukemia; and cancer of the lung, stomach, pancreas, ovary, or uterus), as well as in STAT3 deficient Job's syndrome, DOCK8 deficiency (see below), and CGD. Eosinophilia is commonly present in helminthic infections. IL-5 is the dominant eosinophil growth factor. Therapeutic administration of the cytokines IL-2 or GM-CSF frequently leads to transient eosinophilia. The most dramatic hypereosinophilic syndromes are Loeffler's syndrome, tropical pulmonary eosinophilia, Loeffler's endocarditis, eosinophilic leukemia, and idiopathic hypereosinophilic syndrome (50,000–100,000/μL). IL-5 is the dominant eosinophil growth factor and can be specifically inhibited with the monoclonal antibody mepolizumab.

The idiopathic hypereosinophilic syndrome represents a heterogeneous group of disorders with the common feature of prolonged eosinophilia of unknown cause and organ system dysfunction, including the heart, central nervous system, kidneys, lungs, gastrointestinal tract, and skin. The bone marrow is involved in all affected individuals, but the most severe complications involve the heart and central nervous system. Clinical manifestations and organ dysfunction are highly variable. Eosinophils are found in the involved tissues and likely cause tissue damage by local deposition of toxic eosinophil proteins such as eosinophil cationic protein and major basic protein. In the heart, the pathologic changes lead to thrombosis, endocardial fibrosis, and restrictive endomyocardiopathy. The damage to tissues in other organ systems is similar. Some cases are due to mutations involving the platelet-derived growth factor receptor, and these are extremely sensitive to the tyrosine kinase inhibitor imatinib. Glucocorticoids, hydroxyurea, and IFN-α each have been used successfully, as have therapeutic antibodies against IL-5. Cardiovascular complications are managed aggressively.

The *eosinophilia-myalgia syndrome* is a multisystem disease, with prominent cutaneous, hematologic, and visceral manifestations, that frequently evolves into a chronic course and can occasionally be fatal. The syndrome is characterized by eosinophilia (eosinophil count >1000/μL) and generalized disabling myalgias without other recognized causes. Eosinophilic fasciitis, pneumonitis, and myocarditis; neuropathy culminating in respiratory failure; and encephalopathy may occur. The disease is caused by ingesting contaminants in L-tryptophan–containing products. Eosinophils, lymphocytes, macrophages, and fibroblasts accumulate in the affected tissues, but their role in pathogenesis is unclear. Activation of eosinophils and fibroblasts and the deposition of eosinophil-derived toxic proteins in affected tissues may contribute. IL-5 and transforming growth factor β have been implicated as potential mediators. Treatment is withdrawal of products containing L-tryptophan and the administration of glucocorticoids. Most patients recover fully, remain stable, or show slow recovery, but the disease can be fatal in up to 5% of patients.

Eosinophilic neoplasms are discussed in Chap. 106.

EOSINOPENIA

Eosinopenia occurs with stress, such as acute bacterial infection, and after treatment with glucocorticoids. The mechanism of eosinopenia of acute bacterial infection is unknown but is independent of endogenous glucocorticoids, because it occurs in animals after total adrenalectomy. There is no known adverse effect of eosinopenia.

HYPERIMMUNOGLOBULIN E–RECURRENT INFECTION SYNDROME

The hyperimmunoglobulin E–recurrent infection syndrome, or Job's syndrome, is a rare multisystem disease in which the immune and somatic systems are affected, including neutrophils, monocytes, T cells, B cells, and osteoclasts. Autosomal *dominant* inhibitory mutations in signal transducer and activator of transcription 3 (STAT3) lead to inhibition of normal STAT signaling with broad and profound effects. Patients have characteristic facies with broad nose, kyphoscoliosis, and eczema. The primary teeth erupt normally but do not deciduate, often requiring extraction. Patients develop recurrent sinopulmonary and cutaneous infections that tend to be much less inflamed than appropriate for the degree of infection and have been referred to as "cold abscesses." Characteristically, pneumonias cavitate, leading to pneumatoceles. Coronary artery aneurysms are common, as are cerebral demyelinated plaques that accumulate with age. Importantly, IL-17–producing T cells, which are thought responsible for protection against extracellular and mucosal infections, are profoundly reduced in Job's syndrome. Despite very high IgE levels, these patients have only mildly elevated levels of allergy. An important syndrome with clinical overlap with the dominant negative STAT3 deficiency is due to autosomal recessive defects in dedicator of cytokinesis 8 (DOCK8). In DOCK8 deficiency, IgE elevation is joined to severe allergy, viral susceptibility, and increased rates of cancer. Autosomal dominant *gain-of-function* mutations in STAT3 lead to a disease characterized by onset in childhood of lymphadenopathy, autoimmune cytopenias, multiorgan autoimmunity, infections, and interstitial lung disease.

LABORATORY DIAGNOSIS AND MANAGEMENT

Initial studies of WBC and differential and often a bone marrow examination may be followed by assessment of bone marrow reserves (steroid challenge test), marginated circulating pool of cells (epinephrine challenge test), and marginating ability (endotoxin challenge test) (Fig. 60-7). In vivo assessment of inflammation is possible with a Rebuck skin window test or an in vivo skin blister assay, which measures the ability of leukocytes and inflammatory mediators to accumulate locally in the skin. In vitro tests of phagocyte aggregation, adherence, chemotaxis, phagocytosis, degranulation, and microbicidal activity (for *S. aureus*) may help pinpoint cellular or humoral lesions. Deficiencies of oxidative metabolism are detected with either the nitroblue tetrazolium (NBT) dye test or the dihydrorhodamine (DHR) oxidation test. These tests are based on the ability of products of oxidative metabolism to alter the oxidation states of reporter molecules so that they can be detected microscopically (NBT) or by flow cytometry (DHR). Qualitative studies of superoxide and hydrogen peroxide production may further define neutrophil oxidative function.

Patients with leukopenias or leukocyte dysfunction often have delayed inflammatory responses. Therefore, clinical manifestations may be minimal despite overwhelming infection, and unusual infections must always be suspected. Early signs of infection demand prompt, aggressive culturing for microorganisms, use of antibiotics, and drainage of abscesses. Prolonged courses of antibiotics are often required. In patients with CGD, prophylactic antibiotics (trimethoprim-sulfamethoxazole) and antifungals (itraconazole) markedly diminish the frequency of life-threatening infections. Glucocorticoids may relieve gastrointestinal or genitourinary tract obstruction by granulomas in patients with CGD. Although TNF-α-blocking agents may markedly relieve inflammatory bowel symptoms, extreme caution must be exercised in their use in CGD inflammatory bowel disease, because it profoundly increases these patients' already heightened susceptibility to infection. Recombinant human IFN-γ, which nonspecifically stimulates phagocytic cell function, reduces the frequency of infections in patients with CGD by 70% and reduces the severity of infection. This effect of IFN-γ in CGD is additive to the effect of prophylactic antibiotics. The recommended dose is 50 $\mu g/m^2$ subcutaneously three times weekly. IFN-γ has also been used successfully in the treatment of leprosy, nontuberculous mycobacteria, and visceral leishmaniasis.

Rigorous oral hygiene reduces but does not eliminate the discomfort of gingivitis, periodontal disease, and aphthous ulcers; chlorhexidine mouthwash and tooth brushing with a hydrogen peroxide–sodium bicarbonate paste help many patients. Oral antifungal agents (fluconazole, itraconazole, voriconazole, posaconazole) have reduced mucocutaneous candidiasis in patients with Job's syndrome. Androgens, glucocorticoids, lithium, and immunosuppressive therapy have been used to restore myelopoiesis in patients with neutropenia due to impaired production. Recombinant G-CSF is useful in the management of certain forms of neutropenia due to depressed neutrophil production, including those related to cancer

chemotherapy. Patients with chronic neutropenia with evidence of a good bone marrow reserve need not receive prophylactic antibiotics. Patients with chronic or cyclic neutrophil counts <500/μL may benefit from prophylactic antibiotics and G-CSF during periods of neutropenia. Oral trimethoprim-sulfamethoxazole (160/800 mg) twice daily can prevent infection. Increased numbers of fungal infections are not seen in patients with CGD on this regimen. Oral quinolones such as levofloxacin and ciprofloxacin are alternatives.

In the setting of cytotoxic chemotherapy with severe, persistent lymphocyte dysfunction, trimethoprim-sulfamethoxazole prevents *Pneumocystis jiroveci* pneumonia. These patients, and patients with phagocytic cell dysfunction, should avoid heavy exposure to airborne soil, dust, or decaying matter (mulch, manure), which are often rich in *Nocardia* and the spores of *Aspergillus* and other fungi. Restriction of activities or social contact has no proven role in reducing risk of infection for phagocyte defects.

Although aggressive medical care for many patients with phagocytic disorders can allow them to go for years without a life-threatening infection, there may still be delayed effects of prolonged antimicrobials and other inflammatory complications. Cure of most congenital phagocyte defects is possible by bone marrow transplantation, and rates of success are improving **(Chap. 110)**. The identification of specific gene defects in patients with LAD 1, CGD, and other immunodeficiencies has led to gene therapy trials in a number of genetic white cell disorders.

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61 Bleeding and Thrombosis

Barbara A. Konkle

The human hemostatic system provides a natural balance between procoagulant and anticoagulant forces. The procoagulant forces include platelet adhesion and aggregation and fibrin clot formation; anticoagulant forces include the natural inhibitors of coagulation and fibrinolysis. Under normal circumstances, hemostasis is regulated to promote blood flow; however, it is also prepared to clot blood rapidly to arrest blood flow and prevent exsanguination. After bleeding is successfully halted, the system remodels the damaged vessel to restore normal blood flow. The major components of the hemostatic system, which function in concert, are (1) platelets and other formed elements of blood, such as monocytes and red cells; (2) plasma proteins (the coagulation and fibrinolytic factors and inhibitors); and (3) the vessel wall.

STEPS OF NORMAL HEMOSTASIS

PLATELET PLUG FORMATION

On vascular injury, platelets adhere to the site of injury, usually the denuded vascular intimal surface. Platelet adhesion is mediated primarily by Von Willebrand factor (VWF), a large multimeric protein present in both plasma and the extracellular matrix of the subendothelial vessel wall, which serves as the primary "molecular glue," providing sufficient strength to withstand the high levels of shear stress that would tend to detach them with the flow of blood. Platelet adhesion is also facilitated by direct binding to subendothelial collagen through specific platelet membrane collagen receptors.

Platelet adhesion results in subsequent platelet activation and aggregation. This process is enhanced and amplified by humoral mediators in plasma (e.g., epinephrine, thrombin); mediators released from activated platelets (e.g., adenosine diphosphate, serotonin); and vessel wall extracellular matrix constituents that come in contact with adherent platelets (e.g., collagen, VWF). Activated platelets undergo the release reaction, during which they secrete contents that further promote aggregation and inhibit the naturally anticoagulant endothelial cell factors. During platelet aggregation (platelet-platelet interaction), additional platelets are recruited from the circulation to the site of vascular injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is anchored and stabilized by the developing fibrin mesh.

The platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) complex is the most abundant receptor on the platelet surface. Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active receptor, enabling binding to fibrinogen and VWF. Because the surface of each platelet has about 50,000 Gp IIb/IIIa–binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Because this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy.

FIBRIN CLOT FORMATION

Plasma coagulation proteins (*clotting factors*) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a *waterfall* or a *cascade*. Two pathways of blood coagulation have been described in the past: the so-called extrinsic, or tissue factor, pathway and the so-called intrinsic, or contact activation, pathway. We now know that coagulation is normally initiated through tissue factor (TF) exposure and activation through the classic *extrinsic pathway* but with critically important amplification through elements of the classic *intrinsic pathway*, as illustrated in **Fig. 61-1**. These reactions take place on phospholipid surfaces, usually the activated platelet surface. Coagulation testing in the laboratory can reflect other influences due to the artificial nature of the in vitro systems used (see below).

The immediate trigger for coagulation is vascular damage that exposes blood to TF that is constitutively expressed on the surfaces of subendothelial cellular components of the vessel wall, such as smooth muscle cells and fibroblasts. TF is also present in circulating microparticles, presumably shed from cells including monocytes and platelets. TF binds the serine protease factor VIIa; the complex activates factor X to factor Xa. Alternatively, the complex can indirectly activate factor X by initially converting factor IX to factor IXa, which then activates factor X. The participation of factor XI in hemostasis is not primarily dependent on its activation by factor XIIa but rather on its positive feedback activation by thrombin. Thus, factor XIa functions in the propagation and amplification, rather than in the initiation, of the coagulation cascade.

Factor Xa can be formed through the actions of either the TF/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor) and converts prothrombin to thrombin, the pivotal protease of the coagulation system. The essential cofactor for this reaction is factor Va. Like the homologous factor VIIIa, factor Va is produced by thrombin-induced limited proteolysis of factor V. Thrombin is a multifunctional enzyme that converts soluble plasma fibrinogen to an insoluble fibrin matrix. Fibrin polymerization involves an orderly process of intermolecular

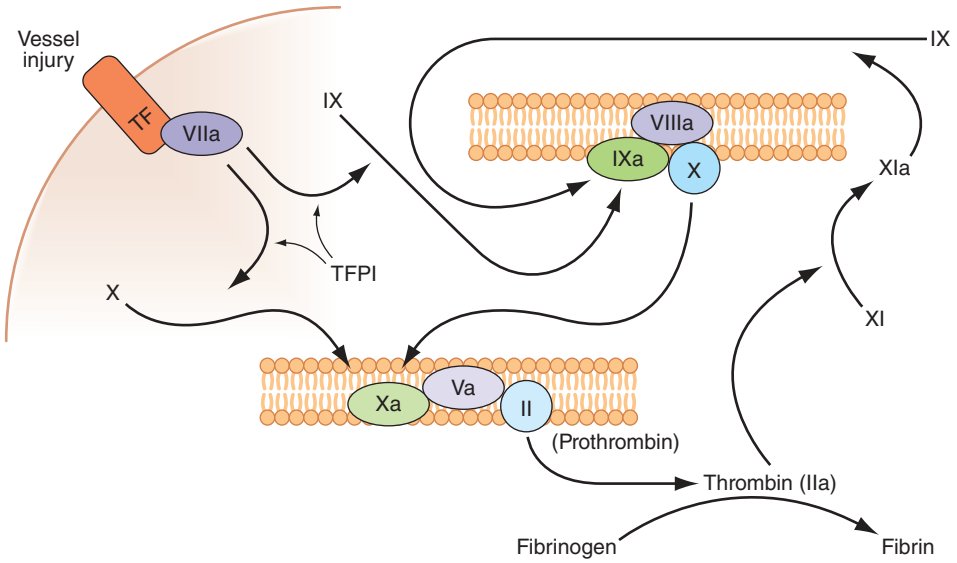

FIGURE 61-1 Coagulation is initiated by tissue factor (TF) exposure, which, with factor (F) VIIa, activates FIX and FX, which in turn, with FVIII and FV as cofactors, respectively, results in thrombin formation and subsequent conversion of fibrinogen to fibrin. Thrombin activates FXI, FVIII, and FV, amplifying the coagulation signal. Once the TF/FVIIa/FXa complex is formed, tissue factor pathway inhibitor (TFPI) inhibits the TF/FVIIa pathway, making coagulation dependent on the amplification loop through FIX/FVIII. Coagulation requires calcium (not shown) and takes place on phospholipid surfaces, usually the activated platelet membrane.

associations (Fig. 61-2). Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor XIIIa, which covalently cross-links and thereby stabilizes the fibrin clot.

The assembly of the clotting factors on activated cell membrane surfaces greatly accelerates their reaction rates and also serves to localize blood clotting to sites of vascular injury. The critical cell membrane components, acidic phospholipids, are not normally exposed on resting cell membrane surfaces. However, when platelets, monocytes, and endothelial cells are activated by vascular injury or inflammatory stimuli, the procoagulant head groups of the membrane anionic phospholipids become translocated to the surfaces of these cells or released as part of microparticles, making them available to support and promote the plasma coagulation reactions.

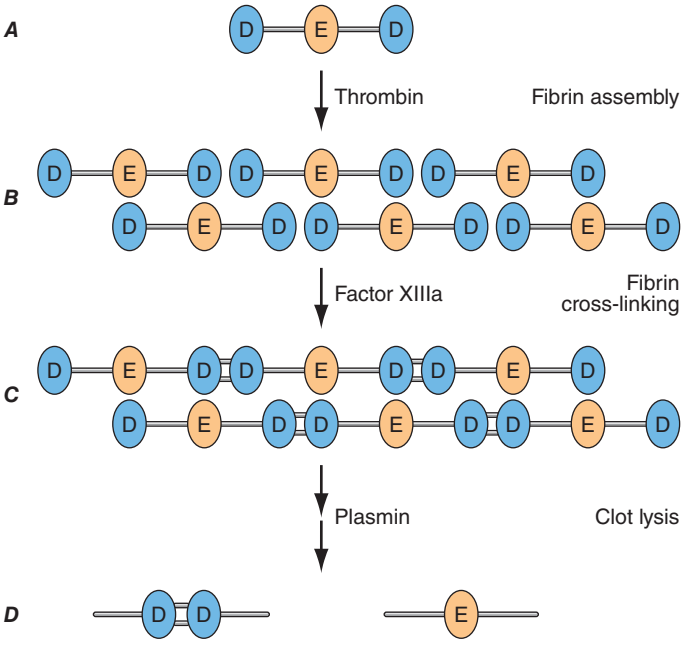

FIGURE 61-2 Fibrin formation and dissolution. (***A***) Fibrinogen is a trinodular structure consisting of two D domains and one E domain. Thrombin activation results in an ordered lateral assembly of protofibrils (***B***) with noncovalent associations. Factor XIIIa cross-links the D domains on adjacent molecules (***C***). Fibrin and fibrinogen (not shown) lysis by plasmin occurs at discrete sites and results in intermediary fibrin(ogen) degradation products (not shown). D-Dimers are the product of complete lysis of fibrin (***D***), maintaining the cross-linked D domains.

ANTITHROMBOTIC MECHANISMS

Several physiologic antithrombotic mechanisms act in concert to prevent clotting under normal circumstances. These mechanisms operate to preserve blood fluidity and to limit blood clotting to specific focal sites of vascular injury. Endothelial cells have many antithrombotic effects. They produce prostacyclin, nitric oxide, and ectoADPase/CD39, which act to inhibit platelet binding, secretion, and aggregation. Endothelial cells produce anticoagulant factors including heparan proteoglycans, antithrombin, TF pathway inhibitor, and thrombomodulin. They also activate fibrinolytic mechanisms through the production of tissue plasminogen activator 1, urokinase, plasminogen activator inhibitor, and annexin-2.

Antithrombin is the major plasma protease inhibitor of thrombin and the other clotting factors in coagulation. Antithrombin neutralizes thrombin and other activated coagulation factors by forming a complex between the active site of the enzyme and the reactive center of antithrombin. The rate of formation of these inactivating complexes increases by a factor of several thousand in the presence of heparin. Antithrombin inactivation of thrombin and other activated clotting factors occurs physiologically on vascular surfaces, where glycosoaminoglycans, including heparan sulfates, are present to catalyze these reactions. Inherited quantitative or qualitative deficiencies of antithrombin lead to a lifelong predisposition to venous thromboembolism.

Protein C is a plasma glycoprotein that becomes an anticoagulant when it is activated by thrombin. The thrombin-induced activation of protein C occurs physiologically on thrombomodulin, a transmembrane proteoglycan-binding site for thrombin on endothelial cell surfaces. The binding of protein C to its receptor on endothelial cells places it in proximity to the thrombin-thrombomodulin complex, thereby enhancing its activation efficiency. (See Fig. 61-3.) Activated protein C acts as an anticoagulant by cleaving and inactivating activated factors V and VIII. This reaction is accelerated by a cofactor, protein S, which, like protein C, is a glycoprotein that undergoes vitamin K–dependent posttranslational modification. Quantitative or qualitative deficiencies of protein C or protein S, or resistance to the action of activated protein C by a specific mutation at its target cleavage site in factor Va (factor V Leiden), lead to hypercoagulable states.

Tissue factor pathway inhibitor (TFPI) is a plasma protease inhibitor that regulates the TF-induced extrinsic pathway of coagulation. TFPI inhibits the TF/factor VIIa/factor Xa complex, essentially turning off the TF/factor VIIa initiation of coagulation, which then becomes dependent on the "amplification loop" via factor XI and factor VIII activation by thrombin. TFPI is bound to lipoprotein and can also be released by heparin from endothelial cells, where it is bound to glycosaminoglycans, and from platelets. The heparin-mediated release of TFPI may play a role in the anticoagulant effects of unfractionated and low-molecular-weight heparins (LMWH).

THE FIBRINOLYTIC SYSTEM

Any thrombin that escapes the inhibitory effects of the physiologic anticoagulant systems is available to convert fibrinogen to fibrin. In response, the endogenous fibrinolytic system is then activated to dispose of intravascular fibrin and thereby maintain or reestablish the patency of the circulation. Just as thrombin is the key protease enzyme

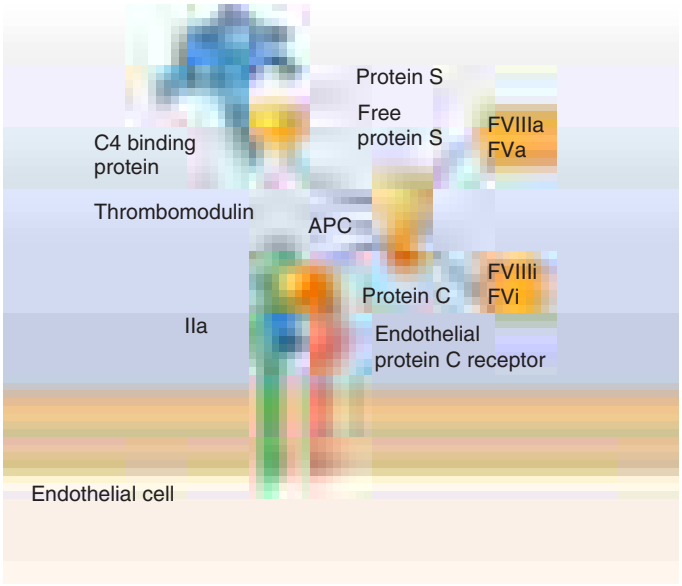

FIGURE 61-3 The activated protein C pathway in regulation of thrombosis. Thrombin generation results in protein C activation through interaction with thrombomodulin and protein C bound to the endothelial protein C receptor (EPCR). Activated protein C (APC) with free protein S converts activated factors (F) VIII and V to inactivate forms, thus in turn decreasing thrombin generation. APC, activated protein C; C4BP, C4 binding protein; EC, endothelial cell; EPCR, endothelial protein C receptor; F, factor; IIa, thrombin; PC, protein C; PS, protein S; TM, thrombomodulin.

of the coagulation system, plasmin is the major protease enzyme of the fibrinolytic system, acting to digest fibrin to fibrin degradation products. The general scheme of fibrinolysis and its control is shown in Fig. 61-4.

The plasminogen activators, tissue type plasminogen activator (tPA) and the urokinase-type plasminogen activator (uPA), cleave the Arg560-Val561 bond of plasminogen to generate the active enzyme plasmin. The lysine-binding sites of plasmin (and plasminogen) permit it to bind to fibrin, so that physiologic fibrinolysis is "fibrin specific." Both plasminogen (through its lysine-binding sites) and tPA possess specific affinity for fibrin and thereby bind selectively to clots. The assembly of a ternary complex, consisting of fibrin, plasminogen, and tPA, promotes the localized interaction between plasminogen and tPA and greatly accelerates the rate of plasminogen activation to plasmin. Moreover, partial degradation of fibrin by plasmin exposes new plasminogen and tPA-binding sites in carboxy-terminus lysine residues

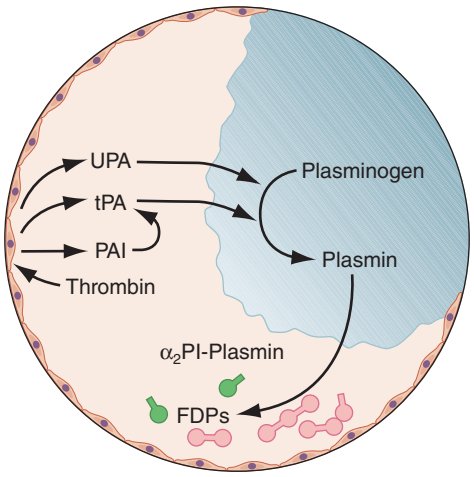

FIGURE 61-4 A schematic diagram of the fibrinolytic system. Tissue plasminogen activator (tPA) is released from endothelial cells, binds the fibrin clot, and activates plasminogen to plasmin. Excess fibrin is degraded by plasmin to distinct degradation products (FDPs). Any free plasmin is complexed with α_2-antiplasmin (α_2PI). PAI, plasminogen activator inhibitor; UPA, urokinase-type plasminogen activator.

of fibrin fragments to enhance these reactions further. This creates a highly efficient mechanism to generate plasmin focally on the fibrin clot, which then becomes plasmin's substrate for digestion to fibrin degradation products.

Plasmin cleaves fibrin at distinct sites of the fibrin molecule, leading to the generation of characteristic fibrin fragments during the process of fibrinolysis (Fig. 61-2). The sites of plasmin cleavage of fibrin are the same as those in fibrinogen. However, when plasmin acts on covalently cross-linked fibrin, D-dimers are released; hence, D-dimers can be measured in plasma as a relatively specific test of fibrin (rather than fibrinogen) degradation. D-Dimer assays can be used as sensitive markers of blood clot formation and have been validated for clinical use to exclude the diagnosis of deep-venous thrombosis (DVT) and pulmonary embolism in selected populations. In addition, D-dimer measurement can be used to stratify patients, particularly women, for risk of recurrent venous thromboembolism (VTE) when measured 1 month after discontinuation of anticoagulation given for treatment of an initial idiopathic event. D-Dimer levels increase with age. Whether a higher cut-off should be used in the elderly is controversial.

Physiologic regulation of fibrinolysis occurs primarily at three levels: (1) plasminogen activator inhibitors (PAIs), specifically PAI-1 and PAI-2, inhibit the physiologic plasminogen activators; (2) the thrombin-activatable fibrinolysis inhibitor (TAFI) limits fibrinolysis; and (3) α_2-antiplasmin inhibits plasmin. PAI-1 is the primary inhibitor of tPA and uPA in plasma. TAFI cleaves the N-terminal lysine residues of fibrin, which aid in localization of plasmin activity. α_2-Antiplasmin is the main inhibitor of plasmin in human plasma, inactivating any nonfibrin clot-associated plasmin.

APPROACH TO THE PATIENT

Bleeding and Thrombosis

CLINICAL PRESENTATION

Disorders of hemostasis may be either inherited or acquired. A detailed personal and family history is key in determining the chronicity of symptoms and the likelihood of the disorder being inherited, as well as providing clues to underlying conditions that have contributed to the bleeding or thrombotic state. In addition, the history can give clues as to the etiology by determining (1) the bleeding (mucosal and/or joint) or thrombosis (arterial and/or venous) site and (2) whether an underlying bleeding or clotting tendency was enhanced by another medical condition or the introduction of medications or dietary supplements.

History of Bleeding A history of bleeding is the most important predictor of bleeding risk. In evaluating a patient for a bleeding disorder, a history of at-risk situations, including the response to past surgeries, should be assessed. Does the patient have a history of spontaneous or trauma/surgery-induced bleeding? Spontaneous hemarthroses are a hallmark of moderate and severe factor VIII and IX deficiency and, in rare circumstances, of other clotting factor deficiencies. Mucosal bleeding symptoms are more suggestive of underlying platelet disorders or Von Willebrand disease (VWD), termed *disorders of primary hemostasis or platelet plug formation.* Disorders affecting primary hemostasis are shown in Table 61-1.

A bleeding score has been validated as a tool to predict patients more likely to have type 1 VWD (International Society on Thrombosis and Haemostasis Bleeding Assessment Tool [*www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf*]). This is the most useful tool in excluding the diagnosis of a bleeding disorder, and thus avoiding unnecessary testing. One study found that a low bleeding score (≤3) and a normal activated partial thromboplastin time (aPTT) had 99.6% negative predictive value for the diagnosis of VWD. Bleeding symptoms that appear to be more common in patients with bleeding disorders include prolonged bleeding with surgery, dental procedures and extractions, and/or trauma, heavy menstrual bleeding (HMB), or postpartum hemorrhage (PPH), and large bruises (often described with lumps).

TABLE 61-1 Primary Hemostatic (Platelet Plug) Disorders
Defects of Platelet Adhesion
Von Willebrand disease
Bernard-Soulier syndrome (absence or dysfunction of platelet Gp Ib-IX-V)
Defects of Platelet Aggregation
Glanzmann's thrombasthenia (absence or dysfunction of platelet glycoprotein [Gp] IIb/IIIa)
Afibrinogenemia
Defects of Platelet Secretion
Decreased cyclooxygenase activity
Drug-induced (aspirin, nonsteroidal anti-inflammatory agents, thienopyridines)
Inherited
Granule storage pool defects
Inherited
Acquired
Nonspecific inherited secretory defects
Nonspecific drug effects
Uremia
Platelet coating (e.g., paraprotein, penicillin)
Defect of Platelet Coagulant Activity
Scott's syndrome

Easy bruising and HMB are common complaints in patients with and without bleeding disorders. Easy bruising can also be a sign of medical conditions in which there is no identifiable coagulopathy; instead, the conditions are caused by an abnormality of blood vessels or their supporting tissues. In Ehlers-Danlos syndrome, there may be posttraumatic bleeding and a history of joint hyperextensibility. Cushing's syndrome, chronic steroid use, and aging result in changes in skin and subcutaneous tissue, and subcutaneous bleeding occurs in response to minor trauma. The latter has been termed *senile purpura*.

Epistaxis is a common symptom, particularly in children and in dry climates, and may not reflect an underlying bleeding disorder. However, it is the most common symptom in hereditary hemorrhagic telangiectasia and in boys with VWD. Clues that epistaxis is a symptom of an underlying bleeding disorder include lack of seasonal variation and bleeding that requires medical evaluation or treatment, including cauterization. Bleeding with eruption of primary teeth is seen in children with more severe bleeding disorders, such as moderate and severe hemophilia. It is uncommon in children with mild bleeding disorders. Patients with disorders of primary hemostasis (platelet adhesion) may have increased bleeding after dental cleanings and other procedures that involve gum manipulation.

Heavy menstrual bleeding is defined quantitatively as a loss of >80 mL of blood per cycle, based on the quantity of blood loss required to produce iron-deficiency anemia. A complaint of heavy menses is subjective and has a poor correlation with excessive blood loss. Predictors of HMB include bleeding resulting in iron-deficiency anemia or a need for blood transfusion, passage of clots >1 in. in diameter, and changing a pad or tampon more than hourly. HMB is a common symptom in women with underlying bleeding disorders and is reported in the majority of women with VWD, women with factor XI deficiency, and symptomatic carriers of hemophilia. Women with underlying bleeding disorders are more likely to have other bleeding symptoms, including bleeding after dental extractions, postoperative bleeding, and postpartum bleeding, and are much more likely to have HMB beginning at menarche than women with HMB due to other causes.

PPH is a common symptom in women with underlying bleeding disorders. In women with type 1 VWD and symptomatic carriers of hemophilia A in whom levels of VWF and factor VIII usually normalize during pregnancy, PPH may be delayed. Women with a history of PPH may have a higher risk of recurrence with subsequent pregnancies. Rupture of ovarian cysts with intraabdominal hemorrhage has also been reported in women with underlying bleeding disorders.

Tonsillectomy is a major hemostatic challenge, because intact hemostatic mechanisms are essential to prevent excessive bleeding from the tonsillar bed. Bleeding may occur early after surgery or after ~7 days postoperatively, with loss of the eschar at the operative site. Similar delayed bleeding is seen after colonic polyp resection. Gastrointestinal (GI) bleeding and hematuria are usually due to underlying pathology, and procedures to identify and treat the bleeding site should be undertaken, even in patients with known bleeding disorders. VWD, particularly types 2 and 3, has been associated with angiodysplasia of the bowel and GI bleeding.

Hemarthroses and spontaneous muscle hematomas are characteristic of moderate or severe congenital factor VIII or IX deficiency. They can also be seen in moderate and severe deficiencies of fibrinogen, prothrombin, and factors V, VII, and X. Spontaneous hemarthroses occur rarely in other bleeding disorders except for severe VWD, with associated factor VIII levels <5%. Muscle and soft tissue bleeds are also common in acquired factor VIII deficiency. Bleeding into a joint results in severe pain and swelling, as well as loss of function, but is rarely associated with discoloration from bruising around the joint. Life-threatening sites of bleeding include bleeding into the oropharynx, where bleeding can obstruct the airway, into the central nervous system, and into the retroperitoneum. Central nervous system bleeding is the major cause of bleeding-related deaths in patients with severe congenital factor deficiencies.

Prohemorrhagic Effects of Medications and Dietary Supplements Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase 1 impair primary hemostasis and may exacerbate bleeding from another cause or even unmask a previously occult mild bleeding disorder such as VWD. All NSAIDs, however, can precipitate GI bleeding, which may be more severe in patients with underlying bleeding disorders. This aspirin effect lasts for the life of the platelet, though in individuals with typical platelet turnover, the functional defect reverts to near-normal within 2–3 days after the last dose. The effect of other NSAIDs is shorter, as the inhibitor effect is reversed when the drug is removed. Inhibitors of the ADP $P2Y_{12}$ receptor (clopidogrel, prasugrel, and ticagrelor) inhibit ADP-mediated platelet aggregation and, like NSAIDs, can precipitate or exacerbate bleeding symptoms. The risk of bleeding with these drugs is higher than with NSAIDs.

Many herbal supplements can impair hemostatic function **(Table 61-2)**. Some are more convincingly associated with a bleeding risk than others. Fish oil or concentrated omega-3 fatty acid supplements impair platelet function. They alter platelet biochemistry to produce more PGI_3, a more potent platelet inhibitor than prostacyclin (PGI_2), and more thromboxane A_3, a less potent platelet activator than thromboxane A_2. In fact, diets naturally rich in omega-3 fatty acids can result in a prolonged bleeding time and abnormal platelet aggregation studies, but the actual associated bleeding risk is unclear. Vitamin E appears to inhibit protein kinase C–mediated platelet aggregation and nitric oxide production. In patients with unexplained bruising or bleeding, it is prudent to review any new medications or supplements and discontinue those that may be associated with bleeding.

Underlying Systemic Diseases that Cause or Exacerbate a Bleeding Tendency Acquired bleeding disorders are commonly secondary to, or associated with, systemic disease. The clinical evaluation of a patient with a bleeding tendency must therefore include a thorough assessment for evidence of underlying disease. Bruising or mucosal bleeding may be the presenting complaint in liver disease, severe renal impairment, hypothyroidism, paraproteinemias or amyloidosis, and conditions causing bone marrow failure. All coagulation factors are synthesized in the liver, and hepatic failure

TABLE 61-2 Herbal Supplements Associated with Increased Bleeding

Herbs with Potential Antiplatelet Activity
Ginkgo (*Ginkgo biloba L.*)
Garlic (*Allium sativum*)
Bilberry (*Vaccinium myrtillus*)
Ginger (*Gingiber officinale*)
Dong quai (*Angelica sinensis*)
Feverfew (*Tanacetum parthenium*)
Asian ginseng (*Panax ginseng*)
American ginseng (*Panax quinquefolius*)
Siberian ginseng/eleuthero (*Eleutherococcus senticosus*)
Turmeric (*Circuma longa*)
Meadowsweet (*Filipendula ulmaria*)
Willow (*Salix* spp.)
Coumarin-Containing Herbs
Motherwort (*Leonurus cardiaca*)
Chamomile (*Matricaria recutita, Chamaemelum mobile*)
Horse chestnut (*Aesculus hippocastanum*)
Red clover (*Trifolium pratense*)
Fenugreek (*Trigonella foenum-graecum*)

TABLE 61-3 Risk Factors for Thrombosis

VENOUS	VENOUS AND ARTERIAL
Inherited	**Inherited**
Factor V Leiden	Homocystinuria
Prothrombin G20210A	Dysfibrinogenemia
Antithrombin deficiency	**Acquired**
Protein C deficiency	Malignancy
Protein S deficiency	Antiphospholipid antibody syndrome
Elevated factor VIII	Hormonal therapy
Acquired	Polycythemia vera
Age	Essential thrombocythemia
Previous thrombosis	Paroxysmal nocturnal hemoglobinuria
Immobilization	Thrombotic thrombocytopenic purpura
Major surgery	Heparin-induced thrombocytopenia
Pregnancy and puerperium	Disseminated intravascular coagulation
Hospitalization	**Unknown**[a]
Obesity	Elevated factor II, IX, XI
Infection	Elevated TAFI levels
APC resistance, nongenetic	Low levels of TFPI
Smoking	

[a]Unknown whether risk is inherited or acquired.

Abbreviations: APC, activated protein C; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor.

results in combined factor deficiencies. This is often compounded by thrombocytopenia associated with liver failure and portal hypertension. Coagulation factors II, VII, IX, and X and proteins C, S, and Z are dependent on vitamin K for posttranslational modification. Although vitamin K is required in both procoagulant and anticoagulant processes, the phenotype of vitamin K deficiency or the warfarin effect on coagulation is bleeding.

The normal blood platelet count is 150,000–450,000/μL. Thrombocytopenia results from decreased production, increased destruction, and/or sequestration. Although the bleeding risk varies somewhat by the reason for the thrombocytopenia, bleeding rarely occurs in isolated thrombocytopenia at counts >50,000/μL and usually not until <10,000–20,000/μL. Coexisting coagulopathies, as is seen in liver failure or disseminated coagulation; infection; platelet-inhibitory drugs; and underlying medical conditions can all increase the risk of bleeding in the thrombocytopenic patient. Most procedures can be performed in patients with a platelet count of 50,000/μL. The level needed for major surgery will depend on the type of surgery and the patient's underlying medical state, although a count of ~80,000/μL is likely sufficient.

HISTORY OF THROMBOSIS

The risk of thrombosis, like that of bleeding, is influenced by both genetic and environmental influences. The major risk factor for arterial thrombosis is atherosclerosis, whereas for venous thrombosis, the risk factors are immobility, surgery, underlying medical conditions such as malignancy, medications such as hormonal therapy, obesity, and genetic predispositions. Factors that increase risks for venous and for both venous and arterial thromboses are shown in Table 61-3.

The most important point in a history related to venous thrombosis is determining whether the thrombotic event was idiopathic (meaning there was no clear precipitating factor) or was a precipitated event. In patients without underlying malignancy, having an idiopathic event is the strongest predictor of recurrence of VTE. In patients who have a vague history of thrombosis, a history of being treated with warfarin suggests a past DVT. Age is an important risk factor for venous thrombosis—the risk of DVT increases per decade, with an approximate incidence of 1/100,000 per year in early childhood to 1/200 per year among octogenarians. Family history is helpful in determining if there is a genetic predisposition and how strong that predisposition appears to be. A genetic thrombophilia that confers a relatively small increased risk, such as being a heterozygote for the prothrombin G20210A or factor V Leiden mutation, is a minor determinant of risk in an elderly individual undergoing a high-risk surgical procedure. As illustrated in Fig. 61-5, a thrombotic event usually has more than one contributing factor. Predisposing factors must be carefully assessed to determine the risk of recurrent thrombosis and, with consideration of the patient's bleeding risk, determine the length of anticoagulation. Testing for inherited thrombophilias in adults should be limited to instances where results would change clinical care.

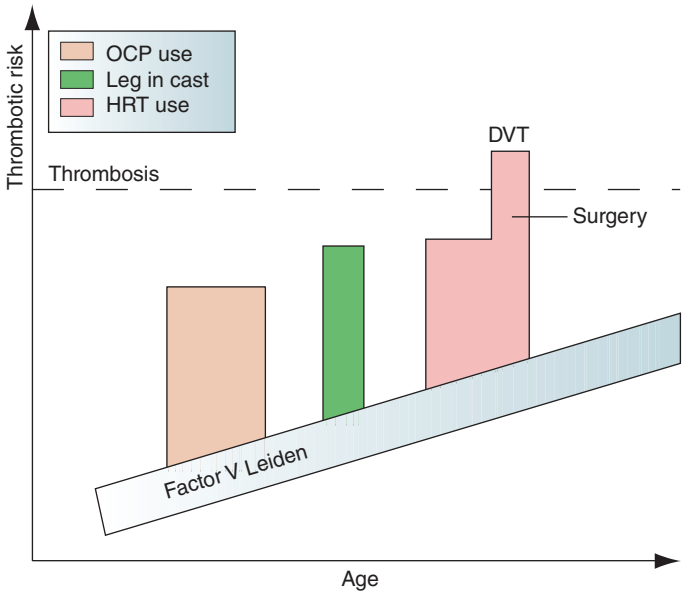

FIGURE 61-5 Thrombotic risk over time. Shown schematically is an individual's thrombotic risk over time. An underlying factor V Leiden mutation provides a "theoretically" constant increased risk. The thrombotic risk increases with age and, intermittently, with oral contraceptive (OCP) or hormone replacement therapy (HRT) use; other events may increase the risk further. At some point, the cumulative risk may increase to the threshold for thrombosis and result in deep-venous thrombosis (DVT). Note: The magnitude and duration of risk portrayed in the figure are meant for example only and may not precisely reflect the relative risk determined by clinical study. *(From BA Konkle, A Schafer, in DP Zipes et al [eds]: Braunwald's Heart Disease, 7th ed. Philadelphia, Saunders, 2005; modified with permission from FR Rosendaal: Venous thrombosis: A multicausal disease. Lancet 353:1167, 1999.)*

LABORATORY EVALUATION

Careful history taking and clinical examination are essential components in the assessment of bleeding and thrombotic risk. The use of laboratory tests of coagulation complement, but cannot substitute for, clinical assessment. No test exists that provides a global assessment of hemostasis. The bleeding time has been used to assess bleeding risk; however, it does not predict bleeding risk with surgery and it is not recommended for this indication. The PFA-100, an instrument that measures platelet-dependent coagulation under flow conditions, is more sensitive and specific for VWD than the bleeding time; however, it is not sensitive enough to rule out mild bleeding disorders. PFA-100 closure times are prolonged in patients with some, but not all, inherited platelet disorders. Also, its utility in predicting bleeding risk has not been determined. Thromboelastography can be useful in guiding intraoperative transfusion but is not broadly applicable for the diagnosis of disorders of hemostasis and thrombosis.

For routine preoperative and pre-procedure testing, an abnormal prothrombin time (PT) may detect liver disease or vitamin K deficiency that had not been previously appreciated. Studies have not confirmed the usefulness of an aPTT in preoperative evaluations in patients with a negative bleeding history. The primary use of coagulation testing should be to confirm the presence and type of bleeding disorder in a patient with a suspicious clinical history.

Because of the nature of coagulation assays, proper sample acquisition and handling is critical to obtaining valid results. In patients with abnormal coagulation assays who have no bleeding history, repeat studies with attention to these factors frequently result in normal values. Most coagulation assays are performed in sodium citrate anticoagulated plasma that is recalcified for the assay. Because the anticoagulant is in liquid solution and needs to be added to blood in proportion to the plasma volume, incorrectly filled or inadequately mixed blood collection tubes will give erroneous results. Vacutainer tubes should be filled to >90% of the recommended fill, which is usually denoted by a line on the tube. An elevated hematocrit (>55%) can result in a false value due to a decreased plasma-to-anticoagulant ratio.

Screening Assays The most commonly used screening tests are the PT, aPTT, and platelet count. The PT assesses the factors I (fibrinogen), II (prothrombin), V, VII, and X **(Fig. 61-6)**. The PT measures the time for clot formation of the citrated plasma after recalcification and addition of thromboplastin, a mixture of TF and phospholipids. The sensitivity of the assay varies by the source of thromboplastin. The relationship between defects in secondary hemostasis (fibrin formation) and coagulation test abnormalities is shown in **Table 61-4**. To adjust for this variability, the overall sensitivity of different thromboplastins to reduction of the vitamin K–dependent clotting factors II, VII, IX, and X in anticoagulation patients is expressed as the International Sensitivity Index (ISI). The international normalized ratio (INR) is determined based on the formula: $INR = (PT_{patient}/PT_{normal\ mean})^{ISI}$.

The INR was developed to assess stable anticoagulation due to reduction of vitamin K–dependent coagulation factors; it is commonly used in the evaluation of patients with liver disease. Although it does allow comparison between laboratories, reagent sensitivity as used to determine the ISI is not the same in liver disease as with warfarin anticoagulation. In addition, progressive liver failure is associated with variable changes in coagulation factors; the degree of prolongation of either the PT or the INR only roughly predicts the bleeding risk. Thrombin generation has been shown to be normal in many patients with mild to moderate liver dysfunction. Because the PT only measures one aspect of hemostasis affected by liver dysfunction, we likely overestimate the bleeding risk of a mildly elevated INR in this setting. PT reagents have variable sensitivity to the direct Xa inhibitors and the PT is usually normal in patients on apixaban.

The aPTT assesses the intrinsic and common coagulation pathways; factors XI, IX, VIII, X, V, and II; fibrinogen; prekallikrein;

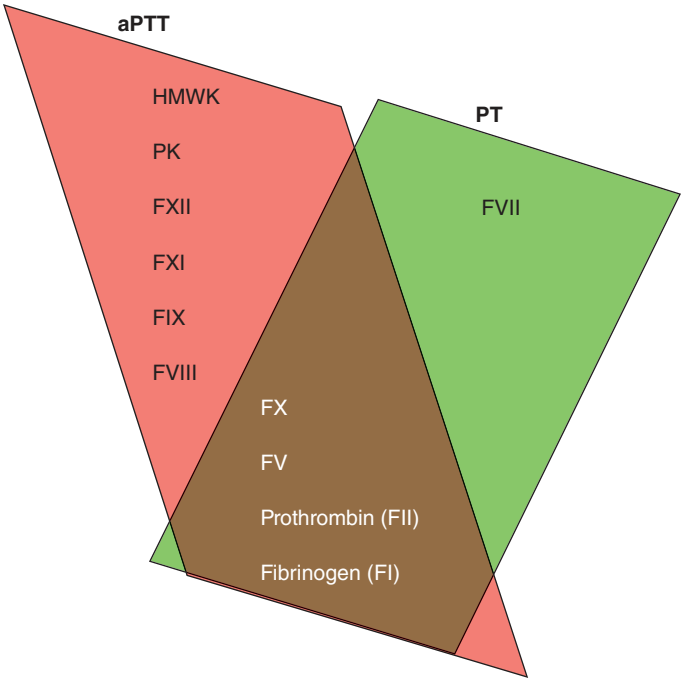

FIGURE 61-6 Coagulation factor activity tested in the activated partial thromboplastin time (aPTT) in red and prothrombin time (PT) in green, or both. F, factor; HMWK, high-molecular-weight kininogen; PK, prekallikrein.

TABLE 61-4 Hemostatic Disorders and Coagulation Test Abnormalities

Prolonged Activated Partial Thromboplastin Time (aPTT)
No clinical bleeding—↓ factor XII, high-molecular-weight kininogen, prekallikrein
Variable, but usually mild, bleeding—↓ factor XI, mild ↓ factor VIII and factor IX
Frequent, severe bleeding—severe deficiencies of factors VIII and IX
Heparin and direct thrombin inhibitors
Prolonged Prothrombin Time (PT)
Factor VII deficiency
Vitamin K deficiency—early
Warfarin anticoagulation
Direct Xa inhibitors (rivaroxaban, edoxaban, apixaban– note PT may be normal)
Prolonged aPTT and PT
Factors II, V, X, or fibrinogen deficiency
Vitamin K deficiency—late
Direct thrombin inhibitors
Prolonged Thrombin Time
Heparin or heparin-like inhibitors
Direct thrombin inhibitors (e.g., dabigatran, argatroban, bivalirudin)
Mild or no bleeding—dysfibrinogenemia
Frequent, severe bleeding—afibrinogenemia
Prolonged PT and/or aPTT Not Corrected with Mixing with Normal Plasma
Bleeding—specific factor inhibitor
No symptoms, or clotting and/or pregnancy loss—lupus anticoagulant
Disseminated intravascular coagulation
Heparin or direct thrombin inhibitor
Abnormal Clot Solubility
Factor XIII deficiency
Inhibitors or defective cross-linking
Rapid Clot Lysis
Deficiency of α_2-antiplasmin or plasminogen activator inhibitor 1
Treatment with fibrinolytic therapy

high-molecular-weight kininogen; and factor XII (Fig. 61-6). The aPTT reagent contains phospholipids derived from either animal or vegetable sources that function as a platelet substitute in the coagulation pathways and includes an activator of the intrinsic coagulation system, such as nonparticulate ellagic acid or the particulate activators kaolin, celite, or micronized silica.

The phospholipid composition of aPTT reagents varies, which influences the sensitivity of individual reagents to clotting factor deficiencies and to inhibitors such as heparin and lupus anticoagulants. Thus, aPTT results will vary from one laboratory to another, and the normal range in the laboratory where the testing occurs should be used in the interpretation. Local laboratories can relate their aPTT values to the therapeutic heparin anticoagulation by correlating aPTT values with direct measurements of heparin activity (anti-Xa or protamine titration assays) in samples from heparinized patients, although correlation between these assays is often poor. The aPTT reagent will vary in sensitivity to individual factor deficiencies and usually becomes prolonged with individual factor deficiencies of 30–50%.

Mixing Studies Mixing studies are used to evaluate a prolonged aPTT or, less commonly PT, to distinguish between a factor deficiency and an inhibitor. In this assay, normal plasma and patient plasma are mixed in a 1:1 ratio, and the aPTT or PT is determined immediately and after incubation at 37°C for varying times, typically 30, 60, and/or 120 min. With isolated factor deficiencies, the aPTT will correct with mixing and stay corrected with incubation. With aPTT prolongation due to a lupus anticoagulant, the mixing and incubation will show no correction. In acquired neutralizing factor antibodies, notably an acquired factor VIII inhibitor, the initial assay may or may not correct immediately after mixing but will prolong or remain prolonged with incubation at 37°C. Failure to correct with mixing can also be due to the presence of other inhibitors or interfering substances such as heparin, fibrin split products, and paraproteins.

Specific Factor Assays Decisions to proceed with specific clotting factor assays will be influenced by the clinical situation and the results of coagulation screening tests. Precise diagnosis and effective management of inherited and acquired coagulation deficiencies necessitate quantitation of the relevant factors. When bleeding is severe, specific assays are urgently required to guide appropriate therapy. Individual factor assays are usually performed as modifications of the mixing study, where the patient's plasma is mixed with plasma deficient in the factor being studied. This will correct all factor deficiencies to >50%, thus making prolongation of clot formation due to a factor deficiency dependent on the factor missing from the added plasma.

Testing for Antiphospholipid Antibodies Antibodies to phospholipids (cardiolipin) or phospholipid-binding proteins (β_2-microglobulin and others) are detected by enzyme-linked immunosorbent assay (ELISA). When these antibodies interfere with phospholipid-dependent coagulation tests, they are termed *lupus anticoagulants*. The aPTT has variability sensitivity to lupus anticoagulants, depending in part on the aPTT reagents used. An assay using a sensitive reagent has been termed an *LA-PTT*. The dilute Russell viper venom test (dRVVT) and the tissue thromboplastin inhibition (TTI) test are modifications of standard tests with the phospholipid reagent decreased, thus increasing the sensitivity to antibodies that interfere with the phospholipid component. The tests, however, are not specific for lupus anticoagulants, because factor deficiencies or other inhibitors will also result in prolongation. Documentation of a lupus anticoagulant requires not only prolongation of a phospholipid-dependent coagulation test but also lack of correction when mixed with normal plasma and correction with the addition of activated platelet membranes or certain phospholipids (e.g., hexagonal phase).

Other Coagulation Tests The thrombin time and the reptilase time measure fibrinogen conversion to fibrin and are prolonged when the fibrinogen level is low (usually <80–100 mg/dL) or qualitatively abnormal, as seen in inherited or acquired dysfibrinogenemias, or when fibrin/fibrinogen degradation products interfere. The thrombin time, but not the reptilase time, is prolonged in the presence of heparin. The thrombin time is markedly prolonged in the presence of the direct thrombin inhibitor, dabigatran; a dilute thrombin time can be used to assess drug activity. Measurement of anti–factor Xa plasma inhibitory activity is a test frequently used to assess LMWH levels, as a direct measurement of unfractionated heparin (UFH) activity, or to assess activity of the direct Xa inhibitors rivaroxaban, apixaban, and edoxaban. Drug in the patient sample inhibits the enzymatic conversion of an Xa-specific chromogenic substrate to colored product by factor Xa. Standard curves are created using multiple concentrations of the specific drug and are used to calculate the concentration of anti-Xa activity in the patient plasma.

Laboratory Testing for Thrombophilia Laboratory assays to detect thrombophilic states include molecular diagnostics and immunologic and functional assays. These assays vary in their sensitivity and specificity for the condition being tested. Furthermore, acute thrombosis, acute illnesses, inflammatory conditions, pregnancy, and medications affect levels of many coagulation factors and their inhibitors. Antithrombin is decreased by heparin and in the setting of acute thrombosis. Protein C and S levels may be increased in the setting of acute thrombosis and are decreased by warfarin. Antiphospholipid antibodies are frequently transiently positive in acute illness. Testing for genetic thrombophilias should, in general, only be performed when there is a strong family history of thrombosis and results would affect clinical decision-making.

Because thrombophilia evaluations are usually performed to assess the need to extend anticoagulation, testing, if indicated, should be performed in a steady state, remote from the acute event. In most instances, warfarin anticoagulation can be stopped after the initial 3–6 months of treatment, and testing can be performed at least 3 weeks later. As a sensitive marker of coagulation activation, the quantitative D-dimer assay, drawn 4 weeks after stopping anticoagulation, can be used to stratify risk of recurrent thrombosis in patients, particularly women, who have an idiopathic event.

Measures of Platelet Function The bleeding time has been used to assess bleeding risk; however, it has not been found to predict bleeding risk with surgery, and it is not recommended for use for this indication. The PFA-100 and similar instruments that measure platelet-dependent coagulation under flow conditions are generally more sensitive and specific for platelet disorders and VWD than the bleeding time; however, data are insufficient to support their use to predict bleeding risk or monitor response to therapy, and they will be normal in some patients with platelet disorders or mild VWD. When they are used in the evaluation of a patient with bleeding symptoms, abnormal results, as with the bleeding time, require specific testing, such as VWF assays and/or platelet aggregation studies. Because all of these "screening" assays may miss patients with mild bleeding disorders, further studies are needed to define their role in hemostasis testing.

For classic platelet aggregometry, various agonists are added to the patient's platelet-rich plasma or whole blood and platelet aggregation is measured. Tests of platelet secretion in response to agonists can also be measured. These tests are affected by many factors, including numerous medications, and the association between minor defects in aggregation or secretion in these assays and bleeding risk is not clearly established.

FURTHER READING

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62 Enlargement of Lymph Nodes and Spleen

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This chapter is intended to serve as a guide to the evaluation of patients who present with enlargement of the lymph nodes (*lymphadenopathy*) or the spleen (*splenomegaly*). Lymphadenopathy is a rather common clinical finding in primary care settings, whereas palpable splenomegaly is less so.

LYMPHADENOPATHY

Lymphadenopathy may be an incidental finding in patients being examined for various reasons, or it may be a presenting sign or symptom of the patient's illness. The physician must eventually decide whether the lymphadenopathy is a normal finding or one that requires further study, up to and including biopsy. Soft, flat, submandibular nodes (<1 cm) are often palpable in healthy children and young adults; healthy adults may have palpable inguinal nodes of up to 2 cm, which are considered normal. Further evaluation of these normal nodes is not warranted. In contrast, if the physician believes the node(s) to be abnormal, then pursuit of a more precise diagnosis is needed.

APPROACH TO THE PATIENT

Lymphadenopathy

Lymphadenopathy may be a primary or secondary manifestation of numerous disorders, as shown in **Table 62-1**. Many of these disorders are infrequent causes of lymphadenopathy. In primary care practice, more than two-thirds of patients with lymphadenopathy have nonspecific causes or upper respiratory illnesses (viral or bacterial) and <1% have a malignancy. In one study, 84% of patients referred for evaluation of lymphadenopathy had a "benign" diagnosis. The remaining 16% had a malignancy (lymphoma or metastatic adenocarcinoma). Of the patients with benign lymphadenopathy, 63% had a nonspecific or reactive etiology (no causative agent found), and the remainder had a specific cause demonstrated, most commonly infectious mononucleosis, toxoplasmosis, or tuberculosis. Thus, the vast majority of patients with lymphadenopathy will have a nonspecific etiology requiring few diagnostic tests.

CLINICAL ASSESSMENT

The physician will be aided in the pursuit of an explanation for the lymphadenopathy by a careful medical history, physical examination, selected laboratory tests, and perhaps an excisional lymph node biopsy.

The *medical history* should reveal the setting in which lymphadenopathy is occurring. Symptoms such as sore throat, cough, fever, night sweats, fatigue, weight loss, or pain in the nodes should be sought. The patient's age, sex, occupation, exposure to pets, sexual behavior, and use of drugs such as diphenylhydantoin are other important historic points. For example, children and young adults usually have benign (i.e., nonmalignant) disorders that account for the observed lymphadenopathy such as viral or bacterial upper respiratory infections; infectious mononucleosis; toxoplasmosis; and, in some countries, tuberculosis. In contrast, after age 50, the incidence of malignant disorders increases and that of benign disorders decreases.

TABLE 62-1 Diseases Associated with Lymphadenopathy

1. Infectious diseases
   a. Viral—infectious mononucleosis syndromes (EBV, CMV), infectious hepatitis, herpes simplex, herpesvirus-6, varicella-zoster virus, rubella, measles, adenovirus, HIV, epidemic keratoconjunctivitis, vaccinia, herpesvirus-8
   b. Bacterial—streptococci, staphylococci, cat-scratch disease, brucellosis, tularemia, plague, chancroid, melioidosis, glanders, tuberculosis, atypical mycobacterial infection, primary and secondary syphilis, diphtheria, leprosy, bartonella
   c. Fungal—histoplasmosis, coccidioidomycosis, paracoccidioidomycosis
   d. Chlamydial—lymphogranuloma venereum, trachoma
   e. Parasitic—toxoplasmosis, leishmaniasis, trypanosomiasis, filariasis
   f. Rickettsial—scrub typhus, rickettsialpox, Q fever
2. Immunologic diseases
   a. Rheumatoid arthritis
   b. Juvenile rheumatoid arthritis
   c. Mixed connective tissue disease
   d. Systemic lupus erythematosus
   e. Dermatomyositis
   f. Sjögren's syndrome
   g. Serum sickness
   h. Drug hypersensitivity—diphenylhydantoin, hydralazine, allopurinol, primidone, gold, carbamazepine, etc.
   i. Angioimmunoblastic lymphadenopathy
   j. Primary biliary cirrhosis
   k. Graft-vs.-host disease
   l. Silicone-associated
   m. Autoimmune lymphoproliferative syndrome
   n. IgG4-related disease
   o. Immune reconstitution inflammatory syndrome (IRIS)
3. Malignant diseases
   a. Hematologic—Hodgkin's disease, non-Hodgkin's lymphomas, acute or chronic lymphocytic leukemia, hairy cell leukemia, malignant histiocytosis, amyloidosis
   b. Metastatic—from numerous primary sites
4. Lipid storage diseases—Gaucher's, Niemann-Pick, Fabry, Tangier
5. Endocrine diseases—hyperthyroidism
6. Other disorders
   a. Castleman's disease (giant lymph node hyperplasia)
   b. Sarcoidosis
   c. Dermatopathic lymphadenitis
   d. Lymphomatoid granulomatosis
   e. Histiocytic necrotizing lymphadenitis (Kikuchi's disease)
   f. Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)
   g. Mucocutaneous lymph node syndrome (Kawasaki's disease)
   h. Histiocytosis X
   i. Familial Mediterranean fever
   j. Severe hypertriglyceridemia
   k. Vascular transformation of sinuses
   l. Inflammatory pseudotumor of lymph node
   m. Congestive heart failure

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus.

The *physical examination* can provide useful clues such as the extent of lymphadenopathy (localized or generalized), size of nodes, texture, presence or absence of nodal tenderness, signs of inflammation over the node, skin lesions, and splenomegaly. A thorough ear, nose, and throat (ENT) examination is indicated in adult patients with cervical adenopathy and a history of tobacco use. Localized or regional adenopathy implies involvement of a single anatomic area. Generalized adenopathy has been defined as involvement of three or more noncontiguous lymph node areas. Many of the causes of lymphadenopathy (Table 62-1) can produce localized *or* generalized adenopathy, so this distinction is of limited utility in the differential diagnosis. Nevertheless, generalized lymphadenopathy is frequently associated with nonmalignant disorders such as infectious mononucleosis (Epstein-Barr virus [EBV] or cytomegalovirus [CMV]), toxoplasmosis, AIDS, other viral infections, systemic lupus erythematosus (SLE), and mixed connective tissue disease. Acute and chronic lymphocytic leukemias and malignant lymphomas also produce generalized adenopathy in adults.

The site of localized or regional adenopathy may provide a useful clue about the cause. Occipital adenopathy often reflects an infection of the scalp, and preauricular adenopathy accompanies conjunctival infections and cat-scratch disease. The most frequent site of regional adenopathy is the neck, and most of the causes are benign—upper respiratory infections, oral and dental lesions, infectious mononucleosis, or other viral illnesses. The chief malignant causes include metastatic cancer from head and neck, breast, lung, and thyroid primaries. Enlargement of supraclavicular and scalene nodes is always abnormal. Because these nodes drain regions of the lung and retroperitoneal space, they can reflect lymphomas, other cancers, or infectious processes arising in these areas. Virchow's node is an enlarged left supraclavicular node infiltrated with metastatic cancer from a gastrointestinal primary. Metastases to supraclavicular nodes also occur from lung, breast, testis, or ovarian cancers. Tuberculosis, sarcoidosis, and toxoplasmosis are nonneoplastic causes of supraclavicular adenopathy. Axillary adenopathy is usually due to injuries or localized infections of the ipsilateral upper extremity. Malignant causes include melanoma or lymphoma and, in women, breast cancer. Inguinal lymphadenopathy is usually secondary to infections or trauma of the lower extremities and may accompany sexually transmitted diseases such as lymphogranuloma venereum, primary syphilis, genital herpes, or chancroid. These nodes may also be involved by lymphomas and metastatic cancer from primary lesions of the rectum, genitalia, or lower extremities (melanoma).

The size and texture of the lymph node(s) and the presence of pain are useful parameters in evaluating a patient with lymphadenopathy. Nodes <1.0 cm^2 in area (1.0 cm × 1.0 cm or less) are almost always secondary to benign, nonspecific reactive causes. In one retrospective analysis of younger patients (9–25 years) who had a lymph node biopsy, a maximum diameter of >2 cm served as one discriminant for predicting that the biopsy would reveal malignant or granulomatous disease. Another study showed that a lymph node size of 2.25 cm^2 (1.5 cm × 1.5 cm) was the best size limit for distinguishing malignant or granulomatous lymphadenopathy from other causes of lymphadenopathy. Patients with node(s) ≤1.0 cm^2 should be observed after excluding infectious mononucleosis and/or toxoplasmosis unless there are symptoms and signs of an underlying systemic illness.

The texture of lymph nodes may be described as soft, firm, rubbery, hard, discrete, matted, tender, movable, or fixed. Tenderness is found when the capsule is stretched during rapid enlargement, usually secondary to an inflammatory process. Some malignant diseases such as acute leukemia may produce rapid enlargement and pain in the nodes. Nodes involved by lymphoma tend to be large, discrete, symmetric, rubbery, firm, mobile, and nontender. Nodes containing metastatic cancer are often hard, nontender, and nonmovable because of fixation to surrounding tissues. The coexistence of splenomegaly in the patient with lymphadenopathy implies a systemic illness such as infectious mononucleosis, lymphoma, acute or chronic leukemia, SLE, sarcoidosis, toxoplasmosis, cat-scratch disease, or other less common hematologic disorders. The patient's story should provide helpful clues about the underlying systemic illness.

Nonsuperficial presentations (thoracic or abdominal) of adenopathy are usually detected as the result of a symptom-directed diagnostic workup. Thoracic adenopathy may be detected by routine chest radiography or during the workup for superficial adenopathy. It may also be found because the patient complains of a cough or wheezing from airway compression; hoarseness from recurrent laryngeal nerve involvement; dysphagia from esophageal compression; or swelling of the neck, face, or arms secondary to compression of the superior vena cava or subclavian vein. The differential diagnosis of mediastinal and hilar adenopathy includes primary lung disorders and systemic illnesses that characteristically involve mediastinal or hilar nodes. In the young, mediastinal adenopathy is associated with infectious mononucleosis and sarcoidosis. In endemic regions, histoplasmosis can cause unilateral paratracheal lymph node involvement that mimics lymphoma. Tuberculosis can also cause unilateral adenopathy. In older patients, the differential diagnosis includes primary lung cancer (especially among smokers), lymphomas, metastatic carcinoma (usually lung), tuberculosis, fungal infection, and sarcoidosis.

Enlarged intraabdominal or retroperitoneal nodes are usually malignant. Although tuberculosis may present as mesenteric lymphadenitis, these masses usually contain lymphomas or, in young men, germ cell tumors.

LABORATORY INVESTIGATION

The laboratory investigation of patients with lymphadenopathy must be tailored to elucidate the etiology suspected from the patient's history and physical findings. One study from a family practice clinic evaluated 249 younger patients with "enlarged lymph nodes, not infected" or "lymphadenitis." No laboratory studies were obtained in 51%. When studies were performed, the most common were a complete blood count (CBC) (33%), throat culture (16%), chest x-ray (12%), or monospot test (10%). Only eight patients (3%) had a node biopsy, and half of those were normal or reactive. The CBC can provide useful data for the diagnosis of acute or chronic leukemias, EBV or CMV mononucleosis, lymphoma with a leukemic component, pyogenic infections, or immune cytopenias in illnesses such as SLE. Serologic studies may demonstrate antibodies specific to components of EBV, CMV, HIV, and other viruses; *Toxoplasma gondii*; *Brucella*; etc. If SLE is suspected, antinuclear and anti-DNA antibody studies are warranted.

The chest x-ray is usually negative, but the presence of a pulmonary infiltrate or mediastinal lymphadenopathy would suggest tuberculosis, histoplasmosis, sarcoidosis, lymphoma, primary lung cancer, or metastatic cancer and demands further investigation.

A variety of imaging techniques (CT, MRI, ultrasound, color Doppler ultrasonography) have been employed to differentiate benign from malignant lymph nodes, especially in patients with head and neck cancer. CT and MRI are comparably accurate (65–90%) in the diagnosis of metastases to cervical lymph nodes. Ultrasonography has been used to determine the long (L) axis, short (S) axis, and a ratio of long to short axis in cervical nodes. An L/S ratio of <2.0 has a sensitivity and a specificity of 95% for distinguishing benign and malignant nodes in patients with head and neck cancer. This ratio has greater specificity and sensitivity than palpation or measurement of either the long or the short axis alone.

The indications for lymph node biopsy are imprecise, yet it is a valuable diagnostic tool. The decision to biopsy may be made early in a patient's evaluation or delayed for up to two weeks. Prompt biopsy should occur if the patient's history and physical findings suggest a malignancy; examples include a solitary, hard, nontender cervical node in an older patient who is a chronic user of tobacco; supraclavicular adenopathy; and solitary or generalized adenopathy that is firm, movable, and suggestive of lymphoma. If a primary

head and neck cancer is suspected as the basis of a solitary, hard cervical node, then a careful ENT examination should be performed. Any mucosal lesion that is suspicious for a primary neoplastic process should be biopsied first. If no mucosal lesion is detected, an excisional biopsy of the largest node should be performed. Fine-needle aspiration should not be performed as the first diagnostic procedure. Most diagnoses require more tissue than such aspiration can provide, and it often delays a definitive diagnosis. Fine-needle aspiration should be reserved for thyroid nodules and for confirmation of relapse in patients whose primary diagnosis is known. If the primary physician is uncertain about whether to proceed to biopsy, consultation with a hematologist or medical oncologist should be helpful. In primary care practices, <5% of lymphadenopathy patients will require a biopsy. That percentage will be considerably larger in referral practices, i.e., hematology, oncology, or ENT.

Two groups have reported algorithms that they claim will identify more precisely those lymphadenopathy patients who should have a biopsy. Both reports were retrospective analyses in referral practices. The first study involved patients 9–25 years of age who had a node biopsy performed. Three variables were identified that predicted those young patients with peripheral lymphadenopathy who should undergo biopsy; lymph node size >2 cm in diameter and abnormal chest x-ray had positive predictive values, whereas recent ENT symptoms had negative predictive values. The second study evaluated 220 lymphadenopathy patients in a hematology unit and identified five variables (lymph node size, location [supraclavicular or nonsupraclavicular], age [>40 years or <40 years], texture [nonhard or hard], and tenderness) that were used in a mathematical model to identify those patients requiring a biopsy. Positive predictive value was found for age >40 years, supraclavicular location, node size >2.25 cm^2, hard texture, and lack of pain or tenderness. Negative predictive value was evident for age <40 years, node size <1.0 cm^2, nonhard texture, and tender or painful nodes. Ninety-one percent of those who required biopsy were correctly classified by this model. Because both of these studies were retrospective analyses and one was limited to young patients, it is not known how useful these models would be if applied prospectively in a primary care setting.

Most lymphadenopathy patients do not require a biopsy, and at least half require no laboratory studies. If the patient's history and physical findings point to a benign cause for lymphadenopathy, careful follow-up at a 2- to 4-week interval can be employed. The patient should be instructed to return for reevaluation if there is an increase in the size of the nodels). Antibiotics are not indicated for lymphadenopathy unless strong evidence of a bacterial infection is present. Glucocorticoids should not be used to treat lymphadenopathy because their lympholytic effect obscures some diagnoses (lymphoma, leukemia, Castleman's disease) and they contribute to delayed healing or activation of underlying infections. An exception to this statement is the life-threatening pharyngeal obstruction by enlarged lymphoid tissue in Waldeyer's ring that is occasionally seen in infectious mononucleosis.

SPLENOMEGALY

STRUCTURE AND FUNCTION OF THE SPLEEN

The spleen is a reticuloendothelial organ that has its embryologic origin in the dorsal mesogastrium at about five weeks' gestation. It arises in a series of hillocks, migrates to its normal adult location in the left upper quadrant (LUQ), and is attached to the stomach via the gastrolienal ligament and to the kidney via the lienorenal ligament. When the hillocks fail to unify into a single tissue mass, accessory spleens may develop in around 20% of persons. The function of the spleen has been elusive. Galen believed it was the source of "black bile" or melancholia, and the word *hypochondria* (literally, beneath the ribs) and the idiom "to vent one's spleen" attest to the beliefs that the spleen had an important influence on the psyche and emotions. In humans, its normal physiologic roles seem to be the following:

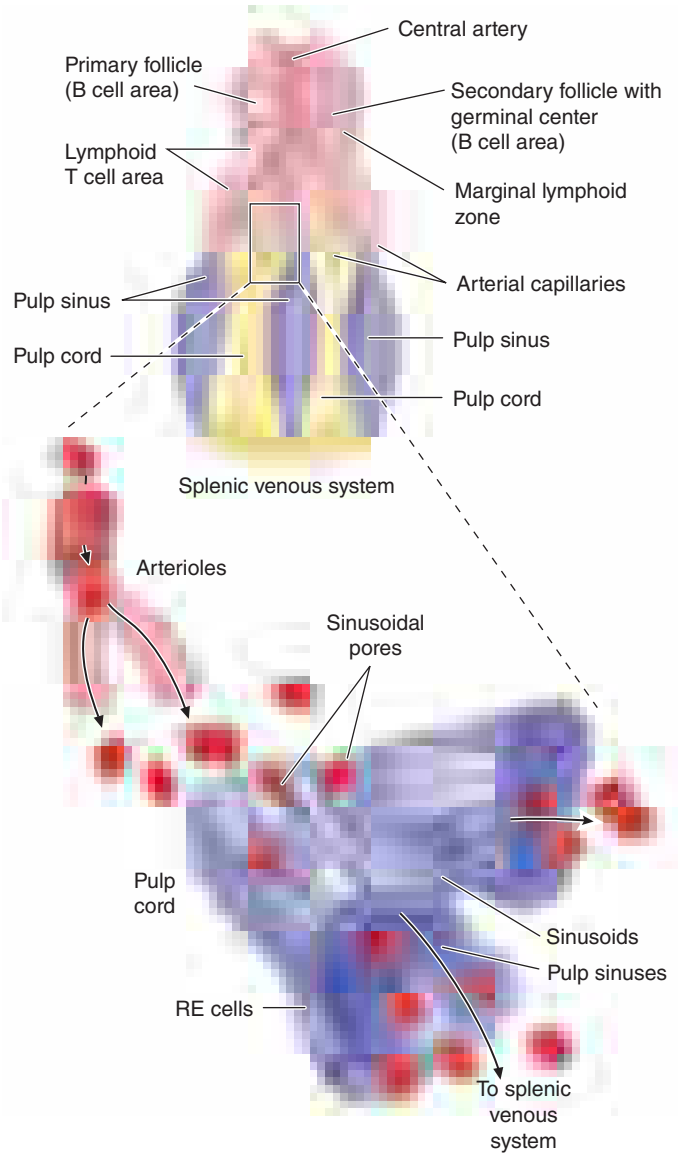

FIGURE 62-1 Schematic spleen structure. The spleen comprises many units of red and white pulp centered around small branches of the splenic artery, called *central arteries*. White pulp is lymphoid in nature and contains B-cell follicles, a marginal zone around the follicles, and T-cell–rich areas sheathing arterioles. The red pulp areas include pulp sinuses and pulp cords. The cords are dead ends. In order to regain access to the circulation, red blood cells must traverse tiny openings in the sinusoidal lining. Stiff, damaged, or old red cells cannot enter the sinuses. RE, reticuloendthelial. *(Bottom portion of figure from RS Hillman, KA Ault: Hematology in Clinical Practice, 4th ed. New York, McGraw-Hill, 2005.)*

1. Maintenance of quality control over erythrocytes in the red pulp by removal of senescent and defective red blood cells. The spleen accomplishes this function through a unique organization of its parenchyma and vasculature **(Fig. 62-1)**.
2. Synthesis of antibodies in the white pulp.
3. The removal of antibody-coated bacteria and antibody-coated blood cells from the circulation.

An increase in these normal functions may result in splenomegaly.

The spleen is composed of *red pulp* and *white pulp*, which are Malpighi's terms for the red blood–filled sinuses and reticuloendothelial cell–lined cords and the white lymphoid follicles arrayed within the red pulp matrix. The spleen is in the portal circulation. The reason for this is unknown but may relate to the fact that lower blood pressure allows less rapid flow and minimizes damage to normal erythrocytes. Blood flows into the spleen at a rate of about 150 mL/min through the splenic artery, which ultimately ramifies into central arterioles. Some blood goes from the arterioles to capillaries and then to splenic veins

and out of the spleen, but the majority of blood from central arterioles flows into the macrophage-lined sinuses and cords. The blood entering the sinuses reenters the circulation through the splenic venules, but the blood entering the cords is subjected to an inspection of sorts. To return to the circulation, the blood cells in the cords must squeeze through slits in the cord lining to enter the sinuses that lead to the venules. Old and damaged erythrocytes are less deformable and are retained in the cords, where they are destroyed and their components recycled. Red cell–inclusion bodies such as parasites **(Chaps. 219, 220, and A6)**, nuclear residua (Howell-Jolly bodies, **see Fig. 59-6**), or denatured hemoglobin (Heinz bodies) are pinched off in the process of passing through the slits, a process called *pitting*. The culling of dead and damaged cells and the pitting of cells with inclusions appear to occur without significant delay because the blood transit time through the spleen is only slightly slower than in other organs.

The spleen is also capable of assisting the host in adapting to its hostile environment. It has at least three adaptive functions: (1) clearance of bacteria and particulates from the blood, (2) the generation of immune responses to certain pathogens, and (3) the generation of cellular components of the blood under circumstances in which the marrow is unable to meet the needs (i.e., extramedullary hematopoiesis). The latter adaptation is a recapitulation of the blood-forming function the spleen plays during gestation. In some animals, the spleen also serves a role in the vascular adaptation to stress because it stores red blood cells (often hemoconcentrated to higher hematocrits than normal) under normal circumstances and contracts under the influence of β-adrenergic stimulation to provide the animal with an autotransfusion and improved oxygen-carrying capacity. However, the normal human spleen does not sequester or store red blood cells and does not contract in response to sympathetic stimuli. The normal human spleen contains approximately one-third of the total body platelets and a significant number of marginated neutrophils. These sequestered cells are available when needed to respond to bleeding or infection.

APPROACH TO THE PATIENT

Splenomegaly

CLINICAL ASSESSMENT

The most common *symptoms* produced by diseases involving the spleen are pain and a heavy sensation in the LUQ. Massive splenomegaly may cause early satiety. Pain may result from acute swelling of the spleen with stretching of the capsule, infarction, or inflammation of the capsule. For many years, it was believed that splenic infarction was clinically silent, which, at times, is true. However, Soma Weiss, in his classic 1942 report of the self-observations by a Harvard medical student on the clinical course of subacute bacterial endocarditis, documented that severe LUQ and pleuritic chest pain may accompany thromboembolic occlusion of splenic blood flow. Vascular occlusion, with infarction and pain, is commonly seen in children with sickle cell crises. Rupture of the spleen, from either trauma or infiltrative disease that breaks the capsule, may result in intraperitoneal bleeding, shock, and death. The rupture itself may be painless.

A palpable spleen is the major *physical sign* produced by diseases affecting the spleen and suggests enlargement of the organ. The normal spleen weighs <250 g, decreases in size with age, normally lies entirely within the rib cage, has a maximum cephalocaudad diameter of 13 cm by ultrasonography or maximum length of 12 cm and/or width of 7 cm by radionuclide scan, and is usually not palpable. However, a palpable spleen was found in 3% of 2200 asymptomatic, male, freshman college students. Follow-up at 3 years revealed that 30% of those students still had a palpable spleen without any increase in disease prevalence. Ten-year follow-up found no evidence for lymphoid malignancies. Furthermore, in some tropical countries (e.g., New Guinea), the incidence of splenomegaly may reach 60%. Thus, the presence of a palpable spleen does not always equate with presence of disease. Even when disease is present, splenomegaly may not reflect the primary disease but rather a reaction to it. For example, in patients with Hodgkin's disease, only two-thirds of the palpable spleens show involvement by the cancer.

Physical examination of the spleen uses primarily the techniques of palpation and percussion. Inspection may reveal fullness in the LUQ that descends on inspiration, a finding associated with a massively enlarged spleen. Auscultation may reveal a venous hum or friction rub.

Palpation can be accomplished by bimanual palpation, ballotment, and palpation from above (Middleton maneuver). For bimanual palpation, which is at least as reliable as the other techniques, the patient is supine with flexed knees. The examiner's left hand is placed on the lower rib cage and pulls the skin toward the costal margin, allowing the fingertips of the right hand to feel the tip of the spleen as it descends while the patient inspires slowly, smoothly, and deeply. Palpation is begun with the right hand in the left lower quadrant with gradual movement toward the left costal margin, thereby identifying the lower edge of a massively enlarged spleen. When the spleen tip is felt, the finding is recorded as centimeters below the left costal margin at some arbitrary point, i.e., 10–15 cm, from the midpoint of the umbilicus or the xiphisternal junction. This allows other examiners to compare findings or the initial examiner to determine changes in size over time. Bimanual palpation in the right lateral decubitus position adds nothing to the supine examination.

Percussion for splenic dullness is accomplished with any of three techniques described by Nixon, Castell, or Barkun:

1. *Nixon's method*: The patient is placed on the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in the posterior axillary line and proceeds diagonally along a perpendicular line toward the lower midanterior costal margin. The upper border of dullness is normally 6–8 cm above the costal margin. Dullness >8 cm in an adult is presumed to indicate splenic enlargement.
2. *Castell's method*: With the patient supine, percussion in the lowest intercostal space in the anterior axillary line (8th or 9th) produces a resonant note if the spleen is normal in size. This is true during expiration or full inspiration. A dull percussion note on full inspiration suggests splenomegaly.
3. *Percussion of Traube's semilunar space*: The borders of Traube's space are the sixth rib superiorly, the left midaxillary line laterally, and the left costal margin inferiorly. The patient is supine with the left arm slightly abducted. During normal breathing, this space is percussed from medial to lateral margins, yielding a normal resonant sound. A dull percussion note suggests splenomegaly.

Studies comparing methods of percussion and palpation with a standard of ultrasonography or scintigraphy have revealed sensitivity of 56–71% for palpation and 59–82% for percussion. Reproducibility among examiners is better for palpation than percussion. Both techniques are less reliable in obese patients or patients who have just eaten. Thus, the physical examination techniques of palpation and percussion are imprecise at best. It has been suggested that the examiner perform percussion first and, if positive, proceed to palpation; if the spleen is palpable, then one can be reasonably confident that splenomegaly exists. However, not all LUQ masses are enlarged spleens; gastric or colon tumors and pancreatic or renal cysts or tumors can mimic splenomegaly.

The presence of an enlarged spleen can be more precisely determined, if necessary, by liver-spleen radionuclide scan, CT, MRI, or ultrasonography. The latter technique is the current procedure of choice for routine assessment of spleen size (normal = a maximum cephalocaudad diameter of 13 cm) because it has high sensitivity and specificity and is safe, noninvasive, quick, mobile, and less costly. Nuclear medicine scans are accurate, sensitive, and reliable

but are costly, require greater time to generate data, and use immobile equipment. They have the advantage of demonstrating accessory splenic tissue. CT and MRI provide accurate determination of spleen size, but the equipment is immobile and the procedures are expensive. MRI appears to offer no advantage over CT. Changes in spleen structure such as mass lesions, infarcts, inhomogeneous infiltrates, and cysts are more readily assessed by CT, MRI, or ultrasonography. None of these techniques is very reliable in the detection of patchy infiltration (e.g., Hodgkin's disease).

DIFFERENTIAL DIAGNOSIS

Many of the diseases associated with splenomegaly are listed in Table 62-2. They are grouped according to the presumed basic mechanisms responsible for organ enlargement:

1. Hyperplasia or hypertrophy related to a particular splenic function such as reticuloendothelial hyperplasia (work hypertrophy) in diseases such as hereditary spherocytosis or thalassemia syndromes that require removal of large numbers of defective red blood cells; immune hyperplasia in response to systemic infection (infectious mononucleosis, subacute bacterial endocarditis) or to immunologic diseases (immune thrombocytopenia, SLE, Felty's syndrome).
2. Passive congestion due to decreased blood flow from the spleen in conditions that produce portal hypertension (cirrhosis, Budd-Chiari syndrome, congestive heart failure).
3. Infiltrative diseases of the spleen (lymphomas, metastatic cancer, amyloidosis, Gaucher's disease, myeloproliferative disorders with extramedullary hematopoiesis).

The differential diagnostic possibilities are much fewer when the spleen is "massively enlarged," palpable >8 cm below the left costal margin or its drained weight is ≥1000 g (Table 62-3). The vast majority of such patients will have non-Hodgkin's lymphoma, chronic

TABLE 62-2 Diseases Associated with Splenomegaly Grouped by Pathogenic Mechanism

Enlargement Due to Increased Demand for Splenic Function	
Reticuloendothelial system hyperplasia (for removal of defective erythrocytes)	Malaria
Spherocytosis	Leishmaniasis
Early sickle cell anemia	Trypanosomiasis
Ovalocytosis	Ehrlichiosis
Thalassemia major	Disordered immunoregulation
Hemoglobinopathies	Rheumatoid arthritis (Felty's syndrome)
Paroxysmal nocturnal hemoglobinuria	Systemic lupus erythematosus
Pernicious anemia	Collagen vascular diseases
Immune hyperplasia	Serum sickness
Response to infection (viral, bacterial, fungal, parasitic)	Immune hemolytic anemias
Infectious mononucleosis	Immune thrombocytopenias
AIDS	Immune neutropenias
Viral hepatitis	Drug reactions
Cytomegalovirus	Angioimmunoblastic lymphadenopathy
Subacute bacterial endocarditis	Sarcoidosis
Bacterial septicemia	Thyrotoxicosis (benign lymphoid hypertrophy)
Congenital syphilis	Interleukin 2 therapy
Splenic abscess	Extramedullary hematopoiesis
Tuberculosis	Myelofibrosis
Histoplasmosis	Marrow damage by toxins, radiation, strontium
	Marrow infiltration by tumors, leukemias, Gaucher's disease
Enlargement Due to Abnormal Splenic or Portal Blood Flow	
Cirrhosis	Splenic artery aneurysm
Hepatic vein obstruction	Hepatic schistosomiasis
Portal vein obstruction, intrahepatic or extrahepatic	Congestive heart failure
Cavernous transformation of the portal vein	Hepatic echinococcosis
Splenic vein obstruction	Portal hypertension (any cause including the above): "Banti's disease"
Infiltration of the Spleen	
Intracellular or extracellular depositions	Hodgkin's disease
Amyloidosis	Myeloproliferative syndromes (e.g., polycythemia vera, essential thrombocytosis)
Gaucher's disease	Angiosarcomas
Niemann-Pick disease	Metastatic tumors (melanoma is most common)
Tangier disease	Eosinophilic granuloma
Hurler's syndrome and other mucopolysaccharidoses	Histiocytosis X
Hyperlipidemias	Hamartomas
Benign and malignant cellular infiltrations	Hemangiomas, fibromas, lymphangiomas
Leukemias (acute, chronic, lymphoid, myeloid, monocytic)	Splenic cysts
Lymphomas	
Unknown Etiology	
Idiopathic splenomegaly	Iron-deficiency anemia
Berylliosis	

TABLE 62-3 Diseases Associated with Massive Splenomegaly*

Chronic myeloid leukemia	Gaucher's disease
Lymphomas	Chronic lymphocytic leukemia
Hairy cell leukemia	Sarcoidosis
Myelofibrosis with myeloid metaplasia	Autoimmune hemolytic anemia
Polycythemia vera	Diffuse splenic hemangiomatosis

*The spleen extends >8 cm below left costal margin and/or weighs >1000 g.

lymphocytic leukemia, hairy cell leukemia, chronic myeloid leukemia, myelofibrosis with myeloid metaplasia, or polycythemia vera.

LABORATORY ASSESSMENT

The major laboratory abnormalities accompanying splenomegaly are determined by the underlying systemic illness. Erythrocyte counts may be normal, decreased (thalassemia major syndromes, SLE, cirrhosis with portal hypertension), or increased (polycythemia vera). Granulocyte counts may be normal, decreased (Felty's syndrome, congestive splenomegaly, leukemias), or increased (infections or inflammatory disease, myeloproliferative disorders). Similarly, the platelet count may be normal, decreased when there is enhanced sequestration or destruction of platelets in an enlarged spleen (congestive splenomegaly, Gaucher's disease, immune thrombocytopenia), or increased in the myeloproliferative disorders such as polycythemia vera.

The CBC may reveal cytopenia of one or more blood cell types, which should suggest *hypersplenism*. This condition is characterized by splenomegaly, cytopenia(s), normal or hyperplastic bone marrow, and a response to splenectomy. The latter characteristic is less precise because reversal of cytopenia, particularly granulocytopenia, is sometimes not sustained after splenectomy. The cytopenias result from increased destruction of the cellular elements secondary to reduced flow of blood through enlarged and congested cords (congestive splenomegaly) or to immune-mediated mechanisms. In hypersplenism, various cell types usually have normal morphology on the peripheral blood smear, although the red cells may be spherocytic due to loss of surface area during their longer transit through the enlarged spleen. The increased marrow production of red cells should be reflected as an increased reticulocyte production index, although the value may be less than expected due to increased sequestration of reticulocytes in the spleen.

The need for additional laboratory studies is dictated by the differential diagnosis of the underlying illness of which splenomegaly is a manifestation.

SPLENECTOMY

Splenectomy is infrequently performed for diagnostic purposes, especially in the absence of clinical illness or other diagnostic tests that suggest underlying disease. More often, splenectomy is performed for symptom control in patients with massive splenomegaly, for disease control in patients with traumatic splenic rupture, or for correction of cytopenias in patients with hypersplenism or immune-mediated destruction of one or more cellular blood elements. Splenectomy is necessary for staging of patients with Hodgkin's disease only in those with clinical stage I or II disease in whom radiation therapy alone is contemplated as the treatment. Noninvasive staging of the spleen in Hodgkin's disease is not a sufficiently reliable basis for treatment decisions because one-third of normal-sized spleens will be involved with Hodgkin's disease and one-third of enlarged spleens will be tumor-free. The widespread use of systemic therapy to test all stages of Hodgkin's disease has made staging laparotomy with splenectomy unnecessary. Although splenectomy in chronic myeloid leukemia (CML) does not affect the natural history of disease, removal of the massive spleen usually makes patients significantly more comfortable and simplifies their management by significantly reducing transfusion requirements. The improvements in therapy of CML have reduced the need for splenectomy for symptom control. Splenectomy is an effective secondary or tertiary treatment for two chronic B cell leukemias, hairy cell leukemia and prolymphocytic leukemia, and for the very rare splenic mantle cell or marginal zone lymphoma. Splenectomy in these diseases may be associated with significant tumor regression in bone marrow and other sites of disease. Similar regressions of systemic disease have been noted after splenic irradiation in some types of lymphoid tumors, especially chronic lymphocytic leukemia and prolymphocytic leukemia. This has been termed the *abscopal effect*. Such systemic tumor responses to local therapy directed at the spleen suggest that some hormone or growth factor produced by the spleen may affect tumor cell proliferation, but this conjecture is not yet substantiated. A common therapeutic indication for splenectomy is traumatic or iatrogenic splenic rupture. In a fraction of patients with splenic rupture, peritoneal seeding of splenic fragments can lead to *splenosis*—the presence of multiple rests of spleen tissue not connected to the portal circulation. This ectopic spleen tissue may cause pain or gastrointestinal obstruction, as in endometriosis. A large number of hematologic, immunologic, and congestive causes of splenomegaly can lead to destruction of one or more cellular blood elements. In the majority of such cases, splenectomy can correct the cytopenias, particularly anemia and thrombocytopenia. In a large series of patients seen in two tertiary care centers, the indication for splenectomy was diagnostic in 10% of patients, therapeutic in 44%, staging for Hodgkin's disease in 20%, and incidental to another procedure in 26%. Perhaps the only contraindication to splenectomy is the presence of marrow failure, in which the enlarged spleen is the only source of hematopoietic tissue.

Often the splenectomy is done by laparoscopy, which is associated with shorter hospital stays and faster recovery than the open procedure; however, concern has emerged that the laparoscopic approach is associated with a higher risk of postoperative portal venous system thrombosis and Budd-Chiari syndrome.

The absence of the spleen has minimal long-term effects on the hematologic profile. In the immediate postsplenectomy period, leukocytosis (up to 25,000/μL) and thrombocytosis (up to 1×10^6/μL) may develop, but within 2–3 weeks, blood cell counts and survival of each cell lineage are usually normal. The chronic manifestations of splenectomy are marked variation in size and shape of erythrocytes (anisocytosis, poikilocytosis) and the presence of Howell-Jolly bodies (nuclear remnants), Heinz bodies (denatured hemoglobin), basophilic stippling, and an occasional nucleated erythrocyte in the peripheral blood. When such erythrocyte abnormalities appear in a patient whose spleen has not been removed, one should suspect splenic infiltration by tumor that has interfered with its normal culling and pitting function.

The most serious consequence of splenectomy is increased susceptibility to bacterial infections, particularly those with capsules such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and some gram-negative enteric organisms. Patients aged <20 years are particularly susceptible to overwhelming sepsis with *S. pneumoniae*, and the overall actuarial risk of sepsis in patients who have had their spleens removed is about 7% in 10 years. The case-fatality rate for pneumococcal sepsis in splenectomized patients is 50–80%. About 25% of patients without spleens will develop a serious infection at some time in their life. The frequency is highest within the first three years after splenectomy. About 15% of the infections are polymicrobial, and lung, skin, and blood are the most common sites. No increased risk of viral infection has been noted in patients who have no spleen. The susceptibility to bacterial infections relates to the inability to remove opsonized bacteria from the bloodstream and a defect in making antibodies to T cell–independent antigens such as the polysaccharide components of bacterial capsules. Pneumococcal vaccine should be administered to all patients 2 weeks before elective splenectomy. The Advisory Committee on Immunization Practices recommends that these patients receive repeat vaccination 5 years post-splenectomy. Efficacy has not been proven for this group, and the recommendation discounts the possibility that administration of the vaccine may actually lower the titer of specific pneumococcal antibodies. A more effective pneumococcal conjugate vaccine that involves T cells in the response is now available (Prevenar, 7-valent). The vaccine to *Neisseria meningitidis* should also be given to patients in whom elective splenectomy is planned. Although

efficacy data for *Haemophilus influenzae* type b vaccine are not available for older children or adults, it may be given to patients who have had a splenectomy.

Splenectomized patients should be educated to consider any unexplained fever as a medical emergency. Prompt medical attention with evaluation and treatment of suspected bacteremia may be lifesaving. Routine chemoprophylaxis with oral penicillin can result in the emergence of drug-resistant strains and is not recommended.

In addition to an increased susceptibility to bacterial infections, splenectomized patients are also more susceptible to the parasitic disease babesiosis. The splenectomized patient should avoid areas where the parasite *Babesia* is endemic (e.g., Cape Cod, MA).

Surgical removal of the spleen is an obvious cause of hyposplenism. Patients with sickle cell disease often suffer from autosplenectomy as a result of splenic destruction by the numerous infarcts associated with sickle cell crises during childhood. Indeed, the presence of a palpable spleen in a patient with sickle cell disease after age 5 suggests a coexisting hemoglobinopathy, e.g., thalassemia or hemoglobin C. In addition, patients who receive splenic irradiation for a neoplastic or autoimmune disease are also functionally hyposplenic. The term *hyposplenism* is preferred to *asplenism* in referring to the physiologic consequences of splenectomy because asplenia is a rare, specific, and fatal congenital abnormality in which there is a failure of the left side of the coelomic cavity (which includes the splenic anlagen) to develop normally. Infants with asplenia have no spleens, but that is the least of their problems. The right side of the developing embryo is duplicated on the left so there is liver where the spleen should be, there are two right lungs, and the heart comprises two right atria and two right ventricles.

Acknowledgment

Patrick H. Henry, MD, friend and mentor now deceased, contributed significantly to the chapter in past editions and much of his work remains in this chapter.

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63 Principles of Clinical Pharmacology

Dan M. Roden

Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among healthcare providers and the lay community that the outcome of drug therapy varies widely among individuals. While this variability has been perceived as an unpredictable, and therefore inevitable, accompaniment of drug therapy, this is not the case. The goal of this chapter is to describe the principles of clinical pharmacology that can be used for the safe and optimal use of available and new drugs.

Drugs interact with specific target molecules to produce their beneficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two components, both of which contribute to variability in drug actions. The first component comprises the processes that determine drug delivery to, and removal from, molecular targets. The resulting description of the relationship between drug concentration and time is termed *pharmacokinetics*. The second component of variability in drug action comprises the processes that determine variability in drug actions despite equivalent drug delivery to effector drug sites. This description of the relationship between drug concentration and effect is termed *pharmacodynamics*. As discussed further below, pharmacodynamic variability can arise as a result of variability in function of the target molecule itself or of variability in the broad biologic context in which the drug-target interaction occurs to achieve drug effects.

Two important goals of clinical pharmacology are (1) to provide a description of conditions under which drug actions vary among human subjects; and (2) to determine mechanisms underlying this variability, with the goal of improving therapy with available drugs as well as pointing to mechanisms whose targeting by new drugs may be effective in the treatment of human disease. The drug development process is briefly described at the end of this chapter.

The first steps in the discipline of clinical pharmacology were empirical descriptions of the influence of disease on drug actions and of individuals or families with unusual sensitivities to adverse drug effects. These important descriptive findings are now being replaced by an understanding of the molecular mechanisms underlying variability in drug actions. Importantly, it is often the personal interaction of the patient with the physician or other health care provider that first identifies unusual variability in drug actions; maintained alertness to unusual drug responses continues to be a key component of improving drug safety.

One useful unifying framework is to consider that the effects of disease, drug coadministration, or familial factors in modulating drug action reflect variability in expression or function of specific genes whose products determine pharmacokinetics and pharmacodynamics. This idea forms the basis for pharmacogenomic science; a few examples are cited in this chapter, and further details are addressed in Chap. 64.

GLOBAL CONSIDERATIONS

It is true across all cultures and diseases that factors such as compliance, genetic variants affecting pharmacokinetics, or pharmacodynamics (which themselves vary by ancestry), and drug interactions contribute to drug responses. Cost issues or cultural factors may determine the likelihood that specific drugs, drug combinations, or over-the-counter (OTC) remedies are prescribed. The broad principles of clinical pharmacology enunciated here can be used to analyze the mechanisms underlying successful or unsuccessful therapy with any drug.

INDICATIONS FOR DRUG THERAPY: RISK VERSUS BENEFIT

It is self-evident that the benefits of drug therapy should outweigh the risks. Benefits fall into two broad categories: those designed to alleviate a symptom and those designed to prolong useful life. An increasing emphasis on the principles of evidence-based medicine and techniques such as large clinical trials and meta-analyses has defined benefits of drug therapy in broad patient populations. However, establishing the balance between risk and benefit is not always simple. An increasing body of evidence supports the idea, with which practitioners are very familiar, that individual patients may display responses that are not expected from large population studies and often have comorbidities that typically exclude them from large clinical trials. In addition, therapies that provide symptomatic benefits but shorten life may be entertained in patients with serious and highly symptomatic diseases such as heart failure or cancer. These considerations illustrate the continuing, highly personal nature of the relationship between the prescriber and the patient.

Adverse Effects Some adverse effects are so common and so readily associated with drug therapy that they are identified very early during clinical use of a drug. By contrast, serious adverse drug reactions may be sufficiently uncommon that they escape detection for many years after a drug begins to be widely used. The issue of how to identify rare but serious adverse effects (that can profoundly affect the benefit-risk perception in an individual patient) has not been satisfactorily resolved. Potential approaches range from an increased understanding of the molecular and genetic basis of variability in drug actions to expanded post-marketing surveillance mechanisms. None of these have been completely effective, so practitioners must be continuously vigilant to the possibility that unusual symptoms may be related to specific drugs, or combinations of drugs, that their patients receive.

Therapeutic Index Beneficial and adverse reactions to drug therapy can be described by a series of dose-response relations (Fig. 63-1). Well-tolerated drugs demonstrate a wide margin, termed the *therapeutic ratio*, *therapeutic index*, or *therapeutic window*, between the doses required to produce a therapeutic effect and those producing toxicity. In cases where there is a similar relationship between plasma drug concentration and effects, monitoring plasma concentrations can be a highly effective aid in managing drug therapy by enabling

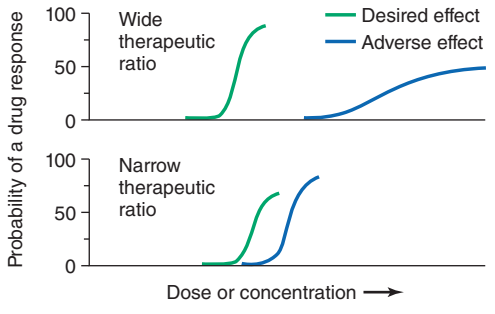

FIGURE 63-1 The concept of a therapeutic ratio. Each panel illustrates the relationship between increasing dose and cumulative probability of a desired or adverse drug effect. ***Top.*** A drug with a wide therapeutic ratio, that is, a wide separation of the two curves. ***Bottom.*** A drug with a narrow therapeutic ratio; here, the likelihood of adverse effects at therapeutic doses is increased because the curves are not well separated. Further, a steep dose-response curve for adverse effects is especially undesirable, as it implies that even small dosage increments may sharply increase the likelihood of toxicity. When there is a definable relationship between drug concentration (usually measured in plasma) and desirable and adverse effect curves, concentration may be substituted on the abscissa. Note that not all patients necessarily demonstrate a therapeutic response (or adverse effect) at any dose, and that some effects (notably some adverse effects) may occur in a dose-independent fashion.

concentrations to be maintained above the minimum required to produce an effect and below the concentration range likely to produce toxicity. Such monitoring has been widely used to guide therapy with specific agents, such as certain antiarrhythmics, anticonvulsants, and antibiotics. Many of the principles in clinical pharmacology and examples outlined below, which can be applied broadly to therapeutics, have been developed in these arenas.

PRINCIPLES OF PHARMACOKINETICS

The processes of absorption, distribution, metabolism, and excretion—collectively termed *drug disposition*—determine the concentration of drug delivered to target effector molecules.

ABSORPTION AND BIOAVAILABILITY

When a drug is administered orally, subcutaneously, intramuscularly, rectally, sublingually, or directly into desired sites of action, the amount of drug actually entering the systemic circulation may be less than with the intravenous route (Fig. 63-2*A*). The fraction of drug available to the systemic circulation by other routes is termed *bioavailability*. Bioavailability may be <100% for two main reasons: (1) absorption is reduced, or (2) the drug undergoes metabolism or elimination prior to entering the systemic circulation. Occasionally, the administered drug formulation is inconsistent or has degraded with time; for example, the anticoagulant dabigatran degrades rapidly (over weeks) once exposed to air, so the amount administered may be less than prescribed.

When a drug is administered by a non-intravenous route, the peak concentration occurs later and is lower than after the same dose given by rapid intravenous injection, reflecting absorption from the site of administration (Fig. 63-2). The extent of absorption may be reduced because a drug is incompletely released from its dosage form, undergoes destruction at its site of administration, or has physicochemical properties such as insolubility that prevent complete absorption from its site of administration. Slow absorption rates are deliberately designed into "slow-release" or "sustained-release" drug formulations in order to minimize variation in plasma concentrations during the interval between doses.

"First-Pass" Effect When a drug is administered orally, it must traverse the intestinal epithelium, the portal venous system, and the liver prior to entering the systemic circulation (Fig. 63-3). Once a drug enters the enterocyte, it may undergo metabolism, be transported into the portal vein, or be excreted back into the intestinal lumen. Both excretion into the intestinal lumen and metabolism decrease systemic bioavailability. Once a drug passes this enterocyte barrier, it may also be taken up into the hepatocyte, where bioavailability can be further limited by metabolism or excretion into the bile. This elimination in intestine and liver, which reduces the amount of drug delivered to the systemic circulation, is termed *presystemic elimination*, *presystemic extraction*, or *first-pass elimination*.

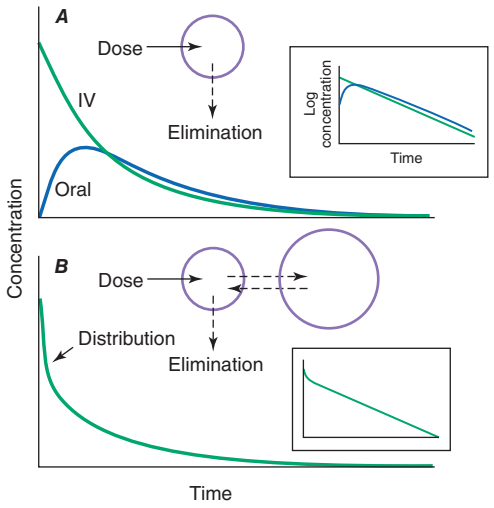

FIGURE 63-2 Idealized time-plasma concentration curves after a single dose of drug. *A.* The time course of drug concentration after an instantaneous IV bolus or an oral dose in the one-compartment model shown. The area under the time-concentration curve is clearly less with the oral drug than the IV, indicating incomplete bioavailability. Note that despite this incomplete bioavailability, concentration after the oral dose can be higher than after the IV dose at some time points. The inset shows that the decline of concentrations over time is linear on a log-linear plot, characteristic of first-order elimination, and that oral and IV drugs have the same elimination (parallel) time course. ***B.*** The decline of central compartment concentration when drug is distributed both to and from a peripheral compartment and eliminated from the central compartment. The rapid initial decline of concentration reflects not drug elimination but distribution.

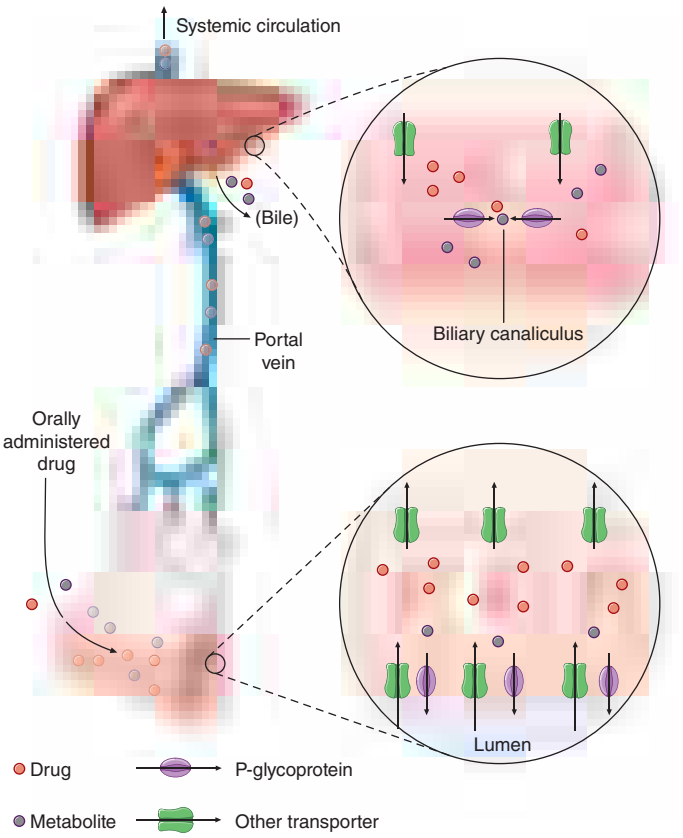

FIGURE 63-3 Mechanism of presystemic clearance. After drug enters the enterocyte, it can undergo metabolism, excretion into the intestinal lumen, or transport into the portal vein. Similarly, the hepatocyte may accomplish metabolism and biliary excretion prior to the entry of drug and metabolites to the systemic circulation. *(Adapted by permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003. Copyright 2003 with permission from Elsevier.)*

DRUG TRANSPORT

Drug movement across the membrane of any cell, including enterocytes and hepatocytes, is a combination of passive diffusion and active transport, mediated by specific drug uptake and efflux molecules. One widely studied drug transport molecule is the drug efflux pump P-glycoprotein, the product of the *ABCB1* (or *MDR1*) gene. P-glycoprotein is expressed on the apical aspect of the enterocyte and on the canalicular aspect of the hepatocyte (Fig. 63-3). In both locations, it serves as an efflux pump, limiting availability of drug to the systemic circulation. P-glycoprotein–mediated drug efflux from cerebral capillaries limits drug brain penetration and is an important component of the blood-brain barrier. Other transporters mediate uptake into cells of drugs and endogenous substrates such as vitamins or nutrients.

DRUG METABOLISM

Drug metabolism generates compounds that are usually more polar and, hence, more readily excreted than parent drug. Metabolism takes place predominantly in the liver but can occur at other sites such as kidney, intestinal epithelium, lung, and plasma. "Phase I" metabolism involves chemical modification, most often oxidation accomplished

TABLE 63-1 Molecular Pathways Mediating Drug Disposition

MOLECULE	SUBSTRATES[a]	INHIBITORS[a]
CYP3A	Calcium channel blockers	Amiodarone
	Antiarrhythmics (lidocaine, quinidine, mexiletine)	Ketoconazole, itraconazole
	HMG-CoA reductase inhibitors ("statins"; see text)	Erythromycin, clarithromycin
	Cyclosporine, tacrolimus	Ritonavir
	Indinavir, saquinavir, ritonavir	
CYP2D6[b]	Timolol, metoprolol, carvedilol	Quinidine (even at ultra-low doses)
	Propafenone, flecainide	Tricyclic antidepressants
	Tricyclic antidepressants	Fluoxetine, paroxetine
	Fluoxetine, paroxetine	
CYP2C9[b]	Warfarin	Amiodarone
	Phenytoin	Fluconazole
	Glipizide	Phenytoin
	Losartan	
CYP2C19[b]	Omeprazole	Omeprazole
	Mephenytoin	
	Clopidogrel	
CYP2B6[b]	Efavirenz	
Thiopurine S-methyltransferase[b]	6-Mercaptopurine, azathioprine	
N-acetyltransferase[b]	Isoniazid	
	Procainamide	
	Hydralazine	
	Some sulfonamides	
UGT1A1[b]	Irinotecan	
Pseudocholinesterase[b]	Succinylcholine	
P-glycoprotein	Digoxin	Quinidine
	HIV protease inhibitors	Amiodarone
	Many CYP3A substrates	Verapamil
		Cyclosporine
		Itraconazole
		Erythromycin
SLCO1B1[b]	Simvastatin and some other statins	

[a]Inhibitors affect the molecular pathway, and thus may affect substrate. [b]Clinically important genetic variants described; **see Chap. 64**.

Note: A listing of CYP substrates, inhibitors, and inducers is maintained at *http://medicine.iupui.edu/clinpharm/ddis/main-table*.

by members of the cytochrome P450 (CYP) monooxygenase superfamily. CYPs and other molecules that are especially important for drug metabolism are presented in **Table 63-1**, and each drug may be a substrate for one or more of these enzymes. "Phase II" metabolism involves conjugation of specific endogenous compounds to drugs or their metabolites. The enzymes that accomplish phase II reactions include glucuronyl-, acetyl-, sulfo-, and methyltransferases. Drug metabolites may exert important pharmacologic activity, as discussed further below.

Clinical Implications of Altered Bioavailability Some drugs undergo near-complete presystemic metabolism and thus cannot be administered orally. Nitroglycerin cannot be used orally because it is completely extracted prior to reaching the systemic circulation. The drug is, therefore, used by the sublingual, transdermal, or intravascular routes, which bypass presystemic metabolism.

Some drugs with very extensive presystemic metabolism can still be administered by the oral route, using much higher doses than those required intravenously. Thus, a typical intravenous dose of verapamil is 1–5 mg, compared to a usual single oral dose of 40–120 mg. Administration of low-dose aspirin can result in exposure of cyclooxygenase in platelets in the portal vein to the drug, but systemic sparing because of first-pass aspirin deacylation in the liver. This is an example of presystemic metabolism being exploited to therapeutic advantage.

HALF-LIFE

Most pharmacokinetic processes, such as elimination, are first-order; that is, the rate of the process depends on the amount of drug present. Elimination can occasionally be zero-order (fixed amount eliminated per unit time), and this can be clinically important (see "Principles of Dose Selection"). In the simplest pharmacokinetic model (Fig. 63-2*A*), a drug bolus (D) is administered instantaneously to a central compartment, from which drug elimination occurs as a first-order process. Occasionally, central and other compartments correspond to physiologic spaces (e.g., plasma volume), whereas in other cases they are simply mathematical functions used to describe drug disposition. The first-order nature of drug elimination leads directly to the relationship describing drug concentration (C) at any time (t) following the bolus:

$$C = \frac{D}{V_c} \bullet e^{(-0.69t/t_{1/2})}$$

where V_c is the volume of the compartment into which drug is delivered and $t_{1/2}$ is elimination half-life. As a consequence of this relationship, a plot of the logarithm of concentration versus time is a straight line (Fig. 63-2*A*, inset). *Half-life* is the time required for 50% of a first-order process to be completed. Thus, 50% of drug elimination is achieved after one drug-elimination half-life, 75% after two, 87.5% after three, etc. In practice, first-order processes such as elimination are near-complete after four–five half-lives.

In some cases, drug is removed from the central compartment not only by elimination but also by distribution into peripheral compartments. In this case, the plot of plasma concentration versus time after a bolus may demonstrate two (or more) exponential components (Fig. 63-2*B*). In general, the initial rapid drop in drug concentration represents not elimination but drug distribution into and out of peripheral tissues (also first-order processes), while the slower component represents drug elimination; the initial precipitous decline is usually evident with administration by intravenous but not by other routes. Drug concentrations at peripheral sites are determined by a balance between drug distribution to and redistribution from those sites, as well as by elimination. Once distribution is near-complete (four–five distribution half-lives), plasma and tissue concentrations decline in parallel.

Clinical Implications of Half-Life Measurements The elimination half-life not only determines the time required for drug concentrations to fall to near-immeasurable levels after a single bolus, it is also the sole determinant of the time required for steady-state plasma concentrations to be achieved after any change in drug dosing **(Fig. 63-4)**. This applies to the initiation of chronic drug therapy (whether by multiple oral doses or by continuous intravenous infusion), a change in chronic drug dose or dosing interval, or discontinuation of drug.

Steady state describes the situation during chronic drug administration when the amount of drug administered per unit time equals drug eliminated per unit time. With a continuous intravenous infusion, plasma concentrations at steady state are stable, while with chronic oral drug administration, plasma concentrations vary during the dosing interval but the time-concentration profile between dosing intervals is stable (Fig. 63-4).

DRUG DISTRIBUTION

In a typical 70-kg human, plasma volume is ~3 L, blood volume is ~5.5 L, and extracellular water outside the vasculature is ~20 L. The volume of distribution of drugs extensively bound to plasma proteins but not to tissue components approaches plasma volume; warfarin is an example. By contrast, for drugs highly bound to tissues, the volume of distribution can be far greater than any physiologic space. For example, the volume of distribution of digoxin and tricyclic antidepressants

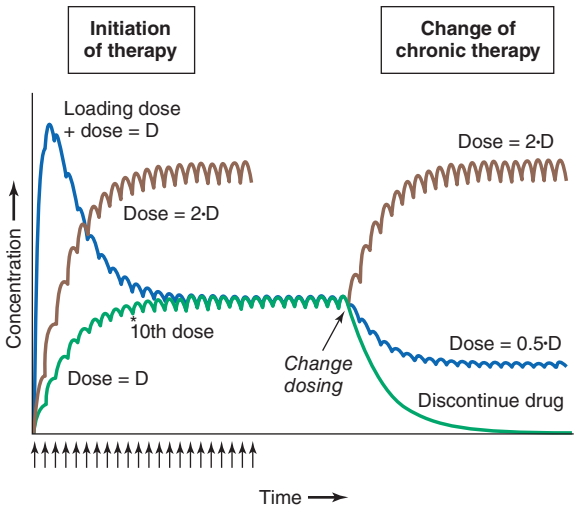

FIGURE 63-4 Drug accumulation to steady state. In this simulation, drug was administered (arrows) at intervals = 50% of the elimination half-life. Steady state is achieved during initiation of therapy after ~5 elimination half-lives, or 10 doses. A loading dose did not alter the eventual steady state achieved. A doubling of the dose resulted in a doubling of the steady state but the same time course of accumulation. Once steady state is achieved, a change in dose (increase, decrease, or drug discontinuation) results in a new steady state in ~5 elimination half-lives. *(Adapted by permission from DM Roden, in DP Zipes, J Jalife [eds]: Cardiac Electrophysiology: From Cell to Bedside, 4th ed. Philadelphia, Saunders, 2003. Copyright 2003 with permission from Elsevier.)*

is hundreds of liters, obviously exceeding total-body volume. Such drugs are not readily removed by dialysis, an important consideration in overdose.

Clinical Implications of Drug Distribution In some cases, pharmacologic effects require drug distribution to peripheral sites. In this instance, the time course of drug delivery to and removal from these sites determines the time course of drug effects; anesthetic uptake into the central nervous system (CNS) is an example.

LOADING DOSES For some drugs, the indication may be so urgent that administration of "loading" dosages is required to achieve rapid elevations of drug concentration and therapeutic effects earlier than with chronic maintenance therapy (Fig. 63-4). Nevertheless, the time required for true steady state to be achieved is still determined only by the elimination half-life.

RATE OF INTRAVENOUS DRUG ADMINISTRATION Although the simulations in Fig. 63-2 use a single intravenous bolus, this is usually inappropriate in practice because side effects related to transiently very high concentrations can result. Rather, drugs are more usually administered orally or as a slower intravenous infusion. Some drugs are so predictably lethal when infused too rapidly that special precautions should be taken to prevent accidental boluses. For example, solutions of potassium for intravenous administration >20 mEq/L should be avoided in all but the most exceptional and carefully monitored circumstances. This minimizes the possibility of cardiac arrest due to accidental increases in infusion rates of more concentrated solutions.

Transiently high drug concentrations after rapid intravenous administration can occasionally be used to advantage. The use of midazolam for intravenous sedation, for example, depends upon its rapid uptake by the brain during the distribution phase to produce sedation quickly, with subsequent egress from the brain during the redistribution of the drug as equilibrium is achieved.

Similarly, adenosine must be administered as a rapid bolus in the treatment of reentrant supraventricular tachycardias **(Chap. 241)** to prevent elimination by very rapid ($t_{1/2}$ of seconds) uptake into erythrocytes and endothelial cells before the drug can reach its clinical site of action, the atrioventricular node.

Clinical Implications of Altered Protein Binding Many drugs circulate in the plasma partly bound to plasma proteins. Since only unbound (free) drug can distribute to sites of pharmacologic action, drug response is related to the free rather than the total circulating plasma drug concentration. In chronic kidney or liver disease, protein binding may be decreased and thus drug actions increased. In some situations (myocardial infarction, infection, surgery), acute phase reactants transiently increase binding of some drugs and thus decrease efficacy. These changes assume the greatest clinical importance for drugs that are highly protein-bound since even a small change in protein binding can result in large changes in free drug; for example, a decrease in binding from 99 to 98% doubles the free drug concentration from 1 to 2%. For some drugs (e.g., phenytoin), monitoring free rather than total drug concentrations can be useful.

DRUG ELIMINATION

Drug elimination reduces the amount of drug in the body over time. An important approach to quantifying this reduction is to consider that drug concentrations at the beginning and end of a time period are unchanged and that a specific volume of the body has been "cleared" of the drug during that time period. This defines clearance as volume/time. Clearance includes both drug metabolism and excretion.

Clinical Implications of Altered Clearance While elimination half-life determines the time required to achieve steady-state plasma concentration (C_{ss}), the *magnitude* of that steady state is determined by clearance (Cl) and dose alone. For a drug administered as an intravenous infusion, this relationship is:

$$C_{ss} = \text{dosing rate}/Cl \quad \text{or} \quad \text{dosing rate} = Cl \bullet C_{ss}$$

When drug is administered orally, the average plasma concentration within a dosing interval ($C_{avg,ss}$) replaces C_{ss}, and the dosage (dose per unit time) must be increased if bioavailability (F) is <100%:

$$\text{Dose/time} = Cl \bullet C_{avg,ss}/F$$

Genetic variants, drug interactions, or diseases that reduce the activity of drug-metabolizing enzymes or excretory mechanisms lead to decreased clearance and, hence, a requirement for downward dose adjustment to avoid toxicity. Conversely, some drug interactions and genetic variants increase the function of drug elimination pathways, and hence, increased drug dosage is necessary to maintain a therapeutic effect.

ACTIVE DRUG METABOLITES

Metabolites may produce effects similar to, overlapping with, or distinct from those of the parent drug. Accumulation of the major metabolite of procainamide, *N*-acetylprocainamide (NAPA), likely accounts for marked QT prolongation and torsades des pointes ventricular tachycardia **(Chap. 247)** during therapy with procainamide. Neurotoxicity during therapy with the opioid analgesic meperidine is likely due to accumulation of normeperidine, especially in renal disease.

Prodrugs are inactive compounds that require metabolism to generate active metabolites that mediate the drug effects. Examples include many angiotensin-converting enzyme (ACE) inhibitors, the angiotensin receptor blocker losartan, the antineoplastic irinotecan, the anti-estrogen tamoxifen, the analgesic codeine (whose active metabolite morphine probably underlies the opioid effect during codeine administration), and the antiplatelet drug clopidogrel. Drug metabolism has also been implicated in bioactivation of procarcinogens and in generation of reactive metabolites that mediate certain adverse drug effects (e.g., acetaminophen hepatotoxicity, discussed below).

THE CONCEPT OF HIGH-RISK PHARMACOKINETICS

When plasma concentrations of active drug depend exclusively on a single metabolic pathway, any condition that inhibits that pathway (be it disease-related, genetic, or due to a drug interaction) can lead to dramatic changes in drug concentrations and marked variability in drug action. Two mechanisms can generate highly variable drug concentrations and effects through such "high-risk pharmacokinetics." *First*, variability in bioactivation of a prodrug can lead to striking variability in drug action; examples include decreased CYP2D6 activity, which prevents analgesia by codeine, and decreased CYP2C19 activity, which

reduces the antiplatelet effects of clopidogrel. The *second* setting is drug elimination that relies on a single pathway. In this case, inhibition of the elimination pathway by genetic variants or by administration of inhibiting drugs leads to marked elevation of drug concentration and, for drugs with a narrow therapeutic window, an increased likelihood of dose-related toxicity. The active S-enantiomer of the anticoagulant warfarin is eliminated by CYP2C9, and co-administration of amiodarone or phenytoin, CYP2C9 inhibitors, may therefore increase the risk of bleeding unless the dose is decreased. When drugs undergo elimination by multiple-drug metabolizing or excretory pathways, absence of one pathway (due to a genetic variant or drug interaction) is much less likely to have a large impact on drug concentrations or drug actions.

PRINCIPLES OF PHARMACODYNAMICS

The Onset of Drug Action For drugs used in the urgent treatment of acute symptoms, little or no delay is anticipated (or desired) between the drug-target interaction and the development of a clinical effect. Examples of such acute situations include vascular thrombosis, shock, or status epilepticus.

For many conditions, however, the indication for therapy is less urgent, and a delay between the interaction of a drug with its pharmacologic target(s) and a clinical effect is clinically acceptable. Common pharmacokinetic mechanisms that can contribute to such a delay include slow elimination (resulting in slow accumulation to steady state), uptake into peripheral compartments, or accumulation of active metabolites. A common pharmacodynamic explanation for such a delay is that the clinical effect develops as a downstream consequence of the initial molecular effect the drug produces. Thus, administration of a proton pump inhibitor or an H_2-receptor blocker produces an immediate increase in gastric pH but ulcer healing that is delayed. Cancer chemotherapy similarly produces delayed therapeutic effects.

Drug Effects May Be Disease Specific A drug may produce no action or a different spectrum of actions in unaffected individuals compared to patients with underlying disease. Further, concomitant disease can complicate interpretation of response to drug therapy, especially adverse effects. For example, high doses of anticonvulsants such as phenytoin may cause neurologic symptoms, which may be confused with the underlying neurologic disease. Similarly, increasing dyspnea in a patient with chronic lung disease receiving amiodarone therapy could be due to the drug, underlying disease, or an intercurrent cardiopulmonary problem. As a result, alternate antiarrhythmic therapies are preferable in patients with chronic lung disease.

While drugs interact with specific molecular receptors, drug effects may vary over time, even if stable drug and metabolite concentrations are maintained. The drug-receptor interaction occurs in a complex biologic milieu that can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and antiarrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or local ischemia. Receptors may be up- or down-regulated by disease or by the drug itself. For example, β-adrenergic blockers upregulate β-receptor density during chronic therapy. While this effect does not usually result in resistance to the therapeutic effect of the drugs, it may produce severe agonist-mediated effects (such as hypertension or tachycardia) if the blocking drug is abruptly withdrawn.

PRINCIPLES OF DOSE SELECTION

The desired goal of therapy with any drug is to maximize the likelihood of a beneficial effect while minimizing the risk of adverse effects. Previous experience with the drug, in controlled clinical trials or in post-marketing use, defines the relationships between dose or plasma concentration and these dual effects (Fig. 63-1) and has important implications for initiation of drug therapy:

1. *The target drug effect should be defined when drug treatment is started.* With some drugs, the desired effect may be difficult to measure objectively, or the onset of efficacy can be delayed for weeks or months; drugs used in the treatment of cancer and psychiatric disease are examples. Sometimes a drug is used to treat a symptom, such as pain or palpitations, and here it is the patient who will report whether the selected dose is effective. In yet other settings, such as anticoagulation or hypertension, the desired response can be repeatedly and objectively assessed by simple clinical or laboratory tests.
2. *The nature of anticipated toxicity often dictates the starting dose.* If side effects are minor, it may be acceptable to start chronic therapy at a dose highly likely to achieve efficacy and down-titrate if side effects occur. However, this approach is rarely, if ever, justified if the anticipated toxicity is serious or life-threatening; in this circumstance, it is more appropriate to initiate therapy with the lowest dose that may produce a desired effect. In cancer chemotherapy, it is common practice to use maximum-tolerated doses.
3. *The above considerations do not apply if these relationships between dose and effects cannot be defined.* This is especially relevant to some adverse drug effects (discussed further below) whose development is not readily related to drug dose.
4. *If a drug dose does not achieve its desired effect, a dosage increase is justified only if toxicity is absent and the likelihood of serious toxicity is small.*

Failure of Efficacy Assuming the diagnosis is correct and the correct drug is prescribed, explanations for failure of efficacy include drug interactions, noncompliance, or unexpectedly low drug concentration due to administration of expired or degraded drug. These are situations in which measurement of plasma drug concentrations, if available, can be especially useful. Noncompliance is an especially frequent problem in the long-term treatment of diseases such as hypertension and epilepsy, occurring in ≥25% of patients in therapeutic environments in which no special effort is made to involve patients in the responsibility for their own health. Multidrug regimens with multiple doses per day are especially prone to noncompliance.

Monitoring response to therapy, by physiologic measures or by plasma concentration measurements, requires an understanding of the relationships between plasma concentration and anticipated effects. For example, measurement of QT interval is used during treatment with sotalol or dofetilide to avoid marked QT prolongation that can herald serious arrhythmias. In this setting, evaluating the electrocardiogram at the time of anticipated peak plasma concentration and effect (e.g., 1–2 h post-dose at steady state) is most appropriate. Maintained high vancomycin levels carry a risk of nephrotoxicity, so dosages should be adjusted on the basis of plasma concentrations measured at trough (pre-dose). Similarly, for dose adjustment of other drugs (e.g., anticonvulsants), concentration should be measured at its lowest during the dosing interval, just prior to a dose at steady state (Fig. 63-4), to ensure a maintained therapeutic effect.

Concentration of Drugs in Plasma as a Guide to Therapy Factors such as interactions with other drugs, disease-induced alterations in elimination and distribution, and genetic variation in drug disposition combine to yield a wide range of plasma levels in patients given the same dose. Hence, if a predictable relationship can be established between plasma drug concentration and beneficial or adverse drug effect, measurement of plasma levels can provide a valuable tool to guide selection of an optimal dose, especially when there is a narrow range between the plasma levels yielding therapeutic and adverse effects. Monitoring is commonly used with certain types of drugs including many anticonvulsants, antirejection agents, antiarrhythmics, and antibiotics. By contrast, if no such relationship can be established (e.g., if drug access to important sites of action outside plasma is highly variable), monitoring plasma concentration may not provide an accurate guide to therapy **(Fig. 63-5)**.

The common situation of first-order elimination implies that average, maximum, and minimum steady-state concentrations are related linearly to the dosing rate. Accordingly, the maintenance dose may be adjusted on the basis of the ratio between the desired and measured concentrations *at steady state*; for example, if a doubling of the steady-state plasma concentration is desired, the dose should be doubled. This does not apply to drugs eliminated by zero-order kinetics (fixed amount per unit time), where small dosage increases will produce

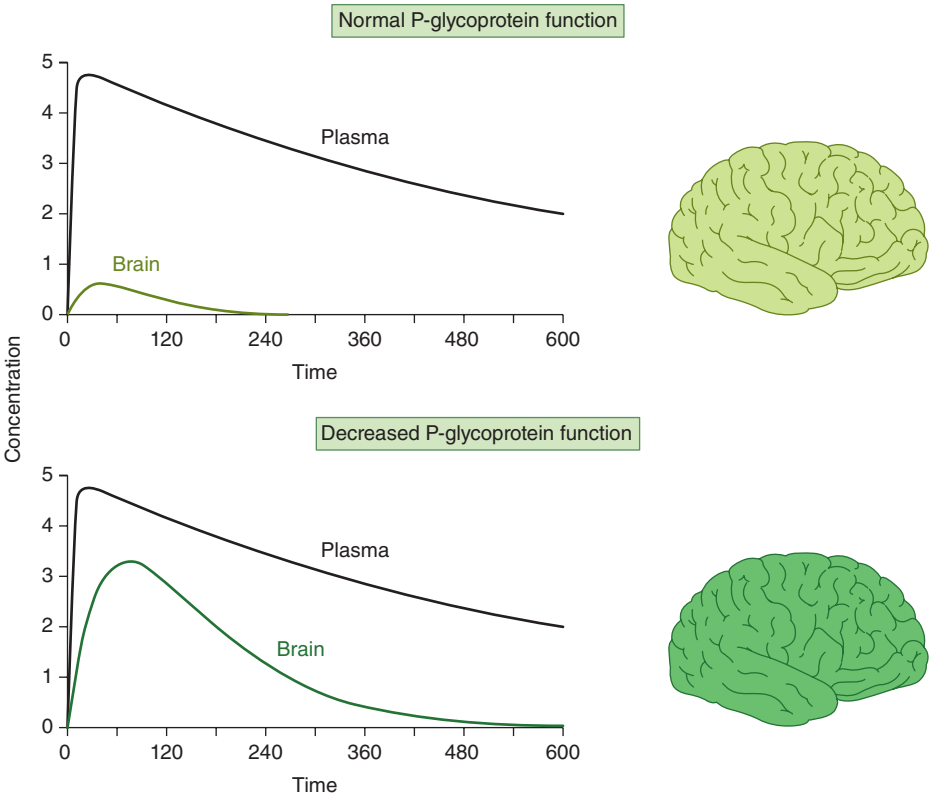

FIGURE 63-5 The efflux pump P-glycoprotein excludes drugs from the endothelium of capillaries in the brain and so constitutes a key element of the blood-brain barrier. Thus, reduced P-glycoprotein function (e.g., due to drug interactions) increases penetration of substrate drugs into the brain, even when plasma concentrations are unchanged.

disproportionate increases in plasma concentration; examples include phenytoin and theophylline.

An increase in dosage is usually best achieved by changing the drug dose but not the dosing interval (e.g., by giving 200 mg every 8 h instead of 100 mg every 8 h). However, this approach is acceptable only if the resulting maximum concentration is not toxic and the trough value does not fall below the minimum effective concentration for an undesirable period of time. Alternatively, the steady state may be changed by altering the frequency of intermittent dosing but not the size of each dose. In this case, the magnitude of the fluctuations around the average steady-state level will change—the shorter the dosing interval, the smaller the difference between peak and trough levels.

EFFECTS OF DISEASE ON DRUG CONCENTRATION AND RESPONSE

RENAL DISEASE

Renal excretion of parent drug and metabolites is generally accomplished by glomerular filtration and by specific drug transporters. If a drug or its metabolites are primarily excreted through the kidneys and increased drug levels are associated with adverse effects (an example of "high-risk pharmacokinetics" described above), drug dosages must be reduced in patients with renal dysfunction to avoid toxicity. The antiarrhythmics dofetilide and sotalol undergo predominant renal excretion and carry a risk of QT prolongation and arrhythmias if doses are not reduced in renal disease. In end-stage renal disease, sotalol has been given as 40 mg after dialysis (every second day), compared to the usual daily dose, 80–120 mg every 12 h. At approved doses, the anticoagulant edoxaban appears to be somewhat more effective in subjects with mild renal dysfunction, possibly reflecting higher drug levels. The narcotic analgesic meperidine undergoes extensive hepatic metabolism, so that renal failure has little effect on its plasma concentration. However, its metabolite, normeperidine, does undergo renal excretion, accumulates in renal failure, and probably accounts for the signs of CNS excitation, such as irritability, twitching, and seizures, that appear when multiple doses of meperidine are administered to patients with renal disease. Protein binding of some drugs (e.g., phenytoin) may be altered in uremia, so measuring free drug concentration may be desirable.

In non-end-stage renal disease, changes in renal drug clearance are generally proportional to those in creatinine clearance, which may be measured directly or estimated from the serum creatinine. This estimate, coupled with the knowledge of how much drug is normally excreted renally versus nonrenally, allows an estimate of the dose adjustment required. In practice, most decisions involving dosing adjustment in patients with renal failure use published recommended adjustments in dosage or dosing interval based on the severity of renal dysfunction indicated by creatinine clearance. Any such modification of dose is a first approximation and should be followed by plasma concentration data (if available) and clinical observation to further optimize therapy for the individual patient.

LIVER DISEASE

Standard tests of liver function are not useful in adjusting doses in diseases like hepatitis or cirrhosis. First-pass metabolism may decrease, leading to increased oral bioavailability as a consequence of disrupted hepatocyte function, altered liver architecture, and portacaval shunts. The oral bioavailability for high first-pass drugs such as morphine, meperidine, midazolam, and nifedipine is almost doubled in patients with cirrhosis, compared to those with normal liver function. Therefore, the size of the oral dose of such drugs should be reduced in this setting.

HEART FAILURE AND SHOCK

Under conditions of decreased tissue perfusion, the cardiac output is redistributed to preserve blood flow to the heart and brain at the expense of other tissues (Chap. 252). As a result, drugs may be distributed into a smaller volume of distribution, higher drug concentrations will be present in the plasma, and the tissues that are best perfused (the brain and heart) will be exposed to these higher concentrations, resulting in increased CNS or cardiac effects. As well, decreased perfusion of the kidney and liver may impair drug clearance. Another consequence of severe heart failure is decreased gut perfusion, which may reduce drug absorption and, thus, lead to reduced or absent effects of orally administered therapies.

DRUG USE IN THE ELDERLY

In the elderly, multiple pathologies and medications used to treat them result in more drug interactions and adverse effects. Aging also results in changes in organ function, especially of the organs involved in drug disposition. Initial doses should be less than the usual adult dosage and should be increased slowly. The number of medications, and doses per day, should be kept as low as possible.

Even in the absence of kidney disease, renal clearance may be reduced by 35–50% in elderly patients. Dosages should be adjusted on the basis of creatinine clearance. Aging also results in a decrease in the size of, and blood flow to, the liver and possibly in the activity of hepatic drug-metabolizing enzymes; accordingly, the hepatic clearance of some drugs is impaired in the elderly. As with liver disease, these changes are not readily predicted.

Elderly patients may display altered drug sensitivity. Examples include increased analgesic effects of opioids, increased sedation from benzodiazepines and other CNS depressants, and increased risk of bleeding while receiving anticoagulant therapy, even when

clotting parameters are well controlled. Exaggerated responses to cardiovascular drugs are also common because of the impaired responsiveness of normal homeostatic mechanisms. Conversely, the elderly display decreased sensitivity to β-adrenergic receptor blockers.

Adverse drug reactions are especially common in the elderly because of altered pharmacokinetics and pharmacodynamics, the frequent use of multidrug regimens, and concomitant disease. For example, use of long half-life benzodiazepines is linked to the occurrence of hip fractures in elderly patients, perhaps reflecting both a risk of falls from these drugs (due to increased sedation) and the increased incidence of osteoporosis in elderly patients. In population surveys of the noninstitutionalized elderly, as many as 10% had at least one adverse drug reaction in the previous year.

DRUG USE IN CHILDREN

While most drugs used to treat disease in children are the same as those in adults, there are few studies that provide solid data to guide dosing. Drug metabolism pathways mature at different rates after birth, and disease mechanisms may be different in children. In practice, doses are adjusted for size (weight or body surface area) as a first approximation unless age-specific data are available.

INTERACTIONS BETWEEN DRUGS

Drug interactions can complicate therapy by increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels. *Interactions must be considered in the differential diagnosis of any unusual response occurring during drug therapy*. Prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A meticulous drug history should include examination of the patient's medications and, if necessary, calls to the pharmacist to identify prescriptions. It should also address the use of agents not often volunteered during questioning, such as OTC drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. While it is unrealistic to expect the practicing physician to memorize these, certain drugs consistently run the risk of generating interactions, often by inhibiting or inducing specific drug elimination pathways. Examples are presented below and in Table 63-2. Accordingly, when these drugs are started or stopped, prescribers must be especially alert to the possibility of interactions.

TABLE 63-2 Drugs with a High Risk of Generating Pharmacokinetic Interactions

DRUG	MECHANISM	EXAMPLES
Antacids Bile acid sequestrants	Reduced absorption	Antacids/tetracyclines Cholestyramine/digoxin
Proton pump inhibitors H_2-receptor blockers	Altered gastric pH	Ketoconazole absorption decreased
Rifampin Carbamazepine Barbiturates Phenytoin St. John's wort Glutethimide Nevirapine (CYP3A; CYP2B6)	Induction of CYPs and/or P-glycoprotein	Decreased concentration and effects of warfarin quinidine cyclosporine losartan oral contraceptives methadone, dabigatran
Tricyclic antidepressants Fluoxetine Quinidine	Inhibitors of CYP2D6	Increased effect of many β blockers Decreased codeine effect; possible decreased tamoxifen effect
Cimetidine	Inhibitor of multiple CYPs	Increased concentration and effects of warfarin theophylline phenytoin
Ketoconazole, itraconazole Erythromycin, clarithromycin Calcium channel blockers Ritonavir	Inhibitor of CYP3A	Increased concentration and toxicity of some HMG-CoA reductase inhibitors, colchicine Cyclosporine, cisapride, terfenadine (now withdrawn) Increased concentration and effects of indinavir (with ritonavir) Decreased clearance and dose requirement for cyclosporine (with calcium channel blockers)
Allopurinol	Xanthine oxidase inhibitor	Azathioprine and 6-mercaptopurine toxicity
Amiodarone	Inhibitor of many CYPs and of P-glycoprotein	Decreased clearance (risk of toxicity) for warfarin digoxin quinidine
Gemfibrozil (and other fibrates)	CYP3A inhibition	Rhabdomyolysis when co-prescribed with some HMG-CoA reductase inhibitors
Quinidine Amiodarone Verapamil Cyclosporine Itraconazole Erythromycin	P-glycoprotein inhibition	Risk of toxicity with P-glycoprotein substrates (e.g., digoxin, dabigatran)
Phenylbutazone Probenecid Salicylates	Inhibition of renal tubular transport	Increased risk of methotrexate toxicity with salicylates

PHARMACOKINETIC INTERACTIONS CAUSING DECREASED DRUG EFFECTS

Gastrointestinal absorption can be reduced if a drug interaction results in drug binding in the gut, as with aluminum-containing antacids, kaolin-pectin suspensions, or bile acid sequestrants. Drugs such as histamine H_2-receptor antagonists or proton pump inhibitors that alter gastric pH may decrease the solubility and hence absorption of weak bases such as ketoconazole.

Expression of some genes responsible for drug elimination, notably *CYP3A* and *ABCB1*, can be markedly increased by inducing drugs, such as rifampin, carbamazepine, phenytoin, St. John's wort, and glutethimide, and by smoking, exposure to chlorinated insecticides, and chronic alcohol ingestion. Administration of inducing agents lowers plasma levels, and thus effects, over 2–3 weeks as gene expression is increased. If a drug dose is stabilized in the presence of an inducer that is subsequently stopped, major toxicity can occur as clearance returns to preinduction levels and drug concentrations rise. Individuals vary in the extent to which drug metabolism can be induced, likely through genetic mechanisms.

Interactions that inhibit the bioactivation of prodrugs will decrease drug effects (Table 63-1).

Interactions that decrease drug delivery to intracellular sites of action can decrease drug effects: tricyclic antidepressants can blunt the antihypertensive effect of clonidine by decreasing its uptake into

adrenergic neurons. Reduced CNS penetration of multiple human immunodeficiency virus (HIV) protease inhibitors (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein-mediated exclusion of the drug from the CNS; indeed, inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS (Fig. 63-5).

PHARMACOKINETIC INTERACTIONS CAUSING INCREASED DRUG EFFECTS

The most common mechanism here is inhibition of drug elimination. In contrast to induction, new protein synthesis is not involved, and the effect develops as drug and any metabolites accumulate (a function of their elimination half-lives). Since shared substrates of a single enzyme can compete for access to the active site of the protein, many CYP substrates are also inhibitors. However, some drugs are especially potent as inhibitors (and occasionally may not even be substrates) of specific drug elimination pathways, and so it is in the use of these agents that clinicians must be most alert to the potential for interactions (Table 63-2). Commonly implicated interacting drugs of this type include amiodarone, cimetidine, erythromycin and some other macrolide antibiotics (clarithromycin but not azithromycin), ketoconazole and other azole antifungals, the antiretroviral agent ritonavir, and high concentrations of grapefruit juice. The consequences of such interactions will depend on the drug whose elimination is being inhibited (see "The Concept of High-Risk Pharmacokinetics," above). Examples include CYP3A inhibitors increasing the risk of cyclosporine toxicity or of rhabdomyolysis with some 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (lovastatin, simvastatin, atorvastatin, but not pravastatin), and P-glycoprotein inhibitors increasing the risk of toxicity with digoxin therapy or of bleeding with the thrombin inhibitor dabigatran.

These interactions can occasionally be exploited to therapeutic benefit. The antiviral ritonavir is a very potent CYP3A4 inhibitor that has been added to anti-HIV regimens, not because of its antiviral effects but because it decreases clearance, and hence increases efficacy, of other anti-HIV agents. Similarly, calcium channel blockers have been deliberately coadministered with cyclosporine to reduce its clearance and thus its maintenance dosage and cost.

Phenytoin, an inducer of many systems, including CYP3A, inhibits CYP2C9 and thus can reduce the bioactivation of losartan, with potential loss of antihypertensive effect, or the elimination of S-warfarin, with attendant increased bleeding risk.

Grapefruit (but not orange) juice inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.

CYP2D6 is markedly inhibited by quinidine, a number of neuroleptic drugs (chlorpromazine and haloperidol), and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine and paroxetine. The clinical consequences of fluoxetine's interaction with CYP2D6 substrates may not be apparent for weeks after the drug is started, because of its very long half-life and slow generation of a CYP2D6-inhibiting metabolite.

Azathioprine is metabolized to 6-mercaptopurine, which is then metabolized by thiopurine methyltransferase and by xanthine oxidase. When allopurinol, an inhibitor of xanthine oxidase, is administered with standard doses of azathioprine or 6-mercaptopurine, life-threatening toxicity (bone marrow suppression) can result.

A number of drugs are secreted by the renal tubular transport systems for organic anions. Inhibition of these systems can cause excessive drug accumulation. Salicylate, for example, reduces the renal clearance of methotrexate, an interaction that may lead to methotrexate toxicity. Renal tubular secretion contributes substantially to the elimination of penicillin, which can be inhibited (to increase its therapeutic effect) by probenecid. Similarly, inhibition of tubular cation transport by cimetidine decreases the renal clearance of dofetilide.

DRUG INTERACTIONS NOT MEDIATED BY CHANGES IN DRUG DISPOSITION

Drugs may act on separate components of a common process to generate effects greater than either has alone. While antithrombotic therapy with combinations of antiplatelet agents (glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel) and anticoagulants (e.g., warfarin, heparins, dabigatran, apixaban, rivaraxaban, edoxaban) is often used in the treatment of vascular disease, such combinations do carry an increased risk of bleeding.

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastric ulcers, and in patients treated with oral anticoagulants, the risk of upper gastrointestinal bleeding is increased almost threefold by concomitant use of an NSAID.

Indomethacin, piroxicam, and probably other NSAIDs antagonize the antihypertensive effects of β-adrenergic receptor blockers, diuretics, ACE inhibitors, and other drugs. The resulting elevation in blood pressure ranges from trivial to severe. This effect is not seen with aspirin and sulindac but has been found with the cyclooxygenase 2 (COX-2) inhibitor celecoxib.

Torsades de pointes ventricular tachycardia during administration of QT-prolonging antiarrhythmics (quinidine, sotalol, dofetilide) occurs much more frequently in patients receiving diuretics, probably reflecting hypokalemia. Low potassium not only prolongs the QT interval in the absence of drug but also potentiates drug block of ion channels that results in QT prolongation. Also, some diuretics have direct electrophysiologic actions that prolong QT.

The administration of supplemental potassium leads to more frequent and more severe hyperkalemia when potassium elimination is reduced by concurrent treatment with ACE inhibitors, spironolactone, eplerenone, amiloride, or triamterene.

The pharmacologic effects of sildenafil result from inhibition of the phosphodiesterase type 5 isoform that inactivates cyclic guanosine monophosphate (GMP) in the vasculature. Nitroglycerin and related nitrates used to treat angina produce vasodilation by elevating cyclic GMP. Thus, coadministration of these nitrates with sildenafil can cause profound hypotension, which can be catastrophic in patients with coronary disease.

Sometimes, combining drugs can increase overall efficacy and/or reduce drug-specific toxicity. Such therapeutically useful interactions are described in chapters dealing with specific disease entities.

ADVERSE DRUG REACTIONS

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these adverse effects often present diagnostic problems because they can involve every organ and system of the body and may be mistaken for signs of underlying disease. As well, some surveys have suggested that drug therapy for a range of chronic conditions such as psychiatric disease or hypertension does not achieve its desired goal in up to half of treated patients; thus, the most common "adverse" drug effect may be failure of efficacy.

Adverse reactions can be classified in two broad groups. Type A reactions result from exaggeration of an intended pharmacologic action of the drug, such as increased bleeding with anticoagulants or bone marrow suppression with some antineoplastics. Type B reactions result from toxic effects unrelated to the intended pharmacologic actions. The latter effects are often unanticipated (especially with new drugs) and frequently severe and may result from recognized (often immunologic) as well as previously undescribed mechanisms.

Drugs may increase the frequency of an event that is common in a general population, and this may be especially difficult to recognize; an excellent example is the increase in myocardial infarctions with the COX-2 inhibitor rofecoxib. Drugs can also cause rare and serious adverse effects, such as hematologic abnormalities, arrhythmias, severe skin reactions, or hepatic or renal dysfunction. Prior to regulatory approval and marketing (see below), new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials and the selected nature of these patients, rare adverse effects are generally not detected prior to a drug's approval; indeed, if they are detected, the new drugs are generally not approved. Therefore,

physicians need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized adverse events.

Elucidating mechanisms underlying adverse drug effects can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure. National adverse reaction reporting systems, such as those operated by the FDA (suspected adverse reactions can be reported online at *http://www.fda.gov/safety/medwatch/default.htm*) and the Committee on Safety of Medicines in Great Britain, can prove useful. The publication or reporting of a newly recognized adverse reaction can in a short time stimulate many similar such reports of reactions that previously had gone unrecognized.

Occasionally, "adverse" effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients led to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. These examples further reinforce the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

Some 25–50% of patients make errors in self-administration of prescribed medicines, and these errors can be responsible for adverse drug effects. Similarly, patients commit errors in taking OTC drugs by not reading or following the directions on the containers. Health care providers must recognize that providing directions with prescriptions does not always guarantee compliance.

In hospitals, drugs are administered in a controlled setting, and patient compliance is, in general, ensured. Errors may occur nevertheless—the wrong drug or dose may be given or the drug may be given to the wrong patient—and improved drug distribution and administration systems should help with this problem.

SCOPE OF THE PROBLEM

One estimate in the United Kingdom was that 6.5% of all hospital admissions are due to adverse drug reactions, and that 2.3% of these patients (0.15%) died as a result. The most common culprit drugs were aspirin, other NSAIDs, diuretics, warfarin, ACE inhibitors, antidepressants, opiates, digoxin, steroids, and clopidogrel. One study in the late 1990s suggested that adverse drug reactions were responsible for >100,000 in-hospital deaths in the United States, making them the 4th to 6th commonest cause of in-hospital death. Another study 10 years later showed no change in this trend.

In hospital, patients receive, on average, 10 different drugs during each hospitalization. The sicker the patient, the more drugs are given, and there is a corresponding increase in the likelihood of adverse drug reactions. When <6 different drugs are given to hospitalized patients, the probability of an adverse reaction is ~5%, but if >15 drugs are given, the probability is >40%. Serious adverse reactions are also well-recognized with "herbal" remedies and OTC compounds; examples include kava-associated hepatotoxicity, L-tryptophan-associated eosinophilia-myalgia, and phenylpropanolamine-associated stroke, each of which has caused fatalities.

TOXICITY UNRELATED TO A DRUG'S PRIMARY PHARMACOLOGIC ACTIVITY

Drugs or more commonly reactive metabolites generated by CYPs can covalently bind to tissue macromolecules (such as proteins or DNA) to cause tissue toxicity. Because of the reactive nature of these metabolites, covalent binding often occurs close to the site of production, typically the liver.

Acetaminophen The most common cause of drug-induced hepatotoxicity is acetaminophen overdosage **(Chap. 333)**. Normally, reactive metabolites are detoxified by combining with hepatic glutathione. When glutathione becomes depleted, the metabolites bind instead to hepatic protein, with resultant hepatocyte damage. The hepatic necrosis produced by the ingestion of acetaminophen can be prevented or attenuated by the administration of substances such as *N*-acetylcysteine that reduce the binding of electrophilic metabolites to hepatic proteins. The risk of acetaminophen-related hepatic necrosis is increased in patients receiving drugs such as phenobarbital or phenytoin, which increase the rate of drug metabolism, or ethanol, which exhausts glutathione stores. Such toxicity has even occurred with therapeutic dosages, so patients at risk through these mechanisms should be warned.

Immunologic Reactions Most pharmacologic agents are haptens, small molecules with low molecular weights (<2000) that are therefore poor immunogens. Generation of an immune response to a drug therefore often requires in vivo activation and covalent linkage to protein, carbohydrate, or nucleic acid.

Drug stimulation of antibody production may mediate tissue injury by several mechanisms. The antibody may attack the drug when the drug is covalently attached to a cell and thereby destroy the cell. This occurs in penicillin-induced hemolytic anemia. Antibody-drug-antigen complexes may be passively adsorbed by a bystander cell, which is then destroyed by activation of complement; this occurs in quinine- and quinidine-induced thrombocytopenia. Heparin-induced thrombocytopenia arises when antibodies against complexes of platelet factor 4 peptide and heparin generate immune complexes that activate platelets; thus, the thrombocytopenia is accompanied by "paradoxical" thrombosis and is treated with thrombin inhibitors. Drugs or their reactive metabolites may alter a host tissue, rendering it antigenic and eliciting autoantibodies. For example, hydralazine and procainamide (or their reactive metabolites) can chemically alter nuclear material, stimulating the formation of antinuclear antibodies and occasionally causing lupus erythematosus. Drug-induced pure red cell aplasia **(Chap. 98)** is due to an immune-based drug reaction.

Serum sickness **(Chap. 345)** results from the deposition of circulating drug-antibody complexes on endothelial surfaces. Complement activation occurs, chemotactic factors are generated locally, and an inflammatory response develops at the site of complex entrapment. Arthralgias, urticaria, lymphadenopathy, glomerulonephritis, or cerebritis may result. Foreign proteins (vaccines, streptokinase, therapeutic antibodies) and antibiotics are common causes. Many drugs, particularly antimicrobial agents, ACE inhibitors, and aspirin, can elicit anaphylaxis with production of IgE, which binds to mast cell membranes. Contact with a drug antigen initiates a series of biochemical events in the mast cell and results in the release of mediators that can produce the characteristic urticaria, wheezing, flushing, rhinorrhea, and (occasionally) hypotension.

Drugs may also elicit cell-mediated immune responses. One serious reaction is Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), which can result in death due to T-cell-mediated massive skin sloughing. As described in **Chap. 64**, specific genetic variants appear necessary but not sufficient to elicit SJS/TEN. The mechanism is thought to be T cell activation by hapten-"self-peptide" interactions or direct binding of drug to HLA or T cell receptors.

DIAGNOSIS AND TREATMENT OF ADVERSE DRUG REACTIONS

The manifestations of drug-induced diseases frequently resemble those of other diseases, and a given set of manifestations may be produced by different and dissimilar drugs. Recognition of the role of a drug or drugs in an illness depends on appreciation of the possible adverse reactions to drugs in any disease, on identification of the temporal relationship between drug administration and development of the illness, and on familiarity with the common manifestations of the drugs.

A suspected adverse drug reaction developing after introduction of a new drug naturally implicates that drug; however, it is also important to remember that a drug interaction may be responsible. Thus, for example, a patient on a chronic stable warfarin dose may develop a bleeding complication after introduction of amiodarone; this does not reflect a direct reaction to amiodarone but rather its effect to inhibit warfarin metabolism. Many associations between particular drugs and specific reactions have been described, but there is always a "first time" for a novel association, and any drug should be suspected of causing an adverse effect if the clinical setting is appropriate.

Illness related to a drug's intended pharmacologic action is often more easily recognized than illness attributable to immune or other mechanisms.

For example, side effects such as cardiac arrhythmias in patients receiving digitalis, hypoglycemia in patients given insulin, or bleeding in patients receiving anticoagulants are more readily related to a specific drug than are symptoms such rash, which may be caused by many drugs or by other factors. Drug fever often escapes initial diagnosis because fever is such a common manifestation of disease.

Electronic listings of adverse drug reactions can be useful. However, exhaustive compilations often provide little sense of perspective in terms of frequency and seriousness, which can vary considerably among patients.

Eliciting a drug history from each patient is important for diagnosis. Attention must be directed to OTC drugs and herbal preparations as well as to prescription drugs. Each type can be responsible for adverse drug effects, and adverse interactions may occur between OTC drugs and prescribed drugs. Loss of efficacy of oral contraceptives or cyclosporine with concurrent use of St. John's wort (a P-glycoprotein inducer) is an example. In addition, it is common for patients to be cared for by several physicians, and duplicative, additive, antagonistic, or synergistic drug combinations may therefore be administered if the physicians are not aware of the patients' drug histories. Every physician should determine what drugs a patient has been taking, for the previous month or two ideally, before prescribing any medications. Medications stopped for inefficacy or adverse effects should be documented to avoid pointless and potentially dangerous reexposure. A frequently overlooked source of additional drug exposure is topical therapy; for example, a patient complaining of bronchospasm may not mention that an ophthalmic beta blocker is being used unless specifically asked. A history of previous adverse drug effects in patients is common. Since these patients have shown a predisposition to drug-induced illnesses, such a history should dictate added caution in prescribing new drugs.

Laboratory studies may include demonstration of serum antibody in some persons with drug allergies involving cellular blood elements, as in agranulocytosis, hemolytic anemia, and thrombocytopenia. For example, both quinine and quinidine can produce platelet agglutination in vitro in the presence of complement and the serum from a patient who has developed thrombocytopenia following use of this drug. Biochemical abnormalities such as G6PD deficiency, serum pseudocholinesterase level, or genotyping may also be useful in diagnosis, especially after an adverse effect has occurred in the patient or a family member **(see Chap. 64)**.

Once an adverse reaction is suspected, discontinuation of the suspected drug followed by disappearance of the reaction is presumptive evidence of a drug-induced illness. Confirming evidence may be sought by cautiously reintroducing the drug and seeing if the reaction reappears. However, that should be done only if confirmation would be useful in the future management of the patient and if the attempt would not entail undue risk. With concentration-dependent adverse reactions, lowering the dosage may cause the reaction to disappear, and raising it may cause the reaction to reappear. When the reaction is thought to be immunologic, however, readministration of the drug may be hazardous, since anaphylaxis may develop.

If the patient is receiving many drugs when an adverse reaction is suspected, the drugs likeliest to be responsible can usually be identified; this should include both potential culprit agents as well as drugs that alter their elimination. All drugs may be discontinued at once or, if this is not practical, discontinued one at a time, starting with the ones most suspect, and the patient observed for signs of improvement. The time needed for a concentration-dependent adverse effect to disappear depends on the time required for the concentration to fall below the range associated with the adverse effect; that, in turn, depends on the initial blood level and on the rate of elimination or metabolism of the drug. Adverse effects of drugs with long half-lives or those not directly related to serum concentration may take a considerable time to disappear.

THE DRUG DEVELOPMENT PROCESS

Drug therapy is an ancient feature of human culture. The first treatments were plant extracts discovered empirically to be effective for indications like fever, pain, or breathlessness. This symptom-based empiric approach to drug development was supplanted in the twentieth century by identification of compounds targeting more fundamental biologic processes, such as bacterial growth or elevated blood pressure. The term "magic bullet," coined by Paul Ehrlich to describe the search for effective compounds for syphilis, captures the essence of the hope that understanding basic biologic processes will lead to highly effective new therapies.

A common starting point for the development of many widely used modern therapies has been basic biologic discovery that implicates potential target molecules: examples of such target molecules include HMG-CoA reductase, a key step in cholesterol biosynthesis, or the *BRAF* V600E mutation that appears to drive the development of some malignant melanomas and other tumors. The development of compounds targeting these molecules has not only revolutionized treatment for diseases such as hypercholesterolemia or malignant melanoma, but has also revealed new biologic features of disease. Thus, for example, initial spectacular successes with vemurafenib (which targets *BRAF* V600E) were followed by near-universal tumor relapse, strongly suggesting that inhibition of this pathway alone would be insufficient for tumor control. This reasoning, in turn, supports a view that many complex diseases will not lend themselves to cure by targeting a single magic bullet, but rather single drugs or combinations that attack multiple pathways whose perturbation results in disease. The use of combination therapy in settings such as hypertension, tuberculosis, HIV infection, and many cancers highlights the potential for such a "systems biology" view of drug therapy.

A common approach in contemporary drug development is to start with a high-throughput screening procedure to identify "lead" chemical(s) modulating the activity of a potential drug target. The next step is application of increasingly sophisticated medicinal chemistry-based modification of the "lead" to develop compounds with specificity for the chosen target, lack of "off-target" effects, and pharmacokinetic properties suitable for human use (e.g., consistent bioavailability, long elimination half-life, and no high-risk pharmacokinetic features). Drug evaluation in human subjects then proceeds from initial safety and tolerance (phase 1), dose finding (phase 2), and efficacy (phase 3). This is a very expensive process and the vast majority of lead compounds fail at some point. Thus, new approaches to identify likely successes and failures early are needed. One idea, described further in **Chap. 64**, is to use genomic and other high throughput profiling approaches not only to identify new drug targets but also to identify disease subsets for which drugs approved for other indications might be "repurposed" thereby avoiding the costly development process.

SUMMARY

Modern clinical pharmacology aims to replace empiricism in the use of drugs with therapy based on in-depth understanding of factors that determine an individual's response to drug treatment. Molecular pharmacology, pharmacokinetics, genetics, clinical trials, and the educated prescriber all contribute to this process. No drug response should ever be termed *idiosyncratic*; all responses have a mechanism whose understanding will help guide further therapy with that drug or successors. This rapidly expanding understanding of variability in drug actions makes the process of prescribing drugs increasingly daunting for the practitioner. However, fundamental principles should guide this process:

- The benefits of drug therapy, however defined, should always outweigh the risk.
- The smallest dosage necessary to produce the desired effect should be used.
- The number of medications and doses per day should be minimized.
- Although the literature is rapidly expanding, accessing it is becoming easier; electronic tools to search databases of literature and unbiased opinion will become increasingly commonplace.

- Genetics play a role in determining variability in drug response and may become a part of clinical practice.
- Electronic medical record and pharmacy systems will increasingly incorporate prescribing advice, such as indicated medications not used; unindicated medications being prescribed; and potential dosing errors, drug interactions, or genetically determined drug responses.
- Prescribers should be particularly wary when adding or stopping specific drugs that are especially liable to provoke interactions and adverse reactions.
- Prescribers should use only a limited number of drugs, with which they are thoroughly familiar.

FURTHER READING

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MACRAE CA et al: The future of cardiovascular therapeutics. Circulation 133:2610, 2016.

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64 Pharmacogenomics

Dan M. Roden

The previous chapter discussed mechanisms underlying variability in drug action, highlighting pharmacokinetic and pharmacodynamic pathways to beneficial and adverse drug events. Work in the past several decades has defined how genetic variation can play a prominent role in modulating these pathways. Initial studies described unusual drug responses due to single genetic variants in individual subjects, defining the field of pharmacogenetics. A more recent view extends this idea to multiple genetic variants across populations, and the term "pharmacogenomics" is often used. Understanding the role of genetic variation in drug response could improve the use of current drugs, avoid drug use in those at increased risk for adverse drug reactions (ADRs), guide development of new drugs, and even be used as a lens through which to understand mechanisms of diseases themselves. This chapter will outline the principles of pharmacogenomics, the evidence as currently available that genetic factors play a role in variable drug actions, and outline areas of controversy and future work.

PRINCIPLES OF GENETIC VARIATION AND DRUG RESPONSE (SEE ALSO CHAPS. 456 AND 457)

A goal of traditional Mendelian genetics is to identify DNA variants associated with a distinct phenotype in multiple related family members (Chap. 457). However, it is unusual for a drug response phenotype to be accurately measured in more than one family member, let alone across a kindred. Some clinical studies have examined drug disposition traits (such as urinary drug excretion after a fixed test dose) in twins, and have in some instances shown greater concordance in monozygotic compared to dizygotic pairs, supporting a genetic contribution to the trait under study. However, in general, non-family-based approaches are generally used to identify and validate DNA variants contributing to variable drug actions.

Types of Genetic Variants Influencing Drug Response (Table 64-1) The commonest type of genetic variant is a single nucleotide polymorphism (SNP), and nonsynonymous SNPs (i.e., those that alter primary amino acid sequence encoded by a gene) are a common cause of variant function in genes regulating drug responses, often termed *pharmacogenes*. Small insertions and deletions can similarly alter protein function, or lead to functionally important splice variation. Examples of synonymous coding region variants altering pharmacogene function have also been described; the postulated mechanism is an alteration in the rate of RNA translation, and hence in folding of the nascent protein. Variation in pharmacogene promoters has been described, and copy number variation (gene deletion or multiple copies of the same gene) is also well described.

Table 64-1 lists examples of individual types of genomic variation and the impact they can have on function of pharmacogenes. Multiple genotyping approaches may be needed to detect important variants; for example, SNP assays may fail to detect large gene duplications, and highly polymorphic regions (such as human leukocyte antigens, HLA-B) are currently best evaluated by sequencing.

Table 64-1 highlights the fact that the frequency of important variation across pharmacogenes can vary strikingly by ancestry, with the result that certain ethnic groups may be at unusually high risk of displaying variant response to specific drugs.

Candidate Gene Approaches Most studies to date have used an understanding of the molecular mechanisms modulating drug action to identify candidate genes in which variants could explain variable drug responses. One very common scenario is that variable drug actions can be attributed to variability in plasma drug concentrations. When plasma drug concentrations vary widely (e.g., more than an order of magnitude), especially if their distribution is non-unimodal as in Fig. 64-1, variants in single genes controlling drug concentrations often contribute. In this case, the most obvious candidate genes are those responsible for drug metabolism and elimination. Other candidate genes are those encoding the target molecules with which drugs interact to produce their effects or molecules modulating that response, including those involved in disease pathogenesis.

Genome-Wide Association Studies The field has also had some success with "unbiased" approaches such as genome-wide association (GWA) (Chap. 456), particularly in identifying single variants associated with high risk for certain forms of drug toxicity. GWA studies have identified variants in the HLA-B locus that are associated with high risk for severe skin rashes during treatment with the anticonvulsant carbamazepine and hepatotoxicity with flucloxacillin, an antibiotic never marketed in the United States. A GWA study of simvastatin-associated myopathy identified a single noncoding SNP in *SLCO1B1*, encoding OATP1B1, a drug transporter known to modulate simvastatin uptake into the liver, which accounts for 60% of myopathy risk. GWA approaches have also implicated interferon variants in antileukemic responses and in response to therapy in hepatitis C. African-American subjects are known to have higher dose requirements to achieve stable anticoagulation with warfarin, due in part to variation in *CYP2C9* and *VKORC1*, discussed below. In addition, a GWA study identified novel SNPs near *CYP2C9* that contribute to this effect in African Americans.

GENETIC VARIANTS AFFECTING PHARMACOKINETICS

Clinically important genetic variants have been described in multiple molecular pathways of drug disposition (Table 64-2). A distinct multimodal distribution of drug disposition (as shown in Fig. 64-1) argues for a predominant effect of variants in a single gene in the metabolism of that substrate. Individuals with two alleles (variants) encoding for nonfunctional protein make up one group, often termed *poor metabolizers* (PM phenotype). For most genes, many variants can produce such a loss of function, and assessing whether they are on the same or different alleles (i.e., the *diplotype*) can complicate the use of genotyping in clinical practice. Furthermore, some variants produce only partial loss of

TABLE 64-1 Examples of Genetic Variation and Ancestry

STRUCTURAL VARIANT	EXAMPLE		FUNCTIONAL EFFECT	MINOR ALLELE FREQUENCY (%)[a]		
	COMMON NAME	dbSNP		EUROPEAN	AFRICAN	EAST ASIAN
Single nucleotide polymorphism (SNP) (or single nucleotide variant, SNV)	CYP2C9*2	rs1799853	R144C: Reduction of function	12.7	2.4	[b]
	CYP2C9*3	rs1057910	I359L: Loss of function	6.9	1.3	3.4
	CYP2C9*8	rs7900194	R150H: Reduction of function	[b]	5.6	[b]
	CYP2C19*2	rs4244285	Splicing defect: Loss of function	14.8	18.1	31.0
	CYP2C19*3	rs4986893	Premature stop: Loss of function	[b]	[b]	6.7
	CYP2C19*17	rs12248560	Gain of function	45	45	<5
	CYP2D6*4[c]	rs3892097	Splicing defect: Loss of function	23.1	11.9	0.4
	CYP2D6*10[c]	Multiple SNPs define CYP2D6*10 (reduction of function allele):				
		rs1065852	P34S	24.9	15.1	59.1
		rs1135840	S486T			
	CYP3A5*3	rs776746	Splicing defect: Loss of function	90	33	85
	VKORC1*2	rs9923231	Promoter variant associated with decreased warfarin dose	39	11	91
	VKORC1	rs61742245	D36Y: Reduction of function, associated with increased warfarin dose	5% in East Africa, Middle East, Oceania; rare elsewhere		
	ABCB1	rs1045642	Synonymous variant; may affect mRNA stability and protein folding	47.2	79.8	62.5
Insertion/deletion	UGT1A1*28		Reduction of function promoter variant (7 TA repeats versus 6 repeats in reference allele); homozygotes have Gilbert's syndrome	31.6	39.1	14.8
Multiple variants constituting specific haplotypes	HLA-B*15:01		Predispose to immunologically mediated adverse drug reactions	[b]	[b]	5
	HLA-B*57:01			6.8	1.0	1.6
Gene deletion	CYP2D6*5		Loss of function	2.7	6	5.6
Gene duplication	CYP2D6*1xN	Duplication of normal allele	Ultra-rapid metabolizer phenotype	0.8	1.5	0.3
				Up to 3% in North Africa and the Middle East		
	CYP2D6*4xN	Duplication of loss of function allele	Extensive or poor metabolizer phenotype, depending on the opposite allele	0.3	1.4	[b]

Note: Allele frequencies from *http://exac.broadinstitute.org/* and *https://cpicpgx.org/*. [a]Includes heterozygotes and homozygotes. [b]Allele frequency <0.05%.

[c]*CYP2D6* is highly polymorphic and multiple SNPs may be required to define a specific variant. For example, rs1065852 is present in both *4 and *10 variants. See *http://www.cypalleles.ki.se*.

function, and the presence of more than one variant may be required to define a specific allele. Individuals with one functional allele, or multiple reduction of function alleles, make up a second (*intermediate metabolizers*) and may or may not be distinguishable from those with two functional alleles (normal metabolizers, often termed *extensive metabolizers*, EMs). *Ultra-rapid metabolizers* (UMs) with especially high enzymatic activity (occasionally due to gene duplication; Table 64-1 and Fig. 64-1) have also been described for some traits. Many drugs in widespread use can inhibit specific drug disposition pathways **(see Chap. 63, Table 63-1)**, and so EM individuals receiving such inhibitors can respond like PM patients (*phenocopying*). Polymorphisms in genes encoding drug uptake or drug efflux transporters may be other contributors to variability in drug delivery to target sites and, hence, in drug effects.

CYP3A Members of the CYP3A family (*CYP3A4*, *CYP3A5*) metabolize the greatest number of drugs in therapeutic use. CYP3A4 activity is highly variable (up to an order of magnitude) among individuals, but non-synonymous coding region polymorphisms (those that change the encoded amino acid) are rare. Thus, the underlying mechanism likely reflects genetic variation in regulatory regions.

Most subjects of European or Asian origin carry a polymorphism that disrupts splicing in the closely related *CYP3A5* gene. As a result, these individuals display reduced CYP3A5 activity whereas CYP3A5 activity tends to be greater in subjects of African origin. Decreased efficacy of the antirejection agent tacrolimus in subjects of African origin has been attributed to more rapid CYP3A5-mediated elimination and a lower risk of vincristine-associated neuropathy has been reported in CYP3A5 "expressers."

CYP2D6 CYP2D6 is second to CYP3A4 in the number of commonly used drugs that it metabolizes. CYP2D6 activity is polymorphically distributed, with 5–10% of European- and African-derived populations (but very few Asians) displaying the PM phenotype (Fig. 64-1). Dozens of loss-of-function variants in *CYP2D6* have been described; the PM phenotype arises in individuals with two such alleles. In addition, ultra-rapid metabolizers with multiple functional copies of *CYP2D6* have been identified especially in East Africa, the Middle East, and Oceania. PMs have slower elimination rates and lower clearance of substrate drugs; as a consequence (Fig. 64-1*B*), steady state concentrations are higher and the time taken to achieve steady state is longer than in EMs **(see Chap. 63)**. Conversely, UMs display very low steady state parent drug concentrations and an abbreviated time to steady state.

Codeine is biotransformed by CYP2D6 to the potent active metabolite morphine, so its effects are blunted in PMs and exaggerated in UMs. Deaths due to respiratory depression in children given codeine after tonsillectomy have been attributed to the UM trait, and the U.S. Food and Drug Administration (FDA) has revised the package insert to include a prominent "black box" warning against its use in this setting. In the case of drugs with beta-blocking properties metabolized by CYP2D6, greater signs of beta blockade (e.g., bronchospasm, bradycardia) are seen in PM subjects than in EMs. This can be seen not only with orally administered beta blockers such as metoprolol and carvedilol, but also with ophthalmic timolol and with the sodium channel–blocking antiarrhythmic propafenone, a CYP2D6 substrate with beta-blocking properties. Ultra-rapid metabolizers may require very high dosages of nortriptyline and other tricyclic antidepressants

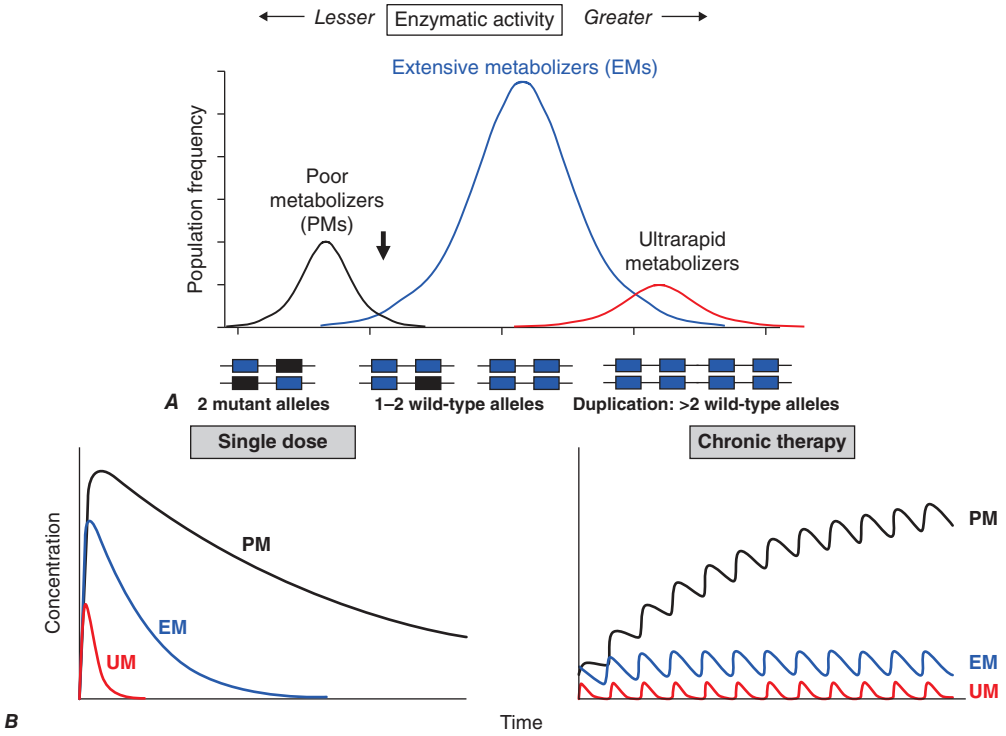

FIGURE 64-1 ***A.*** Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antimode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, blue). Also shown are ultra-rapid metabolizers (UMs, red), with 2–12 functional copies of the gene, displaying the greatest enzyme activity. *(Adapted from M-L Dahl et al: J Pharmacol Exp Ther 274:516, 1995.)* ***B.*** These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse "gene-dose" relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects. The right panel shows that these single dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life).

TABLE 64-2 Genetic Variants and Drug Responses

GENE	DRUGS	EFFECT OF GENETIC VARIANTS[a]
Variants in Drug Metabolism Pathways		
CYP2C9	losartan	Decreased bioactivation and effects (PMs)
	warfarin	Decreased dose requirements; possible increased bleeding risk (PMs)
	phenytoin	Decreased dose requirement (PMs)
CYP2C19	omeprazole, voriconazole	Decreased effect in EMs
	celecoxib	Exaggerated effect in PMs
	clopidogrel	Decreased effect in PMs and IMs Consider alternate drug in PMs and alternate drug or dose increase in IMs Possible increased bleeding risk in carriers of gain of function variants
	citalopram, escitalopram	Choose alternate drug in UMs; reduce dose in PMs
CYP2D6	codeine, tamoxifen	Decreased bioactivation and drug effects in PMs
	codeine	Respiratory depression in UMs
	tricyclic antidepressants[b]	Increased adverse effects in PMs: Consider dose decrease Decreased therapeutic effects in UMs: Consider alternate drug
	metoprolol, carvedilol, timolol, propafenone	Increased beta blockade in PMs
	Fluvoxamine	Reduce dose or chose alternate drug in PMs
CYP3A5	tacrolimus, vincristine	Decreased drug concentrations and effect (CYP3A5*3 carriers)
Dihydropyrimidine dehydrogenase (*DPYD*)	capecitabine, 5-fluorouracil, tegafur	Possible severe toxicity (PMs)
NAT2	rifampin, isoniazid, pyrazinamide, hydralazine, procainamide	Increased risk of toxicity in PMs
Thiopurine S-methyltransferase (*TPMT*)	azathioprine, 6-mercaptopurine, thioguanine	PMs: Increased risk of bone marrow aplasia EMs: Possible decreased drug action at usual dosages
Uridine diphosphate glucuronosyltransferase (*UGT1A1*)	irinotecan	PM homozygotes: Increased risk of severe adverse effects (diarrhea, bone marrow aplasia)
	atazanavir	High risk of hyperbilirubinemia during treatment; can result in drug discontinuation
Pseudocholinesterase (*BCHE*)	succinylcholine and other muscle relaxants	Prolonged paralysis (autosomal recessive). Diagnosis established by genotyping or by measuring serum cholinesterase activity.

(*Continued*)

TABLE 64-2 Genetic Variants and Drug Responses (Continued)

GENE	DRUGS	EFFECT OF GENETIC VARIANTS[a]
Variants in Other Genes		
Glucose 6-phosphate dehydrogenase (*G6PD*)	rasburicase, primaquine, chloroquine	Increased risk of hemolytic anemia in G6PD-deficient subjects
HLA-B*15:02	carbamazepine	Carriers (1 or 2 alleles) at increased risk of SJS/TEN (mainly Asian subjects)
HLA-B*31:01	carbamazepine	Carriers (1 or 2 alleles) at increased risk of SJS/TEN and milder skin toxicities (Caucasian and Asian subjects)
HLA-B*15:02	phenytoin	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
HLA-B*57:01	abacavir	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
HLA-B*58:01	allopurinol	Carriers (1 or 2 alleles) at increased risk of SJS/TEN
IFNL3 (IL28B)	interferon	Variable response in hepatitis C therapy
SLCO1B1	simvastatin	Encodes a drug uptake transporter; variant non-synonymous single nucleotide polymorphism increases myopathy risk especially at higher dosages
VKORC1	warfarin	Decreased dose requirements with variant promoter haplotype Increased dose requirement in individuals with non-synonymous loss of function variants
ITPA	ribavirin	Variants modulate risk for hemolytic anemia
RYR1	general anesthetics	Variants predispose to malignant hyperthermia
CFTR	ivacaftor, lumacaftor	Targeted therapies for cystic fibrosis indicated only in certain genotypes
Variants in Other Genomes (Infectious Agents, Tumors)		
Chemokine C-C motif receptor (CCR5)	maraviroc	Drug effective only in HIV strains with CCR5 detectible
C-KIT	imatinib	In gastrointestinal stromal tumors, drug indicated only with c-kit–positive cases
ALK (anaplastic lymphoma kinase)	Crizotinib	Indicated in patients with non-small cell lung cancer and ALK mutations
Her2/neu overexpression	trastuzumab, lapatinib	Drugs indicated only with tumor overexpression
K-ras mutation	panitumumab, cetuximab	Lack of efficacy with *KRAS* mutation
Philadelphia chromosome	dasatinib, nilotinib, imatinib	Decreased efficacy in Philadelphia chromosome–negative chronic myelogenous leukemia

[a]Drug effect in homozygotes unless otherwise specified. [b]Many tricyclic antidepressants and selective serotonin uptake inhibitors are metabolized by either CYP2D6, CYP2C19, or both, and some metabolites have pharmacologic activity. See *https://www.pharmgkb.org/view/dosing-guidelines.do*.

Note: EM, extensive metabolizer (normal enzymatic activity); IM, intermediate metabolizer (heterozygote for loss of function allele); PM, poor metabolizer (homozygote for reduced or loss of function allele); UM, ultra-rapid metabolizer (enzymatic activity much greater than normal, e.g., with gene duplication, Fig. 64-1). SJS/TEN: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

Further data at:
U.S. Food and Drug Administration: *http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm*
Pharmacogenetics Research Network/Knowledge Base: *http://www.pharmgkb.org*
The Clinical Pharmacogenomics Implementation Consortium: *https://www.pharmgkb.org/page/cpic*

to achieve a therapeutic effect. Tamoxifen undergoes CYP2D6-mediated biotransformation to an active metabolite, so its efficacy may be in part related to this polymorphism. In addition, the widespread use of selective serotonin reuptake inhibitors (SSRIs) to treat tamoxifen-related hot flashes may also alter the drug's effects because many SSRIs, notably fluoxetine and paroxetine, are also CYP2D6 inhibitors.

CYP2C19 The PM phenotype for CYP2C19 is common (20%) among Asians and rarer (2–3%) in other populations. The impact of polymorphic CYP2C19-mediated metabolism has been demonstrated with the proton pump inhibitor omeprazole, where ulcer cure rates with "standard" dosages were much lower in EM patients (29%) than in PMs (100%). Thus, understanding the importance of this polymorphism would have been important in developing the drug, and knowing a patient's *CYP2C19* genotype should improve therapy. CYP2C19 is responsible for bioactivation of the antiplatelet drug clopidogrel, and several large retrospective studies have documented decreased efficacy (e.g., increased myocardial infarction after placement of coronary stents or increased stroke or transient ischemic attacks) among subjects with one or two reduction of function alleles. In addition, some studies suggest that omeprazole and possibly other proton pump inhibitors phenocopy this effect by inhibiting CYP2C19.

CYP2C9 There are common variants in *CYP2C9* that encode proteins with reduction or loss of catalytic function. These variant alleles are associated with increased rates of neurologic complications with phenytoin, hypoglycemia with glipizide, and reduced warfarin dose required to maintain stable anticoagulation. Rare patients homozygous for loss of function alleles may require very low warfarin dosages. Up to 50% of the variability in steady-state warfarin dose requirement is attributable to polymorphisms in *CYP2C9* and in the promoter of *VKORC1*, which encodes the warfarin target with lesser contributions by genes controlling vitamin K metabolism such as *CYP4F2*. The angiotensin-receptor blocker losartan is a prodrug that is bioactivated by CYP2C9; as a result, PMs and those receiving inhibitor drugs may display little response to therapy.

DPYD Individuals homozygous for loss of function alleles in dihydropyrimidine dehydrogenase, encoded by DPYD, are at high risk for severe toxicity when exposed to the substrate anticancer drug 5-Fluorouracil (5-FU), as well as to capecitabine and tegafur, which are metabolized to 5-FU. Dose reductions have been recommended in intermediate metabolizers.

Transferase Variants Thiopurine S-methyltransferase (TPMT) bioinactivates the antileukemic drug 6-mercaptopurine (6-MP) and 6-MP is itself an active metabolite of the immunosuppressive azathioprine. Homozygotes for alleles encoding inactive TPMT (1/300 individuals) predictably exhibit severe and potentially fatal pancytopenia on standard doses of azathioprine or 6-MP. On the other hand, homozygotes for fully functional alleles may display less anti-inflammatory or antileukemic effect with standard doses of the drugs.

N-acetylation is catalyzed by hepatic *N*-acetyl transferase (NAT), which represents the activity of two genes, *NAT1* and *NAT2*. Both enzymes transfer an acetyl group from acetyl coenzyme A to the drug; polymorphisms in *NAT2* are thought to underlie individual differences in the rate at which drugs are acetylated and thus define "rapid acetylators" and "slow acetylators." Slow acetylators make up ~50% of European and African populations but are less common among East Asians. Slow acetylators have an increased incidence of the drug-induced lupus syndrome during procainamide and hydralazine therapy and of hepatitis with isoniazid.

Individuals homozygous for a common promoter polymorphism that reduces transcription of uridine diphosphate glucuronosyltransferase (*UGT1A1*) have benign hyperbilirubinemia (Gilbert's syndrome; **Chap. 330**). This variant has also been associated with diarrhea and increased bone marrow depression with the antineoplastic prodrug irinotecan, whose active metabolite is normally detoxified by UGT1A1-mediated glucuronidation. The antiretroviral atazanavir is a UGT1A1 inhibitor, and individuals with the Gilbert's variant develop higher bilirubin levels during treatment. While this is benign, the hyperbilirubinemia can complicate clinical care because it may raise the question of whether coexistent hepatic injury is present.

Transporter Variants The risk for myotoxicity with simvastatin and possibly other statins appears increased with variants in *SLCO1B1*. Variants in *ABCB1*, encoding the drug efflux transporter P-glycoprotein, may increase digoxin toxicity. Variants in the uptake transporters *MATE1* and *MATE2* have been reported to modulate metformin's glucose-lowering activity.

GENETIC VARIANTS AFFECTING PHARMACODYNAMICS

A variant in the *VKORC1* promoter, especially common in Asian subjects (Table 64-1), reduces transcriptional activity and warfarin dose requirement. Multiple polymorphisms identified in the β_2-adrenergic receptor appear to be linked to specific phenotypes in asthma and congestive heart failure, diseases in which β_2-receptor function might be expected to determine prognosis. Polymorphisms in the β_2-receptor gene have also been associated with response to inhaled β_2-receptor agonists, while those in the β_1-adrenergic receptor gene have been associated with variability in heart rate slowing and blood pressure lowering. In addition, in heart failure, the arginine allele of the common β_1-adrenergic receptor gene polymorphism R389G has been associated with decreased mortality and decreased incidence of atrial fibrillation during treatment with the investigational beta blocker bucindolol.

Drugs may also interact with genetic pathways of disease to elicit or exacerbate symptoms of the underlying conditions. In the porphyrias, CYP inducers are thought to increase the activity of enzymes proximal to the deficient enzyme, exacerbating or triggering attacks **(Chap. 409)**. Deficiency of glucose-6-phosphate dehydrogenase (G6PD), most often in individuals of African, Mediterranean, or South Asian descent, increases the risk of hemolytic anemia in response to the antimalarial primaquine **(Chap. 96)** and the uric acid-lowering agent rasburicase, which does not cause hemolysis in patients with normal amounts of the enzyme. Patients with mutations in *RYR1* encoding the skeletal muscle intracellular release calcium (also termed type 1 ryanodine receptor) are asymptomatic until exposed to certain general anesthetics, which can trigger the rare syndrome of malignant hyperthermia. Certain antiarrhythmics and other drugs can produce marked QT prolongation and torsades de pointes **(Chap. 241)**, and in some patients, this adverse effect represents unmasking of previously subclinical congenital long QT syndrome.

Immunologically Mediated Drug Reactions The Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are potentially fatal skin reactions now increasingly recognized to be linked to specific HLA alleles (see Table 64-2). Some cases of hepatotoxicity have also been linked to variants in this region. The frequency of risk alleles often varies by ancestry (Table 64-1). The HLA risk alleles appear to be necessary but not sufficient to elicit these reactions. For example, HLA-B*57:01 is a risk allele for abacavir-related SJS/TEN and flucloxacillin-related hepatotoxicity. However, while 55% of abacavir-exposed subjects will develop reaction, only 1/10,000 subjects exposed to flucloxacillin develop hepatotoxicity. Thus, a third factor, the nature of which has not yet been established, seems necessary.

Tumor and Infectious Agent Genomes The actions of drugs used to treat infectious or neoplastic disease may be modulated by variants in these nonhuman germline genomes. Genotyping tumors is a rapidly evolving approach to target therapies to underlying mechanisms and to avoid potentially toxic therapy in patients who would derive no benefit **(Chap. 67)**. Trastuzumab, which potentiates anthracycline-related cardiotoxicity, is ineffective in breast cancers that do not express the herceptin receptor. Imatinib targets a specific tyrosine kinase, BCR-Abl1, that is generated by the translocation that creates the Philadelphia chromosome typical of chronic myelogenous leukemia (CML). BCR-Abl1 is not only active but may be central to the pathogenesis of CML; use of imatinib and other BCR-Abl1 inhibitors has resulted in remarkable efficacy not only in CML but also in other BCR-Abl1-positive tumors such as gastrointestinal stromal tumors **(see Chap. 67)**. Similarly, the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab appear especially effective in colon cancers in which K-ras, a G protein in the EGFR pathway, is not mutated. Vemurafenib does not inhibit wild-type *BRAF* but is active against the V600E mutant form of the kinase. Crizotinib is highly effective in non-small cell lung cancers harboring anaplastic lymphoma kinase (ALK) mutations.

INCORPORATING PHARMACOGENETIC INFORMATION INTO CLINICAL PRACTICE

The discovery of common variant alleles with relatively large effects on drug response raises the prospect that these variants could be used to guide therapy. Desired outcomes could be better ways of choosing likely effective drugs and dosages, or avoiding drugs that are likely to produce severe adverse drug events or be ineffective in individual subjects. Indeed, the FDA now incorporates pharmacogenetic data into package inserts meant to guide prescribing. A decision to adopt pharmacogenetically guided dosing for a given drug depends on multiple factors. The most important are the magnitude and clinical importance of the genetic effect and the strength of evidence linking genetic variation to variable drug effects (e.g., anecdote versus post-hoc analysis of clinical trial data versus randomized clinical trial, RCT). The evidence can be strengthened if statistical arguments from clinical trial data are complemented by an understanding of underlying physiologic mechanisms. Cost versus expected benefit may also be a factor.

Reactive versus Preemptive Approaches Two approaches to pharmacogenetic implementation have been put in place at both "early adopter" institutions and are currently being evaluated. In the first, variant-specific assays are ordered at the time of drug prescription and delivered rapidly (often within an hour or two) and the results then used to guide therapy with that specific drug. The alternative to this "reactive" approach is a "preemptive" approach in which pharmacogenetic testing for large numbers of potential variants across many drugs is undertaken prior to prescription of any such drug. The data are then available in electronic health record (EHR) systems and coupled to real time clinical decision support (CDS). When a drug whose effects are known to be influenced by pharmacogenetic variants is prescribed, the EHR system looks up whether variants likely to affect response are present; if so, CDS will alert healthcare providers that an alternate drug or a different dose may be required.

Challenges There are multiple challenges in putting in place either system. Assay validity and reproducibility have been issues in the past, but are less likely now. National consortia are now being put in place to develop standards for pharmacogenetic CDS. While common variants in genes such as those listed in Table 64-1 have been clearly associated with variable drug responses, the effect of rare variants, now readily discoverable by large scale sequencing, is unknown. The extent to which a dose adjustment might be recommended may vary depending on whether zero, one, or two variant alleles are present, and whether such variants are reduction of function, loss-of-function, or gain of function. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed and published guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availability of genetic data. CPIC does not, however, address the question of when or how such genetic testing should be undertaken.

Developing Evidence that Pharmacogenetic Testing Alters Drug Outcomes A major issue is whether pharmacogenetic testing affects important drug response outcomes. When the

evidence is compelling, alternate therapies are not available, and there are clear recommendations for dosage adjustment in subjects with variants, there is a strong argument for deploying genetic testing as a guide to prescribing; HLA-B*57:01 testing for abacavir is an example described below. In other situations, the arguments are less compelling: the magnitude of the genetic effect may be smaller, the consequences may be less serious, alternate therapies may be available, or the drug effect may be amenable to monitoring by other approaches.

One school argues that the physiology and pharmacology are known, and that RCTs are, therefore, unnecessary (and conceivably unethical). The analogy is sometimes drawn to well-recognized dose adjustment of renally excreted drugs in the presence of renal dysfunction. RCTs have not been conducted and the idea of such dose adjustment is well accepted in the medical community and recommended in FDA-approved drug labels. Others have argued that the effect of genetic variants is generally modest and variability in drug actions has many non-genetic sources, so genetic testing might provide marginal benefit at best.

Efforts to demonstrate the value of pharmacogenetic testing have met with mixed results. An RCT clearly showed that HLA-B*57:01 testing eliminates SJS/TEN due to abacavir. Similarly, regulatory authorities in some countries in Southeast Asia mandated HLA-B*15:02 testing prior to initiation of carbamazepine; however, in this case, an unfortunate outcome was that while the use of carbamazepine dropped, it was often substituted by phenytoin (another drug associated with SJS/TEN), so the incidence of the severe ADR was unchanged.

RCTs evaluating the effect of using pharmacogenetically guided therapy to optimize warfarin treatment have shown either no effect or a modest benefit of incorporating genetic information into prescribing the drug. These RCTs focused on time in therapeutic range in the first 4–12 weeks of treatment, and were not powered to examine outcomes such as recurrent thrombosis or bleeding. Retrospective analyses of bleeding cases vs non-bleeding controls in EHRs and administrative databases have suggested a role for CYP2C9*3 or the variants in V433M variant in CYP4F2 in mediating this risk.

While large retrospective analyses indicate that CYP2C19 loss of function variants decrease clopidogrel efficacy, RCTs are difficult to design: many argue that it is unethical to randomize individuals known to be homozygous for loss of function alleles, since administering clopidogrel is then tantamount to administering placebo. However, trials examining outcomes in only heterozygotes might require very large numbers of subjects.

New effective alternate therapies to warfarin and clopidogrel that appear to lack important pharmacogenetic variants have emerged. One approach to therapy, therefore, is to use pharmacogenetic testing to identify subjects in whom variants are absent and therefore standard doses of the conventional inexpensive drugs are likely to be effective and reserve alternate more expensive therapies for subjects likely to have variant responses to warfarin or clopidogrel. As price drops and as experience grows with newer agents, it is likely that clopidogrel and warfarin will be largely supplanted.

GENETICS AND DRUG DEVELOPMENT

Genetic tools are now being increasingly used to identify or validate new drug targets. Initial studies this field suggest that a new drug development program is more likely to succeed if evidence from human genetics supports the role of a possible drug target in disease pathogenesis and suggests that the risk of toxicity due to high risk pharmacokinetics or other mechanisms is small.

Finding Protective Alleles Can Identify Drug Targets One example of using genetics to identify a new drug target started with the discovery that very rare gain of function variants in *PCSK9* are a rare cause of familial hypercholesterolemia. Subsequently, population studies showed that carriers of loss of function SNPs (2.5% of African Americans) had decreased low-density lipoprotein, decreased incidence of coronary artery disease, and no deleterious consequences in other organ systems. These data triggered the development of PCSK9 antagonists which were marketed less than 10 years after the initial population studies. Other targets implicated by similar population genetic studies include SLC30A8 for the prevention of type 2 diabetes and APOC3 for hypertriglyceridemia. In the latter examples, the identification of an apparently protective effect of rare loss-of-function alleles required very large datasets (>100,000) coupling DNA to longitudinal clinical information; long-term epidemiologic studies like the Framingham Heart Study or EHR systems are now being harnessed to address this opportunity.

Cancer In cancer, tumor sequencing has identified new targets for drug development, often constitutively active kinases. A problem in this area has been the rapid emergence of drug resistance, often after extraordinary initial responses. For example, 40% of melanomas appear to be driven by the V600E mutant form of BRAF, and the specific inhibitor vemurafenib can produce clinically spectacular remission. However, durable responses are rare, and it is now apparent that combination therapy, often with inhibitors of the MEK pathway, can provide improved therapy. Another approach that is rapidly gaining wide use in cancer are drugs that reverse immune system inhibition (Chap. 69). In some patients the release of this "break" can provide durable remissions, whereas in others, severe adverse events, including colitis, pneumonitis, and myocarditis, have been reported. Understanding the mechanisms underlying variability to these therapies is a major emerging challenge in the field.

Using Multiple Data Types The development of methods to understand associations across multiple large datasets is another approach that is being explored in drug development. For example, a GWA of risk of rheumatoid arthritis identified multiple risk loci and many encode proteins that are known targets for intervention in the disease. Interestingly, others encode proteins that are targets for drugs used in other conditions, such as certain cancers, raising the question of whether such drugs could be "repurposed" for rheumatoid arthritis. An extension of this approach is the broader issue of systems pharmacology, in which multiple sources of data are used to identify potential molecules or pathways that would be amenable to treatment, by new drugs or by existing agents, using analysis of genomic, transcriptomic, proteomic, and other large datasets. Similar approaches are being developed to predict toxicity expected from targeting specific genes or disease pathways.

SUMMARY

The science of pharmacogenomics has evolved from isolated examples of rare adverse drug actions to a more comprehensive view of the role of genetic variation in mediating the effects of most drugs. Current principles include:

- Genetic variants with an important effect on drug actions can be common and their frequencies often vary by ancestry.
- One common mechanism is modulation of drug concentrations.
- No practitioner can be expected to remember all variants important for all drugs. Electronic data systems can now be accessed to describe this information. Ultimately, this information will be used by linking individual pharmacogenetic data to smart electronic health record systems.
- Incorporating genetic approaches into drug development projects hold the promise of more rapid development of targeted, safe, and effective therapies.

FURTHER READING

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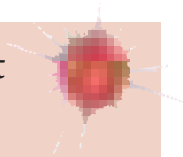
Section 1 Neoplastic Disorders

65 Approach to the Patient with Cancer



Dan L. Longo

The application of current treatment techniques (surgery, radiation therapy, chemotherapy, and biologic therapy) results in the cure of nearly two of three patients diagnosed with cancer. Nevertheless, patients experience the diagnosis of cancer as one of the most traumatic and revolutionary events that has ever happened to them. Independent of prognosis, the diagnosis brings with it a change in a person's self-image and in his or her role in the home and workplace. The prognosis of a person who has just been found to have pancreatic cancer is the same as the prognosis of the person with aortic stenosis who develops the first symptoms of congestive heart failure (median survival, ~8 months). However, the patient with heart disease may remain functional and maintain a self-image as a fully intact person with just a malfunctioning part, a diseased organ ("a bum ticker"). By contrast, the patient with pancreatic cancer has a completely altered self-image and is viewed differently by family and anyone who knows the diagnosis. He or she is being attacked and invaded by a disease that could be anywhere in the body. Every ache or pain takes on desperate significance. Cancer is an exception to the coordinated interaction among cells and organs. In general, the cells of a multicellular organism are programmed for collaboration. Many diseases occur because the specialized cells fail to perform their assigned task. Cancer takes this malfunction one step further. Not only is there a failure of the cancer cell to maintain its specialized function, but it also strikes out on its own; the cancer cell competes to survive using natural mutability and natural selection to seek advantage over normal cells in a recapitulation of evolution. One consequence of the traitorous behavior of cancer cells is that the patient feels betrayed by his or her body. The cancer patient feels that he or she, and not just a body part, is diseased.

THE MAGNITUDE OF THE PROBLEM

No nationwide cancer registry exists; therefore, the incidence of cancer is estimated on the basis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which tabulates cancer incidence and death figures from 13 sites, accounting for about 10% of the U.S. population, and from population data from the U.S. Census Bureau. In 2017, 1.688 million new cases of invasive cancer (836,150 men and 852,630 women) were diagnosed, and 600,920 persons (318,420 men and 282,500 women) died from cancer. The percent distribution of new cancer cases and cancer deaths by site for men and women is shown in Table 65-1. Cancer incidence has been declining by about 2% each year since 1992. Cancer is the cause of one in four deaths in the United States.

The most significant risk factor for cancer overall is age; two-thirds of all cases were in those aged >65 years. Cancer incidence increases as the third, fourth, or fifth power of age in different sites. For the interval between birth and age 49 years, 1 in 29 men and 1 in 19 women will develop cancer; for the interval between ages 50 and 59 years, 1 in 15 men and 1 in 17 women will develop cancer; for the interval between ages 60 and 69 years, 1 in 6 men and 1 in 10 women will develop cancer;

TABLE 65-1 Distribution of Cancer Incidence and Deaths for 2017

MALE			FEMALE		
SITES	**%**	**NUMBER**	**SITES**	**%**	**NUMBER**
Cancer Incidence					
Prostate	19	161,360	Breast	30	252,710
Lung	14	116,990	Lung	12	105,510
Colorectal	9	71,420	Colorectal	8	64,010
Bladder	7	60,490	Endometrial	6	61,380
Melanoma	6	52,170	Thyroid	5	42,470
Kidney	5	40,610	Melanoma	4	34,940
Lymphoma	5	40,080	Lymphoma	4	32,160
Leukemia	4	36,290	Leukemia	3	25,840
Oral Cavity	4	35,720	Pancreas	3	25,700
Liver	3	29,200	Kidney	3	23,380
All others	23	191,820	All others	22	184,530
All sites	100	836,150	All sites	100	852,630
Cancer Deaths					
Lung	27	84,590	Lung	25	71,280
Colorectal	9	27,150	Breast	14	40,610
Prostate	8	26,730	Colorectal	9	23,110
Pancreas	7	22,300	Pancreas	7	20,790
Liver	6	19,610	Ovary	5	14,080
Leukemia	4	14,300	Endometrial	4	10,920
Esophagus	4	12,720	Leukemia	4	10,200
Bladder	4	12,240	Liver	3	9310
Lymphoma	4	11,450	Lymphoma	3	8690
CNS	3	9620	CNS	3	7080
All others	24	77,710	All others	24	66,880
All sites	100	318,420	All sites	100	282,500

Source: From RL Siegel et al: Cancer statistics, 2017. CA Cancer J Clin 67:7, 2017.

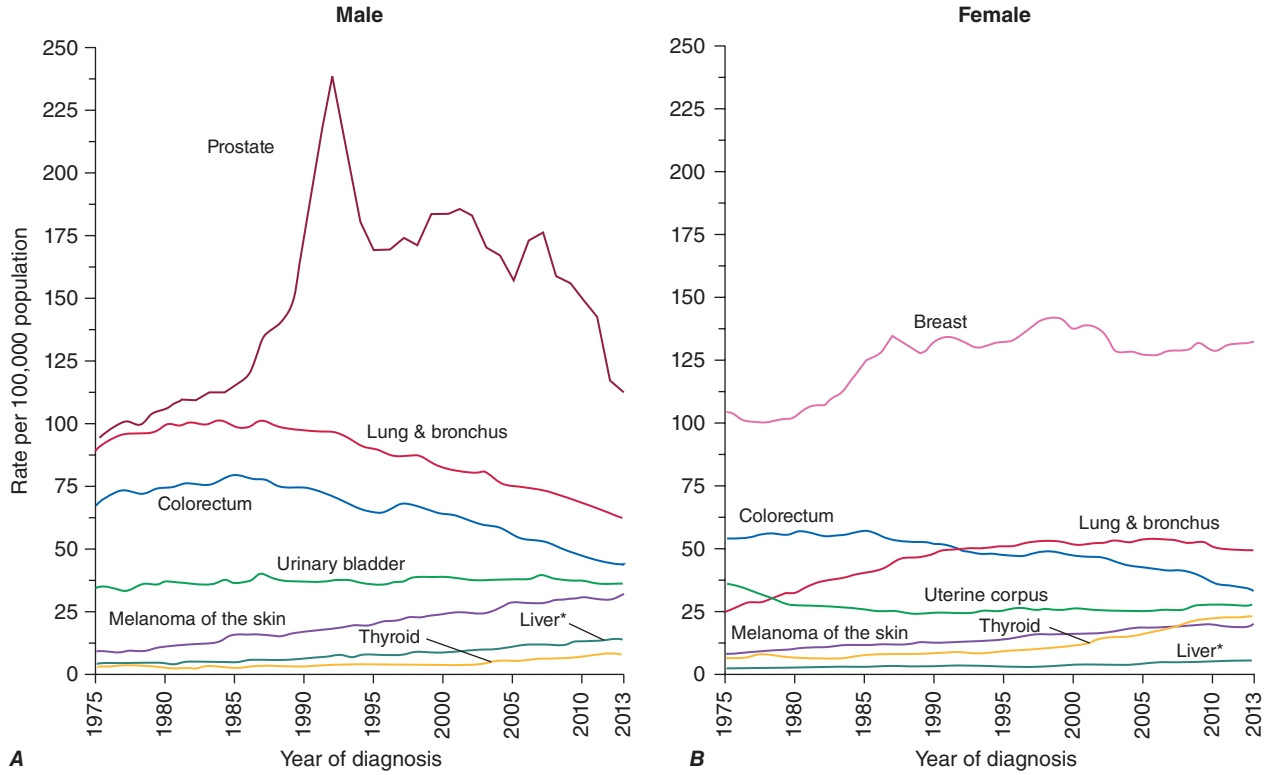


FIGURE 65-1 Incidence rates for particular types of cancer over the last 38 years in men (***A***) and women (***B***). *(From RL Siegel et al: CA Cancer J Clin 67:7, 2017.)*

and for people aged ≥70, 1 in 3 men and 1 in 4 women will develop cancer. Overall, men have a 44% risk of developing cancer at some time during their lives; women have a 38% lifetime risk.

Cancer is the second leading cause of death behind heart disease. Deaths from heart disease have declined 45% in the United States since 1950 and continue to decline. Cancer has overtaken heart disease as the number one cause of death in persons aged <85 years. Incidence trends over time are shown in **Fig. 65-1**. After a 70-year period of increase, cancer deaths began to decline in 1990–1991 **(Fig. 65-2)**. Between 1990 and 2010, cancer deaths decreased by 21% among men and 12.3% among women. The magnitude of the decline is illustrated in **Fig. 65-3**. The five leading causes of cancer deaths are shown for various populations in **Table 65-2**. The 5-year survival for white patients was 39% in 1960–1963 and 69% in 2003–2009. Cancers are more often deadly in blacks; the 5-year survival was 61% for the 2003–2009 interval; however, the racial differences are narrowing over time. Incidence and mortality vary among racial and ethnic groups **(Table 65-3)**. The basis for these differences is unclear.

CANCER AROUND THE WORLD

In 2008, 12.7 million new cancer cases and 7.6 million cancer deaths were estimated worldwide, according to estimates of GLOBOCAN 2008, developed by the International Agency for Research on Cancer (IARC). When broken down by region of the world, ~45% of cases were in Asia, 26% in Europe, 14.5% in North America, 7.1% in Central/South America, 6% in Africa, and 1% in Australia/New Zealand **(Fig. 65-4)**. Lung cancer is the most common cancer and the most common cause of cancer death in the world. Its incidence is highly variable, affecting only 2 per 100,000 African women but as many as 61 per 100,000 North American men. Breast cancer is the second most common cancer worldwide; however, it ranks fifth as a cause of death behind lung, stomach, liver, and colorectal cancer. Among the eight most common forms of cancer, lung (2-fold), breast (3-fold), prostate (2.5-fold), and colorectal (3-fold) cancers are more common in more developed countries than in less developed countries. By contrast, liver (twofold), cervical (twofold), and esophageal (two- to threefold) cancers are more common in less developed countries. Stomach cancer incidence is similar in more and less developed countries but is much more common in Asia than North America or Africa. The most common cancers in Africa are cervical, breast, and liver cancers. It has been estimated that nine modifiable risk factors are responsible for more than one-third of cancers worldwide. These include smoking, alcohol consumption, obesity, physical inactivity, low fruit and vegetable consumption, unsafe sex, air pollution, indoor smoke from household fuels, and contaminated injections.

PATIENT MANAGEMENT

Important information is obtained from every portion of the routine history and physical examination. The duration of symptoms may reveal the chronicity of disease. The past medical history may alert the physician to the presence of underlying diseases that may affect the choice of therapy or the side effects of treatment. The social history may reveal occupational exposure to carcinogens or habits, such as smoking or alcohol consumption, that may influence the course of disease and its treatment. The family history may suggest an underlying familial cancer predisposition and point out the need to begin surveillance or other preventive therapy for unaffected siblings of the patient. The review of systems may suggest early symptoms of metastatic disease or a paraneoplastic syndrome.

DIAGNOSIS

The diagnosis of cancer relies most heavily on invasive tissue biopsy and should never be made without obtaining tissue; no noninvasive diagnostic test is sufficient to define a disease process as cancer. Although in rare clinical settings (e.g., thyroid nodules), fine-needle aspiration is an acceptable diagnostic procedure, the diagnosis generally depends on obtaining adequate tissue to permit careful evaluation of the histology of the tumor, its grade, and its invasiveness and to yield further molecular diagnostic information, such as the expression of cell-surface markers or intracellular proteins that typify a particular cancer, or the presence of a molecular marker, such as the t(8;14) translocation of Burkitt's lymphoma. Increasing evidence links the expression of certain genes with the prognosis and response to therapy **(Chaps. 67 and 68)**.

Occasionally, a patient will present with a metastatic disease process that is defined as cancer on biopsy but has no apparent primary site of disease. Efforts should be made to define the primary site based on age,

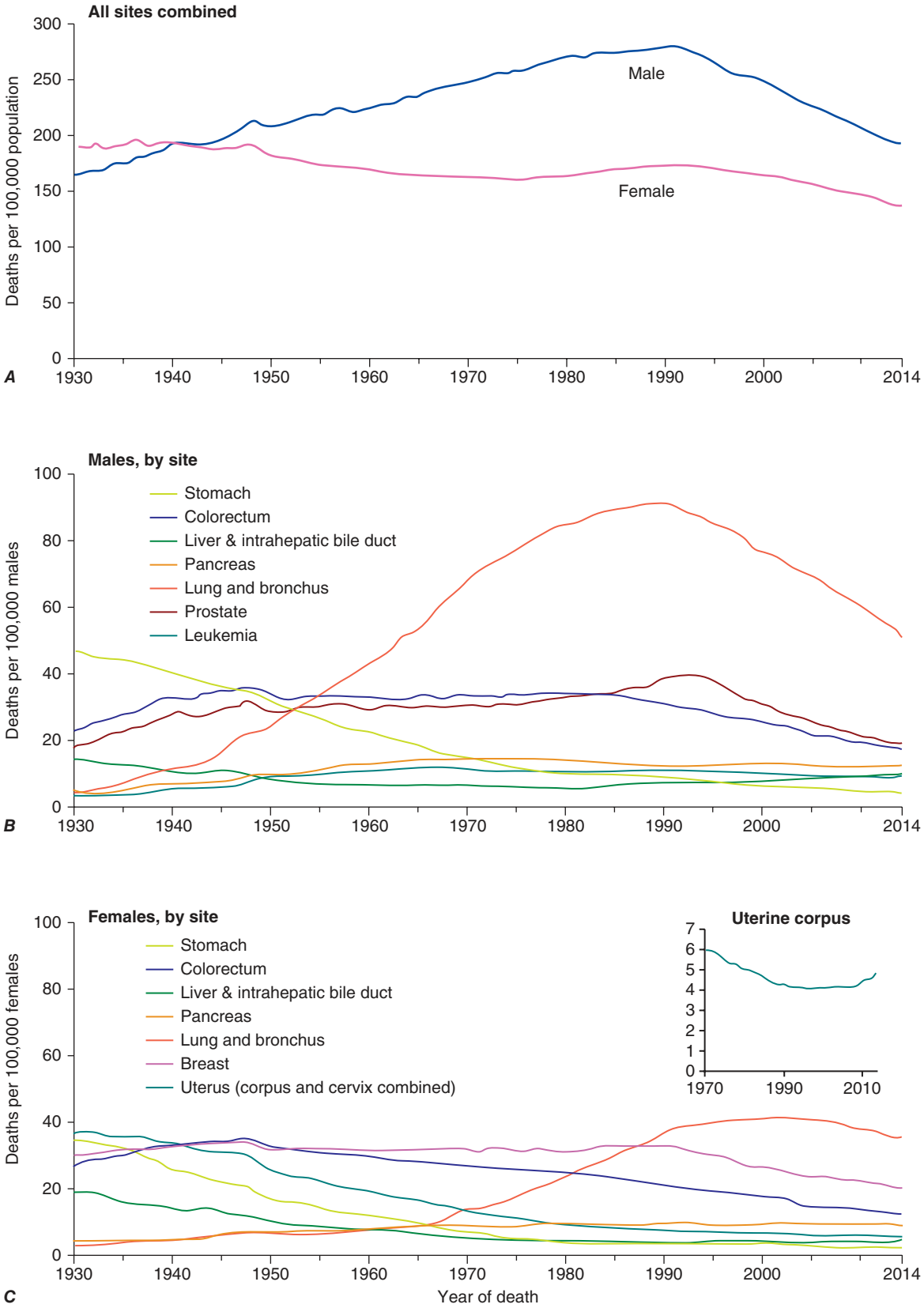


FIGURE 65-2 Eighty-five-year trend in cancer death rates for (***A***) women and (***B***) men by site in the United States, 1930–2014. Rates are per 100,000 age-adjusted to the 2000 U.S. standard population. All sites combined (***A***), individual sites in men (***B***) and individual sites in women (***C***) are shown. *(From RL Siegel et al: CA Cancer J Clin 67:7, 2017.)*

sex, sites of involvement, histology and tumor markers, and personal and family history. Particular attention should be focused on ruling out the most treatable causes **(Chap. 88)**.

Once the diagnosis of cancer is made, the management of the patient is best undertaken as a multidisciplinary collaboration among the primary care physician, medical oncologists, surgical oncologists, radiation oncologists, oncology nurse specialists, pharmacists, social workers, rehabilitation medicine specialists, and a number of other consulting professionals working closely with each other and with the patient and family.

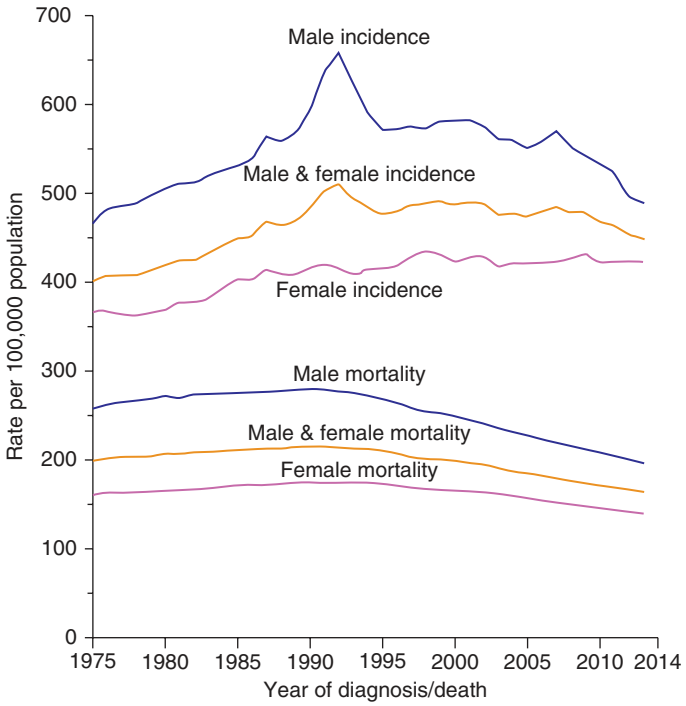


FIGURE 65-3 Trends in cancer incidence and death rates for men and women from 1975 to 2014. *(From RL Siegel et al: CA Cancer J Clin 67:7, 2017.)*

DEFINING THE EXTENT OF DISEASE AND THE PROGNOSIS

The first priority in patient management after the diagnosis of cancer is established and shared with the patient is to determine the extent of disease. The curability of a tumor usually is inversely proportional to the tumor burden. Ideally, the tumor will be diagnosed before symptoms develop or as a consequence of screening efforts **(Chap. 66)**. A very high proportion of such patients can be cured. However, most patients with cancer present with symptoms related to the cancer, caused either by mass effects of the tumor or by alterations associated with the production of cytokines or hormones by the tumor.

For most cancers, the extent of disease is evaluated by a variety of noninvasive and invasive diagnostic tests and procedures. This process is called *staging*. There are two types. *Clinical staging* is based on physical examination, radiographs, isotopic scans, computed tomography (CT) scans, and other imaging procedures; *pathologic staging* takes into account information obtained during a surgical procedure, which might include intraoperative palpation, resection of regional lymph nodes and/or tissue adjacent to the tumor, and inspection and biopsy of organs commonly involved in disease spread. Pathologic staging includes histologic examination of all tissues removed during the surgical procedure. Surgical procedures performed may include a simple lymph node biopsy or more extensive procedures such as thoracotomy, mediastinoscopy, or laparotomy. Surgical staging may occur in a separate procedure or may be done at the time of definitive surgical resection of the primary tumor.

Knowledge of the predilection of particular tumors for spreading to adjacent or distant organs helps direct the staging evaluation.

Information obtained from staging is used to define the extent of disease as localized, as exhibiting spread outside of the organ of origin to regional but not distant sites, or as metastatic to distant sites. The most widely used system of staging is the tumor, node, metastasis (TNM) system codified by the International Union Against Cancer and the American Joint Committee on Cancer. The TNM classification is an anatomically based system that categorizes the tumor on the basis of the size of the primary tumor lesion (T1–4, where a higher number indicates a tumor of larger size), the presence of nodal involvement (usually N0 and N1 for the absence and presence, respectively, of involved nodes, although some tumors have more elaborate systems of nodal grading), and the presence of metastatic disease (M0 and M1 for the absence and presence, respectively, of metastases). The various permutations of T, N, and M scores (sometimes including tumor histologic grade [G]) are then broken into stages, usually designated by the roman numerals I through IV. Tumor burden increases and curability decreases with increasing stage. Other anatomic staging systems are used for some tumors, e.g., the Dukes classification for colorectal cancers, the International Federation of Gynecologists and Obstetricians classification for gynecologic cancers, and the Ann Arbor classification for Hodgkin's disease.

Certain tumors cannot be grouped on the basis of anatomic considerations. For example, hematopoietic tumors such as leukemia, myeloma, and lymphoma are often disseminated at presentation and do not spread like solid tumors. For these tumors, other prognostic factors have been identified **(Chaps. 101–107)**.

In addition to tumor burden, a second major determinant of treatment outcome is the physiologic reserve of the patient. Patients who are bedridden before developing cancer are likely to fare worse, stage for stage, than fully active patients. Physiologic reserve is a determinant of how a patient is likely to cope with the physiologic stresses imposed by the cancer and its treatment. This factor is difficult to assess directly. Instead, surrogate markers for physiologic reserve are used, such as the patient's age or Karnofsky performance status **(Table 65-4)** or Eastern Cooperative Oncology Group (ECOG) performance status **(Table 65-5)**. Older patients and those with a Karnofsky performance status <70 or ECOG performance status ≥3 have a poor prognosis unless the poor performance is a reversible consequence of the tumor.

Increasingly, biologic features of the tumor are being related to prognosis. The expression of particular oncogenes, drug-resistance genes, apoptosis-related genes, and genes involved in metastasis is being found to influence response to therapy and prognosis. The presence of selected cytogenetic abnormalities may influence survival. Tumors

TABLE 65-2 The Five Leading Primary Tumor Sites for Patients Dying of Cancer Based on Age and Sex in 2017

			AGE, YEARS				
RANK	SEX	ALL AGES	UNDER 20	20–39	40–59	60–79	>80
1	M	Lung	CNS	CNS	Lung	Lung	Lung
	F	Lung	CNS	Breast	Lung	Lung	Lung
2	M	Prostate	Leukemia	Leukemia	Colorectal	Colorectal	Prostate
	F	Breast	Leukemia	Cervix	Breast	Breast	Breast
3	M	Colorectal	Bone sarcoma	Colorectal	Liver	Prostate	Colorectal
	F	Colorectal	Bone sarcoma	Colorectal	Colorectal	Colorectal	Colorectal
4	M	Pancreas	Soft tissue sarcoma	Lymphoma	Pancreas	Pancreas	Bladder
	F	Pancreas	Soft tissue sarcoma	Leukemial	Ovary	Pancreas	Pancreas
5	M	Liver	Lymphoma	Lung	Esophagus	Liver	Pancreas
	F	Ovary	Lymphoma	CNS	Pancreas	Ovary	Leukemia

Abbreviations: CNS, central nervous system; F, female; M, male.

Source: From RL Siegel et al: Cancer statistics, 2017. CA Cancer J Clin 67:7, 2017.

TABLE 65-3 Cancer Incidence and Mortality in Racial and Ethnic Groups, United States, 2009–2013

SITE	SEX	WHITE	BLACK	ASIAN/PACIFIC ISLANDER	AMERICAN INDIAN[a]	HISPANIC
Incidence per 100,000 Population						
All	M	519.3	577.3	310.2	426.7	498.1
	F	436.0	408.5	287.1	387.3	329.6
Breast		128.3	125.1	89.3	98.1	91.7
Colorectal	M	46.1	58.3	37.8	51.4	42.8
	F	35.2	42.7	27.8	41.2	29.8
Kidney	M	21.9	24.4	10.8	29.9	20.7
	F	11.3	13.0	4.8	17.6	11.9
Liver	M	9.7	16.9	20.4	18.5	19.4
	F	3.3	5.0	7.6	8.9	7.5
Lung	M	77.7	90.8	46.6	71.3	42.2
	F	58.2	51.0	28.3	56.2	25.6
Prostate		114.8	198.4	63.5	85.1	104.9
Cervix		7.0	9.8	6.1	9.7	9.9
Deaths per 100,000 Population						
All	M	204.0	253.4	122.7	183.6	142.5
	F	145.5	165.9	88.8	129.1	97.7
Breast		21.1	30.0	11.3	14.1	14.4
Colorectal	M	17.3	25.9	12.4	19.5	15.0
	F	12.3	16.9	8.8	14.0	9.2
Kidney	M	5.8	5.7	2.7	8.9	4.9
	F	2.5	2.5	1.1	4.2	2.3
Liver	M	8.0	13.3	14.3	14.9	13.1
	F	3.3	4.6	6.1	6.8	5.8
Lung	M	58.3	69.8	31.7	46.2	27.3
	F	39.8	35.5	18.0	30.8	13.4
Prostate		20.0	42.8	8.8	19.4	16.5
Cervix		2.3	3.9	1.7	2.8	2.6

[a]Based on Indian Health Service delivery areas.

Abbreviations: F, female; M, male.

Source: From RL Siegel R et al: Cancer statistics, 2017. CA Cancer J Clin 67:7, 2017.

with higher growth fractions, as assessed by expression of proliferation-related markers such as proliferating cell nuclear antigen, behave more aggressively than tumors with lower growth fractions. Information obtained from studying the tumor itself will increasingly be used to influence treatment decisions. Host genes involved in drug metabolism can influence the safety and efficacy of particular treatments.

Enormous heterogeneity has been noted by studying tumors; we have learned that morphology is not capable of discerning certain distinct subsets of patients whose tumors have different sets of abnormalities. Tumors that look the same by light microscopy can be very different. Similarly, tumors that look quite different from one another histologically can share genetic lesions that predict responses to treatments. Furthermore, tumor cells vary enormously within a single patient even though the cells share a common origin.

MAKING A TREATMENT PLAN

From information on the extent of disease and the prognosis and in conjunction with the patient's wishes, it is determined whether the treatment approach should be curative or palliative in intent. Cooperation among the various professionals involved in cancer treatment is of the utmost importance in treatment planning. For some cancers, chemotherapy or chemotherapy plus radiation therapy delivered before the use of definitive surgical treatment (so-called neoadjuvant therapy) may improve the outcome, as seems to be the case for locally advanced breast cancer and head and neck cancers. In certain settings in which combined-modality therapy is intended, coordination among the medical oncologist, radiation oncologist, and surgeon is crucial to achieving optimal results. Sometimes the chemotherapy and radiation therapy need to be delivered sequentially, and other times concurrently. Surgical procedures may precede or follow other treatment approaches. It is best for the treatment plan either to follow a standard protocol precisely or else to be part of an ongoing clinical research protocol evaluating new treatments. Ad hoc modifications of standard protocols are likely to compromise treatment results.

The choice of treatment approaches was formerly dominated by the local culture in both the university and the practice settings. However, it is now possible to gain access electronically to standard treatment protocols and to every approved clinical research study in North America through a personal computer interface with the Internet.[1]

The skilled physician also has much to offer the patient for whom curative therapy is no longer an option. Often a combination of guilt and frustration over the inability to cure the patient and the pressure of a busy schedule greatly limit the time a physician spends with a patient who is receiving only palliative care. Resist these forces. In addition to the medicines administered to alleviate symptoms (see below), it is important to remember the comfort that is provided by holding the patient's hand, continuing regular examinations, and taking time to talk.

[1]The National Cancer Institute maintains a database called PDQ (Physician Data Query) that is accessible on the Internet under the name CancerNet at *www.cancer.gov/cancertopics/pdq/cancerdatabase*. Information can be obtained through a facsimile machine using CancerFax by dialing 301-402-5874. Patient information is also provided by the National Cancer Institute in at least three formats: on the Internet via CancerNet at *www.cancer.gov*, through the CancerFax number listed above, or by calling 1-800-4-CANCER. The quality control for the information provided through these services is rigorous.

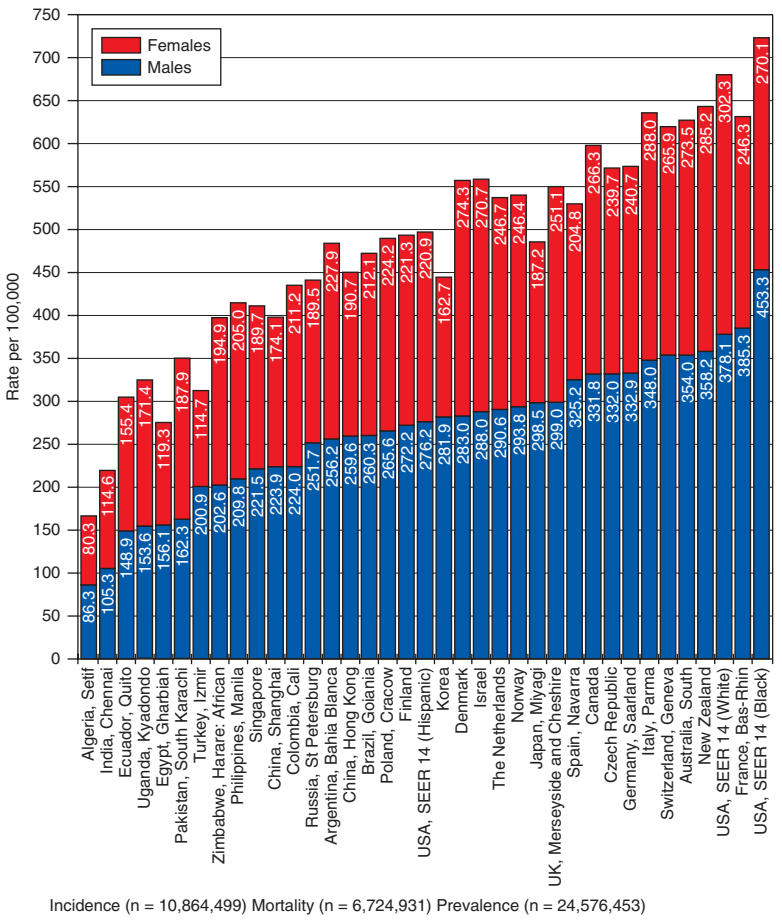


FIGURE 65-4 Worldwide overall annual cancer incidence, mortality, and 5-year prevalence for the period of 1993–2001. *(Adapted from A Jemal et al: Cancer Epidemiol Biomarkers Prev 19:1893, 2010.)*

MANAGEMENT OF DISEASE AND TREATMENT COMPLICATIONS

Because cancer therapies are toxic **(Chap. 69)**, patient management involves addressing complications of both the disease and its treatment as well as the complex psychosocial problems associated with cancer. In the short term during a course of curative therapy, the patient's functional status may decline. Treatment-induced toxicity is less acceptable if the goal of therapy is palliation. The most common side effects of treatment are nausea and vomiting (see below), febrile neutropenia **(Chap. 70)**, and myelosuppression **(Chap. 69)**. Tools are now available to minimize the acute toxicity of cancer treatment.

New symptoms developing in the course of cancer treatment should always be assumed to be reversible until proven otherwise. The fatalistic attribution of anorexia, weight loss, and jaundice to recurrent or progressive tumor could result in a patient dying from a reversible intercurrent cholecystitis. Intestinal obstruction may be due to reversible adhesions rather than progressive tumor. Systemic infections, sometimes with unusual pathogens, may be a consequence of the immunosuppression associated with cancer therapy. Some drugs used to treat cancer or its complications (e.g., nausea) may produce central nervous system symptoms that look like metastatic disease or may mimic paraneoplastic syndromes such as the syndrome of inappropriate antidiuretic hormone. A definitive diagnosis should be pursued and may even require a repeat biopsy.

A critical component of cancer management is assessing the response to treatment. In addition to a careful physical examination in which all sites of disease are physically measured and recorded in a flow chart by date, response assessment usually requires periodic repeating of imaging tests that were abnormal at the time of staging. If imaging tests have become normal, repeat biopsy of previously involved tissue is performed to document complete response by pathologic criteria. Biopsies are not usually required if there is macroscopic residual disease. A *complete response* is defined as disappearance of all evidence of disease, and a *partial response* as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions. The determination of partial response may also be based on a 30% decrease in the sums of the longest diameters of lesions (Response Evaluation Criteria in Solid Tumors [RECIST]). *Progressive disease* is defined as the appearance of any new lesion or an increase of >25% in the sum of the products of the perpendicular diameters of all measurable lesions (or an increase of 20% in the sums of the longest diameters by RECIST). Tumor shrinkage or growth that does not meet any of these criteria is considered *stable disease*. Some sites of involvement (e.g., bone) or patterns of involvement (e.g., lymphangitic lung or diffuse pulmonary infiltrates) are considered unmeasurable. No response is complete without biopsy documentation of their resolution, but partial responses may exclude their assessment unless clear objective progression has occurred.

For some hematologic neoplasms, flow cytometric and genetic assays may determine the presence of residual tumor cells that escape microscopic detection. In general, these techniques can reliably detect as few as 1 tumor cell among 10,000 cells. If such tests do not detect tumor cells, the patient is said to have minimal residual disease negativity, a finding generally associated with more durable remissions. Accumulating data are defining interventions in patients with minimal

TABLE 65-4 Karnofsky Performance Index

PERFORMANCE STATUS	FUNCTIONAL CAPABILITY OF THE PATIENT
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death is not imminent
20	Very sick; hospitalization is necessary; active supportive treatment is necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

TABLE 65-5 The Eastern Cooperative Oncology Group (ECOG) Performance Scale

ECOG Grade 0: Fully active, able to carry on all predisease performance without restriction
ECOG Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
ECOG Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
ECOG Grade 3: Capable of only limited self-care, confined to bed or chair >50% of waking hours
ECOG Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
ECOG Grade 5: Dead

Source: From MM Oken et al: Am J Clin Oncol 5:649, 1982.

residual disease positivity that can extend remission duration and survival.

Tumor markers may be useful in patient management in certain tumors. Response to therapy may be difficult to gauge with certainty. However, some tumors produce or elicit the production of markers that can be measured in the serum or urine, and in a particular patient, rising and falling levels of the marker are usually associated with increasing or decreasing tumor burden, respectively. Some clinically useful tumor markers are shown in Table 65-6. Tumor markers are not in themselves specific enough to permit a diagnosis of malignancy to be made, but once a malignancy has been diagnosed and shown to be associated with elevated levels of a tumor marker, the marker can be used to assess response to treatment.

The recognition and treatment of depression are important components of management. The incidence of depression in cancer patients is ~25% overall and may be greater in patients with greater debility. This diagnosis is likely in a patient with a depressed mood (dysphoria) and/or a loss of interest in pleasure (anhedonia) for at least 2 weeks. In addition, three or more of the following symptoms are usually present: appetite change, sleep problems, psychomotor retardation or agitation, fatigue, feelings of guilt or worthlessness, inability to concentrate, and suicidal ideation. Patients with these symptoms should receive therapy. Medical therapy with a serotonin reuptake inhibitor such as fluoxetine (10–20 mg/d), sertraline (50–150 mg/d), or paroxetine (10–20 mg/d) or a tricyclic antidepressant such as amitriptyline (50–100 mg/d) or desipramine (75–150 mg/d) should be tried, allowing 4–6 weeks for response. Effective therapy should be continued at least 6 months after resolution of symptoms. If therapy is unsuccessful, other classes of antidepressants may be used. In addition to medication, psychosocial interventions such as support groups, psychotherapy, and guided imagery may be of benefit.

Many patients opt for unproven or unsound approaches to treatment when it appears that conventional medicine is unlikely to be curative. Those seeking such alternatives are often well educated and may be early in the course of their disease. Unsound approaches are usually hawked on the basis of unsubstantiated anecdotes and not only cannot help the patient but may be harmful. Physicians should strive to keep communications open and nonjudgmental, so that patients are more likely to discuss with the physician what they are actually doing. The appearance of unexpected toxicity may be an indication that a supplemental therapy is being taken.[2]

TABLE 65-6 Tumor Markers

TUMOR MARKERS	CANCER	NONNEOPLASTIC CONDITIONS
Hormones		
Human chorionic gonadotropin	Gestational trophoblastic disease, gonadal germ cell tumor	Pregnancy
Calcitonin	Medullary cancer of the thyroid	
Catecholamines	Pheochromocytoma	
Oncofetal Antigens		
α Fetoprotein	Hepatocellular carcinoma, gonadal germ cell tumor	Cirrhosis, hepatitis
Carcinoembryonic antigen	Adenocarcinomas of the colon, pancreas, lung, breast, ovary	Pancreatitis, hepatitis, inflammatory bowel disease, smoking
Enzymes		
Prostatic acid phosphatase	Prostate cancer	Prostatitis, prostatic hypertrophy
Neuron-specific enolase	Small-cell cancer of the lung, neuroblastoma	
Lactate dehydrogenase	Lymphoma, Ewing's sarcoma	Hepatitis, hemolytic anemia, many others
Tumor-Associated Proteins		
Prostate-specific antigen	Prostate cancer	Prostatitis, prostatic hypertrophy
Monoclonal immunoglobulin	Myeloma	Infection, MGUS
CA-125	Ovarian cancer, some lymphomas	Menstruation, peritonitis, pregnancy
CA 19-9	Colon, pancreatic, breast cancer	Pancreatitis, ulcerative colitis
CD30	Hodgkin's disease, anaplastic large-cell lymphoma	—
CD25	Hairy cell leukemia, adult T-cell leukemia/lymphoma	—

Abbreviation: MGUS, monoclonal gammopathy of uncertain significance.

LONG-TERM FOLLOW-UP/LATE COMPLICATIONS

At the completion of treatment, sites originally involved with tumor are reassessed, usually by radiography or imaging techniques, and any persistent abnormality is biopsied. If disease persists, the multidisciplinary team discusses a new salvage treatment plan. If the patient has been rendered disease-free by the original treatment, the patient is followed regularly for disease recurrence. The optimal guidelines for follow-up care are not known. For many years, a routine practice has been to follow the patient monthly for 6–12 months, then every other month for a year, every 3 months for a year, every 4 months for a year, every 6 months for a year, and then annually. At each visit, a battery of laboratory and radiographic and imaging tests were obtained on the assumption that it is best to detect recurrent disease before it becomes symptomatic. However, where follow-up procedures have been examined, this assumption has been found to be untrue. Studies of breast cancer, melanoma, lung cancer, colon cancer, and lymphoma have all failed to support the notion that asymptomatic relapses are more readily cured by salvage therapy than symptomatic relapses. In view of the enormous cost of a full battery of diagnostic tests and their manifest lack of impact on survival, new guidelines are emerging for less frequent follow-up visits, during which the history and physical examination are the major investigations performed.

As time passes, the likelihood of recurrence of the primary cancer diminishes. For many types of cancer, survival for 5 years without recurrence is tantamount to cure. However, important medical problems can occur in patients treated for cancer and must be examined (Chap. 91). Some problems emerge as a consequence of the disease and some as a consequence of the treatment. An understanding of these disease- and treatment-related problems may help in their detection and management.

Despite these concerns, most patients who are cured of cancer return to normal lives.

SUPPORTIVE CARE

In many ways, the success of cancer therapy depends on the success of the supportive care. Failure to control the symptoms of cancer and its treatment may lead patients to abandon curative therapy. Of equal importance, supportive care is a major determinant of quality of life. Even when life cannot be prolonged, the physician must strive to preserve its quality. Quality-of-life measurements have become common endpoints of clinical research studies. Furthermore, palliative care has been shown to be cost-effective when approached in an organized fashion. A credo for oncology could be to cure sometimes, to extend life often, and to comfort always.

Pain Pain occurs with variable frequency in the cancer patient: 25–50% of patients present with pain at diagnosis, 33% have pain associated with treatment, and 75% have pain with progressive disease. The pain may have several causes. In ~70% of cases, pain is caused by the tumor itself—by invasion of bone, nerves, blood vessels, or

[2]Information about unsound methods may be obtained from the National Council Against Health Fraud, Box 1276, Loma Linda, CA 92354, or from the Center for Medical Consumers and Health Care Information, 237 Thompson Street, New York, NY 10012.

mucous membranes or obstruction of a hollow viscus or duct. In ~20% of cases, pain is related to a surgical or invasive medical procedure, to radiation injury (mucositis, enteritis, or plexus, or spinal cord injury), or to chemotherapy injury (mucositis, peripheral neuropathy, phlebitis, steroid-induced aseptic necrosis of the femoral head). In 10% of cases, pain is unrelated to cancer or its treatment.

Assessment of pain requires the methodical investigation of the history of the pain, its location, character, temporal features, provocative and palliative factors, and intensity **(Chap. 10)**; a review of the oncologic history and past medical history as well as personal and social history; and a thorough physical examination. The patient should be given a 10-division visual analogue scale on which to indicate the severity of the pain. The clinical condition is often dynamic, making it necessary to reassess the patient frequently. Pain therapy should not be withheld while the cause of pain is being sought.

A variety of tools are available with which to address cancer pain. About 85% of patients will have pain relief from pharmacologic intervention. However, other modalities, including antitumor therapy (such as surgical relief of obstruction, radiation therapy, and strontium-89 or samarium-153 treatment for bone pain), neurostimulatory techniques, regional analgesia, or neuroablative procedures, are effective in an additional 12% or so. Thus, very few patients will have inadequate pain relief if appropriate measures are taken. **A specific approach to pain relief is detailed in Chap. 9.**

Nausea Emesis in the cancer patient is usually caused by chemotherapy **(Chap. 69)**. Its severity can be predicted from the drugs used to treat the cancer. Three forms of emesis are recognized on the basis of their timing with regard to the noxious insult. *Acute emesis*, the most common variety, occurs within 24 h of treatment. *Delayed emesis* occurs 1–7 days after treatment; it is rare, but, when present, usually follows cisplatin administration. *Anticipatory emesis* occurs before administration of chemotherapy and represents a conditioned response to visual and olfactory stimuli previously associated with chemotherapy delivery.

Acute emesis is the best understood form. Stimuli that activate signals in the chemoreceptor trigger zone in the medulla, the cerebral cortex, and peripherally in the intestinal tract lead to stimulation of the vomiting center in the medulla, the motor center responsible for coordinating the secretory and muscle contraction activity that leads to emesis. Diverse receptor types participate in the process, including dopamine, serotonin, histamine, opioid, and acetylcholine receptors. The serotonin receptor antagonists ondansetron and granisetron are effective drugs against highly emetogenic agents, as are neurokinin receptor antagonists like aprepitant and fosaprepitant **(see Chap. 69)**.

As with the analgesia ladder, emesis therapy should be tailored to the situation. For mildly and moderately emetogenic agents, prochlorperazine, 5–10 mg PO or 25 mg PR, is effective. Its efficacy may be enhanced by administering the drug before the chemotherapy is delivered. Dexamethasone, 10–20 mg IV, is also effective and may enhance the efficacy of prochlorperazine. For highly emetogenic agents such as cisplatin, mechlorethamine, dacarbazine, and streptozocin, combinations of agents work best and administration should begin 6–24 h before treatment. Ondansetron, 8 mg PO every 6 h the day before therapy and IV on the day of therapy, plus dexamethasone, 20 mg IV before treatment, is an effective regimen. Addition of oral aprepitant (a substance P/neurokinin 1 receptor antagonist) to this regimen (125 mg on day 1, 80 mg on days 2 and 3) further decreases the risk of both acute and delayed vomiting. Like pain, emesis is easier to prevent than to alleviate.

Delayed emesis may be related to bowel inflammation from the therapy and can be controlled with oral dexamethasone and oral metoclopramide, a dopamine receptor antagonist that also blocks serotonin receptors at high dosages. The best strategy for preventing anticipatory emesis is to control emesis in the early cycles of therapy to prevent the conditioning from taking place. If this is unsuccessful, prophylactic antiemetics the day before treatment may help. Experimental studies are evaluating behavior modification.

Effusions Fluid may accumulate abnormally in the pleural cavity, pericardium, or peritoneum. Asymptomatic malignant effusions may not require treatment. Symptomatic effusions occurring in tumors responsive to systemic therapy usually do not require local treatment but respond to the treatment for the underlying tumor. Symptomatic effusions occurring in tumors unresponsive to systemic therapy may require local treatment in patients with a life expectancy of at least 6 months.

Pleural effusions due to tumors may or may not contain malignant cells. Lung cancer, breast cancer, and lymphomas account for ~75% of malignant pleural effusions. Their exudative nature is usually gauged by an effusion/serum protein ratio of ≥0.5 or an effusion/serum lactate dehydrogenase ratio of ≥0.6. When the condition is symptomatic, thoracentesis is usually performed first. In most cases, symptomatic improvement occurs for <1 month. Chest tube drainage is required if symptoms recur within 2 weeks. Fluid is aspirated until the flow rate is <100 mL in 24 h. Then either 60 units of bleomycin or 1 g of doxycycline is infused into the chest tube in 50 mL of 5% dextrose in water; the tube is clamped; the patient is rotated on four sides, spending 15 min in each position; and, after 1–2 h, the tube is again attached to suction for another 24 h. The tube is then disconnected from suction and allowed to drain by gravity. If <100 mL drains over the next 24 h, the chest tube is pulled, and a radiograph is taken 24 h later. If the chest tube continues to drain fluid at an unacceptably high rate, sclerosis can be repeated. Bleomycin may be somewhat more effective than doxycycline but is very expensive. Doxycycline is usually the drug of first choice. If neither doxycycline nor bleomycin is effective, talc can be used.

Symptomatic pericardial effusions are usually treated by creating a pericardial window or by stripping the pericardium. If the patient's condition does not permit a surgical procedure, sclerosis can be attempted with doxycycline and/or bleomycin.

Malignant ascites is usually treated with repeated paracentesis of small volumes of fluid. If the underlying malignancy is unresponsive to systemic therapy, peritoneovenous shunts may be inserted. Despite the fear of disseminating tumor cells into the circulation, widespread metastases are an unusual complication. The major complications are occlusion, leakage, and fluid overload. Patients with severe liver disease may develop disseminated intravascular coagulation.

Nutrition Cancer and its treatment may lead to a decrease in nutrient intake of sufficient magnitude to cause weight loss and alteration of intermediary metabolism. The prevalence of this problem is difficult to estimate because of variations in the definition of cancer cachexia, but most patients with advanced cancer experience weight loss and decreased appetite. A variety of both tumor-derived factors (e.g., bombesin, adrenocorticotropic hormone) and host-derived factors (e.g., tumor necrosis factor, interleukins 1 and 6, growth hormone) contribute to the altered metabolism, and a vicious cycle is established in which protein catabolism, glucose intolerance, and lipolysis cannot be reversed by the provision of calories.

It remains controversial how to assess nutritional status and when and how to intervene. Efforts to make the assessment objective have included the use of a prognostic nutritional index based on albumin levels, triceps skinfold thickness, transferrin levels, and delayed-type hypersensitivity skin testing. However, a simpler approach has been to define the threshold for nutritional intervention as <10% unexplained body weight loss, serum transferrin level <1500 mg/L (150 mg/dL), and serum albumin <34 g/L (3.4 g/dL).

The decision is important, because it appears that cancer therapy is substantially more toxic and less effective in the face of malnutrition. Nevertheless, it remains unclear whether nutritional intervention can alter the natural history. Unless some pathology is affecting the absorptive function of the gastrointestinal tract, enteral nutrition provided orally or by tube feeding is preferred over parenteral supplementation. However, the risks associated with the tube may outweigh the benefits. Megestrol acetate, a progestational agent, has been advocated as a pharmacologic intervention to improve nutritional status. Research

in this area may provide more tools in the future as cytokine-mediated mechanisms are further elucidated.

Psychosocial Support The psychosocial needs of patients vary with their situation. Patients undergoing treatment experience fear, anxiety, and depression. Self-image is often seriously compromised by deforming surgery and loss of hair. Women who receive cosmetic advice that enables them to look better also feel better. Loss of control over how one spends time can contribute to the sense of vulnerability. Juggling the demands of work and family with the demands of treatment may create enormous stresses. Sexual dysfunction is highly prevalent and needs to be discussed openly with the patient. An empathetic health care team is sensitive to the individual patient's needs and permits negotiation where such flexibility will not adversely affect the course of treatment.

Cancer survivors have other sets of difficulties. Patients may have fears associated with the termination of a treatment they associate with their continued survival. Adjustments are required to physical losses and handicaps, real and perceived. Patients may be preoccupied with minor physical problems. They perceive a decline in their job mobility and view themselves as less desirable workers. They may be victims of job and/or insurance discrimination. Patients may experience difficulty reentering their normal past life. They may feel guilty for having survived and may carry a sense of vulnerability to colds and other illnesses. Perhaps the most pervasive and threatening concern is the ever-present fear of relapse (the Damocles syndrome).

Patients in whom therapy has been unsuccessful have other problems related to the end of life.

Death and Dying The most common causes of death in patients with cancer are infection (leading to circulatory failure), respiratory failure, hepatic failure, and renal failure. Intestinal blockage may lead to inanition and starvation. Central nervous system disease may lead to seizures, coma, and central hypoventilation. About 70% of patients develop dyspnea preterminally. However, many months usually pass between the diagnosis of cancer and the occurrence of these complications, and during this period, the patient is severely affected by the possibility of death. The path of unsuccessful cancer treatment usually occurs in three phases. First, there is optimism at the hope of cure; when the tumor recurs, there is the acknowledgment of an incurable disease, and the goal of palliative therapy is embraced in the hope of being able to live with disease; finally, at the disclosure of imminent death, another adjustment in outlook takes place. The patient imagines the worst in preparation for the end of life and may go through stages of adjustment to the diagnosis. These stages include denial, isolation, anger, bargaining, depression, acceptance, and hope. Of course, patients do not all progress through all the stages or proceed through them in the same order or at the same rate. Nevertheless, developing an understanding of how the patient has been affected by the diagnosis and is coping with it is an important goal of patient management.

It is best to speak frankly with the patient and the family regarding the likely course of disease. These discussions can be difficult for the physician as well as for the patient and family. The critical features of the interaction are to reassure the patient and family that everything that can be done to provide comfort will be done. They will not be abandoned. Many patients prefer to be cared for in their homes or in a hospice setting rather than a hospital. The American College of Physicians has published a book called *Home Care Guide for Cancer: How to Care for Family and Friends at Home* that teaches an approach to successful problem-solving in home care. With appropriate planning, it should be possible to provide the patient with the necessary medical care as well as the psychological and spiritual support that will prevent the isolation and depersonalization that can attend in-hospital death.

The care of dying patients may take a toll on the physician. A "burnout" syndrome has been described that is characterized by fatigue, disengagement from patients and colleagues, and a loss of self-fulfillment. Efforts at stress reduction, maintenance of a balanced life, and setting realistic goals may combat this disorder.

End-of-Life Decisions Unfortunately, a smooth transition in treatment goals from curative to palliative may not be possible in all cases because of the occurrence of serious treatment-related complications or rapid disease progression. Vigorous and invasive medical support for a reversible disease or treatment complication is assumed to be justified. However, if the reversibility of the condition is in doubt, the patient's wishes determine the level of medical care. These wishes should be elicited before the terminal phase of illness and reviewed periodically. Information about advance directives can be obtained from the American Association of Retired Persons, 601 E Street, NW, Washington, DC 20049, 202-434-2277, or Choice in Dying, 250 West 57th Street, New York, NY 10107, 212-366-5540. Some states allow physicians to assist patients who choose to end their lives. This subject is challenging from an ethical and a medical point of view. Discussions of end-of-life decisions should be candid and involve clear informed consent, waiting periods, second opinions, and documentation. **A full discussion of end-of-life management is in Chap. 9.**

FURTHER READING

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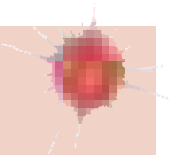
66 Prevention and Early Detection of Cancer



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Improved understanding of carcinogenesis has allowed cancer prevention and early detection to expand beyond the identification and avoidance of carcinogens. Specific interventions to reduce cancer mortality by preventing cancer in those at risk, and effective screening for early detection of cancer, are the goals.

Carcinogenesis is a process that usually extends over years, a continuum of discrete tissue and cellular changes over time resulting in aberrant physiologic processes. Prevention concerns the identification and manipulation of the biologic, environmental, social, and genetic factors in the causal pathway of cancer.

EDUCATION AND HEALTHFUL HABITS

Public education on the avoidance of identified risk factors for cancer and encouraging healthy habits contributes to cancer prevention. The clinician is a powerful messenger in this process. The patient-provider encounter provides an opportunity to teach patients about the hazards of smoking, features of a healthy lifestyle, and use of proven cancer screening methods.

SMOKING CESSATION

Tobacco smoking is a strong, modifiable risk factor for cardiovascular disease, pulmonary disease, and cancer. Smokers have an ~1 in 3 lifetime risk of dying prematurely from a tobacco-related cancer, cardiovascular, or pulmonary disease. Tobacco use causes more deaths from cardiovascular disease than from cancer. Lung cancer and cancers of the larynx, oropharynx, esophagus, kidney, bladder, colon, pancreas, and stomach are all tobacco-related.

The number of cigarettes smoked per day and the level of inhalation of cigarette smoke are correlated with risk of lung cancer mortality. Light- and low-tar cigarettes are not safer, because smokers tend to inhale them more frequently and deeply.

Those who stop smoking have a 30–50% lower 10-year lung cancer mortality rate compared to those who continue smoking, despite the fact that some carcinogen-induced gene mutations persist for years after smoking cessation. Smoking cessation and avoidance would save more lives than any other public health activity.

The risk of tobacco smoke is not limited to the smoker. Environmental tobacco smoke, known as secondhand or passive smoke, causes lung cancer and other cardiopulmonary diseases in nonsmokers.

Tobacco use prevention is a pediatric issue. More than 80% of adult American smokers began smoking before the age of 18 years. Approximately 13% of Americans in grades 9 through 12 reported using two or more tobacco products in the past month. Electronic cigarettes have been advanced as a tool to achieve smoking cessation in adult smokers, but there is concern that they serve as a "gateway" to cigarette uptake in adolescents and are increasing in use. Counseling of adolescents and young adults is critical to prevent smoking. A clinician's simple advice can be of benefit. Providers should query patients on tobacco use and offer smokers assistance in quitting.

Current approaches to smoking cessation recognize smoking as an addiction (Chap. 448). The smoker who is quitting goes through identifiable stages including: contemplation of quitting, an action phase in which the smoker quits, and a maintenance phase. Smokers who quit completely are more likely to be successful than those who gradually reduce the number of cigarettes smoked or change to lower-tar or lower-nicotine cigarettes. More than 90% of the Americans who have successfully quit smoking did so on their own, without participation in an organized cessation program, but cessation programs are helpful for some. The Community Intervention Trial for Smoking Cessation (COMMIT) was a 4-year program showing that light smokers (<25 cigarettes per day) were more likely to benefit from simple cessation messages and cessation programs than those who did not receive an intervention. Quit rates were 30.6% in the intervention group and 27.5% in the control group. The COMMIT interventions were unsuccessful in heavy smokers (>25 cigarettes per day). Heavy smokers may need an intensive broad-based cessation program that includes counseling, behavioral strategies, and pharmacologic adjuncts, such as nicotine replacement (gum, patches, sprays, lozenges, and inhalers), bupropion, and/or varenicline.

The health risks of cigars are similar to those of cigarettes. Smoking one or two cigars daily doubles the risk for oral and esophageal cancers; smoking three or four cigars daily increases the risk of oral cancers more than eightfold and esophageal cancer fourfold. The risks of occasional use are unknown.

Smokeless tobacco also represents a substantial health risk. Chewing tobacco is a carcinogen linked to dental caries, gingivitis, oral leukoplakia, and oral cancer. The systemic effects of smokeless tobacco (including snuff) may increase risks for other cancers. Esophageal cancer is linked to carcinogens in tobacco dissolved in saliva and swallowed. The net effects of e-cigarettes on health are poorly studied.

PHYSICAL ACTIVITY

Physical activity is associated with a decreased risk of colon and breast cancer. A variety of mechanisms have been proposed. However, such studies are prone to confounding factors such as recall bias, association of exercise with other health-related practices, and effects of preclinical cancers on exercise habits (reverse causality).

DIET MODIFICATION

International epidemiologic studies suggest that diets high in fat are associated with increased risk for cancers of the breast, colon, prostate, and endometrium. These cancers have their highest incidence and mortalities in Western cultures, where fat composes an average of one-third of the total calories consumed.

Despite correlations, dietary fat has not been proven to cause cancer. Case-control and cohort epidemiologic studies give conflicting results. In addition, diet is a highly complex exposure to many nutrients and chemicals. Low-fat diets are associated with many dietary changes beyond simple subtraction of fat. Other lifestyle changes are also associated with adherence to a low-fat diet.

In observational studies, dietary fiber is associated with a reduced risk of colonic polyps and invasive cancer of the colon. However, cancer-protective effects of increasing fiber and lowering dietary fat have not been proven in the context of a prospective clinical trial. The putative protective mechanisms are complex and speculative. Fiber binds oxidized bile acids and generates soluble fiber products, such as butyrate, that may have differentiating properties. Fiber does not increase bowel transit times. Two large prospective cohort studies of >100,000 health professionals showed no association between fruit and vegetable intake and risk of cancer.

The Polyp Prevention Trial randomly assigned 2000 elderly persons, who had polyps removed, to a low-fat, high-fiber diet versus routine diet for 4 years. No differences were noted in polyp formation.

The U.S. National Institutes of Health Women's Health Initiative, launched in 1994, was a long-term clinical trial enrolling >100,000 women age 45–69 years. It placed women into 22 intervention groups. Participants received calcium/vitamin D supplementation; hormone replacement therapy; and counseling to increase exercise, eat a low-fat diet with increased consumption of fruits, vegetables, and fiber, and cease smoking. The study showed that although dietary fat intake was lower in the diet intervention group, invasive breast cancers were not reduced over an 8-year follow-up period compared to the control group. No reduction was seen in the incidence of colorectal cancer in the dietary intervention arm. The difference in dietary fat averaged ~10% between the two groups. Evidence does not currently establish the anticarcinogenic value of vitamin, mineral, or nutritional supplements in amounts greater than those provided by a balanced diet.

ENERGY BALANCE

Risk of certain cancers appears to increase modestly (relative risks generally in the 1.0–2.0 range) as body mass index (BMI) increases beyond 25 kg/m^2. A cohort study of >5 million adults included in the U.K. Clinical Practice Research Datalink (a primary care database) found that each 5 kg/m^2 increase in BMI was linearly associated with cancers of the uterus, gallbladder, kidney, cervix, thyroid, and leukemia. Positive associations were also noted between BMI and colon, liver, ovarian, and postmenopausal breast cancers, but these associations were not linear and the effect varied by individual characteristics. High BMI appears to have an inverse association with prostate and premenopausal breast cancer.

SUN AVOIDANCE

Nonmelanoma skin cancers (basal cell and squamous cell) are induced by cumulative exposure to ultraviolet (UV) radiation. Intermittent acute sun exposure and sun damage have been linked to melanoma, but the evidence is inconsistent. Sunburns, especially in childhood and adolescence, may be associated with an increased risk of melanoma in adulthood. Reduction of sun exposure through use of protective clothing and changing patterns of outdoor activities can reduce skin cancer risk. Sunscreens decrease the risk of actinic keratoses, the precursor to squamous cell skin cancer, but melanoma risk may not be reduced. Sunscreens prevent burning, but they may encourage more prolonged exposure to the sun and may not filter out wavelengths of energy that cause melanoma.

Appearance-focused behavioral interventions in young women can decrease indoor tanning use and other UV exposures and may be more effective than messages about long-term cancer risks. Self-examination for skin pigment characteristics associated with skin cancer, such as freckling, may be useful in identifying people at high risk. Those who recognize themselves as being at risk tend to be more compliant with sun-avoidance recommendations. Risk factors for melanoma include a propensity to sunburn, a large number of benign melanocytic nevi, and atypical nevi.

CANCER CHEMOPREVENTION

Chemoprevention involves the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent carcinogenesis before the development of invasive malignancy.

Cancer develops through an accumulation of tissue abnormalities associated with genetic and epigenetic changes, and growth regulatory pathways that are potential points of intervention to prevent cancer. The initial changes are termed *initiation*. The alteration can be inherited or acquired through the action of physical, infectious, or chemical carcinogens. Like most human diseases, cancer arises from an interaction between genetics and environmental exposures **(Table 66-1)**. Influences that cause the initiated cell and its surrounding tissue microenvironment to progress through the carcinogenic process and change phenotypically are termed *promoters*. Promoters include hormones such as androgens, linked to prostate cancer, and estrogen, linked to breast and endometrial cancer. The distinction between an initiator and promoter is indistinct; some components of cigarette smoke are "complete carcinogens," acting as both initiators and promoters.

TABLE 66-1 Suspected Carcinogens

CARCINOGENS[a]	ASSOCIATED CANCER OR NEOPLASM
Alkylating agents	Acute myeloid leukemia, bladder cancer
Androgens	Prostate cancer
Aromatic amines (dyes)	Bladder cancer
Arsenic	Cancer of the lung, skin
Asbestos	Cancer of the lung, pleura, peritoneum
Benzene	Acute myelocytic leukemia
Chromium	Lung cancer
Diethylstilbestrol (prenatal)	Vaginal cancer (clear cell)
Epstein-Barr virus	Burkitt's lymphoma, nasal T-cell lymphoma
Estrogens	Cancer of the endometrium, liver, breast
Ethyl alcohol	Cancer of the breast, liver, esophagus, head and neck
Helicobacter pylori	Gastric cancer, gastric MALT lymphoma
Hepatitis B or C virus	Liver cancer
Human immunodeficiency virus	Non-Hodgkin's lymphoma, Kaposi's sarcoma, squamous cell carcinomas (especially of the urogenital tract)
Human papilloma virus	Cancers of the cervix, anus, oropharynx
Human T-cell lymphotropic virus type 1 (HTLV-1)	Adult T-cell leukemia/lymphoma
Immunosuppressive agents (azathioprine, cyclosporine, glucocorticoids)	Non-Hodgkin's lymphoma
Ionizing radiation (therapeutic or diagnostic)	Breast, bladder, thyroid, soft tissue, bone, hematopoietic, and many more
Nitrogen mustard gas	Cancer of the lung, head and neck, nasal sinuses
Nickel dust	Cancer of the lung, nasal sinuses
Diesel exhaust	Lung cancer (miners)
Phenacetin	Cancer of the renal pelvis and bladder
Polycyclic hydrocarbons	Cancer of the lung, skin (especially squamous cell carcinoma of scrotal skin)
Radon gas	Lung cancer
Schistosomiasis	Bladder cancer (squamous cell)
Sunlight (ultraviolet)	Skin cancer (squamous cell and melanoma)
Tobacco (including smokeless)	Cancer of the upper aerodigestive tract, bladder
Vinyl chloride	Liver cancer (angiosarcoma)

[a]Agents that are thought to act as cancer initiators and/or promoters.

Cancer can be prevented or controlled through interference with the factors that cause cancer initiation, promotion, or progression. Compounds of interest in chemoprevention often have antimutagenic, hormone modulation, anti-inflammatory, antiproliferative, or proapoptotic activity (or a combination).

CHEMOPREVENTION OF CANCERS OF THE UPPER AERODIGESTIVE TRACT

Smoking causes diffuse epithelial injury in the oral cavity, neck, esophagus, and lung. Patients cured of squamous cell cancers of the lung, esophagus, oral cavity, and neck are at risk (as high as 5% per year) of developing second cancers of the upper aerodigestive tract. Cessation of cigarette smoking does not markedly decrease the cured cancer patient's risk of second malignancy, even though it does lower the cancer risk in those who have never developed a malignancy. Smoking cessation may halt the early stages of the carcinogenic process (such as metaplasia), but it may have no effect on late stages of carcinogenesis. This "field carcinogenesis" hypothesis for upper aerodigestive tract cancer has made "cured" patients an important population for chemoprevention of second malignancies.

Persistent oral human papilloma virus (HPV) infection, particularly HPV-16, increases the risk for cancers of the oropharynx. This association exists even in the absence of other risk factors such as smoking or alcohol use (although the magnitude of increased risk appears greater than additive when HPV infection and smoking are both present). Oral HPV infection is believed to be largely sexually acquired. Although the evidence is not definitive, the introduction of the HPV vaccine may eventually reduce oropharyngeal cancer rates.

Oral leukoplakia, a premalignant lesion commonly found in smokers, has been used as an intermediate marker of chemopreventive activity in smaller shorter-duration, randomized, placebo-controlled trials. Response was associated with upregulation of retinoic acid receptor-β (RAR-β). Therapy with high, relatively toxic doses of isotretinoin (13-*cis*-retinoic acid) causes regression of oral leukoplakia. However, the lesions recur when the therapy is withdrawn, suggesting the need for long-term administration. More tolerable doses of isotretinoin have not shown benefit in the prevention of head and neck cancer. Isotretinoin did not prevent second malignancies in patients cured of early-stage non-small cell lung cancer; mortality rates were actually increased in current smokers.

Several large-scale trials have assessed agents in the chemoprevention of lung cancer in patients at high risk. In the α-tocopherol/β-carotene (ATBC) Lung Cancer Prevention Trial, participants were male smokers, age 50–69 years at entry. Participants had smoked an average of one pack of cigarettes per day for 35.9 years. Participants received α-tocopherol, β-carotene, and/or placebo in a randomized, two-by-two factorial design. After median follow-up of 6.1 years, lung cancer incidence and mortality were statistically significantly increased in those receiving β-carotene. α-Tocopherol had no effect on lung cancer mortality, with no apparent interaction between the two drugs. Patients receiving α-tocopherol had a higher incidence of hemorrhagic stroke.

The β-Carotene and Retinol Efficacy Trial (CARET) involved 17,000 American smokers and workers with asbestos exposure. Entrants were randomly assigned to one of four arms and received β-carotene, retinol, and/or placebo in a two-by-two factorial design. This trial also demonstrated harm from β-carotene: a lung cancer rate of 5 per 1000 subjects per year for those taking placebo versus 6 per 1000 subjects per year for those taking β-carotene.

The ATBC and CARET results demonstrate the importance of testing chemoprevention hypotheses thoroughly before widespread implementation because the results contradict a number of observational studies. The Physicians' Health Trial showed no change in the risk of lung cancer for those taking β-carotene; however, fewer of its participants were smokers than those in the ATBC and CARET studies.

CHEMOPREVENTION OF COLON CANCER

Many colon cancer prevention trials are based on the premise that most colorectal cancers develop from adenomatous polyps. These trials use adenoma recurrence or disappearance as a surrogate endpoint (not

yet validated) for colon cancer prevention. Early clinical trial results suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), such as piroxicam, sulindac, and aspirin, may prevent adenoma formation or cause regression of adenomatous polyps. The mechanism of action of NSAIDs is unknown, but they are presumed to work through the cyclooxygenase pathway. Although two randomized controlled trials (the Physicians' Health Study and the Women's Health Study) did not show an effect of aspirin on colon cancer or adenoma incidence in persons with no previous history of colonic lesions after 10 years of therapy, these trials did show an approximately 18% relative risk reduction for colonic adenoma incidence in persons with a previous history of adenomas after 1 year. A meta-analysis of four randomized controlled trials (albeit primarily designed to examine aspirin's effects on cardiovascular events) found that aspirin at doses of at least 75 mg/d resulted in a 33% relative reduction in colorectal cancer incidence after 20 years, with no clear increase in efficacy at higher doses. Based on a systematic review of evidence from randomized trials for primary prevention of cardiovascular disease, the U.S. Preventive Services Task Force concluded that the balance of benefits and harms favored initiating low-dose aspirin for colorectal cancer prevention in adults age 50–59 if they have a 10% or greater 10-year risk of cardiovascular disease. Cyclooxygenase-2 (COX-2) inhibitors have also been considered for colorectal cancer and polyp prevention. Trials with COX-2 inhibitors were initiated, but an increased risk of cardiovascular events in those taking the COX-2 inhibitors was noted, suggesting that these agents are not suitable for chemoprevention in the general population.

Epidemiologic studies suggest that diets high in calcium lower colon cancer risk. Calcium binds bile and fatty acids, which cause proliferation of colonic epithelium. It is hypothesized that calcium reduces intraluminal exposure to these compounds. The randomized controlled Calcium Polyp Prevention Study found that calcium supplementation decreased the absolute risk of adenomatous polyp recurrence by 7% at 4 years; extended observational follow-up demonstrated a 12% absolute risk reduction 5 years after cessation of treatment. However, in the Women's Health Initiative, combined use of calcium carbonate and vitamin D twice daily did not reduce the incidence of invasive colorectal cancer compared with placebo after 7 years.

The Women's Health Initiative demonstrated that postmenopausal women taking estrogen plus progestin have a 44% lower relative risk of colorectal cancer compared to women taking placebo. Of >16,600 women randomized and followed for a median of 5.6 years, 43 invasive colorectal cancers occurred in the hormone group and 72 in the placebo group. The positive effect on colon cancer is mitigated by the modest increase in cardiovascular and breast cancer risks associated with combined estrogen plus progestin therapy.

Most case-control and cohort studies have not confirmed early reports of an association between regular statin use and a reduced risk of colorectal cancer. No randomized controlled trials have addressed this hypothesis. A meta-analysis of statin use showed no protective effect of statins on overall cancer incidence or death.

CHEMOPREVENTION OF BREAST CANCER

Tamoxifen is an antiestrogen with partial estrogen agonistic activity in some tissues, such as endometrium and bone. One of its actions is to upregulate transforming growth factor β, which decreases breast cell proliferation. In a randomized placebo-controlled prevention trial involving >13,000 pre- and postmenopausal women at high risk, tamoxifen decreased the risk of developing breast cancer by 49% (from 43.4 to 22 per 1000 women) after a median follow-up of nearly 6 years. Tamoxifen also reduced bone fractures; a small increase in risk of endometrial cancer, stroke, pulmonary emboli, and deep vein thrombosis was noted. The International Breast Cancer Intervention Study (IBIS-I) and the Italian Randomized Tamoxifen Prevention Trial also demonstrated a reduction in breast cancer incidence with tamoxifen use. A trial comparing tamoxifen with another selective estrogen receptor modulator, raloxifene, performed in postmenopausal women showed that raloxifene is comparable to tamoxifen in cancer prevention, but without the risk of endometrial cancer. Raloxifene was associated with more invasive breast cancers and a trend toward more noninvasive breast cancers, but fewer thromboembolic events than tamoxifen; the drugs are similar in risks of other cancers, fractures, ischemic heart disease, and stroke. Both tamoxifen and raloxifene (the latter for postmenopausal women only) have been approved by the U.S. Food and Drug Administration (FDA) for reduction of breast cancer in women at high risk for the disease (1.66% risk at 5 years based on the Gail risk model: *http://www.cancer.gov/bcrisktool/*).

Because the aromatase inhibitors are even more effective than tamoxifen in adjuvant breast cancer therapy, it has been hypothesized that they would be more effective in breast cancer prevention. A randomized, placebo-controlled trial of exemestane reported a 65% relative reduction (from 5.5 to 1.9 per 1000 women) in the incidence of invasive breast cancer in women at elevated risk after a median follow-up of about 3 years. Common adverse effects included arthralgias, hot flashes, fatigue, and insomnia. No trial has directly compared aromatase inhibitors with selective estrogen receptor modulators for breast cancer chemoprevention.

CHEMOPREVENTION OF PROSTATE CANCER

Finasteride and dutasteride are 5-α-reductase inhibitors. They inhibit conversion of testosterone to dihydrotestosterone (DHT), a potent stimulator of prostate cell proliferation. The Prostate Cancer Prevention Trial (PCPT) randomly assigned men age 55 years or older at average risk of prostate cancer to finasteride or placebo. All men in the trial were being regularly screened with prostate-specific antigen (PSA) levels and digital rectal examination. After 7 years of therapy, the incidence of prostate cancer was 18.4% in the finasteride arm, compared with 24.4% in the placebo arm, a statistically significant difference. However, the finasteride group had more patients with tumors of Gleason score 7 and higher compared with the placebo arm (6.4 vs 5.1%). Long-term (10–15 years) follow-up did not reveal any statistically significant differences in overall mortality between all men in the finasteride and placebo arms or in men diagnosed with prostate cancer, but the power to detect a difference was limited.

Dutasteride has also been evaluated as a preventive agent for prostate cancer. The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a randomized double-blind trial in which ~8200 men with an elevated PSA (2.5–10 ng/mL for men age 50–60 years and 3–10 ng/mL for men age 60 years or older) and negative prostate biopsy on enrollment received daily 0.5 mg of dutasteride or placebo. The trial found a statistically significant 23% relative risk reduction in the incidence of biopsy-detected prostate cancer in the dutasteride arm at 4 years of treatment (659 cases vs 858 cases, respectively). Overall, across years 1 through 4, there was no difference between the arms in the number of tumors with a Gleason score of 7 to 10; however, during years 3 and 4, there was a statistically significant difference in tumors with Gleason score of 8 to 10 in the dutasteride arm (12 tumors vs 1 tumor, respectively).

The clinical importance of the apparent increased incidence of higher-grade tumors in the 5-α-reductase inhibitor arms of these trials is controversial. It may represent an increased sensitivity of PSA and digital rectal exam for high-grade tumors in men receiving these agents. The FDA has analyzed both trials, and it determined that the use of a 5-α-reductase inhibitor for prostate cancer chemoprevention would result in one additional high-grade (Gleason score 8 to 10) prostate cancer for every three to four lower-grade (Gleason score <6) tumors averted. Although it acknowledged that detection bias may have accounted for the finding, a causative role for 5-α-reductase inhibitors could not be conclusively dismissed. These agents are therefore not FDA-approved for prostate cancer prevention.

Because all men in both the PCPT and REDUCE trials were being screened and because screening approximately doubles the rate of prostate cancer, it is not known if finasteride or dutasteride decreases the risk of prostate cancer in men who are not being screened or simply reduces the risk of non-life threatening cancers detectable by screening.

Several favorable laboratory and observational studies led to the formal evaluation of selenium and α-tocopherol (vitamin E) as potential prostate cancer preventives. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) assigned 35,533 men to receive 200 μg/d

selenium, 400 IU/d α-tocopherol, selenium plus vitamin E, or placebo. After a median follow-up of 7 years, a trend toward an increased risk of developing prostate cancer was observed for those men taking vitamin E alone as compared to the placebo arm (hazard ratio 1.17; 95% confidence interval, 1.004–1.36).

VACCINES AND CANCER PREVENTION

A number of infectious agents cause cancer. Hepatitis B and C are linked to liver cancer; some HPV strains are linked to cervical, anal, and head and neck cancer; and *Helicobacter pylori* is associated with gastric adenocarcinoma and gastric lymphoma. Vaccines to protect against these agents may therefore reduce the risk of their associated cancers.

The hepatitis B vaccine is effective in preventing hepatitis and hepatomas due to chronic hepatitis B infection.

A nonavalent vaccine (covering HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available for use in the United States. HPV types 6 and 11 cause genital papillomas. The remaining HPV types cause cervical and anal cancer; reduction in HPV types 16 and 18 alone could prevent >70% of cervical cancers worldwide. For individuals not previously infected with these HPV strains, the vaccine demonstrates high efficacy in preventing persistent strain-specific HPV infections. Studies also confirm the vaccine's ability to prevent preneoplastic lesions (cervical or anal intraepithelial neoplasia [CIN/AIN] I, II, and III). The durability of the immune response beyond 8–10 years is not currently known. The vaccine does not appear to impact preexisting infections and the efficacy appears to be lower for populations that had previously been exposed to vaccine-specific HPV strains. A two-dose schedule is currently recommended in the United States for females and males age 9–14 years; teens and young adults who start the series between 15 and 26 years are recommended to receive three doses of the vaccine.

SURGICAL PREVENTION OF CANCER

Some organs in some individuals are at such high risk of developing cancer that surgical removal of the organ at risk may be considered. Women with severe cervical dysplasia are treated with laser or loop electrosurgical excision or conization and occasionally even hysterectomy. Colectomy is used to prevent colon cancer in patients with familial polyposis or ulcerative colitis.

Prophylactic bilateral mastectomy may be chosen for breast cancer prevention among women with genetic predisposition to breast cancer. In a prospective series of 139 women with *BRCA1* and *BRCA2* mutations, 76 chose to undergo prophylactic mastectomy and 63 chose close surveillance. At 3 years, no cases of breast cancer had been diagnosed in those opting for surgery, but eight patients in the surveillance group had developed breast cancer. A larger (n = 639) retrospective cohort study reported that three patients developed breast cancer after prophylactic mastectomy compared with an expected incidence of 30–53 cases: a 90–94% reduction in breast cancer risk. Postmastectomy breast cancer–related deaths were reduced by 81–94% for high-risk women compared with sister controls and by 100% for moderate-risk women when compared with expected rates.

Prophylactic salpingo-oophorectomy may also be employed for the prevention of ovarian and breast cancers among high-risk women. A prospective cohort study evaluating the outcomes of *BRCA* mutation carriers demonstrated a statistically significant association between prophylactic salpingo-oophorectomy and a reduced incidence of ovarian or primary peritoneal cancer (36% relative risk reduction, or a 4.5% absolute difference). Studies of prophylactic oophorectomy for prevention of breast cancer in women with genetic mutations have shown relative risk reductions of approximately 50%; the risk reduction may be greatest for women having the procedure at younger (i.e., <50 years) ages. The observation that most high-grade serous "ovarian cancers" actually arise in the fallopian tube fimbria raises the possibility that this lethal subtype may be prevented by ovary-sparing salpingectomy.

All of the evidence concerning the use of prophylactic mastectomy and salpingo-oophorectomy for prevention of breast and ovarian cancer in high-risk women has been observational in nature; such studies are prone to a variety of biases, including case selection bias, family relationships between patients and controls, and inadequate information about hormone use. Thus, they may give an overestimate of the magnitude of benefit.

CANCER SCREENING

Screening is a means of early detection in asymptomatic individuals, with the goal of decreasing morbidity and mortality. While screening can potentially reduce disease-specific deaths and has been shown to do so in cervical, colon, lung, and breast cancer, it is also subject to a number of biases that can suggest a benefit when actually there is none. Biases can even mask net harm. Early detection does not in itself confer benefit. Cause-specific mortality, rather than survival after diagnosis, is the preferred endpoint (see below).

Because screening is done on asymptomatic, healthy persons, it should offer substantial likelihood of benefit that outweighs harm. Screening tests and their appropriate use should be carefully evaluated before their use is widely encouraged in screening programs.

A large and increasing number of genetic mutations and nucleotide polymorphisms have been associated with an increased risk of cancer. Testing for these genetic mutations could in theory define a high-risk population. However, most of the identified mutations have very low penetrance and individually provide limited predictive accuracy. The ability to predict the development of a particular cancer may someday present therapeutic options as well as ethical dilemmas. It may eventually allow for early intervention to prevent a cancer or limit its severity. People at high risk may be ideal candidates for chemoprevention and screening; however, efficacy of these interventions in the high-risk population should be investigated. Currently, persons at high risk for a particular cancer can engage in intensive screening. While this course is clinically reasonable, it is not known if it reduces mortality in these populations.

The Accuracy of Screening A screening test's accuracy or ability to discriminate disease is described by four indices: sensitivity, specificity, positive predictive value, and negative predictive value **(Table 66-2)**. *Sensitivity*, also called the true-positive rate, is the proportion of persons with the disease who test positive in the screen (i.e., the ability of the test to detect disease when it is present). *Specificity*, or 1 minus the false-positive rate, is the proportion of persons who do not have the disease that test negative in the screening test (i.e., the ability of a test to correctly indicate that the disease is not present). The *positive predictive value* is the proportion of persons who test positive that actually have the disease. Similarly, *negative predictive value* is the proportion testing negative that do not have the disease. The sensitivity and specificity of a test are independent of the underlying prevalence (or risk) of the disease in the population screened, but the predictive values depend strongly on the prevalence of the disease.

TABLE 66-2 Assessment of the Value of a Diagnostic Test[a]

	CONDITION PRESENT	CONDITION ABSENT
Positive test	*a*	*b*
Negative test	*c*	*d*
a = true positive *b* = false positive *c* = false negative *d* = true negative		
Sensitivity	The proportion of persons with the condition who test positive: $a/(a+c)$	
Specificity	The proportion of persons without the condition who test negative: $d/(b+d)$	
Positive predictive value (PPV)	The proportion of persons with a positive test who have the condition: $a/(a+b)$	
Negative predictive value	The proportion of persons with a negative test who do not have the condition: $d/(c+d)$	

Prevalence, sensitivity, and specificity determine PPV

$$PPV = \frac{\text{prevalence} \times \text{sensitivity}}{(\text{prevalence} \times \text{sensitivity}) + (1 - \text{prevalence})(1 - \text{specificity})}$$

[a]For diseases of low prevalence, such as cancer, poor specificity has a dramatic adverse effect on PPV such that only a small fraction of positive tests are true positives.

Screening is most beneficial, efficient, and economical when the target disease is common in the population being screened. Specificity is at least as important to the ultimate feasibility and success of a screening test as sensitivity.

Potential Biases of Screening Tests Common biases of screening are lead time, length-biased sampling, and selection. These biases can make a screening test seem beneficial when actually it is not (or even causes net harm). Whether beneficial or not, screening can create the false impression of an epidemic by increasing the number of cancers diagnosed. It can also produce a shift in the *proportion* of patients diagnosed at an early stage (even without a reduction in absolute incidence of late-stage disease) and inflate survival statistics without reducing mortality (i.e., the number of deaths from a given cancer relative to the number of those at risk for the cancer). In such a case, the *apparent* duration of survival (measured from date of diagnosis) increases without lives being saved or life expectancy changed.

Lead-time bias occurs whether or not a test influences the natural history of the disease; the patient is merely diagnosed at an earlier date. Survival *appears* increased even if life is not prolonged. The screening test only prolongs the time the subject is aware of the disease and spends as a patient.

Length-biased sampling occurs because screening tests generally can more easily detect slow-growing, less aggressive cancers than fast-growing cancers. Cancers diagnosed due to the onset of symptoms between scheduled screenings are on average more aggressive, and treatment outcomes are not as favorable. An extreme form of length bias sampling is termed *overdiagnosis*, the detection of "pseudo disease." The reservoir of some undetected slow-growing tumors is large. Many of these tumors fulfill the histologic criteria of cancer but will never become clinically significant or cause death during the patient's remaining lifespan. This problem is compounded by the fact that the most common cancers appear most frequently at ages when competing causes of death are more frequent.

Selection bias occurs because the population most likely to seek screening often differs from the general population to which the screening test might be applied. In general, volunteers for studies are more health conscious and likely to have a better prognosis or lower mortality rate, irrespective of the screening result. This is termed the *healthy volunteer effect*.

Potential Drawbacks of Screening Risks associated with screening include harm caused by the screening intervention itself, harm due to the further investigation of persons with positive tests (both true and false positives), and harm from the treatment of persons with a true-positive result, whether or not life is extended by treatment (e.g., even if a screening test reduces relative cause-specific mortality by 20–30%, 70–80% of those diagnosed still go on to die of the target cancer). The diagnosis and treatment of cancers that would never have caused medical problems can lead to the harm of unnecessary treatment and give patients the anxiety of a cancer diagnosis. The psychosocial impact of cancer screening can be substantial when applied to the entire population.

Assessment of Screening Tests Good clinical trial design can offset some biases of screening and demonstrate the relative risks and benefits of a screening test. A randomized controlled screening trial with cause-specific mortality as the endpoint provides the strongest support for a screening intervention. Overall mortality should also be reported to detect an adverse effect of screening and treatment on other disease outcomes (e.g., cardiovascular disease). In a randomized trial, two like populations are randomly established. One is given the usual standard of care (which may be no screening at all) and the other receives the screening intervention being assessed. Efficacy for the population studied is established when the group receiving the screening test has a better cause-specific mortality rate than the control group. Studies showing a reduction in the incidence of advanced-stage disease, improved survival, or a stage shift are weaker (and possibly misleading) evidence of benefit. These latter criteria are early indicators but not sufficient to establish the value of a screening test.

Although a randomized, controlled screening trial provides the strongest evidence to support a screening test, it is not perfect. Unless the trial is population-based, it does not remove the question of generalizability to the target population. Screening trials generally involve thousands of persons and last for years. Less definitive study designs are therefore often used to estimate the effectiveness of screening practices. However, every nonrandomized study design is subject to strong confounders. In descending order of strength, evidence may also be derived from the findings of internally controlled trials using intervention allocation methods other than randomization (e.g., allocation by birth date, date of clinic visit); the findings of analytic observational studies; or the results of multiple time series studies with or without the intervention.

Screening for Specific Cancers Screening for cervical, colon, and breast cancer has the potential to be beneficial for certain age groups. Depending on age and smoking history, lung cancer screening can also be beneficial in specific settings. Special surveillance of those at high risk for a specific cancer because of a family history or a genetic risk factor may be prudent, but few studies have assessed the effect on mortality. A number of organizations have considered whether or not to endorse routine use of certain screening tests. Because criteria have varied, they have arrived at different recommendations. The American Cancer Society (ACS) and the U.S. Preventive Services Task Force (USPSTF) publish screening guidelines **(Table 66-3)**; the American Academy of Family Practitioners (AAFP) often follow/endorse the USPSTF recommendations; and the American College of Physicians (ACP) develops recommendations based on structured reviews of other organizations' guidelines.

BREAST CANCER Breast self-examination, clinical breast examination by a caregiver, mammography, and magnetic resonance imaging (MRI) have all been variably advocated as useful screening tools.

A number of trials have suggested that annual or biennial screening with mammography or mammography plus clinical breast examination in normal-risk women older than age 50 years decreases breast cancer mortality. Each trial has been criticized for design flaws. In most trials, breast cancer-related mortality rates were decreased by 15–30%. Experts disagree on whether average-risk women age 40–49 years should receive regular screening (Table 66-3). The U.K. Age Trial, the only randomized trial of breast cancer screening to specifically evaluate the impact of mammography in women age 40–49 years, found no statistically significant difference in breast cancer mortality for screened women versus controls after about 11 years of follow-up (relative risk 0.83; 95% confidence interval 0.66–1.04); however, <70% of women received screening in the intervention arm, potentially diluting the observed effect. A meta-analysis of nine large randomized trials showed an 8% relative reduction in mortality (relative risk 0.92; 95% confidence interval 0.75–1.02) from mammography screening for women age 39–49 years after 11–20 years of follow-up. This is equivalent to 3 breast cancer deaths prevented per 10,000 women >10 years (although the result is not statistically significant). At the same time, nearly half of women age 40–49 years screened annually will have false-positive mammograms necessitating further evaluation, often including biopsy. Estimates of overdiagnosis range from 10 to 40% of diagnosed invasive cancers. In the United States, widespread screening over the last several decades has not been accompanied by a reduction in incidence of metastatic breast cancer despite a large increase in early-stage disease, suggesting a substantial amount of overdiagnosis at the population level.

Digital breast tomosynthesis is an emerging method of breast cancer screening that reconstructs multiple x-ray images of the breast into superimposed "three-dimensional" slices. Although some evidence is available concerning the test characteristics of this modality, there are currently no data on its effects on health outcomes such as breast cancer-related morbidity, mortality, or overdiagnosis rates.

No study of breast self-examination has shown it to decrease mortality. A randomized controlled trial of approximately 266,000 women in China demonstrated no difference in breast cancer mortality between a group that received intensive breast self-exam instruction and reinforcement/reminders and controls at 10 years of follow-up.

TABLE 66-3 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition[a]

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Breast	Self-examination	"D"[b] (Not in current recommendations; from 2009)	Women, all ages: No specific recommendation
	Clinical examination	Women ≥40 years: "I" (as a stand-alone without mammography) (Not in current recommendations; from 2009)	Women, all ages: Do not recommend
	Mammography	Women 40–49 years: The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. ("C") Women 50–74 years: Every 2 years ("B") Women ≥75 years: "I"	Women 40–44 years: Provide the opportunity to begin annual screening Women 45–54 years: Screen annually Women ≥55 years: Transition to biennial screening or have the opportunity to continue annual screening Women ≥40 should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer
	Magnetic resonance imaging (MRI)	"I" (Not in current recommendations; from 2009)	Women with >20% lifetime risk of breast cancer: Screen with MRI plus mammography annually Women with 15–20% lifetime risk of breast cancer: Discuss option of MRI plus mammography annually Women with <15% lifetime risk of breast cancer: Do not screen annually with MRI
	Tomosynthesis	Women, all ages: "I"	No specific recommendation
Cervical	Pap test (cytology)	Women 21–65 years: Screen every 3 years ("A") Women <21 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D"	Women 21–29 years: Screen every 3 years Women 30–65 years: Acceptable approach to screen with cytology every 3 years (see HPV test below) Women <21 years: No screening Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
	HPV test	Women 30–65 years: Screen in combination with cytology every 5 years if woman desires to lengthen the screening interval (see Pap test above) ("A") Women <30 years: "D" Women >65 years, with adequate, normal prior Pap screenings: "D" Women after total hysterectomy for noncancerous causes: "D"	Women 30–65 years: Preferred approach to screen with HPV and cytology co-testing every 5 years (see Pap test above) Women <30 years: Do not use HPV testing Women >65 years: No screening following adequate negative prior screening Women after total hysterectomy for noncancerous causes: Do not screen
Colorectal	Sigmoidoscopy	Adults, 50–75 years: "A" Screen for colorectal cancer; the risks and benefits of the different screening methods vary Adults, 76 to 85 years: "C" The decision to screen should be an individual one, taking into account the patient's overall health and prior screening history Every 5 years; modeling suggests improved benefit if performed every 10 years in combination with annual FIT	Adults ≥50 years: Screen every 5 years
	Fecal occult blood testing (FOBT)	Every year	Adults ≥50 years: Screen every year
	Colonoscopy	Every 10 years	Adults ≥50 years: Screen every 10 years
	Fecal DNA testing	Every 1 or 3 years	Adults ≥50 years: Screen, but interval uncertain
	Fecal immuno-chemical testing (FIT)	Every year	Adults ≥50 years: Screen every year
	CT colonography	Every 5 years	Adults ≥50 years: Screen every 5 years
Lung	Low-dose computed tomography (CT) scan	Adults 55–80 years, with a ≥30 pack-year smoking history, still smoking or have quit within past 15 years: "B" Discontinue once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability to have curative lung surgery	Men and women, 55–74 years, with ≥30 pack-year smoking history, still smoking or have quit within past 15 years: Discuss benefits, limitations, and potential harms of screening; only perform screening in facilities with the right type of CT scanner and with high expertise/specialists
Ovarian	CA-125 Transvaginal ultrasound	Women, all ages: "D" Women, all ages: "D"	There is no sufficiently accurate test proven effective in the early detection of ovarian cancer. For women at high risk of ovarian cancer and/or who have unexplained, persistent symptoms, the combination of CA-125 and transvaginal ultrasound with pelvic exam may be offered.

(*Continued*)

TABLE 66-3 Screening Recommendations for Asymptomatic Subjects Not Known to Be at Increased Risk for the Target Condition[a] (Continued)

CANCER TYPE	TEST OR PROCEDURE	USPSTF	ACS
Prostate	Prostate-specific antigen (PSA)	Men, all ages: "D"	Starting at age 50, men should talk to a doctor about the pros and cons of testing so they can decide if testing is the right choice for them. If African American or have a father or brother who had prostate cancer before age 65, men should have this talk starting at age 45. How often they are tested will depend on their PSA level
	Digital rectal examination (DRE)	No individual recommendation	As for PSA; if men decide to be tested, they should have the PSA blood test with or without a rectal exam
Skin	Complete skin examination by clinician or patient	Adults, all ages: "I"	Self-examination monthly; clinical exam as part of routine cancer-related checkup

[a]Summary of the screening procedures recommended for the general population by the USPSTF and the ACS. These recommendations refer to asymptomatic persons who are not known to have risk factors, other than age or gender, for the targeted condition. [b]USPSTF lettered recommendations are defined as follows: "A": The USPSTF recommends the service, because there is high certainty that the net benefit is substantial; "B": The USPSTF recommends the service, because there is high certainty that the net benefit is moderate or moderate certainty that the net benefit is moderate to substantial; "C": The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences; there is at least moderate certainty that the net benefit is small; "D": The USPSTF recommends against the service because there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits; "I": The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service.

Abbreviations: ACS, American Cancer Society; USPSTF, U.S. Preventive Services Task Force.

However, more benign breast lesions were discovered and more breast biopsies were performed in the self-examination arm.

Genetic screening for *BRCA1* and *BRCA2* mutations and other markers of breast cancer risk has identified a group of women at high risk for breast cancer. Unfortunately, when to begin and the optimal frequency of screening have not been defined. Mammography is less sensitive at detecting breast cancers in women carrying *BRCA1* and *BRCA2* mutations, possibly because such cancers occur in younger women, in whom mammography is known to be less sensitive. MRI screening may be more sensitive than mammography in women at high risk due to genetic predisposition or in women with very dense breast tissue, but specificity may be lower. An increase in overdiagnosis may accompany the higher sensitivity. The impact of MRI on breast cancer mortality with or without concomitant use of mammography has not been evaluated in a randomized controlled trial.

CERVICAL CANCER Screening with Papanicolaou (Pap) smears decreases cervical cancer mortality. The cervical cancer mortality rate has fallen substantially since the widespread use of the Pap smear. With the onset of sexual activity comes the risk of sexual transmission of HPV, the fundamental etiologic factor for cervical cancer. Screening guidelines recommend regular Pap testing for all women who have reached the age of 21 (before this age, even in individuals that have begun sexual activity, screening may cause more harm than benefit). The recommended interval for Pap screening is 3 years. Screening more frequently adds little benefit but leads to important harms, including unnecessary procedures and overtreatment of transient lesions. Beginning at age 30, guidelines also offer the alternative of combined Pap smear and HPV testing for women. The screening interval for women who test normal using this approach may be lengthened to 5 years.

An upper age limit at which screening ceases to be effective is not known, but women age 65 years with no abnormal results in the previous 10 years may choose to stop screening. Screening should be discontinued in women who have undergone a hysterectomy with cervical excision for noncancerous reasons.

Although the efficacy of the Pap smear in reducing cervical cancer mortality has never been directly confirmed in a randomized, controlled setting, a clustered randomized trial in India evaluated the impact of one-time cervical visual inspection and immediate colposcopy, biopsy, and/or cryotherapy (where indicated) versus counseling on cervical cancer deaths in women age 30–59 years. After 7 years of follow-up, the age-standardized rate of death due to cervical cancer was 39.6 per 100,000 person-years in the intervention group versus 56.7 per 100,000 person-years in controls.

COLORECTAL CANCER Fecal occult blood testing (FOBT), digital rectal examination (DRE), rigid and flexible sigmoidoscopy, colonoscopy, and computed tomography (CT) colonography have been considered for colorectal cancer screening. A meta-analysis of five randomized controlled trials demonstrated a 22% relative reduction in colorectal cancer mortality after 2 to 9 rounds of biennial FOBT at 30 years of follow-up; annual screening was shown to result in a greater colorectal cancer mortality reduction in a single trial (a 32% relative reduction). The sensitivity for FOBT is increased if specimens are rehydrated before testing, but at the cost of lower specificity. The false-positive rate for rehydrated FOBT is high; 1–5% of persons tested have a positive test. Only 2–10% of those with occult blood in the stool have cancer. The high false-positive rate of FOBT substantially increases the number of colonoscopies performed.

Fecal immunochemical tests (FIT) have higher sensitivity for colorectal cancer than nonrehydrated FOBT tests. Multi-targeted stool DNA testing is an emerging screening modality that combines FIT with testing for altered DNA biomarkers in cells that are shed into the stool. Although limited evidence demonstrates that it has a higher single-test sensitivity for colorectal cancer than fecal immunochemical testing alone, its specificity is much lower, resulting in a higher number of false-positive tests and follow-up colonoscopies. There are no studies evaluating its effects on colorectal cancer incidence, morbidity, or mortality.

A blood test for the methylated *SEPT9* gene associated with colorectal cancer is available. However, its sensitivity is low, no longitudinal data have been collected on its performance or efficacy, and it is not recommended as a first-line screening test.

Two meta-analyses of five randomized controlled trials of sigmoidoscopy (i.e., the NORCCAP, SCORE, PLCO, Telemark, and U.K. trials) found an 18% relative reduction in colorectal cancer incidence and a 28% relative reduction in colorectal cancer mortality. Participant ages ranged from 50 to 74 years, with follow-up ranging from 6 to 13 years. Diagnosis of adenomatous polyps by sigmoidoscopy should lead to evaluation of the entire colon with colonoscopy. The most efficient interval for screening sigmoidoscopy is unknown, but an interval of 5 years is often recommended. Case-control studies suggest that intervals of up to 15 years may confer benefit; the randomized U.K. trial demonstrated benefit with one-time screening.

One-time colonoscopy detects ~25% more advanced lesions (polyps >10 mm, villous adenomas, adenomatous polyps with high-grade dysplasia, invasive cancer) than one-time FOBT with sigmoidoscopy; comparative *programmatic* performance of the two modalities over time is not known. Perforation rates are about 4/10,000 for colonoscopy and 1/10,000 for sigmoidoscopy. Debate continues on whether colonoscopy is too expensive and invasive and whether sufficient provider capacity exists to be recommended as the preferred screening tool in standard-risk populations. Some observational studies suggest

that efficacy of colonoscopy to decrease colorectal cancer mortality is primarily limited to the left side of the colon.

CT colonography, if done at expert centers, appears to have a sensitivity for polyps ≥6 mm comparable to colonoscopy. However, the rate of extracolonic findings of abnormalities of uncertain significance that must nevertheless be worked up is high (~5–37%); the long-term cumulative radiation risk of repeated colonography screenings is also a concern.

LUNG CANCER Chest x-ray and sputum cytology have been evaluated in several randomized lung cancer screening trials. The most recent and largest (n = 154,901) of these, a component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, found that, compared with usual care, annual chest x-ray did not reduce the risk of dying from lung cancer (relative risk 0.99; 95% confidence interval 0.87–1.22) after 13 years. Low-dose CT has also been evaluated in several randomized trials. The largest and longest of these, the National Lung Screening Trial (NLST), was a randomized controlled trial of screening for lung cancer in ~53,000 persons age 55–74 years with a 30+ pack-year smoking history. It demonstrated a statistically significant relative reduction of about 15–20% in lung cancer mortality in the CT arm compared to the chest x-ray arm (or about 3 fewer deaths per 1000 people screened with CT). However, the harms include the potential radiation risks associated with multiple scans, the discovery of incidental findings of unclear significance, and a high rate of false-positive test results. Both incidental findings and false-positive tests can lead to invasive diagnostic procedures associated with anxiety, expense, and complications (e.g., pneumo- or hemothorax after lung biopsy). The NLST was performed at experienced screening centers, and the balance of benefits and harms may differ in the community setting at less experienced centers.

OVARIAN CANCER Adnexal palpation, transvaginal ultrasound (TVUS), and serum CA-125 assay have been considered for ovarian cancer screening. A large randomized controlled trial has shown that an annual screening program of TVUS and CA-125 in average-risk women does not reduce deaths from ovarian cancer (relative risk 1.21; 95% confidence interval 0.99–1.48). Adnexal palpation was dropped early in the study because it did not detect any ovarian cancers that were not detected by either TVUS or CA-125. A second large randomized trial that used a two-stage screening approach incorporating a risk of ovarian cancer algorithm which determined whether additional testing with CA-125 or TVUS was required. At 14 years of follow-up, there was no statistically significant reduction in ovarian cancer deaths. The risks and costs associated with the high number of false-positive results are impediments to routine use of these modalities for screening. In the PLCO trial, 10% of participants had a false-positive result from TVUS or CA-125, and one-third of these women underwent a major surgical procedure; the ratio of surgeries to screen-detected ovarian cancer was approximately 20:1. In September 2016, the FDA issued a safety communication recommending against using any screening test, including the risk of ovarian cancer algorithm, for ovarian cancer.

PROSTATE CANCER The most common prostate cancer screening modalities are digital rectal exam (DRE) and serum PSA assay. An emphasis on PSA screening has caused prostate cancer to become the most common nonskin cancer diagnosed in American males. This disease is prone to lead-time bias, length bias, and overdiagnosis, and substantial debate continues among experts as to whether screening should be offered unless the patient specifically asks to be screened. Virtually all organizations stress the importance of informing men about the uncertainty regarding screening efficacy and the associated harms. Prostate cancer screening clearly detects many asymptomatic cancers, but the ability to distinguish tumors that are lethal but still curable from those that pose little or no threat to health is limited, and randomized trials indicate that the effect of PSA screening on prostate cancer mortality across a population is, at best, small. Men older than age 50 years have a high prevalence of indolent, clinically insignificant prostate cancers (about 30–50% of men, increasing further as men age).

Two major randomized controlled trials of the impact of PSA screening on prostate cancer mortality have been published. The PLCO Cancer Screening Trial was a multicenter U.S. trial that randomized almost 77,000 men age 55–74 years to receive either annual PSA testing for 6 years or usual care. At 13 years of follow-up, no statistically significant difference in the number of prostate cancer deaths were noted between the arms (rate ratio 1.09; 95% confidence interval 0.87–1.36). More than half of men in the control arm received at least one PSA test during the trial, which may have potentially diluted a small effect.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) was a multinational study that randomized ~182,000 men between age 50 and 74 years (with a predefined "core" screening group of men age 55–69 years) to receive PSA testing or no screening. Recruitment and randomization procedures, as well as actual frequency of PSA testing, varied by country. After a median follow-up of 13 years, a 21% relative reduction in the risk of prostate cancer death in the screened arm was noted in the "core" screening group. The trial found that 781 (95% CI 490–1,929) men would need to be invited to screening, and 27 (95% CI 17–66) cases of prostate cancer detected, to avert 1 death from prostate cancer. Of the seven countries included in the mortality analysis, two demonstrated statistically significant reductions in prostate cancer deaths, whereas five did not. There was also an imbalance in treatment between the two study arms, with a higher proportion of men with clinically localized cancer receiving radical prostatectomy in the screening arm and receiving it at experienced referral centers.

Screening must be linked to effective therapy in order to have any benefit. In a trial conducted in the United States after the initiation of widespread PSA testing, random assignment to radical prostatectomy compared with "watchful waiting" did not result in a statistically significant decrease in prostate cancer deaths (absolute risk reduction 2.7%; 95% confidence interval—1.3 to 6.2%). Likewise, in a randomized trial conducted in the U.K. comparing monitoring (no curative treatment) to radical prostatectomy and to radiotherapy in men diagnosed in a screening program, prostate-cancer specific survival was very good (about 99%), and nearly identical, in all three study arms at a median of 10 years follow-up. Treatments for low-stage prostate cancer, such as surgery and radiation therapy, can cause substantial morbidity, including impotence and urinary incontinence.

SKIN CANCER Visual examination of all skin surfaces by the patient or by a health care provider is used in screening for basal and squamous cell cancers and melanoma. No prospective randomized study has been performed to look for a mortality decrease. Unfortunately, screening is associated with a substantial rate of overdiagnosis.

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67 Cancer Genetics

Fred Bunz, Bert Vogelstein

CANCER IS A GENETIC DISEASE

Cancer arises through a series of somatic alterations in DNA that result in unrestrained cellular proliferation. Most of these alterations involve subtle sequence changes in DNA (i.e., mutations). The somatic mutations may originate as a consequence of random replication errors or exposure to carcinogens (e.g., radiation) and can be exacerbated by faulty DNA repair processes. While most cancers arise sporadically, clustering of cancers occurs in families that carry a germline mutation in a cancer gene.

HISTORICAL PERSPECTIVE

The idea that cancer progression is driven by sequential somatic mutations in specific genes has only gained general acceptance in the past 30 years. Before the advent of the microscope, cancer was believed to be composed of aggregates of mucus or other noncellular matter. By the middle of the nineteenth century, it became clear that tumors were masses of cells and that these cells arose from the normal cells of the tissue from which the cancer originated. The molecular basis for the uncontrolled proliferation of cancer cells was to remain a mystery for another century. During that time, a number of theories for the origin of cancer were postulated. The great biochemist Otto Warburg proposed the combustion theory of cancer, which stipulated that cancer was due to abnormal oxygen metabolism. Others believed that all cancers were caused by viruses, and that cancer was in fact a contagious disease.

In the end, observations of cancer occurring in chimney sweeps, studies of x-rays, and the overwhelming data demonstrating cigarette smoke as a causative agent in lung cancer, together with Ames's work on chemical mutagenesis, were consistent with the idea that cancer originated through changes in DNA. However, it was not until the somatic mutations responsible for cancer were identified at the molecular level that the genetic basis of cancer was definitively established. Although the viral theory of cancer did not prove to be generally accurate (with the exception of human papillomaviruses, which can cause cervical and other cancers), the study of retroviruses led to the discovery of the first human *oncogenes* in the late 1970s. Oncogenes are one of the two major classes of cancer driver genes. The study of families with genetic predisposition to cancer was instrumental to the discovery of the other major class of cancer driver genes, called *tumor-suppressor genes*. Current technologies permit the sequence analysis of entire cancer genomes, and provide a comprehensive view of the genetic changes that cause tumors to arise and become malignant. The field that studies the various types of mutations, as well as the consequences of these mutations in tumor cells, is now known as *cancer genetics*.

THE CLONAL ORIGIN AND MULTISTEP NATURE OF CANCER

Nearly all cancers originate from a single cell; this clonal origin is a critical discriminating feature between neoplasia and hyperplasia. Multiple cumulative mutational events are invariably required for the progression of a tumor from normal to fully malignant phenotype. The process can be seen as Darwinian microevolution in which, at each successive step, the mutated cells gain a growth advantage resulting in the expansion of a neoplastic clone **(Fig. 67-1)**. Based on observations of cancer frequency increases during aging, the epidemiologists Armitage and Doll and Nordling independently proposed that cancer is a result of three discrete cellular changes. Remarkably, this early model has been validated by extensive sequencing of cancer genomes. These studies revealed that just three causal mutations are required for the development of several of the most common cancers. Overall, it is currently believed that most common solid tumors require a minimum of three mutated cancer driver genes (either oncogenes or tumor suppressor genes) for their development. One or two mutations is sufficient for benign tumorigenesis, but not for the invasive capacity that distinguishes cancers from benign tumors. Less common tumors, such as liquid tumors (leukemias or lymphomas), sarcomas, and childhood tumors, require two driver gene alterations for malignancy. Note that a cancer driver gene is best defined as one containing a mutation that increases the selective growth advantage of the cell containing it. Normally, cell birth and cell death are in perfect equilibrium; every time a cell is born, another in the same lineage dies. Cancer driver gene mutations alter this equilibrium, so that more cells are born than die. The imbalance is often slight, so that the difference between cell birth and cell death is <1%. This explains why tumorigenesis—the journey from a normal cell to a typical malignant, solid tumor—often takes decades.

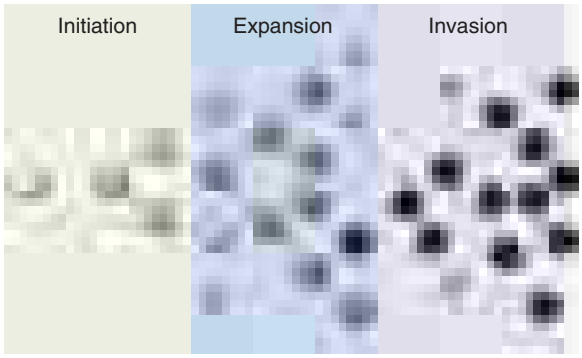

FIGURE 67-1 Multistep clonal development of malignancy. In this diagram a series of three cumulative mutations, each with a modest growth advantage acting alone, eventually results in a malignant tumor. Note that not all such alterations result in progression. The actual number of cumulative mutations necessary to transform from the normal to the malignant state has been estimated to be three for several of the most common types of cancer. *(After P Nowell: Science 194:23, 1976, with permission.)*

We now know the precise nature of the genetic alterations responsible for nearly all malignancies and are beginning to understand how these alterations promote the distinct stages of tumor growth. The prototypical example is colon cancer, in which analyses of genomes from the entire spectrum of neoplastic growths—from normal colon epithelium through adenoma to carcinoma—have identified mutations that are highly characteristic of each type of lesion **(Fig. 67-2)**.

TWO TYPES OF CANCER GENES: ONCOGENES AND TUMOR-SUPPRESSOR GENES

As briefly mentioned above, there are two major types of cancer genes. The first type comprises genes that positively influence growth and are known as *tumor-suppressor genes*. Both oncogenes and tumor-suppressor genes exert their effects on tumor growth through their ability to determine cell fates, influence cell survival and contribute to genome maintenance. The underlying molecular mechanisms can be extremely complex. While tightly regulated in normal cells, oncogenes acquire mutations that typically relieve this control and lead to increased activity of the gene products. This activating mutational event occurs in a single allele and acts in a dominant fashion. In contrast, the normal function of tumor-suppressor genes is usually to restrain cell growth, and this function is lost in cancer. Because of the diploid nature of mammalian cells, both alleles must be inactivated for a cell to completely lose the function of a tumor-suppressor gene. Thus, it requires two genetic events to inactivate a tumor-suppressor gene mutation, while only one genetic event is required to activate an oncogene.

A subset of tumor-suppressor genes controls the ability of the cell to maintain the integrity of its genome. Cells with a deficiency in these genes acquire an increased number of mutations throughout their genomes, including those in oncogenes and tumor-suppressor genes. This "mutator" phenotype was first hypothesized by Loeb to explain how the multiple rare mutational events required for tumorigenesis can occur in the lifetime of an individual. A mutator phenotype underlies several forms of cancer, such as those associated with deficiencies

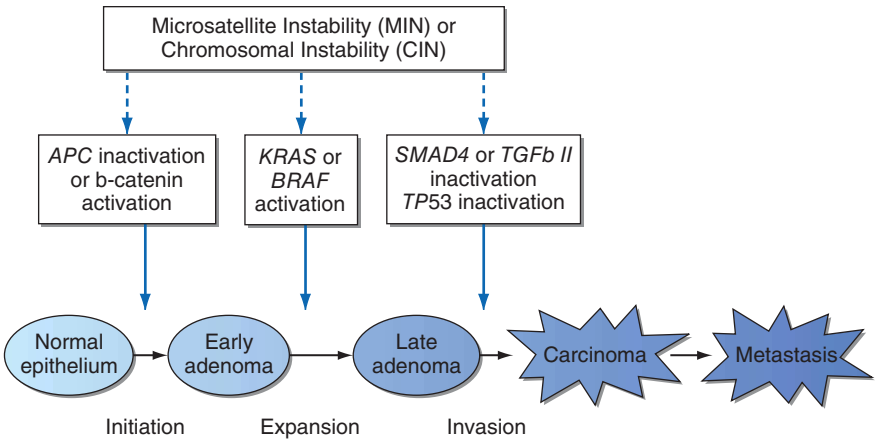

FIGURE 67-2 Progressive somatic mutational steps in the development of colon carcinoma. The accumulation of alterations in a number of different genes results in the progression from normal epithelium through adenoma to full-blown carcinoma. Genetic instability (microsatellite or chromosomal) accelerates the progression by increasing the likelihood of mutation at each step. Patients with familial polyposis are already one step into this pathway, because they inherit a germline alteration of the *APC* gene. TGF, transforming growth factor.

in DNA mismatch repair. The great majority of cancers do not harbor repair deficiencies, and their rate of mutation is similar to that observed in normal cells. Many of these cancers, however, appear to harbor a different kind of genetic instability, affecting the loss or gains of whole chromosomes or large parts thereof (as explained in more detail below).

ONCOGENES IN HUMAN CANCER

Work by Peyton Rous in the early 1900s revealed that a chicken sarcoma could be transmitted from animal to animal in cell-free extracts, suggesting that cancer could be induced by an agent acting positively to promote tumor formation. The agent responsible for the transmission of the cancer was a retrovirus (Rous sarcoma virus, RSV) and the oncogene responsible was identified 75 years later as *V-SRC*. Other oncogenes were also discovered through their presence in the genomes of retroviruses that are capable of causing cancers in chickens, mice, and rats. The non-mutated cellular homologues of these viral genes are called proto-oncogenes and are often targets of mutation or aberrant regulation in human cancer. Whereas many oncogenes were discovered on the basis of their presence in retroviruses, other oncogenes, particularly those involved in translocations characteristic of particular leukemias and lymphomas, were identified through genomic approaches. Investigators cloned the sequences surrounding the chromosomal translocations observed cytogenetically and identified the genes activated at the breakpoints (see below). Some of these were oncogenes previously found in retroviruses (like *ABL*, involved in chronic myeloid leukemia [CML]), whereas others were new (like *BCL2*, involved in B-cell lymphoma). In the normal cellular environment, proto-oncogenes have crucial roles in cell proliferation and differentiation. Table 67-1 is a partial list of oncogenes known to be involved in human cancer.

The normal growth and differentiation of cells is controlled by growth factors that bind to receptors on the surface of the cell. The signals generated by the membrane receptors are transmitted inside the cells through signaling cascades involving kinases, G proteins, and other regulatory proteins. Ultimately, these signals affect the activity of transcription factors in the nucleus, which regulate the expression of genes crucial in cell proliferation, cell differentiation, and cell death. Oncogene products have been found to function at critical steps in these pathways (Chap. 68). Inappropriate activation of these pathways can lead to tumorigenesis.

MECHANISMS OF ONCOGENE ACTIVATION

POINT MUTATION

Point mutation (alternatively known as single nucleotide substitution) is a common mechanism of oncogene activation. For example, mutations in *KRAS* are present in > 95% of pancreatic cancers and 40% of colon cancers but are less common in other cancer types, although they can occur at significant frequencies in leukemia, lung, and thyroid cancers. Remarkably—and in contrast to the diversity of mutations found in tumor-suppressor genes—most of the activated *K*RAS alleles contain point mutations in codons 12, 13, or 61. These mutations reduce RAS GTPase activity, leading to constitutive activation of the mutant RAS protein. The restricted pattern of mutations observed in oncogenes compared to that of tumor-suppressor genes reflects the fact that gain-of-function mutations must occur at specific sites, while a broad variety of mutations can lead to loss of activity. Indeed, inactivation of a gene can in theory be accomplished through the introduction of a stop codon anywhere in the coding sequence, whereas activations require precise substitutions at residues that can somehow lead to an increase in the activity of the encoded protein under particular circumstances within the cell.

DNA AMPLIFICATION

The second mechanism for activation of oncogenes is DNA sequence amplification, leading to overexpression of the gene product. This increase in DNA copy number may cause cytologically recognizable chromosome alterations referred to as *homogeneous staining regions* (HSRs) if integrated within chromosomes, or *double minutes* (dmins) if extrachromosomal. The recognition of DNA amplification is accomplished through various DNA sequence-based methods for copy number analysis. With both microarray and sequencing technologies, the entire genome can be surveyed for gains and losses of DNA sequences, thus pinpointing chromosomal regions likely to contain genes important in the development or progression of cancer.

Numerous genes have been reported to be amplified in cancer. Several of these genes, including *NMYC* and *LMYC*, were identified through their presence within the amplified DNA sequences of a tumor and had homology to known oncogenes. Because the region amplified often includes hundreds of thousands of base pairs, multiple oncogenes may be amplified in a single amplicon in some cancers

TABLE 67-1 Oncogenes Commonly Altered in Human Cancers

ONCOGENE	FUNCTION	ALTERATION IN CANCER	NEOPLASM
AKT1	Serine/threonine kinase	Point mutation	Skin
BRAF	Serine/threonine kinase	Point mutation	Melanoma, thyroid, colorectal
CCND1	Cell cycle progression	Amplification	Esophageal, head and neck
CTNNB1	Signal transduction	Point mutation	Colon, liver, uterine, melanoma
EGFR	Signal transduction	Point mutation	Lung
FLT3	Signal transduction	Point mutation	AML
IDH1	Chromatin modification	Point mutation	Glioma
MDM2	Inhibitor of p53	Amplification	Sarcoma, glioma
MDM4	Inhibitor of p53	Amplification	Breast
MYC	Transcription factor	Amplification	Prostate, ovarian, breast, liver, pancreatic
MYCL1	Transcription factor	Amplification	Ovarian, bladder
MYCN	Transcription factor	Amplification	Neuroblastoma
PIK3CA	Phosphoinositol-3-kinase	Point Mutation	Multiple cancers
KRAS	GTPase	Point mutation	Pancreatic, colorectal, lung
NRAS	GTPase	Point mutation	Melanoma

Abbreviation: AML, acute myeloid leukemia.

TABLE 67-2 Representative Oncogenes at Chromosomal Translocations

GENE (CHROMOSOME)	TRANSLOCATION	MALIGNANCY
BCR-ABL	(9;22)(q34;q11)	Chronic myeloid leukemia
BCL1 (11q13.3)–*IgH* (14q32)	(11;14)(q13;q32)	Mantle cell lymphoma
BCL2 (18q21.3)–*IgH* (14q32)	(14;18)(q32;q21)	Follicular lymphoma
FLI-EWSR1	(11;22)(q24;q12)	Ewing's sarcoma
LCK –TCRB	(1;7)(p34;q35)	T-cell acute lymphocytic leukemia
PAX3–FOXO1	(2;13)(q35;q14)	Rhabdomyosarcoma
PAX8-PPARG	(2;3)(q13;p25)	Thyroid
IL21R-BCL6	(3;16)(q27;p11)	Non-Hodgkin's lymphoma
TAL1–TCTA	(1;3)(p34;p21)	Acute T cell leukemia
TMPRSS2-ERG	Rearrangement on Chr21q22	Prostate

(particularly in sarcomas). Indeed, *MDM2*, *GLI*, *CDK4*, and *TPSPAN31* at chromosomal location 12q13-15 have been shown to be co-amplified in several types of sarcomas and other tumors. Amplification of a cellular gene is often a predictor of poor prognosis; for example, *ERB-B2/HER2* and *NMYC* are often amplified in aggressive breast cancers and neuroblastoma, respectively.

CHROMOSOMAL REARRANGEMENT

Chromosomal alterations provide important clues to the genetic changes in cancer. The chromosomal alterations in human solid tumors such as carcinomas are heterogeneous and complex and occur as a result of the frequent chromosomal instability observed in these tumors (see below). In contrast, the chromosome alterations in myeloid and lymphoid tumors are often simple translocations, that is, reciprocal transfers of chromosome arms from one chromosome to another. The breakpoints of recurring chromosome abnormalities usually occur at the site of cellular oncogenes. Table 67-2 lists representative examples of recurring chromosome alterations in malignancy and the associated gene(s) rearranged or deregulated by the chromosomal rearrangement. Translocations are often observed in liquid tumors in general and are particularly common in lymphoid tumors, probably because these cell types have the capability to rearrange their DNA to generate antigen receptors. Indeed, antigen receptor genes are commonly involved in the translocations, implying that an imperfect regulation of receptor gene rearrangement may be involved in their pathogenesis. In addition to transcription factors and signal transduction molecules, translocation may result in the overexpression of cell cycle regulatory proteins or proteins such as cyclins and of proteins that regulate cell death. Recurrent translocations have more recently been identified in solid tumors such as prostate cancers. Fusions between *TMPRSS2* and *ERG*, which are normally located in tandem on chromosome 21, contribute to about one-third of all prostate cancers and correlate with more aggressive disease.

The first reproducible chromosome abnormality detected in human malignancy was the Philadelphia chromosome detected in CML. This cytogenetic abnormality is generated by reciprocal translocation involving the *ABL* oncogene on chromosome 9, encoding a tyrosine kinase, being placed in proximity to the breakpoint cluster region (*BCR*) gene on chromosome 22. Figure 67-3 illustrates the generation of the translocation and its protein product. The consequence of expression of the *BCR-ABL* gene product is the activation of signal transduction pathways leading to cell growth independent of normal external signals. Imatinib (marketed as Gleevec), a drug that specifically blocks the activity of Abl tyrosine kinase, has shown remarkable efficacy with little toxicity in patients with CML. The successful targeting of *BCR-ABL* by imatinib is the paradigm for molecularly targeted anti-cancer therapies.

CHROMOSOMAL INSTABILITY IN SOLID TUMORS

Solid tumors generally contain an abnormal number of chromosomes, a state known as aneuploidy; chromosomes from aneuploid tumors exhibit structural alterations such as translocations, deletions, and amplifications. These abnormalities reflect an underlying defect in cancer cells known as chromosomal instability. While aneuploidy is a striking cellular phenotype, chromosomal instability is manifest as only a small increase in the tendency of cells to gain, lose, or rearrange chromosomes during any given cell cycle. This intrinsically low rate of chromosome aberration implies that cancer cells become aneuploid only after many generations of clonal expansion. The molecular basis of aneuploidy remains incompletely understood. It is widely believed that defects in checkpoints, the quality-control mechanisms that halt the cell cycle if chromosomes are damaged or misaligned, contribute to chromosomal instability. This hypothesis emerged from experimental

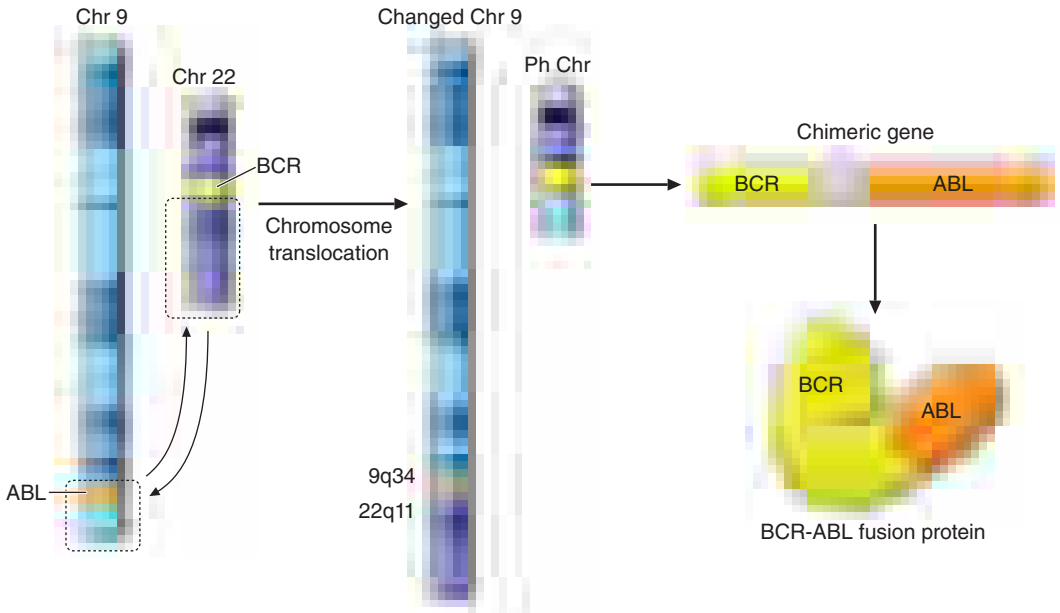

FIGURE 67-3 Specific translocation seen in chronic myeloid leukemia (CML). The Philadelphia chromosome (Ph) is derived from a reciprocal translocation between chromosomes 9 and 22 with the breakpoint joining the sequences of the *ABL* oncogene with the *BCR* gene. The fusion of these DNA sequences allows the generation of an entirely novel fusion protein with modified function.

observations that the tumor suppressor p53 controls checkpoints that regulate the initiation of DNA replication and the onset of mitosis. These processes are therefore defective in many cancer cells. The mitotic spindle checkpoint, which ensures proper chromosome attachment to the mitotic spindle before allowing the sister chromatids to separate, is also altered in some cancers, irrespective of p53 status. The precise relationship between checkpoint deficiency and chromosomal instability remains unclear, but it is believed that even a subtle perturbation of the highly orchestrated process of cell division can impact the ability of a cell to faithfully replicate and segregate its complement of chromosomes. From a therapeutic standpoint, the checkpoint defects that are prevalent in cancers have been proposed as vulnerabilities that may be exploited by novel agents and combinatorial strategies.

In contrast to the genome-wide cytogenetic changes that are typical indications of an underlying chromosomal instability, more focal patterns of chromosomal rearrangement have been recurrently detected in several cancer types. A curious phenomenon known as *chromothripsis* causes dozens of distinct breakpoints that are localized on one or several chromosomes. These striking structural alterations are thought to reflect a single event in which a chromosome is fragmented and then imprecisely reassembled. While the exact process that underlies chromothripsis remains obscure, and its effects on driver genes is not yet clear, a transient period of extreme instability stands in contrast to the gradual loss, gain and rearrangement of chromosomes that is typically observed in serially cultured cancer cells.

TUMOR-SUPPRESSOR GENE INACTIVATION IN CANCER

The first indication of the functional existence of tumor-suppressor genes came from experiments showing that fusion of mouse cancer cells with normal mouse fibroblasts led to a nonmalignant phenotype in the fused cells. The normal role of tumor-suppressor genes is to restrain cell growth, and the function of these genes is inactivated in cancer. The three major types of somatic lesions observed in tumor-suppressor genes during tumor development are *point mutations*, small insertions and/or deletions known as *indels*, and *large deletions*. Point mutations or indels in the coding region of tumor-suppressor genes will frequently lead to truncated protein products or allele-specific loss of RNA expression by the process of *nonsense-mediated decay*. Unlike the highly recurrent point mutations that are found in critical positions of activated oncogenes, known as mutational *hotspots*, the point mutations that cause tumor-suppressor gene inactivation tend to be distributed throughout the open reading frame. Large deletions lead to the loss of a functional product and sometimes encompass the entire gene or even the entire chromosome arm, leading to loss of heterozygosity (LOH) in the tumor DNA compared to the corresponding normal tissue DNA **(Fig. 67-4)**. LOH in tumor DNA often indicates the presence of a tumor-suppressor gene at a particular chromosomal location, and LOH studies have been useful in the positional cloning of many tumor-suppressor genes. The rate of LOH is increased in the presence of chromosomal instability, a relationship that would account for the high prevalence of aneuploidy in late-stage cancers.

Gene silencing, an epigenetic change that leads to the loss of gene expression, occurs in conjunction with hypermethylation of the promoter and histone deacetylation, and is another mechanism of tumor-suppressor gene inactivation. An *epigenetic modification* refers to a covalent modification of chromatin, heritable by cell progeny that may involve DNA but does not involve a change in the DNA sequence. The inactivation of the second X chromosome in female cells is an example of an epigenetic silencing that prevents gene expression from the inactivated chromosome. Genomic regions of hypermethylated and hypomethylated DNA can be detected by specialized techniques, and a subset of these regional modifications has consequences on the cell's behavior.

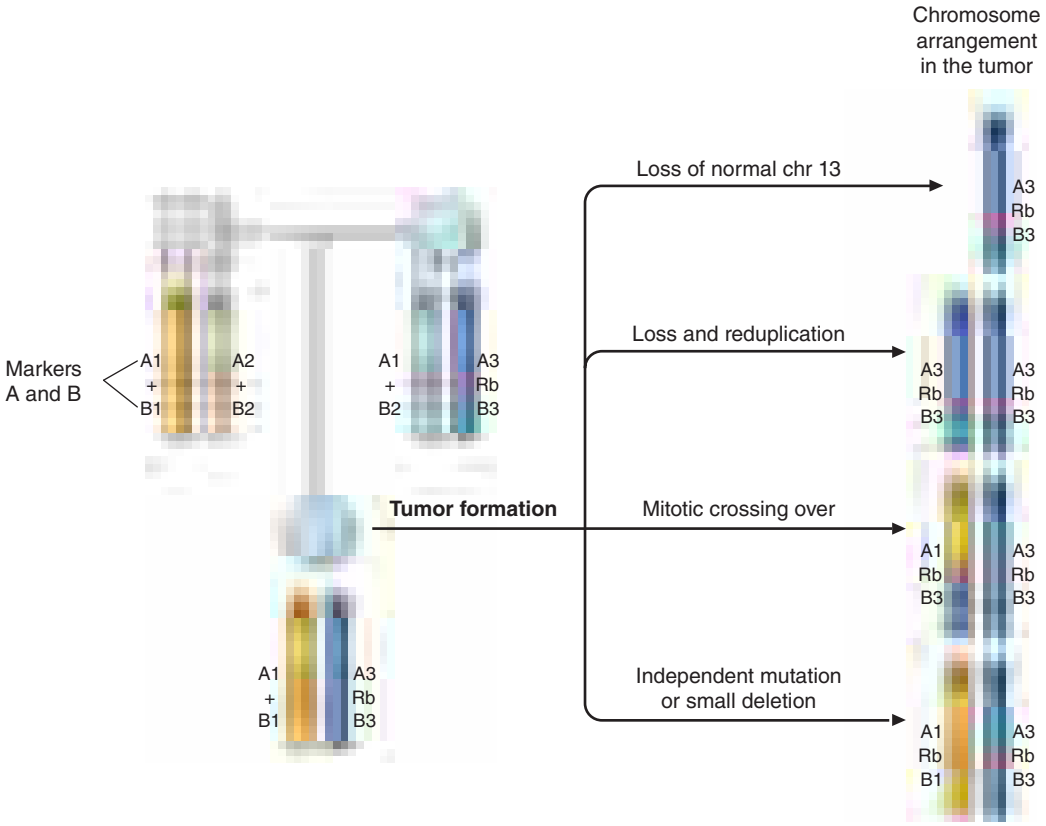

FIGURE 67-4 Diagram of possible mechanisms for tumor formation in an individual with hereditary (familial) retinoblastoma. On the left is shown the pedigree of an affected individual who has inherited the abnormal (Rb) allele from her affected mother. The normal allele is shown as a (+). The four chromosomes of her two parents are drawn to indicate their origin. Flanking the retinoblastoma locus are genetic markers (A and B) also analyzed in this family. Markers A3 and B3 are on the chromosome carrying the retinoblastoma disease gene. Tumor formation results when the normal allele, which this patient inherited from her father, is inactivated. On the right are shown four possible ways in which this could occur. In each case, the resulting chromosome 13 arrangement is shown. Note that in the first three situations, the normal allele (B1) has been lost in the tumor tissue, which is referred to as loss of heterozygosity (LOH) at this locus.

FAMILIAL CANCER SYNDROMES

A small fraction of cancers occurs in patients with a genetic predisposition. Based on studies of inherited and sporadic forms of retinoblastoma, Knudson and others formulated a hypothesis that explains the differences between sporadic and inherited forms of the same tumor type. In inherited forms of cancer, called *cancer predisposition syndromes*, one allele of a particular tumor suppressor gene is inherited in mutant form. This germline mutation is not sufficient to initiate a tumor, however; the other allele, inherited from the unaffected parent, must become somatically mutated in a normal stem cell for tumorigenesis to be initiated. In sporadic (non-inherited) forms of the same disease, all cells in the body start out with two normal copies of the tumor suppressor gene. A single cell must then sequentially acquire mutations in both alleles of the tumor suppressor gene to initiate a tumor. Thus bi-allelic mutations of the same tumor suppressor gene are required for both inherited and non-inherited forms of the disease; the only difference is that individuals with the inherited form have a "head-start": they already have one allele mutated, from conception, and only need one additional mutation to initiate the process (Fig. 67-4). This distinction explains why those with inherited forms of the disease develop more cancers, at an earlier age, than the general population. It also explains why, even though every cell in an individual with a cancer predisposition syndrome has a mutant gene, only a relatively small number of tumors arise during his/her lifetime. The reason is that the vast majority of cells within such individuals are functionally normal because one of the two alleles of the tumor suppressor gene is normal. Mutations are uncommon events, and only the rare cells that develop a mutation in the remaining normal allele will exhibit uncontrolled proliferation. The same principle applies to virtually all types of cancer predisposition syndromes, though the particular genes differ. For example, inherited mutations in *RB1*, *WT1*, *VHL*, *APC*, and *BRCA1* lead to predispositions to retinoblastomas, Wilms' tumors, renal cell carcinomas, colorectal carcinomas, and breast carcinomas, respectively **(Table 67-3)**. Also note that the biallelic inactivation of any of these genes is not sufficient to develop cancer; it requires other, additional somatic mutations for the initiating cells to evolve to malignancy, as noted above.

Roughly 100 familial cancer syndromes have been reported; the great majority are very rare. Most of these syndromes exhibit an autosomal dominant pattern of inheritance, although some of those associated with DNA repair abnormalities (xeroderma pigmentosum, Fanconi's anemia, ataxia telangiectasia) are inherited in an autosomal recessive fashion. Table 67-3 shows a number of cancer predisposition syndromes and the responsible genes.

The next section examines inherited colon cancer predispositions in detail because several lessons of general importance have been derived from the study of these syndromes.

Familial adenomatous polyposis (FAP) is a dominantly inherited colon cancer syndrome caused by germline mutations in the adenomatous polyposis coli (*APC*) tumor-suppressor gene on chromosome 5. Affected individuals develop hundreds to thousands of adenomas in the colon. In each of these adenomas, the *APC* allele inherited from the affected parent has been inactivated by virtue of a somatic mutation (Fig. 67-2). This inactivation usually occurs through a gross chromosomal event resulting in loss of all or a large part of the long arm of chromosome 5, where *APC* resides. In other cases, the remaining allele is inactivated by a subtle intragenic mutation of *APC*, which as a single

TABLE 67-3 Cancer Predisposition Syndromes and Associated Genes

SYNDROME	GENE	CHROMOSOME	INHERITANCE	TUMORS
Ataxia telangiectasia	*ATM*	11q22-q23	AR	Breast
Autoimmune lymphoproliferative syndrome	*FAS* *FASL*	10q24 1q23	AD	Lymphomas
Bloom's syndrome	*BLM*	15q26.1	AR	Various
Cowden's syndrome	*PTEN*	10q23	AD	Breast, thyroid
Familial adenomatous polyposis	*APC* *MUTYH*	5q21 1p34.1	AD AR	Colorectal (early onset)
Familial melanoma	*CDKN2A*	9p21	AD	Melanoma, pancreatic
Familial Wilms' tumor	*WT1*	11p13	AD	Kidney (pediatric)
Hereditary breast/ovarian cancer	*BRCA1* *BRCA2*	17q21 13q12.3	AD	Breast, ovarian, prostate
Hereditary diffuse gastric cancer	*CDH1*	16q22	AD	Stomach
Hereditary multiple exostoses	*EXT1* *EXT2*	8q24 11p11-12	AD	Exostoses, chondrosarcoma
Hereditary retinoblastoma	*RB1*	13q14.2	AD	Retinoblastoma, osteosarcoma
Hereditary nonpolyposis colon cancer (HNPCC)	*MSH2* *MLH1* *MSH6* *PMS2*	2p16 3p21.3 2p16 7p22	AD	Colon, endometrial, ovarian, stomach, small bowel, ureter carcinoma
Hereditary papillary renal carcinoma	*MET*	7q31	AD	Papillary kidney
Juvenile polyposis syndrome	*SMAD4* *BMPR1A*	18q21	AD	Gastrointestinal, pancreatic
Li-Fraumeni syndrome	*TP53*	17p13.1	AD	Sarcoma, breast
Multiple endocrine neoplasia type 1	*MEN1*	11q13	AD	Parathyroid, endocrine, pancreas, and pituitary
Multiple endocrine neoplasia type 2a	*RET*	10q11.2	AD	Medullary thyroid carcinoma, pheochromocytoma
Neurofibromatosis type 1	*NF1*	17q11.2	AD	Neurofibroma, neurofibrosarcoma, brain
Neurofibromatosis type 2	*NF2*	22q12.2	AD	Vestibular schwannoma, meningioma, spine
Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)	*PTCH1*	9q22.3	AD	Basal cell carcinoma, medulloblastoma, jaw cysts
Tuberous sclerosis	*TSC1* *TSC2*	9q34 16p13.3	AD	Angiofibroma, renal angiomyolipoma
von Hippel–Lindau disease	*VHL*	3p25-26	AD	Kidney, cerebellum, pheochromocytoma

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

base substitution resulting in a nonsense codon. Gross chromosomal losses occur more commonly than point mutations in normal cells, explaining why these are the predominant mechanism underlying the inactivation of the normal allele of *APC*. The same is true for other cancer predisposition syndromes caused by other inherited tumor suppressor gene mutations; gross chromosomal events are generally responsible for inactivation of the tumor suppressor gene allele inherited from the non-affected parent. Several thousand adenomas form in FAP patients, and a small subset of the billions of cells within these adenomas will acquire a second mutation, leading to tumor progression, that is, a larger adenoma. A third mutation in such a larger adenoma may convert it to a carcinoma. If untreated (by colectomy), at least one of the adenomas will progress to cancer by the time patients are in their mid-40s. *APC* can be considered to be a gatekeeper for colon tumorigenesis in that the absence of mutation of this gatekeeper (or a gene acting within the same pathway), a colorectal tumor simply cannot be initiated. **Figure 67-5** shows the germline and somatic mutations found in the *APC* gene. A negative regulator of a signaling pathway that determines cell fate during development, the APC protein provides differentiation and apoptotic cues to colonic epithelial cells as they migrate up the crypts. Defects in this process can lead to abnormal accumulation of cells that would otherwise differentiate and eventually undergo apoptosis.

In contrast to patients with FAP, patients with hereditary nonpolyposis colon cancer (HNPCC, or Lynch's syndrome) do not develop polyposis, but instead develop only one or a small number of adenomas that rapidly progress to cancer. HNPCC is due to inherited mutations in one of four DNA mismatch repair genes (Table 67-3) that are components of a repair system responsible for correcting errors in newly replicated DNA. Germline mutations in *MSH2* and *MLH1* account for more than 90% of HNPCC cases, and mutations in *MSH6* and *PMS2* account for the remainder. When a somatic mutation inactivates the remaining wild-type allele of a mismatch repair gene, the cell develops a hypermutable phenotype characterized by profound genomic instability that is most readily apparent in short repeated sequences called *microsatellites* and is sometimes called microsatellite instability (MSI). The high rate of mutation in such cells impacts all genes, including oncogenes and tumor suppressor genes, and thereby accelerates the activation of the former and the inactivation of the latter (Fig. 67-2). HNPCC can be considered a disease of tumor progression; once tumors are initiated (by an inactivating mutation of *APC* or by some other gene in the APC pathway), tumors rapidly progress because of the accelerated mutation rate. Progression from a tiny adenoma to carcinoma takes only a few years in HNPCC patients instead of the two or three decades this progression takes in patients with FAP (or in patients with sporadic colorectal tumors). Approximately half of HNPCC patients develop colorectal cancers by the time they are in their mid-40s—similar to that of FAP patients. This coincidence in age of onset emphasizes that both tumor initiation (abnormal in FAP patients) and tumor progression (abnormal in HNPCC patients) are the two pillars of cancer development and are equally important for cancer development.

Another general principle is apparent from the comparison between FAP and HNPCC patients. The tumors in FAP patients, like those in patients without hereditary predisposition to cancers, are chromosomal instability. MSI and chromosomal instability appear to be mutually exclusive in colon cancers, suggesting that they represent alternative mechanisms for the generation of genomic instability (Fig. 67-2). Other cancer types rarely exhibit MSI. Chromosomal instability is far more prevalent than MSI among all cancer types, perhaps explaining why nearly all cancers are aneuploid.

Although most autosomal dominant inherited cancer syndromes are due to mutations in tumor-suppressor genes (Table 67-3), there are a few interesting exceptions. Multiple endocrine neoplasia type 2, a dominant disorder characterized by pituitary adenomas, medullary carcinoma of the thyroid, and (in some pedigrees) pheochromocytoma, is due to gain-of-function mutations in the proto-oncogene *RET* on chromosome 10. Similarly, gain-of-function mutations in the tyrosine kinase domain of the *MET* oncogene lead to hereditary papillary renal carcinoma. Interestingly, loss-of-function mutations in the *RET* gene cause a completely different disease, Hirschsprung's disease (aganglionic megacolon **[Chaps. 321 and 381]**).

Although the heritable forms of cancer have taught us much about the mechanisms of growth control, most forms of cancer do not follow simple Mendelian patterns of inheritance. The majority of human cancers arise in a sporadic fashion, solely as a result of somatic mutation, and in the absence of any mutations in cancer-predisposing genes in their germlines.

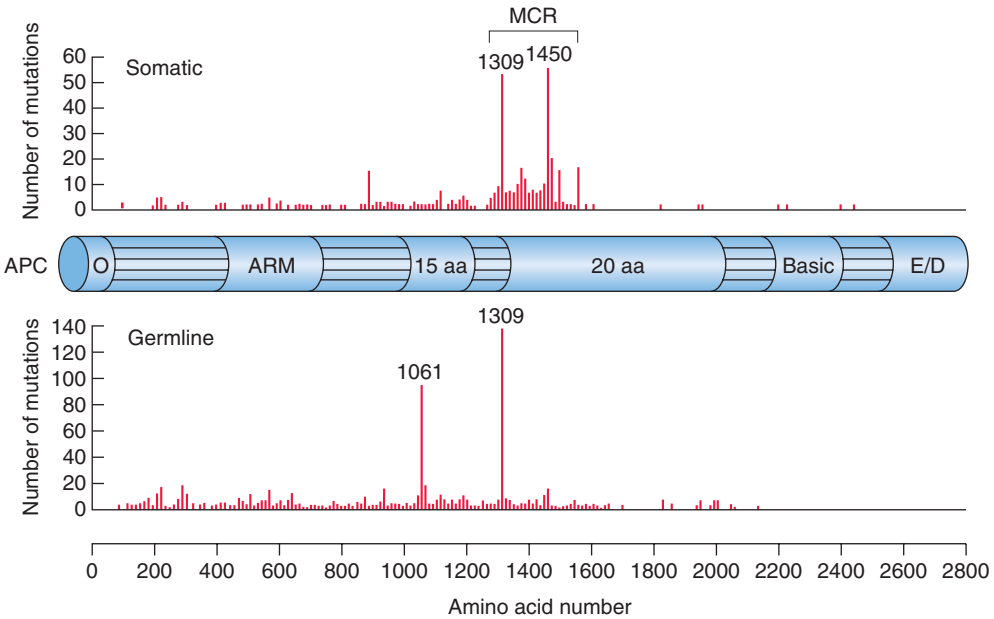

FIGURE 67-5 Germline and somatic mutations in the tumor-suppressor gene adenomatous polyposis coli (*APC*). *APC* encodes a 2843-amino-acid protein with six major domains: an oligomerization region (O), armadillo repeats (ARM), 15-amino-acid repeats (15 aa), 20-amino-acid repeats (20 aa), a basic region, and a domain involved in binding EB1 and the *Drosophila* discs large homologue (E/D). Shown are 650 somatic and 826 germline mutations representative of the mutations that occur within the *APC* gene (from the *APC* database at *www.umd.be/APC*). All known pathogenic mutations of *APC* result in the truncation of the APC protein. Germline mutations are found to be relatively evenly distributed up to codon 1600 except for two mutation hotspots surrounding amino acids 1061 and 1309, which together account for one-third of the mutations found in familial adenomatous polyposis (FAP) families.

GENETIC TESTING FOR FAMILIAL CANCER

The discovery of cancer susceptibility genes raises the possibility of DNA testing to predict the risk of cancer in individuals of affected families. An algorithm for cancer risk assessment and decision making in high-risk families using genetic testing is shown in Fig. 67-6. Once a mutation is discovered in a family, subsequent testing of asymptomatic family members can be crucial in patient management. A negative gene test in these individuals can prevent years of anxiety in the knowledge that their cancer risk is no higher than that of the general population. On the other hand, a positive test may lead to alteration of clinical management, such as increased frequency of cancer screening and, when feasible and appropriate, prophylactic surgery. Potential negative consequences of a positive test result include psychological distress (anxiety, depression) and discrimination, although the Genetic Information Nondiscrimination Act (GINA) makes it illegal for predictive genetic information to be used to discriminate in health insurance or employment. Testing should therefore not be conducted without counseling before and after disclosure of the test result.

Recent technological developments have made it feasible to obtain high-quality sequence of all of the protein-coding DNA sequences, and even of the entire genome, in any given individual. The redundant nature of modern DNA sequencing provides an extremely high level of sensitivity, such that mutations and polymorphisms will inevitably be identified in every subject. In patients lacking a clear family history, the significance of these DNA sequence findings will not be apparent. Even mutations in tumor suppressor genes are difficult to interpret unless there is an obvious functional implication, such as the truncation of the open reading frame, or that particular mutation has previously been associated with cancer. Such germline mutations are very rare in the general population. Vastly more common are *variants of unknown significance* (*VUS*). VUS that are found during genetic testing cannot be used to evaluate the relative risk of cancer, but may nonetheless cause anxiety because they represent a deviation from the reference allele that is established as "normal." Because of the low yield of informative mutations that modify cancer risk and the frequent identification of VUS, it is generally not appropriate to use DNA sequencing to assess cancer risk in individuals unless the family history is suggestive of a germline mutation. Conversely, testing may be appropriate in some subpopulations with a known increased risk, even without a defined family history. For example, two mutations in the breast cancer susceptibility gene *BRCA1*, 185delAG and 5382insC, exhibit a sufficiently high frequency in the Ashkenazi Jewish population that genetic testing based on ethnicity alone may be warranted.

It is important that genetic test results be communicated to families by trained genetic counselors, especially for high-risk high-penetrance conditions such as the hereditary breast and ovarian cancer syndrome (*BRCA1/BRCA2*). To ensure that the families clearly understand its advantages and disadvantages and the impact it may have on disease management and psyche, genetic testing should never be done before counseling. Significant expertise is needed to communicate the results of genetic testing to families.

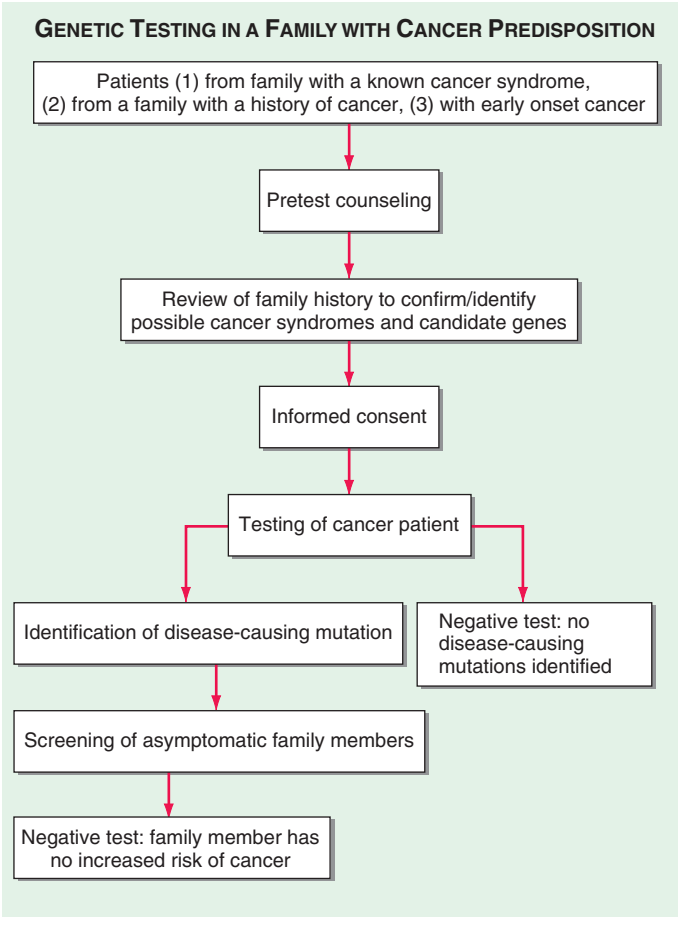

FIGURE 67-6 Algorithm for genetic testing in a family with cancer predisposition. The key step is the identification of a disease-mutation in a cancer patient, which is an indication for the testing of asymptomatic family members. Asymptomatic family members who test positive may require increased screening or surgery, whereas those who test negative are at no greater risk for cancer than the general population. It should be emphasized that no molecular assay used for this sort of testing is 100% sensitive; negative results must be interpreted with this caveat in mind.

VIRUSES IN HUMAN CANCER

Several human malignancies are associated with viruses. Examples include Burkitt's lymphoma (Epstein-Barr virus; Chap. 189), hepatocellular carcinoma (hepatitis viruses), cervical cancer (human papillomavirus [HPV]; Chap. 193), and T cell leukemia (retroviruses; Chap. 196). There are several types of HPV, including the high-risk types 16 and 18 that are strongly associated with the development of cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer. The mechanisms of action of all these viruses involve inactivation of tumor suppressor genes. For example, HPV proteins E6 and E7 bind to and inactivate cellular tumor suppressors p53 and pRB, respectively. This is the reason that HPV is such a potent initiator of cancer: infection with a virus is tantamount to having two of the three mutant driver genes required for cancer, that is, one viral oncogene inactivates p53 and the other inactivates Rb. Though these two inactivated gene products are not sufficient for tumorigenesis, only one additional mutant gene is required to develop a malignancy.

CANCER GENOMES

The advent of relatively inexpensive technologies for rapid and high-throughput DNA sequencing has facilitated the comprehensive analysis of numerous genomes from many types of tumors. This unprecedented view into the genetic nature of cancer has provided remarkable insights. Most cancers do not arise in the context of a mutator phenotype, and accordingly the number of mutations in even the most advanced cancers is relatively modest. Common solid tumors harbor 30–70 subtle mutations that are non-synonymous (i.e., result in an amino acid change in the encoded protein). Liquid tumors such as lymphomas and leukemias, as well as pediatric tumors, typically have fewer than 20 mutations. The vast majority of the mutations detected in tumors are not functionally significant, they simply arose by chance in a single cell that gave rise to an expanding clone. Such mutations, which provide no selective advantage to the cell in which they occur, are known as *passenger* mutations. As noted above, only a small number of the mutations confer a selective growth advantage and thereby promote tumorigenesis. These functional mutations are known as *driver* mutations, and the genes in which they occur are called driver genes.

The frequency and distribution of driver mutations within a single tumor type can be represented as a topographical landscape (Fig. 67-7). The picture that emerges from these studies reveals that most genes that are mutated in tumors are actually mutated at relatively low frequencies, as would be expected of passenger genes, whereas a small number of genes (the driver genes) are mutated in a large proportion of tumors. There are a total of ~200 driver genes that

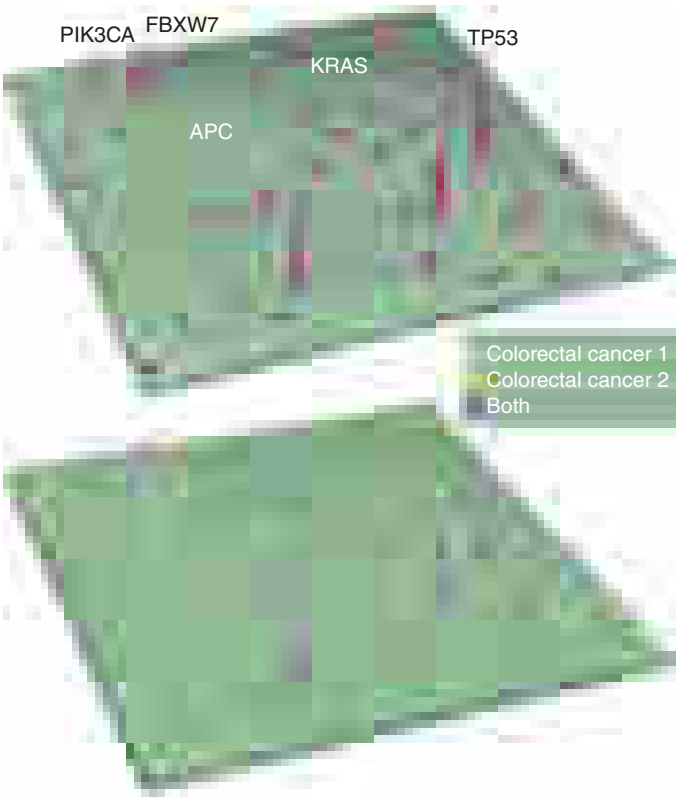

FIGURE 67-7 The mutational topography of colorectal cancer. The two-dimensional landscape represents the positions of the individual genes along the chromosomes. The height of each peak represents the mutation frequency at that locus. The top map is a representation of many sequenced colorectal cancers. The taller peaks represent the genes that are commonly mutated in colon cancer, while the smaller hills indicate the genes that are mutated at lower frequency. On the lower map, the mutations of two individual tumors are indicated. Note that there is little overlap between the mutated genes of the two colorectal tumors shown. These differences represent Type I heterogeneity, as noted in the test, which is the foundation for personalized medicine in cancer. *(From LD Wood et al: Science 318:1108, 2007, with permission.)*

are responsible for the development of all solid tumors, representing only ~1% of the total number of human protein-encoding genes. The majority of the mutations in these driver genes provide a direct selective growth advantage by altering the signaling pathways that mediate cell survival or the determination of cell fate. The remaining driver gene mutations indirectly provide a selective growth advantage by accelerating the mutation rate of proto-oncogenes and tumor suppressor genes. The functions of all these driver genes can be organized into a dozen signaling pathways , as shown in **Table 67-4**.

TABLE 67-4 Signaling Pathways Altered in Cancer

PROCESS	PATHWAY	REPRESENTATIVE DRIVER GENES
Cell survival	Cell cycle regulation/ apoptosis	*RB1, BCL2*
	RAS	*KRAS, BRAF*
	PIK3CA	*PTEN, PIK3CA*
	JAK/STAT	*JAK2, FLT3*
	MAPK	*MAP3K. ERK*
	TGF-β	*BMPR1A, SMAD4*
Cell fate	Notch	*NOTCH1, FBWX7*
	Hedgehog	*PTCH1, SMO*
	WNT/APC	*APC, CTNNB1*
	Chromatin modification	*DNMT1, IDH1*
	Transcriptional regulation	*AR, KLF4*
Genome maintenance	DNA damage signaling and repair	*ATM BRCA1*

TUMOR HETEROGENEITY

The mutant cells that compose a single tumor are not genetically identical. Rather, cells obtained from different sites on a tumor will harbor common mutations as well as mutations that are unique to each sample. Genetic heterogeneity results from the ongoing acquisition of mutations during tumor growth. Each time a genome is replicated, there is a small but quantifiable probability that a mutation will spontaneously arise as a result of a replication error and be passed on to the cellular progeny. This is true in normal cells or in tumor cells. Any randomly chosen cell from the skin of one individual will harbor hundreds of genetic alterations that distinguish it from a different randomly chosen skin cell, and the same is true for all organs of self-renewing tissues. Tumors are actually *less* genetically heterogeneous than normal cells; any two randomly chosen cells from a tumor of an individual will have fewer differences than any two randomly chosen cells from that individual's normal tissues. The reason for this decrease in heterogeneity is clonal expansion, the fundamental feature of tumorigenesis. Every time a clonal expansion occurs, a genetic bottleneck wipes out heterogeneity among the cells that didn't expand; these unexpanded cells either die or form only a minute proportion of the total cells in the expanding tumor.

The mutations that vary between cells of a given tumor are invariably passenger mutations that arose since the last evolutionary bottleneck, that is, those mutations that arose during the expansion of the founder cell that gave rise to the final clonal expansion. In contrast, the passenger mutations that were present in the founder cell will be uniformly present in every cell in the tumor. In that respect, these passenger mutations that are not heterogeneously distributed, that is., those that are present in every cancer cell, are like the driver gene mutations, which are also present in virtually all cancer cells. The total number of mutations and their distribution within tumor cells therefore represents a complex interplay between the age of the patient (the older the patient, the more passenger mutations will have accumulated in the founding cell of the first clonal expansion) and the evolutionary history of the cancer (its age and number of clonal expansions it experienced).

Tumor heterogeneity has been recognized for decades at the cytogenetic, biochemical, and histopathologic levels. However, it is only recently, with the advent of a deep understanding of cancer genetics that genetic heterogeneity can be interpreted in a medically relevant fashion. The first important point to recognize about tumor heterogeneity is that it is only the variation in driver gene alterations that is important; the cellular distribution of passenger gene mutations is completely irrelevant. In this discussion of heterogeneity, we can expand the definition of "driver genes" to include those that provide a selective growth advantage in the face of therapy in addition to those that provide a selective growth advantage during tumor evolution, prior to treatment.

Type I heterogeneity refers to that among tumors of the same type from different patients **(Fig. 67-8)**. Though adenocarcinomas of the lung generally harbor mutations in three or more driver genes, the genes differ among the patients and the precise mutations within the same gene can vary considerably. Type I heterogeneity is the basis for precision medicine, where the goal is to treat patients with drugs that target the proteins encoded by genetic alterations within their specific tumors. Type 2 heterogeneity refers to the genetic heterogeneity among different cells from the same primary tumor. Tumors continue to evolve as they grow, and different cells of the same cancer, in its original site (e.g., the colon), may acquire another driver gene mutations that are not shared among the other cells of the tumor. Such a mutation can result in a small clonal expansion that may or may not be important biologically. In cases in which the primary tumor can be surgically excised, such mutations are unimportant unless they give rise to Type III heterogeneity (described below). The reason they are important is because all primary tumor cells, whether homogeneous or not, are removed by the surgical procedure. In primary tumors that cannot be completely excised (such as most advanced brain tumors and many pancreatic ductal adenocarcinomas), heterogeneity is biomedically important because it can give rise to drug resistance, analogously to that described for Type IV heterogeneity (see below). Type III heterogeneity refers

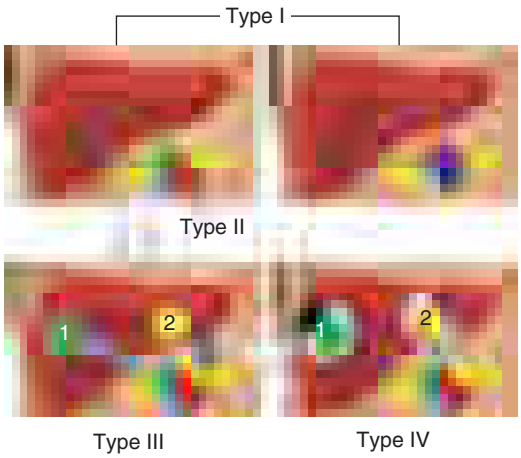

FIGURE 67-8 The four types of tumor heterogeneity. Tumor heterogeneity is the inevitable result of cell proliferation, as new mutations are introduced during clonal expansion. This concept is illustrated by a primary tumor in the pancreas and two metastatic tumors in the liver. The tumors of the founding populations are shown in the middle of each circle, while the distinct subclones are shown around the periphery. Type I: the heterogeneity of tumors that occur among different patients. Type II: the heterogeneity among the cells of a primary tumor, also known as intratumoral heterogeneity. Type III: the heterogeneity among the founding cells of distinct metastatic lesions (marked as 1 and 2) that arise in the same patient, also known as intermetastatic heterogeneity. Type IV: heterogeneity among the cells of each metastasis that develops as each tumor grows, also known as intrametastatic heterogeneity.

to the genetic differences among the founder cells of the metastatic lesions from the same patient. For example, a patient with melanoma may have 100 different metastases distributed throughout various organs. Only if a mutant *BRAF* is present in every founder cell of every metastasis, then the patient has a chance at a complete response to a *BRAF* inhibitor. There have been several recent detailed studies of the metastases from various tumor types. Fortunately, these studies suggest there is very little, if any, Type III heterogeneity among driver genes, a necessary prerequisite for the successful implementation of future targeted therapies. Finally, Type IV heterogeneity refers to that among cells of individual metastatic lesions. As the founder cell of each metastasis expands to become detectable, it acquires mutations, a small number of which can act as "drivers" if the patient is exposed to therapeutics. This type of heterogeneity is of major clinical importance, as it has been shown to be responsible for the development of resistance in virtually all targeted therapies. The development of such resistance is a fait accompli based simply on known mutation rates and known genetic resistance mechanisms. The only way to circumvent acquired resistance is to treat metastatic tumors earlier (i.e., in adjuvant setting, before much tumor expansion has occurred) or to treat with combinations of drugs for which cross-resistance is genetically impossible.

PERSONALIZED CANCER DETECTION AND TREATMENT

High-throughput DNA sequencing has led to an unprecedented understanding of cancer at the molecular level. A comprehensive mutation profile provides a molecular history of a given tumor and insights into how it arose. Because tumor cells and tumor DNA are shed into the blood and other bodily fluids, common driver mutations can be used as highly specific biomarkers for early detection. For diagnosed tumors, tumor-specific mutations can be used to estimate tumor burden, to assess treatment responses and to detect recurrence.

In some cases, information regarding specific genes and pathways that are altered provides patients and physicians with options for personalized therapy. This general approach is sometimes referred to as *precision medicine*. Because tumor behavior is highly variable, even within a tumor type, personalized information-based medicine can supplement and perhaps eventually supplant histology-based tumor assessment, especially in the case of tumors that are resistant to conventional therapeutic approaches. Conversely, molecular nosology has revealed similarities in tumors of diverse histotype. The success of the precision medicine approach in any given patient depends on the presence of tumor-associated genetic alterations that are actionable (i.e., can be targeted with a specific drug). Examples of currently actionable changes include mutations in *BRAF* (targeted by the drug vemurafenib) and *RET* (targeted by sunitinib and sorafenib), and *ALK* rearrangements (targeted by crizotinib). At present, the proportion of tumors that can be treated with such precision medicine approaches is small, but future therapeutic development will hopefully change this situation. The development of new targeted agents is at present hindered by the fact that such agents can only target activated oncogenes, while the great majority of genetic alterations in common solid tumors are those that inactivate tumor suppressor genes. Because all drugs, whether for use in oncology or any other purpose, can only inhibit protein actions, drugs cannot be used to directly target the proteins encoded by inactivated tumor suppressor genes; these proteins are already inactive. More information about the pathways through which tumor suppressor genes act may provide a way around this obstacle. For example, when a tumor suppressor gene is inactivated, some downstream component of the pathway is likely to be activated, thereby presenting a realistic target. An example of this is provided by PARP-1 inhibitors, which have been successfully used to treat patients whose tumors have inactivating mutations of genes involved in DNA repair processes, such as *BRCA1*. Patterns of global gene expression can be used to help unravel such pathways and are already being used to predict drug sensitivities and provide prognostic information in addition to that provided by DNA sequence analysis. Evaluation of proteomic and metabolomics patterns may also prove useful.

THE FUTURE

A revolution in cancer genetics has occurred in the past 30 years. Most types of cancer are now understood at the DNA sequence level and this accomplishment has led us to an increasingly refined understanding of tumorigenesis. Cancer gene mutations have proven to be reliable biomarkers for cancer detection and monitoring as well as for informing therapeutics through precision medicine approaches. Gene-based tests are already standard of care for certain tumor types, such as melanoma, colorectal and pancreatic cancers, and the utility of these tests will undoubtedly be expanding greatly in the coming years as new therapies and ways of predicting responses to therapies are developed. While effective treatment of advanced cancers remains difficult, it is expected that breakthroughs in these areas will continue to emerge and be applicable to an ever-increasing number of cancers. Moreover, with the hoped-for advances in diagnostics, particularly in the earlier detection of cancers, the new and old therapies for cancer can be expected to have a much greater impact on reducing cancer deaths.

Acknowledgments

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68 Cancer Cell Biology

Jeffrey W. Clark, Dan L. Longo

CANCER CELL BIOLOGY

Cancers are characterized by unregulated cell division, avoidance of cell death, tissue invasion, and the ability to metastasize. A neoplasm is *benign* when it grows in an unregulated fashion without tissue invasion. The presence of unregulated growth and tissue invasion is characteristic of *malignant* neoplasms. Cancers are named based on their origin: those derived from epithelial tissue are called *carcinomas*, those derived from mesenchymal tissues are *sarcomas*, and those derived from hematopoietic tissue are *leukemias*, *lymphomas,* and *plasma cell dyscrasias* (including *multiple myeloma*).

Cancers nearly always arise as a consequence of genetic alterations, the vast majority of which begin in a single cell and therefore are monoclonal in origin. However, because a wide variety of genetic and epigenetic changes can occur in different cells within malignant tumors over time, most cancers are characterized by marked heterogeneity in the populations of cells. This heterogeneity significantly complicates the treatment of most cancers because it is likely that there are subsets of cells that will be resistant to therapy and will therefore survive and proliferate even if the majority of cells are killed.

A few cancers appear to, at least initially, be primarily driven by an alteration in a dominant gene that produces uncontrolled cell proliferation. Examples include chronic myeloid leukemia (*abl*), about half of melanomas (*braf*), Burkitt's lymphoma (c-*myc*), and subsets of lung adenocarcinomas (*egfr, alk, ros1, met, and ret*). The genes that can promote cell growth when altered are often called *oncogenes*. They were first identified as critical elements of viruses that cause animal tumors; it was subsequently found that the viral genes had normal counterparts with important functions in the cell and had been captured and mutated by viruses as they passed from host to host.

However, the vast majority of human cancers are characterized by a multiple step process involving many genetic abnormalities, each of which contributes to the loss of control of cell proliferation and differentiation and the acquisition of capabilities, such as tissue invasion, the ability to metastasize, and angiogenesis (development of new blood vessels required for tumor growth). These properties are not found in the normal adult cell from which the tumor is derived. Indeed, normal cells have a large number of safeguards against DNA damage (including multiple DNA repair and extensive DNA damage response mechanisms), uncontrolled proliferation, and invasion. Many cancers go through recognizable steps of progressively more abnormal phenotypes: hyperplasia, to adenoma, to dysplasia, to carcinoma in situ, to invasive cancer with the ability to metastasize **(Table 68-1)**. For most cancers, these changes occur over a prolonged period of time, usually many years.

In most organs, only primitive undifferentiated cells are capable of proliferating and the cells lose the capacity to proliferate as they differentiate and acquire functional capability. The expansion of the primitive cells (stem cells) is linked to some functional need in the host through receptors that receive signals from the local environment or through hormonal and other influences delivered by the vascular supply. In the absence of such signals, the cells are at rest. The signals that keep the primitive cells at rest remain incompletely understood. These signals must be environmental, based on the observations that a regenerating liver stops growing when it has replaced the portion that has been surgically removed post partial hepatectomy and regenerating bone marrow stops growing when the peripheral blood counts return to normal. Cancer cells clearly have lost responsiveness to such controls and do not recognize when they have overgrown the niche normally occupied by the organ from which they are derived. A better understanding of the mechanisms of growth regulation is evolving.

TABLE 68-1 Phenotypic Characteristics of Malignant Cells

Deregulated cell proliferation: Loss of function of negative growth regulators (tumor suppressor genes, i.e., *Rb*, *p53*), and increased action of positive growth regulators (oncogenes, i.e., *Ras*, *Myc*). Leads to aberrant cell cycle control and includes loss of normal checkpoint responses.
Failure to differentiate: Arrest at a stage before terminal differentiation. May retain stem cell properties. (Frequently observed in leukemias due to transcriptional repression of developmental programs by the gene products of chromosomal translocations.)
Loss of normal apoptosis pathways: Inactivation of p53, increases in Bcl-2 (anti-apoptic) family members. This defect enhances the survival of cells with oncogenic mutations and genetic instability and allows clonal expansion and diversification within the tumor without activation of physiologic cell death pathways.
Genetic instability: Defects in DNA repair pathways leading to either single or oligo-nucleotide mutations (as in microsatellite instability, MIN) or more commonly chromosomal instability (CIN) leading to aneuploidy (abnormal number of chromosomes in a cell). Caused by loss of function of a number of proteins including p53, BRCA1/2, mismatch repair genes, DNA repair enzymes, and the spindle checkpoint. Leads to accumulation of a variety of mutations in different cells within the tumor and heterogeneity.
Loss of replicative senescence: Normal cells stop dividing in vitro after 25–50 population doublings. Arrest is mediated by the Rb, $p16^{INK4a}$, and p53 pathways. While most cells remain arrested, genetic and epigenetic changes in a subset of cells allows further replication leading to telomere loss, with crisis leading to death of many cells. Cells that survive often harbor gross chromosomal abnormalities and the ability to continue to proliferate. These cells express telomerase which maintains telomeres and is important for ongoing growth of these cells. Relevance to human in vivo cancer remains uncertain. Many human cancers express telomerase.
Non-responsiveness to external growth-inhibiting signals: Cancer cells have lost responsiveness to signals normally present to stop proliferating when they have overgrown the niche normally occupied by the organ from which they are derived. Our understanding about this mechanism of growth regulation remains limited.
Increased angiogenesis: Due to increased gene expression of proangiogenic factors (VEGF, FGF, IL-8, ANGIOPOEITIN) by tumor or stromal cells, or loss of negative regulators (endostatin, tumstatin, thrombospondin).
Invasion: Cell mobility and ability to move through extracellular matrix and into other tissues or organs. Loss of cell-cell contacts (gap junctions, cadherins) and increased production of matrix metalloproteinases (MMPs). Can take the form of epithelial-to-mesenchymal transition (EMT), with anchored epithelial cells becoming more like motile fibroblasts.
Metastasis: Spread of tumor cells to lymph nodes or distant tissue sites. Limited by the ability of tumor cells to migrate out of initial site and to survive in a foreign environment, including evading the immune system (see below).
Evasion of the immune system: Downregulation of MHC class I and II molecules; induction of T-cell tolerance; inhibition of normal dendritic cell and/or T-cell function; antigenic loss variants and clonal heterogeneity; increase in regulatory T cells.
Shift in cell metabolism: Complex changes including alterations due to tumor stress such as hypoxia, energy generation shifts from oxidative phosphorylation to aerobic glycolysis, generate building blocks for malignant cell production and proliferation.

Abbreviations: FGF, fibroblast growth factor; IL, interleukin; MHC, major histocompatibility complex; VEGF, vascular endothelial growth factor.

CELL CYCLE CHECKPOINTS

The cell division cycle consists of four phases—G1 (growth and preparation for DNA synthesis), S (DNA synthesis), G2 (preparation to divide), and M (mitosis, cell division). Cells can also exit the cell cycle and be quiescent (G0). Progression of a cell through the cell cycle is tightly regulated at a number of checkpoints (especially at the G1/S boundary, the G2/M boundary, and during M [spindle checkpoint]) by an array of genes that are targeted by specific genetic alterations in cancer. Critical proteins in these control processes that are frequently mutated or otherwise inactivated in cancers are called tumor-suppressor genes. Examples include p53 and Rb (discussed below). In the first phase, G_1, preparations are made to replicate the genetic material. The cell stops before entering the DNA synthesis phase, or S phase, to take inventory. Are we ready to replicate our DNA? Is the DNA repair machinery in

place to fix any mutations that are detected? Are the DNA replicating enzymes available? Is there an adequate supply of nucleotides? Is there sufficient energy to proceed? The main brake on the process is the retinoblastoma protein, Rb. When the cell determines that it is prepared to move ahead, sequential activation of cyclin-dependent kinases (CDKs) results in the inactivation of the brake, Rb, by phosphorylation. Phosphorylated Rb releases the S phase–regulating transcription factor, E2F/DP1, and genes required for S phase progression are expressed. If the cell determines that it is unready to move ahead with DNA replication, a number of inhibitors are capable of blocking the action of the CDKs, including $p21^{Cip2/Waf1}$, $p16^{Ink4a}$, and $p27^{Kip1}$. *Nearly every cancer has one or more defects in the G_1 checkpoint that permit progression to S phase despite abnormalities in DNA repair machinery or other deficiencies that would affect normal DNA synthesis.*

At the end of the G2 phase and prior to the M phase, after the cell has exactly duplicated its DNA content, a second inventory is taken at the G2 checkpoint. Have all of the chromosomes been fully duplicated? Were all segments of DNA copied only once? Has all damaged DNA been repaired? Do we have the right number of chromosomes and the right amount of DNA? If so, the cell proceeds to G_2, in which the cell prepares for division by synthesizing mitotic spindle and other proteins needed to produce two daughter cells. When DNA damage is detected, the p53 pathway is normally activated. Called the guardian of the genome, p53 is a transcription factor that is normally present in the cell in very low levels. Its level is generally regulated through its rapid turnover. Normally, p53 is bound to mdm2, an ubiquitin ligase that both inhibits p53 transcriptional activation and also targets p53 for degradation in the proteasome. When damage is sensed, the ATM (ataxia-telangiectasia mutated) pathway is activated; ATM phosphorylates mdm2, which no longer binds to p53, and p53 then stops cell cycle progression, directs the synthesis of repair enzymes, or if the damage is too great, initiates apoptosis (programmed cell death) of the cell to prevent the propagation of a damaged cell **(Fig. 68-1)**.

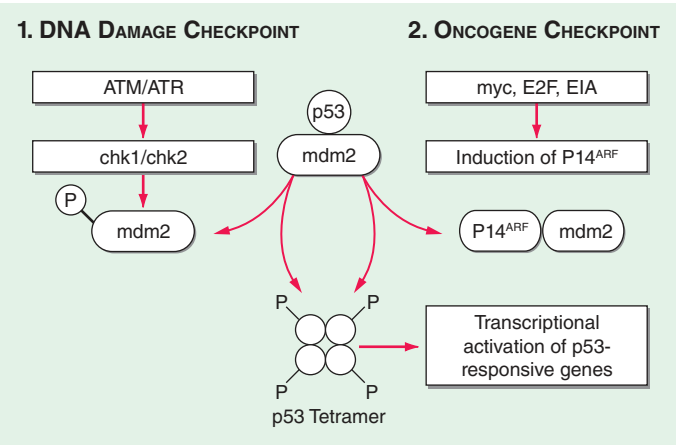

FIGURE 68-1 Induction of p53 by the DNA damage and oncogene checkpoints. In response to noxious stimuli, p53 and mdm2 are phosphorylated by the ataxia-telangiectasia mutated (ATM) and related ATR serine/threonine kinases, as well as the immediate downstream checkpoint kinases, Chk1 and Chk2. This causes dissociation of p53 from mdm2, leading to increased p53 protein levels and transcription of genes leading to cell cycle arrest ($p21^{Cip1/Waf1}$) or apoptosis (e.g., the proapoptotic Bcl-2 family members Noxa and Puma). Inducers of p53 include hypoxemia, DNA damage (caused by ultraviolet radiation, gamma irradiation, or chemotherapy), ribonucleotide depletion, and telomere shortening. A second mechanism of p53 induction is activated by oncogenes such as *Myc*, which promote aberrant G_1/S transition. This pathway is regulated by a second product of the Ink4a locus, $p14^{ARF}$ (p19 in mice), which is encoded by an alternative reading frame (ARF) of the same stretch of DNA that codes for $p16^{Ink4a}$. Levels of ARF are upregulated by *Myc* and E2F, and ARF binds to mdm2 and rescues p53 from its inhibitory effect. This *oncogene checkpoint* leads to the death or senescence (an irreversible arrest in G_1 of the cell cycle) of renegade cells that attempt to enter S phase without appropriate physiologic signals. Senescent cells have been identified in patients whose premalignant lesions harbor activated oncogenes, for instance, dysplastic nevi that encode an activated form of BRAF (see below), demonstrating that induction of senescence is a protective mechanism that operates in humans to prevent the outgrowth of neoplastic cells.

A second method of activating p53 involves the induction of $p14^{ARF}$ by hyperproliferative signals from oncogenes. $p14^{ARF}$ competes with p53 for binding to mdm2, allowing p53 to escape the effects of mdm2 and accumulate in the cell. Then p53 stops cell cycle progression by activating CDK inhibitors such as p21 and/or initiating the apoptosis pathway. Not surprisingly given its critical role in controlling cell cycle progression, mutations in the gene for p53 on chromosome 17p are among the most frequent mutations in human cancers, although percentages vary between different cancers. Most commonly these mutations are acquired in the malignant tissue in one allele and the second allele is inactivated (such as by deletion), leaving the cell unprotected from DNA-damaging agents or activated oncogenes. Some environmental exposures produce signature mutations in p53; for example, aflatoxin exposure leads to mutation of arginine to serine at codon 249 and leads to hepatocellular carcinoma. In rare instances, p53 mutations are in the germline (Li-Fraumeni syndrome) and produce a familial cancer syndrome. The absence of p53 leads to chromosome instability and the accumulation of DNA damage including the acquisition of properties that give the abnormal cell a proliferative and survival advantage. *Like Rb dysfunction, most cancers have mutations that disable the p53 pathway*. Indeed, the importance of p53 and Rb in the development of cancer is underscored by the neoplastic transformation mechanism of human papillomavirus. This virus has two main oncogenes, E6 and E7. E6 acts to increase the rapid turnover of p53, and E7 acts to inhibit Rb function; inhibition of these two targets is required for transformation of epithelial cells.

Another cell cycle checkpoint exists when the cell is undergoing division (M phase), the spindle checkpoint which acts to ensure that there is proper attachment of chromosomes to the mitotic spindle before progression through the cell cycle can occur. If the spindle apparatus does not properly align the chromosomes for division, if the chromosome number is abnormal (i.e., greater or less than 4*n*), or if the centromeres are not properly paired with their duplicated partners, then the cell initiates a cell death pathway to prevent the production of aneuploid progeny (having an altered number of chromosomes). Abnormalities in the spindle checkpoint facilitate the development of aneuploidy which is frequently found in cancers. In some tumors, aneuploidy is a predominant genetic feature. In others, a defect in the cells' ability to repair errors in the DNA, such as due to mutations in genes coding for the proteins critical for mismatched DNA repair, is the primary genetic lesion. Mismatch repair is usually detected by finding alterations in repeat sequences of DNA (called microsatellites), or microsatellite instability, in malignant cells. In general, tumors either have defects in chromosome number or defective DNA repair pathways such as microsatellite instability, but not both. Defects that lead to cancer include abnormal cell cycle checkpoints, inadequate DNA repair, and failure to preserve genome integrity leading to DNA damage. These defects and the stress of the resultant increased DNA damage make cancer cells more vulnerable to additional DNA damage which can be exploited by chemotherapy, radiation therapy, and immunotherapy which are the major systemic therapeutic approaches effective against cancer.

Efforts are also under way to therapeutically restore the defects in cell cycle regulation that characterize cancer, although this remains a challenging problem because it is much more difficult to restore normal biologic function than to inhibit abnormal function of proteins driving cell proliferation, such as occurs with oncogenes. Newer approaches to gene editing (e.g., Clustered Regularly Interspaced Short Palindromic Repeats [CRISPR]) should make this more feasible.

CANCER AS AN ORGAN THAT IGNORES ITS NICHE

The fundamental cellular defects that create a malignant neoplasm act at the cellular level and some of these are cell autonomous. However, that is not the entire story. Cancers consist of both malignant cells as well as other cells in the cancer microenvironment and behave as organs that have lost their specialized function and stopped responding to signals that would limit their growth in tightly regulated normal tissue homeostasis. Human cancers usually become clinically detectable when a primary mass is at least 1 cm in diameter—such a mass consists of about 10^9 cells. More commonly patients present

with tumors that are at least 10^{10} cells. A lethal tumor burden is about 10^{12}–10^{13} cells, although there is significant variability depending on the type and location of the cancer. If all malignant cells were dividing at the time of diagnosis, patients would reach a lethal tumor burden in a very short time. However, human tumors grow by Gompertzian kinetics—this means that not every daughter cell produced by a cell division is actively dividing. In addition, the overall growth rate of a tumor depends on differences between growth rates of different cells within the tumor and rate of cell loss. The growth fraction of a tumor declines with time, largely due to factors in the microenvironment. The growth fraction of the first malignant cell is 100%, and by the time a patient presents for medical care, the growth fraction is estimated to be <10%, although the fraction varies between different types of cancers and even different cancers of the same type in different individuals. This fraction is similar to the growth fraction of normal bone marrow and normal intestinal epithelium, the most highly proliferative normal tissues in the human body, a fact that may explain the dose-limiting toxicities of agents that target dividing cells.

The implication of these data is that the tumor is slowing its own growth over time. How does it do this? The tumor cells have multiple genetic lesions that tend to promote proliferation, yet by the time the tumor is clinically detectable, its capacity for proliferation has declined. Better understanding of how a tumor slows its own growth would provide important clues for better cancer treatment. A number of factors, including those in the tumor microenvironment, are known to contribute to the failure of tumor cells to proliferate in vivo. Some cells are hypoxemic and have inadequate supply of nutrients and energy. Some have sustained too much genetic damage to complete the cell cycle but have lost the capacity to undergo apoptosis and therefore survive but do not proliferate. However, an important subset is not actively dividing but retains the capacity to divide and can start dividing again under certain conditions such as when the tumor mass is reduced by treatments leading to improved conditions in the tumor microenvironment favorable for cell proliferation. Just as the bone marrow increases its rate of proliferation in response to bone marrow–damaging agents, the tumor also seems to sense when tumor cell numbers have been reduced and can respond by increasing growth rate. However, the critical difference is that the marrow stops growing when it has reached its production goals whereas tumors do not.

Additional tumor cell vulnerabilities are likely to be detected when we learn more about how normal cells respond to "stop" signals from their environment, and why and how tumor cells fail to heed such signals.

IS IN VITRO SENESCENCE RELEVANT TO CARCINOGENESIS?

When normal cells are placed in culture in vitro, most are not capable of sustained growth. Fibroblasts are an exception to this rule. When they are cultured, fibroblasts may divide 30–50 times and then they undergo what has been termed a "crisis" during which the majority of cells stop dividing (usually due to an increase in p21 expression, a CDK inhibitor), many die, and a small fraction emerge that have acquired genetic and epigenetic changes that permit their uncontrolled growth. The cessation of growth of normal cells in culture has been termed "senescence" and whether this phenomenon is relevant to any physiologic event in vivo is still an area of investigation, including identifying biomarkers of senescence in vivo.

Among the cellular changes during in vitro propagation is telomere shortening. DNA polymerase is unable to replicate the tips of chromosomes, resulting in the loss of DNA at the specialized ends of chromosomes (called *telomeres*) with each replication cycle. At birth, human telomeres are 15- to 20-kb pairs long and are composed of tandem repeats of a six-nucleotide sequence (TTAGGG) that associates with specialized telomere-binding proteins to form a T-loop structure that protects the ends of chromosomes from being mistakenly recognized as damaged. The loss of telomeric repeats with each cell division cycle causes gradual telomere shortening, leading to growth arrest (called *senescence*) when one or more critically short telomeres trigger a p53-regulated DNA-damage checkpoint response. Cells can bypass this growth arrest if pRb and p53 are nonfunctional, but cell death usually ensues when the unprotected ends of chromosomes lead to chromosome fusions or other catastrophic DNA rearrangements. *The ability to bypass telomere-based growth limitations is thought to be a critical step in the evolution of most malignancies*. This occurs by the reactivation of telomerase expression in cancer cells. Telomerase is an enzyme that adds TTAGGG repeats onto the 3′ ends of chromosomes. It contains a catalytic subunit with reverse transcriptase activity (hTERT) and an RNA component that provides the template for telomere extension. Most normal somatic cells do not express sufficient telomerase to prevent telomere attrition with each cell division. Exceptions include stem cells (such as those found in hematopoietic tissues, gut and skin epithelium, and germ cells) that require extensive cell division to maintain tissue homeostasis. More than 90% of human cancers express high levels of telomerase that prevent telomere shortening to critical levels and allow indefinite cell proliferation. In vitro experiments indicate that inhibition of telomerase activity leads to tumor cell apoptosis. Major efforts are underway to develop methods to inhibit telomerase activity in cancer cells. For example, the protein component of telomerase (hTERT) may act as one of the most widely expressed tumor-associated antigens and can be targeted by vaccine approaches. However, a caveat to targeting telomerase for anticancer treatment is an inadequate understanding of how important its presence is in certain normal cells to maintaining the normal physiologic state.

Although most of the functions of telomerase relate to cell division, it also has several other effects including interfering with the differentiated functions of at least certain stem cells. However, the impact on differentiated function of normal non-stem cells is less clear. The picture is further complicated by the fact that rare genetic defects in the telomerase enzyme seem to cause pulmonary fibrosis, aplastic anemia, or dyskeratosis congenita (characterized by abnormalities in skin, nails, and oral mucasa with increased risk for certain malignancies) but not defects in nutrient absorption in the gut, a site that might be presumed to be highly sensitive to defective cell proliferation. Much remains to be learned about how telomere shortening and telomere maintenance are related to human illness in general and cancer in particular.

SIGNAL TRANSDUCTION PATHWAYS IN CANCER CELLS

Signals that affect cell behavior come from adjacent cells, the stroma in which the cells are located, hormonal signals that originate remotely, and from the cells themselves (autocrine signaling). These signals generally exert their influence on the receiving cell through activation of signal transduction pathways that have as their end result the induction of activated transcription factors that mediate a change in cell behavior or function or the acquisition of effector machinery to accomplish a new task. Although signal transduction pathways can lead to a wide variety of outcomes, many such pathways rely on cascades of signals that sequentially activate different proteins or glycoproteins and lipids or glycolipids, and the activation steps often involve the addition or removal of one or more phosphate groups on a downstream target. Other chemical changes can result from signal transduction pathways, but phosphorylation and dephosphorylation play a major role. The proteins that add phosphate groups to proteins are called kinases. There are two major distinct classes of kinases; one class acts on tyrosine residues and the other acts on serine/threonine residues. The tyrosine kinases often play critical roles in signal transduction pathways; they may be receptor tyrosine kinases (RTKs) or they may be linked to other cell-surface receptors through associated docking proteins and transmit the signal into the cell **(Fig. 68-2)**.

Normally, tyrosine kinase activity is short-lived and reversed by protein tyrosine phosphatases (PTPs). However, in many human cancers, tyrosine kinases or components of their downstream pathways are activated by mutation, gene amplification, or chromosomal translocations. Because these pathways regulate proliferation, survival, migration, and angiogenesis, they have been identified as important targets for cancer therapeutics.

Inhibition of kinase activity is effective in the treatment of a number of neoplasms. Lung cancers with mutations in the epidermal

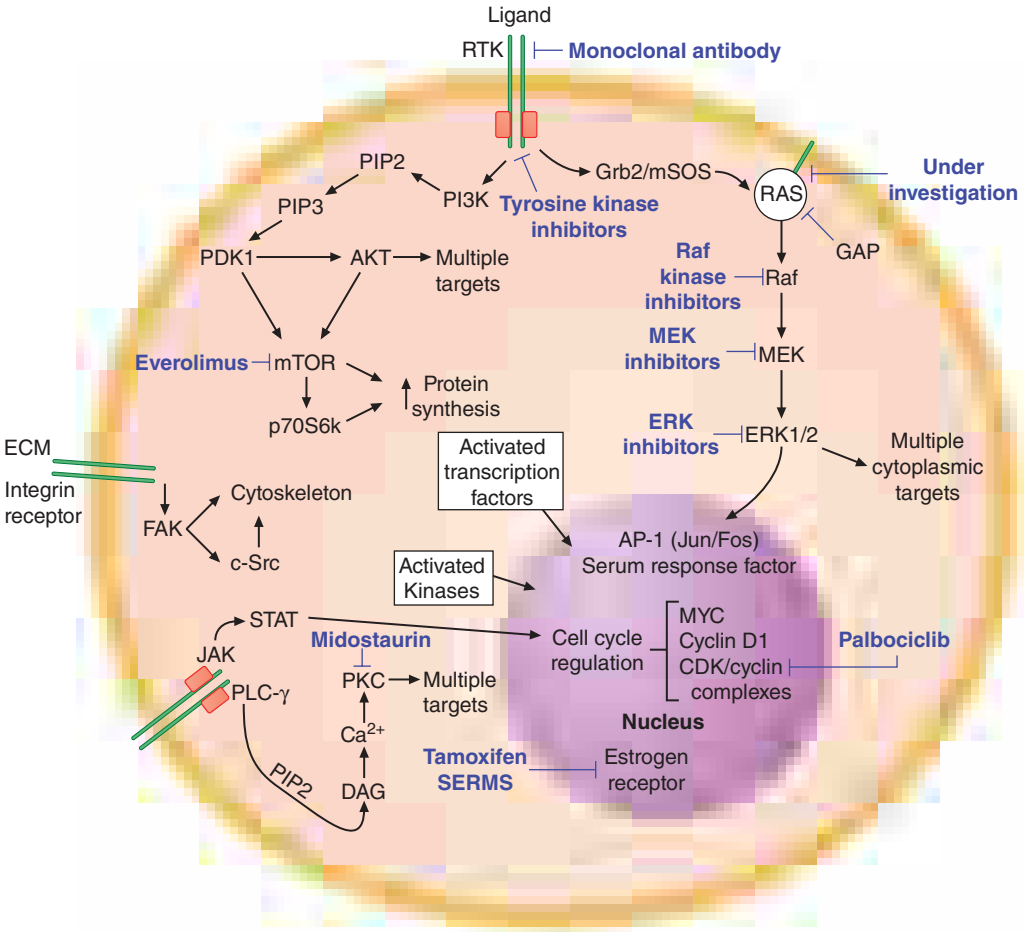

FIGURE 68-2 Therapeutic targeting of signal transduction pathways in cancer cells. Three major signal transduction pathways are activated by receptor tyrosine kinases (RTK). *1.* The protooncogene Ras is activated by the Grb2/mSOS guanine nucleotide exchange factor, which induces an association with Raf and activation of downstream kinases (MEK and ERK1/2). *2.* Activated PI3K phosphorylates the membrane lipid PIP_2 to generate PIP_3, which acts as a membrane-docking site for a number of cellular proteins including the serine/threonine kinases PDK1 and Akt. PDK1 has numerous cellular targets, including Akt and mTOR. Akt phosphorylates target proteins that promote resistance to apoptosis and enhance cell cycle progression, while mTOR and its target p70S6K upregulate protein synthesis to potentiate cell growth. *3.* Activation of PLC-γ leads the formation of diacylglycerol (DAG) and increased intracellular calcium, with activation of multiple isoforms of PKC and other enzymes regulated by the calcium/calmodulin system. Other important signaling pathways involve non-RTKs that are activated by cytokine or integrin receptors. Janus kinases (JAK) phosphorylate STAT (signal transducer and activator of transcription) transcription factors, which translocate to the nucleus and activate target genes. Integrin receptors mediate cellular interactions with the extracellular matrix (ECM), inducing activation of FAK (focal adhesion kinase) and c-Src, which activate multiple downstream pathways, including modulation of the cell cytoskeleton. Many activated kinases and transcription factors migrate into the nucleus, where they regulate gene transcription, thus completing the path from extracellular signals, such as growth factors, to a change in cell phenotype, such as induction of differentiation or cell proliferation. The nuclear targets of these processes include transcription factors (e.g., Myc, AP-1, and serum response factor) and the cell cycle machinery (CDKs and cyclins). Inhibitors of many of these pathways have been developed for the treatment of human cancers. Examples of inhibitors that are either approved or are currently being evaluated in clinical trials are shown in purple type.

growth factor receptor are highly responsive to erlotinib and gefitinib (Table 68-2). Lung cancers with activation of anaplastic lymphoma kinase (ALK) or ROS1 by translocations respond to crizotinib, an ALK and ROS1 inhibitor and additional ALK inhibitors including ceritinib and alectinib are available for treating lung cancers with a number of additional inhibitors currently in trials. BRAF inhibitors are highly effective in melanomas and thyroid cancers in which BRAF is mutated. Targeting a protein (MEK) downstream of BRAF also has activity against BRAF mutant melanomas and combined inhibition of BRAF and MEK is more effective than either alone. Janus kinase (JAK) inhibitors are active in myeloproliferative syndromes in which JAK2 activation is a pathogenetic event. Imatinib (which targets a number of tyrosine kinases) is an effective agent in tumors that have translocations of the c-Abl and BCR gene (such as chronic myeloid leukemia), mutant c-Kit (gastrointestinal stromal cell tumors), or mutant platelet-derived growth factor receptor (PDGFR α; gastrointestinal stromal tumors); second-generation inhibitors of BCR-Abl, dasatinib, and nilotinib are even more effective and the third generation agent bosutinib has activity in some patients who have progressed on other inhibitors, while the third generation ponatinib has activity against the T315I mutation, which is resistant to the other agents. Although almost all tyrosine kinase inhibitors are not entirely selective for one protein, certain inhibitors have significant activity against a broad number of proteins. These include sorafenib, regorafenib, cabozantinib, sunitinib, and lenvatinib. These have shown antitumor activity in various malignancies, including renal cell cancer (RCC) (sorafenib, sunitinib, cabozantinib, lenvatinib), hepatocellular carcinoma (sorafenib, regorafenib, lenvatinib), gastrointestinal stromal tumor (GIST) (sunitinib, regorafenib), thyroid cancer (sorafenib, cabozantinib, lenvatinib), colorectal cancer (regorafenib), and pancreatic neuroendocrine tumors (sunitinib). Inhibitors of the mammalian target of rapamycin (mTOR) are active in RCC, pancreatic neuroendocrine tumors, and breast cancer. The list of active agents and treatment indications is growing rapidly (Table 68-2). These agents have ushered in a new era of personalized therapy. It is becoming more common for resected tumors to be assessed for specific molecular changes that predict response and to have clinical decision-making guided by those results. This is now an important component of standard therapy for metastatic lung, gastroesophageal, melanoma, breast, and colorectal cancers as well as in adjuvant therapy for breast cancer.

However, none of these therapies has yet been curative by themselves for any malignancy, although prolonged periods of disease control lasting many years frequently occur in CML, including a >80% survival rate at 10 years. The reasons for the failure to cure are not completely defined, although resistance to the treatment ultimately develops in most patients. In some tumors, resistance to kinase inhibitors is

TABLE 68-2 Some FDA-Approved Molecularly Targeted Agents for the Treatment of Cancer

DRUG	MOLECULAR TARGET	DISEASE	MECHANISM OF ACTION
All-*trans* retinoic acid	PML-RARα oncogene	Acute promyelocytic leukemia M3 AML; t(15;17)	Inhibits transcriptional repression by PML-RARα
Imatinib	Bcr-Abl, c-Abl, c-Kit, PDGFR-α/β	Chronic myeloid leukemia; GIST	Blocks ATP binding to tyrosine kinase active site
Dasatinib, Nilotinib, Ponatinib, Bosutinib	Bcr-Abl (primarily)	Chronic myeloid leukemia	Blocks ATP binding to tyrosine kinase active site
Sunitinib	c-Kit, VEGFR-2, PDGFR-β, Flt-3	GIST; RCC; PNET	Inhibits activated c-Kit and PDGFR in GIST; inhibits VEGFR in RCC and probably in PNET
Sorafenib	RAF, VEGFR-2, PDGFR-α/β, Flt-3, c-Kit	RCC; hepatocellular carcinoma, differentiated thyroid cancer, desmoid	Targets VEGFR pathways in RCC and HCC. Possible activity against BRAF in thyroid cancer
Regorafenib	VEGFR1-3,TIE-2, FGFR1,KIT,RET, PDGFR	Colorectal cancer; GIST; HCC	Competitive inhibitor ATP binding site of tyrosine kinase domain multiple kinases including VEGFR
Axitinib	VEGFR 1-3	RCC	Competitive inhibitor ATP binding site of tyrosine kinase domain VEGF receptors
Erlotinib	EGFR	NSCLC; pancreatic cancer	Competitive inhibitor of the ATP-binding site of the EGFR
Afitinib	EGFR (and other HER family)	NSCLC	Irreversible inhibitor of ATP-binding site of HER family members
Osimertinib	EGFR(T790M)	NSCLC	Inhibits EGFR mutations including T790M mutant NSCLC
Lapatinib	HER2/neu	Breast Cancer	Competitive inhibitor of the ATP binding site of HER2
Crizotinib, Ceritinib, Alectinib	ALK, ROS1	NSCLC	Inhibitor of ALK and ROS1 tyrosine kinase
Palbociclib, Ribociclib, Abemaciclib	CDK4/6	Breast	Inhibitor of CDK4/6
Bortezomib, Carfilzomib, Ixazomib	Proteasome	Multiple myeloma	Inhibits proteolytic degradation of multiple cellular proteins
Vemurafenib, Dabrafenib	BRAF	Melanoma	Inhibitor of serine-threonine kinase domain of V600E mutant of BRAF
Trametinib, Cobimetinib	MEK	Melanoma	Inhibitor of serine-threonine kinase domain of MEK
Cabozantinib	RET, MET, VEGFR	MTC, RCC	Competitive inhibitor ATP binding site of tyrosine kinase domain multiple kinases, including VEGFR2 and RET
Vandetanib	RET, VEGFR, EGFR	MTC	Competitive inhibitor ATP-binding site of tyrosine kinase domain multiple kinases, including RET
Temsiroliumus	mTOR	RCC	Competitive inhibitor of mTOR serine-threonine kinase
Everolimus	mTOR	RCC; PNET	Binds to immunophilin FK binding protein-12 which forms complex that inhibits mTOR kinase
Vorinostat, Romidepsin, Belinostat	HDAC	CTCL/PTL	HDAC inhibitor, epigenetic modulation
Panobinostat	HDAC	MM	HDAC inhibitor, epigenetic modulation
Ruxolitinib	JAK-1, 2	Myelofibrosis	Competitive inhibitor of tyrosine kinase
Vismodegib	Hedgehog pathway	Basel cell cancer (skin)	Inhibits smoothened in Hedgehog Pathway
Lenvatinib	Multi-Kinase inhibitor (VEGFR, FGFR, PGFR-a, others)	RCC, Thyroid cancer	Competitive inhibitor ATP-binding site of tyrosine kinase domain multiple kinases
Olaparib, rucaparib	PARP	BRCA mutant ovarian (both) and breast (olaparib) cancers	Inhibits PARP and DNA repair
Venetoclax	BCL-2	CLL (with 17p deletion)	Inhibits BCL-2 and enhances apoptosis
Ibrutinib	Bruton Tyrosine Kinase (BTK)	CLL, MCL, MZL, SLL, WM	Inhibitor of BTK
Idealisib	PI3K-delta	CLL, SLL, FL	Inhibits PI3k-delta,preventing proliferation and inducing apoptosis
Monoclonal Antibodies Alone			
Trastuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface and induces receptor internalization
Pertuzumab	HER2/neu (ERBB2)	Breast cancer	Binds HER2 on tumor cell surface at distinct site from Trastuzumab and prevents binding to other receptors
Cetuximab	EGFR	Colon cancer, squamous cell carcinoma of the head and neck	Binds extracellular domain of EGFR and blocks binding of EGF and TGF-α; induces receptor internalization. Potentiates the efficacy of chemotherapy and radiotherapy
Panitumumab	EGFR	Colon cancer	Similar to Cetuximab but fully humanized rather than chimeric
Necitumumab	EGFR	Squamous NSCLC	Binds EGFR
Rituximab	CD20	B-cell lymphomas and leukemias that express CD20	Multiple potential mechanisms, including direct induction of tumor cell apoptosis and immune mechanisms
Alemtuzumab	CD52	Chronic lymphocytic leukemia and CD52-expressing lymphoid tumors	Immune mechanisms
Bevacizumab	VEGF	Colorectal, lung cancers, RCC, glioblastoma	Inhibits angiogenesis by high-affinity binding to VEGF
Ziv-Aflibercept	VEGFA, VEGFB, PLGF	Colorectal cancers	Inhibits angiogenesis by high-affinity binding to VEGFA, B and PLGF
Ramucirumab	VEGFR	Gastric, colorectal, lung cancers	Inhibits angiogenesis by binding to VEGFR

(*Continued*)

TABLE 68-2 Some FDA-Approved Molecularly Targeted Agents for the Treatment of Cancer (Continued)

DRUG	MOLECULAR TARGET	DISEASE	MECHANISM OF ACTION
Ipilumumab	CTLA-4	Melanoma	Blocks CTLA-4 preventing interaction with CD80/86 and T-cell inhibition
Nivolumab Pembrolizumab	PD-1	Melanoma, Head and Neck Cancer, NSCLC, Hodgkins Disease, Urothelial cancer, RCC, HCC, gastric cancer, MSI high cancers	Blocks PD-1 preventing interaction with PDL-1 and T-cell inhibition
Atezolizumab, Durvalumab	PDL1	NSCLC, Urothelial cancer	Blocks PDL1 preventing interaction with PD-1 and T-cell inhibition
Denosumab	Rank ligand	Breast, Prostate	Inhibits Rank ligand, primary signal for bone removal
Dinutuximab	Glycolipid GD2	Neuroblastoma (pediatric)	Immune mediated attack on GD2 expressing cells
Daratumumab	CD38	MM	Binds to CD38 on MM cells causing apoptosis by antibody dependent or compliment mediated cytotoxicity
Elotuzumab	SLAMF7	MM	Activating NK cells to kill MM cells
Olarutumab	PDGFRα	Soft Tissue Sarcomas	Blocks PDGFRα activity
Blinotumumab	CD19 and CD3	PH-relapsed precursor Bcell ALL	Binds CD19 on ALL cells and CD3 on T cells; Immune attack on CD19 expressing cells
Antibody-Chemotherapy Conjugates			
Brentuximab vedotin	CD30	HD, Anaplastic Lymphoma	Delivery of chemotherapeutic agent (MMAE) to CD30 expressing tumor cells
Ado-Trastuzumab emtansine	HER2	Breast Cancer	Delivery of chemotherapeutic agent emtansine to HER2 expressing breast cancer cells
CAR-T Cells			
Kymria, Yescarta	CD19	ALL (Kymria), DLBCL (Yescarta)	Targeted T-cells to protein on surface of malignant cells

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; Flt-3, fms-like tyrosine kinase-3; GIST, gastrointestinal stromal tumor; HDAC-histone deacetylases; MCL, mantle cell lymphoma; MSI, microsatellite instability; MZL, mantle zone lymphoma; NSCLC, nonsmall cell lung cancer; PARP, poly ADP ribose, polymerase; PDGFR, platelet-derived growth factor receptor; PLGF, placenta growth factor; PML-RARα, promyelocytic leukemia-retinoic acid receptor-alpha; PNET, pancreatic neuroendocrine tumors; RCC, renal cell cancer; t(15;17), translocation between chromosomes 15 and 17; SLL, small lymphocytic lymphoma; TGF-α, transforming growth factor-alpha; VEGFR, vascular endothelial growth factor receptor; WM, Waldenstroms macroglobulinemia.

related to an acquired mutation in the target kinase that inhibits drug binding. Many of these kinase inhibitors act as competitive inhibitors of the ATP-binding pocket. ATP is the phosphate donor in these phosphorylation reactions. For example, mutation in the critical BCR-ABL kinase in the ATP-binding pocket (such as the threonine to isoleucine change at codon 315 [T315I]) can prevent imatinib binding. Other resistance mechanisms include alterations in other signal transduction pathways to bypass the inhibited pathway. As resistance mechanisms become better defined, rational strategies to overcome resistance will emerge. In addition, many kinase inhibitors are less specific for an oncogenic target than was hoped, and toxicities related to off-target inhibition of kinases limits the use of the agent at a dose that would optimally inhibit the cancer-relevant kinase.

Targeted agents can also be used to deliver highly toxic compounds. An important component of the technology for developing effective conjugates is the design of the linker between the two which needs to be stable. Examples of currently approved antibody drug conjugates include brentuximab vedotin, which links the microtubule toxin monomethyl auristatin E (MMAE) to an antibody targeting the cell surface antigen CD30, which is expressed on a number of malignant cells but especially in Hodgkin's lymphoma and anaplastic lymphoma. The linker in this case is cleavable which allows diffusion of the drug out of the cell after delivery. A second approved conjugate is ado-trastuzumab emtansine which links the microtubule formation inhibitor mertansine and the monoclonal antibody trastuzumab targeted against HER2 on breast cancer cells. In this case the linker is non-cleavable, thus trapping the chemotherapeutic agent within the cells. There are theoretical pluses and minuses to having either cleavable or non-cleavable linkers and it is likely that both will be used in future developments of antibody-drug conjugates.

Another strategy to enhance the antitumor effects of targeted agents is to use them in rational combinations with each other as well as with chemotherapy or immunotherapy agents that kill cells in ways distinct from agents targeting specific mutant or overexpressed proteins. Combinations of trastuzumab (a monoclonal antibody that targets the HER2 receptor [member of the EGFR family]) with chemotherapy have significant activity against breast and stomach cancers that have high levels of expression of the HER2 protein. The activity of trastuzumab and chemotherapy can be enhanced further by combinations with another targeted monoclonal antibody (pertuzumab) which prevents dimerization of the HER2 receptor with other HER family members including HER3.

Although targeted therapies have not yet resulted in cures when used alone, their use in the adjuvant setting and when combined with other effective treatments has substantially increased the fraction of patients cured. For example, the addition of rituximab, an anti-CD20 antibody, to combination chemotherapy in patients with diffuse large B cell lymphoma improves cure rates by ~15%. The addition of trastuzumab, antibody to HER2, to combination chemotherapy in the adjuvant treatment of HER2-positive breast cancer significantly improves overall survival.

A major effort is underway to develop targeted therapies for mutations in the *ras* family of genes which are the most common mutations in oncogenes in cancers (especially *kras*) but have proved to be very difficult targets for a number of reasons related to the structure of RAS proteins as well as mechanisms of activation and inactivation. Targeted therapies against a subset of proteins downstream of RAS in the signaling pathway (including BRAF and mitogen-activated protein [MAP] kinase) have proven to have significant antitumor activity against V600E BRAF mutant melanoma, with improved efficacy when they are used in combination. However, similar activity is not seen against *ras* mutant tumors. Additional targeted therapies against other proteins downstream of RAS (including ERK, or combinations of MAP kinase inhibitors and immunotherapy) are currently being studied, both individually and in combination. However, at this time, there is no established effective approach to inhibiting RAS mutant tumors. Inhibitors of phospholipid signaling pathways such as the phosphatidylinositol-3-kinase (PI3K) and phospholipase C-gamma pathways, which are involved in a large number of cellular processes that are important in cancer development and progression, are being evaluated. The targeting of a variety of other pathways that are activated in malignant cells, such as the MET pathway, hedgehog pathway, and various angiogenesis pathways are also being explored.

One of the strategies for new drug development is to take advantage of so-called oncogene addiction. This situation **(Fig. 68-3)** is created when a tumor cell develops an activating mutation in an oncogene that becomes a dominant pathway for survival and growth with reduced contributions from other pathways, even when there may be abnormalities in those pathways. This dependency on a single pathway creates

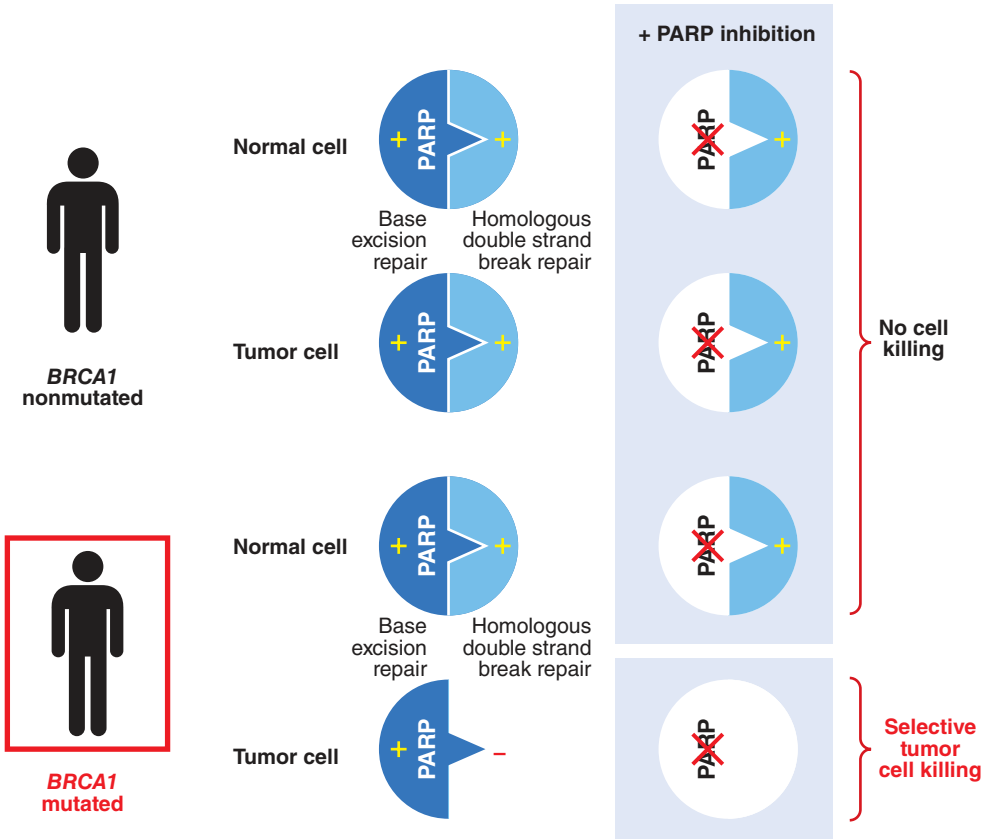

FIGURE 68-3 Synthetic lethality. Genes are said to have a synthetic lethal relationship when mutation of either gene alone is tolerated by the cell, but mutation of both genes leads to lethality, as originally noted by Bridges and later named by Dobzhansky. Thus, mutant *gene a* and *gene b* have a synthetic lethal relationship, implying that the loss of one gene makes the cell dependent on the function of the other gene. In cancer cells, loss of function of a DNA repair gene like *BRCA1*, which repairs double-strand breaks, makes the cell dependent on base excision repair mediated in part by *PARP*. If the PARP gene product is inhibited, the cell attempts to repair the break using the error-prone non-homologous end-joining method, which results in tumor cell death. High-throughput screens can now be performed using isogenic cell line pairs in which one cell line has a defined defect in a DNA repair pathway. Compounds can be identified that selectively kill the mutant cell line; targets of these compounds have a synthetic lethal relationship to the repair pathway, and are potentially important targets for future therapeutics.

a cell that is vulnerable to inhibitors of that oncogene pathway. For example, cells harboring mutations in *BRAF* are very sensitive to MEK inhibitors that inhibit downstream signaling in the BRAF pathway.

Proteins critical for transcription of other proteins essential for malignant cell survival or proliferation provide another potential target for treating cancers. The transcription factor NF-κB is a heterodimer composed of p65 and p50 subunits that associate with an inhibitor, IκB, in the cell cytoplasm. In response to growth factor or cytokine signaling, a multi-subunit kinase called IKK (IκB-kinase) phosphorylates IκB and directs its degradation by the ubiquitin/proteasome system. NF-κB, free of its inhibitor, translocates to the nucleus and activates target genes, many of which promote the survival of tumor cells. One of the mechanisms by which novel drugs called *proteasome inhibitors* are thought to produce an anticancer effect is by blocking the proteolysis of IκB, thereby preventing NF-κB activation. For reasons that have not been fully elucidated, this has a differential toxicity affect on tumor, as compared to normal, cells. Although this mechanism appears to be an important aspect of the antitumor effects of proteasome inhibitors, there are other effects involving the inhibition of the degradation of multiple cellular proteins important in malignant cell survival or proliferation. Proteasome inhibitors (bortezomib, carfilzomib, ixazomib) have activity in patients with multiple myeloma, including partial and complete remissions. Inhibitors of IKK are also in development, with the hope of more selectively blocking the degradation of IκB, thus "locking" NF-κB in an inhibitory complex and rendering the cancer cell more susceptible to apoptosis-inducing agents. Many other transcription factors are activated by phosphorylation, which can be prevented by tyrosine- or serine/threonine kinase inhibitors, a number of which are currently in clinical trials.

Estrogen receptors (ERs) and androgen receptors (ARs), members of the steroid hormone family of nuclear receptors, are targets of inhibition by drugs used to treat breast and prostate cancers, respectively. Selective estrogen receptor modulators (SERMs) have been developed as a treatment approach for ER positive breast cancer. Tamoxifen, a partial agonist and antagonist of ER function, is frequently used in breast cancer and can mediate tumor regression in metastatic breast cancer and can prevent disease recurrence in the adjuvant setting. Tamoxifen binds to the ER and modulates its transcriptional activity, inhibiting activity in the breast but promoting activity in bone but unfortunately also in uterine epithelium leading to a small increased risk of uterine cancer. Attempts have been made to develop SERMs that would have anti-estrogeneic effects in both breast and uterus while maintaining protective effects on bone. However, none of these to date has been an improvement over tamoxifen. Aromatase inhibitors, which block the conversion of androgens to estrogens in breast and subcutaneous fat tissues, have demonstrated improved clinical efficacy compared with tamoxifen in postmenopausal women and are often used as first-line therapy in post menopausal patients with ER-positive disease. They are occasionally utilized in premenopausal patients with ER positive disease in combination with ovarian suppression approaches such as leutinizing hormone receptor (LHRH) agonists. A number of approaches have been developed for blocking androgen stimulation of prostate cancer, including decreasing production by the testicles (e.g., orchiectomy, LHRH agonists or antagonists), directly blocking actions of androgen (a number of agents have been developed to do this), or blocking production by inhibiting the enzyme CYP17 which is central in production of androgens from cholesterol (Chap. 75).

CANCER-SPECIFIC GENETIC CHANGES AND SYNTHETIC LETHALITY

The concepts of oncogene addiction and synthetic lethality have spurred new drug development targeting oncogene- and tumor-suppressor pathways. As discussed earlier in this chapter and outlined in Fig. 68-3, cancer cells can become dependent upon signaling pathways containing activated oncogenes; this can effect proliferation (i.e., mutated KRAS, BRAF, overexpressed Myc, or activated tyrosine kinases). Additional genetic changes in malignant cells or unique features of tumors including defects in DNA repair (e.g., loss of *BRCA1* or *BRCA2* gene function), modifications in cell cycle control (e.g., changes in protein levels or mutations in cyclins and cyclin dependent kinases), enhanced survival mechanisms (overexpression of Bcl-2 or NF-κB), altered cell metabolism (such as occurs when mutant KRAS enhances glucose uptake and aerobic glycolysis), tumor-stromal interactions, and angiogenesis (e.g., production of vascular endothelial growth factor [VEGF] in response to HIF-2α in RCC) can also be successfully exploited to relatively specifically target cancers. However, resistance to inhibition of specific oncogenic pathways almost always eventually develops. In addition, targeting defects in tumor- suppressor genes has been much more difficult, both because the target of mutation is often deleted and because it is much more difficult to restore normal function than to inhibit abnormal function of a protein.

Synthetic lethality occurs when loss of function in either of two or more genes individually has limited effects on cell survival but loss of function in both (or more) genes leads to cell death. In the case of oncogene addicted pathways, identifying genes that have a synthetic lethal relationship with the activated pathway may allow enhanced cell killing and decreased resistance by targeting those genes or their proteins. In the case of mutant tumor-suppressor genes, identifying genes that have a synthetic lethal relationship to those mutated pathways may allow targeting by inhibiting proteins required uniquely by those cells for survival or proliferation (Fig. 68-3). This is a much more tractable approach than attempting to repair normal function of the mutant suppressor gene itself. Examples of synthetic lethality with potential clinical impact have been identified. For instance, cells with mutations in the *BRCA1* or *BRCA2* tumor-suppressor genes (e.g., a subset of breast and ovarian cancers) are unable to repair DNA damage by homologous recombination. Poly ADP ribose, polymerase (PARP) are a family of proteins important for single-strand break (SSB) DNA repair. PARP inhibition results in selective killing of cancer cells which have lost *BRCA1* or *BRCA2* function. Trials have shown effectiveness of PARP inhibition in patients with BRCA mutant ovarian and breast cancers. Both olaparib (ovarian, breast) and rucoparib (ovarian) have been approved for this indication and others are in trials. The concept of synthetic lethality provides a framework for genetic screens to identify other synthetic lethal combinations involving known tumor-suppressor genes, and development of novel therapeutic agents to target dependent pathways. Other unique aspects of malignant tumors, including those outlined elsewhere in the chapter, may also be vulnerable to synthetic lethal interactions.

EPIGENETIC INFLUENCES ON CANCER GENE TRANSCRIPTION

Chromatin structure regulates the hierarchical order of sequential gene transcription that governs differentiation and tissue homeostasis. Disruption of chromatin remodeling (the process of modifying chromatin structure to control exposure of specific genes to transcriptional proteins, thereby controlling the expression of those genes) leads to aberrant gene expression that can significantly alter the biology of cells including inducing proliferation or migration of cells. *Epigenetics* is defined as changes that alter the pattern of gene expression that persist across at least one cell division, but are not caused by changes in the DNA code.

Epigenetic changes include alterations of chromatin structure mediated by methylation of cytosine residues of DNA (primarily in context of CpG dinucleotides in somatic cells), modification of histones by altering acetylation or methylation, or changes in higher-order chromosome structure **(Fig. 68-4)**. Appropriate control of DNA methylation is essential for normal cell function and development and both methylation and hypomethylation of histones occurs in cancers. Hypermethylation of DNA promoter regions is a common mechanism by which tumor-suppressor loci are epigenetically silenced in cancer cells. Thus one allele of a tumor suppressor gene may be inactivated by mutation or deletion (as occurs in loss of heterozygosity), while expression of the other allele is epigenetically silenced, usually by methylation leading to loss of gene function. Aberrant hypomethylation is also frequently found in a number of cancers consistent with the dysregulated pattern of gene transcription that is a hallmark of cancer cells with some genes being inappropriately turned off while others are inappropriately turned on.

Acetylation of the amino terminus of the core histones H3 and H4 induces an open chromatin conformation that promotes transcription initiation. Histone acetylases are components of coactivator complexes recruited to promoter/enhancer regions by sequence-specific transcription factors during the activation of genes (Fig. 68-4). Histone deacetylases (HDACs; multiple HDACs are encoded in the human genome) are recruited to genes by transcriptional repressors and prevent the initiation of gene transcription. Methylated cytosine residues in promoter regions become associated with methyl cytosine–binding proteins that recruit protein complexes with HDAC activity. The balance between permissive and inhibitory chromatin structure is therefore largely

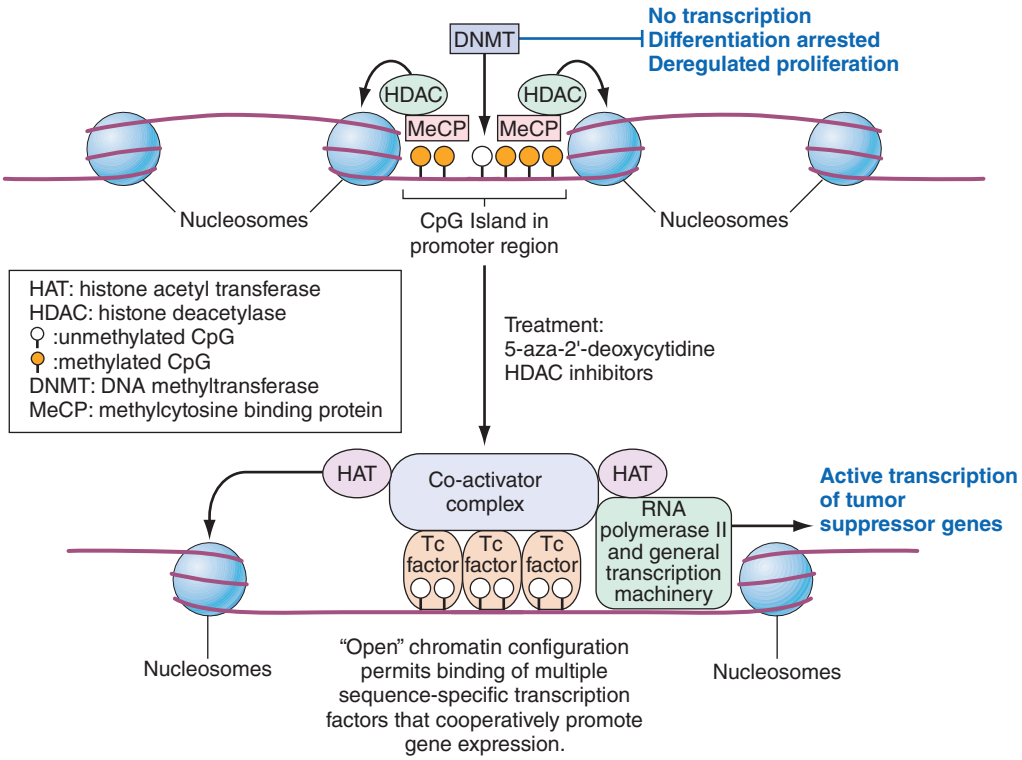

FIGURE 68-4 Epigenetic regulation of gene expression in cancer cells. Tumor-suppressor genes are often epigenetically silenced in cancer cells. In the upper portion, a CpG island within the promoter and enhancer regions of the gene has been methylated, resulting in the recruitment of methyl-cytosine binding proteins (MeCP) and complexes with histone deacetylase (HDAC) activity. Chromatin is in a condensed, nonpermissive conformation that inhibits transcription. Clinical trials are under way utilizing the combination of demethylating agents such as 5-aza-2′-deoxycytidine plus HDAC inhibitors, which together confer an open, permissive chromatin structure (*lower portion*). Transcription factors bind to specific DNA sequences in promoter regions and, through protein-protein interactions, recruit coactivator complexes containing histone acetyl transferase (HAT) activity. This enhances transcription initiation by RNA polymerase II and associated general transcription factors. The expression of the tumor-suppressor gene commences, with phenotypic changes that may include growth arrest, differentiation, or apoptosis.

determined by the activity of transcription factors in modulating the "histone code" and the methylation status of the genetic regulatory elements of genes.

The pattern of gene transcription is aberrant in all human cancers, and in many cases, epigenetic events are responsible. Epigenetic events play a critical role in carcinogenesis (e.g., long-lasting changes in methylation induced by smoking) and are found in pre-malignant lesions. Unlike genetic events that alter DNA primary structure (e.g., deletions), epigenetic changes are potentially reversible and appear amenable to therapeutic intervention. In certain human cancers, including a subset of pancreatic cancers and multiple myeloma, the $p16^{Ink4a}$ promoter is inactivated by methylation, thus permitting the unchecked activity of CDK4/cyclin D and rendering pRb nonfunctional. In sporadic forms of renal, breast, and colon cancer, the von Hippel–Lindau (*VHL*), breast cancer 1 (*BRCA1*), and serine/threonine kinase 11 (*STK11*) genes, respectively, can be epigenetically silenced. Other targeted genes include the $p15^{Ink4b}$ CDK inhibitor, glutathione-S-transferase (which detoxifies reactive oxygen species [ROS]), and the E-cadherin molecule (important for junction formation between epithelial cells). Epigenetic silencing can affect genes involved in DNA repair, thus predisposing to further genetic damage. Examples include MLH1 (mut L homologue in sporadic colon cancers that have microsatellite instability) and MSH2 in a subset of hereditary non-polyposis colon cancer patients who have a mutation in the 3′ end of epithelial cell adhesion molecule (EPCAM). These are critical genes involved in repair of mismatched bases that occur during DNA synthesis and their silencing can lead to mutations in the DNA.

Human leukemias often have chromosomal translocations that code for novel fusion proteins with activities that alter chromatin structure by interacting with HDACs or histone acetyl transferases (HATs). For example, the promyelocytic leukemia–retinoic acid receptorα (PML-RARα) fusion protein, generated by the t(15;17) translocation observed in most cases of acute promyelocytic leukemia (APL), binds to promoters containing retinoic acid response elements and recruits HDACs to these promoters, effectively inhibiting gene expression. This arrests differentiation at the promyelocyte stage and promotes tumor cell proliferation and survival. Treatment with pharmacologic doses of all-*trans* retinoic acid (ATRA), the ligand for RARα, results in the release of HDAC activity and the recruitment of coactivators, which overcome the differentiation block. This induced differentiation of APL cells has improved treatment of these patients but also has led to a novel treatment toxicity when newly differentiated tumor cells infiltrate the lungs. ATRA represents a treatment paradigm for the reversal of epigenetic changes in cancer. Other leukemia-associated fusion proteins, such as Tel-acute myeloid leukemia (AML1), AML1-eight-twenty-one (ETO), and the MLL fusion proteins seen in AML and acute lymphocytic leukemia, also lead to repression through the HDAC complex. Therefore, efforts are ongoing to determine the structural basis for interactions between translocation fusion proteins and chromatin-remodeling proteins and to use this information to rationally design small molecules that will disrupt specific protein-protein associations, although this has proven to be technically difficult. Several drugs that block the enzymatic activity of HDACs are approved for cancer treatment and others are being tested. HDAC inhibitors have demonstrated sufficient antitumor activity against cutaneous T-cell lymphoma (vorinostat, romidepsin), peripheral T-cell lymphoma (romidepsin, belinostat), and multiple myeloma (panobinostat) to be approved by the FDA.

HDAC inhibitors (HDACi) have also demonstrated antitumor activity in clinical studies against some solid tumors and additional studies are ongoing. HDACi may target cancer cells via a number of mechanisms including both epigenetic modulation via histone acetylation as well as effects on other proteins which are acetylated. Some of HDACi's pleiotropic effects include: enhancement of apoptosis by upregulation of a number of proteins that enhance apoptosis including death receptors (DR4/5, FAS, and their ligands) and downregulation of proteins that inhibit apoptosis (e.g., X-linked inhibitor of apoptosis (XIAP); upregulation of proteins that inhibit cell cycle progression (e.g., p21Cip1/Waf1); inhibition of DNA repair and generation of ROS leading to increased DNA damage; and disruption of the chaperone protein HSP90.

Efforts are also under way to modulate other epigenetic processes such as reversing the hypermethylation of CpG islands that characterizes many malignancies. Drugs that induce DNA demethylation, such as 5-aza-2-deoxycytidine, can lead to reexpression of silenced genes in cancer cells with restoration of function, and 5-aza-2-deoxycytidine is approved for use in myelodysplastic syndrome (MDS). However, 5-aza-2-deoxycytidine has limited aqueous solubility and is myelosuppressive limiting its usefulness. Other inhibitors of DNA methyltransferases are in development. In ongoing clinical trials, inhibitors of DNA methylation are being combined with HDAC inhibitors, with the idea that reversing coexisting epigenetic changes will reverse the deregulated patterns of gene transcription in cancer cells. Epigenetic gene regulation can also occur via microRNAs or long non-coding RNAs (lncRNA). MicroRNAs are short (average 22 nucleotides in length) RNA molecules that silence gene expression after transcription by binding and inhibiting the translation or promoting the degradation of mRNA transcripts. It is estimated that >1000 microRNAs are encoded in the human genome. Each tissue has a distinctive repertoire of microRNA expression and this pattern is altered in specific ways in cancers. Specific correlations between microRNA expression and tumor biology and clinical behavior are just now emerging. Therapies targeting microRNAs are not currently at hand but represent an ongoing area of treatment development. LncRNAs are longer than 200 nucleotides and comprise the largest group of noncoding RNAs. Some of them have been shown to play important roles in gene regulation. The potential for altering these RNAs for therapeutic benefit is an area of active investigation, although much more needs to be learned before this will be feasible.

APOPTOSIS AND OTHER MECHANISMS OF CELL DEATH

Tissue homeostasis requires a balance between the death of aged, terminally differentiated cells or severely damaged cells and their renewal by proliferation of committed progenitors. Genetic damage to growth-regulating genes of stem cells could lead to catastrophic results for the host as a whole. Thus, genetic events causing activation of oncogenes or loss of tumor suppressors, which would be predicted to lead to unregulated cell proliferation unless corrected, usually activate signal transduction pathways that block aberrant cell proliferation. These pathways can lead to a form of programmed cell death (*apoptosis*) or irreversible growth arrest (*senescence*). Much as a panoply of intra- and extracellular signals impinge upon the core cell cycle machinery to regulate cell division, so too these signals are transmitted to a core enzymatic machinery that regulates cell death and survival.

Apoptosis is a tightly regulated process induced by two main pathways **(Fig. 68-5)**. The extrinsic pathway of apoptosis is activated by cross-linking members of the tumor necrosis factor (TNF) receptor superfamily, such as CD95 (Fas) and death receptors DR4 and DR5, by their ligands, Fas ligand or TRAIL (TNF-related apoptosis-inducing ligand), respectively. This induces the association of FADD (Fas-associated death domain) and procaspase-8 to death domain motifs of the receptors. Caspase-8 is activated and then cleaves and activates effector caspases-3 and -7, which then target cellular constituents (including caspase-activated DNAse, cytoskeletal proteins, and a number of regulatory proteins), inducing the morphologic appearance characteristic of apoptosis, which pathologists term "karyorrhexis." The intrinsic pathway of apoptosis is initiated by the release of cytochrome *c* and SMAC (second mitochondrial activator of caspases) from the mitochondrial intermembrane space in response to a variety of noxious stimuli, including DNA damage, loss of adherence to the extracellular matrix (ECM), oncogene-induced proliferation, and growth factor deprivation. Upon release into the cytoplasm, cytochrome *c* associates with dATP, procaspase-9, and the adaptor protein APAF-1, leading to the sequential activation of caspase-9 and effector caspases. SMAC binds to and blocks the function of inhibitor of apoptosis proteins (IAP), negative regulators of caspase activation.

The release of apoptosis-inducing proteins from the mitochondria is regulated by pro- and antiapoptotic members of the Bcl-2 family. Antiapoptotic members (e.g., Bcl-2, Bcl-XL, and Mcl-1) associate with

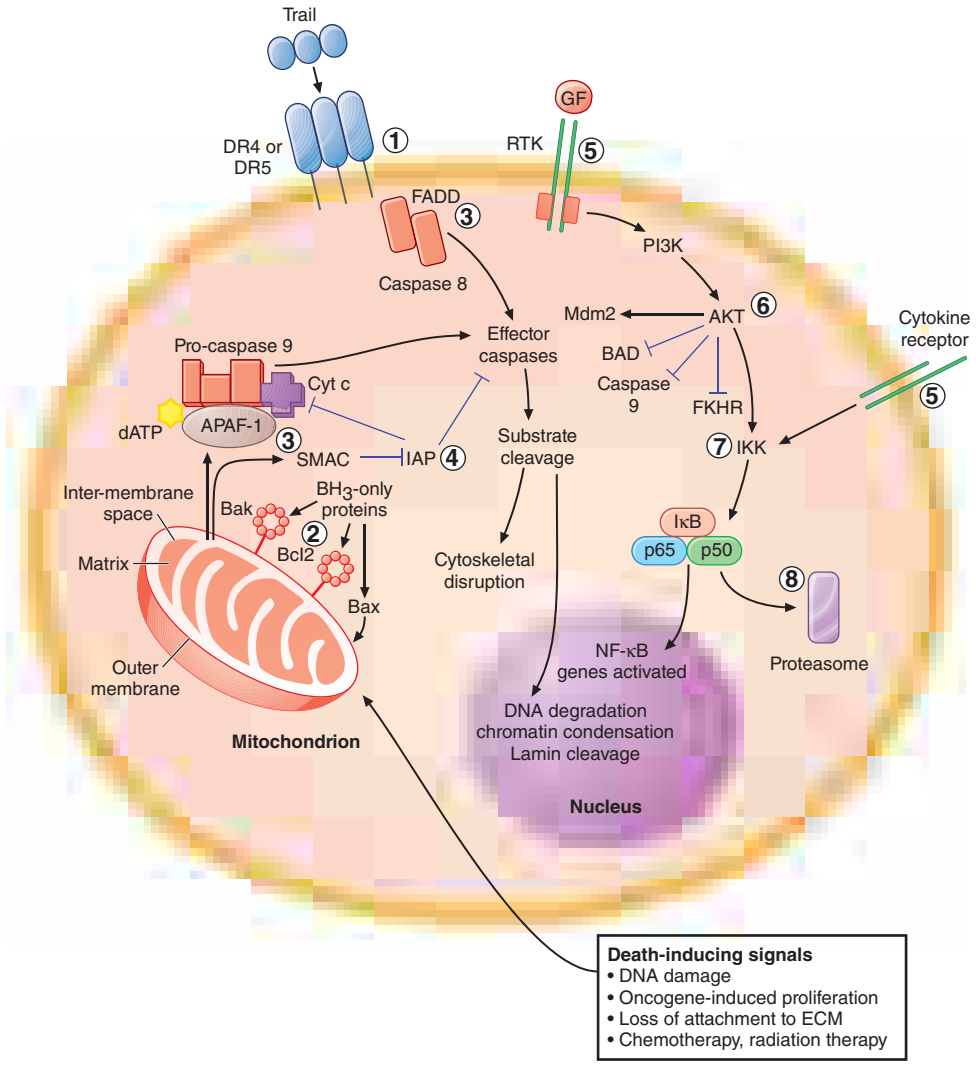

FIGURE 68-5 Therapeutic strategies to overcome aberrant survival pathways in cancer cells. *1.* The extrinsic pathway of apoptosis can be selectively induced in cancer cells by TRAIL (the ligand for death receptors 4 and 5) or by agonistic monoclonal antibodies. *2.* Inhibition of antiapoptotic Bcl-2 family members with antisense oligonucleotides or inhibitors of the BH_3-binding pocket will promote formation of Bak- or Bax-induced pores in the mitochondrial outer membrane. *3.* Epigenetic silencing of APAF-1, caspase-8, and other proteins can be overcome using demethylating agents and inhibitors of histone deacetylases. *4.* Inhibitor of apoptosis proteins (IAP) blocks activation of caspases; small-molecule inhibitors of IAP function (mimicking SMAC action) should lower the threshold for apoptosis. *5.* Signal transduction pathways originating with activation of receptor tyrosine kinase receptors (RTKs) or cytokine receptors promote survival of cancer cells by a number of mechanisms. Inhibiting receptor function with monoclonal antibodies, such as trastuzumab or cetuximab, or inhibiting kinase activity with small-molecule inhibitors can block the pathway. *6.* The Akt kinase phosphorylates many regulators of apoptosis to promote cell survival; inhibitors of Akt may render tumor cells more sensitive to apoptosis-inducing signals; however, the possibility of toxicity to normal cells may limit the therapeutic value of these agents. *7* and *8.* Activation of the transcription factor NF-κB (composed of p65 and p50 subunits) occurs when its inhibitor, IκB, is phosphorylated by IκB-kinase (IKK), with subsequent degradation of IκB by the proteasome. Inhibition of IKK activity should selectively block the activation of NF-κB target genes, many of which promote cell survival. Inhibitors of proteasome function are FDA-approved and may work in part by preventing destruction of IκB, thus blocking NF-κB nuclear localization. NF-κB is unlikely to be the only target for proteasome inhibitors.

the mitochondrial outer membrane via their carboxyl termini, exposing to the cytoplasm a hydrophobic binding pocket composed of Bcl-2 homology (BH) domains 1, 2, and 3 that is crucial for their activity. Perturbations of normal physiologic processes in specific cellular compartments lead to the activation of BH3-only proapoptotic family members (such as Bad, Bim, Bid, Puma, Noxa, and others) that can alter the conformation of the outer-membrane proteins Bax and Bak, which then oligomerize to form pores in the mitochondrial outer membrane resulting in cytochrome *c* release. If proteins comprised only by BH3 domains are sequestered by Bcl-2, Bcl-XL, or Mcl-1, pores do not form and apoptosis-inducing proteins are not released from the mitochondria. The ratio of levels of antiapoptotic Bcl-2 family members and the levels of proapoptotic BH3-only proteins at the mitochondrial membrane determines the activation state of the intrinsic pathway. The mitochondrion must therefore be recognized not only as an organelle with vital roles in intermediary metabolism and oxidative phosphorylation but also as a central regulatory structure of the apoptotic process.

The evolution of tumor cells to a more malignant phenotype requires the acquisition of genetic changes that subvert apoptosis pathways and promote cancer cell survival and resistance to anticancer therapies. However, cancer cells may be more vulnerable than normal cells to therapeutic interventions that target the apoptosis pathways that cancer cells depend upon. For instance, overexpression of Bcl-2 as a result of the t(14;18) translocation contributes to follicular lymphoma and it is highly expressed in many lymphoid malignancies including chronic lymphocytic leukemia (CLL). Upregulation of Bcl-2 expression is also observed in other cancers including prostate, breast, and lung cancers and melanoma. Targeting of antiapoptotic Bcl-2 family members has been accomplished by the identification of several low-molecular-weight compounds that bind to the hydrophobic pockets of either Bcl-2 or Bcl-XL and block their ability to associate with death-inducing BH3-only proteins. These compounds inhibit the antiapoptotic activities of Bcl-2 and Bcl-XL at nanomolar concentrations. An oral BH3 mimetic inhibitor of BCL-2, venetoclax, is approved for use in patients with refractory CLL with 17p deletion.

Preclinical studies targeting death receptors DR4 and -5 have demonstrated that recombinant, soluble, human TRAIL or humanized monoclonal antibodies with agonist activity against DR4 or -5 can induce apoptosis of tumor cells while sparing normal cells. The mechanisms for this selectivity may include expression of decoy receptors or elevated levels of intracellular inhibitors (such as FLIP, which competes with caspase-8 for FADD) by normal cells but not tumor cells. Synergy has been shown between TRAIL-induced apoptosis and chemotherapeutic agents in some preclinical studies. However, clinical studies have not yet shown significant activity of approaches targeting the TRAIL pathway.

Many of the signal transduction pathways perturbed in cancer promote tumor cell survival (Fig. 68-5). These include activation of the PI3K/Akt pathway, increased levels of the NF-κB transcription factor, and epigenetic silencing of genes such as *APAF-1(apoptosis protease activating factor-1 involved in activating caspase-9 and essential for apoptosis)* and *caspase-8*. Each of these pathways is a target for therapeutic agents that, in addition to affecting cancer cell proliferation or gene expression, may render cancer cells more susceptible to apoptosis, thus promoting synergy when combined with other chemotherapeutic agents.

Some tumor cells resist drug-induced apoptosis indirectly by eliminating the noxious stimulus-inducing apoptosis through expression of one or more members of the ABC (ATP-binding casette proteins) family of ATP-dependent efflux pumps that mediate the multidrug-resistance (MDR) phenotype. The prototype member of this family, P-glycoprotein (PGP), spans the plasma membrane 12 times and has two ATP-binding sites. Hydrophobic drugs (e.g., anthracyclines and vinca alkaloids) are recognized by PGP as they enter the cell and are pumped out. Numerous clinical studies have failed to demonstrate that drug resistance can be overcome using inhibitors of PGP. However, ABC transporters have different substrate specificities, and inhibition of a single family member may not be sufficient to overcome the MDR phenotype. Efforts to reverse PGP-mediated drug resistance continue.

Cells, including cancer cells, can also undergo other mechanisms of cell death including *autophagy* (degradation of proteins and organelles by lysosomal proteases) and *necrosis* (digestion of cellular components and rupturing of the cell membrane). Necrosis usually occurs in response to external forces resulting in release of cellular components, which leads to inflammation and damage to surrounding tissues. Although necrosis was thought to be unprogrammed, evidence now suggests that at least some aspects may also be programmed. The exact role of necrosis in cancer cell death in various settings is still being determined. In addition to its role in cell death, autophagy can also serve as a homeostatic mechanism to promote survival for the cell by recycling cellular components to provide necessary energy. The mechanisms that control the balance between enhancing survival versus leading to cell death are still not fully understood. Autophagy appears to play conflicting roles in the development and survival of cancer. Early in the carcinogenic process it can act as a tumor suppressor by preventing the cell from accumulating abnormal proteins and organelles. However, in established tumors, it may serve as a mechanism of survival for cancer cells when they are stressed by damage such as from chemotherapy. Preclinical studies have indicated that inhibition of this process can enhance the sensitivity of cancer cells to chemotherapy and ongoing trials are evaluating inhibitors of autophagy in combination with chemotherapy. Better understanding of the factors that control the survival-promoting versus death-inducing aspects of autophagy is required in order to know how to best manipulate it for therapeutic benefit.

METASTASIS

The metastatic process accounts for the vast majority of deaths from solid tumors and therefore an understanding of this process is critical for improvements in survival from cancer. The biology of metastasis is complex and requires multiple steps. The initial step involves cell migration and invasion through the ECM. The three major features of tissue invasion are cell adhesion to the basement membrane, local proteolysis of the membrane, and movement of the cell through the rent in the membrane and the ECM. Cells that lose contact with the ECM normally undergo programmed cell death (anoikis-apoptosis induced by the loss of contact) and this process has to be suppressed in cells that metastasize. Another process important for many, but not necessarily all, metastasizing epithelial cancer cells is epithelial-mesenchymal transition (EMT). This is a process by which cells lose their epithelial properties and gain mesenchymal properties. This normally occurs during the developmental process in embryos, allowing cells to migrate to their appropriate destinations in the embryo. It also occurs in wound healing, tissue regeneration, and fibrotic reactions, but in all of these processes, cells stop proliferating when the process is complete. Malignant cells that metastasize often undergo EMT as an important step in that process but retain the capacity for unregulated proliferation. However, there is evidence that not all metastasizing cancer cells require EMT, and the exact role of EMT in different metastasizing cancer cells continues to be elucidated. Malignant cells that gain access to the circulation must then repeat those steps at a remote site, find a hospitable niche in a foreign tissue, avoid detection and elimination by host defenses including the immune system, and induce the growth of new blood vessels. Some metastatic cells occur as oligoclonal clusters which appear to be more potent in establishing metastasis than single cells, perhaps through differential and cooperative effects in evading host defenses. The rate-limiting step for metastasis is the ability for tumor cells to survive and expand in the novel microenvironment of the metastatic site, and multiple host-tumor interactions determine the ultimate outcome **(Fig. 68-6)**. Few drugs have been developed to attempt to directly target the process of metastasis, in part because the specifics of the critical steps in the process that would be potentially good targets for drugs are still being identified. However, a number of potential targets are known. HER2 can enhance the metastatic potential of breast cancer cells and as discussed above, the monoclonal antibody trastuzumab which targets HER2, improves survival in the adjuvant setting for HER2+ breast cancer patients. A number of other potential targets that increase metastatic potential of cells in preclinical studies include: HIF-1 and 2, transcription factors induced by hypoxia within tumors; growth factors (e.g., cMET and VEGFR); oncogenes (e.g., SRC); adhesion molecules (e.g., focal adhesion kinase, FAK); ECM proteins (e.g., matrix metaloproteinases 1 and 2); and inflammatory molecules (e.g., COX-2).

The metastatic phenotype is likely restricted to a small fraction of tumor cells (Fig. 68-6). A number of genetic and epigenetic changes are required for tumor cells to be able to metastasize, including activation of metastatic-promoting genes and inhibition of genes that suppress the metastatic ability. Given the role of microRNAs in controlling gene expression (see epigenetic section) including those critical to the metastatic process, efforts are under way to modulate these to try to inhibit metastasis. Cells with metastatic capability frequently express chemokine receptors that are likely important in the metastatic process. A number of candidate metastasis-suppressor genes have been identified, including genes coding for proteins that enhance apoptosis, suppress cell division, are involved in the interactions of cells with each other or the ECM, or suppress cell migration. The loss of function of these genes enhances metastasis. Gene expression profiling is being used to study the metastatic process and other properties of tumor cells that may predict susceptibilities.

An example of the ability of malignant cells to survive and grow in a novel microenvironment is bone metastases. Bone metastases can be extremely painful, cause fractures of weight-bearing bones, can lead to hypercalcemia, and are a major cause of morbidity for cancer patients. Osteoclasts and their monocyte-derived precursors express the surface receptor RANK (receptor activator of NF-κB), which is required for terminal differentiation and activation of osteoclasts. Osteoblasts and other stromal cells express RANK ligand (RANKL), as both a membrane-bound and soluble cytokine. Osteoprotegerin (OPG), a soluble receptor for RANKL produced by stromal cells, acts as a decoy receptor to inhibit RANK activation. The relative balance of RANKL and OPG determines the activation state of RANK on osteoclasts. Many tumors increase osteoclast activity by secretion of substances such as parathyroid hormone (PTH), PTH-related peptide, interleukin (IL)-1, or Mip1 that perturb the homeostatic balance of bone remodeling by

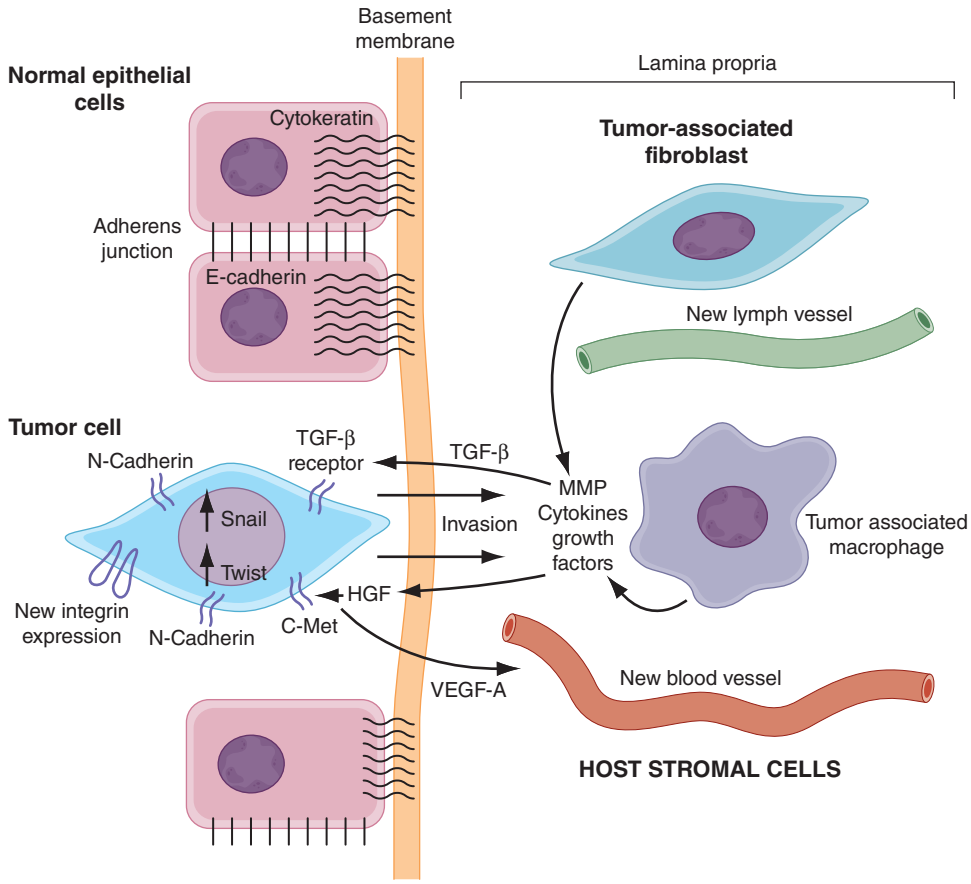

FIGURE 68-6 Oncogene signaling pathways are activated during tumor progression and promote metastatic potential. This figure shows a cancer cell that has undergone epithelial to mesenchymal transition (EMT) under the influence of several environmental signals. Critical components include activated transforming growth factor beta (TGF-β) and the hepatocyte growth factor (HGF)/c-Met pathways, as well as changes in the expression of adhesion molecules that mediate cell-cell and cell–extracellular matrix interactions. Important changes in gene expression are mediated by the Snail and Twist family of transcriptional repressors (whose expression is induced by the oncogenic pathways), leading to reduced expression of E-cadherin, a key component of adherens junctions between epithelial cells. This, in conjunction with upregulation of N-cadherin, a change in the pattern of expression of integrins (which mediate cell–extracellular matrix associations that are important for cell motility), and a switch in intermediate filament expression from cytokeratin to vimentin, results in the phenotypic change from adherent highly organized epithelial cells to motile and invasive cells with a fibroblast or mesenchymal morphology. EMT is thought to be an important step leading to metastasis in some human cancers. Host stromal cells, including tumor-associated fibroblasts and macrophages, play an important role in modulating tumor cell behavior through secretion of growth factors and proangiogenic cytokines, and matrix metalloproteinases that degrade the basement membrane. VEGF-A, -C, and -D are produced by tumor cells and stromal cells in response to hypoxemia or oncogenic signals, and induce production of new blood vessels and lymphatic channels through which tumor cells metastasize to lymph nodes or tissues.

increasing RANK signaling. One example is multiple myeloma, where tumor cell–stromal cell interactions activate osteoclasts and inhibit osteoblasts, leading to the development of multiple lytic bone lesions. Inhibition of RANK ligand by an antibody (denosumab) can prevent further bone destruction. Bisphosphonates are also effective inhibitors of osteoclast function that are used in the treatment of cancer patients with bone metastases.

CANCER STEM CELLS

Normal tissues have stem cells capable of self-renewal and repairing damaged tissue whereas the majority of cells in normal tissues do not have this capacity. Similarly, only a small proportion of the cells within a tumor are capable of initiating colonies in vitro or forming tumors at high efficiency when injected into immunocompromised NOD/SCID mice. For example, acute and chronic myeloid leukemias (AML and CML) have a small population of cells (estimated to be <1%) that have properties of stem cells, such as unlimited self-renewal and the capacity to cause leukemia when serially transplanted in mice. These cells have an undifferentiated phenotype (Thy1–CD34+CD38– and do not express other differentiation markers) and resemble normal stem cells in many ways, but are no longer under homeostatic control (Fig. 68-7). Solid tumors may also contain a population of stem cells. It is not yet known how often cancers may originate within a stem cell population. Cancer stem cells, like their normal counterparts, have unlimited proliferative capacity and paradoxically traverse the cell cycle at a slow rate; cancer growth occurs largely due to expansion of the stem cell pool, the unregulated proliferation of an amplifying population, and failure of apoptosis pathways (Fig. 68-7). Slow cell cycle progression and high levels of expression of antiapoptotic Bcl-2 family members and drug efflux pumps of the MDR family render cancer stem cells less vulnerable to cancer chemotherapy or radiation therapy. Implicit in the cancer stem cell hypothesis is the idea that failure to cure most human cancers is due to the fact that current therapeutic agents do not kill the stem cells. Identification and isolation of cancer stem cells will allow determination of the aberrant signaling pathways that distinguish these cells from normal tissue stem cells. These would serve as potential therapeutic targets. Evidence that cells with stem cell properties can arise from other epithelial cells within the cancer by processes such as epithelial mesenchymal transition also implies that it is essential to treat all of the cancer cells, and not just those with current stem cell-like properties, in order to eliminate the self -renewing cancer cell population. The exact nature of cancer stem cells remains an area of investigation. One of the unanswered questions is the exact origin of cancer stem cells for the different cancers.

PLASTICITY AND RESISTANCE

Cancer cells, and especially stem cells, have the capacity for significant plasticity allowing them to alter multiple aspects of cell biology in response to external factors (e.g., chemotherapy, radiation therapy, inflammation, immune response). In addition, heterogeneity between the different clones of cells within the tumor population and their interactions with each other and the tumor microenvironment provides the

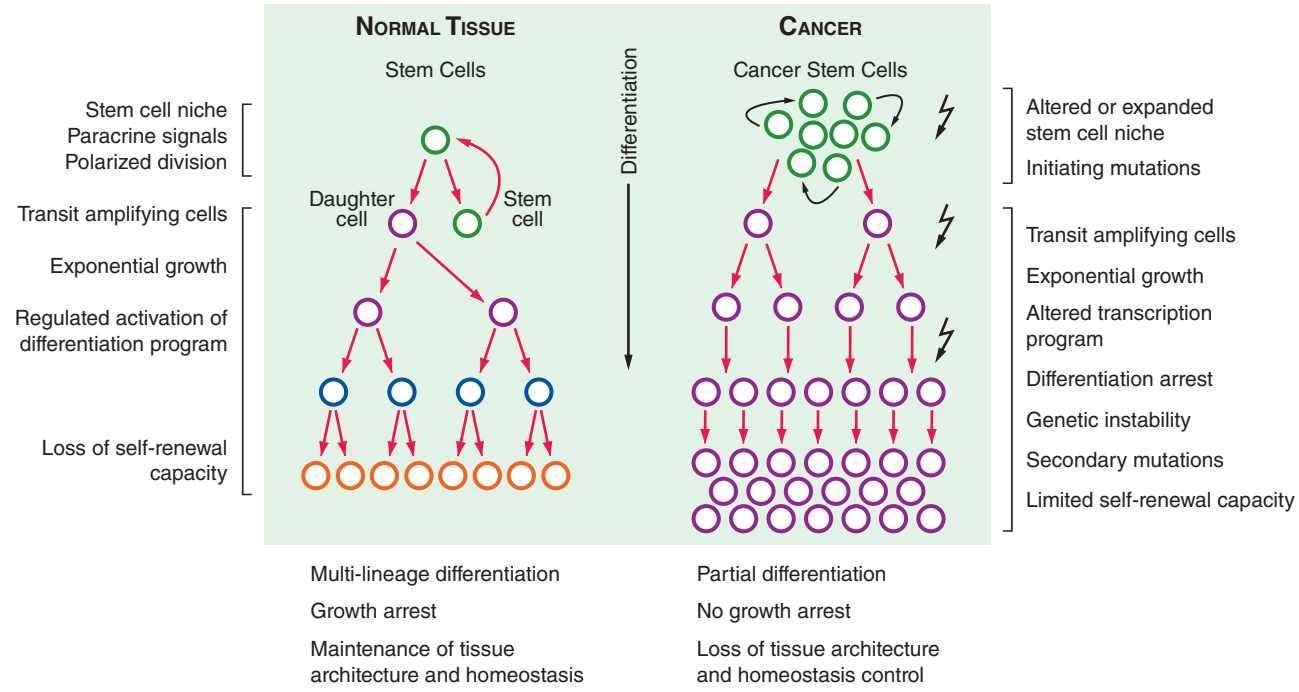

FIGURE 68-7 Cancer stem cells play a critical role in the initiation, progression, and resistance to therapy of malignant neoplasms. In normal tissues (*left*), homeostasis is maintained by asymmetric division of stem cells leading to one progeny cell that will differentiate and one cell that will maintain the stem cell pool. This occurs within highly specific niches unique to each tissue, such as in close apposition to osteoblasts in bone marrow, or at the base of crypts in the colon. Here, paracrine signals from stromal cells, such as sonic hedgehog or Notch-ligands, as well as upregulation of β-catenin and telomerase, help to maintain stem cell features of unlimited self-renewal while preventing differentiation or cell death. This occurs in part through upregulation of the transcriptional repressor Bmi-1 and inhibition of the $p16^{Ink4a}$/Arf and p53 pathways. Daughter cells leave the stem cells niche and enter a proliferative phase (referred to as *transit-amplifying*) for a specified number of cell divisions, during which time a developmental program is activated, eventually giving rise to fully differentiated cells that have lost proliferative potential. Cell renewal equals cell death, and homeostasis is maintained. In this hierarchical system, only stem cells are long-lived. The hypothesis is that cancers harbor stem cells that make up a small fraction (i.e., 0.001–1%) of all cancer cells. These cells share several features with normal stem cells, including an undifferentiated phenotype, unlimited self-renewal potential, a capacity for some degree of differentiation; however, due to initiating mutations (mutations are indicated by lightning bolts), they are no longer regulated by environmental cues. The cancer stem cell pool is expanded, and rapidly proliferating progeny, through additional mutations, may attain stem cell properties, although most of this population is thought to have a limited proliferative capacity. Differentiation programs are dysfunctional due to reprogramming of the pattern of gene transcription by oncogenic signaling pathways. Within the cancer transit-amplifying population, genomic instability generates aneuploidy and clonal heterogeneity as cells attain a fully malignant phenotype with metastatic potential. The cancer stem cell hypothesis has led to the idea that current cancer therapies may be effective at killing the bulk of tumor cells but do not kill tumor stem cells, leading to a regrowth of tumors that is manifested as tumor recurrence or disease progression. Research is in progress to identify unique molecular features of cancer stem cells that can lead to their direct targeting by novel therapeutic agents.

tumor with the capacity for significant plasticity in dealing with both internal and external stresses. Thus, a major problem in cancer therapy is that malignancies have a wide spectrum of mechanisms for both initial and adaptive resistance to treatments. These include inhibiting drug delivery to the cancer cells, blocking drug uptake and retention, increasing drug metabolism, altering levels of target proteins making them less sensitive to drugs, acquiring mutations in target proteins making them no longer sensitive to the drug, modifying metabolism and cell signaling pathways, using alternate signaling pathways, adjusting the cell replication process including mechanisms by which the cell deals with DNA damage, inhibiting apoptosis, and evading the immune system. Thus, most metastatic cancers (except those curable with chemotherapy such as germ cell tumors) eventually become resistant to the therapy being utilized. Overcoming resistance is a major area of research.

CANCER METABOLISM

One of the distinguishing characteristics of cancer cells is that they have altered metabolism as compared with normal cells in supporting survival, their high rates of proliferation, and ability to metastasize. Complicating studies evaluating metabolic differences between normal and malignant cells is that there is heterogeneity in metabolism between different cells within a cancer. Malignant cells must focus a significant fraction of their energy resources into synthesis of proteins and other molecules (building blocks required for the production of new cells) while still maintaining sufficient ATP production to survive and grow. Although normal proliferating cells also have similar needs, there are differences in how cancer cells metabolize glucose and a number of other compounds including the amino acid glutamine as compared to normal cells in part because of genetic and epigenetic changes within cancer cells but also likely due to differences in the environments of cancer and normal cells. Many cancer cells utilize aerobic glycolysis (the Warburg effect) **(Fig. 68-8)** to metabolize glucose leading to increased lactic acid production whereas normal cells utilize oxidative phosphorylation in mitochondria under aerobic conditions, a much more efficient process for generating ATP for energy utilization but one that does not produce the same level of building blocks needed for new cells. One consequence is increased glucose uptake by cancer cells, a fact utilized in fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning to detect tumors. A number of proteins in cancer cells, including cMYC, HIF1, RAS, p53, pRB, and AKT are all involved in modulating glycolytic processes and controlling the Warburg effect. Although these pathways remain difficult to target therapeutically, both the pI3kinase pathway with signaling through mTOR and the AMP-activated kinase (AMPK) pathway that inhibits mTORC1 (a protein complex that includes mTOR) are important in controlling the glycolytic process and thus provide potential targets for inhibiting this process. An inhibitor of MTOR is approved for use against RCC (temsirolimus) and another inhibitor (everolimus) has activity against breast, neuroendocrine, and RCC. Other MTOR inhibitors are in trials and modulators of AMPK are being investigated. The inefficient utilization of glucose by malignant cells also leads to a need for alternative metabolic pathways for other compounds as well, one of which is glutamine. Similar to glucose, this provides both a source for structural molecules as well as energy production. Similarly to glucose, glutamine is also inefficiently utilized by cancer cells. Cancer cells

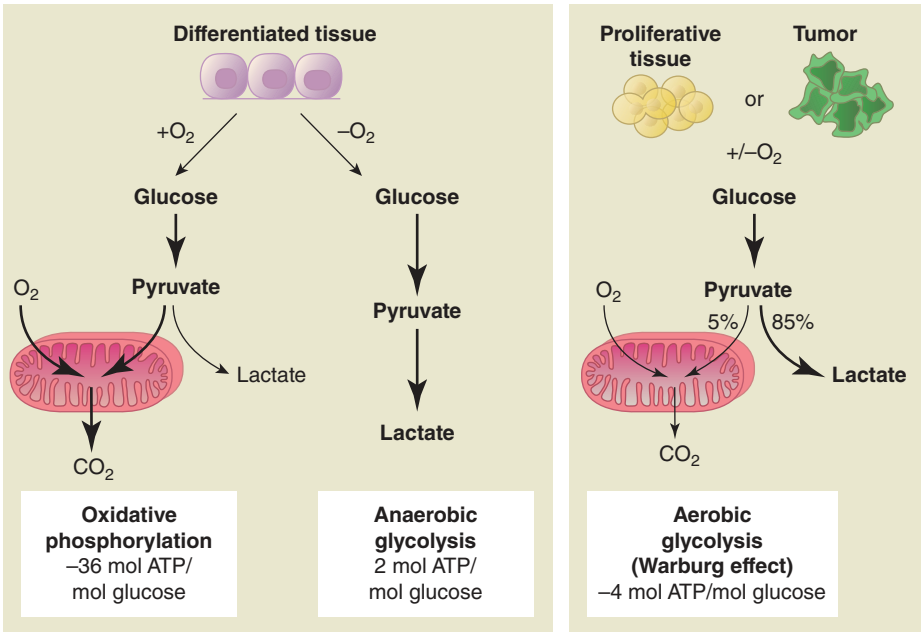

FIGURE 68-8 Warburg vs oxidative phosphorylation. In most normal tissues, the vast majority of cells are differentiated and dedicated to a particular function within the organ in which they reside. The metabolic needs are mainly for energy and not for building blocks for new cells. In these tissues, ATP is generated by oxidative phosphorylation that efficiently generates about 36 molecules of ATP for each molecule of glucose metabolized. By contrast, proliferative tumor tissues, especially in the setting of hypoxia, a typical condition within tumors, use aerobic glycolysis to generate energy for cell survival and generation of building blocks for new cells.

can also take up nutrients released by surrounding cells and tissues increasing the complexity of successfully therapeutically inhibiting metabolism in cancer.

Mutations in genes involved in the metabolic process occur in a number of cancers. Among the most frequently found to date are mutations in isocitrate dehydrogenases 1 and 2 (IDH1 and 2). These have been most commonly seen in gliomas, acute myeloid leukemias (AML), and intra-hepatic cholangiocarcinomas. These mutations lead to the production of an oncometabolite (2-hydroxyglutarate, 2HG) instead of the normal product α-ketoglutarate. Although the exact mechanisms of oncogenesis by 2HG are still being elucidated, α-ketoglutarate is a key cofactor for a number of dioxygenases involved in controlling DNA methylation. 2HG can act as a competitive inhibitor for α-ketoglutarate leading to alterations in methylation status (primarily hypermethylation) of genes (leading to epigenetic changes) that can have profound effects on a number of cellular processes including differentiation. Inhibitors of mutants IDH1 and IDH2 are being developed. To date, they have had some activity against IDH mutant AML but less activity against glioblastomas or cholangiocarcinomas.

Much needs to be learned about the specific differences in metabolism between cancer cells and normal cells; however, even with the currently limited state of knowledge, modulators of metabolism are being tested clinically. The first of these is the anti-diabetic agent metformin, both alone and in combination with chemotherapeutic agents. Metformin inhibits gluconeogenesis and may have direct effects on tumor cells by activating the 5′-adenosine monophosphate-activated kinase (AMPK), a serine/threonine protein kinase which is downstream of the LKB1 tumor suppressor, and thus inhibiting mammalian target of rapamycin complex 1 (mTORC1). This leads to decreased protein synthesis and proliferation. Studies to date have not yet established metformin to have a clear role as an anticancer agent. Additional approaches being evaluated include other modulators of glucose metabolism (e.g., piaglitazone) and inhibiting glutaminase (important for glutamine utilization).

TUMOR MICROENVIRONMENT, ANGIOGENESIS, AND IMMUNE EVASION

Tumors consist not only of malignant cells but also of a complex microenvironment including many other types of cells (including inflammatory cells), ECM, secreted factors (including growth factors), reactive oxygen and nitrogen species, mechanical factors, blood vessels, and lymphatics. This microenvironment is not static but rather is dynamic and continually evolving. Both the complexity and dynamic nature of the microenvironment enhance the difficulty of treating tumors. There are also a number of mechanisms by which the microenvironment can contribute to resistance to anti-cancer therapies.

One of the critical elements of tumor cell proliferation is delivery of oxygen, nutrients, and circulating factors important for growth and survival. The diffusion limit for oxygen in tissues is ~100–200 μm and thus a critical aspect in the growth of tumors is the development of new blood vessels, or angiogenesis. The growth of primary and metastatic tumors to larger than a few millimeters requires the recruitment of blood vessels and vascular endothelial cells (ECs) to support their metabolic requirements. Thus, a critical element in growth of primary tumors and formation of metastatic sites is the *angiogenic switch*: the ability of the tumor to promote the formation of new capillaries from preexisting host vessels. The angiogenic switch is a phase in tumor development when the dynamic balance of pro- and antiangiogenic factors is tipped in favor of vessel formation by the effects of the tumor on its immediate environment. Stimuli for tumor angiogenesis include hypoxemia, inflammation, and genetic lesions in oncogenes or tumor suppressors that alter tumor cell gene expression. Angiogenesis consists of several steps, including the stimulation of ECs by growth factors, degradation of the ECM by proteases, proliferation and migration of ECs into the tumor, and the eventual formation of new capillary tubes.

Tumor blood vessels are not normal; they have chaotic architecture and blood flow. Due to an imbalance of angiogenic regulators such as VEGF and angiopoietins (see below), tumor vessels are tortuous and dilated with an uneven diameter, excessive branching, and shunting. Tumor blood flow is variable, with areas of hypoxemia and acidosis leading to the selection of variants that are resistant to hypoxemia-induced apoptosis (often due to the loss of p53 expression). Tumor vessel walls have numerous openings, widened interendothelial junctions, and discontinuous or absent basement membrane; this contributes to the high vascular permeability of these vessels and, together with lack of functional intratumoral lymphatics, causes increased interstitial pressure within the tumor (which also interferes with the delivery of therapeutics to the tumor; **Figs. 68-9, 68-10, and 68-11**). Tumor blood vessels lack perivascular cells such as pericytes and smooth-muscle cells that normally regulate flow in response to tissue metabolic needs.

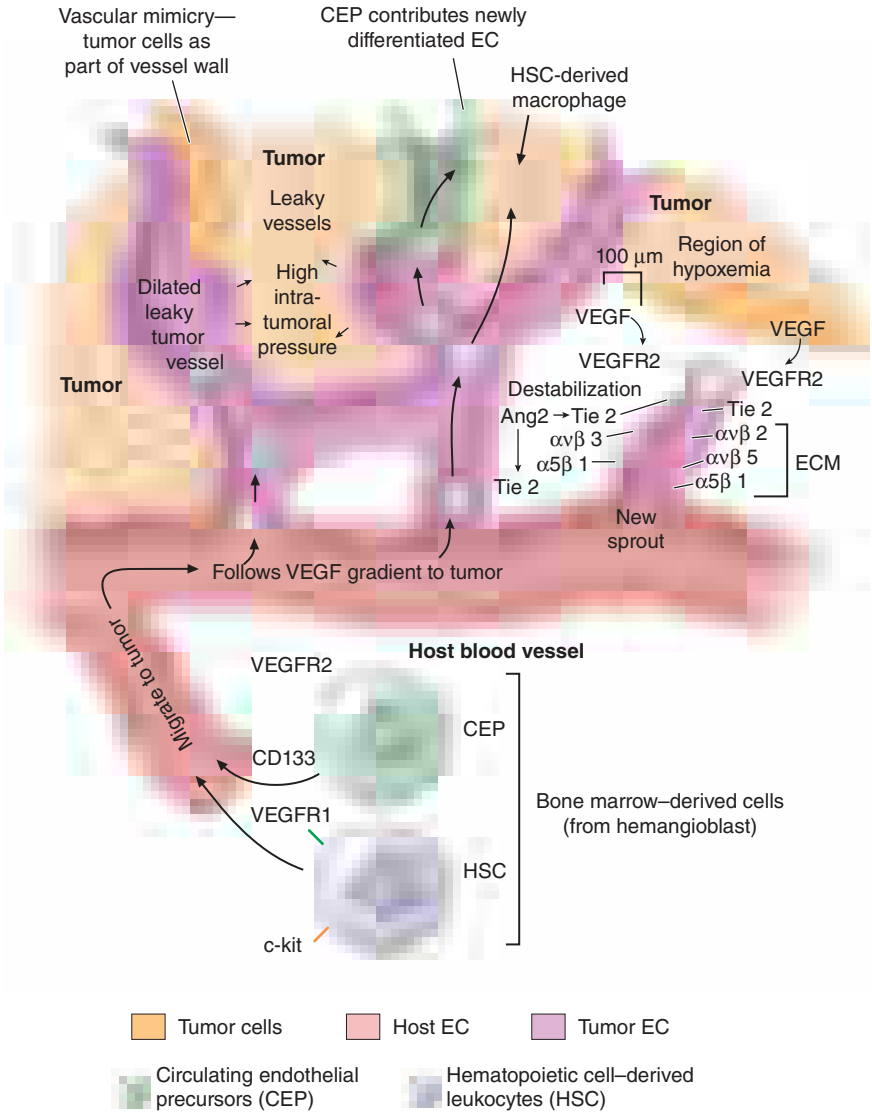

FIGURE 68-9 Tumor angiogenesis is a complex process involving many different cell types that must proliferate, migrate, invade, and differentiate in response to signals from the tumor microenvironment. Endothelial cells (ECs) sprout from host vessels in response to VEGF, bFGF, Ang2, and other proangiogenic stimuli. Sprouting is stimulated by VEGF/VEGFR2, Ang2/Tie-2, and integrin/extracellular matrix (ECM) interactions. Bone marrow–derived circulating endothelial precursors (CEPs) migrate to the tumor in response to VEGF and differentiate into ECs, while hematopoietic stem cells differentiate into leukocytes, including tumor-associated macrophages that secrete angiogenic growth factors and produce MMPs that remodel the ECM and release bound growth factors. Tumor cells themselves may directly form parts of vascular channels within tumors. The pattern of vessel formation is haphazard: vessels are tortuous, dilated, leaky, and branch in random ways. This leads to uneven blood flow within the tumor, with areas of acidosis and hypoxemia (which stimulate release of angiogenic factors) and high intratumoral pressures that inhibit delivery of therapeutic agents.

Unlike normal blood vessels, the vascular lining of tumor vessels is not a homogeneous layer of ECs but often consists of a mosaic of ECs and tumor cells with upregulated genes seen in ECs and vessel formation that can occur in hypoxic conditions because of their plasticity; the concept of cancer cell–derived vascular channels, which may be lined by ECM secreted by the tumor cells, is referred to as *vascular mimicry*. During tumor angiogenesis, ECs are highly proliferative and express a number of plasma membrane proteins that are characteristic of activated endothelium, including growth factor receptors and adhesion molecules such as integrins.

MECHANISMS OF TUMOR VESSEL FORMATION

Tumors use a number of mechanisms to promote vascularization, subverting normal angiogenic processes for this purpose (Fig. 68-9). Primary or metastatic tumor cells sometimes arise in proximity to host blood vessels and grow around these vessels, parasitizing nutrients by co-opting the local blood supply. However, most tumor blood vessels arise by the process of *sprouting*, in which tumors secrete trophic angiogenic molecules, the most potent being VEGFs, that induce the proliferation and migration of host ECs into the tumor. Sprouting in normal and pathogenic angiogenesis is regulated by three families of transmembrane RTKs expressed on ECs and their ligands (VEGFs, angiopoietins, ephrins; Fig. 68-10), which are produced by tumor cells, inflammatory cells, or stromal cells in the tumor microenvironment.

When tumor cells arise in or metastasize to an avascular area, they grow to a size limited by hypoxemia and nutrient deprivation. Hypoxemia, a key regulator of tumor angiogenesis, causes the transcriptional induction of the genes encoding VEGF family members. VEGFs and their receptors are required for embryonic *vasculogenesis* (development of new blood vessels when none pre-exist) and normal (wound healing, corpus luteum formation) and pathologic angiogenesis (tumor angiogenesis, inflammatory conditions such as rheumatoid arthritis). VEGF-A is a heparin-binding glycoprotein with at least four isoforms (splice variants) that regulates blood vessel formation by binding to the RTKs VEGFR1 and VEGFR2, which are expressed on all ECs in addition to a subset of hematopoietic cells (Fig. 68-9). VEGFR2 regulates EC proliferation, migration, and survival, while VEGFR1 may act as an antagonist of R2 in ECs but is probably also important for angioblast differentiation during embryogenesis. Tumor vessels may be more dependent on VEGFR signaling for growth and survival than

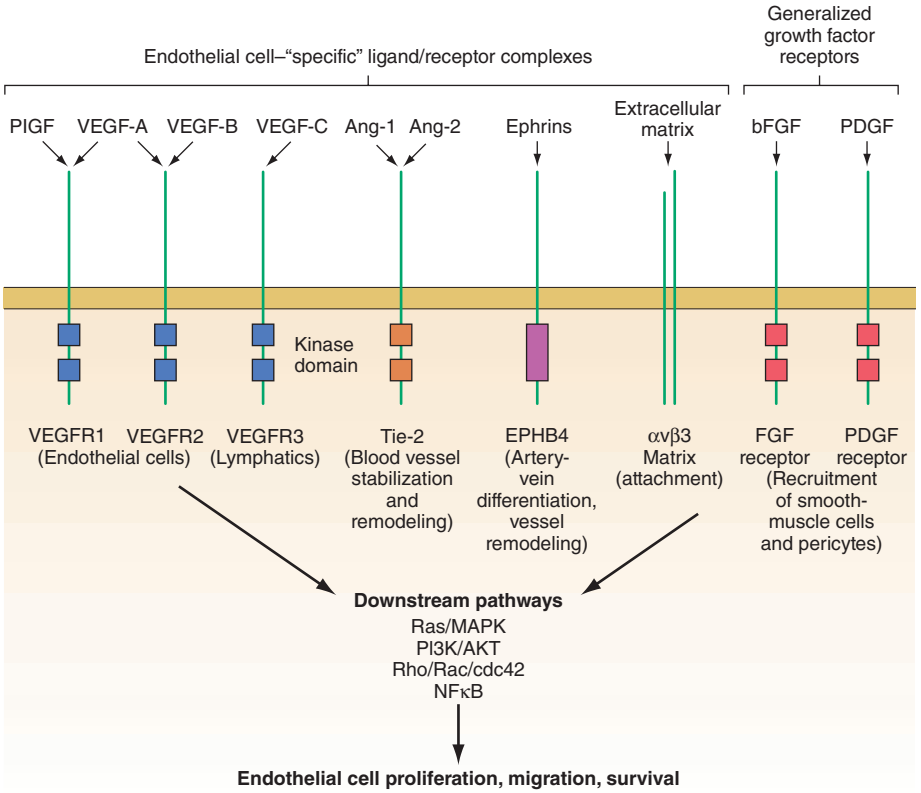

FIGURE 68-10 Critical molecular determinants of endothelial cell biology. Angiogenic endothelium expresses a number of receptors not found on resting endothelium. These include receptor tyrosine kinases (RTKs) and integrins that bind to the extracellular matrix and mediate endothelial cell (EC) adhesion, migration, and invasion. ECs also express RTK (i.e., the fibroblast growth factor [FGF] and platelet-derived growth factor [PDGF] receptors) that are found on many other cell types. Critical functions mediated by activated RTK include proliferation, migration, and enhanced survival of endothelial cells, as well as regulation of the recruitment of perivascular cells and bloodborne circulating endothelial precursors and hematopoietic stem cells to the tumor. Intracellular signaling via EC-specific RTK utilizes molecular pathways that may be targets for future antiangiogenic therapies.

normal ECs. While VEGF signaling is a critical initiator of angiogenesis, this is a complex process regulated by additional signaling pathways (Fig. 68-10). The angiopoietin, Ang1, produced by stromal cells, binds to the EC RTK Tie-2 and promotes the interaction of ECs with the ECM and perivascular cells, such as pericytes and smooth-muscle cells, to form tight, nonleaky vessels. PDGF and basic fibroblast growth factor (bFGF) help to recruit these perivascular cells. Ang1 is required for maintaining the quiescence and stability of mature blood vessels and prevents the vascular permeability normally induced by VEGF and inflammatory cytokines.

For tumor cell–derived VEGF to initiate sprouting from host vessels, the stability conferred by the Ang1/Tie2 pathway must be perturbed; this occurs by the secretion of Ang2 by ECs that are undergoing active remodeling. Ang2 binds to Tie2 and is a competitive inhibitor of Ang1 action: under the influence of Ang2, preexisting blood vessels become more responsive to remodeling signals, with less adherence of ECs to stroma and associated perivascular cells and more responsiveness to VEGF. Therefore, Ang2 is required at early stages of tumor angiogenesis for destabilizing the vasculature by making host ECs more sensitive to angiogenic signals. In the presence of Ang2, there is no stabilization by the Ang1/Tie2 interaction, and tumor blood vessels are leaky, hemorrhagic, and have poor association of ECs with underlying stroma. Sprouting tumor ECs express high levels of the transmembrane protein ephrin-B2 and its receptor, the RTK EPH, whose signaling appears to work with the angiopoietins during vessel remodeling. During embryogenesis, EPH receptors are expressed on the endothelium of primordial venous vessels while the transmembrane ligand ephrin-B2 is expressed by cells of primordial arteries; the reciprocal expression may regulate differentiation and patterning of the vasculature.

A number of ubiquitously expressed host molecules play critical roles in normal and pathologic angiogenesis. Proangiogenic cytokines, chemokines, and growth factors secreted by stromal cells or inflammatory cells make important contributions to neovascularization, including bFGF, transforming growth factor-α (TGF-α), TNF-α, and IL-8. In contrast to normal endothelium, angiogenic endothelium overexpresses specific members of the integrin family of ECM-binding proteins that mediate EC adhesion, migration, and survival. Specifically, expression of integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_5\beta_1$ mediates spreading and migration of ECs and is required for angiogenesis induced by VEGF and bFGF, which in turn can upregulate EC integrin expression. The $\alpha_v\beta_3$ integrin physically associates with VEGFR2 in the plasma membrane and promotes signal transduction from each receptor to promote EC proliferation (via focal adhesion kinase, src, PI3K, and other pathways) and survival (by inhibition of p53 and increasing the Bcl-2/Bax expression ratio). In addition, $\alpha_v\beta_3$ forms cell-surface complexes with matrix metalloproteinases (MMPs), zinc-requiring proteases that cleave ECM proteins, leading to enhanced EC migration and the release of heparin-binding growth factors, including VEGF and bFGF. EC adhesion molecules can be upregulated (i.e., by VEGF, TNF-α) or downregulated (by TGF-β); this, together with chaotic blood flow, explains poor leukocyte-endothelial interactions in tumor blood vessels and may help tumor cells avoid immune surveillance.

Lymphatic vessels also exist within tumors. Development of tumor lymphatics is associated with expression of VEGFR3 and its ligands VEGF-C and VEGF-D. The role of these vessels in tumor cell metastasis to regional lymph nodes remains to be determined. However, VEGF-C levels correlate significantly with metastasis to regional lymph nodes in lung, prostate, and colorectal cancers.

ANTIANGIOGENIC THERAPY

Angiogenesis inhibitors function by targeting the critical molecular pathways involved in EC proliferation, migration, and/or survival, many of which are highly expressed in the activated endothelium in tumors. Inhibition of growth factor and adhesion-dependent signaling pathways can induce EC apoptosis with concomitant inhibition of tumor growth. Different types of tumors can use distinct combinations

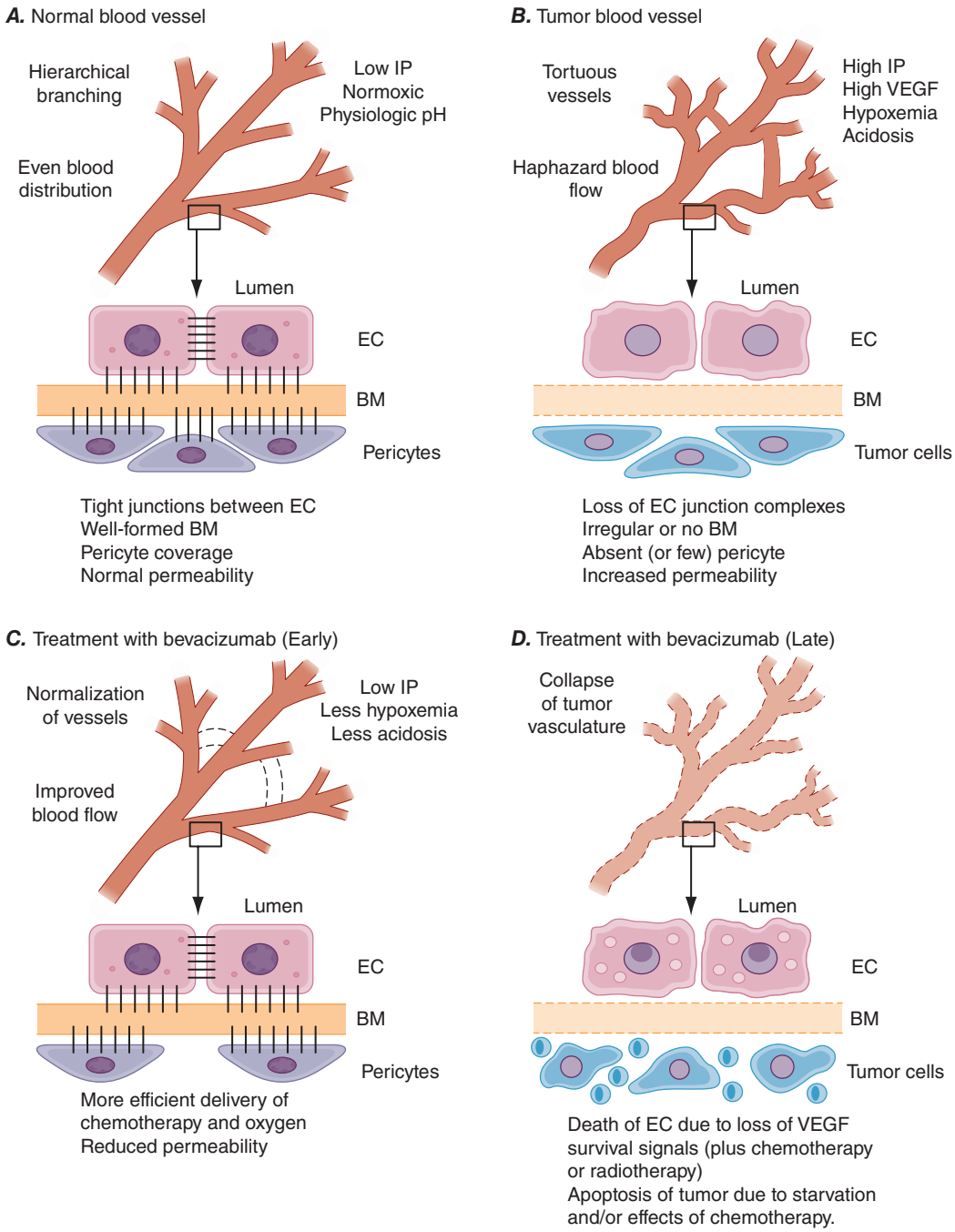

FIGURE 68-11 Normalization of tumor blood vessels due to inhibition of VEGF signaling. ***A.*** Blood vessels in normal tissues exhibit a regular hierarchical branching pattern that delivers blood to tissues in a spatially and temporally efficient manner to meet the metabolic needs of the tissue (top). At the microscopic level, tight junctions are maintained between endothelial cells (ECs), which are adherent to a thick and evenly distributed basement membrane (BM). Pericytes form a surrounding layer that provides trophic signals to the EC and helps maintain proper vessel tone. Vascular permeability is regulated, interstitial fluid pressure is low, and oxygen tension and pH are physiologic. ***B.*** Tumors have abnormal vessels with tortuous branching and dilated, irregular interconnecting branches, causing uneven blood flow with areas of hypoxemia and acidosis. This harsh environment selects genetic events that result in resistant tumor variants, such as the loss of p53. High levels of VEGF (secreted by tumor cells) disrupt gap junction communication, tight junctions, and adherens junctions between EC via src-mediated phosphorylation of proteins such as connexin 43, zonula occludens-1, VE-cadherin, and α/β-catenins. Tumor vessels have thin, irregular BM, and pericytes are sparse or absent. Together, these molecular abnormalities result in a vasculature that is permeable to serum macromolecules, leading to high tumor interstitial pressure, which can prevent the delivery of drugs to the tumor cells. This is made worse by the binding and activation of platelets at sites of exposed BM, with release of stored VEGF and microvessel clot formation, creating more abnormal blood flow and regions of hypoxemia. ***C.*** In experimental systems, treatment with bevacizumab or blocking antibodies to VEGFR2 leads to changes in the tumor vasculature that has been termed *vessel normalization*. During the first week of treatment, abnormal vessels are eliminated or pruned (dotted lines), leaving a more normal branching pattern. ECs partially regain features such as cell-cell junctions, adherence to a more normal BM, and pericyte coverage. These changes lead to a decrease in vascular permeability, reduced interstitial pressure, and a transient increase in blood flow within the tumor. Note that in murine models, this normalization period lasts only for ~5–6 days. ***D.*** After continued anti-VEGF/VEGFR therapy (which is often combined with chemo- or radiotherapy), ECs die, leading to tumor cell death (either due to direct effects of the chemotherapy or lack of blood flow).

of molecular mechanisms to activate the angiogenic switch. Therefore, it is doubtful that a single antiangiogenic strategy will suffice for all human cancers; rather, a number of agents or combinations of agents will be needed, depending on distinct programs of angiogenesis used by different human cancers. Despite this, experimental data indicate that for some tumor types, blockade of a single growth factor (e.g., VEGF) may inhibit tumor-induced vascular growth.

Bevacizumab, an antibody which binds VEGF, potentiates the effects of a number of different types of active chemotherapeutic regimens used to treat a variety of different tumor types including colon, lung,

ovarian, and cervical cancers. It also has activity in combination with interferon against RCCs and alone for glioblastomas. Other protein inhibitors of the VEGF signaling pathway approved for anticancer therapy include ramucirumab (a monoclonal antibody directed against VEGFR2, approved for use against gastric/gastroesophageal, colon and lung cancers) and ziv-aflibercept (a recombinant protein inhibitor of VEGF, approved for colorectal cancer). Hypertension is the most common side effect of inhibitors of VEGF (or its receptors), but can be treated with antihypertensive agents and uncommonly requires discontinuation of therapy. Rare but serious potential risks include arterial thromboembolic events, including stroke and myocardial infarction, hemorrhage, bowel perforation, and inhibition of wound healing.

Several small-molecule inhibitors (SMI) that target VEGF RTK activity but are also inhibitory to other kinases have also been approved to treat certain cancers. Sunitinib (see above and Table 68-2) has activity directed against mutant c-Kit receptors (approved for GIST), but also targets VEGFR and PDGFR, and has antitumor activity against pancreatic neuroendocrine and metastatic renal cell carcinomas (RCC), presumably on the basis of its antiangiogenic activity. Similarly, sorafenib, originally developed as a Raf kinase inhibitor but with potent activity against VEGFR and PDGFR, has activity against RCC, differentiated thyroid and hepatocellular cancers as well as desmoid tumors. A closely related molecule to sorafenib, regorafenib, has activity against colorectal cancer, GIST, and hepatocellular cancer. Other inhibitors of the VEGF pathway approved for the treatment of various cancers include axitinib, pazopanib, lenvatinib, and cabozantinib.

The success in targeting tumor angiogenesis has led to enhanced enthusiasm for the development of drugs that target other aspects of the angiogenic process; some of these therapeutic approaches are outlined in Fig. 68-12. There is also evidence suggesting potential enhanced activity when anti-VEGF agents are used in combination with immunomodulators including immune check point inhibitors. However, it is not yet known whether this will produce a clinically meaningful enhancement of anti-tumor activity.

EVASION OF THE IMMUNE SYSTEM BY CANCERS

There is a complex interaction between tumors and the host from the initiation of the cancer until the establishment of a clinical cancer. Cancers have a number of mechanisms that allow them to evade detection and elimination by the immune system. These include downregulation of cell surface proteins involved in immune recognition (including MHC proteins and tumor-specific antigens), expression of other cell surface proteins that inhibit immune function (including members of the B7 family of proteins such as PD-L1), secretion of proteins and other molecules that are immunosuppressive, recruitment and expansion of immunosuppressive cells such as regulatory T cells, induction of T-cell tolerance, and down regulation of death receptors. Due to the marked heterogeneity of cells within a cancer, a variety of immune suppressive mechanisms are continuously occurring and changing. In addition, the inflammatory effects of some of the immune mediator cells in the tumor microenvironment (especially tissue-associated macrophages and myeloid-derived suppressor cells) can suppress T-cell responses to the tumor as well as stimulate inflammation that can enhance tumor growth. Immunotherapy approaches to treat cancer aimed at activating the immune response against tumors using immunostimulatory molecules such as interferons, IL-2, and monoclonal antibodies have had some successes. A more direct approach to enhance the activity of T cells directed against specific tumors involves isolating T cells from patients and re-engineering the cells to express chimeric antigen receptors (CAR-T cells) that recognize antigens present on the cells of that individual's tumor. The most commonly studied approach to date has been to engineer the cells to express receptors targeting the CD19 antigen on ALL and DLBCL cells. These have been shown to have significant antitumor activity in the treatment of patients with

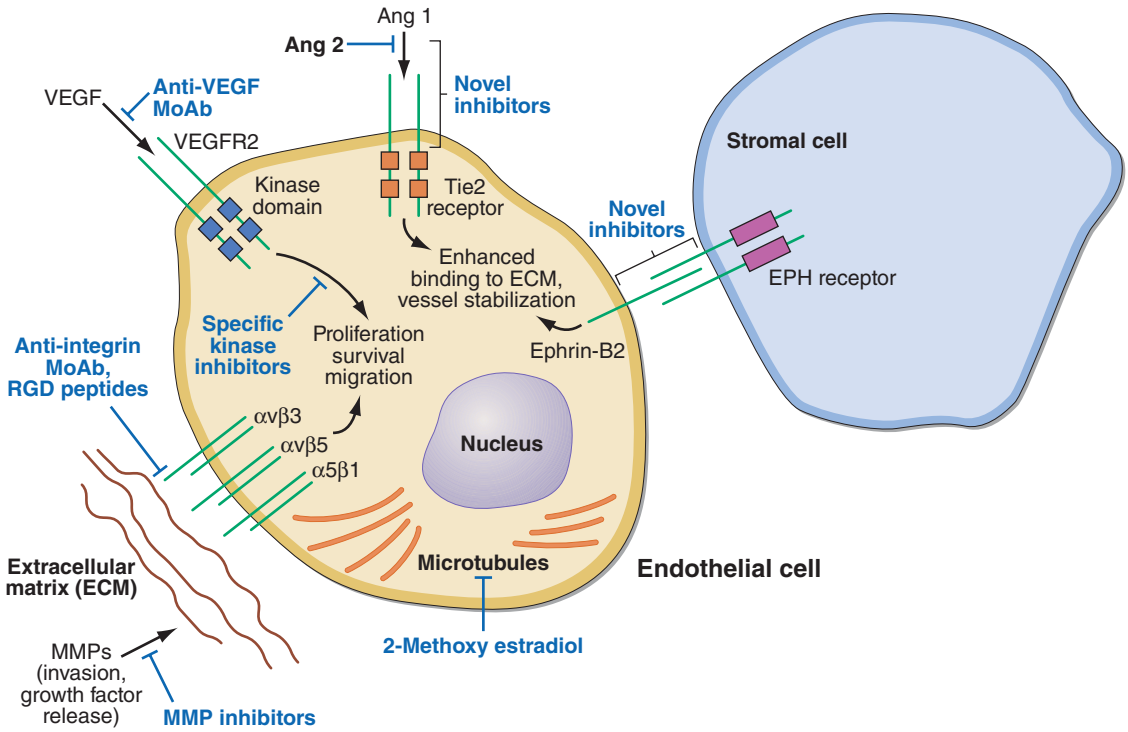

FIGURE 68-12 Knowledge of the molecular events governing tumor angiogenesis has led to a number of therapeutic strategies to block tumor blood vessel formation. The successful therapeutic targeting of VEGF and its receptors VEGFR is described in the text. Other endothelial cell–specific receptor tyrosine kinase pathways (e.g., angiopoietin/Tie2 and ephrin/EPH) are likely targets for the future. Ligation of the $\alpha_v\beta_3$ integrin is required for EC survival. Integrins are also required for EC migration and are important regulators of matrix metalloproteinase (MMP) activity, which modulates EC movement through the ECM as well as release of bound growth factors. Targeting of integrins includes development of blocking antibodies, small peptide inhibitors of integrin signaling, and arg-gly-asp–containing peptides that prevent integrin:ECM binding. Peptides derived from normal proteins by proteolytic cleavage, including endostatin and tumstatin, inhibit angiogenesis by mechanisms that include interfering with integrin function. Signal transduction pathways that are dysregulated in tumor cells indirectly regulate EC function. Inhibition of EGF-family receptors, whose signaling activity is upregulated in a number of human cancers (e.g., breast, colon, and lung cancers), results in downregulation of VEGF and IL-8, while increasing expression of the antiangiogenic protein thrombospondin-1. The Ras/MAPK, PI3K/Akt, and Src kinase pathways constitute important antitumor targets that also regulate the proliferation and survival of tumor-derived EC. The discovery that ECs from normal tissues express tissue-specific "vascular addressins" on their cell surface suggests that targeting specific EC subsets may be possible.

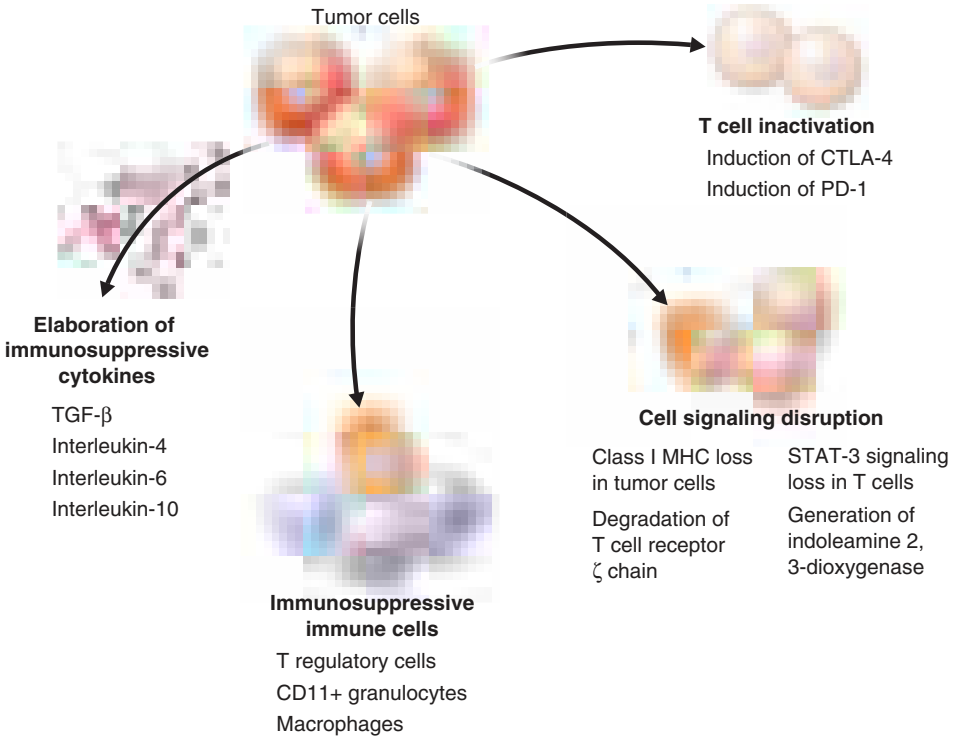

FIGURE 68-13 **Tumor-host interactions** that suppress the immune response to the tumor.

ALL and DLBCL including durable remissions in patients refractory to standard therapies and are approved for these malignancies. However, there have also been significant issues with toxicity including cytokine release syndrome, organ toxicity felt to be due to inadvertent targeting of antigens present in the organ, and neurotoxicity. These patients often require aggressive supportive care by individuals experienced in the delivery of CAR-T cells. In addition, as is true for most anticancer therapies, mechanisms of resistance have developed, most commonly the outgrowth of tumor cells no longer expressing the antigen. Mechanisms for preventing the development of resistant cells are being explored.

Another approach that has shown particular clinical promise is the targeting of proteins or cells (such as regulatory T cells) involved in normal homeostatic control to prevent autoimmune damage to the host but which malignant cells and their stroma can also utilize to inhibit the immune response directed against them. The approach that is furthest along clinically has involved targeting CTLA-4, PD-1, and PDL-1, co-inhibitory molecules that are expressed on the surface of cancer cells, cells of the immune system, and/or stromal cells and are involved in inhibiting the immune response against cancer (Fig. 68-13). A monoclonal antibody directed against CTLA-4 is approved for the treatment of melanoma and antibodies targeting PD-1 or PDL-1 are approved for use against melanoma, RCC, lung cancer, head and neck cancer, urothelial cancer, HCC, gastric cancer, MSI high cancers, and Hodgkin's lymphoma. There is evidence of activity against other cancers including gastroesophageal and hepatocellular cancers and they continue to be evaluated against other malignancies as well. Combination approaches targeting more than one protein or with other anticancer approaches (targeted agents, chemotherapy, radiation therapy) are also being explored and have shown promise in early studies. An important aspect of these approaches is balancing sufficient release of the negative control of the immune response to allow immune mediated attack on the tumors while not allowing too much release and inducing severe autoimmune effects (such as against lung, liver, skin, thyroid, pituitary gland, or the GI tract).

SUMMARY

Although each of the biological aspects of cancers and examples of targeting them has been addressed individually, clearly there is complicated cross-talk between these that occurs in all cancers which needs to be understood to optimally treat different cancers. The explosion of information on tumor cell biology, metastasis, and tumor-host interactions (including angiogenesis, other tumor-stromal interactions, and immune evasion by tumors) has ushered in a new era of rational targeted therapy for cancer. Furthermore, it has become clear that specific molecular factors detected in individual tumors (specific gene mutations, gene-expression profiles, microRNA expression, overexpression of specific proteins) can be used to tailor therapy and maximize antitumor effects.

Acknowledgment

Robert G. Fenton contributed to this chapter in prior editions and important material from those prior chapters has been included here.

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69 Principles of Cancer Treatment

Edward A. Sausville, Dan L. Longo

CANCER PRESENTATION

Localized or systemic cancer is frequent in the differential diagnosis of a variety of common complaints. Although not all forms of cancer are curable at initial diagnosis, affording patients the greatest opportunity for cure or meaningful prolongation of life is greatly aided by diagnosing cancer early in its natural history, and defining treatments that prevent or retard its systemic spread. Indeed, certain forms of cancer, notably breast, colon, and possibly lung cancers in certain patients, can be prevented by screening appropriately selected asymptomatic patients; screening is arguably the earliest point in the spectrum of possible cancer-related interventions where cure is possible **(Table 69-1)**.

DETECTION OF A CANCER

The term *cancer*, as used here, is synonymous with the term *tumor*, whose original derivation from Latin simply meant "swelling," not otherwise specified. We now understand that swelling as a common physical manifestation of a tumor reflects increased interstitial fluid pressure and increased cellular and stromal mass per volume, compared to normal tissue. Leukemias are a special case of a cancer of the blood-forming tissues presenting in a disseminated form frequently without definable tumor masses. In addition to localized swelling, tumors present by altered function of the organ they afflict, such as dyspnea on exertion from the anemia caused by leukemia replacing normal hematopoietic cells, cough from lung cancers, jaundice from tumors disrupting the hepatobiliary tree, or seizures and neurologic signs from brain tumors. Hemorrhage is also a frequent presenting sign of tumors involving hollow viscera, but also may reflect decreases in the number of platelets or altered blood coagulation. Tumors may also present owing to the effects of substances they secrete called a "paraneoplastic" syndrome. Thus, although statistically the fraction of patients with cancer underlying a particular presenting sign or symptom may be low, the implications for a patient with cancer of missing an early-stage tumor call for vigilance; therefore, persistent signs or symptoms should be evaluated as possibly coming from an early-stage tumor.

Evidence of a tumor's existence can objectively be established by careful physical examination, detecting enlarged lymph nodes in lymphomas or a palpable mass in a breast or soft tissue site. A mass may also be detected or confirmed by an imaging modality, such as plain x-ray, computed tomography (CT) scan, ultrasound, positron emission tomography (PET) imaging, or nuclear magnetic resonance approaches. Another way of initially establishing the existence of a possible tumor is through direct visualization of an afflicted organ by endoscopy.

TABLE 69-1 Spectrum of Cancer-Related Interventions

Screening for cancer in an asymptomatic patient
Consideration of cancer in a differential diagnosis
Physical examination, imaging, or endoscopy to define a possible tumor
Diagnosis of cancer by biopsy or removal:
Routine histology
Specialized histology: immunohistochemistry
Molecular studies
Cytogenetic studies
Staging the cancer: Where has it spread?
Treatment
Localized
Systemic
Supportive care
During treatment: related to tumor effects on patient
During treatment to counteract side effects of treatment
Palliative and end of life
When useful treatments are not feasible or desired

ESTABLISHING A CANCER DIAGNOSIS

Once the existence of a likely tumor is defined, unequivocally establishing the diagnosis is the next step in the intervention spectrum. This is usually accomplished by a biopsy procedure and the emergence after pathologic examination of an unequivocal statement that cancer is present, or a non-cancer diagnosis explains the abnormality. Due to tumor heterogeneity, pathologists are better able to make the diagnosis when they have more tissue to examine. In addition to light microscopic inspection of a tumor, sufficient tissue also allows definition of genetic abnormalities and protein expression patterns, such as hormone receptor expression in breast cancers, that may aid in the differential diagnosis or provide information about prognosis or likely response to treatment. Efforts to define "personalized" information from the biology of each patient's tumor and pertinent to each patient's treatment plan are becoming increasingly important in selecting treatment options. The general internist should make sure that a patient's cancer biopsy is appropriately referred from the surgical suite for important molecular studies that can advise the best treatment **(Table 69-2)**.

Coordination among the surgeon, pathologist, and primary care physician is essential to ensure that the amount of information learned from the biopsy material is maximized. These goals are best met by an *excisional biopsy* in which the entire tumor mass is removed with a small margin of normal tissue surrounding it. If an excisional biopsy cannot be performed, *incisional biopsy* is the procedure of second choice. A wedge of tissue is removed, and an effort is made to include the majority of the cross-sectional diameter of the tumor in the biopsy to minimize sampling error. Biopsy techniques that involve cutting into tumor

TABLE 69-2 Diagnostic Biopsy: Standard of Care Molecular and Special Studies

Breast cancer: primary and suspected metastatic
Hormone receptors: estrogen, progesterone
HER2/neu oncoprotein
Lung cancer: primary and suspected metastatic
If nonsquamous non-small cell: epidermal growth factor receptor mutation; alk oncoprotein gene fusion; programmed cell death ligand-1
Colon cancer: suspected metastatic
Ki-ras mutation
Gastrointestinal stromal tumor
c-kit oncoprotein mutation
Melanoma
B-raf oncoprotein mutation
c-kit expression and mutation
Brain tumor gliomas
1p/19q co-deletion
Alkylguanine alkyltransferase promoter methylation
Leukemia (peripheral blood mononuclear cells and/or bone marrow)
Cytogenetics
Flow cytometry
Treatment-defining chromosomal translocations
Bcr-Abl fusion protein
t(15,17)
inversion 16
t(8,21)
Lymphoma
Immunohistochemistry for CD20, CD30, T cell markers
Treatment defining chromosomal translocations:
t(14,18)
t(8,14)

carry with them a risk of facilitating the spread of the tumor, and consideration with a surgeon of whether the biopsy might be the prelude to a curative surgery if certain diagnoses are established should inform the actual approach taken. *Core-needle biopsy* usually obtains considerably less tissue, but this procedure often provides enough information to plan a definitive surgical procedure. *Fine-needle aspiration* generally obtains only a suspension of cells from within a mass. This procedure is minimally invasive, and if positive for cancer, it may allow inception of systemic treatment when metastatic disease is evident, or it can provide a basis for planning a more meticulous and extensive surgical procedure. However, a negative fine-needle aspiration for a neoplastic diagnosis cannot be taken as definitive evidence that a tumor is absent or make a definitive diagnosis in someone not known to have a cancer.

CANCER STAGING

An essential component of correct patient management in many cancer types is defining the extent of disease, because this information critically informs whether localized treatments, "combined-modality" approaches, or systemic treatments should initially be considered. Radiographic and other imaging tests can be helpful in defining the clinical stage; however, pathologic staging requires defining the extent of involvement by documenting the histologic presence of tumor in tissue biopsies obtained through a surgical procedure. Axillary lymph node sampling in breast cancer and lymph node sampling at laparotomy for testicular, colon, and other intraabdominal cancers may provide crucial information for treatment planning and may determine the extent and nature of primary cancer treatment.

For tumors associated with a potential "primary site," staging systems have evolved to define a "T" component related to the size of the tumor or its invasion into local structures, an "N" component related to the number and nature of lymph node groups adjacent to the tumor with evidence of tumor spread, and an "M" component, based on the presence of local or distant metastatic sites. The various "TNM" components are then aggregated to stages, usually stage I to III or IV, depending on the anatomic site. The numerical stages reflect similar long-term survival outcomes of the aggregated TNM groupings in a numeric stage after treatment tailored to the stage. In general, stage I tumors are T1 (reflecting small size), N0 or N1 (reflecting no or minimal node spread), and M0 (no metastases). Such early-stage tumors are amenable to curative approaches with local treatments. On the other hand, stage IV tumors usually have metastasized to distant sites or locally invaded viscera in a nonresectable way and are dealt with using techniques that have palliative intent, except for those diseases with exceptional sensitivity to systemic treatments such as chemotherapy or immunotherapy. Also, the TNM staging system is not useful in diseases such as leukemia, where bone marrow infiltration is never really localized, or central nervous system (CNS) tumors, where tumor histology and the extent of anatomically feasible resection are more important in driving prognosis.

CANCER TREATMENT

The goal of cancer treatment is first to eradicate the cancer. If this primary goal cannot be accomplished, the goal of cancer treatment shifts to palliation, the amelioration of symptoms, and preservation of quality of life while striving to extend life. The dictum *primum non nocere* may not always be the guiding principle of cancer therapy. When cure of cancer is possible, cancer treatments may be considered despite the certainty of severe and perhaps life-threatening toxicities. Every cancer treatment has the potential to cause harm, and treatment may be given that produces toxicity with no benefit. The therapeutic index of many interventions may be quite narrow, with treatments given to the point of toxicity. Conversely, when the clinical goal is palliation, careful attention to minimizing the toxicity of treatments becomes a significant goal.

Cancer treatments are divided into two main types: local and systemic. Local treatments include surgery, radiation therapy (including photodynamic therapy), and ablative approaches, including radiofrequency and cryosurgical approaches. Systemic treatments include chemotherapy (including hormonal therapy and molecularly targeted therapy) and biologic therapy (including immunotherapy). The modalities are often used in combination, and agents in one category can act by several mechanisms. For example, cancer chemotherapy agents can induce differentiation, and antibodies (a form of immunotherapy) can be used to deliver radiation therapy. *Oncology*, the study of tumors including treatment approaches, is a multidisciplinary effort with surgical, radiation, and internal medicine–related areas of oncologic expertise. Treatments for patients with hematologic malignancies are often shared by hematologists and medical oncologists.

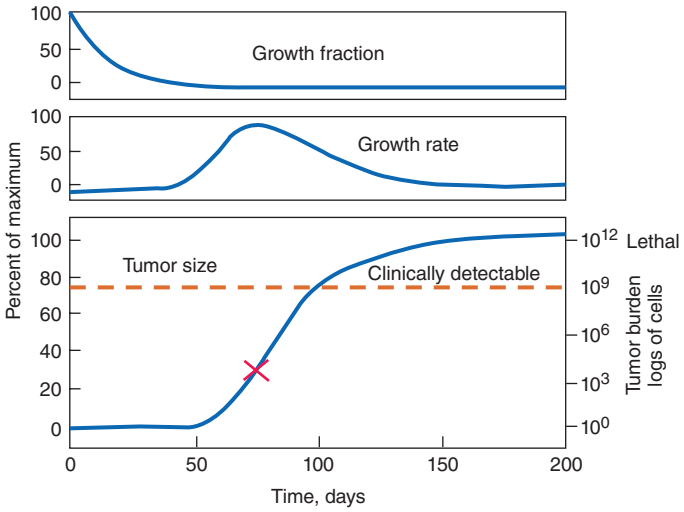

FIGURE 69-1 Gompertzian tumor growth. The growth fraction of a tumor declines exponentially over time (*top*). The growth rate of a tumor peaks before it is clinically detectable (*middle*). Tumor size increases slowly, goes through an exponential phase, and slows again as the tumor reaches the size at which limitation of nutrients or autoregulatory or host regulatory influences can occur. The maximum growth rate occurs at 1/e, the point at which the tumor is about 37% of its maximum size (*marked with an X*). Tumor becomes detectable at a burden of about 10^9 (1 cm^3) cells and kills the patient at a tumor cell burden of about 10^{12} (1 kg). Efforts to treat the tumor and reduce its size can result in an increase in the growth fraction and an increase in growth rate.

Normal organs and cancers share the property of having a population of cells actively progressing through the cell cycle with their division providing a basis for tumor growth, and a population of cells not in cycle; these include *cancer stem cells*, whose properties are being elucidated, as they may serve as a basis for giving rise to tumor initiating or repopulating cells. The stem cell fraction may define new targets for therapies that will retard their ability to reenter the cell cycle.

Tumors follow a Gompertzian growth curve **(Fig. 69-1)**, with the apparent growth fraction of a neoplasm being high with small tumor burdens and declining until, at the time of diagnosis, with a tumor burden of 1–5 × 10^9 tumor cells, the growth fraction is usually 1–4% for many solid tumors. By this view, the most rapid growth rate occurs before the tumor is detectable. An alternative explanation for such growth properties may also emerge from the ability of tumors at metastatic sites to recruit circulating tumor cells from the primary tumor or other metastases. An additional key feature of a successful tumor is the ability to stimulate the development of a new supporting stroma through angiogenesis and production of proteases to allow invasion through basement membranes and normal tissue barriers **(Chap. 68)**.

LOCALIZED CANCER TREATMENTS

SURGERY

Surgery is unquestionably the most effective means of treating cancer. Today at least 40% of cancer patients are cured by surgery. Unfortunately, a large fraction of patients with solid tumors (perhaps 60%) have metastatic disease that is not accessible for removal. Even when cancer is not curable by surgery alone, the removal of tumor can obtain important benefits, including local control of tumor, preservation of organ function, debulking that permits subsequent therapy to be more effective, and staging information on extent of involvement. Cancer surgery aiming for cure is usually planned to excise the tumor

completely with an adequate margin of normal tissue (the margin varies with the tumor and the anatomy), touching the tumor as little as possible to prevent vascular and lymphatic spread, and minimizing operative risk. Such a resection is defined as an R0 resection. R1 and R2 resections, in contrast, are imprecisely defined pathologically as having microscopic or macroscopic, respectively, tumor at resection margins. Such outcomes may be necessitated by proximity of the tumor to vital structures or recognition only in the resected specimen of the extent of tumor involvement, and may be the basis for reoperation to obtain optimal margins if feasible. Extending the procedure to resect draining lymph nodes obtains prognostic information and may, in some anatomic locations, improve survival.

Increasingly, laparoscopic approaches are being used to address primary abdominal and pelvic tumors. Lymph node spread may be assessed using the sentinel node approach, in which the first draining lymph node a spreading tumor would encounter is defined by injecting a dye or radioisotope into the tumor site at operation and then resecting the first node to turn blue or collect isotope. The sentinel node assessment is continuing to undergo clinical evaluation but appears to provide reliable information without the risks (lymphedema, lymphangiosarcoma) associated with resection of all the regional nodes. Advances in adjuvant chemotherapy (chemotherapy given systemically after removal of all local disease by operation and without evidence of active metastatic disease) and radiation therapy following surgery have permitted a substantial decrease in the extent of primary surgery necessary to obtain the best outcomes. Thus, lumpectomy with radiation therapy is as effective as modified radical mastectomy for breast cancer, and limb-sparing surgery followed or preceded by adjuvant radiation therapy and chemotherapy has replaced radical primary surgical procedures involving amputation and disarticulation for childhood rhabdomyosarcomas and osteosarcomas. More limited surgery is also being used to spare organ function, as in larynx and bladder cancer. In some settings (e.g., bulky testicular cancer or stage III breast cancer), surgery is not the first treatment modality used. After an initial diagnostic biopsy, chemotherapy and/or radiation therapy is delivered to reduce the size of the tumor and clinically control undetected metastatic disease. Such therapy is followed by a surgical procedure to remove residual masses; this is called *neoadjuvant therapy*. Because the sequence of treatment is critical to success and is different from the standard surgery-first approach, coordination among the surgical oncologist, radiation oncologist, and medical oncologist is crucial.

Surgery may be curative in a subset of patients with metastatic disease. Patients with lung metastases from osteosarcoma may be cured by resection of the lung lesions. In patients with colon cancer who have fewer than five liver metastases restricted to one lobe and no extrahepatic metastases, hepatic lobectomy may produce long-term disease-free survival in 25% of selected patients. Surgery can also be associated with systemic antitumor effects. In the setting of hormonally responsive tumors, oophorectomy and/or adrenalectomy may eliminate estrogen production, and orchiectomy may reduce androgen production, hormones that drive certain breast and all prostate cancers, respectively; both procedures can have useful effects on metastatic tumor growth. In selecting a surgeon or center for primary cancer treatment, consideration must be given to the volume of cancer surgeries undertaken by the site. Studies in a variety of cancers have shown that increased annual procedure volume appears to correlate with outcome. In addition, facilities with extensive support systems—e.g., for joint thoracic and abdominal surgical teams with cardiopulmonary bypass, if needed—may allow resection of certain tumors that would otherwise not be possible.

Surgery is used in a number of ways for palliative or supportive care of the cancer patient, not related to the goal of curing the cancer. These include insertion and care of central venous catheters, control of pleural and pericardial effusions and ascites, caval interruption for recurrent pulmonary emboli, stabilization of cancer-weakened weight-bearing bones, and control of hemorrhage, among others. Surgical bypass of gastrointestinal, urinary tract, or biliary tree obstruction can alleviate symptoms and prolong survival. Surgical procedures may provide relief of otherwise intractable pain or reverse neurologic dysfunction (cord decompression). Splenectomy may relieve symptoms and reverse hypersplenism. Intrathecal or intrahepatic therapy relies on surgical placement of appropriate infusion portals. Surgery may correct other treatment-related toxicities such as adhesions or strictures. Surgical procedures are also valuable in rehabilitative efforts to restore health or function. Orthopedic procedures may be necessary to ensure proper ambulation. Breast reconstruction can make an enormous impact on the patient's perception of successful therapy. Plastic and reconstructive surgery can correct the effects of disfiguring primary treatment.

Surgery is also a tool valuable in the prevention of cancers in high-risk populations. Prophylactic mastectomy, colectomy, oophorectomy, and thyroidectomy are mainstays of prevention of genetic cancer syndromes. Resection of premalignant skin and uterine cervix lesions and colonic polyps prevents progression to frank malignancy.

RADIATION

Radiation Biology and Medicine Therapeutic radiation is ionizing, causing breaks in DNA and generation of free radicals from cell water that may damage cell membranes, proteins, and organelles. Radiation damage is augmented by oxygen; hypoxic cells are more resistant. Augmentation of oxygen presence is one basis for radiation sensitization. X-rays and gamma rays are the forms of ionizing radiation most commonly used to treat cancer. They are both electromagnetic, nonparticulate waves that cause the ejection of an orbital electron when absorbed. This orbital electron ejection results in ionization. These waves behave biologically as packets of energy, called *photons*. Particulate ionizing radiation using protons has also become available. Most radiation-induced cell damage is due to the formation of hydroxyl radicals from tissue water:

$$\text{Ionizing radiation} + H_2O \rightarrow H_2O^+ + e^-$$
$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^\bullet$$
$$OH^\bullet \rightarrow \text{cell damage}$$

Radiation is quantitated based on the amount of radiation absorbed by the tumor in the patient; it is not based on the amount of radiation generated by the machine. The International System (SI) unit for radiation absorbed is the Gray (Gy): 1 Gy refers to 1 J/kg of tissue; 1 Gy equals 100 centigrays (cGy) of absorbed dose. A historically used unit appearing in the oncology literature, the *rad* (*r*adiation *a*bsorbed *d*ose), is defined as 100 ergs of energy absorbed per gram of tissue and is equivalent to 1 cGy. Radiation dosage is defined by the energy absorbed per mass of tissue. Radiation dose is measured by placing detectors at the body surface or based on radiating phantoms that resemble human form and substance, containing internal detectors. The features that make a particular cell more sensitive or more resistant to the biologic effects of radiation are not completely defined and critically involve DNA repair proteins that, in their physiologic role, protect against environmentally related DNA damage.

Localized Radiation Therapy Radiation effect is influenced by three determinants: total absorbed dose, number of fractions, and time of treatment. A frequent error is to omit the number of fractions and the duration of treatment. Thus, a typical course of radiation therapy should be described as 4500 cGy delivered to a particular target (e.g., mediastinum) over 5 weeks in 180-cGy fractions. Most curative radiation treatment programs are delivered once a day, 5 days a week, in 150- to 200-cGy fractions. Nondividing cells are more resistant than dividing cells, and this is one rationale for delivering radiation in repeated fractions, to ultimately expose a larger number of tumor cells that have entered the division cycle. In addition to these biologic parameters, physical parameters of the radiation are also crucial. The energy of the radiation determines its ability to penetrate tissue. Low-energy x-rays (150–400 kV) scatter when they strike the body, much like light diffuses when it strikes particles in the air. Such beams result in more damage to adjacent normal tissues and less radiation delivered to the tumor. Megavoltage radiation (>1 MeV) has very low lateral scatter; this produces a skin-sparing effect, more homogeneous

distribution of the radiation energy, and greater deposit of the energy in the tumor, or *target volume*. The tissues that the beam passes through to get to the tumor are called the *transit volume*. The maximum dose in the target volume is often the cause of complications to tissues in the transit volume, and the minimum dose in the target volume influences the likelihood of tumor recurrence. Dose homogeneity in the target volume is the goal. Computational approaches and delivery of many beams to converge on a target lesion are the basis for "gamma knife" and related approaches to deliver high doses to small volumes of tumor, sparing normal tissue.

Therapeutic radiation is delivered in three ways: (1) *teletherapy*, with focused beams of radiation generated at a distance and aimed at the tumor within the patient; (2) *brachytherapy*, with encapsulated sources of radiation implanted directly into or adjacent to tumor tissues; and (3) *systemic therapy*, with radionuclides administered, for example, intravenously but targeted by some means to a tumor site. Teletherapy with x-ray or gamma-ray photons is the most commonly used form of radiation therapy. Particulate forms of radiation are also used in certain circumstances, such as the use of proton beams. The difference between photons and protons relates to the volume in which the greatest delivery of energy occurs. Typically, protons have a much narrower range of energy deposition, theoretically resulting in more precise delivery of radiation with improvement in the degree to which adjacent structures may be affected, in comparison to photons. Electron beams are a particulate form of radiation that, in contrast to photons and protons, have a very low tissue penetrance and are used to treat cutaneous tumors. Certain drugs used in cancer treatment may also act as radiation sensitizers. For example, compounds that incorporate into DNA and alter its stereochemistry (e.g., halogenated pyrimidines, cisplatin) augment radiation effects at local sites, as does hydroxyurea, another DNA synthesis inhibitor. These are important adjuncts to the local treatment of certain tumors, such as squamous head and neck, uterine cervix, and rectal cancers.

Toxicity of Radiation Therapy Although radiation therapy is most often administered to a local region, systemic effects, including fatigue, anorexia, nausea, and vomiting, may develop that are related in part to the volume of tissue irradiated, dose fractionation, radiation fields, and individual susceptibility. Injured tissues release cytokines that act systemically to produce these effects. Bone is among the most radioresistant organs, with radiation effects being manifested mainly in children through premature fusion of the epiphyseal growth plate. By contrast, the male testis, female ovary, and bone marrow are the most sensitive organs. Any bone marrow in a radiation field will be eradicated by therapeutic irradiation. Organs with less need for cell renewal, such as heart, skeletal muscle, and nerves, are more resistant to radiation effects. In radiation-resistant organs, the vascular endothelium is the most sensitive component. Organs with more self-renewal as a part of normal homeostasis, such as the hematopoietic system and mucosal lining of the intestinal tract, are more sensitive. Acute toxicities include mucositis, skin erythema (ulceration in severe cases), and bone marrow toxicity. Often these can be alleviated by interruption of treatment.

Chronic toxicities are more serious. Radiation of the head and neck region often produces thyroid failure. Cataracts and retinal damage can lead to blindness. Salivary glands stop making saliva, which leads to dental caries and poor dentition. Taste and smell can be affected. Mediastinal irradiation leads to a threefold increased risk of fatal myocardial infarction. Other late vascular effects include chronic constrictive pericarditis, lung fibrosis, viscus stricture, spinal cord transection, and radiation enteritis. A serious late toxicity is the development of second solid tumors in or adjacent to the radiation fields. Such tumors can develop in any organ or tissue and occur at a rate of ~1% per year beginning in the second decade after treatment. Some organs vary in susceptibility to radiation carcinogenesis. A woman who receives mantle field radiation therapy for Hodgkin's disease at age 25 years has a 30% risk of developing breast cancer by age 55 years. This is comparable in magnitude to genetic breast cancer syndromes. Women treated after age 30 years have little or no increased risk of breast cancer. No data suggest that a threshold dose of therapeutic radiation exists below which the incidence of second cancers is decreased. High rates of second tumors occur in people who receive as little as 1000 cGy.

OTHER LOCALIZED CANCER TREATMENTS

Endoscopy techniques may allow the placement of stents to unblock viscera by mechanical means, palliating, for example, gastrointestinal or biliary obstructions. Radiofrequency ablation (RFA) refers to the use of focused microwave radiation to induce thermal injury within a volume of tissue. RFA can be useful in the control of metastatic lesions, particularly in liver, that may threaten biliary drainage (as one example) and threaten quality and duration of useful life in patients with otherwise unresectable disease. Cryosurgery uses extreme cold to sterilize lesions in certain sites, such as prostate and kidney, when at a very early stage, eliminating the need for modalities with more side effects such as surgery or radiation.

Some chemicals (porphyrins, phthalocyanines) are preferentially taken up by cancer cells by mechanisms not fully defined. When light, usually delivered by a laser, is shone on cells containing these compounds, free radicals are generated and the cells die. Hematoporphyrins and light (phototherapy) are being used with increasing frequency to treat skin cancer; ovarian cancer; and cancers of the lung, colon, rectum, and esophagus. Palliation of recurrent locally advanced disease can sometimes be dramatic and last many months.

Infusion of chemotherapeutic or biologic agents or radiation-bearing delivery devices such as isotope-coated glass spheres into local sites through catheters inserted into specific vascular sites such as liver or an extremity have been used in an effort to control disease limited to that site; in selected cases, prolonged control of truly localized disease has been possible.

SYSTEMIC CANCER TREATMENTS

The concept that systemically administered agents may have a useful effect on cancers was historically derived from three sets of observations. Paul Ehrlich in the nineteenth century observed that different dyes reacted with different cell and tissue components. He hypothesized the existence of compounds that would be "magic bullets" that might bind to tumors, owing to the affinity of the agent for the tumor. A second observation was the toxic effects of certain mustard gas derivatives on the bone marrow during World War I, leading to the idea that smaller doses of these agents might be used to treat tumors of marrow-derived cells. Finally, the observation that certain tumors from hormone-responsive tissues, e.g., breast tumors, could shrink after oophorectomy led to the idea that endogenous substances promoting the growth of a tumor might be antagonized. Chemicals achieving each of the goals are actually or intellectually the forbearers of the currently used cancer chemotherapy agents.

Systemic cancer treatments are of four broad types. *Conventional "cytotoxic" chemotherapy agents* were historically derived by the empirical observation that these "small molecules" (generally with molecular mass <1500 Da) could cause major regression of experimental tumors growing in animals. These agents mainly target DNA structure or segregation of DNA as chromosomes in mitosis. *Targeted agents* refer to small molecules or "biologics" (generally macromolecules such as antibodies or cytokines) designed and developed to interact with a defined molecular target important in maintaining the malignant state or expressed by the tumor cells. As described in **Chap. 68**, successful tumors have activated biochemical pathways that lead to uncontrolled proliferation through the action of, e.g., oncogene products, loss of cell cycle inhibitors, or loss of cell death regulation, and have acquired the capacity to replicate chromosomes indefinitely, invade, metastasize, and evade the immune system. Targeted therapies seek to capitalize on the biology behind the aberrant cellular behavior as a basis for therapeutic effects. *Hormonal therapies* (the first form of targeted therapy) capitalize on the biochemical pathways underlying estrogen and androgen function and action as a therapeutic basis for approaching patients with tumors of breast, prostate, and uterus. *Biologic therapies* are often macromolecules that have a particular target (e.g., anti-growth factor receptor or cytokine antibodies) or may have the capacity to induce a host immune response to kill tumor cells.

Principles The usefulness of any drug is governed by the extent to which a given dose causes a therapeutic effect (in the case of anticancer agents, toxicity to tumor cells) as opposed to a toxic effect to the host. The *therapeutic index* is the degree of separation between toxic and therapeutic doses. Really useful drugs have large therapeutic indices, and this usually occurs when the drug target is expressed in the disease-causing compartment as opposed to the normal compartment. Currently used chemotherapeutic agents have the unfortunate property that their targets are present in both normal and tumor tissues. Therefore, they have relatively narrow therapeutic indices.

Figure 69-2 illustrates steps in cancer drug development. Following demonstration of antitumor activity in animal models, potentially useful anticancer agents are further evaluated to define an optimal schedule of administration and arrive at a drug formulation designed for a given route of administration and schedule. Safety testing in two species on an analogous schedule of administration defines the starting dose for a phase 1 trial in humans, usually but not always in patients with cancer who have exhausted "standard" (already approved) treatments. The initial dose is usually one-sixth to one-tenth of the dose just causing easily reversible toxicity in the more sensitive animal species. Escalating doses of the drug are then given during the human phase 1 trial until reversible toxicity is observed. Dose-limiting toxicity (DLT) defines a dose that conveys greater toxicity than would be acceptable in routine practice, allowing definition of a lower maximum-tolerated dose (MTD). The occurrence of toxicity is, if possible, correlated with plasma drug concentrations. The MTD or a dose just lower than the MTD is usually the dose suitable for phase 2 trials, where a fixed dose is administered to a relatively homogeneous set of patients with a particular tumor type in an effort to define whether the drug causes regression of tumors. In a phase 3 trial, evidence of improved overall survival or improvement in the time to progression of disease on the part of the new drug is sought in comparison to an appropriate control population, which is usually receiving an acceptable "standard of care" approach. A favorable outcome of a phase 3 trial is the basis for application to a regulatory agency for approval of the new agent for commercial marketing as safe and possessing a measure of clinical effectiveness.

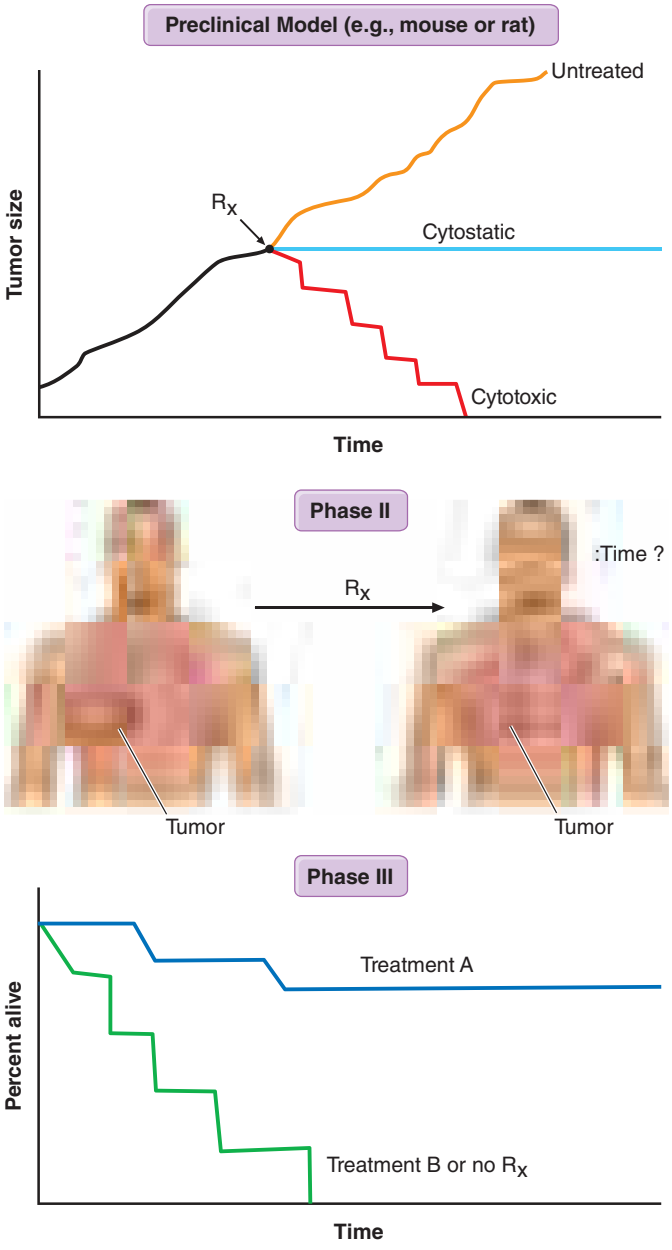

FIGURE 69-2 Steps in cancer drug discovery and development. Preclinical activity (*top*) in animal models of cancers may be used as evidence to support the entry of the drug candidate into phase 1 trials in humans to define a correct dose and observe any clinical antitumor effect that may occur. The drug may then be advanced to phase 2 trials directed against specific cancer types, with rigorous quantitation of antitumor effects (*middle*). Phase 3 trials then may reveal activity superior to standard or no treatment (*bottom*).

Response, defined as tumor shrinkage, is the most immediate indicator of drug effect. To be clinically valuable, responses must translate into clinical benefit. This is conventionally established by a beneficial effect on overall survival, or at least an increased time to further progression of disease. Karnofsky was among the first to champion the evaluation of a chemotherapeutic agent's benefit by carefully quantitating its effect on tumor size and using these measurements to objectively decide the basis for further treatment of a particular patient or further clinical evaluation of a drug's potential. A partial response (PR) is defined conventionally as a decrease by at least 50% in a tumor's bidimensional area; a complete response (CR) connotes disappearance of all tumor; progression of disease signifies an increase in size of existing lesions by >25% from baseline or best response or development of new lesions; and stable disease fits into none of the above categories. Newer evaluation systems, such as Response Evaluation Criteria in Solid Tumors (RECIST), use unidimensional measurement, but the intent is similar in rigorously defining evidence for the activity of the agent in assessing its value to the patient. An active chemotherapy agent conventionally has PR rates of at least 20–25% with reversible non-life-threatening side effects, and it may then be suitable for study in phase 3 trials to assess efficacy in comparison to standard or no therapy. Active efforts are being made to quantitate effects of anticancer agents on quality of life. Cancer drug clinical trials conventionally use a toxicity grading scale where grade 1 toxicities do not require treatment, grade 2 toxicities may require symptomatic treatment but are not life-threatening, grade 3 toxicities are potentially life-threatening if untreated, grade 4 toxicities are actually life-threatening, and grade 5 toxicities are those that result in the patient's death.

Development of targeted agents may proceed quite differently. While phase 1–3 trials are still conducted, molecular analysis of human tumors may allow the precise definition of target expression in a patient's tumor that is necessary for or relevant to the drug's action. This information might then allow selection of patients expressing the drug target for participation in all trial phases. These patients may then have a greater chance of developing a useful response to the drug by virtue of expressing the target in the tumor. Clinical trials may be designed to incorporate an assessment of the behavior of the target in relation to the drug (pharmacodynamic studies). Ideally, the plasma concentration that affects the drug target is known, so escalation to MTD may not be necessary. Rather, the correlation of host toxicity while achieving an "optimal biologic dose" becomes a more relevant endpoint for phase 1 and early phase 2 trials with targeted agents.

Useful cancer drug treatment strategies using conventional chemotherapy agents, targeted agents, hormonal treatments, or biologics have one of two valuable outcomes. They can induce cancer cell death, resulting in tumor shrinkage with corresponding improvement in

patient survival, or increase the time until the disease progresses. Another potential outcome is to induce cancer cell *differentiation* or *dormancy* with loss of tumor cell replicative potential and reacquisition of phenotypic properties resembling normal cells. A general view of how cancer treatments work is that the interaction of a chemotherapeutic drug with its target induces a "cascade" of further signaling steps. These signals ultimately lead to cell death by triggering an "execution phase" where proteases, nucleases, and endogenous regulators of the cell death pathway are activated **(Fig. 69-3)**.

Targeted agents differ from chemotherapy agents in that they do not indiscriminately cause macromolecular lesions but regulate the action of particular pathways. For example, the $p210^{bcr\text{-}abl}$ fusion protein tyrosine kinase drives chronic myeloid leukemia (CML), and HER2/neu stimulates the proliferation of certain breast cancers. The tumor has been described as "addicted" to the function of these molecules in the sense that without the pathway's continued action, the tumor cell cannot survive. In this way, targeted agents directed at $p210^{bcr\text{-}abl}$ or HER2/neu may alter the "threshold" tumors driven by these molecules may have for undergoing cell death without actually creating any molecular lesions such as direct DNA strand breakage or altered membrane function.

Chemotherapy agents may be used for the treatment of active, clinically apparent cancer. The goal of such treatment in some cases is cure of the cancer, that is, elimination of all clinical and pathologic evidence of cancer and return of the patient to an expected survival no different than the general population. **Table 69-3, *A*** lists those tumors considered curable by conventionally available chemotherapeutic agents when used to address disseminated or metastatic cancers. If a tumor is localized to a single site, serious consideration of surgery or primary radiation therapy should be given, because these treatment modalities may be curative as local treatments. Chemotherapy may then be used after the failure of these modalities to eradicate a local tumor or as part of multimodality approaches to offer primary treatment to a clinically localized tumor. In this event, it can allow organ preservation when given with radiation, as in the larynx or other upper airway sites, or sensitize tumors to radiation when given, e.g., to patients concurrently receiving radiation for lung or cervix cancer **(Table 69-3, *B*)**. Chemotherapy can be administered as an *adjuvant*, i.e., in addition to surgery or radiation **(Table 69-3, *C*)**, even after all clinically apparent disease has been removed. This use of chemotherapy has curative potential in breast and colorectal neoplasms, as it attempts to eliminate clinically unapparent tumor that may have already disseminated. *Neoadjuvant* chemotherapy refers to administration of chemotherapy before any surgery or radiation to a local tumor in an effort to enhance the effect of the local treatment.

Chemotherapy is routinely used in "conventional" dose regimens. In general, these doses produce reversible acute side effects, primarily consisting of transient myelosuppression with or without gastrointestinal toxicity (usually nausea), which are readily managed. "High-dose" chemotherapy regimens are predicated on the observation that the dose-response curve for many anticancer agents is rather steep, and increased dose can produce markedly increased therapeutic effect, although at the cost of potentially life-threatening complications that require intensive support, usually in the form of hematopoietic stem cell support from the patient (*autologous*) or from donors matched for histocompatibility loci (*allogeneic*), or pharmacologic "rescue" strategies to repair the effect of the high-dose chemotherapy on normal tissues. High-dose regimens have definite curative potential in defined clinical settings **(Table 69-3, *D*)**.

If cure is not possible, chemotherapy may be undertaken with the goal of palliating some aspect of the tumor's effect on the host. In this usage, value is perceived by the demonstration of improved symptom relief, progression-free survival, or overall survival at a certain time from the inception of treatment in the treated population, compared to a relevant control population established as the result of a clinical research protocol as a basis for U.S. Food and Drug Administration (FDA) approval of a particular cancer treatment as safe and effective. Common tumors that may be meaningfully addressed by chemotherapy with palliative intent are listed in **Table 69-3, *E***.

Usually, tumor-related symptoms manifest as pain, weight loss, or some local symptom related to the tumor's effect on normal structures. Patients treated with palliative intent should be aware of their diagnosis and the limitations of the proposed treatments, have access to supportive care, and have suitable "performance status," according to assessment algorithms such as the one developed by Karnofsky

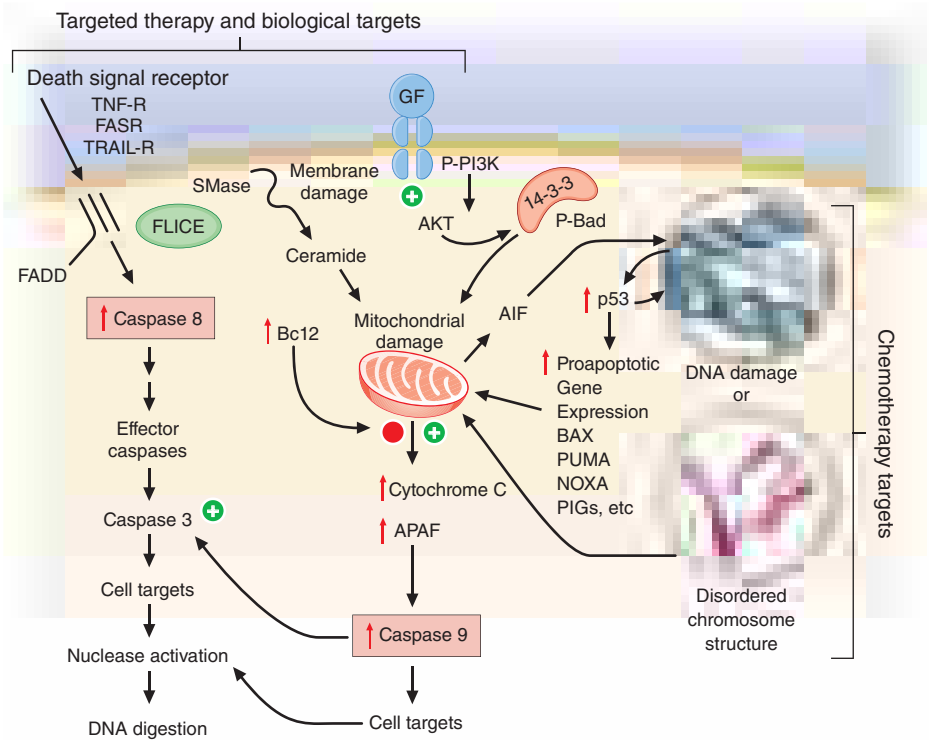

FIGURE 69-3 Integration of cell death responses. Cell death through apoptosis requires active participation of the cell. In response to interruption of growth factor (GF) or propagation of certain cytokine death signals (e.g., tumor necrosis factor receptor [TNF-R]), there is activation of "upstream" cysteine aspartyl proteases (caspases), which then directly digest cytoplasmic and nuclear proteins, resulting in activation of "downstream" caspases; these cause activation of nucleases, resulting in the characteristic DNA fragmentation that is a hallmark of apoptosis. Chemotherapy agents that create lesions in DNA or alter mitotic spindle function seem to activate aspects of this process by damage ultimately conveyed to the mitochondria, perhaps by activating the transcription of genes whose products can produce or modulate the toxicity of free radicals. In addition, membrane damage with activation of sphingomyelinases results in the production of ceramides that can have a direct action at mitochondria. The antiapoptotic protein bcl2 attenuates mitochondrial toxicity, while proapoptotic gene products such as bax antagonize the action of bcl2. Damaged mitochondria release cytochrome C and apoptosis-activating factor (APAF), which can directly activate caspase 9, resulting in propagation of a direct signal to other downstream caspases through protease activation. Apoptosis-inducing factor (AIF) is also released from the mitochondrion and then can translocate to the nucleus, bind to DNA, and generate free radicals to further damage DNA. An additional proapoptotic stimulus is the *bad* protein, which can heterodimerize with *bcl2* gene family members to antagonize apoptosis. Importantly, though, bad protein function can be retarded by its sequestration as phospho-*bad* through the 14-3-3 adapter proteins. The phosphorylation of bad is mediated by the action of the AKT kinase in a way that defines how growth factors that activate this kinase can retard apoptosis and promote cell survival.

TABLE 69-3 Curability of Cancers with Chemotherapy

A. Advanced Cancers with Possible Cure

Acute lymphoid and acute myeloid leukemia (pediatric/adult)
Hodgkin's disease (pediatric/adult)
Lymphomas—certain types (pediatric/adult)
Germ cell neoplasms
- Embryonal carcinoma
- Teratocarcinoma
- Seminoma or dysgerminoma
- Choriocarcinoma

Gestational trophoblastic neoplasia
Pediatric neoplasms
- Wilms' tumor
- Embryonal rhabdomyosarcoma
- Ewing's sarcoma
- Peripheral neuroepithelioma
- Neuroblastoma

Small-cell lung carcinoma
Ovarian carcinoma

B. Advanced Cancers Possibly Cured by Chemotherapy and Radiation

Squamous carcinoma (head and neck)
Squamous carcinoma (anus)
Breast carcinoma
Carcinoma of the uterine cervix
Non-small-cell lung carcinoma (stage III)
Small-cell lung carcinoma

C. Cancers Possibly Cured with Chemotherapy as Adjuvant to Surgery

Breast carcinoma
Colorectal carcinoma[a]
Osteogenic sarcoma
Soft tissue sarcoma

D. Cancers Possibly Cured with "High-Dose" Chemotherapy with Stem Cell Support

Relapsed leukemias, lymphoid and myeloid
Relapsed lymphomas, Hodgkin's and non-Hodgkin's
Chronic myeloid leukemia
Multiple myeloma

E. Cancers Responsive with Useful Palliation, But Not Cure, by Chemotherapy

Bladder carcinoma
Chronic myeloid leukemia
Hairy cell leukemia
Chronic lymphocytic leukemia
Lymphoma—certain types
Multiple myeloma
Gastric carcinoma
Cervix carcinoma
Endometrial carcinoma
Soft tissue sarcoma
Head and neck cancer
Adrenocortical carcinoma
Islet cell neoplasms
Breast carcinoma
Colorectal carcinoma
Renal carcinoma

F. Tumors Poorly Responsive in Advanced Stages to Chemotherapy

Pancreatic carcinoma
Biliary tract neoplasms
Thyroid carcinoma
Carcinoma of the vulva
Non-small-cell lung carcinoma
Prostate carcinoma
Melanoma (subsets)
Hepatocellular carcinoma
Salivary gland cancer

[a]Rectum also receives radiation therapy.

(see Table 65-4) or by the Eastern Cooperative Oncology Group (ECOG) (see Table 65-5). ECOG performance status 0 (PS0) patients are without symptoms; PS1 patients are ambulatory but restricted in strenuous physical activity; PS2 patients are ambulatory but unable to work and are up and about 50% or more of the time; PS3 patients are capable of limited self-care and are up <50% of the time; and PS4 patients are totally confined to bed or chair and incapable of self-care. Only PS0, PS1, and PS2 patients are generally considered suitable for palliative (noncurative) treatment. If there is curative potential, even poor–performance status patients may be treated, but their prognosis is usually inferior to that of good–performance status patients treated with similar regimens.

An important perspective the primary care provider may bring to patients and their families facing incurable cancer is that, given the limited value of chemotherapeutic approaches at some point in the natural history of most metastatic cancers, *palliative care* or *hospice-based* approaches, with meticulous and ongoing attention to symptom relief and with family, psychological, and spiritual support, should receive prominent attention as a valuable therapeutic plan (Chaps. 9 and 65). Optimizing the quality of life rather than attempting to extend it becomes a valued intervention. Patients facing the impending progression of disease in a life-threatening way frequently choose to undertake toxic treatments of little to no potential value, and support provided by the primary caregiver in accessing palliative and hospice-based options in contrast to receiving toxic and ineffective regimen can be critical in providing a basis for patients to make sensible choices.

Cytotoxic Chemotherapy Agents

Table 69-4 lists commonly used cytotoxic cancer chemotherapy agents and pertinent clinical aspects of their use, with particular reference to adverse effects that might be encountered by the generalist in the care of patients. The drugs listed may be usefully grouped into two general categories: those affecting DNA and those affecting microtubules.

DNA-INTERACTIVE AGENTS DNA replication occurs during the synthesis or S-phase of the cell cycle, with chromosome segregation of the replicated DNA occurring in the M, or mitosis, phase. The G_1 and G_2 "gap phases" precede S and M, respectively. Historically, chemotherapeutic agents have been divided into "phase-nonspecific" agents, which can act in any phase of the cell cycle, and "phase-specific" agents, which require the cell to be at a particular cell cycle phase to cause greatest effect. "Checkpoints" in the cell cycle exist where the drug-related damage may be assessed and either repaired or cell death initiated.

Alkylating agents as a class are cell cycle phase–nonspecific agents. They break down, either spontaneously or after normal organ or tumor cell metabolism, to reactive intermediates that covalently modify bases in DNA. This leads to cross-linkage of DNA strands or the appearance of breaks in DNA as a result of repair efforts. "Broken" or cross-linked DNA is intrinsically unable to complete normal replication or cell division; in addition, it is a potent activator of cell cycle checkpoints and further activates cell-signaling pathways that can precipitate apoptosis. Alkylating agents share similar toxicities: myelosuppression, alopecia, gonadal dysfunction, mucositis, and pulmonary fibrosis. They differ greatly in a spectrum of normal organ toxicities. They also share the capacity to cause "second" neoplasms, particularly leukemia, many years after use, particularly when used in low doses for protracted periods.

Cyclophosphamide is inactive unless metabolized by the liver to 4-hydroxy-cyclophosphamide, which decomposes into an alkylating species, as well as to chloroacetaldehyde and acrolein. The latter causes chemical cystitis; therefore, excellent hydration must be maintained while using cyclophosphamide. If severe, the cystitis may be attenuated or prevented altogether (if expected from the dose of cyclophosphamide to be used) by mesna (2-*m*ercapto*e*thanesulfo*na*te). Liver disease impairs cyclophosphamide activation. Sporadic interstitial pneumonitis leading to pulmonary fibrosis can accompany the use of cyclophosphamide, and high doses used in conditioning regimens for bone marrow transplant can cause cardiac dysfunction. Ifosfamide is a cyclophosphamide analogue also activated in the liver, but more slowly, and it requires coadministration of mesna to prevent bladder injury. CNS effects, including somnolence, confusion, and psychosis, can follow ifosfamide use; the incidence appears related to low body surface area or decreased creatinine clearance.

Several alkylating agents are less commonly used. Bendamustine is a nitrogen mustard derivative with evidence of activity in chronic lymphocytic leukemia and certain lymphomas. Busulfan can cause profound myelosuppression, alopecia, and pulmonary toxicity but is relatively "lymphocyte sparing." Its routine use in treatment of CML has been curtailed in favor of imatinib (Gleevec) or dasatinib, but it is still used in transplant preparation regimens. Melphalan shows variable oral bioavailability and undergoes extensive binding to albumin and α_1-acidic glycoprotein. Mucositis appears more prominently; however, it has prominent activity in multiple myeloma.

Nitrosoureas break down to carbamylating species that not only cause a distinct pattern of DNA base pair–directed toxicity but also can covalently modify proteins. They share the feature of causing relatively delayed bone marrow toxicity, which can be cumulative and long-lasting. Procarbazine is metabolized in the liver and possibly in tumor cells to yield a variety of free radical and alkylating species. In addition to myelosuppression, it causes hypnotic and other CNS effects, including vivid nightmares. It can cause a disulfiram-like syndrome on ingestion of ethanol. Dacarbazine (DTIC) is activated in the liver to yield the highly reactive methyl diazonium cation. It causes only modest

TABLE 69-4 Cytotoxic Chemotherapy Agents

DRUG	TOXICITY	INTERACTIONS, ISSUES
Direct DNA-Interacting Agents		
Alkylator		
Cyclophosphamide	Marrow (relative platelet sparing)	Liver metabolism required to activate to phosphoramide mustard + acrolein
	Cystitis	Mesna protects against "high-dose" bladder damage
	Common alkylator[a]	
	Cardiac (high dose)	
Melphalan	Marrow (delayed nadir)	Decreased renal function delays clearance
	GI (high dose)	
Carmustine (BCNU)	Marrow (delayed nadir)	
	GI, liver (high dose)	
	Renal	
Lomustine (CCNU)	Marrow (delayed nadir)	
Ifosfamide	Myelosuppressive	Analogue of cyclophosphamide
	Bladder	Must use mesna
	Neurologic	Greater activity vs testicular neoplasms and sarcomas
	Metabolic acidosis	
Procarbazine	Marrow	Liver and tissue metabolism required
	Nausea	Disulfiram-like effect with ethanol
	Neurologic	Acts as MAOI
	Common alkylator[a]	HBP after tyrosinase-rich foods
Dacarbazine (DTIC)	Marrow	Metabolic activation
	Nausea	
	Flulike	
Temozolomide	Nausea/vomiting	Infrequent myelosuppression
	Headache/fatigue	
	Constipation	
Cisplatin	Nausea	Maintain high urine flow; osmotic diuresis, monitor intake/output K^+, Mg^{2+}
	Neuropathy	Emetogenic—prophylaxis needed
	Auditory	Full dose if CrCl >60 mL/min and tolerate fluid push
	Marrow platelets > WBCs	
	Renal Mg^{2+}, Ca^{2+}	
Carboplatin	Marrow platelets > WBCs	Reduce dose according to CrCl: to AUC of 5–7 mg/mL per min [AUC = dose/(CrCl + 25)]
	Nausea	
	Renal (high dose)	
Oxaliplatin	Nausea	Acute reversible neurotoxicity; chronic sensory neurotoxicity cumulative with dose; reversible laryngopharyngeal spasm
	Anemia	
Antitumor Antibiotics and Topoisomerase Poisons		
Bleomycin	Pulmonary	Inactivate by bleomycin hydrolase (decreased in lung/skin)
	Skin effects	O_2 enhances pulmonary toxicity
	Raynaud's	Cisplatin-induced decrease in CrCl may increase skin/lung toxicity
	Hypersensitivity	Reduce dose if CrCl <60 mL/min
Dactinomycin	Marrow	Radiation recall
	Nausea	
	Mucositis	
	Vesicant	
	Alopecia	
Etoposide (VP16-213)	Marrow (WBCs > platelet)	Hepatic metabolism—renal 30%
	Alopecia	Reduce doses with renal failure
	Hypotension	Schedule-dependent (5-day schedule better than 1-day)
	Hypersensitivity (rapid IV)	Late leukemogenic
	Nausea	Accentuate antimetabolite action
	Mucositis (high dose)	
Topotecan	Marrow	Reduce dose with renal failure
	Mucositis	No liver toxicity
	Nausea	
	Mild alopecia	

(*Continued*)

TABLE 69-4 Cytotoxic Chemotherapy Agents (Continued)

DRUG	TOXICITY	INTERACTIONS, ISSUES
Irinotecan	Diarrhea: "early onset" with cramping, flushing, vomiting; "late onset" after several doses	Prodrug requires enzymatic clearance to active drug "SN 38"
		Early diarrhea due to acetylcholine release
	Marrow	Late diarrhea, use "high-dose" loperamide (2 mg q2–4 h)
	Alopecia	
	Nausea	
	Vomiting	
	Pulmonary	
Doxorubicin and daunorubicin	Marrow	Heparin aggregate; coadministration increases clearance
	Mucositis	Acetaminophen, BCNU increase liver toxicity
	Alopecia	Radiation recall
	Cardiovascular acute/chronic	
	Vesicant	
Idarubicin	Marrow	None established
	Cardiac (less than doxorubicin)	
Epirubicin	Marrow	None established
	Cardiac	
Mitoxantrone	Marrow	Interacts with heparin
	Cardiac (less than doxorubicin)	Less alopecia, nausea than doxorubicin
	Vesicant (mild)	Radiation recall
	Blue urine, sclerae, nails	Less alopecia, nausea than doxorubicin
Indirectly DNA-Interacting Agents		
Antimetabolites		
6-Mercaptopurine (6-MP)	Marrow	Variable bioavailability
	Liver	Metabolize by xanthine oxidase
	Nausea	Decrease dose with allopurinol
		Increased toxicity with thiopurine methyltransferase deficiency
6-Thioguanine	Marrow	Variable bioavailability
	Liver	Increased toxicity with thiopurine methyltransferase deficiency
	Nausea	
2-Chlorodeoxyadenosine	Marrow	Notable use in hairy cell leukemia
	Renal	
	Fever	
Hydroxyurea	Marrow	Decrease dose with renal failure
	Nausea	Augments antimetabolite effect
	Mucositis	
	Skin changes	
	Rare renal, liver, lung, CNS	
Methotrexate	Marrow	Toxicity lessened by "rescue" with leucovorin
	Liver/lung	Excreted in urine
	Renal tubular	Decrease dose in renal failure; NSAIDs increase renal toxicity
	Mucositis	
Pemetrexed	Anemia	Supplement folate/B_{12}
	Neutropenia	Caution in renal failure
Pralatrexate	Thrombocytopenia	Active in peripheral T cell lymphoma
	Myelosuppression	
	Mucositis	
5-Fluorouracil (5FU)	Marrow	Toxicity enhanced by leucovorin by increasing "ternary complex" with thymidylate synthase; dihydropyrimidine dehydrogenase deficiency increases toxicity; metabolism in tissue
	Mucositis	
	Neurologic	
	Skin changes	
Capecitabine	Diarrhea	Prodrug of 5FU due to intratumoral metabolism
	Hand-foot syndrome	
Cytosine arabinoside	Marrow	Enhances activity of alkylating agents
	Mucositis	Metabolizes in tissues by deamination but renal excretion prominent at doses >500 mg; therefore, dose reduce in "high-dose" regimens in patients with decreased CrCl
	Neurologic (high dose)	
	Conjunctivitis (high dose)	
	Noncardiogenic pulmonary edema	

(*Continued*)

TABLE 69-4 Cytotoxic Chemotherapy Agents (Continued)

DRUG	TOXICITY	INTERACTIONS, ISSUES
Azacitidine	Marrow	Use limited to leukemia/myelodysplastic syndrome
Decitabine	Nausea	Altered methylation of DNA alters gene expression
	Liver	
	Neurologic	
	Myalgia	
Gemcitabine	Marrow	
	Nausea	
	Hepatic	
	Fever/"flu syndrome"	
Fludarabine phosphate	Marrow	Dose reduction with renal failure
	Neurologic	Metabolized to F-ara converted to F-ara ATP in cells by deoxycytidine kinase
	Lung	
Asparaginase	Decrease protein synthesis; indirect inhibition of DNA synthesis by decreased histone synthesis	Blocks methotrexate action
	Clotting factors	
	Glucose	
	Albumin	
	Hypersensitivity	
	CNS	
	Pancreatitis	
	Hepatic	
Antimitotic Agents		
Vincristine	Vesicant	Hepatic clearance
	Marrow	Dose reduction for bilirubin >1.5 mg/dL
	Neurologic	Prophylactic bowel regimen
	GI: ileus/constipation; bladder hypotoxicity; SIADH	
	Cardiovascular	
Vinblastine	Vesicant	Hepatic clearance
	Marrow	Dose reduction as with vincristine
	Neurologic (less common but similar spectrum to other vincas)	
	Hypertension	
	Raynaud's	
Vinorelbine	Vesicant	Hepatic clearance
	Marrow	
	Allergic/bronchospasm (immediate)	
	Dyspnea/cough (subacute)	
	Neurologic (less prominent but similar spectrum to other vincas)	
Paclitaxel	Hypersensitivity	Premedicate with steroids, H_1 and H_2 blockers
	Marrow	
	Mucositis	Hepatic clearance
	Alopecia	Dose reduction as with vincas
	Sensory neuropathy	
	CV conduction disturbance	
	Nausea—infrequent	
Docetaxel	Hypersensitivity	Premedicate with steroids, H_1 and H_2 blockers
	Fluid retention syndrome	
	Marrow	
	Dermatologic	
	Sensory neuropathy	
	Nausea infrequent	
	Some stomatitis	
Nab-paclitaxel (protein bound)	Neuropathy	Caution in hepatic insufficiency
	Anemia	
	Neutropenia	
	Thrombocytopenia	
Ixabepilone	Myelosuppression	
	Neuropathy	

[a]Common allkylator: alopecia, pulmonary, infertility, plus teratogenesis.

Abbreviations: ALL, acute lymphocytic leukemia; AUC, area under the curve; CHF, congestive heart failure; CNS, central nervous system; CrCl, creatinine clearance; CV, cardiovascular; GI, gastrointestinal; HBP, high blood pressure; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

myelosuppression 21–25 days after a dose but causes prominent nausea on day 1. Temozolomide is structurally related to dacarbazine but was designed to be activated by nonenzymatic hydrolysis in tumors and is bioavailable orally. Brain tumors with alkylguanine alkyl transferase deficiency are selectively susceptible to temozolomide, which alkylates the O^6 position of guanine.

Cisplatin was discovered fortuitously by observing that bacteria present in electrolysis solutions with platinum electrodes could not divide. Only the *cis* diamine configuration is active as an antitumor agent. In the intracellular environment, a chloride is lost from each position, being replaced by a water molecule. The resulting positively charged species is an efficient bifunctional interactor with DNA, forming Pt-based cross-links. Cisplatin requires administration with adequate hydration, including forced diuresis with mannitol to prevent kidney damage; even with the use of hydration, gradual decrease in kidney function is common, along with noteworthy anemia. Hypomagnesemia frequently attends cisplatin use and can lead to hypocalcemia and tetany. Other common toxicities include neurotoxocity with stocking-and-glove sensorimotor neuropathy. Hearing loss occurs in 50% of patients treated with conventional doses. Cisplatin is intensely emetogenic, requiring prophylactic antiemetics. Myelosuppression is less evident than with other alkylating agents. Chronic vascular toxicity (Raynaud's phenomenon, coronary artery disease) is a more unusual toxicity. Carboplatin displays less nephro-, oto-, and neurotoxicity. However, myelosuppression is more frequent, and because the drug is exclusively cleared through the kidney, adjustment of dose for creatinine clearance must be accomplished through use of various dosing nomograms. Oxaliplatin is a platinum analogue with noteworthy activity in colon cancers refractory to other treatments. It is prominently neurotoxic.

ANTITUMOR ANTIBIOTICS AND TOPOISOMERASE POISONS Antitumor antibiotics are substances produced by bacteria that in nature appear to provide a chemical defense against other hostile microorganisms. As a class, they bind to DNA directly and can frequently undergo electron transfer reactions to generate free radicals in close proximity to DNA, leading to DNA damage in the form of single-strand breaks or cross-links. Topoisomerase poisons include natural products or semisynthetic species derived ultimately from plants, and they modify enzymes that regulate the capacity of DNA to unwind to allow normal replication or transcription. These include topoisomerase I, which creates single-strand breaks that then rejoin following the passage of the other DNA strand through the break. Topoisomerase II creates double-strand breaks through which another segment of DNA duplex passes before rejoining. Owing to the role of topoisomerase I in the procession of the replication fork, topoisomerase I poisons cause lethality if the topoisomerase I–induced lesions are made in S-phase.

Doxorubicin can intercalate into DNA, thereby altering DNA structure, replication, and topoisomerase II function. It can also undergo reduction reactions by accepting electrons into its quinone ring system, with the capacity to undergo reoxidation to form reactive oxygen radicals after reoxidation. It causes predictable myelosuppression, alopecia, nausea, and mucositis. In addition, it causes acute cardiotoxicity in the form of atrial and ventricular dysrhythmias, but these are rarely of clinical significance. In contrast, cumulative doses >550 mg/m^2 are associated with a 10% incidence of chronic cardiomyopathy. The incidence of cardiomyopathy appears to be related to schedule (peak serum concentration), with low-dose, frequent treatment or continuous infusions better tolerated than intermittent higher-dose exposures. Cardiotoxicity has been related to iron-catalyzed oxidation and reduction of doxorubicin. Cardiotoxicity is related to peak plasma dose; thus, lower doses and continuous infusions are less likely to cause heart damage. Doxorubicin's cardiotoxicity is increased when given together with trastuzumab (Herceptin), the anti-HER2/neu antibody. Radiation recall or interaction with concomitantly administered radiation to cause local site complications is frequent. The drug is a powerful vesicant, with necrosis of tissue apparent 4–7 days after an extravasation; therefore, it should be administered into a rapidly flowing intravenous line. Dexrazoxane is an antidote to doxorubicin-induced extravasation. Doxorubicin is metabolized by the liver, so doses must be reduced by 50–75% in the presence of liver dysfunction. Daunorubicin is closely related to doxorubicin and was actually introduced first into leukemia treatment, where it remains part of curative regimens and has been shown preferable to doxorubicin owing to less mucositis and colonic damage. Idarubicin is also used in acute myeloid leukemia treatment and may be preferable to daunorubicin in activity. Encapsulation of daunorubicin into a liposomal formulation has attenuated cardiac toxicity and antitumor activity in Kaposi's sarcoma, other sarcomas, multiple myeloma, and ovarian cancer.

Bleomycin refers to a mixture of glycopeptides that have the unique feature of forming complexes with Fe^{2+} while also bound to DNA. It remains an important component of curative regimens for Hodgkin's disease and germ cell neoplasms. Oxidation of Fe^{2+} gives rise to superoxide and hydroxyl radicals. The drug causes little, if any, myelosuppression. The drug is cleared rapidly, but augmented skin and pulmonary toxicity in the presence of renal failure has led to the recommendation that doses be reduced by 50–75% in the face of a creatinine clearance <25 mL/min. Bleomycin is not a vesicant and can be administered intravenously, intramuscularly, or subcutaneously. Common side effects include fever and chills, facial flush, and Raynaud's phenomenon. The most feared complication of bleomycin treatment is pulmonary fibrosis, which increases in incidence at >300 cumulative units administered and is minimally responsive to treatment (e.g., glucocorticoids). The earliest indicator of an adverse effect is usually a decline in the carbon monoxide diffusing capacity (DLco) or coughing, although cessation of drug immediately upon documentation of a decrease in DLco may not prevent further decline in pulmonary function. Bleomycin is inactivated by a bleomycin hydrolase, whose concentration is diminished in skin and lung. Because bleomycin-dependent electron transport is dependent on O_2, bleomycin toxicity may become apparent after exposure to transient very high fraction of inspired oxygen (F_{IO_2}). Thus, during surgical procedures, patients with prior exposure to bleomycin should be maintained on the lowest F_{IO_2} consistent with maintaining adequate tissue oxygenation.

Mitoxantrone is a synthetic compound that was designed to recapitulate features of doxorubicin but with less cardiotoxicity. It is quantitatively less cardiotoxic (comparing the ratio of cardiotoxic to therapeutically effective doses), but is still associated with a 10% incidence of cardiotoxicity at cumulative doses of >150 mg/m^2. It also causes alopecia. Etoposide binds directly to topoisomerase II and DNA in a reversible ternary complex. It stabilizes the covalent intermediate in the enzyme's action where the enzyme is covalently linked to DNA. Prominent clinical effects include myelosuppression, nausea, and transient hypotension related to the speed of administration of the agent. Etoposide is a mild vesicant but is relatively free from other large-organ toxicities. Camptothecins target topoisomerase I. Topotecan is a camptothecin-derivative approved for use in gynecologic tumors and small-cell lung cancer. Toxicity is limited to myelosuppression and mucositis. CPT-11, or irinotecan, is a camptothecin with evidence of activity in colon carcinoma. In addition to myelosuppression, it causes a secretory diarrhea related to the toxicity of a metabolite called SN-38. Levels of SN-38 are particularly high in the setting of Gilbert's disease, characterized by defective glucuronyl transferase and indirect hyperbilirubinemia, a condition that affects about 10% of the white population in the United States. The diarrhea can be treated effectively with loperamide or octreotide.

ANTIMETABOLITES A broad definition of antimetabolites would include compounds with structural similarity to precursors of purines or pyrimidines, or compounds that interfere with purine or pyrimidine synthesis. Some antimetabolites can cause DNA damage indirectly, through misincorporation into DNA, abnormal timing or progression through DNA synthesis, or altered function of pyrimidine and purine biosynthetic enzymes. They tend to convey greatest toxicity to cells in S-phase, and the degree of toxicity increases with duration of exposure. Common toxic manifestations include stomatitis, diarrhea, and myelosuppression. Second malignancies are not associated with their use.

Methotrexate inhibits dihydrofolate reductase, which regenerates reduced folates from the oxidized folates produced when thymidine monophosphate is formed from deoxyuridine monophosphate.

Without reduced folates, cells die a "thymine-less" death. *N*5-Tetrahydrofolate or *N*5-formyltetrahydrofolate (leucovorin) can bypass this block and rescue cells from methotrexate, which is maintained in cells by polyglutamylation. The drug and other reduced folates are transported into cells by a membrane carrier, and high concentrations of drug can bypass this carrier and allow diffusion of drug directly into cells. These properties have suggested the design of "high-dose" methotrexate regimens with leucovorin rescue of normal marrow and mucosa as part of curative approaches to osteosarcoma in the adjuvant setting and hematopoietic neoplasms of children and adults. Methotrexate is cleared by the kidney via both glomerular filtration and tubular secretion, and toxicity is augmented by renal dysfunction and drugs such as salicylates, probenecid, and nonsteroidal anti-inflammatory agents that undergo tubular secretion. With normal renal function, 15 mg/m^2 leucovorin will rescue 10^{-8}–10^{-6} *M* methotrexate in 3–4 doses. However, with decreased creatinine clearance, doses of 50–100 mg/m^2 are continued until methotrexate levels are $<5 \times 10^{-8}$ *M*. In addition to bone marrow suppression and mucosal irritation, methotrexate can cause renal failure itself at high doses owing to crystallization in renal tubules; therefore, high-dose regimens require alkalinization of urine with increased flow by hydration. Methotrexate can be sequestered in third-space collections and diffuse back into the general circulation, causing prolonged myelosuppression. Less frequent adverse effects include reversible increases in transaminases and hypersensitivity-like pulmonary syndrome. Chronic low-dose methotrexate can cause hepatic fibrosis. When administered to the intrathecal space, methotrexate can cause chemical arachnoiditis and CNS dysfunction.

Pemetrexed is a folate-directed antimetabolite. It inhibits the activity of several enzymes, including thymidylate synthetase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, thereby affecting the synthesis of both purine and pyrimidine nucleic acid precursors. To avoid significant toxicity to the normal tissues, patients receiving pemetrexed should also receive low-dose folate and vitamin B_{12} supplementation. Pemetrexed has notable activity against certain lung cancers and, in combination with cisplatin, also against mesotheliomas. Pralatrexate is an antifolate approved for use in T-cell lymphoma that is very efficiently transported into cancer cells.

5-Fluorouracil (5FU) represents an early example of "rational" drug design in that it originated from the observation that tumor cells incorporate radiolabeled uracil more efficiently into DNA than normal cells, especially gut. 5FU is metabolized in cells to 5′FdUMP, which inhibits TS. In addition, misincorporation can lead to single-strand breaks, and RNA can aberrantly incorporate FUMP. 5FU is metabolized by dihydropyrimidine dehydrogenase, and deficiency of this enzyme can lead to excessive toxicity from 5FU. Oral bioavailability varies unreliably, but prodrugs such as capecitabine have been developed that allow at least equivalent activity to many parenteral 5FU-based approaches. Intravenous administration of 5FU leads to bone marrow suppression after short infusions but to stomatitis after prolonged infusions. Leucovorin augments the activity of 5FU by promoting formation of the ternary covalent complex of 5FU, the reduced folate, and TS. Less frequent toxicities include CNS dysfunction, with prominent cerebellar signs, and endothelial toxicity manifested by thrombosis, including pulmonary embolus and myocardial infarction.

Cytosine arabinoside (ara-C) is incorporated into DNA after formation of ara-CTP, resulting in S-phase–related toxicity. Continuous infusion schedules allow maximal efficiency, with uptake maximal at 5–7 μ*M*. Ara-C can be administered intrathecally. Adverse effects include nausea, diarrhea, stomatitis, chemical conjunctivitis, and cerebellar ataxia. Gemcitabine is a cytosine derivative that is similar to ara-C in that it is incorporated into DNA after anabolism to the triphosphate, rendering DNA susceptible to breakage and repair synthesis, which differs from that in ara-C in that gemcitabine-induced lesions are very inefficiently removed. In contrast to ara-C, gemcitabine appears to have useful activity in a variety of solid tumors, with limited nonmyelosuppressive toxicities.

6-Thioguanine and 6-mercaptopurine (6MP) are used in the treatment of acute lymphoid leukemia. Although administered orally, they display variable bioavailability. 6MP is metabolized by xanthine oxidase and therefore requires dose reduction when used with allopurinol. 6MP is also metabolized by thiopurine methyltransferase; genetic deficiency of thiopurine methyltransferase results in excessive toxicity.

Fludarabine phosphate is a prodrug of F-adenine arabinoside (F-ara-A), which in turn was designed to diminish the susceptibility of ara-A to adenosine deaminase. F-ara-A is incorporated into DNA and can cause delayed cytotoxicity even in cells with low growth fraction, including chronic lymphocytic leukemia and follicular B-cell lymphoma. CNS and peripheral nerve dysfunction and T-cell depletion leading to opportunistic infections can occur in addition to myelosuppression. 2-Chlorodeoxyadenosine is a similar compound with activity in hairy cell leukemia. Hydroxyurea inhibits ribonucleotide reductase, resulting in S-phase block. It is orally bioavailable and useful for the acute management of myeloproliferative states.

Asparaginase is a bacterial enzyme that causes breakdown of extracellular asparagine required for protein synthesis in certain leukemic cells. This effectively stops tumor cell DNA synthesis, as DNA synthesis requires concurrent protein synthesis. The outcome of asparaginase action is therefore very similar to the result of the small-molecule antimetabolites. Because asparaginase is a foreign protein, hypersensitivity reactions are common, as are effects on organs such as pancreas and liver that normally require continuing protein synthesis. This may result in decreased insulin secretion with hyperglycemia, with or without hyperamylasemia and clotting function abnormalities. Close monitoring of clotting functions should accompany use of asparaginase. Paradoxically, owing to depletion of rapidly turning over anticoagulant factors, thromboses particularly affecting the CNS may also be seen with asparaginase.

MITOTIC SPINDLE INHIBITORS Microtubules are cellular structures that form the mitotic spindle, and in interphase cells, they are responsible for the cellular "scaffolding" along which various motile and secretory processes occur. Microtubules are composed of repeating noncovalent multimers of a heterodimer of α and β isoform of the protein tubulin. Vincristine binds to the tubulin dimer with the result that microtubules are disaggregated. This results in the block of growing cells in M-phase; however, toxic effects in G_1 and S-phase are also evident, reflecting effects on normal cellular activities of microtubules. Vincristine is metabolized by the liver, and dose adjustment in the presence of hepatic dysfunction is required. It is a powerful vesicant, and infiltration can be treated by local heat and infiltration of hyaluronidase. At clinically used intravenous doses, neurotoxicity in the form of glove-and-stocking neuropathy is frequent. Acute neuropathic effects include jaw pain, paralytic ileus, urinary retention, and the syndrome of inappropriate antidiuretic hormone secretion. Myelosuppression is not seen. Vinblastine is similar to vincristine, except that it tends to be more myelotoxic, with more frequent thrombocytopenia and also mucositis and stomatitis. Vinorelbine is a vinca alkaloid that appears to have differences in resistance patterns in comparison to vincristine and vinblastine; it may be administered orally.

The taxanes include paclitaxel and docetaxel. These agents differ from the vinca alkaloids in that the taxanes stabilize microtubules against depolymerization. The "stabilized" microtubules function abnormally and are not able to undergo the normal dynamic changes of microtubule structure and function necessary for cell cycle completion. Taxanes are among the most broadly active antineoplastic agents for use in solid tumors, with evidence of activity in ovarian cancer, breast cancer, Kaposi's sarcoma, and lung tumors. They are administered intravenously, and paclitaxel requires use of a Cremophor-containing vehicle that can cause hypersensitivity reactions. Premedication with dexamethasone (8–16 mg orally or intravenously 12 and 6 h before treatment) and diphenhydramine (50 mg) and cimetidine (300 mg), both 30 min before treatment, decreases but does not eliminate the risk of hypersensitivity reactions to the paclitaxel vehicle. A protein-bound formulation of paclitaxel (called *nab-paclitaxel*) has at least equivalent antineoplastic activity and decreased risk of hypersensitivity reactions. Paclitaxel may also cause hypersensitivity reactions, myelosuppression, neurotoxicity in the form of glove-and-stocking numbness, and paresthesia. Docetaxel causes comparable degrees of

myelosuppression and neuropathy. Docetaxel uses a polysorbate 80 formulation that can cause fluid retention in addition to hypersensitivity reactions,; dexamethasone premedication with or without antihistamines is frequently used. Cabazitaxel is a taxane with somewhat better activity in prostate cancers than earlier generations of taxanes, perhaps due to superior delivery to sites of disease.

Epothilones represent a class microtubule-stabilizing agents that have been conscientiously optimized for activity in taxane-resistant tumors. Ixabepilone has clear evidence of activity in breast cancers resistant to taxanes and anthracyclines such as doxorubicin. It retains acceptable expected side effects, including myelosuppression, and can also cause peripheral sensory neuropathy. Eribulin is a microtubule-directed agent with activity in patients who have had progression of disease on taxanes. It alters dynamics of microtubule re-modeling in cells.

Targeted Chemotherapy • **HORMONE RECEPTOR–DIRECTED THERAPY** Steroid hormone receptor–related molecules have emerged as prominent targets for small molecules useful in cancer treatment. When bound to their cognate ligands, these receptors can alter gene transcription and, in certain tissues, induce apoptosis. The pharmacologic effect is a mirror or parody of the normal effects of the agents acting on nontransformed normal tissues. While in some cases, such as breast cancer, demonstration of the target hormone receptor is necessary, in other cases such prostate cancer (androgen receptor) and lymphoid neoplasms (glucocorticoid receptor), the relevant receptor is always present in the tumor.

Glucocorticoids are generally given in "pulsed" high doses in leukemias and lymphomas, where they induce cell death in tumor cells. Cushing's syndrome and inadvertent adrenal suppression on withdrawal from high-dose glucocorticoids can be significant complications, along with infections common in immunosuppressed patients, in particular *Pneumocystis* pneumonia, which classically appears a few days after completing a course of high-dose glucocorticoids.

Tamoxifen is a partial estrogen receptor antagonist; it has a tenfold greater antitumor activity in breast cancer patients whose tumors express estrogen receptors than in those who have low or no levels of expression. It might be considered the prototypic "molecularly targeted" agent. Owing to its agonistic activities in vascular and uterine tissue, side effects include a somewhat increased risk of cardiovascular complications, such as thromboembolic phenomena, and a small increased incidence of endometrial carcinoma, which appears after chronic use (usually >5 years). Progestational agents—including medroxyprogesterone acetate, androgens including fluoxymesterone (Halotestin), and, paradoxically, estrogens—have approximately the same degree of activity in primary hormonal treatment of breast cancers that have elevated expression of estrogen receptor protein. Estrogen itself is not used often owing to prominent cardiovascular and uterotropic activity.

Aromatase refers to a family of enzymes that catalyze the formation of estrogen in various tissues, including the ovary and peripheral adipose tissue and some tumor cells. Aromatase inhibitors are of two types, the irreversible steroid analogues such as exemestane and the reversible inhibitors such as anastrozole or letrozole. Anastrozole is superior to tamoxifen in the adjuvant treatment of breast cancer in postmenopausal patients with estrogen receptor–positive tumors. Letrozole treatment affords benefit following tamoxifen treatment. Adverse effects of aromatase inhibitors may include an increased risk of osteoporosis.

Metastatic prostate cancer is treated by androgen deprivation. Orchiectomy causes responses in 80% of patients. In the event that orchiectomy is not accepted by the patient, testicular androgen suppression can also be effected by luteinizing hormone–releasing hormone (LHRH) agonists such as leuprolide and goserelin. These agents cause tonic stimulation of the LHRH receptor, with the loss of its normal pulsatile activation resulting in decreased output of LH by the anterior pituitary. Therefore, as primary hormonal manipulation in prostate cancer, one can choose orchiectomy or leuprolide, but not both. The addition of androgen receptor blockers, including flutamide or bicalutamide, is of uncertain additional benefit in extending overall response duration, although pretreatment with these agents before LHRH agonists is important to avoid a surge in testosterone after initial LH release. Enzalutamide also binds to the androgen receptor and antagonizes androgen action in a mechanistically distinct way. Somewhat analogous to inhibitors of aromatase, agents have been derived that inhibit testosterone and other androgen synthesis in the testis, adrenal gland, and prostate tissue. Abiraterone inhibits 17 α-hydroxylase/C17,20 lyase (CYP 17A1) and has been shown to be active in prostate cancer patients experiencing progression despite androgen blockade.

Tumors that respond to a primary hormonal manipulation may frequently respond to second and third hormonal manipulations. Thus, breast tumors that had previously responded to tamoxifen have, on relapse, notable response rates to withdrawal of tamoxifen itself or to subsequent addition of an aromatase inhibitor or progestin. Likewise, initial treatment of prostate cancers with leuprolide plus flutamide may be followed after disease progression by response to withdrawal of flutamide. These responses may result from the removal of antagonists from mutant steroid hormone receptors that have come to depend on the presence of the antagonist as a growth-promoting influence.

DIAGNOSTICALLY GUIDED TARGETED THERAPY The basis for discovery of drugs of this type was the prior knowledge of oncogene directed pathways driving tumor growth. **Figure 69-4** summarizes how FDA-approved targeted agents act. In the case of diagnostically guided targeted chemotherapy, prior demonstration of a specific target is necessary to guide the rational use of the agent, while in the case of targeted agents directed at oncogenic pathways, specific diagnosis of pathway activation is not yet necessary or in some cases feasible, although this is an area of ongoing clinical research. **Table 69-5** lists currently approved targeted chemotherapy agents, with features of their use.

In hematologic tumors, the prototypic agent of this type is imatinib, which targets the ATP binding site of the $p210^{bcr\text{-}abl}$ protein tyrosine kinase that is formed as the result of the chromosome 9;22 translocation producing the Philadelphia chromosome in CML. Imatinib is superior to interferon (IFN) plus chemotherapy in the initial treatment of the chronic phase of this disorder. It has lesser activity in the blast phase of CML, where the cells may have acquired additional mutations in $p210^{bcr\text{-}abl}$ itself or other genetic lesions. Its side effects are relatively tolerable in most patients and include hepatic dysfunction, diarrhea, and fluid retention. Rarely, patients receiving imatinib have decreased cardiac function, which may persist after discontinuation of the drug. The quality of response to imatinib enters into the decision about when to refer patients with CML for consideration of transplant approaches. Nilotinib is a tyrosine protein kinase inhibitor with a similar spectrum of activity to imatinib, but with increased potency and perhaps better tolerance by certain patients. Dasatinib, another inhibitor of the $p210^{bcr\text{-}abl}$ oncoproteins, is active in certain mutant variants of $p210^{bcr\text{-}abl}$ that are refractory to imatinib and arise during therapy with imatinib or are present de novo. Dasatinib also has inhibitory action against kinases belonging to the src tyrosine protein kinase family; this activity may contribute to its effects in hematopoietic tumors and suggest a role in solid tumors where src kinases are active. The T315I mutant of $p210^{bcr\text{-}abl}$ is resistant to imatinib, nilotinib, bosutinib, and dasatinib; ponatinib has activity in patients with this $p210^{bcr\text{-}abl}$ variant, but ponatinib has noteworthy associated thromboembolic toxicity. Use of this class of targeted agents is thus critically guided not only by the presence of the $p210^{bcr\text{-}abl}$ tyrosine kinase, but also by the presence of different mutations in the ATP binding site.

All-*trans*-retinoic acid (ATRA) targets the PML-retinoic acid receptor (RAR) α fusion protein, which is the result of the chromosome 15;17 translocation pathogenic for most forms of APL. Administered orally, it causes differentiation of the neoplastic promyelocytes to mature granulocytes and attenuates the rate of hemorrhagic complications. Adverse effects include headache with or without pseudotumor cerebri and gastrointestinal and cutaneous toxicities.

In epithelial solid tumors, the small-molecule epidermal growth factor (EGF) antagonists act at the ATP binding site of the EGF receptor

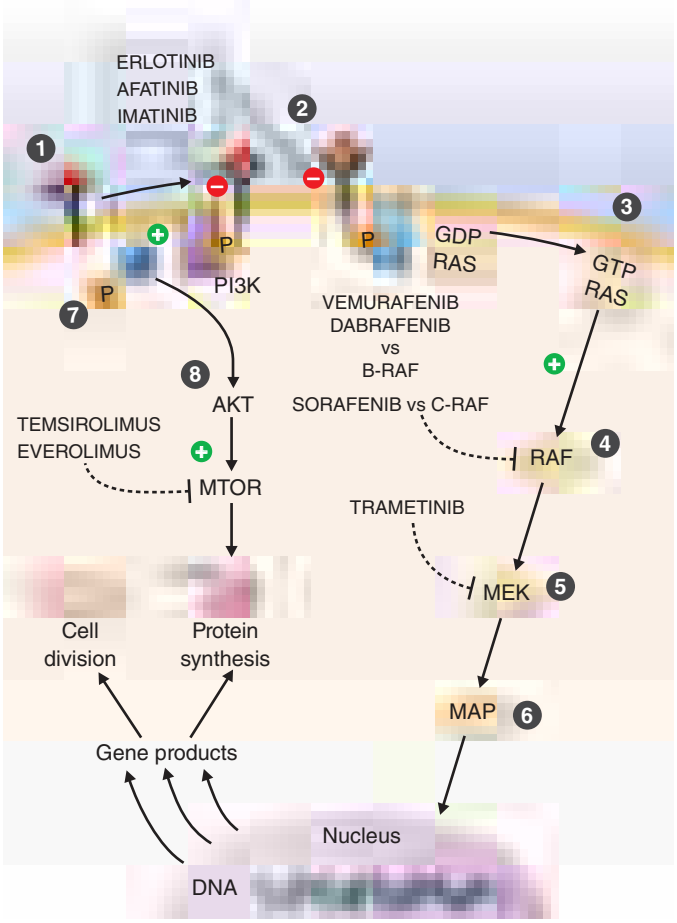

FIGURE 69-4 Targeted chemotherapeutic agents act in most instances by interrupting cell growth factor-mediated signaling pathways. After a growth factor binds to cognate receptor (1), in many cases there is activation of tyrsosine kinase activity particularly after dimerization of the receptors (2). This leads to autophosphorylation of the receptor and docking of "adaptor" proteins. One important pathway activated occurs after exchange of GDP for GTP in the RAS family of protooncogene products (3). GTP-RAS activates the RAF proto-oncogene kinase (4), leading to a phosphorylation cascade of kinases (5, 6) that ultimately impart signals to regulators of gene function to produce transcripts which activate cell cycle progression and increase protein synthesis. In parallel, tyrosine phosphorylated receptors can activate the phosphatidylinositol-3-kinase to produce the phosphorylated lipid phosphatidyl-inositol-3-phosphate (7). This leads to the activation of the AKT kinase (8) which in turn stimulates the mammalian "Target of Rapamycin" kinase (mTOR), which directly increases the translation of key mRNAs for gene products regulating cell growth. Erlotinib and afatinib, are examples of Epidermal Growth Factor receptor tyrosine kinase inhibitors; imatinib can act on the nonreceptor tyrosine kinase bcr-abl or c-KIT membrane bound tyrosine kinase. Vemurafenib and Dabrafenib act on the B isoform of RAF uniquely in melanoma, and c-RAF is inhibited by sorafenib. Trametinib acts on MEK. Temsirolimus and everolimus inhibit mTOR kinase to downregulate translation of oncogenic mRNAs.

tyrosine kinase. In early clinical trials, gefitinib showed evidence of responses in a small fraction of patients with non-small-cell lung cancer (NSCLC). Side effects were generally acceptable, consisting mostly of acneiform rash (treated with glucocorticoid creams and clindamycin gel) and diarrhea. Subsequent analysis of responding patients revealed a high frequency of activating mutations in the EGF receptor. Patients with such activating mutations who initially responded to gefitinib but who then had progression of the disease then acquired additional mutations in the enzyme, analogous functionally to mutational variants responsible for imatinib resistance in CML. Erlotinib is another EGF receptor tyrosine kinase antagonist where the presence of EGF receptor tyrosine kinase mutations has recently been shown to be a basis for recommending erlotinib and afatinib for first-line treatment of advanced NSCLC. Osimertinib is uniquely active in lung cancers with the T790M mutation. Likewise, crizotinib targeting the *alk* protooncogene fusion protein has value in the initial treatment of *alk*-positive NSCLC. Lapatinib is a tyrosine kinase inhibitor with both EGF receptor and HER2/neu antagonist activity, which is important in the treatment of breast cancers expressing the HER2/neu oncoprotein.

In addition to the $p210^{bcr\text{-}abl}$ kinase, imatinib also has activity against the c-kit tyrosine kinase (the receptor for the *steel* growth factor, also called stem cell factor) and the platelet-derived growth factor receptor (PDGFR), both of which can be expressed in gastrointestinal stromal sarcoma (GIST). Imatinib has found clinical utility in GIST, a tumor previously notable for its refractoriness to chemotherapeutic approaches. Imatinib's degree of activity varies with the specific mutational variant of kit or PDGFR present in a particular patient's tumor.

The *BRAF* V600E mutation has been detected in a notable fraction of melanomas, thyroid tumors, and hairy cell leukemia, and preclinical models supported the concept that *BRAF* V600E drives oncogenic signaling in these tumors. Vemurafenib and dabrafenib, with selective capacity to inhibit the *BRAF* V600E serine kinase activity, were each shown to cause noteworthy responses in patients with *BRAF* V600E–mutated melanomas, although early relapse occurred in many patients treated with the drugs as single agents. Trametinib, acting downstream of *BRAF* V600E by directly inhibiting the MEK serine kinase by a non-ATP binding site mechanism, also displayed noteworthy responses in *BRAF* V600E–mutated melanomas, and the combination of trametinib and dabrafenib is even more active, by targeting the *BRAF* V600E–driven pathway at two points in the pathway leading to gene activation.

ONCOGENICALLY ACTIVATED PATHWAYS Agents in this class also target specific regulatory molecules in promoting the viability of tumor cells, but they do not require the diagnostically verified presence of a particular target or target variant at this time.

"Multitargeted" kinase antagonists are small-molecule ATP site-directed antagonists that inhibit more than one protein kinase and have value in the treatment of several solid tumors. Drugs of this type with prominent activity against the vascular endothelial growth factor receptor (VEGFR) tyrosine kinase have activity in renal cell carcinoma. Sorafenib is a VEGFR antagonist with activity against the *raf* serine-threonine protein kinase, and regorafenib is a closely related drug with value in relapsed advanced colon cancer. Pazopanib also prominently targets VEGFR and has activity in renal carcinoma and soft tissue sarcomas. Sunitinib has anti-VEGFR, anti-PDGFR, and anti-c-kit activity. It causes prominent responses and stabilization of disease in renal cell cancers and GISTs. Side effects for agents with anti-VEGFR activity prominently include hypertension, proteinuria, and, more rarely, bleeding and clotting disorders and perforation of scarred gastrointestinal lesions. Also encountered are fatigue, diarrhea, and the hand-foot syndrome, with erythema and desquamation of the distal extremities, in some cases requiring dose modification, particularly with sorafenib.

Temsirolimus and everolimus are mammalian target of rapamycin (mTOR) inhibitors with activity in renal cancers. They produce stomatitis, fatigue, and some hyperlipidemia (10%), myelosuppression (10%), and rare lung toxicity. Everolimus is also useful in patients with hormone receptor–positive breast cancers displaying resistance to hormonal inhibition and in certain neuroendocrine and brain tumors, the latter arising in patients with sporadic or inherited mutations in the pathway activating mTOR. Cyclin dependent kinases (CDKs) are activated as the result of oncogene pathway activity. Palbociclib, a selective inhibititor of CDKs 4 and 6, has noteworthy activity in conjunction with the mTOR inhibitors in advanced breast cancers also expressing the estrogen receptor.

In hematologic neoplasms, bortezomib is an inhibitor of the proteasome, the multisubunit assembly of protease activities responsible for the selective degradation of proteins important in regulating activation of transcription factors, including nuclear factor-κB (NF-κB) and proteins regulating cell cycle progression. It has activity in multiple myeloma and certain lymphomas. Adverse effects include neuropathy, orthostatic hypotension with or without hyponatremia, and reversible thrombocytopenia. Carfilzomib is a proteasome inhibitor chemically unrelated to bortezomib without prominent neuropathy, but with

TABLE 69-5 Molecularly Targeted Agents

DRUG	TARGET	ADVERSE EVENTS	NOTES
Diagnostically Guided Protein Kinase Antagonists			
Imatinib	Bcr-Abl fusion protein (CML/ALL); c-kit mutants, PDGFR variants (GI stromal tumor; eosinophilic syndromes)	Nausea Periorbital edema Rare CHF QTc prolongation	Myelosuppression not frequent in solid tumor indications
Nilotinib	Bcr-Abl fusion protein (CML) and some imatinib-resistant variants	Interaction with CYP3A4-metabolized drugs CHF Hepatotoxicity Hypothyroidism	Chronic phase and in patients resistant to imatinib
Dasatinib	Bcr-Abl fusion protein (CML/ALL); wild-type and imatinib-resistant mutants	Myelosuppression (bleeding, infection) Pulmonary hypertension CHF Fluid retention QTc prolongation	Chronic phase and imatinib or nilotinib resistant
Bosutinib	Bcr-Abl fusion protein (CML); wild-type and imatinib-resistant mutants	Myelosuppression Hepatic QTc prolongation	Chronic phase and imatinib or nilotinib resistant
Ponatinib	T315I mutation of Bcr-Abl fusion protein (CML)	Clotting Hepatic CHF Pancreatitis Neuropathy Rash	
Gefitinib	First-line treatment of NSCLC with ATP site mutation of EGFR	Diarrhea Interstitial pneumonitis	In the United States, only with prior documented benefit in second-line treatment of NSCLC
Erlotinib	First-line treatment of NSCLC with ATP site mutation of EGFR; second-line treatment of wild-type EGFR NSCLC	Rash Diarrhea Rare interstitial pneumonitis	1 h before, 2 h after meals
Afatinib	First-line treatment of NSCLC with ATP site mutation of EGFR	Diarrhea Cutaneous	Interacts with Pgp inhibitors
Crizotinib	EML4-Alk fusion protein	Interstitial pneumonitis Hepatic QTc prolongation Bradycardia	
Vemurafenib	*BRAF* V600E in melanoma	Nausea Rash Cutaneous Second cutaneous neoplasms	
Dabrafenib	*BRAF* V600E in melanoma	Cutaneous Second cutaneous neoplasms	
Trametinib	*BRAF* V600E in melanoma (both as single agent and in combination with dabrafenib)	Rash Diarrhea Lymphedema	In combination with dabrafenib, second neoplasms, hemorrhage, venous thrombosis, CHF, ocular, hyperglycemia
DRUG	**INDICATION**	**ADVERSE EVENTS**	**NOTES**
Diagnostically Guided Retinoid			
Tretinoin	APL t(15,17)	Teratogenic Cutaneous	APL differentiation syndrome: pulmonary dysfunction/infiltrate, pleural/pericardial effusion, fever
Multikinase Inhibitors			
Sorafenib	Renal cell, hepatocellular, differentiated thyroid carcinoma	Diarrhea Hand-foot syndrome Other rash Hypertension CHF	Targets c-raf, VEGFR
Pazopanib	Renal cell carcinoma, soft tissue sarcoma	Fatigue Diarrhea/GI Hypertension Thromboses QTc	Target VEGFR, c-kit, PDGFR

(*Continued*)

TABLE 69-5 Molecularly Targeted Agents (Continued)

DRUG	INDICATION	ADVERSE EVENTS	NOTES
Regorafenib	Second-line colorectal cancer; GI stromal tumor	Hypertension Hand-foot syndrome Thromboses Perforations	VEGFR/TIE2
Sunitinib	Renal cell carcinoma, pancreatic neuroendocrine tumor, GI stromal tumor	Fatigue Diarrhea Neutropenia	Target VEGFR
Vandetanib	Medullary thyroid cancer	Diarrhea Rash Hypertension Prolonged QTc Thromboses	Target VEGFR, ret, EGFR
Cabozantinib	Medullary thyroid cancer	Hypertension Wound healing Fistulas Osteonecrosis Proteinuria	Target VEGFR, c-met
Axitinib	Renal cell carcoinoma, second line	Diarrhea/other GI Fatigue Hand-foot syndrome	Target VEGFR, PDGFR, c-kit
Osimertinib	Non-small cell lung cancer, EGFR T790M mutation	Interstitial lung disease QTc prolongation Cardiomyopathy	
Proteasome Inhibitors			
Bortezomib	Multiple myeloma, mantle cell lymphoma	Neuropathy Thrombocytopenia GI	
Carfilzomib	Multiple myeloma, second line	Infusion reaction CHF Thrombocytopenia Pulmonary Tumor lysis	
Histone Deacetylase Inhibitors			
Vorinostat	Cutaneous T-cell lymphoma, second line	Fatigue Diarrhea Thrombocytopenia Embolism	
Romidepsin	Cutaneous T-cell lymphoma, second line	Nausea Vomiting Cytopenias Cardiac conduction	
mTOR Inhibitors			
Temsirolimus	Renal cell carcinoma, second line or poor prognosis	Stomatitis Thrombocytopenia Nausea Anorexia, fatigue Metabolic (glucose, lipid)	
Everolimus	Renal cell carcinoma, advanced; subependymal giant-cell astrocytoma; breast cancer, hormone receptor positive, resistant to antiestrogen; pancreatic neuroendocrine	Stomatitis Fatigue	
Miscellaneous			
Arsenic trioxide	APL	↑ QT_c	APL differentiation syndrome (see under tretinoin)
Vismodegib	Metastatic basal cell carcinoma	GI Hair loss Fatigue Muscle spasm Dysgeusia	Target smoothened receptor in hedgehog pathway

Abbreviations: APL, acute promyelocytic leukemia; ALL, acute lymphocytic leukemia; CHF, congestive heart failure; CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; mTOR, mammalian target of rapamycin kinase; NSCLC, non-small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; Pgp, P-glycoprotein; VEGFR, vascular endothelial growth factor receptor.

evidence of a cytokine release syndrome, which can be a cardiopulmonary stress. Other agents active in multiple myeloma and certain other hematologic neoplasms include the immunomodulatory agents related to thalidomide, including lenalidomide and pomalidomide. All these agents collectively inhibit aberrant angiogenesis in the bone marrow microenvironment, as well as influence stromal cell immune functions to alter the cytokine milieu supporting the growth of myeloma cells. Thalidomide, although clinically active, has prominent cytopenic, neuropathic, procoagulant, and CNS toxicities that have been somewhat attenuated in the other drugs of the class, although use of these agents frequently entails concomitant anticoagulant prophylaxis.

Ibrutinib and idelalisib are representative of novel classes of inhibitors directed at Bruton's tyrosine kinase and phosphatidyl inositide-3 kinase-δ, respectively, expressed in normal and neoplastic B cells. Initially approved for use in mantle cell lymphoma and chronic lymphocytic leukemia, respectively, they are potentially applicable to a number of B-cell neoplasms that depend on signals through the B-cell antigen receptor. Janus kinases likewise function downstream of a variety of cytokine receptors to amplify cytokine signals, and Janus kinase inhibitors including ruxolitinib have approved activity in myelofibrosis to ameliorate splenomegaly and systemic symptoms.

Vorinostat is an inhibitor of histone deacetylases, which are responsible for maintaining the proper orientation of histones on DNA, with resulting capacity for transcriptional readiness. Acetylated histones allow access of transcription factors to target genes and therefore increase expression of genes that are selectively repressed in tumors. The result can be differentiation with the emergence of a more normal cellular phenotype, or cell cycle arrest with expression of endogenous regulators of cell cycle progression. Vorinostat is approved for clinical use in cutaneous T-cell lymphoma, with dramatic skin clearing and very few side effects. Romidepsin is a distinct molecular class of histone deacetylase inhibitor also active in cutaneous T-cell lymphoma. Panobinostat has activity in multiple myeloma. DNA methyltransferase inhibitors, including 5-aza-cytidine and 2′-deoxy-5-azacytidine (decitabine), can also increase transcription of genes "silenced" during the pathogenesis of a tumor by causing demethylation of the methylated cytosines that are acquired as an "epigenetic" (i.e., after the DNA is replicated) modification of DNA. These drugs were originally considered antimetabolites but have clinical value in myelodysplastic syndromes and certain leukemias when administered at low doses.

Additional toxicities with several therapies affecting ongogene-activated pathways include poorly predicted hepatic and cardiac toxicities (imatinib, dasatinib, sorafenib, pazopanib) or cardiac conduction deficits including prolonged QT interval (pazopanib), and atrial fibrillation (ibrutinib). The occurrence of new cardiac or liver abnormalities in a patient receiving treatment with a protein kinase antagonist should lead to a consideration of the risk versus benefit and the possible relation of the agent to the new adverse event. The existence of prior cardiac dysfunction is a relative contraindication to the use of certain targeted therapies (e.g., trastuzumab), although each patient's needs should be individualized.

CANCER BIOLOGIC THERAPY

Principles The goal of biologic therapy is to manipulate the host–tumor interaction in favor of the host, potentially at an optimum biologic dose that might be different than the MTD. As a class, biologic therapies may be distinguished from molecularly targeted agents in that many biologic therapies require an active response (e.g., reexpression of silenced genes or antigen expression) on the part of the tumor cell or on the part of the host (e.g., immunologic effects) to allow therapeutic effect. This may be contrasted with the more narrowly defined antiproliferative or apoptotic response that is the ultimate goal of molecularly targeted agents discussed above. However, there is much commonality in the strategies to evaluate and use molecularly targeted and biologic therapies.

Antibody-Mediated Therapeutic Approaches In general, antibodies are not very effective at killing cancer cells. Because the tumor seems to influence the host toward making antibodies rather than generating cellular immunity, it is inferred that antibodies are easier for the tumor to fend off. Many patients can be shown to have serum antibodies directed at their tumors, but these do not appear to influence disease progression. However, the ability to grow very large quantities of high-affinity antibody directed at a tumor has led to the application of antibodies in the treatment of cancer. In this approach, antibodies are derived where the antigen-combining regions are grafted onto human immunoglobulin gene products (chimerized or humanized) or derived de novo from mice bearing human immunoglobulin gene loci. Three general strategies have emerged using antibodies. *Tumor-regulatory antibodies* target tumor cells directly or indirectly to modulate intracellular functions or attract immune or stromal cells. *Immunoregulatory antibodies* target antigens expressed on the tumor cells or host immune cells to modulate primarily the host's immune responsiveness to the tumor. Finally, *antibody conjugates* can be made with the antibody linked to drugs, toxins, or radioisotopes to target these "warheads" for delivery to the tumor. **Table 69-6** lists features of currently used or promising antibodies for cancer treatment.

TUMOR-REGULATORY ANTIBODIES Humanized antibodies against the CD20 molecule expressed on B-cell lymphomas (rituximab and ofatumumab) are exemplary of antibodies that affect both signaling events driving lymphomagenesis as well as activating immune responses against B-cell neoplasms. They are used as single agents and in combination with chemotherapy and radiation in the treatment of B-cell neoplasms. Obinutuzumab is an antibody with an altered glycosylation that enhances its ability to activate killer cells; it is also directed against CD20 and is of value in chronic lymphocytic leukemia. It seems to be more effective in this setting than rituximab.

The HER2/neu receptor overexpressed on epithelial cancers, especially breast cancer, was initially targeted by trastuzumab, with noteworthy activity in potentiating the action of chemotherapy in breast cancer as well as some evidence of single-agent activity. Trastuzumab also appears to interrupt intracellular signals derived from HER2/neu and to stimulate immune mechanisms. The anti-HER2 antibody pertuzumab, specifically targeting the domain of HER2/neu responsible for dimerization with other HER2 family members, is more specifically directed against HER2 signaling function and augments the action of trastuzumab.

EGF receptor (EGFR)-directed antibodies (such as cetuximab and panitumumab) have activity in colorectal cancer refractory to chemotherapy, particularly when used to augment the activity of an additional chemotherapy program, and in the primary treatment of head and neck cancers treated with radiation therapy. The mechanism of action is unclear. Direct effects on the tumor may mediate an antiproliferative effect as well as stimulate the participation of host mechanisms involving immune cell or complement-mediated response to tumor cell–bound antibody. Alternatively, the antibody may alter the release of paracrine factors promoting tumor cell survival.

The anti-VEGF antibody bevacizumab shows little evidence of antitumor effect when used alone, but when combined with chemotherapeutic agents, it improves tumor shrinkage and time to disease progression in colorectal and nonsquamous lung cancers. The mechanism for the effect is unclear and may relate to the capacity of the antibody to alter delivery and tumor uptake of the active chemotherapeutic agent. Ziv-aflibercept is not an antibody, but a solubilized VEGF receptor VEGF binding domain, and therefore may have a distinct mechanism of action with comparable side effects.

Unintended side effects of any antibody use include infusion-related hypersensitivity reactions, usually limited to the first infusion, which can be managed with glucocorticoid and/or antihistamine prophylaxis. In addition, distinct syndromes have emerged with different antibodies. Anti-EGFR antibodies produce an acneiform rash that poorly responds to glucocorticoid cream treatment. Trastuzumab (anti-HER2) can inhibit cardiac function, particularly in patients with prior exposure to anthracyclines. Bevacizumab has a number of side effects of medical significance, including hypertension, thrombosis, proteinuria, hemorrhage, and gastrointestinal perforations with or without prior surgeries; these adverse events also occur with small-molecule drugs modulating VEGFR function.

TABLE 69-6 Antibodies Used in Cancer Treatment

DRUG	TARGET	INDICATIONS AND FEATURES OF USE
Tumor Regulatory Antibodies		
Rituximab	CD20	B cell neoplasms (also emerging role in autoimmune disease); chimeric antibody with frequent mouse-derived sequences; frequent infusion reactions, particularly on initial doses; reactivation of infections, particularly hepatitis; progressive multifocal leukoencephalopathy; tumor lysis syndrome
Ofatumumab	CD20	active in CLL; fully human antibody with distinct binding site compared to rituximab; decreased intensity infusion reactions
Trastuzumab	HER2/neu	Active in breast cancer and GI cancers expressing HER2/neu; cardiotoxicity, particularly in setting of prior anthracyclines, requires monitoring; infusion reactions
Pertuzumab	HER2/neu	Breast cancer; targets distinct binding site from trastuzumab, inhibiting dimerization of HER2 family members; infusion reactions; cardiac toxicity
Cetuximab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; head and neck cancers with radiation; rash, diarrhea, infusion reactions
Panitumumab	EGFR	Colorectal cancers with wild-type Ki-ras oncoprotein; fully humanized; decreased infusion reactions; different IgG subtype than cetuximab
Bevacizumab	VEGF	Metastatic colorectal cancer and non-small-cell lung cancer (nonsquamous) with chemotherapy; renal cancer and glioblastoma as single agents; prominent HBP, proteinuria, GI perforations, hemorrhage, thrombosis (venous and arterial)
Daratumumab	CD38	Multiple myeloma
Elotuzumab	CD319	Multiple myeloma, with revlimid and dexamethasone
Olaratumab	PDGF-R	Soft tissue sarcoma, in conjunction with doxorubicin
Immunoregulatory Antibodies		
Alemtuzumab	CD52	CLL, T-cell lymphomas; activates complement after binding to cell surface; infusion reactions, hypersensitivity, tumor lysis, activation of infections, cytopenias
Ipilimumab	CTLA4	Melanoma; inhibits the negative proliferative signal to T cells acting through CTLA4, resulting in prominent T cell activation; side effects include immune-mediated toxicity to liver, skin, pituitary, gut, which if severe calls for steroids, which inhibit antineoplastic effect
Pembrolizumab	PD-1	Non-small cell lung cancer as a first- or second-line treatment if PDL1(+) and no actionable mutations;and as a second-line treatment for head and neck squamous cell carcinoma, after platinum-based chemotherapy; can cause immune-related colitis, hepatitis, hypophysitis, nephritis, and altered thyroid function; also consider steroids for treatment of severe adverse events
Nivolumab	PD-1	Metastatic melanoma in combination with ipilimumab if B-RAF mutation negative; melanoma following treatment with ipilimumab and after a BRAF inhibitor if relevant; second-line treatment for squamous non-small cell lung cancer, renal cancer and for relapsed and refractory Hodgkin's Disease; side effects similar to pembrolizumab
Atezolizumab	PD-L1	Locally advanced or metastatic urothelial carcinoma treatment after failure of chemo- or radiotherapy; metastatic non-small cell lung cancer (NSCLC) whose disease progressed during or following platinum-containing chemotherapy, without actionable mutations

Abbreviations: CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HBP, high blood pressure; VEGF, vascular endothelial growth factor.

IMMUNOREGULATORY ANTIBODIES Purely immunoregulatory antibodies stimulate immune responses to mediate tumor-directed cytotoxicity. First-generation approaches sought to activate complement and are exemplified by alemtuzumab against CD52; these are active in chronic lymphoid leukemia and T-cell malignancies. A more refined understanding of the tumor–host interface has defined that cytotoxic tumor-directed T cells are frequently inhibited by ligands upregulated in the tumor cells. The programmed death ligand 1 (PD-L1; also known as B7-homolog 1) was initially recognized as an entity that induced T cell death through a receptor present on T cells, termed the PD receptor **(Fig. 69-5)**, which physiologically exists to regulate the intensity of the immune response. The PD family of ligands and receptors also regulates macrophage function, present in tumor stroma. These actions raised the hypothesis that antibodies directed against the PD signaling axis (both anti-PD-L1 and anti-PD) might be useful in cancer treatment by allowing reactivation of the immune response against tumors. Nivolumab, directed against the PD-1 receptor, is approved for use in renal cancer, metastatic melanoma, and non-small cell lung cancer, as well as in relapsed Hodgkin's disease. Pembrolizumab is approved for first-line treatment of metastatic non-small cell lung cancer whose tumors express the PD-L1 ligand. This development was a milestone in cancer therapeutics, replacing chemotherapy in this patient subset.

Ipilimumab, an antibody directed against the anti-CTLA4 (cytotoxic T lymphocyte antigen 4), which is expressed on T cells (not tumor cells), responds to signals from antigen-presenting cells (Fig. 69-5), and also downregulates the intensity of the T-cell proliferative response to antigens derived from tumor cells. Indeed, manipulation of the CTLA4 axis was the first demonstration that purely immunoregulatory antibody strategies directed at T-cell physiology could be safe and effective in the treatment of cancer, although it acts at a very early stage in T-cell activation and can be considered somewhat nonspecific in its basis for T-cell stimulation. Ipilimumab alone or in combination with PD1-directed antibodies, is approved for initial treatment of metastatic melanoma.

Prominent activation of autoimmune hepatic, endocrine, cutaneous, neurologic, and gastrointestinal responses is a basis for adverse events with the use of ipilimumab and the PD-1-directed antibodies; the emergent use of glucocorticoids may be required to attenuate severe toxicities, which unfortunately can theoretically attenuate antitumor effect. Importantly for the general internist, these events may occur late after exposure to ipilimumab while the patient may otherwise be enjoying sustained control of tumor growth owing to the beneficial actions of ipilimumab.

Another class of immunoregulatory antibody is the "bispecific" antibody blinatumomab, which was constructed to have an anti-CD19 antigen combining site as one valency of an antibody with anti-CD3 binding site as the other valency. This antibody thus can bring T cells (with its anti-CD3 activity) close to B cells bearing the CD19 determinant. Blinatumomab is active in B-cell neoplasms such as acute lymphocytic leukemia, which may not have prominent expression of the CD20 targeted by rituximab.

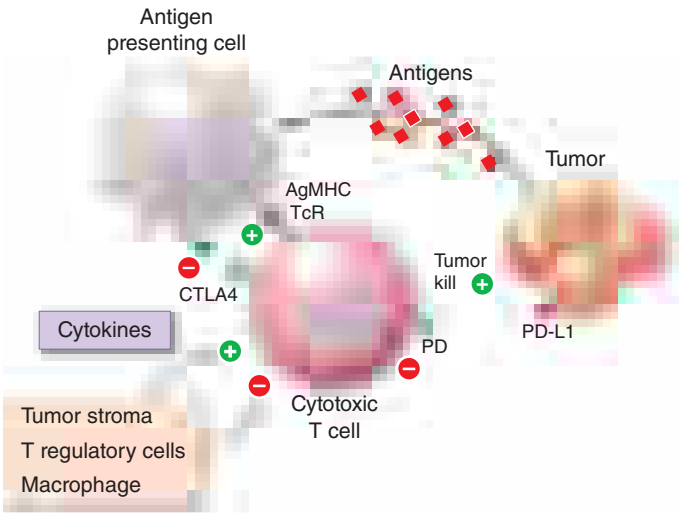

FIGURE 69-5 Tumors possess a microenvironment (tumor stroma) with immune cells including both helper T cells, suppressor T cells (both "regulatory" of other immune cell function), macrophages, and cytotoxic T cells. Cytokines found in the stroma and deriving from macrophages and regulatory T cells modulate the activities of cytotoxic T cells, which have the potential to kill tumor cells. Antigens released by tumor cells are taken up by Antigen Presenting Cells (APCs), also in the stroma. Antigens are processed by the APCs to peptides presented by the Major Histocompatibility Complex to T-cell antigen receptors, thus providing an (+) activation signal for the cytotoxic tumor cells to kill tumor cells bearing that antigen. Negative (–) signals inhibiting cytoxic T cell action include the CTLA4 receptor (on T cells), interacting with the B7 family of negative regulatory signals from APCs, and the PD receptor (on T cells), interacting with the PD-L1 (–) signal coming from tumor cells expressing the PD-1 ligand (PD-l1). As both CTLA4 and PD1 signals attenuate the anti-tumor T cell response, strategies which inhibit CTLA4 and PD1 function are a means of stimulating cytotoxic T cell activity to kill tumor cells. Cytokines from other immune cells and macrophages can provide both (+) and (–) signals for T cell action, and are under investigation as novel immunoregulatory therapeutics.

ANTIBODY CONJUGATES Conjugates of antibodies with drugs and isotopes have also been shown to be effective in the treatment of cancer and have the intent of increasing the therapeutic index of the drug or isotope by delivering the toxic "warhead" directly to the tumor cell or tumor microenvironment. Ado-trastuzumab is a conjugate of the HER2/neu-directed trastuzumab and a highly toxic microtubule targeted drug (emtansine), which by itself is too toxic for human use; the antibody-drug conjugate shows valuable activity in patients with breast cancer who have developed resistance to the "naked" antibody. Brentuximab vedotin is an anti-CD30 antibody drug conjugate with a distinct microtubule poison with activity in neoplasms such as Hodgkin's lymphoma where the tumor cells frequently express CD30. Radioconjugates targeting CD20 on lymphomas have been approved for use (ibritumomab tiuxetan [Zevalin], using yttrium-90 or ^{131}I-tositumomab). Toxicity concerns have limited their use.

Cytokines Only IFN-α and interleukin 2 (IL-2)-related molecules are in routine clinical use. The two recombinant interferons commercially available are IFN-α2a and α2b. IFN is not curative for any tumor but can induce partial responses in follicular lymphoma, hairy cell leukemia, CML, melanoma, and Kaposi's sarcoma. It has been used in the adjuvant setting in stage II melanoma, multiple myeloma, and follicular lymphoma. It produces fever, fatigue, a flulike syndrome, malaise, myelosuppression, and depression and can induce clinically significant autoimmune disease.

IL-2 exerts its antitumor effects indirectly through augmentation of immune function. Its biologic activity is to promote the growth and activity of T cells and natural killer (NK) cells. High doses of IL-2 can produce tumor regression in certain patients with metastatic melanoma and renal cell cancer. About 2–5% of patients may experience complete remissions that are durable, unlike any other treatment for these tumors. IL-2 is associated with intravascular volume depletion, capillary leak syndrome, adult respiratory distress syndrome, hypotension, fever, chills, skin rash, and impaired renal and liver function. Patients may require blood pressure support and intensive care to manage the toxicity. However, once the agent is stopped, most of the toxicities reverse completely within 3–6 days. IL2 has been fused to translate in frame with a fragment of diphtheria toxin. A commercially available construct has activity against certain T-cell lymphomas. The drug's utility derives from the internalization of the targeted receptor and cleavage of the active drug or toxin moiety.

Immune Cell–Mediated Therapies Tumors have a variety of means of avoiding the immune system: (1) they are often only subtly different from their normal counterparts; (2) they are capable of downregulating their major histocompatibility complex antigens, effectively masking them from recognition by T cells; (3) they are inefficient at presenting antigens to the immune system; (4) they can cloak themselves in a protective shell of fibrin to minimize contact with surveillance mechanisms; and (5) they can produce a range of soluble molecules, including potential immune targets, that can distract the immune system from recognizing the tumor cell or can kill or inactivate the immune effector cells. Prominent mediators of this effect are the PD receptors and their ligands described above. Some of the cell products initially polarize the immune response away from cellular immunity (shifting from T_H1 to T_H2 responses; Chap. 342) and ultimately lead to defects in T cells that prevent their activation and cytotoxic activity. A variety of strategies are being tested to overcome these barriers.

Cell-Mediated Immunity The strongest evidence that the immune system can exert clinically meaningful antitumor effects comes from allogeneic bone marrow transplantation. Adoptively transferred T cells from the donor expand in the tumor-bearing host, recognize the tumor as being foreign, and can mediate impressive antitumor effects (graft-versus-tumor effects). Three types of experimental interventions are being developed to take advantage of the ability of T cells to kill tumor cells.

1. *Transfer of allogeneic T cells.* This occurs in three major settings: in allogeneic bone marrow transplantation; as purified lymphocyte transfusions following bone marrow recovery after allogeneic bone marrow transplantation; and as pure lymphocyte transfusions following immunosuppressive (nonmyeloablative) therapy (also called reduced intensity or minitransplants). In each of these settings, the effector cells are donor T cells that recognize the tumor as being foreign, probably through minor histocompatibility differences. The main risk of such therapy is the development of graft-versus-host disease because of the minimal difference between the cancer and the normal host cells. This approach has been highly effective in certain hematologic cancers.
2. *Transfer of autologous T cells.* In this approach, the patient's own T cells are removed from the tumor-bearing host, manipulated in several ways in vitro, and given back to the patient. There are three major classes of autologous T-cell manipulation. First, tumor antigen–specific T cells can be developed and expanded to large numbers over many weeks ex vivo before administration. Second, the patient's T cells can be activated by exposure to polyclonal stimulators such as anti-CD3 and anti-CD28 after a short period ex vivo, and then amplified in the host after transfer by stimulation with IL-2, for example. Short periods removed from the patient permit the cells to overcome the tumor-induced T-cell defects, and such cells traffic and home to sites of disease better than cells that have been in culture for many weeks. In a third approach, genes that encode for a T-cell receptor specific for an antigen expressed by the tumor along with genes that facilitate T-cell activation can be introduced into subsets of a patient's T cells, which, after transfer back into the patient, allow homing of cytotoxic T cells to tumor cells expressing the antigen.
3. *Tumor vaccines aimed at boosting T-cell immunity.* The finding that mutant oncogenes that are expressed only intracellularly can be recognized as targets of T cell killing greatly expanded the possibilities for tumor vaccine development. However, major difficulties remain in getting the tumor-specific peptides presented in a fashion to prime the T cells. Tumors themselves are very poor at presenting their own antigens to T cells at the first antigen exposure (*priming*).

Priming is best accomplished by professional antigen-presenting cells (dendritic cells). Thus, a number of experimental strategies are aimed at priming host T cells against tumor-associated peptides. Vaccine adjuvants such as granulocyte-macrophage colony-stimulating factor (GM-CSF) appear capable of attracting antigen-presenting cells to a skin site containing a tumor antigen. Purified antigen-presenting cells can be pulsed with tumor, its membranes, or particular tumor antigens and delivered as a vaccine. One such vaccine, Sipuleucel-T, is approved for use in patients with hormone-independent prostate cancer. In this approach, the patient undergoes leukapheresis, wherein mononuclear cells (that include antigen-presenting cells) are removed from the patient's blood. The cells are pulsed in a laboratory with an antigenic fusion protein comprising a protein frequently expressed by prostate cancer cells, prostate acid phosphatase, fused to GM-CSF, and matured to increase their capacity to present the antigen to immune effector cells. The cells are then returned to the patient in a well-tolerated treatment. Although no objective tumor response was documented in clinical trials, median survival was increased by about 4 months. Tumor cells can also be transfected with genes that attract antigen-presenting cells.

Another important vaccine strategy is directed at infectious agents whose action ultimately is tied to the development of human cancer. Hepatitis B vaccine in an epidemiologic sense prevents hepatocellular carcinoma, and a tetravalent human papillomavirus vaccine prevents infection by virus types currently accounting for 70% of cervical cancer. Unfortunately, these vaccines are ineffective at treating patients who have developed a virus-induced cancer.

SYSTEMIC RADIATION THERAPY

Although total-body irradiation has a role in preparing a patient to received allogeneic stem cells, and antibodies as described above can specifically target radioisotopes, systemically administered isotopes of iodide salts have an important role in the treatment of thyroid neoplasms, owing to the selective upregulation of the iodide transporter in the tumor cell compartment. Likewise, isotopes of samarium and radium have been found useful in the palliation of symptoms from advanced bony metastases of prostate cancer owing to their selective deposition at the tumor–bone matrix interface, thereby potentially affecting the function of both tumor and stromal cells in the progressive growth of the metastatic deposit.

RESISTANCE TO CANCER TREATMENTS

Resistance mechanisms to the conventional cytotoxic agents were initially characterized in the late twentieth century as defects in drug uptake, metabolism, or export by tumor cells. The *multidrug resistance* (*mdr*) gene defined in vitro in cell lines exposed to increasing concentrations of drugs led to the definition of a family of transport proteins that efficiently excrete the drug from the tumor cells; no clinically useful modulator of this process has yet emerged. Drug-metabolizing enzymes such as cytidine deaminase are upregulated in resistant tumor cells, and this is the basis for so-called "high-dose cytarabine" regimens in the treatment of leukemia. Another resistance mechanism defined during this era involved increased expression of a drug's target, exemplified by amplification of the dihydrofolate reductase gene, in patients who had lost responsiveness to methotrexate, or mutation of topoisomerase II in tumors that relapsed after topoisomerase II modulator treatment.

A second class of resistance mechanisms involves loss of the cellular apoptotic mechanism activated after the engagement of a drug's target by the drug. This occurs in a way that is heavily influenced by the biology of the particular tumor type. For example, decreased alkylguanine alkyltransferase expression defines a subset of glioblastoma patients with the prospect of enhanced benefit from treatment with temozolomide, but has no predictive value for benefit from temozolomide in epithelial neoplasms. Likewise, ovarian cancers resistant to platinating agents have decreased expression of the proapoptotic gene *bax*. These types of findings have prompted the idea that responsive tumors to chemotherapeutic agents are populated by cells that express drug-related cell death controlling genes, creating in effect a state of "synthetic lethality" with the drug (Chap. 68). When drug is not present, absence or mutation in these genes is tolerated, but become lethal in the presence of the drug.

A third class of resistance mechanisms emerged from sequencing of the targets of agents directed at oncogenic kinases. Thus, patients with CML resistant to imatinib have acquired mutations in the ATP binding domain of $p210^{bcr\text{-}abl}$ in some cases, leading to the screening and design of agents with activity against the mutant proteins. Entirely analogous resistance mechanisms have emerged in patients with lung cancer treated with the EGFR antagonists gefitinib and erlotinib.

A final category of tumor resistance mechanisms to targeted agents includes the upregulation of alternate means of activating the pathway targeted by the agent. Thus melanomas initially responsive to *BRAF* V600E antagonists such as vemurafenib may reactivate raf signaling by upregulating isoforms that can bypass the variant blocked by the drug. Likewise, inhibition of HER2/neu signaling in breast cancer cells can lead to the emergence of variants with distinct oncogenic signaling pathways such as PI3 kinase. The susceptibility of a tumor to different treatments as a function of its expression of potential drug targets or their mutational profile has led to efforts to define the dominant pathways driving a patient's tumor by genomic techniques including whole exome sequencing. The difficulty with applying such data to patient treatment is recognizing that these pathways may change during the natural history of a tumor and that different sites in a single patient may have tumors with different patterns of gene mutation.

SUPPORTIVE CARE DURING CANCER TREATMENT

MYELOSUPPRESSION

The common cytotoxic chemotherapeutic agents almost invariably affect bone marrow function. Titration of this effect determines the tolerated dose of the agent on a given schedule. The normal kinetics of blood cell turnover influences the sequence and sensitivity of each of the formed elements. Polymorphonuclear leukocytes (PMNs; $t_{1/2}$ = 6–8 h), platelets ($t_{1/2}$ = 5–7 days), and red blood cells (RBCs; $t_{1/2}$ = 120 days) have most, less, and least susceptibility, respectively, to usually administered cytotoxic agents. The nadir count of each cell type in response to classes of agents is characteristic. Maximal neutropenia occurs 6–14 days after conventional doses of anthracyclines, antifolates, and antimetabolites. Alkylating agents differ from each other in the timing of cytopenias. Nitrosoureas, DTIC, and procarbazine can display delayed marrow toxicity, first appearing 6 weeks after dosing.

Complications of myelosuppression result from the predictable sequelae of the missing cells' function. *Febrile neutropenia* refers to the clinical presentation of fever (one temperature ≥38.5°C or three readings ≥38°C but ≤38.5°C per 24 h) in a neutropenic patient with an uncontrolled neoplasm involving the bone marrow or, more usually, in a patient undergoing treatment with cytotoxic agents. Mortality from uncontrolled infection varies inversely with the neutrophil count. If the nadir neutrophil count is >1000/μL, there is little risk; if <500/μL, risk of death is markedly increased. Management of febrile neutropenia has conventionally included empirical coverage with antibiotics for the duration of neutropenia (Chap. 70). Selection of antibiotics is governed by the expected association of infections with certain underlying neoplasms; careful physical examination (with scrutiny of catheter sites, dentition, mucosal surfaces, and perirectal and genital orifices by gentle palpation); chest x-ray; and Gram stain and culture of blood, urine, and sputum (if any) to define a putative site of infection. In the absence of any originating site, a broadly acting β-lactam with anti-*Pseudomonas* activity, such as ceftazidime, is begun empirically. The addition of vancomycin to cover potential cutaneous sites of origin (until these are ruled out or shown to originate from methicillin-sensitive organisms) or metronidazole or imipenem for abdominal or other sites favoring anaerobes reflects modifications tailored to individual patient presentations. Febrile neutropenic patients can be stratified broadly into two prognostic groups. The first, with expected short duration of neutropenia and no evidence of hypotension or abdominal or other localizing

symptoms, may be expected to do well even with oral regimens, e.g., ciprofloxacin or moxifloxacin, or amoxicillin plus clavulanic acid. A less favorable prognostic group is patients with expected prolonged neutropenia, evidence of sepsis, and end organ compromise, particularly pneumonia. Empirical addition of antifungal agents if fever and neutropenia persist for 7 days without identification of an adequately treated organism or site is frequent.

Transfusion of granulocytes has no role in the management of febrile neutropenia, owing to their exceedingly short half-life, mechanical fragility, and clinical syndromes of pulmonary compromise with leukostasis after their use. Instead, colony-stimulating factors (CSFs) are used to augment bone marrow production of PMNs. The American Society of Clinical Oncology has developed practice guidelines for the use of G-CSF and GM-CSF **(Table 69-7)**.

Primary prophylaxis (i.e., shortly after completing chemotherapy to reduce the nadir) administers G-CSF to patients receiving cytotoxic regimens associated with a 20% incidence of febrile neutropenia. "Dose-dense" regimens, where cycling of chemotherapy is intended to be completed without delay of administered doses, may also benefit, but such patients should be on a clinical trial. Administration of G-CSF in these circumstances has reduced the incidence of febrile neutropenia in several studies by about 50%. Most patients, however, receive regimens that do not have such a high risk of expected febrile neutropenia, and therefore most patients initially should not receive G-CSF or GM-CSF. Special circumstances—such as a documented history of febrile neutropenia with the regimen in a particular patient or categories of patients at increased risk, such as patients aged >65 years with aggressive lymphoma treated with curative chemotherapy regimens; extensive compromise of marrow by prior radiation or chemotherapy; or active, open wounds or deep-seated infection—may support primary treatment with G-CSF or GM-CSF. Administration of G-CSF or GM-CSF to afebrile neutropenic patients or to patients with low-risk febrile neutropenia is not recommended, and patients receiving concomitant chemoradiation treatment, particularly those with thoracic neoplasms, likewise are not generally recommended for treatment. In contrast, administration of G-CSF to high-risk patients with febrile neutropenia and evidence of organ compromise including sepsis syndrome, invasive fungal infection, concurrent hospitalization at the time fever develops, pneumonia, profound neutropenia (<0.1 × 10^9/L), or age >65 years is reasonable.

Secondary prophylaxis refers to the administration of CSFs in patients who have experienced a neutropenic complication from a prior cycle of chemotherapy; dose reduction or delay may be a reasonably considered alternative. G-CSF or GM-CSF is conventionally started 24–72 h after completion of chemotherapy and continued until a PMN count of 10,000/μL is achieved, unless a "depot" preparation of G-CSF such as pegfilgrastim is used, where one dose is administered at least 14 days before the next scheduled administration of chemotherapy. Also, patients with myeloid leukemias undergoing induction therapy may have a slight reduction in the duration of neutropenia if G-CSF is commenced after completion of therapy, but the influence on long-term outcome has not been defined. GM-CSF probably has a more restricted utility than G-CSF, with its use currently limited to patients after autologous bone marrow transplants, although proper head-to-head comparisons with G-CSF have not been conducted in most instances. GM-CSF may be associated with more systemic side effects.

Dangerous degrees of thrombocytopenia do not frequently complicate the management of patients with solid tumors receiving cytotoxic chemotherapy (with the possible exception of certain carboplatin-containing regimens), but they are frequent in patients with certain hematologic neoplasms where marrow is infiltrated with tumor. Severe bleeding related to thrombocytopenia occurs with increased frequency at platelet counts <20,000/μL and is very prevalent at counts <5000/μL.

The precise "trigger" point at which to transfuse patients has been defined as a platelet count of 10,000/μL or less in patients without medical comorbidities that may increase the risk of bleeding. This issue is important not only because of the costs of frequent transfusion, but unnecessary platelet transfusions expose the patient to the risks of allosensitization and loss of value from subsequent transfusion owing to rapid platelet clearance, as well as the infectious and hypersensitivity risks inherent in any transfusion. Prophylactic transfusions to keep platelets >20,000/μL are reasonable in patients with leukemia who are stressed by fever or concomitant medical conditions (the threshold for transfusion is 10,000/μL in patients with solid tumors and no other bleeding diathesis or physiologic stressors such as fever or hypotension, a level that might also be reasonably considered for leukemia patients who are thrombocytopenic but not stressed or bleeding). Careful review of medication lists to prevent exposure to nonsteroidal anti-inflammatory agents and maintenance of clotting factor levels adequate to support near-normal prothrombin and partial thromboplastin time tests are important in minimizing the risk of bleeding in the thrombocytopenic patient.

Anemia associated with chemotherapy can be managed by transfusion of packed RBCs. Transfusion is not undertaken until the hemoglobin falls to <80 g/L (8 g/dL), compromise of end organ function occurs, or an underlying condition (e.g., coronary artery disease) calls for maintenance of hemoglobin >90 g/L (9 g/dL). Randomized trials in certain tumors have raised the possibility that erythropoietin (EPO) use may promote tumor-related adverse events.

TABLE 69-7 Indications for the Clinical Use of G-CSF or GM-CSF

Preventive Uses
With the first cycle of chemotherapy (so-called *primary CSF administration*)
Not needed on a routine basis
Use if the probability of febrile neutropenia is ≥20%
Use if patient has preexisting neutropenia or active infection
Age >65 years treated for lymphoma with curative intent or other tumors treated by similar regimens
Poor performance status
Extensive prior chemotherapy
Dose-dense regimens in a clinical trial or with strong evidence of benefit
With subsequent cycles if febrile neutropenia has previously occurred (so-called *secondary CSF administration*)
Not needed after short-duration neutropenia without fever
Use if patient had febrile neutropenia in previous cycle
Use if prolonged neutropenia (even without fever) delays therapy
Therapeutic Uses
Afebrile neutropenic patients
No evidence of benefit
Febrile neutropenic patients
No evidence of benefit
May feel compelled to use in the face of clinical deterioration from sepsis, pneumonia, or fungal infection, but benefit unclear
In bone marrow or peripheral blood stem cell transplantation
Use to mobilize stem cells from marrow
Use to hasten myeloid recovery
In acute myeloid leukemia
G-CSF of minor or no benefit
GM-CSF of no benefit and may be harmful
In myelodysplastic syndromes
Not routinely beneficial
Use intermittently in subset with neutropenia and recurrent infection
What Dose and Schedule Should Be Used?
G-CSF: 5 mg/kg per day subcutaneously
GM-CSF: 250 mg/m^2 per day subcutaneously
Pegfilgrastim: one dose of 6 mg 24 h after chemotherapy
When Should Therapy Begin and End?
When indicated, start 24–72 h after chemotherapy
Continue until absolute neutrophil count is 10,000/μL
Do not use concurrently with chemotherapy or radiation therapy

Abbreviations: CSF, cerebrospinal fluid; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Source: From the American Society of Clinical Oncology: J Clin Oncol 24:3187, 2006.

NAUSEA AND VOMITING

The most common side effect of chemotherapy administration is nausea, with or without vomiting. Nausea may be acute (within 24 h of chemotherapy), delayed (>24 h), or anticipatory of the receipt of chemotherapy. Patients may be likewise stratified for their risk of susceptibility to nausea and vomiting, with increased risk in young, female, heavily pretreated patients without a history of alcohol or drug use but with a history of motion or morning sickness. Antineoplastic agents vary in their capacity to cause nausea and vomiting. Highly emetogenic drugs (>90%) include mechlorethamine, streptozotocin, DTIC, cyclophosphamide at >1500 mg/m^2, and cisplatin; moderately emetogenic drugs (30–90% risk) include carboplatin, cytosine arabinoside (>1 mg/m^2), ifosfamide, conventional-dose cyclophosphamide, and anthracyclines; low-risk (10–30%) agents include 5FU, taxanes, etoposide, and bortezomib, with minimal risk (<10%) afforded by treatment with antibodies, bleomycin, busulfan, fludarabine, and vinca alkaloids.

Serotonin antagonists (5-HT$_3$) and neurokinin 1 (NK1) receptor antagonists are useful in "high-risk" chemotherapy regimens. The combination acts at both peripheral gastrointestinal and CNS sites that control nausea and vomiting. For example, the 5-HT$_3$ blocker dolasetron, 100 mg intravenously or orally; dexamethasone, 12 mg; and the NK1 antagonist aprepitant, 125 mg orally are combined on the day of administration of severely emetogenic regimens, with repetition of dexamethasone (8 mg) and aprepitant (80 mg) on days 2 and 3 for delayed nausea. Alternate 5-HT$_3$ antagonists include ondansetron, given as 0.15 mg/kg intravenously for three doses just before and at 4 and 8 h after chemotherapy; palonosetron at 0.25 mg over 30 s, 30 min before chemotherapy; and granisetron, given as a single dose of 0.01 mg/kg just before chemotherapy. Emesis from moderately emetic chemotherapy regimens may be prevented with a 5-HT$_3$ antagonist and dexamethasone alone for patients not receiving doxorubicin and cyclophosphamide combinations; the latter combination requires the 5-HT$_3$/dexamethasone/aprepitant on day 1, but aprepitant alone on days 2 and 3. Emesis from low-emetic-risk regimens may be prevented with 8 mg of dexamethasone alone or with non-5-HT$_3$, non-NK1 antagonist approaches including the following.

Antidopaminergic phenothiazines act directly at the chemoreceptor trigger zone (CTZ) in the brainstem medulla and include prochlorperazine (Compazine), 10 mg intramuscularly or intravenously, 10–25 mg orally, or 25 mg per rectum every 4–6 h for up to four doses; and thiethylperazine, 10 mg by potentially all of the above routes every 6 h. Haloperidol is a butyrophenone dopamine antagonist given at 1 mg intramuscularly or orally every 8 h. Metoclopramide acts on peripheral dopamine receptors to augment gastric emptying and is used in high doses for highly emetogenic regimens (1–2 mg/kg intravenously 30 min before chemotherapy and every 2 h for up to three additional doses as needed); intravenous doses of 10–20 mg every 4–6 h as needed or 50 mg orally 4 h before and 8 and 12 h after chemotherapy are used for moderately emetogenic regimens. 5-9-Tetrahydrocannabinol (Marinol) is a rather weak antiemetic compared to other available agents, but it may be useful for persisting nausea and is used orally at 10 mg every 3–4 h as needed.

DIARRHEA

Regimens that include 5FU infusions and/or irinotecan may produce severe diarrhea. Similar to the vomiting syndromes, chemotherapy-induced diarrhea may be immediate or can occur in a delayed fashion up to 48–72 h after the drugs. Careful attention to maintained hydration and electrolyte repletion, intravenously if necessary, along with antimotility treatments such as "high-dose" loperamide, commenced with 4 mg at the first occurrence of diarrhea, with 2 mg repeated every 2 h until 12 h without loose stools, not to exceed a total daily dose of 16 mg. Octreotide (100–150 μg), a somatostatin analogue, or opiate-based preparations may be considered for patients not responding to loperamide.

MUCOSITIS

Irritation and inflammation of the mucous membranes particularly afflicting the oral and anal mucosa, but potentially involving the gastrointestinal tract, may accompany cytotoxic chemotherapy. Mucositis is due to damage to the proliferating cells at the base of the mucosal squamous epithelia or in the intestinal crypts. Topical therapies, including anesthetics and barrier-creating preparations, may provide symptomatic relief in mild cases. Palifermin or keratinocyte growth factor, a member of the fibroblast growth factor family, is effective in preventing severe mucositis in the setting of high-dose chemotherapy with stem cell transplantation for hematologic malignancies. It may also prevent or ameliorate mucositis from radiation.

ALOPECIA

Chemotherapeutic agents vary widely in causing alopecia, with anthracyclines, alkylating agents, and topoisomerase inhibitors reliably causing near-total alopecia when given at therapeutic doses. Antimetabolites are more variably associated with alopecia. Psychological support and the use of cosmetic resources are to be encouraged, and "chemo caps" that reduce scalp temperature to decrease the degree of alopecia are controversial during treatment with curative intent of neoplasms, such as leukemia or lymphoma, or in adjuvant breast cancer therapy. The richly vascularized scalp can certainly harbor micrometastatic or disseminated disease.

GONADAL DYSFUNCTION AND PREGNANCY

Cessation of ovulation and azoospermia reliably result from alkylating agent—and topoisomerase poison—containing regimens. The duration of these effects varies with age and sex. Sperm banking before treatment may be considered. Females experience amenorrhea with anovulation after alkylating agent therapy; egg preservation may be considered, but may delay inception of urgent treatment. Recovery of normal menses is frequent if treatment is completed before age 30 but unlikely to recover menses after age 35. Even those who regain menses usually experience premature menopause. Because the magnitude and extent of decreased fertility can be difficult to predict, patients should be counseled to maintain effective contraception, preferably by barrier means, during and after therapy. Resumption of efforts to conceive should be considered in the context of the patient's likely prognosis. Hormone replacement therapy should be undertaken in women who do not have a hormonally responsive tumor. For patients who have had a hormone-sensitive tumor primarily treated by a local modality, conventional practice would counsel against hormone replacement, but this issue is under investigation.

Chemotherapy agents have variable effects on the success of pregnancy. All agents tend to have increased risk of adverse outcomes when administered during the first trimester, and strategies to delay chemotherapy, if possible, until after this milestone should be considered if the pregnancy is to continue to term. Patients in their second or third trimester can be treated with most regimens for the common neoplasms afflicting women in their childbearing years, with the exception of antimetabolites, particularly antifolates, which have notable teratogenic or fetotoxic effects throughout pregnancy. The need for anticancer chemotherapy per se is infrequently a clear basis to recommend termination of a concurrent pregnancy, although each treatment strategy in this circumstance must be tailored to the individual needs of the patient.

Late effects of cancer and its treatment are reviewed in Chap. 91.

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70 Infections in Patients with Cancer

Robert W. Finberg

Infections are a common cause of death and an even more common cause of morbidity in patients with a wide variety of neoplasms. Autopsy studies show that most deaths from acute leukemia and half of deaths from lymphoma are caused directly by infection. With more intensive chemotherapy, patients with solid tumors have also become more likely to die of infection. Fortunately, an evolving approach to prevention and treatment of infectious complications of cancer has decreased infection-associated mortality rates and will probably continue to do so. This accomplishment has resulted from three major steps:

1. *Early treatment:* The practice of using "early empirical" antibiotics reduced mortality rates among patients with leukemia and bacteremia from 84% in 1965 to 44% in 1972. The mortality rate due to infection in febrile neutropenic patients dropped to <10% by 2013. This dramatic improvement is attributed to early intervention with appropriate antimicrobial therapy.
2. *Empirical treatment:* "Empirical" antifungal therapy has also lowered the incidence of disseminated fungal infection, with dramatic decreases in mortality rates. An antifungal agent is administered—on the basis of likely fungal infection—to neutropenic patients who, after 4–7 days of antibiotic therapy, remain febrile but have no positive cultures.
3. *Prophylaxis:* Use of antibiotics for afebrile neutropenic patients as broad-spectrum prophylaxis against infections has decreased both mortality and morbidity even further. The current approach to treatment of severely neutropenic patients (e.g., those receiving high-dose chemotherapy for leukemia or high-grade lymphoma) is based on initial prophylactic therapy at the onset of neutropenia, subsequent "empirical" antibacterial therapy targeting the organisms whose involvement is likely in light of physical findings (most often fever alone), and finally "empirical" antifungal therapy based on the known likelihood that fungal infection will become a serious issue after 4–7 days of broad-spectrum antibacterial therapy.

A physical predisposition to infection in patients with cancer **(Table 70-1)** can be a result of the neoplasm's production of a break in the skin. For example, a squamous cell carcinoma may cause local invasion of the epidermis, which allows bacteria to gain access to subcutaneous tissue and permits the development of cellulitis. The artificial closing of a normally patent orifice can also predispose to infection; for example, obstruction of a ureter by a tumor can cause urinary tract infection, and obstruction of the bile duct can cause cholangitis. Part of the host's normal defense against infection depends on the continuous emptying of a viscus; without emptying, a few bacteria that are present as a result of bacteremia or local transit can multiply and cause disease.

A similar problem can affect patients whose lymph node integrity has been disrupted by radical surgery, particularly patients who have had radical node dissections. A common clinical problem following radical mastectomy is the development of cellulitis (usually caused by streptococci or staphylococci) because of lymphedema and/or inadequate lymph drainage. In most cases, this problem can be addressed by local measures designed to prevent fluid accumulation and breaks in the skin, but antibiotic prophylaxis has been used in refractory cases.

A life-threatening problem common to many cancer patients is the loss of the reticuloendothelial capacity to clear microorganisms after splenectomy, which may be performed as part of the management of hairy cell leukemia, chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML) and in Hodgkin's disease. Even after curative therapy for the underlying disease, the lack of a spleen predisposes such patients to rapidly fatal infections. The loss of the spleen through trauma similarly predisposes the normal host to overwhelming infection throughout life. The splenectomized patient should be counseled about the risks of infection with certain organisms, such as the protozoan *Babesia* **(Chap. 220)** and *Capnocytophaga canimorsus*, a bacterium carried in the mouths of animals **(Chaps. 136 and 153)**. Because encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) are the organisms most commonly associated with postsplenectomy sepsis, splenectomized persons should be vaccinated (and revaccinated; **Table 70-2** and **Chap. 118**) against the capsular polysaccharides of these organisms. Many clinicians recommend giving splenectomized patients a small supply of antibiotics effective against *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* to avert rapid, overwhelming sepsis in the event that they cannot present for medical attention immediately after the onset of fever or other signs or symptoms of bacterial infection. A few tablets of amoxicillin/clavulanic acid (or levofloxacin if resistant strains of *S. pneumoniae* are prevalent locally) are a reasonable choice for this purpose.

The level of suspicion of infections with certain organisms should depend on the type of cancer diagnosed **(Table 70-3)**. Diagnosis of multiple myeloma or CLL should alert the clinician to the possibility

TABLE 70-1 Disruption of Normal Barriers in Patients with Cancer That May Predispose Them to Infections

TYPE OF DEFENSE	SPECIFIC LESION	CELLS INVOLVED	ORGANISM	CANCER ASSOCIATION	DISEASE
Physical barrier	Breaks in skin	Skin epithelial cells	Staphylococci, streptococci	Head and neck, squamous cell carcinoma	Cellulitis, extensive skin infection
Emptying of fluid collections	Occlusion of orifices: ureters, bile duct, colon	Luminal epithelial cells	Gram-negative bacilli	Renal, ovarian, biliary tree, metastatic diseases of many cancers	Rapid, overwhelming bacteremia; urinary tract infection
Lymphatic function	Node dissection	Lymph nodes	Staphylococci, streptococci	Breast cancer surgery	Cellulitis
Splenic clearance of microorganisms	Splenectomy	Splenic reticuloendothelial cells	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Babesia, Capnocytophaga canimorsus*	Hodgkin's disease, leukemia	Rapid, overwhelming sepsis
Phagocytosis	Lack of granulocytes	Granulocytes (neutrophils)	Staphylococci, streptococci, enteric organisms, fungi	Acute myeloid and acute lymphocytic leukemias, hairy cell leukemia	Bacteremia
Humoral immunity	Lack of antibody	B cells	*S. pneumoniae, H. influenzae, N. meningitidis*	Chronic lymphocytic leukemia, multiple myeloma	Infections with encapsulated organisms, sinusitis, pneumonia
Cellular immunity	Lack of T cells	T cells and macrophages	*Mycobacterium tuberculosis, Listeria*, herpesviruses, fungi, intracellular parasites	Hodgkin's disease, leukemia, T cell lymphoma	Infections with intracellular bacteria, fungi, parasites; virus reactivation

TABLE 70-2 Vaccination of Cancer Patients Receiving Chemotherapy[a]

VACCINE	USE IN INDICATED PATIENTS		
	INTENSIVE CHEMOTHERAPY	HODGKIN'S DISEASE	HEMATOPOIETIC STEM CELL TRANSPLANTATION
Diphtheria-tetanus-pertussis[b]	Primary series and boosters as necessary	No special recommendation	3 doses given 6–12 months after transplantation
Poliomyelitis[c]	Complete primary series and boosters	No special recommendation	3 doses given 6–12 months after transplantation
Haemophilus influenzae type b conjugate	Primary series and booster for children	Single dose for adults	3 doses given 6–12 months after transplantation (separated by 1 month)
Human papillomavirus (HPV)	HPV vaccine is approved for males and females 9–26 years of age. Check Centers for Disease Control and Prevention (CDC) website (*www.cdc.gov/vaccines*) for updated recommendations.	HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations.	HPV vaccine is approved for males and females 9–26 years of age. Check CDC website (*www.cdc.gov/vaccines*) for updated recommendations.
Hepatitis A	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle	As indicated for normal hosts on the basis of occupation and lifestyle
Hepatitis B	Same as for normal hosts	As indicated for normal hosts on the basis of occupation and lifestyle	3 doses given 6–12 months after transplantation
Pneumococcal conjugate vaccine (PCV13) Pneumococcal polysaccharide vaccine (PPSV23)[d]	Finish series prior to chemotherapy if possible.	Patients with splenectomy should receive both PCV13 and PPSV23.	Three doses of PCV13, beginning 3–6 months after transplantation, are followed by a dose of PPSV23 at least 8 weeks later. A second PPSV23 dose can be given 5 years later.
Quadrivalent meningococcal vaccine[e] Meningococcal B vaccine	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories See above.	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years. See above.	Should be administered to splenectomized patients and to patients living in endemic areas, including college students in dormitories. An additional dose can be given after 5 years. See above (see *www.cdc.gov/vaccines* for updated recommendations).
Influenza	Seasonal immunization	Seasonal immunization	Seasonal immunization (A seasonal dose is recommended and can be given as early as 4 months after transplantation; if given <6 months after transplantation, an additional dose is recommended.)
Measles/mumps/rubella	Contraindicated	Contraindicated during chemotherapy	After 24 months in patients without graft-versus-host disease
Varicella-zoster virus[f]	Contraindicated[g]	Contraindicated	Contraindicated (CDC recommends use on a case-by-case basis following reevaluation.)

[a]The latest recommendations by the Advisory Committee on Immunization Practices and the CDC guidelines can be found at *www.cdc.gov/vaccines*. [b]A single dose of TDaP (tetanus–diphtheria–acellular pertussis), followed by a booster dose of Td (tetanus—diphtheria) every 10 years, is recommended for adults. [c]Live-virus vaccine is contraindicated; inactivated vaccine should be used. [d]Two types of vaccines are used to prevent pneumococcal disease. A conjugate vaccine active against 13 serotypes (13-valent pneumococcal conjugate vaccine, or PCV13) is currently administered in three separate doses to all children. A polysaccharide vaccine active against 23 serotypes (23-valent pneumococcal polysaccharide vaccine, or PPSV23) elicits titers of antibody lower than those achieved with the conjugate vaccine, and immunity may wane more rapidly. Because the ablative chemotherapy given to recipients of hematopoietic stem cell transplants (HSCTs) eradicates immunologic memory, revaccination is recommended for all such patients. Vaccination is much more effective once immunologic reconstitution has occurred; however, because of the need to prevent serious disease, pneumococcal vaccine should be administered 6–12 months after transplantation in most cases. Because PPSV23 includes serotypes not present in PCV13, HSCT recipients should receive a dose of PPSV23 at least 8 weeks after the last dose of PCV13. Although antibody titers from PPSV23 clearly decay, experience with multiple doses of PPSV23 is limited, as are data on the safety, toxicity, or efficacy of such a regimen. For this reason, the CDC currently recommends the administration of one additional dose of PPSV23 at least 5 years after the last dose to immunocompromised patients, including transplant recipients, as well as patients with Hodgkin's disease, multiple myeloma, lymphoma, or generalized malignancies. Beyond this single additional dose, further doses are not recommended at this time. [e]Meningococcal conjugate vaccine (MenACWY) is recommended for adults ≤55 years old, and meningococcal polysaccharide vaccine (MPSV4) is recommended for those ≥56 years old. [f]Includes both varicella vaccine for children and zoster vaccine for adults. [g]Contact the manufacturer for more information on use in children with acute lymphocytic leukemia.

of hypogammaglobulinemia. While immunoglobulin replacement therapy can be effective, in most cases prophylactic antibiotics are a cheaper, more convenient method of eliminating bacterial infections in CLL patients with hypogammaglobulinemia. Patients with acute lymphocytic leukemia (ALL), patients with non-Hodgkin's lymphoma, and all cancer patients treated with high-dose glucocorticoids (or glucocorticoid-containing chemotherapy regimens) should receive antibiotic prophylaxis for *Pneumocystis* infection (Table 70-3) for the duration of their chemotherapy. In addition to exhibiting susceptibility to certain infectious organisms, patients with cancer are likely to manifest their infections in characteristic ways. For example, fever—generally a sign of infection in normal hosts—continues to be a reliable indicator in neutropenic patients. In contrast, patients receiving glucocorticoids and agents that impair T cell function and cytokine secretion may have serious infections in the absence of fever. Similarly, neutropenic patients commonly present with cellulitis without purulence and with pneumonia without sputum or even x-ray findings (see below).

The use of monoclonal antibodies that target B and T cells as well as drugs that interfere with lymphocyte signal transduction events is associated with reactivation of latent infections. The use of rituximab, the antibody to CD20 (a B cell surface protein), is associated with the development of reactivation tuberculosis as well as other latent viral infections, including hepatitis B and cytomegalovirus (CMV) infection. Like organ transplant recipients **(Chap. 138)**, patients with latent bacterial disease (like tuberculosis) and latent viral disease (like herpes simplex or zoster) should be carefully monitored for reactivation disease.

TABLE 70-3 Infections Associated with Specific Types of Cancer

CANCER	UNDERLYING IMMUNE ABNORMALITY	ORGANISM(S) CAUSING INFECTION
Multiple myeloma	Hypogammaglobulinemia	*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*
Chronic lymphocytic leukemia	Hypogammaglobulinemia	*S. pneumoniae, H. influenzae, N. meningitidis*
Acute myeloid or lymphocytic leukemia	Granulocytopenia, skin and mucous membrane lesions	Extracellular gram-positive and gram-negative bacteria, fungi
Hodgkin's disease	Abnormal T cell function	Intracellular pathogens (*Mycobacterium tuberculosis, Listeria, Salmonella, Cryptococcus, Mycobacterium avium*); herpesviruses
Non-Hodgkin's lymphoma and acute lymphocytic leukemia	Glucocorticoid chemotherapy, T and B cell dysfunction	*Pneumocystis*
Colon and rectal tumors	Local abnormalities[a]	*Streptococcus bovis* biotype 1 (bacteremia)
Hairy cell leukemia	Abnormal T cell function	Intracellular pathogens (*M. tuberculosis, Listeria, Cryptococcus, M. avium*)

[a]The reason for this association is not well defined.

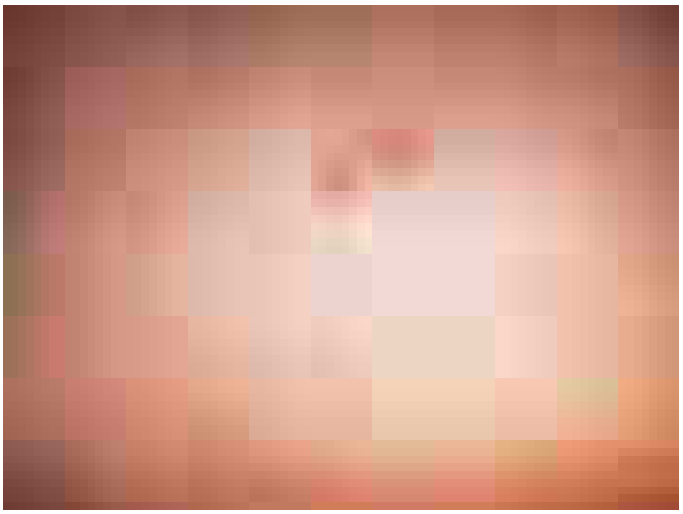
SYSTEM-SPECIFIC SYNDROMES

SKIN-SPECIFIC SYNDROMES

Skin lesions are common in cancer patients, and the appearance of these lesions may permit the diagnosis of systemic bacterial or fungal infection. While cellulitis caused by skin organisms such as *Streptococcus* or *Staphylococcus* is common, neutropenic patients—that is, those with <500 functional polymorphonuclear leukocytes (PMNs)/μL—and patients with impaired blood or lymphatic drainage may develop infections with unusual organisms. Innocent-looking macules or papules may be the first sign of bacterial or fungal sepsis in immunocompromised patients **(Fig. 70-1)**. In the neutropenic host, a macule progresses rapidly to ecthyma gangrenosum **(see Fig. A1-34)**, a usually painless, round, necrotic lesion consisting of a central black or gray-black eschar with surrounding erythema. Ecthyma gangrenosum, which is located in nonpressure areas (as distinguished from necrotic lesions associated with lack of circulation), is often associated with *Pseudomonas aeruginosa* bacteremia **(Chap. 159)** but may be caused by other bacteria.

Candidemia **(Chap. 211)** is also associated with a variety of skin conditions **(see Fig. A1-37)** and commonly presents as a maculopapular rash. Punch biopsy of the skin may be the best method for diagnosis.

Cellulitis, an acute spreading inflammation of the skin, is most often caused by infection with group A *Streptococcus* or *Staphylococcus aureus*, virulent organisms normally found on the skin **(Chap. 124)**. Although cellulitis tends to be circumscribed in normal hosts, it may spread rapidly in neutropenic patients. A tiny break in the skin may lead to spreading cellulitis, which is characterized by pain and erythema; in the affected patients, signs of infection (e.g., purulence) are often lacking. What might be a furuncle in a normal host may require amputation because of uncontrolled infection in a patient presenting with leukemia. A dramatic response to an infection that might be trivial in a normal host can mark the first sign of leukemia. Fortunately, granulocytopenic patients are likely to be infected with certain types of organisms **(Table 70-4)**; thus the selection of an antibiotic regimen is somewhat easier than it might otherwise be (see "Antibacterial Therapy," below). It is essential to recognize cellulitis early and to treat it aggressively. Patients who are neutropenic or who have previously received antibiotics for other reasons may develop cellulitis with unusual organisms (e.g., *Escherichia coli*, *Pseudomonas*, or fungi). Early treatment, even of innocent-looking lesions, is essential to prevent necrosis and loss of



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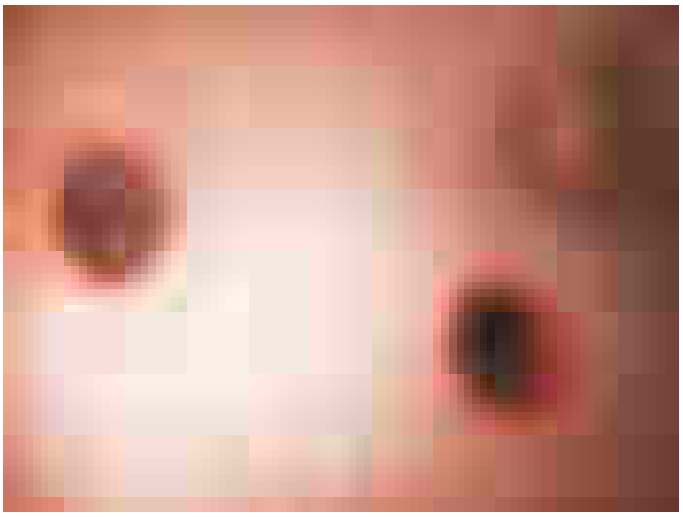

B

FIGURE 70-1 ***A***. Papules related to *Escherichia coli* bacteremia in a patient with acute lymphocytic leukemia. ***B***. The same lesions on the following day.

TABLE 70-4 Organisms Likely to Cause Infections in Granulocytopenic Patients

Gram-Positive Cocci	
Staphylococcus epidermidis	*Staphylococcus aureus*
Viridans *Streptococcus*	*Enterococcus faecalis*
Streptococcus pneumoniae	
Gram-Negative Bacilli	
Escherichia coli	*Serratia* spp.
Klebsiella spp.	*Acinetobacter* spp.[a]
Pseudomonas aeruginosa	*Stenotrophomonas* spp.
Enterobacter spp.	*Citrobacter* spp.
Non-*aeruginosa Pseudomonas* spp.[a]	
Gram-Positive Bacilli	
Diphtheroids	JK bacillus[a]
Fungi	
Candida spp.	*Mucor/Rhizopus*
Aspergillus spp.	

[a]Often associated with intravenous catheters.

tissue. Debridement to prevent spread may sometimes be necessary early in the course of disease, but it can often be performed after chemotherapy, when the PMN count increases.

Sweet syndrome, or *febrile neutrophilic dermatosis*, was originally described in women with elevated white blood cell (WBC) counts. The disease is characterized by the presence of leukocytes in the lower dermis, with edema of the papillary body. Ironically, this disease now is usually seen in neutropenic patients with cancer, most often in association with acute myeloid leukemia (AML) but also in association with a variety of other malignancies. Sweet syndrome usually presents as red or bluish-red papules or nodules that may coalesce and form sharply bordered plaques **(see Fig. A1-40)**. The edema may suggest vesicles, but on palpation the lesions are solid, and vesicles probably never arise in this disease. The lesions are most common on the face, neck, and arms. On the legs, they may be confused with erythema nodosum **(see Fig. A1-39)**. The development of lesions is often accompanied by high fevers and an elevated erythrocyte sedimentation rate. Both the lesions and the temperature elevation respond dramatically to glucocorticoid administration. Treatment begins with high doses of glucocorticoids (prednisone, 60 mg/d) followed by tapered doses over the next 2–3 weeks.

Data indicate that *erythema multiforme* **(see Fig. A1-24)** with mucous membrane involvement is often associated with herpes simplex virus (HSV) infection and is distinct from Stevens-Johnson syndrome, which is associated with drugs and tends to have a more widespread distribution. Because cancer patients are both immunosuppressed (and therefore susceptible to herpes infections) and heavily treated with drugs (and therefore subject to Stevens-Johnson syndrome **[see Fig. A2-4]**), both of these conditions are common in this population.

Cytokines, which are used as adjuvants or primary treatments for cancer, can themselves cause characteristic rashes, further complicating the differential diagnosis. This phenomenon is a particular problem in bone marrow transplant recipients **(Chap. 138)**, who, in addition to having the usual chemotherapy-, antibiotic-, and cytokine-induced rashes, are plagued by graft-versus-host disease.

CATHETER-RELATED INFECTIONS

Because IV catheters are commonly used in cancer chemotherapy and are prone to cause infection **(Chap. 137)**, they pose a major problem in the care of patients with cancer. Some catheter-associated infections can be treated with antibiotics, whereas in others the catheter must be removed **(Table 70-5)**. If the patient has a "tunneled" catheter (which consists of an entrance site, a subcutaneous tunnel, and an exit site), a red streak over the subcutaneous part of the line (the tunnel) is grounds for immediate device removal. Failure to remove catheters under these circumstances may result in extensive cellulitis and tissue necrosis.

More common than tunnel infections are exit-site infections, often with erythema around the area where the line penetrates the skin. Most authorities **(Chap. 142)** recommend treatment (usually with vancomycin) for an exit-site infection caused by coagulase-negative *Staphylococcus*. Treatment of coagulase-positive staphylococcal infection is associated with a poorer outcome, and it is advisable to remove the catheter if possible. Similarly, most clinicians remove catheters associated with infections due to *P. aeruginosa* and *Candida* species, because such infections are difficult to treat and bloodstream infections with these organisms are likely to be deadly. Catheter infections caused by *Burkholderia cepacia*, *Stenotrophomonas* species, *Agrobacterium* species, *Acinetobacter baumannii*, *Pseudomonas* species other than *aeruginosa*, and carbapenem-resistant Enterobacteriaceae are likely to be very difficult to eradicate with antibiotics alone. Similarly, isolation of *Bacillus*, *Corynebacterium*, and *Mycobacterium* species should prompt removal of the catheter.

GASTROINTESTINAL TRACT–SPECIFIC SYNDROMES

Upper Gastrointestinal Tract Disease • INFECTIONS OF THE MOUTH The oral cavity is rich in aerobic and anaerobic bacteria **(Chap. 172)** that normally live in a commensal relationship with the host. The antimetabolic effects of chemotherapy cause a breakdown of mucosal host defenses, leading to ulceration of the mouth and the potential for invasion by resident bacteria. Mouth ulcerations afflict most patients receiving cytotoxic chemotherapy and have been associated with viridans streptococcal bacteremia. *Candida* infections of the mouth are very common. Fluconazole is clearly effective in the treatment of both local infections (thrush) and systemic infections (esophagitis) due to *Candida albicans*. Other azoles (e.g., voriconazole) as well as echinocandins offer similar efficacy as well as activity against the fluconazole-resistant organisms that are associated with chronic fluconazole treatment **(Chap. 211)**.

Noma (*cancrum oris*), commonly seen in malnourished children, is a penetrating disease of the soft and hard tissues of the mouth and adjacent sites, with resulting necrosis and gangrene. It has a counterpart in immunocompromised patients and is thought to be due to invasion of the tissues by *Bacteroides*, *Fusobacterium*, and other normal inhabitants of the mouth. Noma is associated with debility, poor oral hygiene, and immunosuppression.

Viruses, particularly HSV, are a prominent cause of morbidity in immunocompromised patients, in whom they are associated with

TABLE 70-5 Approach to Catheter Infections in Immunocompromised Patients

CLINICAL PRESENTATION OR ISOLATED PATHOGEN	CATHETER REMOVAL	ANTIBIOTICS	COMMENTS
Evidence of Infection, Negative Blood Cultures			
Exit-site erythema	Not necessary if infection responds to treatment	Usually, begin treatment for gram-positive cocci.	Coagulase-negative staphylococci are most common.
Tunnel-site erythema	Required	Treat for gram-positive cocci pending culture results.	Failure to remove the catheter may lead to necrosis of the involved area requiring skin grafts in the future.
Blood Culture–Positive Infections			
Coagulase-negative staphylococci	Line removal optimal but may be unnecessary if patient is clinically stable and responds to antibiotics	Usually, start with vancomycin. Linezolid, quinupristin/dalfopristin, and daptomycin are alternative agents.	If there are no contraindications to line removal, this course of action is optimal. If the line is removed, antibiotics may not be necessary.
Other gram-positive cocci (e.g., *Staphylococcus aureus*, *Enterococcus*); gram-positive rods (*Bacillus*, *Corynebacterium* spp.)	Recommended	Treat with antibiotics to which the organism is sensitive, with duration based on the clinical setting.	The incidence of metastatic infections following *S. aureus* infection and the difficulty of treating enterococcal infection make line removal the recommended course of action. In addition, gram-positive rods do not respond readily to antibiotics alone.
Gram-negative bacteria	Recommended	Use an agent to which the organism is shown to be sensitive.	Organisms like *Stenotrophomonas*, *Pseudomonas*, and *Burkholderia* are notoriously hard to treat, as are carbapenem-resistant organisms.
Fungi	Recommended	—	Fungal infections of catheters are extremely difficult to treat.

severe mucositis. The use of acyclovir, either prophylactically or therapeutically, is of value.

ESOPHAGEAL INFECTIONS The differential diagnosis of esophagitis (usually presenting as substernal chest pain upon swallowing) includes herpes simplex and candidiasis, both of which are readily treatable.

Lower Gastrointestinal Tract Disease Hepatic candidiasis (Chap. 211) results from seeding of the liver (usually from a gastrointestinal source) in neutropenic patients. It is most common among patients being treated for AML and usually presents symptomatically around the time neutropenia resolves. The characteristic picture is that of persistent fever unresponsive to antibiotics, abdominal pain and tenderness or nausea, and elevated serum levels of alkaline phosphatase in a patient with hematologic malignancy who has recently recovered from neutropenia. The diagnosis of this disease (which may present in an indolent manner and persist for several months) is based on the finding of yeasts or pseudohyphae in granulomatous lesions. Hepatic ultrasound or CT may reveal bull's-eye lesions. MRI scans reveal small lesions not visible by other imaging modalities. The pathology (a granulomatous response) and the timing (with resolution of neutropenia and an elevation in granulocyte count) suggest that the host response to *Candida* is an important component of the manifestations of disease. In many cases, although organisms are visible, cultures of biopsied material may be negative. The designation *hepatosplenic candidiasis* or *hepatic candidiasis* is a misnomer because the disease often involves the kidneys and other tissues; the term *chronic disseminated candidiasis* may be more appropriate. Because of the risk of bleeding with liver biopsy, diagnosis is often based on imaging studies (MRI, CT). Treatment should be directed to the causative agent (usually *C. albicans* but sometimes *Candida tropicalis* or other less common *Candida* species).

Typhlitis *Typhlitis* (also referred to as necrotizing colitis, neutropenic colitis, necrotizing enteropathy, ileocecal syndrome, and cecitis) is a clinical syndrome of fever and right-lower-quadrant (or generalized abdominal) tenderness in an immunosuppressed host. This syndrome is classically seen in neutropenic patients after chemotherapy with cytotoxic drugs. It may be more common among children than among adults and appears to be much more common among patients with AML or ALL than among those with other types of cancer. Physical examination reveals right-lower-quadrant tenderness, with or without rebound tenderness. Associated diarrhea (often bloody) is common, and the diagnosis can be confirmed by the finding of a thickened cecal wall on CT, MRI, or ultrasonography. Plain films may reveal a right-lower-quadrant mass, but CT with contrast or MRI is a much more sensitive means of diagnosis. Although surgery is sometimes attempted to avoid perforation from ischemia, most cases resolve with medical therapy alone. The disease is sometimes associated with positive blood cultures (which usually yield aerobic gram-negative bacilli), and therapy is recommended for a broad spectrum of bacteria (particularly gram-negative bacilli, which are likely to be found in the bowel flora).

***Clostridium difficile*–Induced Diarrhea** Patients with cancer are predisposed to the development of *C. difficile* diarrhea (Chap. 129) as a consequence of chemotherapy alone. Thus, they may test positive for *C. difficile* even without receiving antibiotics. Obviously, such patients are also subject to *C. difficile*–induced diarrhea as a result of antibiotic pressure. *C. difficile* should always be considered as a possible cause of diarrhea in cancer patients who have received either chemotherapy or antibiotics. New approaches to treatment of *C. difficile*–induced diarrhea and to prevention of *C. difficile* expansion as part of the gut microbiota may make this disease less troublesome in the future.

CENTRAL NERVOUS SYSTEM–SPECIFIC SYNDROMES

Meningitis The presentation of meningitis in patients with lymphoma or CLL and in patients receiving chemotherapy (particularly with glucocorticoids) for solid tumors suggests a diagnosis of cryptococcal or listerial infection. As noted previously, splenectomized patients are susceptible to rapid, overwhelming infection with encapsulated bacteria (including *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*). Similarly, patients who are antibody-deficient (e.g., those with CLL, those who have received intensive chemotherapy, or those who have undergone bone marrow transplantation) are likely to have infections caused by these bacteria. Other cancer patients, however, because of their defective cellular immunity, are likely to be infected with other pathogens (Table 70-3). Central nervous system (CNS) tuberculosis should be considered, especially in patients from countries where tuberculosis is highly prevalent in the population.

TABLE 70-6 Differential Diagnosis of Central Nervous System Infections in Patients with Cancer

FINDINGS ON CT OR MRI	UNDERLYING PREDISPOSITION	
	PROLONGED NEUTROPENIA	DEFECTS IN CELLULAR IMMUNITY[a]
Mass lesions	*Aspergillus*, *Nocardia*, or *Cryptococcus* brain abscess	Toxoplasmosis, Epstein-Barr virus lymphoma (rare)
Diffuse encephalitis	Progressive multifocal leukoencephalopathy (JC virus)	Infection with varicella-zoster virus, cytomegalovirus, herpes simplex virus, human herpesvirus type 6, JC virus, *Listeria*

[a]High-dose glucocorticoid therapy, cytotoxic chemotherapy.

Encephalitis The spectrum of disease resulting from viral encephalitis is expanded in immunocompromised patients. A predisposition to infections with intracellular organisms similar to those encountered in patients with AIDS (Chap. 197) is seen in cancer patients receiving (1) high-dose cytotoxic chemotherapy, (2) chemotherapy affecting T cell function (e.g., fludarabine), or (3) antibodies that eliminate T cells (e.g., anti-CD3, alemtuzumab, anti-CD52) or cytokine activity (anti–tumor necrosis factor agents or interleukin 1 receptor antagonists). Infection with varicella-zoster virus (VZV) has been associated with encephalitis that may be caused by VZV-related vasculitis. Chronic viral infections may also be associated with dementia and encephalitic presentations. A diagnosis of progressive multifocal leukoencephalopathy (Chap. 133) should be considered when a patient who has received chemotherapy (rituximab in particular) presents with dementia (Table 70-6). Other abnormalities of the CNS that may be confused with infection include normal-pressure hydrocephalus and vasculitis resulting from CNS irradiation. It may be possible to differentiate these conditions by MRI.

Brain Masses Mass lesions of the brain most often present as headache with or without fever or neurologic abnormalities. Infections associated with mass lesions may be caused by bacteria (particularly *Nocardia*), fungi (particularly *Cryptococcus* or *Aspergillus*), or parasites (*Toxoplasma*). Epstein-Barr virus (EBV)–associated lymphoma may also present as single—or sometimes multiple—mass lesions of the brain. A biopsy may be required for a definitive diagnosis.

PULMONARY INFECTIONS

Pneumonia (Chap. 121) in immunocompromised patients may be difficult to diagnose because conventional methods of diagnosis depend on the presence of neutrophils. Bacterial pneumonia in neutropenic patients may present without purulent sputum—or, in fact, without any sputum at all—and may not produce physical findings suggestive of chest consolidation (rales or egophony).

In granulocytopenic patients with persistent or recurrent fever, the chest x-ray pattern may help to localize an infection and thus to determine which investigative tests and procedures should be undertaken and which therapeutic options should be considered (Table 70-7). In this setting, a simple chest x-ray is a screening tool; because the impaired host response results in less evidence of consolidation or infiltration, high-resolution CT is recommended for the diagnosis of pulmonary infections. The difficulties encountered in the management of pulmonary infiltrates relate in part to the difficulties of performing diagnostic procedures on the patients involved. When platelet counts

TABLE 70-7 Differential Diagnosis of Chest Infiltrates in Immunocompromised Patients

	CAUSE OF PNEUMONIA	
INFILTRATE	INFECTIOUS	NONINFECTIOUS
Localized	Bacteria (including *Legionella*, mycobacteria)	Local hemorrhage or embolism, tumor
Nodular	Fungi (e.g., *Aspergillus* or *Mucor*), *Nocardia*	Recurrent tumor
Diffuse	Viruses (especially cytomegalovirus), *Chlamydia*, *Pneumocystis*, *Toxoplasma gondii*, mycobacteria	Congestive heart failure, radiation pneumonitis, drug-induced lung injury, lymphangitic spread of cancer

can be increased to adequate levels by transfusion, microscopic and microbiologic evaluation of the fluid obtained by endoscopic bronchial lavage is often diagnostic. Lavage fluid should be cultured for *Mycoplasma*, *Chlamydia*, *Legionella*, *Nocardia*, more common bacterial pathogens, fungi, and viruses. In addition, the possibility of *Pneumocystis* pneumonia should be considered, especially in patients with ALL or lymphoma who have not received prophylactic trimethoprim-sulfamethoxazole (TMP-SMX). The characteristics of the infiltrate may be helpful in decisions about further diagnostic and therapeutic maneuvers. Nodular infiltrates suggest fungal pneumonia (e.g., that caused by *Aspergillus* or *Mucor*). Such lesions may best be approached by visualized biopsy procedures. It is worth noting that while bacterial pneumonias classically present as lobar infiltrates in normal hosts, bacterial pneumonias in granulocytopenic hosts present with a paucity of signs, symptoms, or radiographic abnormalities; thus, the diagnosis is difficult.

Aspergillus species **(Chap. 212)** can colonize the skin and respiratory tract or cause fatal systemic illness. Although this fungus may cause aspergillomas in a previously existing cavity or may produce allergic bronchopulmonary disease in some patients, the major problem posed by this genus in neutropenic patients is invasive disease, primarily due to *Aspergillus fumigatus* or *Aspergillus flavus*. The organisms enter the host following colonization of the respiratory tract, with subsequent invasion of blood vessels. The disease is likely to present as a thrombotic or embolic event because of this ability of the fungi to invade blood vessels. The risk of infection with *Aspergillus* correlates directly with the duration of neutropenia. In prolonged neutropenia, positive surveillance cultures for nasopharyngeal colonization with *Aspergillus* may predict the development of disease.

Patients with *Aspergillus* infection often present with pleuritic chest pain and fever, which are sometimes accompanied by cough. Hemoptysis may be an ominous sign. Chest x-rays may reveal new focal infiltrates or nodules. Chest CT may reveal a characteristic halo consisting of a mass-like infiltrate surrounded by an area of low attenuation. The presence of a "crescent sign" on chest x-ray or chest CT, in which the mass progresses to central cavitation, is characteristic of invasive *Aspergillus* infection but may develop as the lesions are resolving.

In addition to causing pulmonary disease, *Aspergillus* may invade through the nose or palate, with deep sinus penetration. The appearance of a discolored area in the nasal passages or on the hard palate should prompt a search for invasive *Aspergillus*. This situation is likely to require surgical debridement. Catheter infections with *Aspergillus* usually require both removal of the catheter and antifungal therapy.

Diffuse interstitial infiltrates suggest viral, parasitic, or *Pneumocystis* pneumonia. If the patient has a diffuse interstitial pattern on chest x-ray, it may be reasonable, while considering invasive diagnostic procedures, to institute empirical treatment for *Pneumocystis* with TMP-SMX and for *Chlamydia*, *Mycoplasma*, and *Legionella* with a quinolone or azithromycin. Noninvasive procedures, such as staining of induced sputum smears for *Pneumocystis*, serum cryptococcal antigen tests, and urine testing for *Legionella* antigen, may be helpful. Serum galactomannan and β-D-glucan tests may be of value in diagnosing *Aspergillus* infection, but their utility is limited by their lack of sensitivity and specificity. The presence of an elevated level of β-D-glucan in the serum of a patient being treated for cancer who is not receiving prophylaxis against *Pneumocystis* suggests the diagnosis of *Pneumocystis* pneumonia. Infections with viruses that cause only upper respiratory symptoms in immunocompetent hosts, such as respiratory syncytial virus (RSV), influenza viruses, and parainfluenza viruses, may be associated with fatal pneumonitis in immunocompromised hosts. CMV reactivation occurs in cancer patients receiving chemotherapy, but CMV pneumonia is most common among hematopoietic stem cell transplant (HSCT) recipients **(Chap. 138)**. Polymerase chain reaction testing now allows rapid diagnosis of viral pneumonia, which can lead to treatment in some cases (e.g., influenza). Multiplex studies that can detect a wide array of viruses in the lung and upper respiratory tract are now available and will lead to specific diagnoses of viral pneumonias.

Bleomycin is the most common cause of chemotherapy-induced lung disease. Other causes include alkylating agents (such as cyclophosphamide, chlorambucil, and melphalan), nitrosoureas (carmustine [BCNU], lomustine [CCNU], and methyl-CCNU), busulfan, procarbazine, methotrexate, and hydroxyurea. Both infectious and noninfectious (drug- and/or radiation-induced) pneumonitis can cause fever and abnormalities on chest x-ray; thus, the differential diagnosis of an infiltrate in a patient receiving chemotherapy encompasses a broad range of conditions (Table 70-7). The treatment of radiation pneumonitis (which may respond dramatically to glucocorticoids) or drug-induced pneumonitis is different from that of infectious pneumonia, and a biopsy may be important in the diagnosis. Unfortunately, no definitive diagnosis can be made in ~30% of cases, even after bronchoscopy.

Open-lung biopsy is the gold standard of diagnostic techniques. Biopsy via a visualized thoracostomy can replace an open procedure in many cases. When a biopsy cannot be performed, empirical treatment can be undertaken; a quinolone or an erythromycin derivative (azithromycin) and TMP-SMX are used in the case of diffuse infiltrates, and an antifungal agent is administered in the case of nodular infiltrates. The risks should be weighed carefully in these cases. If inappropriate drugs are administered, empirical treatment may prove toxic or ineffective; either of these outcomes may be riskier than biopsy.

CARDIOVASCULAR INFECTIONS

Patients with Hodgkin's disease are prone to persistent infections by *Salmonella*, sometimes (and particularly often in elderly patients) affecting a vascular site. The use of IV catheters deliberately lodged in the right atrium is associated with a high incidence of bacterial endocarditis, presumably related to valve damage followed by bacteremia. Nonbacterial thrombotic endocarditis (marantic endocarditis) has been described in association with a variety of malignancies (most often solid tumors) and may follow bone marrow transplantation as well. The presentation of an embolic event with a new cardiac murmur suggests this diagnosis. Blood cultures are negative in this disease of unknown pathogenesis.

ENDOCRINE SYNDROMES

Infections of the endocrine system have been described in immunocompromised patients. *Candida* infection of the thyroid may be difficult to diagnose during the neutropenic period. It can be defined by indium-labeled WBC scans or gallium scans after neutrophil counts increase. CMV infection can cause adrenalitis with or without resulting adrenal insufficiency. The presentation of a sudden endocrine anomaly in an immunocompromised patient can be a sign of infection in the involved end organ.

MUSCULOSKELETAL INFECTIONS

Infection that is a consequence of vascular compromise, resulting in gangrene, can occur when a tumor restricts the blood supply to muscles, bones, or joints. The process of diagnosis and treatment of such infection is similar to that in normal hosts, with the following caveats:

1. *In terms of diagnosis*, a lack of physical findings resulting from a lack of granulocytes in the granulocytopenic patient should make the clinician more aggressive in obtaining tissue rather than more willing to rely on physical signs.

2. *In terms of therapy*, aggressive debridement of infected tissues may be required. However, it is usually difficult to operate on patients who have recently received chemotherapy, both because of a lack of platelets (which results in bleeding complications) and because of a lack of WBCs (which may lead to secondary infection). A blood culture positive for *Clostridium perfringens*—an organism commonly associated with gas gangrene—can have a number of meanings **(Chap. 149)**. *Clostridium septicum* bacteremia is associated with the presence of an underlying malignancy. Bloodstream infections with intestinal organisms such as *Streptococcus bovis* biotype 1 and *C. perfringens* may arise spontaneously from lower gastrointestinal lesions (tumor or polyps); alternatively, these lesions may be harbingers of invasive disease. The clinical setting must be considered in order to define the appropriate treatment for each case.

RENAL AND URETERAL INFECTIONS

Infections of the urinary tract are common among patients whose ureteral excretion is compromised (Table 70-1). *Candida*, which has a predilection for the kidney, can invade either from the bloodstream or in a retrograde manner (via the ureters or bladder) in immunocompromised patients. The presence of "fungus balls" or persistent candiduria suggests invasive disease. Persistent funguria (with *Aspergillus* as well as *Candida*) should prompt a search for a nidus of infection in the kidney.

Certain viruses are typically seen only in immunosuppressed patients. BK virus (polyomavirus hominis 1) has been documented in the urine of bone marrow transplant recipients and, like adenovirus, may be associated with hemorrhagic cystitis.

ABNORMALITIES THAT PREDISPOSE TO INFECTION

(Table 70-1)

THE LYMPHOID SYSTEM

It is beyond the scope of this chapter to detail how all the immunologic abnormalities that result from cancer or from chemotherapy for cancer lead to infections. Disorders of the immune system are discussed in other sections of this book. As has been noted, patients with antibody deficiency are predisposed to overwhelming infection with encapsulated bacteria (including *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*). Infections that result from the lack of a functional cellular immune system are described in **Chap. 197**. It is worth mentioning, however, that patients undergoing intensive chemotherapy for any form of cancer will have not only defects due to granulocytopenia but also lymphocyte dysfunction, which may be profound. Thus, these patients—especially those receiving glucocorticoid-containing regimens or drugs that inhibit either T cell activation (calcineurin inhibitors or drugs like fludarabine, which affect lymphocyte function) or cytokine induction—should be given prophylaxis for *Pneumocystis* pneumonia.

Patients receiving treatment that eliminates B cells (e.g., with anti-CD20 antibodies or rituximab) are especially vulnerable to intercurrent viral infections. The incidence of progressive multifocal leukoencephalopathy (caused by JC virus) is elevated among these patients.

THE HEMATOPOIETIC SYSTEM

Initial studies in the 1960s revealed a dramatic increase in the incidence of infections (fatal and nonfatal) among cancer patients with a granulocyte count of <500/μL. The use of prophylactic antibacterial agents has reduced the number of bacterial infections, but 35–78% of febrile neutropenic patients being treated for hematologic malignancies develop infections at some time during chemotherapy. Aerobic pathogens (both gram-positive and gram-negative) predominate in all series, but the exact organisms isolated vary from center to center. Infections with anaerobic organisms are uncommon. Geographic patterns affect the types of fungi isolated. Tuberculosis and malaria are common causes of fever in the developing world and may present in this setting as well.

Neutropenic patients are unusually susceptible to infection with a wide variety of bacteria; thus, antibiotic therapy should be initiated promptly to cover likely pathogens if infection is suspected. Indeed, early initiation of antibacterial agents is mandatory to prevent deaths. Like most immunocompromised patients, neutropenic patients are threatened by their own microbial flora, including gram-positive and gram-negative organisms found commonly on the skin and mucous membranes and in the bowel (Table 70-4). Because treatment with narrow-spectrum agents leads to infection with organisms not covered by the antibiotics used, the initial regimen should target all pathogens likely to be the initial causes of bacterial infection in neutropenic hosts. As noted in the algorithm shown in **Fig. 70-2**, administration of antimicrobial agents is routinely continued until neutropenia resolves—that is, the granulocyte count is sustained above 500/μL for at least 2 days. Fever may not resolve prior to granulocyte recovery. In some cases, patients remain febrile after resolution of neutropenia. In these instances, the risk of sudden death from overwhelming bacteremia is greatly reduced, and the following diagnoses should be seriously considered: (1) fungal infection, (2) bacterial abscesses or undrained foci of infection, and (3) drug fever (including reactions to antimicrobial agents as well as to chemotherapy or cytokines). In the proper setting, viral infection or graft-versus-host disease should be considered. In clinical practice, antibacterial therapy is usually discontinued when the patient is no longer neutropenic and all evidence of bacterial disease has been eliminated. Antifungal agents are then discontinued if there is no evidence of fungal disease. If the patient remains febrile, a search for viral diseases or unusual pathogens is conducted while unnecessary cytokines and other drugs are systematically eliminated from the regimen.

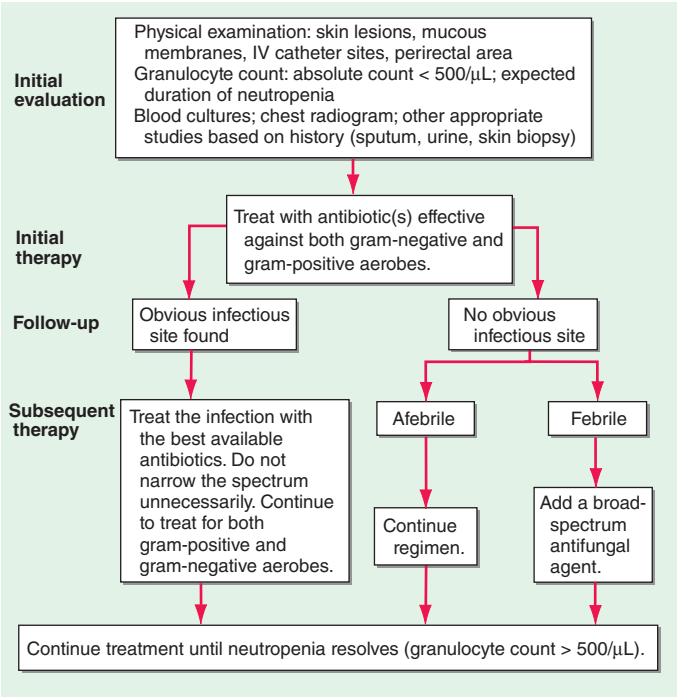

FIGURE 70-2 Algorithm for the diagnosis and treatment of fever and neutropenia.

TREATMENT

Infections in Cancer Patients

ANTIBACTERIAL THERAPY

Hundreds of antibacterial regimens have been tested for use in patients with cancer. The major risk of infection is related to the degree of neutropenia seen as a consequence of either the disease or the therapy. Many of the relevant studies have involved small populations in which the outcomes have generally been good, and most have lacked the statistical power to detect differences among the regimens studied. Each febrile neutropenic patient should be approached as a unique problem, with particular attention given to

previous infections and recent antibiotic exposures. Several general guidelines are useful in the initial treatment of neutropenic patients with fever (Fig. 70-2):

1. In the initial regimen, it is necessary to use antibiotics active against both gram-negative and gram-positive bacteria (Table 70-4).
2. Monotherapy with an aminoglycoside or an antibiotic lacking good activity against gram-positive organisms (e.g., ciprofloxacin or aztreonam) is not adequate in this setting.
3. The agents used should reflect both the epidemiology and the antibiotic resistance pattern of the hospital.
4. If the pattern of resistance justifies its use, a single third-generation cephalosporin constitutes an appropriate initial regimen in many hospitals.
5. Most standard regimens are designed for patients who have not previously received prophylactic antibiotics. The development of fever in a patient who has received antibiotics affects the choice of subsequent therapy, which should target resistant organisms and organisms known to cause infections in patients being treated with the antibiotics already administered.
6. Randomized trials have indicated the safety of oral antibiotic regimens in the treatment of "low-risk" patients with fever and neutropenia. Outpatients who are expected to remain neutropenic for <10 days and who have no concurrent medical problems (such as hypotension, pulmonary compromise, or abdominal pain) can be classified as low risk and treated with a broad-spectrum oral regimen.
7. Several large-scale studies indicate that prophylaxis with a fluoroquinolone (ciprofloxacin or levofloxacin) decreases morbidity and mortality rates among afebrile patients who are anticipated to have neutropenia of long duration.

Commonly used antibiotic regimens for the treatment of febrile patients in whom prolonged neutropenia (>7 days) is anticipated include (1) ceftazidime or cefepime, (2) piperacillin/tazobactam, or (3) imipenem/cilastatin or meropenem. All three regimens have shown equal efficacy in large trials. All three are active against *P. aeruginosa* and a broad spectrum of aerobic gram-positive and gram-negative organisms. Imipenem/cilastatin has been associated with an elevated rate of *C. difficile* diarrhea, and many centers reserve carbapenem antibiotics for treatment of gram-negative bacteria that produce extended-spectrum β-lactamases; these limitations make carbapenems less attractive as an initial regimen. Despite the frequent involvement of coagulase-negative staphylococci, the initial use of vancomycin or its automatic addition to the initial regimen has not resulted in improved outcomes, and the antibiotic does exert toxic effects. For these reasons, only judicious use of vancomycin is recommended—for example, when there is good reason to suspect the involvement of coagulase-negative staphylococci (e.g., the appearance of erythema at the exit site of a catheter or a positive culture for methicillin-resistant *S. aureus* or coagulase-negative staphylococci). Because the sensitivities of bacteria vary from hospital to hospital, clinicians are advised to check their local sensitivities and to be aware that resistance patterns can change quickly, necessitating a change in approach to patients with fever and neutropenia. Similarly, infection control services should monitor for basic antibiotic resistance and for fungal infections. The appearance of a large number of *Aspergillus* infections, in particular, suggests the possibility of an environmental source that requires further investigation and remediation.

The initial antibacterial regimen should be refined on the basis of culture results (Fig. 70-2). Blood cultures are the most relevant basis for selection of therapy; surface cultures of skin and mucous membranes may be misleading. In the case of gram-positive bacteremia or another gram-positive infection, it is important that the antibiotic be optimal for the organism isolated. Once treatment with broad-spectrum antibiotics has begun, it is not desirable to discontinue all antibiotics because of the risk of failing to treat a potentially fatal bacterial infection; the addition of more and more antibacterial agents to the regimen is not appropriate unless there is a clinical or microbiologic reason to do so. Planned progressive therapy (the serial, empirical addition of one drug after another without culture data) is not efficacious in most settings and may have unfortunate consequences. Simply adding another antibiotic for fear that a gram-negative infection is present is a dubious practice. The synergy exhibited by β-lactams and aminoglycosides against certain gram-negative organisms (especially *P. aeruginosa*) provides the rationale for using two antibiotics in this setting, but recent analyses suggest that efficacy is not enhanced by the addition of aminoglycosides, while toxicity may be increased. Mere "double coverage," with the addition of a quinolone or another antibiotic that is not likely to exhibit synergy, has not been shown to be of benefit and may cause additional toxicities and side effects. Cephalosporins can cause bone marrow suppression, and vancomycin is associated with neutropenia in some healthy individuals. Furthermore, the addition of multiple cephalosporins may induce β-lactamase production by some organisms; cephalosporins and double β-lactam combinations should probably be avoided altogether in *Enterobacter* infections.

ANTIFUNGAL THERAPY

Fungal infections in cancer patients are most often associated with neutropenia. Neutropenic patients are predisposed to the development of invasive fungal infections, most commonly those due to *Candida* and *Aspergillus* species and occasionally those caused by *Mucor, Rhizopus*, *Fusarium*, *Trichosporon*, *Bipolaris*, and others. Cryptococcal infection, which is common among patients taking immunosuppressive agents, is uncommon among neutropenic patients receiving chemotherapy for AML. Invasive candidal disease is usually caused by *C. albicans* or *C. tropicalis* but can be caused by *C. krusei*, *C. parapsilosis*, and *C. glabrata*.

For decades, it has been common clinical practice to add amphotericin B to antibacterial regimens if a neutropenic patient remains febrile despite 4–7 days of treatment with antibacterial agents. The rationale for this empirical addition is that it is difficult to culture fungi before they cause disseminated disease and that mortality rates from disseminated fungal infections in granulocytopenic patients are high. Before the introduction of newer azoles into clinical practice, amphotericin B was the mainstay of antifungal therapy. The insolubility of amphotericin B has resulted in the marketing of several lipid formulations that are less toxic than the amphotericin B deoxycholate complex. Echinocandins (e.g., caspofungin) are useful in the treatment of infections caused by azole-resistant *Candida* strains as well as in therapy for aspergillosis and have been shown to be equivalent to liposomal amphotericin B for the empirical treatment of patients with prolonged fever and neutropenia. Newer azoles have also been demonstrated to be effective in this setting. Although fluconazole is efficacious in the treatment of infections due to many *Candida* species, its use against serious fungal infections in immunocompromised patients is limited by its narrow spectrum: it has no activity against *Aspergillus* or against several non-*albicans Candida* species. The broad-spectrum azoles (e.g., voriconazole and posaconazole) provide another option for the treatment of *Aspergillus* infections **(Chap. 212)**, including CNS infection. Clinicians should be aware that the spectrum of each azole is somewhat different and that no drug can be assumed to be efficacious against all fungi. *Aspergillus terreus* is resistant to amphotericin B. Although voriconazole is active against *Pseudallescheria boydii*, amphotericin B is not; however, voriconazole has no activity against *Mucor*. Posaconazole, which is administered orally, is useful as a prophylactic agent in patients with prolonged neutropenia. Studies in progress are assessing the use of these agents in combinations. **For a full discussion of antifungal therapy, see Chap. 206.**

ANTIVIRAL THERAPY

The availability of a variety of agents active against herpes-group viruses, including some new agents with a broader spectrum of activity, has heightened focus on the treatment of viral infections, which pose a major problem in cancer patients. Viral diseases caused by the herpes group are prominent. Serious (and sometimes fatal) infections

due to HSV and VZV are well documented in patients receiving chemotherapy. CMV may also cause serious disease, but fatalities from CMV infection are more common in hematopoietic stem cell transplant recipients. The roles of human herpesvirus (HHV)-6, HHV-7, and HHV-8 (Kaposi's sarcoma–associated herpesvirus) in cancer patients are still being defined **(Chap. 190)**. EBV lymphoproliferative disease (LPD) can occur in patients receiving chemotherapy but is much more common among transplant recipients **(Chap. 138)**. While clinical experience is most extensive with acyclovir, which can be used therapeutically or prophylactically, a number of derivative drugs offer advantages over this agent **(Chap. 186)**.

In addition to the herpes group, several respiratory viruses (especially RSV) may cause serious disease in cancer patients. Although influenza vaccination is recommended (see below), it may be ineffective in this patient population. The availability of antiviral drugs with activity against influenza viruses gives the clinician additional options for the prophylaxis and treatment of these patients **(Chaps. 186 and 195)**.

OTHER THERAPEUTIC MODALITIES

Another way to address the problems posed by the febrile neutropenic patient is to replenish the neutrophil population. Although granulocyte transfusions may be effective in the treatment of refractory gram-negative bacteremia, they do not have a documented role in prophylaxis. Because of the expense, the risk of leukoagglutinin reactions (which has probably been decreased by improved cell-separation procedures), and the risk of transmission of CMV from unscreened donors (which has been reduced by the use of filters), granulocyte transfusion is reserved for patients whose condition is unresponsive to antibiotics. This modality is efficacious for documented gram-negative bacteremia refractory to antibiotics, particularly in situations where granulocyte numbers will be depressed for only a short period. The demonstrated usefulness of granulocyte colony-stimulating factor in mobilizing neutrophils and advances in preservation techniques may make this option more useful than in the past.

A variety of cytokines, including granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, enhance granulocyte recovery after chemotherapy and consequently shorten the period of maximal vulnerability to fatal infections. The role of these cytokines in routine practice is still a matter of some debate. Most authorities recommend their use only when neutropenia is both severe and prolonged, and they should be used only in the appropriate setting (i.e., when stem cells are likely to be responsive) and not as an adjunct to antimicrobial agents. The cytokines themselves may have adverse effects, including fever, hypoxemia, and pleural effusions or serositis in other areas **(Chap. 342)**.

Once neutropenia has resolved, the risk of infection decreases dramatically. However, depending on what drugs they receive, patients who continue on chemotherapeutic protocols remain at high risk for certain diseases. Any patient receiving more than a maintenance dose of glucocorticoids (e.g., in many treatment regimens for diffuse lymphoma) should also receive prophylactic TMP-SMX because of the risk of *Pneumocystis* infection; those with ALL should receive such prophylaxis for the duration of chemotherapy.

PREVENTION OF INFECTION IN CANCER PATIENTS

EFFECT OF THE ENVIRONMENT

Outbreaks of fatal *Aspergillus* infection have been associated with construction projects and materials in several hospitals. The association between spore counts and risk of infection suggests the need for a high-efficiency air-handling system in hospitals that care for large numbers of neutropenic patients. The use of laminar-flow rooms and prophylactic antibiotics has decreased the number of infectious episodes in severely neutropenic patients. However, because of the expense of such a program and the failure to show that it dramatically affects mortality rates, most centers do not routinely use laminar flow to care for neutropenic patients. Some centers use "reverse isolation," in which health care providers and visitors to a patient who is neutropenic wear gowns and gloves. Since most of the infections these patients develop are due to organisms that colonize the patients' own skin and bowel, the validity of such schemes is dubious, and limited clinical data do not support their use. Hand washing by all staff caring for neutropenic patients should be required to prevent the spread of resistant organisms.

The presence of large numbers of bacteria (particularly *P. aeruginosa*) in certain foods, especially fresh vegetables, has led some authorities to recommend a special "low-bacteria" diet. A diet consisting of cooked and canned food is satisfactory to most neutropenic patients and does not involve elaborate disinfection or sterilization protocols. However, there are no studies to support even this type of dietary restriction. Counseling of patients to avoid leftovers, deli foods, undercooked meat, and unpasteurized dairy products is recommended since these foods have been associated with outbreaks of listerial infection.

PHYSICAL MEASURES

Although few studies address this issue, patients with cancer are predisposed to infections resulting from anatomic compromise (e.g., lymphedema resulting from node dissections after radical mastectomy). Surgeons who specialize in cancer surgery can provide specific guidelines for the care of such patients, and patients benefit from common-sense advice about how to prevent infections in vulnerable areas.

IMMUNOGLOBULIN REPLACEMENT

Many patients with multiple myeloma or CLL have immunoglobulin deficiencies as a result of their disease, and all allogeneic bone marrow transplant recipients are hypogammaglobulinemic for a period after transplantation. However, current recommendations reserve intravenous immunoglobulin replacement therapy for those patients with severe, prolonged hypogammaglobulinemia (<400 mg of total IgG/dL) and a history of repeated infections. Antibiotic prophylaxis has been shown to be cheaper and is efficacious in preventing infections in most CLL patients with hypogammaglobulinemia. Routine use of immunoglobulin replacement is not recommended.

SEXUAL PRACTICES

The use of condoms is recommended for severely immunocompromised patients. Any sexual practice that results in oral exposure to feces is not recommended. Neutropenic patients should be advised to avoid any practice that results in trauma, as even microscopic cuts may result in bacterial invasion and fatal sepsis.

ANTIBIOTIC PROPHYLAXIS

Several studies indicate that the use of oral fluoroquinolones prevents infection and decreases mortality rates among severely neutropenic patients. Prophylaxis for *Pneumocystis* is mandatory for patients with ALL and for all cancer patients receiving glucocorticoid-containing chemotherapy regimens.

VACCINATION OF CANCER PATIENTS

In general, patients undergoing chemotherapy respond less well to vaccines than do normal hosts. Their greater need for vaccines thus leads to a dilemma in their management. Purified proteins and inactivated vaccines are almost never contraindicated and should be given to patients even during chemotherapy. For example, all adults should receive diphtheria–tetanus toxoid boosters at the indicated times as well as seasonal influenza vaccine. However, if possible, vaccination should not be undertaken concurrent with cytotoxic chemotherapy. If patients are expected to be receiving chemotherapy for several months and vaccination is indicated (e.g., influenza vaccination in the fall), the vaccine should be given midcycle—as far apart in time as possible from the antimetabolic agents that will prevent an immune response. The meningococcal and pneumococcal polysaccharide vaccines should be given to patients before splenectomy, if possible. The *H. influenzae* type b conjugate vaccine should be administered to all splenectomized patients.

In general, live virus (or live bacterial) vaccines should not be given to patients during intensive chemotherapy because of the risk of disseminated infection. Recommendations on vaccination are summarized in Table 70-2 (see *https://www.cdc.gov/vaccines/hcp/index.html* for updated recommendations).

FURTHER READING

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Taur Y, Pamer EG: Microbiome mediation of infections in the cancer setting. Genome Med 8:40, 2016.

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71 Oncologic Emergencies

Rasim Gucalp, Janice P. Dutcher

Emergencies in patients with cancer may be classified into three groups: pressure or obstruction caused by a space-occupying lesion, metabolic or hormonal problems (paraneoplastic syndromes, **Chap. 89**), and treatment-related complications.

STRUCTURAL-OBSTRUCTIVE ONCOLOGIC EMERGENCIES

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is the clinical manifestation of superior vena cava (SVC) obstruction, with severe reduction in venous return from the head, neck, and upper extremities. Malignant tumors, such as lung cancer, lymphoma, and metastatic tumors, are responsible for the majority of SVCS cases. With the expanding use of intravascular devices (e.g., permanent central venous access catheters, pacemaker/defibrillator leads), the prevalence of benign causes of SVCS is increasing now, accounting for at least 40% of cases. Lung cancer, particularly of small-cell and squamous cell histologies, accounts for ~85% of all cases of malignant origin. In young adults, malignant lymphoma is a leading cause of SVCS. Hodgkin's lymphoma involves the mediastinum more commonly than other lymphomas but rarely causes SVCS. When SVCS is noted in a young man with a mediastinal mass, the differential diagnosis is lymphoma versus primary mediastinal germ cell tumor. Metastatic cancers to the mediastinal lymph nodes, such as testicular and breast carcinomas, account for a small proportion of cases. Other causes include benign tumors, aortic aneurysm, thyromegaly, thrombosis, and fibrosing mediastinitis from prior irradiation, histoplasmosis, or Behçet's syndrome. SVCS as the initial manifestation of Behçet's syndrome may be due to inflammation of the SVC associated with thrombosis.

Patients with SVCS usually present with neck and facial swelling (especially around the eyes), dyspnea, and cough. Other symptoms include hoarseness, tongue swelling, headaches, nasal congestion, epistaxis, hemoptysis, dysphagia, pain, dizziness, syncope, and lethargy. Bending forward or lying down may aggravate the symptoms. The characteristic physical findings are dilated neck veins; an increased number of collateral veins covering the anterior chest wall; cyanosis; and edema of the face, arms, and chest. Facial swelling and plethora are typically exacerbated when the patient is supine. More severe cases include proptosis, glossal and laryngeal edema, and obtundation. The clinical picture is milder if the obstruction is located above the azygos vein. Symptoms are usually progressive, but in some cases, they may improve as collateral circulation develops.

Signs and symptoms of cerebral and/or laryngeal edema, though rare, are associated with a poorer prognosis and require urgent evaluation. Seizures are more likely related to brain metastases than to cerebral edema from venous occlusion. Patients with small-cell lung cancer and SVCS have a higher incidence of brain metastases than those without SVCS.

Cardiorespiratory symptoms at rest, particularly with positional changes, suggest significant airway and vascular obstruction and limited physiologic reserve. Cardiac arrest or respiratory failure can occur, particularly in patients receiving sedatives or undergoing general anesthesia.

Rarely, esophageal varices may develop, particularly in the setting of SVC syndrome due to hemodialysis catheter. These are "downhill" varices based on the direction of blood flow from cephalad to caudad (in contrast to "uphill" varices associated with caudad to cephalad flow from portal hypertension). If the obstruction to the SVC is proximal to the azygous vein, varices develop in the upper one-third of the esophagus. If the obstruction involves or is distal to the azygous vein, varices occur in the entire length of the esophagus. Variceal bleeding may be a late complication of chronic SVCS.

SVC obstruction may lead to bilateral breast edema with bilateral enlarged breast. Unilateral breast dilation may be seen as a consequence of axillary or subclavian vein blockage.

The diagnosis of SVCS is a clinical one. The most significant chest radiographic finding is widening of the superior mediastinum, most commonly on the right side. Pleural effusion occurs in only 25% of patients, often on the right side. The majority of these effusions are exudative and occasionally chylous. However, a normal chest radiograph is still compatible with the diagnosis if other characteristic findings are present. Computed tomography (CT) provides the most reliable view of the mediastinal anatomy. The diagnosis of SVCS requires diminished or absent opacification of central venous structures with prominent collateral venous circulation. Magnetic resonance imaging (MRI) is increasingly being used to diagnose SVC obstruction with a 100% sensitivity and specificity, but dyspneic SVCS patients may have difficulty remaining supine for the entire imaging process. Invasive procedures, including bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and even thoracotomy, can be performed by a skilled clinician without any major risk of bleeding. Endobronchial or esophageal ultrasound-guided needle aspiration may establish the diagnosis safely. For patients with a known cancer, a detailed workup usually is not necessary, and appropriate treatment may be started after obtaining a CT scan of the thorax. For those with no history of malignancy, a detailed evaluation is essential to rule out benign causes and determine a specific diagnosis to direct the appropriate therapy.

TREATMENT

Superior Vena Cava Syndrome

The one potentially life-threatening complication of a superior mediastinal mass is tracheal obstruction. Upper airway obstruction demands emergent therapy. Diuretics with a low-salt diet, head elevation, and oxygen may produce temporary symptomatic relief. Glucocorticoids have a limited role except in the setting of mediastinal lymphoma masses.

Radiation therapy is the primary treatment for SVCS caused by non-small-cell lung cancer and other metastatic solid tumors. Chemotherapy is effective when the underlying cancer is small-cell carcinoma of the lung, lymphoma, or germ cell tumor. SVCS recurs in 10–30% of patients; it may be palliated with the use of intravascular self-expanding stents **(Fig. 71-1)**. Early stenting may be necessary in patients with severe symptoms; however, the prompt increase in venous return after stenting may precipitate heart failure and

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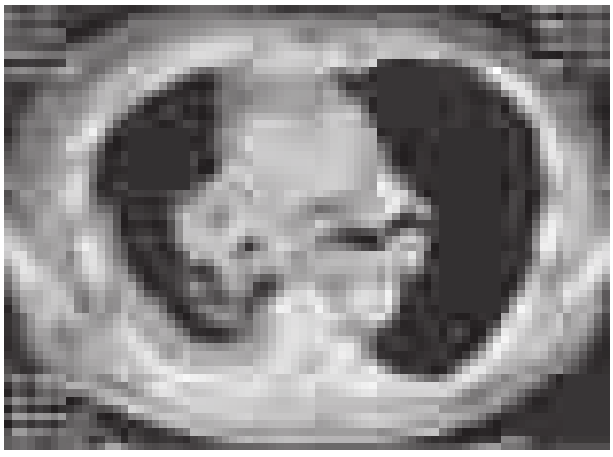

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FIGURE 71-1 Superior vena cava syndrome (SVCS). *A.* Chest radiographs of a 59-year-old man with recurrent SVCS caused by non-small-cell lung cancer showing right paratracheal mass with right pleural effusion. ***B.*** Computed tomography of same patient demonstrating obstruction of the superior vena cava with thrombosis (*arrow*) by the lung cancer (*square*) and collaterals (*arrowheads*). ***C.*** Balloon angioplasty (*arrowhead*) with Wallstent (*arrow*) in same patient.

pulmonary edema. Other complications of stent placement include hematoma at the insertion site, SVC perforation, stent migration in the right ventricle, stent fracture, and pulmonary embolism.

Clinical improvement occurs in most patients, although this improvement may be due to the development of adequate collateral circulation. The mortality associated with SVCS does not relate to caval obstruction but rather to the underlying cause.

SVCS AND CENTRAL VENOUS CATHETERS IN ADULTS

The use of long-term central venous catheters has become common practice in patients with cancer. Major vessel thrombosis may occur. In these cases, catheter removal should be combined with anticoagulation to prevent embolization. SVCS in this setting, if detected early, can be treated by fibrinolytic therapy without sacrificing the catheter. When managing patients with transvenous lead-related SVC syndrome, anticoagulation, local and systemic thrombolytic therapy, and surgical intervention can be effective therapy in select patients. Endovascular stenting has also been shown to be safe and promising, with minimal procedural or clinical complications. The role of anticoagulation after SVC stent placement is controversial.

PERICARDIAL EFFUSION/TAMPONADE

Malignant pericardial disease is found at autopsy in 5–10% of patients with cancer, most frequently with lung cancer, breast cancer, leukemias, and lymphomas. Cardiac tamponade as the initial presentation of extrathoracic malignancy is rare. The origin is not malignancy in ~50% of cancer patients with symptomatic pericardial disease, but it can be related to irradiation, drug-induced pericarditis, including chemotherapeutic agents such all-trans retinoic acid, arsenic trioxide, imatinib and other abl kinase inhibitors, hypothyroidism, idiopathic pericarditis, infection, or autoimmune diseases. Two types of radiation pericarditis occur: an acute inflammatory, effusive pericarditis occurring within months of irradiation, which usually resolves spontaneously, and a chronic effusive pericarditis that may appear up to 20 years after radiation therapy and is accompanied by a thickened pericardium.

Most patients with pericardial metastasis are asymptomatic. However, the common symptoms are dyspnea, cough, chest pain, orthopnea, and weakness. Pleural effusion, sinus tachycardia, jugular venous distention, hepatomegaly, peripheral edema, and cyanosis are the most frequent physical findings. Relatively specific diagnostic findings, such as paradoxical pulse, diminished heart sounds, pulsus alternans (pulse waves alternating between those of greater and lesser amplitude with successive beats), and friction rub are less common than with nonmalignant pericardial disease. Chest radiographs and electrocardiogram (ECG) reveal abnormalities in 90% of patients, but half of these abnormalities are nonspecific. Echocardiography is the most helpful diagnostic test. Pericardial fluid may be serous, serosanguineous, or hemorrhagic, and cytologic examination of pericardial fluid is diagnostic in most patients. Measurements of tumor markers in the pericardial fluid are not helpful in the diagnosis of malignant pericardial fluid. Pericardioscopy with targeted pericardial and epicardial biopsy may differentiate neoplastic and benign pericardial disease. A combination of cytology, pericardial and epicardial biopsy, and guided pericardioscopy gives the best diagnostic yield. CT scan of chest may also reveal the presence of a concomitant thoracic neoplasm. Cancer patients with pericardial effusion containing malignant cells on cytology have a very poor survival, ~7 weeks.

TREATMENT

Pericardial Effusion/Tamponade

Pericardiocentesis with or without the introduction of sclerosing agents, the creation of a pericardial window, complete pericardial stripping, cardiac irradiation, or systemic chemotherapy are effective treatments. Acute pericardial tamponade with life-threatening hemodynamic instability requires immediate drainage of fluid. This can be quickly achieved by pericardiocentesis. The recurrence rate after percutaneous catheter drainage is ~20%. Sclerotherapy (pericardial instillation of bleomycin, mitomycin C, or tetracycline) may

decrease recurrences. Alternatively, subxiphoid pericardiotomy can be performed in 45 min under local anesthesia. Thoracoscopic pericardial fenestration can be employed for benign causes; however, 60% of malignant pericardial effusions recur after this procedure. In a subset of patients, drainage of the pericardial effusion is paradoxically followed by worsening hemodynamic instability. This so-called "postoperative low cardiac output syndrome" occurs in up to 10% of patients undergoing surgical drainage and carries poor short-term survival.

INTESTINAL OBSTRUCTION

Intestinal obstruction and reobstruction are common problems in patients with advanced cancer, particularly colorectal or ovarian carcinoma. However, other cancers, such as lung or breast cancer and melanoma, can metastasize within the abdomen, leading to intestinal obstruction. Metastatic disease from colorectal, ovarian, pancreatic, gastric, and occasionally breast cancer can lead to peritoneal carcinomatosis, with infiltration of the omentum and peritoneal surface, thus limiting bowel motility. Typically, obstruction occurs at multiple sites in peritoneal carcinomatosis. Melanoma has a predilection to involve the small bowel; this involvement may be isolated, and resection may result in prolonged survival. Intestinal pseudoobstruction is caused by infiltration of the mesentery or bowel muscle by tumor, involvement of the celiac plexus, or paraneoplastic neuropathy in patients with small-cell lung cancer. Paraneoplastic neuropathy is associated with IgG antibodies reactive to neurons of the myenteric and submucosal plexuses of the jejunum and stomach. Ovarian cancer can lead to authentic luminal obstruction or to pseudoobstruction that results when circumferential invasion of a bowel segment arrests the forward progression of peristaltic contractions.

The onset of obstruction is usually insidious. Pain is the most common symptom and is usually colicky in nature. Pain can also be due to abdominal distention, tumor masses, or hepatomegaly. Vomiting can be intermittent or continuous. Patients with complete obstruction usually have constipation. Physical examination may reveal abdominal distention with tympany, ascites, visible peristalsis, high-pitched bowel sounds, and tumor masses. Erect plain abdominal films may reveal multiple air-fluid levels and dilation of the small or large bowel. Acute cecal dilation to >12–14 cm is considered a surgical emergency because of the high likelihood of rupture. CT scan is useful in defining the extent of disease and the exact nature of the obstruction and differentiating benign from malignant causes of obstruction in patients who have undergone surgery for malignancy. Malignant obstruction is suggested by a mass at the site of obstruction or prior surgery, adenopathy, or an abrupt transition zone and irregular bowel thickening at the obstruction site. Benign obstruction is more likely when CT shows mesenteric vascular changes, a large volume of ascites, or a smooth transition zone and smooth bowel thickening at the obstruction site. In challenging patients with obstructive symptoms, particularly low-grade small-bowel obstruction (SBO), CT enteroclysis often can help establish the diagnosis by providing distention of small-bowel loops. In this technique, water-soluble contrast is infused through a nasoenteric tube into the duodenum or proximal small bowel followed by CT images. The prognosis for the patient with cancer who develops intestinal obstruction is poor; median survival is 3–4 months. About 25–30% of patients are found to have intestinal obstruction due to causes other than cancer. Adhesions from previous operations are a common benign cause. Ileus induced by vinca alkaloids, narcotics, or other drugs is another reversible cause.

TREATMENT

Intestinal Obstruction

The management of intestinal obstruction in patients with advanced malignancy depends on the extent of the underlying malignancy, options for further antineoplastic therapy, estimated life expectancy, the functional status of the major organs, and the extent of the obstruction. The initial management should include surgical evaluation. Operation is not always successful and may lead to further complications with a substantial mortality rate (10–20%). Laparoscopy can diagnose and treat malignant bowel obstruction in some cases. Self-expanding metal stents placed in the gastric outlet, duodenum, proximal jejunum, colon, or rectum may palliate obstructive symptoms at those sites without major surgery. Patients known to have advanced intraabdominal malignancy should receive a prolonged course of conservative management, including nasogastric decompression. Percutaneous endoscopic or surgical gastrostomy tube placement is an option for palliation of nausea and vomiting, the so-called "venting gastrostomy." Treatment with antiemetics, antispasmodics, and analgesics may allow patients to remain outside the hospital. Octreotide may relieve obstructive symptoms through its inhibitory effect on gastrointestinal secretion. Glucocorticoids have anti-inflammatory effects and may help the resolution of bowel obstruction. They also have antiemetic effects.

URINARY OBSTRUCTION

Urinary obstruction may occur in patients with prostatic or gynecologic malignancies, particularly cervical carcinoma; metastatic disease from other primary sites such as carcinomas of the breast, stomach, lung, colon, and pancreas; or lymphomas. Radiation therapy to pelvic tumors may cause fibrosis and subsequent ureteral obstruction. Bladder outlet obstruction is usually due to prostate and cervical cancers and may lead to bilateral hydronephrosis and renal failure.

Flank pain is the most common symptom. Persistent urinary tract infection, persistent proteinuria, or hematuria in patients with cancer should raise suspicion of ureteral obstruction. Total anuria and/or anuria alternating with polyuria may occur. A slow, continuous rise in the serum creatinine level necessitates immediate evaluation. Renal ultrasound is the safest and cheapest way to identify hydronephrosis. The function of an obstructed kidney can be evaluated by a nuclear scan. CT scan can reveal the point of obstruction and identify a retroperitoneal mass or adenopathy.

TREATMENT

Urinary Obstruction

Obstruction associated with flank pain, sepsis, or fistula formation is an indication for immediate palliative urinary diversion. Internal ureteral stents can be placed under local anesthesia. Percutaneous nephrostomy offers an alternative approach for drainage. The placement of a nephrostomy is associated with a significant rate of pyelonephritis. In the case of bladder outlet obstruction due to malignancy, a suprapubic cystostomy can be used for urinary drainage. An aggressive intervention with invasive approaches to improve the obstruction should be weighed against the likelihood of antitumor response, and the ability to reverse renal insufficiency should be evaluated.

MALIGNANT BILIARY OBSTRUCTION

This common clinical problem can be caused by a primary carcinoma arising in the pancreas, ampulla of Vater, bile duct, or liver or by metastatic disease to the periductal lymph nodes or liver parenchyma. The most common metastatic tumors causing biliary obstruction are gastric, colon, breast, and lung cancers. Jaundice, light-colored stools, dark urine, pruritus, and weight loss due to malabsorption are usual symptoms. Pain and secondary infection are uncommon in malignant biliary obstruction. Ultrasound, CT scan, or percutaneous transhepatic or endoscopic retrograde cholangiography will identify the site and nature of the biliary obstruction.

TREATMENT

Malignant Biliary Obstruction

Palliative intervention is indicated only in patients with disabling pruritus resistant to medical treatment, severe malabsorption, or

infection. Stenting under radiographic control, surgical bypass, or radiation therapy with or without chemotherapy may alleviate the obstruction. The choice of therapy should be based on the site of obstruction (proximal vs distal), the type of tumor (sensitive to radiotherapy, chemotherapy, or neither), and the general condition of the patient. Stenting under radiographic or endoscopic control, surgical bypass, or radiation therapy with or without chemotherapy may alleviate the obstruction. Photodynamic therapy and radiofrequency ablation are promising endoscopic therapies for malignant biliary obstruction.

SPINAL CORD COMPRESSION

Malignant spinal cord compression (MSCC) is defined as compression of the spinal cord and/or cauda equina by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features. Spinal cord compression occurs in 5–10% of patients with cancer. Epidural tumor is the first manifestation of malignancy in ~10% of patients. The underlying cancer is usually identified during the initial evaluation; lung cancer is the most common cause of MSCC.

Metastatic tumor involves the vertebral column more often than any other part of the bony skeleton. Lung, breast, and prostate cancers are the most frequent offenders. Multiple myeloma also has a high incidence of spine involvement. Lymphomas, melanoma, renal cell cancer, and genitourinary cancers also cause cord compression. The thoracic spine is the most common site (70%), followed by the lumbosacral spine (20%) and the cervical spine (10%). Involvement of multiple sites is most frequent in patients with breast and prostate carcinoma. Cord injury develops when metastases to the vertebral body or pedicle enlarge and compress the underlying dura. Another cause of cord compression is direct extension of a paravertebral lesion through the intervertebral foramen. These cases usually involve a lymphoma, myeloma, or pediatric neoplasm. Parenchymal spinal cord metastasis due to hematogenous spread is rare. Intramedullary metastases can be seen in lung cancer, breast cancer, renal cancer, melanoma, and lymphoma, and are frequently associated with brain metastases and leptomeningeal disease.

Expanding extradural tumors induce injury through several mechanisms. Expanding extradural tumors induce mechanical injury to axons and myelin. Compression compromises blood flow, leading to ischemia and/or infarction.

The most common initial symptom in patients with spinal cord compression is localized back pain and tenderness due to involvement of vertebrae by tumor. Pain is usually present for days or months before other neurologic findings appear. It is exacerbated by movement and by coughing or sneezing. It can be differentiated from the pain of disk disease by the fact that it worsens when the patient is supine. Radicular pain is less common than localized back pain and usually develops later. Radicular pain in the cervical or lumbosacral areas may be unilateral or bilateral. Radicular pain from the thoracic roots is often bilateral and is described by patients as a feeling of tight, band-like constriction around the thorax and abdomen. Typical cervical radicular pain radiates down the arm; in the lumbar region, the radiation is down the legs. *Lhermitte's sign*, a tingling or electric sensation down the back and upper and lower limbs upon flexing or extending the neck, may be an early sign of cord compression. Loss of bowel or bladder control may be the presenting symptom but usually occurs late in the course. Occasionally patients present with ataxia of gait without motor and sensory involvement due to involvement of the spinocerebellar tract.

On physical examination, pain induced by straight leg raising, neck flexion, or vertebral percussion may help to determine the level of cord compression. Patients develop numbness and paresthesias in the extremities or trunk. Loss of sensibility to pinprick is as common as loss of sensibility to vibration or position. The upper limit of the zone of sensory loss is often one or two vertebrae below the site of compression. Motor findings include weakness, spasticity, and abnormal muscle stretching. An extensor plantar reflex reflects significant compression. Deep tendon reflexes may be brisk. Motor and sensory loss usually precedes sphincter disturbance. Patients with autonomic dysfunction may present with decreased anal tonus, decreased perineal sensibility, and a distended bladder. The absence of the anal wink reflex or the bulbocavernosus reflex confirms cord involvement. In doubtful cases, evaluation of postvoiding urinary residual volume can be helpful. A residual volume of >150 mL suggests bladder dysfunction. Autonomic dysfunction is an unfavorable prognostic factor. Patients with progressive neurologic symptoms should have frequent neurologic examinations and rapid therapeutic intervention. Other illnesses that may mimic cord compression include osteoporotic vertebral collapse, disk disease, pyogenic abscess or vertebral tuberculosis, radiation myelopathy, neoplastic leptomeningitis, benign tumors, epidural hematoma, and spinal lipomatosis.

Cauda equina syndrome is characterized by low back pain; diminished sensation over the buttocks, posterior-superior thighs, and perineal area in a saddle distribution; rectal and bladder dysfunction; sexual impotence; absent bulbocavernous, patellar, and Achilles' reflexes; and variable amount of lower-extremity weakness. This reflects compression of nerve roots as they form the cauda equina after leaving the spinal cord. The majority of cauda equine tumors are primary tumors of glial or nerve sheath origin; metastases are very rare.

Patients with cancer who develop back pain should be evaluated for spinal cord compression as quickly as possible **(Fig. 71-2)**. Treatment is more often successful in patients who are ambulatory and still have sphincter control at the time treatment is initiated. Patients should have a neurologic examination and plain films of the spine. Those whose physical examination suggests cord compression should receive dexamethasone starting immediately.

Erosion of the pedicles (the "winking owl" sign) is the earliest radiologic finding of vertebral tumor. Other radiographic changes include increased intrapedicular distance, vertebral destruction, lytic or sclerotic lesions, scalloped vertebral bodies, and vertebral body collapse. Vertebral collapse is not a reliable indicator of the presence of tumor; ~20% of cases of vertebral collapse, particularly those in older patients and postmenopausal women, are due not to cancer but to osteoporosis. Also, a normal appearance on plain films of the spine does not exclude the diagnosis of cancer. The role of bone scans in the detection of cord compression is not clear; this method is sensitive but less specific than spinal radiography.

The full-length image of the cord provided by MRI is the imaging procedure of choice. Multiple epidural metastases are noted in 25% of patients with cord compression, and their presence influences treatment plans. On T1-weighted images, good contrast is noted between the cord, cerebrospinal fluid (CSF), and extradural lesions. Owing to its sensitivity in demonstrating the replacement of bone marrow by tumor, MRI can show which parts of a vertebra are involved by tumor. MRI also visualizes intraspinal extradural masses compressing the cord. T2-weighted images are most useful for the demonstration of intramedullary pathology. Gadolinium-enhanced MRI can help to delineate intramedullary disease. MRI is as good as or better than myelography plus postmyelogram CT scan in detecting metastatic epidural disease with cord compression. Myelography should be reserved for patients who have poor MRIs or who cannot undergo MRI promptly. CT scan in conjunction with myelography enhances the detection of small areas of spinal destruction.

In patients with cord compression and an unknown primary tumor, a simple workup including chest radiography, mammography, measurement of prostate-specific antigen, and abdominal CT usually reveals the underlying malignancy.

TREATMENT

Spinal Cord Compression

The treatment of patients with spinal cord compression is aimed at relief of pain and restoration/preservation of neurologic function (Fig. 71-2). Management of MSCC requires a multidisciplinary approach.

Radiation therapy plus glucocorticoids is generally the initial treatment of choice for most patients with spinal cord compression.

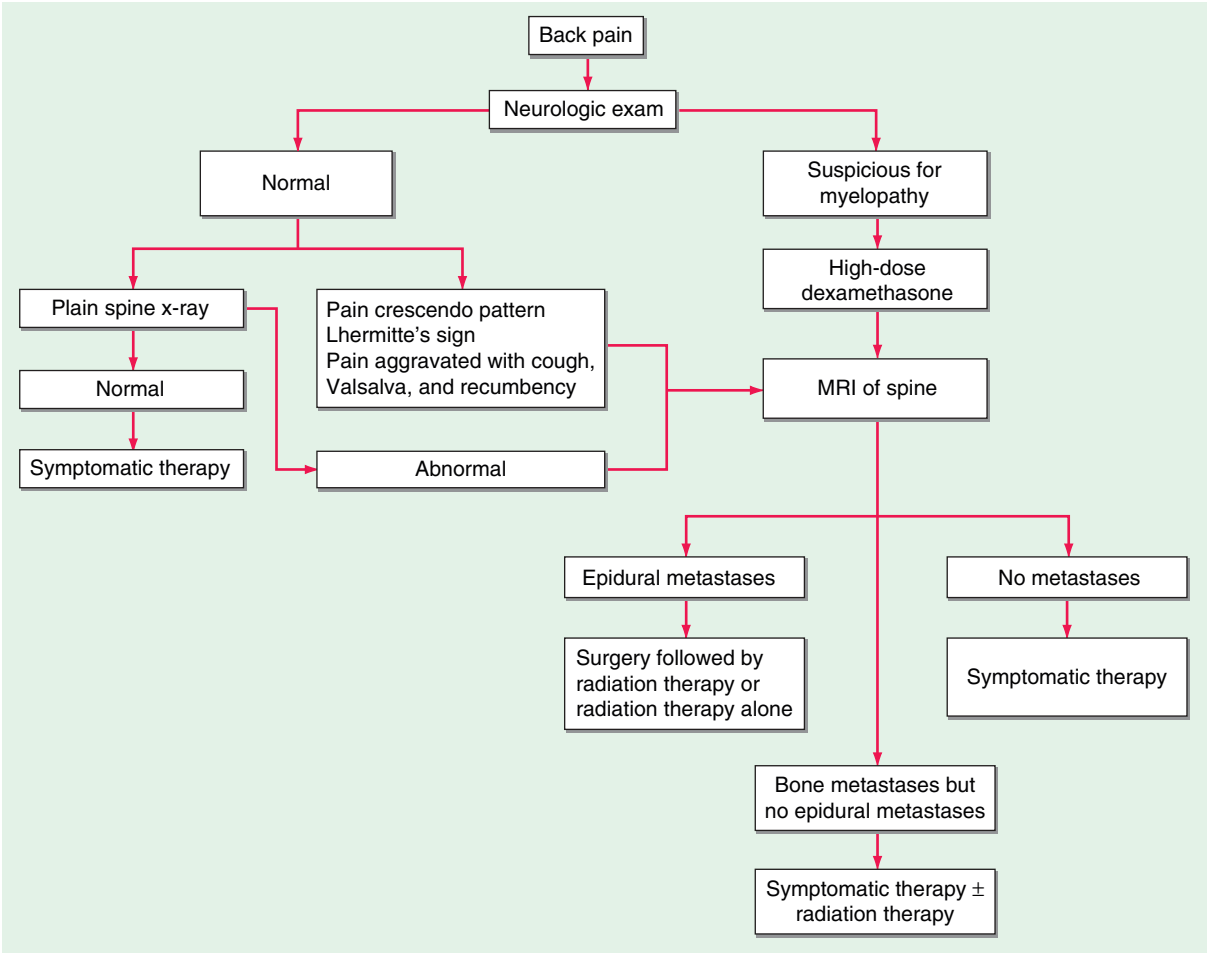


FIGURE 71-2 Management of cancer patients with back pain.

The management decision of SCC involves assessment of neurologic (N), oncologic (O), mechanical (M), and systemic factors (S). NOMS was developed by Memorial Sloan Kettering Cancer Center (MSKCC) researchers to provide an algorithm for management of SCC. The neurologic assessment is based on the degree of epidural SCC, myelopathy, and/or functional radiculopathy. Oncologic assessment involves the radio-sensitivity of the tumor type. In patients with radio-resistant tumors, stereotactic body radiotherapy (SRS) is the preferred approach if radiation is appropriate. Safe delivery of SRS requires a 2- to 3-mm margin away from the spinal cord. Separation surgery followed by SRS is necessary in patients with high-grade SCC due to radio-resistant tumors. In patients with mechanical instability or retropulsion of bone fragments into the spinal canal or cord, a surgical approach is the treatment of choice. Systemic factors that need to be considered are the extent of disease and medical comorbidities that determine the patient's ability to tolerate planned therapy. Chemotherapy may have a role in patients with chemosensitive tumors who have had prior radiotherapy to the same region and who are not candidates for surgery. Patients who previously received radiotherapy for MSCC with an in-field tumor progression can be treated with reirradiation if they are not surgical candidates.

Patients with painful pathologic compression fractures without spinal instability may benefit from percutaneous vertebroplasty or kyphoplasty, the injection of acrylic cement into a collapsed vertebra to stabilize the fracture. Pain palliation is common, and local antitumor effects have been noted. Cement leakage may cause symptoms in ~10% of patients. Bisphosphonates and/or denosumab may be helpful in prevention of SCC in patients with bony involvement.

The histology of the tumor is an important determinant of both recovery and survival. Rapid onset and progression of signs and symptoms are poor prognostic features.

INCREASED INTRACRANIAL PRESSURE

About 25% of patients with cancer die with intracranial metastases. The cancers that most often metastasize to the brain are lung and breast cancers and melanoma. Brain metastases often occur in the presence of systemic disease, and they frequently cause major symptoms, disability, and early death. The initial presentation of brain metastases from a previously unknown primary cancer is common. Lung cancer is most commonly the primary malignancy. CT scans of the chest/abdomen and MRI of the brain as the initial diagnostic studies can identify a biopsy site in most patients.

The signs and symptoms of a metastatic brain tumor are similar to those of other intracranial expanding lesions: headache, nausea, vomiting, behavioral changes, seizures, and focal, progressive neurologic changes. Occasionally the onset is abrupt, resembling a stroke, with the sudden appearance of headache, nausea, vomiting, and neurologic deficits. This picture is usually due to hemorrhage into the metastasis. Melanoma, germ cell tumors, and renal cell cancers have a particularly high incidence of intracranial bleeding. The tumor mass and surrounding edema may cause obstruction of the circulation of CSF, with resulting hydrocephalus. Patients with increased intracranial pressure may have papilledema with visual disturbances and neck stiffness. As the mass enlarges, brain tissue may be displaced through the fixed cranial openings, producing various herniation syndromes.

MRI is superior to CT scan. Gadolinium-enhanced MRI is more sensitive than CT at revealing meningeal involvement and small lesions, particularly in the brainstem or cerebellum. The MRI of the brain shows brain metastases as multiple enhancing lesions of various sizes with surrounding areas of low-density edema.

Intracranial hypertension ("pseudotumor cerebri") secondary to tretinoin therapy for acute promyelocytic leukemia has been reported, as another cause of intracranial pressure in the setting of a malignancy.

TREATMENT

Increased Intracranial Pressure

Dexamethasone is the best initial treatment for all symptomatic patients with brain metastases. Patients with multiple lesions should usually receive whole-brain radiation. Patients with a single-brain metastasis and with controlled extracranial disease may be treated with surgical excision followed by whole-brain radiation therapy, especially if they are aged <60 years. Radioresistant tumors should be resected if possible. Stereotactic radiosurgery (SRS) is recommended in patients with a limited number of brain metastases (one to four) who have stable, systemic disease or reasonable systemic treatment options and in patients who have a small number of metastatic lesions in whom whole-brain radiation therapy has failed. With a gamma knife or linear accelerator, multiple small, well-collimated beams of ionizing radiation destroy lesions seen on MRI. Some patients with increased intracranial pressure associated with hydrocephalus may benefit from shunt placement. If neurologic deterioration is not reversed with medical therapy, ventriculotomy to remove CSF or craniotomy to remove tumors or hematomas may be necessary.

Targeted agents and checkpoint inhibitors have significant activity in brain metastases from non-small-cell lung cancer, breast cancer, renal cancer, and melanoma.

NEOPLASTIC MENINGITIS

Tumor involving the leptomeninges is a complication of both primary central nervous system (CNS) tumors and tumors that metastasize to the CNS. The incidence is estimated at 3–8% of patients with cancer. Melanoma, breast and lung cancer, lymphoma (including AIDS-associated), and acute leukemia are the most common causes. Synchronous intraparenchymal brain metastases are evident in 11–31% of patients with neoplastic meningitis. Leptomeningeal seeding is frequent in patients undergoing resection of brain metastases or receiving stereotactic radiotherapy for brain metastases.

Patients typically present with multifocal neurologic signs and symptoms, including headache, gait abnormality, mental changes, nausea, vomiting, seizures, back or radicular pain, and limb weakness. Signs include cranial nerve palsies, extremity weakness, paresthesia, and decreased deep tendon reflexes.

Diagnosis is made by demonstrating malignant cells in the CSF; however, up to 40% of patients may have false-negative CSF cytology. An elevated CSF protein level is nearly always present (except in HTLV-1–associated adult T-cell leukemia). Patients with neurologic signs and symptoms consistent with neoplastic meningitis who have a negative CSF cytology should have the spinal tap repeated at least one more time for cytologic examination. MRI findings suggestive of neoplastic meningitis include leptomeningeal, subependymal, dural, or cranial nerve enhancement; superficial cerebral lesions; intradural nodules; and communicating hydrocephalus. Spinal cord imaging by MRI is a necessary component of the evaluation of nonleukemia neoplastic meningitis because ~20% of patients have cord abnormalities, including intradural enhancing nodules that are diagnostic for leptomeningeal involvement. Cauda equina lesions are common, but lesions may be seen anywhere in the spinal canal. The value of MRI for the diagnosis of leptomeningeal disease is limited in patients with hematopoietic malignancy. Radiolabeled CSF flow studies are abnormal in up to 70% of patients with neoplastic meningitis; ventricular outlet obstruction, abnormal flow in the spinal canal, or impaired flow over the cerebral convexities may affect distribution of intrathecal chemotherapy, resulting in decreased efficacy or increased toxicity. Radiation therapy may correct CSF flow abnormalities before use of intrathecal chemotherapy. Neoplastic meningitis can also lead to intracranial hypertension and hydrocephalus. Placement of a ventriculoperitoneal shunt may effectively palliate symptoms in these patients.

The development of neoplastic meningitis usually occurs in the setting of uncontrolled cancer outside the CNS; thus, prognosis is poor (median survival 10–12 weeks). However, treatment of the neoplastic meningitis may successfully alleviate symptoms and control the CNS spread.

TREATMENT

Neoplastic Meningitis

Intrathecal chemotherapy, usually methotrexate, cytarabine, or thiotepa, is delivered by lumbar puncture or by an intraventricular reservoir (Ommaya). Among solid tumors, breast cancer responds best to therapy. Focal radiotherapy may have role in bulky disease, and in symptomatic or obstructive lesions. Targeted therapy such as systemically administered epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small-cell lung cancer may improve in subgroups of cancer patients with leptomeningeal spread. Patients with neoplastic meningitis from either acute leukemia or lymphoma may be cured of their CNS disease if the systemic disease can be eliminated.

SEIZURES

Seizures occurring in a patient with cancer can be caused by the tumor itself, by metabolic disturbances, by radiation injury, by cerebral infarctions, by chemotherapy-related encephalopathies, or by CNS infections. Metastatic disease to the CNS is the most common cause of seizures in patients with cancer. However, seizures occur more frequently in primary brain tumors than in metastatic brain lesions. Seizures are a presenting symptom of CNS metastasis in 6–29% of cases. Approximately 10% of patients with CNS metastasis eventually develop seizures. Tumors that affect the frontal, temporal, and parietal lobes are more commonly associated with seizures than are occipital lesions. Both early and late seizures are uncommon in patients with posterior fossa and sellar lesions. Seizures are common in patients with CNS metastases from melanoma and low-grade primary brain tumors. Very rarely, cytotoxic drugs such as etoposide, busulfan, ifosfamide, and chlorambucil cause seizures. Another cause of seizures related to drug therapy is reversible posterior leukoencephalopathy syndrome (RPLS). Chemotherapy, targeted therapy, and immunotherapies have been associated with the development of RPLS. RPLS occurs in patients undergoing allogeneic bone marrow or solid-organ transplantation. RPLS is characterized by headache, altered consciousness, generalized seizures, visual disturbances, hypertension, and symmetric posterior cerebral white matter vasogenic edema on CT/MRI. Seizures may begin focally but are typically generalized.

TREATMENT

Seizures

Patients in whom seizures due to CNS metastases have been demonstrated should receive anticonvulsive treatment with phenytoin or levetiracetam. If this is not effective, valproic acid can be added. Prophylactic anticonvulsant therapy is not recommended. In postcraniotomy patients, prophylactic antiepileptic drugs should be withdrawn during the first week after surgery. Most antiseizure medications including phenytoin induce cytochrome P450 (CYP450), which alters the metabolism of many antitumor agents, including irinotecan, taxanes, and etoposide as well as molecular targeted agents, including imatinib, gefitinib, erlotinib, tipifarnib, sorafenib, sunitinib, temsirolimus, everolimus, and vemurafenib. Levetiracetam and topiramate are anticonvulsant agents not metabolized by the hepatic CYP450 system and do not alter the metabolism of antitumor agents. They have become the preferred drugs. Surgical resection and other antitumor treatments such as radiotherapy and chemotherapy may improve seizure control.

PULMONARY AND INTRACEREBRAL LEUKOSTASIS

Hyperleukocytosis and the leukostasis syndrome associated with it is a potentially fatal complication of acute leukemia (particularly myeloid leukemia) that can occur when the peripheral blast cell count is >100,000/mL. The frequency of hyperleukocytosis is 5–13% in acute myeloid leukemia (AML) and 10–30% in acute lymphoid leukemia; however, leukostasis is rare in lymphoid leukemia. At such high blast cell counts, blood viscosity is increased, blood flow is slowed by aggregates of tumor cells, and the primitive myeloid leukemic cells are capable of invading through the endothelium and causing hemorrhage. Brain and lung are most commonly affected. Patients with brain leukostasis may experience stupor, headache, dizziness, tinnitus, visual disturbances, ataxia, confusion, coma, or sudden death. On examination, papilledema, retinal vein distension, retinal hemorrhages, and focal deficit may be present. Pulmonary leukostasis may present as respiratory distress and hypoxemia and progress to respiratory failure. Chest radiographs may be normal but usually show interstitial or alveolar infiltrates. Hyperleukocytosis rarely may cause acute leg ischemia, renal vein thrombosis, myocardial ischemia, bowel infraction, and priapism. Arterial blood gas results should be interpreted cautiously. Rapid consumption of plasma oxygen by the markedly increased number of white blood cells can cause spuriously low arterial oxygen tension. Pulse oximetry is the most accurate way of assessing oxygenation in patients with hyperleukocytosis. Hydroxyurea can rapidly reduce a high blast cell count while the diagnostic workup is in progress. After the diagnosis is established, the patient should start quickly with effective induction chemotherapy. Leukapheresis should be used in patients with symptoms of hyperleukocytosis. Patients with hyperleukocytosis are also at the risk for disseminated intravascular coagulation and tumor lysis syndrome. The clinician should monitor the patient for these complications and take preventive and therapeutic actions during induction therapy. Intravascular volume depletion and unnecessary blood transfusions may increase blood viscosity and worsen the leukostasis syndrome. Leukostasis is very rarely a feature of the high white cell counts associated with chronic lymphoid or chronic myeloid leukemia.

When acute promyelocytic leukemia is treated with differentiating agents like tretinoin and arsenic trioxide, cerebral or pulmonary leukostasis may occur as tumor cells differentiate into mature neutrophils. This complication can be largely avoided by using cytotoxic chemotherapy together with the differentiating agents.

HEMOPTYSIS

Hemoptysis may be caused by nonmalignant conditions, but lung cancer accounts for a large proportion of cases. Up to 20% of patients with lung cancer have hemoptysis some time in their course. Endobronchial metastases from carcinoid tumors, breast cancer, colon cancer, kidney cancer, and melanoma may also cause hemoptysis. The volume of bleeding is often difficult to gauge. Massive hemoptysis is defined as >200–600 mL of blood produced in 24 h. However, any hemoptysis should be considered massive if it threatens life. When respiratory difficulty occurs, hemoptysis should be treated emergently. The first priorities are to maintain the airway, optimize oxygenation, and stabilize the hemodynamic status. If the bleeding side is known, the patient should be placed in a lateral decubitus position, with the bleeding side down to prevent aspiration into the unaffected lung, and given supplemental oxygen. If large-volume bleeding continues or the airway is compromised, the patient should be intubated and undergo emergency bronchoscopy. If the site of bleeding is detected, either the patient undergoes a definitive surgical procedure or the lesion is treated with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, argon plasma coagulation, or electrocautery. In stable patients, multidetector CT angiography delineates bronchial and nonbronchial systemic arteries and identifies the source of bleeding and underlying pathology with high sensitivity. Massive hemoptysis usually originates from the high-pressure bronchial circulation. Bronchial artery embolization is considered a first-line definite procedure for managing hemoptysis. Bronchial artery embolization may control brisk bleeding in 75–90% of patients, permitting the definitive surgical procedure to be done more safely if it is appropriate.

Embolization without definitive surgery is associated with rebleeding in 20–50% of patients. Recurrent hemoptysis usually responds to a second embolization procedure. A postembolization syndrome characterized by pleuritic pain, fever, dysphagia, and leukocytosis may occur; it lasts 5–7 days and resolves with symptomatic treatment. Bronchial or esophageal wall necrosis, myocardial infarction, and spinal cord infarction are rare complications. Surgery, as a salvage strategy, is indicated after failure of embolization and is associated with better survival when performed in a nonurgent setting.

Pulmonary hemorrhage with or without hemoptysis in hematologic malignancies is often associated with fungal infections, particularly *Aspergillus* sp. After granulocytopenia resolves, the lung infiltrates in aspergillosis may cavitate and cause massive hemoptysis. Thrombocytopenia and coagulation defects should be corrected, if possible. Surgical evaluation is recommended in patients with aspergillosis-related cavitary lesions.

Bevacizumab, an antibody to vascular endothelial growth factor (VEGF) that inhibits angiogenesis, has been associated with life-threatening hemoptysis in patients with non-small-cell lung cancer, particularly of squamous cell histology. Non-small-cell lung cancer patients with cavitary lesions or previous hemoptysis (≥2.5 mL) within the past 3 months have higher risk for pulmonary hemorrhage.

AIRWAY OBSTRUCTION

Airway obstruction refers to a blockage at the level of the mainstem bronchi or above. It may result either from intraluminal tumor growth or from extrinsic compression of the airway. The most common cause of malignant upper airway obstruction is invasion from an adjacent primary tumor, most commonly lung cancer, followed by esophageal, thyroid, and mediastinal malignancies including lymphomas. Extrathoracic primary tumors such as renal, colon, or breast cancer can cause airway obstruction through endobronchial and/or mediastinal lymph node metastases. Patients may present with dyspnea, hemoptysis, stridor, wheezing, intractable cough, postobstructive pneumonia, or hoarseness. Chest radiographs usually demonstrate obstructing lesions. CT scans reveal the extent of tumor. Cool, humidified oxygen, glucocorticoids, and ventilation with a mixture of helium and oxygen (Heliox) may provide temporary relief. If the obstruction is proximal to the larynx, a tracheostomy may be lifesaving. For more distal obstructions, particularly intrinsic lesions incompletely obstructing the airway, bronchoscopy with mechanical debulking and dilation or ablational treatments including laser treatment, photodynamic therapy, argon plasma coagulation, electrocautery, or stenting can produce immediate relief in most patients **(Fig. 71-3)**. However, radiation therapy (either external-beam irradiation or brachytherapy) given together with glucocorticoids may also open the airway. Symptomatic extrinsic compression may be palliated by stenting. Patients with primary airway tumors such as squamous cell carcinoma, carcinoid tumor, adenocystic carcinoma, or non-small-cell lung cancer, if resectable, should have surgery.

METABOLIC EMERGENCIES

HYPERCALCEMIA

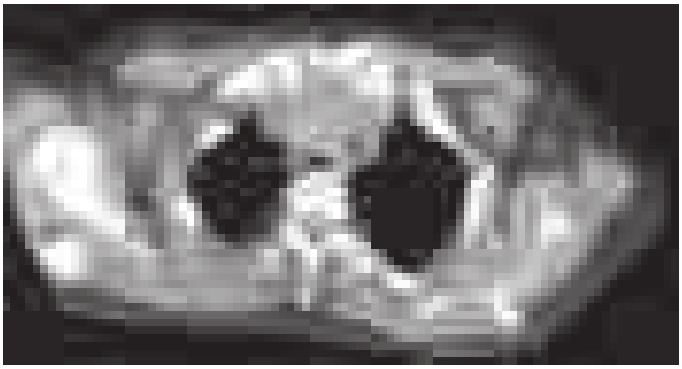
Hypercalcemia is the most common paraneoplastic syndrome. **Its pathogenesis and management are discussed fully in Chaps. 89 and 403.**

SYNDROME OF INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE

Hyponatremia is a common electrolyte abnormality in cancer patients, and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the most common cause among patients with cancer. **SIADH is discussed fully in Chaps. 89 and 374.**

LACTIC ACIDOSIS

Lactic acidosis is a rare and potentially fatal metabolic complication of cancer. Lactic acidosis associated with sepsis and circulatory failure is



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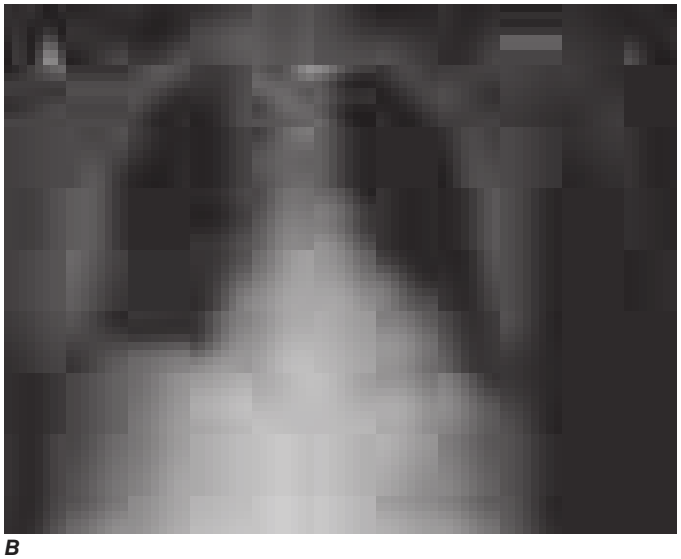

B

FIGURE 71-3 Airway obstruction. *A.* Computed tomography scan of a 62-year-old man with tracheal obstruction caused by renal carcinoma showing paratracheal mass with tracheal invasion/obstruction (*arrow*). ***B.*** Chest x-ray of same patient after stent (*arrows*) placement.

a common preterminal event in many malignancies. Lactic acidosis in the absence of hypoxemia may occur in patients with leukemia, lymphoma, or solid tumors. In some cases, hypoglycemia also is present. Extensive involvement of the liver by tumor is often present. In most cases, decreased metabolism and increased production by the tumor both contribute to lactate accumulation. Tumor cell overexpression of certain glycolytic enzymes and mitochondrial dysfunction can contribute to its increased lactate production. HIV-infected patients have an increased risk of aggressive lymphoma; lactic acidosis that occurs in such patients may be related either to the rapid growth of the tumor or from toxicity of nucleoside reverse transcriptase inhibitors. Symptoms of lactic acidosis include tachypnea, tachycardia, change of mental status, and hepatomegaly. The serum level of lactic acid may reach 10–20 mmol/L (90–180 mg/dL). Treatment is aimed at the underlying disease. *The danger from lactic acidosis is from the acidosis, not the lactate.* Sodium bicarbonate should be added if acidosis is very severe or if hydrogen ion production is very rapid and uncontrolled. Other treatment options include renal replacement therapy, such as hemodialysis, and thiamine replacement. The prognosis is poor regardless of the treatment offered.

HYPOGLYCEMIA

Persistent hypoglycemia is occasionally associated with tumors other than pancreatic islet cell tumors. Usually these tumors are large; tumors of mesenchymal origin, hepatomas, or adrenocortical tumors may cause hypoglycemia. Mesenchymal tumors are usually located in the retroperitoneum or thorax. Obtundation, confusion, and behavioral aberrations occur in the postabsorptive period and may precede the diagnosis of the tumor. These tumors often secrete incompletely processed insulin-like growth factor II (IGF-II), a hormone capable of activating insulin receptors and causing hypoglycemia. Tumors secreting incompletely processed big IGF-II are characterized by an increased IGF-II to IGF-I ratio, suppressed insulin and C-peptide level, and inappropriately low growth hormone and β-hydroxybutyrate concentrations. Rarely, hypoglycemia is due to insulin secretion by a non-islet cell carcinoma. The development of hepatic dysfunction from liver metastases and increased glucose consumption by the tumor can contribute to hypoglycemia. If the tumor cannot be resected, hypoglycemia symptoms may be relieved by the administration of glucose, glucocorticoids, recombinant growth hormone, or glucagon.

Hypoglycemia can be artifactual; hyperleukocytosis from leukemia, myeloproliferative diseases, leukemoid reactions, or colony-stimulating factor treatment can increase glucose consumption in the test tube after blood is drawn, leading to pseudohypoglycemia.

ADRENAL INSUFFICIENCY

In patients with cancer, adrenal insufficiency may go unrecognized because the symptoms, such as nausea, vomiting, anorexia, and orthostatic hypotension, are nonspecific and may be mistakenly attributed to progressive cancer or to therapy. Primary adrenal insufficiency may develop owing to replacement of both glands by metastases (lung, breast, colon, or kidney cancer; lymphoma), to removal of both glands, or to hemorrhagic necrosis in association with sepsis or anticoagulation. Impaired adrenal steroid synthesis occurs in patients being treated for cancer with mitotane, ketoconazole, or aminoglutethimide or undergoing rapid reduction in glucocorticoid therapy. Megestrol acetate, used to manage cancer and HIV-related cachexia, may suppress plasma levels of cortisol and adrenocorticotropic hormone (ACTH). Patients taking megestrol may develop adrenal insufficiency, and even those whose adrenal dysfunction is not symptomatic may have inadequate adrenal reserve if they become seriously ill. Paradoxically, some patients may develop Cushing's syndrome and/or hyperglycemia because of the glucocorticoid-like activity of megestrol acetate. Ipilimumab, an anti-CTLA-4 antibody used for treatment of malignant melanoma, may cause autoimmunity including autoimmune-like enterocolitis, hypophysitis, (leading to secondary adrenal insufficiency), hepatitis, and, rarely, primary adrenal insufficiency. Autoimmune hypophysitis may present with headache, visual field defects, and pituitary hormone deficiencies manifesting as hypopituitarism, adrenal insufficiency (including adrenal crisis), or hypothyroidism. Ipilimumab-associated hypophysitis symptoms occur at an average of 6–12 weeks after initiation of therapy. An MRI usually shows homogenous enhancement of pituitary gland. Early glucocorticoid treatment and hormone replacement are the initial treatment. The role of high-dose glucocorticoids in the treatment of hypophysitis is not clear. High-dose glucocorticoids may not improve the frequency of pituitary function recovery. Autoimmune adrenalitis can also be observed with anti-CTLA-4 antibody. Pituitary dysfunction is usually permanent, requiring long term hormone replacement therapy. Other checkpoint inhibitors, monoclonal antibodies targeting program death-1 (PD-1), an inhibitory receptor expressed by T cells or one of its ligands (PD-L1) may cause hypophysitis infrequently (~1 %). Autoimmune adrenalitis is more frequent with use of PD/PD-L1 than with CTLA-4 inhibitors, but incidence is low. Cranial irradiation for childhood brain tumors may affect the hypothalamus-pituitary-adrenal axis, resulting in secondary adrenal insufficiency. Rarely, metastatic replacement causes primary adrenal insufficiency as the first manifestation of an occult malignancy. Metastasis to the pituitary or hypothalamus is found at autopsy in up to 5% of patients with cancer, but associated secondary adrenal insufficiency is rare.

Acute adrenal insufficiency is potentially lethal. Treatment of suspected adrenal crisis is initiated after the sampling of serum cortisol and ACTH levels **(Chap. 379)**.

TREATMENT-RELATED EMERGENCIES

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, and is caused by the destruction of a large number of rapidly proliferating neoplastic cells. Acidosis may also develop. Acute renal failure occurs frequently.

TLS is most often associated with the treatment of Burkitt's lymphoma, acute lymphoblastic leukemia, and other rapidly proliferating lymphomas, but it also may be seen with chronic leukemias and, rarely, with solid tumors. This syndrome has been seen in patients with chronic lymphocytic leukemia after treatment with nucleosides like fludarabine and is increased in frequency in lymphoid neoplasms treated with venetoclax, a bcl-2 antagonist. TLS has been observed with administration of glucocorticoids, hormonal agents such as letrozole and tamoxifen, and monoclonal antibodies such as rituximab and gemtuzumab. TLS usually occurs during or shortly (1–5 days) after chemotherapy. Rarely, spontaneous necrosis of malignancies causes TLS.

Hyperuricemia may be present at the time of chemotherapy. Effective treatment kills malignant cells and leads to increased serum uric acid levels from the turnover of nucleic acids. Owing to the acidic local environment, uric acid can precipitate in the tubules, medulla, and collecting ducts of the kidney, leading to renal failure. Lactic acidosis and dehydration may contribute to the precipitation of uric acid in the renal tubules. The finding of uric acid crystals in the urine is strong evidence for uric acid nephropathy. The ratio of urinary uric acid to urinary creatinine is >1 in patients with acute hyperuricemic nephropathy and <1 in patients with renal failure due to other causes.

Hyperphosphatemia, which can be caused by the release of intracellular phosphate pools by tumor lysis, produces a reciprocal depression in serum calcium, which causes severe neuromuscular irritability and tetany. Deposition of calcium phosphate in the kidney and hyperphosphatemia may cause renal failure. Potassium is the principal intracellular cation, and massive destruction of malignant cells may lead to hyperkalemia. Hyperkalemia in patients with renal failure may rapidly become life threatening by causing ventricular arrhythmias and sudden death.

The likelihood that TLS will occur in patients with Burkitt's lymphoma is related to the tumor burden and renal function. Hyperuricemia and high serum levels of lactate dehydrogenase (LDH >1500 U/L), both of which correlate with total tumor burden, also correlate with the risk of TLS. In patients at risk for TLS, pretreatment evaluations should include a complete blood count, serum chemistry evaluation, and urine analysis. High leukocyte and platelet counts may artificially elevate potassium levels ("pseudohyperkalemia") due to lysis of these cells after the blood is drawn. In these cases, plasma potassium instead of serum potassium should be followed. In pseudohyperkalemia, no electrocardiographic abnormalities are present. In patients with abnormal baseline renal function, the kidneys and retroperitoneal area should be evaluated by sonography and/or CT to rule out obstructive uropathy. Urine output should be watched closely.

TREATMENT

Tumor Lysis Syndrome

Recognition of risk and prevention are the most important steps in the management of this syndrome **(Fig. 71-4)**. The standard preventive approach consists of allopurinol and aggressive hydration. Urinary alkalization with sodium bicarbonate is no longer recommended. It increases uric acid solubility, but a high pH decreases the solubility of xanthine, hypoxanthine, and calcium phosphate, potentially increasing the likelihood of intratubular crystallization. Intravenous allopurinol may be given in patients who cannot tolerate oral therapy. Febuxostat, a potent nonpurine selective xanthine oxidase inhibitor, is indicated for treatment of hyperuricemia. It has less hypersensitivity reactions than allopurinol. Febuxostat does not require dosage adjustment in patients with mild to moderate renal impairment. Febuxostat achieved significantly superior serum uric acid control in comparison to allopurinol in patients with hematologic malignancies at intermediate to high TLS risk. In some cases, uric acid levels cannot be lowered sufficiently with the standard preventive approach. Rasburicase (recombinant urate oxidase) can be effective in these instances, particularly when renal failure is present. Urate oxidase is missing from primates and catalyzes the conversion of poorly soluble uric acid to readily soluble allantoin. Rasburicase acts rapidly, decreasing uric acid levels within hours; however, it may cause hypersensitivity reactions such as bronchospasm, hypoxemia, and hypotension. Rasburicase should also be administered to high-risk patients for TLS prophylaxis. Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency who are unable to break down hydrogen peroxide, an end product of the urate oxidase reaction. Rasburicase is known to cause ex vivo enzymatic degradation of uric acid in test tube at room temperature. This leads to spuriously low uric acid levels during laboratory monitoring of the patient with TLS. Samples must be cooled immediately to deactivate the urate oxidase. Despite aggressive prophylaxis, TLS and/or oliguric or anuric renal failure may occur. Dialysis is often necessary and should be considered early in the course. Hemodialysis is preferred. Hemofiltration offers a gradual, continuous method of removing cellular by-products and fluid.

HUMAN ANTIBODY INFUSION REACTIONS

The initial infusion of human or humanized antibodies (e.g., rituximab, gemtuzumab, trastuzumab, alemtuzumab, panitumumab, brentuximab vedotin, blinatumomab) is associated with fever, chills, nausea, asthenia, and headache in up to half of treated patients. Bronchospasm and hypotension occur in 1% of patients. Severe manifestations including pulmonary infiltrates, acute respiratory distress syndrome (ARDS), and cardiogenic shock occur rarely. Laboratory manifestations include elevated hepatic aminotransferase levels, thrombocytopenia, and prolongation of prothrombin time. The pathogenesis is thought to be activation of immune effector processes (cells and complement) and release of inflammatory cytokines, such as tumor necrosis factor α, interferon gamma, interleukin 6, and interleukin 10 (cytokine release syndrome [CRS]). Although its origins are not completely understood, CRS is believed to be due to activation of a variety of cell types including monocytes/macrophages and T and B lymphocytes. Severe reactions from rituximab have occurred with high numbers (>50 × 10^9 lymphocytes) of circulating cells bearing the target antigen (CD20) and have been associated with a rapid fall in circulating tumor cells, mild electrolyte evidence of TLS, and, very rarely, death. In addition, increased liver enzymes, D-dimer, and LDH and prolongation of the prothrombin time may occur. Diphenhydramine, hydrocortisone, and acetaminophen can often prevent or suppress the infusion-related symptoms. If they occur, the infusion is stopped and restarted at half the initial infusion rate after the symptoms have abated. Severe CRS may require intensive support for ARDS and resistant hypotension. Emerging clinical experience at several institutions has concluded that tocilizumab is an effective treatment for severe or life-threatening CRS. Tocilizumab prevents IL-6 binding to both cell-associated and soluble IL-6Rs and therefore inhibits both classical and trans-IL-6 signaling.

Adoptive transfer of chimeric antigen receptor (CAR)–engineered T cells is a promising therapy for cancers. The most common acute toxicity of CAR T cells is CRS. CAR T-cell–associated CRS may be associated cardiac dysfunction and neurotoxicity. The management includes supportive care and tocilizumab.

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome (HUS) and, less commonly, thrombotic thrombocytopenic purpura (TTP) **(Chap. 311)** may rarely occur after treatment with antineoplastic drugs, including mitomycin, gemcitabine, cisplatin, and bleomycin, and with VEGF inhibitors. Mitomycin and gemcitabine are the most common offenders. Unlike mitomycin, there is no clear-cut relationship between the cumulative dose of gemcitabine and risk of HUS. It occurs most often in patients with gastric, lung, colorectal, pancreatic, and breast carcinoma. In one series, 35%

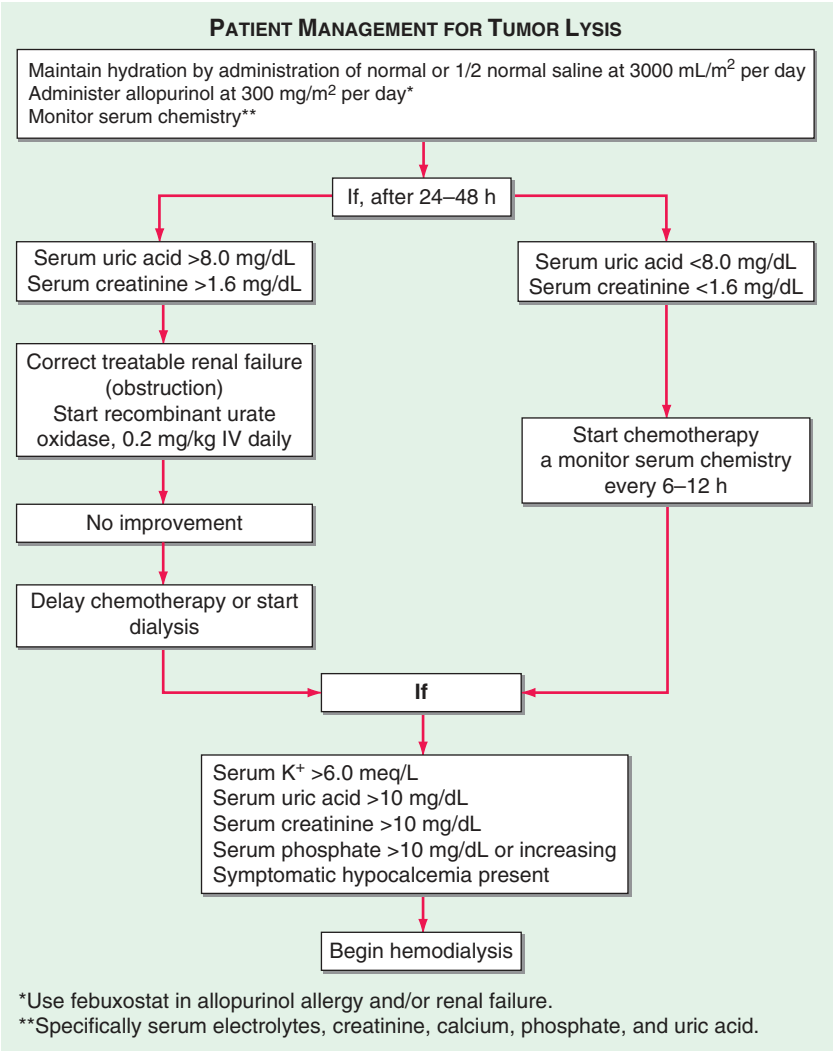

FIGURE 71-4 Management of patients at high risk for the tumor lysis syndrome.

of patients were without evident cancer at the time this syndrome appeared. Secondary HUS/TTP has also been reported as a rare but sometimes fatal complication of BMT.

HUS usually has its onset 4–8 weeks after the last dose of chemotherapy, but it is not rare to detect it several months later. HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Dyspnea, weakness, fatigue, oliguria, and purpura are also common initial symptoms and findings. Systemic hypertension and pulmonary edema frequently occur. Severe hypertension, pulmonary edema, and rapid worsening of hemolysis and renal function may occur after a blood or blood product transfusion. Cardiac findings include atrial arrhythmias, pericardial friction rub, and pericardial effusion. Raynaud's phenomenon is part of the syndrome in patients treated with bleomycin.

Laboratory findings include severe to moderate anemia associated with red blood cell fragmentation and numerous schistocytes on peripheral smear. Reticulocytosis, decreased plasma haptoglobin, and an LDH level document hemolysis. The serum bilirubin level is usually normal or slightly elevated. The Coombs' test is negative. The white cell count is usually normal, and thrombocytopenia (<100,000/μL) is almost always present. Most patients have a normal coagulation profile, although some have mild elevations in thrombin time and in levels of fibrin degradation products. The serum creatinine level is elevated at presentation and shows a pattern of subacute worsening within weeks of the initial azotemia. The urinalysis reveals hematuria, proteinuria, and granular or hyaline casts, and circulating immune complexes may be present.

The basic pathologic lesion appears to be deposition of fibrin in the walls of capillaries and arterioles, and these deposits are similar to those seen in HUS due to other causes. These microvascular abnormalities involve mainly the kidneys and rarely occur in other organs. The pathogenesis of cancer treatment–related HUS is not completely understood, but probably the most important factor is endothelial damage. Primary forms of HUS/TTP are related to a decrease in processing of von Willebrand factor by a protease called ADAMTS13.

The case fatality rate is high; most patients die within a few months. There is no consensus on the optimal treatment for chemotherapy-induced HUS. Treatment modalities for HUS/TTP including immunocomplex removal (plasmapheresis, immunoadsorption, or exchange transfusion), antiplatelet/anticoagulant therapies, immunosuppressive therapies, and plasma exchange have varying degrees of success. The outcome with plasma exchange is generally poor, as in many other cases of secondary TTP. Rituximab is successfully used in patients with chemotherapy-induced HUS as well as in ADAMTS13-deficient TTP.

NEUTROPENIA AND INFECTION

These remain the most common serious complications of cancer therapy. **They are covered in detail in Chap. 70.**

PULMONARY INFILTRATES

Patients with cancer may present with dyspnea associated with diffuse interstitial infiltrates on chest radiographs. Such infiltrates may be due to progression of the underlying malignancy, treatment-related toxicities, infection, and/or unrelated diseases. The cause may be multifactorial; however, most commonly they occur as a consequence of treatment. Infiltration of the lung by malignancy has been described in patients with leukemia, lymphoma, and breast and other solid cancers. Pulmonary lymphatics may be involved diffusely by neoplasm (pulmonary lymphangitic carcinomatosis), resulting in a diffuse increase in interstitial markings on chest radiographs. The patient is often mildly dyspneic at the onset, but pulmonary failure develops over a period of weeks. In some patients, dyspnea precedes changes on the chest radiographs and is accompanied by a nonproductive cough. This syndrome is characteristic of solid tumors. In patients with leukemia, diffuse microscopic neoplastic peribronchial and peribronchiolar infiltration is frequent but may be asymptomatic. However, some patients present with diffuse interstitial infiltrates, an alveolar capillary block syndrome, and respiratory distress. Thickening of bronchovascular bundles and prominence of peripheral arteries are CT findings suggestive of leukemic infiltration. In these situations, glucocorticoids can provide symptomatic relief, but specific chemotherapy should always be started promptly.

Several cytotoxic agents, such as bleomycin, methotrexate, busulfan, nitrosoureas, gemcitabine, mitomycin, vinorelbine, docetaxel, paclitaxel, fludarabine, pentostatin, and ifosfamide may cause pulmonary damage. The most frequent presentations are interstitial pneumonitis, alveolitis, and pulmonary fibrosis. Some cytotoxic agents, including methotrexate and procarbazine, may cause an acute hypersensitivity reaction. Cytosine arabinoside has been associated with noncardiogenic pulmonary edema. Administration of multiple cytotoxic drugs, as well as radiotherapy and preexisting lung disease, may potentiate the pulmonary toxicity. Supplemental oxygen may potentiate the effects of drugs and radiation injury. Patients should always be managed with the lowest F_{IO_2} that is sufficient to maintain hemoglobin saturation.

The onset of symptoms may be insidious, with symptoms including dyspnea, nonproductive cough, and tachycardia. Patients may have bibasilar crepitant rales, end-inspiratory crackles, fever, and cyanosis. The chest radiograph generally shows an interstitial and sometimes an

intraalveolar pattern that is strongest at the lung bases and may be symmetric. A small effusion may occur. Hypoxemia with decreased carbon monoxide diffusing capacity is always present. Glucocorticoids may be helpful in patients in whom pulmonary toxicity is related to radiation therapy or to chemotherapy. Treatment is otherwise supportive.

Molecular targeted agents, imatinib, erlotinib, and gefitinib are potent inhibitors of tyrosine kinases. These drugs may cause interstitial lung disease (ILD). In the case of gefitinib, preexisting fibrosis, poor performance status, and prior thoracic irradiation are independent risk factors; this complication has a high fatality rate. In Japan, incidence of ILD associated with gefitinib was ~4.5% compared to 0.5% in the United States. Temsirolimus and everolimus, both esters a derivative of rapamycin, are agents that block the effects of mammalian target of rapamycin (mTOR), an enzyme that has an important role in regulating the synthesis of proteins that control cell division. It may cause ground-glass opacities in the lung with or without diffuse interstitial disease and lung parenchymal consolidation. Patients may be asymptomatic with only radiologic findings or may be symptomatic. Symptoms include cough, dyspnea, and/or hypoxemia, and sometimes patients present with systemic symptoms such as fever and fatigue. The incidence of everolimus-induced ILD also appears to be higher in Japanese patients. Treatment includes dose reduction or withdrawal and, in some cases, the addition of glucocorticoids.

The Food and Drug Administration (FDA)–approved immune checkpoint inhibitors of the PD-1 and PD-L1 pathway, including nivolumab, pembrolizumab, durvalumab, avelumab, and atezolizumab, enhance antitumor activity by blocking negative regulators of T cell function. Immune-mediated pneumonitis is rare (10%) but a life-threatening complication of these drugs. Pneumonitis symptoms include cough, shortness of breath, dyspnea, and fever, and often involve only asymptomatic radiographic changes. Pneumonitis shows ground-glass patchy lesions and/or disseminated nodular infiltrates, predominantly in the lower lobes. Treatment includes temporary or permanent withdrawal of drug and the addition of high-dose glucocorticoids.

Radiation pneumonitis and/or fibrosis are relatively frequent side effects of thoracic radiation therapy. It may be acute or chronic. Radiation-induced lung toxicity is a function of the irradiated lung volume, dose per fraction, and radiation dose. The larger the irradiated lung field, the higher is the risk for radiation pneumonitis. The use of concurrent chemoradiation, particularly regimens including paclitaxel, increases pulmonary toxicity. Radiation pneumonitis usually develops 2–6 months after completion of radiotherapy. The clinical syndrome, which varies in severity, consists of dyspnea, cough with scanty sputum, low-grade fever, and an initial hazy infiltrate on chest radiographs. The infiltrate and tissue damage usually are confined to the radiation field. The CT scan may show ground-glass opacities, consolidation, fibrosis, atelectatic cicatrization, pleural volume loss, or pleural thickening. The patients subsequently may develop a patchy alveolar infiltrate and air bronchograms, which may progress to acute respiratory failure that is sometimes fatal. A lung biopsy may be necessary to make the diagnosis. Asymptomatic infiltrates found incidentally after radiation therapy need not be treated. However, prednisone should be administered to patients with fever or other symptoms. The dosage should be tapered slowly after the resolution of radiation pneumonitis, because abrupt withdrawal of glucocorticoids may cause an exacerbation of pneumonia. Delayed radiation fibrosis may occur years after radiation therapy and is signaled by dyspnea on exertion. Often it is mild, but it can progress to chronic respiratory failure. Therapy is supportive.

Classic radiation pneumonitis that leads to pulmonary fibrosis is due to radiation-induced production of local cytokines such as platelet-derived growth factor β, tumor necrosis factor, interleukins, and transforming growth factor β in the radiation field.

Stereotactic body radiation therapy (SBRT) is a radiotherapy treatment method that has been applied to the treatment of stage I lung cancers in medically inoperable patients. SBRT accurately delivers a high dose of irradiation in one or few treatment fractions to an image-defined lung mass. Most of the acute changes after SBRT occur later than 3 months after treatment, and the shape of the SBRT-induced injury conforms more tightly to the tumor.

Pneumonia is a common problem in patients undergoing treatment for cancer (see Chap 70). In patients with pulmonary infiltrates who are afebrile, heart failure and multiple pulmonary emboli are in the differential diagnosis.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (typhlitis) is the inflammation and necrosis of the cecum and surrounding tissues that may complicate the treatment of acute leukemia. Nevertheless, it may involve any segment of the gastrointestinal tract including small intestine, appendix, and colon. This complication has also been seen in patients with other forms of cancer treated with taxanes, 5-fluorouracil, irinotecan, vinorelbine, cisplatin, carboplatin, and high-dose chemotherapy **(Fig. 71-5)**. It also has been reported in patients with AIDS, aplastic anemia, cyclic neutropenia, idiosyncratic drug reactions involving antibiotics, and immunosuppressive therapies. The patient develops right lower quadrant abdominal pain, often with rebound tenderness and a tense, distended abdomen, in a setting of fever and neutropenia. Watery diarrhea (often containing sloughed mucosa) and bacteremia are common, and bleeding may occur. Plain abdominal films are generally of little value in the diagnosis; CT scan may show marked bowel wall thickening, particularly in the cecum, with bowel wall edema, mesenteric stranding, and

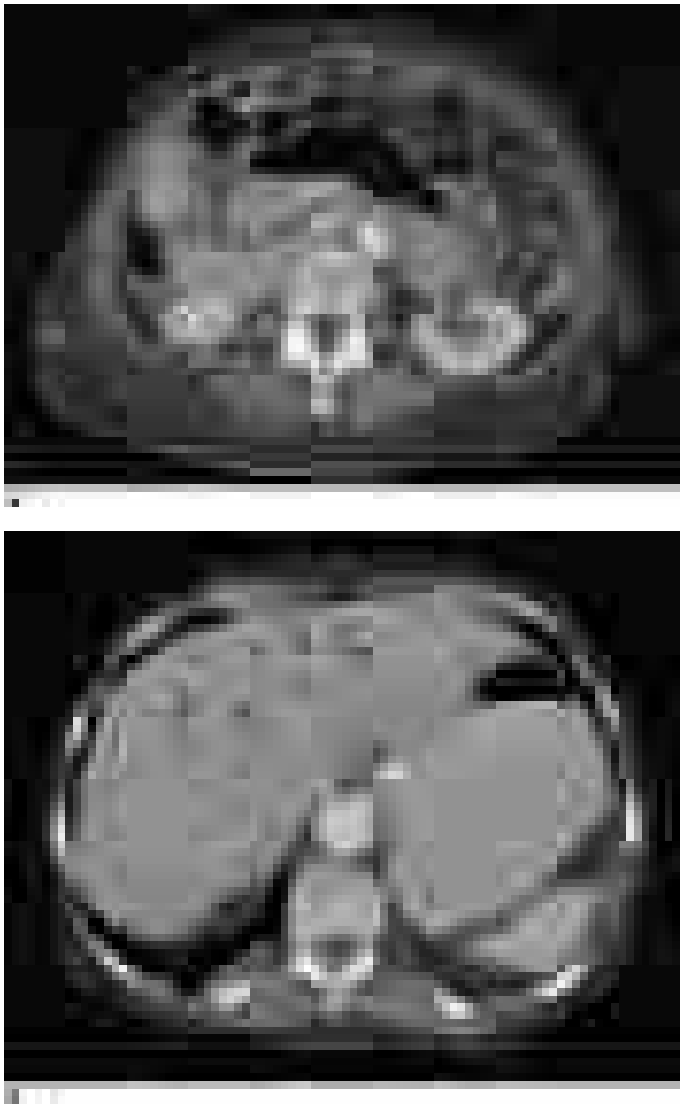

FIGURE 71-5 Abdominal computed tomography (CT) scans of a 72-year-old woman with neutropenic enterocolitis secondary to chemotherapy. *A.* Air in inferior mesenteric vein (*arrow*) and bowel wall with pneumatosis intestinalis. ***B.*** CT scan of upper abdomen demonstrating air in portal vein (*arrows*).

ascites, and may help to differentiate neutropenic colitis from other abdominal disorders such as appendicitis, diverticulitis, and *Clostridium difficile*–associated colitis in this high-risk population. Patients with bowel wall thickness >10 mm on ultrasonogram have higher mortality rates. However, bowel wall thickening is significantly more prominent in patients with *C. difficile* colitis. Pneumatosis intestinalis is a more specific finding, seen only in those with neutropenic enterocolitis and ischemia. The combined involvement of the small and large bowel suggests a diagnosis of neutropenic enterocolitis. Rapid institution of broad-spectrum antibiotics, bowel rest, and nasogastric suction may reverse the process. Use of myeloid growth factors improved outcome significantly. Surgical intervention is reserved for severe cases of neutropenic enterocolitis with evidence of perforation, peritonitis, gangrenous bowel, or gastrointestinal hemorrhage despite correction of any coagulopathy.

C. difficile colitis is increasing in incidence. Newer strains of *C. difficile* produce ~20 times more of toxins A and B compared to previously studied strains. *C. difficile* risk is also increased with chemotherapy. Antibiotic coverage for *C. difficile* should be added if pseudomembranous colitis cannot be excluded.

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis is characterized by diffuse bladder mucosal bleeding that develops secondary to chemotherapy (mostly cyclophosphamide or ifosfamide), radiation therapy, bone marrow transplantation (BMT), and/or opportunistic infections. Both cyclophosphamide and ifosfamide are metabolized to acrolein, which is a strong chemical irritant that is excreted in the urine. Prolonged contact or high concentrations may lead to bladder irritation and hemorrhage. Symptoms include gross hematuria, frequency, dysuria, burning, urgency, incontinence, and nocturia. The best management is prevention. Maintaining a high rate of urine flow minimizes exposure. In addition, 2-mercaptoethanesulfonate (mesna) detoxifies the metabolites and can be coadministered with the instigating drugs. Mesna usually is given three times on the day of ifosfamide administration in doses that are each 20% of the total ifosfamide dose. If hemorrhagic cystitis develops, the maintenance of a high urine flow may be sufficient supportive care. If conservative management is not effective, irrigation of the bladder with a 0.37–0.74% formalin solution for 10 min stops the bleeding in most cases. *N*-Acetylcysteine may also be an effective irrigant. Prostaglandin (carboprost) can inhibit the process. In extreme cases, ligation of the hypogastric arteries, urinary diversion, or cystectomy may be necessary.

In the BMT setting, early-onset hemorrhagic cystitis is related to drugs in the treatment regimen (e.g., cyclophosphamide), and late-onset hemorrhagic cystitis is usually due to the polyoma virus BKV or adenovirus type 11. BKV load in urine alone or in combination with acute graft-versus-host disease correlates with development of hemorrhagic cystitis. Viral causes are usually detected by polymerase chain reaction (PCR)–based diagnostic tests. Treatment of viral hemorrhagic cystitis is largely supportive, with reduction in doses of immunosuppressive agents, if possible. No antiviral therapy is approved, although cidofovir is reported to be effective in a small series. Hyperbaric oxygen therapy has been used successfully in patients with BKV-associated and cyclophosphamide-induced hemorrhagic cystitis during hematopoietic stem cell transplantation, as well as in hemorrhagic radiation cystitis.

HYPERSENSITIVITY REACTIONS TO ANTINEOPLASTIC DRUGS

Many antineoplastic drugs may cause hypersensitivity reaction. These reactions are unpredictable and potentially life threatening. Most reactions occur during or within hours of parenteral drug administration. Taxanes, platinum compounds, asparaginase, etoposide, procarbazine, and biologic agents, including rituximab, bevacizumab, trastuzumab, gemtuzumab, cetuximab, and alemtuzumab, are more commonly associated with acute hypersensitivity reactions than are other agents. Hypersensitivity reactions to some drugs, such as taxanes, occur during the first or second dose administered. Hypersensitivity to platinum compounds occurs after prolonged exposure. Skin testing may identify patients with high risk for hypersensitivity after carboplatin exposure. Premedication with histamine H_1 and H_2 receptor antagonists and glucocorticoids reduces the incidence of hypersensitivity reaction to taxanes, particularly paclitaxel. Despite premedication, hypersensitivity reactions may still occur. In these cases, rapid desensitization in the intensive care unit setting or re-treatment may be attempted with care, but the use of alternative agents may be required. Skin testing is used to assess the involvement of IgE in the reaction. Tryptase levels measured at the time of the reaction help to explain the mechanism of the reaction and its severity. Increased tryptase levels indicate underlying mast cell activation. Candidate patients for desensitization include those who have mild to severe hypersensitivity type I, with mast cell–mediated and IgE-dependent reactions occurring during a chemotherapy infusion or shortly thereafter.

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72 Cancer of the Skin

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MELANOMA

Pigmented lesions are among the most common findings on skin examination. The challenge for the physician is to distinguish cutaneous melanomas, which account for the overwhelming majority of deaths resulting from skin cancer, from the remainder, which are usually benign. Cutaneous melanoma can occur in adults of all ages, even young individuals, and people of all colors; its location on the skin and its distinct clinical features often permit detection at a time when complete surgical excision leads to cure. Examples of malignant and benign pigmented lesions are shown in Fig. 72-1.

EPIDEMIOLOGY

Melanoma is an aggressive malignancy of melanocytes, pigment-producing cells that originate from the neural crest and migrate to the skin, meninges, mucous membranes, upper esophagus, and eyes. Melanocytes in each of these locations have the potential for malignant transformation, but the vast majority arise in the skin. Melanomas can also arise in the mucosa of the head and neck (nasal cavity, paranasal sinuses, and oral cavity), the gastrointestinal tract, the CNS, the female genital tract (vulva, vagina), and the uveal tract of the eye. Cutaneous melanoma is predominantly a malignancy of white-skinned people

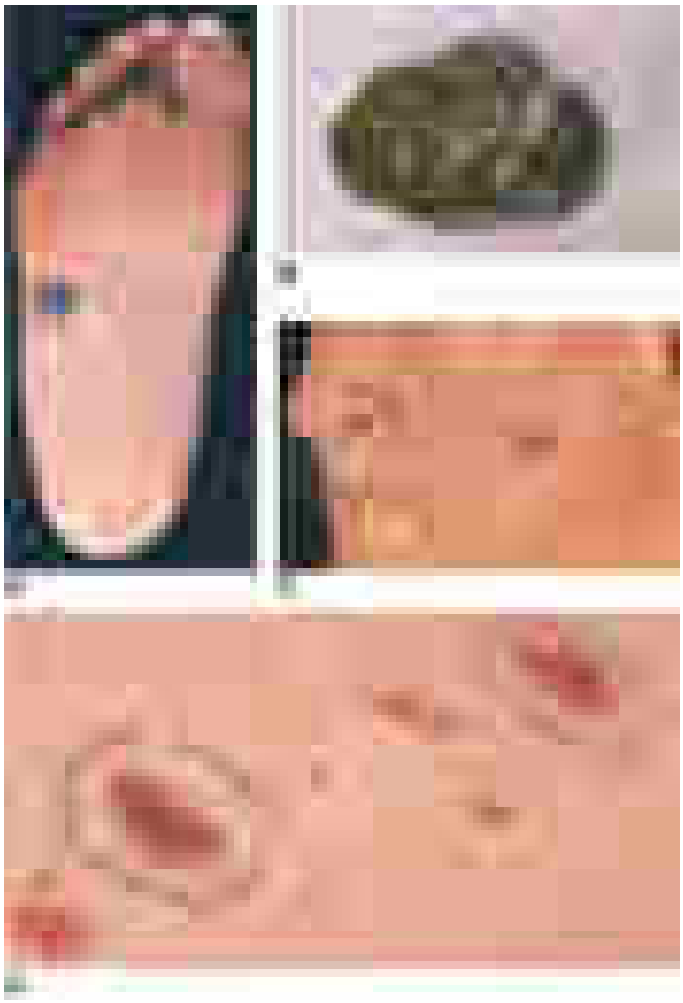

FIGURE 72-1 Atypical and malignant pigmented lesions. The most common melanoma is superficial spreading melanoma (not pictured). ***A***. Acral lentiginous melanoma is the most common melanoma in blacks, Asians, and Hispanics and occurs as an enlarging hyperpigmented macule or plaque on the palms and soles. ***B***. Nodular melanoma most commonly manifests as a rapidly growing, often ulcerated or crusted black nodule. ***C***. Lentigo maligna melanoma occurs on sun-exposed skin as a large, hyperpigmented macule or plaque with irregular borders and variable pigmentation. ***D***. Dysplastic nevi are benign, irregularly pigmented and shaped melanocytic hamartomas with some atypical cellular features and frequently associated with familial melanoma.

(98% of cases), and the incidence correlates with latitude of residence, providing strong evidence for the role of sun exposure. Men are affected slightly more than women (1.3:1), and the median age at diagnosis is the late fifties. In 2016, >76,000 individuals in the United States were expected to develop melanoma, and ~10,130 were expected to die. Mortality rates begin to rise at age 55, with the greatest increase in men age >65 years. Of particular concern is the increase in incidence among women <40 years of age, an increase believed to be associated with a greater emphasis on tanned skin as a marker of beauty, the increased availability and use of indoor tanning beds, and exposure to intense ultraviolet (UV) light in childhood. The latest Surveillance, Epidemiology and End Results (SEER) Registry data reveal that from 2004 to 2013, the rate of new melanoma cases has risen 1.4% each year, while death rates have remained stable. This is in the context of a 5-year relative survival improvement from 93.1% to 93.3% overall, despite a 17.9% survival rate for those diagnosed with distant metastases. These statistics highlight the need to promote prevention and early detection.

GLOBAL CONSIDERATIONS

The incidence of both non-melanoma and melanoma skin cancers around the world has been increasing. Every year between 2 and 3 million people will get non-melanoma skin cancer and in 2012 there were 232,000 cases of melanoma. The highest incidence of melanoma is found in New Zealand and Australia consistent with Caucasians living in latitudes with increased UV exposure. The likelihood of developing melanoma is 25 per 100,000 in non-Hispanic whites, 4 per 100,000 in Hispanics, and 1 per 100,000 in African Americans.

Dark-skinned populations (such as those of India and Puerto Rico), blacks, and east Asians also develop melanoma, albeit at rates 10–20 times lower than those in whites. Cutaneous melanomas in these populations are more often diagnosed at a higher stage, and patients tend to have worse outcomes. Furthermore, in nonwhite populations, the frequency of acral (subungual, plantar, palmar) and mucosal melanomas is much higher. In China, about 20,000 new cases are reported each year and, in contrast to the United States where rates are stable, mortality is increasing. This may be due in part to the gap that remains in the diagnosis and treatment of melanoma between China and Western countries or to the fact that in Asians and dark-skinned populations, the melanomas that arise from the skin (comprising 50–70% of patients versus 90% in the West) arise from acral areas and the others from mucosal areas, all of which carry a poorer prognosis than cutaneous melanomas diagnosed in the West.

RISK FACTORS

Presence of Nevi The risk of developing melanoma is related to genetic, environmental, and host factors. The strongest risk factors for melanoma are the presence of multiple benign or atypical nevi and a family or personal history of melanoma. The presence of >40 melanocytic nevi, common or dysplastic, is a marker for increased risk of melanoma. Nevi have been referred to as precursor lesions because they can transform into melanomas; however, the actual risk of transformation for any individual nevus is exceedingly low. About one-quarter of melanomas are histologically associated with nevi, but the majority arise de novo. The number of clinically atypical moles may vary from one to several hundred, and they usually differ from one another in appearance, although individuals can develop multiple similar atypical nevi (signature nevi). The borders are often hazy and indistinct, and the pigment pattern is more highly varied than that in benign acquired nevi. Individuals with clinically atypical moles and a strong family history of melanoma have been reported to have a >50% lifetime risk for developing melanoma and warrant close follow-up with a dermatologist. Of the 90% of patients whose disease is sporadic (i.e., who lack a family history of melanoma), ~40% have clinically atypical moles, compared with an estimated 5–10% of the population at large.

Congenital melanocytic nevi, which are classified as small (≤1.5 cm), medium (1.5–20 cm), and giant (>20 cm), can be precursors for melanoma. The risk is highest for the giant melanocytic nevus, also called the bathing trunk nevus, a rare malformation that affects 1 in 30,000–100,000 individuals. Since the lifetime risk of melanoma development is estimated to be as high as 6%, prophylactic excision early in life is prudent. This usually requires staged removal with coverage by split-thickness skin grafts. Surgery cannot remove all at-risk nevus cells, as some may penetrate into the muscles or central nervous system (CNS) below the nevus. Small- to medium-size congenital melanocytic nevi affect ~1% of persons; the lifetime risk of melanoma development in a typical nevus is low, estimated to be about 0.03% (1 in 3164) for men and 0.009% (1 in 10,800) for women. The management of small- to medium-size congenital melanocytic nevi remains controversial and is primarily based on histologic findings from biopsies of clinically atypical nevi.

Personal and Family History Once diagnosed, patients with melanoma require a lifetime of surveillance because their risk of developing another melanoma is 10 times that of the general population. First-degree relatives have a twofold higher risk of developing melanoma than do individuals without a family history, but only 5–10% of all melanomas are truly familial. In familial melanoma, patients tend to be younger at first diagnosis, lesions are thinner, and multiple primary melanomas are common.

Genetic Susceptibility Approximately 20–40% of cases of hereditary melanoma (0.2–2% of all melanomas) are due to germline mutations in the cell cycle regulatory gene cyclin-dependent kinase inhibitor 2A (*CDKN2A*). In fact, 70% of all cutaneous melanomas have mutations or deletions affecting the *CDKN2A* locus on chromosome 9p21. This locus encodes two distinct tumor-suppressor proteins from alternate reading frames: p16 and ARF ($p14^{ARF}$). The p16 protein inhibits CDK4/6-mediated phosphorylation and inactivation of the retinoblastoma (RB) protein, whereas ARF inhibits MDM2 ubiquitin-mediated degradation of p53. The end result of the loss of *CDKN2A* is inactivation of two critical tumor-suppressor pathways, RB and p53, which control entry of cells into the cell cycle. Several studies have shown an increased risk of pancreatic cancer among melanoma-prone families with *CDKN2A* mutations. A second high-risk locus for melanoma susceptibility, *CDK4*, is located on chromosome 12q13 and encodes the kinase inhibited by p16. *CDK4* mutations, which also inactivate the RB pathway, are much rarer than *CDKN2A* mutations. Germline mutations in the melanoma lineage-specific oncogene microphthalmia-associated transcription factor (*MITF*) and telomerase reverse transcriptase (TERT) mutations predispose to both familial and sporadic melanomas.

The melanocortin-1 receptor (*MC1R*) gene is a moderate-risk inherited melanoma susceptibility factor. Solar radiation stimulates the production of melanocortin (α-melanocyte-stimulating hormone [α-MSH]), the ligand for *MC1R*, which is a G-protein-coupled receptor that signals via cyclic AMP and regulates the amount and type of pigment produced. *MC1R* is highly polymorphic, and among its 80 variants are those that result in partial loss of signaling and lead to the production of red/yellow pheomelanins, which are not sun-protective and produce red hair, rather than brown/black eumelanins that are photoprotective. This red hair color (RHC) phenotype is associated with fair skin, red hair, freckles, increased sun sensitivity, and increased risk of melanoma. In addition to its weak UV shielding capacity relative to eumelanin, increased pheomelanin production in patients with inactivating polymorphisms of *MC1R* also provides a UV-independent carcinogenic contribution to melanomagenesis via oxidative damage and reduced DNA damage repair.

A number of other more common, low-penetrance polymorphisms that have small effects on melanoma susceptibility include other genes related to pigmentation, nevus count, immune responses, DNA repair, metabolism, and the vitamin D receptor. Approximately 50% of the genetic risk for hereditary melanoma can be ascribed to previously identified melanoma predisposition genes, with ~40% of the risk being due to CDKN2A. The missing inherited risk is most likely due to the inheritance of additional modifier genes and/or shared environmental exposures.

PREVENTION AND EARLY DETECTION

Primary prevention of melanoma and nonmelanoma skin cancer (NMSC) is based on protection from the sun. Public health initiatives, such as the SunSmart program that started in Australia and now is operative in Europe and the United States, have demonstrated that behavioral change can decrease the incidence of NMSC and melanoma. Preventive measures should start early in life because damage from UV light begins early despite the fact that cancers develop years later. Some individuals tan compulsively. There is greater understanding of tanning addiction and the biology of cutaneous-neural connections that may give rise to this behavior. Compulsive tanners exhibit differences in dopamine binding and reactivity in reward pathways in the brain, such as the basal striatum, resulting in cutaneous secretion of β-endorphins after UV exposure. Identifying individuals with tanning addiction may be another method for preventive intervention. Regular use of broad-spectrum sunscreens that block UVA and UVB with a sun protection factor (SPF) of at least 30 and protective clothing should be encouraged. Avoidance of sunburns, tanning beds, and midday sun exposure is recommended.

Secondary prevention comprises education, screening, and early detection. Patients should be taught to recognize the clinical features of melanoma (ABCDEs; see below) and advised to report any change in a pigmented lesion. Brochures are available from the American Cancer Society, the American Academy of Dermatology, the National Cancer Institute, and the Skin Cancer Foundation. Self-examination at monthly intervals may enhance the likelihood of detecting change. Although the U.S. Preventive Services Task Force states that evidence is insufficient to recommend for or against skin cancer screening, a full-body skin exam seems to be a simple, practical way to approach reducing the mortality rate for skin cancer. Depending on the presence or absence of risk factors, strategies for early detection can be individualized. This is particularly true for patients with clinically atypical moles (dysplastic nevi) and those with a personal history of melanoma. For these individuals, surveillance should be performed by the dermatologist and include total-body photography and dermoscopy where appropriate. Individuals with three or more primary melanomas and families with at least one invasive melanoma and two or more cases of melanoma and/or pancreatic cancer among first- or second-degree relatives on the same side of the family may benefit from genetic testing. Precancerous and in situ lesions should be treated early. Early detection of small tumors allows the use of simpler treatment modalities with higher cure rates and lower morbidity.

DIAGNOSIS

The goal is to identify a melanoma before it invades and life-threatening metastases have occurred. Early detection may be facilitated by applying the ABCDEs: *a*symmetry (benign lesions are usually symmetric); *b*order irregularity (most nevi have clear-cut borders); *c*olor variegation (benign lesions usually have uniform light or dark pigment); *d*iameter >6 mm (the size of a pencil eraser); and *e*volving (any change in size, shape, color, or elevation or new symptoms such as bleeding, itching, and crusting). In addition, any nevus that appears atypical and different from the rest of the nevi on that individual (an "ugly duckling") should be considered suspicious.

The entire skin surface, including the scalp and mucous membranes, as well as the nails should be examined in each patient. Bright room illumination is important, and a hand lens is helpful for evaluating variation in pigment pattern. Any suspicious lesions should be biopsied, evaluated by a specialist, or recorded by chart and/or photography for follow-up. A focused method for examining individual lesions, dermoscopy, employs low-level magnification of the epidermis with polarized light and may allow a more precise visualization of patterns of pigmentation than is possible with the naked eye. Additional technologies, including in vivo confocal microscopy, multi- and hyper-spectral imaging, optical coherence tomography, gene expression panels, tape stripping, and electrical conductance methods have been developed and are being refined for improved early detection of melanoma.

Biopsy Any pigmented cutaneous lesion that has changed in size or shape or has other features suggestive of malignant melanoma is a candidate for biopsy. An excisional biopsy with 1- to 3-mm margins is suggested though excision can be accomplished tangentially or in a fusiform fashion. This facilitates pathologic assessment of the lesion, permits accurate measurement of thickness if the lesion is melanoma, and constitutes definitive treatment if the lesion is benign. For lesions that are large or on anatomic sites where excisional biopsy may not be feasible (such as the face, hands, and feet), an incisional biopsy through the most nodular or darkest area of the lesion is acceptable. Incisional biopsy does not appear to facilitate the spread of melanoma. For suspicious lesions, every attempt should be made to preserve the ability to assess the deep and peripheral margins and to perform immunohistochemistry. Shave, saucerization or tangential biopsies are an acceptable alternative, particularly if the suspicion of malignancy is low. They should be deep enough to include the deepest component of the entire lesion and any pigment at the base of the lesion should be removed and included with the biopsy specimen. The biopsy should be read by a pathologist experienced in pigmented lesions, and the report should include Breslow thickness, mitotic rate, presence or absence of ulceration and lymphatic invasion, microsatellitosis and peripheral and deep margin status. Breslow thickness is the greatest thickness of

a primary cutaneous melanoma measured on the slide from the top of the epidermal granular layer, or from the ulcer base, to the bottom of the tumor. To distinguish melanomas from benign nevi in challenging cases, fluorescence in situ hybridization (FISH) with multiple probes and comparative genome hybridization (CGH) can be helpful. Gene expression profiling assays have been developed to enhance diagnosis but are not yet widely applied.

CLASSIFICATION AND PATHOGENESIS

Clinical The features of five major types of cutaneous melanoma are described in Table 72-1. In *superficial spreading melanoma*, *lentigo maligna melanoma*, and *acral lentiginous melanoma*, the lesion has a period of superficial (so-called radial) growth during which it increases in size but does not penetrate deeply. It is during this period that the melanoma is most capable of being cured by surgical excision. A fourth type—*nodular melanoma*—does not have a recognizable radial growth phase and usually presents as a deeply invasive lesion that is capable of early metastasis. Tumors that begin to penetrate deeply into the skin are in the so-called vertical growth phase. Melanomas with a radial growth phase are characterized by irregular and sometimes notched borders, variation in pigment pattern, and variation in color. A fifth type of melanoma, *desmoplastic melanoma*, is associated with a fibrotic response, neural invasion, and a greater tendency for local recurrence. Occasionally, melanomas appear clinically to be amelanotic, in which case the diagnosis is established microscopically after biopsy.

Although these subtypes are clinically and histopathologically distinct, this classification has minimal prognostic value and histologic subtype is not part of American Joint Committee on Cancer (AJCC) staging. Characterizing the genomic and mutational profiles of melanoma has become increasingly common and can reflect the mechanisms of tumorigenesis. These molecular classifications inform treatment and surveillance strategies.

Genomic Considerable evidence from epidemiologic and molecular studies indicate that cutaneous melanomas arise via multiple causal pathways. There are both environmental and genetic components (susceptibility genes discussed earlier), and the major environmental factor in cutaneous melanomagenesis is sun exposure. The major effect of UV solar radiation is to cause genetic changes in the skin. However, it also impairs cutaneous immune function, increases the production of growth factors, and induces the formation of DNA-damaging reactive oxygen species that affect keratinocytes and melanocytes.

The advent of next-generation sequencing (NGS) has led to whole exome sequencing of hundreds of cutaneous melanomas derived from non-glabrous skin. This has revealed a very complex genetic landscape with genetic changes resulting from both germline (described earlier) and somatic mutations. Cutaneous melanomas have one of the highest somatic mutation rates (>10 mutations/Mb) compared to other cancers; the majority (76% primary tumors and 84% of metastatic melanomas) exhibit a mutation signature indicating UVR exposure. The mutation rate varies based on body site; melanomas arising in chronic sun-damaged skin harbor substantially more mutations than melanomas from non-sun-damaged skin.

Melanoma tumors can harbor thousands of mutations, but only a few are driver mutations; a mutation that is causally implicated in oncogenesis by virtue of a conferred growth advantage on the cancer cell. The driver mutations that have been identified for cutaneous melanoma are depicted in Fig. 72-2. As more melanomas are sequenced, more driver mutations have been identified. These mutations tend to be found in a smaller fraction of patients. Driver mutations often affect pathways that promote cell proliferation or inhibit normal pathways of apoptosis in response to DNA repair. They are often found in combination with mutations to the genetic susceptibility genes described earlier. The altered melanocytes accumulate DNA damage, and selection occurs for all the attributes that constitute the malignant phenotype: invasion, metastasis, and angiogenesis.

A recent report from the Cancer Genome Atlas (TCGA) has proposed a genomic classification of cutaneous melanoma based on the pattern of the most prevalent significantly mutated genes: BRAF, RAS, NF-1, and triple-WT (wild type). Distinct patterns of DNA mutations can vary with the site of origin and can be independent of the histologic subtype of the tumor. Thus, although the genetic landscape of melanoma is complex, and continues to evolve, the overall pattern of mutation, amplification, and loss of cancer genes indicates they have convergent effects on key biochemical pathways involved in proliferation, senescence, and apoptosis. An advantage of this classification is that these mutations can be used to select therapy.

TABLE 72-1 Major Histologic Subtypes of Malignant Melanoma

TYPE	SITE	AVERAGE AGE AT DIAGNOSIS, YEARS	APPEARANCE
Lentigo maligna melanoma	Sun-exposed surfaces, particularly malar region and temple	70	In flat portions, brown and tan predominate, but whitish gray occasionally present; in nodules, reddish brown, bluish gray, bluish black
Superficial spreading melanoma	Any site (more common on upper back and, in women, lower legs)	40–50	Brown mixed with bluish red, bluish black, reddish brown, and often whitish pink, and the border of lesion is at least in part visibly and/or palpably elevated
Nodular melanoma	Any	40–50	Reddish blue (purple) or bluish black; either uniform in color or mixed with brown or black
Acral lentiginous melanoma	Palm, sole, nail bed, mucous membrane	60	In flat portions, dark brown predominantly; in raised lesions (plaques), brown-black or blue-black predominantly
Desmoplastic melanoma	Any site (more common head and neck)	60	Highly variable, mimics other lesions; pigmentation is frequently absent

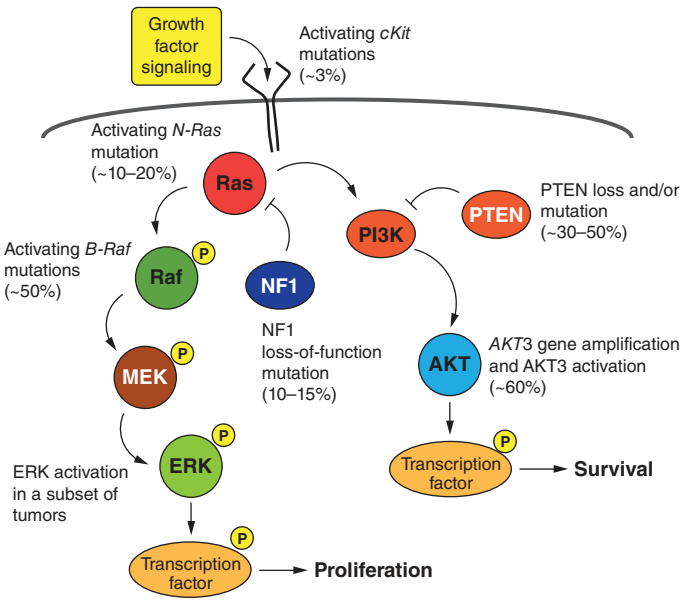

FIGURE 72-2 Major pathways involved in melanoma. The MAP kinase and PI3K/AKT pathways, which promote proliferation and inhibit apoptosis, respectively, are subject to mutations in melanoma. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase; NF-1; neurofibromatosis type 1 gene; PTEN, phosphatase and tensin homolog.

The *p16* mutation that affects cell cycle arrest and the *ARF* mutation that results in defective apoptotic responses to genotoxic damage were described earlier. The proliferative pathways affected were the mitogen-activated protein (MAP) kinase and phosphatidylinositol 3′ kinase/AKT pathways (Fig. 72-2). *RAS* and *BRAF*, members of the MAP kinase pathway, which classically mediates the transcription of genes involved in cell proliferation and survival, undergo somatic mutation in melanoma and thereby generate potential therapeutic targets. *N-RAS* is mutated in ~20% of melanomas, and somatic activating *BRAF* mutations are found in most benign nevi and 40–50% of cutaneous melanomas. Neither mutation by itself appears to be sufficient to cause melanoma; thus, they often are accompanied by other mutations, such as TERT. The *BRAF* mutation is most commonly a point mutation (T→A nucleotide change) that results in a valine-to-glutamate amino acid substitution (V600E). V600E *BRAF* mutations are more common in younger patients and are present in most melanomas that arise on sites with intermittent sun exposure and are less common in melanomas from chronically sun-damaged skin. At present, *BRAF* mutations are the most important in therapeutic decision making in patients with advanced melanoma.

Melanomas also harbor mutations in *AKT* (primarily in *AKT3*) and *PTEN* (phosphatase and tensin homolog). *AKT* can be amplified, and *PTEN* may be deleted or undergo epigenetic silencing that leads to constitutive activation of the PI3K/AKT pathway and enhanced cell survival by antagonizing the intrinsic pathway of apoptosis. Loss of *PTEN*, which dysregulates AKT activity, and mutation of *AKT3* both prolong cell survival through inactivation of BAD, BCL-2-antagonist of cell death, and activation of the forkhead transcription factor FOXO1, which leads to synthesis of prosurvival genes. A loss-of-function mutation in *NF1*, which can affect both MAP kinase and PI3K/AKT pathways, has been described in 10–15% of melanomas. In melanoma, these two signaling pathways (MAP kinase and PI3K/AKT) enhance tumorigenesis, chemoresistance, migration, and cell cycle dysregulation. Drugs that inhibit some of these pathways have been developed, and have proven to be effective therapeutic agents (see below).

PROGNOSTIC FACTORS

The most important prognostic factors for a newly diagnosed patient are incorporated in the staging classification **(Table 72-2)**. The best predictor of metastatic risk is Breslow thickness. The anatomic site of the primary is also prognostic; favorable sites are the forearm and leg (excluding the feet), and unfavorable sites include the scalp, hands, feet, and mucous membranes. In general, women with stage I or II disease have better survival than men, perhaps in part because of earlier

TABLE 72-2 Staging Criteria for Melanoma

PATHOLOGIC AND TNM STAGE	THICKNESS, mm	ULCERATION	NO. OF INVOLVED LYMPH NODES	NODAL INVOLVEMENT	15-YEAR SURVIVAL ESTIMATE (%)
0					98
Tis	In situ	No	0	None	
IA					92
T1a	<1	No, mitosis <1/mm	0	None	
IB					80
T1b	<1	Yes or mitosis >1/mm	0	None	
T2a	1.01–2	No	0	None	
IIA					62
T2b	1.01–2	Yes	0	None	
T3a	2.01–4	No	0	None	
IIB					51
T3b	2.01–4	Yes	0	None	
T4a	>4	No	0	None	
IIC					37
T4b	>4	Yes	0	None	
IIIA					68
N1a	T1-4a	No	1	Microscopic	
N2a	T1-4a	No	2 or 3	Microscopic	
IIIB					38
N1a	Any	Yes	1	Microscopic	
N2a	Any	Yes	2 or 3	Microscopic	
N1b	Any	Yes or no	1	Macroscopic	
N2b	Any	Yes or no	2 or 3	Macroscopic	
N2c	Any	Yes or no	In-transit metastases/satellites, no nodal involvement		
IIIC					22
N1b	Any	Yes or no	1	Macroscopic	
N2b	Any	Yes or no	2 or 3	Macroscopic	
N2c	Any	Yes or no	In-transit metastases/satellites, no nodal involvement		
N3	Any	Yes or no	4+ metastatic nodes, matted nodes or in-transit metastases/satellites, with metastatic nodes		
IV		Distant metastasis			<10
M1a		Skin, subcutaneous			
M1b		Lung			
M1c		Other visceral site			
		Elevated lactate dehydrogenase			

diagnosis; women frequently have melanomas on the lower leg, where self-recognition is more likely and the prognosis is better. The effect of age is not straightforward. Older individuals, especially men >60, have worse prognoses, a finding that has been explained in part by a tendency toward later diagnosis (and thus thicker tumors) and in part by a higher proportion of acral melanomas in men. However, there is a greater risk of lymph node metastasis in young patients. Other important adverse factors recognized via the staging classification include high mitotic rate, presence of ulceration, microsatellite lesions and/or in-transit metastases, evidence of nodal involvement, elevated serum lactate dehydrogenase (LDH), and presence and site of distant metastases.

STAGING

Once the diagnosis of melanoma has been made, the tumor is staged to determine the prognosis and aid in treatment selection. The current melanoma staging criteria and estimated 15-year survival by stage are depicted in Table 72-2. The clinical stage is determined after the microscopic evaluation of the melanoma skin lesion and clinical and radiologic assessment. Pathologic staging also includes the microscopic evaluation of the regional lymph nodes obtained at sentinel lymph node biopsy or completion lymphadenectomy as indicated. All patients should have a complete history, with attention to symptoms that may suggest metastatic disease, such as malaise, weight loss, headaches, visual changes, and pain, and physical examination directed to the site of the primary melanoma, looking for persistent disease or for dermal or subcutaneous nodules that could represent satellite or in-transit metastases, and to the regional draining lymph nodes, CNS, liver, and lungs. A complete blood count (CBC), complete metabolic panel, and LDH should be performed. Although these rarely help uncover occult metastatic disease, a microcytic anemia would raise the possibility of bowel metastases, and the LDH, if elevated, should prompt a more extensive evaluation, including computed tomography (CT) scan or possibly a positron emission tomography (PET) (or CT/PET combined) scan. If signs or symptoms of metastatic disease are present, appropriate diagnostic imaging should be performed. At initial presentation, >80% of patients will have disease confined to the skin and a negative history and physical examination, in which case imaging is not indicated.

TREATMENT

Melanoma

MANAGEMENT OF CLINICALLY LOCALIZED MELANOMA (STAGE I, II)

For a newly diagnosed cutaneous melanoma, wide surgical excision of the lesion with a margin of normal skin is necessary to remove all malignant cells and minimize possible local recurrence. The following margins are recommended for a primary melanoma: in situ, 0.5–1.0 cm; invasive up to 1 mm thick, 1 cm; >1.01–2 mm, 1–2 cm; and >2 mm, 2 cm. For lesions on the face, hands, and feet, strict adherence to these margins must give way to individual considerations about the constraints of surgery and minimization of morbidity. In all instances, however, inclusion of subcutaneous fat in the surgical specimen facilitates adequate thickness measurement and assessment of surgical margins by the pathologist. Topical imiquimod also has been used, particularly for lentigo maligna, in cosmetically sensitive locations.

Sentinel lymph node biopsy (SLNB) is a valuable staging tool that has replaced elective regional node dissection for the evaluation of regional nodal status. SLNB provides prognostic information and helps identify patients at high risk for relapse who may be candidates for adjuvant therapy. The initial (sentinel) draining node(s) from the primary site is (are) identified by injecting a blue dye and a radioisotope around the primary site. The sentinel node(s) then is (are) identified by inspection of the nodal basin for the blue-stained node and/or the node with high uptake of the radioisotope. The identified nodes are removed and subjected to careful histopathologic analysis with serial section using hematoxylin and eosin stains as well as immunohistochemical stains (e.g., S100, HMB45, and MelanA) to identify melanocytes.

Not every patient requires a SLNB. Patients whose melanomas are ≤0.75 mm thick have <5% risk of sentinel lymph node (SLN) disease and do not require a SLNB. Patients with tumors >1 mm thick generally undergo SLNB. For melanomas 0.76–1.0 mm thick, SLNB may be considered for lesions with high-risk features such as ulceration, high mitotic index, or lymphovascular invasion, but wide excision alone is the usual definitive therapy. Most other patients with clinically negative lymph nodes should undergo a SLNB. Patients whose SLNB is negative are spared a complete node dissection and its attendant morbidities, and can simply be followed, or based on the features of the primary melanoma, be considered for adjuvant therapy or a clinical trial. The current standard of care for all patients with a positive SLN is to perform a complete lymphadenectomy; however, complete lymph node dissection is not necessary for patients with lymph node micrometastases <1 mm. Patients with positive lymph nodes should be considered for adjuvant therapy with ipilimumab, interferon alpha or enrollment in a clinical trial.

MANAGEMENT OF REGIONALLY METASTATIC MELANOMA (STAGE III)

Melanomas may recur at the edge of the scar or graft, as satellite metastases, which are separate from but within 2 cm of the scar; as in-transit metastases, which are recurrences >2 cm from the primary lesion but not beyond the regional nodal basin; or, most commonly, as metastasis to a draining lymph node basin. Each of these presentations is managed surgically, following which there is the possibility of long-term disease-free survival. Isolated limb perfusion or infusion with melphalan and hyperthermia are options for patients with extensive cutaneous regional recurrences in an extremity. High complete response rates have been reported and significant palliation of symptoms can be achieved, but there is no change in overall survival. Other options for in-transit disease and distant skin and soft tissue metastases include topical immunotherapy and direct injection of melanoma lesions. Topical therapy with imiquimod has been useful for patients with low-volume dermal lesions. Historically, intralesional bacille Calmette-Guerin (BCG) has been used with high rates of regression of injected lesions and occasional regression of a distant, uninjected lesion. Talimogene laherparepvec is an engineered, oncolytic herpes simplex virus type 1 that is U.S. Food and Drug Administration (FDA) approved for injection of melanoma lesions that cannot be completely removed by surgery.

Patients rendered free of disease after surgery may be at high risk for a local or distant recurrence and should be considered for adjuvant therapy. Radiotherapy can reduce the risk of local recurrence after lymphadenectomy, but does not affect overall survival. Patients with large nodes (>3–4 cm), four or more involved lymph nodes, or extranodal spread on microscopic examination should be considered for radiation. Systemic adjuvant therapy is indicated primarily for patients with stage III disease, but high-risk, node-negative patients (>4 mm thick or ulcerated lesions), and patients with completely resected stage IV disease also may benefit.

Current treatment options include ipilimumab, interferon α2b (IFN-α2b) or investigational therapy. Ipilimumab is a fully human monoclonal antibody that blocks the immune checkpoint cytotoxic T-lymphocyte antigen-4 (CTLA-4) and augments antitumor immune responses. Treatment with ipilimumab 10 mg/kg IV every three weeks for four doses, then every three months for up to three years, improved survival of patients with high-risk stage III disease compared to placebo. IFN-α2b may be administered at high doses for one year or pegylated IFN can be administered at a lower dose for five years. The single study of ipilimumab documented a survival benefit whereas multiple trials of IFN have reported clear improvement in disease-free survival, but questionable improvement in overall survival. The two agents have not been compared directly. Ongoing clinical trials will address this issue as well as evaluate the potential value of other immunotherapies (e.g., PD-1/PD-L1

blocking agents) and targeted therapies in patients with BRAF mutated tumors in the adjuvant setting.

Both IFN and ipilimumab are accompanied by significant toxicity. For IFN, this may include a flulike illness, decline in performance status, and the development of depression. Side effects can be managed in most patients by appropriate treatment of symptoms, dose reduction, and treatment interruption. IFN may need to be discontinued prematurely because of unacceptable toxicity. The major side effects of ipilimumab are discussed below.

TREATMENT

Metastatic Disease

At diagnosis, 84% patients with melanoma will have early-stage disease and 4% will present with metastases. Many others will develop metastases after initial therapy for loco-regional disease. The probability of recurrence is related to initial stage, ranging from <5% with stage IA to >90% for subsets of patients with stage IIIC disease at presentation. Patients with a history of melanoma who develop signs or symptoms suggesting recurrent disease should undergo restaging as described earlier. Distant metastases (stage IV) may involve any organ and commonly involve the skin and lymph nodes as well as viscera, bone, or the brain. The prognosis is better for patients with skin and subcutaneous metastases (M1a) than for lung (M1b) and worst for those with metastases to liver, bone, and brain (M1c). An elevated serum LDH is a poor prognostic factor and places the patient in stage M1c regardless of the site of the metastases (Table 72-2). Although historical data suggest that the 15-year survival of patients with melanoma is <10%; advances in targeted and immunotherapy have improved disease-free and overall survival, especially for patients with M1a and M1b disease.

The treatment for patients with stage IV melanoma has changed dramatically since 2011. FDA-approved agents include three immune T-cell checkpoint inhibitors, ipilimumab, nivolumab, and pembrolizumab, four oral agents that target the MAP kinase pathway: the BRAF inhibitors, vemurafenib and dabrafenib, the MEK inhibitors, trametinib and cobimetinib, and the oncolytic virus talimogene laherparepvec **(Table 72-3)**.

Surgery should be considered for patients with oligometastatic disease because they may experience long-term disease-free survival after metastasectomy. Patients with solitary metastases are the best candidates, but surgery can also be used for patients with metastases at more than one site if a complete resection of all sites can be achieved. Patients rendered free of disease can be considered for adjuvant therapy or a clinical trial because their risk of developing additional metastases is very high. Surgery can also be used as an adjunct to systemic therapy when for example, a few of many metastatic lesions prove resistant to immunotherapy.

TABLE 72-3 Treatment Options for Metastatic Melanoma

Surgery: Metastasectomy for small number of lesions
Immunotherapy:
Interleukin 2
Immune checkpoint blockade
• Anti-CTLA-4: ipilimumab
• Anti-PD-1: nivolumab, pembrolizumab
• Combined ipilimumab and nivolumab
Experimental
• Anti-PD-L1
Molecular targeted therapy:
BRAF inhibitor: vemurafenib, dabrafenib
MEK inhibitor: trametinib, cobimetinib
Oncolytic virus: talimogene laherpaepvec
Chemotherapy: dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin

IMMUNOTHERAPY

Interleukin 2 (IL-2 or aldesleukin) is used effectively to treat stage IV patients who have a good performance status. High-dose IL-2, which requires hospitalization in an intensive care unit–like setting, is administered by intravenous bolus doses over a 1-week cycle mainly at centers with experience managing IL-2-related toxicity. Treatment is continued until maximal benefit is achieved, usually 4–6 cycles distributed over 4–6 months to allow for recovery from toxicities between cycles. Long-term disease-free survival (probable cure) is observed in 5% of treated patients.

Checkpoint Blockade Newer immunotherapies are based on an understanding of the control mechanisms of the normal immune response. Inhibitory receptors or checkpoints, including CTLA-4 and PD-1, are upregulated on T cells after engagement of the T-cell receptor by cognate tumor antigen in the context of the appropriate class I or II HLA molecules during the interaction between a T cell and antigen-presenting cell. An absolute requirement to ensure proper regulation of a normal immune response, the continued expression of inhibitory receptors during chronic infection (hepatitis, HIV) and in cancer patients leads to exhausted T cells with limited potential for proliferation, cytokine production, or cytotoxicity **(Fig. 72-3)**. Checkpoint blockade with an antagonistic monoclonal antibody results in improved T-cell function and eradication of tumor cells in preclinical animal models. Ipilimumab, a fully human IgG1 antibody that binds CTLA-4 and blocks inhibitory signals, was the first drug shown in a randomized trial to improve survival in patients with metastatic melanoma. A full course of therapy is four outpatient infusions of ipilimumab 3 mg/kg every 3 weeks. Although response rates are low (~10%), overall survival is improved.

Chronic T-cell activation also leads to induction of PD-1 on the surface of T cells. Expression of one of its ligands, PD-L1, on tumor cells can protect them from immune destruction (Fig. 72-3). Blockade of the PD-1:PD-L1 axis by IV administration of anti-PD-1 or anti-PD-L1 has substantial clinical activity in patients with advanced melanoma (and lung, renal, bladder and oral head and neck cancers as well as Hodgkin lymphoma) with significantly less toxicity than ipilimumab. The PD-1 blockers, nivolumab and pembrolizumab, have been approved to treat patients with advanced melanoma. Combination T-cell checkpoint therapy, blocking both inhibitory pathways with ipilimumab and nivolumab, leads to superior antitumor activity compared to treatment with either agent alone. Combined therapy with intravenous ipilimumab and nivolumab is administered in the outpatient setting every 3 weeks for 4 doses (induction), followed by nivolumab given every 2 weeks (maintenance) for up to one year. This regimen produces an objective response rate of 56% and enhanced survival compared to

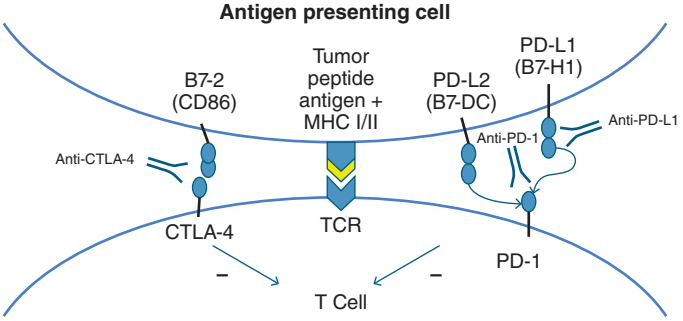

FIGURE 72-3 Inhibitory regulatory pathways that influence T-cell function, memory and lifespan after engagement of the T-cell receptor by tumor peptide antigen presented by antigen-presenting cells in the context of MHC I/II. CTLA-4 and PD-1 are members of the CD28 family and their inhibitory effects can be mitigated by antagonistic antibodies to the receptors or ligand resulting in enhanced T-cell function and anti-tumor effects. TCR: T-cell receptor, MHC: Major Histocompatibility Complex, CTLA-4: Cytotoxic T-Lymphocyte Antigen-4, PD-1: Programmed Death-1, PD-L1: Programmed Death Ligand-1, PD-L2: Programmed Death Ligand-2.

ipilimumab monotherapy. There may be subsets of patients, specifically those who have >5% expression of PD-1 on T cells in a melanoma biopsy sample, who derive a similar level of clinical benefit from nivolumab monotherapy.

The main benefit to patients from immune-based therapy is the durability of the responses achieved. The percentage of patients whose tumors regress following combination anti-CTLA-4 and anti-PD-1 immunotherapy is comparable to the response rate after targeted therapy (see below); however, the durability of immunotherapy-induced responses (>10 years in some cases with checkpoints and greater than 20 years in some patients after IL-2) appears to be superior to responses after targeted therapy and suggests that many of these patients have been cured.

T-cell checkpoint antibodies can also interfere with normal immune regulatory mechanisms, which may produce a novel spectrum of side effects. The most common immune-related adverse events were skin rash and diarrhea (sometimes severe, life-threatening colitis), but toxicity can involve most any organ (e.g., hypophysitis, hepatitis, nephritis, pneumonitis, myocarditis, neuritis). The severity and frequency of toxicity is greatest with combination T-cell checkpoint antibody therapy, followed by anti-CTLA-4 and then anti-PD-1 monotherapies. Vigilance, interruption of therapy and early intervention with steroids or other immunosuppressive agents, such as anti-tumor necrosis factor antibodies or mycophenolate mofetil, can mitigate toxicity and prevent permanent organ damage. The management of drug-induced toxicity with immunosuppressive agents does not appear to interfere with antitumor activity. The use of T-cell checkpoint antibodies for metastatic melanoma has become commonplace, but there is controversy about whether all patients need combined anti-CTLA-4 and anti-PD-1, whether biomarkers can be used to select patients who may benefit from anti-PD-1 alone and the best sequence of targeted and immunotherapy in patients who have a BRAF mutation. There is also a significant economic impact with the cost of combination anti-CTLA-4 and anti-PD-1, which must be placed in the context of the survival benefit.

TARGETED THERAPY

The high frequency of oncogenic mutations in the RAS-RAF-MEK-ERK pathway, which delivers proliferation and survival signals from the cell surface to the cytoplasm and nucleus, has led to the development of inhibitors to BRAF and MEK. RAF and MEK inhibitors of the MAP kinase pathway can induce regression of melanomas that harbor a *BRAF* mutation. Two BRAF inhibitors, vemurafenib and dabrafenib, have been approved for the treatment of patients whose stage IV melanomas harbor a mutation at position 600 in *BRAF*. Monotherapy with BRAF inhibitors has been supplanted with combined BRAF and MEK inhibition to address the rapid adaptation of the majority of melanomas that use MAP kinase pathway reactivation to facilitate growth when BRAF is inhibited. Combined therapy with BRAF and MEK inhibitors (dabrafenib and trametinib or vemurafenib with cobimetinib) improved progression-free survival compared to monotherapy with a BRAF inhibitor. The durability of responses following combined therapy is superior to monotherapy and survival is also enhanced. Long-term results of inhibition of the MAP kinase pathway are not yet available, but the major limitation of both monotherapy and combined therapy appears to be the acquisition of resistance; the vast majority of patients relapse and eventually die. The mechanisms of resistance are diverse and reflect the genomic heterogeneity of melanoma; however, most instances involve reactivation of the MAPK pathway, often through RAS mutations or mutant BRAF amplification. Patients who develop resistance to BRAF and MEK inhibition are candidates for immunotherapy or clinical trials.

Targeted therapy is accompanied by manageable side effects that differ from those experienced during immunotherapy or chemotherapy. A class-specific side effect of BRAF inhibition is the development of numerous skin lesions, some of which are well-differentiated squamous cell skin cancers (SCC) (seen in up to 25% of patients). These hyperproliferative lesions are believed to be due to paradoxical activation of the MAPK pathway resulting from BRAF inhibitor-mediated changes in *BRAF*-wild type cells. The paradoxical activation is blocked by the MEK inhibitor, which explains why these lesions occur much less frequently during combined therapy. Patients should be co-managed with a dermatologist as these skin cancers will need excision. Metastases of the treatment-induced SCCs have not been reported, and BRAF and MEK inhibitors can be continued safely following simple excision. Cardiac and ocular toxicities, although infrequent, can occur with BRAF and MEK inhibitors and require medical evaluation and management.

Activating mutations in the c-kit receptor tyrosine kinase are found in a minority of cutaneous melanomas with chronic sun damage, but are more common in mucosal and acral lentiginous subtypes. Overall, the number of patients with *c-kit* mutations is exceedingly small, but when present, they are similar to those found in gastrointestinal stromal tumors; melanomas with activating *c-kit* mutations can have clinically meaningful responses to imatinib. The probability of objective response in patients whose melanomas harbor a *c-kit* mutation is 29%. *N-RAS* mutations occur in 15–20% of melanomas. At present, there are no effective targeted agents for these patients, but MEK inhibitors are being investigated in clinical trials.

CHEMOTHERAPY

No chemotherapy regimen has ever been shown to improve survival of patients with metastatic melanoma. The advances in immunotherapy and targeted therapy have relegated chemotherapy to the palliation of symptoms. Drugs with antitumor activity include dacarbazine (DTIC) or its orally administered analog temozolomide (TMZ), cisplatin and carboplatin, the taxanes (paclitaxel alone or albumin-bound), and carmustine (BCNU), which have reported response rates of 12–20%.

INITIAL APPROACH TO PATIENT WITH METASTATIC DISEASE

Upon diagnosis of stage IV disease, a sample of the patient's tumor should be submitted for molecular testing to determine whether a druggable mutation (e.g., *BRAF* and c-kit) is present. Analysis of a metastatic lesion biopsy (if possible) is preferred, but any sample will suffice because there is little discordance between primary and metastatic lesions. Treatment algorithms start with the tumor's *BRAF* status. For *BRAF* wild-type tumors, immunotherapy is recommended. For patients whose tumors harbor a *BRAF* mutation, initial therapy with either combination BRAF and MEK inhibitors or immunotherapy is acceptable. Combined therapy with BRAF and MEK inhibitors is favored for patients with rapidly growing and symptomatic disease when a *BRAF* mutation is present. The sequence of immunotherapy and targeted therapy that confers the greatest survival benefit in patients with minimally symptomatic melanoma is not yet known, but ongoing randomized phase III trials should answer this important question. Despite improvements in therapy, the majority of patients with metastatic melanoma are not cured so enrollment in a clinical trial is always an important consideration, even for previously untreated patients.

Since most patients with stage IV disease will eventually experience tumor progression despite therapy and many, because of extensive disease burden, poor performance status, or concomitant illness, will be poor candidates for therapy, the timely integration of palliative care and hospice should be a major focus of care. Future advances in the management of melanoma will likely include biomarkers to select the optimal combination and sequence of agents or to identify patients who are unlikely to respond to extant therapies and for whom clinical trials should be considered. New therapeutic agents could include T-cell co-stimulatory antibodies, engineered T cells, oncolytic viruses and possibly vaccines to prevent melanoma development or recurrence.

FOLLOW-UP

Skin examination and surveillance at least once a year are recommended for all patients with melanoma. Routine blood work and

imaging for patients with stage IA–IIA disease is not recommended unless symptoms are present. In general, because there is no survival benefit to patients, routine surveillance diagnostic imaging is not recommended for patients with higher stage disease and imaging should be reserved for patients with signs or symptoms of recurrent disease. For stage-specific recommendations, please consult the National Comprehensive Cancer Network (NCCN) guidelines (see Further Reading).

NONMELANOMA SKIN CANCER

Nonmelanoma skin cancer (NMSC) is the most common cancer in the United States. Although tumor registries do not routinely gather data on the incidence of basal cell and squamous cell skin cancers, it is estimated that the annual incidence is 1.5–2 million cases in the United States. Basal cell carcinomas (BCCs) account for 70–80% and squamous cell carcinomas (SCCs) ~20% of NMSCs, respectively. SCCs are more significant because they metastasize and account for 2400 deaths annually. There has also been an increase in the incidence of nonepithelial skin cancer, especially Merkel cell carcinoma, with nearly 5000 new diagnoses and 3000 deaths annually.

PATHOPHYSIOLOGY AND ETIOLOGY

The most significant cause of BCC and SCC is UV radiation, whether through direct exposure to sunlight or by artificial UV light sources (tanning beds). Both UVA and UVB light can induce DNA damage. The DNA damage can be repaired or lead to cell death. The mechanism for DNA repair involves excising damaged nucleotides. Inherited disorders of DNA repair, such as xeroderma pigmentosum, are associated with a greatly increased incidence of skin cancer and help to establish the link between UV-induced DNA damage, inadequate DNA repair, and skin cancer. The genes damaged most commonly by UV in BCC involve the hedgehog signaling pathway (Hh) and lead to basal cell proliferation. This is usually the result of loss of function of the tumor-suppressor patched homolog 1 (*PTCH1*), which normally inhibits the signaling of smoothened homolog (*SMO*). Aberrant *PTCH1* signaling is propagated by the nuclear transcription factors Gli1 and Gli2, which are salient in the development of BCC. Two oral SMO inhibitors, vismodegib and sonidegib, have been approved by the FDA to treat advanced inoperable or metastatic BCC and locally advanced BCC that has recurred following surgery or RT, respectively **(Fig. 72-4)**. Vismodegib also reduces the incidence of BCC in patients with basal cell nevus syndrome who have *PTCH1* mutations, affirming the importance of Hh in the onset of BCC.

In SCC, *p53* and *N-RAS* are commonly affected. There is a dose-response relationship between tanning bed use and the incidence of skin cancer. As few as four tanning bed visits per year confers a 15% increase in BCC and an 11% increase in SCC and melanoma. Tanning bed use as a teenager or young adult confers greater risk than comparable exposure in older individuals. Other associations include blond or red hair, blue or green eyes, a tendency to sunburn easily, and an outdoor occupation. The incidence of NMSC increases with decreasing latitude. Most tumors develop on sun-exposed areas of the head and neck. The risk of lip or oral SCC is increased with cigarette smoking and, like SCC of the ear, has a worse prognosis than that seen on other body sites. Human papillomaviruses and UV radiation may act as co-carcinogens.

Chronically immunosuppressed solid organ transplant recipients have a 65-fold increase in SCC and a 10-fold increase in BCC. The frequency of skin cancer is proportional to the level and duration of immunosuppression and the extent of sun exposure before and after transplantation. SCCs in this population also demonstrate higher rates of local recurrence, metastasis, and mortality. Tumor necrosis factor (TNF) antagonist therapy of inflammatory bowel disease and autoimmune disorders, such as rheumatoid and psoriatic arthritis, may also confer an increased risk of NMSC.

Other risk factors include HIV infection, ionizing radiation, thermal burn scars, and chronic ulcerations. Albinism, xeroderma pigmentosum, Muir-Torre syndrome, Rombo's syndrome, Bazex-Dupré-Christol syndrome, dyskeratosis congenita, and basal cell nevus syndrome (Gorlin syndrome) also increase the incidence of NMSC.

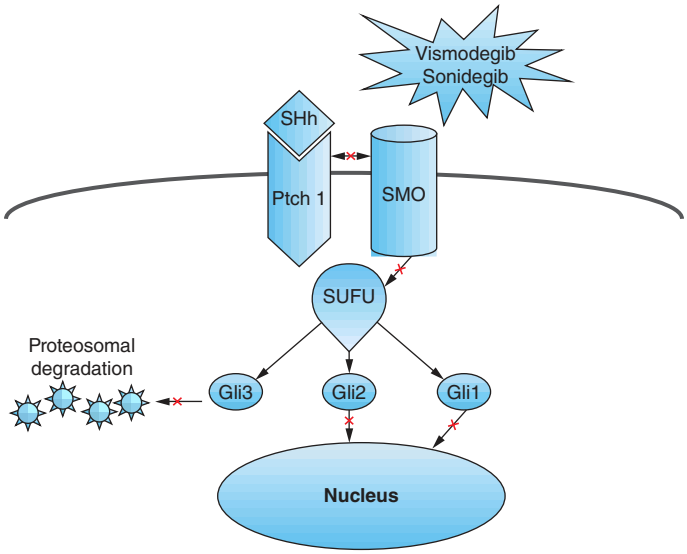

FIGURE 72-4 Inhibition of the hedgehog (Hh) pathway. The Hh pathway promotes gene transcription and is important in the pathogenesis of BCC. Normally, one of three Hh ligands (sonic [SHh], Indian, or desert) binds to patched homolog 1 (PTCH1), causing its degradation and release of smoothened homolog (SMO). SMO release represses another regulatory protein called suppressor of fused (SUFU). SUFU normally binds glioblastoma transcription factors Gli1, Gli2, and Gli3. SUFU repression allows Gli1 and Gli2 to translocate to the nucleus and promote gene transcription. Vismodegib and sonidegib are SMO antagonists. Antagonizing SMO decreases the interaction between SMO and PTCH1, resulting in decreased Hh pathway signaling, gene transcription, and cell division. The Hh pathway events inhibited by vismodegib and sonidegib are indicated in red.

CLINICAL PRESENTATION

Basal Cell Carcinoma BCC arises from epidermal basal cells. The least invasive of BCC subtypes, superficial BCC, consists of often subtle, erythematous scaling plaques that slowly enlarge and are most commonly seen on the trunk and proximal extremities **(Fig. 72-5)**. This BCC subtype may be confused with benign inflammatory dermatoses, especially nummular eczema and psoriasis or premalignant actinic keratoses. BCC also can present as a small, slowly growing pearly nodule, often with tortuous telangiectatic vessels on its surface, rolled borders, and a central crust (nodular BCC). The occasional presence of melanin in this variant of nodular BCC (pigmented BCC) may lead to confusion with melanoma. Morpheaform (fibrosing), infiltrative, and micronodular BCC, the most invasive and potentially aggressive subtypes, manifest as solitary, flat or slightly depressed, indurated whitish, yellowish, or pink scar-like plaques. Borders are typically indistinct, and lesions can be subtle; thus, delay in treatment is common, and tumors can be more extensive than expected clinically.

Squamous Cell Carcinoma Primary *cutaneous SCC* is a malignant neoplasm of keratinizing epidermal cells. SCC has a variable clinical course, ranging from indolent to rapid growth, with the potential to metastasize to regional and distant sites. Commonly, SCC appears as an ulcerated erythematous nodule or superficial erosion on sun-exposed skin of the head, neck, trunk, and extremities **(Fig. 72-5)**. It may also appear as a banal, firm, dome-shaped papule or rough-textured plaque. It is commonly mistaken for a wart or callous when the inflammatory response to the lesion is minimal. Visible overlying telangiectasias are uncommon, although dotted or coiled vessels are a hallmark of SCC when viewed through a dermatoscope. The margins of this tumor may be ill defined, and fixation to underlying structures may occur ("tethering").

A very rapidly growing but low-grade form of SCC, called keratoacanthoma (KA), typically appears as a large dome-shaped papule with a central keratotic crater. Some KAs regress spontaneously without therapy, but because progression to metastatic SCC has been

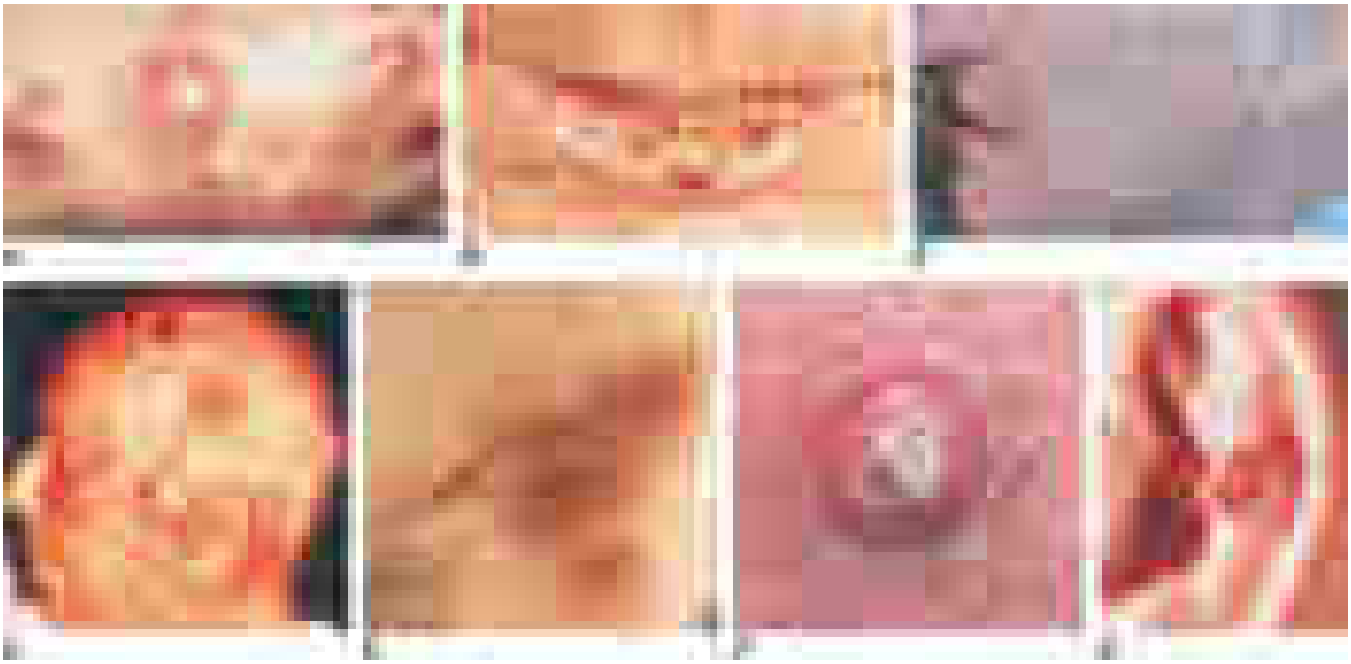

FIGURE 72-5 Cutaneous neoplasms. ***A***. Non-Hodgkin's lymphoma involves the skin with typical violaceous, "plum-colored" nodules. ***B***. Squamous cell carcinoma is seen here as a hyperkeratotic crusted and somewhat eroded plaque on the lower lip. Sun-exposed skin in areas such as the head, neck, hands, and arms represent other typical sites of involvement. ***C***. Actinic keratoses consist of hyperkeratotic erythematous papules and patches on sun-exposed skin. They arise in middle-aged to older adults and can undergo malignant transformation. ***D***. Metastatic carcinoma to the skin is characterized by inflammatory, often ulcerated dermal nodules. ***E***. Mycosis fungoides is a cutaneous T-cell lymphoma, and plaque-stage lesions are seen in this patient. ***F***. Keratoacanthoma is a low-grade squamous cell carcinoma that presents as an exophytic nodule with central keratinous debris. ***G***. This basal cell carcinoma shows central ulceration and a pearly, rolled telangiectatic tumor border.

documented, KAs should be treated in the same manner as other types of cutaneous SCC. KAs occur in 15–25% of patients receiving monotherapy with a BRAF inhibitor.

Actinic keratoses and *cheilitis* (actinic keratoses on the lip), both premalignant forms of SCC, present as hyperkeratotic papules on sun-exposed areas. Malignant transformation occurs in 0.25 to 20% of untreated lesions. SCC in situ, also called *Bowen's disease*, is the intraepidermal form of SCC and usually presents as a scaling, erythematous plaque. SCC in situ most commonly arises on sun-damaged skin, but can occur anywhere on the body. Bowen's disease occurring secondary to infection with human papillomavirus (HPV) can arise on skin with minimal or no prior sun exposure, such as the buttock or posterior thigh. Treatment of premalignant and in situ lesions reduces the subsequent risk of invasive disease.

NATURAL HISTORY

Basal Cell Carcinoma The natural history of BCC is that of a slowly enlarging, locally invasive neoplasm. The degree of local destruction and risk of recurrence vary with the size, duration, location, and histologic subtype of the tumor. Location on the central face, ears, or scalp may portend a higher risk. Small nodular, pigmented, cystic, or superficial BCCs respond well to most treatments. Large lesions and micronodular, infiltrative, and morpheaform subtypes may be more aggressive. The metastatic potential of BCC is low (0.0028–0.1%) in immunocompetent patients, but the risk of recurrence or a new primary NMSC is about 40% over 5 years.

Squamous Cell Carcinoma The natural history of SCC depends on tumor and host characteristics. Tumors arising on sun-damaged skin have a lower metastatic potential than do those on non-sun-exposed areas. Cutaneous SCC metastasizes in 0.3–5.2% of individuals, most frequently to regional lymph nodes. Tumors occurring on the lower lip and ear develop regional metastases in 13 and 11% of patients, respectively, whereas the metastatic potential of SCC arising in scars, chronic ulcerations, and genital or mucosal surfaces is higher. Recurrent SCC has a much higher potential for metastatic disease, approaching 30%. Large, poorly differentiated, deep tumors with perineural or lymphatic invasion, multifocal tumors, and those arising in immunosuppressed patients often behave aggressively.

TREATMENT

Basal Cell and Squamous Cell Carcinoma

BASAL CELL CARCINOMA

Treatments used for BCC include electrodesiccation and curettage (ED&C), excision, cryosurgery, radiation therapy (RT), laser therapy, Mohs micrographic surgery (MMS), topical 5-fluorouracil, photodynamic therapy (PDT), and topical immunomodulators such as imiquimod. The choice of therapy depends on tumor characteristics including depth and location, patient age, medical status, and patient preference. ED&C remains the most commonly employed method for superficial, minimally invasive nodular BCCs and low-risk tumors (e.g., a small tumor of a less aggressive subtype in a favorable location). Wide local excision with standard margins is usually selected for invasive, ill-defined, and more aggressive subtypes of tumors, or for cosmetic reasons. MMS, a specialized type of surgical excision that provides the best method for tumor removal while preserving uninvolved tissue, is associated with cure rates >98%. It is the preferred modality for lesions that are recurrent, in high-risk or cosmetically sensitive locations (including recurrent tumors in these locations), and for which maximal tissue conservation is critical (e.g., the eyelids, lips, ears, nose, and digits). RT can cure patients not considered surgical candidates and can be used as a surgical adjunct in high-risk tumors. Imiquimod can be used to treat superficial and smaller nodular BCCs, although it is not FDA-approved for nodular BCC. Topical 5-fluorouracil therapy should be limited to superficial BCC. PDT, which uses selective activation of a photoactive drug by visible light, has been used in patients with numerous tumors. Intralesional therapy (5-fluorouracil or IFN) can also be employed. Like RT, it remains an option for selected patients who cannot or will not undergo surgery. Systemic therapy with an SMO inhibitor, vismodegib or sonidegib, is indicated for patients with metastatic or advanced BCC that has recurred after

local therapy and who are not candidates for surgery or radiation. Targeted therapy with SMO antagonists does not cure patients with BCC, but induces regression in approximately 50% of patients with a median duration of response greater than 9 months.

SQUAMOUS CELL CARCINOMA

Therapy for cutaneous SCC should be based on the size, location, histologic differentiation, patient age, and functional status. Surgical excision and MMS are standard treatments. Cryosurgery and ED&C have been used for premalignant lesions and small, superficial, in situ primary tumors. Lymph node metastases are treated with surgical resection, RT, or both. Combination chemotherapy that includes cisplatin, and intralesional and systemic 5-fluorouracil, and cetuximab are also options for palliation in patients with advanced disease. SCC and keratoacanthomas that develop in patients receiving BRAF-targeted therapy should be excised, after which BRAF therapy can be continued.

PREVENTION

The general principles for prevention are those described for melanoma earlier. Unique strategies for NMSC include active surveillance for patients on immunosuppressive medications or BRAF-targeted therapy. Chemoprophylaxis using synthetic retinoids and immunosuppression reduction when possible may be useful in controlling new lesions and managing patients with multiple tumors. Field therapy with topical 5-FU, ingenol mebutate, or imiquimod can reduce transformation to SCC in patients with severe sun damaged skin and numerous premalignant actinic keratoses.

OTHER NONMELANOMA CUTANEOUS MALIGNANCIES

Neoplasms of cutaneous adnexae and sarcomas of fibrous, mesenchymal, fatty, and vascular tissues make up the remaining 1–2% of NMSCs.

Merkel cell carcinoma (MCC) is a neural crest–derived highly aggressive malignancy with mortality rates approaching 33% at 3 years. An oncogenic Merkel cell polyomavirus (MCPyV) is present in 80% of tumors and UV exposure also increases the incidence of this malignancy. In patients with MCPyV+ tumors, there is inactivation of tumor suppressor genes, specifically the p53 transcription factor and retinoblastoma protein (Rb). In addition, the viral large T antigen is expressed on tumor cells and many patients have detectable cellular or humoral immune responses to polyoma viral proteins, although this immune response is insufficient to eradicate the malignancy. Survival depends on extent of disease: 90% survive with local disease, 52% with nodal involvement, but only 10% with distant disease. MCC incidence tripled over the last 20 years with an estimated 1600 cases per year in the United States. Immunosuppression increases the incidence and diminishes the prognosis compared to patients with no immunosuppression. MCC lesions typically present as an asymptomatic rapidly expanding bluish-red/violaceous tumor on sun-exposed skin of older white patients. Treatment is surgical excision with sentinel lymph node biopsy for accurate staging in patients with localized disease, often followed by adjuvant RT. Patients with extensive disease can be offered systemic chemotherapy; however, there is no survival benefit. Immunotherapy using anti-PD-1 (pembrolizumab) was associated with a 56% response rate with a progression-free survival at 6 months of 67%. Tumor regression occurred in MCPyV positive and negative tumors. A monoclonal antibody targeting anti-PD-L1 known as avelumab showed objective responses in 33% of patients with advanced MCC that was durable in 82% of the responders. The U.S. FDA approved avelumab for the treatment of patients with metastatic MCC in April 2017. Whenever possible a clinical trial should be considered for patients with this rare but aggressive NMSC.

Extramammary Paget's disease is an uncommon apocrine malignancy arising from stem cells of the epidermis that are characterized histologically by the presence of Paget cells. These tumors present as moist erythematous patches on anogenital or axillary skin of the elderly. Outcomes are generally good with surgery, and 5-year disease-specific survival is ~95% with localized disease. Advanced age and extensive disease at presentation confer diminished prognosis. RT or topical imiquimod can be considered for more extensive disease. Local management may be challenging because these tumors often extend far beyond clinical margins; surgical excision with MMS has the highest cure rates. Similarly, MMS is the treatment of choice in other rare cutaneous tumors with extensive subclinical extension such as *dermatofibromasarcoma protuberans*.

Kaposi's sarcoma (KS) is a soft tissue sarcoma of vascular origin that is induced by the human herpesvirus 8. The incidence of KS increased dramatically during the AIDS epidemic, but has now decreased tenfold with the institution of highly active antiretroviral therapy.

Acknowledgment

Steven Kolker, MD, provided valued feedback and suggested improvements to this chapter.

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73 Head and Neck Cancer

Everett E. Vokes

Epithelial carcinomas of the head and neck arise from the mucosal surfaces in the head and neck and typically are squamous cell in origin. This category includes tumors of the paranasal sinuses, the oral cavity, and the nasopharynx, oropharynx, hypopharynx, and larynx. Tumors of the salivary glands differ from the more common carcinomas of the head and neck in etiology, histopathology, clinical presentation, and therapy. They are rare and histologically highly heterogeneous. **Thyroid malignancies are described in Chap. 378.**

INCIDENCE AND EPIDEMIOLOGY

The number of new cases of head and neck cancers (oral cavity, pharynx, and larynx) in the United States was estimated at 48,330 in 2016, accounting for about 3% of adult malignancies; estimated deaths were 13,190. The worldwide incidence exceeds half a

million cases annually. In North America and Europe, the tumors usually arise from the oral cavity, oropharynx, or larynx. The incidence of oropharyngeal cancers is increasing in recent years, especially in Western countries. Nasopharyngeal cancer is more commonly seen in the Mediterranean countries and in the Far East, where it is endemic in some areas.

ETIOLOGY AND GENETICS

Alcohol and tobacco use are the most significant risk factors for head and neck cancer, and when used together, they act synergistically. Smokeless tobacco is an etiologic agent for oral cancers. Other potential carcinogens include marijuana and occupational exposures such as nickel refining, exposure to textile fibers, and woodworking.

Some head and neck cancers have a viral etiology. Epstein-Barr virus (EBV) infection is frequently associated with nasopharyngeal cancer, especially in endemic areas of the Mediterranean and Far East. EBV antibody titers can be measured to screen high-risk populations and are under investigation to monitor treatment response. Nasopharyngeal cancer has also been associated with consumption of salted fish and in-door pollution.

In Western countries, the human papilloma virus (HPV) is associated with a rising incidence of tumors arising from the oropharynx, that is, the tonsillar bed and base of tongue. Over 50% of oropharyngeal tumors are caused by HPV in the United States, and in many urban centers this proportion is even higher. HPV 16 is the dominant viral subtype, although HPV 18 and other oncogenic subtypes are seen as well. Alcohol- and tobacco-related cancers, on the other hand, have decreased in incidence. HPV-related oropharyngeal cancer occurs in a younger patient population and is associated with increased numbers of sexual partners and oral sexual practices. It is associated with a better prognosis, especially for nonsmokers.

Dietary factors may contribute. The incidence of head and neck cancer is higher in people with the lowest consumption of fruits and vegetables. Certain vitamins, including carotenoids, may be protective if included in a balanced diet. Supplements of retinoids, such as *cis*-retinoic acid, have not been shown to prevent head and neck cancers (or lung cancer) and may increase the risk in active smokers. No specific risk factors or environmental carcinogens have been identified for salivary gland tumors.

HISTOPATHOLOGY, CARCINOGENESIS, AND MOLECULAR BIOLOGY

Squamous cell head and neck cancers are divided into well-differentiated, moderately well-differentiated, and poorly differentiated categories. Poorly differentiated tumors have a worse prognosis than well-differentiated tumors. For nasopharyngeal cancers, the less common differentiated squamous cell carcinoma is distinguished from non-keratinizing and undifferentiated carcinoma (lymphoepithelioma) that contains infiltrating lymphocytes and is commonly associated with EBV.

Salivary gland tumors can arise from the major (parotid, submandibular, sublingual) or minor salivary glands (located in the submucosa of the upper aerodigestive tract). Most parotid tumors are benign, but half of submandibular and sublingual gland tumors and most minor salivary gland tumors are malignant. Malignant tumors include mucoepidermoid and adenoid cystic carcinomas and adenocarcinomas.

The mucosal surface of the entire pharynx is exposed to alcohol- and tobacco-related carcinogens and is at risk for the development of a premalignant or malignant lesion. Erythroplakia (a red patch) or leukoplakia (a white patch) can be histopathologically classified as hyperplasia, dysplasia, carcinoma in situ, or carcinoma. However, most head and neck cancer patients do not present with a history of premalignant lesions. Multiple synchronous or metachronous cancers can also be observed. In fact, over time, patients with treated early-stage head and neck cancer are at greater risk of dying from a second malignancy than from a recurrence of the primary disease.

Second head and neck malignancies are usually not therapy-induced; they reflect the exposure of the upper aerodigestive mucosa to the same carcinogens that caused the first cancer. These second primaries develop in the head and neck area, the lung, or the esophagus. Thus, computed tomography (CT) screening for lung cancer in heavy smokers who have already developed a head and neck cancer is recommended. Rarely, patients can develop a radiation therapy–induced sarcoma after having undergone prior radiotherapy for a head and neck cancer.

Much progress has been made in describing the molecular features of head and neck cancer. These features have allowed investigators to describe the genetic and epigenetic alterations and the mutational spectrum of these tumors. Early reports demonstrated frequent overexpression of the epidermal growth factor receptor (EGFR). Overexpression was shown to correlate with poor prognosis. However, it has not proved to be a good predictor of tumor response to EGFR inhibitors, which are active in only about 10–15% of patients as single agents. Complex genetic analyses, including those by The Cancer Genome Atlas project, have been performed. *p53* mutations are found frequently with other major affected oncogenic driver pathways including the mitotic signaling and Notch pathways and cell cycle regulation in HPV-negative tumors. HPV oncogenes act through direct inhibition of the *p53* and *RB* tumor-suppressor genes, thereby initiating the carcinogenic process. While overall mutation rates are similar in HPV-positive and carcinogen-induced tumors, the specific mutational signature of HPV-positive tumors differs with frequent alteration of the PI3K pathway and occasional mutations in KRAS. Overall, these alterations affect mitogenic signaling, genetic stability, cellular proliferation, and differentiation.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Most tobacco-related head and neck cancers occur in patients older than age 60 years. HPV-related malignancies are frequently diagnosed in younger patients, usually in their forties or fifties, whereas EBV-related nasopharyngeal cancer can occur at all ages, including teenagers. The manifestations vary according to the stage and primary site of the tumor. Patients with nonspecific signs and symptoms in the head and neck area should be evaluated with a thorough otolaryngologic examination, particularly if symptoms persist longer than 2–4 weeks. Males are more frequently affected than women by head and neck cancers, including HPV-positive tumors.

Cancer of the nasopharynx typically does not cause early symptoms. However, it may cause unilateral serous otitis media due to obstruction of the eustachian tube, unilateral or bilateral nasal obstruction, or epistaxis. Advanced nasopharyngeal carcinoma causes neuropathies of the cranial nerves due to skull base involvement.

Carcinomas of the oral cavity present as non-healing ulcers, changes in the fit of dentures, or painful lesions and masses. Tumors of the tongue base or oropharynx can cause decreased tongue mobility and alterations in speech. Cancers of the oropharynx or hypopharynx rarely cause early symptoms, but they may cause sore throat and/or otalgia. HPV-related tumors frequently present with neck lymphadenopathy as the first sign.

Hoarseness may be an early symptom of laryngeal cancer, and persistent hoarseness requires referral to a specialist for indirect laryngoscopy and/or radiographic studies. If a head and neck lesion treated initially with antibiotics does not resolve in a short period, further workup is indicated; to simply continue the antibiotic treatment may be to lose the chance of early diagnosis of a malignancy.

Advanced head and neck cancers in any location can cause severe pain, otalgia, airway obstruction, cranial neuropathies, trismus, odynophagia, dysphagia, decreased tongue mobility, fistulas, skin involvement, and massive cervical lymphadenopathy, which may be unilateral or bilateral. Some patients have enlarged lymph nodes even though no primary lesion can be detected by endoscopy or biopsy; these patients are considered to have carcinoma of unknown primary **(Fig. 73-1)**. Tonsillectomy and directed biopsies of the base of tongue can frequently identify a small primary tumor that frequently will be HPV-related. If the enlarged nodes are located in the upper neck and the tumor

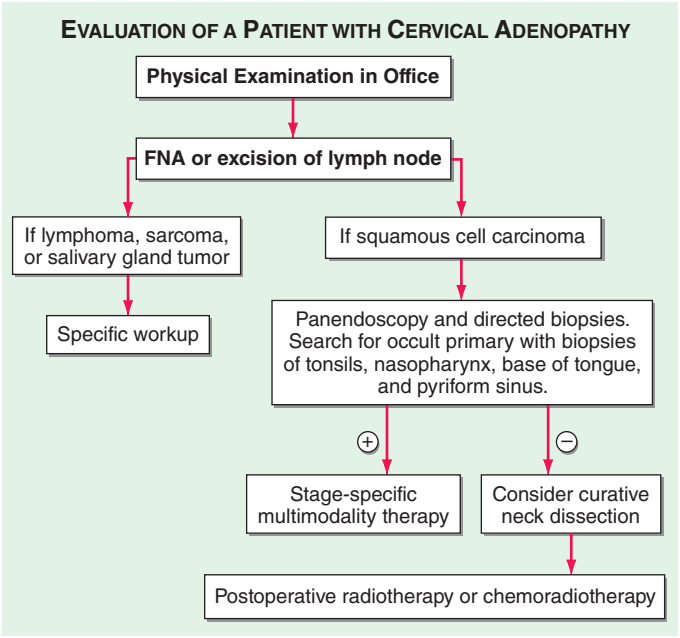


FIGURE 73-1 Evaluation of a patient with cervical adenopathy without a primary mucosal lesion; a diagnostic workup. FNA, fine-needle aspiration.

cells are of squamous cell histology, the malignancy probably arose from a mucosal surface in the head or neck. Tumor cells in supraclavicular lymph nodes may also arise from a primary site in the chest or abdomen.

The physical examination should include inspection of all visible mucosal surfaces and palpation of the floor of the mouth and of the tongue and neck. In addition to tumors themselves, leukoplakia (a white mucosal patch) or erythroplakia (a red mucosal patch) may be observed; these "premalignant" lesions can represent hyperplasia, dysplasia, or carcinoma in situ and require biopsy. Further examination should be performed by a specialist. Additional staging procedures include CT of the head and neck to identify the extent of the disease. Patients with lymph node involvement should have CT scan of the chest and upper abdomen to screen for distant metastases. In heavy smokers, the CT scan of the chest can also serve as a screening tool to rule out a second lung primary tumor. A positron emission tomography (PET) scan may also be administered and can help to identify or exclude distant metastases. CT and PET scans may also be useful in evaluating response to therapy. The definitive staging procedure is an endoscopic examination under anesthesia, which may include laryngoscopy, esophagoscopy, and bronchoscopy; during this procedure, multiple biopsy samples are obtained to establish a primary diagnosis, define the extent of primary disease, and identify any additional premalignant lesions or second primaries.

Head and neck tumors are classified according to the tumor-node-metastasis (TNM) system of the American Joint Committee on Cancer **(Fig. 73-2)**. This classification varies according to the specific anatomic subsite. In general, primary tumors are classified as T1 to T3 by increasing size, whereas T4 usually represents invasion of another structure such as bone, muscle, or root of tongue. Lymph nodes are staged by size, number, and location (ipsilateral vs contralateral to the primary). Distant metastases are found in <10% of patients at initial diagnosis and are more common in patients with advanced lymph node stage; microscopic involvement of the lungs, bones, or liver is more common, particularly in patients with advanced neck lymph node disease. Modern imaging techniques may increase the number of patients with clinically detectable distant metastases in the future. HPV-related oropharyngeal malignancies have consistently been shown to have a better prognosis, and in the upcoming 8th edition of the AJCC staging manual (active in 2018) a separate staging system that takes into account the more favorable outlook of these patients will be included. According to this system, patients with advanced nodal stage can still be considered to have an overall early stage (and associated good prognosis), especially if the patient is a non-smoker or has limited lifelong tobacco exposure.

In patients with lymph node involvement and no visible primary, the diagnosis should be made by lymph node excision (Fig. 73-1). If the results indicate squamous cell carcinoma, a panendoscopy should be performed, with biopsy of all suspicious-appearing areas and directed biopsies of common primary sites, such as the nasopharynx, tonsil, tongue base, and pyriform sinus. HPV-positive tumors especially can have small primary tumors that spread early to locoregional lymph nodes.

TREATMENT

Head and Neck Cancer

Patients with head and neck cancer can be grossly categorized into three clinical groups: those with localized disease, those with locally or regionally advanced disease (lymph node positive), and those with recurrent and/or metastatic disease below the neck. Comorbidities associated with tobacco and alcohol abuse can affect treatment outcome and define long-term risks for patients who are cured of their disease.

LOCALIZED DISEASE

Nearly one-third of patients have localized disease, that is, T1 or T2 (stage I or stage II) lesions without detectable lymph node involvement or distant metastases. These patients are treated with curative intent by either surgery or radiation therapy. The choice of modality differs according to anatomic location and institutional expertise. Radiation therapy is often preferred for laryngeal cancer to preserve voice function, and surgery is preferred for small lesions in the oral cavity to avoid the long-term complications of radiation, such as xerostomia and dental decay. Randomized data suggest that a prophylactic staging neck dissection should be part of the surgical procedure to eliminate occult nodal metastatic disease. Overall 5-year survival is 60–90%. Most recurrences occur within the first 2 years following diagnosis and are usually local.

LOCALLY OR REGIONALLY ADVANCED DISEASE

Locally or regionally advanced disease—disease with a large primary tumor and/or lymph node metastases—is the stage of presentation for >50% of patients. Such patients can also be treated with curative intent, but not with surgery or radiation therapy alone. Combined-modality therapy including surgery, and/or radiation therapy, and chemotherapy is most successful. Chemotherapy can be administered as induction chemotherapy (chemotherapy before surgery and/or radiotherapy) or as concomitant (simultaneous) chemotherapy and radiation therapy. The latter is currently most commonly used and supported by the best evidence. Five-year survival rates exceed 50% in many trials, but part of this increased survival may be due to an increasing fraction of study populations with HPV-related tumors who carry a better prognosis. HPV testing of newly diagnosed tumors is now performed for most patients at the time of diagnosis, and clinical trials for HPV-related tumors are focused on exploring reductions in treatment intensity, especially radiation dose, in order to ameliorate long-term toxicities (fibrosis, swallowing dysfunction).

In patients with intermediate-stage tumors (stage III and early stage IV), concomitant chemoradiotherapy can be administered either as a primary treatment for patients with unresectable disease, to pursue an organ-preserving approach especially for patients with laryngeal cancer (omission of surgery), or in the postoperative setting for smaller resectable tumors.

Induction Chemotherapy In this strategy, patients receive chemotherapy (current standard is a three-drug regimen of docetaxel, cisplatin, and fluorouracil [5-FU]) before surgery and radiation therapy. Most patients who receive three cycles show tumor reduction, and the response is clinically "complete" in up to half of patients. This "sequential" multimodality therapy allows for organ

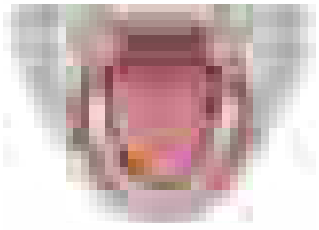
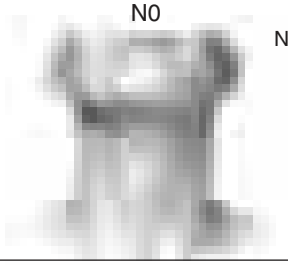
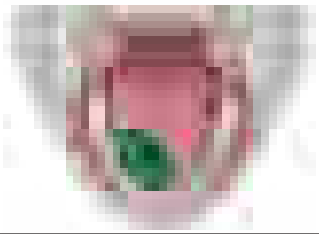
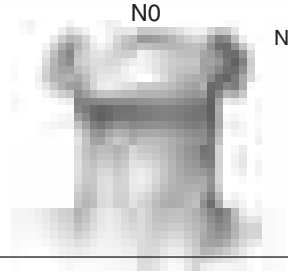
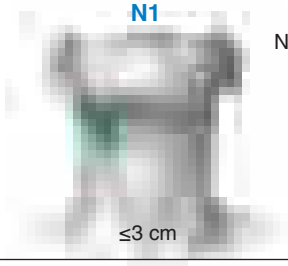
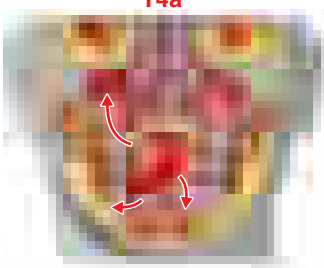
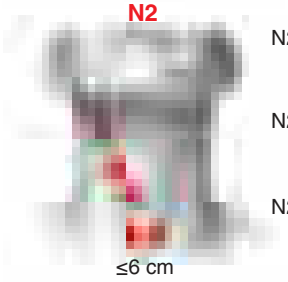
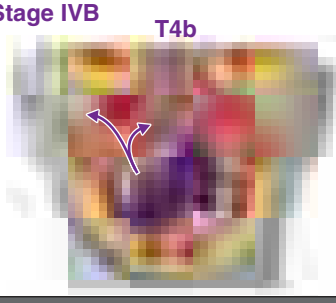
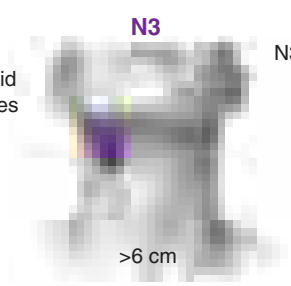
Definition of TNM			Stage groupings		
Stage I	T1  Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension	N0  N0- No regional lymph node metastasis	T1	N0	M0
Stage II	T2  Tumor ≥ 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension	N0  N0- No regional lymph node metastasis	T2	N0	M0
Stage III	T3  Tumor ≥ 4 cm and/or tumor having extraparenchymal extension	N1  ≤3 cm N1- Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greateast dimension	T3 T1 T2 T3	N0 N1 N1 N1	M0 M0 M0 M0
Stage IVA	T4a  Tumor invades skin, mandible, ear canal, and or fascial nerve	N2  ≤6 cm N2a- Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm N2b- Metastasis in a multiple ipsilateral lymph node, none >6 cm N2c- Metastasis in a bilateral or contralateral lymph nodes, none >6 cm	T4a T4a T1 T2 T3 T4a	N0 N1 N2 N2 N2 N2	M0 M0 M0 M0 M0 M0
Stage IVB	T4b  Tumor invades skull base and/or pterygoid plates and/or encases carotid artery	N3  >6 cm N3- Metastasis in a lymph node >6 cm in greatest dimension	T4b Any T	Any N N3	M0 M0
Stage IVC		M1	Any T	Any N	M1

FIGURE 73-2 **Tumor-node-metastasis (TNM)** staging system.

preservation in patients with laryngeal and hypopharyngeal cancer, and it has been shown to result in higher cure rates compared with radiotherapy alone.

Concomitant Chemoradiotherapy With the concomitant strategy, chemotherapy and radiation therapy are given simultaneously rather than in sequence. Tumor recurrences from head and neck cancer develop most commonly locoregionally (in the head and neck area of the primary and draining lymph nodes). The concomitant approach is aimed at enhancing tumor cell killing by radiation therapy in the presence of chemotherapy (radiation enhancement) and is a conceptually attractive approach for bulky tumors. Toxicity (especially mucositis, grade 3 or 4 in 70–80%) is increased with concomitant chemoradiotherapy. However, meta-analyses of randomized trials document an improvement in 5-year survival of 8% with concomitant chemotherapy and radiation therapy. Results seem more favorable in recent trials as more active drugs or more intensive radiotherapy schedules are used. In addition, concomitant

chemoradiotherapy produces better laryngectomy-free survival (organ preservation) than radiation therapy alone in patients with advanced larynx cancer. The use of radiation therapy together with cisplatin has also produced improved survival in patients with advanced nasopharyngeal cancer. The outcome of HPV-related cancers seems to be especially favorable following cisplatin-based chemoradiotherapy.

The success of concomitant chemoradiotherapy in patients with unresectable disease has led to the testing of a similar approach in patients with resected intermediate-stage disease as a postoperative therapy. Concomitant chemoradiotherapy produces a significant improvement over postoperative radiation therapy alone for patients whose tumors demonstrate higher risk features, such as extracapsular spread beyond involved lymph nodes, involvement of multiple lymph nodes, or positive margins at the primary site following surgery.

A monoclonal antibody to EGFR (cetuximab) increases survival rates when administered during radiotherapy. EGFR blockade results in radiation sensitization and has milder systemic side effects than traditional chemotherapy agents, although an acneiform skin rash is commonly observed. Nevertheless, the addition of cetuximab to current standard chemoradiotherapy regimens has failed to show further improvement in survival and is not recommended.

TREATMENT APPROACHES FOR HPV-RELATED HEAD AND NECK CANCERS

Given consistent observations of high survival rates for patients with advanced HPV-related oropharyngeal tumors using combined modality treatment strategies de-escalation protocols have attracted widespread interest. The goal here is to decrease the long-term morbidity resulting from high-dose radiation therapy, including extensive neck fibrosis, swallowing problems, and osteoradionecrosis of the jaw. Current studies are investigating the use of lower radiation doses, the use of induction chemotherapy and subsequent omission of chemotherapy or administration of significantly reduced chemoradiation doses in very good responders, and other strategies. In addition, there has been a resurgence of interest in surgical approaches using robotic surgery which allows better visualization of the base of tongue and tonsil. While technically feasible, this approach remains investigational at this time since a large number of patients with disease involving multiple lymph nodes disease will still require post-operative chemoradiotherapy thus negating the goal of treatment de-escalation. It is expected that distinct treatment guidelines from carcinogen-induced tumors will be defined in the coming years.

RECURRENT AND/OR METASTATIC DISEASE

Five to ten percent of patients present with metastatic disease and 30–50% of patients with locoregionally advanced disease experience recurrence, frequently outside the head and neck region. Patients with recurrent and/or metastatic disease are, with few exceptions, treated with palliative intent. Some patients may require local or regional radiation therapy for pain control, but most are given chemotherapy. Response rates to chemotherapy average only 30–50%; the durations of response are short, and the median survival time is 8–10 months. Therefore, chemotherapy provides transient symptomatic benefit. Drugs with single-agent activity in this setting include methotrexate, 5-FU, cisplatin, paclitaxel, and docetaxel. Combinations of cisplatin with 5-FU, carboplatin with 5-FU, and cisplatin or carboplatin with paclitaxel or docetaxel are frequently used.

EGFR-directed therapies, including monoclonal antibodies (e.g., cetuximab) and tyrosine kinase inhibitors (TKIs) of the EGFR signaling pathway (e.g., erlotinib or gefitinib), have single-agent activity of ~10%. Side effects are usually limited to an acneiform rash and diarrhea (for the TKIs). The addition of cetuximab to standard combination chemotherapy with cisplatin or carboplatin and 5-FU was shown to result in a significant increase in median survival. Drugs targeting specific mutations are under investigation, but no such strategy has yet been shown to be feasible in head and neck cancer.

IMMUNOTHERAPIES

Inhibitors of the immune suppressive lymphocyte-surface receptor PD-1 have shown activity in squamous cell cancers of the head and neck. A randomized trial evaluating the PD-1 inhibitor nivolumab vs traditional chemotherapy in second-line treatment of patients with current or metastatic disease showed a significant increase in survival time (7.5 vs 5.1 months) and 1-year survival rates with fewer severe treatment-related toxicities. Similarly, the PD-1 inhibitor pembrolizumab was shown to result in encouraging response rates and survival times in a single-arm phase II trial.

COMPLICATIONS

Complications from treatment of head and neck cancer are usually correlated to the extent of surgery and exposure of normal tissue structures to radiation. Currently, the extent of surgery has been limited or completely replaced by chemotherapy and radiation therapy as the primary approach. Acute complications of radiation include mucositis and dysphagia. Long-term complications include xerostomia, loss of taste, decreased tongue mobility, second malignancies, dysphagia, and neck fibrosis. The complications of chemotherapy vary with the regimen used but usually include myelosuppression, mucositis, nausea and vomiting, and nephrotoxicity (with cisplatin).

The mucosal side effects of therapy can lead to malnutrition and dehydration. Many centers address issues of dentition before starting treatment, and some place feeding tubes to ensure control of hydration and nutrition intake. About 50% of patients develop hypothyroidism from the treatment; thus, thyroid function should be monitored.

SALIVARY GLAND TUMORS

Most benign salivary gland tumors are treated with surgical excision, and patients with invasive salivary gland tumors are treated with surgery and radiation therapy. These tumors may recur regionally; adenoid cystic carcinoma has a tendency to recur along the nerve tracks. Distant metastases may occur as late as 10–20 years after the initial diagnosis. For metastatic disease, therapy is given with palliative intent, usually chemotherapy with doxorubicin and/or cisplatin. Identification of novel agents with activity in these tumors is a high priority. It is hoped that comprehensive genomic characterization of these rare tumors will facilitate these efforts.

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74 Neoplasms of the Lung

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Lung cancer, which was rare before 1900 with fewer than 400 cases described in the medical literature, is considered a disease of modern man. By the mid-twentieth century, lung cancer had become epidemic and firmly established as the leading cause of cancer-related death in North America and Europe, killing over three times as many men as prostate cancer and nearly twice as many women as breast cancer. Tobacco consumption is the primary cause of lung cancer, a reality firmly established in the mid-twentieth century and codified with the release of the U.S. Surgeon General's 1964 report on the health effects of tobacco smoking. Following the report, cigarette use started to decline in North America and parts of Europe, and with it, so did the incidence of lung cancer. Unfortunately, in many parts of the world cigarette use continues to increase, and along with it, the incidence of lung cancers is also rising. Although tobacco smoking remains the primary cause of lung cancer worldwide, approximately 60% of new lung cancers in the United States occur in former smokers (smoked ≥100 cigarettes per lifetime, quit ≥1 year), many of whom quit decades ago, or never smokers (smoked <100 cigarettes per lifetime). Moreover, one in five women and one in 12 men diagnosed with lung cancer have never smoked. Given the magnitude of the problem, it is incumbent that every internist has a general knowledge of lung cancer and its management.

EPIDEMIOLOGY

Lung cancer is the most common cause of cancer death among American men and women. Approximately 225,000 individuals will be diagnosed with lung cancer in the United States in 2017, and over 150,000 individuals will die from the disease. Lung cancer is uncommon below age 40, with rates increasing until age 80, after which the rate tapers off. The projected lifetime probability of developing lung cancer is estimated to be ~8% among males and ~6% among females. The incidence of lung cancer varies by racial and ethnic group, with the highest age-adjusted incidence rates among African Americans. The excess in age-adjusted rates among African Americans occurs only among men, but examinations of age-specific rates show that below age 50, mortality from lung cancer is more than 25% higher among African American than Caucasian women. Incidence and mortality rates among Hispanics and Native and Asian Americans are ~40–50% those of whites.

RISK FACTORS

Cigarette smokers have a 10-fold or greater increased risk of developing lung cancer compared to those who have never smoked. A large scale genomic study suggested that one genetic mutation is induced for every 15 cigarettes smoked. The risk of lung cancer is lower among persons who quit smoking than among those who continue smoking; former smokers have a ninefold increased risk of developing lung cancer compared to men who have never smoked versus the 20-fold excess in those who continue to smoke. The size of the risk reduction increases with the length of time the person has quit smoking, although generally even long-term former smokers have higher risks of lung cancer than those who never smoked. Cigarette smoking has been shown to increase the risk of all the major types of lung cancer. Environmental tobacco smoke (ETS) or second-hand smoke is also an established cause of lung cancer. The risk from ETS is less than from active smoking, with about a 20–30% increase in lung cancer observed among never smokers married for many years to smokers, in comparison to the 2000% increase among continuing active smokers.

Although cigarette smoking is the cause of the majority of lung cancers, several other risk factors have been identified, including occupational exposures to asbestos, arsenic, bischloromethyl ether, hexavalent chromium, mustard gas, nickel (as in certain nickel-refining processes), and polycyclic aromatic hydrocarbons. Occupational observations also have provided insight into possible mechanisms of lung cancer induction. For example, the risk of lung cancer among asbestos-exposed workers is increased primarily among those with underlying asbestosis, raising the possibility that the scarring and inflammation produced by this fibrotic nonmalignant lung disease may in many cases (although likely not in all) be the trigger for asbestos-induced lung cancer. Several other occupational exposures have been associated with increased rates of lung cancer, but the causal nature of the association is not as clear.

The risk of lung cancer appears to be higher among individuals with low fruit and vegetable intake during adulthood. This observation led to hypotheses that specific nutrients, in particular retinoids and carotenoids, might have chemopreventative effects for lung cancer. However, randomized trials failed to validate this hypothesis. In fact, studies found that the incidence of lung cancer was increased among smokers with supplementation. Ionizing radiation is also an established lung carcinogen, most convincingly demonstrated from studies showing increased rates of lung cancer among survivors of the atom bombs dropped on Hiroshima and Nagasaki and large excesses among workers exposed to alpha irradiation from radon in underground uranium mining. Prolonged exposure to low-level radon in homes might impart a risk of lung cancer equal or greater than that of ETS. Prior lung diseases such as chronic bronchitis, emphysema, and tuberculosis have been linked to increased risks of lung cancer as well.

Smoking Cessation Given the undeniable link between cigarette smoking and lung cancer (not even addressing other tobacco-related illnesses), physicians must promote tobacco abstinence. Physicians also must help their patients who smoke to stop smoking. Smoking cessation, even well into middle age, can minimize an individual's subsequent risk of lung cancer. Stopping tobacco use before middle age avoids more than 90% of the lung cancer risk attributable to tobacco. However, there is little health benefit derived from just "cutting back." Importantly, smoking cessation can even be beneficial in individuals with an established diagnosis of lung cancer, as it is associated with improved survival, fewer side effects from therapy, and an overall improvement in quality of life. Moreover, smoking can alter the metabolism of many chemotherapy drugs, potentially adversely altering the toxicities and therapeutic benefits of the agents. Consequently, it is important to promote smoking cessation even *after* the diagnosis of lung cancer is established.

Physicians need to understand the essential elements of smoking cessation therapy. The individual must want to stop smoking and must be willing to work hard to achieve the goal of smoking abstinence. Self-help strategies alone only marginally affect quit rates, whereas individual and combined pharmacotherapies in combination with counseling can significantly increase rates of cessation. Therapy with an antidepressant (e.g., bupropion) and nicotine replacement therapy (varenicline, a $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist) are approved by the U.S. Food and Drug Administration (FDA) as first-line treatments for nicotine dependence. However, both drugs have been reported to increase suicidal ideation and must be used with caution. In a randomized trial, varenicline was shown to be more efficacious than bupropion or placebo. Prolonged use of varenicline beyond the initial induction phase proved useful in maintaining smoking abstinence. Clonidine and nortriptyline are recommended as second-line treatments. (Chap. 448).

Inherited Predisposition to Lung Cancer Exposure to environmental carcinogens, such as those found in tobacco smoke, induce or facilitate the transformation from bronchoepithelial cells to the malignant phenotype. The contribution of carcinogens on transformation is modulated by polymorphic variations in genes that affect aspects of carcinogen metabolism. Certain genetic polymorphisms of the P450 enzyme system, specifically CYP1A1, and chromosome fragility are associated with the development of lung cancer. These genetic variations occur at relatively high frequency in the population, but their contribution to an individual's lung cancer risk is generally low. However, because of their population frequency, the overall impact on lung cancer risk could be high. In addition, environmental factors,

as modified by inherited modulators, likely affect specific genes by deregulating important pathways to enable the cancer phenotype.

First-degree relatives of lung cancer probands have a two- to threefold excess risk of lung cancer and other cancers, many of which are not smoking-related. These data suggest that specific genes and/or genetic variants may contribute to susceptibility to lung cancer. However, very few such genes have yet been identified. Individuals with inherited mutations in *RB* (patients with retinoblastoma living to adulthood) and *p53* (Li-Fraumeni syndrome) genes may develop lung cancer. Common gene variants involved in lung cancer have been recently identified through large, collaborative, genome-wide association studies. These studies identified three separate loci that are associated with lung cancer (5p15, 6p21, and 15q25) and include genes that regulate acetylcholine nicotinic receptors and telomerase production. A rare germline mutation (T790M) involving the epidermal growth factor receptor (EGFR) maybe be linked to lung cancer susceptibility in never smokers. Likewise, a susceptibility locus on chromosome 6q greatly increases risk lung cancer risk among light and never smokers. Although progress has been made, there is a significant amount of work that remains to be done in identifying heritable risk factors for lung cancer. Currently no molecular criteria are suitable to select patients for more intense screening programs or for specific chemopreventative strategies.

PATHOLOGY

The World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). The WHO classification system divides epithelial lung cancers into four major cell types: small-cell lung cancer (SCLC), adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma; the latter three types are collectively known as non-small-cell carcinomas (NSCLCs) **(Fig. 74-1)**. Small-cell carcinomas consist of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and a high mitotic count. SCLC may be distinguished from NSCLC by the presence of neuroendocrine markers including CD56, neural cell adhesion molecule (NCAM), synaptophysin, and chromogranin. Adenocarcinomas possess glandular differentiation or mucin production and may show acinar, papillary, lepidic, or solid features or a mixture of these patterns. Squamous cell carcinomas of the lung are morphologically identical to extrapulmonary squamous cell carcinomas and cannot be distinguished by immunohistochemistry alone. Squamous cell tumors show keratinization and/or intercellular bridges that arise from bronchial epithelium. The tumor tends to consists of sheets of cells rather than the three-dimensional groups of cells characteristic of adenocarcinomas. Large-cell carcinomas comprise less than 10% of lung carcinomas. These tumors lack the cytologic and architectural features of small-cell carcinoma and glandular or squamous differentiation. Together these four histologic types account for ~90% of all epithelial lung cancers.

All histologic types of lung cancer can develop in current and former smokers, although squamous and small-cell carcinomas are most commonly associated with heavy tobacco use. Through the first half of the twentieth century, squamous carcinoma was the most common subtype of NSCLC diagnosed in the United States. However, with the decline in cigarette consumption over the past six decades, adenocarcinoma has become the most frequent histologic subtype of lung cancer in the United States as both squamous carcinoma and small-cell carcinoma are on the decline. In lifetime never smokers or former light smokers (<10 pack-year history), women, and younger adults (<60 years), adenocarcinoma tends to be the most common form of lung cancer.

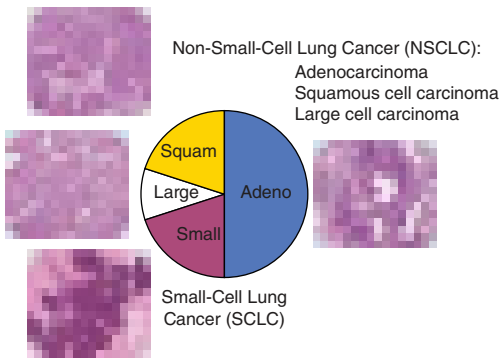


FIGURE 74-1 Traditional histologic view of lung cancer.

In addition to distinguishing between SCLC and NSCLC, because these tumors have quite different natural histories and therapeutic approaches (see below), it is necessary to classify if NSCLC is squamous or nonsquamous because of the recognition that some active chemotherapy agents perform quite differently in squamous carcinomas versus adenocarcinomas and the different recommendations for molecular testing. The revised 2011 classification system, developed jointly by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society, provides an integrated approach to the classification of lung adenocarcinoma that includes clinical, molecular, radiographic, and pathologic information.

It is recognized that most lung cancers present in an advanced stage and are often diagnosed based on small biopsies or cytologic specimens, rendering clear histologic distinctions difficult if not impossible. This was addressed by the WHO 2015 revised classification of lung tumors. The distinction between squamous and nonsquamous lung cancer is viewed as critical to optimal therapeutic decision making, a diagnosis of *non-small-cell carcinoma, not otherwise specified* is no longer considered acceptable. This distinction can be achieved using a single marker for adenocarcinoma (thyroid transcription factor-1 or napsin-A) plus a squamous marker (p40 or p63) and/or mucin stains. If tissue is limited and a clear morphological pattern is evident, a diagnosis can be made without immunohistochemistry staining. Both classification systems recommend preservation of sufficient specimen material for appropriate molecular testing necessary to help guide therapeutic decision making (see below).

The terms *adenocarcinoma in situ* and *minimally invasive adenocarcinoma* are now recommended for small solitary adenocarcinomas (≤3 cm) with either pure lepidic growth (term used to describe single-layered growth of atypical cuboidal cells coating the alveolar walls) or predominant lepidic growth with ≤5 mm invasion. Individuals with these entities experience 100% or near 100% 5-year disease-free survival with complete tumor resection. *Invasive adenocarcinomas*, representing more than 70–90% of surgically resected lung adenocarcinomas, are now classified by their predominant pattern: lepidic, acinar, papillary, and solid patterns. Lepidic-predominant subtype has a favorable prognosis, acinar and papillary have an intermediate prognosis, and solid-predominant has a poor prognosis. The terms *signet ring* and *clear cell adenocarcinoma* have been eliminated from the variants of invasive lung adenocarcinoma, whereas the term *micropapillary*, a subtype with a particularly poor prognosis, has been added. Because of prognostic implications, squamous cell carcinoma has also been modified to consist of keratinizing, nonkeratinizing and basaloid, analogous to head and neck cancers.

IMMUNOHISTOCHEMISTRY

The diagnosis of lung cancer most often rests on the morphologic or cytologic features correlated with clinical and radiographic findings. Immunohistochemistry may be used to verify neuroendocrine differentiation within a tumor, with markers such as neuron-specific enolase (NSE), CD56 or NCAM, synaptophysin, chromogranin, and Leu7. Immunohistochemistry is also helpful in differentiating primary from metastatic adenocarcinomas; thyroid transcription factor-1 (TTF-1), identified in tumors of thyroid and pulmonary origin, is positive in over 70% of pulmonary adenocarcinomas and is a reliable indicator of primary lung cancer, provided a thyroid primary has been excluded. A negative TTF-1, however, does not exclude the possibility of a lung primary. TTF-1 is also positive in neuroendocrine tumors of pulmonary and extrapulmonary origin. Napsin-A (Nap-A) is an aspartic protease that plays an important role in maturation of surfactant B7 and is expressed in cytoplasm of type II pneumocytes. In several studies, Nap-A has been reported in >90% of primary lung adenocarcinomas.

Notably, a combination of Nap-A and TTF-1 is useful in distinguishing primary lung adenocarcinoma (Nap-A positive, TTF-1 positive) from primary lung squamous cell carcinoma (Nap-A negative, TTF-1 negative) and primary SCLC (Nap-A negative, TTF-1 positive). Cytokeratins 7 and 20 used in combination can help narrow the differential diagnosis; nonsquamous NSCLC, SCLC, and mesothelioma may stain positive for CK7 and negative for CK20, whereas squamous cell lung cancer often will be both CK7 and CK20 negative. p63 is a useful marker for the detection of NSCLCs with squamous differentiation when used in cytologic pulmonary samples. Mesothelioma can be easily identified ultrastructurally, but it has historically been difficult to differentiate from adenocarcinoma through morphology and immunohistochemical staining. Several markers in the last few years have proven to be more helpful including CK5/6, calretinin, and Wilms tumor gene-1 (*WT-1*), all of which show positivity in mesothelioma.

MOLECULAR PATHOGENESIS

Cancer is a disease involving dynamic changes in the genome. As proposed by Hanahan and Weinberg, virtually all cancer cells acquire six hallmark capabilities: self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. The order in which these hallmark capabilities are acquired appears quite variable and can differ from tumor to tumor. Events leading to acquisition of these hallmarks can vary widely, although broadly, cancers arise as a result from accumulations of gain-of-function mutations in oncogenes and loss-of-function mutations in tumor-suppressor genes. Further complicating the study of lung cancer, the sequence of events that lead to disease is clearly different for the various histopathologic entities.

The exact cell of origin for lung cancers is not clearly defined. Whether one cell of origin leads to all histologic forms of lung cancer is unclear. However, for lung adenocarcinoma, evidence suggests that type II epithelial cells (or alveolar epithelial cells) have the capacity to give rise to tumors. For SCLC, cells of neuroendocrine origin have been implicated as precursors.

For cancers in general, one theory holds that a small subset of the cells within a tumor (i.e., "stem cells") are responsible for the full malignant behavior of the tumor. As part of this concept, the large bulk of the cells in a cancer are "offspring" of these cancer stem cells. While clonally related to the cancer stem cell subpopulation, most cells by themselves cannot regenerate the full malignant phenotype. The stem cell concept may explain the failure of standard medical therapies to eradicate lung cancers, even when there is a clinical complete response. Disease recurs because therapies do not eliminate the stem cell component, which may be more resistant to chemotherapy or targeted therapy. Precise human lung cancer stem cells have yet to be identified.

Lung cancer cells harbor multiple chromosomal abnormalities, including mutations, amplifications, insertions, deletions, and translocations. One of the earliest sets of oncogenes found to be aberrant was the MYC family of transcription factors (*MYC*, *MYCN*, and *MYCL*). *MYC* is most frequently activated via gene amplification or transcriptional dysregulation in both SCLC and NSCLC. Currently, there are no MYC-specific drugs.

Among lung cancer histologies, adenocarcinomas have been the most extensively catalogued for recurrent genomic gains and losses as well as for somatic mutations **(Fig. 74-2)**. While multiple different kinds of aberrations have been found, a major class involves "driver mutations," which are mutations that occur in genes encoding signaling proteins that when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as potential Achilles' heels for tumors, if their gene products can be targeted appropriately. For example, one set of mutations involves the epidermal growth factor receptor (EGFR), which belongs to the ERBB (HER) family of proto-oncogenes, including *EGFR* (ERBB1), *HER2/neu* (ERBB2), *HER3* (ERBB3), and *HER4* (ERBB4). These genes encode cell-surface receptors consisting of an extracellular ligand-binding domain, a transmembrane structure, and an intracellular tyrosine kinase (TK) domain. The binding of ligand to receptor activates receptor dimerization and TK autophosphorylation, initiating a cascade of intracellular events, and leading to increased cell proliferation, angiogenesis, metastasis, and a decrease in apoptosis. Lung adenocarcinomas can arise when tumors express mutant EGFR. These same tumors display high sensitivity to small-molecule EGFR TK inhibitors (TKIs). Additional examples of driver mutations in lung adenocarcinoma include the GTPase *KRAS*, the serine-threonine kinase *BRAF*, and the lipid kinase *PIK3CA*. More recently, additional subsets of lung adenocarcinoma have been identified as defined by the presence of specific chromosomal rearrangements resulting in the aberrant activation of the tyrosine kinases *ALK*, *ROS1*, *NTRK* and *RET*. Notably, most driver mutations in lung cancer appear to be mutually exclusive, suggesting that acquisition of one of these mutations is sufficient to drive tumorigenesis. Although driver mutations have mostly been found in adenocarcinomas, three potential molecular targets recently have been identified in squamous cell lung carcinomas: *FGFR1* amplification, *DDR2* mutations, and *PIK3CA* mutations/*PTEN* loss **(Table 74-1)**.

A large number of tumor-suppressor genes have also been identified that are inactivated during the pathogenesis of lung cancer. These include *TP53*, *RB1*, *RASSF1A*, *CDKN2A/B*, *LKB1* (*STK11*), and *FHIT*. Nearly 90% of SCLCs harbor mutations in *TP53* and *RB1*. Several tumor-suppressor genes on chromosome 3p appear to be involved in nearly all lung cancers. Allelic loss for this region occurs very early in lung cancer pathogenesis, including in histologically normal smoking-damaged lung epithelium.

EARLY DETECTION AND SCREENING

In lung cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will

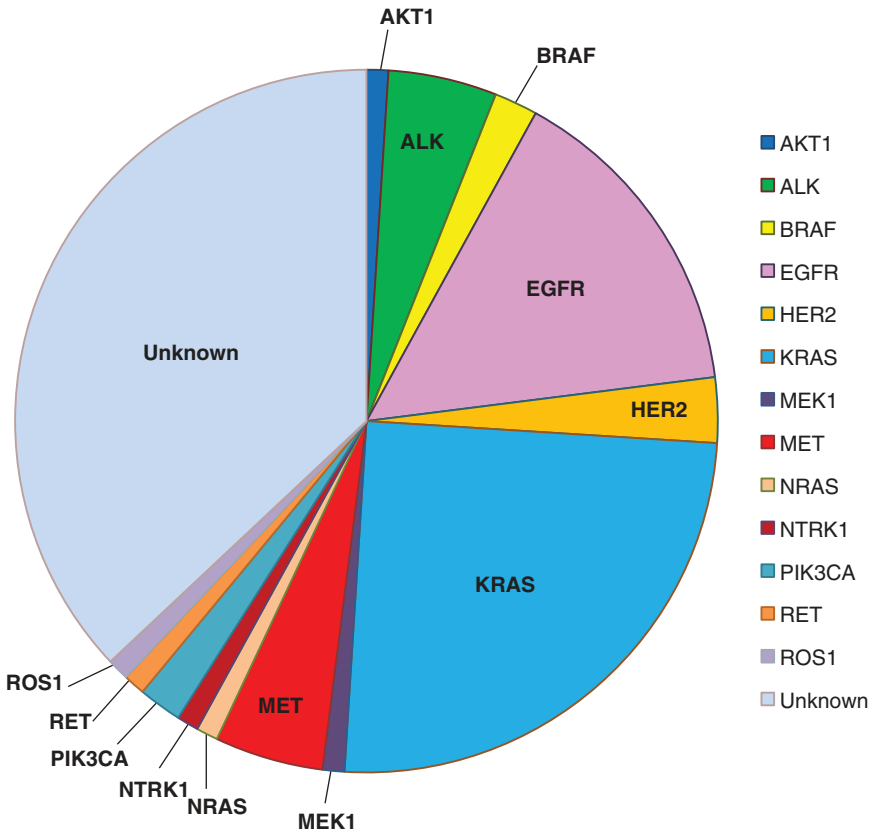


FIGURE 74-2 Driver mutations in lung adenocarcinomas.

TABLE 74-1 Driver Mutations in Non-Small-Cell Lung Cancer (NSCLC)

GENE	ALTERATION	FREQUENCY IN NSCLC	TYPICAL HISTOLOGY
AKT1	Mutation	1%	Adenocarcinoma, squamous
ALK	Rearrangement	3–7%	Adenocarcinoma
BRAF	Mutation	1–3%	Adenocarcinoma
DDR2	Mutation	~4%	Squamous
EGFR	Mutation	10–35%	Adenocarcinoma
FGFR1	Amplification	~20%	Squamous
HER2	Mutation	2–4%	Adenocarcinoma
KRAS	Mutation	15–25%	Adenocarcinoma
MEK1	Mutation	1%	Adenocarcinoma
MET	Amplification	2–4%	Adenocarcinoma
NRAS	Mutation	1%	Adenocarcinoma
NTRK	Rearrangement	1–2%	Adenocarcinoma
PIK3CA	Mutation	1–3%	Squamous
PTEN	Mutation	4–8%	Squamous
ROS1	Rearrangement	1-2%	Adenocarcinoma

lead to improved survival. Early detection is a process that involves screening tests, surveillance, diagnosis, and early treatment. Screening refers to the use of tests across a healthy population in order to identify individuals who harbor asymptomatic disease. For a screening program to be successful, there must be a high burden of disease within the target population; the test must be sensitive, specific, accessible, and cost effective; and there must be effective treatment that can reduce mortality. With any screening procedure, it is important to consider the possible influence of *lead-time bias* (detecting the cancer earlier without an effect on survival), *length-time bias* (indolent cancers are detected on screening and may not affect survival, whereas aggressive cancers are likely to cause symptoms earlier in patients and are less likely to be detected), and *overdiagnosis* (diagnosing cancers so slow growing that they are unlikely to cause the death of the patient).

Because a majority of lung cancer patients present with advanced disease beyond the scope of surgical resection, there is understandable skepticism about the value of screening in this condition. Indeed, randomized controlled trials conducted in the 1960s to 1980s using screening chest x-rays (CXR), with or without sputum cytology, reported no impact on lung cancer–specific mortality in patients characterized as high risk (males age ≥45 years with a smoking history). These studies have been criticized for their design, statistical analyses, and outdated imaging modalities. The results of the more recently conducted Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) are consistent with these earlier reports. Initiated in 1993, participants in the PLCO lung cancer screening trial received annual CXR screening for 4 years, whereas participants in the usual care group received no interventions other than their customary medical care. The diagnostic follow-up of positive screening results was determined by participants and their physicians. The PLCO trial differed from previous lung cancer screening studies in that women and never smokers were eligible. The study was designed to detect a 10% reduction in lung cancer mortality in the interventional group. A total of 154,901 individuals between 55 and 74 years of age were enrolled (77,445 assigned to annual CXR screenings; 77,456 assigned to usual care). Participant demographics and tumor characteristics were well balanced between the two groups. Through 13 years of follow-up, cumulative lung cancer incidence rates (20.1 vs 19.2 per 10,000 person-years; rate ratio [RR], 1.05; 95% confidence interval [CI], 0.98–1.12) and lung cancer mortality (n = 1213 vs n = 1230) were identical between the two groups. The stage and histology of detected cancers in the two groups also were similar. These data corroborate previous recommendations *against* CXR screening for lung cancer.

In contrast to CXR, low-dose, noncontrast, thin-slice spiral chest computed tomography (LDCT) has emerged as an effective tool to screen for lung cancer. In nonrandomized studies conducted in the 1990s, LDCT scans were shown to detect more lung nodules and cancers than standard CXR in selected high-risk populations (e.g., age ≥60 years and a smoking history of ≥10 pack-years). Notably, up to 85% of the lung cancers discovered in these trials were classified as stage I disease and therefore considered potentially curable with surgical resection.

These data prompted the National Cancer Institute (NCI) to initiate the National Lung Screening Trial (NLST), a randomized study designed to determine if LDCT screening could reduce mortality from lung cancer in high-risk populations as compared with standard posterior anterior CXR. High-risk patients were defined as individuals between 55 and 74 years of age, with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. Excluded from the trial were individuals with a previous lung cancer diagnosis, a history of hemoptysis, an unexplained weight loss of >15 lb in the preceding year, or a chest CT within 18 months of enrollment. A total of 53,454 persons were enrolled and randomized to annual screening yearly for three years (LDCT screening, n = 26,722; CXR screening, n = 26,732). Any noncalcified nodule measuring ≥4 mm in any diameter found on LDCT and CXR images with any noncalcified nodule or mass were classified as "positive." Participating radiologists had the option of not calling a final screen positive if a noncalcified nodule had been stable on the three screening examinations. Overall, 39.1% of participants in the LDCT group and 16% in the CXR group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the CXR group. This was consistent across all three rounds. In the LDCT group, 1060 cancers were identified compared with 941 cancers in the CXR group (645 vs 572 per 100,000 person-years; RR, 1.13; 95% CI, 1.03 to 1.23). Nearly twice as many early-stage 1A cancers were detected in the LDCT group compared with the CXR group (40% vs 21%). The overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened population (95% CI, 6.8–26.7%; $p = 0.004$). Compared with the CXR group, the rate of death in the LDCT group from *any* cause was reduced by 6.7% (95% CI, 1.2–13.6; $p = 0.02$) **(Table 74-2)**. The number needed to screen (NNTS) to prevent one lung cancer death was calculated to be 320.

LDCT screening for lung cancer comes with known risks including a high rate of false-positive results, false-negative results, potential for unnecessary follow-up testing, radiation exposure, overdiagnosis, changes in anxiety level and quality of life, and substantial financial costs. By far the biggest challenge confronting the use of CT screening is the high false-positive rate. False positives can have a substantial impact on patients through the expense and risk of unneeded further evaluation and emotional stress. The management of these patients

TABLE 74-2 Results of National Lung Screening Trial

	EVENT NUMBER		RATES OF EVENTS PER 100,000 PERSON-YEARS		RELATIVE RISK (95% CI)	
	LDCT (N = 26,772)	CXR (N = 26,732)	LDCT	CXR	RR	*P* VALUE
Lung cancer mortality	356	443	247	309	0.80 (0.73–0.93)	.004
All-cause mortality	1877	2000	1303	1395	0.93 (0.86–0.99)	.02
Mortality not due to lung cancer	1521	1557	1056	1086	0.99 (0.95–1.02)	.51

Abbreviations: CI, confidence interval; CXR, chest x-ray; LDCT, low-dose computed tomography; RR, rate ratio.

Source: Modified from PB Bach et al: JAMA 307:2418, 2012.

TABLE 74-3 The Benefits and Harms of LDCT Screening for Lung Cancer Based on NLST Data

	LDCT	CXR
Benefits: How did CT scans help compared to CXR?		
4 in 1000 fewer died from lung cancer	13 in 1000	17 in 1000
5 in 1000 fewer died from all causes	70 in 1000	75 in 1000
Harms: What problems did CT scans cause compared to CXR?		
223 in 1000 had at least 1 false alarm	365 in 1000	142 in 1000
18 in 1000 had a false alarm leading to an invasive procedure	25 in 1000	7 in 1000
2 in 1000 had a major complication from an invasive procedure	3 in 1000	1 in 1000

Abbreviations: CXR, chest x-ray; LDCT, low-dose computed tomography; NLST, National Lung Screening Trial.

Source: Modified from S Woloshin et al: N Engl J Med 367:1677, 2012.

usually consists of serial CT scans over time to see if the nodules grow, attempted fine-needle aspirates, or surgical resection. At $300 per scan (NCI estimated cost), the outlay for initial LDCT alone could run into the billions of dollars annually, an expense that only further escalates when factoring in various downstream expenditures an individual might incur in the assessment of positive findings. A formal cost-effectiveness analysis of the NLST demonstrated differences between sex, age, and current smoking status and the method of follow up. Despite some questions, low dose LDCT screening has been recommended for all patients meeting criteria for enrollment on NLST. When discussing the option of LDCT screening, use of absolute risks rather than relative risks is helpful because studies indicate the public can process absolute terminology more effectively than relative risk projections. A useful guide has been developed by the NCI to help patients and physicians assess the benefits and harms of LDCT screening for lung cancer (Table 74-3).

CLINICAL MANIFESTATIONS

Over half of all patients diagnosed with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. The majority of patients present with signs, symptoms, or laboratory abnormalities that can be attributed to the primary lesion, local tumor growth, invasion or obstruction of adjacent structures, growth at distant metastatic sites, or a paraneoplastic syndrome (Tables 74-4 and 74-5). The prototypical lung cancer patient is a current or former smoker of either sex, usually in the seventh decade of life. A history of chronic cough with or without hemoptysis in a current or former smoker with chronic obstructive pulmonary disease (COPD) age 40 years or older should prompt a thorough investigation for lung cancer even in the face of a normal CXR. A persistent pneumonia without constitutional symptoms and unresponsive to repeated courses of antibiotics also should prompt an evaluation for the underlying cause. Lung cancer arising in a lifetime never smoker is more common in women and East Asians. Such patients also tend to be younger than their smoking counterparts at the time of diagnosis. The clinical presentation of lung cancer in never smokers tends to mirror that of current and former smokers.

TABLE 74-4 Presenting Signs and Symptoms of Lung Cancer

SYMPTOM AND SIGNS	RANGE OF FREQUENCY
Cough	8–75%
Weight loss	0–68%
Dyspnea	3–60%
Chest pain	20–49%
Hemoptysis	6–35%
Bone pain	6–25%
Clubbing	0–20%
Fever	0–20%
Weakness	0–10%
Superior vena cava obstruction	0–4%
Dysphagia	0–2%
Wheezing and stridor	0–2%

Source: Reproduced with permission from MA Beckles: Chest 123:97, 2003.

TABLE 74-5 Clinical Findings Suggestive of Metastatic Disease

Symptoms elicited in history	• Constitutional: weight loss >10 lb • Musculoskeletal: pain • Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination	• Lymphadenopathy (>1 cm) • Hoarseness, superior vena cava syndrome • Bone tenderness • Hepatomegaly (>13 cm span) • Focal neurologic signs, papilledema • Soft-tissue mass
Routine laboratory tests	• Hematocrit, <40% in men; <35% in women • Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

Abbreviations: GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase.

Source: Reproduced with permission from GA Silvestri et al: Chest 123(1 Suppl): 147S, 2003.

Patients with central or endobronchial growth of the primary tumor may present with cough, hemoptysis, wheeze, stridor, dyspnea, or postobstructive pneumonitis. Peripheral growth of the primary tumor may cause pain from pleural or chest wall involvement, dyspnea on a restrictive basis, and symptoms of a lung abscess resulting from tumor cavitation. Regional spread of tumor in the thorax (by contiguous growth or by metastasis to regional lymph nodes) may cause tracheal obstruction, esophageal compression with dysphagia, recurrent laryngeal paralysis with hoarseness, phrenic nerve palsy with elevation of the hemidiaphragm and dyspnea, and sympathetic nerve paralysis with Horner's syndrome (enophthalmos, ptosis, miosis, and anhydrosis). Malignant pleural effusions can cause pain, dyspnea, or cough. Pancoast (or superior sulcus tumor) syndromes result from local extension of a tumor growing in the apex of the lung with involvement of the eighth cervical and first and second thoracic nerves, and present with shoulder pain that characteristically radiates in the ulnar distribution of the arm, often with radiologic destruction of the first and second ribs. Often Horner's syndrome and Pancoast syndrome coexist. Other problems of regional spread include superior vena cava syndrome from vascular obstruction; pericardial and cardiac extension with resultant tamponade, arrhythmia, or cardiac failure; lymphatic obstruction with resultant pleural effusion; and lymphangitic spread through the lungs with hypoxemia and dyspnea. In addition, lung cancer can spread transbronchially, producing tumor growth along multiple alveolar surfaces with impairment of gas exchange, respiratory insufficiency, dyspnea, hypoxemia, and sputum production. Constitutional symptoms may include anorexia, weight loss, weakness, fever, and night sweats. Apart from the brevity of symptom duration, these parameters fail to clearly distinguish SCLC from NSCLC or even from neoplasms metastatic to lungs.

Extrathoracic metastatic disease is found at autopsy in more than 50% of patients with squamous carcinoma, 80% of patients with adenocarcinoma and large-cell carcinoma, and more than 95% of patients with SCLC. Approximately one-third of patients present with symptoms as a result of distant metastases. Lung cancer metastases may occur in virtually every organ system, and the site of metastatic involvement largely determines other symptoms. Patients with brain metastases may present with headache, nausea and vomiting, seizures, or neurologic deficits. Patients with bone metastases may present with pain, pathologic fractures, or cord compression. The latter may also occur with epidural metastases. Individuals with bone marrow invasion may present with cytopenias or leukoerythroblastosis. Those with liver metastases may present with hepatomegaly, right upper quadrant

pain, fever, anorexia, and weight loss. Liver dysfunction and biliary obstructions are rare. Adrenal metastases are common but rarely cause pain or adrenal insufficiency unless they are large.

Paraneoplastic syndromes are common in patients with lung cancer, especially those with SCLC, and may be the presenting finding or the first sign of recurrence. In addition, paraneoplastic syndromes may mimic metastatic disease and, unless detected, lead to inappropriate palliative rather than curative treatment. Often the paraneoplastic syndrome may be relieved with successful treatment of the tumor. In some cases, the pathophysiology of the paraneoplastic syndrome is known, particularly when a hormone with biological activity is secreted by a tumor. However, in many cases, the pathophysiology is unknown. Systemic symptoms of anorexia, cachexia, weight loss (seen in 30% of patients), fever, and suppressed immunity are paraneoplastic syndromes of unknown etiology or at least not well defined. Weight loss greater than 10% of total body weight is considered a bad prognostic sign. Endocrine syndromes are seen in 12% of patients; hypercalcemia resulting from ectopic production of parathyroid hormone (PTH), or more commonly, PTH-related peptide, is the most common life-threatening metabolic complication of malignancy, primarily occurring with squamous cell carcinomas of the lung. Clinical symptoms include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, and altered mental status.

Hyponatremia may be caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or possibly atrial natriuretic peptide (ANP) **(Chap. 89)**. SIADH resolves within 1–4 weeks of initiating chemotherapy in the vast majority of cases. During this period, serum sodium can usually be managed and maintained above 128 mEq/L via fluid restriction. Demeclocycline can be a useful adjunctive measure when fluid restriction alone is insufficient. Vasopressin receptor antagonists like tolvaptan also have been used in the management of SIADH. However, there are significant limitations to the use of tolvaptan including liver injury and overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury. Likewise, the cost of tolvaptan may be prohibitive (as high as $300 per tablet in some areas). Of note, patients with ectopic ANP may have worsening hyponatremia if sodium intake is not concomitantly increased. Accordingly, if hyponatremia fails to improve or worsens after 3–4 days of adequate fluid restriction, plasma levels of ANP should be measured to determine the causative syndrome.

Ectopic secretion of ACTH by SCLC and pulmonary carcinoids usually results in additional electrolyte disturbances, especially hypokalemia, rather than the changes in body habitus that occur in Cushing's syndrome from a pituitary adenoma **(Chap. 89)**. Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels. The most effective strategy for management of the Cushing's syndrome is effective treatment of the underlying SCLC. Bilateral adrenalectomy may be considered in extreme cases.

Skeletal–connective tissue syndromes include clubbing in 30% of cases (usually NSCLCs) and hypertrophic primary osteoarthropathy in 1–10% of cases (usually adenocarcinomas). Patients may develop periostitis, causing pain, tenderness, and swelling over the affected bones and a positive bone scan. Neurologic-myopathic syndromes are seen in only 1% of patients but are dramatic and include the myasthenic Eaton-Lambert syndrome and retinal blindness with SCLC, whereas peripheral neuropathies, subacute cerebellar degeneration, cortical degeneration, and polymyositis are seen with all lung cancer types. Many of these are caused by autoimmune responses such as the development of anti-voltage-gated calcium channel antibodies in Eaton-Lambert syndrome. Patients with this disorder present with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely, cranial nerve symptoms or involvement of the bulbar or respiratory muscles. Depressed deep tendon reflexes are frequently present. In contrast to patients with myasthenia gravis, strength improves with serial effort. Some patients who respond to chemotherapy will have resolution of the neurologic abnormalities. Thus, chemotherapy is the initial treatment of choice. Paraneoplastic encephalomyelitis and sensory neuropathies, cerebellar degeneration, limbic encephalitis, and brainstem encephalitis occur in SCLC in association with a variety of antineuronal antibodies such as anti-Hu, anti-CRMP5, and ANNA-3. Paraneoplastic cerebellar degeneration may be associated with anti-Hu, anti-Yo, or P/Q calcium channel autoantibodies. Coagulation or thrombotic or other hematologic manifestations occur in 1–8% of patients and include migratory venous thrombophlebitis (Trousseau's syndrome), nonbacterial thrombotic (marantic) endocarditis with arterial emboli, and disseminated intravascular coagulation with hemorrhage, anemia, granulocytosis, and leukoerythroblastosis. Thrombotic disease complicating cancer is usually a poor prognostic sign. Cutaneous manifestations such as dermatomyositis and acanthosis nigricans are uncommon (1%), as are the renal manifestations of nephrotic syndrome and glomerulonephritis (≤1%).

DIAGNOSING LUNG CANCER

Tissue sampling is required to confirm a diagnosis in all patients with suspected lung cancer. In patients with suspected metastatic disease, a biopsy of a distant site of disease is preferred for tissue confirmation. Given the greater emphasis placed on molecular testing for NSCLC patients, a core biopsy is preferred to ensure adequate tissue for analysis. Tumor tissue may be obtained via minimally invasive techniques such as bronchial or transbronchial biopsy during fiberoptic bronchoscopy, by fine-needle aspiration (FNA) or percutaneous biopsy using image guidance, or via endobronchial ultrasound (EBUS)-guided biopsy. Depending on the location, lymph node sampling may occur via transesophageal endoscopic ultrasound-guided biopsy (EUS), EBUS, or blind biopsy. In patients with clinically palpable disease such as a lymph node or skin metastasis, a biopsy may be obtained. In patients with suspected metastatic disease, a diagnosis may be confirmed by percutaneous biopsy of a soft tissue mass, lytic bone lesion, bone marrow, pleural or liver lesion, or an adequate cell block obtained from a malignant pleural effusion. In patients with a suspected malignant pleural effusion, if the initial thoracentesis is negative, a repeat thoracentesis is warranted. Although the majority of pleural effusions are due to malignant disease, particularly if they are exudative or bloody, some may be parapneumonic. In the absence of distant disease, such patients should be considered for possible curative treatment.

The diagnostic yield of any biopsy depends on several factors including location (accessibility) of the tumor, tumor size, tumor type, and technical aspects of the diagnostic procedure including the experience level of the bronchoscopist and pathologist. In general, central lesions such as squamous cell carcinomas, small-cell carcinomas, or endobronchial lesions such as carcinoid tumors are more readily diagnosed by bronchoscopic examination, whereas peripheral lesions such as adenocarcinomas and large-cell carcinomas are more amenable to transthoracic biopsy. Diagnostic accuracy for SCLC versus NSCLC for most specimens is excellent, with lesser accuracy for subtypes of NSCLC.

Bronchoscopic specimens include bronchial brush, bronchial wash, bronchioloalveolar lavage, transbronchial FNA, and core biopsy. For more accurate histologic classification, mutation analysis, or investigational purposes, reasonable efforts (e.g., a core needle biopsy) should be made to obtain more tissue than what is contained in a routine cytology specimen obtained by FNA. Overall sensitivity for combined use of bronchoscopic methods is ~80%, and together with tissue biopsy, the yield increases to 85–90%. Like transbronchial core biopsy specimens, transthoracic core biopsy specimens are also preferred. Sensitivity is highest for larger lesions and peripheral tumors. In general, core biopsy specimens, whether transbronchial, transthoracic, or EUS-guided, are superior to other specimen types. This is primarily due to the higher percentage of tumor cells with fewer confounding factors such as obscuring inflammation and reactive nonneoplastic cells.

Sputum cytology is inexpensive and noninvasive but has a lower yield than other specimen types due to poor preservation of the cells and more variability in acquiring a good-quality specimen. The yield for sputum cytology is highest for larger and centrally located tumors such as squamous cell carcinoma and small-cell carcinoma histology. The specificity for sputum cytology averages close to 100%, although sensitivity is generally <70%. The accuracy of sputum cytology

improves with increased numbers of specimens analyzed. Consequently, analysis of at least three sputum specimens is recommended.

STAGING LUNG CANCER

Lung cancer staging consists of two parts: first, a determination of the location of the tumor and possible metastatic sites (anatomic staging), and second, an assessment of a patient's ability to withstand various antitumor treatments (physiologic staging). All patients with lung cancer should have a complete history and physical examination, with evaluation of all other medical problems, determination of performance status, and history of weight loss. The most significant dividing line is between those patients who are candidates for surgical resection and those who are inoperable but will benefit from chemotherapy, radiation therapy, or both. Staging with regard to a patient's potential for surgical resection is principally applicable to NSCLC.

ANATOMIC STAGING OF PATIENTS WITH LUNG CANCER

The accurate staging of patients with NSCLC is essential for determining the appropriate treatment in patients with resectable disease and for avoiding unnecessary surgical procedures in patients with advanced disease **(Fig. 74-3)**. All patients with NSCLC should undergo initial radiographic imaging with CT scan, positron emission tomography (PET), or preferably CT-PET. PET scanning attempts to identify sites of malignancy based on glucose metabolism by measuring the uptake of ^{18}F-fluorodeoxyglucose (FDG). Rapidly dividing cells, presumably in the lung tumors, will preferentially take up ^{18}F-FDG and appear as a "hot spot." To date, PET has been mostly used for staging and detection of metastases in lung cancer and in the detection of nodules >15 mm in diameter. Combined ^{18}F-FDG PET-CT imaging has been shown to improve the accuracy of staging in NSCLC compared to visual correlation of PET and CT or either study alone. CT-PET has been found to be superior in identifying pathologically enlarged mediastinal lymph nodes and extrathoracic metastases. A standardized uptake value (SUV) of >2.5 on PET is highly suspicious for malignancy. False negatives can be seen in diabetes, in lesions <8 mm, and in slow-growing tumors (e.g., carcinoid tumors or well-differentiated adenocarcinoma). False positives can be seen in certain infections and granulomatous disease (e.g., tuberculosis). Thus, PET should never be used alone to diagnose lung cancer, mediastinal involvement, or metastases. Confirmation with tissue biopsy is required. For brain metastases, magnetic resonance imaging (MRI) is the most effective method. MRI can also be useful in selected circumstances, such as superior sulcus tumors to rule out brachial plexus involvement, but in general, MRI does not play a major role in NSCLC staging.

In patients with NSCLC, the following are contraindications to potential curative resection: extrathoracic metastases, superior vena cava syndrome, vocal cord and, in most cases, phrenic nerve paralysis, malignant pleural effusion, cardiac tamponade, tumor within 2 cm of the carina (potentially curable with combined chemoradiotherapy), metastasis to the contralateral lung, metastases to supraclavicular lymph nodes, contralateral mediastinal node metastases (potentially curable with combined chemoradiotherapy), and involvement of the main pulmonary artery. In situations where it will make a difference in treatment, abnormal scan findings require tissue confirmation of malignancy so that patients are not precluded from having potentially curative therapy.

The best predictor of metastatic disease remains a careful history and physical examination. If signs, symptoms, or findings from the physical examination suggest the presence of malignancy, then sequential imaging starting with the most appropriate study should be performed. If the findings from the clinical evaluation are negative, then imaging studies beyond CT-PET are unnecessary and the search for metastatic disease is complete. More controversial is how one should assess patients with known stage III disease. Because these patients are more likely to have asymptomatic occult metastatic disease, current guidelines recommend a more extensive imaging evaluation including imaging of the brain with either CT scan or MRI. In patients in whom distant metastatic disease has been ruled out, lymph node status needs to be assessed via a combination of radiographic imaging and/or minimally invasive techniques such as those mentioned above and/or invasive techniques such as mediastinoscopy, mediastinotomy, thoracoscopy, or thoracotomy. Approximately one-quarter to one-half of patients diagnosed with NSCLC will have mediastinal lymph node

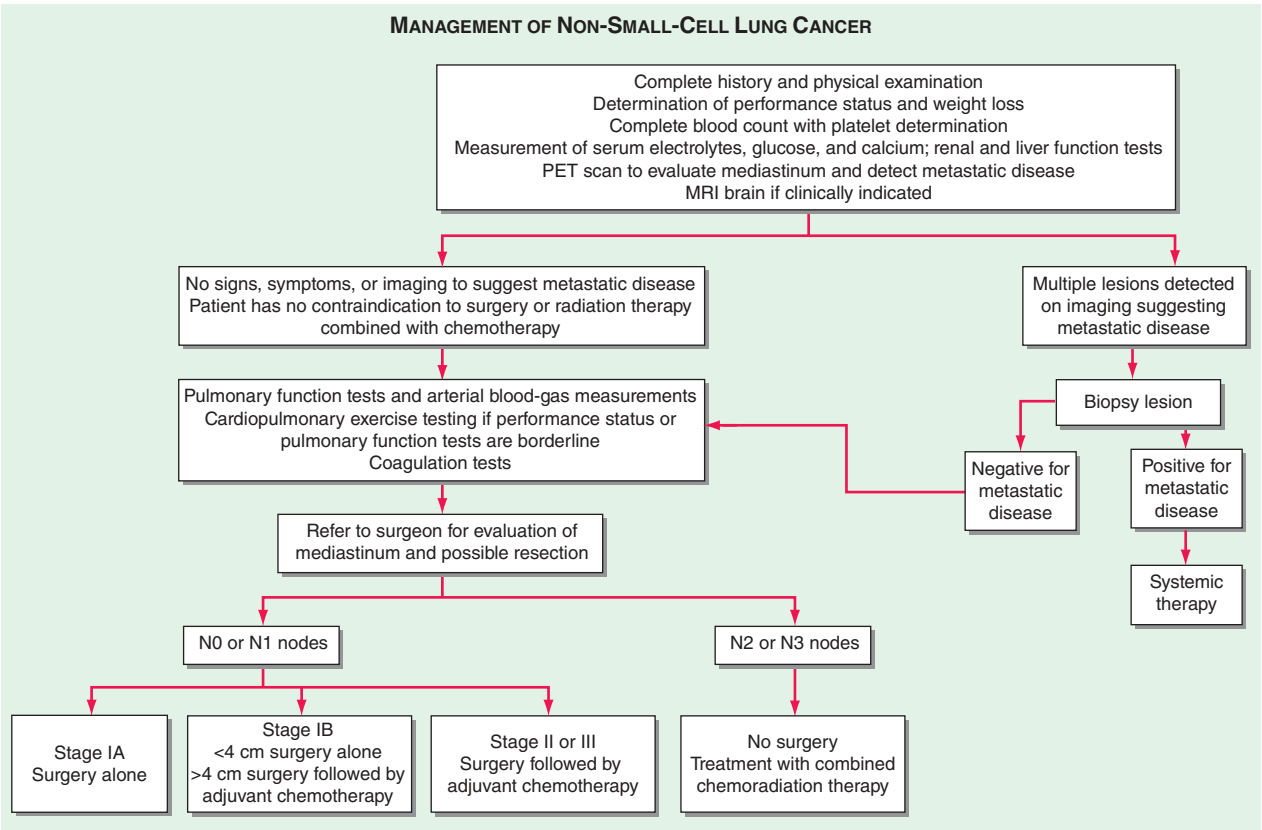


FIGURE 74-3 Algorithm for management of non-small-cell lung cancer. MRI, magnetic resonance imaging; PET, positron emission tomography.

metastases at the time of diagnosis. Lymph node sampling is recommended in all patients with enlarged nodes detected by CT or PET scan and in patients with large tumors or tumors occupying the inner third of the lung. The extent of mediastinal lymph node involvement is important in determining the appropriate treatment strategy: surgical resection followed by adjuvant chemotherapy versus combined chemoradiation alone (see below). A standard nomenclature for referring to the location of lymph nodes involved with lung cancer has evolved **(Fig. 74-4)**.

In SCLC patients, current staging recommendations include a PET-CT scan and MRI of the brain (positive in 10% of asymptomatic patients) **(Fig. 74-5)**. Bone marrow biopsies and aspirations are rarely performed now given the low incidence of isolated bone marrow metastases. Confirmation of metastatic disease, ipsilateral or contralateral lung nodules, or metastases beyond the mediastinum may be achieved by the same modalities recommended earlier for patients with NSCLC.

If a patient has signs or symptoms of spinal cord compression (pain, weakness, paralysis, urinary retention), a spinal CT or MRI scan and examination of the cerebrospinal fluid cytology should be performed. If metastases are evident on imaging, a neurosurgeon should be consulted for possible palliative surgical resection and/or a radiation oncologist should be consulted for palliative radiotherapy to the site of compression. If signs or symptoms of leptomeningitis develop at any time in a patient with lung cancer, an MRI of the brain and spinal cord should be performed, as well as a spinal tap, for detection of malignant cells. If the spinal tap is negative, a repeat spinal tap should be considered. There is currently no approved therapy for the treatment of leptomeningeal disease.

STAGING SYSTEM FOR NON-SMALL-CELL LUNG CANCER

The tumor-node-metastasis (TNM) international staging system provides useful prognostic information and is used to stage all patients

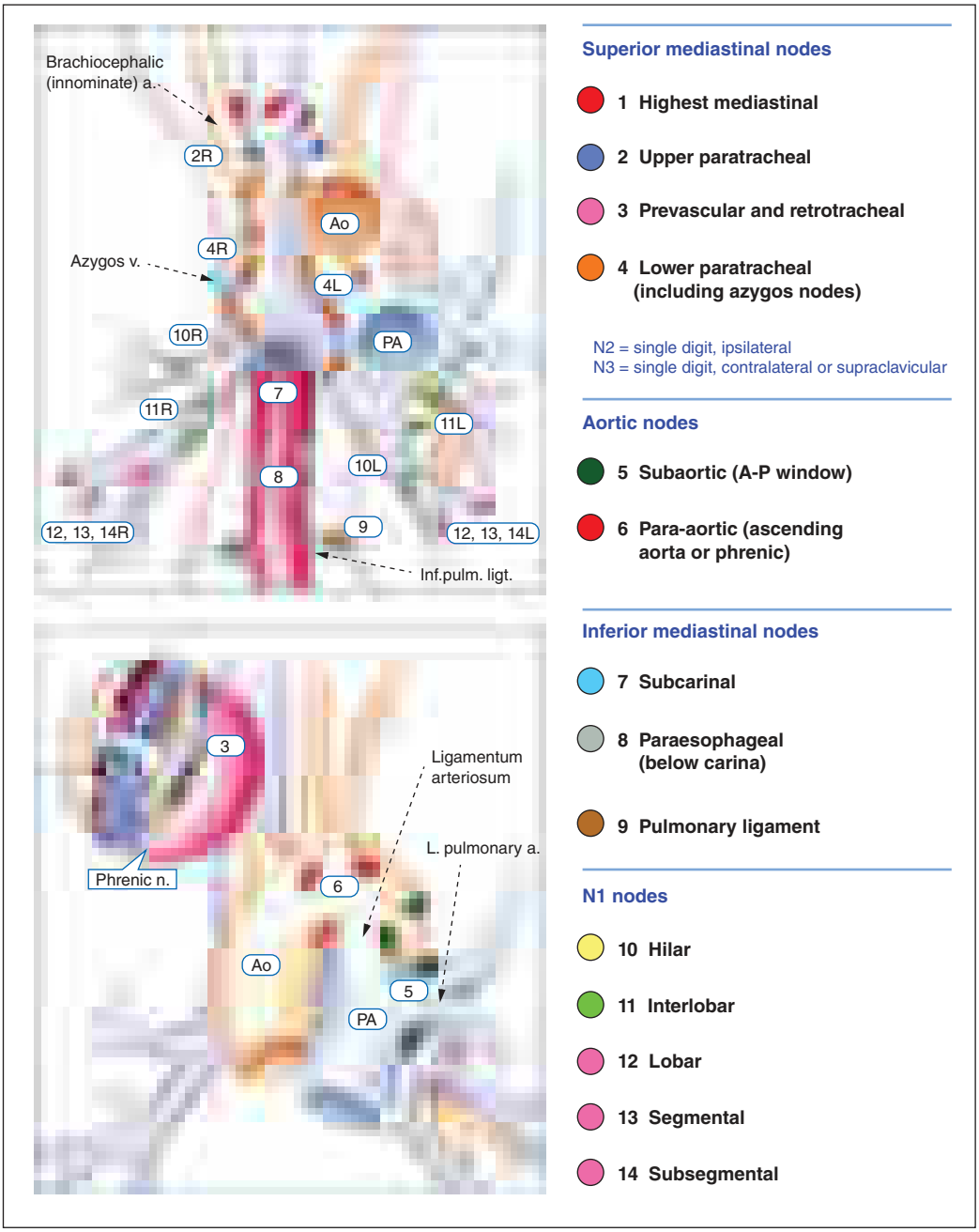


FIGURE 74-4 Lymph node stations in staging non-small-cell lung cancer. The International Association for the Study of Lung Cancer (IASLC) lymph node map, including the proposed grouping of lymph node stations into "zones" for the purposes of prognostic analyses. a., artery; Ao, aorta; Inf. pulm. ligt., inferior pulmonary ligament; n., nerve; PA, pulmonary artery; v., vein.

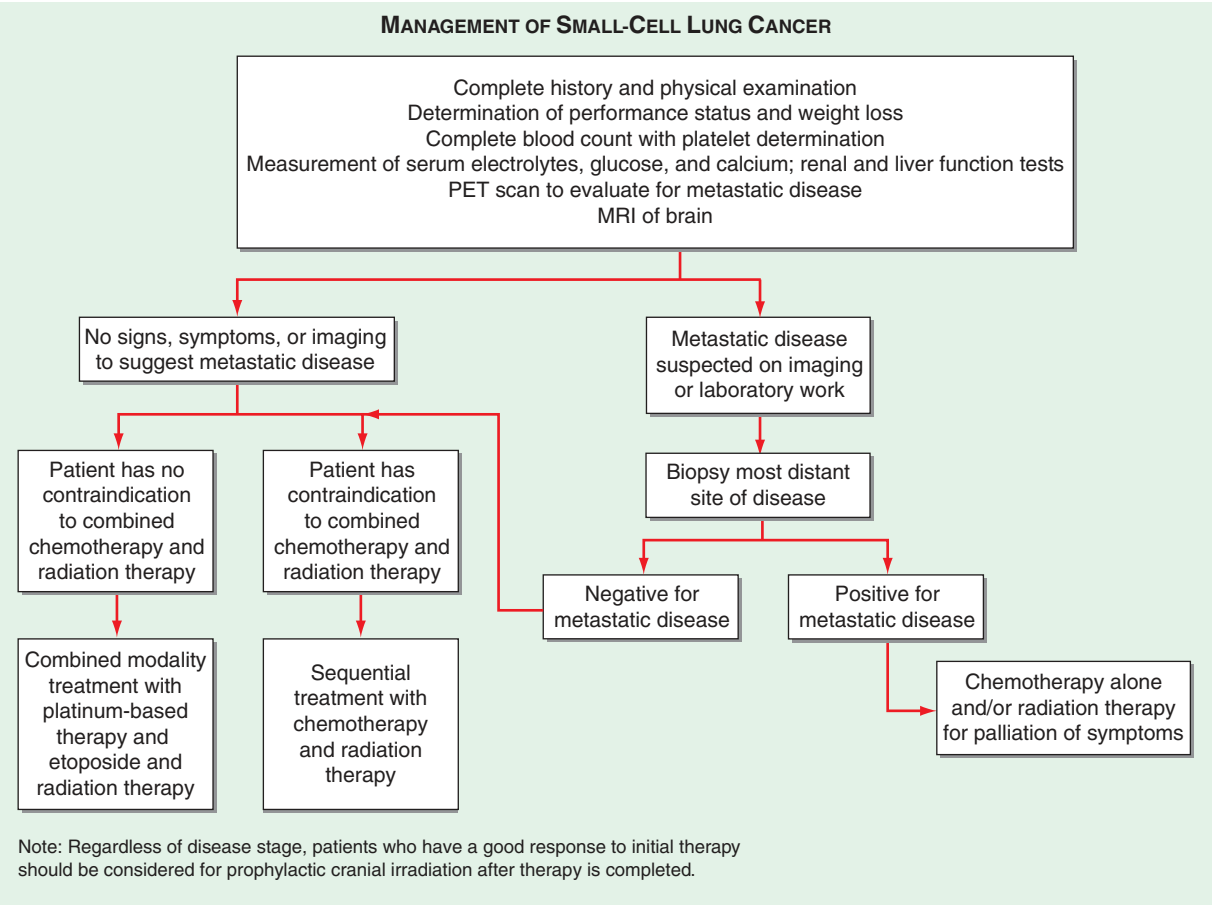


FIGURE 74-5 Algorithm for management of small-cell lung cancer. MRI, magnetic resonance imaging; PET, positron emission tomography.

with NSCLC. The various T (tumor size), N (regional node involvement), and M (presence or absence of distant metastasis) are combined to form different stage groups **(Tables 74-6 and 74-7)**. The seventh edition of the TNM staging system went into effect in 2010 and developed using a much more robust database of more than 100,000 patients with lung cancer who were treated in multiple countries between 1990 and 2000. Data from 67,725 patients with NSCLC were then used to reevaluate the prognostic value of the TNM descriptors. In the current edition T1 tumors are divided into tumors ≤2 cm in size, as these patients were found to have a better prognosis compared to patients with tumors >2 cm but ≤3 cm. T2 tumors are divided into those that are >3 cm but ≤5 cm and those that are >5 cm but ≤7 cm. Tumors that are >7 cm are considered T3 tumors. T3 tumors also include tumors with invasion into local structures such as chest wall and diaphragm and additional nodules in the same lobe. T4 tumors include tumors of any size with invasion into mediastinum, heart, great vessels, trachea, or esophagus or multiple nodules in the ipsilateral lung. The eight edition of the TNM has been proposed and differences are outlined in Tables 74-6 and 74-7. The major changes are in the T and M staging while no changes have been made to the current classification of lymph node involvement (N). Patients with metastasis may be classified as M1a (malignant pleural or pericardial effusion, pleural nodules, or nodules in the contralateral lung) or M1b (distant metastasis; e.g., bone, liver, adrenal, or brain metastasis), M1b single metastasis to a single organ or M1c multiple metastases to a single organ or metastases to multiple organs. Based on these data, approximately one-third of patients have localized disease that can be treated with curative attempt (surgery or radiotherapy), one-third have local or regional disease that may or may not be amenable to a curative attempt, and one-third have metastatic disease at the time of diagnosis.

STAGING SYSTEM FOR SMALL-CELL LUNG CANCER

In patients with SCLC, it is now recommended that both the Veterans Administration system and the American Joint Committee on Cancer/International Union Against Cancer seventh edition system (TNM) be used to classify the tumor stage. The Veterans Administration system is a distinct two-stage system dividing patients into those with limited- or extensive-stage disease. Patients with limited-stage disease (LD) have cancer that is confined to the ipsilateral hemithorax and can be encompassed within a tolerable radiation port. Thus, contralateral supraclavicular nodes, recurrent laryngeal nerve involvement, and superior vena caval obstruction can all be part of LD. Patients with extensive-stage disease (ED) have overt metastatic disease by imaging or physical examination. Cardiac tamponade, malignant pleural effusion, and bilateral pulmonary parenchymal involvement generally qualify disease as ED, because the involved organs cannot be encompassed safely or effectively within a single radiation therapy port. Sixty to 70% of patients are diagnosed with ED at presentation. The TNM staging system is preferred in the rare SCLC patient presenting with what appears to be clinical stage I disease (see above).

PHYSIOLOGIC STAGING

Patients with lung cancer often have other comorbid conditions related to smoking including cardiovascular disease and COPD. To improve their preoperative condition, correctable problems (e.g., anemia, electrolyte and fluid disorders, infections, cardiac disease, and arrhythmias) should be addressed, appropriate chest physical therapy should be instituted, and patients should be encouraged to stop smoking. Patients with a forced expiratory volume in 1 s (FEV_1) of greater than 2 L or greater than 80% of predicted can tolerate a pneumonectomy, and those with an FEV_1 greater than 1.5 L have adequate reserve for a lobectomy. In patients with borderline lung function but a resectable tumor, cardiopulmonary exercise testing could be performed as part of the physiologic evaluation. This test allows an estimate of the maximal oxygen consumption (Vo_{2max}). A Vo_{2max} <15 mL/(kg.min) predicts for a higher risk of postoperative complications. Patients deemed unable to tolerate lobectomy or pneumonectomy from a pulmonary functional standpoint may be candidates for more limited resections, such as wedge

TABLE 74-6 Comparison of Seventh and Eight Edition TNM Staging Systems for Non-Small-Cell Lung Cancer

	TNM STAGING SYSTEM FOR LUNG CANCER (7TH EDITION)	TNM STAGING SYSTEM FOR LUNG CANCER (8TH EDITION)
Primary Tumor (T)		
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus	T1 tumor ≤3 cm in diameter surrounds by lung or visceral pleural without evidence of main bronchus
T1a	Tumor ≤2 cm in diameter	Tumor <1 cm
T1b	Tumor >2 cm but ≤ 3 cm in diameter	Tumor ≥1 cm but ≤2 cm
T1c	N/A	Tumor >2 cm but ≤3 cm
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:	T2 tumor >3 cm but ≤5 cm or tumor with any of the following features that does not involve the entire lung
	Involves main bronchus ≥2 cm distal to carina	Involves main bronchus ≥2 cm distal to carina
	Invades visceral pleura	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	Associate with atelectasis or obstructive pneumonitis that extends to the hilar region
T2a	Tumor >3 cm but ≤5 cm	Tumor > 3 cm but ≤4 cm
T2b	Tumor >5 cm but ≤7 cm	Tumor >4 cm but ≤5 cm
T3	Tumor >7 cm or any of the following:	>5 cm but ≤7 cm or any of the following:
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)	Directly invades any of the following chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
	Atelectasis or obstructive pneumonitis of the entire lung	Atelectasis or obstructive pneumonitis of the entire lung
	Separate tumor nodules in the same lobe	
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe	7 cm or any of the following invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional Lymph Nodes (N)		
N0	No regional lymph node metastases	N0 No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)		
M0	No distant metastasis	M0 No distant metastasis
M1	Distant metastasis	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion	M1 a separate nodule(s) in a contralateral tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis (in extrathoracic organs)	Single metastasis in a single organ
M1c		multiple metastases in a single organ or in several organs

Abbreviation: TNM, tumor-node-metastasis.

Source: Reproduced with permission from P Goldstraw et al: J Thorac Oncol 2:706, 2007.

TABLE 74-7 Comparison of Seventh and Eighth Edition TNM Staging Systems for Non-Small-Cell Lung Cancer

STAGE GROUPINGS SEVENTH EDITION				STAGE GROUPINGS EIGHTH EDITION			
Stage IA	T1a-T1b	N0	M0	Stage IA1	T1a	N0	M0
				Stage IA2	T1b	N0	M0
				Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0	Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0	Stage IIA T2bN0M0	T2b	N0	M0
	T2b	N0	M0				
Stage IIB	T2b	N1	M0	Stage IIB	T1a-T2b	N1	M0
	T3	N0	M0		T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0	Stage IIIA	T1-2b	N2	M0
	T3	N1,N2	M0		T3	N1	M0
	T4	N0,N1	M0		T4	N0/N1	M0
Stage IIIB	T4	N2	M0	Stage IIIB	T1-2b	N3	M0
	Any T	N3	M0		T3/T4	N0/N1	M0
Stage IIIC	N/A				T3/T4	N3	M0
Stage IV	Any T	Any N	M1a or M1b	Stage IVA	Any T	Any N	M1a/M1b
				Stage IV B	Any T	Any N	M1c

or anatomic segmental resection, although such procedures are associated with significantly higher rates of local recurrence and a trend toward decreased overall survival. All patients should be assessed for cardiovascular risk using American College of Cardiology and American Heart Association guidelines. A myocardial infarction within the past 3 months is a contraindication to thoracic surgery because 20% of patients will die of reinfarction. An infarction in the past 6 months is a relative contraindication. Other major contraindications include uncontrolled arrhythmias, an FEV_1 of less than 1 L, CO_2 retention (resting Pco_2 >45 mmHg), DLco <40%, and severe pulmonary hypertension.

TREATMENT

Non-Small-Cell Lung Cancer

The overall treatment approach to patients with NSCLC is shown in Fig. 74-3.

OCCULT AND STAGE 0 CARCINOMAS

Patients with severe atypia on sputum cytology have an increased risk of developing lung cancer compared to those without atypia. In the uncommon circumstance where malignant cells are identified in a sputum or bronchial washing specimen but the chest imaging appears normal (TX tumor stage), the lesion must be localized. More than 90% of tumors can be localized by meticulous examination of the bronchial tree with a fiberoptic bronchoscope under general anesthesia and collection of a series of differential brushings and biopsies. Surgical resection following bronchoscopic localization has been shown to improve survival compared to no treatment. Close follow-up of these patients is indicated because of the high incidence of second primary lung cancers (5% per patient per year).

SOLITARY PULMONARY NODULE AND "GROUND-GLASS" OPACITIES

A solitary pulmonary nodule is defined as an x-ray density completely surrounded by normal aerated lung with circumscribed margins, of any shape, usually 1–6 cm in greatest diameter. The approach to a patient with a solitary pulmonary nodule is based on an estimate of the probability of cancer, determined according to the patient's smoking history, age, and characteristics on imaging **(Table 74-8)**. Prior CXRs and CT scans should be obtained if available for comparison. A PET scan may be useful if the lesion is greater than 7–8 mm in diameter. If no diagnosis is apparent, Mayo investigators reported that clinical characteristics (age, cigarette smoking status, and prior cancer diagnosis) and three radiologic characteristics (nodule diameter, spiculation, and upper lobe location) were independent predictors of malignancy. At present, only two radiographic criteria are thought to predict the benign nature of a solitary pulmonary nodule: lack of growth over a period >2 years and certain characteristic patterns of calcification. Calcification alone, however, does not exclude malignancy; a dense central nidus, multiple punctuate foci, and "bulls eye" (granuloma) and "popcorn ball" (hamartoma) calcifications are highly suggestive of a benign lesion. In contrast, a relatively large lesion, lack of or asymmetric calcification, chest symptoms, associated atelectasis, pneumonitis, or growth of the lesion revealed by comparison with an old x-ray or CT scan or a positive PET scan may be suggestive of a malignant process and warrant further attempts to establish a histologic diagnosis. An algorithm for assessing these lesions is shown in **Fig. 74-6**.

Since the advent of screening CTs, small "ground-glass" opacities (GGOs) have often been observed, particularly as the increased sensitivity of CTs enables detection of smaller lesions. Many of these GGOs, when biopsied, are found to be atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). AAH is usually a nodule of <5 mm and is minimally hazy, also called nonsolid or ground glass (i.e., hazy slightly increased attenuation, no solid component, and preservation of bronchial and vascular margins). On thin-section CT, AIS is usually a nonsolid nodule and tends to be slightly more opaque than AAH. MIA is mainly solid, usually with a small (<5 mm) central solid component. However, overlap exists among the imaging features of the preinvasive and minimally invasive lesions in the lung adenocarcinoma spectrum. Lepidic adenocarcinomas are usually solid but may be nonsolid. Likewise, the small invasive adenocarcinomas also are usually solid but may exhibit a small nonsolid component.

TABLE 74-8 Assessment of Risk of Cancer in Patients with Solitary Pulmonary Nodules

	RISK		
VARIABLE	LOW	INTERMEDIATE	HIGH
Diameter (cm)	<1.5	1.5–2.2	≥2.3
Age (years)	<45	45–60	>60
Smoking status	Never smoker	Current smoker (<20 cigarettes/d)	Current smoker (>20 cigarettes/d)
Smoking cessation status	Quit ≥7 years ago or quit	Quit <7 years ago	Never quit
Characteristics of nodule margins	Smooth	Scalloped	Corona radiata or spiculated

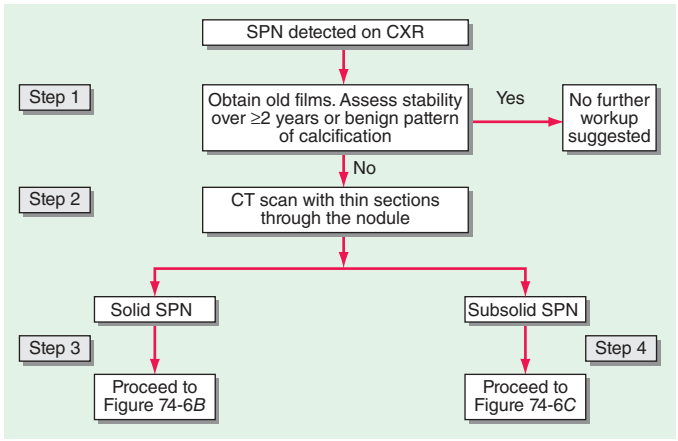
Source: Reproduced with permission from D Ost et al: N Engl J Med 348:2535, 2003.

MANAGEMENT OF STAGES I AND II NSCLC

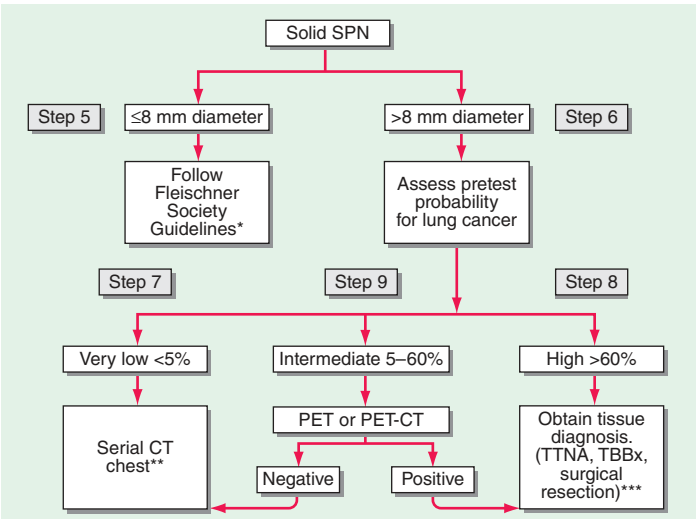
Surgical Resection of Stage I and II NSCLC Surgical resection, ideally by an experienced thoracic surgeon, is the treatment of choice for patients with clinical stage I and II NSCLC who are able to tolerate the procedure. Operative mortality rates for patients resected by thoracic or cardiothoracic surgeons are lower compared to general surgeons. Moreover, survival rates are higher in patients who undergo resection in facilities with a high surgical volume compared to those performing fewer than 70 procedures per year, even though the higher-volume facilities often serve older and less socioeconomic advantaged populations. The improvement in survival is most evident in the immediate postoperative period. The extent of resection is a matter of surgical judgment based on findings at exploration. In patients with stage IA NSCLC, lobectomy is superior to wedge resection with respect to rates of local recurrence. There is also a trend toward improvement in overall survival. In patients with comorbidities, compromised pulmonary reserve, and small peripheral lesions, a limited resection, wedge resection, and segmentectomy (potentially by video-assisted thoracoscopic surgery) may be reasonable surgical option. Pneumonectomy is reserved for patients with central tumors and should be performed only in patients with excellent pulmonary reserve. The 5-year survival rates are 60–80% for patients with stage I NSCLC and 40–50% for patients with stage II NSCLC.

Accurate pathologic staging requires adequate segmental, hilar, and mediastinal lymph node sampling. Ideally this includes a mediastinal lymph node dissection. On the right side, mediastinal stations 2R, 4R, 7, 8R, and 9R should be dissected; on the left side, stations 5, 6, 7, 8L, and 9L should be dissected. Hilar lymph nodes are typically resected and sent for pathologic review, although it is helpful to specifically dissect and label level 10 lymph nodes when possible. On the left side, level 2 and sometimes level 4 lymph nodes are generally obscured by the aorta. Although the therapeutic benefit of nodal dissection versus nodal sampling is controversial, a pooled analysis of three trials involving patients with stages I to IIIA NSCLC demonstrated a superior 4-year survival in patients undergoing resection and a complete mediastinal lymph node dissection compared with lymph node sampling. Moreover, complete mediastinal lymphadenectomy added little morbidity to a pulmonary resection for lung cancer when carried out by an experienced thoracic surgeon.

Radiation Therapy in Stages I and II NSCLC There is currently no role for postoperative radiation therapy in patients following resection of stage I or II NSCLC with negative margins. However, patients with stage I and II disease who either refuse or are not



A



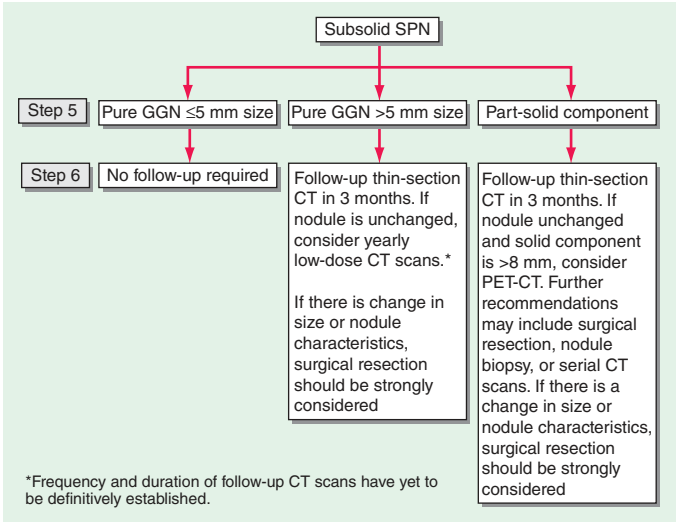
*Fleischner society guidelines; modified from: H. MacMahon, et al: *Radiology* 2005; 237;395–400

Nodule size (a):	Low-risk patient (b):	High-risk patient (c):
≤4 mm	No follow-up needed (d)	Follow-up at 12 months; if unchanged, no further follow-up
>4–≤6 mm	Follow-up CT at 12 months; if unchanged, no further follow-up	Follow-up CT at 6–12 months; then 18–24 months if no change
>6–≤8 mm	Follow-up CT at 6–12 months; then 18–24 months if no change	Follow-up CT at 3–6 months; then 9–12 and 24 months if no change
>8 mm	Follow-up CT at 3, 9, and 24 months; dynamic contrast-enhanced CT, PET, and/or biopsy	Same as low-risk patient

(a) Average of largest and smallest axial diameters of the nodule
(b) No smoking history and absence of other risk factors
(c) Previous or current smoking history or other risk factors
(d) Risk of malignancy (<0.1%) is substantially lower than for an asymptomatic smoker

**ACCP guidelines (see MK Gould et al: Chest 132(suppl 3):108s, 2007).
***Consider patient preference, severity of medical comorbidities, center specific expertise prior to tissue diagnosis.

B



C

FIGURE 74-6 ***A***. Algorithm for evaluation of solitary pulmonary nodule (SPN). ***B***. Algorithm for evaluation of solid SPN. ***C***. Algorithm for evaluation of semisolid SPN. CT, computed tomography; CXR, chest radiograph; GGN, ground-glass nodule; PET, positron emission tomography; TTBx, transbronchial biopsy; TTNA, transthoracic needle biopsy. *(Adapted from VK Patel et al: Chest 143:840, 2013.)*

suitable candidates for surgery should be considered for radiation therapy with *curative* intent. Stereotactic body radiation therapy (SBRT) is a technique used to treat patients with isolated pulmonary nodules (≤5 cm) who are not candidates for or refuse surgical resection. Treatment is typically administered in three to five fractions delivered over 1–2 weeks. In uncontrolled studies, disease control rates are >90%, and 5-year survival rates of up to 60% have been reported with SBRT. By comparison, survival rates typically range from 13 to 39% in patients with stage I or II NSCLC treated with standard external-beam radiotherapy. Cryoablation is another technique occasionally used to treat small, isolated tumors (i.e., ≤3 cm). However, very little data exist on long-term outcomes with this technique.

Chemotherapy in Stages I and II NSCLC Although a landmark meta-analysis of cisplatin-based adjuvant chemotherapy trials in patients with resected stages I to IIIA NSCLC (the Lung Adjuvant Cisplatin Evaluation [LACE] Study) demonstrated a 5.4% improvement in 5-year survival for adjuvant chemotherapy compared to surgery alone, the survival benefit was seemingly confined to patients with stage II or III disease **(Table 74-9)**. By contrast, survival was actually worsened in stage IA patients with the application of adjuvant therapy. In stage IB, there was a modest improvement in survival of questionable clinical significance.

TABLE 74-9 Adjuvant Chemotherapy Trials in Non-Small-Cell Lung Cancer

TRIAL	STAGE	TREATMENT	NO. OF PATIENTS	5-YEAR SURVIVAL (%)	*P*
IALT	I–III	Cisplatin-based	932	44.5	< .03
		Control	835	40.4	
BR10	IB–II	Cisplatin + vinorelbine	242	69	.03
		Control	240	54	
ANITA	IB–IIIA	Cisplatin + vinorelbine	407	60	.017
		Control	433	58	
ALPI	I–III	MVP	548	50	.49
		Control	540	45	
BLT	I–III	Cisplatin-based	192	60	.90
		Control	189	58	
CALGB	IB	Carboplatin + paclitaxel	173	59	.10
			171	57	

Abbreviations: ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; CALGB, Cancer and Lung Cancer Group B; IALT, International Adjuvant Lung Cancer Trial; MVP, mitomycin, vindesine, and cisplatin.

Adjuvant chemotherapy was also detrimental in patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status = 2). These data suggest that adjuvant chemotherapy is best applied in patients with resected stage II or III NSCLC. There is no apparent role for adjuvant chemotherapy in patients with resected stage IA or IB NSCLC. A possible exception to the prohibition of adjuvant therapy in this setting is the stage IB patient with a resected lesion ≥4 cm. At present, targeted therapies and immunotherapies are not used in the adjuvant setting, unless given as part of a clinical trial.

As with any treatment recommendation, the risks and benefits of adjuvant chemotherapy should be considered on an individual patient basis. If a decision is made to proceed with adjuvant chemotherapy, in general, treatment should be initiated 6–12 weeks after surgery, assuming the patient has fully recovered, and should be administered for no more than four cycles. Although a cisplatin-based chemotherapy is the preferred treatment regimen, carboplatin can be substituted for cisplatin in patients who are unlikely to tolerate cisplatin for reasons such as reduced renal function, presence of neuropathy, or hearing impairment. No specific chemotherapy regimen is considered optimal in this setting, although platinum plus vinorelbine is most commonly used.

Neoadjuvant chemotherapy, which is the application of chemotherapy administered *before* an attempted surgical resection, has been advocated by some experts on the assumption that such an approach will more effectively extinguish occult micrometastases compared to postoperative chemotherapy. In addition, it is thought that preoperative chemotherapy might render an inoperable lesion resectable. With the exception of superior sulcus tumors, however, the role of neoadjuvant chemotherapy in stage I to III disease is not well defined. However, a meta-analysis of 15 randomized controlled trials involving more than 2300 patients with stage I to III NSCLC suggested there may be a modest 5-year survival benefit (i.e., ~5%) that is virtually identical to the survival benefit achieved with postoperative chemotherapy. Accordingly, neoadjuvant therapy may prove useful in selected cases (see below). A decision to use neoadjuvant chemotherapy should always be made in consultation with an experienced surgeon.

In should be noted that all patients with resected NSCLC are at high risk of recurrence, most of which occurs within 18–24 months of surgery, or developing a second primary lung cancer. Thus, it is reasonable to follow these patients with periodic imaging studies. Given the results of the NLST, periodic CT scans appear to be the most appropriate screening modality. Based on the timing of most recurrences, some guidelines recommend a contrasted chest CT scan every 6 months for the first 3 years after surgery, followed by yearly CT scans of the chest without contrast thereafter.

MANAGEMENT OF STAGE III NSCLC

Management of patients with stage III NSCLC usually requires a combined-modality approach. Patients with stage IIIA disease commonly are stratified into those with "nonbulky" or "bulky" mediastinal lymph node (N2) disease. Although the definition of "bulky" N2 disease varies somewhat in the literature, the usual criteria include the size of a dominant lymph node (i.e., >2–3 cm in short-axis diameter as measured by CT), groupings of multiple smaller lymph nodes, evidence of extracapsular nodal involvement, or involvement of more than two lymph node stations. The distinction between nonbulky and bulky stage IIIA disease is mainly used to select potential candidates for *upfront* surgical resection or for resection after neoadjuvant therapy. Many aspects of therapy of patients with stage III NSCLC remain controversial, and the optimal treatment strategy has not been clearly defined. Moreover, although there are many potential treatment options, none yields a very high probability of cure. Furthermore, because stage III disease is highly heterogeneous, no single treatment approach can be recommended for all patients. Key factors guiding treatment choices include the particular combination of tumor (T) and nodal (N) disease, the ability to achieve a complete surgical resection if indicated, and the patient's overall physical condition and preferences. For example, in carefully selected patients with limited stage IIIA disease where involved mediastinal lymph nodes can be completed resected, initial surgery followed by postoperative chemotherapy (with or without radiation therapy) may be indicated. By contrast, for patients with clinically evident bulky mediastinal lymph node involvement, the standard approach to treatment is concurrent chemoradiotherapy. Nevertheless, in some cases, the latter group of patients may be candidates for surgery following chemoradiotherapy.

Absent and Nonbulky Mediastinal (N2, N3) Lymph Node Disease For the subset of stage IIIA patients initially thought to have clinical stage I or II disease (i.e., pathologic involvement of mediastinal [N2] lymph nodes is *not* detected preoperatively), surgical resection is often the treatment of choice. This is followed by adjuvant chemotherapy in patients with microscopic lymph node involvement in a resection specimen. Postoperative radiation therapy (PORT) may also have a role for those with close or positive surgical margins. Patients with tumors involving the chest wall or proximal airways within 2 cm of the carina with hilar lymph node involvement (but not N2 disease) are classified as having T3N1 stage IIIA disease. They too are best managed with surgical resection, if technically feasible, followed by adjuvant chemotherapy if completely resected. Patients with tumors exceeding 7 cm in size also are now classified as T3 and are consider stage IIIA if tumor has spread to N1 nodes. The appropriate initial management of these patients involves surgical resection when feasible, provided the mediastinal staging is negative, followed by adjuvant chemotherapy for those who achieve complete tumor resection. Patients with T3N0 or T3N1 disease due to the presence of satellite nodules within the same lobe as the primary tumor also are candidates for surgery, as are patients with ipsilateral nodules in another lobe and negative mediastinal nodes (IIIA, T4N0 or T4N1). Although data regarding adjuvant chemotherapy in the latter subsets of patients are limited, it is often recommended.

Patients with T4N0-1 were reclassified as having stage IIIA tumors in the seventh edition of the TNM system. These patients may have involvement of the carina, superior vena cava, or a vertebral body and yet still be candidates for surgical resection in selected circumstances. The decision to proceed with an attempted resection must be made in consultation with an experienced thoracic surgeon often in association with a vascular or cardiac surgeon and an orthopedic surgeon depending on tumor location. However, if an incomplete resection is inevitable or if there is evidence of N2 involvement (stage IIIB), surgery for T4 disease is contraindicated. Most T4 lesions are best treated with chemoradiotherapy.

The role of PORT in patients with completely resected stage III NSCLC is controversial. To a large extent, the use of PORT is dictated by the presence or absence of N2 involvement and, to a lesser degree, by the biases of the treating physician. Using the Surveillance, Epidemiology, and End Results (SEER) database, a recent meta-analysis of PORT identified a significant increase in survival in patients with N2 disease but not in patients with N0 or N1 disease. An earlier analysis by the PORT Meta-analysis Trialist Group using an older database produced similar results.

Known Mediastinal (N2, N3) Lymph Node Disease When pathologic involvement of mediastinal lymph nodes is documented preoperatively, a combined-modality approach is recommended assuming the patient is a candidate for treatment with curative intent. These patients are at high risk for both local and distant recurrence if managed with resection alone. For patients with stage III disease who are not candidates for initial surgical resection, *concurrent* chemoradiotherapy is most commonly used as the initial treatment. Concurrent chemoradiotherapy has been shown to produce superior survival compared to *sequential* chemoradiotherapy; however, it also is associated with greater host toxicities (including fatigue, esophagitis, and neutropenia). Therefore, for patients with a good performance status, concurrent chemoradiotherapy is the preferred treatment approach, whereas sequential chemoradiotherapy

may be more appropriate for patients with a performance status that is not as good. For patients who are *not* candidates for a combined-modality treatment approach, typically due to a poor performance status or a comorbidity that makes chemotherapy untenable, radiotherapy alone may provide a modest survival benefit in addition to symptom palliation.

For patients with potentially resectable N2 disease, it remains uncertain whether surgery after neoadjuvant chemoradiotherapy improves survival. In an NCI-sponsored Intergroup randomized trial comparing concurrent chemoradiotherapy alone to concurrent chemoradiotherapy followed by attempted surgical resection, no survival benefit was observed in the trimodality arm compared to the bimodality therapy. In fact, patients subjected to a pneumonectomy had a worse survival outcome. By contrast, those treated with a lobectomy appeared to have a survival advantage based on a retrospective subset analysis. Thus, in carefully selected, otherwise healthy patients with nonbulky mediastinal lymph node involvement, surgery may be a reasonable option if the primary tumor can be fully resected with a lobectomy. This is not the case if a pneumonectomy is required to achieve complete resection.

Superior Sulcus Tumors (Pancoast Tumors) Superior sulcus tumors represent a distinctive subset of stage III disease. These tumors arise in the apex of the lung and may invade the second and third ribs, the brachial plexus, the subclavian vessels, the stellate ganglion, and adjacent vertebral bodies. They also may be associated with Pancoast syndrome, characterized by pain that may arise in the shoulder or chest wall or radiate to the neck. Pain characteristically radiates to the ulnar surface of the hand. Horner's syndrome (enophthalmos, ptosis, miosis, and anhydrosis) due to invasion of the paravertebral sympathetic chain may be present as well. Patients with these tumors should undergo the same staging procedures as all patients with stage II and III NSCLC. Neoadjuvant chemotherapy or combined chemoradiotherapy followed by surgery is reserved for those without N2 involvement. This approach yields excellent survival outcomes (>50% 5-year survival in patients with an R0 resection). Patients with N2 disease are less likely to benefit from surgery and can be managed with chemoradiotherapy alone. Patients presenting with metastatic disease can be treated with radiation therapy (with or without chemotherapy) for symptom palliation.

MANAGEMENT OF METASTATIC NSCLC

Approximately 40% of NSCLC patients present with advanced, stage IV disease at the time of diagnosis. In addition, a significant number of patients who first presented with early-stage NSCLC will eventually relapse with distant disease. Patients who have recurrent disease have a better prognosis than those presenting with metastatic disease at the time of diagnosis. Standard medical management, the judicious use of pain medications, and the appropriate use of radiotherapy and systemic therapy—which may compromise of traditional cytotoxic chemotherapy, targeted therapy, and immunotherapy depending on the specific diagnosis and molecular subtype—form the cornerstone of management. Systemic therapy palliates symptoms, improves the quality of life, and improves survival in patients with stage advanced NSCLC, particularly in patients with good performance status. Of note, the early application of palliative care in conjunction with chemotherapy is associated with improved survival and a better quality of life.

Cytotoxic Chemotherapy for Metastatic or Recurrent NSCLC A landmark meta-analysis published in 1995 provided the earliest meaningful indication that chemotherapy could provide a survival benefit in metastatic NSCLC as opposed to supportive care alone. However, the survival benefit was seemingly confined to cisplatin-based chemotherapy regimens (hazard ratio 0.73; 27% reduction in the risk of death; 10% improvement in survival at 1 year). To date, platinum-based regimens remain the cornerstone of the cytotoxic chemotherapy regimens used for patients with metastatic NSCLC **(Table 74-10)**. Several different platinum "doublet" regimens have been used—combining platinum (cisplatin or carboplatin) with another type of chemotherapy (for example, paclitaxel, docetaxel, pemetrexed, gemcitabine, or vinorelbine). Although specific tumor histology was once considered irrelevant to treatment choice in NSCLC, with the recent recognition that selected chemotherapy agents perform quite differently in squamous versus adenocarcinomas, accurate determination of histology has become essential. Specifically, in a landmark randomized phase III trial, patients with nonsquamous NSCLC were found to have an improved survival when treated with cisplatin and pemetrexed compared to cisplatin and gemcitabine. By contrast, patients with squamous carcinoma had an improved survival when treated with cisplatin and gemcitabine. This survival difference is thought to be related to the differential expression of thymidylate synthase (TS), one of the targets of pemetrexed, between tumor types. Squamous cancers have a much higher expression of TS compared to adenocarcinomas, accounting for their lower responsiveness to pemetrexed. By contrast, the activity of gemcitabine is not impacted by the levels of TS.

TABLE 74-10 First-Line Chemotherapy Trials for Metastatic Non-Small-Cell Lung Cancer

TRIAL	REGIMEN	NO. OF PATIENTS	RR (%)	MEDIAN SURVIVAL (MONTHS)
ECOG1594	Cisplatin + paclitaxel	288	21	7.8
	Cisplatin + gemcitabine	288	22	8.1
	Cisplatin + docetaxel	289	17	7.4
	Carboplatin + paclitaxel	290	17	8.1
TAX-326	Cisplatin + docetaxel	406	32	11.3
	Cisplatin + vinorelbine	394	25	10.1
	Carboplatin + docetaxel	404	24	9.4
EORTC	Cisplatin + paclitaxel	159	32	8.1
	Cisplatin + gemcitabine	160	37	8.9
	Paclitaxel + gemcitabine	161	28	6.7
ILCP	Cisplatin + gemcitabine	205	30	9.8
	Carboplatin + paclitaxel	204	32	9.9
	Cisplatin + vinorelbine	203	30	9.5
SWOG	Cisplatin + vinorelbine	202	28	8.0
	Carboplatin + paclitaxel	206	25	8.0
FACS	Cisplatin + irinotecan	145	31	13.9
	Carboplatin + paclitaxel	145	32	12.3
	Cisplatin + gemcitabine	146	30	14.0
	Cisplatin + vinorelbine	145	33	11.4
Scagliotti	Cisplatin + gemcitabine	863	28	10.3
	Cisplatin + pemetrexed	862	31	10.3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; ILCP, Italian Lung Cancer Project; SWOG, Southwest Oncology Group; FACS, Follow-up After Colorectal Surgery.

Maintenance Therapy for Metastatic NSCLC Several large phase III randomized trials have failed to show a meaningful benefit for increasing the duration of platinum-doublet chemotherapy beyond four to six cycles. In fact, longer duration of platinum-doublet chemotherapy has been associated with increased toxicities and impaired quality of life. Maintenance chemotherapy in nonprogressing patients (patients with a complete response, partial response, or stable disease) is divided into two types of maintenance strategies: (1) switch maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and are switched to an entirely different regimen; and (2) continuation maintenance therapy, where patients receive four to six cycles of platinum-based chemotherapy and then the platinum agent is discontinued but the agent it is paired with is continued **(Table 74-11)**. Two studies investigated switch maintenance single-agent chemotherapy with docetaxel or pemetrexed in nonprogressing patients following treatment with first-line platinum-based chemotherapy. Both trials randomized patients to immediate single-agent therapy

TABLE 74-11 Maintenance Therapy Trials

			SURVIVAL	
GROUP	CT	NO. OF PATIENTS	OS (MONTHS)	PFS (MONTHS)
Switch Maintenance				
Fidias	Immediate docetaxel	153	12.3	5.7
	Delayed docetaxel	156	9.7	2.7
Ciuleanu	Pemetrexed	444	13.4	4.3
	BSC	222	10.6	2.6
Paramount	Pemetrexed	472	13.9	4.1
	BSC	297	11.0	2.8
ATLAS	Bev + erlotinib	384	15.9	4.8
	Bev + placebo	384	13.9	3.8
SATURN	Erlotinib	437	12.3	2.9
	Placebo	447	11.1	2.6
Continuation Maintenance				
ECOG4599	Bev 15 mg/kg	444	12.3	6.2
	BSC	434	10.3	4.5
AVAiL	Bev 15 mg/kg	351	13.4	6.5
	Bev 7.5 mg/kg	345	13.6	6.7
	Placebo	347	13.1	6.1
POINTBREAK	Pemetrexed + Bev 15 mg/kg			8.6
	Bev 15 mg/kg			6.9

Abbreviations: Bev, bevacizumab; BSC, best supportive care; CT, chemotherapy; OS, overall survival; PFS, progression-free survival.

versus observation and reported improvements in progression-free and overall survival. In both trials, a significant portion of patients in the observation arm did not receive therapy with the agent under investigation upon disease progression; 37% of study patients never received docetaxel in the docetaxel study and 81% of patients never received pemetrexed in the pemetrexed study. In the trial of maintenance docetaxel versus observation, survival was identical to the treatment group in the subset of patients who received docetaxel on progression, indicating this is an active agent in NSCLC. These data are not available for the pemetrexed study. Two additional trials evaluated switch maintenance therapy with erlotinib after platinum-based chemotherapy in patients with advanced NSCLC and reported an improvement in progression-free survival and overall survival in the erlotinib treatment group; however, erlotinib is not recommended in patients with EGFR wild type tumors. Bevacizumab, a monoclonal antibody against VEGF, has been shown to improve response rate, progression-free survival, and overall survival in patients with advanced disease when combined with chemotherapy. However, bevacizumab cannot be given to patients with squamous cell histology NSCLC because of their tendency to experience serious hemorrhagic effects. Currently, carboplatin/paclitaxel and bevacizumab or carboplatin/pemetrexed and bevacizumab are appropriate regimens for first-line treatment for stage IV nonsquamous NSCLC patients followed by maintenance bevacizumab or maintenance pemetrexed/bevacizumab respectively. Currently, maintenance pemetrexed following platinum-based chemotherapy in patients with advanced NSCLC is also approved by the U.S. FDA. Maintenance erlotinib is only approved in patients with EGFR mutations (see below). It should be noted that there are no approved maintenance regimens for patients with squamous cell histology. Moreover, maintenance therapy is not without toxicity and, at this time, should be considered on an individual patient basis.

Targeted Therapies for Select Molecular Cohorts of NSCLC As the efficacy of traditional cytotoxic chemotherapeutic agents plateaued in NSCLC, there was a critical need to define novel therapeutic treatment strategies. For a cohort of NSCLC patients, the presence of an oncogenic driver allows the use of oral therapies with significant tumor regression. These driver mutations occur in genes encoding signaling proteins that, when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as Achilles' heels for tumors, if their gene products can be targeted therapeutically with small-molecule inhibitors. For example, *EGFR* mutations have been detected in 10–15% of North American patients diagnosed with NSCLC. *EGFR* mutations are associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations within the EGFR TK domain, resulting in hyperactivation of both EGFR kinase activity and downstream signaling. Lung tumors that harbor activating mutations within the EGFR kinase domain display high sensitivity to small-molecule EGFR TKIs. Erlotinib, gefitinib, and afatinib are FDA-approved oral small-molecule TKIs that inhibit EGFR. Several large, international, phase III studies have demonstrated improved response rates, progression-free survival, and overall survival in patients with *EGFR* mutation–positive NSCLC patients treated with an EGFR TKI as compared with standard first-line chemotherapy regimens **(Table 74-12)**. A phase III trial also compared gefitinib to afatinib as first-line therapy in patients with *EGFR* mutation–positive NSCLC and demonstrated superior efficacy, with increasing toxicity for patients treated with afatinib. Unfortunately, all patients with *EGFR* mutation–positive NSCLC treated with EGFR TKIs eventually developed acquired resistance. Disease progression occurs usually around 12 months. Approximately 50% of patients have tumors that harbor a second site mutation, most commonly the T790M mutation occurring within exon 20. Osimertinib, a third generation mutant-selective EGFR TKI received approval in 2015 for patients who progress on erlotinib, gefitinib, or afatinib and whose tumors harbor the T790M mutation.

With the rapid pace of scientific discovery, additional driver mutations in lung cancer have been identified and targeted therapeutically with impressive clinical results. For example, chromosomal rearrangements involving the anaplastic lymphoma kinase (*ALK*) gene on chromosome 2 have been found in ~3–7% of NSCLC. The result of these *ALK* rearrangements is hyperactivation of the ALK TK domain. Similar to EGFR, *ALK* rearrangements are typically (but not exclusively) associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Remarkably, *ALK* rearrangements were initially described in lung cancer in 2007, and by 2011, the first ALK inhibitor, crizotinib, received FDA approval for patients with lung tumors harboring *ALK* rearrangements. Two additional ALK inhibitors, ceritinib and alectinib, are currently approved in patients who progress on crizotinib. ALK testing may be performed via fluorescence in situ hybridization (FISH),

TABLE 74-12 Results of Phase III Trials Comparing Chemotherapy and First-Line EGFR TKI in *EGFR* Mutation–Positive Patients

STUDY	THERAPY	NO. OF PATIENTS	ORR (%)	PFS (MONTHS)
IPASS	CbP	129	47	6.3
	Gefitinib	132	71	9.3
EURTAC	CG	87	15	5.2
	Erlotinib	86	58	9.7
OPTIMAL	CG	72	36	4.6
	Erlotinib	82	83	13.1
NEJ002	CG	114	31	5.4
	Gefitinib	114	74	10.8
WJTOG3405	CD	89	31	6.3
	Gefitinib	88	62	9.2
LUX LUNG 3	CP	115	23	6.9
	Afatinib	230	56	11.1
LUX LUNG 6	CG	122	23	5.6
	Afatinib	242	67	11.0

Abbreviations: CbP, carboplatin and paclitaxel; CD, cisplatin and docetaxel; CG, cisplatin and gemcitabine; CP, cisplatin and paclitaxel; CG, cisplatin and gemcitabine; ORR, overall response rate; PFS, progression-free survival.

immunohistochemistry (IHC), or next generation sequencing. *ROS1* fusions have been identified in ~1% of patients with NSCLC and similar to EGFR and ALK, *ROS* rearrangements are typically associated with younger age and light or never smoking status. Crizotinib, which inhibits both ALK and ROS1 kinases, was recently FDA approved for patients whose tumors harbor a *ROS1* fusion.

In addition to *EGFR*, *ALK*, and *ROS1* other driver mutations have been discovered with varying frequencies in NSCLC, including *KRAS*, *BRAF*, *PIK3CA*, *NRAS*, *AKT1*, *MET*, *MEK1* (*MAP2K1*), *NTRK*, and *RET*. Mutations within the *KRAS* GTPase are found in ~20% of lung adenocarcinomas. To date, however, no small-molecule inhibitors are available to specifically target mutant *KRAS*. Each of the other driver mutations occurs in less than 1–3% of lung adenocarcinomas. The great majority of the driver mutations are mutually exclusive, and there are ongoing clinical studies for their specific inhibitors. For example, the BRAF inhibitors dabrafenib and vemurafenib and the RET inhibitors cabozantinib and vandetanib have already demonstrated efficacy in patients with lung cancer harboring *BRAF* mutations or *RET* gene fusions, respectively. Most of these mutations are present in adenocarcinoma; however, mutations that may be linked to future targeted therapies in squamous cell carcinomas are emerging. In addition, there are active research efforts aimed at defining novel targetable mutations in lung cancer as well as defining mechanisms of acquired resistance to small-molecule inhibitors used in the treatment of patients with NSCLC.

Second-Line Therapy and Beyond Second-line therapy for advanced NSCLC was almost never recommended until a seminal study in 2000 showed that docetaxel improved survival compared to supportive care alone. Little progress had been made in the second-line setting for NSCLC patients until the introduction of immunotherapy agents (see below) with only pemetrexed and docetaxel available as FDA-approved agents, and erlotinib recommended in patients with EGFR mutation–positive NSCLC who did not receive a first line EGFR TKI. Ramucirumab is a recombinant human IgG1 monoclonal antibody that targets VEGFR-2 and blocks the interaction of VEGF ligands and VEGFR-2. A phase III trial demonstrated a significant improvement in progression-free survival and overall survival when ramucirumab was combined with docetaxel as second-line therapy in patients who had progressed on platinum-based chemotherapy. Contrary to bevacizumab, ramucirumab was safe in patients with both squamous and nonsquamous NSCLC and is approved regardless of histology.

Immunotherapy Immune checkpoint inhibitors are a novel class of agents that have significantly improved the quality of life and survival for a group of patients with advanced NSCLC. Immune checkpoint inhibitors work by blocking interactions between T cells and antigen presenting cells (APCs) or tumor cells that lead to T-cell inactivation. By inhibiting this interaction, the immune system is effectively upregulated and T cells become activated against tumor cells. Several large randomized phase III trials demonstrated superior overall survival for both the anti-PD1 antibodies, nivolumab and pembrolizumab and the anti-PD-L1 antibody atezolizumab compared to second-line docetaxel in patients with NSCLC who have progressed on platinum-based chemotherapy **(Table 74-13)**. Nivolumab and atezolizumab are approved as second-line therapy in patients who have progressed following platinum-based chemotherapy regardless of the presence of PD-L1 while pembrolizumab is approved in patients with tumors positive for PD-L1 expression in ≥1% of tumor cells. Pembrolizumab demonstrated superior efficacy to first-line platinum-based chemotherapy in patients with tumors expressing PD-L1 in greater than 50% of tumor cells, as assessed with immunohistochemistry. A similarly designed study did not show efficacy when nivolumab was compared to chemotherapy; however, in this study patients with tumors expressing PD-L1 in greater than 1% of tumor cells were enrolled. Pembrolizumab is approved as first-line therapy in patients with tumors that are positive for PD-L1 expression in ≥50% of tumor cells. While PD-L1 has been identified as a biomarker that can predict response to immune checkpoint inhibitors, responses are observed in patients who do not appear to express the biomarker and not all PD-L1 positive patients respond to checkpoint inhibition. Complicating matter is that each checkpoint inhibitor is being developed in conjunction with its own antibody to assess PD-L1 expression and a large effort is underway to compare these tests. Further evaluation of these agents in both NSCLC and SCLC is ongoing in combination with already approved chemotherapy and targeted agents as well as other checkpoint inhibitors.

TABLE 74-13 Results of Phase III Trials Comparing Chemotherapy and Immunotherapy in Patients with NSCLC

STUDY	THERAPY	NO. OF PATIENTS	OS (MONTHS)	PFS (MONTHS)
Checkmate 017	Docetaxel	137	6.0	2.8
Squamous	Nivolumab	135	9.2	3.5
Checkmate 057	Docetaxel	290	9.4	4.2
Nonsquamous	Nivolumab	292	12.2	2.3
Keynote 10	Docetaxel	212	8.5	4.0
PD-L1 ≥1%	Pembrolizumab 2 mg/kg	259	10.4	2.9
	Pembrolizumab 10 mg/kg	255	12.7	2.9
OAK	Docetaxel	425	10.3	2.8
	Atezolizumab	425	12.6	4.0
Keynote 24	Platinum-chemotherapy	116	NR	6.0
PD-L1 ≥50%	Pembrolizumab	73	NR	10.3
Checkmate 26	Platinum-chemotherapy	212	13.2	5.9
PD-L1 ≥1%	Nivolumab	211	14.4	4.2

Abbreviations: OS, overall survival; PFS, progression-free survival; Platinum-chemotherapy refers to first-line platinum-doublet chemotherapy.

Supportive Care No discussion of the treatment strategies for patients with advanced lung cancer would be complete without a mention of supportive care. Coincident with advances in chemotherapy and targeted therapy was a pivotal study that demonstrated that the early integration of palliative care with standard treatment strategies improved both quality of life and mood for patients with advanced lung cancer **(Chaps. 9 and 65)**. Aggressive pain and symptom control is an important component for optimal treatment of these patients.

TREATMENT

Small-Cell Lung Cancer

The overall treatment approach to patients with SCLC is shown in Fig. 74-5.

SURGERY FOR LIMITED-DISEASE SMALL-CELL LUNG CANCER

SCLC is a highly aggressive disease characterized by its rapid doubling time, high growth fraction, early development of disseminated disease, and dramatic response to first-line chemotherapy and radiation. In general, surgical resection is *not* routinely recommended for patients because even patients with LD-SCLC still have occult micrometastases. However, the most recent American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend surgical resection over nonsurgical treatment in SCLC patients with clinical stage I disease after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation (grade 2C). After resection, these patients should receive platinum-based adjuvant chemotherapy (grade 1C). If the histologic diagnosis of SCLC is made in patients on review of a resected surgical specimen, such patients should receive standard SCLC chemotherapy as well.

CHEMOTHERAPY

Chemotherapy significantly prolongs survival in patients with SCLC. Four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan has been the mainstay of treatment for nearly three decades and is recommended over other chemotherapy regimens irrespective of initial stage. Cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) may be an alternative for patients who are unable to tolerate a platinum-based regimen. Despite response rates to first-line therapy as high as 80%, the median survival ranges from 12 to 20 months for patients with LD and from 7 to 11 months for patients with ED. Regardless of disease extent, the majority of patients relapse and develop chemotherapy-resistant disease. Only 6–12% of patients with LD-SCLC and 2% of patients with ED-SCLC live beyond 5 years. The prognosis is especially poor for patients who relapse within the first 3 months of therapy; these patients are said to have *chemotherapy-resistant disease*. Patients are said to have *sensitive disease* if they relapse more than 3 months after their initial therapy and are thought to have a somewhat better overall survival. These patients also are thought to have the greatest potential benefit from second-line chemotherapy **(Fig. 74-7)**. Topotecan is the only FDA-approved agent for second-line therapy in patients with SCLC. Topotecan has only modest activity and can be given either intravenously or orally. In one randomized trial, 141 patients who were not considered candidates for further IV chemotherapy were randomized to receive either oral topotecan or best supportive care. Although the response rate to oral topotecan was only 7%, overall survival was significantly better in patients receiving chemotherapy (median survival time, 26 weeks vs 14 weeks; $p = 0.01$). Moreover, patients given topotecan had a slower decline in quality of life than did those not receiving chemotherapy. Other agents with similar low levels of activity in the second-line setting include irinotecan, paclitaxel, docetaxel, vinorelbine, oral etoposide, and gemcitabine. Clearly novel treatments for this all too common disease are desperately needed.

THORACIC RADIATION THERAPY

Thoracic radiation therapy (TRT) is a standard component of induction therapy for good performance status and limited-stage SCLC patients. Meta-analyses indicate that chemotherapy combined with chest irradiation improves 3-year survival by ~5% as compared with chemotherapy alone. The 5-year survival rate, however, remains disappointingly low at ~10–15%. Most commonly, TRT is combined with cisplatin and etoposide chemotherapy due to a superior toxicity profile as compared to anthracycline-containing chemotherapy regimens. As observed in locally advanced NSCLC, *concurrent* chemoradiotherapy is more effective than *sequential* chemoradiation but is associated with significantly more esophagitis and hematologic toxicity. Ideally TRT should be administered with the first two cycles of chemotherapy because later application appears slightly less effective. If for reasons of fitness or availability, this regimen cannot be offered, TRT should follow induction chemotherapy. With respect to fractionation of TRT, twice-daily 1.5-Gy fractioned radiation therapy has been shown to improve survival in LD-SCLC patients but is associated with higher rates of grade 3 esophagitis and pulmonary toxicity. Although it is feasible to deliver once-daily radiation therapy doses up to 70 Gy concurrently with cisplatin-based chemotherapy, there are no data to support equivalency of this approach compared with the 45-Gy twice-daily radiotherapy dose. Therefore, the current standard regimen of a 45-Gy dose administered in 1.5-Gy fractions twice daily for 30 days is being compared with higher-dose regimens in two phase III trials, one in the United States and one in Europe. Patients should be carefully selected for concurrent chemoradiation therapy based on good performance status and adequate pulmonary reserve. The role of radiotherapy in ED-SCLC is largely restricted to palliation of tumor-related symptoms such as bone pain and bronchial obstruction.

PROPHYLACTIC CRANIAL IRRADIATION

Prophylactic cranial irradiation (PCI) should be considered in all patients with either LD-SCLC or ED-SCLC who have responded well to initial therapy. A meta-analysis including seven trials and 987 patients with LD-SCLC who had achieved a complete remission after upfront chemotherapy yielded a 5.4% improvement in overall survival for patients treated with PCI. In patients with ED-SCLC who have responded to first-line chemotherapy, a prospective randomized phase III trial showed that PCI reduced the occurrence of symptomatic brain metastases and prolonged disease-free and overall survival compared to no radiation therapy. Long-term toxicities, including deficits in cognition, have been reported after PCI but are difficult to sort out from the effects of chemotherapy or normal aging.

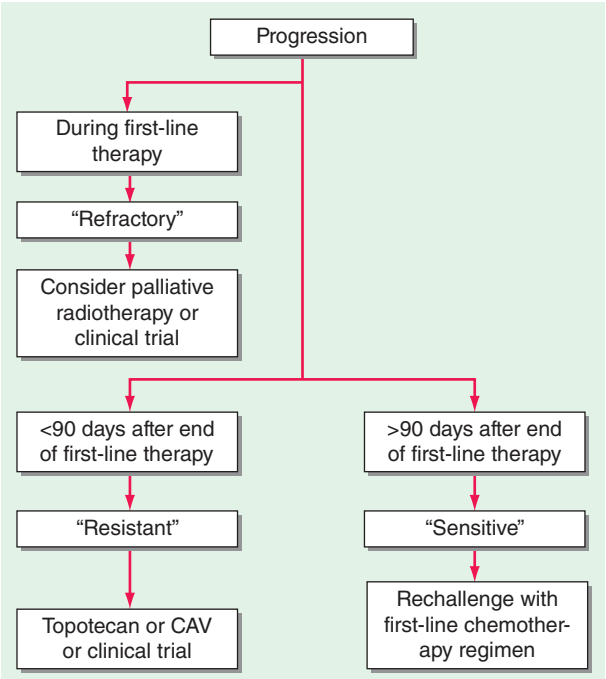


FIGURE 74-7 Management of recurrent small-cell lung cancer (SCLC). CAV, cyclophosphamide, doxorubicin, and vincristine. *(Adapted with permission from JP van Meerbeeck et al: Lancet 378:1741, 2011.)*

THYMIC TUMORS

Thymic tumors are rare malignancies accounting for 0.5–1.5% of all malignancies in the United States with a higher incidence among Asian populations. They are particularly rare among children and young adults with incidence peaking in the fifth decade of life. There is no difference between sexes and no clear risk factors have been identified.

CLINICAL MANIFESTATIONS

The majority of thymic tumors occur in the anterior mediastinum. Approximately 40% of patients with mediastinal masses will be asymptomatic with an incidental finding on chest imaging. In patients presenting with an anterior mediastinal mass, if appropriate, serum beta-HCG (human chorionic gonadotropin) and α fetoprotein (AFP) should be sent to rule out a germ cell tumor. A patient with a sign or symptom of thymoma or thymic carcinoma may present with chest pain, dyspnea, cough or superior vena cava syndrome secondary to effects on adjacent organs or a paraneoplastic syndrome, most commonly myasthenia gravis, pure red cell aplasia or hypogammaglobulinemia. More rare paraneoplastic syndromes include limbic encephalitis, aplastic anemia, hemolytic anemia, and autoimmune disease such as Sjogrens syndrome, polymyositis, rheumatoid arthritis, ulcerative colitis among others.

STAGING

Given the rarity of the tumor, patients with suspected thymoma should be evaluated by a multidisciplinary team including a surgeon, medical

TABLE 74-14 Staging Thymic Tumors

MASAOKA STAGE	DEFINITION
I	Grossly and microscopically encapsulated
IIA	Microscopic transcapsular invasion
IIB	Macroscopic invasion into surrounding tissue excluding pericardium, lung, and great vessels
III	Macroscopic invasion into neighboring organs of the lower neck or upper chest
IVA	Pleural or pericardial dissemination
IVB	Hematogenous or lymphatic dissemination to distal organs
WHO	
A	Tumor with few lymphocytes
AB	Tumor with features of type A and foci rich in lymphoctyes
B1	Tumor with features of normal epithelial cells with vesicular nuclei and distinct nucleoli and an abundant population of lymphocytes. Also known as cortical thymoma, lymphocyte-rich thymoma
B2	Thymoma with no or mild atypia with round or polygonal shaped cells with small component of lymphocytes
B3	Well differentiated thymic carcinoma with mild atypia
C	Thymic carcinoma with high atypia

and radiation oncologist as well as pathologist with experience in treating the disease. A CT scan of the chest with contrast is recommended to determine if the mass is resectable based on relationship to surrounding structures. An MRI with contrast may be performed if clinically indicated. A PET scan may be useful in the evaluation of a patient with thymic tumors although may be less useful in the staging of thymoma compared to thymic carcinoma. A core needle biopsy is considered standard of care for obtaining a histological diagnosis of an anterior mediastinal tumor. This may be obtained via CT or ultrasound imaging. However, in some circumstances a mediastinoscopy or open biopsy may be required.

Thymomas are commonly staged using the Masaoka system or the World Health Organization (WHO) staging system as described in Table 74-14. WHO type A, AB, and B1 tend to be more well-differentiated, type B2 and B3 are moderately differentiated, and C are poorly differentiated.

TREATMENT

Surgical resection is the mainstay of treatment for patients with Masaoka type I and II thymic tumors. In patients with type III and IV who are potentially resectable thymic tumors, neoadjuvant chemotherapy may be given to decrease the tumor size and allow for a resection with negative margins. Surgery remains controversial and provides a limited role in the treatment of stage III and IV disease. No additional therapy may be required in patients with type I who have a resection with negative margins. Postoperative radiation therapy may be recommended based on extracapsular extension and the presence of positive margins in patients with type II or III thymic tumors or histological evaluation WHO B3 and C. Radiation therapy may be beneficial in patients with locally advanced disease (type III or IV) or in patients with symptoms secondary to compression of surrounding structures. Chemotherapy with cisplatin, doxorubicin, and cyclophosphamide (CAP) remains the mainstay of therapy in the neoadjuvant and adjuvant setting as well as first-line therapy in patients with metastatic thymoma, while carboplatin and paclitaxel are often employed in patients with thymic carcinoma. Limited additional agents are recommended based on small phase II trials as second-line therapy and beyond.

SUMMARY

The management of NSCLC has undergone major change in the past decade. To a lesser extent, the same is true for SCLC and thymic tumors. For patients with early-stage disease, advances in radiotherapy and surgical procedures as well as new systemic therapies have greatly improved prognosis in all diseases. For patients with advanced lung cancer, major progress in understanding tumor genetics and tumor immunology has led to the development of rational targets and specific inhibitors which have documented efficacy in specific subsets of NSCLC. Furthermore, increased understanding of how to activate the immune system to drive antitumor immunity has proven to be a successful therapeutic strategy for a subset of patients with advanced lung cancer. In Fig. 74-8, we propose an algorithm of the treatment approach for patient with stage IV NSCLC. However, the reality is that only a small subset of patients responds to immune checkpoint

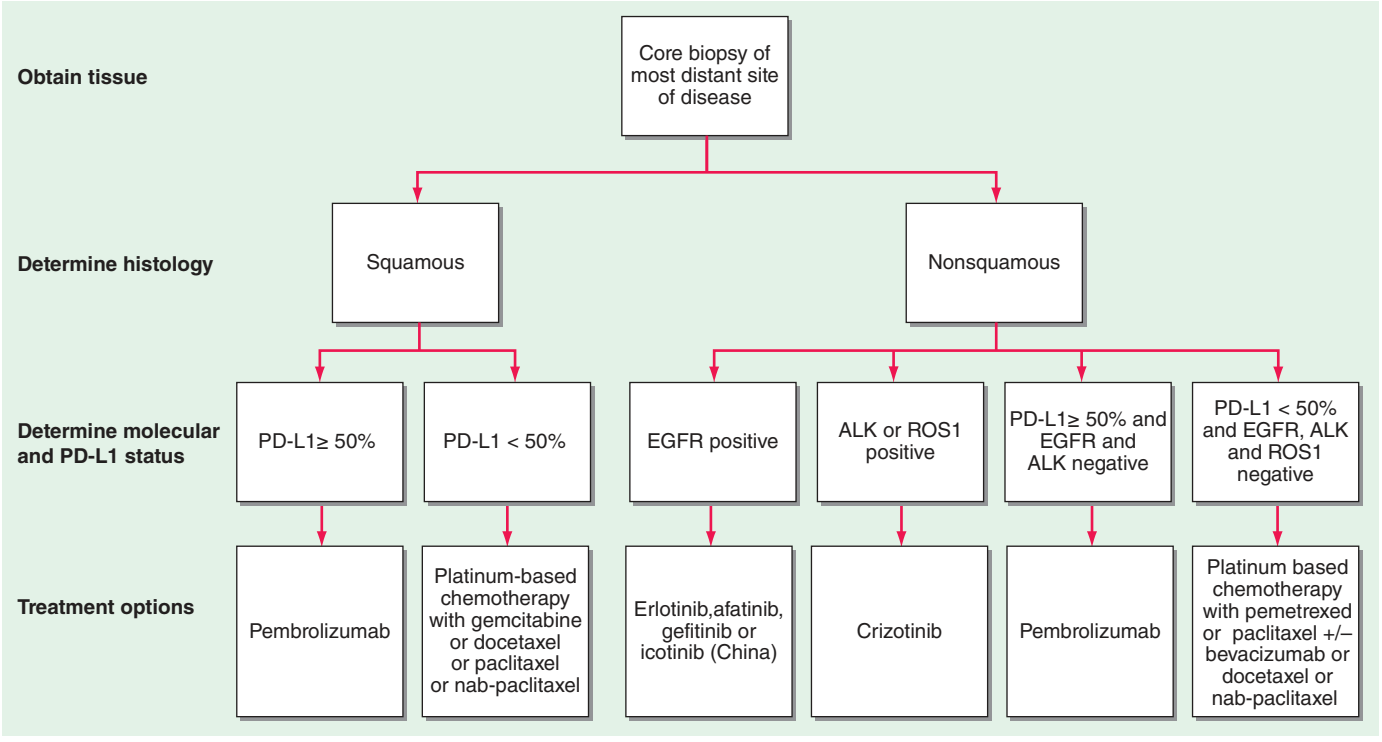


FIGURE 74-8 Approach to first-line therapy in a patient with stage IV non-small-cell lung cancer (NSCLC).

inhibitors and the majority of patients treated with targeted therapies or chemotherapy eventually develop resistance, which provides strong motivation for further research and enrollment of patients onto clinical trials in this rapidly evolving area.

Acknowledgment

David Johnson contributed to this chapter in the prior edition and material from that chapter has been retained here.

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75 Breast Cancer

Daniel F. Hayes, Marc E. Lippman

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast. In the year 2017, ~247,000 cases of invasive and 61,000 cases of in situ breast cancer and 41,000 deaths will occur in the United States. In addition, ~2000 men will be diagnosed with breast cancer. Epithelial malignancies of the breast are the most common cause of cancer in women (excluding skin cancer), accounting for about one-third of all cancer in women. As a result of improved treatment and earlier detection, the mortality rate from breast cancer has begun to decrease very substantially in the United States. This chapter does not consider rare malignancies presenting in the breast, such as sarcomas and lymphomas, but focuses on the epithelial cancers.

EPIDEMIOLOGY AND RISK FACTORS

Breast cancer is principally a disease of older women. Seventy-five percent of all breast cancers occur in women aged >50 years. The female-to-male ratio is ~150:1. It is also a hormone-dependent disease. Women without functioning ovaries, or who experience an early menopause, and who never receive combination estrogen/progesterone replacement therapy, are much less likely to develop breast cancer than those who have a normal menstrual history. A log-log plot of incidence versus age for breast cancer shows two components: a straight-line increase with age but with a decrease in slope beginning at the age of menopause. Length of menstrual life—particularly the fraction occurring before first full-term pregnancy—is a substantial component of the total risk of breast cancer. Breast cancer risk is increased in women with early menarche, late first full-term pregnancy, and late menopause. These three factors account for 70–80% of the variation in breast cancer frequency in different countries. Also, duration of maternal nursing correlates with substantial risk reduction independent of either parity or age at first full-term pregnancy.

International variation and immigration statistics of incidence provide insight into hormonal carcinogenesis. A woman living to age 80 years in North America has one chance in nine of developing invasive breast cancer. Asian women have traditionally had only 1/5th to 1/10th the risk of breast cancer of women in North America or Western Europe. However, with shifts from agrarian to industrialized economic systems, and in immigrant populations, Asian women living in modern, Western-style environments have risks identical to those of their Western counterparts.

Presumably, these differences are secondary to menstrual, and associated intrinsic estrogen exposure, histories. However, differences in diets have also been implicated, although the role of diet in breast cancer etiology is controversial. While there are associative links between total caloric and fat intake and breast cancer risk, the exact role of fat in the diet is unproven and may actually intersect with menstrual history and estrogenic exposure.

Central obesity is both a risk factor for occurrence and recurrence of breast cancer. Moderate alcohol intake also increases the risk by an unknown mechanism. Folic acid supplementation appears to modify risk in women who use alcohol but is not additionally protective in abstainers. Recommendations favoring abstinence from alcohol must be weighed against other social pressures and the possible cardioprotective effect of moderate alcohol intake. Chronic low-dose aspirin use is associated with a decreased incidence of breast cancer. Depression is also associated with both occurrence and recurrence of breast cancer.

Exogenous use of female hormones also plays a role in breast cancer incidence. Oral contraceptive use causes a small increased risk of breast cancer. However, this risk is more than balanced by avoidance of an undesired pregnancy and a substantial protective effect against ovarian epithelial and endometrial cancers.

Hormone replacement therapy (HRT) with conjugated equine estrogens plus progestins increases the risk of breast cancer and adverse cardiovascular events, but decreases the risk of bone fractures and colorectal cancer. On balance, there appear to be more negative events with HRT; 6–7 years of HRT nearly doubled the risk of breast cancer. Of note, administration of conjugated estrogens alone (estrogen replacement therapy in women who have had hysterectomies) produces no significant increase in breast cancer incidence. Thus, there are serious concerns about long-term HRT, especially in combination with progestins, in terms of cardiovascular disease and breast cancer. No comparable safety data are available for other less potent forms of estrogen replacement, such as bioequivalent estrogen found in soy, and they should not be routinely used as substitutes. Rapid decrease in the number of women on HRT has already led to a coincident decrease in breast cancer incidence. HRT in women previously diagnosed with breast cancer, especially of the subtype that expresses estrogen receptors, increases recurrence rates.

In addition to the other factors, radiation is a risk factor in younger women. Women who have been exposed before age 30 years to radiation in the form of multiple fluoroscopies (200–300 cGy) or treatment for Hodgkin's disease (>3600 cGy) have a substantial increase in risk of breast cancer, whereas radiation exposure after age 30 years appears to have a minimal carcinogenic effect on the breast.

GENETIC CONSIDERATIONS

The genetics of breast cancer require an understanding of the distinction between inherited, germline genetic differences among individuals and acquired, somatic genetic changes within cancers. The former, often called single nucleotide polymorphisms (SNPs), if deleterious, may lead to higher susceptibility to developing cancer and/or to a patient's response to or toxicity from a given treatment (pharmacogenetics). Somatic genetic changes that are not inherited, including mutations, amplifications, deletions, translocations, and others, are responsible for the malignant behavior of a cancer, including

unrestrained proliferation, as well as extravasation from one site and migration and establishment of metastases into another.

In this regard, human breast cancer is a clonal disease. One or more transformed cells, which arise due to a combination of inherited germline susceptibility and environmentally driven somatic changes, are eventually able to express full malignant potential. Thus, breast cancer may exist for a long period as either a noninvasive disease or an invasive but nonmetastatic disease. These facts have significant clinical ramifications, including overdiagnosis of biologically nonmalignant but anatomically apparent cancers.

Germline Genetic Susceptibility Although family history is an important risk factor, for most women the increased risk associated with a family member who has had breast cancer appears to be related to both a weak, and probably multi-gene germline susceptibility and/or similar exposure to environmental/life style risk factors. Not >10% of human breast cancers can be linked directly to single germline SNPs. However, when they are present, the relative and absolute risk for that individual's developing breast, and other, cancers in her lifetime are extraordinary.

Of these, the *BRCA1* and *2* genes are the best characterized and have the greatest clinical importance. *BRCA1* has been identified at the chromosomal locus 17q21; this gene encodes a zinc finger protein, and the protein product functions as a transcription factor and is involved in gene repair. Women who inherit a mutated allele of this gene from either parent have at least a 60–80% lifetime chance of developing breast cancer and about a 33% chance of developing ovarian cancer. The cancers that arise within a *BRCA1*-mutated patient are almost exclusively negative for estrogen and progesterone receptors (ER, PgR) and for human epidermal receptor 2 (HER2) (so-called "triple negative" breast cancers), and ~20% of women with triple negative breast cancers will be positive for deleterious germline BRCA1 SNPs. Nonetheless, the risk of breast cancer penetrance is variable within the *BRCA1*-affected population and is higher among women born after 1940, presumably due to promotional effects of hormonal factors. Men who carry a mutant allele of the gene have an increased incidence of prostate cancer and breast cancer.

BRCA2, which has been localized to chromosome 13q12, is also associated with an increased incidence of breast cancer in women. It should be noted that cancers that arise in *BRCA2* contexts are more likely to be ER positive, compared to those in *BRCA1* families, in which they are almost universally negative for ER, PgR, and HER2 expression. Of interest, men with *BRCA2* deleterious SNPs also have a higher risk of breast cancer, although most male breast cancer cases do not occur in *BRCA2*-mutated men, and the risk of breast cancer in men who do carry the *BRCA2* mutation is lower than that in women with this genetic abnormality.

Germline mutations in *BRCA1* and *BRCA2* can be readily detected in blood tests of normal circulating leucocytes. However, most experts do not recommend testing all women, since the rate of germline SNPS in this gene in the general population is quite low (well below 1%) and the tests are not 100% accurate. Further, it is not infrequent to identify variants of unknown significance (VUS) that may increase patient anxiety without a clear-cut set of recommendations about management. Consensus guidelines on who should be tested include any patient with a triple negative breast cancer and any patient with contralateral breast cancer or who has a first-degree relative (mother, father, or sister) with breast cancer. Further, any man with breast cancer should also be tested. Some guidelines suggest testing any patient with breast cancer who is of Ashkenazi descent, since the incidence in this population of a specific founder *BRCA1* mutation (substitution of adenine for guanine at position 185) is ~2%. Patients with these mutations should be counseled appropriately.

Over the last 5 years, panels of germline genes have been offered in addition to *BRCA1* and 2. These include genes that are known to be risk factors for breast cancer if the individual harbors deleterious SNPs, including *p53*, *PTEN*, and *PALB1*. However, several of the other genes included in these panels are less well-studied, and therefore it is less clear how to counsel affected individuals.

Somatic Genetic Changes in Breast Cancer Abnormalities in these and other genes can also be acquired, leading to breast cancer and its specific behavior. The specific causes of these mutations in breast cancer are generally unknown. A *p53* mutation is present in ~40% of human breast cancers as an acquired defect. Acquired mutations in *PTEN* occur in ~10% of the cases. *BRCA1* mutation in sporadic primary breast cancer has not been reported. However, decreased expression of *BRCA1* messenger RNA (mRNA) (possibly via gene methylation) and abnormal cellular location of the BRCA1 protein have been found in some breast cancers. Loss of heterozygosity of *BRCA1* and *BRCA2* suggests that tumor-suppressor activity may be inactivated in sporadic cases of human breast cancer.

Approximately 80% of all breast cancers overexpress ER. Many of these cancers respond to antiestrogen treatments. Likewise, increased expression of the dominant oncogene *erbB2*, often due to amplification, occurs in approximately one-quarter of human breast cancer cases. The product of this gene, HER2, contributes to transformation of human breast epithelium. HER2 is the target of effective systemic therapy in adjuvant and metastatic disease settings.

A series of other acquired "driver" mutations has been identified in sporadic breast cancer by major sequencing consortia. Of interest, activating mutations in the gene that encodes for ER (*ESR1*) have been reported in ~20% of metastatic breast cancers after prior endocrine treatment, but almost never in untreated primary cancers. Similarly, activating mutations in *erb2* are reported in 3–5% of breast cancers. Both these findings may have therapeutic implications. Multiple academic and commercial entities are offering exon sequencing for these and many other possible mutations on either tumor biopsies or on circulating DNA shed from tumors. Unfortunately, most occur in no more than 5% of cases. Further, they are either not associated with any known targeted therapeutic agents, or the abnormalities are associated with response to an agent in another disease, but at present not in breast cancer. Therefore, while appealing, "personalized medicine" is for now more of a dream than a reality.

PREVENTION OF BREAST CANCER

One major reason to determine risk would be to develop and apply effective prevention strategies. These might either be lifestyle changes or surgical or pharmacologic interventions. At present, although diet and exercise are certainly recommended approaches to healthy living, none has been proven to specifically decrease a woman's risk of breast cancer. Avoidance of combined estrogen/progestin HRT avoids their associated increased risk of breast cancer.

Prophylactic removal of the breasts is an effective, albeit usually unacceptable, preventive strategy. Retrospective and prospective registries have demonstrated that bilateral prophylactic mastectomies reduce the risk of breast cancer incidence and mortality by more than 95%. Because breasts are not encapsulated organs, some normal breast tissue is always left behind, and therefore women who elect to have prophylactic mastectomies should be counseled that they still have some risk of developing a new breast cancer. Because of its obvious adverse effect on sexuality, cosmesis, and breast-feeding, this approach is not considered appropriate for a woman of average risk.

As noted, cessation of menses and/or other means of reducing estrogen exposure, such as aromatase inhibition in postmenopausal women, and use of the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene are effective methods to lower breast cancer risk. So-called chemoprevention with SERMs or aromatase inhibition lowers risk of ER-positive breast cancer by approximately one-third to one-half, although it has no effect on the more lethal ER-negative breast cancers. Of interest, prophylactic bilateral oophorectomy and salpingo-oophorectomy, which is often performed in women with high genetic risk (such as those with inherited *BRCA1/2* deleterious SNPs), also reduces breast cancer risk.

SCREENING FOR BREAST CANCER

A recent review by the American Cancer Society (ACS) supports the perception that screening mammography reduces breast cancer mortality by one-quarter to one-third in women aged ≥50 years. The data for

a relative reduction in breast cancer mortality for women between ages 40 and 50 years are almost as positive; however, since the incidence of breast cancer is much lower in younger women, the number of women whose lives are saved is much lower than in older women, and because they have denser breasts, and therefore there are more false-positive findings and the positive predictive factor is lower.

Further, screening mammography and early detection are more likely to identify tumors at a stage more appropriate for conservative local therapy. Better technology, including digitized mammography, routine use of magnified views, and greater skill in mammographic interpretation, have all improved the accuracy of mammography. Newer diagnostic techniques (magnetic resonance spectroscopy [MRI], positron emission tomography [PET], etc.) appear to have higher sensitivity, but their specificity is often lower. Further, many authors have raised concern about diagnosis of anatomically defined cancers that may be biologically insignificant, raising the specter of overdiagnosis and treatment. Since none of these newer technologies has been shown to be superior to mammography in regards to mortality reduction, screening of women with standard risk by any technique other than mammography is not recommended.

Screening with more sensitive but less specific techniques, in particular MRI, is recommended for women with genetic risk, such as *BRCA1* or *BRCA2* carriers or those with Li-Fraumeni, Cowden's, or Bannayan-Riley-Ruvalcaba syndromes; untested first-degree relatives of women with cancer; women with a history of radiation therapy to the chest between ages 10 and 30 years; or women with a lifetime risk of breast cancer of at least 20%. In these women, the positive predictive value of MRI is higher because of the higher incidence of cancer, and, furthermore, many of them are considering prophylactic mastectomy as an alternative, and therefore the lower specificity and risk of a false positive finding has been considered more acceptable.

Research does not show a clear benefit of individual self-examination or by physical breast examinations done by a health professional. Because of this lack of evidence, regular clinical breast examination and breast self-examination are not recommended. Still, all women should be familiar with how their breasts normally look and feel and report any changes to a health care provider right away. Moreover, because the breasts are a common site of potentially fatal malignancy in women, examination of the breast is an essential part of the physical examination. Although breast cancer in men is unusual, unilateral lesions should be evaluated in the same manner as in women, with the recognition that gynecomastia in men can sometimes begin unilaterally and is often asymmetric.

EVALUATION OF BREAST MASSES IN MEN AND WOMEN

Virtually all breast cancer is diagnosed by biopsy of a nodule detected either on a mammogram or by palpation. Algorithms have been developed to enhance the likelihood of diagnosing breast cancer and reduce the frequency of unnecessary biopsy.

THE PALPABLE BREAST MASS

If a patient brings a breast abnormality to the attention of a health care giver, or if a lesion is appreciated during routine examination, proper attention needs to be given to ensure appropriate evaluation and treatment. Lesions with certain features are more likely to be cancerous. These include enigmatically, painless masses, and, more importantly, hard, irregular masses, especially if tethered or fixed to the underlying chest wall. In contrast, those that are cystic appearing on physical examination or are associated with pain, are less likely malignant. However, none of these is a terribly accurate positive or negative finding. Likewise, a negative mammogram in the presence of a persistent lump in the breast does not exclude malignancy. Any concerning, and persistent, breast finding should be referred to an experienced breast diagnostician.

In premenopausal women, lesions that are either equivocal or nonsuspicious on physical examination should be reexamined in 2–4 weeks, during the follicular phase of the menstrual cycle. Days 5–7 of the cycle are the best time for breast examination. A dominant mass in a postmenopausal woman or a dominant mass that persists through a menstrual cycle in a premenopausal woman should be referred to an experienced breast diagnostician for further evaluation, including biopsy if appropriate.

Several points are essential in pursuing these management decision trees. First, risk-factor analysis is not part of the decision structure. No constellation of risk factors, by their presence or absence, can be used to exclude biopsy. Second, fine-needle aspiration should be used only in centers that have proven skill in obtaining such specimens and analyzing them. The patient and physician must be aware of a 1% risk of false negatives. Third, additional technologies such as MRI, ultrasound, and sestamibi imaging cannot be used to exclude the need for biopsy; although in unusual circumstances, they may provoke a biopsy.

THE ABNORMAL MAMMOGRAM

Diagnostic mammography, which is performed after a palpable abnormality has been detected, should not be confused with *screening mammography*, which is performed in an asymptomatic woman with no prediscovered abnormalities. Diagnostic mammography is aimed at evaluating the rest of the breast before biopsy is performed or occasionally is part of the triple-test strategy to exclude immediate biopsy.

Subtle abnormalities that are first detected by screening mammography should be evaluated carefully by compression or magnified views. These abnormalities include clustered, heterogeneous, linear, and branching microcalcifications; densities (especially if spiculated); and new or enlarging architectural distortion. For some nonpalpable lesions, ultrasound may be helpful either to identify cysts or to guide biopsy. If there is no palpable lesion and detailed mammographic studies are unequivocally benign, the patient should have routine follow-up appropriate to the patient's age. If a nonpalpable mammographic lesion has a low index of suspicion, mammographic follow-up in 3–6 months is reasonable. However, it cannot be stressed too strongly that in the presence of a breast lump a negative mammogram does not rule out cancer, and if it persists or enlarges during follow-up, the patient should be referred to an experienced breast diagnostician.

BREAST MASSES IN THE PREGNANT OR LACTATING WOMAN

During pregnancy, the breast grows under the influence of estrogen, progesterone, prolactin, and human placental lactogen. Lactation is suppressed by progesterone, which blocks the effects of prolactin. After delivery, lactation is promoted by the fall in progesterone levels, which leaves the effects of prolactin unopposed. The development of a dominant mass during pregnancy or lactation should never be attributed to hormonal changes. A dominant mass must be treated with the same concern in a pregnant woman as any other. Breast cancer develops in 1 in every 3000–4000 pregnancies. Stage for stage, breast cancer in pregnant patients is no different from premenopausal breast cancer in nonpregnant patients. However, pregnant women often have more advanced disease because the significance of a breast mass was not fully considered and/or because of endogenous hormone stimulation. Persistent lumps in the breast of pregnant or lactating women *cannot* be attributed to benign changes based on physical findings; such patients should be promptly referred for diagnostic evaluation.

BENIGN BREAST MASSES

Only ~1 in every 5–10 breast biopsies leads to a diagnosis of cancer, although the rate of positive biopsies varies in different countries and clinical settings. These differences may be related to interpretation, medico-legal considerations, and availability of mammograms. The vast majority of benign breast masses are due to "fibrocystic" changes, a descriptive term for small fluid-filled cysts and modest epithelial cell and fibrous tissue hyperplasia. The subset of women with ductal or lobular cell proliferation (~30% of patients), particularly the small fraction (3%) with atypical hyperplasia, have a fourfold greater risk of developing breast cancer than those women who have not had a biopsy. The increase in the risk is about nine-fold for women in this category who also have an affected first-degree relative. Thus, careful follow-up of these patients is required. By contrast, patients with a

benign biopsy without atypical hyperplasia are at little risk and may be followed routinely.

STAGING

Correct staging of breast cancer patients is of extraordinary importance. Not only does it permit an accurate prognosis, but in many cases, therapeutic decision making is based largely on the TNM (primary tumor, regional nodes, metastasis) classification. Comparison with historic series should be undertaken with caution, as the staging has changed several times in the past 20 years. The current staging is complex and results in significant changes in outcome by stage as compared with prior staging systems.

NONINVASIVE BREAST CANCER

Breast cancer develops as a series of molecular changes in the epithelial cells that lead to ever more malignant behavior. Increased use of mammography has led to more frequent diagnoses of noninvasive breast cancer. These lesions fall into two groups: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (lobular neoplasia or LCIS). The management of both entities is controversial.

Ductal Carcinoma In Situ Proliferation of cytologically malignant breast epithelial cells within the ducts is termed *ductal carcinoma in situ* (DCIS). Atypical hyperplasia may be difficult to differentiate from DCIS. At least one-third of patients with untreated DCIS develop invasive breast cancer within 5 years. However, many low-grade DCIS lesions do not appear to progress over many years; therefore, many patients are overtreated. Unfortunately, there is no reliable means of distinguishing patients who require treatment from those who may be safely observed.

For many years, the standard treatment for DCIS was mastectomy. Although no studies have compared breast-preserving therapy to mastectomy, the ~100% ten year survival rates with the former suggest that it is a satisfactory strategy. Breast-preserving surgery alone may also be acceptable. However, although survival was identical in the two arms of a randomized trial comparing wide excision plus or minus irradiation, the latter caused a substantial reduction in the local recurrence rate as compared with wide excision alone. Addition of tamoxifen or an aromatase inhibitor (AI) to any DCIS surgical/radiation therapy regimen further improves local control. However, in the largest trial comparing the two in DCIS, anastrozole did not improve distant disease-free or overall survival compared to tamoxifen.

Several prognostic features may help to identify patients at high risk for local recurrence after either lumpectomy alone or lumpectomy with radiation therapy, and therefore might provide an indication for mastectomy. These include extensive disease; age <40; and cytologic features such as necrosis, poor nuclear grade, and comedo subtype with overexpression of *erbB2*. In summary, it is reasonable to recommend breast-preserving surgery for patients who have a localized focus of DCIS with clear margins followed by breast irradiation and tamoxifen or anastrozole. For patients with localized DCIS, axillary lymph node dissection is unnecessary.

More controversial is the question of what management is optimal when there is any degree of invasion. Because of a significant likelihood (10–15%) of axillary lymph node involvement even when the primary lesion shows only microscopic invasion, it is prudent to do at least a sentinel lymph node sampling for all patients with any degree of invasion. Further management is dictated by the presence of nodal spread.

Lobular Neoplasia Proliferation of cytological malignant cells within the lobules is termed *lobular neoplasia* (LCIS). Nearly 30% of patients who have had adequate local excision, or incidentally discovered LCIS, or just a biopsy a needle biopsy of a suspicious area develop a subsequent breast cancer (usually infiltrating ductal carcinoma) over the next 15–20 years. Ipsilateral and contralateral cancers are equally common. Therefore, LCIS may be considered a premalignant condition with associated elevated risk of subsequent breast cancer, rather than a form of malignancy itself, and aggressive local management seems unreasonable. Management options include careful observation with routine mammography or chemoprevention with either a SERM or an AI (for postmenopausal women) for 5 years as well as concurrent and subsequent annual mammography and semiannual physical examinations. A third option, although no more effective and associated with substantial cosmetic, and perhaps emotional, morbidity is bilateral prophylactic mastectomy.

TREATMENT

Breast Cancer

BIOLOGICAL CONSIDERATIONS

One of the most important advances in our understanding of breast cancer has been the appreciation that it can be classified by gene expression patterns into a series of subtypes.

1. **Luminal:** Luminal breast cancers are almost always positive for ER and negative for HER2 amplification. They are divided into two groups:
   - **Luminal A:** Luminal A tumors have the highest levels of ER expression as well as of downstream ER-dependent genes, such as PgR. They are almost universally negative or low in HER2, and they have low proliferative thrust. They are usually low grade, are most likely to respond to endocrine therapy, and have a favorable prognosis. They appear to be less responsive to chemotherapy.
   - **Luminal B:** Luminal B breast cancers are also of luminal epithelial origin, but with a gene expression pattern distinct from luminal A. They tend to be PgR negative and have evidence of higher proliferative activity. They also tend to express HER2, but not to the level of the so-called "HER2 amplified" cancers. Their grade is more often higher than luminal A cancers. Prognosis is somewhat worse. They may be more sensitive to chemotherapy.
2. ***HER2* amplified:** These tumors have amplification of the *HER2* gene on chromosome 17q and frequently exhibit coamplification and overexpression of other genes adjacent to *HER2*. Historically the clinical prognosis of such tumors was poor. However, with the advent of trastuzumab and other targeted therapies, the clinical outcome of *HER2* positive patients is markedly improved compared to 20 or more years ago.
3. **Basal:** These ER/PgR–negative and *HER2*-negative tumors (so-called triple negative) are characterized by markers of basal/myoepithelial cells. They tend to be high grade, and express cytokeratins 5/6 and 17 as well as vimentin, p63, CD10, α-smooth muscle actin, and epidermal growth factor receptor (EGFR). Patients with *BRCA1* mutations also fall within this molecular subtype. They also have stem cell characteristics.
4. **Normal breast-like:** These tumors have a gene expression profile reminiscent of nonmalignant "normal" breast epithelium. Prognosis is similar to the luminal B group. This subtype is somewhat controversial and may represent contamination of the sample by normal mammary epithelium.
5. **Claudin-low:** These cancers are often triple negative but they have low expression of cell-cell junction proteins including E-cadherin. They are frequently associated with lymphocytic infiltration.

GENERAL TREATMENT CONSIDERATIONS

Treatment of breast cancer depends on whether the patient does or does not have evidence of distant (meaning outside the breast, chest wall, and regional lymph nodes) metastases, as detected by scintigraphic or radiologic imaging and biopsy. For patients with no evidence of detectable distant metastases, the goal of therapy is cure, or at least substantial survival prolongation, and is divided into primary and systemic considerations. Primary therapies consist of surgical and radiation treatments directed toward the breast and locoregional lymph nodes. These approaches are designed to excise and eliminate the cancer and sterilize unaffected breast tissue as appropriate. Adjuvant systemic

treatments, consisting of antiestrogen (or endocrine), anti-HER2, and/or chemotherapies, are given to treat micrometastases that may have already escaped to distant sites but are not yet detectable.

All treatments for breast cancer are based on prognostic and predictive factors. Prognostic factors provide an indication of how likely a cancer will recur, either locally or in distant organs, in the future if a patient is not treated with the respective treatments. Predictive factors are used to determine if a given treatment is likely to work or not, assuming the patient's prognosis justifies treatment (or further treatment assuming the patient has been treated in some manner already).

Prognostic features guide both whether and what type of primary and adjuvant systemic treatments should be pursued. Anatomic prognostic features include visual and physical examination findings of locally advanced breast cancer (T4 lesions: skin erythema ["inflammatory"] or edema ["peau d'orange"], nodules, or ulceration or tumor fixation to the chest wall). In patients without any of these findings, the most important prognostic features are tumor size and lymph node status (TN in the staging system). As discussed below, biologic features, such as histologic tumor grade as well as ER, PgR, and HER2, are also prognostic. Over the last decade, several multiparameter tests based on gene expression have been developed to determine prognosis in patients who have node-negative, ER-positive, and HER2-negative disease.

Predictive features are usually used to guide systemic therapies. These include ER for endocrine treatments and HER2 for anti-HER2 therapies, such as trastuzumab. There are no established predictive factors to predict response to radiation treatment. The issue of chemoresistance in luminal A cancers is under large-scale investigations.

EARLY-STAGE BREAST CANCER

Primary Therapies Prior to 1980, the Halsted radical mastectomy, in which the breast, chest wall muscles, and complete axillary nodal contents were removed, was the standard treatment of choice for women with newly diagnosed breast cancer. In the 1980s, prospective randomized trials demonstrated that recurrence and survival rates were the same with the less disfiguring modified radical mastectomy, in which the chest wall muscles were preserved and only a sampling of axillary lymph nodes were removed.

In the same decade, breast-conserving treatments, consisting of the removal of the primary tumor by some form of surgical excision (designated as lumpectomy, quadrantectomy, or partial mastectomy), were shown to result in equal, if not slightly superior, to that associated with mastectomy. Several of these trials also demonstrated that the in-breast recurrence rate was quite high in the absence of breast radiation, while it was reduced substantially if radiation was provided. Therefore, for women undergoing breast conservation, postlumpectomy radiation is usually indicated, although it may be less necessary and withheld in older women with ER-positive, node-negative breast cancer, since their risk of subsequent in-breast recurrence is quite low with surgery and endocrine therapy only. When lumpectomy with negative tumor margins is achieved and radiation is delivered appropriately, breast conservation is associated with a recurrence rate in the breast of ≤5%.

Not all patients are candidates for breast-conserving therapy. Contraindications include large tumor to breast ratio, inability to achieve clear margins with adequate cosmesis after extensive surgery, multifocal cancers, extensive four-quadrant DCIS, and inability to receive radiation. The latter issue arises in women with dermal autoimmune disease (such as lupus erythematosus), prior radiation to the site, and/or lack of available radiation treatment facilities. Further, although not contraindicated, breast-conserving therapy may be less cosmetically acceptable than mastectomy with reconstruction if the nipple-areolar complex is involved with cancer and must be sacrificed. This is a personal choice, and some women prefer mastectomy, especially those with high genetic risks for second breast cancers.

For patients who do undergo mastectomy, postoperative chest wall and regional nodal radiation is also associated with an improvement in survival if they have a high risk of local-regional recurrence, such as tumors ≥5 cm, four or more positive axillary lymph nodes, or postoperative positive margins. Postmastectomy radiation is not indicated in women with cancers <2 cm, negative lymph nodes, and negative margins. It is considered for women who fall into the areas between these (2–5 cm, one to three positive nodes, or close margins), and is usually recommended if a patient has one to three involved axillary lymph nodes.

At present, nearly one-third of women in the United States are managed by lumpectomy, and recent data suggest that the fraction of women treated with breast-conserving therapy is decreasing. It appears that many women still undergo mastectomy who could safely avoid this procedure and probably would if appropriately counseled.

Axillary node sampling or dissection is unnecessary in many cases. Sentinel lymph node mapping and biopsy (SLNB) is generally the standard of care for women with localized breast cancer and clinically negative axilla. If SLNB is negative, more extensive axillary surgery is not required, avoiding much of the risk of lymphedema following more extensive axillary dissections. Even in the presence of sentinel lymph node involvement, further axillary surgery may not be required for selected patients, such as older women and those with ER-positive cancers.

The survival of patients who have recurrence in the breast after proper treatment (adequate surgery and radiation if indicated) is somewhat worse than that of women who do not, but it is not worse than those who suffer local-regional recurrence after mastectomy. Thus, local-regional recurrence is a negative prognostic variable for long-term survival but not the *cause* of distant metastasis. Most patients should consult with a radiation oncologist before making a final decision concerning local therapy. However, a multimodality clinic in which the surgeon, radiation oncologist, medical oncologist, and other caregivers cooperate to evaluate the patient and develop a treatment plan is usually considered a major advantage by patients.

Adjuvant Systemic Therapies The concept of adjuvant systemic therapy is based on the observation that cancer is a condition of genetic instability, and with increasing generations of cellular replication, genetic abnormalities accumulate. Although these occur randomly, and therefore may lead to sensitivity or resistance to therapies, the latter is of greater concern. Thus, as a consequence of accumulation of mutations to resistance, almost all patients with metastatic breast cancer are destined to die with, if not of their cancer.

However, treatment with the same therapies administered earlier, in the setting of micrometastatic disease only, has been repeatedly shown to be more effective than waiting until symptomatic, documented metastases occur. Put simply, the use of systemic therapy as an adjuvant to local management of breast cancer substantially improves survival. More than half of the women who would otherwise die of metastatic breast cancer remain disease-free and experience considerable survival advantaged when treated with the appropriate adjuvant systemic regimen. These data have grown more and more impressive with longer follow-up and more effective regimens.

PROGNOSTIC VARIABLES As noted, prognostic factors help define who most likely needs, or perhaps more importantly does not need, adjuvant systemic therapy. The most important prognostic variables are provided by *tumor staging: tumor size (T), lymph node status (N) and detectable distant metastases (M)* **(Table 75-1)**. *Histologic classification* of the tumor has also been used as a prognostic factor. Tumors with a

TABLE 75-1 5-Year Survival Rate for Breast Cancer by Stage

STAGE	5-YEAR SURVIVAL, %
0	99
I	92
IIA	82
IIB	65
IIIA	47
IIIB	44
IV	14

Source: Modified from data of the National Cancer Institute: Surveillance, Epidemiology, and End Results (SEER).

poor nuclear grade have a higher risk of recurrence than tumors with a good nuclear grade. Semiquantitative measures such as the Elston score improve the reproducibility of this measurement. Importantly, there is no need to perform imaging for distant metastases in a patient with no signs or symptoms of widespread disease and who has a T3 or less tumor and fewer than four involved axillary lymph nodes.

Adjuvant systemic therapy may not be needed at all for patients with very small (<1 cm) tumors and negative lymph nodes. However, there is no patient with invasive breast cancer who does not have some risk of subsequent distant metastases, and therefore who might not benefit at all. This consideration raises two issues: (1) the differences in odds of benefit and odds of toxicities of the various types of therapies and (2) the judgment between the patient and her caregiver regarding the calculated absolute benefit-risk ratio for specific types of adjuvant systemic treatments.

There are three types of adjuvant systemic therapies: (1) chemotherapy; (2) endocrine; and (3) anti-HER2 therapies. The decision whether to apply each of these depends on prognostic and predictive features as well as the combined judgment of the patient and caregiver. For example, a patient might be much more likely to accept endocrine therapy for a very small potential benefit than she would accept chemotherapy for the same calculated advantage, since the former is much less often associated with either life-taking, life-threatening, or permanently life-changing toxicities than the latter. Thus, one has to consider prognostic and predictive factors for each type of therapy, separately.

The greatest controversy concerns the recommendation for adjuvant *chemotherapy*, since there is no good predictive factor for this class of treatments, and the decision must be made on prognosis alone. Large overview analyses suggest that chemotherapy reduces the risk of recurrence over the 10 years subsequent to primary diagnosis by approximately one-third. For patients with positive lymph nodes and/or features that render the cancer T4, the risk of distant recurrence (and thus not being cured) over that decade is 50% or higher. Therefore, a one-third reduction of at least 50% means that 15–20%, or more, women will be cured who would not have been in the absence of adjuvant chemotherapy. The life-taking, life-threatening, or permanently life-changing toxicities of adjuvant chemotherapy are ~1–2%, and therefore almost all medical oncologists would recommend adjuvant chemotherapy in this setting.

In contrast, there is rarely justification for adjuvant chemotherapy in most women with tumors <1 cm in size whose axillary lymph nodes are negative. However, this decision is very much weighed by the expression of ER and HER2. For example, the risk of recurrence of such a patient whose tumor is negative for ER, PgR, and HER2 (so-called triple-negative breast cancer) over the succeeding 10 years without any adjuvant is ~15%. If chemotherapy reduces this risk by approximately one-third or more, which is what large overview analyses suggest, then 5%, or perhaps even higher, of patients will be cured who would otherwise be destined to die of their disease. Likewise, a patient with ER and PgR-negative, but HER2-positive, disease has a slightly worse prognosis (risk of recurrence over 10 years is ~20%), and will benefit not only from the adjuvant chemotherapy but from anti-HER2 therapy as well, so that her potential absolute benefit is even higher. Many, but not all, clinicians would recommend adjuvant chemotherapy for such patients.

On the other hand, patients with ER-positive disease have a better prognosis than those with ER-negative breast cancer, and adjuvant endocrine therapy will further reduce the odds of recurrence by approximately one-half. Therefore, the same patient in the example above (<1 cm, node negative) but who has an ER-positive and HER2-negative cancer has a lower initial risk of recurrence (~10% over 10 years). Given the relatively low life-taking, life-threatening, or permanently life-changing toxicities, she is very likely to accept adjuvant endocrine therapy, further lowering her estimated risk of recurrence to ~5%. If chemotherapy reduces this risk by approximately one-third, no more than 1–2% of patients will benefit. This potential benefit is approximately the same as the number of patients who will suffer life-taking, life-threatening, or permanently life-changing toxicities. Thus, in this case, most clinicians would recommend adjuvant endocrine, but not chemotherapy.

These examples represent extremes. In the screening era, up to 30% of newly diagnosed patients have T2-3, node-negative, ER-positive cancers. These patients have an intermediate risk between the two extremes, and the calculated absolute benefit of adjuvant chemotherapy is ~3–5%. It is unclear if this small but real benefit is sufficient to justify adjuvant chemotherapy. Detection of breast cancer cells either in the circulation or bone marrow is associated with an increased relapse rate. However, the finding of bone marrow micrometastases only portends a slightly worse prognosis, especially in node negative patients, and bone marrow biopsies are not recommended in patients with early stage disease.

The most exciting development in this area is the use of gene expression arrays to analyze patterns of tumor gene expression, especially for node-negative, ER-positive cancers. Several groups have independently defined gene sets that reliably predict disease-free and overall survival far more accurately than any single prognostic variable. The Oncotype DX® Recurrence Score (RS) analysis of 21 genes was the first such assay to be adopted. A number of retrospective and more recently prospective studies have documented its utility in identifying patients with node-negative, ER-positive breast cancer whose prognosis, assuming adequate adjuvant endocrine therapy, is so good that they can forego adjuvant chemotherapy. Basically, the 30–50% of patients with ER positive, node negative, but low RS, appear to have luminal A breast cancers, and they do not need chemotherapy, whereas those with high RS appear to have luminal B cancers and the benefits of adjuvant chemotherapy clearly outweigh the risks. For those with intermediate RS, the answer is still unclear and has been the focus of now completed, but as yet unreported, prospective trials.

More recently, other assays, including the Prosigna,® EndoPredict,® and Breast Cancer Index® have also been shown to have clinical utility in this setting. Only one of these tests should be ordered for a single patient, since they do not always give the same results and there are no data to determine which, in the case of discordance, might be "correct." Also, the use of such standardized risk assessment tools such as Adjuvant! Online (*www.adjuvantonline.com*) is very helpful. These tools are highly recommended in otherwise ambiguous circumstances.

Several *measures of tumor growth rate* correlate with early relapse, but their use is problematic due to analytical variability. Of these, assessment using immunochemical assays for the proliferation marker, Ki67, is the most widespread. However, there is substantial lab-to-lab variability and disagreement regarding optimal cut points. At present, in standard practice outside of a highly skilled laboratory, use of Ki67 is not recommended to make clinical decisions.

Molecular changes in the tumor are also useful. Tumors that overexpress *erbB2* (HER2/neu) have a worse prognosis, but expression of this gene for prognosis is most important in patients with ER-positive, node-negative disease. Indeed, patients with HER2-positive breast cancer are so likely to have a high RS that it is not recommended that the Oncotype DX,® or for that matter any of the other multiparameter assays, be ordered. HER2 should be performed on every breast cancer biopsy, however, because of its predictive role for anti-HER2 therapies.

Predictive Factors to Choose Adjuvant Systemic Therapy

The decision to recommend AST is also based on predictive factors; those that provide a prediction of the likelihood that a given class, or even specific drug within a class, will have activity or not. The two important predictive factors, which should be ordered in all breast cancer biopsies (primary or metastatic), are ER and HER2.

There is no detectable benefit in patients with ER-poor, or -negative, cancers, whereas adjuvant endocrine therapy reduces the risk of recurrence by one-half or more in patients with ER-rich cancers. ER is most commonly measured by counting the percent of positive cells within the cancer after immunohistochemical (IHC) staining. Endocrine therapy is recommended for any patient with ≥10% positive cells, whereas it is not for those whose cancers only have 0–1% staining. The evidence supporting benefit in 1–9% cases is weak, but given the potential benefit and relatively low toxicities of endocrine therapy, it is recommended for patients in this circumstance, with a low threshold for discontinuation if side effects are intolerable.

HER2 is the target for anti-HER2 therapies. Adjuvant trastuzumab therapy reduces the risk of distant recurrence by one-third or more, with associated substantial risk of dying of breast cancer. Most, if not all, of the large adjuvant trastuzumab trials have been performed in patients with HER2-"positive" breast cancer. HER2 status is determined using either IHC staining for protein overexpression, or fluorescent in situ hybridization (FISH) for gene amplification. IHC staining of 3+ (on a scale of 0–3+) is considered positive, whereas 0–1+ is considered negative. For cases with 2+ staining, reflex FISH analysis is recommended. FISH can either be used as the initial evaluation, or for additional evaluation in IHC 2+ cases. FISH results are considered positive if the ratio of HER2 to centromere signal on chromosome 17 is ≥2.0. There is no reason to do FISH if IHC is 3+ or 0–1+, nor is there reason to order IHC testing if FISH is ≥2.0. If note, preclinical studies and retrospective analyses of a few selected cases from the prospective randomized trials have suggested that perhaps trastuzumab might be effective in cases with IHC 1–2+ results. A large prospective randomized clinical trial addressing this issue is completed but not yet reported.

There are no reliable predictive factors for chemotherapy, in general or for specific types of chemotherapies. It has been hypothesized that chemotherapy may be more active in ER-negative and/or HER2-positive cancers. More recently, this issue has evolved to imply that luminal B cancers may be more chemosensitive, whereas luminal A cancers are perceived to be relatively chemoresistant. At present, none of the tests for intrinsic subtype should be used to determine whether to give chemotherapy or not, based on *prediction* of resistance in patients with poor *prognosis*, such as those with T4 or node-positive disease. Attempts to identify reliable predictive factors for individual classes of chemotherapeutic agents (such as anthracyclines, alkylating agents, or taxanes) have been unsuccessful. The platin salts (carbo-, cis -platin) may have higher activity in patients with triple-negative breast cancer and perhaps in patients with HER2-positive disease.

Adjuvant Regimens If chemotherapy is indicated, it should include multiple agents, either in combination or as sequential single agents. If indicated, anti-HER2 therapy should include at least 1 year of trastuzumab, and preliminary data have supported addition of pertuzumab for at least three months. Endocrine therapy should be administered to patients with ER-positive breast cancer following completion of chemotherapy and administered for at least 5 years, and probably longer.

Endocrine Therapy There are two proven endocrine therapy strategies: the SERM, tamoxifen, or estrogen ablation. In addition to being effective in preventing new cancers and reducing the risk of local-regional recurrences in patients with DCIS, tamoxifen reduces the risk of distant recurrence and death due to invasive breast cancer by ~40% over the decade following diagnosis. It is equally effective in pre- and postmenopausal women, although it may be slightly less effective in very young (<40 years) patients. Because tamoxifen is a SERM, it has mixed ER antagonism (in the breast and brain) and agonism (in the bone, liver, and uterus). Therefore, it is active against breast cancer in the prevention, adjuvant, and metastatic settings, but frequently causes hot flashes. The agonistic effect results in reduction of osteopenia/osteoporosis, especially in postmenopausal women, but it increases thrombosis and endometrial cancers due to this effect in the liver and uterus, respectively.

Estrogen depletion can be achieved surgically in premenopausal women by oophorectomy or ovarian suppression with a gonadotropin-releasing hormone super-agonist (GnRH agonist), such as goserelin, that results in tachyphylaxis of the pituitary. However, women with nonfunctioning ovaries, whether induced or by natural menopause, still produce small amounts of estrogen. Estrogen production in these women occurs by adrenal synthesis of estrogen precursors (testosterone, dehydroepiandrosterone [DHEA]) that are converted to estradiol and estrone by aromatase activity in peripheral fat and possible cancer cells. In postmenopausal women, circulating estrogen can be reduced to nearly imperceptible levels with the use of oral AIs. There are three such agents available (anastrozole, letrozole, and exemestane). Although there is no perceptible difference in activity or toxicity among the three AIs, they are all slightly more effective than tamoxifen.

It is recommended that all postmenopausal women with ER-positive breast cancer be treated for at least 3–5 years with an AI, unless there is a contraindication. The most common concern is the presence of severe osteoporosis, since this is the most frequent life-taking or life-threatening toxicity of the AIs. Likewise, ~15–20% of patients cannot tolerate the AIs due to musculoskeletal symptoms mimicking osteoarthritis and arthralgias. For both these groups of women, tamoxifen is a reasonable therapy, again assuming no contraindications exist. The most important of these is a past history of thrombosis, or high risk of cerebrovascular disease.

For premenopausal women, the decision of optimal endocrine therapy depends on prognosis and patient choice. Complete estrogen depletion is slightly more effective than tamoxifen alone, but it may also be associated with more bothersome side effects, such as hot flashes, vaginal dryness, and sexual dysfunction. Recent studies have suggested that complete estrogen depletion, consisting of either oophorectomy or chemical suppression of gonadotropins coupled with an AI, is indicated for women with worse prognosis, in particular node positivity. For those with more favorable prognosis, tamoxifen alone may be preferable. The AIs should not be administered to women with functioning, or dormant, ovaries, since the negative hypothalamic-pituitary feedback can result in a rebound hyperestrogenic production effect.

The duration of adjuvant endocrine treatment is unclear. Until recently, the standard recommendation was at least 5 years of therapy. Several studies have now demonstrated that although 5 years of adjuvant endocrine treatment clearly reduces the risk of recurrence during that time and for a few years after discontinuation, the annual risk of distant recurrence during the subsequent 15 years is 0.5–3%, depending on the initial T and N status. Further, so-called extended adjuvant endocrine therapy with either tamoxifen or an AI, for at least years 6–10, continues to reduce this late risk of relapse. The decision of whether to continue adjuvant endocrine therapy or not after 5 years must therefore take into consideration initial risk (T, N, grade), current side effects and potential cumulative toxicities, and the patient's perception of the relative and absolute benefits and risks.

Chemotherapy If adjuvant chemotherapy is indicated, as discussed above, one must consider the optimal regimen. Several studies, and a combined overview analysis, have demonstrated that multiple-agent chemotherapy is more effective than single agent. However, at least two studies have shown that sequential single-agent chemotherapy is as effective, and may be slightly less toxic, than simultaneous combination chemotherapy although it requires longer total duration to deliver. Administration of four to six cycles of chemotherapy appears to be optimal; one cycle is less effective than six, but more than six have generally increased toxicity without further efficacy.

Several chemotherapeutic agents have activity in the adjuvant setting. These include alkylating agents, (principally cyclophosphamide), anthracyclines (doxorubicin, epirubicin), antimetabolites (5-fluorouracil [5FU], capecitabine, methotrexate), and the taxanes (paclitaxel, docetaxel). Within classes, randomized trials have failed to demonstrate superiority of one agent versus another (e.g., doxorubicin vs epirubicin, or paclitaxel vs docetaxel). Dose escalation above an optimal dose is not more effective. The advantage of more frequent scheduling for most individual agents is unclear, but weekly or every other week paclitaxel is superior to every 3-week infusion, while, enigmatically, the opposite is true for its cousin, docetaxel. However, one benefit of a "dose dense" regimen (e.g., every 2 weeks with cytokine support vs every 3 weeks) is earlier completion of therapy.

These agents are usually combined within a single regimen. The oldest of these is cyclophosphamide, methotrexate, and 5FU (CMF) Addition of an anthracycline, or substitution of an anthracycline for the antimetabolite, improves outcomes slightly, albeit with slightly increased risk of heart failure and secondary leukemia. Addition of a taxane to an anthracycline-based regimen further reduces the chances of distant recurrence and death, albeit only modestly. Recent studies have suggested that addition of an anthracycline to a taxane-based

regimen is also modestly more effective than a taxane plus cyclophosphamide alone.

Which regimen is appropriate for a patient must be individualized based on prognosis, comorbid conditions, and the perspective of the patient. For example, the modest relative improvement of giving an anthracycline, cyclophosphamide, and a taxane (AC-T) may not transfer to a sufficiently large absolute improvement in survival in a patient with a relative small (T2) tumor and negative nodes, whereas that same relative reduction in death may translate to a sufficiently large absolute benefit in a patient with a worse prognosis. Therefore, the former patient might best be served with a taxane/cyclophosphamide (TC) regimen alone, while the latter might wish to accept the added risk of congestive heart failure and leukemia associated with the anthracyclines.

Neoadjuvant treatment involves the administration of adjuvant systemic therapy, most commonly chemotherapy, before definitive surgery and radiation therapy. The objective partial and complete response rates of patients with breast cancer to neoadjuvant chemotherapy exceed 75%. Thus, many patients will be "downstaged" by neoadjuvant chemotherapy. In this circumstance, patients with locally advanced, inoperable cancers may become candidates for surgery, and a small fraction of patients who are not considered eligible for breast-conserving surgery may become so due to shrinkage of their cancer. However, overall survival has not been improved using this approach as compared with the same drugs given postoperatively.

Patients who achieve a pathologic complete remission after neoadjuvant chemotherapy have a substantially improved survival compared to those who do not. It is unknown if this observation implies that the latter group did not benefit, or just had a worse initial prognosis, yet still gained some benefit. Although it is appealing to consider treating patients who have not had a pathologic complete response with even more chemotherapy, no studies have demonstrated that doing so improves overall survival. It is possible that these patients have chemoresistant disease, and therefore more chemotherapy will not be of value. However, it is essential that all patients, regardless of response to neoadjuvant chemotherapy, receive adjuvant endocrine therapy if they have an ER-positive breast cancer and adjuvant anti-HER2 therapy if their cancer is HER2 positive.

The neoadjuvant setting also provides an appealing opportunity for the evaluation of new agents. For example, a second HER2-targeting antibody, pertuzumab, has been shown to provide increased rates of pathologic complete response when combined with trastuzumab in the neoadjuvant setting. However, this approach is controversial; it is not clear that demonstration of higher response rates in the neoadjuvant setting will translate into better overall survival. For example, neoadjuvant trials demonstrated that combination trastuzumab and lapatinib resulted in higher pathologic complete responses than trastuzumab alone, yet a classically performed adjuvant trial failed to demonstrate improved survival for this regimen.

Chemotherapy is associated with nausea, vomiting, and alopecia in ~100% of patients, although the former two are well controlled with modern antiemetics. More importantly, chemotherapy causes neutropenia and fever, with a risk of infection of ~1%. The neutropenia can be prevented in most patients with appropriate use of the growth factor filgrastim. Secondary myelodysplasia and leukemia occur in ~0.5–1% of patients treated with anthracyclines as well as with high cumulative doses of cyclophosphamide, usually occurring within 2–5 years of treatment. The anthracyclines cause cumulative dose-related congestive heart failure, which occurs in ~1% of patients treated with standard four to five cycles at 60 mg/m^2. Peripheral neuropathy is the major dose-limiting and life-changing toxicity of the taxanes. Neuropathy occurs during treatment in ~15–20% of patients, and permanent, chronic neuropathy persists in 3–5%.

Anti-HER2 Therapy The emergence of therapies directed toward HER2 has been one of the great success stories of all oncology. Several trials have demonstrated that the humanized monoclonal antibody, trastuzumab, decreases both risk of recurrence and mortality in early-stage breast cancer. While trastuzumab administered after chemotherapy is effective, the accumulated evidence suggests that it is optimally delivered concurrently with chemotherapy, particularly in association with a taxane. However, concurrent treatment with an anthracycline is generally avoided, since the main toxicity of trastuzumab is cardiac dysfunction, which appears more often when the agent is delivered simultaneously with doxorubicin. Therefore, if an anthracycline is to be used, it is most commonly given prior to administration of trastuzumab—for example as AC for four cycles followed by a taxane plus trastuzumab. In patients with reasonably favorable prognosis (T1 or 2, node negative), single-agent paclitaxel plus trastuzumab appears to be an adequate regimen.

Twelve months of trastuzumab therapy is optimal. Randomized trials have demonstrated no additional benefit beyond 12 months, whereas 6 months has been shown to be inferior to 12. Trastuzumab is administered intravenously weekly or every 3 weeks.

Other, anti-HER2 treatments that are effective in the metastatic setting are appealing candidates for adjuvant therapies. As noted, neoadjuvant studies have demonstrated that chemotherapy with the combination of trastuzumab and pertuzumab results in higher pathologic complete responses than trastuzumab alone. The U.S. Food and Drug Administration (FDA) has granted this combination with accelerated approval, but final approval for the combination is pending more clinically meaningful results (disease-free, overall survival) from now-completed, classic adjuvant trials. Although lapatinib did not add to trastuzumab therapy and single-agent adjuvant lapatinib is inferior to single agent trastuzumab, another anti-HER2 tyrosine kinase inhibitor, neratinib, is superior to no anti-HER2 therapy. Neratinib has not been compared to trastuzumab, either as a single agent or in combination. Ado-trastuzumab emtansine, an antibody-drug conjugate, has activity in the metastatic setting even in patients who have progressed on trastuzumab and is now being tested in the adjuvant setting.

Skeletal Strengthening Agents Bone-strengthening agents that are commonly used to treat osteoporosis appear to have some, but limited, activity in preventing recurrent breast cancer, particularly in postmenopausal women. In an overview analysis of all trials addressing bisphosphonate therapy, improvement in overall survival was not significantly associated with any specific bisphosphonate class, treatment schedule, ER status, nodal status, tumor grade, or concomitant chemotherapy. No differences were seen in nonbreast cancer mortality. Bone fractures were reduced (relative risk [RR] 0.85, 95% confidence interval [CI] 0.75–0.97; 2 p = 0.02). At present, there is no clear consensus regarding routine use of bisphosphonates as an adjuvant therapy, although patients with advancing osteopenia or confirmed osteoporosis should be treated accordingly.

Novel Adjuvant Systemic Agents Other exciting adjuvant strategies are being tested, such as poly–ADP ribose polymerase (PARP) inhibitors in patients with known germline *BRCA1* or *BRCA2* mutations or those with triple-negative cancers that share similar defects in DNA repair in their etiology. The remarkable results of immune checkpoint inhibitors in other cancers have led to studies of this approach in both metastatic and post-neoadjuvant chemotherapy settings but are still considered highly investigational.

Recommendations for adjuvant therapy are found in **Table 75-2**.

STAGE III BREAST CANCER

Between 10 and 25% of patients present with so-called locally advanced, or stage III, breast cancer at diagnosis. Many of these cancers are technically operable, whereas others, particularly cancers with chest wall involvement, inflammatory breast cancers, or cancers with large matted axillary lymph nodes, cannot be managed with surgery initially. As noted, neoadjuvant compared may be no more effective than postsurgical adjuvant chemotherapy in prolonging survival, but the advantages of downstaging and therefore facilitating local therapy are accepted. Radiotherapy either to the chest wall after mastectomy or to the breast after tumor excision is almost always recommended, as is regional lymph node treatment. Adjuvant anti-HER2 and endocrine therapies are also used, as appropriate. These patients should be managed in multimodality clinics to coordinate surgery, radiation

TABLE 75-2 Suggested Approaches to Adjuvant Systemic Therapy[a]

NODAL STATUS	TUMOR SIZE	ER	HER2	MULTI-PARAMETER ASSAY	MENSTRUAL STATUS	CHEMOTHERAPY	ENDOCRINE THERAPY	ANTI-HER2 THERAPY
Positive	Any	Neg	Neg	Not indicated	Any	Multidrug	None	None
		Pos			Prem		Ovarian ablation + AI	
					Post		AI	
		Any	Pos		Any			Trastuzumab X12 mos; pertuzumab X12 weeks
Negative	<1 cm	Neg	Neg	Not indicated	Any	Consider multidrug	None	None
	≥1 cm	Neg	Neg		Any	Multidrug	None	None
	1–5 cm	Pos	Neg	Low RS	Prem	None	Tam	None
					Post		AI	None
				Intermed	Any	Consider multidrug	Tam (pre) or AI (post)	None
				Hi	Any	Multidrug	As for node pos	None
		Any	Pos	Not indicated	Any	Single-agent paclitaxel	As for node pos	Trastuzumab X12 mos

[a]Meant for guidance only. Each patient should be considered independently based on tumor and comorbidity status.

therapy, and systemic chemo-, endocrine, and anti-HER2 therapies, as indicated. Such approaches produce long-term disease-free survival in ~30–50% of patients.

BREAST CANCER SURVIVORSHIP ISSUES

The odds of surviving breast cancer have increased dramatically over the last 35 years due to a combination of early detection and more effective therapies. Although detection bias improves case fatality rates, age-adjusted mortality rates (mortality/100,000 women in society/year) have declined by >30%. Therefore, while ~40,000 American women will die of metastatic breast cancer in 2016, >60,000 would have suffered breast cancer mortality without these advances. Thus, all clinicians, not just oncologists, need to be aware of survivorship issues in patients with previously diagnosed and treated breast cancer.

No special follow-up procedures, such as serial circulating tumor biomarkers or systemic radiographic/scintigraphic imaging, are indicated in an asymptomatic patient with no physical findings of recurrence. Although randomized trials have demonstrated slightly higher incidence of detection of metastases with lead times of 3–12 months by screening asymptomatic patients compared to no special follow-up, there is no evidence of improved overall survival. If anything, one of these studies suggested a worse quality of life due to higher anxiety levels associated with the testing, and toxicities associated with earlier treatment in patients who were otherwise doing well at that time. These recommendations are summarized in Table 75-3.

It is important to carefully assess and evaluate new symptoms, considering whether they might be due to the cancer, the treatment, or an unassociated condition. Judgment needs to be used to decide if blood tests or imaging are required, in order to avoid missing a lesion for which appropriate treatment would improve the patient's quality of life but to diminish overtesting, with associated inconvenience, anxieties, false positives, and cost. Serial echocardiography should be performed every 3 months for patients on adjuvant trastuzumab, but not after it is discontinued.

Likewise, there is no role for serial monitoring for long-term, life-threatening toxicities associated with chemotherapy, such as myelodysplastic syndromes or congestive heart failure, since these are quite uncommon and likely to cause obvious symptoms requiring proper evaluation if they occur.

For patients on endocrine therapy, quality-of-life issues may be critical, including hot flashes, sexual difficulties, musculoskeletal complaints, and risk of osteoporosis. Although estrogen therapy, given orally, transdermally, or transvaginally, effectively reduces these side effects, it should not be given to these patients, since it may counteract the efficacy of the endocrine therapy. Nonhormonal treatments, such as selected antidepressants for hot flashes and musculo-skeletal symptoms, and counseling and water-based lubricants for sexual issues can be quite helpful. It is important to screen bone density in patients on an AI more frequently than is recommended for the average postmenopausal woman, since total estrogen depletion results in enhanced risk of osteoporosis and fracture. All women should be counseled to take daily calcium and vitamin D replacement, and if osteoporosis is present or osteopenia is worsening, bone strengthening agents should be administered.

THERAPY OF METASTATIC DISEASE

About 15–20% of patients treated for localized breast cancer develop metastatic disease in the subsequent decade after diagnosis.

TABLE 75-3 Surveillance Guidelines for Breast Cancer Patients after Primary and Adjuvant Therapy during Routine Follow-up

TEST	FREQUENCY
Recommended	
History; eliciting symptoms; physical examination	q3–6 months × 3 years; q6–12 months × 2 years; then annually
Breast self-examination	Monthly
Mammography	Annually
Pelvic examination	Annually as per age-appropriate guidelines (particularly for patients on SERMs)
Patient education about symptoms of recurrence	Ongoing
Coordination of care	Ongoing
Assessment of side effects if on endocrine therapy	Ongoing
Echocardiography if on trastuzumab	Every 3 months; discontinue when trastuzumab therapy complete
Not Recommended (if asymptomatic)	
Complete blood count	
Serum chemistry studies	
Chest radiographs	
Bone scans	
Ultrasound examination of the liver	
Computed tomography of chest, abdomen, or pelvis	
Tumor markers CA 15-3, CA 27-29, CEA, CTC	
Transvaginal endometrial ultrasonography	

Abbreviations: CA, cancer antigen; CEA, carcinoembryonic antigen; CTC, circulating tumor cell; SERM, selective estrogen receptor modulator.

Source: Recommended Breast Cancer Surveillance Guidelines, ASCO Education Book, Fall, 1997. From J Clin Oncol 15:2149, 1997; with permission.

Soft tissue, bony, and visceral (lung and liver) metastases all account for approximately one-third of sites of initial relapses. However, by the time of death, most patients will have bony involvement. Recurrences can appear at any time after primary therapy, but at least half occur >5 years after initial therapy. This observation is particularly true in patients with ER-positive disease, for whom the risk of distant recurrence remains constant for as long as 20 years and is the basis for recommendation of extended adjuvant endocrine therapy. It is now clear that a variety of host factors can influence recurrence rates, including depression and central obesity, and these diseases should be managed as aggressively as possible.

For patients with no prior history of metastases, a biopsy of suspicious physical or radiographic lesions should be performed, both for confirmation that the lesion does, indeed, represent recurrent cancer and to reevaluate ER and HER2, which can differ between the primary and metastatic lesions in up to 15% of cases. One should not assume that an apparent abnormality is a breast cancer metastasis. Many benign conditions, such as tuberculosis, gallstones, sarcoidosis, or other nonmalignant diseases, can mimic a recurrent breast cancer and are of course treated much differently.

Although treatable, metastatic disease is rarely if ever cured. The median survival for all patients diagnosed with metastatic breast cancer is <3 years, but with remarkable variability depending on intrinsic subtype and effective treatments. Patients with triple-negative metastatic breast cancer have the shortest expected survival, while those with ER-positive disease can expect to live the longest. HER2 positivity was initially found to be a very poor prognostic factor in metastatic breast cancer, but the availability of several effective treatments has improved the expected survival rates to at least those of ER-positive patients, if not better.

In the absence of cure, the overall goal of treatment of metastatic disease is palliation, or, put simply, to "keep the patient feeling as well as she can for as long as she can." A secondary goal is improved survival. It is important to point out that survival has not been improved by advocating more aggressive, or toxic, therapies, such as high-dose or combination chemotherapy, but rather by more selective and biologically based therapy, such as use of endocrine or anti-HER2 therapies in patients with ER- or HER2-positive breast cancers, respectively. Generally, a new treatment is continued until either progression or unacceptable toxicities are evident. These are both evaluated by serial history and physical examinations and periodic serologic evaluation for hematologic or hepatic abnormalities, as well as circulating tumor biomarker tests (assays for MUC1, such as CA15-3 or CA27.29, and for carcinoembryonic antigen or occasionally CA125). If all these evaluations fail to suggest progression, it is unlikely that imaging will contribute. However, if one or more of these suggest progression, whole-body imaging with either a PET/CT or a scintigraphic bone scan and dedicated CT are indicated. Brain imaging is not recommended unless the patient has some sort of central nervous system (CNS) symptom or finding.

The choice of therapy requires consideration of local therapy needs, specifically surgical approaches to particularly worrisome long-bone lytic lesions or isolated CNS metastases. New back pain in patients with breast cancer should be explored aggressively on an emergent basis; to wait for neurologic symptoms is a potentially catastrophic error. Metastatic involvement of endocrine organs can occasionally cause profound dysfunction, including adrenal insufficiency and hypopituitarism. Similarly, obstruction of the biliary tree or other impaired organ function may be better managed with a local therapy than with a systemic approach. Radiation as an adjunct to or instead of surgery is an important consideration for particularly symptomatic disease in long or vertebral bones, local-regional recurrences, and CNS metastases. In many cases, systemic therapy can be withheld while the patient is managed with appropriate local therapy.

There is no evidence that aggressive local treatment, such as excision; radiation; radiofrequency ablation; or cryotherapy of metastases to the lung, liver, or other distant sites, improves survival. Although appealing, these strategies are associated with increased toxicity and cost and should be reserved for palliation.

Selection of the systemic therapy strategy depends on the overall medical condition of the patient, the hormone receptor and HER2 status of the tumor, and clinical judgment. Because therapy of systemic disease is palliative, the potential toxicities of therapies should be balanced against expected response rates. Several variables influence the response to systemic therapy. For example, the presence of ER and PgR is a strong indication for endocrine therapy, even for patients with limited visceral (lung/liver) disease. On the other hand, patients with short disease-free intervals or rapidly progressive visceral disease (liver and lung) with end-organ dysfunction, such as lymphangitic pulmonary disease, are unlikely to respond to endocrine therapy.

Many patients with bone-only or bone-dominant disease have a relatively indolent course. Because the goal of therapy is to maintain well-being for as long as possible, emphasis should be placed on avoiding the most hazardous complications of metastatic disease, including pathologic fracture of the axial skeleton and spinal cord compression. Under such circumstances, systemic chemotherapy has a modest effect, whereas radiation therapy may be effective for long periods. Other systemic treatments, such as strontium-89, may provide a palliative benefit without inducing objective responses. Patients with bone involvement should receive concurrent bone strengthening agents, such as bisphosphonates or the humanized monoclonal anti-RANK ligand antibody, denosumab.

Many patients are inappropriately treated with toxic regimens into their last days of life. Often, oncologists are unwilling to have the difficult conversations that are required with patients nearing the end of life, and not uncommonly, patients and families can pressure physicians into treatments with very little survival value. Palliative care consultation and realistic assessment of treatment expectations need to be reviewed with patients and families. We urge consideration of palliative care consultations for patients who have received at least two lines of therapy for metastatic disease.

Endocrine Therapy ER-positive breast cancer will respond to endocrine therapy ~30–70% of the time. Potential endocrine therapies are summarized in Table 75-4. As in the adjuvant setting, one can choose among the SERM, tamoxifen, the AIs (anastrozole, letrozole, exemestane), or other strategies. Among the latter, the selective estrogen receptor downregulator (SERD), fulvestrant, has substantial activity. Early clinical studies with this drug were unexciting, but more recent studies have proven a very steep dose-response curve, and at higher levels (500 mg/month), it is as or more active than either tamoxifen or the AIs. Additive endocrine therapies, including treatment with progestins, and androgens, and enigmatically, pharmacologic doses of estrogens, are all active, but they may be associated with unacceptable side effects in many women. The mechanism of action of these latter therapies is unknown. Cases in which tumors shrink in response to tamoxifen withdrawal (as well as withdrawal of pharmacologic doses of estrogens) have been reported, but with the advent of so many other therapies for metastatic disease, this strategy is rarely used in modern oncology.

TABLE 75-4 Endocrine Therapies for Breast Cancer

THERAPY	COMMENTS
Castration Surgical LHRH agonists	For premenopausal women
Antiestrogens	
Tamoxifen	Useful in pre- and postmenopausal women[a]
Fulvestrant	Responses in tamoxifen-resistant and aromatase inhibitor–resistant patients[a]
Aromatase inhibitors	Low toxicity; now first choice for metastatic disease[a]
High-dose progestogens	Common fourth-line choice after aromatase inhibitors, tamoxifen, and fulvestrant
Additive androgens or estrogens	Plausible fourth-line therapies; potentially toxic

[a]Consider retreatment with everolimus in combination for disease progression.

Abbreviation: LHRH, luteinizing hormone–releasing hormone.

TABLE 75-5 Common Agents Added to Endocrine Therapies for Metastatic Breast Cancer

CLASS	HOW ADMINISTERED	AGENTS	COMMON TOXICITIES
Anti-mTOR	Oral	Everolimus	Mucositis, diarrhea, rash
CDK4/6 inhibitors	Oral	Palbociclib, ribociclib, abemaciclib (not FDA approved)	Neutropenia; uncommon leukopenia, fatigue, and nausea

Abbreviations: CDK4/6, cyclin D kinase 4/6; FDA, Food and Drug Administration; mTOR, mammalian target of rapamycin.

TABLE 75-6 Common Anti-HER2 Agents for Breast Cancer

CLASS	HOW ADMINISTERED	AGENTS	COMMON TOXICITIES
Humanized monoclonal antibodies	IV	Trastuzumab, pertuzumab	Cardiac dysfunction GI (diarrhea)
Tyrosine Kinase Inhibitors	Oral	Lapatinib neratinib (not FDA approved)	Diarrhea, mucositis, rash
Antibody-drug conjugate	IV	Ado-trastuzumab emtansine	Peripheral neuropathy, thrombocytopenia

The sequence of endocrine therapy is variable. Patients who respond to one endocrine therapy have at least a 50% chance of responding to a second endocrine therapy. It is not uncommon for patients to respond to two or three sequential endocrine therapies. In most postmenopausal patients, the initial endocrine therapy should be an AI rather than tamoxifen. As noted, AIs are not used in premenopausal women because their hypothalamus can respond to estrogen deprivation by producing gonadotropins that promote estrogen synthesis. Tamoxifen and fulvestrant are usually used in sequence after AI therapy. Combination endocrine therapies increase the chances of response initially, but they do not appear to increase the ultimate time to chemotherapy use or overall survival. Combinations of chemotherapy with endocrine therapy are not useful, as summarized in Table 75-4.

At least two different targeted agents have been shown to enhance outcomes of patients with ER-positive metastatic breast cancer when combined with endocrine therapy. Addition of an inhibitor of the mammalian target of rapamycin (mTOR), everolimus, to the hormonal treatment can lead to AIs, tamoxifen, or fulvestrant improves time to progression, and this agent is now being explored as front-line therapy and in the adjuvant setting. Likewise, inhibitors of cyclin D kinase 4/6 (CDK4/6) (palbociclib, ribociclib, abemaciclib) have also been shown to substantially improve progression-free survival when combined either with an AI or fulvestrant. These agents are also being tested in the adjuvant setting. Data regarding overall survival benefits from the mTOR or CDK4/6 inhibitors are still pending, but addition of one or the other in combination with ET for women with ER-positive metastatic breast cancer is becoming the standard of care. These should not be given simultaneously but rather in sequence as appropriate, as summarized in Table 75-5.

Chemotherapy Unlike many other epithelial malignancies, breast cancer responds to multiple chemotherapeutic agents, including anthracyclines, alkylating agents, taxanes, and antimetabolites. Multiple combinations of these agents have been found to improve response rates somewhat, but they have had little effect on duration of response or survival. Unless patients have rapidly progressive visceral (lung, liver) metastases with end-organ dysfunction, single-agent chemotherapy, used in sequence as one drug fails going on the next, is preferable. Given the significant toxicity of most drugs, the use of a single effective agent will minimize toxicity by sparing the patient exposure to drugs that would be of little value. No method to select the drugs most efficacious for a given patient has been demonstrated to be useful.

Most oncologists use either capecitabine or an anthracycline or a taxane for first-line chemotherapy, either in a patient with ER-positive disease that is refractory to endocrine therapy or for a patient with ER-negative breast cancer. Within these general classes, it is not clear that one particular agent (such as doxorubicin vs epirubicin or paclitaxel vs docetaxel) is preferable, and the choice has to be balanced with individual needs. Objective responses in previously treated patients may also be seen with gemcitabine, vinorelbine, and oral etoposide, as well as a new class of agents, epothilones. Platinum-based agents have become far more widely used in both the adjuvant and advanced disease settings for some breast cancers, particularly those of the "triple-negative" subtype.

Anti-HER2 therapy Treatment of patients with anti-HER2 metastatic breast cancer is one of the great success stories in the last 30 years of oncology. Initial use of a trastuzumab, either alone or with chemotherapy, was shown to improve response rate and survival for women with HER2-positive disease. Indeed, anecdotal reports of a few patients with remarkably sustained complete responses suggest that, on occasion, a few may be cured. Chronologically, the tyrosine kinase, lapatinib, was subsequently shown to be effective when added to chemotherapy after patients progressed on prior trastuzumab. Further, both continuation of trastuzumab after progression, in combination with the next chemotherapeutic regimen and combination of trastuzumab and lapatinib in patients who had progressed on trastuzumab are both superior to discontinuing the trastuzumab.

For patients who have become refractory to trastuzumab–based therapy, and more recently even in the upfront setting, other therapies have remarkably high activity. A novel antibody drug conjugate (ADC) that links trastuzumab to a cytotoxic agent, ado-trastuzumab emtansine, is active even in patients who have progressed on trastuzumab. More recently, the combination of chemotherapy and trastuzumab and pertuzumab has been shown to result in prolonged overall survival compared to trastuzumab alone. These recommendations are summarized in Table 75-6.

Other Therapies Bevacizumab is an agent that targets the vascular endothelial growth factor (VEGF). Bevacizumab with paclitaxel or other chemotherapeutic agents modestly increases the response rate and response duration to paclitaxel, but without improvement in overall survival and with occasional major toxicities. After initial excitement and FDA approval, its use has been mostly abandoned in breast cancer. As in the metastatic setting, trials are ongoing testing the value of PARP (poly-ADP ribose polymerase) inhibitors in patients with known germline *BRCA1/2* mutations or cancers that have BRCA-like biologies. The excitement over immune check-point inhibitors has spread to metastatic breast cancer, especially of the triple-negative subtype, but at present there are no agents approved for it.

MALE BREAST CANCER

Breast cancer is ~1/150th as frequent in men as in women; ~2000 men developed breast cancer annually in the United States. Risk factors include inherited, deleterious SNPs in *BRCA2*, as well as Klinefelter's syndrome. Men with Klinefelter's syndrome have two or more copies of the X chromosome and have lower levels of and higher levels of estrogen. Other conditions of hyperestrogenism, such as in hepatic failure, are also associated with higher risk of male breast cancers. However, the vast majority of men who present with breast cancer have none of these conditions.

Breast cancer usually presents in men as a unilateral lump in the breast and is frequently not diagnosed promptly. Given the small amount of soft tissue and the unexpected nature of the problem, locally advanced presentations are somewhat more common. Although gynecomastia may initially be unilateral or asymmetric, any unilateral mass in a man aged >40 years should receive a careful workup including biopsy. On the other hand, bilateral symmetric breast development rarely represents breast cancer and is almost invariably due to endocrine disease or a drug effect. It should be kept in mind, nevertheless, that the risk of cancer is much greater in men with gynecomastia; in such men, gross asymmetry of the breasts should arouse suspicion of cancer.

Approximately 90% of male breast cancers contain ERs, and it behaves similarly to that in a postmenopausal woman. When matched to female breast cancer by age and stage, its overall prognosis is identical. Male breast cancer is best managed by mastectomy and axillary lymph node dissection or SLNB, although some men prefer breast-conserving therapy. Patients with locally advanced disease or positive nodes should also be treated with irradiation, and ~60% of cases with metastatic disease respond to endocrine therapy. Tamoxifen is usually the agent of choice, and it is unknown if the AIs are effective in men. No randomized studies have evaluated adjuvant therapy for male breast cancer. Two historic experiences suggest that the disease responds well to adjuvant systemic therapy, and, if not medically contraindicated, the same criteria for the use of adjuvant therapy in women should be applied to men.

The sites of relapse and spectrum of response to chemotherapeutic drugs are virtually identical for breast cancers in either sex.

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76 Upper Gastrointestinal Tract Cancers

Robert J. Mayer

Upper gastrointestinal cancers include malignancies arising in the esophagus, stomach, and small intestine.

ESOPHAGEAL CANCER

INCIDENCE AND ETIOLOGY

Cancer of the esophagus is an increasingly common and extremely lethal malignancy. The diagnosis was made in 16,940 Americans in 2017 and led to 15,690 deaths. Almost all esophageal cancers are either squamous cell carcinomas or adenocarcinomas; the two histologic subtypes have a similar clinical presentation but different causative factors.

Worldwide, squamous cell carcinoma is the more common cell type, having an incidence that rises strikingly in association with geographic location. It occurs frequently within a region extending from the southern shore of the Caspian Sea on the west to northern China on the east, encompassing parts of Iran, central Asia, Afghanistan, Siberia, and Mongolia. Familial increased risk has been observed in regions with high incidence, although gene associations are not yet defined. High-incidence "pockets" of the disease are also present in such disparate locations as Finland, Iceland, Curaçao, southeastern Africa, and northwestern France. In North America and western Europe, the disease is more common in blacks than whites and in males than females; it appears most often after age 50 and seems to be associated with a lower socioeconomic status. Such cancers generally arise in the cervical and thoracic portions of the esophagus.

A variety of causative factors have been implicated in the development of squamous cell cancers of the esophagus **(Table 76-1)**. In the United States, the etiology of such cancers is primarily related to excess alcohol consumption and/or cigarette smoking. The relative risk increases with the amount of tobacco smoked or alcohol consumed, with these factors acting synergistically. The consumption of whiskey is linked to a higher incidence than the consumption of wine or beer. Squamous cell esophageal carcinoma has also been associated with the ingestion of nitrates, smoked opiates, and fungal toxins in pickled vegetables, as well as mucosal damage caused by such physical insults as long-term exposure to extremely hot tea, the ingestion of lye, radiation-induced strictures, and chronic achalasia. The presence of an esophageal web in association with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome) and congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris) have each been linked with squamous cell esophageal cancer, as have dietary deficiencies of molybdenum, zinc, selenium, and vitamin A. Patients with head and neck cancer are at increased risk of squamous cell cancer of the esophagus.

For unclear reasons, the incidence of squamous cell esophageal cancer has decreased somewhat in both the black and white populations in the United States over the past 40 years, whereas the rate of adenocarcinoma has risen sevenfold, particularly in white males (male-to-female ratio of 6:1). Whereas squamous cell cancers comprised the vast majority of esophageal cancers in the United States as recently as 40–50 years ago, >75% of esophageal tumors are now adenocarcinomas, with the incidence of this histologic subtype continuing to increase rapidly. Understanding the cause for this increase is the focus of current investigation.

Several strong etiologic associations have been observed to account for the development of adenocarcinoma of the esophagus **(Table 76-2)**.

TABLE 76-1 Some Etiologic Factors Associated with Squamous Cell Cancer of the Esophagus

Excess alcohol consumption
Cigarette smoking
Other ingested carcinogens
Nitrates (converted to nitrites)
Smoked opiates
Fungal toxins in pickled vegetables
Mucosal damage from physical agents
Hot tea
Lye ingestion
Radiation-induced strictures
Chronic achalasia
Host susceptibility
Esophageal web with glossitis and iron deficiency (i.e., Plummer-Vinson or Paterson-Kelly syndrome)
Congenital hyperkeratosis and pitting of the palms and soles (i.e., tylosis palmaris et plantaris)
? Dietary deficiencies of selenium, molybdenum, zinc, and vitamin A

TABLE 76-2 Some Etiologic Factors Associated with Adenocarcinoma of the Esophagus
Chronic gastroesophageal reflux
Obesity
Barrett's esophagus
Male sex
Cigarette smoking

Such tumors arise in the distal esophagus in association with chronic gastric reflux, often in the presence of Barrett's esophagus (replacement of the normal squamous epithelium of the distal esophagus by columnar mucosa), which occurs more commonly in obese individuals. Adenocarcinomas arise within dysplastic columnar epithelium in the distal esophagus. Even before frank neoplasia is detectable, aneuploidy and *p53* mutations are found in the dysplastic epithelium. The value of proton-pump inhibitors in reducing the risk of cancer in individuals with chronic gastric reflux or Barrett's esophagus is uncertain. These adenocarcinomas behave clinically like gastric adenocarcinomas, although they are not associated with *Helicobacter pylori* infections. Approximately 15% of esophageal adenocarcinomas overexpress the *HER2/neu* gene.

CLINICAL FEATURES

About 5% of esophageal cancers occur in the upper third of the esophagus (cervical esophagus), 20% in the middle third, and 75% in the lower third. Squamous cell carcinomas and adenocarcinomas cannot be distinguished radiographically or endoscopically.

Progressive dysphagia and weight loss of short duration are the initial symptoms in the vast majority of patients. Dysphagia initially occurs with solid foods and gradually progresses to include semisolids and liquids. By the time these symptoms develop, the disease is already very advanced, because difficulty in swallowing does not occur until >60% of the esophageal circumference is infiltrated with cancer. Dysphagia may be associated with pain on swallowing (odynophagia), pain radiating to the chest and/or back, regurgitation or vomiting, and aspiration pneumonia. The disease most commonly spreads to adjacent and supraclavicular lymph nodes, liver, lungs, pleura, and bone. Tracheoesophageal fistulas may develop, primarily in patients with upper and mid-esophageal tumors. As with other squamous cell carcinomas, hypercalcemia may occur in the absence of osseous metastases, probably from parathormone-related peptide secreted by tumor cells **(Chap. 89)**.

DIAGNOSIS

Attempts at endoscopic and cytologic screening for carcinoma in patients with Barrett's esophagus, while effective as a means of detecting high-grade dysplasia, have not yet been shown to reduce the likelihood of death from esophageal adenocarcinoma. Esophagoscopy should be performed in all patients suspected of having an esophageal abnormality, to both visualize and identify a tumor and also to obtain histopathologic confirmation of the diagnosis. Because the population of persons at risk for squamous cell carcinoma of the esophagus (i.e., smokers and drinkers) also has a high rate of cancers of the lung and the head and neck region, endoscopic inspection of the larynx, trachea, and bronchi should also be carried out. A thorough examination of the fundus of the stomach (by retroflexing the endoscope) is imperative as well. The extent of tumor spread to the mediastinum and para-aortic lymph nodes should be assessed by computed tomography (CT) scans of the chest and abdomen and by endoscopic ultrasound. Positron emission tomography scanning provides a useful assessment of the presence of distant metastatic disease, offering accurate information regarding spread to mediastinal lymph nodes, which can be helpful in defining radiation therapy fields. Such scans, when performed sequentially, appear to provide a means of making an early assessment of responsiveness to preoperative chemotherapy and have increasingly been used in guiding a change in clinical management.

TREATMENT

Esophageal Cancer

The prognosis for patients with esophageal carcinoma is poor. Approximately 10% of patients survive 5 years after the diagnosis; thus, management focuses on symptom control. Surgical resection of all gross tumor (i.e., total resection) is feasible in only 45% of cases, with residual tumor cells frequently present at the resection margins. Such esophagectomies have been associated with a postoperative mortality rate of ~5% due to anastomotic fistulas, subphrenic abscesses, and cardiopulmonary complications. Although debate regarding the comparative benefits of transthoracic versus transhiatal resections has continued, experienced thoracic surgeons are now favoring minimally invasive transthoracic esophagectomies. Endoscopic resections of superficial squamous cell cancers or adenocarcinomas are being examined but have not yet been shown to result in a similar likelihood of survival as observed with conventional surgical procedures. Similarly, the value of endoscopic ablation of dysplastic lesions in an area of Barrett's esophagus on reducing subsequent mortality from esophageal carcinoma is uncertain. Some experts have advocated fundoplication surgery (i.e., the removal of the gastroesophageal junction) as a means of cancer prevention in patients with Barrett's esophagus; again, objective data are not yet available to fully assess the risks versus benefits of this invasive procedure. About 20% of patients who survive a total surgical resection live for 5 years. The evaluation of chemotherapeutic agents in patients with esophageal carcinoma has been hampered by ambiguity in the definition of "response" and the debilitated physical condition of many treated individuals, particularly those with squamous cell cancers. Nonetheless, significant reductions in the size of measurable tumor masses have been reported in 15–25% of patients given single-agent treatment and in 30–60% of patients treated with drug combinations that include a platinum form of chemotherapy. In the small subset of patients whose tumors overexpress the *HER2/neu* gene, the addition of the monoclonal antibody trastuzumab (Herceptin) appears to further enhance the likelihood of benefit, particularly in patients with gastroesophageal lesions. The use of the antiangiogenic agent bevacizumab (Avastin) seems to be of limited value in the setting of esophageal cancer. Combination chemotherapy and radiation therapy as the initial therapeutic approach, either alone or followed by an attempt at operative resection, seems to be beneficial. When administered along with radiation therapy, chemotherapy produces a better survival outcome than radiation therapy alone. The use of preoperative chemotherapy and radiation therapy followed by esophageal resection appears to prolong survival compared with surgery alone according to several randomized trials and a meta-analysis; some reports suggest that no additional benefit accrues when surgery is added if significant shrinkage of tumor has been achieved by the chemoradiation combination.

For the incurable, surgically unresectable patient with esophageal cancer, dysphagia, malnutrition, and the management of tracheoesophageal fistulas are major issues. Approaches to palliation include repeated endoscopic dilatation, the surgical placement of a gastrostomy or jejunostomy for hydration and feeding, endoscopic placement of an expansive metal stent to bypass the tumor, and radiation therapy.

TUMORS OF THE STOMACH

GASTRIC ADENOCARCINOMA

Incidence and Epidemiology For unclear reasons, the incidence and mortality rates for gastric cancer have decreased in the United States during the past 80 years, although the disease remains the third most frequent cause of worldwide cancer-related death. The mortality rate from gastric cancer in the United States has dropped in men from 28 to 7.4 per 100,000 persons, whereas in women, the rate has decreased from 27 to 2.4 per 100,000. Nonetheless,

in 2017, 28,000 new cases of stomach cancer were diagnosed in the United States, and 10,960 Americans died of the disease. Although the incidence of gastric cancer has decreased worldwide, it remains high in such disparate geographic regions as Japan, China, Chile, and Ireland.

The risk of gastric cancer is greater among lower socioeconomic classes. Migrants from high- to low-incidence nations maintain their susceptibility to gastric cancer, whereas the risk for their offspring approximates that of the new homeland. These findings suggest that an environmental exposure, probably beginning early in life, is related to the development of gastric cancer, with dietary carcinogens considered the most likely factor(s).

Pathology About 85% of stomach cancers are adenocarcinomas, with 15% due to lymphomas, gastrointestinal stromal tumors (GISTs), and leiomyosarcomas. Gastric adenocarcinomas may be subdivided into two pathologically defined categories: a *diffuse type*, in which cell cohesion is absent, so that individual cells infiltrate and thicken the stomach wall without forming a discrete mass; and an *intestinal type*, characterized by cohesive neoplastic cells that form glandlike tubular structures. The diffuse carcinomas occur more often in younger patients, develop throughout the stomach (including the cardia), result in a loss of distensibility of the gastric wall (so-called *linitis plastica*, or "leather bottle" appearance), and carry a poorer prognosis. Diffuse cancers have defective intercellular adhesion, mainly as a consequence of loss of expression of E-cadherin. Intestinal-type lesions are frequently ulcerative, more commonly appear in the antrum and lesser curvature of the stomach, and are often preceded by a prolonged precancerous process, often initiated by *H. pylori* infection. Although the incidence of diffuse carcinomas is similar in most populations, the intestinal type tends to predominate in the high-risk geographic regions and is less likely to be found in areas where the frequency of gastric cancer is declining. Thus, different etiologic factor(s) are likely involved in these two subtypes. In the United States, ~30% of gastric cancers originate in the distal stomach, ~20% arise in the midportion of the stomach, and ~40% originate in the proximal third of the stomach. The remaining 10% involve the entire stomach.

Genomic profiling of gastric adenocarcinomas has led to subdividing the disease into four molecularly defined subgroups: chromosomally unstable tumors (50% of cases correlating with intestinal type histology), genomically stable tumors (20% of cases correlating with diffuse type histology), microsatellite unstable tumors (22% of cases), and Epstein-Barr virus (EBV) positive tumors (9% of cases) **(Fig. 76-1)**. Efforts to incorporate these molecular subtypes into clinical management are underway.

Etiology The long-term ingestion of high concentrations of nitrates found in dried, smoked, and salted foods appears to be associated with a higher risk. The nitrates are thought to be converted to carcinogenic nitrites by bacteria **(Table 76-3)**. Such bacteria may be introduced exogenously through the ingestion of partially decayed foods, which are consumed in abundance worldwide by the lower socioeconomic classes. Bacteria such as *H. pylori* may also contribute to this effect by causing chronic inflammatory atrophic gastritis, loss of gastric acidity, and bacterial growth in the stomach. Although the risk for developing gastric cancer is thought to be sixfold higher in people infected with *H. pylori*, it remains uncertain whether eradicating the bacteria after infection has already occurred actually reduces this risk. Loss of acidity may occur when acid-producing cells of the gastric antrum have been removed surgically to control benign peptic ulcer disease or when achlorhydria, atrophic gastritis, and even pernicious anemia develop in the elderly. Serial endoscopic examinations of the stomach in patients with atrophic gastritis have documented replacement of the usual gastric mucosa by intestinal-type cells. This process of intestinal metaplasia may lead to cellular atypia and eventual neoplasia. Because the declining incidence of gastric cancer in the United States primarily reflects a decline in distal, ulcerating, intestinal-type lesions, it is conceivable that better food preservation and the availability of refrigeration for all socioeconomic classes have decreased the dietary ingestion of exogenous bacteria. *H. pylori* has not been associated with the diffuse, more proximal form of gastric carcinoma or with cancers arising at the gastroesophageal junction or in the distal esophagus. Approximately 10–15% of adenocarcinomas appearing in the proximal stomach, the gastroesophageal junction, and the distal esophagus overexpress the *HER2/neu* gene; individuals whose tumors demonstrate this overexpression benefit from treatment directed against this target (i.e., trastuzumab [Herceptin]).

Several additional etiologic factors have been associated with gastric carcinoma. Gastric ulcers and adenomatous polyps have occasionally been linked, but data on a cause-and-effect relationship are unconvincing. The inadequate clinical distinction between benign gastric ulcers and small ulcerating carcinomas may, in part, account for this presumed association. The presence of extreme hypertrophy of gastric rugal folds (i.e., Ménétrier's disease), giving the impression of polypoid

TABLE 76-3 Nitrate-Converting Bacteria as a Factor in the Causation of Gastric Carcinomaa

Exogenous sources of nitrate-converting bacteria:
Bacterially contaminated food (common in lower socioeconomic classes, who have a higher incidence of the disease; diminished by improved food preservation and refrigeration)
Helicobacter pylori infection
Endogenous factors favoring growth of nitrate-converting bacteria in the stomach:
Decreased gastric acidity
Prior gastric surgery (antrectomy) (15- to 20-year latency period)
Atrophic gastritis and/or pernicious anemia
? Prolonged exposure to histamine H_2-receptor antagonists

[a]Hypothesis: Dietary nitrates are converted to carcinogenic nitrites by bacteria.

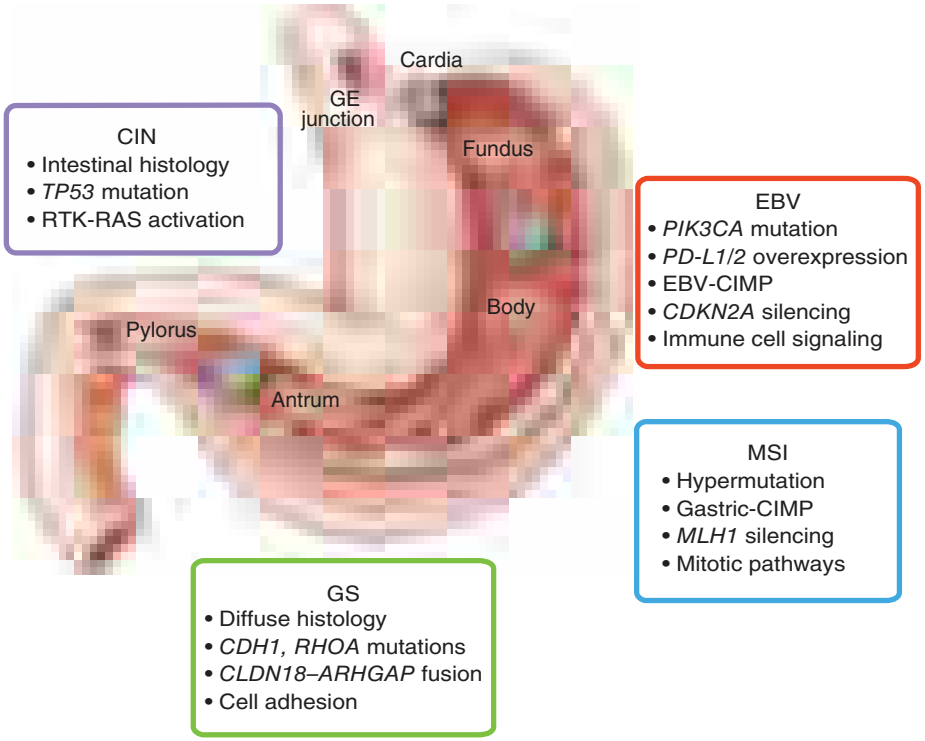

FIGURE 76-1 Molecular/genomic characterization of subtypes of gastric carcinomas. CIMP, CpG-island methylator phenotype; CIN, chromosomally unstable; EBV, Epstein-Barr virus-associated; GS, genomically stable; MSI, microsatellite instability-associated.

lesions, has been associated with a striking frequency of malignant transformation; such hypertrophy, however, does not represent the presence of true adenomatous polyps. Individuals with blood group A have a higher incidence of gastric cancer than persons with blood group O; this observation may be related to differences in the mucous secretion, leading to altered mucosal protection from carcinogens. A germline mutation in the E-cadherin gene (*CDH1*), inherited in an autosomal dominant pattern and coding for a cell adhesion protein, has been linked to a high incidence of occult diffuse-type gastric cancers in young asymptomatic carriers in whom the endoscopic appearance of the gastric mucosa appears normal but foci of tumor are frequently present deeper in the stomach wall; this observation has led to a recommendation that they undergo a prophylactic gastrectomy. Carriers of this mutation are also at greater risk for the development of lobular breast cancer. Duodenal ulcers are not associated with gastric cancer.

Clinical Features Gastric cancers, when superficial and surgically curable, usually produce no symptoms. As the tumor becomes more extensive, patients may complain of an insidious upper abdominal discomfort varying in intensity from a vague, postprandial fullness to a severe, steady pain. Anorexia, often with slight nausea, is very common but is not the usual presenting complaint. Weight loss may eventually be observed, and nausea and vomiting are particularly prominent in patients whose tumors involve the pylorus; dysphagia and early satiety may be the major symptoms caused by diffuse lesions originating in the cardia. There may be no early physical signs. A palpable abdominal mass indicates long-standing growth and predicts regional extension. Gastric carcinomas spread by direct extension through the gastric wall to the perigastric tissues, occasionally adhering to adjacent organs such as the pancreas, colon, or liver. The disease also spreads via lymphatics or by seeding of peritoneal surfaces. Metastases to intraabdominal and supraclavicular lymph nodes occur frequently, as do metastatic nodules to the ovary (Krukenberg's tumor), periumbilical region ("Sister Mary Joseph node"), or peritoneal cul-de-sac (Blumer's shelf palpable on rectal or vaginal examination); malignant ascites may also develop. The liver is the most common site for hematogenous spread of tumor.

The presence of iron-deficiency anemia in men and of occult blood in the stool in both sexes mandates a search for an occult gastrointestinal tract lesion. A careful assessment is of particular importance in patients with atrophic gastritis or pernicious anemia. Unusual clinical features associated with gastric adenocarcinomas include migratory thrombophlebitis, microangiopathic hemolytic anemia, diffuse seborrheic keratoses (so-called Leser-Trélat sign), and acanthosis nigricans.

Diagnosis The use of double-contrast radiographic examinations has been supplanted by esophagogastroscopy and CT scanning for the evaluation of patients with epigastric complaints.

Gastric ulcers identified at the time of such endoscopic procedure may appear benign but merit biopsy in order to exclude a malignancy. Malignant gastric ulcers must be recognized before they penetrate into surrounding tissues, because the rate of cure of early lesions limited to the mucosa or submucosa is >80%. Because gastric carcinomas are difficult to distinguish clinically or endoscopically from gastric lymphomas, endoscopic biopsies should be made as deeply as possible, due to the submucosal location of lymphoid tumors.

The clinical staging system for gastric carcinoma is shown in Table 76-4.

TABLE 76-4 Staging System for Gastric Carcinoma

STAGE	TNM	FEATURES	DATA FROM ACS IN THE UNITED STATES	
			NO. OF CASES, %	5-YEAR SURVIVAL, %
0	T_{is}N0M0	Node negative; limited to mucosa	1	90
IA	T1N0M0	Node negative; invasion of lamina propria or submucosa	7	59
IB	T2N0M0 T1N1M0	Node negative; invasion of muscularis propria	10	44
II	T1N2M0 T2N1M0 T3N0M0	Node positive; invasion beyond mucosa but within wall *or* Node negative; extension through wall	17	29
IIIA	T2N2M0 T3N1-2M0	Node positive; invasion of muscularis propria or through wall	21	15
IIIB	T4N0-1M0	Node negative; adherence to surrounding tissue	14	9
IIIC	T4N2-3M0 T3N3M0	>3 nodes positive; invasion of serosa or adjacent structures 7 or more positive nodes; penetrates wall without invading serosa or adjacent structures		
IV	T4N2M0 T1-4N0-2-M1	Node positive; adherence to surrounding tissue *or* Distant metastases	30	3

Abbreviations: ACS, American Cancer Society; TNM, tumor, node, metastasis.

TREATMENT

Gastric Adenocarcinoma

Complete surgical removal of the tumor with resection of adjacent lymph nodes offers the only chance for cure. However, this is possible in less than a third of patients. A subtotal gastrectomy is the treatment of choice for patients with distal carcinomas, whereas total or near-total gastrectomies are required for more proximal tumors. The inclusion of extended lymph node dissection in these procedures appears to confer an added risk for complications without providing a meaningful enhancement in survival. The prognosis following complete surgical resection depends on the degree of tumor penetration into the stomach wall and is adversely influenced by regional lymph node involvement and vascular invasion, characteristics found in the vast majority of American patients. As a result, the probability of survival after 5 years for the 25–30% of patients able to undergo complete resection is ~20% for distal tumors and <10% for proximal tumors, with recurrences continuing for at least 8 years after surgery. In the absence of ascites or extensive hepatic or peritoneal metastases, even patients whose disease is believed to be incurable by surgery should be offered resection of the primary lesion. Reduction of tumor bulk is the best form of palliation and may enhance the probability of benefit from subsequent therapy. In high-incidence regions such as Japan and Korea, where the use of endoscopic screening programs has identified patients with superficial tumors, the use of laparoscopic gastrectomy has gained popularity. In the United States and western Europe, the use of this less invasive surgical approach remains investigational.

Gastric adenocarcinoma is a relatively radioresistant tumor, and the adequate control of the primary tumor requires doses of external-beam irradiation that exceed the tolerance of surrounding structures, such as bowel mucosa and spinal cord. As a result, the major role of radiation therapy in patients has been palliation of pain. Radiation therapy alone after a complete resection does not prolong survival. In the setting of surgically unresectable disease limited to the epigastrium, patients treated with 3500–4000 cGy did not live longer than similar patients not receiving radiotherapy; however, survival was prolonged slightly when 5-fluorouracil (5-FU) plus leucovorin was given in combination with radiation therapy (3-year survival 50% vs 41% for radiation therapy alone). In this clinical setting, the 5-FU likely functions as a radiosensitizer.

The administration of combinations of cytotoxic drugs to patients with advanced gastric carcinoma has been associated with partial

responses in 30–50% of cases; responders appear to benefit from treatment. Such drug combinations have generally included cisplatin combined with epirubicin or docetaxel and infusional 5-FU or capecitabine, or with either irinotecan or oxaliplatin. Despite the encouraging response rates, complete remissions are uncommon, the partial responses are transient, and the overall impact of multidrug therapy on survival has been limited; the median survival time for patients treated in this manner remains less than 12 months. As with adenocarcinomas arising in the esophagus, the addition of bevacizumab (Avastin) to chemotherapy regimens in treating gastric cancer appears to provide limited benefit. However, preliminary results utilizing another antiangiogenic compound—ramucirumab (Cyranza)—in the treatment of gastric cancer are encouraging, particularly when combined with paclitaxel. Additionally, initial experiences with checkpoint inhibitors (PD-1 and PD-2) have shown such immunotherapy to provide benefit to some patients. The administration of adjuvant chemotherapy alone following the complete resection of a gastric cancer has only minimally improved survival. However, combination chemotherapy administered before and after surgery (*perioperative treatment*) as well as postoperative chemotherapy combined with radiation therapy reduces the recurrence rate and prolongs survival.

PRIMARY GASTRIC LYMPHOMA

Primary lymphoma of the stomach is relatively uncommon, accounting for <15% of gastric malignancies and ~2% of all lymphomas. The stomach is, however, the most frequent extranodal site for lymphoma, and gastric lymphoma has increased in frequency during the past 35 years. The disease is difficult to distinguish clinically from gastric adenocarcinoma; both tumors are most often detected during the sixth decade of life; present with epigastric pain, early satiety, and generalized fatigue; and are usually characterized by ulcerations with a ragged, thickened mucosal pattern demonstrated by contrast radiographs or endoscopic appearance. The diagnosis of lymphoma of the stomach may occasionally be made through cytologic brushings of the gastric mucosa but usually requires a biopsy at gastroscopy or laparotomy. Failure of gastroscopic biopsies to detect lymphoma in a given case should not be interpreted as being conclusive, because superficial biopsies may miss the deeper lymphoid infiltrate. The macroscopic pathology of gastric lymphoma may also mimic adenocarcinoma, consisting of either a bulky ulcerated lesion localized in the corpus or antrum or a diffuse process spreading throughout the entire gastric submucosa and even extending into the duodenum. Microscopically, the vast majority of gastric lymphoid tumors are lymphomas of B-cell origin. Histologically, these tumors may range from well-differentiated, superficial processes (mucosa-associated lymphoid tissue [MALT]) to high-grade, large-cell lymphomas. Like gastric adenocarcinoma, infection with *H. pylori* increases the risk for gastric lymphoma in general and MALT lymphomas in particular. Large-cell lymphomas of the stomach spread initially to regional lymph nodes (often to Waldeyer's ring) and may then disseminate.

TREATMENT

Primary Gastric Lymphoma

Primary gastric lymphoma is a far more treatable disease than adenocarcinoma of the stomach, a fact that underscores the need for making the correct diagnosis. Antibiotic treatment to eradicate *H. pylori* infection has led to regression of about 75% of gastric MALT lymphomas and should be considered before surgery, radiation therapy, or chemotherapy is undertaken in patients having such tumors. A lack of response to such antimicrobial treatment has been linked to a specific chromosomal abnormality, i.e., t(11;18). Responding patients should undergo periodic endoscopic surveillance because it remains unclear whether the neoplastic clone is eliminated or merely suppressed, although the response to antimicrobial treatment is quite durable. Subtotal gastrectomy, usually followed by combination chemotherapy, has led to 5-year survival rates of 40–60% in patients with localized high-grade lymphomas. The need for a major surgical procedure has been questioned, particularly in patients with preoperative radiographic evidence of nodal involvement, for whom chemotherapy (CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]) plus rituximab is highly effective therapy. A role for radiation therapy is not defined because most recurrences develop at distant sites.

GASTRIC (NONLYMPHOID) SARCOMA

Leiomyosarcomas and GISTs make up 1–3% of gastric neoplasms. They most frequently involve the anterior and posterior walls of the gastric fundus and often ulcerate and bleed. Even those lesions that appear benign on histologic examination may behave in a malignant fashion. These tumors rarely invade adjacent viscera and characteristically do not metastasize to lymph nodes, but they may spread to the liver and lungs. The treatment of choice is surgical resection with 3 years of postoperative therapy to be considered following the removal of a GIST if the primary tumor demonstrates high-risk features. All such tumors should be analyzed for a mutation in the c-*kit* receptor. GISTs are unresponsive to conventional chemotherapy; yet ~50% of patients experience objective response and prolonged survival when treated with imatinib mesylate (Gleevec) (400–800 mg PO daily), a selective inhibitor of the c-*kit* tyrosine kinase. Many patients with GIST whose tumors have become refractory to imatinib subsequently benefit from sunitinib (Sutent) or regorafenib (Stivarga), other inhibitors of the c-*kit* tyrosine kinase.

TUMORS OF THE SMALL INTESTINE

Small-bowel tumors comprise <3% of gastrointestinal neoplasms. Because of their rarity and inaccessibility, a correct diagnosis is often delayed. Abdominal symptoms are usually vague and poorly defined, and conventional radiographic studies of the upper and lower intestinal tract often appear normal. Small-bowel tumors should be considered in the differential diagnosis in the following situations: (1) recurrent, unexplained episodes of crampy abdominal pain; (2) intermittent bouts of intestinal obstruction, especially in the absence of inflammatory bowel disease (IBD) or prior abdominal surgery; (3) intussusception in the adult; and (4) evidence of chronic intestinal bleeding in the presence of negative conventional and endoscopic examination. A careful small-bowel barium study should be considered in such a circumstance; the diagnostic accuracy may be improved by infusing barium through a nasogastric tube placed into the duodenum (enteroclysis). Alternatively, capsule endoscopic procedures have been used.

BENIGN TUMORS

The histology of benign small-bowel tumors is difficult to predict on clinical and radiologic grounds alone. The symptomatology of benign tumors is not distinctive, with pain, obstruction, and hemorrhage being the most frequent symptoms. These tumors are usually discovered during the fifth and sixth decades of life, more often in the distal rather than the proximal small intestine. The most common benign tumors are adenomas, leiomyomas, lipomas, and angiomas.

Adenomas These tumors include those of the islet cells and Brunner's glands as well as polypoid adenomas. *Islet cell adenomas* are occasionally located outside the pancreas; the associated syndromes are discussed in **Chap. 80**. *Brunner's gland adenomas* are not truly neoplastic but represent a hypertrophy or hyperplasia of submucosal duodenal glands. These appear as small nodules in the duodenal mucosa that secrete a highly viscous alkaline mucus. Most often, this is an incidental radiographic finding not associated with any specific clinical disorder.

Polypoid Adenomas About 25% of benign small-bowel tumors are polypoid adenomas **(see Table 77-2)**. They may present as single polypoid lesions or, less commonly, as papillary villous adenomas. As in the colon, the sessile or papillary form of the tumor is sometimes associated with a coexisting carcinoma. Occasionally, patients with Gardner's syndrome develop premalignant adenomas in the small bowel; such lesions are generally in the duodenum. Multiple polypoid tumors may occur throughout the small bowel (and occasionally the

stomach and colorectum) in the Peutz-Jeghers syndrome. The polyps are usually hamartomas (juvenile polyps) having a low potential for malignant degeneration. Mucocutaneous melanin deposits as well as tumors of the ovary, breast, pancreas, and endometrium are also associated with this autosomal dominant condition.

Leiomyomas These neoplasms arise from smooth-muscle components of the intestine and are usually intramural, affecting the overlying mucosa. Ulceration of the mucosa may cause gastrointestinal hemorrhage of varying severity. Cramping or intermittent abdominal pain is frequently encountered.

Lipomas These tumors occur with greatest frequency in the distal ileum and at the ileocecal valve. They have a characteristic radiolucent appearance and are usually intramural and asymptomatic, but on occasion cause bleeding.

Angiomas While not true neoplasms, these lesions are important because they frequently cause intestinal bleeding. They may take the form of telangiectasia or hemangiomas. Multiple intestinal telangiectasias occur in a nonhereditary form confined to the gastrointestinal tract or as part of the hereditary Osler-Rendu-Weber syndrome. Vascular tumors may also take the form of isolated hemangiomas, most commonly in the jejunum. Angiography, especially during bleeding, is the best procedure for evaluating these lesions.

MALIGNANT TUMORS

While rare, small-bowel malignancies occur in patients with long-standing regional enteritis and celiac sprue as well as in individuals with AIDS. Malignant tumors of the small bowel are frequently associated with fever, weight loss, anorexia, bleeding, and a palpable abdominal mass. After ampullary carcinomas (many of which arise from biliary or pancreatic ducts), the most frequently occurring small-bowel malignancies are adenocarcinomas, lymphomas, carcinoid tumors, and leiomyosarcomas.

ADENOCARCINOMAS

The most common primary cancers of the small bowel are adenocarcinomas, accounting for ~50% of malignant tumors. These cancers occur most often in the distal duodenum and proximal jejunum, where they tend to ulcerate and cause hemorrhage or obstruction. Radiologically, they may be confused with chronic duodenal ulcer disease or with Crohn's disease if the patient has long-standing regional enteritis. The diagnosis is best made by endoscopy and biopsy under direct vision. Surgical resection is the treatment of choice with suggested postoperative adjuvant chemotherapy options generally following treatment patterns used in the management of colon cancer.

LYMPHOMAS

Lymphoma in the small bowel may be primary or secondary. A diagnosis of a primary intestinal lymphoma requires histologic confirmation in a clinical setting in which palpable adenopathy and hepatosplenomegaly are absent and no evidence of lymphoma is seen on chest radiograph, CT scan, or peripheral blood smear or on bone marrow aspiration and biopsy. Symptoms referable to the small bowel are present, usually accompanied by an anatomically discernible lesion. Secondary lymphoma of the small bowel consists of involvement of the intestine by a lymphoid malignancy extending from involved retroperitoneal or mesenteric lymph nodes (Chap. 104).

Primary intestinal lymphoma accounts for ~20% of malignancies of the small bowel. These neoplasms are non-Hodgkin's lymphomas; they usually have a diffuse, large-cell histology and are of T cell origin. Intestinal lymphoma involves the ileum, jejunum, and duodenum, in decreasing frequency—a pattern that mirrors the relative amount of normal lymphoid cells in these anatomic areas. The risk of small-bowel lymphoma is increased in patients with a prior history of malabsorptive conditions (e.g., celiac sprue), regional enteritis, and depressed immune function due to congenital immunodeficiency syndromes, prior organ transplantation, autoimmune disorders, or AIDS.

The development of localized or nodular masses that narrow the lumen results in periumbilical pain (made worse by eating) as well as weight loss, vomiting, and occasional intestinal obstruction. The diagnosis of small-bowel lymphoma may be suspected from the appearance on contrast radiographs of patterns such as infiltration and thickening of mucosal folds, mucosal nodules, areas of irregular ulceration, or stasis of contrast material. The diagnosis can be confirmed by surgical exploration and resection of involved segments. Intestinal lymphoma can occasionally be diagnosed by peroral intestinal mucosal biopsy, but because the disease mainly involves the lamina propria, full-thickness surgical biopsies are usually required.

Resection of the tumor constitutes the initial treatment modality. While postoperative radiation therapy has been given to some patients following a total resection, most authorities favor short-term (three cycles) systemic treatment with combination chemotherapy. The frequent presence of widespread intraabdominal disease at the time of diagnosis and the occasional multicentricity of the tumor often make a total resection impossible. The probability of sustained remission or cure is ~75% in patients with localized disease but is ~25% in individuals with unresectable lymphoma. In patients whose tumors are not resected, chemotherapy may lead to bowel perforation.

A unique form of small-bowel lymphoma, diffusely involving the entire intestine, was first described in oriental Jews and Arabs and is referred to as *immunoproliferative small intestinal disease* (IPSID), *Mediterranean lymphoma*, or *α heavy chain disease*. This is a B-cell tumor. The typical presentation includes chronic diarrhea and steatorrhea associated with vomiting and abdominal cramps; clubbing of the digits may be observed. A curious feature in many patients with IPSID is the presence in the blood and intestinal secretions of an abnormal IgA that contains a shortened α heavy chain and is devoid of light chains. It is suspected that the abnormal α chains are produced by plasma cells infiltrating the small bowel. The clinical course of patients with IPSID is generally one of exacerbations and remissions, with death frequently resulting from either progressive malnutrition and wasting or the development of an aggressive lymphoma. The use of oral antibiotics such as tetracycline appears to be beneficial in the early phases of the disorder, suggesting a possible infectious etiology. Combination chemotherapy has been administered during later stages of the disease, with variable results. Results are better when antibiotics and chemotherapy are combined.

CARCINOID TUMORS

Carcinoid tumors arise from argentaffin cells of the crypts of Lieberkühn and are found from the distal duodenum to the ascending colon, areas embryologically derived from the midgut. More than 50% of intestinal carcinoids are found in the distal ileum, with most congregating close to the ileocecal valve. Most intestinal carcinoids are asymptomatic and of low malignant potential, but invasion and metastases may occur, leading to the carcinoid syndrome (Chap. 80).

LEIOMYOSARCOMAS

Leiomyosarcomas often are >5 cm in diameter and may be palpable on abdominal examination. Bleeding, obstruction, and perforation are common. Such tumors should be analyzed for the expression of mutant c-*kit* receptor (defining GIST), and in the presence of metastatic disease, justifying treatment with imatinib mesylate (Gleevec) or, in imatinib-refractory patients, sunitinib (Sutent) or regorafenib (Stivarga).

FURTHER READING

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77 Lower Gastrointestinal Cancers

Robert J. Mayer

Lower gastrointestinal cancers include malignant tumors of the colon, rectum, and anus.

COLORECTAL CANCER

INCIDENCE

Cancer of the large bowel is second only to lung cancer as a cause of cancer death in the United States: 135,430 new cases occurred in 2017, and 50,260 deaths were due to colorectal cancer. The incidence rate has decreased significantly during the past 25 years, likely due in large part to enhanced and more compliantly followed screening practices. Similarly, mortality rates in the United States have decreased by ~25%, resulting largely from earlier detection and improved treatment.

POLYPS AND MOLECULAR PATHOGENESIS

Most colorectal cancers, regardless of etiology, arise from adenomatous polyps. A polyp is a grossly visible protrusion from the mucosal surface and may be classified pathologically as a nonneoplastic hamartoma (e.g., *juvenile polyp*), a hyperplastic mucosal proliferation (*hyperplastic polyp*), or an adenomatous polyp. Only adenomas are clearly premalignant, and only a minority of adenomatous polyps evolve into cancer. Adenomatous polyps may be found in the colons of ~30% of middle-aged and ~50% of elderly people; however, <1% of polyps ever become malignant. Most polyps produce no symptoms and remain clinically undetected. Occult blood in the stool is found in <5% of patients with polyps.

A number of molecular changes are noted in adenomatous polyps and colorectal cancers that are thought to reflect a multistep process in the evolution of normal colonic mucosa to life-threatening invasive carcinoma. These developmental steps toward carcinogenesis include, but are not restricted to, point mutations in the K-*ras* protooncogene; hypomethylation of DNA, leading to gene activation; loss of DNA (*allelic loss*) at the site of a tumor-suppressor gene (the adenomatous polyposis coli [*APC*] gene) on the long arm of chromosome 5 (5q21); allelic loss at the site of a tumor-suppressor gene located on chromosome 18q (the deleted in colorectal cancer [*DCC*] gene); and allelic loss at chromosome 17p, associated with mutations in the *p53* tumor-suppressor gene **(see Fig. 67-2)**. Thus, the altered proliferative pattern of the colonic mucosa, which results in progression to a polyp and then to carcinoma, may involve the mutational activation of an oncogene followed by and coupled with the loss of genes that normally suppress tumorigenesis. It remains uncertain whether the genetic aberrations always occur in a defined order. Based on this model, however, cancer is believed to develop only in those polyps in which most (if not all) of these mutational events take place.

Clinically, the probability of an adenomatous polyp becoming a cancer depends on the gross appearance of the lesion, its histologic features, and its size. Polyps may be pedunculated (stalked) or sessile (flat-based), adenomatous or serrated. Invasive cancers develop more frequently in sessile, serrated (i.e. "flat") polyps. Histologically, adenomatous polyps may be tubular, villous (i.e., papillary), or tubulovillous. Villous adenomas, most of which are sessile, become malignant more than three times as often as tubular adenomas. The likelihood that any polypoid lesion in the large bowel contains invasive cancer is related to the size of the polyp, being negligible (<2%) in lesions <1.5 cm, intermediate (2–10%) in lesions 1.5–2.5 cm, and substantial (10%) in lesions >2.5 cm in size.

Following the detection of an adenomatous polyp, the entire large bowel should be visualized endoscopically because synchronous lesions are noted in about one-third of cases. Colonoscopy should then be repeated periodically, even in the absence of a previously documented malignancy, because such patients have a 30–50% probability of developing another adenoma and are at a higher-than-average risk for developing a colorectal carcinoma. Adenomatous polyps are thought to require >5 years of growth before becoming clinically significant; colonoscopy need not be carried out more frequently than every 3 years for the vast majority of patients.

ETIOLOGY AND RISK FACTORS

Risk factors for the development of colorectal cancer are listed in **Table 77-1**.

Diet The etiology for most cases of large-bowel cancer appears to be related to environmental factors. The disease occurs more often in upper socioeconomic populations who live in urban areas. Mortality from colorectal cancer is directly correlated with per capita consumption of calories, meat protein, and dietary fat and oil as well as elevations in the serum cholesterol concentration and mortality from coronary artery disease. Geographic variations in incidence largely are unrelated to genetic differences, since migrant groups tend to assume the large-bowel cancer incidence rates of their adopted countries. Furthermore, population groups such as Mormons and Seventh Day Adventists, whose lifestyle and dietary habits differ somewhat from those of their neighbors, have significantly lower-than-expected incidence and mortality rates for colorectal cancer. The incidence of colorectal cancer has increased in Japan since that nation has adopted a more "Western" diet. At least three hypotheses have been proposed to explain the relationship to diet, none of which is fully satisfactory.

ANIMAL FATS One hypothesis is that the ingestion of animal fats found in red meats and processed meat leads to an increased proportion of anaerobes in the gut microflora, resulting in the conversion of normal bile acids into carcinogens. This provocative hypothesis is supported by several reports of increased amounts of fecal anaerobes in the stools of patients with colorectal cancer. Diets high in animal (but not vegetable) fats are also associated with high serum cholesterol, which is also associated with enhanced risk for the development of colorectal adenomas and carcinomas.

INSULIN RESISTANCE The large number of calories in Western diets coupled with physical inactivity has been associated with a higher prevalence of obesity. Obese persons develop insulin resistance with increased circulating levels of insulin, leading to higher circulating concentrations of insulin-like growth factor type I (IGF-I). This growth factor appears to stimulate proliferation of the intestinal mucosa.

FIBER Contrary to prior beliefs, the results of randomized trials and case-controlled studies have *failed* to show any value for dietary fiber or diets high in fruits and vegetables in preventing the recurrence of colorectal adenomas or the development of colorectal cancer.

The weight of epidemiologic evidence, however, implicates diet as being the major etiologic factor for colorectal cancer, particularly diets high in animal fat and in calories.

HEREDITARY FACTORS AND SYNDROMES

Up to 25% of patients with colorectal cancer have a family history of the disease, suggesting a hereditary predisposition. Inherited large-bowel cancers can be divided into two main groups: the well-studied but uncommon polyposis syndromes and the more common nonpolyposis syndromes **(Table 77-2)**.

TABLE 77-1 Risk Factors for the Development of Colorectal Cancer

Diet: Animal fat
Hereditary syndromes
Polyposis coli
MYH-associated polyposis
Nonpolyposis syndrome (Lynch's syndrome)
Inflammatory bowel disease
Streptococcus bovis bacteremia
? Tobacco use

TABLE 77-2 Hereditable (Autosomal Dominant) Gastrointestinal Polyposis Syndromes

SYNDROME	DISTRIBUTION OF POLYPS	HISTOLOGIC TYPE	MALIGNANT POTENTIAL	ASSOCIATED LESIONS
Familial adenomatous polyposis	Large intestine	Adenoma	Common	None
Gardner's syndrome	Large and small intestines	Adenoma	Common	Osteomas, fibromas, lipomas, epidermoid cysts, ampullary cancers, congenital hypertrophy of retinal pigment epithelium
Turcot's syndrome	Large intestine	Adenoma	Common	Brain tumors
MYH-associated polyposis	Large intestine	Adenoma	Common	None
Nonpolyposis syndrome (Lynch's syndrome)	Large intestine (often proximal)	Adenoma	Common	Endometrial and ovarian tumors (most frequently) gastric, genitourinary, pancreatic, biliary cancers (less frequently)
Peutz-Jeghers syndrome	Small and large intestines, stomach	Hamartoma	Rare	Mucocutaneous pigmentation; tumors of the ovary, breast, pancreas, endometrium
Juvenile polyposis	Large and small intestines, stomach	Hamartoma, rarely progressing to adenoma	Rare	Various congenital abnormalities

Polyposis Coli Polyposis coli (familial polyposis of the colon) is a rare condition characterized by the appearance of thousands of adenomatous polyps throughout the large bowel. It is transmitted as an autosomal dominant trait; the occasional patient with no family history probably developed the condition due to a spontaneous mutation. Polyposis coli is associated with a deletion in the long arm of chromosome 5 (including the *APC* gene) in both neoplastic (somatic mutation) and normal (germline mutation) cells. The loss of this genetic material (i.e., allelic loss) results in the absence of tumor-suppressor genes whose protein products would normally inhibit neoplastic growth. The presence of soft tissue and bony tumors, congenital hypertrophy of the retinal pigment epithelium, mesenteric desmoid tumors, and ampullary cancers in addition to the colonic polyps characterizes a subset of polyposis coli known as *Gardner's syndrome*. The appearance of malignant tumors of the central nervous system accompanying polyposis coli defines *Turcot's syndrome*. The colonic polyps in all these conditions are rarely present before puberty but are generally evident in affected individuals by age 25. If the polyposis is not treated surgically, colorectal cancer will develop in almost all patients aged <40. Polyposis coli results from a defect in the colonic mucosa, leading to an abnormal proliferative pattern and impaired DNA repair mechanisms. Once the multiple polyps are detected, patients should undergo a total colectomy. Medical therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac and selective cyclooxygenase-2 inhibitors such as celecoxib can decrease the number and size of polyps in patients with polyposis coli; however, this effect on polyps is only temporary, and the use of NSAIDs has not been shown to reduce the risk of cancer. Colectomy remains the primary therapy/prevention. The offspring of patients with polyposis coli, who often are prepubertal when the diagnosis is made in the parent, have a 50% risk for developing this premalignant disorder and should be carefully screened by annual flexible sigmoidoscopy until age 35. Proctosigmoidoscopy is a sufficient screening procedure because polyps tend to be evenly distributed from cecum to anus, making more invasive and expensive techniques such as colonoscopy or barium enema unnecessary. Testing for occult blood in the stool is an inadequate screening maneuver. If a causative germline *APC* mutation has been identified in an affected family member, an alternative method for identifying carriers is testing DNA from peripheral blood mononuclear cells for the presence of the specific *APC* mutation. The detection of such a germline mutation can lead to a definitive diagnosis before the development of polyps.

MYH-Associated Polyposis MYH-associated polyposis (MAP) is a rare autosomal recessive syndrome caused by a biallelic mutation in the *MUT4H* gene. This hereditary condition may have a variable clinical presentation, resembling polyposis coli or colorectal cancer occurring in younger individuals without polyposis. Screening and colectomy guidelines for this syndrome are less clear than for polyposis coli, but annual to biennial colonoscopic surveillance is generally recommended starting at age 25–30.

Hereditary Nonpolyposis Colon Cancer Hereditary nonpolyposis colon cancer (HNPCC), also known as *Lynch's syndrome*, is another autosomal dominant trait. It is characterized by the presence of three or more relatives with histologically documented colorectal cancer, one of whom is a first-degree relative of the other two; one or more cases of colorectal cancer diagnosed before age 50 in the family; and colorectal cancer involving at least two generations. In contrast to polyposis coli, HNPCC is associated with an unusually high frequency of cancer arising in the proximal large bowel. The median age for the appearance of an adenocarcinoma is <50 years, 10–15 years younger than the median age for the general population. Despite having a poorly differentiated, mucinous histologic appearance, the proximal colon tumors that characterize HNPCC have a better prognosis than sporadic tumors from patients of similar age. Families with HNPCC often include individuals with multiple primary cancers; the association of colorectal cancer with either ovarian or endometrial carcinomas is especially strong in women, and an increased appearance of gastric, small-bowel, genitourinary, pancreaticobiliary, and sebaceous skin tumors has been reported as well. It has been recommended that members of such families undergo annual or biennial colonoscopy beginning at age 25 years, with intermittent pelvic ultrasonography and endometrial biopsy for afflicted women; such a screening strategy has not yet been validated. HNPCC is associated with germline mutations of several genes, particularly *hMSH2* on chromosome 2 and *hMLH1* on chromosome 3. These mutations lead to errors in DNA replication and are thought to result in DNA instability because of defective repair of DNA mismatches resulting in abnormal cell growth and tumor development. Testing tumor cells through molecular analysis of DNA for "microsatellite instability" or immunohistochemical staining for deficiency in mismatch repair proteins in patients with colorectal cancer and a positive family history for colorectal or endometrial cancer may identify probands with HNPCC.

INFLAMMATORY BOWEL DISEASE

(Chap. 319) Large-bowel cancer is increased in incidence in patients with long-standing inflammatory bowel disease (IBD). Cancers develop more commonly in patients with ulcerative colitis than in those with granulomatous (i.e., Crohn's) colitis, but this impression may result in part from the occasional difficulty of differentiating these two conditions. The risk of colorectal cancer in a patient with IBD is relatively small during the initial 10 years of the disease, but then appears to increase at a rate of ~0.5–1% per year. Cancer may develop in 8–30% of patients after 25 years. The risk is higher in younger patients with pancolitis.

Cancer surveillance strategies in patients with IBD are unsatisfactory. Symptoms such as bloody diarrhea, abdominal cramping, and obstruction, which may signal the appearance of a tumor, are similar to the complaints caused by a flare-up of the underlying disease. In patients with a history of IBD lasting ≥15 years who continue to experience exacerbations, the surgical removal of the colon can significantly

reduce the risk for cancer and also eliminate the target organ for the underlying chronic gastrointestinal disorder. The value of such surveillance techniques as colonoscopy with mucosal biopsies and brushings for less symptomatic individuals with chronic IBD is uncertain. The lack of uniformity regarding the pathologic criteria that characterize dysplasia and the absence of data that such surveillance reduces the development of lethal cancers have made this costly practice an area of controversy.

OTHER HIGH-RISK CONDITIONS

***Streptococcus bovis* Bacteremia** For unknown reasons, individuals who develop endocarditis or septicemia from this fecal bacterium have a high incidence of occult colorectal tumors and, possibly, upper gastrointestinal cancers as well. Endoscopic or radiographic screening appears advisable.

Tobacco Use Cigarette smoking is linked to the development of colorectal adenomas, particularly after >35 years of tobacco use. No biologic explanation for this association has yet been proposed.

PRIMARY PREVENTION

Several orally administered compounds have been assessed as possible inhibitors of colon cancer. The most effective class of chemopreventive agents is aspirin and other NSAIDs, which are thought to suppress cell proliferation by inhibiting prostaglandin synthesis. Regular aspirin use reduces the risk of colon adenomas and carcinomas as well as death from large-bowel cancer; such use also appears to diminish the likelihood for developing additional premalignant adenomas following successful treatment for a prior colon carcinoma. This effect of aspirin on colon carcinogenesis increases with the duration and dosage of drug use. Emerging data linking adequate plasma levels of vitamin D with reduced risk of adenomatous polyps and colorectal cancer appear promising. The value of vitamin D as a form of chemoprevention is under study. Antioxidant vitamins such as ascorbic acid, tocopherols, and β-carotene are ineffective at reducing the incidence of subsequent adenomas in patients who have undergone the removal of a colon adenoma. Estrogen replacement therapy has been associated with a reduction in the risk of colorectal cancer in women, conceivably by an effect on bile acid synthesis and composition or by decreasing synthesis of IGF-I.

SCREENING

The rationale for colorectal cancer screening programs is that the removal of adenomatous polyps will prevent colorectal cancer, and that earlier detection of localized, superficial cancers in asymptomatic individuals will increase the surgical cure rate. Such screening programs are particularly important for individuals with a family history of the disease in first-degree relatives. The relative risk for developing colorectal cancer increases to 1.75 in such individuals and may be even higher if the relative was afflicted before age 60. The prior use of rigid proctosigmoidoscopy as a screening tool was based on the observation that 60% of early lesions are located in the rectosigmoid. For unexplained reasons, however, the proportion of large-bowel cancers arising in the rectum has been decreasing during the past several decades, with a corresponding increase in the proportion of cancers in the more proximal descending colon. As such, the potential for rigid proctosigmoidoscopy to detect a sufficient number of occult neoplasms to make the procedure cost-effective has been questioned.

Screening strategies for colorectal cancer that have been examined during the past several decades are listed in Table 77-3.

Many programs directed at the early detection of colorectal cancers have focused on digital rectal examinations and fecal occult blood (i.e., stool guaiac) testing. The digital examination should be part of any routine physical evaluation in adults aged >40 years, serving as a screening test for prostate cancer in men, a component of the pelvic examination in women, and an inexpensive maneuver for the detection of masses in the rectum. However, because of the proximal migration of colorectal tumors, its value as an overall screening modality for colorectal cancer has become limited. The development of the fecal occult blood test has greatly facilitated the detection of occult fecal blood. Unfortunately, even when performed optimally, the fecal occult blood test has major limitations as a screening technique. About 50% of patients with documented colorectal cancers have a negative fecal occult blood test, consistent with the intermittent bleeding pattern of these tumors. When random cohorts of asymptomatic persons have been tested, 2–4% have fecal occult blood-positive stools. Colorectal cancers have been found in <10% of these "test-positive" cases, with benign polyps being detected in an additional 20–30%. Thus, a colorectal neoplasm will not be found in most asymptomatic individuals with occult blood in their stool. Nonetheless, persons found to have fecal occult blood-positive stool routinely undergo further medical evaluation, including sigmoidoscopy and/or colonoscopy—procedures that are not only uncomfortable and expensive but also associated with a small risk for significant complications. The added cost of these studies would appear justifiable if the small number of patients found to have occult neoplasms because of fecal occult blood screening could be shown to have an improved prognosis and prolonged survival. Prospectively controlled trials have shown a statistically significant reduction in mortality rate from colorectal cancer for individuals undergoing annual stool guaiac screening. However, this benefit only emerged after >13 years of follow-up and was extremely expensive to achieve because all positive tests (most of which were falsely positive) were followed by colonoscopy. Moreover, these colonoscopic examinations quite likely provided the opportunity for cancer prevention through the removal of potentially premalignant adenomatous polyps because the eventual development of cancer was reduced by 20% in the cohort undergoing annual screening.

With the appreciation that the carcinogenic process leading to the progression of the normal bowel mucosa to an adenomatous polyp and then to a cancer is the result of a series of molecular changes, investigators have examined fecal DNA for evidence of mutations associated with such molecular changes as evidence of the occult presence of precancerous lesions or actual malignancies. Such a strategy has been tested in >4000 asymptomatic individuals whose stool was assessed for occult blood and for 21 possible mutations in fecal DNA; these study subjects also underwent colonoscopy. Although the fecal DNA strategy suggested the presence of more advanced adenomas and cancers than did the fecal occult blood testing approach, the overall sensitivity, using colonoscopic findings as the standard, was <50%, diminishing enthusiasm for further pursuit of the fecal DNA screening strategy.

The use of imaging studies to screen for colorectal cancers has also been explored. Air contrast barium enemas had been used to identify sources of occult blood in the stool prior to the advent of fiberoptic endoscopy; the cumbersome nature of the procedure and inconvenience to patients limited its widespread adoption. The introduction of computed tomography (CT) scanning led to the development of virtual (i.e., CT) colonography as an alternative to the growing use of endoscopic screening techniques. Virtual colonography was proposed as being equivalent in sensitivity to colonoscopy and being available in a more widespread manner because it did not require the same degree of operator expertise as fiberoptic endoscopy. However, virtual colonography requires the same cathartic preparation that has limited widespread acceptance in association with endoscopic colonoscopy, is diagnostic but not therapeutic (i.e., patients with suspicious findings

TABLE 77-3 Screening Strategies for Colorectal Cancer

Digital rectal examination
Stool testing
• Occult blood
• Fecal DNA
Imaging
• Contrast barium enema
• Virtual (i.e., computed tomography colonography)
Endoscopy
• Flexible sigmoidoscopy
• Colonoscopy

must undergo a subsequent endoscopic procedure for polypectomy or biopsy), and, in the setting of general radiology practices, appears to be less sensitive as a screening technique when compared with endoscopic procedures.

With the appreciation of the inadequacy of fecal occult blood testing alone, concerns about the practicality of imaging approaches, and the wider adoption of endoscopic examinations by the primary care community, screening strategies in asymptomatic persons have changed. At present, both the American Cancer Society and the National Comprehensive Cancer Network recommend either fecal occult blood testing annually coupled with flexible sigmoidoscopy every 5 years or colonoscopy every 10 years beginning at age 50 in asymptomatic individuals with no personal or family history of polyps or colorectal cancer. The recommendation for the inclusion of flexible sigmoidoscopy is strongly supported by the recently published results of three randomized trials performed in the United States, the United Kingdom, and Italy, involving >350,000 individuals, which consistently showed that periodic (even single) sigmoidoscopic examinations, after more than a decade of median follow-up, lead to an ~21% reduction in the development of colorectal cancer and a >25% reduction in mortality from the malignant disease. Less than 20% of participants in these studies underwent a subsequent colonoscopy. In contrast to the cathartic preparation required before colonoscopic procedures, which is only performed by highly trained specialists, flexible sigmoidoscopy requires only an enema as preparation and can be accurately performed by nonspecialty physicians or physician-extenders. The randomized screening studies using flexible sigmoidoscopy led to the estimate that ~650 individuals needed to be screened to prevent one colorectal cancer death; this contrasts with the data for mammography where the number of women needing to be screened to prevent one breast cancer death is 2500, reinforcing the efficacy of endoscopic surveillance for colorectal cancer screening. Presumably the benefit from the sigmoidoscopic screening is the result of the identification and removal of adenomatous polyps; it is intriguing that this benefit has been achieved using a technique that leaves the proximal half of the large bowel unvisualized.

It remains to be seen whether surveillance colonoscopy, which has gained increasing popularity in the United States for colorectal cancer screening, will prove to be more effective than flexible sigmoidoscopy. Ongoing randomized trials being conducted in Europe are addressing this issue. Although flexible sigmoidoscopy only visualizes the distal half of the large bowel, leading to the assumption that colonoscopy represents a more informative approach, colonoscopy has been reported as being less accurate for screening the proximal rather than the distal colon, perhaps due to technical considerations but also possibly because of a greater frequency of serrated (i.e., "flat") polyps in the right colon, which are more difficult to identify. At present, colonoscopy performed every 10 years has been offered as an alternative to annual fecal occult blood testing with periodic (every 5 years) flexible sigmoidoscopy. Colonoscopy has been shown to be superior to double-contract barium enema and also to have a higher sensitivity for detecting villous or dysplastic adenomas or cancers than the strategy using occult fecal blood testing and flexible sigmoidoscopy. Whether colonoscopy performed every 10 years beginning at age 50 is medically superior and economically equivalent to flexible sigmoidoscopy remains to be determined.

CLINICAL FEATURES

Presenting Symptoms Symptoms vary with the anatomic location of the tumor. Because stool is relatively liquid as it passes through the ileocecal valve into the right colon, cancers arising in the cecum and ascending colon may become quite large without resulting in any obstructive symptoms or noticeable alterations in bowel habits. Lesions of the right colon commonly ulcerate, leading to chronic, insidious blood loss without a change in the appearance of the stool. Consequently, patients with tumors of the ascending colon often present with symptoms such as fatigue, palpitations, and even angina pectoris and are found to have a hypochromic, microcytic anemia indicative of iron deficiency. Because the cancers may bleed intermittently, a random fecal occult blood test may be negative. As a result, the unexplained presence of iron-deficiency anemia in any adult (with the possible exception of a premenopausal, multiparous woman) mandates a thorough endoscopic and/or radiographic visualization of the entire large bowel (Fig. 77-1).

FIGURE 77-1 Double-contrast air-barium enema revealing a sessile tumor of the cecum in a patient with iron-deficiency anemia and guaiac-positive stool. The lesion at surgery was a stage II adenocarcinoma.

Because stool becomes more formed as it passes into the transverse and descending colon, tumors arising there tend to impede the passage of stool, resulting in the development of abdominal cramping, occasional obstruction, and even perforation. Radiographs of the abdomen often reveal characteristic annular, constricting lesions ("apple-core" or "napkin-ring") (Fig. 77-2).

Cancers arising in the rectosigmoid are often associated with hematochezia, tenesmus, and narrowing of the caliber of stool; anemia is an infrequent finding. While these symptoms may lead patients and their

FIGURE 77-2 Annular, constricting adenocarcinoma of the descending colon. This radiographic appearance is referred to as an "apple-core" lesion and is always highly suggestive of malignancy.

physicians to suspect the presence of hemorrhoids, the development of rectal bleeding and/or altered bowel habits demands a prompt digital rectal examination and proctosigmoidoscopy.

Staging, Prognostic Factors, and Patterns of Spread The prognosis for individuals having colorectal cancer is related to the depth of tumor penetration into the bowel wall and the presence of both regional lymph node involvement and distant metastases. These variables are incorporated into a TNM classification method, in which T represents the depth of tumor penetration, N the presence of lymph node involvement, and M the presence or absence of distant metastases **(Fig. 77-3)**. Superficial lesions that do not involve regional lymph nodes and do not penetrate through the submucosa (T1) or the muscularis (T2) are designated as *stage I* (T1–2N0M0) disease; tumors that penetrate through the muscularis but have not spread to lymph nodes are *stage II* disease (T3-4N0M0); regional lymph node involvement defines *stage III* (TXN1-2M0) disease; and metastatic spread to sites such as liver, lung, or bone indicates *stage IV* (TXNXM1) disease. Unless gross evidence of metastatic disease is present, disease stage cannot be determined accurately before surgical resection and pathologic analysis of the operative specimens.

Most recurrences after a surgical resection of a large-bowel cancer occur within the first 4 years, making 5-year survival a fairly reliable indicator of cure. The likelihood for 5-year survival in patients with colorectal cancer is stage-related (Fig. 77-3). That likelihood has improved during the past several decades when similar surgical stages have been compared. The most plausible explanation for this improvement is more thorough intraoperative and pathologic staging. In particular, more exacting attention to pathologic detail has revealed that the prognosis following the resection of a colorectal cancer is not related merely to the presence or absence of regional lymph node involvement; rather, prognosis may be more precisely gauged by the number of involved lymph nodes (one to three lymph nodes ["N1"] vs four or more lymph nodes ["N2"]) and the number of nodes examined. A minimum of 12 sampled lymph nodes is thought necessary to accurately define tumor stage, and the more nodes examined, the better. Other predictors of a poor prognosis after a total surgical resection include tumor penetration through the bowel wall into pericolic fat, poorly differentiated histology, perforation and/or tumor adherence to adjacent organs (increasing the risk for an anatomically adjacent recurrence), and venous invasion by tumor **(Table 77-4)**. Regardless of the clinicopathologic stage, a preoperative elevation of the plasma carcinoembryonic antigen (CEA) level predicts eventual tumor recurrence. The presence of specific chromosomal aberrations, particularly a mutation in the *b-raf* gene in tumor cells, appears to predict for a higher risk for metastatic spread. Conversely, the detection of microsatellite instability in tumor tissue indicates a more favorable outcome. Tumors arising in the left colon are associated with a better prognosis than those appearing in the right colon, likely due to differences in molecular patterns. In contrast to most other cancers, the prognosis in colorectal cancer is not influenced by the size of the primary lesion when adjusted for nodal involvement and histologic differentiation.

TABLE 77-4 Predictors of Poorer Outcomes Following Total Surgical Resection of Colorectal Cancer

Tumor spread to regional lymph nodes
Number of regional lymph nodes involved
Tumor penetration through the bowel wall
Poorly differentiated histology
Perforation
Tumor adherence to adjacent organs
Venous invasion
Preoperative elevation of CEA titer (>5 ng/mL)
Specific chromosomal deletion (e.g., mutation in the *b-raf* gene)
Right-sided location of primary tumor

Abbreviation: CEA, carcinoembryonic antigen.

Cancers of the large bowel generally spread to regional lymph nodes or to the liver via the portal venous circulation. The liver represents the most frequent visceral site of metastasis; it is the initial site of distant spread in one-third of recurring colorectal cancers and is involved in more than two-thirds of such patients at the time of death. In general, colorectal cancer rarely spreads to the lungs, supraclavicular lymph nodes, bone, or brain without prior spread to the liver. A major exception to this rule occurs in patients having primary tumors in the distal rectum, from which tumor cells may spread through the paravertebral venous plexus, escaping the portal venous system and thereby reaching the lungs or supraclavicular lymph nodes without hepatic involvement. The median survival after the detection of distant metastases has increased during the last 30 years from 6–9 months (hepatomegaly, abnormal liver chemistries) to 27–30 months (small

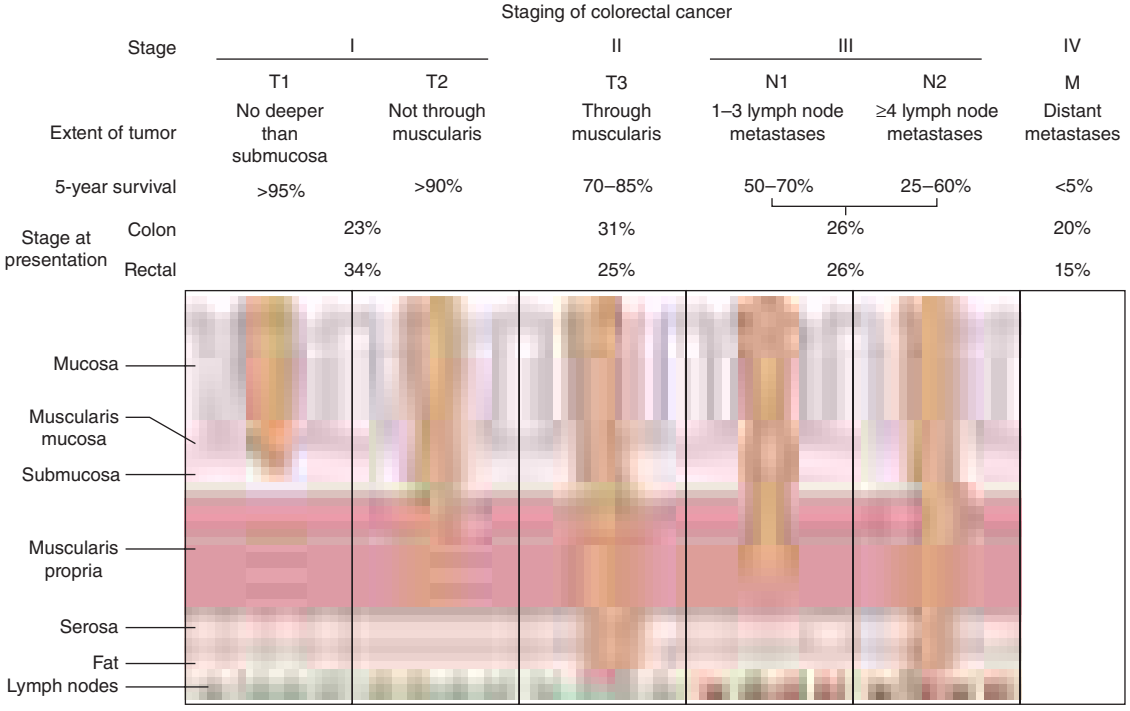

FIGURE 77-3 Staging and prognosis for patients with colorectal cancer.

liver nodule initially identified by elevated CEA level and subsequent CT scan) with increasingly effective systemic therapy improving this prognosis further.

Efforts to use gene expression profiles to identify patients at risk of recurrence or those particularly likely to benefit from adjuvant therapy have not yet yielded practice-changing results. Despite a burgeoning literature examining a host of prognostic factors, pathologic stage at diagnosis remains the best predictor of long-term prognosis. Patients with lymphovascular invasion and high preoperative CEA levels are likely to have a more aggressive clinical course.

TREATMENT

Colorectal Cancer

Total resection of tumor is the optimal treatment when a malignant lesion is detected in the large bowel. An evaluation for the presence of metastatic disease, including a thorough physical examination, biochemical assessment of liver function, measurement of the plasma CEA level, and a CT scan of the chest, abdomen, and pelvis, should be performed before surgery. When possible, a colonoscopy of the entire large bowel should be performed to identify synchronous neoplasms and/or polyps. The detection of metastases should not preclude surgery in patients with tumor-related symptoms such as gastrointestinal bleeding or obstruction, but it often prompts the use of a less radical operative procedure. The necessity for a primary tumor resection in asymptomatic individuals with metastatic disease is an area of controversy. At the time of laparotomy, the entire peritoneal cavity should be examined, with thorough inspection of the liver, pelvis, and hemidiaphragm and careful palpation of the full length of the large bowel. Following recovery from a complete resection, patients should be observed carefully for 5 years by semiannual physical examinations and blood chemistry measurements. If a complete colonoscopy was not performed preoperatively, it should be carried out within the first several postoperative months. Some authorities favor measuring plasma CEA levels at 3-month intervals because of the sensitivity of this test as a marker for otherwise undetectable tumor recurrence. Subsequent endoscopic surveillance of the large bowel, probably at triennial intervals, is indicated, because patients who have been cured of one colorectal cancer have a 3–5% probability of developing an additional bowel cancer during their lifetime and a >15% risk for the development of adenomatous polyps. Anastomotic ("suture-line") recurrences are infrequent in colorectal cancer patients, provided the surgical resection margins were adequate and free of tumor. The value of periodic CT scans of the abdomen, assessing for an early, asymptomatic indication of tumor recurrence, while uncertain, has been recommended annually for the first 3 postoperative years.

Radiation therapy to the pelvis is recommended for patients with rectal cancer because it reduces the 20–25% probability of regional recurrences following complete surgical resection of stage II or III tumors, especially if they have penetrated through the serosa. This alarmingly high rate of local disease recurrence is believed to be due to the fact that the contained anatomic space within the pelvis limits the extent of the resection and because the rich lymphatic network of the pelvic side wall immediately adjacent to the rectum facilitates the early spread of malignant cells into surgically inaccessible tissue. The use of sharp rather than blunt dissection of rectal cancers (*total mesorectal excision*) appears to reduce the likelihood of local disease recurrence to ~10%. Radiation therapy, either pre- or postoperatively, further reduces the likelihood of pelvic recurrences but does not appear to prolong survival. Combining radiation therapy with 5-fluorouracil (5-FU)-based chemotherapy, preferably prior to surgical resection, lowers local recurrence rates and improves overall survival. Preoperative radiotherapy is indicated for patients with large, potentially unresectable rectal cancers; such lesions may shrink enough to permit subsequent surgical removal. Radiation therapy alone is not effective as the primary treatment of colon cancer.

Systemic therapy for patients with colorectal cancer has become more effective. 5-FU remains the backbone of treatment for this disease. Partial responses are obtained in 15–20% of patients. The probability of tumor response appears to be somewhat greater for patients with liver metastases when chemotherapy is infused directly into the hepatic artery, but intraarterial treatment is costly and toxic and does not appear to appreciably prolong survival. The concomitant administration of folinic acid (leucovorin [LV]) improves the efficacy of 5-FU in patients with advanced colorectal cancer, presumably by enhancing the binding of 5-FU to its target enzyme, thymidylate synthase. 5-FU is generally administered intravenously but may also be given orally in the form of capecitabine (Xeloda) with seemingly similar efficacy.

Irinotecan (CPT-11), a topoisomerase 1 inhibitor, has been added to 5-FU and LV (e.g., FOLFIRI) with resultant improvement in response rates and survival of patients with metastatic disease. The *FOLFIRI regimen* is as follows: irinotecan, 180 mg/m^2 as a 90-min infusion on day 1; LV, 400 mg/m^2 as a 2-h infusion during irinotecan administration; immediately followed by 5-FU bolus, 400 mg/m^2, and 46-h continuous infusion of 2.4–3 g/m^2 every 2 weeks. Diarrhea is the major side effect from irinotecan. Oxaliplatin, a platinum analogue, also improves the response rate when added to 5-FU and LV (FOLFOX) as initial treatment of patients with metastatic disease. The *FOLFOX regimen* is as follows: 2-h infusion of LV (400 mg/m^2 per day) followed by a 5-FU bolus (400 mg/m^2 per day) and 22-h infusion (1200 mg/m^2) every 2 weeks, together with oxaliplatin, 85 mg/m^2 as a 2-h infusion on day 1. Oxaliplatin frequently causes a dose-dependent sensory neuropathy that often but not always resolves following the cessation of therapy. FOLFIRI and FOLFOX are equal in efficacy. In metastatic disease, these regimens may produce median survivals of 2 years.

Monoclonal antibodies are also effective in patients with advanced colorectal cancer. Cetuximab (Erbitux) and panitumumab (Vectibix) are directed against the epidermal growth factor receptor (EGFR), a transmembrane glycoprotein involved in signaling pathways affecting growth and proliferation of tumor cells. Both cetuximab and panitumumab, when given alone, have been shown to benefit a small proportion of previously treated patients, and cetuximab appears to have therapeutic synergy with such chemotherapeutic agents as irinotecan, even in patients previously resistant to this drug; this suggests that cetuximab can reverse cellular resistance to cytotoxic chemotherapy. The antibodies are not effective in the ~65% subset of colon tumors that contain mutations in *ras* or *b-raf* genes. The use of both cetuximab and panitumumab can lead to an acne-like rash, with the development and severity of the rash being correlated with the likelihood of antitumor efficacy. Inhibitors of the EGFR tyrosine kinase such as erlotinib (Tarceva) or sunitinib (Sutent) do not appear to be effective in colorectal cancer.

Bevacizumab (Avastin) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) and is thought to act as an antiangiogenesis agent. The addition of bevacizumab to irinotecan-containing combinations and to FOLFOX initially appeared to significantly improve the outcome observed with chemotherapy alone, but subsequent studies have suggested a more modest degree of benefit. The use of bevacizumab can lead to hypertension, proteinuria, and an increased likelihood of thromboembolic events.

Preliminary data suggest that the use of checkpoint inhibitors (i.e., PD-1 and PD-2) as immunotherapy is effective in the small subset of patients with metastatic colorectal cancer whose tumors are mismatch repair protein deficient (i.e., microsatellite unstable). Patients with solitary hepatic metastases without clinical or radiographic evidence of additional tumor involvement should be considered for partial liver resection, because such procedures are associated with 5-year survival rates of 25–30% when performed on selected individuals by experienced surgeons.

The administration of 5-FU and LV for 6 months after resection of tumor in patients with stage III disease leads to a 40% decrease in recurrence rates and 30% improvement in survival. The likelihood of recurrence has been further reduced when oxaliplatin has been

combined with 5-FU and LV (e.g., FOLFOX), particularly in patients whose tumor has spread to 4 or more regional lymph nodes (N2). Unexpectedly, the addition of irinotecan to 5-FU and LV as well as the addition of either bevacizumab or cetuximab to FOLFOX did not significantly enhance outcome. Patients with stage II tumors do not appear to benefit appreciably from adjuvant therapy, with the use of such treatment generally restricted to those patients having biologic characteristics (e.g., perforated tumors, T4 lesions, lymphovascular invasion) that place them at higher likelihood for recurrence. The addition of oxaliplatin to adjuvant treatment for patients aged >70 and those with stage II disease does not appear to provide any therapeutic benefit.

In rectal cancer, the delivery of preoperative or postoperative combined-modality therapy (5-FU or capecitabine plus radiation therapy) reduces the risk of recurrence and increases the chance of cure for patients with stage II and III tumors, with the preoperative approach being better tolerated.

CANCERS OF THE ANUS

Cancers of the anus account for 1–2% of the malignant tumors of the large bowel. Most such lesions arise in the anal canal, the anatomic area extending from the anorectal ring to a zone approximately halfway between the pectinate (or dentate) line and the anal verge. Carcinomas arising proximal to the pectinate line (i.e., in the transitional zone between the glandular mucosa of the rectum and the squamous epithelium of the distal anus) are known as *basaloid*, *cuboidal*, or *cloacogenic* tumors; about one-third of anal cancers have this histologic pattern. Malignancies arising distal to the pectinate line have squamous histology, ulcerate more frequently, and constitute ~55% of anal cancers. The prognosis for patients with basaloid and squamous cell cancers of the anus is identical when corrected for tumor size and the presence or absence of nodal spread.

The development of anal cancer is associated with infection by human papillomavirus, the same organism etiologically linked to cervical cancer. The virus is sexually transmitted. The infection may lead to anal warts (condyloma acuminata), which may progress to anal intraepithelial neoplasia and on to squamous cell carcinoma. The risk for anal cancer is increased among homosexual males, presumably related to anal intercourse. Anal cancer risk is increased in both men and women with AIDS, possibly because their immunosuppressed state permits more severe papillomavirus infection. Vaccination against human papilloma viruses appears to reduce the eventual risk for anal cancer. Anal cancers occur most commonly in middle-aged persons and are more frequent in women than men. At diagnosis, patients may experience bleeding, pain, sensation of a perianal mass, and pruritus.

Radical surgery (abdominal-perineal resection with lymph node sampling and a permanent colostomy) was once the treatment of choice for this tumor type. The 5-year survival rate after such a procedure was 55–70% in the absence of spread to regional lymph nodes and <20% if nodal involvement was present. An alternative therapeutic approach combining external beam radiation therapy with concomitant chemotherapy (5-FU and mitomycin C) has resulted in biopsy-proven disappearance of all tumor in >80% of patients whose initial lesion was <3 cm in size. Tumor recurrences develop in <10% of these patients, meaning that ~70% of patients with anal cancers can be cured with nonoperative treatment and without the need for a colostomy. Surgery should be reserved for the minority of individuals who are found to have residual tumor after being managed initially with radiation therapy combined with chemotherapy.

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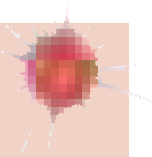
78 Tumors of the Liver and Biliary Tree



Josep M. Llovet

The burden of cancer is increasing worldwide. Lung, breast, and colorectal cancers are the most commonly diagnosed while lung and liver cancers are the most common causes of cancer death. Liver cancer is the sixth most common cancer worldwide, the second leading cause of cancer-related deaths and one of the few neoplasms whose incidence and mortality rates have been steadily increasing. Liver cancer comprises a heterogeneous group of malignant tumors with different histologic features and unfavorable prognosis that range from hepatocellular carcinoma (HCC; 85–90% cases), intrahepatic cholangiocarcinoma (iCCA; 10%), and other malignancies accounting for <1% of tumors, such as fibrolamellar HCC, mixed HCC-iCCA, epithelioid hemangiothelioma, and the pediatric cancer hepatoblastoma. The burden of liver cancer is increasing globally in almost all countries, and it is estimated to reach one million cases by 2030.

HEPATOCELLULAR CARCINOMA

EPIDEMIOLOGY AND RISK FACTORS

Overall, liver cancer accounts for 7% of all cancers (~850,000 new cases each year), and HCC represents 90% of primary liver cancers. The highest incidence rates of HCC occur in Asia and sub-Saharan Africa due to the high prevalence of hepatitis B virus (HBV) infection, with 20–35 cases per 100,000 inhabitants. Southern Europe, and now North America have intermediate incidence rates (10 cases per 100,000), whereas Northern and Western Europe have low incidence rates of less than 5 cases per 100,000 inhabitants. In the United States, liver cancer is ranked number one in terms of increased mortality during the past two decades **(Fig. 78-1)**, with an incidence of 35,000 cases per year. HCC has a strong male preponderance with a male to female ratio estimated to be 2.5. The incidence increases with age, reaching a peak at 65–70 years old. In Chinese and in black African populations (where vertical transmission of HBV occurs), the mean age is 40–50 years. By contrast, in Japan mean age in men is now around 75 years.

The risk factors for HCC are well established **(Fig. 78-2)**. The main risk factor is cirrhosis—and associated chronic liver damage caused by inflammation and fibrosis—of any etiology, which underlies 80% of HCC cases worldwide and results from chronic infection by HBV or hepatitis C virus (HCV) infection, alcohol abuse, metabolic syndrome, and hemochromatosis (associated to *HFE1* gene germ-line mutations). Cirrhotic patients represent 1% of the human population and one-third of them will develop HCC during their lifetime. Long-term follow-up studies have established an annual risk of HCC development of 2% in HBV-infected cirrhotic patients and 3–7% in HCV-infected cirrhotic patients. HCC is less common in cirrhosis associated with alpha-1 antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, and cholestatic liver disorders. Predictors of liver cancer development

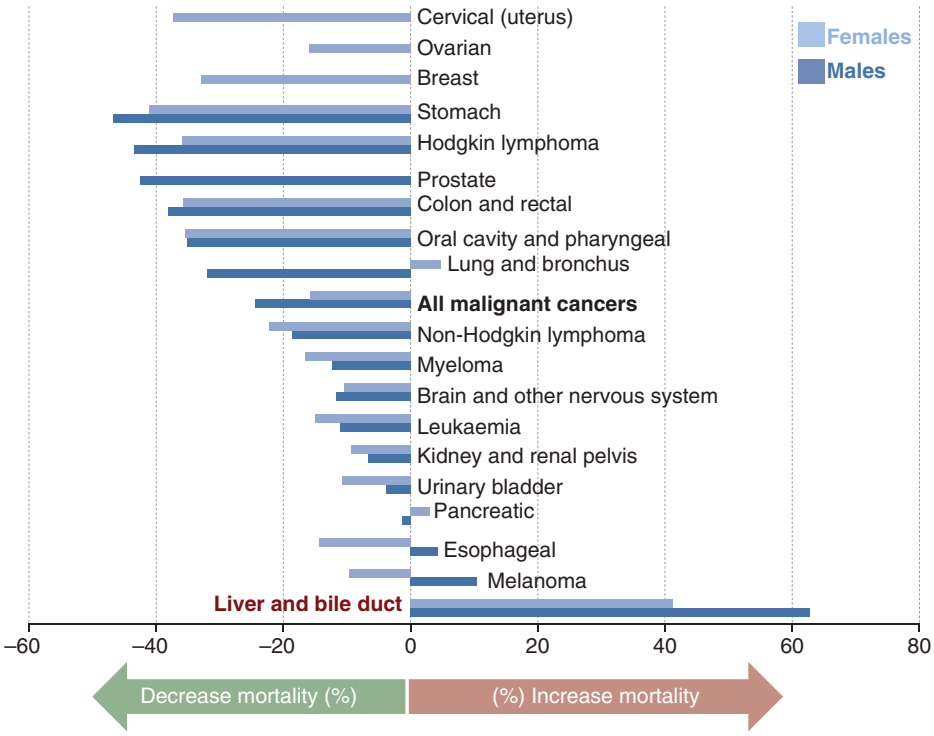


FIGURE 78-1 Mortality trends of patients with different malignancies in the United States between 1990 and 2009. Changes in cancer mortality across tumor types in the United States. Liver and bile duct cancer rank first in terms of increase mortality for both men and women. *(Reprinted with permission from JM Llovet et al: Nat Rev Clin Oncol 12:408, 2015.)*

among cirrhotic patients have been associated with liver disease severity (platelet count of <100,000/mm^3, presence of portal hypertension), the degree of liver stiffness as measured by transient elastography, and liver gene signatures capturing the *cancer field effect*.

In terms of attributable risk fraction, HBV infection—a DNA virus that can cause insertional mutagenesis and affects 400 million people globally—accounts for 50% of HCC cases, and is the predominant cause in Asia and Africa. Among patients with HBV infection, a family history of HCC, HBeAg seropositivity, high viral load and genotype C are independent predictors of HCC development. Chronic treatments with effective antiviral HBV therapies are able to significantly decrease the risk of cancer. HCV infection—an RNA virus that affects 170 million people—is responsible for 30% of cases, and is the main cause of HCC in Europe and North America. Among patients with HCV infection, HCC occurs almost exclusively when relevant liver damage is present (either advanced fibrosis—Metavir F3 [Metavir is a scoring system for hepatic histology that grades fibrosis from 0 to 4 with higher numbers indicating more fibrosis]—or cirrhosis), particularly if associated with HCV genotype 1b. In addition, a polymorphism that activates *EGFR*, the EGF receptor, has been established as associated with HCV-HCC in several studies. Antiviral therapies with interferon regimes are able to prevent cirrhosis development and HCC occurrence. The impact of new direct-acting antiviral (DAA) regimes on HCC incidence has not yet been established.

Alcohol consumption and metabolic syndrome due to diabetes and obesity are responsible for ~20% of cases. Non-alcoholic steatohepatitis (NASH), related to metabolic syndrome, is now an emerging cause of

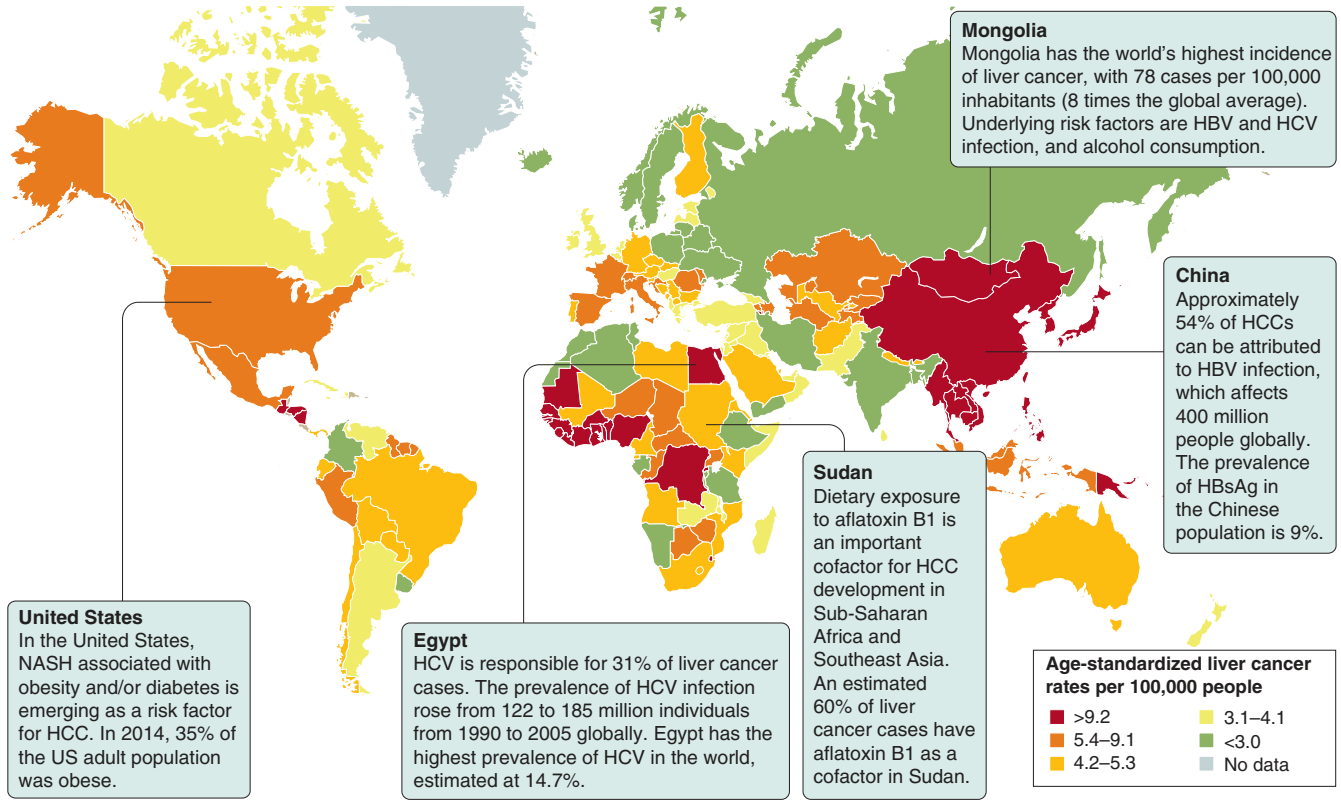


FIGURE 78-2 The global burden of hepatocellular carcinoma. Incidence of hepatocellular carcinoma (HCC) and risk factors. ASR, Age-standardized rate per 100,000 inhabitants. The main risk factors for HCC development are HBV infection (China), HCV infection (example: Egypt), alcohol intake, non-alcoholic steatohepatitis (United States), and aflatoxin B1 (Sudan). Mongolia has the highest incidence of HCC globally, with 78 cases per 100,000 inhabitants. *(Reprinted with permission from JM Llovet et al: Nat Rev Dis Primers 2:16018, 2016.)*

HCC in developed countries. A *PNPLA3* polymorphism is strongly associated with fatty and alcoholic chronic liver diseases and HCC occurrence. Other co-factors contributing to HCC development are tobacco and aflatoxin B1, a fungal carcinogen present in food supplies that induces *TP53* mutations. Finally, infection with adeno-associated virus 2 is associated with HCC in individuals without cirrhosis. Aside from the associations described above, genome-wide association studies have not yet confirmed polymorphisms predisposing to HCC development.

There is a growing incidence of HCC world-wide. The growth in U.S. incidence results from the emergence of end-stage liver disease due to hepatitis C, the increase in HBV-related HCC among immigrants from endemic countries, and the accelerating prevalence of obesity and fatty liver disease. In Europe and Asia, the growth has been less prominent. In some countries the incidence is declining, like Italy and Japan, a country where the impact of HCV-related HCC was first noticed after World War II. Finally, the impact of universal infant vaccination against HBV has decreased the rate of HBV-related HCC in endemic countries, such as Taiwan.

MOLECULAR PATHOGENESIS

HCC development is a complex multistep process that starts with precancerous cirrhotic nodules, so-called low-grade dysplastic nodules (LGDN) that evolve to high-grade dysplastic nodules (HGDN) that can transform into early-stage HCC. Molecular studies support the pivotal role of adult hepatocytes as the cell of origin, either by directly transforming to HCC or by de-differentiating into hepatocyte precursor cells. Alternatively, progenitor cells also give rise to HCC with progenitor markers.

Genomic analysis has provided a clear picture of the main drivers responsible for HCC initiation and progression. This tumor results from the accumulation of around 35–40 somatic genomic alterations per tumor, among which 4–8 are considered driver cancer genes. HCC is a prototypical inflammation-associated cancer, where immune microenvironment and oxidative stress present in chronically damaged livers play pivotal roles in inducing mutations. In pre-neoplastic HGDN, mutations in telomere reverse transcriptase (*TERT*) gene (20% cases) and gains in 8q have been described. Oncogenic transformation occurs upon additional genomic hits including Wnt/β-catenin pathway activation, re-expression of fetal genes, deregulation of protein folding machinery and the response to oxidative stress. Genomic studies and next-generation sequencing conducted during the past decade enables a description of the landscape of mutations, signaling pathways and a molecular classification of the disease. Nonetheless, none of these data have yet translated into actual clinical benefits for molecularly defined tumor subgroups.

Molecular Drivers The landscape of mutational drivers in HCC identified by deep-genome sequencing of ~1,000 samples is detailed in Table 78-1. The most common mutations are in the telomerase reverse transcriptase (*TERT*) promoter (56%), *TP53* (27%), *CTNNB1* (26%), *ARID2* (7%), *ARID1A* (6%), and *AXIN1* (5%) genes. These mutated genes participate in cell-cycle control and senescence -*TERT* or *TP53*-, in cell differentiation—*CTNNB1* and *AXIN-1*, and chromatin remodeling -*ARID2* and *ARID1A*-. Genes commonly mutated in other solid tumors such as *EGFR*, HER2, *PIK3CA, BRAF*, or *KRAS* are rarely mutated in HCC (<5%). Thus, the most prominent drivers are not currently targetable. Some risk factors have been associated with specific molecular aberrations. HBV integrates into the genome of driver genes, such as the *TERT* promoter, *MLL4*, and cyclin E1 (*CCNE1*). HCV infection and alcohol abuse have been significantly associated with *CTNNB1* mutations. *TP53* mutations are the most frequent alterations with a specific hotspot of mutation (R249S) in patients with aflatoxin B1 exposure.

Studies assessing copy-number alterations in HCCs have consistently identified: (i) high level amplifications at 5–10% prevalence containing oncogenes in 11q13 (CCND1 and *FGF19*) and 6p21 (*VEGFA*), *TERT* focal amplification and homozygous deletion of *CDKN2A*; and (ii) common amplifications containing *MYC* (8q gain) and *MET* genes (focal gains 7q31). High-level amplifications of 11q13 include *CCND1* and *FGF19*, which have been demonstrated as prominent oncogenes in HCC and are potential therapeutic targets. Similarly, high-level gains of 6p21 containing more than four copies of *VEGFA* were identified in 4–8% of HCCs. *VEGFA* amplification can induce tumor proliferation by unleashing macrophage-mediated hepatocyte growth factor secretion.

TABLE 78-1 Molecular Aberrations Common in HCC[a]

PATHWAY	TARGET	PREVALENCE (%)
Mutations		
Telomere stability	*TERT* promoter	56
p53/cell cycle control	*TP53*	27
	ATM	3
	RB1	3
Wnt/β-catenin signaling	*CTNNB1*	26
	AXIN1	5
Chromatin remodeling	*ARID1A*	6
	ARID2	7
	KMT2A	3
	KMT2C	3
Ras/PI3K/MTOR pathway	*RPS6KA3*	3
	TSC1/TSC2	3
Oxidative stress	*NFE2L2*	3
	KEAP1	3
High-Level Focal Amplifications		
VEGF signaling	*VEGFA*	3
FGF signaling	*FGF19*	6
Cell-cycle control	*CCND1*	7
Target with Homozygous Deletion		
TP53/cell-cycle control	*CDKN2A*	5
	TP53	4
	RB1	4
Wnt/β-catenin signaling	*AXIN1*	3

[a]Recurrent mutations, focal amplifications or homozygous deletions in HCC based on next-generation sequencing analyses.

Signaling Pathways Several signaling pathways have been implicated in HCC progression and dissemination. Activation of these pathways can result from structural alterations (mutations and amplifications/losses), or epigenetic modifications. In brief, (a) TERT overexpression occurs in 90% of cases, particularly related to promoter *TERT* mutations or amplifications; (b) inactivation of p53 and alterations of cell cycle are major defects in HCC, particularly in cases related to HBV infection; (c) Wnt/β-Catenin pathway activation occurs in 50% of cases, either as a result of β-catenin or *AXIN1* mutation, or overexpression of Frizzled receptors or inactivation of E-cadherin; (d) PI3K/PTEN/Akt/mTOR pathway is activated in 40–50% of HCCs due to mutation and focal deletion of the tuberous sclerosis complex (*TSC*)*1*/*TSC2* genes, *PTEN* or ligand overexpression of EGF or IGF upstream signals; (e) Ras MAPK signaling is activated in half of early and almost all advanced HCCs, activation results from up-stream signaling by EGF, IGF, and MET activation, and from the epigenetic silencing of tumor suppressors such as *NORE1A* and *RASSF1A15*; (f) insulin-like growth factor receptor (IGFR) signaling is activated in 20% of cases through overexpression of the oncogenic ligand IGF2 or allelic loss affecting the tumor suppressor IGF2R; (g) dysregulation of the c-MET receptor and its ligand HGF, critical for hepatocyte regeneration after liver injury, are common events in advanced HCC (50%); (h) vascular endothelial growth factor (VEGF) signaling is the cornerstone of angiogenesis in HCC, along with activated angiogenic pathways such as Ang2 and FGF signaling; and (i) chromatin remodelling complexes and epigenetic regulators are frequently altered in HCC due to *ARID1A* and *ARID2* mutations. Several agents that target these different processes are currently being tested in Phase I-III trials.

Molecular Classes and Prognostic Gene Signatures Genomic studies have revealed two molecular subclasses of HCC, each representing ~50% of patients. The proliferative subclass is enriched by activation of Ras, mTOR, and insulin-like growth factor (IGF) signaling

and *FGF19* amplification, and is associated with HBV-related etiologies, overexpression of α-fetoprotein and poor outcomes (particularly those tumors enriched in progenitor cell markers). By contrast, the so called non-proliferative subclass contains a subtype characterized by *CTNNB1* mutations and better outcome. Another classification based upon immune status has been proposed. It defines an immune HCC class in ~25% of cases characterized by immune infiltrate with expression of PD1/PDL1, enrichment of T-cell activation, and better outcome. Direct translation of molecular subclasses into clinical decision-making is yet to be achieved.

PREVENTION AND EARLY DETECTION

Prevention Primary prevention of HCC can be achieved by vaccination against HBV and effective treatment of HBV and HCV infection. Studies assessing the impact of universal vaccination against HBV infection started in Taiwan in 1984 have reported a significant decrease of the incidence of HCC. Nowadays, HBV vaccination is recommended to all newborns and high risk groups, following World Health Organization guidelines. Vaccination is also recommended in people with risk factors for acquiring HBV infection, such as health workers, travelers to areas where HBV-infection is prevalent, injecting drug users, and people with multiple sex partners.

Effective antiviral treatments for patients with chronic HBV infection—achieving undetectable viral titres (circulating HBV-DNA)—reduce the risk of HCC development. Evidence of this effect is supported by one randomized trial and several cohort studies. Regarding HCV infection, eradication of hepatitis C results in decreased HCC incidence. Anti-viral therapies achieving a sustained virological response (SVR) in patients with chronic hepatitis prevent the development of advanced stage disease and cirrhosis, hence resulting in a decreased risk of HCC development. However, once cirrhosis is established no high-level evidence suggests that SVR leads to HCC prevention. A meta-analysis of observational studies concluded that interferon-based regimens achieving SVR in patients with cirrhosis were associated with a substantially reduced risk of HCC development. Treatment of HCV has dramatically advanced with the new DAAs (drug antiviral agents) that yield >90% SVR rates after 12 weeks of treatment. A few observational studies with a short follow-up reported an HCC annual incidence of 3–5% in patients with cirrhosis following successful DAA therapy, an incidence similar to that of untreated patients, and higher than those observed with interferon-based therapies. Similarly, there is controversy on the effect of DAA-based SVR on HCC recurrence after curative therapies. Some studies suggest a 6-month recurrence rate higher than historical controls, thus emphasizing the need for large prospective studies. It is too early to estimate the effect of DAA therapy on the burden of HCC. Due to all these circumstances, surveillance remains recommended in patients with cirrhosis achieving SVR.

Additional putative chemopreventive agents have been proposed to reduce HCC incidence in at-risk populations, including statins and metformin. Nonetheless, the evidence is not strong enough to recommend using these therapies in at-risk patients. Finally, coffee consumption is associated with a reduced risk of HCC in population studies.

Surveillance The aim of surveillance is to obtain a reduction in disease-related mortality. This is usually achieved through early detection that enhances the applicability and cost-effectiveness of curative therapies. United States and European guidelines recommend surveillance for patients at high risk for HCC on the basis of cost-effectiveness analyses. As a general rule, high-risk populations are considered those presenting an incidence cut-off > 1.5% for patients with cirrhosis and 0.2% for patients with chronic hepatitis B. However, the strength of evidence supporting surveillance is modest, and is based upon two randomized studies conducted in China and meta-analysis of observational studies. Overall, these studies conclude that surveillance identifies patients with smaller tumors who are more likely to undergo curative procedures. Because of lead time bias and length time bias it cannot be concluded that surveillance ultimately reduces HCC-related mortality.

Surveillance is recommended for cirrhotic patients owing to any cause, those with HCV-related advanced fibrosis (Metavir score of F3), and for patients with chronic HBV infection if Asian aged >40 years, African aged >20 years or family history of HCC. In terms of liver dysfunction, the presence of advanced cirrhosis (Child-Pugh class C) prevents potentially curative therapies from being employed, and thus surveillance is not recommended. As an exception, patients on the waiting list for liver transplantation, regardless of liver functional status, should be screened for HCC in order to detect tumors exceeding conventional criteria and to define priority policies for transplantation. Complex scoring systems to identify at-risk populations are not yet recommended by guidelines.

Ultrasonography every 6 months is the recommended method of surveillance. It has a sensitivity of 65–80% and a specificity of >90% for early detection. A 3-month interval does not enhance outcomes, and survival is lower with 12 month compared with 6 month intervals. A shorter follow-up interval (every 3–4 months) is recommended when a nodule of <1 cm has been detected. Computed tomography (CT) and magnetic resonance imaging (MRI) are not recommended as screening tools due to lack of data on accuracy, high cost and possible harm (i.e., radiation with CT). Exceptionally, these techniques can be considered in patients with obesity and fatty liver, where visualization with ultrasound is difficult. Accurate tumor biomarkers for early detection need to be developed. Use of alpha-fetoprotein (AFP) levels identifies patients with HCC with 60% sensitivity, but high false-positive results. One main limitation of AFP is that only a small proportion of early tumors (~20%) present with abnormal AFP serum levels. Combining AFP with ultrasound performed by experienced personnel only increase 6–8% the HCC detection rate. Nonetheless, testing AFP is still widely used and this remains an area of controversy. Particularly, testing AFP might be considered in special populations or health care environments when ultrasound is not available. The accuracy of other serum biomarkers proposed, such as des-γ carboxyprothrombin (DCP) and the L3 fraction of AFP (AFP-L3), in early detection is not known.

Despite the fact that surveillance is cost-effective in HCC, the global implementation of such programs is estimated to engage ~50% of the target population in Europe and ~30% in the United States. Public health policies encouraging the implementation of such programs should lead to an increase in early tumor detection.

Diagnosis HCC is generally diagnosed at early or intermediate stages in Western countries, but at advanced stages in most Asian (except Japan) and African countries. A surveillance program yields early diagnosis in 70–80% of cases. At these stages the tumor is asymptomatic, and diagnosis can be made by non-invasive (radiological) or invasive (biopsy) approaches. Without surveillance, HCC is discovered either as a radiological finding or due to cancer-related symptoms. If symptoms are present the disease is already at an advanced stage with a median life expectancy <1 year. Symptoms include malaise, weight loss, anorexia, abdominal discomfort, or signs related to advanced liver dysfunction.

NON-INVASIVE (RADIOLOGICAL) DIAGNOSIS Patients enrolled in a surveillance program are diagnosed by identification of a new liver nodule on abdominal ultrasound. Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan (four phases are unenhanced, arterial, venous, and delayed) or dynamic contrast-enhanced MRI. A flow-chart of diagnosis and recall policy recommended by U.S. and European guidelines is summarized in Fig. 78-3. Radiological diagnosis is achieved with a high degree of confidence if the lesion is ≥2 cm in diameter and shows the *radiological hallmarks of HCC* by one imaging technique. Using contrast-enhanced imaging techniques, the typical hallmark of HCC consists of vascular uptake of the nodule in the arterial phase with washout in the portal venous or delayed phases. This radiological pattern captures the hypervascular nature characteristic of HCC. In these scenarios the diagnostic specificity is ~95–100% and a biopsy is not necessary. For lesions 1–2 cm in diameter, the radiological hallmarks of HCC define diagnosis, but need to be confirmed by two imaging techniques in non-specialized centers. Nodules <1 cm in size are unlikely to be HCC and would be very difficult to diagnose, and thus ultrasound follow-up at 3–4 months is recommended. MRI with liver specific contrast agents might help in the diagnosis of HCC, but

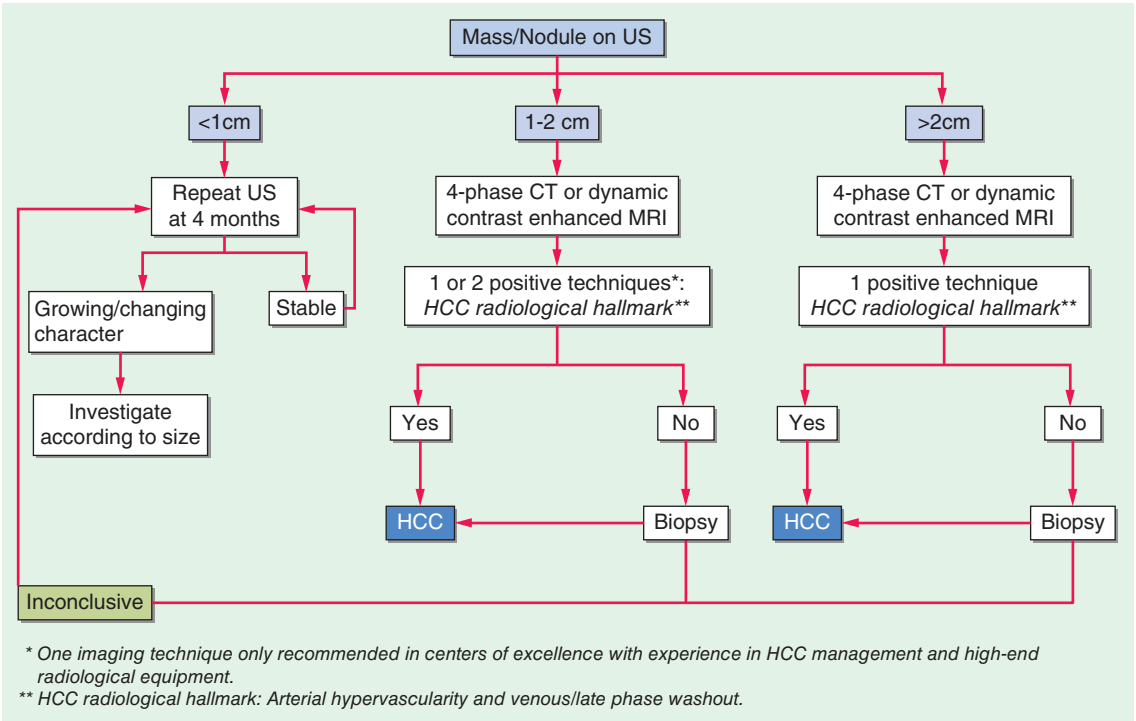


FIGURE 78-3 Recall diagnosis schedule for HCC (EASL). EASL, European Association for the Study of Liver Disease; HCC, hepatocellular carcinoma. *(Reprinted with permission from EASL-EORTC guidelines. J Hepatology 56: 908, 2012.)*

the specificity of these agents is still suboptimal. Contrast-enhanced ultrasound (CEUS) and angiography are less accurate for HCC diagnosis. Positron emission tomography (PET)-scan performs poorly for early diagnosis. AFP levels ≥ 400 ng/dL are highly suspicious, but not diagnostic of HCC according to guidelines.

PATHOLOGICAL DIAGNOSIS Pathological diagnosis is required in two scenarios: (a) in patients without cirrhosis, and (b) if radiology is not typical in at least one of two imaging techniques (CT and MRI). This occurs mainly with early-stage HCC lesions. Biopsy is not an ideal gold standard, because of variation introduced by sampling and complications. Sensitivity of liver biopsies ranges between 70 and 90% for all tumor sizes, but decrease to <50% in tumors 1–2 cm in size. The risk of complications such as tumor seeding and bleeding after liver biopsy is ~3%. Biopsies should be assessed by an expert hepatopathologist. The use of special stains may help to resolve diagnostic uncertainties. Positive staining in two of four markers [glypican 3 (GPC3), glutamine synthetase, heat shock protein 70 (HSP70), and clathrin heavy chain] is highly specific for HCC. Gene expression blueprints (glypican 3, LYVE1, and survivin) are also able to differentiate high grade dysplastic nodules from early HCC. Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularization (CD34). A negative biopsy does not eliminate the diagnosis of HCC. A second biopsy is recommended in case of inconclusive findings, or growth or change in enhancement pattern identified during follow up. European guidelines advocate obtaining tissue samples in the setting of all research studies in HCC, even if radiological criteria are met.

TREATMENT

Staging Systems and Treatment Allocation Staging systems are aimed at stratifying patients according to prognostic factors and outcome, and to allocate the best available therapies according to evidence. The most accepted staging system is the Barcelona-Clinic-Liver Cancer (BCLC) Classification, which is endorsed by U.S. and European clinical practice guidelines (Fig. 78-4). This staging system defines five prognostic subclasses and allocates specific treatments for each stage. The BCLC staging system has been externally validated by numerous studies. It is an evolving system that allows incorporation of new therapies and treatment-dependent variables as new evidence emerges. Six treatments have been demonstrated to improve survival in HCC, five are adopted by guidelines and BCLC classification: surgical resection, liver transplantation, radiofrequency (RF) ablation, chemoembolization, and systemic therapies (sorafenib, regorafenib, lenvatinib, cabozantinib, ramucirumab). The BCLC system will also incorporate lenvatinib in first line and regorafenib as standard of care in patients with advanced HCC progressing on sorafenib as a consequence of a positive randomized controlled trial (RCT). The BCLC assigns each patient with a given treatment allocation. Treatment stage migration is also applied by this scheme, meaning that if patients are not candidates for the selected therapy, the next effective therapy at more advanced stages can be given.

In HCC, three parameters are relevant for defining treatment strategy: tumor status, cancer-related symptoms, and liver dysfunction. The BCLC staging captures all three variables and allocates patients to treatments according to evidence. Since >80% of patients have two diseases, HCC and cirrhosis, a clear measurement of liver dysfunction should be in place. The prognosis of chronic liver disease is commonly assessed using the Child-Pugh score, which uses five clinical measures—total bilirubin, serum albumin, prothrombin time, ascites severity, and hepatic encephalopathy grade—to classify patients into one of three groups (A–C) of predicted survival rates. In brief, Child-Pugh's A reflects well-preserved liver function, Child's B moderate liver dysfunction with a median life expectancy of ~3 years and Child C severe liver dysfunction with life expectancy of ~1 year. At early BCLC stages more granular criteria to define patients with very-well preserved liver function (Child-Pugh's hyper-A class without portal hypertension) needs to be in place to select candidates for resection. Modifications of Child-Pugh scoring or model for end-stage liver disease (MELD) score have not been adopted for treatment allocation, except for prioritization on the waiting list for liver transplantation (MELD score). More sophisticated measures of liver dysfunction (i.e., assessment of portal hypertension) are recommended for preoperative assessment of candidates for resection. Performance status is assessed by Eastern Cooperative Oncology Group (ECOG) and presence of cancer-related symptoms (ECOG 1-2) is considered a sign of advanced stage. Patients with severe liver dysfunction (Child-Pugh's C class) or performance status impairment (ECOG 3-4) are offered supportive care management.

Considering all these prognostic/predictive variables and evidence-based treatment efficacy, five BCLC stages have been defined

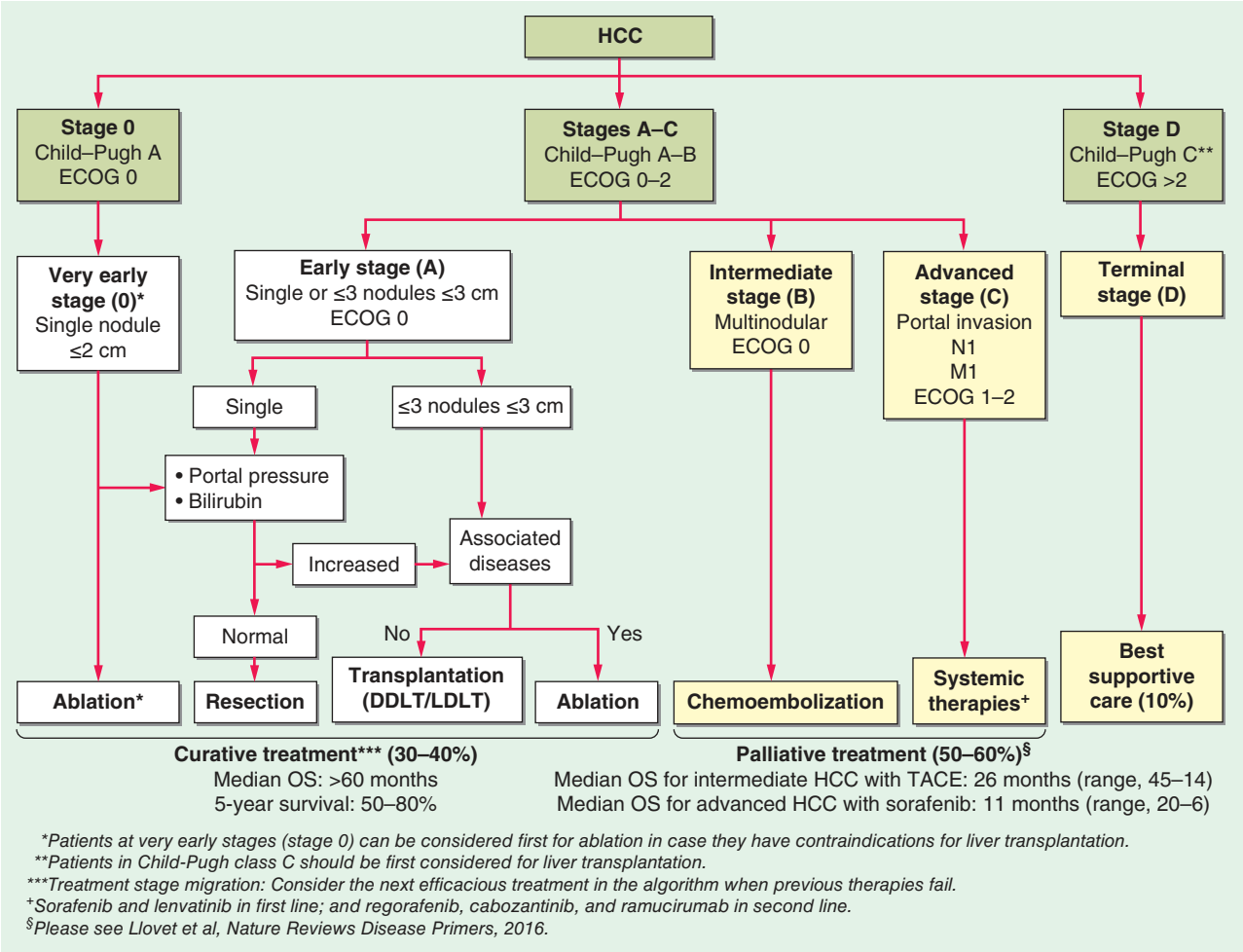


FIGURE 78-4 BCLC staging system and therapeutic strategy. BCLC classification comprises five stages that select the best candidates for therapies according to evidence-based data. Patients with asymptomatic early tumors (stages 0–A) are candidates for radical therapies (resection, transplantation, or local ablation). Asymptomatic patients with multinodular HCC (stage B) are suitable for transcatheter arterial chemoembolization (TACE), whereas patients with advanced symptomatic tumors and/or an invasive tumoral pattern (stage C) are candidates to receive sorafenib. End-stage disease (stage D) includes patients with poor prognosis that should be treated by best supportive care. BCLC, Barcelona Clinic Liver Cancer; DDLT, deceased donor liver transplantation; EASL, European Association for the Study of Liver Disease; ECOG, Eastern Cooperative Oncology Group Performance Status; EORTC, European Organisation for Research and Treatment of Cancer; GRADE, grading of recommendations assessment, development, and evaluation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; OS, overall survival; PEI, percutaneous ethanol injection; RF, radiofrequency ablation; TACE, transcatheter arterial chemoembolization. *(Reprinted with permission from JM Llovet et al: Nat Rev Dis Primers 2:16018, 2016; A Forner, JM Llovet, J Bruix: Hepatocellular carcinoma. Lancet 379:1245, 2012.)*

(Fig. 78-4). Patients with liver only neoplastic disease, no symptoms (ECOG 0) and with mild to moderate liver dysfunction (Child-Pugh A-B) can be classified as very early (Stage 0) or early (Stage A) or intermediate (stage B) stages depending upon tumor size and number. Very early HCC (BCLC 0) is defined by single tumors ≤2 cm (if pathology is available they should be well-differentiated with absence of microvascular invasion or satellites). Early HCC (BCLC A) includes either single tumors or a maximum of three nodules of ≤3 cm in diameter. Intermediate stage (BCLC B) is defined by all other liver-only tumors. Conversely, HCC is considered at advanced stages (BCLC C) when patients present cancer-related symptoms (ECOG 1-2) or tumors with macrovascular invasion (of any type, including branch, hepatic, or portal vein), lymph node involvement, or extrahepatic spread. Finally, end-stage disease (BCLC D) is considered in cases of several impairment of quality of life/cancer-related symptoms (ECOG 3-4) or severe liver dysfunction (Child-Pugh C).

Around 40% of patients are diagnosed at Stages 0 and A, and hence are eligible for potentially curative therapies, resection, transplantation, or local ablation. These treatments provide median survival rates of 60 months and beyond, which are in sharp contrast with outcomes of 36 months reported in historical controls **(Fig. 78-5)**. No adjuvant therapy is recommended. Patients at intermediate stage (Stage B) with preserved liver function have a documented natural history of around 16 months. These patients benefit from transarterial chemoembolization (TACE) as reported in two randomized studies and one meta-analysis, and achieve an estimated survival of 25–30 months. None of the combination therapies with TACE have shown outcome advantages. Patients progressing on TACE or at advanced stage (Stage C) benefit from systemic sorafenib, which extends survival by ~3 months (from 7.9 to 10.7 months). Lenvatinib showed non inferiority results compared to sorafenib (13.6 months vs. 12.3 month, respectively). Regorafenib improves survival from 7.8 to 10.6 months in patients progressing on sorafenib (second-line advanced HCC). Therefore, these treatments have been adopted by guidelines and incorporated to the BCLC classification. Patients with end-stage disease (BCLC D) should be considered for nutritional and psychological support and proper management of pain.

Although the BCLC establishes validated stages and treatment assignment according to evidence, clinical practice is not always aligned with this classification. In large cohort studies and surveys, only half of patients, or even less in Asia, are treated accordingly. Alternative staging or scoring systems have been proposed, but none of them has acquired global consensus. In contrast to BCLC, some proposed systems capture the standard of practice in Asia, such as the Hong Kong classification or the Japan Integrated Staging score. These systems capture extended indications for resection and TACE applied in clinical practice in Asia. Other systems define prognostic stratification, such as the Cancer of the Liver Italian Program (CLIP) score, although they do not incorporate treatment allocation to distinct stages.

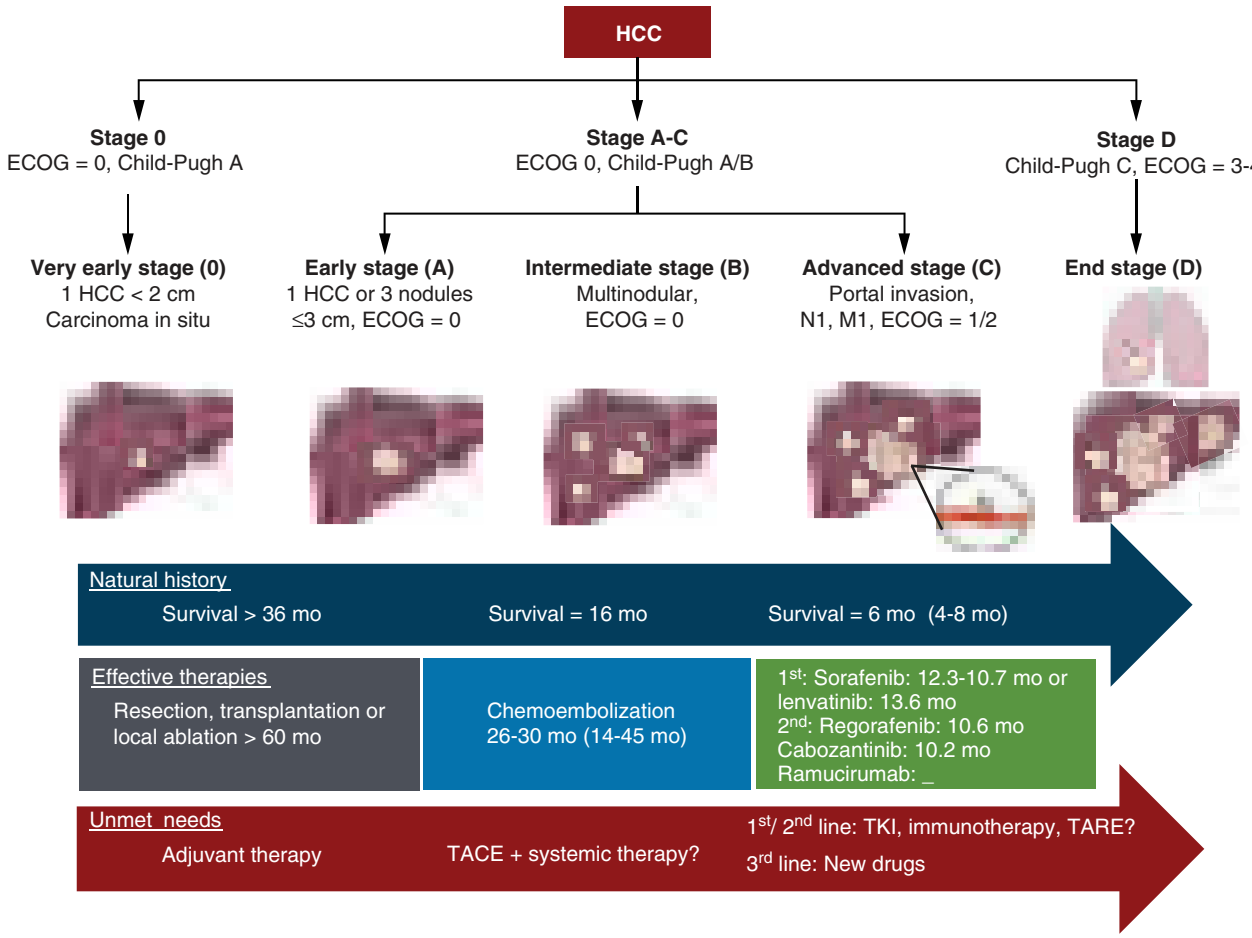


FIGURE 78-5 Natural history, impact of therapies, and unmet needs in HCC.

Finally, the tumor-node-metastasis (TNM) staging system is not used in HCC since it does not incorporate the main prognostic variables related to liver function and performance status.

The BCLC system does not incorporate molecular classes or biomarkers. Some biomarkers (i.e., AFP at a cut-off of >200 or 400 ng/mL) or molecular classes/signatures have prognostic or biological significance. However, they are not ready for clinical application due to the lack of data on biomarker-based response to therapies. A few Phase III studies are currently conducted based upon biomarker-enriched populations (i.e., ramucirumab in AFP >400 ng/mL) or as proof-of-concept studies (i.e., FGFR4 inhibitors in patients with FGF19 amplification/overexpression). Ramucirumab trial has been positive, and thus biomarkers will be incorporated in the treatment allocation system.

Due to the complexities of HCC diagnosis and management, it is recommended to send patients to a referral center where all the armamentarium of therapies can be offered. In principle, patient management and outcome benefit from liver cancer multidisciplinary programs that include hepatologist, oncologist, hepatobiliary and transplant surgeons, interventional and body imaging radiologist, hepatopathologist, and specialized nurses.

SURGICAL THERAPIES

Resection Surgical resection is the first-line option for non-cirrhotic patients at early-stage HCC (BCLC 0 or A) with solitary tumors (Fig. 78-4). In cirrhotic patients, ablation competes with resection for BCLC 0 tumors (<2 cm in diameter). Which is better is not defined. Cost-effectiveness approaches report a benefit for local ablation with RF. For single tumors >2 cm (BCLC A), resection remains the mainstay of treatment in patients with Child-Pugh's hyper-A class, those patients with normal bilirubin and absence of portal hypertension (portal hypertension is defined by hepatic venous pressure gradient ≥10 mmHg). Surrogate measures of portal hypertension are presence of esophageal varices or platelet count <100,000/mm^3 associated with splenomegaly. Anatomic resections following the functional segments of the liver are recommended to spare uninvolved liver parenchyma and to remove satellite tumors. Predictors of recurrence are tumor size, number, presence of microsatellites, or microvascular invasion at the specimen analysis. Macrovascular invasion, extrahepatic involvement, and liver dysfunction (Child-Pugh B-C) are major contraindications for resection.

ADJUVANT TREATMENTS Tumor recurrence represents the major complication of resection (and local ablation) and occurs in 70% of cases at 5 years. Most of recurrences are intrahepatic metastases, but at least one third are considered *de novo* tumor, new clones developing in the cirrhotic carcinogenic field. The type of recurrence can only be defined by molecular studies. So far, no adjuvant therapies have proven to improve outcome or prevent recurrence after resection/ablation. Randomized trials testing adjuvant sorafenib, retinoids, chemotherapies or chemoembolization have been negative. Some trials testing adoptive immunotherapy or interferon showed positive results, but these treatments have not been adopted by guidelines of management due to weakness of the evidence or small magnitude of benefit. Therefore, the current recommendations are that in case of recurrence patients will be re-assessed by BCLC staging, and re-treated accordingly.

Liver Transplantation Liver transplantation is the first treatment choice for cirrhotic patients with single tumors ≤5 cm and portal hypertension (including Child-Pugh's B and C) or with small multinodular tumors (≤3 nodules, each ≤3 cm) (Fig. 78-4). These so-called Milan criteria have been validated over the years and a meta-analysis reported 5-year and 10-year survival rates of ~70 and ~50%, respectively, similar to outcomes achieved in non-HCC transplantation indications. Perioperative mortality rates have been reduced to <3%. Transplantation simultaneously cures the tumor and the underlying cirrhosis, and it is associated with a low risk of recurrence, around 10–15% at 5 years. No immunosuppressive regimens or anti-tumor therapies

after transplantation have demonstrated any preventive effect on recurrence. Milan criteria are integrated in the BCLC treatment strategy (BCLC 0 and A) and have also been adopted by the United Network for Organ Sharing (UNOS) pre-transplant staging for organ allocation in the United States (Stage T2). Aside from size and number, conventional contraindications for organ transplantation procedures (ABO incompatibility, co-morbidities, etc.) are applied in this setting.

Liver transplantation has a couple of important limitations, such as cost and donor availability, which limit this procedure to <5% of HCC cases. The scarcity of donors represents a major drawback of liver transplantation. Donor scarcity varies geographically, and deceased liver donation is almost zero in some Asian countries. Due to the shortage of donors, median waiting times in Western programs is ~6–12 months leading to 20% of candidates dropping off the list due to tumor progression before receiving the procedure. Predictors of drop-out are treatment failure, baseline AFP >400 ng/mL or steady increase of AFP level >15 ng/mL per month. Several strategies have been proposed to overcome this limitation. First, apply neo-adjuvant therapies in patients on the waiting list. Neo-adjuvant treatments testing TACE or RF ablation have been assessed in the setting of cohort and cost-effectiveness studies. In principle, the use of these therapies is recommended when the waiting time exceeds 6 months, even though impact on long-term outcome is uncertain. Second, a priority policy has been established for patients enlisted. UNOS has implemented a scoring system based upon the dropout risk, giving priority to tumors 2–5 cm in size and multinodular tumors.

The Milan criteria are universally used as the basis for transplant eligibility, and adherence to them yields good post-transplant survival. Modest expansion of Milan criteria applying the "up-to-seven" criteria (i.e., those HCCs having the number 7 as the sum of the size of the largest tumor and the number of tumors) in patients without microvascular invasion achieves competitive outcomes. These pathologically-defined criteria are being used in clinical practice to predict the expected outcome after transplantation. Similarly, *down-staging to Milan criteria* is currently explored by several groups. Down-staging is defined as the reduction of HCC burden by loco-regional treatments to achieve Milan staging before transplantation. A few studies claim that down-staging lasting for >3 months achieves competitive outcomes, but robust long-term survival data is scarce, and thus it cannot yet be recommended. Down-staging policy is only endorsed by guidelines for patients outgrowing the Milan criteria while on the waiting list.

Since policies for enhancing organ donation have reached a ceiling during the past several years, alternatives to donation have emerged. Living donor liver transplantation represents a plausible alternative that accounts of ~5% of total transplantations performed globally. Outcomes reported are similar to those with deceased liver donors, and it is recommended as an alternative option in patients on a waiting list exceeding 6–7 months. The risks and benefits of this procedure should take into account both donor (death is estimated in 0.3%) and recipient, a concept known as *double equipoise*. Due to the complexity of this treatment, it must be restricted to centers of excellence in hepatobiliary surgery and transplantation.

LOCO-REGIONAL THERAPIES

Local Ablation RF ablation is recommended as the primary ablative technique (Fig. 78-4). The energy generated by RF ablation (heating of tissue at 80°–100°C) induces coagulative necrosis of the tumor producing a *safety ring* in the peritumoral tissue, which might eliminate small-undetected satellites. Treatment consists of 1 or 2 sessions performed using a percutaneous approach, although in some instances ablation with laparoscopy is needed. RF ablation is more effective in response rate and time-to-recurrence compared with the once-conventional percutaneous ethanol injection. Long-term outcome of HCC patients treated by RF ablation have 5-year survival rates of ~60%. In tumors <2 cm, BCLC 0, RF ablation achieves complete responses in >90% of cases with good long-term outcome and is competitive with resection in terms of cost-effectiveness. For BCLC A cases, RF ablation is the first-line treatment for single tumors 2–5 cm or multinodular up to three nodules, each ≤3 cm in diameter, unsuitable for surgery.

The main limitation of RF ablation is that its failure rate increases in tumors >3 cm because of the heat loss due to perfusion-mediated tissue cooling within the area ablated. In tumors 3–5 cm in diameter, complete pathological tumor necrosis of <50% has been reported. Particularly, ~10–15% of tumors with difficult-to-treat locations, such as a subcapsular location or adjacent to the gallbladder, have a higher risk of incomplete ablation or major complications and can be approached by ethanol injection. Several approaches have been proposed to enhance the anti-tumor activity of RF ablation. The combination of RF ablation with either chemoembolization or with a heat-activated formulation of liposomal doxorubicin yielded good results in cohort studies. Other treatments, such as microwave ablation, high-intensity focused ultrasound or stereotactic body radiotherapy for small tumors are under investigation.

Chemoembolization TACE is the most widely used primary treatment for unresectable HCC worldwide, and the first-line indication for patients with intermediate BCLC B stage (Fig. 78-4). Conventional chemoembolization (c-TACE) consists of the local hepatic artery administration of chemotherapy (either doxorubicin 50 mg/m^2 or cisplatin) mixed with an emulsion of lipiodol followed by obstruction of the feeding artery with sponge particles. c-TACE mainly benefits patients with liver-only disease, Child-Pugh A Class, or B without ascites, good performance status (ECOG 0), and absence of branch or trunk vascular invasion. Median survival is ~20 months (compared to 16 months for pooled control arms). The best randomized trial and subsequent Phase II studies have provided median survivals for TACE of 25–30 months in properly selected populations. Median objective response rates are of 50–70%. In randomized studies, the treatment is performed at a regular schedule of 0, 2, and 6 months (median number of sessions: 3), although no consensus has been established. TACE procedures should be stopped upon tumor progression or any other contraindication. Exceptionally, occurrence of a new small untreated nodule as the only progression feature can be considered for treatment. Around ~50% of patients present a limited postembolization syndrome of fever and abdominal pain related to ischemic injury and release of cytokines. Less than 5% of patients present major complications (liver abscess, ischemic cholecystitis, or liver failure) and in <2% of cases treatment-related death occurs.

Applicability of c-TACE in BCLC B patients is limited to half of cases, mostly as a result of the presence of liver failure (Child B, or ascites or encephalopathy), technical contraindications to the procedure (i.e., impaired portal-vein blood flow), or infiltrative/massive tumor burden (i.e., generally main tumor size >10 cm). Super-selective TACE minimize the ischemic insult to non-tumor tissue. According to guidelines, treatment-stage migration allows performing TACE on patients at early stages not suitable for surgical or ablative therapies. In selective studies, median survival rates of 5 year have been reported in patients with single HCC treated by supra-selective TACE. On the other hand, TACE performed beyond guidelines as a conventional practice to patients with formal contraindications (generally BCLC C) yields poor outcomes.

Drug-eluting beads chemoembolization (DEB-TACE) differs from c-TACE in the use of more standardized embolic spheres of regular size embedded with chemotherapy. This strategy ensures drug release over a 1-week period resulting in an enhancement of drug concentration within the tumor. DEB-TACE achieves similar anti-tumor activity (objective responses of ~60%) as c-TACE associated with significantly less systemic cytotoxic effects and better tolerance, but with no clear differences in clinical outcomes. Phase II and III studies have compared DEB-TACE with the combination of DEB-TACE with sorafenib or brivanib, a VEGF receptor inhibitor. Median survival in both arms of these international trials was 25–30 months.

Radioembolization and Other Intraarterial Therapies Radioembolization using beads coated with yttrium-90 (Y-90)—an isotope that emits short-range β radiation—is the most promising alternative to TACE. Several Phase II studies reported objective responses and overall outcome with a safe profile. Due to the lack of Phase III trials, this treatment is currently not recommended in guidelines. Whether radioembolization might be effective in patients at an intermediate-stage not eligible for TACE needs to be studied. Radioembolization

requires prevention of severe lung shunting and intestinal radiation before the procedure. Around 20% of patients present liver-related toxicity and 3% treatment-related death. Due to the minimally embolic effect of Y-90 microspheres, treatment can be safely used in patients with portal vein thrombosis, a setting where survival results in Phase II were encouraging and Phase III investigations in combination with sorafenib are ongoing. Head to head comparison of Y-90 vs sorafenib did not hit the primary end-point of overall survival.

TACE should be distinguished from other intraarterial therapies, such as chemo-lipiodolization, which involves the delivery of an emulsion of chemotherapy mixed with lipiodol, bland transcatheter embolization (TAE), where no chemotherapeutic agent is delivered, and intra-arterial chemotherapy, where no embolization is performed. None of these approaches is recommended due to the lack of survival benefit.

SYSTEMIC THERAPIES

Conventional systemic chemotherapy and radiotherapy have not produced survival advantages. Randomized studies also failed with anti-estrogen therapies and vitamin D derivatives. External beam liver-directed radiotherapy (stereotactic body radiotherapy) efficacy is currently being tested with and without sorafenib in Phase III trials. In 2007 a Phase III trial demonstrated survival benefits for patients with advanced stage disease treated with sorafenib, and more recently lenvatinib showed similar effects to sorafenib in first line treatment. A second multikinase inhibitor, regorafenib, has been shown to benefit patients progressing to sorafenib.

Molecular Targeted Therapies Sorafenib is the standard of care systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (i.e., BCLC C) or those tumors at intermediate stage (i.e., BCLC B) progressing upon loco-regional therapies (Fig. 78-4). A Phase III study comparing sorafenib vs placebo showed increased survival from 7.9 months to 10.7 months (HR 0.69; 31% reduction of risk of death). In this trial, 80% of patients were BCLC C and 20% BCLC B progressed to TACE. Overall, 35% of patients presented with macrovascular invasion and 50% with extrahepatic spread. A similar magnitude of benefit was observed in another positive Phase III study conducted in parallel in Asian patients, mostly with HBV-related HCC. Interestingly, objective responses account for 2% of patients assessed by RECIST criteria and ~10% assessed by the more refined modified RECIST (mRECIST) criteria. Patients with HCV-related HCC achieve significantly better outcomes with sorafenib, with a median survival of 14 months. No predictive biomarkers of responsiveness to sorafenib have been identified.

The recommended daily dose of sorafenib is 800 mg. Median treatment duration is about six months. Treatment is associated with manageable adverse events, such as diarrhea, hand-foot skin reactions, fatigue, and hypertension. Treatment-related liver failure or life-threatening complications are unusual. These toxicities lead to treatment discontinuation in 20% of patients and dose-reduction in up to half. Not all patients at advanced stages can receive sorafenib. It has been estimated that this therapy cannot be administered to around one-third of the targeted patients due to primary intolerance, advanced age, or liver failure (ascites or encephalopathy). Active vascular disease, either coronary or peripheral, is considered a formal contraindication.

The efficacy of sorafenib probably results from a balance between targeting cancer cells and the microenvironment by blocking up to 40 kinases, including anti-angiogenic (vascular endothelial growth factor receptor [VEGFR], platelet-derived growth factor receptor [PDGFR]), and anti-proliferative drivers (serine/threonine-protein kinase B-raf [BRAF] and mast/stem cell growth factor receptor [c-Kit]). Median time to progression on sorafenib is of 4–5 months in Phase III trials. Activation of MAPK14 signaling, IGF signaling, and enrichment in tumor-initiating cells is the main mechanisms of acquired resistance.

Several other agents have been tested with negative results in most of the cases (Table 78-2). Recently, a phase III study comparing lenvatinib (an inhibitor of VEGFR, fibroblast growth factor receptor [FGFR],

TABLE 78-2 Phase III Trials Testing Molecular Therapies in Advanced HCC the Past 10 Years

	DRUGS**	n	MEDIAN OS (month)	HAZARD RATIO (p-value)	MEDIAN TTP (month)	HAZARD RATIO (p-value)	OBJECTIVE RESPONSE (%)
First-Line							
SHARP	Sorafenib	299	10.7	0.69	5.5	0.58	2.3
	Placebo	303	7.9	(<0.001)	2.8	(<0.001)	0.7
Asian-Pacific	Sorafenib	150	6.5	0.68	2.8	0.57	3.3
	Placebo	76	4.2	(0.01)	1.4	(<0.001)	1.3
Sunitinib	Sunitinib	530	7.9	1.3	4.1	1.13	6.6
	Sorafenib	544	10.2	(0.001)	3.8	(0.308)	6.1
BRISK-FL	Brivanib	577	9.5	1.06	4.2	1.01	12*
	Sorafenib	578	9.9	(0.31)	4.1	(0.853)	8.8*
LIGHT	Linifanib	514	9.1	1.04	5.4	0.76	10.1
	Sorafenib	521	9.8	(0.52)	4	(0.001)	6.1
SEARCH	Sorafenib + Erlotinib	362	9.5	0.92	3.2	1.13	6.6
	Sorafenib	358	8.5	(0.2)	4	(0.18)	3.9
Lenvatinib	Lenvatinib	478	13.6	0.92	8.9	0.63	24*
	Sorafenib	476	12.3	(–)	3.7	(<0.001)	9*
Second-Line							
BRISK-PS	Brivanib	263	9.4	0.89	4.2	0.56	9.9*
	Placebo	132	8.2	(0.33)	2.7	(<0.001)	1.5*
EVOLVE-1	Everolimus	362	7.6	1.05	3	0.93 (NS)	2.2
	Placebo	184	7.3	(0.68)	2.6		1.6
REACH	Ramucirumab	283	9.2	0.86	3.5	0.59	7.1
	Placebo	282	7.6	(0.13)	2.6	(<0.001)	0.7
RESOURCE	Regorafenib	379	10.6	0.63	3.2	0.44	10.6*
	Placebo	194	7.8	(<0.001)	1.5	(<0.001)	4.1*

Abbreviations: NS, not significant; OS, Overall Survival; TTP, Time-to-progression.

*Refers to Objective response by mRECIST criteria. Celestial Cabozantinib: n 470, Median OS (month) 10.2, Hazard ratio (p-value) 0.76, Median TTP (month) 5.5, Hazard ration (p-value) 0.40, Objective response (%) 4 Placebo: n 237, Median OS (month) 8.0, Hazard ration (p-value) 0.0049, Median TTP (month) 1.9, Hazard ratio (p-value) p<0.001, Objective response (%) 0.4.

**Ramucirumab vs placebo (postitive phase III in second line in patients with advanced HCC and AFP>400 Ng/mL).

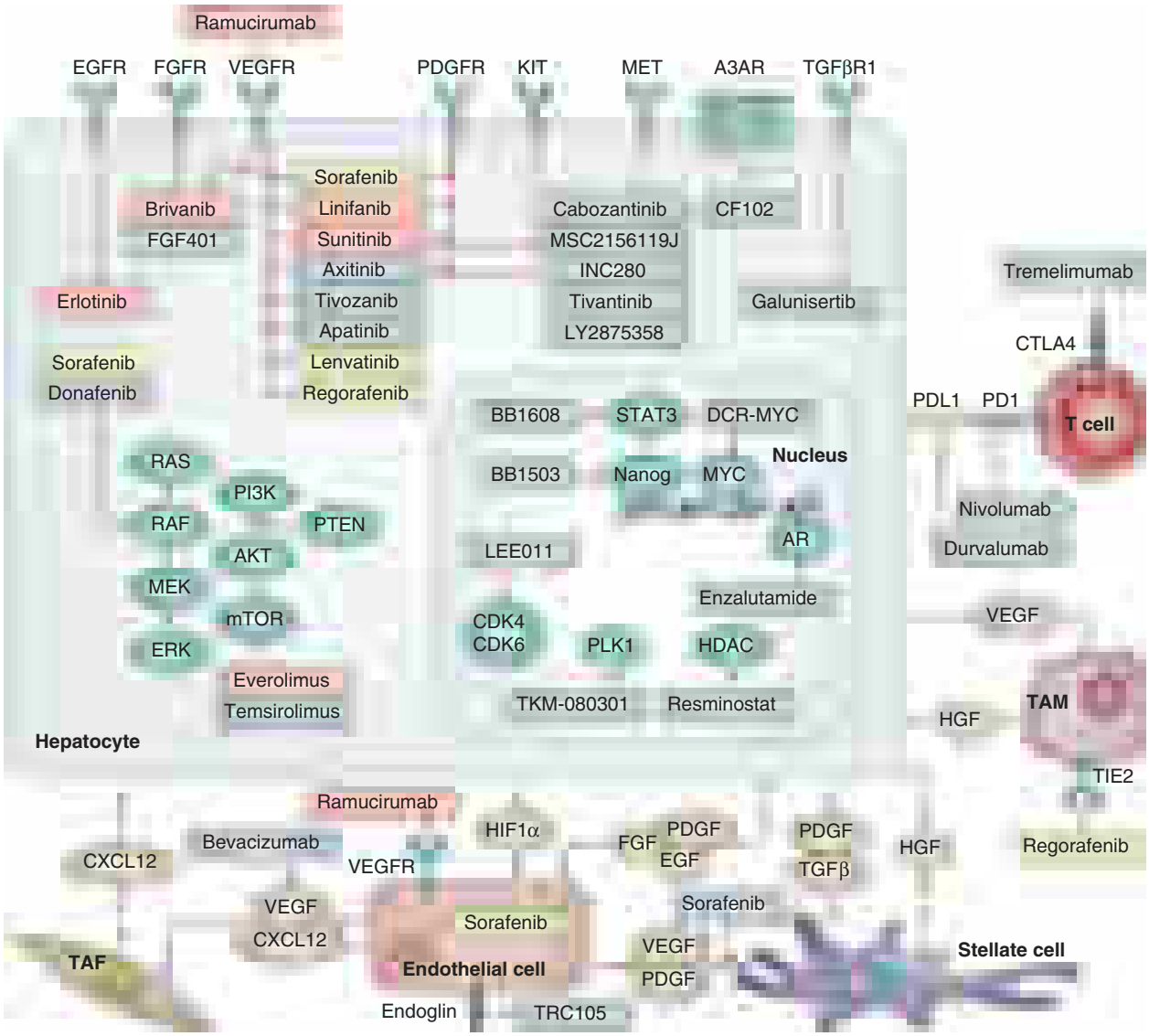


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FIGURE 78-6 Effective and emerging therapies in HCC. Summary of treatments tested in Phase II -III clinical trials. Yellow boxes indicate drugs with positive Phase III studies, red boxes indicate drugs with negative results from Phase III trials and drugs in grey boxes have been tested in Phase II studies. *(Reprinted with permission from JM Llovet et al: Nat Rev Dis Primers 2:16018, 2016.)*

PDGFR, RET, and c-Kit) with sorafenib has shown non-inferiority results in terms of overall survival (HR = 0.92). It is estimated that only half of the patients progressing on sorafenib can be considered for second-line therapies, and their median survival with no treatment is 7–8 months (obtained from patients allocated to the placebo arm).

Recently, lenvatinib showed similar efficacy compared to sorafenib in a phase III trial (median survival 13.6 months vs 12.3 months, respectively). A Phase III study comparing regorafenib (a more potent multikinase inhibitor than sorafenib, but targeting similar kinases) vs placebo in patients progressing to sorafenib has reported a benefit in survival from 7.8 to 10.6 months (HR: 0.62; 38% reduction of risk of death) (Fig. 78-5). Treatment improved survival in all patient subgroups. In this trial, 88% of patients were BCLC C and 12% BCLC B, and all had progressed on sorafenib. Around 30% of patients presented with macrovascular invasion, 70% with extrahepatic spread, and 45% with AFP >400 ng/dL. Response rate was 10% based upon mRECIST. Treatment was started at 160 mg/day (3 weeks on /1 week off). Median time on treatment was 3.5 months. Prevalence of toxicity (hand-foot reaction, fatigue, and hypertension) was higher compared with reported toxicity from sorafenib, but adverse events only led to treatment discontinuation in 10% of cases. Patients progressing after second-line therapy, along with those at a BCLC D stage should receive best supportive palliative care including management of pain, nutrition, and psychological support. Emerging therapies are shown in Fig. 78-6.

CHOLANGIOCARCINOMA

Cholangiocarcinoma (CCA) is classified according to its anatomic location as intrahepatic (iCCA; ~30%), perihilar (pCCA; ~50%), and distal (dCCA: ~20%). The latter two are also known as extrahepatic cholangiocarcinomas (eCCA), with the second-order bile ducts acting as the separation point (Fig. 78-7). This classification is endorsed by the 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual. In addition, iCCA has been recognized as a distinct entity with specific *ad hoc* clinical practice guidelines. Treatment options beyond surgery are limited, and unlike most solid tumors, no molecular targeted therapies have been approved for its treatment. The three subtypes of CCA differ in their anatomic location, epidemiology and risk factors, cell of origin, pathogenesis, and treatment. iCCA originates from adult cholangiocytes, trans-differentiation of adult hepatocytes and hepatic progenitor cells, whereas eCCA arises from the biliary epithelium and peribiliary glands. Moreover, their mutational profile also differs. FGFR2 fusions and IDH1/2 mutations only occur in iCCA, whereas ERBB2 amplifications, APOBEC-associated mutation signatures, and PKA fusions occur in eCCA. Thus, clinical management

FIGURE 78-7 Classification of cholangiocarcinoma subtypes. The 7th edition AJCC/UICC TNM staging classification includes intrahepatic (iCCA, ***A***), perhiliar (pCCA, ***B***) and distal (dCCA, ***C***) tumors. *(Reprinted with permission from S Rizvi, GJ Gores: Hepatology 63:1356, 2016.)*

and trials testing molecular therapies should be tailored according to each biological/anatomical subtype of CCA, as opposed to a common approach for all biliary tract cancers.

EPIDEMIOLOGY, RISK FACTORS, AND MOLECULAR TRAITS

CCA is the second most common liver cancer following HCC, with a 5-year survival of 10%. iCCA has globally increasing incidence and mortality rates. The incidence of iCCA varies according to exposure to risk factors, ranging from 1–2 cases per 100,000 inhabitants in Europe and North America to the highest incidence in some areas of Southeast Asia, particularly in Thailand (>80 cases/100,000 inhabitants). The male/female ratio is 1.2. Overall, most cases occur with unknown risk factors. The classical risk factors for CCA development include primary sclerosing cholangitis (PSC), biliary duct cysts, hepatolithiasis, Caroli's disease. Parasitic biliary infestation with flukes (i.e., most common is *Opisthorchis viverrini* and *Clonorchis sinensis*), is a prevalent etiology in Asia that can be prevented with an antihelminth therapy, praziquantel. PSC is a clear risk factor for iCCA and pCCA development, with a lifetime incidence ranging from 5 to 10%. Surveillance in PSC patients is recommended with annual imaging techniques and CA 19.9 serum determination. Common risk factors for HCC, such as HBV and HCV infection and cirrhosis, have been associated to iCCA development.

Molecular classification and drivers. There is no established molecular classification of CCA. Genomic studies have provided insight on two subclasses of iCCA, a proliferation subclass—characterized by activation of oncogenic signaling pathways (including RAS and MET)—and an inflammation subclass, characterized by activation of inflammatory pathways, overexpression of cytokines, and STAT3 activation. The landscape of mutations discovered by whole exome sequencing techniques defines a distinct mutational fingerprint depending on etiology and CCA subtype (Fig. 78-7). iCCA mutation portrait is characterized by ~50–60% of tumors having at least one targetable driver including *FGFR2* fusion events (~25%), mutations in *IDH1-2* (15%), *KRAS* (15%), *BRAF* (5%) and *EGFR* (3%), and amplifications in *FGF19/CCDN1* (4%). While mutations in P53 (~30%) and *KRAS* (~25%) are more common in eCCA than in iCCA, some molecular drivers are specific for subypes, such as fusion of *PRKACA* or *PRKACB* for eCCA or *ERBB2* amplifications (~20%) for gallbladder cancer. Liver flukes-associated CCA have higher incidence of *TP53* and *SMAD4* mutations. Host genetic polymorphisms predisposing to CCA have not been established.

INTRAHEPATIC CHOLANGIOCARCINOMA

Diagnosis and Staging Diagnosis of iCCA requires pathological confirmation. Guidelines are currently not recommending surveillance for early diagnosis, when patients are asymptomatic, since at-risk populations are ill-defined. Cirrhotic patients at risk of HCC development are enrolled in surveillance programs, and can benefit for early detection of iCCA. Otherwise, incidental diagnosis occurs due to cross-sectional imaging performed for other reasons. In most cases, iCCA is diagnosed at advanced stages where symptoms such as weight loss, malaise, abdominal discomfort, or jaundice are present. Pathological diagnosis of iCCA is based on the WHO criteria. Differential diagnosis should be established with metastatic adenocarcinoma and mixed iCCA-HCC tumors, which may require evaluation of markers such as Hep-Par-1, GPC3, HSP70, and glutamine synthetase markers. Imaging studies with CT/MRI are not accurate enough to establish iCCA non-invasive diagnosis. Dynamic CT scanning characterizes 80% of iCCA as liver mass-forming tumors with progressive contrast uptake from the arterial to the venous/delayed phase. MRI dynamic images also show peripheral enhancement in the arterial phase followed by progressive filling-in of the tumor. Atypical radiological behavior with arterial enhancement recapitulating HCC occurs in 10% of cases. MRI with cholangiopancreatography (MRI/MRCP) is useful to visualize the ductal system and vascular structures. Guidelines do not recommend PET scan for diagnosis. Tumor biomarker carbohydrate antigen (CA) 19-9 at a cut-off level of 100 U/mL has prognostic significance, but lacks accuracy (sensitivity and specificity of ~60%) for early diagnosis.

Radiological criteria are inadequate for iCCA diagnosis in cirrhotic patients. However, in non-cirrhotic patients, guidelines endorse a presumed diagnosis of iCCA (i.e., venous phase contrast enhancement on dynamic CT/MRI) if resection is considered. Assessment of disease extent (venous or arterial invasion and extrahepatic disease) and resectability is best accomplished with CT and/or MRI studies. Doppler ultrasound is accurate in defining vascular invasion. Before surgery, PET scanning may be considered to rule out an occult primary or metastatic site.

Staging system. The staging system for iCCA resected cases is based on the TNM staging as per the 7th edition of the AJCC/UICCA staging, which is a new system that has already been validated. T1 tumors are solitary without vascular invasion; T2 disease includes multiple tumors (e.g., multi-focal disease, satellitosis, intrahepatic metastasis), or with vascular invasion (microvascular or major vascular invasion); T3 tumors directly invade adjacent structures; and T4 disease includes tumors with any periductal-infiltrating component. Regional lymph node metastasis in the hilar, periduodenal, and peripancreatic nodes are considered N1 disease, while distant spread is considered M1 disease. TNM stages I, II, and III overlap with T status, whereas stage IV includes either periductal invasion or N1/M1 disease.

TREATMENT

After adopting the TNM staging system, the International Liver Cancer Association (ILCA) guidelines for management of iCCA proposed the treatment algorithm depicted in Fig. 78-8. Overall, most of the treatments endorsed have a modest level of evidence and, thus guidelines are providing physicians with recommendations as standards of practice rather than standards of care supported by robust evidence-based data. Surgical resection represents the sole curative treatment option in 30–40% of patients with a 5-year survival of 30%. The largest systematic review including ~4500 iCCA patients undergoing resection reported a median survival of 28 months. In non-cirrhotic individuals, the best candidates for resection are patients at TNM stage I-II, whereas in patients with cirrhosis liver function should be assessed as previously described for HCC. Preoperative disease assessment should discard vascular invasion, N1 and M1. Lymphadenectomy of regional nodes is recommended given its prognostic value. The main predictors of recurrence (~50–60% at 3 years) and survival are identified at the pathological examination, including presence of vascular invasion, lymph node metastases, and poor differentiation. There is no established adjuvant therapy. Liver transplantation remains controversial, and few studies have reported good outcomes for single tumors ≤2 cm.

Non-surgical candidates have a dismal life expectancy. Overall, patients at stage III might be considered for loco-regional therapies, such as chemoembolization or radioembolization, but the level of evidence is low, mostly based on cohort studies. A meta-analysis of 14 trials testing loco-regional therapies reported median survival times of 15 months. External beam radiation therapy is not recommended as standard therapy. At more advanced stages (stage IV) in patients ECOG 0-1, systemic chemotherapy with the combination of gemcitabine and cisplatin is considered the standard of practice yielding median survival rates of 11.7 months compared to 8 months for gemcitabine alone. This recommendation for first-line treatment of advanced tumors is based on a subgroup analysis of 80 iCCA patients included in a large randomized Phase III trial (n = 410, ABC trial-02) of patients with advanced biliary tract tumors.

No molecular targeted therapy has been proven effective for iCCA. Patient stratification based on molecular biomarkers is ongoing with FGFR2 aberrations and IDH1/2 mutations. Preliminary data of a Phase II trial testing BGJ398 in advanced iCCA harboring FGFR2 gene fusions reported ~20% objective response.

Mixed HCC-iCCA is a rare neoplasm accounting for <0.5% of all primary liver cancers. Diagnosis is based on pathology. The 2010 WHO classification defined two subtypes: the classical and the stem cell feature type. Molecular data has also characterized a third unique entity, cholangiolocellular carcinoma, with distinct molecular traits and better outcome. Due to its low incidence, the demographic features and clinical behavior of these tumors remain ill-defined. Survival rates are similar to iCCA, and until specific guidelines are available, they should be managed following the treatment algorithm of iCCA.

EXTRAHEPATIC CHOLANGIOCARCINOMA

Perihiliar (pCCA) and Distal Cholangiocarcinoma (dCCA). The 7th edition AJCC/UICC TNM staging classification has established pCCA as tumors that arise between the second-order bile ducts up to the insertion of the cystic duct, whereas dCCA arise from this point to the ampulla of Vater (Fig. 78-7). Thus, dCCA can be difficult to distinguish from early pancreatic cancer. Both entities have a similar diagnostic approach. Acute onset of painless jaundice occurs in 90% of patients with pCCA, and 10% present with cholangitis. Primary biliary cholangitis with a cut-off for CA19.9 >129 U/mL is suspicious for CCA. Imaging assessment starts with CT and MRI; they have a good sensitivity and specificity (>85%) for detecting the degree of bile duct involvement, and hepatic and portal vein invasion. MRI-cholangiography is optimal for defining the extent of the bile duct lesion. Ruling out IgG-4 cholangiopathy by assessing serum IgG4 is mandatory. As a second step, endoscopic retrograde cholangiography with brushing to explore cytology and fluorescence in situ hybridization (FISH)—for exploring polysomy—is recommended. FISH enhances the sensitivity of cytology from 20 to ~40%.

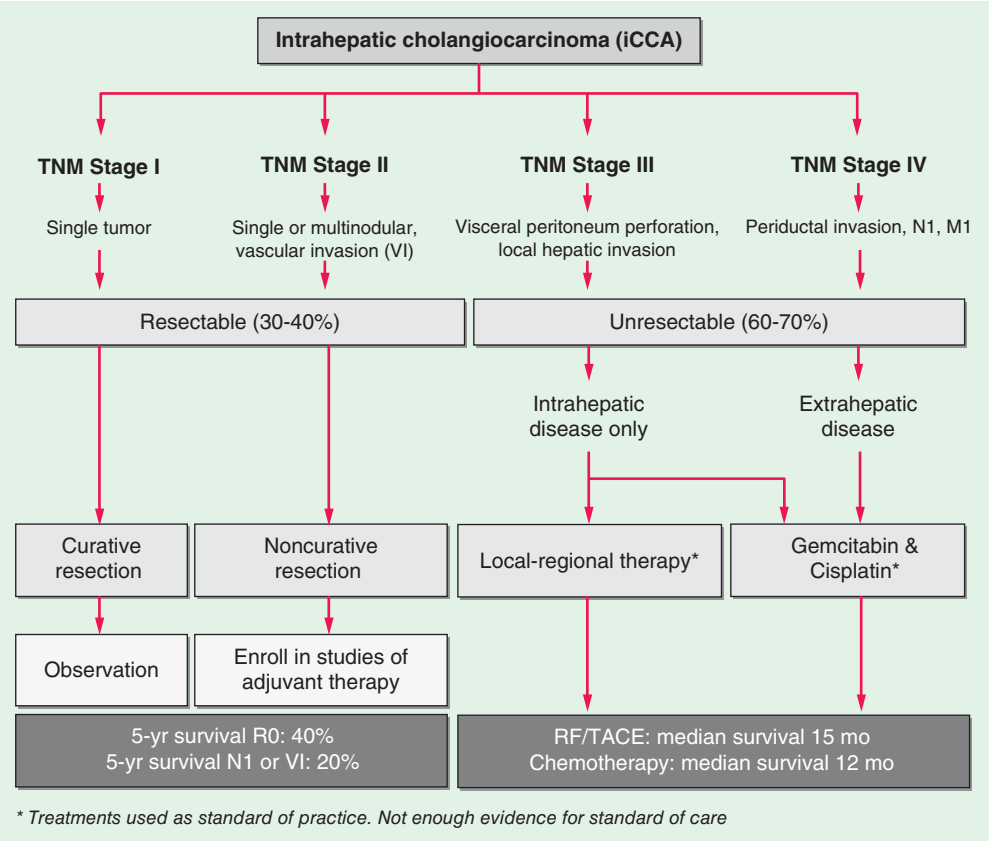

FIGURE 78-8 Staging and treatment schedule for iCCA proposed by the International Liver Cancer Association. *(Reprinted with permission from J Bridgewater: J Hepatology 60:1268–1289, 2014.)*

Diagnosis is based upon pathology. The treatment algorithm for pCCA indicates that in cases of a dominant stricture with positive cytology/biopsy or polysomy, a lymph node biopsy through endoscopic ultrasound should be obtained. pCCA with negative lymph node involvement is best treated by surgery, resection, or transplantation, the sole curative options. Resection entails hepatic and bile duct removal, Roux-en-Y-hepaticojejunostomy with regional lymphadenectomy. Bilobular involvement is considered a surgical contraindication. In few referral centers, unresectable single pCCA <3 cm without dissemination can be considered for liver transplantation with neoadjuvant chemoradiation. This procedure is associated with 5-year survival rates of ~70%. If lymph node involvement is present, systemic chemotherapy can be considered along with biliary tract stenting. Of note, the subgroup analysis of the Phase III ABC trial-02 did not identify differences between gemcitabine alone or in combination with cisplatin for pCCA. Surgical resection (Whipple procedure) is the primary option for management of dCCA, a procedure that achieves a median survival of 2 years and 5-year survival rates of ~25%. Main contraindications for resection are presence of distant lymph node involvement, metastases, or major vascular invasion. At the pathological examination, perineural invasion, lymph node metastasis, R0 resection (absence of residual tumor at pathological examination), and tumor differentiation are predictors of survival. Adjuvant therapy has not shown outcome benefits. There is no evidence of benefit of chemotherapy for unresectable cases. No molecular targeted therapies are available for these entities.

GALLBLADDER CANCER

Gallbladder cancer is the most common cancer of the biliary tract worldwide. The estimated cases of gallbladder cancer in the United States in 2016 are 11,400, more than CCA. The female:male ratio is 3:1. Cholelithiasis is the major risk factor, but <1% of patients with cholelithiasis develop this cancer. Gallbladder polyps at risk of transformation are those with ≥10 mm in diameter. Early cases are discovered incidentally at routine cholecystectomy. Clinical symptoms, such as jaundice, pain, and weight loss, are associated with advanced stages. Staging of gallbladder cancer follows the TNM classification. The most accurate technique to define staging and vascular and biliary tract invasion is the magnetic resonance cholangiopancreatography. CT and PET scan can be also useful for preoperative staging.

The mainstay of treatment is surgical, either simple or radical cholecystectomy (partial hepatectomy and regional lymph node dissection) for stage I or II disease, respectively. Only ~20% of patients are candidates for surgery with a curative intent. Survival rates are near 80–90% at 5 years for stage I, and range from 60 to 90% at 5 years for stage II. Regional nodal status and the depth of tumor invasion (T status) are the two most important prognostic factors. Adjuvant therapy has not proven effective. Gallbladder cancers at stage III and IV are considered unresectable. For patients with ECOG 0-1, chemotherapy with gemcitabine and cisplatin is the standard of practice based on data from the subgroup analysis including 181 patients with gallbladder cancer in the setting of two clinical trials. Overall, median survival is 10–12 months in advanced cases. Percutaneous transhepatic drainage is indicated in case of biliary obstruction. Radiotherapy is not effective.

OTHER MALIGNANT LIVER TUMORS

Fibrolamellar Hepatocellular Carcinoma (FLC) FLC is a rare form of primary liver cancer that typically affects children and young adults (10–30 years of age) without background liver disease. FLC accounts for 0.85% of all primary hepatic malignancies in the United States, and its incidence rate is 0.02 cases per 100,000 inhabitants. FLC is considered a unique entity with a specific fusion oncogene *PRKACA-DNAJB1* present in 80–100% of cases. A few mutations have been described, all at a level of <10%. FLC has a better prognosis than HCC, probably due to the absence of cirrhosis and the earlier age of presentation. Surgical resection is the mainstay of treatment and indications are less restrictive than for HCC. A retrospective series of 575 FLC cases reported a median survival of 70 months after resection. At advanced stages, the expected outcome is <20 months. Chemotherapy is not effective and there is no standard of care.

Hepatoblastoma (HB) HB is the most frequent primary liver tumor in children. The incidence of the disease is 1.5 cases per 1,000,000. Background liver disease is rare in these patients. WNT signaling plays a major role, with *CTNNB1* mutations (70%) as the most frequently reported molecular event. A gene signature is able to discriminate two molecular classes with distinct outcome. Resection followed by chemotherapy with doxorubicin is the mainstay treatment strategy. A study including 1605 patients randomized in eight clinical trials reported better outcome for patients with stage I-II of the PRETEXT classification (out of four stages), age <3 years, AFP >1,000 ng/mL, and absence of metastases. As opposed to HCC, low AFP indicates poor prognosis. Outcomes for best candidates after resection (stages I/II with small tumors, age <3 years and AFP >100 ng/mL) achieve 5-year disease-free survival of 90%, compared with worst candidates (metastatic disease and AFP <100 ng/mL) with 5-year disease-free survival of 20–30%.

BENIGN LIVER TUMORS

The most common benign liver tumors are hemangiomas, focal nodular hyperplasia (FNH), and hepatocellular adenomas (HCA). Most benign tumors are identified incidentally by abdominal ultrasound or other imaging techniques. *Hemangiomas* are present in ~5% of the general population, are diagnosed by ultrasound except in cirrhotic patients or oncology patients where contrast enhanced imaging (contrast enhanced ultrasound, CT, or MRI) is required. Conservative management is appropriate and follow-up is not recommended. Exceptionally, growing lesions causing symptoms by compression can be considered for resection. FNH is a benign tumor present in <2% of the population and occurring mostly in females aged 40–50 years. FNH is a polyclonal hepatocellular proliferation due to an arterial malformation. MRI has the highest diagnostic accuracy with a specificity of 100%, when typical imaging features are present (homogeneous enhancement in the arterial phase with a central scar). Atypical FNH requires biopsy for diagnosis. Treatment is not recommended since these tumors do not degenerate or cause complications. In exceptional cases of expanding symptomatic lesions, surgery is the treatment of choice.

Hepatic adenomas are clonal benign proliferations resulting from single gene driver mutations. HCA have a low prevalence of 0.001% of the population and are frequently diagnosed in women aged 35–40 years. The female:male ratio is 10:1, and the main risk factors are oral contraceptives in females and use of anabolic androgenic steroids in male body builders. HCA have the potential for hemorrhage and HCC development, particularly when sized >5 cm. Nowadays, there is a clear understanding of the molecular classification of HCA: (a) HCA with *CTNNB1* mutations (10–20%) are at-risk of HCC development and are present in men treated with androgens; (b) inflammatory adenomas (50–60%) are associated with single mutations (*Gp130*: 65%) and are more prevalent in females with obesity or diabetes; and (c) adenomas with inactivated *HNF-1A*. Diagnosis is based on MRI imaging, which is able to correlate with molecular subtypes in 80% of cases (Inflammatory and HNF-1A type). For defining HCA with *CTNNB1* mutations, biopsy is required. Upon diagnosis, discontinuation of oral contraceptives and weight loss is recommended. Resection is indicated in all cases of size >5 cm or men or *CTNNB1* mutation. For HCA <5 cm, 1-year follow-up is recommended. In case of active HCA bleeding, embolization followed by resection is the treatment of choice. The presence of multiple HCA is common, and guidelines endorse treating them based on the size of the main nodule.

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79 Pancreatic Cancer

Daniel D. Von Hoff

Pancreatic cancer is the third leading cause of death from cancer in the United States with >53,000 Americans diagnosed and >43,000 dying from the disease each year. Unfortunately, pancreatic cancer is projected to be the second leading cause of death from cancer in the United States by 2030. Worldwide pancreatic cancer is the eleventh most common cancer with 338,000 new patients diagnosed and >334,000 deaths (seventh cause of cancer deaths). Pancreatic cancer currently has the worst survival rate of any cancer with an overall 5-year survival (regardless of stage) of ~8.2%. However, that situation is changing because some advances have been made against the disease with some improvements in survival (see below) that may affect the 5-year survival statistics. In particular, knowledge about specific molecular subsets of the disease has become crucial so that one can provide the best possible care for their patients with pancreatic cancer.

EPIDEMIOLOGY

Pancreatic cancer accounts for 3.2% of all new cancer cases in the United States and for 7.2% of all deaths from cancer in the United States. The lifetime risk of developing pancreatic cancer is ~1.6%. The incidence of pancreatic cancer has been increasing between 0.5 and 1% per year. Pancreatic cancer is more common with increasing age and more common in men than in women. The 5-year survival rate for all stages has increased from 3% in 1975 to 8.2% in 2013. The latest information from the U.S. Surveillance, Epidemiology, and End Results (SEER) database predicts that the 5-year survival for patients with localized pancreatic cancer is about 31.5%, 11.5% for those with regional disease, and 2–5% for patients with advanced metastatic disease. Pancreatic cancer is more common in developed countries (although generally it tracks with the prevalence of smoking). The incidence is highest in North America and Western Europe followed by other areas in Europe, Australia, New Zealand, and South-Central Asia. Of note is that the population at greatest risk are women living in Scandinavian countries, while the lowest risk is seen for women living in middle Africa.

RISK FACTORS

Age is one of the greatest risk factors for pancreatic cancer with median age at diagnosis of 70 years (the disease is most frequently diagnosed in the 65–74 age group). The number of new cases per 100,00 persons and the number of deaths per 100,000 persons are higher for males and blacks of both sexes. Both the number of cases and the number of deaths per 100,000 people are lower for American Indian/Alaskan natives and Asian Pacific Islanders. Both the number of cases and deaths are intermediate for the Hispanic population.

Environment The greatest risk factor for pancreatic cancer is cigarette smoking. The risk correlates with the increased number of cigarettes smoked. It has been estimated that 30% of pancreatic cancer is caused by smoking. Exposure to cadmium as part of cigarette smoking or via exposure to welding, soldering, or dietary exposure has been weakly associated with an increased risk of pancreatic cancer.

Although dietary factors are often difficult to interpret, evidence suggests that high intakes of fat or meat (particularly well-done barbequed meat) are risk factors. High intakes of fruits and vegetables are associated with a decreased risk. Coffee and low-to-moderate alcohol consumption have been determined not to be associated with an increased risk for pancreatic cancers, while consumption of sugary fizzy drinks has been associated with an increased risk.

Microbiome To date, there is no solid evidence of an association between *Helicobacter pylori* infection and pancreatic cancer. Some data link the oral microbiome associated with poor dentition to pancreatic cancer but the evidence is very thin.

Hereditary/Genetics Hereditary factors may account for 10–16% of all pancreatic cancers. It is very important to recognize these factors for determining risk for family members of the patient affected with pancreatic cancer. (These family members should seek participation in an early detection program with genetic counseling, definition of risk and perhaps, if appropriate, periodic MRI screening of the abdomen, though this recommendation is not based on research data.) In addition, the identification of any of these germ-line mutations can lead to specific and effective new therapeutics for patients with these abnormalities in their tumors. Table 79-1 identifies the various germ-line mutations along with their familial cancer syndromes where an increased risk for pancreatic cancer is known.

Knowing the patient has a BRCA2 or PALB2 germ-line mutation or any of the above mutations should lead one to not only refer the patient's relatives to an early detection or high-risk individual clinic but also realize that for the BRCA2/PALB2 germ-line mutation patients consideration for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor should be entertained. Other germ-line mutations are under study to determine their increased risk of pancreatic cancer including *CDK4, FANCC, PALLD, APC, ATM, BMPR1A, BRCA1, EPCAM, MEN1, MLH1, MSH2, MSH6, NF1, PMS2, SMAD4, TP53, TSC1, TSC2,* and *VHL*. Some of these mutations are associated with pancreatic neuroendocrine tumors (Chap. 80).

TABLE 79-1 Germ-line Mutations, Their Familial Cancer Syndrome, and Fold Risk of Pancreatic Cancer

GERM-LINE MUTATION	FAMILIAL CANCER SYNDROME	ESTIMATED INCREASED RISK (FOLD) OF PANCREATIC CANCER
BRCA2[a]	Familial breast/ovarian cancer	3.5–10
PALB2 (partner and localizer of BRCA2)	Familial breast cancer and others	~sixfold
p16/CDKN2A	Familial atypical multiple mole melanoma (FAMMM)	13–38
STKII (LKB1)	Peutz-Jeghers syndrome	132
PRSS1 or SPIN11[b]	Hereditary (familial) pancreatitis	53
ATM	Ataxia-telangiectasia	Not yet established
MLH1, MSH2, MSH6, PMS2	Heredity nonpolyposis colorectal syndrome or Lynch syndrome[c]	9–30

[a]Particularly common in individuals with Ashkenazi Jewish heritage. [b]Forty percent chance of pancreatic cancer by the age of 70. [c]Very important because this is associated with microsatellite instability, which is a marker for response to an anti-PD-1/PD-L1 agent.

In addition to the recognized genetic syndromes, other possible familial pancreatic cancer genes have not yet been discovered. For example, a family history of pancreatic cancer is associated with a 13-fold increase in the disease. If you have one first-degree relative, the risk is increased 4.6-fold, 2 first-degree relatives 6.4-fold, and ≥3 first degree relatives a 32-fold increase. The risk is also increased if a relative developed pancreatic cancer at <55 years old.

Other Considerations Most patients with pancreatic cancer relate that they have had developing symptoms over the last few years. However, Yachida and colleagues suggest that pancreatic cancer could be growing over a period of 21 years. Thus, there is a possibility for early detection of the disease.

Medical Conditions Chronic pancreatitis that is nonfamilial is also associated with an increased risk of pancreatic cancer (2.3–16.5-fold increase). It is also increased in people with chronic pancreatitis associated with cystic fibrosis or tropical pancreatitis.

A clear association exists between diabetes mellitus and pancreatic cancer. Whether this is a causal association or whether the diabetes is the result of the cancer is not exactly clear. What is clear is that when a person presents with new onset diabetes, they should be considered at risk for having pancreatic cancer. The excessive insulin or insulin-like growth factors associated with adult onset diabetes and metabolic syndrome may promote pancreatic carcinogenesis.

Obesity is considered a possible risk factor for pancreatic cancer. A high body mass index (BMI) ≥30 is associated with a doubling of the risk of pancreatic cancer. Since obesity is a risk factor for diabetes, the contribution of obesity alone is unclear. Interestingly, patients with severe obesity who undergo a gastric bypass experience a reduction in the incidence of gastrointestinal (GI) cancer including pancreatic cancer by >30% in the first 3 years (along with a dramatic decrease in their Hgb A1c and blood glucose). Physical inactivity also has been associated with an increased risk in pancreatic cancer.

PATHOLOGY AND MOLECULAR CONSIDERATION

Location The posterior location of the pancreas in the abdomen is likely one of the issues that leads to a late diagnosis **(Fig. 79-1*A*)**.

Pathology Cancers of the pancreas can be divided into neoplasms of the endocrine pancreas **(Chap. 80)** and tumors of the exocrine pancreas. The most common neoplasm of the exocrine pancreas and most deadly is pancreatic infiltrating ductal adenocarcinoma. These tumors arise in the head, body, or tail of the pancreas and are characterized by infiltrating desmoplastic stromal reactions **(Fig. 79-1*B*)**.

Other subtypes of nonneuroendocrine pancreatic cancers include acinar cell carcinoma (tumors of the exocrine enzyme producing cell); medullary carcinoma, adenosquamous, and other rare subtypes. Each of these are different in their behaviors and in their molecular characteristics and often require specific other types of treatment.

Molecular Characteristics The molecular characteristics of pancreatic ductal adenocarcinoma reveal four genes that are commonly mutated or inactivated (sometimes referred to as the "4 horsemen"). The most common is *KRAS* (usually in codon12), which is seen in virtually 100% of pancreatic adenocarcinomas. In fact, with the deep sequencing now available, if a *KRAS* mutation is not detected in the patient's tumor, one should consider the tumor being of a different origin (such as small bowel, gallbladder, or cholangiocarcinoma)—all of which could require different treatments. *p16/CDKn2A* is also noted in >90% of invasive pancreatic adenocarcinomas. *TP53* and *DPC4/MADH4* are mutated in about half of these tumors. As a reference point, the BRCA2 gene noted in Table 79-1 is mutated in 7–10% of pancreatic adenocarcinomas.

Precursor Lesions Many pancreatic adenocarcinomas seem to arise from noninvasive epithelial precursor lesions. Detection of these could allow for early diagnosis of pancreatic cancer. These pancreatic intraepithelial neoplasias (PanINs) have varying degrees of dysplasia designated as PanINs 1–3 (and constitute a progression model for pancreatic cancer). Genetic alterations become more frequent as the PanIN grade increases (e.g., grade 3). Not all PanIN lesions progress to invasive malignancy. PanINs that are ≥1 cm are called *intraductal papillary neoplasms* and are usually noninvasive. If the intraductal tumor is in a branch duct, it is usually noninvasive; however, if the intraductal tumor is in a main duct and is large and nodular, it is more likely to have malignant behavior.

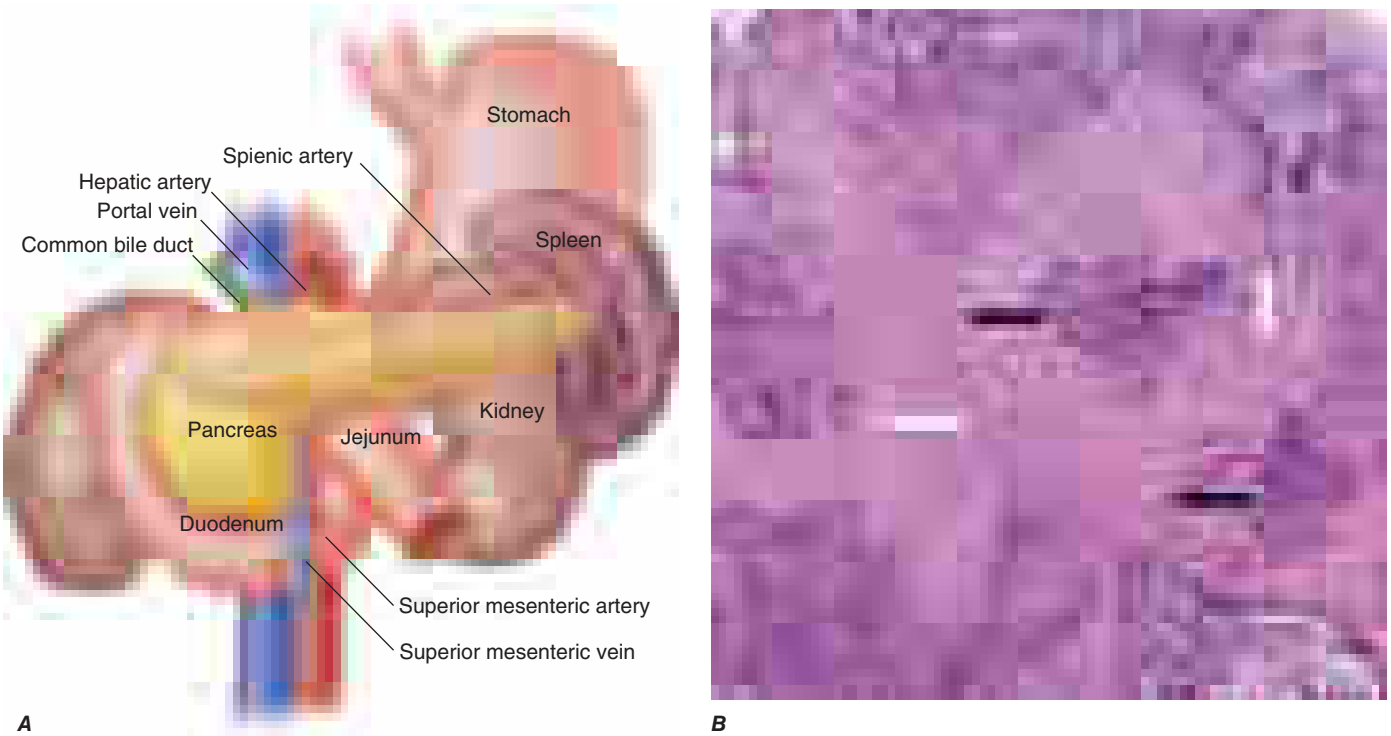

FIGURE 79-1 ***A.*** Note the relationship of the pancreas to the major vessels of the retroperitoneum. ***B.*** Ductal adenocarcinoma of the pancreas (*black arrows*), with intense stromal component (*white arrows*). *(Part A is courtesy of Mary Kay Washington, MD, PhD Vanderbilt University. Part B is courtesy of Haiyong Han, PhD Translational Genomics Research Institute [TGen].)*

One other pancreatic tumor is the mucinous cystic neoplasm; they may be seen as incidental findings on scans. These lesions are less likely invasive (20%) unless they are large and have nodules in them.

CLINICAL FEATURES

History and Physical The classic presentation for a patient with pancreatic cancer has been abdominal pain and weight loss with or without jaundice. The pain is midepigastric (sometimes described as a "boring-like" pain). Often the pain is in the back (due to retroperitoneal invasion of the splanchnic nerve plexus). The pain may be exacerbated by eating or lying flat. Other items of note in a history is lightening in stool color (steatorrhea also causes malodorous stools), or the onset of diabetes in the prior year. Jaundice, first detectable with a bilirubin of 2.5–3.0 mg/dL, is usually associated with tumor in the head of the pancreas. In some instances, depression is noted (with a higher subsequent number of suicides). Pruritis may be seen when the bilirubin reaches 6–8 mg/dL.

Physical signs include jaundice, signs of weight loss, a palpable gallbladder (Courvoisier's sign), hepatomegaly, an abdominal mass, and even an enlarged spleen (usually indicating a portal vein thrombosis). Migratory superficial thrombophlebitis can also be seen (Trousseau's syndrome). Signs of late disease include a lymph node palpable in the supraclavicular fossa (usually on the left where the thoracic duct enters the subclavian vein). This is clinically referred to as Virchow's node. Occasionally one can palpate subcutaneous metastases in the periumbilical area referred to as a Sister Mary Joseph's node—named after one of the scrub nurses on the Mayo Clinic Operative Team who noted that when she prepped that area and felt those nodules, the patient often had peritoneal metastases.

The history and symptoms noted above may lead a person to see a physician; often CT and MRI scanning detects the disease before advanced disease symptoms appear.

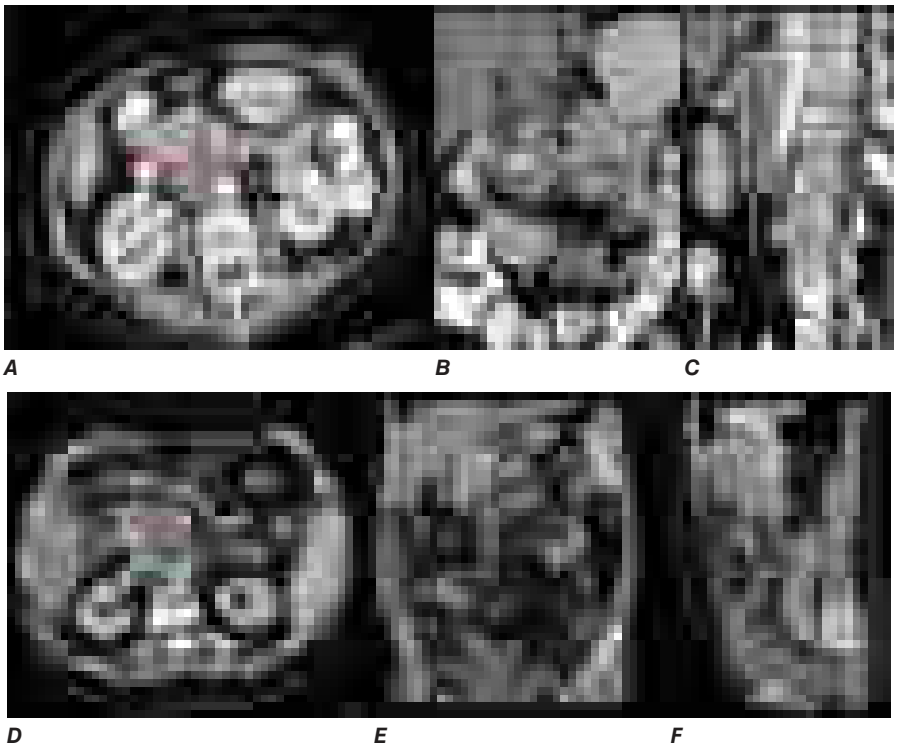

FIGURE 79-2 Selected images from contrast-enhanced CT in patients with locally advanced adenocarcinoma of the pancreas. A high-quality contrast-enhanced CT scan (arterial phase in Panels ***A–C*** and portal venous phase in Panels ***D–F***) is required for optimal staging of pancreas cancer. Panel ***A*** demonstrates the typical features of adenocarcinoma of the pancreas on arterial phase axial CT scans (*dotted outline*) with tumor encasement of the superior mesenteric artery (*white arrow*). Note the dilatation of the common bile duct (*red arrow*). Panels ***B*** (magnified coronal) and ***C*** (sagittal) show reconstruction of CT images into additional orthogonal planes with exquisite details to confirm the unresectable nature of the tumor due to vascular encasement. Panel ***D*** demonstrates the typical features of adenocarcinoma of the pancreas on portal venous phase axial CT scans in a different subject. The dotted line outlines a pancreas cancer lesion in the pancreatic head, which is encasing the portal splenic confluence (*dotted outline*). Panels ***E*** (*white arrow*) and ***F*** show the pinched appearance of the portal splenic confluence by tumor abutment and invasion of the superior mesenteric vein (*white arrow*) on coronal and sagittal views. Note the presence of a stent in the common bile duct (*red arrow*) to help relieve biliary obstruction caused by the tumor. CA, celiac axis; SMA, superior mesenteric artery.

DIAGNOSTIC WORKUP

Imaging Diagnostic imaging plays a major role in diagnosing pancreatic cancer and other intraabdominal diseases. The best technique is the use of a dual-phase contrast-enhanced spiral CT using the pancreatic cancer protocol which allows arterial phase enhancement and portal venous phase enhancement. This special protocol can provide helpful prospective staging and assessment of resectability. Figure 79-2 demonstrates such a CT scan (with vascular involvement). Figure 79-3 demonstrates the use of an 18F glucose positron emission tomography (PET) scan.

Histologic Diagnosis A histologic (tissue) diagnosis is essential and should be obtained with a cutting biopsy needle (not a skinny needle with cytology). Misdiagnosis is more common based on only fine-needle aspirates. Obtaining a tissue diagnosis allows not only for accuracy but also for molecular testing for *KRAS* mutations, microsatellite instability, and other important molecular abnormalities. Those molecular abnormalities and others will be increasingly important as more targeted therapies are developed for patients with pancreatic cancer.

The core needle (16–18 gauge) biopsy can be obtained via endoscopic ultrasound-guided techniques for a tumor localized to the pancreas or, if there are liver lesions or Virchow's node, via percutaneous biopsy by interventional radiologists.

FIGURE 79-3. PET scan demonstrating metastatic disease—baseline and after 6 weeks of chemotherapy with some resolution of liver metastases.

Serum Markers Before treatment, a serum sample should be obtained for levels of CA19-9, carcinoembryonic antigen (CEA), or if both are negative, for CA125 (can be positive when the CA19-9 is negative due to the patient not being a Lewis antigen secretor). These markers are not useful for staging but can be useful in following the course of pancreatic cancer.

IMPORTANT IMMEDIATE CONSIDERATIONS IN PATIENT CARE

While the patient is being evaluated and staged, one must be alert for biliary tract obstruction (and the attendant risk for sepsis from the biliary tree). A stent can be placed (plastic if temporary or metal if needed longer) to relieve the jaundice and pruritus. If surgery is being contemplated, an early surgical consultation is in order as there are surgeons who will want to proceed to surgery without placement of a stent.

Patients with pancreatic cancer are often hypercoagulable and frequently have migratory thrombophlebitis (Trousseau's sign) as well as deep vein thrombosis with pulmonary emboli (a frequent cause of death). Appropriate examinations plus being alert to thromboses on the routine workup are mandatory so appropriate management can be put in place.

Control of pain or of any of the symptoms should be obtained if at all possible to help patients be as comfortable as possible for their decision-making. Sometimes simple approaches like the use of a replacement pancreatic enzyme (at good therapeutic doses) can relieve the bloating, cramping, and diarrhea these patients suffer from. Early involvement of a palliative care team can improve a patient's quality of life and sometimes even its length.

CLINICAL STAGING

The clinical staging of pancreatic cancer according to the American Joint Commission on cancer staging is presented in Table 79-2.

Table 79-3 presents another clinical way to express extent of disease as well as therapeutic approaches (to be discussed later).

For proper staging, some physicians believe that a laparoscopy either before or at the time of contemplated surgery is important. If metastatic disease is found at laparoscopy, one can avoid surgery that would not be helpful because disease is already advanced.

TREATMENT

Resectable Disease

For patients with resectable disease (as defined in Table 79-3), the best option is surgery. Only a small percentage of patients are in this category (10–20%). The surgery for patients with tumors in the head or uncinate body of the pancreas is usually a pylorus-sparing pancreaticoduodenectomy (a modified Whipple procedure). For tumors in the body or tail, a distal pancreatomy is usually performed. Clinical and pathologic findings of the resection are defined as either, an Ro

TABLE 79-2 Definition of Primary Tumor (T)

T CATEGORY	T CRITERIA
TX	Primary tumor cannot be assesed
T0	No evidence of primary tumor
Tis	Carcinoma in situ This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor is ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
M CATEGORY	**M CRITERIA**
M0	No distant metastasis
M1	Distant metastasis
N CATEGORY	**N CRITERIA**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

AJCC Prognostic Stage Groups

WHEN T IS...	AND N IS...	AND M IS...	THEN THE STAGE GROUP IS....
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

Source: Adapted with permission from MB Amin et al (eds): *AJCC Cancer Staging Manual*, 8th ed. Springer, 2017.

TABLE 79-3 Extent of Disease and Therapeutic Approach

DESIGNATION (MEDIAN SURVIVAL)	THERAPEUTIC APPROACHES
1. Resectable (localized): (18–23 mo) • No encasement of celiac axis or superior mesenteric artery (SMA) • Patent superior mesenteric—portal veins • No extrapancreatic disease	Surgical option (or preoperative-neoadjuvant therapy first). Surgery is followed by postsurgery adjuvant therapy • Currently gemcitabine + capecitabine
2. Locally advanced: (6–10 mo) • Encasement of arteries • Venous occlusion (superior mesenteric vein [SMV] or portal) • No extrapancreatic disease	Either chemotherapy or chemotherapy + radiation therapy
3. Metastatic: (8.3–12.8 mo)	Systemic chemotherapy

TABLE 79-4 Combination Chemotherapy Regimens that Have an Impact on Survival

STUDY DESIGN (AUTHOR/REF)	NO. OF PATIENTS	MEDIAN SURVIVAL (MONTHS)
Gemcitabine + erlotinib vs Gemcitabine, (Moore et al: J. Clin Oncol. 26:1960, 2007.)	569	6.24 vs 5.91 (HR 0.82; 95% CI 0.69–0.99, $p = 0.038$)
Folfirinox (folinic acid + 5FU + irinotecan + oxaliplatin) vs Gemcitabine, (Conroy et al: N Eng J Med 364:1817, 2011.)	342	11.1 vs 6.8 (HR 0.57; 95% CI 0.45–0.70, $p < 0.001$)
Nap-paclitaxel + gemcitabine vs gemcitabine, (Von Hoff et al: N Eng J Med 369:1691, 2013.)	861	8.5 vs 6.7 (HR 0.72; 95% CI 0.62–0.83, $p < 0.001$[a]

[a]The 2-year survival rate with this regimen is 9% and the 3+ year rate is 4%. Other studies have not reported on these parameters.

resection (no macroscopic or microscopic disease left after surgery); an R1 resection refers to residual disease likely left behind. Patients with smaller tumors and lymph node negative disease have a better survival (median of about 18–23 months with 5-year survival of about 20%).

Two approaches are being explored to try to improve on this.

(1) Postoperative adjuvant therapy. The standard of care is to use 6 months of adjuvant treatment with gemcitabine + capecitabine (referred to as the ESPAC4 trial). The median survival was 28 months (95% CI (23.5–31.5) for the combination of gemcitabine + capecitabine versus 25.5 months CI with (22.7–27.1) for the gemcitabine alone—hazard ratio 0.82 95% (0.6–0.98) ($p = 0.032$). Toxicities were manageable.

(2) A more experimental approach is the use of neoadjuvant chemotherapy (chemotherapy given before surgery) to try to shrink the tumor and normalize the patient's serum CA19-9 level. Studies of neoadjuvant chemotherapy are ongoing.

Locally Advanced Disease (30% of Patients) For patients with locally advanced disease, the median survival is also quite poor (6–10 months) because many of the patients die with local problems (portal vein thrombosis with bleeding varices, obstruction, sepsis, etc.). The approach has been to try to reduce the bulk of the disease with use of radiation therapy plus chemotherapy or chemotherapy alone, hoping the disease could become resectable. No standard therapy has been agreed upon, but experimental approaches are applying some of the treatments that show promise in advanced metastatic disease.

Advanced Metastatic Disease (60% of Patients) Only a few of the many phase III randomized trials in patients with advanced pancreatic cancer have led to meaningful increases in survival. We have learned that a regimen needs to have at least a 50% improvement in overall survival or 90% improvement in 1-year survival in a pilot trial to predict for any degree of success in large randomized phase III trials.

Patients with the best chance of receiving a benefit from treatment have a good performance status (functioning up and around at least 70% of the day), have a reasonable albumin level (≥3.0 g/dL), and a neutrophil/lymphocyte ratio of ≤5.0.

Single-agent gemcitabine achieves a median survival of 6 months and a 1-year survival rate of 18%. Table 79-4 details three combination regimens that have further improved survival modestly. Median overall survival still ranges from 6 to 11 months. However, 1-year survival is now approaching 35% for these combination regimens with some long-term 4+ year survivors.

Liposomal irinotecan has been approved by the U.S. Food and Drug Administration (FDA) in combination with 5 fluorouracil + leucovorin for patients whose tumors have progressed on gemcitabine based on improved overall survival. PARP inhibitors have clinical activity against pancreatic cancers having mutations in BRCA2 or PALB2 (i.e., defective DNA repair proteins). In addition, tumors with microsatellite instability often have more mutations and such tumors appear to have a higher response rate to immunotherapy with checkpoint inhibitors, anti-PD-1 (pembrolizumab, nivolumab), and anti-PD-L1 antibodies.

Other Potential Factors Influencing Survival Preclinical studies have suggested that vitamin D can inhibit the development and growth of cancer. In models of pancreatic cancer, synthetic analogs of vitamin D had an effect on both tumor cells and on the tumor microenvironment. Clinical studies are conflicting as to whether circulating levels of plasma 25-hydroxyvitaminD (25[OH]D) affect the incidence of pancreatic cancer. However, patients with prediagnostic levels of 25(OH)D that are in the normal range have a longer survival than those who have reduced levels (35% lower hazard for death).

FUTURE DIRECTIONS

Death from pancreatic cancer is often due to progressive inanition. The metabolic consequences of this cancer are being examined. The tumor can be fatal at a modest level of tumor burden based on the profound metabolic effects. Other promising areas of investigation include addressing the florid stromal reaction around the tumor cells (believed to act as a physical barrier to drug delivery and as an immune sanctuary for the tumor cells). This attack on the stroma is being done with enzymatic (hyaluronidase) and other (antisuper enhancer genes) approaches. Also, utilization of hypomethylating and histone deacetylase inhibitors to correct epigenetic defects in the tumor microenvironment are under active study.

Acknowledgment

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80 Neuroendocrine Tumors of the Gastrointestinal Tract and Pancreas

Robert T. Jensen

GENERAL FEATURES OF GASTROINTESTINAL NEUROENDOCRINE TUMORS

Gastrointestinal (GI) neuroendocrine tumors (NETs) are tumors derived from the diffuse neuroendocrine system of the GI tract, which is composed of amine- and acid-producing cells with different hormonal profiles, depending on the site of origin. NETs of the GI tract share many features with other NETs throughout the body and were historically divided into GI-NETs (in the GI tract) (also frequently called *carcinoid tumors*) and pancreatic neuroendocrine tumors (pNETs), although in newer pathologic classifications they are all classified as NETs **(Table 80-1)**. These tumors originally were classified as APUDomas (for *a*mine *p*recursor *u*ptake and *d*ecarboxylation), as were pheochromocytomas, NETs in other locations, melanomas, and medullary thyroid carcinomas, because they share certain cytochemical features as well as various pathologic, biologic, and molecular features. It was originally proposed that APUDomas had a similar embryonic origin from neural crest cells, but it is now known that the peptide-secreting cells are not of neuroectodermal origin.

TABLE 80-1 Comparison of the Criteria for the Tumor Category in the ENETS AJCC TNM Classifications of Pancreatic and Appendiceal NETs (Top Panel) and the WHO/ENETS Grading and Classification (Bottom Panel)

A. TNM Classification

	ENETS TNM	AJCC/UICC TNM
pNETs		
T1	Confined to pancreas, <2 cm	Confined to pancreas, <2 cm
T2	Confined to pancreas, 2–4 cm	Confined to pancreas, >2 cm
T3	Confined to pancreas, >4 cm, or invasion of duodenum or bile duct	Peripancreatic spread, but without major vascular invasion (truncus coeliacus, superior mesenteric artery)
T4	Invasion of adjacent organs or major vessels	Major vascular invasion
Appendiceal NETs		
T1	≤1 cm; invasion of muscularis propria	T1a, ≤1 cm; T1b, >1–2 cm
T2	≤2 cm and <3 mm invasion of subserosa/mesoappendix	>2–4 cm or invasion of cecum
T3	>2 cm or >3 mm invasion of subserosa/mesoappendix	>4 cm or invasion of ileum
T4	Invasion of peritoneum/ other organs	Invasion of peritoneum/other organs

Abbreviations: AJCC, American Joint Committee on Cancer; ENETS, European Neuroendocrine Tumor Society; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; TNM, tumor, node, metastasis; UICC, International Union Against Cancer.

Source: Modified from DS Klimstra: Semin Oncol 40:23, 2013 and G Kloppel et al: Virchow Arch 456:595, 2010.

B. Grading

CLASSIFICATION	GRADE	MITOTIC COUNT (per 10 HPF)	KI_{67} INDEX (%)
NET	G1	<2	≤2
NET	G2	2–20	3–20
NEC (small cell and large cell)	G3	>20	>20

Abbreviations: HPF, high-power field; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

CLASSIFICATION/PATHOLOGY/TUMOR BIOLOGY OF NETS

NETs generally are composed of monotonous sheets of small round cells with uniform nuclei, and mitoses are uncommon. They can be frequently recognized on routine histology; however, these tumors are now recognized principally by their histologic staining patterns due to shared cellular proteins. Historically, silver staining was used, and tumors were classified as showing an argentaffin reaction if they took up and reduced silver or as being argyrophilic if they did not reduce it. Currently, immunocytochemical localization of chromogranins (A, B, C) and synaptophysin are routinely used. Chromogranins are acidic monomeric soluble proteins found in the large secretory granules. Synaptophysin is an integral membrane glycoprotein of 38,000 molecular weight found in small vesicles of neurons and NET. Chromogranin A is the most widely used.

Ultrastructurally, these tumors possess electron-dense neurosecretory granules and frequently contain small clear vesicles that correspond to synaptic vesicles of neurons. NETs synthesize numerous peptides, growth factors, and bioactive amines that may be ectopically secreted, giving rise to a specific clinical syndrome **(Table 80-2)**. The diagnosis of the specific syndrome requires the clinical features of the disease (Table 80-2) and cannot be made from the immunocytochemistry results alone. The presence or absence of a specific clinical syndrome also cannot be predicted from the immunocytochemistry alone.

NETs of the GI tract (GI-NETs) have been classified according to their anatomic area of origin (i.e., foregut, midgut, hindgut) because tumors with similar areas of origin share functional manifestations, histochemistry, and secretory products **(Table 80-3)**. Foregut tumors generally have a low serotonin (5-HT) content, are argentaffin-negative but argyrophilic, occasionally secrete adrenocorticotropic hormone (ACTH) or 5-hydroxytryptophan (5-HTP), causing an atypical carcinoid syndrome **(Fig. 80-1)**; these are often multihormonal and may metastasize to bone. They may produce a clinical syndrome due to the secreted products. Midgut carcinoids are argentaffin-positive, have a high serotonin content, most frequently cause the typical carcinoid syndrome when they metastasize (Table 80-3, Fig. 80-1), release serotonin and tachykinins (substance P, neuropeptide K, substance K), rarely secrete 5-HTP or ACTH, and less commonly metastasize to bone. Hindgut carcinoids (rectum, transverse and descending colon) are argentaffin-negative, are often argyrophilic, rarely contain serotonin or cause the carcinoid syndrome (Fig. 80-1, Table 80-3), rarely secrete 5-HTP or ACTH, contain numerous peptides, and may metastasize to bone.

However, the classification of GI NETs into foregut, midgut, or hindgut even though widely used, has not proved useful for prognostic or therapeutic purposes. More general classifications have been developed that allow NETs with similar features in different locations to be compared, have proven prognostic and tumor management value, and are now recommended in all recent guidelines and have become an essential requirement for management of these patients. The World Health Organization (WHO), European Neuroendocrine Tumor Society (ENETS), and the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) have developed classification systems (Table 80-1). Although there are some differences between these different classification systems, each uses similar information, and it is now recommended that the basic data underlying the classification be included in all standard pathology reports. These classification systems divide NETs from all sites into those that are well differentiated (low grade [G1] or intermediate grade [G2]) and those that are poorly differentiated (high grade [G3] divided into either small-cell carcinoma or large-cell neuroendocrine carcinoma [NEC]) (Table 80-1). In these classification systems, both pNETs and GI-NETs (carcinoids) are classified as NETs, and the old term of carcinoid is equivalent to well-differentiated NETs of the GI tract. These classification systems are based on not only the differentiation of the NET, but also a grading system assessing proliferative indices (Ki_{67} and the mitotic count)

TABLE 80-2 Gastrointestinal Neuroendocrine Tumor Syndromes

NAME	BIOLOGICALLY ACTIVE PEPTIDE(S) SECRETED	INCIDENCE (NEW CASES/10^6 POPULATION/YEAR)	TUMOR LOCATION	MALIGNANT, %	ASSOCIATED WITH MEN 1, %	MAIN SYMPTOMS/SIGNS
I. Established Specific Functional Syndromes						
A. Carcinoid syndrome due to GI-NET						
Carcinoid syndrome	Serotonin, possibly tachykinins, motilin, prostaglandins	0.5–2	Midgut (75–87%) Foregut (2–33%) Hindgut (1–8%) Unknown (2–15%)	95–100	Rare	Diarrhea (32–84%) Flushing (63–75%) Pain (10–34%) Asthma (4–18%) Heart disease (11–41%)
B. Well-established functional pNET syndromes						
Zollinger-Ellison syndrome	Gastrin	0.5–1.5	Duodenum (70%) Pancreas (25%) Other sites (5%)	60–90	20–25	Pain (79–100%) Diarrhea (30–75%) Esophageal symptoms (31–56%)
Insulinoma	Insulin	1–2	Pancreas (>99%)	<10	4–5	Hypoglycemic symptoms (100%)
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	Vasoactive intestinal peptide	0.05–0.2	Pancreas (90%, adult) Other (10%, neural, adrenal, periganglionic)	40–70	6	Diarrhea (90–100%) Hypokalemia (80–100%) Dehydration (83%)
Glucagonoma	Glucagon	0.01–0.1	Pancreas (100%)	50–80	1–20	Rash (67–90%) Glucose intolerance (38–87%) Weight loss (66–96%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%) Duodenum/jejunum (44%)	>70	45	Diabetes mellitus (63–90%) Cholelithiasis (65–90%) Diarrhea (35–90%)
GRFoma	Growth hormone–releasing hormone	Unknown	Pancreas (30%) Lung (54%) Jejunum (7%) Other (13%)	>60	16	Acromegaly (100%)
ACTHoma	ACTH	Rare	Pancreas (4–16% all ectopic Cushing's)	>95	Rare	Cushing's syndrome (100%)
pNET causing carcinoid syndrome	Serotonin, ?tachykinins	Rare (<100 cases)	Pancreas (<1% all carcinoids)	60–88	Rare	Same as carcinoid syndrome above
pNET causing hypercalcemia	PTHrP Others unknown	Rare	Pancreas (rare cause of hypercalcemia)	84	Rare	Abdominal pain due to hepatic metastases
II. Rare Specific Functional Syndromes						
pNET secreting renin	Renin	Rare	Pancreas	Unknown	No	Hypertension
pNET secreting luteinizing hormone	Luteinizing hormone	Rare	Pancreas	Unknown	No	Anovulation, virilization (female); reduced libido (male)
pNET secreting erythropoietin	Erythropoietin	Rare	Pancreas	100	No	Polycythemia
pNET secreting IGF-II	Insulin-like growth factor II	Rare	Pancreas	Unknown	No	Hypoglycemia
pNET secreting GLP-1	Glucagon-like peptide-1	Rare	Pancreas	Unknown	No	Hypoglycemia, diabetes
pNET secreting enteroglucagon	Enteroglucagon	Rare	Pancreas, small intestine	Unknown	Rare	Small intestinal hypertrophy, intestinal stasis, malabsorption
pNET secreting Cholecytokinin	Cholecytokinin	Rare	Pancreas	Unknown	No	Diarrhea, gallstones, peptic ulcer, weight loss
III. Possible Specific Functional pNET Syndromes						
pNET secreting calcitonin	Calcitonin	Rare	Pancreas (rare cause of hypercalcitonemia)	>80	16	Diarrhea (50%)
pNET secreting neurotensin	Neurotensin	Rare	Pancreas (100%)	Unknown	No	Motility disturbances, vascular symptoms
pNET secreting pancreatic polypeptide (PPoma)	Pancreatic polypeptide	1–2	Pancreas	>60	18–44	Watery diarrhea
pNET secreting ghrelin	Ghrelin	Rare	Pancreas	Unknown	No	Effects on appetite, body weight
pNET secreting secretin	Secretin	Rare	Pancreas	Unknown	unknown	Watery diarrhea

(*Continued*)

TABLE 80-2 Gastrointestinal Neuroendocrine Tumor Syndromes (Continued)

NAME	BIOLOGICALLY ACTIVE PEPTIDE(S) SECRETED	INCIDENCE (NEW CASES/10^6 POPULATION/YEAR)	TUMOR LOCATION	MALIGNANT, %	ASSOCIATED WITH MEN 1, %	MAIN SYMPTOMS/SIGNS
IV. Nonfunctional Syndrome pNET						
PPoma/nonfunctional[a]	None	1–2	Pancreas (100%)	>60	18–44	Weight loss (30–90%) Abdominal mass (10–30%) Pain (30–95%)

[a]Pancreatic polypeptide–secreting tumors (PPomas) are listed in two places because most authorities classify these as not associated with a specific hormonal syndrome (nonfunctional); however, rare cases of watery diarrhea proposed to be due to PPomas have been reported.

Abbreviations: ACTH, adrenocorticotropic hormone; GRFoma, growth hormone–releasing factor secreting pancreatic endocrine tumor; IGF-II, insulin-like growth factor II; MEN, multiple endocrine neoplasia; pNET, pancreatic neuroendocrine tumor; PPoma, tumor secreting pancreatic polypeptide; PTHrP, parathyroid hormone–related peptide; VIPoma, tumor secreting vasoactive intestinal peptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria syndrome.

(Table 80-1). Based on these proliferative indices, NETs are classified as low grade (G1), intermediate grade (G2), or high grade (G3) (Table 80-1). In addition to the grading system, a TNM (TNM-tumor staging, T=primary size, N=regional lymph node involvement, M=distant metastases) classification has been proposed that is based on the level of tumor invasion, tumor size, and tumor extent (Table 80-1). Because of the proven prognostic value of these classification and grading systems, as well as the fact that NETs with different classifications/grades respond differently to treatments, these classification systems are now essential for the management of all NETs.

GI-NETs may or may not be associated with a specific functional syndrome (Table 80-2). In the case of pNETs the type of functional syndrome present is used to classify them into nine well-established specific functional syndromes (Table 80-2), seven additional very rare specific functional syndromes (less than five cases described), five possible specific functional syndromes (pNETs secreting calcitonin, neurotensin, pancreatic polypeptide [PP], ghrelin) (Table 80-2), and nonfunctional pNETs. Other functional hormonal syndromes due to nonpancreatic tumors (usually intra-abdominal in location) have been described only rarely and are not included in (Table 80-2). These include secretion by intestinal and ovarian tumors of peptide tyrosine tyrosine (PYY), which results in altered motility and constipation, and ovarian tumors secreting renin or aldosterone causing alterations in blood pressure or somatostatin causing diabetes or reactive hypoglycemia. Each of the functional syndromes listed in Table 80-2 is associated with symptoms due to the specific hormone released. In contrast, nonfunctional pNETs release no products that cause a specific clinical syndrome. "Nonfunctional" is a misnomer in the strict sense because those tumors frequently ectopically secrete a number of peptides (PP, chromogranin A, ghrelin, neurotensin, α subunits of human chorionic gonadotropin, and neuron-specific enolase); however, they cause no specific clinical syndrome. The symptoms caused by nonfunctional pNETs are entirely due to the tumor per se. pNETs frequently ectopically secrete PP (60–85%), neurotensin (30–67%), calcitonin (30–42%), and to a lesser degree, ghrelin (5–65%). Whereas a few studies have proposed that their secretion can cause a specific functional syndrome, most studies support the conclusion that their ectopic secretion is not associated with a specific clinical syndrome, and thus they are listed in Table 80-2 as possible clinical syndromes. Because a large proportion of nonfunctional pNETs (60–90%) secrete PP, these tumors are often referred to as PPomas (Table 80-2). pNETs can secrete secretin (secretinoma) producing watery diarrhea; however, only two possible cases are described.

GI-NETs (carcinoids) can occur in almost any GI tissue (Table 80-3); however, at present, most (70%) have their origin in one of three sites: bronchus, jejunoileum, or colon/rectum. In the past, GI-NET (carcinoids) most frequently were reported in the appendix (i.e., 40%); however, at present they account for <5% (Table 80-3). Overall, the GI tract is the most common site for NETs, accounting for 64%, with the respiratory tract a distant second at 28%. Both race and sex can affect the frequency as well as the distribution of GI-NETs (carcinoids). African Americans have a higher incidence of carcinoids. Race is particularly important for rectal carcinoids, which are found in 41%

TABLE 80-3 GI-NET (Carcinoid) Location, Frequency of Metastases, and Association with the Carcinoid Syndrome

	LOCATION (% OF TOTAL)	INCIDENCE OF METASTASES	INCIDENCE OF CARCINOID SYNDROME
Foregut			
Esophagus	<0.1	—	—
Stomach	4.6	10	9.5
Duodenum	2.0	—	3.4
Pancreas	0.7	71.9	20
Gallbladder	0.3	17.8	5
Bronchus, lung, trachea	27.9	5.7	13
Midgut			
Jejunum	1.8	58.4	9
Ileum	14.9		9
Meckel's diverticulum	0.5	—	13
Appendix	4.8	38.8	<1
Colon	8.6	51	5
Liver	0.4	32.2	—
Ovary	1.0	28	50
Testis	<0.1	—	50
Hindgut			
Rectum	13.6	3.9	—

Abbreviation: GI-NET, gastrointestinal neuroendocrine tumor.

Source: Location is from the PAN-SEER data (1973–1999), and incidence of metastases is from the SEER data (1992–1999), reported by IM Modlin et al: Cancer 97:934, 2003. Incidence of carcinoid syndrome is from 4349 cases studied from 1950 to 1971, reported by JD Godwin: Cancer 36:560, 1975.

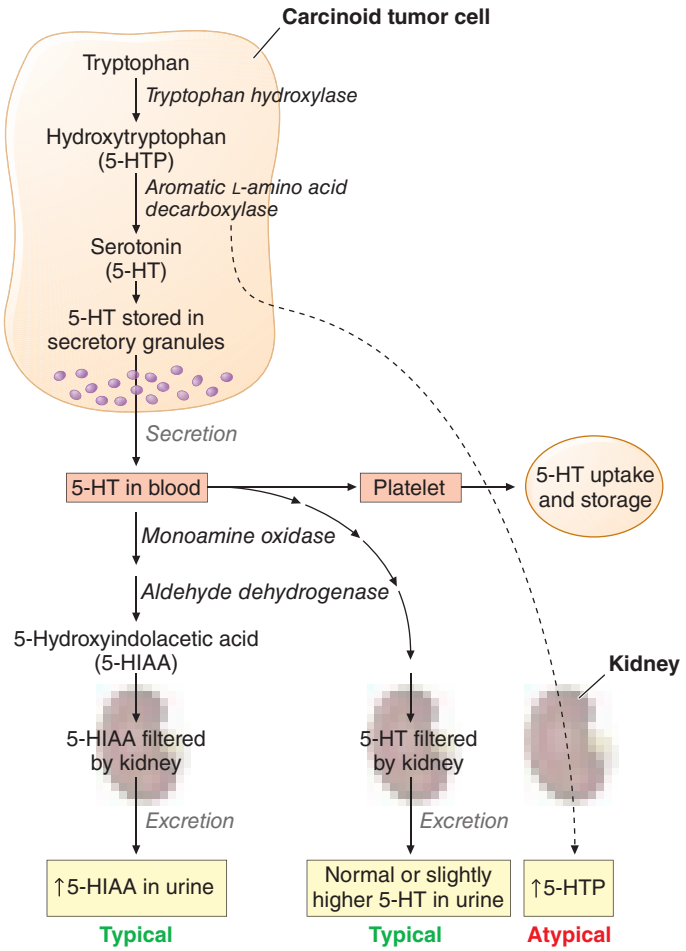

FIGURE 80-1 Synthesis, secretion, and metabolism of serotonin (5-HT) in patients with typical and atypical carcinoid syndromes. 5-HIAA, 5-hydroxyindolacetic acid.

of Asians/Pacific Islanders with NETs compared to 32% of American Indians/Alaskan natives, 26% of African Americans, and 12% of white Americans. Females have a lower incidence of small intestinal and pancreatic carcinoids.

The term *pancreatic neuroendocrine* or *endocrine tumor*, although widely used and therefore retained here, is also a misnomer, strictly speaking, because these tumors can occur either almost entirely in the pancreas (insulinomas, glucagonomas, nonfunctional pNETs, pNETs causing hypercalcemia) or at both pancreatic and extrapancreatic sites (gastrinomas, VIPomas [vasoactive intestinal peptide], somatostatinomas, GRFomas [growth hormone–releasing factor]). pNETs are also called islet cell tumors; however, the use of this term is discouraged because it is not established that they originate from the islets, and many can occur at extrapancreatic sites.

In addition to these classification/grading systems, a number of other factors have been identified that provide important prognostic information that can guide treatment **(Table 80-4)**.

The exact incidence of GI-NETs (carcinoids) or pNETs varies according to whether only symptomatic tumors or all tumors are considered. The incidence of clinically significant carcinoids is 7–13 cases/million population per year, whereas any malignant carcinoids at autopsy are reported in 21–84 cases/million population per year. The incidence of GI-NETs (carcinoids) is ~25–50 cases per million in the United States, which makes them less common than adenocarcinomas of the GI tract. However, their incidence has increased sixfold in the last 30 years. In an analysis of 35,825 GI-NETs (carcinoids) (2004) from the U.S. Surveillance, Epidemiology, and End Results (SEER) database which includes predominately malignant NETs, their incidence was 5.25/100,000 per year, and the 29-year prevalence was 35/100,000. Clinically significant pNETs have a prevalence of 10 cases/million population, with insulinomas, gastrinomas, and nonfunctional pNETs having an incidence of 0.5–2 cases/million population per year (Table 80-2). NF-pNETs are predominating, often making up 50–80% of the series, and increasingly found when asymptomatic. pNETs account for 1–10% of all tumors arising in the pancreas and 1.3% of tumors in the SEER database. VIPomas are 2–8 times less common, glucagonomas are 17–30 times less common, and somatostatinomas are the least common. In autopsy studies, 0.5–1.5% of all cases have a pNET; however, in <1 in 1000 cases was a functional tumor thought to occur.

Both GI-NETs (carcinoids) and pNETs commonly show malignant behavior (Tables 80-2 and 80-3). With pNETs, except for insulinomas in which <10% are malignant, 50–100% in different series are malignant. With GI-NETs (carcinoids), the percentage showing malignant behavior varies in different locations (Table 80-3). For the three most common sites of NET's occurrence, the incidence of metastases varies greatly from the jejunoileum (58%), lung/bronchus (6%), and rectum (4%) (Table 80-3). With both GI-NETs (carcinoids) and pNETs, a number of factors (Table 80-4) are important prognostic factors in determining survival and the aggressiveness of the tumor. Patients with pNETs (excluding insulinomas) generally have a poorer prognosis than do patients with GI-NETs (carcinoids). The presence of liver metastases is the single most important prognostic factor in single and multivariate analyses for both GI-NETs (carcinoids) and pNETs. Particularly important in the development of liver metastases is the size of the primary tumor. For example, with small intestinal carcinoids, which are the most common cause of the carcinoid syndrome due to metastatic disease in the liver (Table 80-2), metastases occur in 15–25% if the tumor is <1 cm in diameter, 58–80% if it is 1–2 cm in diameter, and >75% if it is >2 cm in diameter. Similar data exist for gastrinomas and other pNETs; the size of the primary tumor is an independent predictor of the development of liver metastases. The presence of lymph node metastases, their ratio or presence of extra-hepatic metastases; the depth of invasion; the rapid rate of growth; various histologic features (differentiation, mitotic rates, growth indices, vessel density, vascular endothelial growth factor [VEGF], CD10 metalloproteinase expression, abnormal expression of p53, retinoblastoma or SMAD, and low expression of p27 nuclear staining, low progesterone receptor expression); necrosis; presence of cytokeratin; elevated serum alkaline phosphatase levels; older age; presence of circulating tumor cells; increased uptake on ^{18}(F)-FDG-PET/CT scanning or low uptake (SUV/max) on ^{68}Ga-DOTANOC PET/CT scanning, and flow cytometric results, such as the presence of aneuploidy, are all important prognostic factors for the development of metastatic disease (Table 80-4). For patients with GI-NETs (carcinoids), additional associations with a worse prognosis include the development of the carcinoid syndrome (especially the development of carcinoid heart disease); male sex; the presence of a symptomatic tumor, a secondary malignancy, or greater increases in a number of tumor markers (5-hydroxyindolacetic acid [5-HIAA], neuropeptide K, chromogranin A), and the presence of various molecular features. With pNETs or gastrinomas, a worse prognosis is associated with female sex, overexpression of the Ha-*ras* oncogene or p53, the absence of Multiple Endocrine Neoplasia type 1 (MEN 1), presence of a NF-pNET, higher levels of various tumor markers (i.e., chromogranin A, gastrin, C-reactive protein), and presence of various histologic features (immunohistochemistry for c-KIT, low cyclin B1 or ATM, loss of PTEN/TSC-2, expression of fibroblast growth factor-13) and various molecular features (Table 80-4). The WHO, ENETs, and AJCC/UICC TNM classification systems and the grading systems (G1–G3) have important prognostic value and use in determining therapeutic management, that they are now generally routinely required.

A number of diseases due to various genetic disorders are associated with an increased incidence of NETs **(Table 80-5)**. Each one is caused by a loss of a possible tumor-suppressor gene. The most important is MEN 1, which is an autosomal dominant disorder due to a defect in a 10-exon gene on 11q13, which encodes for a 610-amino-acid nuclear protein, menin **(Chap. 381)**. Patients with MEN 1 develop hyperparathyroidism due to parathyroid hyperplasia in 95–100% of cases, pNETs in 80–100%, pituitary adenomas in 54–80%, adrenal adenomas in 27–36%, bronchial carcinoids in 8%, thymic carcinoids in 8% (predominately males), gastric carcinoids in 13–30% of patients with Zollinger-Ellison syndrome, skin tumors (angiofibromas [88%], collagenomas [72%]),

TABLE 80-4 Prognostic Factors in Neuroendocrine Tumors

I. Both GI-NETs (carcinoids) and pNETs
Symptomatic presentation (p <0.05)
Performance status (p <0.04)
Presence/extent of liver metastases (p <0.01)
Presence of lymph node metastases or lymph node positive ratio (p <0.001)
Development of bone or extrahepatic metastases (p <0.01)
Depth of invasion (p <0.001)
Rapid rate of tumor growth
Elevated serum alkaline phosphatase levels (p = 0.003)
Primary tumor site/site (p <0.005)
High serum chromogranin A level (p <0.01)
Presence of one or more circulating tumor cells (p <0.001)
Increased uptake on (18)F-FDG PET scanning
Low uptake (SUVmax) on (68)Ga-DOTANOC PET/CT scanning
Various histologic/molecular features
Tumor differentiation (p <0.001)
High growth indices (high Ki_{67} index, PCNA expression)
High mitotic counts (p <0.001)
Low progesterone receptor expression (p <0.001)
Necrosis present
Presence of cytokeratin 19 (p <0.02)
Vascular or perineural invasion (p <0.02)
Vessel density (low microvessel density, increased lymphatic density)
High CD10 metalloproteinase expression (in series with all grades of NETs)
Flow cytometric features (i.e., aneuploidy)
High VEGF expression (in low-grade or well-differentiated NETs only)
Abnormal expression of p53, Rb, SMADs
Loss of p27 expression(nuclear) (p <0.001)
WHO, ENETS, AJCC/UICC stage, and grade
Presence of a pNET rather than GI-NET associated with poorer prognosis (p = 0.0001)
Older age (p <0.01)
II. GI-NETs (carcinoids)
Location of primary: appendix < lung, rectum < small intestine < pancreas
Presence of carcinoid syndrome
Laboratory results (urinary 5-HIAA levels [p <0.01], plasma neuropeptide K [p <0.05], serum chromogranin A [p <0.01])
Presence of a second malignancy
Male sex (p <0.001)
Molecular findings (TGF-α expression [p <.05], chr 16q LOH or gain chr 4p [p <.05], gain in chr 14, loss of 3p13, loss of succinate dehydrogenase expression [ileal carcinoid], upregulation of Hoxc6), molecular profiling category (mutations, epigenetic changes, copy number-small intestinal NETs)
III. pNETs
Location of primary: duodenal (gastrinoma) better than pancreatic
Ha-*ras* oncogene or p53 overexpression
Female sex
MEN 1 syndrome absent
Presence of nonfunctional tumor (some studies, not all)
Various histologic features: IHC positivity for c-KIT, low cyclin B1 or ATM expression (p <0.01), loss of PTEN or of tuberous sclerosis-2 IHC, expression of fibroblast growth factor-13; high SSTR2 expression (p = .001);
Laboratory findings (increased chromogranin A in some studies; gastrinomas—increased gastrin level, increased CRP (p <0.001)
Molecular findings (increased HER2/*neu* expression [p = 0.032], chr 1q, 3p, 3q, or 6q LOH [p = 0.0004], EGF receptor overexpression [p = 0.034], gains in chr 7q, 17q, 17p, 20q; alterations in the VHL gene [deletion, methylation]; presence of FGFR4-G388R single-nucleotide polymorphism); loss of ATRX/DAXX or positive for alternative lengthening of telomeres (p <0.001); high nuclear surviving expression (p <0.01)
PHLDA3 LOH; altered miRNA expression (lnc miRNA-21, miRNA-196)

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; AJCC, American Joint Committee on Cancer; ATM, ataxia telangiectasia mutated kinase; ATRX, a-thalassemia/mental retardation X-linked; chr, chromosome; CRP, C-reactive protein; DAXX, death domain-associated protein; EGF, epidermal growth factor; FGFR, fibroblast growth factor receptor; GI-NET, gastrointestinal neuroendocrine tumor; IHC, immunohistochemistry; Ki_{67}, proliferation-associated nuclear antigen recognized by Ki_{67} monoclonal antibody; LOH, loss of heterozygosity; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumors; PCNA, proliferating cell nuclear antigen; PHLDA3, Pleckstrin homology-like domain family A, member 3; pNET, pancreatic neuroendocrine tumor; PTEN, phosphatase and tensin homologue deleted from chromosome 10; Rb, retinoblastoma; SSTR2, somatostatin receptor subtype 2; TGF-α, transforming growth; factor α; TNM, tumor, node, metastasis; UICC, International Union Against Cancer; VEGF, vascular endothelial growth factor; WHO, World Health Organization.

central nervous system (CNS) tumors (meningiomas, ependymomas, schwannomas [<8%]), and smooth-muscle tumors (leiomyomas, leiomyosarcomas [1–7%]). Among patients with MEN 1, 80–100% develop nonfunctional pNETs (most are microscopic with 0–13% large/symptomatic), and functional pNETs occur in 20–80% in different series, with a mean of 54% developing Zollinger-Ellison syndrome, 18% insulinomas, 3% glucagonomas, 3% VIPomas, and <1% GRFomas or somatostatinomas. MEN 1 is present in 20–25% of all patients with Zollinger-Ellison syndrome, 4% of patients with insulinomas, and a low percentage (<5%) of patients with other pNETs.

TABLE 80-5 Genetic Syndromes Associated with an Increased Incidence of Neuroendocrine Tumors (NETs) (GI-NETs [Carcinoids] or pNETs)

SYNDROME	LOCATION OF GENE MUTATION AND GENE PRODUCT	NETS SEEN/ FREQUENCY
Multiple endocrine neoplasia type 1 (MEN 1)	11q13 (encodes 610-amino-acid protein, menin)	80–100% develop pNETs (microscopic), 20–80% (clinical): (nonfunctional > gastrinoma > insulinoma) GI-NETs (Carcinoids): gastric (13–30%), bronchial/thymic (8%)
von Hippel–Lindau disease	3q25 (encodes 213-amino-acid protein)	12–17% develop pNETs (almost always nonfunctional)
von Recklinghausen's disease (neurofibromatosis 1 [NF-1])	17q11.2 (encodes 2485-amino-acid protein, neurofibromin)	0–10% develop pNETs, primarily duodenal somatostatinomas (usually nonfunctional) Rarely insulinoma, gastrinoma
Tuberous sclerosis	9q34 (TSCI) (encodes 1164-amino-acid protein, hamartin), 16p13 (TSC2) (encodes 1807-amino-acid protein, tuberin)	0–9% develop pNETs (nonfunctional and functional [insulinoma, gastrinoma])

Abbreviations: GI, gastrointestinal; PNETs, pancreatic neuroendocrine tumors.

TABLE 80-6 Clinical Characteristics in Patients with Carcinoid Syndrome

	PERCENTAGE (RANGE)	
	AT PRESENTATION	DURING COURSE OF DISEASE
Symptoms/signs		
Diarrhea	32–93%	68–100%
Flushing	23–100%	45–96%
Pain	10%	34%
Asthma/wheezing	4–14%	3–18%
Pellagra	0–7%	0–5%
None	12%	22%
Carcinoid heart disease present	11–40%	14–41%
Demographics		
Male	46–59%	46–61%
Age		
Mean	57 years	59.2 years
Range	25–79 years	18–91 years
Tumor location		
Foregut	5–14%	0–33%
Midgut	57–87%	60–100%
Hindgut	1–7%	0–8%
Unknown	2–21%	0–26%

Three phacomatoses associated with NETs are von Hippel–Lindau disease (VHL), von Recklinghausen's disease (neurofibromatosis type 1 [NF-1]), and tuberous sclerosis (Bourneville's disease) (Table 80-5). VHL is an autosomal dominant disorder due to defects on chromosome 3p25, which encodes for a 213-amino-acid protein that interacts with the elongin family of proteins as a transcriptional regulator **(Chaps. 86, 309, 380, 381)**. In addition to cerebellar hemangioblastomas, renal cancer, and pheochromocytomas, 10–17% develop a pNET. Most are nonfunctional, although insulinomas and VIPomas have been reported. Patients with NF-1 (von Recklinghausen's disease) have defects in a gene on chromosome 17q11.2 that encodes for a 2845-amino-acid protein, neurofibromin, which functions in normal cells as a suppressor of the *ras* signaling cascade **(Chap. 86)**. Up to 10% of these patients develop an upper GI-NET (carcinoid), characteristically in the periampullary region (54%). Many are classified as somatostatinomas because they contain somatostatin immunocytochemically; however, they uncommonly secrete somatostatin and rarely produce a clinical somatostatinoma syndrome. NF-1 has rarely been associated with insulinomas and Zollinger-Ellison syndrome. NF-1 accounts for 48% of all duodenal somatostatinomas and 23% of all ampullary GI-NETs (carcinoids). Tuberous sclerosis is caused by mutations that alter either the 1164-amino-acid protein hamartin (TSC1) or the 1807-amino-acid protein tuberin (TSC2) **(Chap. 86)**. Both hamartin and tuberin interact in a pathway related to phosphatidylinositol 3-kinases and mammalian target of rapamycin (mTOR) signaling cascades. A few cases including nonfunctional and functional pNETs (insulinomas and gastrinomas) have been reported in these patients **(Table 80-6)**.

A few other syndromes involving GI-NETs have been described due to various mutations, but no inherited cases have been reported. Mahvash disease is associated with the development of α-cell hyperplasia, hyperglucagonemia, without features of the glucagonoma syndrome, the development of NF pNETs, and is due to inactivating mutations of the human glucagon receptor. The polycythemia-paraganglioma-somatostatinoma (SSoma) syndrome involves childhood polycythemia, later the development of norepinephrine-producing paragangliomas (mean age 17 years) then SSomas (mean age 29 years) with gallbladder disease. In 28% of the patients, a somatic mutation in hypoxia-inducible factor 2 alphas is found.

Most GI NETs (carcinoids) are sporadic, although as discussed above gastric carcinoids occur (type 2) in MEN1 syndrome, duodenal carcinoids (SSomas) occur in NF-1 and a small percentage of patients (<3%) with small intestinal carcinoids have a familial form of the disease, which in one family was due to mutations in the inositol polyphosphate multikinase gene (IMPK).

Mutations in common oncogenes (*ras, myc, fos, src, jun*) or common tumor-suppressor genes (*p53*, retinoblastoma susceptibility gene) are not commonly found in either pNETs or GI-NETs (carcinoids). However, frequent (70%) gene amplifications in *MDM2, MDM4,* and *WIPI* inactivating the p53 pathway are noted in well-differentiated pNETs, and the retinoblastoma pathway is altered in the majority of pNETs. In addition to these genes, additional alterations that may be important in their pathogenesis include changes in the *MEN1* gene, *p16/MTS1* tumor-suppressor gene, and *DPC4/Smad4* gene; amplification of the HER-2/*neu* protooncogene; alterations in transcription factors (Hoxc6 [GI carcinoids]), growth factors, and their receptors; methylation of a number of genes that probably results in their inactivation; and deletions of unknown tumor-suppressor genes as well as gains in other unknown genes. The clinical antitumor activity of everolimus, an mTOR inhibitor, and sunitinib, a tyrosine kinase inhibitor (PDGFR, VEGFR1, VEGFR2, c-KIT, FLT-3), support the importance of the mTOR-AKT pathway and tyrosine kinase receptors in mediating growth of malignant NETs (especially pNETs). The importance of the mTOR pathway in pNET growth is further supported by the finding that a single-nucleotide polymorphism (FGFR4-G388R, in fibroblast growth factor receptor 4) affects selectivity to the mTOR inhibitor and can result in significantly higher risk of advanced pNET stage and liver metastases (Table 80-4). Comparative genomic hybridization, genome-wide allelotyping studies, and genome-wide single-nucleotide polymorphism analyses have shown that chromosomal losses and gains are common in pNETs and GI-NETs (carcinoids), but they differ between these two NETs, and some have prognostic significance (Table 80-4). Mutations in the *MEN1* gene are probably particularly important. Loss of heterozygosity at the MEN 1 locus on chromosome 11q13 is noted in 93% of sporadic pNETs (i.e., in patients without MEN 1) and in 26–75% of sporadic GI-NETs (carcinoids). Mutations in the *MEN1* gene are reported in 31–34% of sporadic gastrinomas. Exomic sequencing of sporadic pNETs found that the most frequently altered gene was *MEN1*, occurring in 44% of patients, followed by mutations in 43% of patients in genes encoding for two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain-associated protein) and ATRX (α-thalassemia/mental retardation

syndrome X-linked) and in 15% of patients in the mTOR pathway. The presence of a number of these molecular alterations in pNETs or GI-NETs (carcinoids) correlates with tumor growth, tumor size, and disease extent or invasiveness and may have prognostic significance (Table 80-4).

GI NETs (carcinoids) have frequently loss of chromosome 18 (>60%) as well as losses on Chr 9p, 16q and chromosomal gains of 17q, 19p (57%) and lesser gains on 4q, 14q, and Chr 5, but the exact genes mediating possible effects on the tumor in these areas are still unclear. In contrast to pNETs, mutations in GI-NETs (carcinoids) are uncommon, and in one study of 180 small intestinal carcinoids, with exome and genome-sequencing analysis recurrent mutations were only observed in the CDKN1B gene (cyclin-dependent kinase inhibitor 1B [$p27^{Kip1}$]) in 8%. Integrative genomic analysis incorporating DNA methylation, show that small intestinal GI carcinoids commonly have epigenetic changes and three molecular subgroups with differing clinical course and outcomes have been identified (Table 80-4).

CHARACTERISTICS OF THE MOST COMMON GI-NETs (CARCINOIDS)

Appendiceal NETs (Carcinoids) Appendiceal NETs (carcinoids) occur in 1 in every 200–300 appendectomies, usually in the appendiceal tip, have an incidence of 0.15/100,000 per year, comprise 2–5% of all GI-NETs (carcinoids), and comprise 32–80% of all appendiceal tumors. The mean age at diagnosis is 38–51 years. Most (i.e., >90%) are <1 cm in diameter without metastases in older studies, but more recently, 2–35% have had metastases (Table 80-3). In the SEER data of 1570 appendiceal carcinoids, 62% were localized, 27% had regional metastases, and 8% had distant metastases. The risk of metastases increases with size, with those <1 cm having a 0 to <10% risk of metastases and those >2 cm having a 25–44% risk. Besides tumor size, other important prognostic factors for metastases include basal NET location, invasion of mesoappendix, poor differentiation, advanced stage or WHO/ENETS classification, older age, and positive resection margins. The 5-year survival is 88–100% for patients with localized disease, 78–100% for patients with regional involvement, and 12–28% for patients with distal metastases. In patients with tumors <1 cm in diameter, the 5-year survival is 95–100%, whereas it is 29% if tumors are >2 cm in diameter. Most tumors are well-differentiated G1 tumors (87%) (Table 80-1), with the remainder primarily well-differentiated G2 tumors (13%); with poorly differentiated G3 tumors uncommon (<1%). Their percentage of the total number of carcinoids decreased from 43.9% (1950–1969) to 2.4% (1992–1999). Appendiceal goblet cell (GC) NETs (carcinoids)/carcinomas are a rare subtype (<5%) that are mixed adeno-neuroendocrine carcinomas. They are malignant and are thought to comprise a distinct entity; they frequently present with advanced disease and are recommended to be treated as adenocarcinomas, not carcinoid tumors.

SMALL INTESTINAL NETs (CARCINOIDS)

Small intestinal (SI) NETs (carcinoids) have a reported incidence of 0.67/100,000 in the United States, 0.32/100,000 in England, and 1.12/100,000 in Sweden and comprise >50% of all SI tumors. There is a male predominance (1.5:1), and race affects frequency, with a lower frequency in Asians and greater frequency in African Americans. The mean age of presentation is 52–63 years, with a wide range (1–93 years). Familial SI carcinoid families exist but are very uncommon. SI NETs (carcinoids) are frequently multiple; 9–18% occur in the jejunum, 70–80% are present in the ileum, and 70% occur within 6 cm (2.4 in.) of the ileocecal valve. Forty percent are <1 cm in diameter, 32% are 1–2 cm, and 29% are >2 cm. They are characteristically well differentiated; however, they are generally invasive, with 1.2% being intramucosal in location, 27% penetrating the submucosa, and 20% invading the muscularis propria. Metastases occur in a mean of 47–58% (range 20–100%). Liver metastases occur in 38%, to lymph nodes in 37% and more distant in 20–25%. They characteristically cause a marked fibrotic reaction, which can lead to intestinal obstruction. Tumor size is an important variable in the frequency of metastases. However, even small NETs (carcinoids) of the small intestine (<1 cm) have metastases in 15–25% of cases, whereas the proportion increases to 58–100% for tumors 1–2 cm in diameter. Carcinoids also occur in the duodenum, with 31% having metastases. Duodenal tumors <1 cm rarely metastasize, whereas 33% of those >2 cm had metastases. SI NETs (carcinoids) are the most common cause (60–87%) of the carcinoid syndrome (Table 80-6). Important prognostic factors are listed in Table 80-4, and particularly important are the tumor extent, proliferative index by grading, and stage (Table 80-1). SI NETs (carcinoid) are well differentiated in 99% of cases with 61–72% being G1 and 11–37% being G2. The overall survival at 5 years is 55–75%; however, it varies markedly with disease extent, being 65–90% with localized disease, 66–72% with regional involvement, and 36–43% with distant disease.

Rectal NETs (Carcinoids) Rectal NETs (carcinoids) comprise 27% of all GI-NETs (carcinoids) and 16% of all NETs and are increasing in frequency. In Europe they comprise 5–14% of all NETs and in some Asian series (Japan, China, Korea) they comprise 60–89% of all NETs. In the U.S. SEER data, they currently have an incidence of 0.86/100,000 per year (up from 0.2/100,000 per year in 1973) and represent 1–2% of all rectal tumors. They are found in ~1 in every 1500/2500 proctoscopies/colonoscopies or 0.05–0.07% of individuals undergoing these procedures. Nearly all occur between 4 and 13 cm above the dentate line. Most are small, with 66–80% being <1 cm in diameter, and rarely metastasize (5%). Tumors between 1 and 2 cm can metastasize in 5–30%, and those >2 cm, which are uncommon, in >70%. Most invade only to the submucosa (75%), with 2.1% confined to the mucosa, 10% to the muscular layer, and 5% to adjacent structures. Histologically, most are well differentiated (98%) with 72% ENETS/WHO grade G1 and 28% grade G2 (Table 80-1). Overall survival is 88%; however, it is very much dependent of the stage, with 5-year survival of 91% for localized disease, 36–49% for regional disease, and 20–32% for distant disease. Risk factors are listed in Table 80-4 and particularly include tumor size, depth of invasion, presence of metastases, differentiation, and recent TNM classification and grade.

Bronchial NETs (Carcinoids) Bronchial NETs (carcinoids) comprise 25–33% of all well-differentiated NETs and 90% of all the poorly differentiated NETs found, likely due to a strong association with smoking. Their incidence ranges from 0.2 to 2/100,000 per year in the United States and European countries and is increasing at a rate of 6% per year. They are slightly more frequent in females and in whites compared with those of Hispanic/Asian/African descent, and are most commonly seen in the sixth decade of life, with a younger age of presentation for typical carcinoids (45 years) compared to atypical carcinoids (55 years).

A number of different classifications of bronchial GI-NETs (carcinoids) have been proposed. The principal factors used in classifying lung NETs include: morphology, presence or absence of necrosis, mitotic rate and size. In some studies, they are classified into four categories: typical carcinoid (also called bronchial carcinoid tumor, Kulchitsky cell carcinoma I [KCC-I]), atypical carcinoid (also called well-differentiated NEC [KC-II]), intermediate small-cell NEC, and small-cell neuroendocarcinoma (KC-III). Another proposed classification includes three categories of lung NETs: benign or low-grade malignant (typical carcinoid), low-grade malignant (atypical carcinoid), and high-grade malignant (poorly differentiated carcinoma of the large-cell or small-cell type). The WHO classification includes four general categories: typical carcinoid, atypical carcinoid, large-cell NEC, and small-cell carcinoma. The ratio of typical to atypical carcinoids is 8–10:1, with the typical carcinoids comprising 1–2% of lung tumors, atypical 0.1–0.2%, large-cell NETs 0.3%, and small-cell lung cancer 9.8% of all lung tumors. These different categories of lung NETs have different prognoses, varying from excellent for typical carcinoid to poor for small-cell NECs. The occurrence of large-cell and small-cell lung carcinoids, but not typical or atypical lung carcinoids, is related to tobacco use. The 5-year survival is very much influenced by the classification of the tumor, with survival of 92–100% for patients with a typical carcinoid, 61–88% with an atypical carcinoid, 13–57% with a large-cell neuroendocrine tumor, and 5% with a small-cell lung cancer. Typical/atypical lung carcinoids are generally well-differentiated with typical lung carcinoids sharing some homologies with G1 NETs, atypical

sharing some homologies with G2 NETs of the GI tract, whereas small cell and large cell lung NECs are poorly differentiated and correspond to the G3 NEC category of the GI Tract (Table 80-1).

Gastric NET (Carcinoids) Gastric NETs (carcinoids) account for 3 of every 1000 gastric neoplasms and 1.3–2% of all carcinoids, and their relative frequency has increased three- to fourfold over the last five decades (2.2% in 1950 to 9.6% in 2000–2007, SEER data). At present, it is unclear whether this increase is due to better detection with the increased use of upper GI endoscopy or to a true increase in incidence. Gastric NETs (carcinoids) are generally classified into three different categories, and this has important implications for pathogenesis, prognosis, and treatment. Each originates from gastric enterochromaffin-like (ECL) cells, one of the six types of gastric neuroendocrine cells, in the gastric mucosa. Two subtypes are associated with hypergastrinemic states, either chronic atrophic gastritis (type I) (70–80% of all gastric NETs [carcinoids]) or Zollinger-Ellison syndrome, which is almost always a part of the MEN 1 syndrome (type II) (5–6% of all cases). These tumors generally pursue a benign course, with type I uncommonly (<10%) associated with metastases, whereas type II tumors are slightly more aggressive, with 10–30% associated with metastases. Gastric carcinoids type 1 and type 2 are usually multiple, small, and infiltrate only to the submucosa. The third subtype of gastric NETs (carcinoids) (type III) (sporadic) occurs without hypergastrinemia (14–25% of all gastric carcinoids) and has an aggressive course, with 54–66% developing metastases. Sporadic carcinoids are usually single, large tumors; 50% have atypical histology, and they can be a cause of the carcinoid syndrome. Five-year survival is 99–100% in patients with type I, 60–90% in patients with type II, and 50% in patients with type III gastric NETs (carcinoids). Type 1 gastric carcinoids are usually grade G1 and well differentiated; type 2 are well-differentiated grade G1 or G2; and type 3 are characteristically NEC G3 with poor differentiation.

CLINICAL PRESENTATION OF NETs (CARCINOIDS)

GI/Lung NET (Carcinoid) Without the Carcinoid Syndrome

The age of patients at diagnosis ranges from 10 to 93 years, with a mean age of 63 years for the small intestine, 43–60 years for bronchial, and 66 years for the rectum. The presentation is diverse and is related to the site of origin and the extent of malignant spread. In the appendix, NETs (carcinoids) usually are found incidentally during surgery for suspected appendicitis. SI NETs (carcinoids) in the jejunoileum present with periodic abdominal pain (51%), intestinal obstruction with ileus/invagination (31%), an abdominal tumor (17%), or GI bleeding (11%). Because of the vagueness of the symptoms, the diagnosis usually is delayed ~2 years from onset of the symptoms, with a range up to 20 years. Duodenal, gastric, and rectal NETs (carcinoids) are most frequently found by chance at endoscopy. The most common symptoms of rectal carcinoids are melena/bleeding (39%), constipation (17%), and diarrhea (12%). Bronchial NETs (carcinoids) frequently are discovered as a lesion on a chest radiograph, and 31–43% of the patients are asymptomatic. Thymic NETs (carcinoids) present as anterior mediastinal masses, usually on chest radiograph or computed tomography (CT) scan. Ovarian and testicular NETs (carcinoids) usually present as masses discovered on physical examination or ultrasound. Metastatic NETs (carcinoids) in the liver frequently present as hepatomegaly in a patient who may have minimal symptoms and nearly normal liver function test results.

GI-NETs (CARCINOIDS) WITH SYSTEMIC SYMPTOMS DUE TO SECRETED PRODUCTS

GI/lung NETs (carcinoids) immunocytochemically can contain numerous GI peptides: gastrin, insulin, somatostatin, motilin, neurotensin, tachykinins (substance K, substance P, neuropeptide K), glucagon, gastrin-releasing peptide, vasoactive intestinal peptide (VIP), PP, ghrelin, other biologically active peptides (ACTH, calcitonin, growth hormone, GRF), prostaglandins, and bioactive amines (serotonin). These substances may or may not be released in sufficient amounts to cause symptoms. In various studies of patients with GI-NETs (carcinoids), elevated serum levels of PP were found in 43%, motilin in 14%, gastrin in 15%, and VIP in 6%. Foregut NETs (carcinoids) are more likely to produce various GI peptides than are midgut NETs (carcinoids). Ectopic ACTH production causing Cushing's syndrome is seen increasingly with foregut carcinoids (respiratory tract primarily) and, in some series, has been the most common cause of the ectopic ACTH syndrome, accounting for 64% of all cases. Acromegaly due to growth hormone–releasing factor release occurs with foregut NETs (carcinoids), as does the somatostatinoma syndrome, but rarely occurs with duodenal NETs (carcinoids). The most common systemic syndrome with GI-NETs (carcinoids) is the carcinoid syndrome, which is discussed in detail in the next section.

CARCINOID SYNDROME

Clinical Features The cardinal features from a number of series at presentation as well as during the disease course are shown in Table 80-6.

Flushing and diarrhea are the two most common symptoms, occurring in a mean of 69–70% of patients initially and in up to 78% of patients during the course of the disease. The characteristic flush is of sudden onset; it is a deep red or violaceous erythema of the upper body, especially the neck and face, often associated with a feeling of warmth and occasionally associated with pruritus, lacrimation, diarrhea, or facial edema. Flushes may be precipitated by stress; alcohol; exercise; certain foods, such as cheese; or certain agents, such as catecholamines, pentagastrin; and serotonin reuptake inhibitors. Flushing episodes may be brief, lasting 2–5 min, especially initially, or may last hours, especially later in the disease course. Flushing usually is associated with metastatic midgut NETs (carcinoids) but can also occur with foregut NETs (carcinoids). With bronchial NETs (carcinoids), the flushes frequently are prolonged for hours to days, reddish in color, and associated with salivation, lacrimation, diaphoresis, diarrhea, and hypotension. The flush associated with gastric NETs (carcinoids) can also be reddish in color, but with a patchy distribution over the face and neck, although the classic flush seen with midgut NETs (carcinoids) can also be seen with gastric NETs (carcinoids). It may be provoked by food and have accompanying pruritus.

Diarrhea usually occurs with flushing (85% of cases). The diarrhea usually is described as watery, with 60% of patients having <1 L/d of diarrhea. Steatorrhea is present in 67%, and in 46%, it is >15 g/d (normal <7 g). Abdominal pain may be present with the diarrhea or independently in 10–34% of cases.

Cardiac manifestations occur initially in 11–40% (mean 26%) of patients with carcinoid syndrome and in 14–41% (mean 30%) at some time in the disease course. The cardiac disease is due to the formation of fibrotic plaques (composed of smooth-muscle cells, myofibroblasts, and elastic tissue) involving the endocardium, primarily on the right side, although lesions on the left side also occur occasionally (mean 11%, range 0–25), especially if a patent foramen ovale exists. The dense fibrous deposits are most commonly on the ventricular aspect of the tricuspid valve and less commonly on the pulmonary valve cusps. They can result in constriction of the valves, and pulmonic stenosis is usually predominant, whereas the tricuspid valve is often fixed open, resulting in regurgitation predominating. Overall, in patients with carcinoid heart disease, 90–100% have tricuspid insufficiency, 43–59% have tricuspid stenosis, 50–81% have pulmonary insufficiency, 25–59% have pulmonary stenosis, and 11% (0–25%) left-side lesions. Up to 80% of patients with cardiac lesions develop heart failure. Lesions on the left side are much less extensive, occur in 30% at autopsy, and most frequently affect the mitral valve. Up to 80% of patients with cardiac lesions have evidence of heart failure. At diagnosis in various series, 27–43% of patients are in New York Heart Association class I, 30–40% are in class II, 13–31% are in class III, and 3–12% are in class IV. At present, carcinoid heart disease is reported to be decreasing in frequency and severity, with mean occurrence in 20% of patients and occurrence in as few as 3–4% in some reports. Whether this decrease is due to the widespread use of somatostatin analogues, which control the release of bioactive agents thought involved in mediating the heart disease, is unclear.

Other clinical manifestations include wheezing or asthma-like symptoms (8–18%), pellagra-like skin lesions (2–25%), and impaired

cognitive function. A variety of noncardiac problems due to increased fibrous tissue have been reported, including retroperitoneal fibrosis causing urethral obstruction, Peyronie's disease of the penis, intraabdominal fibrosis, and occlusion of the mesenteric arteries or veins.

Pathobiology Carcinoid syndrome occurred in 8% of 8876 patients with GI-NETs (carcinoids), with a rate of 1.7–18.4% in different studies. It occurs only when sufficient concentrations of products secreted by the tumor reach the systemic circulation. In 91–100% of cases, this occurs after distant metastases to the liver. Rarely, primary GI-NETs (carcinoids) with nodal metastases with extensive retroperitoneal invasion, pNETs (carcinoids) with retroperitoneal lymph nodes, or NETs (carcinoids) of the lung, testis or ovary with direct access to the systemic circulation can cause the carcinoid syndrome without hepatic metastases. All GI-NETs (carcinoids) do not have the same propensity to metastasize and cause the carcinoid syndrome (Table 80-3). Midgut NETs (carcinoids) account for 57–67% of cases of carcinoid syndrome, foregut NETs (carcinoids) for 0–33%, hindgut for 0–8%, and an unknown primary location for 2–26% (Tables 80-3 and 80-6).

One of the main secretory products of GI-NETs (carcinoids) involved in the carcinoid syndrome is serotonin (5-HT) (Fig. 80-1), which is synthesized from tryptophan. Up to 50% of dietary tryptophan can be used in this synthetic pathway by tumor cells, and this can result in inadequate supplies for conversion to niacin; hence, some patients (2.5%) develop pellagra-like lesions. Serotonin has numerous biologic effects, including stimulating intestinal secretion with inhibition of absorption, stimulating increases in intestinal motility, and stimulating fibrogenesis. In various studies, 56–88% of all GI-NETs (carcinoids) were associated with serotonin overproduction; however, 12–26% of the patients did not have the carcinoid syndrome. In one study, platelet serotonin was elevated in 96% of patients with midgut NETs (carcinoids), 43% with foregut tumors, and 0% with hindgut tumors. In 90–100% of patients with the carcinoid syndrome, there is evidence of serotonin overproduction. Serotonin is thought to be predominantly responsible for the diarrhea. Patients with the carcinoid syndrome have increased colonic motility with a shortened transit time and possibly a secretory/absorptive alteration that is compatible with the known actions of serotonin in the gut mediated primarily through 5-HT_3 and, to a lesser degree, 5-HT_4 receptors. Serotonin receptor antagonists (especially 5-HT_3 antagonists) relieve the diarrhea in many, but not all, patients. A tryptophan 5-hydroxylase inhibitor, telotristat (LX-10310), which inhibits serotonin synthesis in peripheral tissues, caused a decrease in bowel movement frequency in 40–50% of patients with the carcinoid syndrome. Additional studies suggest that tachykinins may be important mediators of diarrhea in some patients. In one study, plasma tachykinin levels correlated with symptoms of diarrhea. Serotonin does not appear to be involved in the flushing in most patients because serotonin receptor antagonists do not relieve flushing. In patients with gastric carcinoids, the characteristic red, patchy pruritic flush is thought due to histamine release because H_1 and H_2 receptor antagonists can prevent it. Numerous studies have shown that tachykinins (substance P, neuropeptide K) are stored in GI-NETs (carcinoids) and released during flushing. However, some studies have demonstrated that octreotide can relieve the flushing induced by pentagastrin in these patients without altering the stimulated increase in plasma substance P, suggesting that other mediators must be involved in the flushing. A correlation between plasma tachykinin levels (but not substance P levels) and flushing has been reported. Prostaglandin release could be involved in mediating either the diarrhea or flush, but conflicting data exist. Both histamine and serotonin may be responsible for the wheezing as well as the fibrotic reactions involving the heart, causing Peyronie's disease and intraabdominal fibrosis.

The exact mechanism of the heart disease remains unclear, although increasing evidence supports a central role for serotonin. Patients with heart disease have higher plasma levels of neurokinin A, substance P, plasma atrial natriuretic peptide (ANP), pro-brain natriuretic peptide, chromogranin A, and activin A as well as higher urinary 5-HIAA excretion.

The valvular heart disease caused by the appetite-suppressant drugs dexfenfluramine and benfluorex is histologically indistinguishable from that observed in carcinoid disease. Furthermore, ergot-containing dopamine receptor agonists used for Parkinson's disease (pergolide, cabergoline) cause valvular heart disease that closely resembles that seen in the carcinoid syndrome. Furthermore, in animal studies, the formation of valvular plaques/fibrosis occurs after prolonged treatment with serotonin as well as in animals with a deficiency of the 5-HIAA transporter gene, which results in an inability to inactivate serotonin. Metabolites of fenfluramine, as well as the dopamine receptor agonists, have high affinity for serotonin receptor subtype 5-HT_{2B} receptors, whose activation is known to cause fibroblast mitogenesis. Serotonin receptor subtypes 5-$HT_{1B,1D,2A,2B}$ normally are expressed in human heart valve interstitial cells. High levels of 5-HT_{2B} receptors are known to occur in heart valves and occur in cardiac fibroblasts and cardiomyocytes. Studies of cultured interstitial cells from human cardiac valves have demonstrated that these valvulopathic drugs induce mitogenesis by activating 5-HT_{2B} receptors and stimulating upregulation of transforming growth factor β and collagen biosynthesis. These observations support the conclusion that serotonin overproduction by GI-NETs (carcinoids) is important in mediating the valvular changes, possibly by activating 5-HT_{2B} receptors in the endocardium. Both the magnitude of serotonin overproduction and prior chemotherapy are important predictors of progression of the heart disease, whereas patients with high plasma levels of ANP have a worse prognosis. Plasma connective tissue growth factor levels are elevated in many fibrotic conditions; elevated levels occur in patients with carcinoid heart disease and correlate with the presence of right ventricular dysfunction and the extent of valvular regurgitation in patients with GI-NETs (carcinoids).

Patients may develop either a typical or, rarely, an atypical carcinoid syndrome (Fig. 80-1). In patients with the typical form, which characteristically is caused by midgut NETs (carcinoids), the conversion of tryptophan to 5-HTP by tryptophan hydroxylase is the rate-limiting step (Fig. 80-1). Once 5-HTP is formed, it is rapidly converted to 5-HT and stored in secretory granules of the tumor or in platelets. A small amount remains in plasma and is converted to 5-HIAA, which appears in large amounts in the urine. These patients have an expanded serotonin pool size, increased blood and platelet serotonin, and increased urinary 5-HIAA. Some GI-NETs (carcinoids) cause an atypical carcinoid syndrome that is thought to be due to a deficiency in the enzyme dopa decarboxylase; thus, 5-HTP cannot be converted to 5-HT (serotonin), and 5-HTP is secreted into the bloodstream (Fig. 80-1). In these patients, plasma serotonin levels are normal but urinary levels may be increased because some 5-HTP is converted to 5-HT in the kidney. Characteristically, urinary 5-HTP and 5-HT are increased, but urinary 5-HIAA levels are only slightly elevated. Foregut carcinoids are the most likely to cause an atypical carcinoid syndrome; however, they also can cause a typical carcinoid syndrome.

One of the most immediate life-threatening complications of the carcinoid syndrome is the development of a carcinoid crisis. This is more common in patients who have intense symptoms or have greatly increased urinary 5-HIAA levels (i.e., >200 mg/d). The crisis may occur spontaneously; however, it is usually provoked by procedures such as anesthesia, chemotherapy, surgery, biopsy, endoscopy, or radiologic examinations such as during biopsies, hepatic artery embolization, and vessel catheterization. It can be provoked by stress or procedures as mild as repeated palpation of the tumor during physical examination. Patients develop intense flushing, diarrhea, abdominal pain, cardiac abnormalities including tachycardia, hypertension, or hypotension, and confusion or stupor. If not adequately treated, this can be a terminal event.

DIAGNOSIS OF THE CARCINOID SYNDROME AND GI-NETs (CARCINOIDS)

The diagnosis of carcinoid syndrome relies on measurement of urinary or plasma serotonin or its metabolites in the plasma or urine. The measurement of urinary 5-HIAA is used most frequently. False-positive elevations may occur if the patient is eating serotonin-rich foods such as bananas, pineapples, walnuts, pecans, avocados, or hickory nuts or is taking certain medications (cough syrup containing guaifenesin, acetaminophen, salicylates, serotonin reuptake inhibitors, or L-dopa).

The normal range for daily urinary 5-HIAA excretion is 2–8 mg/d. Serotonin overproduction was noted in 92% of patients with carcinoid syndrome in one study, and in another study, 5-HIAA had 73% sensitivity and 100% specificity for carcinoid syndrome. Serotonin overproduction is *not* synonymous with the presence of clinical carcinoid syndrome because 12–26% of patients with serotonin overproduction do not have clinical evidence of the carcinoid syndrome.

Most physicians use only the urinary 24-h 5-HIAA excretion rate; even though a recent study shows an overnight urinary collection is just as accurate. Assessment of plasma and platelet serotonin levels and plasma 5-HIAA, if available, may provide additional information and/or substitute for the 24 h urinary 5-HIAA study. Platelet serotonin levels are more sensitive than urinary 5-HIAA but are not generally available. A single plasma 5-HIAA determination was found to have similar sensitivity/specificity to that with the 24-h urinary 5-HIAA assessment, suggesting this could replace the standard urinary collection because of its greater convenience and avoidance of incomplete or improper collections. It, however, could be affected by renal disease. Because patients with foregut NETs (carcinoids) may produce an atypical carcinoid syndrome, if this syndrome is suspected and the urinary 5-HIAA is minimally elevated or normal, other urinary metabolites of tryptophan, such as 5-HTP and 5-HT, should be measured (Fig. 80-1).

Flushing occurs in a number of other diseases, including systemic mastocytosis, chronic myeloid leukemia with increased histamine release, menopause, reactions to alcohol or glutamate, and side effects of chlorpropamide, calcium channel blockers, and nicotinic acid. None of these conditions causes increased urinary 5-HIAA.

The diagnosis of carcinoid tumor can be suggested by the carcinoid syndrome, recurrent abdominal symptoms in a healthy-appearing individual, or the discovery of hepatomegaly or hepatic metastases associated with minimal symptoms. Ileal NETs (carcinoids), which make up 25% of all clinically detected carcinoids, should be suspected in patients with bowel obstruction, abdominal pain, flushing, or diarrhea.

Serum chromogranin A levels are elevated in 56–100% of patients with GI-NETs (carcinoids), and the level correlates with tumor bulk. Serum chromogranin A levels are not specific for GI-NETs (carcinoids) because they are also elevated in patients with pNETs and other NETs. Furthermore, a major problem is caused by potent acid antisecretory drugs such as proton pump inhibitors (omeprazole and related drugs) because they almost invariably cause elevation of plasma chromogranin A levels; the elevation occurs rapidly (3–5 days) with continued use, and the elevated levels overlap with the levels seen in many patients with NETs. Plasma neuron-specific enolase levels are also used as a marker of GI-NETs (carcinoids) but are less sensitive than chromogranin A, being increased in only 17–47% of patients. Newer markers have been proposed including pancreastatin (a chromogranin A breakdown product), and activin A. The former is not affected by proton pump inhibitors; however, its sensitivity and specificity are not established. Plasma activin elevations are reported to correlate with the presence of cardiac disease with a sensitivity of 87% and specificity of 57%. Plasma levels of N-terminal pro brain natriuretic peptide moderately correlate with carcinoid heart disease severity.

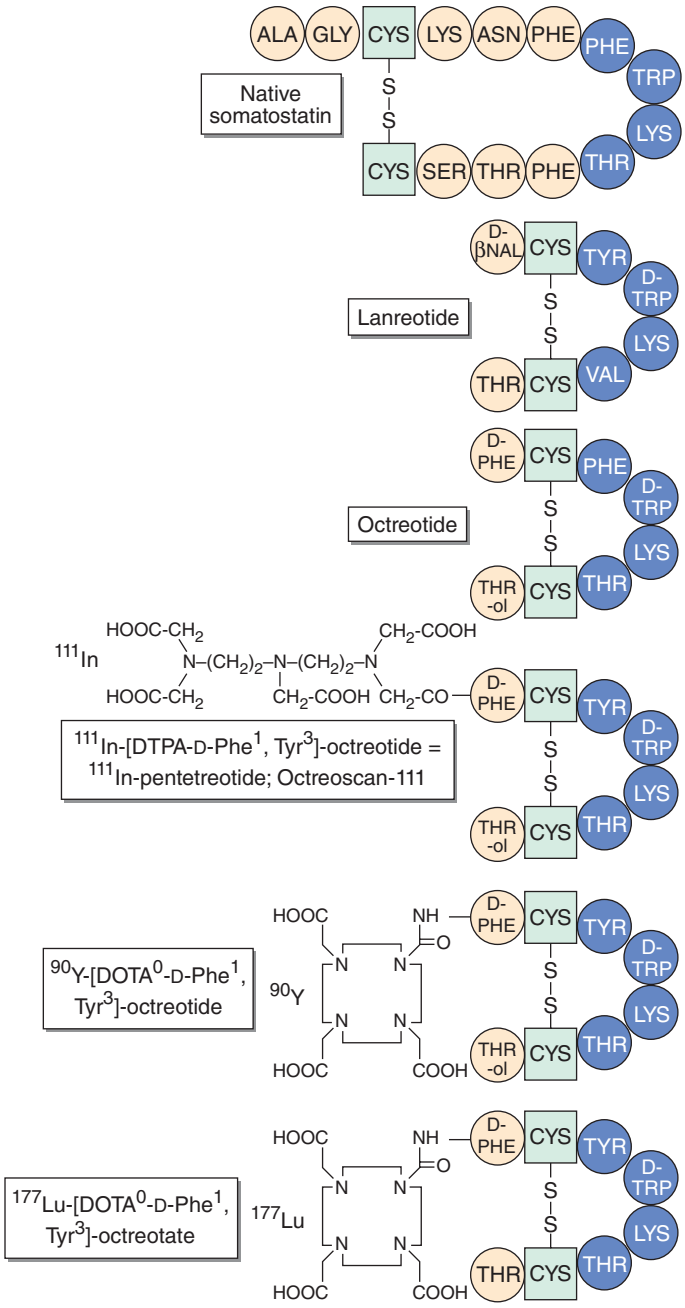

FIGURE 80-2 Structure of somatostatin and synthetic analogues used for diagnostic or therapeutic indications.

TREATMENT

Carcinoid Syndrome and Nonmetastatic Gastrointestinal Neuroendocrine Tumors (Carcinoids)

CARCINOID SYNDROME

Treatment includes avoiding conditions that precipitate flushing, dietary supplementation with nicotinamide, treatment of heart failure with diuretics, treatment of wheezing with oral bronchodilators, and control of the diarrhea with antidiarrheal agents such as loperamide and diphenoxylate. If patients still have symptoms, somatostatin analogues or less frequently, serotonin receptor antagonists, are the drugs of choice **(Fig. 80-2)**. An additional point dealt with in later sections, is the fact that most patients who develop the carcinoid syndrome have metastatic disease to the liver. Numerous antitumor therapies (liver-directed therapies, PRRT, surgery, chemotherapy/targeted drug therapies) also can ameliorate the severity of the carcinoid syndrome.

There are 14 subclasses of serotonin receptors, and antagonists for many are not available. The 5-HT$_1$ and 5-HT$_2$ receptor antagonists methysergide, cyproheptadine, and ketanserin have all been used to control the diarrhea but usually do not decrease flushing. The use of methysergide is limited because it can cause or enhance retroperitoneal fibrosis. Ketanserin diminishes diarrhea in 30–100% of patients. 5-HT$_3$ receptor antagonists (ondansetron, tropisetron, alosetron) can control diarrhea and nausea in up to 100% of patients and occasionally ameliorate the flushing. A combination of histamine H$_1$ and H$_2$ receptor antagonists (i.e., diphenhydramine and cimetidine or ranitidine) may control flushing in patients with foregut carcinoids. A phase 3 prospective, double-blind study provides evidence the peripheral tryptophan hydroxylase inhibitor, telotristat, will be useful to control the diarrhea in many of these patients.

Synthetic analogues of somatostatin (octreotide, lanreotide) are now the most widely used agents to control the symptoms of patients with

carcinoid syndrome (Figs. 80-1 and 80-2). These drugs are effective at relieving symptoms and decreasing urinary 5-HIAA levels in patients with this syndrome. Octreotide-LAR (10–30 mg i.m., monthly) and lanreotide-SR/autogel (Somatuline) (60–120 mg sc-deep, monthly) (sustained-release formulations allowing monthly injections) (Fig. 80-2), control symptoms in 74 and 68% of patients, respectively, with carcinoid syndrome and show a biochemical response in 51 and 64%, respectively. Patients with mild to moderate symptoms usually are treated initially with octreotide 50–100 μg SC every 8 h or lower doses or low doses of the long-acting formulations, and then receive higher doses as needed of the long-acting monthly depot forms (octreotide-LAR or lanreotide-autogel). Forty percent of patients escape control after a median time of 4 months, and the depot dosage may have to be increased as well as supplemented with the shorter-acting formulation, SC octreotide. Pasireotide (SOM230) is a somatostatin analogue with broader selectivity (high-affinity somatostatin receptors [sst_1, sst_2, sst_3, sst_5]) than octreotide/lanreotide (sst_2, sst_5). In a phase II study of patients with refractory carcinoid syndrome, pasireotide controlled symptoms in 27%.

Carcinoid heart disease is associated with a decreased mean survival (3.8 years), and therefore, it should be sought for and carefully assessed in all patients with carcinoid syndrome. Transthoracic echocardiography remains a key element in establishing the diagnosis of carcinoid heart disease and determining the extent and type of cardiac abnormalities. Treatment with diuretics and somatostatin analogues can reduce the negative hemodynamic effects and secondary heart failure. It remains unclear whether long-term treatment with these drugs or with the tryptophan hydroxylase inhibitor, telotristat, when it becomes available, will decrease the progression of carcinoid heart disease. Balloon valvuloplasty for stenotic valves or cardiac valve surgery may be required.

To prevent as well as treat patients with carcinoid crises, somatostatin analogues are recommended, although there is controversy of how effective they are and what dosage should be use. To prevent carcinoid crises development, treatment with somatostatin analogues is recommended prior to the possible precipitating event such as surgery, anesthesia, chemotherapy, and stress. It is generally recommended that octreotide 150–250 μg SC every 6–8 h be used 24–48 h before anesthesia and then continued throughout the procedure. Another commonly used protocol is to use 100 μg/h by continuous infusion with or without a preoperative bolus.

Currently, sustained-release preparations of both octreotide (octreotide-LAR [long-acting release], 10, 20, 30 mg) and lanreotide (lanreotide-PR [prolonged release, lanreotide-autogel], 60, 90, 120 mg) are available and widely used because their use greatly facilitates long-term treatment. Octreotide-LAR (30 mg/month) gives a plasma level ≥1 ng/mL for 25 days, whereas this requires 3–6 injections a day of the non-sustained-release form. Lanreotide-autogel (Somatuline) is given every 4–6 weeks.

Short-term side effects occur in up to one-half of patients. Pain at the injection site and side effects related to the GI tract (59% discomfort, 15% nausea, diarrhea) are the most common. They are usually short-lived and do not interrupt treatment. Important long-term side effects include gallstone formation, steatorrhea, and deterioration in glucose tolerance. The overall incidence of gallstones/biliary sludge varies from 5 to 66%, with 7% having symptomatic disease that required surgical treatment in one study.

Interferon α is reported to be effective in controlling symptoms of the carcinoid syndrome either alone or combined with hepatic artery embolization. With interferon α alone, the clinical response rate is 30–70%, and with interferon α with hepatic artery embolization, diarrhea was controlled for 1 year in 43% and flushing was controlled in 86%. Side effects develop in almost all patients, with the most frequent being a flu-like syndrome (80–100%), followed by anorexia and fatigue, even though these frequently improve with continued treatment. Other more severe side effects include bone marrow toxicity, hepatotoxicity, autoimmune disorders, and rarely CNS side effects (depression, mental disorders, visual problems).

Hepatic artery embolization alone or with chemotherapy (chemoembolization) has been used to control the symptoms of carcinoid syndrome. Embolization alone is reported to control symptoms in up to 76% of patients, and chemoembolization (5-fluorouracil, doxorubicin, cisplatin, mitomycin) controls symptoms in 60–75% of patients. Hepatic artery embolization can have major side effects, including nausea, vomiting, pain, and fever. In two studies, 5–7% of patients died from complications of hepatic artery occlusion.

Other drugs have been used successfully in small numbers of patients to control the symptoms of carcinoid syndrome. Parachlorophenylanine can inhibit tryptophan hydroxylase and therefore the conversion of tryptophan to 5-HTP. However, its severe side effects, including psychiatric disturbances, make it intolerable for long-term use. α-Methyldopa inhibits the conversion of 5-HTP to 5-HT, but its effects are only partial.

Peptide radioreceptor therapy (PRRT; using radiotherapy with radiolabeled somatostatin analogues), cytoreductive surgery, the use of radiolabeled microspheres, and other methods for treatment of advanced metastatic disease can facilitate control of the carcinoid syndrome (see below).

GI-NETS (CARCINOIDS) (NONMETASTATIC)

Surgery is the only potentially curative therapy. Because with most GI-NETs (carcinoids), the probability of metastatic disease increases with increasing size, in most guidelines, the therapeutic approach is determined accordingly. Furthermore, the grade of the tumor is having an increasingly important role in determining the therapeutic approach. With well-differentiated (G1/G2) GI-NETs the size of the primary NET plays an important role. With appendiceal NETs (carcinoids) <1 cm, simple appendectomy was curative in 103 patients followed for up to 35 years. With rectal NETs (carcinoids) <1 cm, local resection is curative. With SI NETs (carcinoids) <1 cm, there is not complete agreement. Because 15–69% of SI NETs (carcinoids) this size have metastases in different studies, most recommend a wide resection with en bloc resection of the adjacent lymph-bearing mesentery. If the tumor is >2 cm for rectal, appendiceal, or SI NETs (carcinoids), a full cancer operation should be done. This includes a right hemicolectomy for appendiceal NETs (carcinoids), an abdominoperineal resection or low anterior resection for rectal NETs (carcinoids), and an en bloc resection of adjacent lymph nodes for SI NETs (carcinoids). For appendiceal NETs (carcinoids) 1–2 cm in diameter, a simple appendectomy is proposed by some, whereas others favor a formal right hemicolectomy. For 1–2 cm rectal NETs (carcinoids), it is recommended that a wide, local, full-thickness excision be performed.

With well-differentiated (G1/G2) type I or II gastric NETs (carcinoids), which are usually <1 cm, endoscopic removal is recommended. In type I or II gastric carcinoids, if the tumor is >2 cm or if there is local invasion, some recommend total gastrectomy, whereas others recommend antrectomy in type I to reduce the hypergastrinemia, which has led to regression of the carcinoids in a number of studies. For types I and II gastric NETs (carcinoids) of 1–2 cm, there is no agreement, with some recommending endoscopic treatment followed by chronic somatostatin treatment and careful follow-up and others recommending surgical treatment. With type III gastric NETs (carcinoids) >2 cm, excision and regional lymph node clearance are recommended. Most tumors <1 cm are treated endoscopically. Type 1 and 2 gastric carcinoids tend to recur after endoscopic treatments so patients need to continue to be followed. Treatment of type 1 or 2 gastric carcinoids using a CCK_B (gastrin) receptor antagonist, netazepide (not yet FDA approved) decreased the size and number of gastric carcinoids. However, netazepide needed to be continued or they would return. Poorly differentiated G3 carcinoids of the GI tract are treated like G3 tumors in other locations, which involve primarily chemotherapy and will discussed in a later section on treatment of advanced/aggressive disease.

Resection of isolated or limited hepatic metastases may be beneficial and will be discussed in a later section on treatment of advanced disease.

PANCREATIC NEUROENDOCRINE TUMORS (pNETs)

Functional pNETs (F-pNETs) usually present clinically with symptoms due to the hormone-excess state (Table 80-2). Only late in the course of the disease does the tumor per se cause prominent symptoms such as abdominal pain. In contrast, all the symptoms due to nonfunctional pNETs (NF-pNET) are due to the tumor per se. The overall result of this is that some F-pNETs may present with severe symptoms with a small or undetectable primary tumor, whereas NF-pNETs usually present late in the disease course with large tumors, which are frequently metastatic. The mean delay between onset of continuous symptoms and diagnosis of a F-pNET syndrome is 4–7 years. Therefore, the diagnoses frequently are missed for extended periods.

TREATMENT

Pancreatic Neuroendocrine Tumor (General Points)

Treatment of pNETs requires two different strategies. First, treatment must be directed at the hormone-excess state such as the gastric acid hypersecretion in gastrinomas or the hypoglycemia in insulinomas. Ectopic hormone secretion usually causes the presenting symptoms and can cause life-threatening complications. Second, with all the tumors except insulinomas, >50% are malignant (Table 80-2); therefore, treatment must also be directed against the tumor per se. Because in many patients these tumors are not surgically curable due to the presence of advanced disease at diagnosis, surgical resection for cure, which addresses both treatment aspects, is often not possible.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

A gastrinoma is an NET that secretes gastrin; the resultant hypergastrinemia causes gastric acid hypersecretion (Zollinger-Ellison syndrome [ZES]). The chronic hypergastrinemia results in marked gastric acid hypersecretion and growth of the gastric mucosa with increased numbers of parietal cells and proliferation of gastric ECL cells. The gastric acid hypersecretion characteristically causes peptic ulcer disease (PUD), often refractory and severe, as well as diarrhea. The most common presenting symptoms are abdominal pain (70–100%), diarrhea (37–73%), gastroesophageal reflux disease (GERD) (30–35%), and 10–20% of patients have diarrhea only. Although peptic ulcers may occur in unusual locations, most patients have a typical duodenal ulcer. Important observations that should suggest this diagnosis include PUD with diarrhea; PUD in an unusual location or with multiple ulcers; PUD refractory to treatment or persistent; PUD associated with prominent gastric folds; PUD associated with findings suggestive of MEN 1 (endocrinopathy, family history of ulcer or endocrinopathy, nephrolithiases); and PUD without *Helicobacter pylori* present. *H. pylori* is present in >90% of idiopathic peptic ulcers but is present in <50% of patients with gastrinomas. Chronic unexplained diarrhea also should suggest ZES.

Approximately 20–25% of patients with ZES have MEN 1 (MEN1/ZES), and in most cases, hyperparathyroidism is present before the ZES develops. In older studies it was generally reported that almost all MEN/ZES presented with the hyperparathyroidism, but in a number of recent series up to one-third of these patients present with the ZES, and while the hyperparathyroidism is present it may be mild and difficult to diagnose without appropriate testing. These patients are treated differently from those without MEN 1 (sporadic ZES); therefore, MEN 1 should be sought in all patients with ZES by family history and by measuring plasma ionized calcium and prolactin levels and plasma hormone levels (parathormone, growth hormone).

Most gastrinomas (50–90%) in sporadic ZES are present in the duodenum, followed by the pancreas (10–40%) and other intraabdominal sites (mesentery, lymph nodes, biliary tract, liver, stomach, ovary). Rarely, the tumor may involve extraabdominal sites (heart, lung cancer). In MEN 1/ZES the gastrinomas are also usually in the duodenum (80–100%), followed by the pancreas (0–20%), and are almost always multiple. About 60–90% of gastrinomas are malignant (Table 80-2) with metastatic spread to lymph nodes and liver. Distant metastases to bone occur in 12–30% of patients with liver metastases.

Diagnosis The diagnosis of ZES requires the demonstration of inappropriate fasting hypergastrinemia, usually by demonstrating hypergastrinemia occurring with an increased basal gastric acid output (BAO) (hyperchlorhydria). More than 98% of patients with ZES have fasting hypergastrinemia, although in 40–60% the level may be elevated less than tenfold. Therefore, when the diagnosis is suspected, a fasting gastrin is usually the initial test performed. It is important to remember that potent gastric acid suppressant drugs such as proton pump inhibitors (PPIs) (omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) can suppress acid secretion sufficiently to cause hypergastrinemia; because of their prolonged duration of action, these drugs have to be tapered or frequently discontinued for a week before the gastrin determination. Withdrawal of PPIs should be performed carefully because PUD complications can rapidly develop in some patients and is best done in consultation with GI units with experience in this area. The widespread use of PPIs can confound the diagnosis of ZES. First, by raising a false-positive diagnosis by causing hypergastrinemia in a patient being treated with idiopathic PUD (without ZES). Second, by leading to a false-negative diagnosis because at routine doses used to treat patients with idiopathic PUD, PPIs control symptoms in most ZES patients and thus mask the diagnosis. If ZES is suspected and the gastrin level is elevated, it is important to show that it is increased when gastric pH is ≤2.0 because physiologically hypergastrinemia secondary to achlorhydria (atrophic gastritis, pernicious anemia) is one of the most common causes of hypergastrinemia. Nearly all ZES patients have a fasting pH ≤2 when off antisecretory drugs. If the fasting gastrin is >1000 pg/mL (increased tenfold) and the pH is ≤2.0, which occurs in 40–60% of patients with ZES, the diagnosis of ZES is established after the possibility of retained antrum syndrome has been ruled out by history. In patients with hypergastrinemia with fasting gastrins <1000 pg/mL (<tenfold increased) and gastric pH ≤2.0, other conditions, such as *H. pylori* infections, antral G-cell hyperplasia/hyperfunction, gastric outlet obstruction, and, rarely, renal failure, can masquerade as ZES. To establish the diagnosis in this group, a determination of BAO and a secretin provocative test should be done. In patients with ZES without previous gastric acid–reducing surgery, the BAO is usually (>90%) elevated (i.e., >15 mEq/h). The secretin provocative test is usually positive, with the criterion of a >120-pg/mL increase over the basal level having the highest sensitivity (94%) and specificity (100%). Unfortunately the diagnosis of ZES is becoming increasing more difficult. This is due not only to the widespread use of PPIs (leading to false-positive results as well as masking ZES presentation), but also recent studies demonstrate than many of the commercial gastrin kits that are used by most laboratories to measure fasting serum gastrin levels are not reliable. In one study, 7 of the 12 tested commercial gastrin kits inaccurately assessed the true serum concentration of gastrin primarily because the antibodies used had inappropriate specificity for the different circulating forms of gastrin and were not adequately validated. Both underestimation and overestimation of fasting serum gastrin levels occurred using these commercial kits. To circumvent this problem, it is either necessary to use one of the five reliable kits identified or, alternatively, to refer the patient to a center with expertise in making the diagnosis in your area, or if this is not possible, to contact such a center and use the gastrin assay they recommend. An accurate gastrin assay is essential for accurate measurement of fasting serum gastrin level as well as for assessing gastrin levels during the secretin provocative test, and thus, the diagnosis of ZES cannot reliably be made without one.

TREATMENT

Zollinger-Ellison Syndrome

Gastric acid hypersecretion in patients with ZES can be controlled in almost every case by oral gastric antisecretory drugs. Because of their long duration of action and potency, which allows dosing once or twice a day, the PPIs (H^+, K^+-ATPase inhibitors) are the drugs of

choice. Histamine H_2-receptor antagonists are also effective, although more frequent dosing (q 4–8 h) and high doses are required. In patients with MEN1/ZES with hyperparathyroidism, correction of the hyperparathyroidism increases the sensitivity to gastric antisecretory drugs and decreases the basal acid output. Long-term treatment with PPIs (>15 years) has proved to be safe and effective, without development of tachyphylaxis. Although patients with ZES, especially those with MEN 1/ZES, more frequently develop gastric NETs (carcinoids), no data suggest that the long-term use of PPIs increases this risk in these patients. With long-term PPI use in ZES patients, vitamin B_{12} deficiency can develop; thus, vitamin B_{12} levels should be assessed during follow-up. Long-term PPI use may be associated with a number of side-effects including; an increased incidence of bone fractures; *Clostridium difficile* infections; dementia; hypomagnesemia; renal disease; and numerous drug interactions; however, at present, there is no report these are increased in ZES patients.

With the increased ability to control acid hypersecretion, >50% of patients who are not cured (>60% of patients) will die from tumor-related causes. At presentation, careful imaging studies are essential to localize the extent of the tumor to determine the appropriate treatment. A third of patients present with hepatic metastases, and in <15% of those patients, the disease is limited, so that surgical resection may be possible. Surgical short-term cure is possible in 60% of all patients without MEN 1/ZES or liver metastases (40% of all patients) and in 30% of patients long term. In patients with MEN 1/ZES, long-term surgical cure is rare without aggressive resection (i.e., Whipple resections), because the tumors are small, multiple, and frequently with lymph node metastases. At present the role of routine surgery for removal of the gastrinoma in MEN1/ZES patients is controversial for the above reason, with most guidelines recommending attempted gastrinoma resection only in MEN1/ZES patients with pNETs ≥1.5–2 cm in diameter. Surgical studies demonstrate that successful resection of the gastrinoma not only decreases the chances of developing liver metastases but also increases the disease-related survival rate. Therefore, all patients with gastrinomas without MEN 1/ZES or a medical condition that limits life expectancy should undergo surgery by a surgeon experienced in the treatment of these disorders.

INSULINOMAS

An insulinoma is an NET of the pancreas that is thought to be derived from beta cells that ectopically secrete insulin, which results in hypoglycemia. The average age of occurrence is 40–50 years old. The most common clinical symptoms are due to the effect of the hypoglycemia on the CNS (neuroglycemic symptoms) and include confusion, headache, disorientation, visual difficulties, irrational behavior, and even coma. Also, most patients have symptoms due to excess catecholamine release secondary to the hypoglycemia, including sweating, tremor, and palpitations. Characteristically, these attacks are associated with fasting.

Insulinomas are generally small (>90% are <2 cm) and usually not multiple (90%); only 5–15% are malignant, and they almost invariably occur only in the pancreas, distributed equally in the pancreatic head, body, and tail. They are associated with the MEN1 syndrome in 4%.

Insulinomas should be suspected in all patients with hypoglycemia, especially when there is a history suggesting that attacks are provoked by fasting, or with a family history of MEN 1. Insulin is synthesized as proinsulin, which consists of a 21-amino-acid α chain and a 30-amino-acid β chain connected by a 33-amino-acid connecting peptide (C peptide). In insulinomas, in addition to elevated plasma insulin levels, elevated plasma proinsulin levels are found, and C-peptide levels are elevated.

Diagnosis The diagnosis of insulinoma requires the demonstration of an elevated plasma insulin level at the time of hypoglycemia. A number of other conditions may cause fasting hypoglycemia, such as the inadvertent or surreptitious use of insulin or oral hypoglycemic agents, severe liver disease, alcoholism, poor nutrition, and other extrapancreatic tumors. Furthermore, postprandial hypoglycemia can be caused by a number of conditions that confuse the diagnosis of insulinoma. Particularly important here is the increased occurrence of hypoglycemia after gastric bypass surgery for obesity, which is now widely performed. A new entity, insulinomatosis, was described that can cause hypoglycemia and mimic insulinomas. It occurs in 10% of patients with persistent hyperinsulinemic hypoglycemia and is characterized by the occurrence of multiple macro-/microadenomas expressing insulin, and it is not clear how to distinguish this entity from insulinoma preoperatively. The most reliable test to diagnose insulinoma is a fast up to 72 h with serum glucose, C-peptide, proinsulin, and insulin measurements every 4–8 h. If at any point the patient becomes symptomatic or glucose levels are persistently <2.2 mmol/L (40 mg/dL), the test should be terminated, and repeat samples for the above studies should be obtained before glucose is given. Some 70–80% of patients will develop hypoglycemia during the first 24 h, and 98% by 48 h. In nonobese normal subjects, serum insulin levels should decrease to <43 pmol/L (<6 μU/mL) when blood glucose decreases to <2.2 mmol/L (<40 mg/dL) and the ratio of insulin to glucose is <0.3 (in mg/dL). In addition to having an insulin level >6 μU/mL when blood glucose is <40 mg/dL, some investigators also require an elevated C-peptide and serum proinsulin level, an insulin/glucose ratio >0.3, and a decreased plasma β-hydroxybutyrate level for the diagnosis of insulinomas. A commonly used set of criteria to make the diagnosis include: low blood glucose levels (≤2.2 mmol/L (≤40 mg/dL); concomitant insulin levels ≥6 U/L (≥ 36 pmol/L; ≥3 U/L by ICMA); C-peptide levels ≥200 pmol/L; proinsulin levels ≥5 pmol/L; β-hydroxybutyrate levels ≤2.7 mmol/L; and absence of sulfonylurea (metabolites) in the plasma and/or urine.

Surreptitious use of insulin or hypoglycemic agents may be difficult to distinguish from insulinomas. The combination of proinsulin levels (normal in exogenous insulin/hypoglycemic agent users), C-peptide levels (low in exogenous insulin users), antibodies to insulin (positive in exogenous insulin users), and measurement of sulfonylurea levels in serum or plasma will allow the correct diagnosis to be made. The diagnosis of insulinoma has been complicated by the introduction of specific insulin assays that do not also interact with proinsulin, as do many of the older radioimmunoassays (RIAs), and therefore give lower plasma insulin levels. The increased use of these specific insulin assays has resulted in increased numbers of patients with insulinomas having lower plasma insulin values (<6 μU/mL) than levels proposed to be characteristic of insulinomas by RIA. In these patients, the assessment of proinsulin and C-peptide levels at the time of hypoglycemia is particularly helpful for establishing the correct diagnosis. An elevated proinsulin level when the fasting glucose level is <45 mg/dL is sensitive and specific.

TREATMENT

Insulinomas

Only 5–15% of insulinomas are malignant; therefore, after appropriate imaging (see below), surgery should be performed. In different studies, 75–100% of patients are cured by surgery. Before surgery, the hypoglycemia can be controlled by frequent small meals and the use of diazoxide (150–800 mg/d). Diazoxide is a benzothiadiazide whose hyperglycemic effect is attributed to inhibition of insulin release. Its side effects are sodium retention and GI symptoms such as nausea. Approximately 50–60% of patients respond to diazoxide. Other agents effective in some patients to control the hypoglycemia include verapamil and diphenylhydantoin. Long-acting somatostatin analogues such as octreotide and lanreotide are acutely effective in 40% of patients. However, octreotide must be used with care because it inhibits growth hormone secretion and can alter plasma glucagon levels; therefore, in some patients, it can worsen the hypoglycemia.

For the 5–15% of patients with malignant insulinomas, these drugs or somatostatin analogues are used initially. In a small number of patients with malignant tumors, mammalian target of rapamycin (mTOR) inhibitors (everolimus, rapamycin) are reported to control the hypoglycemia. If they are not effective, various antitumor treatments such as hepatic arterial embolization, chemoembolization, chemotherapy, and peptide receptor radiotherapy with radiolabeled somatostatin analogues (PRRT) have been used and can be effective, particularly PRRT.

Insulinomas, which are usually benign (>90%) and intrapancreatic in location, are increasingly resected using a laparoscopic approach, which has lower morbidity rates. This approach requires that the insulinoma be localized on preoperative imaging studies.

GLUCAGONOMAS

A glucagonoma is NET of the pancreas that secretes excessive amounts of glucagon, which causes a distinct syndrome characterized by dermatitis, glucose intolerance or diabetes, and weight loss. Glucagonomas principally occur between 45 and 70 years of age. The tumor is clinically heralded by a characteristic dermatitis (migratory necrolytic erythema) (67–90%), accompanied by glucose intolerance (40–90%), weight loss (66–96%), anemia (33–85%), diarrhea (15–29%), and thromboembolism (11–24%). The characteristic rash usually starts as an annular erythema at intertriginous and periorificial sites, especially in the groin or buttock. It subsequently becomes raised, and bullae form; when the bullae rupture, eroded areas form. The lesions can wax and wane. The development of a similar rash in patients receiving glucagon therapy suggests that the rash is a direct effect of the hyperglucagonemia. A characteristic laboratory finding is hypoaminoacidemia, which occurs in 26–100% of patients.

Glucagonomas are generally large tumors at diagnosis (5–10 cm). Some 50–80% occur in the pancreatic tail. From 50 to 82% have evidence of metastatic spread at presentation, usually to the liver. Glucagonomas are rarely extrapancreatic, usually occur singly, and <3% are associated with the MEN1 syndrome.

Two new entities have been described that can also cause hyperglucagonemia and may mimic glucagonomas. Mahvash disease is due to an inactivating mutation (homozygous P86S mutation) of the human glucagon receptor. It is associated with the development of α-cell hyperplasia, hyperglucagonemia, and the development of nonfunctioning pNETs. Subsequently other patients with other inactivating mutations of the human glucagon receptor have been described with similar findings, leading to the suggestion that a hepato-pancreatic feedback regulation of the cells, possibly involving amino acids, may exist in humans. A second disease called *glucagon cell adenomatosis* can mimic glucagonoma syndrome clinically and is characterized by the presence of hyperplastic islets staining positive for glucagon instead of a single glucagonoma.

Diagnosis The diagnosis is confirmed by demonstrating an increased plasma glucagon level. Characteristically, plasma glucagon levels exceed 1000 pg/mL (normal is <150 pg/mL) in 90%; 7% are between 500 and 1000 pg/mL, and 3% are <500 pg/mL. A trend toward lower levels at diagnosis has been noted in the last decade. A plasma glucagon level >1000 pg/mL is considered diagnostic of glucagonoma. Other diseases causing increased plasma glucagon levels include cirrhosis, diabetic ketoacidosis, celiac disease, renal insufficiency, acute pancreatitis, hypercorticism, hepatic insufficiency, severe stress, and prolonged fasting or familial hyperglucagonemia, as well as danazol treatment. With the exception of cirrhosis, these disorders do not increase plasma glucagon >500 pg/mL.

Necrolytic migratory erythema is not pathognomonic for glucagonoma and occurs in myeloproliferative disorders, hepatitis B infection, malnutrition, short-bowel syndrome, inflammatory bowel disease, zinc deficiency, and malabsorption disorders.

TREATMENT

Glucagonomas

In 50–80% of patients, hepatic metastases are present, and so curative surgical resection is not possible. Surgical debulking in patients with advanced disease or other antitumor treatments may be beneficial as well as PRRT with radiolabeled somatostatin analogues (see below). Long-acting somatostatin analogues such as octreotide and lanreotide improve the skin rash in 75% of patients and may improve the weight loss, pain, and diarrhea, but usually do not improve the glucose intolerance.

SOMATOSTATINOMA SYNDROME

The somatostatinoma syndrome is due to an NET that secretes excessive amounts of somatostatin, which causes a distinct syndrome characterized by diabetes mellitus, gallbladder disease, diarrhea, and steatorrhea. There is no general distinction in the literature between a tumor that contains somatostatin-like immunoreactivity (somatostatinoma) and does (11–45%) or does not (55–90%) produce a clinical syndrome (somatostatinoma syndrome) by secreting somatostatin. In a review of 173 cases of somatostatinomas, only 11% were associated with the somatostatinoma syndrome. The mean age is 51 years. Somatostatinomas occur primarily in the pancreas and small intestine, and the frequency of the symptoms and occurrence of the somatostatinoma syndrome differ in each. Each of the usual symptoms is more common in pancreatic than in intestinal somatostatinomas: diabetes mellitus (95% vs 21%), gallbladder disease (94% vs 43%), diarrhea (92% vs 38%), steatorrhea (83% vs 12%), hypochlorhydria (86% vs 12%), and weight loss (90% vs 69%). The somatostatinoma syndrome occurs in 30–90% of pancreatic and 0–5% of SI somatostatinomas. In various series, 43% of all duodenal NETs contain somatostatin; however, the somatostatinoma syndrome is rarely present (<2%). Somatostatinomas occur in the pancreas in 56–74% of cases, with the primary location being the pancreatic head. The tumors are usually solitary (90%) and large (mean size 4.5 cm). Liver metastases are common, being present in 69–84% of patients. Somatostatinomas are rare in patients with MEN 1, occurring in only 0.65%.

The existence of a somatostatinoma syndrome (SSoma syndrome) has been called into question. This occurred because in one review of 821 patients with duodenal or pancreatic NETs, a proportion of which showed predominant somatostatin expression, none had the SSoma syndrome leading to the conclusion it is either very rare or nonexistent. However, in other studies, a proportion of the patients with somatostatin positive pancreatic or duodenal NETs had number of the proposed features of the SSoma syndrome.

Somatostatin is a tetradecapeptide that is widely distributed in the CNS and GI tract, where it functions as a neurotransmitter or has paracrine and autocrine actions. It is a potent inhibitor of many processes, including release of almost all hormones, acid secretion, intestinal and pancreatic secretion, and intestinal absorption. Most of the clinical manifestations are directly related to these inhibitory actions.

Diagnosis In most cases, somatostatinomas have been found by accident either at the time of cholecystectomy or during endoscopy. The presence of psammoma bodies in a duodenal tumor should particularly raise suspicion. Duodenal somatostatin-containing tumors are increasingly associated with von Recklinghausen's disease (NF-1) (Table 80-5). Most of these tumors (>98%) do not cause the SSoma syndrome. The diagnosis of the SSoma syndrome requires the demonstration of elevated plasma somatostatin levels.

TREATMENT

Somatostatinomas

Pancreatic tumors are frequently (70–92%) metastatic at presentation, whereas 30–69% of SI somatostatinomas have metastases. Surgery is the treatment of choice for those without widespread hepatic metastases. Symptoms in patients with the SSoma syndrome are also improved by octreotide treatment.

VIPomas

VIPomas are NETs that secrete excessive amounts of vasoactive intestinal peptide (VIP), which causes a distinct syndrome characterized by large-volume diarrhea, hypokalemia, and dehydration. This syndrome also is called Verner-Morrison syndrome, pancreatic cholera, and WDHA syndrome for *w*atery *d*iarrhea, *h*ypokalemia, and *a*chlorhydria, which some patients develop. The mean age of patients with this syndrome is 49 years; however, it can occur in children, and when it does, it is usually caused by a ganglioneuroma or ganglioneuroblastoma.

The principal symptoms are large-volume diarrhea (100%) severe enough to cause hypokalemia (80–100%), dehydration (83%),

hypochlorhydria (54–76%), and flushing (20%). The diarrhea is secretory in nature, persisting during fasting, and is almost always >1 L/d and in 70% is >3 L/d. In a number of studies, the diarrhea was intermittent initially in up to half the patients. Most patients do not have accompanying steatorrhea (16%), and the increased stool volume is due to increased excretion of sodium and potassium, which, with the anions, accounts for the osmolality of the stool. Patients frequently have hyperglycemia (25–50%) and hypercalcemia (25–50%).

VIP is a 28-amino-acid peptide that is an important neurotransmitter, ubiquitously present in the CNS and GI tract. Its known actions include stimulation of SI chloride secretion as well as effects on smooth-muscle contractility, inhibition of acid secretion, and vasodilatory effects, which explain most features of the clinical syndrome.

In adults, 80–90% of VIPomas are pancreatic in location, with the rest due to VIP-secreting pheochromocytomas, intestinal carcinoids, and rarely ganglioneuromas. These tumors are usually solitary, 50–75% are in the pancreatic tail, and 37–68% have hepatic metastases at diagnosis. In children <10 years old, the syndrome is usually due to ganglioneuromas or ganglioblastomas and is less often malignant (10%).

Diagnosis The diagnosis requires the demonstration of an elevated plasma VIP level and the presence of large-volume diarrhea. A stool volume <700 mL/d is proposed to exclude the diagnosis of VIPoma. When the patient fasts, a number of diseases can be excluded that can cause marked diarrhea because the high volume of diarrhea is not sustained during the fast. Other diseases that can produce a secretory large-volume diarrhea include gastrinomas, chronic laxative abuse, carcinoid syndrome, systemic mastocytosis, rarely medullary thyroid cancer, diabetic diarrhea, sprue, and AIDS. Among these conditions, only VIPomas caused a marked increase in plasma VIP. Chronic surreptitious use of laxatives/diuretics can be particularly difficult to detect clinically. Hence, in a patient with unexplained chronic diarrhea, screens for laxatives should be performed; they will detect many, but not all, laxative abusers. Elevated plasma levels of VIP should not be the only basis of the diagnosis of VIPomas because they can occur with some diarrheal states including inflammatory bowel disease, post small bowel resection, and radiation enteritis. Furthermore, nesidioblastosis can mimic VIPomas by causing elevated plasma VIP levels, diarrhea, and even false-positive location in the pancreatic region on somatostatin receptor scintigraphy (SRS).

TREATMENT

VIPomas

The most important initial treatment in these patients is to correct their dehydration, hypokalemia, and electrolyte losses with fluid and electrolyte replacement. These patients may require >5 L/d of fluid and >350 mEq/d of potassium. Because 37–68% of adults with VIPomas have metastatic disease in the liver at presentation, a significant number of patients cannot be cured surgically. In these patients, long-acting somatostatin analogues such as octreotide and lanreotide (Fig. 80-2) are the drugs of choice.

Octreotide/lanreotide will control the diarrhea short- and long-term in 75–100% of patients. In nonresponsive patients, the combination of glucocorticoids and octreotide/lanreotide has proved helpful in a small number of patients. Other drugs reported to be helpful in small numbers of patients include prednisone (60–100 mg/d), clonidine, indomethacin, phenothiazines, loperamide, lidamidine, lithium, propranolol, and metoclopramide. Treatment of advanced disease with cytoreductive surgery, embolization, chemoembolization, chemotherapy, radiotherapy, radiofrequency ablation (RFA), and peptide receptor radiotherapy may be helpful (see below). Control of the diarrhea in VIPoma patients using the tyrosine kinase inhibitor, sunitinib, has been described in case reports.

NONFUNCTIONAL PANCREATIC NEUROENDOCRINE TUMORS (NF-pNETs)

NF-pNETs are NETs that originate in the pancreas and either secretes no products or their products do not cause a specific clinical syndrome. Their symptoms are due entirely to the tumor per se. NF-pNETs secrete chromogranin A (90–100%), chromogranin B (90–100%), α-HCG (human chorionic gonadotropin) (40%), neuron-specific enolase (31%), and β-HCG (20%), and because 40–90% secrete PP, they are also often called PPomas. A proportion also secrete ghrelin, neurotensin, calcitonin and other GI hormones/neurotransmitters, which are generally accepted as not causing a distinct clinical syndrome. Because the symptoms are due to the tumor mass, patients with NF-pNETs usually present late in the disease course with invasive tumors and hepatic metastases (64–92%), and the tumors are usually large (72% >5 cm). An increasing proportion of NF-PNETs are asymptomatic (up to 30–50%) and are found at screening for various nonspecific symptoms. NF-pNETs are usually solitary except in patients with MEN 1, in which case they are multiple. They occur primarily in the pancreatic head. Even though these tumors do not cause a functional syndrome, immunocytochemical studies show that they synthesize numerous peptides and cannot be distinguished from functional pNETs by immunocytochemistry. In MEN 1, 80–100% of patients have microscopic NF-pNETs, but they become large or symptomatic in a minority (0–13%) of cases. In VHL, 12–17% develop NF-pNETs, and in 4%, they are ≥3 cm in diameter.

The most common symptoms are abdominal pain (30–80%), jaundice (20–35%), and weight loss, fatigue, or bleeding. The average time from the beginning of symptoms to diagnosis is 5 years.

Diagnosis The diagnosis is established by histologic confirmation in a patient without either the clinical symptoms or the elevated plasma hormone levels of one of the established syndromes. The principal difficulty in diagnosis is to distinguish an NF-pNET from a nonendocrine pancreatic tumor, which is more common, as well as from a F-pNET. Even though chromogranin A levels are elevated in almost every patient, this is not specific for this disease as it can be found in F-pNETs, GI-NETs (carcinoids), and other neuroendocrine disorders, as well in patients without any of these, but being treated with PPIs. Plasma PP elevations should strongly suggest the diagnosis in a patient with a pancreatic mass because it is usually normal in patients with pancreatic adenocarcinomas. Elevated plasma PP is not diagnostic of this tumor because it is elevated in a number of other conditions, such as chronic renal failure, old age, inflammatory conditions, alcohol abuse, pancreatitis, hypoglycemia, postprandially, and diabetes. A positive somatostatin receptor scan in a patient with a pancreatic mass should suggest the presence of pNET/NF-pNET rather than a nonendocrine tumor.

TREATMENT

Nonfunctional Pancreatic Neuroendocrine Tumors (NF-pNETs)

Overall survival in patients with sporadic NF-pNET is 30–63% at 5 years, with a median survival of 6 years. Unfortunately, surgical curative resection can be considered only in a minority of these patients because 30–92% present with diffuse metastatic disease. Treatment needs to be directed against the tumor per se using the various modalities discussed below for advanced disease. Whereas the treatment of NF-pNETs in either MEN 1 patients or patients with VHL has remained controversial for a number of years, the treatment in sporadic cases has also become controversial. In these inherited disorders, most recommend surgical resection for any tumor >2–3 cm in diameter; however, there is controversy in patients with smaller NF-pNETs (≤1.5–2 cm), with most guidelines recommending careful surveillance of these patients. This approach is taken because patients with these inherited diseases are not curable without aggressive surgery with its associated mortality/morbidity, because of the multiplicity of the small NF-pNETs; studies show these patients with NF-NETs ≤2 cm have no increased mortality; and most are slow growing. Most of these are low- or intermediate-grade lesions, and <7% are malignant. Similarly in patients with sporadic NF-pNETs in the past almost all were operated on; however, because

of the generally benign course of those that are asymptomatic and ≤2 cm in diameter, increasingly they are not operated, but followed closely. No consensus exists on this point with the result that some advocate a non-operative approach with careful, regular follow-up, whereas others recommend an operative or laparoscopic.

GRFomas

GRFomas are NETs that secrete excessive amounts of growth hormone–releasing factor (GRF) that cause acromegaly. GRF is a 44-amino-acid peptide, and 25–44% of pNETs have GRF immunoreactivity, although it is uncommonly secreted. GRFomas are lung tumors in 47–54% of cases, pNETs in 29–30%, SI carcinoids in 8–10%; and up to 12% occur at other sites. Patients have a mean age of 38 years, and the symptoms usually are due to either acromegaly or the tumor per se. The acromegaly caused by GRFomas is indistinguishable from classic acromegaly. The pancreatic tumors are usually large (>6 cm), and liver metastases are present in 39%. They should be suspected in any patient with acromegaly and an abdominal tumor, a patient with MEN 1 with acromegaly, or a patient without a pituitary adenoma with acromegaly or associated with hyperprolactinemia, which occurs in 70% of GRFomas. GRFomas are an uncommon cause of acromegaly. GRFomas occur in <1% of MEN 1 patients. The diagnosis is established by performing plasma assays for GRF and growth hormone. Most GRFomas have a plasma GRF level >300 pg/mL (normal <5 pg/mL men, <10 pg/mL women). Patients with GRFomas also have increased plasma levels of insulin-like growth factor type I (IGF-I) similar to those in classic acromegaly. Surgery is the treatment of choice if diffuse metastases are not present. Long-acting somatostatin analogues such as octreotide and lanreotide are the agents of choice, with 75–100% of patients responding.

OTHER RARE PANCREATIC NEUROENDOCRINE TUMOR SYNDROMES

Cushing's syndrome (ACTHoma) due to a pNET occurs in 4–16% of all ectopic Cushing's syndrome cases. It occurs in 5% of cases of sporadic gastrinomas, almost invariably in patients with hepatic metastases, and is an independent poor prognostic factor. Paraneoplastic hypercalcemia due to pNETs releasing parathyroid hormone–related peptide (PTHrP), a PTH-like material, or unknown factor, is rarely reported. The tumors are usually large, and liver metastases are usually present. Most (88%) appear to be due to release of PTHrP. pNETs occasionally can cause the carcinoid syndrome and this may occur without the presence of liver metastases. A number of very rare pNET syndromes involving a few cases (less than five) have been described; these include a renin-producing pNET in a patient presenting with hypertension; pNETs secreting luteinizing hormone, resulting in masculinization or decreased libido; a pNET secreting erythropoietin, resulting in polycythemia; pNETs secreting IGF-II, causing hypoglycemia; pNETs secreting enteroglucagon, causing small intestinal hypertrophy, colonic/SI stasis, and malabsorption and a pNET secreting cholecystokinin (CCKoma) which can mimic ZES clinically with patients presenting with severe peptic ulcer disease, diarrhea, weight loss, and gallstones, but with a normal fasting gastrin level (Table 80-2). A number of other possible functional pNETs have been proposed, but most authorities classify these as unclear or as a nonfunctional pNET because in each case numerous patients have been described with similar plasma hormone elevations that do not cause any symptoms. These include pNETs secreting calcitonin, neurotensin (neurotensinoma), PP (PPoma), and ghrelin (Table 80-2).

TUMOR LOCALIZATION

Localization of the primary tumor and knowledge of the extent of the disease are essential to the proper management of all GI-NETs (carcinoids) and pNETs. Without proper localization studies, it is not possible to determine whether the patient is a candidate for surgical resection (curative or cytoreductive) or requires antitumor treatment, to determine whether the patient is responding to antitumor therapies, whether postresection recurrent disease is present or to appropriately classify/stage the patient's disease to assess prognosis.

Numerous tumor localization methods are used in both types of NETs, including cross-sectional imaging studies (CT, magnetic resonance imaging [MRI], trans-abdominal ultrasound), selective angiography, SRS, and positron emission tomography. In pNETs, endoscopic ultrasound (EUS) and functional localization by measuring venous hormonal gradients are also reported to be useful. Bronchial carcinoids are usually detected by standard chest radiography and assessed by CT. Rectal, duodenal, colonic, and gastric carcinoids are usually detected by GI endoscopy. Because of their wide availability, CT and MRI are generally initially used to determine the location of the primary NETs and the extent of disease. NETs are hypervascular tumors, and with both MRI and CT, contrast enhancement is essential for maximal sensitivity, and it is recommended that generally triple-phase scanning be used. The ability of cross-sectional imaging and, to a lesser extent, SRS to detect NETs is a function of NET size. With CT and MRI, <10% of tumors <1 cm in diameter are detected, 30–40% of tumors 1–3 cm are detected, and >50% of tumors >3 cm are detected. Many primary GI-NETs (carcinoids) are small, as are insulinomas and duodenal gastrinomas, and are frequently not detected by cross-sectional imaging, whereas most other pNETs present late in the course of their disease and are large (>4 cm). Selective angiography is more sensitive, localizing 60–90% of all NETs; however, it is now used infrequently. For detecting liver metastases, CT and MRI are more sensitive than ultrasound, and with recent improvements, 5–25% of patients with liver metastases will be missed by CT and/or MRI.

pNETs, as well as GI-NETs (carcinoids), frequently (>80%) overexpress high-affinity sst in both the primary tumors and the metastases. Of the five types of somatostatin receptors ($sst_{1–5}$), radiolabeled octreotide binds with high affinity to sst_2 and sst_5, has a lower affinity for sst_3, and has a very low affinity for sst_1 and sst_4. Between 80 and 100% of well-differentiated (G1, G2 grades) GI-NETs (carcinoids) and pNETs possess sst_2, and many also have some of the other four sst subtypes. Interaction with these receptors can be used to treat these tumors as well as to localize NETs by using radiolabeled somatostatin analogues (i.e. somatostatin receptor imaging [SRI]). In contrast, only 50–70% of poorly differentiated (G3 grade) NETs have sst2 receptors. In the United States, (^{111}In-DTPA-D-Phe^1) octreotide (octreoscan) (Fig. 80-2) is still generally used with gamma camera detection using single-photon emission computed tomography (SPECT) imaging. Using gallium-68-labeled somatostatin analogues and positron emission tomography (^{68}Ga-PET/CT) detection has greater sensitivity than using ^{111}In-labeled somatostatin analogues (^{111}In-SPECT/CT) **(Fig. 80-3)**. It (NEWSPOT) is now approved for use in the United States. Because of its sensitivity and ability to localize tumor throughout the body, SRI is the initial imaging modality of choice for localizing both the primary tumor and metastatic NETs. SRI localizes tumor in 73–95% of patients with GI-NETs (carcinoids) and in 56–100% of patients with pNETs, except insulinomas. Insulinomas are usually small and have low densities of sst receptors, resulting in SRI being positive in only 12–50% of patients with insulinomas. SRS identifies >90–95% of patients with liver metastases due to NETs. Figure 80-3 shows an example with SRI of the increased sensitivity of ^{68}Ga-PET/CT over ^{111}In-SPECT-CT and CT scanning to localize both the primary NET and liver/bone metastases in a patient with a metastatic small intestinal carcinoid (GI-NET). Occasional false-positive responses with SRI can occur (12% in one study) because numerous other normal tissues as well as diseases can have high densities of sst receptors, including granulomas (sarcoid, tuberculosis, etc.), thyroid diseases (goiter, thyroiditis), activated lymphocytes (lymphomas, wound infections), splenunculi, increased osteoblastic activity, meningiomas, and increased physiological uptake in the pancreatic uncinate process (^{68}Ga-DOTATAE PET/CT). If liver metastases are identified by SRI (performed without hybrid CT), to plan the proper treatment, either a CT or an MRI (with contrast enhancement) is recommended to assess the size and exact location of the metastases, because SRI does not provide information on tumor size. For pNETs in the pancreas, EUS is highly sensitive, localizing 77–100% of insulinomas, which occur almost exclusively within the pancreas. EUS is less sensitive for extrapancreatic tumors. It is increasingly used in patients with MEN 1, and to a lesser extent VHL, to detect small pNETs not seen with other modalities or for serial pNET assessments to determine size changes or rapid growth in patients in

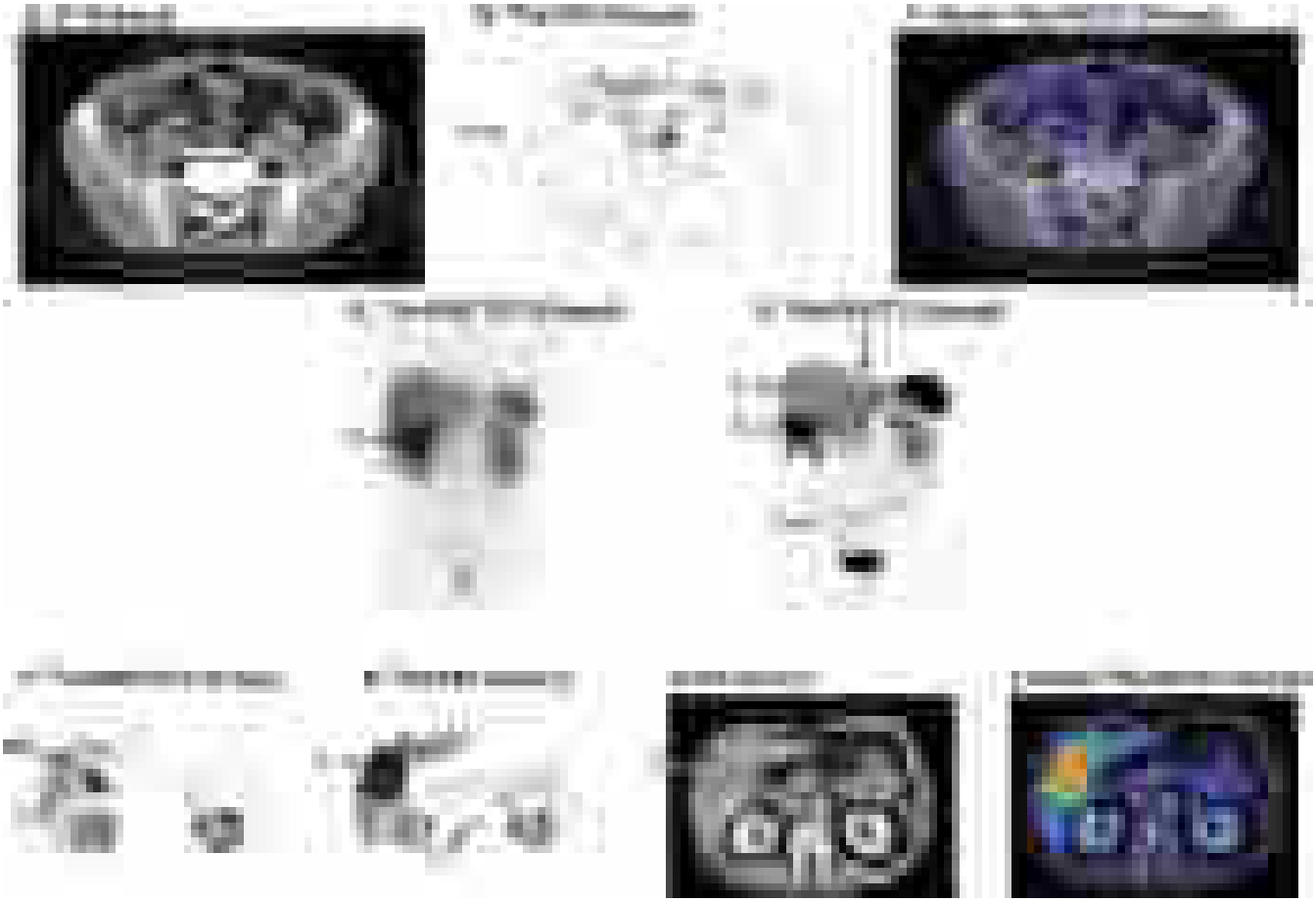

FIGURE 80-3 Enhanced sensitivity of ^{68}Ga-PET/CT to localize lesions in patient with a metastatic small intestinal carcinoid (GI-NET). Panels ***A–C*** show the ability of the ^{68}Ga-PET (transverse images) to localize the primary (T) when the CT is negative. Panels ***D*** and ***E*** (coronal views—maximum intensity projections) show the greater resolution and ability to localize more metastatic lesions (T) in the liver and bone of ^{68}Ga-PET than the ^{111}In-SPECT/CT scanning, which has been generally used in the United States until recently. Panels ***F-I*** (transverse images) show the increased sensitivity of ^{68}Ga-PET over the ^{111}In-SPECT/CT scanning in identifying the extent of the liver metastases as well as identifying bone metastasis. GB, gallbladder; T, tumor; Transv, transverse images. *(Results kindly provided by Prof. Anders Sundin, Department of Radiology, Uppsala University Hospital, Uppsala, Sweden.)*

whom surgery is deferred. EUS with cytologic evaluation also is used frequently to distinguish an NF-pNET from a pancreatic adenocarcinoma or another nonendocrine pancreatic tumor. Not infrequently patients present with liver metastases due to an NET and the primary site is unclear. Occult small intestinal NETs (carcinoids) are increasingly detected by double-balloon enteroscopy or capsule endoscopy.

Insulinomas frequently overexpress receptors for glucagon-like peptide-1 (GLP-1), and radiolabeled GLP-1 analogues have been developed that can detect occult insulinomas not localized by other imaging modalities. This study is only performed in a few specialty centers. Functional localization by measuring hormonal gradients is now uncommonly used with gastrinomas (after intra-arterial secretin injections) but is still frequently used in insulinoma patients in whom other imaging studies are negative (assessing hepatic vein insulin concentrations post-intra-arterial calcium injections). Functional localization measuring hormone gradients in insulinomas or gastrin gradients in gastrinoma is a sensitive method, being positive in 80–100% of patients. The intra-arterial calcium test may also allow differentiation of the cause of the hypoglycemia and indicate whether it is due to an insulinoma or a nesidioblastosis. The latter entity is becoming increasingly important because hypoglycemia after gastric bypass surgery for obesity is increasing in frequency, and it is primarily due to nesidioblastosis, although it can occasionally be due to an insulinoma.

PET and use of hybrid scanners such as CT and SRI has sensitivity because of the greater resolution of PET scanning. PET scanning with ^{18}F-fluoro-DOPA in patients with carcinoids or with ^{11}C-5-HTP in patients with pNETs or GI-NETs (carcinoids) has greater sensitivity than cross-sectional imaging studies and may be used increasingly in the future. PET/CT scanning using ^{18}F-FDG is receiving increasing attention in patients with NETs. It was initially thought that this would not be useful in NETs with the majority being well differentiated (G1, G2 grades, >85–98%) and having a low proliferative rate. However, ^{18}F-FDG PET/CT can identify higher grade NETs, and is particularly helpful for imaging G3 NETs, which are more frequently negative with SRS. There ^{18}F-FDG positivity can not only provide imaging information on location and tumor size, but also prognostic information because the relative survival of patients with the different NET grades is G1>G2>G3.

TREATMENT

Advanced and /or Aggressive Disease (Diffuse Metastatic Disease)

The single most important prognostic factor for survival is the presence of liver metastases **(Fig. 80-4*A, B, D, and E*)**. For patients with foregut carcinoids without hepatic metastases, the 5-year survival in one study was 95%, and with distant metastases, it was 20% (Fig. 80-4***A, B***). With gastrinomas, the 5-year survival without liver metastases is 98%; with limited metastases in one hepatic lobe, it is 78%; and with diffuse metastases, 16%. In a large study of 156 patients (67 pNETs, rest carcinoids), the overall 5-year survival rate was 77%; it was 96% without liver metastases, 73% with liver metastases, and 50% with distant disease.

The recent introduction and validation of the prognostic value of the different classification and grading systems (WHO, ENETS, the American Joint Committee on Cancer/International Union Against

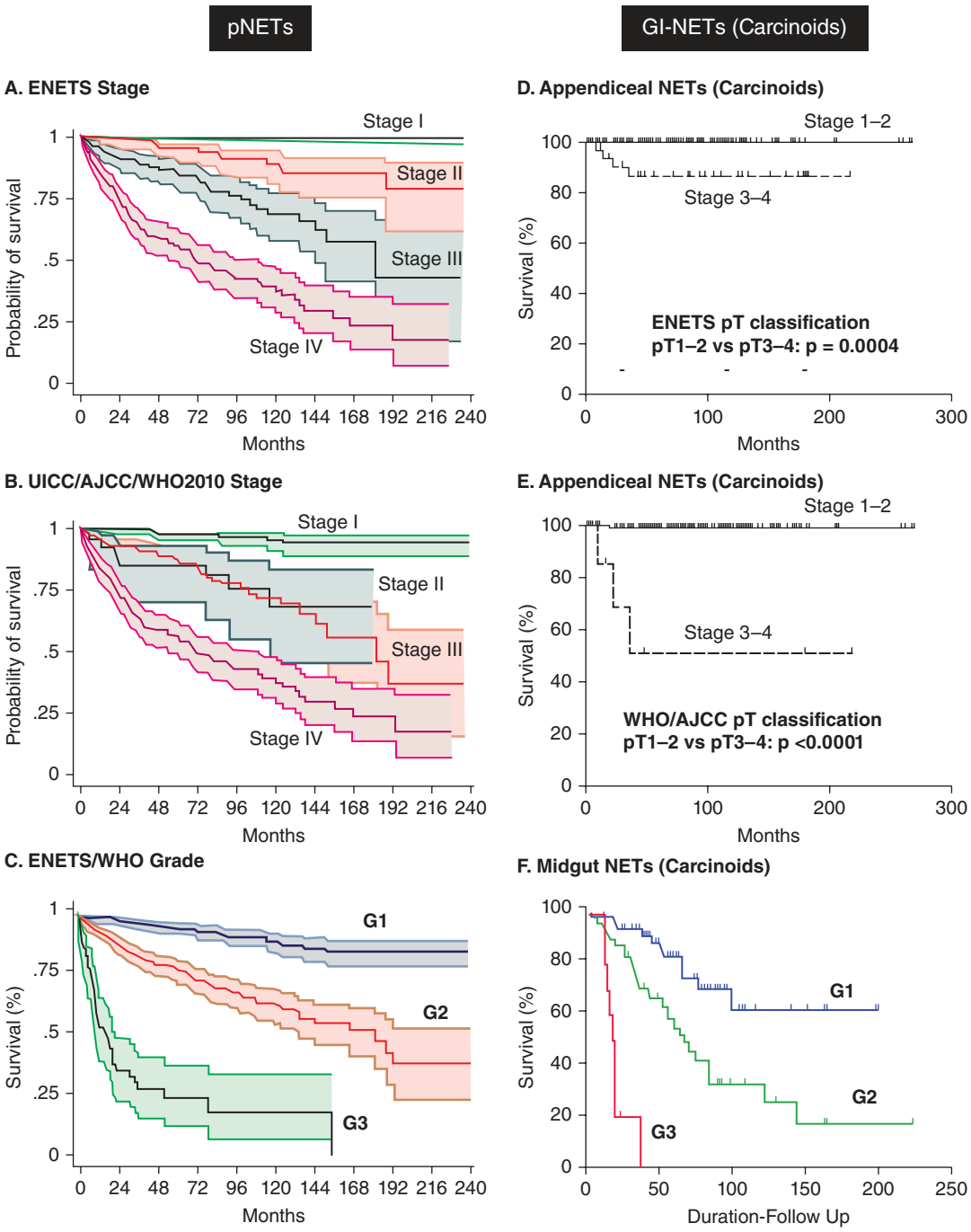

FIGURE 80-4 Survival (Kaplan-Meier plots) of patients with pancreatic neuroendocrine tumors (pNETs; n = 1072) (***A–C***) or gastrointestinal neuroendocrine tumors (GI-NETs; carcinoids) (appendix, n = 138; midgut, n = 238) (***D–F***) stratified according to recent proposed classification and grading systems. *(Panels A–C are drawn from data in G Rindi et al: J Natl Cancer Inst 104:764, 2012; panels D and E are drawn from data in M Volante et al: Am J Surg Pathol 37:606, 2013; and panel F is drawn from data in MS Khan: Br J Cancer 108:1838, 2013.)*

Cancer [AJCC/UICC]) are proving essential to stratify patients into different risk groups. A particular important prognostic factor is whether the NET is well differentiated (G1/G2) or poorly differentiated (<1% of all NETs) (G3) **(Fig. 80-4*C, F*)**. In various series overall, well-differentiated NETs, which are aggressive tumors, have a 5-year survival of 50–80%, whereas poorly differentiated NETs survival of only 0–15% at 5 years (Fig. 80-4*C, F*).

Therefore, treatment for advanced metastatic disease is an important challenge. A number of different modalities are reported to be effective, including cytoreductive surgery (surgically or by RFA), treatment with chemotherapy, somatostatin analogues, interferon α, hepatic embolization alone or with chemotherapy (chemoembolization), molecular targeted therapy, radiotherapy with radiolabeled beads/microspheres, PRRT, and liver transplantation.

SPECIFIC ANTITUMOR TREATMENTS

Cytoreductive surgery is considered if either all of the visible metastatic disease or at last 90% is thought resectable; however, unfortunately, this is possible in only the 9–22% of patients who present with limited hepatic metastases. Although no randomized studies have proven that it extends life, results from a number of studies suggest that it may increase survival; therefore, it is recommended, if possible. RFA can be applied to NET liver metastases if they are limited in number (usually <5) and size (usually <3.5 cm in diameter). It can be used at the time of surgery (either general or laparoscopic) or using radiologic guidance. Response rates are >80%, the responses can last up to 3 years, the morbidity rate is low, and this procedure may be particularly helpful in patients with F-pNETs that are difficult to control medically. Although RFA has not been established in

a controlled trial, both the European and North American Neuroendocrine Tumor Society guidelines (ENETS, NANETS) state it can be an effective antitumor treatment for both refractory functional syndromes and for palliative treatment.

Although there are no controlled, long-term trials, palliative surgical resection of the small intestinal primary and surrounding tumor is generally recommended in most guidelines and expert opinion reviews for patients with midgut carcinoids with carcinoid syndrome, who almost invariably have unresectable live metastases. Systematic analysis of existing data supports the conclusion surgical resection of the primary prevents complications (obstruction, etc.) and also prolongs survival in some studies. At the time of this resection, a cholecystectomy is recommended to possible biliary complications from long-term somatostatin therapy.

Chemotherapy plays a different role in the treatment of patients with pNETs and GI-NETs (carcinoids). Chemotherapy continues to be widely used in the treatment of patients with advanced pNETs with moderate success (response rates 20–70%). However, in general, its results in patients with metastatic GI-NETs (carcinoids) have been disappointing, with response rates of 0–30% with various two- and three-drug combinations, and thus, it is infrequently used in these patients. An important distinction in patients with pNETs is whether the tumor is well differentiated (G1/G2) or poorly differentiated (G3). The chemotherapeutic approach is different for these two groups. The current regimen of choice for patients with well-differentiated pNETs is the combination of streptozotocin and doxorubicin with or without 5-fluorouracil. Streptozotocin is a glucosamine nitrourea compound originally found to have cytotoxic effects on pancreatic islets, and later in studies with doxorubicin with or without 5-fluorouracil, it produced response rates of 20–45% in advanced pNETs. Streptozotocin causes considerable morbidity, with 70–100% of patients developing side effects (most prominent being nausea/vomiting in 60–100% or leukopenia/thrombocytopenia) and 15–70% of patients developing some degree of renal dysfunction (primarily proteinuria and/or decreased creatinine clearance). The combination of temozolomide (TMZ) with capecitabine is receiving increased attention as a possible alternative to streptozotocin-based therapies. Experience is still limited with this protocol and it is being evaluated in a number of current studies; however, analysis of larger retrospective studies shows responded rates from 48 to 70%. The use of TMZ or another alkylating agent in advanced pNETs is supported by some, but not all, studies that show low levels of the DNA repair enzyme O^6-methylguanine DNA methyltransferase in pNETs correlate with the sensitivity to TMZ. Grade G3 NETs are primarily treated by chemotherapy (see below).

In addition to the effectiveness in controlling the functional hormonal state, long-acting somatostatin analogues such as octreotide and lanreotide are increasingly used for their antiproliferative effects. Whereas somatostatin analogues rarely decrease tumor size (i.e., 0–17%), these drugs have tumoristatic effects, stopping additional growth in 26–95% of patients with NETs. In a randomized, double-blind study in patients with metastatic midgut carcinoids (PROMID study), octreotide-LAR demonstrated a marked lengthening of time to progression (14.3 vs 6 months, $p = 0.000072$). This improvement was seen in patients with limited liver involvement. This study did not assess whether such treatment will extend survival. A double-blind, randomized, placebo-controlled, phase III study in patients with well-differentiated, metastatic, inoperable pNETs (45%) or GI-NETs (carcinoids) (55%) (CLARINET study) showed that monthly treatment with lanreotide-autogel reduced tumor progression or death by 53%. Somatostatin analogues can induce apoptosis in GI-NETs (carcinoids), which probably contributes to their tumoristatic effects. Treatment with somatostatin analogues is generally well-tolerated, with most side effects being mild and uncommonly leading to stopping the drug. Potential long-term side effects include diabetes/glucose intolerance, steatorrhea, and the development of gallbladder sludge/gallstones (10–80%), although only 1% of patients develop symptomatic gallbladder disease. Because of these phase III studies, somatostatin analogues are generally recommended as first-line treatment for patients with well-differentiated metastatic NETs.

Interferon α, similar to somatostatin analogues, is effective at controlling the hormonal excess symptoms of NETs and has antiproliferative effects in NETs, which primarily result in disease stabilization (30–80%), with a decrease in tumor size in <15% of patients. Interferon can inhibit DNA synthesis, block cell cycle progression in the G_1 phase, inhibit protein synthesis, inhibit angiogenesis, and induce apoptosis. Interferon α treatment results in side effects in the majority of patients, with the most frequent being a flu-like syndrome (80–100%), anorexia with weight loss, and fatigue. These side effects frequently decrease in severity with continued treatment. In addition, patients become accommodated to the symptoms. More serious side effects include hepatotoxicity (31%), hyperlipidemia (31%), bone marrow toxicity, thyroid disease (19%), and rarely CNS side effects (depression, mental/visual disorders). ENETS 2016 guidelines conclude that in patients with well-differentiated NETs that are slowly progressive, interferon α treatment should be considered if the tumor is somatostatin receptor negative or if somatostatin or targeted therapy (everolimus, sunitinib) treatment fails.

Molecular targeted medical treatment with either an mTOR inhibitor (everolimus) or a tyrosine kinase inhibitor (sunitinib) is now approved treatment in the United States and Europe for patients with metastatic unresectable pNET, each supported by a phase III, double-blind, prospective, placebo-controlled trial. Furthermore, a Phase 3 double-blind study (RADIANT-4) also demonstrated the effectiveness of everolimus in advanced, non-functional NETs of the lung or GI-tract. In this study involving patients with advanced, progressive well differentiated, NF-lung/GI-NETs, everolimus significantly (p <0.000001) improved progression-free survival and led to FDA approval for its use.

mTOR is a serine-threonine kinase that plays an important role in proliferation, cell growth, and apoptosis in both normal and neoplastic cells. Activation of the mTOR cascade is important in mediating NET cell growth. A number of mTOR inhibitors have shown promising antitumor activity in NETs including everolimus and temsirolimus, with the former undergoing two phase III trials (RADIANT-3/RADIANT-4) studies in patients with advance progressive NETs (RADIANT-3=pNETs, RADIANT-4=lung, GI NF-NETs). In the RADIANT-III study which involved 410 patients with advanced, progressive pNETs, everolimus caused significant improvement in progression-free survival (11 vs 4.6 months, $p < 0.001$) and increased by a factor of 3.7 the proportion of patients progression-free at 18 months (37% vs 9%). Everolimus treatment was associated with frequent side effects, causing a twofold increase in adverse events, with the most frequent being grade 1 or 2. Grade 3 or 4 side effects included hematologic, GI (diarrhea), stomatitis, or hypoglycemia occurring in 3–7% of patients. Most grade 3 or 4 side effects were controlled by dose reduction or drug interruption. Similar side-effects were found in the RADIANT-4 study. The ENETS 2016 guidelines conclude that everolimus, similar to sunitinib (below), can be considered as a first-line treatment in well-differentiated pNETs that are unresectable especially if somatostatin analogues are not an option. However, these guidelines recommended that somatostatin analogues be the initial treatment because of their low incidence of side-effects. In patients with GI-NETs, the ENET 2016 guidelines recommended that everolimus could be recommended as second-line therapy after somatostatin analogues.

Like other normal and neoplastic cells, NETs frequently possess multiple types of the 20 different tyrosine kinase (TK) receptors that are known and mediate the action of different growth factors. Numerous studies demonstrate that TK receptors in normal and neoplastic tissues as well as NETs are especially important in mediating cell growth, angiogenesis, differentiation, and apoptosis. Whereas a number of TK inhibitors show antiproliferative activity in NETs, only sunitinib has undergone a phase III controlled trial. Sunitinib is

an orally active small-molecule inhibitor of TK receptors (PDGFRs, VEGFR-1, VEGFR-2, c-KIT, FLT-3). In a phase III study in which 171 patients with progressive, metastatic, nonresectable pNETs were treated with sunitinib (37.5 mg/d) or placebo, sunitinib treatment caused a doubling of progression-free survival (11.4 vs 4.5 months, $p < 0.001$), an increase in objective tumor response rate (9% vs 0%, $p = 0.007$), and an increase in overall survival. Sunitinib treatment was associated with an overall threefold increase in side effects, although most were grade 1 or 2. The most frequent grade 3 or 4 side effects were neutropenia (12%) and hypertension (9.6%), which were controlled by dose reduction or temporary interruption. There is no consensus regarding the order of sunitinib or everolimus use in patients with advanced, well-differentiated, progressive pNETs.

In patients with liver-predominant metastatic disease, a number of locoregional strategies have been used including: transarterial arterial embolization (TAE) alone or with chemotherapeutic agents (TACE); and selective internal radiation therapy (SIRT) or radioembolization. TACE/TAE can be effective because the blood supply to normal liver tissue is primarily from the portal vein whereas tumors receive 70–80% of their supply from the hepatic artery. Occlusion of selective branches of the hepatic artery is now generally performed radiologically. Contraindications include >50–75% liver involvement by tumor, portal vein thrombosis, post-biliary reconstructive surgery, liver failure, and a poor performance rating. Results include a symptomatic response rate of 50–100%, and an objective response rate of 25–86% with a mean duration of response of 6–45 months. Complications include a postembolization syndrome with pain, nausea/vomiting and fever in 10–80% with <6% mortality. SIRT using yttrium-90 (^{90}Y) glass or resin microspheres is a relatively newer approach being evaluated in patients with unresectable NET liver metastases. The treatment requires careful evaluation for vascular shunting before treatment and a pretreatment angiogram to evaluate placement of the catheter and is generally is reserved for patients without extrahepatic metastatic disease and with adequate hepatic reserve. One of two types of ^{90}Y microspheres is used: either microspheres with a 20- to 60-μm diameter and 50 Bq/sphere (SIR-Spheres) or glass microspheres (TheraSpheres) with a 20- to 30-μm diameter and 2500 Bq/sphere. The ^{90}Y-microspheres are delivered to the liver by intraarterial injection from percutaneously placed catheters. The response rate varied from 50 to 61% (partial or complete), tumor stabilization occurred in 22–41%, 60–100% had symptomatic improvement, and overall survival varied from 25 to 70 months. Side effects include postembolization syndrome (pain, fever, nausea/vomiting [frequent]), which is usually mild, although grade 2 (43%) or grade 3 (1%) symptoms can occur; radiation-induced liver disease (<1%); and radiation pneumonitis (<1%). Contraindications to use include excess shunting to the GI tract or lung, inability to isolate the liver arterial supply, and inadequate liver reserve. Because of the limited data available in the ENETS 2012 guidelines, treatment with SIRTs is considered experimental.

PRRT for NETs with radiolabeled somatostatin analogues is now being increasing considered for patients with advanced NETs. The success of this approach is based on the finding that somatostatin sst are overexpressed or ectopically expressed by 60–100% of all NETs, which allows the targeting of cytotoxic, radiolabeled somatostatin receptor ligands. Three different radionuclides have been used including: high doses of [^{111}In-DTPA-D-Phe^1] octreotide, which emits γ-rays, internal conversion, and Auger electrons; ^{90}yttrium, which emits high-energy β-particles coupled by a DOTA chelating group to octreotide or octreotate; and ^{177}lutetium-coupled analogues, which emit both (Fig. 80-2). At present, the ^{177}lutetium-coupled analogues are the most widely used and although not approved for general use in any country, they are frequently available in speciality centers on a special or compassionate basis. A double-blind, prospective, randomized trial (NETTER-1 Study) (using 177Lu-Dotatate [Lutathera]) has supported the efficacy and safety of this approach in patients with advanced inoperable, progressive midgut GI-NETs (carcinoids). In this trial, which included 229 patients with grade G1,2 metastatic midgut carcinoids, a marked increased in progressive-free survival ($p < 0.0001$) was seen with PRRT treatment with a ^{177}Lu-labeled-somatostatin-analog, with an acceptable safety profile and with a suggestion of an improved survival, although final survival analysis is not yet complete. In a number of retropective, non-blinded trials, ^{111}Indium-, ^{90}yttrium-, and ^{177}lutetium-labeled compounds caused tumor stabilization in patients with advanced, progressive NETs in 41–81%, 44–88%, and 23–51%, respectively, and a decrease in tumor size in 8–30%, 6–37%, and 38%, respectively, of patients. In one large study involving 504 patients with malignant NETs, ^{177}lutetium-labeled analogues produced a reduction of tumor size of >50% in 30% of patients (2% complete) and tumor stabilization in 51% of patients. The ENETS 2016, NANETS, Nordic 2010, and European Society for Medical Oncology (ESMO) guidelines list PRRT as an experimental or investigational treatment at present.

The use of liver transplantation has been abandoned for treatment of most metastatic tumors to the liver. However, for metastatic NETs, it is still a consideration by many centers although its use is controversial. An analysis of data from a number of centers showed that the overall 5-year survival is 47–58%, but varies widely in different studies from 36 to 97%; the 5-year disease-free survival was usually 20–30%, but varied from 9 to 77%, with a postoperative mortality <15%. With pNETs the 5-year survival rate varies from 30 to 50% and for GI-NETs from 60 to 90%. In various studies, important prognostic factors for a poor outcome include a major resection performed in addition at the time of the liver transplant; poor tumor differentiation; hepatomegaly; age >45 years; a primary NET in the duodenum or pancreas; the presence of extrahepatic metastatic disease or extensive liver involvement (>50%); Ki_{67} proliferative index >10%; and abnormal E-cadherin staining. The ENETS 2016 guidelines conclude that liver transplantation should be viewed as an option in highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapies.

The management and treatment of patients with G3 NETs (Ki_{67} >20) (WHO classification as NECs) has undergone a number of changes because of some important new insights. It is now realized that G3 NETs are heterogeneous and this has resulted in a proposal that they be divided into at least two categories; this division has important management ramifications because it is proposed they be treated differently. In reviews of G3 patients from a number of centers, a group of patients have G3 grading but with well-differentiated morphology (usually with a Ki_{67} 20–55) and it is proposed these be called G3 NET. These G3 NET patients have a better prognosis than poorly differentiated G3 tumors (usually with Ki_{67} >55), which are proposed to be called G3 NEC tumors. Pathology studies show that G3 NETs frequently have loss of ATRX/DAXX, whereas the G3 NEC poorly differentiated tumors have abnormal expression of p53, retinoblastoma and/or SMAD4. Most patients with G3 NETs have regional or distant metastases at the time of diagnosis and surgery is rarely curative, with the result that chemotherapy is usually recommended. This new subclassification has therapeutic implications because it is proposed to treat the G3 NET tumors similar to treatment for well-differentiated G2 tumors, whereas for G3 NEC tumors, treatment with cisplatin-based regimens with etoposide or other agents (vincristine, paclitaxel) is recommended. The response rates with this protocol are 40–70%; however, responses are generally short-lived (<12 months). This chemotherapy regimen can be associated with significant toxicity including GI toxicities (nausea, vomiting), myelosuppression.

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81 Renal Cell Carcinoma

Robert J. Motzer

Renal cell carcinomas account for 90–95% of malignant neoplasms arising from the kidney. Notable features include diagnosis without symptoms, resistance to cytotoxic agents, infrequent responses to biologic response modifiers such as interleukin (IL)-2, robust activity of antiangiogenesis-targeted agents, and a variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression. The remaining 5–10% of malignant neoplasms arising from the kidney are transitional cell carcinomas (urothelial carcinomas) originating in the lining of the renal pelvis. See Chap. 82 for transitional cell carcinomas.

EPIDEMIOLOGY

The incidence of renal cell carcinoma rose for three decades but has now reached a plateau of ~63,000 cases annually in the United States, resulting in >14,000 deaths per year. It is the ninth most common cancer overall in the United States, seventh most common in males, and tenth most common in females; the male-to-female ratio is 2:1. Though this malignancy may be diagnosed at any age, it is uncommon in those aged <45 years, and incidence peaks between the ages of 50 and 70 years. Many factors have been investigated as possible contributing causes; associations include cigarette smoking, obesity, and hypertension. Risk is also increased for patients who have acquired cystic disease of the kidney associated with end-stage renal disease and for those with tuberous sclerosis.

Most cases of renal cell carcinoma are sporadic, although familial forms have been reported (Table 81-1). One such form is associated with von Hippel-Lindau (VHL) syndrome, an autosomal dominant disorder. Genetic studies identified the *VHL* gene on the short arm of chromosome 3. Approximately 35% of individuals with VHL disease develop clear cell renal cell carcinoma. Other *VHL*-associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, and neuroendocrine tumors and cysts. Birt-Hogg-Dubé syndrome is a rare human autosomal dominant genetic disorder characterized by fibrofolliculomas (benign tumors arising in hair follicles), pulmonary cysts, and kidney tumors. The renal tumors are usually of the chromophobe type, but they can exist as hybrids with other cell types. This disorder is associated with mutations in the *FLCN* gene, which codes for folliculin.

PATHOLOGY AND GENETICS

Renal cell neoplasia represents a heterogeneous group of tumors with distinct histopathologic, genetic, and clinical features ranging from benign to high-grade malignant (Table 81-2). They are classified on the basis of morphology and histology. Categories include clear cell carcinoma (70% of cases), papillary tumors (10%), chromophobe tumors (≤5%), oncocytomas (5–10%), collecting duct or Bellini duct tumors (<1%), and translocation carcinoma (<1%). Papillary tumors tend to be bilateral and multifocal. Chromophobe tumors have a more indolent clinical course, and oncocytomas are considered benign neoplasms. In contrast, Bellini duct carcinomas, which are thought to arise from the collecting ducts within the renal medulla, are rare but often very aggressive. Medullary carcinoma has histopathologic and clinical features similar to those of Bellini duct carcinoma, but it is associated with sickle cell trait.

Clear cell tumors, the predominant histology, are found in >80% of patients who develop metastases. Clear cell tumors arise from the epithelial cells of the proximal tubules and usually show chromosome 3p deletions. Deletions of 3p21–26 (where the *VHL* gene maps) are identified in patients with familial as well as sporadic tumors. *VHL* encodes a tumor suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins. Inactivation of *VHL* leads to overexpression of

TABLE 81-1 Hereditary Renal Cell Tumors

SYNDROME	CHROMOSOME(S)	GENE	PROTEIN	KIDNEY TUMOR TYPE	ADDITIONAL FINDINGS
von Hippel-Lindau syndrome	3p25	*VHL*	von Hippel-Lindau protein	Clear cell	Hemangioblastoma of the retina and central nervous system; pheochromocytoma; pancreatic and renal cysts; neuroendocrine tumors
Hereditary papillary RCC	7p31	*MET*	MET	Papillary (type I)	
Hereditary leiomyomatosis and RCC	1q42	*FH*	Fumarate hydratase	Papillary (non–type I)	Leiomyoma; uterine leiomyoma/leiomyosarcoma
Birt-Hogg-Dubé syndrome	17p11	*FLCN*	Folliculin	Chromophobe, oncocytoma	Facial fibrofolliculoma; pulmonary cysts
Tuberous sclerosis	9q34 16p13	*TSC1* *TSC2*	Hamartin Tuberin	Angiomyolipomas; lymphangioleiomyomatosis; rare RCC with variety of histologic appearances	Angiofibroma, subungual fibroma; cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonary and renal cysts; cortical tuber; subependymal giant cell astrocytomas
Constitutional chromosome 3 translocations	3p13-14	Unknown	Unknown	Clear cell	

Abbreviation: RCC, renal cell carcinoma.

TABLE 81-2 Classification of Epithelial Neoplasms Arising from the Kidney

CARCINOMA TYPE	CHARACTERISTICS GROWTH PATTERN	CELL OF ORIGIN	CYTOGENETICS
Clear cell	Acinar or sarcomatoid	Proximal tubule	3p-, 5q+, 14q-
Papillary	Papillary or sarcomatoid	Proximal tubule	+7, +17, –Y
Chromophobe	Solid, tubular, or sarcomatoid	Distal tubules/cortical collecting duct	Whole arm losses (1, 2, 6, 10, 13, 17, and 21)
Oncocytic	Tumor nests	Cortical collecting duct	–1, –14, –Y; rearrangement involving 11q13; or normal karyotype
Collecting duct	Papillary or sarcomatoid	Medullary collecting duct	Variable or undetermined
MiTF Translocation[a]	Clear and papillary	Undetermined	Gene fusions involving Xp11 (*TFE3*) or t(6;11) (*MALAT1-TFEB*)

[a]Microphthalmia transcription factor gene family.

these agonists of the VEGF and PDGF receptors, which promote tumor angiogenesis and tumor growth. Agents that inhibit proangiogenic growth factor activity show antitumor effects. Enormous genetic variability has been documented in tumors within individual patients. Although the tumors have a clear clonal origin and often contain *VHL* mutations in common, different portions of the primary tumor and different metastatic sites may have wide variation in genetic lesions they contain. This tumor heterogeneity may underlie the emergence of treatment resistance.

While *VHL* is the gene most frequently mutated in clear cell renal cell carcinoma (52% of cases), other genes are implicated as well: *PBRM1* in 40% of cases, *SETD2* in 15% of cases, and *BAP1* in 15% of cases. These three genes, all part of the chromatin remodeling/histone methylation pathway, are also located within a 50-Mb region on the short arm of chromosome 3p. Mutations in *BAP1* have been linked to shorter survival in renal cancer. In a subset of clear cell renal cell carcinomas, alterations have been found in components of the mammalian target of rapamycin (mTOR) pathway, spurring the study of mTOR inhibitors in renal cancer.

Approximately 10% of renal cell carcinomas are of the papillary subtype, where the most common copy-number events are gain of chromosome 7 (where MET is located) and chromosome 17. Alterations in MET are associated with type I papillary renal cell carcinoma, whereas type II papillary tumors are characterized by NFR2-antioxidant response element alterations. In the chromophobe subtype, which comprises ≤5% of cases of renal cell carcinoma, two mutations have been noted: TP53 in 32% of cases and PTEN in 9%.

CLINICAL PRESENTATION

The presenting signs and symptoms include hematuria, flank or abdominal pain, and a flank or abdominal mass. Other symptoms are fever, weight loss, anemia, and a varicocele. The tumor is most commonly detected as an incidental finding on a radiograph. Widespread use of radiologic cross-sectional imaging procedures (computed tomography [CT], ultrasound, magnetic resonance imaging [MRI]) contributes to earlier detection, including incidental renal masses detected during evaluation for other medical conditions. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with renal cell carcinoma and increased use of nephron-sparing surgery (partial nephrectomy). A spectrum of paraneoplastic syndromes has been associated with these malignancies, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer's syndrome), and acquired dysfibrinogenemia. Erythrocytosis is noted at presentation in only ~3% of patients. Anemia, a sign of metastatic disease, is more common. Kidney cancer was called the "internist's tumor" since it was often discovered from the initial presentation of a paraneoplastic syndrome. This was more common before the era of modern imaging, as was initial presentation by the classic triad of hematuria, flank pain, and a palpable abdominal mass.

The standard evaluation of patients with suspected renal cell tumors includes a CT scan of the abdomen and pelvis, chest radiograph, urine analysis, and urine cytology. If metastatic disease is suspected from the chest radiograph, a CT of the chest is warranted. MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus, or when intravenous contrast administration given with CT is prohibited by impaired renal function. In clinical practice, any solid renal masses should be considered malignant until proven otherwise; a definitive diagnosis is required. If no metastases are demonstrated, surgery is indicated, even if the renal vein or inferior vena cava is invaded. The differential diagnosis of a renal mass includes cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other primary or metastatic cancers. Other malignancies that may involve the kidney include transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor. All of these are less common causes of renal masses than is renal cell cancer.

STAGING AND PROGNOSIS

Staging is based on the American Joint Committee on Cancer (AJCC) staging system **(Fig. 81-1)**. Stage I tumors are ≤7 cm in greatest diameter and confined to the kidney, stage II tumors are >7 cm and confined to the kidney, stage III tumors extend through the renal capsule but are confined to Gerota's fascia (IIIa) or involve a single hilar lymph node (N1), and stage IV disease includes tumors that have invaded adjacent organs or involve multiple lymph nodes or distant metastases. Sixty-five percent of patients present with stage I or II disease, 15–20% with stage III, and 15–20% with stage IV. The 5-year survival rate is currently 74% across all renal cell carcinomas, but it varies by stage: 81% for stage I, 74% for stage II, 53% for stage III, and 8% for stage IV.

Prognostic risk models are helpful for counseling patients, and for anticipating survival rates when designing a clinical trial. The most widely used prognostic model, developed by investigators at Memorial Sloan Kettering Cancer Center, incorporated five factors shown to correlate with worse survival in advanced renal cell carcinoma: poor performance status, high serum lactate dehydrogenase, high serum calcium, low hemoglobin concentration, and <1-year interval from diagnosis to treatment. Patients with zero risk factors had significantly longer median survival (30 months) than those with one or two risk factors (14 months) and those with three to five risk factors (5 months).

TREATMENT

Renal Cell Carcinoma

LOCALIZED TUMOR

The standard management for stage I or II tumors and selected cases of stage III disease is radical or partial nephrectomy. A radical nephrectomy involves en bloc removal of Gerota's fascia and its contents, including the kidney, the ipsilateral adrenal gland in some cases, and adjacent hilar lymph nodes. Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomy. The role of a regional lymphadenectomy is controversial. Extension into the renal vein or inferior vena cava (stage III disease) does not preclude resection even if cardiopulmonary bypass is required. If the tumor is resected, half of these patients have prolonged survival.

Nephron-sparing approaches via open or laparoscopic surgery may be appropriate for patients who have impaired renal function or only one kidney, depending on the size and location of the lesion. A nephron-sparing approach can also be used for patients

FIGURE 81-1 Renal cell carcinoma staging. TNM, tumor, node, metastasis.

with bilateral tumors. Partial nephrectomy techniques are applied electively to resect small masses for patients with a normal contralateral kidney. Radical nephrectomy can lead to an increased risk for chronic kidney disease and is associated with increased risks of cardiovascular morbidity and mortality. When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, and reduced frequency of late cardiovascular events.

Adjuvant therapy with interferon-α or radiation therapy following this surgery does not improve outcome, even in cases with a poor prognosis. Adjuvant trials with sunitinib, an orally administered antiangiogenesis inhibitor, do not consistently show a benefit in prolonging time to relapse following nephrectomy.

METASTATIC DISEASE

Surgery has a limited role for patients with metastatic disease. Long-term survival may occur in patients who relapse after nephrectomy in a solitary site that is removed. One indication for nephrectomy with metastases at initial presentation is to alleviate pain or hemorrhage of a primary tumor. Also, a cytoreductive nephrectomy before systemic treatment improves survival for carefully selected patients with stage IV tumors. The most common sites of distant metastases are the lungs, lymph nodes, liver, bone, and brain. These tumors may follow an unpredictable and protracted clinical course. It may be best to document progression before considering systemic treatment.

Radiation therapy is generally used for palliation of bone or brain metastases. The types of radiotherapy most commonly used are external beam therapy and stereotactic radiotherapy. In select cases, stereotactic ablative radiotherapy to a metastatic site may result in local control with relatively minimal toxicity.

Metastatic renal cell carcinoma is refractory to cytotoxic chemotherapy. Cytokine therapy with IL-2 or interferon-α produces regression in 10–15% of patients. IL-2 produces durable complete remission in a small proportion of cases. In general, cytokine therapy is considered unsatisfactory for most patients due to high levels of toxicity and the unpredictability of response.

The situation changed dramatically when two large-scale randomized trials established a role for antiangiogenic therapy, as predicted by the genetic studies. These trials separately evaluated two orally administered antiangiogenic agents, sorafenib and sunitinib, that inhibited receptor tyrosine kinase signaling through the VEGF and PDGF receptors. Both showed efficacy as second-line treatment following progression during cytokine treatment, resulting in approval by regulatory authorities for the treatment of metastatic renal cell carcinoma. A randomized phase III trial comparing sunitinib to interferon-α showed superior efficacy for sunitinib with an acceptable safety profile. This trial resulted in a change in the standard first-line treatment from interferon to sunitinib.

These were followed by eight new systemic agents for metastatic renal cell carcinoma **(Table 81-3)**: pazopanib, axitinib, cabozantinib, and lenvatinib, also tyrosine kinase inhibitors; the antiangiogenic bevacizumab that inhibits the VEGF ligand; the mTOR inhibitors temsirolimus and everolimus; and nivolumab that inhibits PD-1. While the improvements in 5-year renal cancer survival rates over the past decades (50% in the mid-1970s, 57% in the late 1980s, and 74% for 2005–2012) can be attributed to widespread imaging leading to earlier discovery of tumors, the new agents are likely playing a part as well.

Pazopanib was compared to sunitinib in a randomized first-line phase III trial. Efficacy was similar, and there was less fatigue and skin toxicity, resulting in better quality-of-life scores for pazopanib compared with sunitinib. Temsirolimus and everolimus show activity in patients with untreated poor-prognosis tumors and in sunitinib/sorafenib-refractory tumors. Patients benefit from the sequential use of axitinib and everolimus following progression with sunitinib or pazopanib first-line therapy. Nivolumab, cabozantinib, and lenvatinib plus everolimus were compared to everolimus in randomized trials and showed that patients lived longer with each of these agents compared to patients treated with everolimus.

Biomarkers are needed to select appropriate treatment for individual patients and to get quicker confirmation of whether treatment is working. However, though a number of predictive biomarker candidates have been tested in metastatic renal cell carcinoma patients receiving various systemic therapies, none have been validated for clinical use.

GLOBAL CONSIDERATIONS

Worldwide, ~340,000 patients are diagnosed every year with malignant tumors arising from the kidney, resulting in >140,000 deaths annually. Kidney cancer is the ninth most common cancer in men and the fourteenth most common cancer in women. Higher incidence is observed in developed countries, including the United States, Northern Europe, Eastern Europe, and Australia. Relatively low rates are reported in southeast Asia and Africa. The incidence of kidney cancer has been steadily increasing over the past four decades. Mortality trends have stabilized in Europe and the United States but not in less developed countries. This is likely related to access to and availability of optimal therapies. Treatment guidelines for both localized and metastatic renal cancer are similar between U.S. and European documents, and contingent on the access to adequate health care and availability of targeted drugs to treat metastases.

TABLE 81-3 Approved Systemic Therapies for Metastatic Renal Cell Carcinoma

CLASS	DRUG	FIRST FDA APPROVAL FOR RCC	ORIGINALLY APPROVED FOR	CURRENTLY USED FOR
Cytokines	High-dose interleukin-2[a]	1992	Advanced RCC	Advanced RCC first-line
	Interferon-α	2009	Advanced RCC, in combination with bevacizumab	Advanced RCC, in combination with bevacizumab first-line
Antiangiogenic: tyrosine kinase inhibitors	Sorafenib	2005	Advanced RCC second-line	Advanced RCC third-line or later
	Sunitinib	2006	Advanced RCC second-line	Advanced RCC first-line
	Pazopanib	2009	Advanced RCC first-line or after cytokine therapy	Advanced RCC first-line
	Axitinib	2012	Advanced RCC second-line	Advanced RCC second-line
	Cabozantinib	2016	Advanced RCC second-line	Advanced RCC second- or third-line
	Lenvatinib	2016	Advanced RCC second-line in combination with everolimus	Advanced RCC second- or third-line in combination with everolimus
Antiangiogenic: VEGF ligand antibody	Bevacizumab	2009	Advanced RCC first-line in combination with interferon-α	Advanced RCC first-line in combination with interferon-α
mTOR inhibitors	Temsirolimus[b]	2007	Advanced RCC	Advanced RCC with poor prognosis features first-line
	Everolimus	2009	Metastatic RCC second-line	Advanced RCC third-line or later
PD-1 inhibitor	Nivolumab	2015	Advanced RCC second-line	Advanced RCC second- or third-line

[a]Option only for patients with good performance status, no significant comorbidity, and access to medical centers experienced with this agent. [b]Option for poor-risk patients.

Abbreviations: FDA, Food and Drug Administration; mTOR, mammalian target of rapamycin; PD-1, programmed cell death-1; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

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82 Cancer of the Bladder and Urinary Tract

Noah M. Hahn

GLOBAL CONSIDERATIONS

Within the United States, urothelial carcinoma of the bladder and urinary tract are most closely related to tobacco smoking history. However, within developing countries water supplies contaminated with arsenic or schistosomiasis parasites also are major carcinogenic contributors.

INTRODUCTION

Cancers of the urinary tract including the bladder, renal pelvis, ureter, and urethra occur frequently, and they represent the second most common class of genitourinary cancers. Bladder cancer alone represents the fifth most common cancer diagnosis annually in the United States with >76,000 new cases and 16,000 deaths every year. Because cancers of the renal pelvis are often lumped in with all kidney cancers, the true incidence and mortality from nonbladder urinary tract cancers are less precise. While less frequent than bladder cancer, an additional 20,000 new cases and 5000 deaths are estimated every year. While significant advances in therapy options and improvements in patient outcomes have rapidly occurred in many cancers in the past decade, progress in urinary tract cancers has lagged. Fortunately, an accelerated understanding of the molecular underpinnings of bladder and urinary tract cancer biology has led to a significant increase in clinical trials with the first U.S. Food and Drug Administration (FDA) approval of a new drug for advanced bladder and urinary tract cancers in over 25 years with many more expected to follow. This chapter reviews the established, current, and emerging evidence that serves as the basis for the rapidly evolving standards of care for patients with bladder and urinary tract cancers.

CLINICAL EPIDEMIOLOGY AND RISK FACTORS

Bladder cancer typically affects older patients with a median age at diagnosis of 73 years. Males are four times more frequently affected than females. Similarly, bladder cancer is more common in Caucasians than in Asian patients. Singular inheritable genetic risk factors are rare in patients with bladder or urinary tract cancers. Patients with defects in mismatch repair genes leading to microsatellite instability (*MLH1, MSH2, MSH6*, etc.) as part of the familial cancer Lynch syndrome are at particular risk of upper urinary tract cancers of the renal pelvis and ureter. Additionally, patients with Cowden disease (*PTEN* mutations) or retinoblastoma (*RB1* mutations) are at increased risk for developing bladder cancer.

Historically, associations have existed between environmental toxic exposures and higher rates of developing bladder cancer. Carcinogenic agents associated with increased risk of bladder cancer have included the aromatic amines benzidine and beta-naphthylamine that can be present in industrial dyes as well as arsenic that can be found in some drinking water supplies in underdeveloped countries. Other chemicals in the leather, paint, rubber, textiles, and printing industries have been associated with bladder cancer. More recently, associations with exposures to hair dyes and hair sprays in workers in the hairstyling field have been suggested. Additionally, much concern has been raised regarding use of the antidiabetic medication, pioglitazone, and bladder cancer risk. Extensive review of population data by leading

bladder cancer experts has produced mixed associations. An association between chronic inflammatory states and the development of squamous bladder cancer clearly exists in underdeveloped countries in patients chronically infected with the parasitic disease schistosomiasis and in paraplegic patients with chronic indwelling catheters. Above and beyond each of these associations, however, smoking of tobacco products (cigarettes, cigars, pipes, etc.) has been and continues to remain the overwhelming leading risk factor for development of bladder cancer. Among new bladder cancer diagnoses, 90% of cases occur in current or former smokers. Toxicologists have estimated that over 70 confirmed carcinogenic toxins are present within tobacco smoke. It is estimated that one-third of bladder cancer cases could be prevented through simple modification of lifestyle choices, in particular cessation of smoking.

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP

Occasionally, patients will present with flank pain in association with an upper tract renal pelvis or ureter cancer or due to hydronephrosis in association with a bladder tumor obstructing the orifice of the ureter within the bladder. Only in rare cases do patients present with significant cachexia and widespread metastatic disease. For most patients, painless hematuria (either gross or microscopic) represents the initial manifestation of an underlying urinary tract cancer. In females, hematuria due to malignancy can often be mistaken for a urinary tract infection or menstrual bleeding. While treatment with antibiotics is warranted if a concurrent urinary tract infection is noted on initial urinalysis, persistent hematuria requires further workup. Painless hematuria in males is almost always abnormal and should be worked up. Initial investigations in patients of either sex should include urine cytology and visual examination of the bladder by cystoscopy. Cytology is successful in identifying cancer in only 50% of individuals with high-grade bladder cancers. In addition to urine cytology, radiographic evaluation of the kidneys and upper urinary tract by CT urogram should be performed. Because of the increased sensitivity and reduced IV contrast loads, CT urograms have largely replaced IV pyelograms as the preferred upper urinary tract imaging modality. A magnetic resonance (MR) urogram may be substituted in patients with poor renal function. Additional diagnostic testing of the urine to assess for cancer-associated chromosomal changes by fluorescent in situ hybridization, increased levels of nuclear mitotic proteins, increased bladder tumor–associated antigens, or higher levels of staining on cells shed by the bladder may identify some cancers missed by traditional cytology testing. However, they may also produce abnormal results in patients who do not have cancer. For now, these adjunct molecular tests are primarily utilized in detecting recurrent cancer in patients with a prior diagnosis of urinary tract cancer. Small tumors, particularly flat noninvasive tumors of the bladder, may be detected at higher rates with the use of blue light cystoscopy or narrow-band imaging cystoscopy. Both blue light and narrow-band imaging cystoscopies are now used routinely in the initial workup and subsequent monitoring of patients with bladder cancer. For patients with no bladder abnormalities in whom upper tract tumors are suspected, visualization of the upper urinary tracts and renal pelvises should be performed by ureteroscopy or retrograde pyelography.

In all patients with abnormalities noted in the bladder or upper urinary tracts, complete endoscopic resection for histologic diagnosis and staging should be performed when possible via either transurethral resection of bladder tumor (TURBT) or endoscopic resection of upper tract tumors.

HISTOLOGY

Urothelial carcinoma, formerly referred to as *transitional cell carcinoma*, is the most common urinary tract cancer histology that is observed in ~90% of cases. Squamous, glandular, micropapillary, plasmacytoid, sarcomatoid, and other variant features can often be found in portions of urothelial carcinoma tumors; however, pure variant histologies are rare. The presence of some variant histologies including micropapillary and plasmacytoid has been associated with worse surgical outcomes compared to urothelial carcinoma. Nonurothelial variant histologies including squamous cell carcinoma, adenocarcinoma, small-cell carcinoma, and carcinosarcoma collectively account for ≤10% of urinary tract tumors. Examples of traditional urothelial carcinoma and some of the variant histologies are shown in Fig. 82-1.

MOLECULAR BIOLOGY

Clinically, urothelial carcinoma of the bladder displays a biphasic phenotype characterized by (1) low-grade papillary tumors that frequently recur but rarely invade or metastasize and (2) high-grade sometimes flat tumors that invade early leading to lethal metastatic disease. In both of these phenotypes, loss of portions of chromosomes 9q and 9p by loss of heterozygosity analyses is an early molecular event, whose exact significance is not clear. Potential candidate regulatory genes in these

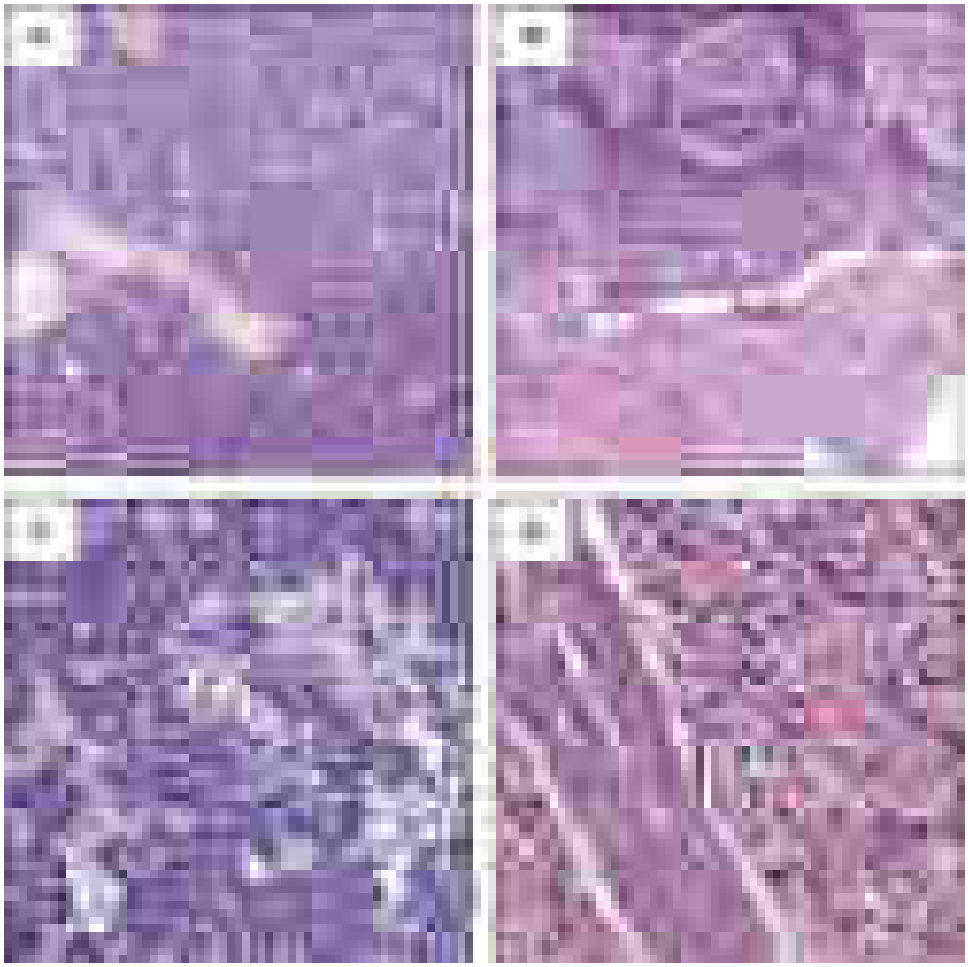

FIGURE 82-1 Bladder and urinary tract cancer histologies. ***A.*** Urothelial carcinoma; ***B.*** squamous cell carcinoma; ***C.*** small-cell carcinoma; ***D.*** plasmacytoid variant. *(Courtesy of Alex Baras, MD, PhD, Johns Hopkins University Department of Pathology.)*

genomic regions include *CDNK2A* and *TSC1*. Early investigations have demonstrated that low-grade tumors are characterized by alterations in the *RAS/RAF* signaling pathway with activating *FGFR3* mutations or gene fusions present in 60–80% of patients. In contrast, the high-grade invasive phenotype is notable for early deleterious mutations in *TP53* and *RB1*, alterations in *CDH1*, and increased expression of *VEGFR2*. In urothelial carcinoma of the renal pelvis and ureter, 10–20% of cases may be associated with Lynch syndrome hereditary defects in the *MLH1*, *MSH2*, *or MSH6* mismatch repair genes leading to microsatellite instability and frequent DNA mutations. Testing for germline mutations in these genes is recommended in patients with upper urinary tract urothelial carcinoma under the age of 60 at diagnosis, with a first-degree relative with a Lynch syndrome–associated cancer diagnosed under the age of 50, or with two first-degree relatives with a Lynch syndrome–associated cancer regardless of the age at diagnosis.

As genomic analysis technologies have improved, so has our understanding of the molecular biology unique to urothelial carcinoma. In 2014, the initial bladder cancer results of The Cancer Genome Atlas (TCGA) project were published. This effort comprehensively analyzed gene mutations, fusions, expression, copy number variations, methylation, and microRNA across the genome of patients with bladder urothelial carcinoma treated with surgery. While this data set will continue to be analyzed for years to come, the initial findings include (1) genomic alterations in genes (e.g., *FGFR3*, *EGFR*, *ERBB2*, *ERBB3*, *PIK3CA*, *TSC1*, etc.) targetable by currently approved drugs or drugs in development in 69% of patients; (2) genomic alterations in chromatin modifying genes (*KDM6A*, *MLL2*, *CREBBP*, *EP300*, etc.) in 89% of patients; (3) hypermethylation of tumor suppressor genes in 34% of patients; and (4) the identification by RNA sequencing of four distinct intrinsic molecular subtypes (luminal 1, luminal 2, basal 3, and basal 4) closely resembling luminal and basal subclassifications of breast cancers. These initial bladder TCGA findings have led to clinical trial designs enriching for patients with specific gene mutation profiles as well as interrogation of candidate biomarkers according to intrinsic molecular subtypes.

STAGING AND OUTCOMES BY STAGE

The staging of bladder cancer is dependent on the depth of invasion within the bladder wall, involvement of lymph nodes, and spread to surrounding and distant organs as depicted in Fig. 82-2. Approximately 75% of bladder cancer presents with non–muscle-invasive bladder cancer (NMIBC), 18% with disease invading into or through the muscular wall of the bladder, and only 3% presenting with metastatic spread to distant organs. NMIBC is defined by tumors that involve only the immediate epithelial layer of cells (carcinoma in situ [CIS] and Ta) or that only penetrate into the connective tissue below the urothelium (T1) but not into the muscular layer known as the *muscularis propria*. Muscle-invasive bladder cancer (MIBC) is defined by tumors that invade into the muscularis propria (T2), through the muscularis propria to involve the surrounding serosa (T3), or into immediately adjacent pelvic organs such as the rectum, prostate, vagina, or cervix (T4). Lymph node staging is classified according to involvement of a solitary node within the true pelvis (N1), multiple nodes involved in the true pelvis (N2), or involvement of the common iliac nodes (N3). Any disease that has spread beyond the true pelvis is considered metastatic (M1). The staging of bladder cancer is driven primarily by the T-stage of the tumor with stages 0a–III defined entirely by the T-stage in the absence of nodal or metastatic disease. Conversely, involvement of either nodal or distant metastases qualifies as stage IV disease. Clinical outcomes of patients with bladder cancer correlate closely with staging at diagnosis with 5-year overall survival rates of 80% for disease confined to the bladder (stage I–II), 35–50% for disease that penetrates through the bladder (stage III), and only 10–20% for disease extending to surrounding organs, lymph nodes, or metastatic sites (stage IV).

TREATMENT APPROACHES

Early-Stage Disease For NMIBC, removal of all visible tumors by TURBT in the operating room is considered the mainstay of surgical treatment. Risk of recurrence can be classified as low, intermediate, or high depending on the presence of features summarized in Table 82-1. For patients with low-risk disease meta-analyses have demonstrated a 12% reduction in early relapses when a single chemotherapy treatment of mitomycin C, epirubicin, or gemcitabine was instilled directly into the bladder (intravesical therapy) within 24 hours of the TURBT. For patients with intermediate- or high-risk tumors, weekly intravesical instillations for 6 consecutive weeks of the attenuated mycobacterium strain known as *Bacille-Calmette Guerin* (BCG) reduce the risk of recurrence at 12 months from 56 to 29%. In addition, BCG treatment has been shown to decrease the rate of progression to MIBC by 27%. Intravesical BCG is generally well tolerated. Side effects can include dysuria, urinary frequency, bladder spasms, hematuria, and, in rare cases (<5%), a systemic inflammatory response that can mimic disseminated BCG infection. Following a 6-week induction BCG schedule, additional maintenance BCG treatments given according to the Southwest Oncology Group schedule further reduce the risk of recurrent NMIBC compared to induction BCG alone. In patients with

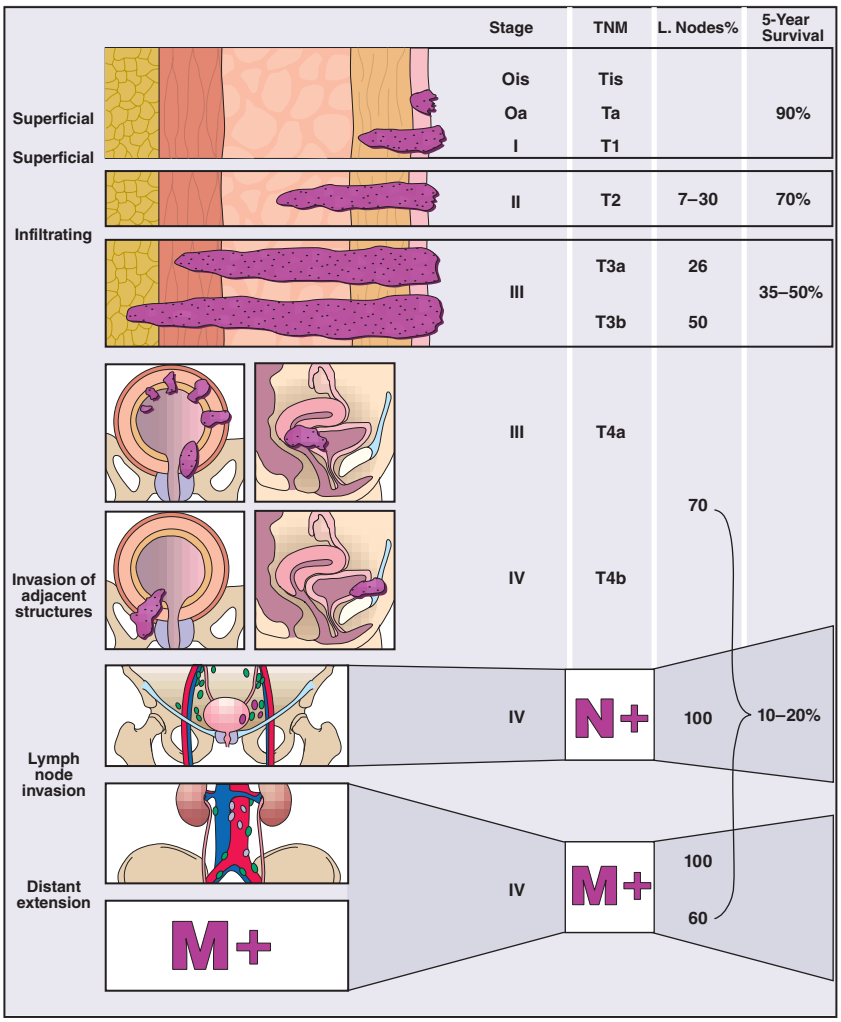

FIGURE 82-2 Bladder cancer staging. TNM, tumor, node metastasis. *(Reprinted with permission from HI Scher, JE Rosenberg, RJ Motzer: Bladder and renal cell carcinomas, in DL Kasper et al [eds]: Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill, Chap. 114, 2015.)*

TABLE 82-1 Non–Muscle-Invasive Bladder Cancer Recurrence Risk Groups

RISK GROUP	CHARACTERISTICS
Low risk	Initial tumor, solitary tumor, low grade, <3 cm, no CIS
Intermediate risk	All tumors not defined in the two adjacent categories (between the category of low and high risk)
High risk	Any of the following: • T1 tumor • High-grade • CIS • Multiple and recurrent and large (>3 cm) Ta low-grade tumors (all conditions must be met for this point on Ta low-grade tumors)

Abbreviation: CIS, carcinoma in situ.

NMIBC that recurs long after initial BCG treatment, a repeat course of BCG can be considered. For patients with recurrence after a second induction course of BCG or with relapsed NMIBC within 6 months of initial BCG exposure, surgical removal of the entire bladder by cystectomy is recommended due to the high risk of progression to MIBC and potentially metastatic disease. For patients who are not fit enough for or who refuse cystectomy, non-BCG alternative intravesical agents (mitomycin C, gemcitabine, docetaxel, valrubicin) can achieve temporary tumor responses.

In patients with urothelial carcinoma of the renal pelvis or ureter, endoscopic tissue acquisition and staging are more challenging than primary tumors located in the bladder. Tumors possessing all of the following are considered low risk: solitary tumor, low grade, size <1 cm, no invasive component on imaging. Low-risk tumors can successfully be treated by laser ureteroscopic ablation or surgical resection and reanastomosis of the remaining ureter ends in tumors that cannot be successfully eradicated endoscopically.

Muscle-Invasive Disease In patients with urothelial carcinoma of the bladder that invades into or through the muscularis propria but with no evidence of metastatic spread, more aggressive therapy options summarized in Table 82-2 are required to achieve cure. In carefully selected patients with no evidence of CIS or hydronephrosis, bladder-sparing combined modality therapy with concurrent chemotherapy and radiation can achieve cure in ~65% of patients. Various chemotherapy regimens have been utilized in combination with radiation including cisplatin, carboplatin, 5-fluorouracil, mitomycin C, paclitaxel, and gemcitabine. It is important to note that a maximal debulking of all visible tumor by TURBT is required prior to initiation of combined modality therapy. In patients who achieve a complete response to combined modality therapy, regular cystoscopic monitoring of the bladder is required with salvage cystectomy offered to patients who develop MIBC in follow-up.

TABLE 82-2 Treatment Approaches to MIBC Patients

TREATMENT	PATIENT SELECTION	CLINICAL OUTCOMES
Bladder-sparing chemoradiation	No CIS, no hydronephrosis, maximal TURBT required	65% cure, 55% bladder intact, highly dependent on patient selection
Bladder-sparing partial cystectomy	Solitary tumors in dome of bladder are ideal	Variable, highly dependent on patient selection
Cystectomy	Any MIBC patient	50% cure with surgery alone, highly dependent on pathologic stage
Neoadjuvant cisplatin-based chemotherapy	Cisplatin-eligible MIBC patients	5–10% improvement in overall survival compared to cystectomy alone
Adjuvant cisplatin-based chemotherapy	Cisplatin-eligible high-risk postcystectomy MIBC patients (pT3-4, N+)	Similar improvement as neoadjuvant treatment, data less robust, many patients not suitable for adjuvant treatment

Abbreviations: CIS, carcinoma in situ; MIBC, muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor.

In a similar fashion, bladder-sparing partial cystectomy can be performed in a very small subset of MIBC patients. The ideal patient for partial cystectomy is the patient with a solitary, clinical T2 urothelial carcinoma in the dome of the bladder. In such patients, the tumor and immediate surrounding urothelium can be resected with reconstruction of the remaining bladder to maintain near physiologic urinary function.

In the majority of patients, however, resection of the entire bladder is required. In males, a cystoprostatectomy with removal of the bladder, prostate, and pelvic lymph nodes is performed while in females an anterior exenteration with removal of the bladder, uterus, ovaries, cervix, and pelvic lymph nodes is performed. With the bladder removed, three options exist to re-route the urine outflow. In an ileostomy, the bilateral ureters are connected to a portion of ileum that is brought through an incision in the abdominal wall to create a stoma that drains urine into an affixed bag outside of the body. In a continent urinary reservoir or "Indiana pouch," the ureters are connected to a portion of ileum that has been separated on both ends from the rest of the small bowel transit to form a urinary reservoir. The remaining small bowel is reanastomosed, and the urinary reservoir is brought up just beneath the abdominal wall muscles with patients catheterizing the urinary reservoir several times per day via a small stoma tract. Last, in a neobladder, the same urinary reservoir described previously is brought down into the pelvis and is anastomosed to the remaining urethra to provide the opportunity to the patient to void urine through the urethra. The choice of which urinary reconstruction to perform is affected not only by patient choice but also by anatomic tumor considerations and urologist experience with each procedure. Regardless of the type of surgery performed, all patients undergo a significant catabolic change in their metabolism following removal of the bladder. While many MIBC patients are affected by weight loss preoperatively, it is not uncommon for postcystectomy patients to lose an additional 10–15 lb in the first month postoperatively. In addition, patients can experience long-term nutritional changes such as low B_{12} levels due to alterations in small bowel physiology caused by all of the urinary diversion options.

Despite aggressive surgery, only half of patients undergoing cystectomy are cured by surgery alone. Therefore, many clinical trials have investigated the role of systemic chemotherapy before (neoadjuvant) or after (adjuvant) surgery. Meta-analyses have shown a 5–10% absolute overall survival advantage when combination chemotherapy regimens utilizing cisplatin have been used before surgery. A similar benefit exists with cisplatin-based combination chemotherapy given after surgery. However, the data in the adjuvant setting are based on smaller, older trials. Furthermore, in the postoperative setting, some patients may not recover sufficiently from their surgery within a time frame optimal for chemotherapy administration. Importantly, non–cisplatin-containing chemotherapy regimens have proven inferior to cisplatin-containing regimens. Therefore, if patients are not suitable candidates for cisplatin administration due to poor functional status or comorbidities (e.g., poor renal function), patients should proceed directly to surgery and forego neoadjuvant therapy.

For patients with high-risk urothelial carcinoma of the upper urinary tract, resection of the kidney and ureter (including the ureter bladder cuff) by nephroureterectomy is preferred. Segmental ureterectomy may be appropriate in patients with decreased renal function in which nephron-sparing outcomes are critical to prevent the need for dialysis. Similarly, in CIS patients, administration of BCG therapy via a nephrostomy tube can be considered to preserve intact renal function. In retrospective series, the use of cisplatin-based neoadjuvant chemotherapy has been associated with a pathologic complete response at surgery of 14% in upper tract urothelial carcinoma patients. While adjuvant chemotherapy can be considered in patients with locally advanced stages (T3, T4, or node positive), due to the removal of a kidney at surgery and subsequent associated drop in renal function, many postoperative upper tract patients cannot receive cisplatin-based regimens.

Metastatic Disease For patients with metastatic urothelial carcinoma regardless of primary tumor origin, systemic chemotherapy is

the most established standard of care. In a randomized phase 3 clinical trial, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) demonstrated an improvement in median overall survival from 8.2 to 12.5 months compared to single-agent cisplatin. In a head-to-head randomized phase 3 clinical trial, the combination of cisplatin and gemcitabine (CG) demonstrated similar overall survival compared to MVAC with a more favorable side-effect profile. Since 2000, treatment with either MVAC or CG has remained the standard for first-line treatment of patients with metastatic urothelial carcinoma with adequate renal function and functional status suitable for cisplatin therapy. For patients with lymph node only metastases and good functional status, cure is achieved in 15–20% of such patients. Unfortunately, only ~5% of metastatic patients fulfill both these criteria. For most patients, chemotherapy may prolong survival, but disease resistance proving lethal eventually develops. Furthermore, approximately half of patients with urothelial carcinoma have renal insufficiency, comorbidities, or frail functional status, and are not candidates for cisplatin treatment. In cisplatin-ineligible patients, carboplatin-based chemotherapy regimens are most often used with median overall survival rates decreased to 9.3 months.

Following front-line chemotherapy treatment, second-line chemotherapy regimens have shown modest 10–20% response rates, but no overall survival benefit. In recent years, exponential development of novel immunotherapy approaches has occurred for patients with urothelial carcinoma. The immune checkpoint targets programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have demonstrated the most encouraging clinical benefits. In normal physiology, PD-1/PD-L1 are upregulated in response to inflammation to dampen and prevent an overactive inflammatory response. In cancers including urothelial carcinoma, however, PD-1/PD-L1 are often upregulated on the tumor surface or immune cells in the tumor microenvironment. Upregulated PD-1/PD-L1 in this situation serves as a mechanism of immune escape that facilitates tumor growth. Atezolizumab (an anti–PD-L1 antibody) was the first drug approved in the United States for metastatic urothelial carcinoma in over two decades based on a response rate of 15% in postplatinum patients. Subsequently, pembrolizumab (an anti–PD-1 antibody) demonstrated an improvement in overall survival from 7.4 to 10.3 months compared to standard second-line chemotherapy options. Multiple other PD-1/PD-L1 agents have demonstrated clinical responses in urothelial carcinoma. In addition, clinical trials investigating immunotherapy, chemotherapy, and radiation combinations are ongoing. Last, leveraging the molecular knowledge gained from the TCGA project, clinical trials are also investigating the role of molecularly targeted therapies in patients with metastatic urothelial carcinoma harboring specific genetic alterations predictive of clinical benefit (e.g., activating *FGFR3* mutations or gene fusions). Collectively, these new emerging options for metastatic urothelial carcinoma patients offer hope for improved outcomes for patients with urothelial carcinoma of all stages in the future.

FURTHER READING

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83 Benign and Malignant Diseases of the Prostate

Howard I. Scher, James A. Eastham

Benign and malignant changes in the prostate increase with age. Autopsies of men in the eighth decade of life show hyperplastic changes in >90% and malignant changes in >70% of individuals. The high prevalence of these diseases among the elderly, who often have competing causes of morbidity and mortality, mandates a risk-adapted approach to diagnosis and treatment. This can be achieved by considering these diseases as a series of states. Each state represents a distinct clinical milestone for which therapy(ies) may be recommended based on disease extent, current symptoms, the risk of developing symptoms, or the risk of death from disease in relation to death from other causes within a given time frame. For benign proliferative disorders, symptoms of urinary frequency, infection, and potential for obstruction are weighed against the side effects and complications of medical or surgical intervention. For prostate malignancies, the likelihood that a clinically significant cancer is present in the gland and the concomitant risk of symptoms or death from cancer are balanced against the morbidities of the recommended treatments and preexisting comorbidities.

ANATOMY AND PATHOLOGY

The prostate is located in the pelvis and is surrounded by the rectum, the bladder, the periprostatic and dorsal vein complexes and neurovascular bundles that are responsible for erectile function, and the urinary sphincter that is responsible for passive urinary control. The prostate is composed of branching tubuloalveolar glands arranged in lobules surrounded by fibromuscular stroma. The acinar unit includes an epithelial compartment made up of epithelial, basal, and neuroendocrine cells and separated by a basement membrane, and a stromal compartment that includes fibroblasts and smooth-muscle cells. Prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) are produced in the epithelial cells. Both prostate epithelial cells and stromal cells express androgen receptors (ARs) and depend on androgens for growth. Testosterone, the major circulating androgen, is converted by the enzyme 5α-reductase to dihydrotestosterone in the gland.

The periurethral portion of the gland increases in size during puberty and after the age of 55 years due to the growth of nonmalignant cells in the transition zone of the prostate that surrounds the urethra. Most cancers develop in the peripheral zone, and cancers in this location may be palpated during a digital rectal examination (DRE).

PROSTATE CANCER

In 2017, ~161,360 prostate cancer cases were diagnosed and 26,730 men died from prostate cancer in the United States. The absolute number of prostate cancer deaths has decreased in the past 10 years, attributed by some to the widespread use of PSA-based detection strategies. However, the paradox of management is that although 1 in 6 men will eventually be diagnosed with prostate cancer, and the disease remains the second leading cause of cancer deaths in men, only 1 man in 30 with prostate cancer will die of his disease.

EPIDEMIOLOGY

Epidemiologic studies show that the risk of being diagnosed with prostate cancer increases 2.5-fold if one first-degree relative is affected and fivefold if two or more are affected. Current estimates are that 40% of early-onset and 5–10% of all prostate cancers are hereditary. Prostate cancer affects ethnic groups differently. Matched for age, African-American males have a higher incidence and present at a more advanced stage with higher-grade, more aggressive tumors. A high risk in families has been linked to the HPC1 (hereditary prostate cancer 1) susceptibility locus in *RNASEL*. Genome-wide association studies (GWAS) have identified >40 prostate cancer susceptibility loci that are estimated to explain up to 25% of prostate cancer risk. Among

the genes implicated in variations in incidence and outcome are single-nucleotide polymorphisms (SNPs) in the vitamin D receptor in African-Americans and variants in the AR, CYP3A4, both involved in the deactivation of testosterone, as well as CYP17, which is involved in steroid biosynthesis.

The prevalence of autopsy-detected cancers is similar around the world, while the incidence of clinical disease varies. Thus, environmental and dietary factors may play a role in prostate cancer growth and progression. High consumption of dietary fats, such as α-linoleic acid or polycyclic aromatic hydrocarbons that form when red meats are cooked, is believed to increase risk. Similar to breast cancer in Asian women, the risk of prostate cancer in Asian men increases when they move to Western environments. Protective factors include consumption of the isoflavonoid genistein (which inhibits 5α-reductase), cruciferous vegetables with isothiocyanate sulforaphane, lycopene found in tomatoes, and inhibitors of cholesterol biosynthesis (e.g., statin drugs). The development of prostate cancer is a multistep process. One early change is hypermethylation of the GSTP1 gene promoter, which leads to loss of function of a gene that detoxifies carcinogens. The finding that many prostate cancers develop adjacent to a lesion termed PIA (proliferative inflammatory atrophy) suggests a role for inflammation. Not smoking, regular exercise, and maintaining a healthy body weight may reduce the risk of progression.

DIAGNOSIS AND TREATMENT BY CLINICAL STATE

The prostate cancer continuum—from the appearance of a preneoplastic and invasive lesion that is localized to the gland, to a metastatic lesion causing symptoms and, ultimately, mortality—can span decades. To limit overdiagnosis of clinically insignificant cancers, and for disease management in general, competing risks are considered in the context of a series of clinical states **(Fig. 83-1)**. The states are defined operationally on the basis of whether or not a cancer diagnosis has been established and, for those with a diagnosis, whether or not metastases are detectable on imaging studies and the measured level of testosterone in the blood. With this approach, an individual resides in only one state and remains in that state until he has progressed. At each assessment, the decision to offer treatment and the specific form of treatment are based on the risk posed by the cancer relative to competing causes of morbidity and mortality that may be present in that individual. It follows that the more advanced the disease, the greater the need for treatment.

For those without a cancer diagnosis, the decision to undergo testing to detect a cancer is based on the individual's estimated life expectancy and, separately, the probability that a clinically significant cancer may be present. For those with a prostate cancer diagnosis, the clinical states model considers the probability of developing symptoms or dying from the disease. Thus, a patient with localized tumor that has been surgically removed remains in the state of localized disease as long as the PSA remains undetectable. The time within a state then becomes a measure of the efficacy of an intervention, though the effect may not be assessable for years. Because many men with active cancer are not at risk for developing metastases, symptoms, or death, the clinical states model allows a distinction between *cure*—the elimination of all cancer cells, the primary therapeutic objective of treatment for most cancers—and *cancer control*, by which the tempo of the illness is determined to be so slow or has been altered to the point where it is unlikely to cause symptoms, to metastasize, or to shorten a patient's life expectancy. Importantly, from a patient standpoint, both outcomes can be considered equivalent therapeutically, assuming the patient has not experienced symptoms of the disease or the treatment needed to control it. Even when a recurrence is documented, immediate therapy is not always necessary. Rather, as at the time of diagnosis, the need for intervention is based on the tempo of the illness as it unfolds in the individual, relative to the risk-to-benefit ratio of the intervention being considered.

NO CANCER DIAGNOSIS

Prevention No agent is currently approved for the prevention of prostate cancer. The results from several large double-blind, randomized chemoprevention trials have established 5α-reductase inhibitors (5ARI) as the predominant therapy to reduce the future risk of a prostate cancer diagnosis. The Prostate Cancer Prevention Trial (PCPT), in which men aged >55 years received placebo or the 5ARI finasteride, which inhibits the type 1 isoform, showed a 25% (95% confidence interval 19–31%) reduction in prostate cancer incidence from 24% with placebo to 18% with finasteride. In REDUCE (Reduction by Dutasteride of Prostate Cancer Events trial), a reduction in incidence from 25% with placebo to 20% with dutasteride was found ($p = 0.001$). Dutasteride inhibits both the type 1 and type 2 5ARI isoforms. While both studies met their endpoint, there was concern that most of the cancers that were prevented were low-risk and that there was a slightly higher rate of clinically significant cancers (those with higher Gleason score) in the treatment arm. Neither drug is approved for prostate cancer prevention. In comparison, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which enrolled African-American men aged ≥50 years and others aged ≥55 years, showed no difference in cancer incidence in patients receiving vitamin E (4.6%) or selenium (4.9%) alone or in combination (4.6%) relative to placebo (4.4%). A similar lack of benefit for vitamin E, vitamin C, and selenium was seen in the Physicians Health Study II.

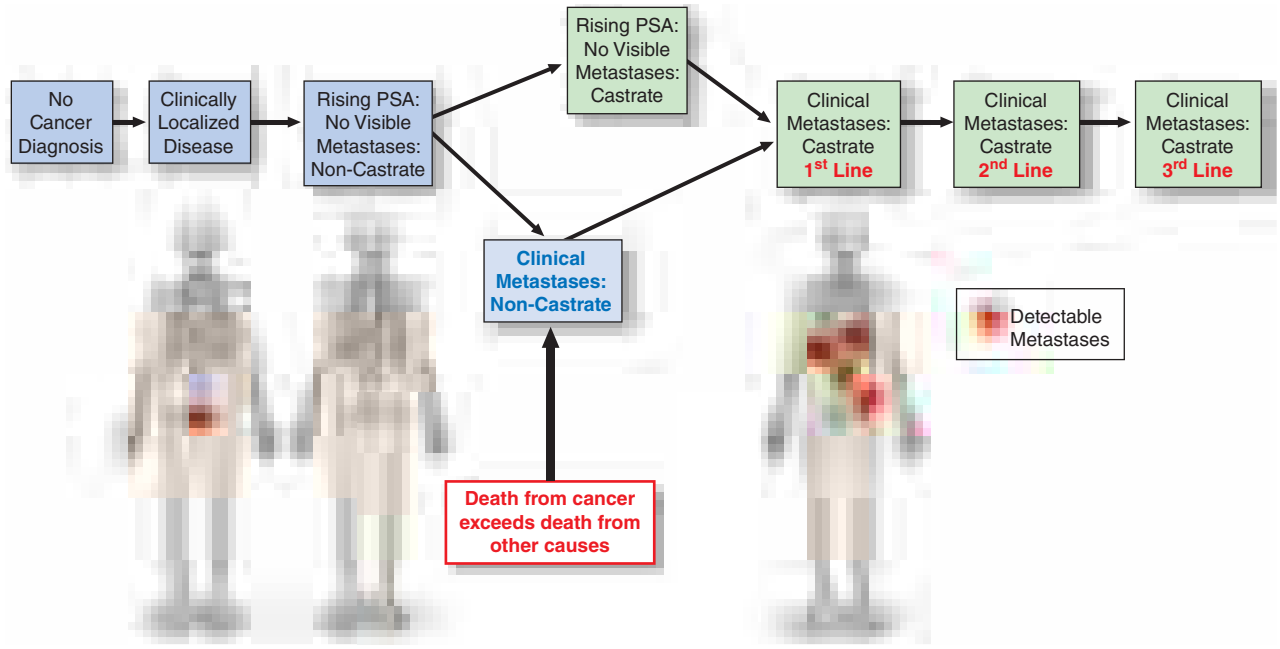

FIGURE 83-1 Clinical states of prostate cancer. PSA, prostate-specific antigen.

Screening/Early Detection and Diagnosis The need to pursue a diagnosis of prostate cancer must balance the benefit from detecting and treating clinically significant cancers that, left untreated, would adversely affect patients' quality and duration of life against the morbidity associated with overdiagnosis and overtreatment of clinically insignificant cancers that are highly prevalent in the general population. The balance is best approached through shared decision making between the patient and physician. Considerations for whether to pursue a diagnosis include symptoms, an abnormal DRE, or more typically, a change in or an elevated serum PSA. Genetic risk is also considered. The urologic history should focus on symptoms of outlet obstruction, continence, potency, or change in ejaculatory pattern.

PHYSICAL EXAMINATION The DRE focuses on prostate size and consistency and abnormalities within or beyond the gland. Many cancers occur in the peripheral zone and may be palpated on DRE. Carcinomas are characteristically hard, nodular, and irregular, while induration may also be due to benign prostatic hyperplasia (BPH) or calculi. Overall, 20–25% of men with an abnormal DRE have prostate cancer.

PROSTATE-SPECIFIC ANTIGEN PSA (kallikrein-related peptidase 3; *KLK3*) is a kallikrein-related serine protease that causes liquefaction of seminal coagulum. It is produced by both nonmalignant and malignant epithelial cells and, as such, is prostate-specific, not prostate cancer–specific. Serum levels may also increase from prostatitis and BPH. Serum levels are not significantly affected by DRE, but the performance of a cystoscopy or prostate biopsy can increase PSA levels up to tenfold for 8–10 weeks. PSA circulating in the blood is inactive and mainly occurs as a complex with the protease inhibitor α_1-antichymotrypsin and as free (unbound) PSA forms. The formation of complexes between PSA, α_2-macroglobulin, or other protease inhibitors is less significant. Free PSA is rapidly eliminated from the blood by glomerular filtration with an estimated half-life of 12–18 h. Elimination of PSA bound to α_1-antichymotrypsin is slow (estimated half-life of 1–2 weeks) as it too is largely cleared by the kidneys. Levels should be undetectable after about 6 weeks if the prostate has been completely removed (radical prostatectomy). Immunohistochemical staining for PSA can be used to establish a prostate cancer diagnosis.

PSA testing was approved by the U.S. Food and Drug Administration (FDA) in 1994 for early detection of prostate cancer, and the widespread use of the test has played a significant role in the proportion of men diagnosed with early-stage cancers: more than 70–80% of newly diagnosed cancers are clinically organ confined. The level of PSA in blood is strongly associated with the risk and outcome of prostate cancer. A single PSA measured at age 60 is associated (area under the curve [AUC] of 0.90) with lifetime risk of death from prostate cancer. Most (90%) prostate cancer deaths occur among men with PSA levels in the top quartile (>2 ng/mL), although only a minority of men with PSA >2 ng/mL will develop lethal prostate cancer. Despite this and mortality rate reductions reported from large randomized prostate cancer screening trials, routine use of the test remains controversial.

In 2012, the United States Preventive Services Task Force (USPSTF) published a review of the evidence for PSA-based screening for prostate cancer and made a clear recommendation against screening. By giving a grade of "D" in the recommendation statement that was based on this review, the USPSTF concluded that "there is moderate or high certainty that this service has no net benefit or that the harms outweigh the benefits." In 2013, the American Urological Association (AUA) updated their consensus statement regarding prostate cancer screening. They concluded that the quality of evidence for the benefits of screening was moderate for men aged 55–69 years. For men outside this age range, evidence was lacking for benefit, but the harms of screening, including overdiagnosis and overtreatment, remained. The AUA recommends shared decision-making for men aged 55–69 years considering PSA-based screening, a target age group for whom benefits may outweigh harms. Outside this age range, PSA-based screening as a routine was not recommended. The entire guideline is available at *http://www.auanet.org/guidelines/early-detection-of-prostate-cancer-(2013-reviewed-and-validity-confirmed-2015)*. As of 2017, the USPSTF has issued a draft of a revised recommendation with a grade of "C" for PSA-based prostate cancer screening for men aged 55–69. They recommend shared decision-making for men aged 55–69 and do not recommend screening for men aged ≥70; this is now roughly in agreement with the 2013 AUA guideline. The USPSTF notes that the increased use of active surveillance (observation with selective delayed treatment) for low-risk prostate cancer has reduced the risks of screening.

We believe that implementation of the following three guidelines will further improve PSA screening outcomes in the United States and will have a greater practical impact on men's health than the USPSTF and AUA recommendations that are based almost solely on age. First, avoid PSA tests in men with little to gain. There is no rationale for recommending PSA screening in asymptomatic men with a short life expectancy. Hence, men aged >75 years should only be tested in special circumstances, such as higher than median PSAs measured before age 70 or excellent overall health. In addition, because a baseline PSA is a strong predictor of the future risk of lethal prostate cancer, men with low PSAs, for example <1 ng/mL, can undergo testing less frequently, perhaps every 5 years, with screening possibly ending at age 60 if the PSA remains at ≤1 ng/mL. Men with PSAs that are above age median but below biopsy thresholds can be counseled about their elevated risk and actively encouraged to return for regular screening and more comprehensive risk assessment. Second, do not treat those who do not need treatment. High proportions of men with screen-detected prostate cancer do not need immediate treatment and can be managed by active surveillance. Third, refer men who do need treatment to high-volume centers. Although it is clearly not feasible to restrict treatment exclusively to high-volume centers, shifting treatment trends so that more patients are treated at such centers by high-volume providers will improve cancer control and decrease complications. The goal of prostate cancer screening should be to maximize the benefits of PSA testing and minimize its harms. Following the three rules outlined here should continue to improve the ratio of harms to benefits from PSA screening.

The PSA criteria used to recommend a diagnostic prostate biopsy have evolved over time. However, based on the commonly used cut-point for prostate biopsy (a total PSA ≥4 ng/mL), most men with a PSA elevation do not have histologic evidence of prostate cancer at biopsy. In addition, many men with PSA levels below this cut-point harbor cancer cells in their prostate. Information from the Prostate Cancer Prevention Trial demonstrates that there is no PSA below which the risk of prostate cancer is zero. Thus, the PSA level establishes the likelihood that a man will harbor cancer if he undergoes a prostate biopsy. The goal is to increase the sensitivity of the test for younger men more likely to die of the disease and to reduce the frequency of detecting cancers of low malignant potential in elderly men more likely to die of other causes. Patients with symptomatic prostatitis should have a course of antibiotics before biopsy. However, the routine use of antibiotics in an asymptomatic man with an elevated PSA level is strongly discouraged.

SECOND-LINE SCREENING TESTS The 4Kscore® Test (OPKO Lab, Nashville, TN) measures four prostate-specific kallikreins (total PSA, free PSA, intact PSA, and human kallikrein 2). The results are combined with clinical information in an algorithm that estimates an individual's percent risk of being found to harbor an aggressive prostate cancer should that individual opt for a prostate biopsy. The 4Kscore test has also been shown to identify the likelihood than an individual will develop aggressive prostate cancer, defined as high grade prostate cancer pathology and/or poor prostate cancer clinical outcomes, within 20 years.

Prostate Health Index (PHI™, Innovative Diagnostic Laboratory, Richmond, VA) is a blood test that estimates the risk of having prostate cancer. The PHI test is a combination of the free PSA, total PSA, and the [-2]proPSA isoform of free PSA. These three tests are combined in a formula that calculates the PHI score. The PHI score is a better predictor of prostate cancer than the total PSA test alone or the free PSA test alone.

PROSTATE BIOPSY A diagnosis of cancer is established by an image-guided needle biopsy. Direct visualization by transrectal ultrasound (TRUS), magnetic resonance imaging (MRI), or fusion of the ultrasound and MRI images ensures that all areas of the gland including suspicious areas are sampled. Contemporary schemas advise an extended-pattern 12-core biopsy that includes sampling from the peripheral zone as

well as a lesion-directed palpable nodule or suspicious image-guided sampling. Because a prostate biopsy is subject to sampling error, men with an abnormal PSA and negative biopsy are frequently advised to undergo additional testing which may include a 4Kscore Test, PHI, prostate MRI, and/or repeat biopsy.

PATHOLOGY Each core of the biopsy is examined for the presence of cancer, and the amount of cancer is quantified based on the length of the cancer within the core and the percentage of the core involved. Of the cancers identified, >95% are adenocarcinomas; the rest are squamous or transitional cell tumors or, rarely, carcinosarcomas. Metastases to the prostate are rare, but in some cases colon cancers or transitional cell tumors of the bladder invade the gland by direct extension.

When prostate cancer is diagnosed, a measure of histologic aggressiveness is assigned using the *Gleason grading system*, in which the dominant and secondary glandular histologic patterns are scored from 1 (well-differentiated) to 5 (undifferentiated) and summed to give a total score of 2–10 for each tumor. The most poorly differentiated area of tumor (i.e., the area with the highest histologic grade) often determines biologic behavior. The presence or absence of perineural invasion and extracapsular spread are also recorded.

Over the years, the Gleason grading system has undergone several changes. Currently, Gleason total scores 2–5 are no longer assigned and in practice the lowest total score is now assigned a 6, although the scale continues to range from 2 to 10. This leads to a logical yet incorrect assumption on the part of patients that their Gleason 6 cancer is in the middle of the scale, triggering the fear that their cancer is serious and the assumption that treatment is necessary despite Gleason score 6 actually being favorable risk. To address these issues, a new 5-grade group system has been developed:

Grade Group 1 (Gleason score ≤6)
Grade Group 2 (Gleason score 3+4 = 7)
Grade Group 3 (Gleason score 4+3 = 7)
Grade Group 4 (Gleason score 4+4 = 8)
Grade Group 5 (Gleason scores 9 and 10)

The new system simplifies the grading of prostate cancer, appropriately classifies the lowest risk as Grade Group 1 (rather than Gleason score 6), and accurately predicts prognosis.

PROSTATE CANCER STAGING The TNM (tumor, nodes, metastasis) staging system includes categories for cancers that are identified solely on the basis of an abnormal PSA (T1c), those that are palpable but clinically confined to the gland (T2), and those that have extended outside the gland (T3 and T4) **(Table 83-1, Fig. 83-2)**. DRE alone is inaccurate in determining the extent of disease within the gland, the presence or absence of capsular invasion, involvement of seminal vesicles, and extension of disease to lymph nodes. Because of the inadequacy of DRE for staging, the TNM staging system was modified to include the results of imaging. Unfortunately, no single test has proven to accurately indicate the stage or the presence of organ-confined disease, seminal vesicle involvement, or lymph node spread.

TRUS is the imaging technique most frequently used to assess the primary tumor, but its chief use is directing prostate biopsies, not staging. No TRUS finding consistently indicates cancer with certainty. Computed tomography (CT) lacks sensitivity and specificity to detect extraprostatic extension and is inferior to MRI in visualization of lymph nodes. In general, MRI is superior to CT to detect cancer in the prostate and to assess local disease extent. T1-weighted MRI produces a high signal in the periprostatic fat, periprostatic venous plexus, perivesicular tissues, lymph nodes, and bone marrow. T2-weighted MRI demonstrates the internal architecture of the prostate and seminal vesicles. Most cancers have a low signal, while the normal peripheral zone has a high signal, although the technique lacks sensitivity and specificity. MRI is also useful for the planning of surgery and radiation therapy.

Radionuclide bone scans (bone scintigraphy) are used to evaluate spread to osseous sites. This test is sensitive but relatively nonspecific because areas of increased uptake are not always related to metastatic disease. Healing fractures, arthritis, Paget's disease, and other conditions will also cause abnormal uptake. True-positive bone scans are uncommon when the PSA is <10 ng/mL unless the tumor is high-grade.

TABLE 83-1 TNM Classification

TNM (tumor, nodes, metastasis) Staging System for Prostate Cancer[a]	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Localized Disease	
T1	Clinically inapparent tumor, neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in ≤5% of resected tissue; not palpable
T1b	Tumor incidental histologic finding in >5% of resected tissue
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate[b]
T2a	Tumor involves half of one lobe or less
T2b	Tumor involves more than one half of one lobe, not both lobes
T2c	Tumor involves both lobes
Local Extension	
T3	Tumor extends through the prostate capsule[c]
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicles
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Metastatic Disease	
N1	Positive regional lymph nodes
M1	Distant metastases

[a]Revised from SB Edge et al (eds): *AJCC Cancer Staging Manual*, 7th ed. New York, Springer, 2010. [b]Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c. [c]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2.

Abbreviation: PSA, prostate-specific antigen.

TREATMENT

LOCALIZED DISEASE OR CLINICALLY LOCALIZED DISEASE

Cancers are those that appear to be nonmetastatic after staging studies are performed. Patients with clinically localized disease are managed by radical prostatectomy, radiation therapy, or active surveillance. Choice of therapy requires the consideration of several factors: the presence of symptoms, the probability that the untreated tumor will adversely affect the quality or duration of survival and thus require treatment, and the probability that the tumor can be cured by single-modality therapy directed at the prostate versus requiring both local and systemic therapy to achieve cure.

Data from the literature (such as the ProtecT trial) do not provide clear evidence for the superiority of any one form of local therapy relative to another. This is due to the lack of prospective randomized trials, referral bias and physician bias, variation in the experience of the treating teams, and differences in trial endpoints and the definitions of cancer control. Often, PSA relapse–free survival is used because an effect on metastatic progression or survival may not be apparent for years. For many patients, however, a PSA recurrence does not necessarily mean that the disease will cause symptoms or shorten survival. After radical surgery to remove all prostate tissue, PSA should become undetectable in the blood within 6 weeks. If PSA remains or becomes detectable after radical prostatectomy, the patient is considered to have persistent or recurrent disease. After radiation therapy, in contrast, PSA does not become undetectable because the remaining nonmalignant elements of the gland continue to produce PSA even if all cancer cells have been eliminated. Similarly, cancer control is not well defined for a patient managed by active surveillance because PSA levels may continue to rise in the absence of therapy. Other outcomes are time to objective progression (local or systemic), cancer-specific survival, and overall survival; however, these outcomes may take years to assess.

The more extensive the local disease, the higher the probability of regional lymph node involvement even when imaging studies are

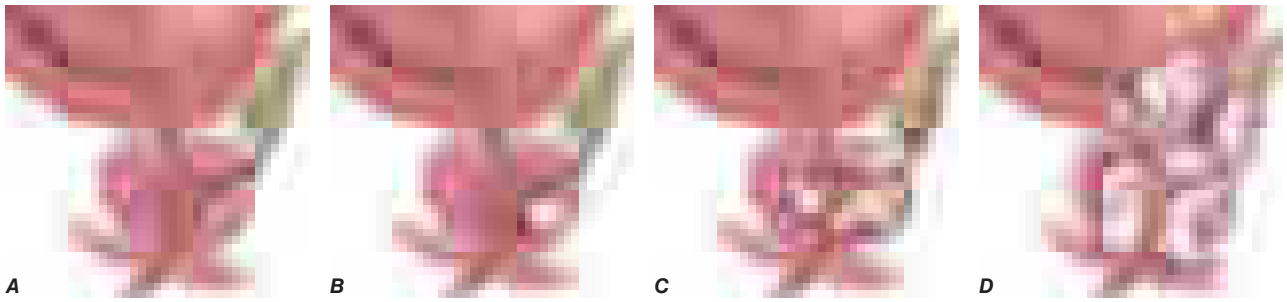

FIGURE 83-2 T stages of prostate cancer. ***A.*** T1—Clinically inapparent tumor, neither palpable nor visible by imaging; ***B.*** T2—Tumor confined within prostate; ***C.*** T3—Tumor extends through prostate capsule and may invade the seminal vesicles; ***D.*** T4—Tumor is fixed or invades adjacent structures. Eighty percent of patients present with local disease (T1 and T2), which is associated with a 5-year survival rate of 100%. An additional 12% of patients present with regional disease (T3 and T4 without metastases), which is also associated with a 100% survival rate after 5 years. Four percent of patients present with distant disease (T4 with metastases), which is associated with a 30% 5-year survival rate. (Three percent of patients are ungraded.) *(Data from AJCC, http://seer.cancer.gov/statfacts/html/prost.html. Figure © Memorial Sloan-Kettering Cancer Center Medical Graphics; used with permission.)*

normal, the lower the probability of local control, and the higher the probability of systemic relapse. More important is that within the categories of T1, T2, and T3 disease are cancers with a range of prognoses. Some T3 tumors are curable with therapy directed solely at the prostate, and some T1 lesions have a high probability of systemic relapse that requires the integration of local and systemic therapy to achieve cure. For T1c cancers in particular, stage alone is inadequate to predict outcome and select treatment; other factors must be considered.

To better assess risk and guide treatment selection, many groups have developed prognostic models or nomograms that use a combination of the initial clinical T stage, biopsy Gleason score, the number of biopsy cores in which cancer is detected, and baseline PSA. Some use discrete cut-points (PSA <10 or ≥10 ng/mL; Gleason score of ≤6, 7, or ≥8); others employ nomograms that use PSA and Gleason score as continuous variables. More than 100 nomograms have been reported to predict (a) the probability that a clinically significant cancer is present, (b) disease extent (organ-confined vs non–organ-confined, node-negative or -positive), or (c) the probability of treatment success for specific local therapies using pretreatment variables. Considerable controversy exists over what constitutes "high risk" based on a predicted probability of success or failure. In these situations, nomograms and predictive models can only go so far. Exactly what probability of success or failure would lead a physician to recommend and a patient to seek alternative approaches is controversial. As an example, it may be appropriate to recommend radical surgery for a younger patient with a low probability of cure. Nomograms are being refined continually to incorporate additional clinical parameters, biologic determinants, and year of treatment, which can also affect outcomes, making treatment decisions a dynamic process.

The frequency of adverse events varies by treatment modality and the experience of the treating team. For example, following radical prostatectomy, incontinence rates range from 2 to 47% and impotence rates range from 25 to 89%. Part of the variability relates to how the complication is defined and whether the patient or physician is reporting the event. The time of the assessment is also important. After surgery, impotence is immediate but may reverse over time, while with radiation therapy impotence is not immediate but may develop over time. Of greatest concern to patients are the effects on continence, sexual potency, and bowel function.

Radical Prostatectomy The goal of radical prostatectomy is to excise the cancer completely with a clear margin, to maintain continence by preserving the external sphincter, and to preserve potency by sparing the autonomic nerves in the neurovascular bundle. The procedure is advised for patients with a life expectancy of 10 years or more and is performed via a retropubic or perineal approach, or via a minimally invasive robotic-assisted or hand-held laparoscopic approach. Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is usually defined as a value >0.1 or 0.2 ng/mL. Specific criteria to guide the choice of one approach over another are lacking. Minimally invasive approaches offer the advantage of a shorter hospital stay and reduced blood loss. Rates of cancer control, recovery of continence and recovery of erectile function are comparable. The individual surgeon rather than the surgical approach used is most important in determining outcomes after surgery.

Neoadjuvant hormonal treatment with gonadotropin-releasing hormone (GnRH) agonists/antagonists alone has also been explored in an attempt to improve the outcomes of surgery for high-risk patients using a variety of definitions. The results of several large trials testing 3 or 8 months of androgen depletion before surgery showed that serum PSA levels decreased by 96%, prostate volumes decreased by 34%, and margin positivity rates decreased from 41 to 17%. Unfortunately, these findings have not been shown to improve PSA relapse–free survival.

Factors associated with incontinence following radical prostatectomy include older age and urethral length, which impacts the ability to preserve the urethra beyond the apex and the distal sphincter. The skill and experience of the surgeon are also factors.

The likelihood of recovery of erectile function is associated with younger age, quality of erections before surgery, and the absence of damage to the neurovascular bundles. In general, erectile function begins to return about 6 months after surgery if neurovascular tissue has been preserved. Potency is reduced by half if at least one neurovascular bundle is sacrificed. Overall, with the availability of drugs such as sildenafil, intraurethral inserts of alprostadil, and intracavernosal injections of vasodilators, many patients recover satisfactory sexual function.

Radiation Therapy Radiation therapy is given by external beam, by radioactive sources implanted into the gland, or by a combination of the two techniques.

External beam radiation therapy Contemporary external beam intensity-modulated radiation therapy (IMRT) permits shaping of the dose, and allows the delivery of higher doses to the prostate and a dramatic reduction in normal tissue exposure compared to three-dimensional conformal treatment alone. These advances have enabled the safe administration of doses >80 Gy and resulted in higher local control rates and fewer side effects.

Cancer control after radiation therapy has been defined by various criteria, including a decline in PSA to <0.5 or 1 ng/mL, "nonrising" PSA values, and a negative biopsy of the prostate 2 years after completion of treatment. The current standard definition of biochemical failure (the Phoenix definition) is a rise in PSA by ≥2 ng/mL higher than the lowest PSA achieved. The date of failure is "at call" and not backdated.

Radiation dose is critical to the eradication of prostate cancer. In a representative study, a PSA nadir of <1.0 ng/mL was achieved in 90% of patients receiving 75.6 or 81.0 Gy vs 76 and 56% of those receiving 70.2 and 64.8 Gy, respectively. Positive biopsy rates at 2.5 years were 4% for those treated with 81 Gy vs 27 and 36% for those receiving 75.6 and 70.2 Gy, respectively.

More recently, hypofractionation schedules, utilizing fewer treatments of higher radiation doses, have been evaluated and shown to provide good cancer control rates based on post-treatment

biopsies showing no evidence of cancer, with no apparent increase in treatment-related morbidity. Hypofractionated treatments can range from as few as 5 treatments to upwards of 26 treatments, both regimens representing substantial reductions in treatment length.

Multiple clinical trials have evaluated the use of androgen deprivation therapy (ADT) in combination with radiation. In patients with intermediate-risk prostate cancer, short-course ADT (6 months), when combined with external beam radiotherapy, has demonstrated significant improvements in overall survival. In patients with high-risk disease, longer courses of ADT (18–36 months) have proven superior to shorter courses and represent the current standard of care when combined with radiotherapy.

Neoadjuvant hormone therapy before radiation therapy is used to decrease the size of the prostate and, consequently, to reduce the exposure of normal tissues to full-dose radiation, to increase local control rates, and to decrease the rate of systemic failure. Short-term hormone therapy can reduce toxicities and improve local control rates, but long-term treatment (2–3 years) is needed to prolong the time to PSA failure and lower the risk of metastatic disease in men with high-risk cancers. The impact on survival has been less clear.

The Prostate Testing for Cancer and Treatment (ProtecT) trial investigated the effects of active monitoring, radical prostatectomy, and radical radiotherapy with hormones on patient-reported outcomes in men diagnosed with low- and intermediate-risk prostate cancer (about 75% with Gleason score 6 or Gleason Grade Group 1 cancer). Patient-reported outcomes among 1643 men who completed questionnaires before diagnosis, at 6 and 12 months, and annually thereafter were compared. Of the three treatments, prostatectomy had the greatest negative effect on sexual function and urinary continence, and although there was some recovery, these outcomes remained worse in the prostatectomy group than in the other groups throughout the trial. The negative effect of radiotherapy on sexual function was greatest at 6 months, but sexual function then recovered somewhat and was stable thereafter; radiotherapy had little effect on urinary continence. Sexual and urinary function declined gradually in the active-monitoring group. Bowel function was worse in the radiotherapy group at 6 months than in the other groups but then recovered somewhat, except for the increasing frequency of bloody stools; bowel function was unchanged in the other groups. Urinary voiding and nocturia were worse in the radiotherapy group at 6 months but then mostly recovered and were similar to the other groups after 12 months. Effects on quality of life mirrored the reported changes in function. No significant differences were observed among the groups in measures of anxiety, depression, or general health-related or cancer-related quality of life.

Brachytherapy Brachytherapy is the direct implantation of radioactive sources (seeds) into the prostate. It is based on the principle that the deposition of radiation energy in tissues decreases as a function of the square of the distance from the source **(Chap. 69)**. The goal is to deliver intensive irradiation to the prostate, minimizing the exposure of the surrounding tissues. The current standard technique achieves a more homogeneous dose distribution by placing seeds according to a customized template based on imaging assessment of the cancer and computer-optimized dosimetry. The implantation is performed transperineally as an outpatient procedure with real-time imaging.

Improvements in brachytherapy techniques have resulted in fewer complications and a marked reduction in local failure rates. In a series of 197 patients followed for a median of 3 years, 5-year actuarial PSA relapse–free survival for patients with pretherapy PSA levels of 0–4, 4–10, and >10 ng/mL were 98, 90, and 89%, respectively. In a separate report of 201 patients who underwent posttreatment biopsies, 80% were negative, 17% were indeterminate, and 3% were positive. The results did not change with longer follow-up. Nevertheless, many physicians feel that implantation is best reserved for patients with good or intermediate prognostic features.

Brachytherapy is well tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Incontinence has been seen in 2–4% of cases. Higher complication rates are observed in patients who have undergone a prior transurethral resection of the prostate (TURP), while those with obstructive symptoms at baseline are at a higher risk for retention and persistent voiding symptoms. Proctitis has been reported in <2% of patients.

Active surveillance Although prostate cancer is the most common form of cancer affecting men in the United States, patients are being diagnosed earlier and more frequently present with early-stage disease. Active surveillance, described previously as *watchful waiting* or *deferred therapy*, evolved from (1) studies that evaluated predominantly elderly men with well-differentiated tumors who demonstrated no clinically significant progression for protracted periods, (2) recognition of the contrast between incidence and disease-specific mortality, (3) the high prevalence of autopsy cancers, and (4) an effort to reduce overtreatment and treatment-related side effects. In practice, active surveillance is the treatment recommended to patients with cancers of low aggressiveness that can be safely monitored at fixed intervals with DREs, PSA measurements, imaging (usually prostate MRI), and repeat prostate biopsies as indicated until histopathologic or serologic changes correlative of progression warrant treatment with curative intent.

Case selection is critical, and determining clinical parameters predictive of cancer aggressiveness that can be used to reliably select men most likely to benefit from treatment by active surveillance is an area of intense study. In one prostatectomy series, it was estimated that 10–15% of those treated had "insignificant" disease. One set of criteria includes men with clinical T1c tumors that are biopsy Gleason grade 6 (Grade Group 1) involving 3 or fewer cores, each core having <50% involvement by tumor, and a PSA density of <0.15.

Concerns about active surveillance include the limited ability to predict pathologic findings by needle biopsy even when multiple cores are obtained, the recognized multifocality of the disease, and the possibility of a missed opportunity to cure the disease. Nomograms to help predict which patients can safely be managed by active surveillance continue to be refined, and as their predictive accuracy improves, it can be anticipated that more patients will be candidates.

RISING PSA AFTER DEFINITIVE LOCAL THERAPY

It includes patients in whom the sole manifestation of disease is a rising PSA after surgery and/or radiation therapy. By definition, there is no evidence of disease on imaging studies. For these patients, the central issue is whether the rise in PSA results from persistent disease in the primary site, systemic disease, or both. In theory, disease in the primary site may still be curable by additional local treatment.

The decision to recommend radiation therapy after prostatectomy is guided by the pathologic findings at surgery and an MRI of the prostate or prostate bed, as CT and radionuclide bone scan are typically uninformative. Others recommend that a biopsy of the urethrovesical anastomosis be obtained before considering radiation. New PET tracers such as C-11 choline, F-18 fluciclovine, (both FDA approved) and F-18 or Ga-68 PSMA (prostate-specific membrane antigen) are more sensitive and can detect low-volume disease in the prostate bed or other sites to better inform the decision to recommend additional local therapies. Detection rates, both in and outside the prostate bed, correlate with the absolute level of PSA. Factors that predict for response to salvage radiation therapy are a positive surgical margin, lower Gleason score in the radical prostatectomy specimen, long interval from surgery to PSA failure, slow PSA doubling time, and low (<0.5–1 ng/mL) PSA value at the time of radiation treatment. Radiation therapy is generally not recommended if the PSA was persistently elevated after surgery, which usually indicates that the disease had spread outside of the area of the prostate bed and is unlikely to be controlled with radiation therapy. As is the case for other disease states, nomograms to predict the likelihood of success are available.

For patients with a rising PSA after radiation therapy, salvage local therapy can be considered if the disease was "curable" at the outset, if persistent disease has been documented by a biopsy of the prostate or by PET or other imaging, and if no disease is detectable outside of the prostate bed or regional lymph nodes. Unfortunately, case selection

is poorly defined in most series, and morbidities are significant. Options include salvage radical prostatectomy, salvage cryotherapy, salvage radiation therapy and salvage irreversible electroporation.

The rise in PSA after surgery or radiation therapy may indicate subclinical or micrometastatic disease with or without local recurrence. In these cases, the need for treatment depends, in part, on the estimated probability that the patient will show evidence of metastatic disease on a scan and in what time frame. That immediate therapy is not always required was shown in a series where patients received no systemic therapy until metastatic disease was documented. Overall, the median time to metastatic progression was 8 years, and 63% of the patients with rising PSA values remained free of metastases at 5 years. Factors associated with progression included the Gleason score of the radical prostatectomy specimen, time to recurrence, and PSA doubling time. For those with Gleason grade ≥8, the probability of metastatic progression was 37, 51, and 71% at 3, 5, and 7 years, respectively. If the time to recurrence was <2 years and PSA doubling time was long (>10 months), the proportion with metastatic disease at the same time intervals was 23, 32, and 53%, vs 47, 69, and 79% if the doubling time was short (<10 months). PSA doubling times are also prognostic for survival. In one series, all patients who succumbed to disease had PSA doubling times of ≤3 months. Most physicians advise treatment when PSA doubling times are ≤12 months. A difficulty with predicting the risk of metastatic spread, symptoms, or death from disease in the rising PSA state is that most patients receive some form of therapy before the development of metastases. Nevertheless, predictive models continue to be refined.

METASTATIC DISEASE: NONCASTRATE

The state of *noncastrate metastatic disease* includes men with metastases visible on an imaging study at the time of diagnosis or after local therapy(ies), and noncastrate levels of testosterone (>150 ng/dL). Symptoms of metastatic disease include pain from osseous spread, although many patients are asymptomatic despite extensive spread. Less common are symptoms related to marrow infiltration by tumor (myelophthisis), coagulopathy, or spinal cord compression.

Standard treatment is to deplete/lower androgens by medical or surgical means, the latter being the least acceptable to patients. A less frequently used treatment is to block androgen binding to the AR with antiandrogens. More than 90% of male hormones originate in the testes; <10% are synthesized in the adrenal gland **(Fig. 83-3)**. Survival benefits were shown for the combination of ADT plus docetaxel, and separately for ADT plus abiraterone plus prednisone in large scale randomized phase 3 trials.

Testosterone-Lowering Agents Medical therapies that lower testosterone levels include the GnRH agonists/antagonists, 17,20-lyase inhibitors, CYP-17 inhibitors, and estrogens such as diethylstilbestrol (DES). The last have fallen out of favor due to the risk of vascular complications such as fluid retention, phlebitis, emboli, and stroke. GnRH agonists/antagonists (leuprolide acetate and goserelin acetate) initially produce a rise in luteinizing hormone and follicle-stimulating hormone followed by a downregulation of receptors in the pituitary gland, which effects a chemical castration. They were approved on the basis of randomized comparisons showing an improved safety profile (specifically, reduced cardiovascular toxicities) relative to DES, with equivalent potency. The initial rise in testosterone may result in a clinical flare of the disease and as such are relatively contraindicated in men with significant obstructive symptoms, cancer-related pain, or spinal cord compromise. Pure androgen antagonists such as bicalutamide can be used to prevent flare. GnRH antagonists such as degarelix achieve castrate levels of testosterone within 48 h without the initial rise in serum testosterone and may be associated with a lower risk of cardiovascular complications.

Agents that lower testosterone are associated with an androgen-deprivation syndrome that includes hot flushes, weakness, fatigue, loss of muscle mass, anemia, change in personality, and depression. Changes in lipids, obesity, and insulin resistance, along with an increased risk of diabetes and cardiovascular disease are also seen, along with a decrease in bone density that worsens over time and results in an increased risk of clinical fractures. This is a particular concern in men with preexisting osteopenia that results from hypogonadism or steroid or alcohol use, and which is significantly underappreciated. Baseline fracture risk can be assessed using the FRAX scale, and to minimize fracture risk patients are advised calcium and vitamin D supplementation, along with a bisphosphonate, RANK-ligand inhibitor (denosumab), or torimefene.

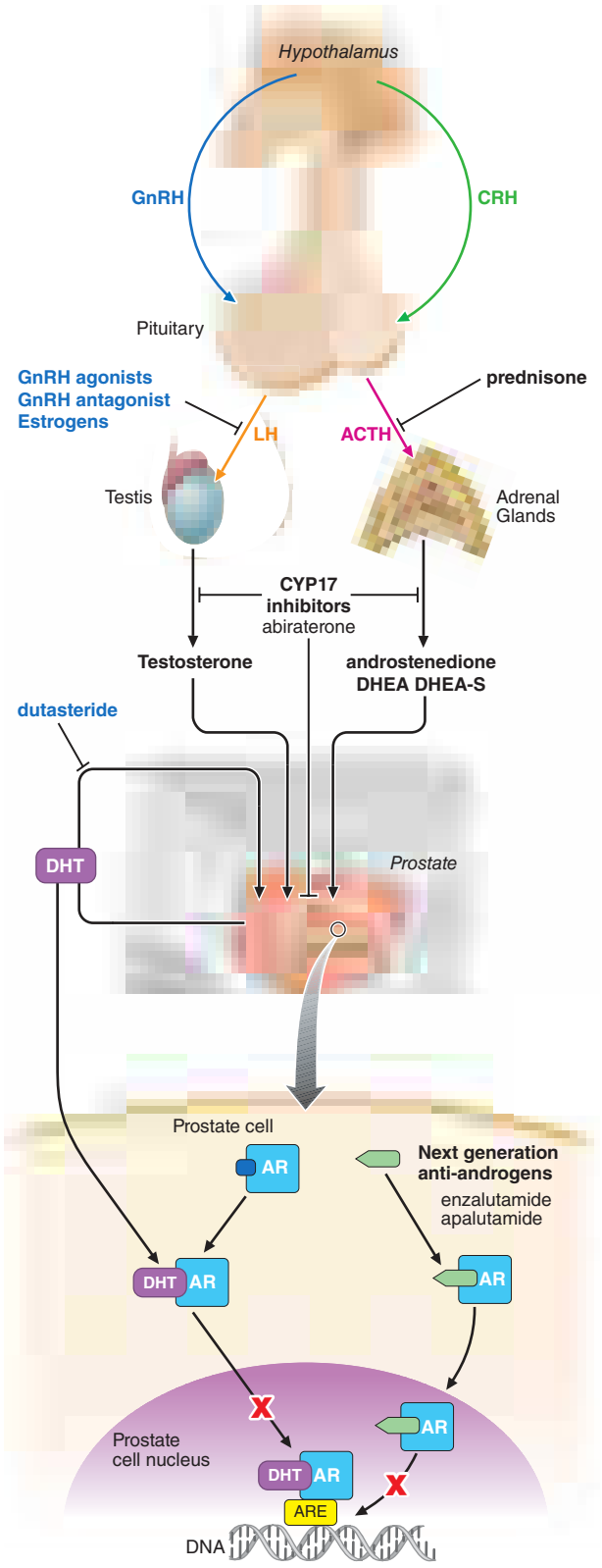

FIGURE 83-3 Sites of action of different hormone therapies.

Antiandrogens Nonsteroidal first-generation antiandrogens such bicalutamide and nilutamide block the ligand binding to the AR and were initially approved to block the flare associated with the rise in serum testosterone associated with GnRH agonist/antagonist therapy. When antiandrogens are given alone, testosterone levels increase, but relative to testosterone-lowering therapies, they cause fewer hot flushes, less of an effect on libido, less muscle wasting, fewer personality changes, and less bone loss. Gynecomastia remains a significant problem but can be prevented in part by tamoxifen or prophylactic breast irradiation.

Most reported randomized trials suggest that the cancer-specific outcomes are inferior when antiandrogens are used alone. Bicalutamide, even at a dose of 150 mg (three times the approved dose for use in combination in GnRH agonists), was associated with a shorter time to progression and inferior survival compared to surgical castration for patients with established metastatic disease.

Improving on the outcomes with ADT alone has been a focus of the field for decades. One approach was to combine a first-generation antiandrogen (flutamide, bicalutamide, or nilutamide) with a GnRH analogue or surgical orchiectomy, which has not been shown to be superior to ADT alone. As a result, use of these first-generation compounds is largely limited to the first 2–4 weeks of treatment, to protect against the flare.

More recently, significant improvements in time to progression and overall survival were reported in large-scale trials for the combination of ADT with docetaxel or with abiraterone acetate plus prednisone, relative to ADT alone. Docetaxel was the first systemic therapy shown to prolong life in metastatic castration-resistant prostate cancer (mCRPC) and was approved in 2004. Abiraterone acetate (a CYP-17 inhibitor shown to reduce androgen levels to the 1–2 ng/dl range) plus prednisone was approved for mCRPC in 2011. With docetaxel, the greatest benefit was seen for patients with "high-volume" disease defined as the presence of ≥4 lesions on radionuclide bone scan or visceral disease. For abiraterone acetate and prednisone, benefit was seen across disease states ranging from high-risk localized to metastatic disease.

Intermittent Androgen Deprivation Therapy (IADT) One way to reduce the side effects of androgen depletion is to administer antiandrogens on an intermittent basis. This was proposed as a way to prevent the selection of cells that are resistant to androgen depletion. The hypothesis is that by allowing endogenous testosterone levels to rise, the cells that survive androgen depletion will induce a normal differentiation pathway. In this way, the surviving cells that are allowed to proliferate in the presence of androgen will retain sensitivity to subsequent androgen depletion. Applied in the clinic, androgen depletion is continued for 2–6 months beyond the point of maximal response. Once treatment is stopped, endogenous testosterone levels increase, and the symptoms associated with hormone treatment abate. PSA levels also begin to rise, and at some level treatment is restarted. With this approach, multiple cycles of regression and proliferation have been documented in individual patients. Unknown is whether the intermittent approach increases, decreases, or does not change the overall duration of sensitivity to androgen depletion. The approach is safe, but long-term data are needed to assess the course in men with low PSA levels. A trial to address this question is ongoing.

Outcomes of Androgen Deprivation The anti–prostate cancer effects of the various androgen depletion strategies are similar, and the clinical course is predictable: an initial response, then a period of stability in which tumor cells are dormant and nonproliferative, followed after a variable period of time by a rise in PSA and regrowth that is visible on a scan as a castration-resistant lesion. Androgen depletion is not curative because cells that survive castration are present when the disease is first diagnosed. Considered by disease manifestation, PSA levels return to normal in 60–70% of patients, and measurable disease regression occurs in 50%; improvements in bone scan occur in 25% of cases, but the majority remain stable. Duration of survival is inversely proportional to disease extent at the time androgen depletion is first started and the nadir level of PSA at 6 months. Patients with nadir values above a certain threshold have markedly inferior survival times and should be considered for alternative approaches.

An unresolved question remains on how early systemic therapies should be offered to patients: in the adjuvant setting after surgery or radiation treatment of the primary tumor; at the time that a PSA recurrence is documented; or wait until metastatic disease or symptoms of disease are manifest? Trials in support of early therapy have been largely underpowered relative to the reported benefit or have been criticized on methodologic grounds. One trial which showed a survival benefit for patients treated with radiation therapy and 3 years of ADT, relative to radiation alone, was criticized for the poor outcomes of the control group. Another trial showing a survival benefit for patients with positive lymph nodes who were randomized to immediate medical or surgical castration compared to observation (p = .02) was criticized because the confidence intervals around the 5- and 8-year survival distributions for the two groups overlapped.

METASTATIC DISEASE: CASTRATE

Castration-resistant prostate cancer (CRPC), disease that progresses while the measured levels of testosterone in the blood are 50 ng/mL or lower, can produce some of the most feared complications of the disease and is lethal for most men. The most common manifestation is a rising PSA, frequently co-occurring with progression in bone. Nodal and/or visceral spread is less frequent and symptoms may or may not be present. The bone- and PSA-dominant pattern limits the ability to assess treatment effects reliably because traditional bone imaging is inaccurate and no PSA-based outcome has been shown to be a true surrogate for survival. It is essential to define therapeutic objectives based on the manifestations of the disease in the individual. As such, for the patient with symptomatic bone disease, relief of pain can be more clinically relevant than lowering the PSA. Naturally, for all patients the central focus is delaying or preventing disease progression, symptom development, and death from cancer.

Through 2010, docetaxel was the only FDA-approved life-prolonging therapy for CRPC. Since then, our understanding of the biology of the disease has increased significantly, which in turn has led to improved therapies. In particular, it is now recognized that the majority of mCRPCs continue to express the AR, which in upwards of 50% of cases harbors a series of oncogenic changes including overexpression of the receptor itself and the enzymes in the androgen biosynthesis pathways. These oncogenic changes have been successfully targeted with the next-generation antiandrogen enzalutamide and the CYP-17 inhibitor abiraterone acetate (given in combination with prednisone), both of which have been proven to prolong life and are FDA-approved for use in CRPC in both the pre- and post-chemotherapy setting. More recently, the results of large-scale molecular profiling efforts have led to biologically based pathway-focused classification that showed a markedly higher than expected frequency of germline and somatic BRCA2 alterations, along with other genes in the DNA damage repair pathway, that has been successfully treated with poly ADP ribose polymerase (PARP) inhibitors. Other classes of therapy that have been approved based on a demonstrated survival benefit include the biologic agent sipuleucel-T, the second-generation taxane cabazitaxel, and the alpha-emitting bone targeting radiopharmaceutical radium-223. An intense of focus of current CRPC research is to understand the optimal sequence in which to utilize these agents to maximize benefit for the individual patient.

Pain Management Pain secondary to osseous metastases is one of the most feared complications of the disease and a major cause of morbidity, worsened by the narcotics needed to control symptoms. Management requires accurate diagnoses because non-cancer etiologies including degenerative disease, spinal stenosis, and vertebral collapse secondary to bone loss are common. Neurologic symptoms, including those suggestive of base of skull disease or spinal cord compromise, require emergency evaluation because loss of function may be permanent if not addressed quickly. Neurologic symptoms

or loss of function are best treated with external beam radiation, as are single sites of pain. Diffuse symptoms in the absence of neurologic deficits can be treated with bone-seeking radioisotopes such as radium-223 or the beta emitter ^{153}Sm-EDTMP, or mitoxantrone, or other systemic therapies such as abiraterone acetate, enzalutamide, and docetaxel. Radium-223 is indicated for patients with symptoms while ^{153}Sm-EDTMP and mitoxantrone are approved for the palliation of pain but not shown to prolong life. Abiraterone, enzalutamide, and docetaxel do not have a formal indication for pain, but were shown to palliate pain in the registration trials that led to their approval by showing a survival benefit.

Other bone-targeting agents, including bisphosphonates such as zoledronic acid and the RANK-ligand inhibitor denosumab, have been shown to reduce the frequency and development of skeletal complications including pain requiring analgesia, neurologic compromise from epidural extension of tumor, and/or the need for surgery or radiation therapy to treat symptomatic osseous disease. It is important to note that for all of these agents, the direct effect on the tumor is modest and benefits are seen without declines in PSA or improvements on imaging.

BENIGN DISEASE

BENIGN PROSTATIC HYPERPLASIA

BPH is a pathologic process that contributes to the development of lower urinary tract symptoms (LUTS) in men. LUTS, arising from lower urinary tract dysfunction, are further subdivided into obstructive symptoms (urinary hesitancy, straining, weak stream, terminal dribbling, prolonged voiding, incomplete emptying) and irritative symptoms (urinary frequency, urgency, nocturia, urge incontinence, small voided volumes). LUTS and other sequelae of BPH are not just due to a mass effect, but also likely due to a combination of the prostatic enlargement and age-related detrusor dysfunction.

Diagnostic Procedures and Treatment LUTS symptoms are generally measured using a validated, reproducible index that is designed to determine disease severity and response to therapy—the American Urological Association's Symptom Index (AUASI), also adopted as the International Prostate Symptom Score (IPSS) (Table 83-2). Serial AUASI is particularly useful in following patients as they are treated with various forms of therapy. Asymptomatic patients do not require treatment regardless of the size of the gland, while those with an inability to urinate, gross hematuria, recurrent infection, or bladder stones may require surgery. In patients with symptoms, uroflowmetry can identify those with normal flow rates who are unlikely to benefit from treatment, and bladder ultrasound can identify those with high postvoid residuals who may need intervention. Pressure-flow (urodynamic) studies detect primary bladder dysfunction. Cystoscopy is recommended if hematuria is documented and to assess the urinary outflow tract before surgery. Imaging of the upper tracts is advised for patients with hematuria, a history of calculi, or prior urinary tract problems.

Symptomatic relief is the most common reason men seek treatment for BPH, and therefore symptomatic relief is usually the goal of therapy for BPH. Alpha-adrenergic receptor antagonists are thought to treat the dynamic aspect of BPH by reducing sympathetic tone of the bladder outlet, thereby decreasing resistance and improving urinary flow. 5ARIs are thought to treat the static aspect of BPH by reducing prostate volume and having a similar, albeit delayed effect. They have also proven to be beneficial in the prevention of BPH progression, as measured by prostate volume, the risk of developing acute urinary retention, and the risk of having BPH-related surgery. The use of an alpha-adrenergic receptor antagonist and a 5ARI as combination therapy seeks to provide symptomatic relief while preventing progression of BPH.

Another class of medications that has shown improvement in LUTS secondary to BPH is phosphodiesterase-5 (PDE5) inhibitors, used currently in the treatment of erectile dysfunction. All four of the PDE5 inhibitors available in the United States, sildenafil, vardenafil, tadalafil, and avanafil, appear to be effective in the treatment of LUTS secondary to BPH. The use of PDE5 inhibitors is not without controversy, however, given the fact that short-active phosphodiesterase inhibitors such as sildenafil need to be dosed separately from alpha blockers such as tamsulosin because of potential hypotensive effects.

Symptoms due to BPH often coexist with symptoms due to overactive bladder, and the most common pharmacologic agents for the treatment of overactive bladder symptoms are anticholinergics. This has led to multiple studies evaluating the efficacy of anticholinergics for the treatment of LUTS secondary to BPH.

Surgical therapy is now considered second-line therapy and is usually reserved for patients after a trial of medical therapy. The goal of surgical therapy is to reduce the size of the prostate, effectively reducing resistance to urine flow. Surgical approaches include TURP, transurethral incision, or removal of the gland via a retropubic, suprapubic, or

TABLE 83-2 AUA Symptom Index

QUESTIONS TO BE ANSWERED	AUA SYMPTOM SCORE (CIRCLE 1 NUMBER ON EACH LINE)					
	NOT AT ALL	LESS THAN 1 TIME IN 5	LESS THAN HALF THE TIME	ABOUT HALF THE TIME	MORE THAN HALF THE TIME	ALMOST ALWAYS
Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0+	1	2	3	4	5
Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	(None)	(1 time)	(2 times)	(3 times)	(4 times)	(5 times)
Sum of 7 circled numbers (AUA Symptom Score): ____						

Abbreviation: AUA, American Urological Association.

Source: MJ Barry et al: J Urol 148:1549, 1992. Used with permission.

perineal approach. Also used are transurethral ultrasound-guided laser-induced prostatectomy (TULIP), stents, and hyperthermia.

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84 Testicular Cancer

David J. Vaughn

Testicular germ cell tumors (GCTs) represent 95% of all testicular neoplasms. Non-germ cell tumors of the testis are much less common. Approximately 5% of GCTs arise in extragonadal locations including the mediastinum, retroperitoneum, and pineal gland. Treatment for testicular GCTs is determined by pathology and stage. The development of effective chemotherapy for this disease represents a landmark achievement in oncology. About 95% of newly diagnosed patients with testicular GCTs will be cured. For this reason, testicular cancer has been called "a model for a curable neoplasm."

INCIDENCE

In 2016, ~8700 cases of testicular GCTs will be diagnosed in the United States, with <400 deaths. These tumors are diagnosed most commonly in men between 20 and 40 years. It has recently been reported that the incidence of GCTs is increasing in men 50 years and older.

GLOBAL CONSIDERATIONS

The incidence of testicular GCTs appears to be increasing worldwide. The disease has the highest incidence in Scandinavia, Western Europe, and Australia/New Zealand. Africa and Asia have the lowest incidence. The incidence in the United States and the United Kingdom is intermediate. While there does not appear to be a distinct biology related to geography, several countries have reported a migration to earlier stage disease in part related to public awareness and earlier diagnosis.

EPIDEMIOLOGY

GCTs are predominantly seen in young Caucasian men. The disease is much less commonly seen in African Americans. Although most patients with GCTs do not have a family history of this disease, there are rare familial cases. Interestingly, the risk of GCT is higher in male siblings and cousins than in offspring of the patient. Although epidemiological studies have been performed attempting to identify a relationship with environmental exposures, no conclusive causal links have been established.

Risk Factors The strongest risk factors for testicular GCT include a prior history of the disease, cryptorchidism, and a history of testicular intratubular germ cell neoplasia (ITGCN). Patients with a prior history of testicular GCT have a 2% risk of developing a contralateral GCT. These are more commonly metachronous than synchronous. Men with cryptorchidism have approximately a four- to sixfold increased risk of developing testicular GCT. Orchidopexy before puberty decreases but does not eliminate this risk. Interestingly, the contralateral descended testis is also at risk for this disease. Men undergoing infertility evaluation in which a testicular biopsy demonstrates ITGCN have a 50% risk of developing GCT. Although scrotal ultrasound of patients with testicular GCT may demonstrate testicular microcalcifications that may be related to ITGCN, the significance of testicular microcalcifications in the general population is unclear.

BIOLOGY

The primordial germ cell is the cell of origin for GCTs. All malignant GCTs arise from ITGCN. The molecular events that result in the development of ITGCN and subsequent malignant GCT have not been fully determined. However, genetic analysis of GCTs have demonstrated an excess copy number of isochromosome 12p (i[12p]) in most cases. Several genome-wide association studies have identified independent loci associated with testicular GCT risk. The strongest of these is the *KITLG* (KIT ligand) locus on chromosome 12.

PATHOLOGY

GCTs are either seminomas or nonseminomas. For a tumor to be considered a seminoma, it must be 100% seminoma. Any mixed GCT is best approached as a nonseminomatous GCT (NSGCT). Seminomas represent ~50% of cases. Seminomas arise most commonly in patients in the fourth decade of life. Seminomas may contain syncytiotrophoblastic cells which may secrete β human chorionic gonadotropin (HCG). Seminomas do not secrete α fetoprotein (AFP). Seminomas are exquisitely sensitive to both chemotherapy and radiation therapy. Seminomas are believed to be a common precursor that subsequently differentiates into the NSGCT subtypes. NSGCTs are most commonly diagnosed in the third decade of life. The histologic subtypes include embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. Embryonal carcinoma is the most undifferentiated NSGCT subtype with the potential to differentiate into the other subtypes. Embryonal carcinoma may secrete AFP, HCG, both, or neither. Yolk sac tumor (also referred to as endodermal sinus tumor) often secretes AFP. Choriocarcinoma is an aggressive subtype, often secreting HCG at very high levels. These NSGCT subtypes are all considered chemotherapy sensitive. Teratoma is composed of somatic cell types that are derived from two or more germinal layers (endoderm, mesoderm, and ectoderm). Teratomas are classified as mature, in which cell types resemble normal adult somatic tissue; immature, in which cell types resemble fetal somatic tissue; and malignant, in which the cell types have undergone malignant transformation into the malignant counterpart of the somatic tissue. Teratomas are chemotherapy resistant and must be approached surgically.

INITIAL PRESENTATION

Signs and Symptoms Although a painless testicular mass is pathognomonic of a GCT, most patients present with testicular swelling, firmness, discomfort, or a combination of these. The differential diagnosis may include epididymitis or orchitis and a trial of antibacterials may be considered. Patients with retroperitoneal metastases may complain of back or flank pain. Patients may have cough, shortness of breath, or hemoptysis as a result of lung metastases. In patients with elevation of serum HCG, gynecomastia may be present. Diagnostic delay is not uncommon, and may be associated with a more advanced stage at diagnosis.

Physical Examination Careful examination of the affected testis and the contralateral normal testis should be performed. Many tumors

will have a hard consistency to palpation. Some patients may show testicular atrophy. Evaluation for supraclavicular lymphadenopathy, gynecomastia, and abdominal mass should be performed. Inguinal lymphadenopathy is rare. Most patients with lung metastases will have normal auscultation of the lungs.

Diagnostic Testing If a firm testicular mass is identified, a scrotal ultrasound should be performed. Patients with suspected epididymitis or orchitis who do not respond to antibiotics should also undergo scrotal ultrasound. Scrotal ultrasound should include both testicles. On ultrasound, a testicular GCT is hypoechoic and may be multifocal. A solid mass identified on ultrasound should be considered malignant until otherwise proven. Transscrotal aspiration or biopsy of a testicular mass should never be performed. Such scrotal violation may result in tumor seeding of the scrotum or inguinal lymph nodes.

Serum Tumor Markers Serum AFP, HCG, and lactate dehydrogenase (LDH) should be measured in patients suspected of testicular GCT. AFP is elevated in ~60–70% of patients who present with NSGCTs. Seminomas never secrete AFP. A patient with a seminoma with elevation of AFP should be approached as having a NSGCT. The half-life of AFP is 5–7 days. A falsely elevated AFP may be seen in patients with hepatic disease or a condition called hereditary persistence of AFP in which patients may have baseline AFP levels that are mildly elevated. HCG may be elevated in both NSGCTs as well as seminomas. Patients with choriocarcinoma may have markedly elevated levels of HCG. The half-life for HCG is 24–36 h. False-positive elevation of HCG may be seen secondary to hypogonadism, marijuana use, or as a result of interfering substances measured by the assay. LDH is a nonspecific marker for GCT. Its principal use is to help in the assessment of the risk classification of a patient with metastatic disease. Although elevation of serum tumor markers support the diagnosis of a testicular GCT, it should be remembered that most patients with a seminoma and up to a third of patients with NSGCTs do not have elevated levels.

INITIAL MANAGEMENT

Inguinal Orchiectomy Prompt referral to urology should be performed if a testicular GCT is suspected. The initial treatment for most patients suspected of having a testicular GCT is radical inguinal orchiectomy with removal of the testicle and spermatic cord to the level of the internal inguinal ring. In patients who present with metastatic disease and the diagnosis of GCT is certain, orchiectomy may be deferred until completion of chemotherapy. Pathologic examination of the entire testicle is important, since testicular GCTs may be multifocal. Given the rarity of this cancer, review by an experienced pathologist is essential for accurate tumor classification. Serum tumor markers should be obtained before and after orchiectomy.

Staging The staging of testicular GCT is based upon an understanding of the pattern of spread. The initial spread is by the lymphatic route to the retroperitoneal lymph nodes. A left-sided testicular GCT spreads first to the primary landing zone of left paraaortic lymph nodes inferior to the left renal vessels. A right-sided testicular GCT spreads first to the primary landing zone of the aortocaval nodes inferior to the right renal vessels. Nodal metastases may extend into the iliac regions. If scrotal violation occurred, inguinal lymph node metastases may be seen. Subsequent lymphatic spread is to the retrocrural, mediastinal, and supraclavicular lymph nodes. Hematogenous spread to the lung is the next most common site of metastasis. Metastases to the liver, bone, and brain are less commonly seen. Patients with newly diagnosed testicular GCTs should undergo computed tomography (CT) scan of the abdomen and pelvis. Chest x-ray should be performed. CT scan of the chest is performed if retroperitoneal metastases are present or if lung nodules are identified on chest x-ray. Bone scan and magnetic resonance imaging (MRI) of the brain are not routinely performed unless clinically indicated. Positron emission tomography (PET) has little role in the initial staging of testicular GCTs.

The American Joint Committee on Cancer tumor/node/metastasis (TNM) staging classification is used. There are three main stages of testicular GCT. Stage I is limited to the testis; stage II involves the retroperitoneal lymph nodes; stage III includes lymph node involvement beyond the retroperitoneum and/or distant metastatic disease.

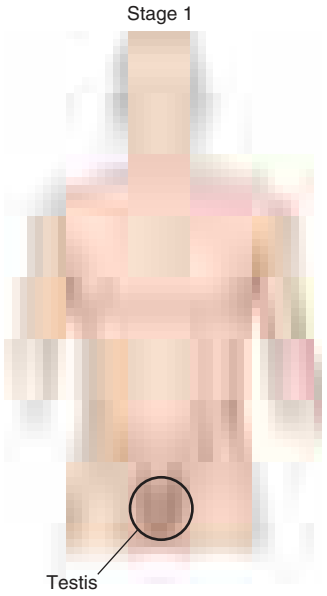
STAGE-BASED MANAGEMENT

Treatment of testicular GCT is based upon two factors: (1) whether the tumor is seminoma or NSGCT, and (2) the stage of the patient. This is summarized in Fig. 84-1.

Stage I • **SEMINOMA** About 70% of newly diagnosed patients with seminoma present with stage I disease. This is defined as no evidence of metastatic disease on imaging of the chest, abdomen, and pelvis. If pre-orchiectomy serum HCG is elevated, this must normalize post-orchiectomy to be considered stage I. Approximately 15% of patients with stage I seminoma have metastatic disease at the microscopic level, usually in the retroperitoneum. Historically, patients with stage I seminoma were treated with a course of adjuvant radiation therapy to the paraaortic lymph nodes. While still an option, this is not usually performed because of concerns for late radiation-induced secondary malignancies. Active surveillance is the most common approach elected by these patients following orchiectomy. With active surveillance, interval physical examination and CT scan of the abdomen are performed. For the 15% of patients that develop metastatic disease during active surveillance, treatment with definitive radiation therapy or chemotherapy is curative in nearly all. A third option for clinical stage I seminoma is adjuvant chemotherapy with carboplatin monotherapy for one cycle. While effective in decreasing the risk of recurrence, it should be remembered that most patients are cured by orchiectomy alone, and therefore the additional treatment is unnecessary. In addition, long-term data on toxicity and efficacy are not available.

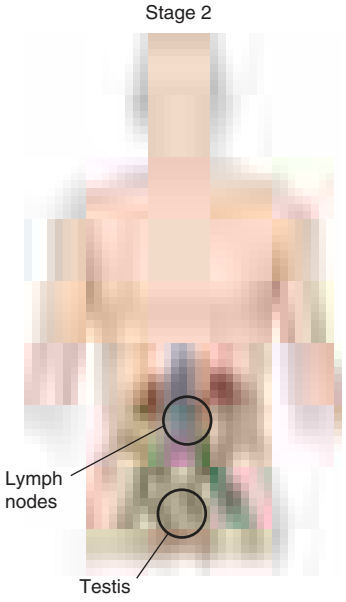
NSGCTs About 40% of newly diagnosed patients with NSGCTs present with stage I disease. Because NSGCTs have an increased potential for invasion and metastasis, spread to the retroperitoneum and beyond is more common than with seminoma. If pre-orchiectomy serum tumor markers are elevated, these must normalize post-orchiectomy to be considered stage I. Patients with persistently elevated or rising serum tumor markers after orchiectomy have stage IS disease and should be treated with cisplatin-based chemotherapy. If the tumor is pT1, defined as limited to testis and epididymis with no vascular or lymphatic invasion and no invasion into tunica vaginalis, the risk of recurrence is approximately 20%. However, if the tumor is pT2, defined as limited to testis and epididymis with vascular or lymphatic invasion, or tumor extension into tunica vaginalis, the risk of recurrence is ~50%. Historically, a prophylactic retroperitoneal lymph node dissection (RPLND) was performed. This surgery is not only diagnostic, but also therapeutic. In fact, most patients who undergo prophylactic RPLND will never require chemotherapy. While still an option, this approach subjects many patients to unnecessary major abdominal surgery. RPLND is also associated with a small risk of retrograde ejaculation due to nerve injury, and nerve sparing techniques have been developed. Active surveillance is frequently performed especially for patients with pT1 disease. Most patients who relapse will be treated with cisplatin-based chemotherapy and achieve cure rates approaching 100%. Active surveillance can also be employed for patients with pT2 disease, although the risk of progression is significantly higher. For this reason, some advocate adjuvant cisplatin-based chemotherapy such as BEP for one cycle for patients with pT2 disease. Other centers favor a prophylactic RPLND. Almost all patients who present with stage I NSGCTs will achieve cure.

Stage II • **SEMINOMA** Approximately 15–20% of newly diagnosed patients with seminoma present with stage II disease. Patients are subgrouped into IIA, IIB, or IIC based upon the size of the retroperitoneal nodes (2 cm or less, more than 2 to 5 cm, or >5 cm, respectively). Patients with stage IIA disease are usually treated with "dogleg" radiation therapy which includes the paraaortic and ipsilateral iliac nodes. Cisplatin-based chemotherapy may also be considered. Stage IIB disease is treated with cisplatin-based chemotherapy or, in select patients, radiation therapy. Most patients treated with radiation therapy that relapse will subsequently be cured with cisplatin-based chemotherapy.



	Seminoma	NSGCT
Stage IA pT1: Testis only, no vascular/lymphatic invasion	Active surveillance; or, Adjuvant carboplatin x 1 cycle; or, Adjuvant para-aortic RT	Active surveillance; or, Nerve sparing RPLND
Stage IB pT2: Testis only, with vascular/lymphatic invasion or extension through tunica albuginea into tunica vaginalis	Active surveillance; or, Adjuvant carboplatin x 1 cycle; or, Adjuvant para-aortic RT	Adjuvant BEP x 1 cycle; or, Active surveillance; or, Nerve sparing RPLND
Stage IS Elevated serum tumor markers post-orchiectomy	BEP x 3 cycles; or, EP x 4 cycles	BEP x 3 cycles; or, EP x 4 cycles

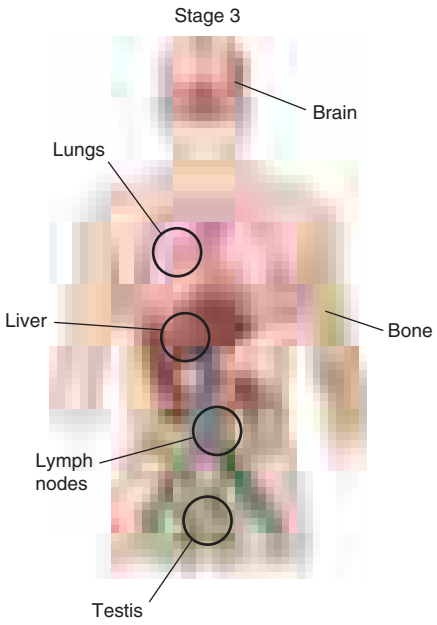
A



	Seminoma	NSGCT
Stage IIA N1: nodes ≤ 2 cm	Para-aortic and ipsilateral iliac RT; or, BEP x 3 cycles or EP x 4 cycles	Nerve-sparing RPLND; or, BEP x 3 cycles or EP x 4 cycles
Stage IIB N2: nodes > 2 to 5 cm	BEP x 3 cycles or EP x 4 cycles; or, Para-aortic and ipsilateral iliac RT	BEP x 3 cycles or EP x 4 cycles +/– post-chemotherapy RPLND
Stage IIC N3: nodes > 5 cm	BEP x 3 cycles or EP x 4 cycles	BEP x 3 cycles or EP x 4 cycles +/– post-chemotherapy RPLND

B

FIGURE 84-1 Stage-based management of testicular GCT.



	Seminoma	NSGCT
Stage IIIA (good-risk)	BEP x 3 cycles; or, EP x 4 cycles	BEP x 3 cycles; or, EP x 4 cycles; +/– Post-chemotherapy surgery
Stage IIIB (intermediate-risk)	BEP x 4 cycles; or, VIP x 4 cycles	BEP x 4 cycles; or, VIP x 4 cycles +/– Post-chemotherapy surgery
Stage IIIC (poor-risk)	N/A	BEP x 4 cycles; or, VIP x 4 cycles +/– Post-chemotherapy surgery

Abbreviations: BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; NSGCT, non-seminomatous germ cell tumor; RPLND, retroperitoneal lymph node dissection; RT, radiation therapy; VIP, etoposide, ifosfamide, cisplatin.

C

FIGURE 84-1 (Continued)

For patients with stage IIC disease, cisplatin-based chemotherapy should be used.

NSGCTs Approximately 15% of newly diagnosed patients with NSGCTs present with clinical stage II disease. Patients with stage IIA disease may be treated with primary RPLND. Alternatively, these patients may be treated with cisplatin-based chemotherapy. Patients with stage IIB and IIC disease are best initially managed with cisplatin-based chemotherapy.

Stage III Patients who present with stage III GCT (seminoma or NSGCT) are treated with cisplatin-based chemotherapy. These patients are classified into good-, intermediate-, or poor-risk categories using the International Germ Cell Consensus Classification system, which is based upon clinical factors including histology, site of primary, the presence of non-pulmonary visceral metastatic disease, and the level of post-orchiectomy serum tumor markers **(Table 84-1)**. Most patients with stage III GCT present with good-risk disease; >90% will be cured. The remainder present with intermediate-risk or poor-risk disease, associated with 5-year survival rates of ~80% and 50%, respectively. Select patients with rapidly progressive metastatic disease and life-threatening symptoms such as hemoptysis in whom there is a high clinical suspicion of GCT should emergently initiate cisplatin-based chemotherapy, even without a tissue diagnosis.

Chemotherapy The development of cisplatin-based chemotherapy represents an important advance in cancer medicine. Through a series of carefully performed clinical trials with the aim of maximizing cure while minimizing the extent of treatment, the chemotherapy approach to the treatment of these patients has been standardized.

TABLE 84-1 International Germ Cell Consensus Classification System

RISK GROUP	SEMINOMA	NSGCT
Good	Any primary site; and normal AFP, any HCG, any LDH; and nonpulmonary visceral metastases absent	Gonadal or retroperitoneal primary; and nonpulmonary visceral metastases absent; and AFP <1000 ng/mL; and HCG <5000 mIU/mL; and LDH <1.5 × ULN
Intermediate	Any primary site; and normal AFP, any HCG, any LDH; and nonpulmonary visceral metastases present	Gonadal or retroperitoneal primary; and nonpulmonary visceral metastases absent; and one of the following: AFP 1000–10,000 ng/mL HCG 5000–50,000 mIU/mL LDH 1.5–10 × ULN
Poor	N/A	Mediastinal primary; or nonpulmonary visceral metastases present; or one of the following: AFP >10,000 ng/mL HCG >50,000 mIU/mL LDH >10 × ULN

Abbreviations: AFP, α fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; N/A, not applicable; NSGCT, nonseminomatous germ cell tumor; ULN, upper limit normal. Nonpulmonary visceral metastases include liver, bone, and brain.

Source: International Germ Cell Cancer Collaborative Group: International Germ-Cell Consensus Classification: A prognostic factor based staging system for metastatic germ cell tumors. J Clin Oncol 15:594, 1997.

Patients with good-risk metastatic GCT are treated with either three cycles of bleomycin, etoposide, cisplatin (BEP) or four cycles of etoposide, cisplatin (EP). Patients with intermediate- and poor-risk metastatic disease are treated with either four cycles of BEP or four cycles of etoposide, ifosfamide, cisplatin (VIP). Maintaining dose and schedule is important, as dose modifications and delays have been associated with inferior outcomes. Serum tumor markers should be monitored throughout treatment and should normalize during or after treatment. Cisplatin-based chemotherapy is associated with myelosuppression, nausea and vomiting, and alopecia. Cisplatin may result in nephrotoxicity, ototoxicity, and peripheral neuropathy. Bleomycin may result in pulmonary toxicity and risk factors for this include age greater than 40, renal failure, tobacco use, and the cumulative dose of bleomycin received. For patients at increased risk of bleomycin-induced pneumonitis, non-bleomycin-containing regimens as noted above may be given. Cisplatin-based chemotherapy is also associated with sterility. Approximately 30% of newly diagnosed testicular GCT patients have severe oligospermia or azospermia. For the remainder with normal baseline spermatogenesis who receive cisplatin-based chemotherapy, all will be azospermic at the completion of therapy. Approximately 80% of these patients will recover spermatogenesis over a period of several years. For this reason, pre-chemotherapy sperm banking should be offered to all patients treated with chemotherapy.

Post-Chemotherapy Surgery Upon completion of cisplatin-based chemotherapy, many patients with normalized serum tumor markers will have radiographic evidence of residual masses. In approximately half of patients with NSGCT, the residual mass is composed of necrosis and/or fibrosis. About 40% will have residual teratoma and only 10% will have residual viable non-teratomatous GCT. Unfortunately, radiographic imaging cannot accurately differentiate between these entities. For this reason NSGCT patients with residual masses after chemotherapy undergo resection of all sites of disease. This most commonly includes a post-chemotherapy RPLND. However, thoracotomy and neck dissection are required in some patients. If the patients are found to have residual necrosis or teratoma, no additional therapy is required. However, for patients with residual viable non-teratomatous GCT, two additional cycles of chemotherapy are frequently administered. It should be noted that in most centers patients with minimal residual tumors defined as retroperitoneal lymph nodes of <10 mm in short axis will forego post-chemotherapy RPLND. Patients who experience normalization of serum tumor markers with first-line chemotherapy but have enlarging tumors, most often cystic masses in the retroperitoneum, may have "growing teratoma syndrome." These patients are best approached with surgery.

For patients with metastatic seminoma, ~20% of residual masses harbor viable tumor; the remainder have only necrosis. Patients with residual masses 3 cm or less may be observed without surgery. For patients with residual masses >3 cm, FDG-PET may be used to distinguish necrosis from viable seminoma and identify patients who should be considered for post-chemotherapy surgery.

RELAPSED DISEASE

Approximately 20–30% of patients with metastatic GCTs treated with cisplatin-based chemotherapy will not achieve durable disease control. Most of these patients will experience disease progression within 2 years following completion of chemotherapy. The International Prognostic Factors Study Group developed a risk stratification classification system for patients in first relapse. Contributors to a worsened prognosis include NSGCT histology, extragonadal primary, incomplete response to first-line chemotherapy, time to relapse of 3 months or less, level of serum tumor markers at relapse, and the presence of non-pulmonary visceral metastatic disease.

Patients in first relapse may be treated with either conventional-dose salvage chemotherapy or high-dose salvage chemotherapy with autologous stem cell rescue. There is controversy concerning which approach is optimal. Some institutions advocate for risk stratification, with more favorable prognosis patients receiving conventional-dose chemotherapy and worse prognosis patients receiving high-dose chemotherapy. The most commonly utilized conventional-dose regimen includes paclitaxel, ifosfamide, and cisplatin (TIP). In one study of TIP in patients with more favorable risk disease, approximately two-thirds experienced 2-year progression-free survival. High-dose chemotherapy consists of initial salvage therapy followed by stem cell harvest and then two or three cycles of high-dose carboplatin and etoposide (CE) with stem cell rescue. The largest series of patients treated with high-dose chemotherapy was reported by researchers at Indiana University where this approach is considered standard for most patients in first relapse regardless of risk classification. In their study, ~70% of patients in first relapse achieved durable progression-free survival. A large retrospective analysis has compared conventional-dose salvage chemotherapy to high-dose salvage chemotherapy in patients in first relapse. This study reports a more favorable outcome with high-dose salvage chemotherapy across nearly all risk groups. However given the retrospective nature of this study and the controversy concerning optimal approaches, an international randomized trial comparing conventional dose chemotherapy (TIP) to high-dose chemotherapy with autologous stem cell rescue (TI-CE) has been initiated.

Some patients who experience disease progression after conventional-dose salvage chemotherapy may successfully be treated with high-dose salvage chemotherapy with autologous stem cell rescue. Patients with disease progression after high-dose salvage chemotherapy may be treated with subsequent chemotherapy regimens that include gemcitabine/oxaliplatin, gemcitabine/paclitaxel, epirubicin/cisplatin, and oral etoposide. While these patients may benefit from third-line chemotherapy, few will achieve durable disease control. Select patients with relapsed but resectable disease may be candidates for salvage or so-called "desperation" surgery.

Patients who experience disease progression >2 years after chemotherapy are considered to have "late relapse." Late relapse appears to have a different biology than early relapse. These patients tend to have more chemotherapy-resistant disease. Patients with late relapse usually have NSGCT with elevation of serum AFP. Many of these patients recur in the retroperitoneum many years after first-line chemotherapy, and this likely represents residual retroperitoneal disease that was not controlled after first-line therapy. These patients are best approached with salvage surgery.

EXTRAGONADAL GCTs

Approximately 5% of patients who present with GCTs have extragonadal primaries. These mainly originate in the mediastinum or retroperitoneum. Patients suspected of extragonadal GCT should undergo scrotal ultrasound to exclude a gonadal primary. Extragonadal seminomas have a similar excellent prognosis as their gonadal counterparts and are approached the same. Mediastinal NSGCTs are classified as poor-risk and are treated with either four cycles of BEP or four cycles of VIP. These patients frequently require post-chemotherapy thoracic surgery for residual disease. For this reason, some advocate avoiding bleomycin in this patient population. Klinefelter's syndrome is associated with an increased risk of mediastinal NSGCTs. Rarely, mediastinal NSGCTs are associated with hematologic disorders including acute myelogenous leukemia. NSGCTs arising in the retroperitoneum do not have a worse prognosis than their gonadal counterparts. Many patients who present with extragonadal GCTs will undergo core needle biopsy for diagnosis. However, select patients with extragonadal tumors and definitive elevation of serum tumor markers may initiate chemotherapy without a tissue diagnosis.

Cancers of unknown primary are defined as histologically proven metastatic malignancy in which the primary site is not obvious. A subgroup of patients with cancer of unknown primary have occult GCTs. Male gender, age <65 years, midline tumors, and nonsmoking status increase the likelihood of this presentation. Pathology may demonstrate a poorly differentiated malignant neoplasm. Immunohistochemical staining is used to exclude lymphoma. Tumor may be analyzed by FISH for i(12p) which confirms the diagnosis. Even if the diagnosis is not certain, patients should be treated with cisplatin-based chemotherapy, which will cure up to 20% of this patient group.

TESTICULAR NON-GERM CELL TUMORS

Rarely, patients may develop testicular non-GCTs. These include lymphoma, most commonly occurring in men over the age of 50; sex cord stromal tumors including Leydig cell tumors and Sertoli cell tumors; mesothelioma of the tunica vaginalis; and, paratesticular sarcoma. Metastasis to the testis is rare, most commonly occurring in patients with advanced prostate cancer and melanoma.

SURVIVORSHIP AND LATE EFFECTS

Because most patients with testicular GCT will experience long-term survival, survivorship care is important. Since many of these patients will be followed by primary care physicians, an understanding of the physical, psychological, and social late effects is important. Late effects are defined as health problems that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be related to the underlying cancer or to the treatment the patient received. In long-term survivors of testicular GCT, increased cardiovascular risk and increased secondary malignancies have been reported. Patients treated with cisplatin-based chemotherapy have an increased risk of hypertension, hyperlipidemia, metabolic syndrome, and cardiovascular events. Patients treated with high cumulative doses of etoposide (such as patients who receive standard chemotherapy, relapse, and then receive salvage high dose chemotherapy) may experience up to a 1–2% risk of developing acute myelogenous leukemia, typically 2–3 years after completing therapy and associated with an 11q23 translocation. Patients treated with radiation therapy, cisplatin-based chemotherapy, or both have an increased risk of developing secondary solid malignancies.

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85 Gynecologic Malignancies

David Spriggs

OVARIAN CANCER

INCIDENCE AND PATHOLOGY

Ovarian cancer remains a leading cause of cancer deaths in American women, ranking behind lung, breast, colon, and pancreatic cancers. The ovary is responsible for the hormone and egg production. Between menarche (11–13 years) and menopause (45–55 years), the ovary is responsible for follicle maturation associated with egg maturation, ovulation, and cyclical sex steroid hormone production. These complex biologic functions are linked to stromal and germ cells within the ovary. These cells can be broadly grouped into stromal cells and ovarian germ cells and the enveloping epithelial cells. Malignancies arising in each group include multiple histological variants with unique neoplastic behaviors. Epithelial tumors are the most common histological variant of ovarian neoplasms; they may be benign (50%), frankly malignant (33%), or of borderline malignancy of low malignant potential (16%). In adnexal masses detected by imaging or physical examination, age influences risk of malignancy; tumors in younger women are more likely benign. In the malignant group, the most common tumors are epithelial. In the group of the ovarian epithelial, malignancies are the serous tumors (60–70%); mucinous tumors (10%), endometrioid (10–15%), and clear cell (10–15%), tumors. The distribution of histologic types varies in different parts of the world. Less common stromal tumors arise from the ancillary, supportive cells such as steroid hormone-producing cells and likewise have different phenotypes and clinical presentations. Most stromal tumors do not produce estrogen, but ectopic hormone production can be seen in certain subtypes. Tumors arising in the ovarian germ cell lineage are generally similar in biology and behavior to testicular tumors in males, although their intraperitoneal location alters some metastatic behaviors (Chap. 84). Ovarian tissue may also host metastatic tumors arising from breast, colon, gastric, and pancreatic primaries. Bilateral ovarian masses from metastatic mucin-secreting gastrointestinal cancers are termed *Krukenberg tumors*. A survey of other potential primaries is commonly required during the diagnostic workup of ovarian masses.

OVARIAN CANCER OF EPITHELIAL ORIGIN

Epidemiology An American woman has ~1 in 72 lifetime risk (1.6%) of developing ovarian cancer, with the majority of affected women developing epithelial tumors. In 2017, 22,440 cases of ovarian cancer with 14,195 deaths are expected in the United States. Sporadic (not familial) epithelial tumors of the ovary have a peak incidence in women in their fifties and sixties, although age at presentation ranges from the third decade to the eighties and nineties. Ovarian cancer risk has been linked to an interactive mixture of epidemiologic, environmental, and genetic factors. Nulliparity, obesity, diet, infertility treatments, and possibly hormone replacement therapy have all been linked to an increase in risk. Protective factors include the use of oral contraceptives, multiparity, tubal ligation, aspirin use, and breast-feeding. Other epidemiologic factors such as the use of perineal talcum agents remain controversial. The mechanisms underlying the various protective factors are largely unknown, but theories include suppression of ovulation, modulation of gonadotropins and progestins, and perhaps reduction of ovarian inflammation and damage associated with the repair of the ovarian cortex associated with ovulation.

GENETICS AND PATHOGENESIS

Ovarian cancers are divided into type 1 cancers and a more aggressive type 2 variant. The type 1 cancers are characterized by low-grade histology and more indolent behavior. These tumors include the low malignant potential tumors, low-grade endometrial and mucinous histologies, and clear cell cancers. Genetic alterations commonly include mutations in *KRAS, BRAF, PTEN*, and *PIK3CA*. In contrast, studies have implicated serial genetic changes in the fallopian tube as the actual site of origin for most type 2 serous epithelial ovarian cancers. These aggressive tumors are more common and linked to losses in *TP53* and DNA repair capacity. Carcinoma in situ has been identified in the tubal epithelium with early losses in *TP53* and the *BRCA1/BRCA2* genes characterizing early tubal intraepithelial cancers. Following these two early genetic events, additional mutations in these transformed cells lead to tumor cell shedding, metastasis, and invasion. These type 2, poorly differentiated "ovarian" cancer cells can then spread to the ovaries, and the peritoneal cavity, aided by the ovarian cancer cell's affinity for mesothelial lining cells.

TABLE 85-1 Staging and Survival in Gynecologic Malignancies

STAGE	OVARIAN	5-YEAR SURVIVAL, %	ENDOMETRIAL	5-YEAR SURVIVAL, %	CERVIX	5-YEAR SURVIVAL, %
0	—		—		Carcinoma in situ	100
I	Confined to ovary	88–95	Confined to corpus	>90	Confined to uterus	85
II	Confined to pelvic organs	70–80	Involves corpus and cervix	~75	Invades beyond uterus but not to pelvic wall	65
III	Intraabdominal spread to omentum, diaphragm or lymph nodes	20–40	Extends outside the uterus but not outside the true pelvis	45–60	Extends to pelvic wall and/or lower third of vagina, or hydronephrosis	35
IV	Spread outside abdominal cavity, parenchymal spread + pleural effusion cytology or extra-abdominal lymph nodes (inguinal, thoracic or supraclavicular)	17	Extends outside the true pelvis or involves the bladder or rectum	~20	Invades mucosa of bladder or rectum or extends beyond the true pelvis	7

In work done as part of the Tumor Genome Atlas, type 2, serous ovarian cancer is principally a disease characterized by amplifications and deletions rather than point mutations. Damage to the tumor suppressor gene *TP53* occurs in >95% of serous ovarian cancers. Damage to homologous DNA repair genes including *BRCA1 and BRCA2* was also common in these tumors. Low prevalence but statistically recurrent somatic mutations in seven other genes including *NF1, RB1*, and *CDK12* were also seen. The most common heritable abnormality linked to ovarian cancer is a germ-line mutation in either *BRCA1* (chromosome 17q12-21) or *BRCA2* (chromosome 13q12-13). These genes are important parts of the homologous DNA repair machinery for double-stranded DNA break repair. Individuals inheriting a single copy of a mutant allele (these act as autosomal dominant genes) have an increased lifetime risk of breast (46–87% for *BRCA1*; 38–84% for *BRCA2*) and ovarian cancer (39–63% for *BRCA1*; 16.5–27% for *BRCA2*). Many of these women have a family history that includes multiple cases of breast and/or ovarian cancer of at an early age. Male breast cancer, pancreatic cancer, and prostate cancer are also linked to familial *BRCA2* mutations. The most common malignancy in these women is breast carcinoma, although women harboring germ-line *BRCA1* mutations have a marked increased risk of developing ovarian malignancies in their forties and fifties. Women harboring a mutation in *BRCA2* have a lower penetrance of ovarian cancer with onset typically in their fifties or sixties. Other uncommon germ-line mutation of other genes encoding proteins linked to homologous DNA repair (e.g., *PALB2*) can also contribute to cancer risk although the frequency mutation and magnitude of risk increment is much lower and not well defined. Screening studies, even in the *mBRCA1/mBRCA2* families, suggest that any of the available screening techniques, including serial evaluation of the CA-125 tumor marker and transvaginal ultrasound, are insufficient to reliably detect early-stage ovarian cancer. Uniform germ-line *BRCA1/BRAC2* testing is recommended for all incident epithelial ovarian cancers to detect probands and identify relatives at risk. Women with these high-risk germ-line mutations are advised to undergo prophylactic removal of fallopian tubes and ovaries after completing childbearing and ideally before age 40. Early prophylactic salpingo-oophorectomy is highly protective. Salpingo-oophorectomy also appears to protect these women from subsequent breast cancer (risk reduction 50%). Prophylactic salpingectomy is almost certainly a key part of any surgical prophylaxis strategy for ovarian cancer, but the benefits of oophorectomy on either ovarian or breast cancer risk have not yet been clearly defined. Although less common, ovarian cancer is also another form of cancer (along with colorectal and endometrial cancer) that may develop in women with Lynch syndrome, type II, caused by mutations in one of the DNA mismatch repair genes (*MSH2, MLH1, MLH6, PMS1, PMS2*). Ovarian cancer may appear in women <50 years of age in this syndrome.

Presentation Neoplasms of the ovary tend to be painless unless they undergo torsion. Symptoms are therefore typically related to compression of local organs or due to symptoms from metastatic disease. Women with tumors localized to the ovary sometimes do have an increased incidence of symptoms including pelvic discomfort, bloating, and perhaps changes in a woman's typical urinary or bowel pattern. Unfortunately, these symptoms are common in primary care and are frequently dismissed by either the woman or her health care team until later stages of disease. The pathogenic factors and timing of spread beyond the ovary are still not well understood. The most common symptoms at presentation include a period of progressive complaints that typically include some combination of nausea, early satiety, bloating, indigestion, constipation, and abdominal pain. Signs include the rapid increase in abdominal girth due to the accumulation of ascites that typically alerts the patient and her physician that the concurrent gastrointestinal symptoms are likely associated with malignant pathology. Radiologic evaluation typically demonstrates a complex adnexal mass with ascites, carcinomatosis, with pelvic, para-aortic and mesenteric adenopathy in advanced disease. Positron emission tomography (PET) scans are generally not required. Laboratory evaluation demonstrates a markedly elevated CA-125, a shed mucin (MUC16) associated with, but not specific for, ovarian cancer. Ovarian cancers are divided into four stages, with stage I tumors confined to the ovary, stage II malignancies confined to the pelvis, and stage III confined to the peritoneal cavity and retroperitoneal nodes **(Table 85-1)**. These three stages are subdivided, with the most common presentation, stage IIIc, defined as tumors with bulky intraperitoneal disease or positive lymph node involvement. About 70% of women present with stage III disease. Stage IV disease includes women with parenchymal metastases (liver, lung, spleen) or, alternatively, abdominal wall or pleural disease. The 30% not presenting with stage III disease are roughly evenly distributed among the other stages.

Screening Ovarian cancer is a highly lethal condition, curable in early stages, and seldom curable in advanced stages; hence, screening is of considerable interest. Early-stage tumors often secrete excessive amounts of normal proteins that can be measured in the serum such as CA-125, mesothelin, and HE-4. Nevertheless, the incidence of ovarian cancer in the middle-aged female population is very low, with only ~1 in 2000 women between the ages of 50 and 60 carrying an asymptomatic and undetected tumor. Thus, effective screening techniques must be both sensitive and highly specific so to minimize the number of false positives. Panels of serum markers have not improved on CA-125 alone, although risk assessment by algorithms with multiple CA-125 is in advanced testing. No other screening strategies have been successful to date. Some large studies have suggested that low specificity screening might even worsen mortality in the screened population. Screening for ovarian cancer is currently not recommended outside of a clinical trial.

TREATMENT

Ovarian Cancer

TREATMENT

Epithelial ovarian cancer can be divided into distinct "disease states" for the purpose of treatment selection as shown in **Fig. 85-1**. Surgery by a skilled gynecologic oncologist remains the mainstay of initial therapy for ovarian cancer. The amount of residual visible

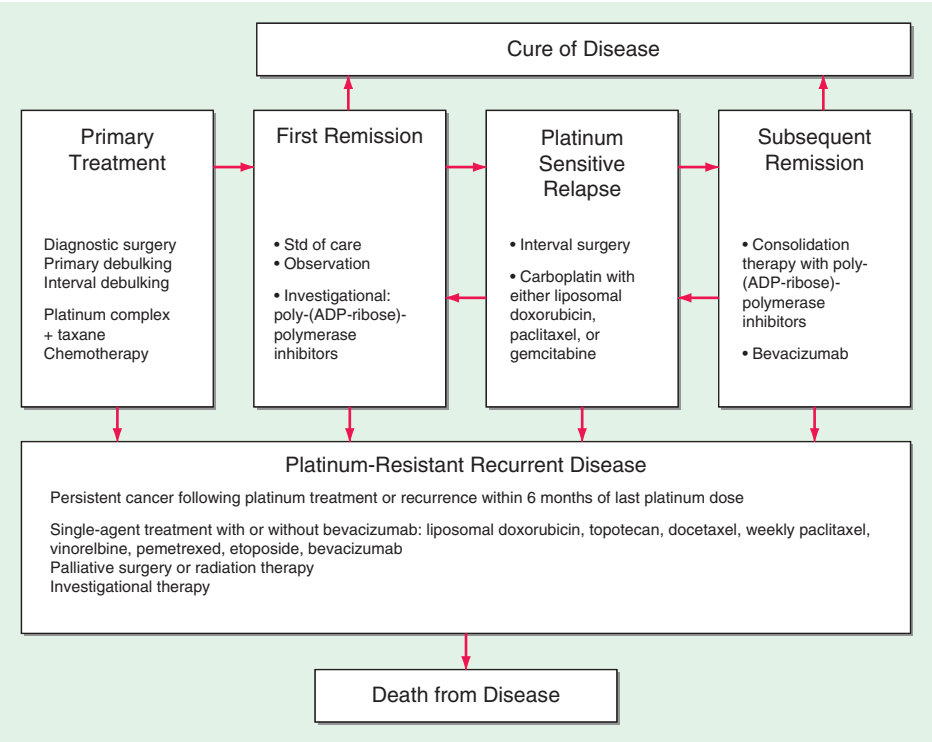

FIGURE 85-1 Disease states model of epithelial ovarian cancer and its treatment. Each box represents a relatively homogeneous group of patients that share a palette of potential treatment choices and have a similar prognosis. The arrows indicate that a single patient may move from one state to another during the course of her illness and the choice of treatments will become different in her new disease state.

cancer at the end of a primary operation is strongly predictive of outcome, and is paired with histology, grade, and stage to determine prognosis and treatment. In women presenting with a localized ovarian mass, the principal diagnostic and therapeutic maneuver is abdominal surgery to determine if the tumor is benign or malignant. In the event that the tumor is malignant, the surgical specimen will determine if the tumor arises in the ovary or is a site of metastatic disease. Metastatic disease to the ovary can be seen from primary tumors of the colon, appendix, stomach (Krukenberg tumors), and breast. Needle biopsy is contraindicated to avoid malignant contamination of the peritoneal cavity with malignant cells. Typically, women undergo laparoscopic evaluation and unilateral salpingo-oophorectomy for diagnostic purposes. If pathology reveals a primary ovarian malignancy or disseminated disease is present, then the procedure should be followed by a total hysterectomy, removal of the remaining tube and ovary, omentectomy, and pelvic node sampling along with biopsies of the peritoneal cavity and diaphragms. This extensive surgical procedure is performed because ~30% of tumors that by visual inspection appear to be confined to the ovary have already disseminated to the peritoneal cavity and/or surrounding lymph nodes. As with axillary dissections in breast cancer, node sampling is diagnostic but full lymphadenectomy appears to provide little or no additional therapeutic advantage over nodal sampling. The desired outcome of an ovarian cancer surgery is always an "R0" resection, with no visible residual cancer. The less favorable "optimal resection" (no disease greater than 1 cm in size) is still clinically useful and the prognosis of those patients is much better than the patients who are left with >1 cm disease at the end of surgery. These "suboptimally debulked" patients derive very little benefit from their surgery. Patients without gross residual disease after resection have a median survival in excess of 60 months, compared to 28–42 months for those left with macroscopic tumor.

After appropriate surgical treatment, primary chemotherapy will consist of combination treatment with paclitaxel and carboplatin. Primary chemotherapy can be delivered intravenously or alternatively, some therapy can be directly administered into the peritoneal cavity via an indwelling catheter. Several randomized studies have demonstrated improved survival with intraperitoneal therapy, but this approach is technically difficult and is increasingly replaced by carboplatin and dose dense (weekly) paclitaxel, which appears to offer similar results in some studies.

With optimal debulking surgery and platinum-based chemotherapy (usually carboplatin dosed to an area under the curve [AUC] of 6.0 plus paclitaxel 175 mg/m^2 by 3-h infusion in monthly cycles), 70% of women who present with advanced-stage tumors respond, and 40–50% experience a complete remission with normalization of their CA-125, CT scans, and physical examination. These patients are sometimes enrolled in consolidation trials to extend remission and increase likelihood of cure. New immunotherapies and poly–ADP ribose polymerase inhibitors (PARPi) such as olaparib are in active testing in these patients because less than half of the complete responders are cured. Disease recurs within 1–4 years from the completion of their primary therapy. CA-125 levels often increase as a first sign of relapse and CT scan findings are confirmatory. Recurrent disease is managed, but rarely cured, with additional surgery and variety of chemotherapeutic agents. Eventually all of these women develop chemotherapy-refractory disease and refractory ascites, poor bowel motility, and obstruction or tumor-infiltrated aperistaltic bowel are all common premorbid events. Limited surgery to relieve intestinal obstruction, localized radiation therapy to relieve pressure or pain from masses, or palliative chemotherapy may be helpful. Agents with >15% response rates include gemcitabine, topotecan, liposomal doxorubicin, and bevacizumab.

Five-year survival correlates with the stage of disease: stage I, 90–95%; stage II, 70–80%; stage III, 25–40%; stage IV, 10–15% (Table 85-1). Prognosis is also influenced by histologic grade: 5-year survival is 88% for well-differentiated tumors, 58% for moderately differentiated tumors, and 27% for poorly differentiated tumors. Histologic type has less influence on outcome.

UNCOMMON OVARIAN TUMORS

Low Malignant Potential Tumors (Borderline Tumors)

These type 1 tumors are found in younger women (ages 40–50), indolent in behavior and few of these patients will succumb to their tumors (10 years survival may approach 98%) although recurrence is not uncommon.

Certain features like micropapillary histology and microinvasion are linked to a more aggressive behavior. Patients with tumors of low malignant potential are managed primarily by surgery; chemotherapy and radiation therapy do not substantially alter survival.

Stromal Tumors Approximately 7% of ovarian neoplasms are stromal tumors, with ~1800 cases expected each year in the United States. Ovarian stromal tumors or sex cord tumors are most common in women in their fifties or sixties, but tumors can present at any age. These tumors arise from the mesenchymal components of the ovary, including both steroid-producing cells and fibroblasts. Most of these tumors are indolent tumors with limited metastatic potential and present as unilateral solid masses. These tumors primarily are discovered by the detection of an abdominal mass sometimes with abdominal pain due to ovarian torsion, intratumoral hemorrhage, or rupture. Rarely, stromal tumors can produce estrogen and present with breast tenderness as well as precocious puberty in children, menstrual disturbances in reproductively active women, or postmenopausal bleeding. In some women, estrogen-associated secondary malignancies, such as endometrial or breast cancer, may present as synchronous malignancies. Sertoli-Leydig tumors often present with hirsutism, virilization due to increased production androgens. Hormonally inert tumors include fibroma that presents as a solitary mass often in association with ascites and occasionally hydrothorax also known as Meigs' syndrome. A subset of these tumors present in individuals with a variety of inherited disorders that predispose them to mesenchymal neoplasia including Ollier's disease (juvenile granulosa cell tumors) and Peutz-Jeghers syndrome (ovarian sex cord tumors). The treatment of these tumors is almost exclusively by surgical resection. Chemotherapy with carboplatin and paclitaxel is generally reserved for either unresectable or multiply recurrent tumors.

Germ Cell Tumors of the Ovary Germ cell tumors, like their counterparts in the testis, are cancers of germ cells. These totipotent cells contain the programming for differentiation to essentially all tissue types, and hence the germ cell tumors include a histologic menagerie of bizarre tumors, including benign teratomas (dermoid cysts) and a variety of malignant tumors, such as dysgerminoma, immature teratomas, yolk sac malignancies, and choriocarcinomas. Benign teratoma (or dermoid cyst) is the most common germ cell neoplasm of the ovary and often presents in young woman. These tumors include a complex mixture of differentiated tissue including tissues from all three germ layers. In older women these differentiated tumors can develop malignant transformation, most commonly squamous cell carcinomas. Malignant germ cell tumors include dysgerminomas, yolk sac tumors, immature teratomas, as well as embryonal and choriocarcinomas. Germ cell tumors can present at all ages, but the peak age of presentation tends to be in adolescents. Typically these tumors will become large ovarian masses, which eventually present as palpable low abdominal or pelvic masses. Like sex cord tumors, torsion or hemorrhage may present urgently or emergently as acute abdominal pain. Some of germ cell tumors produce elevated levels of human chorionic gonadotropin (hCG) or α fetoprotein (AFP). Unlike epithelial ovarian cancer, these tumors have a higher proclivity for nodal or hematogenous metastases. Germ cell tumors typically present in women who are of childbearing age, and because bilateral tumors are uncommon (except in dysgerminoma, 10–15%), the typical treatment is unilateral oophorectomy or salpingo-oophorectomy with lymph node sampling. Most commonly, women with advanced malignant germ cell tumors typically receive bleomycin, etoposide, and cisplatin (BEP) chemotherapy, in an analogous fashion to the treatment of testicular cancers. In the majority of these women, even those with advanced-stage disease, cure is expected. Dysgerminoma is the ovarian counterpart of testicular seminoma and is highly curable. Although the tumor is highly radiation-sensitive, radiation produces infertility in many patients. BEP chemotherapy is as effective or more so without causing infertility.

FALLOPIAN TUBE CANCER

Transport of the egg to the uterus occurs through the fallopian tube, with the distal ends of these tubes composed of fimbriae that drape about the ovarian surface and capture the egg as it erupts from the ovarian cortex. As described previously, the majority of type 2 ovarian cancers are now thought to arise from the tubal epithelium. As might be expected, fallopian tube malignancies are typically serous histology and share the biology and recommended treatment as serous ovarian cancer. These tumors often present as clinically isolated adnexal masses, but like ovarian cancer, these tumors spread relatively early throughout the peritoneal cavity. Fallopian tubal cancers have a natural history and treatment that is essentially identical to ovarian cancer (Table 85-1).

CERVICAL CANCER

ETIOLOGY AND GENETICS

Cervical cancer is the second most common and the most lethal malignancy in women worldwide. Infection with high-risk strains of human papillomavirus (HPV) is the primary neoplastic-initiating event in the vast majority of women with invasive cervical cancer. This double-strand DNA virus infects epithelium near the transformation zone of the cervix where underlying columnar epithelium becomes squamous epithelium. More than 60 types of HPV are known, with ~20 types having the ability to generate high-grade dysplasia and malignancy. HPV16 and 18 are the types most frequently associated with high-grade dysplasia, but types 31, 33, 35, 52, and 58 are also considered to be high-risk variants. The large majority of sexually active adults are exposed to HPV, and most women clear the infection without specific intervention. The 8-kilobase HPV genome encodes seven early genes, most notably *E6* and *E7*, which can bind to *RB* and *p53*, respectively. High-risk types of HPV encode *E6* and *E7* molecules that are particularly effective at inhibiting the normal cell cycle checkpoint functions of these regulatory proteins, leading to immortalization but not full transformation of cervical epithelium. A minority of women will fail to clear the infection with subsequent HPV integration into the host genome. Over as little as a few months to several years, some of these persistently infected women develop worsening dysplasia, a premalignant condition that, untreated, can progress to cervical carcinoma. Complete transformation to cancer occurs over a period years and almost certainly requires the acquisition of other poorly defined genetic mutations within the infected and immortalized epithelium.

Approximately 528,000 new cases of cervical cancer were reported in 2012 worldwide with approximately an estimated 266,000 deaths. Cancer incidence is particularly high in women residing in central and South America, the Caribbean, and southern and eastern Africa. Mortality rate is disproportionately high in Africa. In the United States, an estimated 12,800 women will be diagnosed with cervical cancer this year, and 4210 women will die of the disease. Efforts in developed countries have looked at high-technology screening techniques for HPV involving polymerase chain reaction (PCR) and other molecular technologies.

In the integrated genomic characterization of cervical cancer by the Cancer Genome Atlas (TCGA), integration of HPV sequences was found in all of the HPV18 linked cancers and over 3 quarters of the HPV16 cancers. The cervical tumors also showed a characteristic APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; a family of cytidine deaminases that edit DNA and are endogenous mutagenic enzymes) pattern of mutagenesis with *ERBB3*, *CASP8*, and *TGFRB2* identified as significantly mutated genes presumably linked to progression from dysplasia to carcinoma. Amplification of immune targets PD-L1 and PD-L2 was also seen, which may suggest vulnerability to immunotherapy. In the much smaller number of HPV negative cancers, mutations in the common oncogenes *KRAS*, *ARID1A*, and *PTEN* were commonly seen. The clinical behavior of these cancers is likely to be different.

HPV INFECTION AND PREVENTION

The Pap smear is the primary detection method for asymptomatic preinvasive cervical dysplasia of squamous epithelial lining during a gynecologic examination. Because of the delay between dysplasia and frank cervical cancer is years long; annual (or longer) screening and prevention strategies that detect precancerous dysplasia and carcinoma

in situ can be implemented successfully. Annual or biannual cervical scraping for cytology (Pap Smear) is highly effective in reducing the incidence of cervical cancer by early detection and subsequent surgical treatment. Although no randomized trial data demonstrate the utility of Pap smears, the dramatic drop in cervical cancer incidence and death in developed countries employing wide-scale screening provides strong evidence for its effectiveness. The incorporation of HPV testing by PCR or other molecular techniques increases the sensitivity of detecting cervical pathology but at the cost of lower sensitivity in that it identifies many women with transient infections who require no specific medical intervention. Unfortunately, both the collection of a Pap smear and its cytological evaluation require infrastructure beyond the means of many middle- and low-income countries. High-throughput, low-technology prevention strategies are needed to identify and treat women bearing high-risk but treatable cervical dysplasia.

A primary prevention strategy relies on HPV vaccines. Currently approved vaccines include the recombinant proteins to the late proteins, L1 and L2 of HPV-16 and -18 as well as other, less common cancer causing isotypes 11, 31, 33, 45, 52, and 58. Vaccination of girls aged 11–13 years with two injections (one year apart) before the initiation of sexual activity dramatically reduces the rate of high-risk HPV infection and subsequent dysplasia. There is also partial protection against other HPV types, although vaccinated women are still at risk for HPV infection and still benefit from standard Pap smear screening.

CLINICAL PRESENTATIONS

Risk Factors Clinical risk factors include many HPV infection–linked features: a high number of sexual partners, early age of first intercourse, and history of venereal disease. Smoking is a cofactor; heavy smokers have a higher risk of dysplasia with HPV infection. HIV infection, especially when associated with low CD4+ T-cell counts, is associated with a higher rate of high-grade dysplasia and likely a shorter latency period between infection and invasive disease. Histologically, the majority of cervical malignancies are squamous cell carcinomas associated with HPV, but adenocarcinomas are also HPV-related, and both arise in transitional zone of the endocervical canal; the lesions in the canal or cervical glands may not be seen by visual inspection of the cervix and can be missed by Pap smear screening. Uncommon malignancies including carcinoids, small cell carcinomas, sarcomas, and lymphomas are also found but are linked to HPV infection.

Diagnosis of Cervical Cancer Early cancer of the cervix is asymptomatic and this underlies the recommendations for routine gynecologic care. Larger, invasive carcinomas often have symptoms or signs including postcoital spotting or intermenstrual cycle bleeding or menometrorrhagia. Foul-smelling or persistent yellow discharge may also be seen. Presentations that include pelvic or sacral pain suggest lateral extension of the tumor into pelvic nerve plexus by either the primary tumor or a pelvic node and are signs of advanced-stage disease. Likewise, flank pain from hydronephrosis from ureteral compression or deep venous thrombosis from iliac vessel compression suggests either extensive nodal disease or direct extension of the primary tumor to the pelvic sidewall. The most common finding upon physical examination is a visible tumor on the cervix. Larger tumors may be identified by inspection and biopsied directly. Staging of cervical cancer is performed by clinical examination. Stage I cervical tumors are confined to the cervix, whereas stage II tumors extend into the upper vagina or paracervical soft tissue (Fig. 85-2). Stage III tumors extend to the lower vagina or the pelvic sidewalls, whereas stage IV tumors invade the bladder or rectum or have spread to distant sites. While radiographic studies are not part of the formal clinical staging of cervical cancer, treatment planning requires them for appropriate therapy. CT can detect hydronephrosis indicative of pelvic sidewall disease but is not accurate at evaluating other pelvic structures. MRI is more accurate at estimating uterine extension and paracervical extension of disease into soft tissues typically bordered by broad and cardinal ligaments that support the uterus in the central pelvis. Very small stage I cervical tumors can be treated with a variety of surgical procedures. In young women desiring to maintain fertility, radical trachelectomy removes the cervix with subsequent anastomosis of the upper vagina to the uterine corpus; however, subsequent pregnancies may be more problematic. Large stage I cervical tumors (4 cm) confined to the cervix and all stage II–IV patients are treated with radiation therapy in combination with cisplatin-based chemotherapy. This multimodality treatment can offer the patient with advanced stage disease, a 40–80% of cure depending on the clinical circumstances. Platinum agents (cisplatin or carboplatin) combined with paclitaxel and bevacizumab are generally considered as the best palliative choice for metastatic cervical cancer patients. Secondary chemotherapy confers minimal improvement in most patients.

UTERINE CANCER

EPIDEMIOLOGY

Several different tumor types arise in uterine corpus. Most tumors arise in the glandular lining and are endometrial adenocarcinomas. Benign (leiomyomas) and malignant tumors (leiomyosarcomas) can also arise in the uterine smooth muscle and have very different clinical features. The endometrioid histologic subtype of endometrial cancer is the most common gynecologic malignancy in the United States. In 2017, over 60,000 new corpus cancers of uterus are projected for American women, but the surgical cure rate is high, and about 10,920 deaths from uterine cancers are predicted. Development of these tumors is a multistep process with estrogen playing an important early role in driving endometrial gland proliferation. Relative overexposure to this class of hormones is the principal risk factor for the subsequent development of endometrioid tumors. In contrast, progestins drive glandular maturation and are protective. Hence, women with high endogenous or pharmacologic exposure to estrogens, especially if unopposed by progesterone, are at higher risk for endometrial cancer. Obese women, women treated with postmenopausal estrogens or

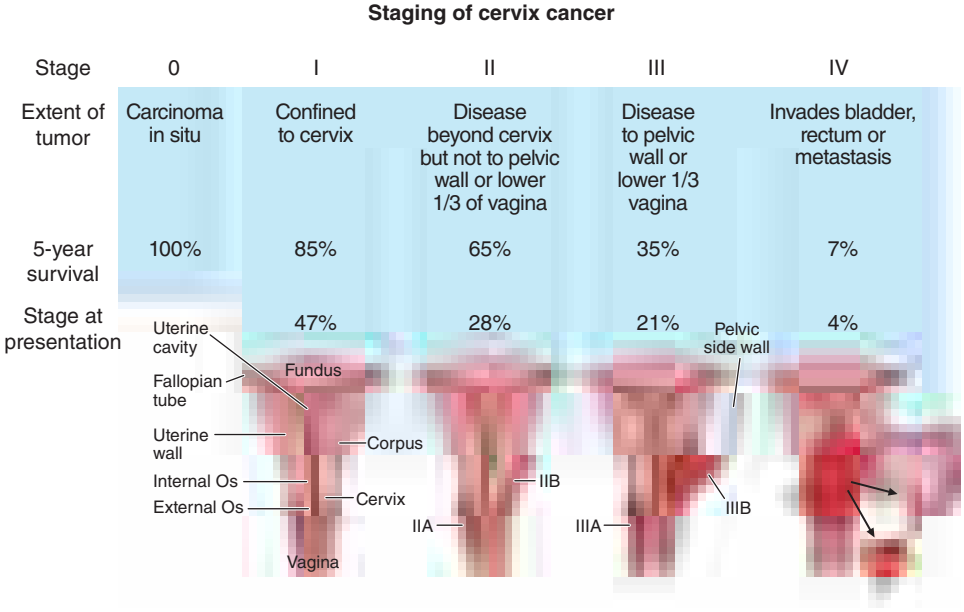

FIGURE 85-2 Anatomic display of the stages of cervix cancer defined by location, extent of tumor, frequency of presentation, and 5-year survival. *(From MV Seiden: Gynecologic malignancies, in Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill.)*

women with estrogen-producing tumors are at higher risk for endometrial cancer. In addition, long-term treatment with tamoxifen, which has antiestrogenic effects in breast tissue but can show weak estrogenic effects in uterine epithelium, is associated with an increased risk of endometrial cancer.

Genetics Women with a germ-line mutation in one of the series of DNA mismatch repair genes associated with the Lynch syndrome, also known as hereditary nonpolyposis colon cancer (HNPCC) syndrome, are at increased risk for endometrioid endometrial carcinoma. These individuals have germ-line mutations in *MSH2*, *MLH1*, and in rare cases *PMS1* and *PMS2*. Individuals who carry these mutations typically have a family history of cancer and are at markedly increased risk for colon cancer and modestly increased risk for ovarian cancer and a variety of other tumors. Middle-aged women with HNPCC carry a 4% annual risk of endometrial cancer and a relative overall risk of approximately 200-fold as compared to age-matched women without HNPCC. In sporadic cancers, secondary events such as mutation of the *PI3K* gene or the loss of the *PTEN* tumor suppressor gene likely serve as secondary "hits" in the carcinogenesis of estrogenic excess. The molecular events that underlie less common endometrial cancers such as clear cell and papillary serous tumors of the uterine corpus are less well understood.

PATHOLOGY

Approximately 75–80% of endometrial cancers are adenocarcinomas and have been characterized as type 1 (estrogen-linked) endometrial cancers and type 2 cancers that have less clear associations with estrogens (clear cell cancers, serous cancers, and mucinous cancers). Endometrial serous cancers show TP53 functional loss and behave clinically like ovarian cancers. Serous endometrial cancers are marked by a much higher risk of distant recurrence and a lower risk for locoregional spread. Prognosis depends on stage, histologic grade, and depth of myometrial invasion.

CLINICAL PRESENTATION

The majority of women with tumors of the uterine corpus present with postmenopausal vaginal bleeding due to shedding of the malignant endometrial lining. Premenopausal women often will present with atypical bleeding between typical menstrual cycles. These signs typically bring a woman to the attention of a health care professional, and the majority of women present with early-stage disease in which the tumor is confined to the uterine corpus and the consequent high cure rate. Diagnosis is typically established by endometrial biopsy. Epithelial tumors may spread to pelvic or para-aortic lymph nodes. Serous tumors tend to have patterns of spread much more reminiscent of ovarian cancer, and patients may present with omental/peritoneal disease and sometimes ascites. Some women with endometrial cancer have a history of endometriosis. Some women presenting with uterine sarcomas will present with pelvic pain. Sarcomas commonly are found by detection of symptomatic large pelvic masses that may or may not be associated with dysfunctional bleeding.

TREATMENT

Uterine Cancer

Most women with endometrial cancer have disease that is localized to the uterus (75% are stage I, Table 85-1), and definitive treatment typically involves a hysterectomy with removal of the ovaries and fallopian tubes. The resection of lymph nodes does not improve outcome, but sentinel node resection does provide staging and prognostic information. Node involvement defines stage IIIC disease. Tumor grade and depth of invasion are the two key prognostic variables in early-stage tumors, and women with low-grade and/or minimally invasive tumors (<50% myometrial penetration) are typically observed after definitive surgical therapy. Patients with high-grade tumors or tumors that are deeply invasive (stage IB) are at higher risk for pelvic recurrence or recurrence at the vaginal cuff, which is typically prevented by intravaginal brachytherapy.

Women with regional metastases or metastatic disease (3% of patients) with low-grade tumors can be treated with progesterone or tamoxifen. Poorly differentiated tumors lack hormone receptors and are typically resistant to hormonal manipulation. The role of adjuvant chemotherapy in stage I–II disease is currently under investigation but is usually employed for advanced stage (III–IV) cancer and most tumors with serous histology. Carboplatin and paclitaxel combinations are the current standard of care. Chemotherapy for metastatic disease is delivered with palliative intent. Potentially active drugs include bevacizumab, mTOR inhibitors (e.g., temsirolimus). Patients with advanced cancer and known mismatch repair deficits may respond particularly well to immunotherapy with antagonists of the PD1/PDL1 axis.

Chemotherapy of leiomyosarcomas of the uterus with docetaxel/gemcitabine, ifosfamide/doxorubicin, and trabectedin can have substantial benefit. Carcinosarcomas of the uterus contain both mesenchymal and epithelial components but will often respond to paclitaxel and platinum complex therapy.

GESTATIONAL TROPHOBLASTIC TUMORS

Gestational trophoblastic diseases represent a spectrum of neoplasia from benign hydatidiform mole to choriocarcinoma due to persistent trophoblastic disease associated most commonly with molar pregnancy but occasionally seen after normal gestation. The most common presentations of trophoblastic tumors are partial and complete molar pregnancies. These represent ~1 in 1500 conceptions in developed Western countries. The incidence widely varies globally, with areas in Southeast Asia having a much higher incidence of molar pregnancy. Regions with high molar pregnancy rates are often associated with diets low in carotene and animal fats.

RISK FACTORS

Trophoblastic tumors result from the outgrowth or persistence of placental tissue. They arise most commonly in the uterus but can also arise in other sites such as the fallopian tubes due to ectopic pregnancy. Risk factors include poorly defined dietary and environmental factors as well as conceptions at the extremes of reproductive age, with the incidence particularly high in females conceiving younger than age 16 or older than age 50. In older women, the incidence of molar pregnancy might be as high as one in three, likely due to increased risk of abnormal fertilization of the aged ova. Most trophoblastic neoplasms are associated with complete moles, diploid tumors with all genetic material from the paternal donor (known as uniparental disomy). This is thought to occur when a single sperm fertilizes an enucleate egg that subsequently duplicates the paternal DNA. Trophoblastic proliferation occurs with exuberant villous stroma. If pseudopregnancy extends out past the 12th week, fluid progressively accumulates within the stroma leading to "hydropic changes." There is no fetal development in complete moles.

Partial moles arise from the fertilization of an egg with two sperm; hence two-thirds of genetic material is paternal in these triploid tumors. Hydropic changes are less dramatic, and fetal development can often occur through late first trimester or early second trimester at which point spontaneous abortion is common. Laboratory findings will include excessively high hCG and high AFP. The risk of persistent gestational trophoblastic disease after partial mole is ~5%. Complete and partial moles can be noninvasive or invasive. Myometrial invasion occurs in no more than one in six complete moles and a lower portion of partial moles.

PRESENTATION OF INVASIVE TROPHOBLASTIC DISEASE

The clinical presentation of molar pregnancy is changing in developed countries due to the early detection of pregnancy with home pregnancy kits and the very early use of Doppler and ultrasound to evaluate the early fetus and uterine cavity for evidence of a viable fetus. Thus, in these countries, the majority of women presenting with trophoblastic disease have their moles detected early and have typical symptoms of early pregnancy including nausea, amenorrhea, and breast tenderness.

With uterine evacuation of early complete and partial moles, most women experience spontaneous remission of their disease as monitored by serial hCG levels. These women require no chemotherapy. Patients with persistent elevation of hCG or rising hCG postevacuation have persistent or actively growing gestational trophoblastic disease and require therapy. Most series suggest that between 15 and 25% of women will have evidence of persistent gestational trophoblastic disease after molar evacuation.

In women who lack access to prenatal care, presenting symptoms can be life threatening including the development of preeclampsia or even eclampsia. Hyperthyroidism can also be seen. Evacuation of large moles can be associated with life-threatening complications including uterine perforation, volume loss, high-output cardiac failure, and adult respiratory distress syndrome (ARDS).

For women with evidence of rising hCG or radiologic confirmation of metastatic or persistent regional disease, prognosis can be estimated through a variety of scoring algorithms that identify those women at low, intermediate, and high risk for requiring multiagent chemotherapy. In general, women with widely metastatic nonpulmonary disease, very elevated hCG, and prior normal antecedent term pregnancy are considered at high risk and typically require multiagent chemotherapy at an expert center for cure. Even very advanced gestational trophoblastic disease is almost uniformly curable when managed by an expert in this rare malignancy.

TREATMENT

Invasive Trophoblastic Disease

Management of invasive trophoblastic disease should be 100% curative and complex patients should be managed by clinicians experienced in this disease. The management for a persistent and rising hCG postevacuation of a molar conception is typically chemotherapy, although surgery can play an important role for chemotherapy-resistant disease that is isolated in the uterus (especially if childbearing is complete) or to control hemorrhage. For women wishing to maintain fertility or with metastatic disease, the preferred treatment is chemotherapy. Trophoblastic disease is exquisitely sensitive to chemotherapy and guided by serial serum hCG testing, successful, curative treatment is the rule. Single-agent treatment with methotrexate or actinomycin D cures 90% of women with low-risk disease. Patients with high-risk disease (very high hCG levels, presentation 4 or more months after pregnancy, brain or liver metastases, failure of methotrexate therapy) are typically treated with multiagent chemotherapy (etoposide, methotrexate, and actinomycin D alternating with cyclophosphamide and vincristine [EMA-CO]), which is typically curative even in those women with extensive metastatic disease. Cisplatin and etoposide alternating with etoposide / methotrexate/ actinomycin D is used for the highest risk patients. In the highest-risk patients with liver lung and brain metastases, hemorrhage from the rich tumor vasculature is a major risk during chemotherapy initiation. Cured women may get pregnant again without evidence of increased fetal or maternal complications.

Acknowledgment

Michael V. Seiden was the author of this chapter in the 19th edition. Material from his chapter has been included here.

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86 Primary and Metastatic Tumors of the Nervous System

Lisa M. DeAngelis, Patrick Y. Wen

Primary brain tumors are diagnosed in ~78,000 people each year in the United States. At least 25,000 are malignant, and most of these are gliomas. Meningiomas account for 35%, vestibular schwannomas 10%, and central nervous system (CNS) lymphomas ~2%. Brain metastases are three times more common than all primary brain tumors combined and are diagnosed in ~150,000 people each year. Metastases to the leptomeninges and epidural space of the spinal cord each occur in ~3–5% of patients with systemic cancer and are also a major cause of neurologic disability.

APPROACH TO THE PATIENT

Primary and Metastatic Tumors of the Nervous System

CLINICAL FEATURES

Brain tumors of any type can present with a variety of symptoms and signs that fall into two categories: general and focal; patients often have a combination of the two **(Table 86-1)**. General or nonspecific symptoms include headache, with or without nausea or vomiting, cognitive difficulties, personality change, and gait disorder. Generalized symptoms arise when the enlarging tumor and its surrounding edema cause an increase in intracranial pressure or compression of cerebrospinal fluid (CSF) circulation leading to hydrocephalus. The classic brain tumor headache predominates in the morning and improves during the day, but this pattern is seen only in a minority of patients. Headaches are often holocephalic but can be ipsilateral to the side of a tumor. Occasionally, headaches have features of a typical migraine with unilateral throbbing pain associated with visual scotoma. Personality changes may include apathy and withdrawal from social situations, mimicking depression. Focal or lateralizing findings include hemiparesis, aphasia, or visual field defect. Lateralizing symptoms are typically subacute and progressive; language difficulties may be mistaken for confusion. Seizures are common, occurring in ~25% of patients with brain metastases or malignant gliomas and are the presenting symptom in up to 90% of patients with a low-grade glioma. All seizures that arise from a brain tumor will have a focal onset whether or not it is apparent clinically.

NEUROIMAGING

Cranial magnetic resonance imaging (MRI) is the preferred diagnostic test for any patient suspected of having a brain tumor and should be performed with gadolinium contrast administration. Computed tomography (CT) scan should be reserved for those patients unable to undergo MRI. Malignant brain tumors—whether primary or metastatic—typically enhance with gadolinium, have central areas of necrosis, and are surrounded by edema of the neighboring white matter. Low-grade gliomas usually do not enhance with gadolinium and are best appreciated on fluid-attenuated inversion recovery (FLAIR) MRIs. Meningiomas have a typical appearance on MRI because they are dural-based enhancing tumors with a dural tail and compress but do not invade the brain. Dural metastases or a dural lymphoma can have a similar appearance. Imaging is characteristic for many primary and metastatic tumors and sometimes will suffice to establish a diagnosis when the location precludes surgical intervention (e.g., brainstem glioma). Functional MRI is useful in presurgical planning to define eloquent sensory, motor, or language cortex. Positron emission tomography (PET) is useful in determining

TABLE 86-1 Symptoms and Signs at Presentation of Brain Tumors

	HIGH-GRADE GLIOMA (%)	LOW-GRADE GLIOMA (%)	MENINGIOMA (%)	METASTASES (%)
Generalized				
Impaired cognitive function	50	10	30	60
Hemiparesis	40	10	36	60
Headache	50	40	37	50
Lateralizing				
Seizures	20	70+	17	18
Aphasia	20	<5	—	18
Visual field deficit	—	—	—	7

the metabolic activity of the lesions seen on MRI; MR perfusion and spectroscopy can provide information on blood flow or tissue composition. These techniques may help distinguish tumor progression from necrotic tissue as a consequence of treatment with radiation and chemotherapy. Neuroimaging is the only test necessary to diagnose a brain tumor. Laboratory tests are rarely useful, although patients with metastatic disease may have elevation of a serum tumor marker (e.g., β human chorionic gonadotropin [β-hCG] from testicular cancer). Additional testing such as cerebral angiogram, electroencephalogram (EEG), or lumbar puncture is rarely indicated or helpful.

TREATMENT

Brain Tumors

Therapy of any intracranial malignancy requires both symptomatic and definitive treatments. Definitive treatment is based on the specific tumor type and includes surgery, radiotherapy, and chemotherapy. However, symptomatic treatments apply to brain tumors of any type. Most high-grade malignancies are accompanied by substantial surrounding edema, which contributes to neurologic disability and raised intracranial pressure. Glucocorticoids are highly effective at reducing perilesional edema and improving neurologic function, often within hours of administration. Dexamethasone has been the glucocorticoid of choice because of its relatively low mineralocorticoid activity; initial doses are 8–16 mg/d. Glucocorticoids rapidly ameliorate symptoms and signs, but their long-term use causes substantial toxicity including insomnia, weight gain, diabetes mellitus, steroid myopathy, and personality changes. Consequently, a taper is indicated as definitive treatment is administered and the patient improves.

Patients with brain tumors who present with seizures require antiepileptic drug therapy. There is no role for prophylactic antiepileptic drugs in patients who have not had a seizure. The agents of choice are those drugs that do not induce the hepatic microsomal enzyme system. These include levetiracetam, topiramate, lamotrigine, valproic acid, and lacosamide **(Chap. 418)**. Other drugs, such as phenytoin and carbamazepine, are used less frequently because they are potent enzyme inducers that can interfere with both glucocorticoid and chemotherapy metabolism. Venous thromboembolic disease occurs in 20–30% of patients with high-grade gliomas or brain metastases. Prophylactic anticoagulants should be used during hospitalization and in nonambulatory patients. Those who have had either a deep vein thrombosis or pulmonary embolus can receive therapeutic doses of anticoagulation safely and without increasing the risk for hemorrhage into the tumor. Inferior vena cava filters are reserved for patients with absolute contraindications to anticoagulation such as recent craniotomy.

PRIMARY BRAIN TUMORS

EPIDEMIOLOGY

No underlying cause has been identified for the majority of primary brain tumors. The only established risk factors are exposure to ionizing radiation (meningiomas, gliomas, and schwannomas) and immunosuppression (primary CNS lymphoma). There is no proven evidence for any association with exposure to electromagnetic fields including cellular telephones, head injury, foods containing *N*-nitroso compounds, or occupational risk factors. A small minority of patients have a family history of brain tumors. Some of these familial cases are associated with genetic syndromes **(Table 86-2)**.

MOLECULAR PATHOGENESIS

As with other neoplasms, brain tumors arise as a result of a multistep process driven by the sequential acquisition of genetic alterations. These include loss of tumor-suppressor genes (e.g., *p53*, cyclin-dependent kinase inhibitor 2A and 2B [*CDKN2A/B*], and phosphatase and tensin homolog on chromosome 10 [*PTEN*]) and amplification and overexpression of protooncogenes such as the epidermal growth factor receptor (*EGFR*) and the platelet-derived growth factor receptors (*PDGFR*). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation.

Important progress has been made in understanding the molecular pathogenesis of several types of brain tumors, including glioblastoma and medulloblastoma, allowing them to be separated into different subtypes with different prognoses. This has led the World Health Organization (WHO) to issue an update on the classification of CNS tumors in 2016 that for the first time incorporates molecular parameters in addition to traditional histology into the diagnosis of brain tumors.

INTRINSIC "MALIGNANT" TUMORS

DIFFUSE GIOMAS

Gliomas are the most common type of malignant primary brain tumor and are derived, based on their presumed lineage, into astrocytomas and oligodendrogliomas. These tumors are classified based on two highly recurrent molecular alterations, isocitrate dehydrogenase (*IDH*) mutations and 1p/19q codeletion, in addition to more conventional histopathologic parameters. Most lower-grade astrocytomas have *IDH* mutations but intact 1p/19q, and often mutations in *ATRX* and *p53*. Oligodendrogliomas usually have *IDH* mutations and codeletion of 1p/19q.

ASTROCYTOMAS

These are infiltrative tumors with a presumptive glial cell of origin. WHO classifies astrocytomas into four prognostic grades based on histologic features: grade I (pilocytic astrocytoma, subependymal giant cell astrocytoma); grade II (astrocytoma); grade III (anaplastic astrocytoma); and grade IV (glioblastoma). Grades I and II are considered low-grade, and grades III and IV high-grade, astrocytomas.

Low-Grade Astrocytoma • GRADE I ASTROCYTOMAS Pilocytic astrocytomas (WHO grade I) are the most common tumor of childhood. They occur typically in the cerebellum but may also be found elsewhere in the neuraxis, including the optic nerves and brainstem. Frequently they appear as cystic lesions with an enhancing mural nodule. Often they have *BRAF* fusions or mutations. These are well-demarcated lesions that are potentially curable if they can be resected completely. Giant-cell subependymal astrocytomas are usually found in the ventricular wall of patients with tuberous sclerosis. They often do not require intervention but can be treated surgically or with inhibitors of the mammalian target of rapamycin (mTOR).

TABLE 86-2 Genetic Syndromes Associated with Primary Brain Tumors

SYNDROME	INHERITANCE	GENE/PROTEIN	ASSOCIATED TUMORS
Cowden's syndrome	AD	Mutations of *PTEN* (ch10p23)	Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease), meningioma, astrocytoma Breast, endometrial, thyroid cancer, trichilemmomas
Familial schwannomatosis	Sporadic Hereditary	Mutations in *INI1/SNF5* (ch22q11)	Schwannomas, gliomas
Gardner's syndrome	AD	Mutations in *APC* (ch5q21)	Medulloblastoma, glioblastoma, craniopharyngioma Familial polyposis, multiple osteomas, skin and soft tissue tumors
Gorlin syndrome (basal cell nevus syndrome)	AD	Mutations in *Patched 1* gene (ch9q22.3)	Medulloblastomas Basal cell carcinoma
Li-Fraumeni syndrome	AD	Mutations in *p53* (ch17p13.1)	Gliomas, medulloblastomas Sarcomas, breast cancer, leukemias, others
Multiple endocrine neoplasia 1 (Werner's syndrome)	AD	Mutations in *Menin* (ch11q13)	Pituitary adenoma, malignant schwannomas Parathyroid and pancreatic islet cell tumors
NF1	AD	Mutations in *NF1*/neurofibromin (ch17q12-22)	Schwannomas, astrocytomas, optic nerve gliomas, meningiomas Neurofibromas, neurofibrosarcomas, others
NF2	AD	Mutations in *NF2*/merlin (ch22q12)	Bilateral vestibular schwannomas, astrocytomas, multiple meningiomas, ependymomas
TSC (Bourneville disease)	AD	Mutations in *TSC1/TSC2* (ch9q34/16)	Subependymal giant-cell astrocytoma, ependymomas, glioma, ganglioneuroma, hamartoma
Turcot syndrome	AD AR	Mutations in *APC*[a] (ch5) hMLH1 (ch3p21)	Gliomas, medulloblastomas Adenomatous colon polyps, adenocarcinoma
VHL	AD	Mutations in *VHL* gene (ch3p25)	Hemangioblastomas Retinal angiomas, renal cell carcinoma, pheochromocytoma, pancreatic tumors and cysts, endolymphatic sac tumors of the middle ear

[a]Various DNA mismatch repair gene mutations may cause a similar clinical phenotype, also referred to as Turcot syndrome, in which there is a predisposition to nonpolyposis colon cancer and brain tumors.

Abbreviations: AD, autosomal dominant; APC, adenomatous polyposis coli; AR, autosomal recessive; ch, chromosome; NF, neurofibromatosis; PTEN, phosphatase and tensin homologue; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau.

GRADE II ASTROCYTOMAS These are infiltrative tumors that usually present with seizures in young adults. They appear as nonenhancing tumors with increased T2/FLAIR signal **(Fig. 86-1)**. If feasible, patients should undergo maximal surgical resection, although complete resection is rarely possible because of the invasive nature of the tumor. In patients at higher risk for recurrence (subtotal resection or above the age of 40 years), there is evidence that radiation therapy (RT) followed by PCV (procarbazine, cyclohexylchloroethylnitrosourea [CCNU], and vincristine) chemotherapy may possibly be of benefit. The tumor transforms to a malignant astrocytoma in most patients, leading to variable survival with a median of ~5–10 years. The minority of grade II astrocytomas without *IDH* mutations have a worse prognosis.

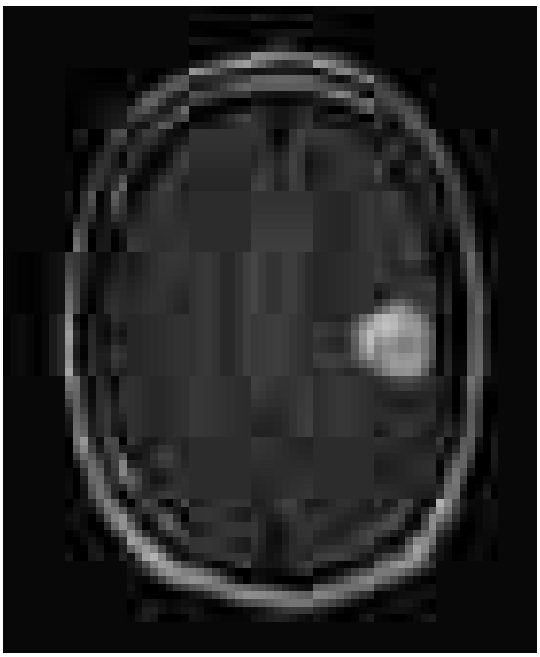


FIGURE 86-1 Fluid-attenuated inversion recovery (FLAIR) MRI of a left frontal low-grade astrocytoma. This lesion did not enhance.

High-Grade Astrocytoma

GRADE III (ANAPLASTIC) ASTROCYTOMA These account for ~15–20% of high-grade astrocytomas. They generally present in the fourth and fifth decades of life as variably enhancing tumors. Treatment is the same as for glioblastoma, consisting of maximal safe surgical resection followed by RT and adjuvant temozolomide alone or RT with concurrent and adjuvant temozolomide.

GRADE IV ASTROCYTOMA (GLIOBLASTOMA) Glioblastoma accounts for the majority of high-grade astrocytomas. Approximately 10% of glioblastoma have *IDH* mutations. These tend to arise from lower-grade tumors (secondary glioblastomas) and have a better prognosis. They are the most common malignant primary brain tumor, with >12,000 cases diagnosed each year in the United States. Patients usually present in the sixth and seventh decades of life with headache, seizures, or focal neurologic deficits. The tumors appear as ring-enhancing masses with central necrosis and surrounding edema **(Fig. 86-2)**. These are highly infiltrative tumors, and the areas of increased T2/FLAIR signal surrounding the main tumor mass contain invading tumor cells. Treatment involves maximal surgical resection followed by partial-field external-beam RT (6000 cGy in thirty 200-cGy fractions) with concomitant temozolomide, followed by 6–12 months of adjuvant temozolomide. With this regimen, median survival is increased to 14.6–18 months compared to only 12 months with RT alone, and 5-year survival is ~10%. Patients whose tumor contains the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) are relatively resistant to temozolomide and have a worse prognosis compared to those whose tumors contain low levels of MGMT as a result of silencing of the MGMT gene by promoter hypermethylation. Implantation of biodegradable polymers containing

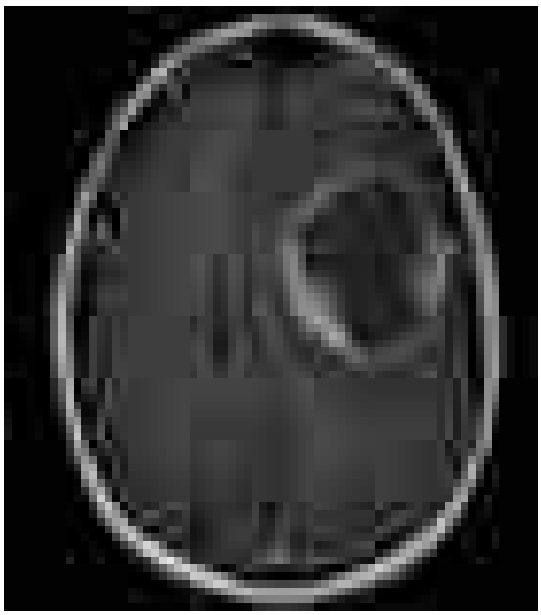


FIGURE 86-2 **Postgadolinium T1 MRI of a large cystic left frontal glioblastoma.**

carmustine chemotherapy into the tumor bed after resection of the tumor, or addition of tumor treating fields (scalp electrodes delivering low intensity electric currents), produces a modest improvement in survival.

For elderly patients aged >65–70 years, a hypofractionated RT regimen of 40 Gy over 3 weeks with temozolomide is well-tolerated and likely leads to similar outcomes as the 6-week standard RT regimen.

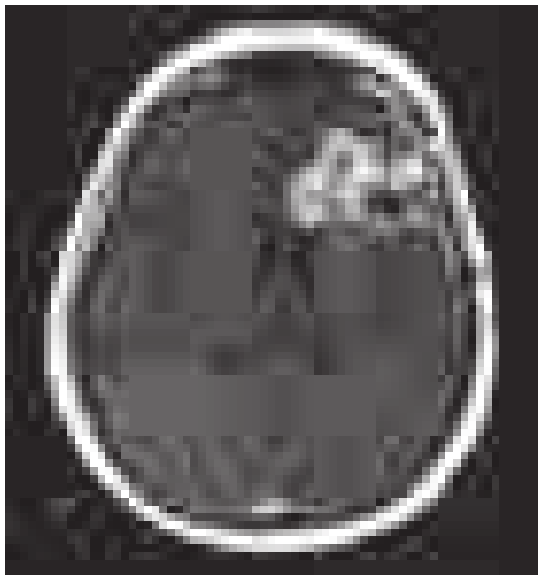
Despite optimal therapy, glioblastomas invariably recur. Treatment options for recurrent disease may include reoperation, carmustine wafers, and alternate chemotherapeutic regimens. Reirradiation is rarely helpful. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, has activity in recurrent glioblastoma, increasing progression-free survival but not overall survival, and reducing peritumoral edema and glucocorticoid use **(Fig. 86-3)**. Treatment decisions for patients with recurrent glioblastoma must be made on an individual basis, taking into consideration such factors as previous therapy, time to relapse, performance status, and quality of life. Whenever feasible, patients with recurrent disease should be enrolled in clinical trials. Novel therapies undergoing evaluation in patients with glioblastoma include targeted molecular agents directed at receptor tyrosine kinases and signal transduction pathways; immunotherapy; oncolytic viruses; antiangiogenic agents; chemotherapeutic agents that cross the blood-brain barrier more effectively than currently available drugs; and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convection-enhanced delivery.

The most important adverse prognostic factors in patients with glioblastomas are older age, absence of *IDH* mutations, unmethylated MGMT promoter, poor Karnofsky performance status, and unresectable tumor.

Gliosarcomas are a variant of glioblastoma containing both an astrocytic and a sarcomatous component and are treated in the same way as glioblastomas.

OLIGODENDROGLIOMA

Oligodendrogliomas account for ~15–20% of gliomas. They are characterized by codeletion of 1p/19q and usually have *IDH* mutations. Oligodendrogliomas are classified by the WHO into oligodendrogliomas (grade II) or anaplastic oligodendrogliomas (AOs) (grade III). Oligodendrogliomas have distinctive pathologic features such as perinuclear clearing—giving rise to a "fried-egg" appearance—and a reticular pattern of blood vessel growth. Some tumors have both an oligodendroglial as well as an astrocytic component. With molecular testing, it is now clear that almost all these mixed tumors (oligoastrocytomas) are genetically either astrocytomas or oligodendrogliomas. As a result, the diagnosis of oligoastrocytoma is now rarely made unless molecular testing is not available.



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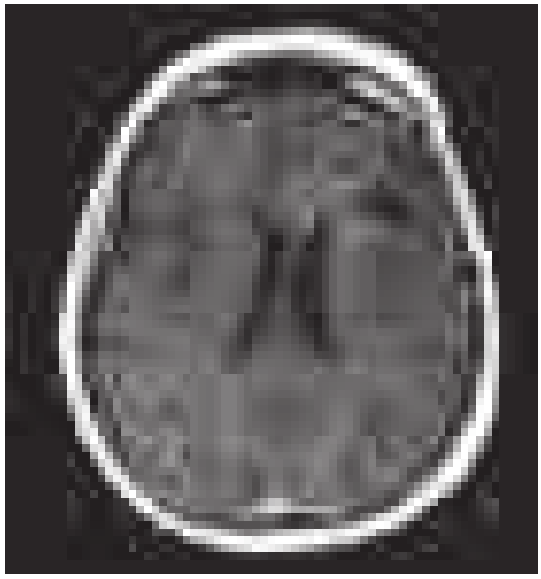


B

FIGURE 86-3 **Postgadolinium T1 MRI of a recurrent glioblastoma** before (***A***) and after (***B***) administration of bevacizumab. Note the decreased enhancement and mass effect.

Grade II oligodendrogliomas are generally more responsive to therapy and have a better prognosis than pure astrocytic tumors. These tumors present similarly to grade II astrocytomas in young adults. The tumors are nonenhancing and often partially calcified. They should be treated with surgery and, in patients with residual disease or aged >40 years, RT and chemotherapy. Patients with oligodendrogliomas have a median survival in excess of 10 years.

AOs present in the fourth and fifth decades as variably enhancing tumors. They are more responsive to therapy than grade III astrocytomas. Treatment involves maximal safe resection followed by RT and PCV or temozolomide chemotherapy. Median survival of patients with AO is in excess of 10 years.

EPENDYMOMAS

Ependymomas are tumors derived from ependymal cells that line the ventricular surface. They account for ~5% of childhood tumors and frequently arise from the wall of the fourth ventricle in the posterior fossa. Although adults can have intracranial ependymomas, they occur more commonly in the spine, especially in the filum terminale of the spinal

cord where they have a myxopapillary histology. Ependymomas that can be completely resected are potentially curable. Partially resected ependymomas will recur and require irradiation. The less common anaplastic ependymoma is more aggressive and is treated with resection and RT; chemotherapy has limited efficacy. Subependymomas are slow-growing benign lesions arising in the wall of ventricles that often do not require treatment.

OTHER LESS COMMON GLIOMAS

Gangliogliomas and pleomorphic xanthoastrocytomas occur in young adults. They behave as more indolent forms of grade I gliomas and are usually treated with surgery. Frequently they will have *BRAFV600E* mutations. Brainstem gliomas usually occur in children or young adults. Despite treatment with RT and chemotherapy, the prognosis is poor, with a median survival of only 1 year.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma accounting for <3% of primary brain tumors. For unclear reasons, its incidence is increasing, particularly in immunocompetent, older individuals.

PCNSL in immunocompetent patients is usually a diffuse large B-cell lymphoma. Immunocompromised patients, especially those infected with the human immunodeficiency virus (HIV) or organ transplant recipients, are at risk for PCNSL that is typically large cell with immunoblastic and more aggressive features. Epstein-Barr virus (EBV) plays an important role in the pathogenesis of PCNSL in this population. These patients are usually severely immunocompromised, with CD4 counts of <50/mL.

Immunocompetent patients with PCNSL are older (median 60 years) compared to those with HIV-related PCNSL (median 31 years). PCNSL usually presents as a mass lesion, with neuropsychiatric symptoms, lateralizing signs, or seizures. Ocular and leptomeningeal involvement each occur in 15–20% of patients.

On contrast-enhanced MRI, PCNSL usually appears as a densely enhancing tumor **(Fig. 86-4)**. Immunocompetent patients have solitary lesions more often than immunosuppressed patients. Frequently there is involvement of the basal ganglia, corpus callosum, or periventricular region. Stereotactic biopsy is necessary to obtain a histologic diagnosis. Whenever possible, glucocorticoids should be withheld until after the biopsy has been obtained because they have a cytolytic effect on lymphoma cells and may lead to nondiagnostic tissue. In addition, patients should be tested for HIV, and the extent of disease should be assessed by performing PET or CT of the body, MRI of the spine, CSF analysis, and slit-lamp examination of the eye. Bone marrow biopsy and testicular ultrasound are occasionally performed.

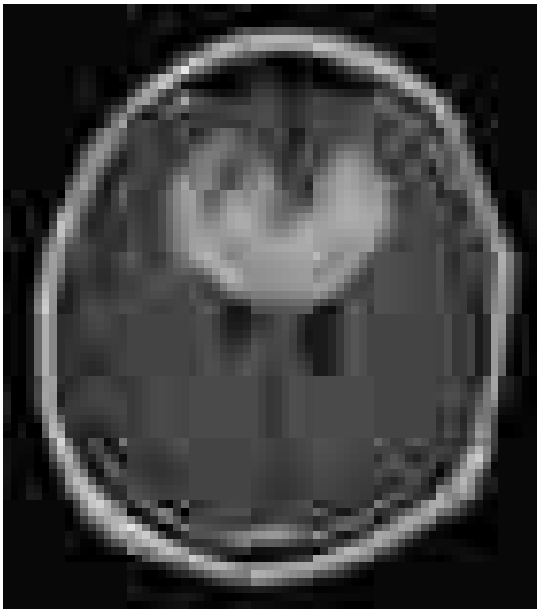


FIGURE 86-4 Postgadolinium T1 MRI demonstrating a large bifrontal primary central nervous system lymphoma (PCNSL). The periventricular location and diffuse enhancement pattern are characteristic of lymphoma.

TREATMENT

Primary Central Nervous System Lymphoma

PCNSL is more sensitive to glucocorticoids, chemotherapy, and RT than other primary brain tumors. Durable complete responses and long-term survival are possible with these treatments. High-dose methotrexate, a folate antagonist that interrupts DNA synthesis, produces response rates ranging from 35 to 80% and median survival of up to 50 months. The combination of methotrexate with other chemotherapeutic agents such as cytarabine increases the response rate to 70–100%. The addition of whole-brain RT to methotrexate-based chemotherapy prolongs progression-free survival but not overall survival, but it is associated with delayed neurotoxicity, especially in patients aged >60 years. As a result, full-dose RT is frequently omitted, but there may be a role for reduced-dose RT. The anti-CD20 monoclonal antibody rituximab has activity in PCNSL and is often incorporated into the chemotherapy regimen. For some patients, high-dose chemotherapy with autologous stem cell rescue may offer the best chance of preventing relapse. At least 50% of patients will eventually develop recurrent disease. Treatment options include RT for patients who have not had prior irradiation, re-treatment with methotrexate, as well as other agents such as temozolomide, rituximab, procarbazine, topotecan, and pemetrexed. High-dose chemotherapy with autologous stem cell rescue may be appropriate in selected patients with relapsed disease.

PCNSL IN IMMUNOCOMPROMISED PATIENTS

PCNSL in immunocompromised patients often produces multiple ring-enhancing lesions that can be difficult to differentiate from metastases or infections such as toxoplasmosis. The diagnosis is usually established by examination of the CSF for cytology and EBV DNA, toxoplasmosis serologic testing, brain PET imaging for hypermetabolism of the lesions which, although nonspecific, can be consistent with tumor, and, if necessary, brain biopsy. Since the advent of highly active antiretroviral drugs, the incidence of HIV-related PCNSL has declined. These patients are preferably treated with high-dose methotrexate-based regimens and initiation of highly active antiretroviral therapy; whole-brain RT is reserved for those who cannot tolerate systemic chemotherapy. In organ transplant recipients, reduction of immunosuppression may improve outcome.

MEDULLOBLASTOMAS

Medulloblastomas are the most common malignant brain tumor of childhood, accounting for ~20% of all primary CNS tumors among children. They arise from granule cell progenitors or from multipotent progenitors from the ventricular zone. Approximately 5% of children with medulloblastoma have an inherited syndrome, such as Gorlin, Turcot, or Li-Fraumeni, which predisposes to the development of medulloblastoma. Histologically, medulloblastomas are highly cellular tumors with abundant dark staining, round nuclei, and rosette formation (Homer-Wright rosettes). In the 2016 WHO pathologic classification, they have been divided into four molecular subgroups: (1) WNT-activated (primarily affects children and has the best outcome); (2) SHH-activated (affects adults, infants, and children with the younger patients having the better outcome and adults doing poorly); (3) non-WNT/non-SHH, group 3 (frequently has disseminated CNS disease at diagnosis and has the worst outcome); and (4) non-WNT/non-SHH, group 4 (30% have metastases at diagnosis, but 5-year progression-free survival is 95%). Regardless of subtype, patients present with headache, ataxia, and signs of brainstem involvement. On MRI they appear as densely enhancing tumors in the posterior fossa, sometimes associated with hydrocephalus. Treatment involves maximal surgical resection, craniospinal irradiation, and chemotherapy with agents such as cisplatin, lomustine, cyclophosphamide, and vincristine. Approximately 70% of

patients overall have long-term survival but usually at the cost of significant neurocognitive impairment. A major goal of current research is to improve survival while minimizing long-term complications, and clinical trials are now being designed for specific molecular subgroups.

PINEAL REGION TUMORS

A large number of tumors can arise in the region of the pineal gland. These typically present with headache, visual symptoms, and hydrocephalus. Patients may have Parinaud's syndrome characterized by impaired upgaze and accommodation. Some pineal tumors such as pineocytomas and benign teratomas can be treated by surgical resection. Germinomas respond to irradiation, whereas pineoblastomas and nongerminomatous germ cell tumors require craniospinal radiation and chemotherapy.

EXTRINSIC "BENIGN" TUMORS

MENINGIOMAS

Meningiomas are diagnosed with increasing frequency as more people undergo neuroimaging for various indications. They are now the most common primary brain tumor, accounting for ~35% of the total. Their incidence increases with age. They tend to be more common in women and in patients with neurofibromatosis type 2 (NF2). They also occur more commonly in patients with a past history of cranial irradiation.

Meningiomas arise from the dura mater and are composed of neoplastic meningothelial (arachnoidal cap) cells. They are most commonly located over the cerebral convexities, especially adjacent to the sagittal sinus, but they can also occur in the skull base and along the dorsum of the spinal cord. Meningiomas are classified by the WHO into three histologic grades of increasing aggressiveness: grade I (benign), grade II (atypical), and grade III (malignant).

Many meningiomas are found incidentally following neuroimaging for unrelated reasons. They can also present with headaches, seizures, or focal neurologic deficits. On imaging studies they have a characteristic appearance usually of a densely enhancing extra-axial tumor arising from the dura **(Fig. 86-5)**. Typically they have a dural tail, consisting of thickened, enhanced dura extending like a tail from the mass. The main differential diagnosis of meningioma is a dural metastasis.

If the meningioma is small and asymptomatic, no intervention is necessary and the lesion can be observed with serial MRI studies. Larger, symptomatic lesions should be resected. If complete resection is achieved, the patient is cured. Incompletely resected tumors tend to recur, although the rate of recurrence can be very slow with grade I tumors. Tumors that cannot be resected, or can only be partially removed, may benefit from external-beam RT or stereotactic radiosurgery (SRS). These treatments may also be helpful in patients whose tumor has recurred after surgery. Hormonal therapy and chemotherapy are currently unproven.

Rarer tumors that resemble meningiomas include hemangiopericytomas and solitary fibrous tumors. Since they share similar molecular alterations, the 2016 WHO classification introduced the combined term solitary fibrous tumor/hemangiopericytoma for this entity. These tumors are treated with surgery and RT but have a higher propensity to recur locally or metastasize systemically.

SCHWANNOMAS

These are generally benign tumors arising from the Schwann cells of cranial and spinal nerve roots. The most common schwannomas, termed *vestibular schwannomas* or *acoustic neuromas*, arise from the vestibular portion of the eighth cranial nerve and account for ~9% of primary brain tumors. Patients with NF2 have a high incidence of vestibular schwannomas that are frequently bilateral. Schwannomas arising from other cranial nerves, such as the trigeminal nerve (cranial nerve V), occur with much lower frequency. Neurofibromatosis type 1 (NF1) is associated with an increased incidence of schwannomas of the spinal nerve roots.

Vestibular schwannomas may be found incidentally on neuroimaging or present with progressive unilateral hearing loss, dizziness, tinnitus, or, less commonly, symptoms resulting from compression of the brainstem and cerebellum. On MRI they appear as densely enhancing lesions, enlarging the internal auditory canal and often extending into the cerebellopontine angle **(Fig. 86-6)**. The differential diagnosis includes meningioma. Very small, asymptomatic lesions can be observed with serial MRIs. Larger lesions should be treated with surgery or SRS. The optimal treatment will depend on the size of the tumor, symptoms, and the patient's preference. In patients with small vestibular schwannomas and relatively intact hearing, early surgical intervention increases the chance of preserving hearing.

PITUITARY TUMORS

These are discussed in detail in **Chap. 373**.

CRANIOPHARYNGIOMAS

Craniopharyngiomas are rare, usually suprasellar, partially calcified, solid, or mixed solid-cystic benign tumors that arise from remnants of Rathke's pouch. They have a bimodal distribution, occurring predominantly in children but also between the ages of 55 and 65 years.

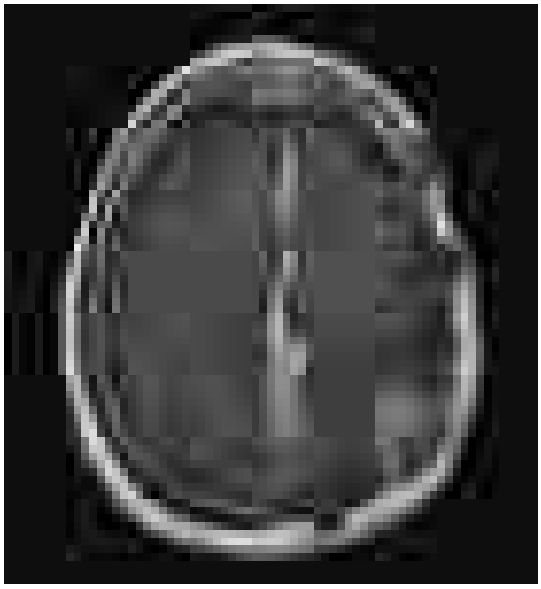


FIGURE 86-5 Postgadolinium T1 MRI demonstrating multiple meningiomas along the falx and left parietal cortex.

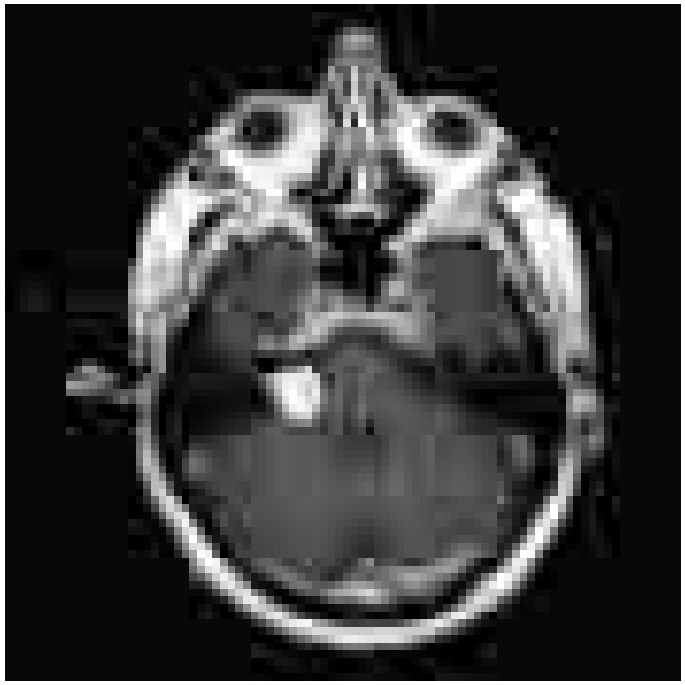


FIGURE 86-6 Postgadolinium MRI of a right vestibular schwannoma. The tumor can be seen to involve the internal auditory canal.

They present with headaches, visual impairment, and impaired growth in children and hypopituitarism in adults. Treatment involves surgery, RT, or a combination of the two.

OTHER BENIGN TUMORS

Dysembryoplastic Neuroepithelial Tumors (DNTs) These are benign, supratentorial tumors, usually in the temporal lobe. They typically occur in children and young adults with a long-standing history of seizures. Surgical resection is curative.

Epidermoid Cysts These consist of squamous epithelium surrounding a keratin-filled cyst. They are usually found in the cerebellopontine angle and the intrasellar and suprasellar regions. They may present with headaches, cranial nerve abnormalities, seizures, or hydrocephalus. MRI demonstrates an extra-axial lesion with characteristics that are similar to CSF but have restricted diffusion. Treatment involves surgical resection.

Dermoid Cysts Like epidermoid cysts, dermoid cysts arise from epithelial cells that are retained during closure of the neural tube. They contain both epidermal and dermal structures such as hair follicles, sweat glands, and sebaceous glands. Unlike epidermoid cysts, these tumors usually have a midline location. They occur most frequently in the posterior fossa, especially the vermis, fourth ventricle, and suprasellar cistern. On MRI, dermoid cysts resemble lipomas, demonstrating T1 hyperintensity and variable signal on T2. Symptomatic dermoid cysts can be treated with surgery.

Colloid Cysts These usually arise in the anterior third ventricle and may present with headaches, hydrocephalus, and, very rarely, sudden death. Surgical resection is curative, or a third ventriculostomy may relieve the obstructive hydrocephalus and be sufficient therapy.

NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES)

A number of genetic disorders are characterized by cutaneous lesions and an increased risk of brain tumors. Most of these disorders have an autosomal dominant inheritance with variable penetrance.

NEUROFIBROMATOSIS TYPE 1 (NF1) (von RECKLINGHAUSEN'S DISEASE)

NF1 is an autosomal dominant disorder with variable penetrance and an incidence of ~1 in 2600–3000. Approximately one-half of cases are familial; the remainder are caused by new mutations arising in patients with unaffected parents. The *NF1* gene on chromosome 17q11.2 encodes neurofibromin, a guanosine triphosphatase (GTPase)-activating protein (GAP) that modulates signaling through the RAS pathway. Mutations of *NF1* result in a large number of nervous system tumors including neurofibromas, plexiform neurofibromas, optic nerve gliomas, astrocytomas, and meningiomas. In addition to neurofibromas, which appear as multiple, soft, rubbery cutaneous tumors, other cutaneous manifestations of NF1 include café-au-lait spots and axillary freckling. NF1 is also associated with hamartomas of the iris termed Lisch nodules, pheochromocytomas, pseudoarthrosis of the tibia, scoliosis, epilepsy, and mental retardation.

NEUROFIBROMATOSIS TYPE 2 (NF2)

NF2 is less common than NF1, with an incidence of 1 in 25,000–40,000. It is an autosomal dominant disorder with full penetrance. As with NF1, approximately one-half of cases arise from new mutations. The *NF2* gene on 22q encodes a cytoskeletal protein, merlin (moesin, ezrin, radixin-like protein) that functions as a tumor suppressor. NF2 is characterized by bilateral vestibular schwannomas in >90% of patients, multiple meningiomas, and spinal ependymomas and astrocytomas. Treatment of bilateral vestibular schwannomas can be challenging because the goal is to preserve hearing for as long as possible. These patients may also have diffuse schwannomatosis that may affect the cranial, spinal, or peripheral nerves; posterior subcapsular lens opacities; and retinal hamartomas.

TUBEROUS SCLEROSIS (BOURNEVILLE DISEASE)

This is an autosomal dominant disorder with an incidence of ~1 in 5000–10,000 live births. It is caused by mutations in either the *TSC1* gene, which maps to chromosome 9q34 and encodes a protein termed hamartin, or the *TSC2* gene, which maps to chromosome 16p13.3 and encodes the protein tuberin. Hamartin forms a complex with tuberin, which inhibits cellular signaling through mTOR, and acts as a negative regulator of the cell cycle. Patients with tuberous sclerosis may have seizures, mental retardation, adenoma sebaceum (facial angiofibromas), shagreen patch, hypomelanotic macules, periungual fibromas, renal angiomyolipomas, and cardiac rhabdomyomas. These patients have an increased incidence of subependymal nodules, cortical tubers, and subependymal giant-cell astrocytomas (SEGAs). Patients frequently require anticonvulsants for seizures. SEGAs do not always require therapeutic intervention, but the most effective therapy is with the mTOR inhibitors sirolimus or everolimus, which often decrease seizures as well as SEGA size.

TUMORS METASTATIC TO THE BRAIN

Brain metastases arise from hematogenous spread and frequently originate from a lung primary or are associated with pulmonary metastases. Most metastases develop at the gray matter–white matter junction in the watershed distribution of the brain where intravascular tumor cells lodge in terminal arterioles. The distribution of metastases in the brain approximates the proportion of blood flow such that ~85% of all metastases are supratentorial and 15% occur in the posterior fossa. The most common sources of brain metastases are lung and breast carcinomas; melanoma has the greatest propensity to metastasize to the brain, being found in 80% of patients at autopsy (Table 86-3). Other tumor types such as ovarian and esophageal carcinoma rarely metastasize to the brain. Prostate and breast cancers also have a propensity to metastasize to the dura and can mimic meningioma. Leptomeningeal metastases are common from hematologic malignancies and also breast and lung cancers. Spinal cord compression primarily arises in patients with prostate and breast cancer, tumors with a strong propensity to metastasize to the axial skeleton.

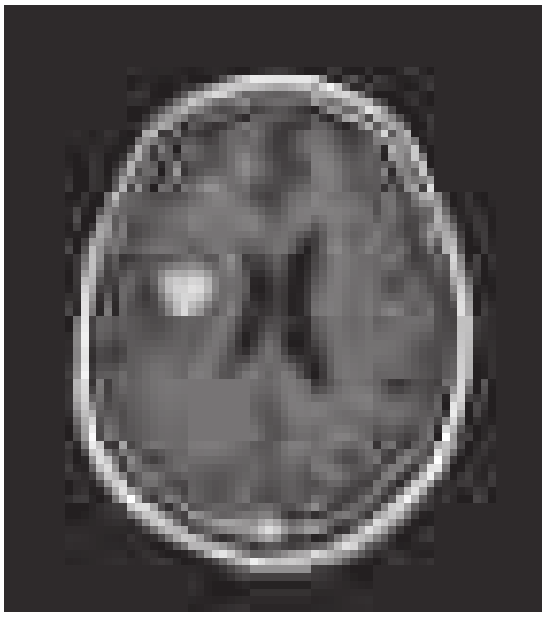
DIAGNOSIS OF METASTASES

Brain metastases are best visualized on MRI, where they usually appear as well-circumscribed lesions (Fig. 86-7). The amount of perilesional edema can be highly variable, with large lesions causing minimal edema and sometimes very small lesions causing extensive edema. Enhancement may be in a ring pattern or diffuse. Occasionally, intracranial metastases will hemorrhage; although melanoma, thyroid, and kidney cancer have the greatest propensity to hemorrhage, the most common cause of a hemorrhagic metastasis is lung cancer because it accounts for the majority of brain metastases. The radiographic appearance of brain metastasis is nonspecific, and similar-appearing lesions can occur with infection including brain abscesses and also with demyelinating lesions, sarcoidosis, radiation necrosis in a previously treated patient, or a primary brain tumor that may be a second malignancy in a patient with systemic cancer. Biopsy is rarely necessary for diagnosis because imaging alone in the appropriate clinical situation usually suffices. However, in

TABLE 86-3 Frequency of Nervous System Metastases by Common Primary Tumors

	BRAIN (%)	LM (%)	ESCC (%)
Lung	41	17	15
Breast	19	57	22
Melanoma	10	12	4
Prostate	1	1	10
GIT	7	—	5
Renal	3	2	7
Lymphoma	<1	10	10
Sarcoma	7	1	9
Other	11	—	18

Abbreviations: ESCC, epidural spinal cord compression; GIT, gastrointestinal tract; LM, leptomeningeal metastases.



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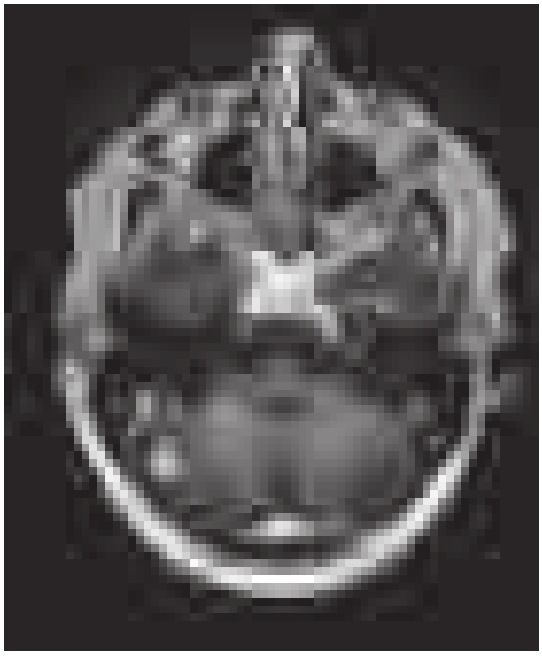

B

FIGURE 86-7 Postgadolinium T1 MRI of multiple brain metastases from non-small-cell lung cancer involving the right frontal (***A***) and right cerebellar (***B***) hemispheres. Note the diffuse enhancement pattern and absence of central necrosis.

~10% of patients, a systemic cancer may present with a brain metastasis, and if there is not an easily accessible systemic site to biopsy, a brain lesion must be removed for diagnostic purposes.

TREATMENT

Tumors Metastatic to the Brain

DEFINITIVE TREATMENT

The number and location of brain metastases often determine the therapeutic options. The patient's overall condition and current or potential control of systemic disease are also major determinants. Brain metastases are single in approximately one-half of patients and multiple in the other half.

RADIATION THERAPY

The standard treatment for brain metastases has previously been whole-brain radiotherapy (WBRT) usually administered to a total dose of 3000 cGy in 10 fractions. This affords rapid palliation, and ~80% of patients improve with glucocorticoids and RT. However, it is not curative, is associated with neurocognitive toxicity, and produces median survival of only 4–6 months. If feasible, SRS has become the primary radiation oncology approach to brain metastases. It can be delivered through a variety of equally effective techniques including the gamma knife, linear accelerator, proton beam, or CyberKnife, all of which can deliver highly focused doses of RT, usually in a single fraction. SRS can effectively sterilize the visible lesions and afford local disease control in 80–90% of patients. Some patients have been cured of their brain metastases using SRS, whereas this is distinctly rare with WBRT. Traditionally SRS was used only for patients with 1–3 metastases, but recent data suggest that SRS can effectively treat up to 10 lesions. It is, however, confined to lesions of ≤3 cm and is most effective in metastases of ≤1 cm. The addition of WBRT to SRS improves disease control in the nervous system but does not prolong survival and thus is rarely employed.

SURGERY

Randomized controlled trials have demonstrated that surgical extirpation of a single brain metastasis followed by WBRT is superior to WBRT alone. Removal of two lesions or a single symptomatic mass, particularly if compressing the ventricular system, can also be useful. This is particularly important in patients who have highly radioresistant lesions such as renal carcinoma. Surgical resection can produce rapid amelioration of symptoms, improve control of edema, and result in prolonged survival. WBRT administered after complete resection of a brain metastasis improves disease control but does not prolong survival. Some centers administer focal RT or even SRS to a resected cavity, especially if there is concern that tumor has been left behind.

CHEMOTHERAPY

Chemotherapy is becoming increasingly useful for brain metastases. Metastases from tumor types that are highly chemosensitive, such as germ cell tumors or small-cell lung cancer, may respond to chemotherapeutic regimens chosen according to the underlying malignancy. Increasingly, there are data demonstrating responsiveness of brain metastases to chemotherapy including targeted therapy, such as for patients with lung cancer harboring EGFR mutations that sensitize them to EGFR inhibitors. Immunotherapy may also be effective against those primary tumors that are sensitive to this approach, such as melanoma. Antiangiogenic agents such as bevacizumab are also effective in the treatment of CNS metastases in those primary tumors for which it is approved.

LEPTOMENINGEAL METASTASES

Leptomeningeal metastases are also described as carcinomatous meningitis, meningeal carcinomatosis, or in the case of specific tumors, leukemic or lymphomatous meningitis. Among the hematologic malignancies, acute leukemias most commonly metastasize to the subarachnoid space, followed in frequency by aggressive diffuse lymphomas. Among solid tumors, breast and lung carcinomas and melanoma most frequently spread in this fashion. Tumor cells reach the subarachnoid space via the arterial circulation or occasionally through retrograde flow in venous systems that drain metastases along the bony spine or cranium. In addition, leptomeningeal metastases may develop as a direct consequence of prior brain metastases and occur in almost 40% of patients who have a metastasis resected from the cerebellum.

CLINICAL FEATURES

Leptomeningeal metastases are characterized by multilevel symptoms and signs along the neuraxis. Combinations of lumbar and cervical radiculopathies, cranial neuropathies, seizures, confusion, and encephalopathy from hydrocephalus or raised intracranial pressure can be present. Focal deficits such as hemiparesis or aphasia are rarely due

to leptomeningeal metastases unless there is direct brain infiltration. New-onset limb pain in patients with breast cancer, lung cancer, or melanoma should prompt consideration of leptomeningeal spread.

LABORATORY AND IMAGING DIAGNOSIS

Leptomeningeal metastases are particularly challenging to diagnose because identification of tumor cells in the subarachnoid compartment may be elusive. MRI can be definitive when there are clear tumor nodules adherent to the cauda equina or spinal cord, enhancing cranial nerves, or subarachnoid enhancement on brain imaging (Fig. 86-8). Imaging is diagnostic in ~75% of patients and is more often positive in patients with solid tumors. Demonstration of tumor cells in the CSF is definitive and often considered the gold standard. However, CSF cytologic examination is positive in only 50% of patients on the first lumbar puncture and still misses 10% after three CSF samples. New technologies, such as rare cell capture, enhance identification of tumor cells in the CSF. CSF cytologic examination is most useful in hematologic malignancies, especially when combined with flow cytometry to identify a clonal population. Accompanying CSF abnormalities include an elevated protein concentration and an elevated white count; hypoglycorrhachia is noted in <25% of patients but is useful when present. Identification of tumor markers may be helpful in some solid tumors.

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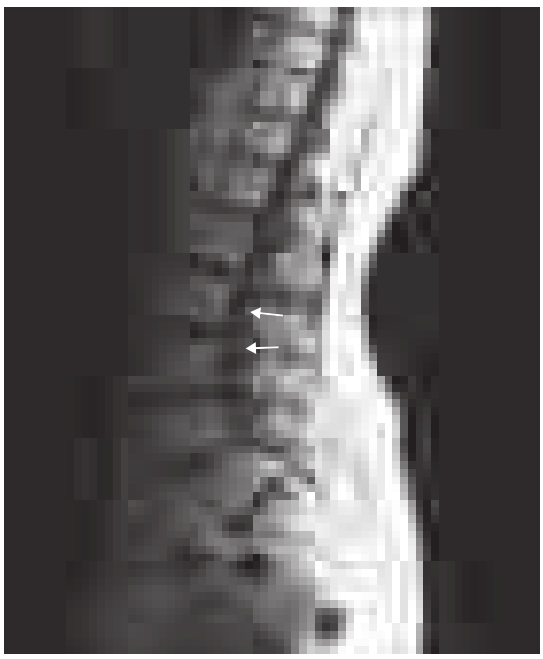

B

FIGURE 86-8 Postgadolinium MRI images of extensive leptomeningeal metastases from breast cancer. Nodules along the dorsal surface of the spinal cord (***A***) and cauda equina (***B***) are seen.

TREATMENT

Leptomeningeal Metastases

The treatment of leptomeningeal metastasis is palliative because there is no curative therapy. RT to the symptomatically involved areas, such as skull base for cranial neuropathy, can relieve pain and sometimes improve function. Whole-neuraxis RT is avoided because it has significant toxicity with myelosuppression and gastrointestinal irritation as well as limited effectiveness. Systemic chemotherapy with agents that can penetrate the blood-CSF barrier may be helpful. Alternatively, intrathecal chemotherapy can be effective, particularly in hematologic malignancies. This is optimally delivered through an intraventricular cannula (Ommaya reservoir) rather than by lumbar puncture. Few drugs can be delivered safely into the subarachnoid space, and they have a limited spectrum of antitumor activity, perhaps accounting for the relatively poor response to this approach. In addition, impaired CSF flow dynamics can compromise intrathecal drug delivery. Surgery has a limited role in leptomeningeal metastasis; a ventriculoperitoneal shunt can relieve raised intracranial pressure; however, it compromises delivery of chemotherapy into the CSF.

EPIDURAL METASTASIS

Epidural metastasis occurs in 3–5% of patients with a systemic malignancy and causes neurologic compromise by compressing the spinal cord or cauda equina. The most common cancers that metastasize to the epidural space are those malignancies that spread to bone, such as breast and prostate. Lymphoma can cause bone involvement and compression, but it can also invade an intervertebral foramen and cause spinal cord compression without bone destruction. The thoracic spine is affected most commonly, followed by the lumbar and then cervical spine.

CLINICAL FEATURES

Back pain is the presenting symptom of epidural metastasis in virtually all patients; the pain may precede neurologic findings by weeks or months. The pain is usually exacerbated by lying down; by contrast, arthritic pain is often relieved by recumbency. Leg weakness is seen in ~50% of patients, as is sensory dysfunction. Sphincter problems are present in ~25% of patients at diagnosis.

DIAGNOSIS

Diagnosis is established by imaging, preferably with an MRI of the entire spine (Fig. 86-9). Contrast is not required to identify bony or epidural lesions. Any patient with cancer who has severe back pain should undergo an MRI. Plain films, bone scans, or even CT scans may show bone metastases, but only MRI can reliably delineate epidural tumor. For patients unable to have an MRI, CT myelography should be performed to outline the epidural space. The differential diagnosis of epidural tumor includes epidural abscess, acute or chronic hematomas, epidural lipomatosis and rarely, extramedullary hematopoiesis.

TREATMENT

Epidural Metastasis

Epidural metastasis requires immediate treatment. A randomized controlled trial demonstrated the superiority of surgical resection followed by RT compared to RT alone. However, patients must be able to tolerate surgery, and the surgical procedure of choice is

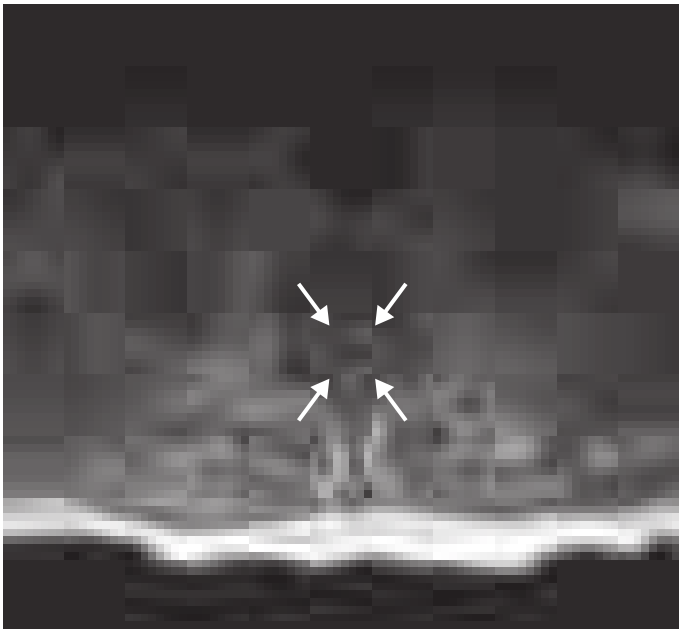

FIGURE 86-9 Postgadolinium T1 MRI showing circumferential epidural tumor around the thoracic spinal cord from esophageal cancer.

a complete removal of the mass, which is typically anterior to the spinal canal, necessitating an extensive approach and resection. Otherwise, RT is the mainstay of treatment and can be used for patients with radiosensitive tumors, such as lymphoma, or for those unable to undergo surgery. SRS is increasingly being used, especially for radioresistant tumor types or for re-irradiation. Chemotherapy is rarely used for epidural metastasis unless the patient has minimal to no neurologic deficit and a highly chemosensitive tumor such as lymphoma or germinoma. Patients generally fare well if treated before there is a severe neurologic deficit. Recovery from paraparesis is better after surgery than with RT alone, but survival is often short due to widespread metastatic tumor.

NEUROLOGIC TOXICITY OF THERAPY

TOXICITY FROM RADIOTHERAPY

RT can cause a variety of toxicities in the CNS. These are usually described based on their relationship in time to the administration of RT: acute (occurring within days of RT), early delayed (months), or late delayed (years). In general, the acute and early delayed syndromes resolve and do not result in persistent deficits, whereas the late delayed toxicities are usually permanent and sometimes progressive.

Acute Toxicity Acute cerebral toxicity may occur during the course of RT to the brain. RT can cause a transient disruption of the blood-brain barrier, resulting in edema and elevated intracranial pressure. This is usually manifest as headache, lethargy, nausea, and vomiting, and can be both prevented and treated with the administration of glucocorticoids. There is no acute RT toxicity that affects the spinal cord.

Early Delayed Toxicity Early delayed toxicity is usually apparent weeks to months after completion of cranial irradiation and is likely due to focal demyelination. Clinically it may be asymptomatic or take the form of worsening or reappearance of a preexisting neurologic deficit. At times a contrast-enhancing lesion can be seen on MRI/CT that can mimic the tumor for which the patient received the RT. For patients with a malignant glioma, this has been described as "pseudoprogression" because it mimics tumor recurrence on MRI but actually represents inflammation and necrotic debris engendered by effective therapy. This is seen with increased frequency when chemotherapy, particularly temozolomide, is given concurrently with RT. Pseudoprogression can resolve on its own or, if very symptomatic, may require resection.

In the spinal cord, early delayed RT toxicity is manifest as a Lhermitte symptom with paresthesias of the limbs or along the spine when the patient flexes the neck. Although frightening, it is benign, resolves on its own, and does not portend more serious problems.

Late Delayed Toxicity Late delayed toxicities are the most serious because they are often irreversible and cause severe neurologic deficits. In the brain, late toxicities can take several forms, the most common of which include radiation necrosis and leukoencephalopathy. Radiation necrosis is a focal mass of necrotic tissue that is contrast enhancing on CT/MRI and may be associated with significant edema. This may appear identical to pseudoprogression but is seen months to years after RT and is always symptomatic. Clinical symptoms and signs include seizures and findings referable to the location of the necrotic mass. The necrosis is caused by the effect of RT on cerebral vasculature with fibrinoid necrosis and occlusion of blood vessels. It can mimic tumor radiographically, but unlike tumor it is typically hypometabolic on a PET scan and has reduced perfusion on perfusion MR sequences. It may require resection for diagnosis and treatment unless it can be managed with glucocorticoids. There are reports of improvement with hyperbaric oxygen or bevacizumab, but symptomatic benefit does not always accompany radiographic improvement.

Leukoencephalopathy is seen most commonly after WBRT as opposed to focal RT. On T2 or FLAIR MR sequences, there is diffusely increased signal seen throughout the hemispheric white matter, often bilaterally and symmetrically. There tends to be a periventricular predominance that may be associated with atrophy and ventricular enlargement. Clinically, patients develop cognitive impairment, a gait disorder, and later urinary incontinence, all of which can progress over time. These symptoms mimic those of normal pressure hydrocephalus, and placement of a ventriculoperitoneal shunt can improve function in some patients but does not reverse the deficits completely. Increased age is a risk factor for leukoencephalopathy but not for radiation necrosis. Necrosis appears to depend on an as yet unidentified predisposition.

Other late neurologic toxicities include endocrine dysfunction if the pituitary or hypothalamus was included in the RT port. An RT-induced neoplasm can occur many years after therapeutic RT for either a prior CNS or a head and neck tumor; accurate diagnosis requires surgical resection or biopsy. In addition, RT causes accelerated atherosclerosis, which can cause stroke either from intracranial vascular disease or carotid plaque from neck irradiation.

The peripheral nervous system is relatively resistant to RT toxicities. Peripheral nerves are rarely affected by RT, but the plexus is more vulnerable. Plexopathy develops more commonly in the brachial than in the lumbosacral distribution. It must be differentiated from tumor progression in the plexus, which is usually visualized by CT/MRI or PET scan demonstrating tumor infiltrating the region. Clinically, tumor progression is usually painful, whereas RT-induced plexopathy is painless. Radiation plexopathy is also more commonly associated with lymphedema of the affected limb. Sensory loss and weakness are seen in both.

TOXICITY FROM CHEMOTHERAPY

Neurotoxicity is second to myelosuppression as the dose-limiting toxicity of chemotherapeutic agents (Table 86-4). Chemotherapy causes peripheral neuropathy from a number of commonly used agents, and the type of neuropathy can vary depending on the drug. Vincristine causes paresthesias but little sensory loss and is associated with motor dysfunction, autonomic impairment (frequently ileus), and, rarely, cranial nerve compromise. Cisplatin causes large fiber sensory loss resulting in sensory ataxia but little cutaneous sensory loss and no weakness. The taxanes also cause a predominately sensory neuropathy. Agents such as bortezomib and thalidomide also cause neuropathy.

Encephalopathy and seizures are common toxicities from chemotherapeutic drugs. Ifosfamide can cause a severe encephalopathy, which is reversible with discontinuation of the drug and the use of methylene blue for severely affected patients. Fludarabine also causes a severe global encephalopathy that may be permanent. Bevacizumab

TABLE 86-4 Neurologic Signs Caused by Agents Commonly Used in Patients with Cancer

Acute encephalopathy (delirium)	Seizures
Methotrexate (high-dose IV, IT)	Methotrexate
Cisplatin	Etoposide (high-dose)
Vincristine	Cisplatin
Asparaginase	Vincristine
Procarbazine	Asparaginase
5-Fluorouracil (± levamisole)	Nitrogen mustard
Cytarabine (high-dose)	Carmustine
Nitrosoureas (high-dose or arterial)	Dacarbazine (intraarterial or high-dose)
Ifosfamide	Busulfan (high-dose)
Etoposide (high-dose)	Myelopathy (IT drugs)
Bevacizumab (PRES)	Methotrexate
Chronic encephalopathy (dementia)	Cytarabine
Methotrexate	Thiotepa
Carmustine	Peripheral neuropathy
Cytarabine	Vinca alkaloids
Fludarabine	Cisplatin
Visual loss	Procarbazine
Tamoxifen	Etoposide
Gallium nitrate	Teniposide
Cisplatin	Cytarabine
Fludarabine	Taxanes
Cerebellar dysfunction/ataxia	Suramin
5-Fluorouracil (± levamisole)	Bortezomib
Cytarabine	
Procarbazine	

Abbreviations: IT, intrathecal; IV, intravenous; PRES, posterior reversible encephalopathy syndrome.

and other anti-VEGF agents can cause posterior reversible encephalopathy syndrome. Cisplatin can cause hearing loss and less frequently vestibular dysfunction. Immunotherapy with monoclonal antibodies such as ipilimumab or nivolumab can cause an autoimmune hypophysitis, Guillain-Barré syndrome, or an autoimmune encephalitis.

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87 Soft Tissue and Bone Sarcomas and Bone Metastases

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Sarcomas are rare (<1% of all malignancies) mesenchymal neoplasms that arise in bone and soft tissues. These tumors are usually of mesodermal origin, although a few are derived from neuroectoderm, and they are biologically distinct from the more common epithelial malignancies. Sarcomas affect all age groups; 15% are found in children <15 years of age, and 40% occur after age 55 years. Sarcomas are one of the most common solid tumors of childhood and are the fifth most common cause of cancer deaths in children. Sarcomas may be divided into two groups, those derived from bone and those derived from soft tissues.

SOFT TISSUE SARCOMAS

Soft tissues include muscles, tendons, fat, fibrous tissue, synovial tissue, vessels, and nerves. Approximately 60% of soft tissue sarcomas arise in the extremities, with the lower extremities involved three times as often as the upper extremities. Thirty percent arise in the trunk, the retroperitoneum accounting for 40% of all trunk lesions. The remaining 10% arise in the head and neck.

INCIDENCE

Approximately 12,310 new cases of soft tissue sarcomas occurred in the United States in 2016. The annual age-adjusted incidence is 3 per 100,000 population, but the incidence varies with age. Soft tissue sarcomas constitute 0.7% of all cancers in the general population and 6.5% of all cancers in children.

EPIDEMIOLOGY

Malignant transformation of a benign soft tissue tumor is extremely rare, with the exception that malignant peripheral nerve sheath tumors (neurofibrosarcoma, malignant schwannoma) can arise from neurofibromas in patients with neurofibromatosis. Several etiologic factors have been implicated in soft tissue sarcomas.

Environmental Factors Trauma or previous injury is rarely involved, but sarcomas can arise in scar tissue resulting from a prior operation, burn, fracture, or foreign body implantation. Chemical carcinogens such as polycyclic hydrocarbons, asbestos, and dioxin may be involved in the pathogenesis.

Iatrogenic Factors Sarcomas in bone or soft tissues occur in patients who are treated with radiation therapy. The tumor nearly always arises in the irradiated field. The risk increases with time.

Viruses Kaposi's sarcoma (KS) in patients with HIV type 1, classic KS, and KS in HIV-negative homosexual men is caused by human herpesvirus (HHV) 8 (Chap. 190). No other sarcomas are associated with viruses.

Immunologic Factors Congenital or acquired immunodeficiency, including therapeutic immunosuppression, increases the risk of sarcoma.

GENETIC CONSIDERATIONS

Li-Fraumeni syndrome is a familial cancer syndrome in which affected individuals have germline abnormalities of the tumor-suppressor gene *p53* and an increased incidence of soft tissue sarcomas and other malignancies, including breast cancer, osteosarcoma, brain tumor, leukemia, and adrenal carcinoma (Chap. 67). Neurofibromatosis 1 (*NF-1*, peripheral form, von Recklinghausen's disease) is characterized by multiple neurofibromas and café-au-lait spots. Neurofibromas occasionally undergo malignant degeneration to become malignant peripheral nerve sheath tumors. The gene for *NF-1*

is located in the pericentromeric region of chromosome 17 and encodes neurofibromin, a tumor-suppressor protein with guanosine 5′-triphosphate (gtp)ase-activating activity that inhibits ras function **(Chap. 86)**. Germline mutation of the *Rb-1* locus (chromosome 13q14) in patients with inherited retinoblastoma is associated with the development of osteosarcoma in those who survive the retinoblastoma and of soft tissue sarcomas unrelated to radiation therapy. Other soft tissue tumors, including desmoid tumors, lipomas, leiomyomas, neuroblastomas, and paragangliomas, occasionally show a familial predisposition.

Ninety percent of synovial sarcomas contain a characteristic chromosomal translocation t(X;18)(p11;q11) involving a nuclear transcription factor on chromosome 18 called *SYT* and two breakpoints on X. Patients with translocations to the second X breakpoint (*SSX2*) may have longer survival than those with translocations involving *SSX1*.

Insulin-like growth factor (IGF) type II is produced by some sarcomas and may act as an autocrine growth factor and as a motility factor that promotes metastatic spread. IGF-II stimulates growth through IGF-I receptors, but its effects on motility are through different receptors. If secreted in large amounts, IGF-II may produce hypoglycemia **(Chaps. 89 and 399)**. A large international sarcoma kindred study including 1162 patients and 6545 Caucasian controls revealed that about half the patients with sarcoma have putatively pathogenic monogenic and polygenic variation in previously reported and new cancer genes, some of them representing therapeutically actionable targets. These patients were diagnosed with sarcoma at an earlier age compared to controls.

CLASSIFICATION

Approximately 20 different groups of sarcomas are recognized on the basis of the pattern of differentiation toward normal tissue. For example, rhabdomyosarcoma shows evidence of skeletal muscle fibers with cross-striations; leiomyosarcomas contain interlacing fascicles of spindle cells resembling smooth muscle; and liposarcomas contain adipocytes. When precise characterization of the group is not possible, the tumors are called *unclassified sarcomas*. All of the primary bone sarcomas can also arise from soft tissues (e.g., extraskeletal osteosarcoma). The entity *malignant fibrous histiocytoma* (*MFH*) includes many tumors previously classified as fibrosarcomas or as pleomorphic variants of other sarcomas and is characterized by a mixture of spindle (fibrous) cells and round (histiocytic) cells arranged in a storiform pattern with frequent giant cells and areas of pleomorphism. As immunohistochemical suggestion of differentiation, particularly myogenic differentiation, may be found in a significant fraction of these patients, many are now characterized as poorly differentiated leiomyosarcomas, and the terms *undifferentiated pleomorphic sarcoma* (UPS) and *myxofibrosarcoma* are replacing MFH and myxoid MFH.

For purposes of treatment, most soft tissue sarcomas can be considered together. However, some specific tumors have distinct features. For example, *liposarcoma* can have a spectrum of behaviors. Pleomorphic liposarcomas and dedifferentiated liposarcomas behave like other high-grade sarcomas; in contrast, well-differentiated liposarcomas (better termed *atypical lipomatous tumors*) lack metastatic potential, and myxoid liposarcomas metastasize infrequently, but, when they do, they have a predilection for unusual metastatic sites containing fat, such as the retroperitoneum, mediastinum, and subcutaneous tissue. Rhabdomyosarcomas, Ewing's sarcoma, and other small-cell sarcomas tend to be more aggressive and are more responsive to chemotherapy than other soft tissue sarcomas.

Gastrointestinal stromal tumors (GISTs), previously classified as gastrointestinal leiomyosarcomas, are now recognized as a distinct entity within soft tissue sarcomas. Its cell of origin resembles the interstitial cell of Cajal, which controls peristalsis. The majority of malignant GISTs have activating mutations of the c-*kit* gene that result in ligand-independent phosphorylation and activation of the KIT receptor tyrosine kinase, leading to tumorigenesis. Approximately 5–10% of tumors will have a mutation in the platelet-derived growth factor receptor α (*PDGFRA*). GISTs that are wild type for both *KIT* and *PDGFRA* mutations may show mutations in *SDH* B, C, or D and may be driven by the IGF-I pathway.

DIAGNOSIS

The most common presentation is an asymptomatic mass. Mechanical symptoms referable to pressure, traction, or entrapment of nerves or muscles may be present. All new and persistent or growing masses should be biopsied, either by a small incision or by a cutting needle (core-needle biopsy) placed so that it can be encompassed in the subsequent excision without compromising a definitive resection. Lymph node metastases occur in 5%, except in synovial and epithelioid sarcomas, clear-cell sarcoma (melanoma of the soft parts), angiosarcoma, and rhabdomyosarcoma, where nodal spread may be seen in 17%. The pulmonary parenchyma is the most common site of metastases. Exceptions are GISTs, which metastasize to the liver; myxoid liposarcomas, which seek fatty tissue; and clear-cell sarcomas, which may metastasize to bones. Central nervous system metastases are rare, except in alveolar soft part sarcoma.

Radiographic Evaluation Imaging of the primary tumor is best with plain radiographs and magnetic resonance imaging (MRI) for tumors of the extremities or head and neck and by computed tomography (CT) for tumors of the chest, abdomen, or retroperitoneal cavity. A radiograph and CT scan of the chest are important for the detection of lung metastases. Other imaging studies may be indicated, depending on the symptoms, signs, or histology.

STAGING AND PROGNOSIS

The histologic grade, relationship to fascial planes, and size of the primary tumor are the most important prognostic factors. The current American Joint Committee on Cancer (AJCC) staging system is shown in **Table 87-1**. Prognosis is related to the stage. Cure is common in the absence of metastatic disease, but a small number of patients with metastases can also be cured. Historically, most patients with stage IV disease used to die within 12 months, but with availability of multiple lines of treatments, median survival in second-line and beyond ranges from 13 to 14 months, and some patients may live with stable or slowly progressive disease for many years.

TREATMENT

Soft Tissue Sarcomas

AJCC stage I patients are adequately treated with surgery alone. Stage II patients are considered for adjuvant radiation therapy. Stage III patients may benefit from adjuvant chemotherapy. Stage IV patients are managed primarily with chemotherapy, with or without other modalities.

SURGERY

Soft tissue sarcomas tend to grow along fascial planes, with the surrounding soft tissues compressed to form a pseudocapsule that gives the sarcoma the appearance of a well-encapsulated lesion. This is invariably deceptive because "shelling out," or marginal excision, of such lesions results in a 50–90% probability of local recurrence. Wide excision with a negative margin, incorporating the biopsy site, is the standard surgical procedure for local disease. The adjuvant use of radiation therapy and/or chemotherapy improves the local control rate and permits the use of limb-sparing surgery with a local control rate (85–90%) comparable to that achieved by radical excisions and amputations. Limb-sparing approaches are indicated except when negative margins are not obtainable, when the risks of radiation are prohibitive, or when neurovascular structures are involved so that resection will result in serious functional consequences to the limb.

RADIATION THERAPY

External-beam radiation therapy is an adjuvant to limb-sparing surgery for improved local control. Preoperative radiation therapy allows the use of smaller fields and smaller doses but results in a higher rate of wound complications. Postoperative radiation therapy must be given to larger fields, because the entire surgical bed must be encompassed, and in higher doses to compensate for hypoxia in

TABLE 87-1 American Joint Committee on Cancer Staging System for Sarcomas

HISTOLOGIC GRADE (G)	TUMOR SIZE (T)	NODE STATUS (N)	METASTASES (M)
Well differentiated (G1)	≤5 cm (T1)	Not involved (N0)	Absent (M0)
Moderately differentiated (G2)	>5 cm (T2)	Involved (N1)	Present (M1)
Poorly differentiated (G3)	Superficial fascial involvement (Ta)		
Undifferentiated (G4)	Deep fascial involvement (Tb)		

DISEASE STAGE	5-YEAR SURVIVAL, %
Stage I A: G1,2; T1a,b; N0; M0 B: G1,2; T2a; N0; M0	98.8
Stage II A: G1,2; T2b; N0; M0 B: G3,4; T1; N0; M0 C: G3,4; T2a; N0; M0	81.8
Stage III: G3,4; T2b; N0; M0	51.7
Stage IV A: any G; any T; N1; M0 B: any G; any T; any N; M1	<20

the operated field. This results in a higher rate of late complications. Brachytherapy or interstitial therapy, in which the radiation source is inserted into the tumor bed, is comparable in efficacy (except in low-grade lesions), less time-consuming, and less expensive.

ADJUVANT CHEMOTHERAPY

Chemotherapy is the mainstay of treatment for Ewing's primitive neuroectodermal tumors (PNET) and rhabdomyosarcomas. Meta-analysis of 14 randomized trials revealed a significant improvement in local control and disease-free survival in favor of doxorubicin-based chemotherapy. Overall survival improvement was 4% for all sites and 7% for the extremity site. An updated meta-analysis including four additional trials with doxorubicin and ifosfamide combination has reported a statistically significant 6% survival advantage in favor of chemotherapy. A chemotherapy regimen including an anthracycline and ifosfamide with growth factor support improved overall survival by 19% for high-risk (high-grade, ≥5 cm primary, or locally recurrent) extremity soft tissue sarcomas. Long-term follow-up of a trial evaluating neo-adjuvant use of the same combination confirms survival advantage and reports a 10-year survival of 61%.

ADVANCED DISEASE

Metastatic soft tissue sarcomas are largely incurable, but up to 20% of patients who achieve a complete response become long-term survivors. The therapeutic intent, therefore, is to produce a complete remission with chemotherapy (<10%) and/or surgery (30–40%). Surgical resection of metastases, whenever possible, is an integral part of the management. Some patients benefit from repeated surgical excision of metastases. The two most active chemotherapeutic agents are doxorubicin and ifosfamide. These drugs show a steep dose-response relationship in sarcomas. Gemcitabine with or without docetaxel has become an established second-line regimen and is particularly active in patients with undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcomas. Dacarbazine also has some modest activity. Taxanes have selective activity in angiosarcomas, and vincristine, etoposide, and irinotecan are effective in rhabdomyosarcomas and Ewing's sarcomas. Pazopanib, an inhibitor of the vascular endothelial growth factor, platelet-derived growth factor (PDGF), and c-kit is now approved for patients with advanced soft tissue sarcomas excluding liposarcomas after failure of chemotherapy. Two additional chemotherapy drugs have gained approval from the Food and Drug Administration (FDA). Trabectedin was compared to dacarbazine in a large phase 3 randomized study in advanced leiomyosarcomas and liposarcomas after failure of an anthracycline, and resulted in significant improvement in progression-free survival. Eribulin was also tested in a similar trial and showed improvement in survival, predominantly in the liposarcoma subgroup and is therefore now approved for that subset. Imatinib targets the KIT and PDGF tyrosine kinase activity and is standard therapy for advanced/metastatic GISTs and dermatofibrosarcoma protuberans. Imatinib is now also indicated as adjuvant therapy for completely resected primary GISTs. Three years of adjuvant imatinib appear to be superior to 1 year of therapy for high-risk GISTs, although the optimal treatment duration remains unknown. Sunitinib and regorafenib are approved for second and third line use respectively in metastatic GIST after failure of or intolerance to imatinib.

Plexiform neurofibromas occurring in neurofibromatosis can be disfiguring and compromise function, particularly when they involve joints. These tumors are characterized by increased RAS-MAPK signaling and may respond to inhibiting MEK1/2 function with selumetinib.

BONE SARCOMAS

INCIDENCE AND EPIDEMIOLOGY

Bone sarcomas are rarer than soft tissue sarcomas; they accounted for only 0.2% of all new malignancies and 3010 new cases in the United States in 2016. Several benign bone lesions have the potential for malignant transformation. Enchondromas and osteochondromas can transform into chondrosarcoma; fibrous dysplasia, bone infarcts, and Paget's disease of bone can transform into either UPS or osteosarcoma.

CLASSIFICATION

Benign Tumors The common benign bone tumors include enchondroma, osteochondroma, chondroblastoma, and chondromyxoid fibroma, of cartilage origin; osteoid osteoma and osteoblastoma, of bone origin; fibroma and desmoplastic fibroma, of fibrous tissue origin; hemangioma, of vascular origin; and giant-cell tumor, of unknown origin.

Malignant Tumors The most common malignant tumors of bone are plasma cell tumors (Chap. 107). The four most common malignant nonhematopoietic bone tumors are osteosarcoma, chondrosarcoma, Ewing's sarcoma, and UPS. Rare malignant tumors include chordoma (of notochordal origin), malignant giant-cell tumor, adamantinoma (of unknown origin), and hemangioendothelioma (of vascular origin).

Musculoskeletal Tumor Society Staging System Sarcomas of bone are staged according to the Musculoskeletal Tumor Society staging system based on grade and compartmental localization. A Roman numeral reflects the tumor grade: stage I is low grade, stage II is high

TABLE 87-2 Staging System for Bone Sarcomas

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Tumor ≤8 cm in greatest dimension
	T2	Tumor >8 cm in greatest dimension
	T3	Discontinuous tumors in the primary bone site
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Lung
	M1b	Other distant sites
Histologic grade (G)	GX	Grade cannot be assessed
	G1	Well differentiated—low grade
	G2	Moderately differentiated—low grade
	G3	Poorly differentiated—high grade
	G4	Undifferentiated—high grade (Ewing's is always classed G4)

Stage Grouping				
Stage IA	T1	N0	M0	G1,2 low grade
Stage IB	T2	N0	M0	G1,2 low grade
Stage IIA	T1	N0	M0	G3,4 high grade
Stage IIB	T2	N0	M0	G3,4 high grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

grade, and stage III includes tumors of any grade that have lymph node or distant metastases. In addition, the tumor is given a letter reflecting its compartmental localization. Tumors designated A are intracompartmental (i.e., confined to the same soft tissue compartment as the initial tumor), and tumors designated B are extracompartmental (i.e., extending into the adjacent soft tissue compartment or into bone). The tumor-node-metastasis (TNM) staging system is shown in Table 87-2.

OSTEOSARCOMA

Osteosarcoma, accounting for almost 45% of all bone sarcomas, is a spindle cell neoplasm that produces osteoid (unmineralized bone) or bone. Approximately 60% of all osteosarcomas occur in children and adolescents in the second decade of life, and ~10% occur in the third decade of life. Osteosarcomas in the fifth and sixth decades of life are frequently secondary to either radiation therapy or transformation in a preexisting benign condition, such as Paget's disease. Males are affected 1.5–2 times as often as females. Osteosarcoma has a predilection for metaphyses of long bones; the most common sites of involvement are the distal femur, proximal tibia, and proximal humerus. The classification of osteosarcoma is complex, but 75% of osteosarcomas fall into the "classic" category, which include osteoblastic, chondroblastic, and fibroblastic osteosarcomas. The remaining 25% are classified as "variants" on the basis of (1) clinical characteristics, as in the case of osteosarcoma of the jaw, postradiation osteosarcoma, or Paget's osteosarcoma; (2) morphologic characteristics, as in the case of telangiectatic osteosarcoma, small-cell osteosarcoma, or epithelioid osteosarcoma; or (3) location, as in parosteal or periosteal osteosarcoma. Diagnosis usually requires a synthesis of clinical, radiologic, and pathologic features. Patients typically present with pain and swelling of the affected area. A plain radiograph reveals a destructive lesion with a moth-eaten appearance, a spiculated periosteal reaction (sunburst appearance), and a cuff of periosteal new bone formation at the margin of the soft tissue mass (Codman's triangle). A CT scan of the primary tumor is best for defining bone destruction and the pattern of calcification, whereas MRI is better for defining intramedullary and soft tissue extension. A chest radiograph and CT scan are used to detect lung metastases. Metastases to the bony skeleton should be imaged by a bone scan or by fluorodeoxyglucose positron emission tomography (FDG-PET). Almost all osteosarcomas are hypervascular and PET-avid. Pathologic diagnosis is established either with a core-needle biopsy, where feasible, or with an open biopsy with an appropriately placed incision that does not compromise future limb-sparing resection. Most osteosarcomas are high-grade. The most important prognostic factor for long-term survival is response to chemotherapy. Preoperative chemotherapy followed by limb-sparing surgery (which can be accomplished in >80% of patients) followed by postoperative chemotherapy is standard management. The effective drugs are doxorubicin, ifosfamide, cisplatin, and high-dose methotrexate with leucovorin rescue. The various combinations of these agents that have been used have all been about equally successful. Long-term survival rates in extremity osteosarcoma range from 60 to 80%. Osteosarcoma is radioresistant; radiation therapy has no role in the routine management. UPS is considered a part of the spectrum of osteosarcoma and is managed similarly.

CHONDROSARCOMA

Chondrosarcoma, which constitutes ~20–25% of all bone sarcomas, is a tumor of adulthood and old age with a peak incidence in the fourth to sixth decades of life. It has a predilection for the flat bones, especially the shoulder and pelvic girdles, but can also affect the diaphyseal portions of long bones. Chondrosarcomas can arise de novo or as a malignant transformation of an enchondroma or, rarely, of the cartilaginous cap of an osteochondroma. Chondrosarcomas have an indolent natural history and typically present as pain and swelling. Radiographically, the lesion may have a lobular appearance with mottled or punctate or annular calcification of the cartilaginous matrix. It is difficult to distinguish low-grade chondrosarcoma from benign lesions by x-ray or histologic examination. The diagnosis is therefore influenced by clinical history and physical examination. A new onset of pain, signs of inflammation, and progressive increase in the size of the mass suggest malignancy. The histologic classification is complex, but most tumors fall within the classic category. Like other bone sarcomas, high-grade chondrosarcomas spread to the lungs. Most chondrosarcomas are resistant to chemotherapy, and surgical resection of primary or recurrent tumors, including pulmonary metastases, is the mainstay of therapy. This rule does not hold for two histologic variants. Dedifferentiated chondrosarcoma has a high-grade osteosarcoma or a malignant fibrous histiocytoma component that responds to chemotherapy. Mesenchymal chondrosarcoma, a rare variant composed of a small-cell element, also is responsive to systemic chemotherapy and is treated like Ewing's sarcoma.

EWING'S SARCOMA

Ewing's sarcoma, which constitutes ~10–15% of all bone sarcomas, is common in adolescence and has a peak incidence in the second decade of life. It typically involves the diaphyseal region of long bones and also has an affinity for flat bones. The plain radiograph may show a characteristic "onion peel" periosteal reaction with a generous soft tissue mass, which is better demonstrated by CT or MRI. This mass is composed of sheets of monotonous, small, round, blue cells and can be confused with lymphoma, embryonal rhabdomyosarcoma, and small-cell carcinoma. The presence of p30/32, the product of the *mic-2* gene (which maps to the pseudoautosomal region of the X and Y chromosomes), is a cell-surface marker for Ewing's sarcoma (and other members of the Ewing's family of tumors, previously also called PNETs). Most PNETs arise in soft tissues; they include peripheral neuroepithelioma, Askin's tumor (chest wall), and esthesioneuroblastoma. Glycogen-filled cytoplasm detected by staining with periodic acid–Schiff is also characteristic of Ewing's sarcoma cells. The classic cytogenetic abnormality associated with this disease is a reciprocal translocation of the long arms of chromosomes 11 and 22, t(11;22), which creates a chimeric gene product of unknown function with components from the *fli-1* gene on chromosome 11 and *ews* on 22.

This disease is very aggressive, and it is therefore considered a systemic disease. Common sites of metastases are lung, bones, and bone marrow. Systemic chemotherapy is the mainstay of therapy, often being used before surgery. Doxorubicin, cyclophosphamide or ifosfamide, etoposide, vincristine, and dactinomycin are active drugs. Topotecan or irinotecan in combination with an alkylating agent is often used in relapsed patients. Targeted therapy with an anti-IGF-I receptor antibody in combination with an inhibitor of mammalian target of rapamycin (mTOR) has shown promising activity in refractory cases. Local treatment for the primary tumor includes surgical resection, usually with limb salvage or radiation therapy. Patients with lesions below the elbow and below the mid-calf have a 5-year survival rate of 80% with effective treatment. Ewing's sarcoma at first presentation is a curable tumor, even in the presence of obvious metastatic disease, especially in children <11 years old.

TUMORS METASTATIC TO BONE

Bone is a common site of metastasis for carcinomas of the prostate, breast, lung, kidney, bladder, and thyroid and for lymphomas and sarcomas. Prostate, breast, and lung primaries account for 80% of all bone metastases. Metastatic tumors of bone are more common than primary bone tumors. Tumors usually spread to bone hematogenously, but local invasion from soft tissue masses also occurs. In descending order of frequency, the sites most often involved are the vertebrae, proximal femur, pelvis, ribs, sternum, proximal humerus, and skull. Bone metastases may be asymptomatic or may produce pain, swelling, nerve root or spinal cord compression, pathologic fracture, or myelophthisis (replacement of the marrow). Symptoms of hypercalcemia may be noted in cases of bony destruction.

Pain is the most frequent symptom. It usually develops gradually over weeks, is usually localized, and often is more severe at night. When patients with back pain develop neurologic signs or symptoms, emergency evaluation for spinal cord compression is indicated **(Chap. 71)**. Bone metastases exert a major adverse effect on quality of life in cancer patients.

Cancer in the bone may produce osteolysis, osteogenesis, or both. Osteolytic lesions result when the tumor produces substances that can directly elicit bone resorption (vitamin D–like steroids, prostaglandins, or parathyroid hormone–related peptide) or cytokines that can induce the formation of osteoclasts (interleukin 1 and tumor necrosis factor). Osteoblastic lesions result when the tumor produces cytokines that activate osteoblasts. In general, purely osteolytic lesions are best detected by plain radiography, but they may not be apparent until they are >1 cm. These lesions are more commonly associated with hypercalcemia and with the excretion of hydroxyproline-containing peptides indicative of matrix destruction. When osteoblastic activity is prominent, the lesions may be readily detected using radionuclide bone scanning (which is sensitive to new bone formation), and the radiographic appearance may show increased bone density or sclerosis. Osteoblastic lesions are associated with higher serum levels of alkaline phosphatase and, if extensive, may produce hypocalcemia. Although some tumors may produce mainly osteolytic lesions (e.g., kidney cancer) and others mainly osteoblastic lesions (e.g., prostate cancer), most metastatic lesions produce both types of lesion and may go through stages where one or the other predominates.

In older patients, particularly women, it may be necessary to distinguish metastatic disease of the spine from osteoporosis. In osteoporosis, the cortical bone may be preserved, whereas cortical bone destruction is usually noted with metastatic cancer.

TREATMENT

Metastatic Bone Disease

Treatment of metastatic bone disease depends on the underlying malignancy and the symptoms. Some metastatic bone tumors are curable (lymphoma, Hodgkin's disease), and others are treated with palliative intent. Pain may be relieved by local radiation therapy. Hormonally responsive tumors are responsive to hormone inhibition (antiandrogens for prostate cancer, antiestrogens for breast cancer). Strontium-89, samarium-153, and radium-223 are bone-seeking radionuclides that can exert antitumor effects and relieve symptoms. Denosumab, a monoclonal antibody that binds to RANK ligand, inhibits osteoclastic activity and increases bone mineral density. Bisphosphonates such as pamidronate may relieve pain and inhibit bone resorption, thereby maintaining bone mineral density and reducing risk of fractures in patients with osteolytic metastases from breast cancer and multiple myeloma. Careful monitoring of serum electrolytes and creatinine is recommended. Monthly administration prevents bone-related clinical events and may reduce the incidence of bone metastases in women with breast cancer. When the integrity of a weight-bearing bone is threatened by an expanding metastatic lesion that is refractory to radiation therapy, prophylactic internal fixation is indicated. Overall survival is related to the prognosis of the underlying tumor. Bone pain at the end of life is particularly common; an adequate pain relief regimen including sufficient amounts of narcotic analgesics is required. **The management of hypercalcemia is discussed in Chap. 403**.

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88 Carcinoma of Unknown Primary

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Carcinoma of unknown primary (CUP) is a biopsy-proven malignancy for which the anatomic site of origin remains unidentified after a focused search. CUP is one of the 10 most frequently diagnosed cancers worldwide, accounting for 3–5% of all cancers. Most investigators limit CUP to epithelial and undifferentiated cancers and do not include lymphomas, metastatic melanomas, and metastatic sarcomas because these cancers have specific histology- and stage-based treatments that guide management even in the absence of a primary cancer.

The emergence of sophisticated imaging, robust immunohistochemistry (IHC), and genomic and proteomic tools has challenged the "unknown" designation. Additionally, effective targeted therapies in several cancers have moved the paradigm from empiricism to considering a personalized approach to CUP management. The reasons cancers present as CUP remain unclear. One hypothesis is that the primary

tumor either regresses after seeding the metastasis or remains so small that it is not detected. It is possible that CUP falls on the continuum of cancer presentation where the primary has been contained or eliminated by the natural body defenses. Alternatively, CUP may represent a specific malignant event that results in an increase in metastatic spread or survival relative to the primary. Whether the CUP metastases truly define a clone that is genetically and phenotypically unique to this diagnosis remains to be determined. Of note, the incidence of intrahepatic cholangiocarcinoma (ICC) is increasing whereas the incidence of CUP is declining during this same time period. Because the liver is a common site of CUP presentation, ICC can be misdiagnosed as CUP. Improvements in diagnostic technologies and awareness among clinicians to differentiate the two are contributing to an increased recognized incidence of ICC.

CUP BIOLOGY

Studies looking for unique signature abnormalities in CUP tumors have not been positive. Abnormalities in chromosomes 1 and 12 and other complex cytogenetic abnormalities have been reported. Aneuploidy has been described in 70% of CUP patients with metastatic adenocarcinoma or undifferentiated carcinoma. The overexpression of various genes, including *Ras*, *bcl-2* (40%), *her-2* (11%), and *p53* (26–53%), has been identified in CUP samples, but they have no effect on response to therapy or survival. The extent of angiogenesis in CUP relative to that in metastases from known primaries has also been evaluated, but no consistent findings have emerged. Current focus is on comprehensive genomic profiling that may identify targeted therapeutic approaches to improve outcomes for this disease as discussed below. Additionally, ongoing profiling efforts may also provide insights into CUP biology through recognition of molecular aberrations that especially drive metastatic growth.

CLINICAL EVALUATION

Initial CUP evaluation has two goals: search for the primary tumor based on pathologic evaluation of the metastases and determine the extent of disease. Obtaining a thorough medical history from CUP patients is essential, including paying particular attention to previous surgeries, removed lesions, and family medical history to assess potential hereditary cancers. Adequate physical examination, including a digital rectal examination in men and breast and pelvic examinations in women, should be performed based on clinical presentation.

Role of Serum Tumor Markers and Cytogenetics Most tumor markers, including CEA, CA-125, CA 19-9, and CA 15-3, when elevated, are nonspecific and not helpful in determining the primary tumor site. Men who present with adenocarcinoma and predominant osteoblastic metastasis should undergo a prostate-specific antigen (PSA) test. In patients with undifferentiated or poorly differentiated carcinoma (especially with a midline tumor), elevated β-human chorionic gonadotropin (β-hCG) and α fetoprotein (AFP) levels suggest the possibility of an extragonadal germ cell (testicular) tumor. AFP should also be considered in patients with a potential diagnosis of hepatoma. With the availability of IHC, cytogenetic studies are rarely needed.

Role of Imaging Studies In the absence of contraindications, a baseline IV contrast computed tomography (CT) scan of the chest, abdomen, and pelvis is the standard of care. This helps to search for the primary tumor, evaluate the extent of disease, and select the most accessible biopsy site. Older studies suggested that the primary tumor site is detected in 20–35% of patients who undergo a CT scan of the abdomen and pelvis, although by current definition, these patients do not have CUP. With precise imaging and reporting, latent primary cancers, defined as appearance of a new primary cancer after a latent period of several months to years, is uncommon and seen in ≤5% of CUP patients, usually in patients with very indolent presentations and/or highly responsive metastatic cancers that allows a latent primary to emerge (grow) over time.

Mammography should be performed in all women who present with metastatic adenocarcinoma, especially in those with adenocarcinoma and isolated axillary lymphadenopathy. Magnetic resonance imaging (MRI) of the breast is a follow-up modality in patients with axillary adenopathy and suspected occult primary breast carcinoma following a negative mammography and ultrasound. The results of these imaging modalities can influence surgical management; a negative MRI of the breast result predicts a low tumor yield at mastectomy.

A conventional workup for a squamous cell carcinoma and cervical CUP (neck lymphadenopathy with no known primary tumor) includes a CT scan or MRI and invasive studies, including indirect and direct laryngoscopy, bronchoscopy, and upper endoscopy. Ipsilateral (or bilateral) staging tonsillectomy has been recommended for these patients. 18-Fluorodeoxyglucose positron emission tomography (18-FDG-PET) scans are useful in this patient population and may help guide the biopsy; determine the extent of disease; facilitate the appropriate treatment, including planning radiation fields; and help with disease surveillance. A smaller radiation field encompassing the primary (when found) and metastatic adenopathy decreases the risk of chronic xerostomia. Several studies have evaluated the utility of PET in patients with squamous cervical CUP, and head and neck primary tumors were identified in ~21–30%.

The diagnostic contribution of PET to the evaluation of other CUP presentations (outside of the neck adenopathy indication) remains controversial and is not routinely recommended. PET-CT can be helpful for patients who are candidates for surgical intervention for solitary metastatic disease because the identification of disease in addition to the solitary metastatic site may affect surgical planning.

Invasive studies, including upper endoscopy, colonoscopy, and bronchoscopy, should be limited to symptomatic patients or those with laboratory, imaging, or pathologic abnormalities that suggest that these techniques will result in a high yield in finding a primary cancer.

Role of Pathologic Studies A detailed pathologic examination of the most accessible biopsied tissue specimen is mandatory in CUP patients. Pathologic evaluation typically consists of hematoxylin and eosin stains and immunohistochemical tests.

LIGHT MICROSCOPY EVALUATION Adequate tissue obtained preferably by excisional biopsy or core-needle biopsy (instead of only a fine-needle aspiration) is stained with hematoxylin and eosin and subjected to light microscopic examination. On light microscopy, 60–65% of CUP is adenocarcinoma, and 5% is squamous cell carcinoma. The remaining 30–35% is poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm. A small percentage of lesions are diagnosed as neuroendocrine cancers (2%), mixed tumors (adenosquamous or sarcomatoid carcinomas), or undifferentiated neoplasms (Table 88-1).

ROLE OF IMMUNOHISTOCHEMICAL ANALYSIS Immunohistochemical stains are peroxidase-labeled antibodies against specific tumor antigens that are used to define tumor lineage. The number of available immunohistochemical stains is ever-increasing and unfortunately, we lack a tiered and uniform approach to tissue evaluation in the CUP setting. For CUP cases, more is not necessarily better, and immunohistochemical stains should be used in conjunction with the patient's clinical presentation and imaging studies to select the best therapy. Communication between the clinician and pathologist is essential. No stain is 100% specific, and overinterpretation should be avoided. PSA and thyroglobulin tissue markers, which are positive in prostate and thyroid cancer, respectively, are the most specific of the current marker panel. However, these cancers rarely present as CUP, so the yield of these tests may be low. Figure 88-1 delineates a simple algorithm for immunohistochemical staining in CUP cases. Table 88-2 lists additional

TABLE 88-1 Major Histologies in Carcinoma of Unknown Primary

HISTOLOGY	PROPORTION, %
Well to moderately differentiated adenocarcinoma	60
Squamous cell cancer	5
Poorly differentiated adenocarcinoma, poorly differentiated carcinoma	30
Neuroendocrine	2
Undifferentiated malignancy	3

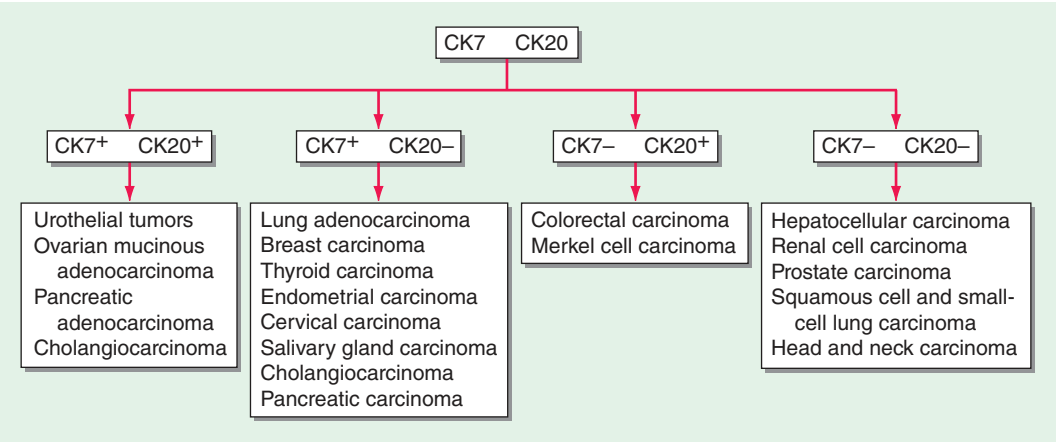

FIGURE 88-1 Approach to cytokeratin (CK7 and CK20) markers used in adenocarcinoma of unknown primary.

tests that may be useful to further define the tumor lineage. A more comprehensive algorithm may improve the diagnostic accuracy but can make the process complex and increase cost. With the use of immunohistochemical markers, electron microscopic analysis, which is time-consuming and expensive, is rarely needed.

There are >20 subtypes of cytokeratin (CK) intermediate filaments with different molecular weights and differential expression in various cell types and cancers. Monoclonal antibodies to specific CK subtypes have been used to help classify tumors according to their site of origin; commonly used CK stains in adenocarcinoma CUP are CK7 and CK20. CK7 is found in tumors of the lung, ovary, endometrium, breast, and upper gastrointestinal tract including pancreaticobiliary cancers, whereas CK20 is normally expressed in the gastrointestinal epithelium, urothelium, and Merkel cells. The nuclear CDX-2 transcription factor, which is the product of a homeobox gene necessary for intestinal organogenesis, is often used to aid in the diagnosis of gastrointestinal adenocarcinomas.

TABLE 88-2 Select Immunohistochemical Stains Useful in the Diagnosis of CUP

LIKELY PRIMARY PROFILE	COMMONLY CONSIDERED IHC TO ASSIST IN DIFFERENTIAL DIAGNOSIS OF CUP[a]
Breast	ER, GCDFP-15, mammaglobin, Her-2/neu, GATA3
Ovarian/mullerian	ER, *WT1* gene, CK7, PAX8, PAX2
Lung adenocarcinoma	TTF-1; nuclear staining, napsin A, SP-A1
Germ cell	β-HCG, AFP, OCT3/4, CKIT, CD30 (embryonal), SALL4
Prostate	PSA, α-methylacyl CoA racemase/P504S (AMACR/P504S), P501S (prostein), and PSMA, NKX3-1
Intestinal	CK7, CK20, CDX-2, CEA
Neuroendocrine	Chromogranin, synaptophysin, CD56
Sarcoma	Desmin (desmoid tumors), factor VIII (angiosarcomas), CD31, smooth muscle actin (leiomyosarcoma), MyoD1 (rhabdomyosarcoma)
Renal	RCC, CD10, PAX8, CD10
Hepatocellular carcinoma	Hep Par-1, Arg-1, glypican-3
Melanoma	S100, SOX-10, vimentin, HMB-45, tyrosinase and melan-A
Urothelial	CK7, CK20, thrombomodulin, uroplakin III
Mesothelioma	Calretinin, *WT1*, D2-40, mesothelin
Lymphoma	LCA, CD3, CD4, CD5, CD20, CD45
SCC	p63, p40 (lung SCC), CK5/6

[a]Patterns emerging from coexpression of stains are better than individual stains to suggest putative primary site. Even with optimization, no IHC panel is 100% sensitive or specific (e.g., ovarian mucinous carcinoma can exhibit positivity with intestinal markers).

Abbreviations: AFP, α fetoprotein; Arg-1, arginase-1; β-hCG, β-human chorionic gonadotropin; CEA, carcinoembryonic antigen; CUP, carcinoma of unknown primary; ER, estrogen receptor; GCDFP-15, gross cystic disease fibrous protein-15; IHC, immunohistochemistry; LCA, leukocyte common antigen; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SCC, squamous cell carcinoma; SP-A1, surfactant protein A precursor; TTF, thyroid transcription factor; WT, Wilms' tumor.

Thyroid transcription factor 1 (TTF-1) nuclear staining is frequently positive in lung and thyroid cancers. Approximately 68% of adenocarcinomas and 25% of squamous cell lung cancers stain positive for TTF-1, which helps differentiate a lung primary tumor from metastatic adenocarcinoma in a pleural effusion, the mediastinum, or the lung parenchyma.

Gross cystic disease fibrous protein-15, a 15-kDa monomer protein, is a marker of apocrine differentiation that is detected in 62–72% of breast carcinomas. GATA3 is being increasingly used in the CUP setting when there is concern for a breast primary, and can be particularly useful as a marker for metastatic breast carcinoma, especially triple-negative and metaplastic carcinomas, which lack specific endocrine markers of mammary origin. UROIII, high-molecular-weight cytokeratin, thrombomodulin, and CK20 are the markers used to diagnose lesions of urothelial origin.

IHC performs the best when used in groups that give rise to patterns that are strongly indicative of certain profiles. For example, the TTF-1/CK7+ and CK20+/CDX-2+/CK7– phenotypes have been reported as very suggestive of lung and lower gastrointestinal cancer profiles, respectively. Despite their practical utility, these patterns have not been validated prospectively in CUP patients. IHC is not without its limitations; several factors affect tissue antigenicity (antigen retrieval, specimen processing, and fixation), interpretation of stains in tumor (nuclear, cytoplasmic, membrane) versus normal tissue, inter- and intraobserver variability, variable performance of different antibodies said to recognize the same antigen, and tissue heterogeneity and inadequacy (given small biopsy sizes). Communication with the pathologist is critical to determine if additional tissue will be beneficial in the pathologic evaluation. Pathologic features should supersede clinical or radiologic findings when considering testing for biomarkers of therapeutic response (e.g., epidermal growth factor receptor [EGFR], Alk mutations, human epidermal growth factor receptor 2 [HER-2]).

ROLE OF CANCER CLASSIFIER MOLECULAR PROFILING In the absence of a known primary, developing therapeutic strategies for CUP is challenging. The current diagnostic yield with imaging and immunochemistry is ~20–30% for CUP patients. To reduce diagnostic uncertainty, sophisticated molecular analytics have been applied to CUP samples. These include gene expression profiling, messenger RNA (mRNA), microRNA, and epigenetic profiling to classify the CUP cancer.

Gene expression profiles are most commonly generated using quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or DNA microarray. Neural network programs are then used to develop predictive algorithms from the gene expression profiles. Typically, a training set of gene profiles from known cancers (preferably from metastatic sites) is used to train the software. Comprehensive gene expression databases that have become available for common malignancies are then applied to CUP samples and the program can then be used to predict the putative origin of a CUP sample.

mRNA- or microRNA-based tissue of origin cancer classifier assays have also been studied in prospective and retrospective CUP trials. More recently, a classifier based on microarray DNA methylation signatures has been studied and validated in known cancers. The DNA methylation profiling predicted a primary cancer in 87% of the 216 CUP patients.

Despite the sophistication of the cancer classifier molecular assays, most of the CUP studies have evaluated assay *performance*, although the challenge with validating the accuracy of an assay for CUP is that, by definition, the primary cancer diagnosis cannot be verified. Thus, current estimates of tissue of origin test accuracy have relied on indirect metrics, including comparison with pathology/IHC, clinical presentation, appearance of latent primaries, and autopsies. Using these measures, the assays suggest a plausible primary in ~70–80% of patients studied. The only outcomes-based study is a single-arm study reporting a median survival of 12.5 months for patients who received assay-directed site-specific therapy. Firm conclusions of therapeutic impact cannot be drawn from this study given the nonrandomized design, statistical biases, confounding variables including use of subsequent lines of (empiric) therapy, and the heterogeneity of the CUP cancers. Additional studies are needed to better understand the clinical influence of tissue of origin profiling tools and how these assays complement IHC and help guide therapy.

ROLE OF NEXT GENERATION SEQUENCING A significant push is being made toward personalized medicine across all cancer types with the goal of identifying driver mutation(s) in a patient who can be treated with targeted agents independent of the site of origin. A retrospective study of 200 CUP tumor specimens reported on genomic alterations (GA) using the hybrid-capture–based FoundationOne assay. The authors reported that a large number of CUP samples (85%) harbored at least one clinically relevant GA with the potential to influence and personalize therapy. The mean number of GAs was 4.2 per tumor, and the most common GAs included *TP53* (55%), *KRAS* (20%), *CDKN2A* (19%), and *ARID1A* (11%). The adenocarcinoma CUP tumors were more frequently driven by GAs in the receptor tyrosine kinase (RTK)/Ras/mitogen-activated protein kinase (MAPK) signaling pathway than nonadenocarcinoma CUP tumors.

Ongoing histology and cellular-context agnostic prospective clinical trials are studying the presence of actionable mutations and matching patients to the right targeted drug. Should this approach eventually be appropriately validated, CUP would be a natural fit for GA-based targeted therapy independent of tumor site.

TREATMENT

Carcinoma of Unknown Primary

GENERAL CONSIDERATIONS

The treatment of CUP continues to evolve, albeit slowly. The median survival duration of most patients with disseminated CUP is ~6–10 months. Systemic chemotherapy is the primary treatment modality in most patients with disseminated disease, but the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of this condition **(Figs. 88-2 and 88-3)**. Prognostic factors include performance status, site and number of metastases, response to chemotherapy, and serum lactate dehydrogenase (LDH) levels. Culine and colleagues developed a prognostic model using performance status and serum LDH levels, which allowed the assignment of patients into two subgroups with divergent outcomes. Future prospective trials using this prognostic model are warranted. Clinically, some CUP diagnoses fall into a favorable prognostic subset. Others, including those with disseminated CUP, do not and have a more unfavorable prognosis.

TREATMENT OF FAVORABLE CUP SUBSETS

Women with Isolated Axillary Adenopathy Women with isolated axillary adenopathy with adenocarcinoma or carcinoma are usually treated for stage II or III breast cancer based on pathologic findings. These patients should undergo a breast MRI if mammogram and ultrasound are negative. Radiation therapy to the ipsilateral breast is indicated if the MRI of the breast is positive. Chemotherapy and/or hormonal therapy are indicated based on patient's age (premenopausal or postmenopausal), nodal disease bulk, and hormone receptor status **(Chap. 75)**. It is important to verify that the pathology suggests a breast cancer profile (morphology, immunohistochemical breast markers including estrogen receptor, mammaglobin, GCDFP-15, GATA3, HER-2 gene expression) before embarking on a breast cancer therapeutic program.

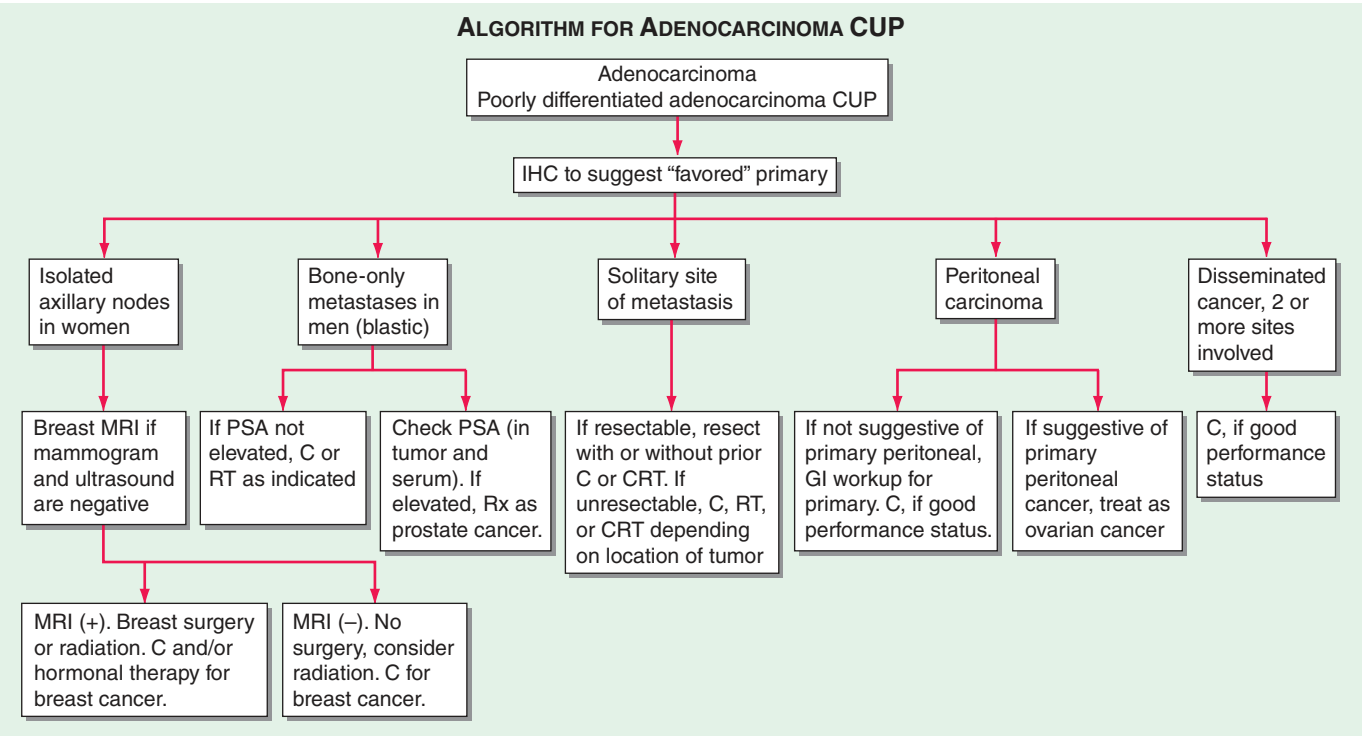

FIGURE 88-2 Treatment algorithm for adenocarcinoma and poorly differentiated adenocarcinoma of unknown primary (CUP). C, chemotherapy; CRT, chemoradiation; GI, gastrointestinal; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RT, radiation.

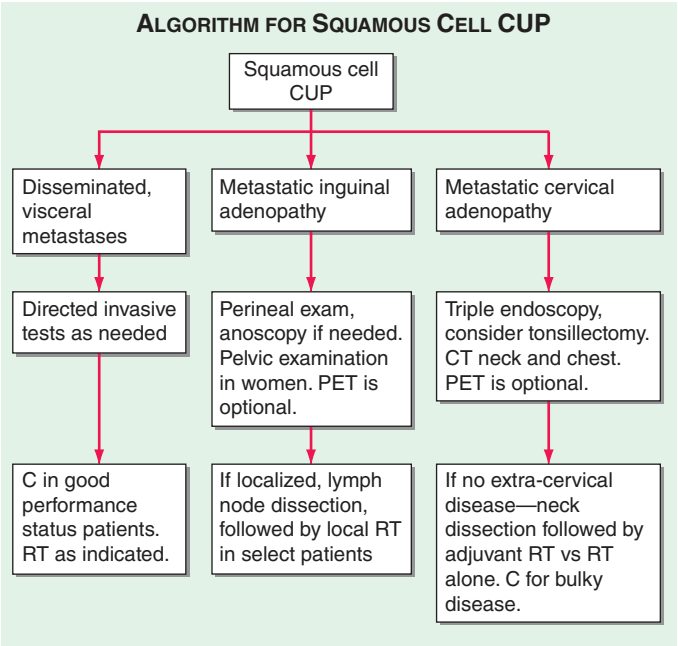

FIGURE 88-3 Treatment algorithm for squamous cell carcinoma of unknown primary (CUP). C, chemotherapy; CT, computed tomography; PET, positron emission tomography; RT, radiation.

WOMEN WITH PERITONEAL CARCINOMATOSIS

The term *primary peritoneal papillary serous carcinoma* (PPSC) has been used to describe CUP with carcinomatosis with the pathologic and laboratory (elevated CA-125 antigen) characteristics of ovarian cancer but no ovarian primary tumor identified on transvaginal sonography or laparotomy. Studies suggest that ovarian cancer and PPSC, which are both of müllerian origin, have similar gene expression profiles. Similar to patients with ovarian cancer, patients with PPSC are candidates for cytoreductive surgery, followed by adjuvant taxane- and platinum-based chemotherapy. In one retrospective study of 258 women with peritoneal carcinomatosis who had undergone cytoreductive surgery and chemotherapy, 22% of patients had a complete response to chemotherapy; the median survival duration was 18 months (range 11–24 months). However, not all peritoneal carcinomatosis in women is PPSC. Careful pathologic evaluation can help diagnose a colon cancer profile (CDX-2+, CK-20+, CK7–) or a pancreaticobiliary cancer or even a mislabeled peritoneal mesothelioma (calretinin positive).

POORLY DIFFERENTIATED CARCINOMA WITH MIDLINE ADENOPATHY **(CHAP. 84)**

Men with poorly differentiated or undifferentiated carcinoma that presents with midline adenopathy should be evaluated for extragonadal germ cell malignancy. If diagnosed and treated as such, they often experience a good response to treatment with platinum-based combination chemotherapy. Response rates of >50% have been noted, and long-term survival rates of 10–15% long have been reported. Older patients, especially smokers, who present with mediastinal adenopathy are more likely to have a lung or head-and-neck cancer profile.

NEUROENDOCRINE CARCINOMA **(CHAP. 80)**

Low-grade neuroendocrine tumor (NET) often has an indolent course, and treatment decisions are based on symptoms and tumor bulk. Urine 5-HIAA and serum chromogranin may be elevated and can be followed as markers. Often, the patient is treated with somatostatin analogues alone for hormone-related symptoms (diarrhea, flushing, nausea). Specific local therapies or systemic therapy would only be indicated if the patient is symptomatic with local pain secondary to significant growth of the metastasis or the hormone-related symptoms are not controlled with endocrine therapy. Novel therapy options have demonstrated benefit in patients with low-grade NET, including sunitinib (which targets the vascular endothelial growth factor pathway) and everolimus (which inhibits the mammalian target of rapamycin). Patients with high-grade NET are treated with platinum-based doublet therapy; 20–25% show a complete response, and up to 10% patients with limited/oligo presentations survive for >5 years.

SQUAMOUS CELL CARCINOMA PRESENTING AS NECK ADENOPATHY

Patients with early-stage squamous cell carcinoma involving the cervical lymph nodes are candidates for node dissection and radiation therapy, which can result in long-term survival. The role of chemotherapy in these patients is undefined, although chemoradiation therapy or induction chemotherapy is often used and is beneficial in bulky N2/N3 lymph node disease.

SOLITARY METASTATIC SITE

Patients with solitary metastases can also experience good treatment outcomes. Some patients who present with locoregional disease are candidates for aggressive trimodality management—both prolonged disease-free survival, and, occasionally, cure is possible.

MEN WITH BLASTIC SKELETAL METASTASES AND ELEVATED PSA **(CHAP. 83)**

Blastic bone-only metastasis is a rare presentation, and elevated serum PSA or tumor staining with PSA may provide confirmatory evidence of prostate cancer in these patients. Those with elevated levels are candidates for hormonal therapy for prostate cancer, although it is important to rule out other primary tumors (lung most common).

MANAGEMENT OF DISSEMINATED CUP

Patients who present with liver, brain, and adrenal metastatic disease usually have a poor prognosis. Patients with peritoneal carcinomatosis secondary to metastatic adenocarcinoma have a broad differential diagnosis, which includes mainly gastrointestinal cancers including gastric, appendiceal, colon, and pancreaticobiliary cancers.

Traditionally, platinum-based combination chemotherapy regimens have been used to treat CUP. Several broadly used regimens have been studied in the last two decades; these include paclitaxel-carboplatin, gemcitabine-cisplatin, gemcitabine-oxaliplatin, and irinotecan and fluoropyrimidine-based therapies. These chemotherapeutic agents used as empiric regimens have shown a response rate of 25–40%, and their use obtains median survival times of 6–13 months.

Outside of favorable subsets, there is a small group of patients with a "definitive" IHC profile. These patients usually have a single diagnosis based on their clinicopathologic presentation and are often treated for the putative primary tumor. This does not guarantee a response, although it increases the probability of response when select drugs are chosen from a class of drugs known to be effective in that cancer type. Patients who do not fall into those categories are candidates for broad-spectrum platinum-based regimens, clinical trials, and additional trial-based genomic and proteomic tests. Today, we do not have many effective drugs for several CUP cancer profiles, and treatments overlap for some cancers. However, as novel therapies are developed for known cancers, these agents will likely impact management of CUP patients.

SUMMARY

Patients with CUP should undergo a directed diagnostic search for the primary tumor on the basis of clinical and pathologic data. Subsets of patients have prognostically favorable disease, as defined by clinical or histologic criteria, and may substantially benefit from aggressive treatment and prolonged survival can be expected. However, for most patients who present with advanced CUP, the prognosis remains poor with early resistance to available cytotoxic therapy. The current focus has shifted away from empirical chemotherapeutic trials to

understanding the metastatic phenotype, tissue of origin profiling in select patients, and next-generation sequencing to evaluate actionable mutations in CUP patients.

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89 Paraneoplastic Syndromes: Endocrinologic/Hematologic

J. Larry Jameson, Dan L. Longo

Neoplastic cells can produce a variety of products that can stimulate hormonal, hematologic, dermatologic, rheumatologic, renal, and neurologic responses. *Paraneoplastic syndromes* is the term used to refer to the disorders that accompany benign or malignant tumors but are not directly related to mass effects or invasion. Tumors of neuroendocrine origin, such as small-cell lung carcinoma (SCLC) and carcinoids are common causes of paraneoplastic syndromes, and produce a wide array of peptide hormones and antibodies. However, almost every type of tumor has the potential to produce hormones or to induce cytokine and immunologic responses. Careful studies of the prevalence of paraneoplastic syndromes indicate that they are more common than is generally appreciated. The signs, symptoms, and metabolic alterations associated with paraneoplastic disorders may be overlooked in the context of a malignancy and its treatment. Consequently, atypical clinical manifestations in a patient with cancer should prompt consideration of a paraneoplastic syndrome. The most common hormonal and hematologic syndromes associated with underlying neoplasia will be discussed here.

ENDOCRINE PARANEOPLASTIC SYNDROMES

Etiology Hormones can be produced from eutopic or ectopic sources. *Eutopic* refers to the expression of a hormone from its normal tissue of origin, whereas *ectopic* refers to hormone production from an atypical tissue source. For example, adrenocorticotropic hormone (ACTH) is expressed eutopically by the corticotrope cells of the anterior pituitary, but it can be expressed ectopically in SCLC. Many hormones are produced at low levels from a wide array of tissues in addition to the classic endocrine source. Thus, ectopic expression is often a quantitative change rather than an absolute change in tissue expression. Nevertheless, the term *ectopic expression* is firmly entrenched and conveys the abnormal physiology associated with hormone production by neoplastic cells. In addition to high levels of hormones, ectopic expression is often characterized by abnormal regulation of hormone production (e.g., defective feedback control) and peptide processing (resulting in large, unprocessed precursors).

A diverse array of molecular mechanisms has been suggested to explain ectopic hormone production. In rare instances, genetic rearrangements account for aberrant hormone expression. For example, translocation of the parathyroid hormone (*PTH*) gene can result in high levels of PTH expression in tissues other than the parathyroid gland because the genetic rearrangement brings the *PTH* gene under the control of atypical regulatory elements. A related phenomenon is well documented in many forms of leukemia and lymphoma, in which somatic genetic rearrangements confer a growth advantage and alter cellular differentiation and function. Although genetic rearrangements cause selected cases of ectopic hormone production, this mechanism is rare, as many tumors are associated with excessive production of numerous peptides. Cellular dedifferentiation probably underlies most cases of ectopic hormone production. Many cancers are poorly differentiated, and certain tumor products, such as human chorionic gonadotropin (hCG), PTH–related protein (PTHrP), and α fetoprotein, are characteristic of gene expression at earlier developmental stages. In contrast, the propensity of certain cancers to produce particular hormones (e.g., squamous cell carcinomas produce PTHrP) suggests that dedifferentiation is partial or that selective pathways are derepressed. These expression profiles probably reflect epigenetic modifications that alter transcriptional repression, microRNA expression, and other pathways that govern cell differentiation.

In SCLC, the pathway of differentiation has been relatively well defined. The neuroendocrine phenotype is dictated in part by the basic-helix-loop-helix (bHLH) transcription factor human achaete-scute homologue 1 (hASH-1), which is expressed at abnormally high levels in SCLC associated with ectopic ACTH. The activity of hASH-1 is inhibited by hairy enhancer of split 1 (HES-1) and by Notch proteins, which also are capable of inducing growth arrest. Thus, abnormal expression of these developmental transcription factors appears to provide a link between cell proliferation and differentiation.

Ectopic hormone production might be considered merely epiphenomenon associated with cancer if it did not result in clinical manifestations. Excessive and unregulated production of hormones such as ACTH, PTHrP, and vasopressin can lead to substantial morbidity and complicate the cancer treatment plan. Moreover, the paraneoplastic endocrinopathies may be a presenting clinical feature of underlying malignancy and prompt the search for an unrecognized tumor.

A large number of paraneoplastic endocrine syndromes have been described, linking overproduction of particular hormones with specific types of tumors. However, certain recurring syndromes emerge from this group **(Table 89-1)**. The most common paraneoplastic endocrine syndromes include hypercalcemia from overproduction of PTHrP and other factors, hyponatremia from excess vasopressin, and Cushing's syndrome from ectopic ACTH.

HYPERCALCEMIA CAUSED BY ECTOPIC PRODUCTION OF PTHRP

(See also Chap. 403)

Etiology Humoral hypercalcemia of malignancy (HHM) occurs in up to 20% of patients with cancer. HHM is most common in cancers of the lung, head and neck, skin, esophagus, breast, and genitourinary tract and in multiple myeloma and lymphomas. There are several distinct humoral causes of HHM, but it is caused most commonly by overproduction of PTHrP. In addition to acting as a circulating humoral factor, bone metastases (e.g., breast, multiple myeloma) may produce PTHrP, leading to local osteolysis and hypercalcemia. PTHrP may also affect the initiation and progression of tumors by acting through pro-survival and chemokine pathways.

TABLE 89-1 Paraneoplastic Syndromes Caused by Ectopic Hormone Production

PARANEOPLASTIC SYNDROME	ECTOPIC HORMONE	TYPICAL TUMOR TYPES[a]
Common		
Hypercalcemia of malignancy	Parathyroid hormone–related protein (PTHrP)	Squamous cell (head and neck, lung, skin), breast, genitourinary, gastrointestinal
	1,25-dihydroxyvitamin D	Lymphomas
	Parathyroid hormone (PTH) (rare)	Lung, ovary
	Prostaglandin E_2 (PGE_2) (rare)	Renal, lung
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Vasopressin	Lung (squamous, small cell), gastrointestinal, genitourinary, ovary
Cushing's syndrome	Adrenocorticotropic hormone (ACTH)	Lung (small cell, bronchial carcinoid, adenocarcinoma, squamous), thymus, pancreatic islet, medullary thyroid carcinoma, pheochromocytoma
	Corticotropin-releasing hormone (CRH) (rare)	Pancreatic islet, carcinoid, lung, prostate
	Ectopic expression of gastric inhibitory peptide (GIP), luteinizing hormone (LH)/human chorionic gonadotropin (hCG), other G protein–coupled receptors (rare)	Macronodular adrenal hyperplasia
Less Common		
Non–islet cell hypoglycemia	Insulin-like growth factor type II (IGF-II)	Mesenchymal tumors, sarcomas, adrenal, hepatic, gastrointestinal, kidney, prostate
	Insulin (rare)	Cervix (small-cell carcinoma)
Male feminization	hCG[b]	Testis (embryonal, seminomas), germinomas, choriocarcinoma, lung, hepatic, pancreatic islet
Diarrhea or intestinal hypermotility	Calcitonin[c]	Lung, colon, breast, medullary thyroid carcinoma
	Vasoactive intestinal peptide (VIP)	Pancreas, pheochromocytoma, esophagus
Rare		
Oncogenic osteomalacia	Phosphatonin (fibroblast growth factor 23 [FGF23])	Hemangiopericytomas, osteoblastomas, fibromas, sarcomas, giant cell tumors, prostate, lung
Acromegaly	Growth hormone–releasing hormone (GHRH)	Pancreatic islet, bronchial, and other carcinoids
	Growth hormone (GH)	Lung, pancreatic islet
Hyperthyroidism	Thyroid-stimulating hormone (TSH)	Hydatidiform mole, embryonal tumors, struma ovarii
Hypertension	Renin	Juxtaglomerular tumors, kidney, lung, pancreas, ovary
Consumptive hypothyroidism	Type 3 deiodinase	Hepatic hemangiomas

[a]Only the most common tumor types are listed. For most ectopic hormone syndromes, an extensive list of tumors has been reported to produce one or more hormones. [b]hCG is produced eutopically by trophoblastic tumors. Certain tumors produce disproportionate amounts of the hCG α or hCG β subunit. High levels of hCG rarely cause hyperthyroidism because of weak binding to the TSH receptor. [c]Calcitonin is produced eutopically by medullary thyroid carcinoma and is used as a tumor marker.

PTHrP is structurally related to PTH and binds to the PTH receptor, explaining the similar biochemical features of HHM and hyperparathyroidism. PTHrP plays a key role in skeletal development and regulates cellular proliferation and differentiation in other tissues, including skin, bone marrow, breast, and hair follicles. The mechanism of PTHrP induction in malignancy is incompletely understood; however, tumor-bearing tissues commonly associated with HHM normally produce PTHrP during development or cell renewal. PTHrP expression is stimulated by hedgehog pathways and Gli transcription factors that are active in many malignancies. Transforming growth factor β (TGF-β), which is produced by many tumors, also stimulates PTHrP. Mutations in certain oncogenes, such as *Ras*, also can activate PTHrP expression, as does loss of the tumor suppressor, p53. In addition to its role in HHM, the PTHrP pathway may also provide a potential target for therapeutic intervention to impede cancer growth.

Another relatively common cause of HHM is excess production of 1,25-dihydroxyvitamin D. Like granulomatous disorders associated with hypercalcemia, lymphomas can produce an enzyme that converts 25-hydroxyvitamin D to the more active 1,25-dihydroxyvitamin D, leading to enhanced gastrointestinal calcium absorption. Other causes of HHM include tumor-mediated production of osteolytic cytokines and inflammatory mediators.

Clinical Manifestations The typical presentation of HHM is a patient with a known malignancy who is found to be hypercalcemic on routine laboratory tests. Less often, hypercalcemia is the initial presenting feature of malignancy. Particularly when calcium levels are markedly increased (>3.5 mmol/L [>14 mg/dL]), patients may experience fatigue, mental status changes, dehydration, or symptoms of nephrolithiasis.

Diagnosis Features that favor HHM, as opposed to primary hyperparathyroidism, include known malignancy, recent onset of hypercalcemia, and very high serum calcium levels. Like hyperparathyroidism, hypercalcemia caused by PTHrP is accompanied by hypercalciuria and hypophosphatemia. Patients with HHM typically have metabolic alkalosis rather than hyperchloremic acidosis, as is seen in hyperparathyroidism. Measurement of PTH is useful to exclude primary hyperparathyroidism; the PTH level should be suppressed in HHM. An elevated PTHrP level confirms the diagnosis, and it is increased in ~80% of hypercalcemic patients with cancer. 1,25-Dihydroxyvitamin D levels may be increased in patients with lymphoma.

TREATMENT

Humoral Hypercalcemia of Malignancy

The management of HHM begins with removal of excess calcium in the diet, medications, or IV solutions. Saline rehydration (typically 200–500 mL/h) is used to dilute serum calcium and promote calciuresis; exercise caution in patients with cardiac, hepatic, or renal insufficiency. Forced diuresis with furosemide (20–80 mg IV in escalating doses) or other loop diuretics can enhance calcium excretion but provides relatively little value except in life-threatening hypercalcemia. When used, loop diuretics should be administered only after complete rehydration and with careful monitoring of fluid balance. Oral phosphorus (e.g., 250 mg Neutra-Phos 3–4 times daily) should be given until serum phosphorus is >1 mmol/L (>3 mg/dL). Bisphosphonates such as pamidronate (60–90 mg IV), zoledronate (4–8 mg IV), and etidronate (7.5 mg/kg per day PO for

3–7 consecutive days) can reduce serum calcium within 1–2 days and suppress calcium release for several weeks. Bisphosphonate infusions can be repeated, or oral bisphosphonates can be used for chronic treatment. Dialysis should be considered in severe hypercalcemia when saline hydration and bisphosphonate treatments are not possible or are too slow in onset. Previously used agents such as calcitonin and mithramycin have little utility now that bisphosphonates are available. Calcitonin (2–8 U/kg SC every 6–12 h) should be considered when rapid correction of severe hypercalcemia is needed. Hypercalcemia associated with lymphomas, multiple myeloma, or leukemia may respond to glucocorticoid treatment (e.g., prednisone 40–100 mg PO in four divided doses).

ECTOPIC VASOPRESSIN: TUMOR-ASSOCIATED SIADH

(See also Chap. 49)

Etiology Vasopressin is an antidiuretic hormone normally produced by the posterior pituitary gland. Ectopic vasopressin production by tumors is a common cause of the syndrome of inappropriate antidiuretic hormone (SIADH), occurring in at least half of patients with SCLC. SIADH also can be caused by a number of nonneoplastic conditions, including central nervous system (CNS) trauma, infections, and medications (Chap. 374). Compensatory responses to SIADH, such as decreased thirst, may mitigate the development of hyponatremia. However, with prolonged production of excessive vasopressin, the osmostat controlling thirst and hypothalamic vasopressin secretion may become reset. In addition, intake of free water, orally or intravenously, can quickly worsen hyponatremia because of reduced renal diuresis.

Tumors with neuroendocrine features, such as SCLC and carcinoids, are the most common sources of ectopic vasopressin production, but it also occurs in other forms of lung cancer and with CNS lesions, head and neck cancer, and genitourinary, gastrointestinal, and ovarian cancers. The mechanism of activation of the vasopressin gene in these tumors is unknown but often involves concomitant expression of the adjacent oxytocin gene, suggesting derepression of this locus.

Clinical Manifestations Most patients with ectopic vasopressin secretion are asymptomatic and are identified because of the presence of hyponatremia on routine chemistry testing. Symptoms may include weakness, lethargy, nausea, confusion, depressed mental status, and seizures. The severity of symptoms reflects the rapidity of onset as well as the severity of hyponatremia. Hyponatremia usually develops slowly but may be exacerbated by the administration of IV fluids or the institution of new medications.

Diagnosis The diagnostic features of ectopic vasopressin production are the same as those of other causes of SIADH (Chaps. 49 and 374). Hyponatremia and reduced serum osmolality occur in the setting of an inappropriately normal or increased urine osmolality. Urine sodium excretion is normal or increased unless volume depletion is present. Other causes of hyponatremia should be excluded, including renal, adrenal, or thyroid insufficiency. Physiologic sources of vasopressin stimulation (CNS lesions, pulmonary disease, nausea), adaptive circulatory mechanisms (hypotension, heart failure, hepatic cirrhosis), and medications, including many chemotherapeutic agents, also should be considered as possible causes of hyponatremia. Vasopressin measurements are not usually necessary to make the diagnosis.

TREATMENT

Ectopic Vasopressin: Tumor-Associated SIADH

Most patients with ectopic vasopressin production develop hyponatremia over several weeks or months. The disorder should be corrected gradually unless mental status is altered or there is risk of seizures. Treatment of the underlying malignancy may reduce ectopic vasopressin production, but this response is slow if it occurs at all. Fluid restriction to less than urine output, plus insensible losses, is often sufficient to correct hyponatremia partially. However, strict monitoring of the amount and types of liquids consumed or administered intravenously is required for fluid restriction to be effective. Salt tablets and saline are not helpful unless volume depletion is also present. Demeclocycline (150–300 mg orally three to four times daily) can be used to inhibit vasopressin action on the renal distal tubule, but its onset of action is relatively slow (1–2 weeks). The vaptan class of drugs act by inhibiting vasopressin receptors (V_{1A}, V_{1B}, V_2). Conivaptan, a nonpeptide V_2-receptor antagonist, can be administered either PO (20–120 mg bid) or IV (10–40 mg) and is particularly effective when used in combination with fluid restriction in euvolemic hyponatremia. Tolvaptan (15 mg PO daily) is another vasopressin antagonist. The dose can be increased to 30–60 mg/d based on response. Severe hyponatremia (Na <115 meq/L) or mental status changes may require treatment with hypertonic (3%) or normal saline infusion together with furosemide to enhance free water clearance. The rate of sodium correction should be slow (0.5–1 meq/L per hour) to prevent rapid fluid shifts and the possible development of central pontine myelinolysis.

CUSHING'S SYNDROME CAUSED BY ECTOPIC ACTH PRODUCTION

(See also Chap. 379)

Etiology Ectopic ACTH production accounts for 10–20% of cases of Cushing's syndrome. The syndrome is particularly common in neuroendocrine tumors. SCLC is the most common cause of ectopic ACTH, followed by bronchial and thymic carcinoids, islet cell tumors, other carcinoids, and pheochromocytomas. Ectopic ACTH production is caused by increased expression of the proopiomelanocortin (*POMC*) gene, which encodes ACTH, along with melanocyte-stimulating hormone (MSH), β lipotropin, and several other peptides. In many tumors, there is abundant but aberrant expression of the *POMC* gene from an internal promoter, proximal to the third exon, which encodes ACTH. However, because this product lacks the signal sequence necessary for protein processing, it is not secreted. Increased production of ACTH arises instead from less abundant, but unregulated, *POMC* expression from the same promoter site used in the pituitary. Because tumors lack many of the enzymes needed to process the POMC polypeptide, it is typically released as multiple large, biologically inactive fragments along with relatively small amounts of fully processed, active ACTH.

Rarely, corticotropin-releasing hormone (CRH) is produced by pancreatic islet cell tumors, SCLC, medullary thyroid cancer, carcinoids, or prostate cancer. When levels are high enough, CRH can cause pituitary corticotrope hyperplasia and Cushing's syndrome. Tumors that produce CRH sometimes also produce ACTH, raising the possibility of a paracrine mechanism for ACTH production.

A distinct mechanism for ACTH-independent Cushing's syndrome involves ectopic expression of various G protein–coupled receptors in the adrenal nodules. Ectopic expression of the gastric inhibitory peptide (GIP) receptor is the best-characterized example of this mechanism. In this case, meals induce GIP secretion, which inappropriately stimulates adrenal growth and glucocorticoid production.

Clinical Manifestations The clinical features of hypercortisolemia are detected in only a fraction of patients with documented ectopic ACTH production. Patients with ectopic ACTH syndrome generally exhibit less marked weight gain and centripetal fat redistribution, probably because the exposure to excess glucocorticoids is relatively brief and because cachexia reduces the propensity for weight gain and fat deposition. The ectopic ACTH syndrome is associated with several clinical features that distinguish it from other causes of Cushing's syndrome (e.g., pituitary adenomas, adrenal adenomas, iatrogenic glucocorticoid excess). The metabolic manifestations of ectopic ACTH syndrome are dominated by fluid retention and hypertension, hypokalemia, metabolic alkalosis, glucose intolerance, and occasionally steroid psychosis. The very high ACTH levels often cause

increased pigmentation, reflecting increased activity of MSH derived from the POMC precursor peptide. The extraordinarily high glucocorticoid levels in patients with ectopic sources of ACTH can lead to marked skin fragility and easy bruising. In addition, the high cortisol levels often overwhelm the renal 11β-hydroxysteroid dehydrogenase type II enzyme, which normally inactivates cortisol and prevents it from binding to renal mineralocorticoid receptors. Consequently, in addition to the excess mineralocorticoids produced by ACTH stimulation of the adrenal gland, high levels of cortisol exert activity through the mineralocorticoid receptor, leading to severe hypokalemia.

Diagnosis The diagnosis of ectopic ACTH syndrome is usually not difficult in the setting of a known malignancy. Urine-free cortisol levels fluctuate but are typically greater than two to four times normal, and the plasma ACTH level is usually >22 pmol/L (>100 pg/mL). A suppressed ACTH level excludes this diagnosis and indicates an ACTH-independent cause of Cushing's syndrome (e.g., adrenal or exogenous glucocorticoid). In contrast to pituitary sources of ACTH, most ectopic sources of ACTH do not respond to glucocorticoid suppression. Therefore, high-dose dexamethasone (8 mg PO) suppresses 8:00 A.M. serum cortisol (50% decrease from baseline) in ~80% of pituitary ACTH-producing adenomas but fails to suppress ectopic ACTH in ~90% of cases. Bronchial and other carcinoids are well-documented exceptions to these general guidelines, as these ectopic sources of ACTH may exhibit feedback regulation indistinguishable from pituitary adenomas, including suppression by high-dose dexamethasone, and ACTH responsiveness to adrenal blockade with metyrapone. If necessary, petrosal sinus catheterization can be used to evaluate a patient with ACTH-dependent Cushing's syndrome when the source of ACTH is unclear. After CRH stimulation, a 3:1 petrosal sinus:peripheral ACTH ratio strongly suggests a pituitary ACTH source. Imaging studies (computed tomography or magnetic resonance imaging) are also useful in the evaluation of suspected carcinoid lesions, allowing biopsy and characterization of hormone production using special stains. If available, positron emission tomography or octreotide scanning may identify some sources of ACTH production.

TREATMENT

Cushing's Syndrome Caused by Ectopic ACTH Production

The morbidity associated with the ectopic ACTH syndrome can be substantial. Patients may experience depression or personality changes because of extreme cortisol excess. Metabolic derangements, including diabetes mellitus and hypokalemia, can worsen fatigue. Poor wound healing and predisposition to infections can complicate the surgical management of tumors, and opportunistic infections caused by organisms such as *Pneumocystis carinii* and mycoses are often the cause of death in patients with ectopic ACTH production. These patients likely have increased risk of venous thromboembolism reflecting the combination of malignancy and altered coagulation factor profiles. Depending on prognosis and treatment plans for the underlying malignancy, measures to reduce cortisol levels are often indicated. Treatment of the underlying malignancy may reduce ACTH levels but is rarely sufficient to reduce cortisol levels to normal. Adrenalectomy is not practical for most of these patients but should be considered during surgery for the malignancy or if the underlying tumor is not resectable and the prognosis is otherwise favorable (e.g., carcinoid). Medical therapy with ketoconazole (300–600 mg PO bid), metyrapone (250–500 mg PO every 6 h), mitotane (3–6 g PO in four divided doses, tapered to maintain low cortisol production), or other agents that block steroid synthesis or action is often the most practical strategy for managing the hypercortisolism associated with ectopic ACTH production. Glucocorticoid replacement should be provided to prevent adrenal insufficiency (Chap. 379). Unfortunately, many patients eventually progress despite medical blockade.

TUMOR-INDUCED HYPOGLYCEMIA CAUSED BY EXCESS PRODUCTION OF IGF-II

(See also Chap. 399) Mesenchymal tumors, hemangiopericytomas, hepatocellular tumors, adrenal carcinomas, and a variety of other large tumors have been reported to produce excessive amounts of insulin-like growth factor type II (IGF-II) precursor, which binds weakly to insulin receptors and more strongly to IGF-I receptors, leading to insulin-like actions. The gene encoding IGF-II resides on chromosome 11p15, a locus that is normally imprinted (that is, expression is exclusively from a single parental allele). Biallelic expression of the IGF-II gene occurs in a subset of tumors, suggesting loss of methylation and loss of imprinting as a mechanism for gene induction. In addition to increased IGF-II production, IGF-II bioavailability is increased due to complex alterations in circulating binding proteins. Increased IGF-II suppresses growth hormone (GH) and insulin, resulting in reduced IGF binding protein 3 (IGFBP-3), IGF-I, and acid-labile subunit (ALS). The reduction in ALS and IGFBP-3, which normally sequester IGF-II, causes it to be displaced to a small circulating complex that has greater access to insulin target tissues. For this reason, circulating IGF-II levels may not be markedly increased despite causing hypoglycemia. In addition to IGF-II–mediated hypoglycemia, tumors may occupy enough of the liver to impair gluconeogenesis.

In most cases, a tumor causing hypoglycemia is clinically apparent (usually >10 cm in size), and hypoglycemia develops in association with fasting. The diagnosis is made by documenting low serum glucose and suppressed insulin levels in association with symptoms of hypoglycemia. Serum IGF-II levels may not be increased (IGF-II assays may not detect IGF-II precursors). Increased IGF-II mRNA expression is found in most of these tumors. Any medications associated with hypoglycemia should be eliminated. Treatment of the underlying malignancy, if possible, may reduce the predisposition to hypoglycemia. Frequent meals and IV glucose, especially during sleep or fasting, are often necessary to prevent hypoglycemia. Glucagon and glucocorticoids have also been used to enhance glucose production.

HUMAN CHORIONIC GONADOTROPIN

hCG is composed of α and β subunits and can be produced as intact hormone, which is biologically active, or as uncombined biologically inert subunits. Ectopic production of intact hCG occurs most often in association with testicular embryonal tumors, germ cell tumors, extragonadal germinomas, lung cancer, hepatoma, and pancreatic islet tumors. Eutopic production of hCG occurs with trophoblastic malignancies. hCG α subunit production is particularly common in lung cancer and pancreatic islet cancer. In men, high hCG levels stimulate steroidogenesis and aromatase activity in testicular Leydig cells, resulting in increased estrogen production and the development of gynecomastia. Precocious puberty in boys or gynecomastia in men should prompt measurement of hCG and consideration of a testicular tumor or another source of ectopic hCG production. Most women are asymptomatic. hCG is easily measured. Treatment should be directed at the underlying malignancy.

ONCOGENIC OSTEOMALACIA

Hypophosphatemic oncogenic osteomalacia, also called tumor-induced osteomalacia (TIO), is characterized by markedly reduced serum phosphorus and renal phosphate wasting, leading to muscle weakness, bone pain, and osteomalacia. Serum calcium and PTH levels are normal, and 1,25-dihydroxyvitamin D is low. Oncogenic osteomalacia is usually caused by benign mesenchymal tumors, such as hemangiopericytomas, fibromas, and giant cell tumors, often of the skeletal extremities or head. It has also been described in sarcomas and in patients with prostate or lung cancer. Resection of the tumor reverses the disorder, confirming its humoral basis. The circulating phosphaturic factor was originally called *phosphatonin*—a factor that inhibits renal tubular reabsorption of phosphate and renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Phosphatonin has been identified as fibroblast growth factor 23 (FGF23). FGF23 levels are increased in some, but not all, patients with osteogenic osteomalacia. FGF23 forms a ternary complex with the klotho protein and renal FGF

receptors to reduce renal phosphate reabsorption. Treatment involves removal of the tumor, if possible, and supplementation with phosphate and vitamin D. Octreotide treatment reduces phosphate wasting in some patients with tumors that express somatostatin receptor subtype 2. Octreotide scans may also be useful in detecting these tumors.

CONSUMPTIVE HYPOTHYROIDISM

Newborns with hepatic hemangiomas can develop a rare form of hypothyroidism caused by overexpression of type 3 deiodinase (D3), an enzyme that degrades and inactivates T4 and T3. The very high expression of D3, and consumption of thyroid hormones, apparently outstrips the thyroid gland's rate of hormone production. The disorder is characterized by low T4, low T3, high TSH, and markedly elevated reverse T3 (rT3), reflecting the degradation of T4 to rT3. In addition to treating the underlying hemangioma (rarely other tumor types), patients are treated with l-thyroxine replacement, titrated to normalize TSH. Steroids and propranolol may provide benefit, perhaps by inhibiting growth factor pathways thought to stimulate D3 production.

HEMATOLOGIC SYNDROMES

The elevation of granulocyte, platelet, and eosinophil counts in most patients with myeloproliferative disorders is caused by the proliferation of the myeloid elements due to the underlying disease rather than to a paraneoplastic syndrome. The paraneoplastic hematologic syndromes in patients with solid tumors are less well characterized than are the endocrine syndromes because the ectopic hormone(s) or cytokines responsible have not been identified in most of these tumors (Table 89-2). The extent of the paraneoplastic syndromes parallels the course of the cancer.

ERYTHROCYTOSIS

Ectopic production of erythropoietin by cancer cells causes most paraneoplastic erythrocytosis. The ectopically produced erythropoietin stimulates the production of red blood cells (RBCs) in the bone marrow and raises the hematocrit. Other lymphokines and hormones produced by cancer cells may stimulate erythropoietin release but have not been proved to cause erythrocytosis.

Most patients with erythrocytosis have an elevated hematocrit (>52% in men, >48% in women) that is detected on a routine blood count. Approximately 3% of patients with renal cell cancer, 10% of patients with hepatoma, and 15% of patients with cerebellar hemangioblastomas have erythrocytosis. In most cases, the erythrocytosis is asymptomatic.

Patients with erythrocytosis due to a renal cell cancer, hepatoma, or CNS cancer should have measurement of red cell mass. If the red cell mass is elevated, the serum erythropoietin level should be measured. Patients with an appropriate cancer, elevated erythropoietin levels, and no other explanation for erythrocytosis (e.g., hemoglobinopathy that causes increased O_2 affinity; Chap. 59) have the paraneoplastic syndrome.

TABLE 89-2 Paraneoplastic Hematologic Syndromes

SYNDROME	PROTEINS	CANCERS TYPICALLY ASSOCIATED WITH SYNDROME
Erythrocytosis	Erythropoietin	Renal cancers, hepatocarcinoma, cerebellar hemangioblastomas
Granulocytosis	G-CSF, GM-CSF, IL-6	Lung cancer, gastrointestinal cancer, ovarian cancer, genitourinary cancer, Hodgkin's disease
Thrombocytosis	IL-6	Lung cancer, gastrointestinal cancer, breast cancer, ovarian cancer, lymphoma
Eosinophilia	IL-5	Lymphoma, leukemia, lung cancer
Thrombophlebitis	Unknown	Lung cancer, pancreatic cancer, gastrointestinal cancer, breast cancer, genitourinary cancer, ovarian cancer, prostate cancer, lymphoma

Abbreviations: G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin.

TREATMENT

Erythrocytosis

Successful resection of the cancer usually resolves the erythrocytosis. If the tumor cannot be resected or treated effectively with radiation therapy or chemotherapy, phlebotomy may control any symptoms related to erythrocytosis.

GRANULOCYTOSIS

Approximately 30% of patients with solid tumors have granulocytosis (granulocyte count >8000/μL). In about half of patients with granulocytosis and cancer, the granulocytosis has an identifiable nonparaneoplastic etiology (infection, tumor necrosis, glucocorticoid administration, etc.). The other patients have proteins in urine and serum that stimulate the growth of bone marrow cells. Tumors and tumor cell lines from patients with lung, ovarian, and bladder cancers have been documented to produce granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and/or interleukin 6 (IL-6). However, the etiology of granulocytosis has not been characterized in most patients.

Patients with granulocytosis are nearly all asymptomatic, and the differential white blood cell count does not have a shift to immature forms of neutrophils. Granulocytosis occurs in 40% of patients with lung and gastrointestinal cancers, 20% of patients with breast cancer, 30% of patients with brain tumors and ovarian cancers, 20% of patients with Hodgkin's disease, and 10% of patients with renal cell carcinoma. Patients with advanced-stage disease are more likely to have granulocytosis than are those with early-stage disease.

Paraneoplastic granulocytosis does not require treatment. The granulocytosis resolves when the underlying cancer is treated.

THROMBOCYTOSIS

Some 35% of patients with thrombocytosis (platelet count >400,000/μL) have an underlying diagnosis of cancer. IL-6, a candidate molecule for the etiology of paraneoplastic thrombocytosis, stimulates the production of platelets in vitro and in vivo. Some patients with cancer and thrombocytosis have elevated levels of IL-6 in plasma. Another candidate molecule is thrombopoietin, a peptide hormone that stimulates megakaryocyte proliferation and platelet production. The etiology of thrombocytosis has not been established in most cases.

Patients with thrombocytosis are nearly all asymptomatic. Thrombocytosis is not clearly linked to thrombosis in patients with cancer. Thrombocytosis is present in 40% of patients with lung and gastrointestinal cancers; 20% of patients with breast, endometrial, and ovarian cancers; and 10% of patients with lymphoma. Patients with thrombocytosis are more likely to have advanced-stage disease and have a poorer prognosis than do patients without thrombocytosis. In ovarian cancer, IL-6 has been shown to directly promote tumor growth. Paraneoplastic thrombocytosis does not require treatment other than treatment of the underlying tumor.

EOSINOPHILIA

Eosinophilia is present in ~1% of patients with cancer. Tumors and tumor cell lines from patients with lymphomas or leukemia may produce IL-5, which stimulates eosinophil growth. Activation of IL-5 transcription in lymphomas and leukemias may involve translocation of the long arm of chromosome 5, to which the genes for IL-5 and other cytokines map.

Patients with eosinophilia are typically asymptomatic. Eosinophilia is present in 10% of patients with lymphoma, 3% of patients with lung cancer, and occasional patients with cervical, gastrointestinal, renal, and breast cancer. Patients with markedly elevated eosinophil counts (>5000/μL) can develop shortness of breath and wheezing. A chest radiograph may reveal diffuse pulmonary infiltrates from eosinophil infiltration and activation in the lungs.

TREATMENT

Eosinophilia

Definitive treatment is directed at the underlying malignancy: Tumors should be resected or treated with radiation or chemotherapy. In most patients who develop shortness of breath related to eosinophilia, symptoms resolve with the use of oral or inhaled glucocorticoids. IL-5 antagonists exist but have not been evaluated in this clinical setting.

THROMBOPHLEBITIS AND DEEP VENOUS THROMBOSIS

Deep venous thrombosis and pulmonary embolism are the most common thrombotic conditions in patients with cancer. Migratory or recurrent thrombophlebitis may be the initial manifestation of cancer. Nearly 15% of patients who develop deep venous thrombosis or pulmonary embolism have a diagnosis of cancer **(Chap. 113)**. The coexistence of peripheral venous thrombosis with visceral carcinoma, particularly pancreatic cancer, is called *Trousseau's syndrome*.

Pathogenesis Patients with cancer are predisposed to thromboembolism because they are often at bed rest or immobilized, and tumors may obstruct or slow blood flow. Postoperative deep venous thrombosis is twice as common in cancer patients who undergo surgery. Chronic IV catheters also predispose to clotting. In addition, clotting may be promoted by release of procoagulants or cytokines from tumor cells or associated inflammatory cells or by platelet adhesion or aggregation. The specific molecules that promote thromboembolism have not been identified.

Chemotherapeutic agents, particularly those associated with endothelial damage, can induce venous thrombosis. The annual risk of venous thrombosis in patients with cancer receiving chemotherapy is about 11%, sixfold higher than the risk in the general population. Bleomycin, L-asparaginase, nitrogen mustard, thalidomide analogues, cisplatin-based regimens, and high doses of busulfan and carmustine are all associated with an increased risk.

In addition to cancer and its treatment causing secondary thrombosis, primary thrombophilic diseases may be associated with cancer. For example, the antiphospholipid antibody syndrome is associated with a wide range of pathologic manifestations **(Chap. 350)**. About 20% of patients with this syndrome have cancers. Among patients with cancer and antiphospholipid antibodies, 35–45% develop thrombosis.

Clinical Manifestations Patients with cancer who develop deep venous thrombosis usually develop swelling or pain in the leg, and physical examination reveals tenderness, warmth, and redness. Patients who present with pulmonary embolism develop dyspnea, chest pain, and syncope, and physical examination shows tachycardia, cyanosis, and hypotension. Some 5% of patients with no history of cancer who have a diagnosis of deep venous thrombosis or pulmonary embolism will have a diagnosis of cancer within 1 year. The most common cancers associated with thromboembolic episodes include lung, pancreatic, gastrointestinal, breast, ovarian, and genitourinary cancers; lymphomas; and brain tumors. Patients with cancer who undergo surgical procedures requiring general anesthesia have a 20–30% risk of deep venous thrombosis.

Diagnosis The diagnosis of deep venous thrombosis in patients with cancer is made by impedance plethysmography or bilateral compression ultrasonography of the leg veins. Patients with a noncompressible venous segment have deep venous thrombosis. If compression ultrasonography is normal and there is a high clinical suspicion for deep venous thrombosis, venography should be done to look for a luminal filling defect. Elevation of D-dimer is not as predictive of deep venous thrombosis in patients with cancer as it is in patients without cancer; elevations are seen in people over age 65 years without concomitant evidence of thrombosis, probably as a consequence of increased thrombin deposition and turnover in aging.

Patients with symptoms and signs suggesting a pulmonary embolism should be evaluated with a chest radiograph, electrocardiogram, arterial blood gas analysis, and ventilation-perfusion scan. Patients with mismatched segmental perfusion defects have a pulmonary embolus. Patients with equivocal ventilation-perfusion findings should be evaluated as described above for deep venous thrombosis in their legs. If deep venous thrombosis is detected, they should be anticoagulated. If deep venous thrombosis is not detected, they should be considered for a pulmonary angiogram.

Patients without a diagnosis of cancer who present with an initial episode of thrombophlebitis or pulmonary embolus need no additional tests for cancer other than a careful history and physical examination. In light of the many possible primary sites, diagnostic testing in asymptomatic patients is wasteful. However, if the clot is refractory to standard treatment or is in an unusual site or if the thrombophlebitis is migratory or recurrent, efforts to find an underlying cancer are indicated.

TREATMENT

Thrombophlebitis and Deep Venous Thrombosis

Patients with cancer and a diagnosis of deep venous thrombosis or pulmonary embolism should be treated initially with IV unfractionated heparin or low-molecular-weight heparin for at least 5 days, and warfarin should be started within 1 or 2 days. The warfarin dose should be adjusted so that the international normalized ratio (INR) is 2–3. Patients with proximal deep venous thrombosis and a relative contraindication to heparin anticoagulation (hemorrhagic brain metastases or pericardial effusion) should be considered for placement of a filter in the inferior vena cava (Greenfield filter) to prevent pulmonary embolism. Warfarin should be administered for 3–6 months. An alternative approach is to use low-molecular-weight heparin for 6 months. The new oral anticoagulants (factor Xa and thrombin inhibitors) are attractive because they do not require close monitoring of the prothrombin time and are not affected by dietary factors. However, data on their use in patients with cancer are not yet mature. Patients with cancer who undergo a major surgical procedure should be considered for heparin prophylaxis or pneumatic boots. Breast cancer patients undergoing chemotherapy and patients with implanted catheters should be considered for prophylaxis. Guidelines recommend that hospitalized patients with cancer and patients receiving a thalidomide analogue receive prophylaxis with low-molecular-weight heparin or low-dose aspirin. Use of prophylaxis routinely during chemotherapy is controversial and not recommended by the American Society of Clinical Oncology.

MISCELLANEOUS REMOTE EFFECTS OF CANCER

Patients with cancer can develop paraneoplastic autoimmune disorders (e.g., thrombocytopenia) and dysfunction of organs not directly invaded or involved with the cancer (rheumatologic and renal abnormalities are among the most frequent). The pathogenesis of these disorders is undefined, but often the conditions reverse if the tumor is removed or successfully treated.

Cutaneous paraneoplastic syndromes are discussed in Chap. 54. Neurologic paraneoplastic syndromes are discussed in Chap. 90.

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90 Paraneoplastic Neurologic Syndromes and Autoimmune Encephalitis

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Paraneoplastic neurologic disorders (PNDs) are cancer-related syndromes that can affect any part of the nervous system (Table 90-1). They are caused by mechanisms other than metastasis or by any of the complications of cancer such as coagulopathy, stroke, metabolic and nutritional conditions, infections, and side effects of cancer therapy. In 60% of patients, the neurologic symptoms precede the cancer diagnosis. Clinically disabling PNDs occur in 0.5–1% of all cancer patients, but they affect 2–3% of patients with neuroblastoma or small-cell lung cancer (SCLC) and 30–50% of patients with thymoma.

PATHOGENESIS

Most PNDs are mediated by immune responses triggered by neuronal proteins (onconeuronal antigens) expressed by tumors. In PNDs of the central nervous system (CNS), many antibody-associated immune responses have been identified (Table 90-2). These antibodies react with both neurons and the patient's tumor, and their detection in serum or cerebrospinal fluid (CSF) usually predicts the presence of cancer. When the antigens are intracellular, most syndromes are associated with extensive infiltrates of CD4+ and CD8+ T cells, microglial activation, gliosis, and variable neuronal loss. The infiltrating T cells are often in close contact with neurons undergoing degeneration, suggesting a primary pathogenic role. T cell–mediated cytotoxicity may contribute directly to cell death in these PNDs. Thus both humoral and cellular immune mechanisms participate in the pathogenesis of many PNDs. This complex immunopathogenesis may underlie the resistance of many of these conditions to therapy.

In contrast to the disorders associated with immune responses against intracellular antigens, those associated with antibodies to antigens expressed on the neuronal cell surface of the CNS or at the neuromuscular junction are more responsive to immunotherapy (Table 90-3, Fig. 90-1). These disorders occur with and without a cancer association and may affect children and young adults, and there is evidence demonstrating a pathogenic role of the antibodies.

Other PNDs are likely immune-mediated, although their antigens are unknown. These include several syndromes of inflammatory neuropathies and myopathies. In addition, many patients with typical PND syndromes are antibody-negative.

For still other PNDs, the cause remains quite obscure. These include, among others, several neuropathies that occur in the terminal stages of cancer and a number of neuropathies associated with plasma cell dyscrasias or lymphoma without evidence of inflammatory infiltrates or deposits of immunoglobulin, cryoglobulin, or amyloid.

TABLE 90-1 Paraneoplastic Syndromes of the Nervous System

CLASSIC SYNDROMES: USUALLY OCCUR WITH CANCER ASSOCIATION	NONCLASSIC SYNDROMES: MAY OCCUR WITH AND WITHOUT CANCER ASSOCIATION
Encephalomyelitis	Brainstem encephalitis
Limbic encephalitis	Stiff-person syndrome
Cerebellar degeneration (adults)	Progressive encephalomyelitis with rigidity and myoclonus
Opsoclonus-myoclonus	Necrotizing myelopathy
Subacute sensory neuronopathy	Motor neuron disease
Gastrointestinal paresis or pseudo-obstruction	Guillain-Barré syndrome
Dermatomyositis (adults)	Subacute and chronic mixed sensory-motor neuropathies
Lambert-Eaton myasthenic syndrome	Neuropathy associated with plasma cell dyscrasias and lymphoma
Cancer- or melanoma-associated retinopathy	Vasculitis of nerve
	Pure autonomic neuropathy
	Acute necrotizing myopathy
	Polymyositis
	Optic neuropathy
	BDUMP
	Peripheral nerve hyperexcitability (neuromyotonia)
	Myasthenia gravis

Abbreviation: BDUMP, bilateral diffuse uveal melanocytic proliferation.

TABLE 90-2 Antibodies to Intracellular Antigens, Syndromes, and Associated Cancers

ANTIBODY	ASSOCIATED NEUROLOGIC SYNDROME(S)	TUMORS
Anti-Hu (ANNA1)	Encephalomyelitis, subacute sensory neuronopathy	SCLC
Anti-Yo (PCA1)	Cerebellar degeneration	Ovary, breast
Anti-Ri (ANNA2)	Cerebellar degeneration, opsoclonus, brainstem encephalitis	Breast, gynecologic, SCLC
Anti-CRMP5 (CV2)	Encephalomyelitis, chorea, optic neuritis, uveitis, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins	Limbic, hypothalamic, brainstem encephalitis	Testicular (Ma2), other (Ma)
Anti-amphiphysin[a]	Stiff-person syndrome, encephalomyelitis	Breast, SCLC
Recoverin, bipolar cell antibodies, others[b]	Cancer-associated retinopathy (CAR) Melanoma-associated retinopathy (MAR)	SCLC (CAR), melanoma (MAR)
Anti-GAD	Stiff-person, cerebellar syndrome, limbic encephalitis	Infrequent tumor association (thymoma and several cancers)

[a]Amphiphysin is likely exposed to the cell surface during synaptic vesicle endocytosis. [b]A variety of target antigens have been identified.

Abbreviations: CRMP, collapsing response-mediator protein; SCLC, small-cell lung cancer.

APPROACH TO THE PATIENT

Paraneoplastic Neurologic Disorders

Three key concepts are important for the diagnosis and management of PNDs. First, it is common for symptoms to appear before the presence of a tumor is known; second, the neurologic syndrome usually develops rapidly, producing severe deficits in a short period of time; and third, there is evidence that prompt tumor control improves the neurologic outcome. Therefore, the major concern of the physician is to recognize a disorder promptly as paraneoplastic and to identify and treat the tumor.

TABLE 90-3 Antibodies to Cell Surface or Synaptic Antigens, Syndromes, and Associated Tumors

ANTIBODY	NEUROLOGIC SYNDROME	TUMOR TYPE WHEN ASSOCIATED
Anti-AChR (muscle)[a]	Myasthenia gravis	Thymoma
Anti-AChR (neuronal)[a]	Autonomic ganglionopathy	SCLC
Anti-VGCC[a]	LEMS, cerebellar degeneration	SCLC
Anti-NMDAR[a]	Anti-NMDAR encephalitis	Teratoma in young women (children and men rarely have tumors)
Anti-LGI1[b]	Limbic encephalitis, hyponatremia, faciobrachial tonic or dystonic seizures	Rarely thymoma
Anti-Caspr2[b]	Morvan's syndrome, neuromyotonia, limbic encephalitis	Thymoma, prostate cancer
Anti-$GABA_BR$[c]	Limbic encephalitis, seizures	SCLC, neuroendocrine
Anti-$GABA_AR$[a]	Encephalitis with prominent seizures and status epilepticus; less often opsoclonus and stiff-person syndrome	Thymoma in ~30% of patients
Anti-AMPAR[a]	Limbic encephalitis with relapses	SCLC, thymoma, breast
Glycine receptor	PERM, stiff-person syndrome	Rarely, thymoma, lung, Hodgkin lymphoma
Anti-DPPX[a]	Agitation, myoclonus, tremor, seizures, hyperekplexia, encephalomyelitis with rigidity	No cancer, but frequent diarrhea or cachexia suggesting paraneoplasia
Anti-Neurexin 3alpha	Autoimmune encephalitis without distinctive features	No cancer association
Anti-Dopamine-2R	Basal ganglia encephalitis	No cancer association
Anti-Tr (DNER)	Cerebellar syndrome	Hodgkin lymphoma, or no tumor
Anti-mGluR1	Cerebellar syndrome	Hodgkin lymphoma, or no tumor
Anti-mGluR5	Autoimmune encephalitis without distinctive features	Hodgkin lymphoma, or no tumor
IgLON5	NREM and REM sleep disorder, and brainstem dysfunction	No tumor association

[a]A direct pathogenic role of these antibodies has been demonstrated in cultured neurons or animal models. [b]Previously named voltage-gated potassium channel antibodies (VGKC); currently included under the term VGKC-complex proteins. Of note, the significance of antibodies to VGKC-complex proteins other than LGI1 and Caspr2 is uncertain (the antigens are unknown, and the response to immunotherapy is variable) [c]This antibody is strongly suspected to be pathogenic.

Abbreviations: AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; DNER, delta/notch-like epidermal growth factor-related receptor; DPPX, dipeptidyl-peptidase-like protein-6; $GABA_BR$, γ-aminobutyric acid B receptor; GAD, glutamic acid decarboxylase; mGluR, metabotropic glutamate receptor; LEMS, Lambert-Eaton myasthenic syndrome; LGI1, leucine-rich glioma-inactivated 1; NMDAR, *N*-methyl-D-aspartate receptor; NREM, non-rapid eye movement; PERM, progressive encephalomyelitis with rigidity and myoclonus; REM, rapid eye movement; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel.

PND OF THE CENTRAL NERVOUS SYSTEM AND DORSAL ROOT GANGLIA

When symptoms involve brain, spinal cord, or dorsal root ganglia, the suspicion of PND is usually based on a combination of clinical, radiologic, and CSF findings. Presence of antineuronal antibodies (Tables 90-2 and 90-3) may help in the diagnosis, but only 60–70% of PNDs of the CNS and <20% of those involving the peripheral nervous system have neuronal or neuromuscular junction antibodies that can be used as diagnostic tests.

Magnetic resonance imaging (MRI) and CSF studies are important to rule out neurologic complications due to the direct spread of cancer, particularly metastatic and leptomeningeal disease. In most PNDs, the MRI findings are nonspecific. Paraneoplastic limbic encephalitis is usually associated with characteristic MRI abnormalities in the mesial temporal lobes (see below), but similar findings can occur with other disorders (e.g., nonparaneoplastic autoimmune limbic encephalitis and human herpesvirus type 6 [HHV-6] encephalitis) **(Fig. 90-2)**. The CSF profile of patients with PND of the CNS or dorsal root ganglia typically consists of mild to moderate pleocytosis (<200 mononuclear cells, predominantly lymphocytes), an increase in the protein concentration, and a variable presence of oligoclonal bands. There are no specific electrophysiologic tests that are diagnostic of PND. Moreover, a biopsy of the affected tissue is often difficult to obtain, and although useful to rule out other disorders (e.g., metastasis) the pathologic findings are not specific for PND.

PND OF NERVE AND MUSCLE

If symptoms involve peripheral nerve, neuromuscular junction, or muscle, the diagnosis of a specific PND is usually established on clinical, electrophysiologic, and pathologic grounds. The clinical history, accompanying symptoms (e.g., anorexia, weight loss), and type of syndrome dictate the studies and degree of effort needed to demonstrate a neoplasm. For example, the frequent association of Lambert-Eaton myasthenic syndrome (LEMS) with SCLC should lead to a chest and abdomen computed tomography (CT) or body positron emission tomography (PET) scan and, if negative, periodic tumor screening for at least 3 years after the neurologic diagnosis. In contrast, the weak association of polymyositis with cancer calls into question, the need for repeated cancer screenings in this situation. Serum and urine immunofixation studies should be considered in patients with peripheral neuropathy of unknown cause; detection of a monoclonal gammopathy suggests the need for additional studies to uncover a B cell or plasma cell malignancy. In paraneoplastic neuropathies, diagnostically useful antineuronal antibodies are limited to CRMP5 and Hu (ANNA1).

For any type of PND, if antineuronal antibodies are negative, the diagnosis relies on the demonstration of cancer and the exclusion of other cancer-related or independent neurologic disorders. Combined CT and PET scans often uncover tumors undetected by other tests. For germ cell tumors of the testis and teratomas of the ovary, ultrasound and CT or MRI of the abdomen and pelvis may reveal tumors undetectable by PET.

SPECIFIC PARANEOPLASTIC NEUROLOGIC SYNDROMES

PARANEOPLASTIC ENCEPHALOMYELITIS AND FOCAL ENCEPHALITIS WITH ANTIBODIES AGAINST INTRACELLULAR NEURONAL PROTEINS

The term *encephalomyelitis* describes an inflammatory process with multifocal involvement of the nervous system, including brain, brainstem, cerebellum, and spinal cord. It is often associated with dorsal root ganglia and autonomic dysfunction. For any given patient, the clinical manifestations are determined by the areas predominantly involved, but pathologic studies almost always reveal abnormalities beyond the symptomatic regions. Several clinicopathologic syndromes may occur alone or in combination: (1) *cortical encephalitis*, which may present as "epilepsia partialis continua"; (2) *limbic encephalitis*, characterized by confusion, depression, agitation, anxiety, severe deficits in forming new memories, partial complex seizures, and sometimes dementia (the MRI usually shows unilateral or bilateral medial temporal lobe abnormalities, best seen with T2 and fluid-attenuated inversion recovery sequences); (3) *brainstem encephalitis*, resulting in eye movement disorders (nystagmus, opsoclonus, supranuclear or nuclear paresis), cranial nerve paresis, dysarthria, dysphagia, and central autonomic dysfunction; (4) *cerebellar gait and limb ataxia*; (5) *myelitis*, which may cause lower or upper motor neuron symptoms, myoclonus, muscle rigidity, and spasms; and (6) *autonomic dysfunction* as a result of involvement of the neuraxis at multiple levels, including hypothalamus, brainstem, and autonomic nerves (see "Paraneoplastic Peripheral Neuropathies," below). Cardiac arrhythmias, postural hypotension, and central hypoventilation are frequent causes of death in patients with encephalomyelitis.

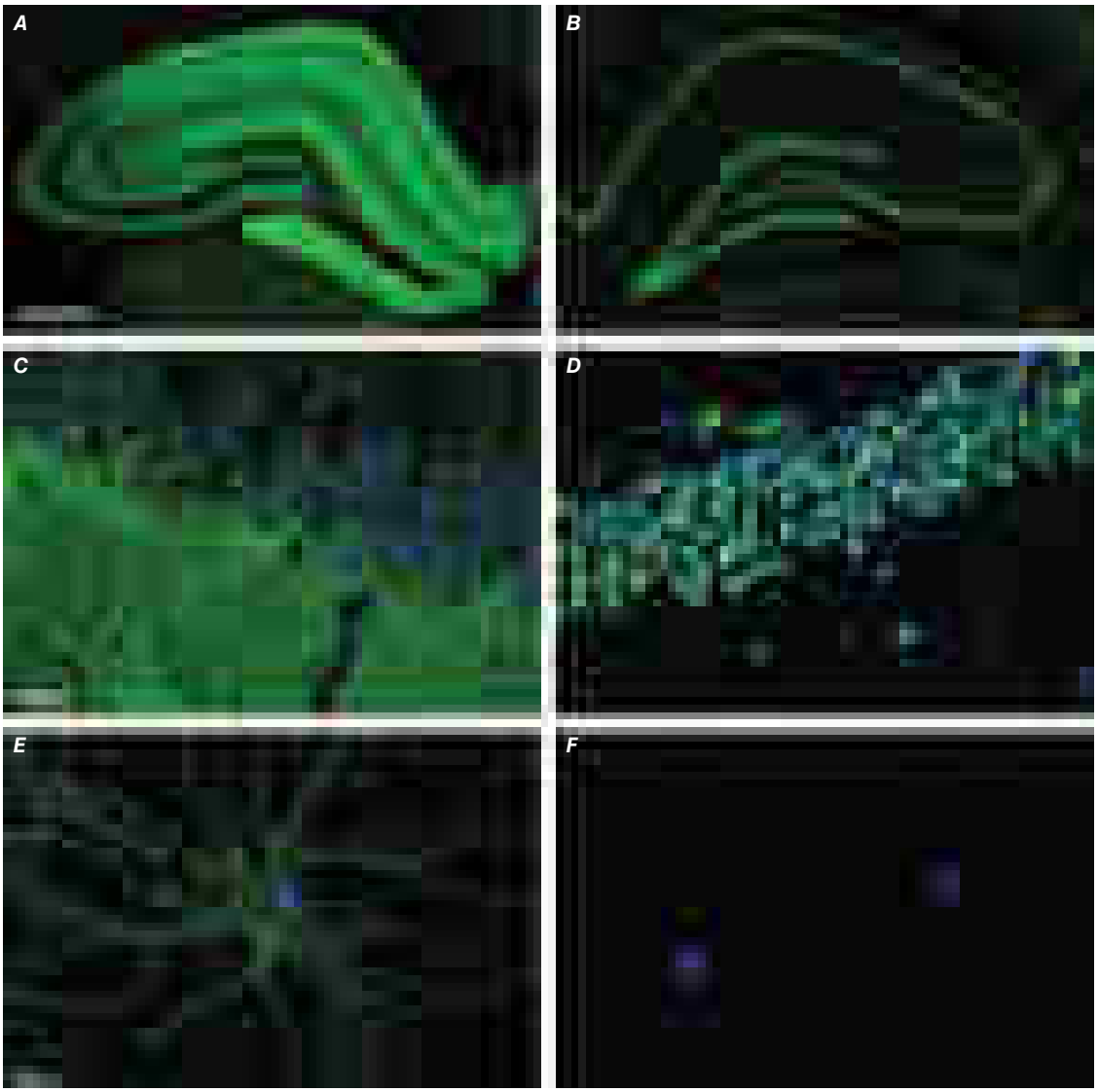

FIGURE 90-1 Comparison of brain and neuronal reactivity of antibodies against a neuronal cell surface, and an intracellular antigen. Coronal section of rat hippocampus immunolabeled with antibodies against a cell surface antigen (*N*-methyl-D-aspartate; NMDA receptor) from a patient with anti-NMDA receptor encephalitis (***A***), compared with the antibodies against an intracellular antigen (Hu) from a patient with small-cell lung cancer and paraneoplastic encephalitis (***B***). Magnification of the reactivity is shown in ***C*** and ***D*** respectively. Compared with the NMDA receptor antibodies that show intense reactivity with the neuropil of hippocampus, the Hu antibodies only show intracellular reactivity after tissue permeabilization. In cultures of dissociated rat hippocampal neurons, only the NMDA receptor antibodies react with the antigen in live non-permeabilized neurons (***E***). The Hu antibodies do not reach the target intracellular antigen in live neurons (***F***). Scale bars: ***A, B*** = 500 μm; ***C, D*** = 20 μm; ***E, F*** = 10 μm. *(From J Dalmau et al: Physiol Rev 97:839, 2017, with permission.)*

Paraneoplastic encephalomyelitis and focal encephalitis are usually associated with SCLC, but many other cancers have been implicated. Patients with SCLC and these syndromes usually have anti-Hu antibodies in serum and CSF. Anti-CRMP5 antibodies occur less frequently; some of these patients may develop chorea, uveitis, or optic neuritis. Antibodies to Ma proteins are associated with limbic, hypothalamic, and brainstem encephalitis and occasionally with cerebellar symptoms; some patients develop hypersomnia, cataplexy, and severe hypokinesia. MRI abnormalities are frequent, including those described with limbic encephalitis and variable involvement of the hypothalamus, basal ganglia, or upper brainstem. The oncologic associations of these antibodies are shown in Table 90-2.

TREATMENT

Encephalomyelitis and Focal Encephalitis

Most types of paraneoplastic encephalitis and encephalomyelitis in which the antigens are intracellular respond poorly to treatment. Stabilization of symptoms or partial neurologic improvement may occur, particularly if there is a satisfactory response of the tumor to treatment. Controlled trials of therapy are lacking, but many reports and the opinion of experts suggest that therapies aimed to remove antibodies against intracellular antigens, such as intravenous immunoglobulin (IVIg) or plasma exchange, usually fail. The main concern should be to treat the tumor and consider immunotherapies, such as cyclophosphamide or tacrolimus, aimed at controlling pathogenic cytotoxic T-cell responses. Approximately 30% of patients with anti-Ma2-associated encephalitis respond to treatment of the tumor (usually a germ cell neoplasm of the testis) and immunotherapy.

ENCEPHALITIDES WITH ANTIBODIES TO CELL-SURFACE OR SYNAPTIC PROTEINS (TABLE 90-3)

These disorders are important for three reasons: (1) they can occur with and without tumor association, (2) some syndromes predominate in young individuals and children, and (3) despite the severity of the symptoms patients usually respond to treatment of the tumor, if found, and immunotherapy (e.g., glucocorticoids, IVIg, plasma exchange, rituximab, or cyclophosphamide).

Encephalitis with N-*methyl*-D-*aspartate (NMDA) receptor antibodies* (Fig. 90-1) usually occurs in young women and children, but men

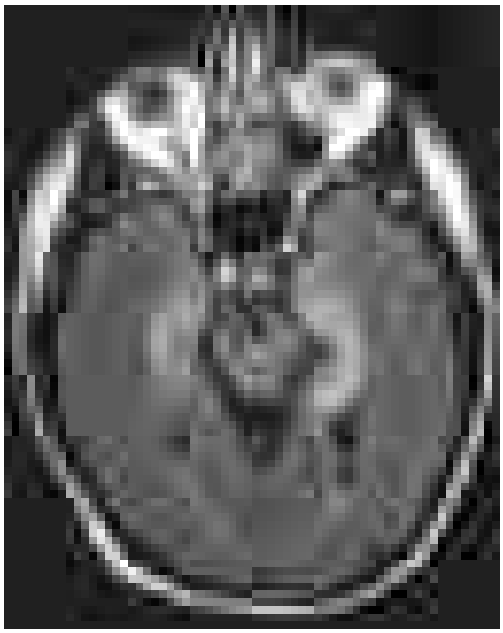

FIGURE 90-2 Fluid-attenuated inversion recovery sequence magnetic resonance imaging of a patient with limbic encephalitis and LGI1 antibodies. Note the abnormal hyperintensity involving the medial aspect of the temporal lobes.

and older patients of both sexes can be affected. The disorder has a characteristic pattern of symptom progression that includes a prodrome resembling a viral process, followed in a few days by the onset of severe psychiatric symptoms, sleep dysfunction (usually insomnia), reduced verbal output, memory loss, seizures, decreased level of consciousness, abnormal movements (orofacial, limb, and trunk dyskinesias, dystonic postures), autonomic instability, and frequent hypoventilation. Monosymptomatic episodes, such as pure psychosis, occur in 4% of the patients. Clinical relapses occur in 12–24% of patients (12% during the first 2 years after initial presentation). Most patients have intrathecal synthesis of antibodies, likely by infiltrating plasma cells in brain and meninges **(Fig. 90-3*A*)**. The syndrome may be misdiagnosed as a viral or idiopathic encephalitis, neuroleptic malignant syndrome, or encephalitis lethargica, and some patients are initially evaluated by psychiatrists with the suspicion of acute psychosis. The detection of an associated teratoma is dependent on age and gender: 46% of female patients aged ≥12 years have uni- or bilateral ovarian teratomas whereas <7% of girls aged <12 have a teratoma **(Fig. 90-3*B*)**. In male patients, the detection of a tumor is rare. Patients aged >45 years are more frequently male; about 20% of these patients have tumors (e.g., cancer of the breast, ovary, or lung).

Approximately 20% of patients with herpes simplex encephalitis develop a form of autoimmune encephalitis that in children usually associates with abnormal movements (choreoathetosis post-herpes simplex encephalitis) and in adults with cognitive and psychiatric symptoms. This disorder develops a few weeks after the viral infection has resolved, associates with new synthesis of antibodies against the NMDA receptor and other neuronal cell surface proteins, and is usually less responsive to immunotherapy than anti-NMDA receptor encephalitis.

Encephalitis with leucine-rich glioma-inactivated 1 (LGI1) antibodies predominates in patients aged >50 years (65% male) and frequently presents with memory loss and seizures (limbic encephalopathy), along with hyponatremia and sleep dysfunction. In some patients, the encephalitis is preceded by or occurs with myoclonic-like movements called faciobrachial dystonic seizures. Less than 10% of patients have thymoma.

Encephalitis with contactin-associated protein-like 2 (Caspr2) antibodies predominates in patients aged >50 years and is associated with Morvan's syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia), or a form of encephalitis with 3 or more of the following core symptoms: encephalopathy, cerebellar symptoms, peripheral nervous system hyperexcitability, dysautonomia, insomnia, neuropathic pain or weight loss. About 20% of patients have thymoma; in patients with Morvan's syndrome the frequency of thymoma appears to be higher.

Encephalitis with γ-aminobutyric acid type B ($GABA_B$) receptor antibodies is usually associated with limbic encephalitis and seizures. In rare instances, patients develop cerebellar symptoms and opsoclonus. Fifty percent of patients have SCLC or a neuroendocrine tumor of the lung. Patients may have additional antibodies to glutamic acid decarboxylase (GAD), which are of unclear significance. Other antibodies to non-neuronal proteins are often found in these patients as well as in patients with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antibodies, indicating a general tendency to autoimmunity.

Encephalitis with $GABA_A$ receptor antibodies may affect children and adults, and associates with prominent seizures and status epilepticus, often requiring pharmacologically induced coma. In ~80% of patients, the brain MRI shows multifocal, asynchronous, cortical-subcortical T2/FLAIR abnormalities predominantly involving temporal and frontal lobes, but also basal ganglia and other regions **(Fig. 90-4)**. Most patients do not have an underlying tumor, but some may have thymoma.

Encephalitis with AMPA receptor antibodies affects middle-aged women, who develop acute limbic dysfunction or, less frequently, prominent psychiatric symptoms; 70% of the patients have an underlying tumor

A ***B***

FIGURE 90-3 Pathologic findings in anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis. Infiltrates of plasma cells (brown cells; stained for CD138) in the meninges and brain of a patient (***A***); the inset is a magnification of some plasma cells. ***B.*** Neurons and neuronal processes in the teratoma of a patient (brown cells; stained with MAP2); these neurons express NMDA receptors (not shown). *(Reproduced in part from E Martinez-Hernandez et al: Neurology 77:589, 2011, with permission.)*

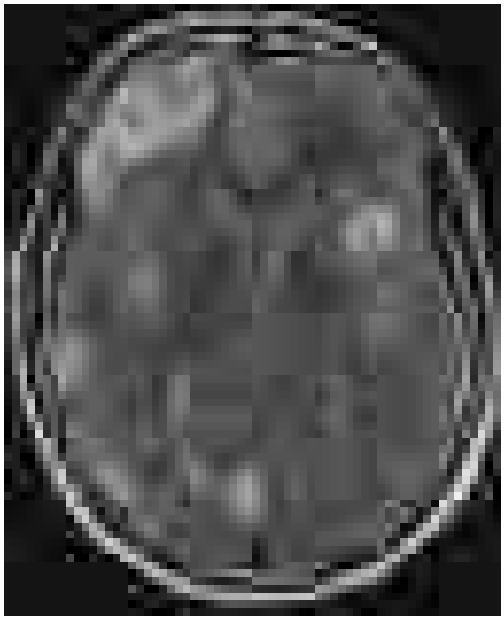

FIGURE 90-4 Fluid-attenuated inversion recovery sequence magnetic resonance imaging of a patient with autoimmune encephalitis and GABAA receptor antibodies. Note the abnormal hyperintensity involving cortical and subcortical brain regions, predominantly in frontal and temporal lobes. (*Reprinted from M Spatola et al: Neurology 88:1012, 2017, with permission.)*

in the lung, breast, or thymus. Neurologic relapses may occur; these also respond to immunotherapy and are not necessarily associated with tumor recurrence.

Encephalitis with glycine receptor (GlyR) antibodies has been described in adults with progressive encephalomyelitis with rigidity and myoclonus (PERM) and stiff-person spectrum of symptoms (with or without GAD antibodies). The disorder usually occurs without tumor association, although some patients have lung cancer, thymoma, or Hodgkin's lymphoma.

Encephalitis with dipeptidyl-peptidase-like protein-6 (or DPPX) antibodies results in symptoms of CNS hyperexcitability including agitation, hallucinations, paranoid delusions, tremor, myoclonus, nystagmus, seizures, and hyperekplexia. Some patients develop progressive encephalomyelitis with rigidity and myoclonus. Diarrhea, other gastrointestinal symptoms, and substantial loss of weight often suggest the presence of an underlying tumor, but in most patients no tumor is identified.

Encephalitis with metabotropic glutamate receptor 5 (mGluR5) antibodies is characterized by the development of encephalopathy associated with Hodgkin lymphoma (Ophelia syndrome). Patients show confusion, agitation, memory loss, delusions, paranoid ideation, hallucinations, psychosis, or seizures that are highly responsive to immunotherapy and tumor treatment.

Encephalitis with antibodies against neurexin 3 alpha does not have distinctive clinical features; the experience is limited and the disorder does not appear to associate with cancer.

Encephalitis with antibodies against the dopamine-2 receptor has been reported in some patients with abnormal movements, gait disturbance, psychiatric symptoms, and evidence of basal ganglia encephalitis. The disorder is rare and does not appear to associate with cancer.

Anti-IgLON5 disease is a chronic or subacute encephalopathy that characteristically associates with non-REM and REM parasomnia, brainstem dysfunction, breathing difficulty, and obstructive sleep apnea. It does not associate with cancer, but shows a strong association with HLA-DRB1*10:01 and HLA-DQB1*05:01. The response to immunotherapy is poor. Neuropathological studies show a neuronal tauopathy predominantly involving hypothalamus and tegmentum of the brainstem.

With the exception of patients with anti-IgLON 5 disease, who rarely respond to treatment, most patients with autoimmune or paraneoplastic encephalopathies associated with antibodies against cell surface or synaptic proteins respond to immunotherapy and treatment of the tumor (if appropriate). Although there are no standardized treatment protocols, the most frequent approach employs progressive escalation of immunotherapy using first a combination of glucocorticoids, IVIg or plasma exchange, and if there is no response, either rituximab or cyclophosphamide.

PARANEOPLASTIC CEREBELLAR DEGENERATION

This disorder is often preceded by a prodrome that may include dizziness, oscillopsia, blurry or double vision, nausea, and vomiting. A few days or weeks later, patients develop dysarthria, gait and limb ataxia, and variable dysphagia. The examination usually shows downbeating nystagmus and, rarely, opsoclonus. Brainstem dysfunction, upgoing toes, or a mild neuropathy may occur. Early in the course, MRI studies are usually normal; later, the MRI reveals cerebellar atrophy. The disorder results from extensive degeneration of Purkinje cells, with variable involvement of other cerebellar cortical neurons, deep cerebellar nuclei, and spinocerebellar tracts. The tumors more frequently involved are SCLC, cancer of the breast and ovary, and Hodgkin's lymphoma.

Anti-Yo (PCA1) antibodies in patients with breast or gynecologic cancers typically associate with prominent or pure cerebellar degeneration. A variable degree of cerebellar dysfunction can be associated with virtually any of the antibodies and PND of the CNS shown in Table 90-2. A number of single case reports have described neurologic improvement after tumor removal, plasma exchange, IVIg, cyclophosphamide, rituximab, or glucocorticoids. However, most patients with paraneoplastic cerebellar degeneration and any of the antibodies shown in Table 90-2 do not improve with treatment.

A cerebellar syndrome can also occur with antibodies against cell-surface or synaptic proteins, including P/Q-type voltage-gated calcium channels (VGCC), Tr (DNER), or mGluR1 (Table 90-3). The frequency and type of tumor association varies with the type of antibody. The cerebellar syndrome of patients with mGluR1 antibodies is highly responsive to treatment of the tumor and immunotherapy, whereas the syndrome of patients with Tr or VGCC antibodies is less treatment responsive.

PARANEOPLASTIC OPSOCLONUS-MYOCLONUS SYNDROME

Opsoclonus is a disorder of eye movement characterized by involuntary, chaotic saccades that occur in all directions of gaze; it is frequently associated with myoclonus and ataxia. Opsoclonus-myoclonus may be cancer-related or idiopathic. When the cause is paraneoplastic, the tumors involved are usually cancer of the lung and breast in adults, neuroblastoma in children, and ovarian teratoma in adolescents and young women. The pathologic substrate of opsoclonus-myoclonus is unclear, but studies suggest that disinhibition of the fastigial nucleus of the cerebellum is involved. Most patients do not have antineuronal antibodies. A small subset of patients with ataxia, opsoclonus, and other eye-movement disorders develop anti-Ri antibodies; these patients may also develop muscle rigidity, laryngeal spasms, and autonomic dysfunction. The tumors most frequently involved in anti-Ri-associated syndromes are breast and ovarian cancer. If the tumor is not successfully treated, the syndrome in adults often progresses to encephalopathy, coma, and death. In addition to treating the tumor, symptoms may respond to immunotherapy (glucocorticoids, plasma exchange, and/or IVIg).

At least 50% of children with opsoclonus-myoclonus have an underlying neuroblastoma. Hypotonia, ataxia, behavioral changes, and irritability are frequent accompanying symptoms. Neurologic symptoms often improve with treatment of the tumor and glucocorticoids, adrenocorticotropic hormone (ACTH), plasma exchange, IVIg, rituximab, or cyclophosphamide. Many patients are left with psychomotor retardation and behavioral and sleep problems.

PARANEOPLASTIC SYNDROMES OF THE SPINAL CORD

The number of reports of paraneoplastic spinal cord syndromes, such as *subacute motor neuronopathy* and *acute necrotizing myelopathy*, has decreased in recent years. This may represent a true decrease in incidence, due to improved and prompt oncologic interventions, or the

identification of nonparaneoplastic etiologies. Some patients with cancer develop *upper* or *lower motor neuron dysfunction* or both, resembling amyotrophic lateral sclerosis. It is unclear whether these disorders have a paraneoplastic etiology or simply coincide with the presence of cancer. There are isolated case reports of cancer patients with motor neuron dysfunction who had neurologic improvement after tumor treatment. A search for lymphoma should be undertaken in patients with a rapidly progressive motor neuron syndrome and a monoclonal protein in serum or CSF.

Paraneoplastic myelitis may present with upper or lower motor neuron symptoms, segmental myoclonus, and rigidity, and can be the first manifestation of encephalomyelitis. *Neuromyelitis optica (NMO) with aquaporin 4 antibodies* may occur in rare instances as a paraneoplastic manifestation of a cancer.

PARANEOPLASTIC STIFF-PERSON SYNDROME

This disorder is characterized by progressive muscle rigidity, stiffness, and painful spasms triggered by auditory, sensory, or emotional stimuli. Rigidity mainly involves the lower trunk and legs, but it can affect the upper extremities and neck. Sometimes, only one extremity is affected (*stiff-limb syndrome*). Symptoms improve with sleep and general anesthetics. Electrophysiologic studies demonstrate continuous motor unit activity. The associated antibodies target proteins (GAD, amphiphysin) involved in the function of inhibitory synapses using γ-aminobutyric acid (GABA) or glycine as neurotransmitters. The presence of amphiphysin antibodies usually indicates a paraneoplastic etiology related to SCLC and breast cancer. By contrast, GAD antibodies may occur in some cancer patients but are much more frequently present in the nonparaneoplastic disorder. GlyR antibodies may occur in some patients with stiff-person syndrome; these antibodies are also detectable in patients with PERM **(Fig. 90-5)**.

Optimal treatment of stiff-person syndrome requires therapy of the underlying tumor, glucocorticoids, and symptomatic use of drugs that enhance GABA-ergic transmission (diazepam, baclofen, sodium valproate, tiagabine, vigabatrin). IVIg and plasma exchange are transiently effective in some patients, and there are reports of responses to rituximab in patients who did not respond to other treatments.

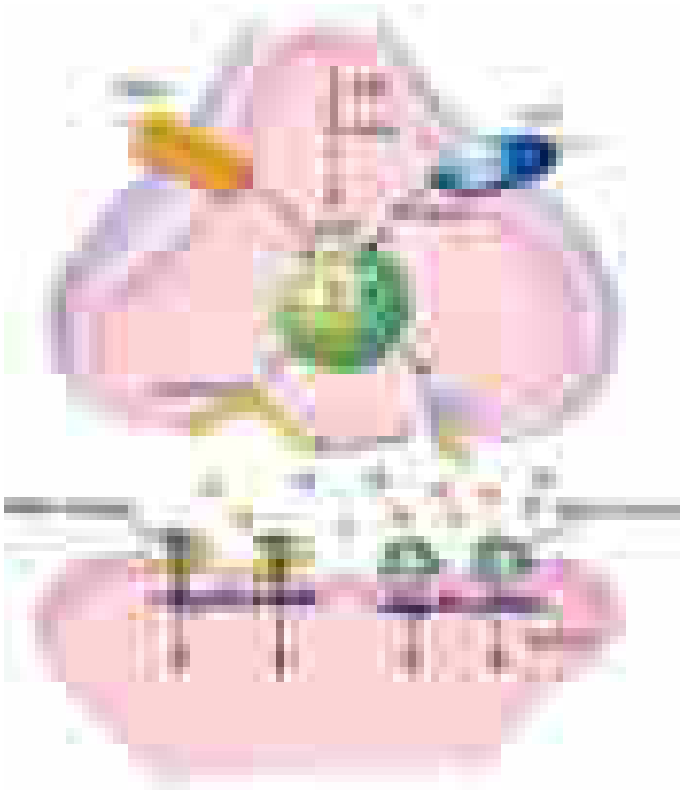

FIGURE 90-5 Autoantibodies in stiff-person spectrum disorders. Schematic representation of an inhibitory synapse including the three main targets of autoantibodies in patients with stiff-person spectrum disorders: the presynaptic proteins GAD and amphiphysin, and the postsynaptic glycine receptor (GlyR). *(From J Dalmau et al: Physiol Rev 97:839, 2017.)*

PARANEOPLASTIC SENSORY NEURONOPATHY OR DORSAL ROOT GANGLIONOPATHY

This syndrome is characterized by sensory deficits that may be symmetric or asymmetric, painful dysesthesias, radicular pain, and decreased or absent reflexes. All modalities of sensation and any part of the body including face and trunk can be involved. Specialized sensations such as taste and hearing can also be affected. Electrophysiologic studies show decreased or absent sensory nerve potentials with normal or near-normal motor conduction velocities. Symptoms result from an inflammatory, likely immune-mediated, process that targets the dorsal root ganglia, causing neuronal loss and secondary degeneration of the posterior columns of the spinal cord. The dorsal and, less frequently, the anterior nerve roots and peripheral nerves may also be involved. This disorder often precedes or is associated with encephalomyelitis and autonomic dysfunction and has the same immunologic and oncologic associations (Hu antibodies, SCLC).

As with anti-Hu-associated encephalomyelitis, the therapeutic approach focuses on prompt treatment of the tumor and use of immune suppressants such as cyclophosphamide or tacrolimus. Glucocorticoids occasionally produce clinical stabilization or improvement. The benefit of IVIg and plasma exchange is not proven.

PARANEOPLASTIC PERIPHERAL NEUROPATHIES

These disorders may develop any time during the course of the neoplastic disease. Neuropathies occurring at late stages of cancer or lymphoma usually cause mild to moderate sensorimotor deficits due to axonal degeneration of unclear etiology. These neuropathies are often masked by concurrent neurotoxicity from chemotherapy and other cancer therapies. In contrast, the neuropathies that develop in the early stages of cancer frequently show a rapid progression, sometimes with a relapsing and remitting course, and evidence of inflammatory infiltrates and axonal loss or demyelination. If demyelinating features predominate **(Chaps. 438 and 439)**, IVIg, plasma exchange, or glucocorticoids may improve symptoms. Occasionally anti-CRMP5 antibodies are present; detection of anti-Hu suggests concurrent dorsal root ganglionitis.

Guillain-Barré syndrome and *brachial plexitis* have occasionally been reported in patients with lymphoma, but there is no clear evidence of a paraneoplastic association **(Chap. 439)**.

Monoclonal gammopathies associated with multiple myeloma, cryoglobulinemia, amyloidosis, Waldenstrom macroglobulinemia, or POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein spike, and skin manifestations) syndrome among others, may cause neuropathy by a variety of mechanisms, including compression of roots and plexuses by metastasis to vertebral bodies and pelvis, by deposits of amyloid in peripheral nerves, or through a direct interaction of the abnormal immunoglobulin with peripheral nerve antigens. In other patients, the mechanisms underlying the neuropathy remain unknown. Neuropathies more often occur with IgM gammopathies than with IgG and IgA isotypes. The phenotype of the neuropathy and likelihood of improvement with successful treatment of the gammopathy is dependent on the underlying hematologic disorder.

Vasculitis of the nerve and muscle causes a painful symmetric or asymmetric distal axonal sensorimotor neuropathy with variable proximal weakness. It predominantly affects elderly men and is associated with an elevated erythrocyte sedimentation rate and increased CSF protein concentration. SCLC and lymphoma are the primary tumors involved. Glucocorticoids and cyclophosphamide often result in neurologic improvement.

Peripheral nerve hyperexcitability (*neuromyotonia,* or *Isaacs' syndrome*) is characterized by spontaneous and continuous muscle fiber activity of peripheral nerve origin. Clinical features include cramps, muscle twitching (fasciculations or myokymia), stiffness, delayed muscle relaxation (pseudomyotonia), and spontaneous or evoked carpal or pedal spasms. The involved muscles may be hypertrophic, and some patients develop paresthesias and hyperhidrosis. CNS dysfunction,

including mood and behavioral changes, sleep disorder, hallucinations, and autonomic symptoms may occur. The electromyogram (EMG) shows fibrillations; fasciculations; and doublet, triplet, or multiplet single-unit (myokymic) discharges that have a high intraburst frequency. Some patients have Caspr2 antibodies usually in the context of Morvan's syndrome, but most patients with isolated neuromyotonia are antibody negative. The disorder often occurs without cancer; if paraneoplastic, benign and malignant thymomas and SCLC are the usual tumors. Phenytoin, carbamazepine, and plasma exchange improve symptoms.

Paraneoplastic autonomic neuropathy usually develops as a component of other disorders, such as LEMS and encephalomyelitis. It may rarely occur as a pure or predominantly autonomic neuropathy with cholinergic or adrenergic dysfunction at the pre- or postganglionic levels. Patients can develop several life-threatening complications, such as gastrointestinal paresis with pseudo-obstruction, cardiac dysrhythmias, and postural hypotension. Other clinical features include abnormal pupillary responses, dry mouth, anhidrosis, erectile dysfunction, and problems in sphincter control. The disorder occurs in association with several tumors, including SCLC, cancer of the pancreas or testis, carcinoid tumors, and lymphoma. Because autonomic symptoms can be the presenting feature of encephalomyelitis, serum anti-Hu and anti-CRMP5 antibodies should be sought. Antibodies to ganglionic (alpha3-type) neuronal acetylcholine receptors are the cause of autoimmune autonomic ganglionopathy, a disorder that frequently occurs without cancer association **(Chap. 432)**.

LAMBERT-EATON MYASTHENIC SYNDROME

LEMS is discussed in Chap. 440.

MYASTHENIA GRAVIS

Myasthenia gravis is discussed in Chap. 440.

POLYMYOSITIS-DERMATOMYOSITIS

Polymyositis and dermatomyositis are discussed in detail in Chap. 358.

ACUTE NECROTIZING MYOPATHY

Patients with this syndrome develop myalgias and rapid progression of weakness involving the extremities, neck, pharyngeal, respiratory, and sometimes cardiac muscles. Serum muscle enzymes are elevated, and muscle biopsy shows extensive necrosis with minimal or absent inflammation and sometimes deposits of complement. The disorder may occur without a cancer association (sometimes as a result of statin exposure, connective tissue disease, or HIV) or with cancer. Patients with antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) and seronegative patients are more likely to have an underlying cancer than those with antibodies against signal recognition particle. No specific type of cancer has been found to predominate. Successful treatment of the tumor and aggressive immunotherapy (glucocorticoids, IVIg, and steroid-sparing immunosuppressants) may lead to complete or substantial recovery.

PARANEOPLASTIC VISUAL SYNDROMES

This group of disorders involves the retina and, less frequently, the uvea and optic nerves. The term *cancer-associated retinopathy* is used to describe paraneoplastic cone and rod dysfunction characterized by photosensitivity, progressive loss of vision and color perception, central or ring scotomas, night blindness, and attenuation of photopic and scotopic responses in the electroretinogram (ERG). The most commonly associated tumor is SCLC. *Melanoma-associated retinopathy* affects patients with metastatic cutaneous melanoma. Patients develop acute onset of night blindness and shimmering, flickering, or pulsating photopsias that often progress to visual loss. The ERG shows reduced b-waves with normal dark adapted a-waves. Paraneoplastic optic neuritis and uveitis can develop in association with encephalomyelitis. Patients with paraneoplastic uveitis and optic neuritis may harbor CRMP5 antibodies.

Some paraneoplastic retinopathies are associated with serum antibodies that specifically react with the subset of retinal cells undergoing degeneration, supporting an immune-mediated pathogenesis (Table 90-2). Paraneoplastic retinopathies rarely show substantial improvement after treatment of the tumor and immunotherapy, however, stabilization of symptoms and partial responses to a variety of immunotherapies (glucocorticoids, plasma exchange, IVIg, rituximab or alemtuzumab) have been reported.

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91 Late Consequences of Cancer and Its Treatment

Carl E. Freter, Dan L. Longo

There are over 10 million American cancer survivors. The vast majority of these will bear some mark of their cancer and its treatment, and a large proportion will experience long-term consequences including medical problems, psychosocial dysfunction, economic hardship, sexual dysfunction, and discrimination regarding employment and insurance. Many of these problems are directly related to cancer treatment. As patients survive longer from more types of malignancies, we are increasingly recognizing the biologic toll our very imperfect therapies take in terms of morbidity and mortality. The human face of these consequences of therapy confronts the cancer specialist who treats them every day. Although long-term survivors of childhood leukemias, Hodgkin's lymphoma, and testicular cancer, as examples, have taught us much about the consequences of cancer treatment, we keep learning more as patients survive longer with newer therapies. Newer "targeted" chemotherapy drugs have their own, often unique, long-term toxicities about which we remain in a learning process. Cancer "survivorship" clinics are increasing to expressly follow patients for long-term toxicities of cancer treatment.

The pace of developing therapies that mitigate treatment-related consequences has been slow, partly due to an understandable aversion to alter regimens that work and partly due to a lack of new, effective, less toxic therapeutic agents with less "collateral damage" to replace known agents with known toxicities. The types of damage from cancer treatment vary. Often, a final common pathway is irreparable damage to DNA. Surgery can create dysfunction, including blind gut loops with absorption problems and loss of function of removed body parts. Radiation may damage end-organ function, for example, loss of potency in prostate cancer patients, pulmonary fibrosis, and neurocognitive impairment, and may act as a direct carcinogen. Cancer chemotherapy can be a direct carcinogen and has a kaleidoscope of other toxicities discussed in this chapter. **Table 91-1** lists the late effects of cancer treatment.

The first goal of therapy is to eradicate or control the malignancy. Late treatment consequences are, indeed, testimony to the increasing success of such treatment. Their occurrence sharply underlines the necessity to develop more effective therapies with less long-term morbidity and mortality. At the same time, a sense of perspective and relative risk is necessary; fear of long-term complications should not prevent the application of effective, particularly curative, cancer treatment.

TABLE 91-1 Late Effects of Cancer Therapy

Surgical Procedure	Effect
Amputation	Functional loss
Lymph node dissection	Risk of lymphedema
Ostomy	Psychosocial impact
Splenectomy	Risk of sepsis
Adhesions	Risk of obstruction
Bowel anastomoses	Malabsorption syndromes
Radiation Therapy	**Effect**
Organ	
Bone	Premature termination of growth, osteonecrosis
Soft tissues	Atrophy, fibrosis
Brain	Neuropsychiatric deficits, cognitive dysfunction
Thyroid	Hypothyroidism, Graves' disease, cancer
Salivary glands	Dry mouth, caries, dysgeusia
Eyes	Cataracts
Heart	Pericarditis, myocarditis, coronary artery disease
Lung	Pulmonary fibrosis
Kidney	Decreased function, hypertension
Liver	Decreased function
Intestine	Malabsorption, stricture
Gonads	Infertility, premature menopause
Any	Secondary neoplasia

Chemotherapy		Effect
Organ	**Drug**	
Bone	Glucocorticoids	Osteoporosis, avascular necrosis
Brain	Methotrexate, cytarabine, others	Neuropsychiatric deficits, cognitive decline?
Peripheral nerves	Vincristine, platinum, taxanes	Neuropathy, hearing loss
Eyes	Glucocorticoids	Cataracts
Heart	Anthracyclines, trastuzumab	Cardiomyopathy
Lung	Bleomycin	Pulmonary fibrosis
	Methotrexate	Pulmonary hypersensitivity
Kidney	Platinum, others	Decreased function, hypomagnesemia
Liver	Various	Altered function
Gonads	Alkylating agents, others	Infertility, premature menopause
Bone marrow	Various	Aplasia, myelodysplasia, secondary leukemia

CARDIOVASCULAR DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Cardiovascular toxicity of cancer chemotherapeutic agents includes dysrhythmias, cardiac ischemia, cardiomyopathic congestive heart failure (CHF), pericardial disease, and peripheral vascular disease. Because these cardiac toxicities are difficult to distinguish from disease that is not associated with cancer treatment, clear etiologic implication of cancer chemotherapeutic agents may be difficult. Cardiovascular complications occurring in an unexpected clinical setting in patients who have undergone cancer therapy are often important in raising suspicion. Dose-dependent myocardial toxicity of anthracyclines with characteristic myofibrillar dropout is pathologically pathognomonic on endomyocardial biopsy. Anthracycline cardiotoxicity occurs through a root mechanism of chemical free radical damage. Fe^{3+}-doxorubicin complexes damage DNA, nuclear and cytoplasmic membranes, and mitochondria. About 5% of patients receiving >450–550 mg/m^2 of doxorubicin will develop CHF. Cardiotoxicity in relation to the dose of anthracycline is clearly not a step function, but rather a continuous function, and occasional patients are seen with CHF at substantially lower doses. Advanced age, other concomitant cardiac disease, hypertension, diabetes, and thoracic radiation therapy are all important cofactors in promoting anthracycline-associated CHF. The risk of cardiac failure appears to be substantially lower when doxorubicin is administered by continuous infusion. Anthracycline-related CHF is difficult to reverse and has a mortality rate as high as 50%, making prevention crucial. Some anthracyclines such as mitoxantrone are associated with less cardiotoxicity, and continuous-infusion regimens and liposomally encapsulated doxorubicin are associated with less cardiotoxicity. Dexrazoxane, an intracellular iron chelator, may limit anthracycline toxicity, but the concern of limiting chemotherapeutic efficacy has somewhat limited its use. Monitoring patients for cardiac toxicity typically involves periodic gated nuclear cardiac blood pool ejection fraction testing (multigated acquisition scan [MUGA]) or cardiac ultrasonography. More recently, cardiac magnetic resonance imaging (MRI) has been used, but MRI is not standard or widespread. Testing is performed more frequently at higher cumulative doses, with additional risk factors, and certainly for any newly developing CHF or other symptoms of cardiac dysfunction.

After anthracyclines, trastuzumab is the next most frequent cardiotoxic drug currently in use. Trastuzumab is frequently used as adjuvant breast cancer therapy, sometimes in conjunction with anthracyclines, which is believed to result in additive or possibly synergistic toxicity. In contrast to anthracyclines, cardiotoxicity is not dose-related, is usually reversible, is not associated with pathologic changes of anthracyclines on cardiac myofibrils, and has a different biochemical mechanism inhibiting intrinsic cardiac repair mechanisms. Toxicity is typically routinely monitored every 3–4 doses using functional cardiac testing as mentioned earlier for anthracyclines.

Other cardiotoxic drugs include lapatinib, phosphoramide mustards (cyclophosphamide), ifosfamide, interleukin 2, ponatinib, imatinib, and sunitinib.

RADIATION THERAPY

Radiation therapy that includes the heart can cause interstitial myocardial fibrosis, acute and chronic pericarditis, valvular disease, and accelerated premature atherosclerotic coronary artery disease. Repeated or high (>6000 cGy) radiation doses are associated with greater risk, as is concomitant or distant cardiotoxic cancer chemotherapy exposure. Symptoms of acute pericarditis, which peaks about 9 months after treatment, include dyspnea, chest pain, and fever. Chronic constrictive pericarditis may develop 5–10 years following radiation therapy. Cardiac valvular disease includes aortic insufficiency from fibrosis or papillary muscle dysfunction resulting in mitral regurgitation. A threefold increased risk of fatal myocardial infarction is associated with mantle field radiation with accelerated coronary artery disease. Carotid radiation similarly increases the risk of embolic stroke.

TREATMENT

Chemotherapeutic/Radiation-Induced Cardiovascular Disease

Therapy for chemotherapeutic/radiation-induced cardiovascular disease is essentially the same as therapy for disease not associated with cancer treatment. Discontinuation of the offending agent is the first step. Diuretics, fluid and sodium restriction, and antiarrhythmic agents are often useful for acute symptoms. Afterload reduction with angiotensin-converting enzyme (ACE) inhibitors or, in some cases, β-adrenergic blockers (carvedilol) often is of significant benefit, and digitalis may be helpful as well.

A hybrid discipline of "cardio-oncology" has been developing in clinics to expressly follow chemotherapy-treated patients for cardiotoxicity. The goals are early intervention using more sensitive techniques, management of cardiotoxicity before it becomes symptomatic, and using clinical trials to identify cardioprotective strategies.

PULMONARY DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Bleomycin generates activated free radical oxygen species and causes pneumonitis associated with a radiographic or interstitial ground-glass appearance diffusely throughout both lungs, often worse in the lower lobes. A nonproductive cough with or without fever may be an early sign. This toxicity is dose-related and dose-limiting. The diffusion capacity of the lungs for carbon dioxide (DL_{CO}) is a sensitive measure of toxicity and recovery, and a baseline value is generally obtained for future comparison prior to bleomycin therapy. Additive or synergistic risk factors include age, prior lung disease, and concomitant use of other chemotherapy, lung irradiation, and high concentrations of inspired oxygen. Other chemotherapeutic agents notable for pulmonary toxicity include mitomycin, nitrosoureas, doxorubicin with radiation, gemcitabine combined with weekly docetaxel, methotrexate, and fludarabine. High-dose alkylating agents, cyclophosphamide, ifosfamide, and melphalan are frequently used in the hematopoietic stem cell transplant setting, often with whole-body radiation. This therapy may result in severe pulmonary fibrosis and/or pulmonary venoocclusive disease.

RADIATION THERAPY

Risk factors for radiation pneumonitis include advanced age, poor performance status, preexisting compromised pulmonary function, and radiation volume and dose. The dose "threshold" is thought to be in the range of 5–20 Gy. Hypoxemia and dyspnea on exertion are characteristic. Fine, high-pitched "Velcro rales" may be an accompanying physical finding, and fever, cough, and pleuritic chest pain are common symptoms. The DL_{CO} is the most sensitive measure of pulmonary functional impairment, and ground-glass infiltrates often correspond with relatively sharp edges to the irradiated volume, although the pneumonitis may progress beyond the field and even occasionally involve the contralateral unirradiated lung.

TREATMENT

Pulmonary Dysfunction

Chemotherapy- and radiation-induced pneumonitis is generally very corticosteroid responsive, except in the case of nitrosoureas. Prednisone 1 mg/kg is often used to control acute symptoms and pulmonary dysfunction with a generally slow taper. Prolonged glucocorticoid therapy requires gastrointestinal protection with proton pump inhibitors, management of hyperglycemia, heightened infection management, and treatment of steroid-induced osteoporosis. Antibiotics, bronchodilators, oxygen in only necessary doses, and diuretics may all play an important role in management of pneumonitis, and consultation with a pulmonologist should be routinely undertaken. Amifostine has been studied as a pulmonary radioprotectant, with inconclusive results, and is associated with skin rash, fatigue, and nausea; hence, it is not considered standard therapy at this time. Transforming growth factor β (TGF-β) is believed to be a major inducer of radiation fibrosis and represents a therapeutic target for development of anti-TGF-β therapies.

NEUROLOGIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Chemotherapy- and radiation-induced neurologic dysfunction is unfortunately increasing in both incidence and severity as a result of improved supportive care leading to more aggressive regimens and longer cancer survivorship allowing the development of late toxicity. Direct effects on myelin, glial cells, and neurons have all been implicated, with alterations in cellular cytoskeleton, axonal transport, and cellular metabolism as mechanisms.

Vinca alkaloids produce a characteristic "stocking-glove" neuropathy with numbness and tingling advancing to loss of motor function, which is highly dose related. Distal sensorimotor polyneuropathy prominently involves loss of deep tendon reflexes with initially loss of pain and temperature sensation, followed by proprioceptive and vibratory loss. This requires careful patient history and physical examination by experienced oncologists to decide when the drug must be stopped due to toxicity. Milder toxicity often slowly completely resolves. Vinca alkaloids may sometimes be associated with jaw claudication, autonomic neuropathy, ileus, cranial nerve palsies, and, in severe cases, encephalopathy, seizures, and coma.

Cisplatin is associated with sensorimotor neuropathy and hearing loss, especially at doses >400 mg/m^2, requiring audiometry in patients with preexisting hearing compromise. Carboplatin is often substituted in such cases given its lesser effect on hearing.

Many of the agents that target kinase enzymes in tumor cells and 5-fluorouracil congeners produce dysesthesias and painful hands and feet known as hand-foot syndrome or palmar-plantar erythrodysesthesia. Symptoms usually abate when the agent is stopped.

Neurocognitive dysfunction has been well described in childhood survivors of acute lymphoblastic leukemia (ALL) treatment, including intrathecal methotrexate or cytosine arabinoside in conjunction with prophylactic cranial irradiation. Methotrexate alone may cause acute leukoencephalopathy characterized by somnolence and confusion that is often reversible. Acute toxicity is dose related, especially at doses >3 g/m^2, with younger patients being at greater risk. Subacute methotrexate toxicity occurs weeks after therapy and is often ameliorated with glucocorticoid therapy. Chronic methotrexate toxicity (leukoencephalopathy) develops months or years after treatment and is characterized clinically as progressive loss of cognitive function and focal neurologic signs, which are irreversible, promoted by synchronous or metachronous radiation therapy, and more pronounced at a younger age.

Neurocognitive decline following chemotherapy alone occurs notably in breast cancer patients receiving adjuvant chemotherapy; this has been referred to as "chemo brain." It is clinically associated with impaired memory, learning, attention, and speed of information processing. There is no clear mechanistic explanation for its cause and no clearly effective therapy. This entity is justifiably attracting more attention and clearly needs to be studied to develop effective therapy or prophylaxis.

Many cancer patients experience intrusive or debilitating concerns about cancer recurrence following successful therapy. In addition, these patients may experience job, insurance, stress, relationship, financial, and sexual difficulties. Oncologists need to ask about and address these issues explicitly with patients and provide appropriate counseling or support systems. Suicidal ideation and suicide have an increased incidence in cancer patients and survivors.

RADIATION THERAPY

Acute radiation central nervous system (CNS) toxicity occurs within weeks; is characterized by nausea, drowsiness, hypersomnia, and ataxia; and is most often associated with recovery. Early delayed toxicity occurring weeks to 3 months following therapy is associated with similar symptoms as acute toxicity and is pathologically associated with reversible demyelination. Chronic, late radiation injury occurs 9 months to up to 10 years following therapy. Focal necrosis is a common pathologic finding, and glucocorticoid therapy may be helpful. Diffuse radiation injury is associated with global CNS neurologic dysfunction and diffuse white matter changes on computed tomography (CT) or MRI. Pathologically, small vessel changes are prominent. Glucocorticoids may be symptomatically useful but do not alter the course. Necrotizing encephalopathy is the most severe form of radiation injury and almost always is associated with chemotherapy, notably methotrexate.

Cranial radiation may also be associated with an array of endocrine abnormalities with disruption of normal pituitary/hypothalamic axis function, and a high index of suspicion needs to be maintained to identify and treat this toxicity.

Radiation-associated spinal cord injury (myelopathy) is highly dose-dependent and rarely occurs with modern radiation therapy. An early, self-limited form involving electric sensations down the spine on neck flexion (Lhermitte's sign) is seen 6–12 weeks after treatment and

generally resolves over weeks. Peripheral nerve toxicity is quite rare owing to relative radiation resistance.

HEPATIC DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Long-term hepatic damage from standard chemotherapy regimens is rare. Long-term methotrexate or high-dose chemotherapy alone or with radiation therapy, for example, in preparative regimens for bone marrow transplantation, may result in venoocclusive disease of the liver. This potentially lethal complication classically presents with anicteric ascites, elevated alkaline phosphatase, and hepatosplenomegaly. Pathologically, there is venous congestion, epithelial cell proliferation, and hepatocyte atrophy progressing to frank fibrosis. Frequent monitoring of liver function tests during any chemotherapy is necessary to avoid both idiosyncratic and expected toxicities.

Certain nucleoside drugs have been associated with hepatic dysfunction; however, this complication is rare in oncology.

RADIATION THERAPY

Hepatic radiation damage depends on dose, volume, fractionation, preexisting liver disease, and synchronous or metachronous chemotherapy. In general, radiation doses to the liver >1500 cGy can produce hepatic dysfunction with a steep dose-injury curve. Radiation-induced liver disease closely mimics hepatic venoocclusive disease.

RENAL/BLADDER DYSFUNCTION

Cisplatin produces reversible decrements in renal function, but may also produce severe irreversible toxicity in the presence of renal disease and may predispose to accentuated damage with subsequent renal insults. Cyclophosphamide and ifosfamide, as prodrugs primarily activated in the liver, have cleavage products (acrolein) that can produce hemorrhagic cystitis. This can be prevented with the free radical scavenger MESNA (mercaptoethane sulfonate), which is required for ifosfamide administration. Hemorrhagic cystitis caused by these agents may predispose to bladder cancer.

REPRODUCTIVE AND ENDOCRINE DYSFUNCTION

CHEMOTHERAPEUTIC AGENTS

Alkylating agents are associated with the highest rates of male and female infertility, which is directly dependent on age, dose, and duration of treatment. The age at treatment is an important determinant of fertility outcome, with prepubertal patients having the highest tolerance. Ovarian failure is age related, and females who resume menses after treatment are still at increased risk for premature menopause. Males generally have reversible azoospermia during lower intensity alkylator chemotherapy, and long-term infertility is associated with doses of cyclophosphamide >9 g/m^2 and with high-intensity therapy, such as that used in hematopoietic stem cell transplantation. Males undergoing potentially sterilizing chemotherapy should be offered sperm banking. Gonadotropin-releasing hormone (GnRH) analogs remain experimental to preserve ovarian function. Assisted reproductive technologies can be helpful to couples with chemotherapy-induced infertility.

RADIATION THERAPY

Testicles and ovaries in prepubertal patients are less sensitive to radiation damage; spermatogenesis is affected by low doses of radiation, and complete azoospermia occurs at 600–700 cGy. Leydig cell dysfunction, in contrast, occurs at <2000 cGy, and hence, endocrine function is lost at much higher radiation doses than spermatogenesis. Erectile dysfunction occurs in up to 80% of men treated with external-beam radiation therapy for prostate cancer. Sildenafil may be useful in reversing erectile dysfunction. Ovarian function damage with radiation is age related and occurs at doses of 150–500 cGy. Premature induction of menopause can have serious medical and psychological sequelae. Hormone replacement therapy is often contraindicated (as in estrogen receptor–positive breast cancer). Attention must be paid to maintenance of bone mass with calcium and vitamin D supplements and oral bisphosphonates, and bone mass should be monitored using bone density determinations. Paroxetine, clonidine, pregabalin, and other drugs may be useful in symptomatically controlling hot flashes.

Long-term survivors of childhood cancer (e.g., ALL) who have received cranial radiation may have altered leptin biology and growth hormone deficiency, leading to obesity and reduced strength, exercise tolerance, and bone density.

Radiation therapy to the neck (e.g., in Hodgkin's lymphoma) may lead to hypothyroidism, Graves' disease, thyroiditis, and thyroid malignancies. Thyroid-stimulating hormone (TSH) is followed routinely in such patients to prevent hypothyroidism, and to suppress persistently elevated levels of TSH, which may cause or drive thyroid cancer.

IMMUNOTHERAPY

The development of treatments that inhibit immune checkpoints like CTLA-4 and PD-1 has led to significant advances in treating a number of malignancies. However, late side effects from these agents may occur. The most serious chronic toxicities include the breaking of self-tolerance and the autoimmune destruction of certain endocrine organs, particularly the thyroid and the adenohypophysis (anterior pituitary). Patients with autoimmune thyroiditis or hypophysitis require life-long hormone replacement. Early recognition is important.

OCULAR COMPLICATIONS

Cataracts may be caused by glucocorticoids, depending on duration and dose; radiation therapy; and uncommonly, tamoxifen. Orbital radiation therapy may cause blindness.

ORAL COMPLICATIONS

Radiation therapy can produce xerostomia (dry mouth), with an attendant increase in caries and poor dentition. Taste and appetite may be suppressed. Bisphosphonate use may result in osteonecrosis of the jaw.

RAYNAUD'S PHENOMENON

Up to 40% of patients treated with bleomycin may develop Raynaud's phenomenon as a result of an unknown mechanism.

SECOND MALIGNANCIES

Second malignancies in patients cured of cancer are a major cause of death, and treated cancer patients must be monitored for their occurrence. The induction of second malignancies is governed by the complex interplay of a number of factors including age, gender, environmental exposures, genetic susceptibility, and cancer treatment itself. In a number of settings, the events leading to the primary cancer themselves increase the risk of second malignancies. Patients with lung cancer are at increased risk of esophageal and head and neck cancers, and vice versa, due to shared risk factors including alcohol and tobacco abuse. Indeed, the risk of developing a second primary head and neck, esophageal, or lung cancer is also increased in these patients. Patients with breast cancer are at increased risk of breast cancer in the opposite breast. Patients with Hodgkin's lymphoma are at risk for non-Hodgkin's lymphomas. Genetic cancer syndromes (e.g., multiple endocrine neoplasia or Li-Fraumeni, Lynch's, Cowden's, and Gardner's syndromes) are examples of genetically based second malignancies of specific types. Cancer treatment itself does not appear to be responsible for the risk of these secondary malignancies. Deficient DNA repair can greatly increase the risk of cancers from DNA-damaging agents, as in ataxia-telangiectasia. Importantly, the risk of treatment-related second malignancies is at least additive and often synergistic with combined chemotherapy and radiation therapy, and hence for such combined-therapy treatment approaches, it is important to establish the necessity of each in the treatment program. All of these patients require special surveillance or, in some cases, prophylactic surgery as part of appropriate treatment and follow-up.

CHEMOTHERAPEUTIC AGENTS

Chemotherapy is significantly associated with two fatal second malignancies: acute leukemia and myelodysplastic syndromes. Two types

of leukemia have been described; in patients treated with alkylating agents, acute myeloid leukemia is associated with deletions in chromosome 5 or 7. The lifetime risk is about 1–5%, is increased by radiation therapy, and increases with age. The incidence of these leukemias peaks at 4–6 years, with risk returning close to baseline at 10 years. The other type of acute myeloid leukemia is related to therapy with topoisomerase inhibitors, is associated with chromosome 10q23 translocations, has an incidence of <1%, and generally occurs 1.5–3 years after treatment. Both of these acute myeloid leukemias are refractory to treatment and have a high mortality. The development of myelodysplastic syndromes is increased following chemotherapy, and these are often associated with leukemic progression and a dismal prognosis. A fraction of the population (those with or without cancer) develops clonal hematopoiesis and the percentage increases with age. In such patients, the hematopoietic stem cells carry mutations that are associated with myeloid malignancy despite normal blood counts. It is thought that the presence of these genetic lesions may predispose patients to develop myeloid malignancies.

RADIATION THERAPY

Patients receiving radiation have an increasing and lifelong risk of second malignancies that is 1–2% in the second decade following treatment but increases to >25% after 25 years. These malignancies include cancers of the thyroid and breast, sarcomas, gastric cancer, and CNS cancers, which often tend to be aggressive, occur in or adjacent to a radiation field, and have a poor prognosis. An example of organ-, age-, and sex-dependent radiation-induced secondary malignancy is breast cancer, in which the risk is small with radiation in women aged <30 years but increases about twentyfold over baseline in women aged >30 years. A 25-year-old woman treated with mantle radiation for Hodgkin's lymphoma has a 29% actuarial risk of developing breast cancer by age 55.

HORMONAL THERAPY

Treatment of breast cancer with tamoxifen for 5 years or longer is associated with a 1–2% risk of endometrial cancer. Surveillance is generally effective at finding these cancers at an early stage. The risk of mortality from tamoxifen-induced endometrial cancer is low compared to the benefit of tamoxifen as adjuvant therapy for breast cancer.

IMMUNOSUPPRESSIVE THERAPY

Immunosuppressive therapy, as used in allogeneic bone marrow transplantation, particularly with T-cell depletion using antithymocyte globulin or other means, increases the risk of Epstein Barr virus–associated B-cell lymphoproliferative disorder. The incidence at 10 years after T-cell depletion is 9–12%. Discontinuing immunosuppressive therapy, if possible, is often associated with complete disease regression.

RECOMMENDATIONS FOR FOLLOW-UP

All former cancer patients should be followed indefinitely. This is most often done by oncologists, but demographic changes suggest that more primary care physicians will need to be trained in the follow-up of treated cancer patients in remission. Cancer patients need to be educated about signs and symptoms of recurrence and potentially adverse effects related to therapy. Localized pain or palpable abnormality in a previously radiated field should prompt radiographic evaluation. Screening tests, when available and validated, should be used on a routine and regular basis (e.g., mammography and Pap smear), particularly in patients receiving radiation to specific organs. Annual mammography should start no later than 10 years after breast radiation. Patients receiving radiation fields encompassing thyroid tissue should have regular thyroid examinations and TSH testing. Patients treated with alkylating agents or topoisomerase inhibitors should have a complete blood count every 6–12 months, and cytopenias, abnormal cells on peripheral smear, or macrocytosis should be evaluated with bone marrow biopsy and aspirate, to include cytogenetics, flow cytometry, or fluorescence in situ hybridization (FISH) studies as appropriate.

As the population of cancer survivors lives longer and grows, cancer survivorship has become an increasingly recognized subject, and the Institute of Medicine and National Research Council have published a monograph entitled *From Cancer Patient to Cancer Survivor: Lost in Transition.* The monograph proposes a plan that would inform clinicians caring for cancer survivors in complete detail of their previous treatments, complications thereof, signs and symptoms of late effects, and recommended screening and follow-up procedures. **Table 91-2** lists long-term treatment effects by cancer type.

TABLE 91-2 Long-Term Treatment Effects by Cancer Type

CANCER TYPE	LATE EFFECTS
Pediatric cancers	Majority have at least one late effect 30% with moderate/severe problems Cardiovascular: radiation, anthracyclines Lungs: radiation Skeletal abnormalities: radiation Psychological, cognitive, and sexual problems Second neoplasms significant cause of death
Hodgkin's lymphoma	Thyroid dysfunction: radiation Premature coronary artery disease: radiation Gonadal dysfunction: chemotherapy Postsplenectomy sepsis Myelodysplasia Acute myeloid leukemia Non-Hodgkin's lymphomas Breast cancer, lung cancer, and melanoma Fatigue, psychological and sexual problems Peripheral neuropathy
Non-Hodgkin's lymphoma	Myelodysplasia Acute leukemia Bladder cancer Peripheral neuropathy
Acute leukemia	Second malignancies: hematologic, solid tumors Neuropsychiatric dysfunction Subnormal growth Thyroid abnormalities Infertility
Bone marrow stem cell transplantation	Infertility Graft-versus-host disease (allogeneic transplant) Psychosexual dysfunction
Head and neck cancer	Poor dentition, dry mouth, poor nutrition: radiation
Breast cancer	Tamoxifen: endometrial cancer, blood clots Aromatase inhibitors: osteoporosis, arthritis Cardiomyopathy: anthracycline ± radiation, trastuzumab Acute leukemia Hormone deficiency symptoms: hot flashes, vaginal dryness, dyspareunia Psychosocial dysfunction "Chemo brain"
Testicular cancer	Raynaud's phenomenon Renal dysfunction Pulmonary dysfunction Retrograde ejaculation: surgery 15% sexual dysfunction
Colon cancer	Major risk is second colon cancer Quality of life high in survivors
Prostate cancer	Impotence Urinary incontinence (0–15%) Chronic proctitis, prostatitis/cystitis: radiation

OUTLOOK

Clearly, the challenge for the future is to combine chemotherapy, targeted agents, biologic therapies, radiation, and surgery to produce better outcomes with less toxicity, including late effects of therapy. This

is easily said but less easily accomplished. As treatment becomes more effective in new patient populations (ovarian, bladder, anal, and laryngeal cancers, for example), we will expect to discover new populations at risk for late effects. These populations will need to be followed carefully, so that such effects are recognized and treated. Cancer survivors represent an underused resource for prevention studies. Childhood cancer survivors, especially, suffer multiple chronic health impairments. The incidence of these late treatment consequences appears to have no plateau with age, throwing in stark relief the necessity of close monitoring and therapies with fewer late consequences of treatment.

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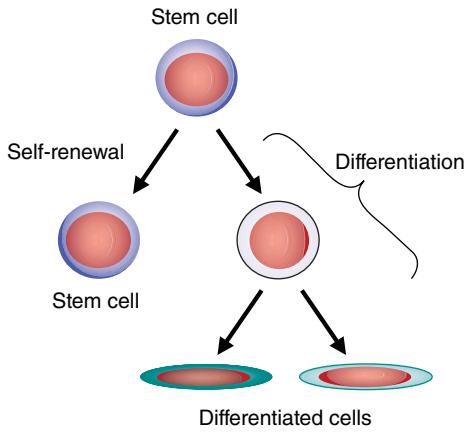

FIGURE 92-1 Signature characteristics of the stem cell. Stem cells have two essential features: the capacity to differentiate into a variety of mature cell types and the capacity for self-renewal. Intrinsic factors associated with self-renewal include expression of *Bmi-1*, *Gfi-1*, *PTEN*, *STAT5*, *Tel/Atv6*, *p21*, *p18*, *MCL-1*, *Mel-18*, *RAE28*, and *HoxB4*. Extrinsic signals for self-renewal include Notch, Wnt, SHH, angiogenin, and Tie2/Ang-1. Based mainly on murine studies, hematopoietic stem cells express the following cell surface molecules: CD34, Thy-1 (CD90), c-Kit receptor (CD117), CD133, CD164, and c-Mpl (CD110, also known as the thrombopoietin receptor).

Section 2 Hematopoietic Disorders

92 Hematopoietic Stem Cells

David T. Scadden, Dan L. Longo

All of the cell types in the peripheral blood and some cells in every tissue of the body are derived from hematopoietic (*hemo*: blood; *poiesis*: creation) stem cells. If the hematopoietic stem cell is damaged and can no longer function (e.g., due to a nuclear accident), a person would survive 2–4 weeks in the absence of extraordinary support measures. With the clinical use of hematopoietic stem cells, tens of thousands of lives are saved each year **(Chap. 110)**. Stem cells produce hundreds of billions of blood cells daily from a stem cell pool that is estimated to be only in the tens of thousands. How stem cells do this, how they persist for many decades despite the production demands, and how they may be better used in clinical care are important issues in medicine.

The study of blood cell production has become a paradigm for how other tissues may be organized and regulated. Basic research in hematopoiesis includes defining stepwise molecular changes accompanying functional changes in maturing cells, aggregating cells into functional subgroups, and demonstrating hematopoietic stem cell regulation by a specialized microenvironment; these concepts are worked out in hematology, but they offer models for other tissues. Moreover, these concepts may not be restricted to normal tissue function but extend to malignancy. Stem cells are rare cells among a heterogeneous population of cell types, and their behavior is assessed mainly in experimental animal models involving reconstitution of hematopoiesis. Thus, much of what we know about stem cells is imprecise and based on inferences from genetically manipulated animals.

CARDINAL FUNCTIONS OF HEMATOPOIETIC STEM CELLS

All stem cell types have two cardinal functions: self-renewal and differentiation **(Fig. 92-1)**. Stem cells exist to generate, maintain, and repair tissues. They function successfully if they can replace a wide variety of shorter-lived mature cells over prolonged periods. The process of self-renewal (see below) assures that a stem cell population can be sustained over time. Without self-renewal, the stem cell pool would become exhausted and tissue maintenance would not be possible. The process of differentiation leads to production of the effectors of tissue function: mature cells. Without proper differentiation, the integrity of tissue function would be compromised and organ failure or neoplasia would ensue.

In the blood, mature cells have variable average life spans, ranging from hours for mature neutrophils to a few months for red blood cells to many years for memory lymphocytes. However, the stem cell pool is the central, durable source of all blood and immune cells, maintaining a capacity to produce a broad range of cells from a single cell source, yet keeping itself vigorous over decades of life. As an individual stem cell divides, it has the capacity to accomplish one of three division outcomes: two stem cells, two cells destined for differentiation, or one stem cell and one differentiating cell. The former two outcomes are the result of symmetric cell division, whereas the latter indicates a different outcome for the two daughter cells—an event termed *asymmetric cell division*. The relative balance for these types of outcomes may change during development and under particular kinds of demands on the stem cell pool.

DEVELOPMENTAL BIOLOGY OF HEMATOPOIETIC STEM CELLS

During development, blood cells are produced at different sites. Initially, the yolk sac provides oxygen-carrying red blood cells and many of the macrophage-like cells that are resident in tissues: cells like microglia in the brain. The placenta and several sites of intraembryonic blood cell production then become involved in sequential order. These move from the genital ridge at a site where the aorta, gonadal tissue, and mesonephros are emerging to the fetal liver and then, in the second trimester, to the bone marrow and spleen. As the location of stem cells changes, the cells they produce also change. The yolk sac provides red cells expressing embryonic hemoglobins and tissue-resident macrophages. Intraembryonic sites of hematopoiesis generate stem cells, red cells, platelets, and the circulating cells of innate immunity. The production of the cells of adaptive immunity occurs when the bone marrow is colonized and the thymus forms. Stem cell proliferation remains high, even in the bone marrow, until shortly after birth, when it appears to dramatically decline. The cells in the bone marrow are thought to arrive by the bloodborne transit of cells from the fetal liver after calcification of the long bones has begun. The presence of stem cells in the circulation is not unique to a time window in development, however, as hematopoietic stem cells circulate throughout life. The time that stem cells spend freely circulating appears to be brief (measured in minutes

in the mouse), but the stem cells that do circulate are functional and can be used for transplantation. The number of stem cells that circulate can be increased in a number of ways to facilitate harvest and transfer to the same or a different host.

MOBILITY OF HEMATOPOIETIC STEM CELLS

Cells entering and exiting the bone marrow do so through a series of molecular interactions. Circulating stem cells (through CD162 and CD44) engage the lectins (carbohydrate binding proteins) P- and E-selectin on the endothelial surface to slow the movement of the cells to a rolling phenotype. Stem cell integrins are then activated and accomplish firm adhesion between the stem cell and vessel wall, with a particularly important role for stem cell VCAM-1 engaging endothelial VLA-4. The chemokine CXCL12 (SDF1) interacting with stem cell CXCR4 receptors and ionic calcium interacting with the calcium sensing receptor appear to be important in the process of stem cells getting from the circulation to where they engraft in the bone marrow. This is particularly true in the developmental move from fetal liver to bone marrow.

However, the role for CXCR4 in adults appears to be more related to retention of stem cells in the bone marrow rather than the process of getting them there. Interrupting that retention process through either specific molecular blockers of the CXCR4/CXCL12 interaction, cleavage of CXCL12, or downregulation of the CXCR4 receptor can all result in the release of stem cells into the circulation. This process is an increasingly important aspect of recovering stem cells for therapeutic use as it has permitted the harvesting process to be done by leukapheresis rather than bone marrow punctures in the operating room. Granulocyte colony-stimulating factor and plerixafor, a macrocyclic compound that can block CXCR4, are both used clinically to mobilize marrow hematopoietic stem cells for transplant. Refining our knowledge of how stem cells get into and out of the bone marrow may improve our ability to obtain stem cells and make them more efficient at finding their way to the specific sites for blood cell production, the so-called stem cell niche.

HEMATOPOIETIC STEM CELL MICROENVIRONMENT

The concept of a specialized microenvironment, or stem cell niche, was first proposed to explain why cells derived from the bone marrow of one animal could be used in transplantation and again be found in the bone marrow of the recipient. This niche is more than just a housing site for stem cells, however. It is an anatomic location where regulatory signals are provided that allow the stem cells to thrive, to expand if needed, and to provide varying amounts of descendant daughter cells. In addition, unregulated growth of stem cells may be problematic based on their undifferentiated state and self-renewal capacity. Thus, the niche must also regulate the number of stem cells produced. In this manner, the niche has the dual function of serving as a site of nurture but imposing limits for stem cells: in effect, acting as both a nutritive and constraining home.

The niche for blood stem cells changes with each of the sites of blood production during development, but for most of human life it is located in the bone marrow. Within the bone marrow, the perivascular space particularly in regions of trabecular bone serves as a niche. The mesenchymal and endothelial cells of the marrow microvessels produce kit ligand and CXCL12, both known to be important for hematopoietic stem cells. Other cell types, such as sympathetic neurons, nonmyelinating Schwann cells, macrophages, megakaryocytes, osteoclasts, and osteoblasts, have been shown to regulate stem cells, some by direct and others by indirect effects. Extracellular matrix proteins like osteopontin and heparan sulfates also affect stem cell function. The endosteal region appears to be particularly important for transplanted cells, in part because many of the mesenchymal cells and sinusoidal blood vessels of the central marrow are disrupted by the conditioning regimens used to prepare a patient for transplantation. The functioning of the niche as a supportive context for stem cells is of obvious importance for maintaining hematopoiesis and in transplantation. An active area of study involves determining whether the niche is altered in disease and whether drugs can modify niche function to improve transplantation or normal stem cell function in hematologic disease.

EXCESS CAPACITY OF HEMATOPOIETIC STEM CELLS

In the absence of disease, one never runs out of hematopoietic stem cells. Indeed, serial transplantation studies in mice suggest that sufficient stem cells are present to reconstitute several animals in succession, with each animal having normal blood cell production. The fact that allogeneic stem cell transplant recipients also never run out of blood cells in their life span, which can extend for decades, argues that even the limiting numbers of stem cells provided to them are sufficient. How stem cells respond to different conditions to increase or decrease their mature cell production remains poorly understood. Clearly, negative feedback mechanisms affect the level of production of most of the cells, leading to the normal tightly regulated blood cell counts. However, many of the regulatory mechanisms that govern production of more mature progenitor cells do not apply or apply differently to stem cells. Similarly, most of the molecules shown to be able to change the size of the stem cell pool have little effect on more mature blood cells. For example, the growth factor erythropoietin, which stimulates red blood cell production from more mature precursor cells, has no effect on stem cells. Similarly, granulocyte colony-stimulating factor drives the rapid proliferation of granulocyte precursors but has little or no effect on the cell cycling of stem cells. Rather, it changes the location of stem cells by indirect means, altering molecules such as CXCL12 that tether stem cells to their niche. Molecules shown to be important for altering the proliferation, self-renewal, or survival of stem cells, such as cyclin-dependent kinase inhibitors, transcription factors like *Bmi-1*, microRNA-processing enzymes like Dicer, or even metabolic regulators like pyruvate kinase isoforms have little or different effects on progenitor cells. Hematopoietic stem cells have governing mechanisms that are distinct from the cells they generate.

HEMATOPOIETIC STEM CELL DIFFERENTIATION

Hematopoietic stem cells sit at the base of a branching hierarchy of cells culminating in the many mature cell types that compose the blood and immune system **(Fig. 92-2)**. The maturation steps leading to terminally differentiated and functional blood cells take place both as a consequence of intrinsic changes in gene expression and niche-directed and cytokine-directed changes in the cells. Our knowledge of the details remains incomplete. As stem cells mature to progenitors, precursors, and, finally, mature effector cells, they undergo a series of functional changes. These include the obvious acquisition of functions defining mature blood cells, such as phagocytic capacity or hemoglobin synthesis. They also include the progressive loss of plasticity (i.e., the ability to become other cell types). For example, the myeloid progenitor can make all cells in the myeloid series but none in the lymphoid series. As common myeloid progenitors mature, they become precursors for either monocytes and granulocytes or erythrocytes and megakaryocytes, but not both. Some amount of reversibility of this process may exist early in the differentiation cascade, but that is lost beyond a distinct stage in normal physiologic conditions. With genetic interventions, however, blood cells, like other somatic cells, can be reprogrammed to become a variety of cell types.

As cells differentiate, they may also lose proliferative capacity **(Fig. 92-3)**. Mature granulocytes are incapable of proliferation and only increase in number by increased production from precursors. The exceptions to the rule are some tissue-resident macrophages, which appear capable of proliferation, and lymphoid cells. Lymphoid cells retain the capacity to proliferate but have linked their proliferation to the recognition of particular proteins or peptides by specific antigen receptors on their surface. Like many tissues with short-lived mature cells such as the skin and intestine, blood cell proliferation is largely accomplished by a more immature progenitor population. In general, cells within the highly proliferative progenitor cell compartment are also relatively short-lived, making their way through the differentiation process in a defined molecular program involving the sequential activation of particular sets of genes. For any particular cell type, the

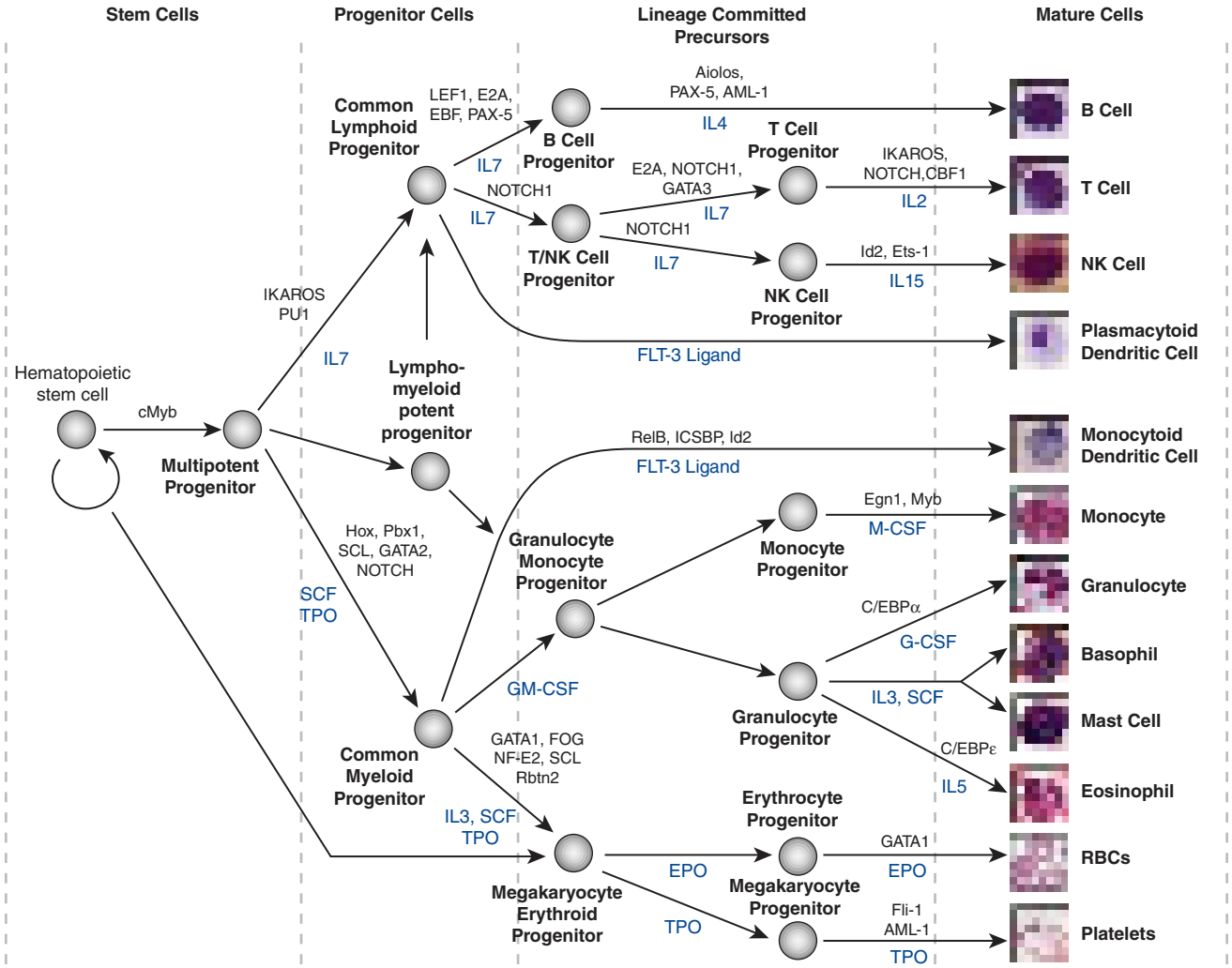

FIGURE 92-2 Hierarchy of hematopoietic differentiation. *Stem cells* are multipotent cells that are the source of all descendant cells and have the capacity to provide either long-term (measured in years) or short-term (measured in months) cell production. *Progenitor cells* have a more limited spectrum of cells they can produce and are generally a shorter-lived, highly proliferative population also known as transient amplifying cells. *Precursor cells* are cells committed to a single blood cell lineage but with a continued ability to proliferate; they do not have all the features of a fully mature cell. *Mature cells* are the terminally differentiated product of the differentiation process and are the effector cells of specific activities of the blood and immune system. Progress through the pathways is mediated by alterations in gene expression. The regulation of the differentiation by soluble factors and cell-cell communications within the bone marrow niche are still being defined. The transcription factors that characterize particular cell transitions are illustrated on the *arrows*; the soluble factors that contribute to the differentiation process are in *blue*. This picture is a simplification of the process. Active research is revealing multiple discrete cell types in the maturation of B cells and T cells and has identified cells that are biased toward one lineage or another (rather than uncommitted) in their differentiation. EPO, erythropoietin; RBC, red blood cell; SCF, stem cell factor; TPO, thrombopoietin.

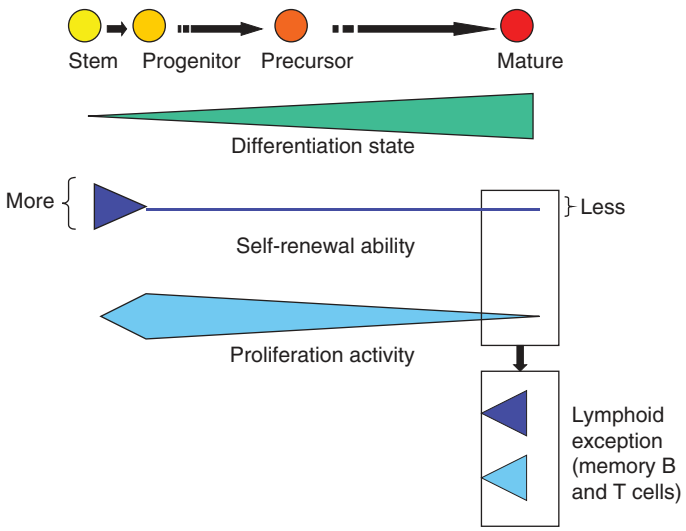

FIGURE 92-3 Relative function of cells in the hematopoietic hierarchy. The boxes represent distinct functional features of cells in the myeloid (*upper box*) versus lymphoid (*lower box*) lineages.

differentiation program is difficult to speed up. The time it takes for hematopoietic progenitors to become mature cells is ~10–14 days in humans, evident clinically by the interval between cytotoxic chemotherapy and blood count recovery in patients.

Although hematopoietic stem cells are generally thought to have the capacity to form all cells of the blood, it is becoming clear that individual stem cells may not be equal in their differentiation potential. That is, some stem cells are "biased" to become mature cells of a particular type. In addition, the general concept of cells having a binary choice of lymphoid or myeloid differentiation is not entirely accurate. A cell population with limited megakaryocytic and erythroid or myeloid (monocyte and granulocyte) and lymphoid potential is now added to the commitment steps stem cells may undergo.

SELF-RENEWAL

The hematopoietic stem cell must balance its three potential fates: apoptosis, self-renewal, and differentiation. The proliferation of cells is generally not associated with the ability to undergo a self-renewing division except among memory T and B cells and among stem cells. Self-renewal capacity has generally been regarded as giving way to differentiation as the only option after cell division when cells leave the stem cell compartment, unless they become memory lymphocytes.

However, emerging data suggest that some myeloid committed progenitors may have self-renewing potential in vivo, providing long-term production of cells. Stem cells all have self-renewing capacity by definition, and they have an additional feature characterizing their proliferation machinery. Stem cells in many mature adult tissues are heterogeneous with some being deeply quiescent, serving as a deep reserve, whereas others are more proliferative and replenish the short-lived progenitor population. In the hematopoietic system, stem cells are generally cytokine-resistant, remaining dormant even when cytokines drive bone marrow progenitors to proliferation rates measured in hours. Stem cells, in contrast, are thought to divide at far longer intervals, measured in months to years, for the most quiescent cells. This quiescence is difficult to overcome in vitro, limiting the ability to effectively expand human hematopoietic stem cells. The process may be controlled by particularly high levels of cyclin-dependent kinase inhibitors like p57 or CDKN1c that restrict entry of stem cells into the cell cycle, blocking the G_1-S transition. Exogenous signals from the niche also appear to enforce quiescence, including angiogenin, interleukin-18, and perhaps angiopoietin 1.

The regulation of stem cell proliferation also appears to change with age. In mice, the cyclin-dependent kinase inhibitor p16INK4a accumulates in stem cells in older animals and is associated with a change in stem cell functions, including cell cycling. Lowering expression of p16INK4a in older animals improves stem cell cycling and capacity to reconstitute hematopoiesis in adoptive hosts, making them similar to younger animals. Mature cell numbers are unaffected. Therefore, molecular events governing the specific functions of stem cells are being gradually made clear and offer the potential of new approaches to changing stem cell function for therapy. One critical stem cell function that remains poorly defined is the molecular regulation of self-renewal.

For medicine, self-renewal is perhaps the most important function of stem cells because it is critical in regulating the number of stem cells. Stem cell number is a key limiting parameter for both autologous and allogeneic stem cell transplantation. Were we to have the ability to use fewer stem cells or expand limited numbers of stem cells ex vivo, it might be possible to reduce the morbidity and expense of stem cell harvests and enable use of other stem cell sources. Specifically, umbilical cord blood is a rich source of stem cells. However, the volume of cord blood units is extremely small, and therefore, the total number of hematopoietic stem cells that can be obtained in any single cord blood unit is generally only sufficient to transplant an individual of <40 kg. This limitation restricts what would otherwise be an extremely promising source of stem cells. Two features of cord blood stem cells are particularly important: (1) They are derived from a diversity of individuals that far exceeds the adult donor pool and therefore can overcome the majority of immunologic cross-matching obstacles. (2) Cord blood stem cells have a large number of T cells associated with them, but (paradoxically) they appear to be associated with a lower incidence of graft-versus-host disease when compared with similarly mismatched stem cells from other sources. If stem cell expansion by self-renewal could be achieved, the number of cells available might be sufficient for use in larger adults. An alternative approach to this problem is to improve the efficiency of engraftment of donor stem cells. Graft engineering is exploring methods of adding cell components that may enhance engraftment. Furthermore, at least some data suggest that depletion of host NK (natural killer) cells may lower the number of stem cells necessary to reconstitute hematopoiesis.

Some limited understanding of self-renewal exists and, intriguingly, implicates gene products that are associated with the chromatin state, a high-order organization of chromosomal DNA that influences transcription. These include members of the polycomb family, a group of zinc finger–containing transcriptional regulators that interact with the chromatin structure, contributing to the accessibility of groups of genes for transcription. One member, *Bmi-1*, is important in enabling hematopoietic stem cell self-renewal through modification of cell cycle regulators such as the cyclin-dependent kinase inhibitors. In the absence of *Bmi-1* or of the transcriptional regulator, Gfi-1, hematopoietic stem cells decline in number and function. In contrast, dysregulation of *Bmi-1* has been associated with leukemia; it may promote leukemic stem cell self-renewal when it is overexpressed. Other transcription regulators have also been associated with self-renewal, particularly homeobox, or "hox," genes. These transcription factors are named for their ability to govern large numbers of genes, including those determining body patterning in invertebrates. HoxB4 is capable of inducing extensive self-renewal of stem cells through its DNA-binding motif. Other members of the hox family of genes have been noted to affect normal stem cells, but they are also associated with leukemia. External signals that may influence the relative self-renewal versus differentiation outcomes of stem cell cycling include specific Wnt ligands. Intracellular signal transducing intermediates are also implicated in regulating self-renewal. They include PTEN, an inhibitor of the AKT pathway, and STAT5, both of which are downstream of activated growth factor receptors and necessary for normal stem cell functions including self-renewal, at least in mouse models. The connections between these molecules remain to be defined, and their role in physiologic regulation of stem cell self-renewal is still poorly understood.

CANCER IS SIMILAR TO AN ORGAN WITH SELF-RENEWING CAPACITY

The relationship of stem cells to cancer is an important evolving dimension of adult stem cell biology. Cancer may share principles of organization with normal tissues. Cancer cells are heterogeneous even within a given patient and may have a hierarchical organization of cells with a base of stem-like cells capable of the signature stem cell features: self-renewal and differentiation. These stem-like cells might be the basis for perpetuation of the tumor and represent a slowly dividing, rare population with distinct regulatory mechanisms, including a relationship with a specialized microenvironment. A subpopulation of self-renewing cells has been defined for some, but not all, cancers. A more sophisticated understanding of the stem cell organization of cancers may lead to improved strategies for developing new therapies for the many common and difficult-to-treat types of malignancies that have been relatively refractory to interventions aimed at dividing cells.

Does the concept of cancer stem cells provide insight into the cellular origin of cancer? The fact that some cells within a cancer have stem cell–like properties does not necessarily mean that the cancer arose in the stem cell itself. Rather, more mature cells could have acquired the self-renewal characteristics of stem cells. Any single genetic event is unlikely to be sufficient to enable full transformation of a normal cell to a frankly malignant one. Rather, cancer is a multistep process, and for the multiple steps to accumulate, the cell of origin must be able to persist for prolonged periods. It must also be able to generate large numbers of daughter cells. The normal stem cell has these properties and, by virtue of its having intrinsic self-renewal capability, may be more readily converted to a malignant phenotype. This hypothesis has been tested experimentally in the hematopoietic system. Taking advantage of the cell-surface markers that distinguish hematopoietic cells of varying maturity, stem cells, progenitors, precursors, and mature cells can be isolated. Powerful transforming gene constructs were placed in these cells, and it was found that the cell with the greatest potential to produce a malignancy was dependent on the transforming gene. In some cases, it was the stem cell, but in others, the progenitor cell functioned to initiate and perpetuate the cancer. This shows that cells can acquire stem cell–like properties in malignancy.

WHAT ELSE CAN HEMATOPOIETIC STEM CELLS DO?

Some experimental data have suggested that hematopoietic stem cells or other cells mobilized into the circulation by the same factors that mobilize hematopoietic stem cells are capable of playing a role in healing the vascular and tissue damage associated with stroke and myocardial infarction. These data are controversial, and the applicability of a stem cell approach to nonhematopoietic conditions remains experimental. However, reprogramming technology offers the potential for using the readily obtained hematopoietic stem cell as a source for cells with other capabilities.

The stem cell, therefore, represents a true dual-edged sword. It has tremendous healing capacity and is essential for life. Uncontrolled, it can threaten the life it maintains. Understanding how stem cells function, the signals that modify their behavior, and the tissue niches that modulate stem cell responses to injury and disease are critical for more effectively developing stem cell–based medicine. That aspect of medicine will include the use of the stem cells and the use of drugs to target stem cells to enhance repair of damaged tissues. It will also include the careful balance of interventions to control stem cells where they may be dysfunctional or malignant.

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93 Iron Deficiency and Other Hypoproliferative Anemias

John W. Adamson

Anemias associated with normocytic and normochromic red cells and an inappropriately low reticulocyte response (reticulocyte index <2–2.5) are *hypoproliferative anemias*. This category includes early iron deficiency (before hypochromic microcytic red cells develop), acute and chronic inflammation (including many malignancies), renal disease, hypometabolic states such as protein malnutrition and endocrine deficiencies, and anemias from marrow damage. **Marrow damage states are discussed in Chap. 98.**

Hypoproliferative anemias are the most common anemias, and in the clinic, iron deficiency anemia is the most common of these followed by the anemia of inflammation. The anemia of inflammation, similar to iron deficiency, is related in part to abnormal iron metabolism. The anemias associated with renal disease, inflammation, cancer, and hypometabolic states are characterized by a suboptimal erythropoietin response to the anemia.

IRON METABOLISM

Iron is a critical element in the function of all cells, although the amount of iron required by individual tissues varies during development. At the same time, the body must protect itself from free iron, which is highly toxic in that it participates in chemical reactions that generate free radicals such as singlet O_2 or OH^-. Consequently, elaborate mechanisms have evolved that allow iron to be made available for physiologic functions while at the same time conserving this element and handling it in such a way that toxicity is avoided.

The major role of iron in mammals is to carry O_2 as part of hemoglobin. O_2 is also bound by myoglobin in muscle. Iron is a critical element in iron-containing enzymes, including the cytochrome system in mitochondria. Iron distribution in the body is shown in Table 93-1. Without iron, cells lose their capacity for electron transport and energy metabolism. In erythroid cells, hemoglobin synthesis is impaired, resulting in anemia and reduced O_2 delivery to tissue.

THE IRON CYCLE IN HUMANS

Figure 93-1 outlines the major pathways of internal iron exchange in humans. Iron absorbed from the diet or released from stores circulates in the plasma bound to *transferrin*, the iron transport protein. Transferrin is a bilobed glycoprotein with two iron-binding sites. Transferrin that carries iron exists in two forms—*monoferric* (one iron atom) or *diferric* (two iron atoms). The turnover (half-clearance time) of transferrin-bound iron is very rapid—typically 60–90 min. Because almost all of the iron transported by transferrin is delivered to the erythroid marrow, the clearance time of transferrin-bound iron from the circulation is affected most by the plasma iron level and the erythroid marrow activity. When erythropoiesis is markedly stimulated, the pool of erythroid cells requiring iron increases, and the clearance time of iron from the circulation decreases. The half-clearance time of iron in the presence of iron deficiency is as short as 10–15 min. With suppression of erythropoiesis, the plasma iron level typically increases, and the half-clearance time may be prolonged to several hours. Normally, the iron bound to transferrin turns over 6–8 times per day. Assuming a normal plasma iron level of 80–100 μg/dL, the amount of iron passing through the transferrin pool is 20–24 mg/d.

The iron-transferrin complex circulates in the plasma until it interacts with specific *transferrin receptors* on the surface of marrow erythroid cells. Diferric transferrin has the highest affinity for transferrin receptors; apotransferrin (not carrying iron) has very little affinity. Although transferrin receptors are found on cells in many tissues within the body—and all cells at some time during development will display transferrin receptors—the cell having the greatest number of receptors (300,000–400,000/cell) is the developing erythroblast.

Once the iron-bearing transferrin interacts with its receptor, the complex is internalized via clathrin-coated pits and transported to an acidic endosome, where the iron is released at the low pH. The iron is then made available for heme synthesis while the transferrin-receptor complex is recycled to the surface of the cell, where the bulk of the

TABLE 93-1 Body Iron Distribution

	IRON CONTENT, mg	
	ADULT MALE, 80 kg	ADULT FEMALE, 60 kg
Hemoglobin	2500	1700
Myoglobin/enzymes	500	300
Transferrin iron	3	3
Iron stores	600–1000	0–300

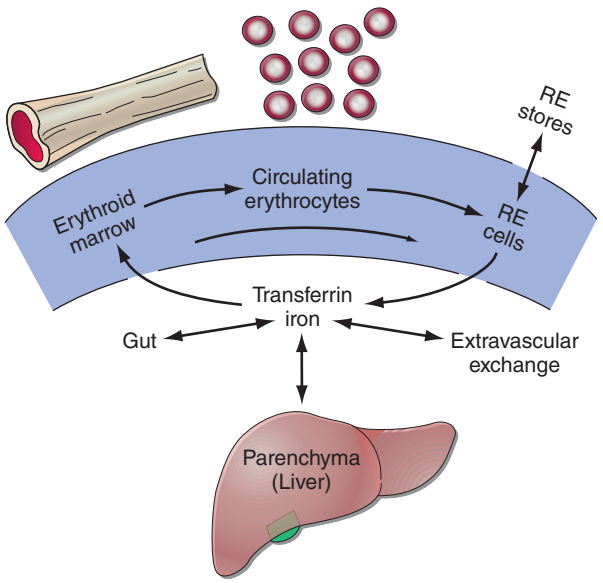

FIGURE 93-1 Internal iron exchange. Normally 80% of iron passing through the plasma transferrin pool is recycled from senescent red cells. Absorption of ~1 mg/d is required from the diet in men, and 1.4 mg/d in women to maintain homeostasis. As long as transferrin saturation is maintained between 20 and 60% and erythropoiesis is not increased, use of iron stores is not required. However, in the event of blood loss, dietary iron deficiency, or inadequate iron absorption, up to 40 mg/d of iron can be mobilized from stores. RE, reticuloendothelial.

transferrin is released back into circulation and the transferrin receptor re-anchors into the cell membrane. At this point a certain amount of the transferrin receptor protein may be released into circulation and can be measured as soluble transferrin receptor protein. Within the erythroid cell, iron in excess of the amount needed for hemoglobin synthesis binds to a storage protein, *apoferritin*, forming *ferritin*. This mechanism of iron exchange also takes place in other cells of the body expressing transferrin receptors, especially liver parenchymal cells where the iron can be incorporated into heme-containing enzymes or stored. The iron incorporated into hemoglobin subsequently enters the circulation as new red cells are released from the bone marrow. The iron is then part of the red cell mass and will not become available for reutilization until the red cell dies.

In a normal individual, the average red cell life span is 120 days. Thus, 0.8–1% of red cells is replaced each day. At the end of its life span, the red cell is recognized as senescent by the cells of the *reticuloendothelial (RE) system*, and the red cell undergoes phagocytosis. Once within the RE cell, the ingested hemoglobin is broken down, the globin and other proteins are returned to the amino acid pool, and the iron is shuttled back to the surface of the RE cell, where it is presented to circulating transferrin. It is the efficient and highly conserved recycling of iron from senescent red cells that supports steady-state (and even mildly accelerated) erythropoiesis.

Because each milliliter of red cells contains 1 mg of elemental iron, the amount of iron needed to replace those red cells lost through senescence amounts to 20 mg/d (assuming an adult with a red cell mass of 2 L). Any additional iron required for daily red cell production comes from the diet. Normally, an adult male will need to absorb at least 1 mg of elemental iron daily to meet needs, while females in the childbearing years will need to absorb an average of 1.4 mg/d. However, to achieve a maximum proliferative erythroid marrow response to anemia, additional iron must be available. With markedly stimulated erythropoiesis, demands for iron are increased by as much as six- to eightfold. With extravascular hemolytic anemia, the rate of red cell destruction is increased, but the iron recovered from the red cells is efficiently reutilized for hemoglobin synthesis. In contrast, with intravascular hemolysis or blood loss anemia, the rate of red cell production is limited by the amount of iron that can be mobilized from stores. Typically, the rate of mobilization under these circumstances will not support red cell production more than 2.5 times normal. If the delivery of iron to the stimulated marrow is suboptimal, the marrow's proliferative response is blunted, and hemoglobin synthesis is impaired. The result is a hypoproliferative marrow accompanied by microcytic, hypochromic anemia.

Whereas blood loss or hemolysis places a demand on the iron supply, inflammatory conditions interfere with iron release from stores and can result in a rapid decrease in the serum iron (see below).

NUTRITIONAL IRON BALANCE

The balance of iron in humans is tightly controlled and designed to conserve iron for reutilization. There is no regulated excretory pathway for iron, and the only mechanisms by which iron is lost are blood loss (via gastrointestinal bleeding, menses, or other forms of bleeding) and the loss of epithelial cells from the skin, gut, and genitourinary tract. Normally, the only route by which iron comes into the body is via absorption from food or from medicinal iron taken orally. Iron may also enter the body through red cell transfusions or injection of iron complexes. The margin between the amount of iron available for absorption and the requirement for iron in growing infants and the adult female is narrow; this accounts for the great prevalence of iron deficiency worldwide—currently estimated at more than one billion people.

The amount of iron required from the diet to replace losses averages ~10% of body iron content a year in men and 15% in women of childbearing age. Dietary iron content is closely related to total caloric intake (~6 mg of elemental iron per 1000 calories). Iron bioavailability is affected by the nature of the foodstuff, with heme iron (e.g., red meat) being most readily absorbed. In the United States, the average iron intake in an adult male is 15 mg/d with 6% absorption; for the average female, the intake is 11 mg/d with 12% absorption. An individual with iron deficiency can increase iron absorption to ~20% of the iron present in a meat-containing diet but only 5–10% of the iron in a vegetarian diet. As a result, one-third of the female population in the United States has virtually no iron stores. Vegetarians are at an additional disadvantage because certain foodstuffs that include phytates and phosphates reduce iron absorption by ~50%. When ionizable iron salts are given together with food, the amount of iron absorbed is reduced. When the percentage of iron absorbed from individual food items is compared with the percentage for an equivalent amount of ferrous salt, iron in vegetables is only about one-twentieth as available, egg iron one-eighth, liver iron one-half, and heme iron one-half to two-thirds.

Infants, children, and adolescents may be unable to maintain normal iron balance because of the demands of body growth and lower dietary intake of iron. During the last two trimesters of pregnancy, daily iron requirements increase to 5–6 mg, and iron supplements are strongly recommended for pregnant women in developed countries.

Iron absorption takes place largely in the duodenum and proximal small intestine and is a carefully regulated process. For absorption, iron must be taken up by the luminal cell. That process is facilitated by the acidic contents of the stomach, which maintains the iron in solution. At the brush border of the absorptive cell, the ferric iron is converted to the ferrous form by a ferrireductase. Transport across the membrane is accomplished by divalent metal transporter type 1 (DMT-1, also known as natural resistance macrophage-associated protein type 2 [Nramp 2] or DCT-1). DMT-1 is a general cation transporter. Once inside the gut cell, iron may be stored as ferritin or transported through the cell to be released at the basolateral surface to plasma transferrin through the membrane-embedded iron exporter, ferroportin. The function of ferroportin is negatively regulated by hepcidin, the principal iron regulatory hormone. In the process of release, iron interacts with another ferroxidase, hephaestin, which oxidizes the iron to the ferric form for transferrin binding. Hephaestin is similar to ceruloplasmin, the copper-carrying protein.

Iron absorption is influenced by a number of physiologic states. Erythroid hyperplasia stimulates iron absorption even in the face of normal or increased iron stores, and hepcidin levels are inappropriately low. Thus, patients with anemias associated with high levels of ineffective erythropoiesis absorb excess amounts of dietary iron. The molecular mechanism underlying this is the production of erythroferrone *(ERFE)* by developing erythroblasts. ERFE suppresses hepcidin production and, over time, this may lead to iron overload and tissue damage. In iron deficiency, hepcidin levels are also low and iron is much more efficiently absorbed; the contrary is true in states of secondary iron overload. The normal individual can reduce iron absorption in situations of excessive intake or medicinal iron intake; however, while the percentage of iron absorbed goes down, the absolute amount goes up. This accounts for the acute iron toxicity occasionally seen when children ingest large numbers of iron tablets. Under these circumstances, the amount of iron absorbed exceeds the transferrin binding capacity of the plasma, resulting in free iron that affects critical organs such as cardiac muscle cells.

IRON-DEFICIENCY ANEMIA

Iron deficiency is one of the most prevalent forms of malnutrition. Globally, 50% of anemia is attributable to iron deficiency and accounts for approximately nearly a million deaths annually worldwide. Africa and parts of Asia bear 71% of the global mortality burden; North America represents only 1.4% of the total morbidity and mortality associated with iron deficiency.

STAGES OF IRON DEFICIENCY

The progression to iron deficiency can be divided into three stages **(Fig. 93-2)**. The first stage is *negative iron balance*, in which the demands for (or losses of) iron exceed the body's ability to absorb iron from the diet. This stage results from a number of physiologic mechanisms, including blood loss, pregnancy (in which the demands for red cell production by the fetus outstrip the mother's ability to provide iron), rapid growth spurts in the adolescent, or inadequate dietary iron intake. Blood loss in excess of 10–20 mL of red cells per day is greater than

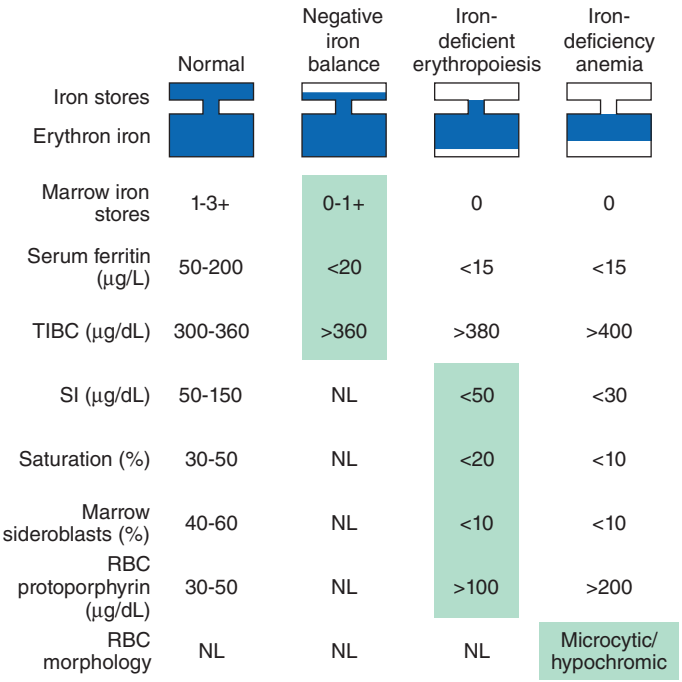

FIGURE 93-2 Laboratory studies in the evolution of iron deficiency. Measurements of marrow iron stores, serum ferritin, and total iron-binding capacity (TIBC) are sensitive to early iron-store depletion. Iron-deficient erythropoiesis is recognized from additional abnormalities in the serum iron (SI), percent transferrin saturation, the pattern of marrow sideroblasts, and the red blood cell (RBC) protoporphyrin level. Patients with iron-deficiency anemia demonstrate all the same abnormalities plus hypochromic microcytic anemia. *(From RS Hillman, CA Finch: The Red Cell Manual, 7th ed. Philadelphia, F.A. Davis and Co, 1996, with permission.)*

the amount of iron that the gut can absorb from a normal diet. Under these circumstances, the iron deficit must be made up by mobilization of iron from RE storage sites. During this period, iron stores—reflected by the serum ferritin level or the appearance of stainable iron on bone marrow aspirations—decrease. As long as iron stores are present and can be mobilized, the serum iron, total iron-binding capacity (TIBC), and red cell protoporphyrin levels remain within normal limits. At this stage, red cell morphology and indices are normal.

When iron stores become depleted, the serum iron begins to fall. Gradually, the TIBC increases, as do red cell protoporphyrin levels. By definition, marrow iron stores are absent when the serum ferritin level is <15 μg/L. As long as the serum iron remains within the normal range, hemoglobin synthesis is unaffected despite the dwindling iron stores. Once the transferrin saturation falls to 15–20%, hemoglobin synthesis becomes impaired. This is a period of *iron-deficient erythropoiesis*. Careful evaluation of the peripheral blood smear reveals the first appearance of microcytic cells, and if the laboratory technology is available, one finds hypochromic reticulocytes in circulation. Gradually, the hemoglobin begins to fall, reflecting *iron-deficiency anemia*. The transferrin saturation at this point is <10–15%.

When moderate anemia is present (hemoglobin 10–13 g/dL), the bone marrow remains hypoproliferative. With more severe anemia (hemoglobin 7–8 g/dL), hypochromia and microcytosis become more prominent, target cells and misshapen red cells (poikilocytes) appear on the blood smear as cigar- or pencil-shaped forms, and the erythroid marrow becomes increasingly ineffective. Consequently, with severe prolonged iron-deficiency anemia, erythroid hyperplasia of the marrow develops, rather than hypoproliferation.

CAUSES OF IRON DEFICIENCY

Conditions that increase demand for iron, increase iron loss, or decrease iron intake or absorption can produce iron deficiency **(Table 93-2)**.

CLINICAL PRESENTATION OF IRON DEFICIENCY

Certain clinical conditions carry an increased likelihood of iron deficiency. Pregnancy, adolescence, periods of rapid growth, and an intermittent history of blood loss of any kind should alert the clinician to possible iron deficiency. A cardinal rule is that the appearance of iron deficiency in an adult male or post-menopausal female means gastrointestinal blood loss until proven otherwise. Signs related to iron deficiency depend on the severity and chronicity of the anemia in addition to the usual signs of anemia—fatigue, pallor, and reduced exercise capacity. *Cheilosis* (fissures at the corners of the mouth) and *koilonychia* (spooning of the fingernails) are signs of advanced tissue iron deficiency. The diagnosis of iron deficiency is typically based on laboratory results.

TABLE 93-2 Causes of Iron Deficiency

Increased Demand for Iron
Rapid growth in infancy or adolescence
Pregnancy
Erythropoietin therapy
Increased Iron Loss
Chronic blood loss
Menses
Acute blood loss
Blood donation
Phlebotomy as treatment for polycythemia vera
Decreased Iron Intake or Absorption
Inadequate diet
Malabsorption from disease (sprue, Crohn's disease)
Malabsorption from surgery (gastrectomy and some forms of bariatric surgery)
Acute or chronic inflammation

LABORATORY IRON STUDIES

Serum Iron and Total Iron-Binding Capacity The serum iron level represents the amount of circulating iron bound to transferrin. The TIBC is an indirect measure of the circulating transferrin. The normal range for the serum iron is 50–150 μg/dL; the normal range for TIBC is 300–360 μg/dL. Transferrin saturation, which is normally 25–50%, is obtained by the following formula: serum iron × 100 ÷ TIBC. Iron-deficiency states are associated with saturation levels <20%. There is a diurnal variation in the serum iron. A transferrin saturation >50% indicates that a disproportionate amount of the iron bound to transferrin is being delivered to nonerythroid tissues. If this persists for an extended time, tissue iron overload may occur.

Serum Ferritin Free iron is toxic to cells, and the body has established an elaborate set of protective mechanisms to bind iron in various tissue compartments. Within cells, iron is stored complexed to protein as ferritin or hemosiderin. Apoferritin binds to free ferrous iron and stores it in the ferric state. As ferritin accumulates within cells of the RE system, protein aggregates are formed as hemosiderin. Iron in ferritin or hemosiderin can be extracted for release by the RE cells, although hemosiderin is less readily available. Under steady-state conditions, the serum ferritin level correlates with total body iron stores; thus, the serum ferritin level is the most convenient laboratory test to estimate iron stores. The normal value for ferritin varies according to the age and gender of the individual **(Fig. 93-3)**. Adult males have serum ferritin values averaging 100 μg/L, while adult females have levels averaging 30 μg/L. As iron stores are depleted, the serum ferritin falls to <15 μg/L. Such levels are diagnostic of absent body iron stores.

Evaluation of Bone Marrow Iron Stores Although RE iron stores can be estimated from the iron stain of a bone marrow aspirate or biopsy, the measurement of serum ferritin has largely supplanted these procedures for determination of storage iron **(Table 93-3)**. The serum ferritin level is a better indicator of iron overload than the marrow iron stain. However, in addition to storage iron, the marrow iron stain provides information about the effective delivery of iron to developing erythroblasts. Normally, when the marrow smear is stained for iron, 20–40% of developing erythroblasts—called *sideroblasts*—will

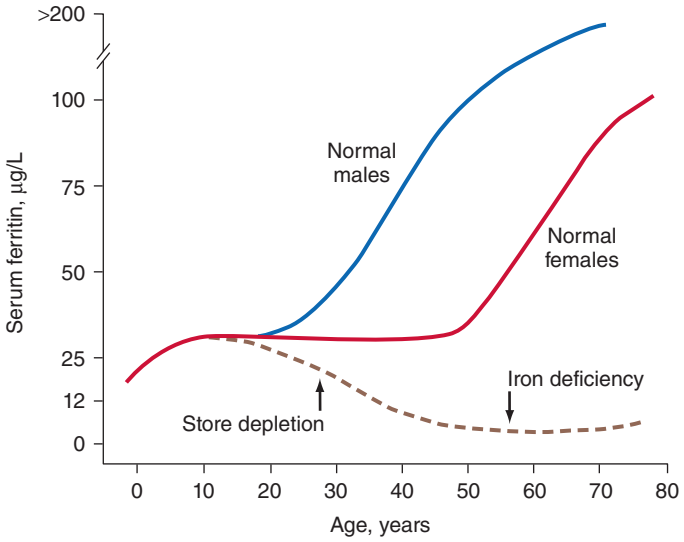

FIGURE 93-3 Serum ferritin levels as a function of sex and age. Iron store depletion and iron deficiency are accompanied by a decrease in serum ferritin level below 20 µg/L. *(From RS Hillman et al: Hematology in Clinical Practice, 5th ed. New York, McGraw-Hill, 2011, with permission.)*

have visible ferritin granules in their cytoplasm. This represents iron in excess of that needed for hemoglobin synthesis. In states in which release of iron from storage sites is blocked, RE iron will be detectable, and there will be few or no sideroblasts. In the myelodysplastic syndromes, mitochondrial dysfunction can occur, and accumulation of iron in mitochondria appears in a necklace fashion around the nucleus of the erythroblast. Such cells are referred to as *ring sideroblasts*.

Red Cell Protoporphyrin Levels Protoporphyrin is an intermediate in the pathway to heme synthesis. Under conditions in which heme synthesis is impaired, protoporphyrin accumulates within the red cell. This reflects an inadequate iron supply to erythroid precursors to support hemoglobin synthesis. Normal values are <30 µg/dL of red cells. In iron deficiency, values >100 µg/dL are seen. The most common causes of increased red cell protoporphyrin levels are absolute or relative iron deficiency and lead poisoning.

Serum Levels of Transferrin Receptor Protein Because erythroid cells have the highest numbers of transferrin receptors of any cell in the body, and because transferrin receptor protein (TRP) is released by cells into the circulation, serum levels of TRP reflect the total erythroid marrow mass. Another condition in which TRP levels are elevated is absolute iron deficiency. Normal values are 4–9 µg/L determined by immunoassay. This laboratory test is becoming increasingly available and, along with the serum ferritin, has been proposed to distinguish between iron deficiency and the anemia of inflammation (see below).

DIFFERENTIAL DIAGNOSIS

Other than iron deficiency, only three conditions need to be considered in the differential diagnosis of a hypochromic microcytic anemia **(Table 93-4)**. The first is an inherited defect in globin chain synthesis: the thalassemias. These are differentiated from iron deficiency most readily by serum iron values; normal or increased serum iron levels and transferrin saturation are characteristic of the thalassemias. In addition, the red blood cell distribution width (RDW) index is generally normal in thalassemia and elevated in iron deficiency.

The second condition is the anemia of inflammation (AI; also referred to as the anemia of chronic disease) with inadequate iron supply to the erythroid marrow. The distinction between true iron-deficiency anemia and AI is among the most common diagnostic problems encountered by clinicians (see below). Usually, AI is normocytic and normochromic. The iron values usually make the differential diagnosis clear, as the ferritin level is normal or increased and the percent transferrin saturation and TIBC are typically below normal.

Finally, the myelodysplastic syndromes represent the third and least common condition. Occasionally, patients with myelodysplasia have impaired hemoglobin synthesis with mitochondrial dysfunction, resulting in impaired iron incorporation into heme. The iron values again reveal normal stores and more than an adequate supply to the marrow, despite the microcytosis and hypochromia.

TABLE 93-3 Iron Store Measurements

IRON STORES	MARROW IRON STAIN, 0–4+	SERUM FERRITIN, µg/L
0	0	<15
1–300 mg	Trace to 1+	15–30
300–800 mg	2+	30–60
800–1000 mg	3+	60–150
1–2 g	4+	>150
Iron overload	—	>500–1000

TREATMENT

Iron-Deficiency Anemia

The severity and cause of iron-deficiency anemia will determine the appropriate approach to treatment. As an example, symptomatic elderly patients with severe iron-deficiency anemia and cardiovascular instability may require red cell transfusions. Younger individuals who have compensated for their anemia can be treated more conservatively with iron replacement. The foremost issue for the latter patient is the precise identification of the cause of the iron deficiency.

For the majority of cases of iron deficiency (pregnant women, growing children and adolescents, patients with infrequent episodes of bleeding, and those with inadequate dietary intake of iron), oral iron therapy will suffice. For patients with unusual blood loss or malabsorption, specific diagnostic tests and appropriate therapy take priority. Once the diagnosis of iron-deficiency anemia and its cause is made, there are three major therapeutic approaches.

RED CELL TRANSFUSION

Transfusion therapy is reserved for individuals who have symptoms of anemia, cardiovascular instability, and continued and excessive blood loss from whatever source and who require immediate intervention. The management of these patients is less related to the iron deficiency than it is to the consequences of the severe anemia. Not only do transfusions correct the anemia acutely, but the transfused red cells provide a source of iron for reutilization, assuming they are not lost through continued bleeding. Transfusion therapy will stabilize the patient while other options are reviewed.

ORAL IRON THERAPY

In the asymptomatic patient with established iron-deficiency anemia and an intact gastrointestinal tract, treatment with oral iron is usually adequate. Multiple preparations are available, ranging from simple iron salts to complex iron compounds designed for sustained release throughout the small intestine **(Table 93-5)**. Although the various preparations contain different amounts of iron, they are generally all absorbed well and are effective in treatment. Some come with other compounds designed to enhance iron absorption, such as ascorbic acid. It is not clear whether the benefits of such compounds justify their costs. Typically, for iron replacement therapy, up to 200 mg of elemental iron per day is given, usually as three or four iron tablets (each containing 50–65 mg elemental iron) given over the course of the day. Ideally, oral iron preparations should be taken on an empty stomach, since food may inhibit iron absorption. Some patients with gastric disease or prior gastric surgery require special treatment with iron solutions because the retention capacity of the stomach may be reduced. The retention capacity is necessary for dissolving the shell of the iron tablet before the release of iron. A dose of 200 mg of elemental iron per day should result in the absorption of iron up to 50 mg/d. This supports a red cell production level of

TABLE 93-4 Diagnosis of Microcytic Anemia

TESTS	IRON DEFICIENCY	INFLAMMATION	THALASSEMIA	SIDEROBLASTIC ANEMIA
Smear	Micro/hypo	Normal micro/hypo	Micro/hypo with targeting	Variable
Serum iron (μg/dL)	<30	<50	Normal to high	Normal to high
TIBC (μg/dL)	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (μg/L)	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with β thalassemia; can be normal with α thalassemia	Normal

Abbreviation: TIBC, total iron-binding capacity.

two to three times normal in an individual with a normally functioning marrow and appropriate erythropoietin stimulus. However, as the hemoglobin level rises, erythropoietin stimulation decreases, and the amount of iron absorbed is reduced. The goal of therapy in individuals with iron-deficiency anemia is not only to repair the anemia, but also to provide stores of at least 0.5–1 g of iron. Sustained treatment for a period of 6–12 months after correction of the anemia will be necessary to achieve this.

Of the complications of oral iron therapy, gastrointestinal distress is the most prominent and is seen in at least 15–20% of patients. Abdominal pain, nausea, vomiting, or constipation may lead to noncompliance. Although small doses of iron or iron preparations with delayed release may help somewhat, the gastrointestinal side effects are a major impediment to the effective treatment of a number of patients.

The response to iron therapy varies, depending on the erythropoietin stimulus and the rate of absorption. Typically, the reticulocyte count should begin to increase within 4–7 days after initiation of therapy and peak at 1–1½ weeks. The absence of a response may be due to poor absorption, noncompliance (which is common), or a confounding diagnosis. A useful test in the clinic to determine the patient's ability to absorb iron is the *iron tolerance test*. Two iron tablets are given to the patient on an empty stomach, and the serum iron is measured serially over the subsequent 2–3 h. Normal absorption will result in an increase in the serum iron of at least 100 μg/dL. If iron deficiency persists despite adequate treatment, it may be necessary to switch to parenteral iron therapy.

PARENTERAL IRON THERAPY

Intravenous iron can be given to patients who are unable to tolerate oral iron; whose needs are relatively acute; or who need iron on an ongoing basis, usually due to persistent gastrointestinal or menstrual blood loss. Parenteral iron use has been increasing rapidly in the last several years with the recognition that recombinant erythropoietin (EPO) therapy induces a large demand for iron—a demand that frequently cannot be met through the physiologic release of iron from RE sources or oral iron absorption. The safety of parenteral iron has been a concern largely driven by the high adverse reaction rate to high-molecular-weight iron dextran. The newer iron complexes that are available, such as ferumoxytol (Feraheme), sodium ferric gluconate (Ferrlecit), iron sucrose (Venofer), low-molecular-weight (LMW) iron dextran (InFed), and ferric carboxymaltose (Injectafer), have much lower rates of adverse effects. Ferumoxytol delivers 510 mg of iron per injection; ferric gluconate 125 mg per injection; LMW iron dextran up to 1500 mg; ferric carboxymaltose 750 mg per injection and iron sucrose 200 mg per injection.

Parenteral iron is used in two ways: one is to administer the total dose of iron required to correct the hemoglobin deficit and provide the patient with at least 500 mg of iron stores; the second is to give repeated small doses of parenteral iron over a protracted period. The latter approach is common in dialysis centers, where it is not unusual for 100 mg of elemental iron to be given weekly for 10 weeks to augment the response to recombinant EPO therapy. The amount of iron needed by an individual patient is calculated by the following formula:

$$\text{Body weight (kg)} \times 2.3 \times (15 - \text{patient's hemoglobin, g/dL}) + 500 \text{ or } 1000 \text{ mg (for stores)}.$$

In administering any intravenous iron preparation, anaphylaxis is a concern. Anaphylaxis is much rarer with the newer preparations. The factors that have correlated with an anaphylactic-like reaction include a history of multiple allergies or a prior allergic reaction to an iron preparation. Generalized symptoms appearing several days after the infusion of a large dose of iron can include arthralgias, skin rash, and low-grade fever. These may be dose-related, but they do not preclude the further use of parenteral iron in the patient. To date, patients with sensitivity to one iron preparation have been safely treated with other parenteral iron preparations. If a large dose of LMW iron dextran is to be given (>100 mg), the iron preparation should be diluted in 5% dextrose in water or 0.9% NaCl solution. The iron solution can then be infused over a 60- to 90-min period (for larger doses) or at a rate convenient for the attending nurse or physician. Although a test dose (25 mg) of parenteral LMW iron dextran is recommended, in reality a slow infusion of a larger dose of parenteral iron solution will afford the same kind of early warning as a separately injected test dose. Early in the infusion of iron, if chest pain, wheezing, a fall in blood pressure, or other systemic symptoms occur, the infusion of iron should be stopped immediately.

TABLE 93-5 Oral Iron Preparations

GENERIC NAME	TABLET (IRON CONTENT), mg	ELIXIR (IRON CONTENT), mg in 5 mL
Ferrous sulfate	325 (65) 195 (39)	300 (60) 90 (18)
Extended release	525 (105)	
Ferrous fumarate	325 (107) 195 (64)	 100 (33)
Ferrous gluconate	325 (39)	300 (35)
Polysaccharide iron	150 (150) 50 (50)	100 (100)

OTHER HYPOPROLIFERATIVE ANEMIAS

In addition to mild to moderate iron-deficiency anemia, the hypoproliferative anemias can be divided into four categories: (1) chronic inflammation, (2) renal disease, (3) endocrine and nutritional deficiencies (hypometabolic states), and (4) marrow damage (Chap. 98). With chronic inflammation, renal disease, or hypometabolism, endogenous EPO production is inadequate for the degree of anemia observed. For the anemia of chronic inflammation, the erythroid marrow also responds inadequately to stimulation, due in part to defective *iron reutilization*. As a result of the lack of adequate EPO stimulation, an examination of the peripheral blood smear will disclose only an occasional polychromatophilic ("shift") reticulocyte. In cases of iron deficiency or marrow damage, appropriate elevations in endogenous EPO levels are typically found, and shift reticulocytes will be present on the blood smear.

ANEMIA OF ACUTE AND CHRONIC INFLAMMATION/INFECTION (AI)

AI—which encompasses inflammation, infection, tissue injury, and conditions (such as cancer) associated with the release of proinflammatory

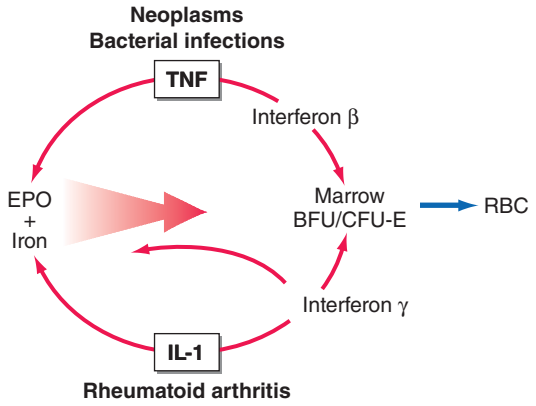

FIGURE 93-4 Suppression of erythropoiesis by inflammatory cytokines. Through the release of tumor necrosis factor (TNF) and interferon β (IFN-β), neoplasms and bacterial infections suppress erythropoietin (EPO) production and the proliferation of erythroid progenitors (erythroid burst-forming units and erythroid colony-forming units [BFU/CFU-E]). The mediators in patients with vasculitis and rheumatoid arthritis include interleukin 1 (IL-1) and IFN-γ. The *red arrows* indicate sites of inflammatory cytokine inhibitory effects. RBC, red blood cell.

cytokines—is one of the most common forms of anemia seen clinically. It is the most important anemia in the differential diagnosis of iron deficiency because many of the features of the anemia are brought about by inadequate iron delivery to the marrow, despite the presence of normal or increased iron stores. This is reflected by a low serum iron, increased red cell protoporphyrin, a hypoproliferative marrow, transferrin saturation in the range of 15–20%, and a normal or increased serum ferritin. The serum ferritin values are often the most distinguishing features between true iron-deficiency anemia and the iron-restricted erythropoiesis associated with inflammation. Typically, serum ferritin values increase threefold over basal levels in the face of inflammation. These changes are due to the effects of inflammatory cytokines and hepcidin, the key iron regulatory hormone, acting at several levels of erythropoiesis **(Fig. 93-4)**.

Interleukin 1 (IL-1) directly decreases EPO production in response to anemia. IL-1, acting through accessory cell release of interferon γ (IFN-γ), suppresses the response of the erythroid marrow to EPO—an effect that can be overcome by EPO administration in vitro and in vivo. In addition, tumor necrosis factor (TNF), acting through the release of IFN-β by marrow stromal cells, also suppresses the response to EPO. Hepcidin, made by the liver, is increased in inflammation via an IL-6 mediated pathway, and acts to suppress iron absorption and iron release from storage sites. The overall result is a chronic hypoproliferative anemia with classic changes in iron metabolism. The anemia is further compounded by a mild to moderate shortening in red cell survival.

With chronic inflammation, the primary disease will determine the severity and characteristics of the anemia. For example, many patients with cancer also have anemia that is typically normocytic and normochromic. In contrast, patients with long-standing active rheumatoid arthritis or chronic infections such as tuberculosis will have a microcytic, hypochromic anemia. In both cases, the bone marrow is hypoproliferative, but the differences in red cell indices reflect differences in the availability of iron for hemoglobin synthesis. Occasionally, conditions associated with chronic inflammation are also associated with chronic blood loss. Under these circumstances, the measurement of soluble transferrin protein may be necessary to rule out absolute iron deficiency. However, the administration of iron in this case will correct the iron deficiency component of the anemia and leave the inflammatory component unaffected.

The anemia associated with acute infection or inflammation is typically mild but becomes more pronounced over time. Acute infection can produce a decrease in hemoglobin levels of 2–3 g/dL within 1 or 2 days; this is largely related to the hemolysis of red cells near the end of their natural life span. The fever and cytokines released exert a selective pressure against cells with more limited capacity to maintain the red cell membrane. In most individuals, the mild anemia is reasonably well tolerated, and symptoms, if present, are associated with the underlying disease. Occasionally, in patients with preexisting cardiac disease, moderate anemia (hemoglobin 10–11 g/dL) may be associated with angina, exercise intolerance, and shortness of breath. The erythropoietic profile that distinguishes the anemia of inflammation from the other causes of hypoproliferative anemias is shown in **Table 93-6**.

ANEMIA OF CHRONIC KIDNEY DISEASE (CKD)

Progressive CKD is usually associated with a moderate to severe hypoproliferative anemia; the level of the anemia correlates with the stage of CKD. Red cells are typically normocytic and normochromic, and reticulocytes are decreased. The anemia is primarily due to a failure of EPO production by the diseased kidney and a reduction in red cell survival. In certain forms of acute renal failure, the correlation between the anemia and renal function is weaker. Patients with the hemolytic-uremic syndrome increase erythropoiesis in response to the hemolysis, despite renal failure. Polycystic kidney disease also shows a smaller degree of EPO deficiency for a given level of renal failure. By contrast, patients with diabetes or myeloma have more severe EPO deficiency for a given level of renal failure.

Assessment of iron status provides information to distinguish the anemia of CKD from the other forms of hypoproliferative anemia (Table 93-6) and to guide management. Patients with the anemia of CKD usually present with normal serum iron, TIBC, and ferritin levels. However, those maintained on chronic hemodialysis may develop iron deficiency from blood loss through the dialysis procedure. Iron must be replenished in these patients to ensure an adequate response to EPO therapy (see below).

ANEMIA IN HYPOMETABOLIC STATES

Patients who are starving, particularly for protein, and those with a variety of endocrine disorders that produce lower metabolic rates, may develop a mild to moderate hypoproliferative anemia. The release of EPO from the kidney is sensitive to the need for O_2, not just O_2 levels. Thus, EPO production is triggered at lower levels of blood O_2 content in disease states (such as hypothyroidism and starvation) where metabolic activity, and thus O_2 demand, is decreased.

Endocrine Deficiency States The difference in the levels of hemoglobin between men and women is related to the effects of androgen and estrogen on erythropoiesis. Testosterone and anabolic steroids augment erythropoiesis; castration and estrogen administration to males decrease erythropoiesis. Patients who are hypothyroid or have deficits in pituitary hormones also may develop a mild anemia. Pathogenesis may be complicated by other nutritional deficiencies because iron and folic acid absorption can be affected by these disorders. Usually, correction of the hormone deficiency reverses the anemia.

Anemia may be more severe in Addison's disease, depending on the level of thyroid and androgen hormone dysfunction; however, anemia

TABLE 93-6 Diagnosis of Hypoproliferative Anemias

TESTS	IRON DEFICIENCY	INFLAMMATION	RENAL DISEASE	HYPOMETABOLIC STATES
Anemia	Mild to severe	Mild	Mild to severe	Mild
MCV (fL)	60–90	80–90	90	90
Morphology	Normo-microcytic	Normocytic	Normocytic	Normocytic
SI (μg/dL)	<30	<50	Normal	Normal
TIBC (μg/dL)	>360	<300	Normal	Normal
Saturation (%)	<10	10–20	Normal	Normal
Serum ferritin (μg/L)	<15	30–200	115–150	Normal
Iron stores	0	2–4+	1–4+	Normal

Abbreviations: MCV, mean corpuscular volume; SI, serum iron; TIBC, total iron-binding capacity.

may be masked by decreases in plasma volume. Once such patients are given cortisol and volume replacement, the hemoglobin level may fall rapidly. Mild anemia complicating hyperparathyroidism may be due to decreased EPO production as a consequence of the renal effects of hypercalcemia or to impaired proliferation of erythroid progenitors.

Protein Starvation Decreased dietary intake of protein may lead to mild to moderate hypoproliferative anemia; this form of anemia may be prevalent in the elderly. The anemia can be more severe in patients with a greater degree of starvation. In marasmus, where patients are both protein- and calorie-deficient, the release of EPO is impaired in proportion to the reduction in metabolic rate; however, the degree of anemia may be masked by volume depletion and becomes apparent after refeeding. Deficiencies in other nutrients (iron, folate) may also complicate the clinical picture but may not be apparent at diagnosis. Changes in the erythrocyte indices on refeeding should prompt evaluation of iron, folate, and B_{12} status.

Anemia in Liver Disease A mild hypoproliferative anemia may develop in patients with chronic liver disease from nearly any cause. The peripheral blood smear may show spur cells and stomatocytes from the accumulation of excess cholesterol in the membrane from a deficiency of lecithin-cholesterol acyltransferase. Red cell survival is shortened, and the production of EPO is inadequate to compensate. In alcoholic liver disease, nutritional deficiencies are common and complicate the management. Folate deficiency from inadequate intake, as well as iron deficiency from blood loss and inadequate intake, can alter the red cell indices.

ANEMIA IN AGING

Anemia is common in people over age 65 years. It has been estimated to affect about 11% of community living older adults and up to 40% of nursing home residents. In at least one-third of these anemic people, a cause for the anemia is not found. Patients with the unexplained anemia of aging do not have nutrient deficiency or renal dysfunction and while older people can have an increase in systemic inflammatory cytokines (the inflammation of aging), the levels are not high enough to mimic the anemia of chronic inflammation. If hepcidin levels are elevated at all, they are minimally so.

Investigations into the cause(s) of this form of anemia have noted that erythropoietin levels are generally in the normal range, that is, they are inappropriately low for the hemoglobin level. In general, in older people who maintain a normal hemoglobin level, erythropoietin levels increase with age. This compensatory increase to maintain normal oxygen delivery seems to be due to a relative resistance to erythropoietin stimulation; studies of red cell life span in older people have not noted a decrease in red cell survival. More data on mechanism are needed.

The importance of this unexplained anemia of aging is that low hemoglobin levels are associated with increases in falls, hospitalizations, development of frailty, and mortality. It is not clear whether reversing the anemia would influence these increased risks.

TREATMENT

Hypoproliferative Anemias

Many patients with hypoproliferative anemias experience recovery of normal hemoglobin levels when the underlying disease is appropriately treated. For those in whom such reversals are not possible—such as patients with end-stage kidney disease, cancer, and chronic inflammatory diseases—symptomatic anemia requires treatment. The two major forms of treatment are transfusions and EPO.

TRANSFUSIONS

Thresholds for transfusion should be determined based on the patient's symptoms. In general, patients without serious underlying cardiovascular or pulmonary disease can tolerate hemoglobin levels above 7–8 g/dL and do not require intervention until the hemoglobin falls below that level. Patients with more physiologic compromise may need to have their hemoglobin levels kept above 11 g/dL. Usually, a unit of packed red cells increases the hemoglobin level by 1 g/dL. Transfusions are associated with certain infectious risks **(Chap. 109)**, and chronic transfusions can produce iron overload. Importantly, the liberal use of blood has been associated with increased morbidity and mortality, particularly in the intensive care setting. Therefore, in the absence of documented tissue hypoxia, a conservative approach to the use of red cell transfusions is preferable.

ERYTHROPOIETIN

EPO is particularly useful in anemias in which endogenous EPO levels are inappropriately low, such as CKD or AI. Iron status must be evaluated and iron replaced to obtain optimal effects from EPO. In patients with CKD, the usual dose of EPO is 50–150 U/kg three times a week intravenously. Hemoglobin levels of 10–12 g/dL are usually reached within 4–6 weeks if iron levels are adequate; 90% of these patients respond. Once a target hemoglobin level is achieved, the EPO dose can be decreased. A decrease in hemoglobin level occurring in the face of EPO therapy usually signifies the development of an infection or iron depletion. Aluminum toxicity and hyperparathyroidism can also compromise the response to EPO. When an infection intervenes, it is best to interrupt the EPO therapy and rely on transfusions to correct the anemia until the infection is adequately treated. The dose of EPO needed to correct chemotherapy-induced anemia in patients with cancer is higher, up to 300 U/kg three times a week, and only ~60% of patients respond. Because of evidence that there is an increased risk of thromboembolic complications and tumor progression with EPO administration, the risks and benefits of using EPO in such patients must be weighed carefully, and the target hemoglobin should be that necessary to avoid transfusions.

Longer-acting preparations of EPO can reduce the frequency of injections. Darbepoetin alfa, a molecularly modified EPO with additional carbohydrate, has a half-life in the circulation that is three to four times longer than recombinant human EPO, permitting weekly or every other week dosing.

Orally bioavailable EPO mimetics that act to increase the biological half-life of active hypoxia-induced factor (HIF) are demonstrating activity to increase hemoglobin levels in patients with chronic renal disease and other settings.

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94 Disorders of Hemoglobin

Edward J. Benz, Jr.

Hemoglobin is critical for normal oxygen delivery to tissues; it is also present in erythrocytes in such high concentrations that it can alter red cell shape, deformability, and viscosity. Hemoglobinopathies are disorders affecting the structure, function, or production of hemoglobin. These conditions are usually inherited and range in severity from asymptomatic laboratory abnormalities to death in utero. Different forms may present as ineffective erythropoiesis, hemolytic anemia, erythrocytosis, cyanosis, or vasoocclusive stigmata.

PROPERTIES OF THE HUMAN HEMOGLOBINS

HEMOGLOBIN STRUCTURE

Different hemoglobins are produced during embryonic, fetal, and adult life **(Fig. 94-1)**. Each consists of a tetramer of globin polypeptide chains: a pair of α-like chains 141 amino acids long and a pair of β-like chains 146 amino acids long. The major adult hemoglobin, HbA, has the structure $\alpha_2\beta_2$. HbF ($\alpha_2\gamma_2$) predominates during most of gestation, and HbA_2 ($\alpha_2\delta_2$) is minor adult hemoglobin. Embryonic hemoglobins need not be considered here.

Each globin chain enfolds a single heme moiety, consisting of a protoporphyrin IX ring complexed with a single iron atom in the ferrous state (Fe^{2+}). Each heme moiety can bind a single oxygen molecule; a molecule of hemoglobin can transport up to four oxygen molecules.

Each globin chain has a highly helical *secondary structure*. Their globular *tertiary structures* cause the exterior surfaces to be rich in polar (hydrophilic) amino acids that enhance solubility, and the interior to be lined with nonpolar groups, forming a hydrophobic pocket into which heme is inserted. The tetrameric *quaternary structure* of HbA contains two αβ dimers. Numerous tight interactions (i.e., $\alpha_1\beta_1$ contacts) hold the α and β chains together. The complete tetramer is held together by interfaces (i.e., $\alpha_1\beta_2$ contacts) between the α-like chain of one dimer and the non-α chain of the other dimer.

The hemoglobin tetramer is highly soluble, but individual globin chains are insoluble. Unpaired globin precipitates, forming inclusions that damage the erythroblast and can trigger apoptosis. Normal globin chain synthesis is balanced so that each newly synthesized α or non-α globin chain will have an available partner with which to pair.

Solubility and reversible oxygen binding are the key properties deranged in hemoglobinopathies. Both depend most on the hydrophilic surface amino acids, the hydrophobic amino acids lining the heme pocket, a key histidine in the F helix, and the amino acids forming the $\alpha_1\beta_1$ and $\alpha_1\beta_2$ contact points. Mutations in these strategic regions tend to be the ones that alter oxygen affinity or solubility.

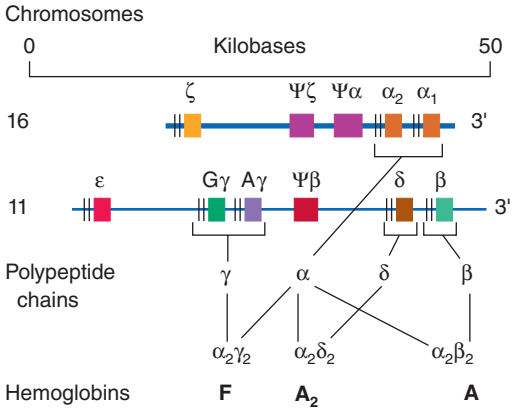

FIGURE 94-1 The globin genes. The α-like genes (α, ζ) are encoded on chromosome 16; the β-like genes (β, γ, δ, ε) are encoded on chromosome 11. The ζ and ε genes encode embryonic globins.

FUNCTION OF HEMOGLOBIN

To support oxygen transport, hemoglobin must bind O_2 efficiently at the partial pressure of oxygen (Po_2) of the alveolus, retain it in the circulation, and release it to tissues at the Po_2 of tissue capillary beds. Oxygen acquisition and delivery over a relatively narrow range of oxygen tensions depend on a property inherent in the tetrameric arrangement of heme and globin subunits within the hemoglobin molecule called *cooperativity* or *heme-heme interaction*.

At low oxygen tensions, the hemoglobin tetramer is fully deoxygenated **(Fig. 94-2)**. Oxygen binding begins slowly as O_2 tension rises. However, as soon as some oxygen has been bound by the tetramer, an abrupt increase occurs in the slope of the curve. Thus, hemoglobin molecules that have bound some oxygen develop a higher oxygen affinity, greatly accelerating their ability to combine with more oxygen. This S-shaped oxygen equilibrium curve (Fig. 94-2), along which substantial amounts of oxygen loading *and unloading* can occur over a narrow range of oxygen tensions, is physiologically more useful than the high-affinity hyperbolic curve of individual monomers.

Oxygen affinity is modulated by several factors. The Bohr effect is the ability of hemoglobin to deliver more oxygen to tissues at low pH. It arises from the stabilizing action of protons on deoxyhemoglobin, which binds protons more readily than oxyhemoglobin because the latter is a weaker acid (Fig. 94-2). Thus, hemoglobin has a lower oxygen affinity at low pH. The major small molecule that alters oxygen affinity in humans is 2,3-bisphosphoglycerate (2,3-BPG; formerly 2,3-DPG), which lowers oxygen affinity when bound to hemoglobin. HbA has a reasonably high affinity for 2,3-BPG. HbF does not bind 2,3-BPG, so it tends to have a higher oxygen affinity in vivo. Hemoglobin also binds nitric oxide reversibly; this interaction influences vascular tone, but its clinical relevance remains incompletely understood. Normal oxygen transport thus depends on the tetrameric structure of the proteins, the proper arrangement of hydrophilic and hydrophobic amino acids, and interaction with protons or 2,3-BPG.

DEVELOPMENTAL BIOLOGY OF HUMAN HEMOGLOBINS

Red cells, first appearing at about 6 weeks after conception, contain the embryonic hemoglobins Hb Portland ($\zeta_2\gamma_2$), Hb Gower I ($\zeta_2\varepsilon_2$), and Hb Gower II ($\alpha_2\varepsilon_2$). At 10–11 weeks, fetal hemoglobin (HbF; $\alpha_2\gamma_2$) becomes predominant. The switch to nearly exclusive synthesis of adult hemoglobin (HbA; $\alpha_2\beta_2$) occurs at about 38 weeks (Fig. 94-1). Fetuses and newborns therefore require α-globin but not β-globin for normal gestation. A major advance in understanding the HbF to HbA transition has been the demonstration that transcription factors such as Bcl11a play a pivotal role in its regulation, and that access to these factors depend on complex chromatin changes that render accessible binding sites for these factors. These "looping out" phenomena are in turn dependent on multiple protein factors.

Small amounts of HbF are produced during postnatal life. A few red cell clones called *F cells* are progeny of a small pool of immature committed erythroid precursors (BFU-e) that retain the ability to produce HbF. Profound erythroid stresses, such as severe hemolytic anemias, bone marrow transplantation, or cancer chemotherapy, cause more of the F-potent BFU-e to be recruited. HbF levels thus tend to rise in some patients with sickle cell anemia or thalassemia. This phenomenon probably explains the ability of hydroxyurea to increase levels of HbF in adults. Agents such as butyrate and histone deacetylase inhibitors can also activate fetal globin genes partially after birth.

GENETICS AND BIOSYNTHESIS OF HUMAN HEMOGLOBIN

The human hemoglobins are encoded in two tightly linked gene clusters; the α-like globin genes are clustered on chromosome 16 and the β-like genes on chromosome 11 (Fig. 94-1). The α-like cluster consists of two α-globin genes and a single copy of the ζ gene. The non-α gene cluster consists of a single ε gene, the Gγ and Aγ fetal globin genes, and the adult δ and β genes.

Important regulatory sequences flank each gene. Immediately upstream are typical promoter elements needed for the assembly of the

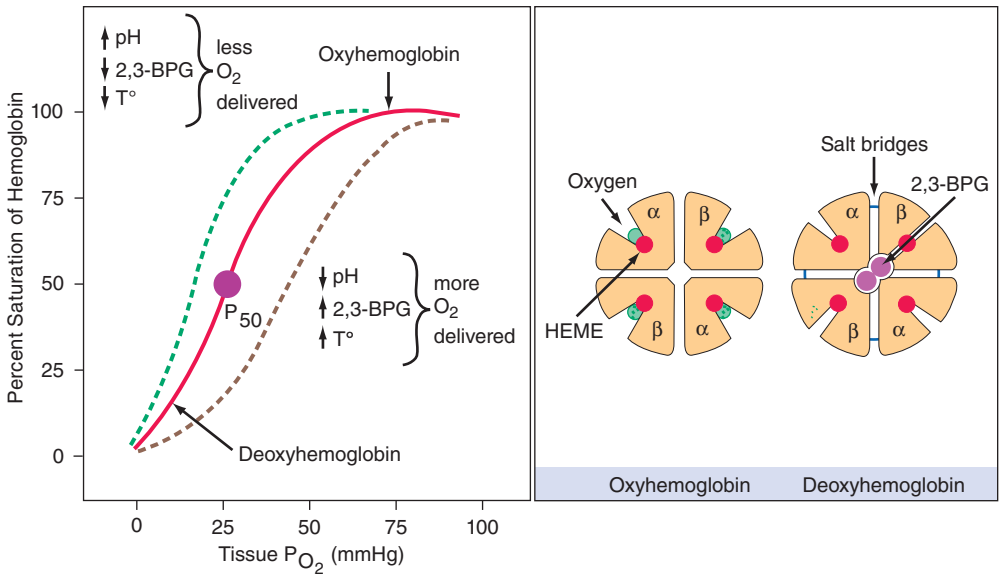

FIGURE 94-2 Hemoglobin-oxygen dissociation curve. The hemoglobin tetramer can bind up to four molecules of oxygen in the iron-containing sites of the heme molecules. As oxygen is bound, 2,3-bisphosphoglycerate (2,3-BPG) and carbon dioxide (CO_2) are expelled. Salt bridges are broken, and each of the globin molecules changes its conformation to facilitate oxygen binding. Oxygen release to the tissues is the reverse process, with salt bridges being formed and 2,3-BPG and CO_2 bound. Deoxyhemoglobin does not bind oxygen efficiently until the cell returns to conditions of higher pH, the most important modulator of O_2 affinity (Bohr effect). When acid is produced in the tissues, the dissociation curve shifts to the right, facilitating oxygen release and CO_2 binding. Alkalosis has the opposite effect, reducing oxygen delivery.

transcription initiation complex. Sequences in the 5′ flanking region of the γ and the β genes appear to be crucial for the correct developmental regulation of these genes, whereas elements that function like classic enhancers and silencers are in the 3′ flanking regions. The locus control region (LCR) elements located far upstream appear to control the overall level of expression of each cluster. These elements achieve their regulatory effects by interacting with *trans*-acting transcription factors. Some of these factors are ubiquitous (e.g., Sp1 and YY1), while others are more or less limited to erythroid cells or hematopoietic cells (e.g., GATA-1, NFE-2, and EKLF). The LCR controlling the α-globin gene cluster is modulated by a SWI/SNF-like protein called *ATRX*; this protein appears to influence chromatin remodeling and DNA methylation. The association of α thalassemia with mental retardation and myelodysplasia in some families appears to be related to mutations in the ATRX pathway. This pathway also modulates genes specifically expressed during erythropoiesis, such as those that encode the enzymes for heme biosynthesis. Normal red blood cell (RBC) differentiation requires the coordinated expression of the globin genes with the genes responsible for heme and iron metabolism. RBC precursors contain a protein, α-hemoglobin-stabilizing protein (AHSP), that enhances the folding and solubility of α globin, which is otherwise easily denatured, leading to insoluble precipitates. These precipitates play an important role in the thalassemia syndromes and certain unstable hemoglobin disorders.

CLASSIFICATION OF HEMOGLOBINOPATHIES

There are five major classes of hemoglobinopathies **(Table 94-1)**. *Structural hemoglobinopathies* occur when mutations alter the amino acid sequence of a globin chain, altering the physiologic properties of the variant hemoglobins and producing the characteristic clinical abnormalities. The most clinically relevant variant hemoglobins polymerize abnormally, as in sickle cell anemia, or exhibit altered solubility or oxygen-binding affinity. *Thalassemia syndromes* arise from mutations that impair production or translation of globin mRNA, leading to deficient globin chain biosynthesis. Clinical abnormalities are attributable to the inadequate supply of hemoglobin and the imbalances in the production of individual globin chains, leading to premature destruction of erythroblasts and RBC. *Thalassemic hemoglobin variants* combine features of thalassemia (i.e., abnormal globin biosynthesis) and of structural hemoglobinopathies (i.e., an abnormal amino acid sequence). *Hereditary persistence of fetal hemoglobin* (HPFH) is characterized by synthesis of high levels of fetal hemoglobin in adult life. *Acquired hemoglobinopathies* include modifications of the hemoglobin molecule by toxins (e.g., acquired methemoglobinemia) and clonal abnormalities of hemoglobin synthesis (e.g., high levels of HbF production in preleukemia and α thalassemia in myeloproliferative disorders).

EPIDEMIOLOGY

Hemoglobinopathies are especially common in areas in which malaria is endemic. This clustering of hemoglobinopathies is assumed to reflect a selective survival advantage for the abnormal RBC, which presumably provides a less hospitable environment

TABLE 94-1 Classification of Hemoglobinopathies

I. Structural hemoglobinopathies—hemoglobins with altered amino acid sequences that result in deranged function or altered physical or chemical properties
  A. Abnormal hemoglobin polymerization—HbS, hemoglobin sickling
  B. Altered O_2 affinity
    1. High affinity—polycythemia
    2. Low affinity—cyanosis, pseudoanemia
  C. Hemoglobins that oxidize readily
    1. Unstable hemoglobins—hemolytic anemia, jaundice
    2. M hemoglobins—methemoglobinemia, cyanosis
II. Thalassemias—defective biosynthesis of globin chains
  A. α thalassemias
  B. β thalassemias
  C. δβ, γδβ, αβ thalassemias
III. Thalassemic hemoglobin variants—structurally abnormal Hb associated with coinherited thalassemic phenotype
  A. HbE
  B. Hb Constant Spring
  C. Hb Lepore
IV. Hereditary persistence of fetal hemoglobin—persistence of high levels of HbF into adult life
V. Acquired hemoglobinopathies
  A. Methemoglobin due to toxic exposures
  B. Sulfhemoglobin due to toxic exposures
  C. Carboxyhemoglobin
  D. HbH in erythroleukemia
  E. Elevated HbF in states of erythroid stress and bone marrow dysplasia

during the obligate RBC stages of the parasitic life cycle. Very young children with α thalassemia are *more* susceptible to infection with the nonlethal *Plasmodium vivax*. Thalassemia might then favor a natural protection against infection with the more lethal *Plasmodium falciparum*.

Thalassemias are the most common genetic disorders in the world, affecting nearly 200 million people worldwide. About 15% of African Americans are silent carriers for α thalassemia; α thalassemia trait (minor) occurs in 3% of African American and in 1–15% of persons of Mediterranean origin. β thalassemia has a 10–15% incidence in individuals from the Mediterranean and Southeast Asia and 0.8% in African Americans. The number of severe cases of thalassemia in the United States is about 1000. Sickle cell disease is the most common structural hemoglobinopathy, occurring in heterozygous form in ~8% of African Americans and in homozygous form in 1 in 400. Between 2 and 3% of African Americans carry a hemoglobin C allele. The chronic nature of hemoglobinopathies and their requirement for complex, resource intensive care pose increasing major public health challenges in regions with emerging economies, as children increasingly survive the traditional causes of childhood mortality.

INHERITANCE AND ONTOGENY

Hemoglobinopathies are autosomal codominant traits—thus, compound heterozygotes who inherit a different abnormal mutant allele from each parent exhibit composite features of each. For example, patients inheriting sickle β thalassemia exhibit features of β thalassemia and sickle cell anemia. The α chain is present in HbA, HbA_2, and HbF; α-chain mutations thus cause abnormalities in all three. The α-globin hemoglobinopathies are symptomatic in utero and after birth because normal function of the α-globin gene is required throughout gestation and adult life. In contrast, infants with β-globin hemoglobinopathies tend to be asymptomatic until 3–9 months of age, when HbA has largely replaced HbF. Prevention or partial reversion of the switch should thus be an effective therapeutic strategy for β-chain hemoglobinopathies.

DETECTION AND CHARACTERIZATION OF HEMOGLOBINOPATHIES–GENERAL METHODS

While electrophoretic techniques are still used for hemoglobin analysis in some settings, high-performance liquid chromatography (HPLC) has largely supplanted electrophoresis in most reference laboratories. Some important variants can be missed by these methods because they co-migrate with normal hemoglobins. Complete characterization, including amino acid sequencing or genotyping by direct DNA analysis, is readily available from several reference laboratories and should be requested if clinical suspicion is high, or when HPLC fails to yield definitive answers.

Quantitation of the hemoglobin profile is often desirable. HbA_2 is frequently elevated in β thalassemia trait and depressed in iron deficiency. HbF is elevated in HPFH, some β thalassemia syndromes, and occasional periods of erythroid stress or marrow dysplasia. For characterization of sickle cell trait, sickle thalassemia syndromes, or HbSC disease, and for monitoring the progress of exchange transfusion therapy to lower the percentage of circulating HbS, quantitation of individual hemoglobins is also required. In most laboratories, quantitation is performed only if the test is specifically ordered.

Functional assays for hemoglobin sickling, solubility, or oxygen affinity should also be performed, as dictated by the clinical presentation. The best sickling assays involve measurement of the degree to which the hemoglobin sample becomes insoluble, or gelated, as it is deoxygenated (i.e., sickle solubility test). Unstable hemoglobins can be detected by their precipitation in isopropanol or after heating to 50°C. High-O_2 affinity and low-O_2 affinity variants can be detected by quantitating the P_{50}, the partial pressure of oxygen at which the hemoglobin sample becomes 50% saturated with oxygen. Direct tests for the percent carboxyhemoglobin and methemoglobin, using spectrophotometric techniques, can readily be obtained from most clinical laboratories on an urgent basis.

Laboratory evaluation remains an adjunct, rather than the sole diagnostic aid. Diagnosis is best established by recognition of a characteristic history, physical findings, peripheral blood smear morphology, and abnormalities of the complete blood cell count (e.g., profound microcytosis with minimal anemia in thalassemia trait).

STRUCTURALLY ABNORMAL HEMOGLOBINS

SICKLE CELL SYNDROMES

The sickle cell syndromes are caused by a mutation in the β-globin gene that changes the sixth amino acid from glutamic acid to valine. HbS ($\alpha_2\beta_2^{6\ Glu\rightarrow Val}$) polymerizes reversibly when deoxygenated to form a gelatinous network of fibrous polymers that stiffen the RBC membrane, increase viscosity, and cause dehydration due to potassium leakage and calcium influx **(Fig. 94-3)**. These changes also produce the sickle shape **(Fig. 94-4)**. Sickled cells lose the pliability needed to traverse small capillaries. They possess altered "sticky" membranes that are abnormally adherent to the endothelium of small venules. These abnormalities provoke unpredictable episodes of microvascular vasoocclusion and premature RBC destruction (hemolytic anemia) in the liver and spleen. The rigid adherent cells also clog small capillaries and venules, causing tissue ischemia, acute pain, and gradual end-organ damage. This venoocclusive component usually dominates the clinical course. Prominent manifestations include episodes of ischemic pain (i.e., painful crises) and ischemic malfunction or frank infarction in the spleen, central nervous system, bones, joints, liver, kidneys, and lungs (Fig. 94-3).

Several sickle syndromes occur as the result of inheritance of HbS from one parent and another hemoglobinopathy, such as β thalassemia or HbC ($\alpha_2\beta_2^{6\ Glu\rightarrow Lys}$), from the other parent. The prototype disease, sickle cell anemia, is the homozygous state for HbS **(Table 94-2)**.

Clinical Manifestations of Sickle Cell Anemia Most patients with sickling syndromes suffer from hemolytic anemia, with hematocrits from 15 to 30%, and significant reticulocytosis. Anemia was once thought to exert protective effects against vasoocclusion by reducing blood viscosity. However, natural history and drug therapy trials suggest that an *increase* in the hematocrit and feedback inhibition of reticulocytosis might be beneficial, even at the expense of slightly increased blood viscosity. The role of adhesive reticulocytes in promoting vasoocclusion might account for these paradoxical effects.

Granulocytosis is common. The white count can fluctuate substantially and unpredictably during and between painful crises, infectious episodes, and other intercurrent illnesses. Granulocytes, platelets, and mononuclear inflammatory cells, and the inflammatory mediators that they release at the sites of vasoocclusion, are being increasingly appreciated as key contributors to the initiation and aggravation of the morbidity associated with vasoocclusive crises.

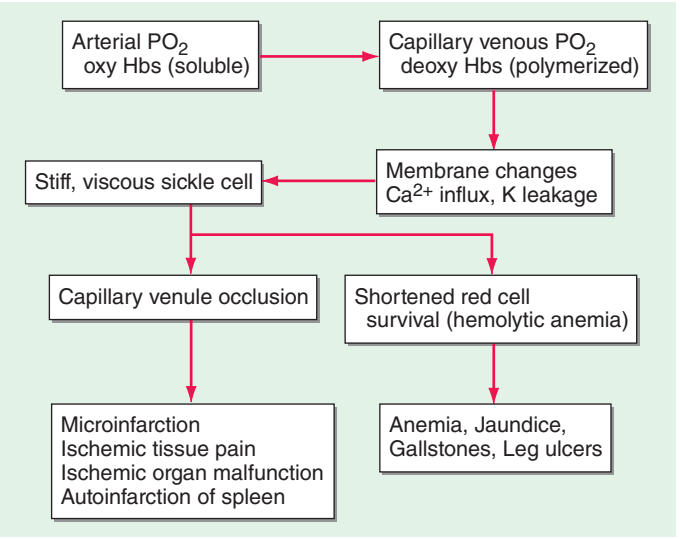

FIGURE 94-3 Pathophysiology of sickle cell crisis.

FIGURE 94-4 Sickle cell anemia. The elongated and crescent-shaped red blood cells seen on this smear represent circulating irreversibly sickled cells. Target cells and a nucleated red blood cell are also seen.

Vasoocclusion causes protean manifestations. Intermittent episodes of vasoocclusion in connective and musculoskeletal structures produce ischemia manifested by acute pain and tenderness, fever, tachycardia, and anxiety. These recurrent episodes, called *painful crises*, are the most common clinical manifestation. Their frequency and severity vary greatly. Pain can develop almost anywhere in the body and may last from a few hours to 2 weeks. Repeated crises requiring hospitalization (>3 episodes per year) correlate with reduced survival in adult life, suggesting that these episodes are associated with accumulation of chronic end-organ damage. Provocative factors include infection, fever, excessive exercise, anxiety, abrupt changes in temperature, hypoxia, or hypertonic dyes.

Repeated microinfarction can destroy tissues having microvascular beds prone to sickling. Thus, splenic function is frequently lost within the first 18–36 months of life, causing susceptibility to infection, particularly by pneumococci. Acute venous obstruction of the spleen (*splenic sequestration crisis*), a rare occurrence in early childhood, may require emergency transfusion and/or splenectomy to prevent trapping of the entire arterial output in the obstructed spleen. Occlusion of retinal vessels can produce hemorrhage, neovascularization, and eventual detachments. Renal papillary necrosis invariably produces isosthenuria. More widespread renal necrosis leads to renal failure in adults, a common late cause of death. Bone and joint ischemia can lead to aseptic necrosis, especially of the femoral or humeral heads, chronic arthropathy, and unusual susceptibility to osteomyelitis, which may be caused by organisms, such as *Salmonella*, rarely encountered in other settings. The *hand-foot syndrome* is caused by painful infarcts of the digits and dactylitis. Stroke is especially common in children; a small subset tends to suffer repeated episodes. Stroke is less common in adults and is often hemorrhagic. A particularly painful complication in males is priapism, due to infarction of the penile venous outflow tracts; permanent impotence is a frequent consequence. Chronic lower leg ulcers probably arise from ischemia and superinfection in the distal circulation.

Acute chest syndrome is a distinctive manifestation characterized by chest pain, tachypnea, fever, cough, and arterial oxygen desaturation. It can mimic pneumonia, pulmonary emboli, bone marrow infarction and embolism, myocardial ischemia, or in situ lung infarction. Acute chest syndrome is thought to be due to in situ sickling within the lung and/or bone marrow microemboli, producing pain and temporary pulmonary dysfunction. Often it is difficult or impossible to distinguish among other possibilities. Pulmonary infarction and pneumonia are the most frequent underlying or concomitant conditions in patients with this syndrome. Repeated episodes of acute chest pain correlate with reduced survival. Acutely, reduction in arterial oxygen saturation is especially ominous because it promotes sickling on a massive scale. Chronic acute or subacute pulmonary crises lead to pulmonary hypertension and cor pulmonale, an increasingly common cause of death as patients survive longer. A possible role played by free plasma HbS in scavenging nitrogen dioxide (NO_2), thus raising pulmonary vascular tone led to trials of sildenafil to restore NO_2 levels. These were terminated because of adverse effects.

Chronic subacute central nervous system damage in the absence of an overt stroke is a distressingly common phenomenon beginning in early childhood. Modern functional imaging techniques have pinpointed circulatory dysfunction due to a likely CNS sickle vasculopathy; these changes correlate with an array of cognitive and behavioral abnormalities in children and young adults. It is important to be aware of these often subtle changes because they can complicate clinical management or be misinterpreted as "difficult patient" behaviors.

Sickle cell syndromes are remarkable for their clinical heterogeneity. Some patients remain virtually asymptomatic into or even through adult life, while others suffer repeated crises requiring hospitalization from early childhood. Patients with sickle thalassemia and sickle-HbE tend to have similar, slightly milder symptoms, perhaps because of the ameliorating effects of the presence of other hemoglobins within the RBC. Hemoglobin SC disease, one of the more common variants of sickle cell anemia, is frequently marked by lesser degrees of hemolytic anemia and a greater propensity for the development of retinopathy and aseptic necrosis of bones. In most respects, however, the clinical manifestations resemble sickle cell anemia. Some rare hemoglobin variants actually aggravate the sickling phenomenon.

The clinical variability in different patients inheriting the same disease-causing mutation (sickle hemoglobin) has made sickle cell disease the focus of efforts to identify modifying genetic polymorphisms in other genes that might account for the heterogeneity. The complexity of the data obtained thus far has dampened the expectation that genome-wide analysis will yield individualized profiles that predict a patient's clinical course. Nevertheless, a number of interesting patterns have emerged from these modifying gene analyses. For example, genes affecting the inflammatory response or cytokine expression appear to be modifying candidates. Genes that affect transcriptional regulation of lymphocytes may also be involved.

Clinical Manifestations of Sickle Cell Trait Sickle cell trait is often asymptomatic. Anemia and painful crises are rare. An uncommon but highly distinctive symptom is painless hematuria often occurring in adolescent males, probably due to papillary necrosis. Isosthenuria is a more common manifestation of the same process.

TABLE 94-2 Clinical Features of Sickle Hemoglobinopathies

CONDITION	CLINICAL ABNORMALITIES	HEMOGLOBIN LEVEL, g/L (g/dL)	MCV, fL	HEMOGLOBIN ELECTROPHORESIS
Sickle cell trait	None; rare painless hematuria	Normal	Normal	HbS/A: 40/60
Sickle cell anemia	Vasoocclusive crises with infarction of spleen, brain, marrow, kidney, lung; aseptic necrosis of bone; gallstones; priapism; ankle ulcers	70–100 (7–10)	80–100	HbS/A: 100/0 HbF: 2–25%
S/β° thalassemia	Vasoocclusive crises; aseptic necrosis of bone	70–100 (7–10)	60–80	HbS/A: 100/0 HbF: 1–10%
S/β+ thalassemia	Rare crises and aseptic necrosis	100–140 (10–14)	70–80	HbS/A: 60/40
Hemoglobin SC	Rare crises and aseptic necrosis; painless hematuria	100–140 (10–14)	80–100	HbS/A: 50/0 HbC: 50%

Sloughing of papillae with urethral obstruction has been reported, as have isolated cases of massive sickling or sudden death due to exposure to high altitudes or extremes of exercise and dehydration. Avoidance of dehydration or extreme physical stress should be advised.

Diagnosis Sickle cell syndromes are suspected on the basis of hemolytic anemia, RBC morphology (Fig. 94-4), and intermittent episodes of ischemic pain. Diagnosis is confirmed by hemoglobin electrophoresis, mass spectroscopy, and the sickling tests already discussed. Thorough characterization of the exact hemoglobin profile of the patient is important, because sickle thalassemia and hemoglobin SC disease have distinct prognoses or clinical features. Diagnosis is usually established in childhood, but occasional patients, often with compound heterozygous states, do not develop symptoms until the onset of puberty, pregnancy, or early adult life. Genotyping of family members and potential parental partners is critical for genetic counseling. Details of the childhood history establish prognosis and need for aggressive or experimental therapies. Factors associated with increased morbidity and reduced survival include more than three crises requiring hospitalization per year, chronic neutrophilia, a history of splenic sequestration or hand-foot syndrome, and second episodes of acute chest syndrome. Patients with a history of cerebrovascular accidents are at higher risk for repeated episodes and require partial exchange transfusion and especially close monitoring using Doppler carotid flow measurements. Patients with severe or repeated episodes of acute chest syndrome may need lifelong transfusion support, using partial exchange transfusion, if possible.

TREATMENT

Sickle Cell Syndromes

Patients with sickle cell syndromes require ongoing continuity of care. Familiarity with the pattern of symptoms provides the best safeguard against excessive use of the emergency room, hospitalization, and habituation to addictive narcotics. Additional preventive measures include regular slit-lamp examinations to monitor development of retinopathy; antibiotic prophylaxis appropriate for splenectomized patients during dental or other invasive procedures; and vigorous oral hydration during or in anticipation of periods of extreme exercise, exposure to heat or cold, emotional stress, or infection. Pneumococcal and *Haemophilus influenzae* vaccines are less effective in splenectomized individuals. Thus, patients with sickle cell anemia should be vaccinated early in life.

The management of an acute painful crisis includes vigorous but careful hydration, thorough evaluation for underlying causes (such as infection), and aggressive analgesia administered by a standing order and/or patient-controlled analgesia (PCA) pump. Morphine (0.1–0.15 mg/kg every 3–4 h) should be used to control severe pain. Bone pain may respond as well to ketorolac (30–60 mg initial dose, then 15–30 mg every 6–8 h). Inhalation of nitrous oxide can provide short-term pain relief, but great care must be exercised to avoid hypoxia and respiratory depression. Nitrous oxide also elevates O_2 affinity, reducing O_2 delivery to tissues. Its use should be restricted to experts. Blockade of the activities of adhesive molecules (e.g., P-selectin) or inflammatory mediators are being used to shorten crises and reduce crisis pain. Many crises can be managed at home with oral hydration and oral analgesia. Use of the emergency room should be reserved for especially severe symptoms or circumstances in which other processes, for example, infection, are strongly suspected. Nasal oxygen should be used as appropriate to protect arterial saturation. Most crises resolve in 1–7 days. Use of blood transfusion should be reserved for extreme cases: transfusions do not shorten the duration of the crisis.

No tests are definitive to diagnose acute painful crisis. Critical to good management is an approach that recognizes that most patients reporting crisis symptoms do indeed have crisis or another significant medical problem. Diligent diagnostic evaluation for underlying causes is imperative, even though these are found infrequently. In adults, the possibility of aseptic necrosis or sickle arthropathy must be considered, especially if pain and immobility become repeated or chronic at a single site. Nonsteroidal anti-inflammatory agents are often effective for sickle cell arthropathy.

Acute chest syndrome is a medical emergency that may require management in an intensive care unit. Hydration should be monitored carefully to avoid the development of pulmonary edema, and oxygen therapy should be especially vigorous for protection of arterial saturation. Diagnostic evaluation for pneumonia and pulmonary embolism should be especially thorough, since these may occur with atypical symptoms. Critical interventions are transfusion to maintain a hematocrit >30, and emergency exchange transfusion if arterial saturation drops to <90%. As patients with sickle cell syndrome increasingly survive into their fifth and sixth decades, end-stage renal failure and pulmonary hypertension are becoming increasingly prominent causes of end-stage morbidity. A sickle cell cardiomyopathy and/or premature coronary artery disease may compromise cardiac function in later years. Sickle cell patients have received kidney transplants, but they often experience an increase in the frequency and severity of crises, possibly due to increased infection as a consequence of immunosuppression.

The most significant advance in the therapy of sickle cell anemia has been the introduction of hydroxyurea as a mainstay of therapy for patients with severe symptoms. Hydroxyurea (10–30 mg/kg per day) increases fetal hemoglobin and may also exert beneficial effects on RBC hydration, vascular wall adherence, and suppression of the granulocyte and reticulocyte counts; dosage is titrated to maintain a white cell count between 5000 and 8000/μL. White cells and reticulocytes may play a major role in the pathogenesis of sickle cell crisis, and their suppression may be an important side benefit of hydroxyurea therapy.

Hydroxyurea should be considered in patients experiencing repeated episodes of acute chest syndrome or with more than three crises per year requiring hospitalization. The utility of this agent for reducing the incidence of other complications (priapism, retinopathy) is under evaluation, as are the long-term side effects. Clinical experience is now sufficient to state that the risk of bone marrow dyscrasias or other neoplasms is minimal. Hydroxyurea offers broad benefits to most patients whose disease is severe enough to impair their functional status; it likely improves survival. HbF levels increase in most patients within a few months.

The antitumor drug 5-azacytidine was the first agent found to elevate HbF. It never achieved widespread use because of concerns about acute toxicity and carcinogenesis. However, low doses of the related agent 5-deoxyazacytidine (decitabine) can elevate HbF with more acceptable toxicity.

Bone marrow transplantation can provide definitive cures but is known to be effective and safe only in children. Clinical trials studying partially myeloablative conditioning regimens ("mini" transplants) are likely to support more widespread use in older patients, and should be considered in adults with significant morbidity. Prognostic features justifying bone marrow transplant are the presence of repeated crises early in life, a high neutrophil count, or the development of hand-foot syndrome. Children at risk for stroke can now be identified through the use of Doppler ultrasound techniques. Prophylactic exchange transfusion appears to substantially reduce the risk of stroke in this population. Children who do suffer a cerebrovascular accident should be maintained for at least 3–5 years on a program of vigorous exchange transfusion, as the risk of second strokes is extremely high. Hydroxyurea therapy could eventually supplant indefinite chronic transfusion in patients responding favorably.

Gene therapy for sickle cell anemia is being intensively pursued, but no safe measures are currently available. The development of newer methods of direct gene correction in situ (e.g., zinc finger nucleases, or "CRISPR" [clustered regularly interspaced short palindromic repeats] technology) could well find clinical use in these patients. Experimental methods of derepressing HbF by manipulating Bcl11a or chromatin looping are also being explored.

TABLE 94-3 Representative Abnormal Hemoglobins with Altered Synthesis or Function

DESIGNATION	MUTATION	POPULATION	MAIN CLINICAL EFFECTS[a]
Sickle or S	$\beta^{6Glu\rightarrow Val}$	African	Anemia, ischemic infarcts
C	$\beta^{6Glu\rightarrow Lys}$	African	Mild anemia; interacts with HbS
E	$\beta^{26Glu\rightarrow Lys}$	Southeast Asian	Microcytic anemia, splenomegaly, thalassemic phenotype
Köln	$\beta^{98Val\rightarrow Met}$	Sporadic	Hemolytic anemia, Heinz bodies when splenectomized
Yakima	$\beta^{99Asp\rightarrow His}$	Sporadic	Polycythemia
Kansas	$\beta^{102Asn\rightarrow Lys}$	Sporadic	Mild anemia
M Iwata	$\alpha^{87His\rightarrow Tyr}$	Sporadic	Methemoglobinemia

[a]See text for details.

UNSTABLE HEMOGLOBINS

Amino acid substitutions that reduce solubility or increase susceptibility to oxidation result in unstable hemoglobins that precipitate, forming inclusion bodies injurious to the RBC membrane. Representative mutations are those that interfere with contact points between the α and β subunits (e.g., Hb Philly [$\beta^{35Tyr\rightarrow Phe}$]), alter the helical segments (e.g., Hb Genova [$\beta^{28Leu\rightarrow Pro}$]), or disrupt interactions of the hydrophobic pockets of the globin subunits with heme (e.g., Hb Köln [$\beta^{98Val\rightarrow Met}$]) **(Table 94-3)**. The inclusions, called *Heinz bodies*, are clinically detectable by staining with supravital dyes such as crystal violet. Removal of these inclusions by the spleen generates pitted, rigid cells that have shortened life spans, producing hemolytic anemia of variable severity, sometimes requiring chronic transfusion support. Splenectomy may be needed to correct the anemia. Leg ulcers and premature gallbladder disease due to bilirubin loading are frequent stigmata.

Unstable hemoglobins occur sporadically, often by spontaneous new mutations. Heterozygotes are often symptomatic because a significant Heinz body burden can develop even when the unstable variant accounts for only a portion of the total hemoglobin. Symptomatic unstable hemoglobins tend to be β-globin variants, because sporadic mutations affecting only one of the four α globins alleles would generate only 20–30% abnormal hemoglobin.

HEMOGLOBINS WITH ALTERED OXYGEN AFFINITY

High-affinity hemoglobins (e.g., Hb Yakima [$\beta^{99Asp\rightarrow His}$]) bind oxygen more readily but deliver less O_2 to tissues at normal capillary Po_2 levels (Fig. 94-2). Mild tissue hypoxia ensues, stimulating RBC production and erythrocytosis (Table 94-3). In extreme cases, the hematocrits can rise to 60–65%, increasing blood viscosity and producing typical symptoms (headache, somnolence, or dizziness). Phlebotomy may be required. Typical mutations alter interactions within the heme pocket or disrupt the Bohr effect or salt-bond site. Mutations that impair the interaction of HbA with 2,3-BPG can increase O_2 affinity because 2,3-BPG binding lowers O_2 affinity.

Low-affinity hemoglobins (e.g., Hb Kansas [$\beta^{102Asn\rightarrow Lys}$]) bind sufficient oxygen in the lungs, despite their lower oxygen affinity, to achieve nearly full saturation. At capillary oxygen tensions, they lose sufficient amounts of oxygen to maintain homeostasis at a low hematocrit (Fig. 94-2) (*pseudoanemia*). Capillary hemoglobin desaturation can also be sufficient to produce clinically apparent cyanosis. Despite these findings, patients usually require no specific treatment.

METHEMOGLOBINEMIAS

Methemoglobin is generated by oxidation of the heme iron moieties to the ferric state, causing a characteristic bluish-brown muddy color resembling cyanosis. Methemoglobin has such high oxygen affinity that virtually no oxygen is delivered. Levels >50–60% are often fatal.

Congenital methemoglobinemia arises from globin mutations that stabilize iron in the ferric state (e.g., HbM Iwata [$\alpha^{87His\rightarrow Tyr}$], Table 94-3) or from mutations that impair the enzymes that reduce methemoglobin to hemoglobin (e.g., methemoglobin reductase, NADP diaphorase). Acquired methemoglobinemia is caused by toxins that oxidize heme iron, notably nitrate and nitrite-containing compounds, including drugs commonly used in cardiology and anesthesiology.

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH UNSTABLE HEMOGLOBINS, HIGH-AFFINITY HEMOGLOBINS, AND METHEMOGLOBINEMIA

Unstable hemoglobin variants should be suspected in patients with nonimmune hemolytic anemia, jaundice, splenomegaly, or premature biliary tract disease. Severe hemolysis usually presents during infancy as neonatal jaundice or anemia. Milder cases may present in adult life with anemia or only as unexplained reticulocytosis, hepatosplenomegaly, premature biliary tract disease, or leg ulcers. Because spontaneous mutation is common, family history of anemia may be absent. The peripheral blood smear often shows anisocytosis, abundant cells with punctate inclusions, and irregular shapes (i.e., poikilocytosis).

The two best tests for diagnosing unstable hemoglobins are the Heinz body preparation and the isopropanol or heat stability test. Many unstable Hb variants are electrophoretically silent. A normal electrophoresis does not rule out the diagnosis. HPLC or direct gene analysis will provide a definitive diagnosis.

Severely affected patients may require transfusion support for the first 3 years of life, because splenectomy before age 3 is associated with a significantly higher immune deficit. Splenectomy is usually effective thereafter, but occasional patients may require lifelong transfusion support. After splenectomy, patients can develop cholelithiasis and leg ulcers, hypercoagulable states, and susceptibility to overwhelming sepsis. Splenectomy should thus be avoided or delayed unless it is the only alternative. Precipitation of unstable hemoglobins is aggravated by oxidative stress, for example, infection and certain antimalarial drugs, which should be avoided where possible.

High-O_2 affinity hemoglobin variants should be suspected in patients with erythrocytosis. The best test for confirmation is measurement of the P_{50}. A high-O_2 affinity hemoglobin causes a significant left shift (i.e., lower numeric value of the P_{50}); confounding conditions, for example, tobacco smoking or carbon monoxide exposure, can also lower the P_{50}.

High-affinity hemoglobins are often asymptomatic; rubor or plethora may be telltale signs. When the hematocrit approaches 60%, symptoms of high blood viscosity and sluggish flow (headache, lethargy, dizziness, etc.) may be present. These persons may benefit from judicious phlebotomy. Erythrocytosis represents an appropriate attempt to compensate for the impaired oxygen delivery by the abnormal variant. Overzealous phlebotomy may stimulate increased erythropoiesis or aggravate symptoms by thwarting this compensatory mechanism. The guiding principle of phlebotomy should be to improve oxygen delivery by reducing blood viscosity and increasing blood flow rather than restoration of a normal hematocrit. Phlebotomy-induced modest iron deficiency may aid in control.

Low-affinity hemoglobins should be considered in patients with cyanosis or a low hematocrit with no other reason apparent after thorough evaluation. The P_{50} test confirms the diagnosis. Counseling and reassurance are the interventions of choice.

Acquired methemoglobinemia should be suspected in patients with hypoxic symptoms who appear cyanotic but have a Pao_2 sufficiently high that hemoglobin should be fully saturated with oxygen. A history of nitrite or other oxidant ingestions may not always be available; some exposures may be inapparent to the patient, and others may result from suicide attempts. The characteristic muddy appearance of freshly drawn blood can be a critical clue. The best diagnostic test is methemoglobin assay, which is usually available on an emergency basis.

Methemoglobinemia often causes symptoms of cerebral ischemia at levels >15%; levels >60% are usually lethal. Intravenous injection of 1 mg/kg of methylene blue is effective emergency therapy. Milder cases and follow-up of severe cases can be treated orally with methylene blue (60 mg three to four times each day) or ascorbic acid (300–600 mg/d). Congenital methemoglobinemia does not usually require treatment other than avoidance of oxidative drugs or agents. Patient and provider awareness is essential in order that inappropriate evaluations for cyanosis be avoided.

THALASSEMIA SYNDROMES

The thalassemia syndromes are inherited disorders of α- or β-globin biosynthesis. The reduced supply of globin diminishes production of hemoglobin tetramers, causing hypochromia and microcytosis. Unbalanced accumulation of α and β subunits occurs because the synthesis of the unaffected globins proceeds at a normal rate. Unbalanced chain accumulation dominates the clinical phenotype. Clinical severity varies widely, depending on the degree to which the synthesis of the affected globin is impaired, altered synthesis of other globin chains, and coinheritance of other abnormal globin alleles.

CLINICAL MANIFESTATIONS OF β THALASSEMIA SYNDROMES

Mutations causing thalassemia can affect any step in the pathway of globin gene expression: transcription, processing of the mRNA precursor, translation, and posttranslational metabolism of the β-globin polypeptide chain. The most common forms arise from mutations that derange splicing of the mRNA precursor or prematurely terminate translation of the mRNA.

Hypochromia and microcytosis characterize all forms of β thalassemia because of the reduced amounts of hemoglobin tetramers (Fig. 94-5). In heterozygotes (β thalassemia trait), this is the only abnormality seen. Anemia is minimal. In more severe homozygous states, unbalanced α- and β-globin accumulation causes accumulation of highly insoluble unpaired α chains. They form toxic inclusion bodies that kill developing erythroblasts in the marrow. Few of the proerythroblasts beginning erythroid maturation survive. The surviving RBCs bear a burden of inclusion bodies that are detected in the spleen, shortening the RBC life span and producing severe hemolytic anemia. The resulting profound anemia stimulates erythropoietin release and compensatory erythroid hyperplasia, but the marrow response is sabotaged by the ineffective erythropoiesis. Anemia persists. Erythroid hyperplasia can become exuberant and produce masses of extramedullary erythropoietic tissue in the liver and spleen.

Massive bone marrow expansion deranges growth and development. Children develop characteristic "chipmunk" facies due to maxillary marrow hyperplasia and frontal bossing. Thinning and pathologic fracture of long bones and vertebrae may occur due to cortical invasion by erythroid elements and profound growth retardation. Hemolytic anemia causes hepatosplenomegaly, leg ulcers, gallstones, and high-output congestive heart failure. The conscription of caloric resources to support erythropoiesis leads to inanition, susceptibility to infection, endocrine dysfunction, and, in the most severe cases, death during the first decade of life. Chronic transfusions with RBCs improve oxygen delivery, suppress the excessive ineffective erythropoiesis, and prolong life, but the inevitable side effects, notably iron overload, often prove fatal by age 30 years.

Severity is highly variable. Known modulating factors are those that ameliorate the burden of unpaired α-globin inclusions. Alleles associated with milder synthetic defects and coinheritance of α thalassemia trait reduce clinical severity by reducing accumulation of excess α globin. HbF persists to various degrees in β thalassemias. γ-Globin gene chains can substitute for β chains, generating more hemoglobin and reducing the burden of α-globin inclusions. The terms *β thalassemia major* and *β thalassemia intermedia* are used to reflect the clinical heterogeneity. Patients with β thalassemia major require intensive transfusion support to survive. Patients with β thalassemia intermedia have a somewhat milder phenotype and can survive without transfusion. The terms *β thalassemia minor* and *β thalassemia trait* describe asymptomatic heterozygotes for β thalassemia.

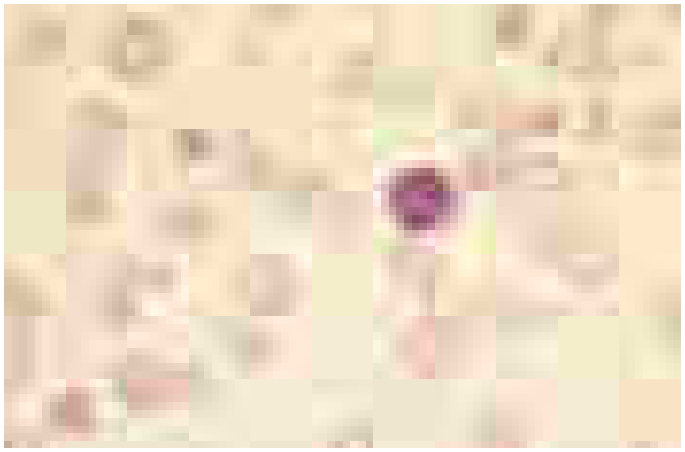

FIGURE 94-5 β Thalassemia intermedia. Microcytic and hypochromic red blood cells are seen that resemble the red blood cells of severe iron-deficiency anemia. Many elliptical and teardrop-shaped red blood cells are noted.

ALPHA THALASSEMIA SYNDROMES

The four classic α thalassemias, most common in Asians, are α thalassemia-2 trait, in which one of the four α-globin loci is deleted; α thalassemia-1 trait, with two deleted loci; HbH disease, with three loci deleted; and hydrops fetalis with Hb Barts, with all four loci deleted (Table 94-4). Nondeletion forms of α thalassemia also exist.

α *Thalassemia-2 trait* is an asymptomatic, silent carrier state. α *Thalassemia-1 trait* resembles β thalassemia minor. Offspring doubly heterozygous for α thalassemia-2 and α thalassemia-1 exhibit a more severe phenotype called *HbH disease*. Heterozygosity for a deletion that removes both genes from the same chromosome (*cis* deletion) is common in Asians and in those from the Mediterranean region, as is homozygosity for α thalassemia-2 (*trans* deletion). Both produce asymptomatic hypochromia and microcytosis.

In *HbH disease*, HbA production is only 25–30% normal. Fetuses accumulate some unpaired γ chains (Hb Barts; γ-chain tetramers). In adults, unpaired β chains accumulate and are soluble enough to form β_4 tetramers called HbH. HbH forms few inclusions in erythroblasts and precipitates in circulating RBC. Patients with HbH disease have thalassemia intermedia characterized by moderately severe hemolytic anemia but milder ineffective erythropoiesis. Survival into mid-adult life without transfusions is common.

The homozygous state for the α thalassemia-1 *cis* deletion (hydrops fetalis) causes total absence of α-globin synthesis. No physiologically useful hemoglobin is produced beyond the embryonic stage. Excess γ globin forms tetramers called *Hb Barts* (γ_4), which has a very high oxygen affinity. It delivers almost no O_2 to fetal tissues, causing tissue asphyxia, edema (hydrops fetalis), congestive heart failure, and death in utero. α Thalassemia-2 trait is common (15–20%) among people of African descent. The *cis* α thalassemia-1 deletion is almost never seen, however. Thus, α thalassemia-2 and the *trans* form of α thalassemia-1 are very common, but HbH disease and hydrops fetalis are rare.

It has been known for some time that some patients with myelodysplasia or erythroleukemia produce RBC clones containing HbH. This phenomenon is due to mutations in the ATRX pathway that affect the LCR of the α-globin gene cluster.

DIAGNOSIS AND MANAGEMENT OF THALASSEMIAS

The diagnosis of β-thalassemia major is readily made during childhood on the basis of severe anemia accompanied by the characteristic signs of massive ineffective erythropoiesis: hepatosplenomegaly, profound microcytosis, a characteristic blood smear (Fig. 94-5), and elevated levels of HbF, HbA_2, or both. Many patients require chronic hypertransfusion therapy designed to maintain a hematocrit of at least 27–30% so that erythropoiesis is suppressed. Splenectomy is required if the annual transfusion requirement (volume of RBCs per kilogram of body weight per year) increases by >50%. Folic acid supplements may be useful. Vaccination with Pneumovax in anticipation of eventual splenectomy is advised, as is close monitoring for infection, leg ulcers, and biliary tract disease. Many patients develop endocrine deficiencies as a result of iron overload. Early endocrine evaluation is required for glucose intolerance, thyroid dysfunction, and delayed onset of puberty or secondary sexual characteristics.

Patients with β thalassemia intermedia exhibit similar stigmata but can survive without chronic hypertransfusion. Management is particularly challenging because a number of factors can aggravate the anemia, including infection, onset of puberty, and development

TABLE 94-4 The α Thalassemias

CONDITION	HEMOGLOBIN A, %	HEMOGLOBIN H (β4), %	HEMOGLOBIN LEVEL, g/L (g/dL)	MCV, fL
Normal	97	0	150 (15)	90
Silent thalassemia: −α/αα	98–100	0	150 (15)	90
Thalassemia trait:−α/−α homozygous α-thal-2[a] or ––/αα heterozygous α-thal-1[a]	85–95	Rare red blood cell inclusions	120–130 (12–13)	70–80
Hemoglobin H disease: ––/−α heterozygous α-thal-1/α-thal-2	70–95	5–30	60–100 (6–10)	60–70
Hydrops fetalis: ––/–– homozygous α-thal-1	0	5–10[b]	Fatal in utero or at birth	

[a]When both α alleles on one chromosome are deleted, the locus is called α-thal-1; when only a single α allele on one chromosome is deleted, the locus is called α-thal-2. [b]90–95% of the hemoglobin is hemoglobin Barts (tetramers of γ chains).

of splenomegaly and hypersplenism. Some patients may eventually benefit from splenectomy. The expanded erythron can cause absorption of excessive dietary iron and hemosiderosis, even without transfusion. Some patients eventually become transfusion dependent.

β Thalassemia minor (i.e., thalassemia trait) usually presents as profound microcytosis and hypochromia with target cells, but only minimal or mild anemia. The mean corpuscular volume is rarely >75 fL; the hematocrit is rarely <30–33%. Hemoglobin analysis classically reveals an elevated HbA_2 (3.5–7.5%), but some forms are associated with normal HbA_2 and/or elevated HbF. Genetic counseling and patient education are essential. Patients with β thalassemia trait should be warned that their blood picture resembles iron deficiency and can be misdiagnosed. They should eschew empirical use of iron, yet iron deficiency requiring replacement therapy can develop during pregnancy or from chronic bleeding.

Persons with α thalassemia trait may exhibit mild hypochromia and microcytosis usually without anemia. HbA_2 and HbF levels are normal. Affected individuals usually require only genetic counseling. HbH disease resembles β thalassemia intermedia, with the added complication that the HbH molecule behaves like moderately unstable hemoglobin. Patients with HbH disease should undergo splenectomy if excessive anemia or a transfusion requirement develops. Oxidative drugs should be avoided. Iron overload leading to death can occur in more severely affected patients.

PREVENTION

Antenatal diagnosis of thalassemia syndromes is now widely available. DNA diagnosis is based on polymerase chain reaction (PCR) amplification of fetal DNA, obtained by amniocentesis or chorionic villus biopsy followed by hybridization to allele-specific oligonucleotide probes or direct DNA sequencing.

THALASSEMIC STRUCTURAL VARIANTS

Thalassemic structural variants are characterized by both defective synthesis and abnormal structure.

HEMOGLOBIN LEPORE

Hb Lepore [$\alpha_2(\delta\beta)_2$] arises by an unequal crossover and recombination event that fuses the proximal end of the δ-gene with the distal end of the closely linked β-gene. It is common in the Mediterranean basin. The resulting chromosome contains only the fused δβ gene. The Lepore (δβ) globin is synthesized poorly because the fused gene is under the control of the weak δ-globin promoter. Hb Lepore alleles have a phenotype like β thalassemia, except for the added presence of 2–20% Hb Lepore. Compound heterozygotes for Hb Lepore and a classic β thalassemia allele may also have severe thalassemia.

HEMOGLOBIN E

HbE (i.e., $\alpha_2\beta_2^{26Glu\rightarrow Lys}$) is extremely common in Cambodia, Thailand, and Vietnam. The gene has become far more prevalent in the United States as a result of immigration of Asian persons, especially in California, where HbE is the most common variant detected. HbE is mildly unstable but not enough to affect RBC life span significantly. Heterozygotes resemble individuals with a mild β-thalassemia trait. HbE homozygosity is a condition associated with mildly asymptomatic microcytosis, hypochromia, and hemoglobin levels rarely <100 g/L (<10 g/dL).

Compound heterozygotes for HbE and a β thalassemia gene can have β thalassemia intermedia or β-thalassemia major, depending on the severity of the coinherited thalassemic gene.

The β^E allele contains a single base change in codon 26 that causes the amino acid substitution. This mutation also activates a cryptic RNA splice site, generating a structurally abnormal globin mRNA that cannot be translated, from about 50% of the initial pre-mRNA molecules. The remaining 40–50% are normally spliced and generate functional mRNA that is translated into β^E-globin because the mature mRNA carries the base change that alters codon 26.

Genetic counseling of the persons at risk for HbE should focus especially on the interaction of HbE with β thalassemia, because HbE homozygosity is a condition associated with microcytosis, hypochromia, and hemoglobin levels rarely below 100 g/L (10 g/dL) and is usually asymptomatic.

HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

HPFH is characterized by continued synthesis of high levels of HbF in adult life. No deleterious effects are apparent, even when all of the hemoglobin produced is HbF. These rare patients demonstrate convincingly that prevention or reversal of the fetal to adult hemoglobin switch would provide effective therapy for sickle cell anemia and β thalassemia.

ACQUIRED HEMOGLOBINOPATHIES

The two most important acquired hemoglobinopathies are carbon monoxide poisoning and methemoglobinemia (see above). Carbon monoxide has a higher affinity for hemoglobin than does oxygen; it can replace oxygen and diminish O_2 delivery. Chronic elevation of carboxyhemoglobin levels to 10 or 15%, as occurs in smokers, can lead to secondary polycythemia. Carboxyhemoglobin is cherry red in color and masks the development of cyanosis usually associated with poor O_2 delivery to tissues.

Abnormalities of hemoglobin biosynthesis have also been described in blood dyscrasias. In some patients with myelodysplasia, erythroleukemia, or myeloproliferative disorders, elevated HbF or a mild form of HbH disease may also be seen. The abnormalities are not severe enough to alter the course of the underlying disease.

TREATMENT

Transfusional Hemosiderosis

Chronic blood transfusion can lead to bloodborne infection, alloimmunization, febrile reactions, and lethal iron overload (Chap. 109). A unit of packed RBCs contains 250–300 mg iron (1 mg/mL). The iron assimilated by a single transfusion of 2 units of packed RBCs is thus equal to a 1- to 2-year oral intake of iron. Iron accumulates in chronically transfused patients because no mechanisms exist for

increasing iron excretion: an expanded erythron causes especially rapid development of iron overload because accelerated erythropoiesis promotes excessive absorption of dietary iron. Vitamin C should not be supplemented because it generates free radicals in iron excess states.

Patients who receive >100 units of packed RBCs usually develop hemosiderosis. The ferritin level rises, followed by early endocrine dysfunction (glucose intolerance and delayed puberty), cirrhosis, and cardiomyopathy. Liver biopsy shows both parenchymal and reticuloendothelial iron. The superconducting quantum-interference device (SQUID) is accurate at measuring hepatic iron but not widely available. Cardiac toxicity is often insidious. Early development of pericarditis is followed by dysrhythmia and pump failure. The onset of heart failure is ominous, often presaging death within a year **(Chap. 407)**.

The decision to start long-term transfusion support should also prompt one to institute therapy with iron-chelating agents. Deferoxamine (Desferal) is for parenteral use. Its iron-binding kinetics require chronic slow infusion via a metering pump. The constant presence of the drug improves the efficiency of chelation and protects tissues from occasional releases of the most toxic fraction of iron—low-molecular-weight iron—which may not be sequestered by protective proteins.

Deferoxamine is relatively nontoxic. Occasional cataracts, deafness, and local skin reactions, including urticaria, occur. Skin reactions can usually be managed with antihistamines. Negative iron balance can be achieved, even in the face of a high transfusion requirement, but this alone does not prevent long-term morbidity and mortality in chronically transfused patients. Irreversible end-organ deterioration develops at relatively modest levels of iron overload, even if symptoms do not appear for many years thereafter. To enjoy a significant survival advantage, chelation must begin before 5–8 years of age in β-thalassemia major.

Deferasirox is an oral iron-chelating agent. Single daily doses of 20–30 mg/kg deferasirox produced reductions in liver iron concentration comparable to deferoxamine in long-term transfused adult and pediatric patients. Deferasirox produces some elevations in liver enzymes and slight but persistent increases in serum creatinine, without apparent clinical consequence. Other toxicities are similar to those of deferoxamine. Its toxicity profile is acceptable, although long-term effects are still being evaluated.

EXPERIMENTAL THERAPIES

BONE MARROW TRANSPLANTATION, GENE THERAPY, AND MANIPULATION OF HBF

Bone marrow transplantation provides stem cells able to express normal hemoglobin; it has been used in a large number of patients with β thalassemia and a smaller number of patients with sickle cell anemia. Early in the course of disease, before end-organ damage occurs, transplantation is curative in 80–90% of patients. In highly experienced centers, the treatment-related mortality is <10%. Because survival into adult life is possible with conventional therapy, the decision to transplant is best made in consultation with specialized centers.

Gene therapy of thalassemia and sickle cell disease has proved to be an elusive goal, but experimental advances are raising expectations. New lentivirus vectors appear to be capable of achieving stable synthesis of anti-sickling hemoglobin variants in some cases without insertional mutagenesis that has been seen with other vectors.

Reestablishing high levels of fetal hemoglobin synthesis should ameliorate the symptoms of β-chain hemoglobinopathies. Cytotoxic agents such as hydroxyurea and cytarabine promote high levels of HbF synthesis, probably by stimulating proliferation of the primitive HbF-producing progenitor cell population (i.e., F cell progenitors). Unfortunately, this regimen has not yet been effective in β thalassemia. Butyrates stimulate HbF production, but only transiently. Pulsed or intermittent administration has been found to sustain HbF induction in the majority of patients with sickle cell disease. It is unclear whether butyrates will have similar activity in patients with β thalassemia.

APLASTIC AND HYPOPLASTIC CRISIS IN PATIENTS WITH HEMOGLOBINOPATHIES

Patients with hemolytic anemias sometimes exhibit an alarming decline in hematocrit during and immediately after acute illnesses. Bone marrow suppression occurs in almost everyone during acute and chronic inflammatory illnesses. In patients with short RBC life spans, suppression can affect RBC counts more dramatically. These hypoplastic crises are usually transient and self-correcting before intervention is required.

Aplastic crisis refers to a profound cessation of erythroid activity in patients with chronic hemolytic anemias. It is associated with a rapidly falling hematocrit. Episodes are usually self-limited. Aplastic crises are caused by infection with a particular strain of parvovirus, B19A. Children infected with this virus usually develop permanent immunity. Aplastic crises do not often recur and are rarely seen in adults. Management requires close monitoring of the hematocrit and reticulocyte count. If anemia becomes symptomatic, transfusion support is indicated. Most crises resolve spontaneously within 1–2 weeks.

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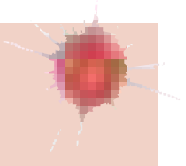
95 Megaloblastic Anemias

A. Victor Hoffbrand



The megaloblastic anemias are a group of disorders characterized by the presence of distinctive morphologic appearances of the developing red cells in the bone marrow. The marrow is usually hypercellular and the anemia is based on ineffective erythropoiesis. The cause is usually a deficiency of either cobalamin (vitamin B_{12}) or folate, but megaloblastic anemia may occur because of genetic or acquired abnormalities that affect the metabolism of these vitamins or because of defects in DNA synthesis not related to cobalamin or folate **(Table 95-1)**. Cobalamin and folate absorption and metabolism are described next, followed by the biochemical basis, clinical and laboratory features, causes, and treatment of megaloblastic anemia.

TABLE 95-1 Causes of Megaloblastic Anemia

Cobalamin deficiency or abnormalities of cobalamin metabolism **(see Tables 95-3, 95-4)**
Folate deficiency or abnormalities of folate metabolism **(see Table 95-5)**
Therapy with antifolate drugs (e.g., methotrexate)
Independent of either cobalamin or folate deficiency and refractory to cobalamin and folate therapy:
Some cases of acute myeloid leukemia, myelodysplasia
Therapy with drugs interfering with synthesis of DNA (e.g., cytosine arabinoside, hydroxyurea, 6-mercaptopurine, azidothymidine [AZT])
Orotic aciduria (responds to uridine)
Thiamine-responsive

COBALAMIN

Cobalamin (vitamin B_{12}) exists in a number of different chemical forms. All have a cobalt atom at the center of a corrin ring. In nature, the vitamin is mainly in the 2-deoxyadenosyl (ado) form, which is located in mitochondria. It is the cofactor for the enzyme L-methylmalonyl coenzyme A (CoA) mutase. The other major natural cobalamin is methylcobalamin, the form in human plasma and in cell cytoplasm. It is the cofactor for methionine synthase. There are also minor amounts of hydroxocobalamin to which methyl- and adocobalamin are converted rapidly by exposure to light.

DIETARY SOURCES AND REQUIREMENTS

Cobalamin is synthesized solely by microorganisms. Ruminants obtain cobalamin from the foregut, but the only source for humans is food of animal origin, for example, meat, fish, and dairy products. Vegetables, fruits, and other foods of nonanimal origin are free from cobalamin unless they are contaminated by bacteria. A normal Western diet contains 5–30 µg of cobalamin daily. Adult daily losses (mainly in the urine and feces) are 1–3 µg (~0.1% of body stores), and because the body does not have the ability to degrade cobalamin, daily requirements are also about 1–3 µg. Body stores are of the order of 2–3 mg, sufficient for 3–4 years if supplies are completely cut off.

ABSORPTION

Two mechanisms exist for cobalamin absorption. One is passive, occurring equally through buccal, duodenal, and ileal mucosa; it is rapid but extremely inefficient, with <1% of an oral dose being absorbed by this process. The normal physiologic mechanism is active; it occurs through the ileum and is efficient for small (a few micrograms) oral doses of cobalamin, and it is mediated by gastric intrinsic factor (IF). Dietary cobalamin is released from protein complexes by enzymes in the stomach, duodenum, and jejunum; it combines rapidly with a salivary glycoprotein that belongs to the family of cobalamin-binding proteins known as haptocorrins (HCs). In the intestine, the HC is digested by pancreatic trypsin and the cobalamin is transferred to IF.

IF (gene at chromosome 11q13) is produced in the gastric parietal cells of the fundus and body of the stomach, and its secretion parallels that of hydrochloric acid. Normally, there is a vast excess of IF. The IF-cobalamin complex passes to the ileum, where IF attaches to a specific receptor (cubilin) on the microvillus membrane of the enterocytes. Cubilin also is present in yolk sac and renal proximal tubular epithelium. Cubilin appears to traffic by means of amnionless (AMN), an endocytic receptor protein that directs sublocalization and endocytosis of cubilin with its ligand IF-cobalamin complex. The cobalamin-IF complex enters the ileal cell, where IF is destroyed. After a delay of about 6 h, the cobalamin appears in portal blood attached to transcobalamin (TC) II.

Between 0.5 and 5 µg of cobalamin enter the bile each day. This binds to IF, and a major portion of biliary cobalamin normally is reabsorbed together with cobalamin derived from sloughed intestinal cells. Because of the appreciable amount of cobalamin undergoing enterohepatic circulation, cobalamin deficiency develops more rapidly in individuals who malabsorb cobalamin than it does in vegans, in whom reabsorption of biliary cobalamin is intact.

TRANSPORT

Two main cobalamin transport proteins exist in human plasma; they both bind cobalamin—one molecule for one molecule. One HC, also known as TC I, is closely related to other cobalamin-binding HCs in milk, gastric juice, bile, saliva, and other fluids. The gene *TCNL* is at chromosome 11q11-q12.3. These HCs differ from each other only in the carbohydrate moiety of the molecule. TC I is derived primarily from the specific granules in neutrophils. Normally, it is about two-thirds saturated with cobalamin, which it binds tightly. TC I does not enhance cobalamin entry into tissues. Glycoprotein receptors on liver cells are involved in the removal of TC I from plasma, and TC I may play a role in the transport of cobalamin analogues (which it binds more effectively than IF) to the liver for excretion in bile.

The other major cobalamin transport protein in plasma is transcobalamin, also known as TC II. The gene is on chromosome 22q11-q13.1. As for IF and HC, there are nine exons. The three proteins are likely to have a common ancestral origin. TC II is synthesized by liver and by other tissues, including macrophages, ileum, and vascular endothelium. It normally carries only 20–60 ng of cobalamin per liter of plasma and readily gives up cobalamin to marrow, placenta, and other tissues, which it enters by receptor-mediated endocytosis involving the TC II receptor and megalin (encoded by the *LRP-2* gene). The TC II cobalamin is internalized by endocytosis via clathrin-coated pits; the complex is degraded, but the receptor probably is recycled to the cell membrane as is the case for transferrin. Export of "free" cobalamin is via the ATP-binding cassette drug transporter alias multidrug resistance protein 1.

FOLATE

DIETARY FOLATE

Folic (pteroylglutamic) acid is a yellow, crystalline, water-soluble substance. It is the parent compound of a large family of natural folate compounds, which differ from it in three respects: (1) they are partly or completely reduced to dihydrofolate (DHF) or tetrahydrofolate (THF) derivatives, (2) they usually contain a single carbon unit **(Table 95-2)**, and (3) 70–90% of natural folates are folate-polyglutamates.

Most foods contain some folate. The highest concentrations are found in liver, yeast, spinach, other greens, and nuts (>100 µg/100 g). The total folate content of an average Western diet is ~250 µg daily, but the amount varies widely according to the type of food eaten and the method of cooking. Folate is easily destroyed by heating, particularly in large volumes of water. Total body folate in the adult is ~10 mg, with the liver containing the largest store. Daily adult requirements are ~100 µg, and so stores are sufficient for only 3–4 months in normal adults and severe folate deficiency may develop rapidly.

ABSORPTION

Folates are absorbed rapidly from the upper small intestine. The absorption of folate polyglutamates is less efficient than that of monoglutamates; on average, ~50% of food folate is absorbed. Polyglutamate forms are hydrolyzed to the monoglutamate derivatives either in the lumen of the intestine or within the mucosa. All dietary folates are converted to 5-methylTHF (5-MTHF) within the small intestinal mucosa before entering portal plasma. The monoglutamates are actively transported across the enterocyte by a proton-coupled folate transporter (PCFT, SCL46A1). This is situated at the apical brush border and is most active at pH 5.5, which is about the pH of the duodenal and jejunal surface. Genetic mutations of this protein underlie hereditary malabsorption of folate (see below). Pteroylglutamic acid at doses >400 µg is absorbed largely unchanged and converted to natural folates in the liver. Lower doses are converted to 5-MTHF during absorption through the intestine.

About 60–90 µg of folate enters the bile each day and is excreted into the small intestine. Loss of this folate, together with the folate of sloughed intestinal cells, accelerates the speed with which folate deficiency develops in malabsorption conditions.

TRANSPORT

Folate is transported in plasma; about one-third is loosely bound to albumin, and two-thirds is unbound. In all body fluids (plasma,

TABLE 95-2 Biochemical Reactions of Folate Coenzymes

REACTION	COENZYME FORM OF FOLATE INVOLVED	SINGLE CARBON UNIT TRANSFERRED	IMPORTANCE
Formate activation	THF	–CHO	Generation of 10-formyl-THF
Purine synthesis			
Formation of glycinamide ribonucleotide	5,10-Methylene-THF	–CHO	Formation of purines needed for DNA, RNA synthesis, but reactions probably not rate-limiting
Formylation of aminoimidazole carboxamide ribonucleotide (AICAR)	10-Formyl (CHO)THF		
Pyrimidine synthesis			
Methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP)	5,10-Methylene-THF	$-CH_3$	Rate limiting in DNA synthesis Oxidizes THF to DHF Some breakdown of folate at the C-9–N-10 bond
Amino acid interconversion			
Serine–glycine interconversion	THF	$=CH_2$	Entry of single carbon units into active pool
Homocysteine to methionine	5-Methyl(M)THF	$-CH_3$	Demethylation of 5-MTHF to THF; also requires cobalamin, flavine adenine dinucleotide, ATP, and adenosylmethionine
Forminoglutamic acid to glutamic acid in histidine catabolism	THF	–HN–CH=	

Abbreviations: DHF, dihydrofolate; THF, tetrahydrofolate.

cerebrospinal fluid, milk, bile), folate is largely, if not entirely, 5-MTHF in the monoglutamate form. Three types of folate-binding protein are involved. A reduced folate transporter (RFC, SLC19A1) is the major route of delivery of plasma folate (5-MTHF) to cells. Two folate receptors, FR2 and FR3 embedded in the cell membrane by a glycosyl phosphatidylinositol anchor, transport folate into the cell via receptor-mediated endocytosis. The third protein, PCFT, transports folate at low pH from the vesicle to the cell cytoplasm. The reduced folate transporter also mediates uptake of methotrexate by cells.

BIOCHEMICAL FUNCTIONS

Folates (as the intracellular polyglutamate derivatives) act as coenzymes in the transfer of single-carbon units (Fig. 95-1 and Table 95-2). Two of these reactions are involved in purine synthesis and one in pyrimidine synthesis necessary for DNA and RNA replication. Folate is also a coenzyme for methionine synthesis, in which methylcobalamin is also involved and in which THF is regenerated. THF is the acceptor of single carbon units newly entering the active pool via conversion of serine to glycine. Methionine, the other product of the methionine synthase reaction, is the precursor for *S*-adenosylmethionine (SAM), the universal methyl donor involved in >100 methyltransferase reactions (Fig. 95-1).

During thymidylate synthesis, 5,10-methylene-THF is oxidized to DHF. The enzyme DHF reductase converts this to THF. The drugs methotrexate, pyrimethamine, and (mainly in bacteria) trimethoprim inhibit DHF reductase and so prevent formation of active THF coenzymes from DHF. A small fraction of the folate coenzyme is not recycled during thymidylate synthesis but is degraded at the C9-N10 bond.

BIOCHEMICAL BASIS OF MEGALOBLASTIC ANEMIA

The common feature of all megaloblastic anemias is a defect in DNA synthesis that affects rapidly dividing cells in the bone marrow. All conditions that give rise to megaloblastic changes have in common a disparity in the rate of synthesis or availability of the four immediate precursors of DNA: the deoxyribonucleoside triphosphates (dNTPs)—dA(adenine)TP and dG(guanine)TP (purines), dT(thymine)TP, and dC(cytosine)TP (pyrimidines). In deficiencies of either folate or cobalamin, there is failure to convert deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), the precursor of dTTP (Fig. 95-1). This is the case because folate is needed as the coenzyme 5,10-methylene-THF polyglutamate for conversion of dUMP to dTMP; the availability of 5,10-methylene-THF is reduced in either cobalamin or folate deficiency. DNA replication from multiple origins along the chromosome is slower than normal during mitosis, and there is failure of joining up the incomplete replicons with resulting single stranded DNA breaks. An alternative theory for megaloblastic anemia in cobalamin or folate deficiency is misincorporation of uracil into DNA because of the accumulation of deoxyuridine triphosphate (dUTP) at the DNA replication fork as a consequence of the block in conversion of dUMP to dTMP.

COBALAMIN-FOLATE RELATIONS

Folate is required for many reactions in mammalian tissues. Only two reactions in the body are known to require cobalamin. Methylmalonyl-CoA isomerization requires adocobalamin, and the methylation of homocysteine to methionine requires both methylcobalamin and 5-MTHF (Fig. 95-1). This reaction is the first step in the pathway by which 5-MTHF, which enters bone marrow and other cells from plasma, is converted into all the intracellular folate coenzymes. The coenzymes are all polyglutamated (the larger size aiding retention in the cell), but the enzyme folate polyglutamate synthase can use only THF, not MTHF, as substrate. In cobalamin deficiency, MTHF accumulates in plasma, and intracellular folate concentrations fall due to failure of formation of THF, the substrate on which folate polyglutamates are built. This has been termed *THF starvation*, or the *methylfolate trap*.

This theory explains the abnormalities of folate metabolism that occur in cobalamin deficiency (high serum folate, low cell folate, positive purine precursor aminoimidazole carboxamide ribonucleotide [AICAR] excretion; Table 95-2) and also why the anemia of cobalamin deficiency responds to folic acid in large doses.

CLINICAL FEATURES

Many symptomless patients are detected through the finding of a raised mean corpuscular volume (MCV) on a routine blood count. The main clinical features in more severe cases are those of anemia. Anorexia is usually marked, and there may be weight loss, diarrhea, or constipation. Glossitis, angular cheilosis, a mild fever in more severely anemic patients, jaundice (unconjugated), and reversible melanin skin hyperpigmentation also may occur with a deficiency of either folate or cobalamin. Thrombocytopenia sometimes leads to bruising, and this may be aggravated by vitamin C deficiency or alcohol in malnourished patients. The anemia and low leukocyte count may predispose to infections, particularly of the respiratory and urinary tracts. Cobalamin deficiency has also been associated in a few studies with impaired bactericidal function of phagocytes and with osteoporosis.

Neurologic Manifestations Vitamin B_{12} is needed for the myelination of the central nervous system. Its deficiency may cause a bilateral peripheral neuropathy or degeneration (demyelination) of the cervical and thoracic posterior and lateral (pyramidal) tracts of the

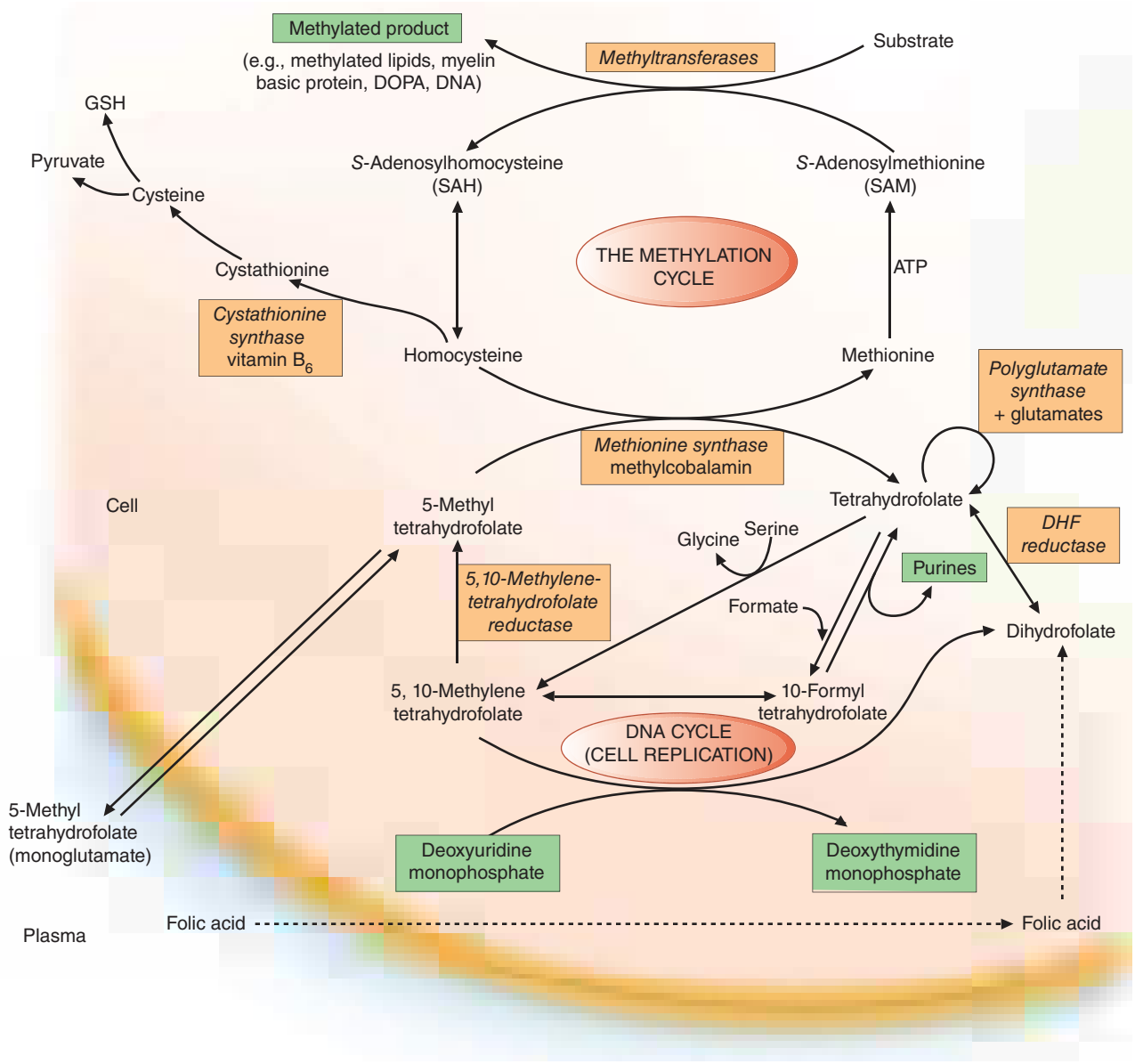


FIGURE 95-1 The role of folates in DNA synthesis and in formation of *S*-adenosylmethionine (SAM), which is involved in numerous methylation reactions. DHF, dihydrofolate; GSH, glutathione. *(Reprinted from AV Hoffbrand et al [eds]: Postgraduate Haematology, 5th ed. Oxford, UK, Blackwell Publishing, 2005; with permission.)*

spinal cord and, less frequently, of the cranial nerves and of the white matter of the brain. Optic atrophy and cerebral symptoms including dementia, depression, psychotic symptoms, and cognitive impairment may be prominent. There may also be anosmia and loss of taste. MRI may show the "spongy" degeneration of the cord.

The patient, more frequently male, typically presents with paresthesias, muscle weakness, or difficulty in walking but sometimes with the dementia, psychotic disturbances, or visual impairment. There is usually loss of proprioception and vibration sensation with positive Romberg and Lhermitte signs. Gait may be ataxic with spasticity (hyperreflexia). Autonomic nervous dysfunction can result in postural hypotension, impotence, and incontinence.

Long-term nutritional cobalamin deficiency in infancy leads to poor brain development and impaired intellectual development. In infancy there may be feeding difficulties, lethargy, and coma. Convulsions and myoclonus have been described. An important clinical problem is the non-anemic patient with neurologic or psychiatric abnormalities and a low or borderline serum cobalamin level. In such patients, it is necessary to try to establish whether there is significant cobalamin deficiency, for example, by careful examination of the blood film, tests for pernicious anemia (PA) by serum gastrin level and for antibodies to IF or parietal cells, along with serum methylmalonic acid (MMA) measurement if available. A trial of cobalamin therapy for at least 3 months will usually also be needed to determine whether the symptoms improve.

The biochemical basis for cobalamin neuropathy remains obscure. Its occurrence in the absence of methylmalonic aciduria in TC II deficiency suggests that the neuropathy is related to the defect in homocysteine-methionine conversion. Accumulation of *S*-adenosylhomocysteine in the brain, resulting in inhibition of transmethylation reactions, has been suggested. Folate deficiency has been suggested to cause organic nervous disease, but this is uncertain, although methotrexate injected into the cerebrospinal fluid may cause brain or spinal cord damage.

Psychiatric disturbance as discussed above is common in both folate and cobalamin deficiencies. This, like the neuropathy, has been attributed to a failure of the synthesis of SAM, which is needed in methylation of biogenic amines (e.g., dopamine) as well as that of proteins, phospholipids, and neurotransmitters in the brain (Fig. 95-1). Associations between lower serum folate or cobalamin levels and higher homocysteine levels and the development of decreased cognitive function and dementia in Alzheimer's disease have been reported. A meta-analysis of randomized, placebo-controlled trials of homocysteine-lowering B-vitamin supplementation of individuals with and

without cognitive impairment, however, showed that supplementation with vitamin B_{12}, vitamin B_6, and folic acid alone or in combination did not improve cognitive function. It is unknown whether prolonged treatment with these B vitamins can reduce the risk of dementia in later life.

GENERAL TISSUE EFFECTS OF COBALAMIN AND FOLATE DEFICIENCIES

Epithelial Surfaces After the marrow, the next most frequently affected tissues are the epithelial cell surfaces of the mouth (with glossitis), stomach, and small intestine and the respiratory, urinary, and female genital tracts. The cells show macrocytosis, with increased numbers of multinucleate and dying cells. The deficiencies may cause cervical smear abnormalities.

Complications of Pregnancy The gonads are also affected, and infertility is common in both men and women with severe deficiency of either vitamin. Maternal folate deficiency has been implicated as a cause of prematurity, and both folate deficiency and cobalamin deficiency have been implicated in recurrent fetal loss and neural tube defects, as discussed below.

Neural Tube Defects Folic acid supplements at the time of conception and in the first 12 weeks of pregnancy reduce by ~70% the incidence of neural tube defects (NTDs) (anencephaly, meningomyelocele, encephalocele, and spina bifida) in the fetus. Most of this protective effect can be achieved by taking folic acid, 0.4 mg daily, at the time of conception.

The incidence of cleft palate and harelip also can be reduced by prophylactic folic acid. There is no clear simple relationship between maternal folate status and these fetal abnormalities, although overall the lower the maternal folate, the greater the risk to the fetus. NTDs also can be caused by antifolate and antiepileptic drugs.

An underlying maternal folate metabolic abnormality has also been postulated. One abnormality has been identified: reduced activity of the enzyme 5,10-methylene-THF reductase (MTHFR) (Fig. 95-1) caused by a common C677T polymorphism in the *MTHFR* gene. In one study, the prevalence of this polymorphism was found to be higher than in controls in the parents of NTD fetuses and in the fetuses themselves: homozygosity for the TT mutation was found in 13% of cases compared with 5% of control subjects. The polymorphism codes for a thermolabile form of MTHFR. The homozygous state results in a lower mean serum and red cell folate level compared with control subjects, as well as significantly higher serum homocysteine levels. Tests for mutations in other enzymes possibly associated with NTDs, for example, methionine synthase and serine–glycine hydroxymethylase, have been negative. Serum vitamin B_{12} levels are also lower in the sera of mothers of NTD infants than in controls. In addition, maternal TC II receptor polymorphisms are associated with increased risk of NTD births. There are, however, no studies showing dietary fortification with vitamin B_{12} reduces the incidence of NTDs.

Cardiovascular Disease Children with severe homocystinuria (blood levels ≥100 μmol/L) due to deficiency of one of three enzymes, methionine synthase, MTHFR, or cystathionine synthase (Fig. 95-1), have vascular disease, for example, ischemic heart disease, cerebrovascular disease, or pulmonary embolus, as teenagers or in young adulthood. Lesser degrees of raised serum homocysteine and low levels of serum folate and homozygous inherited mutations of MTHFR have been found to be associated with cerebrovascular, peripheral vascular, and coronary heart disease and with deep vein thrombosis. Prospective randomized trials of lowering homocysteine levels with supplements of folic acid, vitamin B_{12}, and vitamin B_6 against placebo over a 5-year period in patients with vascular disease or diabetes have not, however, shown a reduction of first event fatal or nonfatal myocardial infarction, nor have these supplements reduced the risk of recurrent cardiovascular disease after an acute myocardial infarct. Meta-analysis showed an 18% reduction in strokes. The benefit for stroke prevention has been confirmed by a large (>20,000 subjects) randomized prospective study in hypertensive subjects in China. This showed a significant reduction in the first incidence of stroke in subjects receiving enalapril and folic acid compared to enalapril alone. This was especially marked in the subjects commencing the prospective trial with the lowest serum folate levels. Venous thrombosis has been reported to be more frequent in folate– or vitamin B_{12}– deficient subjects than in controls and to occur at unusual sites such as cerebral venous sinuses. This was ascribed to raised plasma homocysteine levels in folate or vitamin B_{12} deficiency.

Malignancy Prophylactic folic acid in pregnancy has been found in some but not all studies to reduce the subsequent incidence of acute lymphoblastic leukemia (ALL) in childhood. A significant negative association has also been found with the *MTHFR* C677T polymorphism and leukemias with mixed lineage leukemia (MLL) translocations, but a positive association with hyperdiploidy in infants with ALL or acute myeloid leukemia or with childhood ALL. A second polymorphism in the *MTHFR* gene, A1298C, is also strongly associated with hyperdiploid leukemia. There are various positive and negative associations between polymorphisms in folate-dependent enzymes and the incidence of adult ALL. The C677T polymorphism is thought to lead to increased thymidine pools and "better quality" of DNA synthesis by shunting one-carbon groups toward thymidine and purine synthesis. This may explain its reported association with a lower risk for colorectal cancer. Most but not all studies suggest that prophylactic folic acid also protects against colon adenomas. Other tumors that have been associated with folate polymorphisms or status include follicular lymphoma, breast cancer, and gastric cancer. A meta-analysis of 50,000 individuals given folic acid (0.5–40 mg daily) or placebo in cardiovascular or colon adenoma prevention trials found that folic acid supplementation did not significantly increase or decrease the overall incidence of cancer or of any site-specific cancer during a weighted average scheduled treatment duration of 5.7 years. Because folic acid may "feed" tumors, it probably should be avoided in those with established tumors unless there is severe megaloblastic anemia due to folate deficiency.

HEMATOLOGIC FINDINGS

PERIPHERAL BLOOD

Oval macrocytes, usually with considerable anisocytosis and poikilocytosis, are the main feature **(Fig. 95-2*A*)**. The MCV is usually >100 fL unless a cause of microcytosis (e.g., iron deficiency or thalassemia trait) is present. Some of the neutrophils are hypersegmented (more than five nuclear lobes). There may be leukopenia due to a reduction in granulocytes and lymphocytes, but this is usually $>1.5 \times 10^9$/L; the platelet count may be moderately reduced, rarely to $<40 \times 10^9$/L. The severity of all these changes parallels the degree of anemia. In a nonanemic patient, the presence of a few macrocytes and hypersegmented neutrophils in the peripheral blood may be the only indication of the underlying disorder.

BONE MARROW

In a severely anemic patient, the marrow is hypercellular with an accumulation of primitive cells due to selective death by apoptosis of more mature forms. The erythroblast nucleus maintains a primitive appearance despite maturation and hemoglobinization of the cytoplasm. The cells are larger than normoblasts, and an increased number of cells with eccentric lobulated nuclei or nuclear fragments may be present **(Fig. 95-2*B*)**. Giant and abnormally shaped metamyelocytes and enlarged hyperpolyploid megakaryocytes are characteristic. In severe cases, the accumulation of primitive cells may mimic acute myeloid leukemia, whereas in less anemic patients, the changes in the marrow may be difficult to recognize. The terms *intermediate*, *mild*, and *early* have been used. The term *megaloblastoid* does not mean mildly megaloblastic. It is used to describe cells with both immature-appearing nuclei and defective hemoglobinization and is usually seen in myelodysplasia.

CHROMOSOMES

Bone marrow cells, transformed lymphocytes, and other proliferating cells in the body show a variety of changes, including random breaks, reduced contraction, spreading of the centromere, and exaggeration of secondary chromosomal constrictions and overprominent satellites.

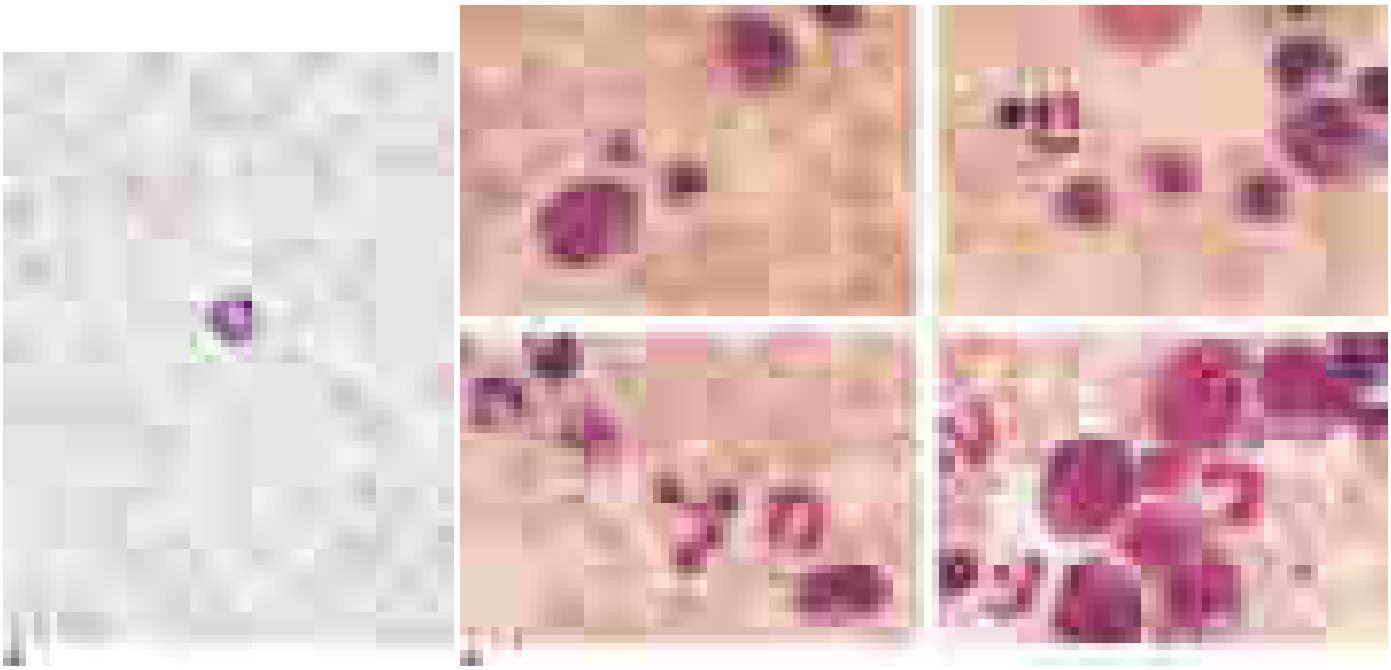


FIGURE 95-2 ***A.*** The peripheral blood in severe megaloblastic anemia. ***B.*** The bone marrow in severe megaloblastic anemia. *(Reprinted from AV Hoffbrand et al [eds]: Postgraduate Haematology, 5th ed. Oxford, UK, Blackwell Publishing, 2005; with permission.)*

Similar abnormalities may be produced by antimetabolite drugs (e.g., cytosine arabinoside, hydroxyurea, and methotrexate) that interfere with either DNA replication or folate metabolism and that also cause megaloblastic appearances.

INEFFECTIVE HEMATOPOIESIS

There is an accumulation of unconjugated bilirubin in plasma due to the death of nucleated red cells in the marrow (ineffective erythropoiesis). Other evidence for this includes raised urine urobilinogen, reduced haptoglobins and positive urine hemosiderin, and a raised serum lactate dehydrogenase. A weakly positive direct antiglobulin test due to complement can lead to a false diagnosis of autoimmune hemolytic anemia.

CAUSES OF COBALAMIN DEFICIENCY

Cobalamin deficiency is usually due to malabsorption. The only other cause is inadequate dietary intake.

INADEQUATE DIETARY INTAKE

Adults Dietary cobalamin deficiency arises in vegans who omit meat, fish, eggs, cheese, and other animal products from their diet. The largest group in the world consists of Hindus, and it is likely that many millions of Indians are at risk of deficiency of cobalamin on a nutritional basis. Subnormal serum cobalamin levels are found in up to 50% of randomly selected, young, adult Indian vegans, but the deficiency usually does not progress to megaloblastic anemia since the diet of most vegans is not totally lacking in cobalamin and the enterohepatic circulation of cobalamin is intact. Dietary cobalamin deficiency may also arise rarely in non-vegetarian individuals who exist on grossly inadequate diets because of poverty or psychiatric disturbance.

Infants Cobalamin deficiency has been described in infants born to severely cobalamin-deficient mothers. These infants develop megaloblastic anemia at about 3–6 months of age, presumably because they are born with low stores of cobalamin and because they are fed breast milk with low cobalamin content. The babies have also shown growth retardation, impaired psychomotor development, and other neurologic sequelae. MRI shows delayed myelination and atrophy.

GASTRIC CAUSES OF COBALAMIN MALABSORPTION

See Tables 95-3 and 95-4.

Formerly, the pathogenesis of B_{12} malabsorption was distinguishable based on the results of a Schilling test in which a radioactive form of B_{12} was administered orally and its appearance in the urine was a sign of absorption. Radioactive B_{12} is no longer available, and Schilling tests are no longer performed. Other approaches to the differential diagnosis of B_{12} malabsorption are now employed.

Pernicious Anemia PA may be defined as a severe lack of IF due to gastric atrophy. It is a common disease in northern Europeans but occurs in all countries and ethnic groups. It is more frequent in people of African than Asian ancestry. The overall incidence is about 120 per 100,000 population in the United Kingdom (UK). The ratio of incidence in men and women among whites is ~1:1.6, and the median age of onset is 70–80 years, with only 10% of patients being <40 years of age. However, in some ethnic groups, notably black individuals and Latin Americans, the age at onset of PA is generally lower. The disease occurs more commonly than by chance in close relatives and in persons with other organ-specific autoimmune diseases, for example, thyroid diseases, vitiligo, hypoparathyroidism, Type 1 diabetes, and Addison's disease. It is also associated with hypogammaglobulinemia, with premature graying or blue eyes, and persons of blood group A. An association with human leukocyte antigen (HLA) 3 has been reported in some but not all series and, in those with endocrine disease, with HLA-B8, -B_{12}, and -BW15. Life expectancy is normal in women once regular

TABLE 95-3 Causes of Cobalamin Deficiency Sufficiently Severe to Cause Megaloblastic Anemia

NUTRITIONAL	VEGANS
Malabsorption	Pernicious anemia
Gastric causes	Congenital absence of intrinsic factor or functional abnormality
	Total or partial gastrectomy
Intestinal causes	Intestinal stagnant loop syndrome: jejunal diverticulosis, ileocolic fistula, anatomic blind loop, intestinal stricture, etc.
	Ileal resection and Crohn's disease
	Selective malabsorption with proteinuria
	Tropical sprue
	Transcobalamin II deficiency
	Fish tapeworm

TABLE 95-4 Malabsorption of Cobalamin May Occur in the Following Conditions but Is Not Usually Sufficiently Severe and Prolonged to Cause Megaloblastic Anemia

Gastric causes
Simple atrophic gastritis (food cobalamin malabsorption)
Zollinger-Ellison syndrome
Gastric bypass or bariatric surgery
Use of proton pump inhibitors
Intestinal causes
Gluten-induced enteropathy
Severe pancreatitis
HIV infection
Radiotherapy
Graft-versus-host disease
Deficiencies of cobalamin, folate, protein, ?riboflavin, ?nicotinic acid
Therapy with colchicine, para-aminosalicylate, neomycin, slow-release potassium chloride, anticonvulsant drugs,?metformin*, cytotoxic drugs
Alcohol

*It is now thought that metformin lowers serum vitamin B_{12} level by lowering the level of TC I.

treatment has begun. Men had a slightly subnormal life expectancy as a result of a higher incidence of carcinoma of the stomach than in control subjects, but current data on their life expectancy are unavailable. Gastric output of hydrochloric acid, pepsin, and IF is severely reduced. The serum gastrin level is raised, and serum pepsinogen I levels are low.

Gastric Biopsy A single endoscopic examination is recommended if PA is diagnosed. Gastric biopsy usually shows atrophy of all layers of the body and fundus, with loss of glandular elements, an absence of parietal and chief cells and replacement by mucous cells, a mixed inflammatory cell infiltrate, and perhaps intestinal metaplasia. The infiltrate of plasma cells and lymphocytes contains an excess of CD4 cells. These are directed against gastric H/K-ATPase. The antral mucosa is usually well preserved. *Helicobacter pylori* infection occurs infrequently in PA, but it has been suggested that *H. pylori* gastritis occurs at an early phase of atrophic gastritis and presents in younger patients as iron-deficiency anemia but in older patients as PA. *H. pylori* is suggested to stimulate an autoimmune process directed against parietal cells, with the *H. pylori* infection then being gradually replaced, in some individuals, by an autoimmune process.

Serum Antibodies Two types of IF immunoglobulin G antibody may be found in the sera of patients with PA. One, the "blocking," or type I, antibody, prevents the combination of IF and cobalamin, whereas the "binding," or type II, antibody prevents attachment of IF to ileal mucosa. Type I occurs in the sera of ~55% of patients, and type II in 35%. IF antibodies cross the placenta and may cause temporary IF deficiency in a newborn infant. Patients with PA also show cell-mediated immunity to IF. Type I antibody has been detected rarely in the sera of patients without PA but with thyrotoxicosis, myxedema, Hashimoto's disease, or diabetes mellitus and in relatives of PA patients. IF antibodies also have been detected in gastric juice in ~80% of PA patients. These gastric antibodies may reduce absorption of dietary cobalamin by combining with small amounts of remaining IF.

Parietal cell antibody is present in the sera of almost 90% of adult patients with PA but is frequently present in other subjects. Thus, it occurs in as many as 16% of randomly selected female subjects age >60 years. The parietal cell antibody is directed against the α and β subunits of the gastric proton pump (H^+, K^+-ATPase).

JUVENILE PERNICIOUS ANEMIA

This usually occurs in older children and resembles PA of adults. Gastric atrophy, achlorhydria, and serum IF antibodies are all present, although parietal cell antibodies are usually absent. About one-half of these patients show an associated endocrinopathy such as autoimmune thyroiditis, Addison's disease, or hypoparathyroidism; in some, mucocutaneous candidiasis occurs.

CONGENITAL INTRINSIC FACTOR DEFICIENCY OR FUNCTIONAL ABNORMALITY

An affected child usually presents with megaloblastic anemia in the first to third year of life; a few have presented as late as the second decade. The child usually has no demonstrable IF but has a normal gastric mucosa and normal secretion of acid. The inheritance is autosomal recessive. Parietal cell and IF antibodies are absent. Variants have been described in which the child is born with IF that can be detected immunologically but is unstable or functionally inactive, unable to bind cobalamin or to facilitate its uptake by ileal receptors.

GASTRECTOMY

After total gastrectomy, cobalamin deficiency is inevitable, and prophylactic cobalamin therapy should be commenced immediately after the operation. After partial gastrectomy, 10–15% of patients also develop this deficiency. The exact incidence and time of onset are most influenced by the size of the resection and the preexisting size of cobalamin body stores.

FOOD COBALAMIN MALABSORPTION

Failure of release of cobalamin from binding proteins in food is believed to be responsible for this condition, which is more common in the elderly. It is associated with low serum cobalamin levels, with or without raised serum levels of MMA and homocysteine. Typically, these patients have normal cobalamin absorption, as measured with crystalline cobalamin, but show malabsorption when a modified test using food-bound cobalamin is used. It is usually due to mild forms of atrophic gastritis or therapy with proton pump inhibitors. Bariatric surgery is likely to be an increasing cause of this form of B_{12} malabsorption and deficiency. The frequency of progression to severe cobalamin deficiency and the reasons for this progression are not clear.

INTESTINAL CAUSES OF COBALAMIN MALABSORPTION

Intestinal Stagnant Loop Syndrome Malabsorption of cobalamin occurs in a variety of intestinal lesions in which there is colonization of the upper small intestine by fecal organisms. This may occur in patients with jejunal diverticulosis, enteroanastomosis, or an intestinal stricture or fistula or with an anatomic blind loop due to Crohn's disease, tuberculosis, or an operative procedure.

Ileal Resection Removal of ≥1.2 m of terminal ileum causes malabsorption of cobalamin. In some patients after ileal resection, particularly if the ileocecal valve is incompetent, colonic bacteria may contribute further to the onset of cobalamin deficiency.

Selective Malabsorption of Cobalamin with Proteinuria (Imerslund's Syndrome; Imerslund-Gräsbeck Syndrome; Congenital Cobalamin Malabsorption; Autosomal Recessive Megaloblastic Anemia; MGA1) This autosomally recessive disease is the most common cause of megaloblastic anemia due to cobalamin deficiency in infancy in Western countries. More than 200 cases have been reported with familial clusters in Finland, Norway, the Middle East, and North Africa. The patients secrete normal amounts of IF and gastric acid but are unable to absorb cobalamin. In Finland, impaired synthesis, processing, or ligand binding of cubilin due to inherited mutations is found. In Norway, mutation of the gene for *AMN* has been reported. Other tests of intestinal absorption are normal. Over 90% of these patients show nonspecific proteinuria, but renal function is otherwise normal, and renal biopsy has not shown any consistent renal defect. A few have shown aminoaciduria and congenital renal abnormalities, such as duplication of the renal pelvis.

Tropical Sprue Nearly all patients with acute and subacute tropical sprue show malabsorption of cobalamin; this may persist as the principal abnormality in the chronic form of the disease, when the patient may present with megaloblastic anemia or neuropathy due to cobalamin deficiency. Absorption of cobalamin usually improves after antibiotic therapy and, in the early stages, folic acid therapy.

Fish Tapeworm Infestation The fish tapeworm (*Diphyllobothrium latum*) lives in the small intestine of humans and accumulates cobalamin from food, rendering the cobalamin unavailable for absorption. Individuals acquire the worm by eating raw or partly cooked fish. Infestation is common around the lakes of Scandinavia, Germany, Japan, North America, and Russia. Megaloblastic anemia or cobalamin neuropathy occurs only in those with a heavy infestation.

Gluten-Induced Enteropathy Malabsorption of cobalamin occurs in ~30% of untreated patients (presumably those in whom the disease extends to the ileum). Cobalamin deficiency is not severe in these patients and is corrected with a gluten-free diet.

Severe Chronic Pancreatitis In this condition, lack of trypsin is thought to cause dietary cobalamin attached to gastric non-IF (R) binder to be unavailable for absorption. It also has been proposed that in pancreatitis, the concentration of calcium ions in the ileum falls below the level needed to maintain normal cobalamin absorption.

HIV Infection Serum cobalamin levels tend to fall in patients with HIV infection and are subnormal in 10–35% of those with AIDS. Malabsorption of cobalamin not corrected by IF has been shown in some, but not all, patients with subnormal serum cobalamin levels. Cobalamin deficiency sufficiently severe to cause megaloblastic anemia or neuropathy is rare.

Zollinger-Ellison Syndrome Malabsorption of cobalamin has been reported in the Zollinger-Ellison syndrome. It is thought that there is a failure to release cobalamin from R-binding protein due to inactivation of pancreatic trypsin by high acidity, as well as interference with IF binding of cobalamin.

Radiotherapy Both total-body irradiation and local radiotherapy to the ileum (e.g., as a complication of radiotherapy for carcinoma of the cervix) may cause malabsorption of cobalamin.

Graft-versus-Host Disease This commonly affects the small intestine. Malabsorption of cobalamin due to abnormal gut flora, as well as damage to ileal mucosa, is common.

Drugs The drugs that have been reported to cause malabsorption of cobalamin are listed in Table 95-4. However, megaloblastic anemia due to these drugs is rare. It has been suggested that metformin lowers serum B_{12} by lowering TC I level rather than causing malabsorption of B_{12}.

ABNORMALITIES OF COBALAMIN METABOLISM

Congenital Transcobalamin II Deficiency or Abnormality Infants with TC II deficiency usually present with megaloblastic anemia within a few weeks of birth. Serum cobalamin and folate levels are normal, but the anemia responds to massive (e.g., 1 mg three times weekly) injections of cobalamin. Some cases show neurologic complications. The protein may be present but functionally inert. Genetic abnormalities found include mutations of an intra-exonic cryptic splice site, extensive deletion, single nucleotide deletion, nonsense mutation, and an RNA editing defect. Malabsorption of cobalamin occurs in all cases, and serum immunoglobulins are usually reduced. Failure to institute adequate cobalamin therapy or treatment with folic acid may lead to neurologic damage.

Congenital Methylmalonic Acidemia and Aciduria Infants with this abnormality are ill from birth with vomiting, failure to thrive, severe metabolic acidosis, ketosis, and mental retardation. Anemia, if present, is normocytic and normoblastic. The condition may be due to a functional defect in either mitochondrial methylmalonyl-CoA mutase or its cofactor adocobalamin. Mutations in the methylmalonyl-CoA mutase are not responsive, or only poorly responsive, to treatment with cobalamin. A proportion of infants with failure of adocobalamin synthesis respond to cobalamin in large doses. Some children have combined methylmalonic aciduria and homocystinuria due to defective formation of both cobalamin coenzymes. This usually presents in the first year of life with feeding difficulties, developmental delay, microcephaly, seizures, hypotonia, and megaloblastic anemia.

Acquired Abnormality of Cobalamin Metabolism: Nitrous Oxide Inhalation Nitrous oxide (N_2O) irreversibly oxidizes methylcobalamin to an inactive precursor; this inactivates methionine synthase. Megaloblastic anemia has occurred in patients undergoing prolonged N_2O anesthesia (e.g., in intensive care units). A neuropathy resembling cobalamin neuropathy has been described in dentists and anesthetists who are exposed repeatedly to N_2O. Methylmalonic aciduria does not occur as adocobalamin is not inactivated by N_2O.

CAUSES OF FOLATE DEFICIENCY
(Table 95-5)

NUTRITIONAL
Dietary folate deficiency is common. Indeed, in most patients with folate deficiency a nutritional element is present. Certain individuals are particularly prone to have diets containing inadequate amounts of folate (Table 95-5). In the United States and other countries where fortification of the diet with folic acid has been adopted, the prevalence of folate deficiency has dropped dramatically and is now almost restricted to high-risk groups with increased folate needs. Nutritional folate deficiency occurs in kwashiorkor and scurvy and in infants with repeated infections or those who are fed solely on goats' milk, which has a low folate content.

MALABSORPTION
Malabsorption of dietary folate occurs in tropical sprue and in gluten-induced enteropathy. In the rare congenital recessive syndrome of selective malabsorption of folate due to mutation of the PCFT, there is an associated defect of folate transport into the cerebrospinal fluid, and these patients show megaloblastic anemia, which responds to

TABLE 95-5 Causes of Folate Deficiency

Dietary[a]
Particularly in: old age, infancy, poverty, alcoholism, chronic invalids, and the psychiatrically disturbed; may be associated with scurvy or kwashiorkor
Malabsorption
Major causes of deficiency
Tropical sprue, gluten-induced enteropathy in children and adults, and in association with dermatitis herpetiformis, specific malabsorption of folate, intestinal megaloblastosis caused by severe cobalamin or folate deficiency
Minor causes of deficiency
Extensive jejunal resection, Crohn's disease, partial gastrectomy, congestive heart failure, Whipple's disease, scleroderma, amyloid, diabetic enteropathy, systemic bacterial infection, lymphoma, sulfasalazine (Salazopyrin)
Excess utilization or loss
Physiologic
Pregnancy and lactation, prematurity
Pathologic
Hematologic diseases: chronic hemolytic anemias, sickle cell anemia, thalassemia major, myelofibrosis
Malignant diseases: carcinoma, lymphoma, leukemia, myeloma
Inflammatory diseases: tuberculosis, Crohn's disease, psoriasis, exfoliative dermatitis, malaria
Metabolic disease: homocystinuria
Excess urinary loss: congestive heart failure, active liver disease
Hemodialysis, peritoneal dialysis
Antifolate drugs[b]
Anticonvulsant drugs (phenytoin, primidone, barbiturates), sulfasalazine
Nitrofurantoin, tetracycline, antituberculosis (less well documented)
Mixed causes
Liver diseases, alcoholism, intensive care units

[a]In severely folate-deficient patients with causes other than those listed under Dietary, poor dietary intake is often present. [b]Drugs inhibiting dihydrofolate reductase are discussed in the text.

physiologic doses of folic acid given parenterally but not orally. They also show mental retardation, convulsions, and other central nervous system abnormalities. Minor degrees of malabsorption may also occur after jejunal resection or partial gastrectomy, in Crohn's disease, and in systemic infections, but in these conditions, if severe deficiency occurs, it is usually largely due to poor nutrition. Malabsorption of folate has been described in patients receiving sulfasalazine (Salazopyrin), cholestyramine, and triamterene.

EXCESS UTILIZATION OR LOSS

Pregnancy Folate requirements are increased by 200–300 µg to ~400 µg daily in a normal pregnancy, partly because of transfer of the vitamin to the fetus but mainly because of increased folate catabolism due to cleavage of folate coenzymes in rapidly proliferating tissues. Megaloblastic anemia due to this deficiency is prevented by prophylactic folic acid therapy. It occurred in 0.5% of pregnancies in the UK and other Western countries before prophylaxis with folic acid, but the incidence is much higher in countries where the general nutritional status is poor.

Prematurity A newborn infant, whether full term or premature, has higher serum and red cell folate concentrations than does an adult. However, a newborn infant's demand for folate has been estimated to be up to 10 times that of adults on a weight basis, and the neonatal folate level falls rapidly to the lowest values at about 6 weeks of age. The falls are steepest and are liable to reach subnormal levels in premature babies, a number of whom develop megaloblastic anemia responsive to folic acid at about 4–6 weeks of age. This occurs particularly in the smallest babies (<1500 g birth weight) and those who have feeding difficulties or infections or have undergone multiple exchange transfusions. In these babies, prophylactic folic acid should be given.

Hematologic Disorders Folate deficiency frequently occurs in chronic hemolytic anemia, particularly in sickle cell disease, autoimmune hemolytic anemia, and congenital spherocytosis. In these and other conditions of increased cell turnover (e.g., myelofibrosis, malignancies), folate deficiency arises because it is not completely reutilized after performing coenzyme functions.

Inflammatory Conditions Chronic inflammatory diseases such as tuberculosis, rheumatoid arthritis, Crohn's disease, psoriasis, exfoliative dermatitis, bacterial endocarditis, and chronic bacterial infections cause deficiency by reducing the appetite and increasing the demand for folate. Systemic infections also may cause malabsorption of folate. Severe deficiency is virtually confined to the patients with the most active disease and the poorest diet.

Homocystinuria This is a rare metabolic defect in the conversion of homocysteine to cystathionine. Folate deficiency occurring in most of these patients may be due to excessive utilization because of compensatory increased conversion of homocysteine to methionine.

Long-Term Dialysis Because folate is only loosely bound to plasma proteins, it is easily removed from plasma by dialysis. In patients with anorexia, vomiting, infections, and hemolysis, folate stores are particularly likely to become depleted. Routine folate prophylaxis is now given.

Congestive Heart Failure, Liver Disease Excess urinary folate losses of >100 µg per day may occur in some of these patients. The explanation appears to be release of folate from damaged liver cells.

ANTIFOLATE DRUGS

A large number of epileptics who are receiving long-term therapy with phenytoin or primidone, with or without barbiturates, develop low serum and red cell folate levels. The exact mechanism is unclear. Alcohol may also be a folate antagonist, as patients who are drinking spirits may develop megaloblastic anemia that will respond to normal quantities of dietary folate or to physiologic doses of folic acid only if alcohol is withdrawn. Macrocytosis of red cells is associated with chronic alcohol intake even when folate levels are normal. Inadequate folate intake is the major factor in the development of deficiency in spirit-drinking alcoholics. Beer is relatively folate-rich in some countries, depending on the technique used for brewing.

The drugs that inhibit DHF reductase include methotrexate, pyrimethamine, and trimethoprim. Methotrexate has the most powerful action against the human enzyme, whereas trimethoprim is most active against the bacterial enzyme and is likely to cause megaloblastic anemia only when used in conjunction with sulfamethoxazole in patients with preexisting folate or cobalamin deficiency. The activity of pyrimethamine is intermediate. The antidote to these drugs is folinic acid (5-formyl-THF).

CONGENITAL ABNORMALITIES OF FOLATE METABOLISM

Some infants with congenital defects of folate enzymes (e.g., cyclohydrolase or methionine synthase) have had megaloblastic anemia.

DIAGNOSIS OF COBALAMIN AND FOLATE DEFICIENCIES

The diagnosis of cobalamin or folate deficiency has traditionally depended on the recognition of the relevant abnormalities in the peripheral blood and analysis of the blood levels of the vitamins.

COBALAMIN DEFICIENCY

Serum Cobalamin This is measured by an automated enzyme-linked immunosorbent assay (ELISA) or competitive-binding luminescence assay (CBLA). Normal serum levels range from 118–148 pmol/L (160–200 ng/L) to ~738 pmol/L (1000 ng/L). In patients with megaloblastic anemia due to cobalamin deficiency, the level is usually <74 pmol/L (100 ng/L). In general, the more severe the deficiency, the lower is the serum cobalamin level. In patients with spinal cord damage due to the deficiency, levels are very low even in the absence of anemia. Values between 74 and 148 pmol/L (100 and 200 ng/L) are regarded as borderline. They may occur, for instance, in pregnancy, in patients with megaloblastic anemia due to folate deficiency. They may also be due to heterozygous, homozygous, or compound heterozygous mutations of the gene *TCN1* that codes for HC (transcobalamin I). There is then no clinical or hematologic abnormality. The serum cobalamin level is sufficiently robust, cost-effective, and most convenient to rule out cobalamin deficiency in the vast majority of patients suspected of having this problem. However, problems have arisen with commercial CBLA assays involving IF in PA patients with intrinsic antibodies in serum. These antibodies may cause false normal serum vitamin B_{12} levels in up to 50% of cases tested. Where clinical indications of PA are strong, a normal serum vitamin B_{12} does not rule out the diagnosis. Serum MMA levels will be elevated in untreated PA (see below).

Folate deficiency, transcobalamin 1 (HC) deficiency, oral contraceptives, and multiple myeloma have all been associated with low serum B_{12} levels that do not indicate B_{12} deficiency. On the other hand, high serum B_{12} levels are usually due to raised serum transcobalamin 1 levels and can be due to the presence of liver, renal, or myeloproliferative diseases or to cancer of the breast, colon, or liver.

Serum Methylmalonate and Homocysteine In patients with cobalamin deficiency sufficient to cause anemia or neuropathy, the serum MMA level is raised. Sensitive methods for measuring MMA and homocysteine in serum have been introduced and recommended for the early diagnosis of cobalamin deficiency, even in the absence of hematologic abnormalities or subnormal levels of serum cobalamin. Serum MMA levels fluctuate, however, in patients with renal failure. Mildly elevated serum MMA and/or homocysteine levels occur in up to 30% of apparently healthy volunteers, with serum cobalamin levels up to 258 pmol/L (350 ng/L) and normal serum folate levels; 15% of elderly subjects, even with cobalamin levels >258 pmol/L (>350 ng/L), have this pattern of raised metabolite levels. These findings bring into question the exact cutoff points for normal MMA and homocysteine levels. It is also unclear at present whether these mildly raised metabolite levels have clinical consequences.

Serum homocysteine is raised in both early cobalamin and folate deficiency but may be raised in other conditions, for example, chronic renal disease, alcoholism, smoking, pyridoxine deficiency, hypothyroidism, and therapy with steroids, cyclosporine, and other drugs. Levels are also higher in serum than in plasma, in men than in premenopausal women, in women taking hormone replacement therapy or in oral contraceptive users, and in elderly persons and patients with several inborn errors of metabolism affecting enzymes in transsulfuration pathways of homocysteine metabolism. Thus, homocysteine levels must be carefully interpreted for diagnosis of cobalamin or folate deficiency.

Tests for the Cause of Cobalamin Deficiency Only vegans, strict vegetarians, or people living on a totally inadequate diet will become vitamin B_{12} deficient because of inadequate intake. Studies of cobalamin absorption once were widely used, but difficulty in obtaining radioactive cobalamin and ensuring that IF preparations are free of viruses has made these tests obsolete. Tests to diagnose PA include serum gastrin, which is raised; serum pepsinogen I, which is low in PA (90–92%) but also in other conditions; and gastric endoscopy. Tests for IF and parietal cell antibodies are also used, as well as tests for individual intestinal diseases.

FOLATE DEFICIENCY

Serum Folate This is also measured by an ELISA technique. In most laboratories, the normal range is from 11 nmol/L (2 µg/L) to ~82 nmol/L (15 µg/L). The serum folate level is low in all folate-deficient patients. It also reflects recent diet. Because of this, serum folate may be low before there is hematologic or biochemical evidence of deficiency. Serum folate rises in severe cobalamin deficiency because of the block in conversion of MTHF to THF inside cells; raised levels have also been reported in the intestinal stagnant loop syndrome due to absorption of bacterially synthesized folate.

Red Cell Folate The red cell folate assay is a valuable test of body folate stores. It is less affected than the serum assay by recent diet and traces of hemolysis. In normal adults, concentrations range from 880 to 3520 µmol/L (160–640 µg/L) of packed red cells. Subnormal levels occur in patients with megaloblastic anemia due to folate deficiency but also in nearly two-thirds of patients with severe cobalamin deficiency. False-normal results may occur if a folate-deficient patient has received a recent blood transfusion or if a patient has a raised reticulocyte count. Serum homocysteine assay is discussed earlier.

Tests for the Cause of Folate Deficiency The diet history is important. Tests for transglutaminase antibodies are performed to confirm or exclude celiac disease. If positive, duodenal biopsy is needed. An underlying disease causing increased folate breakdown should also be excluded.

TREATMENT

Cobalamin and Folate Deficiency

It is usually possible to establish which of the two deficiencies, folate or cobalamin, is the cause of the anemia and to treat only with the appropriate vitamin. In patients who enter the hospital severely ill, however, it may be necessary to treat with both vitamins in large doses once blood samples have been taken for cobalamin and folate assays and a bone marrow biopsy has been performed (if deemed necessary). Transfusion is usually unnecessary and inadvisable. If it is essential, packed red cells should be given slowly, one or two units only, with the usual treatment for heart failure if present. Potassium supplements have been recommended to obviate the danger of the hypokalemia but are not necessary. Occasionally, an excessive rise in platelets occurs after 1–2 weeks of therapy. Antiplatelet therapy, for example, aspirin, should be considered if the platelet count rises to $>800 \times 10^9$/L.

COBALAMIN DEFICIENCY

It is usually necessary to treat patients who have developed cobalamin deficiency with lifelong regular cobalamin injections. In the UK, the form used is hydroxocobalamin; in the United States, cyanocobalamin. In a few instances, the underlying cause of cobalamin deficiency can be permanently corrected, for example, fish tapeworm, tropical sprue, or an intestinal stagnant loop that is amenable to surgery. The indications for starting cobalamin therapy are a well-documented megaloblastic anemia or other hematologic abnormalities and neuropathy due to the deficiency. Patients with borderline serum cobalamin levels but no hematologic or other abnormality may be followed to make sure that the cobalamin deficiency does not progress (see below). If malabsorption of cobalamin or rises in serum MMA levels have been demonstrated, however, these patients also should be given regular maintenance cobalamin therapy. Cobalamin should be given routinely to all patients who have had a total gastrectomy or ileal resection. Patients who have undergone gastric reduction for control of obesity or who are receiving long-term treatment with proton pump inhibitors should be screened and, if necessary, given cobalamin replacement.

Replenishment of body stores should be complete with six 1000-µg IM injections of hydroxocobalamin given at 3- to 7-day intervals. More frequent doses are usually used in patients with cobalamin neuropathy, but there is no evidence that they produce a better response. Allergic reactions are rare and may require desensitization or antihistamine or glucocorticoid cover. For maintenance therapy, 1000 µg hydroxocobalamin IM once every 3 months is satisfactory. Because of the poorer retention of cyanocobalamin, protocols generally use higher and more frequent doses, for example, 1000 µg IM, monthly, for maintenance treatment.

Because a small fraction of cobalamin can be absorbed passively through mucous membranes even when there is complete failure of physiologic IF-dependent absorption, large daily oral doses (1000–2000 µg) of cyanocobalamin are used in PA for replacement (especially in Canada and Sweden) and maintenance of normal cobalamin status in, for example, food malabsorption of cobalamin. Sublingual therapy has also been proposed for those in whom injections are difficult because of a bleeding tendency and who may not tolerate oral therapy. If oral therapy is used, it is important to monitor compliance, particularly with elderly, forgetful patients. This author prefers parenteral therapy for initial treatment, particularly in severe anemia or if a neuropathy is present, and for maintenance in PA. Oral B_{12} therapy even with low doses of 50 µg daily may have a larger role in treating food malabsorption of B_{12}.

For treatment of patients with subnormal serum vitamin B_{12} levels with a normal MCV and no hypersegmentation of neutrophils, a negative IF antibody test in the absence of tests of B_{12} absorption is problematic. Some (perhaps 15%) cases may be due to TC I (HC) deficiency. Homocysteine and/or MMA measurements may help, but in the absence of these tests and with otherwise normal gastrointestinal function, repeat serum B_{12} assay after 6–12 months may help one decide whether to start cobalamin therapy.

Vitamin B_{12} injections are used in a wide variety of diseases, often neurologic, despite normal serum B_{12} and folate levels and a normal blood count and in the absence of randomized, double-blind, controlled trials. These conditions include multiple sclerosis and chronic fatigue syndrome/myalgic encephalomyelitis (ME). It seems probable that any benefit is due to the placebo effect of a usually painless, pink injection. In ME, oral B_{12} therapy, despite providing equally large amounts of B_{12}, has not been beneficial, supporting the view of the effect of the injections being placebo only.

FOLATE DEFICIENCY

Oral doses of 5–15 mg folic acid daily are satisfactory, as sufficient folate is absorbed from these extremely large doses even in patients with severe malabsorption. The length of time therapy must be continued depends on the underlying disease. It is customary to continue therapy for about 4 months, when all folate-deficient red cells will have been eliminated and replaced by new folate-replete populations.

Before large doses of folic acid are given, cobalamin deficiency must be excluded and, if present, corrected; otherwise cobalamin

neuropathy may develop despite a response of the anemia of cobalamin deficiency to folate therapy. Studies in the United States, however, suggest that there is no increase in the proportion of individuals with low serum cobalamin levels and no anemia since food fortification with folic acid, but it is unknown if there has been a change in incidence of cobalamin neuropathy.

Long-term folic acid therapy is required when the underlying cause of the deficiency cannot be corrected and the deficiency is likely to recur, for example, in chronic dialysis or hemolytic anemias. It may also be necessary in gluten-induced enteropathy that does not respond to a gluten-free diet. Where mild but chronic folate deficiency occurs, it is preferable to encourage improvement in the diet after correcting the deficiency with a short course of folic acid. In any patient receiving long-term folic acid therapy, it is important to measure the serum cobalamin level at regular (e.g., once-yearly) intervals to exclude the coincidental development of cobalamin deficiency.

Folinic Acid (5-Formyl-THF) This is a stable form of fully reduced folate. It is given orally or parenterally to overcome the toxic effects of methotrexate or other DHF reductase inhibitors, for example, trimethoprim or cotrimoxazole.

PROPHYLACTIC FOLIC ACID

Prophylactic folic acid is used in chronic dialysis patients and in parenteral feeds. Prophylactic folic acid has been used to reduce homocysteine levels to prevent cardiovascular disease and for cognitive function in the elderly, but there are no firm data to show any benefit.

Pregnancy In over 70 countries (but none in Europe), food is fortified with folic acid (in grain or flour) to reduce the risk of NTDs. Nevertheless, folic acid, 400 µg daily, should be given as a supplement before and throughout pregnancy to prevent megaloblastic anemia and reduce the incidence of NTDs, even in countries with fortification of the diet. The levels of fortification provide up to 400 µg daily on average in Chile, but in most countries, it is nearer to 200 µg, so periconceptual folic acid is still needed. Most if not all the folic acid used in fortification and eaten over three meals a day will be converted during absorption to methyltetrahydrofolate. This compound will not correct the anemia in B_{12} deficiency. Studies in early pregnancy show significant lack of compliance with the folic acid supplements, emphasizing the benefit of food fortification. Supplemental folic acid reduces the incidence of birth defects in babies born to diabetic mothers. In women who have had a previous fetus with an NTD, 5 mg daily is recommended when pregnancy is contemplated and throughout the subsequent pregnancy.

Infancy and Childhood The incidence of folate deficiency is so high in the smallest premature babies during the first 6 weeks of life that folic acid (e.g., 1 mg daily) should be given routinely to those weighing <1500 g at birth and to larger premature babies who require exchange transfusions or develop feeding difficulties, infections, or vomiting and diarrhea.

The World Health Organization currently recommends routine supplementation with iron and folic acid in children in countries where iron deficiency is common and child mortality, largely due to infectious diseases, is high. However, some studies suggest that in areas where malaria rates are high, this approach may increase the incidence of severe illness and death. Even where malaria is rare, there appears to be no survival benefit.

MEGALOBLASTIC ANEMIA NOT DUE TO COBALAMIN OR FOLATE DEFICIENCY OR ALTERED METABOLISM

This may occur with many antimetabolic drugs (e.g., hydroxyurea, cytosine arabinoside, 6-mercaptopurine) that inhibit DNA replication. Antiviral nucleoside analogues used in treatment of HIV infection may also cause macrocytosis and megaloblastic marrow changes. In the rare disease orotic aciduria, two consecutive enzymes in purine synthesis are defective. The condition responds to therapy with uridine, which bypasses the block. In thiamine-responsive megaloblastic anemia, there is a genetic defect in the high-affinity thiamine transport (*SLC19A2*) gene. This causes defective RNA ribose synthesis through impaired activity of transketolase, a thiamine-dependent enzyme in the pentose cycle. This leads to reduced nucleic acid production. It may be associated with diabetes mellitus and deafness and the presence of many ringed sideroblasts in the marrow. The explanation is unclear for megaloblastic changes in the marrow in some patients with acute myeloid leukemia and myelodysplasia.

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96 Hemolytic Anemias

Lucio Luzzatto

DEFINITIONS

A finite life span is a distinct characteristic of red cells. Hence, a logical, time-honored classification of anemias is in three groups: (1) decreased production of red cells, (2) increased destruction of red cells, and (3) acute blood loss. Decreased production is covered in **Chaps. 93, 94, and 98**; acute blood loss in **Chap. 97**; increased destruction is covered in this chapter.

All patients who are anemic as a result of either increased destruction of red cells or acute blood loss have one important element in common: the anemia results from overconsumption of red cells from the peripheral blood, whereas the supply of cells from the bone marrow is normal (indeed, it is usually increased). On the other hand, these two groups differ in that the consequences of physical loss of red cells from the bloodstream or *from* the body itself, as in acute hemorrhage, is fundamentally different from destruction of red cells *within* the body, as in hemolytic anemias (HAs).

With respect to primary etiology, HAs may be *inherited* or *acquired*; from a clinical point of view, they may be more *acute* or more *chronic*, and they may vary from mild to very severe; the site of hemolysis may be predominantly *intravascular* or *extravascular*. With respect to mechanisms, HAs may be due to *intracorpuscular* causes or to *extracorpuscular* causes **(Table 96-1)**. But before reviewing the individual types of HA, it is appropriate to consider what general features they have in common, in terms of clinical aspects and of pathophysiology.

GENERAL CLINICAL AND LABORATORY FEATURES

The clinical presentation of a patient with anemia is greatly influenced in the first place by whether the onset is abrupt or gradual, and HAs are

TABLE 96-1 Classification of Hemolytic Anemias[a]

	INTRACORPUSCULAR DEFECTS	EXTRACORPUSCULAR FACTORS
Inherited	Hemoglobinopathies Enzymopathies Membrane-cytoskeletal defects	Familial (atypical) hemolytic-uremic syndrome
Acquired	Paroxysmal nocturnal hemoglobinuria (PNH)	Mechanical destruction (microangiopathic) Toxic agents Drugs Infectious Autoimmune

[a]Hereditary causes correlate with intracorpuscular defects because these defects are due to inherited mutations; the one exception is PNH because the defect is due to an acquired somatic mutation. Similarly, acquired causes correlate with extracorpuscular factors because mostly these factors are exogenous; the one exception is familial hemolytic-uremic syndrome (HUS; often referred to as atypical HUS) because here an inherited abnormality allows complement activation to be excessive, with bouts of production of membrane attack complex capable of destroying normal red cells. Interestingly, in both PNH and aHUS hemolysis is complement-mediated.

no exception. A patient with autoimmune HA or with favism may be a medical emergency, whereas a patient with mild hereditary spherocytosis (HS) or with cold agglutinin disease (CAD) may be diagnosed after years. This is due in large measure to the remarkable ability of the body to adapt to anemia when it is slowly progressing **(Chap. 59)**.

What differentiates HAs from other anemias is that the patient has signs and symptoms arising directly from hemolysis **(Table 96-2)**. At the clinical level, the main sign is *jaundice*; in addition, the patient may report discoloration of the urine. In many cases of HA, the spleen is enlarged because it is a preferential site of hemolysis; and in some cases, the liver may be enlarged as well. In all severe congenital forms of HA, there may be also skeletal changes due to overactivity of the bone marrow: they are never as severe as in thalassemia major because there is less ineffective erythropoiesis, or none at all.

The laboratory features of HA are related to (i) hemolysis per se, (ii) the erythropoietic response of the bone marrow. In most cases hemolysis is largely extravascular, and it produces an increase in unconjugated bilirubin and aspartate aminotransferase (AST) in the serum; urobilinogen will be increased in both urine and stool. If hemolysis is mainly intravascular, the telltale sign is hemoglobinuria (often associated with hemosiderinuria); in the serum there is free hemoglobin, lactate dehydrogenase (LDH) is increased, and haptoglobin is reduced. In contrast, the serum bilirubin level may be normal or only mildly elevated. The main sign of the erythropoietic response by the bone marrow is an increase in reticulocytes (a test all too often neglected in the initial workup of a patient with anemia). Usually the increase will be reflected in both the percentage of reticulocytes (the more commonly quoted figure) and in the absolute reticulocyte count (the more definitive parameter). The increased number of reticulocytes is associated with an increased mean corpuscular volume (MCV) in the blood count. On the blood smear, this is reflected in the presence of macrocytes; there is also polychromasia, and sometimes one sees nucleated red cells. In most cases, a bone marrow aspirate is not necessary in the diagnostic workup; if it is done, it will show erythroid hyperplasia. In practice, once an HA is suspected, specific tests will usually be required for a definitive diagnosis of a specific type of HA.

TABLE 96-2 Features Common to Most Patients with a Hemolytic Disorder

General examination	Jaundice, pallor
Other physical findings	Spleen may be enlarged; bossing of skull in severe congenital cases
Hemoglobin level	From normal to severely reduced
MCV, MCH	Usually increased
Reticulocytes	Usually Increased
Bilirubin	Almost always increased (mostly unconjugated)
LDH	Increased (up to 10× normal with intravascular hemolysis)
Haptoglobin	Reduced to absent if hemolysis is at least in part intravascular)

Abbreviations: LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume.

GENERAL PATHOPHYSIOLOGY

The mature red cell is the product of a developmental pathway that brings the phenomenon of differentiation to an extreme. An orderly sequence of events produces synchronous changes, whereby the gradual accumulation of a huge amount of hemoglobin in the cytoplasm (to a final level of 340 g/L, i.e., about 5 m*M*) goes hand in hand with the gradual loss of cellular organelles and of biosynthetic abilities. In the end, the erythroid cell undergoes a process that has features of apoptosis, including nuclear pyknosis and eventually extrusion of the nucleus. However, the final result is more altruistic than suicidal; the cytoplasmic body, instead of disintegrating, is now able to provide oxygen to all cells in the human organism for some remaining 120 days of the red cell life span.

As a result of this unique process of differentiation and maturation, intermediary metabolism is drastically curtailed in mature red cells **(Fig. 96-1)**; for instance, cytochrome-mediated oxidative

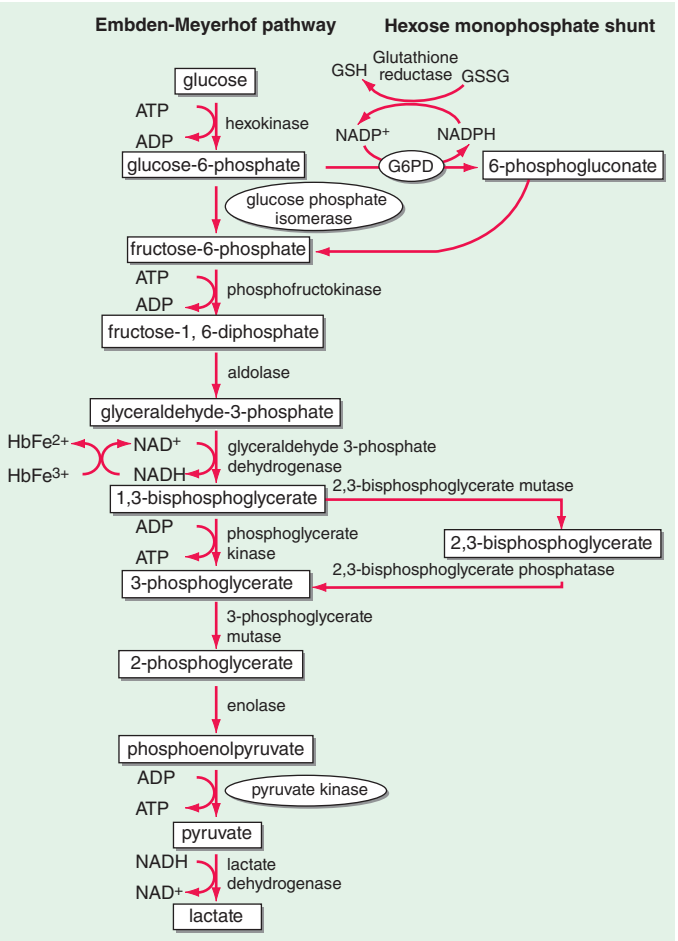

FIGURE 96-1 Red blood cell (RBC) metabolism. The Embden-Meyerhof pathway (glycolysis) generates ATP required for cation transport and for membrane maintenance. The generation of NADH maintains hemoglobin iron in a reduced state. The hexose monophosphate shunt generates NADPH that is used to reduce glutathione, which protects the red cell against oxidant stress; the 6-phosphogluconate, after decarboxylation, can be recycled via pentose sugars to glycolysis. Regulation of the 2,3-bisphosphoglycerate level is a critical determinant of oxygen affinity of hemoglobin. Enzyme deficiency states in order of prevalence: glucose 6-phosphate dehydrogenase (G6PD) > pyruvate kinase > glucose-6-phosphate isomerase > rare deficiencies of other enzymes in the pathway. The more common enzyme deficiencies are encircled.

phosphorylation has been lost with the loss of mitochondria (through a process of physiologic autophagy); therefore, there is no backup to anaerobic glycolysis, which in the red cell is the only provider of adenosine triphosphate (ATP). Also, the capacity of making protein has been lost with the loss of ribosomes. This places the cell's limited metabolic apparatus at risk, because if any protein component deteriorates, it cannot be replaced, as it would be in most other cells; and in fact the activity of most enzymes gradually decreases as red cells age. At the same time, during their long time in circulation, various red cell components inevitably accumulate damage; in senescent red cells, the membrane protein band 3 molecules (see below and Fig. 96-1), having bound hemichromes on their intracellular domains, tend to cluster. Now they bind anti–band 3 IgG antibodies (present in most people) and C3 complement fragments; thus they become opsonized and are eventually removed by phagocytosis in the reticuloendothelial system.

Another consequence of the relative simplicity of red cells is that they have a very limited range of ways to manifest distress under hardship; in essence, any sort of metabolic failure will eventually lead either to structural damage to the membrane or to failure of the cation pump. In either case, the life span of the red cell is reduced, which is the definition of a *hemolytic disorder*. If the rate of red cell destruction exceeds the capacity of the bone marrow to produce more red cells, the hemolytic disorder will manifest as HA.

Thus, the essential pathophysiologic process common to all HAs is an increased red cell turnover; and in many HAs, this is due at least in part to an acceleration of the senescence process described above. The gold standard for proving that the life span of red cells is reduced (compared to the normal value of about 120 days) is a *red cell survival* study, which can be carried out by labeling the red cells with ^{51}Cr and measuring the fall in radioactivity over several days or weeks (this classic test can now be replaced by a methodology using the nonradioactive isotope ^{15}N). If the hemolytic event is transient, it does not usually cause any long-term consequences, except for an increased requirement for erythropoietic factors, particularly folic acid. However, if hemolysis is recurrent or persistent, the increased bilirubin production favors the formation of gallstones. If a considerable proportion of hemolysis takes place in the spleen, as is often the case, splenomegaly may become increasingly a feature, and hypersplenism may develop, with consequent neutropenia and/or thrombocytopenia.

The increased red cell turnover also has metabolic consequences. In normal subjects, the iron from effete red cells is very efficiently recycled by the body; however, with chronic intravascular hemolysis, the persistent hemoglobinuria will cause considerable iron loss, needing replacement. With chronic extravascular hemolysis, the opposite problem, iron overload, is more common, especially if the patient needs frequent blood transfusions; however, if erythropoiesis is massively increased, the hepcidin-mediated regulation of iron absorption may be disturbed, to the extent that iron overload may set in even without blood transfusion. In the long run, in the absence of iron-chelation therapy iron overload will cause secondary hemochromatosis; this will cause damage particularly to the liver, eventually leading to cirrhosis; and to the heart muscle, eventually causing heart failure.

Compensated Hemolysis versus Hemolytic Anemia Red cell destruction is a potent stimulus for erythropoiesis, which is mediated by erythropoietin (EPO) produced by the kidney. This mechanism is so effective that in many cases the increased output of red cells from the bone marrow can fully balance an increased destruction of red cells. In such cases, we say that hemolysis is *compensated*. The pathophysiology of compensated hemolysis is similar to what we have just described, except there is no anemia. This notion is important from the diagnostic point of view, because a patient with a hemolytic condition, even an inherited one, may present without anemia; and it is also important from the point of view of management because compensated hemolysis may become "decompensated," i.e., anemia may suddenly appear in certain circumstances, for instance in pregnancy, folate deficiency, or renal failure interfering with adequate EPO production. Another general feature of chronic HAs is seen when any intercurrent condition, such as an acute infection, depresses erythropoiesis. When this happens, in view of the increased rate of red cell turnover, the effect will be predictably much more marked than in a person who does not have hemolysis. The most dramatic example is infection by parvovirus B19, which may cause a rather precipitous fall in hemoglobin—an occurrence sometimes referred to as *aplastic crisis*.

INHERITED HEMOLYTIC ANEMIAS

There are three essential components in the red cell: (1) hemoglobin, (2) the membrane-cytoskeleton complex, and (3) the metabolic machinery necessary to keep hemoglobin and the membrane-cytoskeleton complex in working order. Diseases caused by inherited abnormalities of hemoglobin, or hemoglobinopathies, are covered in **Chap. 94**. Here we will deal with diseases of the other two components.

Hemolytic Anemias due to Abnormalities of the Membrane-Cytoskeleton Complex The detailed architecture of the red cell membrane is complex, but its basic design is relatively simple **(Fig. 96-2)**. The lipid bilayer incorporates phospholipids and cholesterol, and it is spanned by a number of proteins that have their hydrophobic transmembrane domain(s) embedded in the membrane; most of these proteins also extend to both the outside (extracellular domains) and the inside of the cell (cytoplasmic domains). Other proteins are tethered to the membrane through a glycosylphosphatidylinositol (GPI) anchor; these have only an extracellular domain, and they include ion channels, receptors for complement components, and receptors for other ligands. The most abundant red cell membrane proteins are glycophorins and the so-called *band 3*, an anion transporter. The extracellular domains of many of these proteins are heavily glycosylated, and they carry antigenic determinants that correspond to blood groups. Underneath the membrane, and tangential to it, is a network of other proteins that make up the cytoskeleton. The main

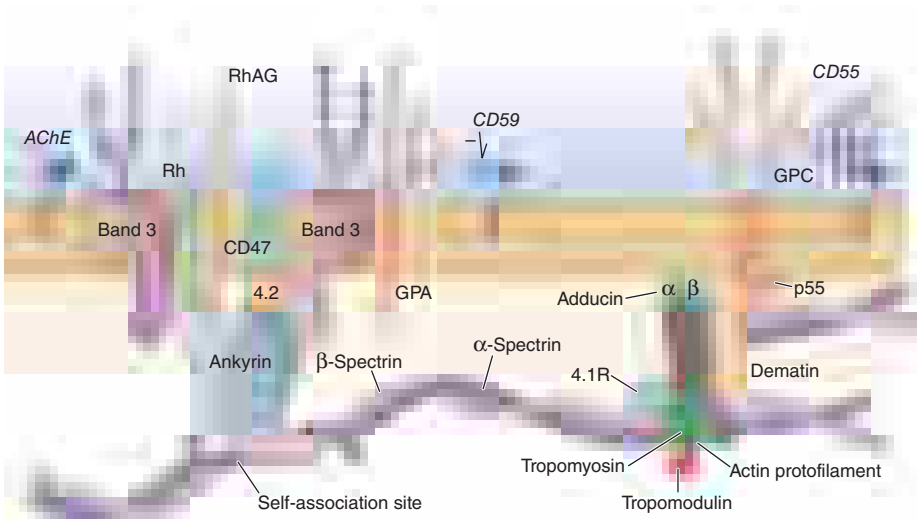

FIGURE 96-2 The red cell membrane. In this figure, one sees, within the lipid bilayer, several membrane proteins, of which band 3 (anion exchanger 1 [AE1]) is the most abundant; the α-β spectrin dimers that associate to form most of the cytoskeleton; and several proteins (e.g., ankyrin) that connect the membrane to the cytoskeleton. In addition, as examples of glycosylphosphatidylinositol (GPI)-linked proteins, one sees acetylcholinesterase (AChE) and the two complement-regulatory proteins CD59 and CD55. The (non-realistic) shapes of the protein moieties of the GPI-linked proteins are meant to indicate that each one of them is different from others and that, unlike with the other membrane proteins shown, the entire polypeptide chain is extracellular. Branched lines symbolize carbohydrate moiety of proteins. The molecules are obviously not drawn to the same scale. Additional explanations can be found in the text. *(From N Young et al: Clinical Hematology. Copyright Elsevier, 2006; with permission.)*

cytoskeletal protein is spectrin, the basic unit of which is a dimer of α-spectrin and β-spectrin. The membrane is physically linked to the cytoskeleton by a third set of proteins (including ankyrin and the so-called *band 4.1* and *band 4.2*), which thus make these two structures intimately connected to each other.

The membrane-cytoskeleton complex has essentially three functions: It is an envelope for the red cell cytoplasm, it maintains the normal red cells shape, it provides highly specific cross-membrane transport of electrolytes and of metabolites such as glucose. In the membrane-cytoskeleton complex the individual components are so intimately integrated with each other that an abnormality of almost any of them will be disturbing or disruptive, causing structural or functional failure, which results ultimately in hemolysis. These abnormalities are almost invariably inherited mutations; thus, diseases of the membrane-cytoskeleton complex belong to the category of inherited HAs. Before the red cells lyse, they often exhibit more or less specific morphologic changes that alter the normal biconcave disk shape. Thus, the majority of the diseases in this group have been known for over a century as hereditary spherocytosis (HS) and *hereditary elliptocytosis* (HE; as well as more rare ones like *stomatocytosis*, *xerocytosis*, etc). Now that their molecular basis has been elucidated, it has emerged **(see Table 96-3)** that, although we are dealing with monogenic disorders, there is no one-to-one correlation between a certain gene and a certain disorder. Rather, what has been regarded as a single disorder (e.g., HS) can arise through mutation of one of several genes; conversely, what have been regarded as different disorders can arise through different mutations of the very same gene **(Fig. 96-3)**.

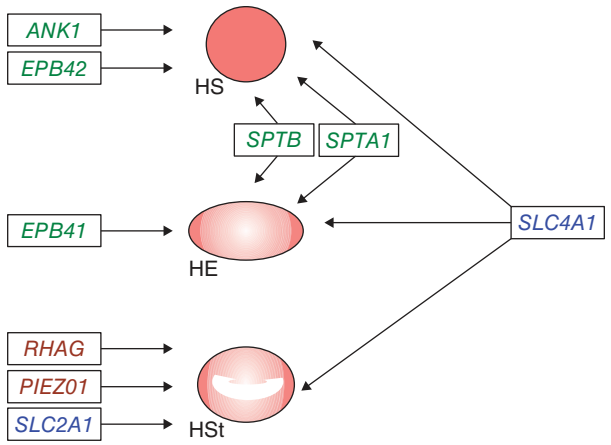

FIGURE 96-3 Hereditary spherocytosis (HS), hereditary elliptocytosis (HE), and hereditary stomatocytosis (HSt) are three morphologically distinct forms of congenital hemolytic anemia. It has emerged that each one can arise from mutation of one of several genes and that different mutations of the same gene can give one or another form. (See also Table 96-3.)

HEREDITARY SPHEROCYTOSIS This is a relatively common type of genetically determined HA, with an estimated frequency of at least 1 in 5000. Its identification is credited to Minkowksy and Chauffard, who, at the end of the nineteenth century, reported families who had the presence of numerous spherocytes in the peripheral blood **(Fig. 96-4*A*)**. In vitro studies revealed that the red cells were abnormally susceptible to lysis in hypotonic media; indeed, the presence of *osmotic fragility* became the main diagnostic test for HS. Today we know that HS, thus defined, is genetically heterogeneous; i.e., it can arise from a variety of mutations in one of several genes (Table 96-3). It has been also recognized that the inheritance of HS is not always autosomal dominant (with the patient being heterozygous); indeed, some of the most severe forms are instead autosomal recessive (with the patient being homozygous).

TABLE 96-3 Inherited Diseases of the Red Cell Membrane-Cytoskeleton Complex

GENE	CHROMOSOMAL LOCATION	PROTEIN PRODUCED	DISEASE(S) WITH CERTAIN MUTATIONS (INHERITANCE)	COMMENTS
SPTA1	1q22-q23	α-Spectrin	HS (recessive) HE (dominant)	Rare Mutations of this gene account for about 65% of HE. More severe forms may be due to coexistence of an otherwise silent mutant allele.
SPTB	14q23-q24.1	β-Spectrin	HS (dominant) HE (dominant)	Rare Mutations of this gene account for about 30% of HE, including some severe forms.
ANK1	8p11.2	Ankyrin	HS (dominant)	May account for majority of HS.
SLC4A1	17q21	Band 3; also known as AE (anion exchanger) or AE1	HS (dominant) Southeast Asia ovalocytosis (dominant) Stomatocytosis	Mutations of this gene may account for about 25% of HS. Polymorphic mutation (deletion of 9 amino acids); in heterozygotes clinically asymptomatic and protective against *Plasmodium falciparum.* Certain specific missense mutations shift protein function from anion exchanger to cation conductance.
EPB41	1p33-p34.2	Band 4.1	HE (dominant)	Mutations of this gene account for about 5% of HE, mostly with prominent morphology but little/no hemolysis in heterozygotes; severe hemolysis in homozygotes.
EPB42	15q15-q21	Band 4.2	HS (recessive)	Mutations of this gene account for about 3% of HS.
RHAG	6p21.1-p11	Rhesus-associated glycoprotein	Chronic nonspherocytic hemolytic anemia (recessive)	Very rare; associated with total loss of all Rh antigens. One specific mutation in this gene causes overhydrated stomatocytosis.
PIEZO1	16q23-q24	PIEZO1 (mechanosensitive cation channel)	Dehydrated hereditary stomatocytosis (dominant)	Also known as xerocytosis with pseudohyperkalemia. Patients may present with perinatal edema.
KCNN4	19q13.31	KCNN4 Intermediate conductance calcium-activated potassium channel protein 4	Dehydrated hereditary stomatocytosis (dominant)	Clinical presentation similar to that of *PIEZO1* mutants.
SLC2A1	1p34.2,	GLUT1 glucose transporter	Over-hydrated hereditary stomatocytosis	Associated with serious neurological manifestations.

Abbreviations: HE, hereditary elliptocytosis; HS, hereditary spherocytosis.

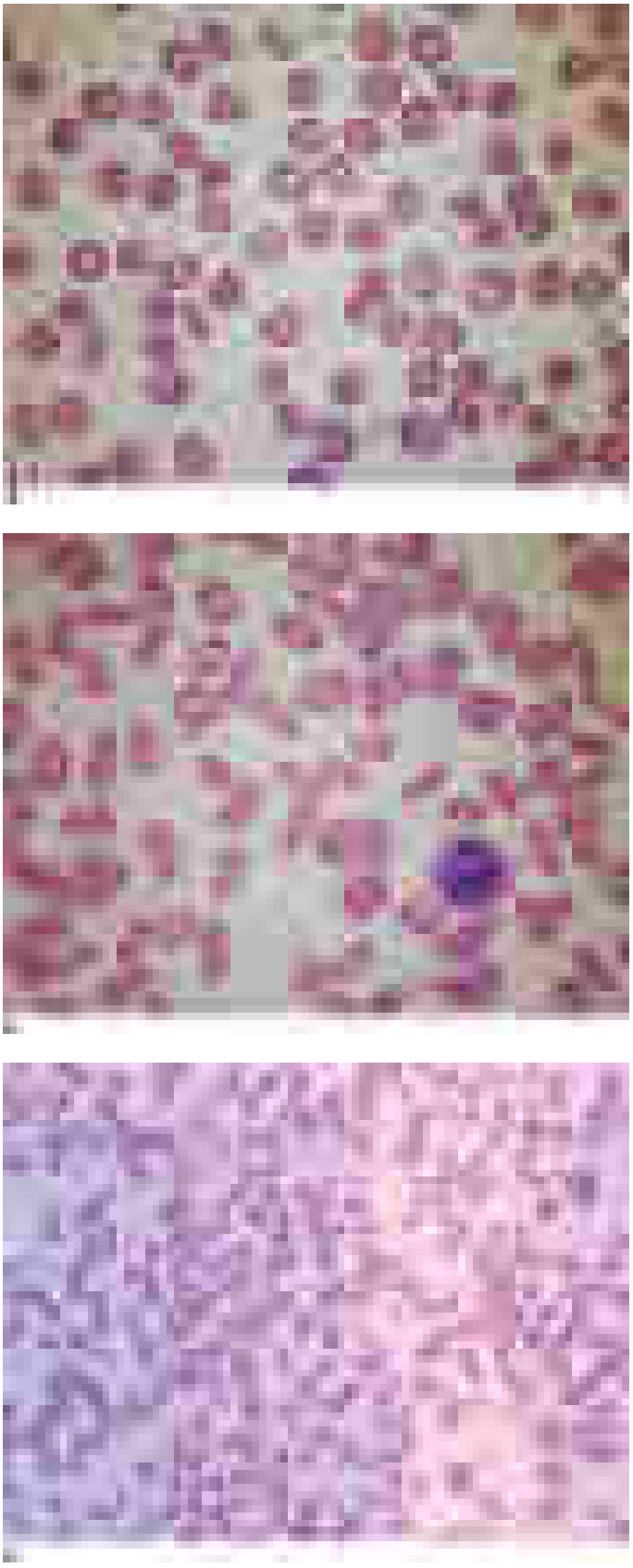

FIGURE 96-4 Peripheral blood smear from patients with membrane-cytoskeleton abnormalities. ***A.*** Hereditary spherocytosis. ***B.*** Hereditary elliptocytosis, heterozygote. ***C.*** Elliptocytosis, with both alleles of the α-spectrin gene mutated.

Clinical Presentation and Diagnosis The spectrum of clinical severity of HS is broad. Severe cases may present in infancy with severe anemia, whereas mild cases may present in young adults or even later in life. The main clinical findings are jaundice, an enlarged spleen, and often gallstones; indeed, it may be the finding of gallstones in a young person that triggers diagnostic investigations.

The variability in clinical manifestations that is observed among patients with HS is largely due to the different underlying molecular lesions (Table 96-3). Not only are mutations of several genes involved: even different mutations of the same gene can give very different clinical manifestations. In milder cases, hemolysis is often compensated (see above), but changes in clinical expression may be seen even in the same patient because intercurrent conditions (e.g., pregnancy, infection) may cause decompensation. The anemia is usually normocytic, with the characteristic morphology that gives the disease its name. An increased mean corpuscular hemoglobin concentration (MCHC >34) on an ordinary blood count report should raise the suspicion of HS, because HS is almost the only condition in which this abnormality occurs. It has been apparent for a long time that the spleen plays a special role in HS through a dual mechanism. On one hand, like in many other HAs, the spleen itself is a major site of destruction; on the other hand, transit through the splenic circulation makes the defective red cells more spherocytic and, therefore, accelerates their demise, even though that may take place elsewhere.

When there is a family history, it is usually easy to make a diagnosis based on features of HA and typical red cell morphology. However, there may be no family history for at least two reasons. First, the patient may have a de novo mutation, i.e., a mutation that has taken place in a germ cell of one of his parents or early after zygote formation. Second, the patient may have a recessive form of HS (Table 96-3). In such cases, more extensive laboratory investigations are required, including osmotic fragility, the acid glycerol lysis test, the eosin-5′-maleimide (EMA)–binding test, and SDS-gel electrophoresis of membrane proteins; these tests are usually carried out in laboratories with special expertise in this area. Sometimes a definitive diagnosis can be obtained only by molecular studies demonstrating a mutation in one of the genes underlying HS (Table 96-3).

TREATMENT

Hereditary Spherocytosis

We do not have a causal treatment for HS; i.e., no way has yet been found to correct the basic defect in the membrane-cytoskeleton structure. Given the special role of the spleen in HS (see above), it has long been thought that an almost obligatory therapeutic measure was splenectomy. Because this operation may have more than trivial consequences, today we have more articulate recommendations, based on disease severity, as follows. In mild cases, avoid splenectomy; in moderate cases, delay splenectomy until puberty; in severe cases, proceed with splenectomy at the age of 4–6. It is also helpful, whenever possible, to know about the outcome of splenectomy in the patient's affected relatives. Antipneumococcal vaccination before splenectomy is imperative, whereas penicillin prophylaxis after splenectomy is controversial. Along with splenectomy, cholecystectomy should not be carried out automatically; it should be carried out, usually by the laparoscopic approach, when clinically indicated.

HEREDITARY ELLIPTOCYTOSIS HE is at least as heterogeneous as HS, both from the genetic point of view (Table 96-3, Fig. 96-3) and from the clinical point of view. Again, it is the shape of the red cells **(Fig. 96-4*B*)** that gives the name to the condition, but there is no direct correlation between the elliptocytic morphology and clinical severity. In fact, some mild or even asymptomatic cases may have nearly 100% elliptocytes (or ovalocytes); whereas in severe cases all kinds of bizarre poikilocytes may predominate. Clinical features and recommended management are similar to those outlined above for HS. Although the spleen may

not have the specific role it has in HS, in severe cases, splenectomy may be beneficial. The prevalence of HE causing clinical disease is similar to that of HS. However, one particular in-frame deletion of nine amino acids in the *SLC4A1* gene encoding band 3, which underlies the so-called *Southeast Asia ovalocytosis* (SAO), has a frequency of up to 7% in certain populations, presumably as a result of malaria selection; it is asymptomatic in heterozygotes and probably lethal in homozygotes.

Disorders of Cation Transport These rare conditions with autosomal dominant inheritance are characterized by increased intracellular sodium in red cells, with concomitant loss of potassium; indeed, they are sometimes discovered through the incidental finding, in a blood test, of a high serum K^+ (*pseudohyperkalemia*). In patients from some families, the cation transport disturbance is associated with gain of water; as a result, the red cells are overhydrated (low MCHC), and on a blood smear, the normally round-shaped central pallor is replaced by a linear-shaped central pallor, which has earned this disorder the name *stomatocyto*sis (Fig. 96-3). In patients from other families, instead, the red cells are dehydrated (high MCHC), and their consequent rigidity has earned this disorder the name *xerocytosis*. One would surmise that in these disorders the primary defect may be in a cation transporter; indeed, xerocytosis results from mutations in *PIEZO1*. In other patients with stomatocytosis, mutations are found in other genes also related to solute transport (Table 96-3), including *SLC4A1* (encoding band 3), the Rhesus gene *RHAG*, and the glucose transporter gene *SLC2A1* responsible for a special form called cryohydrocytosis, an unusual variant in which the red cells swell and burst when they are cooled. In vivo hemolysis can vary from relatively mild to quite severe. From the practical point of view, it is important to know that in stomatocytosis splenectomy is strongly contraindicated because it has been followed in a significant proportion of cases by severe thromboembolic complications.

Enzyme Abnormalities When there is an important defect in a component of the membrane cytoskeleton complex, hemolysis is a direct consequence of the fact that the very structure of the red cell is compromised. Instead, when one of the enzymes is defective, the consequences will depend on the precise role of that enzyme in the metabolic machinery of the red cell. This machinery has two main functions: (1) to provide energy in the form of ATP and (2) to prevent oxidative damage to hemoglobin and to other proteins by providing sufficient reductive potential; the key molecule for this is NADPH.

ABNORMALITIES OF THE GLYCOLYTIC PATHWAY Because red cells, in the course of their differentiation, have sacrificed not only their nucleus and their ribosomes but also their mitochondria, they rely exclusively on the anaerobic portion of the glycolytic pathway for producing ATP, most of which is required by the red cell for cation transport against a concentration gradient across the membrane. If this fails due to a defect of any of the enzymes of the glycolytic pathway (Table 96-4), the result will be hemolytic disease.

Pyruvate Kinase Deficiency Abnormalities of the glycolytic pathway are all inherited and all rare. Among them, deficiency of pyruvate kinase (PK) is the least rare, with an estimated prevalence in most populations of the order of 1:10,000. However, recently, a polymorphic PK mutation

TABLE 96-4 Red Cell Enzyme Abnormalities Causing Hemolysis

	ENZYME (ACRONYM)	GENE SYMBOL; CHROMOSOMAL LOCATION	PREVALENCE OF ENZYME DEFICIENCY (RANK)	CLINICAL MANIFESTATIONS EXTRA-RED CELL	COMMENTS
Glycolytic Pathway					
	Hexokinase (HK)	*HK1*; 10q22	Very rare		May benefit from splenectomy; BMT[c]
	Glucose 6-phosphate isomerase (G6PI)	*GPI*; 19q31.1	Rare (4)[a]	NM, CNS	May benefit from splenectomy
	Phosphofructokinase (PFK)[b]	*PFKM*; 12q13	Very rare	Myopathy; myoglobinuria	
	Aldolase	*ALDOA*; 16q22-24	Very rare	Myopathy	
	Triose phosphate isomerase (TPI)	*TPI1*; 12p13.31	Very rare	CNS (severe), NM	
	Glyceraldehyde 3-phosphate dehydrogenase (GAPD)	*GAPDH*; 12p13.31-	Very rare	Myopathy	
	Bisphosphoglycerate mutase (DPGM)	*BPGM*; 7q33	Very rare		Erythrocytosis rather than hemolysis
	Phosphoglycerate kinase (PGK)	*PGK1*; Xq21.1	Very rare	CNS, NM	May benefit from splenectomy; BMT[c]
	Pyruvate kinase (PK)	*PKLR*; 1q22	Rare (2)[a]		May benefit from splenectomy; BMT[c]
Redox					
	Glucose 6-phosphate dehydrogenase (G6PD)	*G6PD*; Xq28	Common (1)[a]	Very rarely granulocytes	In almost all cases, only AHA from exogenous trigger
	Glutathione synthase	GSS; 20q11.22	Very rare	CNS	
	Glutathione reductase	*GSR:* 8p12	Very rare	Cataracts	AHA from exogenous trigger (favism)
	γ-Glutamylcysteine synthase	*GCLC*; 6p12.1	Very rare	CNS	Mutations affect catalytic subunit
	Cytochrome b5 reductase	*CYB5R3*: 22q13.2	Rare	CNS	Methemoglobinemia rather than hemolysis
Nucleotide Metabolism					
	Adenylate kinase (AK)	*AK1*; 9q34.11	Very rare	CNS	May benefit from splenectomy
	Pyrimidine 5' nucleotidase (P5N)	*NTSC3A*; 7p14.3	Rare (3)[a]		May benefit from splenectomy

[a]The numbers from (1) to (4) indicate the ranking order of these enzymopathies in terms of frequency. [b]PFK deficiency is associated with increased glycogen in muscle, and it is also known as glycogen storage disease type VII or Tarui's disease. [c]Occasional report of successful treatment of the hematologic manifestations by BMT.

Abbreviations: AHA, acquired hemolytic anemia; CNS, central nervous system; NM, neuromuscular.

(E277K) was found in some African populations, with heterozygote frequencies of 1–7%, suggesting that this may be another malaria-related polymorphism. The clinical picture of homozygous (or biallelic) PK deficiency is that of an HA that often presents in the newborn with neonatal jaundice; the jaundice persists, and it is often associated with reticulocytosis. The anemia is of variable severity; sometimes it is so severe as to require regular blood transfusion treatment, whereas sometimes it is mild, bordering on a nearly compensated hemolytic disorder. As a result, the diagnosis may be delayed: in some cases it is made, for instance, in a young woman during her first pregnancy, when the anemia may get worse. The delay in diagnosis may be caused in part by the fact that the anemia is often remarkably well tolerated, because the metabolic block at the last step in glycolysis causes an increase in 2,3-bisphosphoglycerate (or DPG; Fig. 96-1), a major effector of the hemoglobin-oxygen dissociation curve; thus, the oxygen delivery to the tissues is enhanced, a remarkable compensatory feat.

TREATMENT

Pyruvate Kinase Deficiency

The management of PK deficiency is mainly supportive. In view of the marked increase in red cell turnover, oral folic acid supplements should be given constantly. Blood transfusion should be used as necessary, and iron chelation may be required even in some patients who, though not receiving blood transfusion, may be developing iron overload (see "General Pathophysiology" above). In patients who have more severe disease splenectomy may be beneficial, as the anemia improves (paradoxically, reticulocytes often increase considerably). There is a single case report of curative treatment of PK deficiency by bone marrow transplantation (BMT) from an HLA-identical PK-normal sibling. This seems a viable option for severe cases when a sibling donor is available. Prenatal diagnosis has been carried out in a mother who had already had an affected child. A clinical trial of a small molecule that is a specific PK ligand and may increase the stability and/or catalytic efficiency of mutant PK is currently on-going. Rescue of inherited PK deficiency through lentiviral-mediated human PK gene transfer has been successful in mice.

Other Glycolytic Enzyme Abnormalities All of these defects are rare to very rare (Table 96-4), and most of them cause HA with varying degrees of severity. It is not unusual for the presentation to be in the guise of severe neonatal jaundice, which may require exchange transfusion; if the anemia is less severe, it may present later in life, or it may even remain asymptomatic and be detected incidentally when a blood count is done for unrelated reasons. The spleen is often enlarged. When other systemic manifestations occur, they can involve the central nervous system (sometimes entailing severe mental retardation, particularly in the case of triose phosphate isomerase deficiency), the neuromuscular system, or both (see Table 96-4). This is not altogether surprising, if we consider that these are housekeeping genes, i.e., expressed in all tissues. The *diagnosis* of HA is usually not difficult, thanks to the triad of normomacrocytic anemia, reticulocytosis, and hyperbilirubinemia. Enzymopathies should be considered in the differential diagnosis of any chronic Coombs-negative HA. Unlike with membrane disorders, in most cases of glycolytic enzymopathies morphologic abnormalities are conspicuous by their absence. A definitive diagnosis can be made only by demonstrating the deficiency of an individual enzyme by quantitative assays; these are carried out in only a few specialized laboratories. If a particular molecular abnormality is already known in the family, then one could test directly for that defect at the DNA level, thus bypassing the need for enzyme assays. Of course the time may be getting nearer when a patient will present with her or his exome already sequenced, and we will need to concentrate on which genes to look up within the file. The principles for the management of these conditions are similar as for PK deficiency. In isolated cases of glycolytic enzyme abnormalities BMT has been carried out successfully: although unfortunately non-hematologic manifestations, if any, are not reversed.

ABNORMALITIES OF REDOX METABOLISM • Glucose 6-Phosphate Dehydrogenase (G6PD) Deficiency G6PD is a housekeeping enzyme critical in the redox metabolism of all aerobic cells (Fig. 96-1). In red cells, its role is even more critical because it is the only source of NADPH, which directly and via glutathione (GSH) defends these cells against oxidative stress **(Fig. 96-5)**. G6PD deficiency-related HA is a prime example of an HA due to interaction between an intracorpuscular cause and an extracorpuscular cause because in the majority of cases hemolysis is triggered by an exogenous agent. Although a decrease in G6PD activity is present in most tissues of G6PD-deficient subjects, in other cells the decrease is much less pronounced than in red cells, and it does not seem to impact on clinical expression.

GENETIC CONSIDERATIONS

The *G6PD* gene is X-linked, and this has important implications. First, because males have only one *G6PD* gene (i.e., they are hemizygous for this gene), they must be either normal or G6PD deficient. By contrast, females, who have two *G6PD* genes, can be either normal or deficient (homozygous) or intermediate (heterozygous). Second, as a result of the phenomenon of X chromosome inactivation, heterozygous females are genetic mosaics, with a highly variable ratio of G6PD-normal to G6PD-deficient cells and an equally variable degree of clinical expression; some heterozygotes can be just as affected as hemizygous males. The enzymatically active form of G6PD is either a dimer or a tetramer of a single protein subunit of 514 amino acids. G6PD-deficient subjects have been found invariably to have mutations in the coding region of the *G6PD* gene (Fig. 96-5). Almost all of the nearly 200 different mutations known are single missense point mutations, entailing single amino acid replacements in the G6PD protein. In most cases, these mutations cause G6PD deficiency by decreasing the in vivo stability of the protein; thus, the physiologic decrease in G6PD activity that takes place with red cell aging is greatly accelerated. In some cases, an amino acid replacement can also affect the catalytic function of the enzyme.

Among these mutations, those underlying chronic nonspherocytic hemolytic anemia (CNSHA; see below) are a discrete subset. This much more severe clinical phenotype can be ascribed in some cases to adverse qualitative changes (for instance, a decreased affinity for the substrate, glucose 6-phosphate) or simply to the fact that the enzyme deficit is more extreme because of a more severe instability of the enzyme. For instance, a cluster of mutations map at or near the dimer interface, and clearly they compromise severely the formation of the dimer.

Epidemiology G6PD deficiency is widely distributed in tropical and subtropical parts of the world (Africa, Southern Europe, the Middle East, Southeast Asia, and Oceania) **(Fig. 96-6)** and wherever people from those areas have migrated. A conservative estimate is that at least 400 million people have a *G6PD* deficiency gene. In several of these areas, the frequency of a *G6PD* deficiency gene may be as high as 20% or more. It would be quite extraordinary for a trait that causes significant pathology to spread widely and reach high frequencies in many populations without conferring some biologic advantage. Indeed, G6PD is one of the best-characterized examples of genetic polymorphisms in the human species. Clinical field studies and in vitro experiments strongly support the view that G6PD deficiency has been selected by *Plasmodium falciparum* malaria because it confers a relative resistance against this highly lethal infection. As in other cases of balanced polymorphism, it is heterozygotes, therefore females, who are protected. Different G6PD variants underlie G6PD deficiency in different parts of the world. Some of the more widespread variants are G6PD Mediterranean on the shores of that sea, in the Middle East, and in India; G6PD A– in Africa, in the Middle East, and in Southern Europe; G6PD Vianchan and G6PD Mahidol in Southeast Asia; G6PD Canton in China; and G6PD Union worldwide. The heterogeneity of polymorphic G6PD variants is proof of their independent origin, and it supports the notion that they have been selected by a common environmental agent, in keeping with the concept of convergent evolution (Fig. 96-6).

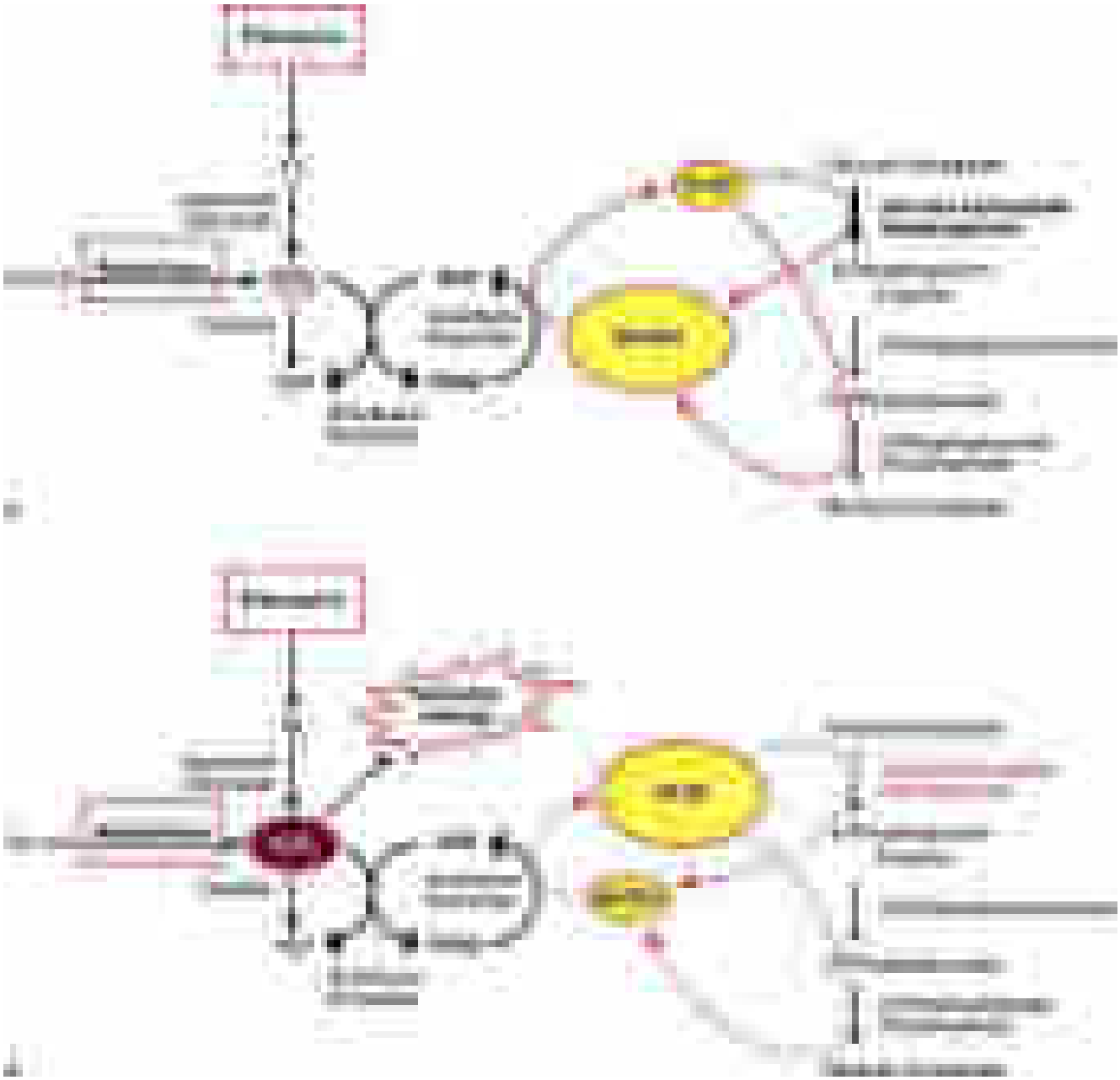

FIGURE 96-5 The role of G6PD in protecting red cells from oxidative damage. ***A.*** In G6PD-normal red cells, G6PD and 6-phosphogluconate dehydrogenase – two of the enzymes of the pentose phosphate pathway—provide ample supply of NADPH, which in turn regenerates GSH when this is oxidized by reactive oxygen species (e.g., O_2^- and H_2O_2). O_2^- is one of the most reactive oxygen species that can be generated from the metabolism of pro-oxidant compounds such as primaquine; rasburicase, on the other hand, produces directly hydrogen peroxide in equimolar amount to uric acid degraded. ***B.*** In G6PD-deficient red cells, where the enzyme activity is reduced, NADPH production is limited, and it may not be sufficient to cope with the excess of reactive oxygen species generated in the presence of pro-oxidant compounds. This diagram also explains why a defect in glutathione reductase has very similar consequences to G6PD deficiency.

Clinical Manifestations The vast majority of people with G6PD deficiency remain clinically asymptomatic throughout their lifetime; however, all of them have an increased risk of developing neonatal jaundice (NNJ) and a risk of developing acute HA (AHA) when challenged by a number of oxidative agents. NNJ related to G6PD deficiency is very rarely present at birth; the peak incidence of clinical onset is between day 2 and day 3, and in most cases, the anemia is not severe. However, NNJ can be very severe in some G6PD-deficient babies, especially in association with prematurity, infection, and/or environmental factors (such as naphthalene-camphor balls, which may be used in babies' bedding and clothing); and the risk of severe NNJ is also increased by the coexistence of a monoallelic or biallelic mutation in the uridyl transferase gene (*UGT1A1*; the same mutations are associated with Gilbert's syndrome). If inadequately managed, NNJ associated with G6PD deficiency can produce kernicterus and permanent neurologic damage.

AHA can develop as a result of three types of triggers: (1) fava beans, (2) infections, and (3) drugs **(Table 96-5)**. Typically, a hemolytic attack starts with malaise, weakness, and abdominal or lumbar pain. After an interval of several hours to 2–3 days, the patient develops jaundice and often dark urine. The onset can be extremely abrupt, especially with favism in children. The anemia is moderate to extremely severe, usually normocytic and normochromic, and due partly to intravascular hemolysis; hence, it is associated with hemoglobinemia, hemoglobinuria, high LDH, and low or absent plasma haptoglobin. The blood film shows anisocytosis, polychromasia, and spherocytes; in addition, the most typical feature of G6PD deficiency is the presence of bizarre poikilocytes, with red cells that appear to have unevenly distributed hemoglobin ("hemighosts") and red cells that appear to have had parts of them bitten away ("bite cells" or "blister cells") **(Fig. 96-7)**. A classical test, now rarely carried out, is supravital staining with methyl violet, which, if done promptly, reveals the presence of Heinz bodies (consisting of

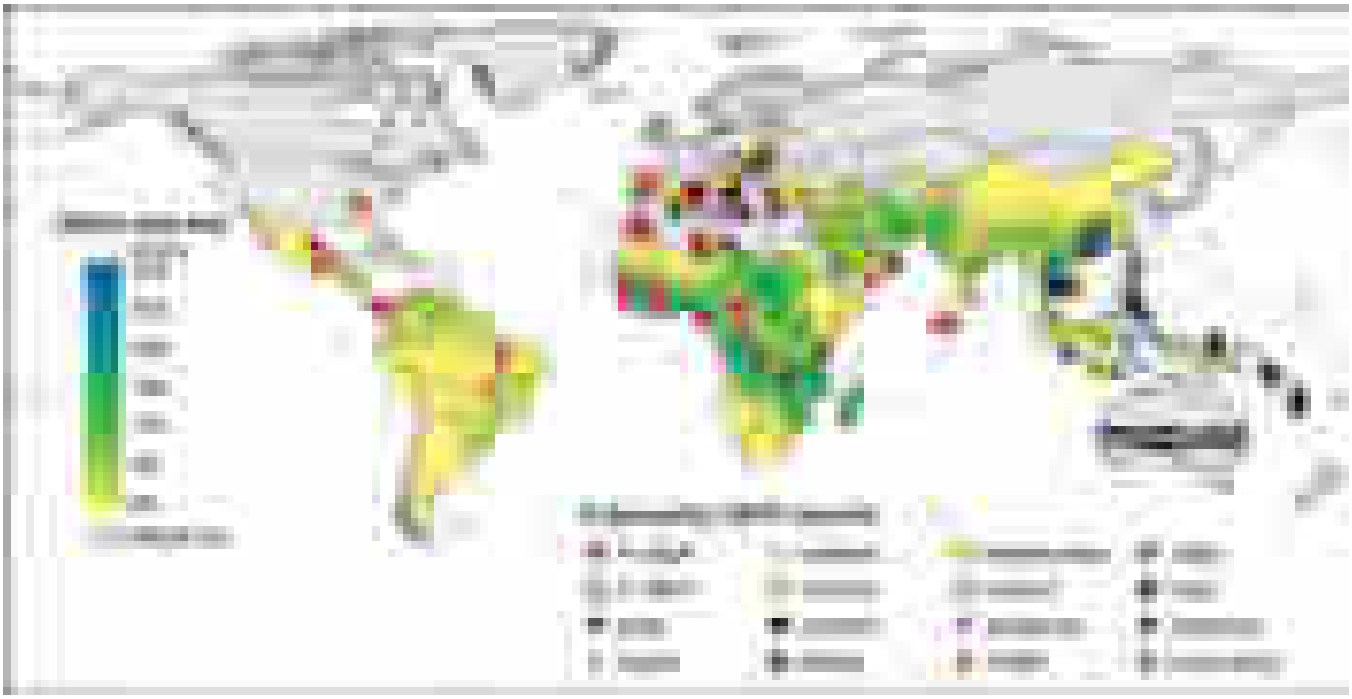

FIGURE 96-6 Epidemiology of glucose 6-phosphate dehydrogenase (G6PD) deficiency throughout the world. Color shades on the map indicate the median allele frequency of G6PD deficiency in malaria endemic and malaria-eliminating countries, according to a geostatistical model. Each colored circle illustrates the geographic distribution of one polymorphic G6PD allele present in more than one population. Dark grey circles indicate "local" polymorphic variants that have been detected only in one population. *(From L Luzzatto et al: Hematology/Oncology Clinics of North America, 30:373, 2016.)*

precipitates of denatured hemoglobin and hemichromes), which are regarded as a signature of oxidative damage to red cells (they are also seen with unstable hemoglobins). Not only LDH is high; also unconjugated bilirubin is high, indicating that there is also extravascular hemolysis. The most serious threat from AHA in adults is the development of acute renal failure (this is exceedingly rare in children). Once the threat of acute anemia is over and in the absence of comorbidity, full recovery from AHA associated with G6PD deficiency is the rule.

It was primaquine (PQ)-induced AHA that led to the discovery of G6PD deficiency, but this drug has not been very prominent subsequently because it is not necessary for the treatment of life-threatening *P. falciparum* malaria. Today there is a revival of interest in PQ because it is the only effective agent for eliminating the gametocytes of *P. falciparum* (thus preventing further transmission) and for eliminating the hypnozoites of *Plasmodium vivax* (thus preventing endogenous relapse). In countries aiming to eliminate malaria, there may be a call for mass administration of PQ; this ought to be associated with G6PD testing. At the other end of the historic spectrum, the latest addition to the list of potentially hemolytic drugs (Table 96-5) is rasburicase; again G6PD testing ought to be made mandatory before giving this drug because fatal cases have been reported in newborns with kidney injury and in adults with tumor lysis syndrome.

Although drug-induced AHA has been prominent in the study of G6PD deficiency, the commonest clinical manifestations are in fact NNJ and favism, both of which are of public health importance in many populations. Contrary to beliefs that are still widespread, fava bean pollen inhalation does not cause favism, and other beans are safe.

A very small minority of subjects with G6PD deficiency have CNSHA of variable severity. The patient is nearly always a male, usually with a history of NNJ, who may present with anemia, unexplained jaundice, or gallstones later in life. The spleen may be enlarged. The severity of anemia ranges in different patients from borderline to transfusion dependent. The anemia is usually normomacrocytic, with reticulocytosis. Bilirubin and LDH are increased. Although hemolysis is, by

TABLE 96-5 Drugs That Carry Risk of Clinical Hemolysis in Persons with Glucose 6-Phosphate Dehydrogenase Deficiency

	DEFINITE RISK	POSSIBLE RISK	DOUBTFUL RISK
Antimalarials	Primaquine Dapsone/chlorproguanil[a]	Chloroquine	Quinine
Sulphonamides/sulphones	Sulfamethoxazole Others Dapsone	Sulfasalazine Sulfadimidine	Sulfisoxazole Sulfadiazine
Antibacterial/antibiotics	Cotrimoxazole Nalidixic acid Nitrofurantoin Niridazole	Ciprofloxacin Norfloxacin	Chloramphenicol *p*-Aminosalicylic acid
Antipyretic/analgesics	Acetanilide Phenazopyridine	Acetylsalicylic acid high dose (>3 g/d)	Acetylsalicylic acid (<3 g/d) Acetaminophen Phenacetin
Other	Naphthalene Methylene blue Rasburicase	Vitamin K analogues Ascorbic acid (>1 g)	Doxorubicin Probenecid

[a]Marketed as Lapdap from 2003 to 2008.

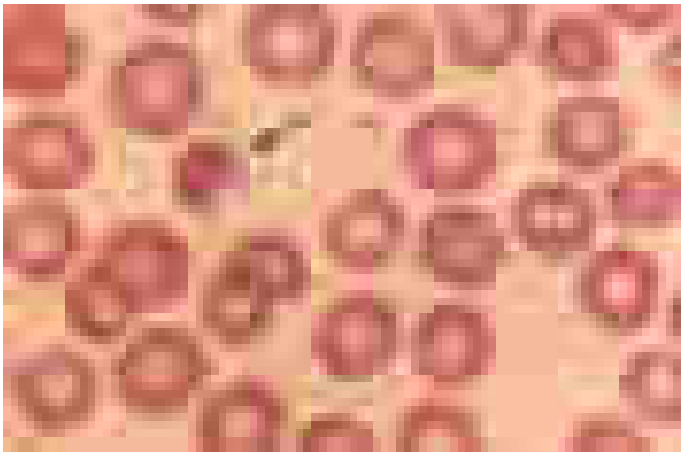

FIGURE 96-7 Peripheral blood smear from a glucose 6-phosphate dehydrogenase (G6PD)-deficient boy experiencing hemolysis. Note the red cells that are misshapen and called "bite" cells. *(From MA Lichtman et al: Lichtman's Atlas of Hematology: http://www.accessmedicine.com. Copyright © The McGraw-Hill Companies, Inc. All rights reserved.)*

definition, chronic in these patients, they are also vulnerable to acute oxidative damage, and therefore the same agents that can cause AHA in people with the ordinary type of G6PD deficiency will cause severe exacerbations in people with CNSHA associated with G6PD deficiency. In some cases of CNSHA, the deficiency of G6PD is so severe in granulocytes that it becomes rate-limiting for their oxidative burst, with consequent increased susceptibility to some bacterial infections.

Laboratory Diagnosis The suspicion of G6PD deficiency can be confirmed by semi-quantitative methods often referred to as screening tests, which are suitable for population studies and can correctly classify male subjects, in the steady state, as G6PD normal or G6PD-deficient. However, in clinical practice, a diagnostic test is usually needed when the patient has had a hemolytic attack; this implies that the oldest, most G6PD-deficient red cells have been selectively destroyed, and young red cells, having higher G6PD activity, are being released into the circulation. Under these conditions, only a quantitative test can give a definitive result. In males, this test will identify normal hemizygotes and G6PD-deficient hemizygotes; among females, some heterozygotes will be missed, but those who are at most risk of hemolysis will be identified. Of course, G6PD deficiency also can be diagnosed by DNA testing. Currently easy-to-use "point of care" tests for G6PD deficiency are becoming available, geared especially to the prospect of mass administration of PQ or other anti-malarials.

TREATMENT

G6PD Deficiency

The AHA of G6PD deficiency is largely preventable by avoiding exposure to triggering factors of previously screened subjects. Of course, the practicability and cost-effectiveness of screening depend on the prevalence of G6PD deficiency in each individual community. Favism is entirely preventable in G6PD-deficient subjects by not eating fava beans. Drug-induced hemolysis can be prevented by testing for G6PD deficiency before prescribing; in many cases one can use alternative drugs. When AHA develops and once its cause is recognized, no specific treatment is needed in most cases. However, if the anemia is severe, it may be a medical emergency, especially in children, requiring immediate action, including blood transfusion. This has been the case with an antimalarial drug combination containing dapsone (called Lapdap, introduced in 2003) that has caused severe acute hemolytic episodes in children with malaria in several African countries; after a few years, the drug was taken off the market. If there is acute renal failure, hemodialysis may be necessary, but if there is no previous kidney disease, recovery is the rule. The management of NNJ associated with G6PD deficiency is no different from that of NNJ due to other causes.

In cases with CNSHA, if the anemia is not severe, regular folic acid supplements and regular hematologic surveillance will suffice. It will be important to avoid exposure to potentially hemolytic drugs, and blood transfusion may be indicated when exacerbations occur, mostly in concomitance with intercurrent infection. In rare patients, regular blood transfusions may be required, in which case appropriate iron chelation should be instituted. Unlike in HS, there is no evidence of selective red cell destruction in the spleen; however, in practice, splenectomy has proven beneficial in severe cases.

Other Abnormalities of the Redox System As mentioned previously, GSH is a key player in the defense against oxidative stress. Inherited defects of GSH metabolism are exceedingly rare, but each one can give rise to chronic HA (Table 96-4). A rare, peculiar, severe but usually self-limited HA occurring in the first month of life, called *infantile poikilocytosis*, may be associated with deficiency of glutathione peroxidase (GSHPX) due not to an inherited abnormality, but to transient nutritional deficiency of selenium, an element essential for the activity of GSHPX.

PYRIMIDINE 5′-NUCLEOTIDASE (P5N) DEFICIENCY P5N is a key enzyme in the catabolism of nucleotides arising from the degradation of nucleic acids that takes place in the final stages of erythroid cell maturation. How exactly its deficiency causes HA is not well understood, but a highly distinctive feature of this condition is a morphologic abnormality of the red cells known as *basophilic stippling*. The condition is rare, but it probably ranks third in frequency among red cell enzyme defects (after G6PD deficiency and PK deficiency). The anemia is lifelong, of variable severity, and may benefit from splenectomy.

Familial (Atypical) Hemolytic-Uremic Syndrome (aHUS)

This term is used to designate a group of rare disorders, mostly affecting children, characterized by microangiopathic HA with presence of fragmented erythrocytes in the peripheral blood smear, thrombocytopenia (usually mild), and acute renal failure. (The word *atypical* in this phrase should be consigned to history: it was introduced originally to distinguish this condition from the hemolytic-uremic syndrome [HUS] caused by infection with *Escherichia coli* producing the Shiga toxin, regarded as *typical*.) The genetic basis of atypical HUS (aHUS) has been elucidated. Studies of >100 families have revealed that those family members who developed HUS had mutations in any one of several genes encoding complement regulatory proteins: complement factor H (*CFH*), CD46 or membrane cofactor protein (*MCP*), complement factor I (*CFI*), complement component C3, complement factor B (*CFB*), thrombomodulin, and others. Thus, whereas all other inherited HAs are due to intrinsic red cell abnormalities, this group is unique in that hemolysis results from an inherited defect external to red cells (Table 96-1). Because the regulation of the complement cascade has considerable redundancy, in the steady state, any of the above abnormalities can be tolerated. However, when an intercurrent infection or some other trigger briskly activates complement the deficiency of one of the complement regulators becomes critical. Endothelial cells get damaged, especially in the kidney; at the same time, and partly as a result of this, there will be brisk hemolysis (thus, the more common Shiga toxin–related HUS **(Chap. 161)** can be regarded as a phenocopy of aHUS). aHUS is a severe disease, with up to 15% mortality in the acute phase and up to 50% of cases progressing to end-stage renal disease (ESRD). Not infrequently, aHUS undergoes spontaneous remission; but because its basis is an inherited abnormality, it is not surprising that, given renewed exposure to a trigger, the syndrome will tend to recur; when it does, the prognosis is always serious. The traditional treatment has been plasma exchange, which will supply the deficient complement regulator. This has changed since the introduction of the anti-C5 complement inhibitor eculizumab (see "Paroxysmal Nocturnal Hemoglobinuria") was found to greatly ameliorate the microangiopathic picture, with improvement in platelet counts and in renal function, thus abrogating the need for plasma exchange, which is not always effective and not free of complications. Since the basis of aHUS is genetic, and even after complete remission relapses are always possible, there is a rationale for continuing eculizumab indefinitely, especially in order to prevent ESRD. Patients who relapsed after discontinuing

TABLE 96-6 Diseases and Clinical Situations in Which Hemolysis Is Largely Intravascular

	ONSET/TIME COURSE	MAIN MECHANISM	APPROPRIATE DIAGNOSTIC PROCEDURE	COMMENTS
Mismatched blood transfusion	Abrupt	Nearly always ABO incompatibility	Repeat cross-match	
Paroxysmal nocturnal hemoglobinuria (PNH)	Chronic with acute exacerbations	Complement (C)-mediated destruction of CD59(−) red cells	Flow cytometry to display a CD59(−) red cell population	Exacerbations due to C activation through any pathway
Paroxysmal cold hemoglobinuria (PCH)	Acute	Immune lysis of normal red cells	Test for Donath-Landsteiner antibody	Often triggered by viral infection
Septicemia	Very acute	Exotoxins produced by *Clostridium perfringens*	Blood cultures	Other organisms may be responsible
Microangiopathic	Acute or chronic	Red cell fragmentation	Red cell morphology on blood smear	Different causes ranging from endothelial damage to hemangioma to leaky prosthetic heart valve
March hemoglobinuria	Abrupt	Mechanical destruction	Targeted history taking	
Favism	Acute	Destruction of older fraction of G6PD-deficient red cells	G6PD assay	Triggered by ingestion of large dish of fava beans[a]

[a]The trigger of acute hemolytic anemia, often with hemoglobinuria, can be infection or a drug (see Table 96-5) rather than fava beans.

Abbreviation: G6PD, glucose 6-phosphate dehydrogenase.

eculizumab have responded again. Discontinuation of eculizumab might be reasonable especially in patients heterozygous for a MCP mutation. However, there is no evidence base at the moment for balancing the pros and cons of lifetime eculizumab (a very expensive drug).

ACQUIRED HEMOLYTIC ANEMIA

Mechanical Destruction of Red Cells Although red cells are characterized by the remarkable deformability that enables them to squeeze through capillaries narrower than themselves for thousands of times in their lifetime, there are at least two situations in which they succumb to shear, if not to wear and tear; the result is intravascular hemolysis, resulting in hemoglobinuria **(Table 96-6)**. One situation is acute and self-inflicted, *march hemoglobinuria*. Why sometimes a marathon runner may develop this complication, whereas on another occasion, this does not happen, we do not know (perhaps her or his footwear needs attention). A similar syndrome may develop after prolonged barefoot ritual dancing or intense playing of bongo drums. The other situation is chronic and iatrogenic (it has been called *microangiopathic hemolytic anemia*). It takes place in patients with prosthetic heart valves, especially when paraprosthetic regurgitation is present. If the hemolysis consequent on mechanical trauma to the red cells is mild, and if the supply of iron is adequate, the loss may be largely compensated; if more than mild anemia develops, reintervention to correct regurgitation may be required.

Infection By far the most frequent infectious cause of HA, in endemic areas, is malaria **(Chap. 219)**. In other parts of the world, the most frequent direct cause is probably Shiga toxin–producing *E. coli* O157:H7, now recognized as the main etiologic agent of HUS, which is more common in children than in adults **(Chap. 156)**. Life-threatening intravascular hemolysis, due to a toxin with lecithinase activity, occurs with *Clostridium perfringens* sepsis, particularly following open wounds, septic abortion, or as a disastrous accident due to a contaminated blood unit. Rarely, and if at all in children, HA is seen with sepsis or endocarditis from a variety of organisms. In addition, bacterial and viral infections can cause HA by indirect mechanisms (see previous section on G6PD deficiency and Table 96-6).

Immune Hemolytic Anemias These can arise through at least two distinct mechanisms. First, when an antibody directed against a certain molecule (e.g., a drug) reacts with that molecule, red cells may get caught in the reaction (the so-called *innocent bystander* mechanism: see section below on Hemolytic Anemia from Toxic Agents and Drugs), whereby they are damaged or destroyed. Second, and more frequently, a true auto-antibody is directed against a red cell antigen, i.e., a molecule present on the surface of red cells.

AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA) This latter mechanism is common to a group of rare disorders (AIHA), with an estimated incidence in the United States of about $2/10^5$/year. AIHA can be serious, since even with appropriate management the mortality is of the order of 5–10%.

Clinical Features The onset is often abrupt and can be dramatic. The hemoglobin level may drop, within days, to as low as 4 g/dL; the massive red cell removal will produce jaundice; and sometimes the spleen is enlarged. When this triad is present, the suspicion of AIHA must be high. When hemolysis is (in part) intravascular, the telltale sign will be hemoglobinuria, which the patient may report or about which we must enquire or test for.

There are few situations in hematology where one laboratory test is so informative as the direct antiglobulin test developed in 1945 by R. R. A. Coombs, and known since then by this name. The currently recommended version of this test uses in the first instance a "broad spectrum" reagent: i.e., one that will detect not only immunoglobulins (Ig) but also complement (C) components (usually C3 fragments) bound to the surface of the patient's red cells. If the test is positive (and barring special circumstances such as previous blood transfusion), it is practically diagnostic of AIHA; and one can then determine, by using specific reagents, whether Ig or C or both are implicated. The sensitivity of the Coombs test varies depending on the techniques that are used: in general, the test is positive if there are an average of at least 400 molecules of Ig and/or C on each red cell; but with more advanced techniques the sensitivity can be pushed to as low as 40 molecules per red cell: therefore liaison with a specialized laboratory is desirable. In the past the diagnosis of "Coombs-negative AIHA" was regarded as a last resort, but it is important to know that a patient with this label may have severe AIHA, because if the antibody is powerful (high affinity/avidity), few molecules may be sufficient to opsonize red cells. Based on the Coombs test findings as well as on the thermal characteristics and the antigenic specificities of the auto-antibodies **(Table 96-7)**, AIHA has been classified into subtypes.

Warm Antibody AIHA This is the more common type of AIHA. As the name suggests, the auto-antibody reacts best at 37°C: it will often react with most red cells, but it is usually Rhesus-specific (sometimes specifically anti-e). Warm antibody AIHA may be seen in isolation (and it is then called *idiopathic*) or as part of a systemic auto-immune disorder such as systemic lupus erythematosus (SLE: sometimes AIHA may be the first manifestation that leads to a diagnosis of SLE). Like all auto-immune diseases, AIHA must arise from a dysregulation of immunity. It is therefore not surprising that it is increasingly being recognized in chronic lymphocytic leukemia (CLL), whether treated or untreated; after BMT; and after solid organ transplantation entailing immuno-suppressive treatment. Recently, warm antibody AIHA has also occurred as a side effect of the use of immune checkpoint inhibitors, such as nivolumab, in patients with various types of cancer.

TABLE 96-7 Classification of Acquired Immune Hemolytic Anemias

CLINICAL SETTING	TYPE OF ANTIBODY: COLD, MOSTLY IgM, OPTIMAL TEMPERATURE 4°C–30°C	TYPE OF ANTIBODY: WARM, MOSTLY IgG, OPTIMAL TEMPERATURE 37°C; OR MIXED
Primary	CAD	AIHA (idiopathic)
Secondary to viral infection	EBV CMV Other	HIV Viral vaccines
Secondary to other infection	Mycoplasma infection: paroxysmal cold hemoglobinuria	
Secondary to/ associated with other disease	CAD in: Waldenström's disease Lymphoma	AIHA in: SLE CLL Other malignancy Chronic inflammatory disorders (e.g., IBD) After allogeneic HSCT After immune checkpoint modulating drugs
Secondary to drugs: drug-induced immune hemolytic anemia	Small minority (e.g., with lenalidomide)	Majority: currently most common culprit drugs are cefotetan, ceftriaxone, piperacillin
	Drug-dependent: antibody destroys red cells only when drug present (e.g., rarely penicillin)	
	Drug-independent: antibody can destroy red cells even when drug no longer present (e.g., methyldopa)	

Abbreviations: AIHA, autoimmune hemolytic anemia; CAD, cold agglutinin disease; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus.

Once a red cell is coated by an autoantibody it will be destroyed by one or more mechanisms. In most cases, the Fc portion of the antibody will be recognized by the Fc receptor of macrophages, and this will trigger erythrophagocytosis. Thus, destruction of red cells will take place wherever macrophages are abundant, i.e., in the spleen, liver, and bone marrow (*extravascular hemolysis* see **Fig. 96-8**). Because of the special anatomy of the spleen, this organ is particularly efficient in trapping antibody-coated red cells, and often this is the predominant site of red cell destruction. In some cases, the nature of the antibody is such (usually an IgM antibody) that the antigen-antibody complex on the surface of red cells is able to activate complement (C); as a result, a large amount of membrane attack complex (MAC) will form, and the red cells may be destroyed directly (*intravascular hemolysis*).

The hematological picture of AIHA includes in most cases reticulocytosis, as the bone marrow responds to anemia: but in some cases reticulocytes may not be increased because they themselves are attacked by the auto-antibody, and this may signify the disease is more severe. In some cases AIHA can be associated, on first presentation or subsequently, with autoimmune thrombocytopenia (Evans' syndrome): this too usually signals severe disease. Evans' syndrome may be a manifestation of common variable immune deficiency, and in children it may suggest one of several primary immune deficiency syndromes.

TREATMENT

Warm Antibody Autoimmune Hemolytic Anemia

Severe acute AIHA can be a medical emergency. The immediate treatment almost invariably includes transfusion of red cells. This may pose a special problem because many or all of the blood units cross-matched may be incompatible. In these cases, it is often correct, if paradoxical, to transfuse ABO-matched but incompatible blood: the rationale being that the transfused red cells will be destroyed no less—but no more—than the patient's own red cells, and in the meantime the patient stays alive. A situation like this requires close liaison and understanding between the clinical unit treating the patient and the blood transfusion/serology lab. Whenever the anemia is not immediately life threatening, blood transfusion should be withheld (because compatibility problems may increase with each unit of blood transfused), and medical treatment started immediately with prednisone (1 mg/kg per day), which will produce a remission promptly in at least one-half of patients. Rituximab (anti-CD20), previously regarded as second-line treatment, is increasingly being used at a relatively low dose (100 mg/wk × 4), together with prednisone as part of first-line treatment. It is especially encouraging that this approach seems to reduce the rate of relapse, a common occurrence in AIHA. For patients who do relapse or are refractory to medical treatment, one may have to consider splenectomy: this procedure does not cure the disease, but it can produce significant benefit by removing a major site of hemolysis, thus improving the anemia and/or reducing the need for other therapies (e.g., the dose of prednisone); of course splenectomy is not free of risk, as it entails increased risk of sepsis and of thrombosis. Since the introduction of rituximab, azathioprine, cyclophosphamide, cyclosporine, and intravenous immunoglobulin have become second- or third-line agents. In very rare severe refractory cases, one may have to consider myelo-immuno-ablative chemotherapy followed by rescue with either autologous or allogeneic hematopoietic stem cell transplantation.

PAROXYSMAL COLD HEMOGLOBINURIA (PCH) PCH is a rather rare form of AIHA occurring mostly in children, usually triggered by a viral infection, usually self-limited, and characterized by the involvement of the so-called Donath-Landsteiner antibody. In vitro, this antibody has unique serologic features; it has anti-P specificity and binds to red cells only at a low temperature (optimally at 4°C), but when the temperature is shifted to 37°C, lysis of red cells takes place in the presence of complement. Consequently, in vivo there is intravascular hemolysis, resulting in hemoglobinuria. Clinically the differential diagnosis must include other causes of hemoglobinuria (Table 96-6), but the presence of the Donath-Landsteiner antibody will prove PCH. Active supportive treatment, including blood transfusion, may be needed to control the anemia; subsequently, recovery is the rule.

COLD AGGLUTININ DISEASE This designation is used for a form of AIHA that usually affects the elderly and has special clinical and pathologic features. First, CAD is characteristically a chronic condition—in contrast to the abrupt onset of warm antibody AIHA. Second, the term *cold* refers to the fact that the autoantibody involved reacts with red cells poorly or not at all at 37°C, whereas it reacts strongly at lower temperatures. As a result, hemolysis is more prominent the more the body is exposed to the cold. The antibody is usually IgM; usually it has an anti-I specificity (the I antigen is present on the red cells of almost everybody), and it may have a very high titer (1:100,000 or more has been observed). Third, the antibody is produced by an expanded B lymohocyte clone (a low-grade mature B cell lymphoma): and sometimes the antibody concentration in the serum is high enough to show up as a spike in plasma protein electrophoresis, i.e., as a monoclonal gammopathy. Indeed, since we are dealing with a clonal disease and the antibody is IgM, CAD must be regarded as a form of Waldenström macroglobulinemia **(see Chap. 107)**. The unique biologic properties of the IgM produced in a patient with CAD give the clinical picture of HA, often well before other clinical features of WM become manifest.

In mild forms of CAD, avoidance of exposure to cold may be all that is needed to enable the patient to have a reasonably comfortable quality of life; but in more severe forms, the management of CAD is not easy. Plasma exchange will remove antibody and is, therefore, in theory, a rational approach, but it is laborious and must be carried out at frequent intervals if it is to be beneficial. The management of CAD has changed significantly with the advent of the anti-CD20 antibody rituximab: up to 60% of patients respond. If remission is followed by relapse

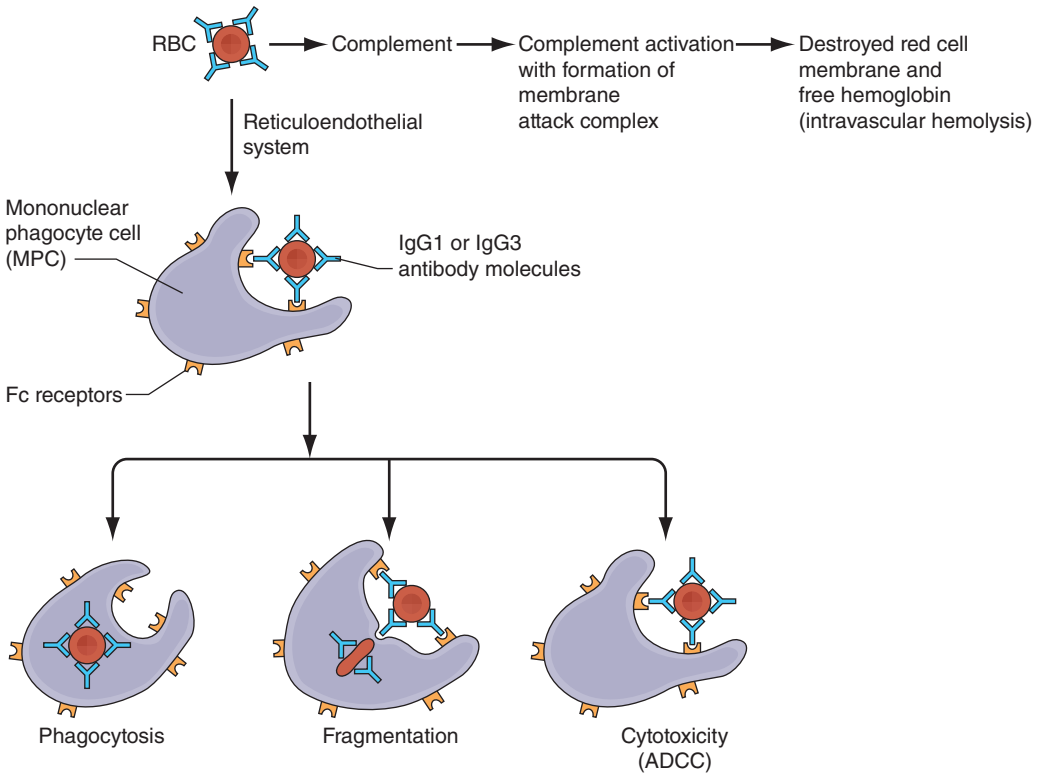

FIGURE 96-8 Mechanism of antibody-mediated immune destruction of red blood cells (RBCs). The three bottom images illustrate three different modalities of extravascular hemolysis. ADCC, antibody-dependent cell-mediated cytotoxicity. *(From N Young et al: Clinical Hematology. Philadelphia, Elsevier, 2006; with permission.)*

a new course of rituximab may be again effective, and remissions may be more durable with a rituximab-fludarabine combination. Therefore, even in the absence of a formal trial, rituximab has become de facto first-line treatment: especially since previously used immunosuppressive/cytotoxic agents such as azathioprine or cyclophosphamide, although they can reduce the antibody titer, have limited clinical efficacy and, in view of the chronic nature of CAD, their side effects may prove unacceptable. Unlike in AIHA, prednisone and splenectomy are ineffective. In terms of supportive treatment blood transfusion may be helpful—in spite of the fact that red cells from the donor, being I-positive, will survive no longer than those of the patient: both the blood bag and the patient's extremities must be kept warm during transfusion.

Hemolytic Anemia from Toxic Agents and Drugs A number of chemicals with oxidative potential, whether medicinal or not, can cause hemolysis even in people who are not G6PD-deficient (for which see above). Examples are hyperbaric oxygen (or 100% oxygen), nitrates, chlorates, methylene blue, dapsone, cisplatin, and numerous aromatic (cyclic) compounds. Other chemicals may be hemolytic through non-oxidative, largely unknown mechanisms; examples include arsine, stibine, copper, and lead. The HA caused by lead poisoning is characterized by basophilic stippling; it is in fact a phenocopy of that seen in P5N deficiency (see above), suggesting it is mediated at least in part by lead inhibiting this enzyme.

In these cases, hemolysis appears to be mediated by a direct chemical action on red cells. But drugs can cause hemolysis through at least two other mechanisms. (1) A drug can behave as a hapten and induce antibody production; in rare subjects, this happens, for instance, with penicillin. Upon a subsequent exposure, red cells are caught, as innocent bystanders, in the reaction between penicillin and anti-penicillin antibodies. Hemolysis will subside as soon as penicillin administration is stopped. (2) A drug can trigger, perhaps through mimicry, the production of an antibody against a red cell antigen. The best known example is methyldopa, an antihypertensive agent no longer in use, which in a small fraction of patients stimulated the production of the Rhesus antibody anti-e. In patients who have this antigen, the anti-e is a true autoantibody, which then causes true AIHA (see above). Usually this will gradually subside once methyldopa is discontinued.

Severe intravascular hemolysis can be caused by the venom of certain snakes (cobras and vipers), and HA can also follow spider bites.

Paroxysmal Nocturnal Hemoglobinuria (PNH) PNH is an acquired chronic HA characterized by persistent intravascular hemolysis with occasional or frequent recurrent exacerbations. In addition to (i) hemolysis, there may be (ii) pancytopenia and (iii) a distinct tendency to venous thrombosis. This triad makes PNH a truly unique clinical condition; however, when not all of these three features are manifest on presentation, the diagnosis is often delayed, although it can always be made by appropriate laboratory investigations (see below).

PNH is encountered in all populations throughout the world, but it is a rare disease, with an estimated prevalence of ~5 per million (it may be somewhat less rare in Southeast Asia and in the Far East). PNH has about the same frequency in men and women. PNH is not inherited, and it has never been reported as a congenital disease, but it can present in small children or as late as in the seventies, although most patients are young adults.

CLINICAL FEATURES When seeking medical attention, the patient may report that one morning, she or he "passed blood instead of urine" **(Fig. 96-9)**. This distressing or frightening event may be regarded as the classic presentation; however, more frequently, this symptom is not noticed or not reported. Indeed, the patient often presents simply as a problem in the differential diagnosis of *anemia*, whether symptomatic or discovered incidentally. Sometimes the anemia is associated from the outset with neutropenia, thrombocytopenia, or both, thus signaling an element of bone marrow failure (see below). Some patients may present with recurrent attacks of severe abdominal pain eventually found to be related to thrombosis in abdominal veins, or attributable to NO depletion associated with intravascular hemolysis. When thrombosis affects the hepatic vein it may produce acute hepatomegaly and ascites, i.e., a full-fledged Budd-Chiari syndrome, which, in the absence of liver disease, ought to raise the suspicion of PNH.

The *natural history* of PNH can extend over decades. In the past, with supportive treatment only, the median survival was estimated to be about 10–20 years; with the most common cause of death being venous thrombosis, followed by infection secondary to severe neutropenia and

FIGURE 96-9 Consecutive urine samples from a patient with paroxysmal nocturnal hemoglobinuria (PNH). The variation in the severity of hemoglobinuria within hours is probably unique to this condition.

hemorrhage secondary to severe thrombocytopenia. Rarely (estimated 1–2% of all cases), PNH may terminate in acute myeloid leukemia. On the other hand, full spontaneous recovery from PNH has been documented, albeit rarely.

LABORATORY INVESTIGATIONS AND DIAGNOSIS The most consistent blood finding is anemia, which may range from mild to moderate to very severe. The anemia is usually normo-macrocytic, with unremarkable red cell morphology. If the MCV is high, it is usually largely accounted for by reticulocytosis, which may be quite marked (up to 20%, or up to 400,000/μL). The anemia may become microcytic if the patient is allowed to become iron-deficient as a result of chronic iron loss through hemoglobinuria. Unconjugated bilirubin is mildly or moderately elevated; LDH is typically markedly elevated (values in the thousands are common); and haptoglobin is usually undetectable. All of these findings make the diagnosis of HA compelling. Hemoglobinuria may be overt in a random urine sample; if it is not, it may be helpful to obtain serial urine samples (Fig. 96-9) because hemoglobinuria can vary dramatically from day to day and even from hour to hour. The bone marrow is usually cellular, with marked to massive erythroid hyperplasia, often with mild to moderate dyserythropoietic features (these overlap with those seen in myelodysplastic syndromes, but PNH remains a separate entity). At some stage of the disease, the marrow may become hypocellular or even frankly aplastic (see below).

The definitive diagnosis of PNH must be based on the demonstration that a substantial proportion of the patient's red cells have an increased susceptibility to complement (C), due to the deficiency on their surface of proteins (particularly CD59 and CD55) that normally protect the red cells from activated C. The sucrose hemolysis test is unreliable; in contrast, the acidified serum (Ham) test is highly reliable but is carried out only in a few labs. The gold standard today is flow cytometry, which can be carried out on granulocytes as well as on red cells, and has a very high sensitivity. In PNH, characteristically, one sees a bimodal distribution of cells, with a discrete population that is CD59 and CD55 negative. Although very small populations of CD59(-) cells are of interest in terms of pathophysiology (particularly of aplastic anemia [AA]), no patient should be diagnosed with PNH unless their proportion is substantial: in first approximation at least 5% of the total red cells and at least 20% of the total granulocytes.

PATHOPHYSIOLOGY Hemolysis in PNH is mainly intravascular and is due to an intrinsic abnormality of the red cell, which makes it exquisitely sensitive to activated C, whether C is activated through the alternative pathway or through an antigen-antibody reaction (classic pathway). The former mechanism is mainly responsible for chronic hemolysis in PNH; the latter explains why the hemolysis can be dramatically exacerbated in the course of a viral or bacterial infection. Hypersusceptibility to C is due to deficiency in the red cell membrane of several protective proteins **(Fig. 96-10)**, among which CD59 is the most important because it is able to hinder the insertion into the membrane of C9 polymers. The molecular basis for the deficiency of these proteins has been pinpointed not to a defect in any of the respective genes, but rather to the shortage of a unique glycolipid molecule, GPI (Fig. 96-2), which, through a peptide bond, anchors these proteins to the surface membrane of cells. The shortage of GPI is due in turn to a somatic mutation in an X-linked gene, called *PIGA*, required for an early step in GPI biosynthesis. As a result, the patient's marrow is a mosaic of mutant and nonmutant cells, and the peripheral blood always contains both GPI-negative (PNH) cells and GPI-positive (non-PNH) cells. Thrombosis is one of the most immediately life-threatening complications of PNH and yet one of the least understood in its pathogenesis. It could be that deficiency of CD59 on the PNH platelet causes inappropriate platelet activation; however, other mechanisms are possible.

BONE MARROW FAILURE (BMF) AND RELATIONSHIP BETWEEN PNH AND APLASTIC ANEMIA (AA) It is not unusual that patients with firmly established PNH have a previous history of AA, sometimes well-documented; indeed, BMF preceding overt PNH is probably the rule rather than the exception. On the other hand, sometimes a patient with PNH becomes less hemolytic and more pancytopenic and ultimately has the clinical picture of AA. The relationship between PNH and AA manifested in the clinical course of patients may reflect a close link in pathogenesis. AA is thought to be an organ-specific autoimmune disease, in which T cells cause damage to hematopoietic stem cells via an as yet unidentified molecular target. The same may be true of PNH, and in this condition the target might be the GPI molecule itself. This would explain why GPI-negative (PNH) stem cells are spared; *PIGA* mutations can be demonstrated in normal people. Thus, PNH results from the combined action of two factors: failure of normal hematopoiesis and massive expansion of a PNH clone. There is evidence from mouse models that PNH stem cells do not expand on their own, and there is evidence from human patients that expansion is associated with negative selection against GPI-positive cells by GPI-specific T cells. Thus, PNH is a prime example of a clonal disease that is not malignant.

TREATMENT

Paroxysmal Nocturnal Hemoglobinuria

Until 10 years ago there were essentially two treatment options for PNH: either allogeneic BMT, providing a definitive cure at the cost of non-negligible risks; or continued supportive treatment for what, unlike other acquired HAs, may be a lifelong condition. A major advance has been the introduction in 2007 of a humanized monoclonal antibody, eculizumab, which binds to the complement component C5 near the site that, when cleaved, will trigger the distal part of the complement cascade leading to formation of the MAC. With C5 blocked, the patient is relieved of intravascular hemolysis and of its attendant consequences, including hemoglobinuria. In the majority of those patients who needed regular blood transfusion, the transfusion requirement is either abolished or significantly reduced. For many PNH patients, eculizumab has meant a real improvement in the quality of life, as well as a decrease in complications, particularly thrombosis. At the same time, it is important to know that in patients on eculizumab the PNH red cells, now protected from being lysed through the MAC, do still bind C3 fragments and thus become opsonized. Therefore hemolysis continues, but it is now extravascular. The extent to which this happens depends in part on a genetic polymorphism of the complement receptor CR1. Those patients who, on eculizumab, are still receiving blood transfusion are at risk of iron overload. Based on its half-life, eculizumab must be administered intravenously every 14 days: a trial of a long-lived anti-C5 antibody is currently under way, and other complement inhibitors are under experimentation.

Eculizumab is very expensive and therefore not accessible to patients in many parts of the world. Therefore, the management of PNH by supportive treatment is still very important. Folic acid supplements (at least 3 mg/d) are mandatory; the serum iron should be checked periodically, and iron supplements should be administered as appropriate. Transfusion of filtered red cells should be used

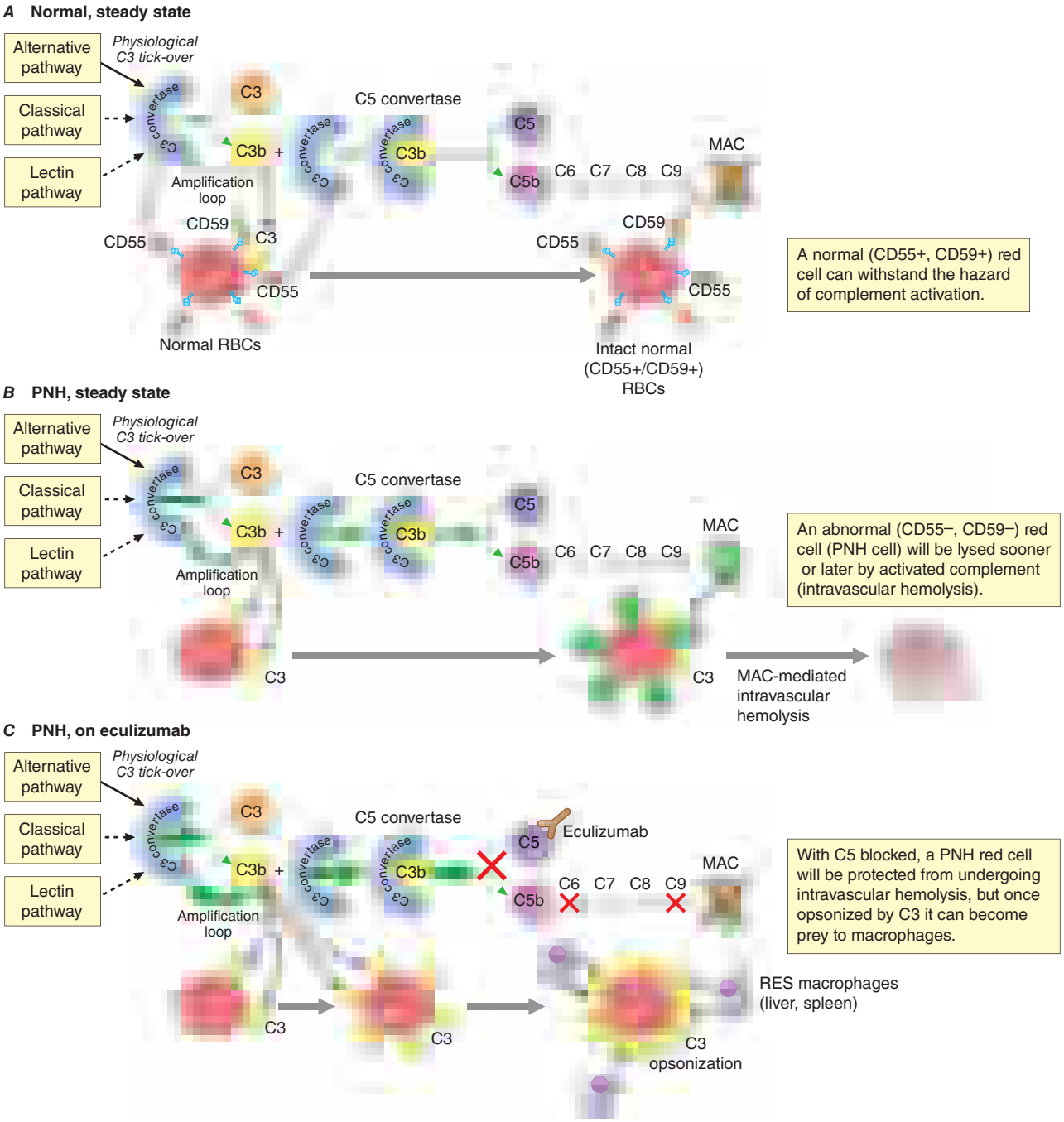

FIGURE 96-10 The complement cascade and the fate of red cells. ***A.*** Normal red cells are protected from complement activation and subsequent hemolysis by CD55 and CD59. These two proteins, being GPI-linked, are missing from the surface of PNH red cells as a result of a somatic mutation of the X-linked *PIG-A* gene that encodes a protein required for an early step of the GPI molecule biosynthesis. ***B.*** In the steady state, PNH erythrocytes suffer from spontaneous (tick-over) complement activation, with consequent intravascular hemolysis through formation of the membrane attack complex (MAC); when extra complement is activated through the classical pathway, an exacerbation of hemolysis will result. ***C.*** On eculizumab, PNH erythrocytes are protected from hemolysis from the inhibition of C5 cleavage; however, upstream complement activation may lead to C3 opsonization and possible extravascular hemolysis. GPI, glycosylphosphatidylinositol; PNH, paroxysmal nocturnal hemoglobinuria. *(From L Luzzatto et al: Haematologica 95:523, 2010.)*

whenever necessary, which, for some patients, means quite frequently. Long-term glucocorticoids are not indicated because there is no evidence that they have any effect on chronic hemolysis; in fact, they are contraindicated because their side effects are considerable. A short course of prednisone may be useful when an inflammatory process exacerbates hemolysis. Any patient who has had venous thrombosis or who has a genetically determined thrombophilic state in addition to PNH should be on regular anticoagulant prophylaxis. With thrombotic complications that do not resolve otherwise, thrombolytic treatment with tissue plasminogen activator may be indicated.

Where eculizumab is available the proportion of PNH patients receiving BMT has decreased significantly. However, when an HLA-identical sibling is available, BMT should be taken into consideration for any young patient with severe PNH; and for patients with the so-called PNH-AA syndrome, since eculizumab has no effect on BMF. For these patients immunosuppressive treatment with antithymocyte globulin and cyclosporine A may be an alternative, and it may be compatible with concurrent administration of eculizumab.

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97 Anemia Due to Acute Blood Loss

Dan L. Longo

Blood loss causes anemia by two main mechanisms: (1) by the direct loss of red cells; and (2) if the loss of blood is protracted, it will gradually deplete iron stores, eventually resulting in iron deficiency. The latter type of anemia is covered in **Chap. 93**; here, we are concerned with the former type, that is, *posthemorrhagic anemia*, which follows *acute* blood loss. This can be *external* (e.g., after trauma or obstetric hemorrhage) or *internal* (e.g., from bleeding in the gastrointestinal tract, rupture of the spleen, rupture of an ectopic pregnancy, subarachnoid hemorrhage). In any of these cases, after the sudden loss of a large amount of blood, there are three clinical/pathophysiologic stages. (1) At first, the dominant feature is hypovolemia, which poses a threat particularly to organs that normally have a high blood supply, like the brain and the kidneys; therefore, loss of consciousness and acute renal failure are major threats. It is important to note that at this stage an ordinary blood count will not show anemia because the hemoglobin concentration is not affected. (2) Next, as an emergency response, baroreceptors and stretch receptors will cause release of vasopressin and other peptides, and the body will shift fluid from the extravascular to the intravascular compartment, producing hemodilution; thus, the hypovolemia gradually converts to anemia. The degree of anemia will reflect the amount of blood lost. If after 3 days the hemoglobin is, for example, 7 g/dL, it means that about half of the entire blood has been lost. (3) Provided bleeding does not continue, the bone marrow response will gradually ameliorate the anemia. In this phase of the process, the reticulocyte count and erythropoietin levels will be elevated.

The diagnosis of acute posthemorrhagic anemia (APHA) is usually straightforward, although sometimes internal bleeding episodes (e.g., after a traumatic injury), even when large, may not be immediately obvious. Whenever an abrupt fall in hemoglobin has taken place, whatever history is given by the patient, APHA should be suspected. Supplementary history may have to be obtained by asking the appropriate questions, and appropriate investigations (e.g., a sonogram or an endoscopy) may have to be carried out.

TREATMENT

Anemia Due to Acute Blood Loss

With respect to treatment, a two-pronged approach is imperative. (1) In many cases, the blood lost needs to be replaced promptly. Unlike with many chronic anemias, when finding and correcting the cause of the anemia is the first priority and blood transfusion may not be even necessary because the body is adapted to the anemia, with acute blood loss the reverse is true; because the body is not adapted to the anemia, blood transfusion takes priority. (2) While the emergency is being confronted, it is imperative to stop the hemorrhage and to eliminate its source.

In an acute hemorrhage situation, plasma may be preferred to saline for volume expansion since dilution of clotting factors with crystalloid may interfere with hemostasis.

A special type of APHA is blood loss during and immediately after surgery, which can be substantial (e.g., up to 2 L in the case of a radical prostatectomy). Of course with elective surgical procedures, the patient's own stored blood may be available (through preoperative autologous blood donation), and in any case, blood loss ought to have been carefully monitored/measured. The fact that this blood loss is iatrogenic dictates that ever more effort should be invested in optimizing its management. **The special features of transfusion medicine are discussed in Chap. 109.**

A Holy Grail of emergency medicine for a long time has been the idea of a blood substitute that would be universally available, suitable for all recipients, easy to store and to transport, safe, and as effective as blood itself. Two main paths have been pursued: (1) fluorocarbon synthetic chemicals that bind oxygen reversibly, and (2) artificially modified hemoglobins, known as hemoglobin-based oxygen carriers (HBOCs). Although there are numerous anecdotal reports of the use of both approaches in humans, and although HBOCs have reached the stage of phase 2–3 clinical trials, no "blood substitute" has yet become standard treatment.

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98 Bone Marrow Failure Syndromes Including Aplastic Anemia and Myelodysplasia

Neal S. Young

The hypoproliferative anemias are normochromic, normocytic, or macrocytic and are characterized by a low reticulocyte count. Hypoproliferative anemia is also a prominent feature of hematologic diseases that are described as bone marrow failure states; these include aplastic anemia, myelodysplastic syndrome (MDS), pure red cell aplasia (PRCA), and myelophthisis. Anemia in these disorders is often not a solitary or even the major hematologic finding. More frequent in bone marrow failure is *pancytopenia*: anemia, leukopenia, and thrombocytopenia. Low blood counts in the marrow failure diseases result from deficient hematopoiesis, as distinguished from blood count depression due to peripheral destruction of red cells (hemolytic anemias), platelets (idiopathic thrombocytopenic purpura [ITP] or due to splenomegaly), and granulocytes (as in the immune leukopenias). Marrow damage and dysfunction also may be secondary to infection, inflammation, or cancer.

Hematopoietic failure syndromes are classified by dominant morphologic features of the bone marrow **(Table 98-1)**. Although practical distinction among these syndromes usually is clear, some processes are so closely related that the diagnosis may be complex. Separation between aplastic anemia and hypocellular MDS can be particularly difficult. Further, identification of constitutional genetic risk factors

TABLE 98-1 Differential Diagnosis of Pancytopenia

Pancytopenia with Hypocellular Bone Marrow	
Acquired aplastic anemia	
Constitutional aplastic anemia (Fanconi anemia, dyskeratosis congenita, and others)	
Hypocellular myelodysplastic syndrome	
Rare aleukemic leukemia	
Some acute lymphoid leukemia	
Rare lymphomas of bone marrow	
Copper deficiency	
Pancytopenia with Cellular Bone Marrow	
Primary bone marrow diseases	Secondary to systemic diseases
Myelodysplastic syndromes	Systemic lupus erythematosus
Paroxysmal nocturnal hemoglobinuria (PNH)	Hypersplenism
	B_{12}, folate deficiency
	Copper deficiency
Myelofibrosis	Alcohol
Aleukemic leukemia	HIV infection
Myelophthisis	Brucellosis
Bone marrow lymphoma	Sarcoidosis
Hairy cell leukemia	Tuberculosis
	Leishmaniasis
	Sepsis
Hypocellular Bone Marrow ± Pancytopenia	
Q fever	
Legionnaires' disease	
Anorexia nervosa, starvation	
Mycobacterium	

has blurred the distinction between acquired and inherited marrow failure. Patients may seem to suffer from two or three related diseases simultaneously, or one diagnosis may appear to evolve into another. Many of these syndromes share an immune-mediated mechanism of marrow destruction and some element of genomic instability resulting in a higher rate of malignant transformation.

It is important that the internist and general practitioner recognize the marrow failure syndromes, as their prognosis may be poor if the patient is untreated; effective therapies are often available but sufficiently complicated in their choice and delivery so as to warrant the care of a hematologist or oncologist. The identification of genes in which pathogenic mutations are etiologic for anemia, leukopenia, and thrombocytopenia, and the commercial availability of assays based on sophisticated DNA sequencing and functional consequences of mutations, should allow precise diagnosis early, by the primary care internist and pediatrician as well as by a specialist.

APLASTIC ANEMIA

DEFINITION

Aplastic anemia is pancytopenia with bone marrow hypocellularity. Acquired aplastic anemia is distinguished from iatrogenic aplasia, marrow hypocellularity after intensive cytotoxic chemotherapy for cancer, and from usually accidental physical and chemical injury, as in radiation poisoning. Aplastic anemia can also be constitutional. Genetic diseases such as Fanconi anemia and dyskeratosis congenita usually (but not always) present in early childhood and have typical physical anomalies. Telomere diseases (see Chap. 470) and hematologic manifestations of mutations in genes such as *GATA2*, *RUNX1*, and *MPL* can present as marrow failure in normal-appearing adults. Acquired aplastic anemia is often stereotypical in its manifestations, with the abrupt onset of low blood counts in a previously well young adult; seronegative hepatitis or a course of an incriminated medical drug may precede the onset. The diagnosis in these instances is uncomplicated. Sometimes blood count depression is moderate or incomplete, resulting in anemia, leukopenia, and thrombocytopenia in some combination. Aplastic anemia is related to both paroxysmal nocturnal hemoglobinuria (PNH; Chap. 96) and to MDS, and a clear distinction among these disorders may not be possible.

EPIDEMIOLOGY

The incidence of acquired aplastic anemia in Europe and Israel is two cases per million persons annually. In Thailand and China, rates of five to seven per million have been established. Men and women are affected with equal frequency, but the age distribution is biphasic, with the major peak in the teens and twenties and a second rise in older adults.

ETIOLOGY

The origins of aplastic anemia have been inferred from several recurring clinical associations (Table 98-2); unfortunately, these relationships are not reliable in an individual patient and may not be etiologic. In addition, although most cases of aplastic anemia are idiopathic, little other than history separates these cases from those with a presumed etiology such as a drug exposure.

Radiation Marrow aplasia is a major acute sequela of radiation. Radiation damages DNA; tissues dependent on active mitosis are

TABLE 98-2 Classification of Aplastic Anemia and Single Cytopenias

ACQUIRED	INHERITED/CONSTITUTIONAL
Aplastic Anemia	
Secondary	Fanconi anemia
Radiation	Dyskeratosis congenita/telomere disease
Drugs and chemicals	Shwachman-Diamond syndrome
Regular effects	Familial aplastic anemia/leukemia predisposition syndromes: *GATA2*, *RUNX1*, *CTLA4*, and others
Idiosyncratic reactions	
Viruses	
Epstein-Barr virus (infectious mononucleosis)	
Hepatitis (non-A, non-B, non-C hepatitis)	Nonhematologic syndromes (Down, Dubowitz, Seckel)
Parvovirus B19 (transient aplastic crisis, pure red cell aplasia [PRCA])	
HIV-1 (AIDS)	
Immune diseases	
Eosinophilic fasciitis	
Hypoimmunoglobulinemia	
Large granular lymphocytosis (LGL)	
Thymoma/thymic carcinoma	
Graft-versus-host disease in immunodeficiency	
Paroxysmal nocturnal hemoglobinuria (PNH)	
Pregnancy	
Idiopathic	
Cytopenias	
PRCA (see Table 98-4)	Congenital PRCA (Diamond-Blackfan anemia)
Neutropenia/agranulocytosis	
Idiopathic	Kostmann syndrome
Drugs, toxins	Shwachman-Diamond syndrome
LGL	Reticular dysgenesis
Pure white cell aplasia (+/– thymoma)	
Thrombocytopenia	
Drugs, toxins	Amegakaryocytic thrombocytopenia
Acquired amegakaryocytic thrombocytopenia	Thrombocytopenia with absent radii
	Other rare germline mutations

particularly susceptible. Nuclear accidents involve not only power plant workers but also employees of hospitals, laboratories, and industry (food sterilization, metal radiography, etc.), as well as innocents exposed to stolen, misplaced, or misused sources. Whereas the radiation dose can be approximated from the rate and degree of decline in blood counts, dosimetry by reconstruction of the exposure can help to estimate the patient's prognosis and also to protect medical personnel from contact with radioactive tissue and excreta. MDS and leukemia, but probably not aplastic anemia, are late effects of radiation.

Chemicals Benzene is a notorious cause of bone marrow failure: epidemiologic, clinical, and laboratory data link benzene to aplastic anemia, acute leukemia, and blood and marrow abnormalities. For leukemia, incidence is correlated with cumulative exposure, but susceptibility must also be important because only a minority of even heavily exposed workers develop myelotoxicity. The employment history is important, especially in industries where benzene is used for a secondary purpose, usually as a solvent. Benzene-related blood diseases have declined with regulation of industrial exposure. Although benzene is no longer generally available as a household solvent, exposure to its metabolites occurs in the normal diet and in the environment. The association between marrow failure and other chemicals is much less well substantiated.

Drugs (Table 98-3) Many chemotherapeutic drugs have marrow suppression as a major toxicity; effects are dose dependent and will occur in all recipients. In contrast, idiosyncratic reactions to a large and diverse group of drugs may lead to aplastic anemia without a clear dose-response relationship. A large international study in Europe in the 1980s quantitated drug relationships, especially for nonsteroidal analgesics, sulfonamides, thyrostatic drugs, some psychotropics, penicillamine, allopurinol, and gold. Association does not equal causation: a drug may have been used to treat the first symptoms of bone marrow failure (antibiotics for fever or a preceding viral illness) or provoked the first symptom of a preexisting disease (petechiae by nonsteroidal anti-inflammatory agents administered to the thrombocytopenic patient). In the context of total drug use, idiosyncratic reactions, although individually devastating, are rare events. Risk estimates are usually lower when determined in population-based studies. Furthermore, the low absolute risk is also made more obvious: even a 10- or 20-fold increase in risk translates, in a rare disease, to just a handful of drug-induced aplastic anemia cases among hundreds of thousands of exposed persons.

TABLE 98-3 Some Drugs and Chemicals Associated with Aplastic Anemia

Agents that regularly produce marrow depression as major toxicity in commonly used doses or normal exposures:
Cytotoxic drugs used in cancer chemotherapy: *alkylating agents*, *antimetabolites*, *antimitotics*, some antibiotics
Agents that frequently but not inevitably produce marrow aplasia:
Benzene
Agents associated with aplastic anemia but with a relatively low probability:
Chloramphenicol
Insecticides
Antiprotozoals: *quinacrine* and chloroquine, mepacrine
Nonsteroidal anti-inflammatory drugs (including *phenylbutazone*, indomethacin, ibuprofen, sulindac, aspirin)
Anticonvulsants (*hydantoins*, *carbamazepine*, phenacemide, felbamate)
Heavy metals (*gold*, arsenic, bismuth, mercury)
Sulfonamides: some antibiotics, antithyroid drugs (methimazole, methylthiouracil, propylthiouracil), antidiabetes drugs (tolbutamide, chlorpropamide), carbonic anhydrase inhibitors (acetazolamide and methazolamide)
Antihistamines (*cimetidine*, chlorpheniramine)
D-Penicillamine
Estrogens (in pregnancy and in high doses in animals)
Agents whose association with aplastic anemia is more tenuous:
Other antibiotics (streptomycin, tetracycline, methicillin, mebendazole, trimethoprim/sulfamethoxazole, flucytosine)
Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon)
Allopurinol
Methyldopa
Quinidine
Lithium
Guanidine
Potassium perchlorate
Thiocyanate
Carbimazole

Note: Terms set in italics show the most consistent association with aplastic anemia.

Infections Posthepatitis marrow failure accounts for ~5% of etiologies in most series. Patients are usually young men who have recovered from a bout of liver inflammation 1–2 months earlier; the subsequent pancytopenia is very severe. The hepatitis is seronegative (non-A, non-B, non-C); intensive laboratory efforts including deep sequencing have not disclosed an infectious agent. Fulminant liver failure in childhood also follows seronegative hepatitis, and marrow failure occurs at a high rate in these patients. Aplastic anemia can rarely follow infectious mononucleosis. Parvovirus B19 does not usually cause generalized bone marrow failure. Transient, mild blood count depression is frequent in the course of many viral and bacterial infections.

Immunologic Diseases Aplasia is a major consequence and the inevitable cause of death in *transfusion-associated graft-versus-host disease* (GVHD) that can occur after infusion of nonirradiated blood products to an immunodeficient recipient. Aplastic anemia is strongly associated with the rare collagen vascular syndrome eosinophilic fasciitis that is characterized by painful induration of subcutaneous tissues (Chap. 353). Thymoma and hypoimmunoglobulinemia are occasional associations with aplastic anemia. Pancytopenia with marrow hypoplasia can also occur in systemic lupus erythematosus (SLE).

Pregnancy Aplastic anemia very rarely may occur and recur during pregnancy and resolve with delivery or with spontaneous or induced abortion.

Paroxysmal Nocturnal Hemoglobinuria An acquired mutation in the *PIG-A* gene in a hematopoietic stem cell is required for the development of PNH, but *PIG-A* mutations probably occur commonly in normal individuals. If the PIG-A mutant stem cell proliferates, the result is a clone of progeny deficient in glycosylphosphatidylinositol-linked cell surface membrane proteins (Chap. 96). Small clones of deficient cells can be detected by sensitive flow cytometry tests in one-half or more of patients with aplastic anemia at the time of presentation. Functional studies of bone marrow from PNH patients, even those with mainly hemolytic manifestations, show evidence of defective hematopoiesis. Patients with an initial clinical diagnosis of PNH, especially younger individuals, may later develop frank marrow aplasia and pancytopenia; patients with an initial diagnosis of aplastic anemia may suffer later from hemolytic PNH years after recovery of blood counts.

Constitutional Disorders Fanconi anemia, an autosomal recessive disorder, manifests as congenital developmental anomalies, progressive pancytopenia, and an increased risk of malignancy. Chromosomes in Fanconi anemia are susceptible to DNA cross-linking agents, the basis for a diagnostic assay. Patients with Fanconi anemia typically have short stature, café au lait spots, and anomalies involving the thumb, radius, and genitourinary tract. At least 17 different genetic defects (all but one with an identified gene) have been defined; the most common, type A Fanconi anemia, is due to a mutation in *FANCA*. Most of the Fanconi anemia gene products form a protein complex that activates FANCD2 by monoubiquitination to play a role in the cellular response to DNA damage and especially interstrand cross-linking.

Dyskeratosis congenita is characterized by the triad of mucous membrane leukoplasia, dystrophic nails, reticular hyperpigmentation, and with the development of aplastic anemia in childhood (Chapter 470). Dyskeratosis congenita is due to mutations in genes of the telomere repair complex, which acts to maintain telomere length in replicating

cells: the X-linked variety is due to mutations in the *DKC1* (*dyskerin*) gene; the more unusual autosomal dominant type is due to mutation in *TERC*, which encodes an RNA template, and *TERT*, which encodes the catalytic reverse transcriptase, telomerase. Mutations can also occur in genes like *TNF2* that encode shelterin proteins, which bind telomere DNA.

In Shwachman-Diamond syndrome, presentation is early in life with neutropenia with pancreatic insufficiency and malabsorption; most patients have compound heterozygous mutations in *SBDS* that may affect both ribosomal biogenesis (as in Diamond-Blackfan anemia; see below) and marrow stroma function.

While these constitutional syndromes can on occasion present in adults, genetic mutations are also risk factors for bone marrow failure. In the recently recognized telomeropathies **(see Chap. 470)**, mutations in *TERT* and *TERC* have subtle effects on hematopoietic function. Typical presentations include moderate aplastic anemia, which can be chronic and not progressive, and isolated macrocytic anemia or thrombocytopenia. Physical anomalies are usually not present, but early hair graying is a clue to the diagnosis. A family history may disclose pulmonary fibrosis and hepatic cirrhosis. Variable penetrance means that *TERT* and *TERC* mutations represent risk factors for marrow failure, as family members with the same mutations may have normal or only slight hematologic abnormalities but more subtle evidence of (compensated) hematopoietic insufficiency.

PATHOPHYSIOLOGY

Bone marrow failure results from severe damage to the hematopoietic cell compartment. In aplastic anemia, replacement of the bone marrow by fat is apparent in the morphology of the biopsy specimen **(Fig. 98-1)** and magnetic resonance imaging (MRI) of the spine. Cells bearing the CD34 antigen, a marker of early hematopoietic cells, are greatly diminished, and in functional studies, committed and primitive progenitor cells are virtually absent; in vitro assays have suggested that the stem cell pool is reduced to ≤1% of normal in severe disease at the time of presentation.

Constitutional Genetic Syndromes

An intrinsic stem cell defect exists for the constitutional aplastic anemias: cells from patients with Fanconi anemia exhibit chromosome damage and death on exposure to certain chemical agents. Telomeres are short in some patients with aplastic anemia, due to heterozygous mutations in genes of the telomere repair complex. Telomeres may also shorten physiologically in acquired marrow failure due to replicative demands on a limited stem cell pool.

Chemical and Drug Injury

Extrinsic damage to the marrow follows massive physical or chemical insults such as high doses of radiation and toxic chemicals. For the more common idiosyncratic reaction to modest doses of medical drugs, altered drug metabolism has been invoked as a mechanism. The metabolic pathways of many drugs and chemicals, especially if they are polar and have limited water solubility, involve enzymatic degradation to highly reactive electrophilic compounds; these intermediates are toxic because of their propensity to bind to cellular macromolecules. For example, derivative hydroquinones and quinolones are responsible for benzene-induced tissue injury. Excessive generation of toxic intermediates or failure to detoxify the intermediates may be genetically determined and apparent only on specific drug challenge; the complexity and specificity of the pathways imply multiple susceptibility loci and would provide an explanation for the rarity of idiosyncratic drug reactions.

Immune-Mediated Stem Cell Destruction

The recovery of marrow function in some patients prepared for bone marrow transplantation with antilymphocyte globulin first suggested that aplastic anemia might be immune mediated. Consistent with this hypothesis was the frequent failure of simple bone marrow transplantation from a syngeneic twin, without conditioning cytotoxic chemotherapy, which also argued both *against* simple stem cell absence as the cause and *for* the presence of a host factor producing marrow failure. Laboratory data support an important role for the immune system in aplastic anemia. Blood and bone marrow cells of patients can suppress normal hematopoietic progenitor cell growth, and removal of T cells from aplastic anemia bone marrow improves colony formation in vitro. Increased numbers of activated cytotoxic T cell clones are observed in aplastic anemia patients and usually decline with successful immunosuppressive therapy; type 1 cytokines are implicated; and interferon γ (IFN-γ) induces Fas expression on CD34 cells, leading to apoptotic cell death. The early immune system events in aplastic anemia are not well understood, but an oligoclonal, T cell response implies antigenic stimulus. The rarity of aplastic anemia despite common exposures (medicines, seronegative hepatitis) suggests that genetically determined features of the immune response can convert a normal physiologic response into a sustained abnormal autoimmune process, including polymorphisms in histocompatibility antigens, cytokine genes, and genes that regulate T cell polarization and effector function.

CLINICAL FEATURES

History

Aplastic anemia can appear abruptly or insidiously. Bleeding is the most common early symptom; a complaint of days to weeks of easy bruising, oozing from the gums, nose bleeds, heavy menstrual flow, and sometimes petechiae will have been noticed. With thrombocytopenia, massive hemorrhage is unusual, but small amounts of bleeding in the central nervous system can result in catastrophic intracranial

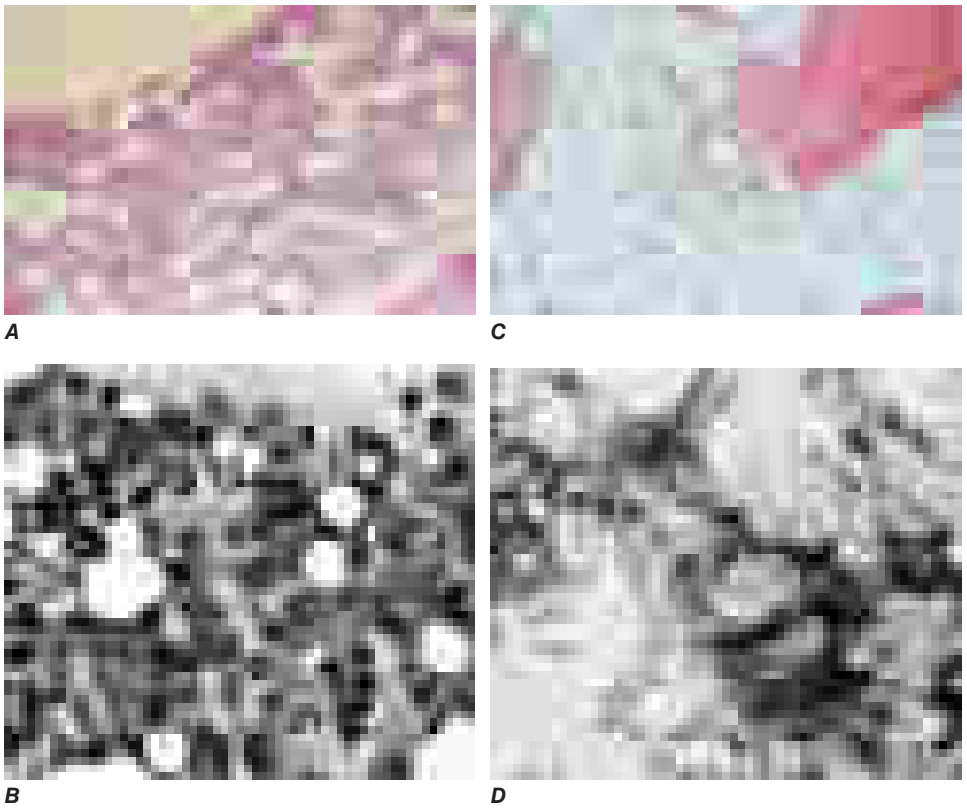

FIGURE 98-1 Normal and aplastic bone marrow. *A.* Normal bone marrow biopsy. ***B.*** Normal bone marrow aspirate smear. The marrow is normally 30–70% cellular, and there is a heterogeneous mix of myeloid, erythroid, and lymphoid cells. ***C.*** Aplastic anemia biopsy. ***D.*** Marrow smear in aplastic anemia. The marrow shows replacement of hematopoietic tissue by fat and only residual stromal and lymphoid cells.

or retinal hemorrhage. Symptoms of anemia are also frequent, including lassitude, weakness, shortness of breath, and a pounding sensation in the ears. Infection is an unusual first symptom in aplastic anemia (unlike in agranulocytosis, where pharyngitis, anorectal infection, or frank sepsis occurs early). Patients often feel and look remarkably well despite drastically reduced blood counts. Systemic complaints and weight loss should point to other etiologies of pancytopenia. Prior medical drug use, chemical exposure, and preceding viral illnesses must often be elicited with directed questioning. A family history of hematologic diseases or blood abnormalities, of pulmonary or liver fibrosis, or of early hair graying points to a telomeropathy; a family history of unusual infections and warts to *GATA2* deficiency.

Physical Examination Petechiae and ecchymoses are typical, and retinal hemorrhages may be present. Pelvic and rectal examinations can often be deferred but, when performed, should be undertaken with great gentleness to avoid trauma; these may show bleeding from the cervical os and blood in the stool. Pallor of the skin and mucous membranes is common. Infection on presentation is unusual but may occur if the patient has been symptomatic for a few weeks. Lymphadenopathy and splenomegaly are highly atypical of aplastic anemia. Café au lait spots and short stature suggest Fanconi anemia; peculiar nails and leukoplakia suggest dyskeratosis congenita; early graying (and use of hair dyes to mask it!) suggest a telomerase defect.

LABORATORY STUDIES

Blood The smear shows large erythrocytes and a paucity of platelets and granulocytes. Mean corpuscular volume (MCV) is commonly increased. Reticulocytes are absent or few, and lymphocyte numbers may be normal or reduced. The presence of immature myeloid forms suggests leukemia or MDS; nucleated red blood cells (RBCs) suggest marrow fibrosis or tumor invasion; abnormal platelets suggest either peripheral destruction or MDS.

Bone Marrow The bone marrow is usually readily aspirated but dilute on smear, and the fatty biopsy specimen may be grossly pale on withdrawal; a "dry tap" instead suggests fibrosis or myelophthisis. In severe aplasia, the smear of the aspirated specimen shows only red cells, residual lymphocytes, and stromal cells; the biopsy (which should be >1 cm in length) is superior for determination of cellularity and shows mainly fat under the microscope, with hematopoietic cells occupying <25% of the marrow space; sometimes, the biopsy is virtually all fat. The correlation between marrow cellularity and disease severity is imperfect; patients with moderate disease by blood counts can have empty iliac crest biopsies, whereas "hot spots" of hematopoiesis may be seen in severe cases. Residual hematopoietic cells should have normal morphology, except for mildly megaloblastic erythropoiesis; megakaryocytes are greatly reduced and usually absent. Granulomas may indicate an infectious etiology of the marrow failure.

Ancillary Studies Chromosome breakage studies of peripheral blood using diepoxybutane or mitomycin C should be performed on children and younger adults to exclude Fanconi anemia. Very short telomere length strongly suggests the presence of a telomerase or shelterin mutation, which can be pursued by family studies and nucleotide sequencing. Chromosome studies of bone marrow cells are often revealing in MDS, but should be negative in typical aplastic anemia. Flow cytometry offers a sensitive diagnostic test for PNH. Serologic studies may show evidence of viral infection, such as Epstein-Barr virus and HIV. Posthepatitis aplastic anemia is seronegative. Occasionally MRI may be helpful to assess the fat content of vertebrae in order to distinguish aplasia from MDS.

DIAGNOSIS

The diagnosis of aplastic anemia is usually straightforward, based on the combination of pancytopenia with a fatty bone marrow. Aplastic anemia is a disease of the young and should be a leading diagnosis in the pancytopenic adolescent or young adult. When pancytopenia is secondary, the primary diagnosis is usually obvious from either history or physical examination: the massive spleen of alcoholic cirrhosis, the history of metastatic cancer or SLE, or miliary tuberculosis on chest radiograph (Table 98-1).

Diagnostic problems can occur with atypical presentations and among related hematologic diseases. Patients with bone marrow hypocellularity may have depression of only one or two of three blood lines, with later progression to pancytopenia. The most important differential diagnosis is between acquired and constitutional aplastic anemia, and between aplastic anemia and MDS. The bone marrow in constitutional aplastic anemia is usually morphologically indistinguishable from the aspirate in acquired disease (an exception is *GATA2* deficiency with it characteristic megakaryocyte atypia). The diagnosis can be suggested by family history, abnormal blood counts since childhood, or the presence of associated physical anomalies. Many laboratories now offer genomic sequencing of a panel of etiologic germline genes, allowing for precision diagnosis. Aplastic anemia may be difficult to distinguish from the hypocellular variety of MDS: MDS is favored by finding morphologic abnormalities, particularly of megakaryocytes and myeloid precursor cells, and typical cytogenetic abnormalities. Somatic mutations can be detected on genomic screening of genes recurrently mutated in MDS, acute myeloid leukemia (AML), and myeloproliferative neoplasms (see below).

PROGNOSIS

The natural history of severe aplastic anemia is rapid deterioration and death. Historically, provision first of RBC and later of platelet transfusions and effective antibiotics were of some benefit, but few patients show spontaneous recovery. The major prognostic determinant is the blood count. Severe disease historically has been defined by the presence of two of three parameters: absolute neutrophil count <500/μL, platelet count <20,000/μL, and corrected reticulocyte count <1% (or absolute reticulocyte count <60,000/μL). In the era of effective immunosuppressive therapies, absolute numbers of reticulocytes (>25,000/μL) and lymphocytes (>1000/μL) may be better predictors of response to treatment and long-term outcome.

TREATMENT

Aplastic Anemia

Severe acquired aplastic anemia can be cured by replacement of the absent hematopoietic cells (and the immune system) by stem cell transplant, or it can be ameliorated by suppression of the immune system to allow recovery of the patient's residual bone marrow function. Glucocorticoids are not of value as primary therapy. Suspect exposures to drugs or chemicals should be discontinued; however, spontaneous recovery of severe blood count depression is rare, and a waiting period before beginning treatment may not be advisable unless the blood counts are only modestly depressed.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

This is the best therapy for the younger patient with a fully histocompatible sibling donor **(Chap. 110)**. Human leukocyte antigen (HLA) typing should be ordered as soon as the diagnosis of aplastic anemia is established in a child or younger adult. In transplant candidates, transfusion of blood from family members should be avoided so as to prevent sensitization to histocompatibility antigens. In general, limited numbers of blood products probably do not greatly affect outcome. For allogeneic transplant from fully matched siblings, long-term survival rates for children are ~90%. Transplant morbidity and mortality are increased among adults, due to the higher risk of chronic GVHD and serious infections.

Most patients do not have a suitable sibling donor. Occasionally, a full phenotypic match can be found within the family and serve as well. Far more available are other alternative donors, either unrelated but histocompatible volunteers or closely but not perfectly matched family members. High-resolution matching at HLA and more effective conditioning regimens and GVHD prophylaxis have led to improved survival rates in patients who proceed to alternative donor transplant. Survival is equivalent between matched unrelated and conventional sibling donors, although complication rates (mainly graft-versus-host disease and infection) are higher

using unrelated donors. Cord blood can be a source of stem cells especially for children. Transplantation from an HLA haploidentical family donor is increasingly popular: a donor is almost always quickly available, and post-transplant cyclophosphamide appears to be effective in preventing graft-versus-host disease. Transplant protocols for marrow failure now usually do not include radiation in order to avoid late occurrence of cancer.

IMMUNOSUPPRESSION

The standard regimen of antithymocyte globulin (ATG) in combination with cyclosporine induces hematologic recovery (independence from transfusion and a leukocyte count adequate to prevent infection) in 60–70% of patients. Children do especially well, whereas older adult patients can suffer complications due to the presence of comorbidities. An early robust hematologic response correlates with long-term survival. Improvement in granulocyte number is generally apparent within 2 months of treatment. Most recovered patients continue to have some degree of blood count depression, the MCV remains elevated, and bone marrow cellularity returns toward normal very slowly if at all. Relapse (recurrent pancytopenia) is frequent, often occurring as cyclosporine is discontinued; most, but not all, patients respond to reinstitution of immunosuppression, but some responders become dependent on continued cyclosporine administration. Development of MDS, with typical marrow morphologic, but more often cytogenetic abnormalities, occurs in ~15% of treated patients, usually but not invariably associated with a return of pancytopenia, and some patients develop leukemia. A laboratory diagnosis of PNH can generally be made at the time of presentation of aplastic anemia by flow cytometry; recovered patients may have frank hemolysis if the PNH clone expands. Bone marrow examinations should be performed if there is an unfavorable change in blood counts.

Horse ATG is administered as intravenous infusions over 4 days; rabbit ATG is much less effective, perhaps because it reduces T-regulatory cell numbers in patients. Serum sickness, a flulike illness with a characteristic cutaneous eruption and arthralgia, often develops ~10 days after initiating treatment. Methylprednisolone is administered with ATG to ameliorate the immune consequences of heterologous protein infusion. (Excessive or extended glucocorticoid therapy is associated with avascular joint necrosis.) Cyclosporine is administered orally at an initial high dose, with subsequent adjustment according to blood levels. Its most important side effects are nephrotoxicity, hypertension, and seizures.

Most patients with aplastic anemia lack a suitable marrow donor, and immunosuppression is the treatment of choice. Overall survival is equivalent with transplantation and immunosuppression. However, successful transplant cures marrow failure, whereas patients who recover adequate blood counts after immunosuppression remain at risk of relapse and malignant evolution. Because of excellent results in children and younger adults, allogeneic transplant should be performed if a suitable sibling donor is available. Increasing age and the severity of neutropenia are the most important factors weighing in the decision between transplant and immunosuppression in adults who have a matched family donor: older patients do better with ATG and cyclosporine, whereas transplant is preferred if neutrocytopenia is profound.

ELTROMBOPAG

Hematopoietic growth factors (HGFs) such as erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF) are not effective in aplastic anemia, probably because endogenous blood levels in patients are extremely high. Circulating thrombopoietin is also elevated, but a thrombopoietin mimetic has shown unexpected activity, and eltrombopag now is approved for use in patients with refractory aplastic anemia. Robust, trilineage responses suggest action on the stem cell. Eltrombopag added to first-line immunosuppression with horse ATG markedly increased overall and complete response rates.

That outcomes following both stem cell transplant and immunosuppression have improved with time has complicated development of consensus algorithms. Children with histocompatible siblings should be offered transplant, but some have advocated for "upfront" transplants from well-matched unrelated donors. Transplant has also been extended to older patients, including from unrelated matched donors and haploidentical donors. Conversely, immunosuppression combined with stem cell stimulation may lead to responses within a few months in almost all patients and can be instituted at diagnosis. Even heavily transfused and infected patients in whom immunosuppression has failed can be salvaged by stem cell transplant later.

ANDROGENS

The effectiveness of androgens has not been verified in controlled trials, but occasional patients will respond or even demonstrate blood count dependence on continued therapy. Sex hormones upregulate telomerase gene activity in vitro, which is possibly also their mechanism of action in improving marrow function. For patients with moderate disease, especially if a telomere gene defect is present, a 3- to 4-month trial may improve all blood counts **(Chap. 470)**.

SUPPORTIVE CARE

Meticulous medical attention is required so that the patient may survive to benefit from definitive therapy or, having failed treatment, to maintain a reasonable existence in the face of pancytopenia. First and most important, infection in the presence of severe neutropenia must be aggressively treated by prompt institution of parenteral, broad-spectrum antibiotics. Therapy is empirical and must not await results of culture, although specific foci of infection such as oropharyngeal or anorectal abscesses, pneumonia, sinusitis, and typhlitis (necrotizing colitis) should be sought on physical examination and with radiographic studies. When indwelling plastic catheters become contaminated, vancomycin should be added. Persistent or recrudescent fever implies fungal disease: *Candida* and *Aspergillus* are common, especially after several courses of antibacterial antibiotics. A major reason for the improved prognosis in aplastic anemia has been the development of better antifungal drugs and the timely institution of such therapy when infection is suspected. Granulocyte transfusions using G-CSF–mobilized peripheral blood can be effective when infections are overwhelming or refractory. Hand washing, the single best method of preventing the spread of infection, remains a neglected practice. Nonabsorbed antibiotics for gut decontamination are poorly tolerated and not of proven value, nor does reverse isolation reduce mortality from infections.

Both platelet and erythrocyte numbers can be maintained by transfusion. Alloimmunization historically limited the usefulness of platelet transfusions and is now minimized by several strategies, including use of single donors to reduce exposure and physical or chemical methods to diminish leukocytes in the product; HLA-matched platelets are usually effective in patients refractory to random donor products. Inhibitors of fibrinolysis such as aminocaproic acid have not been shown to relieve mucosal oozing; the use of low-dose glucocorticoids to induce "vascular stability" is unproven and not recommended. With prophylactic platelet transfusions, the goal is to maintain the platelet count >10,000/μL (oozing from the gut increases precipitously at counts <5000/μL). Menstruation should be suppressed either by oral estrogens or nasal follicle-stimulating hormone/luteinizing hormone antagonists. Aspirin and other nonsteroidal anti-inflammatory agents must be avoided in the presence of thrombocytopenia.

RBCs should be transfused so as to allow patient a normal level of activity, usually at a hemoglobin value of 70 g/L (90 g/L if there is underlying cardiac or pulmonary disease); a regimen of 2 units every 2 weeks will replace normal losses in a patient without a functioning bone marrow. In chronic anemia, the iron chelators, deferoxamine and deferasirox, should be added at approximately the fiftieth transfusion to avoid secondary hemochromatosis.

PURE RED CELL APLASIA

Other more restricted forms of marrow failure occur, in which only a single circulating cell type is affected and the marrow shows corresponding absence or decreased numbers of specific precursor cells: aregenerative anemia as in PRCA (see below), thrombocytopenia with amegakaryocytosis **(Chap. 111)**, and neutropenia without marrow

myeloid cells in agranulocytosis (Chap. 60). In general, and in contrast to aplastic anemia and MDS, the unaffected lineages appear quantitatively and qualitatively normal. Agranulocytosis, the most frequent of these syndromes, is usually a complication of medical drug use (with agents similar to those related to aplastic anemia), either by a mechanism of direct chemical toxicity or by immune destruction. Agranulocytosis has an incidence similar to aplastic anemia but is especially frequent among older adults and in women. The syndrome should resolve with discontinuation of exposure, but significant mortality is attached to neutropenia in the older and often previously unwell patient. Both pure white cell aplasia (agranulocytosis without incriminating drug exposure) and amegakaryocytic thrombocytopenia are exceedingly rare and, like PRCA, appear to be due to destructive antibodies or lymphocytes and can respond to immunosuppressive therapies. In all of the single-lineage failure syndromes, progression to pancytopenia or leukemia is unusual.

DEFINITION AND DIFFERENTIAL DIAGNOSIS

PRCA is characterized by anemia, reticulocytopenia, and absent or rare erythroid precursor cells in the bone marrow. The classification of PRCA is shown in Table 98-4. In adults, PRCA is acquired. An identical syndrome can occur constitutionally: Diamond-Blackfan anemia, or congenital PRCA, is diagnosed at birth or in early childhood and often responds to glucocorticoid treatment; mutations in ribosome protein genes are etiologic. Temporary red cell failure occurs in transient aplastic crisis of hemolytic anemias due to acute parvovirus infection (Chap. 192) and in transient erythroblastopenia of childhood, which occurs in normal children.

TABLE 98-4 Classification of Pure Red Cell Aplasia

Self-limited
Transient erythroblastopenia of childhood
Transient aplastic crisis of hemolysis (acute B19 parvovirus infection)
Fetal red blood cell aplasia
Nonimmune hydrops fetalis (in utero B19 parvovirus infection)
Hereditary pure red cell aplasia
Congenital pure red cell aplasia (Diamond-Blackfan anemia)
Acquired pure red cell aplasia
Cancer
Thymoma
Lymphoid malignancies (and more rarely other hematologic diseases)
Paraneoplastic to solid tumors
Connective tissue disorders with immunologic abnormalities
Systemic lupus erythematosus, juvenile rheumatoid arthritis, rheumatoid arthritis
Multiple endocrine gland insufficiency
Viruses
Persistent B19 parvovirus, hepatitis, adult T cell leukemia virus, Epstein-Barr virus
Pregnancy
Drugs
Especially phenytoin, azathioprine, chloramphenicol, procainamide, isoniazid
Antibodies to erythropoietin
Idiopathic

CLINICAL ASSOCIATIONS AND ETIOLOGY

PRCA has important associations with immune system diseases. A minority of cases occur with a thymoma. More frequently, red cell aplasia can be the major manifestation of large granular lymphocytosis or complicate chronic lymphocytic leukemia. Some patients may be hypogammaglobulinemic. Occasionally (as compared to agranulocytosis), PRCA can be due to an idiosyncratic drug reaction. Subcutaneous administration of EPO has provoked PRCA mediated by neutralizing antibodies to the hormone.

Antibodies to RBC precursors are frequently present in the blood, but T cell inhibition is probably the more common immune mechanism. Cytotoxic lymphocyte activity restricted by histocompatibility locus or specific for human T-cell leukemia/lymphoma virus I–infected cells and natural killer cell activity inhibitory of erythropoiesis have been demonstrated in particularly well-studied individual cases.

PERSISTENT PARVOVIRUS B19 INFECTION

Chronic parvovirus infection is an important, treatable cause of red cell aplasia. This common virus causes a benign exanthem of childhood (fifth disease) and a polyarthralgia/arthritis syndrome in adults. In patients with underlying hemolysis (or any condition that increases demand for RBC production), parvovirus infection can cause a transient aplastic crisis and an abrupt but temporary worsening of the anemia due to failed erythropoiesis. In normal individuals, acute infection is resolved by production of neutralizing antibodies to the virus, but in the setting of congenital, acquired, or iatrogenic immunodeficiency, persistent viral infection may occur. The bone marrow shows red cell aplasia and the presence of giant pronormoblasts (Fig. 98-2), which is the cytopathic

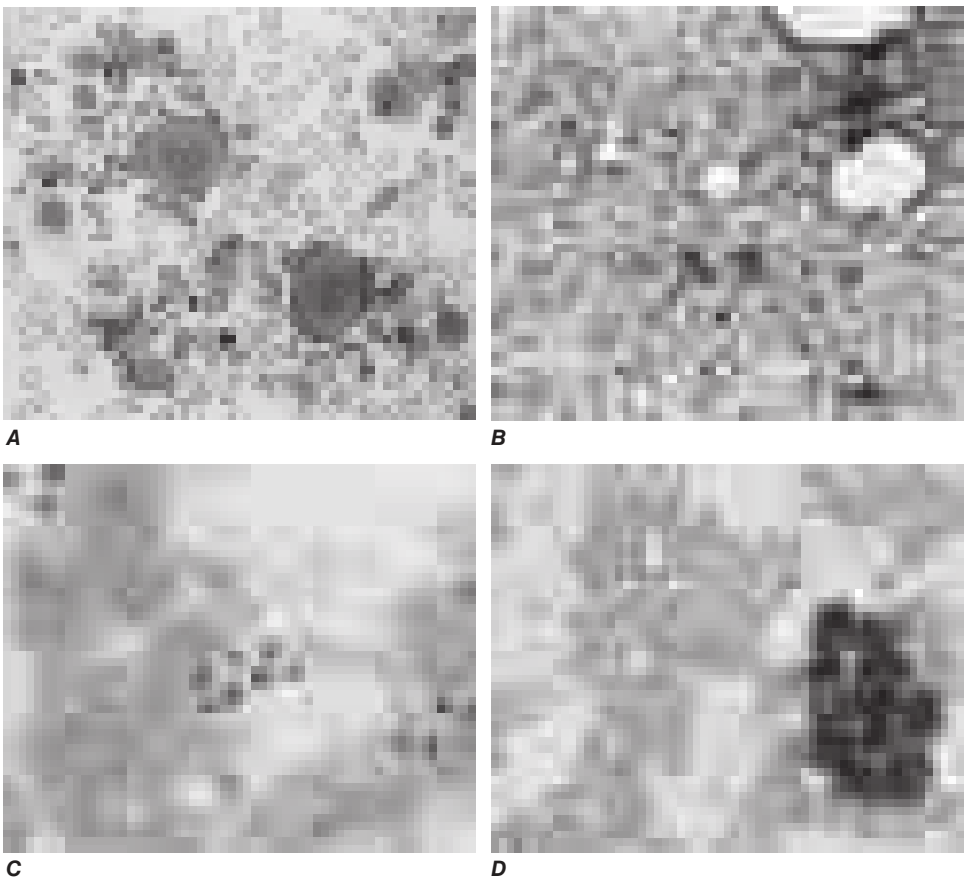

FIGURE 98-2 Pathognomonic cells in marrow failure syndromes. *A.* Giant pronormoblast, the cytopathic effect of B19 parvovirus infection of the erythroid progenitor cell. ***B.*** Uninuclear megakaryocyte and microblastic erythroid precursors typical of the 5q–myelodysplasia syndrome. ***C.*** Ringed sideroblast showing perinuclear iron granules. ***D.*** Tumor cells present on a touch preparation made from the marrow biopsy of a patient with metastatic carcinoma.

sign of B19 parvovirus infection. Viral tropism for human erythroid progenitor cells is due to its use of erythrocyte P antigen as a cellular receptor for entry. Direct cytotoxicity of virus causes anemia if demands on erythrocyte production are high; in normal individuals, the temporary cessation of red cell production is not clinically apparent, and skin and joint symptoms are mediated by immune complex deposition.

TREATMENT

Pure Red Cell Aplasia

History, physical examination, and routine laboratory studies may disclose an underlying disease or a drug exposure. Thymoma should be sought by radiographic procedures; tumor excision is indicated, but anemia does not necessarily improve with surgery. The diagnosis of parvovirus infection requires detection of viral DNA sequences in the blood (IgG and IgM antibodies are commonly absent). The presence of erythroid colonies has been considered predictive of response to immunosuppressive therapy in idiopathic PRCA.

Red cell aplasia is compatible with long-term survival with supportive care alone: a combination of erythrocyte transfusions and iron chelation. For persistent B19 parvovirus infection, almost all patients respond to intravenous immunoglobulin therapy. The majority of patients with idiopathic PRCA respond favorably to immunosuppression: glucocorticoids, cyclosporine, ATG, azathioprine, and cyclophosphamide are effective.

MYELODYSPLASIA

DEFINITION

The MDS are a heterogeneous group of hematologic disorders broadly characterized by both (1) cytopenias due to bone marrow failure and (2) a high risk of development of AML. Anemia, often with thrombocytopenia and neutropenia, occurs with dysmorphic (abnormal appearing) and usually cellular bone marrow, which is evidence of ineffective blood cell production. In patients with "low-risk" MDS, marrow failure dominates the clinical course. In other patients, myeloblasts are present at diagnosis, chromosomes are abnormal, and the "high risk" is due to leukemic progression. MDS may be fatal due, most often, to complications of pancytopenia, or to progression to leukemia, but a large proportion of patients will die of concurrent disease, the comorbidities typical in an elderly population. A useful nosology of these often confusing entities was first developed by the French-American-British Cooperative Group in 1983. Five subtypes were defined then: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). The World Health Organization (WHO) classification (2002) recognized that the distinction between RAEB-t and AML is arbitrary and grouped them together as acute leukemia, and clarified that CMML behaves as a myeloproliferative disease. The current WHO classification of 2016 is complicated **(Table 98-5)**: blast percentage remains critical in defining MDS categories; erythroid predominant leukemias are now largely regarded as MDS; defining cytogenetic abnormalities are reaffirmed; and a single somatic mutation, in *SF3B1*, is now a feature of sideroblastic anemias. Identification of somatically mutated genes and their correlation with clinical outcomes will be increasingly important in defining classification, prognosis, and targeting therapy.

The diagnosis of MDS can be a challenge, even for the expert, because sometimes subtle clinical and pathologic features must be distinguished, and precise diagnostic categorization requires a hematopathologist knowledgeable in the latest classification scheme. Unfortunately, agreement among pathologists on morphologic features and classification is imperfect; changes in the appearance of megakaryocytes are more reliable than loss of granules in neutrophil precursors or dyserythropoiesis. Further, dysplastic changes can be observed in normal individuals, and they can occur with vitamin deficiencies and as drug effects. Genomic testing is increasingly routine and can be difficult to interpret, as in differences between somatic and germline mutations, pathogenic mutations versus those of unknown significance (clonal hematopoiesis increases in frequency with age and involves genetic changes that may be clinically silent or convey an increased risk of hematologic malignancy), and clone size and changes over time. It is important that the internist and primary care physician be sufficiently familiar with MDS to expedite referral to a hematologist because many new therapies are now available to improve hematopoietic function

TABLE 98-5 World Health Organization (WHO) Classification of Myelodysplastic Syndromes (MDS)/Neoplasms

NAME	RING SIDEROBLASTS	MYELOBLASTS	KARYOTYPE
MDS with single lineage dysplasia (MDS-SLD)	<15% (<5%)[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	<15% (<5%)[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)			
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	≥15% / ≥5%[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia (MDS-RS-MLD)	≥15% / ≥5%[a]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except –7 or del (7q)
MDS with excess blasts (MDS-EB)			
MDS-EB-1	None or any	BM 5–9% or PB 2–4%, no Auer rods	Any
MDS-EB-2	None or any	BM 10–19% or PB 5–19% or Auer rods	Any
MDS, unclassifiable (MDS-U)			
· with 1% blood blasts	None or any	BM <5%, PB=1%, no Auer rods	Any
· with single lineage dysplasia and pancytopenia	None or any	BM <5%, PB=1%, no Auer rods	Any
· based on defining cytogenetic abnormality	15%	BM <5%, PB=1%, no Auer rods	MDS-defining abnormality
MDS, unclassifiable (MDS-U)			
· with 1% blood blasts	None or any	BM <5%, PB=1%, no Auer rods	Any
· with single lineage dysplasia and pancytopenia	None or any	BM <5%, PB=1%, no Auer rods	Any
· based on defining cytogenetic abnormality	15%	BM <5%, PB=1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	None	BM <5%, PB <2%	Any

[a]If *SF3B1* mutation is present.

Abbreviations: BM, bone marrow; PB, peripheral blood.

and the judicious use of supportive care can improve the patient's quality of life.

EPIDEMIOLOGY

MDS is a disease of the elderly; the mean age at onset is older than 70 years. There is a slight male preponderance. MDS is a relatively common form of bone marrow failure, with reported incidence rates of 35 to >100 per million persons in the general population and 120 to >500 per million in older adults. Estimates of incidence in the United States range from 30,000 to 40,000 new cases annually and a prevalence of 60,000–120,000 in the population. MDS is rare in children, in whom it often has an identifiable genetic basis. Secondary or therapy-related MDS is not age related. Rates of MDS have increased over time, due to better recognition of the syndrome by physicians, and an aging population.

ETIOLOGY AND PATHOPHYSIOLOGY

MDS is associated with environmental exposures such as radiation and benzene; other risk factors have been reported inconsistently. Secondary, therapy-related MDS occurs as a late toxicity of cancer treatment, radiation and the radiomimetic alkylating agents such as busulfan, nitrosourea, or procarbazine (with a latent period of 5–7 years), or the DNA topoisomerase inhibitors (2-year latency). Acquired aplastic anemia, Fanconi anemia, and other constitutional marrow failure diseases can evolve into MDS; occasionally, MDS in adults is recognized as due to germline *GATA2, RUNX1,* or telomere repair gene mutations. The typical MDS patient does not have a suggestive environmental exposure history or a preceding hematologic disease. MDS is a disease of aging, suggesting random cumulative intrinsic and environmental damage to marrow cells.

MDS is a clonal hematopoietic stem cell disorder characterized by disordered cell proliferation and impaired differentiation, resulting in cytopenias and risk of progression to leukemia. Both chromosomal and genetic instability have been implicated: both are aging-related. Cytogenetic abnormalities are found in approximately one-half of patients, and some of the same specific lesions are also seen in leukemia; aneuploidy (chromosome loss or gain) is more frequent than translocations. Accelerated telomere attrition may destabilize the genome in marrow failure and predispose to acquisition of chromosomal lesions. Cytogenetic abnormalities are not random (loss of all or part of 5, 7, and 20, trisomy of 8) and may be related to etiology (11q23 following topoisomerase II inhibitors). The type and number of cytogenetic abnormalities strongly correlate with the probability of leukemic transformation and survival.

Genomics has illuminated the role of mutations in the pathophysiology of MDS. Recurrent somatic mutations, acquired in the abnormal marrow cells and absent in the germline, have been identified in about 100 genes. Many of the same genes are also mutated in AML without MDS, whereas others are distinctive in subtypes of MDS. A prominent example of the latter is the discovery of mutations in genes of the RNA splicing machinery, especially *SF3B1*, which strongly associates with sideroblastic anemia. Some mutations correlate with prognosis: spliceosome defects with favorable outcome, and mutations in *EZH2, TP53, RUNX1*, and *ASXL1* with poor outcome. Mutations and cytogenetic abnormalities are not independent: *TP53* mutations associate with complex cytogenetic abnormalities and *TET2* mutations with normal cytogenetics. Correlation and exclusion in the pattern of mutations indicate a functional genomic architecture. Analysis of deep sequencing results in patients whose MDS evolved to AML has shown clonal succession, with founder clones acquiring additional mutations to produce clonal dominance. Furthermore, the prevalence of abnormal cells by morphology underestimates bone marrow involvement by MDS clones, as cells normal in appearance are derived from the abnormal clones. Both presenting and evolving hematologic manifestations result from the accumulation of multiple genetic lesions: loss of tumor-suppressor genes, activating oncogene, epigenetic pathways that affect mRNA processing and methylation status, or other harmful alterations. Pathophysiology has been linked to mutations and chromosome abnormalities in some specific MDS syndromes. The 5q– deletion leads to heterozygous loss of a ribosomal protein gene (ribosomal protein gene mutations cause Diamond-Blackfan anemia, like much MDS characterized by deficient erythropoiesis). An immune pathophysiology may underlie trisomy 8 MDS; selected younger MDS patients can respond to immunosuppressive therapy as administered for aplastic anemia. However, in general for MDS, the role of the immune system and its cells and cytokines; the role of the hematopoietic stem cell niche, the microenvironment, and cell–cell interactions; the fate of normal cells in the Darwinian competitive environment of the dysplastic marrow; and how mutant cells produce marrow failure in MDS are still not completely understood.

CLINICAL FEATURES

Anemia dominates the early course. Most symptomatic patients complain of the gradual onset of fatigue and weakness, dyspnea, and pallor, but at least one-half of patients are asymptomatic, and their MDS is discovered only incidentally on routine blood counts. Previous chemotherapy or radiation exposure is an important historic fact. Fever and weight loss should point to a myeloproliferative rather than myelodysplastic process. MDS in childhood is rare and, when diagnosed, implicates an underlying genetic disease. Children with Down syndrome are susceptible to MDS as well as leukemia. A family history may indicate a hereditary form of sideroblastic anemia, Fanconi anemia, or a telomeropathy. Inherited *GATA2* mutations, as in the MonoMAC syndrome (with increased susceptibility to viral, mycobacteria, and fungal infections, as well as deficient numbers of monocytes, natural killer cells, and B lymphocytes), also can cause MDS in young patients.

The physical examination is remarkable for signs of anemia; approximately 20% of patients have splenomegaly. Some unusual skin lesions, including Sweet's syndrome (febrile neutrophilic dermatosis), occur with MDS. Accompanying autoimmune syndromes are not infrequent. In the younger patient, stereotypical anomalies point to a constitutional syndrome (short stature, abnormal thumbs in Fanconi anemia; early graying in the telomeropathies; cutaneous warts in *GATA2* deficiency).

LABORATORY STUDIES

Blood Anemia is present in most cases, either alone or as part of bi- or pancytopenia; isolated neutropenia or thrombocytopenia is more unusual. Macrocytosis is common, as in most marrow failure disease. Platelets also are large and lack granules. In functional studies, they may show marked abnormalities, and patients may have bleeding symptoms despite seemingly adequate numbers. Neutrophils are hypogranulated; have hyposegmented, ringed, or abnormally segmented nuclei; contain Döhle bodies; and may be functionally deficient. Circulating myeloblasts usually correlate with marrow blast numbers, and their quantity is important for classification and prognosis. The total white blood cell count (WBC) is usually normal or low, except in chronic myelomonocytic leukemia. As in aplastic anemia, MDS can be associated with a clonal population of PNH cells. Genetic testing is commercially available for constitutional syndromes.

Bone Marrow The bone marrow is usually normal or hypercellular, but in about 20% of cases it is sufficiently hypocellular to lead to confusion with aplastic anemia. No single characteristic feature of marrow morphology distinguishes MDS, but the following are commonly observed: dyserythropoietic changes (especially nuclear abnormalities) and ringed sideroblasts in the erythroid lineage; hypogranulation and hyposegmentation in granulocytic precursors, with an increase in myeloblasts; and megakaryocytes showing reduced numbers of or disorganized nuclei. Megaloblastic nuclei and defective hemoglobinization in the erythroid lineage are common. Prognosis strongly correlates with the proportion of marrow blasts. Cytogenetic analysis and fluorescent in situ hybridization can identify chromosomal abnormalities.

DIFFERENTIAL DIAGNOSIS

Deficiencies of vitamin B_{12} or folate should be excluded by appropriate blood tests; vitamin B_6 deficiency can be assessed by a therapeutic trial of pyridoxine if the bone marrow shows ringed sideroblasts. Copper deficiency can lead to cytopenias and dysplastic marrows of varying

TABLE 98-6 International Prognostic Scoring System (IPSS)

1. New marrow blast categories
   ≤2%, >2%–<5%, 5–10%, >10–30%
2. Refined cytogenetic abnormalities and risk groups
   16 (vs 6) specific abnormalities, 5 (vs 3) subgroups[a]
3. Evaluation of depth of cytopenias[b]
   Clinically and statistically relevant cutpoints used
4. Inclusion of differentiating features
   Age, performance status, serum ferritin, LDH; β_2-microglobulin
5. Prognostic model with 5 (vs 4) risk categories
   Improved predictive power

[a]Good, normal, –Y, del(5q), del (20q); poor, complex (≥3 abnormalities) or chromosome 7 abnormalities; intermediate, all other abnormalities. [b]Cytopenias defined as hemoglobin <100 g/L, platelet count <100,000/μL, and absolute neutrophil count <1500/μL.

Abbreviation: LDH, lactate dehydrogenase.

cellularity. Marrow dysplasia can be observed in acute viral infections, drug reactions, or chemical toxicity but should be transient. More difficult are the distinctions between hypocellular MDS and aplasia or between RA with excess blasts and early acute leukemia. The WHO considers 20% blasts in the marrow as the criterion that separates AML from MDS. In young patients, underlying, predisposing genetic diseases should be considered and appropriate genomic testing performed (see above).

PROGNOSIS

The median survival varies greatly from years for patients with 5q– or sideroblastic anemia to a few months in RA with excess blasts or severe pancytopenia associated with monosomy 7. The International Prognostic Scoring System, revised in 2012 (IPSS; **Table 98-6**) assists in making predictions. Even "low-risk" MDS has significant morbidity and mortality. More refined (and also more complicated) prognostic scoring systems can separate out Int-1 risk patients who have relatively poor prognoses. Prognostic systems have been developed based on survival from diagnosis, but prognosis changes over time, and hazards ratios for survival and leukemic transformation converge over time among risk categories, consistent with dynamic changes in clonal architecture.

Most patients die as a result of complications of pancytopenia and not due to leukemic transformation; perhaps one-third succumb to diseases unrelated to their MDS. Precipitous worsening of pancytopenia, acquisition of new chromosomal abnormalities on serial cytogenetic determination, increase in the number of blasts, and marrow fibrosis are all poor prognostic indicators. The outlook in therapy-related MDS, regardless of type, is extremely poor, and most patients will progress within a few months to refractory AML.

TREATMENT

Myelodysplasia

Historically, therapy of MDS has been unsatisfactory, but several drugs may not only improve blood counts but delay onset of leukemia and improve survival. The choice of therapy for an individual patient, administration of treatment, and management of toxicities are complicated and require hematologic expertise.

Only hematopoietic stem cell transplantation offers cure of MDS. The survival rate in selected patient cohorts is ~50% at 3 years but improving. Results using unrelated matched donors are now similar to those with siblings, and patients in their fifties and sixties have been successfully transplanted. Nevertheless, treatment-related mortality and morbidity increase with recipient age. The transplant conundrum is that the high-risk patient (by IPSS score and presence of monosomal karyotype), for whom the procedure is most obviously indicated, has a high probability of a poor outcome from transplant-related mortality or disease relapse, whereas the low-risk patient, who is more likely to tolerate transplant, also may do well for years with less aggressive therapies. In practice, only a small proportion of MDS patients undergo transplantation.

MDS has been regarded as particularly refractory to cytotoxic chemotherapy regimens, and as in AML in the older adult, drug toxicity is frequent and often fatal, and remissions if achieved are brief. Low doses of cytotoxic drugs have been administered for their "differentiation" potential, and from this experience, drug therapies have emerged based on pyrimidine analogues. These drugs are classified as epigenetic modulators, believed to act through a demethylating mechanism to alter gene regulation and allow differentiation to mature blood cells from the abnormal MDS stem cell. The hypomethylating agents azacitidine and decitabine are frequently used in bone marrow failure clinics. Azacitidine improves blood counts and survival in MDS, compared to best supportive care. Azacitidine is usually administered subcutaneously, daily for 7 days, at 4-week intervals, for at least four cycles before assessing for response. Overall, generally improved blood counts with a decrease in transfusion requirements occurred in ~50% of patients in published trials. Response is dependent on continued drug administration, and most patients eventually become refractory to drug intervention and experience recurrent cytopenias or progression to AML. Decitabine is closely related to azacitidine and more potent; 30–50% of patients show responses in blood counts, with a duration of response of almost a year. Decitabine is usually administered by continuous intravenous infusion in regimens of varying doses and durations of 3–10 days in repeating cycles. The major toxicity of azacitidine and decitabine is myelosuppression, leading to worsening blood counts. Hypomethylating agents are frequently used in the high-risk patient who is not a candidate for stem cell transplant. In the lower risk patient, they are also effective, but alternative therapies should be considered.

Lenalidomide, a thalidomide derivative with a more favorable toxicity profile, is particularly effective in reversing anemia in MDS patients with 5q– syndrome; not only do a high proportion of these patients become transfusion independent with normal or near-normal hemoglobin levels, but their cytogenetics also become normal. The drug has many biologic activities, and it is unclear which is critical for clinical efficacy. Lenalidomide is administered orally. Most patients will improve within 3 months of initiating therapy. Toxicities include myelosuppression (worsening thrombocytopenia and neutropenia, necessitating blood count monitoring) and an increased risk of deep vein thrombosis and pulmonary embolism.

Immunosuppression also may produce sustained independence from transfusion and improve survival. ATG, cyclosporine, and the anti-CD52 monoclonal antibody alemtuzumab are especially effective in younger MDS patients (<60 years old) with more favorable IPSS scores and who bear the histocompatibility antigen HLA-DR15.

HGFs can improve blood counts but, as in most other marrow failure states, have been most beneficial to patients with the least severe pancytopenia. EPO alone or in combination with G-CSF can improve hemoglobin levels, particularly in those with low serum EPO levels who have no or a modest need for transfusions. Survival may be enhanced by EPO and amelioration of anemia. G-CSF treatment alone failed to improve survival in a controlled trial. Thrombopoietin mimetics appear to improve platelet counts in some MDS patients, with no clear evidence that they increase the rate of leukemic transformation.

The same principles of supportive care described for aplastic anemia apply to MDS. Many patients will be anemic for years. RBC transfusion support should be accompanied by iron chelation to prevent secondary hemochromatosis.

MYELOPHTHISIC ANEMIAS

Fibrosis of the bone marrow **(see Fig. 96-2)**, usually accompanied by a characteristic blood smear picture called *leukoerythroblastosis*, can occur as a primary hematologic disease, called *myelofibrosis* or *myeloid*

metaplasia **(Chap. 99)**, and as a secondary process, called *myelophthisis*. Myelophthisis, or secondary myelofibrosis, is reactive. Fibrosis can be a response to invading tumor cells, usually an epithelial cancer of breast, lung, or prostate origin or neuroblastoma. Marrow fibrosis may occur with infection of mycobacteria (both *Mycobacterium tuberculosis* and *Mycobacterium avium*), fungi, or HIV and in sarcoidosis. Intracellular lipid deposition in Gaucher disease and obliteration of the marrow space related to absence of osteoclast remodeling in congenital osteopetrosis also can produce fibrosis. Secondary myelofibrosis is a late consequence of radiation therapy or treatment with radiomimetic drugs. Usually the infectious or malignant underlying processes are obvious. Marrow fibrosis can also be a feature of a variety of hematologic syndromes, especially chronic myeloid leukemia, multiple myeloma, lymphomas, myeloma, and hairy cell leukemia.

The pathophysiology has three distinct features: proliferation of fibroblasts in the marrow space (myelofibrosis); the extension of hematopoiesis into the long bones and into extramedullary sites, usually the spleen, liver, and lymph nodes (myeloid metaplasia); and ineffective erythropoiesis. The etiology of the fibrosis is unknown but most likely involves dysregulated production of growth factors: platelet-derived growth factor and transforming growth factor β have been implicated. Abnormal regulation of other hematopoietins would lead to localization of blood-producing cells in nonhematopoietic tissues and uncoupling of the usually balanced processes of stem cell proliferation and differentiation. Myelofibrosis is remarkable for pancytopenia despite very large numbers of circulating hematopoietic progenitor cells.

Anemia is dominant in secondary myelofibrosis, usually normocytic and normochromic. The diagnosis is suggested by the characteristic leukoerythroblastic smear **(see Fig. 96-1)**. Erythrocyte morphology is highly abnormal, with circulating nucleated RBCs, teardrops, and shape distortions. WBC numbers are often elevated, sometimes mimicking a leukemoid reaction, with circulating myelocytes, promyelocytes, and myeloblasts. Platelets may be abundant and are often of giant size. Inability to aspirate the bone marrow, the characteristic "dry tap," can allow a presumptive diagnosis in the appropriate setting before the biopsy is decalcified.

The course of secondary myelofibrosis is determined by its etiology, usually a metastatic tumor or an advanced hematologic malignancy. Treatable causes must be excluded, especially tuberculosis and fungus. Transfusion support can relieve symptoms.

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99 Polycythemia Vera and Other Myeloproliferative Neoplasms

Jerry L. Spivak

The World Health Organization (WHO) classification of the chronic myeloproliferative neoplasms (MPNs) includes eight disorders, some of which are rare or poorly characterized **(Table 99-1)** but all of which share an origin in a hematopoietic cell; overproduction of one or more of the formed elements of the blood without significant dysplasia; and a predilection to extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia. Within this broad classification, however, significant phenotypic heterogeneity exists. Some diseases such as chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), and chronic eosinophilic leukemia (CEL) express primarily a myeloid phenotype, whereas in other diseases, such as polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocytosis (ET), erythroid or megakaryocytic hyperplasia predominates. The latter three disorders, in contrast to the former three, also appear capable of transforming into each other.

Such phenotypic heterogeneity has a genetic basis; CML is the consequence of the balanced translocation between chromosomes 9 and 22 (t[9;22][q34;11]); CNL has been associated with a t(15;19) translocation; and CEL occurs with a deletion or balanced translocations involving the *PDGFRα* gene. By contrast, PV, PMF, and ET are characterized by driver mutations that directly or indirectly constitutively activate JAK2, a tyrosine kinase essential for the function of the erythropoietin and thrombopoietin receptors and also utilized by the granulocyte colony-stimulating factor receptor. This important distinction is reflected in the natural histories of CML, CNL, and CEL, which are usually measured in years, with a high rate of leukemic transformation. The natural histories of PV, PMF, and ET, by contrast, are usually measured in decades, and transformation to acute leukemia is uncommon in the absence of chemotherapy. This chapter focuses only on PV, PMF, and ET because their clinical features and driver mutation overlap are substantial, though their disease duration varies.

The other chronic MPNs will be discussed in Chaps. 101 and 106.

POLYCYTHEMIA VERA

PV is a clonal hematopoietic stem cell disorder in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus. The most common of the MPN, PV occurs in 2.5 per 100,000 persons, sparing no adult age group and increasing with age to rates over 10/100,000. Familial transmission is infrequent, and women predominate among sporadic cases.

ETIOLOGY

Nonrandom chromosome abnormalities such as deletion 20q and deletion 13q or trisomy 9 occur in up to 30% of untreated PV patients, but unlike CML, no consistent cytogenetic abnormality

TABLE 99-1 World Health Organization Classification of Chronic Myeloproliferative Neoplasms

Chronic myeloid leukemia, bcr-abl–positive
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia, not otherwise specified
Polycythemia vera
Primary myelofibrosis
Essential thrombocytosis
Mastocytosis
Myeloproliferative neoplasms, unclassifiable

has been associated with the disorder. However, a mutation in the autoinhibitory pseudokinase domain of the tyrosine kinase JAK2 that replaces valine with phenylalanine (V617F), causing constitutive kinase activation—appears to have a central role in PV pathogenesis.

JAK2 is a member of an evolutionarily well-conserved, nonreceptor tyrosine kinase family and serves as the cognate tyrosine kinase for the erythropoietin and thrombopoietin receptors. It also functions as an obligate chaperone for these receptors in the Golgi apparatus and is responsible for their cell-surface expression. The conformational change induced in the erythropoietin and thrombopoietin receptors following binding to their respective cognate ligands, erythropoietin or thrombopoietin, leads to JAK2 autophosphorylation, receptor phosphorylation, and phosphorylation of proteins involved in cell proliferation, differentiation, and resistance to apoptosis. Transgenic animals lacking *JAK2* die as embryos from severe anemia. Constitutive activation of JAK2, on the other hand, explains the erythropoietin hypersensitivity, erythropoietin-independent erythroid colony formation, rapid terminal differentiation, increased Bcl-X_L expression, and apoptosis resistance in the absence of erythropoietin that characterize the in vitro behavior of PV erythroid progenitor cells.

More than 95% of PV patients express this mutation, as do ~50% of PMF and ET patients. Importantly, the *JAK2* gene is located on the short arm of chromosome 9, and loss of heterozygosity on chromosome 9p involving the segment containing the *JAK2* locus over time due to mitotic recombination (uniparental disomy), is the most common cytogenetic abnormality in PV. Loss of heterozygosity in this region leads to homozygosity for *JAK2* V617F and occurs in ~60% of PV patients and to a lesser extent in PMF but is rare in ET. Most PV patients who do not express *JAK2* V617F express a mutation in exon 12 of the gene and are not clinically different from those who do, with the exception of a higher frequency of isolated erythrocytosis, nor do *JAK2* V617F heterozygotes differ clinically from homozygotes. Importantly, the predisposition to acquire *JAK2* mutations appears to be associated with a specific *JAK2* gene haplotype, GGCC. *JAK2* V617F is the basis for many of the phenotypic and biochemical characteristics of PV such as increased blood cell production and increased inflammatory cytokine production; however, it cannot solely account for the entire PV phenotype and is probably not the initiating lesion in any of the MPN. First, PV patients with the same phenotype and documented clonal disease can have mutations in *LNK*, a JAK2 inhibitor, or rarely, calreticulin (*CALR*), an ER chaperone. Second, ET and PMF patients have the same mutation but different clinical phenotypes. Third, familial PV can occur without the mutation, even when other members of the same family express it. Fourth, not all the cells of the malignant clone express *JAK2* V617F. Fifth, inhibition of *JAK2* V617F-expressing hematopoietic progenitor cells by the nonspecific JAK1/2 kinase inhibitor, ruxolitinib, does not affect the behavior of the involved hematopoietic stem cells. Finally, in some *JAK2* V617F–positive PV or ET patients, acute leukemia can occur in a *JAK2* V617F–negative progenitor cell, suggesting the presence of an ancestral precursor cell.

CLINICAL FEATURES

Isolated thrombocytosis, leukocytosis, or splenomegaly may be the initial presenting manifestation of PV, but most often the disorder is first recognized by the incidental discovery of a high hemoglobin, hematocrit, or red cell count. With the exception of aquagenic pruritus, no symptoms distinguish PV from other causes of erythrocytosis.

Uncontrolled erythrocytosis causes hyperviscosity, leading to neurologic symptoms such as vertigo, tinnitus, headache, visual disturbances, and transient ischemic attacks (TIA). Systolic hypertension is also a feature of the red cell mass elevation. In some patients, venous or arterial thrombosis may be the presenting manifestation of PV. Any vessel can be affected; but cerebral, cardiac, and mesenteric vessels are most commonly involved. Hepatic venous thrombosis (Budd-Chiari syndrome) is particularly common in young women and may be catastrophic if sudden and complete obstruction of the hepatic vein occurs. Indeed, PV should be suspected in any patient who develops hepatic vein thrombosis. Digital ischemia, easy bruising, epistaxis, acid-peptic disease, or gastrointestinal hemorrhage may occur due to vascular stasis or thrombocytosis. In the latter instance, absorption and proteolysis of high molecular weight von Willebrand multimers by the large platelet mass causes acquired von Willebrand disease. Erythema, burning, and pain in the extremities, a symptom complex known as erythromelalgia, is another complication of thrombocytosis in PV due to increased platelet stickiness. Given the large turnover of hematopoietic cells, hyperuricemia with secondary gout, uric acid stones, and symptoms due to hypermetabolism can also complicate the disorder.

DIAGNOSIS

When PV presents with erythrocytosis in combination with leukocytosis, thrombocytosis, or splenomegaly or any combination of these, the diagnosis is apparent. However, when patients present with an elevated hemoglobin, hematocrit, or red cell count alone, the diagnostic evaluation is more complex because of the many diagnostic possibilities **(Table 99-2)**. Furthermore, unless the hemoglobin level is ≥20 g/dL (hematocrit ≥60%), it is not possible to distinguish true erythrocytosis from disorders causing plasma volume contraction. This is because uniquely in PV, in contrast to other causes of true erythrocytosis, there is expansion of the plasma volume, which can mask the elevated red cell mass, particularly in women; thus, red cell mass and plasma volume determinations are necessary to establish the presence of an absolute erythrocytosis and distinguish this from relative erythrocytosis due to a reduction in plasma volume alone (also known as *stress* or *spurious erythrocytosis* or *Gaisböck's syndrome*). **Figure 59-18** illustrates a diagnostic algorithm for the evaluation of suspected erythrocytosis. Assay for *JAK2* mutations in the presence of a normal arterial oxygen saturation provides an alternative diagnostic approach to erythrocytosis when red cell mass and plasma volume determinations are not available; a normal serum erythropoietin level does not exclude the presence of PV, but an elevated erythropoietin level is more consistent with a secondary cause for the erythrocytosis.

Other laboratory studies that may aid in diagnosis include the red cell count, mean corpuscular volume, and red cell distribution width (RDW), particularly when the hematocrit or hemoglobin levels are less than 60% or 20 g/dL, respectively. Only three situations cause microcytic erythrocytosis: β-thalassemia trait, hypoxic erythrocytosis, and PV. With β-thalassemia trait, the RDW is usually normal, whereas with hypoxic erythrocytosis and PV, the RDW may be elevated due to associated iron deficiency. Today, however, the assay for *JAK2* V617F has

TABLE 99-2 Causes of Erythrocytosis

Relative Erythrocytosis	
Hemoconcentration secondary to dehydration, diuretics, ethanol abuse, androgens, or tobacco abuse	
Absolute Erythrocytosis	
Hypoxia	**Tumors**
Carbon monoxide intoxication	Hypernephroma
High-oxygen-affinity hemoglobins	Hepatoma
High altitude	Cerebellar hemangioblastoma
Pulmonary disease	Uterine myoma
Right-to-left cardiac or vascular shunts	Adrenal tumors
Sleep apnea syndrome	Meningioma
Hepatopulmonary syndrome	Pheochromocytoma
Renal Disease	**Drugs**
Renal artery stenosis	Androgens
Focal sclerosing or membranous glomerulonephritis	Recombinant erythropoietin
Postrenal transplantation	**Familial (with normal hemoglobin function)**
Renal cysts	Erythropoietin receptor mutations
Bartter's syndrome	*VHL* mutations (Chuvash polycythemia)
	2,3-BPG mutation
	PHD2 and HIF2α mutations
	Polycythemia vera

Abbreviations: 2,3-BPG, 2,3-bisphosphoglycerate; VHL, von Hippel-Lindau.

superseded other tests for establishing the diagnosis of PV. Of course, in patients with associated acid-peptic disease, occult gastrointestinal bleeding may lead to a presentation with hypochromic, microcytic anemia, masking the presence of PV.

A bone marrow aspirate and biopsy provide no specific diagnostic information because these may be normal or indistinguishable from ET or PMF. Similarly, no specific cytogenetic abnormality is associated with the disease, and the absence of a cytogenetic marker does not exclude the diagnosis.

COMPLICATIONS

Many of the clinical complications of PV relate directly to the increase in blood viscosity associated with red cell mass elevation and indirectly to the increased turnover of red cells, leukocytes, and platelets with the attendant increase in uric acid and inflammatory cytokine production. The latter appears to be responsible for constitutional symptoms. Peptic ulcer disease can also be due to *Helicobacter pylori* infection, the incidence of which is increased in PV, while the pruritus associated with this disorder may be a consequence of mast cell activation by JAK2 V617F. A sudden increase in spleen size can be associated with painful splenic infarction. Myelofibrosis appears to be part of the natural history of the disease but is a reactive, reversible process that does not itself impede hematopoiesis and by itself has no prognostic significance. In ~15% of patients, however, myelofibrosis is associated with hematopoietic stem cell failure, manifested by substantial extramedullary hematopoiesis in the liver and spleen and transfusion-dependent anemia. The organomegaly can cause significant mechanical discomfort, portal hypertension, and progressive cachexia. Although the incidence of acute myeloid leukemia is increased in PV, the incidence of acute leukemia in patients not exposed to chemotherapy or radiation therapy is low. Interestingly, chemotherapy, including hydroxyurea, has been associated with acute leukemia in *JAK2* V617F–negative stem cells in some PV patients. *Erythromelalgia* is a curious syndrome of unknown etiology associated with thrombocytosis, primarily involving the lower extremities and usually manifested by erythema, warmth, and pain of the affected appendage and occasionally digital infarction. It occurs with a variable frequency and is usually responsive to salicylates. Some of the central nervous system symptoms observed in patients with PV, such as ocular migraine, appear to represent a variant of erythromelalgia.

Left uncontrolled, erythrocytosis can lead to thrombosis involving vital organs such as the liver, heart, brain, or lungs. Patients with massive splenomegaly are particularly prone to thrombotic events because the associated increase in plasma volume masks the true extent of the red cell mass elevation measured by the hematocrit or hemoglobin level. A "normal" hematocrit or hemoglobin level in a PV patient with massive splenomegaly should be considered indicative of an elevated red cell mass until proven otherwise.

TREATMENT

Polycythemia Vera

PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo. Thrombosis due to erythrocytosis is the most significant complication and often the presenting manifestation; maintenance of the hemoglobin level at ≤140 g/L (14 g/dL; hematocrit <45%) in men and ≤120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications. Phlebotomy serves initially to reduce hyperviscosity by reducing the red cell mass to normal while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and induce a state of iron deficiency that prevents accelerated reexpansion of the red cell mass. In most PV patients, once an iron-deficient state is achieved, phlebotomy is usually only required at 3-month intervals. Neither phlebotomy nor iron deficiency increases the platelet count relative to the effect of the disease itself, and neither thrombocytosis nor leukocytosis are correlated with thrombosis in PV, in contrast to the strong correlation between erythrocytosis and thrombosis. The use of salicylates to prevent thrombosis in PV patients is not only potentially harmful if the red cell mass is not controlled by phlebotomy, but is also an unproven remedy. Anticoagulants are indicated when a thrombosis has occurred and can be difficult to monitor if the red cell mass is substantially elevated owing to the artifactual imbalance between the test tube anticoagulant and plasma that occurs when blood from these patients is assayed for prothrombin or partial thromboplastin activity. Asymptomatic hyperuricemia (<10 mg/dL) requires no therapy, but allopurinol should be administered to avoid further elevation of the uric acid when chemotherapy is used to reduce splenomegaly or leukocytosis or to treat pruritus. Generalized pruritus intractable to antihistamines or antidepressants such as doxepin can be a major problem in PV; the JAK1/2 inhibitor, ruxolitinib, pegylated interferon α (IFN-α), psoralens with ultraviolet light in the A range (PUVA) therapy, and hydroxyurea are other methods of palliation. Asymptomatic thrombocytosis requires no therapy unless the platelet count is sufficiently high to cause bleeding due to acquired von Willebrand's disease, but bleeding in this situation is not usually spontaneous and is responsive to ε-aminocaproic acid. Symptomatic splenomegaly can be treated with either ruxolitinib or pegylated IFN-α. Pegylated IFN-α has the advantage over recombinant IFN-α of being better tolerated and requiring only weekly administration and produced complete hematologic and molecular remissions in ~20% of PV patients; its role in this disorder is currently under investigation. Anagrelide, a phosphodiesterase inhibitor, can reduce the platelet count and, if tolerated, is preferable to hydroxyurea because it lacks marrow toxicity and is also protective against venous thrombosis while hydroxyurea is not. A reduction in platelet number may be necessary for the treatment of erythromelalgia or ocular migraine if salicylates are not effective or if the platelet count is sufficiently high to increase the risk of hemorrhage, but only to the degree that symptoms are alleviated. Alkylating agents and radioactive sodium phosphate (^{32}P) are leukemogenic in PV, and their use should be avoided. If a cytotoxic agent must be used, hydroxyurea is preferred, but this drug does not prevent either thrombosis or myelofibrosis in PV, is itself leukemogenic, and should be used for as short a time as possible. Previously, PV patients with massive splenomegaly unresponsive to reduction by chemotherapy or interferon required splenectomy. However, with the introduction of the nonspecific JAK2 inhibitor ruxolitinib, it has been possible in the majority of patients with PV complicated by myelofibrosis and myeloid metaplasia to reduce spleen size while at the same time alleviating constitutional symptoms and pruritus due to cytokine release and reducing the phlebotomy requirement. Ruxolitinib has also been demonstrated in a phase three clinical trial to be effective in PV patients without myelofibrosis who are intolerant or refractory to hydroxyurea or best available supportive therapy. In some patients with end-stage disease, pulmonary hypertension may develop due to fibrosis or extramedullary hematopoiesis. A role for bone marrow transplantation, either allogeneic or haploidentical, in PV has not been defined.

Most patients with PV can live long lives without functional impairment when their red cell mass is effectively managed with phlebotomy alone. Chemotherapy is never indicated to control the red cell mass unless venous access is inadequate.

PRIMARY MYELOFIBROSIS

Chronic PMF (other designations include *idiopathic myelofibrosis*, *agnogenic myeloid metaplasia*, or *myelofibrosis with myeloid metaplasia*) is a clonal hematopoietic stem cell disorder associated with mutations in *JAK2*, *MPL* or *CALR* and characterized by marrow fibrosis, extramedullary hematopoiesis, and splenomegaly. PMF is the least common MPN, and establishing its diagnosis in the absence of a specific clonal marker is difficult because myelofibrosis and splenomegaly are also features of both PV and CML. Furthermore, myelofibrosis and splenomegaly also occur in a variety of benign and malignant disorders **(Table 99-3)**, many of which are amenable to specific therapies not effective in PMF. In contrast to the other MPN and so-called acute or malignant

TABLE 99-3 Disorders Causing Myelofibrosis

MALIGNANT	NONMALIGNANT
Acute leukemia (lymphocytic, myelogenous, megakaryocytic)	HIV infection
Chronic myeloid leukemia	Hyperparathyroidism
Hairy cell leukemia	Renal osteodystrophy
Hodgkin's disease	Systemic lupus erythematosus
Primary myelofibrosis	Tuberculosis
Lymphoma	Vitamin D deficiency
Multiple myeloma	Thorium dioxide exposure
Myelodysplasia	Gray platelet syndrome
Metastatic carcinoma	
Polycythemia vera	
Systemic mastocytosis	

myelofibrosis, which can occur at any age, PMF primarily afflicts men in their sixth decade or later.

ETIOLOGY

Nonrandom chromosome abnormalities such as 9p, 20q−, 13q−, trisomy 8 or 9, or partial trisomy 1q are common in PMF, but no cytogenetic abnormality specific to the disease has been identified. *JAK2* V617F is present in ~50% of PMF patients, and mutations in the thrombopoietin receptor, *MPL*, occur in about 8%. Most of the rest have mutations in the calreticulin gene (*CALR*) that alter the carboxy-terminal portion of the protein, permitting it to bind and activate MPL. The degree of myelofibrosis and the extent of extramedullary hematopoiesis are not related. Fibrosis in this disorder is associated with overproduction of transforming growth factor β and tissue inhibitors of metalloproteinases, while osteosclerosis is associated with overproduction of osteoprotegerin, an osteoclast inhibitor. Marrow angiogenesis occurs due to increased production of vascular endothelial growth factor. Importantly, fibroblasts in PMF are polyclonal and not part of the neoplastic clone but can be induced by it to produce inflammatory cytokines.

CLINICAL FEATURES

No signs or symptoms are specific for PMF. Many patients are asymptomatic at presentation, and the disease is usually detected by the discovery of splenic enlargement and/or abnormal blood counts during a routine examination. In contrast to its companion MPN, night sweats, fatigue, and weight loss are common presenting complaints. A blood smear will show the characteristic features of extramedullary hematopoiesis: teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes; myeloblasts may also be present **(Fig. 99-1)**.

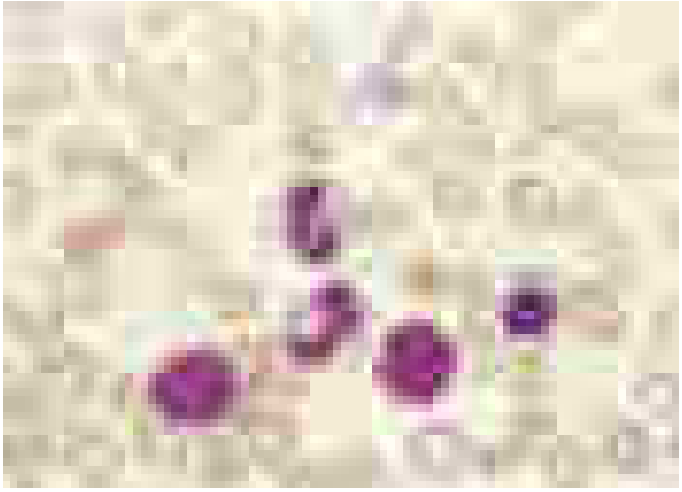

FIGURE 99-1 Teardrop-shaped red blood cells indicative of membrane damage from passage through the spleen, a nucleated red blood cell, and immature myeloid cells indicative of extramedullary hematopoiesis are noted. This peripheral blood smear is related to any cause of extramedullary hematopoiesis.

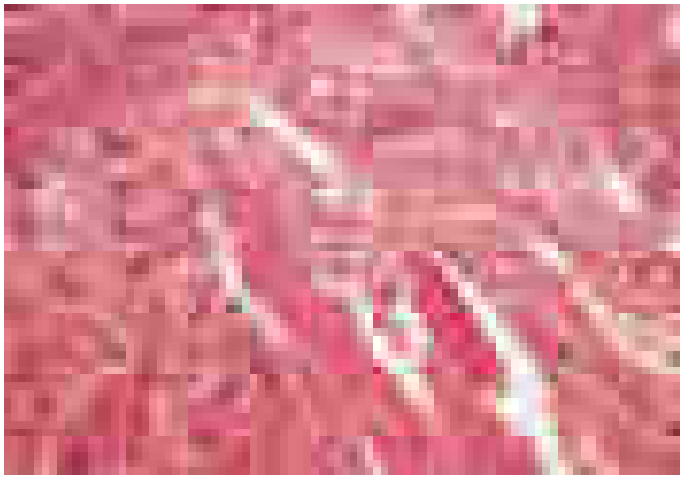

FIGURE 99-2 This marrow section shows the marrow cavity replaced by fibrous tissue composed of reticulin fibers and collagen. When this fibrosis is due to a primary hematologic process, it is called *myelofibrosis*. When the fibrosis is secondary to a tumor or a granulomatous process, it is called *myelophthisis*.

Anemia, usually mild initially, is common, whereas the leukocyte and platelet counts are either normal or increased, but either can be depressed. Mild hepatomegaly may accompany the splenomegaly but is unusual in its absence; isolated lymphadenopathy should suggest another diagnosis. Both serum lactate dehydrogenase and alkaline phosphatase levels can be elevated. Marrow is usually inaspirable due to the myelofibrosis **(Fig. 99-2)**, and bone x-rays may reveal osteosclerosis. Exuberant extramedullary hematopoiesis can cause ascites; portal, pulmonary, or intracranial hypertension; intestinal or ureteral obstruction; pericardial tamponade; spinal cord compression; or skin nodules. Splenic enlargement can be sufficiently rapid to cause splenic infarction with fever and pleuritic chest pain. Hyperuricemia and secondary gout may ensue.

DIAGNOSIS

While the clinical picture described above is characteristic of PMF, all of these clinical features can be observed in PV or CML. Massive splenomegaly commonly masks erythrocytosis in PV, and reports of intraabdominal thrombosis in PMF most likely represent instances of unrecognized PV. In some PMF patients, erythrocytosis has developed during the course of the disease. Furthermore, because many other disorders have features that overlap with PMF but respond to distinctly different therapies, the diagnosis of PMF is one of exclusion, which requires that the disorders listed in Table 99-3 be ruled out.

The presence of teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes establishes the presence of extramedullary hematopoiesis, while the presence of leukocytosis, thrombocytosis with large and bizarre platelets, and circulating myelocytes suggests the presence of an MPN as opposed to a secondary form of myelofibrosis (Table 99-3). Marrow is usually inaspirable due to increased marrow reticulin, but marrow biopsy will reveal a hypercellular marrow with trilineage hyperplasia and, in particular, increased numbers of megakaryocytes in clusters and with large, dysplastic nuclei. However, there are no characteristic bone marrow morphologic abnormalities that distinguish PMF from the other MPN. Splenomegaly due to extramedullary hematopoiesis may be sufficiently massive to cause portal hypertension and variceal formation. In some patients, exuberant extramedullary hematopoiesis can dominate the clinical picture. An intriguing feature of PMF is the occurrence of autoimmune abnormalities such as immune complexes, antinuclear antibodies, rheumatoid factor, or a positive Coombs' test. Whether these represent a host reaction to the disorder or are involved in its pathogenesis is unknown. Cytogenetic analysis of the blood is useful both to exclude CML and for prognostic purposes because the development of complex karyotype abnormalities portends a poor prognosis in PMF. For unknown reasons, the number of circulating CD34+ cells is markedly

TABLE 99-4 Three Current Scoring Systems for Estimating Prognosis in PMF Patients

RISK FACTOR	IPSS (2009)[a]	DIPSS (2010)[b]	DIPSS PLUS (2011)[c]
Anemia (<10 g/dL)	X	X	X
Leukocytosis (>25,000/μL)	X	X	X
Peripheral blood blasts (≥1%)	X	X	X
Constitutional symptoms	X	X	X
Age (>65 years)	X	X	X
Unfavorable karyotype			X
Platelet count (<100,000/μL)			X
Transfusion dependence			X

[a]Blood 113:2895, 2009. [b]Blood 115:1703, 2010. [c]J Clin Oncol 29:392, 2011.

Note: The Dynamic International Prognostic Scoring System (DIPSS) was developed to determine if the International Prognostic Scoring System (IPSS) risk factors identified as important for survival at the time of primary myelofibrosis (PMF) diagnosis could also be used for risk stratification following their acquisition during the course of the disease. One point is assigned to each risk factor for IPSS scoring. For DIPSS, the same is true, but anemia is assigned 2 points. The DIPSS Plus scoring system represents recognition that the addition of unfavorable karyotype, thrombocytopenia, and transfusion dependence improved the DIPSS risk stratification system for which additional points are assigned (Table 99-5). More recent studies suggest that mutational analysis of the *ASXL1, EZH2, SRSF2*, and *IDH1/2* genes further improves risk stratification for survival and leukemic transformation (Leukemia 27:1861, 2013). These prognostic scoring systems are not accurate for risk assessment in PV or ET patients who have developed myelofibrosis (Haematologica 99:e55, 2014).

increased in PMF (>15,000/μL) compared to the other MPN, unless they too develop extramedullary hematopoiesis.

Importantly, ~50% of PMF patients, like patients with its companion MPN, express the *JAK2* V617F mutation, often as homozygotes. Such patients are usually older and have higher hematocrits than patients with *MPL* (8%) or *CALR* (30%) mutations; PMF patients expressing an *MPL* mutation tend to be more anemic and have lower leukocyte counts than *JAK2* V617F-positive patients. Somatic mutations (due to deletions [type 1] or insertions [type 2]) in exon 9 of *CALR* have been found in a majority of patients with PMF who lack mutations in either *JAK2* or *MPL*. In some studies, type 1 mutations, the most common CALR mutation in PMF, had a survival advantage compared to *JAK2* or *MPL* mutations but not with respect to leukemic transformation. PMF patients who lack a known driver mutation have the worst prognosis.

COMPLICATIONS

Survival in PMF varies according to specific risk factors at diagnosis **(Tables 99-4 and 99-5)** but is shorter than in PV and ET patients. The natural history of PMF is one of increasing marrow failure with transfusion-dependent anemia and increasing organomegaly due to extramedullary hematopoiesis. As with CML, PMF can evolve from a chronic to an accelerated phase with constitutional symptoms and increasing marrow failure. About 10% of patients spontaneously transform to an aggressive form of acute leukemia for which therapy is usually ineffective. Additional important prognostic factors for disease acceleration during the course of PMF include the presence of complex cytogenetic abnormalities, thrombocytopenia, and transfusion-dependent anemia. Mutations in the *ASXL1*, *EZH2*, *SRSF2*, and *IDH1/2* genes have been identified as risk factors for early death or transformation to acute leukemia and may prove to be more useful for PMF risk assessment than clinical scoring systems.

TABLE 99-5 IPSS and DIPSS Risk Stratification Systems

	NUMBER OF RISK FACTORS		
RISK CATEGORIES[a]	IPSS	DIPSS	DIPSS PLUS
Low	0	0	0
Intermediate-1	1	1–2	1
Intermediate-2	2	3–4	2–3
High	≥3	>4	4–6

[a]The corresponding survival curves for each risk category can be found in the references cited in the footnotes of Table 99-4.

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System.

TREATMENT

Primary Myelofibrosis

No specific therapy exists for PMF. The causes for anemia are multifarious and include ineffective erythropoiesis uncompensated by splenic extramedullary hematopoiesis, hemodilution due to splenomegaly, splenic sequestration, blood loss secondary to thrombocytopenia or portal hypertension, folic acid deficiency, systemic inflammation, and autoimmune hemolysis. Neither recombinant erythropoietin nor androgens such as danazol have proven to be consistently effective as therapy for anemia. Erythropoietin may worsen splenomegaly and will be ineffective if the serum erythropoietin level is >125 mU/L. Given the inflammatory milieu that characterizes PMF, glucocorticoids can ameliorate anemia as well as constitutional symptoms such as fever, chills, night sweats, anorexia, and weight loss, and combining these with low-dose thalidomide has proved effective as well. Thrombocytopenia can be due to impaired marrow function, splenic sequestration, or autoimmune destruction and may also respond to low-dose thalidomide and prednisone.

Splenomegaly is by far the most distressing and intractable problem for PMF patients, causing abdominal pain, portal hypertension, easy satiety, and cachexia, whereas surgical removal of a massive spleen is associated with significant postoperative complications including mesenteric venous thrombosis, hemorrhage, rebound leukocytosis and thrombocytosis, and hepatic extramedullary hematopoiesis with no amelioration of either anemia or thrombocytopenia when present. For unexplained reasons, splenectomy also increases the risk of blastic transformation. Splenic irradiation is, at best, temporarily palliative and associated with a significant risk of neutropenia, infection, and subsequent operative hemorrhage if splenectomy is attempted. Allopurinol can control significant hyperuricemia, and bone pain can be alleviated by local irradiation. Pegylated IFN-α can ameliorate fibrosis in early PMF, but in advanced disease, it may exacerbate the bone marrow failure. The JAK2 inhibitor, ruxolitinib, has proved effective in reducing splenomegaly and alleviating constitutional symptoms in a majority of advanced PMF patients while also prolonging survival, although it does not significantly influence the *JAK2* V617F neutrophil allele burden. Although anemia and thrombocytopenia are its major side effects, these are dose-dependent, and with time, anemia stabilizes and thrombocytopenia may improve. Allogeneic bone marrow transplantation is the only curative treatment for PMF and should be considered in younger patients and older patients with high risk disease; nonmyeloablative conditioning regimens may permit hematopoietic cell transplantation to be extended to older individuals, and is currently under investigation.

ESSENTIAL THROMBOCYTOSIS

ET (other designations include *essential thrombocythemia*, *idiopathic thrombocytosis*, *primary thrombocytosis*, and *hemorrhagic thrombocythemia*) is a clonal hematopoietic stem cell disorder associated with mutations in *JAK2* (V617F), *MPL*, and *CALR* and manifested clinically by overproduction of platelets without a definable cause. ET has an incidence of 1–2/100,000 and a distinct female predominance in association with *JAK2* V617F, *CALR*, and *MPL* mutations. Canonical MPN driver mutations distinguish 90% of ET patients from the more common nonclonal, reactive forms of thrombocytosis **(Table 99-6)**; mutation-negative ET patients may have an hereditary form of thrombocytosis. Once considered a disease of the elderly and responsible for significant morbidity due to hemorrhage or thrombosis, it is now clear that ET can occur at any age in adults and often without symptoms or disturbances of hemostasis. There is an unexplained female predominance in contrast to PMF or the reactive forms of thrombocytosis where no sex difference

TABLE 99-6 Causes of Thrombocytosis

Tissue inflammation: collagen vascular disease, inflammatory bowel disease	Hemorrhage
Malignancy	Iron-deficiency anemia
Infection	Surgery
Myeloproliferative disorders: polycythemia vera, primary myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia	Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Myelodysplastic disorders: 5q–syndrome, idiopathic refractory sideroblastic anemia	Hemolysis
Postsplenectomy or hyposplenism	Familial: Thrombopoietin overproduction, *JAK2* or *MPL* mutations

exists. Because no specific clonal marker is available, clinical and laboratory criteria have been proposed to distinguish ET from other MPN, which may also present with initially with isolated thrombocytosis but have differing prognoses and therapies (Table 99-6). These criteria are useful in identifying disorders such as CML, PV, PMF, or myelodysplasia, which can masquerade as ET. Furthermore, as with "idiopathic" erythrocytosis, nonclonal benign forms of thrombocytosis exist (such as hereditary overproduction of thrombopoietin and those with noncanonical *JAK2* driver mutations) that are not widely recognized because we currently lack diagnostic assays. Approximately 55% of ET patients express *JAK2* V617F, 36% *CALR* (both type 1 and type 2) and 4% *MPL* mutations. ET patients lacking a canonical MPN driver mutation usually have a benign prognosis.

ETIOLOGY

Megakaryocytopoiesis and platelet production depend on thrombopoietin and its receptor MPL. As in the case of early erythroid and myeloid progenitor cells, early megakaryocytic progenitors require the presence of interleukin 3 (IL-3) and stem cell factor for optimal proliferation in addition to thrombopoietin. Their subsequent terminal development is also enhanced by the chemokine stromal cell-derived factor 1 (SDF-1). Interestingly, terminal megakaryocyte maturation and platelet production do not require thrombopoietin.

Megakaryocytes are unique amongst hematopoietic progenitor cells because reduplication of their genome is endomitotic rather than mitotic and promoted by thrombopoietin. Unlike erythropoietin, thrombopoietin is produced primarily in the liver and to a lesser extent in other organs, most importantly the bone marrow where it functions to maintain hematopoietic stem cells quiescent in the endosteal niche; once released, thrombopoietin promotes the proliferation of these cells in the sinusoidal niche. An inverse correlation exists between the platelet count and plasma thrombopoietin. However, again unlike erythropoietin, thrombopoietin is only constitutively produced and the plasma thrombopoietin level is controlled by the size of the megakaryocyte progenitor cell pool. Also, in contrast to erythropoietin, but like its myeloid counterparts, granulocyte and granulocyte-macrophage colony-stimulating factors, thrombopoietin not only enhances the proliferation of its target cells but also enhances the reactivity of their end-stage product, the platelet.

The clonal nature of ET was established by analysis of glucose-6-phosphate dehydrogenase isoenzyme expression in patients hemizygous for this gene. Although thrombocytosis is its principal manifestation, like the other MPN, a hematopoietic stem cell is involved in ET. Furthermore, a number of families have been described in which ET was inherited, in one instance as an autosomal dominant trait. In addition to ET, PMF and PV have also been observed in such kindreds.

CLINICAL FEATURES

Clinically, ET is most often identified incidentally when a platelet count is obtained during the course of a routine medical evaluation. Occasionally, review of previous blood counts will reveal that an elevated platelet count was present but overlooked for many years. No symptoms or signs are specific for ET, but these patients can have hemorrhagic and thrombotic tendencies expressed as easy bruising for the former and microvascular occlusive events for the latter such as erythromelalgia, ocular migraine, or a TIA. Physical examination is generally unremarkable except occasionally for mild splenomegaly. Significant splenomegaly is indicative of another MPN, in particular PV, PMF, or CML.

Anemia is unusual, but a mild neutrophilic leukocytosis is not. The blood smear is most remarkable for the number of platelets present, some of which may be very large. The large mass of circulating platelets may prevent the accurate measurement of serum potassium due to release of platelet potassium upon blood clotting. This type of hyperkalemia is a test tube artifact and not associated with electrocardiographic abnormalities. Similarly, arterial oxygen measurements can be inaccurate unless thrombocythemic blood is collected on ice. The prothrombin and partial thromboplastin times are normal, whereas abnormalities of platelet function such as a prolonged bleeding time and impaired platelet aggregation can be present. However, despite much study, no platelet function abnormality is characteristic of ET, and no platelet function test predicts the risk of clinically significant bleeding or thrombosis.

The elevated platelet count may hinder marrow aspiration, but marrow biopsy usually reveals megakaryocyte hypertrophy and hyperplasia, as well as an overall increase in marrow cellularity. If marrow reticulin is increased, another diagnosis should be considered. The absence of stainable iron demands an explanation because iron deficiency alone can cause thrombocytosis, and absent marrow iron in the presence of marrow hypercellularity is a feature of PV.

Nonrandom cytogenetic abnormalities occur in ET but are uncommon, and no specific or consistent abnormality is notable, even those involving chromosomes 3 and 1, where the genes for thrombopoietin and its receptor, MPL, respectively, are located.

DIAGNOSIS

Thrombocytosis is encountered in a broad variety of clinical disorders (Table 99-6), in many of which inflammatory cytokine production is increased. The absolute level of the platelet count is not a useful diagnostic aid for distinguishing between benign and clonal causes of thrombocytosis. About 55% of ET patients express the *JAK2* V617F mutation. When *JAK2* V617F is absent, cytogenetic evaluation is mandatory to determine if the thrombocytosis is due to CML or a myelodysplastic disorder such as the 5q– syndrome. Because the bcr-abl translocation can be present in the absence of the Ph chromosome, and because bcr-abl reverse transcriptase polymerase chain reaction is associated with false-positive results, fluorescence in situ hybridization (FISH) analysis for bcr-abl is the preferred assay in patients with thrombocytosis in whom a cytogenetic study for the Ph chromosome is negative. *CALR* (type 1 or type 2) are present in 36%, and *MPL* mutations are present in 4% respectively, of ET patients who do not have a *JAK2* mutation. Anemia and ringed sideroblasts are not features of ET, but they are features of idiopathic refractory sideroblastic anemia, and in some of these patients, the thrombocytosis occurs in association with expression of *JAK2* V617F, *CALR*, or an *MPL* mutation. Significant splenomegaly should suggest the presence of another MPN, and in this setting, a red cell mass determination should be performed because splenomegaly can mask the presence of erythrocytosis. Importantly, what appears to be ET can evolve into PV (usually in women with *JAK2* V617F) or PMF (usually in men with type 1 CALR mutations) after a period of many years due to clonal evolution or succession. There is sufficient overlap of the *JAK2* V617F neutrophil allele burden between ET and PV that this cannot be used as a distinguishing diagnostic feature; only a red cell mass and plasma volume determination can distinguish PV from ET, and importantly in this regard, 64% of *JAK2* V617F–positive ET patients in one study actually were found to have PV when red cell mass and plasma volume determinations were performed. Claims that ET and PV form a biological continuum are unfounded as these disorders have different gene expression profiles and different natural histories.

COMPLICATIONS

Perhaps no other condition in clinical medicine has caused otherwise astute physicians to intervene inappropriately more often than thrombocytosis, particularly if the platelet count is >1 × 10^6/μL. It is commonly believed that a high platelet count causes thrombosis; however, no controlled clinical study has ever established this association, and in patients younger than age 60 years, the incidence of thrombosis was not greater in patients with thrombocytosis than in age-matched controls, and tobacco use appears to be the most important risk factor for thrombosis in ET patients.

To the contrary, very high platelet counts are associated primarily with hemorrhage due to acquired von Willebrand's disease. This is not meant to imply that an elevated platelet count cannot cause symptoms in an ET patient, but rather that the focus should be on the patient, not the platelet count. For example, some of the most dramatic neurologic problems in ET are migraine-related and respond only to lowering of the platelet count, whereas other symptoms such as erythromelalgia respond simply to platelet cyclooxygenase-1 inhibitors such as aspirin or ibuprofen, without a reduction in platelet number. Still others may represent an interaction between an atherosclerotic vascular system and a high platelet count, and others may have no relationship to the platelet count whatsoever. Recognition that PV can present with thrombocytosis alone as well as the discovery of previously unrecognized causes of hypercoagulability **(Chap. 113)** make the older literature on the complications of thrombocytosis unreliable.

TREATMENT

Essential Thrombocytosis

Survival of ET patients is not different than the general population regardless of their driver mutation. An elevated platelet count in an asymptomatic patient without cardiovascular risk factors or tobacco use requires no therapy. Indeed, before any therapy is initiated in a patient with thrombocytosis, the cause of symptoms must be clearly identified as due to the elevated platelet count. When the platelet count rises above 1 × 10^6/μL, a substantial quantity of high-molecular-weight von Willebrand multimers are removed from the circulation and destroyed by the enlarged platelet mass, resulting in an acquired form of von Willebrand's disease. This can be identified by a reduction in ristocetin cofactor activity. In this situation, aspirin could promote hemorrhage. Bleeding in this situation is rarely spontaneous and usually responds to ε-aminocaproic acid, which can be given prophylactically before and after elective surgery. Plateletpheresis is at best a temporary and inefficient remedy that is rarely required. Importantly, ET patients treated with ^{32}P or alkylating agents are at risk of developing acute leukemia without any proof of benefit; combining either therapy with hydroxyurea increases this risk. If platelet reduction is deemed necessary on the basis of symptoms refractory to salicylates alone, pegylated IFN-α, the quinazoline derivative, anagrelide, or hydroxyurea can be used to reduce the platelet count, but none of these is uniformly effective or without significant side effects. Hydroxyurea and aspirin are more effective than anagrelide and aspirin for prevention of TIA because hydroxyurea is an NO donor, but not more effective for the prevention of other types of arterial thrombosis and actually less effective for venous thrombosis. The risk of gastrointestinal bleeding is also higher when aspirin is combined with anagrelide. Normalizing the platelet count does not prevent either arterial or venous thrombosis. Pegylated interferon can produce a complete molecular remission in some ET patients, but a role for it or ruxolitinib in ET management has not yet been established.

As more clinical experience is acquired, ET appears more benign than previously thought. Evolution to acute leukemia is more likely to be a consequence of therapy than of the disease itself. In managing patients with thrombocytosis, the physician's first obligation is to do no harm.

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100 Acute Myeloid Leukemia

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INCIDENCE

Acute myeloid leukemia (AML) is a neoplasm characterized by infiltration of the blood, bone marrow, and other tissues by proliferative, clonal, poorly differentiated cells of the hematopoietic system. These leukemias comprise a spectrum of malignancies that, untreated, are uniformly fatal. In 2016, the estimated number of new AML cases in the United States was 19,950, comprising ~1.2% of all cancer cases. AML is the most common acute leukemia in older patients, with a median age at diagnosis of 67 years. Long-term survival is infrequent; U.S. registry data report that only 27% of patients survive 5 years.

ETIOLOGY

Most cases of AML are idiopathic. Genetic predisposition, radiation, chemical/other occupational exposures, and drugs have been implicated in the development of AML, but AML cases with established etiology are relatively rare. No direct evidence suggests a viral etiology. Genome sequencing studies suggest that most cases of AML arise from a limited number of mutations that accumulate with advancing age. Indeed, genome sequencing is providing paradigm-shifting advances in our understanding of leukemogenesis. The Cancer Genome Atlas (TCGA) and other databases demonstrate that blood cells from up to 5–6% of normal individuals aged >70 years contain potentially "premalignant" mutations that are associated with clonal expansion. The additional insults that subsequently direct "premalignant" blood cells to leukemia are quite heterogeneous and still poorly understood.

Genetic Predisposition Myeloid neoplasms typically occur sporadically in adults; inherited predisposition is rare. Yet, it is clear that myeloid neoplasms with germline predisposition represent an important and growing subset of disease. Germline mutations associated with increased risk of developing a myeloid neoplasm include *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, and *GATA2* **(Table 100-1)**. Likewise, myeloid neoplasms with germline predisposition are a feature of several well-described clinical syndromes, including bone marrow failure disorders (e.g., Fanconi anemia, Shwachman-Diamond syndrome, Diamond-Blackfan anemia), and telomere biology disorders (e.g., dyskeratosis congenita). As new mutations and associations are added to a rapidly growing list, it is increasingly clear that genetic predisposition plays a larger role than has been previously understood.

Several genetic syndromes with somatic cell chromosome aneuploidy, such as Down syndrome with trisomy 21, are associated with an increased incidence of AML. Down syndrome–associated AML in young children (<4 years) is typically of the acute megakaryocytic subtype and is associated with mutation in the *GATA1* gene. Such patients have excellent clinical outcomes but require dose modification of chemotherapy due to high treatment-related toxicities. Inherited

TABLE 100-1 WHO 2016 Classification of Myeloid Neoplasms with Germline Predisposition

CLASSIFICATION[a]
Myeloid neoplasms with germline predisposition without a preexisting disorder or organ dysfunction
Acute myeloid leukemia with germline *CEBPA* mutation
Myeloid neoplasms with germline *DDX41* mutation[b]
Myeloid neoplasms with germline predisposition and preexisting platelet disorders
Myeloid neoplasms with germline *RUNX1* mutation[b]
Myeloid neoplasms with germline *ANKRD26* mutation[b]
Myeloid neoplasms with germline *ETV6* mutation[b]
Myeloid neoplasms with germline predisposition and other organ dysfunction
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Myeloid neoplasms associated with telomere biology disorders
Myeloid neoplasms associated with Noonan syndrome
Myeloid neoplasms associated with Down syndrome[b]

[a]Recognition of familial myeloid neoplasms requires that physicians take a thorough patient and family history to assess for typical signs and symptoms of known syndromes, including data on malignancies and previous bleeding episodes. Molecular genetic diagnostics is guided by a detailed patient and family history. Diagnostics should be performed in close collaboration with a genetic counselor; patients with a suspected heritable myeloid neoplasm, who test negative for known predisposition genes, should ideally be entered on a research study to facilitate new syndrome discovery. [b]Lymphoid neoplasms also reported.

Source: Adapted from Peterson L et al: Myeloid Neoplasms with Germline Predisposition, in *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*, update to 4th ed. IARC, 2017.

TABLE 100-2 WHO 2016 Classification of Acute Myeloid Leukemia and Related Neoplasms

Acute myeloid leukemia (AML) with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
Acute promyelocytic leukemia with *PML-RARA*
AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1); *DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified (NOS)
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

Note: Marrow blast count of ≥20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16).

Source: Adapted from Arber DA et al: Acute myeloid leukaemia (AML) with recurrent genetic abnormalities, in *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*, update to 4th ed. IARC, 2017.

diseases with defective DNA repair (e.g., Fanconi anemia, Bloom syndrome, and ataxia-telangiectasia) are also associated with AML. Each syndrome is associated with unique clinical features and atypical toxicities with chemotherapy, requiring expert care. Congenital neutropenia (Kostmann syndrome), due to mutations in the genes encoding the granulocyte colony-stimulating factor receptor and neutrophil elastase, is another disorder that may evolve into AML.

Chemical, Radiation, and Other Exposures Anticancer drugs are the leading cause of therapy-associated AML. Alkylating agent–associated leukemias occur on average 4–6 years after exposure, and affected individuals often have multilineage dysplasia and monosomy/aberrations in chromosomes 5 and 7. Topoisomerase II inhibitor–associated leukemias occur 1–3 years after exposure, and affected individuals often have AML with monocytic features and aberrations involving chromosome 11q23. Exposure to ionizing radiation, benzene, chloramphenicol, phenylbutazone, and other drugs can uncommonly result in bone marrow failure that may evolve into AML.

CLASSIFICATION

The current categorization of AML uses the World Health Organization (WHO) classification **(Table 100-2)**, which defines biologically distinct groups based on cytogenetic and molecular abnormalities in addition to clinical features and light microscope morphology. Myeloid neoplasms with germline predisposition, as introduced above, are included as a new and important feature of this classification (Table 100-1). The WHO classification enables the identification of subsets of disease that may now (or in the future) be treated differently and advances the care of AML patients by enhancing recognition of the molecular basis of the disease from the time of diagnosis. Marrow (or blood) blast count of ≥20% is required to establish the diagnosis of AML, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16), or t(16;16).

Clinical Features Even with advances in molecular biology, recognizing clinical features remains important in understanding AML. For example, therapy-related AML is a distinct entity that develops following prior chemotherapy (e.g., alkylating agents, topoisomerase II inhibitors) or ionizing radiation. AML with myelodysplasia-related changes is recognized based in part on morphology but also on a medical history of an antecedent myelodysplastic syndrome (MDS) or myelodysplastic/myeloproliferative neoplasm. These clinical features contribute to AML prognosis and have therefore been included in the WHO classification.

Genetic Findings Subtypes of AML are recognized based on the presence or absence of specific, recurrent cytogenetic, and/or genetic abnormalities. For example, the diagnosis of *acute promyelocytic leukemia* (APL) is based on the presence of either the t(15;17)(q22;q12) cytogenetic rearrangement or the *PML-RARA* fusion product of the translocation. Similarly, core binding factor (CBF) AML is designated based on the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22) or the respective fusion products *RUNX1-RUNX1T1* and *CBFB-MYH11*. Each of these groups identifies patients with favorable clinical outcomes when appropriately treated.

Several cytogenetic or genetic AML subtypes often associate with a specific morphologic appearance, such as a complex karyotype and AML with myelodysplasia-related changes. Patients with such changes typically fare poorly with standard treatments. However, only one cytogenetic abnormality is invariably associated with specific morphologic features: t(15;17)(q22;q12) with APL. Other cytogenetic and genetic findings may be commonly but not invariably associated with a morphological description, highlighting the necessity of genetic and cytogenetic testing beyond simple morphology to most accurately diagnose AML. Several chromosomal abnormalities often associate primarily with one morphologic/immunophenotypic group. Examples include inv(16)(p13.1q22) with AML with abnormal bone marrow eosinophils; t(8;21)(q22;q22) with slender Auer rods, expression of CD19, and increased normal eosinophils; and t(9;11)(p22;q23), and other

translocations involving 11q23, with monocytic features. Recurring chromosomal abnormalities in AML may also be loosely associated with specific clinical characteristics. More commonly associated with younger age are t(8;21) and t(15;17), and with older age, del(5q) and del(7q). Myeloid sarcomas are associated with t(8;21); disseminated intravascular coagulation (DIC) is associated with t(15;17). 11q23 aberrations and monocytic leukemia are associated with extramedullary sites of involvement at presentation, especially gingival hypertrophy.

The WHO classification also incorporates molecular abnormalities by recognizing fusion genes or specific genetic mutations with a role in leukemogenesis. As a classic example, t(15;17) results in the fusion gene *PML-RARA* that encodes a chimeric protein, promyelocytic leukemia (Pml)–retinoic acid receptor α (Rarα), which is formed by the fusion of the retinoic acid receptor α (*RARA*) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene from chromosome 15. The *RARA* gene encodes a member of the nuclear hormone receptor family of transcription factors. *PML* is important in many cellular processes, including cell growth control, apoptosis, and senescence; its effects are mediated at least in part by nuclear bodies that store a myriad of proteins/enzymes that are involved in these functions. The PML-RARA fusion protein suppresses gene transcription and blocks differentiation beyond the promyelocyte stage. Pharmacologic concentrations of the Rarα ligand, achieved with the drug all-*trans*-retinoic acid (tretinoin, ATRA), relieve the block and promote hematopoietic cell differentiation. However, the effects of ATRA are not primarily from direct restoration of gene transactivation via RA signaling. Rather, drug treatment induces degradation of the fusion protein. Mechanistic work has demonstrated that the RARA fusion partner PML is far more important in the pathobiology than was initially understood. PML-RARA disturbs nuclear body assembly. This impairs many PML functions, culminating in enhanced self-renewal of leukemic cells. ATRA and arsenic trioxide (ATO) both induce PML-RARA degradation (by different mechanisms), leading to reformation of PML nuclear bodies (or enhanced nuclear body activity). Restored PML functions include the activation of p53 which triggers senescence in leukemic cells. Clinical therapy with ATRA and ATO has revolutionized the care of APL patients (see "Treatment of Acute Promyelocytic Leukemia" section).

Similar examples of molecular subtypes included in the category of AML with recurrent genetic abnormalities are those characterized by the leukemogenic fusion genes *RUNX1-RUNX1T1*, *CBFB-MYH11*, *MLLT3-KMT2A*, and *DEK-NUP214*, resulting, respectively, from t(8;21), inv(16) or t(16;16), t(9;11), and t(6;9)(p23;q34).

The WHO classification of AML continues to expand as knowledge of specific genetic or cytogenetic aberrations grows. Several AML subtypes are defined by the presence of genetic mutations rather than chromosomal aberrations including, for example, *AML with mutated nucleophosmin (nucleolar phosphoprotein B23, numatrin)* (*NPM1*) and *AML with biallelic mutated CEBPA*, respectively. Both entities are associated with more favorable clinical outcomes, though the *NPM1* prognostic impact is affected by coexisting mutation in fms-related tyrosine kinase 3 (*FLT3*). Activating mutations of *FLT3* are present in ~30% of adult AML patients, primarily due to internal tandem duplications (ITD) in the juxtamembrane domain that have negative prognostic impact. In contrast, point mutations of the activating loop of the kinase (called tyrosine kinase domain [TKD] mutations) have uncertain prognostic impact. Aberrant activation of the *FLT3*-encoded protein provides increased proliferation and antiapoptotic signals to the myeloid progenitor cell. *FLT3*-ITD, the more common of the *FLT3* mutations, occurs preferentially in patients with cytogenetically normal AML (CN-AML). The importance of identifying *FLT3*-ITD at diagnosis relates to the fact that is it useful not only as a prognosticator but also may predict response to specific treatment such as a tyrosine kinase inhibitor (TKI); several TKI are currently in clinical investigation (e.g., midostaurin, quizartinib, gilteritinib, crenolanib, sorafenib). The *FLT3* allelic ratio (of the number of mutated alleles to wild type alleles) provides information beyond the mere presence or absence of the mutation. The ratio is affected by several mutational scenarios such as one mutated gene and one wild type gene, or one mutated gene with no (deleted) wild type gene, and the ratio of malignant to nonmalignant cells in the sample.

TABLE 100-3 2017 European LeukemiaNet Risk Stratification by Genetics for Acute Myeloid Leukemia[a]

RISK CATEGORY[b]	GENETIC ABNORMALITY
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD$^{high(c)}$
	Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low(c)}$ (w/o adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM(EVI1)*
	–5 or del(5q); –7; –17/abn(17p)
	Complex karyotype,[e] monosomal karyotype[f]
	Wild type *NPM1* and *FLT3*-ITD$^{high(c)}$
	Mutated *RUNX1*[g]
	Mutated *ASXL1*[g]
	Mutated *TP53*[h]

[a]This table excludes acute promyelocytic leukemia. Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated. [b]Prognostic impact of a marker is treatment-dependent and may change with new therapies. [c]Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve (AUC) "*FLT3*-ITD" divided by AUC "*FLT3*-wild type"; recent studies indicate that acute myeloid leukemia with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and patients should not routinely be assigned to allogeneic hematopoietic-cell transplantation. [d]The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations. [e]Three or more unrelated chromosome abnormalities in the absence of one of the World Health Organization-designated recurring translocations or inversions, i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*. [f]Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML). [g]These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes. [h]*TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Source: Adapted from Döhner H et al: Diagnosis and management of acute myeloid leukemia in adults: 2017 recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 129:424, 2017.

The allelic ratio affects the prognostic impact of the *FLT3*-ITD mutation; patients with *FLT3*-ITD "low" allelic ratio (<0.5) fare better. Accordingly, mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} are both viewed as favorable-risk by the European LeukemiaNet (ELN) risk stratification schema **(Table 100-3)**. Conversely, *FLT3*-ITD^{high} is known to have an adverse prognostic impact; patients with mutated *NPM1* and *FLT3*-ITD with an allelic ratio >0.5 are thus intermediate-risk by ELN stratification. Involving a different tyrosine kinase, AML with *BCR-ABL1* fusion is a new WHO provisional entity, to recognize rare cases that may benefit from *BCR-ABL* TKI therapy (Table 100-2).

Immunophenotypic Findings The immunophenotype of human leukemia cells can be studied by multiparameter flow cytometry after the cells are labeled with monoclonal antibodies to cell-surface antigens. This can be important in quickly distinguishing AML from acute lymphoblastic leukemia and for identifying some subtypes of AML. For example, AML with minimal differentiation, characterized by immature morphology and no lineage-specific cytochemical reactions, may be diagnosed by flow-cytometric demonstration of the myeloid-specific antigens cluster designation (CD) 13 and/or 117. Similarly, acute megakaryoblastic leukemia can often be diagnosed only by expression of the platelet-specific antigens CD41 and/or CD61.

Although flow cytometry is widely used, and in some cases essential for the diagnosis of AML, it has only a supportive role in establishing the different subtypes of AML through the WHO classification. Increasingly, multiparameter flow cytometry is used for the measurement of minimal residual disease (MRD) after remission is achieved.

PROGNOSTIC FACTORS

Several factors predict outcome of AML patients treated with chemotherapy; they should be used for risk stratification and treatment guidance.

Chromosome findings at diagnosis currently provide the most important independent prognostic information. Several reports have categorized patients as having favorable, intermediate, or adverse cytogenetic risk based on the presence of structural and/or numerical aberrations. Patients with t(15;17) have a very good prognosis (~85% cured), and those with t(8;21) and inv(16) have a good prognosis (~55% cured), whereas those with no cytogenetic abnormality have an intermediate outcome risk (~40% cured). Patients with a complex karyotype, t(6;9), inv(3), or –7 have a very poor prognosis. Another cytogenetic subgroup, the monosomal karyotype, has been suggested to adversely impact the outcome of AML patients other than those with t(15;17), t(8;21), or inv(16) or t(16;16). The monosomal karyotype subgroup is defined by the presence of at least two autosomal monosomies (loss of chromosomes other than Y or X) or a single autosomal monosomy with additional structural abnormalities.

For patients lacking prognostic cytogenetic abnormalities, such as those with CN-AML, testing for several mutated genes can help to risk-stratify. In addition to the *NPM1* mutation and/or *FLT3*-ITD as described above, biallelic *CEBPA* mutations have prognostic value. Such mutations predict favorable outcome. Given the proven prognostic importance of *NPM1*, *CEBPA*, and *FLT3*, molecular assessment of these genes at diagnosis has been incorporated into AML management guidelines by the National Comprehensive Cancer Network (NCCN) and the ELN. The same markers help to define genetic groups in the ELN standardized reporting system, which is based on both cytogenetic and molecular abnormalities and is used for comparing clinical features/treatment response among subsets of patients reported across different clinical studies (Table 100-3). These genetic groups should be used for risk stratification and treatment guidance.

In addition to *NPM1* and *CEBPA* mutations and *FLT3*-ITD, molecular aberrations in other genes may be routinely used for prognostication in the future **(Table 100-4)**. Among these mutated genes are those encoding receptor tyrosine kinases (e.g., v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog [*KIT*]), transcription factors (i.e., *RUNX1* and Wilms tumor 1 [*WT1*]), and epigenetic modifiers (i.e., additional sex combs like transcriptional regulator 1 [*ASXL1*], DNA (cytosine-5-)-methyltransferase 3 alpha [*DNMT3A*], isocitrate dehydrogenase 1 [NADP+], soluble [*IDH1*], isocitrate dehydrogenase 2 (NADP+), mitochondrial [*IDH2*], lysine (K)–specific methyltransferase 2A [*KMT2A*, also known as *MLL*], and tet methylcytosine dioxygenase 2 [*TET2*]). Although *KIT* mutations are almost exclusively present in CBF AML and impact adversely the outcome, the remaining markers have been reported primarily in CN-AML. These gene mutations have been shown to be associated with outcome in multivariable analyses independent of other prognostic factors. However, for some of them, data remain unclear on the prognostic impact due to conflicting reports (e.g., *TET2*, *IDH1*, *IDH2*). Increasingly, novel drugs that inhibit/modulate aberrant pathways activated by some of these genes (e.g., *IDH1*, *IDH2*, *KMT2A*, among others) are being incorporated into clinical trials to treat AML.

In addition to gene mutations, deregulation of the expression levels of coding genes and of short noncoding RNAs (microRNAs) also provide prognostic information (Table 100-4). Overexpression of genes such as brain and acute leukemia, cytoplasmic (*BAALC*), v-ets avian erythroblastosis virus E26 oncogene homologue (avian) (*ERG*), meningioma (disrupted in balanced translocation) 1 (*MN1*), and MDS1 and EVI1 complex locus (*MECOM*, also known as *EVI1*) predict poor outcome, especially in CN-AML. Similarly, deregulated expression levels of microRNAs, naturally occurring noncoding RNAs that regulate the expression of proteins via degradation or translational inhibition of their target coding RNAs, have also been associated with prognosis in AML. Overexpression of *miR-155* and *miR-3151* predicts unfavorable outcome in CN-AML, whereas overexpression of *miR-181a* predicts favorable outcome both in CN-AML and cytogenetically abnormal AML.

Because prognostic molecular markers in AML are not mutually exclusive and often occur concurrently (>80% patients have at least two or more prognostic gene mutations), the likelihood that distinct marker combinations may be more informative than single markers is increasingly clear.

Epigenetic changes (e.g., DNA methylation and/or post-translational histone modification) and microRNAs are often involved in deregulation of genes involved in hematopoiesis, contribute to leukemogenesis and may associate with the previously discussed prognostic gene mutations. These changes have been shown to provide biologic insights into leukemogenic mechanisms and also independent prognostic information. Indeed, it is anticipated that with the enormous progress made in DNA and RNA sequencing technology, additional genetic and epigenetic aberrations will soon be discovered, further improving classification and risk-stratification in AML patients.

In addition to cytogenetics and molecular aberrations, several other factors are associated with outcome in AML. Age at diagnosis is one of the most important risk factors. Advancing age is associated with a poor prognosis for two reasons: (1) its influence on the ability to survive induction therapy due to coexisting medical comorbidities, and (2) with each successive decade of age, a greater proportion of patients have intrinsically more resistant disease. A prolonged symptomatic interval with cytopenias preceding AML diagnosis, or a history of antecedent

TABLE 100-4 Molecular Prognostic Markers in AML[a]

GENE SYMBOL	GENE LOCATION	PROGNOSTIC IMPACT
Genes Included in the WHO Classification and ELN Reporting System		
NPM1 mutations	5q35.1	Favorable
CEBPA mutations	19q13.1	Favorable
FLT3-ITD	13q12	Depends on allelic ratio and *NPM1* mutational status
Genes Encoding Receptor Tyrosine Kinases		
KIT mutation	4q12	Adverse
FLT3-TKD	13q12	Unclear
Genes Encoding Transcription Factors		
RUNX1 mutations	21q22.12	Adverse
WT1 mutations	11p13	Adverse
Genes Encoding Epigenetic Modifiers		
ASXL1 mutations	20q11.21	Adverse
DNMT3A mutations	2p23.3	Adverse
IDH mutations (*IDH1* and *IDH2*)	2q34 & 15q26.1	Adverse
KMT2A-PTD	11q23	Adverse
TET2 mutations	4q24	Adverse
Deregulated Genes		
BAALC overexpression	8q22.3	Adverse
ERG overexpression	21q22.3	Adverse
MN1 overexpression	22q12.1	Adverse
EVI1 overexpression	3q26.2	Adverse
Deregulated MicroRNAs		
miR-155 overexpression	21q21.3	Adverse
miR-3151 overexpression	8q22.3	Adverse
miR-181a overexpression	1q32.1 and 9q33.3	Favorable

[a]This table excludes acute promyelocytic leukemia.

Abbreviations: AML, acute myeloid leukemia; ELN, European LeukemiaNet; ITD, internal tandem duplication; PTD, partial tandem duplication; TKD, tyrosine kinase domain; WHO, World Health Organization.

hematologic disorders including MDS or myeloproliferative neoplasms, is often found in older patients. Cytopenia is a clinical feature associated with a lower complete remission (CR) rate and shorter survival time. The CR rate is lower in patients who have had anemia, leukopenia, and/or thrombocytopenia for >3 months before the diagnosis of AML, when compared to those without such a history. Responsiveness to chemotherapy declines as the duration of the antecedent disorder increases. Likewise, AML developing after treatment with cytotoxic agents for other malignancies is usually difficult to treat successfully. In addition, older patients less frequently harbor favorable cytogenetic abnormalities (i.e., t[8;21], inv[16], and t[16;16]) and more frequently harbor adverse cytogenetic (e.g., complex and monosomal karyotypes) and/or molecular (e.g., *ASXL1*, *p53*) abnormalities.

Other factors independently associated with worse outcome are a poor performance status that influences ability to survive induction therapy and a high presenting leukocyte count that in some series is an adverse prognostic factor for attaining a CR. Among patients with hyperleukocytosis (>100,000/μL), early central nervous system bleeding and pulmonary leukostasis contribute to poor outcomes.

Following administration of therapy, achievement of CR is associated with better outcome and longer survival. CR is defined after examination of both blood and bone marrow and essentially represents both eradication of detectable leukemia and restoration of normal hematopoiesis. The blood neutrophil count must be ≥1000/μL and the platelet count ≥100,000/μL. Hemoglobin concentration is not considered in determining CR. Circulating blasts should be absent. Although rare blasts may be detected in the blood during marrow regeneration, they should disappear on successive studies. At CR, the bone marrow should contain <5% blasts, and Auer rods should be absent. Extramedullary leukemia should not be present.

CLINICAL PRESENTATION

Symptoms Patients with AML usually present with nonspecific symptoms that begin gradually, or abruptly, and are the consequence of anemia, leukocytosis, leukopenia/leukocyte dysfunction, or thrombocytopenia. Nearly half have symptoms for ≤3 months before the leukemia is diagnosed.

Fatigue is a frequent first symptom among AML patients. Anorexia and weight loss are common. Fever with or without an identifiable infection is the initial symptom in ~10% of patients. Signs of abnormal hemostasis (bleeding, easy bruising) are common. Bone pain, lymphadenopathy, nonspecific cough, headache, or diaphoresis may also occur.

Rarely, patients may present with symptoms from a myeloid sarcoma (a tumor mass consisting of myeloid blasts occurring at anatomic sites other than bone marrow). Sites involved are most commonly the skin, lymph node, gastrointestinal tract, soft tissue, and testis. This rare presentation, often characterized by chromosome aberrations (e.g., monosomy 7, trisomy 8, 11q23 rearrangement, inv[16], trisomy 4, t[8;21]), may precede or coincide with blood and/or marrow involvement by AML. Patients who present with isolated myeloid sarcoma typically develop blood and/or marrow involvement quickly thereafter and cannot be cured with local therapy (radiation or surgery) alone.

Physical Findings Fever, infection, and hemorrhage are often found at the time of diagnosis; splenomegaly, hepatomegaly, lymphadenopathy, and "bone pain" may also be present less commonly. Hemorrhagic complications are most commonly and, classically, found in APL. APL patients often present with DIC-associated minor hemorrhage but may have significant gastrointestinal bleeding, intrapulmonary hemorrhage, or intracranial hemorrhage. Likewise, thrombosis is another less frequent but well recognized clinical feature of DIC in APL. Bleeding associated with coagulopathy may also occur in monocytic AML and with extreme degrees of leukocytosis or thrombocytopenia in other morphologic subtypes. Retinal hemorrhages are detected in 15% of patients. Infiltration of the gingiva, skin, soft tissues, or meninges with leukemic blasts at diagnosis is characteristic of the monocytic subtypes and those with 11q23 chromosomal abnormalities.

Hematologic Findings Anemia is usually present at diagnosis though it is not typically severe. The anemia is usually normocytic normochromic. Decreased erythropoiesis in the setting of AML often results in a reduced reticulocyte count, and red blood cell (RBC) survival is decreased by accelerated destruction. Active blood loss may rarely contribute to the anemia.

The median presenting leukocyte count is ~15,000/μL. Lower presenting leukocyte counts are more typical of older patients and those with antecedent hematologic disorders. Between 25 and 40% of patients have counts <5000/μL, and 20% have counts >100,000/μL. Fewer than 5% have no detectable leukemic cells in the blood. In AML, the cytoplasm often contains primary (nonspecific) granules, and the nucleus shows fine, lacy chromatin with one or more nucleoli characteristic of immature cells. Abnormal rod-shaped granules called Auer rods are not uniformly present, but when they are, AML is virtually certain **(Fig. 100-1)**.

Platelet counts <100,000/μL are found at diagnosis in ~75% of patients, and ~25% have counts <25,000/μL. Both morphologic and functional platelet abnormalities can be observed, including large and bizarre shapes with abnormal granulation and inability of platelets to aggregate or adhere normally to one another.

Pretreatment Evaluation Once the diagnosis of AML is suspected, thorough evaluation and initiation of appropriate therapy should follow. In addition to clarifying the subtype of leukemia, initial studies should evaluate the overall functional integrity of the major organ systems, including the cardiovascular, pulmonary, hepatic, and renal systems **(Table 100-5)**. Factors that have prognostic significance, either for achieving CR or for predicting CR duration, should also be assessed before initiating treatment, including cytogenetics and molecular markers. Leukemic cells should be obtained from all patients and cryopreserved for future investigational testing as well as potential future use as new diagnostics and therapeutics become available. All patients should be evaluated for infection.

Most patients are anemic and thrombocytopenic at presentation. Replacement of the appropriate blood components, if necessary, should begin promptly. Because qualitative platelet dysfunction or the presence of an infection may increase the likelihood of bleeding, evidence of hemorrhage justifies the immediate use of platelet transfusion, even if the platelet count is only moderately decreased.

About 50% of patients have a mild to moderate elevation of serum uric acid at presentation. Only 10% have marked elevations, but renal precipitation of uric acid and the nephropathy that may result is a serious but uncommon complication. The initiation of chemotherapy may aggravate hyperuricemia, and patients are usually started immediately on allopurinol and hydration at diagnosis. Rasburicase (recombinant uric oxidase) is also useful for treating uric acid nephropathy and often can normalize the serum uric acid level within hours with a single dose of treatment, although its expense suggests that limiting its use to patients with severe hyperuricemia and/or kidney injury may be prudent. The presence of high concentrations of lysozyme, a marker for monocytic differentiation, may be etiologic in renal tubular dysfunction for a minority of patients.

TREATMENT

Acute Myeloid Leukemia

Treatment of the newly diagnosed patient with AML is usually divided into two phases, induction and postremission management (consolidation) **(Fig. 100-2)**. The initial goal is to induce CR. Once CR is obtained, further therapy must be given to prolong survival and achieve cure. The initial induction treatment and subsequent postremission therapy are chosen based on the patient's age, overall fitness, and cytogenetic/molecular risk. Intensive therapy with cytarabine and anthracyclines in younger patients (<60 years) increases the cure rate of AML. In older patients, the benefit of intensive therapy is controversial in all but favorable-risk patients; novel approaches for selecting patients predicted to be responsive to treatment and new therapies are being pursued.

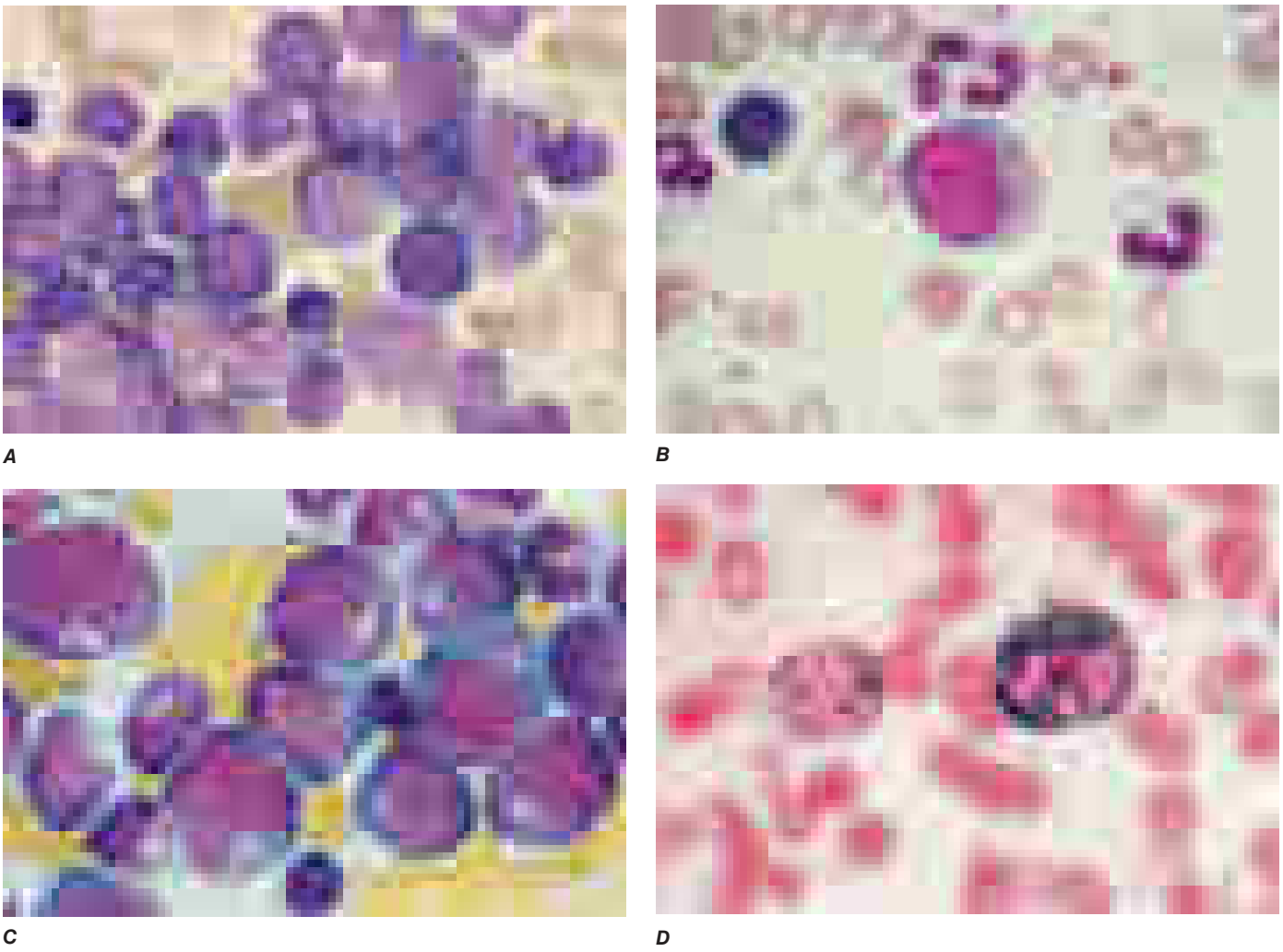

FIGURE 100-1 Morphology of acute myeloid leukemia (AML) cells. ***A.*** Uniform population of primitive myeloblasts with immature chromatin, nucleoli in some cells, and primary cytoplasmic granules. ***B.*** Leukemic myeloblast containing an Auer rod. ***C.*** Promyelocytic leukemia cells with prominent cytoplasmic primary granules. ***D.*** Peroxidase stain shows dark blue color characteristic of peroxidase in granules in AML.

INDUCTION CHEMOTHERAPY

The most commonly used induction regimens (for patients other than those with APL) consist of combination chemotherapy with cytarabine and an anthracycline (e.g., daunorubicin, idarubicin). Cytarabine is a cell cycle S-phase–specific antimetabolite that becomes phosphorylated intracellularly to an active triphosphate form that interferes with DNA synthesis. Anthracyclines are DNA intercalators. Their primary mode of action is thought to be inhibition of topoisomerase II, leading to DNA breaks.

In adults, cytarabine used at standard dose (100–200 mg/m^2) is administered as a continuous intravenous infusion for 7 days. With cytarabine, anthracycline therapy generally consists of daunorubicin (60–90 mg/m^2) or idarubicin (12 mg/m^2) intravenously on days 1, 2, and 3 (the 7 and 3 regimen). Other agents can be added (e.g., cladribine) when 60 mg/m^2 of daunorubicin is used. With the 7 and 3 regimen, it is now clearly established that 45 mg/m^2 dosing of daunorubicin results in inferior outcomes; patients should receive higher doses as described. Patients failing remission after one induction are offered reinduction with the same (or slightly modified) therapy.

In older patients (age ≥60–65 years), the outcome is generally poor due to a higher frequency of resistant disease and increased rate of treatment-related mortality. This is especially true in patients with prior hematologic disorders (MDS or myeloproliferative neoplasms), therapy-related AML, or cytogenetic and genetic abnormalities that adversely impact on clinical outcome. All older patients should be considered for clinical trials, but in particular older patients in the adverse-risk groups delineated above should be offered investigational approaches when possible. Conventional therapy for older patients is similar to that for younger: the 7 and 3 regimen with standard-dose cytarabine and idarubicin (12 mg/m^2), or daunorubicin (60 mg/m^2, or 90 mg/m^2 for those <65 years). For patients aged >65 years, high-dose daunorubicin (90 mg/m^2) has increased toxicity and is not recommended. Older patients and those with adverse-risk genetics may receive lower intensity therapy with a hypomethylating agent (decitabine or azacitidine), clofarabine, or preferably investigational therapy **(Table 100-6)**.

With the 7 and 3 regimen, 60–80% of younger and 33–60% of older patients (among those who are candidates for intensive therapy) with primary AML achieve CR. Of patients who do not achieve CR, most have drug-resistant leukemia, although induction death is more frequent with advancing age and medical comorbidity. Patients with refractory disease after induction should be considered for salvage treatments, preferentially on clinical trials, before receiving allogeneic hematopoietic stem cell transplantation (HCT) that is usually reserved for patients in or near CR. However, fit younger patients with primary refractory disease have ~15–20% cure rates with allogeneic HCT (after myeloablative conditioning); for this reason early consideration of future allogeneic HCT feasibility (including HLA typing, donor search, etc.) should be part of the initial induction approach for most AML patients.

TABLE 100-5 Initial Diagnostic Evaluation and Management of Adult Patients with AML

History
Increasing fatigue or decreased exercise tolerance (anemia)
Excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia)
Fevers or recurrent infections (neutropenia)
Headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed)
Early satiety (splenomegaly)
Family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia-telangiectasia)
History of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors)
Occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides)
Physical Examination
Performance status (prognostic factor)
Ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia)
Fever and tachycardia (signs of infection)
Papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia)
Poor dentition, dental abscesses
Gum hypertrophy (leukemic infiltration, most common in monocytic leukemia)
Skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia)
Lymphadenopathy, splenomegaly, hepatomegaly
Back pain, lower extremity weakness (spinal granulocytic sarcoma, most likely in t[8;21] patients)
Laboratory and Radiologic Studies
CBC with manual differential cell count
Chemistry tests (electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase)
Clotting studies (prothrombin time, partial thromboplastin time, fibrinogen, D-dimer)
Viral serologies (CMV, HSV-1, varicella-zoster)
RBC type and screen
HLA typing for potential allogeneic HCT
Bone marrow aspirate and biopsy (morphology, cytogenetics, flow cytometry, molecular studies for NPM1 and CEBPA mutations and FLT3-ITD)
Cryopreservation of viable leukemia cells
Myocardial function (echocardiogram or MUGA scan)
PA and lateral chest radiograph
Placement of central venous access device
Interventions for Specific Patients
Dental evaluation (for those with poor dentition)
Lumbar puncture (for those with symptoms of CNS involvement)
Screening spine MRI (for patients with back pain, lower extremity weakness, paresthesias)
Social work referral for patient and family psychosocial support
Counseling for All Patients
Provide patients with information regarding their disease and genetic risks, sperm banking or menstrual suppression, financial counseling, and support group contact

Abbreviations: AML, acute myeloid leukemia; BUN, blood urea nitrogen; CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; DIC, disseminated intravascular coagulation; HLA, human leukocyte antigen; HCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; IV, intravenous; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MUGA, multigated acquisition; PA, posteroanterior; RBC, red blood (cell) count.

POSTREMISSION THERAPY

Induction of a durable first CR (CR1) is critical to long-term survival in AML. However, without further therapy virtually all patients relapse. Thus, postremission therapy is designed to eradicate residual (typically undetectable) leukemic cells to prevent relapse and prolong survival. As for induction, the type of postremission therapy in AML is selected for each individual patient based on age, fitness, and cytogenetic/molecular risk.

The choice between consolidation with chemotherapy or transplantation is complex and based on age, risk, and practical considerations. In younger patients receiving chemotherapy, postremission therapy with intermediate/high-dose cytarabine for two to four cycles is standard practice. Higher doses of cytarabine during post remission therapy appear more effective than standard doses (as are used in induction), at least for those who do not have adverse-risk genetics. Recent studies suggest that the long-standing practice of high-dose cytarabine (3 g/m^2, every 12 h on days 1, 3, and 5) may not improve survival over intermediate-dose cytarabine (IDAC, 1-1.5 g/m^2) for such patients. Thus, the ELN has recommended IDAC at 1–1.5 g/m^2, every 12 h, on days 1–3, as the optimal postremission chemotherapy approach for favorable and intermediate-risk younger patients, for two to four cycles. While high-dose cytarabine may not be necessary, it is important to note that younger favorable-risk patients have worse outcomes when doses below $1g/m^2$ are used. In contrast to favorable-risk, intermediate- and adverse-risk patients should be considered for allogeneic HCT CR1 when feasible (see transplant discussion below). As older patients have increased toxicities with higher doses of cytarabine, ELN recommends relatively attenuated cytarabine doses (0.5–$1g/m^2$, every 12 h, on days 1–3) in favorable-risk older patients. There is no clear value for intensive postremission therapy in non–favorable-risk older patients; allogeneic HCT in CR1 (up to age 75 years) or investigational therapy is recommended. Indeed, postremission therapy is an appropriate setting for introduction of new agents in both older and younger patients (Table 100-6).

Allogeneic HCT is the best relapse-prevention strategy currently available for AML. Allogeneic HCT is probably best understood as an opportunity for immunotherapy; residual leukemia cells potentially elicit an immunologic response from donor immune cells, the so-called graft-versus-leukemia (GVL) effect. The benefit of GVL in relapse risk reduction, unfortunately, is offset somewhat by increased morbidity and mortality from complications of allogeneic HCT including graft-versus-host disease (GVHD). Given that relapsed AML is typically resistant to chemotherapy, allogeneic HCT in CR1 is a favored strategy. It is recommended in patients age <75 years who do not have favorable-risk disease and who have a human leukocyte antigen (HLA)–matched donor (related or unrelated). We recommend allogeneic HCT in CR1 for patients with intermediate-risk disease (Table 100-3). However, considerable debate exists regarding whether allogeneic HCT in CR1 is a requirement for younger patients with intermediate-risk AML, as one large series from the Medical Research Council reported that such patients have similar outcomes if transplanted only after relapse (and achievement of CR2), sparing some the long-term morbidity of transplantation. That said, allogeneic HCT is generally recommended as soon as possible after CR1 is achieved unless the patient is in a favorable-risk group. Selected adverse-risk patients without HLA-matched donors are considered for alternative donor transplants (e.g., HLA-mismatched unrelated, haploidentical related, and umbilical cord blood) even in CR1. Notably, more effective methods of in vivo T cell depletion (i.e., post-transplant cyclophosphamide following haploidentical transplantation) have broadened the availability of potential allogeneic HCT donors. Now, virtually any patient with a healthy parent or child (i.e., haploidentical) has an available donor suitable for allogeneic HCT if desired. Long-term outcomes with conventional chemotherapy for older patients are dismal; transplantation for such patients is expanding. For older patients, nonrandomized data demonstrate benefit for older patients in CR1 treated with reduced-intensity conditioning regimens and allogeneic HCT. Prospective data suggest that 40% of older patients in CR1 who are candidates for allogeneic HCT may be cured.

Trials comparing allogeneic HCT with intensive chemotherapy or autologous HCT have shown improved duration of remission with allogeneic HCT. However, the relapse risk reduction that is observed with allogeneic HCT is partially offset by the increase in fatal

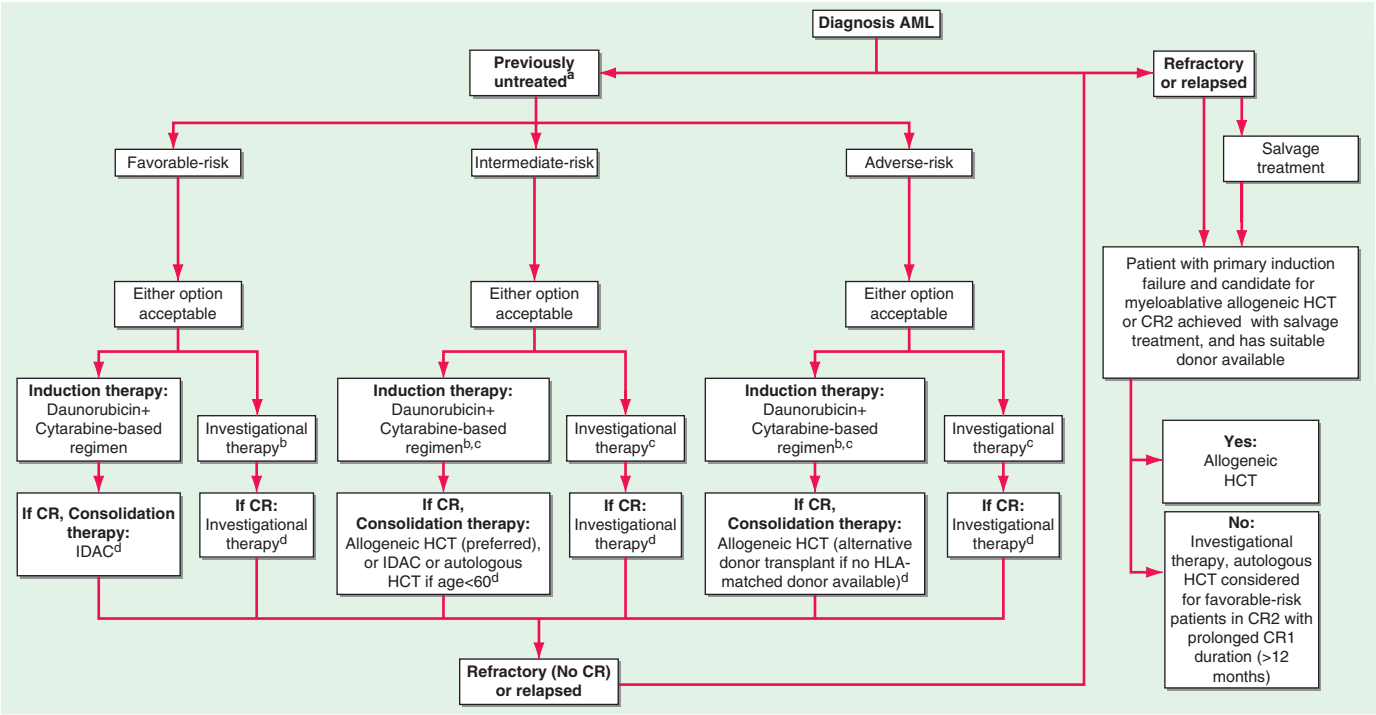

FIGURE 100-2 Flowchart for the therapy of newly diagnosed acute myeloid leukemia (AML). [a]Risk stratification according to the European LeukemiaNet (see Table 100-3). [b]Younger patients (<60–65 years) should routinely be offered investigational therapy on a backbone of standard chemotherapy for induction and consolidation. [c]Older patients, especially those >65 years or with adverse-risk disease, or those who are unfit for intensive daunorubicin + cytarabine regimens, may be considered for investigational therapy alone or in combination with lower intensity chemotherapy regimens (azacitidine, decitabine). [d]Investigational therapy as maintenance should be considered if available (after consolidation for younger patients and older patients with favorable-risk disease, and for all other older patients after induction).

For all forms of AML except acute promyelocytic leukemia (APL), standard induction therapy includes a regimen based on a 7-day continuous infusion of cytarabine (100–200 mg/m^2/d) and a 3-day course of daunorubicin (60–90 mg/m^2/d) with or without additional drugs. Idarubicin (12 mg/m^2/d) could be used in place of daunorubicin (not shown). The value of postremission/consolidation therapy for older patients (>60 years) who do not have favorable-risk disease is uncertain. Patients who achieve complete remission (CR) undergo postremission consolidation therapy, including sequential courses of intermediate-risk cytarabine, allogeneic HCT, autologous HCT, or novel therapies, based on their predicted risk of relapse (i.e., risk-stratified therapy). Patients with APL (see text for treatment) usually receive tretinoin and arsenic trioxide–based regimens with or without anthracycline-based chemotherapy and possibly maintenance with tretinoin. HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen; IDAC, intermediate dose cytarabine.

treatment-related toxicity (GVHD, organ toxicity). Despite this, there is no debate that patients with adverse-risk AML have improved long-term survival with early allogeneic HCT. Alternatively, high-dose chemotherapy with autologous HCT rescue is another post-remission approach in non-adverse risk subsets. Autologous HCT patients receive their own stem cells (collected during remission and cryopreserved), following administration of myeloablative chemotherapy. The toxicity is relatively low with autologous HCT (5% mortality rate), but the relapse rate is higher than with allogeneic HCT, due to the absence of the GVL effect. Favorable and intermediate-risk patients may benefit from autologous HCT more so than adverse-risk patients. Practically speaking, however, autologous HCT in AML patients is less frequently employed currently due to enhanced relapse risk reduction seen with allogeneic HCT and the growing use of HLA mismatched donors (in novel transplantation approaches).

Prognostic factors help to select the appropriate postremission therapy in patients in CR1. Our approach includes allogeneic HCT in first CR for patients without favorable cytogenetics or genotype (e.g., patients who do not have CEBPA biallelic mutations or NPM1 mutations without FLT3-ITD/with *FLT3*-ITD^{low}). Patients with adverse-risk disease should proceed to allogeneic HCT at CR1 if possible. The decision for allogeneic HCT for younger intermediate-risk patients is complex and individualized as described above; we recommend it when an HLA-matched donor is available. Subsets of patients may benefit from targeted therapy given during remission; emerging data demonstrate survival benefit from incorporation of the FLT3 inhibitor midostaurin, for example, into induction and postremission therapies for patients with *FLT3* mutated AML. On April 28, 2017, the U.S. Food and Drug Administration (FDA) approved midostaurin (RYDAPT, Novartis Pharmaceuticals Corp.) for the treatment of adult patients with newly diagnosed AML who are *FLT3* mutation-positive (either ITD or TKD+), in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Allogeneic transplantation in CR1 is still recommended for these patients.

For patients in morphologic CR, measurement of MRD remains a very important and challenging research area. Cytogenetics are a mainstay of disease assessment, and persistence of abnormal karyotype (in spite of morphologic CR) is clearly associated with poor clinical outcomes. Immunophenotyping to detect minute populations of blasts or sensitive molecular assays (e.g., reverse transcriptase polymerase chain reaction [RT-PCR]) to detect AML-associated molecular abnormalities (e.g., NPM1 mutation, the CBF AML RUNX1/RUNX1T1 and CBFB/MYH11 transcripts, the APL PML/RARA transcript) can be performed to assess whether MRD is present at sequential time points during or after treatment. Whether emerging next-generation sequencing or serial quantitative assessment using flow or RT-PCR, performed during remission, can effectively direct successful subsequent therapy and improve clinical outcome remains to be determined. Currently, no consensus exists for the optimal MRD measurement technique, or its application. Data suggest that MRD measurement can in some settings be a reliable discriminator between patients who will continue in CR or relapse, but whether subsequent therapy (i.e., allogeneic HCT or additional chemotherapy) can effectively eradicate disease in such patients is not yet clear. In the subset of patients with APL, serial RT-PCR (for the *PML/RARA* transcript) is a very useful and reliable tool to detect

TABLE 100-6 Novel Therapies in Clinical Development in Acute Myeloid Leukemia

Protein kinase inhibitors	• FLT3 inhibitors (midostaurin, quizartinib, gilteritinib, crenolanib, sorafenib) • KIT inhibitors • PI3K/AKT/mTOR inhibitors • Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CHK1, WEE1, and MPS1 inhibitors • SRC and HCK inhibitors • Syk inhibitors
Epigenetic modulators	• New DNA methyltransferase inhibitors (SGI-110) • Histone deacetylase (HDAC) inhibitors • IDH1 and IDH2 inhibitors • DOT1L inhibitors • BET-bromodomain inhibitors
Chemotherapeutic agents	• CPX-351 (especially in secondary AML) • Vosaroxin • Nucleoside analogues
Mitochondrial inhibitors	• Bcl-2, Bcl-xL, and Mcl-1 inhibitors • Caseinolytic protease inhibitors
Therapies targeting oncogenic proteins	• Fusion transcripts targeting • EVI1 targeting • NPM1 targeting • Hedgehog inhibitors (glasdegib)
Antibodies and immunotherapies	• Monoclonal antibodies against CD33, CD44, CD47, CD123, CLEC12A • Immunoconjugates (e.g., gemtuzumab ozogamicin, SGN33A) • Bispecific T-cell engagers (BiTEs) and dual affinity re-targeting molecules (DARTs) • Chimeric antigen-receptor (CAR) T cells or genetically engineered T-cell receptor (TCR) T cells • Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4) • Anti-KIR antibody (lirilumab) • Vaccines (e.g., WT1)
Therapies targeting AML environment	• CXCR4 and CXCL12 antagonists • Anti-angiogenic therapies

Source: Adapted from Döhner H et al: Diagnosis and management of acute myeloid leukemia in adults: 2017 recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 129:424, 2017.

early relapse and direct initiation of reinduction therapy prior to onset of overt relapse.

SUPPORTIVE CARE

Measures geared to supporting patients through several weeks of neutropenia and thrombocytopenia are critical to successful AML therapy. Patients with AML should be treated in centers expert in providing supportive care. Multilumen central venous catheters should be inserted as soon as newly diagnosed AML patients have been stabilized. They should be used thereafter for administration of intravenous medications/chemotherapy and transfusions, as well as for blood drawing instead of venipuncture.

Adequate and prompt blood bank support is critical to therapy of AML. Platelet transfusions should be given as needed to maintain a platelet count ≥10,000/μL. The platelet count should be kept at higher levels in febrile patients and during episodes of active bleeding or DIC. Patients with poor posttransfusion platelet count increments may benefit from administration of platelets from HLA-matched donors. RBC transfusions should be administered to keep the hemoglobin level >70–80 g/L (7–8 g/dL) in the absence of active bleeding, DIC, or congestive heart failure, which require higher hemoglobin levels. Blood products leukodepleted by filtration should be used to avert or delay alloimmunization as well as febrile reactions. Blood products may also be irradiated to prevent transfusion-associated GVHD. Cytomegalovirus (CMV)–negative blood products should be used for CMV-seronegative patients who are potential candidates for allogeneic HCT; fortunately white blood cell filtration is quite effective at reducing CMV exposure as well.

Neutropenia (neutrophils <500/μL or <1000/μL and predicted to decline to <500/μL over the next 48 h) can be part of the initial presentation and/or a side effect of the chemotherapy treatment in AML patients. Thus, infectious complications remain the major cause of morbidity and death during induction and postremission chemotherapy for AML. Antibacterial (i.e., quinolones) and antifungal (i.e., posaconazole) prophylaxis, especially in conjunction with regimens that cause mucositis, is beneficial. For patients who are herpes simplex virus or varicella-zoster seropositive, antiviral prophylaxis should be initiated (e.g., acyclovir, valacyclovir).

Fever develops in most patients with AML, but infections are documented in only half of febrile patients. Early initiation of empirical broad-spectrum antibacterial and antifungal antibiotics has significantly reduced the number of patients dying of infectious complications **(Chap. 70)**. An antibiotic regimen adequate to treat gram-negative organisms should be instituted at the onset of fever in a neutropenic patient after clinical evaluation, including a detailed physical examination with inspection of the indwelling catheter exit site and a perirectal examination (for perirectal abscess), as well as procurement of cultures and radiographs aimed at documenting the source of fever. Specific antibiotic regimens should be based on institutional antibiotic sensitivity data obtained from where the patient is being treated. Acceptable regimens for empiric antibiotic therapy include monotherapy with imipenem-cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime). The combination of an aminoglycoside with an antipseudomonal penicillin (e.g., piperacillin) or an aminoglycoside in combination with an extended-spectrum antipseudomonal cephalosporin should be considered in complicated or resistant cases. Aminoglycosides should be avoided, if possible, in patients with renal insufficiency. Empirical vancomycin should be added in neutropenic patients with catheter-related infections, blood cultures positive for gram-positive bacteria before final identification and susceptibility testing, hypotension or shock, or known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*. In special situations where decreased susceptibility to vancomycin, vancomycin-resistant organisms, or vancomycin toxicity is documented, other options including linezolid, daptomycin, and quinupristin/dalfopristin need to be considered.

Caspofungin (or a similar echinocandin), voriconazole, isavuconazonium, or liposomal amphotericin B should be considered for antifungal treatment if fever persists for 4–7 days following initiation of empiric antibiotic therapy. Amphotericin B has long been used for antifungal therapy. Although liposomal formulations have improved the toxicity profile of this agent, its use has been limited to situations with high risk of or documented mold infections. Caspofungin has been approved for empiric antifungal treatment. Voriconazole has also been shown to be equivalent in efficacy and less toxic than amphotericin B; isavuconazonium may also be effective with fewer drug-drug interactions. Antibacterial and antifungal antibiotics should be continued until patients are no longer neutropenic, regardless of whether a specific source has been found for the fever. Unfortunately, this practice likely contributes to development of resistance and increased incidence of nosocomial infections such as *Clostridium difficile* colitis, so great care should be taken preferably in hospital-wide antibiotic surveillance and isolation strategies to reduce these complications. Recombinant hematopoietic growth factors have a limited role in AML; myeloid growth factors may be useful in the postremission setting but are not recommended in induction or for "palliative" care for patients not in remission.

TREATMENT FOR REFRACTORY OR RELAPSED AML

In patients who relapse after achieving CR, the length of first CR is predictive of response to salvage chemotherapy treatment; patients with longer first CR (>12 months) generally relapse with

drug-sensitive disease and have a higher chance of attaining a CR, even with the same chemotherapeutic agents used for first remission induction. Whether initial CR was achieved with one or two courses of chemotherapy and the type of postremission therapy may also predict achievement of second CR. Similar to patients with refractory disease, patients with relapsed disease are rarely cured by salvage chemotherapy treatments. Therefore, patients who eventually achieve a second CR and are eligible for allogeneic HCT should be transplanted. However, there is no consensus on optimal treatment for patients who relapse after allogeneic HCT; outcomes in this setting are very poor.

Because achievement of a second CR with routine salvage therapies is relatively uncommon, especially in patients who relapse rapidly after achievement of first CR (<12 months), these patients and those lacking HLA-compatible donors or who are not candidates for allogeneic HCT should be considered for innovative approaches on clinical trials. Many new agents are in current testing (Table 100-6). The discovery of novel gene mutations and mechanisms of leukemogenesis that might represent actionable therapeutic targets has prompted the development of many new targeting agents. In addition to kinase inhibitors for *FLT3*-mutated AML, other compounds targeting the aberrant activity of mutant proteins (e.g., IDH1/2 inhibitors) and numerous other biologic mechanisms are being tested in clinical trials. Furthermore, approaches with antibodies targeting markers commonly expressed on leukemia blasts (e.g., CD33) or leukemia-initiating cells (e.g., CD123) are also under investigation. Once these compounds have demonstrated safety and activity as single agents, investigation of combinations with other molecular targeting compounds and/or chemotherapy should be pursued.

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

APL is a highly curable AML subtype, and ~85% of these patients achieve long-term survival with current approaches. APL has long been shown to be responsive to cytarabine and daunorubicin, but in the past patients who were treated with these drugs alone frequently died from DIC induced by the release of granule components by the chemotherapy-treated leukemia cells. However, the prognosis of APL patients has changed dramatically with the introduction of tretinoin (ATRA), an oral drug that induces the differentiation of leukemic cells bearing the t(15;17), where disruption of the *RARA* gene encoding a retinoid acid receptor occurs. ATRA decreases the frequency of DIC but often produces another complication called the APL (differentiation) syndrome. Occurring within the first 3 weeks of treatment, it is characterized by fever, fluid retention, dyspnea, chest pain, pulmonary infiltrates, pleural and pericardial effusions, and hypoxemia. The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium. Glucocorticoids, chemotherapy, and/or supportive measures can be effective for management of the APL syndrome. Temporary discontinuation of ATRA is necessary in cases of severe APL syndrome (i.e., patients developing renal failure or requiring admission to the intensive care unit due to respiratory distress). The mortality rate of this syndrome is ~10%. APL syndrome may also occur, less commonly, with ATO in APL.

In low-risk APL (low leukocyte count at presentation), ATRA (45 mg/m^2/d) plus ATO (0.15 mg/kg/d) was recently compared to ATRA plus concurrent idarubicin chemotherapy. ATRA/ATO was superior and is the new standard of care for such patients. CR rates in low-risk disease approach 100%, with excellent long-term survival. Notably, patients with high-risk APL (high leukocyte count) must be uniquely treated, as they require immediate cytoreduction with chemotherapy due to life-threatening APL syndrome often with rapidly rising leukocyte count after initiation of ATRA. High-risk patients are at increased risk for induction death due to this syndrome as well as increased frequency of hemorrhagic complications (related to DIC).

Assessment of residual disease by RT-PCR amplification of the t(15;17) chimeric gene product PML-RARA following the final cycle of treatment is important. Disappearance of the signal is associated with long-term disease-free survival; its persistence or reemergence invariably predicts relapse. Sequential monitoring of RT-PCR for PML-RARA is now considered standard for postremission monitoring of APL, at least in high-risk patients.

Patients in molecular, cytogenetic, or clinical relapse should be salvaged with ATO with or without ATRA; in patients who were treated with ATRA plus chemotherapy in the frontline setting, ATO-based therapy at relapse produces meaningful responses in up to 85% of patients. Though experience with relapsed APL in patients who received ATO during initial induction is limited (given that few relapses occur in low-risk patients, and widespread use of ATO during first-line therapy is relatively new), ATO remains the preferred reinduction therapy for patients who relapse. Achievement of CR2 should be followed by consolidation with autologous HCT (for patients who achieve RT-PCR negative status). In the minority who do not achieve negative RT-PCR or who relapse again, allogeneic HCT may still be potentially curative.

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101 Chronic Myeloid Leukemia

Hagop Kantarjian, Jorge Cortes

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder. The disease is driven by the *BCR-ABL1* chimeric gene product, that codes for a constitutively active tyrosine kinase, resulting from a reciprocal balanced translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34.1;q11.2), known as the Philadelphia chromosome (Ph) **(Fig. 101-1)**. Untreated, the course of CML is typically biphasic or triphasic, with an early indolent or chronic phase, followed often by an accelerated phase and a terminal blastic phase. Before the era of selective BCR-ABL1 tyrosine kinase inhibitors (TKIs),

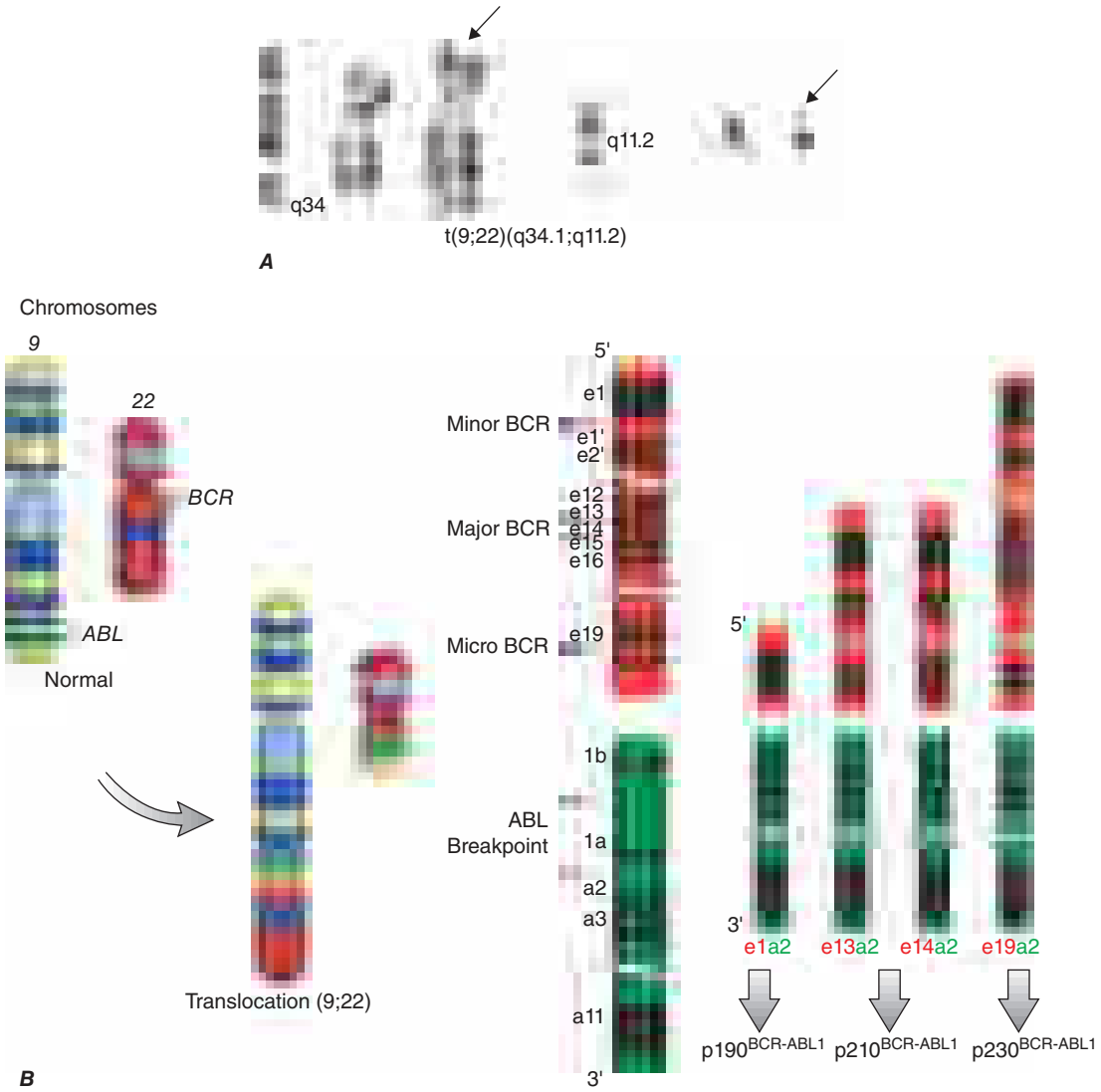

FIGURE 101-1 ***A.*** The Philadelphia (Ph) chromosome cytogenetic abnormality. ***B.*** Breakpoints in the long arms of chromosome 9 (*ABL* locus) and chromosome 22 (*BCR* regions) result in at least three different BCR-ABL1 oncoprotein messages, $p210^{BCR\text{-}ABL1}$ (most common message in chronic myeloid leukemia [CML]), $p190^{BCR\text{-}ABL1}$ (present in two-thirds of patients with Ph-positive acute lymphocytic leukemia; rare in CML), and $p230^{BCR\text{-}ABL1}$ (rare in CML and associated with an indolent course). Other rearrangements (e.g., b14a3) are less common. *(© 2013 The University of Texas MD Anderson Cancer Center.)*

the median survival in CML was 3–7 years, and the 10-year survival rate was 30% or less. Introduced into standard CML therapy in 2000, TKIs have revolutionized the treatment, natural history, and prognosis of CML. Today, the estimated 10-year survival rate with imatinib mesylate, the first BCR-ABL1 TKI approved, is 85%. Allogeneic stem cell transplantation (SCT), a curative approach but one that involves more risks, is now more often offered as second- or third-line therapy after failure of TKIs.

INCIDENCE AND EPIDEMIOLOGY

CML accounts for ~15% of all cases of leukemia. There is a slight male preponderance (male:female ratio 1.6:1). The median age at diagnosis is 55–65 years. It is uncommon in children; only 3% of patients with CML are younger than 20 years although in recent years a higher proportion of young patients seem to be diagnosed. CML incidence increases slowly with age, with a steeper increase after the age of 40–50 years. The annual incidence of CML is 1.5 cases per 100,000 individuals. In the United States this translates into about 8000 new cases per year. The incidence of CML has not changed over several decades. By extrapolation, the worldwide annual incidence of CML is about 100,000–120,000 cases. With a median survival of 6 years before 2000, the disease prevalence in the United States was 25,000–30,000 cases. With TKI therapy, the annual mortality has been reduced from 10–20% to about 2%. Therefore, the prevalence of CML in the United States is expected to continue to increase (approximately 100,000 in 2016). The worldwide prevalence will depend on the treatment penetration of TKIs and their effect on reduction of worldwide annual mortality. Ideally, with full TKI treatment penetration, the worldwide prevalence should plateau at 35 times the incidence, or around 3–4 million patients.

ETIOLOGY

There are no familial associations in CML. The risk of developing CML is not increased in monozygotic twins or in relatives of patients. No etiologic agents are incriminated, and no associations exist with exposures to benzene or other toxins, fertilizers, insecticides, or viruses. CML is not a frequent secondary leukemia following therapy of other cancers with alkylating agents and/or radiation. Exposure to ionizing radiation (e.g., nuclear accidents, radiation treatment for ankylosing spondylitis or cervical cancer) has increased the risk of CML, which peaks at 5–10 years after exposure and is dose-related. The median time to development of CML among atomic bomb survivors was 6.3 years. Following the Chernobyl accident, the incidence of CML did not increase, suggesting that larger dose exposures of radiation are required to cause CML. Because of adequate protection, the risk of CML is not increased in individuals working in the nuclear industry or among radiologists in recent times.

PATHOPHYSIOLOGY

The t(9;22)(q34.1;q11.2) is present in >90% of classical CML cases. It results from a balanced reciprocal translocation between the long arms of chromosomes 9 and 22. It is present in hematopoietic cells (myeloid, erythroid, megakaryocytes, and monocytes; less often mature B lymphocytes; rarely mature T lymphocytes, but not stromal cells), but not in other cells in the human body. As a result of the translocation, DNA sequences from the cellular oncogene *ABL1* are translocated next to the major breakpoint cluster region (*BCR*) gene on chromosome 22, generating a hybrid oncogene, *BCR-ABL1*. This fusion gene typically encodes for a novel oncoprotein of molecular weight 210 kDa, referred to as $p210^{BCR\text{-}ABL1}$ (Fig. 101-1*B*). This BCR-ABL1 oncoprotein exhibits constitutive kinase activity that leads to excessive proliferation and reduced apoptosis of CML cells, endowing them with a growth advantage over their normal counterparts. Over time, normal hematopoiesis is suppressed, but normal stem cells can persist and reemerge following effective therapy, for example with TKIs. In most instances of Ph-positive acute lymphoblastic leukemia (ALL) and in rare cases of CML, the breakpoint in *BCR* is more centromeric, in a region called the minor *BCR* region (*mBCR*). As a result, a shorter sequence of *BCR* is fused to *ABL1*, with a consequent smaller BCR-ABL1 oncoprotein, $p190^{BCR\text{-}ABL1}$. When occurring in Ph-positive CML, this translocation may predict for a worse outcome. A third rarer breakpoint in *BCR* occurs telomeric to the major *BCR* region and is called *micro-BCR* (μ-BCR). It juxtaposes a larger fragment of the *BCR* gene to *ABL1* and produces a larger $p230^{BCR\text{-}ABL1}$ oncoprotein, which is associated with a more indolent CML course. Other rearrangements, such as b14a3, occur much less frequently.

The constitutive activation of *BCR-ABL1* results in autophosphorylation and activation of multiple downstream pathways that affect gene transcription, apoptosis, stromal adherence, skeletal organization, and degradation of inhibitory proteins. These transduction pathways may involve RAS, mitogen-activated protein (MAP) kinases, signal transducers and activators of transcription (STAT), phosphatidylinositol-3-kinase (PI3k), MYC, and others. These interactions are mostly mediated through tyrosine phosphorylation and require binding of BCR-ABL1 to adapter proteins such as GRB-2, CRK, CRK-like (CRK-L) protein, and Src homology containing proteins (SHC). Most BCR-ABL1 TKIs bind to the *BCR-ABL1* ATP-binding domain, preventing the activation of transformation pathways and inhibiting downstream signaling. As a result, proliferation of CML cells is inhibited and apoptosis induced, allowing the reemergence of normal hematopoiesis. A plethora of signaling pathways have been implicated in BCR-ABL1-mediated cellular transformation. The emerging picture is a complex and redundant transformation network. An additional layer of complexity is related to differences in signal transduction between CML-differentiated cells and early progenitors. Beta-catenin, Wnt1, Foxo3a, transforming growth factor β, interleukin-6, PP2A, SIRT1, and others have been implicated in CML stem cell survival.

Experimental models have established the causal relationship between the *BCR-ABL1* rearrangement and the development of CML. In animal models, expression of *BCR-ABL1* in normal hematopoietic cells produced CML-like disorders or lymphoid leukemia, demonstrating the leukemogenic potential of *BCR-ABL1* as a single oncogenic abnormality. Other models however suggest the need for a "second hit."

The cause of the *BCR-ABL1* molecular rearrangement is unknown. Molecular techniques that detect *BCR-ABL1* at a level of 1 in 10^8 identify this molecular abnormality in the blood of up to 25% of normal adults and 5% of infants, but 0% of cord blood samples. This suggests that *BCR-ABL1* is not sufficient to cause overt CML in the overwhelming majority of individuals in whom it occurs. Because CML develops in only 1.5 of 100,000 individuals annually, it is evident that additional molecular events or poor immune recognition of the rearranged cells are needed to cause overt CML.

CML is defined by the presence of *BCR-ABL1* fusion gene in a patient with a myeloproliferative neoplasm. In some patients with a typical morphologic picture of CML, the Ph chromosome is not detectable by standard G-banding karyotype, but fluorescence in situ hybridization (FISH) and/or molecular studies (polymerase chain reaction [PCR]) detect *BCR-ABL1*. These patients have a course similar to Ph-positive CML and respond to TKI therapy. Many of the remaining patients have atypical morphologic or clinical features and belong to other diagnostic groups, such as atypical CML, chronic myelomonocytic leukemia, and myelodysplastic-myeloproliferative neoplasms (MDS-MPN). These individuals do not respond to TKI therapy and have a poor prognosis with a median survival of about 2–3 years. Detection of mutations in the granulocyte colony-stimulating factor receptor (*CSF3R*) in chronic neutrophilic leukemia (90% of cases) and in some cases of atypical CML, of mutations in *SETBP1* in atypical CML (25% of cases), and of mutations in *SF3B1* in MDS-MPN with ringed sideroblasts and marked thrombocytosis (MDS-MPD-RST; 50–70% of cases, associated with longer median survival of 7 years vs 3.3 years with wild-type *SF3B1*), confirmed that they are distinct molecular and biologic entities.

The events associated with the transition of CML from a chronic to accelerated-blastic phase are poorly understood. They are often associated with characteristic chromosomal abnormalities such as a double Ph, trisomy 8, isochromosome 17 or deletion of 17p (loss of *TP53*), 20q–, and others. Molecular events associated with transformation include mutations in *TP53*, retinoblastoma 1 (*RB1*), myeloid transcriptions factors like *RUNX1*, and cell cycle regulators like *p16*. A plethora of other mutations or functional abnormalities have been implicated in blastic transformation, but no unifying theme has emerged other than the fact that *BCR-ABL1* itself induces genetic instability that favors the acquisition of additional molecular events and eventually to blastic transformation. In this frame of thinking, one critical effect of TKIs is their ability to stabilize the CML genome, leading to a much reduced transformation rate. In particular, the previously observed sudden blastic transformations (i.e., abrupt transformation to blastic phase in a patient who had been in cytogenetic response) have become uncommon, occurring rarely in younger patients in the first 1–2 years of TKI therapy (usually sudden lymphoid blastic transformations). Sudden transformations beyond the third year of TKI therapy are rare in patients who continue on TKI therapy. Moreover, initial experience suggests that the course of CML has become significantly more indolent, even without cytogenetic responses, in patients on TKI-based therapy compared to previous experience with hydroxyurea/busulfan.

Among patients developing resistance to TKIs, several resistance mechanisms have been observed. The most clinically relevant one is the development of different *ABL1* kinase domain mutations that may prevent the binding of TKIs to the catalytic site (ATP-binding site) of the kinase or maintain the kinase activity despite the presence of a TKI. More than 100 *BCR-ABL1* mutations have now been described, many of which confer relative or absolute resistance to imatinib. This has resulted in the development of second-generation TKIs (i.e., dasatinib, nilotinib, bosutinib) and of a third-generation TKI (ponatinib) with significant efficacy against T315I, a "gatekeeper" mutation that prevents binding of and causes resistance to all other TKIs.

CLINICAL PRESENTATION

The presenting signs and symptoms in CML depend on the availability of and access to health care, including physical examinations and screening tests. In the United States, because of the wider access to health care screening and physical examinations, 50–60% of patients are diagnosed on routine blood tests and have minimal symptoms at presentation, such as fatigue. In geographic locations where access to health care is more limited, patients often present with high CML burden including splenomegaly, anemia, and related symptoms (abdominal pain, weight loss, fatigue), which translate into a higher frequency of high-risk CML. Presenting findings in patients diagnosed in the United States are shown in **Table 101-1**.

Symptoms Most patients with CML (90%) present in the indolent or chronic phase. Depending on the timing of diagnosis, patients are often asymptomatic (if the diagnosis is discovered during health care screening tests). Common symptoms, when present, are manifestations of anemia and splenomegaly. These may include fatigue, malaise, weight loss (if high leukemia burden), or early satiety and left upper quadrant pain or masses (from splenomegaly). Less common presenting findings

TABLE 101-1 Presenting Signs and Symptoms of Newly Diagnosed Philadelphia Chromosome–Positive Chronic Myeloid Leukemia in Chronic Phase

PARAMETER	PERCENTAGE
Age ≥60 years (median)	40–50 (55–65)
Female gender	35–45
Splenomegaly	30
Hepatomegaly	5–10
Lymphadenopathy	5
Other extramedullary disease	2
Hemoglobin <10 g/dL	10–15
Platelets	
>450 × 10^9 cells/L	30–35
<100 × 10^9 cells/L	3–5
White blood cells ≥50 × 10^9 cells/L	35–40
Marrow	
≥5% blasts	5
≥5% basophils	10–15
Peripheral blood	
≥3% blasts	8–10
≥7% basophils	10
Cytogenetic clonal evolution other than the Philadelphia chromosome	4–5
Sokal risk	
Low	60–65
Intermediate	25–30
High	10

include thrombotic or hyperviscosity-related events (from severe leukocytosis or thrombocytosis). These include priapism, cardiovascular complications, myocardial infarction, venous thrombosis, visual disturbances, dyspnea and pulmonary insufficiency, drowsiness, loss of coordination, confusion, or cerebrovascular accidents. Manifestations of bleeding diatheses include retinal hemorrhages, gastrointestinal bleeding, and others. Patients who present with, or progress to, the accelerated or blastic phases frequently have additional symptoms including unexplained fever, significant weight loss, severe fatigue, bone and joint pain, bleeding and thrombotic events, and infections.

Physical Findings Splenomegaly is the most common physical finding, occurring in 20–70% of patients depending on health care screening frequency. Other less common findings include hepatomegaly (5–10%), lymphadenopathy (5–10%), and extramedullary disease (skin or subcutaneous lesions). The latter indicates CML transformation if a biopsy confirms predominance of blasts. Other physical findings are manifestations of complications of high tumor burden described earlier (e.g., cardiovascular, cerebrovascular, bleeding). High basophil counts may be associated with histamine overproduction causing pruritus, diarrhea, flushing, and even gastrointestinal ulcers.

Hematologic and Marrow Findings In untreated CML, leukocytosis ranging from 10–500 × 10^9/L is common. The peripheral blood differential shows left-shifted hematopoiesis with predominance of neutrophils and the presence of bands, myelocytes, metamyelocytes, promyelocytes, and blasts (usually ≤5%). Basophils and/or eosinophils are frequently increased. Thrombocytosis is common, but thrombocytopenia is rare and, when present, suggests a worse prognosis, disease acceleration, or an unrelated etiology. Anemia is present in one-third of patients. Cyclic oscillations of counts are noted in 10–20% of patients without treatment. Biochemical abnormalities include a low leukocyte alkaline phosphatase score and high levels of vitamin B_{12}, uric acid, lactic dehydrogenase, and lysozyme. The presence of unexplained and sustained leukocytosis, with or without splenomegaly, should lead to a marrow examination and cytogenetic analysis.

The bone marrow is hypercellular with marked myeloid hyperplasia and a high myeloid-to-erythroid ratio of 15–20:1. Marrow blasts are 5% or less; when higher, they carry a worse prognosis or represent transformation to accelerated phase (if they are ≥15%). Increased reticulin fibrosis (by Snook's silver stain) is common, with 30–40% of patients demonstrating grade 3–4 reticulin fibrosis. This was considered adverse in the pre-TKI era. With TKI therapy, reticulin fibrosis resolves in most patients and is not an indicator of poor prognosis. Collagen fibrosis (Wright-Giemsa stain) is rare at diagnosis. Disease progression with a "spent phase" of myelofibrosis (myelophthisis, or burnt-out marrow) was common with busulfan therapy (20–30%) but is rare with TKI therapy.

Cytogenetic and Molecular Findings The diagnosis of CML is straightforward and depends on documenting the t(9;22)(q34.1;q11.2), which is identified by G-banding in 90% of cases. This is known as the Philadelphia chromosome (initially identified in Philadelphia as a minute chromosome), later identified to be chromosome 22 (Fig. 101-1). Some patients may have complex translocations (variant Ph) involving three or more chromosomes including chromosomes 9 and 22 and one or more additional chromosomes. Others may have a "masked Ph," involving translocations between chromosome 9 and a chromosome other than 22 (but molecularly showing the *BCR-ABL1* rearrangement). The prognosis of these patients and their response to TKI therapy are similar to those in patients with Ph. About 5–10% of patients may have additional chromosomal abnormalities in the Ph-positive cells. These usually involve trisomy 8, a double Ph, isochromosome 17 or 17p deletion, 20q–, or others. This is referred to as cytogenetic clonal evolution and was historically a sign of adverse prognosis, particularly when trisomy 8, double Ph, or chromosome 17 abnormalities were noted. A less common abnormality involving chromosome 3q26.2 also carries a poor prognosis.

Techniques such as FISH and PCR are now used to aid in the diagnosis of CML. They are more sensitive approaches to estimate the CML burden in patients on TKI therapy. They can be done on peripheral blood, and thus are more convenient to patients. Patients with CML at diagnosis should have a FISH analysis to quantify the percentage of Ph-positive cells, if FISH is used to replace marrow cytogenetic analysis in monitoring response to therapy. FISH will not detect additional chromosomal abnormalities (clonal evolution); thus, a cytogenetic analysis is usually recommended at the time of diagnosis. The *BCR-ABL1* rearrangement is usually one of two variants: e13a2 (formerly b2a2) and e14a2 (formerly b3a2). About 2–5% of patients may have other RNA fusion types (e.g., e1a2, e13a3, or e14a3). In these patients, the routine real-time PCR primers may not amplify the *BCR-ABL1* transcripts, thus leading to false-negative results. Therefore, molecular studies at diagnosis are important to document the type and presence of *BCR-ABL1* transcripts to avoid erroneously "undetectable" *BCR-ABL1* transcripts on follow-up studies, with the false impression of a complete molecular response. The presence of the Philadelphia chromosome with "negative" PCR with standard methodology should prompt investigation of atypical transcripts.

Both FISH and PCR studies can be falsely positive at low levels or falsely negative because of technical issues. Therefore, a diagnosis of CML must always rely on a marrow analysis with routine cytogenetics. The diagnostic bone marrow confirms the presence of the Ph chromosome, detects clonal evolution, that is, chromosomal abnormalities in the Ph-positive cells (which may be prognostic), and also quantifies the percentage of marrow blasts and basophils. In 10% of patients, the percentage of marrow blasts and basophils can be significantly higher than in the peripheral blood, conferring poorer prognosis or even representing disease transformation.

Monitoring patients on TKI therapy by cytogenetics, FISH, and molecular studies has become an important standard practice to assess response to therapy, emphasize compliance, evaluate possible treatment resistance, identify the need to change TKI therapy, and determine the need to assess for kinase domain mutations. It is thus important to recognize the comparability of these measures in monitoring response. A partial cytogenetic response is defined as the presence of 35% or less Ph-positive metaphases by routine cytogenetic analysis. This is roughly equivalent to *BCR-ABL1* transcripts by the

International Scale (IS) of 10% or less. A complete cytogenetic response refers to the absence of Ph-positive metaphases (0% Ph positivity). This is approximately equivalent to *BCR-ABL1* transcripts (IS) of 1% or less. A major molecular response refers to *BCR-ABL1* transcripts (IS) ≤0.1%, or roughly a 3-log or greater reduction of *BCR-ABL1* transcripts from a standardized basline. A molecular response MR4.5 refers to *BCR-ABL1* transcripts (IS) ≤0.0032%, roughly equivalent to a 4.5-log reduction or greater of transcripts.

Findings in CML Transformation Progression of CML is usually associated with leukocytosis resistant to therapy, increasing anemia, fever and constitutional symptoms, and increased blasts and basophils in the peripheral blood or marrow. Criteria of accelerated-phase CML, historically associated with median survival of <1.5 years, include the presence of 15% or more peripheral blasts, 30% or more peripheral blasts plus promyelocytes, 20% or more peripheral basophils, cytogenetic clonal evolution (presence of chromosomal abnormalities in addition to Ph), and thrombocytopenia <100 × 10^9/L (unrelated to therapy). About 5–10% of patients present with de novo accelerated phase or blastic phase. The prognosis of de novo accelerated phase with TKI therapy has improved significantly, with an estimated 8-year survival rate of 75%. The median survival of accelerated phase evolving from chronic phase has also improved from a historical median survival of 18 months to an estimated 4-year survival rate of 70% on TKI therapy. Therefore, the criteria for accelerated-phase CML should be revisited because most clinical criteria defining accelerated phase have lost much of their prognostic significance. Blastic-phase CML is defined by the presence of 30% or more peripheral or marrow blasts or the presence of sheets of blasts in extramedullary disease (usually skin, soft tissues, or lytic bone lesions). Blastic-phase CML is commonly myeloid (60%) but can present uncommonly as erythroid, promyelocytic, monocytic, or megakaryocytic. Lymphoid blastic phase occurs in about 25% of patients. Lymphoblasts are terminal deoxynucleotide transferase positive and peroxidase negative (although occasionally with low positivity up to 3–5%) and express lymphoid markers (CD10, CD19, CD20, CD22). However, they also often express myeloid markers (50–80%), resulting in diagnostic challenges. This is important because, unlike other morphologic blastic phases, lymphoid blastic-phase CML is quite responsive to anti-ALL-type chemotherapy (e.g., hyper-CVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone]) in combination with TKIs (complete response rates 60–70%; median survival 2–3 years).

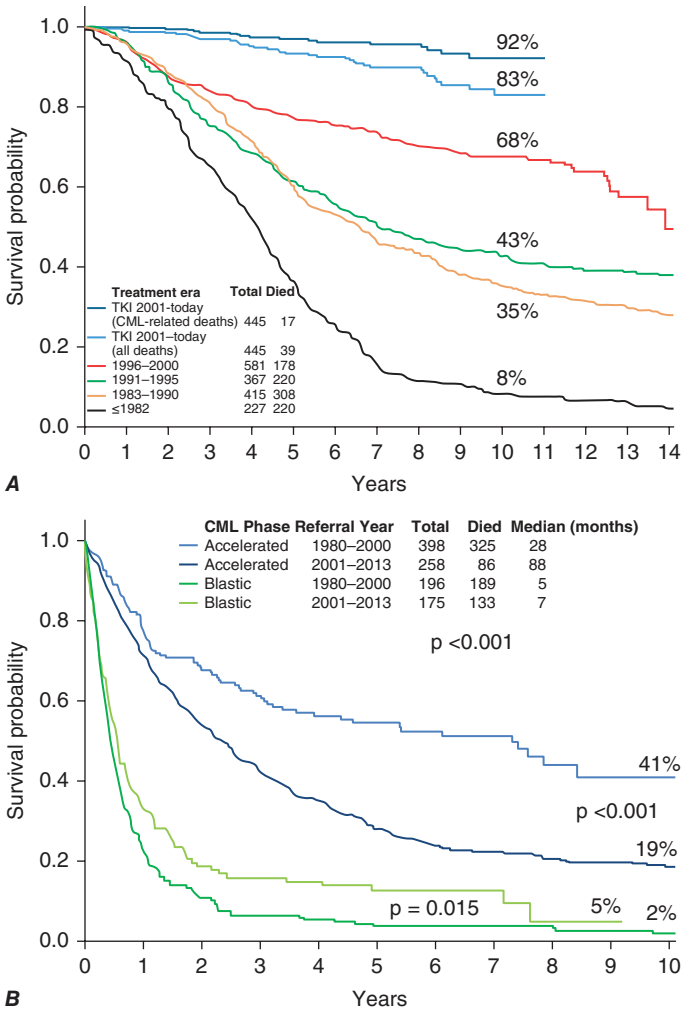

FIGURE 101-2 ***A.*** Survival in newly diagnosed chronic-phase chronic myeloid leukemia (CML) by era of therapy (MD Anderson Cancer Center experience from 1965 to present). Causes of non-CML deaths in 22 patients were other cancers (n = 7), postsurgical complications (n = 3), car accident (n = 2), suicide (n = 1), neurologic events (n = 3), cardiac (n = 3), pneumonia (n = 1), and unknown (n = 2). ***B.*** Survival in patients with accelerated- and blastic-phase CML referred to MD Anderson Cancer Center by era of therapy, demonstrating the significant survival benefit in the tyrosine kinase inhibitor (TKI) era in accelerated-phase CML but the modest benefit in blastic-phase CML. Referred cases included de novo and post-chronic-phase transformations.

PROGNOSIS AND CML COURSE

Before the imatinib era, the annual mortality in CML was 10% in the first 2 years and 15–20% thereafter. The median survival time in CML was 3–7 years (with hydroxyurea-busulfan and interferon α). Without a curative option of allogeneic SCT, the course of CML was toward transformation to, and death from, accelerated or blastic phases for most patients as the rate of complete cytogenetic response with interferon was low. Even apparent disease stability was unpredictable, with some patients demonstrating sudden transformation to a blastic phase. With imatinib therapy, the annual mortality in CML has decreased to 2% in the first 16 years of observation. More than half of the deaths are from factors other than CML, such as aging-related comorbidities, accidents, suicides, other cancers, and other medical conditions (e.g., infections, surgical procedures). The estimated 10-year survival rate is 85%, or 93% if only CML-related deaths are considered **(Fig. 101-2)**. The course of CML has also become quite predictable. In the first 2 years of TKI therapy, rare sudden transformations are still reported (1–2%), usually lymphoid blastic transformations that respond to combinations of chemotherapy and TKIs followed by allogeneic SCT. These may be explained by the intrinsic mechanisms of sudden transformation already existing in the CML clones before the start of therapy that were not amenable to TKI inhibition, in particular imatinib. Second-generation TKIs (nilotinib, dasatinib) used as frontline therapy have reduced the incidence of transformation in the first 2–3 years from 6–8% with imatinib to 2–5% with nilotinib or dasatinib. Disease transformation to accelerated or blastic phase is rare with continued TKI therapy, estimated at <1% annually in years 4–10 of follow-up on the original imatinib trials. Patients usually develop resistance in the form of cytogenetic resistance or relapse, followed by hematologic relapse and subsequent transformation, rather than the previously feared sudden transformations without the warning signals of cytogenetic-hematologic relapse.

Before the imatinib era, several pretreatment prognostic factors predicted for worse outcome in CML and have been incorporated into prognostic models and staging systems. These have included older age, significant splenomegaly, anemia, thrombocytopenia or thrombocytosis, high percentages of blasts and basophils (and/or eosinophils), marrow fibrosis, deletions in the long arm of chromosome 9, clonal evolution, and others. Different risk models and staging systems, derived from multivariate analyses, were proposed to define different risk groups. As with the introduction of cisplatin into testicular cancer therapy, the introduction of TKIs into CML therapy has decreased or, in some instances, eliminated the prognostic impact of most of these prognostic factors and the significance of the CML models (e.g., Sokal, Hasford, European Treatment and Outcome Study [EUTOS]). Treatment-related prognostic factors have emerged as the most important prognostic factors in the era of imatinib therapy. Achievement of complete cytogenetic response has become the major therapeutic endpoint and is the only endpoint associated with improvement in

survival. Achievement of a major molecular response is associated with decreased risk of events (relapse) and CML transformation, but has not been associated with survival prolongation among patients with complete cytogenetic response. This may be due to the efficacy of salvage TKI therapies, which are and should be implemented at the first evidence of cytogenetic relapse. Achievement of undetectable *BCR-ABL1* transcripts, particularly when sustained (>2–3 years), may offer the possibility of treatment-free remission (molecular cure rather than functional cure) in the context of investigational trials, and may allow temporary therapy interruption in women pursuing pregnancy. The lack of achievement of major or "complete" molecular responses should not be considered as "failure" of a particular TKI therapy and/or an indication to change the TKI or to consider allogeneic SCT.

Long-term updates of randomized trials suggest that second generation TKIs and imatinib are more similarly effective in lower-risk CML, but second generation TKIs may offer a greater therapeutic advantage for patients with high-risk CML.

TREATMENT

Chronic Myeloid Leukemia

With TKI therapy, the estimated 10-year survival in CML is 85%. Since 2001, six agents have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of CML. These include five oral TKIs: imatinib (Gleevec, Glivec), nilotinib (Tasigna), dasatinib (Sprycel), bosutinib (Bosulif), and ponatinib (Iclusig). Imatinib 400 mg orally daily, nilotinib 300 mg orally twice a day (on an empty stomach), dasatinib 100 mg orally daily, and bosutinib 400 mg orally daily are approved for frontline therapy of CML. All four are also approved for salvage therapy (nilotinib 400 mg twice daily; bosutinib 500 mg daily), in addition to ponatinib (45 mg daily). Because of concerns of arterio-occlusive events with ponatinib, the dose is often reduced to 15–30 mg daily after a response is achieved. Imatinib, dasatinib (140 mg daily), bosutinib, and ponatinib are also approved for the treatment of CML in transformation (accelerated and blastic phase), whereas nilotinib is only approved for chronic and accelerated phase. Dasatinib, nilotinib, and bosutinib are referred to as second-generation TKIs; ponatinib is referred to as a third-generation TKI as it is the only currently approved TKI that has clinical activity in the setting of T315I mutation (in addition to unmutated BCR-ABL1 and BCR-ABL1 with other common mutations). Nilotinib is similar in structure to imatinib but 30 times more potent. Dasatinib and bosutinib inhibit SRC family of kinases in addition to ABL1, with dasatinib reported to be 300 times more potent and bosutinib 30–50 times more potent than imatinib. In contrast to all other TKI, bosutinib has no activity against c-Kit or PDGFR. Ponatinib is effective against wild-type, and mutant *BCR-ABL1* clones. It is currently the only available BCR-ABL1 TKI active against T315I, a gatekeeper mutation resistant to the other four TKIs **(Table 101-2)**. Ponatinib also inhibits VEGFR which may be related to the high incidence of hypertension observed with this agent (Table 101-2). The sixth approved agent is omacetaxine (Synribo), a protein synthesis inhibitor with presumed more selective inhibition of the synthesis of the BCR-ABL1 oncoprotein. It is approved for the treatment of chronic and accelerated phase CML after failure of two or more TKIs, at 1.25 mg/m^2 subcutaneously twice a day for 14 days for induction and for 7 days for consolidation-maintenance. The main adverse event of omacetaxine is prolonged myelosuppression: omacetaxine 5–7 days induction and 2–5 days maintenance, perhaps combined with a TKI, may be equally effective and less toxic (Table 101-2).

Imatinib, nilotinib, and dasatinib are all acceptable frontline therapies in CML. The long-term results of imatinib are very favorable. The 8-year follow-up results show a cumulative complete cytogenetic response rate (occurring at least once) of 83%, with 60–65% of patients being in complete cytogenetic response at 5-year follow-up. The estimated 10-year survival rate is 85%. Among patients continuing on imatinib, the annual rate of transformation to accelerated -blastic phase in years 4–8 is <1%. In two randomized studies, one comparing nilotinib 300 mg twice daily or 400 mg twice daily with imatinib (ENESTnd) and the other comparing dasatinib 100 mg daily with imatinib (DASISION), the second-generation TKIs were associated with better outcomes in early surrogate endpoints, including higher rates of complete cytogenetic responses (85–87% vs 77–82%), major molecular responses (5-year rates 76–77% vs 60–64%), and MR4.5 (5-year rates 42–53% vs 31–33%), with lower rates of transformation to accelerated and blastic phase (2–5% vs 7%). However, neither study has shown a survival benefit with second-generation TKIs (with a minimum follow-up times of 5–6 years). This may be because the rate of complete cytogenetic response is ultimately similarly high with either agent, and also because sequential therapy with TKIs (following close observation and treatment change at progression) provides highly effective therapy for most patients that allows adequate long-term outcome despite relapse or intolerance after initial therapy.

Salvage therapy in chronic phase with dasatinib, nilotinib, bosutinib, or ponatinib is associated with complete cytogenetic response rates of 30–60%, depending on the salvage status (cytogenetic vs hematologic relapse), prior response to other TKIs, and the mutations at the time of relapse. Complete cytogenetic responses are generally durable, particularly in the absence of clonal evolution and mutations. Ponatinib is the only TKI active in the setting of T315I mutation, with complete cytogenetic response rates of 50–70% among patients who have received 2 or more TKI. The estimated 5-year survival rates with new TKIs as salvage are 70–75% (compared with <50% before their availability). For example, with dasatinib salvage after imatinib failure in chronic-phase CML, the estimated 7-year rate of major molecular was 46%, the estimated 7-year survival rate was 65%, and progression-free survival rate was 42%. Thus, TKIs in the salvage setting have already reduced the annual mortality from the historical rate of 10–15% to ≤5%.

TABLE 101-2 Medical Therapeutic Options in Chronic Myeloid Leukemia

AGENT (BRAND NAME)	APPROVED INDICATIONS	DOSE SCHEDULE	NOTABLE TOXICITIES
Imatinib mesylate (Gleevec)	All phases	400 mg daily	See text
Dasatinib (Sprycel)	All phases	First-line: 100 mg daily Salvage: 100 mg daily in chronic phase; 140 mg daily in transformation	Myelosuppression; pleural and pericardial effusions; pulmonary hypertension
Nilotinib (Tasigna)	All phases except blastic phase	First-line: 300 mg twice daily Salvage: 400 mg twice daily	Diabetes; arterio-occlusive disease; pancreatitis
Bosutinib (Bosulif)	All phases except frontline	500 mg daily	Diarrhea, liver toxicity
Ponatinib (Iclusig)	Optimal TKI if T315I mutation Failure of ≥2 tyrosine kinase inhibitors	45 mg daily (may consider lower starting doses in the future, e.g., 30 mg daily)	Skin rashes (10–20%); pancreatitis (5%); arterio-occlusive disease (10–20%); systemic hypertension (10–15%)
Omacetaxine mepesuccinate (Synribo)	Failure ≥2 tyrosine kinase inhibitors	1.25 mg/m^2 subcutaneously twice daily for 14 days of induction; 7 days of maintenance every month (may consider shorter dose schedules, 7 days of induction, 2–5 days of maintenance)	Myelosuppression

The goal of CML therapy is viewed differently in the context of research versus standard practice. In current practice, functional cure, which can be considered when the relative survival is similar to that of the general population, is the current goal of therapy. CML is now considered an indolent disease, which, with appropriate continuous TKI therapy, treatment compliance, careful monitoring, and early change to other TKIs as indicated, can be associated with close to normal survival. Therefore, in standard practice, achievement and maintenance of a complete cytogenetic response are the aims of therapy because complete cytogenetic response is the only outcome associated with survival prolongation. Lack of achievement of a major molecular response (protects against events; associated with longer event-free survival) or of negative *BCR-ABL1* transcripts (offers the potential of TKI interruption on investigational studies) should not be considered indications to change TKI therapy or to consider allogeneic SCT. A general practice rule is to continue the particular TKI chosen at the most tolerable dose schedule not associated with grade 3–4 side effects or with bothersome chronic side effects, for as long as possible, until either cytogenetic relapse or the persistence of unacceptable side effects. These two factors (i.e., cytogenetic relapse and intolerable side effects as judged by the patient and treating physician) are the indicators of "failure" of a particular TKI therapy. A second emerging general practice rule is that patients with CML should always receive daily TKI therapy throughout their lifetime (chronic, transformation), either alone (chronic) or in combinations (possibly for those in transformation although combinations not formally approved), except perhaps in situations of "molecular cure" (elective discontinuation of TKI with close observation if *BCR-ABL* transcripts undetectable are sustained for >2–3 years) or after allogeneic SCT with undetectable disease.

Because of the increasing prevalence of CML (cost of TKI therapy) and the emerging evidence of possible organ toxicities with long-term use (e.g., renal with imatinib, arterio-occlussive with nilotinib, dasatinib, and ponatinib), a goal of therapy of increasing interest in CML is to achieve eradication of the disease (molecular cure) that is prolonged and durable, with recovery of non-neoplastic, non-clonal hematopoiesis off TKI therapy. The first step toward this aim is to obtain the highest rates of undetectable *BCR-ABL1* transcripts lasting for at least 2 or more years. This is currently achievable in about 25–30% of patients treated with imatinib and in 40–45% of patients treated with second-generation TKIs. As a result, molecular cures (off TKI therapy) are estimated to be about 15% post-imatinib therapy and 20–25% post–second-generation TKIs.

Recommendations provided by the National Comprehensive Cancer Network (NCCN) and by the European LeukemiaNet (ELN) propose optimal/expected, suboptimal/warning, and failure response scenarios at different time points of TKI treatment duration. Unfortunately, they may have been misinterpreted in current practice, because oncologists often report that their aim of treatment is the achievement of major molecular response and disease eradication. Significantly, a substantial proportion of oncologists consider a change of TKI therapy in a patient in complete cytogenetic response if they note "loss of major molecular response" (increase of *BCR-ABL1* transcripts ([IS] from ≤0.1 to >0.1%). This perception may be the result of confusion regarding the aims of the NCCN and ELN guidelines, which have been updated often as a result of maturing data and have multiple treatment endpoint considerations. Although such endpoints may have been suggested as possible criteria for failure or suboptimal response, it is important to emphasize that no randomized study has yet shown that a change of TKI treatment in patients with complete cytogenetic response because of a loss of major molecular response, versus changing at the time of cytogenetic relapse, has been shown to improve survival or other long-term outcome. This is likely because of the high efficacy of salvage TKI therapy at the time of cytogenetic relapse.

Side effects of TKIs are generally mild to moderate, although with long-term TKI therapy, they could affect the patient's quality of life. Serious side effects occur in <5–10% of patients. With imatinib therapy, common mild to moderate side effects include fluid retention, weight gain, nausea, diarrhea, skin rashes, periorbital edema, bone or muscle aches, fatigue, and others (rates of 10–20%). In general, second-generation TKIs are associated with lower rates of these bothersome adverse events. However, dasatinib 100 mg daily is associated with higher rates of myelosuppression (20–30%), particularly thrombocytopenia, with pleural (10–25%) or pericardial effusions (≤5%), and with pulmonary hypertension (<5%). Nilotinib is associated with higher rates of hyperglycemia (10–20%), pruritus and skin rashes, hyperbilirubinemia (typically among patients with Gilbert's syndrome and mostly of no clinical consequences), and headaches. Nilotinib is also associated with occasional instances of pancreatitis (<5%). Bosutinib is associated with higher rates of liver toxicity and of early and self-limited gastrointestinal adverse events, particularly diarrhea (70–85%). Ponatinib is associated with higher rates of skin rashes (10–15%), pancreatitis (10%), elevations of amylase/lipase (10%), and systemic hypertension (50–60%; severe in 20%). Arterio-occlusive events (cardiovascular, cerebrovascular, and peripheral arterial) have been reported with most TKI. The incidence appears to be highest with ponatinib, but both nilotinib and dasatinib are associated with these events at an incidence significantly higher than imatinib. Nilotinib and dasatinib may cause prolongation of the QTc interval; therefore, they should be evaluated cautiously in patients with prolonged QTc interval on electrocardiogram (>470–480 ms), and drugs given for other medical conditions should have relatively smaller or no effects on QTc. These side effects can often be dose-dependent and are generally reversible with treatment interruptions and dose reductions. Dose reductions can be individualized. However, the lowest estimated effective doses of TKIs (from different studies and treatment practices) are imatinib 200–300 mg daily; nilotinib 150–200 mg twice daily; dasatinib 20 mg daily; bosutinib 300 mg daily; and ponatinib 15 mg daily.

With long-term follow-up, rare but clinically relevant serious toxicities are emerging. Renal dysfunction and occasionally renal failure (creatinine elevations >2–3 mg/dL) are observed in 2–3% of patients, more frequently with imatinib and bosutinib than other TKI, and usually reverse with TKI discontinuation and/or dose reduction. Rarely, patients may develop TKI-related peripheral neuropathy or even central neurotoxicities that are misdiagnosed as dementia or Alzheimer's disease; they may reverse slowly after TKI discontinuation. Pulmonary hypertension has been reported with dasatinib (<1–2%) and should be considered in a patient with shortness of breath and a normal chest x-ray (echocardiogram with emphasis on measurement of pulmonary artery pressure). This may be reversible with dasatinib discontinuation and occasionally the use of sildenafil citrate. Systemic hypertension has been observed more often with ponatinib. Hyperglycemia and occasionally diabetes have been noted more frequently with nilotinib. Finally, mid- and small-vessel arterio-occlusive and vasospastic events have been reported at low but significant rates with nilotinib and ponatinib and should be considered possibly TKI-related and represent indications to interrupt or reduce the dose of the TKI. These events include angina, coronary artery disease, myocardial infarction, peripheral arterial occlusive disease, transient ischemic attacks, cerebral vascular accidents, Raynaud's phenomenon, and accelerated atherosclerosis. Although these events are uncommon (<5%) (10-year cumulative rates 10% with nilotinib 300 mg BID, 16% with 400 mg BID, compared with 2.5% with imatinib), they are clinically significant for the patient's long-term prognosis and occur at significantly higher rates than in the general population. Serious arterio-occlusive and vasospastic events are more common with ponatinib 45 mg daily (5-year rates 20%).

Discontinuation of TKIs and Treatment-Free Remissions or "Molecular Cures" Several studies have confirmed that TKI discontinuation among patients who achieve undetectable *BCR-ABL1* transcripts for longer than 2–3 years can result in treatment-free remission rates of 40–60%. Since the incidence of durable undetectable *BCR-ABL1* transcripts is 20–45%, about 13–22% of all patients with CML on TKI therapy may achieve treatment-free remission status or molecular cure. This approach is still considered investigational, but may be ready for community practice provided it is done under optimal

conditions. These include the following: patients must have low Sokal-risk CML in first chronic phase (no evidence of transformation), with history of quantifiable *BCR-ABL1* transcripts (e13a2, e14a2), on long-term TKI therapy (5 to 8+ years), with documented undetectable *BCR-ABL1* transcripts for >2–3 years (assessed every 6 months during this timespan and with a PCR with adequate sensitivity), and should be monitored at referral centers that offer rigorous testing of residual CML disease. Patients must also be compliant to frequent monitoring (PCR studies every 1–2 months for the first 6 months, then every 2 months until 2 years and every 3–6 months thereafter).

ALLOGENEIC STEM CELL TRANSPLANT

Allogeneic SCT, a curative modality in CML, is associated with long-term survival rates of 40–60% when implemented in the chronic phase. It is associated with early (1-year) mortality rates of 5–30%. Although the 5- to 10-year survival rates were reported to be around 50–60% (and considered as cure rates), about 10–15% of patients die in the subsequent 1–2 decades from subtle long-term complications of the transplant (rather than from CML relapse). These are related to chronic graft-versus-host disease (GVHD), organ dysfunction, development of second cancers, and hazard ratios for mortality higher than in the normal population. Other significant morbidities include infertility, chronic immune-mediated complications, cataracts, hip necrosis, and other morbidities affecting quality of life. The cure and early mortality rates in chronic-phase CML are also associated with several factors: patient age, duration of chronic phase, whether the donor is related or unrelated, degree of matching, preparative regimen, and others. In accelerated-phase CML, the cure rates with allogeneic SCT are 20–40%, depending on the definition of accelerated disease. Patients with clonal evolution as the only criterion have cure rates of up to 40–50%. Patients undergoing allogeneic SCT in second chronic phase have cure rates of 40–50%. The cure rates with allogeneic SCT in blastic phase CML are ≤15%. Post–allogeneic SCT strategies are now implemented in the setting of molecular or cytogenetic relapse or in hematologic relapse/transformation. These include the use of TKIs for prevention or treatment of relapse, donor lymphocyte infusions, and second allogeneic SCTs, among others. TKIs appear to be highly successful at reinducing cytogenetic/molecular remissions in the setting of cytogenetic or molecular relapse after allogeneic SCT.

Choice and Timing of Allogeneic SCT Allogeneic SCT was considered first-line CML therapy before 2000. The maturing positive experience with TKIs has now relegated its use to after first-line TKI failures. An important question is the optimal timing and sequence of TKIs and allogeneic SCT (whether allogeneic SCT should be used as second- or third-line therapy). Among patients who present with or evolve to blastic phase, combinations of chemotherapy and TKIs should be used to induce remission, followed by allogeneic SCT as soon as possible. The same applies to patients who evolve from chronic to accelerated phase. Patients with de novo accelerated-phase CML may do well with long-term TKI therapy (estimated 8-year survival rate 75%); the timing of allogeneic SCT depends on their optimal response to TKI (achievement of complete cytogenetic response). Among patients who relapse in chronic phase, the treatment sequence depends on several factors: (1) patient age and availability of appropriate donors; (2) risk of allogeneic SCT; (3) presence or absence of clonal evolution and mutations; (4) patient's prior history and comorbidities; and (5) patient and physician preferences **(Table 101-3)**. Patients with T315I mutations at relapse should be offered ponatinib and considered for allogeneic SCT particularly in blastic phase and perhaps also in accelerated phase (because of the short follow-up with ponatinib). Patients with mutations involving Y253H, E255K/V, and F359V/C/I respond better to dasatinib or bosutinib. Patients with mutations involving V299L, T315A, and F317L/F/I/C respond better to nilotinib. Comorbidities such as diabetes, hypertension, pulmonary hypertension, chronic lung disease, cardiac conditions, and pancreatitis may influence the choice for or against a particular

TABLE 101-3 General Suggestions Regarding the Use of Tyrosine Kinase Inhibitors (TKIs) and Allogeneic Stem Cell Transplantation (SCT) in Chronic Myeloid Leukemia (CML)

CML PHASE	USE OF TKI	CONSIDERATION OF ALLOGENEIC SCT
Accelerated or blastic	Interim therapy to achieve minimal CML burden	As soon as possible (exception: de novo accelerated phase)
T315I mutation	Ponatinib to achieve minimal CML burden	Depends on longer term follow-up results of ponatinib efficacy
Imatinib failure in chronic phase; no clonal evolution, no mutations, good initial response; no T315I	Second-line tyrosine kinase inhibitors long-term	Third-line after second-line TKI failures
Clonal evolution or mutations, or no cytogenetic response to second-line TKI	Interim therapy with alternative second generation TKI or ponatinib to achieve minimal CML burden	Second-line
Older patients (≥65–70 years) after imatinib failure in chronic phase	Salvage TKIs as longer-term therapy	May forgo allogeneic SCT in favor of good quality of life and survival in chronic phase
Imatinib failure; emerging nation	–	Second-line: curative, one-time cost $20,000–100,000 (versus >$40,000–100,000/year with TKI)

Note: Mutations involving Y253H, E255K/V, or F359V/C/I: prefer dasatinib or bosutinib. Mutations involving V299L, T315A, or F317L/F/I/C: prefer nilotinib.

TKI. Patients with clonal evolution, unfavorable mutations, or lack of major/complete cytogenetic response within 1 year of salvage TKI therapy have short remission durations and should consider allogeneic SCT as more urgent in the setting of salvage. Patients without clonal evolution or mutations at relapse and who achieve a complete cytogenetic response with TKI salvage, have long-lasting complete remissions and may delay the option of allogeneic SCT to third-line therapy. Finally, older patients (age 65–70 years or older) and those with high risk of mortality with allogeneic SCT may forgo this curative option for several years of disease control in chronic phase with or without cytogenetic response (Table 101-3). In emerging nations, where generic imatinib is now available at the annual price of $400–3000, frontline imatinib is a cost-effective therapy. However, second-line therapy with allogeneic SCT, a one-time curative option with a cost of $20,000–100,000, may be considered (in preference to second-generation TKIs—annual cost above $40,000–100,000) as a more cost-effective national health-care strategy in CML. Table 101-3 summarizes a general guidance to the choice of TKIs versus allogeneic SCT.

MONITORING THERAPY IN CML

Achievement of complete cytogenetic response by 12 months of imatinib therapy and its persistence later, the only consistent prognostic factor associated with survival, is now the main therapeutic endpoint in CML. Failure to achieve a complete cytogenetic response by 12 months or occurrence of later cytogenetic or hematologic relapse are considered as treatment failure and an indication to change therapy. Because salvage therapy with other TKIs re-establishes good outcome, it is important to ensure patient compliance to continued TKI therapy and change therapy when cytogenetic relapse is confirmed unless this is related to non-adherence. Patients on frontline imatinib therapy should be closely monitored until documentation of complete cytogenetic response, at which time they can be monitored every 6 months with peripheral blood FISH and PCR studies (to check for concordance of results), or more frequently if there are concerns about changes in *BCR-ABL1* transcripts (e.g., every 3 months). Monitoring by PCR only is reasonable in patients who

are in major molecular response. Cytogenetic relapse on imatinib is an indication of treatment failure and need to change TKI therapy. Mutational analysis in this instance helps in the selection of the next TKI and identifies mutations in 30–50% of patients. Mutational studies by standard Sanger sequencing (which is the technique currently available in most clinical laboratories) in patients in complete cytogenetic response (in whom there may be concerns of increasing *BCR-ABL1* transcripts) identify mutations in ≤5% and are therefore not indicated. Earlier response has been identified as a prognostic factor for long-term outcome, including achievement of partial cytogenetic response (*BCR-ABL1* transcripts ≤10%) by 3–6 months of therapy. Failure to achieve such a response has been associated with significantly worse survival.

The use of second-generation TKIs (nilotinib, dasatinib) as frontline therapy changed the monitoring approach slightly. Patients are expected to achieve major cytogenetic response (or *BCR-ABL1* transcripts ≤10%) by 3–6 months of therapy. Failure to do so is associated with worse event-free survival, transformation rates, and survival. However, the 3- to 5-year estimated survival among such patients is still high, around 80–90%, which is better than what would be anticipated if such patients were offered allogeneic SCT at that time. Changes of therapy for patients with "slow" response have not been proven to be of long-term benefit compared to changes when more obvious signs of resistance appear. Thus, this adverse response to therapy is considered a warning signal, but it is not known whether changing therapy to other TKIs at that time would improve longer-term outcome.

TREATMENT OF ACCELERATED AND BLASTIC PHASES

Patients in accelerated or blastic phase may receive therapy with TKIs, preferably second- or third-generation TKIs (dasatinib, nilotinib, bosutinib, ponatinib), alone or in combination with chemotherapy, to reduce the CML burden, before undergoing allogeneic SCT. Response rates (major hematologic) with single-agent TKIs range from 30 to 50% in accelerated phase and from 20 to 30% in blastic phase. Cytogenetic responses, particularly complete cytogenetic responses, are uncommon (10–30%) and transient in blastic phase. Studies of TKIs in combination with chemotherapy are ongoing; the general experience suggests that combined TKI-chemotherapy strategies increase the response rates and their durability and improve survival. This is particularly true in CML lymphoid blastic phase, where the combination of anti-ALL chemotherapy with TKIs results in complete response rates of 60–70% and median survival times of 2–3 years (compared with historical response rates of 40–50% and median survival times of 12–18 months). This allows many patients to undergo allogeneic SCT in a state of minimal CML burden or second chronic phase, which are associated with higher probability of long-term survival. In CML nonlymphoid blastic phase, anti-AML chemotherapy combined with TKIs results in CR rates of 30–50% and median survival times of 9–12 months (compared with historical response rates of 20–30% and median survival times of 3–5 months). In accelerated phase, response to single TKIs is significant in conditions where "softer" accelerated phase criteria are considered (e.g., clonal evolution alone, thrombocytosis alone, significant splenomegaly or resistance to hydroxyurea, but without evidence of high blast and basophil percentages). In accelerated phase, combinations frequently include TKIs with low-intensity chemotherapy such as low-dose cytarabine, low-dose idarubicin, decitabine, interferon α, hydroxyurea, or others.

OTHER TREATMENTS AND SPECIAL THERAPEUTIC CONSIDERATIONS

Interferon α Interferon α is considered in combination with TKIs (an investigational approach), sometimes after CML failure on TKIs, occasionally in patients during pregnancy, or as part of investigational strategies with TKIs to eradicate residual molecular disease.

Chemotherapeutic Agents Hydroxyurea remains a safe and effective agent (at daily doses of 0.5–10 g) to reduce initial CML burden, as a temporary measure in between definitive therapies, or in combination with TKIs to sustain complete hematologic or cytogenetic responses. Busulfan is often used in allogeneic SCT preparative regimens. Because of its side effects (delayed myelosuppression, Addison-like disease, pulmonary and cardiac fibrosis, myelofibrosis), it is now only rarely used in the chronic management of CML. Low-dose cytarabine, decitabine, anthracyclines, 6-mercaptopurine, 6-thioguanine, thiotepa, anagrelide, and other agents are sometimes useful in different CML settings to control the disease burden.

Others Splenectomy is now seldom considered to alleviate symptoms of massive splenomegaly and/or hypersplenism. Splenic irradiation is rarely used, if at all, because of the postirradiation adhesions and complications. Leukapheresis is occasionally used in patients presenting with extreme leukocytosis and leukostatic complications. Single doses of high-dose cytarabine or high doses of hydroxyurea, with tumor lysis management, may be as effective and less cumbersome.

Special Considerations Women with CML who become pregnant should discontinue TKI therapy immediately. Among 125 babies delivered to women with CML who discontinued imatinib therapy as soon as the pregnancy was known, three babies were born with neurologic, skeletal, and renal malformations, suggesting the teratogenicity of imatinib known from animal studies. A similar experience has been reported with dasatinib, the incidence of malformations was reported to be higher, 10–12%. There are no or little data with other TKIs. Control of CML during pregnancy can be managed with leukapheresis for severe symptomatic leukocytosis in the first trimester and with hydroxyurea subsequently until delivery. There are case reports of successful pregnancies and deliveries of normal babies with interferon α therapy and registry studies in essential thrombocytosis of its safety, but interferon α can be antiangiogenic and may increase the risk of spontaneous abortions.

Approximately 10–15% of patients on TKI therapy may develop chromosomal abnormalities in the Ph-negative cells. These may involve loss of chromosome Y, trisomy 8, 20q–, chromosome 5 or 7 abnormalities, and others. Most chromosomal abnormalities disappear spontaneously and may be indicative of the genetic instability of the hematopoietic stem cells that predisposes the patient to develop CML in the first place. Rarely (in <1% of instances), abnormalities involving chromosomes 5 or 7 may be truly clonal and evolve into myelodysplastic syndrome or acute myeloid leukemia. This is thought to be part of the natural course of patients in whom CML was suppressed and who live long enough to develop other hematologic malignancies.

GLOBAL ASPECTS OF CML

Routine physical examinations and blood tests in the United States and advanced countries result in early detection of CML in most patients. About 50–70% of patients with CML are diagnosed incidentally, and high-risk CML as defined by prognostic models (e.g., Sokal risk groups) is found in only 10% of patients. This is not the same situation in emerging nations where most patients are diagnosed following evaluation for symptoms and many present with high tumor burden, such as massive splenomegaly, and advanced phases of CML (high-risk CML documented in 20–30%). Therefore, the prognosis of such patients on TKI therapy may be worse than the published experience.

The high cost of TKI therapies (annual costs of $90,000–140,000 in the United States; lower but variable in the rest of the world) makes the general affordability of such treatments difficult. Although TKI treatment penetration is high in nations where cost of therapy is not an issue (e.g., Sweden, European Union), it may be less so in other nations, even in advanced ones like the United States, where out-of-pocket expenses may be prohibitive to a subset of patients. Based on the sales of imatinib worldwide and charity-free drug supplies, it is estimated that <30% of patients are treated with imatinib (or other TKIs) consistently. Although the estimated 10-year survival in CML is 85% in single-institution studies (e.g., MD Anderson Cancer Center), in national studies in countries with TKI affordability (Sweden)

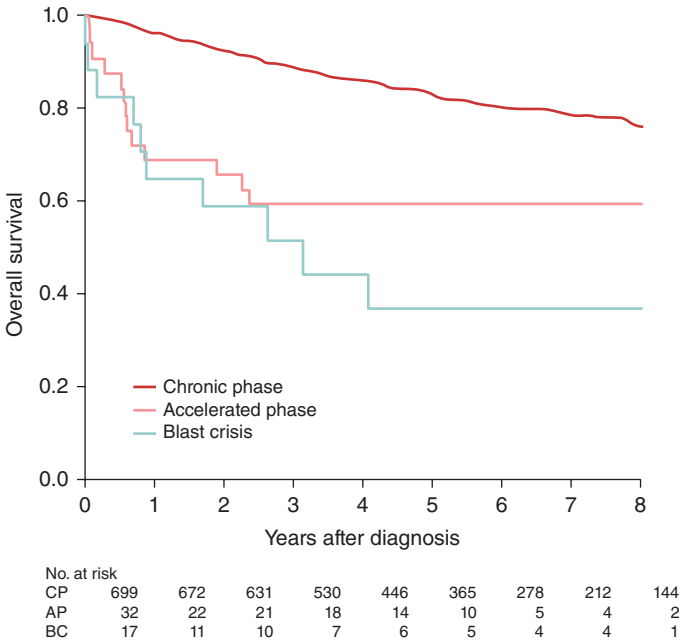

FIGURE 101-3 Survival in chronic (CP), accelerated (AP), and blastic crisis (BC) phases of chronic myeloid leukemia (CML) in the population-based Swedish national registry study. The accelerated- and blastic-phase cases are de novo presentations. The favorable outcome with de novo blastic phase may be due to use of 20% blasts or more to define blastic phase. *(With permission from Dr. Martin Hoglund, Swedish CML Registry, 2013.)*

(Figs. 101-2 and 101-3) or in company-sponsored studies (where all patients have access to TKIs throughout their care), the estimated 10-year survival worldwide, even 16 years after the introduction of TKI therapies, is likely to be <50%. The Surveillance, Epidemiology, and End Results (SEER) data from the United States report an estimated 5-year survival rate of 60% in the era of TKIs.

The current high cost of TKI therapies poses two additional considerations. The first are the treatment pathways and guidelines in nations where TKIs may not be affordable by patients or the health care system. In these conditions, there are trends of pathways advocating allogeneic SCT as frontline or second-line therapy (i.e., after imatinib failure; as a one time cost of $20,000–100,000) despite the associated mortality and morbidities. The second is the choice of frontline TKI therapy once imatinib becomes available in generic forms, hopefully at much lower annual prices, e.g., $2000–10,000 per year (currently $400 per year in India). This will depend on the maturing data in randomized studies of second-generation TKIs versus imatinib in relation to important long-term outcome endpoints, particularly survival, but also event-free survival, transformation-free survival, and treatment-free remission.

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102 Acute Lymphoid Leukemia

Dieter Hoelzer

In acute lymphoblastic leukemia (ALL), the malignant clone arises from hematopoietic progenitors in the bone marrow or lymphatic system resulting in an increase of immature nonfunctioning leukemic cells. Infiltration of bone marrow leads to anemia, granulocytopenia, and thrombocytopenia with the clinical manifestations of fatigue, weakness, infection, and hemorrhages. These symptoms are more often the reason a patient first seeks medical advice rather than consequences of tumor bulk, such as lymph node enlargement, hepatosplenomegaly caused by leukemic infiltration, or symptoms of the central nervous system (meningeosis leukemica).

The diagnosis of ALL is made by morphology from smears of peripheral blood or bone marrow. The classification includes cytochemistry, immunological markers, cytogenetic, and molecular genetic analysis.

INCIDENCE AND AGE

ALL is the most frequent neoplastic disease in children with an early peak at the age of 3–4 years. The incidence in adults ranges from 0.7 to 1.8/100,000 per year, being somewhat higher in younger adults (1–1.5 for the age group 15–24 years) and decreasing thereafter, only to increase again in elderly people to 2.3 for age >65 years. The frequency of immunological, cytogenetic, and genetic subtypes changes with age.

ETIOLOGY

The etiology of acute leukemias is unknown. There are, however, internal and external factors that influence the incidence of leukemia. In ALL, inheritance of certain diseases and exposure to ionizing radiation or to chemicals, including prior chemotherapy, are associated with an increased risk of developing leukemia, but less than in acute myeloid leukemia (AML).

CONGENITAL DISORDERS

Patients with some rare congenital chromosomal abnormalities have a higher risk of development of acute leukemia; e.g., Klinefelter's syndrome, Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, and neurofibromatosis. There is a twentyfold increased incidence of leukemia in patients with Down syndrome, in whom ALL is increased in childhood or AML at an older age. Genetic predisposition may play a part in acute leukemia even, when not associated with another inherited disease, as the identical twin of a leukemic child has a fivefold risk of developing acute leukemia.

INFECTIOUS AGENTS

Human T-cell leukemia virus I (HTLV-I), endemic in Japan and the Caribbean, is the etiological agent for adult T-cell leukemia/

lymphoma, an aggressive adult T-cell leukemia (see Chap. 196). In the endemic African type of Burkitt's lymphoma, the Epstein-Barr virus, a DNA virus of the herpes family, has been implicated as a potential causative agent.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of acute leukemia is made by examination of the peripheral blood and bone marrow. Classification of the patient's disease also requires cytochemical stains, assessment of expression of immunological markers, cytogenetic analysis, and molecular markers. The major aim of classification is to distinguish between AML and ALL because of the different treatment approaches and drug sensitivities. The immunological markers are the major criteria to subdivide ALL into B-cell lineage or T-cell lineage (T-ALL) leukemias. Cytogenetic and molecular evaluation provide further identification of ALL subgroups.

PERIPHERAL BLOOD

Peripheral blood counts and a differential count from a Wright-Giemsa-stained blood smear are essential at the time of presentation. The white blood cell count in about 40% of ALL patients is reduced or normal (Table 102-1). Thus, in the frequently used automatic blood cell counter, the disease may not be detected. One-third of the patients have a moderately increased initial white blood cell count, between 10×10^9 and 50×10^9/L. Leukemic blast cells (LBC) in the peripheral blood are largely responsible for the rise in white blood cell count, but it is noteworthy that in 8% of the ALL patients, no circulating leukemic blast cells are observed.

Peripheral blood observation shows characteristic anemia, thrombocytopenia, and neutropenia. The reduction in the level of hemoglobin is usually mild to moderate, but nearly one-third of the patients have hemoglobin levels <7–8 g/dL. A platelet count below the critical number of 20×10^9/L is seen in one-fifth of the ALL patients. The proportion of patients with granulocyte count $<0.5 \times 10^9$/L usually associated with high risk of infection was only one-fifth in adult ALL series.

BONE MARROW EXAMINATION

Bone marrow aspirates are important for immunological, cytogenetic, and genomic markers. Direct smears from the bone marrow are essential to confirm the diagnosis of acute leukemia and to distinguish between AML and ALL. The bone marrow is usually heavily packed with leukemic blast cells comprising >90% of the nucleated cells in ~70% of patients. The normal hemopoietic elements are greatly reduced or absent. A biopsy of the bone marrow will further demonstrate marked hypercellularity with replacement of fat spaces and normal elements by infiltration with leukemic cells.

TABLE 102-1 Laboratory Values at Diagnosis of Acute Lymphoblastic Leukemia

		ALL
N		1273*
Initial white blood cell count ($\times 10^9$/L)	<10	41%
	10–50	31%
	>50	28%
Neutrophils	<50–100	12%
	<100,000	16%
Platelets ($\times 10^9$/L)	<20	22%
	21–40	22%
	41–100	29%
	>100	27%
Hemoglobin (g/dL)	<7	20%
	7–9	33%
	>9	47%
Leukemic blasts in PB	0%	8%
	25–75%	34%
	>75%	36%
Leukemic blasts in BM	<50%	4%
	51–90%	25%
	>90%	71%

Source: Data from three consecutive German Multicenter Trials for Adult ALL (GMALL).

LUMBAR PUNCTURE

The examination of the cerebrospinal fluid is an essential routine diagnostic measure for ALL. There are different opinions as to when the first lumbar puncture should be done. One procedure is to delay the examination until remission is achieved in order to avoid seeding the central nervous system (CNS) by circulating leukemic blast cells from the peripheral blood. On the other hand, early recognition of CNS disease will lead to immediate CNS-specific therapy, which is required for such patients. Thus, other clinicians prefer to perform the lumbar puncture before treatment starts. This procedure is restricted to patients with an adequate platelet count ($>20 \times 10^9$/L), an absence of manifest clinical hemorrhage, and without a high white blood cell count. For safety reasons, all patients should receive intrathecal methotrexate at the first lumbar puncture.

MORPHOLOGICAL SUBTYPES IN ALL

Three morphologic subgroups of acute lymphoblastic leukemia are distinguished by the French-American-British classification. Whereas the distinction between L1 and L2 morphology has no clinical consequences, the detection of L3 ALL is of clinical and prognostic relevance. It is observed in up to 5% of adult patients and should be distinguished as it is indicative of mature B-ALL, usually termed Burkitt's leukemia, with distinct treatment options. A surface marker confirmation should be obtained.

IMMUNOLOGICAL SUBTYPES OF ALL

A series of monoclonal antibodies is employed to identify antigens expressed on the surface of normal or leukemic cells. The main aim of the immunological classification is to subdivide ALLs according to the presence or absence of B-cell or T-cell markers, or B-phenotypic/hybrid acute leukemia. A marker is positive if >20% of the cells are stained with the monoclonal antibody (Table 102-2).

B-Cell Lineage More than 70% of adult ALLs are of B-cell origin, and the most frequent immunological subtype, common ALL, is characterized by the presence of ALL antigen, a glycoprotein (gp100/CD10). Common ALL blast cells do not carry markers of mature B cells such as cytoplasmic immunoglobulins or surface membrane immunoglobulins. Pre-B-ALL (early B-ALL) is characterized by the expression of cytoplasmic immunoglobulin, being negative in common ALL but is otherwise identical with all other cell markers. Very rarely, the common ALL antigen may be absent in this subtype. Mature B-ALL comprises about 3–4% of adult ALL patients. The blast cells express surface antigens of mature B cells, including the sIgM. Common ALL antigens may also be present and also occasionally cytoplasmic immunoglobulin. Pro-B-ALL (also termed *early B-precursor ALL*) is a leukemia that was formerly termed *non-T, non-B-ALL*, or *null-ALL* as neither T-cell nor B-cell features could be demonstrated. This subtype is Tdt (terminal) deoxynucleotidyl transferase, and CD19 positive and forms about 11% of adult ALL.

T-Cell Lineage Approximately 25% of adult ALL belongs to the T-cell lineage. All cases express the T-cell antigen (gp40, CD7) and cytoplasmatic or surface CD3. They may, according to their step of T-cell differentiation, express other T-cell antigens, e.g., the E-rosette receptor (CD2) and/or the cortical thymocyte antigen T6 (CD1). A minority of T-ALL blast cells may also express common ALL antigen together with other T-cell antigens. According to these markers, it is possible to distinguish a pro-T-ALL (also termed *early T-precursor ALL*), cortical, or thymic T-ALL and a mature T-ALL expressing different stages of differentiation.

Biphenotypic or Mixed Leukemias Biphenotypic leukemias are defined as those in which markers of lymphoid and myeloid lineages are coexpressed on the same leukemic cells without the typical phenotype of either ALL or AML. Bilineage leukemias are those

TABLE 102-2 Immunological, Cytogenetic, Molecular, and Clinical Characteristics of Adult ALL

SUBTYPES	MARKER	INCIDENCE	FREQUENT CYTOGENETIC ABERRATIONS	FUSION TRANSCRIPTS AND MUTATIONS	CLINICAL CHARACTERISTICS	RELAPSE KINETICS AND LOCALIZATION
B-lineage ALL	HLA-DR+, TdT+, CD19+ and/or CD79a+ and/or CD22+	76%				
Pro B-ALL	No additional differentiation markers, Freq. myeloid coexpression (>50%)	12%	t(4;11) (q21;q23)	70% ALL1-AF4 (20% Flt3 in MLL+)	High WBC (>100.000/mL) (26%)	Mainly BM (>90%)
Common ALL	CD10	49%	t(9;22)(q34;q11) del(6q)	33% BCR–ABL (30–50% in c/preB)	Higher age >50 years (24%)	Mainly BM (>90%) Prolonged relapse kinetics (up to 5–7 years)
Pre-B-ALL	CD10±, cylg+	11%	t(9;22)(q34;q11) t(1;19)(q23;p13)	4% t(1;19)/ PBX-E2A		
Mature B-ALL	CD10 ±, slg+	4%	t(8;14)(q24;q32) t(2;8)(p12;q24) t(8;22)(q24;q11)		Higher age >55 years (27%) Frequent organ involvement (32%) and CNS-involvement (13%)	Frequent CNS (10%) Short relapse kinetics (up to 1–1.5 years)
T-lineage ALL	cyCD3 or sCD3	24%			Younger age (90% <50 years) Frequent mediastinal tumors (60%) Frequent CNS involvement (8%) High WBC (>50/mL) (46%)	Frequent CNS (10%)/ extramedullary (6%) Intermediate relapse kinetics (up to 3–4 years)
Early Pro/Pre T-ALL Cortical T-ALL Mature T-ALL	No additional differentiation markers, mostly CD2- CD1a+, sCD3± sCD3+, CD1a-	6% 12% 6%	t(10;14)(q24;q11) t(11;14)(p13;q11)	5% HOX11-TCR <5% LMO/TCR 2% SIL-TAL1 In T-ALL 4% NUP213-ABL1 33% HOX11b 5% HOX11L2b 50% Notch1b		

with two populations of blast cells with either lymphoid or myeloid antigens. They must be differentiated from AML by coexpression of lymphoid markers and from ALL by coexpression of myeloid markers.

CYTOGENETIC AND MOLECULAR ANALYSIS

Cytogenetic analysis should be performed in all cases of acute leukemia. The demonstration of a specific karyotype may be required for the confirmation of the diagnosis, but chromosome abnormalities may be also important independent prognostic variables for disease-free survival or may lead to a specific targeted therapy.

DIAGNOSTICS

The diagnostic techniques are standard cytogenetics, fluorescence in situ hybridization, and reverse transcriptase polymerase chain reaction. These methods allow the detection of Ph+ ALL, with the chromosomal translocation t(9;22)(q34;q11), and the detection of the corresponding *BCR-ABL1* gene rearrangement. Further ALL entities that have been identified are t(4;11)(q21;q23)/*MLL-AFA4*, abn11q23/*MLL*, and t(1;19)(q23;p13)/*PBX-E2A*.

Gene expression profiling, single nucleotide polymorphism array analysis, array-comparative genomic hybridization, and next generation sequencing recognize newly defined ALL entities with poor prognosis: Ph-like ALL and early T-precursor ALL.

NEW ENTITIES

Ph-Like ALL, also called *BCR-ABL1*-like ALL, is characterized by genetic lesions similar to Ph+ ALL, associated with *IKZF1* deletion, *CLRF2* overexpression, and tyrosine kinase activating rearrangements involving *ABL1*, *JAK2*, *PDGFRB*, and several others. The frequency is 10% in children and 25–30% in young adults, but does not increase further with age. Treatment could be directed at the underlying genetic pattern with BCR-ABL inhibitors (e.g., dasatinib) or JAK2 inhibitors (e.g., ruxolitinib).

Early T-Precursor ALL (ETP-ALL) is characterized by lack of CD1a and CD8, weak CD5 expression, at least one myeloid/stem cell marker, a specific transcriptional profile and the possible involvement of several critical genes. No new treatment approaches are currently available for this subtype, and thus hematopoietic stem cell transplantation in first complete remission is the preferred option.

MINIMAL RESIDUAL DISEASE (MRD)

MRD is the detection of residual leukemic cells, not recognizable by light microscopy.

Methods for determining MRD are based on the detection of leukemia-specific aberrant immunophenotypes by flow cytometry, the evaluation of leukemia-specific rearranged immunoglobulin or T-cell receptor sequences by real-time quantitative polymerase chain reaction, or the detection of fusion genes associated with chromosomal abnormalities (e.g., BCR-ABL, MLL-AF4). The detection limit with these methods is 10^{-3}–10^{-5} (0.1–0.001%). The phenotypic aberrations are unique to each patient with ALL and can be detected in up to 95% of individuals. Methods for MRD evaluation and standardization of MRD quantification have been extensively described.

MRD RESPONSE AND TERMINOLOGY

Molecular response can be evaluated only for patients in complete cytological remission, with one marker or more for MRD analysis and

TABLE 102-3 Response Parameters According to MRD

TERMINOLOGY	DEFINITION
Complete (hematologic) remission	Leukemic cells not detectable by light microscopy (<5% blast cells in bone marrow)
Complete molecular remission MRD-negativity	Patient in complete remission, MRD not detectable, ≤0.01% = ≤1 leukemia blast cell in 10,000
Molecular failure/ MRD-positivity	Patient in complete hematologic remission but not in molecular complete remission >0.01%
Molecular relapse/ MRD-positivity	Patient still in complete remission had prior molecular complete remission Leukemic blast cells detectable in bone marrow not detectable (<5%)
Hematologic relapse	>5% ALL cells in bone marrow/blood

samples available at diagnosis and followed at specific time points during the course of disease. Results are classified as presented in Table 102-3.

MOLECULAR RESPONSE AFTER INDUCTION THERAPY AND IMPACT ON OUTCOME

Achievement of molecular complete response/molecular remission is the most relevant independent prognostic factor for disease-free survival and overall survival. Patients with molecular complete remission after induction therapy had significantly superior outcome in several studies, with a disease-free survival of 54–74%, compared to 17–40% for MRD-positive patients. Patients with molecular failure after induction therapy should proceed to a targeted therapy to reduce the tumor load, to be followed by immediate allogeneic hematopoietic stem cell transplant.

PROGNOSTIC FACTORS, RISK STRATIFICATION, AND MRD

The aim of identification of prognostic parameters at diagnosis, which include age, white blood cell count, specific immunophenotypes, and cytogenetic and genetic aberrations, is to stratify patients into risk groups: standard-risk patients without any poor-risk factors, with a good chance of cure by chemotherapy, and high-risk patients with one or more of those risk factors. High-risk patients are most often candidates for a stem cell transplant in first complete remission.

WILL MINIMAL RISK DISEASE EVALUATION REPLACE PRETHERAPEUTIC RISK FACTORS?

The question arises as to whether the evaluation of MRD overcomes all of those pretherapeutic risk factors, or whether they should be combined. A practical approach is to enter the conventional prognostic factors and MRD into a decision algorithm. Thereby defined standard-risk patients who are highly likely to achieve molecular remission (about 90–95%) will remain as standard-risk patients, whereas those who are MRD-positive will be defined accordingly as high-risk patients. Clinically defined high-risk patients are potential candidates for a stem cell transplant in first complete remission. However, it is not clear how to proceed if they achieve a complete molecular remission, since some studies suggest a lack of benefit from transplant in those who are MRD negative. If MRD information is not available, the risk stratification should rely on clinical risk factors evaluated at diagnosis. Unfortunately, 20–30% of adult ALL patients who are MRD-negative after induction will relapse. Potential reasons include loss of sensitivity, evolution of leukemic subclones, and extramedullary origin of disease.

TREATMENT PRINCIPLES

The goal of induction therapy is the achievement of a complete remission, or even better, a molecular complete remission, mostly evaluated within 6–16 weeks of starting chemotherapy. With current regimens (see Fig. 102-1), the complete remission rate has increased to 80–90%, being higher for standard-risk patients (≥90%), and lower for high-risk patients (~80%). The outcome of ALL is strictly related to the age of the patient, and treatment protocols considering the age of an individual patient have emerged.

TREATMENT IN ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Pediatric-Inspired Therapies Pediatric-inspired therapies for adolescents and young adults provide increased drug intensity at several stages of treatment, including larger cumulative doses of drugs such as glucocorticoids, vincristine, L-asparaginase, and consequent central nervous system-directed therapy, which should be strictly adhered to, thereby reducing the role of stem cell transplant in such cases. In a 2012 meta-analysis of 11 trials, including 2489 adolescents and young adults, pediatric-inspired regimens were superior to conventional adult chemotherapy. However, none of the trials was a randomized comparison. Table 102-4 gives the outcome of recent studies with pediatric-inspired regimens for adolescents and young adults with a median age of 27 years. The complete remission rate was very high with 93% (85–98%), and the overall survival rate of 70% (60–78%) was very encouraging. Survival rates at ≥5 years were 70% (67–78%) compared to 34–41% with the former protocols.

Adult ALL The treatment results for adult ALL patients have moderately improved (Table 102-4). The overall survival is 36% with a wide variation from 27 to 60% due to differences in the intensity of the chemotherapy regimen and the outcome of stem cell transplantation.

In several current multicenter prospective trials, the overall survival rate for standard-risk adult ALL patients is now 50–70% with chemotherapy alone. Overall survival for high-risk patients increased from 20–30% to >50% when they received an allogeneic stem cell transplant in first complete remission.

Elderly ALL Since palliative treatments or intensive chemotherapy regimens have failed, with either low complete remission rates or high early death rates, short elderly specific ALL protocols have been initiated, with less intensive therapy (avoiding anthracyclines and alkylating agents). With these protocols, the complete remission rate was increased to 73%, early death could be reduced to 13% (0–36%), and overall survival was 42%.

MAINTENANCE

Maintenance therapy usually consists of 6-mercaptopurine and methotrexate, a strategy transferred from childhood ALL. The duration of maintenance therapy is between 2 and 2.5 years. The potential effect of further intensification cycles of maintenance therapy remains unclear. In a large multicenter Italian study after intensive consolidation treatment, patients were randomly assigned to postconsolidation therapy with conventional maintenance or to intensified maintenance with additional alternating treatment courses of different intensity. There was no difference in the survival rate at 10 years between the treatment groups, which may suggest that, after adequate induction and consolidation therapy, the intensity of the maintenance therapy has no influence on survival.

Maintenance therapies should be adapted to immunological subtypes of ALL. In mature B-ALL, maintenance is not required. In T-ALL and B-Lineage ALL with relapses up to 2.5 years, maintenance therapy is necessary. In Ph-positive ALL, maintenance should include a BCR/ABL tyrosine kinase inhibitor (TKI), most likely the one that was used during induction and consolidation therapy. It is now also standard to give a TKI after allogeneic stem cell transplant in Ph-positive ALL as a maintenance therapy. The duration of maintenance therapy with a TKI is also 2–2.5 years and may be guided by MRD evaluation.

PROPHYLAXIS OF CENTRAL NERVOUS SYSTEM LEUKEMIA

Without some form of prophylactic CNS-directed therapy, in very early studies without any intensive systemic chemotherapy, around 30% of adults with ALL developed CNS leukemia. Prophylactic CNS therapy in ALL is essential for several reasons: CNS leukemia is more easily prevented than treated; once CNS leukemia has developed, it is generally followed by systemic relapse shortly after; and effective CNS prophylaxis also prevents systemic relapse.

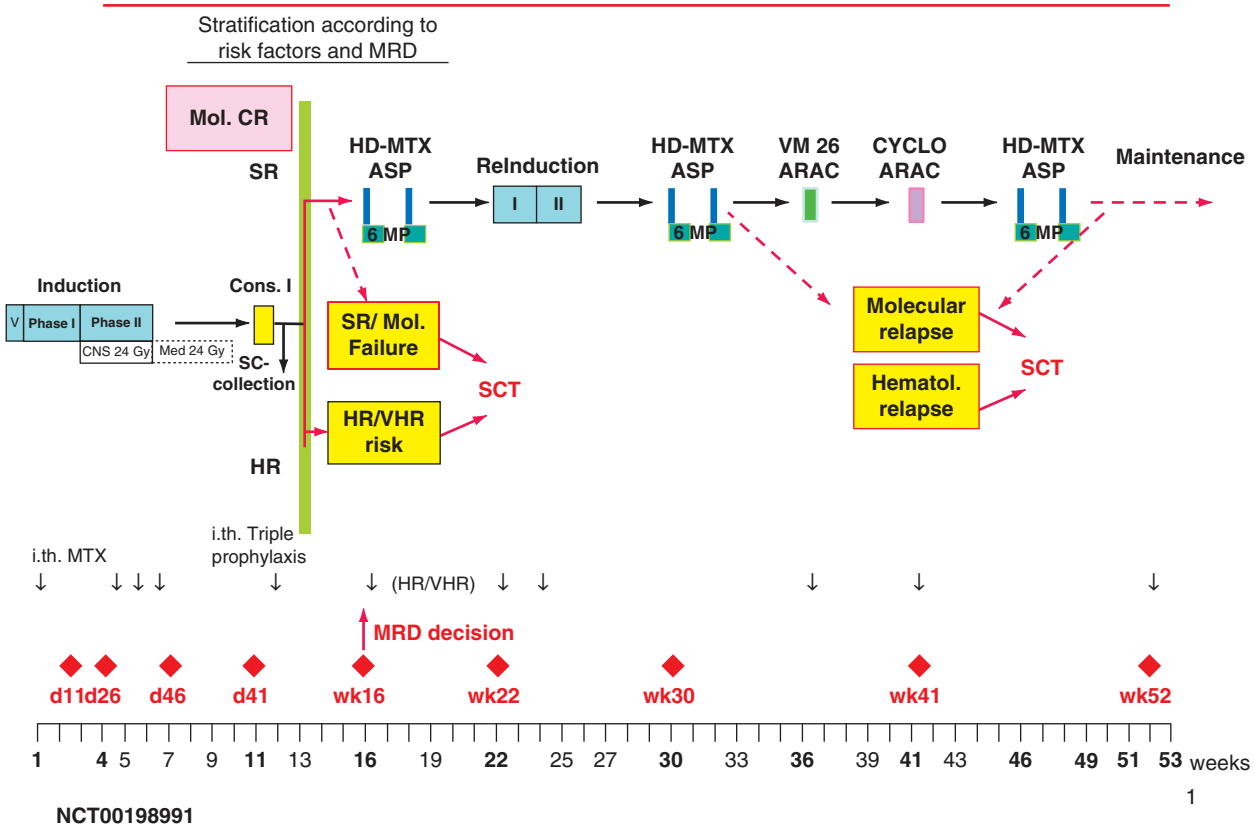

FIGURE 102-1 An example treatment schema for adult ALL. A variety of effective treatment programs are available. Each generally includes an induction phase followed by a consolidation phase and concludes with a maintenance phase. 6-MP, 6-mercaptopurine; arac, cytosine arabinoside, or cytarabine; ASP, L-asparaginase; cyclo, cyclophosphamide; HD-MTX, systemic high-dose methotrexate; HR, high risk; i.th. MTX, intrathecal methotrexate; SCT, stem cell transplantation; SR, standard risk; VM26, teniposide.

Several treatment options are available for prevention of CNS relapse: intrathecal (i.th.) therapy, cranial radiation therapy (CRT), and systemic high-dose or intrathecal therapy is usually based on methotrexate as single drug, but combinations with cytosine arabinoside and/or glucocorticoids are used in some studies. The route of application is generally lumbar puncture. CRT (18–24 Gy in 12 fractions >16 days) may be administered with or without parallel intrathecal therapy. Systemic high-dose chemotherapy may include methotrexate or cytosine arabinoside since both drugs reach cytotoxic drug levels in the cerebrospinal fluid (CSF) and showed efficacy in overt CNS leukemia. A liposomal preparation of cytosine arabinoside has been introduced for the treatment of CNS in patients with ALL or lymphoma; this formulation is more effective since it has a half-life of >2 weeks, compared to only a few hours for the other used intrathecal drugs.

In Ph-positive ALL, tyrosine kinase inhibitors are now an essential part of the treatment strategy. TKIs are equally effective at crossing the blood-brain barrier; dasatinib and ponatinib do, whereas imatinib and nilotinib do not.

In several studies with combined modalities of CNS prophylaxis, the CNS relapse rate was ≤5%. In trials with early high-dose chemotherapy and intrathecal therapy with or without CNS irradiation, the CNS relapse rate was as low as 2%.

THERAPY OF CNS DISEASE

About 5–10% of adult patients present with manifestations of CNS leukemia. The incidence is correlated with the immunological subtype and is higher in mature B-ALL up to 10–15% and in T-ALL up to 10%. For the treatment of CNS leukemia, the same treatment measures as those used for CNS prophylaxis are employed, either intrathecal MTX alone or in combination with cytosine arabinoside or hydrocortisone. The intrathecal therapy is given 2–3 times per week, continued for >2 or 3 weeks until two consecutive CSF examinations show no evidence

TABLE 102-4 Outcome of Adult ALL

TREATMENT APPROACHES	TIME PERIOD	NUMBER STUDIES	NUMBER PATIENTS	AGE* YEARS	CR* RATE	EARLY* DEATH	OVERALL* SURVIVAL
Pediatric-inspired for adult ALL	2008–2015	6	832	**27** (15–60)	**93%** (85–98%)	**5%** (1–7%)	**70%** (60–78%)
Adult protocols	1998–2016	20	7961	**32.7** (12–92)	**84%** (74–93%)	**7%** (1–10%)	**36%** (27–60%)
Elderly protocols	1996–2016			**62**			
Palliative		4	94	60–91	**43%**	**24%**	7 months
Intensive		12	519	60–92	**56%**	**23%**	**14%**
Age-specific		11	653	55–85	**73%**	**13%**	**42%**

*Weighted mean and range.

of leukemic infiltration. When adult ALL patients with initial CNS leukemia are treated adequately, leukemia-free survival and CNS relapse rate are not inferior to those without CNS involvement.

Relapse in the CNS is difficult to treat. Mostly it occurs synchronously with bone marrow relapse, and if leukemic blasts are not seen morphologically, MRD is positive in nearly all cases. This requires a local as well as a systemic therapy. The outcome after CNS relapse is still dismal, and an allogeneic stem cell transplantation is the most promising option to achieve a remission.

STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplantation is an essential part in the treatment strategy of adult ALL. As a stem cell source, peripheral blood cells are increasingly used compared to bone marrow. Also with regard to the donors, there is a shift from sibling donors to matched unrelated donors or haploidentical transplants from relatives. Indications for stem cell transplantation in first remission are controversial. However, in most studies, it is recommended for patients with persistent MRD and all high-risk patients either defined by conventional clinical prognostic factors or by MRD positivity. High-risk patients have a survival rate of ≥50% if transplanted in first remission. For standard risk patients with sustained molecular remission, allogeneic stem cell transplantation is not recommended in first remission. Autologous stem cell transplantation in first remission is restricted to a few disease entities, e.g., in Ph+ ALL, and should be done only in patients who are MRD negative or older patients.

For all relapsed adult ALL patients, an allogeneic stem cell transplant is the only curative option to date, and it is recommended to all patients in second or later complete remission. The potential advantages of stem cell transplant short treatment duration, favorable outcome in some trials must be balanced against the disadvantages; mortality of about 20%, morbidity, late complications, reduced quality of life, and has to be assessed in relation to the improved outcome with targeted therapies.

TARGETED THERAPIES

Substantial progress in adult acute lymphoblastic leukemia has been made in the last decade by the introduction of targeted therapies, either with tyrosine kinase inhibitors or by immunotherapeutic approaches (Table 102-5).

TYROSINE KINASE INHIBITORS IN PHILADELPHIA POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA

Patients with Ph+ ALL constitute ~25% of adult B-lineage ALL, with the incidence increasing to about 50% among elderly patients. In the "pre-Imatinib era," complete remission rates were 60–70%, the survival in those patients treated with chemotherapy alone was ~10%, and after allogeneic stem cell transplant it was ~30%. The results improved substantially when the first-generation TKI imatinib became available, with complete remission rates of 80–90%, but particularly the rate of molecular remissions (*BCR-ABL*-negativity) increased from 5 to 50% or higher, and the 5-year survival increased to ≥50–60%.

TABLE 102-5 Targeted Therapies in Ph-Positive Adult ALL

Tyrosine Kinase Inhibitors
Ph/BCR-ABL+ ALL
TKIs
Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib
Ph-/BCR-ABL-like ALL
ABL1, ABL2; Dasatinib, JAK2; Ruxolitinib
Immunologic Approaches (see Table 102-6)
Antibodies directed leukemia surface antigens
Monovalent antibodies
Bivalent antibodies against the tumor and CD3 (e.g., blinatumomab)
Adoptive cellular therapy
T cells engineered to kill leukemic cells

TABLE 102-6 Expression of Antigens in B-Cell Lineage ALL for Potential Antibody Therapy

SURFACE ANTIGEN	ALL SUBTYPE	EXPRESSION ON LBC	MONOCLONAL ANTIBODY
CD20	Burkitt lymphoma/ leukemia	86–100%	Rituximab Ofatumomab
	B-precursor	30–40%	
CD22	B-precursor	93–98%	Inotuzumab
	Mature B-ALL	~100%	Epratuzumab Moxetumomab pasudotox
CD19	B-precursor	95–<100%	T-cell-activating therapies
	Mature B-ALL	94–<100%	Blinatumomab Bispecific CD3/CD19 CAR T cells (Chimeric antigen receptor modified T cells)

Abbreviation: LBC, leukemic blast count.

Source: D Hoelzer: Hematology Am Soc Hematol Educ Program 2011:243, 2011.

Treating adult Ph+ ALL with an allogeneic stem cell transplant in first complete remission is still the best treatment option. However, patients may receive only chemotherapy plus a TKI as primary treatment, not undergoing a stem cell transplant in first remission. Thus, a Ph+ group with lower relapse risk could probably be identified by MRD response, absence of additional chromosomal abnormalities, or *IKZF1* gene deletion. Faster and deeper molecular responses are achieved with second-generation TKIs (dasatinib, nilotinib), but it is not clear whether this translates into a survival benefit. A third-generation TKI is ponatinib, which targets the T315I and other resistant mutations either present at diagnosis, or developing after treatment with other TKIs.

IMMUNOTHERAPEUTIC APPROACHES

Immunologically based treatments with monoclonal antibodies or activated T cells are showing encouraging antitumor effects in patients with ALL.

B-lineage blast cells express a variety of specific antigens, such as CD19, CD20, and CD22. Monoclonal antibodies have been developed to target these antigens.

Anti-CD20 The anti-CD20 monoclonal antibody rituximab has substantially improved the outcome of patients with de novo Burkitt leukemia/lymphoma. With repeated short cycles of intensive chemotherapy combined with rituximab, the overall survival of such patients increased to >80% compared to earlier results of <60% without rituximab.

Anti-CD22 Monoclonal antibodies directed against CD22, linked to cytotoxic agents, such as calicheamicin (inotuzumab ozogamicin), or to plant or bacterial toxins (epratuzumab) are being explored in refractory/relapsed adult ALL. In a trial of patients with relapsed/refractory ALL treated with inotuzumab ozogamicin, the complete response rate (including responses without blood cell count recovery) was 66%, and of those, 78% achieved a molecular complete remission. When inotuzumab is combined with less intensive chemotherapy (anthracyclines and alkylating agents) encouraging results were obtained in elderly patients (>60 years) as first-line therapy.

Anti-CD19 Targeting CD19 is of great interest, as this antigen is expressed in all B-lineage cells, most likely including early lymphoid precursor cells. A promising approach is the bi-specific antibody blinatumomab, which combines single chain antibodies to CD19 and CD3, such that T cells are brought into proximity with and lyse the CD19-bearing B cells.

This antibody was effective in patients with positive MRD, and 80% converted to MRD-negativity; some patients had promising survival durations even without stem cell transplantation. In a trial of adult patients with refractory/relapsed ALL treated with blinatumomab, the rate of complete remissions was 43%, and the MRD response rate was 82%.

Chimeric Antigen Receptor (CAR) T cells The adoptive transfer of CAR-modified T cells directed against CD19 is a promising approach to the treatment of CD19+ childhood or adult ALL. Complete response rates in adults ranged from 67 to 91% with an MRD negativity in 60–81% of the complete responders. The rate of allogeneic stem cell transplantation after CAR T cells varied from about 10 to 50%. Since patients who underwent an allogeneic stem cell transplant after CAR T-cell therapy had a similar outcome as the nontransplanted patients, the value of the transplant is unclear. CAR T-cell therapy can be highly toxic. The accompanying cytokine release syndrome related to systemic immune activation produces fever, hypotension, confusion, and delirium. These effects appear in the first week of therapy and generally abate, but severe neurotoxicity may be slow to recover. The CD19 negative relapse rate after CAR T-cell therapy is 10–20%, and those patients have limited treatment options.

CONCLUSION AND FUTURE DIRECTIONS

Progress in ALL has led to the recognition of better defined ALL subentities, the importance of MRD as a prognostic factor and therapeutic target, and the value of new targeted therapies. Treatment outcome of adult ALL has improved with about half of the patients surviving >5 years and those surviving 5 years are most likely cured. Newer options, such as less intensive chemotherapy, reduction of stem cell transplantation, and incorporation of targeted therapies are promising options to reduce toxicities and improve the life quality.

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103 Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is a monoclonal proliferation of mature B lymphocytes defined by an absolute number of malignant cells in the blood (5×10^9/mL). The presence of malignant B cells under this count in the blood without nodal, spleen, or liver involvement and absent cytopenias is a precursor of this disease called *monoclonal B-cell lymphocytosis* (MBL) with ~1–2% chance per year of progressing to overt CLL. CLL is a heterogeneous disease in terms of natural history, with some patients presenting asymptomatically and never requiring therapy, whereas others present with symptomatic disease, require multiple lines of therapy, and eventually die of their disease. Over the past 10–15 years, the understanding of CLL origin and biology has grown exponentially, leading first to more refined disease definition, prognostic markers, and, subsequently, introduction of novel therapies that have significantly changed the natural history of this disease. In this chapter, we review the epidemiology, biology, and management of CLL, with a focus on new knowledge that is currently changing standards of care.

EPIDEMIOLOGY

CLL is primarily a disease of older adults, with a median age at diagnosis of 71 and an age-adjusted incidence of 4.5/100,000 people in the United States. The prevalence of CLL has increased over the past decades due to improvements in therapy for this disease and also survival of older patients from other medical ailments. In 1980, the 5-year overall survival of patients was 69%, and this increased to 87.9% in 2007 and is likely even higher today. The male:female ratio is 2:1; however, as patients age, the ratio becomes more even, and over the age of 80, the incidence is equal between men and women. The disease is most common in Caucasians, less common in Hispanic and African Americans, and is rare in the Asian population.

Unlike many other malignancies, there have been no definitive links between CLL and exposures. Indeed, CLL is one of the only types of leukemia not linked to radiation exposure. Agent Orange exposure has been implicated, and CLL is thus a service-connected condition for those who were exposed to Agent Orange in the Vietnam conflict.

CLL is one of the most familial-associated malignancies, and the first-degree relative of a CLL patient has an 8.5-fold elevated risk of developing CLL than the general population. MBL is also more common in families with two first-degree relatives having CLL, further supporting a genetic predisposition of this disease. Despite this, specific genes conferring risk in the familial setting outside of specific families have been difficult to identify. In genome-wide association studies (GWAS), ~30 SNPs have been identified, which is estimated to account for 19% of the familial risk of CLL. Genes involved in apoptosis, telomere function, B-cell receptor (BCR) activation, and B cell differentiation have all been implicated in GWAS. Variants in shelterin complex proteins involved in telomere maintenance such as POT1 have been identified in a small number of families.

BIOLOGY AND PATHOPHYSIOLOGY

CELL OF ORIGIN

The cell of origin in CLL has not definitively been established. The morphology, immunophenotype, and gene expression pattern of CLL cells are that of a mature B cell **(Fig 103-1)**, and so it has been presumed that the initiating cell is a mature lymphocyte, perhaps memory B cells. However, many facets of CLL biology do not support this idea,

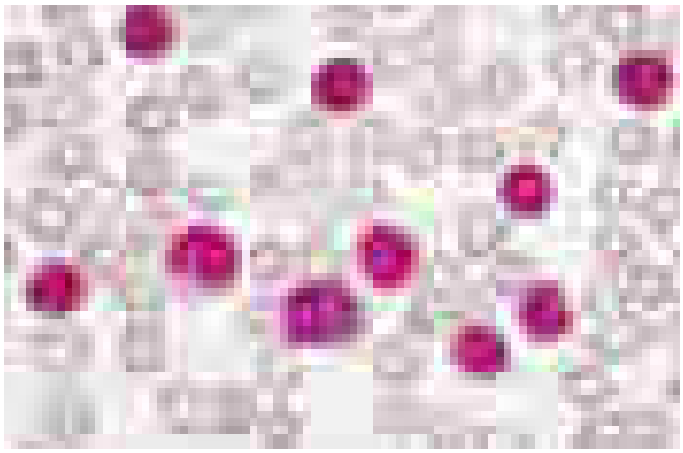


FIGURE 103-1 Chronic lymphoid leukemia in the peripheral blood. *(From Williams Hematology, 7th ed, in M Lichtman et al [eds]: New York, McGraw-Hill, 2005.)*

including antigen-binding characteristics of CLL cells and the presence of stereotyped BCRs. Other possibilities include a stepwise process including a series of transforming events at various stages of B-cell development, potentially including de-differentiation of more mature cells. The self-renewing, multipotent hematopoietic stem cell (HSC) might also be the originating cell of CLL, postulated based on transplant studies in mice showing clonal leukemic cell development with same or different characteristics from donor leukemia after transplantation of HSC. More work will be required to elucidate the origins of CLL.

B-CELL RECEPTOR SIGNALING IN CLL

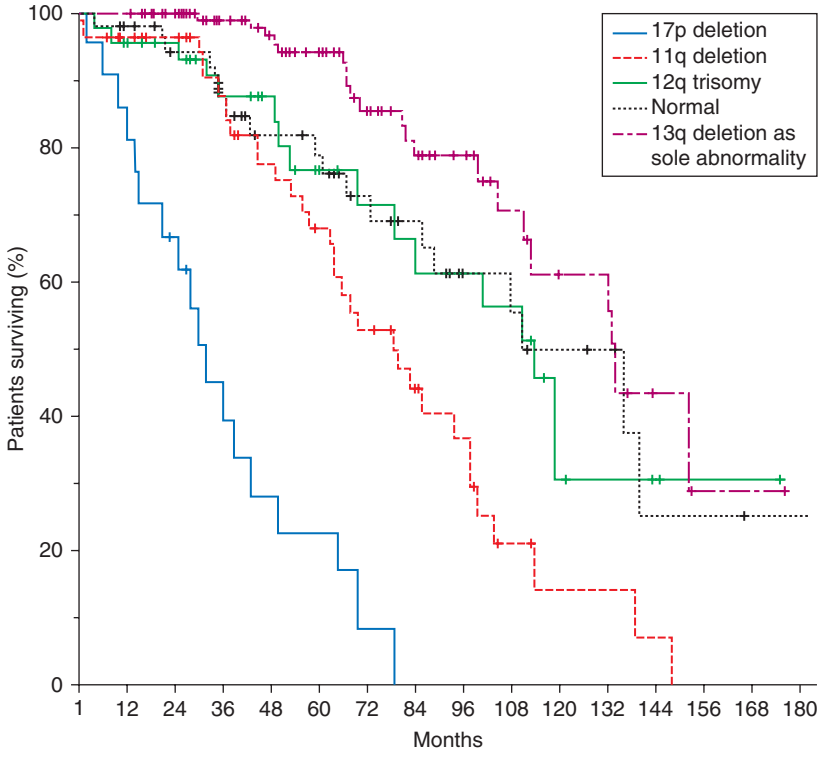
Perhaps the most important advancement in CLL biology is the understanding of the role of BCR signaling in the disease. CLL has distinct BCR signaling as compared to normal B cells, which is characterized by low-level IgM expression, variable response to antigen stimulation, and tonic activation of antiapoptotic signaling pathways that promote tumor survival. CLL cells by gene expression profiling share many features with antigen-activated mature B cells, suggesting a role for activation of BCR signaling in the disease pathogenesis. Tissue-based microarrays have revealed upregulation of BCR pathway genes in the lymph nodes and bone marrow compared to the peripheral blood, suggesting a particular importance of this pathway in microenvironmental homing.

Fitting with the role of BCR signaling in CLL, one of the most influential prognostic factors identified in this disease is the mutational status of the immunoglobulin heavy chain variable (IGHV) region. During normal B-cell maturation, the variable regions of the immunoglobulin heavy chain undergo somatic hypermutation. In CLL, ~60% of patients have IGVH that is ≥2% mutated from germline. This may indicate a more mature, postgerminal center progenitor, and is typically associated with a more indolent disease course. Conversely, ~40% of patients will have IGVH <2% mutated from germline, which is associated with more rapid progression of disease and short survival. Unfavorable biologic properties including enhanced telomerase activity, overexpression of activation-induced cytidine deaminase, increased nuclear factor-κB (NF-κB) activity, high-risk genomic features, and clonal evolution are also associated with IGHV unmutated disease.

Because IGHV sequencing was initially cumbersome to perform, a number of surrogate factors have been identified; however, none yet have been shown to be equal or superior to IGVH sequencing. The most prevalent of these surrogate markers are Zap-70 expression, *ZAP-70* methylation, and surface CD38 expression. Zap-70 protein is a normal intracellular T-cell signaling protein that is aberrantly expressed in most IGHV unmutated CLL cells. CD38 is a marker that is also more highly expressed on the surface of IGHV unmutated CLL cells. Both these prognostic factors are widely used but limited in their applicability. Zap-70 protein status is difficult to measure by flow cytometry, and it has low reproducibility. Measurement of methylation status of the *ZAP-70* promoter is much more precise but not widely available. CD38 expression is easier to measure by flow cytometry but not as highly predictive of outcomes and can change during the course of disease.

CYTOGENETIC ABNORMALITIES

Besides IGHV mutational status, recurrent cytogenetic abnormalities are the most robust prognostic factor clinically available in CLL. These abnormalities are typically identified by fluorescent in situ hybridization (FISH) analysis; however, stimulated metaphase karyotype has a role as well. The most well-characterized abnormalities include del(13)(q14.3), trisomy 12, del(11)(q22.3), and del(17)(p13.1) **(Fig. 103-2)**. The presence of sole del(13)(q14.3) is associated with more indolent disease, prolonged survival, and good response to traditional therapies. Usually



No. AT Risk

17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

FIGURE 103-2 Outcomes among CLL patients with various cytogenetic abnormalities. *(From Döhner H et al: N Engl J Med 343:1910, 2000.)*

this abnormality is not seen on banded karyotype analysis, and when present on karyotype, it indicates a larger deletion involving the retinoblastoma gene, which negates the favorable prognosis associated with this marker. Trisomy 12 has a more intermediate prognosis. The del(11)(q23.3) results in deletion of the *ATM* gene and is associated with bulky lymphadenopathy and aggressive disease in young patients, with inferior prognosis, more rapid progression to symptomatic disease, and shorter survival. The del(17)(p13.1) results in loss of one allele of the tumor suppressor TP53 and is associated with the poorest prognosis in CLL with rapid disease progression, poor response to traditional therapies, and shorter survival. Other abnormalities have been shown to be important in smaller studies but are not routinely performed at all centers. Finally, complex karyotype (three or more abnormalities) on stimulated metaphase karyotype analysis has significant adverse impact on time to treatment and overall survival.

Clonal evolution, or acquisition of cytogenetic or molecular abnormalities, is common in CLL, especially in patients with IGHV unmutated CLL. Because the cytogenetics of patients can change even in the absence of therapy, it is recommended that FISH +/− cytogenetics are checked before every line of therapy, mostly to evaluate acquisition of del(17)(p13.1).

GENE MUTATIONS AND MIR ALTERATIONS

Compared with many other malignancies, the genome in CLL is relatively simple, with an average CLL genome carrying ~20 nonsynonymous alterations and ~5 structural abnormalities. And, unlike many other hematologic malignancies, there is no unifying genetic lesion, and most recurrent genetic driving mutations exist at frequencies of <5%. Whole genome and whole exome sequencing have identified the most common mutations in CLL to be in *SF3B1*, *NOTCH1*, *MYD88*, *ATM*, and *TP53* **(Table 103-1).** Most of the identified mutations in these genes are common among different malignancies, and with the exception of MYD88, they are generally subclonal drivers identified with much higher frequency in IGHV unmutated disease.

NOTCH1 mutations are present in ~15% of CLL patients and are commonly associated with trisomy 12. Although multiple different mutations are seen, most are located within the PEST (proline, glutamic acid, serine, and threonine) domain and result in constitutive NOTCH signaling. *NOTCH1* mutations have been associated with lower sensitivity to CD20 antibody therapy and increased risk of transformation to aggressive diffuse large B-cell lymphoma (DLBCL; Richter's transformation).

SF3B1 is a component of the RNA spliceosome and is mutated in 10–15% of CLL cases. Mutations appear to be associated with intermediate-risk disease, and, functionally, SF3B1 may be important in the response to DNA damage.

Mutations of the tumor suppressor *TP53* are found in ~5% of CLL in previously untreated early stage disease and up to 40% in later stages. Seventy percent of the time these mutations coexist with del(17)(p13.1), effectively eliminating TP53 function. As expected, and consistent with other malignancies, TP53 mutations are associated with a poor prognosis and expected lack of response to DNA-damaging therapies.

TABLE 103-1 Recurrent Mutations in CLL

GENE	FREQUENCY OF MUTATIONS (%)
SF3B1	8–14
TP53	5–13
NOTCH1	10–13
MYD88	4–8
ATM	8–11
BIRC3	<5
XPO1	<5
FBXW7	<5
POT1	<5
BRAF	<5
EGR2	<5
IKZF3	<5

Abbreviation: CLL, chronic lymphocytic leukemia.

ATM mutations, which are heterogeneous and occur throughout the gene, occur in 10–15% of CLL patients. *ATM* mutations often coexist with del(11)(q22.3), eliminating *ATM* on the alternate allele. Similar to *TP53*, mutations in *ATM* tend to result in impaired response to DNA damage, which can reduce responsiveness to chemotherapy.

In contrast to the aforementioned mutations, those in MYD88 tend to occur in IGHV mutated CLL and be associated with a more indolent prognosis. This gene is involved in Toll-like receptor signaling, and the most common mutation, L265P, results in constitutive activation and NF-κB activity.

Along with abnormalities in coding genes, it has become apparent that noncoding genes such as microRNAs are recurrently altered in CLL. The most common cytogenetic abnormality, del(13)(q14.3) results in loss of the miR15/16 cluster, which is important in the pathogenesis of CLL. In normal cells, miR15A/miR16A inhibit antiapoptotic gene expression (including BCL2, CCND1&3, and CDK6), and this specific deletion allows for overexpression of these genes and thus increased cell survival. Loss of other miR expression such as mir-181a leads to overexpression of proteins such as the antiapoptotic gene MCL-1 and TCL1. Overexpression of miR-155, an onco-miR associated with B-cell transformation, has also been documented in the majority of CLL patients.

IMMUNOLOGY

CLL is characterized by dysregulation of the normal immune system in addition to the malignant immune cells. Besides numerical abnormalities due to bone marrow dysfunction, even in the early stages of disease there are skewed ratios of immune cells and functional abnormalities. Innate immune system defects associated with CLL include reduced complement proteins and activity, qualitative neutrophil defects, and functional defects of natural killer cells.

More focus has been placed on the impairments in the adaptive immune system in this disease. Within the CD4+ T-cell compartment, a qualitative defect is noted similar to chronic antigen stimulation inducing a phenotype of T-cell exhaustion typical of what is seen in chronic viral infections such as hepatitis. This has been demonstrated to lead to impaired T-cell cytotoxic capacity and reduced proliferative ability. Additionally, there are physical changes in the T-cell cytoskeleton that causes impaired immune synapse formation with antigen presenting cells. In addition to a lack of capacity to respond to pathogens, the T-cell defect in CLL also likely leads to tumor cell tolerance. During the course of the disease, the polarization of the CD4+ T cells shifts from a Th1 (cytotoxic) phenotype to a Th2 phenotype, which leads to expansion of immunosuppressive cytokines such as IL-10. Additionally, in the later stage of disease T regulatory cells are expanded, which contributes to an immunosuppressive phenotype.

Other components of the immune microenvironment are altered as well to form a more supportive environment for the malignant cells. M2 monocytes have been shown to differentiate into a type of tumor-associated macrophage known as a *nurse-like cell* in CLL. These cells promote survival by secreting chemokines and cytokines that increase migration and activation.

The humoral immune system in CLL is also dysregulated, as is expected for a malignancy that results in very few normal B cells. Hypogammaglobulinemia is very common and affects all subclasses of immunoglobulins, occurring in ~85% of patients at some time in their disease course, and is more common as disease progresses. A correlation between low IgG and IgA and infection risk has been established, but isolated IgM reduction does not seem to be associated with excess infection risk. Also, CLL cells can secrete monoclonal IgM in a small number of cases, and this can correlate with disease progression.

CLINICAL PRESENTATION AND DIAGNOSIS OF CLL

CLINICAL PRESENTATION AND DIAGNOSIS

The presentation of CLL most commonly occurs as an incidental diagnosis made at the time of medical evaluation for another cause. In this regard, CLL is most commonly diagnosed on routine blood work

TABLE 103-2 Typical Immunophenotype of CLL Compared with Other B-Cell Malignancies

	CD5	CD10	CD19	CD20	CD23	CYCLIN D1	SURFACE IG
Disease							
CLL	+	–	+	+ (dim)	+	–	+ (dim)
Mantle cell lymphoma	+	–	+	+ (mod/bright)	–	+	+ (mod/bright)
Marginal zone lymphoma	–/+	–	+	+ (mod/bright)	–/+	–	+ (mod/bright)
Follicular lymphoma	–	+	+	+	+	–	

Abbreviation: CLL, chronic lymphocytic leukemia.

demonstrating an elevated lymphocyte count in asymptomatic individuals, although some patients present with symptoms and require early therapy. When noting either an elevated total white blood cell (WBC) count with lymphocytic predominance or a normal WBC with a differential showing a lymphocytosis, the next step is to perform flow cytometry on the peripheral blood. In CLL, this will reveal the typical immunophenotype that includes the typical B-cell markers CD19, CD20, CD22, CD23, the T-cell marker CD5 (CD5 is also expressed on the B1 subset of B cells that typically has unmutated immunoglobulin and responds to antigens independent of cognate T-cell help), and dim surface immunoglobulin of either kappa or lambda type **(Table 103-2)**. Atypical phenotypes can be seen as well and usually can be differentiated on the basis of morphology, cytogenetics, or clinical presentation. In cases in which the clonal B cell count based on flow cytometry is $\geq 5 \times 10^9$/L, no further workup is needed to confirm the diagnosis of CLL.

Some patients will present with a small clonal proliferation of CLL cells in the peripheral blood but will also have lymphadenopathy or splenomegaly. In these cases, the likely diagnosis is small lymphocytic lymphoma (SLL), a semantic designation from CLL that denotes a primarily tissue-based disease rather than bone marrow/blood-based disease. The genetic and molecular features of SLL are identical to those of CLL. The retention of the cells in tissues may be related to the expression of particular adhesion molecule. Thus, SLL patients are managed identically to CLL, and often in the later stages of disease these patients will often have blood and bone marrow involvement as well.

MONOCLONAL B-CELL LYMPHOCYTOSIS

Patients who do not meet the diagnostic criteria for CLL based on quantification of clonal B cells in the peripheral blood and who do not have associated signs of CLL including lymphadenopathy, organomegaly, or cytopenias have a disorder known as monoclonal B-cell lymphocytosis (MBL), which is now thought to precede every case of CLL. Analogous to monoclonal gammopathy of uncertain significance (MGUS) in myeloma, not all MBL progresses to CLL. MBL is initially characterized by a CLL-like immunophenotype in ~75% of cases but can also be atypical (CD23 negative or bright CD20) or CD5 negative. More relevant for prognosis is characterization by count, with low-count MBL defining those patients with $<0.5 \times 10^9$ clonal B cells/L, and high-count MBL defining those with $>0.5 \times 10^9$ but $<5 \times 10^9$/L. Patients with low-count MBL have a negligible rate of progression to CLL, whereas those with high count progress to overt CLL at a rate of 1–2% per year, warranting continued monitoring. Population-based studies have estimated the prevalence of MBL up to ~12% in the general population, where it is most common in elderly men. It is especially common in first-degree relatives of CLL patients, where the frequency is ~18%.

Although the risk of MBL progression is relatively low, it has become apparent that patients still experience complications that suggest an immune dysfunction in MBL that is similar to that seen with CLL. Rates of serious infections requiring hospitalization appear to be significantly increased in MBL, similar to the rates seen in CLL. In a case-control study, patients with MBL had a 16% chance of hospitalization over a 4-year time period, compared with 18.4% in patients with newly diagnosed CLL. Secondary cancers also appear to be increased in MBL. These data suggest that monitoring for patients with MBL should focus on vaccinations and age-appropriate cancer screening, as the probability of complications appears to be higher than the risk of progression in most of these patients. Follow-up for patients with MBL can occur with the primary care physician as this does not represent a malignancy, whereas CLL is mostly comanaged with both a primary care physician and a hematologist.

COMPLICATIONS OF CLL

A significant amount of morbidity and mortality related to CLL is due to complications of the disease. In general, complications besides disease progression include infections, secondary cancers, autoimmune complications, and transformation to a more aggressive clonally related lymphoma.

INFECTIONS

Infections are a leading cause of both disease-related morbidity and death in patients with CLL, with ~30–50% of deaths in CLL patient attributed to infection. Owing to the immune dysfunction associated with the disease, patients are at risk for both typical and atypical infections. Besides this baseline risk of infections, most CLL therapies can increase infection risk. For many nucleoside analog-based chemotherapy regimens used in CLL, prophylaxis for *Pneumocystis* pneumonia is indicated for at least 6 months following therapy to allow recovery of functional T cells. Viral prophylaxis is also indicated for many chemotherapy regimens and for patients with a history of varicella zoster to diminish reactivation and morbidity from this virus.

Because of the abnormalities in cellular and humoral immunity, vaccine responses in CLL are limited in many patients, especially in the later stages of disease. In one study, one dose of 13-valent pneumococcal vaccine produced an adequate immune response in only 58% of patients compared with 100% in age-matched controls. Despite the known limitations, vaccination against influenza and pneumococcal pneumonia is recommended in CLL. Live vaccines, such as the varicella zoster vaccine, should be avoided because of the small risk of viral reactivation with an immunocompromised host.

As discussed earlier, hypogammaglobulinemia is common in CLL and can be associated with significant risk for infections, primarily of mucocutaneous etiology such as sinusitis and bronchitis. In addition, women can have frequent urinary tract infections. While administration of prophylactic intravenous immunoglobulin (IVIg) has not been shown to improve survival, it has been shown to reduce the number of minor or moderate bacterial infections, and thus is indicated in patients with hypogammaglobulinemia who suffer from recurrent infections or have pulmonary bronchiectasis. It is also our practice to administer at least one dose immunoglobulin to CLL patients who develop influenza with coexisting hypogammaglobulinemia to diminish risk of post-influenza pneumococcal pneumonia. IVIg is probably indicated in patients who have been hospitalized for a serious infection and in those whose IgG level is <300 mg/dL.

SECONDARY MALIGNANCIES

Multiple population-based studies have shown that patients with CLL are at an elevated risk to develop other cancers, with a rate up to three times that of the general population, even in the absence of cytotoxic chemotherapy. The most common types of cancers seen in CLL are skin cancers, prostate, and breast cancers, although other cancers are seen as well. Skin cancers are particularly common, with a rate of 8- to 15-fold higher than the general population, and may behave more aggressively. All CLL patients should be counseled on the use of sunscreen while outdoors and should undergo preventative skin examinations.

In one single-center study, older age at CLL diagnosis, male sex, high β_2 microglobulin, high lactate dehydrogenase (LDH), and chronic kidney disease were associated with excess risk of other cancers; other CLL-specific risk factors have not shown association with other cancer risk.

While cancer risk is higher, there are no specific recommendations for increased cancer screening in CLL patients. Age- and sex-appropriate screenings should be recommended.

Conflicting data exist regarding the risk of cancers following CLL-specific therapy. Chemoimmunotherapy, in particular alkylator-containing regimens, seems to be associated with an increased risk for secondary cancers.

AUTOIMMUNE COMPLICATIONS

Autoimmune complications are frequent in CLL. Most commonly, these include autoimmune cytopenias, but autoimmune complications of other organs including glomerulonephritis, vasculitis, and neuropathies have also been reported. Of the autoimmune cytopenias, the most common is autoimmune hemolytic anemia (AIHA), which is an antibody-mediated destruction of autologous red blood cells (RBCs). Second most common is immune thrombocytopenia (ITP), which shares some features with AIHA and has a similar mechanism targeting platelets. These two syndromes may occur in isolation, sequentially in the same patient, or present in combination as Evan's syndrome. Pure red cell aplasia (PRCA) and autoimmune granulocytopenia (AIG) are comparatively rare and can occur alone or in combination with other AIC. It is difficult to tease out whether autoimmune cytopenias lead to worse prognosis in CLL because of various complicating factors. However, it is clear that these can lead to significant morbidity, both due to the process itself and due to therapies required for management.

AIHA usually presents as an isolated anemia with an elevated reticulocyte count and features of hemolysis including elevated bilirubin and LDH, and low haptoglobin. Detection of a warm IgG antibody on the surface of RBCs with a Coombs test can help solidify the diagnosis, although Coombs-negative cases can occur. Immediate therapy is almost always necessary, and consists of transfusion and immunosuppression. Glucocorticoids are often used for initial therapy, although in most cases additional treatment is needed due to either poor response or recurrence with taper of steroid dosing. Rituximab can be successful, and therapy directed toward the underlying CLL is often effective in more resistant cases. Transfusion of blood in cases of robust AIHA must be initiated with caution as transfusion reactions can be seen due to poorly matched blood.

ITP can be more difficult to diagnose, as it may be difficult to differentiate from progression of disease due to the lack of laboratory tests that identify platelet destruction from this mechanism. Signs that point toward ITP include isolated thrombocytopenia and rapid decline in platelet levels in the absence of an alternative etiology. A bone marrow biopsy showing normal or increased megakaryocytes can be used to confirm the diagnosis but is often not necessary. In CLL, treatment for ITP is usually instituted when platelet levels drop to 20–30,000 or if there is evidence of bleeding complications or need for invasive procedures. Like AIHA, initial therapy consists of glucocorticoids and IVIG, with rituximab also being an effective method to induce long-term remissions. Also, the thrombopoietin receptor agonists romiplostim and eltrombopag are effective in secondary ITP. In many cases, ITP can be successfully treated without treating the underlying CLL. In cases in which anemia or thrombocytopenia appear, it is important to investigate the mechanism as the approach to therapy of autoimmune cytopenias in CLL differs from cytopenias due to marrow replacement.

RICHTER'S TRANSFORMATION

One of the most devastating complications of CLL is Richter's transformation, transformation of CLL to an aggressive lymphoma, most commonly DLBCL. The World Health Organization also recognizes Hodgkin's lymphoma (HL) as a variant of Richter's transformation; other aggressive lymphomas are rarely identified. Some older series have included prolymphocytic transformation in this category, although this has much less prognostic impact on long-term outcome. The prevalence of Richter's transformation is difficult to estimate based on previous studies, but one prospective observational study estimated a rate of 0.5% per year for DLBCL and 0.05% per year for HL. Risk factors for development include bulky lymphadenopathy, *NOTCH1* mutations, del(17)(p13.1), and a specific stereotyped IGVH usage. Lymphomas arising in the setting of CLL can either be clonally related or unrelated to the initial CLL, with prognosis significantly better for clonally unrelated lymphomas. In addition, patients with Hodgkin's transformation have improved outcome, particularly in the absence of prior fludarabine treatment.

Clinical signs of Richter's transformation include rapid progression in adenopathy, often in a specific area, and constitutional symptoms including fatigue, night sweats, fever, and weight loss. LDH is usually high. In suspected cases, the first step is ^{18}FDG-PET/CT (fluorodeoxyglucose–positron emission tomography combined with computed tomography) scan to localize an area for biopsy. Standardized uptake values (SUV) <5 is consistent with CLL and can rule out Richter's transformation in many cases. SUV >5 are suspicious for Richter's transformation, with SUV ≥10 very concerning. Excisional biopsy is diagnostic. Needle biopsy should be discouraged.

Therapy for DLBCL Richter's transformation usually involves combination chemoimmunotherapy. Outcomes are poor with median survivals of 6–16 months in most series for clonally related Richter's versus ~5 years for clonally unrelated. This highlights an area of unmet need in CLL therapy and an area of active investigation. For fit patients who achieve a response with therapy, stem cell transplantation has the possibility to induce long-term remissions and should be explored. Patients with Hodgkin's disease can be treated according to the algorithm for this disease, with many individuals being cured.

WORKUP OF CLL AND APPROACH TO THERAPY

WORKUP AND STAGING

Workup of a patient with new diagnosis of CLL based on typical immunophenotyping includes a detailed history of infectious history; family history of CLL; and careful physical examination with attention to the lymph nodes, spleen, and liver. In patients desiring to know the expected natural history of their CLL, prognostic testing using FISH and stimulated karyotype as well as IGHV sequencing can be performed. Imaging with CT scan is usually not necessary unless there are symptoms and concern for intra-abdominal nodes out of proportion to peripheral nodes. Bone marrow biopsy is not undertaken until therapy is initiated except in cases of unexplained cytopenias.

STAGING

There are two widely used staging systems in CLL: The Rai staging system is used more commonly in the United States, whereas the Binet system is more commonly used in Europe. Both characterize CLL on the basis of disease bulk and marrow failure **(Table 103-3)**. Both rely on physical examination and laboratory studies and do not require imaging or bone marrow analysis. While the initial staging systems could reliably predict survival in CLL, with the changes in therapy

TABLE 103-3 Staging of CLL

Rai Staging System	
Low risk (stage 0)	Lymphocytosis only
Intermediate risk (stage I/II)	Lymphocytosis with lymphadenopathy, with or without splenomegaly or hepatomegaly
High risk (stage III/IV)	Lymphocytosis with anemia or thrombocytopenia due to bone marrow involvement
Binet Staging System	
A	<3 areas of lymphadenopathy
B	≥3 areas of lymphadenopathy
C	Hemoglobin ≤10 g/dL and/or platelets <100,000/μL

Abbreviation: CLL, chronic lymphocytic leukemia.

TABLE 103-4 Criteria for the Initiation of Therapy

Symptoms Indicating Need for Therapy in CLL
Evidence of progressive marrow failure (worsening of anemia or thrombocytopenia not due to autoimmune destruction)
Massive (≥6 cm below costal margin), progressive, or symptomatic splenomegaly
Massive (≥10 cm), progressive, or symptomatic lymphadenopathy
Autoimmune anemia or thrombocytopenia not responsive to standard therapy
Constitutional symptoms (one or more of the following: unintentional weight loss ≥10% over 6 months, significant fatigue, fevers ≥100.5°C for 2+ weeks without infection, night sweats for >1 month without infection)

Abbreviation: CLL, chronic lymphocytic leukemia.

since the original description of the stages, the impact of initial stage on survival is not as clear. Cytogenetic and genomic testing can help refine outcome of these staging tests. An international collaboration integrated both clinical and genomic staging to better predict outcome at diagnosis and time of initial treatment.

CRITERIA FOR THE INITIATION OF THERAPY

Currently, a watchful waiting strategy is used for most patients with CLL, with therapy reserved for patients with symptomatic disease. This recommendation is based on multiple trials showing no survival advantage with earlier therapy, although this question is currently being revisited with novel targeted therapies.

With the exception of patients participating on early intervention studies in CLL, disease-related symptoms that require the initiation of therapy are outlined in Table 103-4. Except for the rare patient who presents with disease requiring urgent therapy, most times these symptoms can be monitored over short periods to determine relatedness to CLL and need for therapy.

INITIAL THERAPY FOR CLL

Chemoimmunotherapy and Monoclonal Antibody Therapy

Chemotherapy and chemoimmunotherapy are the standard therapies for CLL. For patients who are young (≤65 years), the gold standard for therapy is a combination of the nucleoside analogue fludarabine, the alkylator cyclophosphamide, and the anti-CD20 monoclonal antibody rituximab (FCR). In phase III study, this combination produced an overall response rate (ORR) of 93% with a complete response (CR) rate of 44%. Median progression-free survival (PFS) is almost 5 years. Substitution of bendamustine for fludarabine and cyclophosphamide or addition of other chemotherapy-based treatments to FCR have not improved outcome. A subset of patients treated with the FCR regimen has durable responses over 10 years. This group is primarily composed of those patients with mutated IGVH and good cytogenetic risk. However, despite the efficacy of this regimen, short- and long-term toxicities limit its adaptability to many patients with IGHV-mutated disease. Short-term toxicities are mostly related to myelosuppression and include neutropenia and infection. Long-term cytopenias are less common, but they do occur. Also, there is about a 3–5% risk of therapy-related myeloid neoplasm with this regimen that is almost always fatal. Trials in the future will need to focus on the superiority of FCR versus targeted regimens for patients who may be cured by chemoimmunotherapy.

For older patients or those with multiple comorbidities, FCR is not an appropriate option due to toxicities. For these patients, the alkylator chlorambucil in combination with the anti-CD20 antibody obinutuzumab or bendamustine with rituximab are appropriate options. While neither produces remissions as durable as FCR, both can induce CRs and remissions of 2–3 years in many patients. Toxicities with these regimens mostly relate to myelosuppression, but neither is as immunosuppressive as FCR.

Monoclonal antibodies given alone or in combination with chemotherapy were the first targeted therapies to be successful in CLL. Anti-CD20 monoclonal antibodies including rituximab, ofatumumab, and obinutuzumab are all used in this disease. Rituximab was the first agent to show a survival advantage in CLL, where the combination of FCR improved survival over the combination chemotherapy regimen FC. Alone, this antibody has shown modest activity, but activity is improved with higher doses and increased frequency of administration. Both ofatumumab and obinutuzumab are effective as single agents, but it is likely that monoclonal antibodies will be most widely used in combination. Current trials are focused on combining anti-CD20 antibodies with therapies that target BCR signaling or antiapoptotic proteins. Antibodies against other targets are also being developed, including CD19, BAFF receptor, and CD37.

B-Cell Receptor Signaling Inhibitors Three specific targets were the first identified: spleen tyrosine kinase, phosphoinositide-3-kinase (PI3K), and Bruton's tyrosine kinase (BTK). Therapeutics directed at the latter two targets have moved forward through clinical trials and are now utilized in clinical practice.

Idelalisib is a reversible, p110 delta isoform-specific PI3K inhibitor. Because the delta isoform is specific for B lymphocytes, this agent has selective effects on the CLL cells with relative sparing of other hematopoietic cells. The definitive phase III study of the idelalisib plus rituximab regimen assessed this combination versus placebo plus rituximab in 220 patients and showed an ORR of 77% (vs 15% with rituximab plus placebo) with improved progression-free and overall survival. Toxicity specific to idelalisib included elevated alanine transaminase (ALT) and aspartate transaminase (AST) in the first 3 months of therapy and diarrhea, colitis, pneumonitis, and rash later (9+ months) into treatment. These side effects appear to be more common in younger patients given idelalisib earlier in the course of their disease.

Ibrutinib is a relatively selective, irreversible inhibitor of BTK. This target is attractive because, unlike other kinases in the BCR pathway, BTK does not have natural redundancy and is selective for B cells, so inhibition leads to a B-cell–specific phenotype. As initial therapy, ibrutinib was compared with chlorambucil, and there was an 84% lower risk of progression or death with ibrutinib, with 90% of ibrutinib-treated patients alive and progression-free at 18 months. In the relapsed phase III study, ibrutinib was compared to the CD20 monoclonal antibody ofatumumab, and there was a 78% reduction in the risk of progression or death with ibrutinib. Side effects distinct to ibrutinib include rash, diarrhea, dyspepsia, increased risk of bleeding (particularly when on anticoagulation therapy or with surgery), and atrial fibrillation. Second-generation BTK inhibitors with more specificity such as acalabrutinib are in clinical trials and may diminish these side effects. Although direct comparison of agents targeting p110 delta PI3 kinase and BTK has not occurred, BTK inhibitors appear to induce more durable remissions.

The success of ibrutinib and idelalisib has generated significant interest in other molecules targeting PI3K, BTK, and other members of the BCR signaling pathway. One issue with most drugs targeting this pathway in CLL is that while durable responses are common, CRs are not, which leads to the recommendation for indefinite therapy with these molecules. Combination clinical trials are currently underway to determine whether combinations with other active agents might allow discontinuation of drug in some settings.

Antiapoptotic Therapies BCL2 is another promising target in CLL. Venetoclax is an orally bioavailable, selective BCL2 inhibitor. It is currently Food and Drug Administration (FDA) approved for marketing in patients with relapsed or refractory CLL who have the del(17)(p13.1). In a phase I study, the ORR with this agent in relapsed/refractory CLL was 79%, with 69% of patients on the recommended phase II dose being progression-free at 15 months. Unlike the BCR signaling antagonists, venetoclax is able to induce very deep responses including CRs with minimal residual disease negativity in a subset of patients. Distinct toxicities associated with venetoclax include neutropenia, diarrhea, and acute tumor lysis syndrome. Tumor lysis syndrome risk can be mitigated with stepped-up dosing at the beginning of treatment.

Immune Therapies Current immune therapies include allogenic stem cell transplantation, chimeric antigen receptor (CAR) T-cell therapy, and oral immunomodulatory agents such as lenalidomide.

TABLE 103-5 Response Criteria in CLL

	LYMPHOCYTE COUNT	LYMPH NODES[a]	SPLEEN/LIVER SIZE[b]	BONE MARROW[c]	PERIPHERAL BLOOD COUNTS
CR	<4000/μL	None >1.5 cm	Not palpable	Normocellular, <30% lymphocytes, no B lymphoid nodules	• Platelet count >100,000/μL • Hemoglobin >11 g/dL • Neutrophils >1500/μL
PR	Decrease ≥50% from baseline	Decrease ≥50% from baseline	Decrease ≥50% from baseline	Infiltrate ≤50% of baseline	One of the following: • Platelet count >100,000/μL or ≥50% from baseline • Hemoglobin >11 g/dL or ≥50% from baseline • Neutrophils >1500/μL or ≥50% from baseline
Stable disease	Not meeting CR/PR/PD criteria	Not meeting CR/PR/PD criteria	Not meeting CR/PR/PD criteria	Not meeting CR/PR/PD criteria	Not meeting CR/PR/PD criteria
PD	Increase ≥50%	Increase ≥50%	Increase ≥50%		• Platelet count ≤50% of baseline due to CLL • Hemoglobin decrease >2 g/dL due to CLL

[a]Refers to sum of the products of multiple lymph nodes evaluated by CT scan. [b]Based on physical examination. [c]Bone marrow only required to confirm CR.

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; PD, progressive disease; PR, partial response.

Stem cell transplantation is currently considered the only standard curative approach to CLL. Because most CLL patients are older and many have significant comorbidities, myeloablative transplants incur extensive morbidity and mortality, making them prohibitive in many individuals. Reduced intensity conditioning (RIC) allogeneic transplants have been successfully incorporated into the treatment of patients up to ~75 years in age but still have a ≥50% frequency of chronic graft-versus-host disease.

ASSESSING RESPONSE TO THERAPY AND MINIMAL RESIDUAL DISEASE IN CLL

Following the completion of therapy or during therapy for indefinite targeted agents, response is initially assessed using physical examination and laboratory studies (Table 103-5). If residual disease is not detected using these methodologies, CT scans are used to assess response. Bone marrow biopsies with flow cytometry are indicated if no disease is detected to confirm CR.

It has been established in various malignancies that complete tumor eradication is associated with longer survival. In CLL, if no malignant cells can be detected in the bone marrow down to a level of 1 CLL cell in 10^4 leukocytes (0.01%), the patient is said to be negative for minimal residual disease (MRD). Following combination chemoimmunotherapy, eradication of MRD correlates with long-term survival and potentially cure in a subset of patients receiving FCR chemoimmunotherapy. It has yet to be established whether MRD negativity in the setting of targeted therapies is a meaningful endpoint.

CONCLUSION

CLL is treated only when it becomes symptomatic. At the time of therapy chemoimmunotherapy in a small subset of patients is potentially curative. In the majority of remaining individuals with symptomatic CLL, targeted therapy directed at BTK greatly improves survival and also reverses the immune deficiency associated with the disease.

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104 Non-Hodgkin's Lymphoma

Caron A. Jacobson, Dan L. Longo

Non-Hodgkin's lymphomas (NHL) are cancers of mature B, T, and NK cells. They were distinguished from Hodgkin lymphoma (HL) upon recognition of the Reed-Sternberg (RS) cell, and differ from HL with respect to their biologic and clinical characteristics. Whereas ~80–85% of patients with HL will be cured of their lymphoma by chemotherapy with or without radiotherapy, the prognosis and natural history of NHL tends to be more variable. NHL can be classified as either a mature B-NHL, or a mature T/NK-NHL depending on whether the cancerous lymphocyte is a B, T, or NK-cell, respectively. Within each category are lymphomas that grow quickly and behave aggressively, as well as lymphomas that are more indolent, or slow growing in nature. For a list of the World Health Organization (WHO) classification of lymphoid neoplasms, see Table 104-1.

EPIDEMIOLOGY AND ETIOLOGY

In 2017 over 72,000 new cases of NHL were diagnosed in the United States, about 4% of all new cancers in both males and females making it the eighth and ninth most common cause of cancer-related death in women and men, respectively. The incidence is nearly 10 times the incidence of Hodgkin's lymphoma. There is a slight male-to-female predominance and a higher incidence for Caucasians than for African Americans. The incidence rises steadily with age, especially after age 40, but lymphomas are also among the most common malignancies in adolescent and young adult patients. The incidence of NHL has nearly doubled over the last 20–40 years, and continues to rise by 1.5–2% each year. Patients with both primary and secondary immunodeficiency states are predisposed to developing non-NHL. These include patients with HIV infection; patients who have undergone organ transplantation; and patients with inherited immune deficiencies and autoimmune conditions. The 5-year survival rates for NHL is 72% for Caucasians and 63% for African Americans.

TABLE 104-1 WHO Classification of Lymphoid Malignancies

B CELL	T CELL
Mature (peripheral) B-cell neoplasms	Mature (peripheral) T-cell neoplasms
Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia)	T-cell granular lymphocytic leukemia
Hairy cell leukemia	Adult T-cell leukemia/lymphoma (HTLV-1+)
Splenic marginal zone B-cell lymphoma	Extranodal NK/T-cell lymphoma, nasal type
Extranodal marginal zone B-cell lymphoma of MALT type	Enteropathy-associated T-cell lymphoma
Nodal marginal zone B-cell lymphoma	Hepatosplenic T-cell lymphoma
Follicular lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Mantle cell lymphoma	Mycosis fungoides
Diffuse large B-cell lymphoma (including subtypes)	Sezary syndrome
High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements	Peripheral T-cell lymphoma, NOS
High grade B-cell lymphoma NOS	Angioimmunoblastic T-cell lymphoma
Burkitt's lymphoma/Burkitt's cell leukemia	Anaplastic large cell lymphoma, ALK+
Primary mediastinal large B-cell lymphoma	Anaplastic large cell lymphoma, ALK-
Plasmablastic lymphoma	
Primary effusion lymphoma	
HHV8+ DLBCL NOS	
Intravascular large B-cell lymphoma	
ALK+ large B-cell lymphoma	

Abbreviations: HTLV, human T-cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer; WHO, World Health Organization.

Source: Adapted from SH Swerdlow et al: *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 5th ed. IARC, 2016.

The incidence of NHL and the patterns of expression of the various subtypes differ geographically and across age groups. T-cell lymphomas are more common in Asia than in Western countries, while certain subtypes of B-cell lymphomas such as follicular lymphoma (FL) are more common in Western countries. A specific subtype of non-Hodgkin's lymphoma known as the angiocentric nasal T/natural killer- (NK-) cell lymphoma has a striking geographic occurrence, being most frequent in Southern Asia and parts of Latin America. Another subtype of non-Hodgkin's lymphoma associated with infection by human T-cell lymphotropic virus (HTLV) 1 is seen particularly in southern Japan and the Caribbean. Likewise, there are differences in the age-dependent incidence of NHL by histologic subtype, with aggressive lymphomas like diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma (BL) being the most common entities in children, and DLBCL and indolent lymphomas including FL being the most common forms in adults. The relative frequencies of the various types of lymphoid malignancies, including Hodgkin's lymphoma, plasma cell disorders, and lymphoid leukemias is shown in **Fig. 104-1**.

A number of environmental factors have been implicated in the occurrence of non-Hodgkin's lymphoma, including infectious agents, chemical exposures, and medical treatments. Several studies have demonstrated an association between exposure to agricultural chemicals and an increased incidence of non-Hodgkin's lymphoma. Patients treated for Hodgkin's lymphoma can develop non-Hodgkin's lymphoma; it is unclear whether this is a consequence of the Hodgkin's lymphoma or its treatment, especially radiation.

Several NHL are associated with infectious agents **(Table 104-2)**. Epstein-Barr Virus (EBV) is associated with the development of Burkitt's lymphoma in Central Africa and the occurrence of aggressive NHL in immunosuppressed patients in Western countries. The majority of primary central nervous system (CNS) lymphomas are associated with EBV. EBV infection is strongly associated with the occurrence of extranodal nasal NK/T-cell lymphomas in Asia and South America. HTLV-1 infects T cells and leads directly to the development of adult T-cell lymphoma (ATL) in a small percentage of patients infected as babies through ingestion of breast milk of infected mothers. The median age of patients with ATL is ~56 years; thus, HTLV-1 demonstrates a long latency from infection to oncogenesis **(Chap. 196)**. Infection with HIV predisposes to the development of aggressive, B-cell non-Hodgkin's lymphoma. This may be through overexpression of interleukin 6 by infected macrophages. Infection of the stomach by the bacterium *Helicobacter pylori* induces the development of gastric MALT (mucosa-associated lymphoid tissue) lymphomas. This association is

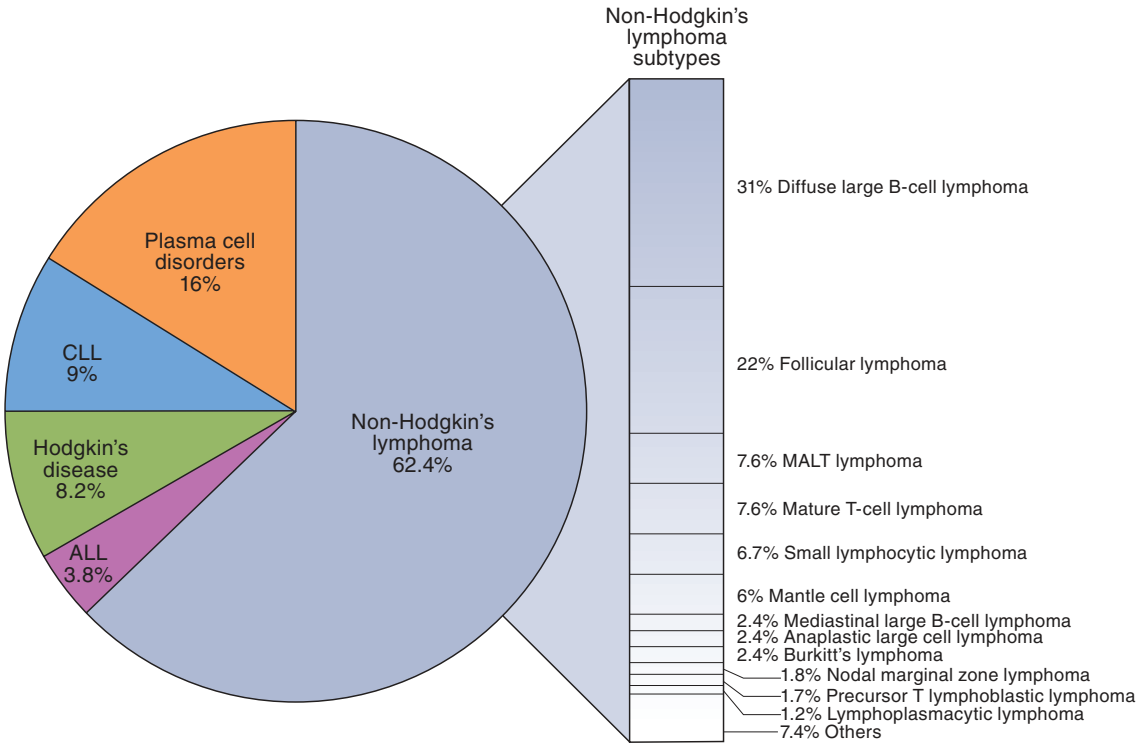

FIGURE 104-1 Relative frequency of lymphoid malignancies. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; MALT, mucosa-associated lymphoid tissue.

TABLE 104-2 Infectious Agents Associated with the Development of Lymphoid Malignancies

INFECTIOUS AGENT	LYMPHOID MALIGNANCY
Epstein-Barr virus	Burkitt's lymphoma
	Post–organ transplant lymphoma
	Primary CNS diffuse large B-cell lymphoma
	Hodgkin's lymphoma
	Extranodal NK/T-cell lymphoma, nasal type
HTLV-1	Adult T-cell leukemia/lymphoma
HIV	Diffuse large B-cell lymphoma
	Burkitt's lymphoma
Hepatitis C virus	Lymphoplasmacytic lymphoma
Helicobacter pylori	Gastric MALT lymphoma
Human herpesvirus 8	Primary effusion lymphoma
	Multicentric Castleman's disease

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; HTLV, human T cell lymphotropic virus; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

supported by evidence that patients treated with antibiotics to eradicate *H. pylori* have regression of their MALT lymphoma. The bacterium does not transform lymphocytes to produce the lymphoma; instead, a vigorous immune response is made to the bacterium, and the chronic antigenic stimulation leads to the neoplasia. MALT lymphomas of the skin may be related to *Borrelia* sp. infections in Europe, those of the eyes to *Chlamydophila psittaci*, and those of the small intestine to *Campylobacter jejuni*. Chronic hepatitis C virus infection has been associated with the development of lymphoplasmacytic lymphoma and splenic marginal zone lymphoma (MZL). Human herpesvirus 8 is associated with primary effusion lymphoma in HIV-infected persons and multicentric Castleman's disease, a diffuse lymphadenopathy associated with systemic symptoms of fever, malaise, and weight loss.

In addition to infectious agents, a number of other diseases or exposures may predispose to developing lymphoma **(Table 104-3)**. Diseases of inherited and acquired immunodeficiency as well as autoimmune diseases are associated with an increased incidence of lymphoma. The association between immunosuppression and induction of NHLs is compelling since if the immunosuppression can be reversed, a percentage of these lymphomas regress spontaneously. The incidence of NHL is nearly hundredfold increased for patients undergoing organ transplantation necessitating chronic immunosuppression, and is greatest in the first year post-transplant. About 30% of these arise as a polyclonal B-cell proliferation that evolves into a clonal B-cell malignancy. The NHLs that occur in the context of immunosuppression or immunodeficiency, including HIV infection, are frequently associated with EBV. Histologically, DLBCLs are most frequently associated with immunosuppression and autoimmune diseases, although almost all histologies can be seen, especially MALT lymphomas in the context of autoimmune diseases like Sjogren's and Hashimoto's thyroiditis. The rare inherited immunodeficiency diseases X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, Chédiak-Higashi syndrome, ataxia telangiectasia, and common variable immunodeficiency syndrome are complicated by highly aggressive lymphomas. The elevated incidence of lymphoma in iatrogenic immunosuppression, AIDS, and autoimmune disease argues strongly for immune dysregulation contributing in the pathogenesis of some lymphomas. An increased risk of NHL has been observed in first-degree relatives with NHL, Hodgkin's lymphoma or chronic lymphocytic leukemia (CLL). In large databases studies, about 9% of patients with lymphoma or CLL have a first-degree relative with a lymphoproliferative disorder.

TABLE 104-3 Diseases or Exposures Associated with Increased Risk of Development of Malignant Lymphoma

Inherited immunodeficiency disease	Autoimmune disease
Klinefelter's syndrome	Sjögren's syndrome
Chédiak-Higashi syndrome	Celiac sprue
Ataxia-telangiectasia syndrome	Rheumatoid arthritis and systemic lupus erythematosus
Wiskott-Aldrich syndrome	Chemical or drug exposures
Common variable immunodeficiency disease	Phenytoin
Acquired immunodeficiency diseases	Dioxin, phenoxy herbicides
Iatrogenic immunosuppression	Radiation
HIV-1 infection	Prior chemotherapy and radiation therapy
Acquired hypogammaglobulinemia	

IMMUNOLOGY

All lymphoid cells are derived from a common hematopoietic progenitor that gives rise to lymphoid, myeloid, erythroid, monocyte, and megakaryocyte lineages. Through the ordered and sequential activation of a series of transcription factors, the cell first becomes committed to the lymphoid lineage and then gives rise to B and T cells.

About 90% of all lymphomas are of B-cell origin. A cell becomes committed to B-cell development when it expresses the master B lineage transcription factor PAX5, which ultimately results in a transcriptional program that leads to the rearrangement of its immunoglobulin genes, which involves chromosomal recombination as well as somatic hypermutation to create an immunoglobulin gene that is unique to that B cell. The sequence of cellular changes, including changes in cell-surface phenotype that characterizes normal B-cell development is shown in **Fig. 104-2.** Most B-cell lymphomas arise following the process of immunoglobulin gene recombination and somatic hypermutation, which leads to class switching and affinity maturation of the mature immunoglobulin, respectively, suggesting that it is the error-prone nature of these genetic events that contributes to oncogenesis. Certainly the frequency of chromosomal translocations that result in the activation of an oncogene or the inactivation of a tumor suppressor gene in B-cell NHL may be the result of these normal cellular processes gone awry (see below). In addition, the key roles of the transcription factors MYC and BCL6 and the anti-apoptotic protein BCL2 in the process of B-cell development explain why the genes encoding these proteins are commonly mutated in B-cell lymphomas.

A cell becomes committed to T-cell differentiation upon migration to the thymus and rearrangement of T-cell receptor (TCR) genes. This requires the expression of the T-cell master regulatory transcription factor, NOTCH-1. As in B cells, the development of the mature TCR involves the rearrangement and recombination of the TCR loci, which is error-prone and potentially oncogenic. The sequence of the events that characterize T-cell development is depicted in **Fig. 104-3.**

Although lymphoid malignancies often retain the cell-surface phenotype of lymphoid cells at particular stages of differentiation, this information is of little clinical or prognostic consequence. The so-called stage of differentiation of a malignant lymphoma does not predict its natural history. The antigen footprint, or immunophenotype, of the cell, however, is valuable diagnostically as it allows for the distinguishing of specific NHL subtypes. It can be detected by flow cytometry of single cell suspension from blood, bone marrow, body fluid or disaggregated tissue using fluorescently labeled antibodies against these antigens, or by immunohistochemical staining of paraffin-embedded tissue sections with enzyme-linked antibodies against these antigens followed by a colorimetric reaction.

As already mentioned, malignancies of lymphoid cells are associated with recurring genetic abnormalities including chromosomal translocations and genetic mutations that may in part be the result of aberrant immunoglobulin or TCR development. While specific genetic abnormalities have not been identified for all subtypes of lymphoid malignancies, it is presumed that they exist. As previously discussed, B cells are even more susceptible to acquiring mutations during their maturation in germinal centers; the generation of antibody of higher affinity requires the introduction of mutations into the variable region genes in the germinal centers. Given this, other nonimmunoglobulin genes, e.g., *bcl-6*, may acquire mutations as well. Likewise, many lymphomas contain balanced chromosomal translocations involving the antigen receptor genes; immunoglobulin genes on chromosomes 2, 14,

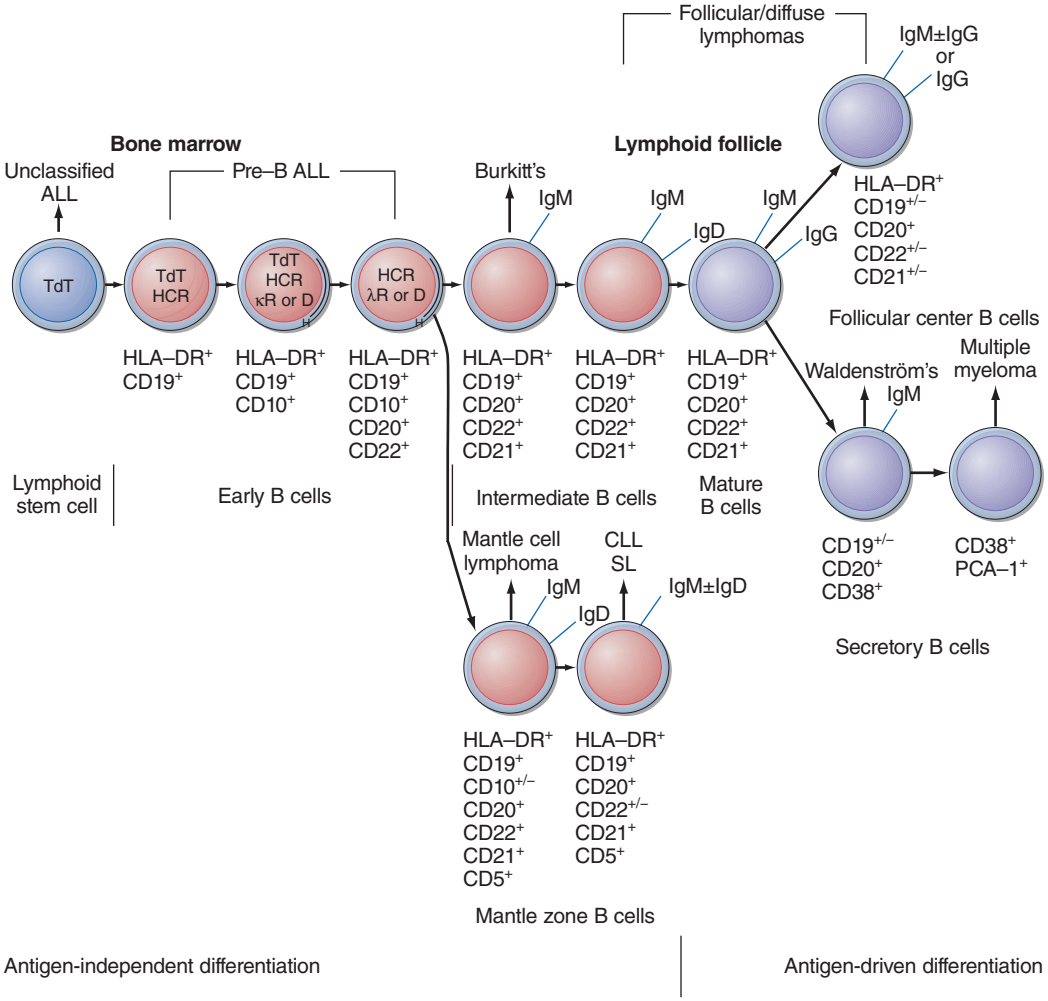

FIGURE 104-2 Pathway of normal B-cell differentiation and relationship to B-cell lymphomas. HLA-DR, CD10, CD19, CD20, CD21, CD22, CD5, and CD38 are cell markers used to distinguish stages of development. Terminal transferase (TdT) is a cellular enzyme. Immunoglobulin heavy chain gene rearrangement (HCR) and light chain gene rearrangement or deletion (κR or D, λR or D) occur early in B-cell development. The approximate normal stage of differentiation associated with particular lymphomas is shown. ALL, acute lymphoid leukemia; CLL, chronic lymphoid leukemia; SL, small lymphocytic lymphoma.

and 22 in B cells; and T-cell antigen receptor genes on chromosomes 7 and 14 in T cells. The rearrangement of chromosome segments to generate mature antigen receptors must create a site of vulnerability to aberrant recombination. Examples of this type of event include the (8;14)(q24;q32) translocation in BL, involving the *MYC* proto-oncogene and the IgH gene; the (14;18)(q32;q32) translocation in FL, involving the *BCL2* proto-oncogene and the IgH gene; and the (11;14) (q13;q32) translocation in mantle cell lymphoma (MCL), involving the gene encoding cyclin D1 (*CCDN1*) and the IgH gene. Less commonly, chromosomal translocations produce fusion genes that encode chimeric oncogenic proteins. Examples of this include the (2;5)(p23;q35) translocation involving the *ALK* and *NPM1* genes in anaplastic large cell lymphoma (ALCL) and the t(11;18)(q21;q21) translocation involving the *API2* and *MLT* genes in MALT lymphoma. Table 104-4 presents the most common translocations and associated oncogenes for various subtypes of lymphoid malignancies.

Gene profiling using array technology allows the simultaneous assessment of the expression of thousands of genes. This technology provides the possibility to identify new genes with pathologic importance in lymphomas, the identification of patterns of gene expression with diagnostic and/or prognostic significance, and the identification of new therapeutic targets. Recognition of patterns of gene expression is complicated and requires sophisticated mathematical techniques. Early successes using this technology in lymphoma include the identification of previously unrecognized subtypes of DLBCL whose gene expression patterns resemble either those of follicular, or germinal center B (GCB) cells or activated peripheral blood B cells (ABC). Patients whose lymphomas have a GCB-like pattern of gene expression have a considerably better prognosis than those whose lymphomas have a pattern resembling ABCs. This improved prognosis is independent of other known prognostic factors. Similar information is being generated in FL and MCL. The challenge remains to provide information from such techniques in a clinically useful time frame.

APPROACH TO THE PATIENT

Regardless of the type of lymphoid malignancy, the initial evaluation of the patient should include performance of a careful history and physical examination. These will help confirm the diagnosis, identify those manifestations of the disease that might require prompt attention, and aid in the selection of further studies to optimally characterize the patient's status to allow the best choice of therapy. It is difficult to overemphasize the importance of a carefully done history and physical examination. They might provide observations that lead to reconsidering the diagnosis, provide hints at etiology, clarify the stage, and allow the physician to establish rapport with the patient that will make it possible to develop and carry out a therapeutic plan.

The duration of symptoms and pace of symptomatic progression are important in distinguishing aggressive from more indolent lymphomas, as are the presence or absence of "B" symptoms, such as

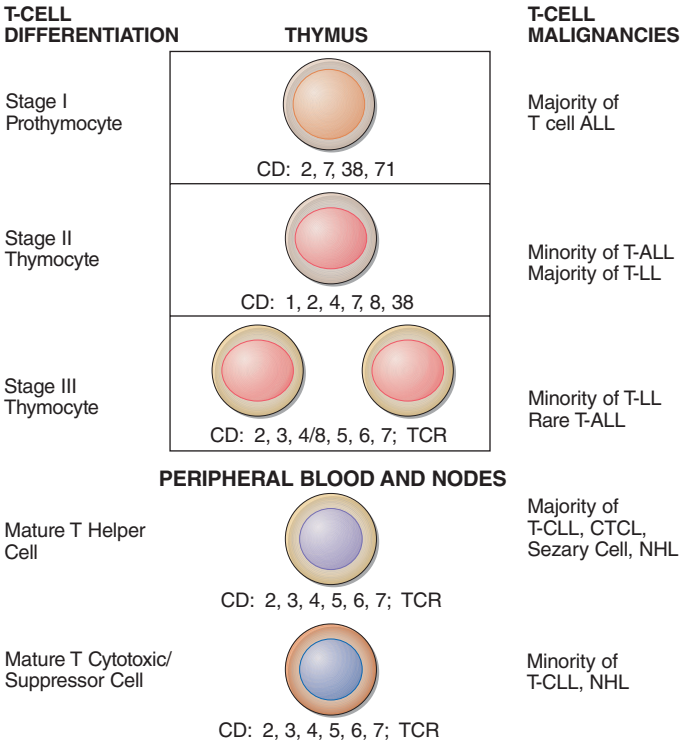

FIGURE 104-3 Pathway of normal T-cell differentiation and relationship to T-cell lymphomas. CD1, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD38, and CD71 are cell markers used to distinguish stages of development. T-cell antigen receptors (TCR) rearrange in the thymus, and mature T cells emigrate to nodes and peripheral blood. ALL, acute lymphoid leukemia; T-ALL, T-cell ALL; T-LL, T-cell lymphoblastic lymphoma; T-CLL, T-cell chronic lymphoid leukemia; CTCL, cutaneous T-cell lymphoma; NHL, non-Hodgkin's lymphoma.

TABLE 104-4 Genetic Features of B- and T-Cell Lymphomas

GENETIC FEATURE	GENES	LYMPHOMA
t(8;14) **t(2;8)** **t(8;22)**	*MYC/IgH* *MYC/Igκ* *MYC/Igλ*	Burkitt's lymphoma
t(11;14)	*BCL1 (CCND1)/IgH*	Mantle cell lymphoma; multiple myeloma
t(14;18) **t(3;14)**	*BCL2/IgH* *BCL6/IgH*	Follicular lymphoma, diffuse large B-cell lymphoma (DLBCL)
t(11;18) **t(1;14)** **t(14;18)** **t(3;14)**	*API2/MALT1* *BCL10/IgH* *MALT1/IgH* *FOXP1/IgH*	MALT lymphoma
Trisomy 3 **7q21 deletion**	*Unknown* *CDK6*	Splenic marginal zone lymphoma
t(9;14) **6q21 deletion**	*PAX5/IgH* *Unknown*	Lymphoplasmacytic lymphoma
inv(14) **t(14;14)**	*TCRα/TCL1*	Peripheral T-cell lymphoma, NOS; T-PLL
t(2;5) **t(1;2)** **t(2;3)** **t(2;17)** **inv(2)**	*NPM1/ALK* *TPM3/ALK* *TFG/ALK* *CTLC/ALK* *ATIC/ALK*	Anaplastic large cell lymphoma (ALCL)
Trisomy 3 **Trisomy 5**	*Unknown* *Unknown*	Angioimmunoblastic T-cell lymphoma
Isochromosome 7q	*Unknown*	Hepatosplenic T-cell lymphoma

Abbreviation: MALT, mucosa-associated lymphoid tissue.

fevers, night sweats, or unexplained weight loss. Patients should be asked about localizing symptoms that may point towards lymphomatous involvement of specific sites, such as the chest, abdomen, or CNS. Comorbid diagnoses that may impact therapy or monitoring on therapy should be reviewed and acknowledged, including a history of diabetes or congestive heart failure. A physical examination should pay close attention to all the peripherally accessible sites of lymph nodes, the liver and spleen size, Waldeyer's ring, whether there is a pleural or pericardial effusion or abdominal ascites, whether there is an abdominal, testicular or breast mass, and whether there is cutaneous involvement as all of these findings may influence further evaluation and disease management.

Laboratory studies should include a complete blood count, routine chemistries, liver function tests, and serum protein electrophoresis to document the presence of circulating monoclonal paraproteins. The serum β-2 microglobulin level and serum lactate dehydrogenase (LDH) are important independent prognostic factors in NHL. Staging of certain diseases may involve a bone marrow biopsy; results of other laboratory and staging studies may also warrant a marrow evaluation. A lumbar puncture for evaluation of lymphomatous involvement may be indicated in the setting of concerning neurologic signs or symptoms, or diseases that are high risk for CNS involvement. The latter may include disease involving the paranasal sinuses, testes, breast, kidneys, adrenal glands, and epidural space, as well as highly aggressive histologies like BL. Since HIV and hepatitis B and C infection can be risk factors for developing NHL, and since treatment for some NHL can result in the potentially life threatening reactivation of hepatitis B, patients with a new diagnosis of NHL should be screened for these viruses as well.

Lymphoma histology and clinical presentation dictates which imaging studies should be ordered. Chest, abdominal, and pelvic computed tomography (CT) scans are essential for accurate staging to assess lymphadenopathy for indolent lymphomas, whereas positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG PET) is useful for aggressive lymphomas, including BL, DLBCL, plasmablastic lymphoma, and the aggressive T-cell NHLs. It is highly sensitive for detecting both nodal and extranodal sites involved by NHL. The intensity of FDG avidity, or SUV, correlates with histologic aggressiveness, and may be useful in cases when disease transformation of an indolent lymphoma to a diffuse aggressive lymphoma is suspected. PET scanning can also differentiate between treated disease and active disease at the end of therapy in patients with residual masses on CT scans. Consensus recommendations regarding PET scanning were published as a result of an International Harmonization Project, and state that PET should only be used for DLBCL and Hodgkin's lymphoma, that scanning during therapy should only be done as part of clinical trials, and that the end-of-treatment scan should not be done before 3 weeks but preferably 6–8 weeks after chemotherapy and 8–12 weeks after radiation or chemoradiotherapy. There is no evidence that long-term follow-up should include PET scanning. More recently, though, PET scan results at the end of therapy for FL have been associated with prognosis, with patients with residual PET avid disease at the end of treatment having a poorer prognosis than those who are PET negative, and so it may be used for this prognostic purpose. Finally, magnetic resonance imaging (MRI) is useful in detecting bone, bone marrow and CNS disease in the brain and spinal cord. The staging evaluation is outlined in **Table 104-5**.

The Ann Arbor staging system developed in 1971 for HL was adapted for staging NHLs **(Table 104-6)**. This staging system focuses on the number of tumor sites (nodal and extranodal), location, and the presence or absence of systemic, or B, symptoms. Table 104-6 summarizes the essential features of the Ann Arbor system.

This anatomic based system is less useful in NHL, which disseminates widely, not in an ordered stepwise fashion. A majority of patients with NHL have advanced stage disease at diagnosis. Apart from early-stage disease limited to a radiation field where local

TABLE 104-5 Staging Evaluation for Non-Hodgkin's Lymphoma

Physical examination
Documentation of B symptoms
Laboratory evaluation
Complete blood counts
Liver function tests
Uric acid
Calcium
Serum protein electrophoresis
Serum β_2-microglobulin
Chest radiograph
CT scan of abdomen, pelvis, and usually chest
Bone marrow biopsy
Lumbar puncture in lymphoblastic, Burkitt's, and diffuse large B-cell lymphoma with positive marrow biopsy
Gallium scan (SPECT) or PET scan in large cell lymphoma

Abbreviations: CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

TABLE 104-7 International Prognostic Index for NHL

Five Clinical Risk Factors	
Age ≥60 years	
Serum lactate dehydrogenase levels elevated	
Performance status ≥2 (ECOG) or ≤70 (Karnofsky)	
Ann Arbor stage III or IV	
>1 site of extranodal involvement	
For Diffuse Large B-cell Lymphoma	
0, 1 factor = low risk	35% of cases; 5-year survival, 73%
2 factors = low-intermediate risk	27% of cases; 5-year survival, 51%
3 factors = high-intermediate risk	22% of cases; 5-year survival, 43%
4, 5 factors = high risk	16% of cases; 5-year survival, 26%
For Diffuse Large B-cell Lymphoma Treated With R-CHOP	
0 factor = good	10% of cases; 4-year survival, 94%
1, 2 factors = intermediate	45% of cases; 4-year survival, 80%
3, 4, 5 factors = poor	45% of cases; 4-year survival, 53%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

therapy with radiation is an option, all other disease is treated the same regardless of stage. Histology and clinical parameters at presentation are more important than stage with respect to prognosis. The International Prognostic Index (IPI) is perhaps the best predictor of outcome (Table 104-7). The IPI was developed based on the analysis of over 2000 patients with aggressive NHLs treated with an anthracycline containing regimen. Age (≤60 vs >60); serum LDH (≤normal vs >normal); performance status (0 or 1 vs 2–4); stage (I or II vs III or IV); and extranodal involvement (<1 site vs >1 site) were identified as independently prognostic for overall survival (OS). A point is awarded for each risk factor and then summed, defining four risk groups: low-risk (0 or 1); low-intermediate (2); high-intermediate (3); and high (4–5). The 5-year OS rates for patients with scores of 0 to 1, 2, 3, and 4–5 were 73, 51, 43, and 26%, respectively. The age-adjusted IPI separates patients ≤60 from patients >60. For the age adjusted IPI, only stage, LDH, and performance status were important. Younger patients with 0, 1, 2, or 3 risk factors had 5-year survival rates of 83%, 69%, 46%, and 32%, compared to 56%, 44%, 37%, and 21% for older patients. When factoring in the introduction and clinical benefit of rituximab, the 4-year progression-free survival is 94%, 80%, and 53% for 0 and 1, 2, or 3 or more risk factors, respectively.

The follicular lymphoma prognostic index (FLIPI) is a similar predictive model for FL, derived from the analysis of over 4000 patients. Age >60, stage III/IV disease, the presence of >4 nodal sites, an elevated serum LDH concentration and a hemoglobin <12 were identified as independent prognostic variables, and summation of each variable identified three risk groups. The median 10-year survival rates for patients with zero to one (low-risk), two (intermediate-risk), or three or more (high-risk) of these adverse factors were 71, 51, and 36%, respectively. Similar disease-specific IPIs have been developed for MCL and peripheral T-cell lymphoma (PTCL) as well. These prognostic indices take into account the proliferative index and cell surface markers, respectively.

Finally, as mentioned previously, gene expression profiling has identified DLBCLs with differential prognoses: GCB and ABC, where GCB-like DLBCL is associated with a significantly better OS. A more readily accessible immunohistochemical algorithm has been developed, based on the presence of absence of CD10, BCL6, and MUM1 that correlates closely with gene expression profiles and can differentiate the majority of GCB from non-GCB-like DLBCL. These profiles have prognostic importance but to date do not alter treatment recommendations for the primary treatment of DLBCL. Current clinical trials do stratify by DLBCL subtype, and it appears that agents like the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and lenalidomide are most active in non-GCB DLBCL in the relapsed setting. Treatment may then be differentiated by these subtypes in the future.

TABLE 104-6 Ann Arbor Staging for Lymphoma*

STAGE	DESCRIPTION
I	Involvement of a single lymph node region (I) or single extranodal site (IE)
II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous, extralymphatic organ or tissue (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS), or limited, contiguous, extralymphatic organ or tissue (IIIE), or both (IIIES)
IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

*All stages are further subdivided according to the absence (A) or presence (B) of systemic B symptoms including fevers, night sweats, and/or weight loss (>10% of body weight over 6 months prior to diagnosis).

CLINICAL FEATURES, TREATMENT, AND PROGNOSIS OF SPECIFIC NHL

MATURE B-CELL NEOPLASMS

B-cell NHLs can be characterized into two broad groups—those that behave aggressively, require immediate or urgent treatment with combination chemotherapy regimens, and are potentially curable, and those that are more indolent in nature, can be observed and treated only when they cause symptoms or signs of organ function impairment, are very responsive to therapy, but are not ultimately curable in the vast majority of cases. Among the aggressive diseases, the most common are NHL and DLBCL; and the most rapidly prolific are NHL and BL. FL is the second most common NHL and the most common indolent NHL. Other indolent NHLs include MZL, lymphoplasmacytic lymphoma (LPL), and hairy cell leukemia (HCL). MCL is an intermediate grade lymphoma that shares some characteristics with the aggressive lymphomas (fairly urgent need for treatment and aggressive upfront combination chemotherapy regimens), but like the indolent lymphomas, it is not readily curable with conventional dose therapies.

Burkitt's Lymphoma Burkitt's lymphoma/leukemia is a rare disease in adults in the United States, making up <1% of NHL, but it makes up ~30% of childhood non-Hodgkin's lymphoma. It is one of the fastest growing neoplasms, with a doubling time of <24 h. In general it is a pediatric tumor that has three major clinical presentations. The endemic (African) form presents as a jaw or facial bone tumor that spreads to extranodal sites including ovary, testis, kidney, breast, and especially to the bone marrow and meninges. The non-endemic form has an

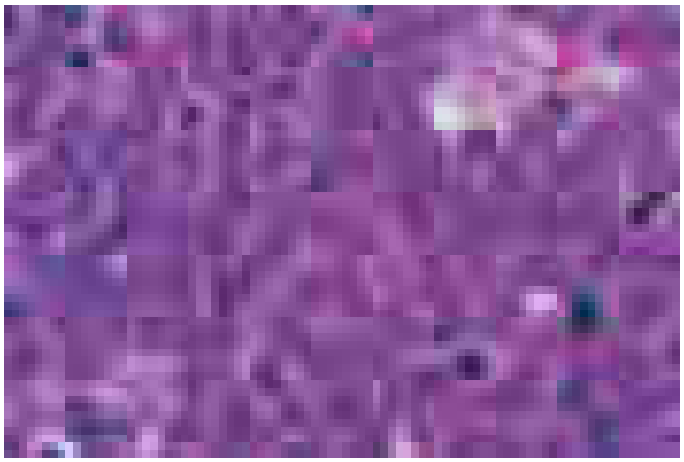

FIGURE 104-4 Burkitt's lymphoma. The neoplastic cells are homogeneous, medium-sized B cells with frequent mitotic figures, a morphologic correlate of high growth fraction. Reactive macrophages are scattered through the tumor, and their pale cytoplasm in a background of blue-staining tumor cells gives the tumor a so-called starry sky appearance.

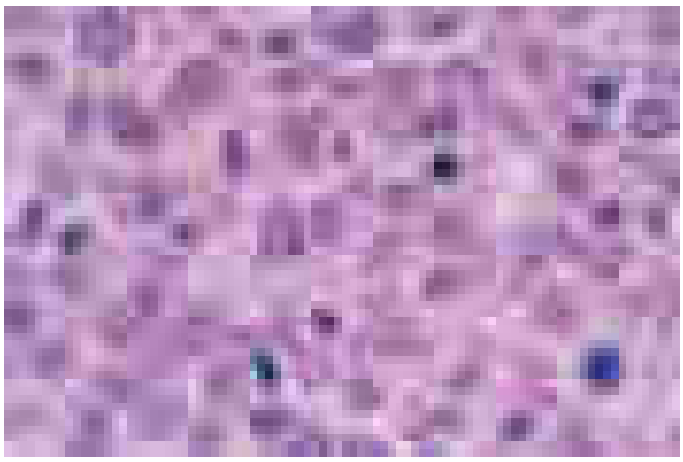

FIGURE 104-5 Diffuse large B-cell lymphoma. The neoplastic cells are heterogeneous but predominantly large cells with vesicular chromatin and prominent nucleoli.

abdominal presentation with massive disease, ascites, and renal, testis, and/or ovarian involvement, and, like the endemic form, also spreads to the bone marrow and CNS. Immunodeficiency-related cases more often involve lymph nodes and may present as acute leukemia. BL has a male predominance and is typically seen in patients <35 years of age.

On biopsy, there is a monotonous infiltration of medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm with vacuoles. The proliferation rate is ~100%, and tingible body macrophages give rise to the classic "starry sky" appearance of this tumor **(Fig. 104-4)**. Tumor cells are positive for B-cell antigens CD19, CD20, and surface immunoglobulin. They are also uniformly positive for CD10 and BCL6 but negative for BCL2. Endemic BLs are EBV positive, whereas the majority of non-endemic BLs are EBV negative. BL is associated with a translocation involving MYC on chromosome 8q24 in >95% of the cases. The most common partners are chromosomes 14, 2, or 22, rearrangements that produce fusions of MYC with either the IgH (80%), kappa (15%), or lambda (5%) light chain genes, respectively.

While exquisitely chemosensitive, it is imperative that treatment for BL be initiated quickly given the rapid doubling time and high morbidity of this disease. There are several effective intensive combination chemotherapy regimens, all of which incorporate high doses of cyclophosphamide. Prophylactic therapy to the CNS is mandatory. Cure can be expected in 70–80% of patients when treated promptly and correctly. Salvage therapy has been generally ineffective in patients whose disease progresses after upfront therapy, emphasizing the importance of the initial treatment approach and referral to a tertiary cancer center with experience treating this disease.

Diffuse Large B-Cell Lymphoma Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of NHL diagnosed, representing about one-third of all cases. Previously felt to be "one disease" it is now recognized as a heterogeneous collection of multiple entities. It is slightly more common in Caucasians and men, and the median age at diagnosis is 64. The relative risk of DLBCL is higher amongst people with affected first-degree relatives (RR 3.5-fold), and patients with congenital or acquired immunodeficiency, patients on immunosuppression, and patients with autoimmune disorders also have a higher risk of developing DLBCL, often EBV-related. The majority of patients present with advanced stage disease, with only 30–40% of patients having stage I or II disease; about 40% of patients will have "B" symptoms, and 50% of patients will have an elevated LDH. Up to 40% of patients will have involvement of non-lymph node sites including bone marrow, CNS, GI track, thyroid, liver, and skin. Patients with extensive bone marrow involvement, or involvement of the testes, breast, kidney, adrenal gland, paranasal sinus, or epidural space are at increased risk of CNS dissemination.

The tumor consists of a diffuse proliferation of large, atypical lymphocytes with a high proliferative index **(Fig. 104-5)**. These cells typically express the B-cell antigens CD19, CD20, and CD79a. Expression of CD10 and BCL6 is consistent with the tumor cell being of germinal center origin (GCB), while the expression of MUM1 corresponds with the non-GC or activated B cell (ABC) subtype. BCL2 is overexpressed in anywhere from 25 to 80% of DLBCL, whereas BCL6 is positive in more than two-thirds of cases, either as the result of translocations, gain of copy number, or promoter mutations. MYC is rearranged in 10% of DLBCLs, and ~20% of MYC-rearranged cases have concurrent BCL2 or BCL6 rearrangements, a combination referred to as "double-hit lymphoma." These double-hit lymphomas are associated with an extremely poor prognosis with a median OS of only 12–18 months. Amplification and/or overexpression of MYC independent of rearrangements or amplification has also been described and is also associated with a poor, albeit better, prognosis.

Combination chemotherapy offers potentially curative therapy for DLBCL, regardless of the stage. The addition of the anti-CD20 antibody rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) improved survival beyond CHOP alone and is the standard first-line chemotherapy for this disease. For patients with early stage disease localized to a radiation field, treatment options include full course chemotherapy with R-CHOP every 3 weeks for 6 cycles, or abbreviated chemotherapy for 3–4 cycles followed by involved field radiotherapy. For advanced stage DLBCL, therapy is with a full course of chemotherapy. On average, about 60–65% of patients with DLBCL can be expected to be cured with this approach, and the likelihood of cure is predicted by the IPI, gene expression profile cell of origin, and/or MYC cytogenetics and expression. Several studies have investigated alternative anthracycline-containing chemotherapy regimens and/or consolidation autologous stem cell transplantation in first remission for higher-risk disease without improvement over R-CHOP alone. Dose adjusted R-EPOCH (rituximab, infusional etoposide/vincristine/adriamycin, cyclophosphamide, prednisone) is one such regimen. Although this regimen is no better than R-CHOP for DLBCL in general, it is often used to treat primary mediastinal large B-cell lymphoma and double-hit DLBCL based on results from phase 2 and retrospective studies, respectively. CNS prophylaxis with either intrathecal chemotherapy or high-dose systemic methotrexate and leucovorin rescue should be considered for patients with high risk of CNS dissemination. This includes patients with primary testicular involvement and breast involvement, as well as patients with several IPI risk factors and diffuse bone marrow involvement, renal involvement, or adrenal involvement. The use of CNS prophylaxis for disease involving the paranasal sinuses or the epidural space is less clear but may be considered.

Over one-third of patients will either have primary refractory disease or disease that relapses after first-line chemotherapy. These patients may still be cured with salvage chemotherapy regimens

followed by autologous stem cell transplantation. Patients with a poor performance status or advanced age that are not candidates for such an approach, however, are often managed with palliative intentions. Radiation to symptomatic areas of disease can be transiently helpful. Less intensive chemotherapy with drugs like gemcitabine, cytarabine, or bendamusine can help control disease and symptoms for a limited period of time. These patients should be referred for clinical trials when applicable. For patients in whom more aggressive therapy is an option, treatment is with combination chemotherapy using various combinations of drugs primarily in order to identify patients with chemosensitive disease. Patients with chemosensitive disease have the greatest likelihood of benefiting from high-dose chemotherapy and autologous stem cell transplant, which improves response duration and survival over salvage chemotherapy alone and leads to long-term disease free survival in about 40–50% of patients. For patients with chemorefractory disease, clinical trials or palliative therapy or clinical trials should be considered, with a goal of achieving a disease response sufficient for allogeneic stem cell transplant. Several new agents have shown some promise in patients with relapsed DLBCL, including ibrutinib, particularly in the ABC cell of origin subtype, lenalidomide, and everolimus.

Chimeric antigen receptor T cells (CAR-T cells) are an investigational immunotherapy approach for treating malignancies that have had early success in CLL and B-cell acute lymphoblastic leukemia, as well as B-cell NHL. This strategy uses T cells collected from a patient that are genetically modified to express a receptor that will bind to a surface antigen expressed on the patient's own tumor cells. In the case of B-cell malignancies, CD19 has been targeted most commonly. After infusion, autologous CAR-T cells home to sites of disease and also persist over time. The CARs consist of an extracellular antigen recognition domain (typically a single chain Fv variable fragment from a monoclonal antibody) linked via a transmembrane domain to an intracellular signaling domain (usually the CD3ζ endodomain), resulting in the redirection of T-cell specificity toward target antigen-positive cells, and one or more costimulatory domains including CD28, 4-1BB, or OX40 to enhance cytokine secretion and effector cell expansion, and prevent activation-induced apoptosis and immune suppression by tumor-related metabolites. Anti-CD19 CAR-T cells have been approved for the treatment of relapsed/refractory DLBCL following two prior systemic therapies. This would include patients with chemoinsensitive disease following second-line salvage chemotherapy for whom autologous stem cell transplant is not an option, or for patients who relapse after autologous stem cell transplant. In this setting, the response rate of CAR-T cells is over 80%, with over 50% of patients achieving a complete response. These responses appear to be durable, with 70% of complete responders still in remission past 1 year of therapy.

Other large B-cell lymphomas include intravascular large B-cell lymphoma, T-cell/histiocyte–rich large B-cell lymphoma, EBV-positive DLBCL of the elderly, and ALK-positive large B-cell lymphoma. Patients with the latter two diseases tend to have a poor prognosis, whereas the addition of rituximab to CHOP chemotherapy has dramatically improved outcomes with intravascular large B-cell lymphoma, and the outcomes in T-cell/histiocyte-rich large B-cell lymphoma are similar to DLBCL. R-CHOP remains the treatment of choice for each of these lymphomas.

Follicular Lymphoma FLs are the second leading NHL diagnosis in the United States and Europe and makes up 22% of NHL worldwide and at least 30% of NHL diagnosed in the United States. This type of lymphoma can be diagnosed accurately on morphologic findings alone and has been the diagnosis in the majority of patients in therapeutic trials for "low-grade" lymphoma in the past.

Evaluation of an adequate biopsy by an expert hematopathologist is sufficient to make a diagnosis of FL. The tumor is composed of small cleaved and large cells in varying proportions organized in a follicular pattern of growth **(Fig. 104-6)**. Confirmation of B-cell immunophenotype (monoclonal immunoglobulin light chain, CD19, CD20, CD10 and BCL6 positive, and CD5 and CD23 negative) and the existence of the t(14;18) and abnormal expression of BCL-2 protein are confirmatory. While >85% of FL will harbor a t(14;18) and overexpress the antiapoptotic protein BCL2, this genetic event is necessary but not sufficient for malignant transformation of the B lymphocytes and multiple genetic events are required for the development of FL. Studies have identified the most common recurrent genetic events in FL, and they included mutations in several epigenetic modifying genes, including *MLL2, EZH2, CREBBP*, and *EP300*. The major differential diagnosis is between lymphoma and reactive follicular hyperplasia. The coexistence of DLBCL must be considered. Patients with FL are often subclassified, or graded, into those with predominantly small cells, those with a mixture of small and large cells, and those with predominantly large cells. The WHO Classification adopted grading from 1 to 3 based on the number of centroblasts, or large cells, counted per high power field (hpf): grade I, from 0 to 5 centroblasts/hpf; grade II, from 6 to 15 centroblasts/hpf; and grade III, >15 centroblasts/hpf. Grade III has been subdivided into grade IIIa, in which centrocytes predominate, and grade IIIb, in which there are sheets of centroblasts. While this distinction cannot be made simply or very reproducibly, these subdivisions do have prognostic significance. Patients with FL with predominantly large cells have a higher proliferative fraction, progress more rapidly, and have a shorter OS with simple chemotherapy regimens. Grade IIIb FL is an aggressive disease and considered most similar to DLBCL and treated as such with curative intent.

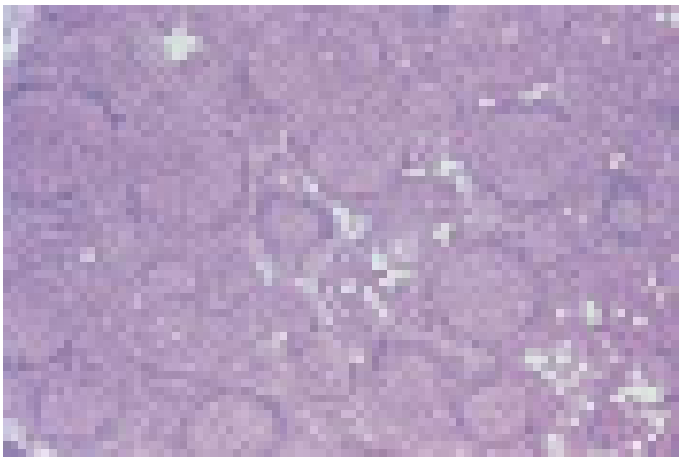

FIGURE 104-6 Follicular lymphoma. The normal nodal architecture is effaced by nodular expansions of tumor cells. Nodules vary in size and contain predominantly small lymphocytes with cleaved nuclei along with variable numbers of larger cells with vesicular chromatin and prominent nucleoli.

The most common presentation for FL is with new, painless lymphadenopathy. Multiple sites of lymphoid involvement are typical, and unusual sites such as epitrochlear nodes are sometimes seen. However, essentially any organ can be involved, and extranodal presentations do occur. Most patients do not have an elevated LDH or fevers, night sweats, or weight loss, although histologic transformation to DLBCL does occur at a rate of ~3% per year and can be associated with these signs/symptoms. As discussed previously, prognosis is best predicted by the FLIPI. Staging is typically done with CT scans of the chest, abdomen and pelvis, as well as the neck if neck disease is suspected, although PET/CT scans can be helpful in cases where disease transformation is suspected, as transformed disease will be more FDG avid than indolent disease, or for confirmation of early-stage disease, where definitive local therapy with radiation may be considered.

Although FL is highly sensitive to chemotherapy and radiotherapy, these therapies are usually not ultimately curative, except in the setting of early-stage disease. If the disease can be encompassed in a radiation field, involved field radiotherapy at a dose of 24–30 Gy may be curative, with 5-, 10-, and 15-year freedom from treatment failure of 72%, 46%, and 39%, and an overall 5-, 10-, and 15-year survival rates of 93%, 75%, and 62%, respectively. If radiation therapy would not be tolerated, or if a patient prefers not to receive radiation, observation is a reasonable alternative with a median time to treatment not reached at 7 years of follow-up in one study. Many of these patients are diagnosed incidentally or at a time when their lymphoma is not causing symptoms

or signs of organ function impairment. Numerous studies have shown that treating patients with asymptomatic disease does not improve survival compared with a program of close observation with treatment reserved for symptomatic disease progression or organ dysfunction. Thus, asymptomtic patients should be observed. When treatment is indicated, there are a variety of treatment options, ranging from the use of the monoclonal antibody against CD20, rituximab, alone or its use in combination with chemotherapy. Treatment decisions are often determined by the indication for treatment and/or by the volume of disease being treated. For patients requiring therapy for inflammatory or autoimmune phenomenon thought to be driven by FL, or for patients with low volume disease, single-agent rituximab is associated with a response rate of ~70% and a median response duration of >2 years. This response duration is improved with the addition of maintenance rituximab following a favorable response to rituximab induction therapy. For patients with a larger volume of disease at the time of treatment initiation, the addition of rituximab to chemotherapy like cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or cyclophosphamide, vincristine, and prednisone (CVP) has improved survival in this disease. The combination of bendamustine and rituximab (BR) has been compared to R-CHOP and results in longer response duration and less toxicity. BR then has become the standard of care for the first-line therapy of medium to high-volume FL. Similarly, the addition of maintenance rituximab following a good response to R-CHOP or R-CVP improves response duration when used in newly treated FL patients.

In patients with FL, the disease nearly always recurs following therapy, after which retreatment is again reserved for symptomatic disease or disease interfering with organ function. Single agent rituximab or alternative chemotherapy regimens can again be employed. Both autologous and allogeneic hematopoietic stem cell transplantation yield high complete response rates in patients with relapsed FL, and long-term remissions can occur in 40 and 60% of patients, respectively. The latter is associated with considerable treatment-related morbidity and mortality and so is usually reserved for patients with multiply relapsed FL that is no longer responsive to chemotherapy. More targeted oral therapies like lenalidomide and the PI3 kinase inhibitor idelalisib are active in both untreated and relapsed FL. On average, most patients will live with FL for 15–20 years, a number that is increasing given our improved understanding of the genetics and microenvironment of FL, and the increasing number of drugs and therapies being tested in this disease. However, in addition to a high risk FLIPI, patients who do not have a complete metabolic response by PET/CT scanning to their primary therapy, and patients who relapse within 2 years of the completion of their primary chemotherapy tend to do poorly with chemotherapy.

Patients with FL have a high rate of histologic transformation to DLBCL (~3% per year). This is recognized ~40% of the time during the course of the illness by repeat biopsy and is present in almost all patients at autopsy. This transformation is usually heralded by rapid growth of lymph nodes—often localized—and the development of systemic symptoms such as fevers, sweats, and weight loss. When this happens in patients who have had previously untreated FL, treatment with R-CHOP chemotherapy, as for DLBCL, can be curative for the aggressive component while the FL may eventually recur. In patients with previously treated FL that transforms to DLBCL, prognosis is poor, and successful therapy with an aggressive combination chemotherapy regimen should be consolidated with an autologous stem cell transplant. Finally, as discussed previously, grade 3B FL is more similar to DLBCL than it is to FL and should be treated as such.

Marginal Zone Lymphoma The second most common indolent B-cell NHL is MZL. There are three main types: splenic MZL, extranodal MZL of MALT, and nodal MZL.

Nodal MZL most closely resembles FL clinically, and much of the way we manage and treat it is based on studies done in FL. Tumor biopsies in this disease show parafollicular and perivascular infiltration by monocytoid-appearing atypical lymphocytes with folded nuclear contours that are positive for CD19, CD20, and CD79a but negative for CD10 and largely negative for CD5. Some cases can have plasmacytoid differentiation and can be associated with a monoclonal expression of kappa or lambda light chains and with small monoclonal immunoglobulin spikes.

Splenic MZL is largely a disease of older Caucasian patients; infection with hepatitis C is a risk factor for this disease and treatment of hepatitis C can result in regression of the lymphoma. Patients present with a lymphocytosis with or without cytopenias and splenomegaly. Bone marrow involvement is common. Diagnosis can be made by flow cytometry of the peripheral blood; malignant lymphocytes will be positive for surface immunoglobulin, CD19, and CD20 and will generally lack CD5 and CD10. On peripheral smear they have small nuclei and abundant cytoplasm with "shaggy" or villous projections. It can be differentiated from hairy cell leukemia by the absence of CD25, CD103, and annexin A1. Recurrent cytogenetic abnormalities include trisomy 3 and abnormalities of chromosome 7q. Therapy is indicated for symptomatic disease or significant cytopenias. Splenectomy is reasonable for selected patients with excellent relief of symptoms and cytopenias. Splenectomy is associated with an overall response rate of 85% and an estimated progression-free and OS at 5 years of 58 and 77%, respectively. Single-agent rituximab can improve splenomegaly and cytopenias in >90% of patients. In a study of induction with weekly rituximab followed by maintenance, the response rate was 95%, with overall and progression-free survival at 5 years of 92 and 73%, respectively. Other options for therapy at relapse are similar to those used for FL and include retreatment with rituximab, alkylating agents, and purine analogues in combination with rituximab. The survival rate of patients is in excess of 70% at 10 years.

MALT lymphoma is an MZL lymphoma of extranodal tissue, most commonly the stomach but other common sites include the skin, salivary glands, lung, small bowel, ocular adnexa, breasts, bladder, thyroid, dura, and synovium. It is associated with states of chronic inflammation either due to autoimmune diseases like Sjogren's syndrome or Hashimoto's thyroiditis, or chronic infections with organisms like *Helicobacter pylori* (gastric), *Borrelia burgdorferi* (skin), *Chlamydia psittaci* (conjunctiva), *Campylobacter jejuni* (intestines), and hepatitis C virus. The essential pathologic feature of MALT lymphoma is the presence of lymphepithelial lesions, which result from invasion of mucosal glands and crypts by the neoplastic lymphocytes. These cells are positive for CD19, CD20, and CD79a and negative for CD5 and CD10. Recurrent cytogentic abnormalities include t(11;18), t(14;18), t(1;14), t(3;14), and trisomy 8. The t(11;18) is most common, occurring in up to 50% of MALT lymphomas. It results in the fusion of the apoptosis inhibitor 2 (API2) gene and the MALT1 gene, resulting in activation of nuclear factor κB (NFκB). Unlike other indolent B-cell lymphomas, MALT lymphomas present most commonly with stage I or II disease. In these cases, radiation therapy may be curative. Alternatively, patients may respond to antibiotics for the associated underlying infection. Treatment of symptomatic or organ impairing relapsed, refractory, or advanced stage disease is similar to approaches used in FL with chemotherapy, immunotherapy, or chemoimmunotherapy.

Lymphoplasmacytic Lymphoma About 1% of all NHLs will be lymphoplasmacytic lymphomas, which are indolent B-cell NHLs with lymphoplasmacytic differentiation, most commonly associated with a monoclonal IgM paraprotein. Nearly all patients will have stage IV disease at diagnosis with bone marrow involvement. Patients with high levels of circulating IgM paraproteins constitute a specific entity known as Waldenstrom macroglobulinemia and can have symptoms due to hyperviscosity as a result of the circulating IgM. Activating mutations in MYD88, an adaptor protein that is involved in signaling downstream of the Ig receptor leading to NFκB activation, is present in >90% of cases. Tumor biopsies are notable for proliferation of small lymphocytes, lymphoplasmacytic cells, and plasma cells, and malignant lymphocytes are positive for CD19, CD20, and surface IgM but generally negative for CD5 and CD10. Like the other indolent NHLs, treatment is indicated for disease that causes symptoms or interferes with organ function; hyperviscosity related to elevated serum IgM and paraneoplastic neuropathy are additional indications for therapy. Single-agent rituximab may be useful for low-volume disease, but can be associated with a transient rise in serum IgM concentrations that

can cause or exacerbate hyperviscosity. Chemoimmunotherapy with regimens like BR and rituximab, cyclophosphamide, and dexamethasone are active, as are myeloma therapies such as bortezomib. Given that 85% of IgM remains intravascular, acute relief of hyperviscosity symptoms can be obtained by plasmapheresis. For recurrent disease, one can often utilize agents that were previously used. For patients with more refractory LPL, the mTOR inhibitor everolimus and the oral BTK ibrutinib are active. Selected patients with relapsed disease are considered for high-dose therapy with ASCT or alloSCT. The results seen are similar to that of other indolent lymphomas.

Mantle Cell Lymphoma MCL comprises about 6% of NHLs. It is an intermediate grade lymphoma that like the indolent B-cell NHLs is not curable with conventional therapies, but like the aggressive lymphomas often requires more aggressive chemoimmunotherapy regimens with or without an autologous stem cell transplant to achieve a reasonable response duration. This therapy is not curative, however, and median survival with this disease is on the order of 5–10 years. An exception to this is a more indolent, SOX11 variant that often presents with circulating disease with splenomegaly but without significant lymphadenopathy and with a low Ki67 (<10%). This subset behaves more like the indolent B-cell NHLs and can be observed until treatment is indicated by symptoms or organ function impairment. Similarly, there is a blastic variant with a high Ki67 index that is associated with a poor prognosis and a median OS of only 18 months. For other patients, prognosis is best predicted by the biologic mantle cell prognostic index (MIPI), which factors in age, performance status, LDH, white blood cell count, and Ki67 expression to determine a risk group. This disease is more common in men, and the average age of diagnosis is 63. Over two-thirds of patients will have stage IV disease, mostly with bone marrow and peripheral blood involvement, at the time of diagnosis. Other common extranodal sites of involvement include the GI tract where diffuse lymphomatous polyposis may be seen.

The pathognomonic cytogentic finding in MCL is t(11;14), which brings the gene for the cell cycle control protein cyclin D1 under the control of the immunoglobulin heavy chain gene promoter on chromosome 14. This translocation is present in >90% of cases. The remaining cases usually overexpress cyclin D2, cyclin D3, or cyclin E. Tumor cells also are positive for B-cell markers CD19 and CD20, as well as CD5. They usually lack CD10 and CD23.

Therapies for MCL are evolving. Patients with localized disease might be treated with combination chemotherapy followed by radiotherapy; however, these patients are exceedingly rare. Similarly, patients with the indolent variant can be observed until disease progresses to cause symptoms or signs of organ function impairment. For the usual presentation with disseminated disease, standard lymphoma treatments like R-CHOP have been unsatisfactory, with the minority of patients achieving complete remission. The addition of high dose cytarabine to an R-CHOP-like backbone with or without consolidation autologous stem cell transplantation in first remission has improved progression-free survival, but it has not elicited cures in this disease. These include the Nordic regimens and R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate). BR has activity in this disease and is more effective and better tolerated than R-CHOP. Newer studies with short follow-up suggest that strategies that combine BR with cytarabine with or without autologous stem cell transplant may be effective and well tolerated. Maintenance rituximab, following a good response to induction chemotherapy or after autologous stem cell transplant, also improves outcomes over observation alone. For relapsed disease, the BTK inhibitor ibrutinib has single-agent activity with a response rate of almost 70% but a response duration of only 18 months. Drugs like lenalidomide, bortezomib, and temsirolimus can similarly induce transient partial responses. Appropriate patients who respond to salvage therapy should be considered for allogeneic stem cell transplant, which can lead to long-term disease-free survival in 30–50% of patients.

MATURE (PERIPHERAL) T-CELL DISORDERS

Mature T-cell disorders include cutaneous lymphomas, like mycosis fungoides, and the PTCLs, some of which are distinguished based on specific clinical presentations or contexts or by molecular or biologic features, but many of which fall into the category of PTCL not otherwise specified (NOS). T-cell NHLs are significantly more rare than the B-cell NHLs, and as such, our understanding of their biology is less advanced, and our therapies are less well developed. While some T-cell lymphomas, like mycosis fungoides, can behave indolently and some, like ALK-positive ALCL, can be cured with chemotherapy, the majority are associated with a poor prognosis. The advent of genomic technologies is enhancing our ability to understand the genetic and biologic basis of these neoplasms.

Mycosis Fungoides Mycosis fungoides is also known as cutaneous T-cell lymphoma. This lymphoma is more often seen by dermatologists than internists. The median age of onset is in the mid-fifties, and the disease is more common in males and in blacks.

Mycosis fungoides is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. The skin lesions progress from patch stage to plaque stage to cutaneous tumors. Early in the disease, biopsies are often difficult to interpret, and the diagnosis may only become apparent by observing the patient over time. Adenopathy may reflect involvement with mycosis fungoides or be read as dermatopathic change. In advanced stages, the lymphoma can spread to lymph nodes and visceral organs. Patients with this lymphoma may develop generalized erythroderma and circulating tumor cells, called *Sézary's syndrome*.

Rare patients with localized early-stage mycosis fungoides can be cured with radiotherapy, often total-skin electron beam irradiation. More advanced disease has been treated with topical glucocorticoids, topical nitrogen mustard, phototherapy, psoralen with ultraviolet A (PUVA), extracorporeal photopheresis, retinoids (bexarotene), electron beam radiation, interferon, antibodies, fusion toxins, histone deacetylase inhibitors, and systemic cytotoxic therapy. Unfortunately, these treatments are palliative.

Peripheral T-Cell Lymphoma, Not Otherwise Specified PTCLs include a number of entities, which constitute 15% of all NHLs in adults. PTCL, NOS, comprising 6% of all NHLs, is the term used for cases that are not other entities defined in the WHO classification. Named varieties include ALCL, angioimmunoblastic T-cell lymphoma (AITL), hepatosplenic T-cell lymphoma, enteropathy-associated T-cell lymphoma, and subcutaneous panniculitis T-cell lymphoma. PTCL NOS is a disease of older individuals, with a median age at presentation of 65, and the majority of patients will have advanced-stage disease at diagnosis, with involvement of the bone marrow, liver, spleen, and skin being common. Associated "B" symptoms and pruritis are also common. These lymphomas can be associated with a reactive eosinophilia as well as hemophagocytic syndrome. The IPI has been applied to PTCL NOS and provides some assessment of outcomes, but even the low-risk group has a median OS of just >2 years.

This diagnostic category is a collection of heterogeneous lymphomas that vary widely and lack typical findings of other specific PTCL subgroups. Because of this heterogeneity, histology, immunophenotype, and genetics are variable. Often lymph nodes are effaced by atypical lymphoid cells of various sizes, sometimes associated with vascular proliferation or an infiltrate of eosinophils and/or macrophages. As most of these lymphomas behave aggressively, note is often made of mitotic and apoptotic figures as well as geographic necrosis. The cells often are positive for CD3, and the majority of PTCL NOS is positive for CD4 rather than CD8, but some are negative for both markers. There can be loss of more mature T-cell markers like CD5 and CD7, and this is associated with a more aggressive course. There are some recurrent translocations, including t(7;14), t(11;14), inv(14), and t(14;14), all of which involve the TCR genes.

The most common primary therapy for PTCL NOS involves a CHOP-like chemotherapy backbone—either CHOP alone or CHOP in combination with etoposide, or CHOEP. The latter may provide the most benefit to younger patients and patients with more favorable disease risk factors. Autologous stem cell transplant has been investigated for patients in their first remission and does seem to improve PFS in certain contexts. Drugs like gemcitabine, bendamustine, and

pralatrexate have activity in relapsed disease, as do the histone deacetylase inhibitors romidepsin and belinostat. All of these agents are associated with transient responses in a minority of patients. Patients should be considered for clinical trials. For patients who do achieve remission, reduced intensity allogeneic stem cell transplantation can yield long-term non-relapse survival on the order of 40–50%.

Angioimmunoblastic T-Cell Lymphoma AITL constitutes about 20% of T-cell NHL and about 4% of all NHL diagnosed. Patients present with a variety of signs and symptoms, most often including lymphadenopathy, hepatosplenomegaly, B symptoms, rash, polyarthritis, and hemolytic anemia. Over 80% of patients have advanced stage disease at diagnosis, and bone marrow involvement is common. Polyclonal hypergammaglobulinemia is common, as are elevated LDH, eosinophilia, a positive Coombs test, and opportunistic infections.

On biopsy, lymph nodes are effaced by a polymorphous infiltrate of lymphoctyes, ranging in size and shape, and of immunoblasts. The neoplastic lymphocytes are positive for CD3 as well as CXCL13, PD-1, CD10, and BCL6, most closely resembling CD4-positive follicular helper T cells. There is an expanded follicular dendritic cell network surrounding tumor cells. Scattered immunoblasts are often EBV positive and may give rise to secondary EBV-positive B-cell lymphomas at a later time. Genetic analysis of this disease has revealed recurrent mutations in *TET2* (76%), *DNMT3* (33%), and *IDH2* (20%).

There is a subset of AITL that can remit with immunosuppression with agents like glucocorticoids or methotrexate. Most patients, however, will need combination chemotherapy with regimens like those used in PTCL NOS. Median response duration is short, median OS is only 15–36 months. Treatment of relapsed disease is similar to that of relapsed PTCL NOS.

Anaplastic Large Cell Lymphoma ALCL is the next most common T-cell lymphoma after AITL but is more common in children, accounting for up to 10% of pediatric lymphomas. Approximately 40–60% of cases with harbor t(2;5) which fuses a portion of the nucleolar protein nucleophosmin-1 (NPMI) gene to a part of the anaplastic lymphoma kinase (ALK) gene, the product of which has constitutive tyrosine kinase activity. These patients have a much more favorable prognosis compared to ALK-negative ALCL, akin to that of DLBCL. There is an additional, more indolent and favorable subtype that occurs in the breast tissue of patients with breast implants, and there is a cutaneous variant. In general, this is a disease that is more common in men. ALK-positive disease is a disease of younger patients with a median age at diagnosis of 34 years, whereas the median age at diagnosis of ALK negative patients is 58. With the exception of the cutaneous variant and the variant associated with breast implants, most patients present with rapidly growing lymphadenopathy with or without extranodal involvement; B symptoms are common.

Most cases of ALCL involve large atypical lymphocytes with a horseshoe-shaped nuclei with prominent nucleoli ("hallmark" cells). Tumor cells tend to be localized within the lymph node sinuses, and almost all are positive for CD30 but negative for CD15. A majority will also express CD3, CD25, CD43, and CD4. ALK rearranged ALCL can be diagnosed by FISH cytogenetics for t(2;5) or by immunohistochemical staining for ALK.

ALCL is generally treated with CHOP, although like PTCL NOS, CHOEP may benefit younger patients, particularly with ALK+ disease. Overall, ALCL has a better prognosis than PTCL, and this is particularly true for ALK-positive disease, which has an 8-year OS of 82 versus 49% for ALK-negative disease. Relapsed ALK-positive ALCL is treated similarly to relapsed DLBCL, with salvage combination chemotherapy to identify chemotherapy sensitivity followed by autologous stem cell transplant. For patients with chemoinsensitive diseaese or for ALK-negative disease, the conjugated anti-CD30 antibody to monomethyl aurostatin E (MMAE) brentuximab is highly active with a response rate of 86% and a complete response rate of 57%. It is currently being investigated in combination with cyclophosphamide, adriamycin, and prednisone for the primary treatment of disease. The ALK inhibitors, including crizotinib, are active in refractory ALK-positive ALCL with excellent outcomes.

Other PTCL Subtypes Enteropathy-associated T-cell lymphoma, hepatosplenic T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma are other less common PTCL subtypes. Enteropathy-type intestinal T-cell lymphoma is a rare disorder. Type I occurs in patients with a history of gluten-sensitive enteropathy and is associated with HLADQA1*0501, DQB1*0201; a gluten-free diet can prevent the development of this lymphoma. Type II is not associated with celiac disease and may be a separate disease entity. Patients are frequently cachectic and sometimes present with intestinal perforation. The prognosis is poor with a median survival of 10 months. Therapy is often with combination chemotherapy, including high-dose methotrexate, and autologous stem cell transplant in first remission. *Hepatosplenic γδ T-cell lymphoma* is a systemic illness that presents with sinusoidal infiltration of the liver, spleen, and bone marrow by malignant T cells. Tumor masses generally do not occur. The disease is associated with systemic symptoms and is often difficult to diagnose. Recurrent genetic events include isochromosome 7q and trisomy 8. Treatment outcome is poor, but regimens that include ifosphamide, like ifosphamide, carboplatin, etoposide (ICE) or ifosphamide, etoposide, cytarabine (IVAC), are associated with better outcomes in small series of patients. Responding patients should be considered for allogeneic stem cell transplantation. *Subcutaneous panniculitis-like T-cell lymphoma* is a rare disorder that is often confused with panniculitis. Patients present with multiple subcutaneous nodules, which progress and can ulcerate. There is a more indolent form that tends to express α/β TCRs and can be managed with immune suppression, whereas lymphomas that express γ/δ TCRs are more aggressive and are associated with a worse prognosis and coincident hemophagocytic syndrome. This is a disease of young men in their fifth and sixth decades of life. Patients with aggressive disease are managed with multiagent chemotherapy, and responding patients should be considered for allogeneic stem cell transplantation.

Adult T-Cell Leukemia/Lymphoma Adult T-cell leukemia/lymphoma (ATLL) is a disease that is most prevalent in Japan and the Caribbean basin. It is a neoplasm that is driven by HTLV-1, often contracted through the breast milk of infected mothers. The average age at diagnosis is 60, so there is a long latency between viral infection and viral transformation, and only 4% of infected patients will develop the disease. This suggests that HTLV-1 may not be sufficient to cause the malignant phenotype. There are four disease variants: acute (60% of patients), lymphomatous (20% of patients), chronic (15% of patients), and smoldering (5% of patients). Prognosis varies across these groups with with median survivals of 6 months, 10 months, 24 months, and not yet reached, respectively. Presentation depends on the subtype, but most commonly patients present with circulating disease and bone marrow involvement, hypercalcemia, lytic bone lesions, lymphadenopathy, heptosplenomegaly, skin lesions, and opportunistic infections.

The pathognomonic finding is the malignant "flower cell" that is positive for CD4 and CD25, as well as CD2, CD3, and CD5 but lacking CD7 **(Fig. 104-7).** Combination chemotherapy is generally used,

FIGURE 104-7 Adult T-cell leukemia/lymphoma. Peripheral blood smear showing leukemia cells with typical "flower-shaped" nucleus.

but for patients fortunate enough to respond, response durations are very short. Other active agents in this disease include the antiretroviral agent zidovudine, interferon α, and arsenic. In any patients who do respond to therapy, allogeneic stem cell transplant should be considered.

Extranodal NK/T-Cell Lymphoma, Nasal Type Extranodal NK/T-cell lymphoma, nasal type, is a lymphoma that is associated with EBV infection in nearly all cases and more common in Asia and native populations in Peru. It usually presents with a mass and obstructive symptoms in the upper aerodigestive tract with occasional extranodal sites, but over two-thirds of patients will have localized disease. It is more common in men, and the median age at diagnosis is 60. This disease has its own prognostic score, which takes into account the presence or absence of B symptoms, disease stage, whether LDH is elevated, and whether there is lymph node involvement. EBV viral load at diagnosis and end of therapy is also predictive.

Treatment for early stage disease is usually with combined modality therapy of chemotherapy (commonly using etoposide, ifosfamide, cisplating, and dexamethasone) and intensity-modulated radiation therapy (50–55 Gy), and patients with localized disease involving the nasal passages do quite well, with 3-year OS of ~85%. Patients with more advanced stage disease do poorly with disseminated extranodal relapse occurring frequently, and median OS is only 4.3 months. The most commonly used regimen for the regimens is the SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide).

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105 Hodgkin's Lymphoma

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Hodgkin's lymphoma (HL) is a malignancy of mature B lymphocytes. It represents ~10% of all lymphomas diagnosed each year. The majority of HL diagnoses are classical HL (cHL), but there is a second subtype of HL, nodular lymphocyte predominant HL (NLPHL). While this diagnosis does resemble cHL morphologically in certain respects, there is some evidence that it is more related to the indolent B-cell NHLs biologically than it is to cHL. The majority of this chapter will be specific to cHL, with a discussion of NLPHL at the end.

Classical HL is one of the success stories of modern oncology. Until the advent of extended-field radiotherapy in the mid-twentieth century, it was a highly fatal disease of young people. Radiation therapy cured some patients with early stage disease, and the introduction of multi-agent chemotherapy in the 1970s resulted in further improved cure rates, both for patients with early and advanced stage disease. Cure rates now are >85%. The new challenge in the treatment of HL is late therapy-related toxicity, including a high rate of secondary malignancies and cardiovascular disease. Current clinical trials are aimed at minimizing this risk while preserving efficacy.

EPIDEMIOLOGY AND ETIOLOGY

HL is of B-cell origin. The incidence of HL appears fairly stable, with 8260 new cases diagnosed in 2017 in the United States. HL is more common in whites than in blacks and more common in males than in females. A bimodal distribution of age at diagnosis has been observed, with one peak incidence occurring in patients in their twenties and the other in those in their eighties. Some of the late age peak may be attributed to confusion among entities with similar appearance such as anaplastic large cell lymphoma and T-cell/histiocyte–rich B-cell lymphoma. There are four distinct subtypes of classical Hodgkin's lymphoma (cHL) that are differentiated based on their histopathologic features **(Table 105-1)**: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted. Patients in the younger age groups diagnosed in the United States largely have the nodular sclerosing subtype of HL. Elderly patients, patients infected with HIV, and patients in Third World countries more commonly have mixed-cellularity HL or lymphocyte-depleted HL. Together, nodular sclerosis and mixed cellularity types account for nearly 95% of cases. Infection by HIV is a risk factor for developing HL. In addition, an association between infection by Epstein-Barr virus (EBV) and HL has been suggested. A monoclonal or oligoclonal proliferation of EBV-infected cells in 20–40% of the patients with HL has led to proposals for this virus having an etiologic role in HL. However, the matter is not settled definitively. Viral oncogenesis appears to play a greater role in HIV-related cHL: EBV can be detected in nearly all cases of HIV-associated cHL, compared to only one-third of cases of non-HIV-associated cHL. Reed-Sternberg (HRS) cells are the malignant cells in HL. HRS cells in HIV-associated cHL express the EBV-transforming protein latent membrane protein 1 (LMP-1), and the EBV genomes from multiple disease sites in the same HIV-associated cHL patient are episomal and clonal, suggesting that EBV is directly involved in early lymphomagenesis.

Histologically, the HRS cell is diagnostic of cHL **(Fig. 105-1)**. These cells are large cells with abundant cytoplasm with bilobed and/or multiple nuclei. By immunohistochemistry they are often PAX-5 positive but have low to no expression of other B-cell antigens like CD19 and CD20. They express CD15 and CD30 in 85 and 100% of cases, respectively. These cells, though, comprise <1% of the tumor cellularity, with the majority of the tumor made up of a surrounding inflammatory infiltrate of polyclonal lymphocytes, eosinophils, neutrophils, macrophages, plasma cells, fibroblasts, and collagen. The HRS cell interacts with its microenvironment via cell-cell contact and elaboration of growth factors and cytokines, which results in a surrounding cellular milieu that protects it from host immune attack. The surrounding environmental cells likewise support the HRS cells via cell-cell signaling and cytokine production which provides signals that promote proliferation and survival of the HRS cell itself. Interestingly, 97% of HRS cells in cHL harbor genetic aberrations in the PD-L1 locus on chromosome 9p24.1, resulting in overexpression of PD-L1, the ligand for

TABLE 105-1 WHO Classification of Hodgkin's Lymphoma

Nodular lymphocyte predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis
Lymphocyte-rich
Mixed cellularity
Lymphocyte-depleted

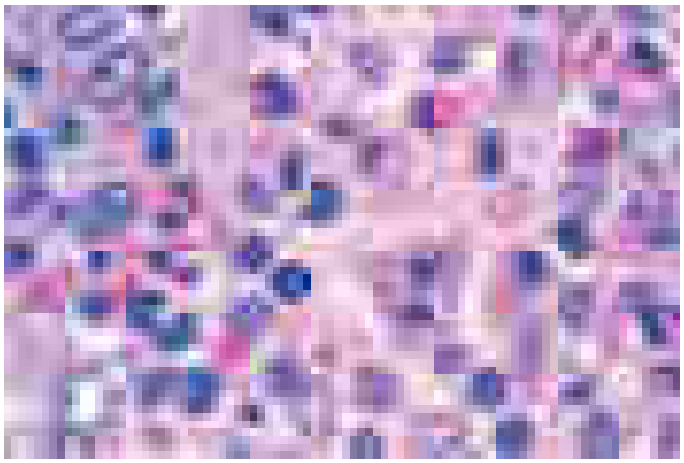

FIGURE 105-1. Hodgkin's disease: A classic Reed-Sternberg (RS) cell is present near the center of the field. RS cells are large cells with a bilobed nucleus and prominent nucleoli surrounded by a pleiomorphic cellular infiltrate.

the inhibitory PD-1 receptor on immune cells. This is one mechanism whereby the HRS cell may be able to avoid immune destruction in its inflammatory microenvironment and may contribute to the generalized immune suppression in HL patients.

APPROACH TO THE PATIENT

Classic Hodgkin's Lymphoma

Most patients with cHL present with palpable lymphadenopathy that is nontender; in most patients, these lymph nodes are in the neck, supraclavicular area, and axilla. More than half of the patients will have mediastinal adenopathy at diagnosis, and this is sometimes the initial manifestation. Subdiaphragmatic presentation of cHL is unusual and more common in older males. One-third of patients present with fevers, night sweats, and/or weight loss, or "B" symptoms. Occasionally, HL can present as a fever of unknown origin. This is more common in older patients who are found to have mixed-cellularity HL in an abdominal site. Rarely, the fevers persist for days to weeks, followed by afebrile intervals and then recurrence of the fever. This pattern is known as *Pel-Ebstein* fever. HL can occasionally present with unusual manifestations. These include severe and unexplained itching, cutaneous disorders such as erythema nodosum and ichthyosiform atrophy, paraneoplastic cerebellar degeneration and other distant effects on the CNS, nephrotic syndrome, immune hemolytic anemia and thrombocytopenia, hypercalcemia, and pain in lymph nodes on alcohol ingestion.

Evaluation of patients with HL will typically begin with a careful history and physical examination. Patients should be asked about the presence or absence of "B" symptoms. Comorbid diagnoses that may impact therapy should be reviewed, including a history of pulmonary disease and congestive heart failure given the use of chemotherapy drugs that can cause both lung and heart toxicity. A physical examination should pay attention to the peripherally accessible sites of lymph nodes and to the liver and spleen size. Laboratory evaluation should include a complete blood count with differential; erythrocyte sedimentation rate; chemistry studies reflecting major organ function including serum albumin; and HIV and hepatitis virus testing. A PET/CT scan is used for staging, and is more accurate than a bone marrow biopsy for evaluation of bone marrow involvement as the bone marrow involvement in cHL tends to be patchy and therefore potentially missed on a unilateral bone marrow biopsy. The initial evaluation of a patient with HL or NHL is similar. In both situations, the determination of an accurate anatomic stage is an important part of the evaluation. Staging is done using the Ann Arbor staging system **(Table 105-2)**.

TABLE 105-2 The Ann Arbor Staging System for Hodgkin's Lymphoma

STAGE	DEFINITION
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E"
	More than one extranodal deposit at any location
	Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation
	Unexplained, persistent, or recurrent fever with temperatures >38°C during the previous month
	Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

The diagnosis of HL is established by review of an adequate biopsy specimen by an expert hematopathologist. HL is a tumor characterized by rare neoplastic cells of B-cell origin (immunoglobulin genes are rearranged but not expressed) in a tumor mass that is largely polyclonal inflammatory infiltrate, probably a reaction to cytokines produced by the tumor cells. The differential diagnosis of a lymph node biopsy suspicious for HL includes inflammatory processes, mononucleosis, NHL, phenytoin-induced adenopathy, and nonlymphomatous malignancies.

Staging for cHL is anatomically based given the propensity of the disease to march from one lymph node group to the next group, often contiguous to the first. Staging is important for selecting therapy of appropriate intensity, but the outcome of optimal therapy for all the stages is excellent. Patients are stratified based on whether they have early stage, stage I or II, or advanced stage, stage III or IV, disease. Patients with early stage disease have a better prognosis overall but are further classified as favorable or unfavorable based on a variety of factors. These factors vary from study to study but include bulky disease, number of lymph node areas involved, an elevated ESR (>30 if B symptoms are present; >50 if B symptoms are absent), and age. Prognosis in advanced stage disease is best predicted by the International Prognostic Score (IPS), which ascribes a point for male sex, older age (>45 years), stage IV disease, serum albumin <4 g/dL, hemoglobin <10.5 g/dL, white blood cell count ≥15,000/μL, and a lymphocyte count <600/μL and/or <8% of white blood cell count. Five-year progression-free survival ranges from 88% for patients with no risk factors, to 62% for patients with four or more factors, but very few patients have multiple risk factors.

TREATMENT

Classic Hodgkin's Lymphoma

The overwhelming majority of patients with HL will be cured with either chemotherapy alone, or a combination of chemotherapy and radiation therapy. It has long been appreciated that patients with advanced stage disease do not benefit from the addition of radiation

therapy to chemotherapy and are thus treated with chemotherapy alone. For early stage disease, however, treatment with combined modality therapy has been associated with a small decrease in risk of relapse but with an increased risk of late toxicity including secondary malignancies, thyroid disease, and premature cardiovascular disease and stroke resulting in minimal or no improvement in long-term survival. Much of this risk can be attributed to radiation therapy. Thus, investigation into the treatment of early stage HL at present is aimed at trying to maximize treatment outcome without using radiotherapy. This is an area of controversy in the treatment of HL.

EARLY STAGE DISEASE

The most common chemotherapy regimen used to treat HL in the United States is ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). This regimen is given every other week, with each cycle including two treatments. In patients with low-risk, or favorable disease, the use of 4–6 cycles of ABVD alone, without radiation therapy, results in progression-free and overall survivals of 88–92% and 97–100% at 5–7 years. This may be associated with a slightly increased risk of relapse when compared with abbreviated chemotherapy (ABVD x4 cycles) followed by involved field radiation therapy (30 Gy), but with no difference in overall survival owing to the excellent salvage strategies used for relapsed HL and to the late toxicities seen following radiation therapy to the chest. German studies have examined a very abbreviated chemotherapy regimen (ABVD x2 cycles) and low-dose radiation (20 Gy) for particularly good risk disease with two or fewer lymph node areas involved and found that this was equally effective to standard combined modality therapy of ABVD x4 cycles and 30 Gy of radiation, though long-term follow-up is not yet available to assess the impact of the lower radiotherapy dose on late toxicities. Finally, the use of an early interim PET/CT scan can aid decisions on the duration and extent of therapy. In one study, a negative PET/CT scan after 3 cycles of ABVD predicted for excellent outcomes with no additional therapy; in another, a negative PET/CT scan after 2 cycles of ABVD predicted for good outcomes with 2 additional cycles of ABVD alone, without radiation therapy.

For unfavorable risk disease, the omission of radiation therapy following chemotherapy is associated with a more significant increased risk of relapse compared to favorable risk disease, but again with no change in overall survival. For these patients, treatment options would include ABVD x4 cycles followed by involved field radiation therapy or ABVD alone for 6 cycles. Treatment decisions are often based on the extent of the radiation field and the unfavorable risk factor, with patients with non-bulky disease being candidates for chemotherapy alone if radiation would be contraindicated for another reason. Combined modality therapy has typically been used for patients with bulky disease, although patients with bulky disease who have a negative PET/CT scan after chemotherapy may not benefit from additional radiation therapy.

Alternative chemotherapy regimens to ABVD have been developed and include the Stanford V regimen and escalated BEACOPP. Neither of these regimens has resulted in improved outcomes in patients with early stage disease.

ADVANCED STAGE DISEASE

Patients with advanced stage disease do not benefit from the addition of radiation therapy after a complete response to chemotherapy alone and should be treated with chemotherapy alone. The most common regimen used in the United States is ABVD x6 cycles. Again, Stanford V and escalated BEACOPP have been evaluated in advanced stage disease and are not associated with an improvement in overall survival but are associated with increased toxicity. The small fraction of patients who do not achieve complete remission with chemotherapy alone (partial responders with persistent PET scan positivity account for <10% of patients) may benefit from the addition of involved field radiotherapy.

Newer drugs have been developed for the treatment of relapsed HL (see "Relapsed Disease," below). These include the antibody drug conjugate brentuximab, which is an antibody against CD30 conjugated to the microtubule inhibitor MMAE. This drug has been combined with adriamycin, bleomycin, and dacarbazine in early phase studies for advanced stage HL with favorable efficacy compared to historical controls. We await the data from the randomized trial of AVD+brentuximab compared to ABVD. Drugs that target the PD-1/PD-L1 axis have been developed in an attempt to boost the host immune recognition of tumors. This was particularly attractive in HL given the overexpression of PD-L1 on the HRS cell surface. In the setting of relapsed disease, these drugs, which include pembrolizumab and nivolumab, have very high response rates and are associated with durable responses. These are now being tested in conjunction with chemotherapy both as salvage therapy for relapsed disease and in previously untreated patients.

RELAPSED DISEASE

Patients who relapse after primary therapy of Hodgkin's lymphoma can frequently still be cured. Patients who relapse after an effective chemotherapy regimen are usually not curable with subsequent chemotherapy administered at standard doses. Alternative salvage chemotherapy administered at standard doses, then, is given in order to document sensitivity to chemotherapy and to achieve maximum reduction of tumor mass. For patients who respond completely or nearly so, autologous bone marrow transplantation can cure over half of patients. Standard salvage chemotherapy regimens include ICE (ifosfamide, carboplatin, etoposide) or GND (gemcitabine, navelbine, doxil). For patients with early stage disease who do not respond sufficiently to salvage chemotherapy, radiation therapy can be very effective to achieve a remission; whether to consolidate such a remission with an autologous stem cell transplant is debated. For patients with advanced stage disease in whom salvage chemotherapy fails, the antibody drug conjugate brentuximab vedotin, a CD30-directed antibody linked to the microtubule toxin MMAE, is active and can be tried as a bridge to allogeneic transplant. This immunotoxin is also being combined with chemotherapy for use in both the first-line salvage setting and for the upfront treatment of both early- and advanced-stage disease. The anti-PD-1 immune checkpoint inhibitors, nivolumab and pembrolizumab, have efficacy in relapsed HL, and many responses are durable.

SURVIVORSHIP

Because of the very high cure rate in patients with HL, long-term complications have become a major focus for clinical research. In fact, in some series of patients with early-stage disease, more patients died from late complications of therapy than from HL itself. This is particularly true in patients with localized disease. The most serious late side effects include second malignancies and cardiac injury. Patients are at risk for the development of acute leukemia in the first 10 years after treatment with combination chemotherapy regimens that contain alkylating agents plus radiation therapy. The risk for development of acute leukemia is greater after MOPP-like and BEACOPP-like regimens than with ABVD. The risk of development of acute leukemia after treatment for HL is also related to the number of exposures to potentially leukemogenic agents (i.e., multiple treatments after relapse) and the age of the patient being treated, with those aged >60 years at particularly high risk. The development of carcinomas as a complication of treatment for HL is a major problem. These tumors usually occur ≥10 years after treatment and are associated with use of radiotherapy. For this reason, young women treated with thoracic radiotherapy for HL should institute screening mammograms 5–10 years after treatment, and all patients who receive thoracic radiotherapy for HL should be discouraged from smoking. Mediastinal radiation also accelerates coronary artery disease, and patients should be encouraged to minimize risk factors for coronary artery disease such as smoking and elevated cholesterol levels. Cervical radiation therapy increases the risk of carotid atherosclerosis and stroke and thyroid disease, including cancer.

A number of other late side effects from the treatment of HL are well known. Patients who receive thoracic radiotherapy are at very high risk for the eventual development of hypothyroidism and should be observed for this complication; intermittent measurement of thyrotropin should be made to identify the condition before it becomes symptomatic. Lhermitte's syndrome occurs in ~15% of patients who receive thoracic radiotherapy. This syndrome is manifested by an "electric shock" sensation into the lower extremities on flexion of the neck. Because of the young age at which HL is often diagnosed, infertility is a concern for patients undergoing treatment for HL. Chemotherapy regimens containing alkylating agents induce permanent infertility in nearly all men. The risk of permanent infertility in women treated with alkylating agent-containing chemotherapy is age-related, with younger women more likely to recover fertility. Infertility is very rare after treatment with ABVD.

NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

NLPHL is now recognized as an entity distinct from cHL. Previous classification systems recognized that biopsies from a small subset of patients diagnosed as having HL contained a predominance of small lymphocytes and rare Reed-Sternberg-like cells; tumors have a nodular growth pattern and a clinical course that varied from that of patients with cHL. This is an unusual clinical entity and represents <5% of cases of HL and defines NLPHL.

NLPHL has a number of characteristics that suggest its relationship to NHL, rather than cHL, however. The HRS-like cell, or L&H (lymphocyte and histiocyte) or "popcorn" cell, is a clonal proliferation of B cells that are positive for B cell markers CD45, CD79a, CD20, CD19, and BCL2. They do not express two markers normally found on HRS cells, CD30 and CD15. This lymphoma tends to have a chronic, relapsing course and sometimes transforms to diffuse large B-cell lymphoma, including a specific subtype of diffuse large B-cell lymphoma known as T cell/histiocyte-rich B-cell lymphoma, which shares an immunophenotype with the L&H cell. This natural history most closely resembles that of the indolent B cell NHLs outlined in **Chaps. 104 and 106.**.

Patients with NLPHL are more commonly male (75%). Like cHL, the age distribution of patients with this disease has two peaks, but unlike cHL these peaks include children and adults ages 30–40 years, respectively. The majority of patients diagnosed have stage I or II disease (75%), with a minority having advanced stage disease at diagnosis. B symptoms are uncommon.

Patients with early stage disease at diagnosis should be treated with definitive radiotherapy. This is associated with a 15-year non-relapse survival of 82%. The treatment of patients with advanced stage NLPHL is controversial. Some clinicians favor no treatment of asymptomatic disease and merely close follow-up, akin to the indolent B cell NHLs. For patients who need therapy due to symptoms or signs of organ function impairment, both cHL regimens and B-cell NHL regimens have been used, including ABVD and R-CHOP. A single institution experience with R-CHOP resulted in a 100% response rate in a small group of patients without a single relapse with 42 months follow-up. Although this is short follow-up for an indolent disease, some believe R-CHOP may be curative in this disease and advocate treating with advanced stage disease at diagnosis, regardless of symptoms or organ function.

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106 Less Common Hematologic Malignancies

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The most common lymphoid malignancies are discussed in **Chaps. 102, 103, 104, 105 and 107**, myeloid leukemias in **Chaps. 100 and 101**, myelodysplastic syndromes (MDS) in **Chap. 98**, and myeloproliferative syndromes in **Chap. 99**. This chapter will focus on the more unusual forms of hematologic malignancy. The diseases discussed here are listed in **Table 106-1**. Each of these entities accounts for <1% of hematologic neoplasms.

TABLE 106-1 Unusual Lymphoid and Myeloid Malignancies

Lymphoid
Mature B-cell neoplasms
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Nodal marginal zone B-cell lymphoma
Mediastinal large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Lymphomatoid granulomatosis
Mature T-cell and natural killer (NK) cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK cell leukemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Blastic NK cell lymphoma
Primary cutaneous CD30+ T-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Myeloid
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia/hypereosinophilic syndrome
Histiocytic and Dendritic Cell Neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Mast Cells
Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis
Mast cell sarcoma
Extracutaneous mastocytoma

RARE LYMPHOID MALIGNANCIES

All the lymphoid tumors discussed here are mature B-cell or T-cell natural killer (NK) cell neoplasms.

MATURE B-CELL NEOPLASMS

B-Cell Prolymphocytic Leukemia (B-PLL) This is a malignancy of medium-sized (about twice the size of a normal small lymphocyte), round lymphocytes with a prominent nucleolus and light blue cytoplasm on Wright's stain. It dominantly affects the blood, bone marrow (BM), and spleen and usually does not cause adenopathy. The median age of affected patients is 70 years, and men are more often affected than women (male-to-female ratio is 1.6). This entity is distinct from chronic lymphoid leukemia (CLL) and does not develop as a consequence of that disease.

Clinical presentation is generally from symptoms of splenomegaly or incidental detection of an elevated white blood cell (WBC) count. The clinical course can be rapid. The cells express surface IgM (with or without IgD) and typical B-cell markers (CD19, CD20, CD22). CD23 is absent, and about one-third of cases express CD5. The CD5 expression along with the presence of the t(11;14) translocation in 20% of cases leads to confusion in distinguishing B-PLL from the leukemic form of mantle cell lymphoma. No reliable criteria for the distinction have emerged and gene expression studies suggest a close relationship between mantle cell lymphoma and B-PLL and significant differences with CLL. About half of patients have mutation or loss of p53, and deletions have been noted in 11q23 and 13q14. Nucleoside analogues like fludarabine and cladribine and combination chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) have produced responses. CHOP plus rituximab may be more effective than CHOP alone, but the disease is sufficiently rare that large series have not been reported. Splenectomy can produce palliation of symptoms but appears to have little or no impact on the course of the disease. BM transplantation may be curative. Imatinib may also have activity.

Splenic Marginal Zone Lymphoma (SMZL) This tumor of mainly small lymphocytes originates in the marginal zone of the spleen white pulp, grows to efface the germinal centers and mantle, and invades the red pulp. Splenic hilar nodes, BM, and peripheral blood (PB) may be involved. The circulating tumor cells have short surface villi and are called villous lymphocytes. Table 106-2 shows differences in tumor cells of a number of neoplasms of small lymphocytes that aid in the differential diagnosis. SMZL cells express surface immunoglobulin and CD20, but are negative for CD5, CD10, CD43, and CD103. Lack of CD5 distinguishes SMZL from CLL, and lack of CD103 separates SMZL from hairy cell leukemia.

The median age of patients with SMZL is mid-fifties, and men and women are equally represented. Patients present with incidental or symptomatic splenomegaly or incidental detection of lymphocytosis in the PB with villous lymphocytes. Autoimmune anemia or thrombocytopenia may be present. The immunoglobulin produced by these cells contains somatic mutations that reflect transit through a germinal center, and ongoing mutations suggest that the mutation machinery has remained active. About 40% of patients have either deletions or translocations involving 7q21, the site of the *FLNC* gene (filamin Cγ, involved in cross-linking actin filaments in the cytoplasm). *NOTCH2* mutations are seen in 25% of patients. Chromosome 8p deletions may also be noted. The genetic lesions typically found in extranodal marginal zone lymphomas (e.g., trisomy 3 and t[11;18]) are uncommon in SMZL.

The clinical course of disease is generally indolent with median survivals exceeding 10 years. Patients with elevated lactate dehydrogenase (LDH) levels, anemia, and hypoalbuminemia generally have a poorer prognosis. Long remissions can be seen after splenectomy. Rituximab is also active. A small fraction of patients undergo histologic progression to diffuse large B-cell lymphoma with a concomitant change to a more aggressive natural history. Experience with combination chemotherapy in SMZL is limited.

Hairy Cell Leukemia Hairy cell leukemia is a tumor of small lymphocytes with oval nuclei, abundant cytoplasm, and distinctive membrane projections (hairy cells). Patients have splenomegaly and diffuse BM involvement. While some circulating cells are noted, the clinical picture is dominated by symptoms from the enlarged spleen and pancytopenia. The mechanism of the pancytopenia is not completely clear and may be mediated by both inhibitory cytokines and marrow replacement. The marrow has an increased level of reticulin fibers; indeed, hairy cell leukemia is a common cause of inability to aspirate BM or so-called "dry tap" (Table 106-3). Monocytopenia is profound and may explain a predisposition to atypical mycobacterial infection that is observed clinically. The tumor cells have strong expression of CD22, CD25, and CD103; soluble CD25 level in serum is an excellent tumor marker for disease activity. The cells also express tartrate-resistant acid phosphatase. The immunoglobulin genes are rearranged and mutated, indicating the influence of a germinal center. No specific cytogenetic abnormality has been found, but most cases contain the activating *BRAF* mutation V600E.

The median age of affected patients is mid-fifties, and the male-to-female ratio is 5:1. Treatment options are numerous. Splenectomy is often associated with prolonged remission. Nucleosides including cladribine and deoxycoformycin are highly active but are also associated with further immunosuppression and can increase the risk of certain opportunistic infections. However, after brief courses of these agents, patients usually obtain very durable remissions during which immune function spontaneously recovers. Interferon α is also an effective therapy but is not as effective as nucleosides. Chemotherapy-refractory patients have responded to vemurafenib, a BRAF inhibitor. It is not yet clear if vemurafenib can induce long-term remissions without continuous treatment.

Nodal Marginal Zone B-Cell Lymphoma This rare node-based disease bears an uncertain relationship with extranodal marginal zone lymphomas, which are often mucosa-associated and are called mucosa-associated lymphoid tissue (MALT) lymphomas, and SMZLs. Patients may have localized or generalized adenopathy. The neoplastic cell is a marginal zone B cell with monocytoid features and has been called monocytoid B-cell lymphoma in the past. Up to one-third of the patients may have extranodal involvement, and involvement of the lymph nodes can be secondary to the spread of a mucosal primary lesion. In authentic nodal primaries, the cytogenetic abnormalities

TABLE 106-2 Immunophenotype of Tumors of Small Lymphocytes

	CD5	CD20	CD43	CD10	CD103	sIg	CyclinD1
Follicular lymphoma	neg	pos	pos	pos	neg	pos	neg
Chronic lymphoid leukemia	pos	pos	pos	neg	neg	pos	neg
B-cell prolymphocytic leukemia	pos	pos	pos	neg	neg	pos	pos
Mantle cell lymphoma	pos	pos	pos	neg	neg	pos	pos
Splenic marginal zone lymphoma	neg	pos	neg	neg	neg	pos	neg
Hairy cell leukemia	neg	pos	?	neg	pos	pos	neg

Abbreviations: neg, negative; pos, positive.

TABLE 106-3 Differential Diagnosis of "Dry Tap"—Inability to Aspirate Bone Marrow

Dry taps occur in about 4% of attempts and are associated with:	
Metastatic carcinoma infiltration	17%
Chronic myeloid leukemia	15%
Myelofibrosis	14%
Hairy cell leukemia	10%
Acute leukemia	10%
Lymphomas, Hodgkin's disease	9%
Normal marrow	Rare

associated with MALT lymphomas (trisomy 3 and t[11;18]) are very rare. The clinical course is indolent. Patients often respond to combination chemotherapy, although remissions have not been durable. Few patients have received CHOP plus rituximab, which is likely to be an effective approach to management.

Mediastinal (Thymic) Large B-Cell Lymphoma This entity was originally considered a subset of diffuse large B-cell lymphoma; however, additional study has identified it as a distinct entity with its own characteristic clinical, genetic, and immunophenotypic features. This is a disease that can be bulky in size but usually remains confined to the mediastinum. It can be locally aggressive, including progressing to produce a superior vena cava obstruction syndrome or pericardial effusion. About one-third of patients develop pleural effusions, and 5–10% can disseminate widely to kidney, adrenal, liver, skin, and even brain. The disease affects women more often than men (male-to-female ratio is 1:2–3), and the median age is 35–40 years.

The tumor is composed of sheets of large cells with abundant cytoplasm accompanied by variable, but often abundant, fibrosis. It is distinguished from nodular sclerosing Hodgkin's disease by the paucity of normal lymphoid cells and the absence of lacunar variants of Reed-Sternberg cells. However, more than one-third of the genes that are expressed to a greater extent in primary mediastinal large B-cell lymphoma than in usual diffuse large B-cell lymphoma are also overexpressed in Hodgkin's disease, suggesting a possible pathogenetic relationship between the two entities that affect the same anatomic site. Tumor cells may overexpress *MAL*. The genome of tumor cells is characterized by frequent chromosomal gains and losses. The tumor cells in mediastinal large B-cell lymphoma express CD20, but surface immunoglobulin and HLA class I and class II molecules may be absent or incompletely expressed. Expression of lower levels of class II HLA identifies a subset with poorer prognosis. The cells are CD5 and CD10 negative but may show light staining with anti-CD30. The cells are CD45 positive, unlike cells of classical Hodgkin's disease.

Methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) and rituximab plus CHOP are effective treatments, achieving 5-year survival of 75–87%. Dose-adjusted therapy with prednisone, etoposide, vincristine, cyclophosphamide, and doxorubicin (EPOCH) plus rituximab has produced 5-year survival of 97%. A role for mediastinal radiation therapy has not been definitively demonstrated, but it is frequently used, especially in patients whose mediastinal area remains positron emission tomography–avid after 4–6 cycles of chemotherapy.

Intravascular Large B-Cell Lymphoma This is an extremely rare form of diffuse large B-cell lymphoma characterized by the presence of lymphoma in the lumen of small vessels, particularly capillaries. It is also known as malignant angioendotheliomatosis or angiotropic large cell lymphoma. It is sufficiently rare that no consistent picture has emerged to define a clinical syndrome or its epidemiologic and genetic features. It is thought to remain inside vessels because of a defect in adhesion molecules and homing mechanisms, an idea supported by scant data suggesting absence of expression of β-1 integrin and ICAM-1. Patients commonly present with symptoms of small-vessel occlusion, skin lesions, or neurologic symptoms. The tumor cell clusters can promote thrombus formation. In general, the clinical course is aggressive and the disease is poorly responsive to therapy. Often a diagnosis is not made until very late in the course of the disease.

Primary Effusion Lymphoma This entity is another variant of diffuse large B-cell lymphoma that presents with pleural effusions, usually without apparent tumor mass lesions. It is most common in the setting of immune deficiency disease, especially AIDS, and is caused by human herpes virus 8 (HHV-8)/Kaposi's sarcoma herpes virus (KSHV). It is also known as *body cavity–based lymphoma*. Some patients have been previously diagnosed with Kaposi's sarcoma. It can also occur in the absence of immunodeficiency in elderly men of Mediterranean heritage, similar to Kaposi's sarcoma but even less common.

The malignant effusions contain cells positive for HHV-8/KSHV, and many are also co-infected with Epstein-Barr virus. The cells are large with large nuclei and prominent nucleoli that can be confused with Reed-Sternberg cells. The cells express CD20 and CD79a (immunoglobulin-signaling molecule), although they often do not express immunoglobulin. Some cases aberrantly express T-cell markers such as CD3 or rearranged T-cell receptor genes. No characteristic genetic lesions have been reported, but gains in chromosome 12 and X material has been seen, similar to other HIV-associated lymphomas. The clinical course is generally characterized by rapid progression and death within 6 months. CHOP plus lenalidomide or bortezomib may produce responses. HAART therapy for HIV should be maintained during treatment.

Lymphomatoid Granulomatosis This is an angiocentric, angiodestructive lymphoproliferative disease comprised by neoplastic Epstein-Barr virus–infected monoclonal B cells accompanied and outnumbered by a polyclonal reactive T-cell infiltrate. The disease is graded based on histologic features such as cell number and atypia in the B cells. It is most often confused with extranodal NK/T-cell lymphoma, nasal type, which can also be angiodestructive and is Epstein-Barr virus–related. The disease usually presents in adults (males > females) as a pulmonary infiltrate. Involvement is often entirely extranodal and can include kidney (32%), liver (29%), skin (25%), and brain (25%). The disease often but not always occurs in the setting of immune deficiency.

The disease can be remitting and relapsing in nature or can be rapidly progressive. The course is usually predicted by the histologic grade. The disease is highly responsive to combination chemotherapy and is curable in most cases. Some investigators have claimed that low-grade disease (grade I and II) can be treated with interferon α.

MATURE T-CELL AND NK CELL NEOPLASMS

T-Cell Prolymphocytic Leukemia This is an aggressive leukemia of medium-sized prolymphocytes involving the blood, marrow, nodes, liver, spleen, and skin. It accounts for 1–2% of all small lymphocytic leukemias. Most patients present with elevated WBC count (often >100,000/μL), hepatosplenomegaly, and adenopathy. Skin involvement occurs in 20%. The diagnosis is made from PB smear, which shows cells about 25% larger than those in small lymphocytes, with cytoplasmic blebs and nuclei that may be indented. The cells express T-cell markers like CD2, CD3, and CD7; two-thirds of patients have cells that are CD4+ and CD8–, and 25% have cells that are CD4+ and CD8+. T-cell receptor β chains are clonally rearranged. In 80% of patients, inversion of chromosome 14 occurs between q11 and q32. Ten percent have t(14;14) translocations that bring the T-cell receptor alpha/beta gene locus into juxtaposition with oncogenes *TCL1* and *TCL1b* at 14q32.1. Chromosome 8 abnormalities are also common. Deletions in the *ATM* gene are also noted. Activating *JAK3* mutations have also been reported.

The course of the disease is generally rapid, with median survival of about 12 months. Responses have been seen with the anti-CD52 antibody, alemtuzumab, nucleoside analogs, and CHOP chemotherapy. Histone deacetylase inhibitors like vorinostat and romidepsin may also have activity. Small numbers of patients with T-cell prolymphocytic leukemia have also been treated with high-dose therapy and allogeneic BM transplantation after remission has been achieved with conventional-dose therapy.

T-Cell Large Granular Lymphocytic Leukemia T-cell large granular lymphocytic leukemia (LGL leukemia) is characterized by increases in the number of LGLs in the PB (2000–20,000/μL) often accompanied by severe neutropenia, with or without concomitant anemia. Patients may have splenomegaly and frequently have evidence of systemic autoimmune disease, including rheumatoid arthritis, hypergammaglobulinemia, autoantibodies, and circulating immune complexes. BM involvement is mainly interstitial in pattern, with fewer than 50% lymphocytes on differential count. Usually the cells express CD3, T-cell receptors, and CD8; NK-like variants may be CD3–. The leukemic cells often express Fas and Fas ligand.

The course of the disease is generally indolent and dominated by the neutropenia. Paradoxically, immunosuppressive therapy with cyclosporine, methotrexate, or cyclophosphamide plus glucocorticoids can produce an increase in granulocyte counts. Nucleosides have been used anecdotally. Occasionally the disease can accelerate to a more aggressive clinical course.

Aggressive NK Cell Leukemia NK neoplasms are very rare, and they may follow a range of clinical courses from very indolent to highly aggressive. They are more common in Asians than whites, and the cells frequently harbor a clonal Epstein-Barr virus episome. The PB white count is usually not greatly elevated, but abnormal large lymphoid cells with granular cytoplasm are noted. The aggressive form is characterized by symptoms of fever and laboratory abnormalities of pancytopenia. Hepatosplenomegaly is common; node involvement is less common. Patients may have hemophagocytosis, coagulopathy, or multiorgan failure. Serum levels of Fas ligand are elevated.

The cells express CD2 and CD56 and do not have rearranged T-cell receptor genes. Deletions involving chromosome 6 are common. The disease can be rapidly progressive. Some forms of NK neoplasms are more indolent. They tend to be discovered incidentally with LGL lymphocytosis and do not manifest the fever and hepatosplenomegaly characteristic of the aggressive leukemia. The cells are also CD2 and CD56 positive, but they do not contain clonal forms of Epstein-Barr virus and are not accompanied by pancytopenia or autoimmune disease.

Extranodal NK/T-Cell Lymphoma, Nasal Type Like lymphomatoid granulomatosis, extranodal NK/T-cell lymphoma tends to be an angiocentric and angiodestructive lesion, but the malignant cells are not B cells. In most cases, they are CD56+ Epstein-Barr virus–infected cells; occasionally they are CD56–Epstein-Barr virus–infected cytotoxic T cells. They are most commonly found in the nasal cavity. Historically, this illness was called lethal midline granuloma, polymorphic reticulosis, and angiocentric immunoproliferative lesion. This form of lymphoma is prevalent in Asia, Mexico, and Central and South America; it affects males more commonly than females. When it spreads beyond the nasal cavity, it may affect soft tissue, the gastrointestinal tract, or the testis. In some cases, hemophagocytic syndrome (HPS) may influence the clinical picture. Patients may have B symptoms. Many of the systemic manifestations of disease are related to the production of cytokines by the tumor cells and the cells responding to their signals. Deletions and inversions of chromosome 6 are common.

Many patients with extranodal NK/T-cell lymphoma, nasal type have excellent antitumor responses with combination chemotherapy regimens, particularly those with localized disease. Radiation therapy is often used after completion of chemotherapy. Four risk factors have been defined, including B symptoms, advanced stage, elevated LDH, and regional lymph node involvement. Patient survival is linked to the number of risk factors: 5-year survival is 81% for zero risk factors, 64% for one risk factor, 32% for two risk factors, and 7% for three or four risk factors. Combination regimens without anthracyclines have been touted as superior to CHOP, but data are sparse. High-dose therapy with stem cell transplantation has been used, but its role is unclear.

Enteropathy-Type T-Cell Lymphoma Enteropathy-type T-cell lymphoma is a rare complication of longstanding celiac disease. It most commonly occurs in the jejunum or the ileum. In adults, the lymphoma may be diagnosed at the same time as celiac disease, but the suspicion is that the celiac disease was a longstanding precursor to the development of lymphoma. The tumor usually presents as multiple ulcerating mucosal masses, but may also produce a dominant exophytic mass or multiple ulcerations. The tumor expresses CD3 and CD7 nearly always and may or may not express CD8. The normal-appearing lymphocytes in the adjacent mucosa often have a similar phenotype to the tumor. Most patients have the HLA genotype associated with celiac disease, HLA DQA1*0501 or DQB1*0201.

The prognosis of this form of lymphoma is typically (median survival is 7 months) poor, but some patients have a good response to CHOP chemotherapy. Patients who respond can develop bowel perforation from responding tumor. If the tumor responds to treatment, recurrence may develop elsewhere in the celiac disease–affected small bowel.

Hepatosplenic T-Cell Lymphoma Hepatosplenic T-cell lymphoma is a malignancy derived from T cells expressing the gamma/delta T-cell antigen receptor that affects mainly the liver and fills the sinusoids with medium-size lymphoid cells. When the spleen is involved, dominantly the red pulp is infiltrated. It is a disease of young people, especially young people with an underlying immunodeficiency or with an autoimmune disease that demands immunosuppressive therapy. The use of thiopurine and infliximab is particularly common in the history of patients with this disease. The cells are CD3+ and usually CD4– and CD8–. The cells may contain isochromosome 7q, often together with trisomy 8. The lymphoma has an aggressive natural history. Combination chemotherapy may induce remissions, but most patients relapse. Median survival is about 2 years. The tumor does not appear to respond to reversal of immunosuppressive therapy.

Subcutaneous Panniculitis-Like T-Cell Lymphoma Subcutaneous panniculitis-like T-cell lymphoma involves multiple subcutaneous collections of neoplastic T cells that are usually cytotoxic cells in phenotype (i.e., contain perforin and granzyme B and express CD3 and CD8). The rearranged T-cell receptor is usually alpha/beta-derived, but occasionally the gamma/delta receptors are involved, particularly in the setting of immunosuppression. The cells are negative for Epstein-Barr virus. Patients may have a HPS in addition to the skin infiltration; fever and hepatosplenomegaly may also be present. Nodes are generally not involved. Patients frequently respond to combination chemotherapy, including CHOP. When the disease is progressive, the HPS can be a component of a fulminant downhill course. Effective therapy can reverse the HPS.

Blastic NK Cell Lymphoma The neoplastic cells express NK cell markers, especially CD56, and are CD3 negative. They are large blastic-appearing cells and may produce a leukemia picture, but the dominant site of involvement is the skin. Morphologically, the cells are similar to the neoplastic cells in acute lymphoid and myeloid leukemia. No characteristic chromosomal abnormalities have been described. The clinical course is rapid, and the disease is largely unresponsive to typical lymphoma treatments.

Primary Cutaneous CD30+ T-Cell Lymphoma This tumor involves the skin and is composed of cells that appear similar to the cells of anaplastic T-cell lymphoma. Among cutaneous T-cell tumors, about 25% are CD30+ anaplastic lymphomas. If dissemination to lymph nodes occurs, it is difficult to distinguish between the cutaneous and systemic forms of the disease. The tumor cells are often CD4+, and the cells contain granules that are positive for granzyme B and perforin in 70% of cases. The typical t(2;5) of anaplastic T-cell lymphoma is absent; indeed, its presence should prompt a closer look for systemic involvement and a switch to a diagnosis of anaplastic T-cell lymphoma. This form of lymphoma has sporadically been noted as a rare complication of silicone on saline breast implants. The natural history of breast implant associated lymphoma is generally indolent. Cutaneous CD30+ T-cell lymphoma often responds to therapy. The anti-CD30 immunotoxin conjugate, brentuximab vedotin, is active. Radiation therapy can be effective, and surgery can also produce long-term disease control. Five-year survival exceeds 90%.

Angioimmunoblastic T-Cell Lymphoma Angioimmunoblastic T-cell lymphoma is a systemic disease that accounts for about 15% of all T-cell lymphomas. Patients frequently have fever, advanced stage, diffuse adenopathy, hepatosplenomegaly, skin rash, polyclonal hypergammaglobulinemia, and a wide range of autoantibodies including cold agglutinins, rheumatoid factor, and circulating immune complexes. Patients may have edema, arthritis, pleural effusions, and ascites. The nodes contain a polymorphous infiltrate of neoplastic T cells and nonneoplastic inflammatory cells together with proliferation of high endothelial venules and follicular dendritic cells (FDCs). The most common chromosomal abnormalities are trisomy 3, trisomy 5, and

an extra X chromosome. Aggressive combination chemotherapy can induce regressions. The underlying immune defects make conventional lymphoma treatments more likely to produce infectious complications.

RARE MYELOID MALIGNANCIES

The World Health Organization (WHO) system uses PB counts and smear analysis, BM morphology, cytogenetic and molecular genetic tests in order to classify myeloid malignancies into several major categories **(Table 106-4)**. Amongst them, acute myeloid leukemia (AML) is discussed in **Chap. 100**, MDS in **Chap. 98**, chronic myeloid leukemia (CML) in **Chap. 101**, and *JAK2* mutation-enriched myeloproliferative neoplasms (MPN) in **Chap. 99**. In this chapter, we focus on the rest (listed in Table 106-4) including chronic neutrophilic leukemia (CNL), "atypical CML, *BCR-ABL1* negative (aCML)," chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), "chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)," mastocytosis, "MPN, unclassifiable (MPN-U)," MDS/MPN, unclassifiable (MDS/MPN-U), "MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)," and "myeloid/lymphoid neoplasms with eosinophilia and rearrangements of *PDGFRA, PDGFRB, FGFR1* or with *PCM1-JAK2*." This chapter also includes histiocytic and DC neoplasms, transient myeloproliferative disorders (TMD) as well as a broader discussion on primary eosinophilic disorders including hypereosinophilic syndrome (HES).

CHRONIC NEUTROPHILIC LEUKEMIA

CNL is a clonal proliferation of mature neutrophils with few or no circulating immature granulocytes. In 2013, CNL was associated with activating mutations of the gene (*CSF3R*) encoding for the receptor for granulocyte colony-stimulating factor (G-CSF), also known as colony stimulating factor 3 (CSF3). Patients with CNL might be asymptomatic at presentation but also display constitutional symptoms, splenomegaly, anemia, and thrombocytopenia. Median survival is ~2 years and causes of death include leukemic transformation, progressive disease associated with severe cytopenias, and marked treatment-refractory leukocytosis. CNL is rare with <200 reported cases. Median age at diagnosis is ~67 years, and the disease is equally prevalent in both genders.

TABLE 106-4 World Health Organization Classification of Myeloid Malignancies

1. **Acute myeloid leukemia (AML) and related precursor neoplasms**
2. **Myeloproliferative neoplasms (MPN)**
   - **2.1.** Chronic myeloid leukemia (CML), *BCR-ABL1* positive
   - **2.2.** *JAK2* mutation-enriched MPN
     - **2.2.1.** Polycythemia vera
     - **2.2.2.** Primary myelofibrosis
     - **2.2.3.** Essential thrombocythemia
   - **2.3.** Chronic neutrophilic leukemia (CNL)
   - **2.4.** Chronic eosinophilic leukemia, not otherwise specified (CEL-NOS)
   - **2.5.** Myeloproliferative neoplasm, unclassifiable (MPN-U)
3. **Myelodysplastic syndromes (MDS)**
   - **3.1.** MDS with single lineage dysplasia
   - **3.2.** MDS with ring sideroblasts (MDS-RS)
   - **3.3.** MDS with multilineage dysplasia
   - **3.4.** MDS with excess blasts
   - **3.5.** MDS with isolated del(5q)
   - **3.6.** MDS, unclassifiable (MDS-U)
   - **3.7.** *Provisional entity: Refractory cytopenia of childhood*
4. **MDS/MPN overlap**
   - **4.1.** Chronic myelomonocytic leukemia (CMML)
   - **4.2.** Atypical chronic myeloid leukemia (aCML), *BCR-ABL1* negative
   - **4.3.** Juvenile myelomonocytic leukemia (JMML)
   - **4.4.** MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
   - **4.5.** MDS/MPN, unclassifiable (MDS/MPN-U)
5. **Mastocytosis**
6. **Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1* or with *PCM1-JAK2***
   - **6.1.** Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
   - **6.2.** Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
   - **6.3.** Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
   - **6.4.** *Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2 translocation*

Myeloid neoplasms with germline predisposition

Pathogenesis CSF3 is the main growth factor for granulocyte proliferation and differentiation. Accordingly, recombinant CSF3 is used for the treatment of severe neutropenia, including severe congenital neutropenia (SCN). Some patients with SCN acquire *CSF3R* mutations and the frequency of such mutations is significantly higher (~ 80%) in those patients who experience leukemic transformation. SCN-associated *CSF3R* mutations occur in the region of the gene coding for the cytoplasmic domain of CSF3R, and result in truncation of the C-terminal-negative regulatory domain. In 2013, Maxson et al. described a different class of *CSF3R* mutations in ~ 90% of patients with CNL; these were mostly membrane proximal, the most frequent being a C-to-T substitution at nucleotide 1853 (T618I). In a subsequent confirmatory study, *CSF3R* mutations were found to be specific to WHO-defined CNL. About 40% of the T618I-mutated cases also harbored *SETBP1* mutations. *CSF3R*T618I has been shown to induce lethal myeloproliferative disorder in a mouse model and in vitro sensitivity to JAK inhibition.

Diagnosis Diagnosis of CNL requires exclusion of the more common causes of neutrophilia including infections and inflammatory processes. In addition, one should be mindful of the association between some forms of metastatic cancer or plasma cell neoplasms with secondary neutrophilia. Neoplastic neutrophilia also occurs in other myeloid malignancies including aCML and CMML. Accordingly, the WHO diagnostic criteria for CNL are designed to exclude the possibilities of both secondary/reactive neutrophilia and leukocytosis associated with myeloid malignancies other than CNL (Table 106-2): leukocytosis ($\geq 25 \times 10^9$/L), ≥80% segmented/band neutrophils, <10% immature myeloid cells, <1% circulating blasts and absence of dysgranulopoiesis or monocytosis (monocyte count $< 1 \times 10^9$/L). BM in CNL is hypercellular and displays increased number and percentage of neutrophils with very high myeloid to erythroid ratio and minimal left shift, myeloid dysplasia or reticulin fibrosis.

The recent discovery of *CSF3R* mutations (see above) and their almost invariable association with WHO-defined CNL has allowed its incorporation in the WHO diagnostic criteria **(Table 106-5)**. In practical terms, the presence of a membrane proximal *CSF3R* mutation in a patient with predominantly neutrophilic granulocytosis should be sufficient for the diagnosis of CNL, regardless of the degree of leukocytosis. Unfortunately, several exclusionary criteria still need to be met for diagnosing CNL in the absence of *CSF3R* mutations (Table 106-5).

Treatment Current treatment in CNL is largely palliative and suboptimal in its efficacy. Several drugs alone or in combination have been tried and none have shown remarkable efficacy. As such, allogeneic stem cell transplant (ASCT) is reasonable to consider in the presence of symptomatic disease, especially in younger patients. Otherwise, cytoreductive therapy with hydroxyurea is probably as good as anything, and a more intensive combination chemotherapy may not have additional value. However, response to hydroxyurea therapy is often transient, and some have successfully used interferon α as an alternative drug. Response to treatment with ruxolitinib (a JAK1 and JAK2 inhibitor) has been reported in several case reports but, as is the case with hydroxyurea treatment, the response is often incomplete and temporary.

ATYPICAL CHRONIC MYELOID LEUKEMIA

"Atypical chronic myeloid leukemia, *BCR-ABL1* negative (aCML)" is formally classified under the MDS/MPN category of myeloid malignancies and is characterized by left shifted granulocytosis and

TABLE 106-5 2016 World Health Organization (WHO) Diagnostic Criteria for Chronic Neutrophilic Leukemia (CNL), Atypical Chronic Myeloid Leukemia, *BCR-ABL1*-negative (aCML), and Chronic Myelomonocytic Leukemia (CMML)

VARIABLES	CHRONIC NEUTROPHILIC LEUKEMIA	ATYPICAL CHRONIC MYELOID LEUKEMIA	CHRONIC MYELOMONOCYTIC LEUKEMIA
PB leukocyte count	≥25 × 10^9/L	Granulocytosis	
PB segmented neutrophils/bands	≥80%		
PB immature granulocytes[a]	<10%	≥10%	
PB blast count	<1%	<20%	<20%
PB monocyte count	<1 x 10(9)/L	No or minimal monocytosis	≥1 × 10^9/L Persistent and lasting for at least 3 months
Dysgranulopoiesis	No	Yes	
PB basophil percentage		<2%	
PB monocyte percentage		<10%	≥10%
Bone marrow	Hypercellular ↑Neutrophils, number and % <5% blasts Normal neutrophilic maturation	Hypercellular ↑Granulocyte proliferation Granulocytic dysplasia ±erythroid/megakaryocyte Dysplasia <20% blasts	Dysplasia in ≥1 myeloid lineages or clonal cytogenetic/molecular abnormality <20% blasts or promonocytes
BCR-ABL1	No	No	No
PDGFRA, *PDGFRB*, *FGFR1*, or *PCM1-JAK2* rearrangement	No	No	No
CSF3R T618I or other activating CSF3R mutation or persistent neutrophilia, splenomegaly, and no identifiable cause of reactive neutrophilia	Yes		
PB and BM blasts/promonocytes		<20%	<20%
Evidence for other MPN: CML, PV, ET, or PMF	No	No	No
Evidence for reactive Leukocytosis[b] or monocytosis	No		No

[a]Immature granulocytes include myeloblasts, promyelocytes, myelocytes, and metamyelocytes. [b]Causes of reactive neutrophilia include plasma cell neoplasms, solid tumor, infections, and inflammatory processes.

Abbreviations: BM, bone marrow; CML, chronic myeloid leukemia; ET, essential thrombocythemia; MPN, myeloproliferative neoplasms; PB, peripheral blood; PMF, primary myelofibrosis; PV, polycythemia vera.

dysgranulopoiesis. The differential diagnosis of aCML includes CML, which is distinguished by the presence of *BCR-ABL1*; CNL, which is distinguished by the absence of dysgranulopoiesis and presence of *CSF3R* mutations; and CMML, which is distinguished by the presence of monocytosis (absolute monocyte count ≥1 × 10^9/L). The WHO diagnostic criteria for aCML are listed in Table 106-5 and include granulocytosis, dysgranulopoiesis, ≥10% immature granulocytes, <20% PB or BM myeloblasts, <10% PB monocytes, <2% basophils, absence of otherwise specific mutations such as *BCR-ABL1, PDGFRA, PDGFRB, FGFR1,* or *PCM1-JAK2* and not meeting WHO criteria for CML, PMF, PV, or ET. The BM in aCML is hypercellular with granulocyte proliferation and dysplasia with or without erythroid or megakaryocytic dysplasia.

The molecular pathogenesis of aCML is incompletely understood; about a fourth of the patients express *SETBP1* mutations, which are, however, also found in several other myeloid malignancies, including CNL and CMML. *SETBP1* mutations in aCML were prognostically detrimental and mostly located between codons 858 and 871; similar mutations are seen with Schinzel-Giedion syndrome (a congenital disease with severe developmental delay and various physical stigmata including midface retraction, large forehead, and macroglossia). A somatic missense mutation in ethanolamine kinase 1 (*ETNK1*N244S) was described in 9% of patients with aCML but was also seen in 14% of patients with CMML, 6% of patients with mastocytosis (especially in association with eosinophilia), and rarely in other MPN.

In a series of 55 patients with WHO-defined aCML, median age at diagnosis was 62 years with female preponderance (57%), splenomegaly was reported in 54% of the patients, red cell transfusion requirement in 65%, abnormal karyotype in 20% (20q- and trisomy 8 being the most frequent) and leukemic transformation in 40%. Median survival was 25 months. Outcome was worse in patients with marked leukocytosis, transfusion requirement, and increased immature cells in the PB. Conventional chemotherapy is largely ineffective in the treatment of aCML. However, a favorable experience with ASCT was reported in nine patients; after a median follow-up of 55 months, the majority of the patients remained in complete remission.

CHRONIC MYELOMONOCYTIC LEUKEMIA

CMML is classified under the WHO category of MDS/MPN and is defined by an absolute monocyte count (AMC) of ≥1 × 10^9/L in the PB and accounting for ≥10% of the leukocyte count. Median age at diagnosis ranges between 65 and 75 years and there is a 2:1 male predominance. Clinical presentation is variable and depends on whether the disease presents with MDS-like or MPN-like phenotype; the former is associated with cytopenias and the latter with splenomegaly and features of myeloproliferation such as fatigue, night sweats, weight loss, and cachexia. About 20% of patients with CMML experience serositis involving the joints (arthritis), pericardium (pericarditis and pericardial effusion), pleura (pleural effusion), or peritoneum (ascites).

Pathogenesis Clonal cytogenetic abnormalities are seen in about a third of patients with CMML and include trisomy 8 and abnormalities of chromosome 7. Almost all patients with CMML harbor somatic mutations involving epigenetic regulator genes (e.g., *ASXL1, TET2*), spliceosome pathway genes (e.g., *SRSF2*), DNA damage response genes (e.g., *TP53*), and tyrosine kinases/transcription factors (e.g., *KRAS, NRAS, CBL*, and *RUNX1*). However, none of these mutations are specific to CMML, and their precise pathogenetic contribution is unclear.

Diagnosis Reactive monocytosis is uncommon but has been reported in association with certain infections and inflammatory conditions. Clonal (i.e., neoplastic) monocytosis defines CMML but is also seen with JMML and AML with monocytic differentiation. The WHO diagnostic criteria for CMML are listed in Table 106-5 and include (1) persistent PB monocyte count of ≥1 × 10^9/L with monocyte percentage

of ≥10%, (2) absence of *BCR-ABL1, PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2 rearrangements*, (3) not meeting WHO criteria for CML, PV, ET, or PMF, (4) <20% blasts and promonocytes in the PB and BM, and (5) dysplasia involving one or more myeloid lineages or, in the absence of dysplasia, presence of an acquired clonal cytogenetic or molecular genetic abnormality or non-reactive monocytosis lasting for at least 3 months.

The BM in CMML is hypercellular with granulocytic and monocytic proliferation. Dysplasia is often present and may involve one, two, or all myeloid lineages. On immunophenotyping the abnormal cells often express myelomonocytic antigens such as CD13 and CD33, with variable expression of CD14, CD68, CD64, and CD163. Monocytic-derived cells are almost always positive for the cytochemical non-specific esterases (e.g., butyrate esterase), while normal granulocytic precursors are positive for lysozyme and chloroacetate esterase. In CMML, it is common to have a hybrid cytochemical staining pattern with cells expressing both chloroacetate and butyrate esterases simultaneously (dual esterase staining).

Prognosis A recent meta-analysis showed median survival of 1.5 years in CMML. Numerous prognostic systems have attempted to better define and stratify the natural history of CMML. One of these, the Mayo prognostic model, assigns one point each to the following four independent prognostic variables: AMC >10 × 10^9/L, presence of circulating immature cells, hemoglobin <10 gm/dL and platelet count <100,000/mL. This model stratified patients into three risk groups: low (0 points), intermediate (1 point), and high (≥2 points), translating to median survival of 32, 18, and 10 months, respectively.

A French study incorporated *ASXL1* mutational status in 312 CMML patients. In a multivariable model, independent predictors of poor survival were WBC >15 × 10^9/L (3 points), *ASXL1* mutations (2 points), age >65 years (2 points), platelet count <100,000/mL (2 points), and hemoglobin <10 gm/dL in females and <11 gm/dL in males (2 points). This model stratified patients into three groups: low (0–4 points), intermediate (5–7 points), and high risk (8–12 points), with median survival of "not reached," 38.5 and 14.4 months, respectively.[27] *ASXL1* and *DNMT3A* mutations also have an adverse effect on CMML.

Treatment Current treatment in CMML consists of hydroxyurea and supportive care, including red cell transfusions and use of erythropoiesis-stimulating agents (ESA). The value of hydroxyurea was reinforced by a randomized trial against oral etoposide. No other single or combination chemotherapy has been shown to be superior to hydroxyurea. ASCT is a viable treatment option for transplant-eligible patients with poor prognostic features. Given the MDS/MPN overlap phenotype and the presence of MDS-like genetic/methylation abnormalities in CMML, hypomethylating agents such as 5-azacitidine and decitabine have been used with limited efficacy; in a study using decitabine in CMML, overall response rate was 48% with 17% complete remissions and median survival of 17 months. The experience with 5-azacytidine was somewhat similar.

JUVENILE MYELOMONOCYTIC LEUKEMIA

JMML is primarily a disease of early childhood and is included, along with CMML, in the "MDS/MPN" WHO category. Both CMML and JMML feature leukocytosis, monocytosis, and hepatosplenomegaly. Additional characteristic features in JMML include thrombocytopenia and elevated fetal hemoglobin. Myeloid progenitors in JMML display GM-CSF hypersensitivity that has been attributed to dysregulated RAS/MAPK signaling. The latter is believed to result from mutually exclusive mutations involving *RAS*, *PTPN11*, and *NF1*. A third of patients with JMML that is not associated with Noonan syndrome carry *PTPN11* mutations while the incidence of *NF1* in patients without neurofibromatosis, type 1 and *RAS* mutations are ~15% each. In general, in about 85% of JMML cases, one of the classical RAS pathway mutations (*PTPN11*, *NRAS*, *KRAS*, *NF1*, and *CBL*) is present; in addition, a myrof other mutations, such as *ASXL1*, *RUNX1*, *SETBP1*, *JAK3*, *CUX1*, and others have been reported. Drug therapy is relatively ineffective in JMML, and the treatment of choice is ASCT, which results in a 5-year survival of ~50%.

The 2016 revised WHO diagnostic criteria for JMML requires the presence of PB monocyte count ≥1 × 10^9/L, <20% blasts in blood or BM, splenomegaly, and absence of *BCR-ABL1*. Diagnosis also requires the presence of one of the following: somatic mutation of *PTPN11, KRAS*, or *NRAS*; clinical diagnosis of NF1 or *NF1* mutation; germline mutation of *CBL* and loss of heterozygosity. Diagnosis of JMML can still be considered without the aforementioned genetic features, in the presence of monosomy 7 or any other cytogenetic abnormality or in the presence of two of the following: increased hemoglobin F, presence of myeloid or erythroid precursors in the PB, GM-CSF hypersensitivity in colony assay, and hyperphosphorylation of STAT5.

MDS/MPN, UNCLASSIFIABLE (MDS/MPN-U)

The WHO classifies patients with morphologic and laboratory features that resemble both MDS and MPN as "MDS/MPN overlap." This category includes CMML, aCML, and JMML, which have been described above. In addition, MDS/MPN includes a fourth category referred to as MDS/MPN, unclassifiable (MDS/MPN-U). Diagnosis of MDS/MPN-U requires the presence of both MDS and MPN features that are not adequate to classify patients as CMML, aCML, or JMML. MDS/MPN also includes the provisional category of refractory anemia with ring sideroblasts and thrombocytosis (RARS-T); the 2016 revision of the WHO classification document has changed the term RARS-T into "MDS/MPN-RS-T."

In a study of 85 patients with MDS/MPN-U, median age was 70 years and 72% were males. Splenomegaly at presentation was present in 33%, thrombocytosis in 13%, leukocytosis in 18%, *JAK2* mutations in 30%, and abnormal karyotype 51%; the most frequent cytogenetic abnormality was trisomy 8. Median survival was 12.4 months and favorably affected by thrombocytosis. Treatment with hypomethylating agents, immunomodulators, or ASCT did not appear to favorably affect survival.

MDS/MPN WITH RING SIDEROBLASTS AND THROMBOCYTOSIS (MDS/MPN-RS-T)

MDS/MPN-RS-T is classified in the MDS/MPN category because it shares dysplastic features with MDS-RS and myeloproliferative features with ET. The 2016 revised WHO diagnostic criteria for MDS/MPN-RS-T includes anemia associated with erythroid lineage dysplasia, presence of ≥15% ring sideroblasts, blast count of <5% in BM and <1% in the PB, platelet count of ≥450 × 10^9/L, and absence of *BCR-ABL1*, *PDGFRA, PDGFRB, FGFR1, PCM1-JAK2* mutations or t(3;3)(q21;q26), inv(3)(q21q26), or del(5q). These diagnostic criteria also require the absence of history of MPN, MDS, or other type of MDS/MPN and also either the presence of *SF3B1* mutation or absence of exposure to cytotoxic or other treatment that could be blamed for the morphologic abnormalities.

One hundred eleven patients with MDS/MPN-RS-T were compared with 33 patients with RARS. The frequency of *SF3B1* mutations in MDS/MPN-RS-T-T (87%) was similar to that in MDS-RS (85%). *JAK2 V617F* mutation was detected in 49% of MDS/MPN-RS-T patients (including 48% of those mutated for *SF3B1*), but none of those with MDS-RS. In MDS/MPN-RS-T, *SF3B1* mutations were more frequent in females (95%) than in males (77%), and mean ring sideroblast counts were higher in *SF3B1-mutated* patients. Median overall survival was 6.9 years in *SF3B1-mutated* vs 3.3 years in unmutated cases. Six-year survival was 67% in *JAK2*-mutated vs 32% in unmutated cases. Multivariable analysis identified younger age, *JAK2* and *SF3B1* mutations as favorable factors. Predictors of poor survival in MDS/MPN-RS-T include anemia, abnormal karyotype, and presence of *ASXL1* or *SETBP1* mutations. Interestingly, the presence of *SF3B1* mutations in MDS/MPN-RS-T is associated with increased risk of thrombosis. Several case reports have suggested that treatment with lenalidomide might induce red cell transfusion independence and complete remissions in MDS/MPN-RS-T.

MYELOPROLIFERATIVE NEOPLASM, UNCLASSIFIABLE (MPN-U)

The category of MPN-U includes MPN-like neoplasms that cannot be clearly classified as one of the other seven subcategories of MPN

(Table 106-4). Examples include patients presenting with unusual thrombosis or unexplained organomegaly with normal blood counts but found to carry MPN-characteristic mutations such as *JAK2* and *CALR* or display BM morphology that is consistent with MPN. It is possible that some cases of MPN-U represent earlier disease stages in PV or ET, which however fail to meet the threshold hemoglobin levels or platelet counts that are required per WHO diagnostic criteria. Specific treatment interventions might not be necessary in asymptomatic patients with MPN-U, whereas patients with arterial thrombotic complications might require cytoreductive and aspirin therapy, and those with venous thrombosis might require systemic anticoagulation.

MYELOID NEOPLASMS WITH GERM LINE PREDISPOSITION

The 2016 WHO revision on the classification of myeloid neoplasms adds a section referred to as "myeloid neoplasms with germ line predisposition" and includes cases of AML, MDS, and MDS/MPN that arise in the setting of a germ line predisposition mutation, such as *CEBPA, DDX41, RUNX1, ANKRD26, ETV6*, or *GATA2*. This particular category of diseases also includes myeloid neoplasms that arise in the background of BM failure syndromes, Down syndrome, Noonan syndrome, neurofibromatosis, and telomeropathies.

TRANSIENT MYELOPROLIFERATIVE DISORDER

TMD, also referred to as transient abnormal myelopoiesis (TAM), constitutes an often but not always transient phenomenon of abnormal megakaryoblast proliferation, which occurs in ~10% of infants with Down syndrome. TMD is usually recognized at birth and either undergoes spontaneous regression (75% of the cases) or progress into acute megakaryoblastic leukemia (AMKL) (25% of the cases). Almost all patients with TMD and TMD-derived AMKL display somatic *GATA1* mutations. TMD-associated *GATA1* mutations constitute exon 2 insertions, deletions, or missense mutations, affecting the N-terminal transactivation domain of GATA-1 and result in loss of full-length (50-kD) GATA-1 and its replacement with a shorter isoform (40-kD) that retains friend of GATA-1 (FOG-1) binding. In contrast, inherited forms of exon 2 *GATA1* mutations produce a phenotype with anemia whereas exon 4 mutations that affect the N-terminal, FOG-1-interactive domain, produce familial dyserythropoietic anemia with thrombocytopenia[51] or X-linked macrothrombocytopenia.

PRIMARY EOSINOPHILIA

Eosinophilia refers to a PB absolute eosinophil count (AEC) that is above the upper normal limit of the reference range. The term "hypereosinophilia" is used when the AEC is above 1500×10^9/L. Eosinophilia is operationally classified into secondary (non-neoplastic proliferation of eosinophils) and primary (proliferation of eosinophils that is either neoplastic or otherwise unexplained). Secondary eosinophilia is by far the most frequent cause of eosinophilia and is often associated with infections, especially those related to tissue-invasive helminths, allergic/vasculitic diseases, drugs, and metastatic cancer. Primary eosinophilia is the focus of this chapter and is considered when a cause for secondary eosinophilia is not readily apparent.

Primary eosinophilia is classified as clonal or idiopathic. Diagnosis of clonal eosinophilia requires morphologic, cytogenetic, or molecular evidence of a myeloid neoplasm. Idiopathic eosinophilia is considered when both secondary and clonal eosinophilias have been ruled out as a possibility. HES is a subcategory of idiopathic eosinophilia with persistent AEC of $\geq 1.5 \times 10^9$/L and associated with eosinophil-mediated organ damage **(Table 106-6)**. An HES-like disorder that is associated with clonal or phenotypically abnormal T cells is referred to as "lymphocytic variant hypereosinophilia" (Table 106-6).

Clonal Eosinophilia Examples of clonal eosinophilia include eosinophilia associated with AML, MDS, CML, mastocytosis, and MDS/MPN overlap. Myeloid neoplasm-associated eosinophilia also includes the WHO MPN subcategory of chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) and the WHO myeloid malignancy subcategory referred to as "myeloid/lymphoid neoplasms with eosinophilia and rearrangement of platelet-derived growth factor receptor (*PDGFR*) α/β or fibroblast growth factor receptor 1 (*FGFR1*)" or with *PCM1-JAK2* (Table 106-4).

The diagnostic workup for clonal eosinophilia that is not associated with morphologically overt myeloid malignancy should start with PB mutation screening for *FIP1L1-PDGFRA* and *PDGFRB* mutations using fluorescence in situ hybridization (FISH) or reverse transcription-polymerase chain reaction. This is crucial since such eosinophilia is easily treated with imatinib. If mutation screening is negative, a BM examination with cytogenetic studies is indicated. In this regard, one must first pay attention to the presence or absence of 5q33, 4q12, 8p11.2, or t(8;9)(p22;p24.1) translocations, which, if present, would suggest *PDGFRB*, *PDGFRA*, or *FGFR1*-rearranged or *PCM1-JAK2*-associated clonal eosinophilia, respectively. The presence of 5q33 or 4q12 translocations predicts favorable response to treatment with imatinib mesylate and that of t(8;9)(p22;p24.1), a transient response to ruxolutinib while 8p11.2 translocations are associated with aggressive myeloid malignancies that are refractory to current drug therapy.

Chronic Eosinophilic Leukemia, Not Otherwise Specified (CEL-NOS) CEL-NOS is a subset of clonal eosinophilia that is neither molecularly defined nor classified as an alternative clinicopathologically assigned myeloid malignancy. We prefer to use the term strictly in patients with an "HES" phenotype who also display either a clonal cytogenetic/molecular abnormality or excess blasts in the BM or PB. The WHO defines CEL-NOS in the presence of $\geq 1.5 \times 10^9$/L AEC that is accompanied by either the presence of myeloblast excess (either >2% in the PB or 5–19% in the BM) or evidence of myeloid clonality. Cytogenetic abnormalities in CEL, other than those that are associated

TABLE 106-6 Primary Eosinophilia Classification

VARIABLES	EOSINOPHILIA ASSOCIATED WITH *PDGFRA, PDGFRB, FGFR1* OR *PCM1-JAK2* ABNORMALITY	CHRONIC EOSINOPHILIA NOT OTHERWISE SPECIFIED (CEL-NOS)	LYMPHOCYTIC VARIANT HYPEREOSINOPHILIA	HYPEREOSINOPHILIC SYNDROME
Absolute eosinophil count	>600 × 10^9/L	>1500 × 10^9/L	>1500 × 10^9/L	>1500 × 10^9/L
Peripheral blood blast >2%	Yes or no	Yes or no	No	No
Bone marrow blast >5%	Yes or no	Yes or No	No	No
Abnormal karyotype	Yes or no	Yes or no	No	No
PDGFRA, *PDGFRB*, *FGFR1* or *PCM1-JAK2* abnormality	Yes	No	No	No
BCR-ABL1	No	No	No	No
Abnormal T lymphocyte phenotype or clonal T cell clones	No	No	Yes	No
Eosinophil-mediated tissue damage	Yes or no	Yes or no	Yes or no	Yes

with molecularly defined eosinophilic disorders, include trisomy 8 (the most frequent), t(10;11)(p14;q21), and t(7;12)(q11;p11). CEL-NOS does not respond to imatinib, and treatment strategies are often not different from those utilized in other similar MPNs; ASCT for transplant-eligible patients with poor risk factors and participation in experimental treatment protocols otherwise.

***PDGFR* Mutated Eosinophilia** Both platelet-derived growth factor receptors α (*PDGFRA* located on chromosome 4q12) and β (*PDGFRB* located on chromosome 5q31-q32) are involved in MPN-relevant activating mutations. Clinical phenotype in both instances includes prominent blood eosinophilia and excellent response to imatinib therapy. In regards to *PDGFRA* mutations, the most popular is *FIP1L1-PDGFRA*, a karyotypically occult del(4)(q12), that was described in 2003 as an imatinib-sensitive activating mutation. Functional studies have demonstrated transforming properties in cell lines and the induction of MPN in mice. Cloning of the *FIP1L1-PDGFRA* fusion gene identified a novel molecular mechanism for generating this constitutively active fusion tyrosine kinase, wherein a ~800kb interstitial deletion within 4q12 fuses the 5′ portion of *FIP1L1* to the 3′ portion of *PDGFRA*.[57] *FIP1L1-PDGFRA* occurs in a very small subset of patients who present with the phenotypic features of either SM or HES, but the presence of the mutation reliably predicts complete hematologic and molecular response to imatinib therapy.

The association between eosinophilic myeloid malignancies and *PDGFRB* rearrangement was first characterized and published in 1994 where fusion of the tyrosine kinase encoding region of *PDGFRB* to the *ets*- like gene, *ETV6* (*ETV6-PDGFRB*, t(5;12)(q33;p13) was demonstrated. The fusion protein was transforming to cell lines and resulted in constitutive activation of PDGFRB signaling. Since then, several other *PDGFRB* fusion transcripts with similar disease phenotypes have been described, cell line transformation and MPD-induction in mice has been demonstrated, and imatinib therapy was effective when employed.

FGFR1 Mutated Eosinophilia The 8p11 myeloproliferative syndrome (EMS) (also known as human stem cell leukemic/lymphoma syndrome) constitutes a clinical phenotype with features of both lymphoma and eosinophilic MPN and characterized by a fusion mutation that involves the gene for fibroblast growth factor receptor-1 (*FGFR1*), which is located on chromosome 8p11. In EMS, both myeloid and lymphoid lineage cells exhibit the 8p11 translocation, thus demonstrating the stem cell origin of the disease. The disease features several 8p11-linked chromosome translocations and some of the corresponding fusion *FGFR1* mutants have been shown to transform cell lines and induce EMS- or CML-like disease in mice depending on the specific *FGFR1* partner gene, *ZNF 198* or *BCR*, respectively. Consistent with this laboratory observation, some patients with *BCR-FGFR1* mutation manifest a more indolent CML-like disease. The mechanism of FGFR1 activation in EMS is similar to that seen with PDGFRB-associated MPD; the tyrosine kinase domain of FGFR1 is juxtaposed to a dimerization domain from the partner gene. EMS is aggressive and requires combination chemotherapy followed by ASCT.

PCM1-JAK2 Associated Myeloid/Lymphoid Neoplasm with Eosinophilia The 2016 revised WHO document includes a provisional entity under myeloid/lymphoid neoplasms with eosinophilia referred to as "myeloid/lymphoid neoplasms with *PCM1-JAK2*." The entity is characterized by the t(8;9)(p22;p24.1) cytogenetic abnormality and a phenotype that displays marked male predominance, organomegaly, eosinophilia, and hetereogenous morphologic features similar to MPN, MDS, or MDS/MPN. Current drug therapy for *PCM1-JAK2*-associated disease is suboptimal, although some affected patients have displayed transient responses to ruxolutinib therapy.

Hypereosinophilic Syndrome Blood eosinophilia that is neither secondary nor clonal is operationally labeled as being "idiopathic." HES is a sub-category of idiopathic eosinophilia with persistent increase of the AEC to $\geq 1.5 \times 10^9$/L and presence of eosinophil-mediated organ damage, including cardiomyopathy, gastroenteritis, cutaneous lesions, sinusitis, pneumonitis, neuritis, and vasculitis. In addition, some patients manifest thromboembolic complications, hepatosplenomegaly, and either cytopenia or cytosis.

BM histological and cytogenetic/molecular studies should be examined before a working diagnosis of HES is made. Additional blood studies that are currently recommended during the evaluation of "HES" include serum tryptase (an increased level suggests mastocytosis and warrants molecular studies to detect *FIP1L1-PDGFRA*), T-cell immunophenotyping, as well as T-cell receptor antigen gene rearrangement analysis (a positive test suggests an underlying clonal or phenotypically abnormal T-cell disorder). In addition, initial evaluation in HES should include echocardiogram and measurement of serum troponin levels to screen for myocardial involvement by the disease.

Initial evaluation of the patient with eosinophilia should include tests that facilitate assessment of target organ damage: complete blood count, chest x-ray, echocardiogram, and serum troponin level. Increased level of serum cardiac troponin has been shown to correlate with the presence of cardiomyopathy in HES. Typical echocardiographic findings in HES include ventricular apical thrombus, posterior mitral leaflet or tricuspid valve abnormality, endocardial thickening, dilated left ventricle, and pericardial effusion.

In a Mayo Clinic study of 98 consecutive patients with idiopathic eosinophilia, including HES, median age was 53 years (55% males), and overt organ involvement was seen >80% of the cases including 54% involving organs other than the skin. The frequencies of cardiac involvement, hepatosplenomegaly, increased serum tryptase and interleukin-5 levels were 8, 4, 24, and 31%, respectively. The study also revealed that 11% of the affected patients harbored pathogenetic mutations including *TET2*, *ASXL1*, and *KIT*; the presence of such mutations did not appear to influence phenotype and the number of informative cases was too small to assess prognostic relevance. Instead, the study identified anemia and presence of cardiac involvement or hepatosplenomegaly as risk factors for survival.

Glucocorticoids are the cornerstone of therapy in HES. Treatment with oral prednisone is usually started at 1mg/kg/d and continued for 1 to 2 weeks before the dose is tapered slowly over the ensuing 2 to 3 months. If symptoms recur at a prednisone dose level of >10 mg/d, either hydroxyurea or interferon α is used as steroid-sparing agent. In patients who do not respond to usual therapy as outlined above, mepolizumab or alemtuzumab might be considered. Mepolizumab targets IL-5, a well-recognized survival factor for eosinophils. Alemtuzumab targets the CD52 antigen, which has been shown to be expressed by eosinophils but not by neutrophils.

MASTOCYTOSIS

Mast cell disease (MCD) is defined as tissue infiltration by morphologically as well as immunophenotypically abnormal mast cells. MCD is classified into two broad categories; cutaneous and systemic mastocytosis (SM). MCD in adults is usually systemic and the clinical course can be either indolent or aggressive, depending on the respective absence or presence of impaired organ function. Symptoms and signs of MCD include urticaria pigmentosa, mast cell mediator release symptoms (e.g., headache, flushing, lightheadedness, syncope, anaphylaxis, pruritus, urticaria, angioedema, nausea, diarrhea, abdominal cramps), and organ damage (lytic bone lesions, osteoporosis, hepatosplenomegaly, cytopenia). Aggressive SM can be associated with another myeloid malignancy, including MPN, MDS, MDS/MPN overlap (e.g., CMML), or present as overt mast cell leukemia (MCL). In general, life expectancy is near normal in indolent SM but significantly shortened in aggressive SM.

Diagnosis of SM is based on BM examination that shows clusters of morphologically abnormal, spindle-shaped mast cells that are best evaluated by the use of immunohistochemical stains that are specific to mast cells (tryptase, CD117). In addition, mast cell immunophenotyping reveals aberrant CD25 expression by neoplastic mast cells. Other laboratory findings in SM include increased levels of serum tryptase, histamine and urine histamine metabolites and prostaglandins. SM is associated with *KIT* mutations, usually *KIT*D816V, in the majority of patients. Accordingly, mutation screening for *KIT*D816V is diagnostically useful. However, the ability to detect *KIT*D816V depends on assay

sensitivity and mast cell content of the test sample. The 2016 WHO classification of mastocytosis includes (1) cutaneous mastocytosis (CM), (2) SM, and (3) mast cell sarcoma (MCS). SM is further classified into (a) indolent SM (ISM), (b) smoldering SM (SSM), (c) SM with an associated hematological neoplasm (SM-AHN), (d) aggressive SM (ASM), and (e) MCL.

Both indolent and aggressive SM patients might experience mast cell mediator release symptoms, which are usually managed by both H-1 and H-2 histamine receptor blockers as well as cromolyn sodium. In addition, patients with propensity to vasodilatory shock should wear a medical alert bracelet as well as carry an Epi-Pen self-injector for self-administration of subcutaneous epinephrine. Urticaria pigmentosa shows variable response to both topical and systemic corticosteroid therapy. Cytoreductive therapy is not recommended for indolent SM. In aggressive SM, either interferon α or cladribine is considered first-line therapy and benefits the majority of patients. In contrast, imatinib is ineffective in the treatment of *PDGFR*-unmutated SM. A controlled study of patients with ISM or SSM demonstrated marginal value of masitinib (oral tyrosine kinase inhibitor that inhibits KIT and LYN) with reported cumulative symptomatic response rate of 18.7% vs 7.4% for placebo. Treatment responses were more impressive in another study that used the multikinase inhibitor midostaurin in patients with the more aggressive forms of SM, with 45% of the patients achieving major response.

DENDRITIC AND HISTIOCYTIC NEOPLASMS

DC and histiocyte/macrophage neoplasms are extremely rare. DCs are antigen-presenting cells, whereas histiocyte/macrophages are antigen-processing. BM myeloid stem cells (CD34+) give rise to monocyte (CD14+, CD68+, CD11c+, CD1a–) and DC (CD14-, CD11c+/–, CD1a+/c) precursors. Monocyte precursors, in turn, give rise to macrophages (CD14+, CD68+, CD11c+, CD163+, lysozyme+) and interstitial DCs (CD68+, CD1a–). DC precursors give rise to Langerhans cell DCs (Birbeck granules, CD1a+, S100+, langerin+) and plasmacytoid DCs (CD68+, CD123+). Follicular DCs (CD21+, CD23+, CD35+) originate from mesenchymal stem cells. Dendritic and histiocytic neoplasms are operationally classified into macrophage/histiocyte-related and DC-related. The former includes histiocytic sarcoma/malignant histiocytosis (MH) and the latter Langerhans cell (LC) histiocytosis, LC sarcoma, interdigitating DC sarcoma, and follicular DC sarcoma.

Histiocytic Sarcoma/Malignant Histiocytosis Histiocytic sarcoma represents malignant proliferation of mature tissue histiocytes and is often localized. Median age at diagnosis is estimated at 46 years with slight male predilection. Some patients might have history of lymphoma, MDS, or germ cell tumors at time of disease presentation. The three typical disease sites are lymph nodes, skin, and the gastrointestinal system. Patients may or may not have systemic symptoms including fever and weight loss, and other symptoms include hepatosplenomegaly, lytic bone lesions, and pancytopenia. Immunophenotype includes presence of histiocytic markers (CD68, lysozyme, CD11c, CD14) and absence of myeloid or lymphoid markers. Prognosis is poor and treatment often ineffective. The term MH refers to a disseminated disease and systemic symptoms. Lymphoma-like treatment induces complete remissions in some patients and median survival is estimated at 2 years.

Langerhans Cell Histiocytosis LCs are specialized DCs that reside in mucocutaneous tissue and upon activation become specialized for antigen presentation to T cells. LC histiocytosis (LCH; also known as histiocytosis X) represents neoplastic proliferation of LCs (S-100+, CD1a+, and Birbeck granules on electron microscopy). LCH incidence is estimated at 5 per million and the disease typically affects children with a male predilection. Presentation can be either uni- (eosinophilic granuloma) or multi-focal. The former usually affects bones and less frequently lymph nodes, skin, and lung, while the latter is more disseminated. Unifocal disease often affects older children and adults while multisystem disease affects infants. LCH of the lung in adults is characterized by bilateral nodules. Prognosis depends on organs involved. Only 10% of patients progress from unifocal to multiorgan disease. LCH of the lung might improve upon cessation of smoking. Approximately 55% of patients with LCH harbor *BRAF*V600E gain-of-function mutations, which indicates high-risk disease and resistance to first-line therapy, while responses to targeted therapy with vemurafenib have been reported.

Langerhans Cell Sarcoma Langerhans cell sarcoma (LCS) also represents neoplastic proliferation of LCs with overtly malignant morphology. The disease can present de novo or progress from antecedent LCH. There is a female predilection and median age at diagnosis is estimated at 41 years. Immunophenotype is similar to that seen in LCH and liver, spleen, lung, and bone are the usual sites of disease. Prognosis is poor and treatment generally ineffective.

Interdigitating Dendritic Cell Sarcoma Interdigitating DC sarcoma (IDCS), also known as reticulum cell sarcoma, represents neoplastic proliferation of IDCs. The disease is extremely rare and affects elderly adults with no sex predilection. Typical presentation is asymptomatic solitary lymphadenopathy. Immunophenotype includes S-100+ and negative for vimentin and CD1a. Prognosis ranges from benign local disease to widespread lethal disease.

Follicular Dendritic Cell Sarcoma FDC reside in B-cell follicles and present antigen to B cells. FDC neoplasms (FDCN) are usually localized and often affect adults. FDCN might be associated with Castleman's disease in 10–20% of cases and increased incidence in schizophrenia has been reported. Cervical lymph nodes are the most frequent site of involvement in FDCN and other sites include maxillary, mediastinal, and retroperitoneal lymph nodes, oral cavity, the gastrointestinal system, skin, and breast. Sites of metastasis include lung and liver. Immunophenotype includes CD21, CD35, and CD23. Clinical course is typically indolent, and treatment includes surgical excision followed by regional radiotherapy and sometimes systemic chemotherapy.

Hemophagocytic Syndromes HPS represents non-neoplastic proliferation and activation of macrophages that induces cytokine-mediated BM suppression and features of intense phagocytosis in BM and liver. HPS may result from genetic or acquired disorders of macrophages. The former entail genetically determined inability to regulate macrophage proliferation and activation. Acquired HPS is often precipitated by viral infections, most notably Epstein-Barr virus. HPS might also accompany certain malignancies such as T-cell lymphoma. It is characterized by pancytopenia and elevated ferritin levels. Interferon γ is thought to play a role. Clinical course is often fulminant and fatal.

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107 Plasma Cell Disorders

Nikhil C. Munshi, Dan L. Longo, Kenneth C. Anderson

The *plasma cell disorders* are monoclonal neoplasms related to each other by virtue of their development from common progenitors in the late B-lymphocyte lineage. Multiple myeloma (MM), Waldenström's macroglobulinemia, primary amyloidosis **(Chap. 108)**, and the heavy chain diseases comprise this group and may be designated by a variety of synonyms such as *monoclonal gammopathies, paraproteinemias, plasma cell dyscrasias*, and *dysproteinemias*. Mature B lymphocytes destined to produce IgG bear surface immunoglobulin molecules of both μ and γ heavy chain isotypes with both isotypes having identical idiotypes (variable regions). Under normal circumstances, maturation to antibody-secreting plasma cells and their proliferation is stimulated by exposure to the antigen for which the surface immunoglobulin is specific; however, in the plasma cell disorders, the control over this process is lost. The clinical manifestations of all the plasma cell disorders relate to the expansion of the neoplastic cells, to the secretion of cell products (immunoglobulin molecules or subunits, lymphokines), and to some extent to the host's response to the tumor. **Normal development of B lymphocytes is discussed in Chap. 342 and depicted in Fig. 104-2.**

Three categories of structural variation are present among immunoglobulin molecules that form antigenic determinants, and these are used to classify immunoglobulins. *Isotypes* are those determinants that distinguish among the main classes of antibodies of a given species and are the same in all normal individuals of that species. Therefore, isotypic determinants are, by definition, recognized by antibodies from a distinct species (heterologous sera) but not by antibodies from the same species (homologous sera). There are five heavy chain isotypes (M, G, A, D, E) and two light chain isotypes (κ, λ). *Allotypes* are distinct determinants that reflect regular small differences between individuals of the same species in the amino acid sequences of otherwise similar immunoglobulins. These differences are determined by allelic genes; by definition, they are detected by antibodies made in the same species. *Idiotypes* are the third category of antigenic determinants. They are unique to the molecules produced by a given clone of antibody-producing cells. Idiotypes are formed by the unique structure of the antigen-binding portion of the molecule.

Antibody molecules **(Fig. 107-1)** are composed of two heavy chains (~50,000 mol wt) and two light chains (~25,000 mol wt). Each chain has a constant portion (limited amino acid sequence variability) and a variable region (extensive sequence variability). The light and heavy chains are linked by disulfide bonds and are aligned so that their variable regions are adjacent to one another. This variable region forms the antigen recognition site of the antibody molecule; its unique structural features form idiotypes that are reliable markers for a particular clone of cells because each antibody is formed and secreted by a single clone. Because of the mechanics of the gene rearrangements necessary to specify the immunoglobulin variable regions (VDJ joining for the heavy chain, VJ joining for the light chain), a particular clone rearranges only one of the two chromosomes to produce an immunoglobulin molecule of only one light chain isotype and only one allotype (allelic exclusion) (Fig. 107-1). After exposure to antigen, the variable region may become associated with a new heavy chain isotype (class switch). Each clone of cells performs these sequential gene arrangements in a unique way. This results in each clone producing a unique immunoglobulin molecule. In most plasma cells, light chains are synthesized in slight excess, secreted as free light chains, and cleared by the kidney, but <10 mg of such light chains is excreted per day.

Electrophoretic analysis permits separation of components of the serum proteins **(Fig. 107-2)**. The immunoglobulins move heterogeneously in an electric field and form a broad peak in the gamma region, which is usually increased in the sera of patients with plasma cell tumors. There is a sharp spike in this region called an *M component* (M for monoclonal). Less commonly, the M component may appear in the β_2 or α_2 globulin region. The monoclonal antibody must be present at a concentration of at least 5 g/L (0.5 g/dL) to be accurately quantitated by this method. This corresponds to ~10^9 cells producing the antibody. Confirmation of the type of immunoglobulin and that it is truly monoclonal is determined by immunoelectrophoresis that reveals a single heavy and/or light chain type. Hence immunoelectrophoresis and electrophoresis provide qualitative and quantitative assessment of the M component, respectively. Once the presence of an M component has been confirmed, the amount of M component in the serum is a reliable measure of the tumor burden, making M component an excellent tumor marker to manage therapy, yet it is not specific enough to be used to screen asymptomatic patients. In addition to the plasma cell disorders, M components may be detected in other lymphoid neoplasms such as chronic lymphocytic leukemia (CLL) and lymphomas of B- or T-cell origin; nonlymphoid neoplasms such as chronic myeloid leukemia, breast cancer, and colon cancer; a variety of nonneoplastic conditions such as cirrhosis, sarcoidosis, parasitic diseases, Gaucher's disease, and pyoderma gangrenosum; and a number of autoimmune conditions, including rheumatoid arthritis, myasthenia gravis, and cold agglutinin disease. Monoclonal proteins are also observed in immunosuppressed patients after organ transplant and, rarely, allogeneic transplant. At least two very rare skin diseases—lichen myxedematosus (also known as papular mucinosis) and necrobiotic xanthogranuloma—are associated with a monoclonal gammopathy. In papular mucinosis, highly cationic IgG is deposited in the dermis of patients. This organ specificity may reflect the specificity of the antibody for some antigenic component of the dermis. Necrobiotic xanthogranuloma is a histiocytic infiltration of the skin, usually of the face, that produces red or yellow nodules that can enlarge to plaques. Approximately 10% progress to myeloma. Five percent of patients with sensory motor neuropathy also have a monoclonal paraprotein.

The nature of the M component is variable in plasma cell disorders. It may be an intact antibody molecule of any heavy chain subclass, or it may be an altered antibody or fragment. Isolated light or heavy chains may be produced. In some plasma cell tumors such as extramedullary or solitary bone plasmacytomas, less than one-third of patients will have an M component. In ~20% of myelomas, only light chains are produced and, in most cases, are secreted in the urine as Bence Jones proteins. The frequency of myelomas of a particular heavy chain class is roughly proportional to the serum concentration, and therefore, IgG myelomas are more common than IgA and IgD myelomas. In ~1% of patients with myeloma, biclonal or triclonal gammopathy is observed.

MULTIPLE MYELOMA

DEFINITION

MM represents a malignant proliferation of plasma cells derived from a single clone. The tumor, its products, and the host response to it result in a number of organ dysfunctions and symptoms, including bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity.

ETIOLOGY

The cause of myeloma is not known. Myeloma occurred with increased frequency in those exposed to the radiation of nuclear warheads in World War II after a 20-year latency. Myeloma has been seen more commonly than expected among farmers, wood workers, leather workers, and those exposed to petroleum products. A variety of chromosomal alterations have been found in patients with myeloma: hyperdiploidy, 13q14 deletions, translocations t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16), 1q amplification or 1p deletion, and 17p13 deletions. Evidence is strong that errors in switch recombination—the genetic mechanism to change antibody heavy chain isotype—participate in the early transformation process. However, no single common molecular pathogenetic pathway has yet emerged. Genome sequencing studies have failed to identify any recurrent

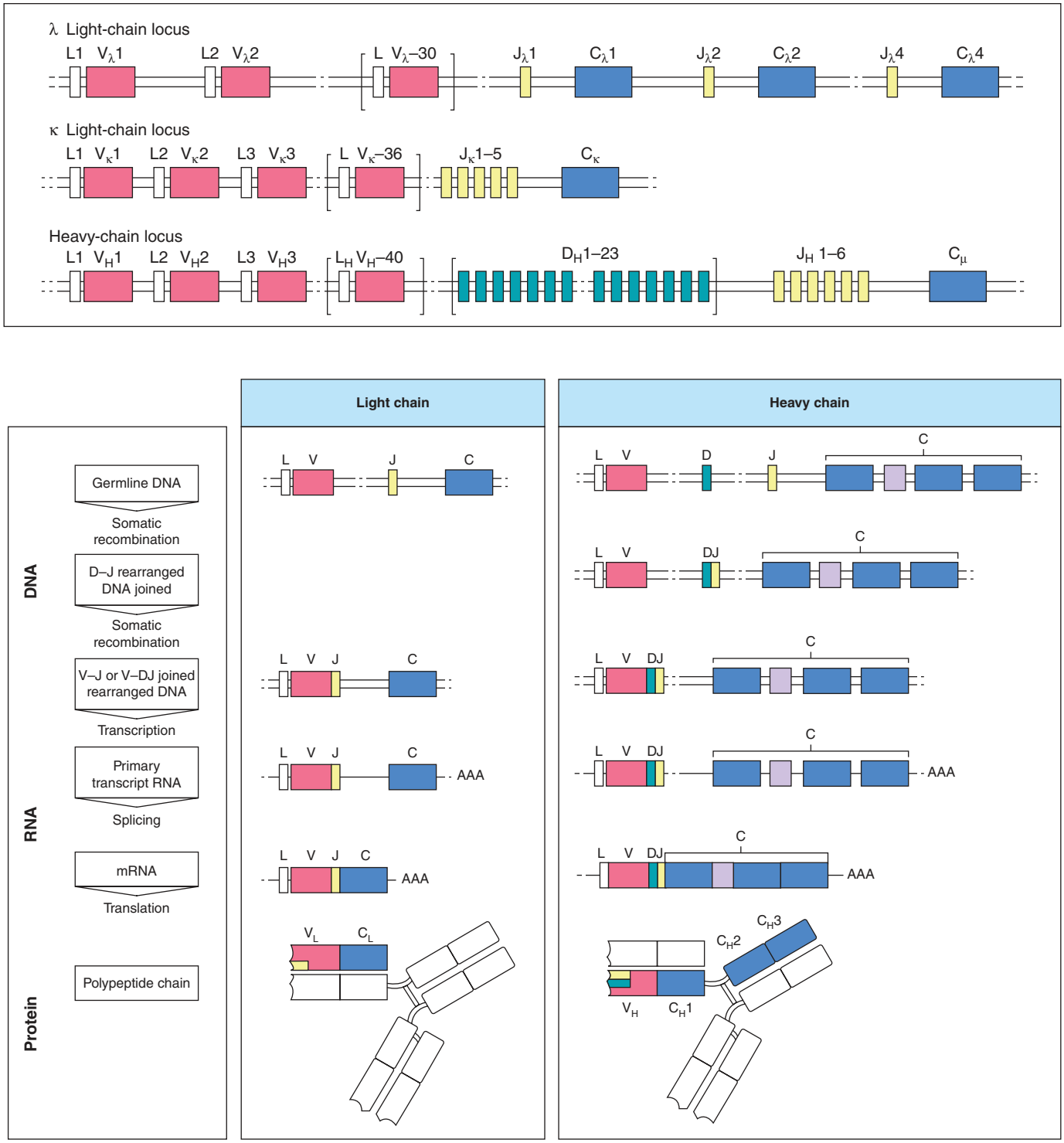


FIGURE 107-1 Immunoglobulin genetics and the relationship of gene segments to the antibody protein. The *top* portion of the figure is a schematic of the organization of the immunoglobulin genes, λ on chromosome 22, κ on chromosome 2, and the heavy chain locus on chromosome 14. The heavy chain locus is >2 megabases, and some of the D region gene segments are only a few bases long, so the figure depicts the schematic relationship among the segments, not their actual size. The *bottom* portion of the figure outlines the steps in going from the noncontiguous germline gene segments to an intact antibody molecule. Two recombination events juxtapose the V-D-J (or V-J for light chains) segments. The rearranged gene is transcribed, and RNA splicing cuts out intervening sequences to produce an mRNA, which is then translated into an antibody light or heavy chain. The sites on the antibody that bind to antigen (the so-called CDR3 regions) are encoded by D and J segments for heavy chains and the J segments for light chains. *(From K Murphy: Janeway's Immunobiology, 8th ed. Garland Science, 2011.)*

mutation with frequency >20%; *N-ras*, *K-ras*, and *B-raf* mutations are most common and combined occur in >40% of patients. Evidence of complex clusters of subclonal variants is present at diagnosis, acquires additional mutations over time, indicative of genomic evolution that may drive disease progression. Interleukin (IL) 6 may play a role in driving myeloma cell proliferation. It remains difficult to distinguish benign from malignant plasma cells based on morphologic criteria in all but a few cases **(Fig. 107-3)**.

INCIDENCE AND PREVALENCE

An estimated 30,280 new cases of myeloma were diagnosed in 2017, and 12,590 people died from the disease in the United States. Myeloma increases in incidence with age. The median age at diagnosis is 69 years; it is uncommon under age 40. Males are more commonly affected than females, and blacks have nearly twice the incidence of whites. Myeloma accounts for 1.3% of all malignancies in whites and 2% in blacks, and 13% of all hematologic cancers in whites and 33% in blacks.

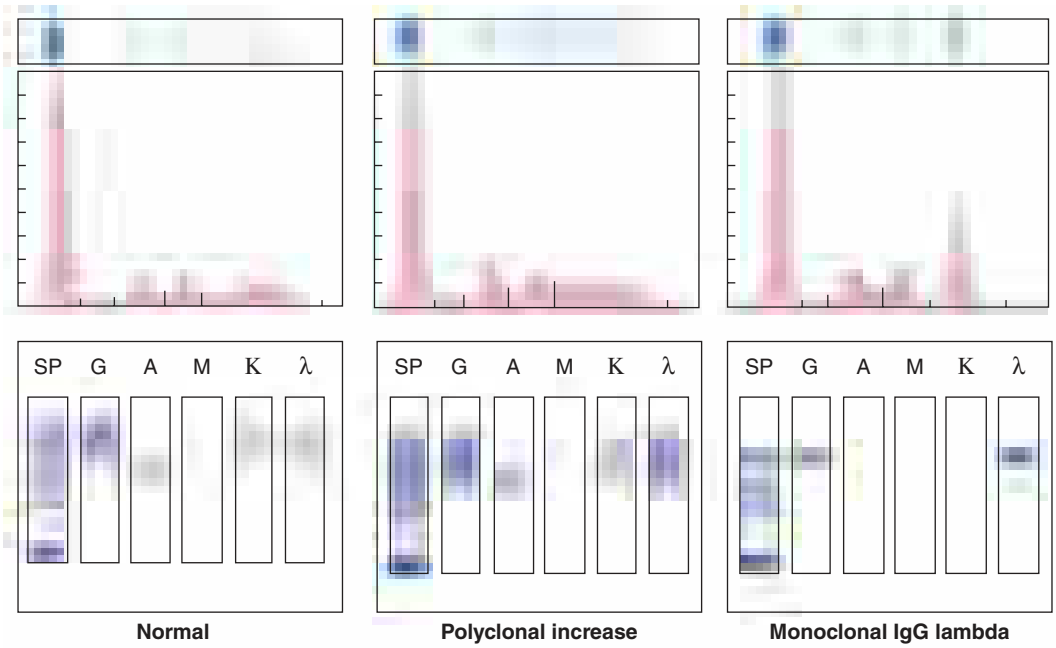


FIGURE 107-2 Representative patterns of serum electrophoresis and immunofixation. The *upper panels* represent agarose gel, middle panels are the densitometric tracing of the gel, and *lower panels* are immunofixation patterns. Panel on the *left* illustrates the normal pattern of serum protein on electrophoresis. Because there are many different immunoglobulins in the serum, their differing mobilities in an electric field produce a broad peak. In conditions associated with increases in polyclonal immunoglobulin, the broad peak is more prominent (*middle panel*). In monoclonal gammopathies, the predominance of a product of a single cell produces a "church spire" sharp peak, usually in the γ globulin region (*right panel*). The immunofixation (*lower panel*) identifies the type of immunoglobulin. For example, normal and polyclonal increase in immunoglobulins produce no distinct bands; however, the *right panel* shows distinct bands in IgG and lambda protein lanes, confirming the presence of IgG lambda monoclonal protein. *(Courtesy of Dr. Neal I. Lindeman; with permission.)*

GLOBAL CONSIDERATIONS

The incidence of myeloma is highest in African Americans and Pacific Islanders; intermediate in Europeans and North American whites; and lowest in people from developing countries including Asia. The higher incidence in more developed countries may result from the combination of a longer life expectancy and more frequent medical surveillance. Incidence of MM in other ethnic groups including native Hawaiians, female Hispanics, American Indians from New Mexico, and Alaskan natives is higher relative to U.S. whites in the same geographic area. Chinese and Japanese populations have a lower incidence than whites. Immunoproliferative small-intestinal disease (IPSID) with alpha heavy chain disease is most prevalent in the Mediterranean area. Despite these differences in prevalence, the characteristics, response to therapy, and prognosis of myeloma are similar worldwide.

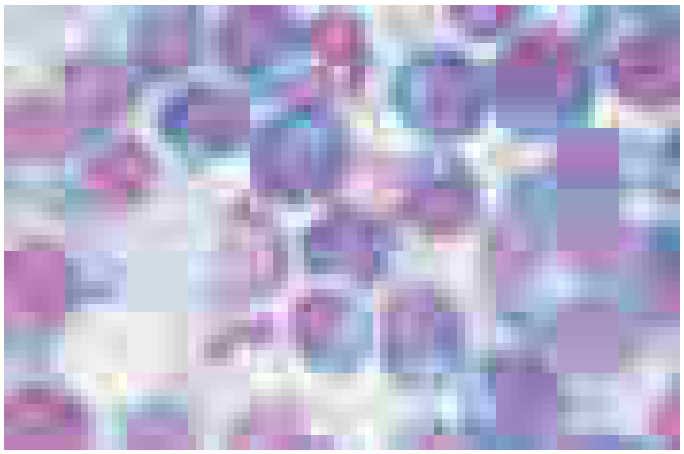


FIGURE 107-3 Multiple myeloma (marrow). The cells bear characteristic morphologic features of plasma cells, round or oval cells with an eccentric nucleus composed of coarsely clumped chromatin, a densely basophilic cytoplasm, and a perinuclear clear zone containing the Golgi apparatus. Binucleate and multinucleate malignant plasma cells can be seen.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

MM cells bind via cell-surface adhesion molecules to bone marrow stromal cells (BMSCs) and extracellular matrix (ECM), which triggers MM cell growth, survival, drug resistance, and migration in the bone marrow milieu **(Fig. 107-4)**. These effects are due both to direct MM cell–BMSC binding via adhesion molecules and to induction of various cytokines, including IL-6, insulin-like growth factor type I (IGF-I), vascular endothelial growth factor (VEGF), and stromal cell–derived growth factor (SDF)-1α. Growth, drug resistance, and migration are mediated via Ras/Raf/mitogen-activated protein kinase, PI3K/Akt, and protein kinase C signaling cascades, respectively.

Bone pain is the most common symptom in myeloma, affecting nearly 70% of patients. Persistent localized pain usually signifies a pathologic fracture. The bone lesions of myeloma are caused by the proliferation of tumor cells, activation of osteoclasts that destroy bone, and suppression of osteoblasts that form new bone. The increased osteoclast activity is mediated by osteoclast activating factors (OAFs) produced by the myeloma cells (mediated by several cytokines, including IL-1, lymphotoxin, VEGF, receptor activator of NF-κB [RANK] ligand, macrophage inhibitory factor [MIP]-1α, and tumor necrosis factor [TNF]). The bone lesions are lytic in nature **(Fig. 107-5)** and are rarely associated with osteoblastic new bone formation due to their suppression by dickhoff-1 (DKK-1) produced by myeloma cells. Therefore, radioisotopic bone scanning is less useful in diagnosis than is plain radiography. The bony lysis results in substantial mobilization of calcium from bone, and serious acute and chronic complications of hypercalcemia may dominate the clinical picture (see below). Localized bone lesions may cause the collapse of vertebrae leading to spinal cord compression. The next most common clinical problem in patients with myeloma is susceptibility to bacterial infections. The most common infections are pneumonias and pyelonephritis, and the most frequent pathogens are *Streptococcus pneumoniae, Staphylococcus aureus*, and *Klebsiella pneumoniae* in the lungs and *Escherichia coli* and other gram-negative organisms in the urinary tract. In ~25% of patients, recurrent infections are the presenting features, and >75% of patients will have a serious infection at some time in their course. The susceptibility to infection has several contributing causes. First, patients with myeloma have diffuse hypogammaglobulinemia if

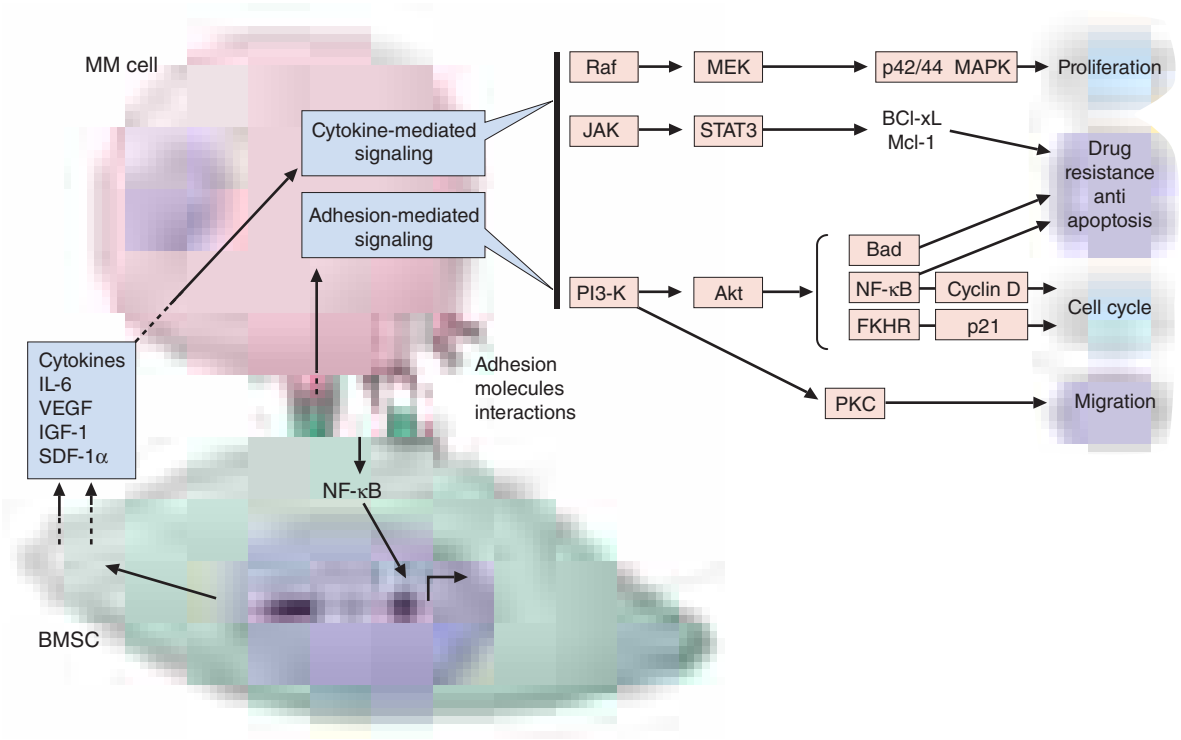
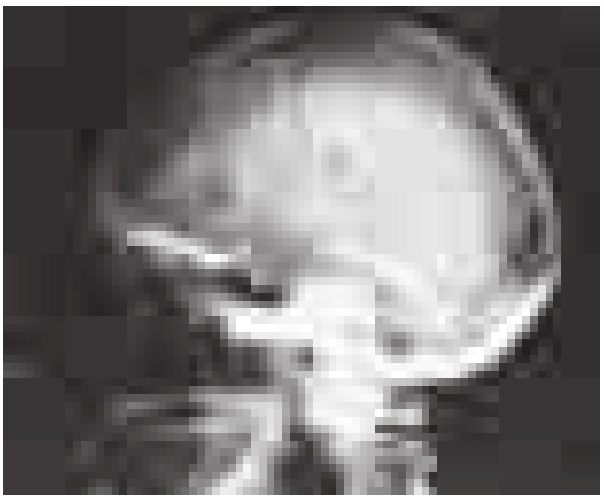


FIGURE 107-4 Pathogenesis of multiple myeloma. Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production. This triggers cytokine-mediated signaling that provides growth, survival, and antiapoptotic effects as well as development of drug resistance.

the M component is excluded. The hypogammaglobulinemia is related to both decreased production and increased destruction of normal antibodies. The large M component results in fractional catabolic rates of 8–16% instead of the normal 2%. Moreover, some patients generate a population of circulating regulatory cells in response to their myeloma that can suppress normal antibody synthesis. These patients have very poor antibody responses, especially to polysaccharide antigens such as those on bacterial cell walls. Various abnormalities in T-cell function are also observed including decreased Th_1 response, increase in Th17 cells producing proinflammatory cytokines, and aberrant T_{reg} cell function. Granulocyte lysozyme content is low, and granulocyte migration is not as rapid as normal in patients with myeloma, probably the result of a tumor product. There are also a variety of abnormalities in complement functions in myeloma patients. All these factors contribute to the immune deficiency in these patients. Some commonly used therapeutic agents, e.g., dexamethasone, suppress immune responses and increase susceptibility to bacterial and fungal infection, and bortezomib predisposes to herpesvirus reactivation.

Renal failure occurs in nearly 25% of myeloma patients, and some renal pathology is noted in >50%. Of many contributing factors, hypercalcemia is the most common cause of renal failure. Glomerular deposits of amyloid, hyperuricemia, recurrent infections, frequent use of nonsteroidal anti-inflammatory agents for pain control, use of iodinated contrast dye for imaging, bisphosphonate use, and occasional infiltration of the kidney by myeloma cells all may contribute to renal dysfunction. However, tubular damage associated with the excretion of light chains is almost always present. Normally, light chains are filtered, reabsorbed in the tubules, and catabolized. With the increase in the amount of light chains presented to the tubule, the tubular cells become overloaded with these proteins, and tubular damage results either directly from light chain toxic effects or indirectly from the release of intracellular lysosomal enzymes. The earliest manifestation of this tubular damage is the adult Fanconi's syndrome (a type 2 proximal renal tubular acidosis), with loss of glucose and amino acids, as well as defects in the ability of the kidney to acidify and concentrate the urine. The proteinuria is not accompanied by hypertension, and the protein is nearly all light chains. Generally, very little albumin is in the urine because glomerular function is usually normal. When the glomeruli are involved, nonselective proteinuria is also observed. Patients with myeloma also have a decreased anion gap [i.e., $Na^+ - (Cl^- + HCO_3^-)$] because the M component is cationic, resulting in retention of chloride. This is often accompanied by hyponatremia that is felt to be artificial (pseudohyponatremia) because each volume of serum has less water as a result of the increased protein. Renal dysfunction due to light chain deposition disease, light chain cast nephropathy, and amyloidosis is partially reversible with effective therapy. Myeloma patients are susceptible to developing acute renal failure if they become dehydrated.

Normocytic and normochromic anemia occurs in ~80% of myeloma patients. It is usually related to the replacement of normal marrow by expanding tumor cells, to the inhibition of hematopoiesis by factors made by the tumor, to reduced production of erythropoietin by the kidney, and to the effects of long-term therapy. In addition, mild hemolysis may contribute to the anemia. A larger than expected fraction of patients may have megaloblastic anemia due to either folate or vitamin B_{12} deficiency. Granulocytopenia and thrombocytopenia are rare except when therapy-induced. Clotting abnormalities may be seen due to the failure of antibody-coated platelets to function properly; the interaction of the M component with clotting factors I, II, V, VII, or VIII; antibody to clotting factors; or amyloid damage of endothelium. Deep venous thrombosis is also observed with use of thalidomide, lenalidomide, or pomalidomide in combination with dexamethasone. Raynaud's phenomenon and impaired circulation may result if the M component forms cryoglobulins, and hyperviscosity syndromes may develop depending on the physical properties of the M component (most common with IgM, IgG3, and IgA paraproteins). Hyperviscosity is defined based on the relative viscosity of serum as compared with water. Normal relative serum viscosity is 1.8 (i.e., serum is normally almost twice as viscous as water). Symptoms of hyperviscosity occur at a level greater than 4 centipoise (cP), which is usually reached at paraprotein concentrations of ~40 g/L (4 g/dL) for IgM, 50 g/L (5 g/dL) for IgG3, and 70 g/L (7 g/dL) for IgA; however, depending on chemical and physical properties of the paraprotein molecule, it can occasionally be observed at lower levels.



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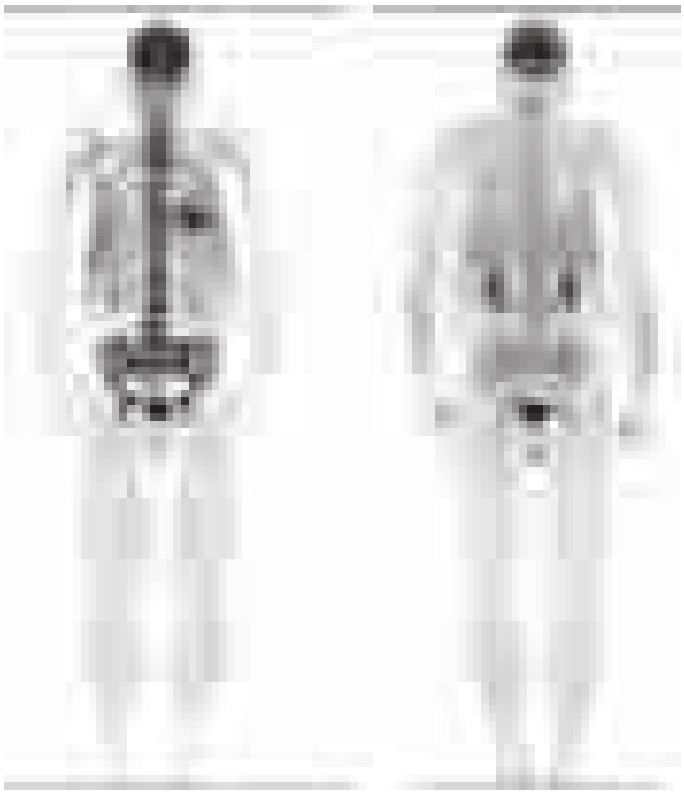

B

FIGURE 107-5 Bony lesions in multiple myeloma (MM). ***A.*** The skull demonstrates the typical "punched out" lesions characteristic of MM. The lesion represents a purely osteolytic lesion with little or no osteoblastic activity (above). ***B.*** PET/CT showing multiple fluorodeoxyglucose (FDG)-avid lesions in skeleton (left panel) with their resolution on achieving complete response (CR) (right panel). *(Part A courtesy of Dr. Geraldine Schechter; with permission. Part B courtesy of Dr. Sundar Jagannath; with permission.)*

Although neurologic symptoms occur in a minority of patients, they may have many causes. Hypercalcemia may produce lethargy, weakness, depression, and confusion. Hyperviscosity may lead to headache, fatigue, shortness of breath, exacerbation or precipitation of heart failure, visual disturbances, ataxia, vertigo, retinopathy, somnolence, and coma. Bony damage and collapse may lead to cord compression, radicular pain, and loss of bowel and bladder control. Infiltration of peripheral nerves by amyloid can be a cause of carpal tunnel syndrome and other sensorimotor mono- and polyneuropathies. Neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) and myeloma is more frequently sensory than motor neuropathy and is associated with IgM more than other isotypes. In >50% of patients with neuropathy, the IgM monoclonal protein is directed against myelin-associated globulin (MAG). Sensory neuropathy is also a side effect of therapy, specifically thalidomide and bortezomib.

Many of the clinical features of myeloma, e.g., cord compression, pathologic fractures, hyperviscosity, sepsis, and hypercalcemia, can present as medical emergencies. Despite the widespread distribution of plasma cells in the body, tumor expansion is dominantly within bone and bone marrow and, for reasons unknown, rarely causes enlargement of spleen, lymph nodes, or gut-associated lymphatic tissue.

DIAGNOSIS AND STAGING

The diagnosis of myeloma requires marrow plasmacytosis (>10%), a serum and/or urine M component, and at least one of the myeloma defining events detailed in **Table 107-1**. Bone marrow plasma cells are CD138+ and either monoclonal kappa or lambda light chain positive. The most important differential diagnosis in patients with myeloma involves their separation from individuals with MGUS or smoldering multiple myeloma (SMM). MGUS is vastly more common than myeloma, occurring in 1% of the population aged >50 years and in up to 10% of individuals aged >75 years. The diagnostic criteria for MGUS, SMM, and myeloma are described in Table 107-1. Although ~1% of patients per year with MGUS go on to develop myeloma, all cases of myeloma are preceded by MGUS. Non-IgG subtype, abnormal kappa/lambda free light chain ratio, and serum M protein >15 g/L (1.5 g/dL) are associated with higher incidence of progression of MGUS to myeloma. Absence of all three features predicts a 5% chance of progression, whereas higher risk MGUS with the presence of all three features predicts a 60% chance of progression >20 years. The features responsible for higher risk of progression from SMM to MM are bone marrow plasmacytosis >10%, abnormal kappa/lambda free light chain ratio, and serum M protein >30 g/L (3 g/dL). Patients with only one of these three features have a 25% chance of progression to MM in 5 years, whereas patients with high-risk SMM with all three features have a 76% chance of progression. There are two important variants of myeloma—solitary bone plasmacytoma and solitary extramedullary plasmacytoma. These lesions are associated with an M component in <30% of the cases, they may affect younger individuals, and both are associated with median survivals of ≥10 years. Solitary bone plasmacytoma is a single lytic bone lesion without marrow plasmacytosis. Extramedullary plasmacytomas usually involve the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis. Both tumors are highly responsive to local radiation therapy. If an M component is present, it should disappear after treatment. Solitary bone plasmacytomas may recur in other bony sites or evolve into myeloma. Extramedullary plasmacytomas rarely recur or progress.

Serum protein electrophoresis and measurement of serum immunoglobulins and free light chains are useful for detecting and characterizing M spikes, supplemented by immunoelectrophoresis, which is especially sensitive for identifying low concentrations of M components not detectable by protein electrophoresis. A 24-h urine specimen is necessary to quantitate Bence Jones protein excretion. Serum alkaline phosphatase is usually normal even with extensive bone involvement because of the absence of osteoblastic activity. It is also important to quantitate serum β_2-microglobulin and albumin (see below).

The serum M component will be IgG in 53% of patients, IgA in 25%, and IgD in 1%; 20% of patients will have only light chains in serum and urine. Dipsticks for detecting proteinuria are not reliable at identifying light chains, and the heat test for detecting Bence Jones protein is falsely negative in ~50% of patients with light chain myeloma. Fewer than 1% of patients have no identifiable M component; these patients usually have light chain myeloma in which renal catabolism has made the light chains undetectable in the urine. In most of these patients, light chains can now be detected by serum free light chain assay. IgD myeloma may also present with light chain disease. About two-thirds of patients with serum M components also have urinary light chains. The light chain isotype may have an impact on disease behavior. Whether this is due to some genetically important determinant of cell proliferation or because lambda light chains are more likely to cause renal damage and form amyloid than are kappa light chains is unclear. The heavy chain

TABLE 107-1 Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Undetermined Significance

Monoclonal Gammopathy of Undetermined Significance (MGUS)
Serum monoclonal protein (non-IgM type) <30 g/L
Clonal bone marrow plasma cells <10%*
Absence of myeloma defining events or amyloidosis that can be attributed to the plasma cell proliferative disorder
Smoldering Multiple Myeloma (Asymptomatic Myeloma)
Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60% • Absence of myeloma defining events or amyloidosis
Symptomatic Multiple Myeloma

Clonal bone marrow plasma cells or biopsy-proven bony or extramedullary plasmacytoma[a] and any one or more of the following myeloma defining events:
• Evidence of one or more end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  • Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  • Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 μmol/L (>2 mg/dL)
  • Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
  • Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT[c]
  • Any one or more of the following biomarkers of malignancy:
  • Clonal bone marrow plasma cell percentage[a] ≥60%
  • Involved: uninvolved serum free light chain ratio[d] ≥100
  • >1 focal lesions on MRI studies[e]

Nonsecretory Myeloma
No M protein in serum and/or urine with immunofixation[f] Bone marrow clonal plasmacytosis ≥10% or plasmacytoma[a] Myeloma-related organ or tissue impairment (end-organ damage, as described above)
Solitary Plasmacytoma
Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells[a] Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder
POEMS Syndrome
All of the following four criteria must be met: 1. Polyneuropathy 2. Monoclonal plasma cell proliferative disorder 3. Any one of the following: (a) sclerotic bone lesions; (b) Castleman's disease; (c) elevated levels of vascular endothelial growth factor (VEGF) 4. Any one of the following: (a) organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy); (b) extravascular volume overload (edema, pleural effusion, or ascites); (c) endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic); (d) skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails); (e) papilledema; (f) thrombocytosis/polycythemia[g]

PET-CT=^{18}F-fluorodeoxyglucose PET with CT. [a]Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. [b]Measured or estimated by validated equations. [c]If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. [d]These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. [e]Each focal lesion must be 5 mm or more in size. [f]A small M component may sometimes be present. [g]These features should have no attributable other causes and have temporal relation with each other.

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

isotype may have an impact on patient management as well. About half of patients with IgM paraproteins develop hyperviscosity compared with only 2–4% of patients with IgA and IgG M components. Among IgG myelomas, it is the IgG3 subclass that has the highest tendency to form both concentration- and temperature-dependent aggregates, leading to hyperviscosity and cold agglutination at lower serum concentrations. A standard workup directed at detecting monoclonal plasma cells and myeloma-defining events as well as prognosis is detailed in **Table 107-2**. A complete blood count with differential may reveal anemia. Erythrocyte sedimentation rate is elevated. Rare patients (~1%) may have plasma cell leukemia with >2000 plasma cells/μL. This may be seen in disproportionate frequency in IgD (12%) and IgE (25%) myelomas. Serum calcium, urea nitrogen, creatinine, and uric acid levels may be elevated.

The clinical evaluation of patients with myeloma includes a careful physical examination searching for tender bones and masses. Chest and bone radiographs may reveal lytic lesions or diffuse osteopenia. Magnetic resonance imaging (MRI) offers a sensitive means to document extent of bone marrow infiltration and cord or root compression in patients with pain syndromes. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT is a valuable tool to assess bone damage and detect extramedullary sites of the disease (Fig. 107-5). The use of ^{18}F-FDG PET/CT is recommended to distinguish between smoldering and active MM and to confirm a suspected diagnosis of solitary plasmacytoma. It is also a valuable tool to evaluate response in patients with oligo- or nonsecretory myeloma.

PROGNOSIS

Serum β_2-microglobulin is the single most powerful predictor of survival and can substitute for staging. β_2-Microglobulin is the light chain of the class I major histocompatibility antigens (HLA-A, -B, -C) on the surface of every cell. Combination of serum β_2-microglobulin and albumin levels forms the basis for a three-stage International Staging System (ISS) **(Table 107-3)** that predicts survival. With the use of high-dose therapy and the newer agents, the Durie-Salmon staging system is unable to predict outcome and thus is no longer used. High labeling

TABLE 107-2 Standard Investigative Workup in MM

Investigations to Evaluate for Clonal Plasma Cells
Bone marrow aspirate and biopsy (fine needle aspiration of plasmacytoma if indicated)
- Histology
- Clonality by kappa/lambda immunostaining by flow cytometry or immunohistochemistry
Investigations to Evaluate Clonal Paraprotein
Serum protein electrophoresis and immunofixation
Quantitative serum immunoglobulin levels (IgG, IgA, and IgM)
24-h Urine protein electrophoresis and immunofixation
Serum free light chain and ratio
Immunofixation for IgD or IgE in select cases
Investigation to Evaluate End-Organ Damage
Hemogram to assess for anemia
Chemistry panel for renal function and calcium
Skeletal survey to evaluate bone lesions
- PET/CT or MRI if SMM or solitary plasmacytoma with no other MDE or extramedullary disease
Investigation for Risk Stratification
- β-2 microglobulin and serum albumin for ISS stage
- Fluorescent in situ hybridization for hyperdipoidy, del17p, t(4;14); t(14;16), amp1q34, and del 13 on bone marrow sample
- LDH
Specialized Investigation in Selected Cases
Abdominal fat pad for amyloid
Serum viscosity if IgM component or high IgA levels or serum M-component >7 g/dL

Abbreviations: ISS, International Staging System; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET/CT, positron emission tomography/computerized tomography.

TABLE 107-3 Risk Stratification in Myeloma

CHROMOSOMAL ABNORMALITIES		
METHOD	**STANDARD RISK (80%) (EXPECTED SURVIVAL 6–7+ YEARS)**	**HIGH RISK (20%) (EXPECTED SURVIVAL 2–3 YEARS)**
Karyotype	No chromosomal aberration	Any abnormality on conventional karyotype
FISH	t(11;14) t(6:14) Del(13)	Del(17p) t(4:14) t(14:16) t(14;20) amp 1q34
INTERNATIONAL STAGING SYSTEM		
	STAGE	**MEDIAN SURVIVAL, MONTHS**
β_2M <3.5, alb ≥3.5	I (28%)[a]	62
β_2M <3.5, alb <3.5 *or* β_2M = 3.5–5.5	II (39%)	44
β_2M >5.5	III (33%)	29
Other features suggesting high-risk disease: De novo plasma cell leukemia Extramedullary disease Elevated lactate dehydrogenate (LDH) High-risk gene expression profile		

[a]Percentage of patients presenting at each stage.

Abbreviations: β_2M, serum β_2-microglobulin in mg/L; alb, serum albumin in g/dL; FISH, fluorescent in situ hybridization.

index, circulating plasma cells, performance status, and high levels of lactate dehydrogenase are also associated with poor prognosis.

Other factors that may influence prognosis are the presence of cytogenetic abnormalities and hypodiploidy by karyotype, fluorescent in situ hybridization (FISH)–identified chromosome 17p deletion, and translocations t(4;14), (14;16), and t(14;20) and 1q34 amplification. Chromosome 13q deletion, previously thought to predict poor outcome, is not a predictor following the use of newer agents. The ISS system, along with cytogenetic changes, is the most widely used method for assessing prognosis (Table 107-3). Microarray profiling has formed the basis for RNA-based prognostic staging systems. Genome sequencing efforts have allowed for characterization of critical genes, pathways, and clonal heterogeneity in myeloma. The median number of mutations per transcribed genome in myeloma is around 58. A very heterogeneous mutational landscape with no unifying mutation has been observed. The most frequently mutated genes are *KRAS* and *NRAS* (about 20% each), followed by *TP53, DIS3, FAM46C*, and *BRAF*, all mutated in 5–10% of the patients. All other mutations were observed in <5% of the patients. These results are now being applied to develop new targeted personalized therapies in myeloma.

TREATMENT

Multiple Myeloma

No specific intervention is indicated for patients with MGUS. Follow-up once a year or less frequently is adequate except in higher risk MGUS, where serum protein electrophoresis, complete blood count, creatinine, and calcium should be repeated every 6 months. A patient with MGUS and severe polyneuropathy is considered for therapeutic intervention if a causal relationship can be assumed, especially in the absence of any other potential causes for neuropathy. Therapy can include plasmapheresis and occasionally rituximab in patients with IgM MGUS or myeloma-like therapy in those with IgG or IgA disease. About 10% of patients have smoldering MM (SMM) and will have an indolent course demonstrating only slow progression of disease over many years. For patients with SMM, no specific therapeutic intervention is indicated, although early intervention with lenalidomide and dexamethasone may prevent progression from high-risk SMM to active MM. At present, patients with SMM only require antitumor therapy when myeloma-defining events are identified. Patients with solitary bone plasmacytomas and extramedullary plasmacytomas may be expected to enjoy prolonged disease-free survival after local radiation therapy at a dose of around 40 Gy. Occult marrow involvement may occur at low incidence in patients with solitary bone plasmacytoma. Such patients are usually identified because their serum M component falls slowly or disappears initially after local therapy, only to return after a few months. These patients respond well to systemic therapy.

Patients with symptomatic and/or progressive myeloma require therapeutic intervention. In general, such therapy has two purposes: (1) systemic therapy to control myeloma; and (2) supportive care to control symptoms of the disease, its complications, and adverse effects of therapy. Therapy can significantly prolong survival and improve the quality of life for myeloma patients.

The therapy of myeloma includes an initial induction regimen followed by consolidation and/or maintenance therapy and, on subsequent progression, management of relapsed disease. A number of agents available for use at various stages of the therapy and their doses, schedules, and combinations are detailed in **Table 107-4**. Therapy is partly dictated by the patient's age and comorbidities, which may affect a patient's ability to undergo high-dose therapy and transplantation (**Fig. 107-6**).

Thalidomide, when combined with dexamethasone, achieved responses in two-thirds of newly diagnosed MM patients. Subsequently, lenalidomide, an immunomodulatory derivative of thalidomide, and bortezomib, a proteasome inhibitor, have each been combined with dexamethasone with high response rates (>80%) in newly diagnosed patients with MM. Importantly, their lower toxicity profile with improved efficacy has made them the preferred agents for induction therapy. Efforts to improve the depth of response and the fraction of patients responding have involved using three-drug

TABLE 107-4 Standard Therapeutic Agents in Myeloma

CLASS	AGENT	STANDARD DOSAGE AND ADMINISTRATION	COMBINATION	MYELOMA INDICATION
Immunomodulatory agents	Thalidomide (T)	Oral 50–200 mg qd	TD, VTD	Newly diagnosed and relapsed
	Lenalidomide (R)	Oral 5–25 mg daily × 21 days q 4 week	RD, RVD, DaRD, ERD, KRD, IRD	Relapsed
	Pomalidomide (P)	Oral 2–4 mg daily × 21 days q 4 week	PD	Relapsed
Proteasome inhibitor	Bortezomib (V)	IV or SC 1.3 mg/m^2 days 1, 4, 8, 11 OR 1, 8, 15	VD, VTD, VRD, DaVD, VCD	Newly diagnosed and relapsed
	Carfilzomib (K)	IV 20–56 mg/m^2 days 1, 2, 8, 9, 15, 16 q 4 weeks	KD, KRD	Relapsed
	Ixazomib (I)	Oral 4 mg days 1,8,15	IRD	Relapsed
Antibodies	Daratumumab (Da)	IV 16 mg/kg/week for 8 weeks then every 2 weeks for 16 weeks and then every 4 weeks thereafter	Dara, DaRD, DaVD	Relapsed
	Elotuzumab (E)	IV 10 mg/kg days 1, 8, 15, and 22 for first two cycles then on days 1 and 15. Along with RD	EloRD	Relapsed
Histone deacetylase inhibitor	Panobinostat (Pa)		PaVD	Relapsed
Alkylating agents	Melphalan (M)	Oral melphalan, 0.25 mg/kg per day for 4 days (with Pred) every 4–6 weeks	MP, MPT, MPR, MPV, high-dose M	Newly diagnosed and relapsed conditioning
	Cyclophosphamide (C)	IV—300–500 mg/m^2 weekly × 2 q 4 weeks Oral—50 mg qd × 21 days	VCD	Newly diagnosed and relapsed
	Bendamustine (B)	IV 70–90 mg days 1, 2 or days 1, 8 q 4 weeks	BD or BVD	Relapsed
Steroid	Dexamethasone (D) Prednisone (P)	Oral 10–40 mg q week Oral 1 mg/kg		All stages

regimens. The combination of lenalidomide, bortezomib, and dexamethasone achieves close to a 100% response rate and 30% complete response (CR) rate, making it one of the preferred induction regimens in transplant-eligible patients. Other similar three-drug combinations (bortezomib, thalidomide, and dexamethasone or bortezomib, cyclophosphamide, and dexamethasone) also achieve >90% response rate. Herpes zoster prophylaxis is indicated if bortezomib is used, and neuropathy attendant to bortezomib can be decreased both by its subcutaneous administration and administration on a weekly schedule. Lenalidomide use requires prophylaxis for deep-vein thrombosis (DVT) with either aspirin or if patients are at a greater risk of DVT, warfarin or low-molecular-weight heparin.

In patients receiving lenalidomide, stem cells should be collected within 6 months, because the continued use of lenalidomide may compromise the ability to collect adequate numbers of stem cells. Initial therapy is continued until maximal cytoreduction. In patients who are transplant candidates, alkylating agents such as melphalan should be avoided because they damage stem cells, leading to decreased ability to collect stem cells for autologous transplant.

In patients who are not transplant candidates due to physiologic age >70 years, significant cardiopulmonary problems, or other comorbid illnesses, the same two- or three-drug combinations described above are considered standard of care as induction therapy. Previously, therapy consisting of intermittent pulses of

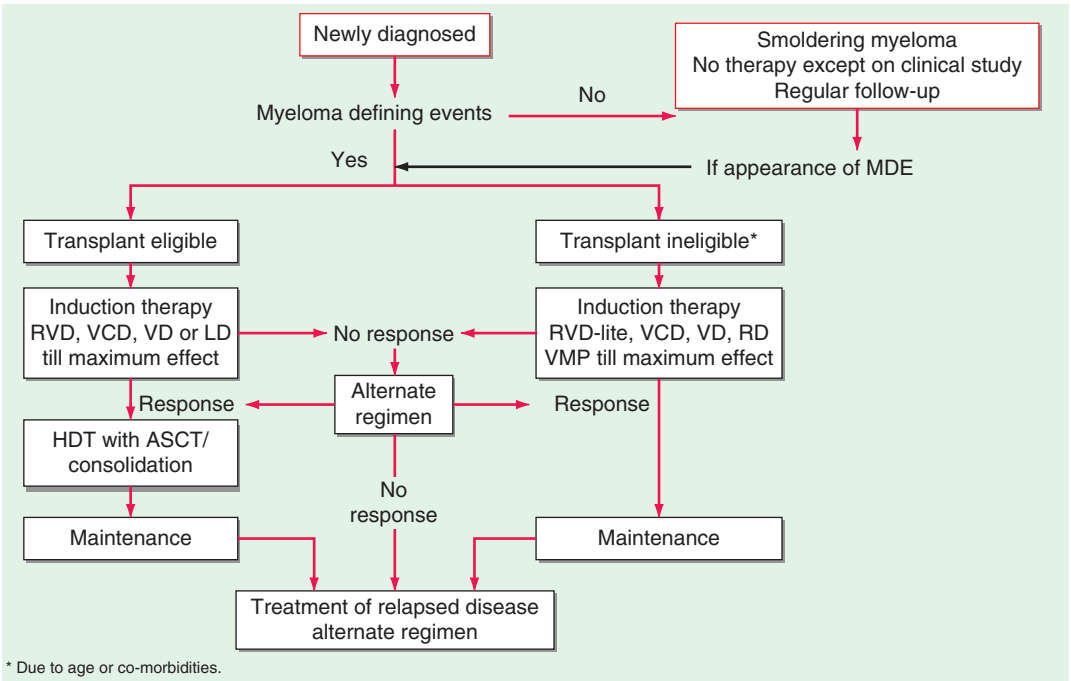

FIGURE 107-6 Treatment algorithm for multiple myeloma. C, cyclophosphamide; D, dexamethasone; M, melphalan; P, prednisone; R, lenalidomide; RVD-lite, weekly regimen; V, bortezomib. Alternate regimen-combinations including daratumumab; elotuzumab; panobinostat; carfilzomib; ixazomib, pomalidomide or agents; ASCT, autologous stem cell transplantation; HDT, high-dose therapy; MDE, myeloma defining events.

melphalan, an alkylating agent, with prednisone (MP) was used. However, a number of studies have combined novel agents with MP and reported superior response and survival outcomes. In patients >65 years old, combining thalidomide with MP (MPT) obtains higher response rates and overall survival compared with MP alone. Similarly, significantly improved response (71 vs 35%) and overall survival (3-year survival 72 vs 59%) were observed with the combination of bortezomib and MP compared with MP alone. Lenalidomide added to MP followed by lenalidomide maintenance also prolonged progression-free survival compared with MP alone. These combinations of novel agents with MP also achieve high CR rates (MPT, ~15%; MP plus bortezomib, ~30%; MP plus lenalidomide, ~20%; and MP, ~2–4%). Continuous use of the lenalidomide and dexamethasone combination appears to be superior to the MPT regimen, making it a standard of care for older adults with myeloma.

High-dose therapy (HDT) and consolidation/maintenance are standard practice in the majority of eligible patients. Randomized studies comparing standard-dose therapy to high-dose melphalan therapy with hematopoietic stem cell support have shown that HDT can achieve high overall response rates, with up to 25–40% additional CRs and prolonged progression-free and overall survival; however, few, if any, patients are cured. Although two successive HDTs (tandem transplantations) are more effective than single HDT, the benefit is only observed in the subset of patients who do not achieve a complete or very good partial response to the first transplantation, which is rare. Moreover, a randomized study failed to show any significant difference in overall survival between early transplantation after induction therapy versus delayed transplantation at relapse. These data allow an option to delay transplantation, especially with the availability of more agents and combinations. Allogeneic transplantations may also produce high response rates, but with significant toxicities. Nonmyeloablative allogeneic transplantation can reduce toxicity but is recommended only under the auspices of a clinical trial to exploit an immune graft-versus-myeloma effect while avoiding attendant toxicity.

Maintenance therapy prolongs remissions following standard-dose regimens as well as HDT. Two phase 3 studies have demonstrated improved progression-free survival, and one study showed prolonged overall survival in patients receiving lenalidomide compared to placebo as maintenance therapy after HDT. In nontransplant candidates, two phase 3 studies showed prolonged progression-free survival with lenalidomide maintenance after MP plus lenalidomide or lenalidomide with dexamethasone induction therapy. Although concern arises regarding an increased incidence of second primary malignancies in patients receiving lenalidomide maintenance, its benefits in reducing the risk of progressive disease and death from myeloma far outweigh the small increased risk of second cancers. In patients with high-risk cytogenetics, lenalidomide and bortezomib have been combined and show promise as maintenance therapy after transplantation.

Relapsed myeloma can be treated with a number of agents including lenalidomide and/or bortezomib, if previously not used. These agents in combination with dexamethasone can achieve a partial response rate of up to 60% and a 10–15% CR rate in patients with relapsed disease. The combination of bortezomib and liposomal doxorubicin is active in relapsed myeloma. Thalidomide, if not used as initial therapy, can achieve responses in refractory cases. The second-generation proteasome inhibitor carfilzomib and immunomodulatory agent pomalidomide have shown efficacy in relapsed and refractory MM, even MM refractory to lenalidomide and bortezomib. An oral proteasome inhibitor, ixazomib has also been approved in combination with lenalidomide and dexamethasone as an all-oral regimen for relapsed MM. Two antibodies are approved for treatment of relapsed MM. Daratumumab targeting CD38 achieves high response rates and improved progression-free survival as a single agent with further improvement in response and survival when added to bortezomib and dexamethasone, or lenalidomide and dexamethasone. Elotuzumab targeting SLAMF7 has shown significant activity in combination with lenalidomide and dexamethasone in relapsed/refractory myeloma but not as a single agent. Panobinostat, a histone deacetylase inhibitor, in combination with bortezomib and dexamethasone has been approved for treatment of relapsed refractory myeloma based on superior response and progression-free survival compared to bortezomib and dexamethasone alone. Incorporation of the large number of active agents at various stages of therapies including in the newly diagnosed patients is improving survival as well as quality of life.

Improvement in the serum M component may lag behind the symptomatic improvement due to longer half-life (~3 weeks) of the immunoglobulin. The fall in M component depends on the rate of tumor kill and the fractional catabolic rate of immunoglobulin. Light chain excretion, with a functional half-life of ~6 h, may fall within the first week of treatment. Because urine light chain levels may relate to renal tubular function, they are not a reliable measure of tumor cell kill in patients with renal dysfunction; however, improvements in serum free light chain measurement are often seen sooner. Sequencing- and multicolor flow cytometry-based methods are now used to assess minimal residual disease (MRD) in bone marrow. Absence of MRD predicts longer survival. Although patients may not achieve complete remission, clinical responses may last for long periods of time.

The median overall survival of patients with myeloma is 8+ years, with subsets of younger patients surviving >10 years. The major causes of death are progressive myeloma, renal failure, sepsis, or therapy-related myelodysplasia. Nearly a quarter of patients die of myocardial infarction, chronic lung disease, diabetes, or stroke—all intercurrent illnesses related more to the age of the patient group than to the tumor.

Supportive care directed at the anticipated complications of the disease may be as important as primary antitumor therapy. Hypercalcemia generally responds well to bisphosphonates, glucocorticoid therapy, hydration, and natriuresis, and rarely requires calcitonin as well. Bisphosphonates (e.g., pamidronate 90 mg or zoledronate 4 mg initially once a month and later less frequently) reduce osteoclastic bone resorption and preserve performance status and quality of life, decrease bone-related complications, and may also have antitumor effects. Osteonecrosis of the jaw and renal dysfunction can occur in a minority of patients receiving bisphosphonate therapy. Treatments aimed at strengthening the skeleton such as fluorides, calcium, and vitamin D, with or without androgens, have been suggested, but are not of proven efficacy. Kyphoplasty or vertebroplasty should be considered in patients with painful collapsed vertebra. Iatrogenic worsening of renal function may be prevented by maintaining a high fluid intake to prevent dehydration and enhance excretion of light chains and calcium. In the event of acute renal failure, plasmapheresis is ~10 times more effective at clearing light chains than peritoneal dialysis; however, its role in reversing renal failure remains controversial. Importantly, reducing the protein load by effective antitumor therapy with agents such as bortezomib may result in improvement in renal function in over half of the patients. Use of lenalidomide in renal failure is possible but requires dose modification, as it is renally excreted. Urinary tract infections should be watched for and treated early. Plasmapheresis may be the treatment of choice for hyperviscosity syndromes. Although the pneumococcus is a dreaded pathogen in myeloma patients, pneumococcal polysaccharide vaccines may not elicit an antibody response. The pneumococcal conjugate vaccines may be more protective. Prophylactic administration of intravenous γ globulin preparations is used in the setting of recurrent serious infections. Chronic oral antibiotic prophylaxis is not warranted. Patients developing neurologic symptoms in the lower extremities, severe localized back pain, or problems with bowel and bladder control may need emergency MRI and local radiation therapy and glucocorticoids if cord compression is identified. In patients in whom neurologic deficit is increasing or substantial, emergent surgical decompression may be necessary. Most bone lesions respond to analgesics and systemic therapy, but certain painful lesions may respond most promptly to localized

radiation. The anemia associated with myeloma may respond to erythropoietin along with hematinics (iron, folate, cobalamin). The pathogenesis of the anemia should be established and specific therapy instituted, whenever possible.

WALDENSTRÖM'S MACROGLOBULINEMIA

In 1948, Waldenström described a malignancy of lymphoplasmacytoid cells that secreted IgM. In contrast to myeloma, the disease was associated with lymphadenopathy and hepatosplenomegaly, but the major clinical manifestation was hyperviscosity syndrome. The disease resembles the related diseases CLL, myeloma, and lymphocytic lymphoma. It originates from a postgerminal center B cell that has undergone somatic mutations and antigenic selection in the lymphoid follicle and has the characteristics of an IgM-bearing memory B cell. Waldenström's macroglobulinemia (WM) and IgM myeloma follow a similar clinical course, but therapeutic options are different. The diagnosis of IgM myeloma is usually reserved for patients with lytic bone lesions and predominant infiltration with CD138+ plasma cells in the bone marrow. Such patients are at greater risk of pathologic fractures than patients with WM.

A familial occurrence is common in WM, but its molecular bases are yet unclear. A distinct *MYD88* L265P somatic mutation is present in >90% of patients with WM and the majority of IgM MGUS. Other commonly occurring mutations include *CXCR4* (30–40%), *ARID1A* (17%), and *CD79B* (8–15%). Presence of *MYD88* mutation status is now used as a diagnostic test to discriminate WM from marginal zone lymphomas (MZLs), IgM-secreting myeloma, and CLL with plasmacytic differentiation. This mutation also explains the molecular pathogenesis of the disease, with involvement of Toll-like receptor (TLR) and interleukin 1 receptor (IL-1R) signaling leading to activation of IL-1R–associated kinase (IRAK) 4 and IRAK1 followed by nuclear factor-κB (NF-κB) activation. *MYD88* mutation also triggers Burton's tyrosine kinase (BTK), hemopoietic cell kinase (HCK) growth, and survival signaling, which are now important therapeutic targets in WM. *CXCR4* mutations induce AKT and extracellular regulated kinase-1/2 (ERK 1/2) signaling. This pathway can lead to development of drug resistance in the presence of its ligand CXCL12.

The disease is similar to myeloma in being slightly more common in men and occurring with increased incidence with increasing age (median 64 years). The IgM in some patients with macroglobulinemia may have specificity for myelin-associated glycoprotein (MAG), a protein that has been associated with demyelinating disease of the peripheral nervous system and may be lost earlier and to a greater extent than the better known myelin basic protein in patients with multiple sclerosis. Sometimes patients with macroglobulinemia develop a peripheral neuropathy, and half of these patients are positive for anti-MAG antibody. The neuropathy may precede the appearance of the neoplasm. The whole process may begin with a viral infection that may elicit an antibody response that cross-reacts with a normal tissue component.

Like myeloma, the disease involves the bone marrow, but unlike myeloma, it does not cause bone lesions or hypercalcemia. Bone marrow shows >10% infiltration with lymphoplasmacytic cells (surface IgM+, CD19+, CD20+, and CD22+, rarely CD5+, but CD10− and CD23−) with an increase in number of mast cells. Like myeloma, an M component is present in the serum in excess of 30 g/L (3 g/dL), but unlike myeloma, the size of the IgM paraprotein results in little renal excretion, and only ~20% of patients excrete light chains. Therefore, renal disease is not common. The light chain isotype is kappa in 80% of the cases. Patients present with weakness, fatigue, and recurrent infections similar to myeloma patients, but epistaxis, visual disturbances, and neurologic symptoms such as peripheral neuropathy, dizziness, headache, and transient paresis are much more common in macroglobulinemia. Presence of *MYD88* and *CXCR4* mutations also affects disease presentation. Presence of *CXCR4* mutations is associated with higher bone marrow disease burden and higher incidence of hyperviscosity. Patients with wild-type *MYD88* show lower bone marrow disease burden.

Physical examination reveals adenopathy and hepatosplenomegaly, and ophthalmoscopic examination may reveal vascular segmentation and dilation of the retinal veins characteristic of hyperviscosity states. Patients may have a normocytic, normochromic anemia, but rouleaux formation and a positive Coombs' test are much more common than in myeloma. Malignant lymphocytes are usually present in the peripheral blood. About 10% of macroglobulins are cryoglobulins. These are pure M components and are not the mixed cryoglobulins seen in rheumatoid arthritis and other autoimmune diseases. Mixed cryoglobulins are composed of IgM or IgA complexed with IgG, for which they are specific. In both cases, Raynaud's phenomenon and serious vascular symptoms precipitated by the cold may occur, but mixed cryoglobulins are not commonly associated with malignancy. Patients suspected of having a cryoglobulin based on history and physical examination should have their blood drawn into a warm syringe and delivered to the laboratory in a container of warm water to avoid errors in quantitating the cryoglobulin.

TREATMENT

Waldenström's Macroglobulinemia

Control of serious hyperviscosity symptoms such as an altered state of consciousness or paresis can be achieved acutely by plasmapheresis because 80% of the IgM paraprotein is intravascular. The median survival of affected individuals is ~50 months. However, many patients with WM have indolent disease that does not require therapy. Pretreatment parameters including older age, male sex, general symptoms, and cytopenias define a high-risk population. Treatment is usually not initiated unless the disease is symptomatic or increasing anemia, hyperviscosity, lymphadenopathy, or hepatosplenomegaly is present. Ibrutinib is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in patients with symptomatic WM. It targets the constitutively activated BTK. In patients with one prior line of therapy, the overall response to ibrutinib was 91%. Best responses to ibrutinib are observed in patients with mutated *MYD88* and wild-type *CXCR4* status, while delayed and lower response rates to ibrutinib are observed in patients with mutated *CXCR4*. The other first line treatments include rituximab (anti-CD20) alone or combined with alkylators (bendamustine and cyclophosphamide), or proteasome inhibitors (bortezomib). Rituximab can produce IgM flare, so either plasmapheresis should be used before rituximab or its use should be initially withheld in patients with high IgM levels. Fludarabine (25 mg/m^2 per day for 5 days every 4 weeks) and cladribine (0.1 mg/kg per day for 7 days every 4 weeks) are also highly effective single agents. With identification of the *MYD88* mutation, inhibitors targeting IRAK1/4 and BCL2 are being evaluated. Although high-dose therapy plus autologous transplantation is an option, its use has declined due to the availability of other effective agents.

POEMS SYNDROME

The features of this syndrome are *p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M*-protein, and *s*kin changes (POEMS). Diagnostic criteria are described in Table 107-1. Patients usually have a severe, progressive sensorimotor polyneuropathy associated with sclerotic bone lesions from myeloma. Polyneuropathy occurs in ~1.4% of myelomas, but the POEMS syndrome is only a rare subset of that group. Unlike typical myeloma, hepatomegaly and lymphadenopathy occur in about two-thirds of patients, and splenomegaly is seen in one-third. The lymphadenopathy frequently resembles Castleman's disease histologically, a condition that has been linked to IL-6 overproduction. The endocrine manifestations include amenorrhea in women and impotence and gynecomastia in men. Hyperprolactinemia due to loss of normal inhibitory control by the hypothalamus may be associated with other central nervous system manifestations such as papilledema and elevated cerebrospinal fluid pressure and protein. Type 2 diabetes mellitus occurs in about one-third of patients. Hypothyroidism and adrenal insufficiency are occasionally noted. Skin changes are diverse: hyperpigmentation, hypertrichosis, skin thickening, and digital clubbing. Other manifestations include peripheral edema, ascites, pleural effusions, fever, and

thrombocytosis. Not all the components of POEMS syndrome may be present initially.

The pathogenesis of the disease is unclear, but high circulating levels of the proinflammatory cytokines IL-1, IL-6, VEGF, and TNF have been documented, and levels of the inhibitory cytokine transforming growth factor β are lower than expected. Treatment of the myeloma may result in an improvement in the other disease manifestations.

Patients are often treated similarly to those with myeloma. Plasmapheresis does not appear to be of benefit in POEMS syndrome. Patients presenting with isolated sclerotic lesions may have resolution of neuropathic symptoms after local therapy for plasmacytoma with radiotherapy. Similar to MM, novel agents and high-dose therapy with autologous stem cell transplantation have been pursued in selected patients and have been associated with prolonged progression-free survival.

HEAVY CHAIN DISEASES

The heavy chain diseases are rare lymphoplasmacytic malignancies. Their clinical manifestations vary with the heavy chain isotype. Patients have absence of light chain and secrete a defective heavy chain that usually has an intact Fc fragment and a deletion in the Fd region. Gamma, alpha, and mu heavy chain diseases have been described, but no reports of delta or epsilon heavy chain diseases have appeared. Molecular biologic analysis of these tumors has revealed structural genetic defects that may account for the aberrant chain secreted.

GAMMA HEAVY CHAIN DISEASE (FRANKLIN'S DISEASE)

This disease affects individuals of widely different age groups and countries of origin. It is characterized by lymphadenopathy, fever, anemia, malaise, hepatosplenomegaly, and weakness. It is frequently associated with autoimmune diseases, especially rheumatoid arthritis. Its most distinctive symptom is palatal edema, resulting from involvement of nodes in Waldeyer's ring, and this may progress to produce respiratory compromise. The diagnosis depends on the demonstration of an anomalous serum M component (often <20 g/L [<2 g/dL]) that reacts with anti-IgG but not antilight chain reagents. The M component is typically present in both serum and urine. Most of the paraproteins have been of the γ_1 subclass, but other subclasses have been seen. The patients may have thrombocytopenia, eosinophilia, and nondiagnostic bone marrow that may show increased numbers of lymphocytes or plasma cells that do not stain for light chain. Patients usually have a rapid downhill course and die of infection; however, some patients have survived 5 years with chemotherapy. Therapy is indicated when symptomatic and involves chemotherapeutic combinations used in low-grade lymphoma. Rituximab has also been reported to show efficacy.

ALPHA HEAVY CHAIN DISEASE (SELIGMANN'S DISEASE)

This is the most common of the heavy chain diseases. It is closely related to a malignancy known as Mediterranean lymphoma, a disease that affects young persons in parts of the world where intestinal parasites are common, such as the Mediterranean, Asia, and South America. The disease is characterized by an infiltration of the lamina propria of the small intestine with lymphoplasmacytoid cells that secrete truncated alpha chains. Demonstrating alpha heavy chains is difficult because the alpha chains tend to polymerize and appear as a smear instead of a sharp peak on electrophoretic profiles. Despite the polymerization, hyperviscosity is not a common problem in alpha heavy chain disease. Without J chain–facilitated dimerization, viscosity does not increase dramatically. Light chains are absent from serum and urine. The patients present with chronic diarrhea, weight loss, and malabsorption and have extensive mesenteric and paraaortic adenopathy. Respiratory tract involvement occurs rarely. Patients may vary widely in their clinical course. Some may develop diffuse aggressive histologies of malignant lymphoma. Chemotherapy may produce long-term remissions. Rare patients appear to have responded to antibiotic therapy, raising the question of the etiologic role of antigenic stimulation, perhaps by some chronic intestinal infection. Chemotherapy plus antibiotics may be more effective than chemotherapy alone. IPSID is recognized as an infectious pathogen–associated human lymphoma that has association with *Campylobacter jejuni*. It involves mainly the proximal small intestine resulting in malabsorption, diarrhea, and abdominal pain. IPSID is associated with excessive plasma cell differentiation and produces truncated alpha heavy chain proteins lacking the light chains as well as the first constant domain. Early-stage IPSID responds to antibiotics (30–70% complete remission). Most untreated IPSID patients progress to lymphoplasmacytic and immunoblastic lymphoma. Patients not responding to antibiotic therapy are considered for treatment with combination chemotherapy used to treat low-grade lymphoma.

MU HEAVY CHAIN DISEASE

The secretion of isolated mu heavy chains into the serum appears to occur in a very rare subset of patients with CLL. The only features that may distinguish patients with mu heavy chain disease are the presence of vacuoles in the malignant lymphocytes and the excretion of kappa light chains in the urine. The diagnosis requires ultracentrifugation or gel filtration to confirm the nonreactivity of the paraprotein with the light chain reagents because some intact macroglobulins fail to interact with these serums. The tumor cells seem to have a defect in the assembly of light and heavy chains because they appear to contain both in their cytoplasm. Such patients are not treated differently from other patients with CLL **(Chap. 104)**.

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108 Amyloidosis

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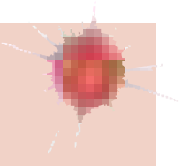

GENERAL PRINCIPLES

Amyloidosis is the term for a group of protein misfolding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. A robust cellular machinery exists to chaperone proteins during the process of synthesis and secretion, to ensure that they achieve correct tertiary conformation and function, and to eliminate proteins that misfold. However, genetic mutation, incorrect processing, and other factors may favor misfolding, with consequent loss of normal protein function and intracellular or extracellular aggregation. Many diseases, ranging from cystic fibrosis to

Alzheimer's disease, are now known to involve protein misfolding. In the amyloidoses, the aggregates are typically extracellular, and the misfolded protein subunits assume a common antiparallel, β-pleated sheet–rich structural conformation that leads to the formation of higher-order oligomers and then fibrils with unique staining properties. The term *amyloid* was coined around 1854 by the pathologist Rudolf Virchow, who thought that these deposits resembled starch (Latin *amylum*) under the microscope.

Amyloid diseases, defined by the biochemical nature of the protein composing the fibril deposits, are classified according to whether they are systemic or localized, whether they are acquired or inherited, and their clinical patterns **(Table 108-1)**. The standard nomenclature is *AX*, where *A* indicates amyloidosis and *X* represents the protein present in the fibril. This chapter focuses primarily on the systemic forms. *AL* refers to amyloid composed of immunoglobulin light chains (LCs); this disorder, formerly termed *primary systemic amyloidosis*, arises from a clonal B cell or plasma cell disorder and can be associated with myeloma or lymphoma. *ATTR* refers to the most prevalent of the *familial amyloidoses*, which are most commonly due to mutations in transthyretin (TTR), the transport protein for thyroid hormone and retinol-binding protein. *AA* amyloid is composed of the acute-phase reactant protein serum amyloid A (SAA) and occurs in the setting of chronic inflammatory or infectious diseases; for this reason, this type was formerly known as *secondary amyloidosis*. *$A\beta_2M$* amyloid results from misfolded β_2-microglobulin, occurring in individuals with long-standing renal disease who have undergone dialysis, typically for years. *Aβ*, the most common form of localized amyloidosis, is found in the brain of patients with Alzheimer's disease after abnormal proteolytic processing and aggregation of polypeptides derived from the amyloid precursor protein.

Diagnosis and treatment of the amyloidoses rest upon the histopathologic identification of amyloid deposits and immunohistochemical, biochemical, or genetic determination of amyloid type **(Fig. 108-1)**. In the systemic amyloidoses, the clinically involved organs can be biopsied, but amyloid deposits may be found in any tissue of the body. Historically, blood vessels of the gingiva or rectal mucosa were often examined, but the most easily accessible tissue—positive in more than 80% of patients with systemic amyloidosis—is abdominal fat. After local anesthesia, fat is aspirated from the abdominal pannus with a 16-gauge needle. Fat globules expelled onto a glass slide can be stained, thus avoiding a surgical procedure. If this material is negative, more invasive biopsies of the kidney, heart, liver, or gastrointestinal tract can be considered in patients in whom amyloidosis is suspected. The regular β-sheet structure of amyloid deposits exhibits a unique "apple green" birefringence by polarized light microscopy when stained with Congo red dye; other regular protein structures (e.g., collagen) appear white under these conditions. The 10-nm-diameter fibrils can also be visualized by electron microscopy of paraformaldehyde-fixed tissue. Once amyloid is found, the precursor protein type must be determined by immunohistochemistry, immunoelectron microscopy, or extraction and biochemical analysis employing mass spectrometry; gene sequencing is used to identify mutants causing hereditary amyloidosis. The patient's history, physical findings, and clinical presentation, including age and ethnic origin, organ system involvement, underlying diseases, and family history, may provide helpful clues as to the type of amyloidosis. However, there can be considerable overlap in clinical presentations, and accurate typing is essential to guide appropriate therapy.

The mechanisms of fibril formation and tissue toxicity remain controversial. The "amyloid hypothesis," as it is currently understood, proposes that precursor proteins undergo a process of reversible unfolding or misfolding; misfolded proteins form oligomeric aggregates, higher-order polymers, and then fibrils that deposit in tissues. Accumulating evidence suggests that the oligomeric intermediates may constitute the most toxic species. Oligomers are more capable than large fibrils of interacting with cells and inducing formation of reactive oxygen species and stress signaling. Ultimately, the fibrillar tissue deposits are likely to interfere with normal organ function. A more sophisticated understanding of the mechanisms leading to amyloid formation and cell and tissue dysfunction will continue to provide new targets for therapies.

The clinical syndromes of the amyloidoses are associated with relatively nonspecific alterations in routine laboratory tests. Blood counts are usually normal, although the erythrocyte sedimentation rate is frequently elevated. Patients with glomerular kidney involvement generally have proteinuria, often in the nephrotic range, leading to

TABLE 108-1 Amyloid Precursor Proteins and Their Clinical Syndromes

DESIGNATION	PRECURSOR	CLINICAL SYNDROME	CLINICAL INVOLVEMENT
Systemic Amyloidoses			
AL	Immunoglobulin light chain	Primary or myeloma-associated[a]	Any
AH	Immunoglobulin heavy chain	Rare variant of primary or myeloma-associated	Any
AA	Serum amyloid A protein	Secondary; reactive[b]	Renal, heart, other
$A\beta_2M$	β_2-Microglobulin	Hemodialysis-associated	Synovial tissue, bone
ATTR	Transthyretin	Familial (mutant)	Cardiac, peripheral and autonomic nerves
		Age-related (wild type)	
AApoAI	Apolipoprotein AI	Familial	Hepatic, renal
AApoAII	Apolipoprotein AII	Familial	Renal
AGel	Gelsolin	Familial	Cornea, cranial nerves, skin, renal
AFib	Fibrinogen Aα	Familial	Renal
ALys	Lysozyme	Familial	Renal, hepatic
ALECT2	Leukocyte chemotactic factor 2	Undefined	Renal
Localized Amyloidoses			
Aβ	Amyloid β protein	Alzheimer's disease; Down's syndrome	Central nervous system
ACys	Cystatin C	Cerebral amyloid angiopathy	Central nervous system, vascular
APrP	Prion protein	Spongiform encephalopathies	Central nervous system
AIAPP	Islet amyloid polypeptide (amylin)	Diabetes-associated	Pancreas
ACal	Calcitonin	Medullary carcinoma of the thyroid	Thyroid
AANF	Atrial natriuretic factor	Atrial fibrillation	Cardiac atria
APro	Prolactin	Endocrinopathy	Pituitary
ASgl	Semenogelin I	Age-related; incidental autopsy or biopsy finding	Seminal vesicles

[a]Localized AL deposits can occur in skin, conjunctiva, urinary bladder, and the tracheobronchial tree. [b]Secondary to chronic inflammation or infection or to a hereditary periodic fever syndrome such as familial Mediterranean fever.

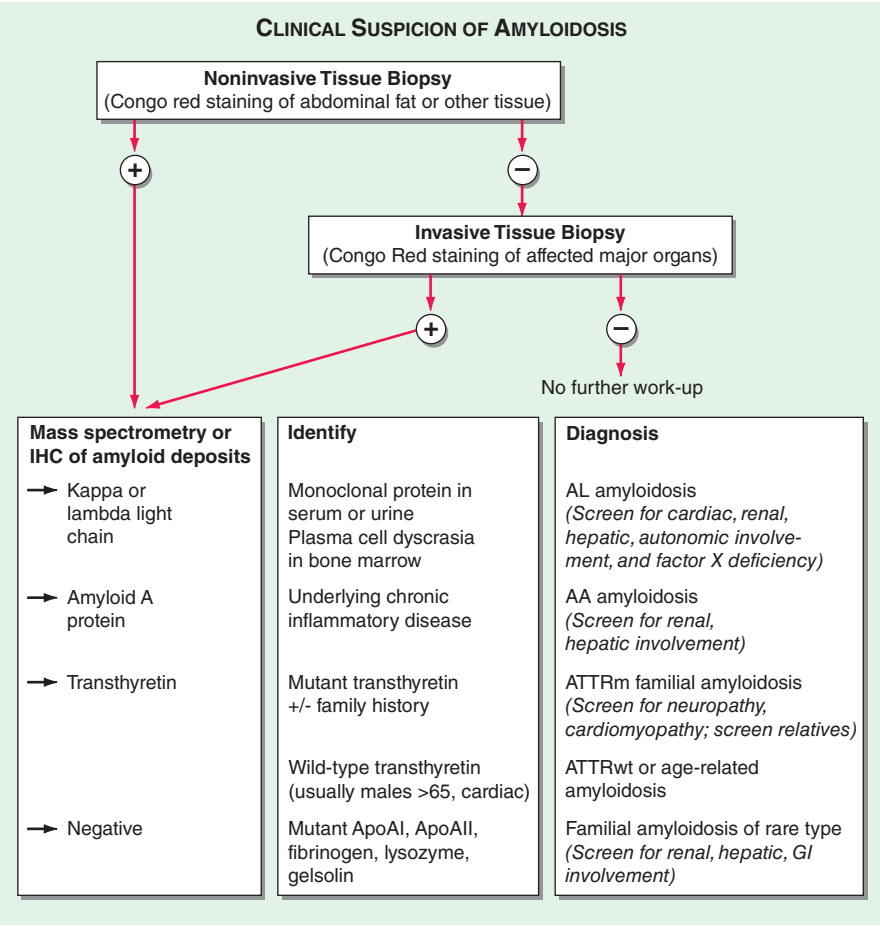

FIGURE 108-1 Algorithm for the diagnosis of amyloidosis and determination of type. Clinical suspicion: unexplained nephropathy, cardiomyopathy, neuropathy, enteropathy, arthropathy, and macroglossia. ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; GI, gastrointestinal.

hypoalbuminemia that may be severe; patients with serum albumin levels <2 g/dL generally have pedal edema or anasarca. Amyloid cardiomyopathy is characterized by concentric ventricular hypertrophy and diastolic dysfunction associated with elevation of brain natriuretic peptide or N-terminal pro–brain natriuretic peptide as well as troponin. These cardiac biomarkers can be used for disease staging, prognostication, and disease activity monitoring in patients with AL amyloidosis. Notably, renal insufficiency can falsely elevate levels of these biomarkers. Recently, biomarkers of cardiac remodeling—that is, matrix metalloproteinases and tissue inhibitors of metalloproteinases—have been found to be altered in the serum of patients with amyloid cardiomyopathy. Electrocardiographic and echocardiographic features of amyloid cardiomyopathy are described below. Patients with liver involvement, even when advanced, usually develop cholestasis with an elevated alkaline phosphatase concentration with minimal alteration of the aminotransferases and preservation of synthetic function. In AL amyloidosis, endocrine organs may be infiltrated with fibrils, and hypothyroidism, hypoadrenalism, or even hypopituitarism can occur. Although none of these findings is specific for amyloidosis, the presence of abnormalities in multiple organ systems should raise suspicion regarding this diagnosis.

AL AMYLOIDOSIS

Etiology and Incidence AL amyloidosis is most frequently caused by a clonal expansion of bone-marrow plasma cells that secrete a monoclonal immunoglobulin LC depositing as amyloid fibrils in tissues. Whether the clonal plasma cells produce a LC that misfolds and leads to AL amyloidosis or an LC that folds properly, allowing the cells to inexorably expand over time and develop into multiple myeloma (Chap. 107), may depend upon primary sequence of the clonal LC or other genetic or epigenetic factors. AL amyloidosis can occur with multiple myeloma or other B lymphoproliferative diseases, including non-Hodgkin's lymphoma (Chap. 104) and Waldenström's macroglobulinemia (Chap. 107). AL amyloidosis is the most common type of systemic amyloidosis diagnosed in North America. Its incidence has been estimated at 4.5 cases/100,000 population; however, ascertainment continues to be inadequate, and the true incidence may be much higher. AL amyloidosis, like other plasma cell diseases, usually occurs after age 40 and is often rapidly progressive and fatal if untreated.

Pathology and Clinical Features Amyloid deposits are usually widespread in AL amyloidosis and can be present in the interstitium of any organ outside the central nervous system. The amyloid fibril deposits are composed of full-length 23-kDa monoclonal immunoglobulin LCs as well as fragments. Accessory molecules co-deposited with LC fibrils (as well as with other amyloid fibrils) include serum amyloid P component, apolipoproteins e and AIV, glycosaminoglycans, and metal ions. Although all kappa and lambda LC subtypes have been identified in AL amyloid fibrils, lambda subtypes predominate. The lambda 6 subtype appears to have unique structural properties that predispose it to fibril formation, often in the kidney.

AL amyloidosis is often a rapidly progressive disease that presents as a pleiotropic set of clinical syndromes, recognition of which is key for initiation of the appropriate workup. Nonspecific symptoms of fatigue and weight loss are common; however, the diagnosis is rarely considered until symptoms referable to a specific organ develop. The kidneys are the most frequently involved organ and are affected in 70–80% of patients. Renal amyloidosis usually manifests as proteinuria, often in the nephrotic range and associated with hypoalbuminemia, secondary hypercholesterolemia and hypertriglyceridemia, and edema or anasarca. In some patients, interstitial rather than glomerular amyloid deposition can produce azotemia without proteinuria. The heart is the second most commonly affected organ (50–60% of patients), and cardiac involvement is the leading cause of death from AL amyloidosis. Early on, the electrocardiogram may show low voltage in the limb leads with a pseudo-infarct pattern. Echocardiographic features of disease include concentrically thickened ventricles and diastolic dysfunction with an abnormal global longitudinal strain pattern; a "sparkly" appearance has been described but is often not seen with modern high-resolution echocardiographic techniques. Poor atrial contractility occurs even in sinus rhythm, and patients with cardiac amyloidosis are at risk for development of atrial thrombi and stroke. Cardiac MRI can show increased wall thickness, and characteristic delayed enhancement of the subendocardium has been described following injection of gadolinium contrast. Nervous system symptoms include peripheral sensorimotor neuropathy and/or autonomic dysfunction manifesting as gastrointestinal motility disturbances (early satiety, diarrhea, constipation), dry eyes and mouth, impotence, orthostatic hypotension, and/or neurogenic bladder. Macroglossia (Fig. 108-2*A*), a pathognomonic sign of AL amyloidosis, is seen in only ~10% of patients. Liver involvement causes cholestasis and hepatomegaly. The spleen is frequently involved, and there may be functional hyposplenism in the absence of significant splenomegaly. Many patients experience "easy bruising" due to amyloid deposits in capillaries or deficiency of clotting factor X due to binding to amyloid fibrils; cutaneous ecchymoses appear, particularly around the eyes,

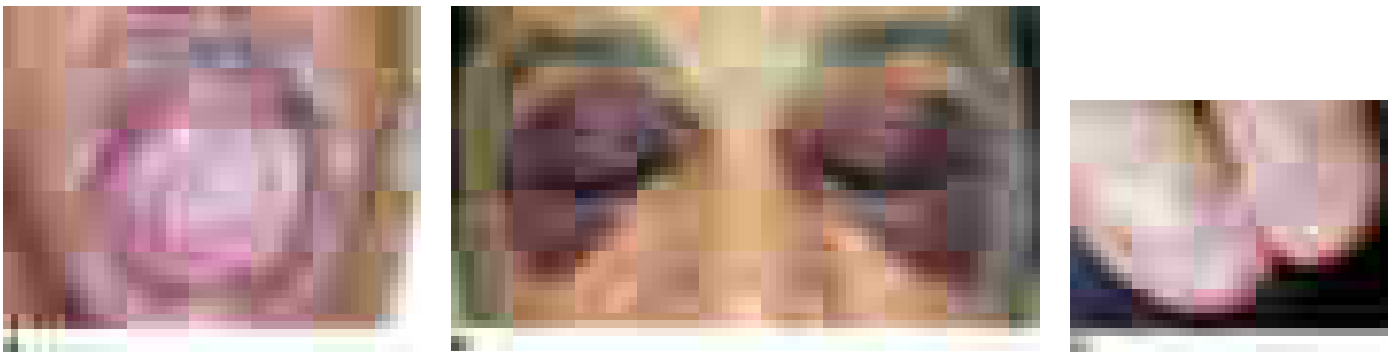

FIGURE 108-2 Clinical signs of AL amyloidosis. *A.* Macroglossia. ***B.*** Periorbital ecchymoses. ***C.*** Fingernail dystrophy.

producing another uncommon but pathognomonic finding, the "raccoon-eye" sign (Fig. 108-2*B*). Other findings include nail dystrophy (Fig. 108-2*C*), alopecia, and amyloid arthropathy with thickening of synovial membranes in the wrists and shoulders. The presence of a multisystemic illness or general fatigue along with any of these clinical syndromes should prompt a workup for amyloidosis.

Diagnosis Identification of an underlying clonal plasma cell or B lymphoproliferative process and a clonal LC are key to the diagnosis of AL amyloidosis. Serum protein electrophoresis and urine protein electrophoresis, although of value in multiple myeloma, are *not* useful screening tests if AL amyloidosis is suspected because the clonal LC or whole immunoglobulin often is not present in sufficient amounts to produce a monoclonal "M-spike" in the serum or LC (Bence Jones) protein in the urine. However, more than 90% of patients with AL amyloidosis have serum or urine monoclonal LC or whole immunoglobulin detectable by immunofixation electrophoresis of serum (SIFE) or urine (UIFE) (Fig. 108-3*A*) or by

A

B

FIGURE 108-3 Laboratory features of AL amyloidosis. *A.* Serum immunofixation electrophoresis reveals an IgGκ monoclonal protein in this example; serum protein electrophoresis is often normal. ***B.*** Bone-marrow biopsy sections stained by immunohistochemistry with antibody to CD138 (syndecan, highly expressed on plasma cells) (*left*) or by in situ hybridization with fluorescein-tagged probes (Ventana Medical Systems) binding to κ mRNA (*center*) and λ mRNA (*right*) in plasma cells. *(Photomicrograph courtesy of C. O'Hara; with permission.)*

nephelometric measurement of serum "free" LCs (i.e., LCs circulating in monomeric form rather than in an immunoglobulin tetramer with heavy chain). Examining the ratio as well as the absolute amount of serum-free LCs is essential, as renal insufficiency reduces LC clearance, nonspecifically elevating both isotypes. In addition, an increased percentage of plasma cells in the bone marrow—typically 5–30% of nucleated cells—is found in ~90% of patients. Kappa or lambda clonality should be demonstrated by flow cytometry, immunohistochemistry, or in situ hybridization for LC mRNA **(Fig. 108-3*B*)**.

A monoclonal serum protein by itself is not diagnostic of amyloidosis, since monoclonal gammopathy of uncertain significance is common in older patients **(Chap. 107)**. However, when monoclonal gammopathy of uncertain significance is found in patients with biopsy-proven amyloidosis, the AL type should be ruled out. Similarly, patients thought to have "smoldering myeloma" because of a modest elevation of bone-marrow plasma cells should be screened for AL amyloidosis if they have signs or symptoms of renal, cardiac, or neurologic disease. Accurate tissue amyloid typing is essential for appropriate treatment. Immunohistochemical staining of the amyloid deposits is useful if they selectively bind one LC antibody in preference to the other; some AL deposits bind antibodies nonspecifically. Immunoelectron microscopy is more reliable, while mass spectrometry–based microsequencing of small amounts of protein extracted from fibril deposits has become the diagnostic standard. In ambiguous cases, other forms of amyloidosis should be thoroughly excluded with appropriate genetic and other testing.

TREATMENT

AL Amyloidosis

Extensive multisystemic involvement typifies AL amyloidosis, and the median survival period without treatment is usually only ~1–2 years from the time of diagnosis. Current therapies target the clonal bone-marrow plasma cells, using approaches employed for multiple myeloma. Treatment with oral melphalan and prednisone can decrease the plasma cell burden but rarely leads to complete hematologic remission, meaningful organ responses, or improved survival and is no longer widely used. The substitution of dexamethasone for prednisone produces a higher response rate and more durable remissions, although dexamethasone is not always well tolerated by patients with significant edema or cardiac disease. High-dose IV melphalan followed by autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses in ~40% of treated patients, as determined by loss of clonal plasma cells in the bone marrow and disappearance of the amyloidogenic monoclonal LC, as determined by SIFE/UIFE and free LC quantitation. Six to 12 months after achieving a hematologic responses, improvements in organ function and quality of life may occur. Hematologic responses appear to be more durable after HDM/SCT than in multiple myeloma, with remissions continuing in some patients beyond 15 years without additional treatment. Unfortunately, only about 30–40% of all AL amyloidosis patients are suitable for aggressive treatment, and, even at specialized treatment centers, transplantation-related mortality rates are higher than those for other hematologic diseases because of impaired organ function at initial presentation. Amyloid cardiomyopathy, poor nutritional and performance status, and multiorgan disease contribute to excess morbidity and mortality. A bleeding diathesis resulting from adsorption of clotting factor X to amyloid fibrils also increases mortality rates; however, this syndrome occurs in only 5–10% of patients. A randomized multicenter trial conducted in France compared oral melphalan and dexamethasone with HDM/SCT and failed to show a benefit of dose-intensive treatment, although the transplantation-related mortality rate in this study was very high. It has become clear that careful selection of patients and expert peritransplantation management are essential in reducing transplantation-related mortality.

For patients with AL amyloidosis and impaired cardiac function or arrhythmias due to involvement of the myocardium, the median survival period is only ~6 months without treatment. In these patients, cardiac transplantation can be performed and followed by HDM/SCT to eliminate the noxious LC clone and prevent amyloid deposition in the transplanted heart or other organs.

Novel anti–plasma cell agents have been investigated for treatment of plasma cell diseases. The immunomodulators thalidomide, lenalidomide, and pomalidomide display activity; dosing may need to be adjusted compared to their usage for myeloma. The proteasome inhibitor bortezomib has also been found to be effective in single-center and multicenter trials. Anti-fibril small molecules and humanized monoclonal antibodies are also being tested. Clinical trials are essential in improving therapy for this rare disease.

Supportive care is important for patients with any type of amyloidosis. For nephrotic syndrome, diuretics and supportive stockings can ameliorate edema; angiotensin-converting enzyme inhibitors should be used with caution and have not been shown to slow renal disease progression. Effective diuresis can be facilitated with albumin infusions to raise intravascular oncotic pressure. Congestive heart failure due to amyloid cardiomyopathy is best treated with diuretics; it is important to note that digitalis, calcium channel blockers, and beta blockers are relatively contraindicated as they can interact with amyloid fibrils and produce heart block and worsening heart failure. Amiodarone has been used for atrial and ventricular arrhythmias. Automatic implantable defibrillators appear to have reduced effectiveness due to the thickened myocardium, but they may benefit some patients. Atrial ablation is an effective approach for atrial fibrillation. For conduction abnormalities, ventricular pacing may be indicated. Atrial contractile dysfunction is common in amyloid cardiomyopathy and associated with increased thromboembolic complications, prompting considerations of anticoagulation even in the absence of atrial fibrillation. Autonomic neuropathy can be treated with α agonists such as midodrine to support postural blood pressure; gastrointestinal dysfunction may respond to motility or bulk agents. Nutritional supplementation, either oral or parenteral, is also important.

In localized AL amyloidosis, amyloid deposits can be produced by clonal plasma cells infiltrating local sites in the airways, bladder, skin, or lymph nodes (Table 108-1). These deposits may respond to surgical intervention or elimination of the responsible plasma cell clone by low-dose radiation therapy (typically only 20 Gy); systemic treatment generally is not appropriate. Patients should be referred to a center familiar with management of these rare manifestations of amyloidosis.

AA AMYLOIDOSIS

Etiology and Incidence AA amyloidosis can occur in association with almost any chronic inflammatory state (e.g., rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever **[Chap. 362]**, or other periodic fever syndromes) or chronic infections such as tuberculosis or subacute bacterial endocarditis. In the United States and Europe, AA amyloidosis has become less common, occurring in fewer than 2% of patients with these diseases, presumably because of advances in anti-inflammatory and antimicrobial therapies. It has also been described in association with Castleman's disease, lymphomas, renal cell carcinoma, emphasizing the diagnostic importance of CT scanning to look for such tumors as well as serologic and microbiologic studies. In up to 30% of patients, AA amyloidosis can also be seen without any identifiable underlying disease. AA is the most frequent systemic amyloidosis that occurs in children.

Pathology and Clinical Features Organ involvement in AA amyloidosis usually begins in the kidneys. Hepatomegaly, splenomegaly, and autonomic neuropathy can also occur as the disease

progresses; cardiomyopathy occurs in later disease. The symptoms and signs of AA disease cannot be reliably distinguished from those of AL amyloidosis. AA amyloid fibrils are usually composed of an 8-kDa, 76-amino-acid *N*-terminal portion of the 12-kDa precursor protein SAA. This acute-phase apoprotein is synthesized in the liver and transported by high-density lipoprotein (HDL3) in the plasma. Several years of an underlying inflammatory disease causing chronic elevation of SAA levels usually precede fibril formation, although infections can lead to AA deposition more rapidly.

TREATMENT

AA Amyloidosis

Primary therapy for AA amyloidosis consists of treatment of the underlying inflammatory or infectious disease. Treatment that suppresses or eliminates the inflammatory state or infection decreases the SAA concentration and rate of amyloid fibril formation. For familial Mediterranean fever, colchicine at a dose of 1.2–1.8 mg/d is the standard treatment. However, colchicine has not been helpful for AA amyloidosis of other causes or for other amyloidoses. Tumor necrosis factor and interleukin 1 antagonists can be effective in syndromes related to cytokine elevation. Efforts to develop a fibril-specific agent (eprodisate) that interferes with the interaction of serum amyloid A protein and glycosaminoglycans to prevent or disrupt fibril formation failed in phase III trials.

ATTR AND AF AMYLOIDOSIS

The familial amyloidoses are autosomal dominant diseases in which, beginning in midlife, a variant (FINE) plasma protein forms amyloid deposits. These diseases are rare, with an estimated incidence of <1 case/100,000 population in the United States, although founder effects in isolated areas of Portugal, Sweden, and Japan have led to a much higher incidence. The most common form of AF amyloidosis is ATTRm in the updated nomenclature, caused by mutation of the abundant plasma protein transthyretin (TTR, also known as *prealbumin*). More than 120 TTR mutations are known, and most are associated with ATTR amyloidosis. One variant, V122I, has a carrier frequency of nearly 4% in the African-American population and is associated with late-onset cardiac amyloidosis. The actual incidence and penetrance of disease in the African-American population is the subject of ongoing research, but ATTR amyloidosis warrants consideration in the differential diagnosis of African-American patients who present with concentric cardiac hypertrophy and evidence of diastolic heart failure, particularly in the absence of a history of hypertension. Other familial amyloidoses, caused by variant apolipoproteins AI or AII, gelsolin, fibrinogen Aα, or lysozyme, are reported in only a few families worldwide. New amyloidogenic serum proteins continue to be identified periodically, including recently the leukocyte chemotactic factor LECT2, a cause of renal amyloidosis in Hispanic and Pakistani populations. To date, no mutation in the coding sequence for the LECT2 gene has been identified, so the heritability of ALECT2 remains uncertain.

Amyloid deposits composed of unmutated precursor protein (wild type TTR) occur with aging. Due to a rapidly aging world population, wild-type ATTR (ATTRwt) is being diagnosed with increasing frequency in Caucasian men >65 years of age with amyloid cardiomyopathy. Formerly termed senile systemic amyloidosis, ATTRwt has been found at autopsy in 25% of hearts from men older than age 80 years. Why a wild type protein becomes amyloidogenic, and why patients bearing mutant TTR genes do not express disease until adulthood, remains a mystery.

Clinical Features and Diagnosis AF amyloidosis has a presentation that is variable but is usually consistent within kindreds affected by the same mutant protein. A family history makes AF disease more likely, but many patients present with previously unrecognized familial disease or sporadically with new mutations. ATTRm amyloidosis typically presents as a syndrome of familial amyloidotic polyneuropathy or familial amyloidotic cardiomyopathy. Peripheral neuropathy begins as a small-fiber length-dependent lower-extremity sensorimotor neuropathy and progresses to the upper extremities. Autonomic neuropathy manifests as diarrhea with weight loss and orthostatic hypotension. Patients with ATTR V30M, the most common mutation, often develop conduction defects late in the disease. Patients with ATTR T60A and several other mutations have myocardial thickening similar to that caused by AL amyloidosis, although heart failure is less common and long-term untreated survival rates are usually better. Vitreous opacities caused by amyloid deposits are pathognomonic for ATTR amyloidosis.

Typical syndromes associated with other forms of AF disease include renal amyloidosis with mutant fibrinogen, lysozyme, or apolipoproteins; hepatic amyloidosis with apolipoprotein AI; and amyloidosis of cranial nerves and cornea with gelsolin. Patients with AF amyloidosis can present with clinical syndromes that mimic those of patients with AL disease. Rarely, AF carriers can develop AL disease or AF patients may have monoclonal gammopathy without AL. Thus, it is important to screen both for plasma cell disorders and for mutations in patients with amyloidosis. Variant TTRs can usually be detected by isoelectric focusing, but DNA sequencing is now standard for diagnosis of ATTRm and other AF mutations.

TREATMENT

ATTR Amyloidosis

Without intervention, the survival period after onset of ATTR disease is 5–15 years. Orthotopic liver transplantation replaces the major source of variant TTR production with one producing normal TTR. While liver transplantation can slow disease progression and improve chances of survival, it does not reverse sensorimotor neuropathy. Liver transplants are most successful in young patients with early peripheral neuropathy; older patients with familial amyloidotic cardiomyopathy or advanced polyneuropathy often experience end-organ disease progression despite successful liver transplantation. Post-transplant ATTR disease progression results from deposition of wild-type TTR onto pre-existing fibrillar deposits principally composed of mutant TTR.

The rate-limiting step in ATTR amyloidosis is dissociation of the TTR tetramer into monomeric protein followed by misfolding, oligomerization, and fibril aggregation. TTR tetramers can be stabilized by thyroxine binding or by thyroxine-mimetic small molecules such as the non-steroidal anti-inflammatory drug diflunisal or the rationally designed small-molecule therapeutic tafamidis. A placebo-controlled randomized trial of diflunisal demonstrated a significant reduction in the progression of polyneuropathy and maintenance of quality of life in patients with a wide variety of ATTR mutations who received the "repurposed" diflunisal. Tafamidis tested in a similar fashion in patients with the V30M ATTR mutation failed to meet its primary endpoints but was approved for marketing by the European Medicines Agency since most secondary endpoints favored the drug. These agents are now being investigated for effects on ATTR cardiomyopathy. In vitro data and serendipitous observations in patients suggest that ATTRm disease can be ameliorated by "transsuppression," in which a T119M TTR variant stabilizes tetramers that also contain amyloidogenic subunits. Interestingly, in a large population study in Denmark, 0.5% of participants were heterozygous for the T119M allele, and this small group had higher levels of TTR in their blood, a reduced incidence of cerebrovascular disease, and a 5- to 10-year survival advantage compared with participants lacking this allele. The newest approach to controlling ATTR disease, TTR gene silencing, involves nearly complete suppression of TTR production by the liver, effectively preventing amyloid fibril formation by eliminating the precursor protein. TTR gene silencers including RNA interference and anti-sense oligonucleotide agents directed against TTR RNA are in phase III clinical trials to determine their effect on progression of ATTR polyneuropathy and cardiomyopathy.

Aβ$_2$M AMYLOIDOSIS

Aβ$_2$M amyloid is composed of β$_2$-microglobulin, the invariant chain of class I human leukocyte antigens, and produces rheumatologic manifestations in patients undergoing long-term hemodialysis. β$_2$-Microglobulin is excreted by the kidney, and levels become elevated in end-stage renal disease. The molecular mass of β$_2$M is 11.8 kDa—above the cutoff of some dialysis membranes. The incidence of this disease appears to be declining with the use of newer membranes in high-flow dialysis techniques. Aβ$_2$M amyloidosis usually presents as carpal tunnel syndrome, persistent joint effusions, spondyloarthropathy, or cystic bone lesions. Carpal tunnel syndrome is often the first symptom. In the past, persistent joint effusions accompanied by mild discomfort were found in up to 50% of patients who had undergone dialysis for >12 years. Involvement is bilateral, and large joints (shoulders, knees, wrists, and hips) are most frequently affected. The synovial fluid is noninflammatory, and β$_2$M amyloid can be found if the sediment is stained with Congo red. Although less common, visceral β$_2$M amyloid deposits do occasionally occur in the gastrointestinal tract, heart, tendons, and subcutaneous tissues of the buttocks. There is no specific therapy for Aβ$_2$M amyloidosis, but cessation of dialysis after renal allografting may lead to symptomatic improvement.

THERAPEUTIC FRONTIERS

To date, treatment strategies have focused on limiting formation of amyloidogenic proteins. Disruption of existing amyloid by targeting ubiquitous components of the tissue deposits may offer means to improving major end organ function. Two antibody approaches—one involving an epitope exposed during immunoglobulin light chain misfolding (AL disease) and the other directed against serum amyloid P component—are undergoing evaluation in early phase III studies.

SUMMARY

A diagnosis of amyloidosis should be considered in patients with unexplained nephropathy, cardiomyopathy (particularly with diastolic dysfunction), neuropathy (either peripheral or autonomic), enteropathy, or the pathognomonic soft tissue findings of macroglossia or periorbital ecchymoses. Pathologic identification of amyloid fibrils can be made with Congo red staining of aspirated abdominal fat or of an involved-organ biopsy specimen. Accurate typing by a combination of immunologic, biochemical, and genetic testing is essential in selecting appropriate therapy (Fig. 108-1). Systemic amyloidosis should not be considered an untreatable condition, as anti–plasma cell chemotherapy is highly effective in AL disease and targeted therapies are being developed for AA and ATTR disease. The combination of precursor and end organ amyloid therapeutics may permit not only disease control but also functional improvement to patients with amyloidosis. Tertiary referral centers can provide specialized diagnostic techniques and access to clinical trials for patients with these rare diseases.

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109 Transfusion Biology and Therapy

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BLOOD GROUP ANTIGENS AND ANTIBODIES

Antigens systems important in transfusion medicine comprise red blood cell (RBC), platelet, neutrophil, and the widely distributed human leukocytes (HLA) antigens.

The study of RBC antigens and antibodies forms the foundation of transfusion medicine. Serologic studies initially characterized these antigens, but now the molecular composition and structure of many are known. Antigens, either carbohydrate or protein, are assigned to a blood group system based on the structure and similarity of the determinant epitopes. Other cellular blood elements such as platelets and plasma proteins are also antigenic and can result in alloimmunization, the production of antibodies directed against antigenic determinants of another individual. These antibodies, called alloantibodies, can comprise anti-RBC Abs, anti-human platelet antigens (HPA) Abs, as well as anti-human leukocytes antigens (HLA) Ab.

Antibodies directed against RBC antigens may result from "natural" exposure, particularly to carbohydrates that mimic some blood group antigens that are present in the environment, particularly saprophyte bacteria. Those antibodies that occur via natural stimuli are usually produced by a T cell–independent response (thus, generating no immune memory) and are mainly IgM isotype. *Autoantibodies* (antibodies against autologous blood group antigens) arise spontaneously or as the result of infectious sequelae (e.g., from *Mycoplasma pneumoniae*) and are also often IgM. These antibodies are often clinically insignificant due to their low affinity for antigen at body temperature. However, IgM antibodies can activate the complement cascade and result in hemolysis. Autoantibodies can also arise in an autoimmune setting with most often an IgG isotype. Antibodies that result from allogeneic exposure, such as transfusion or pregnancy, are usually IgG. IgG antibodies commonly bind to antigen at warmer temperatures and may hemolyze RBCs. Unlike IgM antibodies, IgG antibodies can cross the placenta and bind fetal erythrocytes bearing the corresponding antigen, resulting in hemolytic disease of the newborn, or *hydrops fetalis*. The same holds true for IgG directed against HPA antigens on platelets that can lead to fetal or neonatal immunization and result in intracranial hemorrhage.

Recipient alloimmunization to leukocytes, platelets, and plasma proteins may also result in transfusion complications such as fevers and urticaria as well as platelet transfusion refractoriness, but generally does not cause hemolysis. Such an alloimmunization in the blood donor may also result in a severe lung disorder called transfusion-related acute lung injury (TRALI). Assay for these non-hemolytic alloantibodies is not routinely performed; however, they may be detected using special assays.

ABO ANTIGENS AND ANTIBODIES

The first blood group antigen system, recognized in 1900, was ABO, the most important in transfusion medicine. The major blood groups of this system are A, B, AB, and O. O type RBCs lack A or B antigens. These antigens are carbohydrates attached to a precursor backbone, may be found on the cellular membrane either as glycosphingolipids or glycoproteins, and are secreted into plasma and body fluids as glycoproteins. H substance is the immediate precursor on which the A and B antigens are added. This H substance is formed by the addition of fucose to the glycolipid or glycoprotein backbone. The subsequent addition of *N*-acetylgalactosamine creates the A antigen, while the addition of galactose produces the B antigen.

The genes that determine the A and B phenotypes are found on chromosome 9p and are expressed in a Mendelian codominant manner. The gene products are glycosyl transferases, which confer the enzymatic

capability of attaching the specific antigenic carbohydrate. Individuals who lack the "A" and "B" transferases are phenotypically type "O," while those who inherit both transferases are type "AB." Rare individuals lack the H gene, which codes for fucose transferase, and cannot form H substance. These individuals are homozygous for the silent h allele (hh) and have Bombay phenotype (O_h).

The ABO blood group system is important because essentially all individuals produce antibodies to the ABH carbohydrate antigen that they lack. The "naturally" occurring anti-A and anti-B antibodies are termed *isoagglutinins*. Thus, type A individuals produce anti-B, while type B individuals make anti-A. Neither isoagglutinin is found in type AB individuals, while type O individuals produce both anti-A and anti-B. Thus, persons with type AB are considered "universal recipients" with regard to RBC transfusion because they do not have antibodies against any ABO phenotype, while persons with type O blood can donate to essentially all recipients because their cells are not recognized by any ABO isoagglutinins. The rare individuals with Bombay phenotype produce antibodies to H substance (which is present on all red cells except those of *hh* phenotype) as well as to both A and B antigens and are therefore compatible only with other *hh* donors.

In most people (80%), A, B, and H antigens are secreted by the cells and are present in the circulation as well as in various secretions such as saliva (*Se* phenotype). Others, called "nonsecretors" do not secrete A, B, and H antigens (*se* phenotype). ABO and Se/se systems influence the susceptibility to a variety of diseases. For example, malaria is less severe in O than non O patients. Conversely, group O is associated with enhanced susceptibility to *Helicobacter pylori* (and gastric ulcer) as well as to cholera bacillus or to norovirus. Furthermore, group O individuals exhibit a lesser procoagulation phenotype when compared to non O individuals.

RH SYSTEM

The Rh system is the second most important blood group system in pretransfusion testing. The Rh antigens are found on a 30- to 32-kDa RBC membrane protein that has no defined function. Although >40 different antigens in the Rh system have been described, five determinants account for the vast majority of phenotypes. The two RH genes are located on chromosome 1. The RHD gene codes for the RhD protein. The RHCE gene codes for RhCE proteins expressing C and/or c, and E and/or e antigens. The presence of the D antigen confers Rh "positivity," while persons who lack the D antigen are Rh negative. Two allelic antigen pairs, E/e and C/c, are also found on the Rh protein. These two Rh genes, RHD and RHCE, determine eight main haplotypes (DCe, DcE, Dce, DCE, dce, dCe, dcE, and dCE) whose frequencies differ among different populations. The high diversity of the RH antigens includes weak or partial expression. Identifying individuals (especially young female of childbearing potential and multi-transfused patients) with a weak or RhD antigen is important to adequately select RhD positive or negative RBC. Molecular biology is now routinely applied to resolve such situations.

The D antigen is a potent alloantigen. About 15% of individuals lack this antigen. Exposure of these Rh-negative people to even small amounts of Rh-positive cells, by either transfusion or pregnancy, can result in the production of anti-D alloantibody.

OTHER BLOOD GROUP SYSTEMS AND ALLOANTIBODIES

Thirty-six RBC group systems, six collections (related set of antigens not sufficiently distinct from existing systems to qualify as systems) and two series (low frequency ["private"] and high frequency ["public"] individual antigens) are presently recognized, composed of more than 350 antigens. The presence or absence of certain antigens has been associated with various diseases and anomalies; antigens also act as receptors for infectious agents. Alloantibodies of importance in routine clinical practice are listed in **Table 109-1**.

Antibodies to *Lewis system* carbohydrate antigens are the most common cause of incompatibility during pretransfusion screening. The Lewis gene product is a fucosyl transferase and maps to chromosome 19. The antigen is not an integral membrane structure but is adsorbed to the RBC membrane from the plasma. Antibodies to Lewis antigens are usually IgM and cannot cross the placenta. Lewis antigens may be adsorbed onto tumor cells and may be targets of therapy.

TABLE 109-1 RBC Blood Group Systems and Alloantigens

BLOOD GROUP SYSTEM	ANTIGEN	ALLOANTIBODY	CLINICAL SIGNIFICANCE
Rh (D, C/c, E/e)	RBC protein	IgG	HTR, HDN
Lewis (Le^a, Le^b)	Oligosaccharide	IgM/IgG	Rare HTR
Kell (K/k)	RBC protein	IgG	HTR, HDN
Duffy (Fy^a/Fy^b)	RBC protein	IgG	HTR, HDN
Kidd (Jk^a/Jk^b)	RBC protein	IgG	HTR (often delayed), HDN (mild)
I	Carbohydrate	IgM	None
MNS	RBC protein	IgM/IgG	Anti-M rare HDN, anti-S, -s, and -U HDN, HTR

Abbreviations: HDN, hemolytic disease of the newborn; HTR, hemolytic transfusion reaction; RBC, red blood cell.

I system antigens are also oligosaccharides related to H, A, B, and Le. I and i are not allelic pairs but are carbohydrate antigens that differ only in the extent of branching. The i antigen is an unbranched chain that is converted by the I gene product, a glycosyltransferase, into a branched chain. The branching process affects all the ABH antigens, which become progressively more branched in the first 2 years of life. Some patients with cold agglutinin disease or lymphomas can produce anti-I autoantibodies that cause RBC destruction. Occasional patients with mononucleosis or *Mycoplasma* pneumonia may develop cold agglutinins of either anti-I or anti-i specificity. Most adults lack i expression; thus, finding a donor for patients with anti-i is not difficult. Even though most adults express I antigen, binding is generally low at body temperature. Thus, administration of warm blood prevents isoagglutination.

The *P system* is another group of carbohydrate antigens controlled by specific glycosyltransferases. The very rare individuals lacking the P antigen produce an anti-P antibody. Finding a compatible donor for such individuals is difficult. P antigen is also the target of auto-antibodies in diseases such as syphilis and viral diseases in children, and can result in paroxysmal cold hemoglobinuria. In the latter case, an autoantibody to P binds to RBCs in the cold and fixes complement upon warming. Antibodies with these biphasic properties are called *Donath-Landsteiner antibodies*. The P antigen is the cellular receptor of parvovirus B19 and also may be a receptor for *Escherichia coli* binding to urothelial cells.

The *MNS system* is regulated by genes on chromosome 4. M and N are determinants on glycophorin A, an RBC membrane protein, and S and s are determinants on glycophorin B. Anti-S and anti-s IgG antibodies may develop after pregnancy or transfusion and lead to hemolysis. Glycophorin B expresses a public antigen named U. Anti-U antibodies can occur in the rare individuals lacking the U antigen. Such occurrence is problematic; virtually every donor is incompatible because nearly all persons express U.

The *Kell* protein is very large (720 amino acids), and its secondary structure contains many different antigenic epitopes. The immunogenicity of Kell is third behind the ABO and Rh systems. The Kell protein is linked to another blood group protein termed Kx. The rare absence of this protein (controlled by a gene on X) is associated with weak KEL antigen, acanthocytosis, shortened RBC survival, and a progressive form of muscular dystrophy that includes cardiac defects. This rare condition is called the *McLeod phenotype*. The K_x gene is linked to the 91-kDa component of the NADPH-oxidase on the X chromosome, deletion or mutation of which accounts for about 60% of cases of chronic granulomatous disease. Such individuals can produce an anti-Kx antibody that makes finding a compatible blood product difficult.

The *Duffy* antigens are codominant alleles, Fy^a and Fy^b, that also serve as receptors for *Plasmodium vivax*. More than 70% of persons in sub-Saharan Africa lack these antigens, probably from selective

influences of malaria infection on the population. For unknown reasons, the lack of the Duffy antigen receptor for cytokines (DARC) is associated with mild neutropenia.

The *Kidd* antigens, Jk^a and Jk^b, may elicit antibodies transiently. A delayed hemolytic transfusion reaction (DHTR) that occurs with blood tested as compatible is often related to delayed appearance of anti-Jk^a.

PRETRANSFUSION TESTING

Pretransfusion testing of a potential recipient consists of the "type and screen." The "forward type" determines the ABO and Rh phenotype of the recipient's RBC by using antisera directed against the A, B, and D antigens. The "reverse type" detects isoagglutinins in the patient's serum and should correlate with the ABO phenotype, or forward type. Additional typing for other main Rh antigens (CcEe), the K antigen, and more rarely Duffy, Kidd and Ss antigens, can be required depending on the clinical setting. Molecular typing is increasingly used to predict the RBC phenotype and facilitate the selection of a compatible blood component.

The alloantibody screen identifies antibodies directed against other RBC antigens. The alloantibody screen is performed by mixing patient serum with type O RBCs that contain the major antigens of most blood group systems and whose extended phenotype is known. The specificity of the alloantibody is identified by correlating the presence or absence of antigen with the results of the agglutination. Special attention should be given to patients receiving monoclonal antibody treatment that may bind to RBC (such as anti-CD38 treatment for myeloma) and therefore interfere with alloantibody screening.

Cross-matching is ordered when there is a high probability that the patient will require a packed RBC (PRBC) transfusion. In the setting of a systematic alloantibody screen, such a crossmatch can be restricted to alloimmunized patients as well as patients at high risk of alloimmunization (prior pregnancies, transfusions). Blood selected for cross-matching must be ABO compatible and lack antigens for which the patient has alloantibodies. Nonreactive cross-matching confirms the absence of any major incompatibility and reserves that unit for the patient.

In the case of Rh (D) -negative patients, every attempt must be made to provide Rh-negative blood components to prevent alloimmunization to the D antigen. In an emergency, Rh-positive blood can be safely transfused to an Rh-negative patient who lacks anti-D; however, the recipient is likely to become alloimmunized and produce anti-D. Rh-negative women of childbearing age who are transfused with products containing Rh-positive RBCs should receive passive immunization with anti-D (RhoGam or WinRho) to reduce or prevent sensitization.

BLOOD COMPONENTS

Blood products intended for transfusion are routinely collected as whole blood (450 mL) in various anticoagulants. Most donated blood is processed into components: PRBCs, platelets, and fresh-frozen plasma (FFP) or cryoprecipitate **(Table 109-2)**. Whole blood can be first separated into PRBCs and platelet-rich plasma by slow centrifugation. The platelet-rich plasma is then centrifuged at high speed to yield one unit of random donor (RD) platelets (subsequently pooled) and one unit of FFP. Alternatively, whole blood can undergo high speed centrifugation to separate a PRBC, a FFP and a "buffy-coat" containing leukocytes and platelets. The buffy coat then undergoes pooling and is centrifuged at low speed to produce pooled platelets. The leukocyte level of blood products can be lowered by an additional filtration step after which they are referred to as leukoreduced (or leukodepleted) (<1 to 5×10^6 leukocytes per product). Cryoprecipitate is produced by thawing FFP to precipitate the plasma proteins, then separated by centrifugation.

Apheresis technology is used for the collection of multiple units of platelets from a single donor. These single-donor apheresis platelets (SDAP) contain the equivalent of at least five units of RD platelets and before eventual leukoreduced, have fewer contaminating leukocytes than pooled RD platelets.

Plasma as well as RBCs and granulocytes may also be collected by apheresis. Plasma-derived products such as albumin, intravenous immunoglobulin, antithrombin, and coagulation factor concentrates are prepared from pooled plasma from many donors. Plasma fractionation includes steps that eliminate infectious agents.

TABLE 109-2 Characteristics of Selected Blood Components

COMPONENT	VOLUME, mL	CONTENT	CLINICAL RESPONSE
PRBC	250–300 (including additive solution)	RBCs with variable leukocyte content and small amount of plasma	Increase hemoglobin 10 g/L and hematocrit 3%
Platelets (from whole blood)	50–70 /RD unit pool of 4 to 6 RD unit	5.5×10^{10}/RD unit	Increase platelet count 5000–10,000/μL/ RD unit
Platelets (from apheresis)	200–400	$\geq 2 \times 10^{11}$/SDAP product	For pooled RD and SDAP: CCI $\geq 10 \times 10^9$/L within 1 h and $\geq 7.5 \times 10^9$/L within 24 h posttransfusion
FFP	200–250	Plasma proteins—coagulation factors, proteins C and S, antithrombin	Increases coagulation factors about 2%
Cryoprecipitate (may be used as topical fibrin glue as well)	10–15 /unit, pool of 4 to 5 units	Cold-insoluble plasma proteins, fibrinogen, factor VIII, factor XIII, vWF fibronectin	Increased plasma fibrinogen 0,3-1 g/L, increased factor VIII

Abbreviations: CCI, corrected count increment; FFP, fresh-frozen plasma; PRBC, packed red blood cells; RBC, red blood cell; RD, random donor; SDAP, single-donor apheresis platelets; vWF, von Willebrand factor.

WHOLE BLOOD

Whole blood provides both oxygen-carrying capacity and volume expansion. It is the ideal component for patients who have sustained acute hemorrhage of ≥25% total blood volume loss. Whole blood is stored at 4°C to maintain erythrocyte viability, but platelet dysfunction and degradation of some coagulation factors occur. In addition, 2,3-bisphosphoglycerate levels fall over time, leading to an increase in the oxygen affinity of the hemoglobin and a decreased capacity to deliver oxygen to the tissues, a problem with all red cell storage. Fresh whole blood avoids these problems, but it is typically used only in emergency settings (i.e., military). Whole blood is not readily available, since it is routinely processed into components.

PACKED RBCS

This product increases oxygen-carrying capacity in the anemic patient. PRBC are stored in additive solution up to 35–42 days at 4°C. Adequate oxygenation can be maintained with a hemoglobin content of 70 g/L in the normovolemic patient without cardiac disease; however, comorbid factors may necessitate transfusion at a higher threshold. The decision to transfuse should be guided by the clinical situation and not by an arbitrary laboratory value. In the critical care setting, liberal use of transfusions to maintain near-normal levels of hemoglobin has not proven advantageous. In most patients requiring transfusion, levels of hemoglobin of 80 g/L are sufficient to keep oxygen supply from being critically low.

PRBCs may be modified to prevent certain adverse reactions. The majority of cellular blood products are now leukocyte-reduced and universal prestorage leukocyte reduction has been recommended. Prestorage filtration appears superior to bedside filtration as smaller amounts of cytokines are generated in the stored product. These PRBC units contain <1 to 5.10^6 donor leukocytes, and their use lowers the incidence of posttransfusion fever and chills, cytomegalovirus (CMV) infections, and alloimmunization. Other theoretical benefits include less immunosuppression in the recipient and lower risk of infections with intracellular pathogens (in addition to CMV). Plasma, which may cause allergic reactions, can be removed from cellular blood components by washing. Patients with hemoglobinopathies such as sickle cell disease may undergo RBC exchange, an apheresis procedure by which sickled RBCs are replaced by donor RBCs.

PLATELETS

Thrombocytopenia is a risk factor for hemorrhage, and platelet transfusion reduces the incidence of bleeding. Platelets are stored in plasma or in additive solution up to 5–7 days at 20–24°C and under permanent motion. The threshold for prophylactic platelet transfusion is 10,000/μL. In patients without fever or infections, a threshold of 5000/μL may be sufficient to prevent spontaneous hemorrhage. For invasive procedures, 50,000/μL platelets is the usual target level.

Platelets are given either as pools of 4 to 6 prepared RDs or as SDAPs from a single donor. In an unsensitized patient without increased platelet consumption (splenomegaly, fever, disseminated intravascular coagulation [DIC]), two units of transfused RD per square-meter body surface area (BSA) is anticipated to increase the platelet count by ~10,000/uL. Patients who have received multiple transfusions may be alloimmunized to many HLA- and platelet-specific antigens and have little or no increase in their posttransfusion platelet counts. Patients who may require multiple transfusions are best served by receiving leukocyte-reduced components to lower the risk of alloimmunization.

Refractoriness to platelet transfusion may be evaluated using the corrected count increment (CCI):

$$\text{CCI} = \frac{\text{posttransfusion count}\,(/\mu\text{L}) - \text{pretransfusion count}\,(/\mu\text{L})}{\text{number of platelets transfused} \times 10^{-11}} \times \text{BSA}\ (\text{m}^2)$$

where BSA is body surface area measured in square meters. The platelet count performed 1 h after the transfusion is acceptable if the CCI is 10×10^9/mL, and after 18–24 h an increment of 7.5×10^9/mL is expected. Patients who have suboptimal responses are likely to have received multiple transfusions and have antibodies directed against class I HLA antigens. Refractoriness can be investigated by detecting anti-HLA antibodies in the recipient's serum. Patients who are sensitized will often react with 100% of the lymphocytes used for the HLA-antibody screen, and HLA-matched SDAPs should be considered for those patients who require transfusion. Although ABO-identical HLA-matched SDAPs provide the best chance for increasing the platelet count, locating these products is difficult. Platelet cross-matching is available in some centers. Additional clinical causes for a low platelet CCI include fever, bleeding, splenomegaly, DIC, or medications in the recipient.

FRESH-FROZEN PLASMA

FFP contains stable coagulation factors and plasma proteins: fibrinogen, antithrombin, albumin, as well as proteins C and S. Indications for FFP include correction of coagulopathies, including the rapid reversal of warfarin; supplying deficient plasma proteins; and treatment of auto-antibody-mediated thrombotic thrombocytopenic purpura (TTP). In the latter case, therapeutic plasma exchange allows both the removal of the autoantibody and the supplementation of the depleted enzyme (ADAMTS13). Other auto-immune diseases such as Guillain-Barré syndrome and myasthenia gravis may benefit from plasma exchange. FFP should not be routinely used to expand blood volume. FFP is an acellular component and does not transmit intracellular infections, e.g., CMV. In addition to FFP, pre-thawed or never frozen plasma as well as freeze-dried plasma are increasingly used to insure immediate availability when required. Patients who are IgA-deficient and require plasma support should receive FFP from IgA-deficient donors to prevent anaphylaxis (see below).

CRYOPRECIPITATE

Cryoprecipitate is a source of fibrinogen, factor VIII, and von Willebrand factor (vWF). It is ideal for supplying fibrinogen to the volume-sensitive patient. When factor VIII concentrates are not available, cryoprecipitate may be used since each unit contains ~80 units of factor VIII. Cryoprecipitate may also supply vWF to patients with dysfunctional (type II) or absent (type III) von Willebrand disease.

PLASMA DERIVATIVES

Plasma from thousands of donors may be pooled to derive specific protein concentrates, including albumin, intravenous immunoglobulin, antithrombin, and coagulation factors. In addition, donors who have high-titer antibodies to specific agents or antigens provide hyperimmune globulins, such as anti-D (RhoGam, WinRho), and antisera to hepatitis B virus (HBV), varicella-zoster virus, CMV, and other infectious agents.

ADVERSE REACTIONS TO BLOOD TRANSFUSION

Adverse reactions to transfused blood components occur despite multiple tests, inspections, and checks. Fortunately, the most common reactions are not life threatening, although serious reactions can present with mild symptoms and signs. Some reactions can be reduced or prevented by modified (filtered, washed, or irradiated) blood components. Blood product pathogen reduction is an option for platelets and plasma, and underway for whole blood and PRBC. When an adverse reaction is suspected, the transfusion should be stopped and reported to the blood bank for investigation.

Transfusion reactions may result from immune and nonimmune mechanisms. Immune-mediated reactions are often due to preformed donor or recipient antibody; however, cellular elements may also cause adverse effects. Nonimmune causes of reactions are due to the chemical and physical properties of the stored blood component and its additives.

Transfusion-transmitted viral infections are increasingly rare due to improved screening and testing. As the risk of viral infection is reduced, the relative risk of other reactions increases, such as hemolytic transfusion reactions and sepsis from bacterially contaminated components. However, one must remain concerned by novel or previously unidentified viral risks. Pretransfusion quality assurance improvements further increase the safety of transfusion therapy. Infections, like any adverse transfusion reaction, must be brought to the attention of the blood bank for appropriate actions **(Table 109-3)**.

IMMUNE-MEDIATED REACTIONS

Acute Hemolytic Transfusion Reactions Immune-mediated hemolysis occurs when the recipient has preformed antibodies that lyse donor erythrocytes. The anti-A or anti-B antibodies are responsible for the majority of these reactions. However, alloantibodies directed against other RBC antigens, i.e., Rh, Kell, and Duffy, are responsible for fatal hemolytic transfusion reactions as well.

Acute hemolytic reactions may present with hypotension, tachypnea, tachycardia, fever, chills, hemoglobinemia, hemoglobinuria, chest and/or flank pain, and discomfort at the infusion site. Monitoring the patient's vital signs before and during the transfusion is important to identify reactions promptly. When acute hemolysis is suspected, the transfusion must be stopped immediately, intravenous access maintained, and the reaction reported to the blood bank. A correctly labeled posttransfusion blood sample and any untransfused blood should be sent to the blood bank for analysis. The laboratory evaluation for hemolysis includes the measurement of serum haptoglobin, lactate dehydrogenase (LDH), and indirect bilirubin levels.

The immune complexes that result in RBC lysis can cause renal dysfunction and failure. Diuresis should be induced with intravenous fluids and furosemide or mannitol. Tissue factor released from the lysed erythrocytes may initiate DIC. Coagulation studies including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and platelet count should be monitored in patients with hemolytic reactions.

Errors at the patient's bedside, such as mislabeling the sample or transfusing the wrong patient, are responsible for the majority of these reactions. The blood bank investigation of these reactions includes examination of the pre- and posttransfusion samples for hemolysis and repeat typing of the patient samples; direct antiglobulin test (DAT), sometimes called the *direct Coombs test*, of the posttransfusion sample; repeating the cross-matching of the blood component; and checking all clerical records for errors. DAT detects the presence of antibody or complement bound to RBCs in vivo **(Fig. 109-1)**.

Delayed Hemolytic and Serologic Transfusion Reactions DHTRs are not completely preventable. These reactions occur in

TABLE 109-3 Risks of Transfusion Complications

	FREQUENCY, EPISODES: UNIT
Main Reactions	
Circulatory overload (TACO)	· 10.9:100,000
Febrile (FNHTR)	· 100–1000:100,000, frequently under reported
Allergic	· 100–400:100,000, product-dependent
TRALI	· 0,4–1:100,000, with mitigation, product-dependent
Delayed hemolytic	· 40:100,000
Acute hemolytic	· 2.5–7.9:100,000
Infections[a]	
Bacteria (septic transfusion reaction)	· 0,3–25:1,000,000 (product and detection- or pathogen-reduction-dependent
Hepatitis B	· 1:300,000 (<1:1,000,000*)
Hepatitis C*	· <0,1–1:1,000,000
HIV-1*, -2	· 0,1–1:1,000,000
HTLV-I and -II	· 1:3,000,000
Malaria	· 1:4,000,000
*: with nucleic acid testing (NAT) screening	
Other Complications	
RBC allosensitization	· 1:100
HLA allosensitization	· 1:10 (in the absence of leukodepletion)
Graft-versus-host disease	Extremely rare (with blood product irradiation in immunosuppressed patients)

[a]Other infectious agents associated with transfusion include arborvirus (West Nile virus, Dengue virus, Zika virus) hepatitis A and E virus, parvovirus B-19, *Babesia microti* and *Babesia duncani* (babesiosis), *Anaplasma phagocytophilum* (human granulocytic ehrlichiosis), *Trypanosoma cruzi* (Chagas disease), *Treponema pallidum*, and human herpesvirus-8. Frequency of infectious risks differ significantly world-wide.

Abbreviations: FNHTR, febrile nonhemolytic transfusion reaction; TRALI, transfusion-related acute lung injury; HTLV, human T lymphotropic virus; RBC, red blood cell; TACO, transfusion-associated circulatory overload.

patients previously sensitized to RBC alloantigens who have a negative alloantibody screen due to low antibody levels. When the patient is transfused with antigen-positive blood, an anamnestic response results in the early production of alloantibody that binds donor RBCs. The alloantibody is detectable 1–2 weeks following the transfusion, and the posttransfusion DAT may become positive due to circulating donor RBCs coated with antibody or complement. The transfused, alloantibody-coated erythrocytes are cleared by the reticuloendothelial system. These reactions are detected most commonly in the blood bank when a subsequent patient sample reveals a positive alloantibody screen or a new alloantibody in a recently transfused recipient.

No specific therapy is usually required, although additional RBC transfusions may be necessary. Delayed serologic transfusion reactions are similar to DHTR, as the DAT is positive and alloantibody is detected; however, RBC clearance is not increased.

Febrile Nonhemolytic Transfusion Reaction The most frequent reaction associated with the transfusion of cellular blood components is a febrile nonhemolytic transfusion reaction (FNHTR). These reactions are characterized by chills and rigors and a ≥1°C rise in temperature. FNHTR is diagnosed when other causes of fever in the transfused patient are ruled out. Antibodies directed against donor leukocyte and HLA antigens may mediate these reactions; thus, multiply transfused patients and multiparous women are felt to be at increased risk. Although anti-HLA antibodies may be demonstrated in the recipient's serum, investigation is not routinely done because of the mild nature of most FNHTRs. The use of leukocyte-reduced blood products may prevent or delay sensitization to leukocyte antigens and thereby reduce the incidence of these febrile episodes. Cytokines released from leukocytes within stored blood components may mediate FNHTR; thus, leukoreduction before storage may prevent these reactions. Likewise, cytokines and chemokines released from platelets components, released during storage may also mediate FNHTR.

Allergic Reactions Urticarial reactions are related to plasma proteins found in transfused components. Mild reactions may be treated symptomatically by temporarily stopping the transfusion and administering antihistamines (diphenhydramine, 50 mg orally or intramuscularly). The transfusion may be completed after the signs and/or symptoms resolve. Patients with a history of allergic transfusion reaction may be premedicated with an antihistamine. Cellular components can be washed to remove residual plasma for the extremely sensitized patient. Most of the allergic presentation may not depend on preformed antibodies and may be attributable to biological response modifiers triggering histamine and serotonin release from platelets and leukocytes.

Anaphylactic Reaction This severe allergic reaction presents after transfusion of only a few milliliters of the blood component. Symptoms and signs include difficulty breathing, coughing, nausea and vomiting, hypotension, bronchospasm, loss of consciousness, respiratory arrest, and shock. Treatment includes stopping the transfusion, maintaining vascular access, and administering epinephrine (0.5–1 mL of 1:1000 dilution subcutaneously). Glucocorticoids may be required in severe cases.

Patients who are IgA-deficient, <1% of the population, may be sensitized to this Ig class and are at risk for anaphylactic reactions associated with plasma transfusion. Individuals with severe IgA deficiency should therefore receive only IgA-deficient plasma and washed cellular blood components. Patients who have anaphylactic or repeated allergic reactions to blood components should be tested for IgA deficiency. Of note, the importance of the allergic risk associated with IgA deficiency may be overestimated and is currently debated.

Graft-Versus-Host Disease Graft-versus-host disease (GVHD) is a frequent complication of allogeneic stem cell transplantation, in which lymphocytes from the donor attack and cannot be eliminated by an immunodeficient host. Transfusion-related GVHD is mediated by donor T lymphocytes that recognize host HLA antigens as foreign and mount an immune response, which is manifested clinically by the development of fever, a characteristic cutaneous eruption, diarrhea, and liver function abnormalities. GVHD can also occur when blood components that contain viable T lymphocytes are transfused to immunodeficient recipients or to immunocompetent recipients who share HLA antigens with the donor (e.g., a family donor). In addition to the aforementioned clinical features of GVHD, transfusion-associated GVHD (TA-GVHD) is characterized by marrow aplasia and pancytopenia. TA-GVHD is highly resistant to treatment with immunosuppressive therapies, including glucocorticoids, cyclosporine, antithymocyte globulin, and ablative therapy followed by allogeneic bone marrow transplantation. Clinical manifestations appear at 8–10 days, and death occurs at 3–4 weeks posttransfusion.

TA-GVHD can be prevented by irradiation of cellular components (minimum of 2500 cGy) before transfusion to patients at risk. Recently, pathogen inactivation technologies have shown to prevent TA-GVHD as well. Patients at risk for TA-GVHD include fetuses receiving intrauterine transfusions, selected immunocompetent (e.g., lymphoma patients) or immunocompromised recipients, recipients of donor units known to be from a blood relative, and recipients who have undergone marrow transplantation. Directed donations by family members should be discouraged (they are not less likely to transmit infection); lacking other options, the blood products from family members should always be irradiated.

Transfusion-Related Acute Lung Injury TRALI is among the most common cause of transfusion related fatalities. The recipient develops symptoms of hypoxia ($PaO_2/FiO_2 < 300$ mmHg) and signs of noncardiogenic pulmonary edema, including bilateral interstitial infiltrates on chest x-ray, either during or within 6 h of transfusion. Treatment is

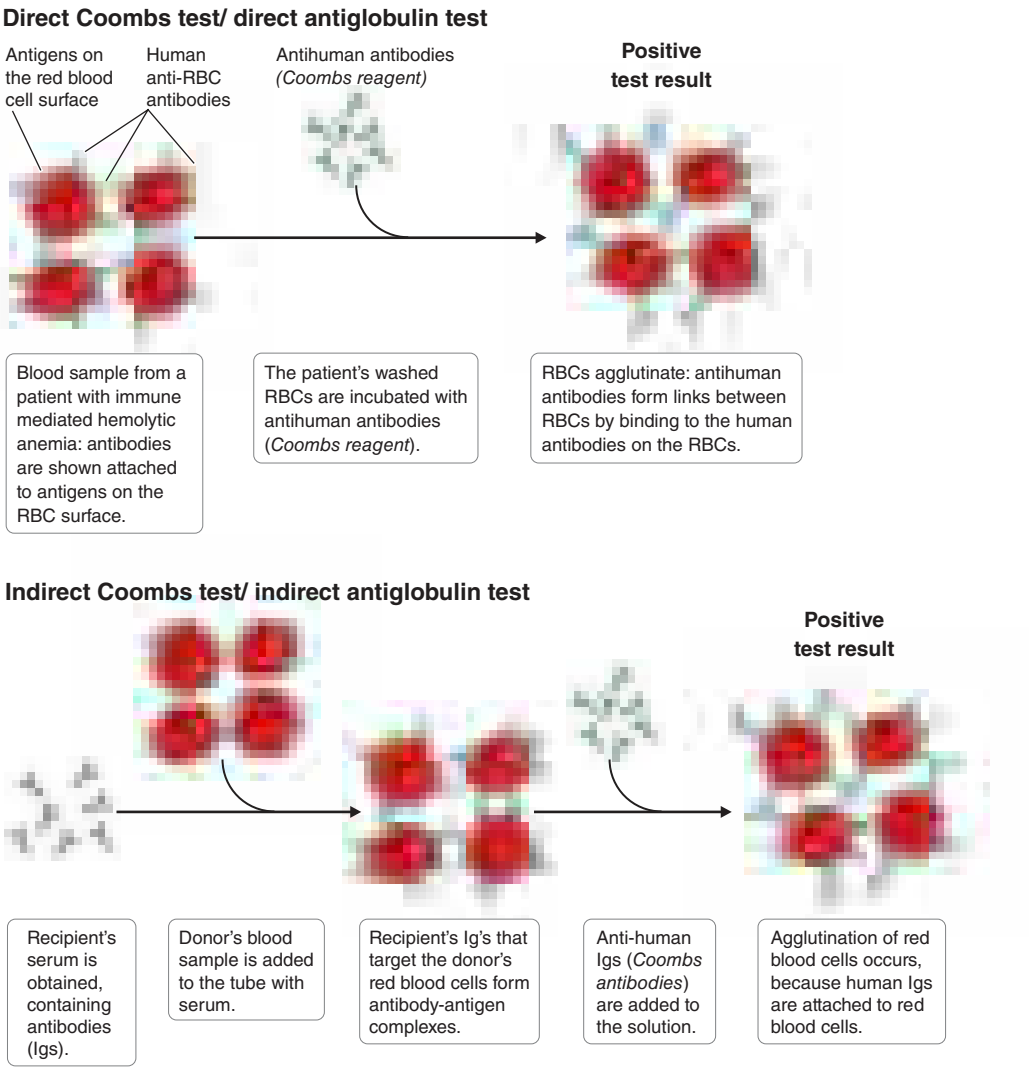

FIGURE 109-1 Direct and indirect Coombs test. The direct Coombs (antiglobulin) test detects the presence of antibodies (or complement) on the surface of erythrocytes. The indirect Coombs (antiglobulin) test detects antibodies in the serum that may bind to donor erythrocytes. RBC, red blood cell. *(Adapted from http://upload.wikimedia.org/wikipedia/commons/1/1c/coombs_test_schematic.png.)*

supportive, and patients usually recover without sequelae. TRALI usually results from the transfusion of donor plasma that contains high-titer anti-HLA class II antibodies that bind recipient leukocytes. Anti-HLA class I and anti-human neutrophil antigen (HNA) antibodies can be involved as well. The leukocytes aggregate in the pulmonary vasculature and release mediators that increase capillary permeability. Testing the donor's plasma for anti-HLA antibodies can support this diagnosis. The implicated donors are frequently multiparous women. The transfusion of plasma and platelets from male and nulliparous women donors reduces the risk of TRALI. Recipient factors that are associated with increased risk of TRALI include smoking, chronic alcohol use, shock, liver surgery (transplantation), mechanical ventilation with >30 cm H_20 pressure support and positive fluid balance.

Posttransfusion Purpura This reaction presents as thrombocytopenia 7–10 days after platelet transfusion and occurs predominantly in women. Platelet-specific antibodies are found in the recipient's serum, and the most frequently recognized antigen is HPA-1a found on the platelet glycoprotein IIIa receptor. The delayed thrombocytopenia is due to the production of antibodies that react to both donor and recipient platelets. Additional platelet transfusions can worsen the thrombocytopenia and should be avoided. Treatment with intravenous immunoglobulin may neutralize the effector antibodies, or plasmapheresis can be used to remove the antibodies.

Alloimmunization A recipient may become alloimmunized to a number of antigens on cellular blood elements and plasma proteins. Alloantibodies to RBC antigens are detected during pretransfusion testing, and their presence may delay finding antigen-negative cross-match-compatible products for transfusion. Women of childbearing age who are sensitized to certain RBC antigens (i.e., D, c, E, Kell, or Duffy) are at risk for bearing a fetus with hemolytic disease of the newborn. Matching for RBC antigen is the only pretransfusion selection test to prevent RBC alloimmunization.

Alloimmunization to antigens on leukocytes and platelets can result in refractoriness to platelet transfusions. Once alloimmunization has developed, HLA-compatible platelets from donors who share similar antigens with the recipient may be difficult to find. Hence, prudent transfusion practice is directed at preventing sensitization through the use of leukocyte-reduced cellular components, as well as limiting antigenic exposure by the judicious use of transfusions and use of SDAPs.

NONIMMUNOLOGIC REACTIONS

Fluid Overload Blood components are excellent volume expanders, and transfusion may quickly lead to transfusion-associated circulatory overload (TACO). Dyspnea with O_2% <90 on room air, bilateral infiltrates on CXR with systolic hypertension are found with TACO. Brain natriuretic peptide (BNP) is often elevated (>1.5) that of pre-transfusion levels. Monitoring the rate and volume of the transfusion and using a diuretic can minimize this problem.

Hypothermia Refrigerated (4°C) or frozen (−18°C or below) blood components can result in hypothermia when rapidly infused. Cardiac

dysrhythmias can result from exposing the sinoatrial node to cold fluid. Use of an in-line warmer will prevent this complication.

Electrolyte Toxicity RBC leakage during storage increases the concentration of potassium in the unit. Neonates and patients in renal failure are at risk for hyperkalemia. Preventive measures, such as using fresh or washed RBCs, are warranted for neonatal transfusions because this complication can be fatal.

Citrate, commonly used to anticoagulate blood components, chelates calcium and thereby inhibits the coagulation cascade. Hypocalcemia, manifested by circumoral numbness and/or tingling sensation of the fingers and toes, may result from multiple rapid transfusions. Because citrate is quickly metabolized to bicarbonate, calcium infusion is seldom required in this setting. If calcium or any other intravenous infusion is necessary, it must be given through a separate line.

Iron Overload Each unit of RBCs contains 200–250 mg of iron. Symptoms and signs of iron overload affecting endocrine, hepatic, and cardiac function are common after 100 units of RBCs have been transfused (total-body iron load of 20 g). Preventing this complication by using alternative therapies (e.g., erythropoietin) and judicious transfusion is preferable and cost effective. Chelating agents, such as deferoxamine and deferasirox, are available, but the response though is often suboptimal.

Hypotensive Reactions Transient hypotension may be noted among transfused patients who take angiotensin-converting enzyme (ACE) inhibitors. Since blood products contain bradykinin that is normally degraded by ACE, patients on ACE inhibitors may have increased bradykinin levels that cause hypotension in the recipient. The blood pressure typically returns to normal without intervention.

Immunomodulation Transfusion of allogeneic blood is immunosuppressive. Multiply transfused renal transplant recipients are less likely to reject the graft, and transfusion may result in poorer outcomes in cancer patients and increase the risk of infections. Transfusion-related immunomodulation is thought to be mediated by transfused leukocytes. Leukocyte-depleted cellular products may cause less immunosuppression, though controlled data are unlikely to be obtained as the blood supply becomes universally leukocyte-depleted.

INFECTIOUS COMPLICATIONS

The blood supply is initially screened by selecting healthy donors without high-risk lifestyles, medical conditions, or exposure to transmissible pathogens, such as intravenous drug use or visiting malaria endemic areas. Multiple tests performed on donated blood to detect the presence of infectious agents using nucleic acid amplification testing (NAT) or evidence of prior infections by testing for antibodies to pathogens and sterility of platelet products further reduce the risk of transfusion-acquired infections. Pathogen reduction of platelets and plasma offer an additional mean to reduce such risk.

Viral Infections • **HEPATITIS C VIRUS** Blood donations are tested for antibodies to HCV and HCV RNA. The risk of acquiring HCV through transfusion is now calculated to be 0,1 to 1 in 1,000,000 units. Infection with HCV may be asymptomatic or lead to chronic active hepatitis, cirrhosis, and liver failure.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 Donated blood is tested for antibodies to HIV-1, HIV-1 p24 antigen, and HIV RNA using NAT. The risk of HIV-1 infection per transfusion episode is 0,1 to 1 in 1 million. Antibodies to HIV-2 are also measured in donated blood. No cases of HIV-2 infection in blood donors have been reported in the United States since 1992.

HEPATITIS B VIRUS Donated blood is screened for HBV using assays for hepatitis B surface antigen (HbsAg) most combined with NAT testing. The risk of transfusion-associated HBV infection is several times greater than for HCV. Vaccination of individuals who require long-term transfusion therapy can prevent this complication.

OTHER HEPATITIS VIRUSES Hepatitis A virus is rarely transmitted by transfusion; infection is typically asymptomatic and does not lead to chronic disease. Hepatitis E (HEV) can be transmitted by transfusion and may lead to chronic disease. Routine HEV RNA testing has been introduced in several European countries starting in 2015. West Nile virus (WNV) Transfusion-transmitted WNV infections were documented in 2002. This RNA virus can be detected using NAT; routine screening began in 2003. WNV infections range in severity from asymptomatic to fatal, with the older population at greater risk.

CYTOMEGALOVIRUS This ubiquitous virus infects ≥50% of the general population and is transmitted by the infected "passenger" leukocytes found in transfused PRBCs or platelet components. Cellular components that are leukocyte-reduced have a decreased risk of transmitting CMV, regardless of the serologic status of the donor. Groups at risk for CMV infections include immunosuppressed patients, CMV-seronegative transplant recipients, and neonates; these patients should receive leukocyte-depleted components or CMV seronegative products.

HUMAN T LYMPHOTROPIC VIRUS (HTLV) TYPE I Assays to detect HTLV-I and -II are used to screen all donated blood. HTLV-I is associated with adult T cell leukemia/lymphoma and tropical spastic paraparesis in a small percentage of infected persons (Chap. 196). The risk of transfusion-mediated HTLV-1 infection is further mitigated by blood product leukoreduction. HTLV-II is not clearly associated with any disease.

PARVOVIRUS B-19 Blood components and pooled plasma products can transmit this virus, the etiologic agent of erythema infectiosum, or fifth disease, in children. Parvovirus B-19 shows tropism for erythroid precursors and inhibits both erythrocyte production and maturation. Pure red cell aplasia, presenting either as acute aplastic crisis or chronic anemia with shortened RBC survival, may occur in individuals with an underlying hematologic disease, such as sickle cell disease or thalassemia (Chap. 94). The fetus of a seronegative woman is at risk for developing hydrops from this virus.

Bacterial Contamination The relative risk of transfusion-transmitted bacterial infection has increased as the absolute risk of viral infections has dramatically decreased.

Most bacteria do not grow well at cold temperatures; thus, PRBCs and FFP are not common sources of bacterial contamination. However, some gram-negative bacteria can grow at 1° to 6°C. *Yersinia*, *Pseudomonas*, *Serratia*, *Acinetobacter*, and *Escherichia* species have all been implicated in infections related to PRBC transfusion. Platelet concentrates, which are stored at room temperature, are more likely to contain skin contaminants such as gram-positive organisms, including coagulase-negative staphylococci. It is estimated that 1 in 1000–2000 platelet components is contaminated with bacteria. The risk of death due to transfusion-associated sepsis is estimated to be in the order of 1 in 200,000–400,000 platelets products. Since 2004, blood banks have instituted methods to detect contaminated platelet components. Pathogen-reduced platelets have been available and offer an alternative to prevent transfusion-transmitted bacterial infection.

Recipients of transfusion contaminated with bacteria may develop fever and chills, which can progress to septic shock and DIC. These reactions may occur abruptly, within minutes of initiating the transfusion, or after several hours. The onset of symptoms and signs is often sudden and fulminant, which distinguishes bacterial contamination from an FNHTR. The reactions, particularly those related to gram-negative contaminants, are the result of infused endotoxins formed within the contaminated stored component.

When these reactions are suspected, the transfusion must be stopped immediately. Therapy is directed at reversing any signs of shock, and broad-spectrum antibiotics should be given. The blood bank should be notified to identify any clerical or serologic error. The blood component bag should be sent for culture and Gram stain.

Other Infectious Agents Various parasites, including those causing malaria, babesiosis, and Chagas disease, can be transmitted by blood transfusion. Geographic migration and travel of donors shift the incidence of these infections. Other agents implicated in transfusion transmission include dengue, zika virus, variant Creutzfeldt-Jakob disease, *Anaplasma phagocytophilum*, and yellow fever vaccine virus

and the list will grow. Tests for some pathogens are available, such as *Trypanosoma cruzi*, but not universally required while others are being developed (Babesia microti). These infections should be considered in the transfused patient in the appropriate clinical setting.

ALTERNATIVES TO TRANSFUSION

Alternatives to allogeneic blood transfusions that avoid homologous donor exposures with attendant immunologic and infectious risks remain attractive. Autologous blood remains an option when transfusion is anticipated. However, the cost-benefit ratio of autologous transfusion remains high. No transfusion is a zero-risk event; clerical errors and bacterial contamination remain potential complications even with autologous transfusions. Additional methods of autologous transfusion in the surgical patient include preoperative hemodilution, recovery of shed blood from sterile surgical sites, and postoperative drainage collection. Directed or designated donation from friends and family of the potential recipient has not been safer than volunteer donor component transfusions. Such directed donations may in fact place the recipient at higher risk for complications such as GVHD and alloimmunization.

Granulocyte and granulocyte-macrophage colony-stimulating factors are clinically useful to hasten leukocyte recovery in patients with leukopenia related to high-dose chemotherapy. Erythropoietin stimulates erythrocyte production in patients with anemia of chronic renal failure and other conditions, thus avoiding or reducing the need for transfusion. This hormone can also stimulate erythropoiesis in the autologous donor to enable additional donation.

Gene therapy approaches in patients with sickle cell or major thalassemia offers the potential of dramatically reducing their transfusion needs. Stem cell-derived blood cells such as RBCs or platelets may in the future become a suitable alternative to very rare blood donors.

Lastly, optimizing the use of blood products through patient blood management programs can improve the therapeutic index of transfusion medicine.

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110 Hematopoietic Cell Transplantation

Frederick R. Appelbaum

Bone marrow transplantation was the original term used to describe the collection and transplantation of hematopoietic stem cells, but with the demonstration that peripheral blood and umbilical cord blood are also useful sources of stem cells, *hematopoietic cell transplantation* (HCT) has become the preferred generic term for this process. HCT is used to treat patients with an abnormal but nonmalignant lymphohematopoietic system by replacing it with one from a normal donor. HCT is also used to treat malignancy by allowing the administration of higher doses of myelosuppressive therapy than would otherwise be possible, and in the setting of allogeneic HCT, by conferring an immunologic graft-versus-tumor effect. The use of HCT has been increasing, both because of its efficacy in selected diseases and because of increasing availability of donors.

The Center for International Blood and Marrow Transplant Research (*http://www.cibmtr.org*) estimates that worldwide about 70,000 transplants were performed in 2016. The frequency of transplantation varied widely from country to country with a close association of transplant rates with Gross National Income (GNI)/capita. However, even among countries with similar GNIs/capita, there are substantial differences between countries and regions concerning the frequency of transplantation, disease indications, and choice of donor type.

THE HEMATOPOIETIC STEM CELL

Several features of the hematopoietic stem cell make transplantation clinically feasible, including its remarkable regenerative capacity, its ability to home to the marrow space following intravenous injection, and the ability of the stem cell to be cryopreserved **(Chap. 92)**. Transplantation of a single stem cell can replace the entire lymphohematopoietic system of an adult mouse. In humans, transplantation of a small percentage of a donor's bone marrow volume regularly results in complete and sustained replacement of the recipient's entire lymphohematopoietic system, including all red cells, granulocytes, B and T lymphocytes, and platelets, as well as cells comprising the fixed macrophage population, including Kupffer cells of the liver, pulmonary alveolar macrophages, osteoclasts, Langerhans cells of the skin, and brain microglial cells. The ability of the hematopoietic stem cell to home to the marrow following intravenous injection is mediated, in part, by an interaction between CXCL12, also known as stromal cell–derived factor 1, produced by marrow stromal cells and the alpha-chemokine receptor CXCR4 found on stem cells. Homing is also influenced by the interaction of cell-surface molecules, termed *selectins*, including E- and L-selectin, on bone marrow endothelial cells with ligands, termed *integrins*, such as VLA-4, on early hematopoietic cells. Human hematopoietic stem cells can survive freezing and thawing with little, if any, damage, making it possible to remove and store a portion of the patient's own bone marrow for later reinfusion following treatment of the patient with high-dose myelotoxic therapy.

CATEGORIES OF HCT

HCT can be described according to the relationship between the patient and the donor and by the anatomic source of stem cells. In ~1% of cases, patients have identical twins who can serve as donors. With the use of syngeneic donors, there is no risk of graft-versus-host disease (GVHD), and unlike the use of autologous marrow, there is no risk that the stem cells are contaminated with tumor cells.

Allogeneic transplantation involves a donor and a recipient who are not genetically identical. Following allogeneic transplantation, immune cells transplanted with the stem cells or developing from them can react against the patient, causing GVHD. Alternatively, if the immunosuppressive preparative regimen used to treat the patient before transplant is inadequate, immunocompetent cells of the patient can cause graft rejection. The risks of these complications are greatly influenced by the degree of matching between donor and recipient for human leukocyte antigen (HLA) molecules encoded by genes of the major histocompatibility complex.

HLA molecules are responsible for binding antigenic proteins and presenting them to T cells. The antigens presented by HLA molecules may derive from exogenous sources (e.g., during active infections) or may be endogenous proteins. If individuals are not HLA-matched, T cells from one individual will react strongly to the mismatched HLA, or "major antigens," of the second. Even if the individuals are HLA-matched, the T cells of the donor may react to differing endogenous or "minor antigens" presented by the HLA of the recipient. Reactions to minor antigens tend to be less vigorous. The genes of major relevance to transplantation

include HLA-A, -B, -C, and -D; they are closely linked and therefore tend to be inherited as haplotypes, with only rare crossovers between them. Thus, the odds that any one full sibling will match a patient are one in four, and the probability that the patient has an HLA-identical sibling is $1 - (0.75)^n$, where n equals the number of siblings.

With standard techniques, the risk of graft rejection is 1–3%, and the risk of severe, life-threatening acute GVHD is ~15% following transplantation between HLA-identical siblings. The incidence of graft rejection and GVHD increases progressively with the use of family member donors mismatched for one, two, or three antigens. Although survival following a one-antigen mismatched transplant is not markedly altered, survival following two- or three-antigen mismatched transplants is reduced. Since the formation of the National Marrow Donor Program and other registries, it has become possible to identify HLA-matched unrelated donors for many patients. The genes encoding HLA antigens are highly polymorphic, and thus the odds of any two unrelated individuals being HLA identical are extremely low, somewhat less than 1 in 10,000. However, by identifying and typing >25 million volunteer donors, HLA-matched donors can now be found for ~60% of patients for whom a search is initiated, with higher rates among whites and lower rates among minorities and patients of mixed race. It takes, on average, 3–4 months to complete a search and schedule and initiate an unrelated donor transplant. With improvements in HLA typing and supportive care measures, survival following matched unrelated donor transplantation is essentially the same as that seen with HLA-matched siblings. Methods have recently been developed that enable the selection of "permissive" single-antigen mismatched unrelated donors that result in transplant outcomes similar to those seen with full matches.

Allogeneic HCT can be carried out across ABO blood barriers by removing isoagglutinins and/or incompatible red blood cells from the donor graft. However, depending on the direction of the mismatch, hemolysis of donor cells by persistent isoagglutinins in the host, or hemolysis of recipient red cells by isoagglutinins in the graft or developing from it may occur despite appropriate manipulation of the donor cell product.

Autologous transplantation involves the removal and storage of the patient's own stem cells with subsequent reinfusion after the patient receives high-dose myeloablative therapy. Unlike allogeneic transplantation, there is no risk of GVHD or graft rejection with autologous transplantation. On the other hand, autologous transplantation lacks a graft-versus-tumor (GVT) effect, and the autologous stem cell product can be contaminated with tumor cells, which could lead to relapse. A variety of techniques have been developed to "purge" autologous products of tumor cells, but no prospective randomized trials have yet shown that any approach results in a decrease in relapse rates or improvement in disease-free or overall survival.

Bone marrow aspirated from the posterior and anterior iliac crests initially was the source of hematopoietic stem cells for transplantation. Typically, anywhere from 1.5 to 5×10^8 nucleated marrow cells per kilogram are collected for allogeneic transplantation. Several studies have found improved survival in the settings of both matched sibling and unrelated transplantation by transplanting higher numbers of bone marrow cells.

Hematopoietic stem cells circulate in the peripheral blood but in very low concentrations. Following the administration of a myeloid growth factor such as granulocyte colony-stimulating factor (G-CSF) and during recovery from intensive chemotherapy, the concentration of hematopoietic progenitor cells in blood, as measured either by colony-forming units or expression of the CD34 antigen, increases markedly. This has made it possible to harvest adequate numbers of stem cells from the peripheral blood for transplantation. Donors are typically treated with 4 or 5 days of hematopoietic growth factor, following which stem cells are collected in one or two 4-h pheresis sessions. In the autologous setting, transplantation of $>2.5 \times 10^6$ CD34 cells per kilogram, a number that can be collected in most circumstances, leads to rapid and sustained engraftment in virtually all cases. In the 10–20% of patients who fail to mobilize sufficient CD34+ cells with growth factor alone, the addition of plerixafor, an antagonist of CXCR4, may be useful. When compared to the use of autologous marrow, use of peripheral blood stem cells results in more rapid hematopoietic recovery. Although this more rapid recovery diminishes the morbidity rate of transplantation, no studies show improved survival.

TABLE 110-1 Probability of Identifying a Donor Based on Stem Cell Source and Patient Ethnicity

	UNRELATED ADULT %		UNRELATED CORD %
Ethnicity	8/8[a]	7/8[a]	≥4/6[b]
Caucasian	75	90	>95
Hispanic	35	75	95
Black	18	70	90

[a]Matching for HLA-A, -B, -C, and DRB1. [b]Matching for HLA-A, -B, and DRB1.

Clinical trials have shown that the use of growth factor–mobilized peripheral blood stem cells from HLA-matched family members leads to faster engraftment without an increase in acute GVHD. Chronic GVHD may be increased with peripheral blood stem cells, but in trials conducted so far, this has been more than balanced by reductions in relapse rates and non-relapse mortality rates, with the use of peripheral blood stem cells resulting in improved overall survival. However, in the setting of matched unrelated donor transplantation, use of peripheral blood results in more chronic GVHD without a compensatory survival advantage, favoring the use of bone marrow in this setting.

Umbilical cord blood contains a high concentration of hematopoietic progenitor cells, allowing for its use as a source of stem cells for transplantation. Cord blood transplantation from family members has been explored in the setting where the immediate need for transplantation precludes waiting the 9 or so months generally required for the baby to mature to the point of donating marrow. Use of cord blood results in slower peripheral count recovery than seen with marrow but a lower incidence of GVHD, perhaps reflecting the low number of T cells in cord blood. Multiple cord blood banks have been developed to harvest and store cord blood for possible transplantation to unrelated patients from material that would otherwise be discarded. Currently more than 500,000 units are cryopreserved and available for use. The advantages of unrelated cord blood are rapid availability and decreased immune reactivity allowing for the use of partially matched units, which is of particular importance for those without matched unrelated donors. The risks of graft failure and transplant-related mortality are related to the dose of cord blood cells per kilogram, which previously limited the application of single cord blood transplantation to pediatric and smaller adult patients. Subsequent trials have found that for patients without suitable single cord units, the use of double cord transplants diminishes the risk of graft failure and early mortality even though only one of the donors ultimately engrafts. Survival rates are now similar with unrelated donor and cord blood transplantation with the result that a potential allogeneic donor can be found for almost every patient in need **(see Table 110-1)**.

THE TRANSPLANT PREPARATIVE REGIMEN

The treatment regimen administered to patients immediately preceding transplantation is designed to eradicate the patient's underlying disease and, in the setting of allogeneic transplantation, immunosuppress the patient adequately to prevent rejection of the transplanted marrow. The appropriate regimen therefore depends on the disease setting and source of marrow. For example, when transplantation is performed to treat severe combined immunodeficiency and the donor is a histocompatible sibling, no treatment is needed because no host cells require eradication and the patient is already too immunoincompetent to reject the transplanted marrow. For aplastic anemia, there is no large population of cells to eradicate, and high-dose cyclophosphamide plus antithymocyte globulin are sufficient to immunosuppress the patient adequately to accept the marrow graft. In the setting of thalassemia and sickle cell anemia, high-dose busulfan is frequently added to cyclophosphamide in order to eradicate hyperplastic host hematopoiesis. A variety of different regimens have been developed to treat malignant diseases. Most of these regimens include agents that have high activity against the tumor in question at conventional doses and have

myelosuppression as their predominant dose-limiting toxicity. Therefore, these regimens commonly include busulfan, cyclophosphamide, melphalan, thiotepa, carmustine, etoposide, and total-body irradiation in various combinations.

Although high-dose treatment regimens were the initial approach to transplantation for malignancies, the understanding that much of the antitumor effect of transplantation derives from an immunologically mediated GVT response led investigators to ask if reduced-intensity conditioning regimens might be effective and more tolerable. Evidence for a GVT effect comes from studies showing that post-transplant relapse rates are lowest in patients who develop acute and chronic GVHD, higher in those without GVHD, and higher still in recipients of T cell–depleted allogeneic or syngeneic marrow. The demonstration that complete remissions can be obtained in many patients who have relapsed after transplant by simply administering viable lymphocytes from the original donor further strengthens the argument for a potent GVT effect. Accordingly, a variety of alternative regimens have been studied, ranging from non-myeloablative that are the very minimum required to achieve engraftment (e.g., fludarabine plus 200 cGy total-body irradiation) and would cause only transient myelosuppression if no transplant were performed, to so-called reduced intensity regimens, which would cause significant but not necessarily fatal myelosuppression in the absence of transplantation (e.g., fludarabine plus melphalan). Studies to date document that engraftment can be readily achieved with less toxicity than seen with conventional transplantation. Complete sustained responses have been documented in many patients, particularly those with more indolent hematologic malignancies. In general, relapse rates are higher following reduced-intensity conditioning, but transplant-related mortality is lower, favoring the use of reduced-intensity conditioning in patients with significant comorbidities. High-dose regimens are favored in all those felt able to tolerate the treatment.

THE TRANSPLANT PROCEDURE

Marrow is usually collected from the donor's posterior and sometimes anterior iliac crests, with the donor under general or spinal anesthesia. Typically, 10–15 mL/kg of marrow is aspirated, placed in heparinized media, and filtered through 0.3- and 0.2-mm screens to remove fat and bony spicules. The collected marrow may undergo further processing depending on the clinical situation, such as the removal of red cells to prevent hemolysis in ABO-incompatible transplants, the removal of donor T cells to prevent GVHD, or attempts to remove possible contaminating tumor cells in autologous transplantation. Marrow donation is safe, with only very rare complications reported.

Peripheral blood stem cells are collected by leukapheresis after the donor has been treated with hematopoietic growth factors or, in the setting of autologous transplantation, sometimes after treatment with a combination of chemotherapy and growth factors. Stem cells for transplantation are infused through a large-bore central venous catheter. Such infusions are usually well tolerated, although occasionally patients develop fever, cough, or shortness of breath. These symptoms typically resolve with slowing of the infusion. When the stem cell product has been cryopreserved using dimethyl sulfoxide, patients more often experience short-lived nausea or vomiting due to the odor and taste of the cryoprotectant.

ENGRAFTMENT AND IMMUNE RECONSTITUTION

Peripheral blood counts usually reach their nadir several days to a week after transplant as a consequence of the preparative regimen; then cells produced by the transplanted stem cells begin to appear in the peripheral blood. The rate of recovery depends on the source of stem cells and the use of post-transplant growth factors. If marrow is the source of stem cells, recovery to 100 granulocytes/μL occurs on average by day 16 and to 500/μL by day 22. Use of G-CSF–mobilized peripheral blood stem cells speeds the rate of recovery by ~1 week when compared to marrow, whereas engraftment following cord blood transplantation is typically delayed by ~1 week compared to marrow. Use of a myeloid growth factor after transplant can accelerate recovery by 3–5 days. Platelet counts usually recover shortly after granulocytes.

While granulocytes and other components of innate immunity recover rapidly after HCT, adaptive immunity, which consists of cellular (T cell) and humoral (B cell) immunity, may take 1–2 years to fully recover. Survival and peripheral expansion of infused donor T cells is the dominant mechanism for T cell recovery in the first months after HCT and results in mostly CD8+ T cells with a limited repertoire. After several months, de novo generation of donor-derived CD4+ and CD8+ T cells becomes dominant providing a more diverse T cell repertoire. B cell counts recover by 6 months after autologous HCT and 9 months after allogeneic HCT. In general, immune recovery occurs more rapidly after autologous than allogeneic HCT and after receipt of unmodified grafts compared to the setting of in vivo or ex vivo T-cell depletion.

Following allogeneic transplantation, engraftment can be documented using fluorescence in situ hybridization of sex chromosomes if donor and recipient are sex-mismatched or by analysis of short tandem repeat polymorphisms after DNA amplification.

COMPLICATIONS FOLLOWING HEMATOPOIETIC CELL TRANSPLANT

Early Direct Chemoradiotoxicities The transplant preparative regimen may cause a spectrum of acute toxicities that vary according to intensity of the regimen and the specific agents used but frequently include nausea, vomiting, and mild skin erythema (Fig. 110-1). High-dose cyclophosphamide can result in hemorrhagic cystitis, which can usually be prevented by bladder irrigation or with the sulfhydryl compound mercaptoethanesulfonate (MESNA). Most high-dose preparative regimens will result in oral mucositis, which typically develops 5–7 days after transplant and often requires narcotic analgesia. Use of a patient-controlled analgesic pump provides the greatest patient satisfaction and results in a lower cumulative dose of narcotic. Keratinocyte growth factor (palifermin) can shorten the duration of mucositis by several days following autologous transplantation. Patients begin losing their hair 5–6 days after transplant and by 1 week are usually profoundly pancytopenic.

Depending on the intensity of the conditioning regimen, 3–10% of patients will develop sinusoidal obstruction syndrome (SOS) of the liver (formerly called venoocclusive disease), a syndrome that results from direct cytotoxic injury to hepatic-venular and sinusoidal endothelium, with subsequent deposition of fibrin and the development of a local hypercoagulable state. This chain of events leads to the clinical symptoms of tender hepatomegaly, ascites, jaundice, and fluid retention. These symptoms can develop any time during the first month after transplant, with the peak incidence at day 16. Predisposing factors include prior exposure to intensive chemotherapy, pre-transplant

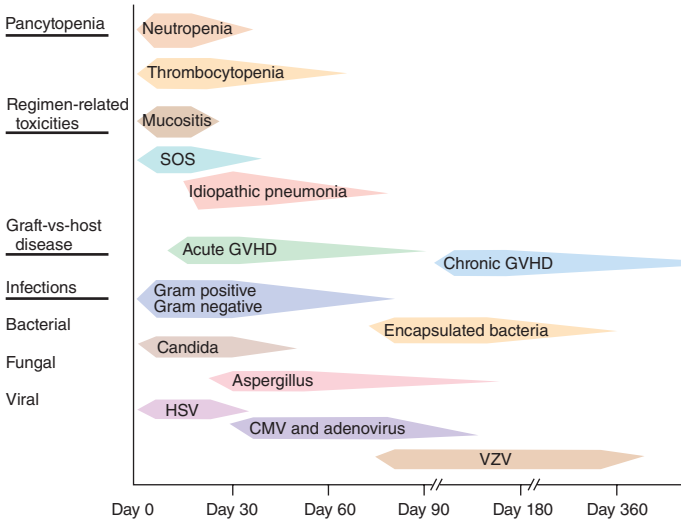

FIGURE 110-1 Major syndromes complicating marrow transplantation. CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; SOS, sinusoidal obstructive syndrome (formerly venoocclusive disease); VZV, varicella-zoster virus. The size of the shaded area roughly reflects the period of risk of the complication.

hepatitis of any cause, and use of more intense conditioning regimens. The mortality rate of sinusoidal obstruction syndrome is ~30%, with progressive hepatic failure culminating in a terminal hepatorenal syndrome. Treatment of severe SOS with defibrotide, a polydeoxyribonucleotide, can reduce mortality.

Although most pneumonias developing early after transplant are caused by infectious agents, in a small percent of patients a diffuse interstitial pneumonia will develop that is a result of direct toxicity of high-dose preparative regimens. Bronchoalveolar lavage usually shows alveolar hemorrhage, and biopsies are typically characterized by diffuse alveolar damage, although some cases may have a more clearly interstitial pattern. High-dose glucocorticoids or antitumor necrosis factor therapies are sometimes used as treatment, although randomized trials proving their utility have not been reported.

Late Direct Chemoradiotoxicities Two categories of chronic pulmonary disease occur in patients more than 3 months after HCT. Cryptogenic organizing pneumonia is a restrictive lung disease characterized by dry cough, shortness of breath, and chest imaging showing a diffuse, fluffy infiltrate. Biopsy shows granulation tissue within alveolar spaces and small airways and no infectious agents. The disease responds well to corticosteroids and is entirely reversible. Bronchiolitis obliterans is an obstructive disease presenting with cough, progressive dyspnea, and radiologic evidence of air trapping. Pathology shows collagen and granulation tissue in and around bronchial structures and eventually obliteration of small airways. The disease is usually associated with chronic GVHD and while it may respond to increasing immunosuppression, complete reversal is uncommon.

Other late complications of the preparative regimen include decreased growth velocity in children and delayed development of secondary sex characteristics. These complications can be partly ameliorated with the use of appropriate growth and sex hormone replacement. Most men become azoospermic, and most postpubertal women will develop ovarian failure, which should be treated. However, pregnancy is possible after transplantation, and patients should be counseled accordingly. Thyroid dysfunction, usually well compensated, is sometimes seen. Cataracts develop in 10–20% of patients and are most common in patients treated with total-body irradiation and those who receive glucocorticoid therapy after transplant for treatment of GVHD. Aseptic necrosis of the femoral head is seen in 10% of patients and is particularly frequent in those receiving chronic glucocorticoid therapy. Both acute and late chemoradiotoxicities (except those due to glucocorticoids and other agents used to treat GVHD) are less frequent in recipients of reduced-intensity compared to high-dose preparative regimens.

Graft Failure Although complete and sustained engraftment is usually seen after transplant, occasionally marrow function either does not return or, after a brief period of engraftment, is lost. Graft failure after autologous transplantation can be the result of inadequate numbers of stem cells being transplanted, damage during ex vivo treatment or storage, or exposure of the patient to myelotoxic agents after transplant. Infections with cytomegalovirus (CMV) or human herpesvirus type 6 have also been associated with loss of marrow function. Graft failure after allogeneic transplantation can also be due to immunologic rejection of the graft by immunocompetent host cells. Such rejection is generally thought to be mostly T-cell mediated, but the presence of pre-HCT of donor-specific HLA antibodies in the patient is associated with poor engraftment, leading to the recommendation for screening for donor-directed anti-HLA antibodies in recipients prior to transplant. Immunologically based graft rejection is more common following use of less immunosuppressive preparative regimens, in recipients of T cell–depleted stem cell products, and in patients receiving grafts from HLA-mismatched donors or cord blood.

Treatment of graft failure usually involves removing all potentially myelotoxic agents from the patient's regimen and attempting a short trial of a myeloid growth factor. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic rejection. Reinfusion of donor stem cells in such patients is usually unsuccessful unless preceded by a second immunosuppressive preparative regimen. Standard high-dose preparative regimens are generally tolerated poorly if administered within 100 days of a first transplant because of cumulative toxicities. However, use of reduced-intensity conditioning regimens has been effective in some cases.

Graft-versus-Host Disease Acute GVHD usually occurs within the first 3 months after allogeneic transplant with a peak onset around 4 weeks and is characterized by an erythematous maculopapular rash; by persistent anorexia or diarrhea, or both; and by liver disease with increased serum levels of bilirubin, alanine and aspartate aminotransferase, and alkaline phosphatase. Because many conditions can mimic acute GVHD, the diagnosis usually requires skin, liver, or endoscopic biopsy for confirmation. In all these organs, endothelial damage and lymphocytic infiltrates are seen. In skin, the epidermis and hair follicles are damaged; in liver, the small bile ducts show segmental disruption; and in intestines, destruction of the crypts and mucosal ulceration may be noted. A commonly used rating system for acute GVHD is shown in Table 110-2. Grade I acute GVHD is of little clinical significance, does not affect the likelihood of survival, and does not require treatment. In contrast, grades II to IV GVHD are associated with significant symptoms and a poorer probability of survival, and require aggressive therapy. The incidence of acute GVHD is higher in recipients of stem cells from mismatched or unrelated donors, in older patients, and in patients unable to receive full doses of drugs used to prevent the disease.

Currently, the standard approach to GVHD prevention is the administration of a calcinuerin inhibitor (cyclosporine or tacrolimus) combined with an antimetabolite (methotrexate or mycophenolate mofetil) following transplantation. The addition of anti T-cell immune globulin (ATG) may further reduce the incidence of GVHD but has not been shown to improve survival. Other approaches being tested in phase III studies include the addition of sirolimus to the standard two-drug regimen, the removal of subsets or all T cells from the stem cell inoculum, and the use of cyclophosphamide administered several days after transplant in an effort to deplete activated allo-reactive T cells.

Despite prophylaxis, significant acute GVHD will develop in ~30% of recipients of stem cells from matched siblings. Factors associated with a greater risk of acute GVHD include HLA-mismatching between

TABLE 110-2 Clinical Staging and Grading of Acute Graft-versus-Host Disease

CLINICAL STAGE	SKIN	LIVER—BILIRUBIN, μmol/L (mg/dL)	GUT
1	Rash <25% body surface	34–51 (2–3)	Diarrhea 500–1000 mL/d
2	Rash 25–50% body surface	51–103 (3–6)	Diarrhea 1000–1500 mL/d
3	Generalized erythroderma	103–257 (6–15)	Diarrhea >1500 mL/d
4	Desquamation and bullae	>257 (>15)	Ileus
OVERALL CLINICAL GRADE	**SKIN STAGE**	**LIVER STAGE**	**GUT STAGE**
I	1–2	0	0
II	1–3	1	1
III	1–3	2–3	2–3
IV	2–4	2–4	2–4

recipient and donor, patient and donor age, use of more intense preparative regimens and use of multiparous women as donors. Biomarkers, including ST2, REG32, and TNF R1 have been identified that are able to predict the severity of acute GVHD. The disease is usually treated with prednisone at a daily dose of 1–2 mg/kg. Patients who fail to respond to prednisone sometimes respond to alternative immunosuppressants or ATG.

Chronic GVHD occurs most commonly between 3 months and 2 years after allogeneic transplant, developing in 20–50% of recipients. The disease is more common in older patients, in recipients of mismatched or unrelated stem cells, and in those with a preceding episode of acute GVHD. The disease resembles an autoimmune disorder with malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, and bile duct degeneration and cholestasis. Mild chronic GVHD can sometimes be managed using local therapies (topical glucocorticoids to skin and cyclosporine eye drops). More severe disease requires systemic therapy usually with prednisone alone or in combination with cyclosporine. Mortality rates from chronic GVHD average around 15%, but range from 5 to 50% depending on severity. In most patients, chronic GVHD resolves, but it may require 1–3 years of immunosuppressive treatment before these agents can be withdrawn without the disease recurring. Because patients with chronic GVHD are susceptible to significant infection, they should receive prophylactic trimethoprim-sulfamethoxazole, and all suspected infections should be investigated and treated aggressively.

Although onset before or after 3 months after transplant is often used to discriminate between acute and chronic GVHD, occasional patients will develop signs and symptoms of acute GVHD after 3 months (late-onset acute GVHD), whereas others will exhibit signs and symptoms of both acute and chronic GVHD (overlap syndrome). There are as yet no data to suggest that these patients should be treated differently than those with classic acute or chronic GVHD.

From 3 to 5% of patients will develop an autoimmune disorder following allogeneic HCT, most commonly autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. Unrelated donor source and chronic GVHD are risk factors, but autoimmune disorders have been reported in patients with no obvious GVHD. Treatment is with prednisone, cyclosporine, or rituximab.

Infection Post-transplant patients, particularly recipients of allogeneic transplantation, require unique approaches to the problem of infection. Early after transplantation, patients are profoundly neutropenic, and because the risk of bacterial infection is so great, most centers place patients on broad spectrum antibiotics once the granulocyte count falls to <500/μL. Prophylaxis against fungal infections reduces rates of infection and improves overall survival. Fluconazole is often used for patients with standard risk, while prophylaxis with mold active agents (voriconizole or posaconazole) should be considered for patients at higher risk, such as those with a prior fungal infection. Patients seropositive for herpes simplex should receive acyclovir prophylaxis. One approach to infection prophylaxis is shown in Table 110-3. Despite these prophylactic measures, most patients will develop fever and signs of infection after transplant. The management of patients who become febrile despite bacterial and fungal prophylaxis is a difficult challenge and is guided by individual aspects of the patient and by the institution's experience.

TABLE 110-3 Approach to Infection Prophylaxis in Allogeneic Transplant Recipients

ORGANISM	AGENT	APPROACH
Bacterial	Levofloxacin	750 mg PO or IV daily
Fungal	Fluconazole	400 mg PO qd to day 75 posttransplant
Pneumocystis carinii	Trimethoprim-sulfamethoxazole	1 double-strength tablet PO bid 2 days/week until day 180 or off immunosuppression
Viral		
Herpes simplex	Acyclovir	800 mg PO bid to day 30
Varicella-zoster	Acyclovir	800 mg PO bid to day 365
Cytomegalovirus	Ganciclovir	5 mg/kg IV bid for 7 days, then 5 (mg/kg)/d 5 days/week to day 100

The general problem of infection in the immunocompromised host is discussed in Chap. 138.

Once patients engraft, the incidence of bacterial infection diminishes; however, patients, particularly allogeneic transplant recipients, remain at significant risk of infection. During the period from engraftment until about 3 months after transplant, the most common causes of infection are gram-positive bacteria, fungi (particularly *Aspergillus*), and viruses including CMV. CMV infection, which in the past was frequently seen and often fatal, can be prevented in seronegative patients transplanted from seronegative donors by the use of either seronegative blood products or products from which the white blood cells have been removed. In seropositive patients or patients transplanted from seropositive donors, the use of ganciclovir, either as prophylaxis beginning at the time of engraftment or initiated when CMV first reactivates as evidenced by development of antigenemia or viremia, can significantly reduce the risk of CMV disease. Foscarnet is effective for some patients who develop CMV antigenemia or infection despite the use of ganciclovir or who cannot tolerate the drug, but can be associated with severe electrolyte wasting.

Pneumocystis jiroveci pneumonia, once seen in 5–10% of patients, can be prevented by treating patients with oral trimethoprim-sulfamethoxazole for 1 week before transplant and resuming the treatment once patients have engrafted.

Respiratory viruses that cause community-acquired infections, including respiratory syncytial virus (RSV), parainfluenza virus, influenza virus and, metapneumovirus can be life threatening or fatal in the post-transplant patient. Protection of patients from infected visitors and staff by avoiding such contacts is critical. Neuraminidase inhibitors are effective for influenza infections. Inhaled ribavirin is sometimes used for RSV.

The risk of infection diminishes considerably beyond 3 months after transplant unless chronic GVHD develops, requiring continuous immunosuppression. Most transplant centers recommend continuing trimethoprim-sulfamethoxazole prophylaxis while patients are receiving any immunosuppressive drugs and also recommend careful monitoring for late CMV reactivation. In addition, many centers recommend prophylaxis against varicella-zoster, using acyclovir for 1 year after transplant. Patients should be revaccinated against tetanus, diphtheria, *Haemophilus influenzae*, polio, and pneumococcal pneumonia starting at 12 months after transplant and against measles, mumps, and rubella (MMR), varicella-zoster virus, and possibly pertussis at 24 months.

TREATMENT OF SPECIFIC DISEASES USING HEMATOPOIETIC CELL TRANSPLANTATION

TREATMENT

Nonmalignant Diseases

IMMUNODEFICIENCY DISORDERS

By replacing abnormal stem cells with cells from a normal donor, HCT can cure patients of a variety of immunodeficiency disorders including severe combined immunodeficiency, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. The widest experience has been with severe combined immunodeficiency disease, where cure rates of 90% can be expected with HLA-identical donors and success rates of 50–70% have been reported using haplotype-mismatched parents as donors **(Table 110-4)**.

APLASTIC ANEMIA

Transplantation from matched siblings after a preparative regimen of high-dose cyclophosphamide and antithymocyte globulin can cure up to 90% of patients age <40 years with severe aplastic anemia. Results in older patients and in recipients of mismatched family member or unrelated marrow are less favorable; therefore, a

TABLE 110-4 Estimated 5-Year Survival Rates Following Transplantation[a]

DISEASE	ALLOGENEIC, %	AUTOLOGOUS, %
Severe combined immunodeficiency	90	N/A
Aplastic anemia	90	N/A
Thalassemia	90	N/A
Acute myeloid leukemia		
First remission	55–60	50
Second remission	40	30
Acute lymphocytic leukemia		
First remission	50	40
Second remission	40	30
Chronic myeloid leukemia		
Chronic phase	70	ID
Accelerated phase	40	ID
Blast crisis	15	ID
Chronic lymphocytic leukemia	50	ID
Myelodysplasia	45	ID
Multiple myeloma—initial therapy	N/A	60
Non-Hodgkin's lymphoma		
First relapse/second remission	40	40
Hodgkin's disease		
First relapse/second remission	40	50

[a]These estimates are generally based on data reported by the International Bone Marrow Transplant Registry. The analysis has not been reviewed by their Advisory Committee.

Abbreviations: ID, insufficient data; N/A, not applicable.

trial of immunosuppressive therapy is generally recommended for such patients before considering transplantation. Transplantation is effective in all forms of aplastic anemia including, for example, the syndromes associated with paroxysmal nocturnal hemoglobinuria and Fanconi's anemia. Patients with Fanconi's anemia are abnormally sensitive to the toxic effects of alkylating agents, and so less intensive preparative regimens must be used in their treatment **(Chap. 98)**.

HEMOGLOBINOPATHIES

Marrow transplantation from an HLA-identical sibling following a preparative regimen of busulfan and cyclophosphamide can cure 80–90% of patients with thalassemia major. The best outcomes can be expected if patients are transplanted before they develop hepatomegaly or portal fibrosis and if they have been given adequate iron chelation therapy. Among such patients, the probabilities of 5-year survival and disease-free survival are 95 and 90%, respectively. Although prolonged survival can be achieved with aggressive chelation therapy, transplantation is the only curative treatment for thalassemia. Transplantation is potentially curative for patients with sickle cell anemia. Two-year survival and disease-free survival rates of 95 and 85%, respectively, have been reported following matched sibling or cord blood transplantation. Decisions about patient selection and the timing of transplantation remain difficult, but transplantation represents a reasonable option for children and young adults who have suffered complications of sickle cell anemia including stroke, recurrent vasoocclusive pain, sickle cell lung disease, or sickle nephropathy **(Chap. 94)**.

OTHER NONMALIGNANT DISEASES

Theoretically, HCT should be able to cure any disease that results from an inborn error of the lymphohematopoietic system. Transplantation has been used successfully to treat congenital disorders of white blood cells such as Kostmann's syndrome, chronic granulomatous disease, and leukocyte adhesion deficiency. Congenital anemias such as Blackfan-Diamond anemia can also be cured with transplantation. Since the penetrance of some congenital marrow failure states is variable, potential family member donors should be carefully screened before use to assure they are not affected. Infantile malignant osteopetrosis is due to an inability of the osteoclast to resorb bone, and because osteoclasts derive from the marrow, transplantation can cure this rare inherited disorder.

HCT has been used as treatment for a number of storage diseases caused by enzymatic deficiencies, such as Gaucher's disease, Hurler's syndrome, Hunter's syndrome, and infantile metachromatic leukodystrophy. Transplantation for these diseases has not been uniformly successful, but treatment early in the course of these diseases, before irreversible damage to extramedullary organs has occurred, increases the chance for success.

Transplantation is being explored as a treatment for severe acquired autoimmune disorders. These trials are based on studies demonstrating that transplantation can reverse autoimmune disorders in animal models and on the observation that occasional patients with coexisting autoimmune disorders and hematologic malignancies have been cured of both with transplantation.

TREATMENT

Malignant Diseases

ACUTE LEUKEMIA

Allogeneic HCT cures 15–20% of patients who do not achieve complete response after induction chemotherapy for acute myeloid leukemia (AML) and is the only form of therapy that can cure such patients. Thus, all patients with AML who are possible transplant candidates should have their HLA type determined soon after diagnosis to enable HCT for those who fail to enter remission. Cure rates of 30–35% are seen when patients are transplanted in second remission or in first relapse. The best results with allogeneic transplantation are achieved when applied during first remission, with disease-free survival rates averaging 55–60%. Meta-analyses of studies comparing matched related donor transplantation to chemotherapy for adult AML patients age <60 years show a survival advantage with transplantation. This advantage is greatest for those with unfavorable-risk AML and is lost in those with favorable-risk disease. While HCT can be performed in patients up to age 75 and possibly beyond, prospective trials comparing HCT with chemotherapy are lacking for older patients. The role of autologous transplantation in the treatment of AML is less well defined. The rates of disease recurrence with autologous transplantation are higher than those seen after allogeneic transplantation, and cure rates are somewhat less.

Similar to patients with AML, adults with acute lymphocytic leukemia who do not achieve a complete response to induction chemotherapy can be cured in 15–20% of cases with immediate transplantation. Cure rates improve to 30–50% in second remission, and therefore transplantation can be recommended for adults who have persistent disease after induction chemotherapy or who have subsequently relapsed. Transplantation in first remission results in cure rates about 55%. Transplantation appears to offer a survival advantage over chemotherapy for patients with high-risk disease, such as those with Philadelphia chromosome–positive disease. Debate continues about whether adults with standard-risk disease should be transplanted in first remission or whether transplantation should be reserved until relapse. Autologous transplantation is associated with a higher relapse rate but a somewhat lower risk of non-relapse mortality when compared to allogeneic transplantation. There is no obvious role of autologous transplantation for acute lymphocytic leukemia in first remission, and for second-remission patients, most experts recommend use of allogeneic stem cells if an appropriate donor is available.

CHRONIC LEUKEMIA

Allogeneic HCT is indicated for patients with chronic myeloid leukemia who are in chronic phase but have failed therapy with two or more tyrosine kinase inhibitors. In such patients, cure rates of 70% can be expected. HCT is also recommended for patients with CML

who present or progress to accelerated phase or blast crisis, although lower cure rates are seen in such patients **(Chap. 101)**.

Although allogeneic transplantation can cure patients with chronic lymphocytic leukemia (CLL), it has not been extensively studied because of the chronic nature of the disease, the age profile of patients and, more recently, the availability of multiple effective therapies. In those cases where it was studied, complete remissions were achieved in the majority of patients, with disease-free survival rates of ~50% at 3 years, despite the advanced stage of the disease at the time of transplant.

MYELODYSPLASIA AND MYELOPROLIFERATIVE DISORDERS

Between 20 and 65% of patients with myelodysplasia appear to be cured with allogeneic transplantation. Results are better among younger patients and those with less advanced disease. However, patients with early-stage myelodysplasia can live for extended periods without intervention, and so transplantation is generally reserved for patients with an International Prognostic Scoring System (IPSS) score of Int-2 or higher, or for selected patients with an IPSS score of Int-1 who have other poor prognostic features **(Chap. 98)**. Allogeneic HCT can cure patients with primary myelofibrosis or myelofibrosis secondary to polycythemia vera or essential thrombocythemia, with 5-year progression-free survival rates in excess of 65% being reported. It may require many months for the fibrosis to resolve.

LYMPHOMA

Patients with disseminated intermediate- or high-grade non-Hodgkin's lymphoma who have not been cured by first-line chemotherapy and are transplanted in first relapse or second remission can still be cured in 40–50% of cases. This represents a clear advantage over results obtained with conventional-dose salvage chemotherapy. It is unsettled whether patients with high-risk disease benefit from transplantation in first remission. Most experts favor the use of autologous rather than allogeneic transplantation for patients with intermediate- or high-grade non-Hodgkin's lymphoma, because fewer complications occur with this approach and survival appears equivalent. Although autologous transplantation results in high response rates in patients with recurrent disseminated indolent non-Hodgkin's lymphoma, the availability of newer agents for this category of patient leaves the role of transplantation unsettled. Reduced-intensity conditioning regimens followed by allogeneic transplantation result in high rates of complete and enduring complete responses in patients with recurrent indolent lymphomas.

The role of transplantation in Hodgkin's disease is similar to that in intermediate- and high-grade non-Hodgkin's lymphoma. With transplantation, 5-year disease-free survival is 20–30% in patients who never achieve a first remission with standard chemotherapy and up to 70% for those transplanted in second remission. Transplantation has no defined role in first remission in Hodgkin's disease.

MYELOMA

Patients with myeloma who have progressed on first-line therapy can sometimes benefit from allogeneic or autologous transplantation. Prospective randomized studies demonstrate that the inclusion of autologous transplantation as part of the initial therapy of patients results in improved disease-free survival and overall survival. Further benefit is seen with the use of lenalidomide maintenance therapy following transplantation. The use of autologous transplantation followed by non-myeloablative allogeneic transplantation has yielded mixed results.

SOLID TUMORS

Patients with testicular cancer in whom first-line platinum-containing chemotherapy has failed can still be cured in ~50% of cases if treated with high-dose chemotherapy with autologous stem cell support, an outcome better than that seen with low-dose salvage chemotherapy. The use of high-dose chemotherapy with autologous stem cell support is being studied for several other solid tumors, including neuroblastoma and pediatric sarcomas. As in most other settings, the best results have been obtained in patients with limited amounts of disease and where the remaining tumor remains sensitive to conventional-dose chemotherapy. Few randomized trials of transplantation in these diseases have been completed.

POSTTRANSPLANT RELAPSE

Patients who relapse following autologous transplantation sometimes respond to further chemotherapy and may be candidates for possible allogeneic transplantation, particularly if the remission following the initial autologous transplant was long. Several options are available for patients who relapse following allogeneic transplantation. Treatment with infusions of unirradiated donor lymphocytes results in complete responses in as many as 75% of patients with chronic myeloid leukemia, 40% in myelodysplasia, 25% in AML, and 15% in myeloma have been reported. Major complications of donor lymphocyte infusions include transient myelosuppression and the development of GVHD. These complications depend on the number of donor lymphocytes given and the schedule of infusions, with less GVHD seen with lower dose, fractionated schedules.

FURTHER READING

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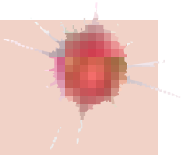
Section 3 Disorders of Hemostasis



111 Disorders of Platelets and Vessel Wall

Barbara A. Konkle

Hemostasis is a dynamic process in which the platelet and the blood vessel wall play key roles. Platelets become activated upon adhesion to von Willebrand factor (VWF) and collagen in the exposed subendothelium after injury. Platelet activation is also mediated through shear forces imposed by blood flow itself, particularly in areas where the vessel wall is diseased, and is also affected by the inflammatory state of the endothelium. The activated platelet surface provides the major physiologic site for coagulation factor activation, which results in further platelet activation and fibrin formation. Genetic and acquired

influences on the platelet and vessel wall, as well as on the coagulation and fibrinolytic systems, determine whether normal hemostasis or bleeding or clotting symptoms will result.

THE PLATELET

Platelets are released from the megakaryocyte, likely under the influence of flow in the capillary sinuses. The normal blood platelet count is 150,000–450,000/μL. The major regulator of platelet production is the hormone thrombopoietin (TPO), which is synthesized in the liver. Synthesis is increased with inflammation and specifically by interleukin 6. TPO binds to its receptor on platelets and megakaryocytes, by which it is removed from the circulation. Thus a reduction in platelet and megakaryocyte mass increases the level of TPO, which then stimulates platelet production. Platelets circulate with an average life span of 7–10 days. Approximately one-third of the platelets reside in the spleen, and this number increases in proportion to splenic size, although the platelet count rarely decreases to <40,000/μL as the spleen enlarges. Platelets are physiologically very active, but are anucleate, and thus have limited capacity to synthesize new proteins.

Normal vascular endothelium contributes to preventing thrombosis by inhibiting platelet function **(Chap. 61)**. When vascular endothelium is injured, these inhibitory effects are overcome, and platelets adhere to the exposed intimal surface primarily through VWF, a large multimeric protein present in both plasma and in the extracellular matrix of the subendothelial vessel wall. Platelet adhesion results in the generation of intracellular signals that lead to activation of the platelet glycoprotein (Gp) IIb/IIIa ($\alpha_{IIb}\beta_3$) receptor and resultant platelet aggregation.

Activated platelets undergo release of their granule contents, which include nucleotides, adhesive proteins, growth factors, and procoagulants that serve to promote platelet aggregation and blood clot formation and influence the environment of the forming clot. During platelet aggregation, additional platelets are recruited to the site of injury, leading to the formation of an occlusive platelet thrombus. The platelet plug is stabilized by the fibrin mesh that develops simultaneously as the product of the coagulation cascade.

THE VESSEL WALL

Endothelial cells line the surface of the entire circulatory tree, totaling $1–6 \times 10^{13}$ cells, enough to cover a surface area equivalent to about six tennis courts. The endothelium is physiologically active, controlling vascular permeability, flow of biologically active molecules and nutrients, blood cell interactions with the vessel wall, the inflammatory response, and angiogenesis.

The endothelium normally presents an antithrombotic surface **(Chap. 61)** but rapidly becomes prothrombotic when stimulated, which promotes coagulation, inhibits fibrinolysis, and activates platelets. In many cases, endothelium-derived vasodilators are also platelet inhibitors (e.g., nitric oxide) and, conversely, endothelium-derived vasoconstrictors (e.g., endothelin) can also be platelet activators. The net effect of vasodilation and inhibition of platelet function is to promote blood fluidity, whereas the net effect of vasoconstriction and platelet activation is to promote thrombosis. Thus, blood fluidity and hemostasis are regulated by the balance of antithrombotic/prothrombotic and vasodilatory/vasoconstrictor properties of endothelial cells.

DISORDERS OF PLATELETS

THROMBOCYTOPENIA

Thrombocytopenia results from one or more of three processes: (1) decreased bone marrow production; (2) sequestration, usually in an enlarged spleen; and/or (3) increased platelet destruction. Disorders of production may be either inherited or acquired. In evaluating a patient with thrombocytopenia, a key step is to review the peripheral blood smear and to first rule out "pseudothrombocytopenia," particularly in a patient without an apparent cause for the thrombocytopenia. Pseudothrombocytopenia **(Fig. 111-1*B*)** is an in vitro artifact resulting from platelet agglutination via antibodies (usually IgG, but also IgM and IgA) when the calcium content is decreased by blood collection in ethylenediamine tetraacetic (EDTA) (the anticoagulant present in tubes [purple top] used to collect blood for complete blood counts [CBCs]). If a low platelet count is obtained in EDTA-anticoagulated blood, a blood smear should be evaluated and a platelet count determined in blood collected into sodium citrate (blue top tube) or heparin (green top tube), or a smear of freshly obtained unanticoagulated blood, such as from a finger stick, can be examined.

APPROACH TO THE PATIENT

Thrombocytopenia

The history and physical examination, results of the CBC, and review of the peripheral blood smear are all critical components in the initial evaluation of thrombocytopenic patients **(Fig. 111-2)**. The overall health of the patient and whether he or she is receiving drug treatment will influence the differential diagnosis. A healthy young adult with thrombocytopenia will have a much more limited differential diagnosis than an ill hospitalized patient who is receiving multiple medications. Except in unusual inherited disorders, decreased platelet production usually results from bone marrow disorders that also affect red blood cell (RBC) and/or white blood cell (WBC) production. Because myelodysplasia can present with isolated thrombocytopenia, the bone marrow should be examined in patients presenting with isolated thrombocytopenia who are older than 60 years of age. While inherited thrombocytopenia is rare, any prior platelet counts should be retrieved and a family history regarding thrombocytopenia obtained. A careful history of drug ingestion should be obtained, including nonprescription and herbal remedies, because drugs are the most common cause of thrombocytopenia.

The physical examination can document an enlarged spleen, evidence of chronic liver disease, and other underlying disorders. Mild to moderate splenomegaly may be difficult to appreciate in many individuals due to body habitus and/or obesity but can be easily assessed by abdominal ultrasound. A platelet count of ~5000–10,000 is required to maintain vascular integrity in the microcirculation. When the count is markedly decreased, petechiae first appear in areas of increased venous pressure, the ankles and feet in an ambulatory patient. Petechiae are pinpoint, nonblanching hemorrhages and are usually a sign of a decreased platelet number and not platelet dysfunction. Wet purpura, blood blisters that form on the oral mucosa, are thought to denote an increased risk of life-threatening hemorrhage in the thrombocytopenic patient. Excessive bruising is seen in disorders of both platelet number and function.

Infection-Induced Thrombocytopenia Many viral and bacterial infections result in thrombocytopenia and are the most common noniatrogenic cause of thrombocytopenia. This may or may not be associated with laboratory evidence of disseminated intravascular coagulation (DIC), which is most commonly seen in patients with systemic infections with gram-negative bacteria. Infections can affect both platelet production and platelet survival. In addition, immune mechanisms can be at work, as in infectious mononucleosis and early HIV infection. Late in HIV infection, pancytopenia and decreased and dysplastic platelet production are more common. Immune-mediated thrombocytopenia in children usually follows a viral infection and almost always resolves spontaneously. This association of infection with immune thrombocytopenic purpura is less clear in adults.

Drug-Induced Thrombocytopenia Many drugs have been associated with thrombocytopenia. A predictable decrease in platelet count occurs after treatment with many chemotherapeutic drugs due to bone marrow suppression **(Chap. 69)**. Drugs that cause isolated thrombocytopenia and have been confirmed with positive laboratory testing are listed in **Table 111-1**, but all drugs should be suspect in a patient with thrombocytopenia without an apparent cause and should be stopped, or substituted, if possible. A helpful website, Platelets on the Internet (*http://www.ouhsc.edu/platelets/*), lists drugs and supplements reported to have caused thrombocytopenia and the level of evidence supporting the association. Although not as well studied, herbal and

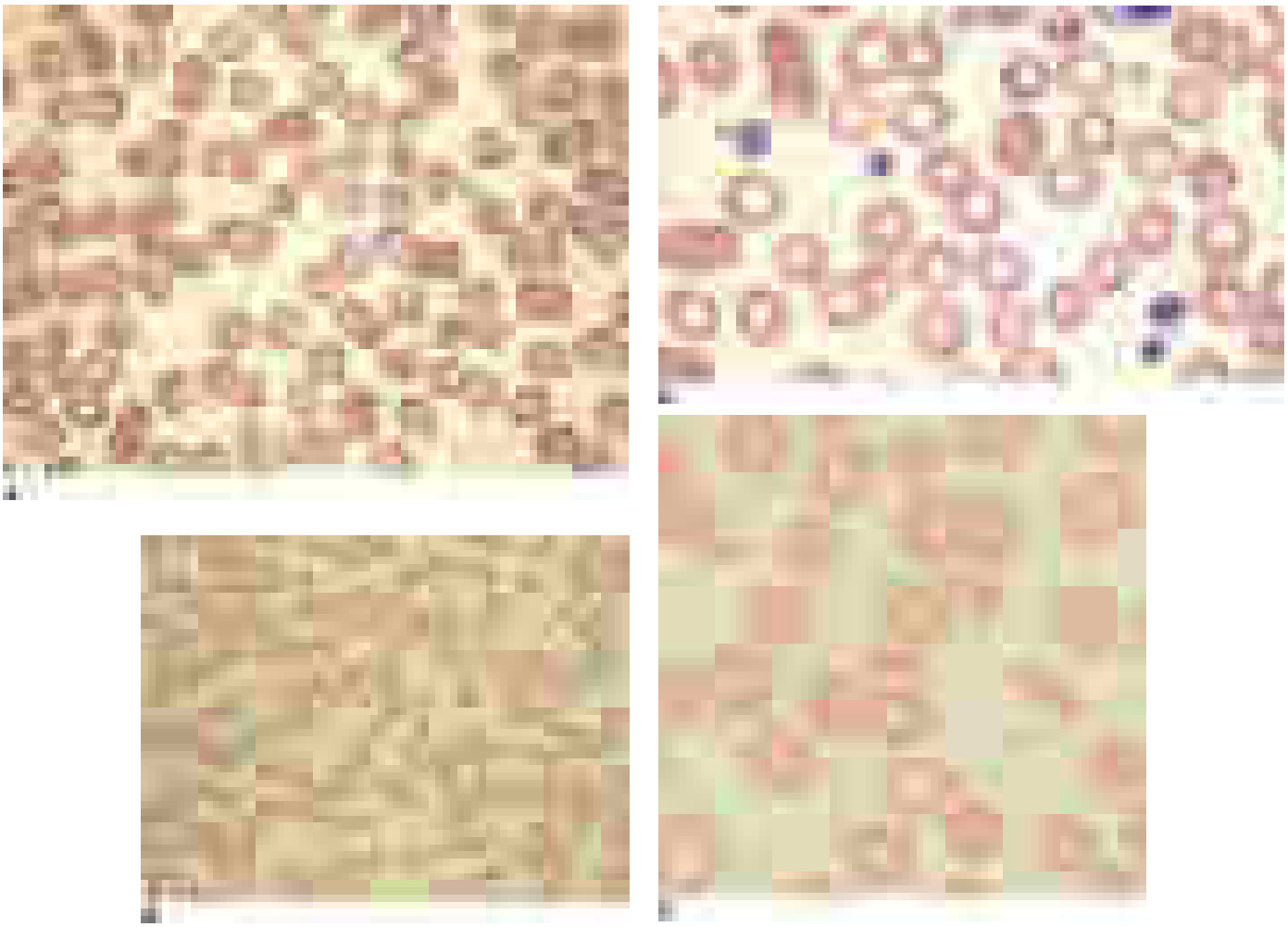


FIGURE 111-1 Photomicrographs of peripheral blood smears. ***A.*** Normal peripheral blood. ***B.*** Platelet clumping in pseudothrombocytopenia. ***C.*** Abnormal large platelet in autosomal dominant macrothrombocytopenia. ***D.*** Schistocytes and decreased platelets in microangiopathic hemolytic anemia.

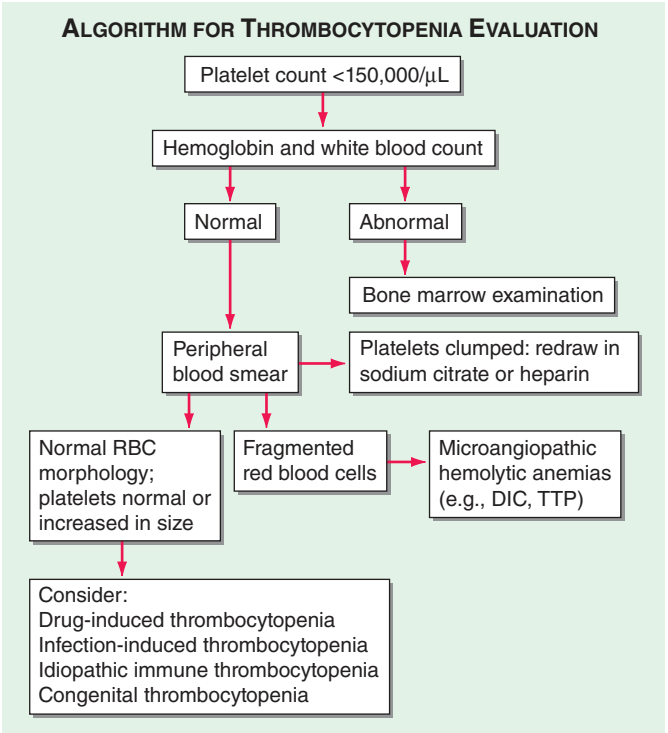


FIGURE 111-2 Algorithm for evaluating the thrombocytopenic patient. DIC, disseminated intravascular coagulation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura.

over-the-counter preparations may also result in thrombocytopenia and should be discontinued in patients who are thrombocytopenic.

Classic drug-dependent antibodies are antibodies that react with specific platelet surface antigens and result in thrombocytopenia only when the drug is present. Many drugs are capable of inducing these

TABLE 111-1 Drugs Reported as Definitely or Probably Causing Isolated Thrombocytopenia[a]

Abciximab	Mirtazapine
Acetaminophen	Naproxen
Amiodarone	Oxaliplatin
Amlodipine	Penicillin
Ampicillin	Phenytoin
Carbamazepine	Piperacillin
Ceftriaxone	Quinine
Cephamandole	Quinidine
Ciprofloxacin	Ranitidine
Diazepam	Rosiglitazone
Eptifibatide	Roxifiban
Furosemide	Sulfisoxazole
Gold	Suramin
Haloperidol	Tirofiban
Heparin	Tranilast
Ibuprofen	Trimethoprim/sulfamethoxazole
Lorazepam	Vancomycin

[a]Based on scoring requiring a compatible clinical picture and positive laboratory testing.

Source: Adapted from DM Arnold et al: J Thromb Hemost 11:169, 2013.

antibodies, but for some reason, they are more common with quinine and sulfonamides. Drug-dependent antibody binding can be demonstrated by laboratory assays, showing antibody binding in the presence of, but not without, the drug present in the assay. The thrombocytopenia typically occurs after a period of initial exposure (median length 21 days), or upon reexposure, and usually resolves in 7–10 days after drug withdrawal. The thrombocytopenia caused by the platelet Gp IIb/IIIa inhibitory drugs, such as abciximab, differs in that it may occur within 24 h of initial exposure. This appears to be due to the presence of naturally occurring antibodies that cross-react with the drug bound to the platelet.

Heparin-Induced Thrombocytopenia Drug-induced thrombocytopenia due to heparin differs from that seen with other drugs in two major ways. (1) The thrombocytopenia is not usually severe, with nadir counts rarely <20,000/μL. (2) Heparin-induced thrombocytopenia (HIT) is not associated with bleeding and, in fact, markedly increases the risk of thrombosis. HIT results from antibody formation to a complex of the platelet-specific protein platelet factor 4 (PF4) and heparin. The anti-heparin/PF4 antibody can activate platelets through the FcγRIIa receptor and also activate monocytes and endothelial cells. Many patients exposed to heparin develop antibodies to heparin/PF4, but do not appear to have adverse consequences. A fraction of those who develop antibodies will develop HIT, and a portion of those (up to 50%) will develop thrombosis (HITT).

HIT can occur after exposure to low-molecular-weight heparin (LMWH) as well as unfractionated heparin (UFH), although it is more common with the latter. Most patients develop HIT after exposure to heparin for 5–14 days **(Fig. 111-3)**. It occurs before 5 days in those who were exposed to heparin in the prior few weeks or months (<~100 days) and have circulating anti-heparin/PF4 antibodies. Rarely, thrombocytopenia and thrombosis begin several days after all heparin has been stopped (termed *delayed-onset HIT*). The "4T's" have been recommended to be used in a diagnostic algorithm for HIT: *t*hrombocytopenia, *t*iming of platelet count drop, *thrombosis* and other sequelae such as localized skin reactions, and o*t*her causes of thrombocytopenia not evident. Application of the 4T scoring system is very useful in excluding a diagnosis of HIT but will result in over-diagnosis of HIT in situations where thrombocytopenia and thrombosis due to other etiologies are common, such as in the intensive care unit.

LABORATORY TESTING FOR HIT HIT (anti-heparin/PF4) antibodies can be detected using two types of assays. The most widely available is an enzyme-linked immunoassay (ELISA) with PF4/polyanion complex as the antigen. Because many patients develop antibodies but do not develop clinical HIT, the test has a low specificity for the diagnosis of HIT. This is especially true in patients who have undergone cardiopulmonary bypass surgery, where ~50% of patients develop these antibodies postoperatively. IgG-specific ELISAs increase specificity but may decrease sensitivity. The other assay is a platelet activation assay, most commonly the serotonin release assay, which measures the ability of the patient's serum to activate platelets in the presence of heparin in a concentration-dependent manner. This test has lower sensitivity but higher specificity than the ELISA. However, HIT remains a clinical diagnosis.

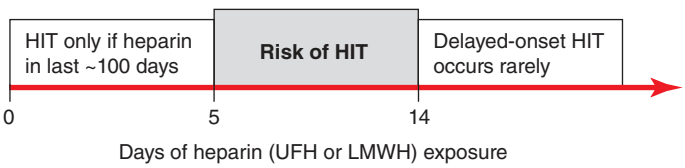


FIGURE 111-3 Time course of heparin-induced thrombocytopenia (HIT) development after heparin exposure. The timing of development after heparin exposure is a critical factor in determining the likelihood of HIT in a patient. HIT occurs early after heparin exposure in the presence of preexisting heparin/platelet factor 4 (PF4) antibodies, which disappear from circulation by ~100 days following a prior exposure. Rarely, HIT may occur later after heparin exposure (termed delayed-onset HIT). In this setting, heparin/PF4 antibody testing is usually markedly positive. HIT can occur after exposure to either unfractionated (UFH) or low-molecular-weight heparin (LMWH).

TREATMENT

Heparin-Induced Thrombocytopenia

Early recognition is key in treatment of HIT, with prompt discontinuation of heparin and use of alternative anticoagulants if bleeding risk does not outweigh thrombotic risk. Thrombosis is a common complication of HIT, even after heparin discontinuation, and can occur in both the venous and arterial systems. Patients with higher anti-heparin/PF4 antibody titers may have a higher risk of thrombosis. In patients diagnosed with HIT, imaging studies to evaluate the patient for thrombosis (at least lower extremity duplex Doppler imaging) are recommended. Patients requiring anticoagulation should be switched from heparin to an alternative anticoagulant. The direct thrombin inhibitor (DTI) argatroban is effective in HITT. The DTI bivalirudin and the antithrombin-binding pentasaccharide fondaparinux are also effective but not approved by the U.S. Food and Drug Administration (FDA) for this indication. Danaparoid, a mixture of glycosaminoglycans with anti-Xa activity, has been used extensively for the treatment of HITT; it is no longer available in the United States but is available in other countries. HIT antibodies cross-react with LMWH, and these preparations should not be used in the treatment of HIT.

Because of the high rate of thrombosis in patients with HIT, anticoagulation should be considered, even in the absence of thrombosis. In patients with thrombosis, patients can be transitioned to warfarin, with treatment usually for 3–6 months. In patients without thrombosis, the duration of anticoagulation needed is undefined. An increased risk of thrombosis is present for at least 1 month after diagnosis; however, most thromboses occur early, and whether thrombosis occurs later if the patient is initially anticoagulated is unknown. Options include continuing anticoagulation until a few days after platelet recovery or for 1 month. Introduction of warfarin alone in the setting of HIT or HITT may precipitate thrombosis, particularly venous gangrene, presumably due to clotting activation and severely reduced levels of proteins C and S. Warfarin therapy, if started, should be overlapped with a DTI or fondaparinux and started after resolution of the thrombocytopenia and lessening of the prothrombotic state. Evidence for use of an oral direct Xa inhibitor in this setting is growing, but more data are needed to establish efficacy.

Immune Thrombocytopenic Purpura Immune thrombocytopenic purpura (ITP; also termed *idiopathic thrombocytopenic purpura*) is an acquired disorder in which there is immune-mediated destruction of platelets and possibly inhibition of platelet release from the megakaryocyte. In children, it is usually an acute disease, most commonly following an infection, and with a self-limited course. In adults, it is a more chronic disease, although in some adults, spontaneous remission occurs, usually within months of diagnosis. ITP is termed *secondary* if it is associated with an underlying disorder; autoimmune disorders, particularly systemic lupus erythematosus (SLE), and infections, such as HIV and hepatitis C, are common causes. The association of ITP with *Helicobacter pylori* infection is unclear but appears to have a geographic distribution.

ITP is characterized by mucocutaneous bleeding and a low, often very low, platelet count, with an otherwise normal peripheral blood cells and smear. Patients usually present either with ecchymoses and petechiae, or with thrombocytopenia incidentally found on a routine CBC. Mucocutaneous bleeding, such as oral mucosa, gastrointestinal, or heavy menstrual bleeding, may be present. Rarely, life-threatening, including central nervous system, bleeding can occur. Wet purpura (blood blisters in the mouth) and retinal hemorrhages may herald life-threatening bleeding.

LABORATORY TESTING IN ITP Laboratory testing for antibodies (serologic testing) is usually not helpful due to the low sensitivity and specificity of the current tests. Bone marrow examination can be reserved for those who have other signs or laboratory abnormalities not explained by ITP or in patients who do not respond to initial therapy. The peripheral blood smear may show large platelets, with otherwise normal

morphology. Depending on the bleeding history, iron-deficiency anemia may be present.

Laboratory testing is performed to evaluate for secondary causes of ITP and should include testing for HIV infection and hepatitis C (and other infections if indicated). Serologic testing for SLE, serum protein electrophoresis, immunoglobulin levels to potentially detect hypogammaglobulinemia, selective testing for IgA deficiency or monoclonal gammopathies, and testing for *H. pylori* infection should be considered, depending on the clinical circumstance. If anemia is present, direct antiglobulin testing (Coombs' test) should be performed to rule out combined autoimmune hemolytic anemia with ITP (Evans' syndrome).

TREATMENT

Immune Thrombocytopenic Purpura

The treatment of ITP uses drugs that decrease reticuloendothelial uptake of the antibody-bound platelet, decrease antibody production, and/or increase platelet production. The diagnosis of ITP does not necessarily mean that treatment must be instituted. Patients with platelet counts >30,000/μL appear not to have increased mortality related to the thrombocytopenia.

Initial treatment in patients without significant bleeding symptoms, severe thrombocytopenia (<5000/μL), or signs of impending bleeding (such as retinal hemorrhage or large oral mucosal hemorrhages) can be instituted as an outpatient using single agents. Traditionally, this has been prednisone at 1 mg/kg, although Rh_0(D) immune globulin therapy (WinRho SDF), at 50–75 μg/kg, is also being used in this setting. Rh_0(D) immune globulin must be used only in Rh-positive patients because the mechanism of action is production of limited hemolysis, with antibody-coated cells "saturating" the Fc receptors, inhibiting Fc receptor function. Monitoring patients for 8 h after infusion is now advised by the FDA because of the rare complication of severe intravascular hemolysis. Intravenous gamma globulin (IVIgG), which is pooled, primarily IgG antibodies, also blocks the Fc receptor system, but appears to work primarily through different mechanism(s). IVIgG has more efficacy than anti-Rh_0(D) in postsplenectomized patients. IVIgG is dosed at 1–2 g/kg total, given over 1–5 days. Side effects are usually related to the volume of infusion and infrequently include aseptic meningitis and renal failure. All immunoglobulin preparations are derived from human plasma and undergo treatment for viral inactivation.

For patients with severe ITP and/or symptoms of bleeding, hospital admission and combined-modality therapy is given using high-dose glucocorticoids with IVIgG or anti-Rh_0(D) therapy and, as needed, additional immunosuppressive agents. Rituximab, an anti-CD20 (B cell) antibody, has shown efficacy in the treatment of refractory ITP, although long-lasting remission only occurs in ~30% of patients.

Splenectomy has been used for treatment of patients who relapse after glucocorticoids are tapered. Splenectomy remains an important treatment option; however, more patients than previously thought will go into a remission over time. Observation, if the platelet count is high enough, or intermittent treatment with anti-Rh_0(D) or IVIgG, or initiation of treatment with a TPO receptor agonist (see below) may be a reasonable approach to see if the ITP will resolve. Vaccination against encapsulated organisms (especially pneumococcus, but also meningococcus and *Haemophilus influenzae*, depending on patient age and potential exposure) is recommended before splenectomy. Accessory spleen(s) are a very rare cause of relapse.

TPO receptor agonists are available for the treatment of ITP. This approach stems from the finding that many patients with ITP do not have increased TPO levels, as was previously hypothesized. TPO levels reflect megakaryocyte mass, which is usually normal in ITP. TPO levels are not increased in the setting of platelet destruction. Two agents, one administered subcutaneously (romiplostim) and another orally (eltrombopag), are effective in raising platelet counts in patients with ITP and are recommended for adults at risk of bleeding who relapse after splenectomy or who have been unresponsive to at least one other therapy, particularly in those who have a contraindication to splenectomy. However, with the recognition that ITP will resolve spontaneously in some adult patients, short-term treatment with a TPO agonist can be considered before splenectomy in patients who need therapy. Eltrombopag is FDA approved for use in children over 1 year of age. Romiplostim is not yet FDA approved in children but a randomized trial supports efficacy.

Inherited Thrombocytopenia Thrombocytopenia is rarely inherited, either as an isolated finding or as part of a syndrome, and may be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern. Many forms of autosomal dominant thrombocytopenia are now known to be associated with mutations in the nonmuscle myosin heavy chain *MYH9* gene. Interestingly, these include the May-Hegglin anomaly, and Sebastian, Epstein's, and Fechtner syndromes, all of which have distinct distinguishing features. A common feature of these disorders is large platelets (Fig. 111-1*C*). Autosomal recessive disorders include congenital amegakaryocytic thrombocytopenia, thrombocytopenia with absent radii, and Bernard-Soulier syndrome. The latter is primarily a functional platelet disorder due to absence of Gp Ib-IX-V, the VWF adhesion receptor. X-linked disorders include Wiskott-Aldrich syndrome and a dyshematopoietic syndrome resulting from a mutation in *GATA-1*, an important transcriptional regulator of hematopoiesis.

THROMBOTIC THROMBOCYTOPENIC PURPURA AND HEMOLYTIC-UREMIC SYNDROME

Thrombotic thrombocytopenic microangiopathies are a group of disorders characterized by thrombocytopenia, a microangiopathic hemolytic anemia evident by fragmented RBCs (Fig. 111-1*D*) and laboratory evidence of hemolysis, and microvascular thrombosis. They include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), as well as syndromes complicating bone marrow transplantation, certain medications and infections, pregnancy, and vasculitis. In DIC, although thrombocytopenia and microangiopathy are seen, a coagulopathy predominates, with consumption of clotting factors and fibrinogen resulting in an elevated prothrombin time (PT) and often activated partial thromboplastin time (aPTT). The PT and aPTT are characteristically normal in TTP or HUS.

Thrombotic Thrombocytopenic Purpura TTP and HUS were previously considered overlap syndromes. However, with better understanding of the pathophysiology of both TTP and HUS they are clearly separate entities. TTP was first described in 1924 by Eli Moschcowitz and characterized by a pentad of findings that include microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic findings, and fever. The full-blown syndrome is less commonly seen now, probably due to earlier diagnosis. The introduction of treatment with plasma exchange markedly improved the prognosis in patients, with a decrease in mortality from 85–100% to 10–30%.

The pathogenesis of inherited (Upshaw-Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, the metalloprotease ADAMTS13, which cleaves VWF. VWF is normally secreted as ultra-large multimers, which are then cleaved by ADAMTS13. The persistence of ultra-large VWF molecules is thought to contribute to pathogenic platelet adhesion and aggregation **(Fig. 111-4)**. This defect alone, however, is not sufficient to result in TTP because individuals with a congenital absence of ADAMTS13 develop TTP only episodically. The level of ADAMTS13 activity, as well as antibodies, can be detected by laboratory assays. ADAMTS13 activity levels of <10% are more clearly associated with idiopathic (antibody-mediated) TTP.

Idiopathic TTP appears to be more common in women than in men. No geographic or racial distribution has been defined. TTP is more common in patients with HIV infection and in pregnant women. Medication-related microangiopathic hemolytic anemia may be secondary to antibody formation (ticlopidine and possibly clopidogrel) or direct endothelial toxicity (cyclosporine, mitomycin C, tacrolimus, quinine), although this is not always so clear, and fear of withholding treatment, as well as lack of other treatment alternatives, may result in initial application of plasma exchange. However, withdrawal, or

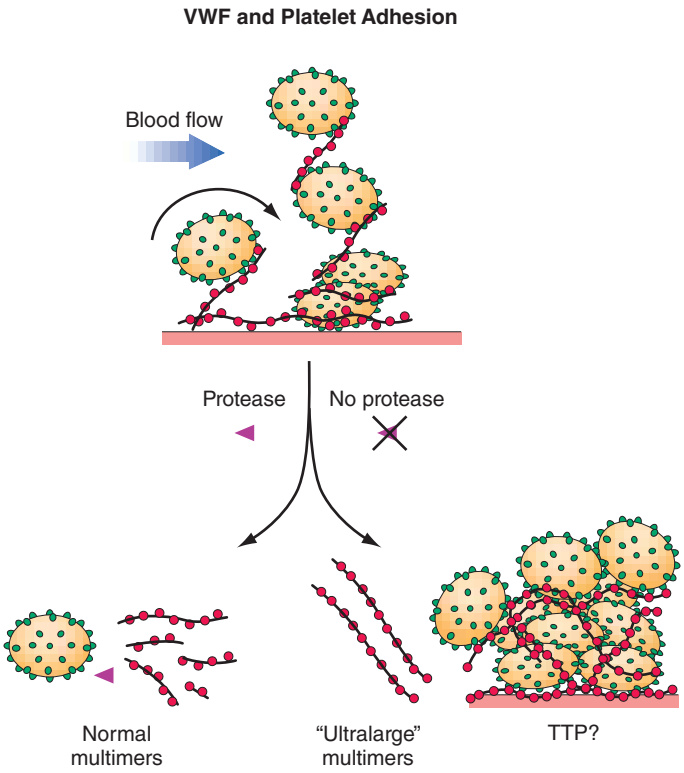


FIGURE 111-4 Pathogenesis of thrombotic thrombocytopenic purpura (TTP). Normally the ultra-high-molecular-weight multimers of von Willebrand factor (VWF) produced by the endothelial cells are processed into smaller multimers by a plasma metalloproteinase called ADAMTS13. In TTP, the activity of the protease is inhibited, and the ultra-high-molecular-weight multimers of VWF initiate platelet aggregation and thrombosis.

reduction in dose, of endothelial toxic agents usually decreases the microangiopathy.

TREATMENT

Thrombotic Thrombocytopenic Purpura

TTP is a devastating disease if not diagnosed and treated promptly. In patients presenting with new thrombocytopenia, with or without evidence of renal insufficiency and other elements of classic TTP, laboratory data should be obtained to rule out DIC and to evaluate for evidence of microangiopathic hemolytic anemia. Findings to support the TTP diagnosis include an increased lactate dehydrogenase and indirect bilirubin, decreased haptoglobin, and increased reticulocyte count, with a negative direct antiglobulin test. The peripheral smear should be examined for evidence of schistocytes (Fig. 111-1*D*). Polychromasia is usually also present due to the increased number of young red blood cells, and nucleated RBCs are often present, which is thought to be due to infarction in the microcirculatory system of the bone marrow.

Plasma exchange remains the mainstay of treatment of TTP. ADAMTS13 antibody-mediated TTP (idiopathic TTP) appears to respond best to plasma exchange. Plasma exchange is continued until the platelet count is normal and signs of hemolysis are resolved for at least 2 days. Although never evaluated in clinical trials, the use of glucocorticoids seems a reasonable approach, but should only be used as an adjunct to plasma exchange. Additionally, other immunomodulatory therapies have been reported to be successful in refractory or relapsing TTP, including rituximab, vincristine, cyclophosphamide, and splenectomy, with rituximab having the most evidence for efficacy. A significant relapse rate is noted; 25–45% of patients relapse within 30 days of initial "remission," and 12–40% of patients have late relapses. Relapses are more frequent in patients with severe ADAMTS13 deficiency at presentation.

Hemolytic-Uremic Syndrome HUS is a syndrome characterized by acute renal failure, microangiopathic hemolytic anemia, and thrombocytopenia. It is seen preceded by an episode of diarrhea, often hemorrhagic in nature, predominantly in children. *Escherichia coli* O157:H7 is the most frequent, although not only, etiologic serotype. HUS not associated with diarrhea is more heterogeneous in presentation and course. Atypical HUS (aHUS) is usually due to genetic defects that result in chronic complement activation or antibodies directed against complement regulatory proteins. Laboratory testing for DNA variants in complement regulatory genes is available, although assigning pathogenicity to variants remains challenging. Currently there is not a functional assay that is diagnostic of the disease.

TREATMENT

Hemolytic-Uremic Syndrome

Treatment of HUS is primarily supportive. In HUS associated with diarrhea, many (~40%) children require at least some period of support with dialysis; however, the overall mortality is <5%. In HUS not associated with diarrhea, the mortality is higher, ~26%. Plasma infusion or plasma exchange has not been shown to alter the overall course. ADAMTS13 levels are generally reported to be normal in HUS, although occasionally they have been reported to be decreased. In patients with aHUS, eculizumab, a humanized monoclonal antibody against C5 that blocks terminal complement, has efficacy in resolution of HUS and improving or preserving renal function. Patients with aHUS may initially be treated with plasma exchange, until the ADAMTS13 level is returned and the diagnosis more clear, since aHUS remains a diagnosis of exclusion. However, plasma exchange has not been shown to affect clinical outcomes in aHUS.

THROMBOCYTOSIS

Thrombocytosis is almost always due to (1) iron deficiency; (2) inflammation, cancer, or infection (reactive thrombocytosis); or (3) an underlying myeloproliferative process (essential thrombocythemia or polycythemia vera) (Chap. 99) or, rarely, the 5q– myelodysplastic process (Chap. 98). Patients presenting with an elevated platelet count should be evaluated for underlying inflammation or malignancy, and iron deficiency should be ruled out. Thrombocytosis in response to acute or chronic inflammation has not been clearly associated with an increased thrombotic risk. In fact, patients with markedly elevated platelet counts (>1.5 million), usually seen in the setting of a myeloproliferative disorder, have an increased risk of bleeding. This appears to be due, at least in part, to acquired von Willebrand disease (VWD) due to platelet-VWF binding and removal from the circulation.

QUALITATIVE DISORDERS OF PLATELET FUNCTION

Inherited Disorders of Platelet Function Inherited platelet function disorders are thought to be relatively rare, although the prevalence of mild disorders of platelet function is unclear, in part because our testing for such disorders is suboptimal. Rare qualitative disorders include the autosomal recessive disorders Glanzmann's thrombasthenia (absence of the platelet Gp IIb/IIIa receptor) and Bernard-Soulier syndrome (absence of the platelet Gp Ib-IX-V receptor). Both are inherited in an autosomal recessive fashion and present with bleeding symptoms in childhood.

Platelet storage pool disorder (SPD) is the classic autosomal dominant qualitative platelet disorder. This results from abnormalities of platelet granule formation. It is also seen as a part of inherited disorders of granule formation, such as Hermansky-Pudlak syndrome. Bleeding symptoms in SPD are variable, but often are mild. The most common inherited disorders of platelet function prevent normal secretion of granule content and are termed *secretion defects*. Few of these abnormalities have been dissected at the molecular level, but they likely result from various DNA variants.

TREATMENT

Inherited Disorders of Platelet Dysfunction

Bleeding symptoms or prevention of bleeding in patients with severe platelet dysfunction frequently requires platelet transfusion. Care is taken to limit the risk of alloimmunization by limiting exposure, using HLA-matched leuko-depleted platelet concentrates for transfusion. Platelet disorders associated with milder bleeding symptoms frequently respond to desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]). DDAVP increases plasma VWF and factor VIII levels; it may also have a direct effect on platelet function. Particularly for mucosal bleeding symptoms, antifibrinolytic therapy (ε-aminocaproic acid or tranexamic acid) is used alone or in conjunction with DDAVP or platelet therapy.

Acquired Disorders of Platelet Function Acquired platelet dysfunction is common, usually due to medications, either intentionally as with antiplatelet therapy or unintentionally as with high-dose penicillins. Acquired platelet dysfunction occurs in uremia. This is likely multifactorial, but the resultant effect is defective adhesion and activation. The platelet defect is improved most by dialysis but may also be improved by increasing the hematocrit to 27–32%, giving DDAVP (0.3 μg/kg), or use of conjugated estrogens. Platelet dysfunction also occurs with cardiopulmonary bypass due to the effect of the artificial circuit on platelets, and bleeding symptoms respond to platelet transfusion. Platelet dysfunction seen with underlying hematologic disorders can result from nonspecific interference by circulating paraproteins or intrinsic platelet defects in myeloproliferative and myelodysplastic syndromes.

VON WILLEBRAND DISEASE

VWD is the most common inherited bleeding disorder. Estimates from laboratory data suggest a prevalence of ~1%, but data based on symptomatic individuals suggest that it is closer to 0.1% of the population. VWF serves two roles: (1) as the major adhesion molecule that tethers the platelet to the exposed subendothelium; and (2) as the binding protein for factor VIII (FVIII), resulting in significant prolongation of the FVIII half-life in circulation. The platelet-adhesive function of VWF is critically dependent on the presence of large VWF multimers, whereas FVIII binding is not. Most of the symptoms of VWD are "platelet-like" except in more severe VWD when the FVIII is low enough to produce symptoms similar to those found in FVIII deficiency (hemophilia A).

VWD has been classified into three major types, with four subtypes of type 2 (Table 111-2; Fig. 111-5). By far the most common type of VWD is type 1 disease, with a parallel decrease in VWF protein, VWF function, and FVIII levels, accounting for at least 80% of cases. Patients have predominantly mucosal bleeding symptoms, although postoperative bleeding can also be seen. Bleeding symptoms are very uncommon in infancy and usually manifest later in childhood with excessive bruising and epistaxis. Because these symptoms occur commonly in childhood, the clinician should particularly note bruising at sites unlikely to be traumatized and/or prolonged epistaxis requiring medical attention. Menorrhagia is a common manifestation of VWD. Menstrual bleeding resulting in anemia should warrant an evaluation for VWD and, if negative, functional platelet disorders. Frequently, mild type 1 VWD first manifests with dental extractions, particularly wisdom tooth extraction, or tonsillectomy.

Not all patients with low VWF levels have bleeding symptoms. Whether patients bleed or not will depend on the overall hemostatic balance they have inherited, along with environmental influences and the type of hemostatic challenges they experience. Although the inheritance of VWD is autosomal, many factors modulate both VWF levels and bleeding symptoms. These have not all been defined, but include blood type, thyroid hormone status, race, stress, exercise, hormonal (both endogenous and exogenous) influences, and modulators of VWF clearance. Patients with type O blood have VWF protein levels of approximately one-half that of patients with AB blood type; and, in fact, the normal range for patients with type O blood overlaps that which has been considered diagnostic for VWD. A mildly decreased VWF level should be viewed more as a risk factor for bleeding than as an actual disease.

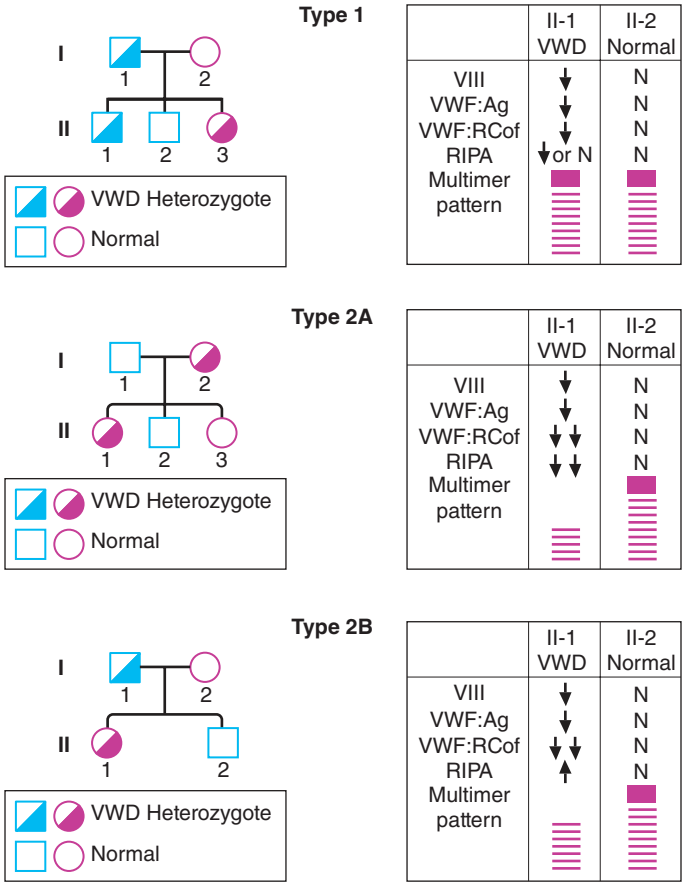


FIGURE 111-5 Pattern of inheritance and laboratory findings in von Willebrand disease (VWD). The assays of platelet function include a coagulation assay of factor VIII bound and carried by von Willebrand factor (VWF), abbreviated as VIII; immunoassay of total VWF protein (VWF:Ag); bioassay of the ability of patient plasma to support ristocetin-induced agglutination of normal platelets (VWF:RCoF), a measure of VWF activity; and ristocetin-induced aggregation of patient platelets, abbreviated RIPA. The multimer pattern illustrates the multimer bands present when plasma is electrophoresed in a polyacrylamide gel. The II-1 and II-2 columns refer to the phenotypes of the second-generation offspring.

TABLE 111-2 Laboratory Diagnosis of von Willebrand Disease (VWD)

TYPE	APTT	VWF ANTIGEN	VWF ACTIVITY	FVIII ACTIVITY	MULTIMER
1	NI or ↑	↓	↓	↓	Normal distribution, decreased in quantity
2A	NI or ↑	↓	↓↓	↓	Loss of high- and intermediate-MW multimers
2B[a]	NI or ↑	↓	↓↓	↓	Loss of high-MW multimers
2M	NI or ↑	↓	↓↓	↓	Normal distribution, decreased in quantity
2N	↑↑	NI or ↓[b]	NI or ↓[b]	↓↓	Normal distribution
3	↑↑	↓↓	↓↓	↓↓	Absent

[a]Usually also decreased platelet count. [b]For type 2N, in the homozygous state, FVIII is very low; in the heterozygous state, it is only seen in conjunction with type 1 VWD.

Abbreviations: aPTT, activated partial thromboplastin time; F, factor; MW, molecular weight; NI, normal; VWF, von Willebrand factor.

Patients with type 2 VWD have functional defects; thus, the VWF antigen measurement is significantly higher than the test of function. For types 2A, 2B, and 2M VWD, platelet-binding and/or collagen-binding VWF activity is decreased. In type 2A VWD, the impaired function is due either to increased susceptibility to cleavage by ADAMTS13, resulting in loss of intermediate- and high-molecular-weight multimers, or to decreased production of these multimers by the cell. Type 2B VWD results from gain-of-function mutations that result in increased spontaneous binding of VWF to platelets in circulation, with increased cleavage by ADAMTS13 and clearance of this complex by the reticuloendothelial system. The resulting VWF in the patients' plasma lacks the highest molecular-weight multimers, and the platelet count is usually modestly reduced. Type 2M occurs as a consequence of a group of DNA variants that cause dysfunction but do not affect multimer structure.

Type 2N VWD is due to variants in the *VWF* gene that affect binding of FVIII. As FVIII is stabilized by binding to VWF, the FVIII in patients with type 2N VWD has a very short half-life, and the FVIII level is markedly decreased. This is sometimes termed *autosomal hemophilia*. Type 3 VWD, or severe VWD, describes patients with virtually no VWF protein and FVIII levels <10%. Patients experience mucosal and joint bleeding, surgery-related bleeding, and other bleeding symptoms. Some patients with type 3 VWD, particularly those with large VWF gene deletions, are at risk of developing antibodies to infused VWF.

Acquired VWD is a rare disorder, most commonly seen in patients with underlying lymphoproliferative disorders, including monoclonal gammopathies of underdetermined significance (MGUS), multiple myeloma, and Waldenström's macroglobulinemia. It is seen most commonly in the setting of MGUS and should be suspected in patients, particularly elderly patients, with a new onset of severe mucosal bleeding symptoms. Laboratory evidence of acquired VWD is found in some patients with aortic valvular disease. Heyde's syndrome (aortic stenosis with gastrointestinal bleeding) is attributed to the presence of angiodysplasia of the gastrointestinal tract in patients with aortic stenosis. The shear stress on blood passing through the stenotic aortic valve appears to unfold VWF, making it susceptible to proteolysis. Consequently, large multimer forms are lost, leading to an acquired type 2 VWD, but return when the stenotic valve is replaced.

TREATMENT

von Willebrand Disease

The mainstay of treatment for type 1 VWD is DDAVP (desmopressin), which results in release of VWF and FVIII from endothelial stores. DDAVP can be given intravenously or by a high-concentration intranasal spray (1.5 mg/mL). The peak activity when given intravenously is ~30 min, whereas it is 2 h when given intra-nasally. The usual dose is 0.3 μg/kg intravenously or two squirts (one in each nostril) for patients >50 kg (one squirt for those <50 kg). It is recommended that patients with VWD be tested with DDAVP to assess their response before using it. In patients who respond well (increase in laboratory values of two- to fourfold), it can be used for procedures with minor to moderate risk of bleeding. Depending on the procedure, additional doses may be needed; it is usually given every 12–24 h. Less frequent dosing may result in less tachyphylaxis, which occurs when synthesis cannot compensate for the released stores. The major side effect of DDAVP is hyponatremia due to decreased free water clearance. This occurs most commonly in the very young and the very old, but fluid restriction should be advised for all patients for the 24 h following each dose.

Some patients with types 2A and 2M VWD respond to DDAVP such that it can be used for minor procedures. For the other subtypes, for type 3 disease, and for major procedures requiring longer periods of normal hemostasis, VWF replacement can be given. Virally inactivated VWF-plasma-derived and recombinant factor concentrates are safer than cryoprecipitate as the replacement product.

Antifibrinolytic therapy using either ε-aminocaproic acid or tranexamic acid is an important therapy, either alone or in an adjunctive capacity, particularly for the prevention or treatment of mucosal bleeding. These agents are particularly useful in treatment of menorrhagia and post partum hemorrhage, prophylaxis for dental procedures, and with DDAVP or factor concentrate for dental extractions, tonsillectomies, and prostate procedures. Antifibrinolytic agents are contraindicated in the setting of upper urinary tract bleeding, due to the risk of ureteral obstruction.

DISORDERS OF THE VESSEL WALL

The vessel wall is an integral part of hemostasis, and separation of a fluid phase is artificial, particularly in disorders such as TTP or HIT that clearly involve the endothelium as well. Inflammation localized to the vessel wall, such as vasculitis, and inherited connective tissue disorders are abnormalities inherent to the vessel wall.

METABOLIC AND INFLAMMATORY DISORDERS Acute febrile illnesses may result in vascular damage. This can result from immune complexes containing viral antigens or the viruses themselves. Certain pathogens, such as the rickettsiae causing Rocky Mountain spotted fever, replicate in endothelial cells and damage them. Vascular purpura may occur in patients with polyclonal gammopathies but more commonly in those with monoclonal gammopathies, including Waldenström's macroglobulinemia, multiple myeloma, and cryoglobulinemia. Patients with mixed cryoglobulinemia develop a more extensive maculopapular rash due to immune complex–mediated damage to the vessel wall.

Patients with scurvy (vitamin C deficiency) develop painful episodes of perifollicular skin bleeding as well as more systemic bleeding symptoms. Vitamin C is needed to synthesize hydroxyproline, an essential constituent of collagen. Patients with Cushing's syndrome or on chronic glucocorticoid therapy develop skin bleeding and easy bruising due to atrophy of supporting connective tissue. A similar phenomenon is seen with aging, where following minor trauma, blood spreads superficially under the epidermis. This has been termed *senile purpura*. It is most common on skin that has been previously damaged by sun exposure.

Henoch-Schönlein, or anaphylactoid, purpura is a distinct, self-limited type of vasculitis that occurs in children and young adults. Patients have an acute inflammatory reaction with IgA and complement components in capillaries, mesangial tissues, and small arterioles leading to increased vascular permeability and localized hemorrhage. The syndrome is often preceded by an upper respiratory infection, commonly with streptococcal pharyngitis, or is triggered by drug or food allergies. Patients develop a purpuric rash on the extensor surfaces of the arms and legs, usually accompanied by polyarthralgias or arthritis, abdominal pain, and hematuria from focal glomerulonephritis. All coagulation tests are normal, but renal impairment may occur. Glucocorticoids can provide symptomatic relief but do not alter the course of the illness.

INHERITED DISORDERS OF THE VESSEL WALL Patients with inherited disorders of the connective tissue matrix, such as Marfan's syndrome, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum, frequently report easy bruising. Inherited vascular abnormalities can result in increased bleeding. This is notably seen in hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu disease), a disorder where abnormal telangiectatic capillaries result in frequent bleeding episodes, primarily from the nose and gastrointestinal tract. Arteriovenous malformation (AVM) in the lung, brain, and liver may also occur in HHT. The telangiectasia can often be visualized on the oral and nasal mucosa. Signs and symptoms develop over time. Epistaxis begins, on average, at the age of 12 and occurs in >95% of affected individuals by middle age. Approximately 25% have GI bleeding usually beginning after the age of 50. HHT is caused by pathogenic DNA variants in number of genes involved in the TGFβ/BMP signaling cascade.

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112 Coagulation Disorders

Valder R. Arruda, Katherine A. High

Deficiencies of coagulation factors have been recognized for centuries. Patients with genetic deficiencies of plasma coagulation factors exhibit lifelong recurrent bleeding episodes into joints, muscles, and closed spaces, either spontaneously or following an injury. The most common inherited factor deficiencies are the hemophilias, X-linked diseases caused by deficiency of factor (F) VIII (hemophilia A) or FIX (hemophilia B). Rare congenital bleeding disorders due to deficiencies of other factors, including FII (prothrombin), FV, FVII, FX, FXI, FXIII, and fibrinogen, are commonly inherited in an autosomal recessive manner **(Table 112-1)**. Advances in characterization of the molecular bases of clotting factor deficiencies have contributed to better understanding of the disease phenotypes and may eventually allow more targeted therapeutic approaches through the development of small molecules, recombinant proteins, or cell- and gene-based therapies.

Commonly used tests of hemostasis provide the initial screening for clotting factor activity **(Fig. 112-1)**, and disease phenotype often correlates with the level of clotting activity. An isolated abnormal prothrombin time (PT) suggests FVII deficiency, whereas a prolonged activated partial thromboplastin time (aPTT) indicates most commonly hemophilia or FXI deficiency (Fig. 112-1). The prolongation of both PT and aPTT suggests deficiency of FV, FX, FII, or fibrinogen abnormalities. The addition of the missing factor at a range of doses to the subject's plasma will correct the abnormal clotting times; the result is expressed as a percentage of the activity observed in normal subjects.

Acquired deficiencies of plasma coagulation factors are more frequent than congenital disorders; the most common disorders include hemorrhagic diathesis of liver disease, disseminated intravascular coagulation (DIC), and vitamin K deficiency. In these disorders, blood coagulation is hampered by the deficiency of more than one clotting factor, and the bleeding episodes are the result of perturbation of both primary (e.g., platelet and vessel wall interactions) and secondary (coagulation) hemostasis.

The development of alloantibodies to coagulation plasma proteins, clinically termed *inhibitors*, is a relatively rare disease that often affects hemophilia A or B and FXI-deficient patients on repetitive exposure to the missing protein to control bleeding episodes. Inhibitory autoantibodies also occur among subjects without genetic deficiency of clotting factors (e.g., in the postpartum setting as a manifestation of underlying autoimmune or neoplastic disease, or idiopathically). Rare cases of inhibitors to thrombin or FV have been reported in patients receiving topical bovine thrombin preparation as a local hemostatic agent in complex surgeries. The diagnosis of inhibitors is based on the same tests as those used to diagnose inherited plasma coagulation factor deficiencies. However, the addition of the missing protein to the plasma of a subject with an inhibitor does not correct the abnormal aPTT and/or PT tests (known as mixing tests). This is the major laboratory difference between deficiencies and inhibitors. Additional tests are required to measure the specificity of the inhibitor and its titer.

The treatment of these bleeding disorders often requires replacement of the deficient protein using recombinant or purified plasma-derived products or fresh-frozen plasma (FFP). Therefore, it is imperative to arrive at a proper diagnosis to optimize patient care without unnecessary exposure to suboptimal treatment and the risks of bloodborne disease.

HEMOPHILIA

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the *F8* gene (hemophilia A or classic hemophilia) or *F9* gene (hemophilia B). The disease affects 1 in 10,000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases. Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic. Family history of the disease is absent in ~30% of cases, and in these cases, 80% of the mothers are carriers of the de novo mutated allele. More than 500 different mutations have been identified in the *F8* or *F9* genes of patients with hemophilia A or B,

TABLE 112-1 Genetic and Laboratory Characteristics of Inherited Coagulation Disorders

CLOTTING FACTOR DEFICIENCY	INHERITANCE	PREVALENCE IN GENERAL POPULATION	LABORATORY ABNORMALITY[a]			MINIMUM HEMOSTATIC LEVELS	TREATMENT	PLASMA HALF-LIFE
			aPTT	PT	TT			
Fibrinogen	AR	1 in 1,000,000	+	+	+	100 mg/dL	Cryoprecipitate	2–4 d
Prothrombin	AR	1 in 2,000,000	+	+	–	20–30%	FFP/PCC	3–4 d
Factor V	AR	1 in 1,000,000	+/–	+/–	–	15–20%	FFP[c]	36 h
Factor VII	AR	1 in 500,000	–	+	–	15–20%	FFP/PCC	4–6 h
Factor VIII	X-linked	1 in 5,000	+	–	–	30%	FVIII concentrates	8–12 h
Factor IX	X-linked	1 in 30,000	+	–	–	30%	FIX concentrates	18–24 h
Factor X	AR	1 in 1,000,000	+/–	+/–	–	15–20%	FFP/PCC	40–60 h
Factor XI	AR	1 in 1,000,000	+	–	–	15–20%	FFP	40–70 h
Factor XII	AR	ND	+	–	–	[b]	[b]	60 h
HK	AR	ND	+	–	–	[b]	[b]	150 h
Prekallikrein	AR	ND	+	–	–	[b]	[b]	35 h
Factor XIII	AR	1 in 2,000,000	–	–	+/–	2–5%	Cryoprecipitate/ FXIII concentrates	11–14 d

[a]Values within normal range (–) or prolonged (+). [b]No risk for bleeding; treatment is not indicated. [c]Since platelets contain FV, platelet transfusion can be used as therapy.

Abbreviations: aPTT, activated partial thromboplastin time; AR, autosomal recessive; FFP, fresh-frozen plasma; HK, high-molecular-weight kininogen; ND, not determined; PCC, prothrombin complex concentrates; PT, prothrombin time; TT, thrombin time.

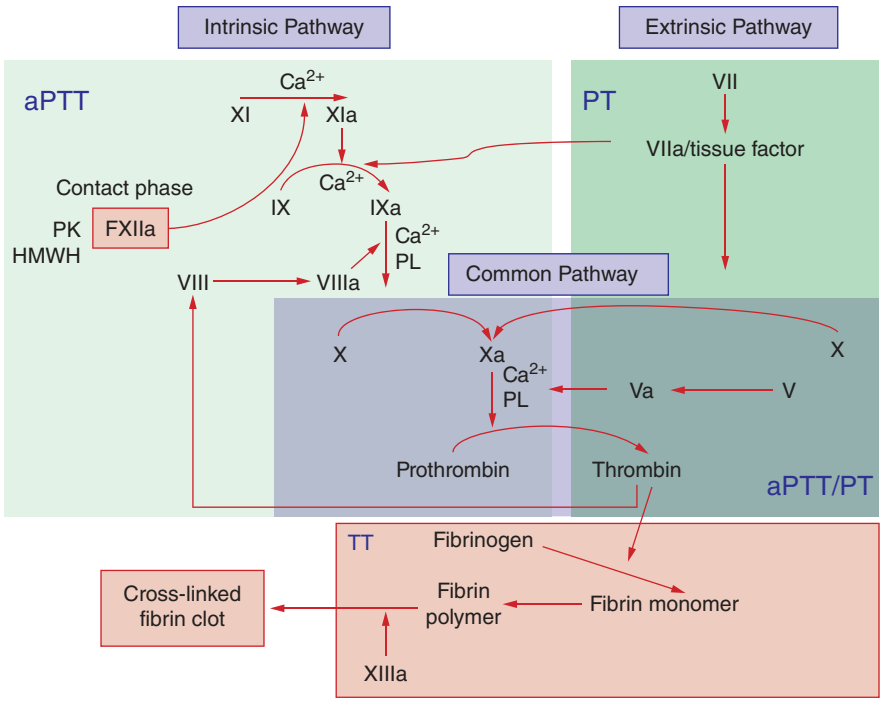

FIGURE 112-1 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).

respectively. One of the most common hemophilia A mutations results from an inversion of the intron 22 sequence, and it is present in 40% of cases of severe hemophilia A. Advances in molecular diagnosis now permit precise identification of mutations, allowing accurate diagnosis of women carriers of the hemophilia gene in affected families.

Clinically, hemophilia A and hemophilia B are indistinguishable. The disease phenotype correlates with the residual activity of FVIII or FIX and can be classified as severe (<1%), moderate (1–5%), or mild (6–30%). In the severe and moderate forms, the disease is characterized by bleeding into the joints (hemarthrosis), soft tissues, and muscles after minor trauma or even spontaneously. Patients with mild disease experience infrequent bleeding that is usually secondary to trauma. Among those with residual FVIII or FIX activity >25% of normal, the disease is discovered only by bleeding after major trauma or during routine presurgery laboratory tests. Typically, the global tests of coagulation show only an isolated prolongation of the aPTT assay. Patients with hemophilia have normal bleeding times and platelet counts. The diagnosis is made after specific determination of FVIII or FIX clotting activity.

Early in life, bleeding may present after circumcision or rarely as intracranial hemorrhages. The disease is more evident when children begin to walk or crawl. In the severe form, the most common bleeding manifestations are the recurrent hemarthroses, which can affect every joint but mainly affect knees, elbows, ankles, shoulders, and hips. Acute hemarthroses are painful, and clinical signs are local swelling and erythema. To avoid pain, the patient may adopt a fixed position, which leads eventually to muscle contractures. Very young children unable to communicate verbally show irritability and a lack of movement of the affected joint. Chronic hemarthroses are debilitating, with synovial thickening and synovitis in response to the intraarticular blood. After a joint has been damaged, recurrent bleeding episodes result in the clinically recognized "target joint," which then establishes a vicious cycle of bleeding, resulting in progressive joint deformity that in critical cases requires surgery as the only therapeutic option. Hematomas into the muscle of distal parts of the limbs may lead to external compression of arteries, veins, or nerves that can evolve to a compartment syndrome.

Bleeding into the oropharyngeal spaces, central nervous system (CNS), or retroperitoneum is life threatening and requires immediate therapy. Retroperitoneal hemorrhages can accumulate large quantities of blood with formation of masses with calcification and inflammatory tissue reaction (pseudotumor syndrome) and also result in damage to the femoral nerve. Pseudotumors can also form in bones, especially long bones of the lower limbs. Hematuria is frequent among hemophilia patients, even in the absence of genitourinary pathology. It is often self-limited and may not require specific therapy.

TREATMENT

Hemophilia

Without treatment, severe hemophilia may limit life expectancy. Advances in the blood fractionation industry during World War II resulted in the realization that plasma could be used to treat hemophilia, but the volumes required to achieve even modest elevation of circulating factor levels limit the utility of plasma infusion as an approach to disease management. The discovery in the 1960s that the cryoprecipitate fraction of plasma was enriched for FVIII, and the eventual purification of FVIII and FIX from plasma, led to the introduction of home infusion therapy with factor concentrates in the 1970s. The availability of factor concentrates resulted in a dramatic improvement in life expectancy and in quality of life for people with severe hemophilia. However, the contamination of the blood supply with hepatitis viruses and, subsequently, HIV resulted in widespread transmission of these bloodborne infections within the hemophilia population; complications of HIV and of hepatitis C are now the leading causes of death among U.S. adults with severe hemophilia. The introduction of viral inactivation steps in the preparation of plasma-derived products in the mid-1980s greatly reduced the risk of HIV and hepatitis, and the risks were further reduced by the successful production of recombinant FVIII and FIX proteins, both licensed in the 1990s. It is uncommon for hemophilic patients born after 1985 to have contracted either hepatitis or HIV, and for these individuals, life expectancy is ~65 years. In fact, since 1998, no evidence of new infections with viral hepatitis or HIV has been reported in patients using blood products. Factor replacement therapy for hemophilia can be provided either in response to a bleeding episode or as a prophylactic treatment. Primary prophylaxis is

defined as a strategy for maintaining the missing clotting factor at levels ~1% or higher on a regular basis in order to prevent bleeds, especially the onset of hemarthroses. Hemophilic boys receiving regular infusions of FVIII (3 days/week) or FIX (2 days/week) can reach puberty without detectable joint abnormalities. Prophylaxis has become gradually more common in young patients. The Centers for Disease Control and Prevention reported that 51% of children with severe hemophilia who are aged <6 years receive prophylaxis, increasing considerably from 33% in 1995. Prophylaxis is the standard care for children; however, teenagers and young adults do not always maintain the treatment regularly. Although highly recommended, the high cost and difficulties in accessing peripheral veins in young patients and the potential infectious and thrombotic risks of long-term central vein catheters are important limiting factors for many young patients. Prophylaxis is also increasing among adults with severe hemophilia.

General considerations regarding the treatment of bleeds in hemophilia include the following: (1) Treatment should begin as soon as possible because symptoms often precede objective evidence of bleeding; because of the superior efficacy of early therapeutic intervention, classic symptoms of bleeding into the joint in a reliable patient, headaches, or automobile or other accidents require prompt replacement and further laboratory investigation. (2) Drugs that hamper platelet function, such as aspirin or aspirin-containing drugs, should be avoided; to control pain, drugs such as ibuprofen or propoxyphene are preferred. FVIII and FIX are dosed in units. One unit is defined as amount of FVIII (100 ng/mL) or FIX (5 μg/mL) in 1 mL of normal plasma. One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase FVIII levels to 100% in a 70-kg severe hemophilia patient (<1%) using the simple formula below. Thus, 3500 units of FVIII will raise the circulating level to 100%.

$$\text{FVIII dose (IU)} = \text{Target FVIII levels} - \text{FVIII baseline levels} \times \text{body weight (kg)} \times 0.5 \text{ unit/kg}$$

The doses for FIX replacement are different from those for FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is as follows:

$$\text{FIX dose (IU)} = \text{Target FIX levels} - \text{FIX baseline levels} \times \text{body weight (kg)} \times 1 \text{ unit/kg}$$

The FVIII half-life of 8–12 h requires injections twice a day to maintain therapeutic levels, whereas the FIX half-life is longer, ~24 h, so that once-a-day injection is sufficient. In specific situations such as after surgery, continuous infusion of factor may be desirable because of its safety in achieving sustained factor levels at a lower total cost.

Cryoprecipitate is enriched with FVIII protein (each bag contains ~80 IU of FVIII) and was commonly used for the treatment of hemophilia A decades ago; it is still in use in some developing countries, but because of the risk of bloodborne diseases, this product should be avoided in hemophilia patients when factor concentrates are available.

Mild bleeds such as uncomplicated hemarthroses or superficial hematomas require initial therapy with factor levels of 30–50%. Additional doses to maintain levels of 15–25% for 2 or 3 days are indicated for severe hemarthroses, especially when these episodes affect the "target joint." Large hematomas, or bleeds into deep muscles, require factor levels of 50% or even higher if the clinical symptoms do not improve, and factor replacement may be required for a period of 1 week or longer. The control of serious bleeds including those that affect the oropharyngeal spaces, CNS, and the retroperitoneum require sustained protein levels of 50–100% for 7–10 days. Prophylactic replacement for surgery is aimed at achieving normal factor levels (100%) for a period of 7–10 days; replacement can then be tapered depending on the extent of the surgical wounds. Oral surgery is associated with extensive tissue damage that usually requires factor replacement for 1–3 days coupled with oral antifibrinolytic drugs.

NONTRANSFUSION THERAPY IN HEMOPHILIA

DDAVP (1-Amino-8-D-Arginine Vasopressin) DDAVP is a synthetic vasopressin analog that causes a transient rise in FVIII and von Willebrand factor (VWF), but not FIX, through a mechanism involving release from endothelial cells. Patients with moderate or mild hemophilia A should be tested to determine if they respond to DDAVP before a therapeutic application. DDAVP at doses of 0.3 μg/kg body weight, over a 20-min period, is expected to raise FVIII levels by two- to threefold over baseline, peaking between 30 and 60 min after infusion. DDAVP does not improve FVIII levels in severe hemophilia A patients because there are no stores to release. Repeated dosing of DDAVP results in tachyphylaxis because the mechanism is an increase in release rather than de novo synthesis of FVIII and VWF. More than three consecutive doses become ineffective, and if further therapy is indicated, FVIII replacement is required to achieve hemostasis.

Antifibrinolytic Drugs Bleeding in the gums, gastrointestinal tract, and during oral surgery requires the use of oral antifibrinolytic drugs such as ε-amino caproic acid (EACA) or tranexamic acid to control local hemostasis. The duration of the treatment depending on the clinical indication is 1 week or longer. Tranexamic acid is given at doses of 25 mg/kg three to four times a day. EACA treatment requires a loading dose of 200 mg/kg (maximum of 10 g) followed by 100 mg/kg per dose (maximum 30 g/d) every 6 h. These drugs are not indicated to control hematuria because of the risk of formation of an occlusive clot in the lumen of genitourinary tract structures.

COMPLICATIONS

Inhibitor Formation The formation of alloantibodies to FVIII or FIX is currently the major complication of hemophilia treatment. The prevalence of inhibitors to FVIII is estimated to be ~30% of severe hemophilia A patients and 10% among patients with nonsevere hemophilia A. Inhibitors to FIX are detected in only 3–5% of all hemophilia B patients. The high-risk group for inhibitor formation includes severe deficiency (>80% of all cases of inhibitors), familial history of inhibitor, African descent, mutations in the FVIII or FIX gene resulting in deletion of large coding regions, or gross gene rearrangements. Inhibitors usually appear early in life, at a median of 2 years of age, and after 10 cumulative days of exposure. However, intensive replacement therapy such as for major surgery, intracranial bleeding, or trauma increases the risk of inhibitor formation for patients of all ages and degree of clinical severity, which requires close laboratory monitoring in the following weeks.

The clinical diagnosis of an inhibitor is suspected when patients do not respond to factor replacement at therapeutic doses. Inhibitors increase both morbidity and mortality in hemophilia. Because early detection of an inhibitor is critical to a successful correction of the bleeding or to eradication of the antibody, most hemophilia centers perform annual screening for inhibitors. The laboratory test required to confirm the presence of an inhibitor is an aPTT with a mix (with normal plasma). In most hemophilia patients, a 1:1 mix with normal plasma completely corrects the aPTT. In inhibitor patients, the aPTT on a 1:1 mix is abnormally prolonged because the inhibitor neutralizes the FVIII clotting activity of the normal plasma. The Bethesda assay uses a similar principle and defines the specificity of the inhibitor and its titer. The results are expressed in Bethesda units (BU), in which 1 BU is the amount of antibody that neutralizes 50% of the FVIII or FIX present in normal plasma after 2 h of incubation at 37°C. Clinically, inhibitor patients are classified as low responders or high responders, which provides guidelines for optimal therapy. Therapy for inhibitor patients has two goals: the control of acute bleeding episodes and the eradication of the inhibitor. For the control of bleeding episodes, low responders, those with titer <5 BU, respond well to high doses of human FVIII (50–100 U/kg), with minimal or no increase in the inhibitor titers. However, high-responder patients,

those with initial inhibitor titer >5 BU or an anamnestic response in the antibody titer to >5 BU, even if low titer initially, do not respond to FVIII. The control of bleeding episodes in high-responder patients can be achieved by using concentrates enriched for prothrombin, FVII, FIX, FX (prothrombin complex concentrates [PCCs] or activated PCCs [aPCCs]), and recombinant activated factor VII (FVIIa) known as "bypass agents" (Fig. 112-1). For FIX inhibitor patients, high doses of FIX can be used (<5 BU); however, allergic or anaphylactic reactions are common in FIX inhibitors, thus the use of bypass products should be used to treat or prevent bleeding as well as for those cases of high titer inhibitors. For eradication of the inhibitory antibody, immunosuppression alone is not effective. The most effective strategy is the immune tolerance induction (ITI) based on daily infusion of missing protein until the inhibitor disappears, typically requiring periods >1 year, with success rates of ~60%. The management of patients with severe hemophilia and inhibitors resistant to ITI is challenging. The use of anti-CD20 monoclonal antibody (rituximab) combined with ITI was thought to be effective. Although this therapy may reduce the inhibitor titers in some cases, sustained eradication is uncommon.

Novel Therapeutic Approaches in Development for Hemophilia

Clinical studies using long-acting clotting factors with enhanced half-lives are in the late phase of clinical testing, and these new-generation products (for FVIII and FIX) may facilitate prophylaxis by requiring fewer injections to maintain circulating levels >1%. In hemophilia A, the use of these products reduced the frequency of injections of FVIII from 3 to 2 days a week, and notably for hemophilia B, most patients will require once-a-week injections of long-acting FIX.

The use of recombinant interleukin 11 in patients with moderate or mild hemophilia A unresponsive to DDAVP has been tested in early-phase clinical trials and may be an alternate therapeutic strategy for clinical situations that require transient increases in FVIII levels.

Gene therapy trials for hemophilia A and B using adeno-associated viral vectors are ongoing **(Chap. 458)**.

INFECTIOUS DISEASES

Hepatitis C virus (HCV) infection is the major cause of morbidity and the second leading cause of death in hemophilia patients exposed to older clotting factor concentrates. The vast majority of young patients treated with plasma-derived products from 1970 to 1985 became infected with HCV. It has been estimated that >80% of patients aged >20 years are HCV antibody positive as of 2006. The comorbidity of the underlying liver disease in hemophilia patients is clear when these individuals require invasive procedures; correction of both genetic and acquired (secondary to liver disease) deficiencies may be needed. Infection with HIV also swept the population of patients using plasma-derived concentrates two decades ago. Co-infection of HCV and HIV, present in almost 50% of hemophilia patients, is an aggravating factor for the evolution of liver disease. The response to HCV antiviral therapy in hemophilia is restricted to <30% of patients and even poorer among those with both HCV and HIV infection. The development of effective direct-acting antivirals for the treatment of HCV may change this scenario. End-stage liver disease requiring organ transplantation may be curative for both the liver disease and for hemophilia

EMERGING CLINICAL PROBLEMS IN AGING HEMOPHILIA PATIENTS

There has been continuous improvement of the management of hemophilia since the increase in the population of adults living beyond middle age in the developing world. The life expectancy of a patient with severe hemophilia is only ~10 years shorter than the general male population. In patients with mild or moderate hemophilia, life expectancy is approaching that of the male population without coagulopathy. Elderly hemophilia patients have different problems compared to the younger generation; they have more severe arthropathy and chronic pain, due to suboptimal treatment, and high rates of HCV and/or HIV infections.

Early data indicate that mortality from coronary artery disease is lower in hemophilia patients than the general male population. The underlying hypocoagulability probably provides a protective effect against thrombus formation, but it does not prevent atherogenesis. Similar to the general population, these patients are exposed to cardiovascular risk factors such as age, obesity, and smoking. Moreover, physical inactivity, hypertension, and chronic renal disease are commonly observed in hemophilia patients. In HIV patients on combined antiretroviral therapy, there may be a further increase in the risk of cardiovascular disease. Therefore, these patients should be carefully considered for preventive and therapeutic approaches to minimize the risk of cardiovascular disease.

Excessive replacement therapy should be avoided, and it is prudent to slowly infuse factor concentrates. Continuous infusion of clotting factor is preferable to bolus dosing in patients with cardiovascular risk factors undergoing invasive procedures. The management of an acute ischemic event and coronary revascularization should include the collaboration of hematologists and internists. The early assumption that hemophilia would protect against occlusive vascular disease may change in this aging population. Cancer is a common cause of mortality in aging hemophilia patients because they are at risk for HIV- and HCV-related malignancies. Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and a common cause of death in HIV-negative patients. The recommendations for cancer screening for the general population should be the same for age-matched hemophilia patients. Among those with high-risk HCV, a semiannual or annual ultrasound and α fetoprotein are recommended for HCC. Screening for urogenital neoplasm in the presence of hematuria or hematochezia may be delayed due to the underlying bleeding disease, thus preventing early intervention. Multidisciplinary interaction should facilitate the attempts to ensure optimal cancer prevention and treatment recommendations for those with hemophilia.

MANAGEMENT OF CARRIERS OF HEMOPHILIA

Usually hemophilia carriers, with factor levels of ~50% of normal, have not been considered to be at risk for bleeding. However, a wide range of values (22–116%) have been reported due to random inactivation of the X chromosomes (*lyonization*). Therefore, it is important to measure the factor level of carriers to recognize those at risk of bleeding and to optimize preoperative and postoperative management. During pregnancy, both FVIII and FIX levels increase gradually until delivery. FVIII levels increase approximately two- to threefold compared to nonpregnant women, whereas an FIX increase is less pronounced. After delivery, there is a rapid fall in the pregnancy-induced rise of maternal clotting factor levels. This represents an imminent risk of bleeding that can be prevented by infusion of factor concentrate to levels of 50–70% for 3 days in the setting of vaginal delivery and up to 5 days for cesarean section. In mild cases, the use of DDAVP and/or antifibrinolytic drugs is recommended.

FACTOR XI DEFICIENCY

Factor XI is a zymogen of an active serine protease (FIXa) in the intrinsic pathway of blood coagulation that activates FIX (Fig. 112-1). There are two pathways for the formation of FXIa. In an aPTT-based assay, the protease is the result of activation by FXIIa in conjunction with high-molecular-weight kininogen and kallikrein. In vivo data suggest that thrombin is the physiologic activator of FXI. The generation of thrombin by the tissue factor/factor VIIa pathway activates FXI on the platelet surface that contributes to additional thrombin generation after the clot has formed and thus augments resistance to fibrinolysis through a thrombin-activated fibrinolytic inhibitor (TAFI).

Factor XI deficiency is a rare bleeding disorder that occurs in the general population at a frequency of one in a million. However, the disease is highly prevalent among Ashkenazi and Iraqi Jewish populations, reaching a frequency of 6% as heterozygotes and 0.1–0.3% as homozygotes. More than 65 mutations in the FXI gene have been reported, whereas fewer mutations (two to three) are found among affected Jewish populations.

Normal FXI clotting activity levels range from 70 to 150 U/dL. In heterozygous patients with moderate deficiency, FXI ranges from 20 to 70 U/dL, whereas in homozygous or double heterozygote patients, FXI levels are <1–20 U/dL. Patients with FXI levels <10% of normal have a high risk of bleeding, but the disease phenotype does not always correlate with residual FXI clotting activity. A family history is indicative of the risk of bleeding in the propositus. Clinically, the presence of mucocutaneous hemorrhages such as bruises, gum bleeding, epistaxis, hematuria, and menorrhagia are common, especially following trauma. This hemorrhagic phenotype suggests that tissues rich in fibrinolytic activity are more susceptible to FXI deficiency. Postoperative bleeding is common but not always present, even among patients with very low FXI levels.

FXI replacement is indicated in patients with severe disease required to undergo a surgical procedure. A negative history of bleeding complications following invasive procedures does not exclude the possibility of an increased risk for hemorrhage.

TREATMENT

Factor XI Deficiency

The treatment of FXI deficiency is based on the infusion of FFP at doses of 15–20 mL/kg to maintain trough levels ranging from 10 to 20%. Because FXI has a half-life of 40–70 h, the replacement therapy can be given on alternate days. The use of antifibrinolytic drugs is beneficial to control bleeds, with the exception of hematuria or bleeds in the bladder. The development of an FXI inhibitor was observed in 10% of severely FXI-deficient patients who received replacement therapy. Patients with severe FXI deficiency who develop inhibitors usually do not bleed spontaneously. However, bleeding following a surgical procedure or trauma can be severe. In these patients, FFP and FXI concentrates should be avoided. The use of PCC/aPCC or recombinant activated FVII has been effective.

RARE BLEEDING DISORDERS

Collectively, the inherited disorders resulting from deficiencies of clotting factors other than FVIII, FIX, and FXI (Table 112-1) represent a group of rare bleeding diseases. The bleeding symptoms in these patients vary from asymptomatic (dysfibrinogenemia or FVII deficiency) to life-threatening (FX or FXIII deficiency). There is no pathognomonic clinical manifestation that suggests one specific disease, but overall, in contrast to hemophilia, hemarthrosis is a rare event and bleeding in the mucosal tract or after umbilical cord clamping is common. Individuals heterozygous for plasma coagulation deficiencies are often asymptomatic. The laboratory assessment for the specific deficient factor following screening with general coagulation tests (Table 112-1) will define the diagnosis.

Replacement therapy using FFP or PCCs (containing prothrombin, FVII, FIX, and FX) provides adequate hemostasis in response to bleeds or as prophylactic treatment. The use of PCC should be carefully monitored and avoided in patients with underlying liver disease, or those at high risk for thrombosis because of the risk of DIC.

FAMILIAL MULTIPLE COAGULATION DEFICIENCIES

There are several bleeding disorders characterized by the inherited deficiency of more than one plasma coagulation factor. To date, the genetic defects in two of these diseases have been characterized, and they provide new insights into the regulation of hemostasis by gene-encoding proteins outside blood coagulation.

Combined Deficiency of FV and FVIII Patients with combined FV and FVIII deficiency exhibit ~5% of residual clotting activity of each factor. Interestingly, the disease phenotype is a mild bleeding tendency, often following trauma. An underlying mutation has been identified in the *lectin mannose binding 1* (*LMAN1*) gene, a mannose-binding protein localized in the Golgi apparatus that functions as a chaperone for both FV and FVIII. In other families, mutations in the multiple coagulation factor deficiency 2 (*MCFD2*) gene have been defined; this gene encodes a protein that forms a Ca^{2+} dependent complex with LMAN1 and provides cofactor activity in the intracellular mobilization of both FV and FVIII. The replacement therapy to control or prevent bleeding consisted of FFP to maintain FV levels and DDAVP or FVIII concentrate to achieve FVIII levels of 20–40%. Alternatively, since platelets contain FV, transfusion of platelets can also be used.

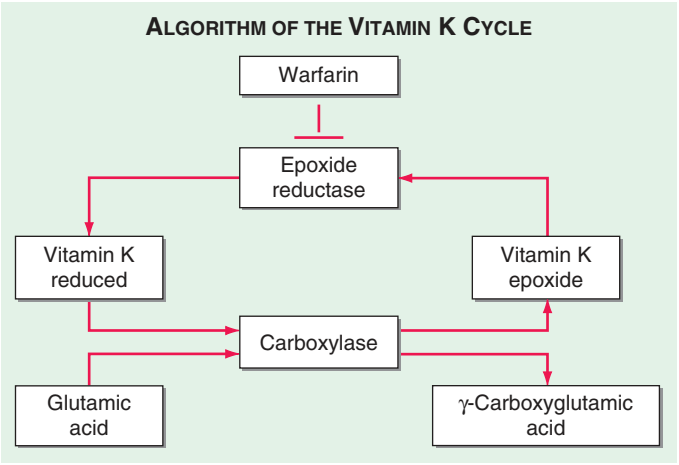

FIGURE 112-2 The vitamin K cycle. Vitamin K is a cofactor for the formation of γ-carboxyglutamic acid residues on coagulation proteins. Vitamin K–dependent γ-glutamylcarboxylase, the enzyme that catalyzes the vitamin K epoxide reductase, regenerates reduced vitamin K. Warfarin blocks the action of the reductase and competitively inhibits the effects of vitamin K.

Multiple Deficiencies of Vitamin K–Dependent Coagulation Factors Two enzymes involved in vitamin K metabolism have been associated with combined deficiency of all vitamin K–dependent proteins, including the procoagulant proteins prothrombin, VII, IX, and X and the anticoagulant proteins C and S. Vitamin K is a fat-soluble vitamin that is a cofactor for carboxylation of the gamma carbon of the glutamic acid residues in the vitamin K–dependent factors, a critical step for calcium and phospholipid binding of these proteins (Fig. 112-2). The enzymes γ-glutamylcarboxylase and epoxide reductase are critical for the metabolism and regeneration of vitamin K. Mutations in the genes encoding the γ-carboxylase (GGCX) or vitamin K epoxide reductase complex 1 (VKORC1) result in defective enzymes and thus in vitamin K–dependent factors with reduced activity, varying from 1 to 30% of normal. The disease phenotype is characterized by mild to severe bleeding episodes present from birth. Some patients respond to oral administration of vitamin K1 (5–20 mg/d), or in poor responders parenteral vitamin K1 at doses of 5–20 mg/week could be considered. For severe bleeding, replacement therapy with FFP or PCC may be necessary to achieve full hemostatic control.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC is a clinicopathologic syndrome characterized by widespread intravascular fibrin formation in response to excessive blood protease activity that overcomes the natural anticoagulant mechanisms. There are several underlying pathologies associated with DIC (Table 112-2).

The most common causes are bacterial sepsis, malignant disorders such as solid tumors or acute promyelocytic leukemia, and obstetric causes. DIC is diagnosed in almost one-half of pregnant women with abruptio placentae or with amniotic fluid embolism. Trauma, particularly to the brain, can also result in DIC. The exposure of blood to phospholipids from damaged tissue, hemolysis, and endothelial damage are all contributing factors to the development of DIC in this setting. Purpura fulminans is a severe form of DIC resulting from thrombosis of extensive areas of the skin; it affects predominantly young children following viral or bacterial infection, particularly those with inherited or acquired hypercoagulability due to deficiencies of the components of the protein C pathway. Neonates homozygous for protein C

TABLE 112-2 Common Clinical Causes of Disseminated Intravascular Coagulation

SEPSIS	IMMUNOLOGIC DISORDERS
• Bacterial: Staphylococci, streptococci, pneumococci, meningococci, gram-negative bacilli • Viral • Mycotic • Parasitic • Rickettsial	• Acute hemolytic transfusion reaction • Organ or tissue transplant rejection • Immunotherapy • Graft-versus-host disease
TRAUMA AND TISSUE INJURY	**DRUGS**
• Brain injury (gunshot) • Extensive burns • Fat embolism • Rhabdomyolysis	• Fibrinolytic agents • Aprotinin • Warfarin (especially in neonates with protein C deficiency) • Prothrombin complex concentrates • Recreational drugs (amphetamines)
VASCULAR DISORDERS	**ENVENOMATION**
• Giant hemangiomas (Kasabach-Merritt syndrome) • Large vessel aneurysms (e.g., aorta)	• Snake • Insects
OBSTETRICAL COMPLICATIONS	**LIVER DISEASE**
• Abruptio placentae • Amniotic fluid embolism • Dead fetus syndrome • Septic abortion	• Fulminant hepatic failure • Cirrhosis • Fatty liver of pregnancy
CANCER	**MISCELLANEOUS**
• Adenocarcinoma (prostate, pancreas, etc.) • Hematologic malignancies (acute promyelocytic leukemia)	• Shock • Respiratory distress syndrome • Massive transfusion

deficiency also present high risk for purpura fulminans with or without thrombosis of large vessels.

The central mechanism of DIC is the uncontrolled generation of thrombin by exposure of the blood to pathologic levels of tissue factor (Fig. 112-3). Simultaneous suppression of physiologic anticoagulant mechanisms and abnormal fibrinolysis further accelerate the process. Together, these abnormalities contribute to systemic fibrin deposition in small and midsize vessels. The duration and intensity of the fibrin deposition can compromise the blood supply of many organs, especially the lung, kidney, liver, and brain, with consequent organ failure. The sustained activation of coagulation results in consumption of clotting factors and platelets, which in turn leads to systemic bleeding. This is further aggravated by secondary hyperfibrinolysis. Studies in animals demonstrate that the fibrinolytic system is indeed suppressed at the time of maximal activation of coagulation. Interestingly, in patients with acute promyelocytic leukemia, a severe hyperfibrinolytic state often occurs in addition to the coagulation activation. The release of several proinflammatory cytokines such as interleukin 6 and tumor necrosis factor α plays a central role in mediating the coagulation defects in DIC and symptoms associated with systemic inflammatory response syndrome (SIRS).

Clinical manifestations of DIC are related to the magnitude of the imbalance of hemostasis, to the underlying disease, or to both. The most common findings are bleeding ranging from oozing from venipuncture sites, petechiae, and ecchymoses to severe hemorrhage from the gastrointestinal tract, lung, or into the CNS. In chronic DIC, the bleeding symptoms are discrete and restricted to skin or mucosal surfaces. The hypercoagulability of DIC manifests as the occlusion of vessels in the microcirculation and resulting organ failure. Thrombosis of large vessels and cerebral embolism can also occur. Hemodynamic complications and shock are common among patients with acute DIC. The mortality ranges from 30 to >80% depending on the underlying disease, the severity of the DIC, and the age of the patient.

The diagnosis of clinically significant DIC is based on the presence of clinical and/or laboratory abnormalities of coagulation or thrombocytopenia. The laboratory diagnosis of DIC should prompt a search for the underlying disease if it is not already apparent. There is no single test that establishes the diagnosis of DIC. The laboratory investigation should include coagulation tests (aPTT, PT, thrombin time [TT]) and markers of fibrin degradation products (FDPs), in addition to platelet and red cell count and analysis of the blood smear. These tests should be repeated over a period of 6–8 h because an initially mild abnormality can change dramatically in patients with severe DIC.

Common findings include the prolongation of PT and/or aPTT; platelet counts μ100,000/μL, or a rapid decline in platelet numbers; the presence of schistocytes (fragmented red cells) in the blood smear; and elevated levels of FDP. The most sensitive test for DIC is the FDP

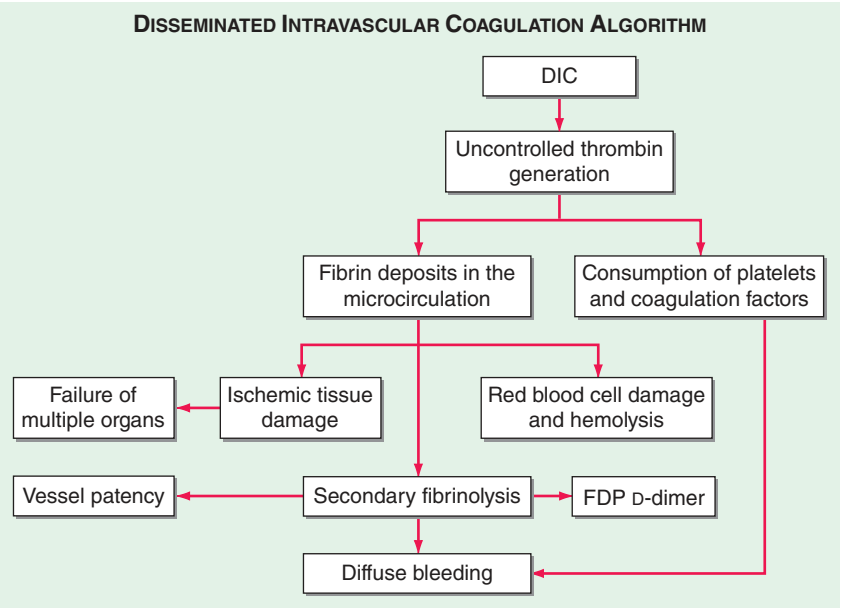

FIGURE 112-3 The pathophysiology of disseminated intravascular coagulation (DIC). Interactions between coagulation and fibrinolytic pathways result in bleeding and thrombosis in the microcirculation in patients with DIC. FDP, fibrin degradation product.

level. DIC is an unlikely diagnosis in the presence of normal levels of FDP. The D-dimer test is more specific for detection of fibrin—but not fibrinogen—degradation products and indicates that the cross-linked fibrin has been digested by plasmin. Because fibrinogen has a prolonged half-life, plasma levels diminish acutely only in severe cases of DIC. High-grade DIC is also associated with levels of antithrombin III or plasminogen activity <60% of normal.

Chronic DIC Low-grade, compensated DIC can occur in clinical situations including giant hemangioma, metastatic carcinoma, or the dead fetus syndrome. Plasma levels of FDP or D-dimers are elevated. aPTT, PT, and fibrinogen values are within the normal range or high. Mild thrombocytopenia or normal platelet counts are also common findings. Red cell fragmentation is often detected but at a lower degree than in acute DIC.

Differential Diagnosis The differential diagnosis between DIC and severe liver disease is challenging and requires serial measurements of the laboratory parameters of DIC. Patients with severe liver disease are at risk for bleeding and manifest laboratory features including thrombocytopenia (due to platelet sequestration, portal hypertension, or hypersplenism), decreased synthesis of coagulation factors and natural anticoagulants, and elevated levels of FDP due to reduced hepatic clearance. However, in contrast to DIC, these laboratory parameters in liver disease do not change rapidly. Other important differential findings include the presence of portal hypertension or other clinical or laboratory evidence of an underlying liver disease.

Microangiopathic disorders such as thrombotic thrombocytopenic purpura present an acute clinical onset of illness accompanied by thrombocytopenia, red cell fragmentation, and multiorgan failure. However, there is no consumption of clotting factors or hyperfibrinolysis.

Over the last few years, several clinical trials on immune therapies for neoplasias using monoclonal antibodies or gene-modified T cells targeting tumor-specific antigens showed unwanted inflammatory responses with increased cytokine release. These complications are sometimes associated with increased D-dimers and decreased fibrinogen levels, cytopenias, and liver dysfunction; thus, careful screening tests for DIC are indicated.

TREATMENT

Disseminated Intravascular Coagulation

The morbidity and mortality associated with DIC are primarily related to the underlying disease rather than the complications of the DIC. The control or elimination of the underlying cause should therefore be the primary concern. Patients with severe DIC require control of hemodynamic parameters, respiratory support, and sometimes invasive surgical procedures. Attempts to treat DIC without accompanying treatment of the causative disease are likely to fail.

MANAGEMENT OF HEMORRHAGIC SYMPTOMS

Administration of FFP and/or platelet concentrates is indicated for patients with active bleeding or at high risk of bleeding, such as in preparation for invasive procedures or after chemotherapy. The control of bleeding in DIC patients with marked thrombocytopenia (platelet counts <10,000–20,000/μL) and low levels of coagulation factors will require replacement therapy. The PT (>1.5 times the normal) provides a good indicator of the severity of the clotting factor consumption. Replacement with FFP is indicated (1 unit of FFP increases most coagulation factors by 30% in an adult without DIC). Low levels of fibrinogen (<100 mg/dL) or brisk hyperfibrinolysis will require infusion of cryoprecipitate (plasma fraction enriched for fibrinogen, FVIII, and VWF). The replacement of 10 U of cryoprecipitate for every 2–3 U of FFP is sufficient to correct the hemostasis. The transfusion scheme must be adjusted according to the patient's clinical and laboratory evolution. Platelet concentrates at a dose of 1–2 U/10 kg body weight are sufficient for most DIC patients with severe thrombocytopenia. Clotting factor concentrates are not recommended for control of bleeding in DIC because of the limited efficacy afforded by replacement of single factors (FVIII or FIX concentrates) and the high risk of products containing traces of aPCCs that further aggravate the disease.

REPLACEMENT OF COAGULATION OR FIBRINOLYSIS INHIBITORS

Drugs to control coagulation such as heparin, antithrombin III (ATIII) concentrates, or antifibrinolytic drugs have all been tried in the treatment of DIC. Low doses of continuous-infusion heparin (5–10 U/kg per h) may be effective in patients with low-grade DIC associated with solid tumor, acute promyelocytic leukemia, or in a setting with recognized thrombosis. Heparin is also indicated for the treatment of purpura fulminans during the surgical resection of giant hemangiomas and during removal of a dead fetus. In acute DIC, the use of heparin is likely to aggravate bleeding. To date, the use of heparin in patients with severe DIC has no proven survival benefit. The use of antifibrinolytic drugs, EACA, or tranexamic acid to prevent fibrin degradation by plasmin may reduce bleeding episodes in patients with DIC and confirmed hyperfibrinolysis. However, these drugs can increase the risk of thrombosis, and concomitant use of heparin is indicated. Patients with acute promyelocytic leukemia or those with chronic DIC associated with giant hemangiomas are among the few patients who may benefit from this therapy. The use of protein C concentrates to treat purpura fulminans associated with acquired protein C deficiency or meningococcemia has been proven efficacious. The results from the replacement of ATIII in early-phase studies are promising but require further study.

Guidance for diagnosis and treatment of DIC had been proposed by the International Society of Thrombosis and Haemostasis. This initiative will permit more detailed clinical data on diagnosis and treatment of DIC. The clinical utility of these scoring systems and therapeutic recommendations contained in these guidelines is not yet known.

VITAMIN K DEFICIENCY

Vitamin K–dependent proteins are a heterogenous group, including clotting factor proteins and also proteins found in bone, lung, kidney, and placenta. Vitamin K mediates posttranslational modification of glutamate residues to γ-carboxylglutamate, a critical step for the activity of vitamin K–dependent proteins for calcium binding and proper assembly to phospholipid membranes (Fig. 112-2). Inherited deficiency of the functional activity of the enzymes involved in vitamin K metabolism, notably the GGCX or VKORC1 (see above), results in bleeding disorders. The amount of vitamin K in the diet is often limiting for the carboxylation reaction; thus recycling of the vitamin K is essential to maintain normal levels of vitamin K–dependent proteins. In adults, low dietary intake alone is seldom reason for severe vitamin K deficiency but may become common in association with the use of broad-spectrum antibiotics. Disease or surgical interventions that affect the ability of the intestinal tract to absorb vitamin K, either through anatomic alterations or by changing the fat content of bile salts and pancreatic juices in the proximal small bowel, can result in significant reduction of vitamin K levels. Chronic liver diseases such as primary biliary cirrhosis also deplete vitamin K stores. Neonatal vitamin K deficiency and the resulting hemorrhagic disease of the newborn have been almost entirely eliminated by routine administration of vitamin K to all neonates. Prolongation of PT values is the most common and earliest finding in vitamin K–deficient patients due to reduction in prothrombin, FVII, FIX, and FX levels. FVII has the shortest half-life among these factors that can prolong the PT before changes in the aPTT. Parenteral administration of vitamin K at a total dose of 10 mg is sufficient to restore normal levels of clotting factor within 8–10 h. In the presence of ongoing bleeding or a need for immediate correction before an invasive procedure, replacement with FFP or PCC is required. The latter should be avoided in patients with

severe underlying liver disorders due to high risk of thrombosis. The reversal of excessive anticoagulant therapy with warfarin or warfarin-like drugs can be achieved by minimal doses of vitamin K (1 mg orally or by intravenous injection) for asymptomatic patients. This strategy can diminish the risk of bleeding while maintaining therapeutic anticoagulation for an underlying prothrombotic state.

In patients with life-threatening bleeds, the use of recombinant factor VIIa in nonhemophilia patients on anticoagulant therapy has been shown to be effective at restoring hemostasis rapidly, allowing emergency surgical intervention. However, patients with underlying vascular disease, vascular trauma and other comorbidities are at risk for thromboembolic complications that affect both arterial and venous systems. Thus, the use of factor VIIa in this setting is limited to administration of low doses given for only a limited number of injections. Close monitoring for vascular complications is highly indicated.

COAGULATION DISORDERS ASSOCIATED WITH LIVER FAILURE

The liver is central to hemostasis because it is the site of synthesis and clearance of most procoagulant and natural anticoagulant proteins and of essential components of the fibrinolytic system. Liver failure is associated with a high risk of bleeding due to deficient synthesis of procoagulant factors and enhanced fibrinolysis. Thrombocytopenia is common in patients with liver disease, and may be due to congestive splenomegaly (hypersplenism) or immune-mediated shortened platelet lifespan (primary biliary cirrhosis). In addition, several anatomic abnormalities secondary to underlying liver disease further promote the occurrence of hemorrhage **(Table 112-3)**. Dysfibrinogenemia is a relatively common finding in patients with liver disease due to impaired fibrin polymerization. The development of DIC concomitant to chronic liver disease is not uncommon and may enhance the risk for bleeding. Laboratory evaluation is mandatory for an optimal therapeutic strategy, either to control ongoing bleeding or to prepare patients with liver disease for invasive procedures. Typically, these patients present with prolonged PT, aPTT, and TT depending on the degree of liver damage, thrombocytopenia, and normal or slight increase of FDP. Fibrinogen levels are diminished only in fulminant hepatitis, decompensated cirrhosis, or advanced liver disease, or in the presence of DIC. The presence of prolonged TT and normal fibrinogen and FDP levels suggest dysfibrinogenemia. FVIII levels are often normal or elevated in patients with liver failure, and decreased levels suggest superimposing DIC. Because FV is only synthesized in the hepatocyte and is not a vitamin K–dependent protein, reduced levels of FV may be an indicator of hepatocyte failure. Normal levels of FV and low levels of FVII suggest vitamin K deficiency. Vitamin K levels may be reduced in patients with liver failure due to compromised storage in hepatocellular disease, changes in bile acids, or cholestasis that can diminish the absorption of vitamin K. Replacement of vitamin K may be desirable (10 mg given by slow intravenous injection) to improve hemostasis.

Treatment with FFP is the most effective to correct hemostasis in patients with liver failure. Infusion of FFP (5–10 mL/kg; each bag contains ~200 mL) is sufficient to ensure 10–20% of normal levels of clotting factors but not correction of PT or aPTT. Even high doses of FFP (20 mL/kg) do not correct the clotting times in all patients. Monitoring for clinical symptoms and clotting times will determine if repeated doses are required 8–12 h after the first infusion. Platelet concentrates are indicated when platelet counts are <10,000–20,000/μL to control an ongoing bleed or immediately before an invasive procedure if counts are <50,000/μL. Cryoprecipitate is indicated only when fibrinogen levels are less than 100 mg/mL; dosing is six bags for a 70-kg patient daily. PCC infusion in patients with liver failure should be avoided due to the high risk of thrombotic complications. The safety of the use of antifibrinolytic drugs to control bleeding in patients with liver failure is not yet well defined and should be avoided.

Liver Disease and Thromboembolism The clinical bleeding phenotype of hemostasis in patients with stable liver disease is often mild or even asymptomatic. However, as the disease progresses, the hemostatic balance is less stable and more easily disturbed than in healthy individuals. Furthermore, the hemostatic balance is compromised by comorbid complications such as infections and renal failure **(Fig. 112-4)**. Based on the clinical bleeding complications in patients with cirrhosis and laboratory evidence of hypocoagulation such as a prolonged PT/aPTT, it has long been assumed that these patients are protected against thrombotic disease. Cumulative clinical experience, however, has demonstrated that these patients are at risk for thrombosis, especially those with advanced liver disease. Although hypercoagulability could explain the occurrence of venous thrombosis, according to Virchow's triad, hemodynamic changes and damaged vasculature may also be a contributing factor, and both processes may potentially also occur in patients with liver disease. Liver-related thrombosis, in particular, thrombosis of the portal and mesenteric veins, is common in patients with advanced cirrhosis. Hemodynamic changes, such as decreased portal flow, and evidence that inherited thrombophilia may enhance the risk for portal vein thrombosis in patients with cirrhosis suggest that hypercoagulability may play a role as well. Patients with liver disease develop deep-vein thrombosis and pulmonary embolism at appreciable rates (ranging from 0.5 to 1.9%). The implication of these findings is relevant to the erroneous exclusion of thrombosis in patients with advanced liver disease, even in the presence of prolongation of routine clotting times, and caution should be advised on overcorrection of these laboratory abnormalities.

Acquired Inhibitors of Coagulation Factors An acquired inhibitor is an immune-mediated disease characterized by the presence of an autoantibody against a specific clotting factor. FVIII is the most common target of antibody formation, and is sometimes referred to as acquired hemophilia A, but inhibitors to prothrombin, FV, FIX, FX, and FXI are also reported. Acquired inhibitor to FVIII occurs predominantly in older adults (median age of 60 years), but occasionally in pregnant or postpartum women with no previous history of bleeding. In 50% of patients with inhibitors, no underlying disease is identified at the time of diagnosis. In the remaining patients, the causes are autoimmune diseases, malignancies (lymphomas, prostate cancer), dermatologic diseases, and pregnancy. Bleeding episodes occur commonly in soft tissues, the gastrointestinal or urinary tracts, and skin. In contrast to hemophilia, hemarthrosis is rare in these patients. Retroperitoneal

TABLE 112-3 Coagulation Disorders and Hemostasis in Liver Disease

Bleeding
Portal hypertension
Esophageal varices
Thrombocytopenia
Splenomegaly
Chronic or acute DIC
Decreased synthesis of clotting factors
Hepatocyte failure
Vitamin K deficiency
Systemic fibrinolysis
DIC
Dysfibrinogenemia
Thrombosis
Decreased synthesis of coagulation inhibitors: protein C, protein S, antithrombin
Hepatocyte failure
Vitamin K deficiency (protein C, protein S)
Failure to clear activated coagulation proteins (DIC)
Dysfibrinogenemia
Iatrogenic: Transfusion of prothrombin complex concentrates
Antifibrinolytic agents: EACA, tranexamic acid

Abbreviations: DIC, disseminated intravascular coagulation; EACA, ε-aminocaproic acid.

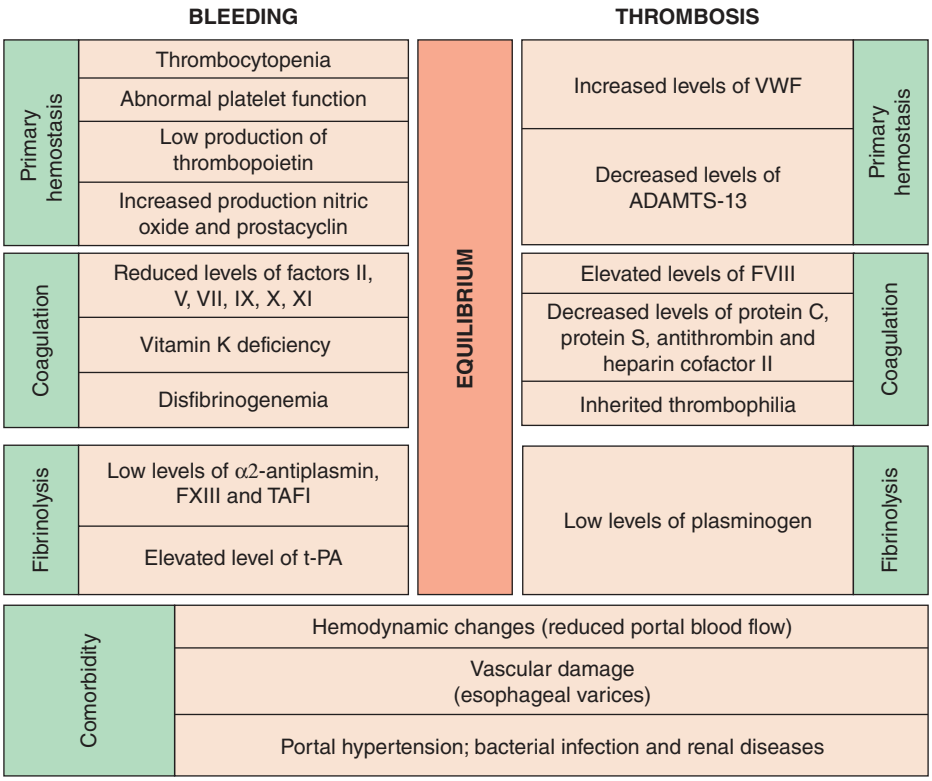

FIGURE 112-4 Balance of hemostasis in liver disease. TAFI, thrombin-activated fibrinolytic inhibitor; t-PA, tissue plasminogen activator; VWF, von Willebrand factor.

hemorrhages and other life-threatening bleeding may appear suddenly. The overall mortality in untreated patients ranges from 8 to 22%, and most deaths occur within the first few weeks after presentation. The diagnosis is based on the prolonged aPTT with normal PT and TT. The aPTT remains prolonged after mixture of the test plasma with equal amounts of pooled normal plasma for 2 h at 37°C. The Bethesda assay using factor specific-deficient plasma as performed for inhibitor detection in hemophilia will confirm the diagnosis. Major bleeding is treated with bypass products such as PCC/aPCC or recombinant FVIIa. Recombinant porcine FVIII is also available for the treatment of acquired hemophilia.

In contrast to hemophilia, inhibitors in nonhemophilic patients are typically responsive to immune suppression, and therapy should be initiated early for most cases. The first choice includes steroid or a combination of steroid with cytotoxic therapy (e.g., cyclophosphamide), with complete eradication of the inhibitors in more than 70% of patients. High-dose intravenous γ-globulin and anti-CD20 monoclonal antibody have been reported to be effective in patients with autoantibodies to FVIII; however, there is no firm evidence that these alternatives are superior to the first line of immunosuppressive drugs. Notably, relapse of the inhibitor to FVIII is relatively common (up to 20%) within the first 6 months following withdrawal of immunosuppression. Thus, after eradication, patients should be followed up regularly for early therapeutic intervention when indicated or prior to invasive procedure.

Topical plasma-derived bovine and human thrombin are commonly used in the United States and worldwide. These effective hemostatic sealants are used during major surgery such as for cardiovascular, thoracic, neurologic, pelvic, and trauma indications, as well as in the setting of extensive burns. The development of antibody formation to the xenoantigen or its contaminant (bovine clotting protein) has the potential to show cross-reactivity with human clotting factors that may hamper their function and induce bleeding.

Clinical features of these antibodies include bleeding from a primary hemostatic defect or coagulopathy that sometimes can be life threatening. The clinical diagnosis of these acquired coagulopathies is often complicated by the fact that the bleeding episodes may be detectable during or immediately following major surgery and could be assumed to be due to the procedure itself.

Notably, the risk of this complication is further increased by repeated exposure to topical thrombin preparations. Thus, a careful medical history of previous surgical interventions that may have occurred even decades earlier is critical to assessing risk.

The laboratory abnormalities are reflected by combined prolongation of the aPTT and PT that often fails to improve by transfusion of FFP and vitamin K. The abnormal laboratory tests cannot be corrected by mixing a test with equal parts of normal plasma that denotes the presence of inhibitory antibodies. The diagnosis of a specific antibody is obtained by the determination of the residual activity of human FV or other suspected human clotting factor. There are no commercially available assays specific for bovine thrombin coagulopathy.

There are no established treatment guidelines. Platelet transfusions have been used as a source of FV replacement for patients with FV inhibitors. Frequent injections of FFP and vitamin K supplementation may function as co-adjuvant rather than an effective treatment of the coagulopathy itself. Experience with recombinant FVIIa as a bypass agent is limited, and outcomes have been generally poor. Specific treatments to eradicate the antibodies based on immunosuppression with steroids, intravenous immunoglobulin, or serial plasmapheresis have been sporadically reported. Patients should be advised to avoid any topical thrombin sealant in the future.

Novel plasma-derived and recombinant human thrombin preparations for topical hemostasis have been approved by the U.S. Food and Drug Administration. These preparations have demonstrated hemostatic efficacy with reduced immunogenicity compared to the first generation of bovine thrombin products.

The presence of lupus anticoagulant can be associated with venous or arterial thrombotic disease. However, bleeding has also been reported in lupus anticoagulant; it is due to the presence of antibodies to prothrombin, which results in hypoprothrombinemia. Both disorders show a prolonged PTT that does not correct on mixing. To distinguish acquired inhibitors from lupus anticoagulant, note that the dilute Russell's viper venom test and the hexagonal-phase phospholipids test will be negative in patients with an acquired inhibitor and positive in patients with lupus anticoagulants. Moreover, lupus anticoagulant interferes with the clotting activity of many factors (FVIII, FIX, FXII, FXI), whereas acquired inhibitors are specific to a single factor.

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113 Arterial and Venous Thrombosis

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OVERVIEW OF THROMBOSIS

GENERAL OVERVIEW

Thrombosis, the obstruction of blood flow due to the formation of clot, may result in tissue anoxia and damage, and it is a major cause of morbidity and mortality in a wide range of arterial and venous diseases and patient populations. In 2013 in the United States, cardiovascular disease accounted for 30.8% (800,937) of all 2,596,993 deaths, or about 1 of every 3 deaths. Approximately 735,000 people had a new or recurrent myocardial infarction, and ~690,000 people experienced a new or recurrent ischemic stroke. It is estimated that 300,000–600,000 people each year have a pulmonary embolism or deep-venous thrombotic event. In the nondiseased state, physiologic hemostasis reflects a delicate interplay between factors that promote and inhibit blood clotting, favoring the former. This response is crucial as it prevents uncontrolled hemorrhage and exsanguination following injury. In specific settings, the same processes that regulate normal hemostasis can cause pathologic thrombosis, leading to arterial or venous occlusion. Importantly, many commonly used therapeutic interventions may also alter the thrombotic–hemostatic balance adversely.

Hemostasis and thrombosis primarily involve the interplay among three factors: the vessel wall, coagulation and fibrinolytic proteins, and platelets. Many prevalent acute vascular diseases are due to thrombus formation within a vessel, including myocardial infarction, thrombotic cerebrovascular events, and venous thrombosis. Although the end result is vessel occlusion and tissue ischemia, the pathophysiologic processes governing these pathologies have similarities as well as distinct differences. While many of the pathways regulating thrombus formation are similar to those that regulate hemostasis, the processes triggering or perpetuating thrombosis may be distinct and can vary in different clinical and genetic settings. In venous thrombosis, primary hypercoagulable states reflecting defects in the proteins governing coagulation and/or fibrinolysis or secondary hypercoagulable states involving abnormalities of blood vessels and blood flow or stasis lead to thrombosis. By contrast, arterial thrombosis is highly dependent on the state of the vessel wall, the platelet, and factors related to blood flow.

ARTERIAL THROMBOSIS

OVERVIEW OF ARTERIAL THROMBOSIS

In arterial thrombosis, platelets and abnormalities of the vessel wall typically play a key role in vessel occlusion. Arterial thrombus forms via a series of sequential steps in which platelets adhere to the vessel wall, additional platelets are recruited, and thrombin is activated (Fig. 113-1). The regulation of platelet adhesion, activation, aggregation, and recruitment will be described in detail below. In addition, while the primary function of platelets is regulation of hemostasis, our understanding of their role in other processes, such as immunity, metastasis, wound healing, and inflammation, continues to evolve.

ARTERIAL THROMBOSIS AND VASCULAR DISEASE

Arterial thrombosis is a major cause of morbidity and mortality both in the United States and, increasingly, worldwide. Although the rates have declined in the United States, the overall burden remains high. Overall, in 2013 coronary heart disease was estimated to cause about 1 of every 7 deaths in the United States. In addition to the 660,000 Americans who will have a new coronary event, an additional 160,000 silent first myocardial infarctions are projected to occur annually. Although the rate of strokes has fallen by a third, each year, about 690,000 people experience a new or recurrent ischemic stroke. It is estimated that 1 of every 20 deaths in the United States is due to stroke.

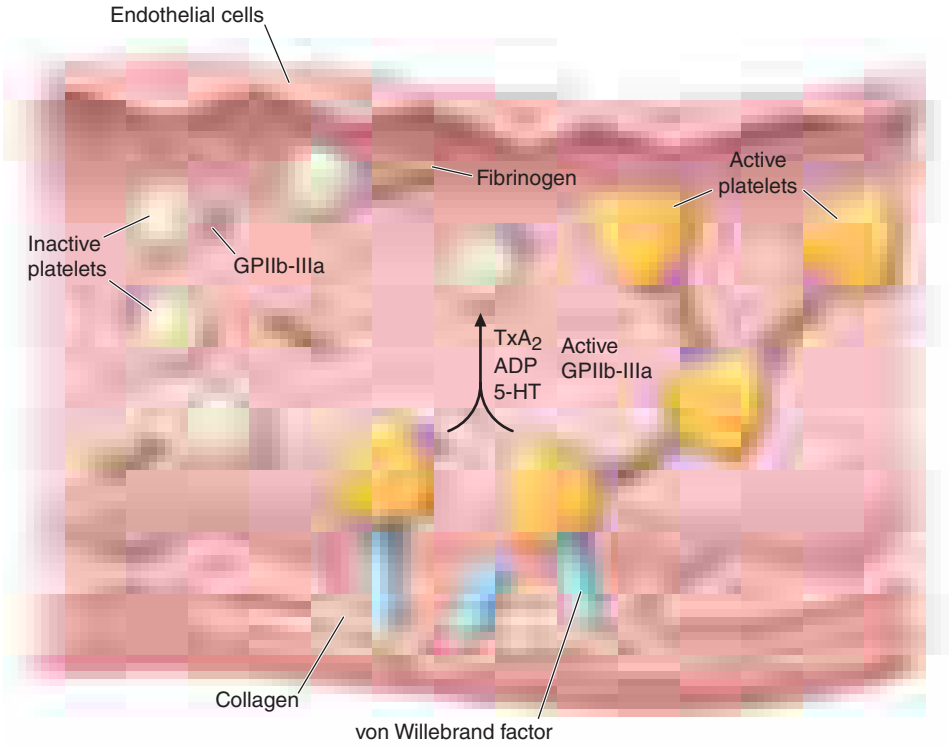

FIGURE 113-1 Platelet activation and thrombosis. Platelets circulate in an inactive form in the vasculature. Damage to the endothelium and/or external stimuli activates platelets that adhere to the exposed subendothelial von Willebrand factor and collagen. This adhesion leads to activation of the platelet, shape change, and the synthesis and release of thromboxane (TxA_2), serotonin (5-HT), and adenosine diphosphate (ADP). Platelet stimuli cause conformational change in the platelet integrin glycoprotein (GP) IIb/IIIa receptor, leading to the high-affinity binding of fibrinogen and the formation of a stable platelet thrombus.

THE PLATELET

Many processes in platelets have parallels with other cell types, such as the presence of specific receptors and signaling pathways; however, unlike most cells, platelets lack a nucleus and are unable to adapt to changing biologic settings by altered gene transcription. Platelets sustain limited protein synthetic capacity from megakaryocyte-derived and intracellularly transported messenger RNA (mRNA) and microRNA (miRNA). Most of the molecules needed to respond to various stimuli, however, are maintained in storage granules and membrane compartments.

Platelets are disc-shaped, very small, anucleate cells (1–5 μm in diameter) that circulate in the blood at concentrations of 200–400,000/μL, with an average life span of 7–10 days. Platelets are derived from megakaryocytes, polyploidal hematopoietic cells found in the bone marrow. The primary regulator of platelet formation is thrombopoietin (TPO). The precise mechanism by which megakaryocytes produce and release fully formed platelets is unclear, but the process likely involves formation of proplatelets, pseudopod-like structures generated by the evagination of the cytoplasm from which platelets bud. After release into the circulation, (young, large) platelets may continue to divide. Platelet granules are synthesized in

megakaryocytes before thrombopoiesis and contain an array of prothrombotic, proinflammatory, and antimicrobial mediators. The two major types of platelet granules, alpha and dense, are distinguished by their size, abundance, and content. Alpha-granules contain soluble coagulation proteins, adhesion molecules, growth factors, integrins, cytokines, and inflammatory modulators. Platelet dense-granules are smaller than alpha-granules and less abundant. Whereas alpha-granules contain proteins that may be more important in the inflammatory response, dense-granules contain high concentrations of small molecules, including adenosine diphosphate (ADP) and serotonin that influence platelet aggregation and other related vascular processes, such as vasomotor tone.

Platelet Adhesion (See Fig. 113-1) The formation of a thrombus is initiated by the adherence of platelets to the damaged vessel wall. Damage exposes subendothelial components responsible for triggering platelet reactivity, including collagen, von Willebrand factor, fibronectin, and other adhesive proteins, such as vitronectin and thrombospondin. The hemostatic response may vary, depending on the extent of damage, the specific proteins exposed, and flow conditions. Certain proteins are expressed on the platelet surface that subsequently regulate collagen-induced platelet adhesion, particularly under flow conditions, and include glycoprotein (GP) IV, GPVI, and the integrin $\alpha_2\beta_1$. The platelet GPIb-IX-V complex adhesive receptor is central both to platelet adhesion and to the initiation of platelet activation. Damage to the blood vessel wall exposes subendothelial von Willebrand factor and collagen to the circulating blood. The GPIb-IX-V complex binds to the exposed von Willebrand factor, causing platelets to adhere (Fig. 113-1). In addition, the engagement of the GPIb-IX-V complex with ligand induces signaling pathways that lead to platelet activation. von Willebrand factor–bound GPIb-IX-V promotes a calcium-dependent conformational change in the GPIIb/IIIa receptor, transforming it from an inactive low-affinity state to an active high-affinity receptor for fibrinogen.

Platelet Activation The activation of platelets is controlled by a variety of surface receptors that regulate various functions in the activation process. Platelet receptors control many distinct processes and are stimulated by a wide variety of agonists and adhesive proteins that result in variable degrees of activation. In general terms, the stimulation of platelet receptors triggers two specific processes: (1) activation of internal signaling pathways that lead to further platelet activation and granule release, and (2) the capacity of the platelet to bind to other adhesive proteins/platelets. Both of these processes contribute to the formation of a thrombus. Stimulation of nonthrombotic receptors results in platelet adhesion or interaction with other vascular cells, including endothelial cells, neutrophils, and mononuclear cells.

Many families and subfamilies of receptors are found on platelets that regulate a variety of platelet functions. These include the seven transmembrane receptor family, which is the main agonist-stimulated receptor family. Several seven transmembrane receptors are found on platelets, including the ADP receptors, prostaglandin receptors, lipid receptors, and chemokine receptors. Receptors for thrombin comprise the major seven transmembrane receptors found on platelets. Among this last group, the first identified was the protease activation receptor 1 (PAR1). The PAR class of receptors has a distinct mechanism of activation that involves specific cleavage of the N-terminus by thrombin, which, in turn, acts as a ligand for the receptor. Other PAR receptors are present on platelets, including PAR2 (not activated by thrombin) and PAR4. Adenosine receptors are responsible for transduction of ADP-induced signaling events, which are initiated by the binding of ADP to purinergic receptors on the platelet surface. There are several distinct ADP receptors, classified as $P2X_1$, $P2Y_1$, and $P2Y_{12}$. The activation of both the $P2Y_{12}$ and $P2Y_1$ receptors is essential for ADP-induced platelet aggregation. The thienopyridine derivatives, clopidogrel and prasugrel, are clinically used inhibitors of ADP-induced platelet aggregation.

Platelet Aggregation Activation of platelets results in a rapid series of signal transduction events, including tyrosine kinase, serine/threonine kinase, and lipid kinase activation. In unstimulated platelets, the major platelet integrin GPIIb/IIIa is maintained in an inactive conformation and functions as a low-affinity adhesion receptor for fibrinogen. This integrin is unique as it is only expressed on platelets. After stimulation, the interaction between fibrinogen and GPIIb/IIIa forms intercellular connections between platelets, leading to the formation of a platelet aggregate (Fig. 113-1). A calcium-sensitive conformational change in the extracellular domain of GPIIb/IIIa enables the high-affinity binding of soluble plasma fibrinogen as a result of a complex network of inside-out signaling events. The GPIIb/IIIa receptor serves as a bidirectional conduit with GPIIb/IIIa-mediated signaling (outside-in) occurring immediately after the binding of fibrinogen. This leads to additional intracellular signaling that further stabilizes the platelet aggregate and transforms platelet aggregation from a reversible to an irreversible process (inside-out).

THE ROLE OF PLATELETS AND THROMBOSIS IN INFLAMMATION

Inflammation plays an important role during the acute thrombotic phase of acute coronary syndromes. In the setting of acute upper respiratory infections, people are at higher risk of myocardial infarction and thrombotic stroke. Patients with acute coronary syndromes have not only increased interactions between platelets (homotypic aggregates), but also increased interactions between platelets and leukocytes (heterotypic aggregates) detectable in circulating blood. These latter aggregates form when platelets are activated and adhere to circulating leukocytes. Platelets bind via P-selectin (CD62P) expressed on the surface of activated platelets to the leukocyte receptor, P-selectin glycoprotein ligand 1 (PSGL-1). This association leads to increased expression of CD11b/CD18 (Mac-1) on leukocytes, which itself supports interactions with platelets partially via bivalent fibrinogen linking this integrin with its platelet surface counterpart, GPIIb/IIIa. Platelet surface P-selectin also induces the expression of tissue factor on monocytes, which promotes fibrin formation.

In addition to platelet–monocyte aggregates, the immunomodulator, soluble CD40 ligand (CD40L or CD154), also reflects a link between thrombosis and inflammation. The CD40 ligand is a trimeric transmembrane protein of the tumor necrosis factor family and, with its receptor CD40, is an important contributor to the inflammatory process leading both to thrombosis and atherosclerosis. While many immunologic and vascular cells have been found to express CD40 and/or CD40 ligand, in platelets, CD40 ligand is rapidly translocated to the surface after stimulation and is upregulated in the newly formed thrombus. The surface-expressed CD40 ligand is cleaved from the platelet to generate a soluble fragment (soluble CD40 ligand).

Links have also been established among platelets, infection, immunity, and inflammation. Bacterial and viral infections are associated with a transient increase in the risk of acute thrombotic events, such as acute myocardial infarction and stroke. In addition, platelets contribute significantly to the pathophysiology and high mortality rates of sepsis. The expression, functionality, and signaling pathways of Toll-like receptors (TLRs) have been established in platelets. Stimulation of platelet TLR2, TLR3, and TLR4 directly and indirectly activates the platelet's thrombotic and inflammatory responses, and live bacteria induce a proinflammatory response in platelets in a TLR2-dependent manner, suggesting a mechanism by which specific bacteria and bacterial components can directly activate platelet-dependent thrombosis. Additionally, viruses, such as HIV, HCV, and Dengue, are also known to cause elevated levels of thrombosis, and, recently, platelets have been shown to regulate immune responses to viruses via receptors TLR7 and TLR8.

Risk Factors for Arterial Thrombosis Various factors increase the risk of developing arterial thrombosis. Classically, the cardiovascular-dependent risk factors implicated in thrombosis have been hypertension, high levels of low-density lipoprotein-cholesterol, and smoking. However, diabetes, pregnancy, age, chemotherapeutics, and infectious burden may also contribute to arterial thrombosis. Stillbirth and loss of multiple pregnancies may increase the risk of ischemic stroke and MI as does hormonal replacement therapy. Systemic lupus erythematosus and rheumatoid arthritis are now well-recognized risks

for thrombosis, and the former, in particular, may contribute in the pediatric population. The antiphospholipid syndrome is also another widely recognized autoimmune prothrombotic risk for arterial (and venous) thrombosis.

GENETICS OF ARTERIAL THROMBOSIS

Some studies have associated arterial thrombosis with genetic variants (Table 113-1 *A*); however, the associations have been weak and not confirmed in larger series. Platelet count and mean platelet volume have been studied by genome-wide association studies (GWAS), and this approach identified signals located to noncoding regions. Of 15 quantitative trait loci associated with mean platelet volume and platelet count, one located at 12q24 is also a risk locus for coronary artery disease.

In the area of genetic variability and platelet function, studies have primarily dealt with pharmacogenetics, the field of pharmacology dealing with the interindividual variability in drug response based on genetic determinants (Table 113-2). This focus has been driven by the wide variability among individuals in terms of response to antithrombotic drugs and the lack of a common explanation for this variance. The best described is the issue of "aspirin resistance," although heterogeneity for other antithrombotics (e.g., clopidogrel) has also been extensively examined. Primarily, platelet-dependent genetic determinants have been defined at the level of (1) drug effect, (2) drug compliance, and (3) drug metabolism. Many candidate platelet genes have been studied for their interaction with antiplatelet and antithrombotic agents.

TABLE 113-1 Heritable Causes of Arterial and Venous Thrombosis

A. Arterial Thrombosis
Platelet Receptors
β3 and α2 integrins
P_l A2 polymorphism
Fc(gamma)RIIA
GPIV T13254C polymorphism
GPIb
Thrombin receptor PAR1-5061 → D
Redox Enzymes
Plasma glutathione peroxidase, GPx3, promoter haploytpe H2
H2 promoter haplotype
Endothelial nitric oxide synthase
–786T/C, –922A/G, –1468T/A
Paraoxonase
–107T allele, 192R allele
Homocysteine
Cystathionine β-synthase 833T → C
5,10-Methylene tetrahydrofolate reductase (MTHFR) 677C → T
B. Venous Thrombosis
Procoagulant Proteins
Fibrinogen
–455G/A, –854G/A
Prothrombin (20210G → A)
Protein C Anticoagulant Pathway
Factor V Leiden: 1691G → A (Arg506Gln)
Thrombomodulin 1481C → T (Ala455Val)
Fibrinolytic Proteins with Known Polymorphisms
Tissue plasminogen activator (tPA)
7351C/T, 20 099T/C in exon 6, 27 445T/A in intron 10
Plasminogen activator inhibitor (PAI-1)
4G/5G insertion/deletion polymorphism at position –675
Homocysteine
Cystathionine β-synthase 833T → C
5,10-MTHFR 677C → T

TABLE 113-2 Genetic Variation and Pharmacogenetic Responses to Platelet Inhibitors

POTENTIAL GENE ALTERED	TARGET THERAPEUTIC CLASS	SPECIFIC DRUG
P2Y1 and *P2Y12* *CYP2C19, CYP3A4, CYP3A5*	ADP receptor inhibitors	Clopidogrel, prasugrel
COX1, COX2	Cyclooxygenase inhibitors	Aspirin
PIA1/A2	Receptor inhibitors	Abciximab, eptifibatide, tirofiban
INTB3, GPIbA	Glycoprotein IIb-IIIa receptor inhibitors	

Many patients have an inadequate response to the inhibitory effects of aspirin. Heritable factors contribute to the variability; however, ex vivo tests of residual platelet responsiveness after aspirin administration have not provided firm evidence for a pharmacogenetic interaction between aspirin and *COX1* or other relevant platelet receptors. As such, currently, there is no clinical indication for genotyping to optimize aspirin's antiplatelet efficiency. For the platelet P2Y12 receptor inhibitor clopidogrel, additional data suggest that genetics may affect the drug's responsiveness and utility. The responsible genetic variant appears not to be the expected P2Y12 receptor but an enzyme responsible for drug metabolism. Clopidogrel is a prodrug, and liver metabolism by specific cytochrome P450 enzymes is required for activation. The genes encoding the CYP-dependent oxidative steps are polymorphic, and carriers of specific alleles of the CYP2C19 and CYP3A4 loci have increased platelet aggregability. Increased platelet activity has also been specifically associated with the CYP2C19*2 allele, which causes loss of platelet function in select patients. Because these are common genetic variants, this observation has been shown to be clinically relevant in large studies. In summary, although the loss-of-function polymorphisms in CYP2C19 is the strongest individual variable affecting pharmacokinetics and antiplatelet response to clopidogrel; it only accounts for 5–12% of the variability in ADP-induced platelet aggregation on clopidogrel. In addition, genetic variables do not appear to contribute significantly to the clinical outcomes of patients treated with the P2Y12 receptor antagonists prasugrel or ticagrelor.

VENOUS THROMBOSIS

OVERVIEW OF VENOUS THROMBOSIS

Coagulation is the process by which thrombin is activated and soluble plasma fibrinogen is converted into insoluble fibrin. These steps account for both normal hemostasis and the pathophysiologic processes influencing the development of venous thrombosis. The primary forms of venous thrombosis are deep-vein thrombosis (DVT) in the extremities and the subsequent embolization to the lungs (pulmonary embolism), referred to together as venous thromboembolic disease (VTE). Venous thrombosis occurs due to heritable causes (Table 113-1 *B*) and acquired causes (Table 113-3).

DEEP-VENOUS THROMBOSIS AND PULMONARY EMBOLISM

It is estimated that 300,000–600,000 new cases of venous thromboembolism occur each year with 60,000–80,000 deaths attributed to DVT or PE. Of new cases, up to 30% of patients die within 30 days and one-fifth suffer sudden death due to pulmonary embolism; 30% go on to develop recurrent venous thromboembolism within 10 years. Data from the Atherosclerosis Risk in Communities (ARIC) study reported a 9% 28-day fatality rate from DVT and a 15% fatality rate from pulmonary embolism. Pulmonary embolism in the setting of cancer has a 25% fatality rate. The mean incidence of first DVT in the general population is 5 per 10,000 person-years; the incidence is similar in males and females when adjusting for factors related to reproduction and birth control and increases dramatically with age from 2 to 3 per 10,000 person-years at 30–49 years of age to 20 per 10,000 person-years at 70–79 years of age.

TABLE 113-3 Acquired Causes of Venous Thrombosis
Surgery
Neurosurgery
Major abdominal surgery
Malignancy
Antiphospholipid syndrome
Other
Trauma
Pregnancy
Long-distance travel
Obesity
Oral contraceptives/hormone replacement
Myeloproliferative disorders
Polycythemia vera

OVERVIEW OF THE COAGULATION CASCADE AND ITS ROLE IN VENOUS THROMBOSIS

Coagulation is defined as the formation of fibrin by a series of linked enzymatic reactions in which each reaction product converts the subsequent inactive zymogen into an active serine protease (Fig. 113-2). This coordinated sequence is called the coagulation cascade and is a key mechanism for regulating hemostasis. Central to the function of the coagulation cascade is the principle of amplification: due to a series of linked enzymatic reactions, a small stimulus can lead to much greater quantities of fibrin, the end product that prevents hemorrhage at the site of vascular injury. In addition to the known risk factors relevant to hypercoagulopathy, stasis, and vascular dysfunction, newer areas of research have identified contributions from procoagulant microparticles, inflammatory cells, microvesicles, and fibrin structure.

The coagulation cascade is primarily initiated by vascular injury exposing tissue factor to blood components (Fig. 113-2). Tissue factor may also be found in bloodborne cell-derived microparticles and, under pathophysiologic conditions, in leukocytes or platelets. Plasma factor VII (FVII) is the ligand for and is activated (FVIIa) by binding to tissue factor exposed at the site of vessel damage. The binding of FVII/VIIa to tissue factor activates the downstream conversion of factor X (FX) to active FX (FXa). In an alternative reaction, the FVII/FVIIa–tissue factor complex initially converts FIX to FIXa, which then activates FX in conjunction with its cofactor factor VIII (FVIIIa). Factor Xa with its cofactor FVa converts prothrombin to thrombin, which then converts soluble plasma fibrinogen to insoluble fibrin, leading to clot or thrombus formation. Thrombin also activates FXIII to FXIIIa, a transglutaminase that covalently cross-links and stabilizes the fibrin clot. Formation of thrombi is affected by mechanisms governing fibrin structure and stability, including specific fibrinogen variants and how they alter fibrin formation, strength, and structure.

Several antithrombotic factors also regulate coagulation; these include antithrombin, tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein C/protein S. Under normal conditions, these factors limit the production of thrombin to prevent the perpetuation of coagulation and thrombus formation. Typically, after the clot has caused occlusion at the damaged site and begins to expand toward adjacent uninjured vessel segments, the anticoagulant reactions governed by the normal endothelium become pivotal in limiting the extent of this hemostatically protective clot.

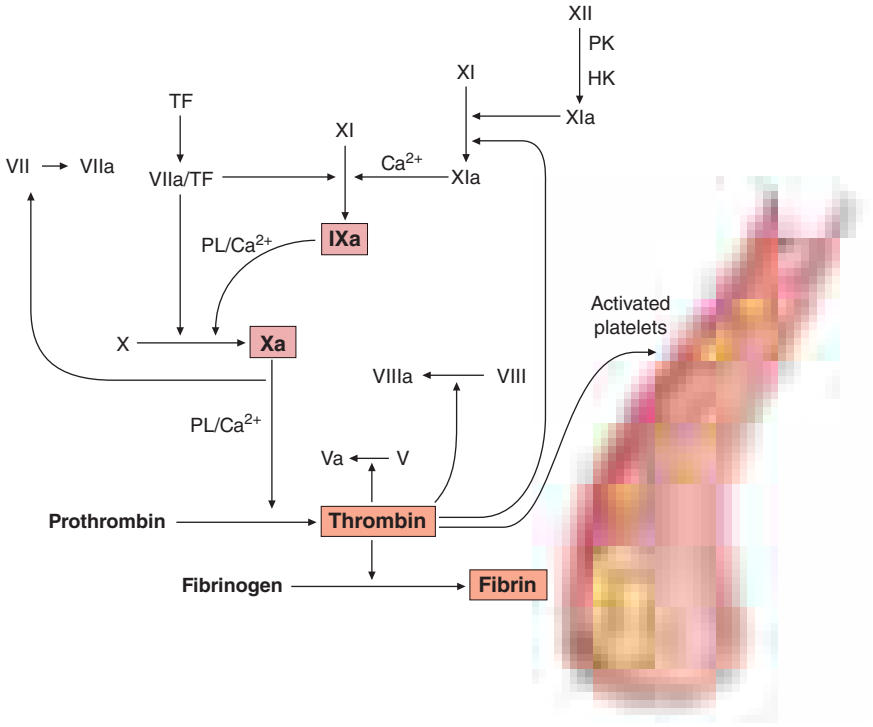

FIGURE 113-2 Summary of the coagulation pathways. Specific coagulation factors ("a" indicates activated form) are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin. This process occurs via a series of linked reactions in which the enzymatically active product subsequently converts the downstream inactive protein into an active serine protease. In addition, the activation of thrombin leads to stimulation of platelets. HK, high-molecular-weight kininogen; PK, prekallikrein; TF, tissue factor.

RISK FACTORS FOR VENOUS THROMBOSIS

An array of different factors contributes to the risk of VTE, and it is notable that women and men of all ages, races, and ethnicities are at risk for venous thromboembolism. The risk factors for venous thrombosis are primarily related to hypercoagulability, which can be genetic (Table 113-1) or acquired, or due to immobilization and venous stasis. Independent predictors for recurrence include increasing age, obesity, malignant neoplasm, and acute extremity paresis. It is estimated that 5–8% of the U.S. population has a genetic risk factor known to predispose to venous thrombosis. Often, multiple risk factors are present in a single individual. Significant risk is incurred by major orthopedic, abdominal, or neurologic surgeries. Cancer patients have an approximately fourfold increased risk of VTE as compared with the general population, and cancer patients with VTE have reduced survival. Hospitalized patients have a greatly increased risk of venous thrombosis with risk factors (increased age, male, ethnicity) and comorbid conditions, including infection, renal disease, and weight loss. Moderate risk is promoted by prolonged bedrest; certain types of cancer, pregnancy, hormone replacement therapy, or oral contraceptive use; and other sedentary conditions such as long-distance plane travel. It has been reported that the risk of developing a venous thromboembolic event doubles after air travel lasting 4 h, although the absolute risk remains low (1 in 6000). The relative risk of VTE among pregnant or postpartum women is 4.3, and the overall incidence (absolute risk) is 199.7 per 100,000 woman-years.

GENETICS OF VENOUS THROMBOSIS

(See Table 113-2) Less common causes of venous thrombosis are those due to genetic variants. These abnormalities include loss-of-function mutations of endogenous anticoagulants as well as gain-of-function mutations of procoagulant proteins. Heterozygous antithrombin deficiency and homozygosity of the factor V Leiden mutation significantly increase the risk of venous thrombosis. While homozygous protein C or protein S deficiencies are rare and may lead to fatal purpura fulminans, heterozygous deficiencies are associated with a moderate risk of thrombosis. Activated protein C impairs coagulation by proteolytic

degradation of FVa. Patients resistant to the activity of activated protein C may have a point mutation in the FV gene located on chromosome 1, a mutant denoted factor V Leiden. Mildly increased risk has been attributed to elevated levels of procoagulant factors, as well as low levels of tissue factor pathway inhibitor. Polymorphisms of methylene tetrahydrofolate reductase as well as hyperhomocysteinemia have been shown to be independent risk factors for venous thrombosis, as well as arterial vascular disease; however, many of the initial descriptions of genetic variants and their associations with thromboembolism are being questioned in larger, more contemporary studies.

FIBRINOLYSIS AND THROMBOSIS

Specific abnormalities in the fibrinolytic system have been associated with enhanced thrombosis. Factors such as elevated levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor type 1 (PAI-1) have been associated with decreased fibrinolytic activity and an increased risk of arterial thrombotic disease. Specific genetic variants have been associated with decreased fibrinolytic activity, including the 4G/5G insertion/deletion polymorphism in the (plasminogen activator type 1) *PAI-1* gene. Additionally, the 311-bp Alu insertion/deletion in tPA's intron 8 has been associated with enhanced thrombosis; however, genetic abnormalities have not been associated consistently with altered function or tPA levels, raising questions about the relevant pathophysiologic mechanism. Thrombin-activatable fibrinolysis inhibitor (TAFI) is a carboxypeptidase that regulates fibrinolysis; elevated plasma TAFI levels have been associated with an increased risk of both DVT and cardiovascular disease.

The metabolic syndrome also is accompanied by altered fibrinolytic activity. This syndrome, which comprises abdominal fat (central obesity), altered glucose and insulin metabolism, dyslipidemia, and hypertension, has been associated with atherothrombosis. The mechanism for enhanced thrombosis appears to be due both to altered platelet function and to a procoagulant and hypofibrinolytic state. One of the most frequently documented prothrombotic abnormalities reported in this syndrome is an increase in plasma levels of PAI-1.

In addition to contributing to platelet function, inflammation plays a role in both coagulation-dependent thrombus formation and thrombus resolution. Both polymorphonuclear neutrophils and monocytes/macrophages contribute to multiple overlapping thrombotic functions, including fibrinolysis, chemokine and cytokine production, and phagocytosis.

THE DISTINCTION BETWEEN ARTERIAL AND VENOUS THROMBOSIS

Although there is overlap, venous thrombosis and arterial thrombosis are initiated differently, and clot formation progresses by somewhat distinct pathways. In the setting of stasis or states of hypercoagulability, venous thrombosis is activated with the initiation of the coagulation cascade primarily due to exposure of tissue factor; this leads to the formation of thrombin and the subsequent conversion of fibrinogen to fibrin. In the artery, thrombin formation also occurs, but thrombosis is primarily promoted by the adhesion of platelets to an injured vessel and stimulated by exposed extracellular matrix (Figs. 113-1 and 113-2). There is wide variation in individual responses to vascular injury, an important determinant of which is the predisposition an individual has to arterial or venous thrombosis. This concept has been supported indirectly in prothrombotic animal models in which there is poor correlation between the propensity to develop venous versus arterial thrombosis.

Despite considerable progress in understanding the role of hypercoagulable states in VTE, the contribution of hypercoagulability to arterial vascular disease is much less well understood. Although specific thrombophilic conditions, such as factor V Leiden and the prothrombin G20210A mutation, are risk factors for DVT, pulmonary embolism, and other venous thromboembolic events, their contribution to arterial thrombosis is less well defined. In fact, to the contrary, many of these thrombophilic factors have not been found to be clinically important risk factors for arterial thrombotic events, such as acute coronary syndromes.

Clinically, although the pathophysiology is distinct, arterial and venous thrombosis do share common risk factors, including age, obesity, cigarette smoking, diabetes mellitus, arterial hypertension, hyperlipidemia, and metabolic syndrome. Select genetic variants, including those of the glutathione peroxidase-3 (GPx3) gene, have also been associated with arterial and venous thrombo-occlusive disease. Importantly, arterial and venous thrombosis may both be triggered by pathophysiologic stimuli responsible for activating inflammatory and oxidative pathways.

The diagnosis and treatment of ischemic heart disease are discussed in Chap. 267. Stroke diagnosis and management are discussed in Chap. 301. The diagnosis and management of DVT and pulmonary embolus are discussed in Chap. 273.

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114 Antiplatelet, Anticoagulant, and Fibrinolytic Drugs

Jeffrey I. Weitz

Thromboembolic disorders are major causes of morbidity and mortality. Thrombosis can occur in arteries or veins. Arterial thrombosis is the most common cause of acute myocardial infarction (MI), ischemic stroke, and limb gangrene. Venous thromboembolism encompasses deep vein thrombosis (DVT), which can lead to postthrombotic syndrome, and pulmonary embolism (PE), which can be fatal or can result in chronic thromboembolic pulmonary hypertension.

Most arterial thrombi are superimposed on disrupted atherosclerotic plaque because plaque rupture exposes thrombogenic material in the core to the blood. This material then triggers platelet aggregation and fibrin formation, which results in the generation of a platelet-rich thrombus that can temporarily or permanently occlude blood flow. In contrast, venous thrombi rarely form at sites of obvious vascular disruption. Although they can develop after surgical trauma to veins or secondary to indwelling venous catheters, venous thrombi usually originate in the valve cusps of the deep veins of the calf or in the muscular sinuses. Sluggish blood flow reduces the oxygen supply to the avascular valve cusps. Endothelial cells lining these valve cusps become activated and express adhesion molecules on their surface. Tissue factor–bearing leukocytes and microparticles adhere to these

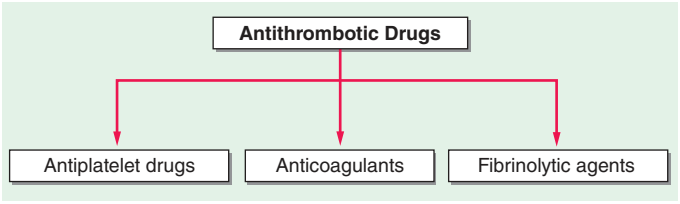

FIGURE 114-1 Classification of antithrombotic drugs.

activated cells and induce coagulation. DNA extruded from neutrophils forms neutrophil extracelluar traps (NETs) that provide a scaffold that binds platelets and promotes their activation and aggregation. Local thrombus formation is exacerbated by reduced clearance of activated clotting factors as a result of impaired blood flow. If the thrombi extend from the calf veins into the popliteal and more proximal veins of the leg, thrombus fragments can dislodge, travel to the lungs, and produce a PE.

Arterial and venous thrombi are composed of platelets, fibrin, and trapped red blood cells, but the proportions differ. Arterial thrombi are rich in platelets because of the high shear in the injured arteries. In contrast, venous thrombi, which form under low shear conditions, contain relatively few platelets and are predominantly composed of fibrin and trapped red cells. Because of the predominance of platelets, arterial thrombi appear white, whereas venous thrombi are red in color, reflecting the trapped red cells.

Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include (1) antiplatelet drugs, (2) anticoagulants, and (3) fibrinolytic agents **(Fig. 114-1)**. With the predominance of platelets in arterial thrombi, strategies to attenuate arterial thrombosis focus mainly on antiplatelet agents, although, in the acute setting, may include anticoagulants and fibrinolytic agents. Anticoagulants are the mainstay of prevention and treatment of venous thromboembolism because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi. Fibrinolytic therapy is used in selected patients with venous thromboembolism. For example, patients with massive PE can benefit from systemic or catheter-directed fibrinolytic therapy. Pharmaco-mechanical therapy also is used to restore blood flow in patients with extensive DVT involving the iliac and/or femoral veins.

ANTIPLATELET DRUGS

ROLE OF PLATELETS IN ARTERIAL THROMBOSIS

In healthy vasculature, circulating platelets are maintained in an inactive state by nitric oxide (NO) and prostacyclin released by endothelial cells lining the blood vessels. In addition, endothelial cells also express CD39 on their surface, a membrane-associated ecto-adenosine diphosphatase (ADPase) that degrades ADP released from activated platelets. When the vessel wall is damaged, release of these substances is impaired and subendothelial matrix is exposed. Platelets adhere to exposed collagen via $\alpha_2\beta_1$ and glycoprotein (Gp) V1 and to von Willebrand factor (VWF) via Gp Ibα and Gp IIb/IIIa ($\alpha_{IIb}\beta_3$)—receptors that are constitutively expressed on the platelet surface. Adherent platelets undergo a change in shape, secrete ADP from their dense granules, and synthesize and release thromboxane A_2. Released ADP and thromboxane A_2, which are platelet agonists, activate ambient platelets and recruit them to the site of vascular injury **(Fig. 114-2)**.

Disruption of the vessel wall also exposes tissue factor–expressing cells to the blood. Tissue factor binds factor VIIa and initiates coagulation. Activated platelets potentiate coagulation by providing a surface that binds clotting factors and supports the assembly of activation complexes that enhance thrombin generation. In addition to converting fibrinogen to fibrin, thrombin serves as a potent platelet agonist and recruits more platelets to the site of vascular injury. Thrombin also amplifies its own generation by feedback activation of factors V, VIII, and XI and solidifies the fibrin network by activating factor XIII, which then cross-links the fibrin strands.

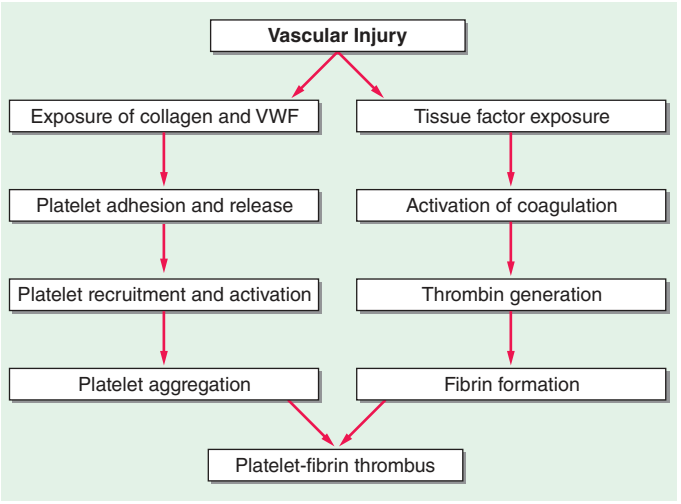

FIGURE 114-2 Coordinated role of platelets and the coagulation system in thrombogenesis. Vascular injury simultaneously triggers platelet activation and aggregation and activation of the coagulation system. Platelet activation is initiated by exposure of subendothelial collagen and von Willebrand factor (VWF), onto which platelets adhere. Adherent platelets become activated and release ADP and thromboxane A_2, platelet agonists that activate ambient platelets and recruit them to the site of injury. When platelets are activated, glycoprotein IIb/IIIa on their surface undergoes a conformational change that enables it to ligate fibrinogen and/or VWF and mediate platelet aggregation. Coagulation is triggered by tissue factor exposed at the site of injury. Tissue factor triggers thrombin generation. As a potent platelet agonist, thrombin amplifies platelet recruitment to the site of injury. Thrombin also converts fibrinogen to fibrin, and the fibrin strands then weave the platelet aggregates together to form a platelet/fibrin thrombus.

When platelets are activated, Gp IIb/IIIa, the most abundant receptor on the platelet surface, undergoes a conformational change that enables it to bind fibrinogen and, under high shear conditions, VWF. Divalent fibrinogen or multivalent VWF molecules bridge adjacent platelets together to form platelet aggregates. Fibrin strands, generated through the action of thrombin, then weave these aggregates together to form a platelet/fibrin mesh.

Antiplatelet drugs target various steps in this process. The commonly used drugs include aspirin, ADP receptor inhibitors, which include the thienopyridines (clopidogrel and prasugrel) as well as ticagrelor and cangrelor, dipyridamole, Gp IIb/IIIa antagonists, and vorapaxar.

ASPIRIN

The most widely used antiplatelet agent worldwide is aspirin. As a cheap and effective antiplatelet drug, aspirin serves as the foundation of most antiplatelet strategies.

Mechanism of Action Aspirin produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet cyclooxygenase (COX)-1 **(Fig. 114-3)**, a critical enzyme in the biosynthesis of thromboxane A_2. At high doses (~1 g/d), aspirin also inhibits COX-2, an inducible COX isoform found in endothelial cells and inflammatory cells. In endothelial cells, COX-2 initiates the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.

Indications Aspirin is widely used for secondary prevention of cardiovascular events in patients with established coronary artery, cerebral artery, or peripheral artery disease. Compared with placebo in this setting, aspirin produces a 25% reduction in the risk of cardiovascular death, MI, or stroke. Use of aspirin for primary prevention is controversial. It is unclear whether the benefits of daily aspirin for primary cardiac protection outweigh its associated risks for gastrointestinal and intracerebral hemorrhage. Consequently, aspirin is no longer recommended for primary cardiac prevention unless the baseline cardiovascular risk is at least 1% per year and 10% at 10 years and patients are at low risk for bleeding.

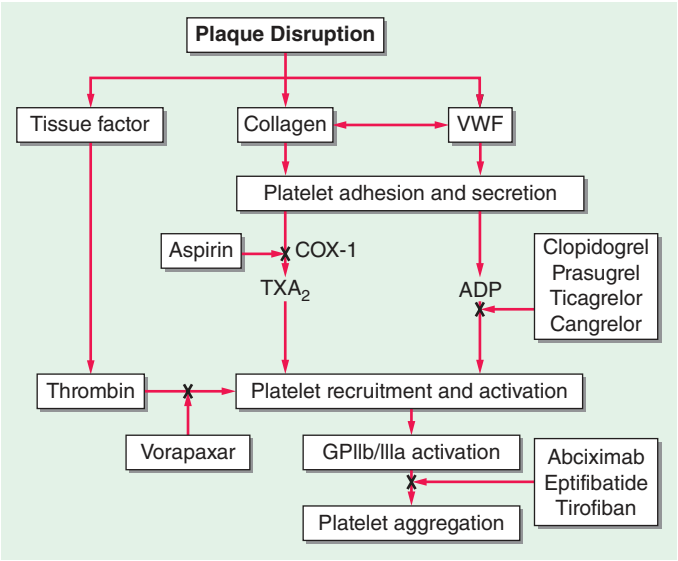

FIGURE 114-3 Site of action of antiplatelet drugs. Aspirin inhibits thromboxane A_2 (TXA_2) synthesis by irreversibly acetylating cyclooxygenase-1 (COX-1). Reduced TXA_2 release attenuates platelet activation and recruitment to the site of vascular injury. Clopidogrel and prasugrel irreversibly block $P2Y_{12}$, a key ADP receptor on the platelet surface; cangrelor and ticagrelor are reversible inhibitors of $P2Y_{12}$. Abciximab, eptifibatide, and tirofiban inhibit the final common pathway of platelet aggregation by blocking fibrinogen and von Willebrand factor binding to activated glycoprotein (Gp) IIb/IIIa. Vorapaxar inhibits thrombin-mediated platelet activation by targeting protease-activated receptor-1 (PAR-1), the major thrombin receptor on human platelets.

Dosages Aspirin is usually administered at doses of 75–325 mg once daily. Higher doses of aspirin are not more effective than lower aspirin doses, and some analyses suggest reduced efficacy with higher doses. Because the side effects of aspirin are dose-related, daily aspirin doses of 75–100 mg are recommended for most indications. When rapid platelet inhibition is required, an initial aspirin dose of at least 160 mg should be given.

Side Effects The most common side effects are gastrointestinal and range from dyspepsia to erosive gastritis or peptic ulcers with bleeding and perforation. These side effects are dose-related. Use of enteric-coated or buffered aspirin in place of plain aspirin does not eliminate gastrointestinal side effects. The overall risk of major bleeding with aspirin is 1–3% per year. The risk of bleeding is increased two- to threefold when aspirin is given in conjunction with other antiplatelet drugs, such as clopidogrel, or with anticoagulants, such as warfarin. When dual or triple therapy is prescribed, low-dose aspirin should be given (75–100 mg daily). Eradication of *Helicobacter pylori* infection and administration of proton pump inhibitors may reduce the risk of aspirin-induced upper gastrointestinal bleeding in patients with peptic ulcer disease.

Aspirin should not be administered to patients with a history of aspirin allergy characterized by bronchospasm. This problem occurs in ~0.3% of the general population but is more common in those with chronic urticaria or asthma, particularly in individuals with nasal polyps or chronic rhinitis. Hepatic and renal toxicity are observed with aspirin overdose.

Aspirin Resistance Clinical aspirin resistance is defined as the failure of aspirin to protect patients from ischemic vascular events. This is not a helpful definition because it is made after the event occurs. Furthermore, it is not realistic to expect aspirin, which only blocks thromboxane A_2–induced platelet activation, to prevent all vascular events.

Aspirin resistance has also been described biochemically as failure of the drug to produce its expected inhibitory effects on tests of platelet function, such as thromboxane A_2 synthesis or arachidonic acid-induced platelet aggregation. Potential causes of aspirin resistance include poor compliance, reduced absorption, drug-drug interaction with ibuprofen, and overexpression of COX-2. Unfortunately, the tests for aspirin resistance have not been well standardized, and there is little evidence that they identify patients at increased risk of recurrent vascular events, or that resistance can be reversed by giving higher doses of aspirin or by adding other antiplatelet drugs. Until such information is available, testing for aspirin resistance remains a research tool.

ADP RECEPTOR ANTAGONISTS

The ADP receptor antagonists include the thienopyridines (clopidogrel and prasugrel) as well as ticagrelor and cangrelor. All of these drugs target $P2Y_{12}$, the key ADP receptor on platelets.

Thienopyridines • **MECHANISM OF ACTION** The thienopyridines are structurally related drugs that selectively inhibit ADP-induced platelet aggregation by irreversibly blocking $P2Y_{12}$ (Fig. 114-3). Clopidogrel and prasugrel are prodrugs that require metabolic activation by the hepatic cytochrome P450 (CYP) enzyme system. Prasugrel is about tenfold more potent than clopidogrel and has a more rapid onset of action because of better absorption and more streamlined metabolic activation.

INDICATIONS When compared with aspirin in patients with recent ischemic stroke, recent MI, or a history of peripheral arterial disease, clopidogrel reduced the risk of cardiovascular death, MI, and stroke by 8.7%. Therefore, clopidogrel is more effective than aspirin but is also more expensive. In some patients, clopidogrel and aspirin are combined to capitalize on their capacity to block complementary pathways of platelet activation. For example, the combination of aspirin plus clopidogrel is recommended for at least 4 weeks after implantation of a bare metal stent in a coronary artery and for at least 6 months in those with a drug-eluting stent. Concerns about late in-stent thrombosis with drug-eluting stents have led some experts to recommend longer-term use of clopidogrel plus aspirin for the latter indication in patients without bleeding complications.

The combination of clopidogrel and aspirin is also effective in patients with unstable angina. Thus, in 12,562 such patients, the risk of cardiovascular death, MI, or stroke was 9.3% in those randomized to the combination of clopidogrel and aspirin and 11.4% in those given aspirin alone. This 20% relative risk reduction with combination therapy was highly statistically significant. However, combining clopidogrel with aspirin increases the risk of major bleeding to about 2% per year. This bleeding risk persists even if the daily dose of aspirin is ≤100 mg. Therefore, the combination of clopidogrel and aspirin should only be used when there is a clear benefit. For example, this combination has not proven to be superior to clopidogrel alone in patients with acute ischemic stroke or to aspirin alone for primary prevention in those at risk for cardiovascular events.

Prasugrel was compared with clopidogrel in 13,608 patients with acute coronary syndromes who were scheduled to undergo percutaneous coronary intervention. The incidence of the primary efficacy endpoint, a composite of cardiovascular death, MI, or stroke, was significantly lower with prasugrel than with clopidogrel (9.9% and 12.1%, respectively), mainly reflecting a reduction in the incidence of nonfatal MI. The incidence of stent thrombosis also was significantly lower with prasugrel (1.1% and 2.4%, respectively). However, these advantages were at the expense of significantly higher rates of fatal bleeding (0.4% and 0.1%, respectively) and life-threatening bleeding (1.4% and 0.9%, respectively) with prasugrel. Because patients older than age 75 years and those with a history of prior stroke or transient ischemic attack have a particularly high risk of bleeding, prasugrel should generally be avoided in older patients, and the drug is contraindicated in those with a history of cerebrovascular disease. Caution is required if prasugrel is used in patients weighing <60 kg or in those with renal impairment.

When prasugrel was compared with clopidogrel in 7243 patients with unstable angina or MI without ST-segment elevation, prasugrel failed to reduce the rate of the primary efficacy endpoint, which was a composite of cardiovascular death, MI, and stroke. Because of the negative results of this study, prasugrel is reserved for patients undergoing percutaneous coronary intervention. In this setting, prasugrel is usually given in conjunction with aspirin. To reduce the risk of bleeding, the daily aspirin dose should be ≤100 mg.

DOSING Clopidogrel is given once daily at a dose of 75 mg. Loading doses of clopidogrel are given when rapid ADP receptor blockade is desired. For example, patients undergoing coronary stenting are often given a loading dose of 300–600 mg, which produces inhibition of ADP-induced platelet aggregation in about 4–6 h. After a loading dose of 60 mg, prasugrel is given once daily at a dose of 10 mg. Patients older than age 75 years or weighing less than 60 kg should receive a lower daily prasugrel dose of 5 mg.

SIDE EFFECTS The most common side effect of clopidogrel and prasugrel is bleeding. Because of its greater potency, bleeding is more common with prasugrel than clopidogrel. To reduce the risk of bleeding, clopidogrel and prasugrel should be stopped 5–7 days before major surgery. In patients taking clopidogrel or prasugrel who present with serious bleeding, platelet transfusion may be helpful.

Hematologic side effects, including neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura, are rare.

THIENOPYRIDINE RESISTANCE The capacity of clopidogrel to inhibit ADP-induced platelet aggregation varies among subjects. This variability reflects, at least in part, genetic polymorphisms in the CYP isoenzymes involved in the metabolic activation of clopidogrel. Most important of these is CYP2C19. Clopidogrel-treated patients with the loss-of-function *CYP2C19*2* allele exhibit reduced platelet inhibition compared with those with the wild-type *CYP2C19*1* allele and experience a higher rate of cardiovascular events. This is important because estimates suggest that up to 25% of whites, 30% of African Americans, and 50% of Asians carry the loss-of-function allele, which would render them resistant to clopidogrel. Even patients with the reduced function *CYP2C19*3*, **4*, or **5* alleles may derive less benefit from clopidogrel than those with the full-function *CYP2C19*1* allele. Concomitant administration of clopidogrel with proton pump inhibitors, which are inhibitors of *CYP2C19*, produces a small reduction in the inhibitory effects of clopidogrel on ADP-induced platelet aggregation. The extent to which this interaction increases the risk of cardiovascular events remains controversial.

In contrast to their effect on the metabolic activation of clopidogrel, *CYP2C19* polymorphisms appear to be less important determinants of the activation of prasugrel. Thus, no association was detected between the loss-of-function allele and decreased platelet inhibition or increased rate of cardiovascular events with prasugrel. The observation that genetic polymorphisms affecting clopidogrel absorption or metabolism influence clinical outcomes raises the possibilities that pharmacogenetic profiling may be useful to identify clopidogrel-resistant patients and that point-of-care assessment of the extent of clopidogrel-induced platelet inhibition may help detect patients at higher risk for subsequent cardiovascular events. Clinical trials designed to evaluate these possibilities have thus far been negative. Although administration of higher doses of clopidogrel can overcome a reduced response to clopidogrel, the clinical benefit of this approach is uncertain. Instead, prasugrel or ticagrelor may be better choices for these patients.

Ticagrelor As an orally active inhibitor of $P2Y_{12}$, ticagrelor differs from the thienopyridines in that ticagrelor does not require metabolic activation and it produces reversible inhibition of the ADP receptor.

MECHANISM OF ACTION Like the thienopyridines, ticagrelor inhibits $P2Y_{12}$. Because it does not require metabolic activation, ticagrelor has a more rapid onset and offset of action than clopidogrel, and it produces greater and more predictable inhibition of ADP-induced platelet aggregation than clopidogrel.

Indications When compared with clopidogrel in patients with acute coronary syndromes, ticagrelor produced a greater reduction in the primary efficacy endpoint—a composite of cardiovascular death, MI, and stroke at 1 year—than clopidogrel (9.8% and 11.7%, respectively; $p = 0.001$). This difference reflected a significant reduction in both cardiovascular death (4.0% and 5.1%, respectively; $p = 0.001$) and MI (5.8% and 6.9%, respectively; $p = 0.005$) with ticagrelor compared with clopidogrel. Rates of stroke were similar with ticagrelor and clopidogrel (1.5% and 1.3%, respectively), and no difference in rates of major bleeding was noted. When minor bleeding was added to the major bleeding results, however, ticagrelor showed an increase relative to clopidogrel (16.1% and 14.6%, respectively; $p = 0.008$). Ticagrelor also was superior to clopidogrel in patients with acute coronary syndrome who underwent percutaneous coronary intervention or cardiac surgery. Based on these observations, guidelines give preference to ticagrelor over clopidogrel, particularly in higher risk patients.

DOSING Ticagrelor is initiated with an oral loading dose of 180 mg followed by 90 mg twice daily. The dose does not require adjustment in patients with renal impairment, but the drug should be used with caution in patients with hepatic disease and in those receiving potent inhibitors or inducers of CYP3A4 because ticagrelor is metabolized in the liver via CYP3A4. Ticagrelor is usually administered in conjunction with aspirin; the daily aspirin dose should not exceed 100 mg.

SIDE EFFECTS In addition to bleeding, the most common side effects of ticagrelor are dyspnea, which can occur in up to 15% of patients, and asymptomatic ventricular pauses. The dyspnea, which tends to occur soon after initiating ticagrelor, is usually self-limiting and mild in intensity. The mechanism responsible for this side effect is unknown.

To reduce the risk of bleeding, ticagrelor should be stopped 5–7 days prior to major surgery. Platelet transfusions are unlikely to be of benefit in patients with ticagrelor-related bleeding because the drug will bind to $P2Y_{12}$ on the transfused platelets.

Cangrelor Cangrelor is a rapidly acting reversible inhibitor of P2Y12 that is administered intravenously. It has an immediate onset of action, a half-life of 3–5 min, and an offset of action within an hour. Cangrelor is licensed for use in patients undergoing percutaneous coronary intervention and produces rapid ADP receptor blockade in those who have not received pre-treatment with clopidogrel, prasugrel, or ticagrelor.

DIPYRIDAMOLE

Dipyridamole is a relatively weak antiplatelet agent on its own, but an extended-release formulation of dipyridamole combined with low-dose aspirin, a preparation known as *Aggrenox*, is used for prevention of stroke in patients with transient ischemic attacks.

Mechanism of Action By inhibiting phosphodiesterase, dipyridamole blocks the breakdown of cyclic adenosine monophosphate (AMP). Increased levels of cyclic AMP reduce intracellular calcium and inhibit platelet activation. Dipyridamole also blocks the uptake of adenosine by platelets and other cells. This produces a further increase in local cyclic AMP levels because the platelet adenosine A_2 receptor is coupled to adenylate cyclase **(Fig. 114-4)**.

Indications Dipyridamole plus aspirin was compared with aspirin or dipyridamole alone, or with placebo, in patients with an ischemic stroke or transient ischemic attack. The combination reduced the risk of stroke by 22.1% compared with aspirin and by 24.4% compared with dipyridamole. A second trial compared dipyridamole plus aspirin with aspirin alone for secondary prevention in patients with ischemic stroke. Vascular death, stroke, or MI occurred in 13% of patients given combination therapy and in 16% of those treated with aspirin alone. Another trial randomized 20,332 patients with noncardioembolic ischemic stroke to either Aggrenox or clopidogrel. The primary efficacy endpoint of recurrent stroke occurred in 9.0% of those given Aggrenox and in 8.8% of patients treated with clopidogrel. Although this difference was not statistically significant, the study failed to meet the prespecified margin to claim noninferiority of Aggrenox relative to clopidogrel. These results have dampened enthusiasm for the use of Aggrenox.

Because of its vasodilatory effects and the paucity of data supporting the use of dipyridamole in patients with symptomatic coronary artery disease, Aggrenox should not be used for stroke prevention in such patients. Clopidogrel is a better choice in this setting.

Dosing Aggrenox is given twice daily. Each capsule contains 200 mg of extended-release dipyridamole and 25 mg of aspirin.

Side Effects Because dipyridamole has vasodilatory effects, it must be used with caution in patients with coronary artery disease.

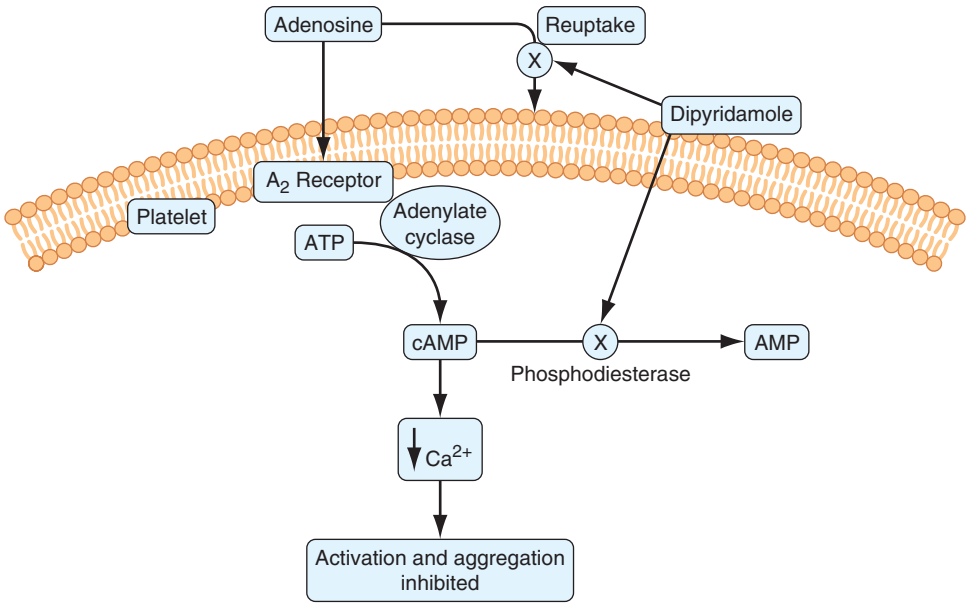

FIGURE 114-4 Mechanism of action of dipyridamole. Dipyridamole increases levels of cyclic AMP (cAMP) in platelets by (1) blocking the reuptake of adenosine and (2) inhibiting phosphodiesterase-mediated cyclic AMP degradation. By promoting calcium uptake, cyclic AMP reduces intracellular levels of calcium. This, in turn, inhibits platelet activation and aggregation.

Gastrointestinal complaints, headache, facial flushing, dizziness, and hypotension can also occur. These symptoms often subside with continued use of the drug.

GP IIB/IIIA RECEPTOR ANTAGONISTS

As a class, parenteral Gp IIb/IIIa receptor antagonists have an established niche in patients with acute coronary syndromes. The three agents in this class are abciximab, eptifibatide, and tirofiban.

Mechanism of Action A member of the integrin family of adhesion receptors, Gp IIb/IIIa is found on the surface of platelets and megakaryocytes. With about 80,000 copies per platelet, Gp IIb/IIIa is the most abundant receptor. Consisting of a noncovalently linked heterodimer, Gp IIb/IIIa is inactive on resting platelets. When platelets are activated, inside-outside signal transduction pathways trigger a conformational activation of the receptor. Once activated, Gp IIb/IIIa binds adhesive molecules, such as fibrinogen and, under high shear conditions, VWF. Binding is mediated by the Arg-Gly-Asp (RGD) sequence found on the α chains of fibrinogen and on VWF, and by the Lys-Gly-Asp (KGD) sequence located within a unique dodecapeptide domain on the γ chains of fibrinogen. Once bound, fibrinogen and/or VWF bridge adjacent platelets together to induce platelet aggregation.

Although abciximab, eptifibatide, and tirofiban all target the Gp IIb/IIIa receptor, they are structurally and pharmacologically distinct (Table 114-1). Abciximab is a Fab fragment of a humanized murine monoclonal antibody directed against the activated form of Gp IIb/IIIa. Abciximab binds to the activated receptor with high affinity and blocks the binding of adhesive molecules. In contrast, eptifibatide and tirofiban are synthetic small molecules. Eptifibatide is a cyclic heptapeptide that binds Gp IIb/IIIa because it incorporates the KGD motif, whereas tirofiban is a nonpeptidic tyrosine derivative that acts as an RGD mimetic. Abciximab has a long half-life and can be detected on the surface of platelets for up to 2 weeks; eptifibatide and tirofiban have short half-lives.

TABLE 114-1 Features of GpIIb/IIIa Antagonists

FEATURE	ABCIXIMAB	EPTIFIBATIDE	TIROFIBAN
Description	Fab fragment of humanized mouse monoclonal antibody	Cyclical KGD-containing heptapeptide	Nonpeptidic RGD mimetic
Specific for Gp IIb/IIIa	No	Yes	Yes
Plasma half-life	Short (min)	Long (2.5 h)	Long (2.0 h)
Platelet-bound half-life	Long (days)	Short (s)	Short (s)
Renal clearance	No	Yes	Yes

Indications Abciximab and eptifibatide are used in patients undergoing percutaneous coronary interventions, particularly those who have not been pretreated with an ADP receptor antagonist. Tirofiban is used in high-risk patients with unstable angina. Eptifibatide also can be used for this indication.

Dosing All of the Gp IIb/IIIa antagonists are given as an IV bolus followed by an infusion. The recommended dose of abciximab is a bolus of 0.25 mg/kg followed by an infusion of 0.125 μg/kg per minute to a maximum of 10 μg/kg for 12 h. Eptifibatide is given as two 180 μg/kg boluses given 10 min apart, followed by an infusion of 2.0 μg/kg per minute for at least 12 h. Tirofiban is given as a bolus of 25 μg/kg; the drug is then continued at a rate of 0.15 μg/kg per minute for up to 18 h. Because these agents are cleared by the kidneys, the doses of eptifibatide and tirofiban must be reduced in patients with renal insufficiency. Thus, the eptifibatide infusion is reduced to 1 μg/kg per minute in patients with a creatinine clearance below 50 mL/min, whereas the post loading dose of tirofiban is cut in half for patients with a creatinine clearance below 60 mL/min.

Side Effects In addition to bleeding, thrombocytopenia is the most serious complication. Thrombocytopenia is immune-mediated and is caused by antibodies directed against neoantigens on Gp IIb/IIIa that are exposed upon antagonist binding. With abciximab, thrombocytopenia occurs in up to 5% of patients. Thrombocytopenia is severe in ~1% of these individuals. Thrombocytopenia is less common with the other two agents, occurring in ~1% of patients.

VORAPAXAR

An orally active PAR-1 antagonist, vorapaxar is slowly eliminated with a half-life of about 200 h. When compared with placebo in 12,944 patients with acute coronary syndrome without ST-segment elevation, vorapaxar failed to significantly reduce the primary efficacy endpoint, a composite of cardiovascular death, MI, stroke, recurrent ischemia requiring rehospitalization, and urgent coronary revascularization. Moreover, vorapaxar was associated with increased rates of bleeding, including intracranial bleeding.

In a second trial, vorapaxar was compared with placebo for secondary prevention in 26,449 patients with prior MI, ischemic stroke, or peripheral arterial disease. Overall, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 13%, but doubled the risk of intracranial bleeding. In the prespecified subgroup of 17,779 patients with prior MI, however, vorapaxar reduced the risk for cardiovascular death, MI, or stroke by 20% compared with placebo (from 9.7% to 8.1%, respectively). The rate of intracranial hemorrhage was higher with vorapaxar than with placebo (0.6% and 0.4%, respectively; $p = 0.076$) as was the rate of moderate or severe bleeding (3.4% and 2.1%, respectively; $P < 0.0001$). Based on these data, vorapaxar is licensed for patients younger than 75 years with MI who have no history of stroke, transient ischemic attack, or history of intracranial bleeding and weigh more than 60 kg.

ANTICOAGULANTS

There are both parenteral and oral anticoagulants. The parenteral anticoagulants include heparin, low-molecular-weight heparin (LMWH), fondaparinux (a synthetic pentasaccharide), lepirudin, desirudin, bivalirudin, and argatroban. Currently available oral anticoagulants include warfarin; dabigatran etexilate, an oral thrombin inhibitor; and rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors.

PARENTERAL ANTICOAGULANTS

Heparin A sulfated polysaccharide, heparin is isolated from mammalian tissues rich in mast cells. Most commercial heparin is derived from porcine intestinal mucosa and is a polymer of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine residues.

MECHANISM OF ACTION Heparin acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa. Antithrombin, the obligatory plasma cofactor for heparin, is a member of the serine protease inhibitor (serpin) superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes.

To activate antithrombin, heparin binds to the serpin via a unique pentasaccharide sequence that is found on one-third of the chains of commercial heparin (Fig. 114-5). Heparin chains without this pentasaccharide sequence have little or no anticoagulant activity. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. This conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude but has little effect on the rate of thrombin inhibition. To catalyze thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously. Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby promoting the formation of a stable covalent thrombin-antithrombin complex.

Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which correspond to a molecular weight of 5400) are of sufficient length to bridge thrombin and antithrombin together. With a mean molecular weight of 15,000, and a range of 5000–30,000, almost all of the chains of unfractionated heparin are long enough to do so. Consequently, by definition, heparin has equal capacity to promote the inhibition of thrombin and factor Xa by antithrombin and is assigned an anti-factor Xa to anti-factor IIa (thrombin) ratio of 1:1.

Heparin causes the release of tissue factor pathway inhibitor (TFPI) from the endothelium. A factor Xa–dependent inhibitor of tissue factor–bound factor VIIa, TFPI may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more TFPI than shorter ones.

PHARMACOLOGY Heparin must be given parenterally. It is usually administered SC or by continuous IV infusion. When used for therapeutic purposes, the IV route is most often employed. If heparin is given SC for treatment of thrombosis, the dose of heparin must be high enough to overcome the limited bioavailability associated with this method of delivery.

In the circulation, heparin binds to the endothelium and to plasma proteins other than antithrombin. Heparin binding to endothelial cells explains its dose-dependent clearance. At low doses, the half-life of heparin is short because it binds rapidly to the endothelium. With higher doses of heparin, the half-life is longer because heparin is cleared more slowly once the endothelium is saturated. Clearance is mainly extra renal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation. Because of its dose-dependent clearance mechanism, the plasma half-life of heparin ranges from 30 to 60 min with bolus IV doses of 25 and 100 units/kg, respectively.

Once heparin enters the circulation, it binds to plasma proteins other than antithrombin, a phenomenon that reduces its anticoagulant activity. Some of the heparin-binding proteins found in plasma are acute-phase reactants whose levels are elevated in ill patients. Others, such as high-molecular-weight multimers of VWF, are released from activated platelets or endothelial cells. Activated platelets also release platelet factor 4 (PF4), a highly cationic protein that binds heparin with high affinity. The large amounts of PF4 found in the vicinity of platelet-rich arterial thrombi can neutralize the anticoagulant activity of heparin. This phenomenon may attenuate heparin's capacity to suppress thrombus growth.

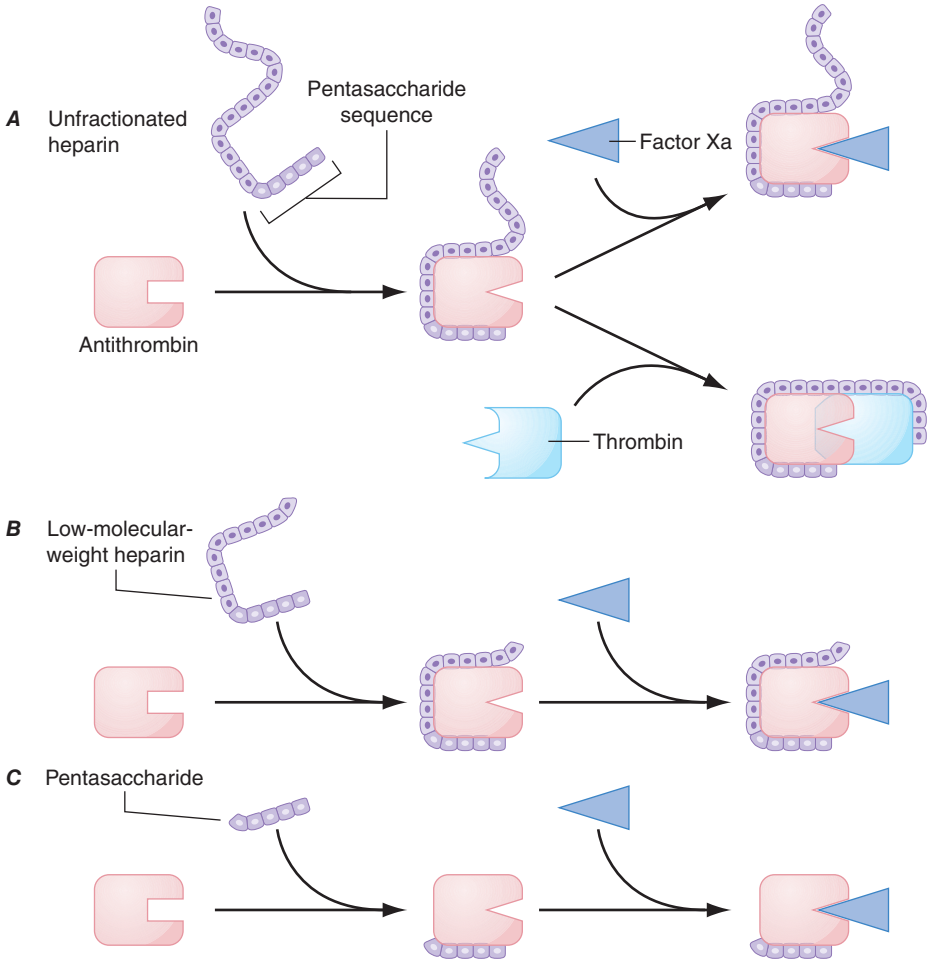

FIGURE 114-5 Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. ***A.*** Heparin binds to antithrombin via its pentasaccharide sequence. This induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. Only heparin chains composed of at least 18 saccharide units, which correspond to a molecular weight of 5400, are of sufficient length to perform this bridging function. With a mean molecular weight of 15,000, all of the heparin chains are long enough to do this. ***B.*** LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because, with a mean molecular weight of 4500–5000, at least half of the LMWH chains are too short to bridge antithrombin to thrombin. ***C.*** The pentasaccharide only accelerates factor Xa inhibition by antithrombin because the pentasaccharide is too short to bridge antithrombin to thrombin.

Because the levels of heparin-binding proteins in plasma vary from person to person, the anticoagulant response to fixed or weight-adjusted doses of heparin is unpredictable. Consequently, coagulation monitoring is essential to ensure that a therapeutic response is obtained. This is particularly important when heparin is administered for treatment of established thrombosis because a subtherapeutic anticoagulant response may render patients at risk for recurrent thrombosis, whereas excessive anticoagulation increases the risk of bleeding.

MONITORING THE ANTICOAGULANT EFFECT Heparin therapy can be monitored using the activated partial thromboplastin time (aPTT) or anti-factor Xa level. Although the aPTT is the test most often used for this purpose, there are problems with this assay. aPTT reagents vary in their sensitivity to heparin, and the type of coagulometer used for testing can influence the results. Consequently, laboratories must establish a therapeutic aPTT range with each reagent-coagulometer combination by measuring the aPTT and anti-factor Xa level in plasma samples collected from heparin-treated patients. For most of the aPTT reagents and coagulometers in current use, therapeutic heparin levels are achieved with a two- to threefold prolongation of the aPTT. Anti-factor Xa levels also can be used to monitor heparin therapy. With this test, therapeutic heparin levels range from 0.3 to 0.7 units/mL.

Up to 25% of heparin-treated patients with venous thromboembolism require >35,000 units/d to achieve a therapeutic aPTT. These patients are considered heparin-resistant. It is useful to measure anti-factor Xa levels in heparin-resistant patients because many will have a therapeutic anti-factor Xa level despite a subtherapeutic aPTT. This dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both of which are acute-phase proteins, shorten the aPTT but have no effect on anti-factor Xa levels. Heparin therapy in patients who exhibit this phenomenon is best monitored using anti-factor Xa levels instead of the aPTT. Patients with congenital or acquired antithrombin deficiency and those with elevated levels of heparin-binding proteins may also need high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa level. If there is good correlation between the aPTT and the anti-factor Xa levels, either test can be used to monitor heparin therapy.

DOSING For prophylaxis, heparin is usually given in fixed doses of 5000 units SC two or three times daily. With these low doses, coagulation monitoring is unnecessary. In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response. At least two heparin nomograms have been validated in patients with venous thromboembolism and reduce the time required to achieve a therapeutic aPTT. Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an IV heparin bolus of 5000 units or 70 units/kg, a heparin infusion rate of 12–15 units/kg per hour is usually administered. In contrast, weight-adjusted heparin nomograms for patients with venous thromboembolism use an initial bolus of 5000 units or 80 units/kg, followed by an infusion of 18 units/kg per hour. Thus, patients with venous thromboembolism appear to require higher doses of heparin to achieve a therapeutic aPTT than do patients with acute coronary syndromes. This may reflect differences in the thrombus burden. Heparin binds to fibrin, and the amount of fibrin in patients with extensive DVT is greater than that in those with coronary thrombosis.

Heparin manufacturers in North America have traditionally measured heparin potency in USP units, with a unit defined as the concentration of heparin that prevents 1 mL of citrated sheep plasma from clotting for 1 h after calcium addition. In contrast, manufacturers in Europe measured heparin potency with anti-Xa assays using an international heparin standard for comparison. Because of problems with heparin contamination with oversulfated chondroitin sulfate, which the USP assay system does not detect, North American heparin manufacturers now use the anti-Xa assay to assess heparin potency. The use of international units in place of USP units results in a 10% reduction in heparin doses, which is a difference unlikely to affect patient care because monitoring ensures that a therapeutic anticoagulant response has been achieved.

TABLE 114-2 Pharmacokinetic and Biophysical Limitations of Heparin

LIMITATIONS	MECHANISM
Poor bioavailability at low doses	Binds to endothelial cells and macrophages
Dose-dependent clearance	Binds to macrophages
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of heparin-antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

LIMITATIONS Heparin has pharmacokinetic and biophysical limitations (Table 114-2). The pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to inhibit factor Xa when it is incorporated into the prothrombinase complex, the complex that converts prothrombin to thrombin, and to inhibit thrombin bound to fibrin. Consequently, factor Xa bound to activated platelets within platelet-rich thrombi has the potential to generate thrombin, even in the face of heparin. Once this thrombin binds to fibrin, it too is protected from inhibition by the heparin-antithrombin complex. Clot-associated thrombin can then trigger thrombus growth by locally activating platelets and amplifying its own generation through feedback activation of factors V, VIII, and XI. Further compounding the problem is the potential for heparin neutralization by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus.

SIDE EFFECTS The most common side effect of heparin is bleeding. Other complications include thrombocytopenia, osteoporosis, and elevated levels of transaminases.

Bleeding The risk of bleeding rises as the dose of heparin is increased. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk of bleeding, as does recent surgery or trauma. Heparin-treated patients with serious bleeding can be given protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given IV. Anaphylactoid reactions to protamine sulfate can occur, and drug administration by slow IV infusion is recommended to reduce the risk.

THROMBOCYTOPENIA Heparin can cause thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process that is triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein. These antibodies, which are usually of the IgG isotype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors and promote thrombin generation.

The clinical features of HIT are illustrated in Table 114-3. Typically, HIT occurs 5–10 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months. A platelet count <100,000/μL or a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT

TABLE 114-3 Features of Heparin-Induced Thrombocytopenia

FEATURES	DETAILS
Thrombocytopenia	Platelet count of ≤100,000/μL or a decrease in platelet count of ≥50%
Timing	Platelet count falls 5–10 days after starting heparin
Type of heparin	More common with unfractionated heparin than low-molecular-weight heparin
Type of patient	More common in surgical patients and patients with cancer than general medical patients; more common in women than in men
Thrombosis	Venous thrombosis more common than arterial thrombosis

in those receiving heparin. HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, occurs more frequently in females than in males.

HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as DVT and/or PE, is more common than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute MI. Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia.

The diagnosis of HIT is established using enzyme-linked immunoassays to detect antibodies against heparin-PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive but can be positive in the absence of any clinical evidence of HIT. However, because of its sensitivity, negative enzyme-linked immunoassay excludes the diagnosis of HIT. The most specific diagnostic test for HIT is the serotonin release assay. This test is performed by quantifying serotonin release when washed platelets loaded with labeled serotonin are exposed to patient serum in the absence or presence of varying concentrations of heparin. If the patient serum contains the HIT antibody, heparin addition induces platelet activation and serotonin release.

Management of HIT is outlined in Table 114-4. Heparin should be stopped in patients with suspected or documented HIT, and an alternative anticoagulant should be administered to prevent or treat thrombosis. The agents most often used for this indication are parenteral direct thrombin inhibitors, such as lepirudin, argatroban, or bivalirudin, or factor Xa inhibitors, such as fondaparinux or rivaroxaban.

Patients with HIT, particularly those with associated thrombosis, often have evidence of increased thrombin generation that can lead to consumption of protein C. If these patients are given warfarin without a concomitant parenteral anticoagulant to inhibit thrombin or thrombin generation, the further decrease in protein C levels induced by the vitamin K antagonist can trigger skin necrosis. To avoid this problem, patients with HIT should be treated with a direct thrombin inhibitor or with fondaparinux or rivaroxaban until the platelet count returns to normal levels. At this point, low-dose warfarin therapy can be introduced, and the thrombin inhibitor can be discontinued when the anticoagulant response to warfarin has been therapeutic for at least 2 days. Alternatively, the patient can be maintained or switched to rivaroxaban.

Osteoporosis Treatment with therapeutic doses of heparin for >1 month can cause a reduction in bone density. This complication has been reported in up to 30% of patients given long-term heparin therapy, and symptomatic vertebral fractures occur in 2–3% of these individuals.

TABLE 114-4 Management of Heparin-Induced Thrombocytopenia

Stop all heparin.
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, fondaparinux or rivaroxaban.
Do not give platelet transfusions.
Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the INR to normal.
Evaluate for thrombosis, particularly deep vein thrombosis.

Abbreviation: INR, international normalized ratio.

TABLE 114-5 Advantages of LMWH over Heparin

ADVANTAGE	CONSEQUENCE
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

Abbreviation: LMWH, low-molecular-weight heparin.

Heparin causes bone loss both by decreasing bone formation and by enhancing bone resorption. Thus, heparin affects the activity of both osteoblasts and osteoclasts.

Elevated Levels of Transaminases Therapeutic doses of heparin are frequently associated with modest elevations in the serum levels of hepatic transaminases without a concomitant increase in the level of bilirubin. The levels of transaminases rapidly return to normal when the drug is stopped. The mechanism responsible for this phenomenon is unknown.

Low-Molecular-Weight Heparin

Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is about 5000, one-third the mean molecular weight of unfractionated heparin. LMWH has advantages over heparin (Table 114-5) and has replaced heparin for most indications.

MECHANISM OF ACTION Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (Fig. 114-5). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently, LMWH catalyzes factor Xa inhibition by antithrombin more than thrombin inhibition. Depending on their unique molecular weight distributions, LMWH preparations have anti-factor Xa to anti-factor IIa ratios ranging from 2:1 to 4:1.

PHARMACOLOGY Although usually given SC, LMWH also can be administered IV if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin. These advantages reflect the fact that shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins. Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance that is a characteristic of unfractionated heparin. Instead, the clearance of LMWH is dose-independent and its plasma half-life is longer. Based on measurement of anti-factor Xa levels, LMWH has a plasma half-life of ~4 h. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insufficiency.

LMWH exhibits about 90% bioavailability after SC injection. Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given SC once or twice daily without coagulation monitoring, even when the drug is given in treatment doses. These properties render LMWH more convenient than unfractionated heparin. Capitalizing on this feature, studies in patients with venous thromboembolism have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous IV infusions of heparin. Outpatient treatment with LMWH streamlines care, reduces health care costs, and increases patient satisfaction.

MONITORING In the majority of patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti-factor Xa levels must be measured because most LMWH preparations have little effect on the aPTT. Therapeutic anti-factor Xa levels with LMWH range from 0.5 to 1.2 units/mL when measured 3–4 h after drug administration. When LMWH is given in prophylactic doses, peak anti-factor Xa levels of 0.2–0.5 units/mL are desirable.

Indications for LMWH monitoring include renal insufficiency and obesity. LMWH monitoring in patients with a creatinine clearance of ≤50 mL/min is advisable to ensure that there is no drug accumulation. Although weight-adjusted LMWH dosing appears to produce therapeutic anti-factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obesity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester. Monitoring should also be considered in high-risk settings, such as in patients with mechanical heart valves who are given LMWH for prevention of valve thrombosis, and when LMWH is used in treatment doses in infants or children.

DOSING The doses of LMWH recommended for prophylaxis or treatment vary depending on the LMWH preparation. For prophylaxis, once-daily SC doses of 4000–5000 units are often used, whereas doses of 2500–3000 units are given when the drug is administered twice daily. For treatment of venous thromboembolism, a dose of 150–200 units/kg is given if the drug is administered once daily. If a twice-daily regimen is used, a dose of 100 units/kg is given. In patients with unstable angina, LMWH is given SC on a twice-daily basis at a dose of 100–120 units/kg.

SIDE EFFECTS The major complication of LMWH is bleeding. Meta-analyses suggest that the risk of major bleeding is lower with LMWH than with unfractionated heparin. HIT and osteoporosis are less common with LMWH than with unfractionated heparin.

Bleeding Like the situation with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with antiplatelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk of bleeding with LMWH.

Although protamine sulfate can be used as an antidote for LMWH, protamine sulfate incompletely neutralizes the anticoagulant activity of LMWH because it only binds the longer chains of LMWH. Because longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti-factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti-factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind to protamine sulfate. Consequently, patients at high risk for bleeding may be more safely treated with continuous IV unfractionated heparin than with SC LMWH.

Thrombocytopenia The risk of HIT is about fivefold lower with LMWH than with heparin. LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower affinity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies.

LMWH should not be used to treat HIT patients because most HIT antibodies exhibit cross-reactivity with LMWH. This in vitro cross-reactivity is not simply a laboratory phenomenon because there are case reports of thrombosis when HIT patients were switched from heparin to LMWH.

Osteoporosis

Because the risk of osteoporosis is lower with LMWH than with heparin, LMWH is a better choice for extended treatment.

Fondaparinux

A synthetic analogue of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in several ways (Table 114-6). Fondaparinux is licensed for thromboprophylaxis in general medical or surgical patients and in high-risk orthopedic patients and as an alternative to heparin or LMWH for initial treatment of patients with established venous thromboembolism. Although fondaparinux is used in Europe as an alternative to heparin or LMWH in patients with acute coronary syndrome, the drug is not licensed for this indication in the United States.

TABLE 114-6 Comparison of LMWH and Fondaparinux

FEATURES	LMWH	FONDAPARINUX
Number of saccharide units	15–17	5
Catalysis of factor Xa inhibition	Yes	Yes
Catalysis of thrombin inhibition	Yes	No
Bioavailability after subcutaneous administration (%)	90	100
Plasma half-life (h)	4	17
Renal excretion	Yes	Yes
Induces release of tissue factor pathway inhibitor	Yes	No
Neutralized by protamine sulfate	Partially	No

MECHANISM OF ACTION As a synthetic analogue of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (Fig. 114-5) and is too short to bridge thrombin to antithrombin. Consequently, fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition.

PHARMACOLOGY Fondaparinux exhibits complete bioavailability after SC injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is dose-independent and its plasma half-life is 17 h. The drug is given SC once daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindicated in patients with a creatinine clearance <30 mL/min and should be used with caution in those with a creatinine clearance <50 mL/min.

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for prevention of venous thromboembolism. For initial treatment of established venous thromboembolism, fondaparinux is given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing <50 kg and increased to 10 mg for those >100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for initial treatment of patients with DVT or PE and produces similar rates of bleeding.

Fondaparinux is used at a dose of 2.5 mg once daily in patients with acute coronary syndromes. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non-ST-segment elevation acute coronary syndrome, there was no difference in the rate of cardiovascular death, MI, or stroke at 9 days. However, the rate of major bleeding was 50% lower with fondaparinux than with enoxaparin, a difference that likely reflects the fact that the dose of fondaparinux was lower than that of enoxaparin. In acute coronary syndrome patients who require percutaneous coronary intervention, there is a risk of catheter thrombosis with fondaparinux unless adjunctive heparin is given.

SIDE EFFECTS Fondaparinux does not cause HIT because it does not bind to PF4. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently, fondaparinux appears to be effective for treatment of HIT patients, although large clinical trials supporting its use are lacking.

The major side effect of fondaparinux is bleeding. There is no antidote for fondaparinux. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers, but it is unknown whether this agent controls fondaparinux-induced bleeding.

Parenteral Direct Thrombin Inhibitors

Direct thrombin inhibitors bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include recombinant hirudins (lepirudin and desirudin), argatroban, and bivalirudin (Table 114-7). Lepirudin and argatroban are licensed for

TABLE 114-7 Comparison of the Properties of Lepirudin, Bivalirudin, and Argatroban

	LEPIRUDIN/ DESIRUDIN	BIVALIRUDIN	ARGATROBAN
Molecular mass	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (min)	60 (IV) 120–180 (SC)	25	45

treatment of patients with HIT, desirudin is licensed for thromboprophylaxis after elective hip arthroplasty, and bivalirudin is approved as an alternative to heparin in patients undergoing percutaneous coronary intervention, including those with HIT.

LEPIRUDIN AND DESIRUDIN Recombinant forms of hirudin, lepirudin and desirudin are bivalent direct thrombin inhibitors that interact with the active site and exosite 1, the substrate-binding site on thrombin. For rapid anticoagulation, lepirudin is given by continuous IV infusion, but the drug can be given SC. Lepirudin has a plasma half-life of 60 min after IV infusion and is cleared by the kidneys. Consequently, lepirudin accumulates in patients with renal insufficiency. For thromboprophylaxis, desirudin is given SC twice daily in fixed doses; the half-life of desirudin is 2–3 h after SC injection.

A high proportion of lepirudin-treated patients develop antibodies against the drug; antibody formation is rare with SC desirudin. Although lepirudin-directed antibodies rarely cause problems, in a small subset of patients, they can delay lepirudin clearance and enhance its anticoagulant activity. Serious bleeding has been reported in some of these patients.

Lepirudin is usually monitored using the aPTT, and the dose is adjusted to maintain an aPTT that is 1.5–2.5 times the control. The aPTT is not an ideal test for monitoring lepirudin therapy because the clotting time plateaus with higher drug concentrations. Although the clotting time with ecarin, a snake venom that converts prothrombin to meizothrombin, provides a better index of lepirudin dose than the aPTT, the ecarin clotting time is not widely available. When used for thromboprophylaxis, desirudin does not require monitoring.

ARGATROBAN A univalent inhibitor that targets the active site of thrombin, argatroban is metabolized in the liver. Consequently, this drug must be used with caution in patients with hepatic insufficiency. Argatroban is not cleared via the kidneys, so this drug is safer than lepirudin for HIT patients with renal insufficiency.

Argatroban is administered by continuous IV infusion and has a plasma half-life of ~45 min. The aPTT is used to monitor its anticoagulant effect, and the dose is adjusted to achieve an aPTT 1.5–3 times the baseline value, but not to exceed 100 s. Argatroban also prolongs the international normalized ratio (INR), a feature that can complicate the transitioning of patients to warfarin. This problem can be circumvented by using the levels of factor X to monitor warfarin in place of the INR. Alternatively, argatroban can be stopped for 2–3 h before INR determination.

BIVALIRUDIN A synthetic 20-amino-acid analogue of hirudin, bivalirudin is a divalent thrombin inhibitor. Thus, the N-terminus of bivalirudin interacts with the active site of thrombin, whereas its C-terminus binds to exosite 1. Bivalirudin has a plasma half-life of 25 min, the shortest half-life of all the parenteral direct thrombin inhibitors. Bivalirudin is degraded by peptidases and is partially excreted via the kidneys. When given in high doses in the cardiac catheterization laboratory, the anticoagulant activity of bivalirudin is monitored using the activated clotting time. With lower doses, its activity can be assessed using the aPTT.

Bivalirudin is licensed as an alternative to heparin in patients undergoing percutaneous coronary intervention. Bivalirudin also has been used successfully in HIT patients who require percutaneous coronary intervention or cardiac bypass surgery.

ORAL ANTICOAGULANTS

For many years, vitamin K antagonists such as warfarin were the only available oral anticoagulants. This situation changed with the introduction of the direct oral anticoagulants, which include dabigatran, rivaroxaban, apixaban, and edoxaban.

Warfarin A water-soluble vitamin K antagonist initially developed as a rodenticide, warfarin is the coumarin derivative most often prescribed in North America. Like other vitamin K antagonists, warfarin interferes with the synthesis of the vitamin K–dependent clotting proteins, which include prothrombin (factor II) and factors VII, IX, and X. The synthesis of the vitamin K–dependent anticoagulant proteins, proteins C and S, is also reduced by vitamin K antagonists.

MECHANISM OF ACTION All of the vitamin K–dependent clotting factors possess glutamic acid residues at their N termini. A posttranslational modification adds a carboxyl group to the γ-carbon of these residues to generate γ-carboxyglutamic acid. This modification is essential for expression of the activity of these clotting factors because it permits their calcium-dependent binding to negatively charged phospholipid surfaces. The γ-carboxylation process is catalyzed by a vitamin K–dependent carboxylase. Thus, vitamin K from the diet is reduced to vitamin K hydroquinone by vitamin K reductase **(Fig. 114-6)**. Vitamin K hydroquinone serves as a cofactor for the carboxylase enzyme, which in the presence of carbon dioxide replaces the hydrogen on the γ-carbon of glutamic acid residues with a carboxyl group. During this process, vitamin K hydroquinone is oxidized to vitamin K epoxide, which is then reduced to vitamin K by vitamin K epoxide reductase.

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby blocking the γ-carboxylation process. This results in the synthesis of vitamin K–dependent clotting proteins that are only partially γ-carboxylated. Warfarin acts as an anticoagulant because these partially γ-carboxylated proteins have reduced or absent biologic activity.

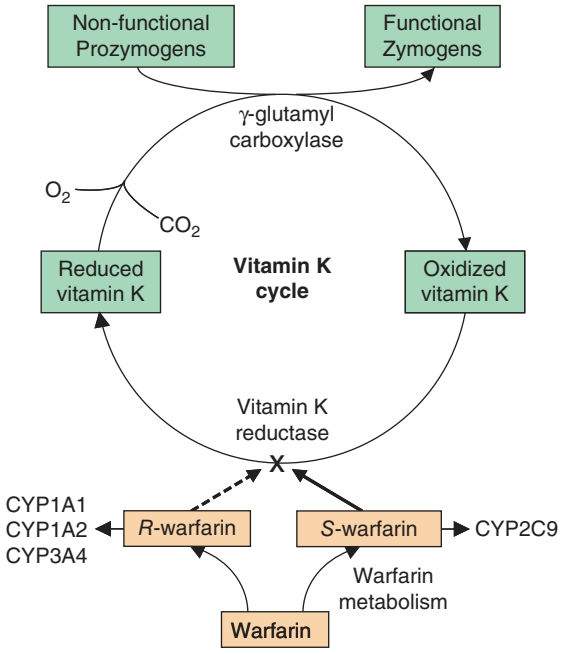

FIGURE 114-6 Mechanism of action of warfarin. A racemic mixture of *S*- and *R*-enantiomers, *S*-warfarin is most active. By blocking vitamin K epoxide reductase, warfarin inhibits the conversion of oxidized vitamin K into its reduced form. This inhibits vitamin K–dependent γ-carboxylation of factors II, VII, IX, and X because reduced vitamin K serves as a cofactor for γ-glutamyl carboxylase, which catalyzes the γ-carboxylation process, thereby converting prozymogens to zymogens capable of binding calcium and interacting with anionic phospholipid surfaces. *S*-warfarin is metabolized by CYP2C9. Common genetic polymorphisms in this enzyme can influence warfarin metabolism. Polymorphisms in the C1 subunit of vitamin K epoxide reductase (VKORC1) also can affect the susceptibility of the enzyme to warfarin-induced inhibition, thereby influencing warfarin dosage requirements.

The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

The antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 and 72 h, respectively. Because the antithrombotic effect of warfarin is delayed, patients with established thrombosis or at high risk for thrombosis require concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux, for at least 5 days.

PHARMACOLOGY Warfarin is a racemic mixture of R and S isomers. Warfarin is rapidly and almost completely absorbed from the gastrointestinal tract. Levels of warfarin in the blood peak about 90 min after drug administration. Racemic warfarin has a plasma half-life of 36–42 h, and >97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.

Warfarin accumulates in the liver where the two isomers are metabolized via distinct pathways. *CYP2C9* mediates oxidative metabolism of the more active S isomer **(Fig. 114-6)**. Two relatively common variants, *CYP2C9*2* and *CYP2C9*3*, encode an enzyme with reduced activity. Patients with these variants require lower maintenance doses of warfarin. Approximately 25% of Caucasians have at least one variant allele of *CYP2C9*2* or *CYP2C9*3*, whereas those variant alleles are less common in African Americans and Asians **(Table 114-8)**. Heterozygosity for *CYP2C9*2* or *CYP2C9*3* decreases the warfarin dose requirement by 20–30% relative to that required in subjects with the wild-type *CYP2C9*1/*1* alleles, whereas homozygosity for the *CYP2C9*2* or *CYP2C9*3* alleles reduces the warfarin dose requirement by 50–70%.

Consistent with their decreased warfarin dose requirement, subjects with at least one *CYP2C9* variant allele are at increased risk for bleeding. Compared with individuals with no variant alleles, the relative risks for warfarin-associated bleeding in *CYP2C9*2* or *CYP2C9*3* carriers are 1.9 and 1.8, respectively.

Polymorphisms in *VKORC1* also can influence the anticoagulant response to warfarin. Several genetic variations of *VKORC1* are in strong linkage disequilibrium and have been designated as non-A haplotypes. *VKORC1* variants are more prevalent than variants of *CYP2C9*. Asians have the highest prevalence of *VKORC1* variants, followed by Caucasians and African Americans (Table 114-8). Polymorphisms in *VKORC1* likely explain 30% of the variability in warfarin dose requirements. Compared with *VKORC1* non-A/non-A homozygotes, the warfarin dose requirement decreases by 25 and 50% in A haplotype heterozygotes and homozygotes, respectively. These findings prompted the Food and Drug Administration to amend the prescribing information for warfarin to indicate that lower initiation doses should be considered for patients with *CYP2C9* and *VKORC1* genetic variants. In addition to genotype data, other pertinent patient information has been incorporated into warfarin dosing algorithms. Although such algorithms help predict suitable warfarin doses, it remains unclear whether better dose identification improves patient outcome in terms of reducing hemorrhagic complications or recurrent thrombotic events.

TABLE 114-8 Frequencies of *CYP2C9* Genotypes and *VKORC1* Haplotypes in Different Populations and Their Effect on Warfarin Dose Requirements

GENOTYPE/ HAPLOTYPE	FREQUENCY, %			DOSE REDUCTION COMPARED WITH WILD-TYPE
	CAUCASIANS	AFRICAN AMERICANS (A/A)	ASIANS (A)	
CYP2C9				
*1/*1	70	90	95	–
*1/*2	17	2	0	22
*1/*3	9	3	4	34
*2/*2	2	0	0	43
*2/*3	1	0	0	53
*3/*3	0	0	1	76
VKORC1				
Non-A/non-A	37	82	7	–
Non-A/A	45	12	30	26
A/A	18	6	63	50

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter absorption, clearance, or metabolism of warfarin. Because of the variability in the anticoagulant response to warfarin, coagulation monitoring is essential to ensure that a therapeutic response is obtained.

MONITORING Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII, and factor X. The test is performed by adding thromboplastin, a reagent that contains tissue factor, phospholipid, and calcium, to citrated plasma and determining the time to clot formation. Thromboplastins vary in their sensitivity to reductions in the levels of the vitamin K–dependent clotting factors. Thus, less sensitive thromboplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. This is problematic because higher doses of warfarin increase the risk of bleeding.

The INR was developed to circumvent many of the problems associated with the prothrombin time. To calculate the INR, the patient's prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), which is an index of the sensitivity of the thromboplastin used for prothrombin time determination to reductions in the levels of the vitamin K–dependent clotting factors. Highly sensitive thromboplastins have an ISI of 1.0. Most current thromboplastins have ISI values that range from 0.9 to 1.4.

Although the INR has helped to standardize anticoagulant practice, problems persist. The precision of INR determination varies depending on reagent-coagulometer combinations. This leads to variability in the INR results. Also complicating INR determination is unreliable reporting of the ISI by thromboplastin manufacturers. Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers using the same coagulometer that is used for patient samples.

For most indications, warfarin is administered in doses that produce a target INR of 2.0–3.0. An exception is patients with mechanical heart valves, particularly those in the mitral position or older ball and cage valves in the aortic position, where a target INR of 2.5–3.5 is recommended. Studies in atrial fibrillation demonstrate an increased risk of cardioembolic stroke when the INR falls to <1.7 and an increase in intracranial bleeding with INR values >4.5. These findings highlight the fact that vitamin K antagonists have a narrow therapeutic window. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked venous thromboembolism demonstrated a higher rate of recurrent venous thromboembolism with a target INR of 1.5–1.9 compared with a target INR of 2.0–3.0.

DOSING Warfarin is usually started at a dose of 5–10 mg. Lower doses are used for patients with *CYP2C9* or *VKORC1* polymorphisms, which affect the pharmacodynamics or pharmacokinetics of warfarin and render patients more sensitive to the drug. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant initial treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Early prolongation of the INR reflects reduction in the functional levels of factor VII. Consequently, concomitant treatment with the parenteral anticoagulant should be continued until the INR has been therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of factor Xa and prothrombin have been reduced into the therapeutic range with warfarin.

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is maintained. Even patients with stable warfarin dose requirements should have their INR determined every 3–4 weeks. More frequent monitoring is necessary when new medications are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin.

SIDE EFFECTS Like all anticoagulants, the major side effect of warfarin is bleeding. A rare complication is skin necrosis. Warfarin crosses the placenta and can cause fetal abnormalities. Consequently, warfarin should not be used during pregnancy.

Bleeding At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur.

To minimize the risk of bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 3.5 and 10, warfarin should be withheld until the INR returns to the therapeutic range. If the INR is over 10, oral vitamin K should be administered, at a dose of 2.5–5 mg, although there is no evidence that doing so reduces the bleeding risk. Higher doses of oral vitamin K (5–10 mg) produce more rapid reversal of the INR but may render patients temporarily resistant to warfarin when the drug is restarted.

Patients with serious bleeding need more aggressive treatment. These patients should be given 5–10 mg of vitamin K by slow IV infusion. Additional vitamin K should be given until the INR is in the normal range. Treatment with vitamin K should be supplemented with four factor prothrombin complex concentrate, which contains all four vitamin K–dependent clotting proteins. Prothrombin complex concentrate normalizes the INR more rapidly than transfusion of fresh frozen plasma.

Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation into the cause of the bleeding. Those with gastrointestinal or genitourinary bleeding often have an underlying lesion.

Skin Necrosis A rare complication of warfarin, skin necrosis usually is seen 2–5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein S. Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect through lowering of the functional levels of factor X and prothrombin. The resultant procoagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear.

Treatment involves discontinuation of warfarin and reversal with vitamin K, if needed. An alternative anticoagulant, such as heparin or LMWH, should be given in patients with thrombosis. Protein C concentrate can be given to protein C–deficient patients to accelerate healing of the skin lesions; fresh-frozen plasma may be of value if protein C concentrate is unavailable and for those with protein S deficiency. Occasionally, skin grafting is necessary when there is extensive skin loss.

Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when initiating warfarin therapy. Warfarin should be started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2–3 consecutive days. Alternatively, treatment with rivaroxaban or apixaban could be given although there is limited information about their efficacy and safety in patients with severe protein C or S deficiency.

Pregnancy Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk of embryopathy is highest if warfarin is given in the first trimester of pregnancy. Central nervous system abnormalities can also occur with exposure to warfarin at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus that can cause bleeding. This is of particular concern at delivery when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for prevention or treatment of thrombosis.

Warfarin does not pass into the breast milk. Consequently, warfarin can safely be given to nursing mothers.

Special Problems Patients with a lupus anticoagulant and those who need urgent or elective surgery present special challenges. Although observational studies suggested that patients with thrombosis complicating the antiphospholipid syndrome required higher intensity warfarin regimens to prevent recurrent thromboembolic events, two randomized trials showed that targeting an INR of 2.0–3.0 is as effective as higher intensity treatment and produces less bleeding. Monitoring warfarin therapy can be problematic in patients with antiphospholipid syndrome if the lupus anticoagulant prolongs the baseline INR; chromogenic factor X levels can be used instead of the INR in such patients.

There is no need to stop warfarin before procedures associated with a low risk of bleeding; these include dental cleaning, simple dental extraction, cataract surgery, or skin biopsy. For procedures associated with a moderate or high risk of bleeding, warfarin should be stopped 5 days before the procedure to allow the INR to return to normal levels. Patients at high risk for thrombosis, such as those with mechanical heart valves, can be bridged with once- or twice-daily SC injections of LMWH when the INR falls to <2.0. The last dose of LMWH should be given 12–24 h before the procedure, depending on whether LMWH is administered twice or once daily. After the procedure, treatment with warfarin can be restarted.

Direct Oral Anticoagulants

Direct oral anticoagulants are available as alternatives to warfarin. These agents include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. All of these drugs have a rapid onset and offset of action and have half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the direct oral agents are more convenient to administer than warfarin because they are given in fixed doses without routine coagulation monitoring.

MECHANISM OF ACTION The direct oral anticoagulants are small molecules that bind reversibly to the active site of their target enzyme. Table 114-9 summarizes the distinct pharmacological properties of these agents.

INDICATIONS The direct oral anticoagulants have been compared with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation in four randomized trials that enrolled 71,683 patients. A meta-analysis of these data demonstrates that compared with warfarin, the higher doses of the direct oral anticoagulants significantly reduce stroke or systemic embolism by 19% ($p = 0.001$), primarily driven by a 51% reduction in hemorrhagic stroke ($p < 0.0001$), and are associated with a 10% reduction in mortality ($p < 0.0001$). The direct oral anticoagulants reduce intracranial hemorrhage by 52% compared with warfarin ($p < 0.0001$), but increase gastrointestinal bleeding by about 24% ($p = 0.04$). Overall, the direct oral anticoagulants demonstrate a favorable benefit-to-risk profile compared with warfarin, and their relative efficacy and safety are maintained across a wide spectrum of atrial fibrillation patients, including those over the age of 75 years and those with a prior history of stroke. Based on these findings, dabigatran, rivaroxaban, apixaban, and edoxaban are licensed as alternatives to warfarin for stroke prevention in nonvalvular atrial fibrillation, which is defined as atrial fibrillation occurring in patients without mechanical heart valves or severe rheumatic valvular disease, particularly mitral stenosis and/or regurgitation.

TABLE 114-9 Comparison of the Pharmacologic Properties of the New Oral Anticoagulants

CHARACTERISTIC	RIVAROXABAN	APIXABAN	EDOXABAN	DABIGATRAN
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	Yes
Bioavailability	80%	60%	50%	6%
Dosing	qd (bid)	bid	qd	bid (qd)
Half-life	7–11 h	12 h	9–11 h	12–17 h
Renal excretion	33% (66%)	25%	35%	80%
Interactions	CYP 3A4/P-gp	CYP 3A4/P-gp	P-gp	P-gp

Abbreviations: bid, twice a day; CYP, cytochrome P450; P-gp, P-glycoprotein; qd, once a day.

The direct oral anticoagulants were compared with conventional anticoagulation therapy in 27,023 patients with acute venous thromboembolism. The primary efficacy endpoint in these trials was recurrent venous thromboembolism, while the primary safety outcome was either major bleeding or the composite of major and clinically relevant non-major bleeding. In a pooled analysis of these trials, recurrent fatal and non-fatal venous thromboembolism occurred in 2.0% of those given direct oral anticoagulants compared with 2.2% of those given a vitamin K antagonist (relative risk [RR] 0.90, 95% confidence interval [CI]: 0.77–1.06). Compared with vitamin K antagonists, direct oral anticoagulants were associated with a 39% reduction in the risk of major bleeding (RR 0.61, 95% CI: 0.45–0.83), a 63% reduction in intracranial bleeding (RR 0.37, 95% CI: 0.21–0.68), and a 64% reduction in fatal bleeding (RR 0.36, 95% CI: 0.15–0.84). In addition, clinically relevant non-major bleeding was reduced by 27% with the direct oral anticoagulants compared with vitamin K antagonists (RR 0.73, 95% CI: 0.58–0.93). Therefore, the direct oral anticoagulants are non-inferior to well-managed vitamin K antagonist therapy for treatment of venous thromboembolism, but are associated with significantly less bleeding.

Whereas dabigatran and edoxaban were started after a minimum of a 5-day course of parenteral anticoagulant therapy, rivaroxaban and apixaban were administered in all-oral regimens starting with a higher dose for 21 days and 7 days, respectively. When used in this all-oral fashion, both agents were non-inferior to conventional therapy and were associated with significantly less major bleeding. Therefore, rivaroxaban and apixaban simplify treatment and facilitate out-of-hospital management of most patients with DVT and many with PE, thereby reducing healthcare costs. With these advantages, clinical guidelines now endorse the direct oral anticoagulants for first-line treatment of venous thromboembolism in patients without active cancer. For those with active cancer, LMWH remains the preferred therapy.

Dabigatran, rivaroxaban, and apixaban have also been compared with enoxaparin for thromboprophylaxis after elective hip or knee arthroplasty and although all three are licensed for this indication, dabigatran is rarely used.

DOSING For stroke prevention in patients with nonvalvular atrial fibrillation, dabigatran is given at a dose of 150 mg twice daily with a dose reduction to 75 mg twice daily in those with a creatinine clearance of 15–30 mL/min; rivaroxaban is given at a dose of 20 mg once daily with a dose reduction to 15 mg once daily in patients with a creatinine clearance of 15–49 mL/min; apixaban is given at a dose of 5 mg twice daily with a dose reduction to 2.5 mg twice daily for patients with at least two of the following criteria: age of 80 years or more, body weight of 60 kg or less, and serum creatinine >1.5 g/dL; and edoxaban is given at a dose of 60 mg once daily with a dose reduction to 30 mg once daily for patients with a creatinine clearance of 15–50 mL/min, body weight of 60 kg or less, or receiving potent P-glycoprotein inhibitors such as dronedarone or verapamil.

For treatment of venous thromboembolism, dabigatran is given at a dose of 150 mg twice daily after a minimum of a 5-day course of heparin or LMWH; rivaroxaban is started at a dose of 15 mg twice daily for 21 days, and the dose is then reduced to 20 mg once daily thereafter; apixaban is started at a dose of 10 mg twice daily for 7 days, and the dose is then reduced to 5 mg twice daily for the following 6 months after which the dose can be further reduced to 2.5 mg twice daily; and edoxaban is given at a dose of 60 mg once daily after a minimum of a 5-day course of heparin or LMWM with the dose reduced to 30 mg once daily for patients with a creatinine clearance of 15–50 mL/min, body weight of 60 kg or less, or receiving potent P-glycoprotein inhibitors.

For thromboprophylaxis after elective hip or knee replacement surgery, rivaroxaban is given at a dose of 10 mg once daily, whereas apixaban is given at a dose of 2.5 mg twice daily. The drugs are usually given for 14 days after knee arthroplasty and for 35 days after hip arthroplasty.

MONITORING Although designed to be administered without routine monitoring, there are situations where determination of the anticoagulant activity of the new oral anticoagulants can be helpful. These include assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity prior to surgery or intervention. For qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the aPTT for dabigatran. Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban. In fact, because apixaban has such a limited effect on the prothrombin time, anti-factor Xa assays are needed to assess its activity. The effect of the drugs on tests of coagulation varies depending on the time that the blood is drawn relative to the timing of the last dose of the drug and the reagents used to perform the tests. Chromogenic anti-factor Xa assays and a diluted thrombin clotting time with appropriate calibrators provide quantitative assays to measure the plasma levels of the factor Xa inhibitors and dabigatran, respectively.

SIDE EFFECTS Like all anticoagulants, bleeding is the most common side effect of the direct oral anticoagulants. The direct oral anticoagulants are associated with less intracranial bleeding than warfarin. The increased risk of intracranial bleeding with warfarin likely reflects the reduction in functional levels of factor VII, which precludes efficient thrombin generation at sites of microvascular bleeding in the brain. Because the direct oral anticoagulants target downstream coagulation enzymes, they produce less impairment of hemostatic plug formation at sites of vascular injury.

A downside of the new oral anticoagulants is the increased risk of gastrointestinal bleeding. This likely occurs because unabsorbed active drug in the gut exacerbates bleeding from lesions. Although dabigatran etexilate is a prodrug, only 7% is absorbed and the remainder passes through the gut where at least two-thirds is metabolically activated to dabigatran by gut esterases.

Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by administering the drug with food. Dyspepsia is rare with rivaroxaban, apixaban, and edoxaban.

PERIPROCEDURAL MANAGEMENT Like warfarin, the new oral anticoagulants must be stopped before procedures associated with a moderate or high risk of bleeding. The drugs should be held for 1–2 days, or longer if renal function is impaired. Assessment of residual anticoagulant activity before procedures associated with a high bleeding risk is prudent.

MANAGEMENT OF BLEEDING With minor bleeding, holding one or two doses of drug is usually sufficient. The approach to serious bleeding is similar to that with warfarin except that vitamin K administration is of no benefit. Thus, the anticoagulant and antiplatelet drugs should be held, the patient should be resuscitated with fluids and blood products as necessary, and, if possible, the bleeding site should be identified and managed. Coagulation testing will determine the extent of anticoagulation and renal function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important; administration of oral activated charcoal may help to prevent absorption of drug administered in the past 2–4 h.

Anticoagulant reversal should be considered in patients with life-threatening bleeding, such as intracranial bleeding, if bleeding continues despite supportive measures or if patients require urgent surgery. Idarucizumab is a specific reversal agent for dabigatran. A monoclonal antibody fragment, idarucizumab binds dabigatran with high affinity to form a 1:1 complex that is then cleared by the kidneys. Idarucizumab is given as an intravenous bolus of 5 g.

Andexanet alfa and ciraparantag are under development for reversal of rivaroxaban, apixaban, and edoxaban but neither is approved. Until these reversal agents are available, prothrombin complex concentrate should be considered for reversal of the oral factor Xa inhibitors in patients with life-threatening or ongoing bleeding.

PREGNANCY As small molecules, the direct oral anticoagulants can all pass through the placenta. Consequently, these agents are contraindicated in pregnancy, and when used by women of childbearing potential, appropriate contraception is important. The direct oral anticoagulants should be avoided in nursing mothers and their safety in children has yet to be established.

FIBRINOLYTIC DRUGS

ROLE OF FIBRINOLYTIC THERAPY

Fibrinolytic drugs can be used to degrade thrombi and are administered systemically or can be delivered via catheters directly into the substance of the thrombus. Systemic delivery is used for treatment of acute MI, acute ischemic stroke, and most cases of massive PE. The goal of therapy is to produce rapid thrombus dissolution, thereby restoring blood flow. In the coronary circulation, restoration of blood flow reduces morbidity and mortality rates by limiting myocardial damage, whereas in the cerebral circulation, rapid thrombus dissolution decreases the neuronal death and brain infarction that produce irreversible brain injury. For patients with massive PE, the goal of thrombolytic therapy is to restore pulmonary artery perfusion.

Peripheral arterial thrombi and thrombi in the proximal deep veins of the leg are most often treated using catheter-directed thrombolytic therapy. Catheters with multiple side holes can be used to enhance drug delivery. In some cases, intravascular devices that fragment and extract the thrombus are used to hasten treatment. These devices can be used alone or in conjunction with fibrinolytic drugs.

MECHANISM OF ACTION

Currently approved fibrinolytic agents include streptokinase; acylated plasminogen streptokinase activator complex (anistreplase); urokinase; recombinant tissue-type plasminogen activator (rtPA), which is also known as alteplase or activase; and two recombinant derivatives of rtPA, tenecteplase and reteplase. All of these agents act by converting plasminogen, the zymogen, to plasmin, the active enzyme **(Fig. 114-7)**. Plasmin then degrades the fibrin matrix of thrombi and produces soluble fibrin degradation products.

Endogenous fibrinolysis is regulated at two levels. Plasminogen activator inhibitors, particularly the type 1 form (PAI-1), prevent excessive plasminogen activation by regulating the activity of tPA and urokinase-type plasminogen activator (uPA). Once plasmin is generated, it is regulated by plasmin inhibitors, the most important of which is α_2-antiplasmin. The plasma concentration of plasminogen is twofold higher than that of α_2-antiplasmin. Consequently, with pharmacologic doses of plasminogen activators, the concentration of plasmin that is generated can exceed that of α_2-antiplasmin. In addition to degrading fibrin, unregulated plasmin can also degrade fibrinogen and other clotting factors. This process, which is known as the *systemic lytic state*, reduces the hemostatic potential of the blood and increases the risk of bleeding.

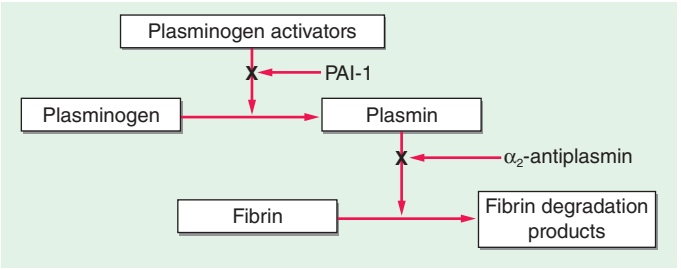

FIGURE 114-7 The fibrinolytic system and its regulation. Plasminogen activators convert plasminogen to plasmin. Plasmin then degrades fibrin into soluble fibrin degradation products. The system is regulated at two levels. Type 1 plasminogen activator inhibitor (PAI-1) regulates the plasminogen activators, whereas α_2-antiplasmin serves as the major inhibitor of plasmin.

The endogenous fibrinolytic system is geared to localize plasmin generation to the fibrin surface. Both plasminogen and tPA bind to fibrin to form a ternary complex that promotes efficient plasminogen activation. In contrast to free plasmin, plasmin generated on the fibrin surface is relatively protected from inactivation by α_2-antiplasmin, a feature that promotes fibrin dissolution. Furthermore, C-terminal lysine residues, exposed as plasmin degrades fibrin, serve as binding sites for additional plasminogen and tPA molecules. This creates a positive feedback that enhances plasmin generation. When used pharmacologically, the various plasminogen activators capitalize on these mechanisms to a lesser or greater extent.

Plasminogen activators that preferentially activate fibrin-bound plasminogen are considered fibrin-specific. In contrast, nonspecific plasminogen activators do not discriminate between fibrin-bound and circulating plasminogen. Activation of circulating plasminogen results in the generation of unopposed plasmin that can trigger the systemic lytic state. Alteplase and its derivatives are fibrin-specific plasminogen activators, whereas streptokinase, anistreplase, and urokinase are nonspecific agents.

STREPTOKINASE

Unlike other plasminogen activators, streptokinase is not an enzyme and does not directly convert plasminogen to plasmin. Instead, streptokinase forms a 1:1 stoichiometric complex with plasminogen. Formation of this complex induces a conformational change in plasminogen that exposes its active site **(Fig. 114-8)**. The streptokinase-plasminogen complex then converts additional plasminogen to plasmin.

Streptokinase has no affinity for fibrin, and the streptokinase-plasminogen complex activates both free and fibrin-bound plasminogen. Activation of circulating plasminogen generates sufficient amounts of plasmin to overwhelm α_2-antiplasmin. Unopposed plasmin not only degrades fibrin in the occlusive thrombus but also induces a systemic lytic state.

When given systemically to patients with acute MI, streptokinase reduces mortality. For this indication, the drug is usually given as an IV infusion of 1.5 million units over 30–60 min. Patients who receive streptokinase can develop antibodies against the drug, as can patients with prior streptococcal infection. These antibodies can reduce the effectiveness of streptokinase.

Allergic reactions occur in ~5% of patients treated with streptokinase. These may manifest as a rash, fever, chills, and rigors. Although anaphylactic reactions can occur, these are rare. Transient hypotension is common with streptokinase and has been attributed to plasmin-mediated release of bradykinin from kininogen. The hypotension usually responds to leg elevation and administration of IV fluids and low doses of vasopressors, such as dopamine or norepinephrine.

ANISTREPLASE

To generate this drug, streptokinase is combined with equimolar amounts of Lys-plasminogen, a plasmin-cleaved form of plasminogen

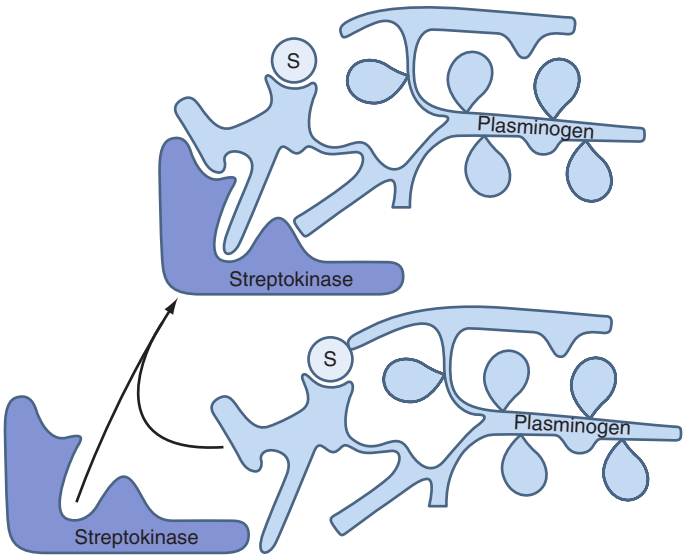

FIGURE 114-8 Mechanism of action of streptokinase. Streptokinase binds to plasminogen and induces a conformational change in plasminogen that exposes its active site. The streptokinase/plasmin(ogen) complex then serves as the activator of additional plasminogen.

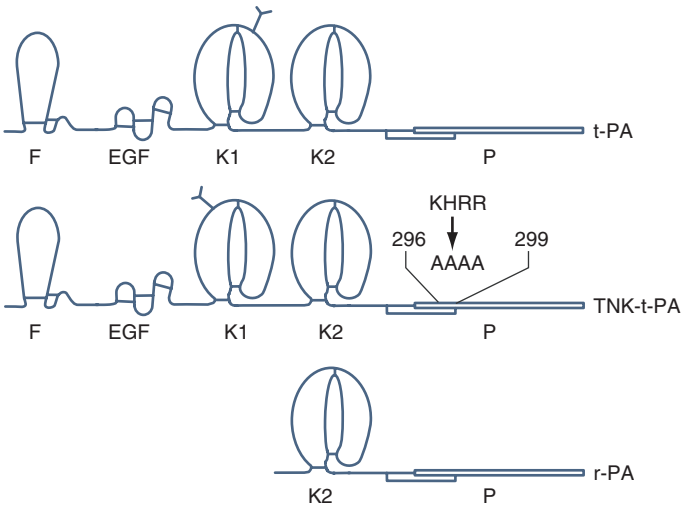

FIGURE 114-9 Domain structures of alteplase (tPA), tenecteplase (TNK-tPA), and reteplase (r-PA). The finger (F), epidermal growth factor (EGF), first and second kringles (K1 and K2, respectively), and protease (P) domains are illustrated. The glycosylation site (Y) on K1 has been repositioned in tenecteplase to endow it with a longer half-life. In addition, a tetra-alanine substitution in the protease domain renders tenecteplase resistant to type 1 plasminogen activator inhibitor (PAI-1) inhibition. Reteplase is a truncated variant that lacks the F, EGF, and K1 domains.

with a Lys residue at its N terminal. The active site of Lys-plasminogen that is exposed upon combination with streptokinase is then masked with an anisoyl group. After IV infusion, the anisoyl group is slowly removed by deacylation, giving the complex a half-life of ~100 min. This allows drug administration via a single bolus infusion.

Although it is more convenient to administer, anistreplase offers few mechanistic advantages over streptokinase. Like streptokinase, anistreplase does not distinguish between fibrin-bound and circulating plasminogen. Consequently, it too produces a systemic lytic state. Likewise, allergic reactions and hypotension are just as frequent with anistreplase as they are with streptokinase.

When anistreplase was compared with alteplase in patients with acute MI, reperfusion was obtained more rapidly with alteplase than with anistreplase. Improved reperfusion was associated with a trend toward better clinical outcomes and reduced mortality rate with alteplase. These results and the high cost of anistreplase have dampened the enthusiasm for its use.

UROKINASE

Urokinase is a two-chain serine protease derived from cultured fetal kidney cells with a molecular weight of 34,000. Urokinase converts plasminogen to plasmin directly by cleaving the Arg560-Val561 bond. Unlike streptokinase, urokinase is not immunogenic and allergic reactions are rare. Urokinase produces a systemic lytic state because it does not discriminate between fibrin-bound and circulating plasminogen.

Despite many years of use, urokinase has never been systemically evaluated for coronary thrombolysis. Instead, urokinase is often employed for catheter-directed lysis of thrombi in the deep veins or the peripheral arteries. Because of production problems, the availability of urokinase is limited.

ALTEPLASE

A recombinant form of single-chain tPA, alteplase has a molecular weight of 68,000. Alteplase is rapidly converted into its two-chain form by plasmin. Although single- and two-chain forms of tPA have equivalent activity in the presence of fibrin, in its absence, single-chain tPA has tenfold lower activity.

Alteplase consists of five discrete domains (Fig. 114-9); the N-terminal A chain of two-chain alteplase contains four of these domains. Residues 4 through 50 make up the finger domain, a region that resembles the finger domain of fibronectin; residues 50 through 87 are homologous with epidermal growth factor, whereas residues 92 through 173 and 180 through 261, which have homology to the kringle domains of plasminogen, are designated as the first and second kringle, respectively. The fifth alteplase domain is the protease domain; it is located on the C-terminal B chain of two-chain alteplase.

The interaction of alteplase with fibrin is mediated by the finger domain and, to a lesser extent, by the second kringle domain. The affinity of alteplase for fibrin is considerably higher than that for fibrinogen. Consequently, the catalytic efficiency of plasminogen activation by alteplase is two to three orders of magnitude higher in the presence of fibrin than in the presence of fibrinogen. This phenomenon helps to localize plasmin generation to the fibrin surface.

Although alteplase preferentially activates plasminogen in the presence of fibrin, alteplase is not as fibrin-selective as was first predicted. Its fibrin specificity is limited because like fibrin, (DD)E, which is the complex of D-dimer non-covalently linked to fragment E is the major soluble degradation product of cross-linked fibrin. (DD)E binds alteplase and plasminogen with high affinity. Consequently, (DD)E is as potent as fibrin as a stimulator of plasminogen activation by alteplase. Whereas plasmin generated on the fibrin surface results in thrombolysis, plasmin generated on the surface of circulating (DD)E degrades fibrinogen. Fibrinogen degradation results in the accumulation of fragment X, a high-molecular-weight clottable fibrinogen degradation product. Incorporation of fragment X into hemostatic plugs formed at sites of vascular injury renders them susceptible to lysis. This phenomenon may contribute to alteplase-induced bleeding.

A trial comparing alteplase with streptokinase for treatment of patients with acute MI demonstrated significantly lower mortality with alteplase than with streptokinase, although the absolute difference was small. The greatest benefit was seen in patients age <75 years with anterior MI who presented <6 h after symptom onset.

For treatment of acute MI or acute ischemic stroke, alteplase is given as an IV infusion over 60–90 min. The total dose of alteplase usually ranges from 90 to 100 mg. Allergic reactions and hypotension are rare, and alteplase is not immunogenic.

TENECTEPLASE

Tenecteplase is a genetically engineered variant of tPA and was designed to have a longer half-life than tPA and to be resistant to inactivation by PAI-1. To prolong its half-life, a new glycosylation site was added to the first kringle domain (Fig. 114-9). Because addition of this extra carbohydrate side chain reduced fibrin affinity, the existing glycosylation site on the first kringle domain was removed. To render the molecule resistant to inhibition by PAI-1, a tetra-alanine substitution

was introduced at residues 296–299 in the protease domain, the region responsible for the interaction of tPA with PAI-1.

Tenecteplase is more fibrin-specific than tPA. Although both agents bind to fibrin with similar affinity, the affinity of tenecteplase for (DD)E is significantly lower than that of tPA. Consequently, (DD)E does not stimulate systemic plasminogen activation by tenecteplase to the same extent as tPA. As a result, tenecteplase produces less fibrinogen degradation than tPA.

For coronary thrombolysis, tenecteplase is given as a single IV bolus. In a large phase III trial that enrolled >16,000 patients, the 30-day mortality rate with single-bolus tenecteplase was similar to that with accelerated-dose tPA. Although rates of intracranial hemorrhage were also similar with both treatments, patients given tenecteplase had fewer noncerebral bleeds and a reduced need for blood transfusions than those treated with tPA. The improved safety profile of tenecteplase likely reflects its enhanced fibrin specificity.

RETEPLASE

Reteplase is a single-chain, recombinant tPA derivative that lacks the finger, epidermal growth factor, and first kringle domains (Fig. 114-9). This truncated derivative has a molecular weight of 39,000. Reteplase binds fibrin more weakly than tPA because it lacks the finger domain. Because it is produced in *Escherichia coli*, reteplase is not glycosylated. This endows it with a plasma half-life longer than that of tPA. Consequently, reteplase is given as two IV boluses, which are separated by 30 min. Clinical trials have demonstrated that reteplase is at least as effective as streptokinase for treatment of acute MI, but the agent is not superior to tPA.

CONCLUSIONS AND FUTURE DIRECTIONS

Thrombosis involves a complex interplay among the vessel wall, platelets, the coagulation system, and the fibrinolytic pathways. Activation of coagulation also triggers inflammatory pathways that may exacerbate thrombosis. A better understanding of the biochemistry of blood coagulation and advances in structure-based drug design have identified new targets and resulted in the development of novel antithrombotic drugs. Well-designed clinical trials have provided detailed information on which drugs to use and when to use them. Despite these advances, however, thromboembolic disorders remain a major cause of morbidity and mortality. Therefore, the search for better and safer targets continues.

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Section 1 Basic Considerations in Infectious Diseases

115 Approach to the Patient with an Infectious Disease

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HISTORICAL PERSPECTIVE

The origins of the field of infectious diseases are humble. The notion that communicable diseases were due to a *miasma* ("bad air") can be traced back to at least the mid-sixteenth century. Not until the work of Louis Pasteur and Robert Koch in the late nineteenth century was there credible evidence supporting the germ theory of disease—i.e., that microorganisms are the direct cause of infections. In contrast to this relatively slow start, the twentieth century saw remarkable advances in the field of infectious diseases, and the etiologic agents of numerous infectious diseases were soon identified. Furthermore, the discovery of antibiotics and the advent of vaccines against some of the most deadly and debilitating infections greatly altered the landscape of human health. Indeed, the twentieth century saw the elimination of smallpox, one of the great scourges in the history of humanity. These remarkable successes prompted Sir Frank MacFarlane Burnet, a noted immunologist and Nobel laureate, to write in a 1962 publication entitled *Natural History of Infectious Diseases*: "In many ways one can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of infectious disease." Professor Burnet was not alone in this view. Robert Petersdorf, a renowned infectious disease expert and former editor of this textbook, wrote in 1978 that "even with my great personal loyalties to infectious diseases, I cannot conceive a need for 309 more [graduating trainees in infectious diseases] unless they spend their time culturing each other." Given the enormous growth of interest in the microbiome in the past 10 years, Dr. Petersdorf's statement might have been ironically clairvoyant, although he could have had no idea what was in store for humanity, with an onslaught of new, emerging, and re-emerging infectious diseases.

Clearly, even with all the advances of the twentieth century, infectious diseases continue to represent a formidable challenge for patients and physicians alike. Furthermore, during the latter half of the century, several chronic diseases were demonstrated to be directly or indirectly caused by infectious microbes; perhaps the most notable examples are the associations of *Helicobacter pylori* with peptic ulcer disease and gastric carcinoma, human papillomavirus with cervical cancer, and hepatitis B and C viruses with liver cancer. In fact, ~16% of all malignancies are now known to be associated with an infectious cause. In addition, numerous emerging and re-emerging infectious diseases continue to have a dire impact on global health: HIV/AIDS, pandemic influenza, Ebola, and Zika are but a few examples. The fear of weaponizing pathogens for bioterrorism is ever present and poses a potentially enormous threat to public health. Moreover, escalating antimicrobial resistance in clinically relevant microbes (e.g., *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Plasmodium* species, and HIV) signifies that the administration of antimicrobial agents—once thought to be a panacea—requires appropriate stewardship. For all these reasons, infectious diseases continue to exert grim effects on individual patients as well as on international public health. Even with all the successes of the past century, physicians must be as thoughtful about infectious diseases now as they were at the beginning of the twentieth century.

GLOBAL CONSIDERATIONS

Infectious diseases remain the second leading cause of death worldwide. Although the rate of infectious disease–related deaths has decreased dramatically over the past 25 years, there were still 10.9 million such deaths in 2013 **(Fig. 115-1*A*)**. These deaths disproportionately affect children <1 year of age, adults older than 70 years, and persons living in low- and middle-income countries **(Fig. 115-1*B* and 115-1*C*; Chap. 462)**; in 2013, 20% of all deaths worldwide were related to infectious diseases, with rates >50% in most sub-Saharan African countries.

Given that infectious diseases are still a major cause of global mortality, understanding the local epidemiology of disease is critically important in evaluating patients. Diseases such as HIV/AIDS have decimated sub-Saharan Africa, with HIV-infected adults representing 19–29% of the total population in countries like South Africa, Botswana, and Swaziland. Moreover, drug-resistant tuberculosis is rampant throughout the former Soviet-bloc countries, India, China, and South Africa. The ready availability of this type of information allows physicians to develop appropriate differential diagnoses and treatment plans for individual patients. Programs such as the Global Burden of Disease seek to quantify human losses (e.g., deaths, disability-adjusted life years) due to diseases by age, sex, and country over time; these data not only help inform local, national, and international health policy but can also help guide local medical decision-making.

Even though some diseases (e.g., pandemic influenza, Middle East respiratory syndrome) are seemingly geographically restricted, the increasing ease of rapid worldwide travel has raised concern about their swift spread around the globe. Indeed, human migration has historically been the source of epidemics: *Yersinia pestis* spread along trade routes in the fourteenth century, Native American populations were devastated by diseases such as smallpox and measles that were imported by European explorers in the fifteenth and sixteenth centuries, military maneuvers helped facilitate the spread of the 1918 influenza pandemic, and religious pilgrimages (e.g., the Hajj) provide the means for worldwide dissemination of diseases. The introduction of cholera into Haiti, the transmission of Ebola within the United States, and the emerging outbreak of Zika virus infection are recent examples that highlight the continued effects of global travel on the spread of infectious diseases. Not only can travelers carry person-to-person transmitted infections (e.g., influenza, HIV) anywhere in the world, but they can also introduce vector-borne infections to new geographic areas (e.g., chikungunya and Zika viruses) and contribute to the worldwide spread of multidrug-resistant organisms. The world's increasing interconnectedness has profound implications not only for the global economy but also for medicine and the spread of infectious diseases.

UNDERSTANDING THE MICROBIOTA

Normal, healthy humans are colonized with ~50 trillion bacteria as well as countless viruses, fungi, and archaea; taken together, these microorganisms outnumber human cells by ~10 times in the human body **(Chap. 459)**. The major reservoir of these microbes is the gastrointestinal tract, but substantial numbers of microbes live in the female genital tract, the oral cavity, and the nasopharynx. There is increasing interest in the skin and lungs as sites where microbial colonization might be highly relevant to the biology and disease susceptibility of the host. These commensal organisms provide the host with myriad benefits, from aiding in metabolism to shaping the immune system. With regard to infectious diseases, the vast majority of infections are caused by organisms that are part of the normal microbiota (e.g., *S. aureus*, *S. pneumoniae*, *Pseudomonas aeruginosa*), with relatively few infections due to organisms that are strictly pathogens (e.g., *Neisseria gonorrhoeae*, rabies virus). Perhaps it is not surprising that a general understanding of the microbiota is essential in the evaluation of infectious diseases. Individuals' microbiotas likely have a major impact on their susceptibility to infectious diseases and even their responses to

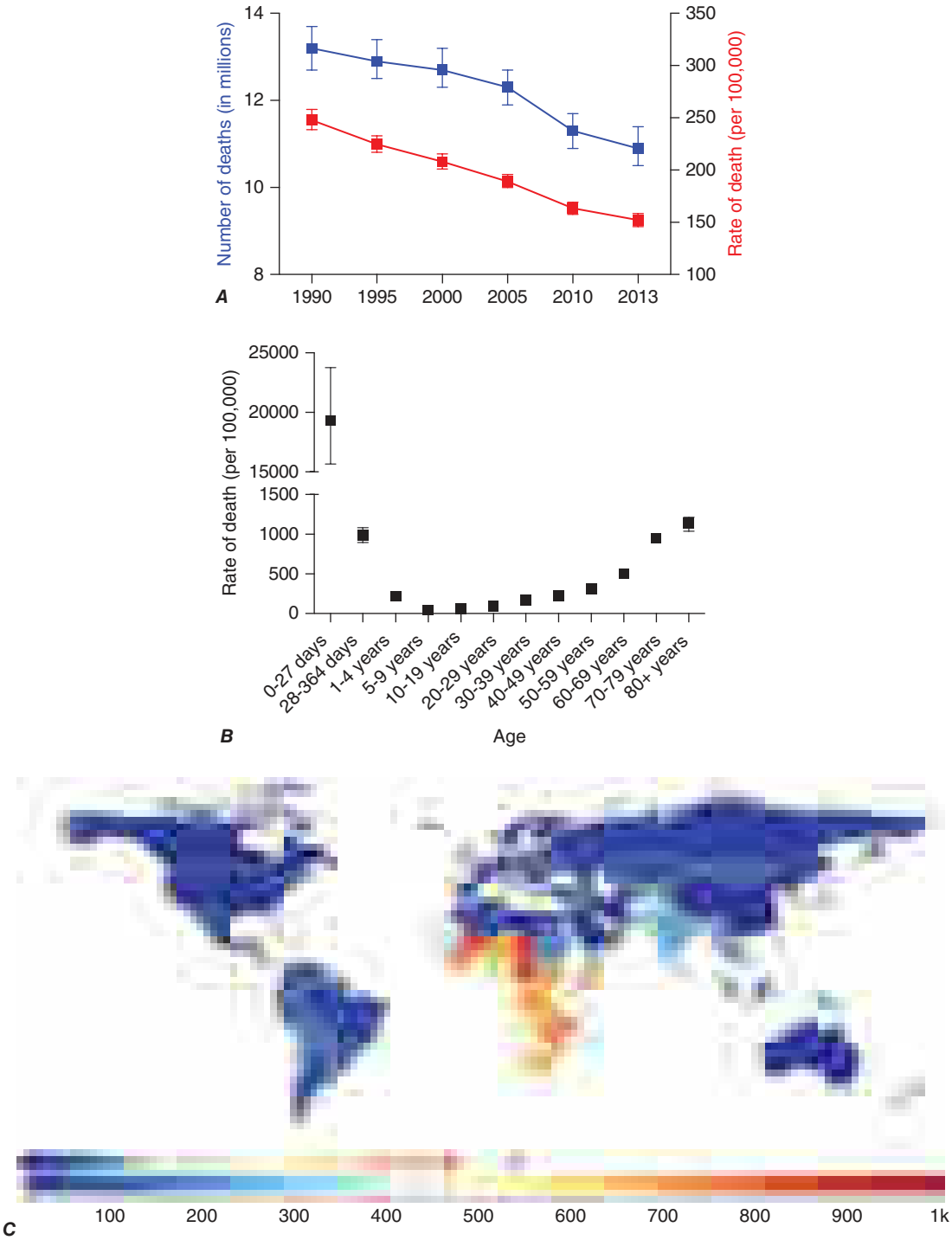

FIGURE 115-1 Magnitude of infectious disease–related deaths globally. *A.* The absolute number (*blue line; left axis*) and rate (*red line; right axis*) of infectious disease–related deaths throughout the world since 1990. ***B.*** Age-specific rates of infectious disease–related deaths in 2013. In both ***A*** and ***B***, the charts depict the mean estimate and 95% uncertainty intervals. ***C.*** A map depicting country-specific data for the percentages of total deaths that were attributable to communicable, maternal, neonatal, and nutritional disorders in 2013. *(Source: Global Burden of Disease Study, Institute for Health Metrics and Evaluation.)*

vaccines. Site-specific knowledge of the indigenous microbiota may facilitate appropriate interpretation of culture results, aid in selection of empirical antimicrobial therapy based on the likely causative agents, and provide additional impetus for rational antibiotic use to minimize the untoward effects of these drugs on the "beneficial" microbes that inhabit the body.

WHEN TO CONSIDER AN INFECTIOUS ETIOLOGY

The title of this chapter may appear to presuppose that the physician knows when a patient has an infectious disease. In reality, this chapter can serve only as a guide to the evaluation of a patient in whom an infectious disease is a possibility. Once a specific diagnosis is made, the reader should consult the subsequent chapters that deal with specific microorganisms in detail. The challenge for the physician is to recognize which patients may have an infectious disease as opposed to some other underlying disorder. This task is greatly complicated by the fact that infections have an infinite range of presentations, from acute life-threatening conditions (e.g., meningococcemia) to chronic diseases of varying severity (e.g., *H. pylori*–associated peptic ulcer disease) to no symptoms at all (e.g., latent *M. tuberculosis* infection). While it is impossible to generalize about a presentation that encompasses all infections, common findings in the history, physical examination, and basic laboratory testing often suggest that the patient either has an infectious disease or should be more closely evaluated for one. This chapter focuses on these common findings and how they may direct the ongoing evaluation of the patient.

APPROACH TO THE PATIENT

Infectious Disease

See also Chap. 117.

HISTORY

As in all of medicine, a complete and thorough history is paramount in the evaluation of a patient with a possible infectious disease. The history is critical for developing a focused differential diagnosis and for guiding the physical exam and initial diagnostic testing. Although a detailing of all the elements of a history is beyond the scope of this chapter, specific components relevant to infectious diseases require particular attention. In general, these aspects focus on two areas: (1) an exposure history that may identify microorganisms with which the patient may have come into contact and (2) host-specific factors that may predispose to the development of an infection.

Exposure History • **History of infections or exposure to drug-resistant microbes** Information about a patient's previous infections, with the associated microbial susceptibility profiles, is very helpful in determining possible etiologic agents. Specifically, knowing whether a patient has a history of infection with drug-resistant organisms (e.g., methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococcus* species, enteric organisms that produce an extended-spectrum β-lactamase or carbapenemase) or may have been exposed to drug-resistant microbes (e.g., during a recent stay in a hospital, nursing home, or long-term acute-care facility) may alter the choice of empirical antibiotics. For example, a patient presenting with sepsis who is known to have a history of invasive infection with a multidrug-resistant isolate of *P. aeruginosa* should be treated empirically with an antimicrobial regimen that will cover this strain.

Social history Although the social history taken by physicians is often limited to inquiries about a patient's alcohol and tobacco use, a complete social history can offer a number of clues to the underlying diagnosis. Knowing whether the patient has any high-risk behaviors (e.g., unsafe sexual behaviors, IV drug use), potential hobby-associated exposures (e.g., avid gardening, with possible *Sporothrix schenckii* exposure), or occupational exposures (e.g., increased risk for *M. tuberculosis* exposure in funeral service workers) can facilitate diagnosis. The importance of the social history is exemplified by a case in 2009 in which a laboratory researcher died of a *Y. pestis* infection acquired during his work; although this patient had visited both an outpatient clinic and an emergency department, his records at both sites failed to include his occupation—information that potentially could have led quickly to appropriate treatment and infection control measures.

Dietary habits As certain pathogens are associated with specific dietary habits, inquiring about a patient's diet can provide insight into possible exposures. For example, Shiga toxin–producing strains of *Escherichia coli* and *Toxoplasma gondii* are associated with the consumption of raw or undercooked meat; *Salmonella typhimurium*, *Listeria monocytogenes*, and *Mycobacterium bovis* with unpasteurized milk; *Leptospira* species, parasites, and enteric bacteria with unpurified water; and *Vibrio* species, norovirus, helminths, and protozoa with raw seafood.

Animal exposures Because animals are often important vectors of infectious diseases, patients should be asked about exposures to any animals, including contact with their own pets, visits to petting zoos, or random encounters (e.g., home rodent infestation). For example, dogs can carry ticks that serve as agents for the transmission of several infectious diseases, including Lyme disease, Rocky Mountain spotted fever, and ehrlichiosis. Cats are associated with *Bartonella henselae* infection, reptiles with *Salmonella* infection, rodents with leptospirosis, and rabbits with tularemia **(Chap. 136)**.

Travel history Attention should be paid to both international and domestic travel. Fever in a patient who has recently returned from abroad significantly broadens the differential diagnosis **(Chap. 119)**; even a remote history of international travel may reflect patients' exposure to infections with pathogens such as *M. tuberculosis* or *Strongyloides stercoralis*. Similarly, domestic travel may have exposed patients to pathogens that are not normally found in their local environment and therefore may not routinely be considered in the differential diagnosis. For example, a patient who has recently visited California or Martha's Vineyard may have been exposed to *Coccidioides immitis* or *Francisella tularensis*, respectively. Beyond simply identifying locations that a patient may have visited, the physician needs to delve deeper to learn what kinds of activities and behaviors the patient engaged in during travel (e.g., the types of food and sources of water consumed, freshwater swimming, animal exposures) and whether the patient had the necessary immunizations and/or took the necessary prophylactic medications prior to travel; these additional exposures, which the patient may not think to report without specific prompting, are as important as exposures during a patient's routine daily living.

Host-Specific Factors Because many opportunistic infections (e.g., with *Pneumocystis jirovecii*, *Aspergillus* species, or JC virus) affect primarily immunocompromised patients, it is of vital importance to determine the immune status of the patient. Defects in the immune system may be due to an underlying disease (e.g., malignancy, HIV infection, malnutrition), a medication (e.g., chemotherapy, glucocorticoids, monoclonal antibodies to components of the immune system), a treatment modality (e.g., total body irradiation, splenectomy), or a primary immunodeficiency. The type of infection for which the patient is at increased risk varies with the specific type of immune defect. In concert with determining whether a patient is immunocompromised for any reason, the physician should review the immunization record to ensure that the patient is adequately protected against vaccine-preventable diseases **(Chap. 118)**.

PHYSICAL EXAMINATION

Like the history, a thorough physical examination is crucial in evaluating patients with an infectious disease. Some elements of the physical exam (e.g., skin, lymphatics) that are often performed in a cursory manner as a result of the ever-increasing pace of medical practice may help identify the underlying diagnosis. Moreover, serial exams are critical since new findings may appear as the illness progresses. A description of all the elements of a physical exam is beyond the scope of this chapter, but the following components have particular relevance to infectious diseases.

Vital Signs Given that elevations in temperature are often a hallmark of infection, paying close attention to the temperature may be of value in diagnosing an infectious disease. The idea that 37°C (98.6°F) is the normal human body temperature dates back to the nineteenth century and was initially based on axillary measurements. Rectal temperatures more accurately reflect the core body temperature and are 0.4°C (0.7°F) and 0.8°C (1.4°F) higher than oral and axillary temperatures, respectively. Although the definition of fever varies greatly throughout the medical literature, the most common definition, which is based on studies defining fever of unknown origin **(Chap. 17)**, uses a core temperature ≥38.3°C (≥101°F). Although fever is very commonly associated with infection, it is also documented in many other diseases **(Chap. 15)**. For every 1°C (1.8°F) increase in core temperature, the heart rate typically rises by 15–20 beats/min. **Table 115-1** lists infections that are associated with relative bradycardia (*Faget's sign*), where patients have a lower heart rate than might be expected for a given body temperature. Although this pulse–temperature dissociation is not highly sensitive or specific for establishing a diagnosis, it is potentially useful in low-resource settings given its ready availability and simplicity.

Lymphatics There are ~600 lymph nodes throughout the body, and infections are an important cause of lymphadenopathy. A physical examination should include evaluation of lymph nodes in multiple regions (e.g., popliteal, inguinal, epitrochlear, axillary, multiple cervical regions), with notation of the location, size (normal, <1 cm),

TABLE 115-1 Causes of Relative Bradycardia

Infectious Causes	
Intracellular organisms	
Gram-negative bacteria	*Salmonella typhi*
	Francisella tularensis
	Brucella spp.
	Coxiella burnetii (Q fever)
	Leptospira interrogans
	Legionella pneumophila
	Mycoplasma pneumoniae
Tick-borne organisms	*Rickettsia* spp.
	Orientia tsutsugamushi (scrub typhus)
	Babesia spp.
Other	*Corynebacterium diphtheriae*
	Plasmodium spp. (malaria)
Viruses/viral infections	Yellow fever virus
	Dengue virus
	Viral hemorrhagic fevers[a]
	Viral myocarditis
Noninfectious Causes	
	Drug fever
	Beta blocker use
	Central nervous system lesions
	Malignant lymphoma
	Factitious fever

[a]Primarily early in the course of infection with Marburg or Ebola virus.

presence or absence of tenderness, and consistency (soft, firm, or rubbery) and of whether the nodes are matted (i.e., connected and moving together). Nodes that are small and firm can also be described as "shotty," referring to the size and consistency of buckshot pellets. Of note, palpable epitrochlear nodes are always pathologic. Of patients presenting with lymphadenopathy, 75% have localized findings, and the remaining 25% have generalized lymphadenopathy (i.e., that involving more than one anatomic region). Localized lymphadenopathy in the head and neck region is found in 55% of patients, inguinal lymphadenopathy in 14%, and axillary lymphadenopathy in 5%. Determining whether the patient has generalized versus localized lymphadenopathy can help narrow the differential diagnosis, as various infections present differently.

Skin The fact that many infections have cutaneous manifestations gives the skin examination particular importance in the evaluation of patients **(Chaps. 16, 54, 124, and A1)**. It is important to perform a complete skin exam, with attention to both front and back. Specific rashes are often extremely helpful in narrowing the differential diagnosis of an infection **(Chaps. 16 and A1)**. In numerous anecdotal instances, patients in the intensive care unit have had "fever of unknown origin" that was actually due to unrecognized pressure ulcers. Moreover, close examination of the distal extremities for splinter hemorrhages, Janeway lesions, or Osler's nodes may yield evidence of endocarditis or other causes of septic emboli.

Foreign Bodies As previously mentioned, many infections are caused by members of the indigenous microbiota. These infections typically occur when these microbes escape their normal habitat and enter a new one. Thus, maintenance of epithelial barriers is one of the most important mechanisms in protection against infection. However, hospitalization of patients is often associated with breaches of these barriers—e.g., due to placement of IV lines, surgical drains, or tubes (such as endotracheal tubes and Foley catheters) that allow microorganisms to localize in sites to which they normally would not have access **(Chap. 137)**. Accordingly, knowing what lines, tubes, and drains are in place is helpful in ascertaining what body sites might be infected.

DIAGNOSTIC TESTING

Laboratory and radiologic testing has advanced greatly over the past few decades and has become an important component in the evaluation of patients. The dramatic increase in the number of serologic diagnostics, antigen tests, and molecular diagnostics available to the physician has, in fact, revolutionized medical care. However, all of these tests should be viewed as adjuncts to the history and physical examination—not a replacement for them. The selection of initial tests should be based directly on the patient's history and physical exam findings. Moreover, diagnostic testing should generally be limited to those conditions that are reasonably likely and treatable, important in terms of public health considerations, and/or capable of providing a definitive diagnosis that will consequently limit other testing.

White Blood Cell (WBC) Count Elevations in the WBC count are often associated with infection, though many viral infections are associated with leukopenia. It is important to assess the WBC differential, given that different classes of microbes are associated with various leukocyte types. For example, bacteria are associated with an increase in polymorphonuclear neutrophils, often with elevated levels of earlier developmental forms such as bands; viruses are associated with an increase in lymphocytes; and certain parasites are associated with an increase in eosinophils. **Table 115-2** lists the major infectious causes of eosinophilia.

Inflammatory Markers The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level are indirect and direct measures of the acute-phase response, respectively, that can be used to assess a patient's general level of inflammation. Moreover, these markers can be followed serially over time to monitor disease progress/resolution. It is noteworthy that the ESR changes relatively slowly, and its measurement more often than weekly usually is not useful; in contrast, CRP concentrations change rapidly, and daily measurements can be useful in the appropriate context. Although these markers are sensitive indicators of inflammation, neither is very specific. An extremely elevated ESR (>100 mm/h) has a 90% predictive value for a serious underlying disease **(Table 115-3)**. Work is ongoing to identify other potentially useful inflammatory markers (e.g., procalcitonin, serum amyloid A protein); however, their clinical utility requires further validation.

Analysis of Cerebrospinal Fluid (CSF) Assessment of CSF is critical for patients with suspected meningitis or encephalitis. An opening pressure should always be recorded, and fluid should routinely be sent for cell counts, Gram's stain and culture, and determination of glucose and protein levels. A CSF Gram's stain typically requires $>10^5$ bacteria/mL for reliable positivity; its specificity approaches 100%. **Table 115-4** lists the typical CSF profiles for various infections. In general, CSF with lymphocytic pleocytosis and a low glucose concentration suggests either infection (e.g., with *Listeria*, *M. tuberculosis*, or a fungus) or a noninfectious disorder (e.g., neoplastic meningitis, sarcoidosis). Bacterial antigen tests of CSF (e.g., latex agglutination tests for *Haemophilus influenzae* type b, group B *Streptococcus*, *S. pneumoniae*, and *Neisseria meningitidis*) are not recommended for screening, given that these tests are no more sensitive than Gram's stain; however, these assays can be helpful in presumptively identifying organisms seen on Gram's stain. In contrast, other antigen tests (e.g., for *Cryptococcus*) and some CSF serologic testing (e.g., for *Treponema pallidum*, *Coccidioides*) are highly sensitive and are useful for select patients. In addition, polymerase chain reaction (PCR) analysis of CSF is increasingly being used for the diagnosis of bacterial (e.g., *N. meningitidis*, *S. pneumoniae*, mycobacteria) and viral (e.g., herpes simplex virus, enterovirus) infections; while these molecular tests permit rapid diagnosis with a high degree of sensitivity and specificity, they often do not allow determination of antimicrobial resistance profiles.

Cultures The mainstays of infectious disease diagnosis include the culture of infected tissue (e.g., surgical specimens) or fluid

TABLE 115-2 Major Infectious Causes of Eosinophilia[a]

ORGAN INVOLVED	ORGANISM	EXPOSURE	GEOGRAPHIC DISTRIBUTION	DEGREE OF EOSINOPHILIA[b]
Central nervous system	*Angiostrongylus*	Raw seafood	Asia	Mild
	Gnathostoma	Raw poultry and seafood	Asia	Moderate to extreme
Eye	*Loa loa*	Insect bite	Africa	Moderate (expatriates), mild (patients living in endemic areas)
	Onchocerca	Insect bite	Africa	Mild (expatriates), moderate (patients living in endemic areas)
Lung	*Chlamydia trachomatis*	Sexual transmission	Worldwide	Mild
	Strongyloides	Soil	Tropical	Moderate (acute), mild (chronic)
	Toxocara canis/Toxocara cati[c]	Dogs, soil	Worldwide	Moderate to extreme
	Paragonimus	Crabs and crayfish	Asia	Moderate (acute), mild (chronic)
	Coccidioides immitis	Soil	Southwestern United States	Mild (acute), extreme (disseminated)
	Brugia malayi	Insect bite	Asia	Mild to moderate
	Pneumocystis jirovecii	Air	Worldwide	Mild
Liver	*Schistosoma japonicum*	Freshwater swimming	Asia	Moderate (acute), mild (chronic)
	Schistosoma mansoni	Freshwater swimming	Africa, Middle East, Latin America	Moderate (acute), mild (chronic)
	Fasciola	Watercress	Worldwide	Moderate
	Clonorchis	Raw seafood	Asia	Mild to moderate
	Opisthorchis	Raw seafood	Asia	Mild to moderate
Intestines	*Ascaris*[d]	Raw fruits and vegetables, contaminated water	Worldwide	Mild to extreme
	Hookworm	Soil	Worldwide	Mild to moderate
	Trichuris	Raw fruits and vegetables, contaminated water	Tropical	Mild
	Cystoisospora belli	Contaminated water and food	Worldwide	Mild
	Dientamoeba fragilis	Unclear; spread via fecal–oral route	Worldwide	Mild
	Capillaria	Raw seafood	Asia	Extreme
	Heterophyes	Raw seafood	Asia, Middle East	Mild
	Anisakis	Raw seafood	Worldwide	Mild
	Baylisascaris procyonis[e]	Soil	North America	Moderate to extreme
	Hymenolepis nana	Contaminated water, soil	Worldwide	Mild
Bladder	*Schistosoma haematobium*	Freshwater swimming	Africa, Middle East	Moderate (acute), mild (chronic)
Muscle	*Trichinella*	Pork	Worldwide	Moderate to extreme
Lymphatics	*Wuchereria bancrofti*[d]	Insect bite	Tropical	Moderate to extreme[f]
	Bartonella henselae	Cats	Worldwide	Mild
Other	Recovery from bacterial or viral infections	—	—	Mild
	HIV	Contaminated bodily fluid	Worldwide	Mild
	Cryptococcus neoformans	Soil	Worldwide	Moderate to extreme (disseminated)

[a]There are numerous noninfectious causes of eosinophilia, such as atopic disease, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, and pernicious anemia, which can cause mild eosinophilia; drug hypersensitivity and serum sickness, which can cause mild to moderate eosinophilia; collagen vascular disease, which can cause moderate eosinophilia; and malignancy, Churg-Strauss syndrome, and hyper-IgE syndromes, which can cause moderate to extreme eosinophilia. [b]Mild: 500–1500 cells/μL; moderate: 1500–5000 cells/μL; extreme: >5000 cells/μL. [c]Can also affect the liver and the eyes. [d]Can also affect the lungs. [e]Can also affect the eyes and the central nervous system. [f]Levels are typically higher with pulmonary infections.

(e.g., blood, urine, sputum, pus from a wound). Samples can be sent for culture of bacteria (aerobic or anaerobic), fungi, or viruses. Ideally, specimens are collected before the administration of antimicrobial therapy; in instances where this order of events is not clinically feasible, microscopic examination of the specimen (e.g., Gram-stained or potassium hydroxide [KOH]–treated preparations) is particularly important. Culture of the organism(s) allows identification of the etiologic agent(s), determination of the antimicrobial susceptibility profile, and—when there is concern about an outbreak—isolate typing. While cultures are extremely useful in the evaluation of patients, determining whether culture results are clinically meaningful or represent contamination (e.g., a non-*aureus*, non-*lugdunensis* staphylococcal species growing in a blood culture) can sometimes be challenging and requires an understanding of the patient's immune status, exposure history, and microbiota. In some cases, serial cultures to demonstrate clearance of the organism may be helpful.

Pathogen-Specific Testing Numerous pathogen-specific tests (e.g., serology, antigen testing, PCR testing) are commercially available, and many hospitals now offer some of these tests in-house to facilitate rapid turnaround that ultimately enhances patient care. The reader is directed to relevant chapters on the pathogens of interest for specific details. Some of these tests (e.g., universal PCRs) identify organisms that currently are not cultivable and have unclear relationships to disease, thereby complicating diagnosis. As these tests become more commonplace and the work of the Human Microbiome Project progresses, the relevance of some of these previously unrecognized bacteria to human health will likely become more apparent.

Radiology Imaging provides an important adjunct to the physical examination, allowing evaluation for lymphadenopathy in regions that are not externally accessible (e.g., mediastinum, intraabdominal sites), assessment of internal organs for evidence of infection,

TABLE 115-3 Causes of an Extremely Elevated Erythrocyte Sedimentation Rate (>100 mm/h)

ETIOLOGIC CATEGORY (% OF CASES)	SPECIFIC CAUSES
Infectious diseases (35–40)	Subacute bacterial endocarditis
	Abscesses
	Osteomyelitis
	Tuberculosis
	Urinary tract infection
Inflammatory diseases (15–20)	Giant cell arteritis
	Rheumatoid arthritis
	Systemic lupus erythematosus
Malignancies (15–20)	Multiple myeloma
	Leukemias
	Lymphomas
	Carcinomas
Other (20–35)	Drug hypersensitivity reactions (drug fever)
	Ischemic tissue injury/trauma
	Renal diseases

and facilitation of image-guided percutaneous sampling of deep spaces. The choice of imaging modality (e.g., CT, MRI, ultrasound, nuclear medicine, use of contrast) is best made in consultation with a radiologist to ensure that the results will address the physician's specific concerns.

TREATMENT

Physicians often must balance the need for empirical antibiotic treatment with the patient's clinical condition. When clinically feasible, it is best to obtain relevant samples (e.g., blood, CSF, tissue, purulent exudate) for culture prior to the administration of antibiotics, as antibiotic treatment often makes subsequent diagnosis more difficult. Although a general maxim for antibiotic treatment is to use a regimen with as narrow a spectrum as possible **(Chap. 139)**, empirical regimens are necessarily somewhat broad, given that a specific diagnosis has not yet been made. **Table 115-5** lists empirical antibiotic treatment regimens for commonly encountered infectious presentations. These regimens should be narrowed as appropriate once a specific diagnosis is made. In addition to antibiotics, there is sometimes a role for adjunctive therapies, such as intravenous immunoglobulin G (IVIG) pooled from healthy adults or hyperimmune globulin prepared from the blood of individuals with high titers of specific antibodies to select pathogens (e.g., cytomegalovirus, hepatitis B virus, rabies virus, vaccinia virus, *Clostridium tetani*, varicella-zoster virus, *Clostridium botulinum* toxin). Although the data suggesting efficacy are limited, IVIG is sometimes used for patients with suspected staphylococcal or streptococcal toxic shock syndrome.

INFECTION CONTROL

When evaluating a patient with a suspected infectious disease, the physician must consider what infection control methods are necessary to prevent transmission of any possible infection to other people. In 2007, the U.S. Centers for Disease Control and Prevention published guidelines for isolation precautions that are available for download at *www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html*. Persons exposed to certain pathogens (e.g., *N. meningitidis*, HIV, *Bacillus anthracis*) should receive postexposure prophylaxis to prevent disease acquisition. (See relevant chapters for details on specific pathogens.)

WHEN TO OBTAIN AN INFECTIOUS DISEASE CONSULT

At times, primary physicians need assistance with patient management from a diagnostic and/or therapeutic perspective. Multiple studies have demonstrated that an infectious disease consult is associated with improved outcomes, shorter length of hospital stay, and decreased costs for patients with various diseases. For example, in a prospective cohort study of patients with *S. aureus* bacteremia, infectious disease consultation was independently associated with a 56% reduction in 28-day mortality. In addition, infectious disease specialists provide other services (e.g., infection control, antimicrobial stewardship, management of outpatient antibiotic therapy, occupational exposure programs) that have been shown to benefit patients. Whenever such assistance would be advantageous to a patient with a possible infection, the primary physician should opt for an infectious disease consult. Specific situations that might prompt a consult include (1) difficult-to-diagnose patients with presumed infections, (2) patients who are not responding to treatment as expected, (3) patients with a complicated medical history (e.g., organ transplant recipients, patients immunosuppressed due to autoimmune or inflammatory conditions), and (4) patients with "exotic" diseases (i.e., diseases that are not typically seen within the region).

TABLE 115-4 Typical Cerebrospinal Fluid Profiles for Meningitis and Encephalitis[a]

	NORMAL	BACTERIAL MENINGITIS	VIRAL MENINGITIS	FUNGAL MENINGITIS[b]	PARASITIC MENINGITIS	TUBERCULOUS MENINGITIS	ENCEPHALITIS
WBC count (per μL)	<5	>1000	25–500	40–600	150–2000	25–100	50–500
Differential of WBC	60–70% lymphocytes, ≤30% monocytes/macrophages	↑↑PMNs (≥80%)	Predominantly lymphocytes[c]	Lymphocytes or PMNs, depending on specific organism	↑↑ Eosinophils (≥50%)[d]	Predominantly lymphocytes[c]	Predominantly lymphocytes[c]
Gram's stain	Negative	Positive (in >60% of cases)	Negative	Rarely positive	Negative	Occasionally positive[e]	Negative
Glucose (mg/dL)	40–85	<40	Normal	↓ to normal	Normal	<50 in 75% of cases	Normal
Protein (mg/dL)	15–45	>100	20–80	150–300	50–200	100–200	50–100
Opening pressure (mmH_2O)	50–180	>300	100–350	160–340	Normal	150–280	Normal to ↑
Common causes	—	*Streptococcus pneumoniae*, *Neisseria meningitidis*	Enteroviruses	*Candida*, *Cryptococcus*, and *Aspergillus* spp.	*Angiostrongylus cantonensis*, *Gnathostoma spinigerum*, *Baylisascaris procyonis*	*Mycobacterium tuberculosis*	Herpesviruses, enteroviruses, influenza virus, rabies virus

[a]Numbers indicate typical results, but actual results may vary. [b]Cerebrospinal fluid characteristics depend greatly on the specific organism. [c]Neutrophils may predominate early in the disease course. [d]Patients typically have striking eosinophilia as well. [e]Sensitivity can be increased by examination of a smear of protein coagulum (pellicle) and the use of acid-fast stains.

Abbreviations: PMNs, polymorphonuclear neutrophils; WBC, white blood cell.

TABLE 115-5 Initial Empirical Antibiotic Therapy for Common Infectious Disease Presentations[a]

CLINICAL SYNDROME	COMMON ETIOLOGIES	ANTIBIOTIC(S)	COMMENTS	SEE CHAPTER(S)
Septic shock	*Staphylococcus aureus, Streptococcus pneumoniae,* enteric gram-negative bacilli	Vancomycin, 15 mg/kg q12h[b] ***plus*** A broad-spectrum antipseudomonal β-lactam (piperacillin-tazobactam, 4.5 g q6h; imipenem, 1 g q8h; meropenem, 1 g q8h; or cefepime, 1–2 g q8–12h)	—	**297**
Meningitis	*S. pneumoniae*, *Neisseria meningitidis*	Vancomycin, 15 mg/kg q12h[b] ***plus*** Ceftriaxone, 2 g q12h	Dexamethasone (0.15 mg/kg IV q6h for 2–4 d) should be added for patients with suspected or proven pneumococcal meningitis, with the first dose administered 10–20 min before the first dose of antibiotics.	**133** and pathogen-specific chapters
CNS abscess	*Streptococcus* spp., *Staphylococcus* spp., anaerobes, gram-negative bacilli	Vancomycin, 15 mg/kg q12h[b] ***plus*** Ceftriaxone, 2 g q12h ***plus*** Metronidazole, 500 mg q8h	—	**133**
Acute endocarditis (native valve)	*S. aureus*, *Streptococcus* spp., coagulase-negative staphylococci	Vancomycin, 15 mg/kg q12h[b] ***plus*** Cefepime, 2 g q8h	—	**123**
Pneumonia			If MRSA is a consideration, add vancomycin (15 mg/kg q12h[b]) or linezolid (600 mg q12h); daptomycin should not be used in patients with pneumonia.	**121** and pathogen-specific chapters
Community-acquired, outpatient	*S. pneumoniae, Mycoplasma pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*	Azithromycin, 500 mg PO × 1, then 250 mg PO qd × 4 days		
Inpatient, non-ICU	Above plus *Legionella* spp.	A respiratory fluoroquinolone (moxifloxacin, 400 mg IV/PO qd; gemifloxacin, 320 mg PO qd; or levofloxacin, 750 mg IV/PO qd) ***or*** A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) *plus* azithromycin		
Inpatient, ICU	Above plus *S. aureus*	A β-lactam ***plus*** Azithromycin *or* a respiratory fluoroquinolone		
Hospital-acquired pneumonia[d]	*S. pneumoniae*, *H. influenzae*, *S. aureus*, gram-negative bacilli (e.g., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Acinetobacter* spp.)	An antipseudomonal β-lactam (cefepime, 1–2 g q8–12h; ceftazidime, 2 g q8h; imipenem, 1 g q8h; meropenem, 1 g q8h; or piperacillin-tazobactam, 4.5 g q6h) ***plus*** An antipseudomonal fluoroquinolone (levofloxacin or ciprofloxacin, 400 mg q8h) *or* an aminoglycoside (amikacin, 20 mg/kg q24h[c]; gentamicin, 7 mg/kg q24h[e]; or tobramycin, 7 mg/kg q24h[e])		
Complicated intraabdominal infection			If MRSA is a consideration, add vancomycin (15 mg/kg q12h[b]).	**127**, **172**, and pathogen-specific chapters
Mild to moderate severity	Anaerobes (*Bacteroides* spp., *Clostridium* spp.), gram-negative bacilli (*Escherichia coli*), *Streptococcus* spp.	Cefoxitin, 2 g q6h ***or*** A combination of metronidazole (500 mg q8–12h) *plus one of the following*: cefazolin (1–2 g q8h), cefuroxime (1.5 g q8h), ceftriaxone (1–2 g q12–24h), cefotaxime (1–2 g q6–8h)		
High-risk patient or high degree of severity	Same as above	A carbapenem (imipenem, 1 g q8h; meropenem, 1 g q8h; doripenem, 500 mg q8h) ***or*** Piperacillin-tazobactam, 3.375 g q6h[f] ***or*** A combination of metronidazole (500 mg q8–12h) *plus either* an antipseudomonal cephalosporin (cefepime, 2 g q8–12h; ceftazidime, 2 g q8h) *or* an antipseudomonal fluoroquinolone (ciprofloxacin, 400 mg q12h; levofloxacin, 750 mg q24h)		

(*Continued*)

TABLE 115-5 Initial Empirical Antibiotic Therapy for Common Infectious Disease Presentations[a] (Continued)

CLINICAL SYNDROME	COMMON ETIOLOGIES	ANTIBIOTIC(S)	COMMENTS	SEE CHAPTER(S)
Skin and soft tissue infection	*S. aureus*, *Streptococcus pyogenes*	Dicloxacillin, 250–500 mg PO qid ***or*** Cephalexin, 250–500 mg PO qid ***or*** Clindamycin, 300–450 mg PO tid ***or*** Nafcillin/oxacillin, 1–2 g q4h	If MRSA is a consideration, clindamycin, vancomycin (15 mg/kg q12h[b]), linezolid (600 mg IV/PO q12h), or TMP-SMX (1–2 double-strength tablets PO bid[g]) can be used.	**124** and pathogen-specific chapters

[a]This table refers to immunocompetent adults with normal renal and hepatic function. All doses listed are for parenteral administration unless indicated otherwise. Local antimicrobial susceptibility profiles may influence the choice of antibiotic. Therapy should be tailored once a specific etiologic agent and its susceptibilities are identified. [b]Trough levels for vancomycin should be 15–20 μg/mL. [c]Trough levels for amikacin should be <4 μg/mL. [d]In patients with late onset (i.e., after ≥5 days of hospitalization) or risk factors for multidrug-resistant organisms. [e]Trough levels for gentamicin and tobramycin should be <1 μg/mL. [f]If *P. aeruginosa* is a concern, the dosage may be increased to 3.375 g IV q4h or 4.5 g IV q6h. [g]Data on the efficacy of TMP-SMX in skin and soft tissue infections are limited.

Abbreviations: CNS, central nervous system; ICU, intensive care unit; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

PERSPECTIVE

The study of infectious diseases is really a study of host–bacterial interactions and represents evolution by both the host and the bacteria—an endless struggle in which microbes have generally been more creative and adaptive. Given that one-fifth of deaths worldwide are still related to infectious diseases, it is clear that the war against infectious diseases has not been won. For example, a cure for HIV infection is still lacking, there have been only marginal improvements in the methods for detection and treatment of tuberculosis after more than a half century of research, new infectious disease outbreaks (e.g., pandemic influenza, viral hemorrhagic fevers, Zika) continue to emerge, and the threat of microbial bioterrorism remains high. The subsequent chapters in Part 5 detail—on both a syndrome and a microbe-by-microbe basis—the current state of medical knowledge about infectious diseases. At their core, all of these chapters carry a similar message: Despite numerous advances in the diagnosis, treatment, and prevention of infectious diseases, much work and research are required before anyone can confidently claim we have achieved "the virtual elimination of infectious disease." In reality, this goal will never be attained, given the rapid adaptability of microbes.

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116 Molecular Mechanisms of Microbial Pathogenesis

Gerald B. Pier

Over the past five decades, molecular studies of the pathogenesis of microorganisms have yielded a torrent of information about the various microbial and host molecules that contribute to the processes of infection and disease. These processes can be classified into several stages: microbial encounter with and entry into the host; microbial growth after entry; avoidance of innate host defenses; tissue invasion and tropism; tissue damage; and transmission to new hosts. *Virulence* is the measure of an organism's capacity to cause disease and is a function of the pathogenic factors elaborated by microbes. These factors promote *colonization* (the simple presence of potentially pathogenic microbes in or on a host), *infection* (attachment and growth of pathogens and avoidance of host defenses), and *disease* (often, but not always, the result of activities of secreted toxins or toxic metabolites). In addition, the host's inflammatory response to infection greatly contributes to disease and its attendant clinical signs and symptoms. A recent explosion of interest in the *microbiome* (the collection of microbial genomes present in or on mammalian organisms) and the *microbiota* (the collection of microbes residing in and on mammalian organisms) and their impact on physiology of, susceptibility to, and response to infection and on immune system development has greatly expanded our understanding of host–pathogen interactions. Furthermore, investigations in this field have documented effects of the microbiome on all aspects of animal—and even plant—physiology, greatly increasing our knowledge of the everyday influence of host–microbe interactions on life.

MICROBIAL ENTRY AND ADHERENCE

The Microbiome We now know that the indigenous microbial organisms living in close association with almost all animals and plants are organized into complex communities that strongly modulate overall host physiology, including the ability of pathogenic microbes to establish themselves in or on host surfaces. The sheer numbers of these microbes and their genomic variability often exceed the numbers of host cells and the variability of host genes in a typical animal. Changes and differences in microbiomes within and between individuals, currently characterized by high-throughput DNA sequencing techniques and bioinformatic analysis, impact such diverse conditions as obesity; type 1 diabetes; cognition; neurologic states; autoimmune diseases; skin, gastrointestinal, respiratory, and vaginal infectious diseases; and development and control of the immune system. It has been difficult to directly associate specific types of microbiomes with pathophysiologic states, and our understanding of the degree to which microbial species are conserved or variable within human and other animal microbiotas is evolving. Experimental studies in laboratory animals, particularly in germ-free mammals, show the potent ability of changes in the microbiota to manipulate health status and outcomes. One of the clearest functions of the microbiota is to influence and mature the cells of the immune system, thereby exerting a major effect on susceptibility and resistance to microbial infection. The degree to which studies of the microbiome will translate into strategies for the management of human health and disease (e.g., the use of fecal transplants to treat and prevent recurrences of serious *Clostridium difficile* infection) is still an open question. For the moment, defining clusters of organisms associated with diseases may be more feasible than identifying single organisms or microbial molecules. Results from the Human Microbiome Project suggest a high level of variability among individuals in microbiome components, although many individuals appear to maintain a fairly conserved microbiome throughout their lives. In the context of infectious diseases, changes and disruptions of the indigenous

microbiome—i.e., alterations of the normal flora due to antibiotic and immunosuppressive drug use, environmental changes, and the effects of microbial virulence factors used to displace the indigenous microbial flora and thus to facilitate pathogen colonization—have a strong and often fundamental impact on the progression of infection. While the technology for defining and understanding the microbiome is still quite young, there is little doubt that the resulting data will markedly affect our concepts of and approaches to microbial pathogenesis and infectious disease treatment.

Entry Sites A microbial pathogen can potentially enter any part of a host organism. In general, the type of disease produced by a particular microbe is often a direct consequence of its route of entry into the body. The most common sites of entry are mucosal surfaces (the respiratory, alimentary, and urogenital tracts) and the skin. Ingestion, inhalation, and sexual contact are typical routes of microbial entry. Other portals of entry include sites of skin injury (cuts, bites, burns, trauma) along with injection via natural (e.g., vector-borne) or artificial (e.g., needlestick injury) routes. A few pathogens, such as *Schistosoma* species, can penetrate unbroken skin. The conjunctiva can serve as an entry point for pathogens of the eye, which occasionally spread systemically from that site.

Microbial entry usually relies on the presence of specific factors needed for persistence and growth in a tissue. Fecal–oral spread via the alimentary tract requires a biologic profile consistent with survival in the varied environments of the gastrointestinal tract (including the low pH of the stomach and the high bile content of the intestine) as well as in contaminated food or water outside the host. Organisms that gain entry via the respiratory tract survive well in small moist droplets produced during sneezing and coughing. Pathogens that enter by venereal routes often survive best in the warm moist environment of the urogenital mucosa and have restricted host ranges (e.g., *Neisseria gonorrhoeae*, *Treponema pallidum*, and HIV).

The biology of microbes entering through the skin is highly varied. Some of these organisms can survive under a broad range of environmental conditions, such as those in the salivary glands or alimentary tracts of arthropod vectors, the mouths of larger animals, soil, and water. A complex biology allows protozoan parasites such as *Plasmodium*, *Leishmania*, and *Trypanosoma* species to undergo morphogenic changes that permit transmission of the organism to mammalian hosts during insect feeding for blood meals. Plasmodia are injected as infective sporozoites from the salivary glands during mosquito feeding. *Leishmania* parasites are regurgitated as promastigotes from the alimentary tract of sandflies and injected by bite into a susceptible host. Trypanosomes are first ingested from infected hosts by reduviid bugs; the pathogens then multiply in the gastrointestinal tract of the insects and are released in feces onto the host's skin during subsequent feedings. Most microbes that land directly on intact skin are destined to die, as survival on the skin or in hair follicles requires resistance to fatty acids, low pH, and other antimicrobial factors on the skin. Once it is damaged (and particularly if it becomes necrotic), the skin can be a major portal of entry and growth for pathogens and elaboration of their toxic products. Burn wound infections and tetanus are clear examples. After animal bites, pathogens resident in the animal's saliva gain access to the victim's tissues through the damaged skin. Rabies is the paradigm for this pathogenic process; rabies virus grows in striated muscle cells at the site of inoculation.

Microbial Adherence Once in or on a host, many microbes must situate themselves favorably to avoid clearance mechanisms, in part by microbial anchoring to a tissue or tissue factor. (One possible exception is an organism that directly enters the bloodstream and multiplies there.) Because most host cells—responding to activation of innate immunity (see "Avoidance of Innate Host Defenses," below)—express multiple surface and cytoplasmic molecules that detect pathogens and pathogen factors, a complex interplay ensues and determines whether the microbe will avoid host clearance and remain in a tissue. Viruses and intracellular pathogens like *Mycobacterium tuberculosis* must bind to cells and enter them, whereas common extracellular bacterial pathogens of the human respiratory tract survive better if they avoid binding to pulmonary epithelial cells.

TABLE 116-1 Examples of Microbial Ligand–Receptor Interactions

MICROORGANISM	TYPE OF MICROBIAL LIGAND	HOST RECEPTOR
Viral Pathogens		
Influenza virus	Hemagglutinin	Sialic acid
Measles virus		
Vaccine strain	Hemagglutinin	CD46/moesin/signaling lymphocytic activation molecule (SLAM)/nectin-4
Wild-type strains	Hemagglutinin	
Human herpesvirus type 6A	Glycoprotein complex gH/gL/gQ1/gQ2	CD46
Herpes simplex virus	Glycoprotein C	Heparan sulfate
HIV	Surface glycoprotein	CD4 and chemokine receptors (CCR5 and CXCR4)
Epstein-Barr virus	Envelope protein	CD21 (CR2)
Adenovirus	Fiber protein	Coxsackie-adenovirus receptor (CAR)
Coxsackievirus	Viral coat proteins	CAR and major histocompatibility class I antigens
Bacterial Pathogens		
Neisseria spp.	Pili	Membrane cofactor protein (CD46)
Pseudomonas aeruginosa	Pili and flagella	Asialo-GM1
	Lipopolysaccharide	Cystic fibrosis transmembrane conductance regulator (CFTR)
Escherichia coli	Pili	Ceramides/mannose and digalactosyl residues
Streptococcus pyogenes	Hyaluronic acid capsule	CD44
Yersinia spp.	Invasin/accessory invasin locus	β_1 Integrins
Bordetella pertussis	Filamentous hemagglutinin	CR3
Legionella pneumophila	Adsorbed C3bi	CR3
Mycobacterium tuberculosis	Adsorbed C3bi	CR3; DC-SIGN
Fungal Pathogens		
Blastomyces dermatitidis	WI-1	Possibly matrix proteins and integrins
Candida albicans	Int1p	Extracellular matrix proteins
Protozoal Pathogens		
Plasmodium vivax	Merozoite form	Duffy Fy antigen
Plasmodium falciparum	Erythrocyte-binding protein 175 (EBA-175)	Glycophorin A
Entamoeba histolytica	Surface lectin	*N*-Acetylglucosamine

Specific ligands or adhesins for host receptors constitute a major area of study in microbial pathogenesis. Adhesins comprise a wide range of surface structures, anchoring the microbe to a tissue and promoting cellular entry as well as eliciting host responses critical to innate immunity (Table 116-1). Most microbes produce multiple adhesins specific for multiple host receptors that often are redundant, are serologically variable, and act additively or synergistically with other microbial factors to promote sticking to host tissues. In addition, some microbes adsorb host proteins onto their surface and use the natural host protein receptor for binding and entry into cells. While it is clear that, for some pathogenic organisms, blocking adherence can be a means to prevent infection, for others it could have unintended consequences, decreasing the innate host response that facilitates elimination of the infecting microbe.

VIRAL ADHESINS All viral pathogens must bind to host cells, enter them, and replicate within them. Viral coat proteins serve as ligands

for cellular entry, and more than one ligand–receptor interaction may be needed. In some types of viruses, such as lipid bilayer–encapsulated Retroviridae or Rhabdoviridae, a single protein mediates both viral binding and entry via fusion with the host cell membrane. In other cases, a second viral fusion protein is needed to complete viral entry. HIV uses its envelope glycoprotein (gp) 120 to enter host cells by binding to both CD4 and one of two receptors for chemokines (CCR5 or CXCR4). Measles virus requires two proteins for cellular entry: the hemagglutinin (H) glycoprotein of wild-type measles virus binds to the signaling lymphocytic activation molecule (SLAM or CD150) on macrophages and dendritic cells, where the virus initially replicates, and also to nectin-4 on respiratory epithelial cells, where later replication occurs. The vaccine strain of measles virus binds to both CD46 and SLAM. For full cellular entry, however, measles virus requires a second fusion (F) protein. The gB and gC proteins on herpes simplex virus bind to heparan sulfate, although this adherence is not essential for entry but rather serves to concentrate virions close to the cell surface; this step is followed by attachment to mammalian cells mediated by the viral gD protein, with subsequent formation of a homotrimer of viral gB protein or a heterodimer of viral gH and gL proteins that permits fusion of the viral envelope with the host cell membrane. Herpes simplex virus can use a number of eukaryotic cell-surface receptors for entry, including the herpesvirus entry mediator, members of the immunoglobulin superfamily, the proteins nectin-1 and nectin-2, and modified heparan sulfate.

BACTERIAL ADHESINS Among the adhesins studied in greatest detail are bacterial pili and flagella **(Fig. 116-1)**. *Pili* or *fimbriae* are commonly used by gram-negative bacteria for attachment to host cells and tissues; similar factors are produced by gram-positive organisms such as group B streptococci. In electron micrographs, these hairlike projections (up to several hundred per cell) may be confined to one end of the organism (*polar pili*) or distributed more evenly over the surface. An individual cell may have pili with a variety of functions. Most pili are made up of a major pilin protein subunit (17,000–30,000 Da) that polymerizes to form the pilus. Many strains of *Escherichia coli* isolated from urinary tract infections express a mannose-binding type 1 pilus that attaches to the uroplakins coating the cells in the bladder epithelium. Other strains produce the Pap (pyelonephritis-associated) or P pilus adhesin that mediates binding to digalactose (gal-gal) residues on globosides of the human P blood groups. Both of these pili have proteins located at the tips of the main pilus unit that are critical to the binding specificity of the whole pilus unit. *E. coli* cells causing diarrheal disease express pilus-like receptors for enterocytes on the small bowel, along with other receptors termed *colonization factors*.

The type IV pili found in *Neisseria* species, *Moraxella* species, *Vibrio cholerae*, *Legionella pneumophila, Salmonella enterica* serovar Typhi, enteropathogenic *E. coli*, and *Pseudomonas aeruginosa* often mediate adherence of organisms to target surfaces. Type IV pili tend to have a relatively conserved amino-terminal region and a more variable carboxyl-terminal region. For some species (e.g., *N. gonorrhoeae, Neisseria meningitidis*, and enteropathogenic *E. coli*), the pili are critical for attachment to mucosal epithelial cells. For others, such as *P. aeruginosa*, the pili may inhibit colonization; recent studies of *P. aeruginosa* colonization showed that, in a bank of mutants in which all nonessential genes were interrupted, those unable to produce type IVa pili were actually better able to colonize the gastrointestinal and lung mucosa of mice. *V. cholerae* cells appear to use two different types of pili for intestinal colonization. Whereas interference with this stage of colonization would appear to be an effective antibacterial strategy, attempts to develop pilus-based vaccines against human diseases have not been highly successful to date.

Flagella are long appendages attached at one or both ends of the bacterial cell (*polar flagella*) or distributed over the entire cell surface (*peritrichous flagella*). Flagella, like pili, are composed of a polymerized or aggregated basic protein. In flagella, the protein subunits form a tight helical structure and vary serologically with the species. Spirochetes such as *T. pallidum* and *Borrelia burgdorferi* have axial filaments similar to flagella running down the long axis of the center of the cell, and they "swim" by rotation around these filaments. Some bacteria can glide over a surface in the absence of obvious motility structures.

Other bacterial structures involved in adherence to host tissues include staphylococcal and streptococcal proteins that bind to human extracellular matrix proteins such as fibrin, fibronectin, fibrinogen, laminin, and collagen. Fibronectin is a commonly used receptor for various pathogens; a particular amino acid sequence in fibronectin, Arg-Gly-Asp or RGD, is a conserved target used by bacteria to bind to host tissues. Binding of the *Staphylococcus aureus* surface protein clumping factor A (ClfA) to fibrinogen has been implicated in many aspects of pathogenesis. The conserved outer-core portion of the lipopolysaccharide (LPS) of *P. aeruginosa* mediates binding to the cystic fibrosis transmembrane conductance regulator (CFTR) on airway epithelial cells—an event that appears to be critical for normal host resistance to infection, initiating recruitment of polymorphonuclear neutrophils (PMNs) to the lung mucosa to kill the cells via opsonophagocytosis. A large number of microbial pathogens encompassing major gram-positive bacteria (staphylococci and streptococci), gram-negative bacteria (major enteric species and coccobacilli), fungi (*Candida*, *Fusobacterium*, *Aspergillus*), and even eukaryotic pathogens (*Trichomonas vaginalis* and *Plasmodium falciparum*) express a surface polysaccharide composed of β-1-6-linked-poly-*N*-acetyl-D-glucosamine (PNAG). One of its functions is to promote binding to synthetic materials used in catheters and other types of implanted devices. This polysaccharide may be a critical factor in the establishment of device-related infections by pathogens such as staphylococci and *E. coli*. High-powered imaging techniques (e.g., atomic force microscopy) have revealed that bacterial cells have a nonhomogeneous surface that is probably attributable to different concentrations of cell surface molecules, including microbial adhesins, at specific locations (Fig. 116-1, panels C and D).

FUNGAL ADHESINS Fungi produce adhesins that mediate colonization of epithelial surfaces, adhering particularly to structures like fibronectin,

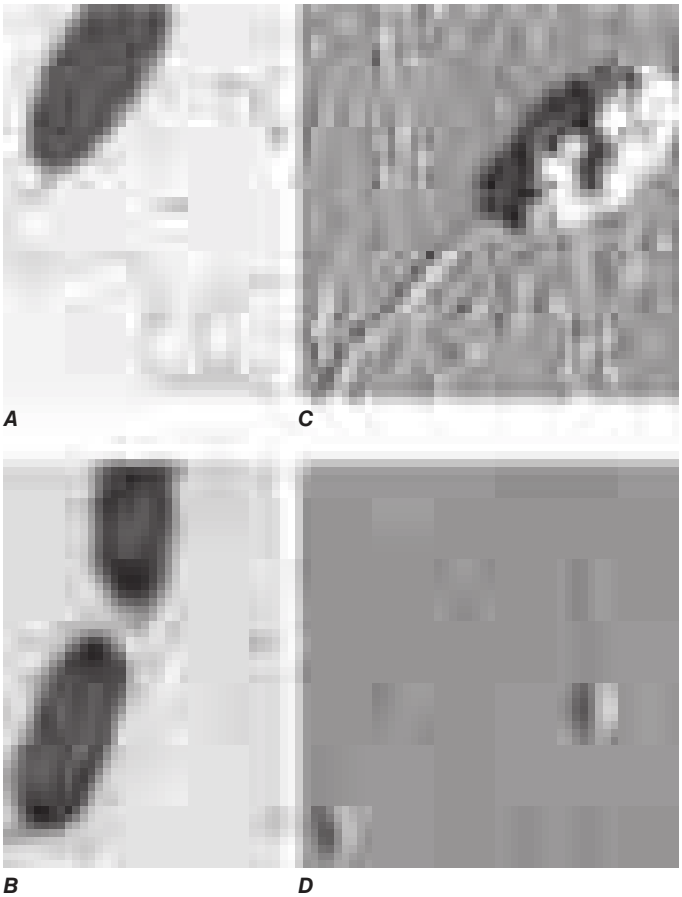

FIGURE 116-1 Bacterial surface structures. ***A*** and ***B.*** Traditional electron micrographic images of fixed cells of *Pseudomonas aeruginosa*. Flagella (***A***) and pili (***B***) project out from the bacterial poles. ***C*** and ***D.*** Atomic force microscopic image of live *P. aeruginosa* freshly planted onto a smooth mica surface. This technology reveals the fine, three-dimensional detail of the bacterial surface structures.

laminin, and collagen. The *Candida albicans* INT1 protein bears similarity to mammalian integrins that bind to extracellular matrix proteins. The agglutinin-like sequence (ALS) adhesins are large cell-surface glycoproteins mediating adherence of pathogenic *Candida* to host tissues. These adhesins possess a conserved three-domain structure composed of an N-terminus that mediates adherence to host tissue receptors, a central motif consisting of a number of repeats of a conserved sequence of 36 amino acids, and a C-terminal domain that varies in length and sequence and contains a glycosylphosphatidylinositol (GPI) anchor addition that allows the adhesins to bind to the fungal cell wall. Variability in the number of central domains characterizes different ALS proteins with specificity for different host receptors. The ALS adhesins are expressed under certain environmental conditions and are crucial for pathogenesis of fungal infections.

For several respiratory fungal pathogens, the inoculum is ingested by alveolar macrophages in which the fungal cells transform to pathogenic phenotypes. Like *C. albicans*, *Blastomyces dermatitidis* produces a 120-kDa surface protein, designated WI-1, that binds to CD11b/CD18 integrins as well as to CD14 on macrophages. An unidentified factor on *Histoplasma capsulatum* also mediates binding to the integrin surface proteins.

EUKARYOTIC PATHOGEN ADHESINS Eukaryotic parasites use complicated surface glycoproteins as adhesins, some of which are lectins (proteins that bind to specific carbohydrates on host cells). *Plasmodium vivax*, one of six *Plasmodium* species causing malaria, binds (via Duffy-binding protein) to the Duffy blood group carbohydrate antigen Fy on erythrocytes. *Entamoeba histolytica*, the third leading cause of death from parasitic diseases, expresses two proteins that bind to the disaccharide galactose/*N*-acetyl galactosamine. Children with mucosal IgA antibody to one of these lectins are resistant to reinfection with virulent *E. histolytica*. A major surface glycoprotein (gp63) of *Leishmania* promastigotes is needed for these parasites to enter human macrophages—the principal target cell of infection. This glycoprotein promotes complement binding but inhibits complement lytic activity, allowing the parasite to use complement receptors for entry into macrophages; gp63 also binds to fibronectin receptors on macrophages. As part of hepatic granuloma formation, *Schistosoma mansoni* expresses a carbohydrate epitope related to the Lewis X blood group antigen that promotes adherence of helminthic eggs to vascular endothelial cells under inflammatory conditions.

Host Receptors Host receptors are found both on target cells (such as epithelial cells lining mucosal surfaces) and within the mucus layer covering these cells. Microbial pathogens bind to a wide range of host receptors to establish infection (Table 116-1). Selective loss of host receptors for a pathogen may confer natural resistance to an otherwise susceptible population. For example, 70% of individuals in western Africa lack Fy antigens and are resistant to *P. vivax* infection. *S. enterica* serovar Typhi, the etiologic agent of typhoid fever, produces a pilus protein that binds to CFTR to enter the gastrointestinal submucosa after being ingested by enterocytes. As homozygous mutations in *CFTR* are the cause of the life-shortening disease cystic fibrosis, heterozygote carriers (e.g., 4–5% of individuals of European ancestry) may have had a selective advantage due to decreased susceptibility to typhoid fever.

Numerous virus–target cell interactions have been described, and it is now clear that different viruses can use similar host cell receptors for entry. The list of certain and likely host receptors for viral pathogens is long. Among the host membrane components that can serve as receptors for viruses are sialic acids, gangliosides, glycosaminoglycans, integrins and other members of the immunoglobulin superfamily, histocompatibility antigens, and regulators and receptors for complement components. An example of the effect of host receptors on the pathogenesis of infection has emerged from studies comparing the binding of avian influenza A virus subtype H5N1 with that of influenza A strains expressing the H1 hemagglutinin subtype. These subtypes are highly pathogenic and transmissible from human to human, and they bind to a receptor composed of two sugar molecules: sialic acid linked α-2-6 to galactose. This receptor is expressed at high levels in the human airway epithelium; when virus is shed from this surface, its transmission via coughing and aerosol droplets is facilitated. In contrast, the H5N1 avian influenza virus binds to sialic acid linked α-2-3 to galactose, and this receptor is expressed at high levels on cells in the terminal bronchioles, including type II pneumocytes, alveolar macrophages, and nonciliated cuboidal epithelial cells. Infection at these sites is thought to underlie the high mortality rate associated with avian influenza but also the low interhuman transmissibility of this strain, which is not readily transported to the airways from which it can be expelled by coughing. Nonetheless, it has been shown that H5 hemagglutinins can acquire mutations leading to binding to α-2-6-linked sialic acids that increase their human transmissibility but retain their high level of lethality.

MICROBIAL GROWTH AFTER ENTRY

Once established on a mucosal or skin site, pathogenic microbes must replicate before causing full-blown infection and disease. Within cells, viral particles release their nucleic acids, which may be directly translated into viral proteins (positive-strand RNA viruses), transcribed from a negative strand of RNA into a complementary mRNA (negative-strand RNA viruses), or transcribed into a complementary strand of DNA (retroviruses). For DNA viruses, mRNA may be transcribed directly from viral DNA, either in the cell nucleus or in the cytoplasm. To grow, bacteria must acquire specific nutrients or synthesize them from precursors in host tissues. Many infectious processes are most often found in specific sites—e.g., H1 influenza in the respiratory mucosa, gonorrhea in the urogenital epithelium, and shigellosis in the gastrointestinal epithelium. While there are multiple reasons for this specificity, one important consideration is the ability of these pathogens to obtain the nutrients needed for growth and survival.

Temperature restrictions also play a role in limiting certain pathogens to specific tissues. Rhinoviruses, a cause of the common cold, grow best at 33°C and replicate in cooler nasal tissues but not in the lung. Leprosy lesions due to *Mycobacterium leprae* are found in and on relatively cool body sites. Fungal pathogens that infect the skin, hair follicles, and nails (dermatophyte infections) remain confined to the cooler, exterior, keratinous layer of the epithelium.

A topic of major interest is the ability of many bacterial, fungal, and protozoal species to grow in multicellular masses referred to as *biofilms*. These masses are biochemically and morphologically quite distinct from the free-living individual cells referred to as *planktonic cells*. Growth in biofilms leads to altered microbial metabolism, production of extracellular virulence factors, and decreased susceptibility to biocides, antimicrobial agents, and host defense molecules and cells. *P. aeruginosa* growing on the bronchial mucosa during chronic infection, staphylococci and other pathogens growing on implanted medical devices, and dental pathogens growing on tooth surfaces to form plaques represent several examples of microbial biofilm growth associated with human disease. Many other pathogens can form biofilms during in vitro growth. This mode of growth contributes to microbial virulence and induction of disease and can also be an important factor in microbial survival outside the host, promoting transmission to additional susceptible individuals.

AVOIDANCE OF INNATE HOST DEFENSES

Microbes have interacted with mucosal/epithelial surfaces since the emergence of multicellular organisms. Thus it is not surprising that multicellular hosts have a variety of innate surface defense mechanisms that can sense when pathogens are present and contribute to their elimination. The skin is acidic and bathed with fatty acids toxic to many microbes. Skin pathogens such as staphylococci must tolerate these adverse conditions. Mucosal surfaces are covered by a barrier composed of a thick mucus layer that entraps microbes and facilitates their transport out of the body by mucociliary clearance, coughing, and urination. Mucous secretions, saliva, and tears contain antibacterial factors such as lysozyme and antimicrobial peptides as well as antiviral factors such as interferons (IFNs). Gastric acidity and bile salts are inimical to the survival of many ingested organisms, and most mucosal surfaces—particularly the nasopharynx, vaginal tract, and gastrointestinal tract—contain a resident flora of commensal microbes

that interfere with the ability of pathogens to colonize and infect a host. Major advances in the use of nucleic acid sequencing now allow extensive identification and characterization of the vast array of commensal organisms that have come to be referred to as the *microbiota*. In addition to its role in providing competition for mucosal colonization, acquisition of a normal microbiota is critical for proper development of the immune system, impacting maturation and differentiation of components of both the innate and acquired immune systems.

Pathogens that survive local antimicrobial factors must still contend with host endocytic, phagocytic, and inflammatory responses as well as with host genetic factors that determine the degree to which a pathogen can survive and grow. The growth of viral pathogens entering skin or mucosal epithelial cells can be limited by a variety of host genetic factors, including production of IFNs, modulation of receptors for viral entry, and age- and hormone-related susceptibility factors; by nutritional status; and even by personal habits such as smoking and exercise. The list of genes whose variants can affect host susceptibility and resistance to infection is rapidly expanding. A classic example is a 32-bp deletion in the gene for the HIV-1 co-receptor known as chemokine receptor 5 (CCR5), which, when present in the homozygous state, confers high-level resistance to HIV-1 infection. A now-famous case is that of the "Berlin Patient," a man infected with HIV who received a hematopoietic stem-cell transplant from a donor homozygous for the 32-bp CCR5 deletion to treat acute myeloid leukemia. The apparent sterilizing cure of this patient's HIV infection is likely due to his having only HIV-resistant T cells after the stem cell transplantation.

Encounters with Epithelial Cells Over the past two decades, many pathogens have been shown to enter epithelial cells **(Fig. 116-2)** by using specialized surface structures that bind to receptors, with consequent internalization. However, the exact role and the importance of this process in infection and disease are not well defined for most of these pathogens. Microbial entry into host epithelial cells is seen as a path for translocation to adjacent or deeper tissues or as a route to a sanctuary site to avoid killing by professional phagocytes. Epithelial cell entry is a critical aspect of dysentery induction by *Shigella*.

Curiously, less virulent strains of many bacterial pathogens are more adept at entering epithelial cells than are more virulent strains; examples include pathogens that lack the surface polysaccharide capsule needed to cause serious disease. Thus, for *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (group B *Streptococcus*), *N. meningitidis*, and *S. pyogenes*, isogenic mutants or variants lacking capsules enter epithelial cells more easily than the wild-type, encapsulated parental forms that cause disseminated disease. These observations have led to the proposal that epithelial cell entry may be primarily a manifestation of host defense, resulting in bacterial clearance by both shedding of epithelial cells containing internalized bacteria and initiation of a protective and nonpathogenic inflammatory response. However, a possible consequence of this process could be the opening of a hole in the epithelium, potentially allowing uningested organisms to enter the submucosa. This scenario has been documented in murine *S. enterica* serovar Typhimurium infections and in experimental bladder infections caused by uropathogenic *E. coli*. In the latter system, bacterial pilus-mediated attachment to *uroplakins* induces exfoliation of the cells with attached bacteria. Subsequently, infection is produced by residual bacterial cells that invade the superficial bladder epithelium, where they can grow intracellularly into biofilm-like masses encased in an extracellular polysaccharide-rich matrix and surrounded by uroplakin. It is likely that at low bacterial inocula epithelial cell ingestion and subclinical inflammation are efficient means to eliminate pathogens, whereas at higher inocula a proportion of surviving bacterial cells enter host tissue through the damaged mucosal surface and multiply, producing disease. Alternatively, failure of the appropriate epithelial cell response to a pathogen may allow the organism to survive on a mucosal surface where, if it avoids other host defenses, it can grow and cause a local infection. Along these lines, as noted above, *P. aeruginosa* is taken into epithelial cells by CFTR, a protein missing or nonfunctional in most patients with severe cases of cystic fibrosis. The major clinical consequence of this disease is chronic airway-surface infection with

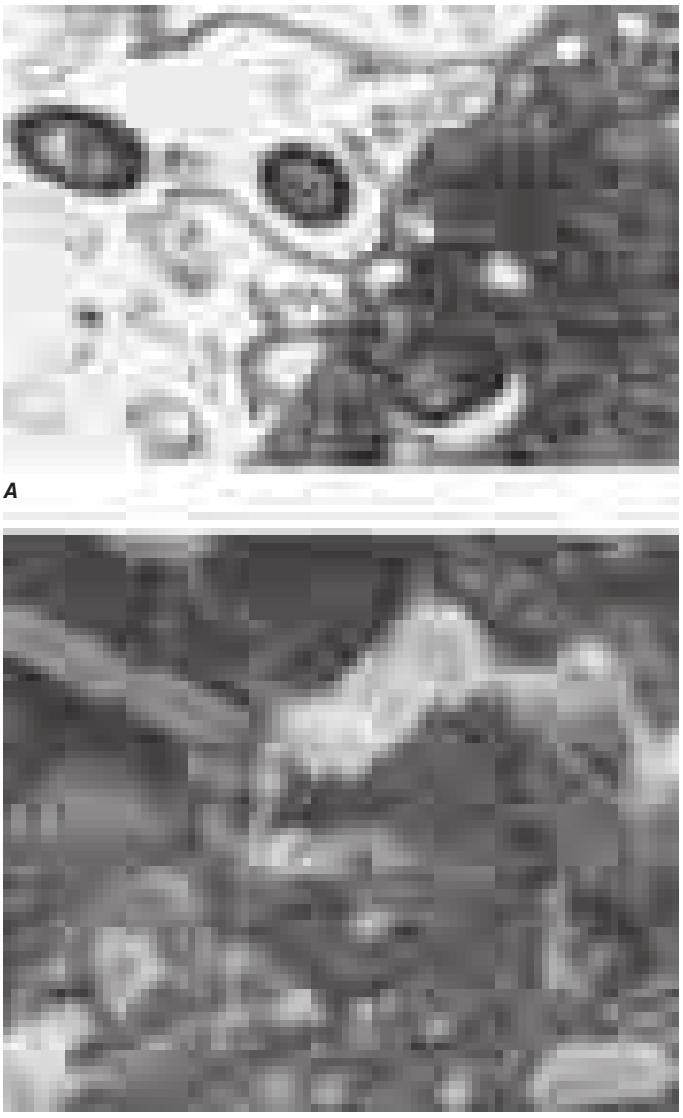

FIGURE 116-2 Entry of bacteria into epithelial cells. ***A.*** Internalization of *Pseudomonas aeruginosa* by cultured airway epithelial cells expressing wild-type cystic fibrosis transmembrane conductance regulator, the cell receptor for bacterial ingestion. ***B.*** Entry of *P. aeruginosa* into murine tracheal epithelial cells after infection of mice by the intranasal route.

P. aeruginosa in 80–90% of patients. The failure of airway epithelial cells to ingest and promote the removal of *P. aeruginosa* via a properly regulated inflammatory response has been proposed as a key component of the hypersusceptibility of these patients to chronic airway infection with this organism.

Encounters with Phagocytes • PHAGOCYTOSIS AND INFLAMMATION Phagocytosis of microbes is a major innate host defense that limits the growth and spread of pathogens. Phagocytes appear rapidly at sites of infection in conjunction with the initiation of inflammation. Ingestion of microbes by both tissue-fixed macrophages and migrating phagocytes probably accounts for the limited ability of most microbial agents to cause disease. A family of related molecules called *collectins*, *soluble defense collagens*, or *pattern-recognition molecules* are found in blood (mannose-binding lectins), lung (surfactant proteins A and D), and most likely other tissues and bind to carbohydrates on microbial surfaces to promote phagocyte clearance. Bacterial pathogens are ingested principally by PMNs, while eosinophils are frequently found at sites of infection by protozoan or multicellular parasites. Successful pathogens, by definition, must avoid being cleared by professional phagocytes. One of several antiphagocytic strategies employed by bacteria and by the fungal pathogen *Cryptococcus neoformans* is to elaborate large-molecular-weight surface polysaccharide antigens,

often in the form of a capsule that coats the cell surface. Most pathogenic bacteria produce such antiphagocytic capsules. On occasion, proteins or polypeptides form capsule-like coatings for organisms such as group A streptococci and *Bacillus anthracis*.

An area of both intense interest and controversy is the role of the release of neutrophil extracellular traps (NETs) in protection against infection. NETs are composed of DNA and other intracellular components with antimicrobial properties, such as histones, myeloperoxidase, and elastase. NET release has been described as both a "suicidal" event, wherein, in response to stimuli, PMNs lyse and release NET components, and a "vital" event, wherein intracellular NET components are released but neutrophils remain viable and functional. Microbial particle size might regulate release of NETs, as has been reported for larger microbial structures like *C. albicans* hyphae or cellular aggregates. NET formation can also be pathologic as these networks are associated with damage to cells, thrombosis, inhibition of wound healing, and autoimmunity.

As activation of local phagocytes in tissues is a key step in initiating inflammation and migration of additional phagocytes into infected sites, much attention has been paid to microbial factors that initiate inflammation. These are usually conserved factors critical to the microbes' survival and are referred to as *pathogen-associated molecular patterns* (PAMPs). Cellular responses to microbial encounters with phagocytes are governed largely by the structure of the microbial PAMPs that elicit inflammation, and detailed knowledge of these structures of bacterial pathogens has contributed greatly to our understanding of molecular mechanisms of microbial pathogenesis mediated by activation of host cell molecules such as Toll-like receptors (TLRs; **Fig. 116-3**). One of the best-studied systems involves the interaction of LPS from gram-negative bacteria with the GPI-anchored membrane protein CD14 found on the surface of professional phagocytes, including migrating and tissue-fixed macrophages and PMNs. A soluble form of CD14 is also found in plasma and on mucosal surfaces. A plasma protein, LPS-binding protein, transfers LPS to membrane-bound CD14

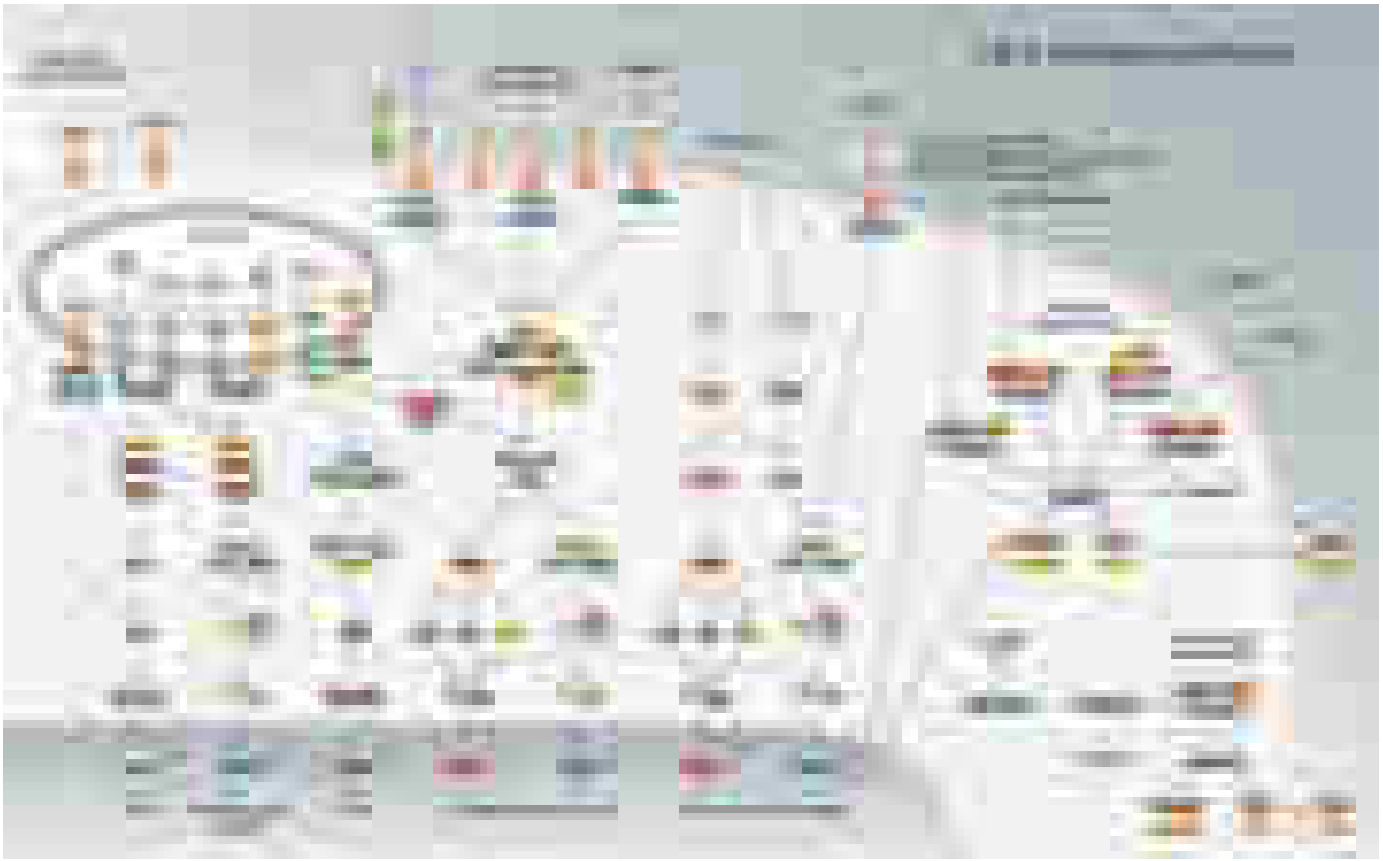

FIGURE 116-3 Toll-like receptor (TLR) and NOD-like receptor (NLR) signaling pathways. Microbial cell-surface constituents interact with TLRs, in some cases requiring additional factors such as MD2, which facilitates the response to lipopolysaccharide (LPS) via TLR4. Although microbial cell-surface constituents are depicted as interacting with the TLRs on the cell surface, TLRs contain extracellular leucine-rich domains that become localized to the lumen of the phagosome upon uptake of bacterial cells. The internalized TLRs can bind to microbial products. The TLRs are oligomerized, usually forming homodimers, and then bind to the general adapter protein MyD88 via the C-terminal Toll/interleukin 1 receptor (IL-1R) (TIR) domains, which also bind to TIRAP (TIR domain–containing adapter protein), a molecule that participates in the transduction of signals from TLRs 1, 2, 4, and 6. The MyD88/TIRAP complex activates signal-transducing molecules such as IRAK4 (IL-1R-associated kinase 4), which in turn activates IRAK1. This activation can be blocked by IRAKM and Toll interacting protein (TOLLIP). IRAK1 activates TRAF6 (tumor necrosis factor receptor–associated factor 6), TAK1 (transforming growth factor β–activating kinase 1), and TAB1/2 (TAK1-binding protein 1/2). This signaling complex associates with the ubiquitin-conjugating enzyme Ubc13 and the Ubc-like protein UEV1A to catalyze the formation of a polyubiquitin chain on TRAF6. Polyubiquitination of TRAF6 activates TAK1, which, along with TAB1/2 (a protein that binds to lysine residue 63 in polyubiquitin chains via a conserved zinc-finger domain), phosphorylates the inducible kinase complex: IKKα, -β, and -γ. IKKγ is also called NEMO [nuclear factor κB (NF-κB) essential modulator]. This large complex phosphorylates the inhibitory component of NF-κB, IκBα, resulting in release of IκBα from NF-κB. Phosphorylated (PP) IκB is then ubiquitinated (ub) and degraded, and the two components of NF-κB—p50 (or Rel) and p65—translocate to the nucleus, where they bind to regulatory transcriptional sites on target genes, many of which encode inflammatory proteins. In addition to inducing NF-κB nuclear translocation, the TAK1/TAB1/2 complex activates MAP kinase transducers such as MKK 4/7 and MKK 3/6, an event that can lead to nuclear translocation of transcription factors such as AP1. TLR4 can also activate NF-κB nuclear translocation via the MyD88-independent TRIF [TIR domain–containing, adapter-inducing interferon β (IFN-β)] and TRAM (TRIF-related adapter molecule) cofactors. Intracellular TLRs 3, 7, 8, and 9 also use MyD88 and TRIF to activate IFN response factors 3 and 7 (IRF3 and IRF7), which also function as transcriptional factors in the nucleus. The nucleotide-binding oligomerization domain–like receptor (NLR) family of proteins is involved in the regulation of innate immune responses. These proteins sense pathogen-associated molecular patterns (PAMPs) in the cytosol as well as the host-derived signals known as *damage-associated molecular patterns* (DAMPs). Certain NLRs induce the assembly of large caspase 1–activating complexes called *inflammasomes*. Activation of caspase 1 through autoproteolytic maturation leads to the processing and secretion of the proinflammatory cytokines interleukin 1β (IL-1β) and IL-18. So far, four inflammasomes have been identified and defined by the NLR protein they contain: the NLRP1/NALP1b inflammasome, the NLRC4/IPAF inflammasome, the NLRP3/NALP3 inflammasome, and the AIM2 (absent in melanoma 2)–containing inflammasome. (*Pathway diagram reproduced with permission from InvivoGen; www.invivogen.com/review-inflammasome.)*

on myeloid cells and promotes binding of LPS to soluble CD14. Soluble CD14/LPS/LPS-binding protein complexes bind to many cell types and may be internalized to initiate cellular responses to microbial pathogens. It has been shown that peptidoglycan and lipoteichoic acid from gram-positive bacteria and cell surface products of mycobacteria and spirochetes can interact with CD14 (Fig. 116-3). Additional molecules, such as MD-2, also participate in the recognition of bacterial activators of inflammation.

GPI-anchored receptors do not have intracellular signaling domains; therefore, it is the TLRs that transduce signals for cellular activation due to LPS binding. Binding of microbial factors to TLRs to activate signal transduction occurs in the phagosome—and not on the surface—of dendritic cells that have internalized the microbe. This binding is probably due to the release of the microbial surface factor from the cell in the environment of the phagosome, where the liberated factor can bind to its cognate TLRs. TLRs initiate cellular activation through a series of signal-transducing molecules (Fig. 116-3) that lead to nuclear translocation of the transcription factor nuclear factor κB (NF-κB), a master-switch for production of important inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 1 (IL-1).

The initiation of inflammation can also occur with viral particles and other microbial products such as polysaccharides, enzymes, and toxins. Bacterial flagella activate inflammation by binding of a conserved sequence to TLR5. Some pathogens (e.g., *Campylobacter jejuni, Helicobacter pylori,* and *Bartonella bacilliformis*) make flagella that lack this sequence and do not bind to TLR5; thus efficient host responses to infection are prevented. Bacteria also produce a high proportion of DNA molecules with unmethylated CpG residues that activate inflammation through TLR9. TLR3 recognizes double-strand RNA, a pattern-recognition molecule produced by many viruses during their replicative cycle. TLR1 and TLR6 associate with TLR2 to promote recognition of acylated microbial proteins and peptides.

The myeloid differentiation factor 88 (MyD88) molecule and the Toll/IL-1R (TIR) domain–containing adapter protein (TIRAP) bind to the cytoplasmic domains of TLRs and also to receptors that are part of the IL-1 receptor families. Numerous studies have shown that MyD88/TIRAP-mediated transduction of signals from TLRs and other receptors is critical for innate resistance to infection, activating MAP kinases and NF-κB and thereby leading to production of cytokines/chemokines. Mice lacking MyD88 are more susceptible than normal mice to infections with a broad range of pathogens. In one study, nine children homozygous for defective MyD88 genes had recurrent infections with *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*—three bacterial species showing increased virulence in MyD88-deficient mice. The MyD88-deficient children seemed to have no greater susceptibility to other bacteria, viruses, fungi, or parasites. Another component of the MyD88-dependent signaling pathway is a molecule known as IL-1 receptor–associated kinase 4 (IRAK4). Individuals with a homozygous deficiency in genes encoding this protein are at increased risk for *S. pneumoniae* and *S. aureus* infections and, to some degree, *P. aeruginosa* infections as well.

Some TLRs (e.g., TLR3 and TLR4) can also activate signal transduction via a MyD88-independent pathway involving TIR domain–containing, adapter-inducing IFN-β (TRIF) and the TRIF-related adapter molecule (TRAM). Signaling through TRIF and TRAM activates the production of both NF-κB-dependent cytokines/chemokines and type 1 IFNs. The type 1 IFNs bind to the IFN-α receptor composed of two protein chains, IFNAR1 and IFNAR2. Humans produce three type 1 IFNs: IFN-α, IFN-β, and IFN-γ. These molecules activate another class of proteins known as signal transducer and activator of transcription (STAT) complexes. The STAT factors are important in regulating immune system genes and thus play a critical role in responses to microbial infections.

Another intracellular complex of proteins found to be a major factor in the host cell response to infection is the *inflammasome* (Fig. 116-3), where inflammatory cytokines IL-1 and IL-18 are changed from their precursors to active forms by the cysteine protease caspase 1 and then secreted. The inflammasome is composed of proteins that are members of the nucleotide binding and oligomerization domain (NOD)–like receptor (NLR) family. Like the TLRs, NOD proteins within inflammasomes sense the presence of the conserved microbial factors either internalized from outside the cell to form canonical inflammasomes or released inside a cell (probably after microbial uptake) to directly activate pro-caspase-2. Recognition of these PAMPs by NLRs leads to caspase 1 or caspase 2 activation and to secretion of active IL-1 and IL-18. Studies of mice indicate that as many as four canonical inflammasomes with different components can be formed (Fig. 116-3). The components depend on the type of stimulus driving inflammasome formation and activation. A fifth, noncanonical inflammasome responding to intracellular LPS also has been described (Fig. 116-3).

Some recent additions to the identified intracellular components responding to microbial infection are autophagy **(Fig. 116-4)**, initially described as an intracellular process for degradation and recycling of cellular components for reuse, and several pathways leading to cell death, including apoptosis, RIPK1-dependent apoptosis, and necroptosis (Fig. 116-4). The latter three pathways are means by which cells undergo a death program in response to infection (notably, viral infection) and inflammation. Autophagy is an early defense mechanism mediated by caspases in response to pathogens wherein, after ingestion, microbes in either vacuoles or the cytoplasm are delivered to lysosomal compartments for degradation. Avoidance of this process is critical if pathogens are to cause disease. Pathogens can avoid autophagy by multiple mechanisms; examples include the inhibition of proteins within the autophagic vacuole by *Shigella*, the recruitment of host proteins to prevent autophagy of *Listeria monocytogenes*, and the inhibition of vacuole formation by *L. pneumophila*. In the death pathways, cell death to inhibit viral replication (Fig. 116-4) is mediated by a series of reactions commencing with TNF-α production and binding of this molecule to its receptor, TNFR1. In the two apoptotic pathways, the final steps are activation of effector caspases 3 and 7 and apoptotic cell death. In necroptosis, oligomers of the mixed-lineage kinase domain–like protein (MLKL) form and insert into the cell's plasma membrane; their insertion leads to lysis and release of damage-associated molecular patterns (DAMPs), resulting in protective innate immune responses. Finally, additional pathways of cell death are being described, including ferroptosis, oxytosis, parthanatos, pyronecrosis, and pyroptosis. The impact of these pathways on host–pathogen interactions is only beginning to be investigated.

ADDITIONAL INTERACTIONS OF MICROBIAL PATHOGENS AND PHAGOCYTES Other ways that microbial pathogens avoid destruction by phagocytes include production of factors that are toxic to these cells or that interfere with their chemotactic and ingestion function. Hemolysins, leukocidins, and the like are microbial proteins that can kill phagocytes. *S. aureus* elaborates a family of bi-component leukocidins that bind to host receptors such as the HIV co-receptor CCR5, which is also a receptor for the LukE/D toxin, and the receptor of the C5a component of activated complement used by LukF/S, also known as the *Panton-Valentine leukocidin*. The cytolytic staphylococcal α hemolysin binds to the disintegrin and metalloprotease 10 (ADAM-10) protein expressed on a variety of cells and also activates the NLRP3 inflammasome in monocytic cells, with consequent production of inflammatory cytokines as well as cell death. Streptolysin O made by *S. pyogenes* binds to cholesterol in phagocyte membranes and initiates a process of internal degranulation, with the release of normally granule-sequestered toxic components into the phagocyte's cytoplasm. *E. histolytica*, an intestinal protozoan that causes amebic dysentery, can disrupt phagocyte membranes after direct contact via the release of protozoal phospholipase A and pore-forming peptides.

MICROBIAL SURVIVAL INSIDE PHAGOCYTES Many important microbial pathogens use a variety of strategies to survive inside phagocytes (particularly macrophages) after ingestion. Inhibition of fusion of the phagocytic vacuole (the phagosome) containing the initially ingested microbe with the lysosomal granules containing antimicrobial substances (the lysosome) allows *M. tuberculosis*, *S. enterica* serovar Typhi, and *Toxoplasma gondii* to survive inside macrophages. Some organisms, such as *L. monocytogenes*, escape into the phagocyte's cytoplasm to grow and eventually spread to other cells. Resistance to killing within

the macrophage and subsequent growth are critical to successful infection by herpes-type viruses, measles virus, poxviruses, *Salmonella*, *Yersinia*, *Legionella*, *Mycobacterium*, *Trypanosoma*, *Nocardia*, *Histoplasma*, *Toxoplasma*, and *Rickettsia*. *Salmonella* species use a master regulatory system—in which the *PhoP*/*PhoQ* genes control other genes—to enter and survive within cells, with intracellular survival entailing structural changes in the cell envelope LPS.

TISSUE INVASION AND TISSUE TROPISM

Tissue Invasion Most viral pathogens cause disease by growth at skin or mucosal entry sites, but some pathogens spread from the initial site to deeper tissues. Virus can spread via the nerves (rabies virus) or plasma (picornaviruses) or within migratory blood cells (poliovirus, Epstein-Barr virus, and many others). Specific viral genes determine where and how individual viral strains can spread.

Bacteria may invade deeper layers of mucosal tissue via intracellular uptake by epithelial cells, traversal of epithelial cell junctions, or penetration through denuded epithelial surfaces. Among virulent *Shigella* strains and invasive *E. coli*, outer-membrane proteins are critical to epithelial cell invasion and bacterial multiplication. *Neisseria* and *Haemophilus* species penetrate mucosal cells by poorly understood mechanisms before dissemination into the bloodstream. Staphylococci and streptococci elaborate a variety of extracellular enzymes, such as hyaluronidase, lipases, nucleases, and hemolysins, that are probably important in breaking down cellular and matrix structures and allowing the bacteria access to deeper tissues and blood. Staphylococcal α hemolysin binding to ADAM-10 leads to endothelial cell damage and disruption of vascular barrier function, events that are probably critical for systemic spread of *S. aureus* from an initial infectious site. Organisms that colonize the gastrointestinal tract can often translocate through the mucosa into the blood and, under circumstances in which host defenses are inadequate, cause bacteremia. *Yersinia enterocolitica* can invade the mucosa through the activity of the invasin protein. The complex milieu of basement membrane–containing structures such as laminin and collagen that anchor epithelial cells to mucosal surfaces must often be breached. A family of microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) can attach bacteria to the extracellular matrix and, along with proteases that degrade the basement proteins as well as surface-bound plasminogen and matrix metalloproteinases recruited from the host, permit breaching of this structure. Some bacteria (e.g., *Brucella*) can be carried from a mucosal site to a distant site by phagocytic cells that ingest but fail to kill the bacteria.

Fungal pathogens almost always take advantage of host immunocompromise to spread hematogenously to deeper tissues. The AIDS epidemic has resoundingly illustrated this principle: the immunodeficiency of many HIV-infected patients permits the development of life-threatening fungal infections of the lung, blood, and brain. Other than the capsule of *C. neoformans*, specific fungal antigens involved in tissue invasion are not well characterized. Both fungal pathogens and protozoal pathogens (e.g., *Plasmodium* species and *E. histolytica*) undergo morphologic changes to spread within a host. *C. albicans* undertakes a yeast–hyphal transformation wherein the hyphal forms are found where the fungus is infiltrating the mucosal barrier of tissues, while the yeast form grows on epithelial cell surfaces as well as the tips of hyphae that have infiltrated tissues. Malarial parasites grow in liver cells as merozoites and are released into the blood to invade erythrocytes and become trophozoites. *E. histolytica* is found as both a cyst and a trophozoite in the intestinal lumen, through which this pathogen enters the host, but only the trophozoite form can spread systemically to cause amebic liver abscesses. Other protozoal pathogens, such as *T. gondii*, *Giardia lamblia*, and *Cryptosporidium*, also undergo extensive morphologic changes after initial infection to spread to other tissues.

Tissue Tropism While it is well known that certain microbes cause disease by infecting specific tissues, the molecular basis for tissue tropism is understood somewhat better for viral pathogens than for other infectious agents. Specific receptor–ligand interactions clearly underlie the ability of certain viruses to enter cells within tissues and disrupt normal tissue function, but the mere presence of a receptor for a virus on a target tissue is not sufficient for tissue tropism. Factors in the cell, route of viral entry, viral capacity to penetrate into cells, viral genetic elements that regulate gene expression, and pathways of viral spread in a tissue all affect tissue tropism. Some viral genes are best transcribed in specific target cells, such as hepatitis B genes in liver cells and Epstein-Barr virus genes in B lymphocytes. The route of inoculation of poliovirus determines its neurotropism, although the molecular basis for this association is not understood.

Compared with viral tissue tropism, the tissue tropism of bacterial and parasitic infections has not been as clearly elucidated, but studies of *Neisseria* species have provided insights. Both *N. gonorrhoeae,* which colonizes and infects the human genital tract, and *N. meningitidis*, which principally colonizes the human oropharynx but can spread to the brain, produce type IV pili (Tfp) that mediate adherence to host tissues. In the case of *N. gonorrhoeae*, the Tfp bind to a glucosamine-galactose-containing adhesin on the surface of cervical and urethral cells; in the case of *N. meningitidis*, the Tfp bind to cells in the human meninges in order to cross the blood-brain barrier. *N. gonorrhoeae* can use cytidine monophosphate *N*-acetylneuraminic acid from host tissues to add *N*-acetylneuraminic acid (sialic acid) to its lipooligosaccharide O side chain, and this alteration makes the organism resistant to host defenses. Lactate, present at high levels on genital mucosal surfaces, stimulates sialylation of gonococcal lipooligosaccharide. Bacteria with sialic acid sugars in their capsules, such as *N. meningitidis*, *E. coli* K1, and group B streptococci, have a propensity to cause meningitis, but this generalization has many exceptions. For example, all recognized serotypes of group B streptococci contain sialic acid in their capsules, but only one serotype (III) is responsible for most cases of group B streptococcal meningitis. Moreover, both *H. influenzae* and *S. pneumoniae* can readily cause meningitis, but these organisms do not have sialic acid in their capsules.

TISSUE DAMAGE AND DISEASE

Disease is a complex phenomenon resulting from tissue invasion and destruction, toxin elaboration, and host response. Viruses cause much of their damage by exerting a cytopathic effect on host cells and inhibiting host defenses. The growth of bacterial, fungal, and protozoal parasites in tissue, which may or may not be accompanied by toxin elaboration, can also compromise tissue function and lead to disease. For some bacterial and possibly some fungal pathogens, toxin production is one of the best-characterized molecular mechanisms of pathogenesis, while host factors such as IL-1, TNF-α, kinins, inflammatory proteins, products of complement activation, and mediators derived from arachidonic acid metabolites (leukotrienes) and cellular degranulation (histamines) readily contribute to the severity of disease.

Viral Disease Viral pathogens inhibit host immune responses by a variety of mechanisms—e.g., by decreasing production of major histocompatibility complex molecules (adenovirus E3 protein), diminishing cytotoxic T cell recognition of virus-infected cells (Epstein-Barr virus nuclear antigen 1 and cytomegalovirus intermediate–early protein), producing virus-encoded complement receptor proteins that protect infected cells from complement-mediated lysis (herpesvirus and vaccinia virus), making proteins that interfere with the action of IFN (influenza virus and poxvirus), and elaborating superantigen-like proteins (mouse mammary tumor virus and related retroviruses and the rabies nucleocapsid). Superantigens activate large populations of T cells that express particular subsets of the T cell receptor β protein, causing massive cytokine release and subsequent host reactions. Dengue virus is the most common insect-transmitted virus in the world, causing symptoms ranging from none to serious systemic illness or "break-bone" fever (severe fever and pain). Along with the recent epidemic of the related flavivirus Zika virus, disruptions to host innate immunity and inhibition of programmed cell death that allows continued viral replication underlie the ability of these viruses to cause infections. Infections of pregnant women with Zika virus can result in viral crossing of the placenta; viral entry into and growth in fetal brain tissues result in the birth of neonates with microcephaly. Viruses also produce peptide growth factors for host cells, which disrupt normal cellular

B

A

FIGURE 116-4 Autophagy, apoptosis, and necroptosis. ***A.*** *Autophagy* is a catabolic process that results in the autophagosomic–lysosomal degradation of bulk cytoplasmic contents, abnormal protein aggregates, and excess or damaged organelles. Autophagy is generally activated by conditions of nutrient deprivation but has also been associated with physiologic as well as pathologic processes such as development, differentiation, neurodegenerative disease, stress, infection, and cancer. The kinase mTOR is a critical regulator of autophagy induction, with activated mTOR (Akt and MAPK signaling) suppressing autophagy and negative regulation of mTOR (AMPK and p53 signaling) promoting it. Three related serine/threonine kinases—UNC-51-like kinases 1, 2, and 3 (ULK1, ULK2, ULK3), which play a role similar to that played by the yeast Atg1—act downstream of the mTOR complex. ULK1 and ULK2 form a large complex with the mammalian homolog of an autophagy-related (Atg) gene product (mAtg13) and the scaffold protein FIP200 (an ortholog of yeast Atg17). The class III PI3K complex, containing hVps34, beclin-1 (a mammalian homolog of yeast Atg6), p150 (a mammalian homolog of yeast Vps15), and Atg14-like protein (Atg14L or Barkor) or ultraviolet irradiation resistance–associated gene (UVRAG), is required for the induction of autophagy. The Atg genes control autophagosome formation through Atg12-Atg5 and LC3-II (Atg8-II) complexes. Atg12 is conjugated to Atg5 in a ubiquitin-like reaction that requires Atg7 and Atg10 (E1- and E2-like enzymes, respectively). The Atg12-Atg5 conjugate then interacts noncovalently with Atg16 to form a large complex. LC3/Atg8 is cleaved at its C-terminus by Atg4 protease to generate the cytosolic LC3-I. LC3-I is conjugated to phosphatidylethanolamine (PE), also in a ubiquitin-like reaction that requires Atg7 and Atg3 (E1- and E2-like enzymes, respectively). The lipidated form of LC3, known as LC3-II, is attached to the autophagosome membrane. Autophagy and apoptosis are connected both positively and negatively, and extensive crosstalk exists between the two processes. During nutrient deficiency, autophagy functions as a pro-survival mechanism; however, excessive autophagy may lead to cell death, a process morphologically distinct from apoptosis. Several pro-apoptotic signals, such as tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), and FAS-associated death domain (FADD), also induce autophagy. Moreover, Bcl-2 inhibits beclin-1-dependent autophagy, thereby functioning as both a pro-survival and an anti-autophagic regulator. *Mitophagy* is a selective autophagic process specifically designed for the removal of damaged or unneeded mitochondria from a cell. Upon mitochondrial damage, the protein PINK, which is continually degraded in the healthy state through the action of PARL, is stabilized and recruits the E3 ligase Parkin to initiate mitophagy. Polyubiquitination of mitochondrial membrane proteins by Parkin results in the recruitment of autophagy adaptor proteins SQSTM1/p62, NBR1, and Ambra1, which bind to LC3 via their LC3-interacting region (LIR). In addition, BNIP3 and BNIP3L/NIX, which also contain LIRs, directly recruit autophagic machinery by a ubiquitin-independent mechanism to induce autophagosome formation in certain cell types. *[Reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).]* ***B.*** Apoptosis and necroptosis are initiated by the binding of TNF to its cognate receptor TNFR1, triggering the assembly of complex I, which comprises TNFR1, TNFR1-associated death domain (TRADD), receptor-interacting serine/threonine-protein kinase 1 (RIPK1), TNFR-associated factor 2 (TRAF2), cellular inhibitor of apoptosis protein 1/2 (cIAP1/2), and linear ubiquitin chain assembly complex (LUBAC). Complex I provides the platform for Lys63-linked ubiquitylation (gray circles) or linear ubiquitylation (green circles) of RIPK1 by cIAP1/2 and LUBAC, respectively. This ubiquitylation is implicated in the decision between NF-κB or survival signaling and cell death signaling. Ubiquitylation leads to the recruitment of other factors, such as transforming growth factor β–activated kinase (TAK1), TAK1-binding protein 1 (TAB1), TAB2, NF-κB essential modulator (NEMO), and the inhibitor of the NF-κB kinase-α (IKKα)–IKKβ complex; this recruitment usually triggers canonical NF-κB signaling. In the presence of the translational inhibitor cycloheximide (CHX), TNF stimulation leads to the formation of cytosolic complex IIa, in which RIPK1 disappears, whereas interaction of TRADD and FADD leads to the activation of caspase 8 and effector caspases (e.g., caspase 3 and caspase 7) and to apoptotic cell death. With cIAP1/2 inhibitors [second mitochondria-derived activator of caspase (SMAC) mimetics], knockdown of cIAPs, or inhibition or depletion of TAK1 or NEMO, complex IIb is formed. Complex IIb consists of RIPK1, RIPK3, FADD, and caspase 8 and favors RIPK1-kinase activity–dependent apoptosis. Heteromeric pro-caspase 8–FLICE-like inhibitory protein long isoform ($FLIP_L$) inhibits necroptosis, probably by cleaving RIPK1, RIPK3, and cylindromatosis (CYLD). With sufficient expression of RIPK3 and concomitant inhibition or reduced expression of pro-caspase 8 and $FLIP_L$, complex IIc (also known as the necrosome) is formed. The formation of complex IIc entails the association of RIPK1 and RIPK3 followed by a series of auto- and transphosphorylation events of RIPK1 and RIPK3. Activated RIPK3 phosphorylates and recruits mixed-lineage kinase domain–like protein (MLKL), eventually leading to the formation of a supramolecular protein complex at the plasma membrane and necroptosis. SMAC mimetics are being developed to impair survival signaling and to sensitize cells to the triggering of cell death in the context of tumor treatment. Z-VAD-FMK is a bona fide pan-caspase inhibitor. Necrostatin-1 (Nec-1) and the more specific Nec-1s, Cpd27, and (more recently) PN10—a hybrid molecule consisting of Nec-1s and ponatinib—all inhibit the kinase activity of RIPK1 and thus inhibit necroptotic signaling. Additional necroptosis inhibitors include the RIPK3 inhibitors GSK′840, GSK′843 and GSK′872 as well as the MLKL inhibitors necrosulfonamide (NSA) and compound 1. However, the specificity of these MLKL inhibitors is not restricted to inhibition of MLKL, and their efficacy is probably also due to effects on other steps in the necroptosis pathway. ActD, actinomycin D. *(Reprinted by permission from Macmillan Publishers Ltd: M Conrad et al: Regulated necrosis: Disease relevance and therapeutic opportunities. Nature Reviews Drug Discovery 15:348, copyright 2016.)*

growth, proliferation, and differentiation. In addition, viral factors can bind to and interfere with the function of host receptors for signaling molecules. Modulation of cytokine production during viral infection can stimulate viral growth inside cells with receptors for the cytokine, and virus-encoded cytokine homologues (e.g., the Epstein-Barr virus BCRF1 protein, which is highly homologous to the immunoinhibitory IL-10 molecule) can prevent immune-mediated clearance of viral particles. Viruses cause disease in neural cells by interfering with levels of neurotransmitters without necessarily destroying the cells, or they may induce either programmed cell death (apoptosis) to destroy tissues or inhibitors of apoptosis to allow prolonged viral infection of cells. For infection to spread, many viruses must be released from cells. The HIV protein U (Vpu) facilitates virus release, a process that is specific to certain cells. Mammalian cells produce a restriction factor that inhibits release of some viruses; for HIV, this factor is designated BST-2 (bone marrow stromal antigen 2)/HM1.24/CD317, or tetherin. Vpu of HIV interacts with tetherin, allowing release of infectious virus. Overall, virus-induced disruption of normal cellular and tissue function promotes clinical disease.

Bacterial Toxins Among the first infectious diseases to be understood were those due to toxin-elaborating bacteria. Diphtheria, botulism, and tetanus toxins are responsible for the diseases associated with local infections due to *Corynebacterium diphtheriae*, *Clostridium botulinum*, and *Clostridium tetani*, respectively. *C. difficile* is an anaerobic gram-positive organism that elaborates two toxins, A and B, responsible for disruption of the intestinal mucosa when its numbers expand in the intestine, leading to antibiotic-associated diarrhea and potentially pseudomembranous colitis. A clinical trial evaluating prevention of recurrence of *C. difficile* infection by monoclonal antibodies to toxins A and B showed that antibody to toxin B, but not toxin A, had a significant impact. Enterotoxins produced by *E. coli*, *Salmonella*, *Shigella*, staphylococci, and *V. cholerae* contribute to diarrheal disease caused by these organisms. Staphylococci, streptococci, *P. aeruginosa*, and *Bordetella* elaborate various toxins that cause or contribute to disease, including toxic shock syndrome toxin 1; erythrogenic toxin; exotoxins A, S, T, and U; and pertussis toxin. A number of these toxins (e.g., cholera toxin, diphtheria toxin, pertussis toxin, *E. coli* heat-labile toxin, and *P. aeruginosa* exotoxin) have adenosine diphosphate ribosyl transferase activity; i.e., the toxins enzymatically catalyze the transfer of the adenosine diphosphate ribosyl portion of nicotinamide adenine diphosphate to target proteins and inactivate them. The staphylococcal enterotoxins, toxic shock syndrome toxin 1, and the streptococcal pyogenic exotoxins behave as superantigens, stimulating certain T cells to proliferate without processing of the protein toxin by antigen-presenting cells. Part of this process involves stimulation of the antigen-presenting cells to produce IL-1 and TNF-α, which have been implicated in many clinical features of diseases like toxic shock syndrome and scarlet fever. A number of gram-negative pathogens (*Salmonella*, *Yersinia*, and *P. aeruginosa*) can inject toxins directly into host target cells by means of a complex set of proteins referred to as the *type III secretion system*. Loss or inactivation of this virulence system usually greatly reduces the capacity of a bacterial pathogen to cause disease.

Endotoxin The lipid A portion of LPS in some gram-negative bacteria has potent biologic activities that cause many of the clinical manifestations of gram-negative bacterial sepsis, including fever, muscle proteolysis, uncontrolled intravascular coagulation, and shock. The effects of lipid A appear to be mediated by the production of potent cytokines due to LPS binding to CD14 and signal transduction via TLRs, particularly TLR4. Cytokines exhibit potent hypothermic activity through effects on the hypothalamus; they also increase vascular permeability, alter the activity of endothelial cells, and induce endothelial-cell procoagulant activity. Numerous therapeutic strategies aimed at neutralizing the effects of endotoxin are under investigation, and while studies with laboratory animals have been promising, they have not yet translated into positive results for human septic shock.

Invasion Many diseases are caused primarily by pathogens growing to high levels in tissues. Pneumococcal pneumonia is mostly attributable to the growth of *S. pneumoniae* in the lung and the attendant host inflammatory response, although specific factors that enhance this process (e.g., pneumolysin) may be responsible for some of the pathogenic properties of the pneumococcus. Disease that follows bacteremia and invasion of the meninges by meningitis-producing bacteria such as *N. meningitidis*, *H. influenzae*, *E. coli* K1, and group B streptococci appears to be due solely to the ability of these organisms to gain access to these tissues, multiply in them, and provoke cytokine production leading to tissue-damaging host inflammation.

Specific molecular mechanisms accounting for tissue invasion by fungal and protozoal pathogens are less well described. Except for studies pointing to factors like capsule and melanin production by *C. neoformans*, and possibly levels of cell wall glucans in some pathogenic fungi, the molecular basis for fungal invasiveness is not well defined. Melanism has been shown to protect the fungal cell against death caused by phagocyte factors such as nitric oxide, superoxide, and hypochlorite. Morphogenic variation and production of proteases (e.g., the *Candida* aspartyl proteinase) have been implicated in fungal invasion of host tissues.

If pathogens are to invade host tissues (particularly the blood), they must avoid the major host defenses represented by complement and phagocytic cells. Bacteria most often avoid these defenses through their surface polysaccharides—either capsular polysaccharides or long O-side-chain antigens characteristic of the smooth LPS of gram-negative bacteria. These molecules can prevent the activation and/or deposition of complement opsonins or can limit the access of phagocytic cells with receptors for complement opsonins to these molecules when they are deposited on the bacterial surface below the capsular layer. Another potential mechanism of microbial virulence is the ability of some organisms to present the capsule as an apparent self antigen through molecular mimicry. For example, the polysialic acid capsule of group B *N. meningitidis* is chemically identical to an oligosaccharide found on human brain cells.

Immunochemical studies of capsular polysaccharides have led to an appreciation of the tremendous chemical diversity that can result from the linking of a few monosaccharides. For example, three hexoses can link up in more than 300 different, potentially serologically distinct ways, while three amino acids have only six possible peptide combinations. Capsular polysaccharides have been used as effective vaccines against meningococcal meningitis as well as against pneumococcal and *H. influenzae* infections and may prove to be of value as vaccines against any organism that expresses a nontoxic, immunogenic capsular polysaccharide. In addition, most encapsulated pathogens become virtually avirulent when capsule production is interrupted by genetic manipulation; this observation emphasizes the importance of this structure in pathogenesis. A capsule-like surface polysaccharide, PNAG, has been found as a conserved structure shared by many microbes but generally is a poor target for antibody-mediated immunity because of the propensity of most humans and animals, all of which are colonized by PNAG-producing microbes, to produce a nonprotective type of antibody. Altering the structure of PNAG by removing the acetate substituents on the *N*-acetyl glucosamine monomers leads to an immunogenic form, deacetylated PNAG, that has been reported to induce antibodies that are protective in animals against diverse microbial pathogens.

Host Response The inflammatory response of the host is critical for interruption and resolution of the infectious process but also is often responsible for the signs and symptoms of disease. Infection promotes a complex series of host responses involving the complement, kinin, and coagulation pathways. The production of cytokines such as IL-1, IL-17, IL-18, TNF-α, IFN-γ, and other factors regulated in part by the NF-κB transcription factor leads to fever, muscle proteolysis, and other effects. An inability to kill or contain the microbe usually results in further damage due to the progression of inflammation and infection. For example, in many chronic infections, degranulation of host inflammatory cells leads to release of host proteases, elastases, histamines, and other toxic substances that can degrade host tissues. Chronic inflammation in any tissue can lead to the destruction of that tissue and to clinical disease associated with loss of organ function, such as sterility from pelvic inflammatory disease caused by chronic infection with *N. gonorrhoeae*.

The nature of the host response elicited by the pathogen often determines the pathology of a particular infection. Local inflammation produces local tissue damage, while systemic inflammation, such as that seen during sepsis, can result in the signs and symptoms of septic shock. The severity of septic shock is associated with the degree of production of host effectors. Disease due to intracellular parasitism results from the formation of granulomas wherein the host attempts to wall off the parasite inside a fibrotic lesion surrounded by fused epithelial cells that make up so-called multinucleated giant cells. A number of pathogens, particularly anaerobic bacteria, staphylococci, and streptococci, provoke the formation of an abscess, probably because of the presence of zwitterionic surface polysaccharides such as the capsular polysaccharide of *Bacteroides fragilis*. The outcome of an infection depends on the balance between an effective host response that eliminates a pathogen and an excessive inflammatory response that is associated with an inability to eliminate a pathogen and with the resultant tissue damage that leads to disease.

TRANSMISSION TO NEW HOSTS

As part of the pathogenic process, most microbes are shed from the host, often in a form infectious for susceptible individuals. However, the rate of transmissibility may not necessarily be high, even if the disease is severe in the infected individual, as these traits are not linked. Most pathogens exit via the same route by which they entered: respiratory pathogens by aerosols from sneezing or coughing or through salivary spread, gastrointestinal pathogens by fecal–oral spread, sexually transmitted diseases by venereal spread, and vector-borne organisms by either direct contact with the vector through a blood meal or indirect contact with organisms shed into environmental sources such as water. Microbial factors that specifically promote transmission are not well characterized. Respiratory shedding is facilitated by overproduction of mucous secretions, with consequently enhanced sneezing and coughing. Diarrheal toxins such as cholera toxin, *E. coli* heat-labile toxins, and *Shigella* toxins probably facilitate fecal–oral spread of microbial cells in the high volumes of diarrheal fluid produced during infection. The ability to produce phenotypic variants that resist hostile environmental factors (e.g., the highly resistant cysts of *E. histolytica* shed in feces) represents another mechanism of pathogenesis relevant to transmission. Blood parasites such as *Plasmodium* species change phenotype after ingestion by a mosquito—a prerequisite for the continued transmission of this pathogen. Venereally transmitted pathogens may undergo phenotypic variation due to the production of specific factors to facilitate transmission, but shedding of these pathogens into the environment does not result in the formation of infectious foci.

SUMMARY

In summary, the molecular mechanisms used by pathogens to colonize, invade, infect, and disrupt the host are numerous and diverse. Each phase of the infectious process involves a variety of microbial and host factors interacting in a manner that can result in disease. Recognition of the coordinated genetic regulation of virulence factor elaboration when organisms move from their natural environment into the mammalian host emphasizes the complex nature of the host–parasite interaction. Fortunately, the need for diverse factors in successful infection and disease implies that a variety of therapeutic strategies may be developed to interrupt this process and thereby prevent and treat microbial infections.

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117 Approach to the Acutely Ill Infected Febrile Patient

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The physician treating the acutely ill febrile patient must be able to recognize infections that require emergent attention. If such infections are not adequately evaluated and treated at initial presentation, the opportunity to alter an adverse outcome may be lost. In this chapter, the clinical presentations of and approach to patients with relatively common infectious disease emergencies are discussed. These infectious processes and their treatments are discussed in detail in other chapters.

APPROACH TO THE PATIENT

Acute Febrile Illness

Before the history is elicited and a physical examination is performed, an immediate assessment of the patient's general appearance can yield valuable information. The perceptive physician's subjective sense that a patient is septic or toxic often proves accurate. Visible agitation or anxiety in a febrile patient can be a harbinger of critical illness.

HISTORY

Presenting symptoms are frequently nonspecific. Detailed questions should be asked about the onset and duration of symptoms and about changes in severity or rate of progression over time. Host factors and comorbid conditions may increase the risk of infection with certain organisms or of a more fulminant course than is usually seen. Lack of splenic function, alcoholism with significant liver disease, IV drug use, HIV infection, diabetes, malignancy, organ transplantation, and chemotherapy all predispose to specific infections and frequently to increased severity. The patient should be questioned about factors that might help identify a nidus for invasive infection, such as recent upper respiratory tract infections, influenza, or varicella; prior trauma; disruption of cutaneous barriers due to lacerations, burns, surgery, body piercing, or decubiti; and the presence of foreign bodies, such as nasal packing after rhinoplasty, tampons, or prosthetic joints. Travel, contact with pets or other animals, or activities that might result in tick or mosquito exposure can lead to diagnoses that would not otherwise be considered. Recent dietary intake, medication use, social or occupational contact with ill individuals, vaccination history, recent sexual contacts, and menstrual history may be relevant. Pregnancy might increase the risk and severity of some illnesses, such as influenza, or increase the risk of significant morbidity for the fetus, as in *Listeria* or Zika virus infection. A review of systems should focus on any neurologic signs or sensorium alterations, rashes or skin lesions, and focal pain or tenderness and should also include a general review of respiratory, gastrointestinal, or genitourinary symptoms.

PHYSICAL EXAMINATION

A complete physical examination should be performed, with special attention to several areas that are sometimes given short shrift in routine examinations. Assessment of the patient's general appearance and vital signs, skin and soft tissue examination, and the neurologic evaluation are of particular importance.

The patient may appear either anxious and agitated or lethargic and apathetic. Fever is usually present, although elderly patients and compromised hosts (e.g., patients who are uremic or cirrhotic and those who are taking glucocorticoids or nonsteroidal anti-inflammatory drugs) may be afebrile despite serious underlying infection. Critically ill patients may be hypothermic, with a high risk of organ failure and mortality. Measurement of blood pressure, heart rate, and respiratory rate helps determine the degree of hemodynamic and metabolic

compromise. The patient's airway must be evaluated to rule out the risk of obstruction from an invasive oropharyngeal infection.

The etiologic diagnosis may become evident in the context of a thorough skin examination **(Chap. 16)**. Petechial rashes are typically seen with meningococcemia or Rocky Mountain spotted fever (RMSF; **see Fig. A1-16**); erythroderma is associated with toxic shock syndrome (TSS) and drug fever. The soft tissue and muscle examination is critical. Areas of erythema or duskiness, edema, and tenderness may indicate underlying necrotizing fasciitis, myositis, or myonecrosis. The neurologic examination must include a careful assessment of mental status for signs of early encephalopathy. Evidence of nuchal rigidity or focal neurologic findings should be sought.

DIAGNOSTIC WORKUP

After a quick clinical assessment, diagnostic material should be obtained rapidly and antibiotic and supportive treatment begun. Blood (for cultures; baseline complete blood count with differential; measurement of serum electrolytes, blood urea nitrogen, serum creatinine, and serum glucose; and liver function tests) can be obtained at the time an IV line is placed and before antibiotics are administered. The blood lactate concentration also should be measured. Three sets of blood cultures should be performed for patients with possible acute endocarditis. Blood smears from patients at risk for severe parasitic disease, such as malaria or babesiosis **(Chaps. 219, 220, and A6)**, must be examined for the diagnosis and quantitation of parasitemia. Blood smears may also be diagnostic in ehrlichiosis and anaplasmosis.

Patients with possible meningitis should have cerebrospinal fluid (CSF) drawn before the initiation of antibiotic therapy. Focal findings, depressed mental status, or papilledema should be evaluated by brain imaging prior to lumbar puncture, which, in this setting, could initiate herniation. *Antibiotics should be administered before imaging but after blood for cultures has been drawn*. If CSF cultures are negative, blood cultures will provide the diagnosis in 50–70% of cases. Molecular diagnostic techniques (e.g., broad-range 16S rRNA gene polymerase chain reaction testing for bacterial meningitis pathogens) are of increasing importance in the rapid diagnosis of life-threatening infections.

Focal abscesses necessitate immediate CT or MRI as part of an evaluation for surgical intervention. Other diagnostic procedures, such as wound cultures, should not delay the initiation of treatment for more than minutes. Once emergent evaluation, diagnostic procedures, and (if appropriate) surgical consultation (see below) have been completed, other laboratory tests can be conducted. Appropriate radiography, computed axial tomography, MRI, urinalysis, measurement of the erythrocyte sedimentation rate and/or C-reactive protein level, procalcitonin monitoring, and transthoracic or transesophageal echocardiography all may prove important.

TREATMENT

The Acutely Ill Patient

In the acutely ill patient, empirical antibiotic therapy is critical and should be administered without undue delay in addition to fluid resuscitation and vasopressor support as needed. Increased prevalence of antibiotic resistance in community-acquired bacteria must be considered when antibiotics are selected. **Table 117-1** lists first-line empirical regimens for infections considered in this chapter. In addition to the rapid initiation of antibiotic therapy, several of these infections require urgent surgical attention. Neurosurgical evaluation for subdural empyema, otolaryngologic surgery for possible mucormycosis, and cardiothoracic surgery for critically ill patients with acute endocarditis are as important as antibiotic therapy. For infections such as necrotizing fasciitis and clostridial myonecrosis, rapid surgical intervention supersedes other diagnostic or therapeutic maneuvers.

Adjunctive treatments may reduce morbidity and mortality rates and include dexamethasone for bacterial meningitis or IV immunoglobulin for TSS and necrotizing fasciitis caused by group A *Streptococcus*. Adjunctive therapies should usually be initiated within the first hours of treatment; however, dexamethasone for bacterial meningitis must be given before or at the time of the first dose of antibiotic. Glucocorticoids can also be harmful, sometimes resulting in worse outcomes—e.g., when given in the setting of cerebral malaria or viral hepatitis.

SPECIFIC PRESENTATIONS

The infections considered below according to common clinical presentation can have rapidly catastrophic outcomes, and their immediate recognition and treatment can be life-saving. Recommended empirical therapeutic regimens are presented in Table 117-1.

SEPSIS WITHOUT AN OBVIOUS FOCUS OF PRIMARY INFECTION

Patients initially have a brief prodrome of nonspecific symptoms and signs that progresses quickly to hemodynamic instability with hypotension, tachycardia, tachypnea, respiratory distress, and altered mental status. Disseminated intravascular coagulation (DIC) with clinical evidence of a hemorrhagic diathesis is a poor prognostic sign.

Septic Shock (See also Chap. 297) Patients with bacteremia leading to septic shock may have a primary site of infection (e.g., pneumonia, pyelonephritis, or cholangitis) that is not evident initially. Elderly patients with comorbid conditions, hosts compromised by malignancy and neutropenia, and patients who have recently undergone a surgical procedure or hospitalization are at increased risk for an adverse outcome. Gram-negative bacteremia with organisms such as *Pseudomonas aeruginosa* or *Escherichia coli* and gram-positive infection with organisms such as *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) or group A streptococci can present as intractable hypotension and multiorgan failure. Treatment can usually be initiated empirically on the basis of the presentation, host factors **(Chap. 297)**, and local patterns of bacterial resistance. Outcomes are worse when antimicrobial treatment is delayed or when the responsible pathogen ultimately proves not to be susceptible to the initial regimen. Active empirical antimicrobial coverage administered before admission to the intensive care unit is strongly associated with improved survival. Broad-spectrum antimicrobial agents are therefore recommended and should be instituted rapidly, preferably within the first hours after presentation. Risk factors for fungal infection should be assessed, as the incidence of fungal septic shock is increasing. Biomarkers such as C-reactive protein and procalcitonin have not proved reliable diagnostically but, when measured over time, can facilitate appropriate de-escalation of therapy and predict outcome. Glucocorticoids are often considered for patients with severe sepsis who do not respond to fluid resuscitation and vasopressor therapy. However, conclusive evidence for the efficacy of glucocorticoids in this setting is lacking.

Overwhelming Infection in Asplenic Patients (See also Chap. 297) Patients without splenic function are at risk for overwhelming bacterial sepsis. Asplenic adult patients succumb to sepsis at 58 times the rate of the general population. Most infections are thought to occur within the first 1 or 2 years, but the increased risk persists throughout life. The median interval between splenectomy and sepsis is 5.75 years, with a range of 1–19 years. In asplenia, encapsulated bacteria cause the majority of infections. Adults, who are more likely to have antibody to these organisms, are at lower risk than children. *Streptococcus pneumoniae* is the most common isolate, causing 40–70% of cases. The risk of infection with *Haemophilus influenzae* or *Neisseria meningitidis* is also greater in patients without splenic function, but reported cases are declining. Severe clinical manifestations of infections due to *E. coli*, *S. aureus*, group B streptococci, *P. aeruginosa*, *Bordetella holmesii*, and *Capnocytophaga*, *Babesia*, and *Plasmodium* species have been described.

TABLE 117-1 Empirical Treatment for Common Infectious Disease Emergencies[a]

CLINICAL SYNDROME	POSSIBLE ETIOLOGIES	TREATMENT	COMMENTS	SEE CHAP(S).
Sepsis without a Clear Focus				
Septic shock	*Pseudomonas* spp., gram-negative enteric bacilli, *Staphylococcus* spp., *Streptococcus* spp.	Vancomycin (15 mg/kg q12h)[b] *plus* gentamicin (5 mg/kg per day) ***plus either*** Piperacillin/tazobactam (3.375–4.5 g q6h) *or* cefepime (2 g q8h)[c]	Empirical therapy should be tailored to local resistance patterns. Adjust treatment when culture data become available.	**142, 143, 156, 159, 297**
Overwhelming post-splenectomy sepsis	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*	Ceftriaxone (2 g q12h) *plus* vancomycin (15 mg/kg q12h)[b]	If a β-lactam-sensitive strain is identified, vancomycin can be discontinued.	**297**
Babesiosis	*Babesia microti* (U.S.), *B. divergens* (Europe)	Clindamycin (600 mg q8h) *plus* quinine (650 mg q8h)	Atovaquone and azithromycin can be used in less severe disease and are associated with fewer side effects. Treatment with doxycycline (100 mg bid) for potential co-infection with *Borrelia burgdorferi* or *Anaplasma* spp. may be prudent.	**217, 220**
Sepsis with Skin Findings				
Meningococcemia	*N. meningitidis*	Penicillin (4 mU q4h) *or* ceftriaxone (2 g q12h)	Ceftriaxone eradicates nasopharyngeal carriage of the organism. Close contacts require chemoprophylaxis with rifampin (600 mg q12h for 2 days) or ciprofloxacin (a single dose, 500 mg).	**150**
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	Doxycycline (100 mg bid)	If both meningococcemia and RMSF are being considered, use ceftriaxone (2 g q12h) *plus* doxycycline (100 mg bid). If RMSF is diagnosed, doxycycline is the proven superior agent.	**182**
Purpura fulminans	*S. pneumoniae*, *H. influenzae*, *N. meningitidis*	Ceftriaxone (2 g q12h) *plus* vancomycin (15 mg/kg q12h)[b]	If a β-lactam-sensitive strain is identified, vancomycin can be discontinued.	**141, 150, 152, 297**
Erythroderma: toxic shock syndrome	Group A *Streptococcus*, *Staphylococcus aureus*	Vancomycin (15 mg/kg q12h)[b] *plus* clindamycin (600 mg q8h	If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 2 mU q4h; or oxacillin, 2 g IV q4h). The site of toxigenic bacteria should be debrided; IV immunoglobulin can be used in severe cases.[d]	**142, 143**
Sepsis with Soft Tissue Findings				
Necrotizing fasciitis	Group A *Streptococcus*, mixed aerobic/anaerobic flora, CA-MRSA[e]	Vancomycin (15 mg/kg q12h)[b] *plus* clindamycin (600 mg q8h) *plus* gentamicin (5 mg/kg per day)	Urgent surgical evaluation is critical. Adjust treatment when culture data become available.	**124, 142, 143**
Clostridial myonecrosis	*Clostridium perfringens*	Penicillin (2 mU q4h) *plus* clindamycin (600 mg q8h)	Urgent surgical evaluation is critical.	**149**
Neurologic Infections				
Bacterial meningitis	*S. pneumoniae*, *N. meningitidis*	Ceftriaxone (2 g q12h) *plus* vancomycin (15 mg/kg q12h)[b]	If a β-lactam–sensitive strain is identified, vancomycin can be discontinued. If the patient is >50 years old or has comorbid disease, add ampicillin (2 g q4h) for *Listeria* coverage. Dexamethasone (10 mg q6h for 4 days) improves outcome in adults with meningitis (especially pneumococcal).	**133**
Brain abscess, suppurative intracranial infections	*Streptococcus* spp., *Staphylococcus* spp., anaerobes, gram-negative bacilli	Vancomycin (15 mg/kg q12h)[b] *plus* metronidazole (500 mg q8h) *plus* ceftriaxone (2 g q12h)	Urgent surgical evaluation is critical. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 mU q4h; *or* oxacillin, 2 g q4h).	**133**
Cerebral malaria	*Plasmodium falciparum*	Artesunate (2.4 mg/kg IV at 0, 12, and 24 h; then once daily)[f] *or* quinine (IV loading dose of 20 mg salt/kg; then 10 mg/kg q8h)	Do not use glucocorticoids. Use IV quinidine if IV quinine is not available. During IV quinidine treatment, blood pressure and cardiac function should be monitored continuously and blood glucose periodically.	**217, 219**
Spinal epidural abscess	*Staphylococcus* spp., gram-negative bacilli	Vancomycin (15 mg/kg q12h)[b] ***plus either*** Piperacillin/tazobactam (3.375–4.5 g q6h) *or* cefepime (2 g q8h)[c]	Surgical evaluation is essential. If a penicillin- or oxacillin-sensitive strain is isolated, these agents are superior to vancomycin (penicillin, 4 mU q4h; *or* oxacillin, 2 g q4h).	**434**
Focal Infections				
Acute bacterial endocarditis	*S. aureus*, β-hemolytic streptococci, HACEK group,[g] *Neisseria* spp., *S. pneumoniae*	Ceftriaxone (2 g q12h) *plus* vancomycin (15 mg/kg q12h)[b]	Adjust treatment when culture data become available. Surgical evaluation is essential.	**123**

[a]These empirical regimens include coverage for gram-positive pathogens that are resistant to β-lactam antibiotics. Local resistance patterns should be considered and may alter the need for empirical vancomycin. [b]A vancomycin loading dose of 20–25 mg/kg can be considered in critically ill patients. [c]β-Lactam antibiotics may exhibit unpredictable pharmacodynamics in sepsis. Higher dosing or prolonged or continuous infusions can be considered. [d]The optimal dose of IV immunoglobulin has not been determined, but the median dose in observational studies is 2 g/kg (total dose administered for 1–5 days). [e]Community-acquired methicillin-resistant *S. aureus*. [f]In the United States, artesunate must be obtained through the Centers for Disease Control and Prevention. For patients diagnosed with severe malaria, full doses of parenteral antimalarial treatment should be started with whichever recommended antimalarial agent is first available. [g]*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Babesiosis (See also Chap. 220) A history of recent travel to endemic areas raises the possibility of infection with *Babesia*. Between 1 and 4 weeks after a tick bite, the patient experiences chills, fatigue, anorexia, myalgia, arthralgia, shortness of breath, nausea, and headache; ecchymosis and/or petechiae are occasionally seen. The tick that most commonly transmits *Babesia*, *Ixodes scapularis*, also transmits *Borrelia burgdorferi* (the agent of Lyme disease) and *Anaplasma*; coinfection can occur, resulting in more severe disease. Infection with the European species *Babesia divergens* is more frequently fulminant than that due to the U.S. species *Babesia microti*. *B. divergens* causes a febrile syndrome with hemolysis, jaundice, hemoglobinemia, and renal failure and is associated with a mortality rate of >40%. Severe babesiosis is especially common in asplenic hosts but does occur in hosts with normal splenic function, particularly those >60 years of age and those with underlying immunosuppressive conditions such as HIV infection or malignancy. Complications include renal failure, acute respiratory failure, and DIC.

Other Sepsis Syndromes Tularemia (Chap. 165) is seen throughout the United States, but most cases recorded in 2015 occurred in South Dakota, Nebraska, Colorado, and Wyoming. This disease is associated with wild rabbit, tick, and tabanid fly contact. It can be transmitted by arthropod bite, handling of infected animal carcasses, consumption of contaminated food and water, or inhalation. The typhoidal form can be associated with gram-negative septic shock and a mortality rate of >30%, especially in patients with underlying comorbid or immunosuppressive conditions. Plague occurs infrequently in the United States (Chap. 166), primarily after contact with ground squirrels, prairie dogs, or chipmunks, but is endemic in other parts of the world, with >90% of all cases occurring in Africa. The septic form is particularly rare and is associated with shock, multiorgan failure, and a 30% mortality rate. These infections should be considered in the appropriate epidemiologic setting. The Centers for Disease Control and Prevention lists *Francisella tularensis* and *Yersinia pestis* (the agents of tularemia and plague, respectively) along with *Bacillus anthracis* (the agent of anthrax) as important organisms that might be used for bioterrorism (Chap. S2).

SEPSIS WITH SKIN MANIFESTATIONS (SEE ALSO CHAP. 16)

Maculopapular rashes may reflect early meningococcal or rickettsial disease but are usually associated with nonemergent infections. Exanthems are usually viral. Primary HIV infection commonly presents with a rash that is typically maculopapular and involves the upper part of the body but can spread to the palms and soles. The patient is usually febrile and can have lymphadenopathy, severe headache, dysphagia, diarrhea, myalgias, and arthralgias. Recognition of this syndrome provides an opportunity to prevent transmission and to institute treatment and monitoring early on.

Petechial rashes caused by viruses are seldom associated with hypotension or a toxic appearance, although there can be exceptions (e.g., severe measles or arboviral infection). Petechial rashes limited to the distribution of the superior vena cava are rarely associated with severe disease. In other settings, petechial rashes require more urgent attention.

Meningococcemia (See also Chap. 150) Almost three-quarters of patients with *N. meningitidis* bacteremia have a rash. Meningococcemia most often affects young children (i.e., those 6 months to 5 years old). In sub-Saharan Africa, the high prevalence of serogroup A meningococcal disease has been a threat to public health for more than a century. Thousands of deaths occur annually in this area, which is known as the "meningitis belt," and large epidemic waves occur approximately every 8–12 years. Serogroups W135 and X are also important emerging pathogens in Africa. In the United States, sporadic cases and outbreaks occur in day-care centers, schools (grade school through college, particularly among college freshmen living in residential halls), and army barracks. Household contacts of index cases are at 400–800 times greater risk of disease than the general population. Patients may have fever, headache, nausea, vomiting, myalgias, changes in mental status, and meningismus. However, the rapidly progressive form of disease is not usually associated with meningitis. The rash is initially pink, blanching, and maculopapular, appearing on the trunk and extremities, but then becomes hemorrhagic, forming petechiae. Petechiae are first seen at the ankles, wrists, axillae, mucosal surfaces, and palpebral and bulbar conjunctiva, with subsequent spread on the lower extremities and to the trunk. A cluster of petechiae may be seen at pressure points—e.g., where a blood pressure cuff has been inflated. In rapidly progressive meningococcemia (10–20% of cases), the petechial rash quickly becomes purpuric (see Fig. A1-41), and patients develop DIC, multiorgan failure, and shock; 50–60% of these patients die, and survivors often require extensive debridement or amputation of gangrenous extremities. Hypotension with petechiae for <12 h is associated with significant mortality. Cyanosis, coma, oliguria, metabolic acidosis, and elevated partial thromboplastin time also are associated with a fatal outcome. Antibiotics given in the office by the primary care provider before hospital evaluation and admission may improve prognosis; this observation suggests that early initiation of treatment may be life-saving. Meningococcal conjugate vaccines are protective against serogroups A, C, Y and W135 and are recommended for children 11–18 years of age and for other high-risk patients. Vaccines active against serogroup B are available and are recommended for high-risk individuals >10 years of age.

Rocky Mountain Spotted Fever and Other Rickettsial Diseases (See also Chap. 182) RMSF is a tickborne disease caused by *Rickettsia rickettsii* that occurs throughout North and South America. Other rickettsiae (e.g., *R. parkeri*, *R. akari*) can also cause spotted fever. Up to 40% of patients do not report a history of a tick bite, but a history of travel or outdoor activity (e.g., camping in tick-infested areas) can often be ascertained. For the first 3 days, headache, fever, malaise, myalgias, nausea, vomiting, and anorexia are documented. By day 3, half of patients have skin findings. Blanching macules develop initially on the wrists and ankles and then spread over the legs and trunk. The lesions become hemorrhagic and are frequently petechial. The rash spreads to palms and soles later in the course. The centripetal spread is a classic feature of RMSF but occurs in a minority of patients. Moreover, 10–15% of patients with RMSF never develop a rash. The patient can be hypotensive and develop noncardiogenic pulmonary edema, confusion, lethargy, and encephalitis progressing to coma. The CSF contains 10–100 cells/μL, usually with a predominance of mononuclear cells. The CSF glucose level is often normal; the protein concentration may be slightly elevated. Renal and hepatic injury as well as bleeding secondary to vascular damage are noted. For untreated infections, mortality rates are 20–30%. Delayed recognition and treatment are associated with a greater risk of death; Native Americans, children 5–9 years of age, adults >70 years old, and persons with underlying immunosuppression are at a 3- to 5-fold increased risk of death.

Other rickettsial diseases cause significant morbidity and mortality worldwide. *Mediterranean spotted fever* caused by *Rickettsia conorii* is found in Africa, southwestern and south-central Asia, and southern Europe. Patients have fever, flu-like symptoms, and an inoculation eschar at the site of the tick bite. A maculopapular rash develops within 1–7 days, involving the palms and soles but sparing the face. Elderly patients or those with diabetes, alcoholism, uremia, or congestive heart failure are at risk for severe disease characterized by neurologic involvement, respiratory distress, and gangrene of the digits or purpura fulminans. Mortality rates associated with this severe form of disease approach 50%. *Epidemic typhus*, caused by *Rickettsia prowazekii*, is transmitted in louse-infested environments and emerges in conditions of extreme poverty, war, and natural disaster. Patients experience a sudden onset of high fevers, severe headache, cough, myalgias, and abdominal pain. A maculopapular rash develops (primarily on the trunk) in more than half of patients and can progress to petechiae and purpura. Serious signs include delirium, coma, seizures, noncardiogenic pulmonary edema, skin necrosis, and peripheral gangrene. Mortality rates approached 60% in the preantibiotic era and continue to exceed 10–15% in contemporary outbreaks. *Scrub typhus*, caused by *Orientia tsutsugamushi* (a separate genus in the

family Rickettsiaceae), is transmitted by larval mites or chiggers and is one of the most common infections in southeastern Asia and the western Pacific. The organism is found in areas of heavy scrub vegetation (e.g., along riverbanks). Patients may have an inoculation eschar and may develop a maculopapular rash, lymphadenopathy, and dyspnea. Severe cases progress to pneumonia, meningoencephalitis, myocarditis, DIC, and renal failure. Mortality rates range from 1% to 70% and vary by location, increasing age, myocarditis, delirium, pneumonitis, or signs of hemorrhage.

If recognized in a timely fashion, rickettsial disease is very responsive to treatment. Doxycycline (100 mg twice daily for 3–14 days) is the treatment of choice for both adults and children. The newer macrolides may be a suitable alternative, but mortality rates are higher when tetracycline-based treatment is not given.

Purpura Fulminans (See also Chaps. 150 and 297) Purpura fulminans is the cutaneous manifestation of DIC and presents as large ecchymotic areas and hemorrhagic bullae. Progression of petechiae to purpura, ecchymoses, and gangrene is associated with congestive heart failure, septic shock, acute renal failure, acidosis, hypoxia, hypotension, and death. Purpura fulminans has been associated primarily with *N. meningitidis* but, in splenectomized patients, may be associated with *S. pneumoniae*, *H. influenzae*, and *S. aureus*.

Ecthyma Gangrenosum Septic shock caused by *P. aeruginosa* or *Aeromonas hydrophila* can be associated with ecthyma gangrenosum (see Figs. 159-1 and A1-34): hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration. These gram-negative bacteremias are most common among patients with neutropenia, extensive burns, and hypogammaglobulinemia.

Other Infections Associated with Rash *Vibrio vulnificus* and other noncholera *Vibrio* bacteremic infections (Chap. 163) can cause focal skin lesions and overwhelming sepsis in hosts with chronic liver disease, heavy alcohol consumption, iron storage disorders, diabetes, renal insufficiency, hematologic disease, or malignancy or other immunocompromising conditions. After ingestion of contaminated raw shellfish (typically oysters from the Gulf Coast in U.S. cases), there is a sudden onset of malaise, chills, fever, and hypotension. The patient develops bullous or hemorrhagic skin lesions, usually on the lower extremities, and 75% of patients have leg pain. The mortality rate can be as high as 50–60%, particularly when the patient presents with hypotension. Outcomes are improved when patients are treated with fluoroquinolones with or without cephalosporins or with tetracycline-containing regimens. Other infections, caused by agents such as *Aeromonas*, *Klebsiella*, and *E. coli*, can cause hemorrhagic bullae and death due to overwhelming sepsis in cirrhotic patients. *Capnocytophaga canimorsus* can cause septic shock in asplenic patients. Infection typically follows a dog bite. Patients present with fever, chills, myalgia, vomiting, diarrhea, dyspnea, confusion, and headache. Findings can include an exanthem or erythema multiforme (see Figs. 52-9 and A1-24), cyanotic mottling or peripheral cyanosis, petechiae, and ecchymosis. About 30% of patients with this fulminant form die of overwhelming sepsis and DIC, and survivors may require amputation because of gangrene.

Erythroderma TSS (Chaps. 142 and 143) is usually associated with erythroderma. The patient presents with fever, malaise, myalgias, nausea, vomiting, diarrhea, and confusion. There is a sunburn-type rash that may be subtle and patchy but is usually diffuse and is found on the face, trunk, and extremities. Erythroderma, which desquamates after 1–2 weeks, is more common in *Staphylococcus*-associated than in *Streptococcus*-associated TSS. Hypotension develops rapidly—often within hours—after the onset of symptoms. Multiorgan failure occurs. Early renal failure may precede hypotension and distinguishes this syndrome from other septic shock syndromes. There may be no indication of a primary focal infection, although possible cutaneous or mucosal portals of entry for the organism can be ascertained when a careful history is taken. Colonization rather than overt infection of the vagina or a postoperative wound, for example, is typical with staphylococcal TSS, and the mucosal areas appear hyperemic but not infected. Streptococcal TSS is more often associated with skin or soft tissue infection (including necrotizing fasciitis), and patients are more likely to be bacteremic. TSS caused by *Clostridium sordellii* is associated with childbirth or with skin injection of black-tar heroin. The diagnosis of TSS is defined by the clinical criteria of fever, rash, hypotension, and multiorgan involvement. (Of note, fever is typically absent when TSS is caused by *C. sordellii*.) The mortality rate is 5% for menstruation-associated TSS, 10–15% for nonmenstrual TSS, 30–70% for streptococcal TSS, and up to 90% for obstetric *C. sordellii* TSS. Clindamycin improves outcomes when included in the treatment regimen. Some studies have shown that use of IV immunoglobulin is associated with improved survival as well.

Viral Hemorrhagic Fevers Viral hemorrhagic fevers (Chaps. 204 and 205) are zoonotic illnesses caused by viruses that reside in either animal reservoirs or arthropod vectors. These diseases occur worldwide and are restricted to areas where the host species live. They are caused by four major groups of viruses: Arenaviridae (e.g., Lassa fever in Africa), Bunyaviridae (e.g., Rift Valley fever in Africa; hantavirus hemorrhagic fever with renal syndrome in Asia; and Crimean-Congo hemorrhagic fever, which has an extensive geographic distribution), Filoviridae (e.g., Ebola and Marburg virus infections in Africa), and Flaviviridae (e.g., yellow fever in Africa and South America and dengue in Asia, Africa, and the Americas). Lassa fever and Ebola and Marburg virus infections are also transmitted from person to person. The vectors for most viral fevers are found in rural areas; dengue and yellow fever are important exceptions. After a prodrome of fever, myalgias, and malaise, patients develop evidence of vascular damage, petechiae, and local hemorrhage. Shock, multifocal hemorrhaging, and neurologic signs (e.g., seizures or coma) predict a poor prognosis. Dengue (Chap. 204) is the most common arboviral disease worldwide. More than half a million cases of dengue hemorrhagic fever occur each year, with at least 12,000 deaths. Patients have a triad of symptoms: hemorrhagic manifestations, evidence of plasma leakage, and platelet counts of <100,000/μL. Mortality rates are 10–20%. If dengue shock syndrome develops, mortality rates can reach 40%. Ebola infection has been associated with outbreaks with high mortality rates. The 2014 outbreak in West Africa had a mortality rate of >50%. Symptoms can appear 2–21 days after exposure, but most patients become ill within 9 days. The patient first presents with fatigue, fever, headache, and muscle pains, and the illness can progress to multiorgan failure and hemorrhaging. Careful volume-replacement therapy to maintain blood pressure and intravascular volume is key to survival in these infections. Ribavirin also may be useful against Arenaviridae and Bunyaviridae.

Other viral illnesses with rash, such as measles, can be associated with significant mortality rates. Steroids may sometimes be useful in severe disease in malnourished populations, especially if neurologic complications are present.

SEPSIS WITH A SOFT TISSUE/MUSCLE PRIMARY FOCUS

See also Chap. 124.

Necrotizing Fasciitis This infection is characterized by extensive necrosis of the subcutaneous tissue and fascia. It may arise at a site of minimal trauma or surgical incision and may also be associated with recent varicella, childbirth, or muscle strain. The most common causes of necrotizing fasciitis are group A streptococci alone (Chap. 143) and a mixed facultative and anaerobic flora (Chap. 124); the incidence of group A streptococcal necrotizing fasciitis has been increasing for the past quarter-century. Diabetes mellitus, IV drug use, chronic liver or renal disease, and malignancy are associated risk factors. Physical findings are initially minimal compared with the severity of pain and the degree of fever. The examination is often unremarkable except for soft tissue edema and erythema. The infected area is red, hot, shiny, swollen, and exquisitely tender. In untreated infection, the overlying skin develops blue-gray patches after 36 h, and cutaneous bullae and necrosis develop after 3–5 days. Necrotizing fasciitis due to a mixed flora, but not that due to group A streptococci, can be associated with gas production.

Without treatment, pain decreases because of thrombosis of the small blood vessels and destruction of the peripheral nerves—an ominous sign. The mortality rate is 15–34% overall, >70% in association with TSS, and nearly 100% without surgical intervention. Necrotizing fasciitis may also be due to *Clostridium perfringens* (Chap. 149); in this condition, the patient is extremely toxic and the mortality rate is high. Within 48 h, rapid tissue invasion and systemic toxicity associated with hemolysis and death ensue. The distinction between this entity and clostridial myonecrosis is made by muscle biopsy. Necrotizing fasciitis caused by community-acquired MRSA also has been reported.

Clostridial Myonecrosis (See also Chap. 149) Myonecrosis is often associated with trauma or surgery but can develop spontaneously. The incubation period is usually 12–24 h long, and massive necrotizing gangrene develops within hours of onset. Systemic toxicity, shock, and death can occur within 12 h. The patient's pain and toxic appearance are out of proportion to physical findings. On examination, the patient is febrile, apathetic, tachycardic, and tachypneic and may express a feeling of impending doom. Hypotension and renal failure develop later, and hyperalertness is evident preterminally. The skin over the affected area is bronze-brown, mottled, and edematous. Bullous lesions with serosanguineous drainage and a mousy or sweet odor can develop. Crepitus can occur secondary to gas production in muscle tissue. The mortality rate is >65% for spontaneous myonecrosis, which is often associated with *Clostridium septicum* or *C. tertium* and underlying malignancy. The mortality rates associated with trunk and limb infection are 63% and 12%, respectively, and any delay in surgical treatment increases the risk of death.

NEUROLOGIC INFECTIONS WITH OR WITHOUT SEPTIC SHOCK

Bacterial Meningitis (See also Chap. 133) Bacterial meningitis is one of the most common infectious disease emergencies involving the central nervous system. Although hosts with cell-mediated immune deficiency (including transplant recipients, diabetic patients, elderly patients, and cancer patients receiving certain chemotherapeutic agents) are at particular risk for *Listeria monocytogenes* meningitis, most cases in adults are due to *S. pneumoniae* (30–60%) and *N. meningitidis* (10–35%). The classic presentation of fever, meningismus, and altered mental status is seen in only one-half to two-thirds of patients. The elderly can present without fever or meningeal signs. Cerebral dysfunction is evidenced by confusion, delirium, and lethargy that can progress to coma. In some cases, the presentation is fulminant, with sepsis and brain edema; papilledema at presentation is unusual and suggests another diagnosis (e.g., an intracranial lesion). Focal signs, including cranial nerve palsies (IV, VI, VII), can be seen in 10–20% of cases; 50–70% of patients have bacteremia. A poor outcome is associated with coma, seizures, hypotension, a pneumococcal etiology, respiratory distress, a CSF glucose level of <0.6 mmol/L (<10 mg/dL), a CSF protein level of >2.5 g/L, a peripheral white blood cell count of <5000/μL, and a serum sodium level of <135 mmol/L. Rapid initiation of treatment is essential; the odds of an unfavorable outcome may increase by 30% for each hour that treatment is delayed. Dexamethasone is an adjunctive treatment for meningitis in adults, especially for infections caused by *S. pneumoniae*. It must be given before or with the first dose of antibiotics; otherwise, it is unlikely to improve outcomes.

Suppurative Intracranial Infections (See also Chap. 135) In suppurative intracranial infections, rare intracranial lesions present along with sepsis and hemodynamic instability. Rapid recognition of the toxic patient with central neurologic signs is crucial to improvement of the dismal prognosis of these entities. Patients with diabetes or hematologic disease may be at increased risk for these infections. *Subdural empyema* arises from the paranasal sinus in 60–70% of cases. Microaerophilic streptococci and staphylococci are the predominant etiologic organisms. The patient is toxic, with fever, headache, and nuchal rigidity. Of all patients, 75% have focal signs and 6–20% die. Despite improved survival rates, 15–44% of patients are left with permanent neurologic deficits. *Septic cavernous sinus thrombosis* follows a facial or sphenoid sinus infection; 70% of cases are due to staphylococci (including MRSA), and the remainder are due primarily to aerobic or anaerobic streptococci. Fungi have been common in some series. A unilateral or retro-orbital headache progresses to a toxic appearance and fever within days. Three-quarters of patients have unilateral periorbital edema that becomes bilateral and then progresses to ptosis, proptosis, ophthalmoplegia, and papilledema. The mortality rate is as high as 30%. *Septic thrombosis of the superior sagittal sinus* spreads from the ethmoid or maxillary sinuses and is caused by *S. pneumoniae*, other streptococci, and staphylococci. The fulminant course is characterized by headache, nausea, vomiting, rapid progression to confusion and coma, nuchal rigidity, and brainstem signs. If the sinus is totally thrombosed, the mortality rate exceeds 80%. Broad-spectrum antibiotics and early surgical intervention at the primary site of infection may improve outcomes. Anticoagulation or steroids are of uncertain benefit.

Brain Abscess (See also Chap. 135) Brain abscess often occurs without systemic signs. Almost half of patients are afebrile, and presentations are more consistent with a space-occupying lesion in the brain; 70% of patients have headache and/or altered mental status, 50% have focal neurologic signs, and 25% have papilledema. Abscesses can present as single or multiple lesions resulting from contiguous foci or hematogenous infection, such as endocarditis, or after surgery or trauma. The infection progresses over several days from cerebritis to an abscess with a mature capsule. More than half of infections are polymicrobial, with an etiology consisting of aerobic bacteria (primarily streptococcal species) and anaerobes. Abscesses arising hematogenously are especially apt to rupture into the ventricular space, causing a sudden and severe deterioration in clinical status and a high mortality rate. Otherwise, mortality is low (<20%) but morbidity is high (30–55%). Patients presenting with stroke and a parameningeal infectious focus, such as sinusitis or otitis, may have a brain abscess, and physicians must maintain a high level of suspicion. Prognosis worsens in patients with a fulminant course, delayed diagnosis, abscess rupture into the ventricles, multiple abscesses, or abnormal neurologic status at presentation. In one study, mortality at 1 year was 19%.

Cerebral Malaria (See also Chap. 219) This entity should be urgently considered if patients who have recently traveled to areas endemic for malaria present with a febrile illness and lethargy or other neurologic signs. Fulminant malaria is caused by *Plasmodium falciparum* and is associated with temperatures of >40°C (>104°F), hypotension, jaundice, acute respiratory distress syndrome, and bleeding. By definition, any patient with a change in mental status or repeated seizure in the setting of fulminant malaria has cerebral malaria. In adults, this nonspecific febrile illness progresses to coma over several days; occasionally, coma occurs within hours and death within 24 h. Nuchal rigidity and photophobia are rare. On physical examination, symmetric encephalopathy is typical, and upper motor neuron dysfunction with decorticate and decerebrate posturing can be seen in advanced disease. Unrecognized infection results in a 20–30% mortality rate.

Intracranial and Spinal Epidural Abscesses (See also Chap. 434) Spinal and intracranial epidural abscesses (SEAs and ICEAs) can result in permanent neurologic deficits, sepsis, and death. At-risk patients include those with diabetes mellitus; IV drug use; chronic alcohol abuse; recent spinal trauma, surgery, or epidural anesthesia; and other comorbid conditions, such as HIV infection. Fungal epidural abscess and meningitis can follow epidural or paraspinal glucocorticoid injections. In the United States and Canada, where early treatment of otitis and sinusitis is typical, ICEA is rare but the number of cases of SEA is on the rise. In Africa and areas with limited access to health care, SEAs and ICEAs cause significant morbidity and mortality. ICEAs typically present as fever, mental status changes, and neck pain, while SEAs often present as fever, localized spinal tenderness, and back pain. ICEAs are typically polymicrobial, whereas SEAs are most often due to hematogenous seeding, with staphylococci the most common etiologic agent. Early diagnosis and treatment, which may include surgical drainage, minimize rates of mortality and permanent neurologic sequelae. Outcomes are worse for SEA due to MRSA, for infection at

a higher vertebral-body level, for impaired neurologic status on presentation, and for dorsal rather than ventral location of the abscess. Elderly patients and persons with renal failure, malignancy, and other comorbidities also have less favorable outcomes.

OTHER FOCAL SYNDROMES WITH A FULMINANT COURSE

Infection at virtually any primary focus (e.g., osteomyelitis, pneumonia, pyelonephritis, or cholangitis) can result in bacteremia and sepsis. Lemierre's syndrome—jugular septic thrombophlebitis caused by *Fusobacterium necrophorum*—is associated with metastatic infectious emboli (primarily to the lung but sometimes to the liver or other organs) and sepsis, with mortality rates of >15%. TSS has been associated with focal infections such as septic arthritis, peritonitis, sinusitis, and wound infection. Rapid clinical deterioration and death can be associated with destruction of the primary site of infection, as is seen in endocarditis and in infections of the oropharynx (e.g., Ludwig's angina or epiglottitis, in which edema suddenly compromises the airway).

Rhinocerebral Mucormycosis **(See also Chap. 213)** Individuals with diabetes or immunocompromising conditions such as solid organ transplants or hematologic malignancies are at risk for invasive rhinocerebral mucormycosis. Patients present with low-grade fever, dull sinus pain, diplopia, decreased mental status, decreased ocular motion, chemosis, proptosis, dusky or necrotic nasal turbinates, and necrotic hard-palate lesions that respect the midline. Without rapid recognition and intervention, the process continues on an inexorable invasive course, with mortality rates of 50–85% or greater. Uncontrolled diabetes and increasing age are negative prognostic factors.

Acute Bacterial Endocarditis **(See also Chap. 123)** This entity presents with a much more aggressive course than subacute endocarditis. Bacteria such as *S. aureus*, *S. pneumoniae*, *L. monocytogenes*, *Haemophilus* species, and streptococci of groups A, B, and G attack native valves. Native-valve endocarditis caused by *S. aureus* (including MRSA strains) is increasing, particularly in health care settings. Mortality rates range from 10% to 40%. The host may have comorbid conditions such as underlying malignancy, diabetes mellitus, IV drug use, or alcoholism. The patient presents with fever, fatigue, and malaise <2 weeks after onset of infection. On physical examination, a changing murmur and congestive heart failure may be noted. Hemorrhagic macules on palms or soles (*Janeway lesions*) sometimes develop. Petechiae, Roth's spots, splinter hemorrhages, and splenomegaly are unusual. Rapid valvular destruction, particularly of the aortic valve, results in pulmonary edema and hypotension. Myocardial abscesses can form, eroding through the septum or into the conduction system and causing life-threatening arrhythmias or high-degree conduction block. Large friable vegetations can result in major arterial emboli, metastatic infection, or tissue infarction. Older patients with *S. aureus* endocarditis are especially likely to present with nonspecific symptoms—a circumstance that delays diagnosis and worsens prognosis. Rapid intervention is crucial for a successful outcome.

Inhalational Anthrax **(See also Chap. S2)** Inhalational anthrax, the most severe form of disease caused by *B. anthracis*, had not been reported in the United States for more than 25 years until the use of this organism as an agent of bioterrorism in 2001. Patients presented with malaise, fever, cough, nausea, drenching sweats, shortness of breath, and headache. Rhinorrhea was unusual. All patients had abnormal chest roentgenograms at presentation. Pulmonary infiltrates, mediastinal widening, and pleural effusions were the most common findings. Hemorrhagic meningitis was documented in 38% of these patients. Survival was more likely when antibiotics were given during the prodromal period and when multidrug regimens were used. In the absence of urgent intervention with antimicrobial agents and supportive care, inhalational anthrax progresses rapidly to hypotension, cyanosis, and death.

Viral Respiratory Tract Illness Viral respiratory tract illnesses can cause severe disease; several new syndromes have been described in the past decade. For patients who present with a respiratory illness and a relevant exposure and travel history, these viral illnesses must be considered and appropriate infection control measures instituted in addition to supportive care.

Avian and Swine Influenza **(See also Chap. 195)** Human cases of avian influenza have occurred primarily in Southeast Asia, particularly Vietnam (H5N1) and China (H7N9). Avian influenza should be considered in patients with severe respiratory tract illness, particularly if they have been exposed to poultry. Patients present with high fever, an influenza-like illness, and lower respiratory tract symptoms; this illness can progress rapidly to bilateral pneumonia, acute respiratory distress syndrome, multiorgan failure, and death. Younger age appears to be associated with a lower risk of complications. Early antiviral treatment with neuraminidase inhibitors should be initiated along with aggressive supportive measures. Unlike avian influenza, whose human-to-human transmission has so far been rare and has not been sustained, influenza caused by a novel swine-associated A/H1N1 virus has spread rapidly throughout the world; by 2012, 214 countries had diagnosed cases of influenza A/H1N1, with 18,449 deaths. Patients most at risk of severe disease are children <5 years of age, elderly persons, patients with underlying chronic conditions, and pregnant women. Obesity also has been identified as a risk factor for severe illness. Immunosuppression and co-infection with *S. aureus* at presentation are independent risk factors for increased mortality.

SARS and MERS Severe acute respiratory syndrome (SARS) was identified in 2002 in China but has been diagnosed in several countries, primarily in Asia. Possible animal reservoirs include bats and civets. SARS is caused by a coronavirus and is characterized by efficient human transmission but relatively low mortality. It spreads from person to person via droplets; "super-spreader" airborne events have occurred. The potential pandemic with SARS was controlled through identification and isolation of infected patients. A 3- to 7-day prodrome characterized by fever, malaise, headache, and myalgia can progress to nonproductive cough, dyspnea, and respiratory failure. The risk of contagion is low during the prodrome. Older patients and those with diabetes mellitus, chronic hepatitis B, and other comorbidities can have less favorable outcomes.

Middle East respiratory syndrome (MERS) is caused by a novel betacoronavirus and was first recognized in 2012 in Saudi Arabia. Human cases have been associated with direct and indirect contact with dromedary camels. Unlike SARS, MERS exhibits inefficient human transmission but carries a high mortality rate. As of 2015, 1180 cases had been confirmed, with 40% mortality. MERS ranges from asymptomatic infection to acute respiratory distress syndrome, multiorgan failure, and death. Elderly men with comorbidities appear to be at highest risk for poor outcomes. Despite little documented human-to-human transmission in the community, nosocomial infection must be prevented by adherence to strict infection control practices. MERS is currently a low-level public health threat and is likely to remain so unless the virus mutates and its transmissibility increases.

Hantavirus Pulmonary Syndrome **(See also Chap. 204)** Hantavirus pulmonary syndrome has been documented in the United States since 1993 (primarily the southwestern states, west of the Mississippi River), Canada, and South America. Most cases occur in rural areas and are associated with exposure to rodents. Patients present with a nonspecific viral prodrome of fever, malaise, myalgias, nausea, vomiting, and dizziness that may progress to pulmonary edema, respiratory failure, and death. Hantavirus pulmonary syndrome causes myocardial depression and increased pulmonary vascular permeability; therefore, careful fluid resuscitation and use of pressor agents are crucial. Aggressive cardiopulmonary support during the first few hours of illness can be life-saving in this high-mortality syndrome. The early onset of thrombocytopenia may help distinguish this syndrome from other febrile illnesses in an appropriate epidemiologic setting.

***Clostridium difficile* Infection** *C. difficile* infection (CDI) is a toxin-mediated diarrheal syndrome that is strongly associated with prior antibiotic use. Proton-pump inhibitors have also been identified as a potential risk factor for the disease. Although most cases of CDI

have occurred in the health care setting, community-onset CDI is increasing. Overall, community-onset cases occur in younger patients than nosocomial cases. Patients with community-onset CDI are less likely to have a history of antibiotic or protein-pump inhibitor use. CDI is associated with significant morbidity and mortality, particularly among older patients. The Centers for Disease Control and Prevention has reported that *C. difficile* infection is one of the top three health threats associated with antibiotic use.

SUMMARY

Acutely ill febrile patients with the syndromes discussed in this chapter require close observation, aggressive supportive measures, and—in most cases—admission to intensive care units. The most important task of the physician is to distinguish these patients from other infected febrile patients whose illness will not progress to fulminant disease. The alert physician must recognize the acute infectious disease emergency and then proceed with appropriate urgency.

FURTHER READING

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118 Immunization Principles and Vaccine Use

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Few medical interventions of the past century can rival the effect that immunization has had on longevity, economic savings, and quality of life. Seventeen diseases are now preventable through vaccines routinely administered to children and adults in the United States (Table 118-1), and most vaccine-preventable diseases of childhood are at historically low levels (Table 118-2). Health care providers deliver the vast majority of vaccines in the United States in the course of providing routine health services and therefore play an integral role in the nation's public health system.

VACCINE IMPACT

Direct and Indirect Effects Immunizations against specific infectious diseases protect individuals against infection and thereby prevent symptomatic illnesses. Specific vaccines may blunt the severity of clinical illness (e.g., rotavirus vaccines and severe gastroenteritis) or reduce complications (e.g., zoster vaccines and postherpetic neuralgia). Some immunizations also reduce transmission of infectious disease agents from immunized people to others, thereby reducing the impact of infection spread. This indirect impact is known as *herd immunity*. The level of immunization in a population that is required to achieve indirect protection of unimmunized people varies substantially with the specific vaccine and disease.

Since childhood vaccines have become widely available in the United States, major declines in rates of vaccine-preventable diseases among both children and adults have become evident (Table 118-2). For example, vaccination of children <5 years of age against seven types of *Streptococcus pneumoniae* led to a >90% overall reduction in invasive disease caused by those types. Among children born during 1994–2013, a series of childhood vaccines targeting 13 vaccine-preventable diseases will prevent 322 million illnesses and 732,000 deaths over the course of their lifetimes and save $1.38 trillion (U.S.).

TABLE 118-1 Diseases Preventable with Vaccines Routinely Administered in the United States to Children and/or Adults

CONDITION	TARGET POPULATION(S) FOR ROUTINE USE
Pertussis	Children, adolescents, adults
Diphtheria	Children, adolescents, adults
Tetanus	Children, adolescents, adults
Poliomyelitis	Children
Measles	Children
Mumps	Children
Rubella, congenital rubella syndrome	Children
Hepatitis B	Children and high-risk adults
Haemophilus influenzae type b infection	Children
Hepatitis A	Children
Influenza	Children, adolescents, adults
Varicella	Children
Pneumococcal disease	Children, older adults
Meningococcal disease	Adolescents and high-risk adults
Rotavirus infection	Infants
Human papillomavirus infection, cervical and anogenital cancers	Adolescents and young adults
Zoster	Older adults

Control, Elimination, and Eradication of Vaccine-Preventable Diseases Immunization programs are associated with the goals of controlling, eliminating, or eradicating a disease. *Control* of a vaccine-preventable disease reduces poor illness outcomes and often limits the disruptive impacts associated with outbreaks of

TABLE 118-2 Decline in Vaccine-Preventable Diseases in the United States Following Widespread Implementation of National Vaccine Recommendations

CONDITION	ANNUAL NO. OF PREVACCINE CASES (AVERAGE)	NO. OF CASES REPORTED IN 2016[a]	REDUCTION (%) IN CASES AFTER WIDESPREAD VACCINATION
Smallpox	29,005	0	100
Diphtheria	21,053	0	100
Measles	530,217	69	>99
Mumps	162,344	5311	97
Pertussis	200,752	15,737	92
Polio (paralytic)	16,316	0	100
Rubella	47,745	5	>99
Congenital rubella syndrome	152	1	99
Tetanus	580	33	94
Haemophilus influenzae type b infection	20,000	22[b]	>99
Hepatitis A	117,333	2500[c]	98
Hepatitis B (acute)	66,232	19,200[c]	71
Invasive pneumococcal infection: all ages	63,067	29,000[d]	54
Varicella	4,085,120	126,639[e]	97

[a]2016 reported cases unless otherwise specified. [b]An additional 11 type b infections are estimated to have occurred among 222 reports of *H. influenzae* infection caused by unknown types among children <5 years of age. [c]Data are from the CDC's Viral Hepatitis Surveillance, 2014. [d]Data are from the CDC's Active Bacterial Core Surveillance 2015 Provisional Report. [e]Data are from Morb Mortal Wkly Rep 65:1306, 2016 (2015 final data).

Source: Adapted from SW Roush et al: JAMA 298:2155, 2007 and Morb Mortal Wkly Rep 65:924, 2017.

disease in communities, schools, and institutions. Control programs can also reduce absences from work for ill persons and for parents caring for sick children, decrease absences from school, and limit health care utilization associated with treatment visits.

Elimination of a disease is a more demanding goal than control, usually requiring the reduction to zero of cases in a defined geographic area but sometimes defined as reduction in the indigenous sustained transmission of an infection in a geographic area. As of 2016, the United States had eliminated indigenous transmission of measles, rubella, poliomyelitis, and diphtheria. Importation of pathogens from other parts of the world continues to be important, and public health efforts are intended to respond promptly to such cases in order to limit forward spread of the infectious agent.

Eradication of a disease is achieved when its elimination can be sustained without the need to continue interventions. The only vaccine-preventable disease of humans that has been globally eradicated thus far is smallpox. Although smallpox vaccine is no longer given routinely, the disease has not reemerged naturally because all chains of human transmission were interrupted through earlier vaccination efforts and humans were the only natural reservoir of the virus. Currently, a major health initiative is targeting the global eradication of polio. Sustained transmission of polio has been eliminated from most nations but has not yet been interrupted in Afghanistan and Pakistan. In 2016, after Nigeria completed 2 years without a wild polio case detected, three cases were identified in a region where vaccinators have been unable to reach hundreds of thousands of children because of insurgency and the virus is likely to have been circulating undetected. Detection of a case of disease that has been targeted for eradication or elimination is considered a sentinel event that could permit the infectious agent to become reestablished in the community or region. Therefore, such episodes must be promptly reported to public health authorities.

Outbreak Detection and Control Clusters of cases of a vaccine-preventable disease detected in an institution, a medical practice, or a community may signal important changes in the pathogen, vaccine, or environment. Several factors can give rise to increases in vaccine-preventable disease, including (1) low rates of immunization that result in an accumulation of susceptible people (e.g., measles resurgence among vaccination abstainers); (2) changes in the infectious agent that permit it to escape vaccine-induced protection (e.g., non-vaccine-type pneumococci); (3) waning of vaccine-induced immunity (e.g., pertussis among adolescents and adults vaccinated in early childhood); and (4) point-source introductions of large inocula (e.g., food-borne exposure to hepatitis A virus). Reporting episodes of outbreak-prone diseases to public health authorities can facilitate recognition of clusters that require further interventions.

PUBLIC HEALTH REPORTING Recognition of suspected cases of diseases targeted for elimination or eradication—along with other diseases that require urgent public health interventions, such as contact tracing, administration of chemo- or immunoprophylaxis, or epidemiologic investigation for common-source exposure—is typically associated with special reporting requirements. Many diseases against which vaccines are routinely used, including measles, pertussis, *Haemophilus influenzae* type b invasive disease, and varicella, are nationally notifiable. Clinicians and laboratory staff have a responsibility to report some vaccine-preventable disease occurrences to local or state public health authorities according to specific case-definition criteria. All providers should be aware of state or city disease-reporting requirements and the best ways to contact public health authorities. A prompt response to vaccine-preventable disease outbreaks can greatly enhance the effectiveness of control measures.

GLOBAL CONSIDERATIONS Several international health initiatives currently focus on reducing vaccine-preventable diseases in regions throughout the world. The American Red Cross, the World Health Organization (WHO), the United Nations Foundation, the United Nations Children's Fund (UNICEF), and the Centers for Disease Control and Prevention (CDC) are partners in the Measles & Rubella Initiative, which targets reduction of worldwide measles deaths. During 2000–2014, global measles mortality rates declined by 78%—i.e., from an estimated 535,300 deaths in 2000 to 114,900 deaths in 2014. In 2015, the Americas became the first WHO region to be declared free of endemic transmission of rubella. Rotary International, UNICEF, the CDC, and the WHO are leading partners in the global eradication of polio, an endeavor that reduced the annual number of paralytic polio cases from 350,000 in 1988 to 74 in 2015. The GAVI Alliance and the Bill and Melinda Gates Foundation have brought substantial momentum to global efforts to reduce vaccine-preventable diseases, expanding on earlier efforts by the WHO, UNICEF, and governments in developed and developing countries.

Enhancing Immunization in Adults Although immunization has become a centerpiece of routine pediatric medical visits, it has not been as well integrated into routine health care visits for adults. This chapter focuses on immunization principles and vaccine use in adults. Accumulating evidence suggests that immunization coverage can be increased through efforts directed at consumer-, provider-, institution-, and system-level factors. The literature suggests that the application of multiple strategies is more effective at raising coverage rates than is the use of any single strategy.

RECOMMENDATIONS FOR ADULT IMMUNIZATIONS The CDC's Advisory Committee on Immunization Practices (ACIP) is the main source of recommendations for administration of vaccines approved by the U.S. Food and Drug Administration (FDA) for use in children and adults in the U.S. civilian population. The ACIP is a federal advisory committee that consists of 15 voting members (experts in fields associated with immunization) appointed by the Secretary of the U.S. Department of Health and Human Services; 8 ex officio members representing federal agencies; and 30 nonvoting representatives of various liaison organizations, including major medical societies and managed-care organizations. The ACIP recommendations, which are available at *www.cdc.gov/vaccines/hcp/acip-recs/*, are harmonized to the greatest extent possible with vaccine recommendations made by other organizations, including the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, and the American College of Physicians.

ADULT IMMUNIZATION SCHEDULES Immunization schedules for adults in the United States are updated annually and can be found online (*www.cdc.gov/vaccines/schedules/hcp/adult.html*). In February, the schedules are published in *American Family Physician*, *Annals of Internal Medicine*, and *Morbidity and Mortality Weekly Report* (*www.cdc.gov/mmwr*). The adult immunization schedules for 2016 are summarized in Fig. 118-1. Additional information and specifications are contained in the footnotes to these schedules. In the time between annual publications, additions and changes to schedules are published in *Morbidity and Mortality Weekly Report*.

IMMUNIZATION PRACTICE STANDARDS

Administering immunizations to adults involves a number of processes, such as deciding whom to vaccinate, assessing vaccine contraindications and precautions, providing vaccine information statements (VISs), ensuring appropriate storage and handling of vaccines, administering vaccines, and maintaining vaccine records. In addition, provider reporting of adverse events that follow vaccination is an essential component of the vaccine safety monitoring system. In 2014, the standards for adult immunization were revised to focus on vaccinating adults at every opportunity.

Deciding Whom to Vaccinate Every effort should be made to ensure that adults receive all indicated vaccines as expeditiously as possible. When adults present for care, their immunization history should be assessed and recorded, and this information should be used to identify needed vaccinations according to the most current version of the adult immunization schedule. Decision-support tools incorporated into electronic health records can provide prompts for needed vaccinations. Standing orders, which are often used for routinely indicated vaccines (e.g., influenza and pneumococcal vaccines), permit a nurse or another approved licensed practitioner to administer

Recommended immunization schedule for adults aged 19 years or older by age group, United States, 2018

This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	19–21 years	22–26 years	27–49 years	50–64 years	≥65 years
Influenza[1]	1 dose annually				
Tdap[2] or Td[2]	1 dose Tdap, then Td booster every 10 yrs				
MMR[3]	1 or 2 doses depending on indication (if born in 1957 or later)				
VAR[4]	2 doses				
RZV[5](preferred)				2 doses RZV (preferred)	
or				or	
ZVL[5]					1 dose ZVL
HPV–Female[6]	2 or 3 doses depending on age at series initiation				
HPV–Male[6]	2 or 3 doses depending on age at series initiation				
PCV13[7]	1 dose				
PPSV23[7]	1 or 2 doses depending on indication				1 dose
HepA[8]	2 or 3 doses depending on vaccine				
HepB[9]	3 doses				
MenACWY[10]	1 or 2 doses depending on indication, then booster every 5 yrs if risk remains				
MenB[10]	2 or 3 doses depending on vaccine				
Hib[10]	1 or 3 doses depending on indication				

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with other indications

No recommendation

Recommended immunization schedule for adults aged 19 years or older by medical condition and other indications, United States, 2018

This figure should be reviewed with the accompanying footnotes. This figure and the footnotes describe indications for which vaccines, if not previously administered, should be administered unless noted otherwise.

Vaccine	Pregnancy[1-6]	Immuno-compromised (excluding HIV infection)[3-7,11]	HIV infection CD4+ count (cells/μL)[3-7,9-10] <200	HIV infection CD4+ count (cells/μL)[3-7,9-10] ≥200	Asplenia, complement deficiencies[7,10,11]	End-stage renal disease, on hemodialysis[7,9]	Heart or lung disease, alcoholism[7]	Chronic liver disease[7-9]	Diabetes[7,9]	Health care personnel[3,4,9]	Men who have sex with men[6,8,9]
Influenza[1]	1 dose annually										
Tdap[2] or Td[2]	1 dose Tdap each pregnancy	1 dose Tdap, then Td booster every 10 yrs									
MMR[3]	contraindicated			1 or 2 doses depending on indication							
VAR[4]	contraindicated			2 doses							
RZV[5](preferred)					2 doses RZV at age ≥50 yrs (preferred)						
or					or						
ZVL[5]	contraindicated				1 dose ZVL at age ≥60 yrs						
HPV–Female[6]		3 doses through age 26 yrs			2 or 3 doses through age 26 yrs						
HPV–Male[6]		3 doses through age 26 yrs			2 or 3 doses through age 21 yrs						2 or 3 doses through age 26 yrs
PCV13[7]		1 dose									
PPSV23[7]		1, 2, or 3 doses depending on indication									
HepA[8]		2 or 3 doses depending on vaccine									
HepB[9]		3 doses									
MenACWY[10]		1 or 2 doses depending on indication , then booster every 5 yrs if risk remains									
MenB[10]		2 or 3 doses depending on vaccine									
Hib[11]		3 doses HSCT recipients only			1 dose						

Recommended for adults who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended for adults with other indications

Contraindicated

No recommendation

FIGURE 118-1 Recommended adult immunization schedules, United States, 2018. Additional information, including footnotes for each vaccine, contraindications, and precautions, can be found at *https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html*. The recommendations in this schedule were approved by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Nurse-Midwives (ACNM). For complete statements by the ACIP, visit *www.cdc.gov/vaccines/hcp/acip-recs/*.

vaccines without a specific physician order, thus lowering barriers to adult immunization.

Assessing Contraindications and Precautions Before vaccination, all patients should be screened for contraindications and precautions. A *contraindication* is a condition that increases the risk of a serious adverse reaction to vaccination. A vaccine should not be administered when a contraindication is documented. For example, a history of an anaphylactic reaction to a dose of vaccine or to a vaccine component is a contraindication for further doses. A *precaution* is a condition that may increase the risk of an adverse event or that may compromise the ability of the vaccine to evoke immunity (e.g., administering measles vaccine to a person who has recently received a blood transfusion and may consequently have transient passive immunity to measles virus). Normally, a vaccine is not administered when a precaution is noted. However, situations may arise when the benefits of vaccination outweigh the estimated risk of an adverse event, and the provider may decide to vaccinate the patient despite the precaution.

In some cases, contraindications and precautions are temporary and may lead to mere deferral of vaccination until a later time. For example, moderate or severe acute illness with or without fever is generally considered a transient precaution to vaccination and results in postponement of vaccine administration until the acute phase has resolved; thus the superimposition of adverse effects of vaccination on the underlying illness and the mistaken attribution of a manifestation of the underlying illness to the vaccine are avoided. Contraindications and precautions to vaccines licensed in the United States for use in civilian adults are summarized in **Table 118-3**. It is important to recognize conditions that are *not* contraindications in order not to miss opportunities for vaccination. For example, in most cases, mild acute illness (with or without fever), a history of a mild to moderate local reaction to a previous dose of the vaccine, and breast-feeding are not contraindications to vaccination.

HISTORY OF IMMEDIATE HYPERSENSITIVITY TO A VACCINE COMPONENT A severe allergic reaction (e.g., anaphylaxis) to a previous dose of a vaccine or to one of its components is a contraindication to vaccination. While most vaccines have many components, substances to which individuals are most likely to have had a severe allergic reaction include egg protein, gelatin, and yeast. In addition, although natural rubber (latex) is not a vaccine component, some vaccines are supplied in vials or syringes that contain natural rubber latex. These vaccines can be identified by the product insert and should not be administered to persons who report a severe (anaphylactic) allergy to latex unless the benefit of vaccination clearly outweighs the risk for a potential allergic reaction. The much more common local or contact hypersensitivity to latex, such as to medical gloves (which contain synthetic latex that is not linked to allergic reactions), is *not* a contraindication to administration of a vaccine supplied in a vial or syringe that contains natural rubber latex. Vaccines routinely indicated for adults that, as of February 2015, were sometimes supplied in a vial or syringe containing natural rubber include Havrix hepatitis A vaccine (syringe); Vaqta hepatitis A vaccine (vial and syringe); Engerix-B hepatitis B vaccine (syringe); Recombivax HB hepatitis B vaccine (vial); Cervarix HPV vaccine (syringe); Fluvirin, Agriflu (syringe), and Flucelvax (syringe) influenza vaccines; Adacel and Boostrix Tdap (tetanus and diphtheria toxoids and acellular pertussis) vaccines (syringe); Td (tetanus and diphtheria toxoids) vaccines (syringe); Twinrix hepatitis A and B vaccine (syringe); Menomune meningococcal polysaccharide vaccine (vial); and Bexsero meningococcal serogroup B vaccine (syringe).

PREGNANCY Live-virus vaccines are contraindicated during pregnancy because of the hypothetical risk that vaccine virus replication will cause congenital infection or have other adverse effects on the fetus. Most live-virus vaccines, including varicella vaccine, are not secreted in breast milk; therefore, breast-feeding is not a contraindication for live-virus or other vaccines. Pregnancy is not a contraindication to administration of inactivated vaccines, but most are avoided during pregnancy because relevant safety data are limited. Two inactivated vaccines, Tdap vaccine and inactivated influenza vaccine, are routinely recommended for pregnant women in the United States. Tdap vaccine is recommended during each pregnancy, regardless of prior vaccination status, in order to prevent pertussis in neonates. Annual influenza vaccination is recommended for all persons 6 months of age and older, regardless of pregnancy status. Some other inactivated vaccines, such as meningococcal vaccines, may be given to pregnant women in certain circumstances.

IMMUNOSUPPRESSION Live-virus vaccines elicit an immune response due to replication of the attenuated (weakened) vaccine virus that is contained by the recipient's immune system. In persons with compromised immune function, enhanced replication of vaccine viruses is possible and could lead to disseminated infection with the vaccine virus. For this reason, live-virus vaccines are contraindicated for persons with severe immunosuppression, the definition of which may vary with the vaccine. Severe immunosuppression may be caused by many disease conditions, including HIV infection and hematologic or generalized malignancy. In some of these conditions, all affected persons are severely immunocompromised. In others (e.g., HIV infection), the degree to which the immune system is compromised depends on the severity of the condition, which in turn depends on the stage of disease or treatment. For example, measles-mumps-rubella (MMR) vaccine may be given to HIV-infected persons who are not severely immunocompromised. Severe immunosuppression may also be due to therapy with immunosuppressive agents, including high-dose glucocorticoids. In this situation, the dose, duration, and route of administration may influence the degree of immunosuppression.

VACCINE INFORMATION STATEMENTS

A VIS is a one-page (two-sided) information sheet produced by the CDC that informs vaccine recipients (or their parents or legal representatives) about the benefits and risks of a vaccine. VISs are mandated by the National Childhood Vaccine Injury Act (NCVIA) of 1986 and—whether the vaccine recipient is a child or an adult—must be provided for any vaccine covered by the Vaccine Injury Compensation Program. As of July 2016, vaccines that are covered by the NCVIA and that are licensed for use in adults include Td, Tdap, hepatitis A, hepatitis B, human papillomavirus, inactivated influenza, live intranasal influenza, MMR, pneumococcal conjugate, meningococcal conjugate, serogroup B meningococcal, polio, and varicella vaccines. When combination vaccines for which no separate VIS exists are given (e.g., hepatitis A and B combination vaccine), all relevant VISs should be provided. VISs also exist for some vaccines not covered by the NCVIA, such as pneumococcal polysaccharide, Japanese encephalitis, rabies, herpes zoster, typhoid, anthrax, and yellow fever vaccines. The use of these VISs is encouraged but is not mandated.

All current VISs are available on the Internet at two websites: the CDC's Vaccines & Immunizations site *(www.cdc.gov/vaccines/hcp/vis/)* and the Immunization Action Coalition's site *(www.immunize.org/vis/)*. (The latter site also includes translations of the VISs.) VISs from these sites can be downloaded and printed.

STORAGE AND HANDLING

Injectable vaccines are packaged in multidose vials, single-dose vials, or manufacturer-filled single-dose syringes. The live attenuated nasal-spray influenza vaccine is packaged in single-dose sprayers. Oral typhoid vaccine is packaged in capsules. Some vaccines, such as MMR, varicella, zoster, and meningococcal polysaccharide vaccines, come as lyophilized (freeze-dried) powders that must be reconstituted (i.e., mixed with a liquid diluent) before use. The lyophilized powder and the diluent come in separate vials. Diluents are not interchangeable but rather are specifically formulated for each type of vaccine; only the specific diluent provided by the manufacturer for each type of vaccine should be used. Once lyophilized vaccines have been reconstituted, their shelf-life is limited and they must be stored under appropriate temperature and light conditions. For example, varicella and zoster vaccines must be protected from light and administered within 30 min of reconstitution; MMR vaccine likewise must be protected from light but can be used up to 8 h after reconstitution. Single-dose vials of

TABLE 118-3 Contraindications and Precautions for Commonly Used Vaccines in Adults

VACCINE FORMULATION	CONTRAINDICATIONS AND PRECAUTIONS
All vaccines	**Contraindication**
	Severe allergic reaction (e.g., anaphylaxis) after a previous vaccine dose or to a vaccine component
	Precaution
	Moderate or severe acute illness with or without fever. Defer vaccination until illness resolves.
Td	**Precautions**
	GBS within 6 weeks after a previous dose of TT-containing vaccine
	History of Arthus-type hypersensitivity reactions after a previous dose of TD- or DT-containing vaccines (including MCV4). Defer vaccination until at least 10 years have elapsed since the last dose.
	History of severe allergic reaction to dry natural rubber (latex) (certain formulations; syringe; see text)
Tdap	**Contraindication**
	History of encephalopathy (e.g., coma or prolonged seizures) not attributable to another identifiable cause within 7 days of administration of a vaccine with pertussis components, such as DTaP or Tdap
	Precautions
	GBS within 6 weeks after a previous dose of TT-containing vaccine
	Progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy. Defer vaccination until a treatment regimen has been established and the condition has stabilized.
	History of Arthus-type hypersensitivity reactions after a previous dose of TT- or DT-containing vaccines (including MCV4). Defer vaccination until at least 10 years have elapsed since the last dose.
	History of severe allergic reaction to dry natural rubber (latex) (syringe; see text)
HPV	**Contraindications**
	History of immediate hypersensitivity to yeast (for Gardasil)
	History of severe allergic reaction to dry natural rubber (latex) (certain formulations; see text)
	Precaution
	Pregnancy (If a woman is found to be pregnant after initiation of the vaccination series, the remainder of the 3-dose regimen should be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. Exposure to Gardasil during pregnancy should be reported to Merck at 800-986-8999; exposure to Cervarix during pregnancy should be reported to GlaxoSmithKline at 888-452-9622.)
MMR	**Contraindications**
	History of immediate hypersensitivity reaction to gelatin[a] or neomycin
	Pregnancy
	Known severe immunodeficiency (e.g., hematologic and solid tumors; chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy; severe immunocompromise due to HIV infection)
	Precautions
	Recent receipt (within 11 months) of antibody-containing blood product
	History of thrombocytopenia or thrombocytopenic purpura
Varicella	**Contraindications**
	Pregnancy
	Known severe immunodeficiency
	History of immediate hypersensitivity reaction to gelatin[a] or neomycin
	Precaution
	Recent receipt (within 11 months) of antibody-containing blood product
Influenza, inactivated, injectable	**Contraindication**
	History of severe allergic reaction to dry natural rubber (latex) (certain formulations; see text)
	Precaution[b]
	History of GBS within 6 weeks after a previous influenza vaccine dose
Influenza, live attenuated nasal spray	**Contraindications**[b]
	Age ≥50 years
	Pregnancy
	Immunosuppression, including that caused by medications or by HIV infection; known severe immunodeficiency (e.g., hematologic and solid tumors; chemotherapy; congenital immunodeficiency; long-term immunosuppressive therapy; severe immunocompromise due to HIV infection)
	Certain chronic medical conditions, such as diabetes mellitus; chronic pulmonary disease (including asthma); chronic cardiovascular disease (except hypertension); renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders
	Close contact with severely immunosuppressed persons who require a protected environment, such as isolation in a bone marrow transplantation unit
	Close contact with persons with lesser degrees of immunosuppression (e.g., persons receiving chemotherapy or radiation therapy who are not being cared for in a protective environment; persons with HIV infection) is *not* a contraindication or a precaution. Health care personnel in neonatal intensive care units or oncology clinics may receive live attenuated influenza vaccine.
	Precautions
	History of GBS within 6 weeks of a previous influenza vaccine dose
	Receipt of specific antiviral agents (i.e., amantadine, rimantadine, zanamivir, or oseltamivir) within 48 h before vaccination

(*Continued*)

TABLE 118-3 Contraindications and Precautions for Commonly Used Vaccines in Adults (Continued)

VACCINE FORMULATION	CONTRAINDICATIONS AND PRECAUTIONS
Pneumococcal polysaccharide	None, other than those listed for all vaccines
Pneumococcal conjugate	None, other than those listed for all vaccines
Hepatitis A	**Contraindication** History of severe allergic reaction to dry natural rubber (latex) (syringe; see text)
Hepatitis B	**Contraindications** History of immediate hypersensitivity to yeast History of severe allergic reaction to dry natural rubber (latex) (syringe; see text)
Meningococcal conjugate	None, other than those listed for all vaccines
Meningococcal polysaccharide	**Contraindication** History of severe allergic reaction to dry natural rubber (latex)
Serogroup B meningococcal	**Contraindication** History of severe allergic reaction to dry natural rubber (latex) (certain formulations; syringe; see text)
Zoster	**Contraindications** Pregnancy Known severe immunodeficiency History of immediate hypersensitivity reaction to gelatin[a] or neomycin **Precaution** Receipt of specific antiviral agents (i.e., acyclovir, famciclovir, or valacyclovir) within 24 h before vaccination

[a]Extreme caution must be exercised in administering MMR, varicella, or zoster vaccine to persons with a history of anaphylactic reaction to gelatin or gelatin-containing products. Before administration, skin testing for sensitivity to gelatin can be considered. However, no specific protocols for this purpose have been published. [b]History of severe allergic reaction (e.g., anaphylaxis) to egg is a labeled contraindication to the use of inactivated influenza vaccine and live attenuated influenza vaccine. However, CDC's Advisory Committee on Immunization Practices recommends that any licensed, recommended, and appropriate inactivated influenza vaccine or recombinant influenza vaccine may be administered to persons with egg allergy of any severity *(www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html).*

Abbreviations: DT, diphtheria toxoid; DTaP, diphtheria, tetanus, and pertussis; GBS, Guillain-Barré syndrome; HPV, human papillomavirus; MCV4, quadrivalent meningococcal conjugate vaccine; MMR, measles, mumps, and rubella; Td, tetanus and diphtheria toxoids; Tdap, tetanus and diphtheria toxoids and acellular pertussis; TT, tetanus toxoid.

meningococcal polysaccharide vaccine must be used within 30 min of reconstitution, while multidose vials must be used within 35 days.

Vaccines are stored either at refrigerator temperature (2–8°C) or at freezer temperature (–15°C or colder). In general, inactivated vaccines (e.g., inactivated influenza, pneumococcal polysaccharide, and meningococcal conjugate vaccines) are stored at refrigerator temperature, while vials of lyophilized-powder live-virus vaccines (e.g., varicella, zoster, and MMR vaccines) are stored at freezer temperature. Diluents for lyophilized vaccines may be stored at refrigerator or room temperature. Live attenuated influenza vaccine—a live-virus liquid formulation administered by nasal spray—is stored at refrigerator temperature.

Vaccine storage and handling errors can result in the loss of vaccines worth millions of dollars, and administration of improperly stored vaccines may elicit inadequate immune responses in patients. To improve the standard of vaccine storage and handling practices, the CDC has published detailed guidance (available at *www.cdc.gov/vaccines/hcp/admin/storage/toolkit/storage-handling-toolkit.pdf*). For vaccine storage, the CDC recommends stand-alone units—i.e., self-contained units that either refrigerate or freeze but do not do both—as these units maintain the required temperatures better than combination refrigerator/freezer units. Dormitory-style combined refrigerator/freezer units should never be used for vaccine storage.

The temperature of refrigerators and freezers used for vaccine storage must be monitored and recorded at least twice each workday. Ideally, continuous thermometers that measure and record temperature all day and all night are used, and minimal and maximal temperatures are read and documented each workday. The CDC recommends the use of calibrated digital thermometers with a probe in thermal-buffered material; more detailed information on specifications of storage units and temperature-monitoring devices is provided at the link given above.

ADMINISTRATION OF VACCINES

Most parenteral vaccines recommended for routine administration to adults in the United States are given by either the IM or the SC route; one influenza vaccine formulation approved for use in adults 18–64 years of age is given intradermally. Live-virus vaccines such as varicella, zoster, and MMR are given SC. Most inactivated vaccines are given IM. The 23-valent pneumococcal polysaccharide vaccine may be given either IM or SC, but IM administration is preferred because it is associated with a lower risk of injection-site reactions.

Vaccines given to adults by the SC route are administered with a 5/8-inch needle into the upper outer-triceps area. Vaccines administered to adults by the IM route are injected into the deltoid muscle **(Fig. 118-2)** with a needle whose length should be selected on the basis of the recipient's sex and weight to ensure adequate penetration into the muscle. Current guidelines indicate that, for men and women weighing <152 lbs (<70 kg), a 1-inch needle is sufficient; for women weighing 152–200 lbs (70–90 kg) and men weighing 152–260 lbs (70–118 kg), a 1- to 1.5-inch needle is needed; and for women weighing >200 lbs (>90 kg) and men weighing >260 lbs (>118 kg), a 1.5-inch needle is required. Additional illustrations of vaccine injection locations and techniques may be found at *www.immunize.org/catg.d/p2020a.pdf*.

FIGURE 118-2 Technique for IM administration of vaccine. *(Photo credit: James Gathany, Centers for Disease Control and Prevention; accessible at Public Health Image Library, www.cdc.gov. PHIL ID#9420.)*

Aspiration, the process of pulling back on the plunger of the syringe after skin penetration but prior to injection, is not necessary because no large blood vessels are present at the recommended vaccine injection sites.

Multiple vaccines can be administered at the same visit; indeed, administration of all needed vaccines at one visit is encouraged. Studies have shown that vaccines are as effective when administered simultaneously as they are individually, and simultaneous administration of multiple vaccines is not associated with an increased risk of adverse effects. If more than one vaccine must be administered in the same limb, the injection sites should be separated by 1–2 inches so that any local reactions can be differentiated. If a vaccine and an immune globulin preparation are administered simultaneously (e.g., Td vaccine and tetanus immune globulin), a separate anatomic site should be used for each injection.

For certain vaccines (e.g., HPV vaccine and hepatitis B vaccine), multiple doses are required for an adequate and persistent antibody response. The recommended vaccination schedule specifies the interval between doses. Many adults who receive the first dose in a multiple-dose vaccine series do not complete the series or do not receive subsequent doses within the recommended interval; this lack of adherence to protocol compromises vaccine efficacy and/or the duration of protection. Providers should implement recall systems that will prompt patients to return for subsequent doses in a vaccination series at the appropriate intervals. With the exception of oral typhoid vaccination, an interruption in the schedule does not require restarting of the entire series or the addition of extra doses.

Syncope may follow vaccination, especially in adolescents and young adults. Serious injuries, including skull fracture and cerebral hemorrhage, have occurred. Adolescents and adults should be seated or lying down during vaccination. The majority of reported syncope episodes after vaccination occur within 15 min. The ACIP recommends that vaccine providers strongly consider observing patients, particularly adolescents, with patients seated or lying down for 15 min after vaccination. If syncope develops, patients should be observed until the symptoms resolve.

Anaphylaxis is a rare complication of vaccination. All facilities providing immunizations should have an emergency kit containing aqueous epinephrine for administration in the event of a systemic anaphylactic reaction.

MAINTENANCE OF VACCINE RECORDS

All vaccines administered should be fully documented in the patient's permanent medical record. Documentation should include the date of administration, the name or common abbreviation of the vaccine, the vaccine lot number and manufacturer, the administration site, the VIS edition, the date the VIS was provided, and the name, address, and title of the person who administered the vaccine. Increasing use of two-dimensional bar codes on vaccine vials and syringes that can be scanned for data entry into compatible electronic medical records and immunization information systems may facilitate more complete and accurate recording of required information.

VACCINE SAFETY MONITORING AND ADVERSE EVENT REPORTING

Prelicensure Evaluations of Vaccine Safety Before vaccines are licensed by the FDA, they are evaluated in clinical trials with volunteers. These trials are conducted in three progressive phases. Phase 1 trials are small, usually involving fewer than 100 volunteers. Their purposes are to provide a basic evaluation of safety and to identify common adverse events. Phase 2 trials, which are larger and may involve several hundred participants, collect additional information on safety and are usually designed to evaluate immunogenicity as well. Data gained from phase 2 trials can be used to determine the composition of the vaccine, the number of doses required, and a profile of common adverse events. Vaccines that appear promising are evaluated in phase 3 trials, which typically involve several hundred to several thousand volunteers and are generally designed to demonstrate vaccine efficacy and provide additional information on vaccine safety.

Postlicensure Monitoring of Vaccine Safety After licensure, a vaccine's safety is assessed by several mechanisms. The NCVIA of 1986 requires health care providers to report certain adverse events that follow vaccination. As a mechanism for that reporting, the Vaccine Adverse Event Reporting System (VAERS) was established in 1990 and is jointly managed by the CDC and the FDA. This safety surveillance system collects reports of adverse events associated with vaccines currently licensed in the United States. *Adverse events* are defined as untoward events that occur after immunization and that might be caused by the vaccine product or vaccination process. While the VAERS was established in response to the NCVIA, any adverse event following vaccination—whether in a child or an adult, and whether or not it is believed to have actually been caused by vaccination—may be reported through the VAERS. The adverse events that health care providers are required to report are listed in the reportable-events table on the VAERS website at *vaers.hhs.gov/reportable.htm*. During 2011–2014, approximately 30,000 VAERS reports were filed annually, with ~7% reporting serious events resulting in hospitalization, life-threatening illness, disability, or death.

Anyone can file a VAERS report, including health care providers, manufacturers, and vaccine recipients or their parents or guardians. VAERS reports may be submitted online (*https://vaers.hhs.gov/reportevent.html*) or by completing a paper form requested by email (info@vaers.org) or phone (800-822-7967). The VAERS form asks for the following information: the type of vaccine received; the timing of vaccination; the time of onset of the adverse event; and the recipient's current illnesses or medications, history of adverse events following vaccination, and demographic characteristics (e.g., age and sex). This information is entered into a database. The individual who reported the adverse event then receives a confirmation letter by mail with a VAERS identification number that can be used if additional information is submitted later. In selected cases of serious adverse reaction, the patient's recovery status may be followed up at 60 days and 1 year after vaccination. The FDA and the CDC have access to VAERS data and use this information to monitor vaccine safety and conduct research studies. VAERS data (minus personal information) are also available to the public.

While the VAERS provides useful information on vaccine safety, this passive reporting system has important limitations. One is that events following vaccination are merely reported; the system cannot assess whether a given type of event occurs more often than expected after vaccination. A second is that event reporting is incomplete and is biased toward events that are believed to be more likely to be due to vaccination and that occur relatively soon after vaccination. To obtain more systematic information on adverse events occurring in both vaccinated and unvaccinated persons, the Vaccine Safety Datalink project was initiated in 1991. Directed by the CDC, this project includes nine managed-care organizations in the United States; member databases include information on immunizations, medical conditions, demographics, laboratory results, and medication prescriptions. The Department of Defense oversees a similar system monitoring the safety of immunizations among active-duty military personnel. In addition, postlicensure evaluations of vaccine safety may be conducted by the vaccine manufacturer. In fact, such evaluations are often required by the FDA as a condition of vaccine licensure.

CONSUMER ACCESS TO AND DEMAND FOR IMMUNIZATION

By removing barriers to the consumer or patient, providers and health care institutions can improve vaccine use. Financial barriers have traditionally been important constraints, particularly among uninsured adults. Even for insured adults, out-of-pocket costs associated with newer, more expensive adult vaccines (e.g., zoster vaccine) are an obstacle to be overcome. After influenza vaccine was included by Medicare for all beneficiaries in 1993, coverage among persons ≥65 years of age doubled (from ~30% in 1989 to >60% in 1997). Other strategies that enhance patients' access to vaccination include extended office hours (e.g., evening and weekend hours) and scheduled vaccination-only clinics where waiting times are reduced. Provision of vaccines outside

the "medical home" (e.g., through occupational clinics, universities, pharmacies, and retail settings) can expand access for adults who do not make medical visits frequently. Increasing proportions of adults are being vaccinated in these settings.

Health promotion efforts aimed at increasing the demand for immunization are common. Direct-to-consumer advertising by pharmaceutical companies has been used for some newer adolescent and adult vaccines. Efforts to raise consumer demand for vaccines have not increased immunization rates unless implemented in conjunction with other strategies that target strengthening of provider practices or reduction of consumer barriers. Attitudes and beliefs related to vaccination can be considerable impediments to consumer demand. Many adults view vaccines as important for children but are less familiar with vaccinations targeting disease prevention in adults. Several vaccines are recommended for adults with certain medical risk factors, but self-identification as a high-risk individual is relatively rare. Communication research suggests that adults are motivated to get vaccines to protect their own health and many would get vaccinated to protect loved ones. Adults with chronic conditions are more likely to be aware that they need to protect their own health. Some vaccines are explicitly recommended for persons at relatively low risk of serious complications, with the goal of reducing the risk of transmission to higher-risk contacts. For example, for protection of newborns, vaccinations against influenza and pertussis are recommended for pregnant women.

STRATEGIES FOR PROVIDERS AND HEALTH CARE FACILITIES

Recommendation from the Provider Health care providers can have great influence on patients with regard to immunization. A recommendation from a doctor or nurse carries more weight than do recommendations from professional societies or endorsements by celebrities. Providers should be well informed about vaccine risks and benefits so that they can address patients' common concerns. The CDC, the American College of Physicians, and the American Academy of Family Physicians review and update the schedule for adult immunization on an annual basis and have developed educational materials to facilitate provider–patient discussions about vaccination (*www.cdc.gov/vaccines/hcp.htm*).

System Supports Medical offices can incorporate a variety of methods to ensure that providers consistently offer specific immunizations to patients with indications for specific vaccines. Decision-support tools have been incorporated into some electronic health records to alert the provider when specific vaccines are indicated. Manual or automated reminders and standing orders have been discussed (see "Deciding Whom to Vaccinate," above) and have consistently improved vaccination coverage in both office and hospital settings. Most clinicians' estimates of their own performance diverge from objective measurements of their patients' immunization coverage; quantitative assessment and feedback have been shown in pediatric and adolescent practices to increase immunization performance significantly. Some health plans have instituted incentives for providers with high rates of immunization coverage. Specialty providers, including obstetrician–gynecologists, may be the only providers serving some high-risk patients with indications for selected vaccines (e.g., Tdap, influenza, or pneumococcal polysaccharide vaccine).

Immunization Requirements Vaccination against selected communicable diseases is required for attendance at many universities and colleges as well as for service in the U.S. military or in some occupational settings (e.g., child care, laboratory, veterinary, and health care). Immunizations are recommended and sometimes required for travel to certain countries **(Chap. 119)**.

Vaccination of Health Care Staff A particular area of focus for medical settings is vaccination of health care workers, including those with and without direct patient-care responsibilities. The Joint Commission (which accredits health care organizations), the CDC's Healthcare Infection Control Practices Advisory Committee, and the ACIP all recommend influenza vaccination of all health care personnel; recommendations also focus on requiring documentation of declination for providers who do not accept annual influenza vaccination. As part of their participation in the Centers for Medicare and Medicaid Services' Hospital Inpatient Quality Reporting program, acute-care hospitals are required to report the proportion of their health care personnel who have received seasonal influenza vaccine. Some institutions and jurisdictions have added mandates on influenza vaccination of health care workers and have expanded on earlier requirements related to vaccination or proof of immunity for hepatitis B, measles, mumps, rubella, and varicella.

VACCINATION IN NONMEDICAL SETTINGS

Receipt of vaccination in medical offices is most frequent among young children and adults ≥65 years of age. Patients in these age groups make more office visits and are more likely to receive care in a consistent "medical home" than are older children, adolescents, and nonelderly adults. Vaccination outside the medical home can expand access to those whose health care visits are limited and reduce the burden on busy clinical practices. In some locations, financial constraints related to inventory and storage requirements have led providers to stock few or no vaccines. Outside private office and hospital settings, vaccination may also occur at health department venues, workplaces, retail sites (including pharmacies and supermarkets), and schools or colleges.

When vaccines are given in nonmedical settings, it remains important for standards of immunization practice to be followed. Consumers should be provided with information on how to report adverse events (e.g., via provision of a VIS), and procedures should ensure that documentation of vaccine administration is forwarded to the primary care provider and the state or city public health immunization registry. Detailed documentation may be required for employment, school attendance, and travel. Personalized health records can help consumers keep track of their immunizations, and some occupational health clinics have incorporated automated immunization reports that help employees stay up-to-date with recommended vaccinations. Some pharmacy chain establishments are using automated systems to report immunization information to the state or local immunization information system.

PERFORMANCE MONITORING

Tracking of immunization coverage at national, state, institution, and practice levels can yield feedback to practitioners and programs and facilitate quality improvement. Healthcare Effectiveness Data and Information Set (HEDIS) measures related to adult immunization facilitate comparison of health plans. The CDC's National Immunization Survey and National Health Interview Survey provide selected information on immunization coverage among adults and track progress toward achievement of Healthy People 2020 targets for immunization coverage. Influenza and pneumococcal vaccine coverage rates have been higher among persons ≥65 years of age (60–70%) than among high-risk 18- to 64-year-olds. Figures on state-specific immunization coverage with pneumococcal polysaccharide and influenza vaccines (as measured through the CDC's Behavioral Risk Factor Surveillance System) reveal substantial geographic variation in coverage. There are persistent disparities in adult immunization coverage rates between whites and racial and ethnic minorities. In contrast, racial and economic disparities in immunization of young children have been dramatically reduced during the past 20 years. Much of this progress is attributed to the Vaccines for Children Program, which since 1994 has entitled uninsured children to receive free vaccines.

FUTURE TRENDS

Although most vaccines developed in the twentieth century targeted common acute infectious diseases of childhood, more recently developed vaccines prevent chronic conditions prevalent among adults. Hepatitis B vaccine prevents hepatitis B–related cirrhosis and hepatocellular carcinoma, and HPV vaccine prevents some types of cervical cancer, genital warts, and anogenital cancers and may also prevent some oropharyngeal cancers. A new herpes zoster subunit vaccine that

was licensed in 2017 should substantially improve protection against zoster and postherpetic neuralgia. New targets of vaccine development and research may further broaden the definition of vaccine-preventable disease. Research is ongoing on vaccines to prevent insulin-dependent diabetes mellitus, nicotine addiction, and Alzheimer's disease. Expanding strategies for vaccine development are incorporating molecular approaches such as DNA, vector, and peptide vaccines. New technologies, such as the use of transdermal and other needle-less routes of administration, are being applied to vaccine delivery.

FURTHER READING

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119 Health Recommendations for International Travel

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According to the United Nations World Tourism Organization, international tourist arrivals grew dramatically from 25 million in 1950 to >1 billion in 2016; limited data suggest that the only areas without the growth of tourism were in Africa. Not only are more people traveling; travelers are seeking more exotic and remote destinations. In addition to tourism travel, travel across borders has increased in other sectors as well—e.g., for visits with friends and relatives (VFRs) in travelers' places of birth, for immigration, for business, and for missionary and volunteer work. Travel from industrialized to developing regions has been increasing, with Asia and the Pacific and the Middle East the emerging destinations. **Figure 119-1** summarizes the monthly incidence of health problems during travel in developing countries. Studies continue to show that 50–75% of short-term travelers to the tropics or subtropics report some health impairment. Most of these health problems are minor: only 5% require medical attention, and <1% require hospitalization. Although infectious agents contribute substantially to morbidity among travelers, these pathogens account for only ~1% of deaths in this population. Cardiovascular disease and injuries are the most frequent causes of death among travelers from the United States, accounting for 49 and 22% of deaths, respectively. Age-specific rates of death due to cardiovascular disease are similar among travelers and non-travelers. In contrast, rates of death due to injury (the majority from motor vehicle, drowning, or aircraft accidents) are several times higher among travelers. Motor vehicle accidents account for >40% of travelers' deaths that are not due to cardiovascular disease or preexisting illness.

GENERAL ADVICE

Health maintenance recommendations are based not only on the traveler's destination but also on assessment of risk, which is determined by such variables as health status, specific itinerary, purpose of travel, season, and lifestyle during travel. Detailed information regarding country-specific risks and recommendations may be obtained from the Centers for Disease Control and Prevention (CDC) publication *Health Information for International Travel* (available at *www.cdc.gov/travel*).

Fitness for travel is an issue of growing concern in view of the increased numbers of elderly and chronically ill individuals journeying to exotic destinations (see "Travel and Special Hosts," below). Since most commercial aircraft are pressurized to 2500 m (8000 ft) above sea level (corresponding to a PaO_2 of ~55 mmHg), individuals with serious cardiopulmonary problems or anemia should be evaluated before travel. In addition, those who have recently had surgery, a myocardial infarction, a cerebrovascular accident, or a deep-vein thrombosis may be at high risk for adverse events during flight. A summary of current recommendations regarding fitness to fly has been published by the Aerospace Medical Association Air Transport Medicine Committee (*www.asma.org/publications/medical-publications-for-airline-travel*). A pretravel health assessment is advisable for individuals considering particularly adventurous recreational activities, such as mountain climbing and scuba diving.

IMMUNIZATIONS FOR TRAVEL

Immunizations for travel fall into three broad categories: *routine* (childhood/adult immunizations and boosters that are important regardless of travel), *required* (immunizations that are mandated by international regulations for entry into certain areas or for border crossings), and *recommended* (immunizations that are desirable because of travel-related risks). Required and recommended vaccines commonly given to travelers are listed in **Table 119-1**.

Routine Immunizations • DIPHTHERIA, TETANUS, AND POLIO

Diphtheria **(Chap. 145)** continues to be a problem worldwide. Large outbreaks have occurred in countries that do not have rigorous vaccination programs or that have reduced their public vaccination programs. Serologic surveys show that tetanus **(Chap. 147)** antibodies are lacking in many North Americans, especially in women aged >50. With the recent increase in pertussis among adults, the diphtheria–tetanus–acellular pertussis (Tdap) combination is now recommended for adults as a once-only replacement for the 10-year tetanus–diphtheria (Td) booster.

The risk of polio **(Chap. 199)** to the international traveler is extremely low despite challenges faced by eradication programs. Wild-type poliovirus has been eradicated from most areas of the world; Nigeria, Afghanistan, and Pakistan are the only countries where polio continues to be endemic. Some countries may actually require travelers who have been in country for >4 weeks to show proof on exiting that they have received polio vaccine within the previous year. (Because this list of countries changes, providers should check the CDC travelers' health website at *www.cdc.gov/travel*.) Studies in the United States suggest that 12% of adult travelers are unprotected against at least one poliovirus serogroup. Foreign travel offers an ideal opportunity to have polio immunization updated.

MEASLES Measles (rubeola) continues to be a major cause of morbidity and death in the developing world **(Chap. 200)**. Several outbreaks of measles in the United States and Canada have been linked to imported cases, especially from Europe, where large outbreaks have occurred. The group at highest risk consists of persons born after 1956 and vaccinated before 1980, in many of whom primary vaccination failed. The measles–mumps–rubella (MMR) vaccine is typically used; its coverage of rubella also addresses a growing concern in some areas of Eastern Europe and Asia.

INFLUENZA Influenza **(Chap. 195)**—possibly the most common vaccine-preventable infection in travelers—occurs year-round in the tropics and during the summer months in the Southern Hemisphere (coinciding with the winter months in the Northern Hemisphere). One prospective study showed that influenza developed in 1% of travelers to Southeast Asia per month of stay. Annual vaccination should be considered for all travelers who do not have a contraindication. The speed of global spread of the pandemic H1N1 virus in 2009 illustrated why influenza immunization is so important for travelers.

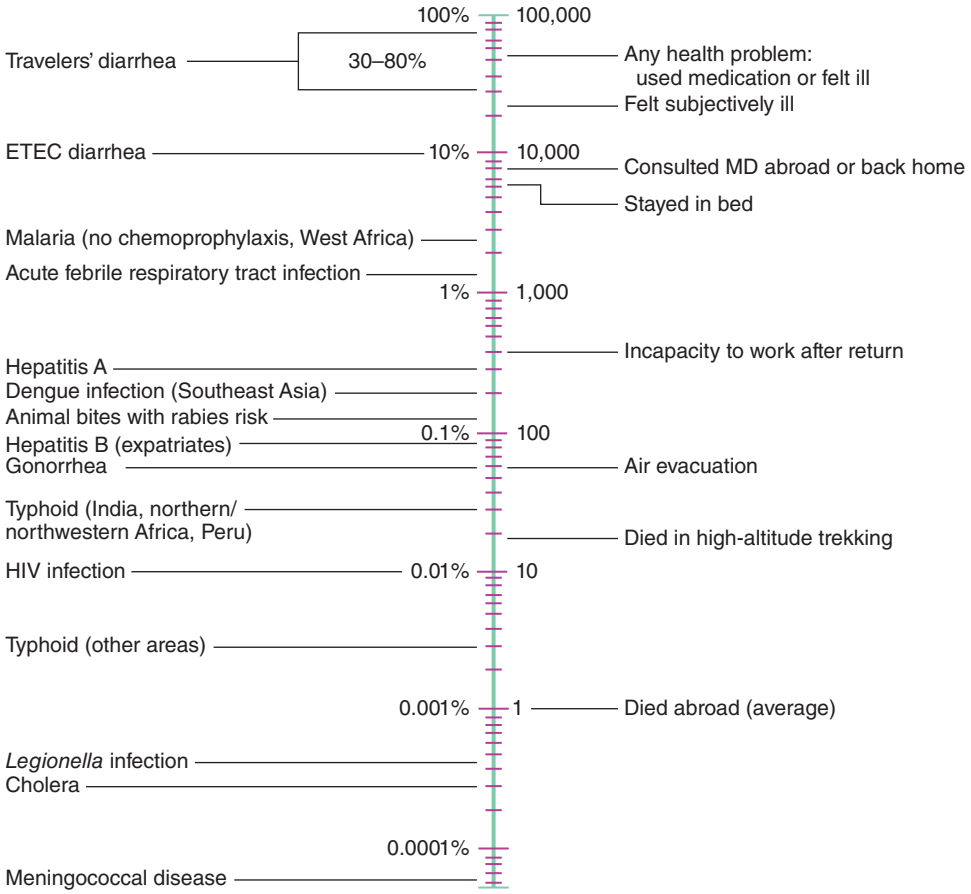

FIGURE 119-1 Monthly incidence rates of health problems during stays in developing countries. ETEC, enterotoxigenic *Escherichia coli. (From R Steffen et al: Int J Antimicrob Agents 21:89, 2003. Reprinted with permission from Elsevier Science B.V. and International Society of Chemotherapy. https://www.sciencedirect.com/journal/international-journal-of-antimicrobial-agents.)*

PNEUMOCOCCAL INFECTION Regardless of travel, pneumococcal vaccine (Chap. 141) should be administered routinely to all persons aged >65 and to persons between the ages of 2 and 64 who are at high risk of serious infection, including those with diabetes mellitus; those with chronic heart, lung, or kidney disease; those who have been splenectomized or are immunocompromised; and those who have sickle cell disease.

Required Immunizations

• **YELLOW FEVER** Documentation of vaccination against yellow fever (Chap. 204) may be required or recommended as a condition for entry into or passage through countries of sub-Saharan Africa and equatorial South America, where the disease is endemic or epidemic, or (according to the International Health Regulations [IHR]) for entry into countries at risk of having the infection introduced. In 2014, the World Health Organization (WHO) adopted a recommendation to remove the 10-year booster-dose requirement from the IHR as of June 2016. Thus one dose of yellow fever vaccine and a completed International Certificate of Vaccination or Prophylaxis should be valid for the lifetime of the vaccinee. Some countries have already adopted this change, as noted on the CDC's website under the yellow fever vaccine requirements on each country's destination page. However, it is uncertain when and whether all countries with yellow fever vaccination requirements will adopt this change. Some countries may still require a booster after 10 years, and a booster may be recommended for other travelers as well. This vaccine is given only by state-authorized yellow fever centers, and its administration must be documented on an official International Certificate of Vaccination or Prophylaxis. A registry of U.S. clinics that provide the vaccine is available from the CDC (*www.cdc.gov/travel*). Data suggest that fewer than 50% of travelers entering areas endemic for yellow fever are immunized, and lack of coverage is a serious problem. Severe adverse events associated with this vaccine have increased in incidence. First-time vaccine recipients may present with a syndrome characterized as either neurotropic (1 case per 125,000 doses) or viscerotropic (overall, 1 case per 250,000 doses; among persons 60–69 years of age, 1 case per 100,000 doses; and among persons ≥70 years of age, 1 case per 40,000 doses). Immunosuppression and thymic disease increase the risk of these adverse events (*https://www.cdc.gov/vaccines/hcp/vis/vis-statements/yf.pdf*).

MENINGOCOCCAL MENINGITIS Protection against meningitis is required for entry into Saudi Arabia during the Hajj (Chap. 150). Hajj visas cannot be issued without proof of meningococcal vaccination. All adults and children >2 years of age must have received a single dose of quadrivalent A/C/Y/W-135 vaccine and must show proof of vaccination on a valid International Certificate of Vaccination or Prophylaxis.

Recommended Immunizations

• **HEPATITIS A AND B** Hepatitis A (Chap. 332) is one of the most common vaccine-preventable infections of travelers. Older data demonstrated a risk six times greater for travelers who stray from the usual tourist routes. The mortality rate for hepatitis A increases with age, reaching almost 2% among individuals aged >50. Of the four hepatitis A vaccines currently available in North America (two in the United States), all are interchangeable and have an efficacy of >95%. Hepatitis A vaccine is currently given to all children in the United States. Since the most frequently identified risk factor for hepatitis A in the United States is international travel, and since morbidity and mortality risk increase with age, it seems appropriate that all adults be immune prior to travel.

Long-stay overseas workers appear to be at considerable risk for hepatitis B infection (Chap. 332), although even short-term travelers can acquire this infection if they indulge in behaviors that place them at risk. The recommendation that all travelers be immunized against hepatitis B before departure is supported by two studies showing that 17% of the assessed travelers who received health care abroad had some type of injection; according to the WHO, nonsterile equipment is used for up to 75% of all injections given in parts of the developing world. A 3-week accelerated schedule of the combined hepatitis A and B vaccine has been approved in the United States. Although no data are available on the specific risk of infection with hepatitis B virus among U.S. travelers, ~240 million people in the world have chronic infection. All children and adolescents in the United States are immunized against this illness. Hepatitis B vaccination should be considered for all travelers.

TYPHOID AND PARATYPHOID FEVER Most cases of typhoid fever in North America are due to travel, with ~300 cases seen per year in the United States. The attack rate for typhoid fever (Chap. 160) is 1 case per 30,000 travelers per month of travel to the developing world. In the United States, >80% of reports of typhoid fever and >90% of reports of paratyphoid fever caused by *Salmonella* Paratyphi A are in travelers to southern Asia. One group at particular risk are immigrants and their families who have returned to their homelands for VFRs. Between 1999 and 2006 in the United States, 66% of imported cases of *S. typhi* infection involved the latter group. Unfortunately, data show that both *S. typhi* and *S. paratyphi* A have become increasingly resistant to fluoroquinolone antibiotics (especially strains acquired on the Indian subcontinent). Both of the available vaccines—one oral (live) and the other injectable (polysaccharide)—have efficacy rates of ~70% but are not protective against Paratyphi disease. In some countries, a combined hepatitis A/typhoid vaccine is available.

TABLE 119-1 Vaccines Commonly Used for Travel in Adults

VACCINE	PRIMARY SERIES	BOOSTER INTERVAL
Cholera: Dukoral[a] (inactivated whole-cell recombinant subunit; available in Canada and Europe), Vaxchora (live attenuated; available in U.S.)	1 dose	2 years for Dukoral; unknown for Vaxchora
Hepatitis A (Havrix), 1440 enzyme immunoassay U/mL	2 doses, 6–12 months apart, IM	None required
Hepatitis A (VAQTA, AVAXIM, EPAXAL)	2 doses, 6–18 months apart, IM	None required
Hepatitis A/B combined (Twinrix)	3 doses at 0, 1, and 6 months or 0, 7, and 21–30 days plus booster at 1 year, IM	None required *except* 12 months (once only, for accelerated schedule)
Hepatitis B (Engerix B): accelerated schedule	3 doses at 0, 1, and 2 months or 0, 7, and 21 days plus booster at 1 year, IM	12 months, once only
Hepatitis B (Engerix B or Recombivax): standard schedule	3 doses at 0, 1, and 6 months, IM	None required
Japanese encephalitis (Ixiaro)	2 doses at 0 and 28 days, IM	>1 year after primary series (optimal booster schedule not yet determined)
Meningococcus, quadrivalent (Menomune [polysaccharide], Menactra, Menveo [conjugate])	1 dose (Menactra/Menveo, IM; Menomune, SC)	>3 years (optimal booster schedule not yet determined)
Rabies human diploid cell vaccine (Imovax), rabies vaccine absorbed (RVA), or purified chick embryo cell vaccine (RabAvert)	3 doses at 0, 7, and 21 or 28 days, IM	None required except with exposure
Typhoid Ty21a, oral live attenuated (Vivotif)	1 capsule every other day × 4 doses	5 years
Typhoid Vi capsular polysaccharide, injectable (Typhim Vi)	1 dose IM	2 years
Yellow fever	1 dose SC	1 lifetime dose

[a]Cross-protects against enterotoxigenic *Escherichia coli* and provides 30–50% protection against travelers' diarrhea.

MENINGOCOCCAL MENINGITIS Although the risk of meningococcal disease among travelers has not been quantified, it is likely to be higher among travelers who live with poor indigenous populations in overcrowded conditions (Chap. 150). Because of its enhanced ability to prevent nasal carriage (compared with the older polysaccharide vaccine), a quadrivalent conjugate vaccine is the product of choice (regardless of age) for immunization of persons traveling to sub-Saharan Africa during the dry season or to areas of the world where there are epidemics. The vaccine, which protects against serogroups A, C, Y, and W-135, has an efficacy rate of >90%. Except in rare outbreak situations, there is no role for meningococcal serogroup B immunization of travelers.

JAPANESE ENCEPHALITIS The risk of Japanese encephalitis (Chap. 204), an infection transmitted by night-biting mosquitoes in rural Asia and Southeast Asia, can be as high as ~1 case per 5000 travelers per month of stay in an endemic area. Most infections are asymptomatic; however, among the very small proportion of infected persons who become ill, death and severe neurologic sequelae are common. Most symptomatic infections in recent years have occurred in tourists to Southeast Asia, of whom one-third had traveled for <1 month in an endemic area. The vaccine efficacy rate is >90%, and vaccination is recommended by the CDC for persons staying >1 month in rural endemic areas or for shorter periods if their activities in these areas (e.g., camping, bicycling, hiking) will increase exposure risk. Recent studies suggest that the vaccine schedule (off-label) may be accelerated to 2 doses within 1 week for last-minute travelers.

CHOLERA The risk of cholera (Chap. 163) is extremely low, with ~1 case per 500,000 journeys to endemic areas. A live oral cholera vaccine was recently approved in the United States by the U.S. Food and Drug Administration (FDA). Its use should be considered for aid and health care workers in refugee camps or in disaster-stricken/war-torn areas.

RABIES Domestic animals, primarily dogs, are the major transmitters of rabies in developing countries (Chap. 203). Several studies have shown that the risk of rabies posed by a dog bite in an endemic area translates into 1–3.6 cases per 1000 travelers per month of stay. Countries where canine rabies is highly endemic include Mexico, the Philippines, Sri Lanka, India, Thailand, China, and Vietnam. The two vaccines available in the United States provide >90% protection. Rabies vaccine is recommended for long-stay travelers, particularly children (who tend to play with animals and may not report bites), and for persons who may be occupationally exposed to rabies in endemic areas; however, in a large-scale study, almost 50% of potential exposures occurred within the first month of travel. Even after receipt of a preexposure rabies vaccine series, two postexposure doses are required; rabies immune globulin (which is often unavailable in developing countries) is not necessary.

PREVENTION OF MALARIA AND OTHER INSECT-BORNE DISEASES

It is estimated that >30,000 American and European travelers develop malaria each year (Chap. 219). The risk to travelers is highest in Oceania and sub-Saharan Africa (estimated at 1:5 and 1:50 per month of stay, respectively, among persons not using chemoprophylaxis); intermediate in malarious areas on the Indian subcontinent and in Southeast Asia (1:250–1:1000 per month); and low in South and Central America (1:2500–1:10,000 per month). Malaria surveillance in the United States from 2012 to 2013 showed a 2% increase in cases, and annual increases have been reported since the early 1970s. Of the more than 1700 cases reported in 2014, 66% were due to *Plasmodium falciparum*; of cases in which a purpose of travel was reported, 58% were associated with VFRs. Patients traveling for VFRs are at the highest risk of acquiring malaria and may die of the disease if their immunity has waned after living outside an endemic area. There were five deaths due to malaria in the United States in 2014. Only 8% of those infected had adhered to CDC guidelines for chemoprophylaxis. With the worldwide increase in chloroquine- and multidrug-resistant falciparum malaria, decisions about chemoprophylaxis have become more difficult. Table 119-2 lists the currently recommended drugs of choice for prophylaxis of malaria, by destination.

Several studies indicate that fewer than 50% of travelers adhere to basic recommendations for malaria prevention. Keys to the prevention

TABLE 119-2 Malaria Chemosuppressive Regimens, According to Geographic Area[a]

GEOGRAPHIC AREA	DRUG OF CHOICE[b]	ALTERNATIVES
Central America (north of Panama), Iraq, Turkey, northern Argentina, and Paraguay	Chloroquine	Atovaquone-proguanil[c] Doxycycline Mefloquine Primaquine
South America (but not northern Argentina or Paraguay, where chloroquine may be used); Central America (only Panama east of the Canal); Asia (including Southeast Asia); Africa; and Oceania	Doxycycline Atovaquone-proguanil[c] Mefloquine	
Thai–Myanmar and Thai–Cambodian borders, central Vietnam	Atovaquone-proguanil[c] Doxycycline	

[a]See the CDC's *Health Information for International Travel 2018* (*www.cdc.gov/travel*). [b]In all areas where chloroquine can still be used, the other drugs listed may be used as alternatives. [c]Malarone.

Note: See also Chap. 219.

of malaria include both personal protection measures against mosquito bites (especially between dusk and dawn) and malaria chemoprophylaxis. The former measures entail the use of DEET or picaridin-containing insect repellents, permethrin-impregnated bed nets and clothing, screened sleeping accommodations, and protective clothing. Thus, in regions where infections such as malaria are transmitted, protective products are recommended, even for children and infants. In general, higher concentrations of any active ingredient provide a longer duration of protection. However, studies suggest that concentrations of DEET above ~50% do not offer a marked increase in protection time against mosquitoes. The CDC also recommends oil of lemon eucalyptus (PMD, para-menthane-3,8-diol) and IR3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester). Personal protection measures also help prevent other insect-transmitted illnesses, such as dengue, chikungunya, and Zika **(Chap. 204)**.

Over the past decade, the incidence of dengue has increased considerably, particularly in the Caribbean region, Latin America, Southeast Asia, and Africa. Chikungunya, another mosquito-borne infection that clinically resembles dengue but primarily causes symptoms and signs of arthralgia and arthritis (at times chronic and destructive) has particularly affected the Caribbean in the last few years. Zika virus has also emerged in the past 2 years. Although only 20% of those who are infected have symptoms, Zika virus has been associated with severe complications (microcephaly and other neurologic and organ-system problems) in newborns of women who become infected during pregnancy. In addition, Guillain-Barré syndrome has been associated with Zika virus. Many questions linger with respect to this illness, its complications, and its transmission, especially its sexual transmission.

The CDC travelers' health website must be checked prior to travel in order to assess the risk of all these mosquito-borne diseases at specific destinations. Pregnant women should not travel to Zika-affected areas. Dengue, chikungunya, and Zika viruses are transmitted by an urban-dwelling mosquito that may be found indoors and that bites during daylight, primarily at dawn and dusk. Mosquito avoidance measures are crucial for all travelers to regions where these vector-borne diseases are transmitted.

PREVENTION OF GASTROINTESTINAL ILLNESS

Diarrhea, the leading cause of illness in travelers **(Chap. 128)**, is usually a short-lived, self-limited condition. However, 40% of affected individuals need to alter their scheduled activities, and another 20% are confined to bed. The most important determinant of risk is the destination. Incidence rates per 2-week stay have been reported to be 10–40%, with the highest rates in parts of Africa and southern Asia. Infants and young adults are at particularly high risk for gastrointestinal illness and for complications such as dehydration. Recent reviews suggest that there is little correlation between dietary indiscretions and the occurrence of travelers' diarrhea (TD). Earlier studies of U.S. students in Mexico showed that eating meals in restaurants and cafeterias or consuming food from street vendors was associated with increased risk. For further discussion, see "Precautions," below.

Etiology **(See also Table 128-3)** The most frequently identified pathogens causing TD are enterotoxigenic *Escherichia coli* (ETEC) and enteroaggregative *E. coli* (EAEC) **(Chap. 156)**, although in some parts of the world (notably northern Africa and Southeast Asia) *Campylobacter* infections **(Chap. 162)** appear to predominate. Other common causative organisms include *Salmonella* **(Chap. 160)**, *Shigella* **(Chap. 161)**, rotavirus **(Chap. 198)**, and norovirus **(Chap. 198)**. The latter virus has caused numerous outbreaks on cruise ships and is an increasingly recognized cause of TD, causing up to 30% of such cases in some studies. Except for giardiasis **(Chap. 224)**, parasitic infections are uncommon causes of TD in short-term travelers. A growing problem for travelers is the development of antibiotic resistance among many bacterial pathogens and the movement of such pathogens worldwide. In centers that have molecular diagnostics capacity, other organisms are being identified in stools of patients with acute and chronic TD, although difficulties are encountered in their significance. The greater availability of these new modes for detection of pathogens in stool samples will reveal more about other and perhaps new pathogens responsible for TD.

Precautions Some experts think that it is not only *what* travelers eat but also *where* they eat that puts them at risk of illness. Food sold by street vendors can carry a high risk, and restaurant hygiene can be a major problem over which the traveler has no control. In addition to discretion in choosing the source of food and water, general precautions include eating foods piping hot; avoiding foods that are raw or poorly cooked; and drinking only boiled or commercially bottled beverages, particularly those that are carbonated. Heating kills diarrhea-causing organisms, whereas freezing does not; therefore, ice cubes made from unpurified water should be avoided. In spite of these recommendations, the literature has repeatedly documented dietary indiscretions by 98% of travelers within the first 72 h after arrival at their destination. The maxim "Boil it, cook it, peel it, or forget it!" is easy to remember but apparently difficult to follow. Using hand sanitizer regularly has been shown to reduce TD.

Self-Treatment **(See also Table 128-5)** As TD often occurs despite rigorous food and water precautions, travelers may want to carry medications for self-treatment. An antibiotic is useful in reducing the frequency of bowel movements and the duration of illness in moderate to severe diarrhea. The standard regimen is a 3-day course of a quinolone taken twice daily (or, in the case of some formulations, once daily) or, alternatively, a short regimen of azithromycin. However, studies have shown that one double dose of a quinolone or one dose of azithromycin may be equally effective. For diarrhea acquired in areas such as southern and Southeast Asia, where *Campylobacter* and other infections may be quinolone-resistant, azithromycin is the antibiotic of choice. Rifaximin, a poorly absorbed rifampin derivative, is highly effective against noninvasive bacterial pathogens such as ETEC and EAEC. The current approach to self-treatment of moderate to severe TD for the typical short-term traveler is to carry three once-daily doses of an antibiotic and to use as many doses as necessary to resolve the illness. If neither high fever nor blood in the stool accompanies diarrhea, loperamide may be taken alone or in combination with an antibiotic; studies have shown that the combination is better than the antibiotic alone and does not prolong illness.

Because of the growing problem of antimicrobial resistance worldwide, there is an effort to remind travelers that mild to moderate diarrhea may be managed with loperamide alone. For diarrhea that interferes with activity, adding an antibiotic is reasonable. However, the downside of antibiotic use is the change in the gut microbiota leading to carriage with extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae that can persist for many months after return (50% for 1 month and 10% for 1 year). In one study, 28–80% of returned travelers carried these organisms after antibiotic self-treatment.

Prophylaxis Bismuth subsalicylate remains a good option for the prophylaxis of TD but is only ~60% effective. For certain high-risk individuals (e.g., athletes, persons with a repeated history of TD, and persons with chronic diseases), a daily dose of a quinolone, azithromycin, or rifaximin during travel of <1 month's duration is 75–90% efficacious in preventing TD. A recommendation for the use of probiotics or prebiotics is premature; not enough information is available about the efficacy of using agents containing different organisms, the ideal number of organisms per dose, and the lack of product standardization. Further research on the gut microbiome will further elucidate this area. In Europe and Canada, an oral subunit cholera vaccine (Dukoral) that cross-protects against ETEC has been shown to provide 30–50% protection against TD. However, given the epidemiology of ETEC-induced TD, it is expected that only ~10% of travelers will benefit from this vaccine.

Illness after Return Although extremely common, acute TD is usually self-limited or amenable to antibiotic therapy. Persistent bowel problems after the traveler returns home have a less well-defined etiology and usually require medical attention from a specialist. Infectious agents (e.g., *Giardia lamblia, Cyclospora cayetanensis, Entamoeba histolytica*) appear to be responsible for only a small proportion of cases with persistent bowel symptoms. One of the most common diagnoses in persistent diarrhea after travel is postinfectious irritable

bowel syndrome. In as many as 4–13% of cases, symptoms may last months or years. When no infectious etiology can be identified, a trial of metronidazole therapy for presumed giardiasis (or small-intestinal bowel overgrowth), a strict lactose-free diet for a short period, or a trial of high-dose hydrophilic mucilloid may relieve symptoms. Because management of postinfectious irritable bowel syndrome can be quite complicated, these patients should be referred to a specialist.

PREVENTION OF OTHER TRAVEL-RELATED PROBLEMS

Travelers are at high risk for sexually transmitted diseases **(Chap. 131)**. Surveys have shown that large numbers of travelers engage in casual sex, and condoms are not used consistently. Increasing numbers of travelers are being diagnosed with illnesses such as schistosomiasis **(Chap. 229)**, Zika **(Chap. 204)**, dengue **(Chap. 204)**, chikungunya **(Chap. 204)**, and tick-borne rickettsial disease **(Chap. 182)**. Travelers are cautioned to avoid bathing, swimming, or wading in freshwater lakes, streams, or rivers in parts of northeastern South America, parts of the Caribbean, Africa, and Southeast Asia. Travelers should avoid walking barefoot because of the risk of hookworm and *Strongyloides* infections **(Chap. 227)** and snakebites **(Chap. 451)**. Insect repellents are important for prevention not only of malaria but also of other vector-borne diseases.

Prevention of travel-associated injury depends mostly on commonsense precautions. Riding on motorcycles (especially without helmets) and in overcrowded public vehicles is not recommended; in developing countries, individuals should *never* travel by road in rural areas after dark. Of persons who die during travel, fewer than 1% die of infection, whereas 40% die in motor vehicle accidents. Excessive alcohol use has been a significant factor in motor vehicle accidents, drownings, assaults, and injuries. During travel, situational awareness is important; wearing culturally appropriate clothing, avoiding flashy jewelry, and protecting one's money and passport are safety essentials.

THE TRAVELER'S MEDICAL KIT

A traveler's medical kit is strongly advisable. The contents may vary widely, depending on the itinerary, duration of stay, style of travel, and local medical facilities. While many medications are available abroad (often over the counter), directions for their use may be nonexistent or in a foreign language, or a product may be outdated or counterfeit. Recent studies of antimalarial products in sub-Saharan Africa and Southeast Asia showed that 30–50% were counterfeit or contained inadequate amounts of active drug. The sale and marketing of such medications are a growing industry that is expected to expand. In the medical kit, the short-term traveler should consider carrying an analgesic; an antidiarrheal agent and an antibiotic for self-treatment of TD; antihistamines; a laxative; oral rehydration salts; a sunscreen with broad-spectrum protection (UVA and UVB, with the latter at a level of at least 30 SPF); a DEET- or picaridin-containing insect repellent; an insecticide for clothing (permethrin); and, if necessary, an antimalarial drug. To these medications, the long-stay traveler might add a broad-spectrum general-purpose antibiotic (levofloxacin or azithromycin), an antibacterial eye and skin ointment, and a topical antifungal cream. The appropriate use of all antimicrobial agents should be reviewed prior to travel. Regardless of the duration of travel, a first-aid kit containing such items as scissors, tweezers, and bandages should be considered.

TRAVEL AND SPECIAL HOSTS

PREGNANCY AND TRAVEL

(See also Chap. 466) A woman's medical history and itinerary, the quality of medical care at her destinations, and her degree of flexibility determine whether travel is wise during pregnancy. According to the American College of Obstetrics and Gynecology, the safest part of pregnancy in which to travel is between 18 and 24 weeks, when there is the least danger of spontaneous abortion or premature labor. Some obstetricians prefer that women stay within a few hundred miles of home after the 28th week of pregnancy in case problems arise. In general, however, healthy women may be advised that it is acceptable to travel.

Relative contraindications to international travel during pregnancy include a history of miscarriage, premature labor, incompetent cervix, or toxemia. General medical problems such as diabetes, heart failure, severe anemia, or a history of thromboembolic disease also should prompt the pregnant woman to postpone her travels. Finally, destinations in which the pregnant woman and her fetus may be at excessive risk (e.g., those in Zika-affected areas, those at high altitudes, those where live-virus vaccines are required, and those where multidrug-resistant malaria is endemic) should be avoided.

Malaria Malaria during pregnancy carries a significant risk of morbidity and mortality. Levels of parasitemia are highest and failure to clear the parasites after treatment is most frequent among primigravidae. Severe disease, with complications such as cerebral malaria, massive hemolysis, and renal failure, is especially likely in pregnancy. Fetal sequelae include spontaneous abortion, stillbirth, preterm delivery, and congenital infection. Chloroquine and mefloquine are considered to be safe in all trimesters.

Enteric Infections Pregnant travelers must be extremely cautious regarding their food and beverage intake. Dehydration due to TD can lead to inadequate placental blood flow. Infections such as toxoplasmosis, hepatitis E, and listeriosis also can cause serious sequelae in pregnancy.

The mainstay of therapy for TD during pregnancy is rehydration. Loperamide may be used if necessary. For self-treatment, azithromycin may be the best option. Although quinolones are increasingly being used safely during pregnancy and rifaximin is poorly absorbed from the gastrointestinal tract, these drugs are not approved for this indication.

Because of the serious problems encountered when infants are given local foods and beverages, women are strongly encouraged to breast-feed when traveling with a neonate. A nursing mother with TD should not stop breast-feeding but should increase her fluid intake.

Air Travel and High-Altitude Destinations Commercial air travel is not a risk to the healthy pregnant woman or to the fetus. The higher radiation levels reported at altitudes of >10,500 m (>35,000 ft) should pose no problem for the healthy pregnant traveler. Since each airline has a policy regarding pregnancy and flying, it is best to check with the specific carrier when booking reservations. Domestic air travel is usually permitted until the 36th week, whereas international air travel is generally curtailed after the 32nd week.

There are no known risks for pregnant women who travel to high-altitude destinations and stay for short periods. However, there are likewise no data on the safety of pregnant women at altitudes of >4500 m (15,000 ft). A prominent concern is that most of these destinations are remote.

THE HIV-INFECTED TRAVELER

(See also Chap. 197) The HIV-infected traveler is at special risk of serious infections due to a number of pathogens that may be more prevalent at travel destinations than at home. However, the degree of risk depends primarily on the state of the immune system at the time of travel. For persons whose CD4+ T cell counts are normal or >500/μL, data suggest no greater risk during travel than for persons without HIV infection. Individuals with AIDS (CD4+ T cell counts of <200/μL) and others who are symptomatic need special counseling and should visit a travel medicine practitioner before departure, especially when traveling to developing countries.

Several countries deny entry to HIV-positive individuals for prolonged stay, even though these restrictions do not appear to decrease rates of transmission of the virus. In general, HIV testing is required for individuals who wish to stay abroad for >3 months or who intend to work or study abroad. Some countries will accept an HIV serologic test done within 6 months of departure, whereas others will not accept a blood test done at any time in the traveler's home country. Border officials often have the authority to make inquiries of individuals entering a country and to check the medications they are carrying. If antiretroviral drugs are identified, the person may be barred from entering the

country. Information on testing requirements for specific countries is available from consular offices but is subject to frequent change.

Immunizations All of the HIV-infected traveler's routine immunizations should be up to date **(Chap. 118)**. The response to immunization may be impaired at CD4+ T cell counts of <200/μL and in some cases at even higher counts. Thus HIV-infected persons should be vaccinated as early as possible to ensure adequate immune responses. For patients receiving antiretroviral therapy, at least 3 months must elapse before regenerated CD4+ T cells can be considered fully functional; therefore, vaccination of these patients should be delayed. However, when the risk of illness is high or the sequelae of illness are serious, immunization is recommended. In certain circumstances, it may be prudent to check the adequacy of the serum antibody response before departure.

Because of the increased risk of infections due to *Streptococcus pneumoniae* and other bacterial pathogens that cause pneumonia after influenza, the conjugate pneumococcal vaccine (Prevnar 13) followed by the 23-valent polysaccharide vaccine (Pneumovax) as well as influenza vaccine should be administered. The estimated rates of response to influenza vaccine are >80% among persons with asymptomatic HIV infection and <50% among those with AIDS.

In general, live attenuated vaccines are contraindicated for persons with immune dysfunction. Because measles (rubeola) can be a severe or lethal infection in HIV-positive patients, these patients should receive the measles vaccine (or the combination MMR vaccine) unless the CD4+ T cell count is <200/μL. Between 18 and 58% of symptomatic HIV-infected vaccinees develop adequate measles antibody titers, and 50–100% of asymptomatic HIV-infected persons seroconvert.

In asymptomatic HIV-infected individuals, CD4+ T cell counts of 200–499/μL (moderate immune suppression) are considered a precaution for yellow fever vaccination; since there is no contraindication, yellow fever vaccine may be considered when these persons travel to endemic areas. Studies of these individuals, along with asymptomatic persons whose CD4+ T cell count is >500/μL, found no serious adverse events, although their immunologic response may be decreased. If the CD4+ T cell count is <200/μL, an alternative itinerary that poses no risk of exposure to yellow fever is recommended. If the traveler is passing through or traveling to an area where the vaccine is required but the disease risk is low, a physician's waiver should be issued. Although the WHO indicates that a single dose of yellow fever vaccine provides lifetime protection, the CDC recommends boosters every 10 years for HIV-infected individuals.

A transient increase in HIV viremia (lasting days to weeks) has been demonstrated in HIV-infected individuals after immunization against influenza, pneumococcal infection, and tetanus **(Chap. 197)**. At this point, however, no evidence indicates that this transient increase is detrimental.

Gastrointestinal Illness Decreased levels of gastric acid, abnormal gastrointestinal mucosal immunity, other complications of HIV infection, and medications taken by HIV-infected patients make TD especially problematic in these individuals. TD is likely to occur more frequently, to be more severe, to be accompanied by bacteremia, and to be more difficult to treat. *Cryptosporidium*, *Isospora belli*, and *Microsporidium* infections, although uncommon, are associated with increased morbidity and mortality rates in patients with AIDS.

The HIV-infected traveler must be careful to consume only appropriately prepared foods and beverages, and some may benefit from antibiotic prophylaxis for TD. Sulfonamides (as used to prevent pneumocystosis) are ineffective because of widespread resistance.

Other Travel-Related Infections Data are lacking on the severity of many vector-borne diseases in HIV-infected individuals. Malaria is especially severe in asplenic persons and in those with AIDS. The HIV load doubles during malaria, with subsidence in ~8–9 weeks; the significance of this increase in viral load is unknown.

Visceral leishmaniasis **(Chap. 221)** has been reported in numerous HIV-infected travelers. Diagnosis may be difficult, given that splenomegaly and hyperglobulinemia are often lacking and serologic results are frequently negative. Sandfly bites may be prevented by evening use of insect repellents.

Certain respiratory illnesses, such as histoplasmosis and coccidioidomycosis, cause greater morbidity and mortality among patients with AIDS. Although tuberculosis is common among HIV-infected persons (especially in developing countries), its acquisition by the short-term HIV-infected traveler has not been reported as a major problem. From a prospective study, it is estimated that, for travelers not engaged in health care, the risk of tuberculosis infection is ~3% per year of travel.

Medications Adverse events due to medications and drug interactions are common and raise complex issues for HIV-infected persons. Rates of cutaneous reaction (e.g., increased cutaneous sensitivity to sulfonamides) are unusually high among patients with AIDS. Doxycycline appears to have no clinically significant interactions with either the protease inhibitors or the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Zidovudine levels may be increased with atovaquone. The drug combination atovaquone/proguanil may interact with antiretroviral protease inhibitors such as ritonavir, darunavir, atazanavir, indinavir, and lopinavir as well as the NNRTIs nevirapine, etravirine, and efavirenz. In spite of potential interactions, atovaquone/proguanil is well tolerated and remains the choice for most HIV-infected travelers.

Concomitant administration of the antimalarial drug mefloquine and antiretroviral protease inhibitors such as ritonavir, lopinavir, darunavir, and atazanavir may result in increased levels of mefloquine, with an increased risk of QT prolongation. Similarly, ritonavir may increase chloroquine levels. On the other hand, serum levels of mefloquine may be lowered with the use of efavirenz, nevirapine, or etravirine. Because of the increase in antiretroviral agents and the lack of accumulated data on their interactions with antimalarial agents, decisions about malaria chemoprophylaxis continue to be difficult; with a short duration of travel, an interaction may be inconsequential. With regard to malaria treatment, a hypothetical concern is that the antimalarial drugs lumefantrine (combined with artemether in Coartem) and halofantrine (no longer recommended due to toxicity) may interact with HIV protease inhibitors and NNRTIs since drugs in the latter two categories are known to be potent inhibitors of cytochrome P450. In keeping current with antiretroviral drug interactions, a website from the University of Liverpool (*www.hiv-druginteractions.org*) is helpful.

CHRONIC ILLNESS, DISABILITY, AND TRAVEL

Chronic health problems need not prevent travel, but special measures can make the journey safer and more comfortable.

Heart Disease Cardiovascular events are the main cause of deaths among travelers and of in-flight emergencies on commercial aircraft. Extra supplies of all medications should be kept in carry-on luggage, along with a copy of a recent electrocardiogram and the name and telephone number of the traveler's physician at home. Pacemakers are not affected by airport security devices, although electronic telephone checks of pacemaker function cannot be transmitted by international satellites. Travelers with electronic defibrillators should carry a note to that effect and ask for hand screening. A traveler may benefit from supplemental oxygen; since oxygen delivery systems are not standard, supplementary oxygen should be ordered by the traveler's physician well before flight time. Travelers may benefit from aisle seating and should walk, perform stretching and flexing exercises, consider wearing support hose, and remain hydrated during the flight to prevent venous thrombosis and pulmonary embolism.

Chronic Lung Disease Chronic obstructive pulmonary disease is one of the most common diagnoses in patients who require emergency-department evaluation for symptoms occurring during airline flights. The best predictor of the development of in-flight problems is the sea-level Pao_2. A Pao_2 of at least 72 mmHg corresponds to an in-flight arterial Pao_2 of ~55 mmHg when the cabin is pressurized to 2500 m (8000 ft). If the traveler's baseline Pao_2 is <72 mmHg, the provision of supplemental oxygen should be considered. Contraindications to flight include active bronchospasm, lower respiratory infection, lower-limb deep-vein phlebitis, pulmonary hypertension, and recent

thoracic surgery (within the preceding 3 weeks) or pneumothorax. Decreased outdoor activity at the destination should be considered if air pollution is excessive.

Diabetes Mellitus Alterations in glucose control and changes in insulin requirements are common problems among patients with diabetes who travel. Changes in time zones, in the amount and timing of food intake, and in physical activity demand vigilant assessment of metabolic control. Because of the risk of foot ulcers, travelers should wear closed footwear that has been proven to be comfortable. The traveler with diabetes should pack medication (including a bottle of regular insulin for emergencies), insulin syringes and needles, equipment and supplies for glucose monitoring, and snacks in carry-on luggage. Insulin is stable for ~3 months at room temperature but should be kept as cool as possible. The name and telephone number of the home physician and a card and bracelet listing the patient's medical problems and the type and dose of insulin used should accompany the traveler. In order to facilitate international border crossings, travelers should carry a physician's letter authorizing the carriage of needles and syringes. In traveling eastward (e.g., from the United States to Europe), the patient may need to decrease the morning insulin dose on arrival. The blood glucose can then be checked during the day to determine whether additional insulin is required. For flights westward, with lengthening of the day, an additional dose of regular insulin may be required.

Other Special Groups Other groups for whom special travel measures are encouraged include patients undergoing dialysis, those with transplants, and those with other disabilities. Up to 13% of travelers have some disability, but few advocacy groups and tour companies dedicate themselves to this growing population. Medication interactions are a source of serious concern for these travelers, and appropriate medical information should be carried, along with the home physician's name and telephone number. Some travelers taking glucocorticoids carry stress doses in case they become ill. Immunization of these immunocompromised travelers may result in less than adequate protection. Thus the traveler and the physician must carefully consider which destinations are appropriate.

TRAVEL HEALTH INSURANCE

Today, more elderly or chronically ill individuals travel, and more of these individuals journey to remote locations and enjoy adventurous activities. Illness or injury abroad is not uncommon and is best considered before the journey. Persons who develop health problems abroad may incur enormous out-of-pocket expenses. Thus prospective travelers should consider purchasing supplemental travel health insurance and should check with their health insurance company regarding whether they have coverage for illness or injury overseas. Unfortunately, many insurance companies will not cover preexisting illness if it is the reason for trip cancellation or illness abroad. Most countries do not accept routine health insurance from other countries unless there is a special traveler supplement. In most circumstances, travelers are asked to pay in cash for services rendered on an emergency basis, whether in a physician's office, in an emergency or urgent care center, or even in a hospital. There are several types of travel insurance. It is wise to purchase *trip cancellation insurance*, especially, for example, if the traveler has an underlying chronic illness and may need to cancel a trip due to an exacerbation of disease. *Travel health insurance* will cover expenses in the event that medical care abroad is needed. *Evacuation insurance* will cover medical evacuation, usually to a medical center in another location where it is deemed that the care is similar to that available in the traveler's home country. The cost of medical evacuation can easily exceed $100,000 U.S. There are a number of travel insurance providers, and it is very important to read the fine print carefully and to determine exactly what each company provides, thereby ensuring an appropriate fit for the individual's particular circumstances. The U.S. Department of State website lists travel health insurance companies and provides information about whom to contact in an emergency through STEP (the Smart Traveler Enrollment Program: *https://travel.state.gov/content/passports/en/go/health/doctors.html*).

MEDICAL TOURISM

Travel for the purpose of obtaining health care abroad has received a great deal of attention in the medical literature and the media. Although the data are difficult to confirm, it has been estimated that at least 750,000 Americans travel each year for medical purposes. According to the Department of Commerce website, the numbers of such travelers have doubled recently, and some experts predict massive increases. Lower cost is usually cited as the motivation for this type of tourism, and an entire industry has flourished as a result of this phenomenon. However, the quality of facilities, assistance services, and care is neither uniform nor regulated; thus, in most instances, responsibility for assessing the suitability of an individual program or facility lies solely with the traveler. Persons considering this option must recognize that they are almost always at a disadvantage when being treated in a foreign country, particularly if there are complications. Concerns to be addressed include the quality of the health care facility and its staff; language and cultural differences that may impede accurate interpretation of both verbal and nonverbal communication; religious and ethical differences that may be encountered over issues such as efforts to preserve life and limb or the provision of care for the terminally ill; lack of familiarity with the local medical system; limited access of the care provider to the patient's medical history; the use of unfamiliar drugs and medicines; the relative difficulty of arranging follow-up care back in the United States; and the possibility that such follow-up care may be fraught with problems should there be complications. If serious issues arise, legal recourse may be difficult or impossible. Patients planning to travel abroad to obtain health care, particularly when surgery is involved, should be immunized for hepatitis B and should consider having baseline hepatitis C and HIV tests preoperatively. Prevalence rates of hepatitis B and C and HIV infection vary considerably around the world and are generally higher in developing regions than in the United States and Western Europe. The latest information available on the safety of the blood supply outside the United States is the WHO's Global Database on Blood Safety based on data from 2011 (*www.who.int/topics/blood_safety/en*). Persons researching the accreditation status of overseas facilities should note that, although these facilities may be part of a chain, they are surveyed and accredited individually. Accreditation resources include (1) the Joint Commission International (*www.jointcommissioninternational.org*), (2) the Australian Council for Healthcare Standards International (*www.achs.org.au/achs-international/*), and (3) Accreditation Canada International (*www.internationalaccreditation.ca*). The American Medical Association also offers guidelines for medical tourism (*www.medretreat.com/templates/UserFiles/Documents/Whitepapers/AMAGuidelines.pdf*).

PROBLEMS AFTER RETURN

The most common medical problems encountered by travelers after their return home are diarrhea, fever, respiratory illnesses, and skin diseases **(Fig. 119-2)**. Frequently ignored problems are fatigue and emotional stress, especially in long-stay travelers. The approach to diagnosis requires some knowledge of geographic medicine, in particular the epidemiology and clinical presentation of infectious disorders. A geographic history should focus on the traveler's exact itinerary, including dates of arrival and departure; exposure history (food indiscretions, drinking-water sources, freshwater contact, sexual activity, animal contact, insect bites); location and style of travel (urban vs rural, first-class hotel accommodation vs. camping); immunization history; and use of antimalarial chemosuppression. Recently, some travelers who have been hospitalized abroad have been shown on return to be colonized with multidrug-resistant bacteria such as Enterobacteriaceae producing ESBLs and bacteria producing NDM-1 (New Delhi metallo-β-lactamase 1); these bacteria may be transmitted to family members and other contacts, especially within the health care system.

DIARRHEA

See "Prevention of Gastrointestinal Illness," above.

FEVER

Fever in a traveler who has returned from a malarious area should be considered a medical emergency because death from *Plasmodium*

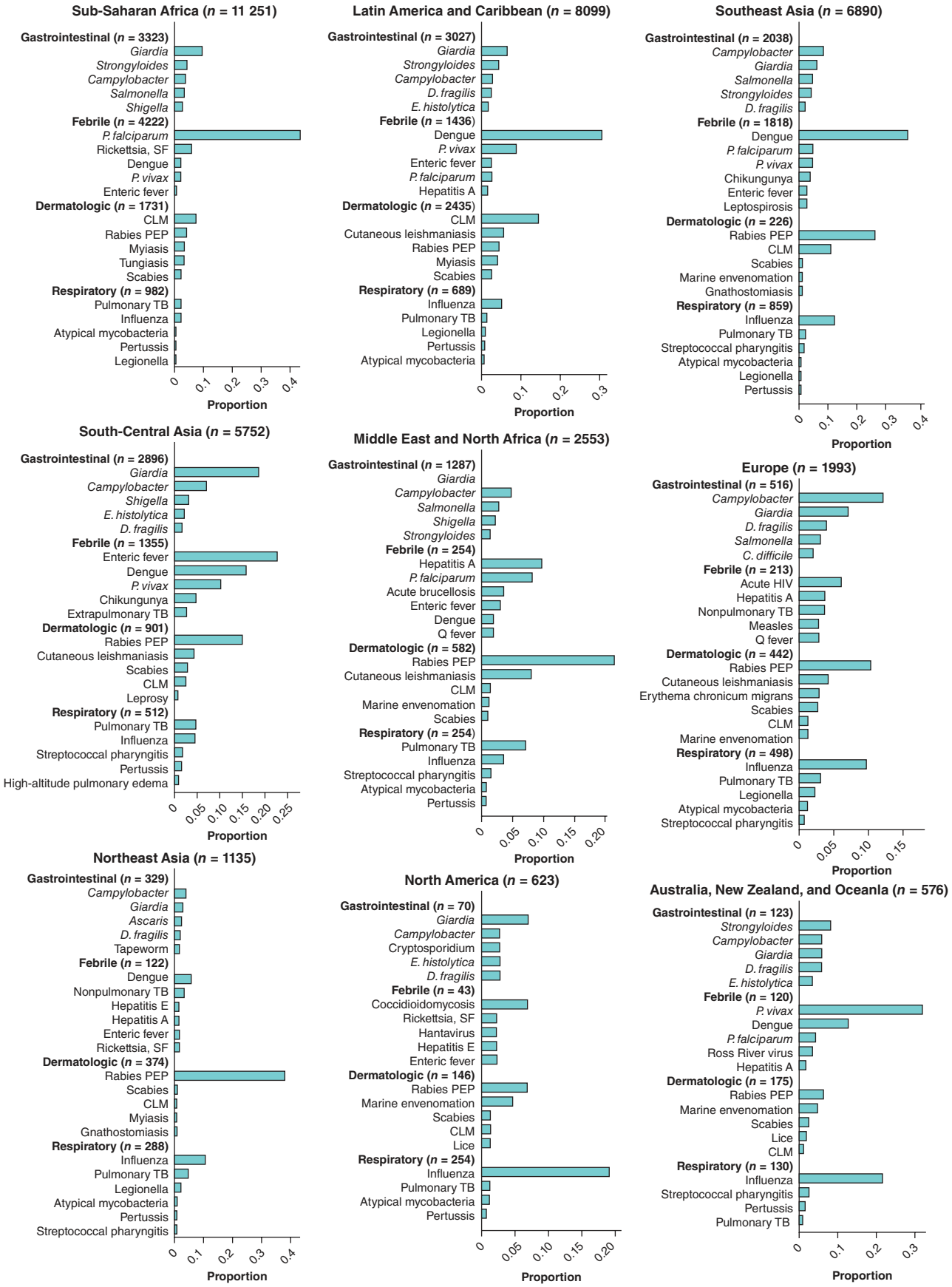

FIGURE 119-2 Top identified causes of gastrointestinal, febrile, dermatologic, and respiratory illnesses, by region, among ill returned travelers. More than five diagnoses are shown if more than one cause had equal numbers of cases. These graphs represent proportions, and there is variability in the number of ill travelers represented from panel to panel (shown from largest to smallest traveler numbers). CLM, cutaneous larva migrans; *D. fragilis*, *Dientamoeba fragilis*; *E. histolytica*, *Entamoeba histolytica*; *P. falciparum*, *Plasmodium falciparum*; *P. vivax*, *Plasmodium vivax*; PEP, postexposure prophylaxis; SF, spotted fever; TB, tuberculosis. *(Reprinted with permission from K Leder et al: Ann Intern Med 158:456, 2013.)*

falciparum malaria can follow an illness of only several days' duration. Although "fever from the tropics" does not always have a tropical cause, malaria should be the first diagnosis considered. The risk of *P. falciparum* malaria is highest among travelers returning from Africa or Oceania and among those who become symptomatic within the first 2 months after return. Other important causes of fever after travel include dengue, chikungunya, Zika, viral hepatitis (A and E), typhoid and paratyphoid fever, bacterial enteritis, rickettsial infections (including tick typhus, scrub typhus, and Q fever), and—in rare instances—leptospirosis, acute HIV infection, and amebic liver abscess. Studies published by GeoSentinel (an emerging infectious disease surveillance group established by the CDC and the International Society of Travel Medicine) have informed providers about specific illness and syndrome risks in ill returned travelers (Fig. 119-2). Outbreaks of dengue, previously considered to be very rare in Africa, have been documented recently across central Africa. However, in at least 25% of cases, no etiology of fever in a returning traveler can be found, and the fever resolves spontaneously. Clinicians should keep in mind that no present-day antimalarial agent guarantees protection from malaria and that some immunizations (notably, that against typhoid fever) are only partially protective.

When no specific diagnosis is forthcoming, the following investigations, where applicable, are suggested: complete blood count, liver function tests, thick/thin blood films or rapid diagnostic testing for malaria (repeated several times if necessary), urinalysis, urine and blood cultures (repeated once), rapid influenza diagnostic testing, chest x-ray, and collection of an acute-phase serum sample to be held for subsequent examination along with a paired convalescent-phase serum sample.

SKIN DISEASES

Pyodermas, sunburn, insect bites, skin ulcers, and cutaneous larva migrans are the most common skin conditions affecting travelers after their return home. In individuals with persistent skin ulcers, a diagnosis of cutaneous leishmaniasis, mycobacterial infection, or fungal infection should be considered. Careful, complete inspection of the skin is important in detecting the rickettsial eschar in a febrile patient or the central breathing hole in a "boil" due to myiasis.

EMERGING INFECTIOUS DISEASES

In recent years, travel and commerce have fostered the worldwide spread of chikungunya, Zika, influenza caused by novel serotypes, severe acute respiratory syndrome (SARS), and (earlier) HIV infection and the reemergence of cholera as a global health threat. For travelers, some of these issues, along with others, remain a concern. Dengue continues to pose serious health threats in Latin America and Southeast Asia; schistosomiasis is being described in previously unaffected lakes in Africa; and antibiotic-resistant strains of sexually transmitted and enteric pathogens are emerging at an alarming rate.

CONCLUSIONS

The growth of global travel and migration now demand that the clinician become as familiar as possible with travel medicine. Practitioners may choose either to refer their patients to a travel clinic before departure or to acquire knowledge that enables them to provide pre-travel counseling and to prescribe appropriate vaccinations and chemoprophylaxis. It is equally important for physicians seeing ill returned travelers to be familiar with common post-travel syndromes and diseases, particularly those that may have been acquired in the developing world, and to identify other physicians who can assist with complex post-travel illnesses. The CDC publishes a biennial text, *Health Information for International Travel* (accessed through their website at *www.cdc.gov/travel*), that provides pre-travel health recommendations. The International Society of Travel Medicine (*www.istm.org*) publishes a list of travel clinics, and the American Society of Tropical Medicine and Hygiene (*www.astmh.org*) publishes a list of clinical tropical medicine specialists.

As Nobel Laureate Dr. Joshua Lederberg pointed out, "The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global pandemic tomorrow." The vigilant clinician understands that the importance of a thorough travel history cannot be overemphasized.

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120 Climate Change and Infectious Disease

Aaron S. Bernstein

The release of greenhouse gases—principally carbon dioxide—into Earth's atmosphere since the late nineteenth century has contributed to a climate unfamiliar to our species, *Homo sapiens*. This new climate has already altered the epidemiology of some infectious diseases. Continued accumulation of greenhouse gases in the atmosphere will further alter the planet's climate. In some cases climate change may establish conditions favoring the emergence of infectious diseases, while in others it may render areas that are presently suitable for certain diseases unsuitable. This chapter presents the current state of knowledge regarding the known and prospective infectious-disease consequences of climate change.

OVERVIEW

The term *climate change* refers to long-term alterations in temperature, precipitation, wind, humidity, and other components of weather. Over the past 2.5 million years, the earth has warmed and cooled, cycling between glacial and interglacial periods during which average global temperatures moved up and down by 4–7°C. During the last glacial period, which ended roughly 12,000 years ago, global temperatures were, on average, 5°C cooler than in the mid-twentieth century **(Fig. 120-1)**.

The present climate period, known as the Holocene, is remarkable for its stability: temperatures have largely remained within a range of 2–3°C. This stability has enabled the successful population and cultivation of much of the earth's landmass by humanity. Current climate change differs from that in the past not only because its primary cause is human activities but also because its pace is faster. The current rate of warming on Earth is unprecedented in the last 50 million years.

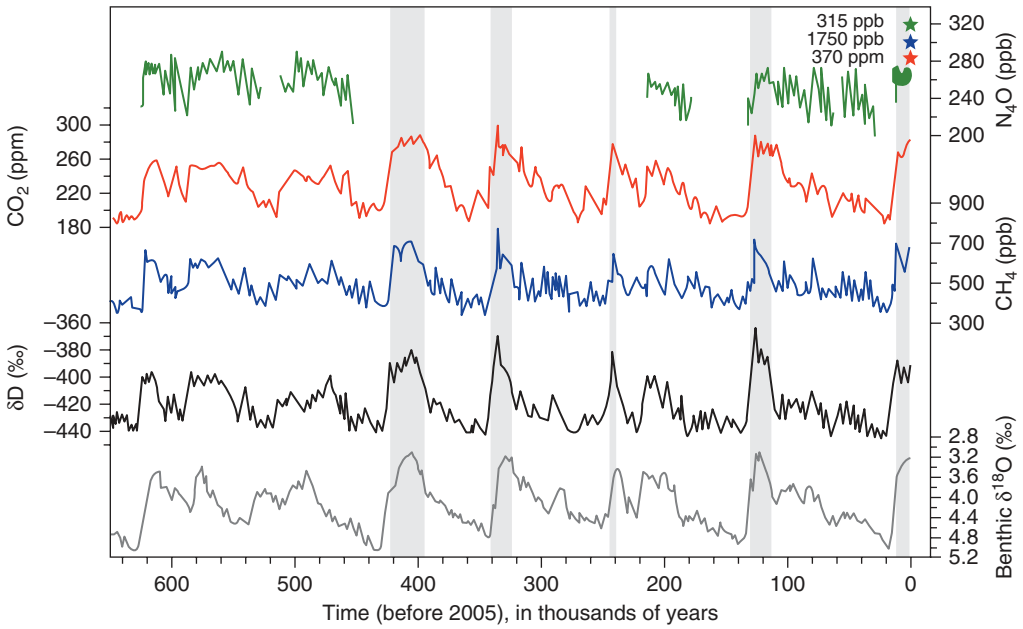

FIGURE 120-1 Overview of the earth's temperature and primary greenhouse gases over the last 600,000 years. Variations of deuterium (δD; *black*) serve as a proxy for temperature. Atmospheric concentrations of greenhouse gases—CO_2 (*red*), CH_4 (*blue*), and nitrous oxide (N_2O; *green*)—were derived from air trapped within Antarctic ice cores and from recent atmospheric measurements. *Shaded areas* indicate interglacial periods. Benthic $\delta^{18}O$ marine records (*dark gray*) are a proxy for global ice-volume fluctuations and can be compared to the ice core data. Downward trends in the benthic $\delta^{18}O$ curve reflect increasing ice volumes on land. The *stars* and *labels* indicate atmospheric concentrations as of the year 2000. CO_2 levels surpassed 400 ppm as of 2013 and are rising at a rate of 2–2.5 ppm per year. *(From Intergovernmental Panel on Climate Change Fourth Assessment Report. Working Group I, Chapter 6, Figure 6.3. Cambridge University Press, 2007.)*

The 5°C of warming that occurred at the end of the last ice age about 12,000 years ago took roughly 5000 years, whereas such a temperature increment may occur within the next 150 years unless the release of greenhouse gases is substantially reduced in coming decades. Climate science, although still a relatively new discipline, has provided an ever-clearer picture of how the changing chemistry of the atmosphere has influenced, and will continue to influence, the global climate.

GREENHOUSE GASES

Greenhouse gases **(Table 120-1 and Fig. 120-2)** are a group of gases in Earth's atmosphere that absorb infrared radiation and thus retain heat inside the atmosphere. In the absence of these gases, the earth's average temperature would be about 33°C colder. Carbon dioxide, released into the atmosphere primarily from fossil fuel combustion and deforestation, has had the greatest effect on climate since the Industrial Revolution. Of note, the Swedish scientist Svante Arrhenius first suggested in the late nineteenth century that the addition of carbon dioxide to the Earth's atmosphere would increase the planet's surface temperature. Water vapor is the most abundant and a highly potent greenhouse gas but, given its short atmospheric life span and sensitivity to temperature, is not a major factor in recently observed climate change.

The atmosphere, some of the aerosols suspended in it, and clouds reflect a portion of incoming solar radiation back toward space. The remainder reaches Earth's surface, where it is absorbed and some is then emitted back at the atmosphere. The earth emits energy absorbed from the sun at longer wavelengths, primarily infrared, that greenhouse gases are able to absorb. The change in wavelength that occurs as solar radiation is absorbed and re-emitted from the earth's surface is fundamental to the greenhouse effect **(Fig. 120-3)**.

TEMPERATURE

Climate change has become nearly synonymous with global warming, as a clear signal from rising greenhouse gas concentrations has been an increase in the mean global surface temperature of ~0.85°C since 1880. However, this mean warming belies warming that is occurring much faster in certain regions. The Arctic has warmed twice as fast overall, and winters are warming faster than summers. Nighttime minimum temperatures are also rising faster than daytime high temperatures. Each of these nuances bears upon the incidence of infectious diseases in general and vector-borne disease specifically.

A moderate projection based on the best available scientific evidence suggests that average global temperatures will warm an additional 1.4–3.1°C by 2100 as compared to the period 1986–2005. Because of climate change, extreme heat waves have already become more common and are expected to be even more frequent later in this century. Besides contributing directly to morbidity and mortality in human populations, heat waves wilt crops and are expected to contribute substantially to predicted agricultural losses. For example, the 2010 heat wave in Russia, which was unprecedented in its severity, contributed to hundreds of forest fires that generated enough air pollution to kill an estimated 56,000

TABLE 120-1 Greenhouse Gases: Sources, Sinks, and Forcings

GAS	HUMAN SOURCES	SINK[a]	RADIATIVE FORCING[b] (95% CONFIDENCE INTERVAL)
Carbon dioxide (CO_2)	Fossil fuel combustion, deforestation	Uptake by oceans (~30%), plants	1.68 (1.33–2.03)
Methane (CH_4)	Fossil fuel production, ruminant animals, decomposition in landfills	Hydroxyl radicals in the troposphere	0.97 (0.74–1.20)
Nitrous oxide (N_2O)	Fertilizer, fossil fuel combustion, biomass burning, livestock manure	Photolysis in the stratosphere	0.17 (0.14–0.23)
Halocarbons	Refrigerants, electrical insulation, aluminum production	Hydroxyl radicals in the troposphere, sunlight in the stratosphere	0.18 (0.01–0.35)

[a]In this table, a *sink* refers to the place where greenhouse gases are naturally stored or the mechanism through which they are destroyed. [b]*Radiative forcing*, measured in watts per meter squared, refers to how much an entity can alter the balance of incoming and outgoing radiation to and from Earth's atmosphere. It is measured relative to a preindustrial (i.e., 1750) baseline. Greenhouse gases have a positive "forcing"; that is, on balance, they increase the amount of radiation (and specifically infrared radiation) that is retained in Earth's atmosphere.

Sources: Intergovernmental Panel on Climate Change Fifth Assessment Report, Working Group 1, Chapter 8; American Chemical Society "Greenhouse gas sources and sinks," available at *www.acs.org/content/acs/en/climatescience/greenhousegases/sourcesandsinks.html*.

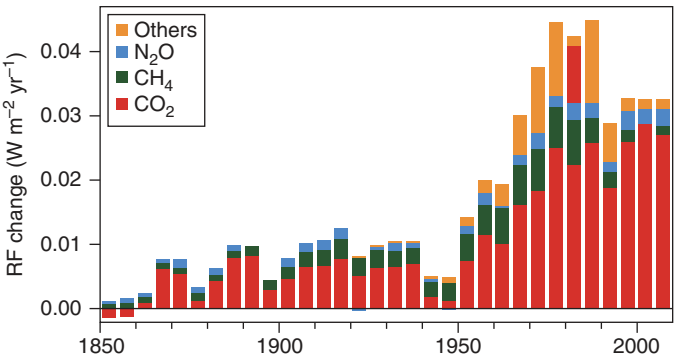

FIGURE 120-2 Acceleration of radiative forcing (RF) from release of major greenhouse gases, 1850–2011. For definition of *radiative forcing*, see footnote *b* to Table 120-1. *(From Intergovernmental Panel on Climate Change Fifth Assessment Report, Working Group 1, Chapter 8, Figure 8.6, p. 677.)*

people and that burned 300,000 acres of crops, including roughly 25% of the nation's wheat fields. Nutritional deficiencies underlie a substantial portion of the global burden of many infectious diseases.

PRECIPITATION

In addition to changing temperature, the emission of greenhouse gases and the consequent increase in energy in Earth's atmosphere have influenced the planet's water cycle. Since 1950, substantial increases in the heaviest precipitation events (i.e., those above the 95th percentile) have been observed in Europe and North America. While trends over that same interval are less clear in other regions because of limited data, regions of Southeast Asia and southern South America have likely experienced increases in heavy precipitation as well. Other areas have seen greater drought, notably southern Australia and the southwestern United States.

A warmer atmosphere holds more water vapor; specifically, there is 6–7.5% more water vapor per degree (Celsius) of warming in the lower atmosphere. For areas that have traditionally had more precipitation on average, warming tends to promote heavier precipitation events. In contrast, in regions prone to drought, warming tends to result in greater periods between rainfalls and in the risk of drought.

HURRICANES

The world's oceans have absorbed 90% of the excess heat that greenhouse gases have kept in Earth's atmosphere since the 1960s. Ocean heat provides energy for hurricanes, and warmer years tend to have greater hurricane activity. Atlantic hurricanes are the best studied and have the most data available. An analysis of satellite observations from 1983 to 2005 has shown a trend toward increasing severity—albeit decreasing frequency—of Atlantic hurricanes. Modeling of future tropical cyclones suggests that their intensity may increase 2–11% by 2100 and that the average storm will bring 20% more rainfall.

SEA LEVEL RISE

Between 1901 and 2010, the global sea level rose ~200 mm, or ~1.7 mm per year on average. From 1993 to 2010, the rate of rise nearly doubled—i.e., to 3.2 mm annually. Most of this sea level rise has resulted from the thermal expansion of water. Glacial ice melt is the second greatest factor, and its contribution is accelerating. By 2100, global sea level may rise by 0.8–2 m, with an annual rate of rise of 8–16 mm at the century's end. A large section of the West Antarctic ice sheet has begun to fall apart, and its melting alone may cause sea level to rise by ≥3 m in coming centuries.

Sea level rise is not uniform. The rate of rise on the eastern seaboard of North America has been roughly double the global rate. Compounding sea level rise is the subsidence of coastal areas due to human settlement. In the absence of levee upgrades, an estimated 170 million people living near coasts worldwide will be at risk of flooding in 2100 because of the combined effects of subsidence, erosion, and sea level rise.

Along with extreme storms and overuse of coastal aquifers, rising seas also contribute to salinization of coastal groundwater. About 1 billion people rely on coastal aquifers for potable water.

EL NIÑO SOUTHERN OSCILLATION

The *El Niño Southern Oscillation* (ENSO) refers to periodic changes in water temperature in the eastern Pacific Ocean that occur roughly every 5 years. ENSO cycles have dramatic effects on weather around the globe. Warmer-than-average water temperatures in the eastern Pacific define *El Niño events* (see below), whereas cooler-than-average water temperatures define La Niña periods. Evidence is accruing that climate change may be increasing the frequency and severity of El Niño events.

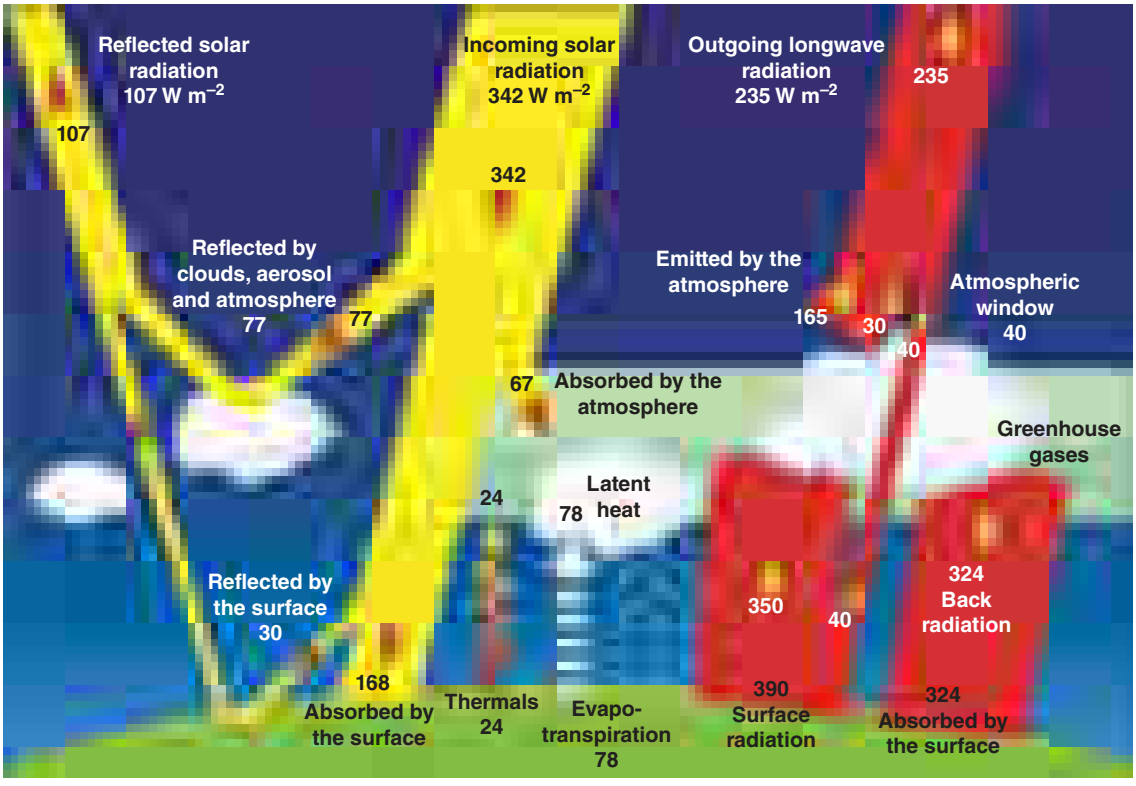

FIGURE 120-3 Earth's energy balance. *(From JT Kiehl: Earth's annual global mean energy budget. Bull Am Meteor Soc 78: 197, 1997, Fig 7.)*

El Niño events drive alterations in weather worldwide (Fig. 120-4) and are associated with extreme events and consequently higher rates of morbidity and mortality. Hurricane Mitch, one of the most powerful hurricanes ever observed, with winds reaching 290 km/h, dropped 1–1.8 m (3–6 feet) of rain over 72 h on parts of Honduras and Nicaragua. As a result of this storm, 11,000 people died and 2.7 million were displaced. Outbreaks of cholera, leptospirosis, and dengue occurred in the storm's aftermath.

POPULATION MIGRATION AND CONFLICT

The final common outcome of all climate-change effects is often population migration. Sea level rise, extreme heat and precipitation, droughts, and salinization of water supplies all conspire to make regions (including some inhabited by humans for millennia) uninhabitable. Among climate-change migrants in the near future may be the inhabitants of low-lying South Pacific islands that are vulnerable to sea level rise and residents of the Alaskan archipelago, where melting of permafrost has rendered traditional means of cold food storage difficult.

Climate change may also be contributing to humanitarian crises and conflicts. A severe 2011 drought in East Africa may have incited the Somali famine that resulted in 1 million refugees; mortality rates reached 7.4/10,000 in some refugee camps. Crop losses associated with the 2010 Russian heat wave led Russia to halt grain exports, causing higher grain prices on the world market and food riots in developing nations.

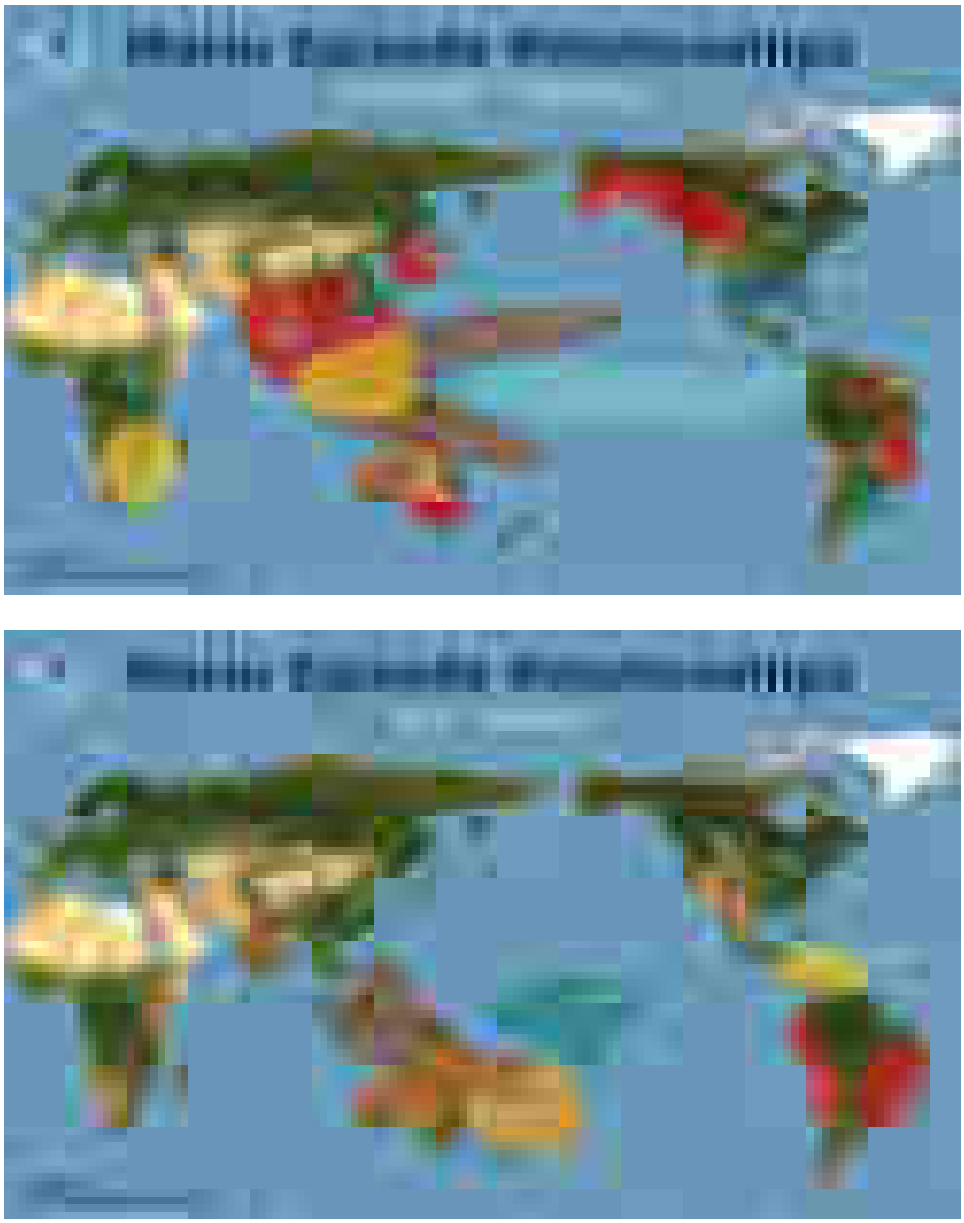

FIGURE 120-4 Characteristic weather anomalies, by season, during El Niño events. *(Source: www.cpc.ncep.noaa.gov/products/precip/CWlink/ENSO/ENSO-Global-Impacts/High-Resolution/.)*

EFFECTS OF CLIMATE CHANGE ON INFECTIOUS DISEASE

The incidence of most, if not all, infectious diseases depends on climate. For any given infection, however, climate change is but one of many factors that determine disease epidemiology, and often it is not the most influential factor. Even in instances in which climate change creates conditions favorable to the spread of infections, diseases may be kept in check through interventions such as vector control or antibiotic treatment.

Detecting climate-change influence on an emerging human disease can be challenging. Research with animal pathogens, which in most instances are less well monitored and intervened upon than that with their human counterparts, has suggested how climate change may influence disease spread. For example, the life cycle of nematode parasites of caribou and musk oxen shortens as temperatures rise. As the Arctic has warmed, higher nematode burdens and consequently higher rates of morbidity and mortality have been observed. Other examples from animals, such as the spread of the protozoan parasite *Perkinsus marinus* in oysters, demonstrate how warming can enable range expansion of pathogens previously held in check by colder temperatures.

As these and other examples from studies of animals make clear, the influence of climate change on infectious diseases can be pronounced. The following sections deal with the infectious diseases for which research has explored the influence of climate change.

VECTOR-BORNE DISEASE

Because insects are cold-blooded, ambient temperature dictates their geographic distribution. With increases in temperatures (in particular, nighttime minimum temperatures), insects are freed to move poleward and up mountainsides. At the same time, as new areas become climatically suitable, current mosquito habitats may become unsuitable as a result of heat extremes.

In addition, insects tend to be sensitive to water availability. Mosquitoes that transmit malaria, dengue, and other infections may breed in pools of water created by heavy downpours. As has been observed in the Amazon, breeding pools can also appear during periods of drought when rivers recede and leave behind stagnant pools of water for *Anopheles* mosquitoes. These circumstances have raised interest in the potentially favorable impact of water-cycle intensification on the spread of mosquito-borne disease.

Malaria • **TEMPERATURE** Higher temperatures promote higher mosquito-biting rates, shorter parasite reproductive cycles, and the potential for the survival of mosquito vectors of *Plasmodium* infection in locations previously too cold to sustain them. Modeling experiments have identified highland areas of East Africa and South America as

perhaps most vulnerable to increased malarial incidence as a result of rising temperatures. In addition, an analysis of interannual malaria in Ecuador and Colombia has documented a greater incidence of malaria at higher altitudes in warmer years. Highland populations may be more vulnerable to malaria epidemics because they lack immunity.

Although rising temperature has the potential to expand the viable range of disease, malaria incidence is not associated with temperature in a strictly linear fashion. While mosquitoes and parasites may adapt to a warming climate, the present optimal temperature for malaria transmission is ~25°C, with a range of transmission temperatures between 16°C and 34°C. Rising temperatures also can have differential effects on parasite development during external incubation and on the mosquitoes' gonotrophic cycle. Asynchrony between these two temperature-sensitive processes has been shown to decrease the vectorial capacity of mosquitoes.[1]

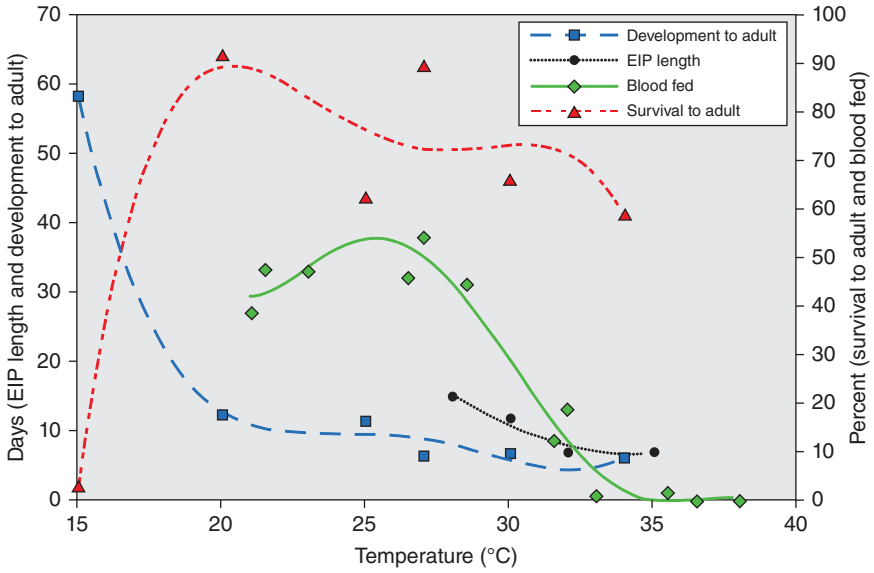

FIGURE 120-5 Effects of temperature on variables associated with dengue transmission. Shown are the number of days required for development of immature *Aedes aegypti* mosquitoes to adults, the length of the dengue virus type 2 extrinsic incubation period (EIP), the percentage of *A. aegypti* mosquitoes that complete a blood meal within 30 min after a blood source is made available, and the percentage of hatched *A. aegypti* larvae surviving to adulthood. *(Reproduced from CW Morin et al: Climate and dengue transmission: Evidence and implications. Environ Health Perspect 121:1264, 2013.)*

PRECIPITATION The abundance of *Anopheles* mosquitoes is strongly correlated with the availability of surface-water pools for mosquito breeding, and biting rates have been linked to soil moisture (a surrogate for breeding pools). Research in the East African highlands has documented that increased variance in rainfall over time has strengthened the association between precipitation and disease incidence. These disease-promoting effects of precipitation may be countered by the potential for extreme rainfall to flush mosquito larvae from breeding sites.

PROJECTIONS Climate models have begun to deliver output on regional scales, permitting projections of climate-suitable regions to assist national and local health authorities. Climate models speak to the temperature and precipitation ranges necessary for malaria transmission but do not—and cannot—account for the capacity of malaria control programs to halt the spread of disease. The global reduction in malaria distribution over the past century makes it clear that, even with climate change, malaria occurs in far fewer places today because of public health interventions.

Despite intensive efforts, malaria remains the single greatest vector-borne disease cause of morbidity and death in the world. Particularly in regions that are most affected by malaria and where the public health infrastructure is inadequate to contain it, climate modeling may provide a useful tool in determining where the disease may spread. Modeling studies in sub-Saharan Africa have suggested that, although East African nations may encompass regions that will become more climatically suitable for malaria over this century, West African nations may not. By 2100, temperatures in West Africa may largely exceed those optimal for malaria transmission, and the climate may become drier; in contrast, higher temperatures and changes in precipitation may allow malaria to move up the mountainsides of East African countries. Climate change may create conditions favorable to malaria in subtropical and temperate regions of the Americas, Europe, and Asia as well.

Dengue Like malaria epidemics, dengue fever epidemics depend on temperature **(Fig. 120-5)**. Higher temperatures increase the rate of larval development and accelerate the emergence of adult *Aedes* mosquitoes. The daily temperature range may also influence dengue virus transmission, with a smaller range corresponding to a higher transmission potential. Temperatures <15°C or >36°C substantially reduce mosquito feeding. In a *Rhesus* model of dengue, viral replication can occur in as little as 7 days with temperatures of >32–35°C; at 30°C, replication takes ≥12 days; and replication does not reliably occur at 26°C. Research on dengue in New Caledonia has shown peak transmission at ~32°C, reflecting combined effects of a shorter extrinsic incubation period, a higher feeding frequency, and more rapid development of mosquitoes. Along with temperature, peak relative humidity is a strong predictor of dengue outbreaks.

The association between dengue epidemics and precipitation is less consistent in the peer-reviewed literature, possibly because of the mosquito vector's greater reliance on domestic breeding sites than on natural pools of water. For instance, in some studies, increased access to a piped water supply has been linked to dengue epidemics, presumably because of associated increased domestic water storage. Nonetheless, several studies have established rainfall as a predictor of the seasonal timing of dengue epidemics.

The current global distribution of dengue largely overlaps the geographic spread of *Aedes* mosquitoes **(Fig. 120-6)**. The presence of *Aedes* without dengue endemicity in large regions of North and South America and Africa illustrates the relevance of variables other than climate to disease incidence. Nevertheless, coupled climatic–epidemiologic modeling suggests dramatic shifts in the relative vectorial capacity for dengue by the end of this century should little or no mitigation of greenhouse gas emissions occur **(Fig. 120-7)**. Given the joint effects of climate change and population growth, the number of people exposed to *A. aegypti* globally may nearly double by 2100 from roughly 4 billion to 8 billion or more.

Other Arbovirus Infections Climate change may favor increased geographic spread of other arboviral diseases, including Zika virus disease, chikungunya virus disease, West Nile virus disease, and eastern equine encephalitis. Zika virus moved to the Western Hemisphere from French Polynesia around 2013 and rapidly spread in Brazil in 2016. Although air travel was essential for the delivery of the virus to the Americas, the available evidence suggests that the 2015 El Niño event provided an optimal climate for the infection to take root and spread. *A. aegypti* is the primary vector for Zika virus. Chikungunya virus disease emerged in Italy in 2007, having previously been mostly a disease of African nations. Climate models predict that, should competent vectors be present, conditions will be suitable for chikungunya virus to gain a foothold in Western Europe, especially France, in the

[1] rVc is the vectorial capacity relative to the vector-to-human population ratio and is defined by the equation $rVc = a^2 b_h b_m e^{-\mu m n}/\mu_m$ where a is the vector biting rate; b_h is the probability of vector-to-human transmission per bite; b_m is the probability of human-to-vector infection per bite; n is the duration of the extrinsic incubation period; and μ_m is the vector mortality rate.

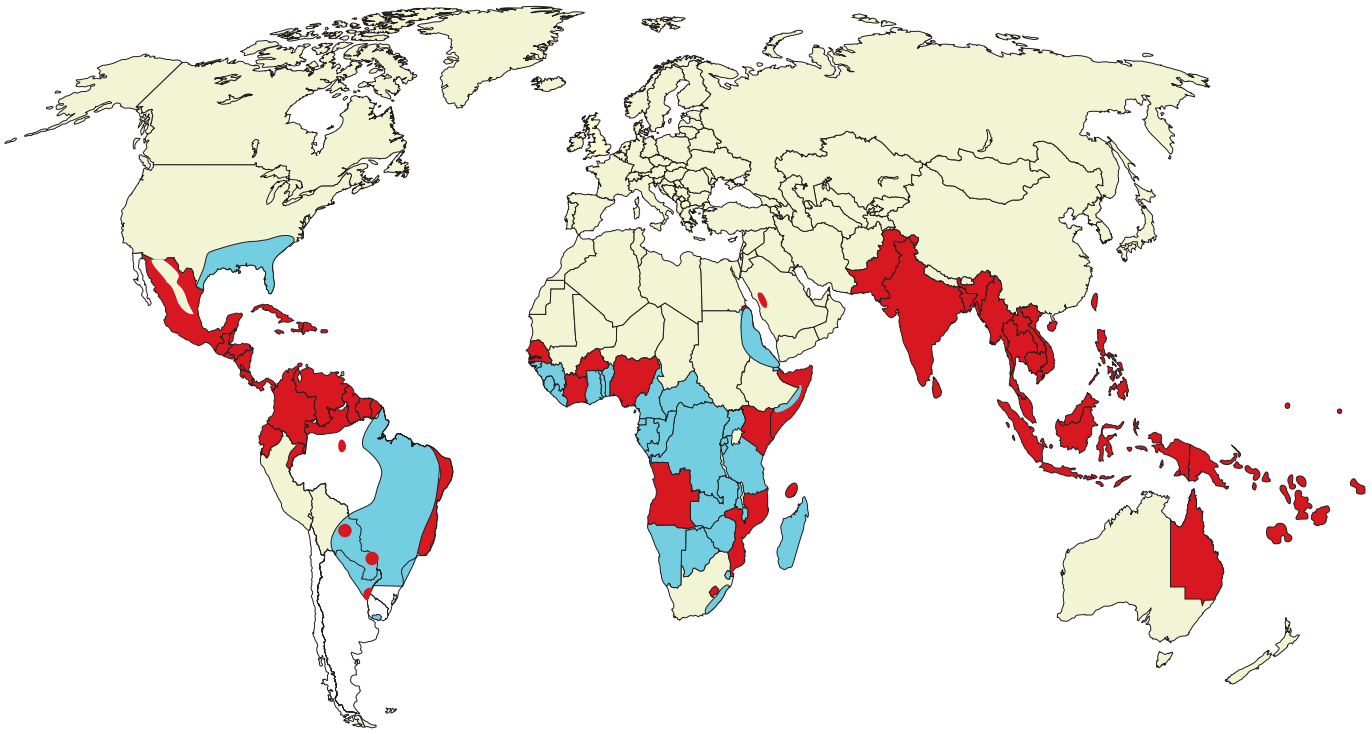

FIGURE 120-6 Distribution of *Aedes aegypti* mosquitoes (*turquoise*) and dengue fever epidemics (*red*). *(Map produced by the Agricultural Research Service of the U.S. Department of Agriculture.)*

first half of the twenty-first century. In North America, areas favorable to West Nile virus outbreaks are expected to shift northward in this century. Current hotspots in North America are the California Central Valley, southwestern Arizona, southern Texas, and Louisiana, which have both compatible climates and avian reservoirs for the disease. By mid-century, the upper Midwest and New England will be more climatically suited to West Nile virus; by the end of the century, the area of risk may shift even further north to southern Canada. Whether the disease will ultimately move northward will depend on reservoir availability and mosquito control programs, among other factors.

Lyme Disease In the past few decades, *Ixodes scapularis*, the primary tick vector for Lyme disease as well as for anaplasmosis and babesiosis in New England, has become established in Canada because of warming temperatures. With climate change, the range of the tick is expected to expand further **(Fig. 120-8)**.

Lyme disease, caused by the spirochete *Borrelia burgdorferi*, is the most commonly reported vector-borne disease in North America, with ~30,000 cases per year. The model used in Fig. 120-8 showed 95% accuracy in predicting current *I. scapularis* distribution and suggests substantial expansion of tick habitat and consequently of populations at risk for the diseases this tick transmits, particularly in Quebec, Iowa, and Arkansas, by 2080. Of note, some areas on the Gulf Coast may become less suitable for ticks by the end of the century.

WATERBORNE DISEASE

Outbreaks of waterborne disease are associated with heavy rainfall events. A review of 548 waterborne disease outbreaks in the United States found that 51% were preceded by precipitation levels above the 90th percentile. Since 1900, most regions of the United States except the Southwest and Hawaii have experienced an increase in heavy downpours **(Fig. 120-9)**, with the greatest intensification of the water cycle in New England and Alaska. Climate models suggest that by 2100 daily heavy-precipitation events, which are defined as a cumulative daily amount that now occurs once every 20 years, will increase nationwide **(Fig. 120-10)**. This scenario may be from two to as much as five times more likely, depending on the extent of greenhouse gas emission reductions achieved early in the twenty-first century.

Most disease outbreaks after heavy precipitation occur through contamination of drinking-water supplies. While outbreaks related to surface-water contamination generally occur within a month of the precipitation event, disease outbreaks from groundwater contamination tend to occur ≥2 months later. According to a review of published reports of waterborne disease outbreaks, *Vibrio* and *Leptospira* species are the pathogens most commonly involved in the wake of heavy precipitation.

Combined Sewer Systems Roughly 40 million people in the United States and millions more around the world rely on combined sewer systems in which storm water and sanitary wastewater are conveyed in the same pipe to treatment facilities. These systems were designed on the basis of the nineteenth-century climate, in which heavy downpours were less frequent than they are today. The frequency of combined sewer overflows resulting in untreated sewage discharge, usually into freshwater bodies, has been increasing in cities worldwide. Overflows are associated with discharges of heavy metals and other chemical pollutants as well as a variety of pathogens. Outbreaks of hepatitis A, *Escherichia coli* O157:H7 infection, and cryptosporidial disease have been associated with sewer overflows in the United States.

Rising Temperatures and *Vibrio* Species Warmer temperatures favor proliferation of *Vibrio* species and disease outbreaks, as has been demonstrated in countries surrounding the Baltic Sea, Chile, Israel, northwestern Spain, and the U.S. Pacific Northwest. Around the Baltic Sea, outbreaks of *Vibrio* infection may be particularly likely because of faster warming near the poles and the sea's relatively low salt content. In 2004, a *Vibrio parahaemolyticus* outbreak arising from consumption of Alaskan oysters occurred. This pathogen was unknown in Alaskan oysters prior to this event and extended the known geographic range of the disease 1000 km northward.

ENSO-Related Outbreaks In the past, El Niño events were used as a model to investigate the potential for extreme weather–related infectious disease epidemics occurring in association with climate change. Recent evidence indicates that climate change itself may be strengthening El Niño events. These events tend to promote epidemic infections in certain regions **(Fig. 120-11)**.

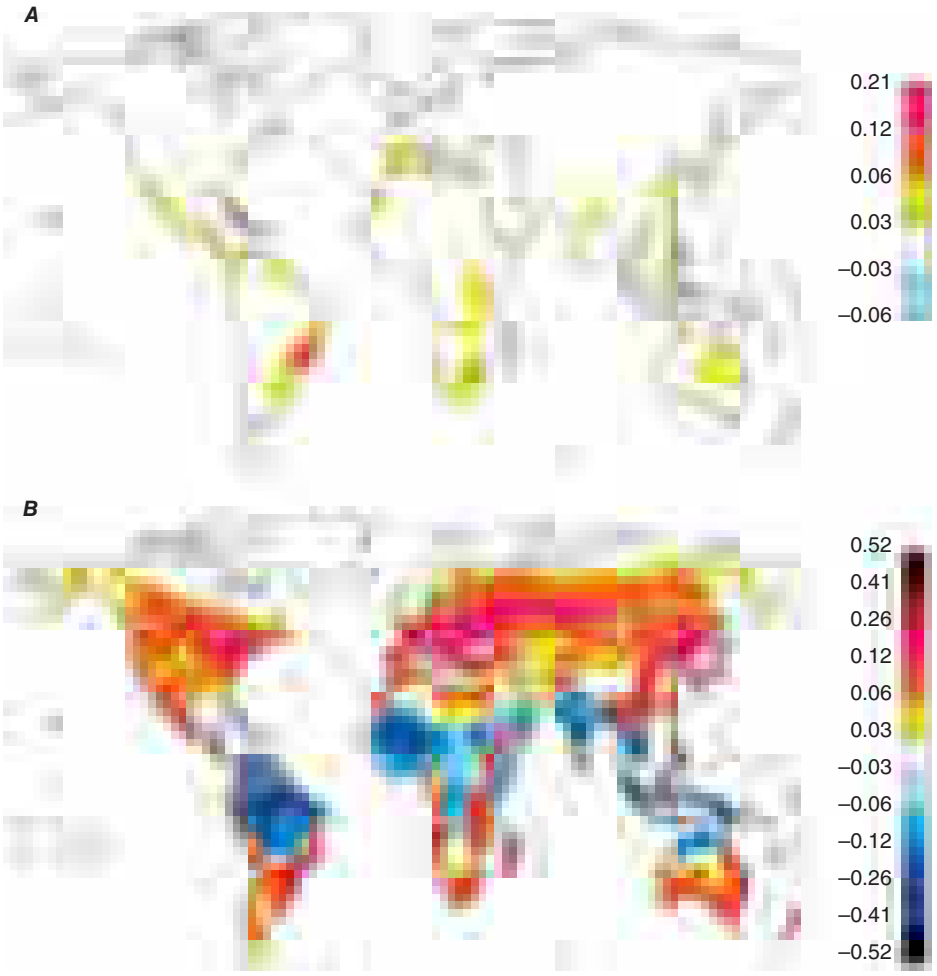

FIGURE 120-7 Trend of annually averaged global dengue epidemic potential (*rVc*). Differences in rVc are based on 30-year averages of temperature and daily temperature range. ***A.*** Differences between 1980–2009 and 1901–1930. ***B.*** Differences between 2070–2099 and 1980–2009. The mean value of rVc was averaged from five global climate models under RCP8.5, a scenario of high greenhouse-gas emission. The color bar describes the values of the rVc. *(From J Liu-Helmersson et al: Vectorial capacity of Aedes aegypti: Effects of temperature and implications for global dengue epidemic potential. PLoS ONE 9:e89783, 2014 [doi:10.1371/journal.pone.0089783].)*

Associations of El Niño with outbreaks of Rift Valley fever in eastern and southern Africa have been known since the 1950s. El Niño favors wet conditions suitable for the insect vectors of the disease in these regions. Given the strong association between El Niño conditions and disease incidence, models have successfully predicted Rift Valley fever epidemics in humans and animals. In the 2006–2007 El Niño season, for example, outbreaks of Rift Valley fever were accurately predicted 2–6 weeks prior to epidemics in Somalia, Kenya, and Tanzania.

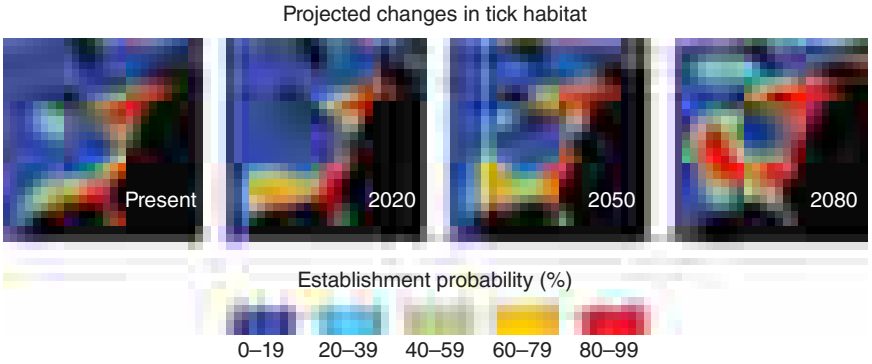

FIGURE 120-8 Present and projected probability of establishment of *Ixodes scapularis*. *(From U.S. National Climate Assessment 2014, adapted from JS Brownstein et al: Effect of climate change on Lyme disease risk in North America. Ecohealth 2:38, 2005.)*

El Niño has had inconsistent associations with malaria incidence in African countries. Some of the strongest associations between El Niño and malaria have been identified in South Africa and Swaziland, where available data on incidence are relatively robust; however, even in these instances, the observed increased risk did not reach statistical significance. A stronger link to El Niño has been found in several studies done in South America. Research on malaria incidence in Colombia between 1960 and 2006 found that a 1°C temperature rise contributed to a 20% increase in incidence.

El Niño years are often associated with an increased incidence of dengue. Research on dengue outbreaks in Thailand from 1996 to 2005 revealed that 15–22% of the variance in monthly dengue disease incidence was attributable to El Niño. In South America, data on dengue outbreaks between 1995 and 2010 showed an increased incidence during the El Niño events of 1997–1998 and 2006–2007.

CLIMATE CHANGE, POPULATION DISPLACEMENT, AND INFECTIOUS DISEASE EPIDEMICS

For many reasons, including freshwater shortages, flooding, food shortages, and climate change–driven conflicts, climate change has and will continue to put pressure on human populations to move. Human migrations have long been associated with epidemic disease in the migrating populations themselves and in the communities in which they settle. The specific pathogens and patterns of disease that may appear after population migration relate to endemic diseases present in the migrant populations.

Large-scale migrations are common after extreme precipitation events. Hurricane Katrina, for instance, displaced about 1 million people from the U.S. Gulf Coast. Among Katrina refugees, outbreaks of respiratory, diarrheal, and skin diseases were most common. While attribution of a single weather event to increased greenhouse-gas emissions is difficult, research can provide information on the likelihood of such events. It is expected, for example, that warming by 1°C increases the odds of a storm as strong as or stronger than Katrina two- to sevenfold.

In the developing world, infectious disease outbreaks associated with population displacement due to extreme weather events may be especially hard to detect and respond to. Mitigation of disease risk requires overlaying of climate-related migration risk with foci of disease epidemics.

A BROADER VIEW OF CLIMATE CHANGE AND HEALTH

Climate change has far-reaching implications for the distribution and spread of infectious diseases worldwide. However, the greatest disease burdens related to climate change may not be due to infections. Because climate change disrupts the foundations of health, such as access to safe drinking water and food, it has the potential to undermine progress against major existing health problems

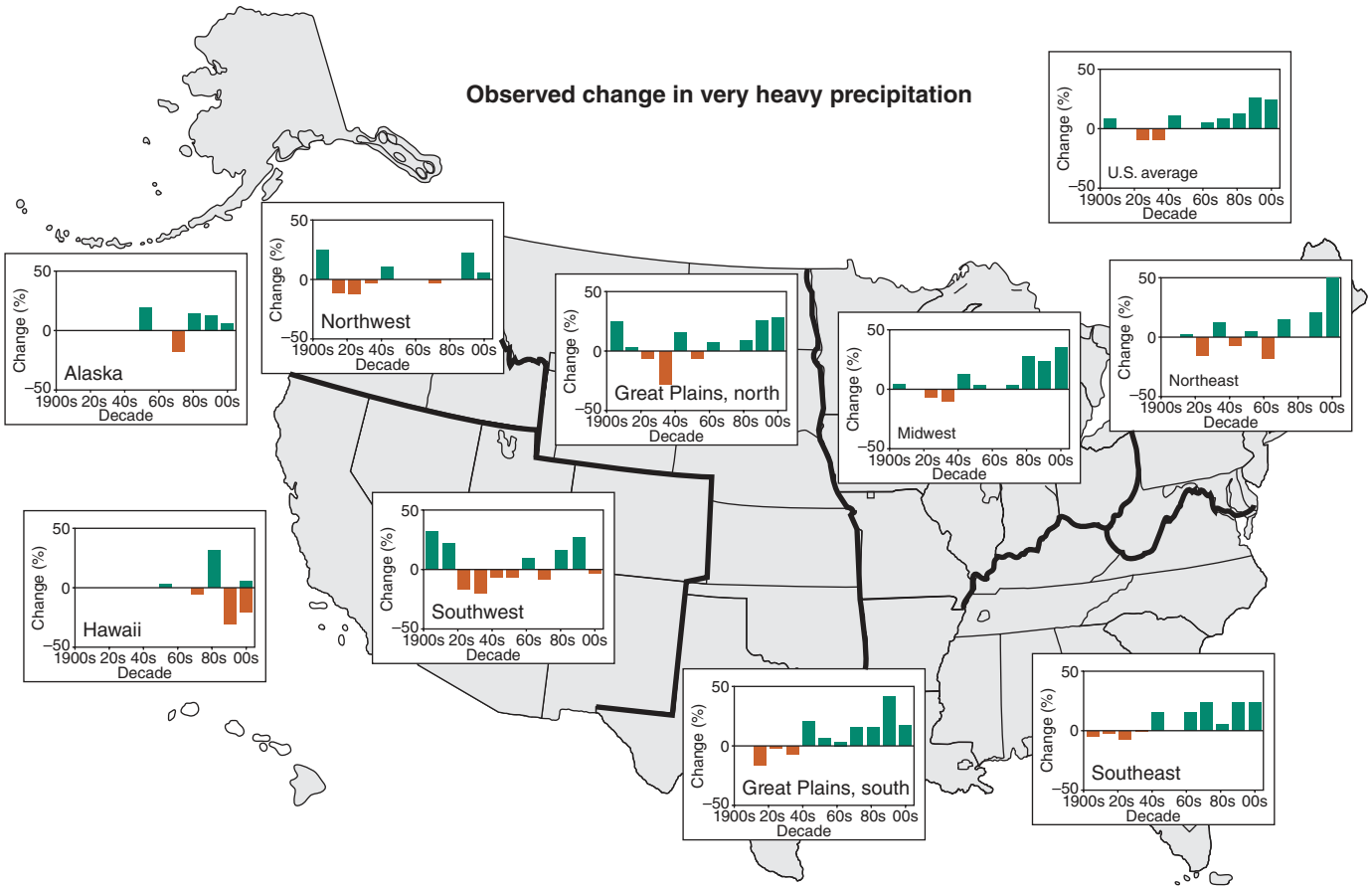

FIGURE 120-9 Percentage changes in the annual amount of precipitation falling in very heavy events, defined as the heaviest 1% of all daily events from 1901 to 2012 for each region. Changes are relative to a 1901–1960 average for all regions except values for Alaska and Hawaii, which are relative to the 1951–1980 average. *(From U.S. National Climate Assessment 2014, NOAA National Climate Data Center/Cooperative Institute for Climate and Satellites, North Carolina.)*

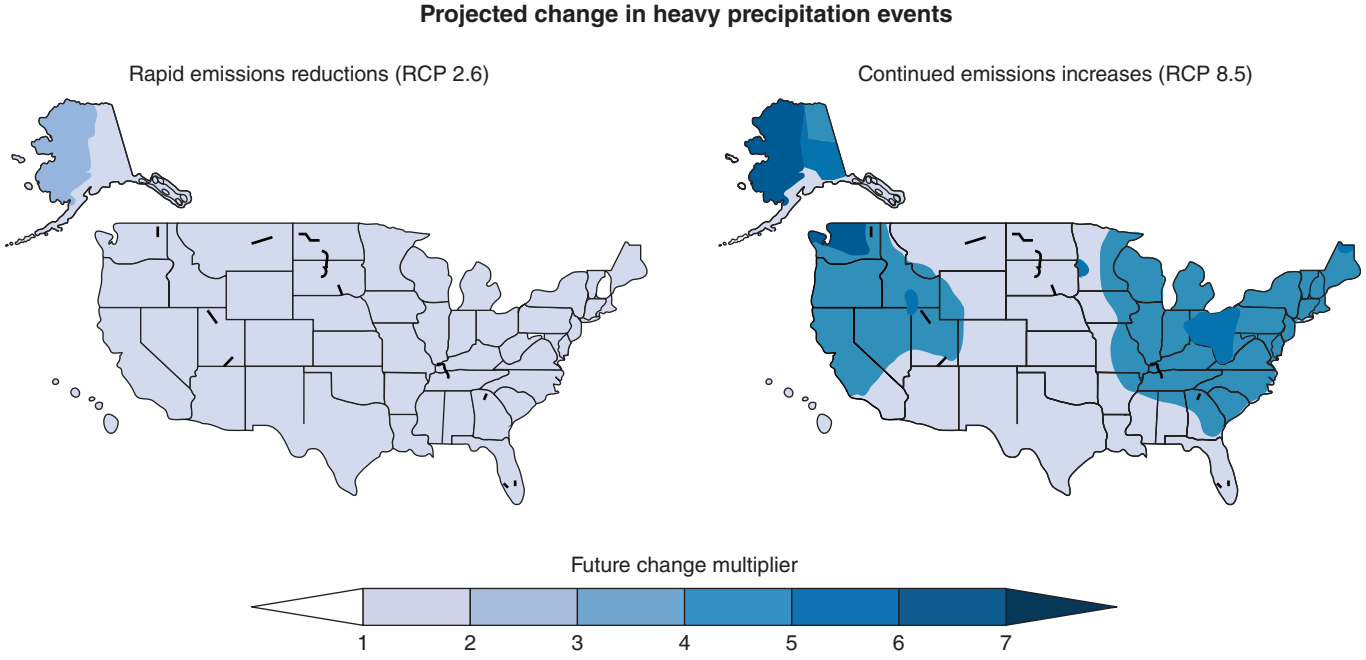

FIGURE 120-10 Increased frequency of extreme daily precipitation events (defined as a daily amount that now occurs once in 20 years) by the latter part of the twenty-first century (2081–2100) compared to the frequency in the latter part of the twentieth century (1981–2000). A representative concentration pathway (RCP) describes a plausible climate future based on a net radiative forcing (e.g., 2.6 or 8.5) in 2100. *(From U.S. National Climate Assessment 2014, NOAA National Climate Data Center/Cooperative Institute for Climate and Satellites, North Carolina.)*

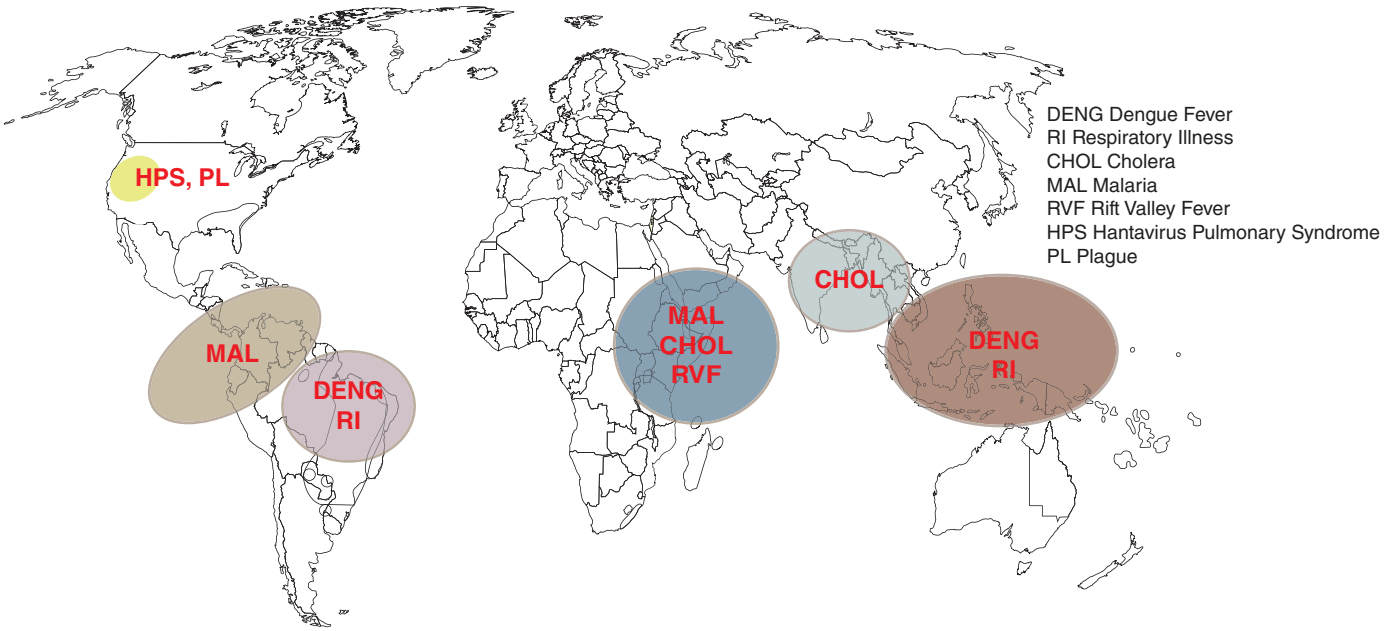

FIGURE 120-11 Characteristic patterns of disease outbreaks associated with El Niño events, determined on the basis of 2006–2007 conditions. *(From A Anyamba et al: Developing global climate anomalies suggest potential disease risks for 2006–2007. Int J Health Geogr 5:60, 2006.)*

such as malnutrition. In addition, resource scarcity and climate instability are increasingly associated with conflicts. Scholars have argued that events related to climate change were a factor in the revolutions of the Arab Spring and the Syrian civil war.

The public health response to climate change entails both mitigation and adaptation measures. *Mitigation* represents primary prevention and involves the reduction of greenhouse gas emissions into the atmosphere. Although no clear safety threshold of greenhouse gas emissions has been agreed upon, national governments from the major industrialized countries have agreed to set a warming target of <2°C above preindustrial levels by 2050; the attainment of this goal will require reducing greenhouse gas emissions by 40–70% below 2010 levels. The 2016 Paris Agreement on climate change provides a framework for the establishment of a global carbon market that may speed reductions in greenhouse gas emissions, along with several other seminal provisions. Mitigation also confers co-benefits, including better air quality that results when fewer bio- or fossil fuels are burned. Biofuel-burning cookstoves, for instance, used by some 3 billion people around the world, release air pollution that constitutes about one-fourth of the global black-carbon emissions that warm the planet and kill roughly 4 million people a year. Clean cookstoves simultaneously mitigate climate change and indoor air pollution–related mortality.

Adaptation represents secondary prevention and is aimed at reducing the harms associated with sea level rise, heat waves, floods, droughts, wildfires, and other greenhouse gas–driven events. The efficacy of adaptation is constrained by the challenges inherent in predicting the precise location, duration, and severity of extreme weather events and flooding related to sea level rise, among other considerations.

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Section 2 Clinical Syndromes: Community-Acquired Infections

121 Pneumonia

Lionel A. Mandell, Richard Wunderink

DEFINITION

Pneumonia is an infection of the pulmonary parenchyma. Despite being the cause of significant morbidity and mortality, it is often misdiagnosed, mistreated, and underestimated. Pneumonia historically was typically classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP). A fourth category, health care–associated pneumonia (HCAP), was introduced recently. This category was meant to encompass those cases of CAP that were caused by multidrug-resistant (MDR) pathogens typically associated with HAP. Unfortunately, the original definitions appear to have been overly sensitive, resulting in the treatment of a high proportion of patients who had community-onset pneumonia with broad-spectrum antibiotics consistent with HAP treatment. Retrospective studies have actually suggested a worse outcome when broad-spectrum antibiotics were used in these cases.

Rather than relying on a predefined subset or category of pneumonia cases, it is likely to be of greater value to assess each case individually on the basis of risk factors for infection with an MDR organism. Rather than

TABLE 121-1 Risk Factors for Pathogens Resistant to Usual Therapy for Community-Acquired Pneumonia[a]

MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA AND MRSA	NOSOCOMIAL MRSA	COMMUNITY-ACQUIRED MRSA
Hospitalization ≥2 days in previous 90 days	Hospitalization ≥ 2 days in previous 90 days	Cavitary infiltrate or necrosis
Use of antibiotics in previous 90 days	Use of antibiotics in previous 90 days	Gross hemoptysis
Immunosuppression	Chronic hemodialysis in previous 30 days	Neutropenia
Nonambulatory status	Documented prior MRSA colonization	Erythematous rash
Tube feedings	Congestive heart failure	Concurrent influenza
Gastric acid suppression	Gastric acid suppression	Young, previously healthy status
Severe COPD or bronchiectasis[b]		Summer-month onset

[a]Cephalosporin/macrolide or respiratory fluoroquinolone. [b]Risk for *Pseudomonas aeruginosa* infection.

Abbreviations: COPD, chronic obstructive pulmonary disease; MRSA, methicillin-resistant *Staphylococcus aureus*.

originating in primary pneumonia research, the original HCAP definition was modified from a study of health care–associated bacteremia. Recent studies have more closely identified patients at risk for pathogens resistant to the antibiotics usually used; have defined risk factors for infection with methicillin-resistant *Staphylococcus aureus* (MRSA) independent of other MDR pathogens; and have found that at least two, if not three, risk factors are required before the probability of drug-resistant pathogens is sufficient to influence initial empirical broad-spectrum antibiotic therapy. These risk factors are listed in **Table 121-1**.

This chapter deals with pneumonia in patients who are not considered to be immunocompromised. **Pneumonia in severely immunocompromised patients, some of whom overlap with the groups of patients considered in this chapter, warrants separate discussion (see Chaps. 70, 138, and 197).**

PATHOPHYSIOLOGY

Pneumonia results from the proliferation of microbial pathogens at the alveolar level and the host's response to those pathogens. Microorganisms gain access to the lower respiratory tract in several ways. The most common is by aspiration from the oropharynx. Small-volume aspiration occurs frequently during sleep (especially in the elderly) and in patients with decreased levels of consciousness. Rarely, pneumonia occurs via hematogenous spread (e.g., from tricuspid endocarditis) or by contiguous extension from an infected pleural or mediastinal space.

Mechanical factors are critically important in host defense. The hairs and turbinates of the nares capture larger inhaled particles before they reach the lower respiratory tract. The branching architecture of the tracheobronchial tree traps microbes on the airway lining, where mucociliary clearance and local antibacterial factors either clear or kill the potential pathogen. The gag and cough reflexes offer critical protection from aspiration. In addition, the normal flora adhering to mucosal cells of the oropharynx, whose components are remarkably constant, prevents pathogenic bacteria from binding and thereby decreases the risk of pneumonia.

When these barriers are overcome or when microorganisms are small enough to be inhaled to the alveolar level, resident alveolar macrophages are extremely efficient at clearing and killing pathogens. Macrophages are assisted by proteins that are produced by the alveolar epithelial cells (e.g., surfactant proteins A and D) and that have intrinsic opsonizing properties or antibacterial or antiviral activity. Once engulfed by the macrophage, the pathogens—even if they are not killed—are eliminated via either the mucociliary elevator or the lymphatics and no longer represent an infectious challenge. Only when the capacity of the alveolar macrophages to ingest or kill the microorganisms is exceeded does clinical pneumonia become manifest. In that situation, the alveolar macrophages initiate the inflammatory response to bolster lower respiratory tract defenses. The host inflammatory response, rather than proliferation of microorganisms, triggers the clinical syndrome of pneumonia. The release of inflammatory mediators, such as interleukin 1 and tumor necrosis factor, results in fever. Chemokines, such as interleukin 8 and granulocyte colony-stimulating factor, stimulate the release of neutrophils and their attraction to the lung, producing both peripheral leukocytosis and increased purulent secretions. Inflammatory mediators released by macrophages and the newly recruited neutrophils create an alveolar capillary leak equivalent to that seen in acute respiratory distress syndrome, although in pneumonia this leak is localized (at least initially). Even erythrocytes can cross the alveolar–capillary membrane, with consequent hemoptysis. The capillary leak results in a radiographic infiltrate and rales detectable on auscultation, and hypoxemia results from alveolar filling. Moreover, some bacterial pathogens appear to interfere with the hypoxemic vasoconstriction that would normally occur with fluid-filled alveoli, and this interference can result in severe hypoxemia. Increased respiratory drive in the systemic inflammatory response syndrome **(Chap. 297)** leads to respiratory alkalosis. Decreased compliance due to capillary leak, hypoxemia, increased respiratory drive, increased secretions, and occasionally infection-related bronchospasm all lead to dyspnea. If severe enough, the changes in lung mechanics secondary to reductions in lung volume and compliance and the intrapulmonary shunting of blood may cause respiratory failure and death.

The presence of a normal alveolar microbiota raises the possibility of an alternative pathway for development of pneumonia. This microbiota is similar to the oropharyngeal microbiota; both are predominantly gram-positive in contrast to the gram-negative milieu of the normal gastrointestinal microbiota. Rather than invasion of a sterile lower respiratory tract by pathogens to cause pneumonia, alterations in host defense may allow overgrowth of one or more components of the normal bacterial flora. The fact that many CAP pathogens are components of the normal alveolar microbiota supports this alternative-pathogenesis model. The two most likely sources of an altered alveolar microbiota are viral upper respiratory tract infections for CAP and antibiotic therapy for HAP/VAP.

PATHOLOGY

Classic pneumonia evolves through a series of pathologic changes. The initial phase is one of *edema*, with the presence of a proteinaceous exudate—and often of bacteria—in the alveoli. This phase is rarely evident in clinical or autopsy specimens because of the rapid transition to the *red hepatization* phase. The presence of erythrocytes in the cellular intra-alveolar exudate gives this second stage its name, but neutrophil influx is more important with regard to host defense. Bacteria are occasionally seen in pathologic specimens collected during this phase. In the third phase, *gray hepatization*, no new erythrocytes are extravasating, and those already present have been lysed and degraded. The neutrophil is the predominant cell, fibrin deposition is abundant, and bacteria have disappeared. This phase corresponds with successful containment of the infection and improvement in gas exchange. In the final phase, *resolution*, the macrophage reappears as the dominant cell type in the alveolar space, and the debris of neutrophils, bacteria, and fibrin has been cleared, as has the inflammatory response.

This pattern has been described best for lobar pneumococcal pneumonia and may not apply to pneumonia of all etiologies, especially viral or *Pneumocystis* pneumonia. In VAP, respiratory bronchiolitis may precede the development of a radiologically apparent infiltrate. Because of the microaspiration mechanism, a bronchopneumonia pattern is most common in nosocomial pneumonias, whereas a lobar pattern is more common in bacterial CAP. Despite the radiographic appearance, viral and *Pneumocystis* pneumonias represent alveolar rather than interstitial processes.

COMMUNITY-ACQUIRED PNEUMONIA

ETIOLOGY

The extensive list of potential etiologic agents in CAP includes bacteria, fungi, viruses, and protozoa. Newly identified pathogens include metapneumoviruses, the coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and community-acquired strains of MRSA. Most cases of CAP, however, are caused by relatively few pathogens **(Table 121-2)**.

TABLE 121-2 Microbial Causes of Community-Acquired Pneumonia, by Site of Care

	HOSPITALIZED PATIENTS	
OUTPATIENTS	NON-ICU	ICU
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*Chlamydia pneumoniae*	*Legionella* spp.
C. pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses[a]	*Legionella* spp.	*H. influenzae*
	Respiratory viruses[a]	Respiratory viruses

[a]Influenza A and B viruses, human metapneumovirus, adenoviruses, respiratory syncytial viruses, parainfluenza viruses.

Abbreviation: ICU, intensive care unit.

TABLE 121-3 Epidemiologic Factors Suggesting Possible Causes of Community-Acquired Pneumonia

FACTOR	POSSIBLE PATHOGEN(S)
Alcoholism	*Streptococcus pneumoniae*, oral anaerobes, *Klebsiella pneumoniae*, *Acinetobacter* spp., *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Legionella* spp., *S. pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa*, *Burkholderia cepacia*, *Staphylococcus aureus*
Dementia, stroke, decreased level of consciousness	Oral anaerobes, gram-negative enteric bacteria
Lung abscess	CA-MRSA, oral anaerobes, endemic fungi, *M. tuberculosis*, atypical mycobacteria
Travel to Ohio or St. Lawrence river valley	*Histoplasma capsulatum*
Travel to southwestern United States	Hantavirus, *Coccidioides* spp.
Travel to Southeast Asia	*Burkholderia pseudomallei*, avian influenza virus
Stay in hotel or on cruise ship in previous 2 weeks	*Legionella* spp.
Local influenza activity	Influenza virus, *S. pneumoniae*, *S. aureus*
Exposure to bats or birds	*H. capsulatum*
Exposure to birds	*Chlamydia psittaci*
Exposure to rabbits	*Francisella tularensis*
Exposure to sheep, goats, parturient cats	*Coxiella burnetii*

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* COPD, chronic obstructive pulmonary disease.

Although *Streptococcus pneumoniae* is most common, other organisms must also be considered in light of the patient's risk factors and severity of illness. Separation of potential agents into "typical" bacterial pathogens or "atypical" organisms may be helpful. The former category includes *S. pneumoniae*, *Haemophilus influenzae*, and (in selected patients) *S. aureus* and gram-negative bacilli such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* The "atypical" organisms include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species as well as respiratory viruses such as influenza viruses, adenoviruses, human metapneumovirus, and respiratory syncytial viruses. Overall, with the increasing use of pneumococcal vaccine, the incidence of pneumococcal pneumonia appears to be decreasing. Cases due to *M. pneumoniae* and *C. pneumoniae*, however, appear to be increasing in incidence, especially among young adults. Viruses may be responsible for a large proportion of CAP cases that require hospital admission, even in adults. Polymerase chain reaction (PCR)–based testing shows that viruses may be present in 20–30% of healthy adults and in the same percentage of patients with pneumonia, including those who are severely ill. The most common of these viruses are influenza, parainfluenza, and respiratory syncytial viruses. Whether they are etiologic pathogens, co-pathogens, or simply colonizers cannot always be determined. Atypical organisms cannot be cultured on standard media or seen on Gram's stain. The frequency and importance of atypical pathogens have significant implications for therapy. They are intrinsically resistant to all β-lactam agents and must be treated with a macrolide, a fluoroquinolone, or a tetracycline. In the ~10–15% of CAP cases that are polymicrobial, the etiology usually includes a combination of typical and atypical pathogens.

Anaerobes play a significant role only when an episode of aspiration has occurred days to weeks before presentation for pneumonia. The combination of an unprotected airway (e.g., in patients with alcohol or drug overdose or a seizure disorder) and significant gingivitis constitutes the major risk factor. Anaerobic pneumonias are often complicated by abscess formation and by significant empyemas or parapneumonic effusions.

S. aureus pneumonia is well known to complicate influenza infection. However, MRSA has been reported as a primary etiologic agent of CAP. While this entity is still relatively uncommon, clinicians must be aware of its potentially serious consequences, such as necrotizing pneumonia. Two important developments have led to this problem: the spread of MRSA from the hospital setting to the community and the emergence of genetically distinct strains of MRSA in the community. The community-acquired MRSA (CA-MRSA) strains may infect healthy individuals with no association with health care.

Unfortunately, despite a careful history and physical examination as well as routine radiographic studies, the causative pathogen in a case of CAP is difficult to predict with any degree of certainty; in more than one-half of cases, a specific etiology is never determined. Nevertheless, epidemiologic and risk factors may suggest the involvement of certain pathogens **(Table 121-3)**.

EPIDEMIOLOGY

More than 5 million CAP cases occur annually in the United States. Along with influenza, CAP is the eighth leading cause of death in this country. Usually, 80% of the affected patients are treated as outpatients and 20% as inpatients. The mortality rate among outpatients is usually <5%, whereas among hospitalized patients the rate can range from ~12% to 40%, depending on whether treatment is provided in or outside of the intensive care unit (ICU). In the United States, CAP is the number one cause of death from infection among patients >65 years of age. Further compounding its impact is the fact that 18% of hospitalized CAP patients are readmitted within 1 month of discharge. CAP results in more than 1.2 million hospitalizations and more than 55,000 deaths annually. The overall yearly cost associated with CAP is estimated at $17 billion. The incidence rates are highest at the extremes of age. The overall annual rate in the United States is 12 cases/1000 persons, but the figure increases to 12–18/1000 among children <4 years of age and to 20/1000 among persons >60 years of age.

The risk factors for CAP in general and for pneumococcal pneumonia in particular have implications for treatment regimens. Risk factors for CAP include alcoholism, asthma, immunosuppression, institutionalization, and an age of ≥70 years. In the elderly, factors such as decreased cough and gag reflexes as well as reduced antibody and Toll-like receptor responses increase the likelihood of pneumonia. Risk factors for pneumococcal pneumonia include dementia, seizure disorders, heart failure, cerebrovascular disease, alcoholism, tobacco smoking, chronic obstructive pulmonary disease (COPD), and HIV infection. CA-MRSA pneumonia is more likely in patients with skin colonization or infection with CA-MRSA. Enterobacteriaceae tend to infect patients who have recently been hospitalized and/or received antibiotic therapy or who have comorbidities such as alcoholism, heart failure, or renal failure. *P. aeruginosa* is a particular problem in patients with severe structural lung disease, such as bronchiectasis, cystic fibrosis, or severe COPD. Risk factors for *Legionella* infection include diabetes, hematologic malignancy, cancer, severe renal disease, HIV infection, smoking, male gender, and a recent hotel stay or ship cruise.

CLINICAL MANIFESTATIONS

CAP can vary from indolent to fulminant in presentation and from mild to fatal in severity. Manifestations of progression and severity include both constitutional findings and those limited to the lung and associated structures.

The patient is frequently febrile with tachycardia or may have a history of chills and/or sweats. Cough may be either nonproductive or productive of mucoid, purulent, or blood-tinged sputum. Gross hemoptysis is suggestive of CA-MRSA pneumonia. Depending on severity, the patient may be able to speak in full sentences or may be very short of breath. If the pleura is involved, the patient may experience pleuritic chest pain. Up to 20% of patients may have gastrointestinal symptoms such as nausea, vomiting, and/or diarrhea. Other symptoms may include fatigue, headache, myalgias, and arthralgias.

Findings on physical examination vary with the degree of pulmonary consolidation and the presence or absence of a significant pleural effusion. An increased respiratory rate and use of accessory muscles of respiration are common. Palpation may reveal increased or decreased tactile fremitus, and the percussion note can vary from dull to flat, reflecting underlying consolidated lung and pleural fluid, respectively. Crackles, bronchial breath sounds, and possibly a pleural friction rub may be heard on auscultation. The clinical presentation may not be so obvious in the elderly, who may initially display new-onset or worsening confusion and few other manifestations. Severely ill patients may have septic shock and evidence of organ failure.

The risk of cardiac complications secondary to enhanced inflammation and procoagulant activity is increased. These complications include myocardial infarction, congestive heart failure, and arrhythmias, particularly in the elderly. In pneumococcal CAP, the increased risk of acute coronary events may be partially driven by pneumolysis, which increases platelet activation. Up to 90% of acute coronary syndromes occur in the first week after onset of CAP, and the risk of new-onset congestive heart failure in elderly hospitalized CAP patients can extend up to 1 year.

DIAGNOSIS

When confronted with possible CAP, the physician must ask two questions: Is this pneumonia, and, if so, what is the likely etiology? The former question is typically answered by clinical and radiographic methods, whereas the latter requires the aid of laboratory techniques.

Clinical Diagnosis The differential diagnosis includes both infectious and noninfectious entities such as acute bronchitis, acute exacerbations of chronic bronchitis, heart failure, pulmonary embolism, hypersensitivity pneumonitis, and radiation pneumonitis. The importance of a careful history cannot be overemphasized. For example, known cardiac disease may suggest worsening pulmonary edema, while underlying carcinoma may suggest lung injury secondary to irradiation.

Unfortunately, the sensitivity and specificity of the findings on physical examination are less than ideal, averaging 58% and 67%, respectively. As mentioned earlier, the elderly may initially present with confusion alone. Therefore, chest radiography is often necessary to differentiate CAP from other conditions. Radiographic findings may include risk factors for increased severity (e.g., cavitation or multilobar involvement). Occasionally, radiographic results suggest an etiologic diagnosis. For example, pneumatoceles suggest infection with *S. aureus*, and an upper-lobe cavitating lesion suggests tuberculosis. CT may be of value in a patient with suspected postobstructive pneumonia caused by a tumor or foreign body or suspected cavitary disease. For outpatients, the clinical and radiologic assessments are usually all that is done before treatment for CAP is started since most laboratory results are not available soon enough to influence initial management significantly. In certain cases, the availability of rapid point-of-care outpatient diagnostic tests can be very important; for example, rapid diagnosis of influenza virus infection can prompt specific anti-influenza drug treatment and secondary prevention.

Etiologic Diagnosis The etiology of pneumonia usually cannot be determined solely on the basis of clinical presentation. Except for CAP patients admitted to the ICU, no data exist to show that treatment directed at a specific pathogen is statistically superior to empirical therapy. The benefit of establishing a microbial etiology can therefore be questioned, particularly in light of the cost of diagnostic testing. However, a number of reasons can be advanced for attempting an etiologic diagnosis. Identification of an unexpected pathogen allows narrowing of the initial empirical regimen, thereby decreasing antibiotic selection pressure and lessening the risk of resistance. Pathogens with important public safety implications, such as *Mycobacterium tuberculosis* and influenza virus, may be found in some cases. Finally, without culture and susceptibility data, trends in resistance cannot be followed accurately, and appropriate empirical therapeutic regimens are harder to devise.

GRAM'S STAIN AND CULTURE OF SPUTUM The main purpose of the sputum Gram's stain is to ensure that a sample is suitable for culture. However, Gram's staining may also identify certain pathogens (e.g., *S. pneumoniae*, *S. aureus*, and gram-negative bacteria) by their characteristic appearance. To be adequate for culture, a sputum sample must have >25 neutrophils and <10 squamous epithelial cells per low-power field. The sensitivity and specificity of the sputum Gram's stain and culture are highly variable. Even in cases of proven bacteremic pneumococcal pneumonia, the yield of positive cultures from sputum samples is ≤50%.

Many patients, particularly elderly individuals, may not be able to produce an appropriate expectorated sputum sample. Others may already have started a course of antibiotics that can interfere with culture results at the time a sample is obtained. Inability to produce sputum can result from dehydration, and its correction may result in increased sputum production and a more obvious infiltrate on chest radiography. For patients admitted to the ICU and intubated, a deep-suction aspirate or bronchoalveolar lavage sample (obtained either via bronchoscopy or non-bronchoscopically) has a high yield on culture when sent to the microbiology laboratory as soon as possible. Since the etiologies in severe CAP are somewhat different from those in milder disease (Table 121-2), the greatest benefit of staining and culturing respiratory secretions is to alert the physician of unsuspected and/or resistant pathogens and to permit appropriate modification of therapy. Other stains and cultures (e.g., specific stains for *M. tuberculosis* or fungi) may be useful as well.

BLOOD CULTURES The yield from blood cultures, even when samples are collected before antibiotic therapy, is disappointingly low. Only 5–14% of cultures of blood from patients hospitalized with CAP are positive, and the most frequently isolated pathogen is *S. pneumoniae.* Since recommended empirical regimens all provide pneumococcal coverage, a blood culture positive for this pathogen has little, if any, effect on clinical outcome. However, susceptibility data may allow narrowing of antibiotic therapy in appropriate cases. Because of the low yield and the lack of significant impact on outcome, blood cultures are no longer considered *de rigueur* for all hospitalized CAP patients. Certain high-risk patients—including those with neutropenia secondary to pneumonia, asplenia, complement deficiencies, chronic liver disease, or severe CAP—should have blood cultured.

URINARY ANTIGEN TESTS Two commercially available tests detect pneumococcal and *Legionella* antigen in urine. The test for *Legionella pneumophila* detects only serogroup 1, but this serogroup accounts for most community-acquired cases of Legionnaires' disease in the United States. The sensitivity and specificity of the *Legionella* urine antigen test are as high as 70% and 99%, respectively. The pneumococcal urine antigen test is also quite sensitive and specific (70% and >90%, respectively). Although false-positive results can be obtained with samples from pneumococcus-colonized children, the test is generally reliable. Both tests can detect antigen even after the initiation of appropriate antibiotic therapy.

POLYMERASE CHAIN REACTION PCR tests, which amplify a microorganism's DNA or RNA, are available for a number of pathogens. PCR of nasopharyngeal swabs, for example, has become the standard for diagnosis of respiratory viral infection. In addition, PCR can detect the nucleic acid of *Legionella* species, *M. pneumoniae*, *C. pneumoniae*, and mycobacteria. The cost-effectiveness of PCR testing, however, has not been definitively established. In patients with pneumococcal pneumonia, an increased bacterial load documented in whole blood by PCR is associated with an increased risk of septic shock, the need for mechanical ventilation, and death. Clinical availability of such a test could conceivably help identify patients suitable for ICU admission.

SEROLOGY A fourfold rise in specific IgM antibody titer between acute- and convalescent-phase serum samples is generally considered diagnostic of infection with the pathogen in question. In the past, serologic tests were used to help identify atypical pathogens as well as selected unusual organisms such as *Coxiella burnetii*. Recently, however, they have fallen out of favor because of the time required to obtain a final result for the convalescent-phase sample and the difficulty of interpretation.

BIOMARKERS A number of substances can serve as markers of severe inflammation. The two most commonly in use are C-reactive protein (CRP) and procalcitonin (PCT). Levels of these acute-phase reactants increase in the presence of an inflammatory response, particularly to bacterial pathogens. CRP may be of use in the identification of worsening disease or treatment failure, and PCT may play a role in distinguishing bacterial from viral infection, determining the need for antibacterial therapy, or deciding when to discontinue treatment. PCT testing can result in less antibiotic use in CAP with no concomitant increase in treatment failure or mortality risk. These tests should not be used on their own, but, when interpreted in conjunction with other findings from the history, physical examination, radiology, and laboratory tests, may help with antibiotic stewardship and appropriate management of seriously ill patients with CAP.

TREATMENT

Community-Acquired Pneumonia

SITE OF CARE

The cost of inpatient management exceeds that of outpatient treatment by a factor of 20, and hospitalization accounts for most CAP-related expenditures. Thus the decision to hospitalize a patient with CAP has considerable implications, and late admission to the ICU is associated with increased mortality risk. Certain patients can be managed at home, and others clearly require treatment in the hospital, but the choice is sometimes difficult. Tools that objectively assess the risk of adverse outcomes, including severe illness and death, can minimize unnecessary hospital admissions. Although a number of prediction rules exist, the two most frequently used are the Pneumonia Severity Index (PSI), a prognostic model used to identify patients at low risk of dying, and the CURB-65 criteria, a severity-of-illness score.

To determine the PSI, points are given for 20 variables, including age, coexisting illness, and abnormal physical and laboratory findings. On the basis of the resulting score, patients are assigned to one of five classes with the following mortality rates: class 1, 0.1%; class 2, 0.6%; class 3, 2.8%; class 4, 8.2%; and class 5, 29.2%. Determination of the PSI is often impractical in a busy emergency-department setting because of the number of variables. However, clinical trials demonstrate that routine use of the PSI results in lower admission rates for class 1 and class 2 patients. Patients in class 3 could ideally be admitted to an observation unit until a further decision can be made.

The CURB-65 criteria include five variables: confusion (C); urea >7 mmol/L (U); respiratory rate ≥30/min (R); blood pressure, systolic ≤90 mmHg or diastolic ≤60 mmHg (B); and age ≥65 years. Patients with a score of 0, among whom the 30-day mortality rate is 1.5%, can be treated outside the hospital. With a score of 1 or 2, the patient should be hospitalized unless the score is entirely or in part attributable to an age of ≥65 years. In such cases, hospitalization may not be necessary. Among patients with scores of ≥3, mortality rates are 22% overall; these patients may require ICU admission.

It is not clear which assessment tool is superior. Whichever system is used, these objective criteria must always be tempered by careful consideration of factors relevant to individual patients, including the ability to comply reliably with an oral antibiotic regimen and the resources available to the patient outside the hospital.

Neither PSI nor CURB-65 is accurate in determining the need for ICU admission. Septic shock or respiratory failure in the emergency department is an obvious indication for ICU care. However, mortality rates are higher among less ill patients who are admitted to the floor and then deteriorate than among equally ill patients monitored in the ICU. A variety of scores have been proposed to identify patients most likely to have early deterioration **(Table 121-4)**. Most factors in these scores are similar to the minor severity criteria proposed by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) in their guidelines for the management of CAP. Recent data suggest that thrombocytopenia, leukopenia, and hypothermia can be removed from the list of minor criteria.

TABLE 121-4 Risk Factors for Early Deterioration in Community-Acquired Pneumonia

Multilobar infiltrates	Hypoalbuminemia
Severe hypoxemia (arterial saturation <90%)	Neutropenia
Severe acidosis (pH <7.30)	Thrombocytopenia
Mental confusion	Hyponatremia
Severe tachypnea (>30 breaths/min)	Hypoglycemia

ANTIBIOTIC RESISTANCE

Antimicrobial resistance is a significant problem that threatens to diminish our therapeutic armamentarium. Misuse of antibiotics results in increased antibiotic selection pressure that can affect resistance locally and globally by clonal dissemination. For CAP, the main resistance issues currently involve *S. pneumoniae* and CA-MRSA.

S. pneumoniae In general, pneumococcal resistance is acquired by direct DNA incorporation and remodeling resulting from contact with closely related oral commensal bacteria, by the process of natural transformation, or by mutation of certain genes.

The minimal inhibitory concentration (MIC) cutoffs for penicillin in pneumonia are ≤2 μg/mL for susceptible, >2–4 μg/mL for intermediate, and ≥8 μg/mL for resistant. A change in susceptibility thresholds resulted in a dramatic decrease in the proportion of pneumococcal isolates considered nonsusceptible. For meningitis, MIC thresholds remain at the former higher levels. Fortunately, resistance to penicillin appeared to plateau even before the change in MIC thresholds. Pneumococcal resistance to β-lactam drugs is due solely to low-affinity penicillin-binding proteins. Risk factors for penicillin-resistant pneumococcal infection include recent antimicrobial therapy, an age of <2 years or >65 years, attendance at day-care centers, recent hospitalization, and HIV infection.

In contrast to penicillin resistance, resistance to macrolides is increasing through several mechanisms. *Target-site modification* caused by ribosomal methylation in 23S rRNA encoded by the *ermB* gene results in high-level resistance (MICs, ≥64 μg/mL) to macrolides, lincosamides, and streptogramin B–type antibiotics. The *efflux mechanism* encoded by the *mef* gene (*M phenotype*) is usually associated with low-level resistance (MICs, 1–32 μg/mL). These two mechanisms account for ~45% and ~65%, respectively, of resistant pneumococcal isolates in the United States. High-level resistance to macrolides is more common in Europe, whereas lower-level resistance predominates in North America. In some countries, including the United States, the prevalence of macrolide-resistant *S. pneumoniae* exceeds 25%. In such situations, a macrolide should not be used as empirical monotherapy.

Pneumococcal resistance to fluoroquinolones (e.g., ciprofloxacin and levofloxacin) has been reported. Changes can occur in one or both target sites (topoisomerases II and IV) from mutations in the *gyrA* and *parC* genes, respectively. In addition, an efflux pump may play a role in pneumococcal resistance to fluoroquinolones.

Isolates resistant to drugs from three or more antimicrobial classes with different mechanisms of action are considered MDR strains. The propensity for an association of pneumococcal resistance to penicillin with reduced susceptibility to other drugs, such as macrolides, tetracyclines, and trimethoprim-sulfamethoxazole,

is also of concern. In the United States, 58.9% of penicillin-resistant pneumococcal isolates from blood are also resistant to macrolides.

The most important risk factor for antibiotic-resistant pneumococcal infection is use of a specific antibiotic within the previous 3 months. Therefore, a patient's history of prior antibiotic treatment is a critical factor in avoiding the use of an inappropriate antibiotic.

M. pneumoniae Macrolide-resistant *M. pneumoniae* has been reported in a number of countries, including Germany (3%), Japan (30%), China (95%), and France and the United States (5–13%). *Mycoplasma* resistance to macrolides is on the rise as a result of binding-site mutation in domain V of 23S rRNA.

CA-MRSA CAP due to MRSA may be caused by the classic hospital-acquired strains or by genotypically and phenotypically distinct community-acquired strains. Most infections with the former strains have been acquired either directly or indirectly by contact with the health care environment (Table 121-1). However, in some hospitals, CA-MRSA strains are displacing the classic hospital-acquired strains—a trend suggesting that the newer strains may be more robust and blurring this distinction.

Methicillin resistance in *S. aureus* is determined by the *mecA* gene, which encodes for resistance to all β-lactam drugs. At least five *staphylococcal chromosomal cassette mec* (*SCCmec*) types have been described. The typical hospital-acquired strain usually has type II or III, whereas CA-MRSA has a type IV SCC*mec* element. CA-MRSA isolates tend to be less resistant than the older hospital-acquired strains and are often susceptible to trimethoprim-sulfamethoxazole, clindamycin, and tetracycline in addition to vancomycin and linezolid. However, the most important distinction is that CA-MRSA strains also carry genes for superantigens, such as enterotoxins B and C and Panton-Valentine leukocidin, a membrane-tropic toxin that can create cytolytic pores in polymorphonuclear neutrophils, monocytes, and macrophages.

Gram-Negative Bacilli A detailed discussion of resistance among gram-negative bacilli is beyond the scope of this chapter **(see Chap. 156)**. Fluoroquinolone resistance among isolates of *Escherichia coli* from the community appears to be increasing. *Enterobacter* species are typically resistant to cephalosporins; the drugs of choice for use against these bacteria are usually fluoroquinolones or carbapenems. Similarly, when infections due to bacteria producing extended-spectrum β-lactamases are documented or suspected, a fluoroquinolone or a carbapenem should be used.

INITIAL ANTIBIOTIC MANAGEMENT

Since the etiology of CAP is rarely known at the outset of treatment, initial therapy is usually empirical, designed to cover the most likely pathogens (Table 121-2). In all cases, antibiotic treatment should be initiated as expeditiously as possible. The CAP treatment guidelines in the United States (summarized in **Table 121-5**) represent joint statements from the IDSA and the ATS; the Canadian guidelines come from the Canadian Infectious Disease Society and the Canadian Thoracic Society. In these guidelines, coverage is always provided for the pneumococcus and atypical pathogens. In contrast, guidelines from some European countries do not always include atypical coverage based on local epidemiologic data. The U.S./Canadian approach is supported by retrospective data derived from administrative databases including thousands of patients. Atypical pathogen coverage provided by the addition of a macrolide to a β-lactam or by the use of a fluoroquinolone alone has been consistently associated with a significant reduction in mortality rates compared with those for β-lactam coverage alone.

For the treatment of severe CAP, accumulating data continue to demonstrate the benefits of including a macrolide, such as reduced mortality. However, two recent studies of patients hospitalized with moderate CAP yielded differing results. One study demonstrated a more rapid return to clinical stability and fewer adverse events with a β-lactam–macrolide combination than with a β-lactam alone. Using cluster randomization, the second study reported no difference among three regimens—a β-lactam alone, a β-lactam–macrolide combination, and a fluoroquinolone—but had significant design flaws, including a lack of chest radiographic confirmation in 24% of cases and significant rates of noncompliance with the assigned regimen.

Empirical treatment regimens for CAP are listed in Table 121-5. In general, the recommendations in the IDSA/ATS guidelines published in 2007 continue to apply but with a possible exception for treatment of outpatients who have previously been well and have not received an antibiotic within 3 months. Given the rise of macrolide resistance among pneumococci, consideration of local epidemiologic and susceptibility data as well as the patient's recent use of any antibiotics is imperative before selection of a regimen, particularly as regards macrolide monotherapy. If concern exists about macrolide resistance, the patient is otherwise well and has not recently received antibiotics, and the local doxycycline resistance rate among pneumococcal isolates is <25%, doxycycline may be used instead of macrolide monotherapy. Otherwise, a fluoroquinolone or a β-lactam plus a macrolide should be used.

TABLE 121-5 Empirical Antibiotic Treatment of Community-Acquired Pneumonia

Outpatients

1. Previously healthy and no antibiotics in past 3 months
   - A macrolide [clarithromycin (500 mg PO bid) or azithromycin (500 mg PO once, then 250 mg qd)] *or*
   - Doxycycline (100 mg PO bid)
2. Comorbidities or antibiotics in past 3 months: select an alternative from a different class
   - A respiratory fluoroquinolone [moxifloxacin (400 mg PO qd), gemifloxacin (320 mg PO qd), levofloxacin (750 mg PO qd)] *or*
   - A β-lactam [preferred: high-dose amoxicillin (1 g tid) or amoxicillin/clavulanate (2 g bid); alternatives: ceftriaxone (1–2 g IV qd), cefpodoxime (200 mg PO bid), or cefuroxime (500 mg PO bid)] *plus* a macrolide[a]
3. In regions with a high rate of "high-level" pneumococcal macrolide resistance,[b] consider alternatives listed above for patients with comorbidities.

Inpatients, Non-ICU

- A respiratory fluoroquinolone [e.g., moxifloxacin (400 mg PO or IV qd) or levofloxacin (750 mg PO or IV qd)]
- A β-lactam[c] [e.g., ceftriaxone (1–2 g IV qd), ampicillin (1–2 g IV q4–6h), cefotaxime (1–2 g IV q8h), ertapenem (1 g IV qd)] *plus* a macrolide[d] [e.g., oral clarithromycin or azithromycin as listed above or IV azithromycin (1 g once, then 500 mg qd)]

Inpatients, ICU

- A β-lactam[e] [e.g., ceftriaxone (2 g IV qd), ampicillin-sulbactam (2 g IV q8h), or cefotaxime (1–2 g IV q8h)] *plus* either azithromycin or a fluoroquinolone (as listed above for inpatients, non-ICU)

Special Concerns

If Pseudomonas is a consideration:

- An antipseudomonal β-lactam [e.g., piperacillin/tazobactam (4.5 g IV q6h), cefepime (1–2 g IV q12h), imipenem (500 mg IV q6h), meropenem (1 g IV q8h)] *plus* either ciprofloxacin (400 mg IV q12h) or levofloxacin (750 mg IV qd)
- The above β-lactams *plus* an aminoglycoside [amikacin (15 mg/kg qd) or tobramycin (1.7 mg/kg qd)] *plus* azithromycin
- The above β-lactams[f] *plus* an aminoglycoside *plus* an antipneumococcal fluoroquinolone

If CA-MRSA is a consideration:

- Add linezolid (600 mg IV q12h) or vancomycin (15 mg/kg q12h initially, with adjusted doses) *plus* clindamycin (300 mg q6h)

[a]Doxycycline (100 mg PO bid) is an alternative to the macrolide. [b]MICs >16 μg/mL in 25% of isolates. [c]A respiratory fluoroquinolone should be used for penicillin-allergic patients. [d]Doxycycline (100 mg IV q12h) is an alternative to the macrolide. [e]For penicillin-allergic patients, use a respiratory fluoroquinolone and aztreonam (2 g IV q8h). [f]For penicillin-allergic patients, substitute aztreonam.

Abbreviations: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* ICU, intensive care unit.

A meta-analysis found ceftaroline to be superior to ceftriaxone as the β-lactam component of IV empirical treatment of CAP in hospitalized patients in PORT risk class III or IV who have not received prior antibiotics. Clinical response rates for patients infected with *S. pneumoniae* or *S. aureus* also favored ceftaroline. Patients who had documented or suspected infection due to *P. aeruginosa* were excluded.

Once the etiologic agent(s) and their susceptibilities are known, therapy may be altered to target the specific pathogen(s). However, this decision is not always straightforward. If blood cultures yield *S. pneumoniae* sensitive to penicillin after 2 days of treatment with a macrolide plus a β-lactam or with a fluoroquinolone alone, should therapy be switched to penicillin alone? The concern here is that a β-lactam alone would not be effective in the potential 15% of cases with atypical co-infection. No standard approach exists. Some experts think that 3 days of macrolide therapy is adequate for *Mycoplasma* infection and that, unless the test for *Legionella* urinary antigen is positive, treatment can be continued with a β-lactam alone. In all cases, the individual patient and the various risk factors must be considered.

Management of bacteremic pneumococcal pneumonia is also controversial. Data from nonrandomized studies suggest that combination therapy (especially with a β-lactam–macrolide combination) is associated with a lower mortality rate than monotherapy, particularly in severely ill patients. The exact reason is unknown, but possible explanations include an additive or synergistic antibacterial effect, antimicrobial tolerance, atypical co-infection, or the immunomodulatory effects of the macrolides.

For CAP patients admitted to the ICU, the risk of infection with *P. aeruginosa* or CA-MRSA is increased. Empirical coverage should be considered when a patient has risk factors or a Gram's stain suggestive of these pathogens (Table 121-5). If CA-MRSA is suspected, either linezolid or vancomycin—with or without clindamycin to inhibit toxin production—can be added to the initial empirical regimen. There is increasing concern about vancomycin's loss of potency against MRSA, poor penetration into epithelial lining fluid, and lack of effect on toxin production relative to linezolid.

Although hospitalized patients have traditionally received initial therapy by the IV route, some drugs—particularly the fluoroquinolones—are very well absorbed and can be given orally from the outset to certain patients. For patients initially treated IV, a switch to oral treatment is appropriate as long as the patient can ingest and absorb the drugs, is hemodynamically stable, and is showing clinical improvement.

The duration of treatment for CAP has generated considerable interest. Studies with fluoroquinolones and telithromycin suggest that a 5-day course is sufficient for otherwise uncomplicated CAP but a longer course may be required for patients with bacteremia, metastatic infection, or infection with a virulent pathogen such as *P. aeruginosa* or CA-MRSA.

ADJUNCTIVE MEASURES

In addition to appropriate antimicrobial therapy, certain adjunctive measures should be used. Adequate hydration, oxygen therapy for hypoxemia, vasopressors, and assisted ventilation when necessary are critical to successful treatment. Randomized placebo-controlled trials have shown a benefit in treatment of hospitalized patients and patients who have severe CAP with prednisone and methylprednisolone, respectively. The value of adjunctive therapy with agents such as statins and angiotensin-converting enzyme inhibitors remains unproven in the management of CAP.

FAILURE TO IMPROVE

Patients slow to respond to therapy should be reevaluated at about day 3 (sooner if their condition is worsening rather than simply not improving), and several possible scenarios should be considered. A number of noninfectious conditions mimic pneumonia, including pulmonary edema, pulmonary embolism, lung carcinoma, radiation and hypersensitivity pneumonitis, and connective tissue disease involving the lungs. If the patient truly has CAP and empirical treatment is aimed at the correct pathogen, lack of response may be explained in a number of ways. The pathogen may be resistant to the drug selected, or a sequestered focus (e.g., lung abscess or empyema) may be blocking access of the antibiotic(s) to the pathogen. The patient may be getting either the wrong drug or the correct drug at the wrong dose or frequency of administration. Another possibility is that CAP is the correct diagnosis but an unsuspected pathogen (e.g., CA-MRSA, *M. tuberculosis*, or a fungus) is the cause. Nosocomial superinfections—both pulmonary and extrapulmonary—are other possible explanations for a hospitalized patient's failure to improve or deterioration. In all cases of delayed response or worsening condition, the patient must be carefully reassessed and appropriate studies initiated, possibly including procedures such as CT or bronchoscopy.

COMPLICATIONS

Complications of severe CAP include respiratory failure, shock and multiorgan failure, coagulopathy, and exacerbation of comorbid illnesses. Three particularly noteworthy conditions are metastatic infection, lung abscess, and complicated pleural effusion. Metastatic infection (e.g., brain abscess or endocarditis) is very unusual and will require a high degree of suspicion and a detailed workup for proper treatment. Lung abscess may occur in association with aspiration or with infection caused by a single CAP pathogen, such as CA-MRSA, *P. aeruginosa*, or (rarely) *S. pneumoniae.* Aspiration pneumonia is typically a polymicrobial infection involving both aerobes and anaerobes. A significant pleural effusion should be tapped for both diagnostic and therapeutic purposes. If the fluid has a pH of <7, a glucose level of <2.2 mmol/L, and a lactate dehydrogenase concentration of >1000 U/L or if bacteria are seen or cultured, it should be completely drained; a chest tube is often required, and video-assisted thoracoscopy may be needed for late treatment or difficult cases.

FOLLOW-UP

Fever and leukocytosis usually resolve within 2–4 days in otherwise healthy patients with CAP, but physical findings may persist longer. Chest radiographic abnormalities are slowest to resolve (4–12 weeks), with the speed of clearance depending on the patient's age and underlying lung disease. Patients may be discharged from the hospital once their clinical conditions, including comorbidities, are stable. The site of residence after discharge (nursing home, home with family, home alone) is an important discharge consideration, particularly for elderly patients. For a hospitalized patient, a follow-up radiograph ~4–6 weeks later is recommended. If relapse or recurrence is documented, particularly in the same lung segment, the possibility of an underlying neoplasm must be considered.

PROGNOSIS

The prognosis of CAP depends on the patient's age, comorbidities, and site of treatment (inpatient or outpatient). Young patients without comorbidity do well and usually recover fully after ~2 weeks. Older patients and those with comorbid conditions can take several weeks longer to recover fully. The overall mortality rate for the outpatient group is <5%. For patients requiring hospitalization, the overall mortality rate ranges from 2 to 40%, depending on the category of patient and the processes of care, particularly the administration of appropriate antibiotics as soon as possible.

PREVENTION

The main preventive measure is vaccination **(Chap. 118)**. Recommendations of the Advisory Committee on Immunization Practices should be followed for influenza and pneumococcal vaccines.

A pneumococcal polysaccharide vaccine (PPSV23) and a protein conjugate pneumococcal vaccine (PCV13) are available in the United States **(Chap. 141)**. The former product contains capsular material from 23 pneumococcal serotypes; in the latter, capsular polysaccharide from 13 of the most common pneumococcal pathogens affecting children is linked to an immunogenic protein. PCV13 produces T cell–dependent

antigens that result in long-term immunologic memory. Administration of this vaccine to children has led to an overall decrease in the prevalence of antimicrobial-resistant pneumococci and in the incidence of invasive pneumococcal disease among both children and adults. However, vaccination can be followed by the replacement of vaccine serotypes with nonvaccine serotypes, as was seen with serotypes 19A and 35B after introduction of the original 7-valent conjugate vaccine. PCV13 is also recommended for the elderly and for younger immunocompromised patients. Because of an increased risk of pneumococcal infection, even among patients without obstructive lung disease, smokers should be strongly encouraged to stop smoking.

The influenza vaccine is available in an inactivated or recombinant form. The live attenuated influenza vaccine or "nasal spray" vaccine is no longer recommended. In the event of an influenza outbreak, unprotected patients at risk from complications should be vaccinated immediately and given chemoprophylaxis with either oseltamivir or zanamivir for 2 weeks—i.e., until vaccine-induced antibody levels are sufficiently high.

VENTILATOR-ASSOCIATED PNEUMONIA

Most research on hospital-acquired pneumonia has focused on VAP. However, the information and principles based on this research can be applied to non-ICU HAP as well. The greatest difference between VAP and HAP studies is the dependence on expectorated sputum for a microbiologic diagnosis of HAP (as for that of CAP), which is further complicated by frequent colonization by pathogens in patients with HAP. Therefore, most of the literature has focused on HAP resulting in intubation, where, once again, access to the lower respiratory tract facilitates an etiologic diagnosis.

ETIOLOGY

Potential etiologic agents of VAP include both MDR and non-MDR bacterial pathogens **(Table 121-6)**. The non-MDR group is nearly identical to the pathogens found in severe CAP (Table 121-2); it is not surprising that such pathogens predominate if VAP develops in the first 5–7 days of the hospital stay. However, if patients have other risk factors, MDR pathogens are a consideration, even early in the hospital course. The relative frequency of individual MDR pathogens can vary significantly from hospital to hospital and even between different critical care units within the same institution. Most hospitals have problems with *P. aeruginosa* and MRSA, but other MDR pathogens are often institution-specific. Less commonly, fungal and viral pathogens cause VAP, usually affecting severely immunocompromised patients. Rarely, community-associated viruses cause mini-epidemics, usually when introduced by ill health care workers.

EPIDEMIOLOGY

Pneumonia is a common complication among patients requiring mechanical ventilation. Prevalence estimates vary between 6 and 52 cases per 100 patients, depending on the population studied. On any given day in the ICU, an average of 10% of patients will have pneumonia—VAP in the overwhelming majority of cases. The frequency of diagnosis is not static but changes with the duration of mechanical ventilation, with the highest hazard ratio in the first 5 days and a plateau in additional cases (1% per day) after ~2 weeks. However, the cumulative rate among patients who remain ventilated for as long as 30 days is as high as 70%. These rates often do not reflect the recurrence of VAP in the same patient. Once a ventilated patient is transferred to a chronic-care facility or to home, the incidence of pneumonia drops significantly, especially in the absence of other risk factors for pneumonia. However, in chronic ventilator units, purulent tracheobronchitis becomes a significant issue, often interfering with efforts to wean patients off mechanical ventilation **(Chap. 295)**.

Three factors are critical in the pathogenesis of VAP: colonization of the oropharynx with pathogenic microorganisms, aspiration of these organisms from the oropharynx into the lower respiratory tract, and compromise of the normal host defense mechanisms. Most risk factors and their corresponding prevention strategies pertain to one of these three factors **(Table 121-7)**.

The most obvious risk factor is the endotracheal tube, which bypasses the normal mechanical factors preventing aspiration. While the presence of an endotracheal tube may prevent large-volume aspiration, microaspiration is actually exacerbated by secretions pooling above the cuff. The endotracheal tube and the concomitant need for suctioning can damage the tracheal mucosa, thereby facilitating tracheal colonization. In addition, pathogenic bacteria can form a glycocalyx biofilm on the tube's surface that protects them from both antibiotics and host defenses. The bacteria can also be dislodged during

TABLE 121-6 Microbiologic Causes of Ventilator-Associated Pneumonia

NON-MDR PATHOGENS	MDR PATHOGENS
Streptococcus pneumoniae	*Pseudomonas aeruginosa*
Other *Streptococcus* spp.	Methicillin-resistant *S. aureus*
Haemophilus influenzae	*Acinetobacter* spp.
Methicillin-sensitive *Staphylococcus aureus*	Antibiotic-resistant Enterobacteriaceae
Antibiotic-sensitive Enterobacteriaceae	ESBL-positive strains
Escherichia coli	Carbapenem-resistant strains
Klebsiella pneumoniae	*Legionella pneumophila*
Proteus spp.	*Burkholderia cepacia*
Enterobacter spp.	*Aspergillus* spp.
Serratia marcescens	

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant.

TABLE 121-7 Pathogenic Mechanisms and Corresponding Prevention Strategies for Ventilator-Associated Pneumonia

PATHOGENIC MECHANISM	PREVENTION STRATEGY
Oropharyngeal colonization with pathogenic bacteria	
Elimination of normal flora	Avoidance of prolonged antibiotic courses
Large-volume oropharyngeal aspiration around time of intubation	Short course of prophylactic antibiotics for comatose patients[a]
Gastroesophageal reflux	Postpyloric enteral feeding[b]; avoidance of high gastric residuals, prokinetic agents
Bacterial overgrowth of stomach	Avoidance of prophylactic agents that raise gastric pH[b]; selective decontamination of digestive tract with nonabsorbable antibiotics[b]
Cross-infection from other colonized patients	Hand washing, especially with alcohol-based hand rub; intensive infection control education[a]; isolation; proper cleaning of reusable equipment
Large-volume aspiration	Endotracheal intubation; rapid-sequence intubation technique; avoidance of sedation; decompression of small-bowel obstruction
Microaspiration around endotracheal tube	
Endotracheal intubation	Noninvasive ventilation[a]
Prolonged duration of ventilation	Daily awakening from sedation,[a] weaning protocols[a]
Abnormal swallowing function	Early percutaneous tracheostomy[a]
Secretions pooled above endotracheal tube	Head of bed elevated[a]; continuous aspiration of subglottic secretions with specialized endotracheal tube[a]; avoidance of reintubation; minimization of sedation and patient transport
Altered lower respiratory host defenses	Tight glycemic control[b]; lowering of hemoglobin transfusion threshold

[a]Strategies demonstrated to be effective in at least one randomized controlled trial. [b]Strategies with negative randomized trials or conflicting results.

suctioning and can reinoculate the trachea, or tiny fragments of glycocalyx can embolize to distal airways, carrying bacteria with them.

In a high percentage of critically ill patients, the normal oropharyngeal flora is replaced by pathogenic microorganisms. The most important risk factors are antibiotic selection pressure, cross-infection from other infected/colonized patients or contaminated equipment, and malnutrition. Of these factors, antibiotic exposure poses the greatest risk by far. Pathogens such as *P. aeruginosa* almost never cause infection in patients without prior exposure to antibiotics. The recent emphasis on hand hygiene has lowered the cross-infection rate.

How the lower respiratory tract defenses become overwhelmed remains poorly understood. Almost all intubated patients experience microaspiration and are at least transiently colonized with pathogenic bacteria. However, only around one-third of colonized patients develop VAP. Colony counts increase to high levels, sometimes days before the development of clinical pneumonia; these increases suggest that the final step in VAP development, independent of aspiration and oropharyngeal colonization, is the overwhelming of host defenses. Severely ill patients with sepsis and trauma appear to enter a state of immunoparalysis several days after admission to the ICU—a time that corresponds to the greatest risk of developing VAP. The mechanism of this immunosuppression is not clear, although several factors have been suggested. Hyperglycemia and more frequent transfusions adversely affect the immune response.

CLINICAL MANIFESTATIONS

The clinical manifestations are generally the same in VAP as in all other forms of pneumonia: fever, leukocytosis, increase in respiratory secretions, and pulmonary consolidation on physical examination, along with a new or changing radiographic infiltrate. The frequency of abnormal chest radiographs before the onset of pneumonia in intubated patients and the limitations of portable radiographic technique make interpretation of radiographs more difficult than in patients who are not intubated. Other clinical features may include tachypnea, tachycardia, worsening oxygenation, and increased minute ventilation.

DIAGNOSIS

No single set of criteria is reliably diagnostic of pneumonia in a ventilated patient. The inability to accurately identify such patients compromises efforts to prevent and treat VAP and even calls into question estimates of the impact of VAP on mortality rates.

Application of the clinical criteria typical for CAP consistently results in overdiagnosis of VAP, largely because of three common findings in at-risk patients: (1) frequent tracheal colonization with pathogenic bacteria in patients with endotracheal tubes, (2) multiple alternative causes of radiographic infiltrates in mechanically ventilated patients, and (3) the high frequency of other sources of fever in critically ill patients. The differential diagnosis of VAP includes a number of entities such as atypical pulmonary edema, pulmonary contusion, alveolar hemorrhage, hypersensitivity pneumonitis, acute respiratory distress syndrome, and pulmonary embolism. Clinical findings in ventilated patients with fever and/or leukocytosis may have alternative causes, including antibiotic-associated diarrhea, central line–associated infection, sinusitis, urinary tract infection, pancreatitis, and drug fever. Conditions mimicking pneumonia are often documented in patients in whom VAP has been ruled out by accurate diagnostic techniques. Most of these alternative diagnoses do not require antibiotic treatment; require antibiotics different from those used to treat VAP; or require some additional intervention, such as surgical drainage or catheter removal, for optimal management.

This diagnostic dilemma has led to debate and controversy. The major question is whether a quantitative-culture approach as a means of eliminating false-positive clinical diagnoses is superior to the clinical approach enhanced by principles learned from quantitative-culture studies. The most recent IDSA/ATS guidelines for HAP/VAP gave a weak recommendation for the clinical approach based on availability of resources, cost, and availability of expertise. The guidelines did acknowledge that the use of a quantitative approach may result in less antibiotic use, which may be critical for antibiotic stewardship in the ICU. Therefore, the approach at each institution, or potentially for each patient, should balance the frequency of complex illnesses that are associated with (1) greater frequency of alternative causes of the clinical manifestations, (2) higher colonization rates, and (3) more frequent prior antibiotic therapy versus availability and expertise of invasive techniques with quantitative cultures.

Quantitative-Culture Approach The essence of the quantitative-culture approach is discrimination between colonization and true infection through determination of the bacterial burden. The more distal in the respiratory tree the diagnostic sampling, the more specific the results and therefore the lower the threshold of growth necessary to diagnose pneumonia and exclude colonization. For example, a quantitative endotracheal aspirate yields proximate samples, and the diagnostic threshold is 10^6 cfu/mL. The protected specimen brush method, in contrast, obtains distal samples and has a threshold of 10^3 cfu/mL. Conversely, sensitivity declines as more distal secretions are obtained, especially when they are collected blindly (i.e., by a technique other than bronchoscopy). Additional tests that may increase the diagnostic yield include Gram's staining, differential cell counts, staining for intracellular organisms, and detection of local protein levels elevated in response to infection.

The key piece of a quantitative-culture approach is to base subsequent antibiotic therapy on the results of the quantitative cultures. In a study comparing the quantitative with the clinical approach, the use of bronchoscopic quantitative cultures resulted in significantly less antibiotic use at 14 days after study entry, a lower 14-day mortality rate, and a lower 28-day severity-adjusted mortality rate. In addition, more alternative sites of infection were found in patients randomized to the quantitative-culture strategy. A critical aspect of this study was that antibiotic treatment was initiated only in patients whose gram-stained respiratory sample was positive or who displayed signs of hemodynamic instability. Fewer than half as many patients were treated for pneumonia in the bronchoscopy group, and only one-third as many microorganisms were cultured. Other randomized trials of the quantitative-culture approach did not closely link antibiotic management with the results of cultures; thus the validity of their results was compromised.

The Achilles heel of the quantitative approach is the effect of antibiotic therapy. With sensitive microorganisms, a single antibiotic dose can reduce colony counts below the diagnostic threshold. Recent changes in antibiotic therapy are the most significant. After 3 days, the operating characteristics of the tests improve to the point at which they are equivalent to results when no prior antibiotic therapy has been given. Conversely, colony counts above the diagnostic threshold during antibiotic therapy suggest that the current antibiotics are ineffective. Even the normal host response may be sufficient to reduce quantitative-culture counts below the diagnostic threshold if sampling is delayed. In short, expertise in quantitative-culture techniques is critical, with a specimen obtained as soon as pneumonia is suspected and before antibiotic therapy is initiated or changed.

Clinical Approach General knowledge of the lack of specificity of a clinical diagnosis of VAP and results from invasive quantitative-culture studies have actually improved the clinical approach to the diagnosis of VAP. Tracheal aspirates generally yield at least twice as many potential pathogens as quantitative cultures. However, the causative pathogen is almost always present. The absence of bacteria in gram-stained endotracheal aspirates makes pneumonia an unlikely cause of fever or pulmonary infiltrates. These findings, coupled with a heightened awareness of the alternative diagnoses possible in patients with suspected VAP, can prevent inappropriate overtreatment for pneumonia. Furthermore, the absence of an MDR pathogen in tracheal aspirate cultures eliminates the need for MDR coverage, allowing empirical antibiotic therapy to be de-escalated. Since the main benefits of bronchoscopic quantitative cultures are decreased antibiotic selection pressure (which reduces the risk of subsequent infection with MDR pathogens) and the identification of alternative sources of infection, a clinical diagnostic approach that incorporates such principles may result in similar outcomes.

TREATMENT

Ventilator-Associated Pneumonia

Many studies have demonstrated higher mortality rates with initially inappropriate empirical antibiotic therapy. The key to appropriate antibiotic management of VAP is an appreciation of the resistance patterns of the most likely pathogens in a given patient.

ANTIBIOTIC RESISTANCE

If not for the higher risk of infection with MDR pathogens (Table 121-6), VAP could be treated with the same antibiotics used for severe CAP. However, antibiotic selection pressure leads to the frequent involvement of MDR pathogens by selecting either for drug-resistant isolates of common pathogens (MRSA and Enterobacteriaceae producing extended-spectrum β-lactamases or carbapenemases) or for intrinsically resistant pathogens (*P. aeruginosa* and *Acinetobacter* species). Frequent use of β-lactam drugs, especially cephalosporins, appears to be the major risk factor for infection with MRSA and extended-spectrum β-lactamase–positive strains.

P. aeruginosa has demonstrated the ability to develop resistance to all routinely used antibiotics. Unfortunately, even if initially sensitive, *P. aeruginosa* isolates also have a propensity to develop resistance during treatment. Either de-repression of resistance genes or selection of resistant clones within the large bacterial inoculum associated with most pneumonias may be the cause. *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* are intrinsically resistant to many of the empirical antibiotic regimens employed (see below). VAP caused by these pathogens emerges during treatment of other infections, and resistance is always evident at initial diagnosis.

EMPIRICAL THERAPY

Recommended options for empirical therapy are listed in **Table 121-8**. Treatment should be started once diagnostic specimens have been obtained. The major factor in the selection of agents is the presence of risk factors for MDR pathogens. Choices among the various options listed depend on local patterns of resistance and—a very important factor—the patient's prior antibiotic exposure. Knowledge of the local hospital's—and even the specific ICU's—antibiogram and the local incidence of specific MDR pathogens (e.g., MRSA) is critical in selecting appropriate empirical therapy.

The majority of patients *without* risk factors for MDR infection can be treated with a single agent. Unfortunately, the proportion of patients with no MDR risk factors is <10% in some ICUs and is unknown for HAP patients. The major difference from CAP is the markedly lower incidence of atypical pathogens in VAP; the exception is *Legionella*, which can be a nosocomial pathogen, especially with breakdowns in the treatment of potable water in the hospital. The standard recommendation for patients *with* risk factors for MDR infection is for three antibiotics: two directed at *P. aeruginosa* and one at MRSA. A β-lactam agent provides the greatest coverage, yet even the broadest-spectrum agent—a carbapenem—still provides inappropriate initial therapy in up to 10–15% of cases at some centers. The emergence of carbapenem resistance at some institutions requires the addition of polymyxins to the combination-therapy options.

TABLE 121-8 Empirical Antibiotic Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia

NO RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN	RISK FACTORS FOR RESISTANT GRAM-NEGATIVE PATHOGEN[a] *(CHOOSE ONE FROM EACH COLUMN)*	
Piperacillin-tazobactam (4.5 g IV q6h[b])	Piperacillin-tazobactam (4.5 g IV q6h[b])	Amikacin (15–20 mg/kg IV q24h)
Cefepime (2 g IV q8h)	Cefepime (2 g IV q8h)	Gentamicin (5–7 mg/kg IV q24h)
Levofloxacin (750 mg IV q24h)	Ceftazidime (2 g IV q8h)	Tobramycin (5–7 mg/kg IV q24h)
	Imipenem (500 mg IV q6h[b])	Ciprofloxacin (400 mg IV q8h)
	Meropenem (1 g IV q8h)	Levofloxacin (750 mg IV q24h)
		Colistin (loading dose of 5 mg/kg IV followed by maintenance doses of 2.5 mg × [1.5 × CrCl + 30] IV q12h)
		Polymyxin B (2.5–3.0 mg/kg per day IV in 2 divided doses)
Risk Factors for MRSA[b] *(Add to above)*		
Linezolid (600 mg IV q12h) *or*		
Adjusted-dose vancomycin (trough level, 15–20 mg/dL)		

[a]Prior antibiotic therapy, prior hospitalization, local antibiogram. [b]Prior antibiotic therapy, prior hospitalization, known MRSA colonization, chronic hemodialysis, local documented MRSA pneumonia rate >10% (or local rate unknown).

Abbreviations: CrCl, creatinine clearance rate; MRSA, methicillin-resistant *Staphylococcus aureus*.

SPECIFIC TREATMENT

Once an etiologic diagnosis is made, broad-spectrum empirical therapy can be modified to specifically address the known pathogen. For patients with MDR risk factors, antibiotic regimens can be reduced to a single agent in most cases. Only a minority of cases require a complete course with two or three drugs. A negative tracheal-aspirate culture or growth below the threshold for quantitative cultures of samples obtained before any antibiotic change strongly suggests that antibiotics should be discontinued or that a search for an alternative diagnosis should be pursued. Identification of other confirmed or suspected sites of infection may require ongoing antibiotic therapy, but the spectrum of pathogens (and the corresponding antibiotic choices) may be different from those for VAP. A 7- or 8-day course of therapy is just as effective as a 2-week course and is associated with less frequent emergence of antibiotic-resistant strains.

The major controversy regarding specific therapy for VAP concerns the need for ongoing combination treatment of *Pseudomonas* pneumonia. No randomized controlled trials have demonstrated a benefit of combination therapy with a β-lactam and an aminoglycoside, nor have subgroup analyses in other trials found a survival benefit with such a regimen. The unacceptably high rates of clinical failure and death for VAP caused by *P. aeruginosa* despite combination therapy (see "Failure to Improve," below) indicate that better regimens are needed, perhaps including aerosolized antibiotics. Current guidelines recommend against continued combination therapy for most cases of *Pseudomonas* pneumonia.

FAILURE TO IMPROVE

Treatment failure is not uncommon in VAP, especially that caused by MDR pathogens. VAP caused by MRSA is associated with a 40% clinical failure rate when treated with standard-dose vancomycin. One proposed but unproven solution is the use of high-dose individualized treatment, although the risk of renal toxicity increases with this strategy. In addition, the MIC of vancomycin has been increasing, and a high percentage of clinical failures occur when the MIC is in the upper range of sensitivity (i.e., 1.5–2 μg/mL). Linezolid appears to be 15% more efficacious than even adjusted-dose vancomycin and is clearly preferred in patients with renal insufficiency and those infected with high-MIC isolates of MRSA. VAP due to *Pseudomonas* has a 40–50% failure rate, no matter what the regimen. Causes of clinical failure vary with the pathogen(s) and the antibiotic(s). Inappropriate initial therapy can usually be minimized by use of the recommended combination regimen (Table 121-8). However, the emergence of β-lactam resistance during therapy is an important problem, especially in infection with *Pseudomonas* and *Enterobacter* species. Recurrent VAP caused by the same pathogen is possible because the biofilm on endotracheal tubes allows reintroduction of the microorganism. Studies of VAP caused by *Pseudomonas* show that approximately half of recurrent cases are caused by a new strain.

Treatment failure is very difficult to diagnose early in the therapeutic course, and discrimination among the various potential causes is a challenge. Pneumonia due to a new superinfection, the presence of extrapulmonary infection, and drug toxicity must be considered in the differential diagnosis of treatment failure. Serial measurements of procalcitonin levels appear to track the clinical response accurately, while repeat quantitative cultures may clarify the microbiologic response.

COMPLICATIONS

Apart from death, the major complication of VAP is prolongation of mechanical ventilation, with corresponding increases in the duration of ICU stay and hospitalization. In most studies, an additional week of mechanical ventilation resulting from VAP is common. The additional expense of this complication often warrants costly and aggressive efforts at prevention.

In rare cases, necrotizing pneumonia (e.g., that due to *P. aeruginosa*) can cause significant pulmonary hemorrhage. More commonly, necrotizing infections result in the long-term complications of bronchiectasis and parenchymal scarring leading to recurrent pneumonia. Other long-term complications of pneumonia are underappreciated. Pneumonia results in a catabolic state in a patient already nutritionally at risk. The muscle loss and general debilitation from an episode of VAP often require prolonged rehabilitation and, in the elderly, often result in an inability to return to independent function and the need for nursing home placement.

FOLLOW-UP

Clinical improvement, if it occurs, is usually evident within 48–72 h of the initiation of antimicrobial treatment. Because findings on chest radiography often worsen initially during treatment, they are less helpful than clinical criteria as an indicator of clinical response in severe pneumonia.

PROGNOSIS

VAP is associated with crude mortality rates as high as 50–70%, but the real issue is attributable mortality. Many patients with VAP have underlying diseases that would result in death even if VAP did not occur. Attributable mortality exceeded 25% in one matched-cohort study, while more recent studies have suggested much lower rates. Some variability in VAP mortality rates is clearly related to the type of patient and ICU studied. VAP in trauma patients is not associated with attributable mortality, possibly because many of the patients were otherwise healthy before being injured. The causative pathogen also plays a major role. Generally, MDR pathogens are associated with significantly greater attributable mortality than non-MDR pathogens. Pneumonia caused by some pathogens (e.g., *S. maltophilia*) is simply a marker for a patient whose immune system is so compromised that death is almost inevitable.

PREVENTION (TABLE 121-7)

Because of the significance of endotracheal intubation as a risk factor for VAP, the most important preventive intervention is to avoid intubation or minimize its duration. Successful noninvasive ventilation avoids many of the problems associated with endotracheal tubes. Strategies that minimize the duration of ventilation through daily holding of sedation and formal weaning protocols have also been highly effective in preventing VAP.

Unfortunately, a tradeoff in risks is sometimes necessary. Aggressive attempts to extubate early may result in reintubation(s) and increase aspiration, posing a risk of VAP. Heavy continuous sedation increases VAP risk, but self-extubation because of insufficient sedation is also a risk. The tradeoffs also apply to antibiotic therapy. Short-course antibiotic prophylaxis can decrease the risk of VAP in comatose patients requiring intubation, and data suggest that antibiotics decrease VAP rates overall. However, the major benefit appears to be a decrease in the incidence of early-onset VAP, which is usually caused by the less pathogenic non-MDR microorganisms. Conversely, prolonged courses of antibiotics consistently increase the risk of VAP caused by more lethal MDR pathogens. Despite its virulence and associated mortality, VAP caused by *Pseudomonas* is rare among patients who have not recently received antibiotics.

Minimizing microaspiration around the endotracheal tube cuff is also a strategy for avoidance of VAP. Simply elevating the head of the bed (at least 30° above horizontal but preferably 45°) decreases VAP rates. Specially modified endotracheal tubes that allow removal of the secretions pooled above the cuff may also prevent VAP. The risk-to-benefit ratio of transporting the patient outside the ICU for diagnostic tests or procedures should be carefully considered, since VAP rates are increased among transported patients.

The role played by overgrowth of the normal bowel flora in the stomach in the pathogenesis of VAP is questionable. MRSA and the nonfermenters *P. aeruginosa* and *Acinetobacter* species are not normally part of the bowel flora but reside primarily in the nose and on the skin, respectively. Therefore, emphasis on controlling overgrowth of the bowel flora by avoidance of agents that raise gastric pH may be relevant only in certain populations, such as liver transplant recipients and patients who have undergone other major intraabdominal procedures or who have bowel obstruction.

In outbreaks of VAP due to specific pathogens, the possibility of a breakdown in infection control measures (particularly contamination of reusable equipment) should be investigated. Even high rates of pathogens that are already common in a particular ICU may result from cross-infection. Education and reminders of the need for consistent hand washing and other infection-control practices can minimize this risk.

HOSPITAL-ACQUIRED PNEUMONIA

While significantly less well studied than VAP, HAP in non-intubated patients—both inside and outside the ICU—is similar to VAP. The main differences are the higher frequency of non-MDR pathogens and the generally better underlying host immunity in non-intubated patients. The lower frequency of MDR pathogens allows monotherapy in a larger proportion of cases of HAP than of VAP.

The only pathogens that may be more common in the non-VAP population are anaerobes. The greater risk of macroaspiration by non-intubated patients and the lower oxygen tensions in the lower respiratory tract of these patients increase the likelihood of a role for anaerobes. While more common in patients with HAP, anaerobes usually contribute only to polymicrobial pneumonias. As in the management of CAP, specific therapy targeting anaerobes probably is not needed since many of the recommended antibiotics are active against anaerobes.

Diagnosis is even more difficult for HAP in the non-intubated patient than for VAP. Lower respiratory tract samples appropriate for culture are considerably more difficult to obtain from non-intubated patients. Many of the underlying diseases that predispose a patient to HAP are also associated with an inability to cough adequately. Since blood cultures are infrequently positive (<15% of cases), the majority of patients with HAP do not have culture data on which antibiotic modifications can be based. Therefore, de-escalation of therapy is less likely in patients with risk factors for MDR pathogens. Despite these difficulties, the better host defenses in non-ICU patients result in lower mortality rates than are documented for VAP. In addition, the risk of antibiotic failure is lower in HAP.

GLOBAL IMPACT

From the available data, it is virtually impossible to accurately assess the impact of pneumonia from a global perspective. Any differences in incidence, disease burden, and costs across different age, ethnic, and racial groups are compounded by differences among countries in terms of etiologic pathogens, resistance rates, access to health-care and diagnostic facilities, and vaccine availability and usage.

A standard approach with clearly defined outcome measures is needed before the impact of pneumonia can be accurately evaluated. However, simple extrapolation from U.S. data for CAP and HAP/VAP shows that pneumonia has a significant impact on quality of life,

morbidity, health costs, and mortality rates and that this impact has implications for patients and for society as a whole.

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122 Lung Abscess

Rebecca M. Baron, Miriam Baron Barshak

Lung abscess represents necrosis and cavitation of the lung following microbial infection. Lung abscesses can be single or multiple but usually are marked by a single dominant cavity >2 cm in diameter.

ETIOLOGY

The low prevalence of lung abscesses makes them difficult to study in randomized controlled trials. Although the incidence of lung abscesses has decreased in the antibiotic era, they are still a source of significant morbidity and mortality.

Lung abscesses are usually characterized as either primary (~80% of cases) or secondary. *Primary* lung abscesses usually arise from aspiration, are often caused principally by anaerobic bacteria, and occur in the absence of an underlying pulmonary or systemic condition. *Secondary* lung abscesses arise in the setting of an underlying condition, such as a postobstructive process (e.g., a bronchial foreign body or tumor) or a systemic process (e.g., HIV infection or another immunocompromising condition). Lung abscesses can also be characterized as acute (<4–6 weeks in duration) or chronic (~40% of cases).

EPIDEMIOLOGY

The majority of the existing epidemiologic information involves primary lung abscesses. In general, middle-aged men are more commonly affected than middle-aged women. The major risk factor for primary lung abscesses is aspiration. Patients at particular risk for aspiration, such as those with altered mental status, alcoholism, drug overdose, seizures, bulbar dysfunction, prior cerebrovascular or cardiovascular events, or neuromuscular disease, are most commonly affected. In addition, patients with esophageal dysmotility or esophageal lesions (strictures or tumors) and those with gastric distention and/or gastroesophageal reflux, especially those who spend substantial time in the recumbent position, are at risk for aspiration.

It is widely thought that colonization of the gingival crevices by anaerobic bacteria or microaerophilic streptococci (especially in patients with gingivitis and periodontal disease), combined with a risk of aspiration, is important in the development of lung abscesses. In fact, many physicians consider it extremely rare for lung abscesses to develop in the absence of teeth as a nidus for bacterial colonization.

The importance of these risk factors in the development of lung abscesses is highlighted by a significant reduction in abscess incidence in the late 1940s that coincided with a change in oral surgical technique: beginning at that time, these operations were no longer performed with the patient in the seated position without a cuffed endotracheal tube, and the frequency of perioperative aspiration events was thus decreased. In addition, the introduction of penicillin around the same time significantly reduced the incidence of and mortality rate from lung abscess.

PATHOGENESIS

Primary Lung Abscesses The development of primary lung abscesses is thought to originate when chiefly anaerobic bacteria (as well as microaerophilic streptococci) in the gingival crevices are aspirated into the lung parenchyma in a susceptible host **(Table 122-1)**. Patients who develop primary lung abscesses usually carry an overwhelming burden of aspirated material or are unable to clear the bacterial load. Pneumonitis develops initially (exacerbated in part by tissue damage caused by gastric acid); then, over a period of 7–14 days, the anaerobic bacteria produce parenchymal necrosis and cavitation whose extent depends on host–pathogen interaction **(Fig. 122-1)**. Anaerobes are thought to produce more extensive tissue necrosis in polymicrobial infections in which virulence factors of the various bacteria can act synergistically to cause more significant tissue destruction.

Secondary Lung Abscesses The pathogenesis of secondary abscesses depends on the predisposing factor. For example, in cases of bronchial obstruction from malignancy or a foreign body, the obstructing lesion prevents clearance of oropharyngeal secretions, leading to abscess development. With underlying systemic conditions (e.g., immunosuppression after bone marrow or solid organ transplantation), impaired host defense mechanisms lead to increased susceptibility to the development of lung abscesses caused by a broad range of pathogens, including opportunistic organisms (Table 122-1).

Lung abscesses also arise from septic emboli, either in tricuspid valve endocarditis (often involving *Staphylococcus aureus*) or in Lemierre's syndrome, in which an infection begins in the pharynx (classically involving *Fusobacterium necrophorum*) and then spreads to the neck and the carotid sheath (which contains the jugular vein) to cause septic thrombophlebitis.

TABLE 122-1 Examples of Microbial Pathogens That Can Cause Lung Abscesses

CLINICAL CONDITION	PATHOGENS
Primary lung abscess (usually with risk factors for aspiration)	Anaerobes (e.g., *Peptostreptococcus* spp., *Prevotella* spp., *Bacteroides* spp., *Streptococcus milleri*), microaerophilic streptococci
Secondary lung abscess (often with underlying immunocompromise)	*Staphylococcus aureus*, gram-negative rods (e.g., *Pseudomonas aeruginosa*, Enterobacteriaceae), *Nocardia* spp., *Aspergillus* spp., Mucorales, *Cryptococcus* spp., *Legionella* spp., *Rhodococcus equi*, *Pneumocystis jirovecii*
Embolic lesions	*Staphylococcus aureus* (often from endocarditis), *Fusobacterium necrophorum* (Lemierre's syndrome; see text for details)
Endemic infections (with or without underlying immunocompromise)	*Mycobacterium tuberculosis* (as well as *Mycobacterium avium* and *Mycobacterium kansasii*), *Coccidioides* spp., *Histoplasma capsulatum*, *Blastomyces* spp., parasites (e.g., *Entamoeba histolytica*, *Paragonimus westermani*, *Strongyloides stercoralis*)
Miscellaneous conditions	Bacterial pathogen (often *S. aureus*) after influenza or another viral infection, *Actinomyces* spp.

A B

FIGURE 122-1 Representative chest CT scans demonstrating development of lung abscesses. This patient was immunocompromised by underlying lymphoma and developed severe *Pseudomonas aeruginosa* pneumonia, as represented by a left lung infiltrate with concern for central regions of necrosis (*panel* ***A****, black arrow*). Two weeks later, areas of cavitation with air-fluid levels were visible in this region and were consistent with the development of lung abscesses (*panel* ***B****, white arrow*). *(Images provided by Dr. Ritu Gill, Division of Chest Radiology, Brigham and Women's Hospital, Boston; with permission.)*

PATHOLOGY AND MICROBIOLOGY

Primary Lung Abscesses The dependent segments (posterior upper lobes and superior lower lobes) are the most common locations of primary lung abscesses, given the predisposition of aspirated materials to be deposited in these areas. Generally, the right lung is affected more commonly than the left because the right mainstem bronchus is less angulated.

The microbiology of primary lung abscesses is often polymicrobial, primarily including anaerobic organisms as well as microaerophilic streptococci (Table 122-1). The retrieval and culture of anaerobes can be complicated by the contamination of samples with microbes from the oral cavity, the need for expeditious transport of the cultures to the laboratory, the need for early plating with special culture techniques, the prolonged time required for culture growth, and the need for collection of specimens prior to administration of antibiotics. When attention is paid to these factors, rates of recovery of specific isolates are reportedly as high as 78%.

Because it is not clear that knowing the identity of the causative anaerobic isolate alters the response to treatment of a primary lung abscess, practice has shifted away from the use of specialized techniques to obtain material for culture, such as transtracheal aspiration and bronchoalveolar lavage with protected brush specimens that allow recovery of culture material while avoiding contamination from the oral cavity. When no pathogen is isolated from a primary lung abscess (which is the case as often as 40% of the time), the abscess is termed a *nonspecific lung abscess*, and the presence of anaerobes is often presumed. A *putrid lung abscess* refers to cases with foul-smelling breath, sputum, or empyema; these manifestations are essentially diagnostic of an anaerobic lung abscess.

Secondary Lung Abscesses The location of secondary abscesses may vary with the underlying cause. The microbiology of secondary lung abscesses can encompass quite a broad bacterial spectrum, with infection by *Pseudomonas aeruginosa* and other gram-negative rods most common. In addition, a broad array of pathogens can be identified in patients from certain endemic areas and in specific clinical scenarios (e.g., a significant incidence of fungal infections among immunosuppressed patients following bone marrow or solid organ transplantation). Because immunocompromised hosts and patients without the classic presentation of a primary lung abscess can be infected with a wide array of unusual organisms (Table 122-1), it is of special importance to obtain culture material in order to target therapy.

CLINICAL MANIFESTATIONS

Clinical manifestations may initially be similar to those of pneumonia, with fevers, cough, sputum production, and chest pain; a more chronic and indolent presentation that includes night sweats, fatigue, and anemia is often observed with anaerobic lung abscesses. A subset of patients with putrid lung abscesses may report discolored phlegm and foul-tasting or foul-smelling sputum. Patients with lung abscesses due to non-anaerobic organisms, such as *S. aureus*, may present with a more fulminant course characterized by high fevers and rapid progression.

Findings on physical examination may include fevers, poor dentition, and/or gingival disease as well as amphoric and/or cavernous breath sounds on lung auscultation. Additional findings may include digital clubbing and the absence of a gag reflex.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lung abscesses is broad and includes other noninfectious processes that result in cavitary lung lesions, including lung infarction, malignancy, sequestration, cryptogenic organizing pneumonia, sarcoidosis, vasculitides and other autoimmune diseases (e.g., granulomatosis with polyangiitis), lung cysts or bullae containing fluid, and septic emboli (e.g., from tricuspid valve endocarditis). Other less common entities can include pulmonary manifestations of diseases that usually present at locations other than the chest (e.g., inflammatory bowel disease, pyoderma gangrenosum).

DIAGNOSIS

Lung abscesses are documented by chest imaging. Although a chest radiograph usually detects a thick-walled cavity with an air-fluid level, CT permits better definition and may provide earlier evidence of cavitation. CT may also yield additional information regarding a possible underlying cause of lung abscess, such as malignancy, and may help distinguish a peripheral lung abscess from a pleural infection. This distinction has important implications for treatment because a pleural space infection, such as an empyema, may require urgent drainage.

As described earlier (see "Pathology and Microbiology," above), more invasive diagnostics (such as transtracheal aspiration) were traditionally undertaken for primary lung abscesses, whereas empirical therapy that includes drugs targeting anaerobic organisms currently is used more often. While sputum can be collected noninvasively for Gram's stain and culture, which may yield a pathogen, the infection is likely to be polymicrobial, and culture results may not reflect the presence of anaerobic organisms. As stated above, many physicians consider putrid-smelling sputum to be virtually diagnostic of an anaerobic infection.

When a secondary lung abscess is present or empirical therapy fails to elicit a response, sputum and blood cultures are advised in addition to serologic studies for opportunistic pathogens (e.g., viruses and fungi causing infections in immunocompromised hosts). Additional diagnostics, such as bronchoscopy with bronchoalveolar lavage or protected brush specimen collection and CT-guided percutaneous needle aspiration, can be undertaken. Risks posed by these more invasive diagnostics include spillage of abscess contents into the other lung (with bronchoscopy) and pneumothorax and bronchopleural fistula development (with CT-guided needle aspiration). However, early diagnostics in secondary abscesses, especially in immunocompromised hosts, are particularly important, because the patients involved may be especially fragile, at risk for infection with a broad array of pathogens, and therefore less likely than other patients to respond to empirical therapy.

TREATMENT

Lung Abscess

The availability of antibiotics in the 1940s and 1950s established therapy with this drug class as the primary approach to the treatment of lung abscess. Previously, surgery had been relied upon much more frequently. For many decades, penicillin was the antibiotic of choice for primary lung abscesses in light of its anaerobic coverage; however, because oral anaerobes can produce β-lactamases, clindamycin has proved superior to penicillin in clinical trials. For primary lung abscesses, the recommended regimens are (1) clindamycin (600 mg IV three times daily; then, with the disappearance of fever and clinical

improvement, 300 mg PO four times daily) or (2) an IV-administered β-lactam/β-lactamase combination, followed—once the patient's condition is stable—by orally administered amoxicillin-clavulanate. This therapy should be continued until imaging demonstrates that the lung abscess has cleared or regressed to a small scar. Treatment duration may range from 3–4 weeks to as long as 14 weeks. One small study suggested that moxifloxacin (400 mg/d PO) is as effective and well tolerated as ampicillin-sulbactam. Notably, metronidazole is not effective as a single agent: it covers anaerobic organisms but not the microaerophilic streptococci that are often components of the mixed flora of primary lung abscesses.

In secondary lung abscesses, antibiotic coverage should be directed at the identified pathogen, and a prolonged course (until resolution of the abscess is documented) is often required. Treatment regimens and courses vary widely, depending on the immune state of the host and the identified pathogen. Other interventions may be necessary as well, such as relief of an obstructing lesion or treatment directed at the underlying condition predisposing the patient to lung abscess. Similarly, if the condition of patients with presumed primary lung abscess fails to improve, additional studies to rule out an underlying predisposing cause for a secondary lung abscess are indicated.

Although it can take as long as 7 days for patients receiving appropriate therapy to defervesce, as many as 10–20% of patients may not respond at all, with continued fevers and progression of the abscess cavity on imaging. An abscess >6–8 cm in diameter is less likely to respond to antibiotic therapy without additional interventions. Options for patients who do not respond to antibiotics and whose additional diagnostic studies fail to identify an additional pathogen that can be treated include surgical resection and percutaneous drainage of the abscess, especially when the patient is a poor surgical candidate. Timing of surgical intervention can be challenging; the goal is to balance the morbidity/mortality risk of a procedure with the need for definitively clearing the abscess in the setting of persistent infection that is not responsive to nonsurgical approaches. Possible complications of percutaneous drainage include bacterial contamination of the pleural space as well as pneumothorax and hemothorax.

COMPLICATIONS

Larger cavity size on presentation may correlate with the development of persistent cystic changes (pneumatoceles) or bronchiectasis. Additional possible complications include recurrence of abscesses despite appropriate therapy, extension to the pleural space with development of empyema, life-threatening hemoptysis, and massive aspiration of lung abscess contents.

PROGNOSIS AND PREVENTION

Reported mortality rates for primary abscesses have been as low as 2%, while rates for secondary abscesses are generally higher—as high as 75% in some case series. Other poor prognostic factors include an age of >60, the presence of aerobic bacteria, sepsis at presentation, symptom duration of >8 weeks, and abscess size of >6 cm.

Mitigation of underlying risk factors may be the best approach to prevention of lung abscesses, with attention directed toward airway protection, oral hygiene, and minimized sedation with elevation of the head of the bed for patients at risk for aspiration. Prophylaxis against certain pathogens in at-risk patients (e.g., recipients of bone marrow or solid organ transplants or patients whose immune systems are significantly compromised by HIV infection) may be undertaken.

APPROACH TO THE PATIENT

Lung Abscess

For patients with a lung abscess and a low likelihood of malignancy (e.g., smokers <45 years old) and with risk factors for aspiration, it is reasonable to administer empirical treatment and then to pursue further evaluation if therapy does not elicit a response. However, some clinicians may opt for up-front cultures, even in primary lung abscesses. In patients with risk factors for malignancy or other underlying conditions (especially immunocompromised hosts) or with an atypical presentation, earlier diagnostics should be considered, such as bronchoscopy with biopsy or CT-guided needle aspiration. Bronchoscopy should be performed early in patients whose history, symptoms, or imaging findings are consistent with possible bronchial obstruction. In patients from areas endemic for tuberculosis or patients with other risk factors for tuberculosis (e.g., underlying HIV infection), induced sputum samples should be examined early in the workup to rule out this disease.

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123 Infective Endocarditis

Adolf W. Karchmer

The prototypic lesion of infective endocarditis, the *vegetation* **(Fig. 123-1)**, is a mass of platelets, fibrin, microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves but may also occur on the low-pressure side of a ventricular septal defect, on mural endocardium damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices themselves. The analogous process involving arteriovenous shunts, arterio-arterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called *infective endarteritis*.

Endocarditis can be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or the predisposing risk factor (e.g., injection drug use, association with health care). *Acute endocarditis* is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites, and, if untreated, progresses to death within weeks. *Subacute endocarditis* follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm.

In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year and has remained relatively stable during recent decades. While congenital heart diseases remain a constant predisposition, predisposing conditions in developed countries have shifted from chronic rheumatic heart disease (still a common predisposition in developing countries) to illicit IV drug use, degenerative valve disease, and intracardiac devices. The incidence of endocarditis is notably increased among the elderly. In developed countries, 25–35% of cases of native-valve endocarditis (NVE) are associated with health care, and 16–30% of all cases are prosthetic-valve infections (PVE). The risk of PVE is greatest during the first 6–12 months after valve replacement; gradually declines to a low, stable rate thereafter; and is similar for mechanical and bioprosthetic devices. The incidence of infection involving transcatheter implanted aortic valves (a new form of PVE that is beyond the scope of this chapter) is

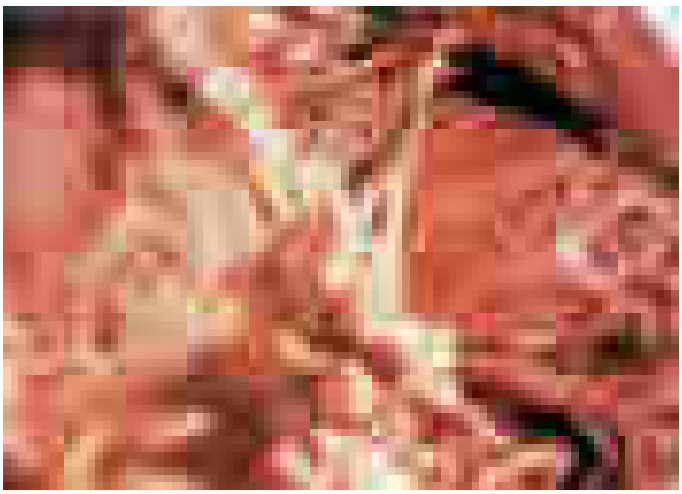


FIGURE 123-1 Vegetations (arrows) due to viridans streptococcal endocarditis involving the mitral valve.

0.97% in the initial year of follow-up. Endocarditis involving cardiovascular implantable electronic devices (CIEDs)—primarily permanent pacemakers and implantable cardioverter-defibrillators—occurs in 0.5–1.14 cases per 1000 device recipients, with higher rates among patients with an implantable cardioverter-defibrillator than among those with a permanent pacemaker.

ETIOLOGY

Although many species of bacteria and fungi cause sporadic episodes of endocarditis, a few bacterial species cause the majority of cases (Table 123-1). The oral cavity, skin, and upper respiratory tract are the respective primary portals for viridans streptococci, staphylococci, and HACEK organisms (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*). *Streptococcus gallolyticus* subspecies *gallolyticus* (formerly *S. bovis* biotype 1) originates from the gastrointestinal tract, where it is associated with polyps and colonic tumors, and enterococci enter the bloodstream primarily from the genitourinary tract. Health care–associated NVE, most commonly caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and enterococci, may have either a nosocomial onset (55%) or a community onset (45%) in patients who have had extensive contact with the health care system. Endocarditis complicates 6–25% of episodes of catheter-associated *S. aureus* bacteremia; the higher rates are detected in high-risk patients studied by transesophageal echocardiography (TEE) (see "Cardiac Imaging" below).

PVE arising within 2 months of valve surgery—i.e., early PVE—is generally nosocomial and is the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication. This nosocomial origin is reflected in the primary microbial causes: *S. aureus*, CoNS, facultative gram-negative bacilli, diphtheroids, and fungi. The portals of entry and organisms causing cases beginning >12 months after surgery—i.e., late PVE—are similar to those in community-acquired NVE. PVE due to CoNS that presents 2–12 months after surgery often represents delayed-onset nosocomial infection. Regardless of the time of onset after surgery, at least 68–85% of CoNS strains that cause PVE are resistant to methicillin.

CIED endocarditis involves the device or the endothelium at points of device contact. Occasionally, there is concurrent aortic or mitral valve infection. One-third of cases of CIED endocarditis present within 3 months after device implantation or manipulation, one-third present at 4–12 months, and one-third present at >1 year. *S. aureus* and CoNS, both of which are often resistant to methicillin, cause the majority of cases.

Injection drug use–associated endocarditis, especially that involving the tricuspid valve, is commonly caused by *S. aureus*, which in many cases is resistant to methicillin. Left-sided valve infections in addicts have a more varied etiology. In addition to the usual causes of endocarditis, these cases can be due to *Pseudomonas aeruginosa* and *Candida* species, and sporadic cases can be caused by unusual organisms such

TABLE 123-1 Organisms Causing Major Clinical Forms of Endocarditis

	PERCENTAGE OF CASES								
	NATIVE-VALVE ENDOCARDITIS		PROSTHETIC-VALVE ENDOCARDITIS AT INDICATED TIME OF ONSET (MONTHS) AFTER VALVE SURGERY			ENDOCARDITIS IN INJECTION DRUG USERS			
ORGANISM(S)	COMMUNITY-ACQUIRED (*N* = 1718)	HEALTH CARE–ASSOCIATED (*N* = 1110)	<2 (*N* = 144)	2–12 (*N* = 31)	>12 (*N* = 194)	RIGHT-SIDED (*N* = 346)	LEFT-SIDED (*N* = 204)	TOTAL (*N* = 675)[a]	CIED (*N* = 337)
Streptococci[b]	40	13	1	9	31	5	15	12	2
Pneumococci	2	—	—	—	—	—	—	—	—
Enterococci[c]	9	16	8	12	11	2	24	9	4
Staphylococcus aureus	28	52[d]	22	12	18	77	23	57	36
Coagulase-negative staphylococci	5	11	33	32	11	—	—	—	41
Fastidious gram-negative coccobacilli (HACEK group)[e]	3	—	—	—	6	—	—	—	—
Gram-negative bacilli	1	1	13	3	6	5	13	7	6
Candida spp.	<1	1	8	12	1	—	12	4	2
Polymicrobial/ miscellaneous	3	3	3	6	5	8	10	7	2
Diphtheroids	—	<1	6	—	3	—	—	0.1	1
Culture-negative	9	3	5	6	8	3	3	3	6

[a]The total number of cases is larger than the sum of right- and left-sided cases because the location of infection was not specified in some cases. [b]Includes viridans streptococci; *Streptococcus gallolyticus*; other non–group A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant, pyridoxal-requiring streptococci). [c]Primarily *E. faecalis* or nonspeciated isolates; occasionally *E. faecium* or other, less likely species. [d]Methicillin resistance is common among these *S. aureus* strains. [e]Includes *Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Abbreviation: CIED, cardiac implantable electronic device.

Note: Data are compiled from multiple studies.

as *Bacillus*, *Lactobacillus*, and *Corynebacterium* species. Polymicrobial endocarditis occurs among injection drug users. HIV infection in drug users does not significantly influence the causes of endocarditis.

From 5 to 15% of patients with endocarditis have negative blood cultures; in one-third to one-half of these cases, cultures are negative because of prior antibiotic exposure. The remainder of these patients are infected by fastidious organisms, such as some streptococci (nutritionally variant bacteria now designated *Granulicatella* and *Abiotrophia* species), HACEK organisms, *Coxiella burnetii*, and *Bartonella* species. Some fastidious organisms occur in characteristic geographic settings (e.g., *C. burnetii* and *Bartonella* species in Europe, *Brucella* species in the Middle East). *Tropheryma whipplei* causes an indolent, culture-negative, afebrile form of endocarditis. *C. burnetii* has a predilection for prosthetic valves. *Corynebacterium* species and *Propionibacterium acnes* may involve intracardiac devices and be slow to grow in blood cultures. Lastly, atrial myxoma, marantic endocarditis, and the antiphospholipid antibody syndrome may mimic culture-negative infectious endocarditis.

PATHOGENESIS

The undamaged endothelium is resistant to infection by most bacteria and to thrombus formation. Endothelial injury (e.g., at the site of impact of high-velocity blood jets or on the low-pressure side of a cardiac structural lesion) allows either direct infection by virulent organisms or the development of a platelet–fibrin thrombus—a condition called *nonbacterial thrombotic endocarditis* (NBTE). This thrombus serves as a site of bacterial attachment during transient bacteremia. The cardiac conditions most commonly resulting in NBTE are mitral regurgitation, aortic stenosis, aortic regurgitation, ventricular septal defects, and complex congenital heart disease. NBTE also arises as a result of a hypercoagulable state; this phenomenon gives rise to *marantic endocarditis* (uninfected vegetations seen in patients with malignancy and chronic diseases) and to bland vegetations complicating systemic lupus erythematosus and antiphospholipid antibody syndrome.

Organisms that cause endocarditis enter the bloodstream from mucosal surfaces, the skin, or sites of focal infection. Except for more virulent bacteria (e.g., *S. aureus*) that can adhere directly to intact endothelium or exposed subendothelial tissue, microorganisms in the blood adhere at sites of NBTE. The organisms that commonly cause endocarditis have surface adhesin molecules, collectively called microbial surface components recognizing adhesin matrix molecules (MSCRAMMs), that mediate adherence to NBTE sites or injured endothelium. Adherence is facilitated by fibronectin-binding proteins present on many gram-positive bacteria; by clumping factor (a fibrinogen- and fibrin-binding surface protein) on *S. aureus*; by fibrinogen-binding surface proteins (Fss2), collagen-binding surface protein (Ace), and Ebp pili (the latter mediating platelet adherence) on *Enterococcus faecalis*; and by glucans or FimA (a member of the family of oral mucosal adhesins) on streptococci. Fibronectin-binding proteins are required for *S. aureus* invasion of intact endothelium; thus these surface proteins may facilitate infection of previously normal valves. If resistant to the bactericidal activity of serum and the microbicidal peptides released locally by platelets, adherent organisms proliferate to form dense microcolonies. Microorganisms also induce platelet deposition and a localized procoagulant state by eliciting tissue factor from the endothelium and, in the case of *S. aureus*, from monocytes as well. Fibrin deposition combines with platelet aggregation and microorganism proliferation to generate an infected vegetation. Organisms deep in vegetations are metabolically inactive (nongrowing) and relatively resistant to killing by antimicrobial agents. Proliferating surface organisms are shed into the bloodstream continuously.

The clinical manifestations of endocarditis—other than constitutional symptoms, which probably result from cytokine production—arise from damage to intracardiac structures; embolization of vegetation fragments, leading to infection or infarction of remote tissues; hematogenous infection of sites during bacteremia; and tissue injury due to the deposition of circulating immune complexes or immune responses to deposited bacterial antigens.

CLINICAL MANIFESTATIONS

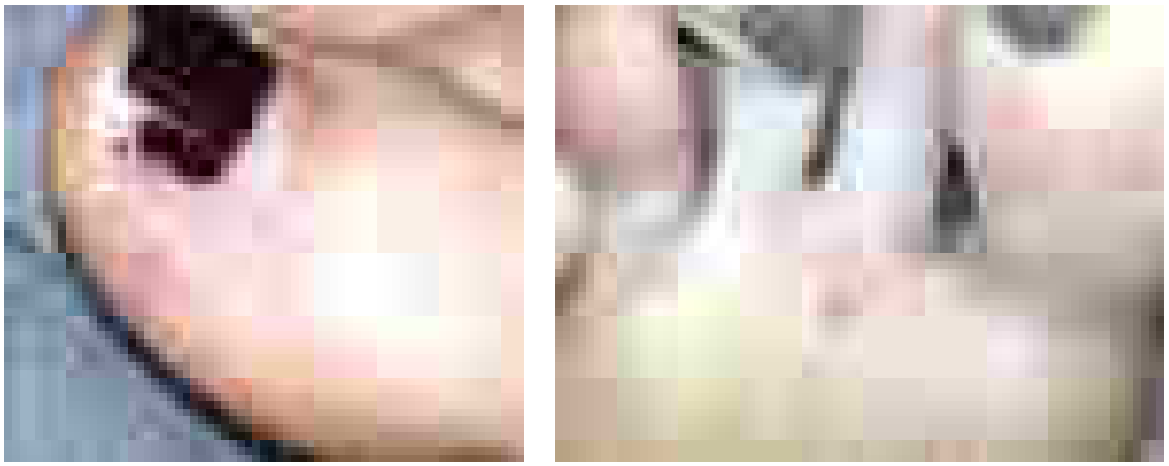
The clinical endocarditis syndrome is highly variable and spans a continuum between acute and subacute presentations. NVE, PVE, and endocarditis due to injection drug use share clinical and laboratory manifestations **(Table 123-2)**. The causative microorganism is primarily responsible for the temporal course of endocarditis. β-Hemolytic streptococci, *S. aureus*, and pneumococci typically result in an acute course, although *S. aureus* occasionally causes subacute disease. Endocarditis caused by *Staphylococcus lugdunensis* (a coagulase-negative species) or by enterococci may present acutely. Subacute endocarditis is typically caused by viridans streptococci, enterococci, CoNS, and the HACEK group. Endocarditis caused by *Bartonella* species, *T. whipplei*, or *C. burnetii* is exceptionally indolent.

In patients with subacute presentations, fever is typically low-grade and rarely exceeds 39.4°C (103°F); in contrast, temperatures of 39.4°–40°C (103°–104°F) are often noted in acute endocarditis. Fever may be blunted in patients who are elderly, are severely debilitated, or have renal failure.

Cardiac Manifestations Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of endocarditis, valvular damage and ruptured chordae may result in new regurgitant murmurs. In acute endocarditis involving a normal valve, murmurs may be absent initially but ultimately are detected in 85% of cases. Congestive heart failure (CHF) develops in 30–40% of patients as a consequence of valve dysfunction or, occasionally, intracardiac fistulae. Heart failure due to aortic valve dysfunction progresses more rapidly than does that due to mitral valve dysfunction. Extension of infection beyond valve leaflets into adjacent annular or myocardial tissue results in perivalvular abscesses, which in turn may cause intracardiac fistulae with new murmurs. Abscesses may burrow from the aortic valve annulus into the upper ventricular septum, where they may interrupt the conduction system, leading to varying degrees of heart block. Mitral perivalvular abscesses, which are usually more distant from the conduction system, only rarely cause conduction abnormalities. Emboli to a coronary artery occur in 2% of patients and may result in myocardial infarction.

TABLE 123-2 Clinical and Laboratory Features of Infective Endocarditis

FEATURE	FREQUENCY, %
Fever	80–90
Chills and sweats	40–75
Anorexia, weight loss, malaise	25–50
Myalgias, arthralgias	15–30
Back pain	7–15
Heart murmur	80–85
New/worsened regurgitant murmur	20–50
Arterial emboli	20–50
Splenomegaly	15–50
Clubbing	10–20
Neurologic manifestations	20–40
Peripheral manifestations (Osler's nodes, subungual hemorrhages, Janeway lesions, Roth's spots)	2–15
Petechiae	10–40
Laboratory manifestations	
Anemia	70–90
Leukocytosis	20–30
Microscopic hematuria	30–50
Elevated erythrocyte sedimentation rate	60–90
Elevated C-reactive protein level	>90
Rheumatoid factor	50
Circulating immune complexes	65–100
Decreased serum complement	5–40



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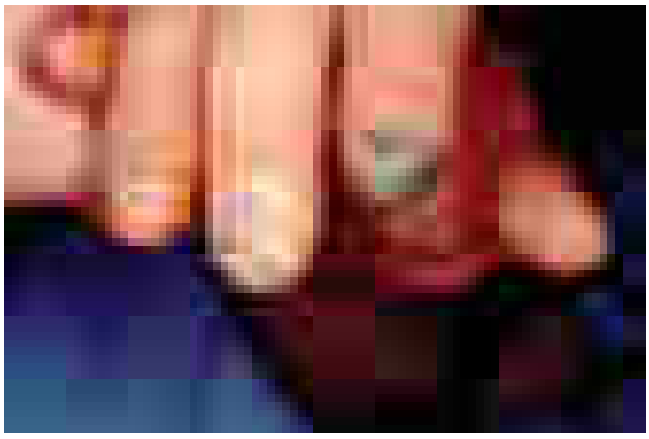

B

FIGURE 123-2 ***A.*** Janeway lesions on the toe (*left*) and plantar surface (*right*) of the foot in subacute *Neisseria mucosa* endocarditis. *(Images courtesy of Rachel Baden, MD.)* ***B.*** Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* endocarditis.

Noncardiac Manifestations The classic nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions; Fig. 123-2*A*) are related to prolonged infection; with early diagnosis and treatment, these have become infrequent. In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler's nodes) is common in patients with acute *S. aureus* endocarditis (Fig. 123-2*B*). Musculoskeletal pain usually remits promptly with treatment but must be distinguished from focal metastatic infections (e.g., spondylodiscitis), which may complicate 10–15% of cases. Hematogenously seeded focal infection occurs most often in the skin, spleen, kidneys, skeletal system, and meninges. Arterial emboli, one-half of which precede the diagnosis of endocarditis, are clinically apparent in up to 50% of patients. Endocarditis caused by *S. aureus,* mobile vegetations >10 mm in diameter, and infection involving the mitral valve, especially the anterior leaflet, are independently associated with an increased risk of embolization. Embolic arterial occlusion causes regional pain or ischemia-induced organ dysfunction (e.g., of the kidney, spleen, bowel, extremity). Cerebrovascular emboli presenting as strokes or occasionally as encephalopathy complicate 15–35% of cases of endocarditis; however, evidence of clinically asymptomatic emboli is found on MRI in 30–65% of patients with left-sided endocarditis. The frequency of stroke is 8 per 1000 patient-days during the week prior to diagnosis; the subsequent fall in frequency—to 4.8 and 1.7 per 1000 patient-days during the first and second weeks of effective antimicrobial therapy, respectively—is unrelated to change in vegetation size. Only 3% of strokes occur after 1 week of effective therapy. Emboli occurring late during or after effective therapy do not in themselves constitute evidence of failed antimicrobial treatment.

Other neurologic complications include aseptic or purulent meningitis, intracranial hemorrhage due to hemorrhagic infarcts or ruptured mycotic aneurysms, and seizures. (*Mycotic aneurysms* are focal dilations of arteries occurring at points in the artery wall that have been weakened by infection in the vasa vasorum or where septic emboli have lodged.) Microabscesses in brain and meninges occur commonly in *S. aureus* endocarditis; surgically drainable intracerebral abscesses are infrequent.

Immune complex deposition on the glomerular basement membrane causes diffuse hypocomplementemic glomerulonephritis and renal dysfunction, which typically improve with effective antimicrobial therapy. Embolic renal infarcts cause flank pain and hematuria but rarely cause renal dysfunction.

Manifestations of Specific Predisposing Conditions Almost 50% of endocarditis associated with injection drug use is limited to the tricuspid valve and presents with fever but with faint or no murmur and no peripheral manifestations. Septic pulmonary emboli, which are common with tricuspid endocarditis, cause cough, pleuritic chest pain, nodular pulmonary infiltrates, and occasionally empyema or pyopneumothorax. Infection of the aortic or mitral valves presents with the typical clinical features of endocarditis, including peripheral manifestations.

If not associated with an intracardiac device or masked by the symptoms of concurrent comorbid illness, health care–associated endocarditis has typical manifestations. CIED endocarditis may be associated with obvious (especially within 6 months of device manipulation) or cryptic generator pocket infection and results in fever, minimal murmur, and pulmonary symptoms due to septic emboli. Late-onset PVE presents with typical clinical features. In early PVE, typical symptoms may be obscured by comorbidity associated with recent surgery. In both early and late PVE, perivalvular infection is common and often results in partial valve dehiscence, regurgitant murmurs, CHF, or disruption of the conduction system.

DIAGNOSIS

Careful clinical, microbiologic, and echocardiographic evaluations should be pursued when febrile patients have endocarditis predispositions, cardiac or noncardiac (e.g., stroke or splenic infarct) features of endocarditis, or blood cultures yielding an endocarditis-associated organism.

Duke Criteria The diagnosis of infective endocarditis is established with certainty only when vegetations are examined histologically and microbiologically. Nevertheless, a highly sensitive and specific diagnostic schema—known as the *modified Duke criteria*—is based on clinical, laboratory, and echocardiographic findings commonly encountered in patients with endocarditis **(Table 123-3)**. Although developed as a research tool, the criteria can help with diagnosis if the appropriate data are collected. Nevertheless, clinical judgment must be exercised in order to use the criteria effectively. Documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria allows a clinical diagnosis of definite endocarditis. The diagnosis of endocarditis is rejected if an alternative diagnosis is established, if symptoms resolve and do not recur with ≤4 days of antibiotic therapy, or if surgery or autopsy after ≤4 days of antimicrobial therapy yields no histologic evidence of endocarditis. Illnesses not classified as definite endocarditis or rejected as such are considered cases of possible infective endocarditis when either one major and one minor criterion or three minor criteria are fulfilled. Requiring some clinical features of endocarditis for classification as possible infective endocarditis increases the specificity of the schema without significantly reducing its sensitivity. Unless there are extenuating circumstances, patients with definite or possible endocarditis are treated as having endocarditis.

TABLE 123-3 The Modified Duke Criteria for the Clinical Diagnosis of Infective Endocarditis[a]

Major Criteria

1. Positive blood culture
   - Typical microorganism for infective endocarditis from two separate blood cultures
     - Viridans streptococci, *Streptococcus gallolyticus*, HACEK group organisms, *Staphylococcus aureus*, *or*
     - Community-acquired enterococci in the absence of a primary focus,
     - ***or***
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
     - Blood cultures drawn >12 h apart; *or*
     - All of 3 or a majority of ≥4 separate blood cultures, with first and last drawn at least 1 h apart
     - ***or***
   - Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer of >1:800
2. Evidence of endocardial involvement
   - Positive echocardiogram[b]
     - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or in implanted material, in the absence of an alternative anatomic explanation, *or*
     - Abscess, *or*
     - New partial dehiscence of prosthetic valve,
     - ***or***
   - New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Criteria

1. Predisposition: predisposing heart conditions[c] or injection drug use
2. Fever ≥38.0°C (≥100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
5. Microbiologic evidence: positive blood culture but not meeting major criterion, as noted previously,[d] *or* serologic evidence of active infection with an organism consistent with infective endocarditis

[a]Definite endocarditis is defined by documentation of two major criteria, of one major criterion and three minor criteria, or of five minor criteria. See text for further details. [b]Transesophageal echocardiography is required for optimal assessment of possible prosthetic valve endocarditis or complicated endocarditis. [c]Valvular disease with stenosis or regurgitation, presence of a prosthetic valve, congenital heart disease including corrected or partially corrected conditions (except isolated atrial septal defect, repaired ventricular septal defect, or closed patent ductus arteriosus), prior endocarditis, or hypertrophic cardiomyopathy. [d]Excluding single positive cultures for coagulase-negative staphylococci and diphtheroids, which are common culture contaminants, or for organisms that do not cause endocarditis frequently, such as gram-negative bacilli.

Source: Adapted from JS Li et al: Clin Infect Dis 30:633, 2000. With permission from Oxford University Press.

The modified Duke criteria emphasize bacteremia and echocardiographic findings typical of endocarditis. The requirement for multiple positive blood cultures over time is consistent with the continuous low-density bacteremia characteristic of endocarditis. The diagnostic criteria attach significance to the species of organism isolated from blood cultures. To fulfill a major criterion, an organism that causes both endocarditis and non-endocarditis-related bacteremia (e.g., *S. aureus*, enterococci) must be recovered in multiple blood cultures (i.e., persistent bacteremia) and in the absence of an extracardiac focus of infection. Organisms that rarely cause endocarditis but commonly contaminate blood cultures (e.g., diphtheroids, CoNS) must be found in repeated blood cultures if they are to satisfy a major criterion.

Blood Cultures Isolation of the causative microorganism from blood cultures is critical for diagnosis and for treatment planning. In patients with suspected NVE, PVE, or CIED endocarditis who have not received antibiotics during the prior 2 weeks, three 2-bottle blood culture sets, separated from one another by at least 2 h, should be obtained from different venipuncture sites over 24 h. If the cultures remain negative after 48–72 h, two or three additional blood culture sets should be obtained, and the laboratory should be consulted for advice regarding optimal culture techniques. Pending culture results, empirical antimicrobial therapy should be withheld initially from hemodynamically stable patients with suspected subacute endocarditis, especially those who have received antibiotics within the preceding 2 weeks. The delay allows blood for additional cultures to be obtained without the confounding effect of empirical treatment. Patients with acute endocarditis or with deteriorating hemodynamics who may require urgent surgery should receive empirical treatment immediately after three sets of blood cultures are obtained over several hours.

Non-Blood-Culture Tests Serologic tests can be used to implicate organisms that are difficult to recover by blood culture: *Brucella*, *Bartonella*, *Legionella*, *Chlamydia psittaci*, and *C. burnetii*. In vegetations recovered at surgery or by embolectomy, pathogens can also be identified by culture; by microscopic examination with special stains; and by polymerase chain reaction (PCR) recovery of microbial DNA or DNA encoding the 16S or 28S ribosomal unit (16S rRNA or 28S rRNA), which when sequenced allows identification of bacteria and fungi, respectively.

Cardiac Imaging Echocardiography anatomically confirms and measures vegetations, detects intracardiac complications, and assesses cardiac function **(Fig. 123-3)**. Transthoracic echocardiography (TTE) is noninvasive and exceptionally specific; however, it cannot image vegetations <2 mm in diameter, and in 20% of patients the images are inadequate. TTE detects vegetations in 65–80% of patients with definite clinical endocarditis but is not optimal for evaluating prosthetic valves or detecting intracardiac complications. TEE is safe and detects vegetations in >90% of patients with definite endocarditis; nevertheless, initial studies may yield false-negative results in 6–18% of endocarditis patients. When endocarditis is likely, a negative TEE result does not exclude the diagnosis but rather warrants repeating the study in 7–10 days. TEE is the optimal method for the diagnosis of PVE and CIED endocarditis as well as for the detection of myocardial abscess, valve perforations, or intracardiac fistulae. In patients with a CIED and a low likelihood of intracardiac infection, a mass adherent to the lead may be a bland thrombosis rather than an infected vegetation.

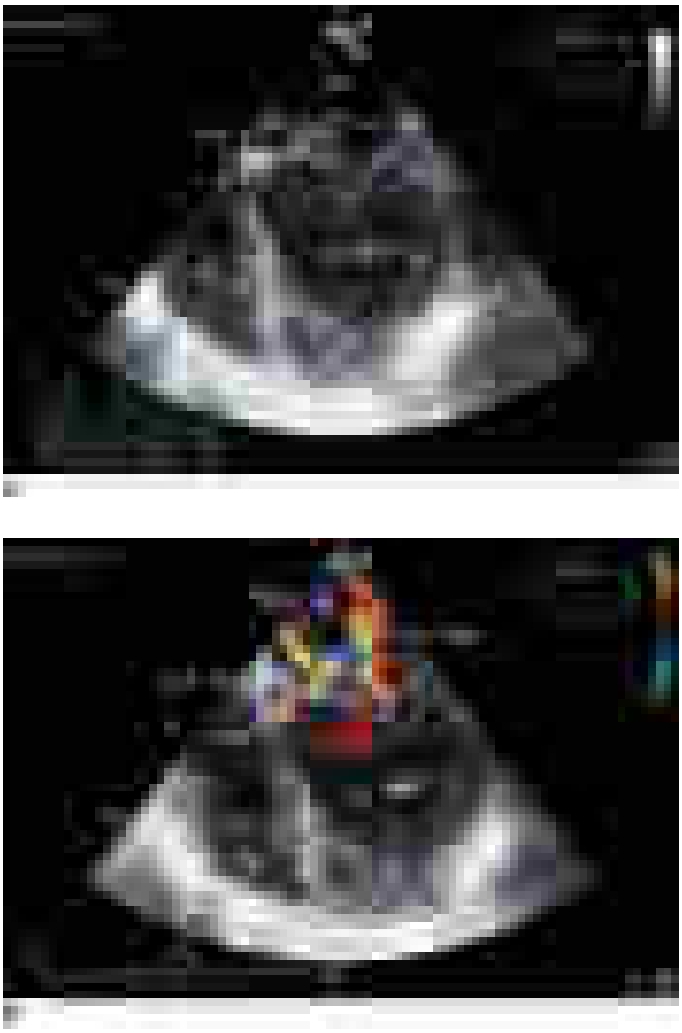

FIGURE 123-3 Imaging of a mitral valve infected with *Staphylococcus aureus* by low-esophageal, four-chamber view, transesophageal echocardiography (TEE). ***A.*** Two-dimensional echocardiogram showing a large vegetation with an adjacent echolucent abscess cavity. ***B.*** Color-flow Doppler image showing severe mitral regurgitation through both the abscess-fistula and the central valve orifice. A, abscess; A-F, abscess-fistula; L, valve leaflets; LA, left atrium; LV, left ventricle; MR, mitral central valve regurgitation; RV, right ventricle; veg, vegetation. *(With permission of Andrew Burger, MD.)*

Three-dimensional TEE may occasionally augment the findings of standard TEE. In addition, 18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, a technique still under evaluation, may identify perivalvular or perigraft infection not seen on TEE in patients with PVE or prosthesis–aorta graft infection (Bental procedure).

Because *S. aureus* bacteremia is associated with a high prevalence of endocarditis, routine echocardiographic evaluation (TTE or preferably TEE) is recommended in these patients. Patients with nosocomial *S. aureus* bacteremia are at increased risk of endocarditis if one or more of the following are present: positive blood cultures for 2–4 days, hemodialysis dependency, a permanent intracardiac device, spine infection, nonvertebral osteomyelitis, or an endocarditis-predisposing valve abnormality. Ideally, these patients should be evaluated with TEE. In patients with none of these findings, the risk of endocarditis is low and evaluation with TTE may suffice.

Experts favor echocardiographic evaluation of all patients with a clinical diagnosis of endocarditis; however, the test should not be used to screen patients with a low probability of endocarditis. An approach to echocardiographic evaluation of patients with suspected endocarditis is illustrated in Fig. 123-4.

Other Studies Many studies that are not diagnostic—i.e., complete blood count, creatinine determination, liver function tests, chest radiography, and electrocardiography—are important in the management of patients with endocarditis. The erythrocyte sedimentation rate, C-reactive protein level, rheumatoid factor, and circulating immune complex titer are commonly increased in endocarditis (Table 123-2). Cardiac catheterization is used to assess coronary artery patency in older individuals who are to undergo surgery for endocarditis.

TREATMENT

Infective Endocarditis

ANTIMICROBIAL THERAPY

To cure endocarditis, all bacteria in the vegetation must be killed. However, it is difficult to eradicate these bacteria because local host defenses are deficient and because the bacteria are largely nongrowing and metabolically inactive and thus are less easily killed by antibiotics. Accordingly, therapy must be bactericidal and prolonged. Antibiotics are generally given parenterally to achieve serum concentrations that, through passive diffusion, result in effective concentrations in the depths of the vegetation. To select effective therapy requires knowledge of the susceptibility of the causative microorganisms. The decision to initiate treatment empirically must balance the need to establish a microbiologic diagnosis against the potential progression of disease or the need for urgent surgery (see "Blood Cultures," above). Simultaneous infection at other sites (such as the meninges), allergies, end-organ dysfunction, interactions with concomitantly administered medications, and risks of adverse events must be considered in the selection of therapy.

Although given for several weeks longer, the regimens recommended for the treatment of PVE (except that caused by staphylococci) are similar to those used to treat NVE **(Table 123-4)**. Recommended doses and durations of therapy should be followed unless alterations are required by end-organ dysfunction or adverse events. The duration of therapy is measured from the time blood cultures become negative.

Organism-Specific Therapies • **Streptococci** The recommended therapies for streptococcal endocarditis are based on the minimal inhibitory concentration (MIC) of penicillin for the causative isolate (Table 123-4). The 2-week penicillin/gentamicin and ceftriaxone/gentamicin regimens should not be used to treat PVE or NVE complicated by cardiac or extracardiac abscess. Caution should be exercised in considering aminoglycoside-containing regimens for the treatment of patients at increased risk for aminoglycoside toxicity (renal or eighth cranial nerve). The regimens recommended for relatively penicillin-resistant streptococci are advocated for treatment of group B, C, or G streptococcal endocarditis. *Granulicatella* or *Abiotrophia* species (nutritionally variant streptococci) and *Gemella* species are treated with the regimens for moderately penicillin-resistant streptococci, as is PVE caused by these organisms or by streptococci with a penicillin MIC of >0.1 μg/mL (Table 123-4).

Enterococci Enterococci are resistant to oxacillin, nafcillin, and the cephalosporins and are only inhibited—not killed—by penicillin, ampicillin, teicoplanin (not available in the United States), and vancomycin. Enterococci are killed by the synergistic interaction of a cell wall–active antibiotic that is effective at achievable serum concentrations (penicillin, ampicillin, vancomycin, or teicoplanin) combined with an aminoglycoside (gentamicin or streptomycin) to which the isolate does not exhibit high-level resistance. An isolate's resistance to cell wall–active agents or its ability to replicate in the presence of gentamicin at ≥500 μg/mL or streptomycin at 1000–2000 μg/mL—a phenomenon called *high-level aminoglycoside resistance*—indicates that the ineffective antimicrobial agent cannot participate in the interaction to produce killing. High-level resistance to gentamicin predicts that tobramycin, netilmicin, amikacin, and kanamycin will be ineffective also. In fact, even when enterococci are not highly resistant to gentamicin, it is difficult to predict that aminoglycosides other than gentamicin and streptomycin will participate in synergistic killing; consequently, only these

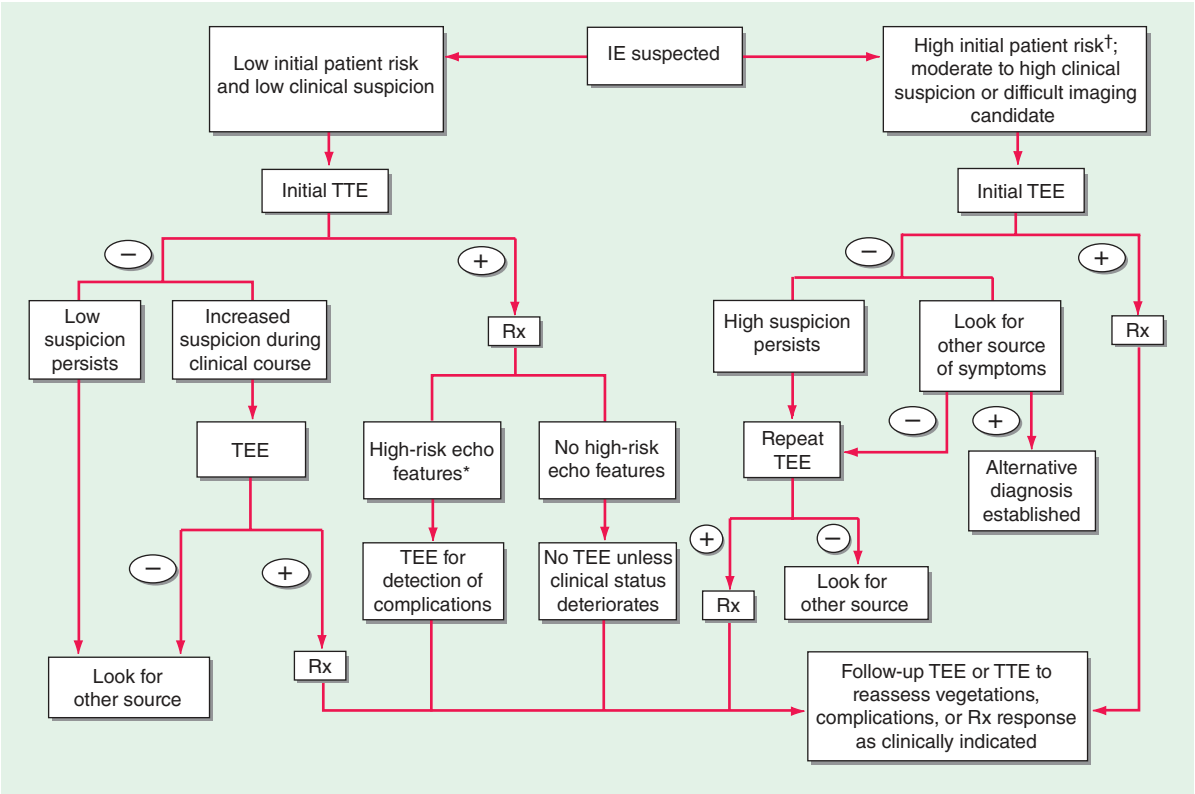

FIGURE 123-4 The diagnostic use of transesophageal and transtracheal echocardiography (TEE and TTE, respectively). †High initial patient risk for infective endocarditis (IE), as listed in Table 123-8, or evidence of intracardiac complications (new regurgitant murmur, new electrocardiographic conduction changes, or congestive heart failure). *High-risk echocardiographic features include large vegetations, valve insufficiency, paravalvular infection, or ventricular dysfunction. Rx indicates initiation of antibiotic therapy. *(Reproduced with permission from Diagnosis and Management of Infective Endocarditis and Its Complications. Circulation 98:2936, 1998. © 1998 American Heart Association.)*

two aminoglycosides should be considered for synergy in treating enterococcal endocarditis. High concentrations of ampicillin plus ceftriaxone or cefotaxime, by expanded binding of penicillin-binding proteins, also kill *E. faecalis* in vitro and in animal models of endocarditis.

Enterococci must be tested for high-level resistance to streptomycin and gentamicin, β-lactamase production, and susceptibility to penicillin and ampicillin (MIC, <8 μg/mL) and to vancomycin (MIC, ≤4 μg/mL) and teicoplanin (MIC, ≤2 μg/ml). If the isolate produces β-lactamase, ampicillin/sulbactam or vancomycin can be used as the cell wall–active component; if the penicillin/ampicillin MIC is ≥8 μg/mL, vancomycin can be considered; and if the vancomycin MIC is ≥8 μg/mL, penicillin or ampicillin can be considered. In the absence of high-level resistance, gentamicin or streptomycin should be used as the aminoglycoside (Table 123-4). Although the dose of gentamicin used to achieve bactericidal synergy in treating enterococcal endocarditis is smaller than that used in standard therapy, nephrotoxicity (or vestibular toxicity with streptomycin) is not uncommon during treatment lasting 4–6 weeks. Regimens in which the gentamicin component is given for only 2–3 weeks have been curative and associated with less nephrotoxicity than those using longer courses. Thus some experts prefer regimens wherein gentamicin is administered for only 2–3 weeks.

If there is high-level resistance to both gentamicin and streptomycin, a synergistic bactericidal effect cannot be achieved with an aminoglycoside; thus an aminoglycoside should not be given. Instead, an 8- to 12-week course of a single cell wall–active agent can be considered; however, high doses of ampicillin combined with ceftriaxone or cefotaxime have been suggested for *E. faecalis* endocarditis (Table 123-4). Nonrandomized comparative studies suggest that ampicillin-ceftriaxone may be as effective as (and less nephrotoxic than) penicillin or ampicillin plus an aminoglycoside in the treatment of *E. faecalis* endocarditis and may provide effective treatment when strains possess high-level resistance to gentamicin and streptomycin. This regimen may also be preferred in patients who are at increased risk for aminoglycoside nephrotoxicity or in lieu of streptomycin.

If the enterococcal isolate is resistant to all of the commonly used agents, suppression of bacteremia followed by surgical treatment should be considered. The role of agents potentially active against multidrug-resistant enterococci (quinupristin/dalfopristin [*E. faecium* only], linezolid, and daptomycin) in the treatment of endocarditis has not been established.

Staphylococci The regimens used to treat staphylococcal endocarditis (Table 123-4) are based not on coagulase production but rather on the presence or absence of a prosthetic valve or foreign device, the native valve(s) involved (right vs left side), and the susceptibility of the isolate to penicillin, methicillin, and vancomycin. All staphylococci are considered potentially penicillin resistant and, except in specific countries, methicillin resistant. Thus empirical therapy for possible staphylococcal NVE should use a regimen that covers methicillin-resistant organisms. Therapy should be revised to a β-lactam agent if the isolate is susceptible to methicillin. The addition of 3–5 days of gentamicin to a β-lactam antibiotic or vancomycin to enhance therapy for left-sided NVE has not improved survival rates and is associated with nephrotoxicity. Most guidelines do not recommend the routine addition of gentamicin, fusidic acid, or rifampin to regimens for *S. aureus* NVE.

For treatment of NVE due to *methicillin-resistant S. aureus* (MRSA), vancomycin, dosed to achieve trough concentrations of 15–20 μg/mL, is recommended, with the caveat that this regimen may be associated with nephrotoxicity. Although resistance to vancomycin among staphylococci is rare, reduced vancomycin susceptibility among MRSA strains is increasingly encountered. Isolates with a vancomycin MIC of 4–16 μg/mL have intermediate susceptibility and are referred to as *vancomycin-intermediate S. aureus* (VISA). Isolates with

TABLE 123-4 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a]

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
Streptococci		
Penicillin-susceptible streptococci, *S. gallolyticus* (MIC ≤0.12 μg/mL[b])	• Penicillin G (2–3 mU IV q4h for 4 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable.
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use ceftriaxone in patients with non-immediate penicillin allergy.
	• Vancomycin[c] (15 mg/kg IV q12h for 4 weeks)	Use vancomycin in patients with severe or immediate β-lactam allergy.
	• Penicillin G (2–3 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 2 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Avoid 2-week regimen when risk of aminoglycoside toxicity is increased and in prosthetic–valve or complicated endocarditis.
Relatively penicillin-resistant streptococci, *S. gallolyticus* (MIC >0.12 μg/mL and <0.5 μg/mL[f])	• Penicillin G (4 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 4 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM, as a single dose[e] or divided into equal doses q8h for 2 weeks)	Can use ampicillin or amoxicillin (2 g IV q4h) if penicillin is unavailable. Penicillin alone at this dose for 6 weeks or with gentamicin during the initial 2 weeks is preferred for prosthetic–valve endocarditis caused by streptococci with penicillin MICs of ≤0.1 μg/mL.
	• Vancomycin[c] as noted above for 4 weeks	Use vancomycin if unable to tolerate penicillins. Ceftriaxone alone or with gentamicin can be used in patients with non-immediate β-lactam allergy.
Moderately penicillin-resistant streptococci (MIC, ≥0.5 μg/mL and <8 μg/mL[g]); *Granulicatella*, *Abiotrophia*, or *Gemella* spp.	• Penicillin G (4–5 mU IV q4h) *or* ceftriaxone (2 g IV qd) for 6 weeks ***plus*** Gentamicin[d] (3 mg/kg qd IV or IM as a single dose[e] *or* divided into equal doses q8h for 6 weeks)	Preferred for PVE caused by streptococci with penicillin MICs of >0.1 μg/mL.
	• Vancomycin[c] as noted above for 4 weeks	Regimen is preferred by some.
Enterococci[h]		
	• Penicillin G (4–5 mU IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can treat NVE for 4 weeks if symptoms last <3 months. Treat PVE and NVE with >3 months of symptoms for 6 weeks. Can abbreviate gentamicin course in some patients (see text). Can use streptomycin (7.5 mg/kg q12h) in lieu of gentamicin if there is not high-level resistance to streptomycin
	• Ampicillin (2 g IV q4h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 4–6 weeks	Can use amoxicillin in lieu of ampicillin (same dose)
	• Vancomycin[c] (15 mg/kg IV q12h) *plus* gentamicin[d] (1 mg/kg IV q8h), both for 6 weeks	Use vancomycin plus gentamicin only for penicillin-allergic patients (preferable to desensitize to penicillin) and for isolates resistant to penicillin/ampicillin.
	• Ampicillin (2 g IV q4h) *plus* ceftriaxone (2 g IV q12h), both for 6 weeks	Use for *E. faecalis* isolates with or without high-level resistance to gentamicin and streptomycin or for patients at high risk for aminoglycoside nephrotoxicity (creatinine clearance rate <50 mL/min; see text).
Staphylococci (*S. aureus* and coagulase-negative)		
MSSA infecting native valves (no foreign devices)	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 4–6 weeks)	Can use penicillin (4 mU q4h) if isolate is penicillin susceptible (i.e., does not produce β-lactamase); 6-week course preferred
	• Cefazolin (2 g IV q8h for 4–6 weeks)	Can use cefazolin regimen for patients with non-immediate penicillin allergy; 6-week course preferred
	• Vancomycin[c] (15 mg/kg IV q12h for 4–6 weeks)	Only use vancomycin for patients with immediate (urticarial) or severe penicillin allergy; see text regarding addition of gentamicin, fusidic acid, or rifampin. A 6-week course is preferred.
MRSA infecting native valves (no foreign devices)	• Vancomycin[c] (15 mg/kg IV q8–12h for 4–6 weeks)	No role for routine use of rifampin (see text). Consider high-dose daptomycin treatment (see text) for MRSA with vancomycin MIC >1.0 or persistent bacteremia during vancomycin therapy.
MSSA infecting prosthetic valves	• Nafcillin, oxacillin, *or* flucloxacillin (2 g IV q4h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** • Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine susceptibility to gentamicin before initiating rifampin (see text); if patient is highly allergic to penicillin, use regimen for MRSA; if β-lactam allergy is of the minor non-immediate type, cefazolin can be substituted for oxacillin, nafcillin, or flucloxacillin.
MRSA infecting prosthetic valves	• Vancomycin[c] (15 mg/kg IV q12h for 6–8 weeks) ***plus*** Gentamicin[d] (1 mg/kg IM or IV q8h for 2 weeks) ***plus*** Rifampin[i] (300 mg PO q8h for 6–8 weeks)	Use gentamicin during initial 2 weeks; determine gentamicin susceptibility before initiating rifampin (see text).

(*Continued*)

TABLE 123-4 Antibiotic Treatment for Infective Endocarditis Caused by Common Organisms[a] (Continued)

ORGANISM(S)	DRUG (DOSE, DURATION)	COMMENTS
HACEK Organisms		
	• Ceftriaxone (2 g/d IV as a single dose for 4 weeks)	Can use another third-generation cephalosporin at comparable dose.
	• Ampicillin/sulbactam (3 g IV q6h for 4 weeks)	If the isolate is susceptible, ciprofloxacin (400 mg IV q12h) can be used.
Coxiella burnetii		
	• Doxycycline (100 mg PO q12h) *plus* hydroxychloroquine (200 mg PO q8h), both for at least 18 (native valve) or 24 (prosthetic valve) months	Follow serology to monitor response during treatment (antiphase I IgG and IgA decreased 4-fold and IgM antiphase II negative) and thereafter for relapse.
***Bartonella* spp.**		
	• Doxycycline (100 mg q12h PO) for 6 weeks ***plus*** Gentamicin (1 mg/kg IV q8h for 2 weeks)	If doxycycline is not tolerated, use azithromycin (500 mg PO qd). Some experts recommend that doxycycline be continued for 3–6 months unless all infection is resected surgically.

[a]Regimens adapted from the guidelines of the American Heart Association, the European Society of Cardiology (ESC), and to a lesser extent the British Society for Antimicrobial Chemotherapy (BSAC). Doses of gentamicin, streptomycin, and vancomycin must be adjusted for reduced renal function. Ideal body weight is used to calculate doses of gentamicin and streptomycin per kilogram (men = 50 kg + 2.3 kg per inch over 5 feet; women = 45.5 kg + 2.3 kg per inch over 5 feet). [b]MIC ≤0.125 μg/mL per ESC and BSAC. [c]Vancomycin dose is based on actual body weight. Adjust for trough level of 10–15 μg/mL for streptococcal and enterococcal infections and 15–20 μg/mL for staphylococcal infections. [d]Aminoglycosides should not be administered as single daily doses for enterococcal endocarditis and should be introduced as part of the initial treatment. Target peak and trough serum concentrations of divided-dose gentamicin 1 h after a 20- to 30-min infusion or IM injection are ~3.5 μg/mL and ≤1 μg/mL, respectively; target peak and trough serum concentrations of streptomycin (timing as with gentamicin) are 20–35 μg/mL and <10 μg/mL, respectively. [e]Netilmicin (4 mg/kg qd, as a single dose) can be used in lieu of gentamicin. [f]MIC >0.125 μg/mL and ≤2.0 μg/mL per ESC; MIC >0.125 μg/mL and ≤0.5 μg/mL per BSAC. [g]MIC >2.0 μg/mL per ESC; treat with regimen for enterococci (BSAC). [h]Antimicrobial susceptibility must be evaluated; see text. [i]Rifampin increases warfarin and dicumarol requirements for anticoagulation.

Abbreviations: MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; NVE, native-valve endocarditis; PVE, prosthetic-valve endocarditis.

a vancomycin MIC of 2 μg/mL may harbor subpopulations with higher MICs. Isolates with these subpopulations, called *heteroresistant VISA* (hVISA), are not detectable by routine susceptibility testing and yet may impair vancomycin efficacy. Because of the pharmacokinetics/pharmacodynamics of vancomycin, killing of MRSA with a vancomycin MIC of >1.0 μg/mL is unpredictable, even with aggressive vancomycin dosing. As an alternative to vancomycin, daptomycin (8–10 mg/kg IV once daily) has provided effective treatment for left-sided NVE caused by documented daptomycin-susceptible VISA, hVISA, or isolates with a vancomycin MIC of >1.0 μg/mL (not approved by the U.S. Food and Drug Administration for this indication). Daptomycin activity against MRSA—even against some isolates with reduced daptomycin susceptibility—is enhanced in combination with nafcillin or ceftaroline. Case series suggest that either high-dose daptomycin combined with nafcillin or ceftaroline or ceftaroline alone (600 mg IV q8h) may be effective treatment for vancomycin-unresponsive MRSA endocarditis. Infectious disease consultation is recommended for treatment of MRSA endocarditis when bacteremia persists despite therapy. The efficacy of linezolid or telavancin for left-sided MRSA endocarditis has not been established. Although it is not advocated by other groups, the British Society for Antimicrobial Chemotherapy recommends the addition of a second drug to vancomycin (rifampin) or to daptomycin (rifampin, gentamicin, or linezolid) for the treatment of MRSA NVE.

Methicillin-susceptible *S. aureus* endocarditis that is uncomplicated and limited to the tricuspid or pulmonic valve can often be treated with a 2-week course that combines oxacillin or nafcillin (but not vancomycin) with gentamicin. However, patients with prolonged fever (≥5 days) during therapy or multiple septic pulmonary emboli should receive standard-duration therapy. Vancomycin plus gentamicin for 2 weeks for right-sided endocarditis caused by MRSA yields suboptimal results; thus this entity is treated for at least 4 weeks with vancomycin or daptomycin (6 mg/kg as a single daily dose).

Staphylococcal PVE is treated for 6–8 weeks with a multidrug regimen (Table 123-4). Rifampin is an essential component because it kills staphylococci that are adherent to foreign material in a biofilm. Two other agents (selected on the basis of susceptibility testing) are combined with rifampin to prevent in vivo emergence of rifampin resistance. Because many staphylococci (particularly MRSA and *Staphylococcus epidermidis* causing PVE) are resistant to gentamicin, the isolate's susceptibility to gentamicin or an alternative agent should be established before rifampin treatment is begun. Possible alternatives for gentamicin include another aminoglycoside, a fluoroquinolone (chosen on the basis of susceptibility), ceftaroline, or another active agent.

Other Organisms In the absence of meningitis, endocarditis caused by *Streptococcus pneumoniae* isolates with a penicillin MIC of ≤4 μg/mL can be treated with IV penicillin (4 million units every 4 h), ceftriaxone (2 g/d as a single dose), cefotaxime (at a comparable dose), or vancomycin. Ceftriaxone or vancomycin is preferred for pneumococcal strains with a penicillin MIC of ≥2 μg/mL. If meningitis is suspected, treatment with vancomycin plus ceftriaxone—at the doses advised for meningitis—should be initiated until susceptibility results are known. Definitive therapy should then be selected on the basis of meningitis breakpoints (penicillin MIC, 0.06 μg/mL; or ceftriaxone MIC, 0.5 μg/mL). Pneumococcal NVE is treated for 4 weeks and pneumococcal PVE for 6 weeks. *P. aeruginosa* endocarditis is treated with an antipseudomonal β-lactam (piperacillin or a cephalosporin) and high doses of tobramycin (8 mg/kg per day in three divided doses). Endocarditis caused by Enterobacteriaceae is treated with a potent β-lactam antibiotic plus an aminoglycoside. Corynebacterial endocarditis is treated with penicillin plus an aminoglycoside (if the organism is susceptible to the aminoglycoside) or with vancomycin, which is highly bactericidal for most strains. Therapy for *Candida* endocarditis consists of a lipid formulation of amphotericin B (3–5 mg/kg IV qd) plus flucytosine (25 mg/kg PO q6h) or a high-dose echinocandin (caspofungin or micafungin, 150 mg IV qd; or anidulafungin, 200 mg IV qd). Early surgery is advised, as is long-term (if not indefinite) suppression with an oral azole.

Empirical Therapy and Treatment for Culture-Negative Endocarditis

In designing therapy to be administered before culture results are known or when cultures are truly negative, clinical clues to etiology (e.g., acute vs. subacute presentation, NVE, early or late PVE, the patient's predispositions) as well as epidemiologic clues (region of residence, animal exposure) must be considered. Thus empirical therapy for acute endocarditis in an injection drug user or for

health care–associated NVE should cover MRSA and potentially antibiotic-resistant gram-negative bacilli. Treatment with vancomycin plus gentamicin or cefepime, initiated immediately after blood cultures are obtained, covers these organisms as well as many other potential causes. For empirical treatment of NVE with a subacute presentation, vancomycin plus ceftriaxone is reasonable. For blood culture–pending PVE, vancomycin, gentamicin, and cefepime should be used if the prosthetic valve has been in place for ≤1 year. Empirical therapy for infected prosthetic valves in place for >1 year is similar to that for culture-negative NVE. Therapy is revised once a pathogen has been identified.

In the treatment of blood culture–negative episodes, marantic endocarditis and the antiphospholipid antibody syndrome must be considered. Fastidious organisms should be investigated by serologic testing. In the absence of prior antibiotic therapy, it is unlikely that infection due to *S. aureus*, CoNS, enterococci, or Enterobacteriaceae will present with negative blood cultures; thus, in this situation, recommended empirical therapy targets not these organisms but rather fastidious streptococci, nutritionally variant organisms, the HACEK group, and *Bartonella* species. Pending the availability of diagnostic data, blood culture–negative subacute NVE is treated with vancomycin plus ampicillin-sulbactam (12 g every 24 h) or ceftriaxone; doxycycline (100 mg twice daily) is added for enhanced *Bartonella* coverage. If cultures are negative because of prior antibiotic administration, pathogens that are likely to be inhibited by the specific prior therapy should be considered.

CIED Endocarditis Antimicrobial therapy for CIED endocarditis (as well as for generator pocket and lead infection) is adjunctive to complete removal of the device. The antimicrobial selected is based on the causative organism and should be used as recommended for NVE (Table 123-4). Bacteremic CIED infection may be complicated by coincident left-sided NVE, PVE, or remote-site infection (e.g., osteomyelitis) and may require modification of antimicrobial therapy. A 4- to 6-week course of endocarditis-targeted therapy is recommended for patients with CIED endocarditis and for those with bacteremia that continues during ongoing antimicrobial therapy after device removal. Generator pocket infection without bacteremia is treated with a 10- to 14-day course, some of which can be given orally. In the absence of another source, *S. aureus* bacteremia (and persistent CoNS bacteremia) in patients with a CIED is likely to be indicative of CIED or valvular endocarditis and should be managed accordingly. However, not all bloodstream infections in these patients indicate endocarditis. If evidence suggesting endocarditis is lacking, bloodstream infection due to gram-negative bacilli, streptococci, enterococci, and *Candida* species may not indicate endocarditis and can be treated with an abbreviated course of antimicrobial therapy. However, in the absence of another source, bacteremia relapse after antimicrobial therapy increases the likelihood of CIED endocarditis and warrants treatment as such. Attempted salvage of an infected CIED with antibiotics alone is usually unsuccessful and should be reserved for patients whose devices cannot be removed or who refuse removal.

Outpatient Antimicrobial Therapy Fully compliant, clinically stable patients who are no longer bacteremic, are not febrile, and have no clinical or echocardiographic findings that suggest an impending complication may complete therapy as outpatients. Careful follow-up and a stable home setting are necessary, as are predictable IV access and use of antimicrobial agents that are stable in solution. Recommended regimens should not be compromised to accommodate outpatient therapy.

Monitoring Antimicrobial Therapy Antibiotic toxicity, including allergic reactions, occurs in 25–40% of endocarditis patients and commonly arises after several weeks of therapy. Blood tests to detect renal, hepatic, and hematologic toxicity should be performed periodically. Serum concentrations of aminoglycosides and vancomycin should be monitored periodically and doses adjusted to optimize treatment and to avoid or address toxicity.

Blood cultures should be repeated daily until sterile in patients with endocarditis due to *S. aureus* or difficult-to-treat organisms, rechecked if there is recrudescent fever, and performed again 4–6 weeks after therapy to document cure. Blood cultures become sterile within 2 days after the start of appropriate therapy when infection is caused by viridans streptococci, enterococci, or HACEK organisms. In *S. aureus* endocarditis, β-lactam therapy results in sterile cultures in 3–5 days, whereas in MRSA endocarditis, positive cultures may persist for 7–9 days with vancomycin or daptomycin treatment. MRSA bacteremia persisting despite an adequate dosage of vancomycin or daptomycin may indicate emergence of reduced susceptibility in the infecting strain and point to a need for alternative therapy. When fever persists for 7 days despite appropriate antibiotic therapy, patients should be evaluated for paravalvular abscess, extracardiac abscesses (spleen, kidney), or complications (embolic events). Recrudescent fever raises the possibility of these complications but also of drug reactions or complications of hospitalization. Vegetations become smaller with effective therapy; however, 3 months after cure, 50% are unchanged and 25% are slightly larger or smaller.

Antithrombotic Therapy A decision to initiate antithrombotic (anticoagulant or antiplatelet) therapy in patients with infective endocarditis requires careful consideration of the risks and benefits, including temporal considerations of each. Patients with infective endocarditis are at risk for emboli, for hemorrhagic transformation of embolic strokes, and for intracerebral hemorrhage from septic arteritis or ruptured mycotic aneurysms. Antithrombotic therapy can render this bleeding catastrophic. Neither anticoagulant nor antiplatelet therapy reduces the risk of emboli in patients with NVE, and thus such treatment is not indicated for that purpose. However, patients with infective endocarditis may have coexisting conditions wherein anticoagulation is indicated. Thus, in the absence of a contraindication (i.e., no clinical or imaging evidence of a recent large embolic stroke, intracerebral hemorrhage, or mycotic aneurysm), anticoagulant therapy is given to patients who have a mechanical prosthetic valve, atrial fibrillation with either mitral stenosis or a CHADS2 score ≥2, or deep-vein thrombophlebitis. Most experts prefer to use unfractionated or low-molecular-weight heparin for ease of reversal. Anticoagulant therapy should be reversed, at least temporarily, in most patients who have had an acute ischemic stroke or an intracerebral hemorrhage.

SURGICAL TREATMENT

Intracardiac and central nervous system complications of endocarditis are important causes of morbidity and death. In some cases, effective treatment for these complications requires surgery. The indications for cardiac surgical treatment of endocarditis **(Table 123-5)** have been derived from observational studies and expert opinion. The strength of individual indications varies; thus the risks and benefits as well as the timing of surgery must be individualized **(Table 123-6)**. These complex considerations are best weighed by a team that includes cardiologists, cardiac surgeons, infectious disease physicians, and neurologists if there have been neurologic complications. From 25 to 40% of patients with left-sided endocarditis undergo cardiac surgery during active infection, with slightly higher surgery rates for PVE than NVE. Intracardiac complications and CHF are the most commonly cited indications for surgery. The benefit of surgery has been assessed primarily in studies comparing populations of medically and surgically treated patients matched for the necessity of surgery, with adjustments for predictors of death (comorbidities) and the timing of surgical intervention (a correction for survival bias). Although study results vary, surgery for NVE based on current indications appears to convey a significant survival benefit (27–55%) that becomes increasingly apparent among patients with the most pressing indications and with follow-up for ≥6 months. The effect of surgery for PVE is more nuanced, with survival benefits accruing largely to those with intracardiac complications. Of note, surgery itself carries mortality risks that may offset survival benefits in patients with lesser indications.

TABLE 123-5 Indications for Cardiac Surgical Treatment in Patients with Endocarditis

Surgery Required for Optimal Outcome
Native-valve or prosthetic-valve endocarditis
Moderate or severe congestive heart failure or shock due to valve dysfunction
Perivalvular extension of infection with abscess, fistula, or heart block
Persistent bacteremia without an extracardiac cause despite 7–10 days of optimal antimicrobial therapy
Lack of effective antimicrobial therapy (e.g., fungal, *Brucella*, multidrug-resistant gram-negative bacillary endocarditis)
Prosthetic-valve endocarditis
Partially dehisced unstable prosthetic valve
Surgery to Be Strongly Considered for Improved Outcome[a]
Prosthetic-valve endocarditis
S. aureus infection with intracardiac complications
Relapse after optimal antimicrobial therapy
Native-valve endocarditis
Large (>10-mm) hypermobile vegetation, particularly with prior systemic embolus and significant valve dysfunction[b]
Very large (>30-mm) vegetation
Persistent unexplained fever (≥10 days) in blood culture–negative endocarditis
Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or gram-negative bacilli

[a]Carefully consider surgery. Multiple findings are often combined to justify surgery. [b]In the group with an estimated low cardiac-surgery mortality risk.

Indications • **Congestive Heart Failure** Moderate to severe refractory CHF caused by new or worsening valve dysfunction or intracardiac fistulae is the major indication for cardiac surgery. Surgery can relieve functional stenosis due to large vegetations or restore competence to damaged regurgitant valves by repair or replacement. At 6–12 months of follow-up, the mortality rate is 50% among patients with left-sided NVE or PVE and moderate to severe heart failure due to valve dysfunction who are treated medically, while that among matched patients treated surgically is 15%. The survival benefit with surgery is inversely related to the severity of preoperative CHF; thus surgery should not be delayed in the face of deteriorating hemodynamics.

Perivalvular Infection This complication, which is most common with aortic valve infection, occurs in 10–15% of patients with NVE and in 45–60% of those with PVE. It is suggested clinically by persistent unexplained fever during appropriate therapy, new electrocardiographic conduction disturbances, or pericarditis. TEE with color Doppler is the test of choice to detect perivalvular abscesses (sensitivity, ≥85%). Occasionally, three-dimensional TEE and FDG-PET/CT demonstrate perivalvular infection not detected by TEE. For optimal outcome, surgery is required, especially when fever persists, fistulae develop, prostheses are dehisced and unstable, or infection relapses after appropriate treatment. Cardiac rhythm must be monitored since high-grade heart block may require insertion of a pacemaker.

Uncontrolled Infection Continued positive blood cultures or otherwise unexplained persistent fevers despite optimal antibiotic therapy may reflect uncontrolled infection that warrants surgery. Surgical treatment is also advised for endocarditis caused by organisms against which effective antimicrobial therapy is lacking (e.g., yeasts, fungi, *P. aeruginosa*, other highly antibiotic-resistant bacteria, *Brucella* species).

***S. aureus* Endocarditis** The mortality rate for *S. aureus* PVE exceeds 50% with medical treatment but is reduced to 25% with surgical treatment. When patients have intracardiac complications, surgical treatment reduces the mortality rate twentyfold. However, surgery is not routinely advised for uncomplicated *S. aureus* PVE. Surgical treatment should be considered for patients with MRSA left-sided NVE who remain septic and unresponsive to alternative antibiotics. Isolated tricuspid-valve *S. aureus* endocarditis, even with persistent fever, rarely requires surgery.

Prevention of Systemic Emboli Persisting morbidity and/or death may result from cerebral or coronary artery emboli. Antithrombotic therapy does not prevent systemic emboli in NVE. The frequency of embolization decreases rapidly with effective antimicrobial therapy. Thus, to further reduce emboli through cardiac surgery, the surgery must be performed very early. Predicting a high risk of systemic embolization by echocardiographic determination of vegetation

TABLE 123-6 Timing of Cardiac Surgical Intervention in Patients with Endocarditis

	INDICATION FOR SURGICAL INTERVENTION	
TIMING	STRONG SUPPORTING EVIDENCE	CONFLICTING EVIDENCE, BUT MAJORITY OF OPINIONS FAVOR SURGERY
Emergent (same day)	Valve dysfunction with pulmonary edema or cardiogenic shock Acute aortic regurgitation plus preclosure of mitral valve Sinus of Valsalva abscess ruptured into right heart Rupture into pericardial sac	
Urgent (within 1–2 days)	Valve obstruction by vegetation Unstable (dehisced) prosthesis Acute aortic or mitral regurgitation with heart failure (New York Heart Association class III or IV) Septal perforation Perivalvular extension of infection with or without new electrocardiographic conduction system changes Lack of effective antibiotic therapy	Vegetation diameter >10 mm plus severe but not urgent aortic or mitral valve dysfunction[a] Major embolus plus persisting large vegetation (>10 mm) Mobile vegetation >30 mm
Elective (earlier usually preferred)	Progressive paravalvular prosthetic regurgitation Valve dysfunction plus persisting infection after ≥7–10 days of antimicrobial therapy Fungal (mold) endocarditis	Staphylococcal prosthetic-valve endocarditis with intracardiac complications Early prosthetic–valve endocarditis (≤2 months after valve surgery) *Candida* spp. endocarditis Antibiotic-resistant organisms

[a]Supported by a single-institution randomized trial showing benefit from early surgery. Implementation requires clinical judgment. If surgery is elected, it must be done early (see text).

Source: Adapted from L Olaison, G Pettersson: Infect Dis Clin North Am 16:453, 2002.

size and anatomy does not identify those patients in whom surgery to prevent emboli will result in increased survival. In a small randomized trial in patients who were at low risk of surgery-related mortality and had large vegetations (>10 mm) and significant valve dysfunction, emboli were prevented by early surgery (≤48 h after diagnosis), but there was no survival benefit. Rarely is the indication for surgery solely to prevent systemic emboli; however, this goal may be an additional benefit of early surgery for other indications. Valve repair, with the consequent avoidance of a prosthesis, improves the benefit-to-risk ratio of surgery performed to eliminate vegetations.

CIED Endocarditis Removal of all hardware is recommended for patients with established CIED endocarditis as well as for pocket or intracardiac lead infection. Percutaneous lead extraction is preferred; with retained hardware after attempted percutaneous extraction, surgical removal should be considered. With lead vegetations >2 cm, there is a risk of a pulmonary embolism; nevertheless, the need for surgical removal of the CIED is unclear. Removal of the infected CIED during the initial hospitalization is associated with increased 30-day and 1-year survival rates over those attained with antibiotic therapy and attempted device retention. The CIED, if needed, can be reimplanted at a new site after at least 10–14 days of effective antimicrobial therapy. CIEDs should be replaced when patients undergo surgery for endocarditis.

Timing of Cardiac Surgery With life-threatening indications for surgery (valve dysfunction and severe CHF, perivalvular abscess, major prosthesis dehiscence), surgery during the initial days of therapy is associated with greater survival than later surgery. With less compelling indications, surgery may reasonably be delayed to allow further treatment as well as improvement in overall health (Table 123-6). Recrudescent endocarditis on a newly implanted prosthetic valve follows surgery for active NVE and PVE in 2% and 6–15% of patients, respectively. These frequencies do not justify the increased mortality risk associated with delaying surgery in patients with severe heart failure, valve dysfunction, and uncontrolled infections. Delay is justified when infection is controlled and CHF is resolved with medical therapy.

Neurologic complications of endocarditis may be exacerbated during cardiac surgery. The risk of neurologic deterioration is related to the type and severity of the preoperative neurologic complication and the interval between the complication and surgery. When the surgical indication is not urgent, cardiac surgery should be delayed for 2–3 weeks after a large nonhemorrhagic embolic infarction and for 4 weeks after a cerebral hemorrhage. A ruptured mycotic aneurysm should be treated before cardiac surgery. In a non-obtunded patient with an ischemic stroke and hemorrhage excluded by imaging, cardiac surgery, if urgent, should be performed early.

Antibiotic Therapy after Cardiac Surgery Organisms have been detected on Gram's stain—or their DNA has been detected by PCR—in excised valves from 45% of patients who have successfully completed the recommended therapy for endocarditis. In only 7% of these patients were the organisms—most of which are unusual and antibiotic resistant—cultured from the valve. Detection of organisms or their DNA does not necessarily indicate antibiotic failure; in fact, relapse after surgery for active endocarditis is uncommon. Thus, when valve cultures are negative in uncomplicated NVE caused by susceptible organisms, the duration of preoperative plus postoperative treatment should equal the total duration of recommended therapy. For endocarditis complicated by perivalvular abscess, partially treated PVE, or culture-positive valves, a full course of therapy should be given postoperatively.

Extracardiac Complications Splenic abscess develops in 3–5% of patients with endocarditis. Effective therapy requires either image-guided percutaneous drainage or splenectomy. Mycotic aneurysms occur in 2–15% of endocarditis patients; one-half of these cases involve the cerebral arteries and present as headaches, focal neurologic symptoms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that persist, enlarge, or leak should be treated surgically if possible. Extracerebral aneurysms present as local pain, a mass, local ischemia, or bleeding; these aneurysms are treated surgically.

OUTCOME

Endocarditis is a heterogeneous disease that occurs in extremely heterogeneous patient populations. Many factors can adversely affect outcome; these include older age, severe comorbid conditions and diabetes, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (*S. aureus*) or antibiotic-resistant (*P. aeruginosa*, yeast) pathogen, intracardiac and major neurologic complications, and an association of infection with health care. Death or poor outcome often is related not to failure of antibiotic therapy but rather to the interactions of comorbidities and endocarditis-related end-organ complications. In developed countries, overall survival rates are 80–85%; however, rates vary considerably among subpopulations of endocarditis patients. Thus predicting the outcome for a given patient must focus on that individual's infection, the complexity of required therapy, and preexisting comorbidities. Survival rates for patients with NVE caused by viridans streptococci, HACEK organisms, or enterococci (susceptible to synergistic therapy) are 85–90%. For *S. aureus* NVE in patients who do not inject drugs, survival rates are 55–70%, whereas 85–90% of injection drug users survive their initial episode of *S. aureus* endocarditis. However, if addiction is not successfully addressed in the latter group, the longer-term prognosis is guarded. PVE beginning within 2 months after valve replacement results in mortality rates of 40–50%, whereas rates are only 10–20% in later-onset cases. Overall survival rates 1 year after successful endocarditis treatment are 80–90%.

PREVENTION

Prevention of endocarditis has long been a goal in clinical practice. However, expert committees have concluded that the evidence favoring antibiotic prophylaxis for endocarditis is insufficient to recommend this treatment as a widespread standard of care. Weighing the potential benefits, potential adverse events, and costs associated with antibiotic prophylaxis, the American Heart Association and the European Society of Cardiology now recommend prophylactic antibiotics **(Table 123-7)** only for those patients at highest risk for severe morbidity or death from endocarditis **(Table 123-8)**. Maintaining good dental hygiene in at-risk patients is essential and a recommended goal. Prophylaxis is recommended only when there is manipulation of gingival tissue or the

TABLE 123-7 Antibiotic Regimens for Prophylaxis of Endocarditis in Adults with High-Risk Cardiac Lesions[a,b]

A. Standard oral regimen
Amoxicillin: 2 g PO 1 h before procedure
B. Inability to take oral medication
Ampicillin: 2 g IV or IM within 1 h before procedure
C. Penicillin allergy
1. Clarithromycin or azithromycin: 500 mg PO 1 h before procedure
2. Cephalexin[c]: 2 g PO 1 h before procedure
3. Clindamycin: 600 mg PO 1 h before procedure
D. Penicillin allergy, inability to take oral medication
1. Cefazolin[c] or ceftriaxone[c]: 1 g IV or IM 30 min before procedure
2. Clindamycin: 600 mg IV or IM 1 h before procedure

[a]Dosing for children: for amoxicillin, ampicillin, cephalexin, or cefadroxil, use 50 mg/kg PO; cefazolin, 25 mg/kg IV; clindamycin, 20 mg/kg PO or 25 mg/kg IV; clarithromycin, 15 mg/kg PO; and vancomycin, 20 mg/kg IV. [b]For high-risk lesions, see Table 123-8. Prophylaxis is not advised for other lesions. [c]Do not use cephalosporins in patients with immediate hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; and G Habib et al: Eur Heart J 30:2369, 2009).

TABLE 123-8 High-Risk Cardiac Lesions for Which Endocarditis Prophylaxis Is Advised Before Dental Procedures

Prosthetic heart valves
Prior endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts or conduits
Completely repaired congenital heart defects during the 6 months after repair
Incompletely repaired congenital heart disease with residual defects adjacent to prosthetic material
Valvulopathy developing after cardiac transplantation[a]

[a]Not a target population for prophylaxis according to recommendations of the European Society for Cardiology.

Source: Table created using the guidelines published by the American Heart Association and the European Society of Cardiology (W Wilson et al: Circulation 116:1736, 2007; and G Habib et al: Eur Heart J 30:2369, 2009).

periapical region of the teeth or perforation of the oral mucosa (including surgery on the respiratory tract). Prophylaxis is not advised for patients undergoing gastrointestinal or genitourinary tract procedures. High-risk patients should be treated before or when they undergo procedures on an infected genitourinary tract or infected skin. The National Institute for Health and Clinical Excellence in the United Kingdom has advised discontinuation of all antibiotic prophylaxis for endocarditis. Surveillance studies have attempted to assess the impact of these new prophylaxis guidelines but have been inconclusive because of inadequate data.

In patients with aortic or mitral valve regurgitation or a prosthetic valve, treatment of acute Q fever for 12 months with doxycycline plus hydroxychloroquine (see Table 123-4) is highly effective in preventing *C. burnetii* endocarditis.

FURTHER READING

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124 Infections of the Skin, Muscles, and Soft Tissues

Dennis L. Stevens

Skin and soft tissue infections occur in all races, all ethnic groups, and all geographic locations, although some have unique geographic niches. In modern times, the frequency and severity of some skin and soft tissue infections have increased for several reasons. First, microbes are rapidly disseminated throughout the world via efficient air travel, acquiring genes for virulence factors and antibiotic resistance. Second, natural disasters, such as earthquakes, tsunamis, tornadoes, and hurricanes, appear to be increasing in frequency, and the injuries sustained during these events commonly cause major skin and soft-tissue damage that predisposes to infection. Third, trauma and casualties resulting from combat and terrorist activities can markedly damage or destroy tissues and provide both endogenous and exogenous pathogens with ready access to deeper structures. Unfortunately, because the marvels of modern medicine may not be available during human-instigated and natural disasters, primary treatment may be delayed and the likelihood of severe infection and death increased.

ANATOMIC RELATIONSHIPS: CLUES TO THE DIAGNOSIS OF SOFT TISSUE INFECTIONS

Skin and soft tissue infections have been common human afflictions for centuries. However, between 2000 and 2004, hospital admissions for these infections rose by 27%, a remarkable increase that was attributable largely to the emergence of the USA300 clone of methicillin-resistant *Staphylococcus aureus* (MRSA). This chapter provides an anatomic approach to understanding the types of soft tissue infections and the diverse microbes responsible.

Protection against infection of the epidermis depends on the mechanical barrier afforded by the stratum corneum, since the epidermis itself is devoid of blood vessels **(Fig. 124-1)**. Disruption of this layer by burns or bites, abrasions, foreign bodies, primary dermatologic disorders (e.g., herpes simplex, varicella, ecthyma gangrenosum), surgery, or vascular or pressure ulcer allows penetration of bacteria to the deeper structures. Similarly, the hair follicle can serve as a portal either for components of the normal flora (e.g., *Staphylococcus*) or for extrinsic bacteria (e.g., *Pseudomonas* in hot-tub folliculitis). Intracellular infection of the squamous epithelium with vesicle formation may arise from cutaneous inoculation, as in infection with herpes simplex

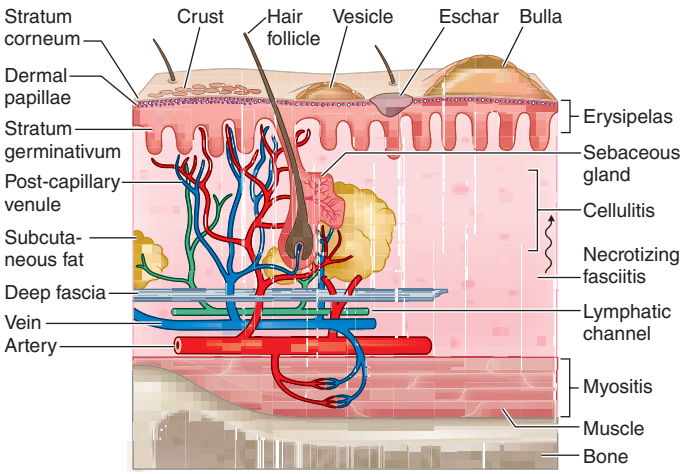

FIGURE 124-1 Structural components of the skin and soft tissues, superficial infections, and infections of the deeper structures. The rich capillary network beneath the dermal papillae plays a key role in the localization of infection and in the development of the acute inflammatory reaction.

virus (HSV) type 1; from the dermal capillary plexus, as in varicella and infections due to other viruses associated with viremia; or from cutaneous nerve roots, as in herpes zoster. Bacteria infecting the epidermis, such as *Streptococcus pyogenes*, may be translocated laterally to deeper structures via lymphatics, an event that results in the rapid superficial spread of erysipelas. Later, engorgement or obstruction of lymphatics causes flaccid edema of the epidermis, another characteristic of erysipelas.

The rich plexus of capillaries beneath the dermal papillae provides nutrition to the stratum germinativum, and physiologic responses of this plexus produce important clinical signs and symptoms. For example, infective vasculitis of the plexus results in petechiae, Osler's nodes, Janeway lesions, and palpable purpura, which, if present, are important clues to the existence of endocarditis **(Chap. 123)**. In addition, metastatic infection within this plexus can result in cutaneous manifestations of disseminated fungal infection **(Chap. 211)**, gonococcal infection **(Chap. 151)**, *Salmonella* infection **(Chap. 160)**, *Pseudomonas* infection (i.e., ecthyma gangrenosum; **Chap. 159**), meningococcemia **(Chap. 150)**, and staphylococcal infection **(Chap. 142)**. The plexus also provides bacteria with access to the circulation, thereby facilitating local spread or bacteremia. The postcapillary venules of this plexus are a prominent site of polymorphonuclear leukocyte sequestration, diapedesis, and chemotaxis to the site of cutaneous infection.

Amplification of these physiologic mechanisms by excessive levels of cytokines or bacterial toxins causes leukostasis, venous occlusion, and pitting edema. Edema with purple bullae, ecchymosis, and cutaneous anesthesia suggests loss of vascular integrity and necessitates exploration of the deeper structures for evidence of necrotizing fasciitis or myonecrosis. An early diagnosis requires a high level of suspicion in instances of unexplained fever and of pain and tenderness in the soft tissue, even in the absence of acute cutaneous inflammation.

Table 124-1 indicates the chapters in which the infections described below are discussed in greater detail. Many of these infections are illustrated in the chapters cited or in **Chap. A1**.

INFECTIONS ASSOCIATED WITH VESICLES

(Table 124-1) Vesicle formation due to infection is caused by viral proliferation within the epidermis. In varicella and variola, viremia precedes the onset of a diffuse centripetal rash that progresses from macules to vesicles, then to pustules, and finally to scabs over the course of 1–2 weeks. Vesicles of varicella have a "dewdrop" appearance and develop in crops randomly about the trunk, extremities, and face over 3–4 days. Herpes zoster occurs in a single dermatome; the appearance of vesicles is preceded by pain for several days. Zoster may occur in persons of any age but is most common among immunosuppressed individuals and elderly patients, whereas most cases of varicella occur in young children. Vesicles due to HSV are found on or around the lips (HSV-1) or genitals (HSV-2) but also may appear on the head and neck of young wrestlers (herpes gladiatorum) or on the digits of health care workers (herpetic whitlow). Recurrent herpes labialis (HSV-1) and herpes genitalis commonly follow primary infection. Coxsackievirus A16 characteristically causes vesicles on the hands, feet, and mouth of children. Orf is caused by a DNA virus related to smallpox virus and infects the fingers of individuals who work around goats and sheep. Molluscum contagiosum virus induces flaccid vesicles on the skin of healthy and immunocompromised individuals. Although variola (smallpox) in nature was eradicated as of 1977, postmillennial terrorist events have renewed interest in this devastating infection **(Chap. S2)**. Viremia beginning after an incubation period of 12 days is followed by a diffuse maculopapular rash, with rapid evolution to vesicles, pustules, and then scabs. Secondary cases can occur among close contacts.

Rickettsialpox begins after mite-bite inoculation of *Rickettsia akari* into the skin. A papule with a central vesicle evolves to form a 1- to 2.5-cm painless crusted black eschar with an erythematous halo and proximal adenopathy. While more common in the northeastern United States and Ukraine in 1940–1950, rickettsialpox has recently been described in Ohio, Arizona, and Utah. Blistering dactylitis is a painful, vesicular, localized *S. aureus* or group A streptococcal infection of the pulps of the distal digits of the hands.

INFECTIONS ASSOCIATED WITH BULLAE

(Table 124-1) Staphylococcal scalded-skin syndrome (SSSS) in neonates is caused by a toxin (exfoliatin) from phage group II *S. aureus*. SSSS must be distinguished from toxic epidermal necrolysis (TEN), which occurs primarily in adults, is drug-induced, and is associated with a higher mortality rate. Punch biopsy with frozen section is useful in making this distinction since the cleavage plane is the stratum corneum in SSSS and the stratum germinativum in TEN (Fig. 124-1). Intravenous γ-globulin is a promising treatment for TEN. Necrotizing fasciitis and gas gangrene also induce bulla formation (see "Necrotizing Fasciitis," below). Halophilic vibrio infection can be as aggressive and fulminant as necrotizing fasciitis; a helpful clue in its diagnosis is a history of exposure to waters of the Gulf of Mexico or the Atlantic seaboard or (in a patient with cirrhosis) the ingestion of raw seafood. The etiologic organism (*Vibrio vulnificus*) is highly susceptible to tetracycline.

INFECTIONS ASSOCIATED WITH CRUSTED LESIONS

(Table 124-1) Impetigo contagiosa is caused by *S. pyogenes*, and bullous impetigo is due to *S. aureus*. Both skin lesions may have an early bullous stage but then appear as thick crusts with a golden-brown color. Epidemics of impetigo caused by MRSA have been reported. Streptococcal lesions are most common among children 2–5 years of age, and epidemics may occur in settings of poor hygiene, particularly among children in lower socioeconomic settings in tropical climates. It is important to recognize impetigo contagiosa because of its relationship to poststreptococcal glomerulonephritis. Rheumatic fever is not a complication of skin infection caused by *S. pyogenes*. Superficial dermatophyte infection (ringworm) can occur on any skin surface, and skin scrapings with KOH staining are diagnostic. Primary infections with dimorphic fungi such as *Blastomyces dermatitidis* and *Sporothrix schenckii* can initially present as crusted skin lesions resembling ringworm. Disseminated infection with *Coccidioides immitis* can also involve the skin, and biopsy and culture should be performed on crusted lesions when the patient is from an endemic area. Crusted nodular lesions caused by *Mycobacterium chelonei* have been described in HIV-seropositive patients. Treatment with clarithromycin looks promising.

FOLLICULITIS

(Table 124-1) Hair follicles serve as portals for a number of bacteria, although *S. aureus* is the most common cause of localized folliculitis. Sebaceous glands empty into hair follicles and ducts and, if these portals are blocked, form sebaceous cysts that may resemble staphylococcal abscesses or may become secondarily infected. Inflammation of sweat glands (hidradenitis suppurativa) also can mimic infection of hair follicles, particularly in the axillae, but new treatments with potent anti-inflammatory agents hold promise. Chronic folliculitis is uncommon except in acne vulgaris, where constituents of the normal flora (e.g., *Propionibacterium acnes*) may play a role.

Diffuse folliculitis occurs in two settings. *Hot-tub folliculitis* is caused by *Pseudomonas aeruginosa* in waters that are insufficiently chlorinated and maintained at temperatures of 37–40°C. Infection is usually self-limited, although bacteremia and shock have been reported. *Swimmer's itch* occurs when a skin surface is exposed to water infested with freshwater avian schistosomes. Warm water temperatures and alkaline pH are suitable for mollusks that serve as intermediate hosts between birds and humans. Free-swimming schistosomal cercariae readily penetrate human hair follicles or pores but quickly die and elicit a brisk allergic reaction, causing intense itching and erythema.

PAPULAR AND NODULAR LESIONS

(Table 124-1) Raised lesions of the skin occur in many different forms. *Mycobacterium marinum* infections of the skin may present as cellulitis or as raised erythematous nodules. Similar lesions caused by *Mycobacterium abscessus* and *M. chelonei* have been described among patients undergoing cosmetic laser surgery and tattooing, respectively. Erythematous papules are early manifestations of cat-scratch disease (with lesions developing at the primary site of inoculation of *Bartonella henselae*) and

TABLE 124-1 Skin and Soft Tissue Infections

LESION, CLINICAL SYNDROME	INFECTIOUS AGENT(S)	SEE ALSO CHAP(S).
Vesicles		
Smallpox	Variola virus	S2
Chickenpox	Varicella-zoster virus	188
Shingles (herpes zoster)	Varicella-zoster virus	188
Cold sores, herpetic whitlow, herpes gladiatorum	Herpes simplex virus	187
Hand-foot-and-mouth disease	Coxsackievirus A16	199
Orf	Parapoxvirus	191
Molluscum contagiosum	Molluscum contagiosum poxvirus	191
Rickettsialpox	*Rickettsia akari*	182
Blistering distal dactylitis	*Staphylococcus aureus* or *Streptococcus pyogenes*	142, 143
Bullae		
Staphylococcal scalded-skin syndrome	*S. aureus*	142
Necrotizing fasciitis	*S. pyogenes*, *Clostridium* spp., mixed aerobes and anaerobes	143, 149, 172
Gas gangrene	*Clostridium* spp.	149
Halophilic vibrio	*Vibrio vulnificus*	163
Crusted lesions		
Bullous impetigo/ecthyma	*S. aureus*	142
Impetigo contagiosa	*S. pyogenes*	143
Ringworm	Superficial dermatophyte fungi	214
Sporotrichosis	*Sporothrix schenckii*	214
Histoplasmosis	*Histoplasma capsulatum*	207
Coccidioidomycosis	*Coccidioides immitis*	208
Blastomycosis	*Blastomyces dermatitidis*	209
Cutaneous leishmaniasis	*Leishmania* spp.	221
Cutaneous tuberculosis	*Mycobacterium tuberculosis*	173
Nocardiosis	*Nocardia asteroides*	169
Folliculitis		
Furunculosis	*S. aureus*	142
Hot-tub folliculitis	*Pseudomonas aeruginosa*	159
Swimmer's itch	*Schistosoma* spp.	229
Acne vulgaris	*Propionibacterium acnes*	53
Papular and nodular lesions		
Fish-tank or swimming-pool granuloma	*Mycobacterium marinum*	175
Creeping eruption (cutaneous larva migrans)	*Ancylostoma braziliense*	226
Dracunculiasis	*Dracunculus medinensis*	228
Cercarial dermatitis	*Schistosoma mansoni*	229
Verruca vulgaris	Human papillomaviruses 1, 2, 4	193
Condylomata acuminata (anogenital warts)	Human papillomaviruses 6, 11, 16, 18	193
Onchocerciasis nodule	*Onchocerca volvulus*	228
Cutaneous myiasis	*Dermatobia hominis*	452
Verruca peruana	*Bartonella bacilliformis*	167
Cat-scratch disease	*Bartonella henselae*	167
Lepromatous leprosy	*Mycobacterium leprae*	174
Secondary syphilis (papulosquamous and nodular lesions, condylomata lata)	*Treponema pallidum*	177
Tertiary syphilis (nodular gummatous lesions)	*T. pallidum*	177
Ulcers with or without eschars		
Anthrax	*Bacillus anthracis*	S2
Ulceroglandular tularemia	*Francisella tularensis*	165, S2
Bubonic plague	*Yersinia pestis*	166, S2
Buruli ulcer	*Mycobacterium ulcerans*	175
Leprosy	*M. leprae*	174
Cutaneous tuberculosis	*M. tuberculosis*	173
Chancroid	*Haemophilus ducreyi*	152
Primary syphilis	*T. pallidum*	177
Erysipelas	*S. pyogenes*	143
Cellulitis	*Staphylococcus* spp., *Streptococcus* spp., various other bacteria	Various
Necrotizing fasciitis		
Streptococcal gangrene	*S. pyogenes*	143
Fournier's gangrene	Mixed aerobic and anaerobic bacteria	172
Staphylococcal necrotizing fasciitis	Methicillin-resistant *S. aureus*	142
Myositis and myonecrosis		
Pyomyositis	*S. aureus*	142
Streptococcal necrotizing myositis	*S. pyogenes*	143
Gas gangrene	*Clostridium* spp.	149
Nonclostridial (crepitant) myositis	Mixed aerobic and anaerobic bacteria	172
Synergistic nonclostridial anaerobic myonecrosis	Mixed aerobic and anaerobic bacteria	172

bacillary angiomatosis (also caused by *B. henselae*). Raised serpiginous or linear eruptions are characteristic of cutaneous larva migrans, which is caused by burrowing larvae of dog or cat hookworms (*Ancylostoma braziliense*) and which humans acquire through contact with soil that has been contaminated with dog or cat feces. Similar burrowing raised lesions are present in dracunculiasis caused by migration of the adult female nematode *Dracunculus medinensis*. Nodules caused by *Onchocerca volvulus* measure 1–10 cm in diameter and occur mostly in persons bitten by *Simulium* flies in Africa. The nodules contain the adult worm encased in fibrous tissue. Migration of microfilariae into the eyes may result in blindness. Verruga peruana is caused by *Bartonella bacilliformis*, which is transmitted to humans by the sandfly *Phlebotomus*. This condition can take the form of single gigantic lesions (several centimeters in diameter) or multiple small lesions (several millimeters in diameter). Numerous subcutaneous nodules may also be present in cysticercosis caused by larvae of *Taenia solium*. Multiple erythematous papules develop in schistosomiasis; each represents a cercarial invasion site. Skin nodules as well as thickened subcutaneous tissue are prominent features of lepromatous leprosy. Large nodules or gummas are features of tertiary syphilis, whereas flat papulosquamous lesions are characteristic of secondary syphilis. Human papillomavirus may cause singular warts (verruca vulgaris) or multiple warts in the anogenital area (condylomata acuminata). The latter are major problems in HIV-infected individuals.

ULCERS WITH OR WITHOUT ESCHARS

(Table 124-1) Cutaneous anthrax begins as a pruritic papule, which develops within days into an ulcer with surrounding vesicles and edema and then into an enlarging ulcer with a black eschar. Cutaneous anthrax may cause chronic nonhealing ulcers with an overlying dirty-gray membrane, although lesions may also mimic psoriasis, eczema, or impetigo. Ulceroglandular tularemia may have associated ulcerated skin lesions with painful regional adenopathy. Although buboes are the major cutaneous manifestation of plague, ulcers with eschars, papules, or pustules are also present in 25% of cases.

Mycobacterium ulcerans typically causes chronic skin ulcers on the extremities of individuals living in the tropics. *Mycobacterium leprae* may be associated with cutaneous ulcerations in patients with lepromatous leprosy related to Lucio's phenomenon, in which immune-mediated destruction of tissue bearing high concentrations of *M. leprae* bacilli occurs, usually several months after initiation of effective therapy. *Mycobacterium tuberculosis* also may cause ulcerations, papules, or erythematous macular lesions of the skin in both immunocompetent and immunocompromised patients.

Decubitus ulcers are due to tissue hypoxemia secondary to pressure-induced vascular insufficiency and may become secondarily infected with components of the skin and gastrointestinal flora, including anaerobes. Ulcerative lesions on the anterior shins may be due to pyoderma gangrenosum, which must be distinguished from similar lesions of infectious etiology by histologic evaluation of biopsy sites. Ulcerated lesions on the genitals may be either painful (chancroid) or painless (primary syphilis).

ERYSIPELAS

(Table 124-1) Erysipelas is due to *S. pyogenes* and is characterized by an abrupt onset of fiery-red swelling of the face or extremities. The distinctive features of erysipelas are well-defined indurated margins, particularly along the nasolabial fold; rapid progression; and intense pain. Flaccid bullae may develop during the second or third day of illness, but extension to deeper soft tissues is rare. Treatment with penicillin is effective; swelling may progress despite appropriate treatment, although fever, pain, and the intense red color diminish. Desquamation of the involved skin occurs 5–10 days into the illness. Infants and elderly adults are most commonly afflicted, and the severity of systemic toxicity varies.

CELLULITIS

(Table 124-1) Cellulitis is an acute inflammatory condition of the skin that is characterized by localized pain, erythema, swelling, and heat. It may be caused by indigenous flora colonizing the skin and appendages (e.g., *S. aureus* and *S. pyogenes*) or by a wide variety of exogenous bacteria. Because the exogenous bacteria involved in cellulitis occupy unique niches in nature, a thorough history (including epidemiologic data) offers important clues to etiology. When there is drainage, an open wound, or an obvious portal of entry, Gram's stain and culture provide a definitive diagnosis. In the absence of these findings, the bacterial etiology of cellulitis is difficult to establish, and in some cases staphylococcal and streptococcal cellulitis may have similar features. Even with needle aspiration of the leading edge or a punch biopsy of the cellulitis tissue itself, cultures are positive in only 20% of cases. This observation suggests that relatively low numbers of bacteria may cause cellulitis and that the expanding area of erythema within the skin may be a direct effect of extracellular toxins or of the soluble mediators of inflammation elicited by the host.

Bacteria may gain access to the epidermis through cracks in the skin, abrasions, cuts, burns, insect bites, surgical incisions, and IV catheters. Cellulitis caused by *S. aureus* spreads from a central localized infection, such as an abscess, folliculitis, or an infected foreign body (e.g., a splinter, a prosthetic device, or an IV catheter). MRSA is rapidly replacing methicillin-sensitive *S. aureus* (MSSA) as a cause of cellulitis in both inpatient and outpatient settings. Cellulitis caused by MSSA or MRSA is usually associated with a focal infection, such as a furuncle, a carbuncle, a surgical wound, or an abscess; the U.S. Food and Drug Administration preferentially refers to these types of infection as *purulent cellulitis*. In contrast, cellulitis due to *S. pyogenes* is a more rapidly spreading, diffuse process that is frequently associated with lymphangitis and fever and should be referred to as *nonpurulent cellulitis*. Recurrent streptococcal cellulitis of the lower extremities may be caused by organisms of group A, C, or G in association with chronic venous stasis or with saphenous venectomy for coronary artery bypass surgery. Streptococci also cause recurrent cellulitis among patients with chronic lymphedema resulting from elephantiasis, lymph node dissection, or Milroy disease. Recurrent staphylococcal cutaneous infections are more common among individuals who have eosinophilia and elevated serum levels of IgE (Job syndrome) and among nasal carriers of staphylococci. Cellulitis caused by *Streptococcus agalactiae* (group B *Streptococcus*) occurs primarily in elderly patients and those with diabetes mellitus or peripheral vascular disease. *Haemophilus influenzae* typically causes periorbital cellulitis in children in association with sinusitis, otitis media, or epiglottitis. It is unclear whether this form of cellulitis will (like meningitis) become less common as a result of the impressive efficacy of the *H. influenzae* type b vaccine.

Many other bacteria also cause cellulitis. It is fortunate that these organisms occur in such characteristic settings that a good history provides useful clues to the diagnosis. Cellulitis associated with cat bites and, to a lesser degree, with dog bites is commonly caused by *Pasteurella multocida*, although in the latter case *Staphylococcus intermedius* and *Capnocytophaga canimorsus* also must be considered. Sites of cellulitis and abscesses associated with dog bites and human bites also contain a variety of anaerobic organisms, including *Fusobacterium*, *Bacteroides*, aerobic and anaerobic streptococci, and *Eikenella corrodens*. *Pasteurella* is notoriously resistant to dicloxacillin and nafcillin but is sensitive to all other β-lactam antimicrobial agents as well as to quinolones, tetracycline, and erythromycin. Amoxicillin-clavulanate, ampicillin-sulbactam, and cefoxitin are good choices for the treatment of animal or human bite infections. *Aeromonas hydrophila* causes aggressive cellulitis and occasionally necrotizing fasciitis in tissues surrounding lacerations sustained in freshwater (lakes, rivers, and streams). This organism remains sensitive to aminoglycosides, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole, and third-generation cephalosporins; it is resistant to ampicillin, however. *P. aeruginosa* causes three types of soft tissue infection: ecthyma gangrenosum in neutropenic patients, hot-tub folliculitis, and cellulitis following penetrating injury. Most commonly, *P. aeruginosa* is introduced into the deep tissues when a person steps on a nail. Treatment includes surgical inspection and drainage, particularly if the injury also involves bone or joint capsule. Choices for empirical treatment while antimicrobial susceptibility data are awaited include an aminoglycoside, a third-generation cephalosporin (ceftazidime, cefoperazone, or cefotaxime), a semisynthetic

penicillin (ticarcillin, mezlocillin, or piperacillin), or a fluoroquinolone (although drugs of the last class are not indicated for the treatment of children <13 years old).

Gram-negative bacillary cellulitis, including that due to *P. aeruginosa*, is most common among hospitalized, immunocompromised hosts. Cultures and sensitivity tests are critically important in this setting because of multidrug resistance **(Chap. 159)**.

The gram-positive aerobic rod *Erysipelothrix rhusiopathiae* is most often associated with fish and domestic swine and causes cellulitis primarily in bone renderers and fishmongers. *E. rhusiopathiae* remains susceptible to most β-lactam antibiotics (including penicillin), erythromycin, clindamycin, tetracycline, and cephalosporins but is resistant to sulfonamides, chloramphenicol, and vancomycin. Its resistance to vancomycin, which is unusual among gram-positive bacteria, is of potential clinical significance since this agent is sometimes used in empirical therapy for skin infection. Fish food containing the water flea *Daphnia* is sometimes contaminated with *M. marinum*, which can cause cellulitis or granulomas on skin surfaces exposed to the water in aquariums or injured in swimming pools. Rifampin plus ethambutol has been an effective therapeutic combination in some cases, although no comprehensive studies have been undertaken. In addition, some strains of *M. marinum* are susceptible to tetracycline or to trimethoprim-sulfamethoxazole.

NECROTIZING FASCIITIS

(Table 124-1) Necrotizing fasciitis, formerly called streptococcal gangrene, may be associated with group A *Streptococcus* or mixed aerobic–anaerobic bacteria or may occur as a component of gas gangrene caused by *Clostridium perfringens*. Strains of MRSA that produce the Panton-Valentine leukocidin (PVL) toxin have been reported to cause necrotizing fasciitis. Early diagnosis may be difficult when pain or unexplained fever is the only presenting manifestation. Swelling then develops and is followed by brawny edema and tenderness. With progression, dark-red induration of the epidermis appears, along with bullae filled with blue or purple fluid. Later the skin becomes friable and takes on a bluish, maroon, or black color. By this stage, thrombosis of blood vessels in the dermal papillae (Fig. 124-1) is extensive. Extension of infection to the level of the deep fascia causes this tissue to take on a brownish-gray appearance. Rapid spread occurs along fascial planes, through venous channels and lymphatics. Patients in the later stages are toxic and frequently manifest shock and multiorgan failure.

Necrotizing fasciitis caused by mixed aerobic–anaerobic bacteria begins with a breach in the integrity of a mucous membrane barrier, such as the mucosa of the gastrointestinal or genitourinary tract. The portal can be a malignancy, a diverticulum, a hemorrhoid, an anal fissure, or a urethral tear. Other predisposing factors include peripheral vascular disease, diabetes mellitus, surgery, and penetrating injury to the abdomen. Leakage into the perineal area results in a syndrome called *Fournier's gangrene*, characterized by massive swelling of the scrotum and penis with extension into the perineum or the abdominal wall and the legs.

Necrotizing fasciitis caused by *S. pyogenes* has increased in frequency and severity since 1985. There are two distinct clinical presentations: those with no portal of entry and those with a defined portal of entry. Infections in the first category often begin deep at the site of a nonpenetrating minor trauma, such as a bruise or a muscle strain. Seeding of the site via transient bacteremia is likely, although most patients deny antecedent streptococcal infection. The affected patients present with only severe pain and fever. Late in the course, the classic signs of necrotizing fasciitis, such as purple (violaceous) bullae, skin sloughing, and progressive toxicity, develop. In infections of the second type, *S. pyogenes* may reach the deep fascia from a site of cutaneous infection or penetrating trauma. These patients have early signs of superficial skin infection with progression to necrotizing fasciitis. In either case, toxicity is severe, and renal impairment may precede the development of shock. In 20–40% of cases, myositis occurs concomitantly, and, as in gas gangrene (see below), serum creatine phosphokinase levels may be markedly elevated. Necrotizing fasciitis due to mixed aerobic–anaerobic bacteria may be associated with gas in deep tissue, but gas usually is not present when the cause is *S. pyogenes* or MRSA. Prompt surgical exploration down to the deep fascia and muscle is essential. Necrotic tissue must be surgically removed, and Gram's staining and culture of excised tissue are useful in establishing whether group A streptococci, mixed aerobic–anaerobic bacteria, MRSA, or *Clostridium* species are present (see "Treatment," below).

MYOSITIS AND MYONECROSIS

(Table 124-1) Muscle involvement can occur with viral infection (e.g., influenza, dengue, or coxsackievirus B infection) or parasitic invasion (e.g., trichinellosis, cysticercosis, or toxoplasmosis). Although myalgia develops in most of these infections, severe muscle pain is the hallmark of pleurodynia (coxsackievirus B), trichinellosis, and bacterial infection. Acute rhabdomyolysis predictably occurs with clostridial and streptococcal myositis but may also be associated with influenza virus, echovirus, coxsackievirus, Epstein-Barr virus, and *Legionella* infections.

Pyomyositis is usually due to *S. aureus*, is common in tropical areas, and generally has no known portal of entry. Cases of pyomyositis caused by MRSA producing the PVL toxin have been described among children in the United States. Muscle infection begins at the exact site of blunt trauma or muscle strain. Infection remains localized, and shock does not develop unless organisms produce toxic shock syndrome toxin 1 or certain enterotoxins and the patient lacks antibodies to the toxin produced by the infecting organisms. In contrast, *S. pyogenes* may induce primary myositis (referred to as *streptococcal necrotizing myositis*) in association with severe systemic toxicity. Myonecrosis occurs concomitantly with necrotizing fasciitis in ~50% of cases. Both are part of the streptococcal toxic shock syndrome.

Gas gangrene usually follows severe penetrating injuries that result in interruption of the blood supply and introduction of soil into wounds. Such cases of traumatic gangrene are usually caused by the clostridial species *C. perfringens*, *C. septicum*, and *C. histolyticum*. Rarely, latent or recurrent gangrene can occur years after penetrating trauma; dormant spores that reside at the site of previous injury are most likely responsible. Spontaneous nontraumatic gangrene among patients with neutropenia, gastrointestinal malignancy, diverticulosis, or recent radiation therapy to the abdomen is caused by several clostridial species, of which *C. septicum* is the most commonly involved. The tolerance of this anaerobe to oxygen probably explains why it can initiate infection spontaneously in normal tissue anywhere in the body.

Gas gangrene of the uterus, especially that due to *Clostridium sordellii,* historically occurred as a consequence of illegal or self-induced abortion and nowadays also follows spontaneous abortion, vaginal delivery, and cesarean section. *C. sordellii* has also been implicated in medically induced abortion. Postpartum *C. sordellii* infections in young, previously healthy women present as a unique clinical picture: little or no fever, lack of a purulent discharge, refractory hypotension, extensive peripheral edema and effusions, hemoconcentration, and a markedly elevated white blood cell count. The infection is almost uniformly fatal, with death ensuing rapidly. *C. sordellii* and *C. novyi* have also been associated with cutaneous injection of black tar heroin; mortality rates are lower among the affected individuals, probably because their aggressive injection-site infections are readily apparent and diagnosis is therefore prompt.

Synergistic nonclostridial anaerobic myonecrosis, also known as necrotizing cutaneous myositis and synergistic necrotizing cellulitis, is a variant of necrotizing fasciitis caused by mixed aerobic and anaerobic bacteria with the exclusion of clostridial organisms (see "Necrotizing Fasciitis," above).

DIAGNOSIS

This chapter emphasizes the physical appearance and location of lesions within the soft tissues as important diagnostic clues. Other crucial considerations in narrowing the differential diagnosis are the temporal progression of the lesions as well as the patient's travel history, animal exposure or bite history, age, underlying disease status, and lifestyle. However, even the astute clinician may find it challenging to diagnose all infections of the soft tissues by history and inspection alone.

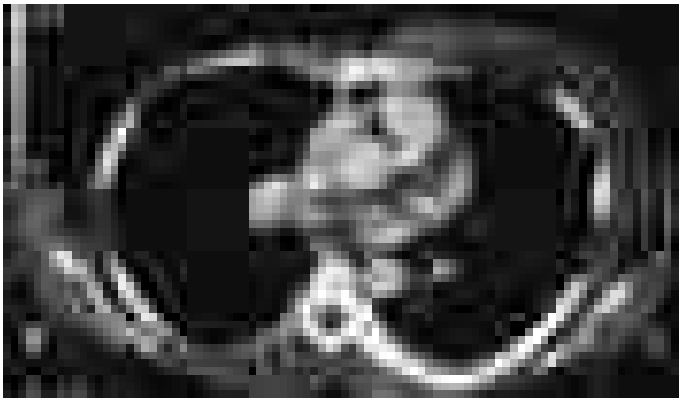

FIGURE 124-2 CT showing edema and inflammation of the left chest wall in a patient with necrotizing fasciitis and myonecrosis caused by group A *Streptococcus*.

Soft tissue radiography, CT (Fig. 124-2), and MRI may be useful in determining the depth of infection and should be performed when the patient has rapidly progressing lesions or evidence of a systemic inflammatory response syndrome. These tests are particularly valuable for defining a localized abscess or detecting gas in tissue. Unfortunately, they may reveal only soft tissue swelling and thus are not specific for fulminant infections such as necrotizing fasciitis or myonecrosis caused by group A *Streptococcus* (Fig. 124-2), where gas is not found in lesions.

Aspiration of the leading edge or punch biopsy with frozen section may be helpful if the results of imaging tests are positive, but false-negative results occur in ~80% of cases. There is some evidence that aspiration alone may be superior to injection and aspiration with normal saline. Frozen sections are especially useful in distinguishing SSSS from TEN and are quite valuable in cases of necrotizing fasciitis. Open surgical inspection, with debridement as indicated, is clearly the best way to determine the extent and severity of infection and to obtain material for Gram's staining and culture. Such an aggressive approach is important and may be lifesaving if undertaken early in the course of fulminant infections where there is evidence of systemic toxicity.

TREATMENT

Infections of the Skin, Muscles, and Soft Tissues

A full description of the treatment of all the clinical entities described herein is beyond the scope of this chapter. As a guide to the clinician in selecting appropriate treatment, the antimicrobial agents useful in the most common and the most fulminant cutaneous infections are listed in Table 124-2.

Furuncles, carbuncles, and abscesses caused by MRSA and MSSA are common, and their treatment depends upon the size of the lesion. Furuncles <2.5 cm in diameter are usually treated with moist heat. Those that are larger (4.5 cm of erythema and induration) require surgical drainage, and the occurrence of these larger lesions in association with fever, chills, or leukocytosis requires both drainage and antibiotic treatment. Previous studies in children demonstrated that surgical drainage of abscesses (mean diameter, 3.8 cm) was as effective when used alone as when combined with trimethoprim-sulfamethoxazole treatment. However, the rate of recurrence of new lesions was lower in the group undergoing both drainage and antibiotic treatment. Recent studies in adults with predominantly MRSA localized abscesses suggested that a 7- to 10-day course of treatment with trimethoprim-sulfamethoxazole was associated with higher cure rates and fewer recurrences. In children, a 3-day course was not as effective as a 7-day course.

Early and aggressive surgical exploration is essential in cases of suspected necrotizing fasciitis, myositis, or gangrene in order to (1) visualize the deep structures, (2) remove necrotic tissue, (3) reduce compartment pressure, and (4) obtain suitable material for Gram's staining and for aerobic and anaerobic cultures. Appropriate empirical antibiotic treatment for mixed aerobic–anaerobic infections could consist of ampicillin-sulbactam, cefoxitin, or the following

TABLE 124-2 Treatment of Common Infections of the Skin

DIAGNOSIS/CONDITION	PRIMARY TREATMENT	ALTERNATIVE TREATMENT	SEE ALSO CHAP(S).
Animal bite (prophylaxis or early infection)[a]	Amoxicillin–clavulanate (875/125 mg PO bid)	Doxycycline (100 mg PO bid)	136
Animal bite[a] (established infection)	Ampicillin–sulbactam (1.5–3 g IV q6h)	Clindamycin (600–900 mg IV q8h) ***plus*** Ciprofloxacin (400 mg IV q12h) *or* cefoxitin (2 g IV q6h)	136
Bacillary angiomatosis	Erythromycin (500 mg PO qid)	Doxycycline (100 mg PO bid)	167
Herpes simplex (primary genital)	Acyclovir (400 mg PO tid for 10 days)	Famciclovir (250 mg PO tid for 5–10 days) *or* valacyclovir (1000 mg PO bid for 10 days)	187
Herpes zoster (immunocompetent host >50 years of age)	Acyclovir (800 mg PO 5 times daily for 7–10 days)	Famciclovir (500 mg PO tid for 7–10 days) *or* valacyclovir (1000 mg PO tid for 7 days)	188
Cellulitis (staphylococcal or streptococcal[b,c])	Nafcillin or oxacillin (2 g IV q4–6h)	Cefazolin (1–2 g q8h) *or* ampicillin/sulbactam (1.5–3 g IV q6h) *or* erythromycin (0.5–1 g IV q6h) *or* clindamycin (600–900 mg IV q8h)	142, 143
MRSA skin infection[d]	Vancomycin (1 g IV q12h)	Linezolid (600 mg IV q12h)	142
Necrotizing fasciitis (group A streptococcal[b])	Clindamycin (600–900 mg IV q6–8h) *plus* penicillin G (4 million units IV q4h)	Clindamycin (600–900 mg IV q6–8h) *plus* a cephalosporin (first- or second-generation)	143
Necrotizing fasciitis (mixed aerobes and anaerobes)	Ampicillin (2 g IV q4h) *plus* clindamycin (600–900 mg IV q6–8h) *plus* ciprofloxacin (400 mg IV q6–8h)	Vancomycin (1 g IV q6h) *plus* metronidazole (500 mg IV q6h) *plus* ciprofloxacin (400 mg IV q6–8h)	117, 172
Gas gangrene	Clindamycin (600–900 mg IV q6–8h) *plus* penicillin G (4 million units IV q4–6h)	Clindamycin (600–900 mg IV q6–8h) *plus* cefoxitin (2 g IV q6h)	149

[a]*Pasteurella multocida*, a species commonly associated with both dog and cat bites, is resistant to cephalexin, dicloxacillin, clindamycin, and erythromycin. *Eikenella corrodens*, a bacterium commonly associated with human bites, is resistant to clindamycin, penicillinase-resistant penicillins, and metronidazole but is sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones. [b]The frequency of erythromycin resistance in group A *Streptococcus* is currently ~5% in the United States but has reached 70–100% in some other countries. Most, but not all, erythromycin-resistant group A streptococci are susceptible to clindamycin. Approximately 90% of *Staphylococcus aureus* strains are sensitive to clindamycin, but resistance—both intrinsic and inducible—is increasing. [c]Severe hospital-acquired *S. aureus* infections or community-acquired *S. aureus* infections that are not responding to the β-lactam antibiotics recommended in this table may be caused by methicillin-resistant strains, requiring a switch to vancomycin, daptomycin, or linezolid. [d]Some strains of methicillin-resistant *S. aureus* (MRSA) remain sensitive to tetracycline and trimethoprim-sulfamethoxazole. Daptomycin (4 mg/kg IV q24h) or tigecycline (100-mg loading dose followed by 50 mg IV q12h) is an alternative treatment for MRSA.

combination: (1) clindamycin (600–900 mg IV every 8 h) or metronidazole (500 mg every 6 h) plus (2) ampicillin or ampicillin-sulbactam (1.5–3 g IV every 6 h) plus (3) gentamicin (1–1.5 mg/kg every 8 h). Group A streptococcal and clostridial infection of the fascia and/or muscle carries a mortality rate of 20–50% with penicillin treatment. In experimental models of streptococcal and clostridial necrotizing fasciitis/myositis, clindamycin has exhibited markedly superior efficacy, but no comparative clinical trials have been performed. A retrospective study of children with invasive group A streptococcal infection demonstrated higher survival rates with clindamycin treatment than with β-lactam antibiotic therapy. Hyperbaric oxygen treatment also may be useful in gas gangrene due to clostridial species. Antibiotic treatment should be continued until all signs of systemic toxicity have resolved, all devitalized tissue has been removed, and granulation tissue has developed **(Chaps. 143, 149, and 172)**.

In summary, infections of the skin and soft tissues are diverse in presentation and severity and offer a great challenge to the clinician. This chapter provides an approach to diagnosis and understanding of the pathophysiologic mechanisms involved in these infections. More in-depth information is found in chapters on specific infections.

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125 Infectious Arthritis

Lawrence C. Madoff

Although *Staphylococcus aureus*, *Neisseria gonorrhoeae*, and other bacteria are the most common causes of infectious arthritis, various mycobacteria, spirochetes, fungi, and viruses also infect joints **(Table 125-1)**. Since acute bacterial infection can destroy articular cartilage rapidly, all inflamed joints must be evaluated without delay to exclude noninfectious processes and determine appropriate antimicrobial therapy and drainage procedures. For more detailed information on infectious arthritis caused by specific organisms, the reader is referred to the chapters on those organisms.

Acute bacterial infection typically involves a single joint or a few joints. Subacute or chronic monarthritis or oligoarthritis suggests mycobacterial or fungal infection; episodic inflammation is seen in syphilis, Lyme disease, and the reactive arthritis that follows enteric infections and chlamydial urethritis. Acute polyarticular inflammation occurs as an immunologic reaction during the course of endocarditis, rheumatic fever, disseminated neisserial infection, and acute hepatitis B. Bacteria and viruses occasionally infect multiple joints, the former most commonly in persons with rheumatoid arthritis.

TABLE 125-1 Differential Diagnosis of Arthritis Syndromes

ACUTE MONARTICULAR ARTHRITIS	CHRONIC MONARTICULAR ARTHRITIS	POLYARTICULAR ARTHRITIS
Staphylococcus aureus	*Mycobacterium tuberculosis*	*Neisseria meningitidis*
Streptococcus pneumoniae	Nontuberculous mycobacteria	*N. gonorrhoeae*
β-Hemolytic streptococci	*Borrelia burgdorferi*	Nongonococcal bacterial arthritis
Gram-negative bacilli	*Treponema pallidum*	Bacterial endocarditis
Neisseria gonorrhoeae	*Candida* spp.	*Candida* spp.
Candida spp.	*Sporothrix schenckii*	Poncet's disease (tuberculous rheumatism)
Crystal-induced arthritis	*Coccidioides immitis*	Hepatitis B virus
Fracture	*Blastomyces dermatitidis*	Parvovirus B19
Hemarthrosis	*Aspergillus* spp.	HIV
Foreign body	*Cryptococcus neoformans*	Human T-lymphotropic virus type 1
Osteoarthritis	*Nocardia* spp.	Rubella virus
Ischemic necrosis	*Brucella* spp.	Arthropod-borne viruses
Monarticular rheumatoid arthritis	Legg-Calvé-Perthes disease	Sickle cell disease flare
	Osteoarthritis	Reactive arthritis
		Serum sickness
		Acute rheumatic fever
		Inflammatory bowel disease
		Systemic lupus erythematosus
		Rheumatoid arthritis/ Still's disease
		Other vasculitides
		Sarcoidosis

APPROACH TO THE PATIENT

Infectious Arthritis

Aspiration of synovial fluid—an essential element in the evaluation of potentially infected joints—can be performed without difficulty in most cases by the insertion of a large-bore needle into the site of maximal fluctuance or tenderness or by the route of easiest access. Ultrasonography or fluoroscopy may be used to guide aspiration of difficult-to-localize effusions of the hip and, occasionally, the shoulder and other joints. Normal synovial fluid contains <180 cells (predominantly mononuclear cells) per microliter. Synovial cell counts averaging 100,000/μL (range, 25,000–250,000/μL), with >90% neutrophils, are characteristic of acute bacterial infections. Crystal-induced, rheumatoid, and other noninfectious inflammatory arthritides usually are associated with <30,000–50,000 cells/μL; cell counts of 10,000–30,000/μL, with 50–70% neutrophils and the remainder lymphocytes, are common in mycobacterial and fungal infections. Definitive diagnosis of an infectious process relies on identification of the pathogen in stained smears of synovial fluid, isolation of the pathogen from cultures of synovial fluid and blood, or detection of microbial nucleic acids and proteins by nucleic acid amplification (NAA)–based assays and immunologic techniques.

ACUTE BACTERIAL ARTHRITIS

PATHOGENESIS

Bacteria enter the joint from the bloodstream; from a contiguous site of infection in bone or soft tissue; or by direct inoculation during surgery, injection, animal or human bite, or trauma. In hematogenous infection, bacteria escape from synovial capillaries, which have no limiting basement membrane, and within hours provoke neutrophilic infiltration of the synovium. Neutrophils and bacteria enter the joint space; later,

bacteria adhere to articular cartilage. Degradation of cartilage begins within 48 h as a result of increased intraarticular pressure, release of proteases and cytokines from chondrocytes and synovial macrophages, and invasion of the cartilage by bacteria and inflammatory cells. Histologic studies reveal bacteria lining the synovium and cartilage as well as abscesses extending into the synovium, cartilage, and—in severe cases—subchondral bone. Synovial proliferation results in the formation of a pannus over the cartilage, and thrombosis of inflamed synovial vessels develops. Bacterial factors that appear important in the pathogenesis of infective arthritis include various surface-associated adhesins in *S. aureus* that permit adherence to cartilage and endotoxins that promote chondrocyte-mediated breakdown of cartilage.

MICROBIOLOGY

The hematogenous route of infection is the most common route in all age groups, and nearly every bacterial pathogen is capable of causing septic arthritis. In infants, group B streptococci, gram-negative enteric bacilli, and *S. aureus* are the most common pathogens. Since the advent of the *Haemophilus influenzae* vaccine, the predominant causes among children <5 years of age have been *S. aureus*, *Streptococcus pyogenes* (group A *Streptococcus*), and (in some centers) *Kingella kingae*. Among young adults and adolescents, *N. gonorrhoeae* is the most commonly implicated organism. *S. aureus* accounts for most nongonococcal isolates in adults of all ages; gram-negative bacilli, pneumococci, and β-hemolytic streptococci—particularly groups A and B but also groups C, G, and F—are involved in up to one-third of cases in older adults, especially those with underlying comorbid illnesses.

Infections after surgical procedures or penetrating injuries are due most often to *S. aureus* and occasionally to other gram-positive bacteria or gram-negative bacilli. Infections with coagulase-negative staphylococci are unusual except after the implantation of prosthetic joints or arthroscopy. Anaerobic organisms, often in association with aerobic or facultative bacteria, are found after human bites and when decubitus ulcers or intraabdominal abscesses spread into adjacent joints. Polymicrobial infections complicate traumatic injuries with extensive contamination. Bites and scratches from cats and other animals may introduce *Pasteurella multocida* or *Bartonella henselae* into joints either directly or hematogenously, and bites from humans may introduce *Eikenella corrodens* or other components of the oral flora. Penetration of a sharp object through a shoe is associated with *Pseudomonas aeruginosa* arthritis in the foot.

NONGONOCOCCAL BACTERIAL ARTHRITIS

Epidemiology Although hematogenous infections with virulent organisms such as *S. aureus*, *H. influenzae*, and pyogenic streptococci occur in healthy persons, there is an underlying host predisposition in many cases of septic arthritis. Patients with rheumatoid arthritis have the highest incidence of infective arthritis (most often secondary to *S. aureus*) because of chronically inflamed joints; glucocorticoid therapy; and frequent breakdown of rheumatoid nodules, vasculitic ulcers, and skin overlying deformed joints. Diabetes mellitus, glucocorticoid therapy, hemodialysis, and malignancy all carry an increased risk of infection with *S. aureus* and gram-negative bacilli. Tumor necrosis factor inhibitors (e.g., etanercept, infliximab), which increasingly are used for the treatment of rheumatoid arthritis, predispose to mycobacterial infections and possibly to other pyogenic bacterial infections and could be associated with septic arthritis in this population. Pneumococcal infections complicate alcoholism, deficiencies of humoral immunity, and hemoglobinopathies. Pneumococci, *Salmonella* species, and *H. influenzae* cause septic arthritis in persons infected with HIV. Persons with primary immunoglobulin deficiency are at risk for mycoplasmal arthritis, which results in permanent joint damage if tetracycline and replacement therapy with IV immunoglobulin are not administered promptly. IV drug users acquire staphylococcal and streptococcal infections from their own flora and acquire pseudomonal and other gram-negative infections from drugs and injection paraphernalia.

Clinical Manifestations Some 90% of patients present with involvement of a single joint—most commonly the knee; less frequently the hip; and still less often the shoulder, wrist, or elbow. Small joints of the hands and feet are more likely to be affected after direct inoculation or a bite. Among IV drug users, infections of the spine, sacroiliac joints, and sternoclavicular joints **(Fig. 125-1)** are more common than infections of the appendicular skeleton. Polyarticular infection is most common among patients with rheumatoid arthritis and may resemble a flare of the underlying disease.

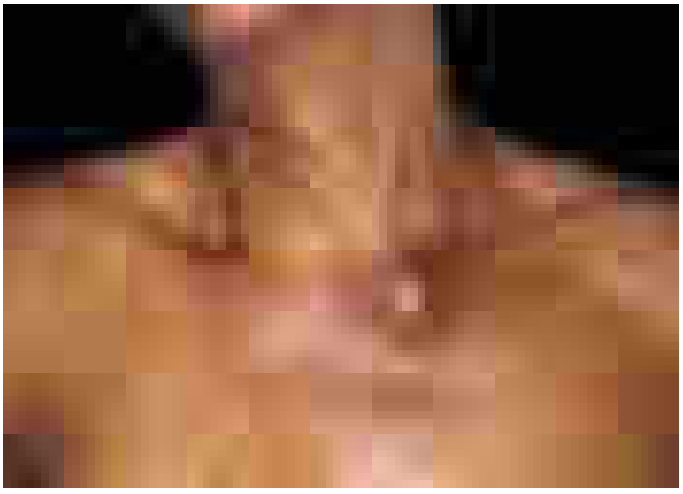

FIGURE 125-1 Acute septic arthritis of the sternoclavicular joint. A man in his forties with a history of cirrhosis presented with a new onset of fever and lower neck pain. He had no history of IV drug use or previous catheter placement. Jaundice and a painful swollen area over his left sternoclavicular joint were evident on physical examination. Cultures of blood drawn at admission grew group B *Streptococcus*. The patient recovered after treatment with IV penicillin. *(Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.)*

The usual presentation consists of moderate to severe pain that is uniform around the joint, effusion, muscle spasm, and decreased range of motion. Fever in the range of 38.3–38.9°C (101–102°F) and sometimes higher is common but may not be present, especially in persons with rheumatoid arthritis, renal or hepatic insufficiency, or conditions requiring immunosuppressive therapy. The inflamed, swollen joint is usually evident on examination except in the case of a deeply situated joint such as the hip, shoulder, or sacroiliac joint. Cellulitis, bursitis, and acute osteomyelitis, which may produce a similar clinical picture, should be distinguished from septic arthritis by their greater range of motion and less-than-circumferential swelling. A focus of extraarticular infection, such as a boil or pneumonia, should be sought. Peripheral-blood leukocytosis with a left shift and elevation of the erythrocyte sedimentation rate or C-reactive protein level are common.

Plain radiographs show evidence of soft-tissue swelling, joint-space widening, and displacement of tissue planes by the distended capsule. Narrowing of the joint space and bony erosions indicate advanced infection and a poor prognosis. Ultrasound is useful for detecting effusions in the hip, and CT or MRI can demonstrate infections of the sacroiliac joint, the sternoclavicular joint, and the spine very well.

Laboratory Findings Specimens of peripheral blood and synovial fluid should be obtained before antibiotics are administered. Blood cultures are positive in up to 50–70% of *S. aureus* infections but are less frequently positive in infections due to other organisms. The synovial fluid is turbid, serosanguineous, or frankly purulent. Gram-stained smears confirm the presence of large numbers of neutrophils. Levels of total protein and lactate dehydrogenase in synovial fluid are elevated, and the glucose level is depressed; however, these findings are not specific for infection, and measurement of these levels is not necessary for diagnosis. The synovial fluid should be examined for crystals because gout and pseudogout can resemble septic arthritis clinically and infection and crystal-induced disease occasionally occur together. Organisms are seen on synovial fluid smears in nearly three-quarters of infections with *S. aureus* and streptococci and in 30–50% of infections due to gram-negative and other bacteria. Cultures of synovial

fluid are positive in >90% of cases. Inoculation of synovial fluid into bottles containing liquid media for blood cultures increases the yield of a culture, especially if the pathogen is a fastidious organism or the patient is taking an antibiotic. NAA-based assays for bacterial DNA, when available, can be useful for the diagnosis of partially treated or culture-negative bacterial arthritis.

TREATMENT

Nongonococcal Bacterial Arthritis

Prompt administration of systemic antibiotics and drainage of the involved joint can prevent destruction of cartilage, postinfectious degenerative arthritis, joint instability, or deformity. Once samples of blood and synovial fluid have been obtained for culture, empirical antibiotics should be directed against the bacteria visualized on smears or the pathogens that are likely in light of the patient's age and risk factors. Initial therapy should consist of IV-administered bactericidal agents; direct instillation of antibiotics into the joint is not necessary to achieve adequate levels in synovial fluid and tissue. An IV third-generation cephalosporin such as cefotaxime (1 g every 8 h) or ceftriaxone (1–2 g every 24 h) provides adequate empirical coverage for most community-acquired infections in adults when smears show no organisms. IV vancomycin (1 g every 12 h) is used if there are gram-positive cocci on the smear. If methicillin-resistant *S. aureus* is an unlikely pathogen (e.g., when it is not widespread in the community), cefazolin (2 g every 8 h), oxacillin (2 g every 4 h), or nafcillin (2 g every 4 h) should be given. In addition, an aminoglycoside or third-generation cephalosporin should be given to IV drug users and to other patients in whom *P. aeruginosa* may be the responsible agent.

Definitive therapy is based on the identity and antibiotic susceptibility of the bacteria isolated in culture. Infections due to staphylococci are treated with cefazolin, oxacillin, nafcillin, or vancomycin for 4 weeks. Pneumococcal and streptococcal infections due to penicillin-susceptible organisms respond to 2 weeks of therapy with penicillin G (2 million units IV every 4 h); infections caused by *H. influenzae* and by strains of *Streptococcus pneumoniae* that are resistant to penicillin are treated with cefotaxime or ceftriaxone for 2 weeks. Most enteric gram-negative infections can be cured in 3–4 weeks by a second- or third-generation cephalosporin given IV or by a fluoroquinolone such as levofloxacin (500 mg IV or PO every 24 h). *P. aeruginosa* infection should be treated for at least 2 weeks with a combination regimen composed of an aminoglycoside plus either an extended-spectrum penicillin such as mezlocillin (3 g IV every 4 h) or an antipseudomonal cephalosporin such as ceftazidime (1 g IV every 8 h). If tolerated, this regimen is continued for an additional 2 weeks; alternatively, a fluoroquinolone such as ciprofloxacin (750 mg PO twice daily) is given by itself or with the penicillin or cephalosporin in place of the aminoglycoside.

Timely drainage of pus and necrotic debris from the infected joint is required for a favorable outcome. Needle aspiration of readily accessible joints such as the knee may be adequate if loculations or particulate matter in the joint does not prevent its thorough decompression. Arthroscopic drainage and lavage may be employed initially or within several days if repeated needle aspiration fails to relieve symptoms, decrease the volume of the effusion and the synovial white cell count, and clear bacteria from smears and cultures. In some cases, arthrotomy is necessary to remove loculations and debride infected synovium, cartilage, or bone. Septic arthritis of the hip is best managed with arthrotomy, particularly in young children, in whom infection threatens the viability of the femoral head. Septic joints do not require immobilization except for pain control before symptoms are alleviated by treatment. Weight bearing should be avoided until signs of inflammation have subsided, but frequent passive motion of the joint is indicated to maintain full mobility. Although addition of glucocorticoids to antibiotic treatment improves the outcome of *S. aureus* arthritis in experimental animals, no clinical trials have evaluated this approach in humans.

GONOCOCCAL ARTHRITIS

Epidemiology Although its incidence has declined in recent years, gonococcal arthritis **(Chap. 151)** has accounted for up to 70% of episodes of infectious arthritis in persons <40 years of age in the United States. Arthritis due to *N. gonorrhoeae* is a consequence of bacteremia arising from gonococcal infection or, more frequently, from asymptomatic gonococcal mucosal colonization of the urethra, cervix, or pharynx. Women are at greatest risk during menses and during pregnancy and overall are two to three times more likely than men to develop disseminated gonococcal infection (DGI) and arthritis. Persons with complement deficiencies, especially of the terminal components, are prone to recurrent episodes of gonococcemia. Strains of gonococci that are most likely to cause DGI include those which produce transparent colonies in culture, have the type IA outer-membrane protein, or are of the AUH-auxotroph type.

Clinical Manifestations and Laboratory Findings The most common manifestation of DGI is a syndrome of fever, chills, rash, and articular symptoms. Small numbers of papules that progress to hemorrhagic pustules develop on the trunk and the extensor surfaces of the distal extremities. Migratory arthritis and tenosynovitis of the knees, hands, wrists, feet, and ankles are prominent. The cutaneous lesions and articular findings are believed to be the consequence of an immune reaction to circulating gonococci and immune-complex deposition in tissues. Thus, cultures of synovial fluid are consistently negative, and blood cultures are positive in fewer than 45% of patients. Synovial fluid may be difficult to obtain from inflamed joints and usually contains only 10,000–20,000 leukocytes/μL.

True gonococcal septic arthritis is less common than the DGI syndrome and always follows DGI, which is unrecognized in one-third of patients. A single joint such as the hip, knee, ankle, or wrist is usually involved. Synovial fluid, which contains >50,000 leukocytes/μL, can be obtained with ease; the gonococcus is evident only occasionally in Gram-stained smears, and cultures of synovial fluid are positive in fewer than 40% of cases. Blood cultures are almost always negative.

Because it is difficult to isolate gonococci from synovial fluid and blood, specimens for culture should be obtained from potentially infected mucosal sites. NAA-based urine tests also may be positive. Cultures and Gram-stained smears of skin lesions are occasionally positive. All specimens for culture should be plated onto Thayer-Martin agar directly or in special transport media at the bedside and transferred promptly to the microbiology laboratory in an atmosphere of 5% CO_2, as generated in a candle jar. NAA-based assays are extremely sensitive in detecting gonococcal DNA in synovial fluid. A dramatic alleviation of symptoms within 12–24 h after the initiation of appropriate antibiotic therapy supports a clinical diagnosis of the DGI syndrome if cultures are negative.

TREATMENT

Gonococcal Arthritis

Initial treatment consists of ceftriaxone (1 g IV or IM every 24 h) to cover possible penicillin-resistant organisms. Once local and systemic signs are clearly resolving, the 7-day course of therapy can be completed with an oral fluoroquinolone such as ciprofloxacin (500 mg twice daily) if the organism is known to be susceptible. If penicillin-susceptible organisms are isolated, amoxicillin (500 mg three times daily) may be used. Suppurative arthritis usually responds to needle aspiration of involved joints and 7–14 days of antibiotic treatment. Arthroscopic lavage or arthrotomy is rarely required. Patients with DGI should be treated for *Chlamydia trachomatis* infection unless this infection is ruled out by appropriate testing. Addition of azithromycin (1 g orally as a single dose) is recommended to treat chlamydial co-infection, which is common. Sexual partners should be offered testing and presumptive treatment for gonorrhea and chlamydial infection.

It is noteworthy that arthritis symptoms similar to those seen in DGI occur in meningococcemia. A dermatitis–arthritis syndrome,

purulent monarthritis, and reactive polyarthritis have been described. All respond to treatment with IV penicillin.

SPIROCHETAL ARTHRITIS

LYME DISEASE

Lyme disease **(Chap. 181)** due to infection with the spirochete *Borrelia burgdorferi* causes arthritis in up to 60% of persons who are not treated. Intermittent arthralgias and myalgias—but not arthritis—occur within days or weeks of inoculation of the spirochete by the *Ixodes* tick. Later, there are three patterns of joint disease: (1) Fifty percent of untreated persons experience intermittent episodes of monarthritis or oligoarthritis involving the knee and/or other large joints. The symptoms wax and wane without treatment over months, and each year 10–20% of patients report loss of joint symptoms. (2) Twenty percent of untreated persons develop a pattern of waxing and waning arthralgias. (3) Ten percent of untreated patients develop chronic inflammatory synovitis that results in erosive lesions and destruction of the joint. Serologic tests for IgG antibodies to *B. burgdorferi* are positive in more than 90% of persons with Lyme arthritis, and an NAA-based assay detects *Borrelia* DNA in 85%.

TREATMENT

Lyme Arthritis

Lyme arthritis generally responds well to therapy. A regimen of oral doxycycline (100 mg twice daily for 28 days), oral amoxicillin (500 mg three times daily for 28 days), or parenteral ceftriaxone (2 g/d for 2–4 weeks) is recommended. Patients who do not respond to a total of 2 months of oral therapy or 1 month of parenteral therapy are unlikely to benefit from additional antibiotic therapy and are treated with anti-inflammatory agents or synovectomy. Failure of therapy is associated with host features such as the human leukocyte antigen DR4 (HLA-DR4) genotype, persistent reactivity to OspA (outer-surface protein A), and the presence of hLFA-1 (human leukocyte function–associated antigen 1), which cross-reacts with OspA.

SYPHILITIC ARTHRITIS

Articular manifestations occur in different stages of syphilis **(Chap. 177)**. In early congenital syphilis, periarticular swelling and immobilization of the involved limbs (*Parrot's pseudoparalysis*) complicate osteochondritis of long bones. *Clutton's joint*, a late manifestation of congenital syphilis that typically develops between ages 8 and 15 years, is caused by chronic painless synovitis with effusions of large joints, particularly the knees and elbows. Secondary syphilis may be associated with arthralgias, with symmetric arthritis of the knees and ankles and occasionally of the shoulders and wrists, and with sacroiliitis. The arthritis follows a subacute to chronic course with a mixed mononuclear and neutrophilic synovial-fluid pleocytosis (typical cell counts, 5000–15,000/μL). Immunologic mechanisms may contribute to the arthritis, and symptoms usually improve rapidly with penicillin therapy. In tertiary syphilis, Charcot joint results from sensory loss due to tabes dorsalis. Penicillin is not helpful in this setting.

MYCOBACTERIAL ARTHRITIS

Tuberculous arthritis **(Chap. 173)** accounts for ~1% of all cases of tuberculosis and 10% of extrapulmonary cases. The most common presentation is chronic granulomatous monarthritis. An unusual syndrome, *Poncet's disease*, is a reactive symmetric form of polyarthritis that affects persons with visceral or disseminated tuberculosis. No mycobacteria are found in the joints, and symptoms resolve with antituberculous therapy.

Unlike tuberculous osteomyelitis **(Chap. 126)**, which typically involves the thoracic and lumbar spine (50% of cases), tuberculous arthritis primarily involves the large weight-bearing joints, in particular the hips, knees, and ankles, and only occasionally involves smaller non-weight-bearing joints. Progressive monarticular swelling and pain develop over months or years, and systemic symptoms are seen in only half of all cases. Tuberculous arthritis occurs as part of a disseminated primary infection or through late reactivation, often in persons with HIV infection or other immunocompromised hosts. Coexistent active pulmonary tuberculosis is unusual.

Aspiration of the involved joint yields fluid with an average cell count of 20,000/μL, with ~50% neutrophils. Acid-fast staining of the fluid yields positive results in fewer than one-third of cases, and cultures are positive in 80%. Culture of synovial tissue taken at biopsy is positive in ~90% of cases and shows granulomatous inflammation in most. NAA methods can shorten the time to diagnosis to 1 or 2 days. Radiographs reveal peripheral erosions at the points of synovial attachment, periarticular osteopenia, and eventually joint-space narrowing. Therapy for tuberculous arthritis is the same as that for tuberculous pulmonary disease, requiring the administration of multiple agents for 6–9 months. Therapy is more prolonged in immunosuppressed individuals, such as those infected with HIV.

Various atypical mycobacteria **(Chap. 175)** found in water and soil may cause chronic indolent arthritis. Such disease results from trauma and direct inoculation associated with farming, gardening, or aquatic activities. Smaller joints, such as the digits, wrists, and knees, are usually involved. Involvement of tendon sheaths and bursae is typical. The mycobacterial species involved include *Mycobacterium marinum*, *M. avium-intracellulare*, *M. terrae*, *M. kansasii*, *M. fortuitum*, and *M. chelonae*. In persons who have HIV infection or are receiving immunosuppressive therapy, hematogenous spread to the joints has been reported for *M. kansasii*, *M. avium* complex, and *M. haemophilum*. Diagnosis usually requires biopsy and culture, and therapy is based on antimicrobial susceptibility patterns.

FUNGAL ARTHRITIS

Fungi are an unusual cause of chronic monarticular arthritis. Granulomatous articular infection with the endemic dimorphic fungi *Coccidioides immitis*, *Blastomyces dermatitidis*, and (less commonly) *Histoplasma capsulatum* **(Fig. 125-2)** results from hematogenous seeding or direct extension from bony lesions in persons with disseminated disease. Joint involvement is an unusual complication of sporotrichosis (infection with *Sporothrix schenckii*) among gardeners and other persons who work with soil or sphagnum moss. Articular sporotrichosis is six times more common among men than among women, and alcoholics and other debilitated hosts are at risk for polyarticular infection.

Candida infection involving a single joint—usually the knee, hip, or shoulder—results from surgical procedures, intraarticular injections, or (among critically ill patients with debilitating illnesses such as diabetes mellitus or hepatic or renal insufficiency and patients receiving immunosuppressive therapy) hematogenous spread. *Candida* infections in IV drug users typically involve the spine, sacroiliac joints, or other fibrocartilaginous joints. Unusual cases of arthritis due to *Aspergillus* species, *Cryptococcus neoformans*, *Pseudallescheria boydii*, and the dematiaceous fungi also have resulted from direct inoculation or disseminated hematogenous infection in immunocompromised persons. In the United States, a 2012 national outbreak of fungal arthritis (and meningitis) caused by *Exserohilum rostratum* was linked to intraspinal and intraarticular injection of a contaminated preparation of methylprednisolone acetate.

The synovial fluid in fungal arthritis usually contains 10,000–40,000 cells/μL, with ~70% neutrophils. Stained specimens and cultures of synovial tissue often confirm the diagnosis of fungal arthritis when studies of synovial fluid give negative results. Treatment consists of drainage and lavage of the joint and systemic administration of an antifungal agent directed at a specific pathogen. The doses and duration of therapy are the same as for disseminated disease **(see Part 5, Section 16)**. Intraarticular instillation of amphotericin B has been used in addition to IV therapy.

VIRAL ARTHRITIS

Viruses produce arthritis by infecting synovial tissue during systemic infection or by provoking an immunologic reaction that involves joints. As many as 50% of women report persistent arthralgias and 10% report

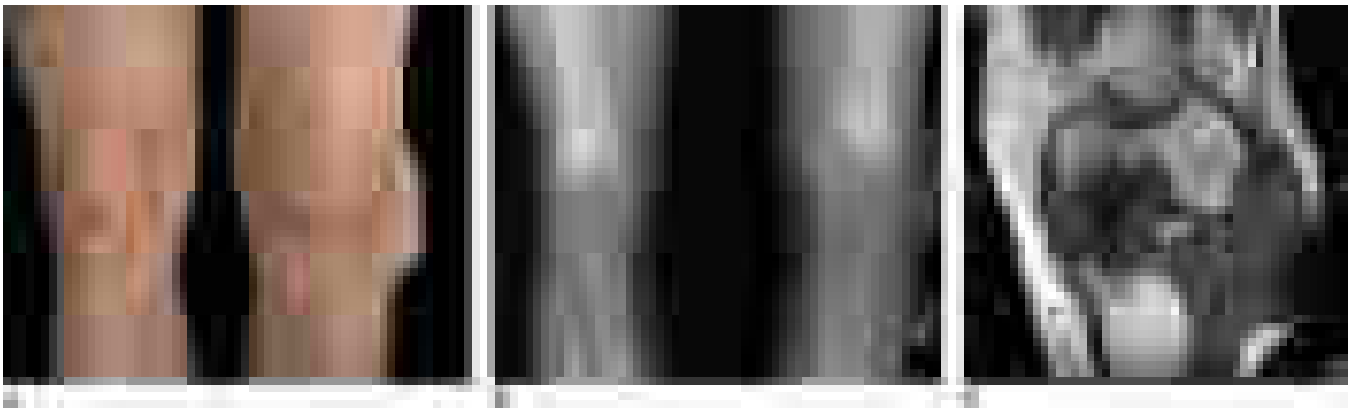

FIGURE 125-2 Chronic arthritis caused by *Histoplasma capsulatum* in the left knee. *A.* A man in his sixties from El Salvador presented with a history of progressive knee pain and difficulty walking for several years. He had undergone arthroscopy for a meniscal tear 7 years before presentation (without relief) and had received several intraarticular glucocorticoid injections. The patient developed significant deformity of the knee over time, including a large effusion in the lateral aspect. ***B.*** An x-ray of the knee showed multiple abnormalities, including severe medial femorotibial joint-space narrowing, several large subchondral cysts within the tibia and the patellofemoral compartment, a large suprapatellar joint effusion, and a large soft-tissue mass projecting laterally over the knee. ***C.*** MRI further defined these abnormalities and demonstrated the cystic nature of the lateral knee abnormality. Synovial biopsies demonstrated chronic inflammation with giant cells, and cultures grew *H. capsulatum* after 3 weeks of incubation. All clinical cystic lesions and the effusion resolved after 1 year of treatment with itraconazole. The patient underwent a left total-knee replacement for definitive treatment. *(Courtesy of Francisco M. Marty, MD, Brigham and Women's Hospital, Boston; with permission.)*

frank arthritis within 3 days of the rash that follows natural infection with rubella virus and within 2–6 weeks after receipt of live-virus vaccine. Episodes of symmetric inflammation of fingers, wrists, and knees uncommonly recur for >1 year, but a syndrome of chronic fatigue, low-grade fever, headaches, and myalgias can persist for months or years. IV immunoglobulin has been helpful in selected cases. Self-limited monarticular or migratory polyarthritis may develop within 2 weeks of the parotitis of mumps; this sequela is more common among men than among women. Approximately 10% of children and 60% of women develop arthritis after infection with parvovirus B19. In adults, arthropathy sometimes occurs without fever or rash. Pain and stiffness, with less prominent swelling (primarily of the hands but also of the knees, wrists, and ankles), usually resolve within weeks, although a small proportion of patients develop chronic arthropathy.

About 2 weeks before the onset of jaundice, up to 10% of persons with acute hepatitis B develop an immune complex–mediated, serum sickness–like reaction with maculopapular rash, urticaria, fever, and arthralgias. Less common developments include symmetric arthritis involving the hands, wrists, elbows, or ankles and morning stiffness that resembles a flare of rheumatoid arthritis. Symptoms resolve at the time jaundice develops. Many persons with chronic hepatitis C infection report persistent arthralgia or arthritis, both in the presence and in the absence of cryoglobulinemia.

Painful arthritis involving larger joints often accompanies the fever and rash of several arthropod-borne viral infections, including those caused by Zika, chikungunya, O'nyong-nyong, Ross River, Mayaro, and Barmah Forest viruses **(Chap. 204)**. Symmetric arthritis involving the hands and wrists may occur during the convalescent phase of infection with lymphocytic choriomeningitis virus. Patients infected with an enterovirus frequently report arthralgias, and echovirus has been isolated from patients with acute polyarthritis.

Several arthritis syndromes are associated with HIV infection. Reactive arthritis with painful lower-extremity oligoarthritis often follows an episode of urethritis in HIV-infected persons. HIV-associated reactive arthritis appears to be extremely common among persons with the HLA-B27 haplotype, but sacroiliac joint disease is unusual and is seen mostly in the absence of HLA-B27. Up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis. Painless monarthropathy and persistent symmetric polyarthropathy occasionally complicate HIV infection. Chronic persistent oligoarthritis of the shoulders, wrists, hands, and knees occurs in women infected with human T-lymphotropic virus type 1. Synovial thickening, destruction of articular cartilage, and leukemic-appearing atypical lymphocytes in synovial fluid are characteristic, but progression to T cell leukemia is unusual.

PARASITIC ARTHRITIS

Arthritis due to parasitic infection is rare. The guinea worm *Dracunculus medinensis* may cause destructive joint lesions in the lower extremities as migrating gravid female worms invade joints or cause ulcers in adjacent soft tissues that become secondarily infected. Hydatid cysts infect bones in 1–2% of cases of infection with *Echinococcus granulosus*. The expanding destructive cystic lesions may spread to and destroy adjacent joints, particularly the hip and pelvis. In rare cases, chronic synovitis has been associated with the presence of schistosomal eggs in synovial biopsies. Monarticular arthritis in children with lymphatic filariasis appears to respond to therapy with diethylcarbamazine even in the absence of microfilariae in synovial fluid. Reactive arthritis has been attributed to hookworm, *Strongyloides*, *Cryptosporidium*, and *Giardia* infection in case reports, but confirmation is required.

POSTINFECTIOUS OR REACTIVE ARTHRITIS

Reactive polyarthritis develops several weeks after ~1% of cases of nongonococcal urethritis and 2% of enteric infections, particularly those due to *Yersinia enterocolitica*, *Shigella flexneri*, *Campylobacter jejuni*, and *Salmonella* species. Only a minority of these patients have the other findings of classic reactive arthritis, including urethritis, conjunctivitis, uveitis, oral ulcers, and rash. Studies have identified microbial DNA or antigen in synovial fluid or blood, but the pathogenesis of this condition is poorly understood.

Reactive arthritis is most common among young men (except after *Yersinia* infection) and has been linked to the HLA-B27 locus as a potential genetic predisposing factor. Patients report painful, asymmetric oligoarthritis that affects mainly the knees, ankles, and feet. Low-back pain is common, and radiographic evidence of sacroiliitis is found in patients with long-standing disease. Most patients recover within 6 months, but prolonged recurrent disease is more common in cases that follow chlamydial urethritis. Anti-inflammatory agents help relieve symptoms, but the role of prolonged antibiotic therapy in eliminating microbial antigen from the synovium is controversial.

Migratory polyarthritis and fever constitute the usual presentation of acute rheumatic fever in adults **(Chap. 352)**. This presentation is distinct from that of poststreptococcal reactive arthritis, which also follows infections with group A *Streptococcus* but is not migratory, lasts beyond the typical 3-week maximum of acute rheumatic fever, and responds poorly to aspirin.

INFECTIONS IN PROSTHETIC JOINTS

Infection complicates 1–4% of total joint replacements. The majority of infections are acquired intraoperatively or immediately postoperatively as a result of wound breakdown or infection; less commonly,

these joint infections develop later after joint replacement and are the result of hematogenous spread or direct inoculation. The presentation may be acute, with fever, pain, and local signs of inflammation, especially in infections due to *S. aureus*, pyogenic streptococci, and enteric bacilli. Alternatively, infection may persist for months or years without causing constitutional symptoms when less virulent organisms, such as coagulase-negative staphylococci or diphtheroids, are involved. Such indolent infections usually are acquired during joint implantation and are discovered during evaluation of chronic unexplained pain or after a radiograph shows loosening of the prosthesis; the erythrocyte sedimentation rate and C-reactive protein level are usually elevated in such cases.

The diagnosis is best made by needle aspiration of the joint; accidental introduction of organisms during aspiration must be avoided meticulously. Synovial fluid pleocytosis with a predominance of polymorphonuclear leukocytes is highly suggestive of infection, since other inflammatory processes uncommonly affect prosthetic joints. Culture and Gram's stain usually yield the responsible pathogen. Sonication of explanted prosthetic material can improve the yield of culture, presumably by breaking up bacterial biofilms on the surfaces of prostheses. Use of special media for unusual pathogens such as fungi, atypical mycobacteria, and *Mycoplasma* may be necessary if routine and anaerobic cultures are negative.

TREATMENT

Prosthetic Joint Infections

Treatment includes surgery and high doses of parenteral antibiotics, which are given for 4–6 weeks because bone is usually involved. In most cases, the prosthesis must be replaced to cure the infection. Implantation of a new prosthesis is best delayed for several weeks or months because relapses of infection occur most commonly within this time frame. In some cases, reimplantation is not possible, and the patient must manage without a joint, with a fused joint, or even with amputation. Cure of infection without removal of the prosthesis is occasionally possible in cases that are due to streptococci or pneumococci and that lack radiologic evidence of loosening of the prosthesis. In these cases, antibiotic therapy must be initiated within several days of the onset of infection, and the joint should be drained vigorously by open arthrotomy or arthroscopically. In selected patients who prefer to avoid the high morbidity rate associated with joint removal and reimplantation, suppression of the infection with antibiotics may be a reasonable goal. A high cure rate with retention of the prosthesis has been reported when the combination of oral rifampin and another antibiotic (e.g., a quinolone, an antistaphylococcal penicillin, or vancomycin) is given for 3–6 months to persons with staphylococcal prosthetic joint infection of short duration. This approach, which is based on the ability of rifampin to kill organisms adherent to foreign material and in the stationary growth phase, requires confirmation in prospective trials.

PREVENTION

To avoid the disastrous consequences of infection, candidates for joint replacement should be selected with care. Rates of infection are particularly high among patients with rheumatoid arthritis, persons who have undergone previous surgery on the joint, and persons with medical conditions requiring immunosuppressive therapy. Perioperative antibiotic prophylaxis, usually with cefazolin, and measures to decrease intraoperative contamination, such as laminar flow, have lowered the rates of perioperative infection to <1% in many centers. After implantation, measures should be taken to prevent or rapidly treat extra-articular infections that might give rise to hematogenous spread to the prosthesis. The effectiveness of prophylactic antibiotics for the prevention of hematogenous infection after dental procedures has not been demonstrated; in fact, viridans streptococci and other components of the oral flora are extremely unusual causes of prosthetic joint infection. Accordingly, the American Dental Association and the American Academy of Orthopaedic Surgeons do not recommend antibiotic prophylaxis for most dental patients with total joint replacements and have stated that there is no convincing evidence to support its use. Similarly, guidelines issued by the American Urological Association and the American Academy of Orthopaedic Surgeons do not recommend the use of prophylactic antibiotics for most patients with prosthetic joints who are undergoing urologic procedures but state that prophylaxis should be considered in certain situations—e.g., for patients (especially immunocompromised patients) who are undergoing a procedure posing a relatively high risk of bacteremia (such as lithotripsy or surgery involving bowel segments).

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126 Osteomyelitis

Werner Zimmerli

Osteomyelitis, an infection of bone, can be caused by various microorganisms that arrive at bone through different routes. Spontaneous hematogenous osteomyelitis may occur in otherwise healthy individuals, whereas local microbial spread mainly affects either individuals who have underlying disease (e.g., vascular insufficiency) or patients who have compromised skin or other tissue barriers, with consequent exposure of bone. The latter situation typically follows surgery involving bone, such as sternotomy or orthopedic repair.

The manifestations of osteomyelitis are different in children and adults. In children circulating microorganisms seed mainly long bones, whereas in adults the vertebral column is the most commonly affected site.

Management of osteomyelitis differs greatly depending on whether an implant is involved. The most important aim of the management of either type of osteomyelitis is to prevent progression to chronic osteomyelitis by rapid diagnosis and prompt treatment. Device-related bone and joint infection necessitates a multidisciplinary approach requiring antibiotic therapy and, in many cases, surgical removal of the device. For most types of osteomyelitis, the optimal duration of antibiotic treatment has not been established in clinical trials. Therefore, the recommendations for therapy in this chapter reflect mainly expert opinions.

CLASSIFICATION

There is no generally accepted, comprehensive system for classification of osteomyelitis, primarily because of the multifaceted presentation of this infection. Different specialists are confronted with different facets

of bone disease. Most often, however, general practitioners or internists are the first to encounter patients with the initial signs and symptoms of osteomyelitis. These primary care physicians should be able to recognize this disease in any of its forms. Osteomyelitis cases can be classified by various criteria, including pathogenesis, duration of infection, location of infection, and presence or absence of foreign material. The widely used Cierny-Mader staging system classifies osteomyelitis according to anatomic site, comorbidity, and radiographic findings, with stratification of long-bone osteomyelitis to optimize surgical management; this system encompasses both systemic and local factors affecting immune status, metabolism, and local vascularity.

Any of three mechanisms can underlie osteomyelitis: (1) hematogenous spread; (2) spread from a contiguous site following surgery; and (3) secondary infection in the setting of vascular insufficiency or concomitant neuropathy. Hematogenous osteomyelitis in adults typically involves the vertebral column. In only about half of patients a primary focus can be detected. The most common primary foci of infection are the urinary tract, skin/soft tissue, intravascular catheterization sites, and the endocardium. Spread from a contiguous source follows either bone trauma or surgical intervention. Wound infection leading to osteomyelitis typically occurs after cardiovascular intervention involving the sternum, orthopedic repair after open fracture, or prosthetic joint insertion. Osteomyelitis secondary to vascular insufficiency or peripheral neuropathy most often follows chronic, progressively deep skin and soft tissue infection of the foot. The most common underlying condition is diabetes. In diabetes that is poorly controlled, the *diabetic foot syndrome* is caused by skin, soft tissue, and bone ischemia combined with motor, sensory, and autonomic neuropathy.

Classification of osteomyelitis according to the duration of infection, although ill defined, is useful because the management of acute and chronic osteomyelitis differs. Whereas acute osteomyelitis can generally be treated with antibiotics alone, antibiotic treatment for chronic osteomyelitis should be combined with debridement surgery. Acute hematogenous or contiguous osteomyelitis evolves over a short period—i.e., a few days or weeks. In contrast, subacute or chronic osteomyelitis lasts for weeks or months before treatment is started. Typical examples of a subacute course are vertebral osteomyelitis due to tuberculosis or brucellosis and delayed implant-associated infections caused mainly by low-virulence microorganisms (coagulase-negative staphylococci, *Propionibacterium acnes*). Chronic osteomyelitis develops when insufficient therapy leads to persistence or recurrence, most often after sternal, mandibular, or foot infection.

Classification by location distinguishes among cases in the long bones, the vertebral column, and the periarticular bones. Long bones are generally involved after hematogenous seeding in children or contiguous spread following trauma or surgery. The risk of vertebral osteomyelitis in adults increases with age. Periarticular osteomyelitis, which complicates septic arthritis that has not been adequately treated, is especially common in periprosthetic joint infection.

Osteomyelitis involving a foreign device requires surgical management for cure. Even acute implant-associated infection calls for prolonged antimicrobial therapy. Therefore, identification of this type of disease is of practical importance.

VERTEBRAL OSTEOMYELITIS

PATHOGENESIS

Vertebral osteomyelitis, also referred to as disk-space infection, septic diskitis, spondylodiskitis, or spinal osteomyelitis, is the most common manifestation of hematogenous bone infection in adults. This designation reflects a pathogenic process leading to involvement of the adjacent vertebrae and the corresponding intervertebral disk. In adults, the disk is avascular. Microorganisms invade via the segmental arterial circulation in adjacent endplates and then spread into the disk. Alternative routes of infection are retrograde seeding through the prevertebral venous plexus and direct inoculation during spinal surgery, epidural infiltration, or trauma. In the setting of implant surgery, microorganisms are inoculated either during the procedure or, if wound healing is impaired, in the early postoperative period.

EPIDEMIOLOGY

Vertebral osteomyelitis occurs more often in male than in female patients (ratio, 1.5:1). Between 1995 and 2008, the incidence rate increased from 2.2 to 5.8 cases/100,000 person-years. There is a clear age-dependent increase from 0.3 case/100,000 at ages <20 years to 6.5 cases/100,000 at ages >70 years. The observed increase in reported cases during the past two decades may reflect improvements in diagnosis resulting from the broad availability of MRI technology. In addition, the fraction of cases of vertebral osteomyelitis acquired in association with health care is increasing as a consequence of comorbidity and the rising number of invasive interventions.

MICROBIOLOGY

Vertebral osteomyelitis is typically classified as pyogenic or nonpyogenic. However, this distinction is arbitrary: in "nonpyogenic" cases (tuberculous, brucellar), macroscopic pus formation (caseous necrosis, abscess) is quite common. A more accurate scheme is to classify cases as acute or subacute/chronic. Whereas the microbiologic spectrum of acute cases is similar in different parts of the world, the spectrum of subacute/chronic cases varies according to the geographic region. The great majority of cases are monomicrobial in etiology. Of episodes of acute vertebral osteomyelitis, 40–50% are caused by *Staphylococcus aureus*, 12% by streptococci, and 20% by gram-negative bacilli—mainly *Escherichia coli* (9%) and *Pseudomonas aeruginosa* (6%). Subacute vertebral osteomyelitis is typically caused by *Mycobacterium tuberculosis* or *Brucella* species in regions where these microorganisms are endemic. Osteomyelitis due to viridans streptococci also has a subacute presentation; these infections most often occur as secondary foci in patients with endocarditis. In vertebral osteomyelitis due to *Candida* species, the diagnosis is often delayed by several weeks; this etiology should be suspected in IV drug users who do not use sterile paraphernalia. In implant-associated spinal osteomyelitis, coagulase-negative staphylococci and *P. acnes*—which, in the absence of an implant, are generally considered contaminants—typically cause low-grade (chronic) infections. As an exception, coagulase-negative staphylococci can cause native spinal osteomyelitis in cases of prolonged bacteremia (e.g., in patients with infected pacemaker electrodes or implanted vascular catheters that are not promptly removed).

CLINICAL MANIFESTATIONS

The signs and symptoms of vertebral osteomyelitis are nonspecific. Only about half of patients develop fever >38°C (>100.4°F), perhaps because patients frequently use analgesic drugs. Back pain is the leading initial symptom (>85% of cases). The location of the pain corresponds to the site of infection: the cervical spine in ~10% of cases, the thoracic spine in 30%, and the lumbar spine in 60%. One exception is involvement at the thoracic level in two-thirds of cases of tuberculous osteomyelitis and at the lumbar level in only one-third. This difference is due to direct mycobacterial spread via pleural or mediastinal lymph nodes in pulmonary tuberculosis.

Neurologic deficits, such as radiculopathy, weakness, or sensory loss, are observed in about one-third of cases of vertebral osteomyelitis. In brucellar vertebral osteomyelitis, neurologic impairment is less common; in tuberculous osteomyelitis, it is about twice as common as in cases of other etiologies. Neurologic signs and symptoms are caused mostly by spinal epidural abscess. This complication starts with severe localized back pain and progresses to radicular pain, reflex changes, sensory abnormalities, motor weakness, bowel and bladder dysfunction, and paralysis.

A primary focus should always be sought but is found in only half of cases. Overall, endocarditis is identified in ~10% of patients. In osteomyelitis caused by viridans streptococci, endocarditis is the source in about half of patients.

Implant-associated spinal osteomyelitis can present as either early- or late-onset infection. Early-onset infection is diagnosed within 30 days after implant placement. *S. aureus* is the most common pathogen. Wound healing impairment and fever are the leading findings. Late-onset infection is diagnosed beyond 30 days after surgery, with low-virulence organisms such as coagulase-negative staphylococci or *P. acnes* as typical

infecting agents. Fever is rare. One-quarter of patients have a sinus tract. Because of the delayed course and the lack of classic signs of infection, rapid diagnosis requires a high degree of suspicion.

DIAGNOSIS

Leukocytosis and neutrophilia have low levels of diagnostic sensitivity (only 65 and 40%, respectively). In contrast, an increased erythrocyte sedimentation rate or C-reactive protein (CRP) level has been reported in 98 and 100% of cases, respectively; thus, these tests are helpful in excluding vertebral osteomyelitis. The fraction of blood cultures that yield positive results depends heavily on whether the patient has been pretreated with antibiotics; across studies, the range is from 30 to 78%. In view of this low rate of positive blood culture after antibiotic treatment, such therapy should be withheld until microbial growth is proven unless the patient has sepsis syndrome. In patients with negative blood cultures, CT-guided or open biopsy is needed. Whether a CT-guided biopsy with a negative result is repeated or followed by open biopsy depends on the experience of personnel at the specific center. Bone samples should be cultured for aerobic, anaerobic, and fungal agents, with a portion of the sample sent for histopathologic study. In cases with a subacute/chronic presentation, a suggestive history, or a granuloma detected during histopathologic analysis, mycobacteria and brucellae also should be sought. When blood and tissue cultures are negative despite suggestive histopathology, broad-range polymerase chain reaction analysis of biopsy specimens or aspirated pus should be considered. This technique allows detection of unusual pathogens such as *Tropheryma whipplei*.

Given that signs and symptoms of osteomyelitis are nonspecific, the clinical differential diagnosis of febrile back pain is broad, including pyelonephritis, pancreatitis, and viral syndromes. In addition, multiple noninfectious pathologies of the vertebral column, such as osteoporotic fracture, seronegative spondylitis (ankylosing spondylitis, psoriasis, reactive arthritis, enteropathic arthritis), and spinal stenosis must be considered.

Imaging procedures are the most important tools not only for the diagnosis of vertebral osteomyelitis but also for the detection of pyogenic complications and alternative conditions (e.g., bone metastases or osteoporotic fractures). Plain radiography is a reasonable first step in evaluating patients without neurologic symptoms and may reveal an alternative diagnosis. Because of its low sensitivity, plain radiography generally is not helpful in acute osteomyelitis, but it can be useful in subacute or chronic cases. The gold standard is MRI, which should be performed expeditiously in patients with neurologic impairment in order to rule out a herniated disk or to detect pyogenic complications in a timely manner. Even if the pathologic findings on MRI suggest vertebral osteomyelitis, alternative diagnoses should be considered, especially when blood cultures are negative. The most common alternative diagnosis is erosive osteochondrosis. Septic bone necrosis, gouty spondylodiskitis, and erosive diskovertebral lesions (Andersson lesions) in ankylosing spondylitis may likewise mimic vertebral osteomyelitis. CT is less sensitive than MRI but may be helpful in guiding a percutaneous biopsy. In the future, positron-emission tomography (PET) with ^{18}F-fluorodeoxyglucose, which has a high degree of diagnostic accuracy, may be an alternative imaging procedure when MRI is contraindicated. ^{18}F-fluorodeoxyglucose PET should be considered for patients with implants and patients in whom several foci are suspected.

TREATMENT

Vertebral Osteomyelitis

The aims of therapy for vertebral osteomyelitis are (1) elimination of the pathogen(s), (2) protection from further bone loss, (3) relief of back pain, (4) prevention of complications, and (5) stabilization, if needed.

Table 126-1 summarizes suggested antimicrobial regimens for infections attributable to the most common etiologic agents. For optimal antimicrobial therapy, identification of the infecting agent is required. Therefore, in patients without sepsis syndrome, antibiotics should not be administered until the pathogen is identified in a blood culture, a bone biopsy, or an aspirated pus collection. Traditionally, bone infections are at least initially treated by the IV route. Unfortunately, relevant controlled trials are lacking, and the preference for the IV route is not evidence based. There are no good arguments for the assumption that IV therapy is superior to oral administration if the following requirements are met: (1) optimal antibiotic spectrum, (2) excellent bioavailability of the oral drug, (3) clinical studies confirming efficacy of the oral drug, (4) normal intestinal function, and (5) no vomiting. However, a short initial course of parenteral therapy with a β-lactam antibiotic may lower the risk of emergence of fluoroquinolone resistance, especially if *P. aeruginosa* infection is treated with ciprofloxacin or staphylococcal infection with the combination of a fluoroquinolone plus rifampin. These suggestions are based on observational studies and expert opinion. A recent randomized, controlled trial showed that 6 weeks of antibiotic treatment is not inferior to a 12-week course in patients

TABLE 126-1 Antibiotic Therapy for Osteomyelitis in Adults Without Implants[a]

MICROORGANISM	ANTIMICROBIAL AGENT (DOSE,[b] ROUTE)
Staphylococcus spp.	
Methicillin-susceptible	Nafcillin or oxacillin[c] (2 g IV q6h)
	followed by
	Rifampin (300–450 mg PO q12h) plus levofloxacin (750 mg PO q24h or 500 mg PO q12h)
Methicillin-resistant	Vancomycin[d] (15 mg/kg IV q12h) or daptomycin (>6–8 mg/kg IV q24h)
	followed by
	Rifampin (300–450 mg PO q12h)
	plus
	Levofloxacin (750 mg PO q24h or 500 mg PO q12h) or TMP-SMX[e] (1 double-strength tablet PO q8h) or fusidic acid (500 mg PO q8h)
Streptococcus spp.	Penicillin G[c] (5 million units IV q6h) or ceftriaxone (2 g IV q24h)
Enterobacteriaceae	
Quinolone-susceptible	Ciprofloxacin (750 mg PO q24h)
Quinolone-resistant[f]	Imipenem (500 mg IV q6h)
Pseudomonas aeruginosa	Cefepime or ceftazidime (2 g IV q8h) *plus* an aminoglycoside[g]
	or
	Piperacillin-tazobactam (4.5 g IV q8h) plus an aminoglycoside[g] for 2–4 weeks
	followed by
	Ciprofloxacin[h] (750 mg PO q12h)
Anaerobes	Clindamycin (600 mg IV q6–8h) for 2–4 weeks
	followed by
	Clindamycin[i] (300 mg PO q6h)

[a]Unless otherwise indicated, the total duration of antimicrobial treatment is generally 6 weeks. [b]All dosages are for adults with normal renal function. [c]When the patient has delayed-type penicillin hypersensitivity, cefuroxime (1.5 g IV q6–8h) can be administered. When the patient has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h). [d]Target vancomycin trough level: 15–20 μg/mL. [e]Trimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. [f]Including isolates producing extended-spectrum β-lactamase. [g]The need for addition of an aminoglycoside has not yet been proven. However, this addition may decrease the risk of emergence of resistance to the β-lactam. [h]The rationale for starting ciprofloxacin treatment only after pretreatment with a β-lactam is the increased risk of emergence of quinolone resistance in the presence of a heavy bacterial load. [i]Alternatively, penicillin G (5 million units IV q6h) or ceftriaxone (2 g IV q24h) can be used against gram-positive anaerobes (e.g., *Propionibacterium acnes*), and metronidazole (500 mg IV/PO q8h) can be used against gram-negative anaerobes (e.g., *Bacteroides* spp.).

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with pyogenic vertebral osteomyelitis. The cure rate was 90.9% in both groups 1 year after therapy. Thus, prolonged antibiotic therapy is required only for patients with undrained abscesses and for patients with spinal implants. Treatment efficacy should be regularly monitored through inquiries about signs and symptoms (fever, pain) and assessment for signs of inflammation (elevated CRP concentrations). Follow-up MRI is appropriate only for patients with pyogenic complications, since the correlation between clinical healing and improvement on MRI is very poor.

Surgical treatment generally is not needed in acute hematogenous vertebral osteomyelitis. However, it is always necessary in implant-associated spinal infection. Early infections (those occurring up to 30 days after internal stabilization) can be cured with debridement, implant retention, and a 3-month course of antibiotics **(Table 126-2)**. In contrast, in late infection with a duration of >30 days, implant removal and a 6-week course of antibiotics (Table 126-1) are required for complete elimination of the infection. If implants cannot be removed, oral suppressive long-term treatment should follow the initial course of IV antibiotics. The optimal duration of suppressive therapy is unknown. However, if antibiotic therapy is discontinued after, for example, 1 year, close clinical and laboratory (CRP) follow-up is needed.

COMPLICATIONS

Complications should be suspected when there is persistent pain, a persistently increased CRP level, and new-onset or persistent neurologic impairment. In cases of persistent pain with or without signs of inflammation, paravertebral, epidural, or psoas abscesses **(Fig. 126-1)** must be sought. Epidural abscesses occur in 15–20% of cases. This complication is more common in the cervical column (30%) than in the lumbar spine (12%). Persistent pain despite normalization of CRP

TABLE 126-2 Antibiotic Therapy for Osteomyelitis Associated with Orthopedic Devices

MICROORGANISM	ANTIMICROBIAL AGENT[a] (DOSE, ROUTE)
Staphylococcus spp.	*Recommendation for initial treatment phase (2 weeks with implant)*
Methicillin-susceptible	Rifampin (450 mg PO/IV q12h[b])
	plus
	Nafcillin or oxacillin[c] (2 g IV q6h)
Methicillin-resistant	Rifampin (450 mg PO/IV q12h[b])
	plus
	Vancomycin (15 mg/kg IV q12h) or daptomycin (6–10 mg/kg IV q24h)
Staphylococcus spp.	*Recommendation after completion of initial treatment phase*
	Rifampin (450 mg PO q12h[b])
	plus
	Levofloxacin (750 mg PO q24h or 500 mg PO q12h) or ciprofloxacin (750 mg PO q12h) or fusidic acid (500 mg PO q8h) or TMP-SMX[d] (1 double-strength tablet PO q8h) or minocycline (100 mg PO q12h) or linezolid (600 mg PO q12h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses)
Streptococcus spp.[e]	Penicillin G[c] (18–24 million units/d IV in 6 divided doses) or ceftriaxone (2 g IV q24h) for 4 weeks
	followed by
	Amoxicillin (750–1000 mg PO q6–8h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses)
Enterococcus spp.[f]	
Penicillin-susceptible	Penicillin G[c] (24 million units/d IV in 6 divided doses) *or* ampicillin or amoxicillin[g] (2 g IV q4–6h)
Penicillin-resistant	Vancomycin (15 mg/kg IV q12h) or daptomycin (6–10 mg/kg IV q24h) or linezolid (600 mg IV/PO q12h)
Enterobacteriaceae	A β-lactam selected in light of in vitro susceptibility profile for 2 weeks[h]
	followed by
	Ciprofloxacin (750 mg PO q12h)
Enterobacter spp.[i] and nonfermenters[j] (e.g., *Pseudomonas aeruginosa*)	Cefepime or ceftazidime (2 g IV q8h) *or* meropenem (1 g IV q8h[k]) for 2–4 weeks
	followed by
	Ciprofloxacin (750 mg PO q12h)
Propionibacterium spp.	Penicillin G[c] (18–24 million units/d IV in 6 divided doses) or clindamycin (600–900 mg IV q8h) for 2–4 weeks
	followed by
	Amoxicillin (750–1000 mg PO q6–8h) or clindamycin (1200–1350 mg/d PO in 3 or 4 divided doses)
Gram-negative anaerobes (e.g., *Bacteroides* spp.)	Metronidazole (500 mg IV/PO q8h)
Mixed bacteria (without methicillin-resistant staphylococci)	Ampicillin-sulbactam (3 g IV q6h) or amoxicillin-clavulanate[l] (2.2 g IV q6h) or piperacillin-tazobactam (4.5 g IV q8h) or imipenem (500 mg IV q6h) or meropenem (1 g IV q8h[k]) for 2–4 weeks
	followed by
	Individualized oral regimens chosen in light of antimicrobial susceptibility

[a]Antimicrobial agents should be chosen in light of the isolate's in vitro susceptibility, the patient's drug allergies and intolerances, potential drug interactions, and contraindications to specific drugs. All dosages recommended are for adults with normal renal and hepatic function. See text for total durations of antibiotic treatment. [b]Other dosages and intervals of administration with equivalent success rates have been reported. [c]When the patient has delayed-type penicillin hypersensitivity, cefazolin (2 g IV q8h) can be administered. When the patient has immediate-type penicillin hypersensitivity, the penicillin should be replaced by vancomycin (1 g IV q12h). [d]Trimethoprim-sulfamethoxazole. A double-strength tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole. [e]Determination of the minimal inhibitory concentration (MIC) of penicillin is advisable. [f]Combination therapy with an aminoglycoside is optional since its superiority to monotherapy for prosthetic joint infection is unproved. When using combination therapy, monitor for signs of aminoglycoside ototoxicity and nephrotoxicity; the latter is potentiated by other nephrotoxic agents (e.g., vancomycin). [g]For patients with hypersensitivity to penicillin, see treatment options for penicillin-resistant enterococci.[h]Ciprofloxacin (PO or IV) can be administered to patients with hypersensitivity to β-lactams. [i]Ceftriaxone and ceftazidime should not be administered for treatment targeting *Enterobacter* species, even strains that test susceptible in the laboratory, but can be used against nonfermenters. Strains producing extended-spectrum β-lactamases should not be treated with any cephalosporin, including cefepime. *Enterobacter* infections can also be treated with ertapenem (1 g IV q24h); however, ertapenem is not effective against *Pseudomonas* spp. and other nonfermenters. [j]Addition of an aminoglycoside is optional. Use of two active drugs can be considered in light of the patient's clinical condition. [k]The recommended dosage is in line with the guidelines of the Infectious Diseases Society of America. In Europe, 2 g IV q8h is suggested for *P. aeruginosa* infections. [l]Not available as an IV formulation in the United States.

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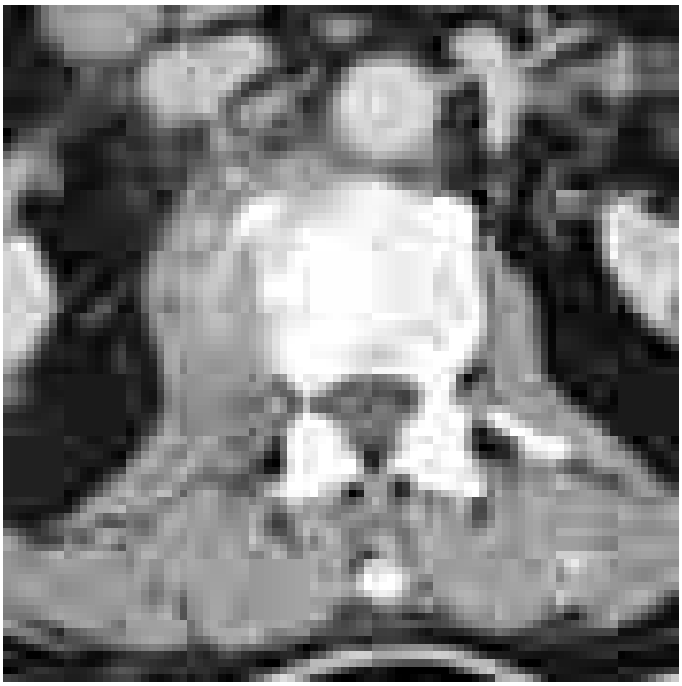

FIGURE 126-1 CT scan of acute vertebral osteomyelitis (L1/L2) due to *Staphylococcus aureus* in a 64-year-old man. Low-grade fever persisted despite appropriate IV antibiotic therapy. The scan revealed a psoas abscess on the right side.

values indicates mechanical complications such as severe osteonecrosis or spinal instability. These patients require a consult with an experienced orthopedic surgeon.

GLOBAL CONSIDERATIONS

The incidence rate of acute vertebral osteomyelitis is similar in different regions of the world. In contrast, subacute/chronic vertebral osteomyelitis predominates in defined regions. Cases attributable to brucellosis predominate in endemic areas such as the Middle East, Africa, Central and South America, and the Indian subcontinent. Tuberculosis is an especially frequent cause in Africa and Asia (India, Indonesia, China), where more than two-thirds of the global tuberculosis burden is reported. Thus, specific diagnostic tests are needed in patients either living in or having traveled to these regions.

OSTEOMYELITIS IN LONG BONES

PATHOGENESIS

Osteomyelitis in long bones is a consequence of hematogenous seeding, exogenous contamination during trauma (open fracture), or perioperative contamination during orthopedic repairs. Its presentation is either acute (with a duration of days to a few weeks) or chronic. Hematogenous infection in long bones typically occurs in children. Ineffectively treated hematogenous osteomyelitis during childhood can progress to chronic disease. In adults, the leading pathogenic source is exogenous infection, mainly associated with internal fixation devices. Chronic osteomyelitis can recur after a symptom-free interval of >70 years. Such recurrences are most common among elderly patients who developed osteomyelitis in the preantibiotic era.

EPIDEMIOLOGY

In adults, most cases of long-bone osteomyelitis are posttraumatic or postsurgical; less frequently, late recurrence arises from hematogenous infections during childhood. The risk of infection depends on the type of fracture. After closed fracture, implant-associated infection occurs in fewer than 1% of patients. In contrast, after open fracture, the risk of osteomyelitis ranges from ~2 up to 30%, with the precise figure depending on the degree of tissue damage during trauma and the time between injury and admission to a specialized center.

MICROBIOLOGY

The spectrum of microorganisms causing hematogenous long-bone osteomyelitis does not differ from that in vertebral osteomyelitis. *S. aureus* is most commonly isolated in each type of osteomyelitis. In rare cases, mycobacteria or fungal agents such as *Cryptococcus* species, *Sporothrix schenckii*, *Blastomyces dermatitidis*, or *Coccidioides* species are found in patients who live or have traveled in endemic regions. Impaired cellular immunity (e.g., in HIV infection or after transplantation) predisposes to these etiologies. Coagulase-negative staphylococci are the second most common etiologic agents (after *S. aureus*) in implant-associated osteomyelitis. After open fracture, contiguous long-bone osteomyelitis is typically caused by gram-negative bacilli or a polymicrobial mixture of organisms.

CLINICAL MANIFESTATIONS

The leading symptoms in adults with primary or recurrent hematogenous long-bone osteomyelitis are pain and low-grade fever. Infection occasionally manifests as clinical sepsis and local signs of inflammation (erythema and swelling). After internal fixation, osteomyelitis can be classified as early (acute; <3 weeks), delayed (3–10 weeks), or late (chronic) infection. Early/acute long-bone osteomyelitis manifests as signs of surgical site infection, such as erythema and impaired wound healing. Acute implant-associated infection may also follow hematogenous seeding at any time after implantation of a device. Typical symptoms are new-onset pain and signs of sepsis. Delayed or late (chronic) infections are usually caused by low-virulence microorganisms or occur after ineffective treatment of early-onset infection. Patients may present with persisting pain, subtle local signs of inflammation, intermittent discharge of pus, or fluctuating erythema over the scar **(Fig. 126-2)**.

DIAGNOSIS

The diagnostic workup for acute hematogenous long-bone osteomyelitis is similar to that for vertebral osteomyelitis. Bone remodeling and thus marker uptake are increased for at least 1 year after surgery. Therefore, the three-phase bone scan is not useful during this interval. However, in late recurrences it allows rapid diagnosis at low cost. If the results are positive, CT is required in order to estimate the extent of inflamed tissue and to detect bone necrosis (sequesters). Implant-associated infection should be suspected if CRP values do not return to the normal range or rise after an initial decrease. Clinical and laboratory suspicion should prompt surgical exploration and sampling.

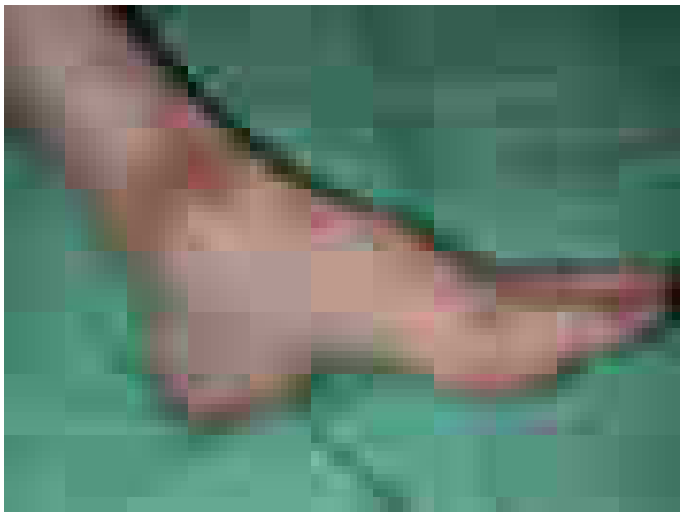

FIGURE 126-2 A 42-year-old man who had had a malleolar fracture 6 weeks previously had persistent pain and slight inflammation after orthopedic repair. His infection was treated with oral antibiotics without debridement surgery. This insufficient management of an implant-associated *Staphylococcus aureus* infection was complicated by a sinus tract.

In chronic osteomyelitis of >1 year's duration, single-photon emission CT plus conventional CT (SPECT/CT) is a good option, either with ^{99m}Tc methylene diphosphonate (^{99m}Tc-MDP)–labeled leukocytes or with labeled monoclonal antibodies to granulocytes. Surgical debridement is needed for diagnostic (biopsy culture, histology) and therapeutic reasons.

TREATMENT

Osteomyelitis in Long Bones

Treatment for acute hematogenous infection in long bones is identical to that for acute vertebral osteomyelitis (Table 126-1). The suggested duration of antibiotic therapy is 4–6 weeks. In contrast to chronic or implant-associated osteomyelitis, acute hematogenous infection does not generally require surgical intervention. Initial IV administration of antimicrobial agents is followed by long-term oral treatment. The duration of the initial IV phase of therapy has not been defined. The IV course can be as short as 2 days for a drug with excellent bioavailability. In recurrences of chronic osteomyelitis as well as in each type of exogenous osteomyelitis (acute, chronic, with or without an implant), a combination of surgical debridement, obliteration of dead space, and long-term antibiotic therapy is needed.

The therapeutic aims in patients whose infections are associated with internal fixation devices are consolidation of the fracture and prevention of chronic osteomyelitis. Stable implants can be maintained except in patients with uncontrolled sepsis. Appropriate antimicrobial therapies are listed in Table 126-2. The cure rate for early staphylococcal implant-associated infections treated with a fluoroquinolone plus rifampin is >90%. Rifampin is efficacious against staphylococcal biofilms of ≤3 weeks' duration. Similarly, fluoroquinolones are active against biofilms formed by gram-negative bacilli. In these cases, an initial 2-week course of IV therapy with a β-lactam is suggested in order to minimize the risk of emergence of resistance to the oral drugs. The total duration of treatment is 3 months, and the device can be retained even after antibiotics have been discontinued. In contrast, in cases caused by rifampin-resistant staphylococci or fluoroquinolone-resistant gram-negative bacilli, the hardware should be removed after consolidation of the fracture and before discontinuation of antibiotics. These patients are treated with an oral antibiotic (suppressive therapy) as long as retention of the hardware is necessary.

COMPLICATIONS

The main complication of long-bone osteomyelitis is the persistence of infection with progression to chronic osteomyelitis. This risk is especially high after internal fixation of an open fracture and among patients with implant-associated osteomyelitis that is treated without surgical debridement. In chronic osteomyelitis, recurrent sinus tracts result in severe damage to skin and soft tissue (Fig. 126-2). Patients who have chronic open wounds need a therapeutic approach combining orthopedic repair and plastic reconstructive surgery.

GLOBAL CONSIDERATIONS

In North American and Western European countries, tuberculous osteomyelitis is extremely rare, occurring mainly in very old people, in HIV-infected patients, and in immigrants from endemic countries. In contrast, in countries where the prevalence of tuberculosis is high (India, Indonesia, China), tuberculous osteomyelitis must routinely be considered.

PERIPROSTHETIC JOINT INFECTION

PATHOGENESIS

Implanted foreign material is highly susceptible to local infection due to local immunodeficiency around the device. Infection occurs by either the exogenous or the hematogenous route. More rarely, contiguous spread from adjacent sites of osteomyelitis or deep soft-tissue infection may cause periprosthetic joint infection (PJI). The fact that foreign devices are covered with host proteins such as fibronectin favors the adherence of staphylococci and the formation of a biofilm that resists phagocytosis.

EPIDEMIOLOGY

The risk of infection manifesting during the first 2 postoperative years varies according to the joint. It is lowest after hip and knee arthroplasty (0.3–1.5%) and highest after ankle and elbow replacement (4–10%). The risk of hematogenous PJI is highest in the early postoperative period. However, hematogenous seeding occurs throughout life, and most cases therefore develop >2 years after implantation. The rate of risk for secondary PJI during *S. aureus* bacteremia is 30–40%.

MICROBIOLOGY

About 50–70% of cases of PJI are caused by staphylococci (*S. aureus* and coagulase-negative staphylococci), 6–10% by streptococci, 4–10% by gram-negative bacilli, and the rest by various other microorganisms. In some centers, the fraction of PJI cases caused by gram-negative bacilli is much higher for unknown reasons. All microorganisms can cause PJI, including fungi and mycobacteria. *P. acnes* causes up to one-third of episodes of periprosthetic shoulder infection.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

PJI is traditionally classified as early (<3 months after implantation), delayed (3–24 months after surgery), or late (>2 years after implantation). For therapeutic decision-making (see below), it is more useful to classify PJI as (1) acute hematogenous PJI with <3 weeks of symptoms, (2) early postinterventional PJI manifesting within 1 month after surgery, or (3) chronic PJI with symptom duration of >3 weeks.

Acute exogenous PJI typically presents with local signs of infection (Fig. 126-3). In contrast, acute hematogenous PJI, most often caused by *S. aureus*, is characterized by new-onset pain that initially is not accompanied by prominent local inflammatory signs. In most cases, an ongoing sepsis syndrome dominates the clinical picture. Key findings in chronic PJI are joint effusion, local pain, implant loosening, and occasionally a sinus tract. Chronic PJI is most commonly caused by low-virulence microorganisms such as coagulase-negative staphylococci or *P. acnes*. These infections are characterized by nonspecific symptoms, such as chronic pain caused by low-grade inflammation or early loosening.

DIAGNOSIS

Blood tests such as the measurement of CRP (elevated levels, ≥10 mg/L) and erythrocyte sedimentation rate (elevated rates, ≥30 mm/h) are sensitive (91–97%) but not specific (70–78%). Synovial fluid cell counts are ~90% sensitive and specific, with threshold values of 1700 leukocytes/μL in periprosthetic knee infection and 4200 leukocytes/μL in periprosthetic hip infection. In the future, α-defensin, a biomarker that can be tested in synovial fluid, may replace cell counts. This test is expensive but accurate and easy to perform. During debridement surgery, at least

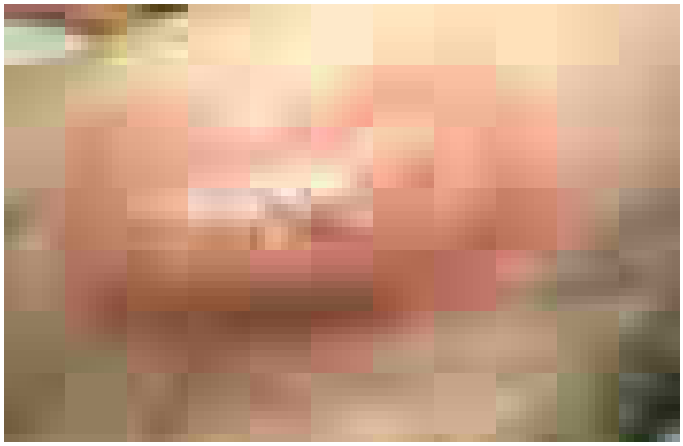

FIGURE 126-3 Acute postoperative periprosthetic joint infection of the left hip caused by group B streptococci in a 68-year-old woman.

three but optimally six tissue samples should be obtained for culture and histopathology. If implant material (modular parts, screws, or the prosthesis) is removed, sonication of this material followed by culture and/or use of molecular methods to examine the sonicate fluid allows the detection of microorganisms in biofilms.

The three-phase bone scan is very sensitive for detecting PJI but is not specific. As mentioned above, this test does not differentiate bone remodeling from infection and therefore is not useful during at least the first year after implantation. CT and MRI detect soft tissue infection, prosthetic loosening, and bone erosion, but imaging artifacts caused by metal implants limit their use. ^{18}F-fluorodeoxyglucose PET (^{18}F-FD-PET) is an alternative method with fair sensitivity and specificity for the detection of PJI. However, ^{18}F-FDG-PET/CT still is not an established technique for the diagnosis of PJI because of controversial published results.

TREATMENT

Periprosthetic Joint Infection

Treatment of PJI requires a multidisciplinary approach involving an experienced orthopedic surgeon, an infectious disease specialist, a plastic reconstructive surgeon, and a microbiologist. Therefore, most patients are referred to a specialized center. In general, the goal of treatment is cure—i.e., a pain-free functional joint with complete eradication of the infecting pathogen(s). However, for patients with severe comorbidity, lifelong suppressive antimicrobial therapy may be preferred. As a rule, antimicrobial therapy without surgical intervention is not curative but merely suppressive. There are four curative surgical options: debridement and implant retention, one-stage implant exchange, two-stage implant exchange, and implant removal without replacement. Implant retention offers a good chance of infection-free survival (>80%) only if the following conditions are fulfilled: (1) acute infection, (2) stable implant, (3) pathogen susceptible to a biofilm-active antimicrobial agent (see below), and (4) skin and soft tissue in good condition.

Table 126-2 summarizes pathogen-specific antimicrobial therapy for PJI. Initial IV therapy is followed by long-term oral antibiotics. Efficacious treatment is best defined in staphylococcal implant-associated infections. Rifampin exhibits excellent activity against biofilms composed of susceptible staphylococci. Because of the risk of rapid emergence of resistance, rifampin must always be combined with another effective antibiotic. If gram-negative infections are treated with implant retention, fluoroquinolones should be used because of their activity against gram-negative biofilms.

PREVENTION OF HEMATOGENOUS INFECTION

As mentioned above, hematogenous seeding may occur throughout life. This risk is highest during *S. aureus* bacteremia from a distant focus. Therefore, documented bacterial infections should be promptly treated in patients with prosthetic joints. However, according to a large prospective case–control study, the risk of prosthetic hip or knee infection is not increased following dental procedures. Therefore, antibiotic prophylaxis is not needed during dental work.

GLOBAL CONSIDERATIONS

Rifampin and fluoroquinolones are still the only antimicrobial agents with good activity against staphylococcal and gram-negative biofilms, respectively. Thus, in countries with high rates of rifampin resistance in staphylococci and/or high rates of fluoroquinolone resistance in gram-negative bacilli, debridement with implant retention generally does not yield a good cure rate.

STERNAL OSTEOMYELITIS

PATHOGENESIS

Sternal osteomyelitis occurs primarily after sternal surgery (with the entry of exogenous organisms) and more rarely by hematogenous seeding or contiguous extension from adjacent sites of sternocostal arthritis. Exogenous sternal osteomyelitis after open sternal surgery is also called *deep sternal-wound infection.* Exogenous infection may follow minor sternal trauma, sternal fracture, and manubriosternal septic arthritis. Tuberculous sternal osteomyelitis typically manifests during hematogenous seeding in children or as reactivated infection in adults. Reactivation is sometimes preceded by blunt trauma. In rare cases, tuberculous sternal osteomyelitis is caused by continuous infection from an infected internal mammary lymph node.

EPIDEMIOLOGY

The incidence of poststernotomy wound infection varies from 0.5 to 2%, but figures are even higher among patients with risk factors such as diabetes, obesity, chronic renal failure, emergency surgery, use of bilateral internal mammary arteries, and re-exploration for bleeding. Rapid diagnosis and correct management of superficial sternal wound infection prevent its progression to sternal osteomyelitis. Primary (hematogenous) sternal osteomyelitis accounts for only 0.3% of all cases of osteomyelitis. Risk factors are IV drug use, HIV infection, radiotherapy, blunt trauma, cardiopulmonary resuscitation, alcohol abuse, liver cirrhosis, and hemoglobinopathy.

MICROBIOLOGY

Poststernotomy osteomyelitis is generally caused by *S. aureus* (10–20% of cases), coagulase-negative staphylococci (40–60%), gram-negative bacilli (15–25%), or *P. acnes* (2–10%). Fungal infections caused by *Candida* species also play a role. The fact that ~20% of cases are polymicrobial is indicative of exogenous superinfection during therapy. Hematogenous sternal osteomyelitis is caused most commonly by *S. aureus*. Other microorganisms play a role in special populations—e.g., *P. aeruginosa* in IV drug users, *Salmonella* species in individuals with sickle cell anemia, and *M. tuberculosis* in patients from endemic areas who have previously had tuberculosis.

CLINICAL MANIFESTATIONS

Exogenous sternal osteomyelitis manifests as fever, increased local pain, erythema, wound discharge, and sternal instability **(Fig. 126-4)**. Contiguous mediastinitis is a feared complication, occurring in ~10–30% of patients with sternal osteomyelitis. Hematogenous sternal osteomyelitis is characterized by sternal pain, swelling, and erythema. In addition, most patients have systemic signs and symptoms of sepsis.

The differential diagnosis of hematogenous sternal osteomyelitis includes immunologic processes typically presenting as systemic or multifocal inflammation of the sternum or of the sternoclavicular or sternocostal joints (e.g., SAPHO [synovitis, acne, pustulosis, hyperostosis, osteitis], vasculitis, and chronic multifocal relapsing osteomyelitis).

DIAGNOSIS

In primary sternal osteomyelitis, the diagnostic workup does not differ from that in other types of hematogenous osteomyelitis (see above).

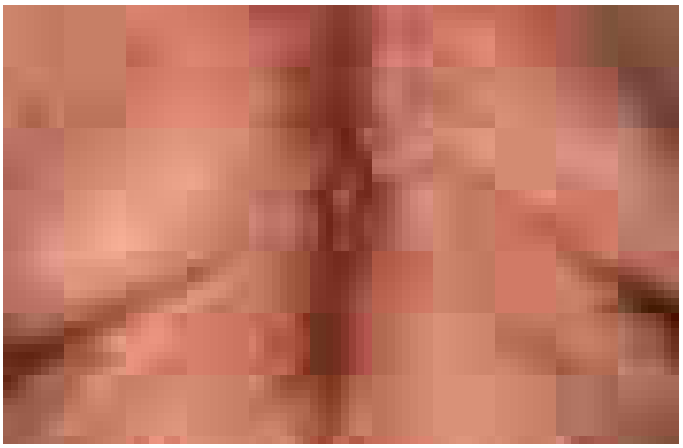

FIGURE 126-4 Sternal osteomyelitis caused by *Staphylococcus epidermidis* 5 weeks after sternotomy for aortocoronary bypass in a 72-year-old man.

When a patient has grown up in regions where tuberculosis is endemic, a specific workup for mycobacterial infection should be performed, especially if osteomyelitis had its onset after a blunt sternal trauma. In secondary sternal osteomyelitis, leukocyte counts may be normal, but the CRP level is >100 mg/L in most cases. Tissue sampling for microbiologic studies is crucial. In osteomyelitis associated with sternal wires, low-virulence microorganisms, such as coagulase-negative staphylococci, play an important role. In order to differentiate between colonization and infection, samples from at least three deep biopsies should be subjected to microbiologic examination. Superficial swab cultures are not diagnostic and may be misleading. No studies have compared the value of the various imaging modalities in suspected primary sternal osteomyelitis. However, MRI is the current gold standard for detection of each type of osteomyelitis.

TREATMENT

Sternal Osteomyelitis

In cases of deep sternal-wound infection, antibiotic therapy should be started immediately after samples have been obtained for microbiologic analyses in order to control clinical sepsis. To protect a newly inserted heart valve, initial treatment should be directed against staphylococci, with consideration of the local susceptibility pattern. In centers with a high prevalence of methicillin-resistant *S. aureus*, vancomycin or daptomycin should be added to a broad-spectrum β-lactam drug. As soon as cultures of blood and/or deep wound biopsies have confirmed the pathogen's identity and susceptibility pattern, treatment should be optimized and narrowed accordingly. Tables 126-1 and 126-2 show appropriate therapeutic choices for the most frequently identified microorganisms causing sternal osteomyelitis in the absence and presence, respectively, of an implanted device. In a recent observational study of patients with staphylococcal deep sternal-wound infection, the use of a rifampin-containing regimen was predictive of success. The optimal duration of antibiotic therapy has not been established. In acute sternal osteomyelitis without hardware, a 6-week course is the rule. In patients with remaining sternal wires, treatment duration is generally prolonged to 3 months (Table 126-2). Like other types of tuberculous bone infection, tuberculous sternal osteomyelitis is treated for 6–12 months.

Primary sternal osteomyelitis can generally be treated without surgery. In contrast, in secondary sternal osteomyelitis, debridement is always required. This procedure should be performed by a team of experienced surgeons, since mediastinitis, bone infection, and skin and soft tissue damage may need to be treated during the same intervention.

PROGNOSIS

Primary sternal osteomyelitis poses a minimal mortality risk. In contrast, the in-hospital mortality rates from secondary sternal osteomyelitis are 15–30% after sternal surgery.

GLOBAL CONSIDERATIONS

In endemic areas, microorganisms such as *M. tuberculosis*, *Salmonella* species, and *Brucella* species should be considered during sampling for microbiologic diagnosis.

FOOT OSTEOMYELITIS

PATHOGENESIS

Osteomyelitis of the foot usually occurs in patients with diabetes, peripheral arterial insufficiency, or peripheral neuropathy and after foot surgery. These entities are often linked to each other, especially in diabetic patients with late complications. However, foot osteomyelitis is also seen in patients with isolated peripheral neuropathy and can manifest as implant-associated osteomyelitis in patients without comorbidity due to a deep wound infection after foot surgery (hallux valgus surgery, arthrodesis, total ankle arthroplasty). Foot osteomyelitis is acquired almost exclusively by the exogenous route. It is a complication of deep pressure ulcers and of impaired wound healing after surgery.

EPIDEMIOLOGY

The incidence of diabetic foot infection is 30–40 cases/1000 persons with diabetes per year. The condition starts with skin and soft tissue lesions and progresses to osteomyelitis, especially in patients with risk factors. About 20–60% of patients with diabetic foot infection have confirmed osteomyelitis. Diabetic foot osteomyelitis increases the risk of amputation. With adequate management of the early stage of diabetic foot infections, the rate of amputation can be lowered.

RISK FACTORS

Risk factors for diabetic foot infection are (1) peripheral motor, sensory, and autonomic neuropathy; (2) neuro-osteoarthropathic deformities (Charcot foot; Fig. 126-5); (3) arterial insufficiency; (4) uncontrolled hyperglycemia; (5) disabilities such as reduced vision; and (6) maladaptive behavior.

MICROBIOLOGY

The correlation between cultures from bone biopsy and those from wound swabs or even deep soft-tissue punctures is poor. In a study of 31 patients with simultaneous sampling, the correlation between needle biopsy and bone biopsy cultures was only 24%. The correlation is better when *S. aureus* is isolated (40–50%) than when anaerobes (20–35%), gram-negative bacilli (20–30%), or coagulase-negative staphylococci (0–20%) are identified. When only bone-biopsy samples are considered, the leading pathogens are *S. aureus* (25–40%), anaerobes (5–20%), and various gram-negative bacilli (18–40%). The precise distribution depends on whether the patient has already been treated with antibiotics. Anaerobes are especially prevalent in chronic wounds. Pretreatment typically selects for *P. aeruginosa*, methicillin-resistant *S. aureus*, or enterococci.

DIAGNOSIS

In many cases, foot osteomyelitis can be diagnosed clinically, without imaging procedures. Most clinicians rely on the "probe-to-bone" test, which has a positive predictive value of ~90% in populations with a high pretest probability. Thus, in a patient with diabetes who is hospitalized for a chronic deep foot ulcer, the diagnosis of foot osteomyelitis is highly probable if bone can be directly touched with a metal instrument. In a patient with a lower pretest probability, MRI should

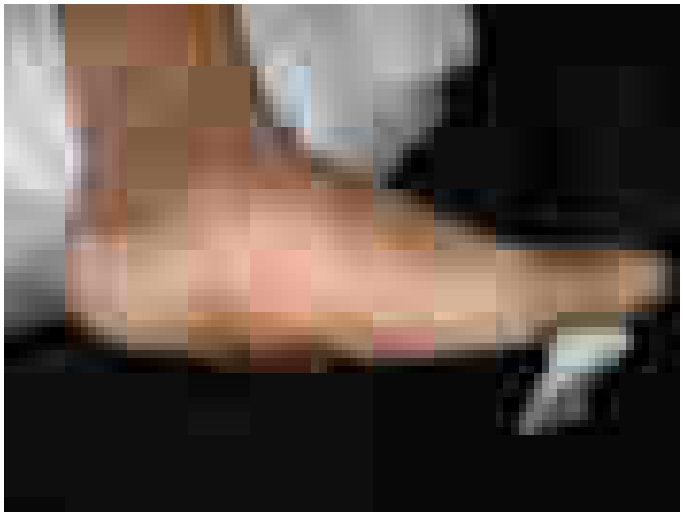

FIGURE 126-5 Neuropathic joint disease (Charcot foot) complicated by chronic foot osteomyelitis in a 78-year-old woman with diabetes mellitus complicated by severe neuropathy.

be performed because of its high degree of sensitivity (80–100%) and specificity (80–90%). Plain radiography has a sensitivity of only 30–90% and a specificity of only 50–90%; it may be considered for follow-up of patients with confirmed diabetic foot osteomyelitis.

TREATMENT

Foot Osteomyelitis

As mentioned above, correlation between cultures of bone and those of wound swabs or wound punctures is poor. Antibiotic treatment should be based on bone culture. If no bone biopsy is performed, empirical therapy chosen in light of the most common infecting agents and the type of clinical syndrome should be given. Wound debridement combined with a 4- to 6-week course of antibiotics renders amputation unnecessary in about two-thirds of patients. According to the 2012 Infectious Diseases Society of America's clinical practice guideline for the diagnosis and treatment of diabetic foot infections, the following management strategies should be considered. If a foot ulcer is clinically infected, prompt empirical antimicrobial therapy may prevent progression to osteomyelitis. When the risk of methicillin-resistant *S. aureus* is considered high, an agent active against these strains (e.g., vancomycin) should be chosen. If the patient has not recently received antibiotics, the spectrum of the selected antibiotic must include gram-positive cocci (e.g., clindamycin, ampicillin-sulbactam). If the patient has received antibiotics within the past month, the spectrum of empirical antibiotics should include gram-negative bacilli (e.g., clindamycin plus a fluoroquinolone). If the patient has risk factors for *Pseudomonas* infection (previous colonization, residence in a warm climate, frequent exposure of the foot to water), an empirical antipseudomonal agent (e.g., piperacillin-tazobactam, cefepime) is indicated. If osteomyelitis is suspected either on clinical grounds (probe to bone) or on the basis of imaging procedures (MRI), bone biopsy should be performed. If infected bone is not entirely removed by surgery, the patient should be treated for 4–6 weeks in line with the identified pathogen(s) and their susceptibility. Treatment should initially be given by the IV route. Whether therapy can later be administered by the oral route depends on the bioavailability of oral drugs that cover the infecting agents. If dead bone cannot be removed, long-term therapy (at least 3 months) should be considered. In such cases, cure of osteomyelitis is usually the exception, and repetitive suppressive treatment may be needed.

GLOBAL CONSIDERATIONS

The number of multiresistant microorganisms causing diabetic foot infection is increasing. The prevalence of methicillin-resistant *S. aureus* is 5–43% in various countries. In a study of 102 patients with diabetic foot infection from India, 69% of aerobic gram-negative bacilli produced extended-spectrum β-lactamase and 43% of *S. aureus* isolates were methicillin resistant. Risk factors for multidrug-resistant microorganisms are poor glycemic control, prolonged duration of infection, and large ulcer size.

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127 Intraabdominal Infections and Abscesses

Miriam Baron Barshak, Dennis L. Kasper

Intraperitoneal infections generally arise because a normal anatomic barrier is disrupted. This disruption may result from a variety of causes—e.g., when the appendix, a diverticulum, or an ulcer ruptures; when the bowel wall is weakened by ischemia, tumor, or inflammation (e.g., in inflammatory bowel disease); or with adjacent inflammatory processes, such as pancreatitis or pelvic inflammatory disease, in which enzymes (in the former case) or organisms (in the latter) may leak into the peritoneal cavity. Whatever the inciting event, once inflammation develops and organisms usually contained within the bowel or another organ enter the normally sterile peritoneal space, a knowable series of events takes place. Intraabdominal infections occur in two stages: peritonitis and—if the patient survives this stage and goes untreated—abscess formation. The types of microorganisms predominating in each stage of infection are responsible for the pathogenesis of disease.

PERITONITIS

Peritonitis is a life-threatening event that is often accompanied by bacteremia and sepsis syndrome **(Chap. 297)**. The peritoneal cavity is large but is divided into compartments. The upper and lower peritoneal cavities are divided by the transverse mesocolon; the greater omentum extends from the transverse mesocolon and from the lower pole of the stomach to line the lower peritoneal cavity. The pancreas, duodenum, and ascending and descending colon are located in the anterior retroperitoneal space; the kidneys, ureters, and adrenals are found in the posterior retroperitoneal space. The other organs, including the liver, stomach, gallbladder, spleen, jejunum, ileum, transverse and sigmoid colon, cecum, and appendix, are within the peritoneal cavity. The cavity is lined with a serous membrane that can serve as a conduit for fluids—a property exploited in peritoneal dialysis **(Fig. 127-1)**. A small amount of serous fluid is normally present in the peritoneal space, with a protein content (consisting mainly of albumin) of <30 g/L

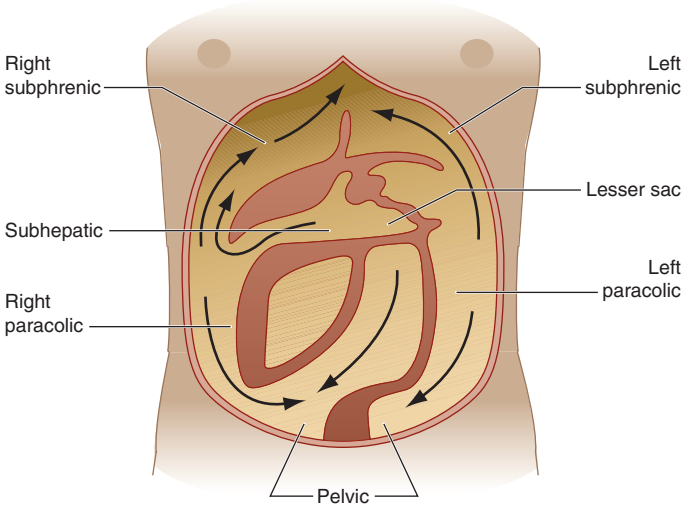

FIGURE 127-1 Diagram of the intraperitoneal spaces, showing the circulation of fluid and potential areas for abscess formation. Some compartments collect fluid or pus more often than others. These compartments include the pelvis (the lowest portion), the subphrenic spaces on the right and left sides, and Morrison's pouch, which is a posterosuperior extension of the subhepatic spaces and is the lowest part of the paravertebral groove when a patient is recumbent. The falciform ligament separating the right and left subphrenic spaces appears to act as a barrier to the spread of infection; consequently, it is unusual to find bilateral subphrenic collections. *(Reprinted with permission from B Lorber [ed]: Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, p 1.13.)*

and <300 white blood cells (WBCs, generally mononuclear cells) per microliter. In bacterial infections, leukocyte recruitment into the infected peritoneal cavity consists of an early influx of polymorphonuclear leukocytes (PMNs) and a prolonged subsequent phase of mononuclear cell migration. The phenotype of the infiltrating leukocytes during the course of inflammation is regulated primarily by resident-cell chemokine synthesis.

PRIMARY (SPONTANEOUS) BACTERIAL PERITONITIS

Peritonitis is either primary (without an apparent source of contamination) or secondary. The types of organisms found and the clinical presentations of these two processes are different. In adults, primary bacterial peritonitis (PBP) occurs most commonly in conjunction with cirrhosis of the liver (frequently the result of alcoholism). However, the disease has been reported in adults with metastatic malignant disease, postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, systemic lupus erythematosus, and lymphedema as well as in patients with no underlying disease. Although PBP virtually always develops in patients with preexisting ascites, it is, in general, an uncommon event, occurring in ≤10% of cirrhotic patients. The cause of PBP has not been established definitively but is believed to involve hematogenous spread of organisms in a patient in whom a diseased liver and altered portal circulation result in a defect in the usual filtration function. Organisms multiply in ascites, a good medium for growth. Proteins of the complement cascade are found in peritoneal fluid, with lower levels in cirrhotic patients than in patients with ascites of other etiologies. The opsonic and phagocytic properties of PMNs are diminished in patients with advanced liver disease. Cirrhosis is associated with alterations in the gut microbiota, including an increased prevalence of potentially pathogenic bacteria such as Enterobacteriaceae. Small-intestinal bacterial overgrowth is frequently present in advanced stages of liver cirrhosis and has been linked with pathologic bacterial translocation and PBP. Factors promoting these changes in cirrhosis may include deficiencies in Paneth cell defensins, reduced intestinal motility, decreased pancreatobiliary secretions, and portal-hypertensive enteropathy.

The presentation of PBP differs from that of secondary peritonitis. The most common manifestation is fever, which is reported in up to 80% of patients. Ascites is found but virtually always predates infection. Abdominal pain, an acute onset of symptoms, and peritoneal irritation during physical examination can be helpful diagnostically, but the absence of any of these findings does not exclude this often-subtle diagnosis. Nonlocalizing symptoms (such as malaise, fatigue, or encephalopathy) without another clear etiology should also prompt consideration of PBP in a susceptible patient. It is vital to sample the peritoneal fluid of any cirrhotic patient with ascites and fever. The finding of >250 PMNs/μL is diagnostic for PBP, according to Conn. This criterion does not apply to secondary peritonitis (see below). The microbiology of PBP is also distinctive. While enteric gram-negative bacilli such as *Escherichia coli* are most commonly encountered, gram-positive organisms such as streptococci, enterococci, or even pneumococci are sometimes found. In an important development, widespread use of quinolones to prevent PBP in high-risk subgroups of patients, frequent hospitalizations, and exposure to broad-spectrum antibiotics have led to a change in the etiology of infections in patients with cirrhosis, with more gram-positive bacteria and extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae in recent years. Risk factors for multidrug-resistant infections include nosocomial origin of infection, long-term norfloxacin prophylaxis, recent infection with multiresistant bacteria, and recent use of β-lactam antibiotics. In PBP, a single organism is typically isolated; anaerobes are found less frequently in PBP than in secondary peritonitis, in which a mixed flora including anaerobes is the rule. In fact, if PBP is suspected and multiple organisms including anaerobes are recovered from the peritoneal fluid, the diagnosis must be reconsidered and a source of secondary peritonitis sought.

The diagnosis of PBP is not easy. It depends on the exclusion of a primary intraabdominal source of infection. Contrast-enhanced CT is useful in identifying an intraabdominal source for infection. It may be difficult to recover organisms from cultures of peritoneal fluid, presumably because the burden of organisms is low. However, the yield can be improved if 10 mL of peritoneal fluid is placed directly into a blood culture bottle. Because bacteremia frequently accompanies PBP, blood should be cultured simultaneously. To maximize the yield, culture samples should be collected prior to administration of antibiotics. No specific radiographic studies are helpful in the diagnosis of PBP. A plain film of the abdomen would be expected to show ascites. Chest and abdominal radiography should be performed when patients have abdominal pain to exclude free air, which signals a perforation **(Fig. 127-2)**.

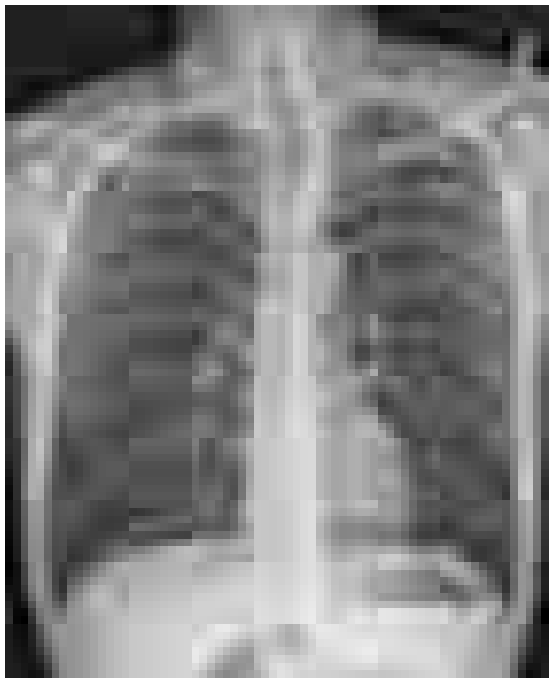

FIGURE 127-2 Pneumoperitoneum. Free air under the diaphragm on an upright chest film suggests the presence of a bowel perforation and associated peritonitis. *(Image courtesy of Dr. John Braver; with permission.)*

TREATMENT

Primary Bacterial Peritonitis

Treatment for PBP is directed at the isolate from blood or peritoneal fluid. Gram's staining of peritoneal fluid often gives negative results in PBP. Therefore, until culture results become available, therapy should cover gram-negative aerobic bacilli and gram-positive cocci. Third-generation cephalosporins such as cefotaxime (2 g q8h, administered IV) provide reasonable initial coverage in moderately ill patients. Broad-spectrum antibiotics, such as penicillin/β-lactamase inhibitor combinations (e.g., piperacillin/tazobactam, 3.375 g q6h IV for adults with normal renal function) or ceftriaxone (2 g q24h IV), are also options. Broader empirical coverage aimed at resistant hospital-acquired gram-negative bacteria (e.g., treatment with a carbapenem) may be appropriate for nosocomially acquired PBP until culture results become available. Empirical coverage for anaerobes is not necessary. A mortality benefit from albumin (1.5 g/kg of body weight within 6 h of detection and 1.0 g/kg on day 3) has been demonstrated for patients who present with serum creatinine levels ≥1 mg/dL, blood urea nitrogen levels ≥30 mg/dL, or total bilirubin levels ≥4 mg/dL but not for patients who do not meet these criteria. After the infecting organism is identified, therapy should be narrowed to target the specific pathogen. Patients with PBP usually respond within 72 h to appropriate antibiotic therapy. Antimicrobial treatment can be administered for as little as 5 days if rapid improvement occurs and blood cultures are negative, but a course of up to 2 weeks may be required for patients with bacteremia and for those

whose improvement is slow. Persistence of WBCs in the ascitic fluid after therapy should prompt a search for additional diagnoses.

Prevention • **PRIMARY PREVENTION** Several observational studies and a meta-analysis raise the concern that gastric acid suppression may increase the risk of PBP. No prospective studies have yet addressed whether avoidance of such therapy may prevent PBP. Nonselective beta blockers may prevent secondary bacterial peritonitis. A 2012 guideline from the American Association for the Study of Liver Diseases recommends chronic antibiotic prophylaxis with a regimen described in the next section for patients who are at highest risk for PBP—that is, those with an ascitic-fluid total protein level <1.5 g/dL along with impaired renal function (creatinine, ≥1.2 mg/dL; blood urea nitrogen, ≥25 mg/dL; or serum sodium, ≤130 mg/dL) and/or liver failure (Child-Pugh score, ≥9; and bilirubin, ≥3 mg/dL). A 7-day course of antibiotic prophylaxis is recommended for patients with cirrhosis and gastrointestinal bleeding.

SECONDARY PREVENTION PBP has a high rate of recurrence. Up to 70% of patients experience a recurrence within 1 year. Antibiotic prophylaxis is recommended for patients with a history of PBP to reduce this rate to <20% and improve short-term survival rates. Prophylactic regimens for adults with normal renal function include fluoroquinolones (ciprofloxacin, 500 mg weekly; or norfloxacin [not available in the United States], 400 mg/d) or trimethoprim-sulfamethoxazole (one double-strength tablet daily). However, long-term administration of broad-spectrum antibiotics in this setting has been shown to increase the risk of severe staphylococcal infections.

SECONDARY PERITONITIS

Secondary peritonitis develops when bacteria contaminate the peritoneum as a result of spillage from an intraabdominal viscus. The organisms found almost always constitute a mixed flora in which facultative gram-negative bacilli and anaerobes predominate, especially when the contaminating source is colonic. Early in the course of infection, when the host response is directed toward containment, exudate containing fibrin and PMNs is found. Early death in this setting is attributable to gram-negative bacillary sepsis and to potent endotoxins circulating in the bloodstream **(Chap. 297)**. Gram-negative bacilli, particularly *E. coli*, are common bloodstream isolates, but *Bacteroides fragilis* bacteremia also occurs. The severity of abdominal pain and the clinical course depend on the inciting process. The organisms isolated from the peritoneum also vary with the source of the initial process and the normal flora at that site. Secondary peritonitis can result primarily from chemical irritation and/or bacterial contamination. For example, as long as the patient is not achlorhydric, a ruptured gastric ulcer will release low-pH gastric contents that will serve as a chemical irritant. The normal flora of the stomach comprises the same organisms found in the oropharynx but in lower numbers. Thus, the bacterial burden in a ruptured ulcer is negligible compared with that in a ruptured appendix. The normal flora of the colon below the ligament of Treitz contains ~10^{11} anaerobic organisms/g of feces but only 10^8 aerobes/g; therefore, anaerobic species account for 99.9% of the bacteria **(Chap. 459)**. Leakage of colonic contents (pH 7–8) does not cause significant chemical peritonitis, but infection is intense because of the heavy bacterial load.

Depending on the inciting event, local symptoms may occur in secondary peritonitis—for example, epigastric pain from a ruptured gastric ulcer. In appendicitis **(Chap. 324)**, the initial presenting symptoms are often vague, with periumbilical discomfort and nausea followed in a number of hours by pain more localized to the right lower quadrant. Unusual locations of the appendix (including a retrocecal position) can complicate this presentation further. Once infection has spread to the peritoneal cavity, pain increases, particularly with infection involving the parietal peritoneum, which is innervated extensively. Patients usually lie motionless, often with knees drawn up to avoid stretching the nerve fibers of the peritoneal cavity. Coughing and sneezing, which increase pressure within the peritoneal cavity, are associated with sharp pain. There may or may not be pain localized to the infected or diseased organ from which secondary peritonitis has arisen. Patients with secondary peritonitis generally have abnormal findings on abdominal examination, with marked voluntary and involuntary guarding of the anterior abdominal musculature. Later findings include tenderness, especially rebound tenderness. In addition, there may be localized findings in the area of the inciting event. In general, patients are febrile, with marked leukocytosis and a left shift of the WBCs to band forms.

While recovery of organisms from peritoneal fluid is easier in secondary than in primary peritonitis, a tap of the abdomen is rarely the procedure of choice in secondary peritonitis. An exception is in cases involving trauma, where the possibility of a hemoperitoneum may need to be excluded early. Emergent studies (such as abdominal CT) to find the source of peritoneal contamination should be undertaken if the patient is hemodynamically stable; unstable patients may require surgical intervention without prior imaging. Results of cultures from drain sites are not reliable for defining the etiology of infections.

TREATMENT

Secondary Peritonitis

Treatment for secondary peritonitis includes early administration of antibiotics aimed particularly at aerobic gram-negative bacilli and anaerobes (see below). The most appropriate regimen depends on the anticipated flora and the degree of illness. Community-acquired infections associated with mild to moderate disease can be treated with many drugs covering these organisms, including broad-spectrum penicillin/β-lactamase inhibitor combinations (e.g., ticarcillin/clavulanate, 3.1 g q4–6h IV; or piperacillin/tazobactam, 3.375 g q6h IV) or a combination of either a fluoroquinolone (e.g., levofloxacin, 750 mg q24h IV) or a third-generation cephalosporin (e.g., ceftriaxone, 2 g q24h IV) plus metronidazole (500 mg q8h IV). Patients in intensive care units and/or those with health care–associated infections should receive antibiotics targeting more resistant gram-negative organisms such as *Pseudomonas aeruginosa*—e.g., imipenem (500 mg q6h IV), meropenem (1 g q8h IV), higher-dose piperacillin/tazobactam (4.5 g IV q6h), or drug combinations such as cefepime (2 g IV q8h) or ceftazidime (2 g IV q8h) plus metronidazole. The role of enterococci and *Candida* species in mixed infections is controversial; however, because cephalosporin-based regimens lack activity against enterococci, ampicillin or vancomycin can be added to these regimens for enterococcal coverage in very ill patients until culture results are available. For patients known to be colonized with ampicillin-resistant, vancomycin-resistant enterococci (VRE), a VRE-active agent, such as linezolid or daptomycin, should be included. Antifungal coverage is warranted if there is growth of *Candida* species from a sterile site. Patients who are known to be colonized with highly resistant gram-negative organisms may require treatment with a newer agent such as ceftazidime/avibactam or ceftolozane/tazobactam. Secondary peritonitis usually requires both surgical intervention to address the inciting process and antibiotics to treat early bacteremia, to decrease the incidence of abscess formation and wound infection, and to prevent distant spread of infection. Although surgery is rarely indicated in PBP in adults, it may be life-saving in secondary peritonitis. Recombinant human activated protein C (APC) was considered at one time for treatment of severe sepsis from causes including secondary peritonitis but was withdrawn from the market in 2011 after it was determined that the drug was associated with an increased risk of bleeding and that evidence for its beneficial effects was inadequate. Thus APC should not be used for sepsis or septic shock outside randomized clinical trials.

Peritonitis may develop as a complication of abdominal surgeries. These infections may be accompanied by localizing pain and/or nonlocalizing signs or symptoms such as fever, malaise, anorexia, and toxicity. As a nosocomial infection, postoperative peritonitis may be associated with organisms such as staphylococci, components of the gram-negative hospital microflora, and the microbes that cause PBP and secondary peritonitis, as described above.

PERITONITIS IN PATIENTS UNDERGOING CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

A third type of peritonitis arises in patients who are undergoing continuous ambulatory peritoneal dialysis (CAPD). Unlike PBP and secondary peritonitis, which are caused by endogenous bacteria, CAPD-associated peritonitis usually involves skin organisms. The pathogenesis of infection is similar to that of intravascular device–related infection, in which skin organisms migrate along the catheter, which both serves as an entry point and exerts the effects of a foreign body. Exit-site or tunnel infection may or may not accompany CAPD-associated peritonitis. Like PBP, CAPD-associated peritonitis is usually caused by a single organism. Peritonitis is, in fact, the most common reason for discontinuation of CAPD. Improvements in equipment design, especially the Y-set connector, have resulted in a decrease from one case of peritonitis per 9 months of CAPD to one case per 24 months.

The clinical presentation of CAPD peritonitis resembles that of secondary peritonitis in that diffuse pain and peritoneal signs are common. The dialysate is usually cloudy and contains >100 WBCs/μL, >50% of which are neutrophils. However, the number of cells depends in part on dwell time. According to a guideline from the International Society for Peritoneal Dialysis (2016), for patients undergoing automated peritoneal dialysis who present during their nighttime treatment and whose dwell time is much shorter than with CAPD, the clinician should use the percentage of PMNs rather than the absolute number of WBCs to diagnose peritonitis. As the normal peritoneum has very few PMNs, a proportion above 50% is strong evidence of peritonitis even if the absolute WBC count does not reach 100/μL. Meanwhile, patients undergoing automated peritoneal dialysis without a daytime exchange who present with abdominal pain may have no fluid to withdraw, in which case 1 L of dialysate should be infused and permitted to dwell a minimum of 1–2 h, then drained, examined for turbidity, and sent for cell count with differential and culture. The differential (with a shortened dwell time) may be more useful than the absolute WBC count. In equivocal cases or in patients with systemic or abdominal symptoms in whom the effluent appears clear, a second exchange is performed, with a dwell time of at least 2 h. Clinical judgment should guide initiation of therapy.

The most common organisms are *Staphylococcus* species, which accounted for ~45% of cases in one series. Historically, coagulase-negative staphylococcal species were identified most commonly in these infections, but these isolates have more recently been decreasing in frequency. *Staphylococcus aureus* is more often involved among patients who are nasal carriers of the organism than among those who are not, and this organism is the most common pathogen in overt exit-site infections. Gram-negative bacilli and fungi such as *Candida* species are also found. Vancomycin-resistant enterococci and vancomycin-intermediate *S. aureus* have been reported to produce peritonitis in CAPD patients. The finding of more than one organism in dialysate culture should prompt evaluation for secondary peritonitis. As with PBP, culture of dialysate fluid in blood culture bottles improves the yield. To facilitate diagnosis, several hundred milliliters of removed dialysis fluid should be concentrated by centrifugation before culture.

TREATMENT

CAPD Peritonitis

Empirical therapy for CAPD peritonitis should be directed at *S. aureus*, coagulase-negative *Staphylococcus*, and gram-negative bacilli until the results of cultures become available. Guidelines suggest that agents should be chosen on the basis of local experience with resistant organisms. In some centers, a first-generation cephalosporin such as cefazolin (for gram-positive bacteria) and a fluoroquinolone or a third-generation cephalosporin such as ceftazidime (for gram-negative bacteria) may be reasonable; in areas with high rates of infection with methicillin-resistant *S. aureus*, vancomycin should be used instead of cefazolin, and gram-negative coverage may need to be broadened—e.g., with an aminoglycoside, ceftazidime, cefepime, or a carbapenem. Broad coverage including vancomycin should be particularly considered for patients with septic physiology or exit-site infections. Vancomycin should also be included in the regimen if the patient has a history of colonization or infection with methicillin-resistant *S. aureus* or has a history of severe allergy to penicillins and cephalosporins. Loading doses are administered intraperitoneally; doses depend on the dialysis method and the patient's renal function. Antibiotics are given either continuously (i.e., with each exchange) or intermittently (i.e., once daily, with the dose allowed to remain in the peritoneal cavity for at least 6 h). If the patient is severely ill, IV antibiotics should be added at doses appropriate for the patient's degree of renal failure. The clinical response to an empirical treatment regimen should be rapid; if the patient has not responded after 48–96 h of treatment, new samples should be collected for cell counts and cultures, and catheter removal should be considered. For patients who lack exit-site or tunnel infection, the typical duration of antibiotic treatment is 14 days. For patients with exit-site or tunnel infection, catheter removal should be considered, and a longer duration of antibiotic therapy (up to 21 days) may be appropriate. In fungal infections, the catheter should be removed immediately.

TUBERCULOUS PERITONITIS

See Chap. 173.

INTRAABDOMINAL ABSCESSES

INTRAPERITONEAL ABSCESSES

Abscess formation is common in untreated peritonitis if overt gram-negative sepsis either does not develop or develops but is not fatal. In experimental models of abscess formation, mixed aerobic and anaerobic organisms have been implanted intraperitoneally. Without therapy directed at anaerobes, animals develop intraabdominal abscesses. As in humans, these experimental abscesses may stud the peritoneal cavity, lie within the omentum or mesentery, or even develop on the surface of or within viscera such as the liver.

Pathogenesis and Immunity There is often disagreement about whether an abscess represents a disease state or a host response. In a sense, it represents both: while an abscess is an infection in which viable infecting organisms and PMNs are contained in a fibrous capsule, it is also a process by which the host confines microbes to a limited space, thereby preventing further spread of infection. In any event, abscesses do cause significant symptoms, and patients with abscesses can be quite ill. Experimental work has helped to define both the host cells and the bacterial virulence factors responsible—most notably in the case of *B. fragilis*. This organism, although accounting for only 0.5% of the normal colonic flora, is the anaerobe most frequently isolated from intraabdominal infections, is especially prominent in abscesses, and is the most common anaerobic bloodstream isolate. On clinical grounds, therefore, *B. fragilis* appears to be uniquely virulent. Moreover, *B. fragilis* acts alone to cause abscesses in animal models of intraabdominal infection, whereas most other *Bacteroides* species must act synergistically with a facultative organism to induce abscess formation.

Of the several virulence factors identified in *B. fragilis*, one is critical: the capsular polysaccharide complex found on the bacterial surface. This complex comprises at least eight distinct surface polysaccharides. Structural analysis of these polysaccharides has shown an unusual motif of oppositely charged sugars. Polysaccharides having these *zwitterionic* characteristics, such as polysaccharide A, evoke a host response in the peritoneal cavity that localizes bacteria into abscesses. *B. fragilis* and polysaccharide A have been found to adhere to primary mesothelial cells in vitro; this adherence, in turn, stimulates the production of tumor necrosis factor α and intercellular adhesion molecule 1 by peritoneal macrophages. Although abscesses characteristically contain PMNs, the process of abscess induction depends on the stimulation of T lymphocytes by these unique zwitterionic polysaccharides.

The stimulated CD4+ T lymphocytes secrete leukoattractant cytokines and chemokines. The alternative pathway of complement and fibrinogen also participate in abscess formation.

While antibodies to the capsular polysaccharide complex enhance bloodstream clearance of *B. fragilis*, CD4+ T cells are critical in immunity to abscesses. When administered experimentally, *B. fragilis* polysaccharide A has immunomodulatory characteristics and stimulates CD4+ T regulatory cells via an interleukin 2–dependent mechanism to produce interleukin 10. Interleukin 10 downregulates the inflammatory response, thereby preventing abscess formation.

Clinical Presentation Of all intraabdominal abscesses, 74% are intraperitoneal or retroperitoneal and are not visceral. Most intraperitoneal abscesses result from fecal spillage from a colonic source, such as an inflamed appendix. Abscesses can also arise from other processes. They usually form within weeks of the development of peritonitis and may be found in a variety of locations from omentum to mesentery, pelvis to psoas muscles, and subphrenic space to a visceral organ such as the liver, where they may develop either on the surface of the organ or within it. Periappendiceal and diverticular abscesses occur commonly. Diverticular abscesses are least likely to rupture. Infections of the female genital tract and pancreatitis are also among the more common causative events. When abscesses occur in the female genital tract—either as a primary infection (e.g., tuboovarian abscess) or as an infection extending into the pelvic cavity or peritoneum—*B. fragilis* figures prominently among the organisms isolated. *B. fragilis* is not found in large numbers in the normal vaginal flora. For example, it is encountered less commonly in pelvic inflammatory disease and endometritis without an associated abscess. In pancreatitis with leakage of damaging pancreatic enzymes, inflammation is prominent. Therefore, clinical findings such as fever, leukocytosis, and even abdominal pain do not distinguish pancreatitis itself from complications such as pancreatic pseudocyst, pancreatic abscess **(Chap. 341)**, or intraabdominal collections of pus. Especially in cases of necrotizing pancreatitis, in which the incidence of local pancreatic infection may be as high as 30%, needle aspiration under CT guidance is performed to sample fluid for culture. Traditionally, many centers have prescribed preemptive antibiotics for patients with necrotizing pancreatitis. Imipenem is frequently used for this purpose because it reaches high tissue levels in the pancreas (although it is not unique in this regard). Randomized controlled studies have not demonstrated a benefit from this practice, and many guidelines no longer recommend preemptive antibiotics for patients with acute pancreatitis. If needle aspiration yields infected fluid in the setting of acute necrotizing pancreatitis, antibiotic treatment is appropriate in conjunction with surgical and/or percutaneous drainage of infected material. Infected pseudocysts that occur remotely from acute pancreatitis are unlikely to be associated with significant amounts of necrotic tissue and may be treated with either surgical or percutaneous catheter drainage in conjunction with appropriate antibiotic therapy.

Diagnosis Scanning procedures have considerably facilitated the diagnosis of intraabdominal abscesses. Abdominal CT probably has the highest yield, although ultrasonography is particularly useful for the right upper quadrant, kidneys, and pelvis. Both indium-labeled WBCs and gallium tend to localize in abscesses and may be useful in finding a collection. Because gallium is taken up in the bowel, indium-labeled WBCs may have a slightly greater yield for abscesses near the bowel. Neither indium-labeled WBC scans nor gallium scans serve as a basis for a definitive diagnosis, however; both need to be followed by other, more specific studies, such as CT, if an area of possible abnormality is identified. Abscesses contiguous with or contained within diverticula are particularly difficult to diagnose with scanning procedures. Although barium should not be injected if a perforation is suspected, a barium enema occasionally may detect a diverticular abscess not diagnosed by other procedures. If one study is negative, a second study sometimes reveals a collection. Although exploratory laparotomy has been less commonly used since the advent of CT, this procedure still must be undertaken on occasion if an abscess is strongly suspected on clinical grounds.

TREATMENT

Intraperitoneal Abscesses

An algorithm for the management of patients with intraabdominal (including intraperitoneal) abscesses by percutaneous drainage is presented in **Fig. 127-3**. Treatment of intraabdominal infections involves determination of the initial focus of infection, administration of broad-spectrum antibiotics targeting the organisms involved, and performance of a drainage procedure if one or more definitive abscesses have formed. Antimicrobial therapy, in general, is adjunctive to drainage and/or surgical correction of an underlying lesion or process in intraabdominal abscesses. Results of cultures from drain sites are not reliable for defining the etiology of infections. Unlike the intraabdominal abscesses resulting from most causes, for which drainage of some kind is generally required, abscesses associated with diverticulitis usually wall off locally after rupture of a diverticulum, so that surgical intervention is not routinely required.

A number of agents exhibit excellent activity against aerobic gram-negative bacilli. Because death in intraabdominal sepsis is linked to gram-negative bacteremia, empirical therapy for intraabdominal infection always needs to include adequate coverage of gram-negative aerobic, facultative, and anaerobic organisms. Even if anaerobes are not cultured from clinical specimens, they still must be covered by the therapeutic regimen. Empirical antibiotic therapy should be the same as that discussed above for secondary peritonitis. Most clinical treatment failures are due to failure to drain the abscess and thereby achieve source control. The appropriate duration of antibiotic treatment for abdominal abscesses depends on whether the presumptive source of the intraabdominal infection has been controlled. With adequate source control, antibiotic treatment may be limited to 4 or 5 days.

VISCERAL ABSCESSES

Liver Abscesses The liver is the organ most subject to the development of abscesses. In one study of 540 intraabdominal abscesses, 26% were visceral. Liver abscesses made up 13% of the total number, or 48% of all visceral abscesses. Liver abscesses may be solitary or multiple; they may arise from hematogenous spread of bacteria or from local spread from contiguous sites of infection within the peritoneal cavity. In the past, appendicitis with rupture and subsequent spread of infection was the most common source for a liver abscess. Currently, associated disease of the biliary tract is most common. Pylephlebitis (suppurative thrombosis of the portal vein), usually arising from infection in the

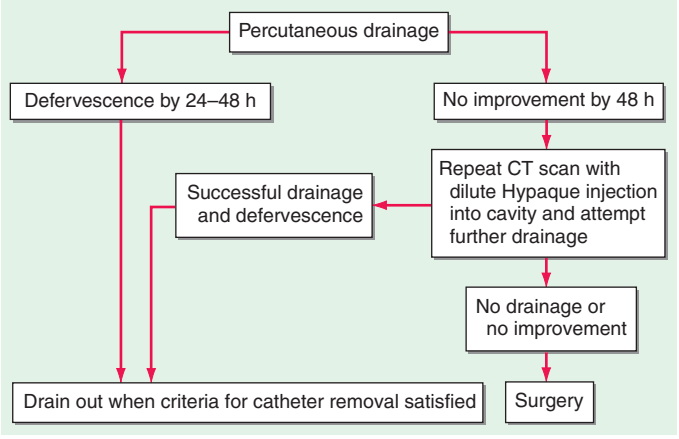

FIGURE 127-3 Algorithm for the management of patients with intraabdominal abscesses by percutaneous drainage. Antimicrobial therapy should be administered concomitantly. *(Reprinted with permission from B Lorber [ed]: Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, p 1.30, as adapted from OD Rotstein, RL Simmons, in SL Gorbach et al [eds]: Infectious Diseases. Philadelphia, Saunders, 1992, p 668.)*

pelvis but sometimes from infection elsewhere in the peritoneal cavity, is another common source for bacterial seeding of the liver.

Fever is the most common presenting sign of liver abscess. Some patients, particularly those with associated disease of the biliary tract, have symptoms and signs localized to the right upper quadrant, including pain, guarding, punch tenderness, and even rebound tenderness. Nonspecific symptoms, such as chills, anorexia, weight loss, nausea, and vomiting, may also develop. Only 50% of patients with liver abscesses, however, have hepatomegaly, right-upper-quadrant tenderness, or jaundice; thus, one-half of patients have no symptoms or signs to direct attention to the liver. Fever of unknown origin may be the only manifestation of liver abscess, especially in the elderly. Diagnostic studies of the abdomen, especially the right upper quadrant, should be a part of any workup for fever of unknown origin. The single most reliable laboratory finding is an elevated serum concentration of alkaline phosphatase, which is documented in 70% of patients with liver abscesses. Other tests of liver function may yield normal results, but 50% of patients have elevated serum levels of bilirubin, and 48% have elevated concentrations of aspartate aminotransferase. Other laboratory findings include leukocytosis in 77% of patients, anemia (usually normochromic, normocytic) in 50%, and hypoalbuminemia in 33%. Concomitant bacteremia is found in one-third to one-half of patients. A liver abscess is sometimes suggested by chest radiography, especially if a new elevation of the right hemidiaphragm is seen; other suggestive findings include a right basilar infiltrate and a right pleural effusion.

Imaging studies are the most reliable methods for diagnosing liver abscesses. These studies include ultrasonography, CT **(Fig. 127-4)**, indium-labeled WBC or gallium scan, and MRI. More than one such study may be required.

Organisms recovered from liver abscesses vary with the source. In liver infection arising from the biliary tree, enteric gram-negative aerobic bacilli and enterococci are common isolates. *Klebsiella pneumoniae* liver abscess has been well described in Southeast Asia for more than 20 years and has become an emerging syndrome in North America and elsewhere. These community-acquired infections have been linked to a virulent hypermucoviscous *K. pneumoniae* phenotype and to a specific genotype. The typical syndrome includes liver abscess, bacteremia, and metastatic infection. Ampicillin/amoxicillin therapy started within the previous 30 days has been associated with increased risk for this syndrome, presumably because of selection for the causative strain. Unless previous surgery has been performed, anaerobes are not generally involved in liver abscesses arising from biliary infections. In contrast, in liver abscesses arising from pelvic and other intraperitoneal sources, a mixed flora including both aerobic and anaerobic species is common; *B. fragilis* is the species most frequently isolated. With hematogenous spread of infection, usually only a single organism is encountered; this species may be *S. aureus* or a streptococcal species such as one in the *Streptococcus milleri* group. Liver abscesses may also be caused by *Candida* species; such abscesses usually follow fungemia in patients receiving chemotherapy for cancer and often present when PMNs return after a period of neutropenia. Amebic liver abscesses are not an uncommon problem **(Chap. 218)**. Amebic serologic testing gives positive results in >95% of cases. In addition, polymerase chain reaction (PCR) testing has been used in recent years. Negative results from these studies help to exclude this diagnosis.

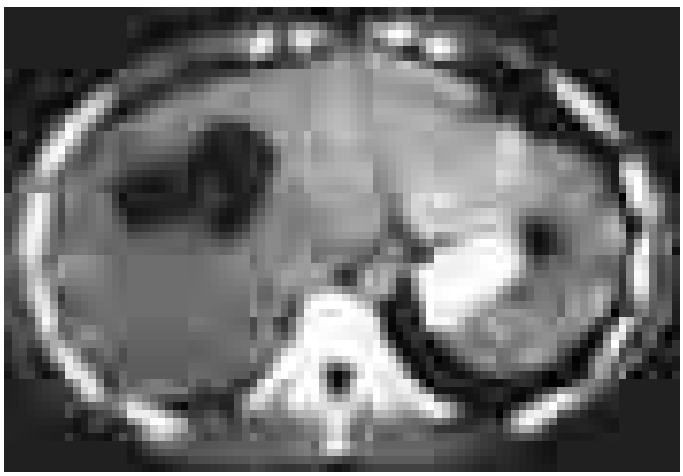

FIGURE 127-4 Multilocular liver abscess on CT scan. Multiple or multilocular abscesses are more common than solitary abscesses. *(Reprinted with permission from B Lorber [ed]: Atlas of Infectious Diseases, vol VII: Intra-abdominal Infections, Hepatitis, and Gastroenteritis. Philadelphia, Current Medicine, 1996, Fig. 1.22.)*

TREATMENT

Liver Abscesses

(Fig. 127-3) Drainage is the mainstay of therapy for intraabdominal abscesses, including liver abscesses; the approach can be either percutaneous (with a pigtail catheter kept in place or possibly with a device that can perform pulse lavage to fragment and evacuate the semisolid contents of a liver abscess) or surgical. However, there is growing interest in medical management alone for pyogenic liver abscesses. The drugs used for empirical therapy include the same ones used in intraabdominal sepsis and secondary bacterial peritonitis. Usually, blood cultures and a diagnostic aspirate of abscess contents should be obtained before the initiation of empirical therapy, with antibiotic choices adjusted when the results of Gram's staining and culture become available. Cases treated without definitive drainage generally require longer courses of antibiotic therapy. When percutaneous drainage was compared with open surgical drainage, the average length of hospital stay for the former was almost twice that for the latter, although both the time required for fever to resolve and the mortality rate were the same for the two procedures. The mortality rate was appreciable despite treatment, averaging 15%. Several factors predict the failure of percutaneous drainage and therefore may favor primary surgical intervention. These factors include the presence of multiple, sizable abscesses; viscous abscess contents that tend to plug the catheter; associated disease (e.g., disease of the biliary tract) requiring surgery; the presence of yeast; communication with an untreated obstructed biliary tree; or the lack of a clinical response to percutaneous drainage in 4–7 days.

Treatment of candidal liver abscesses often entails initial administration of liposomal amphotericin B (3–5 mg/kg IV daily) or an echinocandin, with subsequent fluconazole therapy **(Chap. 211)**. In some cases, therapy with fluconazole alone (6 mg/kg daily) may be used—e.g., in clinically stable patients whose infecting isolate is susceptible to this drug.

Splenic Abscesses Splenic abscesses are much less common than liver abscesses. The incidence of splenic abscesses has ranged from 0.14 to 0.7% in various autopsy series. The clinical setting and the organisms isolated usually differ from those for liver abscesses. The degree of clinical suspicion for splenic abscess needs to be high because this condition is frequently fatal if left untreated. Even in the most recently published series, diagnosis was made only at autopsy in 37% of cases. Although splenic abscesses may arise occasionally from contiguous spread of infection or from direct trauma to the spleen, hematogenous spread of infection is more common. Bacterial endocarditis is the most common associated infection **(Chap. 123)**. Splenic abscesses can develop in patients who have received extensive immunosuppressive therapy (particularly those with malignancy involving the spleen) and in patients with hemoglobinopathies or other hematologic disorders (especially sickle cell anemia).

Although ~50% of patients with splenic abscesses have abdominal pain, the pain is localized to the left upper quadrant in only one-half of these cases. Splenomegaly is found in ~50% of cases. Fever and leukocytosis are generally present; the development of fever preceded diagnosis by an average of 20 days in one series. Left-sided chest findings may include abnormalities to auscultation, and chest radiographic findings may include an infiltrate or a left-sided pleural effusion. CT scan of the abdomen has been the most sensitive diagnostic tool.

Ultrasonography can yield the diagnosis but is less sensitive. Liver–spleen scan or gallium scan may also be useful. Streptococcal species are the most common bacterial isolates from splenic abscesses, followed by *S. aureus*—presumably reflecting the associated endocarditis. An increase in the prevalence of gram-negative aerobic isolates from splenic abscesses has been reported; these organisms often derive from a urinary tract focus, with associated bacteremia, or from another intraabdominal source. *Salmonella* species are seen fairly commonly, especially in patients with sickle cell hemoglobinopathy. Anaerobic species accounted for only 5% of isolates in the largest collected series, but the reporting of a number of "sterile abscesses" may indicate that optimal techniques for the isolation of anaerobes were not used.

TREATMENT

Splenic Abscesses

Because of the high mortality figures reported for splenic abscesses, splenectomy with adjunctive antibiotics has traditionally been considered standard treatment and remains the best approach for complex, multilocular abscesses or multiple abscesses. However, percutaneous drainage has worked well for single, small (<3-cm) abscesses in some studies and may also be useful for patients with high surgical risk. Patients undergoing splenectomy should be vaccinated against encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*). The most important factor in successful treatment of splenic abscesses is early diagnosis.

Perinephric and Renal Abscesses Perinephric and renal abscesses are not common. The former accounted for only ~0.02% of hospital admissions and the latter for ~0.2% in Altemeier's series of 540 intraabdominal abscesses. Before antibiotics became available, most renal and perinephric abscesses were hematogenous in origin, usually complicating prolonged bacteremia, with *S. aureus* most commonly recovered. Now, in contrast, >75% of perinephric and renal abscesses arise from a urinary tract infection. Infection ascends from the bladder to the kidney, with pyelonephritis preceding abscess development. Bacteria may directly invade the renal parenchyma from medulla to cortex. Local vascular channels within the kidney may also facilitate the transport of organisms. Areas of abscess developing within the parenchyma may rupture into the perinephric space. The kidneys and adrenal glands are surrounded by a layer of perirenal fat that, in turn, is surrounded by Gerota's fascia, which extends superiorly to the diaphragm and inferiorly to the pelvic fat. Abscesses extending into the perinephric space may track through Gerota's fascia into the psoas or transversalis muscles, into the anterior peritoneal cavity, superiorly to the subdiaphragmatic space, or inferiorly to the pelvis. Of the risk factors that have been associated with the development of perinephric abscesses, the most important is concomitant nephrolithiasis obstructing urinary flow. Of patients with perinephric abscess, 20–60% have renal stones. Other structural abnormalities of the urinary tract, prior urologic surgery, trauma, and diabetes mellitus have also been identified as risk factors.

The organisms most frequently encountered in perinephric and renal abscesses are *E. coli*, *Proteus* species, and *Klebsiella* species. *E. coli*, the aerobic species most commonly found in the colonic flora, seems to have unique virulence properties in the urinary tract, including factors promoting adherence to uroepithelial cells. The urease of *Proteus* species splits urea, thereby creating a more alkaline and more hospitable environment for bacterial proliferation. *Proteus* species are frequently found in association with large struvite stones caused by the precipitation of magnesium ammonium sulfate in an alkaline environment. These stones serve as a nidus for recurrent urinary tract infection. Although a single bacterial species is usually recovered from a perinephric or renal abscess, multiple species may also be found. If a urine culture is not contaminated with periurethral flora and is found to contain more than one organism, a perinephric or renal abscess should be considered in the differential diagnosis. Urine cultures may also be polymicrobial in cases of bladder diverticulum.

Candida species can cause renal abscesses. Fungi of this genus may spread to the kidney hematogenously or by ascension from the bladder. The hallmark of the latter route of infection is ureteral obstruction with large fungal balls.

The presentation of perinephric and renal abscesses is quite nonspecific. Flank pain and abdominal pain are common. At least 50% of patients are febrile. Pain may be referred to the groin or leg, particularly with extension of infection. The diagnosis of perinephric abscess, like that of splenic abscess, is frequently delayed, and the mortality rate in some series is appreciable, although lower than in the past. Perinephric or renal abscess should be most seriously considered when a patient presents with symptoms and signs of pyelonephritis and remains febrile after 4 or 5 days of treatment. Moreover, when a urine culture yields a polymicrobial flora, when a patient is known to have renal stones, or when fever and pyuria coexist with a sterile urine culture, these diagnoses should be entertained.

Renal ultrasonography and abdominal CT are the most useful diagnostic modalities. If a renal or perinephric abscess is diagnosed, nephrolithiasis should be excluded, especially when a high urinary pH suggests the presence of a urea-splitting organism.

TREATMENT

Perinephric and Renal Abscesses

Treatment for perinephric and renal abscesses, like that for other intraabdominal abscesses, includes drainage of pus and antibiotic therapy directed at the organism(s) recovered. For perinephric abscesses, percutaneous drainage is usually successful.

Psoas Abscesses The psoas muscle is another location in which abscesses are encountered. Psoas abscesses may arise from a hematogenous source, by contiguous spread from an intraabdominal or pelvic process, or by contiguous spread from nearby bony structures (e.g., vertebral bodies). Associated osteomyelitis due to spread from bone to muscle or from muscle to bone is common in psoas abscesses. When Pott's disease was common, *Mycobacterium tuberculosis* was a frequent cause of psoas abscess. Currently, either *S. aureus* or a mixture of enteric organisms including aerobic and anaerobic gram-negative bacilli is usually isolated from psoas abscesses in the United States. *S. aureus* is most likely to be isolated when a psoas abscess arises from hematogenous spread or a contiguous focus of osteomyelitis; a mixed enteric flora is the most likely etiology when the abscess has an intraabdominal or pelvic source. Patients with psoas abscesses frequently present with fever, lower abdominal or back pain, or pain referred to the hip or knee. CT is the most useful diagnostic technique.

TREATMENT

Psoas Abscesses

Treatment includes surgical drainage and the administration of an antibiotic regimen directed at the inciting organism(s).

Pancreatic Abscesses See Chap. 341.

Acknowledgment

The substantial contributions of Dori F. Zaleznik, MD, to this chapter in previous editions are gratefully acknowledged.

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128 Acute Infectious Diarrheal Diseases and Bacterial Food Poisoning

Richelle C. Charles, Stephen B. Calderwood, Regina C. LaRocque

Acute diarrheal disease is a leading cause of illness globally and is associated with an estimated 1.7 million deaths per year. Among children <5 years of age, diarrheal disease is second only to lower respiratory infection as the most common infectious cause of death. The morbidity from diarrhea also is significant. Recurrent intestinal infections are associated with physical and mental stunting, wasting, micronutrient deficiencies, and malnutrition. In short, diarrheal disease is a driving factor in global morbidity and mortality.

The wide range of clinical manifestations of acute gastrointestinal illnesses is matched by the wide variety of infectious agents involved, including viruses, bacteria, and parasites **(Table 128-1)**. This chapter discusses factors that enable gastrointestinal pathogens to cause disease, reviews host defense mechanisms, and delineates an approach to the evaluation and treatment of patients presenting with acute diarrhea. Individual organisms causing acute gastrointestinal illnesses are discussed in detail in subsequent chapters.

PATHOGENIC MECHANISMS

Enteric pathogens have developed a variety of tactics to overcome host defenses. Understanding the virulence factors employed by these organisms is important in the diagnosis and treatment of clinical disease.

INOCULUM SIZE

The number of microorganisms that must be ingested to cause disease varies considerably from species to species. For *Shigella*, enterohemorrhagic *Escherichia coli*, *Giardia lamblia*, or *Entamoeba*, as few as 10–100 bacteria or cysts can produce infection, while 10^5–10^8 *Vibrio cholerae* organisms must be ingested to cause disease. The infective dose of *Salmonella* varies widely, depending on the species, host, and food vehicle. The ability of organisms to overcome host defenses has important implications for transmission; *Shigella*, enterohemorrhagic *E. coli*, *Entamoeba*, and *Giardia* can spread by person-to-person contact, whereas under some circumstances *Salmonella* may need to grow in food for several hours before reaching an effective infectious dose.

ADHERENCE

Many organisms must adhere to the gastrointestinal mucosa as an initial step in the pathogenic process; thus, organisms that can compete with the normal bowel flora and colonize the mucosa have an important advantage in causing disease. Specific cell-surface proteins involved in attachment of bacteria to intestinal cells are important virulence determinants. *V. cholerae*, for example, adheres to the brush border of small-intestinal enterocytes via specific surface adhesins, including the toxin-coregulated pilus and other accessory colonization factors. Enterotoxigenic *E. coli*, which causes watery diarrhea, produces an adherence protein called *colonization factor antigen* that is necessary for colonization of the upper small intestine by the organism prior to the production of enterotoxin. Enteropathogenic *E. coli*, an agent of diarrhea in young children, and enterohemorrhagic *E. coli*, which causes hemorrhagic colitis and the hemolytic-uremic syndrome, produce virulence determinants that allow these organisms to attach to and efface the brush border of the intestinal epithelium.

TOXIN PRODUCTION

The production of one or more exotoxins is important in the pathogenesis of numerous enteric organisms. Such toxins include *enterotoxins*, which cause watery diarrhea by acting directly on secretory mechanisms in the intestinal mucosa; *cytotoxins*, which cause destruction of mucosal cells and associated inflammatory diarrhea; and *neurotoxins*, which act directly on the central or peripheral nervous system.

The prototypical enterotoxin is cholera toxin, a heterodimeric protein composed of one A and five B subunits. The A subunit contains the enzymatic activity of the toxin, while the B subunit pentamer binds holotoxin to the enterocyte surface receptor, the ganglioside GM1. After the binding of holotoxin, a fragment of the A subunit is translocated across the eukaryotic cell membrane into the cytoplasm, where it catalyzes the adenosine diphosphate ribosylation of a guanosine triphosphate–binding protein and causes persistent activation of adenylate cyclase. The end result is an increase of cyclic adenosine monophosphate in the intestinal cell, which increases Cl^- secretion and decreases Na^+ absorption, leading to a loss of fluid and the production of diarrhea.

Enterotoxigenic strains of *E. coli* may produce a protein called *heat-labile enterotoxin* (LT) that is similar to cholera toxin and causes secretory diarrhea by the same mechanism. Alternatively, enterotoxigenic strains of *E. coli* may produce *heat-stable enterotoxin* (ST), one form of which causes diarrhea by activation of guanylate cyclase and elevation of intracellular cyclic guanosine monophosphate. Some enterotoxigenic strains of *E. coli* produce both LT and ST.

Bacterial cytotoxins, in contrast, destroy intestinal mucosal cells and produce the syndrome of dysentery, with bloody stools containing inflammatory cells. Enteric pathogens that produce such cytotoxins include *Shigella dysenteriae* type 1, *Vibrio parahaemolyticus*, and *Clostridium difficile*. *S. dysenteriae* type 1 and Shiga toxin–producing strains of *E. coli*

TABLE 128-1 Gastrointestinal Pathogens Causing Acute Diarrhea

MECHANISM	LOCATION	ILLNESS	STOOL FINDINGS	EXAMPLES OF PATHOGENS INVOLVED
Noninflammatory (enterotoxin)	Proximal small bowel	Watery diarrhea	No fecal leukocytes; mild or no increase in fecal lactoferrin	*Vibrio cholerae*, enterotoxigenic *Escherichia coli* (LT and/or ST), enteroaggregative *E. coli*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, rotavirus, norovirus, enteric adenoviruses, *Giardia lamblia*, *Cryptosporidium* spp., *Cyclospora* spp., microsporidia
Inflammatory (invasion or cytotoxin)	Colon or distal small bowel	Dysentery or inflammatory diarrhea	Fecal polymorphonuclear leukocytes; substantial increase in fecal lactoferrin	*Shigella* spp., *Salmonella* spp., *Campylobacter jejuni*, enterohemorrhagic *E. coli*, enteroinvasive *E. coli*, *Yersinia enterocolitica*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Clostridium difficile*, *A. hydrophila*, *P. shigelloides*, *Entamoeba histolytica*, *Klebsiella oxytoca*
Penetrating	Distal small bowel	Enteric fever	Fecal mononuclear leukocytes	*Salmonella* Typhi, *Y. enterocolitica*

Abbreviations: LT, heat-labile enterotoxin; ST, heat-stable enterotoxin.

produce potent cytotoxins and have been associated with outbreaks of hemorrhagic colitis and hemolytic-uremic syndrome.

Neurotoxins are usually produced by bacteria outside the host and therefore cause symptoms soon after ingestion. Included are the staphylococcal and *Bacillus cereus* toxins, which act on the central nervous system to produce vomiting.

INVASION

Dysentery may result not only from the production of cytotoxins but also from bacterial invasion and destruction of intestinal mucosal cells. Infections due to *Shigella* and enteroinvasive *E. coli* are characterized by the organisms' invasion of mucosal epithelial cells, intraepithelial multiplication, and subsequent spread to adjacent cells. *Salmonella* causes inflammatory diarrhea by invasion of the bowel mucosa, but generally is not associated with the destruction of enterocytes or the full clinical syndrome of dysentery. *Salmonella* Typhi and *Yersinia enterocolitica* can penetrate intact intestinal mucosa, multiply intracellularly in Peyer's patches and intestinal lymph nodes, and then disseminate through the bloodstream to cause enteric fever—a syndrome characterized by fever, headache, relative bradycardia, abdominal pain, splenomegaly, and leukopenia.

HOST DEFENSES

Given the enormous number of microorganisms ingested with every meal, the normal host must combat a constant influx of potential enteric pathogens. Studies of infections in patients with alterations in defense mechanisms have led to a greater understanding of the variety of ways in which the normal host can protect itself against disease.

INTESTINAL MICROBIOTA

The large numbers of bacteria that normally inhabit the intestine (*the intestinal microbiota*) act as an important host defense mechanism, preventing colonization by potential enteric pathogens. Persons with fewer intestinal bacteria, such as infants who have not yet developed normal enteric colonization or patients receiving antibiotics, are at significantly greater risk of developing infections with enteric pathogens. The composition of the intestinal microbiota is as important as the number of organisms present. More than 99% of the normal colonic microbiota is made up of anaerobic bacteria, and the acidic pH and volatile fatty acids produced by these organisms appear to be critical elements in resistance to colonization.

GASTRIC ACID

The acidic pH of the stomach is an important barrier to enteric pathogens, and an increased frequency of infections due to *Salmonella*, *G. lamblia*, and a variety of helminths has been reported among patients who have undergone gastric surgery or are achlorhydric for some other reason. Neutralization of gastric acid with antacids, proton pump inhibitors, or H_2 blockers—a common practice in the management of hospitalized patients—similarly increases the risk of enteric colonization. In addition, some microorganisms can survive the extreme acidity of the gastric environment; rotavirus, for example, is highly stable to acidity.

INTESTINAL MOTILITY

Normal peristalsis is the major mechanism for clearance of bacteria from the proximal small intestine. When intestinal motility is impaired (e.g., by treatment with opiates or other antimotility drugs, anatomic abnormalities, or hypomotility states), the frequency of bacterial overgrowth and infection of the small bowel with enteric pathogens is increased. Some patients whose treatment for *Shigella* infection consists of diphenoxylate hydrochloride with atropine (Lomotil) experience prolonged fever and shedding of organisms, while patients treated with opiates for mild *Salmonella* gastroenteritis have a higher frequency of bacteremia than those not treated with opiates.

INTESTINAL MUCIN

A complex layer of mucus, produced by specialized secretory cells, covers the stomach, small intestine, and large intestine and separates the commensal microbiota from the epithelium. The thickness and constituents of this mucus barrier vary throughout the gastrointestinal tract. The mucus barrier turns over rapidly and comprises glycoproteins and a range of antimicrobial molecules and secreted immunoglobulins directed against specific microbial antigens. Enteric pathogens have evolved a wide range of strategies to overcome this barrier and thus to reach the underlying epithelium and cause disease. For example, pathogens can penetrate the mucus layer by secreting enzymes to degrade the mucus or through flagella-mediated motility. Some organisms, such as *Shigella*, secrete toxins that can diffuse through the mucus layer and disrupt the underlying epithelium. The resulting reduction of mucus production allows the pathogen to reach the cell surface.

IMMUNITY

Both cellular immune responses and antibody production play important roles in protection from enteric infections. Humoral immunity to enteric pathogens consists of systemic IgG and IgM as well as secretory IgA. The mucosal immune system may be the first line of defense against many gastrointestinal pathogens. The binding of bacterial antigens to the luminal surface of M cells in the distal small bowel and the subsequent presentation of antigens to subepithelial lymphoid tissue lead to the proliferation of sensitized lymphocytes. These lymphocytes circulate and populate all of the mucosal tissues of the body as IgA-secreting plasma cells.

GENETIC DETERMINANTS

Host genetic variation influences susceptibility to diarrheal diseases. People with blood group O show increased susceptibility to disease due to *V. cholerae*, *Shigella*, *E. coli* O157, and norovirus. Polymorphisms in genes encoding inflammatory mediators have been associated with the outcome of infection with enteroaggregative *E. coli*, enterotoxin-producing *E. coli*, *Salmonella*, *C. difficile*, and *V. cholerae*.

APPROACH TO THE PATIENT

Infectious Diarrhea or Bacterial Food Poisoning

The approach to the patient with possible infectious diarrhea or bacterial food poisoning is shown in **Fig. 128-1**.

HISTORY

The answers to questions with high discriminating value can quickly narrow the range of potential causes of diarrhea and help determine whether treatment is needed. Important elements of the narrative history are detailed in Fig. 128-1.

PHYSICAL EXAMINATION

The examination of patients for signs of dehydration provides essential information about the severity of the diarrheal illness and the need for rapid therapy. Mild dehydration is indicated by thirst, dry mouth, decreased axillary sweat, decreased urine output, and slight weight loss. Signs of moderate dehydration include an orthostatic fall in blood pressure, skin tenting, and sunken eyes (or, in infants, a sunken fontanelle). Signs of severe dehydration include lethargy, obtundation, feeble pulse, hypotension, and frank shock.

DIAGNOSTIC APPROACH

After the severity of illness is assessed, the clinician must distinguish between *inflammatory* and *noninflammatory* disease. Using the history and epidemiologic features of the case as guides, the clinician can then rapidly evaluate the need for further efforts to define a specific etiology and for therapeutic intervention. Examination of a stool sample may supplement the narrative history. Grossly bloody or mucoid stool suggests an inflammatory process. A test for fecal leukocytes (preparation of a thin smear of stool on a glass slide, addition of a drop of methylene blue, and examination of the wet mount) can suggest inflammatory disease in patients with diarrhea, although the predictive value of this test is still debated. A test for fecal lactoferrin, which is a marker of fecal leukocytes, is more sensitive and is available in latex agglutination and enzyme-linked immunosorbent assay formats. Causes of acute infectious diarrhea, categorized as inflammatory and noninflammatory, are listed in Table 128-1.

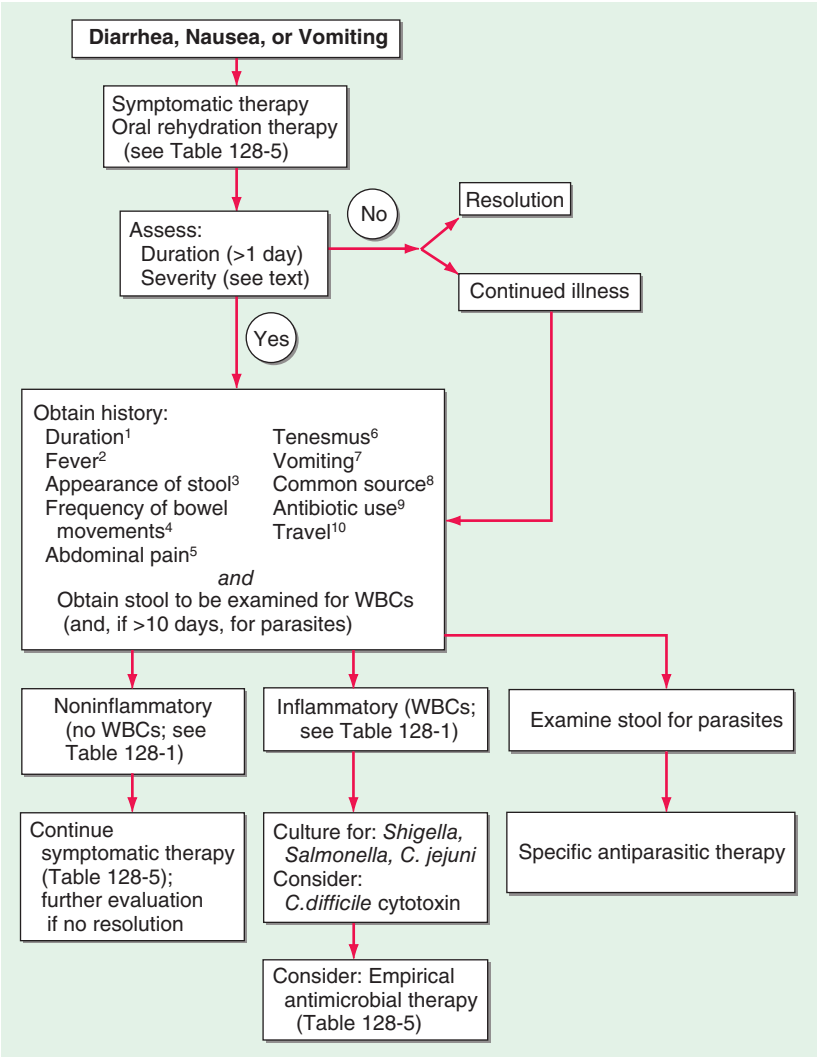

FIGURE 128-1 Clinical algorithm for the approach to patients with community-acquired infectious diarrhea or bacterial food poisoning. Key to superscripts: 1. Diarrhea lasting >2 weeks is generally defined as chronic; in such cases, many of the causes of acute diarrhea are much less likely, and a new spectrum of causes needs to be considered. 2. Fever often implies invasive disease, although fever and diarrhea may also result from infection outside the gastrointestinal tract, as in malaria. 3. Stools that contain blood or mucus indicate ulceration of the large bowel. Bloody stools without fecal leukocytes should alert the laboratory to the possibility of infection with Shiga toxin–producing enterohemorrhagic *Escherichia coli*. Bulky white stools suggest a small-intestinal process that is causing malabsorption. Profuse "rice-water" stools suggest cholera or a similar toxigenic process. 4. Frequent stools over a given period can provide the first warning of impending dehydration. 5. Abdominal pain may be most severe in inflammatory processes like those due to *Shigella*, *Campylobacter*, and necrotizing toxins. Painful abdominal muscle cramps, caused by electrolyte loss, can develop in severe cases of cholera. Bloating is common in giardiasis. An appendicitis-like syndrome should prompt a culture for *Yersinia enterocolitica* with cold enrichment. 6. Tenesmus (painful rectal spasms with a strong urge to defecate but little passage of stool) may be a feature of cases with proctitis, as in shigellosis or amebiasis. 7. Vomiting implies an acute infection (e.g., a toxin-mediated illness or food poisoning) but can also be prominent in a variety of systemic illnesses (e.g., malaria) and in intestinal obstruction. 8. Asking patients whether anyone else they know is sick is a more efficient means of identifying a common source than is constructing a list of recently eaten foods. If a common source seems likely, specific foods can be investigated. See text for a discussion of bacterial food poisoning. 9. Current antibiotic therapy or a recent history of treatment suggests *Clostridium difficile* diarrhea **(Chap. 129)**. Stop antibiotic treatment if possible and consider tests for *C. difficile* toxins. Antibiotic use may increase the risk of chronic intestinal carriage following salmonellosis. 10. See text (and **Chap. 119**) for a discussion of traveler's diarrhea. *(After TS Steiner, RL Guerrant: Principles and syndromes of enteric infection, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed, GL Mandell et al [eds]. Philadelphia, Churchill Livingstone, 2010, pp 1335–1351; RL Guerrant, DA Bobak: N Engl J Med 325:327, 1991; with permission.)*

POST-DIARRHEA COMPLICATIONS

Chronic complications may follow the resolution of an acute diarrheal episode. The clinician should inquire about prior diarrheal illness if the conditions listed in **Table 128-2** are observed.

EPIDEMIOLOGY

TRAVEL HISTORY

Of the several million people who travel from temperate industrialized countries to tropical regions of Asia, Africa, and Central and South America each year, 20–50% experience a sudden onset of abdominal cramps, anorexia, and watery diarrhea; thus *traveler's diarrhea* is the most common travel-related infectious illness **(Chap. 119)**. The time of onset is usually 3 days to 2 weeks after the traveler's arrival in a resource-poor area; most cases begin within the first 3–5 days. The illness is generally self-limited, lasting 1–5 days. The high rate of diarrhea among travelers to underdeveloped areas is related to the ingestion of contaminated food or water.

The organisms that cause traveler's diarrhea vary considerably with location **(Table 128-3)**, as does the pattern of antimicrobial resistance. In all areas, enterotoxigenic and enteroaggregative strains of *E. coli* are the most common isolates from persons with the classic secretory traveler's diarrhea syndrome. Infection with *Campylobacter jejuni* is especially common in areas of Asia.

LOCATION

Closed and semi-closed communities, including day-care centers, schools, residential facilities, and cruise ships, are important settings for outbreaks of enteric infections. Norovirus, which is highly

TABLE 128-2 Post-Diarrhea Complications of Acute Infectious Diarrheal Illness

COMPLICATION	COMMENTS
Chronic diarrhea (diarrhea lasting >4 weeks) • Lactase deficiency • Small-bowel bacterial overgrowth • Malabsorption syndromes (tropical and celiac sprue)	Occurs in ~1% of travelers with acute diarrhea • Protozoa account for ~1/3 of cases
Initial presentation or exacerbation of inflammatory bowel disease	May be precipitated by traveler's diarrhea
Irritable bowel syndrome	Occurs in ~10% of travelers with traveler's diarrhea
Reactive arthritis	Particularly likely after infection with invasive organisms (*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*)
Hemolytic-uremic syndrome (hemolytic anemia, thrombocytopenia, and renal failure)	Follows infection with Shiga toxin–producing bacteria (*Shigella dysenteriae* type 1 and enterohemorrhagic *Escherichia coli*)
Guillain-Barré syndrome	Particularly likely after *Campylobacter* infection

contagious and robust in surviving on surfaces, is the most common etiologic agent associated with outbreaks of acute gastroenteritis. Other common organisms, often spread by fecal–oral contact in such communities, are *Shigella*, *C. jejuni*, and *Cryptosporidium*. Rotavirus is rarely a cause of pediatric diarrheal outbreaks in the United States since rotavirus vaccination was broadly recommended in 2006. Similarly, hospitals are sites in which enteric infections are concentrated. Diarrhea is one of the most common manifestations of nosocomial infections. *C. difficile* is the predominant cause of nosocomial diarrhea among adults in the United States, and outbreaks of norovirus infection are common in health care settings. *Klebsiella oxytoca* has been identified as a cause of antibiotic-associated hemorrhagic colitis. Enteropathogenic *E. coli* has been associated with outbreaks of diarrhea in nurseries for newborns. One-third of elderly patients in chronic-care institutions develop a significant diarrheal illness each year; more than one-half of these cases are caused by cytotoxin-producing *C. difficile*. Antimicrobial therapy can predispose to pseudomembranous colitis by altering the normal colonic flora and allowing the multiplication of *C. difficile* **(Chap. 129)**.

TABLE 128-3 Causes of Traveler's Diarrhea

ETIOLOGIC AGENT	APPROXIMATE PERCENTAGE OF CASES	COMMENTS
Bacteria	**50–75**	
Enterotoxigenic *Escherichia coli*	10–45	Single most important agent
Enteroaggregative *E. coli*	5–35	Emerging enteric pathogen with worldwide distribution
Campylobacter jejuni	5–25	More common in Asia
Shigella	0–15	Major cause of dysentery
Salmonella	0–15	—
Others	0–5	Including *Aeromonas*, *Plesiomonas*, and *Vibrio cholerae*
Viruses	**0–20**	
Norovirus	0–10	Associated with cruise ships
Rotavirus	0–5	Particularly common among children
Parasites	**0–10**	
Giardia lamblia	0–5	Affects hikers and campers who drink from freshwater streams
Cryptosporidium	0–5	Resistant to chlorine treatment of water sources
Entamoeba histolytica	<1	—
Cyclospora	<1	—
Other	**0–10**	
Acute food poisoning[a]	0–5	—
No pathogen identified	10–50	—

[a]For etiologic agents, see Table 128-4.

Source: After DR Hill et al: The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1499, 2006.

AGE

Globally, most morbidity and mortality from enteric pathogens involves children <5 years of age. Breast-fed infants are protected from pathogens in contaminated food and water and derive some protection from maternal antibodies, but their risk of infection rises dramatically when they begin to eat solid foods. Exposure to rotavirus is universal, with most children experiencing their first infection in the first or second year of life if not vaccinated. Older children and adults are more commonly infected with norovirus. Other organisms with higher attack rates among children than among adults include enterotoxigenic, enteropathogenic, and enterohemorrhagic *E. coli*; *Shigella*; *C. jejuni*; and *G. lamblia*.

HOST IMMUNE STATUS

Immunocompromised hosts are at elevated risk of acute and chronic infectious diarrhea. Individuals with defects in cell-mediated immunity (including those with AIDS) are at particularly high risk of invasive enteropathies, including salmonellosis, listeriosis, and cryptosporidiosis. Individuals with hypogammaglobulinemia are at particular risk of *C. difficile* colitis and giardiasis. Patients with cancer are more likely to develop *C. difficile* infection as a result of chemotherapy and frequent hospitalizations. Infectious diarrhea can be life-threatening in immunocompromised hosts, with complications including bacteremia and metastatic seeding of infection. Furthermore, dehydration may compromise renal function and increase the toxicity of immunosuppressive drugs.

BACTERIAL FOOD POISONING

If the history and the stool examination indicate a noninflammatory etiology of diarrhea and there is evidence of a common-source outbreak, questions concerning the ingestion of specific foods and the time of onset of diarrhea after a meal can provide clues to the bacterial cause of the illness. Potential causes of bacterial food poisoning are shown in Table 128-4.

Bacterial disease caused by an enterotoxin elaborated outside the host, such as that due to *Staphylococcus aureus* or *B. cereus*, has the shortest incubation period (1–6 h) and generally lasts <12 h. Most cases of staphylococcal food poisoning are caused by contamination from infected human carriers. Staphylococci can multiply at a wide range of temperatures; thus, if food is left to cool slowly and remains at room temperature after cooking, the organisms will have the opportunity to form enterotoxin. Outbreaks following picnics where potato salad, mayonnaise, and cream pastries have been served offer classic examples of staphylococcal food poisoning. Diarrhea, nausea, vomiting, and abdominal cramping are common, while fever is less so.

B. cereus can produce either a syndrome with a short incubation period—the *emetic* form, mediated by a staphylococcal type of enterotoxin—or one with a longer incubation period (8–16 h)—the *diarrheal* form, caused by an enterotoxin resembling *E. coli* LT, in which diarrhea and abdominal cramps are characteristic but vomiting is uncommon. The emetic form of *B. cereus* food poisoning is associated with contaminated fried rice; the organism is common in uncooked rice, and its heat-resistant spores survive boiling. If cooked rice is not refrigerated, the spores can germinate and produce toxin. Frying before serving may not destroy the preformed, heat-stable toxin.

Food poisoning due to *Clostridium perfringens* also has a slightly longer incubation period (8–14 h) and results from the survival of heat-resistant spores in inadequately cooked meat, poultry, or legumes. After ingestion, toxin is produced in the intestinal tract, causing moderately severe abdominal cramps and diarrhea; vomiting is rare, as is fever. The illness is self-limited, rarely lasting >24 h.

TABLE 128-4 Bacterial Food Poisoning

INCUBATION PERIOD, ORGANISM	SYMPTOMS	COMMON FOOD SOURCES
1–6 h		
Staphylococcus aureus	Nausea, vomiting, diarrhea	Ham, poultry, potato or egg salad, mayonnaise, cream pastries
Bacillus cereus	Nausea, vomiting, diarrhea	Fried rice
8–16 h		
Clostridium perfringens	Abdominal cramps, diarrhea (vomiting rare)	Beef, poultry, legumes, gravies
B. cereus	Abdominal cramps, diarrhea (vomiting rare)	Meats, vegetables, dried beans, cereals
>16 h		
Vibrio cholerae	Watery diarrhea	Shellfish, water
Enterotoxigenic *Escherichia coli*	Watery diarrhea	Salads, cheese, meats, water
Enterohemorrhagic *E. coli*	Bloody diarrhea	Ground beef, roast beef, salami, raw milk, raw vegetables, apple juice
Salmonella spp.	Inflammatory diarrhea	Beef, poultry, eggs, dairy products
Campylobacter jejuni	Inflammatory diarrhea	Poultry, raw milk
Shigella spp.	Dysentery	Potato or egg salad, lettuce, raw vegetables
Vibrio parahaemolyticus	Dysentery	Mollusks, crustaceans

Not all food poisoning has a bacterial cause. Nonbacterial agents of short-incubation food poisoning include capsaicin, which is found in hot peppers, and a variety of toxins found in fish and shellfish **(Chap. 451)**.

LABORATORY EVALUATION

Many cases of noninflammatory diarrhea are self-limited or can be treated empirically, and in these instances, the clinician may not need to determine a specific etiology. Potentially pathogenic *E. coli* cannot be distinguished from normal fecal flora by routine culture, and tests to detect enterotoxins are not available in most clinical laboratories. In situations in which cholera is a concern, stool should be cultured on selective media such as thiosulfate–citrate–bile salts–sucrose (TCBS) or tellurite–taurocholate–gelatin (TTG) agar. A latex agglutination test has made the rapid detection of rotavirus in stool practical for many laboratories, while reverse-transcriptase polymerase chain reaction (PCR) and specific antigen enzyme immunoassays have been developed for the identification of norovirus. Stool specimens should be examined by immunofluorescence-based rapid assays or (less sensitive) standard microscopy for *Giardia* cysts or *Cryptosporidium* if the level of clinical suspicion regarding the involvement of these organisms is high.

All patients with fever and evidence of inflammatory disease acquired outside the hospital should have stool evaluated for *Salmonella*, *Shigella*, and *Campylobacter*. *Salmonella* and *Shigella* can be selected on MacConkey agar as non-lactose-fermenting (colorless) colonies or can be grown on *Salmonella–Shigella* agar or in selenite enrichment broth, both of which inhibit most organisms except these pathogens. Evaluation of nosocomial diarrhea should initially focus on *C. difficile*; stool culture for other pathogens in this setting has an extremely low yield and is not cost-effective. Toxins A and B produced by pathogenic strains of *C. difficile* can be detected by rapid enzyme immunoassays, latex agglutination tests, or PCR **(Chap. 129)**. Isolation of *C. jejuni* requires inoculation of fresh stool onto selective growth medium and incubation at 42°C in a microaerophilic atmosphere. In many laboratories in the United States, *E. coli* O157:H7 is among the most common pathogens isolated from visibly bloody stools. Strains of this enterohemorrhagic serotype can be identified in specialized laboratories by serotyping but also can be identified presumptively in hospital laboratories as lactose-fermenting, indole-positive colonies of sorbitol nonfermenters (white colonies) on sorbitol MacConkey plates. If the clinical presentation suggests the possibility of intestinal amebiasis, stool should be examined by a rapid antigen detection assay or by (less sensitive and less specific) microscopy. Multiplex nucleic acid amplification methods for detection of many stool pathogens (viral, bacterial, and parasitic) are increasingly being used in clinical microbiology laboratories to decrease the time to detection of a pathogen. Although these tests may be more sensitive and rapid than standard culture methods, the lack of a microbial isolate prevents determination of antimicrobial susceptibility and typing of strains by public health authorities in order to detect and respond to common-source outbreaks. For this reason, the Centers for Disease Control and Prevention suggests that diagnosis of an enteric bacterial infection by a nucleic acid amplification method should be followed by attempted isolation of the pathogen by culture.

TREATMENT

Infectious Diarrhea or Bacterial Food Poisoning

In many cases, a specific diagnosis is not necessary or not available to guide treatment. The clinician can proceed with the information obtained from the history, stool examination, and evaluation of dehydration severity. Empirical regimens for the treatment of traveler's diarrhea are listed in **Table 128-5**.

The mainstay of treatment is adequate rehydration. The treatment of cholera and other dehydrating diarrheal diseases was

TABLE 128-5 Treatment of Traveler's Diarrhea on the Basis of Clinical Features[a]

CLINICAL SYNDROME	SUGGESTED THERAPY
Watery diarrhea (no blood in stool, no fever), 1 or 2 unformed stools per day without distressing enteric symptoms	Oral fluids (oral rehydration solution, Pedialyte, Lytren, or flavored mineral water) and saltine crackers
Watery diarrhea (no blood in stool, no fever), 1 or 2 unformed stools per day with distressing enteric symptoms	Bismuth subsalicylate (for adults): 30 mL or 2 tablets (262 mg/tablet) every 30 min for 8 doses; or loperamide[b]: 4 mg initially followed by 2 mg after passage of each unformed stool, not to exceed 8 tablets (16 mg) per day (prescription dose) or 4 caplets (8 mg) per day (over-the-counter dose); drugs can be taken for 2 days. Antibacterial drug[c] can be considered in selected circumstances.
Dysentery (passage of bloody stools) or fever (>37.8°C)	Antibacterial drug[c]
Vomiting, minimal diarrhea	Bismuth subsalicylate (for adults; see dose above)
Diarrhea in infants (<2 years old)	Fluids and electrolytes (oral rehydration solution, Pedialyte, Lytren); continue feeding, especially with breast milk; seek medical attention for moderate dehydration, fever lasting >24 h, bloody stools, or diarrhea lasting more than several days

[a]All patients should take oral fluids (Pedialyte, Lytren, or flavored mineral water) plus saltine crackers. If diarrhea becomes moderate or severe, if fever persists, or if bloody stools or dehydration develops, the patient should seek medical attention. [b]Loperamide should not be used by patients with fever or dysentery; its use may prolong diarrhea in patients with infection due to *Shigella* or other invasive organisms. [c]The recommended antibacterial drugs are as follows:

If the level of suspicion is low for fluoroquinolone-resistant *Campylobacter*:
Adults: (1) A fluoroquinolone such as ciprofloxacin, 750 mg as a single dose or 500 mg bid for 3 days; levofloxacin, 500 mg as a single dose or 500 mg qd for 3 days; or norfloxacin, 800 mg as a single dose or 400 mg bid for 3 days. (2) Azithromycin, 1000 mg as a single dose or 500 mg qd for 3 days. (3) Rifaximin, 200 mg tid or 400 mg bid for 3 days (not recommended for use in dysentery). *Children:* Azithromycin, 10 mg/kg on day 1, 5 mg/kg on days 2 and 3 if diarrhea persists.

If fluoroquinolone-resistant *Campylobacter* is suspected (for example, following travel to Southeast Asia):
Adults: Azithromycin (at above dose for adults). *Children:* Same as for children traveling to other areas (see above).

Source: After DR Hill et al: The practice of travel medicine: Guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1499, 2006.

revolutionized by the promotion of oral rehydration solution (ORS), the efficacy of which depends on the fact that glucose-facilitated absorption of sodium and water in the small intestine remains intact in the presence of cholera toxin. The use of ORS has reduced cholera mortality rates from >50% (in untreated cases) to <1%. A number of ORS formulas have been used. Initial preparations were based on the treatment of patients with cholera and included a solution containing 3.5 g of sodium chloride, 2.5 g of sodium bicarbonate (or 2.9 g of sodium citrate), 1.5 g of potassium chloride, and 20 g of glucose (or 40 g of sucrose) per liter of water. Such a preparation can still be used for the treatment of severe cholera. Many causes of secretory diarrhea, however, are associated with less electrolyte loss than occurs in cholera. Beginning in 2002, the World Health Organization recommended a "reduced-osmolarity/reduced-salt" ORS that is better tolerated and more effective than classic ORS. This preparation contains 2.6 g of sodium chloride, 2.9 g of trisodium citrate, 1.5 g of potassium chloride, and 13.5 g of glucose (or 27 g of sucrose) per liter of water. ORS formulations containing rice or cereal as the carbohydrate source may be even more effective than glucose-based solutions. Patients who are severely dehydrated or in whom vomiting precludes oral therapy should receive IV solutions such as Ringer's lactate.

Most secretory forms of traveler's diarrhea (usually due to enterotoxigenic or enteroaggregative *E. coli* or to *Campylobacter*) can be treated effectively with rehydration, bismuth subsalicylate, or antiperistaltic agents. Antimicrobial agents can shorten the duration of illness from 3–4 days to 24–36 h but may be associated with the acquisition of multidrug-resistant organisms. Changes in diet have not been shown to have an impact on the duration of illness, while the efficacy of probiotics continues to be debated. Most individuals who present with dysentery (bloody diarrhea and fever) should be treated empirically with an antimicrobial agent (e.g., a fluoroquinolone or a macrolide) pending microbiologic analysis of stool. Individuals with shigellosis should receive a 3- to 7-day course. Individuals with more severe or prolonged *Campylobacter* infection often benefit from antimicrobial treatment as well. Because of widespread resistance of *Campylobacter* to fluoroquinolones, especially in parts of Asia, a macrolide antibiotic such as erythromycin or azithromycin may be preferred for this infection.

Treatment of salmonellosis must be tailored to the individual patient. Since administration of antimicrobial agents often prolongs intestinal colonization with *Salmonella*, these drugs are usually reserved for individuals at high risk of complications from disseminated salmonellosis, such as infants, patients with prosthetic devices, patients over age 50, and immunocompromised persons. Antimicrobial agents should not be administered to individuals (especially children) in whom enterohemorrhagic *E. coli* infection is suspected. Laboratory studies of enterohemorrhagic *E. coli* strains have demonstrated that a number of antibiotics induce replication of Shiga toxin–producing lambdoid bacteriophages, thereby significantly increasing toxin production by these strains. Clinical studies have supported these laboratory results, and antibiotics may increase by twentyfold the risk of hemolytic-uremic syndrome and renal failure during enterohemorrhagic *E. coli* infection. A clinical clue in the diagnosis of the latter infection is bloody diarrhea with low fever or none at all.

PROPHYLAXIS

Improvements in hygiene to limit fecal–oral spread of enteric pathogens will be necessary if the prevalence of diarrheal diseases is to be significantly reduced in developing countries. Travelers can reduce their risk of diarrhea by eating only hot, freshly cooked food; by avoiding raw vegetables, salads, and unpeeled fruit; and by drinking only boiled or treated water and avoiding ice. Historically, few travelers to tourist destinations adhere to these dietary restrictions. Bismuth subsalicylate is an inexpensive agent for the prophylaxis of traveler's diarrhea; it is taken at a dosage of 2 tablets (525 mg) four times a day. Treatment appears to be effective and safe for up to 3 weeks, but adverse events such as temporary darkening of the tongue and tinnitus can occur. A meta-analysis suggests that probiotics may lessen the likelihood of traveler's diarrhea by ~15%. Prophylactic antimicrobial agents, although effective, are not generally recommended for the prevention of traveler's diarrhea except when travelers are immunosuppressed or have other underlying illnesses that place them at high risk for morbidity from gastrointestinal infection. If prophylaxis is indicated, the nonabsorbed antibiotic rifaximin can be considered.

The possibility of exerting a major impact on the worldwide morbidity and mortality associated with diarrheal diseases has led to intensive efforts to develop effective vaccines against the common bacterial and viral enteric pathogens. An effective rotavirus vaccine is available. Vaccines against *S.* Typhi and *V. cholerae* also are available, although the protection they offer is incomplete and/or short lived. At present, there are no effective commercially available vaccines against *Shigella*, *Campylobacter*, nontyphoidal *Salmonella*, norovirus, or intestinal parasites.

Acknowledgment

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129 *Clostridium difficile* Infection, Including Pseudomembranous Colitis

Dale N. Gerding, Stuart Johnson

DEFINITION

Clostridium difficile infection (CDI) is a unique colonic disease that is acquired most commonly in association with antimicrobial use and the consequent disruption of the normal colonic microbiota. The most commonly diagnosed diarrheal illness acquired in the hospital, CDI results from the ingestion of spores of *C. difficile* that vegetate, multiply, and secrete toxins, causing diarrhea and, in the most severe cases, pseudomembranous colitis (PMC).

ETIOLOGY AND EPIDEMIOLOGY

C. difficile is an obligately anaerobic, gram-positive, spore-forming bacillus whose spores are found widely in nature, particularly in the environment of hospitals and chronic-care facilities. CDI occurs frequently in hospitals and nursing homes (or shortly after discharge from these facilities) where the level of antimicrobial use is high and the environment is contaminated by *C. difficile* spores.

Clindamycin, ampicillin, and cephalosporins were the first antibiotics associated with CDI. The second- and third-generation cephalosporins, particularly cefotaxime, ceftriaxone, cefuroxime, and ceftazidime, are agents frequently responsible for this condition, and the fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin) are the most recent

drug class to be implicated in hospital outbreaks. Penicillin/β-lactamase-inhibitor combinations such as ticarcillin/clavulanate and piperacillin/tazobactam pose significantly less risk. However, all antibiotics, including vancomycin and metronidazole (the agents most commonly used to treat CDI), have been found to carry a risk of subsequent CDI. A few cases, especially in the community, are reported in patients without documentation of prior antibiotic exposure.

C. difficile is acquired exogenously—most often in the hospital or nursing home, but also in the outpatient setting—and is carried in the stool of both symptomatic and asymptomatic patients. The rate of fecal colonization increases in proportion to length of hospital stay and is often ≥20% among adult patients hospitalized for >2 weeks; in contrast, the rate is 1–3% among community residents. CDI is now the most common health care–associated infection in the United States, with an estimated 453,000 cases annually. The incidence is higher among female patients, Caucasians, and persons ≥65 years of age. The estimated number of first recurrences of CDI is 83,000, and the estimated number of CDI-associated deaths is 29,300. Community-onset CDI without recent hospitalization, nursing home residence, or outpatient health-care contact probably accounts for ≤10% of all cases.

Asymptomatic fecal carriage of *C. difficile* in healthy neonates is very common, with repeated colonization by multiple strains in infants <1–2 years of age, but associated disease in these infants is extremely rare if it occurs at all. Spores of *C. difficile* are found on environmental surfaces (where the organism can persist for months) and on the hands of hospital personnel who fail to practice good hand hygiene. Hospital epidemics of CDI have been attributed to a single *C. difficile* strain and to multiple strains present simultaneously. Other identified risk factors for CDI include older age, greater severity of underlying illness, gastrointestinal surgery, use of electronic rectal thermometers, enteral tube feeding, and antacid treatment. Use of proton pump inhibitors may be a risk factor, but this risk is probably modest, and no firm data have implicated these agents in patients who are not already receiving antibiotics.

PATHOLOGY AND PATHOGENESIS

Spores of toxigenic *C. difficile* are ingested, survive gastric acidity, germinate in the small bowel, and colonize the lower intestinal tract, where they elaborate two large toxins: toxin A (an enterotoxin) and toxin B (a cytotoxin). These toxins initiate processes resulting in the disruption of epithelial-cell barrier function, diarrhea, and pseudomembrane formation. Toxin A is a potent neutrophil chemoattractant, and both toxins glucosylate the GTP-binding proteins of the Rho subfamily that regulate the actin cell cytoskeleton. Data from studies using molecular disruption of toxin genes in isogenic mutants suggest that toxin B may be the more important virulence factor; this possibility, if confirmed, might account for the occurrence of clinical disease caused by toxin A–negative strains but not by toxin B-negative strains. Disruption of the cytoskeleton results in loss of cell shape, adherence, and tight junctions, with consequent fluid leakage. A third toxin, binary toxin CDT, was previously found in only ~6% of strains but is present in all isolates of the widely recognized epidemic NAP1/BI/027 strain (see "Global Considerations," below); this toxin is related to *C. perfringens* iota toxin. Its role in the pathogenesis of CDI has not yet been defined.

The pseudomembranes of PMC are confined to the colonic mucosa and initially appear as 1- to 2-mm whitish-yellow plaques. The intervening mucosa appears unremarkable, but, as the disease progresses, the pseudomembranes coalesce to form larger plaques and become confluent over the entire colon wall **(Fig. 129-1)**. The whole colon is usually involved, but 10% of patients have rectal sparing. Viewed microscopically, the pseudomembranes have a mucosal attachment point and contain necrotic leukocytes, fibrin, mucus, and cellular debris. The epithelium is eroded and necrotic in focal areas, with neutrophil infiltration of the mucosa.

Patients colonized with *C. difficile* were initially thought to be at high risk for CDI. However, four prospective studies have shown that colonized patients who have not previously had CDI actually have a decreased risk of CDI, possibly because many of these patients are colonized by nontoxigenic strains. At least three events are proposed

FIGURE 129-1 Autopsy specimen showing confluent pseudomembranes covering the cecum of a patient with pseudomembranous colitis. Note the sparing of the terminal ileum (*arrow*).

as essential for the development of CDI **(Fig. 129-2)**. Exposure to antimicrobial agents is the first event and establishes susceptibility to CDI, most likely through disruption of the normal gastrointestinal microbiota. The second event is exposure to toxigenic *C. difficile*. Given that the majority of patients do not develop CDI after the first two events, a third event is clearly essential for its occurrence. Candidate third events include exposure to a *C. difficile* strain of particular virulence, exposure to antimicrobial agents especially likely to cause CDI, and an inadequate host immune response. The host anamnestic serum IgG antibody response to toxin A of *C. difficile* is the most likely third event that determines which patients develop diarrhea and which patients remain asymptomatic. The majority of humans probably first develop

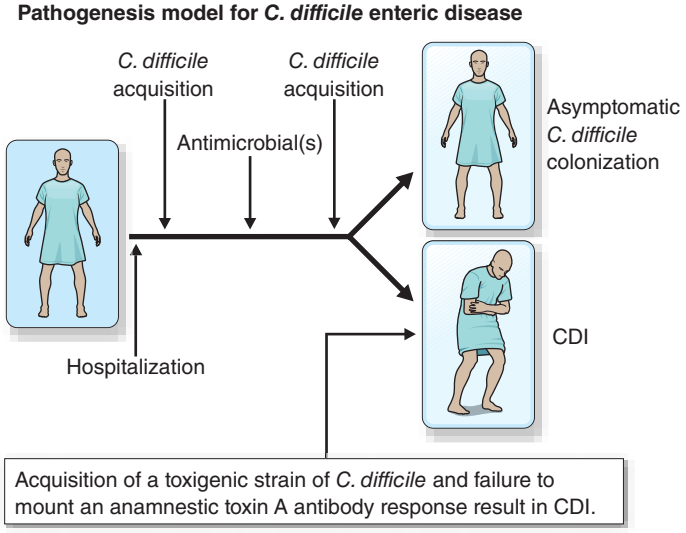

FIGURE 129-2 Pathogenesis model for hospital-acquired *Clostridium difficile* infection (CDI). At least three events are integral to *C. difficile* pathogenesis. Exposure to antibiotics establishes susceptibility to infection. Once susceptible, the patient may acquire nontoxigenic (nonpathogenic) or toxigenic strains of *C. difficile* as a second event. Acquisition of toxigenic *C. difficile* may be followed by asymptomatic colonization or CDI, depending on one or more additional events, including an inadequate host anamnestic IgG response to *C. difficile* toxin A.

antibody to *C. difficile* toxins when colonized asymptomatically during the first year of life or after CDI in childhood. Infants are thought not to develop symptomatic CDI because they lack suitable mucosal toxin receptors that develop later in life. In adulthood, serum levels of IgG antibody to toxin A increase more in response to infection in individuals who become asymptomatic carriers than in those who develop CDI. For persons who develop CDI, increasing levels of antitoxin A during treatment correlate with a lower risk of recurrence. Two large clinical trials in which intravenous monoclonal antibodies to toxin A and toxin B were used together and as single agents in addition to standard antibiotic therapy showed that rates of recurrent CDI were significantly lower with the combination of antibodies and with the toxin B antibody alone than with placebo plus standard therapy. Antibody to toxin A alone was ineffective.

GLOBAL CONSIDERATIONS

Rates and severity of CDI in the United States, Canada, and Europe have increased markedly since the year 2000. Rates in U.S. hospitals tripled between 2000 and 2005. Hospitals in Montreal, Quebec, reported rates in 2005 that were four times higher than the 1997 baseline, with directly attributable mortality of 6.9% (increased from 1.5%). An epidemic strain, variously known as toxinotype III, REA type BI, PCR ribotype 027, and pulsed-field type NAP1 (collectively designated NAP1/BI/027), is thought to account for much of the increase in incidence and has been found in North America, Europe, and Asia. It is now recognized that two clones of NAP1/BI/027 originated in the United States and Canada and spread to the United Kingdom, Europe, and Asia. The epidemic organism is characterized by (1) an ability to produce 16–23 times as much toxin A and toxin B as control strains in vitro, (2) the presence of binary toxin CDT, and (3) high-level resistance to all fluoroquinolones. New strains have been and will probably continue to be implicated in outbreaks, including a strain commonly found in food animals that also carries binary toxin and has been associated with high mortality rates in human infections (toxinotype V, ribotype 078). In the last 5 years, the rates of CDI in the United Kingdom have markedly decreased, and the frequency of the NAP1/BI/027 strain has decreased in the European Union. The rate of CDI caused by NAP1/BI/027 is similarly decreasing in the United States, where recent epidemiologic data from the Centers for Disease Control and Prevention (CDC) indicate that this strain has been replaced as the most frequently isolated community-associated strain by ribotype 106/REA group DH, which was previously found to be epidemic in the United Kingdom.

CLINICAL MANIFESTATIONS

Diarrhea is the most common manifestation caused by *C. difficile*. Stools are almost never grossly bloody and range from soft and unformed to watery or mucoid in consistency, with a characteristic odor. Clinical and laboratory findings include fever in 28% of cases, abdominal pain in 22%, and leukocytosis in 50%. When adynamic ileus (which is seen on x-ray in ~20% of cases) results in cessation of stool passage, the diagnosis of CDI is frequently overlooked. A clue to the presence of unsuspected CDI in these patients is unexplained leukocytosis, with ≥15,000 white blood cells (WBCs)/μL. Such patients are at high risk for complications of *C. difficile* infection, particularly toxic megacolon and sepsis.

C. difficile diarrhea recurs after treatment in ~15–30% of cases; this figure may have increased as a result of NAP1/BI/027. Recurrences may represent either relapses due to the same strain or reinfections with a new strain. Susceptibility to recurrence of clinical CDI is likely a result of continued disruption of the normal fecal microbiota caused by the antibiotic used to treat CDI.

DIAGNOSIS

The diagnosis of CDI is based on a combination of clinical criteria: (1) diarrhea (≥3 unformed stools per 24 h for ≥2 days) with no other recognized cause plus (2) detection of toxin A or B in the stool, detection of toxin-producing *C. difficile* in the stool by nucleic acid amplification testing (NAAT; e.g., polymerase chain reaction [PCR]) or by culture, or visualization of pseudomembranes in the colon. PMC is a more advanced form of CDI and is visualized at endoscopy in only ~50% of patients with diarrhea who have a positive stool culture and toxin assay for *C. difficile* **(Table 129-1)**. Endoscopy is a rapid diagnostic tool in seriously ill patients with suspected PMC and an acute abdomen, but a negative result in this examination does not rule out CDI.

Despite the array of tests available for *C. difficile* and its toxins (Table 129-1), no single test has high sensitivity, high specificity, and rapid turnaround. Most laboratory tests for toxins, including enzyme immunoassays (EIAs), lack sensitivity. However, testing of multiple additional stool specimens is not recommended. NAATs (including PCR) are widely used diagnostically and are both rapid and sensitive; however, concern has been raised that PCR may detect colonization with toxigenic *C. difficile* in patients who have diarrhea for a reason other than CDI. Confirmation of the presence of toxin in the stool in addition to PCR or glutamate dehydrogenase (GDH) positivity is recommended in the European CDI guidelines for diagnosis of CDI. Empirical treatment is appropriate if CDI is strongly suspected on clinical grounds and stool testing is delayed. Testing of asymptomatic patients is not recommended

TABLE 129-1 Relative Sensitivity and Specificity of Diagnostic Tests for *Clostridium difficile* Infection (CDI)

TYPE OF TEST	RELATIVE SENSITIVITY[a]	RELATIVE SPECIFICITY[a]	COMMENT
Stool culture for *C. difficile*	++++	+++	Most sensitive test; specificity of ++++ if the *C. difficile* isolate tests positive for toxin; turnaround time too slow for practical use
Cell culture cytotoxin test on stool	+++	++++	With clinical data, is diagnostic of CDI; highly specific but not as sensitive as stool culture; slow turnaround time
Enzyme immunoassay for toxins A and B in stool	++ to +++	+++	With clinical data, is diagnostic of CDI; rapid results, but not as sensitive as stool culture or cell culture cytotoxin test
Enzyme immunoassay for *C. difficile* common antigen in stool	+++ to ++++	+++	Detects glutamate dehydrogenase found in toxigenic and nontoxigenic strains of *C. difficile* and other stool organisms; more sensitive and less specific than enzyme immunoassay for toxins; requires confirmation with a toxin test; rapid results
Nucleic acid amplification tests for *C. difficile* toxin A or B gene in stool	++++	+++	Detects toxigenic *C. difficile* in stool; widely used in U.S. for clinical testing; more sensitive than enzyme immunoassay toxin testing; marked increase in CDI diagnoses when implemented
Colonoscopy or sigmoidoscopy	+	++++	Highly specific if pseudomembranes are seen; insensitive compared with other tests

[a]According to both clinical and test-based criteria.

Note: ++++, >90%; +++, 71–90%; ++, 51–70%; +, ~50%.

except for epidemiologic study purposes. In particular, so-called tests of cure following treatment are not recommended because more than 50% of patients continue to harbor the organism and its toxin after diarrhea has ceased and test results do not always predict the recurrence of CDI. The results of such tests should not be used to restrict placement of patients in long-term care or nursing home facilities.

TREATMENT

Clostridium difficile Infection

PRIMARY CDI

When possible, discontinuation of any ongoing antimicrobial administration is recommended as the first step in treatment of CDI. Earlier studies indicated that 15–23% of patients respond to this simple measure. However, with the advent of the NAP1/BI/027 epidemic strain and the associated rapid clinical deterioration of some patients, prompt initiation of specific CDI treatment has become the standard. General treatment guidelines include hydration and the avoidance of antiperistaltic agents and opiates, which may mask symptoms and possibly worsen disease. Nevertheless, antiperistaltic agents have been used safely with vancomycin or metronidazole treatment for mild to moderate CDI.

Oral administration of vancomycin, fidaxomicin, or metronidazole has been recommended for CDI treatment. IV vancomycin is ineffective for CDI. Fidaxomicin is available only for oral administration. Two large clinical trials comparing vancomycin and fidaxomicin indicated comparable clinical resolution of diarrhea in ~90% of patients, and the rate of recurrent CDI was significantly lower with fidaxomicin. When IV metronidazole is administered, fecal bactericidal drug concentrations are achieved during acute diarrhea; however, in the presence of adynamic ileus, IV metronidazole treatment of CDI has failed. In previous randomized trials, diarrhea response rates to oral therapy with vancomycin or metronidazole were ≥94%, but four observational studies found that response rates for metronidazole had declined to 62–78%. In addition to observational reports of increases in metronidazole failures, a prospective, randomized, double-blind, placebo-controlled study demonstrated the superiority of vancomycin over metronidazole for treatment of severe CDI. Furthermore, the largest randomized controlled trial of vancomycin vs metronidazole showed that the vancomycin cure rate was superior to the metronidazole cure rate (81% vs 73%; $p = 0.034$) for all patients with CDI, regardless of severity. Although the mean time to resolution of diarrhea is 2–4 days, the response to metronidazole may be much slower. Treatment should not be deemed a failure until a drug has been given for at least 6 days. On the basis of data for shorter courses of vancomycin and the results of four large clinical trials, it is recommended that vancomycin, fidaxomicin, or metronidazole be given for at least 10 days. Metronidazole is not approved for CDI by the U.S. Food and Drug Administration (FDA), and, despite its low cost, its use for CDI treatment is likely to decline once the results of recent randomized trials are incorporated into CDI treatment guidelines. It is important to initiate treatment with oral vancomycin for patients who appear seriously ill, particularly if they have a high WBC count (>15,000/μL) or a creatinine level that is ≥1.5 times higher than the premorbid value **(Table 129-2)**. Small randomized trials of nitazoxanide, bacitracin, rifaximin, and fusidic acid for treatment of CDI have been conducted. These drugs have not been extensively studied, shown to be superior, or approved by the FDA for CDI, but they provide potential alternatives to vancomycin and fidaxomicin.

RECURRENT CDI

Overall, ~15–30% of successfully treated patients experience recurrences of CDI, either as relapses caused by the original organism or as reinfections following treatment. CDI recurrence is significantly lower in patients treated with fidaxomicin than in those treated with vancomycin. Vancomycin and metronidazole have comparable recurrence rates. Recurrence rates are higher among patients ≥65 years old, those who continue to take antibiotics while being treated for CDI, and those who remain in the hospital after the initial episode of CDI. Patients who have a first recurrence of CDI have a high rate of second recurrence (38%). Fidaxomicin is superior to vancomycin in reducing further recurrences in patients who have had one CDI recurrence (Table 129-2). Recurrent disease, once thought to be relatively mild, has now been documented to pose a significant (11%) risk of serious complications (shock, megacolon, perforation, colectomy, or death within 30 days). There is no standard treatment

TABLE 129-2 Recommendations for the Treatment of *Clostridium difficile* Infection (CDI)

CLINICAL SETTING	TREATMENT(S)	COMMENTS
Initial episode, mild to moderate	Oral vancomycin (125 mg qid × 10 d) ***or*** Fidaxomicin (200 mg bid × 10 d) ***or*** Oral metronidazole (500 mg tid × 10–14 d)	Oral metronidazole is less effective than the other options and may necessitate a longer treatment course for response. Metronidazole is recommended only if vancomycin or fidaxomicin is not readily accessible.
Initial episode, severe	Oral vancomycin (125 mg qid × 10 d) ***or*** Fidaxomicin (200 mg bid × 10 d)	Indicators of severe disease may include leukocytosis (≥15,000 white blood cells/μL) and a creatinine level ≥1.5 times the premorbid value.
Initial episode, fulminant	Vancomycin (500 mg PO or via nasogastric tube) plus metronidazole (500 mg IV q8h) ***plus consider*** Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h)	Fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be >2 weeks and is dictated by response.
First recurrence	Oral vancomycin (125 mg qid × 10 d) ***or*** Oral vancomycin followed by a taper-and-pulse regimen,[a] ***or*** Fidaxomicin (200 mg bid × 10 d)	Treatment for the initial episode should be considered when choosing treatment for the first recurrence.
Multiple recurrences	Oral vancomycin treatment followed by a taper-and-pulse regimen ***or*** Vancomycin (125 mg qid × 10 d), then stop vancomycin and start rifaximin (400 mg bid × 2 weeks); ***or*** Fidaxomicin (200 mg bid × 10 d) ***or*** Fecal microbiota transplantation (FMT)	FMT has been compared to a treatment course of vancomycin and vancomycin followed by a taper-and-pulse vancomycin regimen. The true efficacy of a single FMT may be only 50–60%. It is recommended that FMT given by enema be considered only after appropriate antibiotic treatment for ≥2 recurrent CDI episodes. Other options for multiple CDI recurrences are lacking good comparative data but include: Nitazoxanide (500 mg bid × 10 d) ***or*** Vancomycin (125 mg qid × 10 d) followed by fidaxomicin (200 mg daily × 7 doses, then every other day × 13 doses)

[a]A typical taper-and-pulse vancomycin regimen following a 10-day treatment course includes: 125 mg bid × 1 week, then daily × 1 week, then q2–3d for 2–8 weeks.

for multiple recurrences, but long or repeated metronidazole courses should be avoided because of potential neurotoxicity. The use of vancomycin in tapering doses or with pulsed dosing every other day for 2–8 weeks may be the most practical approach to treating patients with multiple recurrences. Other experimental approaches include (1) administration of vancomycin followed by fecal microbiota transplantation (FMT) via nasoduodenal tube, colonoscope, or enema and (2) intentional colonization of the patient with a nontoxigenic strain of *C. difficile*. There is currently much interest in the use of FMT in patients with multiple recurrences of CDI, for which it appears to be effective. However, neither of these biotherapeutic approaches, including FMT, has been approved by the FDA for use in the United States. The results of randomized controlled trials of FMT continue to be reported, and, as would be expected, the results are not as impressive as in observational trials. Other FDA-unapproved antibiotic strategies include (1) sequential treatment with vancomycin (125 mg four times daily for 10–14 days) followed by rifaximin (400 mg twice daily for 14 days), (2) treatment with nitazoxanide (500 mg twice daily for 10 days), and (3) vancomycin (125 mg 4 times daily for 10 days) followed by fidaxomicin (200 mg daily for 7 days, then every other day for 13 doses).

SEVERE COMPLICATED OR FULMINANT CDI

Fulminant (rapidly progressive and severe) CDI presents the most difficult treatment challenge. Patients with fulminant disease often do not have diarrhea, and their illness mimics an acute surgical abdomen. Sepsis (hypotension, fever, tachycardia, leukocytosis) may result from fulminant CDI. An acute abdomen (with or without toxic megacolon) may include signs of obstruction, ileus, colon-wall thickening and ascites on abdominal CT, and peripheral-blood leukocytosis (≥20,000 WBCs/μL). With or without diarrhea, the differential diagnosis of an acute abdomen, sepsis, or toxic megacolon should include CDI if the patient has received antibiotics in the past 2 months. Cautious sigmoidoscopy or colonoscopy to visualize PMC and an abdominal CT examination are the best diagnostic tests in patients without diarrhea.

Medical management of fulminant CDI is suboptimal because of the difficulty of delivering oral fidaxomicin, metronidazole, or vancomycin to the colon in the presence of ileus (Table 129-2). The combination of vancomycin (given orally or via nasogastric tube and by retention enema) plus IV metronidazole has been used with some success in uncontrolled studies, as has IV tigecycline in small-scale uncontrolled studies. Surgical colectomy may be life-saving if there is no response to medical management. If possible, colectomy should be performed before the serum lactate level reaches 5 mmol/L. The incidence of fulminant CDI requiring colectomy appears to be increasing in the evolving epidemic. However, mortality and morbidity associated with colectomy may be reduced by performing instead a laparoscopic ileostomy followed by colon lavage with polyethylene glycol and vancomycin infusion into the colon via the ileostomy.

PROGNOSIS

The mortality rate attributed to CDI, previously found to be 0.6–3.5%, has reached 6.9% in recent outbreaks and is progressively higher with increasing age. Most patients recover, but recurrences are common.

PREVENTION AND CONTROL

Strategies for the prevention of CDI are of two types: those aimed at preventing transmission of the organism to the patient and those aimed at reducing the risk of CDI if the organism is transmitted. Transmission of *C. difficile* in clinical practice has been prevented by gloving of personnel, elimination of the use of contaminated electronic thermometers, and use of hypochlorite (bleach) solution for environmental decontamination of patients' rooms. Hand hygiene is critical; hand washing is recommended in CDI outbreaks because alcohol hand gels are not sporicidal. CDI outbreaks have been best controlled by restricting the use of specific antibiotics, such as clindamycin, second- and third-generation cephalosporins, and fluoroquinolones. Outbreaks of CDI due to clindamycin-resistant strains have resolved promptly when clindamycin use is restricted. Future prevention strategies include use of monoclonal antibodies, vaccines, and biotherapeutics with live organisms that restore protection from colonization.

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130 Urinary Tract Infections, Pyelonephritis, and Prostatitis

Kalpana Gupta, Barbara W. Trautner

Urinary tract infection (UTI) is a common and painful human illness that, fortunately, is rapidly responsive to modern antibiotic therapy. In the preantibiotic era, UTI caused significant morbidity. Hippocrates, writing about a disease that appears to have been acute cystitis, said that the illness could last for a year before either resolving or worsening to involve the kidneys. When chemotherapeutic agents used to treat UTI were introduced in the early twentieth century, they were relatively ineffective, and persistence of infection after 3 weeks of therapy was common. Nitrofurantoin, which became available in the 1950s, was the first tolerable and effective agent for the treatment of UTI.

Since the most common manifestation of UTI is acute cystitis and since acute cystitis is far more prevalent among women than among men, most clinical research on UTI has involved women. Many studies have enrolled women from college campuses or large health maintenance organizations in the United States. Therefore, when reviewing the literature and recommendations concerning UTI, clinicians must consider whether the findings are applicable to their patient populations.

DEFINITIONS

UTI may be asymptomatic (subclinical infection) or symptomatic (disease). Thus, the term *urinary tract infection* encompasses a variety of clinical entities, including asymptomatic bacteriuria (ASB), cystitis, prostatitis, and pyelonephritis. The distinction between symptomatic UTI and ASB has major clinical implications. Both UTI and ASB connote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine.

However, ASB occurs in the absence of symptoms attributable to the bacteria in the urinary tract and usually does not require treatment, while UTI has more typically been assumed to imply symptomatic disease that warrants antimicrobial therapy. Much of the literature concerning UTI, particularly catheter-associated infection, does not differentiate between UTI and ASB. In this chapter, the term *urinary tract infection* denotes symptomatic disease; *cystitis*, symptomatic infection of the bladder; and *pyelonephritis*, symptomatic infection of the kidneys. *Uncomplicated urinary tract infection* refers to acute cystitis or pyelonephritis in nonpregnant outpatient women without anatomic abnormalities or instrumentation of the urinary tract; the term *complicated urinary tract infection* encompasses all other types of UTI. *Recurrent urinary tract infection* is not necessarily complicated; individual episodes can be uncomplicated and treated as such. *Catheter-associated bacteriuria* can be either symptomatic (CAUTI) or asymptomatic.

EPIDEMIOLOGY AND RISK FACTORS

Except among infants and the elderly, UTI occurs far more commonly in females than in males. During the neonatal period, the incidence of UTI is slightly higher among males than among females because male infants more commonly have congenital urinary tract anomalies. After 50 years of age, obstruction from prostatic hypertrophy becomes common in men, and the incidence of UTI is almost as high among men as among women. Between 1 year and ~50 years of age, UTI and recurrent UTI are predominantly diseases of females. The prevalence of ASB is ~5% among women between ages 20 and 40 and may be as high as 40–50% among elderly women and men.

As many as 50–80% of women in the general population acquire at least one UTI during their lifetime—uncomplicated cystitis in most cases. Recent use of a diaphragm with spermicide, frequent sexual intercourse, and a history of UTI are independent risk factors for acute cystitis. Cystitis is temporally related to recent sexual intercourse in a dose–response manner, with an increased relative risk ranging from 1.4 with one episode of intercourse in the preceding week to 4.8 with five episodes. In healthy postmenopausal women, sexual activity, diabetes mellitus, and incontinence are risk factors for UTI.

Many factors predisposing women to cystitis also increase the risk of pyelonephritis. Factors independently associated with pyelonephritis in young healthy women include frequent sexual intercourse, a new sexual partner, a UTI in the previous 12 months, a maternal history of UTI, diabetes, and incontinence. The shared risk factors for cystitis and pyelonephritis are not surprising given that pyelonephritis typically arises through the ascent of bacteria from the bladder to the upper urinary tract. However, pyelonephritis can occur without symptomatic antecedent cystitis.

About 20–30% of women who have had one episode of UTI will have recurrent episodes. Early recurrence (within 2 weeks) is usually regarded as relapse rather than reinfection and may indicate the need to evaluate the patient for a sequestered focus. Intracellular pods of infecting organisms within the bladder epithelium have been demonstrated in animal models of UTI, but the clinical impact of this phenomenon in humans is not yet clear. The rate of recurrence ranges from 0.3 to 7.6 infections per patient per year, with an average of 2.6 infections per year. It is not uncommon for multiple recurrences to follow an initial infection, resulting in clustering of episodes. Clustering may be related temporally to the presence of a new risk factor, to the sloughing of the protective outer bladder epithelial layer in response to bacterial attachment during acute cystitis, or possibly to antibiotic-related alteration of the normal flora. The likelihood of a recurrence decreases with increasing time since the last infection. A case–control study of predominantly white premenopausal women with recurrent UTI identified frequent sexual intercourse, use of spermicide, a new sexual partner, a first UTI before 15 years of age, and a maternal history of UTI as independent risk factors for recurrent UTI. The only consistently documented behavioral risk factors for recurrent UTI include frequent sexual intercourse and spermicide use. In postmenopausal women, major risk factors for recurrent UTI include a history of premenopausal UTI and anatomic factors affecting bladder emptying, such as cystoceles, urinary incontinence, and residual urine.

In pregnant women, ASB has clinical consequences, and both screening for and treatment of this condition are indicated. Specifically, ASB during pregnancy is associated with maternal pyelonephritis, which in turn is associated with preterm delivery. Antibiotic treatment of ASB in pregnant women can reduce the risk of pyelonephritis, preterm delivery, and low-birth-weight babies.

The majority of men with UTI have a functional or anatomic abnormality of the urinary tract, most commonly urinary obstruction secondary to prostatic hypertrophy. That said, not all men with UTI have detectable urinary abnormalities; this point is particularly relevant for men ≤45 years of age. Lack of circumcision is associated with an increased risk of UTI because *Escherichia coli* is more likely to colonize the glans and prepuce and subsequently migrate into the urinary tract of uncircumcised men.

Women with diabetes have a two- to threefold higher rate of ASB and UTI than women without diabetes; there is insufficient evidence on which to base a corresponding statement about men. Increased duration of diabetes and the use of insulin rather than oral medication are associated with an elevated risk of UTI among women with diabetes. Poor bladder function, obstruction in urinary flow, and incomplete voiding are additional factors commonly found in patients with diabetes that increase the risk of UTI. Impaired cytokine secretion may contribute to ASB in diabetic women. The sodium–glucose co-transporter 2 (SGLT2) inhibitors used for treatment of diabetes result in glycosuria and may be associated with small increases in the risk of UTI.

ETIOLOGY

The uropathogens causing UTI vary by clinical syndrome but are usually enteric gram-negative rods that have migrated to the urinary tract. The susceptibility patterns of these organisms vary by clinical syndrome and by geography. In acute uncomplicated cystitis in the United States, the etiologic agents are highly predictable: *E. coli* accounts for 75–90% of isolates; *Staphylococcus saprophyticus* for 5–15% (with particularly frequent isolation from younger women); and *Klebsiella, Proteus, Enterococcus*, and *Citrobacter* species, along with other organisms, for 5–10%. Similar etiologic agents are found in Europe and Brazil. The spectrum of agents causing uncomplicated pyelonephritis is similar, with *E. coli* predominating. In complicated UTI (e.g., CAUTI), *E. coli* remains the predominant organism, but other aerobic gram-negative rods, such as *Pseudomonas aeruginosa* and *Klebsiella*, *Proteus*, *Citrobacter*, *Acinetobacter*, and *Morganella* species, also are frequently isolated. Gram-positive bacteria (e.g., enterococci and *Staphylococcus aureus*) and yeasts also are important pathogens in complicated UTI. Data on etiology and resistance are generally obtained from laboratory surveys and should be understood in the context that organisms are identified only in cases in which urine is sent for culture—typically, when complicated UTI or pyelonephritis is suspected. Genetic sequencing of the bladder microbiome or of all the bacteria that can be identified in the bladder has consistently demonstrated that more bacterial species are present than can be identified by routine culture methods, in both symptomatic and asymptomatic states. The clinical significance of these non-cultivatable organisms is unknown but has challenged the assumption that the bladder is normally a sterile site.

The available data demonstrate a worldwide increase in the resistance of *E. coli* to antibiotics commonly used to treat UTI. North American and European surveys from women with acute cystitis have documented resistance rates of >20% to trimethoprim-sulfamethoxazole (TMP-SMX) in many regions and >10% to ciprofloxacin in some regions. In community-acquired infections, the increased prevalence of multidrug-resistant uropathogens has left few oral options for therapy in some cases. Since resistance rates vary by local geographic region, with individual patient characteristics, and over time, it is important to use current and local data when choosing a treatment regimen.

PATHOGENESIS

The urinary tract can be viewed as an anatomic unit linked by a continuous column of urine extending from the urethra to the kidneys. In the majority of UTIs, bacteria establish infection by ascending from

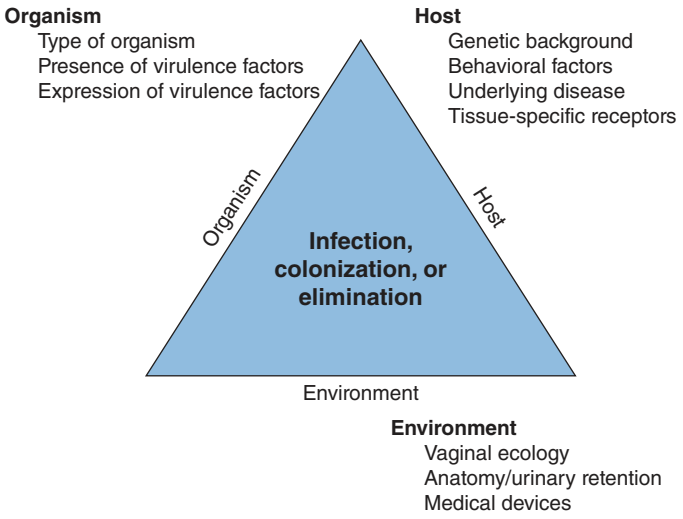


FIGURE 130-1 Pathogenesis of urinary tract infection. The relationship among specific host, pathogen, and environmental factors determines the clinical outcome.

the urethra to the bladder. Continuing ascent up the ureter to the kidney is the pathway for most renal parenchymal infections. However, introduction of bacteria into the bladder does not inevitably lead to sustained and symptomatic infection. The interplay of host, pathogen, and environmental factors determines whether tissue invasion and symptomatic infection will ensue **(Fig. 130-1)**. For example, bacteria often enter the bladder after sexual intercourse, but normal voiding and innate host defense mechanisms in the bladder eliminate these organisms. Any foreign body in the urinary tract, such as a urinary catheter or stone, provides an inert surface for bacterial colonization. Abnormal micturition and/or significant residual urine volume promotes infection. In the simplest of terms, anything that increases the likelihood of bacteria entering the bladder and staying there increases the risk of UTI.

Bacteria can gain access to the urinary tract through the bloodstream. However, hematogenous spread accounts for <2% of documented UTIs and usually results from bacteremia caused by relatively virulent organisms, such as *Salmonella* and *S. aureus*. Indeed, the isolation of either of these pathogens from a patient without a catheter or other instrumentation warrants a search for a bloodstream source. Hematogenous infections may produce focal abscesses or areas of pyelonephritis within a kidney and result in positive urine cultures. The pathogenesis of candiduria is distinct in that the hematogenous route is common. The presence of *Candida* in the urine of a non-instrumented immunocompetent patient implies either genital contamination or potentially widespread visceral dissemination.

Environmental Factors • **VAGINAL ECOLOGY** Vaginal ecology is an important environmental factor affecting the risk of UTI in women. Colonization of the vaginal introitus and periurethral area with organisms from the intestinal flora (usually *E. coli*) is the critical initial step in the pathogenesis of UTI. Sexual intercourse is associated with an increased risk of vaginal colonization with *E. coli* and thereby increases the risk of UTI. Nonoxynol-9 in spermicide is toxic to the normal vaginal lactobacilli and thus is likewise associated with an increased risk of *E. coli* vaginal colonization and bacteriuria. In postmenopausal women, the previously predominant vaginal lactobacilli are replaced with colonizing gram-negative bacteria. The use of topical estrogens to prevent UTI in postmenopausal women is controversial; given the side effects of systemic hormone replacement, oral estrogens should not be used to prevent UTI.

ANATOMIC AND FUNCTIONAL ABNORMALITIES Any condition that permits urinary stasis or obstruction predisposes the individual to UTI. Foreign bodies such as stones or urinary catheters provide an inert surface for bacterial colonization and formation of a persistent biofilm. Thus, vesicoureteral reflux, ureteral obstruction secondary to prostatic hypertrophy, neurogenic bladder, and urinary diversion surgery create an environment favorable to UTI. In persons with such conditions, *E. coli* strains lacking typical urinary virulence factors are often the cause of infection. Inhibition of ureteral peristalsis and decreased ureteral tone leading to vesicoureteral reflux are important in the pathogenesis of pyelonephritis in pregnant women. Anatomic factors—specifically, the distance of the urethra from the anus—are considered to be the primary reason why UTI is predominantly an illness of young women rather than of young men.

Host Factors The genetic background of the host influences the individual's susceptibility to recurrent UTI, at least among women. A familial disposition to UTI and to pyelonephritis is well documented. Women with recurrent UTI are more likely to have had their first UTI before the age of 15 years and to have a maternal history of UTI. A component of the underlying pathogenesis of this familial predisposition to recurrent UTI may be persistent vaginal colonization with *E. coli*, even during asymptomatic periods. Vaginal and periurethral mucosal cells from women with recurrent UTI bind threefold more uropathogenic bacteria than do mucosal cells from women without recurrent infection. Epithelial cells from women who are non-secretors of certain blood group antigens may possess specific types of receptors to which *E. coli* can bind, thereby facilitating colonization and invasion. Mutations in host innate immune response genes (e.g., those coding for Toll-like receptors and the interleukin 8 receptor) also have been linked to recurrent UTI and pyelonephritis. The genetic patterns that predispose to cystitis and pyelonephritis appear to be distinct.

Microbial Factors An anatomically normal urinary tract presents a stronger barrier to infection than a compromised urinary tract. Thus, strains of *E. coli* that cause invasive symptomatic infection of the urinary tract in otherwise normal hosts often possess and express genetic virulence factors, including surface adhesins that mediate binding to specific receptors on the surface of uroepithelial cells. The best-studied adhesins are the P fimbriae, hair-like protein structures that interact with a specific receptor on renal epithelial cells. (The letter *P* denotes the ability of these fimbriae to bind to blood group antigen P, which contains a D-galactose-D-galactose residue.) P fimbriae are important in the pathogenesis of pyelonephritis and subsequent bloodstream invasion from the kidney.

Another adhesin is the type 1 pilus (fimbria), which all *E. coli* strains possess but not all *E. coli* strains express. Type 1 pili are thought to play a key role in initiating *E. coli* bladder infection; they mediate binding to mannose on the luminal surface of bladder uroepithelial cells. Toxins, metal (iron) acquisition systems, biofilm formation, and capsules can also contribute to the ability of pathogenic *E. coli* to thrive in the bladder.

APPROACH TO THE PATIENT

Clinical Syndromes

The most important issue to be addressed when a UTI is suspected is the characterization of the clinical syndrome as ASB, uncomplicated cystitis, pyelonephritis, prostatitis, or complicated UTI. This information will shape the diagnostic and therapeutic approach.

ASYMPTOMATIC BACTERIURIA

A diagnosis of ASB can be considered only when the patient does not have local or systemic symptoms referable to the urinary tract. The clinical presentation is usually bacteriuria detected incidentally when a patient undergoes a screening urine culture for a reason unrelated to the genitourinary tract. Systemic signs or symptoms such as fever, altered mental status, and leukocytosis in the setting of a positive urine culture are nonspecific and do not merit a diagnosis of symptomatic UTI unless other potential etiologies have been considered.

CYSTITIS

The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia, hesitancy, suprapubic discomfort, and gross

hematuria are often noted as well. Unilateral back or flank pain is generally an indication that the upper urinary tract is involved. Fever also is an indication of invasive infection of either the kidney or the prostate.

PYELONEPHRITIS

Mild pyelonephritis can present as low-grade fever with or without lower-back or costovertebral-angle pain, whereas severe pyelonephritis can manifest as high fever, rigors, nausea, vomiting, and flank and/or loin pain. Symptoms are generally acute in onset, and symptoms of cystitis may not be present. Fever is the main feature distinguishing cystitis from pyelonephritis. The fever of pyelonephritis typically exhibits a high spiking "picket-fence" pattern and resolves over 72 h of therapy. Bacteremia develops in 20–30% of cases of pyelonephritis. Patients with diabetes may present with obstructive uropathy associated with acute papillary necrosis when the sloughed papillae obstruct the ureter. Papillary necrosis may also be evident in some cases of pyelonephritis complicated by obstruction, sickle cell disease, analgesic nephropathy, or combinations of these conditions. In the rare cases of bilateral papillary necrosis, a rapid rise in the serum creatinine level may be the first indication of the condition. *Emphysematous* pyelonephritis is a particularly severe form of the disease that is associated with the production of gas in renal and perinephric tissues and occurs almost exclusively in diabetic patients **(Fig. 130-2)**. *Xanthogranulomatous* pyelonephritis occurs when chronic urinary obstruction (often by staghorn calculi), together with chronic infection, leads to suppurative destruction of renal tissue **(Fig. 130-3)**. On pathologic examination, the residual renal tissue frequently has a yellow coloration, with infiltration by lipid-laden macrophages. Pyelonephritis can also be complicated by intraparenchymal abscess formation; this development should be suspected when a patient has continued fever and/or bacteremia despite antibacterial therapy.

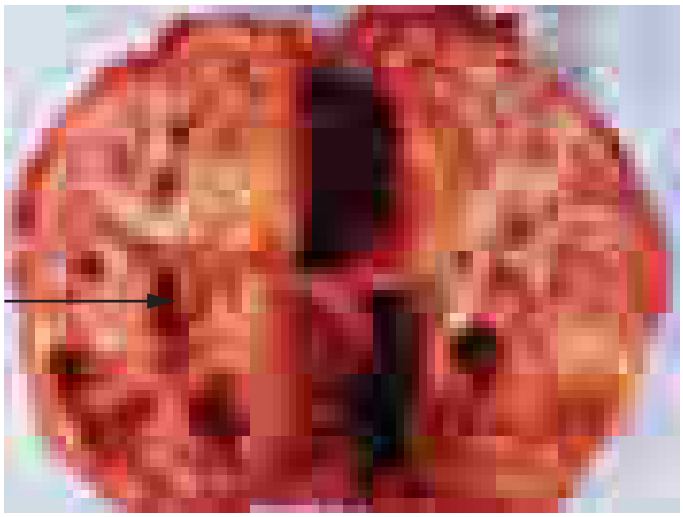
PROSTATITIS

Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always bacterial in nature, and are far less common than the noninfectious entity *chronic pelvic pain syndrome* (formerly known as chronic prostatitis). Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic pelvic or perineal area. Fever and chills are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus as well as urinary retention.

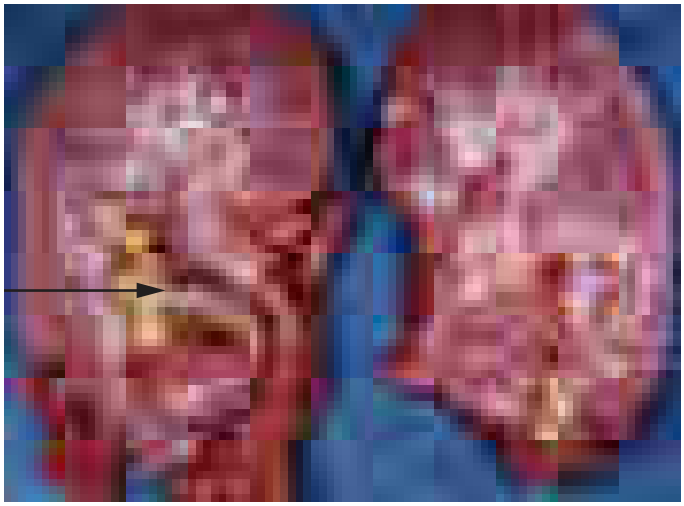
COMPLICATED UTI

Complicated UTI presents as a symptomatic episode of cystitis or pyelonephritis in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

FIGURE 130-2 Emphysematous pyelonephritis. Infection of the right kidney of a diabetic man by *Escherichia coli*, a gas-forming, facultative anaerobic uropathogen, has led to destruction of the renal parenchyma (*arrow*) and tracking of gas through the retroperitoneal space (*arrowhead*).



A



B

FIGURE 130-3 Xanthogranulomatous pyelonephritis. *A.* This photograph shows extensive destruction of renal parenchyma due to long-standing suppurative inflammation. The precipitating factor was obstruction by a staghorn calculus, which has been removed, leaving a depression (*arrow*). The mass effect of xanthogranulomatous pyelonephritis can mimic renal malignancy. ***B.*** A large staghorn calculus (*arrow*) is seen obstructing the renal pelvis and calyceal system. The lower pole of the kidney shows areas of hemorrhage and necrosis with collapse of cortical areas. *(Images courtesy of Dharam M. Ramnani, MD, Virginia Urology Pathology Laboratory, Richmond, VA.)*

DIAGNOSTIC TOOLS

History The diagnosis of any of the UTI syndromes or ASB begins with a detailed history **(Fig. 130-4)**. The history given by the patient

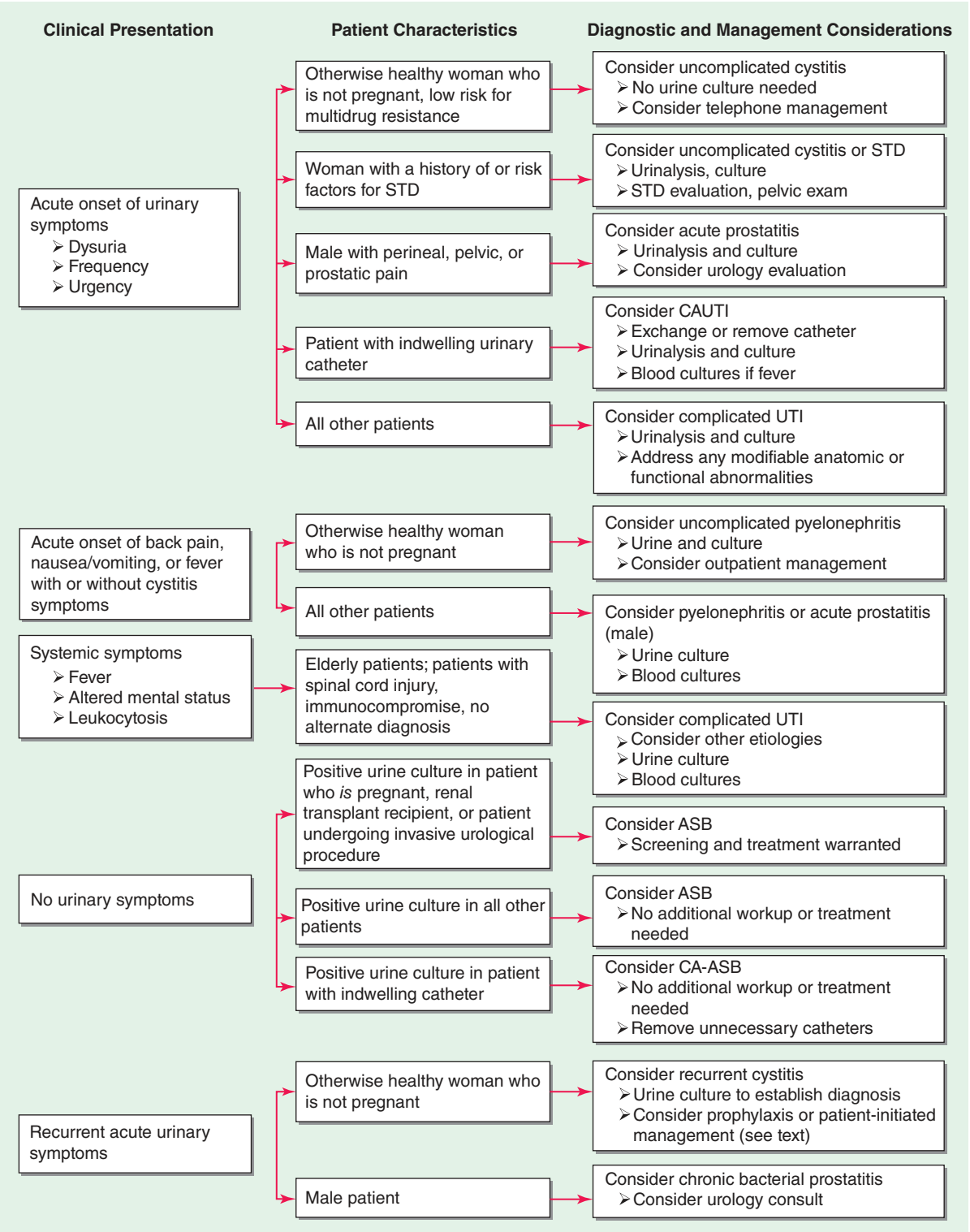


FIGURE 130-4 Diagnostic approach to urinary tract infection (UTI). ASB, asymptomatic bacteriuria; CA-ASB, catheter-associated ASB; CAUTI, catheter-associated UTI; STD, sexually transmitted disease.

has a high predictive value in uncomplicated cystitis. A meta-analysis evaluating the probability of acute UTI on the basis of history and physical findings concluded that, in women presenting with at least one symptom of UTI (dysuria, frequency, hematuria, or back pain) and without complicating factors, the probability of acute cystitis or pyelonephritis is 50%. The even higher rates of accuracy of self-diagnosis among women with recurrent UTI probably account for the success of patient-initiated treatment of recurrent cystitis. If vaginal discharge and complicating factors are absent and risk factors for UTI are present, then the probability of UTI is close to 90%, and no laboratory evaluation is needed. A combination of dysuria and urinary frequency in the absence of vaginal discharge increases the probability of UTI to 96%. Further laboratory evaluation with dipstick testing or urine culture is not necessary in such patients before the initiation of definitive therapy.

In applying the patient's history as a diagnostic tool, the physician must remember that the studies included in the meta-analysis cited above did not enroll children, adolescents, pregnant women, men, or patients with complicated UTI. One significant concern is that sexually transmitted disease—that caused by *Chlamydia trachomatis* in particular—may be inappropriately treated as UTI. This concern is particularly relevant for female patients under the age of 25. The differential diagnosis

to be considered when women present with dysuria includes cervicitis (*C. trachomatis, Neisseria gonorrhoeae*), vaginitis (*Candida albicans, Trichomonas vaginalis*), herpetic urethritis, interstitial cystitis, and noninfectious vaginal or vulvar irritation. Women with more than one sexual partner and inconsistent use of condoms are at high risk for both UTI and sexually transmitted disease, and symptoms alone do not always distinguish between these conditions.

Urine Dipstick Test, Urinalysis, and Urine Culture Useful diagnostic tools include the urine dipstick test and urinalysis, both of which provide point-of-care information, and the urine culture, which can retrospectively confirm a prior diagnosis. Understanding the parameters of the dipstick test is important in interpreting its results. Only members of the family Enterobacteriaceae convert nitrate to nitrite, and enough nitrite must accumulate in the urine to reach the threshold of detection. If a woman with acute cystitis is forcing fluids and voiding frequently, the dipstick test for nitrite is less likely to be positive, even when *E. coli* is present. The leukocyte esterase test detects this enzyme in polymorphonuclear leukocytes in the host's urine, whether the cells are intact or lysed. Many reviews have attempted to describe the diagnostic accuracy of dipstick testing. The bottom line for clinicians is that a urine dipstick test can confirm the diagnosis of uncomplicated cystitis in a patient with a reasonably high pretest probability of this disease; either nitrite or leukocyte esterase positivity can be interpreted as a positive result. Blood in the urine also may suggest a diagnosis of UTI. A dipstick test negative for both nitrite and leukocyte esterase in this type of patient should prompt consideration of other explanations for the patient's symptoms and collection of urine for culture. A negative dipstick test is not sufficiently sensitive to rule out bacteriuria in pregnant women, in whom it is important to detect all episodes of bacteriuria.

Urine microscopy reveals pyuria in nearly all cases of cystitis and hematuria in ~30% of cases. In current practice, most hospital laboratories use an automated system rather than manual examination for urine microscopy. A machine aspirates a sample of the urine and then classifies the particles in the urine by size, shape, contrast, light scatter, volume, and other properties. These automated systems can be overwhelmed by high numbers of dysmorphic red blood cells, white blood cells, or crystals; in general, counts of bacteria are less accurate than are counts of red and white blood cells. The authors' clinical recommendation is that the patient's symptoms and presentation should outweigh an incongruent result on automated urinalysis.

The detection of bacteria in a urine culture is the diagnostic gold standard for UTI; unfortunately, however, culture results do not become available until 24 h after the patient's presentation. Identifying specific organism(s) can require an additional 24 h. Studies of women with symptoms of cystitis have found that a colony count threshold of $\geq 10^2$ bacteria/mL is more sensitive (95%) and specific (85%) than a threshold of 10^5/mL for the diagnosis of acute cystitis in women. In men, the minimal level indicating infection appears to be 10^3/mL. Urine specimens frequently become contaminated with the normal microbial flora of the distal urethra, vagina, or skin. These contaminants can grow to high numbers if the collected urine is allowed to stand at room temperature. In most instances, a culture that yields mixed bacterial species is contaminated except in settings of long-term catheterization, chronic urinary retention, or the presence of a fistula between the urinary tract and the gastrointestinal or genital tract.

DIAGNOSTIC APPROACH

The approach to diagnosis is influenced by which of the clinical UTI syndromes is suspected (Fig. 130-4).

Uncomplicated Cystitis in Women Uncomplicated cystitis in women can be treated on the basis of history alone. However, if the symptoms are not specific or if a reliable history cannot be obtained, then a urine dipstick test should be performed. A positive nitrite or leukocyte esterase result in a woman with one symptom of UTI increases the probability of UTI from 50% to ~80%, and empirical treatment can be considered without further testing. In this setting, a negative dipstick result does not rule out UTI, and a urine culture, close clinical follow-up, and possibly a pelvic examination are recommended. In women with complicated UTI (e.g., due to pregnancy, suspected bacterial resistance, or recent UTI), a urine culture is warranted to guide appropriate therapy.

Cystitis in Men The signs and symptoms of cystitis in men are similar to those in women, but this disease differs in several important ways in the male population. Collection of urine for culture is strongly recommended when a man has symptoms of UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the very common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and thus is not usually responsive to antibacterial therapy. Men with febrile UTI often have an elevated serum level of prostate-specific antigen as well as an enlarged prostate and enlarged seminal vesicles on ultrasound—findings indicative of prostate involvement. In a study of 85 men with febrile UTI, symptoms of urinary retention, early recurrence of UTI, hematuria at follow-up, and voiding difficulties were predictive of surgically correctable disorders. Men with none of these symptoms had normal upper and lower urinary tracts on urologic workup. In general, men with a first febrile UTI should have imaging performed (CT or ultrasound); if the diagnosis is unclear or if UTI is recurrent, referral for urologic consultation and further evaluation—including potential localization cultures using the two- or four-glass Meares-Stamey test (urine collection after prostate massage)—is appropriate.

Asymptomatic Bacteriuria The diagnosis of ASB involves both microbiologic and clinical criteria. The microbiologic criterion (including in urinary catheter–associated asymptomatic bacteriuria) is $\geq 10^5$ bacterial CFU/mL of urine. The clinical criterion is an absence of signs or symptoms referable to UTI.

TREATMENT

Urinary Tract Infections

Treatment of UTI accounts for a major proportion of antimicrobial use in ambulatory care, inpatient care, and long-term-care settings. Responsible use of antibiotics for this common infection has broad implications for preserving antibiotic effectiveness into the future. That said, antimicrobial therapy is warranted for any UTI that is truly symptomatic. The choice of antimicrobial agent, the dose, and the duration of therapy depend on the site of infection and the presence or absence of complicating conditions. Each category of UTI warrants a different approach based on the particular clinical syndrome.

Antimicrobial resistance among uropathogens varies from region to region and impacts the approach to empirical treatment of UTI. *E. coli* ST131 is the predominant multilocus sequence type found worldwide as the cause of multidrug-resistant UTI. Recommendations for treatment must be considered in the context of local resistance patterns and national differences in some agents' availability. For example, fosfomycin and pivmecillinam are not available in all countries but are considered first-line options where they are available because they retain activity against a majority of uropathogens that produce extended-spectrum β-lactamases. Thus, therapeutic choices should depend on local resistance, drug availability, and individual patient factors such as recent travel and antimicrobial use.

UNCOMPLICATED CYSTITIS IN WOMEN

Since the species and antimicrobial susceptibilities of the bacteria that cause acute uncomplicated cystitis are highly predictable, many episodes of uncomplicated cystitis can be managed over the telephone (Fig. 130-4). Most patients with other UTI syndromes require further diagnostic evaluation. Although the risk of serious complications with telephone management appears to be low, studies of telephone management algorithms generally have involved otherwise healthy women who are at low risk of complications of UTI.

In 1999, TMP-SMX was recommended as the first-line agent for treatment of uncomplicated UTI in the published guidelines of the Infectious Diseases Society of America. Since then, antibiotic resistance among uropathogens causing uncomplicated cystitis has increased, appreciation of the importance of collateral damage (as defined below) has increased, and newer agents have been studied. Unfortunately, there is no longer a single best agent for acute uncomplicated cystitis.

Collateral damage refers to the adverse ecologic effects of antimicrobial therapy, including killing of the normal flora and selection of drug-resistant organisms. The implication of collateral damage for UTI management is that a drug that is highly efficacious for the treatment of UTI is not necessarily the optimal first-line agent if it also has pronounced secondary effects on the normal flora or is likely to adversely affect resistance patterns. Drugs used for UTI that have a minimal effect on fecal flora include pivmecillinam, fosfomycin, and nitrofurantoin. In contrast, trimethoprim, TMP-SMX, quinolones, and ampicillin affect the fecal flora more significantly; these drugs are notably the agents for which rising resistance levels have been documented.

Choosing judiciously whether to initiate antibiotic therapy and then selecting the most urinary-focused agent for the shortest appropriate duration are important factors in global efforts to stem the rise of antimicrobial-resistant organisms. Several effective therapeutic regimens are available for acute uncomplicated cystitis in women **(Table 130-1)**. Well-studied first-line agents include TMP-SMX and nitrofurantoin. Second-line agents include β-lactams. There is increasing experience with the use of fosfomycin for UTIs (including complicated infections), particularly for infections caused by multidrug-resistant *E. coli*. According to an advisory from the U.S. Food and Drug Administration (FDA), fluoroquinolones should not be used for uncomplicated cystitis unless no alternatives are available. Pivmecillinam is not currently available in the United States or Canada but is a popular agent in some European countries. The pros and cons of specific agents are discussed briefly below.

Traditionally, TMP-SMX has been recommended as first-line treatment for acute cystitis, and it remains appropriate to consider the use of this drug in regions with resistance rates not exceeding 20%. In women with recurrent UTI, prior cultures can be used as a guide to TMP-SMX susceptibility, although interim acquisition of resistant bacteria can occur. TMP-SMX resistance has clinical significance: in TMP-SMX-treated patients with resistant isolates, the time to symptom resolution is longer and rates of both clinical and microbiologic failure are higher. Individual host factors associated with an elevated risk of UTI caused by a strain of *E. coli* resistant to TMP-SMX include recent use of TMP-SMX or another antimicrobial agent and recent travel to an area with high rates of TMP-SMX resistance. The optimal setting for empirical use of TMP-SMX is uncomplicated UTI in a female patient who has an established relationship with the practitioner and who can thus seek further care if her symptoms do not respond promptly.

Resistance to nitrofurantoin remains low despite >60 years of use, as several mutational steps are required for the development of bacterial resistance to this drug. Nitrofurantoin remains highly active against *E. coli* and most non–*E. coli* isolates. *Proteus*, *Pseudomonas*, *Serratia*, *Enterobacter*, and yeasts are all intrinsically resistant to this drug. Although nitrofurantoin has traditionally been prescribed as a 7-day regimen, guidelines now recommend a 5-day course, which is as effective as a 3-day course of TMP-SMX for treatment of acute cystitis; 3-day courses of nitrofurantoin are not recommended for acute cystitis. Nitrofurantoin does not reach significant levels in tissue and cannot be used to treat pyelonephritis.

Most fluoroquinolones are highly effective as short-course therapy for cystitis; the exception is moxifloxacin, which may not reach adequate urinary levels. The fluoroquinolones commonly used for UTI include ciprofloxacin and levofloxacin. The two main concerns about fluoroquinolone use for acute cystitis are the propagation of fluoroquinolone resistance, not only among uropathogens but also among other organisms causing more serious and difficult-to-treat infections at other sites, and their rare but potentially serious adverse effects. For example, quinolone use in certain populations, including adults >60 years of age, has been associated with an increased risk of Achilles tendon rupture. Other potential side effects include irreversible neuropathy. In light of these detrimental effects, the FDA issued an advisory against using fluoroquinolones to treat acute cystitis in patients who have other therapeutic options.

β-Lactam agents generally have not performed as well as TMP-SMX or fluoroquinolones in acute cystitis. Rates of pathogen eradication are lower and relapse rates are higher with β-lactam drugs. The generally accepted explanation is that β-lactams fail to eradicate uropathogens from the vaginal reservoir. Many strains of *E. coli* that are resistant to TMP-SMX are also resistant to amoxicillin and cephalexin; thus, these drugs should be used only for patients infected with susceptible strains.

Urinary analgesics are appropriate in certain situations to speed resolution of bladder discomfort. The urinary tract analgesic phenazopyridine is widely used but can cause significant nausea. Combination analgesics containing urinary antiseptics (methenamine, methylene blue), a urine-acidifying agent (sodium phosphate), and an antispasmodic agent (hyoscyamine) also are available.

Interest in the responsible use of antibiotics has led to exploration of antibiotic-sparing approaches to the treatment of acute uncomplicated cystitis. Both placebo and analgesics alone have proved inferior to antibiotics for resolution of symptoms and prevention of pyelonephritis. Delayed therapy, in which a woman receives a prescription for antibiotics but fills it only if symptoms fail to resolve in a day or two, has the potential advantage of avoiding antibiotic

TABLE 130-1 Treatment Strategies for Acute Uncomplicated Cystitis

DRUG AND DOSE	ESTIMATED CLINICAL EFFICACY, %	ESTIMATED BACTERIAL EFFICACY,[a] %	COMMON SIDE EFFECTS
Nitrofurantoin, 100 mg bid × 5–7 d	87–95	82–92	Nausea, headache
TMP-SMX, 1 DS tablet bid × 3 d	86–100	85–100	Rash, urticaria, nausea, vomiting, hematologic abnormalities
Fosfomycin, 3-g single-dose sachet	83–95	78–98	Diarrhea, nausea, headache
Pivmecillinam, 400 mg bid × 3–7 d	55–82	74–84	Nausea, vomiting, diarrhea
Fluoroquinolones, dose varies by agent; 3-d regimen	81–98	78–96	Nausea, vomiting, diarrhea, headache, drowsiness, insomnia
β-Lactams, dose varies by agent; 5- to 7-d regimen	79–98	74–98	Diarrhea, nausea, vomiting, rash, urticaria

[a]Microbial response as measured by reduction of bacterial counts in the urine.

Note: Efficacy rates are averages or ranges calculated from the data and studies included in the 2010 Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases guideline for treatment of uncomplicated UTI and the 2014 *JAMA* systematic review on UTI in the outpatient setting. Ranges are estimates from published studies and may vary by specific agent and by rate of resistance.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

use in those who either do not have cystitis to begin with or have a mild case that resolves spontaneously. The downside is that women who really do have cystitis endure discomfort for a longer period and may meanwhile progress to pyelonephritis. However, one certain measure for more responsible use of antibiotics in cystitis is to treat for the correct duration; in practice, many episodes of acute cystitis are treated longer than is recommended by evidence-based guidelines.

PYELONEPHRITIS

Since patients with pyelonephritis have tissue-invasive disease, the treatment regimen chosen should have a very high likelihood of eradicating the causative organism and should reach therapeutic blood levels quickly. High rates of TMP-SMX-resistant *E. coli* in patients with pyelonephritis have made fluoroquinolones the first-line therapy for acute uncomplicated pyelonephritis. Whether the fluoroquinolones are given orally or parenterally depends on the patient's tolerance for oral intake. A randomized clinical trial demonstrated that a 7-day course of therapy with oral ciprofloxacin (500 mg twice daily, with or without an initial IV 400-mg dose) was highly effective for the initial management of pyelonephritis in the outpatient setting. Oral TMP-SMX (one double-strength tablet twice daily for 14 days) also is effective for treatment of acute uncomplicated pyelonephritis if the uropathogen is known to be susceptible. If the pathogen's susceptibility is not known and TMP-SMX is used, an initial IV 1-g dose of ceftriaxone is recommended. Oral β-lactam agents are less effective than the fluoroquinolones and should be used with caution and close follow-up. Options for parenteral therapy for uncomplicated pyelonephritis include fluoroquinolones, an extended-spectrum cephalosporin with or without an aminoglycoside, or a carbapenem. Combinations of a β-lactam and a β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam) or a carbapenem (imipenem-cilastatin, ertapenem, meropenem) can be used in patients with more complicated histories, previous episodes of pyelonephritis, anticipated antimicrobial resistance, or recent urinary tract manipulations; in general, the treatment of such patients should be guided by urine culture results. Once the patient has responded clinically, oral therapy should be substituted for parenteral therapy.

UTI IN PREGNANT WOMEN

Nitrofurantoin, ampicillin, and the cephalosporins are considered relatively safe in early pregnancy. One retrospective case-control study suggesting an association between nitrofurantoin and birth defects has not been confirmed. Sulfonamides should clearly be avoided both in the first trimester (because of possible teratogenic effects) and near term (because of a possible role in the development of kernicterus). Fluoroquinolones are avoided because of possible adverse effects on fetal cartilage development. Ampicillin and the cephalosporins have been used extensively in pregnancy and are the drugs of choice for the treatment of asymptomatic or symptomatic UTI in this group of patients. Generally, pregnant women with ASB are treated for 4–7 days in the absence of evidence to support single-dose therapy. For pregnant women with overt pyelonephritis, parenteral β-lactam therapy with or without aminoglycosides is the standard of care.

UTI IN MEN

Since the prostate is involved in the majority of cases of febrile UTI in men, the goal in these patients is to eradicate the prostatic infection as well as the bladder infection. A 7- to 14-day course of a fluoroquinolone or TMP-SMX is recommended if the uropathogen is susceptible. If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures. Therapy can be tailored to urine culture results and should be continued for 2–4 weeks. For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary. Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment.

COMPLICATED UTI

Complicated UTI (other than that discussed above) occurs in a heterogeneous group of patients with a wide variety of structural and functional abnormalities of the urinary tract and kidneys. The range of species and their susceptibility to antimicrobial agents are likewise heterogeneous. As a consequence, therapy for complicated UTI must be individualized and guided by urine culture results. Frequently, a patient with complicated UTI will have prior urine-culture data that can be used to guide empirical therapy while current culture results are pending. Xanthogranulomatous pyelonephritis is treated with nephrectomy. Percutaneous drainage can be used as the initial therapy in emphysematous pyelonephritis and can be followed by elective nephrectomy as needed. Papillary necrosis with obstruction requires intervention to relieve the obstruction and to preserve renal function.

ASYMPTOMATIC BACTERIURIA

Treatment of ASB does not decrease the frequency of symptomatic infections or complications except in pregnant women, persons undergoing urologic surgery, and perhaps neutropenic patients and renal transplant recipients. Treatment of ASB in pregnant women and patients undergoing urologic procedures should be directed by urine culture results. In all other populations, screening for and treatment of ASB are discouraged. The majority of cases of catheter-associated bacteriuria are asymptomatic and do not warrant antimicrobial therapy.

CATHETER-ASSOCIATED UTI

Multiple institutions have released guidelines for the treatment of CAUTI, which is defined by bacteriuria and symptoms in a catheterized patient. The signs and symptoms either are localized to the urinary tract or can include otherwise unexplained systemic manifestations, such as fever. The accepted threshold for bacteriuria to meet the definition of CAUTI is $\geq 10^3$ CFU/mL of urine, while the threshold for bacteriuria to meet the definition of ASB is $\geq 10^5$ CFU/mL.

As catheters provide a conduit for bacteria to enter the bladder, bacteriuria is inevitable with long-term catheter use. The typical signs and symptoms of UTI, including pain, urgency, dysuria, fever, peripheral leukocytosis, and pyuria, have less predictive value for the diagnosis of infection in catheterized patients. Furthermore, the presence of bacteria in the urine of a patient who is febrile and catheterized does not necessarily mean that the patient has CAUTI, and other explanations for the fever should be considered.

The etiology of CAUTI is diverse, and urine culture results are essential to guide treatment. Fairly good evidence supports the practice of catheter change during treatment for CAUTI. The goal is to remove biofilm-associated organisms that could serve as a nidus for reinfection. Pathology studies reveal that many patients with long-term catheters have occult pyelonephritis. A randomized trial in persons with spinal cord injury who were undergoing intermittent catheterization found that relapse was more common after 3 days of therapy than after 14 days. In general, a 7- to 14-day course of antibiotics is recommended, but further studies on the optimal duration of therapy are needed.

The best strategy for prevention of CAUTI is to avoid insertion of unnecessary catheters and to remove catheters once they are no longer necessary. Quality-improvement collaboratives that have addressed technical aspects of CAUTI prevention (such as avoidance of inappropriate catheterization) as well as team communication strategies have shown the benefit of this approach in decreasing CAUTI in both acute- and long-term-care settings. Antimicrobial catheters impregnated with silver or nitrofurazone have not been shown to provide significant clinical benefit in terms of reducing rates of symptomatic UTI. Evidence is insufficient to recommend suprapubic catheters and condom catheters as alternatives to indwelling urinary catheters as a means to prevent bacteriuria. However, intermittent catheterization may be preferable to long-term indwelling urethral catheterization in certain populations

(e.g., spinal cord–injured persons) to prevent both infectious and anatomic complications.

CANDIDURIA

The appearance of *Candida* in the urine is an increasingly common complication of indwelling catheterization, particularly for patients in the intensive care unit, those taking broad-spectrum antimicrobial drugs, and those with underlying diabetes mellitus. In many studies, >50% of urinary *Candida* isolates have been found to be non-*albicans* species. The clinical presentation varies from a laboratory finding without symptoms to pyelonephritis and even sepsis. Removal of the urethral catheter results in resolution of candiduria in more than one-third of asymptomatic cases. Treatment of asymptomatic patients does not appear to decrease the frequency of recurrence of candiduria. Therapy is recommended for patients who have symptomatic cystitis or pyelonephritis and for those who are at high risk for disseminated disease. High-risk patients include those with neutropenia, those who are undergoing urologic manipulation, those who are clinically unstable, and low-birth-weight infants. Fluconazole (200–400 mg/d for 7–14 days) reaches high levels in urine and is the first-line regimen for *Candida* infections of the urinary tract. Although instances of successful eradication of candiduria by some of the newer azoles and echinocandins have been reported, these agents are characterized by only low-level urinary excretion and thus are not recommended. For *Candida* isolates with high levels of resistance to fluconazole, oral flucytosine and/or parenteral amphotericin B are options. Bladder irrigation with amphotericin B generally is not recommended.

PREVENTION OF RECURRENT UTI IN WOMEN

Recurrence of uncomplicated cystitis in reproductive-age women is common, and a preventive strategy is indicated if recurrent UTIs are interfering with a patient's lifestyle. The threshold of two or more symptomatic episodes per year is not absolute; decisions about interventions should take the patient's preferences into account.

Three prophylactic strategies are available: continuous, postcoital, and patient-initiated therapy. Continuous prophylaxis and postcoital prophylaxis usually entail low doses of TMP-SMX, a fluoroquinolone, or nitrofurantoin. These regimens are all highly effective during the period of active antibiotic intake. Typically, a prophylactic regimen is prescribed for 6 months and then discontinued, at which point the rate of recurrent UTI often returns to baseline. If bothersome infections recur, the prophylactic program can be reinstituted for a longer period. Selection of resistant strains in the fecal flora has been documented in studies of women taking prophylactic antibiotics for 12 months.

Patient-initiated therapy involves supplying the patient with materials for urine culture and with a course of antibiotics for self-medication at the first symptoms of infection. The urine culture is refrigerated and delivered to the physician's office for confirmation of the diagnosis. When an established and reliable patient–provider relationship exists, the urine culture can be omitted as long as the symptomatic episodes respond completely to short-course therapy and are not followed by relapse.

Non-antimicrobial prevention is increasingly being studied. Lactobacillus probiotics are one appealing approach to UTI prevention, but there is a paucity of data to support this strategy. Similarly, studies of cranberry products for UTI prevention have produced mixed results. Varied dosing and product composition between studies remains an issue for providing clinical guidance.

PROGNOSIS

Cystitis is a risk factor for recurrent cystitis and pyelonephritis. ASB is common among elderly and catheterized patients but does not in itself increase the risk of death. The relationships among recurrent UTI, chronic pyelonephritis, and renal insufficiency have been widely studied. In the absence of anatomic abnormalities such as reflux, recurrent infection in children and adults does not lead to chronic pyelonephritis or to renal failure. Moreover, infection does not play a primary role in chronic interstitial nephritis; the primary etiologic factors in this condition are analgesic abuse, obstruction, reflux, and toxin exposure. In the presence of underlying renal abnormalities (particularly obstructing stones), infection as a secondary factor can accelerate renal parenchymal damage. In spinal cord–injured patients, use of a long-term indwelling bladder catheter is a well-documented risk factor for bladder cancer. Chronic bacteriuria resulting in chronic inflammation is one possible explanation for this observation.

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131 Sexually Transmitted Infections: Overview and Clinical Approach

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CLASSIFICATION AND EPIDEMIOLOGY

Worldwide, most adults acquire at least one sexually transmitted infection (STI), and many remain at risk for complications. Each day, for example, more than 1 million STIs are acquired worldwide, placing many affected persons at risk for adverse reproductive health outcomes and neoplasia. Certain STIs, such as syphilis, gonorrhea, HIV infection, hepatitis B, and chancroid, often occur in highly interconnected sexual networks characterized by high rates of partner change or multiple concurrent partners. Such networks, for example, often include persons who engage in transactional sex, men who have sex with men (MSM), and persons involved in the use of illicit drugs, particularly methamphetamine. Other STIs are distributed more evenly throughout populations. For example, chlamydial infections, genital human papillomavirus (HPV) infections, and genital herpes can spread efficiently even in relatively low-risk populations. Finally, modern technologies based on detection of nucleic acid have accelerated elucidation of the role of sexual transmission in the spread of some viruses, including Ebola virus and Zika virus, and have provided new evidence of apparent sexual transmission of several bacteria, including group C *Neisseria meningitidis* and anaerobes associated with bacterial vaginosis (BV).

In general, the product of three factors determines the initial rate of spread of any STI within a population: rate of sexual exposure of susceptible to infectious people, efficiency of transmission per exposure, and duration of infectivity of those infected. Accordingly, efforts to prevent and control STIs aim to decrease the rate of sexual exposure of susceptible to infected persons (e.g., through education and efforts to change sexual behavior norms and through control efforts aimed at reducing the proportion of the population infected); to decrease the duration of infectivity (through early diagnosis and curative or

suppressive treatment); and to decrease the efficiency of transmission (through promotion of condom use and safer sexual practices, use of effective vaccines, and male medical circumcision).

In all societies, STIs rank among the most common of all infectious diseases, with at least 40 microorganisms now classified as predominantly sexually transmitted or as frequently sexually transmissible **(Table 131-1)**. In developing countries, with three-quarters of the world's population and 90% of the world's STIs, factors such as population growth (especially in adolescent and young-adult age groups), rural-to-urban migration, wars, limited or no provision of reproductive health services for women, and poverty create exceptional vulnerability to disease resulting from unprotected sex. During the 1990s in China, Russia, the other states of the former Soviet Union, and South Africa, internal social structures changed rapidly as borders opened to the West, unleashing enormous new epidemics of HIV infection and other STIs. Despite advances in the provision of highly effective antiretroviral therapy worldwide, HIV remains the leading cause of death in some developing countries, and HPV and hepatitis B virus (HBV) remain important causes of cervical and hepatocellular carcinoma, respectively—two of the most common (and preventable) malignancies in the developing world. Sexually transmitted herpes simplex virus (HSV) infection causes most genital ulcer disease throughout the world, and an increasing proportion of cases of genital herpes occur in developing countries with generalized HIV epidemics, where the positive-feedback loop between HSV and HIV transmission remains intractable. Despite this consistent link, randomized trials evaluating the efficacy of antiviral therapy in suppressing HSV in both HIV-uninfected and HIV-infected persons have demonstrated no protective effect against acquisition or transmission of HIV. The World Health Organization estimated that 357 million new cases of four curable STIs—gonorrhea, chlamydial infection, syphilis, and trichomoniasis—occurred annually in recent years. Up to 50% of women of reproductive age in developing countries have BV (arguably acquired sexually). All of these curable STIs have been associated with increased risk of HIV transmission or acquisition.

In the United States, the prevalence of antibody to HSV-2 began to fall in the late 1990s, especially among adolescents and young adults; the decline was presumably due to delayed sexual debut, increased condom use, and lower rates of multiple (four or more) sex partners—all well documented by the U.S. Youth Risk Behavior Surveillance System. The estimated annual incidence of HBV infection has also declined dramatically since the mid-1980s; this decrease is probably attributable to now-widespread administration of hepatitis B vaccine in infancy. Genital HPV remains the most common sexually transmitted pathogen in the United States, infecting 60% of a cohort of initially HPV-negative, sexually active Washington state college women within 5 years in a study conducted from 1990 to 2000—i.e., during the pre–HPV immunization era. The scale-up of HPV vaccine coverage among young women has already shown promise in reducing the incidence of infection with the HPV types included in the vaccines and of conditions associated with these viruses.

In industrialized countries, fear of HIV infection in the mid-1980s and through the mid-2000s, coupled with widespread behavioral interventions and better-organized systems of care for the curable STIs, initially helped curb the transmission of several STDs. However, with well-tolerated and highly effective antiretroviral therapy now available, HIV has become for many a chronic disease associated with a normal life span and high quality of life. Rates of gonorrhea and syphilis remain higher in the United States than in any other Western industrialized country.

In the United States, the Centers for Disease Control and Prevention (CDC) has compiled reported rates of STIs since 1941. The incidence of reported gonorrhea peaked at 468 cases per 100,000 population in the mid-1970s and fell to a low of 98 cases per 100,000 in 2012. With increased testing and more sensitive tests, the incidence of reported *Chlamydia trachomatis* infection has been increasing steadily since reporting began in 1984, reaching an all-time peak of 457.6 cases per 100,000 in 2011. The incidence of primary and secondary syphilis per 100,000 peaked at 71 cases in 1946, fell rapidly to 3.9 cases in 1956, ranged from ~10 to 15 cases through 1987 (with markedly increased rates among MSM and African Americans), and then fell to a nadir of 2.1 cases in 2000–2001 (with rates falling most rapidly among heterosexual African Americans). However, since 1996, with the introduction of highly active antiretroviral therapy, gonorrhea, syphilis, and chlamydial infection have had a remarkable resurgence among MSM in North America and Europe, where outbreaks of a rare type of chlamydial infection (lymphogranuloma venereum [LGV]) that had virtually disappeared during the AIDS era have occurred. In 2014, ~75% of primary and secondary syphilis cases reported to the CDC were in MSM. Moreover, the uptake of daily oral emtricitabine/tenofovir as oral pre-exposure prophylaxis for HIV-1 acquisition has increased among MSM since its initial approval for this purpose in 2012 and has been associated with reports of reduced condom-use frequency and concomitantly increased STI acquisition. These developments have resulted in a soaring incidence of STIs, with increasing co-infection with HIV and other sexually transmitted pathogens (particularly *Treponema pallidum*, the cause of syphilis; and *Neisseria gonorrhoeae*, the cause of gonorrhea), primarily among MSM.

TABLE 131-1 Sexually Transmitted and Sexually Transmissible Microorganisms

BACTERIA	VIRUSES	OTHER[a]
Transmitted in Adults Predominantly by Sexual Intercourse		
Neisseria gonorrhoeae *Chlamydia trachomatis* *Treponema pallidum* *Haemophilus ducreyi* *Klebsiella (Calymmatobacterium) granulomatis* *Ureaplasma urealyticum* *Mycoplasma genitalium*	HIV (types 1 and 2) Human T-cell lymphotropic virus type 1 Herpes simplex virus type 2 Human papillomavirus (multiple genital genotypes) Hepatitis B virus[b] Molluscum contagiosum virus	*Trichomonas vaginalis* *Pthirus pubis*
Sexual Transmission Repeatedly Described but Not Well Defined or Not the Predominant Mode		
Mycoplasma hominis *Gardnerella vaginalis* and other vaginal bacteria Group B *Streptococcus* *Mobiluncus* spp. *Helicobacter cinaedi* *Helicobacter fennelliae* Anaerobes associated with bacterial vaginosis *Leptotrichia/Sneathia* Group C *Neisseria meningitidis*	Cytomegalovirus Human T-cell lymphotropic virus type 2 Hepatitis C virus (?) Hepatitis D virus Herpes simplex virus type 1 Zika virus Ebola virus (?) Epstein-Barr virus Human herpesvirus type 8	*Candida albicans* *Sarcoptes scabiei*
Transmitted by Sexual Contact Involving Oral–Fecal Exposure; of Declining Importance in Men Who Have Sex with Men		
Shigella spp. *Campylobacter* spp.	Hepatitis A virus	*Giardia lamblia* *Entamoeba histolytica*

[a]Includes protozoa, ectoparasites, and fungi. [b]Among U.S. patients for whom a risk factor can be ascertained, most hepatitis B virus infections are transmitted sexually.

MANAGEMENT OF COMMON SEXUALLY TRANSMITTED DISEASE (STD) SYNDROMES

Although other chapters discuss management of specific STIs, most patients are managed (at least initially) on the basis of presenting symptoms and signs and associated risk factors, even in industrialized countries. **Table 131-2** lists some of the most common clinical STD syndromes and their microbial etiologies. Strategies for their management are outlined below. **Chapters 196 and 197 address the management of infections with human retroviruses.**

TABLE 131-2 Major Sexually Transmitted Disease Syndromes and Sexually Transmitted Microbial Etiologies

SYNDROME	SEXUALLY TRANSMITTED MICROBIAL ETIOLOGIES
AIDS	HIV types 1 and 2
Urethritis: males	*Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum* (subspecies *urealyticum*), *Trichomonas vaginalis,* HSV, some anaerobic bacteria, *Leptotrichia/Sneathia*
Epididymitis	*C. trachomatis, N. gonorrhoeae*, and (in older men or men who have sex with men) coliform bacteria
Lower genital tract infections: females	
Cystitis/urethritis	*C. trachomatis, N. gonorrhoeae,* HSV
Mucopurulent cervicitis	*C. trachomatis, N. gonorrhoeae, M. genitalium*
Vulvitis	*Candida albicans,* HSV
Bartholinitis	*C. albicans, T. vaginalis*
Vulvovaginitis	*C. albicans, T. vaginalis*
BV	BV-associated bacteria (see text)
Acute pelvic inflammatory disease	*N. gonorrhoeae, C. trachomatis,* BV-associated bacteria, *M. genitalium,* group B streptococci
Infertility	*N. gonorrhoeae, C. trachomatis,* BV-associated bacteria
Ulcerative lesions of the genitalia	HSV-1, HSV-2, *Treponema pallidum, Haemophilus ducreyi, C. trachomatis* (LGV strains), *Klebsiella (Calymmatobacterium) granulomatis*
Complications of pregnancy/puerperium	Several pathogens implicated
Intestinal infections	
Proctitis	*C. trachomatis, N. gonorrhoeae,* HSV, *T. pallidum*
Proctocolitis or enterocolitis	*Campylobacter* spp., *Shigella* spp., *Entamoeba histolytica, Helicobacter* spp., other enteric pathogens
Enteritis	*Giardia lamblia*
Acute arthritis with urogenital infection or viremia	*N. gonorrhoeae* (e.g., DGI), *C. trachomatis* (e.g., reactive arthritis), HBV
Genital and anal warts	HPV (30 genital types)
Mononucleosis syndrome	CMV, HIV, EBV
Hepatitis	Hepatitis viruses, *T. pallidum,* CMV, EBV
Neoplasias	
Squamous cell dysplasias and cancers of the cervix, anus, vulva, vagina, or penis	HPV (especially types 16, 18, 31, 45)
Kaposi's sarcoma, body-cavity lymphomas	HHV-8
T cell leukemia	HTLV-1
Hepatocellular carcinoma	HBV
Tropical spastic paraparesis	HTLV-1
Scabies	*Sarcoptes scabiei*
Pubic lice	*Pthirus pubis*

Abbreviations: BV, bacterial vaginosis; CMV, cytomegalovirus; DGI, disseminated gonococcal infection; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HHV-8, human herpesvirus type 8; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; LGV, lymphogranuloma venereum.

STD care and management begin with risk assessment and proceed to clinical assessment, diagnostic testing or screening, treatment, and prevention. Risk assessment guides detection and interpretation of symptoms that could denote an STD; decisions on screening or prophylactic/preventive treatment; risk reduction counseling and intervention (e.g., hepatitis B vaccination); treatment of partners of patients with known infections; and behavioral risk reduction by the patient. Consideration of routine demographic data (e.g., gender, age, area of residence) is a simple first step in this risk assessment. For example, national guidelines strongly recommend routine screening of sexually active females ≤25 years of age for *C. trachomatis* infection. Table 131-3 provides a set of 11 STD/HIV risk-assessment questions that clinicians can pose verbally or that health care systems can adapt (with yes/no responses) into a routine self-administered questionnaire. The initial framing statement gives permission to discuss topics that may be difficult for the patient to disclose.

Risk assessment is followed by clinical assessment (elicitation of information on specific current symptoms and signs of STDs). Confirmatory diagnostic tests (for persons with symptoms or signs) or screening tests (for those without symptoms or signs) may involve microscopic examination, culture, nucleic acid amplification tests (NAATs), or serology. Initial syndrome-based treatment should cover the most likely causes. For certain syndromes, results of rapid tests can narrow the spectrum of this initial therapy (e.g., pH of vaginal fluid for women with vaginal discharge, Gram's stain of urethral discharge for men with urethral discharge, rapid plasma reagin test for genital ulcer to assess the probability of syphilis). After the institution of treatment, STD management proceeds to the "4 Cs" of prevention and control: contact tracing (see "Prevention and Control of STIs," below),

TABLE 131-3 Eleven-Question STD/HIV Risk Assessment

Framing Statement

In order to provide the best care for you today and to understand your risk for certain infections, it is necessary for us to talk about your sexual behavior.

Screening Questions

(1) Do you have any reason to think you might have a sexually transmitted infection? If so, what reason?

(2) For all adolescents <18 years old: Have you begun having any kind of sex yet?

STD History

(3) Have you ever had any sexually transmitted infections or any genital infections? If so, which ones?

Sexual Preference

(4) Have you had sex with men, women, or both?

Injection Drug Use

(5) Have you ever injected yourself ("shot up") with drugs? (If yes, have you ever shared needles or injection equipment?)

(6) Have you ever had sex with a gay or bisexual man or with anyone who had ever injected drugs?

Characteristics of Partner(s)

(7) Has your sex partner had any sexually transmitted infections? If so, which ones?

(8) Has your sex partner had other sex partners during the time you've been together?

STD Symptoms Checklist

(9) Have you recently developed any of these symptoms?

For Men	For Women
(a) Discharge of pus (drip) from the penis	(a) Abnormal vaginal discharge (increased amount, abnormal odor, abnormal yellow color)
(b) Genital sores (ulcers) or rash	(b) Genital sores (ulcers), rash, or itching

Sexual Practices, Past 2 Months (for patients answering yes to any of the above questions, to guide examination and testing)

(10) Now I'd like to ask what parts of your body may have been sexually exposed to an STD (e.g., your penis, mouth, vagina, anus).

Query about Interest in STD Screening Tests (for patients answering no to all of the above questions)

(11) Would you like to be tested for HIV or any other STDs today? (If yes, clinician can explore which STD and why.)

Source: Adapted from JR Curtis, KK Holmes, in KK Holmes et al (eds): *Sexually Transmitted Diseases,* 4th ed. New York, McGraw-Hill, 2008.

ensuring compliance with therapy, and counseling on risk reduction, including condom promotion and provision as well as motivational interviewing for risk reduction.

Consistent with current guidelines, all adults should be screened for infection with HIV-1 at least once, and more frequently if they are at elevated risk for acquisition of this infection.

URETHRITIS IN MEN

Urethritis in men produces urethral discharge, dysuria, or both, usually without frequency of urination. Causes include *N. gonorrhoeae, C. trachomatis, Mycoplasma genitalium, Ureaplasma urealyticum, Trichomonas vaginalis*, HSV, and (rarely) adenovirus.

Until recently, *C. trachomatis* caused ~30–40% of cases of nongonococcal urethritis (NGU), particularly in heterosexual men; however, the proportion of cases due to this organism has probably declined in some populations served by effective chlamydial control programs, and older men with urethritis appear less likely to have chlamydial infection. HSV and *T. vaginalis* each cause a small proportion of NGU cases in the United States. Recently, multiple studies have consistently implicated *M. genitalium* as a probable cause of many *Chlamydia*-negative cases. Fewer studies than in the past have implicated *Ureaplasma*; the ureaplasmas have been differentiated into *U. urealyticum* and *Ureaplasma parvum*, and a few studies suggest that *U. urealyticum*—but not *U. parvum*—is associated with NGU. Coliform bacteria can cause urethritis in men who practice insertive anal intercourse. More recently, anaerobic bacteria that are characteristically involved in BV, especially *Leptotrichia/Sneathia* species, have occasionally been associated with urethritis in heterosexual men. Recommendations for the initial diagnosis of urethritis in men currently include specific tests only for *N. gonorrhoeae* and *C. trachomatis*; they do not yet include testing for *M. genitalium*, although a NAAT is now commercially available for the latter.

APPROACH TO THE PATIENT

Urethritis in Men

The following summarizes the approach to the male patient with suspected urethritis:

1. *Establish the presence of urethritis*. If proximal-to-distal "milking" of the urethra does not express a purulent or mucopurulent discharge, even after the patient has not voided for several hours (or preferably overnight), a Gram's-stained smear of an anterior urethral specimen obtained by passage of a small urethrogenital swab 2–3 cm into the urethra usually reveals ≥2 neutrophils per 1000× field when urethritis is present; in gonococcal infection, such a smear usually reveals gram-negative intracellular diplococci as well. Alternatively, the centrifuged sediment of the first 20–30 mL of voided urine—ideally collected as the first morning specimen—can be examined for inflammatory cells, either by microscopy showing ≥10 leukocytes per high-power field or by the leukocyte esterase test. Patients with symptoms who lack objective evidence of urethritis generally do not benefit from repeated courses of antibiotics, and other etiologies of such symptoms may be considered.
2. *Evaluate for complications or alternative diagnoses*. A brief history and examination can exclude epididymitis and systemic complications, such as disseminated gonococcal infection (DGI) and reactive arthritis. Although digital examination of the prostate gland seldom contributes to the evaluation of sexually active young men with urethritis, men with dysuria who lack evidence of urethritis as well as sexually inactive men with urethritis should undergo prostate palpation, urinalysis, and urine culture to exclude bacterial prostatitis and cystitis.
3. *Evaluate for gonococcal and chlamydial infection*. An absence of typical gram-negative diplococci on Gram's-stained smear of urethral exudate containing inflammatory cells warrants a preliminary diagnosis of NGU, as this test is 98% sensitive for the diagnosis of gonococcal urethral infection. However, an increasing proportion of men with symptoms and/or signs of urethritis are simultaneously assessed for infection with *N. gonorrhoeae* and *C. trachomatis* by NAATs of first-catch urine. The urine specimen tested should consist of the first 10–15 mL of the stream, and, if possible, patients should not have voided for the prior 2 h. Culture or NAAT for *N. gonorrhoeae* may yield positive results even when Gram's staining is negative; certain strains of *N. gonorrhoeae* can result in negative urethral Gram's stains in up to 30% of cases of urethral infection. Results of tests for gonococcal and chlamydial infection predict the patient's prognosis (with greater risk for recurrent NGU if neither chlamydiae nor gonococci are found than if either is detected) and can guide both the counseling given to the patient and the management of the patient's sexual partner(s).
4. *Treat urethritis promptly while test results are pending*.

TREATMENT

Urethritis in Men

Table 131-4 summarizes the steps in management of urethral discharge and/or dysuria in sexually active men.

In practice, if Gram's stain does not reveal gonococci, urethritis is treated with a regimen effective for NGU, such as azithromycin or doxycycline. Both are effective. Although azithromycin has been more effective than doxycycline for *M. genitalium* infection, the efficacy of azithromycin for treatment of *M. genitalium* is rapidly declining. Alternatives include moxifloxacin and pristinamycin, a stretogramin antibiotic available in some countries. If gonococci are demonstrated by Gram's stain or if no diagnostic tests are performed to exclude gonorrhea definitively, treatment should include parenteral cephalosporin therapy for gonorrhea (Chap. 151) plus oral azithromycin, primarily for additive activity against *N. gonorrhoeae* given concerns about evolving cephalosporin resistance. Azithromycin is effective for treating *C. trachomatis* infection, which can cause urethral co-infection in men with gonococcal urethritis. Sexual partners should also be tested for gonorrhea and chlamydial infection. Regardless of whether

TABLE 131-4 Management of Urethral Discharge in Men

USUAL CAUSES	USUAL INITIAL EVALUATION
Chlamydia trachomatis	Demonstration of urethral discharge or pyuria
Neisseria gonorrhoeae	Exclusion of local or systemic complications
Mycoplasma genitalium	Urethral Gram's stain to confirm urethritis, detect gram-negative diplococci
Ureaplasma urealyticum	Test for *N. gonorrhoeae*, *C. trachomatis*
Trichomonas vaginalis	
Herpes simplex virus	
Initial Treatment for Patient and Partners	
Treat gonorrhea (unless excluded): Ceftriaxone (250 mg IM[a]) plus azithromycin (1 g PO)	
Management of Recurrence	
Confirm objective evidence of urethritis. If patient was reexposed to untreated or new partner, repeat treatment of patient and partner. If patient was not reexposed, consider infection with *T. vaginalis*[b] or antibiotic-resistant *M. genitalium*[c] or *Ureaplasma*, and consider treatment with metronidazole, azithromycin, or both.	

[a]Neither oral cephalosporins nor fluoroquinolones are recommended for treatment of gonorrhea in the United States because of the emergence of increasing fluoroquinolone resistance in *N. gonorrhoeae*, especially (but not only) among men who have sex with men, and the decreasing susceptibility of a still-small proportion of gonococci to ceftriaxone (Fig. 131-1). Updates on the emergence of antimicrobial resistance in *N. gonorrhoeae* can be obtained from the Centers for Disease Control and Prevention at *http://www.cdc.gov/std.* [b]In men, the diagnosis of *T. vaginalis* infection requires culture, DNA testing, or nucleic acid amplification testing (where available) of early-morning first-voided urine sediment or of a urethral swab specimen obtained before voiding. [c]*M. genitalium* is often resistant to doxycycline and azithromycin but is usually susceptible to the fluoroquinolone moxifloxacin. Moxifloxacin can be considered for treatment of refractory nongonococcal, nonchlamydial urethritis.

they are tested for these infections, however, they should receive the same regimen given to the male index case. Patients with confirmed persistence or recurrence of urethritis after treatment should be re-treated with the initial regimen if they did not comply with the original treatment or were reexposed to an untreated partner. Most persistent urethritis is due to *M. genitalium*, and prompt diagnostic testing and/or treatment for *M. genitalium* is recommended.

National and international guidelines do exist for treatment of gonococcal urethritis, typically with ceftriaxone plus azithromycin. However, consensus is still lacking on treatment of urethritis that persists after treatment and cure of gonorrhea. Ideally, the approach would involve testing for potential causes of the persistent urethritis (e.g., *M. genitalium*) and antimicrobial susceptibility testing in settings and populations where antimicrobial resistance is emerging. Currently, assays are available that can detect *M. genitalium*, and some experts believe it is time to integrate such testing into STD care. If *M. genitalium* is detected, the persistent urethritis can be treated with azithromycin or moxifloxacin in light of local patterns of antimicrobial susceptibility.

In heterosexual men with a high likelihood of exposure to trichomoniasis, an intraurethral swab specimen and a first-voided urine sample should be tested for *T. vaginalis* (often by culture, although NAATs are more sensitive and are approved for the diagnosis of trichomoniasis in women), and presumptive treatment with metronidazole or tinidazole (2 g by mouth in a single dose) should be given. For MSM, trichomoniasis is unlikely, and consideration of a course of moxifloxacin is warranted. Because MSM also have the highest prevalence rates of antimicrobial-resistant *N. gonorrhoeae*, this possibility, even if apparently ruled out at the initial presentation, should be kept in mind.

EPIDIDYMITIS

Acute epididymitis, almost always unilateral, produces pain, swelling, and tenderness of the epididymis, with or without symptoms or signs of urethritis. This condition must be differentiated from testicular torsion, tumor, and trauma. Torsion, a surgical emergency, usually occurs in the second or third decade of life and produces a sudden onset of pain, elevation of the testicle within the scrotal sac, rotation of the epididymis from a posterior to an anterior position, and absence of blood flow on Doppler ultrasound. Persistence of symptoms after a course of therapy for epididymitis suggests the possibility of testicular tumor or of a chronic granulomatous disease, such as tuberculosis. In sexually active men under age 35, acute epididymitis is caused most frequently by *C. trachomatis* and less commonly by *N. gonorrhoeae* and is usually associated with overt or subclinical urethritis. Acute epididymitis occurring in older men or following urinary tract instrumentation is usually caused by urinary pathogens. These older men usually have no urethritis but do have bacteriuria. Similarly, epididymitis in MSM who have practiced insertive rectal intercourse is often caused by Enterobacteriaceae.

TREATMENT

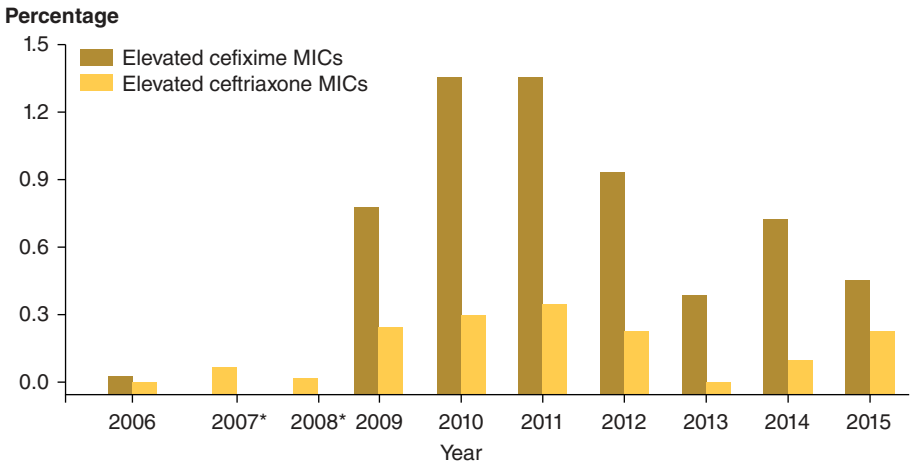
Epididymitis

Ceftriaxone (250 mg as a single dose IM) followed by doxycycline (100 mg by mouth twice daily for 10 days) constitutes effective treatment for epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*. Neither oral cephalosporins nor fluoroquinolones are recommended for treatment of gonorrhea in the United States because of resistance in *N. gonorrhoeae*, especially (but not only) among MSM **(Fig. 131-1)**. When infection with Enterobacteriaceae is suspected, oral levofloxacin (500 mg once daily for 10 days) or ofloxacin (300 mg twice daily for 10 days) is effective for syndrome-based initial treatment of epididymitis; however, because this regimen is not effective against gonococcal or chlamydial infection, it should be combined with effective therapy for possible gonococcal or chlamydial infection of the epididymis unless bacteriuria with Enterobacteriaceae is confirmed.

URETHRITIS AND THE URETHRAL SYNDROME IN WOMEN

C. trachomatis, *N. gonorrhoeae*, and occasionally HSV cause symptomatic urethritis—known as *the urethral syndrome* in women—that is characterized by "internal" dysuria (usually without urinary urgency or frequency), pyuria, and an absence of *Escherichia coli* and other uropathogens at counts of $\geq 10^2$/mL in urine. In contrast, the dysuria associated with vulvar herpes or vulvovaginal candidiasis (and perhaps with trichomoniasis) is often described as "external," being caused by painful contact of urine with the inflamed or ulcerated labia or introitus. Acute onset, association with urinary urgency or frequency, hematuria, or suprapubic bladder tenderness suggests bacterial cystitis. Among women with symptoms of acute bacterial cystitis, costovertebral pain and tenderness or fever suggest acute pyelonephritis. **The management of bacterial urinary tract infection (UTI) is discussed in Chap. 130.**

Signs of vulvovaginitis, coupled with symptoms of external dysuria, suggest vulvar infection (e.g., with HSV or *Candida albicans*). Among dysuric women without signs of vulvovaginitis, bacterial UTI must be differentiated from the urethral syndrome by assessment of risk, evaluation of the pattern of symptoms and signs, and specific microbiologic testing. An STI etiology of the urethral syndrome is



*Isolates not tested for cefixime susceptibility in 2007 and 2008.

FIGURE 131-1 Proportion of *Neisseria gonorrhoeae* isolates with elevated minimal inhibitory concentrations (MICs) of ceftriaxone (≥0.125 µg/mL) and cefixime (≥0.25 µg/mL), United States, 2006–2015. *(From the Centers for Disease Control and Prevention: Gonococcal Isolate Surveillance Project [GISP], 2016.)*

suggested by young age, more than one current sexual partner, a new partner within the past month, a partner with urethritis, or coexisting mucopurulent cervicitis (see below). The finding of a single urinary pathogen, such as *E. coli* or *Staphylococcus saprophyticus*, at a concentration of $\geq 10^2$/mL in a properly collected specimen of midstream urine from a dysuric woman with pyuria indicates probable bacterial UTI, whereas pyuria with $<10^2$ conventional uropathogens per milliliter of urine ("sterile" pyuria) suggests acute urethral syndrome due to *C. trachomatis* or *N. gonorrhoeae*. Gonorrhea and chlamydial infection should be sought by specific tests (e.g., NAATs of vaginal secretions collected with a swab). Among dysuric women with sterile pyuria caused by infection with *N. gonorrhoeae* or *C. trachomatis*, appropriate treatment alleviates dysuria. The role of *M. genitalium* in the urethral syndrome in women remains undefined.

VULVOVAGINAL INFECTIONS

Abnormal Vaginal Discharge If directly questioned about vaginal discharge during routine health checkups, many women acknowledge having nonspecific symptoms of vaginal discharge that do not correlate with objective signs of inflammation or with actual infection. However, unsolicited reporting of abnormal vaginal discharge often denotes BV or trichomoniasis. Specifically, an abnormally increased amount or an abnormal odor of the discharge is associated with one or both of these conditions. Cervical infection with *N. gonorrhoeae* or *C. trachomatis* does not often cause an increased amount or abnormal odor of discharge; however, when these pathogens cause cervicitis, they—like *T. vaginalis*—often result in an increased number of neutrophils in vaginal fluid, which thus takes on a yellow color. Vulvar conditions such as genital herpes or vulvovaginal candidiasis can cause vulvar pruritus, burning, irritation, or lesions as well as external dysuria (as urine passes over the inflamed vulva or areas of epithelial disruption) or vulvar dyspareunia.

Certain vulvovaginal infections may have serious sequelae. Trichomoniasis, BV, and vulvovaginal candidiasis have all been associated with increased risk of acquisition of HIV infection; BV promotes HIV transmission from HIV-infected women to their male sex partners. Vaginal trichomoniasis and BV early in pregnancy independently predict premature onset of labor. BV can also lead to anaerobic bacterial infection of the endometrium and salpinges. Vaginitis may be an early and prominent feature of toxic shock syndrome, and recurrent or chronic vulvovaginal candidiasis develops with increased frequency among women who have systemic illnesses, such as diabetes mellitus or HIV-related immunosuppression (although only a very small proportion of women with recurrent vulvovaginal candidiasis in industrialized countries actually have a serious predisposing illness).

Thus vulvovaginal symptoms or signs warrant careful evaluation, including speculum and pelvic examination, diagnostic testing, and appropriate therapy specific for the infection identified. Unfortunately, clinicians do not always perform the tests required to establish the cause of such symptoms. Further, self-diagnosis of a specific type of infection—including vulvovaginal candidiasis—is often incorrect. The diagnosis and treatment of the three most common types of vaginal infection are summarized in **Table 131-5**.

Inspection of the vulva and perineum may reveal tender genital ulcerations or fissures (typically due to HSV infection or vulvovaginal candidiasis) or discharge visible at the introitus before insertion of a speculum (suggestive of BV or trichomoniasis). Speculum examination permits the clinician to discern whether the discharge appears abnormal and whether it emanates from the cervical os (mucoid and, if abnormal, yellow) or from the vagina (not mucoid, since the vaginal epithelium does not produce mucus). Symptoms or signs of abnormal vaginal discharge should prompt testing of vaginal fluid for pH, for a fishy odor when mixed with 10% KOH, and for certain microscopic features when mixed with saline (motile trichomonads and/or "clue cells") and with 10% KOH (pseudohyphae or hyphae indicative of vulvovaginal candidiasis). Additional objective laboratory tests, described below, are useful for establishing the cause of abnormal vaginal discharge. Gram's staining of vaginal fluid can be used to characterize the vaginal bacteria using the Nugent score but is used primarily for research purposes and requires familiarity with the morphotypes and scale involved.

TREATMENT

Vaginal Discharge

Patterns of treatment for abnormal vaginal discharge vary widely. In developing countries, where clinics or pharmacies often dispense treatment based on symptoms alone without examination or testing, oral treatment with metronidazole—particularly with a 7-day regimen—provides reasonable coverage against both trichomoniasis and BV, the usual causes of symptoms of vaginal discharge. Metronidazole treatment of sex partners prevents reinfection of women with *T. vaginalis*, although it does not help prevent the recurrence of BV. Guidelines for syndromic management promulgated by the World Health Organization suggest consideration of treatment for cervical infection and for trichomoniasis, BV, and vulvovaginal candidiasis in women with symptoms of abnormal vaginal discharge. However, it is important to note that the majority of chlamydial and gonococcal cervical infections produce no symptoms.

In industrialized countries, clinicians treating symptoms and signs of abnormal vaginal discharge should, at a minimum, differentiate between BV and trichomoniasis, because optimal management of patients and partners differs for these two conditions.

Vaginal Trichomoniasis **(See also Chap. 224)** Symptomatic trichomoniasis characteristically produces a profuse, yellow, purulent, homogeneous vaginal discharge and vulvar irritation, sometimes with visible inflammation of the vaginal and vulvar epithelium and petechial lesions on the cervix (the so-called strawberry cervix, best visualized by colposcopy). The pH of vaginal fluid—normally <4.7—usually rises to ≥5. Microscopic examination of vaginal discharge mixed with saline reveals motile trichomonads in most culture-positive cases. However, saline microscopy probably detects only one-half of all cases, and, especially in the absence of symptoms or signs, culture or NAAT is usually required for detection of the organism. NAAT for *T. vaginalis* is more sensitive than culture. Treatment of asymptomatic as well as symptomatic cases reduces rates of transmission and prevents later development of symptoms.

TREATMENT

Vaginal Trichomoniasis

Only nitroimidazoles (e.g., metronidazole and tinidazole) consistently cure trichomoniasis. A single 2-g oral dose of metronidazole is effective and less expensive than the alternatives. Tinidazole has a longer half-life than metronidazole, causes fewer gastrointestinal symptoms, and may be useful in treating trichomoniasis that fails to respond to metronidazole. Treatment of sexual partners—facilitated by dispensing metronidazole to the female patient to give to her partner(s), with a warning about avoiding the concurrent use of alcohol—significantly reduces both the risk of reinfection and the reservoir of infection; treating partners is the standard of care. Intravaginal treatment with 0.75% metronidazole gel is not reliable for vaginal trichomoniasis. Thus, systemic use of metronidazole is still recommended throughout pregnancy for treatment of trichomoniasis. In a large randomized trial, metronidazole treatment of trichomoniasis during pregnancy was associated with an increased frequency of perinatal morbidity. However, most studies, including randomized controlled trials, have shown no adverse effects of metronidazole use during pregnancy on preterm birth or birth defects.

Bacterial Vaginosis BV is a syndrome characterized by symptoms of vaginal malodor and increased white-gray discharge, which appears homogeneous, is low in viscosity, and uniformly covers the

TABLE 131-5 Diagnostic Features and Management of Vaginal Infection

FEATURE	NORMAL VAGINAL EXAMINATION	VULVOVAGINAL CANDIDIASIS	TRICHOMONAL VAGINITIS	BACTERIAL VAGINOSIS
Etiology	Uninfected; lactobacilli predominant	*Candida albicans*	*Trichomonas vaginalis*	Associated with *Gardnerella vaginalis*, various anaerobic and/or noncultured bacteria, and mycoplasmas
Typical symptoms	None	Vulvar itching and/or irritation	Profuse discharge; vulvar itching	Malodorous, slightly increased discharge
Discharge				
Amount	Variable; usually scant	Scant	Often profuse	Moderate
Color[a]	Clear or translucent	White	White or yellow	White or gray
Consistency	Nonhomogeneous, flocculent	Clumped; adherent plaques	Homogeneous	Homogeneous, low viscosity; uniformly coats vaginal walls
Inflammation of vulvar or vaginal epithelium	None	Erythema of vaginal epithelium, introitus; vulvar dermatitis, fissures common	Erythema of vaginal and vulvar epithelium; colpitis macularis	None
pH of vaginal fluid[b]	Usually ≤4.5	Usually ≤4.5	Usually ≥5	Usually >4.5
Amine ("fishy") odor with 10% KOH	None	None	May be present	Present
Microscopy[c]	Normal epithelial cells; lactobacilli predominant	Leukocytes, epithelial cells; mycelia or pseudomycelia in up to 80% of *C. albicans* culture–positive persons with typical symptoms	Leukocytes; motile trichomonads seen in 80–90% of symptomatic patients, less often in the absence of symptoms	Clue cells; few leukocytes; no lactobacilli or only a few outnumbered by profuse mixed microbiota, nearly always including *G. vaginalis* plus anaerobic species on Gram's stain (Nugent's score ≥7)
Other laboratory findings		Isolation of *Candida* spp.	Isolation of *T. vaginalis* or positive NAAT[d]	
Usual treatment	None	Azole cream, tablet, or suppository—e.g., miconazole (100-mg vaginal suppository) or clotrimazole (100-mg vaginal tablet) once daily for 7 days Fluconazole, 150 mg orally (single dose)	Metronidazole or tinidazole, 2 g orally (single dose) Metronidazole, 500 mg PO bid for 7 days	Metronidazole, 500 mg PO bid for 7 days Metronidazole gel, 0.75%, one applicator (5 g) intravaginally once daily for 5 days Clindamycin, 2% cream, one full applicator vaginally each night for 7 days
Usual management of sexual partner	None	None; topical treatment if candidal dermatitis of penis is detected	Examination for sexually transmitted infection; treatment with metronidazole, 2 g PO (single dose)	None

[a]Color of discharge is best determined by examination against the white background of a swab. [b]A pH determination is not useful if blood is present or if the test is performed on endocervical secretions. [c]To detect fungal elements, vaginal fluid is digested with 10% KOH prior to microscopic examination; to examine for other features, fluid is mixed (1:1) with physiologic saline. Gram's stain is also excellent for detecting yeasts (less predictive of vulvovaginitis) and pseudomycelia or mycelia (strongly predictive of vulvovaginitis) and for distinguishing normal flora from the mixed flora seen in bacterial vaginosis, but it is less sensitive than the saline preparation for detection of *T. vaginalis*. [d]NAAT, nucleic acid amplification test (where available).

vaginal mucosa. BV has been associated with an increased risk of acquiring several other genital infections, including those caused by HIV, *C. trachomatis*, and *N. gonorrhoeae*. Other possible risk factors include recent unprotected vaginal intercourse, having a female sex partner, and vaginal douching. Although bacteria associated with BV have been detected under the foreskin of uncircumcised men and have been associated with urethritis, metronidazole treatment of male partners has not reduced the rate of recurrence of BV among affected women.

Among women with BV, culture of vaginal fluid has shown markedly increased prevalences and concentrations of *Gardnerella vaginalis, Mycoplasma hominis*, and several anaerobic bacteria (e.g., *Mobiluncus, Prevotella* [formerly *Bacteroides*], and some *Peptostreptococcus* species) as well as an absence of hydrogen peroxide–producing *Lactobacillus* species that constitute most of the normal vaginal microbiota and help protect against cervical and vaginal infections. Broad-range polymerase chain reaction (PCR) amplification of 16S rDNA in vaginal fluid, with subsequent identification of specific bacterial species by various methods, has documented even greater bacterial diversity, including several unique species not previously identified in culture **(Fig. 131-2)** and *Atopobium vaginae*, an organism that is strongly associated with BV and is resistant to metronidazole. Other genera newly implicated in BV include *Megasphaera, Leptotrichia, Eggerthella*, and *Dialister*.

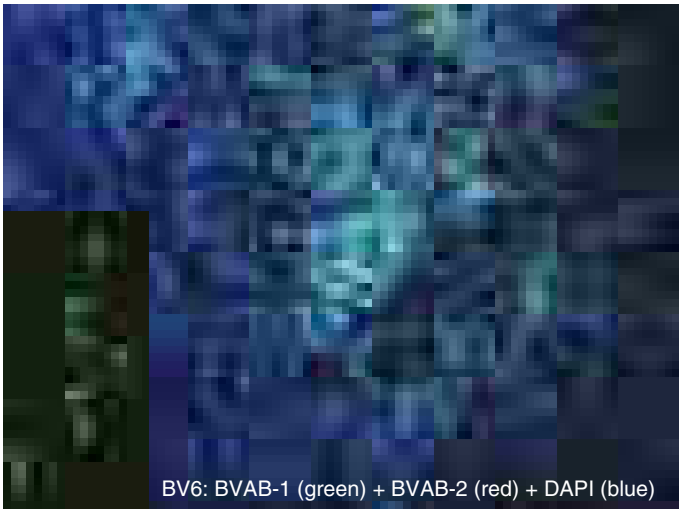


FIGURE 131-2 Broad-range polymerase chain reaction amplification of 16S rDNA in vaginal fluid from a woman with bacterial vaginosis (BV) shows a field of bacteria hybridizing with probes for BV-associated bacterium 1 (BVAB-1, visible as a thin, curved green rod) and for BVAB-2 (red). The *inset* shows that BVAB-1 has a morphology similar to that of *Mobiluncus* (curved rod). *(Reprinted with permission from DN Fredricks et al: N Engl J Med 353:1899, 2005.)*

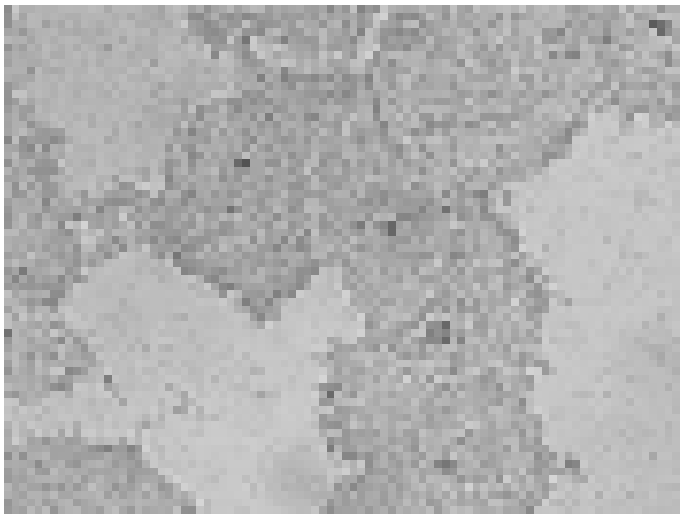


FIGURE 131-3 Wet mount of vaginal fluid showing typical clue cells from a woman with bacterial vaginosis. Note the obscured epithelial cell margins and the granular appearance attributable to many adherent bacteria (×400). *(Photograph provided by Lorna K. Rabe, reprinted with permission from S Hillier et al, in KK Holmes et al [eds]: Sexually Transmitted Diseases, 4th ed. New York, McGraw-Hill, 2008.)*

BV is conventionally diagnosed clinically with the Amsel criteria, which include any three of the following four clinical abnormalities: (1) objective signs of increased white homogeneous vaginal discharge; (2) a vaginal discharge pH of >4.5; (3) liberation of a distinct fishy odor (attributable to volatile amines such as trimethylamine) immediately after vaginal secretions are mixed with a 10% solution of KOH; and (4) microscopic demonstration of "clue cells" (vaginal epithelial cells coated with coccobacillary organisms, which have a granular appearance and indistinct borders; Fig. 131-3) on a wet mount prepared by mixing vaginal secretions with normal saline in a ratio of ~1:1.

TREATMENT

Bacterial Vaginosis

The standard dosage of oral metronidazole for the treatment of BV is 500 mg twice daily for 7 days. The single 2-g oral dose of metronidazole recommended for trichomoniasis produces significantly lower short-term cure rates and should not be used. Intravaginal treatment with 2% clindamycin cream (one full applicator [5 g containing 100 mg of clindamycin phosphate] each night for 7 nights) or with 0.75% metronidazole gel (one full applicator [5 g containing 37.5 mg of metronidazole] twice daily for 5 days) is also approved for use in the United States and does not elicit systemic adverse reactions; the response to both of these treatments is similar to the response to oral metronidazole. Other alternatives include oral clindamycin (300 mg twice daily for 7 days), clindamycin ovules (100 g intravaginally once at bedtime for 3 days), and oral tinidazole (1 g daily for 5 days or 2 g daily for 3 days). Unfortunately, recurrence over the long term (i.e., several months later) is distressingly common after either oral or intravaginal treatment. A randomized trial comparing intravaginal gel containing 37.5 mg of metronidazole with a suppository containing 500 mg of metronidazole plus nystatin (the latter not marketed in the United States) showed significantly higher rates of recurrence with the 37.5-mg regimen; this result suggests that higher metronidazole dosages may be important in topical intravaginal therapy. Recurrences can be significantly lessened with the twice-weekly use of suppressive intravaginal metronidazole gel.

Efforts to replenish numbers of vaginal lactobacilli that produce hydrogen peroxide and probably sustain vaginal health have been unsuccessful. While one randomized trial of orally ingested lactobacilli found reduced rates of recurrent BV, this result has not yet been either confirmed or refuted, and a randomized multicenter trial in the United States found no benefit of repeated intravaginal inoculation of a vaginal peroxide-producing *Lactobacillus* species following treatment of BV with metronidazole. A meta-analysis of 18 studies concluded that BV during pregnancy substantially increased the risk of preterm delivery and of spontaneous abortion. However, in most studies, topical intravaginal treatment of BV with clindamycin during pregnancy has not reduced adverse pregnancy outcomes. Numerous trials of oral metronidazole treatment during pregnancy have given inconsistent results, and recent reviews have concluded that antenatal treatment of women with BV—including those with previous preterm delivery—did not reduce the risk of preterm delivery. The U.S. Preventive Services Task Force thus recommends against routine screening of pregnant women for BV.

Vulvovaginal Pruritus, Burning, or Irritation Vulvovaginal candidiasis produces vulvar pruritus, burning, or irritation, generally without symptoms of increased vaginal discharge or malodor. Genital herpes can produce similar symptoms, with lesions sometimes difficult to distinguish from the fissures and inflammation caused by candidiasis. Signs of vulvovaginal candidiasis include vulvar erythema, edema, fissures, and tenderness. With candidiasis, a white scanty vaginal discharge sometimes takes the form of white thrush-like plaques or cottage cheese-like curds adhering loosely to the vaginal epithelium. *C. albicans* accounts for nearly all cases of symptomatic vulvovaginal candidiasis, which probably arise from endogenous strains of *C. albicans* that have colonized the vagina or the intestinal tract. Complicated vulvovaginal candidiasis includes cases that recur four or more times per year; are unusually severe; are caused by non-*albicans Candida* species; or occur in women with uncontrolled diabetes, debilitation, immunosuppression, or pregnancy.

In addition to compatible clinical symptoms, the diagnosis of vulvovaginal candidiasis involves the demonstration of pseudohyphae or hyphae by microscopic examination of vaginal fluid mixed with saline or 10% KOH or subjected to Gram's staining. Microscopic examination is less sensitive than culture but correlates better with symptoms. Culture is typically reserved for cases that do not respond to standard first-line antimycotic agents and is undertaken to rule out imidazole or azole resistance (often associated with *Candida glabrata*) or before the initiation of suppressive antifungal therapy for recurrent disease.

TREATMENT

Vulvovaginal Pruritus, Burning, or Irritation

Symptoms and signs of vulvovaginal candidiasis warrant treatment, usually intravaginal administration of any of several imidazole antibiotics (e.g., miconazole or clotrimazole) for 3–7 days or of a single dose of oral fluconazole (Table 131-5). Over-the-counter marketing of such preparations has reduced the cost of care and made treatment more convenient for many women with recurrent yeast vulvovaginitis. However, most women who purchase these preparations do not have vulvovaginal candidiasis, whereas many have other vaginal infections that require different treatment. Therefore, only women with classic symptoms of vulvar pruritus and a history of previous episodes of yeast vulvovaginitis documented by an experienced clinician should self-treat. Short-course topical intravaginal azole drugs are effective for the treatment of uncomplicated vulvovaginal candidiasis (e.g., clotrimazole, two 100-mg vaginal tablets daily for 3 days; or miconazole, a 1200-mg vaginal suppository as a single dose). Single-dose oral treatment with fluconazole (150 mg) is also effective and is preferred by many patients. Management of complicated cases (see above) and those that do not respond to the usual intravaginal or single-dose oral therapy often involves prolonged or periodic oral therapy; this situation is discussed extensively in the 2015 CDC STD treatment guidelines (*http://www.cdc.gov/std/treatment*). Treatment of sexual partners is not routinely indicated.

Other Causes of Vaginal Discharge or Vaginitis In the ulcerative vaginitis associated with staphylococcal toxic shock syndrome, *Staphylococcus aureus* should be promptly identified in vaginal fluid by Gram's stain and by culture. In desquamative inflammatory vaginitis, smears of vaginal fluid reveal neutrophils, massive vaginal epithelial-cell exfoliation with increased numbers of parabasal cells, and gram-positive cocci; this syndrome may respond to treatment with 2% clindamycin cream, often given in combination with topical steroid preparations for several weeks. Additional causes of vaginitis and vulvovaginal symptoms include retained foreign bodies (e.g., tampons), cervical caps, vaginal spermicides, vaginal antiseptic preparations or douches, vaginal epithelial atrophy (in postmenopausal women or during prolonged breast-feeding in the postpartum period), allergic reactions to latex condoms, vaginal aphthae associated with HIV infection or Behçet's syndrome, and vestibulitis.

MUCOPURULENT CERVICITIS

Mucopurulent cervicitis (MPC) refers to inflammation of the columnar epithelium and subepithelium of the endocervix and of any contiguous columnar epithelium that lies exposed in an ectopic position on the ectocervix. MPC in women represents the "silent partner" of urethritis in men, being equally common and often caused by the same agents (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*); however, MPC is more difficult than urethritis to recognize, given the nonspecific nature of symptoms (e.g., abnormal vaginal discharge) and the need for visualization by pelvic examination. As the most common manifestation of these serious bacterial infections in women, MPC can be a harbinger or sign of upper genital tract infection, also known as *pelvic inflammatory disease* (PID; see below). In pregnant women, MPC can lead to obstetric complications. In the pre-NAAT era, more than one-third of cervicovaginal specimens tested for *C. trachomatis, N. gonorrhoeae, M. genitalium*, HSV, and *T. vaginalis* revealed no identifiable etiology for MPC **(Fig. 131-4)**. More recent studies employing NAATs for these pathogens have still failed to identify a microbiologic etiology in nearly one-half of women with MPC. Individual bacteria associated with BV may also elicit an inflammatory reaction at the cervix; thus, BV may be a cause of MPC.

The diagnosis of MPC rests on the detection of cardinal signs at the cervix, including yellow mucopurulent discharge from the cervical os, endocervical bleeding upon gentle swabbing, and edematous cervical ectopy (see below); the latter two findings are somewhat more common with MPC due to chlamydial infection, but signs alone do not allow a distinction among the causative pathogens. Unlike the endocervicitis produced by gonococcal or chlamydial infection, cervicitis caused by HSV produces ulcerative lesions on the stratified squamous epithelium of the ectocervix as well as on the columnar epithelium. Yellow cervical mucus on a white swab removed from the endocervix indicates the presence of polymorphonuclear leukocytes (PMNs). Gram's staining may confirm their presence, although it adds relatively little to the diagnostic value of assessment for cervical signs. The presence of ≥20 PMNs per 1000× microscopic field within strands of cervical mucus not contaminated by vaginal squamous epithelial cells or vaginal bacteria indicates endocervicitis. Detection of intracellular gram-negative diplococci in carefully collected endocervical mucus is quite specific but ≤50% sensitive for gonorrhea. Therefore, NAATs for *N. gonorrhoeae* and *C. trachomatis* are always indicated in the evaluation of MPC, as is a careful evaluation of vaginal discharge for the causes of vaginitis discussed above.

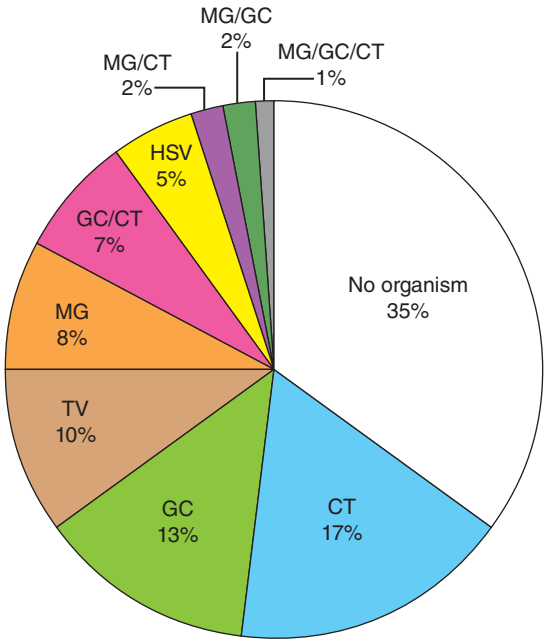


FIGURE 131-4 Organisms detected among female sexually transmitted disease clinic patients with mucopurulent cervicitis (*n* = 167). CT, *Chlamydia trachomatis*; GC, gonococcus; MG, *Mycoplasma genitalium*; TV, *Trichomonas vaginalis*; HSV, herpes simplex virus. *(Courtesy of Dr. Lisa Manhart; with permission.)*

TREATMENT

Mucopurulent Cervicitis

Although the above criteria for MPC are neither highly specific nor highly predictive of gonococcal or chlamydial infection in some settings, the 2015 CDC STD guidelines call for consideration of empirical treatment for MPC, pending test results, in most cases. Presumptive treatment with antibiotics active against *C. trachomatis* should be provided for women at increased risk for this common STI (risk factors: age <25 years, new or multiple sex partners, and unprotected sex), especially if follow-up cannot be ensured. Concurrent therapy for gonorrhea is indicated if the prevalence of this infection is substantial in the relevant patient population (e.g., young adults, a clinic with documented high prevalence). In this situation, therapy should include a single-dose regimen effective for gonorrhea plus treatment for chlamydial infection, as outlined in Table 131-4 for the treatment of urethritis. In settings where gonorrhea is much less common than chlamydial infection, initial therapy for chlamydial infection alone suffices, pending test results for gonorrhea. The etiology and potential benefit of treatment for endocervicitis not associated with gonorrhea or chlamydial infection have not been established. Although the antimicrobial susceptibility of *M. genitalium* is not yet well defined, the organism frequently persists after doxycycline therapy, and it currently seems reasonable to use azithromycin to treat possible *M. genitalium* infection in such cases. With resistance of *M. genitalium* to azithromycin now recognized, moxifloxacin may be a reasonable alternative. The sexual partner(s) of a woman with MPC should be examined and given a regimen similar to that chosen for the woman unless results of tests for gonorrhea or chlamydial infection in either partner warrant different therapy or no therapy.

CERVICAL ECTOPY

Cervical ectopy, often mislabeled "cervical erosion," is easily confused with infectious endocervicitis. Ectopy represents the presence of the one-cell-thick columnar epithelium extending from the endocervix out onto the visible ectocervix. In ectopy, the cervical os may contain clear or slightly cloudy mucus but usually not yellow mucopus. Colposcopy shows intact epithelium. Normally found during adolescence and early adulthood, ectopy gradually recedes through the second and third decades of life, as squamous metaplasia replaces the ectopic columnar epithelium. Oral contraceptive use favors the persistence or reappearance of ectopy, while smoking apparently accelerates squamous metaplasia. Cauterization of ectopy is not warranted. Ectopy may render the cervix more susceptible to infection with *N. gonorrhoeae*, *C. trachomatis*, or HIV.

PELVIC INFLAMMATORY DISEASE

The term *pelvic inflammatory disease* usually refers to infection that ascends from the cervix or vagina to involve the endometrium and/or fallopian tubes. Infection can extend beyond the reproductive

tract to cause pelvic peritonitis, generalized peritonitis, perihepatitis, perisplenitis, or pelvic abscess. Rarely, infection not related to specific sexually transmitted pathogens extends secondarily to the pelvic organs (1) from adjacent foci of inflammation (e.g., appendicitis, regional ileitis, or diverticulitis) or BV, (2) as a result of hematogenous dissemination (e.g., of tuberculosis or staphylococcal bacteremia), or (3) as a complication of certain tropical diseases (e.g., schistosomiasis). Intrauterine infection can be primary (spontaneously occurring and usually sexually transmitted) or secondary to invasive intrauterine surgical procedures (e.g., dilation and curettage, termination of pregnancy, insertion of an intrauterine device [IUD], or hysterosalpingography) or to parturition.

Etiology The agents most often implicated in acute PID include the primary causes of endocervicitis (*N. gonorrhoeae, C. trachomatis*, and *M. genitalium*) and anaerobes associated with BV. In general, PID is most often caused by *N. gonorrhoeae* in settings where there is a high incidence of gonorrhea. *M. genitalium* has also been significantly associated with histopathologic diagnoses of endometritis and with salpingitis.

Anaerobic and facultative organisms (especially *Prevotella* species, peptostreptococci, *E. coli, Haemophilus influenzae*, and group B streptococci) as well as genital mycoplasmas have been isolated from the peritoneal fluid or fallopian tubes in a varying proportion (typically one-fourth to one-third) of women with PID studied in the United States. The difficulty of determining the exact microbial etiology of an individual case of PID—short of using invasive procedures for specimen collection—has implications for the approach to empirical antimicrobial treatment of this infection.

Epidemiology In the United States, the estimated annual number of initial visits to physicians' offices for PID by women 15–44 years of age fell from an average of 400,000 during the 1980s to 250,000 in 1999 and then to 51,000 in 2014. Hospitalizations for acute PID in the United States also declined steadily throughout the 1980s and early 1990s but have remained fairly constant at 70,000–100,000 per year since 1995. Important risk factors for acute PID include the presence of endocervical infection or BV, a history of salpingitis or of recent vaginal douching, and recent insertion of an IUD. Certain other iatrogenic factors, such as dilation and curettage or cesarean section, can increase the risk of PID, especially among women with endocervical gonococcal or chlamydial infection or BV. Symptoms of *N. gonorrhoeae*–associated and *C. trachomatis*–associated PID often begin during or soon after the menstrual period; this timing suggests that menstruation is a risk factor for ascending infection from the cervix and vagina. Experimental inoculation of the fallopian tubes of nonhuman primates has shown that repeated exposure to *C. trachomatis* leads to the greatest degree of tissue inflammation and damage; thus, immunopathology probably contributes to the pathogenesis of chlamydial salpingitis. Women using oral contraceptives appear to be at decreased risk of symptomatic PID, and tubal sterilization reduces the risk of salpingitis by preventing intraluminal spread of infection into the tubes.

Clinical Manifestations • **ENDOMETRITIS: A CLINICAL PATHOLOGIC SYNDROME** A study of women with clinically suspected PID who were undergoing both endometrial biopsy and laparoscopy showed that those with endometritis alone differed from those who also had salpingitis in significantly less often having lower-quadrant, adnexal, or cervical motion or abdominal rebound tenderness; fever; or elevated C-reactive protein levels. In addition, women with endometritis alone differed from those with neither endometritis nor salpingitis in more often having gonorrhea, chlamydial infection, and risk factors such as douching or IUD use. Thus, women with endometritis alone were intermediate between those with neither endometritis nor salpingitis and those with salpingitis with respect to risk factors, clinical manifestations, cervical infection prevalence, and elevated C-reactive protein level. Women with endometritis alone are at lower risk of subsequent tubal occlusion and resulting infertility than are those with salpingitis.

SALPINGITIS Symptoms of nontuberculous salpingitis classically evolve from a yellow or malodorous vaginal discharge caused by MPC and/or BV to midline abdominal pain and abnormal vaginal bleeding caused by endometritis and then to bilateral lower abdominal and pelvic pain caused by salpingitis, with nausea, vomiting, and increased abdominal tenderness if peritonitis develops.

The abdominal pain in nontuberculous salpingitis is usually described as dull or aching. In some cases, pain is lacking or atypical, but active inflammatory changes are found in the course of an unrelated evaluation or procedure, such as a laparoscopic evaluation for infertility. Abnormal uterine bleeding precedes or coincides with the onset of pain in ~40% of women with PID, symptoms of urethritis (dysuria) occur in 20%, and symptoms of proctitis (anorectal pain, tenesmus, and rectal discharge or bleeding) are occasionally seen in women with gonococcal or chlamydial infection.

Speculum examination shows evidence of MPC (yellow endocervical discharge, easily induced endocervical bleeding) in the majority of women with gonococcal or chlamydial PID. Cervical motion tenderness is produced by stretching of the adnexal attachments on the side toward which the cervix is pushed. Bimanual examination reveals uterine fundal tenderness due to endometritis and abnormal adnexal tenderness due to salpingitis that is usually, but not necessarily, bilateral. Adnexal swelling is palpable in about one-half of women with acute salpingitis, but evaluation of the adnexae in a patient with marked tenderness is not reliable. The initial temperature is >38°C in only about one-third of patients with acute salpingitis. Laboratory findings include elevation of the erythrocyte sedimentation rate (ESR) in 75% of patients with acute salpingitis and elevation of the peripheral white blood cell count in up to 60%.

Unlike nontuberculous salpingitis, genital tuberculosis often occurs in older women, many of whom are postmenopausal. Presenting symptoms include abnormal vaginal bleeding, pain (including dysmenorrhea), and infertility. About one-quarter of these women have had adnexal masses. Endometrial biopsy shows tuberculous granulomas and provides optimal specimens for culture.

PERIHEPATITIS AND PERIAPPENDICITIS Pleuritic upper-abdominal pain and tenderness, usually localized to the right upper quadrant (RUQ), develop in 3–10% of women with acute PID. Symptoms of perihepatitis arise during or after the onset of symptoms of PID and may overshadow lower-abdominal symptoms, thereby leading to a mistaken diagnosis of cholecystitis. In perhaps 5% of cases of acute salpingitis, early laparoscopy reveals perihepatic inflammation ranging from edema and erythema of the liver capsule to exudate with fibrinous adhesions between the visceral and parietal peritoneum. When treatment is delayed and laparoscopy is performed late, dense "violin-string" adhesions can be seen over the liver; chronic exertional or positional RUQ pain ensues when traction is placed on the adhesions. Although perihepatitis, also known as the *Fitz-Hugh–Curtis syndrome*, was for many years specifically attributed to gonococcal salpingitis, most cases are now attributed to chlamydial salpingitis. In patients with chlamydial salpingitis, serum titers of microimmunofluorescent antibody to *C. trachomatis* are typically much higher when perihepatitis is present than when it is absent.

Physical findings include RUQ tenderness and usually include adnexal tenderness and cervicitis, even in patients whose symptoms do not suggest salpingitis. Results of liver function tests and RUQ ultrasonography are nearly always normal. The presence of MPC and pelvic tenderness in a young woman with subacute pleuritic RUQ pain and normal ultrasonography of the gallbladder points to a diagnosis of perihepatitis.

Periappendicitis (appendiceal serositis without involvement of the intestinal mucosa) has been found in ~5% of patients undergoing appendectomy for suspected appendicitis and can occur as a complication of gonococcal or chlamydial salpingitis.

Among women with salpingitis, HIV infection is associated with increased severity of salpingitis and with tuboovarian abscess requiring hospitalization and surgical drainage. Nonetheless, among women with HIV infection and salpingitis, the clinical response to conventional antimicrobial therapy (coupled with drainage of tuboovarian abscess, when found) has usually been satisfactory.

Diagnosis Treatment appropriate for PID must not be withheld from patients who have an equivocal diagnosis; it is better to err on the side of overdiagnosis and overtreatment. On the other hand,

it is essential to differentiate between salpingitis and other pelvic pathology, particularly surgical emergencies such as appendicitis and ectopic pregnancy.

Nothing short of laparoscopy definitively identifies salpingitis, but routine laparoscopy to confirm suspected salpingitis is generally impractical. Most patients with acute PID have lower abdominal pain of <3 weeks' duration, pelvic tenderness on bimanual pelvic examination, and evidence of lower genital tract infection (e.g., MPC). Approximately 60% of such patients have salpingitis at laparoscopy, and perhaps 10–20% have endometritis alone. Among the patients with these findings, a rectal temperature >38°C, a palpable adnexal mass, and elevation of the ESR to >15 mm/h also raise the probability of salpingitis, which has been found at laparoscopy in 68% of patients with one of these additional findings, 90% of patients with two, and 96% of patients with three. However, only 17% of all patients with laparoscopy-confirmed salpingitis have had all three additional findings.

In a woman with pelvic pain and tenderness, increased numbers of PMNs (30 per 1000× microscopic field in strands of cervical mucus) or leukocytes outnumbering epithelial cells in vaginal fluid (in the absence of trichomonal vaginitis, which also produces PMNs in vaginal discharge) increase the predictive value of a clinical diagnosis of acute PID, as do onset with menses, history of recent abnormal menstrual bleeding, presence of an IUD, history of salpingitis, and sexual exposure to a male with urethritis. Appendicitis or another disorder of the gut is favored by the early onset of anorexia, nausea, or vomiting; the onset of pain later than day 14 of the menstrual cycle; or unilateral pain limited to the right or left lower quadrant. Whenever the diagnosis of PID is being considered, serum assays for human β-chorionic gonadotropin should be performed; these tests are usually positive with ectopic pregnancy. Ultrasonography and MRI can be useful for the identification of tuboovarian or pelvic abscess. MRI of the tubes can also show increased tubal diameter, intratubal fluid, or tubal wall thickening in cases of salpingitis.

The primary value of laparoscopy in women with lower abdominal pain is for the exclusion of other surgical problems that cannot be resolved with non-invasive imaging. Some of the most common or serious problems that may be confused with salpingitis (e.g., acute appendicitis, ectopic pregnancy, corpus luteum bleeding, ovarian tumor) are unilateral. Unilateral pain or pelvic mass, although not incompatible with PID, is a strong indication for laparoscopy unless the clinical picture warrants laparotomy instead. Atypical clinical findings such as the absence of lower genital tract infection, a missed menstrual period, a positive pregnancy test, or failure to respond to appropriate therapy are other common indications for laparoscopy. Endometrial biopsy is relatively sensitive and specific for the diagnosis of endometritis, which correlates well with the presence of salpingitis.

Vaginal or endocervical swab specimens should be obtained for NAATs for *N. gonorrhoeae* and *C. trachomatis*. At a minimum, vaginal fluid should be evaluated for the presence of PMNs, and endocervical secretions ideally should be assessed by Gram's staining for PMNs and gram-negative diplococci, which indicate gonococcal infection. The clinical diagnosis of PID made by expert gynecologists is confirmed by laparoscopy or endometrial biopsy in ~90% of women who also have cultures positive for *N. gonorrhoeae* or *C. trachomatis*. Even among women with no symptoms suggestive of acute PID who were attending an STD clinic or a gynecology clinic in Pittsburgh, endometritis was significantly associated with endocervical gonorrhea or chlamydial infection or with BV, being detected in 26%, 27%, and 15% of women with these conditions, respectively.

TREATMENT

Pelvic Inflammatory Disease

Recommended combination regimens for ambulatory or parenteral management of PID are presented in **Table 131-6**. Women managed as outpatients should receive a combined regimen with broad activity, such as ceftriaxone (to cover possible gonococcal infection) followed by doxycycline (to cover possible chlamydial infection). Metronidazole can be added to enhance activity against anaerobes; this addition should be strongly considered if BV is documented. Although few methodologically sound clinical trials (especially with prolonged follow-up) have been conducted, one meta-analysis suggested a benefit of providing good coverage against anaerobes.

TABLE 131-6 Combination Antimicrobial Regimens Recommended for Outpatient Treatment or for Parenteral Treatment of Pelvic Inflammatory Disease

OUTPATIENT REGIMENS[a]	PARENTERAL REGIMENS
Ceftriaxone (250 mg IM once) ***plus*** Doxycycline (100 mg PO bid for 14 days) ***plus***[b] Metronidazole (500 mg PO bid for 14 days)	Initiate parenteral therapy with either of the following regimens; continue parenteral therapy until 48 h after clinical improvement; then change to outpatient therapy, as described in the text **Regimen A** Cefotetan (2 g IV q12h) *or* cefoxitin (2 g IV q6h) ***plus*** Doxycycline (100 mg IV or PO q12h) **Regimen B** Clindamycin (900 mg IV q8h) ***plus*** Gentamicin (loading dose of 2 mg/kg IV or IM, then maintenance dose of 1.5 mg/kg q8h)

[a]See text for discussion of options in the patient who is intolerant of cephalosporins. [b]The addition of metronidazole is recommended by some experts, particularly if bacterial vaginosis is present.

Source: Adapted from Centers for Disease Control and Prevention: MMWR Recomm Rep 59(RR-12):1, 2010.

The CDC STD treatment guidelines recommend initiation of empirical treatment for PID in sexually active young women and other women at risk for PID if they are experiencing pelvic or lower abdominal pain, if no other cause for the pain can be identified, and if pelvic examination reveals one or more of the following criteria for PID: cervical motion tenderness, uterine tenderness, or adnexal tenderness. Women with suspected PID can be treated as either outpatients or inpatients. In the multicenter Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) trial, 831 women with mild to moderately severe symptoms and signs of PID were randomized to receive either inpatient treatment with IV cefoxitin and doxycycline or outpatient treatment with a single IM dose of cefoxitin plus oral doxycycline. Short-term clinical and microbiologic outcomes and long-term outcomes were equivalent in the two groups. Nonetheless, hospitalization should be considered when (1) the diagnosis is uncertain and surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded, (2) the patient is pregnant, (3) pelvic abscess is suspected, (4) severe illness or nausea and vomiting preclude outpatient management, (5) the patient has HIV infection, (6) the patient is assessed as unable to follow or tolerate an outpatient regimen, or (7) the patient has failed to respond to outpatient therapy. Some experts also prefer to hospitalize adolescents with PID for initial therapy, although younger women do as well as older women on outpatient therapy.

Currently, no agents other than parenteral cephalosporins provide reliable coverage for gonococcal infection. Thus, adequate oral treatment of women with serious intolerance to cephalosporins is a challenge. If penicillins are an option, amoxicillin/clavulanic acid combined with doxycycline has elicited a short-term clinical response in one trial. Clinical trials performed outside the United States support the effectiveness of oral moxifloxacin. In this case, it is imperative to perform a sensitive diagnostic test for gonorrhea (ideally, a culture to test for antimicrobial susceptibility) before initiation of therapy. For women whose PID involves

quinolone-resistant *N. gonorrhoeae*, treatment is uncertain but could include parenteral gentamicin or oral azithromycin, although the latter agent has not been studied for this purpose.

For hospitalized patients, the following two parenteral regimens (Table 131-6) have given nearly identical results in a multicenter randomized trial:

1. Doxycycline plus either cefotetan or cefoxitin: Administration of these drugs should be continued by the IV route for at least 48 h after the patient's condition improves and then followed with oral doxycycline (100 mg twice daily) to complete 14 days of therapy.
2. Clindamycin plus gentamicin in patients with normal renal function: Once-daily administration of gentamicin (with combination of the total daily dose into a single daily dose) has not been evaluated in PID but has been efficacious in other serious infections and could be substituted. Treatment with these drugs should be continued for at least 48 h after the patient's condition improves and then followed with oral doxycycline (100 mg twice daily) or clindamycin (450 mg four times daily) to complete 14 days of therapy. In cases with tuboovarian abscess, clindamycin rather than doxycycline for continued therapy provides better coverage for anaerobic infection.

FOLLOW-UP

Hospitalized patients should show substantial clinical improvement within 3–5 days. Women treated as outpatients should be clinically reevaluated within 72 h. A follow-up telephone survey of women seen in an emergency department and given a prescription for 10 days of oral doxycycline for PID found that 28% never filled the prescription and 41% stopped taking the medication early (after an average of 4.1 days), often because of persistent symptoms, lack of symptoms, or side effects. Women not responding favorably to ambulatory therapy should be hospitalized for parenteral therapy and further diagnostic evaluations, including a consideration of laparoscopy. Male sex partners should be evaluated and treated empirically for gonorrhea and chlamydial infection. After completion of treatment, tests for persistent or recurrent infection with *N. gonorrhoeae* or *C. trachomatis* should be performed if symptoms persist or recur or if the patient has not complied with therapy or has been reexposed to an untreated sex partner.

SURGERY

Surgery is necessary for the treatment of salpingitis only in the face of life-threatening infection (such as rupture or threatened rupture of a tuboovarian abscess) or for drainage of an abscess. Conservative surgical procedures are usually sufficient. Pelvic abscesses can often be drained by posterior colpotomy, and peritoneal lavage can be used for generalized peritonitis.

Prognosis Late sequelae include infertility due to bilateral tubal occlusion, ectopic pregnancy due to tubal scarring without occlusion, chronic pelvic pain, and recurrent salpingitis. The overall post-salpingitis risk of infertility due to tubal occlusion in a large study in Sweden was 11% after one episode of salpingitis, 23% after two episodes, and 54% after three or more episodes. A University of Washington study found a sevenfold increase in the risk of ectopic pregnancy and an eightfold increase in the rate of hysterectomy after PID.

Prevention A randomized controlled trial designed to determine whether selective screening for chlamydial infection reduces the risk of subsequent PID showed that women randomized to undergo screening had a 56% lower rate of PID over the following year than did women receiving the usual care without screening. This report helped prompt U.S. national guidelines for risk-based chlamydial screening of young women to reduce the incidence of PID and the prevalence of post-PID sequelae, while also reducing sexual transmission of *C. trachomatis*. The CDC and the U.S. Preventive Services Task Force recommend that sexually active women ≤25 years of age be screened annually for genital chlamydial infection. Despite this recommendation, screening coverage in many primary care settings remains low.

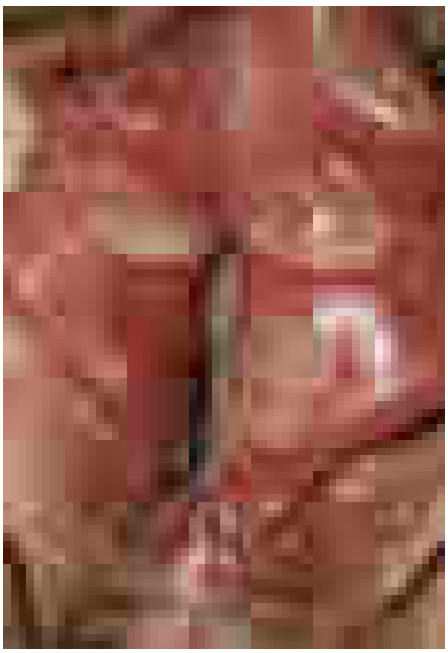


FIGURE 131-5 Chancroid: multiple, painful, punched-out ulcers with undermined borders on the labia occurring after autoinoculation.

ULCERATIVE GENITAL OR PERIANAL LESIONS

Genital ulceration reflects a set of important STIs, most of which sharply increase the risk of sexual acquisition and shedding of HIV. In a 1996 study of genital ulcers in 10 of the U.S. cities with the highest rates of primary syphilis, PCR testing of ulcer specimens demonstrated HSV in 62% of patients, *T. pallidum* in 13%, and *Haemophilus ducreyi* (the cause of chancroid) in 12–20%. Today, genital herpes represents an even higher proportion of genital ulcers in the United States and other industrialized countries.

In Asia and Africa, chancroid **(Fig. 131-5)** was once considered the most common type of genital ulcer, followed in frequency by primary syphilis and then genital herpes **(Fig. 131-6)**. With increased efforts to control chancroid and syphilis and widespread use of broad-spectrum antibiotics to treat STI-related syndromes, together with more frequent recurrences or persistence of genital herpes attributable to HIV infection, PCR testing of genital ulcers now clearly

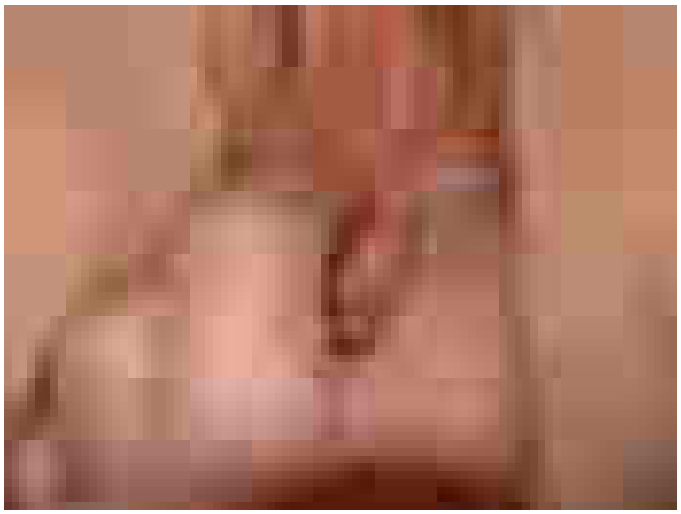


FIGURE 131-6 Genital herpes. A relatively mild, superficial ulcer is typically seen in episodic outbreaks. *(Courtesy of Michael Remington, University of Washington Virology Research Clinic.)*

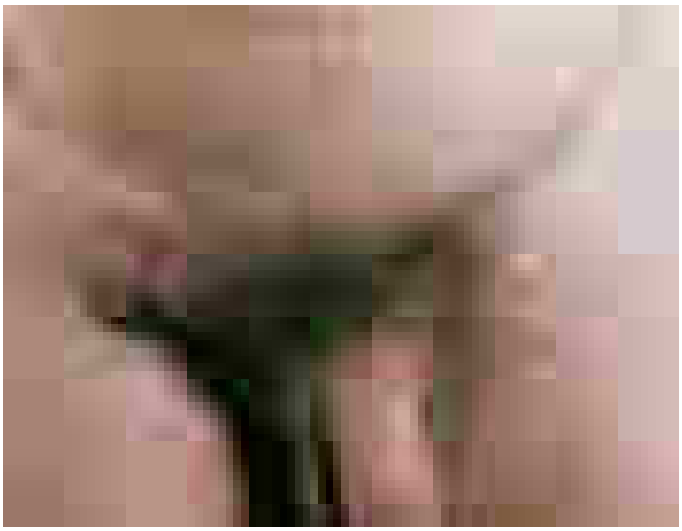


FIGURE 131-7 Lymphogranuloma venereum (LGV): striking tender lymphadenopathy occurring at the femoral and inguinal lymph nodes, separated by a groove made by Poupart's ligament. This "sign-of-the-groove" is not considered specific for LGV; for example, lymphomas may present with this sign.

implicates genital herpes as by far the most common cause of genital ulceration in most developing countries. LGV due to *C. trachomatis* **(Fig. 131-7)** and donovanosis (granuloma inguinale, due to *Klebsiella granulomatis*; **see Fig. 168-1**) continue to cause genital ulceration in some developing countries. LGV virtually disappeared in industrialized countries during the first 20 years of the HIV pandemic, but outbreaks are again occurring in Europe (including the United Kingdom), in North America, and in Australia. In these outbreaks, LGV typically presents as proctitis, with or without anal lesions, in men who report unprotected receptive anal intercourse, very often in association with HIV and/or hepatitis C virus infection; the latter may be an acute infection acquired through the same exposure. Other causes of genital ulcers include (1) candidiasis and traumatized genital warts—both readily recognized; (2) lesions due to genital involvement by more widespread dermatoses; (3) cutaneous manifestations of systemic diseases such as genital mucosal ulceration in Stevens-Johnson syndrome or Behçet's disease; (4) superinfections of lesions that may originally have been sexually acquired (for example, methicillin-resistant *S. aureus* complicating a genital ulcer due to HSV-2); and (5) localized drug reactions, such as the ulcers occasionally seen with topical paromomycin cream or boric acid preparations.

Diagnosis Although most genital ulcerations cannot be diagnosed confidently on clinical grounds alone, clinical findings **(Table 131-7)** and epidemiologic considerations can usually guide initial management **(Table 131-8)** pending results of specific tests. Clinicians should order a rapid serologic test for syphilis in all cases of genital ulcer. To evaluate lesions except those highly characteristic of infection with HSV (i.e., those with herpetic vesicles), dark-field microscopy, direct immunofluorescence, and a NAAT for *T. pallidum* can be useful but are rarely available. It is important to note that 30% of syphilitic chancres—the primary ulcer of syphilis—are associated with an initially nonreactive syphilis serology. All patients presenting with genital ulceration should be counseled and tested for HIV infection.

Typical vesicles or pustules or a cluster of painful ulcers preceded by vesiculopustular lesions suggest genital herpes. These typical clinical manifestations make detection of the virus optional; however, many patients want confirmation of the diagnosis, and differentiation of HSV-1 from HSV-2 has prognostic implications, because the latter causes more frequent genital recurrences and is more infectious to vulnerable sex partners.

Painless, nontender, indurated ulcers with firm, nontender inguinal adenopathy suggest primary syphilis. If results of dark-field examination and a rapid serologic test for syphilis are initially negative, or if these tests are not available, presumptive therapy should be provided on the basis of the individual's risk. With historically high rates of syphilis among MSM in the United States, therapy for this infection should not be withheld pending watchful waiting and/or subsequent detection of seroconversion. Repeated serologic testing for syphilis 1 or 2 weeks after treatment of seronegative primary syphilis usually demonstrates seroconversion.

"Atypical" or clinically trivial ulcers may be more common manifestations of genital herpes than classic vesiculopustular lesions. Specific tests for HSV in such lesions are therefore indicated **(Chap. 187)**. Commercially available type-specific serologic tests for serum antibody to HSV-2 may give negative results, especially when patients present early with the initial episode of genital herpes or when HSV-1 is the cause of genital herpes (as is often the case today). Furthermore, a positive test for antibody to HSV-2 does not prove that the current lesions are herpetic, because nearly one-fifth of the general population of the United States (and no doubt a higher proportion of those at risk for other STIs) becomes seropositive for HSV-2 during early adulthood. Although even "type-specific" tests for HSV-2 that are commercially available in the United States are not 100% specific, a positive HSV-2 serology does enable the clinician to tell the patient that he or she has probably had genital herpes, should learn to recognize symptoms, and should avoid sex during recurrences. In addition, because genital

TABLE 131-7 Clinical Features of Genital Ulcers

FEATURE	SYPHILIS	HERPES	CHANCROID	LYMPHOGRANULOMA VENEREUM	DONOVANOSIS
Incubation period	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 months)
Early primary lesions	Papule	Vesicle	Pustule	Papule, pustule, or vesicle	Papule
No. of lesions	Usually one	Multiple	Usually multiple, may coalesce	Usually one; often not detected, despite lymphadenopathy	Variable
Diameter	5–15 mm	1–2 mm	Variable	2–10 mm	Variable
Edges	Sharply demarcated, elevated, round, or oval	Erythematous	Undermined, ragged, irregular	Elevated, round, or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth, nonpurulent, relatively nonvascular	Serous, erythematous, nonvascular	Purulent, bleeds easily	Variable, nonvascular	Red and velvety, bleeds readily
Induration	Firm	None	Soft	Occasionally firm	Firm
Pain	Uncommon	Frequently tender	Usually very tender	Variable	Uncommon
Lymphadenopathy	Firm, nontender, bilateral	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral	Tender, may suppurate, loculated, usually unilateral	None; pseudobuboes

Source: From RM Ballard, in KK Holmes et al (eds): *Sexually Transmitted Diseases*, 4th ed. New York, McGraw-Hill, 2008.

TABLE 131-8 Initial Management of Genital or Perianal Ulcer

Causative Pathogens
HSV
Treponema pallidum (primary syphilis)
Haemophilus ducreyi (chancroid)
Usual Initial Laboratory Evaluation
Dark-field examination (if available), direct FA, or PCR for *T. pallidum*
RPR, VDRL, or EIA serologic test for syphilis[a]
Culture, direct FA, ELISA, or PCR for HSV
HSV-2-specific serology (consider)
In chancroid-endemic area: PCR or culture for *H. ducreyi*
Initial Treatment
Herpes confirmed or suspected (history or sign of vesicles):
Treat for genital herpes with acyclovir, valacyclovir, or famciclovir.
Syphilis confirmed (dark-field, FA, or PCR showing *T. pallidum*, or RPR reactive):
Benzathine penicillin (2.4 million units IM once to patient, to recent [e.g., within 3 months] seronegative partner[s], and to all seropositive partners)[b]
Chancroid confirmed or suspected (diagnostic test positive, or HSV and syphilis excluded, and persistent lesion):
Ciprofloxacin (500 mg PO as single dose) *or*
Ceftriaxone (250 mg IM as single dose) *or*
Azithromycin (1 g PO as single dose)

[a]If results are negative but primary syphilis is suspected, treat presumptively when indicated by epidemiologic and sexual risk assessment; repeat in 1 week. [b]The same treatment regimen is also effective in HIV-infected persons with early syphilis.

Abbreviations: EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; FA, fluorescent antibody; HSV, herpes simplex virus; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

shedding and sexual transmission of HSV-2 often occur in the absence of symptoms and signs of recurrent herpetic lesions, persons who have a history of genital herpes or who are seropositive for HSV-2 should consider the use of condoms or suppressive antiviral therapy, both of which can reduce the risk of HSV-2 transmission to a sexual partner.

Demonstration of *H. ducreyi* by culture (or by PCR, where available) is most useful when ulcers are painful and purulent, especially if inguinal lymphadenopathy with fluctuance or overlying erythema is noted; if chancroid is prevalent in the community; or if the patient has recently had a sexual exposure elsewhere in a chancroid-endemic area (e.g., a developing country). Enlarged, fluctuant lymph nodes should be aspirated for culture or PCR to detect *H. ducreyi* as well as for Gram's staining and culture to rule out the presence of other pyogenic bacteria.

When genital ulcers persist beyond the natural history of initial episodes of herpes (2–3 weeks) or of chancroid or syphilis (up to 6 weeks) and do not resolve with syndrome-based antimicrobial therapy, then—in addition to the usual tests for herpes, syphilis, and chancroid—biopsy is indicated to exclude donovanosis as well as carcinoma and other nonvenereal dermatoses.

TREATMENT

Ulcerative Genital or Perianal Lesions

Immediate syndrome-based treatment for acute genital ulcer (after collection of all necessary diagnostic specimens at the first visit) is often appropriate before all test results become available because patients with typical initial or recurrent episodes of genital or anorectal herpes can benefit from prompt oral antiviral therapy **(Chap. 187)**; because early treatment of sexually transmitted causes of genital ulcers decreases further transmission; and because some patients do not return for test results and treatment. A thorough assessment of the patient's sexual-risk profile and medical history is critical in determining the course of initial management. The patient who has risk factors consistent with exposure to syphilis (e.g., a male patient who reports sex with other men or who has HIV infection) should generally receive initial treatment for syphilis. Empirical therapy for chancroid should be considered if there has been an exposure in an area of the world where chancroid occurs or if regional lymph node suppuration is evident. Finally, empirical antimicrobial therapy may be indicated if ulcers persist and the diagnosis remains unclear after a week of observation despite attempts to diagnose herpes, syphilis, and chancroid.

PROCTITIS, PROCTOCOLITIS, ENTEROCOLITIS, AND ENTERITIS

Sexually acquired *proctitis*, with inflammation limited to the rectal mucosa (the distal 10–12 cm), results from direct rectal inoculation of typical STD pathogens. In contrast, inflammation extending from the rectum to the colon (*proctocolitis*), involving both the small and the large bowel (*enterocolitis*), or involving the small bowel alone (*enteritis*) can result from ingestion of typical intestinal pathogens through oral–anal exposure during sexual contact. Anorectal pain and mucopurulent, bloody rectal discharge suggest proctitis or protocolitis. Proctitis commonly produces tenesmus (causing frequent attempts to defecate, but not true diarrhea) and constipation, whereas proctocolitis and enterocolitis more often cause true diarrhea. In all three conditions, anoscopy usually shows mucosal exudate and easily induced mucosal bleeding (i.e., a positive "wipe test"), sometimes with petechiae or mucosal ulcers. Exudate should be sampled for Gram's staining and other microbiologic studies. Sigmoidoscopy or colonoscopy shows inflammation limited to the rectum in proctitis or disease extending at least up into the sigmoid colon in proctocolitis.

The AIDS era brought an extraordinary shift in the clinical and etiologic spectrum of intestinal infections among MSM. The number of cases of the acute intestinal STIs described above fell as high-risk sexual behaviors became less common in this group. At the same time, the number of AIDS-related opportunistic intestinal infections increased rapidly, many associated with chronic or recurrent symptoms. The incidence of these opportunistic infections has since fallen with increasingly widespread coverage of HIV-infected persons with effective antiretroviral therapy. Two species initially isolated in association with intestinal symptoms in MSM—now known as *Helicobacter cinaedi* and *Helicobacter fennelliae*—have both been isolated from the blood of HIV-infected men and other immunosuppressed persons, often in association with a syndrome of multifocal dermatitis and arthritis.

Acquisition of HSV, *N. gonorrhoeae*, or *C. trachomatis* (including LGV strains of *C. trachomatis*) during receptive anorectal intercourse causes most cases of infectious proctitis in women and MSM. Primary and secondary syphilis can also produce anal or anorectal lesions, with or without symptoms. Gonococcal or chlamydial proctitis typically involves the most distal rectal mucosa and the anal crypts and is clinically mild, without systemic manifestations. In contrast, primary proctitis due to HSV and proctocolitis due to the strains of *C. trachomatis* that cause LGV usually produce severe anorectal pain and often cause fever. Perianal ulcers and inguinal lymphadenopathy, most commonly due to HSV, can also occur with LGV or syphilis. Sacral nerve root radiculopathies, usually presenting as urinary retention, laxity of the anal sphincter, or constipation, may complicate primary herpetic proctitis. In LGV, rectal biopsy typically shows crypt abscesses, granulomas, and giant cells—findings resembling those in Crohn's disease; such findings should always prompt rectal culture and serology for LGV, which is a curable infection. Syphilis can also produce rectal granulomas, usually in association with infiltration by plasma cells or other mononuclear cells. Syphilis, LGV, and HSV infection involving the rectum can produce perirectal adenopathy that is sometimes mistaken for malignancy; syphilis, LGV, HSV infection, and chancroid involving the anus can produce inguinal adenopathy because anal lymphatics drain to inguinal lymph nodes.

Diarrhea and abdominal bloating or cramping pain without anorectal symptoms and with normal findings on anoscopy and sigmoidoscopy occur with inflammation of the small intestine (enteritis) or with proximal colitis. In MSM without HIV infection, enteritis is often attributable to *Giardia lamblia*. Sexually acquired proctocolitis is most often due to *Campylobacter* or *Shigella* species.

TREATMENT

Proctitis, Proctocolitis, Enterocolitis, and Enteritis

Acute proctitis in persons who have practiced receptive anorectal intercourse is usually sexually acquired. Such patients should undergo anoscopy to detect rectal ulcers or vesicles and petechiae after swabbing of the rectal mucosa; to examine rectal exudates for PMNs and gram-negative diplococci; and to obtain rectal swab specimens for testing for rectal gonorrhea, chlamydial infection, herpes, and syphilis. Pending test results, patients with proctitis should receive empirical syndromic treatment—e.g., with ceftriaxone (a single IM dose of 250 mg for gonorrhea) plus doxycycline (100 mg by mouth twice daily for 7 days for possible chlamydial infection) plus treatment for herpes or syphilis if indicated. If LGV proctitis is proven or suspected, the recommended treatment is doxycycline (100 mg by mouth twice daily for 21 days); alternatively, 1 g of azithromycin once a week for 3 weeks is likely to be effective but is little studied.

PREVENTION AND CONTROL OF STIs

Prevention and control of STIs require the following:

1. Reduction of the average rate of sexual exposure to STIs through alteration of sexual risk behaviors and behavioral norms among both susceptible and infected persons in all population groups. The necessary changes include reduction in the total number of sexual partners and the number of concurrent sexual partners. The U.S. Preventive Services Task Force recommends intensive behavioral counseling for all sexually active adolescents and adults who are at increased risk for STIs (grade B recommendation). Motivational interviewing is one approach that has elicited behavioral changes, including safer sex practices and more consistent contraception, that contribute to these goals.
2. Reduction of the efficiency of transmission through the promotion of safer sexual practices, the use of condoms during casual or commercial sex, vaccination against HBV and HPV infection, male circumcision (which reduces risk of acquisition of HIV infection, chancroid, and perhaps other STIs), and a growing number of other approaches (e.g., early detection and treatment of other STIs to reduce the efficiency of sexual transmission of HIV). Longitudinal studies have shown that consistent condom use is associated with significant protection of both males and females against all STIs that have been examined, including HIV, HPV, and HSV infections as well as gonorrhea and chlamydial infection. The only exceptions are probably sexually transmitted *Pthirus pubis* and *Sarcoptes scabiei* infestations.
3. Shortening of the duration of infectivity of STIs through early detection and curative or suppressive treatment of patients and their sexual partners. The availability of curative therapy for hepatitis C virus infection and suppressive therapy for HBV infection exemplifies new opportunities for shortening infectivity in major STIs.

Financial and time constraints imposed by many clinical practices, along with the reluctance of some clinicians to ask questions about stigmatized sexual behaviors, often curtail screening and prevention services. As outlined in **Fig. 131-8**, the success of clinicians' efforts to detect and treat STIs depends in part on societal efforts to teach young people how to recognize symptoms of STIs; to motivate individuals with symptoms to seek care promptly; to educate persons who are at risk but have no symptoms about what tests they should undergo routinely; and to make high-quality, appropriate care accessible, affordable, and acceptable, especially to the young indigent patients most likely to acquire an STI.

STI RISK ASSESSMENT

Because many infected individuals develop no symptoms or fail to recognize and report symptoms, clinicians should routinely perform an STI risk assessment for teenagers and young adults as a guide to selective screening. As stated earlier, the U.S. Preventive Services Task

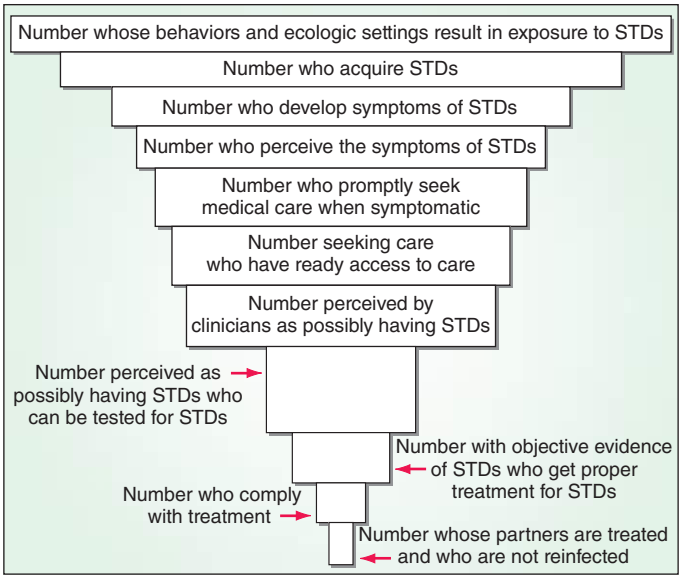


FIGURE 131-8 Critical control points for preventive and clinical interventions against sexually transmitted diseases (STDs). *(Adapted from HT Waller and MA Piot: Bull World Health Organ 41:75, 1969 and 43:1, 1970; and from "Resource allocation model for public health planning—a case study of tuberculosis control," Bull World Health Organ 48[Suppl], 1973.)*

Force recommends screening sexually active female patients ≤25 years of age for *C. trachomatis* whenever they present for health care (at least once a year); older women should be tested if they have more than one sexual partner, have begun a new sexual relationship since the previous test, or have another STI diagnosed. In women 25–29 years of age, chlamydial infection is uncommon but still may reach a prevalence of 3–5% in some settings; information provided by women in this age group on a sex partner's concurrency (whether a male partner has had another sex partner during the time they have been together) is helpful in identifying women at increased risk. In some regions of the United States, widespread selective screening and treatment of young women for cervical *C. trachomatis* infection have been associated with a 50–60% drop in prevalence. Such screening and treatment also protect the individual woman from PID. Sensitive urine-based genetic amplification tests permit expansion of screening to men, teenage boys, and girls in settings where examination is not planned or is impractical (e.g., during pre-participation sports examinations or during initial medical evaluation of adolescent girls). Vaginal swabs—collected either by the health care provider at a pelvic examination or by the woman herself—are highly sensitive and specific for the diagnosis of chlamydial and gonococcal infection; they are now the preferred type of specimen for screening and diagnosis of these infections.

Although gonorrhea is now substantially less common than chlamydial infection in industrialized countries, screening tests for *N. gonorrhoeae* are still appropriate for women and teenage girls attending STD clinics and for sexually active teens and young women from areas of high gonorrhea prevalence. Multiplex NAATs that combine screening for *N. gonorrhoeae* and *C. trachomatis*—and, more recently, for *T. vaginalis*—in a single low-cost assay now facilitate the prevention and control of these infections for populations at high risk.

All patients who have newly detected STIs or are at high risk for STIs according to routine risk assessment as well as all pregnant women should be encouraged to undergo serologic testing for syphilis and HIV infection, with appropriate HIV counseling before and after testing. Randomized trials have shown that risk-reduction counseling of patients with STIs significantly lowers subsequent risk of acquiring an STI; such counseling should now be considered a standard component of STI management. Preimmunization serologic testing for antibody to HBV is indicated for unvaccinated persons who are known to be at high risk, such as MSM and people who use injection drugs. In most young persons, however, it is more cost-effective to vaccinate against HBV without serologic screening. It is important

to recognize that, while immunization against HBV has contributed to marked reductions in the incidence of infection with this virus, the majority of new cases that do occur are acquired through sex. In 2006, the CDC's Advisory Committee on Immunization Practices (ACIP) recommended the following: (1) Universal hepatitis B vaccination should be implemented for all unvaccinated adults in settings in which a high proportion of adults have risk factors for HBV infection (e.g., STD clinics, HIV testing and treatment facilities, drug-abuse treatment and prevention settings, health care settings targeting services to injection drug users or MSM, and correctional facilities). (2) In other primary care and specialty medical settings that provide care to adults at risk for HBV infection, health care providers should inform all patients about the health benefits of vaccination, the risk factors for HBV infection, and the persons for whom vaccination is recommended; they should vaccinate adults who report risk factors for HBV infection as well as any adult who requests protection from HBV infection. To promote vaccination in all settings, health care providers should implement standing orders to identify adults recommended for hepatitis B vaccination, should administer hepatitis B vaccine as part of routine clinical services, should not require acknowledgment of an HBV infection risk factor for adult vaccination, and should use available reimbursement mechanisms to remove financial barriers to hepatitis B vaccination.

In 2007, the ACIP made its first recommendation for routine immunization of 9- to 26-year-old girls and women with the quadrivalent HPV vaccine (against HPV types 6, 11, 16, and 18). In 2011, the ACIP recommended routine administration of quadrivalent HPV vaccine to boys at 11 or 12 years of age and to males 13–21 years of age who have not yet been vaccinated or who have not completed the three-dose vaccine series; HBV vaccination of men 22–26 years of age has also been recommended. Since that time, a nonavalent HPV vaccine has become available and has largely replaced the earlier vaccines. The optimal age for recommended vaccination is 11–12 years because of the very high risk of HPV infection after sexual debut.

Partner notification is the process of identifying and informing partners of infected patients about possible exposure to an STI and of examining, testing, vaccinating, and treating partners as appropriate. In a series of 22 reports concerning partner notification during the 1990s, index patients with gonorrhea or chlamydial infection named a mean of 0.75–1.6 partners, of whom one-fourth to one-third were infected; those with syphilis named 1.8–6.3 partners, with one-third to one-half infected; and those with HIV infection named 0.76–5.31 partners, with up to one-fourth infected. Persons who transmit infection or who have recently been infected and are still in the incubation period usually have no symptoms or only mild symptoms and seek medical attention only when notified of their exposure. Therefore, the clinician must encourage patients to participate in partner notification, must ensure that exposed persons are notified and treated, and must guarantee confidentiality to all involved. In the United States, local health departments often offer assistance in partner notification, treatment, and/or counseling. It seems both feasible and most useful to notify those partners exposed within the patient's likely period of infectiousness, which is often considered the preceding 1 month for gonorrhea, 1–2 months for chlamydial infection, and up to 3 months for early syphilis.

Persons with a new-onset STI always have a *source* contact who gave them the infection; in addition, they may have a *secondary* (*spread* or *exposed*) contact with whom they had sex after becoming infected. The identification and treatment of these two types of contacts have different objectives. Treatment of the source contact (often a casual contact) benefits the community by preventing further transmission and benefits the source contact; treatment of the recently exposed secondary contact (typically a spouse or another steady sexual partner) prevents the development of serious complications (such as PID) in the partner, reinfection of the index patient, and further spread of infection. A survey of a random sample of U.S. physicians found that most instructed patients to abstain from sex during treatment, to use condoms, and to inform their sex partners after being diagnosed with gonorrhea, chlamydial infection, or syphilis; physicians sometimes gave the patients drugs for their partners. However, follow-up of the partners by physicians was infrequent. A randomized trial compared patients' delivery of therapy to partners exposed to gonorrhea or chlamydial infection with conventional notification and advice to partners to seek evaluation for STD; patients' delivery of partners' therapy, also known as *expedited partner therapy* (EPT), significantly reduced combined rates of reinfection of the index patient with *N. gonorrhoeae* or *C. trachomatis*. State-by-state variations in regulations governing this approach have not been well defined, but the 2015 CDC STD treatment guidelines describe its potential use. EPT, which is now commonly used by many practicing physicians, is currently permissible in 39 states and potentially allowable in another 8. (Updated information on the legal status of EPT is available at *http://www.cdc.gov/std/ept*.)

In summary, clinicians and public health agencies share responsibility for the prevention and control of STIs. In the current health care environment, the role of primary care clinicians has become increasingly important in STI prevention as well as in diagnosis and treatment, and the resurgence of bacterial STIs like syphilis and LGV among MSM—particularly those co-infected with HIV—emphasizes the need for risk assessment and routine screening.

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132 Encephalitis

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DEFINITION

Encephalitis is defined as an inflammation of the brain caused either by infection, usually with a virus, or from a primary autoimmune process. This chapter will focus on infectious causes of encephalitis; noninfectious etiologies are considered elsewhere **(Chaps. 90, 436, and 437)**. In contrast to meningitis **(Chaps. 133 and 134)**, in which the infectious process and associated inflammatory response are limited largely to the meninges, in encephalitis the brain parenchyma is also involved. Many patients with encephalitis also have evidence of associated meningitis (meningoencephalitis) and, in some cases, involvement of the spinal cord or nerve roots (encephalomyelitis, encephalomyeloradiculitis).

CLINICAL MANIFESTATIONS

In addition to the acute febrile illness with evidence of meningeal involvement characteristic of meningitis, the patient with encephalitis commonly has an altered level of consciousness (confusion, behavioral abnormalities), or a depressed level of consciousness ranging from mild lethargy to coma, and evidence of either focal or diffuse neurologic signs and symptoms. Patients with encephalitis may have hallucinations, agitation, personality change, behavioral disorders, and, at times, a frankly psychotic state. Focal or generalized seizures occur in many patients with encephalitis. Virtually every possible type of focal neurologic disturbance has been reported in viral encephalitis; the signs and symptoms reflect the sites of infection and inflammation. The most commonly encountered focal findings are aphasia, ataxia, upper or lower motor neuron patterns of weakness, involuntary movements (e.g., myoclonic jerks, tremor), and cranial nerve deficits (e.g., ocular palsies, facial weakness). Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or the development of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Even though neurotropic viruses typically cause pathologic injury in distinct regions of the central nervous system (CNS), variations in clinical presentations make it impossible to reliably establish the etiology of a specific case of encephalitis on clinical grounds alone (see "Differential Diagnosis," below).

ETIOLOGY

In the United States, there are an estimated ~20,000 cases of encephalitis per year, although the actual number of cases is likely to be significantly larger. Despite comprehensive diagnostic efforts, the majority of cases of acute encephalitis of suspected viral etiology remain of unknown cause. Hundreds of viruses are capable of causing encephalitis, although only a limited subset is responsible for most cases in which a specific cause is identified **(Table 132-1)**. The most commonly identified viruses causing sporadic cases of acute encephalitis in immunocompetent adults are herpesviruses (herpes simplex virus [HSV], varicella-zoster virus [VZV], Epstein-Barr virus [EBV]). Epidemics of encephalitis are caused by arboviruses, which belong to several different viral taxonomic groups including *Alphaviruses* (e.g., eastern equine encephalitis [EEE] virus), *Flaviviruses* (e.g., West Nile virus [WNV], St. Louis encephalitis virus, Japanese encephalitis virus, Powassan virus), and *Bunyaviruses* (e.g., California encephalitis virus serogroup, La Crosse virus). Historically, the largest number of cases of arbovirus encephalitis in the United States has been due to St. Louis encephalitis virus and the California encephalitis virus serogroup. However, since 2002, WNV has been responsible for the majority of arbovirus meningitis and encephalitis cases in the United States. WNV caused 21,405 confirmed cases of neuroinvasive disease (encephalitis, meningitis, or myelitis) in the years 1995–2016 with 1877 deaths. It is important to recognize that WNV epidemics are unpredictable and that cases have occurred in every state in the continental United States. New causes of viral CNS infections are constantly appearing, as evidenced by the outbreak of cases of encephalitis in Southeast Asia caused by Nipah virus, a member of the Paramyxoviridae family; meningitis in Europe caused by Toscana virus, an arbovirus belonging to the Bunyavirus family; neurological disorders associated with Zika virus, a flavivirus, in South America; and neurologic disorders associated with major epidemics of Chikungunya virus, a togavirus in Africa, India, and Southeast Asia. Parechoviruses including human parechovirus 3 (HPeV3), members of the Picornavirus family, have been reported as causes of fever, sepsis, and meningitis in infants (age <3 months) in the United States and abroad.

TABLE 132-1 Viruses Causing Acute Encephalitis in North America

COMMON	LESS COMMON
Herpesviruses	Rabies
Cytomegalovirus[a]	Eastern equine encephalitis virus
Herpes simplex virus 1[b]	Powassan virus
Herpes simplex virus 2	Cytomegalovirus[a]
Human herpesvirus 6	Colorado tick fever virus
Varicella-zoster virus	Mumps
Epstein-Barr virus	
Arthropod-borne viruses	
La Crosse virus	
West Nile virus[c]	
St. Louis encephalitis virus	
Zika	
Enteroviruses	

[a]Immunocompromised host. [b]The most common cause of sporadic encephalitis. [c]The most common cause of epidemic encephalitis.

LABORATORY DIAGNOSIS

CSF Examination Cerebrospinal fluid (CSF) examination should be performed in all patients with suspected viral encephalitis unless contraindicated by the presence of severely increased intracranial pressure (ICP). Ideally at least 20 mL should be collected with 5–10 mL stored frozen for later studies as needed. The characteristic CSF profile is indistinguishable from that of viral meningitis and typically consists of a lymphocytic pleocytosis, a mildly elevated protein concentration, and a normal glucose concentration. A CSF pleocytosis (>5 cells/μL) occurs in >95% of immunocompetent patients with documented viral encephalitis. In rare cases, a pleocytosis may be absent on the initial lumbar puncture (LP) but present on subsequent LPs. Patients who are severely immunocompromised by HIV infection, glucocorticoid or other immunosuppressant drugs, chemotherapy, or lymphoreticular malignancies may fail to mount a CSF inflammatory response. CSF cell counts exceed 500/μL in only about 10% of patients with encephalitis. Infections with certain arboviruses (e.g., EEE virus or California encephalitis virus), mumps, and lymphocytic choriomeningitis virus (LCMV) may occasionally result in cell counts >1000/μL, but this degree of pleocytosis should suggest the possibility of nonviral infections or other inflammatory processes. Atypical lymphocytes in the CSF may be seen in EBV infection and less commonly with other viruses, including cytomegalovirus (CMV), HSV, and enteroviruses. Increased numbers of plasmacytoid or Mollaret-like large mononuclear cells have been reported in WNV encephalitis. Polymorphonuclear pleocytosis occurs in ~45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in immunocompromised patients. Large numbers of CSF polymorphonuclear leukocytes may be present in patients with encephalitis due to EEE virus, echovirus 9, and, more rarely, other enteroviruses. However, persisting CSF neutrophilia should prompt consideration of bacterial infection, leptospirosis, amebic infection, and noninfectious processes such as acute hemorrhagic leukoencephalitis. About 20% of patients with encephalitis will have a significant number of red blood cells (>500/μL) in the CSF in a nontraumatic tap. The pathologic correlate of this finding may be a hemorrhagic encephalitis of the type seen with HSV; however, CSF red blood cells occur with similar frequency and in similar numbers in patients with nonherpetic focal encephalitides. A decreased CSF glucose concentration is distinctly unusual in viral encephalitis and should suggest the possibility of bacterial, fungal, tuberculous, parasitic, leptospiral, syphilitic, sarcoid, or neoplastic meningitis. Rare patients with mumps, LCMV, or advanced HSV encephalitis and many patients with CMV myeloradiculitis have low CSF glucose concentrations.

CSF POLYMERASE CHAIN REACTION

CSF PCR has become the primary diagnostic test for CNS infections caused by CMV, EBV, HHV-6, and enteroviruses. In the case of VZV CNS infection, CSF PCR and detection of virus-specific IgM or intrathecal antibody synthesis both provide important aids to diagnosis. The sensitivity and specificity of CSF PCRs vary with the virus being tested. The sensitivity (~96%) and specificity (~99%) of HSV CSF PCR are equivalent to or exceed those of brain biopsy. It is important to recognize that HSV CSF PCR results need to be interpreted after considering the likelihood of disease in the patient being tested, the timing of the test in relationship to onset of symptoms, and the prior use of antiviral therapy. A negative HSV CSF PCR test performed by a qualified laboratory at the appropriate time during illness in a patient with a high likelihood of HSV encephalitis based on clinical and laboratory

abnormalities significantly reduces the likelihood of HSV encephalitis but does not exclude it. For example, in a patient with a pretest probability of 35% of having HSV encephalitis, a negative HSV CSF PCR reduces the posttest probability to ~2%, and for a patient with a pretest probability of 60%, a negative test reduces the posttest probability to ~6%. In both situations, a positive test makes the diagnosis almost certain (98–99%). There have been reports of initially negative HSV CSF PCR tests that were obtained early (≤72 h) following symptom onset and that became positive when repeated 1–3 days later. The frequency of positive HSV CSF PCRs in patients with herpes encephalitis also decreases as a function of the duration of illness, with only ~20% of cases remaining positive after ≥14 days. PCR results are generally not affected by ≤1 week of antiviral therapy. In one study, 98% of CSF specimens remained PCR-positive during the first week of antiviral therapy, but the numbers fell to ~50% by 8–14 days and to ~21% by >15 days after initiation of antiviral therapy.

The sensitivity and specificity of CSF PCR tests for viruses other than HSV have not been definitively characterized. Enteroviral (EV) CSF PCR appears to have a sensitivity and specificity of >95%. EV PCR sensitivity for EV71 may be considerably lower (~30% in some reports). Parechoviruses are also not detected by standard EV RT-PCRs. The specificity of EBV CSF PCR has not been established. Positive EBV CSF PCRs associated with positive tests for other pathogens have been reported and may reflect reactivation of EBV latent in lymphocytes that enter the CNS as a result of an unrelated infectious or inflammatory process. In patients with CNS infection due to VZV, CSF antibody and PCR studies should be considered complementary because patients may have evidence of intrathecal synthesis of VZV-specific antibodies and negative CSF PCRs. In the case of WNV infection, CSF PCR appears to be less sensitive than detection of WNV-specific CSF IgM, although PCR testing remains useful in immunocompromised patients who may not mount an effective anti-WNV antibody response.

Unbiased rapid parallel sequencing technologies capable of identifying infectious genomes in CSF, brain, and other tissues have recently shown great promise for rapid diagnosis of obscure cases of encephalitis and other brain infections.

CSF Culture CSF culture is generally of limited utility in the diagnosis of acute viral encephalitis. Culture may be insensitive (e.g., >95% of patients with HSV encephalitis have negative CSF cultures as do virtually all patients with EBV-associated CNS disease) and often takes too long to significantly effect immediate therapy.

Serologic Studies and Antigen Detection For many arboviruses including WNV, serologic studies remain important diagnostic tools. Serum antibody determination is less useful for viruses with high seroprevalence rates in the general population such as HSV, VZV, CMV, and EBV. For viruses with low seroprevalence rates, diagnosis of acute viral infection can be made by documenting seroconversion between acute-phase and convalescent sera (typically obtained after 2–4 weeks) or by demonstrating the presence of virus-specific IgM antibodies. For viruses with high seroprevalence such as VZV and HSV, demonstration of synthesis of virus-specific antibodies in CSF, as shown by an increased IgG index or the presence of CSF IgM antibodies, may be useful and can provide presumptive evidence of CNS infection. Unfortunately, the delay between onset of infection and the host's generation of a virus-specific antibody response often means that serologic data are useful mainly for the retrospective establishment of a specific diagnosis, rather than in aiding acute diagnosis or management.

In patients with HSV encephalitis, antibodies to HSV-1 glycoproteins and HSV glycoprotein antigens have been detected in the CSF. Optimal detection of both HSV antibodies and antigen typically occurs after the first week of illness, limiting the utility of these tests in acute diagnosis. Nonetheless, HSV CSF antibody testing is of value in selected patients whose illness is >1 week in duration and who are CSF PCR–negative for HSV. In the case of VZV infection, CSF antibody tests may be positive when PCR fails to detect viral DNA, and both tests should be considered complementary rather than mutually exclusive.

Demonstration of WNV IgM antibodies is diagnostic of WNV encephalitis because IgM antibodies do not cross the blood-brain barrier, and their presence in CSF is therefore indicative of intrathecal synthesis. Timing of antibody collection may be important because the rate of CSF WNV IgM seropositivity increases by ~10% per day during the first week after illness onset, reaching 80% or higher on day 7 after symptom onset. Although serum and CSF IgM antibodies generally persist for only a few months after acute infection, there are exceptions to this rule, and WNV serum IgM has been shown to persist in some patients for >1 year following acute infection.

MRI, CT, and EEG Patients with suspected encephalitis almost invariably undergo neuroimaging studies and often electroencephalogram (EEG). These tests help identify or exclude alternative diagnoses and assist in the differentiation between a focal, as opposed to diffuse, encephalitic process. Focal findings in a patient with encephalitis should always raise the possibility of HSV encephalitis. Examples of focal findings include: (1) areas of increased signal intensity in the frontotemporal, cingulate, or insular regions of the brain on T2-weighted, fluid-attenuated inversion recovery (FLAIR), or diffusion-weighted MRI **(Fig. 132-1)**; (2) focal areas of low absorption, mass effect, and contrast enhancement on CT; or (3) periodic focal temporal lobe spikes on a background of slow or low-amplitude ("flattened") activity on EEG. Approximately 10% of patients with PCR-documented HSV encephalitis will have a normal MRI, although nearly 80% will have abnormalities in the temporal lobe, and an additional 10% in extratemporal regions. The lesions are typically hyperintense on T2-weighted images. The addition of FLAIR and diffusion-weighted images to the standard MRI sequences enhances sensitivity. Children with HSV encephalitis may have atypical patterns of MRI lesions and often show involvement of brain regions outside the frontotemporal areas. CT is less sensitive than MRI and is normal in up to 20–35% of patients. EEG abnormalities occur in >75% of PCR-documented cases of HSV encephalitis; they typically involve the temporal lobes but are often nonspecific. Some patients with HSV encephalitis have a distinctive EEG pattern consisting of periodic, stereotyped, sharp-and-slow complexes originating in one or both temporal lobes and repeating at regular intervals of 2–3 s. The periodic complexes are typically noted between days 2 and 15 of the illness and are present in two-thirds of pathologically proven cases of HSV encephalitis.

Significant MRI abnormalities are found in only approximately two-thirds of patients with WNV encephalitis, a frequency less than that with HSV encephalitis. When present, abnormalities often involve deep brain structures, including the thalamus, basal ganglia, and brainstem, rather than the cortex and may only be apparent on FLAIR images. EEGs in patients with WNV encephalitis typically show generalized slowing that may be more anteriorly prominent rather than the

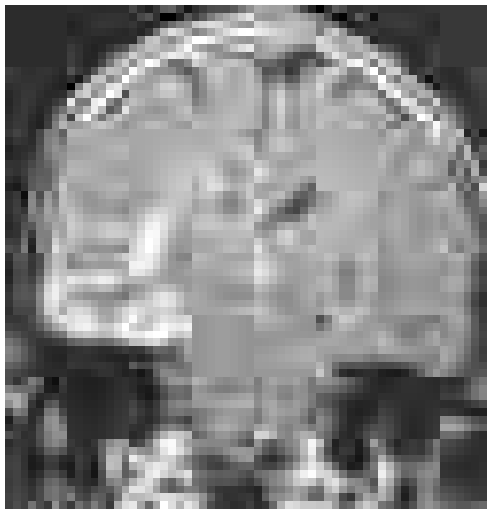

FIGURE 132-1 Coronal fluid-attenuated inversion recovery (FLAIR) magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (*left side of image*) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

TABLE 132-2 Use of Diagnostic Tests in Encephalitis

The best test for WNV encephalitis is the *CSF IgM antibody test.* The prevalence of positive CSF IgM tests increases by about 10% per day after illness onset and reaches 70–80% by the end of the first week. Serum WNV IgM can provide evidence for recent WNV infection, but in the absence of other findings does not establish the diagnosis of neuroinvasive disease (meningitis, encephalitis, acute flaccid paralysis).
Approximately 80% of patients with proven HSV encephalitis have *MRI* abnormalities involving the temporal lobes. This percentage likely increases to >90% when FLAIR and diffusion-weighted MRI sequences are also used. The absence of temporal lobe lesions on MRI reduces the likelihood of HSV encephalitis and should prompt consideration of other diagnostic possibilities.
The *CSF HSV PCR* test may be negative in the first 72 h of symptoms of HSV encephalitis. A repeat study should be considered in patients with an initial early negative PCR in whom diagnostic suspicion of HSV encephalitis remains high and no alternative diagnosis has yet been established.
Detection of *intrathecal synthesis* (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of *HSV-specific antibody* may be useful in diagnosis of HSV encephalitis in patients in whom only late (>1 week after onset) CSF specimens are available and PCR studies are negative. Serum serology alone is of no value in diagnosis of HSV encephalitis due to the high seroprevalence rate in the general population.
Negative *CSF viral cultures* are of no value in excluding the diagnosis of HSV or EBV encephalitis.
VZV CSF IgM antibodies may be present in patients with a negative VZV CSF PCR. Both tests should be performed in patients with suspected VZV CNS disease.
The specificity of *EBV CSF PCR* for diagnosis of CNS infection is unknown. Positive tests may occur in patients with a CSF pleocytosis due to other causes. Detection of EBV CSF IgM or intrathecal synthesis of antibody to VCA supports the diagnosis of EBV encephalitis. Serologic studies consistent with acute EBV infection (e.g., IgM VCA, presence of antibodies against EA but not against EBNA) can help support the diagnosis.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; EA, early antigen; EBNA, EBV-associated nuclear antigen; EBV, Epstein-Barr virus; FLAIR, fluid-attenuated inversion recovery; HSV, herpes simplex virus; IgM, immunoglobulin M; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; VCA, viral capsid antibody; VZV, varicella-zoster virus; WNV, West Nile virus.

temporally predominant pattern of sharp or periodic discharges more characteristic of HSV encephalitis. Patients with VZV encephalitis may show multifocal areas of hemorrhagic and ischemic infarction, reflecting the tendency of this virus to produce a CNS vasculopathy rather than a true encephalitis. Immunocompromised adult patients with CMV often have enlarged ventricles with areas of increased T2 signal on MRI outlining the ventricles and subependymal enhancement on T1-weighted postcontrast images. **Table 132-2** highlights specific diagnostic test results in encephalitis that can be useful in clinical decision-making.

Brain Biopsy Brain biopsy is now generally reserved for patients in whom CSF PCR studies fail to lead to a specific diagnosis, who have focal abnormalities on MRI, no serologic evidence of autoimmune disease, and who continue to show progressive clinical deterioration despite treatment with acyclovir and supportive therapy.

DIFFERENTIAL DIAGNOSIS

Infection by a variety of other organisms can mimic viral encephalitis. In studies of biopsy-proven HSV encephalitis, common infectious mimics of focal viral encephalitis included mycobacteria, fungi, rickettsiae, *Listeria, Mycoplasma*, and other bacteria (including *Bartonella* sp.). There are an increasing number of antibodies reported that cause autoimmune encephalitis, including those associated with antibodies against *N*-methyl-D-aspartate (NMDA) receptor, voltage-gated potassium channels/leucine-rich glioma inactivated protein-1 (VGKC/LGI-I), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid (GABA) receptors, and glutamic acid decarboxylase (GAD 65), that can mimic that caused by viral infection. In most cases, diagnosis is made by detection of the specific autoantibodies in serum and/or CSF. NMDA receptor antibodies have been reported in some patients with HSE encephalitis, and their presence should not exclude appropriate testing and treatment for HSV encephalitis. It has been suggested that development of NMDAR antibodies in patients with HSE may contribute to delayed recovery or clinical relapse. Autoimmune encephalitis may also be associated with specific cancers (paraneoplastic) and onconeuronal antibodies (e.g., anti-Hu, Yo, Ma2, amphiphysin, CRMP5, CV2) **(Chap. 90)**. Subacute or chronic forms of encephalitis may occur in association with autoantibodies against thyroglobulin and thyroperoxidase (Hashimoto's encephalopathy) and with prion diseases.

Infection caused by the ameba *Naegleria fowleri* can also cause acute meningoencephalitis (primary amebic meningoencephalitis), whereas that caused by *Acanthamoeba* and *Balamuthia* more typically produces subacute or chronic granulomatous amebic meningoencephalitis. *Naegleria* thrive in warm, iron-rich pools of water, including those found in drains, canals, and both natural and human-made outdoor pools. Infection has typically occurred in immunocompetent children with a history of swimming in potentially infected water. The CSF, in contrast to the typical profile seen in viral encephalitis, often resembles that of bacterial meningitis with a neutrophilic pleocytosis and hypoglycorrhachia. Motile trophozoites can be seen in a wet mount of warm, fresh CSF. There have been an increasing number of cases of *Balamuthia mandrillaris* amebic encephalitis mimicking acute viral encephalitis in children and immunocompetent adults. This organism has also been associated with encephalitis in recipients of transplanted organs from a donor with unrecognized infection. No effective treatment has been identified, and mortality approaches 100%.

Encephalitis can be caused by the raccoon pinworm *Baylisascaris procyonis*. Clues to the diagnosis include a history of raccoon exposure, especially of playing in or eating dirt potentially contaminated with raccoon feces. Most patients are children, and many have an associated eosinophilia.

Once nonviral causes of encephalitis have been excluded, the major diagnostic challenge is to distinguish HSV from other viruses that cause encephalitis. This distinction is particularly important because in virtually every other instance the therapy is supportive, whereas specific and effective antiviral therapy is available for HSV, and its efficacy is enhanced when it is instituted early in the course of infection. HSV encephalitis should be considered when clinical features suggest involvement of the inferomedial frontotemporal regions of the brain, including prominent olfactory or gustatory hallucinations, anosmia, unusual or bizarre behavior or personality alterations, or memory disturbance. HSV encephalitis should always be suspected in patients with signs and symptoms consistent with acute encephalitis with focal findings on clinical examination, neuroimaging studies, or EEG. The diagnostic procedure of choice in these patients is CSF PCR analysis for HSV. A positive CSF PCR establishes the diagnosis, and a negative test dramatically reduces the likelihood of HSV encephalitis (see above).

The anatomic distribution of lesions may provide an additional clue to diagnosis. Patients with rapidly progressive encephalitis and prominent brainstem signs, symptoms, or neuroimaging abnormalities may be infected by flaviviruses (WNV, St. Louis encephalitis virus, Japanese encephalitis virus), HSV, enterovirus 71 (EV71), rabies, or *Listeria monocytogenes*. Significant involvement of deep gray matter structures, including the basal ganglia and thalamus, should also suggest possible flavivirus infection. These patients may present clinically with prominent movement disorders (tremor, myoclonus) or parkinsonian features. Patients with WNV infection can also present with a poliomyelitis-like acute flaccid paralysis, as can patients infected with EV71, Enterovirus D-68 (EV-D68) and less commonly, other enteroviruses. Acute flaccid paralysis is characterized by the acute onset of a lower motor neuron type of weakness with flaccid tone, reduced or absent reflexes, and relatively preserved sensation. The complete eradication of polio remains an ongoing challenge despite a continuing World Health Organization poliovirus elimination campaign. There have been small outbreaks of poliomyelitis associated with vaccine strains of virus that have reverted to virulence through mutation or recombination with circulating wild-type enteroviruses in Hispaniola, China, the Philippines, Indonesia, Nigeria, and Madagascar.

Epidemiologic factors may provide important clues to the diagnosis of viral encephalitis. Particular attention should be paid to the season

of the year; the geographic location and travel history; and possible exposure to animal bites or scratches, rodents, and ticks. Although transmission from the bite of an infected dog remains the most common cause of rabies worldwide, in the United States very few cases of dog rabies occur, and the most common risk factor is exposure to bats—although a clear history of a bite or scratch is often lacking. The classic clinical presentation of encephalitic (furious) rabies is fever, fluctuating consciousness, and autonomic hyperactivity. Phobic spasms of the larynx, pharynx, neck muscles, and diaphragm can be triggered by attempts to swallow water (*hydrophobia*) or by inspiration (*aerophobia*). Patients may also present with paralytic (dumb) rabies characterized by acute ascending paralysis. Rabies due to the bite of a bat has a different clinical presentation than classic rabies due to a dog or wolf bite. Patients present with focal neurologic deficits, myoclonus, seizures, and hallucinations; phobic spasms are not a typical feature. Patients with rabies have a CSF lymphocytic pleocytosis and may show areas of increased T2 signal abnormality in the brainstem, hippocampus, and hypothalamus. Diagnosis can be made by finding rabies virus antigen in brain tissue or in the neural innervation of hair follicles at the nape of the neck. PCR amplification of viral nucleic acid from CSF and saliva or tears may also enable diagnosis. Serology is frequently negative in both serum and CSF in the first week after onset of infection, which limits its acute diagnostic utility. No specific therapy is available, and cases are almost invariably fatal, with isolated survivors having devastating neurologic sequelae.

State public health authorities provide a valuable resource concerning isolation of particular agents in individual regions. Regular updates concerning the number, type, and distribution of cases of arboviral encephalitis can be found on the CDC and U.S. Geological Survey (USGS) websites (*http://www.cdc.gov* and *http://diseasemaps.usgs.gov*).

TREATMENT

Viral Encephalitis

Specific antiviral therapy should be initiated when appropriate. Vital functions, including respiration and blood pressure, should be monitored continuously and supported as required. In the initial stages of encephalitis, many patients will require care in an intensive care unit. Basic management and supportive therapy should include careful monitoring of ICP, fluid restriction, avoidance of hypotonic intravenous solutions, and suppression of fever. Seizures should be treated with standard anticonvulsant regimens, and prophylactic therapy should be considered in view of the high frequency of seizures in severe cases of encephalitis. As with all seriously ill, immobilized patients with altered levels of consciousness, encephalitis patients are at risk for aspiration pneumonia, stasis ulcers and decubiti, contractures, deep-venous thrombosis and its complications, and infections of indwelling lines and catheters.

Acyclovir is of benefit in the treatment of HSV and should be started empirically in patients with suspected viral encephalitis, especially if focal features are present, while awaiting viral diagnostic studies. Treatment should be discontinued in patients found not to have HSV encephalitis, with the possible exception of patients with severe encephalitis due to VZV or EBV. HSV, VZV, and EBV all encode an enzyme deoxypyrimidine (thymidine) kinase that phosphorylates acyclovir to produce acyclovir-5′-monophosphate. Host cell enzymes then phosphorylate this compound to form a triphosphate derivative. It is the triphosphate that acts as an antiviral agent by inhibiting viral DNA polymerase and by causing premature termination of nascent viral DNA chains. The specificity of action depends on the fact that uninfected cells do not phosphorylate significant amounts of acyclovir to acyclovir-5′-monophosphate. A second level of specificity is provided by the fact that the acyclovir triphosphate is a more potent inhibitor of viral DNA polymerase than of the analogous host cell enzymes.

Adults should receive a dose of 10 mg/kg of acyclovir intravenously every 8 h (30 mg/kg per day total dose) for 21 days. Neonatal HSV CNS infection is less responsive to acyclovir therapy than HSV encephalitis in adults; it is recommended that neonates with HSV encephalitis receive 20 mg/kg of acyclovir every 8 h (60 mg/kg per day total dose) for a minimum of 21 days.

Prior to intravenous administration, acyclovir should be diluted to a concentration ≤7 mg/mL. (A 70-kg person would receive a dose of 700 mg, which would be diluted in a volume of 100 mL.) Each dose should be infused slowly over 1 h, rather than by rapid or bolus infusion, to minimize the risk of renal dysfunction. Care should be taken to avoid extravasation or intramuscular or subcutaneous administration. The alkaline pH of acyclovir can cause local inflammation and phlebitis (9%). Dose adjustment is required in patients with impaired renal glomerular filtration. Penetration into CSF is excellent, with average drug levels ~50% of serum levels. Complications of therapy include elevations in blood urea nitrogen and creatinine levels (5%), thrombocytopenia (6%), gastrointestinal toxicity (nausea, vomiting, diarrhea) (7%), and neurotoxicity (lethargy or obtundation, disorientation, confusion, agitation, hallucinations, tremors, seizures) (1%). Acyclovir resistance may be mediated by changes in either the viral deoxypyrimidine kinase or DNA polymerase. To date, acyclovir-resistant isolates have not been a significant clinical problem in immunocompetent individuals. However, there have been reports of clinically virulent acyclovir-resistant HSV isolates from sites outside the CNS in immunocompromised individuals, including those with AIDS.

Oral antiviral drugs with efficacy against HSV, VZV, and EBV, including acyclovir, famciclovir, and valacyclovir, have not been evaluated in the treatment of encephalitis either as primary therapy or as supplemental therapy following completion of a course of parenteral acyclovir. The National Institute of Allergy and Infectious Diseases (NIAID)/National Institute of Neurological Disorders and Stroke–sponsored phase III trial of supplemental oral valacyclovir therapy (2 g tid for 3 months) following the initial 14- to 21-day course of therapy with parenteral acyclovir (*www.clinicaltrials.gov*, identifier NCT00031486) was terminated early due to low enrollment. Although analysis was compromised due to low numbers, no differences were seen in the 12-month endpoints including dementia rating scale, mini-mental state examination, and Glasgow Coma Score in patients receiving valacyclovir versus placebo. The role of adjunctive intravenous glucocorticoids in treatment of HSV and VZV infection remains unclear. Experimental models and case reports of HSV encephalitis suggest that glucocorticoids may be efficacious and a randomized clinical trial comparing acyclovir alone and acyclovir plus dexamethasone (10 mg every 6 h intravenously for 4 days) in patients with HSV encephalitis is underway in Europe (NCT03084783).

Ganciclovir and foscarnet, either alone or in combination, are often used in the treatment of CMV-related CNS infections, although their efficacy remains unproven. Cidofovir (see below) may provide an alternative in patients who fail to respond to ganciclovir and foscarnet, although data concerning its use in CMV CNS infections are extremely limited.

Ganciclovir is a synthetic nucleoside analogue of 2′-deoxyguanosine. The drug is preferentially phosphorylated by virus-induced cellular kinases. Ganciclovir triphosphate acts as a competitive inhibitor of the CMV DNA polymerase, and its incorporation into nascent viral DNA results in premature chain termination. Following intravenous administration, CSF concentrations of ganciclovir are 25–70% of coincident plasma levels. The usual dose for treatment of severe neurologic illnesses is 5 mg/kg every 12 h given intravenously at a constant rate over 1 h. Induction therapy is followed by maintenance therapy of 5 mg/kg every day for an indefinite period. Induction therapy should be continued until patients show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR testing (where available). Doses should be adjusted in patients with renal insufficiency. Treatment is often limited by the development of granulocytopenia and thrombocytopenia (20–25%), which may require reduction in or discontinuation of therapy. Gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal pain, occur in ~20% of patients. Some

patients treated with ganciclovir for CMV retinitis have developed retinal detachment, but the causal relationship to ganciclovir treatment is unclear. Valganciclovir is an orally bioavailable prodrug that can generate high serum levels of ganciclovir, although studies of its efficacy in treating CMV CNS infections are limited.

Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerases by binding to the pyrophosphate-binding site. Following intravenous infusion, CSF concentrations range from 15 to 100% of coincident plasma levels. The usual dose for serious CMV-related neurologic illness is 60 mg/kg every 8 h administered by constant infusion over 1 h. Induction therapy for 14–21 days is followed by maintenance therapy (60–120 mg/kg per day). Induction therapy may need to be extended in patients who fail to show a decline in CSF pleocytosis and a reduction in CSF CMV DNA copy number on quantitative PCR tests (where available). Approximately one-third of patients develop renal impairment during treatment, which is reversible following discontinuation of therapy in most, but not all, cases. This is often associated with elevations in serum creatinine and proteinuria and is less frequent in patients who are adequately hydrated. Many patients experience fatigue and nausea. Reductions in serum calcium, magnesium, and potassium occur in ~15% of patients and may be associated with tetany, cardiac rhythm disturbances, or seizures.

Cidofovir is a nucleotide analogue that is effective in treating CMV retinitis and equivalent to or better than ganciclovir in some experimental models of murine CMV encephalitis, although data concerning its efficacy in human CMV CNS disease are limited. The usual dose is 5 mg/kg intravenously once weekly for 2 weeks, then biweekly for two or more additional doses, depending on clinical response. Patients must be prehydrated with normal saline (e.g., 1 L over 1–2 h) prior to each dose and treated with probenecid (e.g., 1 g 3 h before cidofovir and 1 g 2 and 8 h after cidofovir). Nephrotoxicity is common; the dose should be reduced if renal function deteriorates.

Intravenous ribavirin (15–25 mg/kg per day in divided doses given every 8 h) has been reported to be of benefit in isolated cases of severe encephalitis due to California encephalitis (La Crosse) virus. Ribavirin might be of benefit for the rare patients, typically infants or young children, with severe adenovirus or rotavirus encephalitis and in patients with encephalitis due to LCMV or other arenaviruses. However, clinical trials are lacking. Hemolysis, with resulting anemia, has been the major side effect limiting therapy.

No specific antiviral therapy of proven efficacy is currently available for treatment of WNV encephalitis. Patients have been treated with interferon-α, ribavirin, an Israeli IVIg preparation that contains high-titer anti-WNV antibody (Omr-IgG-am) (*www.clinicaltrials.gov*, identifier NCT00069316 and 0068055), and humanized monoclonal antibodies directed against the viral envelope glycoprotein (*www.clinicaltrials.gov*, identifier NCT00927953 and 00515385). WNV chimeric vaccines, in which WNV envelope and premembrane proteins are inserted into the background of another flavivirus, DNA plasmid vaccines and inactivated virus vaccines have all been tested in phase I clinical trials and have been found to be both safe and immunogenic in healthy adults but have not yet been tested for disease prevention in humans (see *www.clinicaltrials.gov).* Both chimeric and killed inactivated WNV vaccines have been found to be safe and effective in preventing equine WNV infection, and effective vaccines are already in human use for prevention of other flavivirus infections including Japanese encephalitis, and yellow fever, suggesting that efficacy testing and commercial considerations rather than scientific issues will be the major impediment to creating a WNV vaccine.

SEQUELAE

There is considerable variation in the incidence and severity of sequelae in patients surviving viral encephalitis. In the case of EEE virus infection, nearly 80% of survivors have severe neurologic sequelae. At the other extreme are infections due to EBV, California encephalitis virus, and Venezuelan equine encephalitis virus, where severe sequelae are unusual. For example, ~5–15% of children infected with La Crosse virus have a residual seizure disorder, and 1% have persistent hemiparesis. Detailed information about sequelae in patients with HSV encephalitis treated with acyclovir is available from the NIAID-Collaborative Antiviral Study Group (CASG) trials. Of 32 acyclovir-treated patients, 26 survived (81%). Of the 26 survivors, 12 (46%) had no or only minor sequelae, 3 (12%) were moderately impaired (gainfully employed but not functioning at their previous level), and 11 (42%) were severely impaired (requiring continuous supportive care). The incidence and severity of sequelae were directly related to the age of the patient and the level of consciousness at the time of initiation of therapy. Patients with severe neurologic impairment (Glasgow Coma Score 6) at initiation of therapy either died or survived with severe sequelae. Young patients (<30 years) with good neurologic function at initiation of therapy did substantially better (100% survival, 62% with no or mild sequelae) compared with their older counterparts (>30 years; 64% survival, 57% no or mild sequelae). Many patients with WNV infection have sequelae, including cognitive impairment; weakness; and hyper- or hypokinetic movement disorders, including tremor, myoclonus, and parkinsonism. In a large longitudinal study of prognosis in 156 patients with WNV infection, the mean time to achieve recovery (defined as 95% of maximal predicted score on specific validated tests) was 112–148 days for fatigue, 121–175 days for physical function, 131–139 days for mood, and 302–455 days for mental function (the longer interval in each case representing patients with invasive CNS disease).

CHRONIC ENCEPHALITIS

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Clinical Features and Pathology Progressive multifocal leukoencephalopathy (PML) is characterized pathologically by multifocal areas of demyelination of varying size distributed throughout the brain but sparing the spinal cord and optic nerves. In addition to demyelination, there are characteristic cytologic alterations in both astrocytes and oligodendrocytes. Astrocytes are enlarged and contain hyperchromatic, deformed, and bizarre nuclei and frequent mitotic figures. Oligodendrocytes have enlarged, densely staining nuclei that contain viral inclusions formed by crystalline arrays of JC virus (JCV) particles. Patients often present with visual deficits (45%), typically a homonymous hemianopia; mental impairment (38%) (dementia, confusion, personality change); weakness, including hemi- or monoparesis; and ataxia. Seizures occur in ~20% of patients, predominantly in those with lesions abutting the cortex.

Almost all patients have an underlying immunosuppressive disorder or are receiving immunomodulatory therapy. In recent series, the most common associated conditions were AIDS (80%), hematologic malignancies (13%), transplant recipients (5%), and chronic inflammatory diseases (2%). It has been estimated that up to 5% of AIDS patients will develop PML. There have been >700 reported cases of PML occurring in patients being treated for multiple sclerosis and inflammatory bowel disease with natalizumab, a humanized monoclonal antibody that inhibits lymphocyte trafficking into CNS and bowel mucosa by binding to α_4 integrins. Overall risk in these patients has been estimated at ~4.2 PML cases per 1000 treated patients, but the risk depends on a variety of factors including anti-JCV antibody serostatus and the magnitude of the JCV antibody response, prior immunosuppressive therapy use, and duration of natalizumab therapy. Patients who lack detectable JCV antibody have a risk of developing PML of <0.1 case/1000 patients, whereas those who are JCV seropositive and have been exposed to prior immunosuppressive therapy and have received >24 months of natalizumab therapy have a risk of >1.3 case/100 treated patients. PML cases have also been reported in patients receiving other humanized monoclonal antibodies with immunomodulatory activity including efalizumab and rituximab, although the relative risks have not been clearly established. The basic clinical and diagnostic features appear to be similar in HIV-associated

PML and PML associated with immunomodulatory drugs with the exception of an increased likelihood of MRI enhancement of PML lesions in immunomodulatory cases. In natalizumab-associated PML, patients will also almost invariably develop clinical and radiographic worsening of lesions with discontinuation of therapy, attributed to development of immune reconstitution inflammatory syndrome (IRIS).

Diagnostic Studies The diagnosis of PML is frequently suggested by MRI. MRI reveals multifocal asymmetric, coalescing white matter lesions located periventricularly, in the centrum semiovale, in the parietal-occipital region, and in the cerebellum. These lesions have increased signal on T2 and FLAIR images and decreased signal on T1-weighted images. HIV-PML lesions are classically nonenhancing (90%), but patients with immunomodulatory drug-associated PML may have peripheral ring enhancement. PML lesions are not typically associated with edema or mass effect. CT scans, which are less sensitive than MRI for the diagnosis of PML, often show hypodense nonenhancing white matter lesions.

The CSF is typically normal, although mild elevation in protein and/or IgG may be found. Pleocytosis occurs in <25% of cases, is predominantly mononuclear, and rarely exceeds 25 cells/μL. PCR amplification of JCV DNA from CSF has become an important diagnostic tool. The presence of a positive CSF PCR for JCV DNA in association with typical MRI lesions in the appropriate clinical setting is diagnostic of PML, reflecting the assay's relatively high specificity (92–100%); however, sensitivity is variable, and a negative CSF PCR does not exclude the diagnosis. In HIV-negative patients and HIV-positive patients not receiving highly active antiviral therapy (HAART), sensitivity is likely 70–90%. In HAART-treated patients, sensitivity may be closer to 60%, reflecting the lower JCV CSF viral load in this relatively more immunocompetent group. Patients with natalizumab-associated PML have highly variable amounts of JCV DNA in CSF. Some patients may have negative CSF PCRs performed in commercial laboratories where assay detection thresholds are typically >100 JCV DNA copies/μL, but positive results in reference laboratories using supersensitive techniques (detection of 10 JCV copies/μL or less). CSF studies with quantitative JCV PCR indicate that patients with low JCV loads (<100 copies/μL) have a generally better prognosis than those with higher viral loads. Patients with negative CSF PCR studies may require brain biopsy for definitive diagnosis. In biopsy or necropsy specimens of brain, JCV antigen and nucleic acid can be detected by immunocytochemistry, in situ hybridization, or PCR amplification.

Serologic studies are of no utility in diagnosis due to high basal seroprevalence level, but may contribute to risk stratification in patients contemplating therapy with immunomodulatory drugs such as natalizumab.

TREATMENT

Progressive Multifocal Leukoencephalopathy

No effective therapy for PML is available. There are case reports of potential beneficial effects of the 5-HT_{2a} receptor antagonist mirtazapine, which may inhibit binding of JCV to its receptor on oligodendrocytes. Retrospective non-controlled studies have also suggested a possible beneficial effect of treatment with interferon-α. Neither of these agents has been tested in randomized controlled clinical trials. A prospective multicenter clinical trial to evaluate the efficacy of the antimalarial drug mefloquine failed to show benefit. Intravenous and/or intrathecal cytarabine were not shown to be of benefit in a randomized controlled trial in HIV-associated PML, although some experts suggest that cytarabine may have therapeutic efficacy in situations where breakdown of the blood-brain barrier allows sufficient CSF penetration. A randomized controlled trial of cidofovir in HIV-associated PML also failed to show significant benefit. Because PML almost invariably occurs in immunocompromised individuals, any therapeutic interventions designed to enhance or restore immunocompetence should be considered. Perhaps the most dramatic demonstration of this is disease stabilization and, in rare cases, improvement associated with the improvement in the immune status of HIV-positive patients with AIDS following institution of HAART. In HIV-positive PML patients treated with HAART, 1-year survival is ~50%, although up to 80% of survivors may have significant neurologic sequelae. HIV-positive PML patients with higher CD4 counts (>300/μL) and low or nondetectable HIV viral loads have a better prognosis than those with lower CD4 counts and higher viral loads. Although institution of HAART enhances survival in HIV-positive PML patients, the associated immune reconstitution in patients with an underlying opportunistic infection such as PML may also result in a severe CNS inflammatory syndrome (IRIS) associated with clinical worsening, CSF pleocytosis, and the appearance of new enhancing MRI lesions. Patients receiving natalizumab or other immunomodulatory antibodies who are suspected of having PML should have therapy immediately halted. Removal of drugs with long pharmacokinetic or biological half-lives, such as natalizumab, with plasma exchange or immunoadsorption is frequently utilized, although whether this improves outcomes has not been definitively established. Patients should be closely monitored for development of IRIS, which is generally treated with intravenous glucocorticoids, although controlled clinical trials of efficacy remain lacking.

SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

SSPE is a rare, chronic, progressive demyelinating disease of the CNS associated with a chronic nonpermissive infection of brain tissue with measles virus. The frequency has been estimated at 1 in 100,000–500,000 measles cases. An average of five cases per year is reported in the United States. The incidence has declined dramatically since the introduction of a measles vaccine. Most patients give a history of primary measles infection at an early age (2 years), which is followed after a latent interval of 6–8 years by the development of a progressive neurologic disorder. Some 85% of patients are between 5 and 15 years old at diagnosis. Initial manifestations include poor school performance and mood and personality changes. Typical signs of a CNS viral infection, including fever and headache, do not occur. As the disease progresses, patients develop progressive intellectual deterioration, focal and/or generalized seizures, myoclonus, ataxia, and visual disturbances. In the late stage of the illness, patients are unresponsive, quadriparetic, and spastic, with hyperactive tendon reflexes and extensor plantar responses.

Diagnostic Studies MRI is often normal early, although areas of increased T2 signal develop in the white matter of the brain and brainstem as disease progresses. The EEG may initially show only nonspecific slowing, but with disease progression, patients develop a characteristic periodic pattern with bursts of high-voltage, sharp, slow waves every 3–8 s, followed by periods of attenuated ("flat") background. The CSF is acellular with a normal or mildly elevated protein concentration and a markedly elevated gamma globulin level (>20% of total CSF protein). CSF antimeasles antibody levels are invariably elevated, and oligoclonal antimeasles antibodies are often present. Measles virus can be cultured from brain tissue using special cocultivation techniques. Viral antigen can be identified immunocytochemically, and viral genome can be detected by in situ hybridization or PCR amplification.

TREATMENT

Subacute Sclerosing Panencephalitis

No definitive therapy for SSPE is available. Treatment with isoprinosine (Inosiplex, 100 mg/kg per day), alone or in combination with intrathecal or intraventricular interferon-α, has been reported to prolong survival and produce clinical improvement in some patients but has never been subjected to a controlled clinical trial.

PROGRESSIVE RUBELLA PANENCEPHALITIS

This is an extremely rare disorder that primarily affects males with congenital rubella syndrome, although isolated cases have been reported

following childhood rubella. After a latent period of 8–19 years, patients develop progressive neurologic deterioration. The manifestations are similar to those seen in SSPE. CSF shows a mild lymphocytic pleocytosis, slightly elevated protein concentration, markedly increased gamma globulin, and rubella virus–specific oligoclonal bands. No therapy is available. Universal prevention of both congenital and childhood rubella through the use of the available live attenuated rubella vaccine would be expected to eliminate the disease.

FURTHER READING

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133 Acute Meningitis

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BACTERIAL MENINGITIS

DEFINITION

Bacterial meningitis is an acute purulent infection within the subarachnoid space (SAS). It is associated with a CNS inflammatory reaction that may result in decreased consciousness, seizures, raised intracranial pressure (ICP), and stroke. The meninges, SAS, and brain parenchyma are all frequently involved in the inflammatory reaction (*meningoencephalitis*).

EPIDEMIOLOGY

Bacterial meningitis is the most common form of suppurative CNS infection, with an annual incidence in the United States of >2.5 cases/100,000 population. The organisms most often responsible for community-acquired bacterial meningitis are *Streptococcus pneumoniae* (~50%), *Neisseria meningitidis* (~25%), group B streptococci (~15%), and *Listeria monocytogenes* (~10%). *Haemophilus influenzae* type b accounts for <10% of cases of bacterial meningitis in most series. *N. meningitidis* is the causative organism of recurring epidemics of meningitis every 8–12 years.

ETIOLOGY

S. pneumoniae **(Chap. 143)** is the most common cause of meningitis in adults >20 years of age, accounting for nearly half the reported cases (1.1 per 100,000 persons per year). There are a number of predisposing conditions that increase the risk of pneumococcal meningitis, the most important of which is pneumococcal pneumonia. Additional risk factors include coexisting acute or chronic pneumococcal sinusitis or otitis media, alcoholism, diabetes, splenectomy, hypogammaglobulinemia, complement deficiency, and head trauma with basilar skull fracture and CSF rhinorrhea. The mortality rate remains ~20% despite antibiotic therapy.

The incidence of meningitis due to *N. meningitidis* **(Chap. 150)** has decreased with the routine immunization of 11- to 18-year-olds with the quadrivalent (serogroups A, C, W-135, and Y) meningococcal glycoconjugate vaccine. The vaccine does not contain serogroup B, which is responsible for one-third of cases of meningococcal disease. The Advisory Committee on Immunization Practices (ACIP) recommends that adolescents and young adults aged 16–23 years may be vaccinated with the serogroup B meningococcal (MenB) vaccine. The presence of petechial or purpuric skin lesions can provide an important clue to the diagnosis of meningococcal infection. In some patients the disease is fulminant, progressing to death within hours of symptom onset. Infection may be initiated by nasopharyngeal colonization, which can result in either an asymptomatic carrier state or invasive meningococcal disease. The risk of invasive disease following nasopharyngeal colonization depends on both bacterial virulence factors and host immune defense mechanisms, including the host's capacity to produce antimeningococcal antibodies and to lyse meningococci by both classic and alternative complement pathways. Individuals with deficiencies of any of the complement components, including properdin, are highly susceptible to meningococcal infections.

Gram-negative bacilli cause meningitis in individuals with chronic and debilitating diseases such as diabetes, cirrhosis, or alcoholism and in those with chronic urinary tract infections. Gram-negative meningitis can also complicate neurosurgical procedures, particularly craniotomy, and head trauma associated with CSF rhinorrhea or otorrhea.

Otitis, mastoiditis, and sinusitis are predisposing and associated conditions for meningitis due to *Streptococci* sp., gram-negative anaerobes, *Staphylococcus aureus, Haemophilus* sp., and Enterobacteriaceae. Meningitis complicating endocarditis may be due to viridans streptococci, *S. aureus, Streptococcus bovis,* the HACEK group (*Haemophilus* sp., *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*), or enterococci.

Group B *Streptococcus*, or *Streptococcus agalactiae*, was previously responsible for meningitis predominantly in neonates, but it has been reported with increasing frequency in individuals aged >50 years, particularly those with underlying diseases.

L. monocytogenes **(Chap. 146)** is an increasingly important cause of meningitis in neonates (<1 month of age), pregnant women, individuals >60 years, and immunocompromised individuals of all ages. Infection is acquired by ingesting foods contaminated by *Listeria*. Foodborne human listerial infection has been reported from contaminated coleslaw, milk, soft cheeses, and several types of "ready-to-eat" foods, including delicatessen meat and uncooked hotdogs.

The frequency of *H. influenzae* type b (Hib) meningitis in children has declined dramatically since the introduction of the Hib conjugate vaccine, although rare cases of Hib meningitis in vaccinated children have been reported. More frequently, *H. influenzae* causes meningitis in unvaccinated children and older adults, and non-b *H. influenzae* is an emerging pathogen.

S. aureus and coagulase-negative staphylococci **(Chap. 142)** are important causes of meningitis that occurs following invasive neurosurgical procedures, particularly shunting procedures for hydrocephalus, or as a complication of the use of subcutaneous Ommaya reservoirs for administration of intrathecal chemotherapy.

PATHOPHYSIOLOGY

The most common bacteria that cause meningitis, *S. pneumoniae* and *N. meningitidis*, initially colonize the nasopharynx by attaching to nasopharyngeal epithelial cells. Bacteria are transported across epithelial cells in membrane-bound vacuoles to the intravascular space or invade the intravascular space by creating separations in the apical tight junctions of columnar epithelial cells. Once in the bloodstream, bacteria are able to avoid phagocytosis by neutrophils and classic complement-mediated bactericidal activity because of the presence of a polysaccharide capsule. Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells, and gain access to the cerebrospinal fluid (CSF). Some bacteria, such as *S. pneumoniae*, can adhere to cerebral capillary endothelial cells and subsequently migrate through or between these cells to reach the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defenses. Normal CSF contains few white blood

cells (WBCs) and relatively small amounts of complement proteins and immunoglobulins. The paucity of the latter two prevents effective opsonization of bacteria, an essential prerequisite for bacterial phagocytosis by neutrophils. Phagocytosis of bacteria is further impaired by the fluid nature of CSF, which is less conducive to phagocytosis than a solid tissue substrate.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Many of the neurologic manifestations and complications of bacterial meningitis result from the immune response to the invading pathogen rather than from direct bacteria-induced tissue injury. As a result, neurologic injury can progress even after the CSF has been sterilized by antibiotic therapy.

The lysis of bacteria with the subsequent release of cell-wall components into the SAS is the initial step in the induction of the inflammatory response and the formation of a purulent exudate in the SAS **(Fig. 133-1)**. Bacterial cell-wall components, such as the lipopolysaccharide (LPS) molecules of gram-negative bacteria and teichoic acid and peptidoglycans of *S. pneumoniae*, induce meningeal inflammation by stimulating the production of inflammatory cytokines and chemokines by microglia, astrocytes, monocytes, microvascular endothelial cells, and CSF leukocytes. In experimental models of meningitis, cytokines including tumor necrosis factor alpha (TNF-α) and interleukin 1β (IL-1β) are present in CSF within 1–2 h of intracisternal inoculation of LPS. This cytokine response is quickly followed by an increase in CSF protein concentration and leukocytosis. Chemokines (cytokines that induce chemotactic migration in leukocytes) and a variety of other proinflammatory cytokines are also produced and secreted by leukocytes and tissue cells that are stimulated by IL-1β and TNF-α. In addition, bacteremia and the inflammatory cytokines induce the production of excitatory amino acids, reactive oxygen and nitrogen species (free oxygen radicals, nitric oxide, and peroxynitrite), and other mediators that can induce death of brain cells, especially in the dentate gyrus of the hippocampus.

Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines. TNF-α and IL-1β act synergistically to increase the permeability of the blood-brain barrier, resulting in induction of vasogenic edema and the leakage of serum proteins into the SAS (Fig. 133-1). The subarachnoid exudate of proteinaceous material and leukocytes obstructs the flow of CSF through the ventricular system and diminishes the resorptive capacity of the arachnoid granulations in the dural sinuses, leading to obstructive and communicating hydrocephalus and concomitant interstitial edema.

Inflammatory cytokines upregulate the expression of selectins on cerebral capillary endothelial cells and leukocytes, promoting leukocyte adherence to vascular endothelial cells and subsequent migration into the CSF. The adherence of leukocytes to capillary endothelial cells increases the permeability of blood vessels, allowing for the leakage of plasma proteins into the CSF, which adds to the inflammatory exudate. Neutrophil degranulation results in the release of toxic metabolites that contribute to cytotoxic edema, cell injury, and death. Contrary to previous beliefs, CSF leukocytes probably do little to contribute to the clearance of CSF bacterial infection.

During the very early stages of meningitis, there is an increase in cerebral blood flow, soon followed by a decrease in cerebral blood flow and a loss of cerebrovascular autoregulation **(Chap. 301)**. Narrowing of the large arteries at the base of the brain due to encroachment by the purulent exudate in the SAS and infiltration of the arterial wall by inflammatory cells with intimal thickening (*vasculitis*) also occur and may result in ischemia and infarction, obstruction of branches of the middle cerebral artery by thrombosis, thrombosis of the major cerebral venous sinuses, and thrombophlebitis of the cerebral cortical veins. The combination of interstitial, vasogenic, and cytotoxic edema leads to raised ICP and coma. Cerebral herniation usually results from the effects of cerebral edema, either focal or generalized; hydrocephalus and dural sinus or cortical vein thrombosis may also play a role.

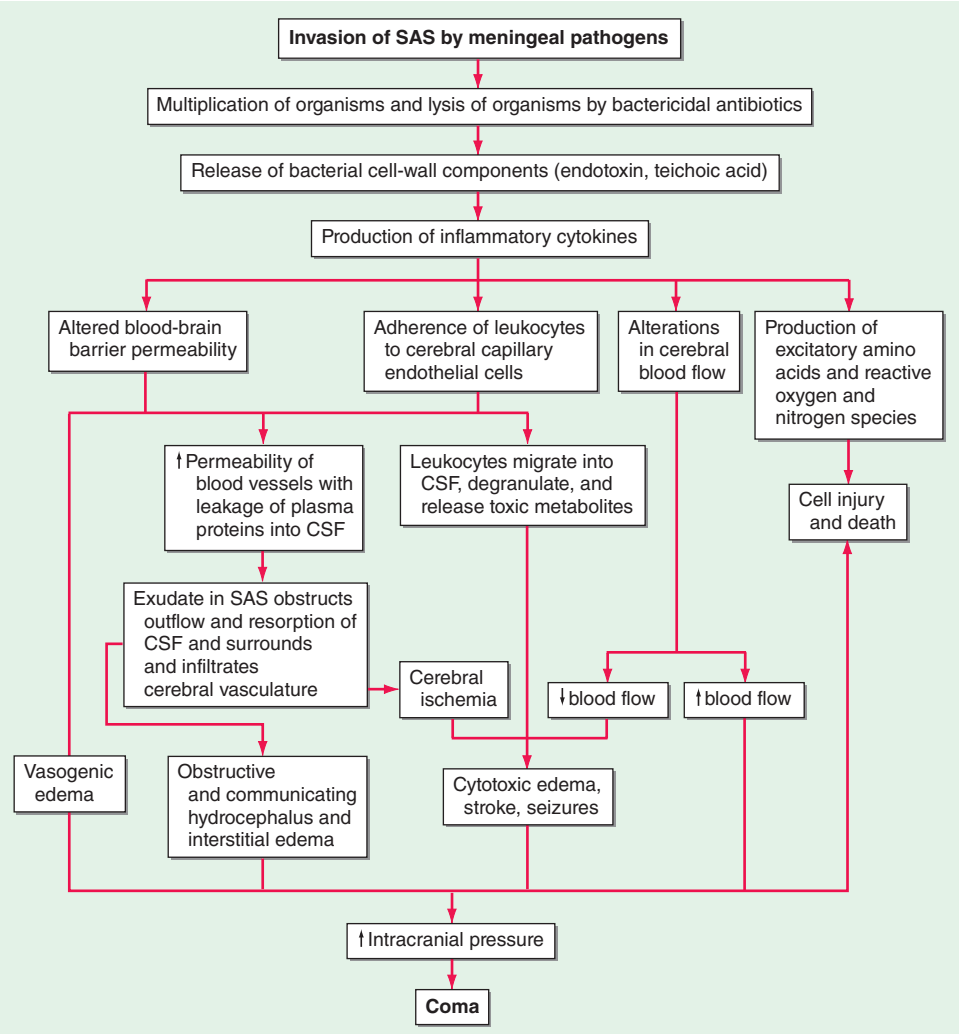

FIGURE 133-1 The pathophysiology of the neurologic complications of bacterial meningitis. CSF, cerebrospinal fluid; SAS, subarachnoid space.

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classic clinical triad of meningitis is fever, headache, and nuchal rigidity, but the classic triad may not be present. A decreased level of consciousness occurs in >75% of patients and can vary from lethargy to coma. Fever and either headache, stiff neck, or an altered level of consciousness will be present in nearly every patient with bacterial meningitis. Nausea, vomiting, and photophobia are also common complaints.

Nuchal rigidity ("stiff neck") is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs

of meningeal irritation. *Kernig's sign* is elicited with the patient in the supine position. The thigh is flexed on the abdomen, with the knee flexed; attempts to passively extend the knee elicit pain when meningeal irritation is present. *Brudzinski's sign* is elicited with the patient in the supine position and is positive when passive flexion of the neck results in spontaneous flexion of the hips and knees. Although commonly tested on physical examinations, the sensitivity and specificity of Kernig's and Brudzinski's signs are uncertain. Both may be absent or reduced in very young or elderly patients, immunocompromised individuals, or patients with a severely depressed mental status. The high prevalence of cervical spine disease in older individuals may result in false-positive tests for nuchal rigidity.

Seizures occur as part of the initial presentation of bacterial meningitis or during the course of the illness in 20–40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema. Generalized seizure activity and status epilepticus may be due to hyponatremia, cerebral anoxia, or, less commonly, the toxic effects of antimicrobial agents.

Raised ICP is an expected complication of bacterial meningitis and the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mmH_2O, and 20% have opening pressures >400 mmH_2O. Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations). The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

Specific clinical features may provide clues to the diagnosis of individual organisms and are discussed in more detail in specific chapters devoted to individual pathogens. The most important of these clues is the rash of meningococcemia, which begins as a diffuse erythematous maculopapular rash resembling a viral exanthem; however, the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

DIAGNOSIS

When bacterial meningitis is suspected, blood cultures should be immediately obtained and empirical antimicrobial and adjunctive dexamethasone therapy initiated without delay **(Table 133-1)**. The diagnosis of bacterial meningitis is made by examination of the CSF **(Table 133-2)**. The need to obtain neuroimaging studies (CT or MRI) prior to lumbar puncture (LP) requires clinical judgment. In an immunocompetent patient with no known history of recent head trauma, a normal level of consciousness, and no evidence of papilledema or focal neurologic deficits, it is considered safe to perform LP without prior neuroimaging studies. If LP is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained. Antibiotic therapy initiated a few hours prior to LP will not significantly alter the CSF WBC count or glucose concentration, nor is it likely to prevent visualization of organisms by Gram's stain or detection of bacterial nucleic acid by polymerase chain reaction (PCR) assay.

The classic CSF abnormalities in bacterial meningitis (Table 133-2) are (1) polymorphonuclear (PMN) leukocytosis (>100 cells/μL in 90%), (2) decreased glucose concentration (<2.2 mmol/L [<40 mg/dL] and/or CSF/serum glucose ratio of <0.4 in ~60%), (3) increased protein concentration (>0.45 g/L [>45 mg/dL] in 90%), and (4) increased opening pressure (>180 mmH_2O in 90%). CSF bacterial cultures are positive in >80% of patients, and CSF Gram's stain demonstrates organisms in >60%.

CSF glucose concentrations <2.2 mmol/L (<40 mg/dL) are abnormal, and a CSF glucose concentration of zero can be seen in bacterial meningitis. Use of the CSF/serum glucose ratio corrects for hyperglycemia that may mask a relative decrease in the CSF glucose concentration. The CSF glucose concentration is low when the CSF/serum glucose ratio is <0.6. A CSF/serum glucose ratio <0.4 is highly suggestive of bacterial meningitis but may also be seen in other conditions, including fungal, tuberculous, and carcinomatous meningitis. It takes from 30 min to several hours for the concentration of CSF glucose to reach equilibrium with blood glucose levels; therefore, administration of 50 mL of 50% glucose (D50) prior to LP, as commonly occurs in emergency room settings, is unlikely to alter CSF glucose concentration significantly unless more than a few hours have elapsed between glucose administration and LP.

TABLE 133-1 Antibiotics Used in Empirical Therapy of Bacterial Meningitis and Focal Central Nervous System Infections[a]

INDICATION	ANTIBIOTIC
Preterm infants to infants <1 month	Ampicillin + cefotaxime
Infants 1–3 months	Ampicillin + cefotaxime or ceftriaxone
Immunocompetent children >3 months and adults <55	Cefotaxime, ceftriaxone, or cefepime + vancomycin
Adults >55 and adults of any age with alcoholism or other debilitating illnesses	Ampicillin + cefotaxime, ceftriaxone or cefepime + vancomycin
Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity	Ampicillin + ceftazidime or meropenem + vancomycin

	TOTAL DAILY DOSE AND DOSING INTERVAL	
ANTIMICROBIAL AGENT	CHILD (>1 MONTH)	ADULT
Ampicillin	300 (mg/kg)/d, q6h	12 g/d, q4h
Cefepime	150 (mg/kg)/d, q8h	6 g/d, q8h
Cefotaxime	225–300 (mg/kg)/d, q6h	12 g/d, q4h
Ceftriaxone	100 (mg/kg)/d, q12h	4 g/d, q12h
Ceftazidime	150 (mg/kg)/d, q8h	6 g/d, q8h
Gentamicin	7.5 (mg/kg)/d, q8h[b]	7.5 (mg/kg)/d, q8h
Meropenem	120 (mg/kg)/d, q8h	6 g/d, q8h
Metronidazole	30 (mg/kg)/d, q6h	1500–2000 mg/d, q6h
Nafcillin	100–200 (mg/kg)/d, q6h	9–12 g/d, q4h
Penicillin G	400,000 (U/kg)/d, q4h	20–24 million U/d, q4h
Vancomycin	45–60 (mg/kg)/d, q6h	45–60 (mg/kg)d, q6–12h[b]

[a]All antibiotics are administered intravenously; doses indicated assume normal renal and hepatic function. [b]Doses should be adjusted based on serum peak and trough levels: gentamicin therapeutic level: peak: 5–8 μg/mL; trough: <2 μg/mL; vancomycin therapeutic level: peak: 25–40 μg/mL; trough: 5–15 μg/mL.

TABLE 133-2 Cerebrospinal Fluid (CSF) Abnormalities in Bacterial Meningitis

Opening pressure	>180 mmH_2O
White blood cells	10/μL to 10,000/μL; neutrophils predominate
Red blood cells	Absent in nontraumatic tap
Glucose	<2.2 mmol/L (<40 mg/dL)
CSF/serum glucose	<0.4
Protein	>0.45 g/L (>45 mg/dL)
Gram's stain	Positive in >60%
Culture	Positive in >80%
PCR	Detects bacterial DNA
Latex agglutination	May be positive in patients with meningitis due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b, *Escherichia coli*, group B streptococci
Limulus lysate	Positive in cases of gram-negative meningitis

Abbreviation: PCR, polymerase chain reaction.

There are a number of "CSF pathogen panels" available that use specific bacterial primers to detect the nucleic acid of *S. pneumoniae, N. meningitidis, Escherichia coli, L. monocytogenes, H. influenzae*, and *S. agalactiae* (Group B streptococci). The latex agglutination (LA) test for the detection of bacterial antigens of *S. pneumoniae, N. meningitidis, H. influenzae* type b, group B *Streptococcus*, and *E. coli* K1 strains in the CSF has been useful for making a diagnosis of bacterial meningitis but is being replaced by the CSF bacterial PCR assay. The CSF LA test has a *specificity* of 95–100% for *S. pneumoniae* and *N. meningitidis*, so a positive test is virtually diagnostic of bacterial meningitis caused by these organisms. However, the *sensitivity* of the CSF LA test is only 70–100% for detection of *S. pneumoniae* and 33–70% for detection of *N. meningitidis* antigens, so a negative test does not exclude infection by these organisms. The Limulus amebocyte lysate assay is a rapid diagnostic test for the detection of gram-negative endotoxin in CSF and thus for making a diagnosis of gram-negative bacterial meningitis. The test has a specificity of 85–100% and a sensitivity approaching 100%. Thus, a positive Limulus amebocyte lysate assay occurs in virtually all patients with gram-negative bacterial meningitis, but false positives may occur.

Almost all patients with bacterial meningitis will have neuroimaging studies performed during the course of their illness. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia. In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Petechial skin lesions, if present, should be biopsied. The rash of meningococcemia results from the dermal seeding of organisms with vascular endothelial damage, and biopsy may reveal the organism on Gram's stain.

DIFFERENTIAL DIAGNOSIS

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis (encephalitis). HSV encephalitis typically presents with headache, fever, altered consciousness, focal neurologic deficits (e.g., dysphasia, hemiparesis), and focal or generalized seizures. The findings on CSF studies, neuroimaging, and electroencephalogram (EEG) distinguish HSV encephalitis from bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to the PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis. The CSF HSV PCR has a 96% sensitivity and a 99% specificity when CSF is examined 72 h following symptom onset, and in the first week of antiviral therapy. MRI abnormalities (other than meningeal enhancement) are not seen in uncomplicated bacterial meningitis. By contrast, in HSV encephalitis, on T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI images, high signal intensity lesions are seen in the orbitofrontal, anterior, and medial temporal lobes in the majority of patients within 48 h of symptom onset. Some patients with HSV encephalitis have a distinctive periodic pattern on EEG.

Rickettsial disease can resemble bacterial meningitis **(Chap. 182)**. Rocky Mountain spotted fever (RMSF) is transmitted by a tick bite and caused by the bacteria *Rickettsia rickettsii*. The disease may present acutely with high fever, prostration, myalgia, headache, nausea, and vomiting. Most patients develop a characteristic rash within 96 h of the onset of symptoms. The rash is initially a diffuse erythematous maculopapular rash that may be difficult to distinguish from that of meningococcemia. It progresses to a petechial rash, then to a purpuric rash, and if untreated, to skin necrosis or gangrene. The color of the lesions changes from bright red to very dark red, then yellowish-green to black. The rash typically begins in the wrist and ankles and then spreads distally and proximally within a matter of a few hours, involving the palms and soles. Diagnosis is made by immunofluorescent staining of skin biopsy specimens. Ehrlichioses are also transmitted by a tick bite. These are small gram-negative coccobacilli of which two species cause human disease. *Anaplasma phagocytophilum* causes human granulocytic ehrlichiosis (anaplasmosis), and *Ehrlichia chaffeensis* causes human monocytic ehrlichiosis. The clinical and laboratory manifestations of the infections are similar. Patients present with fever, headache, confusion, nausea, and vomiting. Twenty percent of patients have a maculopapular or petechial rash. There is laboratory evidence of leukopenia, thrombocytopenia, and anemia, and mild to moderate elevations in alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase. Patients with RMSF and those with ehrlichial infections may have an altered level of consciousness ranging from mild lethargy to coma, confusion, focal neurologic signs, cranial nerve palsies, hyperreflexia, and seizures.

Focal suppurative CNS infections, including subdural and epidural empyema and brain abscess, should also be considered, especially when focal neurologic findings are present. MRI should be performed promptly in all patients with suspected meningitis who have focal features, both to detect the intracranial infection and to search for associated areas of infection in the sinuses or mastoid bones.

A number of noninfectious CNS disorders can mimic bacterial meningitis. Subarachnoid hemorrhage (SAH; **Chap. 301**) is generally the major consideration. Other possibilities include medication-induced hypersensitivity meningitis; chemical meningitis due to rupture of tumor contents into the CSF (e.g., from a cystic glioma or craniopharyngioma epidermoid or dermoid cyst); carcinomatous or lymphomatous meningitis; meningitis associated with inflammatory disorders such as sarcoid, systemic lupus erythematosus (SLE), and Behçet's syndrome; pituitary apoplexy; and uveomeningitic syndromes (Vogt-Koyanagi-Harada syndrome).

On occasion, subacutely evolving meningitis **(Chap. 134)** may be considered in the differential diagnosis of acute meningitis. The principal causes include *Mycobacterium tuberculosis* **(Chap. 173)**, *Cryptococcus neoformans* **(Chap. 210)**, *Histoplasma capsulatum* **(Chap. 207)**, *Coccidioides immitis* **(Chap. 208)**, and *Treponema pallidum* **(Chap. 177)**.

TREATMENT

Acute Bacterial Meningitis

EMPIRICAL ANTIMICROBIAL THERAPY

(Table 133-1) Bacterial meningitis is a medical emergency. The goal is to begin antibiotic therapy within 60 min of a patient's arrival in the emergency room. Empirical antimicrobial therapy is initiated in patients with suspected bacterial meningitis before the results of CSF Gram's stain and culture are known. *S. pneumoniae* **(Chap. 141)** and *N. meningitidis* **(Chap. 150)** are the most common etiologic organisms of community-acquired bacterial meningitis. Due to the emergence of penicillin- and cephalosporin-resistant *S. pneumoniae*, empirical therapy of community-acquired suspected bacterial meningitis in children and adults should include a combination of dexamethasone, a third- or fourth-generation cephalosporin (e.g., ceftriaxone, cefotaxime, or cefepime), and vancomycin, plus acyclovir, as HSV encephalitis is the leading disease in the differential diagnosis, and doxycycline during tick season to treat tick-borne bacterial infections. Ceftriaxone or cefotaxime provides good coverage for susceptible *S. pneumoniae*, group B streptococci, and *H. influenzae* and adequate coverage for *N. meningitidis*. Cefepime is a broad-spectrum fourth-generation cephalosporin with in vitro activity similar to that of cefotaxime or ceftriaxone against *S. pneumoniae* and *N. meningitidis* and greater activity against *Enterobacter* species and *Pseudomonas aeruginosa*. In clinical trials, cefepime has been demonstrated to be equivalent to cefotaxime in the treatment of penicillin-sensitive pneumococcal and meningococcal meningitis, and it has been used successfully in some patients with meningitis due to *Enterobacter* species and *P. aeruginosa*. Ampicillin should be added to the empirical regimen for coverage of *L. monocytogenes* in individuals <3 months of age, those >55, or those with suspected impaired cell-mediated immunity because of chronic illness, organ transplantation, pregnancy, malignancy, or immunosuppressive therapy. Metronidazole is added to the empirical regimen to cover gram-negative anaerobes in patients with otitis, sinusitis, or mastoiditis. In hospital-acquired

meningitis, and particularly meningitis following neurosurgical procedures, staphylococci and gram-negative organisms including *P. aeruginosa* are the most common etiologic organisms. In these patients, empirical therapy should include a combination of vancomycin and ceftazidime or meropenem. Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients and in neutropenic patients, because ceftriaxone and cefotaxime do not provide adequate activity against CNS infection with *P. aeruginosa*. Meropenem is a carbapenem antibiotic that is highly active in vitro against *L. monocytogenes*, has been demonstrated to be effective in cases of meningitis caused by *P. aeruginosa*, and shows good activity against penicillin-resistant pneumococci. In experimental pneumococcal meningitis, meropenem was comparable to ceftriaxone and inferior to vancomycin in sterilizing CSF cultures. The number of patients with bacterial meningitis enrolled in clinical trials of meropenem has not been sufficient to definitively assess the efficacy of this antibiotic.

SPECIFIC ANTIMICROBIAL THERAPY

Meningococcal Meningitis (Table 133-3) Although ceftriaxone and cefotaxime provide adequate empirical coverage for *N. meningitidis*, penicillin G remains the antibiotic of choice for meningococcal meningitis caused by susceptible strains. Isolates of *N. meningitidis* with moderate resistance to penicillin have been identified and are increasing in incidence worldwide. CSF isolates of *N. meningitidis* should be tested for penicillin and ampicillin susceptibility, and if resistance is found, cefotaxime or ceftriaxone should be substituted for penicillin. A 7-day course of intravenous antibiotic therapy is adequate for uncomplicated meningococcal meningitis. The index case and all close contacts should receive chemoprophylaxis with a 2-day regimen of rifampin (600 mg every 12 h for 2 days in adults and 10 mg/kg every 12 h for 2 days in children >1 year). Rifampin is not recommended in pregnant women. Alternatively, adults can be treated with one dose of azithromycin (500 mg) or one intramuscular dose of ceftriaxone (250 mg). Close contacts are defined as those individuals who have had contact with oropharyngeal secretions, either through kissing or by sharing toys, beverages, or cigarettes.

Pneumococcal Meningitis Antimicrobial therapy of pneumococcal meningitis is initiated with a cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin. All CSF isolates of *S. pneumoniae* should be tested for sensitivity to penicillin and the cephalosporins. Once the results of antimicrobial susceptibility tests are known, therapy can be modified accordingly (Table 133-3). For *S. pneumoniae* meningitis, an isolate of *S. pneumoniae* is considered to be susceptible to penicillin with a minimal inhibitory concentration (MIC) <0.06 μg/mL and to be resistant when the MIC is >0.12 μg/mL. Isolates of *S. pneumoniae* that have cephalosporin MICs ≤0.5 μg/mL are considered sensitive to the cephalosporins (cefotaxime, ceftriaxone, cefepime). Those with MICs of 1 μg/mL are considered to have intermediate resistance, and those with MICs ≥2 μg/mL are considered resistant. For meningitis due to pneumococci, with cefotaxime or ceftriaxone MICs ≤0.5 μg/mL, treatment with cefotaxime or ceftriaxone is usually adequate. For MIC >1 μg/mL, vancomycin is the antibiotic of choice. Rifampin can be added to vancomycin for its synergistic effect but is inadequate as monotherapy because resistance develops rapidly when it is used alone.

A 2-week course of intravenous antimicrobial therapy is recommended for pneumococcal meningitis.

Patients with *S. pneumoniae* meningitis should have a repeat LP performed 24–36 h after the initiation of antimicrobial therapy to document sterilization of the CSF. Failure to sterilize the CSF after 24–36 h of antibiotic therapy should be considered presumptive evidence of antibiotic resistance. Patients with penicillin- and cephalosporin-resistant strains of *S. pneumoniae* who do not respond to intravenous vancomycin alone may benefit from the addition of intraventricular vancomycin. The intraventricular route of administration is preferred over the intrathecal route because adequate concentrations of vancomycin in the cerebral ventricles are not always achieved with intrathecal administration.

***Listeria* Meningitis** Meningitis due to *L. monocytogenes* is treated with ampicillin for at least 3 weeks (Table 133-3). Gentamicin is added in critically ill patients (2 mg/kg loading dose, then 7.5 mg/kg per day given every 8 h and adjusted for serum levels and renal function). The combination of trimethoprim (10–20 mg/kg per day) and sulfamethoxazole (50–100 mg/kg per day) given every 6 h may provide an alternative in penicillin-allergic patients.

Staphylococcal Meningitis Meningitis due to susceptible strains of *S. aureus* or coagulase-negative staphylococci is treated with nafcillin (Table 133-3). Vancomycin is the drug of choice for methicillin-resistant staphylococci and for patients allergic to penicillin. In these patients, the CSF should be monitored during therapy. If the CSF is not sterilized after 48 h of intravenous vancomycin therapy, then either intraventricular or intrathecal vancomycin, 20 mg once daily, can be added.

Gram-Negative Bacillary Meningitis The third-generation cephalosporins—cefotaxime, ceftriaxone, and ceftazidime—are equally efficacious for the treatment of gram-negative bacillary meningitis, with the exception of meningitis due to *P. aeruginosa*, which should be treated with ceftazidime or meropenem (Table 133-3). A 3-week course of intravenous antibiotic therapy is recommended for meningitis due to gram-negative bacilli.

TABLE 133-3 Antimicrobial Therapy of Central Nervous System Bacterial Infections Based on Pathogen[a]

ORGANISM	ANTIBIOTIC
Neisseria meningitides	
Penicillin-sensitive	Penicillin G or ampicillin
Penicillin-resistant	Ceftriaxone or cefotaxime
Streptococcus pneumoniae	
Penicillin-sensitive	Penicillin G
Penicillin-intermediate	Ceftriaxone or cefotaxime or cefepime
Penicillin-resistant	Ceftriaxone (or cefotaxime or cefepime) + vancomycin
Gram-negative bacilli (except *Pseudomonas* spp.)	Ceftriaxone or cefotaxime
Pseudomonas aeruginosa	Ceftazidime or meropenem
Staphylococci spp.	
Methicillin-sensitive	Nafcillin
Methicillin-resistant	Vancomycin
Listeria monocytogenes	Ampicillin + gentamicin
Haemophilus influenzae	Ceftriaxone or cefotaxime or cefepime
Streptococcus agalactiae	Penicillin G or ampicillin
Bacteroides fragilis	Metronidazole
Fusobacterium spp.	Metronidazole

[a]Doses are as indicated in Table 133-1.

ADJUNCTIVE THERAPY

The release of bacterial cell-wall components by bactericidal antibiotics leads to the production of the inflammatory cytokines IL-1β and TNF-α in the SAS. Dexamethasone exerts its beneficial effect by inhibiting the synthesis of IL-1β and TNF-α at the level of mRNA, decreasing CSF outflow resistance, and stabilizing the blood-brain barrier. The rationale for giving dexamethasone 20 min before antibiotic therapy is that dexamethasone inhibits the production of TNF-α by macrophages and microglia only if it is administered before these cells are activated by endotoxin. Dexamethasone does not alter TNF-α production once it has been induced. The results of clinical trials of dexamethasone therapy in meningitis due to *H. influenzae*, *S. pneumoniae*, and *N. meningitidis* have demonstrated its efficacy in decreasing meningeal inflammation and neurologic sequelae such as the incidence of sensorineural hearing loss.

A prospective European trial of adjunctive therapy for acute bacterial meningitis in 301 adults found that dexamethasone reduced the number of unfavorable outcomes (15 vs 25%, $p = .03$) including death (7 vs 15%, $p = .04$). The benefits were most striking in patients with pneumococcal meningitis. Dexamethasone (10 mg intravenously) was

administered 15–20 min before the first dose of an antimicrobial agent, and the same dose was repeated every 6 h for 4 days. These results were confirmed in a second trial of dexamethasone in adults with pneumococcal meningitis. Therapy with dexamethasone should ideally be started 20 min before, or not later than concurrent with, the first dose of antibiotics. It is unlikely to be of significant benefit if started >6 h after antimicrobial therapy has been initiated. Dexamethasone may decrease the penetration of vancomycin into CSF, and it delays the sterilization of CSF in experimental models of *S. pneumoniae* meningitis. As a result, to assure reliable penetration of vancomycin into the CSF, children and adults are treated with vancomycin in a dose of 45–60 mg/kg per day. Alternatively, vancomycin can be administered by the intraventricular route. In clinical trials, dexamethasone has also been shown to reduce rates of death and hearing loss with no adverse effects in patients with meningococcal meningitis.

One of the concerns for using dexamethasone in adults with bacterial meningitis is that in experimental models of meningitis, dexamethasone therapy increased hippocampal cell injury and reduced learning capacity. This has not been the case in clinical series. The efficacy of dexamethasone therapy in preventing neurologic sequelae is different between high- and low-income countries. Three large randomized trials in low-income countries (sub-Saharan Africa, Southeast Asia) failed to show benefit in subgroups of patients. The lack of efficacy of dexamethasone in these trials has been attributed to late presentation to the hospital with more advanced disease, antibiotic pretreatment, malnutrition, infection with HIV, and treatment of patients with probable, but not microbiologically proven, bacterial meningitis. The results of these clinical trials suggest that patients in sub-Saharan Africa and those in low-income countries with negative CSF Gram's stain and culture should not be treated with dexamethasone.

INCREASED INTRACRANIAL PRESSURE

Emergency treatment of increased ICP includes elevation of the patient's head to 30–45°, intubation and hyperventilation ($Paco_2$ 25–30 mmHg), and mannitol. Patients with increased ICP should be managed in an intensive care unit; accurate ICP measurements are best obtained with an ICP monitoring device.

Treatment of increased ICP is discussed in detail in Chap. 301.

PROGNOSIS

Mortality rate is 3–7% for meningitis caused by *H. influenzae, N. meningitidis*, or group B streptococci; 15% for that due to *L. monocytogenes*; and 20% for *S. pneumoniae*. In general, the risk of death from bacterial meningitis increases with (1) decreased level of consciousness on admission, (2) onset of seizures within 24 h of admission, (3) signs of increased ICP, (4) young age (infancy) and age >50, (5) the presence of comorbid conditions including shock and/or the need for mechanical ventilation, and (6) delay in the initiation of treatment. Decreased CSF glucose concentration (<2.2 mmol/L [<40 mg/dL]) and markedly increased CSF protein concentration (>3 g/L [> 300 mg/dL]) have been predictive of increased mortality and poorer outcomes in some series. Moderate or severe sequelae occur in ~25% of survivors, although the exact incidence varies with the infecting organism. Common sequelae include decreased intellectual function, memory impairment, seizures, hearing loss and dizziness, and gait disturbances.

VIRAL MENINGITIS

CLINICAL MANIFESTATIONS

Immunocompetent adult patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with an inflammatory CSF profile (see below). Headache is almost invariably present and often characterized as frontal or retroorbital and frequently associated with photophobia and pain on moving the eyes. Nuchal rigidity is present in most cases but may be mild and present only near the limit of neck anteflexion. Constitutional signs can include malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients often have mild lethargy or drowsiness; however, profound alterations in consciousness, such as stupor, coma, or marked confusion, do not occur in viral meningitis and suggest the presence of encephalitis or other alternative diagnoses. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.

TABLE 133-4 Viruses Causing Acute Meningitis in North America

COMMON	LESS COMMON
Enteroviruses (coxsackieviruses, echoviruses, and human enteroviruses 68–71)	Herpes simplex virus 1
Varicella-zoster virus	Human herpesvirus 6
Herpes simplex virus 2	Cytomegalovirus
Epstein-Barr virus	Lymphocytic choriomeningitis virus
Arthropod-borne viruses	Mumps
HIV	Zika

ETIOLOGY

Using a variety of diagnostic techniques, including CSF PCR, culture, and serology, a specific viral cause can be found in 60–90% of cases of viral meningitis. The most important agents are enteroviruses (including echoviruses and coxsackieviruses in addition to numbered enteroviruses), varicella-zoster virus (VZV), HSV (HSV-2 > HSV-1), HIV, and arboviruses **(Table 133-4)**. CSF cultures are positive in 30–70% of patients, with the frequency of isolation depending on the specific viral agent. Approximately two-thirds of culture-negative cases of "aseptic" meningitis have a specific viral etiology identified by CSF PCR testing (see below).

EPIDEMIOLOGY

Viral meningitis is not a nationally reportable disease; however, it has been estimated that the incidence is ~60,000–75,000 cases per year. In temperate climates, there is a substantial increase in cases during the nonwinter months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections in the summer and fall, with a peak monthly incidence of about 1 reported case per 100,000 population.

LABORATORY DIAGNOSIS

CSF Examination The most important laboratory test in the diagnosis of viral meningitis is examination of the CSF. The typical profile is a pleocytosis, a normal or slightly elevated protein concentration (0.2–0.8 g/L [20–80 mg/dL]), a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are *not* seen on Gram's stain of CSF. The total CSF cell count in viral meningitis is typically 25–500/μL, although cell counts of several thousand/μL are occasionally seen, especially with infections due to lymphocytic choriomeningitis virus (LCMV) and mumps virus. Lymphocytes are typically the predominant cell. Rarely, PMNs may predominate in the first 48 h of illness, especially with infections due to echovirus 9, West Nile virus (WNV), eastern equine encephalitis (EEE) virus, or mumps. A PMN pleocytosis occurs in 45% of patients with WNV meningitis and can persist for a week or longer before shifting to a lymphocytic pleocytosis. PMN pleocytosis with low glucose may also be a feature of cytomegalovirus (CMV) infections in immunocompromised hosts. Despite these exceptions, the presence of a CSF PMN pleocytosis in a patient with suspected viral meningitis in whom a specific diagnosis has not been established should prompt consideration of alternative diagnoses, including bacterial meningitis or parameningeal infections. The CSF glucose concentration is typically normal in viral infections, although it may be decreased in 10–30% of cases due to mumps or LCMV. Rare instances of decreased CSF glucose concentration occur in cases of meningitis due to echoviruses and other enteroviruses, HSV-2, and VZV. As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal or tuberculous meningitis, *Listeria* meningoencephalitis, or noninfectious disorders (e.g., sarcoid, neoplastic meningitis).

A number of tests measuring levels of various CSF proteins, enzymes, and mediators—including C-reactive protein, lactic acid, lactate dehydrogenase, neopterin, quinolinate, IL-1β, IL-6, soluble IL-2 receptor, β_2-microglobulin, and TNF—have been proposed as potential discriminators between viral and bacterial meningitis or as markers of specific types of viral infection (e.g., infection with HIV), but they remain of uncertain sensitivity and specificity and are not widely used for diagnostic purposes.

Polymerase Chain Reaction Amplification of Viral Nucleic Acid Amplification of viral-specific DNA or RNA from CSF using PCR amplification has become the single most important method for diagnosing CNS viral infections. In both enteroviral and HSV infections of the CNS, CSF PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures. HSV CSF PCR is also an important diagnostic test in patients with recurrent episodes of "aseptic" meningitis, many of whom have amplifiable HSV DNA in CSF despite negative viral cultures. CSF PCR is also used routinely to diagnose CNS viral infections caused by CMV, Epstein-Barr virus (EBV), VZV, and human herpesvirus 6 (HHV-6). CSF PCR tests are available for WNV but are not as sensitive as detection of WNV-specific CSF IgM. PCR is also useful in the diagnosis of CNS infection caused by *Mycoplasma pneumoniae,* which can mimic viral meningitis and encephalitis. PCR of throat washings may assist in diagnosis of enteroviral and mycoplasmal CNS infections. PCR of stool specimens may also assist in diagnosis of enteroviral infections (see below).

Viral Culture The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor. In addition to CSF, specific viruses may also be isolated from throat swabs, stool, blood, and urine. Enteroviruses and adenoviruses may be found in feces; arboviruses, some enteroviruses, and LCMV in blood; mumps and CMV in urine; and enteroviruses, mumps, and adenoviruses in throat washings. During enteroviral infections, viral shedding in stool may persist for several weeks. The presence of enterovirus in stool is not diagnostic and may result from residual shedding from a previous enteroviral infection; it also occurs in some asymptomatic individuals during enteroviral epidemics.

Serologic Studies The basic approach to the serodiagnosis of viral meningitis is identical to that discussed earlier for viral encephalitis (see Chap. 132). Serologic studies are important for the diagnosis of arboviruses such as WNV, however these tests are less useful for viruses such as HSV, VZV, CMV, and EBV that have a high seroprevalence in the general population.

CSF oligoclonal gamma globulin bands occur in association with a number of viral infections. The associated antibodies are often directed against viral proteins. Oligoclonal bands also occur commonly in certain noninfectious neurologic diseases (e.g., multiple sclerosis) and may be found in nonviral infections (e.g., neurosyphilis, Lyme neuroborreliosis).

Other Laboratory Studies All patients with suspected viral meningitis should have a complete blood count and differential, liver and renal function tests, erythrocyte sedimentation rate (ESR), and C-reactive protein, electrolytes, glucose, creatine kinase, aldolase, amylase, and lipase. Neuroimaging studies (MRI preferable to CT) are not absolutely necessary in patients with uncomplicated viral meningitis but should be performed in patients with altered consciousness, seizures, focal neurologic signs or symptoms (see "Differential Diagnosis" below), atypical CSF profiles, or underlying immunocompromising treatments or conditions.

DIFFERENTIAL DIAGNOSIS

The most important issue in the differential diagnosis of viral meningitis is to consider diseases that can mimic viral meningitis, including (1) untreated or partially treated bacterial meningitis; (2) early stages of meningitis caused by fungi, mycobacteria, or *Treponema pallidum* (neurosyphilis), in which a lymphocytic pleocytosis is common, cultures may be slow growing or negative, and hypoglycorrhachia may not be present early; (3) meningitis caused by agents such as *Mycoplasma, Listeria* spp., *Brucella* spp., *Coxiella* spp., *Leptospira* spp., and *Rickettsia* spp.; (4) parameningeal infections; (5) neoplastic meningitis; and (6) meningitis secondary to noninfectious inflammatory diseases, including medication-induced hypersensitivity meningitis, SLE and other rheumatologic diseases, sarcoidosis, Behçet's syndrome, and the uveomeningitic syndromes. Studies in children >28 days of age suggest that the presence of CSF protein >0.5 g/L (sensitivity 89%, specificity 78%) and elevated serum procalcitonin levels >0.5 ng/mL (sensitivity 89%, specificity 89%) were clues to the presence of bacterial as opposed to "aseptic" meningitis. A variety of clinical algorithms for differentiating bacterial from aseptic meningitis have been developed. One such prospectively validated system, the *bacterial meningitis score*, suggests that the probability of bacterial meningitis is 0.3% or less (negative predictive value 99.7%, 95% confidence interval 99.6–100%) in children with CSF pleocytosis who have (1) a negative CSF Gram's stain, (2) CSF neutrophil count <1000 cells/μL, (3) CSF protein <80 mg/dL, (4) peripheral absolute neutrophil count of <10,000 cells/μL, and (5) no prior history or current presence of seizures.

SPECIFIC VIRAL ETIOLOGIES

Enteroviruses (EV) (Chap. 199) are the most common cause of viral meningitis, accounting for >85% of cases in which a specific etiology can be identified. Cases may either be sporadic or occur in clusters. EV71 has produced large epidemics of neurologic disease outside the United States, especially in Southeast Asia, but most recently reported cases in the United States have been sporadic. Enteroviruses are the most likely cause of viral meningitis in the summer and fall months, especially in children (<15 years), although cases occur at reduced frequency year round. Although the incidence of enteroviral meningitis declines with increasing age, some outbreaks have preferentially affected older children and adults. Meningitis outside the neonatal period is usually benign. Patients present with sudden onset of fever; headache; nuchal rigidity; and often constitutional signs, including vomiting, anorexia, diarrhea, cough, pharyngitis, and myalgias. The physical examination should include a careful search for stigmata of enterovirus infection, including exanthems, hand-foot-mouth disease, herpangina, pleurodynia, myopericarditis, and hemorrhagic conjunctivitis. The CSF profile is typically a lymphocytic pleocytosis (100–1000 cells/μL) with normal glucose and normal or mildly elevated protein concentration. However, up to 15% of patients, most commonly young infants rather than older children or adults, have a normal CSF leukocyte count. In rare cases, PMNs may predominate during the first 48 h of illness. CSF reverse transcriptase PCR (RT-PCR) is the diagnostic procedure of choice and is both sensitive (>95%) and specific (>100%). CSF PCR has the highest sensitivity if performed within 48 h of symptom onset, with sensitivity declining rapidly after day 5 of symptoms. PCR of throat washings or stool specimens may be positive for several weeks, and positive results can help support the diagnosis of an acute enteroviral infection. The sensitivity of routine enteroviral PCRs for detecting EV71 is low, and specific testing may be required. Treatment is supportive, and patients usually recover without sequelae. Chronic and severe infections can occur in neonates and in individuals with hypo- or agammaglobulinemia.

Arbovirus infections (Chap. 204) occur predominantly in the summer and early fall. Arboviral meningitis should be considered when clusters of meningitis and encephalitis cases occur in a restricted geographic region during the summer or early fall. In the United States, the most important causes of arboviral meningitis and encephalitis are WNV, St. Louis encephalitis virus, and the California encephalitis group of viruses. In WNV epidemics, avian deaths may serve as sentinel infections for subsequent human disease. A history of tick exposure or travel or residence in the appropriate geographic area should suggest the possibility of Colorado tick fever virus or Powassan virus infection, although nonviral tick-borne diseases, including RMSF and Lyme neuroborreliosis, may present similarly. Arbovirus meningitis is typically associated with a CSF lymphocytic pleocytosis, normal glucose concentration, and normal or mildly elevated protein concentration. However,

~45% of patients with WNV meningitis have CSF neutrophilia, which can persist for a week or more. The rarity of hypoglycorrhachia in WNV infection, the absence of positive Gram's stains, and the negative cultures help distinguish these patients from those with bacterial meningitis. Definitive diagnosis of arboviral meningitis is based on demonstration of viral-specific IgM in CSF or seroconversion. The prevalence of CSF IgM increases progressively during the first week after infection, peaking at >80% in patients with neuroinvasive disease; as a result, repeat studies may be needed when disease suspicion is high and an early study is negative. CSF PCR tests are available for some viruses in selected diagnostic laboratories and at the Centers for Disease Control and Prevention (CDC), but in the case of WNV, sensitivity (~70%) of CSF PCR is less than that of CSF serology. WNV CSF PCR may be useful in immunocompromised patients who may have absent or reduced antibody responses.

HSV meningitis **(Chap. 187)** has been increasingly recognized as a major cause of viral meningitis in adults, and overall, it is probably second in importance to enteroviruses as a cause of viral meningitis, accounting for 5% of total cases overall and undoubtedly a higher frequency of those cases occurring in adults and/or outside of the summer-fall period when enterovirus infections are increasingly common. In adults, the majority of cases of uncomplicated meningitis are due to HSV-2, whereas HSV-1 is responsible for 90% of cases of HSV encephalitis. HSV meningitis occurs in ~25–35% of women and ~10–15% of men at the time of an initial (primary) episode of genital herpes. Of these patients, 20% go on to have recurrent attacks of meningitis. Diagnosis of HSV meningitis is usually by HSV CSF PCR because cultures may be negative, especially in patients with recurrent meningitis. Demonstration of intrathecal synthesis of HSV-specific antibody may also be useful in diagnosis, although antibody tests are less sensitive and less specific than PCR and may not become positive until after the first week of infection. Although a history of or the presence of HSV genital lesions is an important diagnostic clue, many patients with HSV meningitis give no history and have no evidence of active genital herpes at the time of presentation. Most cases of recurrent viral or "aseptic" meningitis, including cases previously diagnosed as Mollaret's meningitis, are due to HSV.

VZV meningitis should be suspected in the presence of concurrent chickenpox or shingles. However, it is important to recognize that VZV is being increasingly identified as an important cause of both meningitis and encephalitis in patients without rash. The frequency of VZV as a cause of meningitis is extremely variable, ranging from as low as 3% to as high as 20% in different series. Diagnosis is usually based on CSF PCR, although the sensitivity of this test is not as high as for the other herpesviruses. VZV serologic studies complement PCR testing, and the diagnosis of VZV CNS infection can be made by the demonstration of VZV-specific intrathecal antibody synthesis and/or the presence of VZV CSF IgM antibodies, or by positive CSF cultures.

EBV infections may also produce aseptic meningitis, with or without associated infectious mononucleosis. The presence of atypical lymphocytes in the CSF or peripheral blood is suggestive of EBV infection but may occasionally be seen with other viral infections. EBV is almost never cultured from CSF. Serum and CSF serology help establish the presence of acute infection, which is characterized by IgM viral capsid antibodies (VCAs), antibodies to early antigens (EAs), and the absence of antibodies to EBV-associated nuclear antigen (EBNA). CSF PCR is another important diagnostic test, although false-positive results may reflect viral reactivation associated with other infectious or inflammatory processes or the presence of latent viral DNA in lymphocytes recruited due to other inflammatory conditions.

HIV meningitis should be suspected in any patient presenting with a viral meningitis with known or suspected risk factors for HIV infection. Meningitis may occur following primary infection with HIV in 5–10% of cases and less commonly at later stages of illness. Cranial nerve palsies, most commonly involving cranial nerves V, VII, or VIII, are more common in HIV meningitis than in other viral infections. Diagnosis can be confirmed by detection of HIV genome in blood or CSF. Seroconversion may be delayed, and patients with negative HIV serologies who are suspected of having HIV meningitis should be monitored for delayed seroconversion. **For further discussion of HIV infection, see Chap. 197.**

Mumps **(Chap. 202)** should be considered when meningitis occurs in the late winter or early spring, especially in males (male-to-female ratio 3:1). With the widespread use of the live attenuated mumps vaccine in the United States since 1967, the incidence of mumps meningitis has fallen by >95%; however, mumps remains a potential source of infection in nonimmunized individuals and populations. Rare cases (10–100:100,000 vaccinated individuals) of vaccine-associated mumps meningitis have been described, with onset typically 2–4 weeks after vaccination. The presence of parotitis, orchitis, oophoritis, pancreatitis, or elevations in serum lipase and amylase is suggestive of mumps meningitis; however, their absence does not exclude the diagnosis. Clinical meningitis was previously estimated to occur in 10–30% of patients with mumps parotitis; however, in a recent U.S. outbreak of nearly 2600 cases of mumps, only 11 cases of meningitis were identified, suggesting the incidence may be lower than previously suspected. Mumps infection confers lifelong immunity, so a documented history of previous infection excludes this diagnosis. Patients with meningitis have a CSF pleocytosis that can exceed 1000 cells/μL in 25%. Lymphocytes predominate in 75%, although CSF neutrophilia occurs in 25%. Hypoglycorrhachia occurs in 10–30% of patients and may be a clue to the diagnosis when present. Diagnosis is typically made by culture of virus from CSF or by detecting IgM antibodies or seroconversion. CSF PCR is available in some diagnostic and research laboratories.

LCMV infection **(Chap. 204)** should be considered when aseptic meningitis occurs in the late fall or winter and in individuals with a history of exposure to house mice (*Mus musculus*), pet or laboratory rodents (e.g., hamsters, rats, mice), or their excreta. Some patients have an associated rash, pulmonary infiltrates, alopecia, parotitis, orchitis, or myopericarditis. Laboratory clues to the diagnosis of LCMV, in addition to the clinical findings noted above, may include the presence of leukopenia, thrombocytopenia, or abnormal liver function tests. Some cases present with a marked CSF pleocytosis (>1000 cells/μL) and hypoglycorrhachia (<30%). Diagnosis is based on serology and/or culture of virus from CSF.

TREATMENT

Acute Viral Meningitis

Treatment of almost all cases of viral meningitis is primarily symptomatic and includes use of analgesics, antipyretics, and antiemetics. Fluid and electrolyte status should be monitored. Patients with suspected bacterial meningitis should receive appropriate empirical therapy pending culture results (see above). Hospitalization may not be required in immunocompetent patients with presumed viral meningitis and no focal signs or symptoms, no significant alteration in consciousness, and a classic CSF profile (lymphocytic pleocytosis, normal glucose, negative Gram's stain) if adequate provision for monitoring at home and medical follow-up can be ensured. Immunocompromised patients; patients with significant alteration in consciousness, seizures, or the presence of focal signs and symptoms suggesting the possibility of encephalitis or parenchymal brain involvement; and patients who have an atypical CSF profile should be hospitalized. Oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or 2 and in cases of severe EBV or VZV infection. Data concerning treatment of HSV, EBV, and VZV meningitis are extremely limited. Seriously ill patients should probably receive intravenous acyclovir (15–30 mg/kg per day in three divided doses), which can be followed by an oral drug such as acyclovir (800 mg five times daily), famciclovir (500 mg tid), or valacyclovir (1000 mg tid) for a total course of 7–14 days. Patients who are less ill can be treated with oral drugs alone. Patients with HIV meningitis should receive highly active antiretroviral therapy **(Chap. 197)**. There is no specific therapy of proven benefit for patients with arboviral encephalitis, including that caused by WNV.

Patients with viral meningitis who are known to have deficient humoral immunity (e.g., X-linked agammaglobulinemia) and who

are not already receiving either intramuscular gamma globulin or intravenous immunoglobulin (IVIg) should be treated with these agents. Intraventricular administration of immunoglobulin through an Ommaya reservoir has been tried in some patients with chronic enteroviral meningitis who have not responded to intramuscular or intravenous immunoglobulin.

Vaccination is an effective method of preventing the development of meningitis and other neurologic complications associated with poliovirus, mumps, measles, rubella, and varicella infection. A live attenuated VZV vaccine (Varivax) is available in the United States. Clinical studies indicate an effectiveness rate of 70–90% for this vaccine, but a booster may be required after ~10 years to maintain immunity. A live attenuated vaccine (Zostavax) is recommended for prevention of herpes zoster (shingles) in adults aged >60 at the present time. A new vaccine should be available soon. The herpes zoster subunit vaccine (HZ/su) containing recombinant varicella-zoster virus glycoprotein E and an adjuvant system has greater efficacy in preventing zoster in adults aged ≥70 years than the live attenuated vaccine. An inactivated varicella vaccine is available for transplant recipients and others for whom live viral vaccines are contraindicated.

PROGNOSIS

In adults, the prognosis for full recovery from viral meningitis is excellent. Rare patients complain of persisting headache, mild mental impairment, incoordination, or generalized asthenia for weeks to months. The outcome in infants and neonates (<1 year) is less certain; intellectual impairment, learning disabilities, hearing loss, and other lasting sequelae have been reported in some studies.

SUBACUTE MENINGITIS

CLINICAL MANIFESTATIONS

Patients with subacute meningitis typically have an unrelenting headache, stiff neck, low-grade fever, and lethargy for days to several weeks before they present for evaluation. Cranial nerve abnormalities and night sweats may be present. **This syndrome overlaps that of chronic meningitis, discussed in detail in Chap. 134, but is included here as the meningeal pathogens of subacute meningitis can also present as an acute meningitis.**

ETIOLOGY

Common causative organisms include *M. tuberculosis, C. neoformans, H. capsulatum, C. immitis*, and *T. pallidum*. Initial infection with *M. tuberculosis* is acquired by inhalation of aerosolized droplet nuclei. Tuberculous meningitis in adults does not develop acutely from hematogenous spread of tubercle bacilli to the meninges. Rather, millet seed–sized (miliary) tubercles form in the parenchyma of the brain during hematogenous dissemination of tubercle bacilli in the course of primary infection. These tubercles enlarge and are usually caseating. The propensity for a caseous lesion to produce meningitis is determined by its proximity to the SAS and the rate at which fibrous encapsulation develops. Subependymal caseous foci cause meningitis via discharge of bacilli and tuberculous antigens into the SAS. Mycobacterial antigens produce an intense inflammatory reaction that leads to the production of a thick exudate that fills the basilar cisterns and surrounds the cranial nerves and major blood vessels at the base of the brain.

Fungal infections are typically acquired by the inhalation of airborne fungal spores. The initial pulmonary infection may be asymptomatic or present with fever, cough, sputum production, and chest pain. The pulmonary infection is often self-limited. A localized pulmonary fungal infection can then remain dormant in the lungs until there is an abnormality in cell-mediated immunity that allows the fungus to reactivate and disseminate to the CNS. The most common pathogen causing fungal meningitis is *C. neoformans*. This fungus is found worldwide in soil and bird excreta. *H. capsulatum* is endemic to the Ohio and Mississippi River valleys of the central United States and to parts of Central and South America. *C. immitis* is endemic to the desert areas of the southwest United States, northern Mexico, and Argentina.

Syphilis is a sexually transmitted disease that is manifest by the appearance of a painless chancre at the site of inoculation. *T. pallidum* invades the CNS early in the course of syphilis. Cranial nerves VII and VIII are most frequently involved.

LABORATORY DIAGNOSIS

The classic CSF abnormalities in tuberculous meningitis are as follows: (1) elevated opening pressure, (2) lymphocytic pleocytosis (10–500 cells/μL), (3) elevated protein concentration in the range of 1–5 g/L, and (4) decreased glucose concentration in the range of 1.1–2.2 mmol/L (20–40 mg/dL). *The combination of unrelenting headache, stiff neck, fatigue, night sweats, and fever with a CSF lymphocytic pleocytosis and a mildly decreased glucose concentration is highly suspicious for tuberculous meningitis.* The last tube of fluid collected at LP is the best tube to send for a smear for acid-fast bacilli (AFB). If there is a pellicle in the CSF or a cobweb-like clot on the surface of the fluid, AFB can best be demonstrated in a smear of the clot or pellicle. Positive smears are typically reported in only 10–40% of cases of tuberculous meningitis in adults. Cultures of CSF take 4–8 weeks to identify the organism and are positive in ~50% of adults. Culture remains the gold standard to make the diagnosis of tuberculous meningitis. PCR for the detection of *M. tuberculosis* DNA should be sent on CSF if available, but the sensitivity and specificity on CSF have not been defined. The CDC recommends the use of nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis.

The characteristic CSF abnormalities in fungal meningitis are a mononuclear or lymphocytic pleocytosis, an increased protein concentration, and a decreased glucose concentration. There may be eosinophils in the CSF in *C. immitis* meningitis. Large volumes of CSF are often required to demonstrate the organism on India ink smear or grow the organism in culture. If spinal fluid examined by LP on two separate occasions fails to yield an organism, CSF should be obtained by high-cervical or cisternal puncture.

The cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal meningitis. A reactive CSF cryptococcal antigen test establishes the diagnosis. The detection of the *Histoplasma* polysaccharide antigen in CSF establishes the diagnosis of a fungal meningitis but is not specific for meningitis due to *H. capsulatum*. It may be falsely positive in coccidioidal meningitis. The CSF complement fixation antibody test is reported to have a specificity of 100% and a sensitivity of 75% for coccidioidal meningitis.

The diagnosis of syphilitic meningitis is made when a reactive serum treponemal test (fluorescent treponemal antibody absorption test [FTA-ABS] or microhemagglutination assay–*T. pallidum* [MHA-TP]) is associated with a CSF lymphocytic or mononuclear pleocytosis and an elevated protein concentration, or when the CSF Venereal Disease Research Laboratory (VDRL) test is positive. A reactive CSF FTA-ABS is not definitive evidence of neurosyphilis. The CSF FTA-ABS can be falsely positive from blood contamination. A negative CSF VDRL does not rule out neurosyphilis. A negative CSF FTA-ABS or MHA-TP rules out neurosyphilis.

TREATMENT

Subacute Meningitis

Empirical therapy of tuberculous meningitis is often initiated on the basis of a high index of suspicion without adequate laboratory support. Initial therapy is a combination of isoniazid (300 mg/d), rifampin (10 mg/kg per day), pyrazinamide (30 mg/kg per day in divided doses), ethambutol (15–25 mg/kg per day in divided doses), and pyridoxine (50 mg/d). When the antimicrobial sensitivity of the *M. tuberculosis* isolate is known, ethambutol can be discontinued. If the clinical response is good, pyrazinamide can be discontinued after 8 weeks and isoniazid and rifampin continued alone for the next 6–12 months. A 6-month course of therapy is acceptable, but therapy should be prolonged for 9–12 months in patients who have

an inadequate resolution of symptoms of meningitis or who have positive mycobacterial cultures of CSF during the course of therapy. Dexamethasone therapy is recommended for HIV-negative patients with tuberculous meningitis. The dose is 12–16 mg/d for 3 weeks, and then tapered over 3 weeks.

Meningitis due to *C. neoformans* in non-HIV, nontransplant patients is treated with induction therapy with amphotericin B (AmB) (0.7 mg/kg IV per day) plus flucytosine (100 mg/kg per day in four divided doses) for at least 4 weeks if CSF culture results are negative after 2 weeks of treatment. Therapy should be extended for a total of 6 weeks in the patient with neurologic complications. Induction therapy is followed by consolidation therapy with fluconazole 400 mg/d for 8 weeks. Organ transplant recipients are treated with liposomal AmB (3–4 mg/kg per day) or AmB lipid complex (ABLC) 5 mg/kg per day plus flucytosine (100 mg/kg per day in four divided doses) for at least 2 weeks or until CSF culture is sterile. Follow CSF yeast cultures for sterilization rather than the cryptococcal antigen titer. This treatment is followed by an 8- to 10-week course of fluconazole (400–800 mg/d [6–12 mg/kg] PO). If the CSF culture is sterile after 10 weeks of acute therapy, the dose of fluconazole is decreased to 200 mg/d for 6 months to a year. Patients with HIV infection are treated with AmB or a lipid formulation plus flucytosine for at least 2 weeks, followed by fluconazole for a minimum of 8 weeks. HIV-infected patients may require indefinite maintenance therapy with fluconazole 200 mg/d. Meningitis due to *H. capsulatum* is treated with AmB (0.7–1.0 mg/kg per day) for 4–12 weeks. A total dose of 30 mg/kg is recommended. Therapy with AmB is not discontinued until fungal cultures are sterile. After completing a course of AmB, maintenance therapy with itraconazole 200 mg two or three times daily is initiated and continued for at least 9 months to a year. *C. immitis* meningitis is treated with either high-dose fluconazole (1000 mg daily) as monotherapy or intravenous AmB (0.5–0.7 mg/kg per day) for >4 weeks. Intrathecal AmB (0.25–0.75 mg/d three times weekly) may be required to eradicate the infection. Lifelong therapy with fluconazole (200–400 mg daily) is recommended to prevent relapse. AmBisome (5 mg/kg per day) or AmB lipid complex (5 mg/kg per day) can be substituted for AmB in patients who have or who develop significant renal dysfunction. The most common complication of fungal meningitis is hydrocephalus. Patients who develop hydrocephalus should receive a CSF diversion device. A ventriculostomy can be used until CSF fungal cultures are sterile, at which time the ventriculostomy is replaced by a ventriculoperitoneal shunt.

Syphilitic meningitis is treated with aqueous penicillin G in a dose of 3–4 million units intravenously every 4 h for 10–14 days. An alternative regimen is 2.4 million units of procaine penicillin G intramuscularly daily with 500 mg of oral probenecid four times daily for 10–14 days. Either regimen is followed with 2.4 million units of benzathine penicillin G intramuscularly once a week for 3 weeks. The standard criterion for treatment success is reexamination of the CSF. The CSF should be reexamined at 6-month intervals for 2 years. The cell count is expected to normalize within 12 months, and the VDRL titer to decrease by two dilutions or revert to nonreactive within 2 years of completion of therapy. Failure of the CSF pleocytosis to resolve or an increase in the CSF VDRL titer by two or more dilutions requires retreatment.

FURTHER READING

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134 Chronic and Recurrent Meningitis

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Chronic inflammation of the meninges (pia, arachnoid, and dura) can produce profound neurologic disability and may be fatal if not successfully treated. Chronic meningitis is diagnosed when a characteristic neurologic syndrome exists for >4 weeks and is associated with a persistent inflammatory response in the cerebrospinal fluid (CSF) (white blood cell count >5/μL). The causes are varied, and appropriate treatment depends on identification of the etiology. Five categories of disease account for most cases of chronic meningitis: (1) meningeal infections, (2) malignancy, (3) autoimmune inflammatory disorders, (4) chemical meningitis, and (5) parameningeal infections.

CLINICAL PATHOPHYSIOLOGY

Neurologic manifestations of chronic meningitis **(Table 134-1)** are determined by the anatomic location of the inflammation and its consequences. Persistent headache, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes are the cardinal features. These can occur alone or in combination. When they appear in combination, widespread dissemination of the inflammatory process along CSF pathways has occurred. In some cases, the presence of an underlying systemic illness points to a specific agent or class of agents as the probable cause. The diagnosis of chronic meningitis is usually made when the clinical presentation prompts the physician to examine the CSF for signs of inflammation. CSF is produced by the choroid plexus of the cerebral ventricles, exits through narrow foramina into the subarachnoid space surrounding the brain and spinal cord, circulates around the base of the brain and over the cerebral hemispheres, and is resorbed by arachnoid villi projecting into the superior sagittal sinus. CSF flow provides a pathway for rapid spread of infectious and other infiltrative processes over the brain, spinal cord, cranial, and spinal nerve roots. Spread from the subarachnoid space into brain parenchyma may occur via the arachnoid cuffs that surround blood vessels that penetrate brain tissue (Virchow-Robin spaces).

Intracranial Meningitis Nociceptive nerve fibers of the meninges are stimulated by the inflammatory process, resulting in headache, neck pain, or back pain. Obstruction of CSF pathways at the foramina or arachnoid villi may produce hydrocephalus and signs

TABLE 134-1 Symptoms and Signs of Chronic Meningitis

SYMPTOM	SIGN
Chronic headache	± Papilledema
Neck or back pain/stiffness	Brudzinski's or Kernig's sign of meningeal irritation
Change in personality	Altered mental status—drowsiness, inattention, disorientation, memory loss, frontal release signs (grasp, suck, snout), perseveration
Facial weakness	Peripheral seventh CN paresis
Double vision	Paresis of CNs III, IV, VI
Diminished vision	Papilledema, optic atrophy
Hearing loss	Eighth CN paresis
Arm or leg weakness	Myelopathy or radiculopathy
Numbness in arms or legs	Myelopathy or radiculopathy
Urinary retention/incontinence	Myelopathy or radiculopathy Frontal lobe dysfunction (hydrocephalus)
Clumsiness	Ataxia

Abbreviation: CN, cranial nerve.

and symptoms of raised intracranial pressure (ICP), including headache, vomiting, apathy or drowsiness, gait instability, papilledema, visual loss, impaired upgaze, or palsy of the sixth cranial nerve (CN) (Chap. 433). Cognitive and behavioral changes during the course of chronic meningitis may also result from vascular damage due to inflammation around the blood vessels that course in the subarachnoid space, causing infarction. Inflammatory deposits seeded via the CSF circulation are often prominent around the brainstem and cranial nerves and along the undersurface of the frontal and temporal lobes. Such cases, termed basal meningitis, often present as multiple cranial neuropathies, with decreased vision (CN II), facial weakness (CN VII), decreased hearing (CN VIII), diplopia (CNs III, IV, and VI), sensory or motor abnormalities of the oropharynx (CNs IX, X, and XII), decreased olfaction (CN I), or decreased facial sensation and masseter weakness (CN V).

Spinal Meningitis Injury may occur to motor and sensory nerve roots as they traverse the subarachnoid space and penetrate the meninges. These cases present as multiple radiculopathies with combinations of radicular pain, sensory loss, motor weakness, and urinary or fecal incontinence. In some cases chronic inflammation causes clumping of the lower nerve roots and thickening of the meninges, so called pachymeningitis. Meningeal inflammation can encircle and damage the cord, resulting in a myelopathy. Patients with slowly progressive involvement of multiple cranial nerves and/or spinal nerve roots are likely to have chronic meningitis. Electrophysiologic testing (electromyography, nerve conduction studies, and evoked response testing) may be helpful in determining whether there is involvement of cranial and spinal nerve roots.

Systemic Manifestations In some patients, evidence of systemic disease provides clues to the underlying cause of chronic meningitis. A complete history of travel, sexual practice, and exposure to infectious agents should be sought. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system. Infectious causes are of major concern in the immunosuppressed patient, especially in patients with HIV infection, in whom chronic meningitis may present without headache or fever. Noninfectious inflammatory disorders most often produce systemic manifestations first, but meningitis may be the initial manifestation. Carcinomatous meningitis may or may not be accompanied by clinical evidence of the primary neoplasm.

APPROACH TO THE PATIENT

Chronic Meningitis

The occurrence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient should prompt consideration of a lumbar puncture for evidence of meningeal inflammation. On occasion, the diagnosis is made when a contrast-enhanced imaging study (CT or MRI) shows leakage of contrast agent into the meninges. Meningeal enhancement is always concerning with the exception of dural enhancement after lumbar puncture, neurosurgical procedures, concussion, or spontaneous CSF leakage. Once chronic meningitis is confirmed by CSF examination, effort is focused on identifying the cause (Tables 134-2 and 134-3) by (1) further analysis of the CSF, (2) diagnosis of an underlying systemic infection or noninfectious inflammatory condition, or (3) pathologic examination of meningeal biopsy specimens.

Two clinical forms of chronic meningitis exist. In the first, the symptoms are chronic and persistent, whereas in the second there are recurrent, discrete episodes of illness. In the latter group, all

TABLE 134-2 Infectious Causes of Chronic Meningitis

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Common Bacterial Causes			
Partially treated suppurative meningitis	Mononuclear or mixed mononuclear-polymorphonuclear cells	CSF culture and Gram's stain; CSF 16s rRNA PCR	History consistent with acute bacterial meningitis and incomplete treatment
Parameningeal infection	Mononuclear or mixed mononuclear-polymorphonuclear cells	Contrast-enhanced CT or MRI to detect parenchymal, subdural, epidural, or sinus infection	Otitis media, pleuropulmonary infection, right-to-left cardiopulmonary shunt for brain abscess; focal neurologic signs; neck, back, ear, or sinus tenderness
Mycobacterium tuberculosis	Mononuclear cells except polymorphonuclear cells in early infection (commonly <500 WBC/μL); low CSF glucose; high protein	Tuberculin skin test may be negative; interferon gamma release assay; PCR and AFB culture of CSF (sputum, urine, gastric contents if indicated); identify tubercle bacillus on acid-fast stain of CSF or protein pellicle	Exposure history; previous tuberculous illness; immunosuppressed, anti-TNF therapy or AIDS; young children; fever, meningismus, night sweats, miliary TB on x-ray or liver biopsy; stroke due to arteritis
Lyme disease (Bannwarth's syndrome) *Borrelia burgdorferi*	Mononuclear cells; elevated protein	Serum Lyme antibody titer; western blot confirmation; (patients with syphilis may have false-positive Lyme titer)	History of tick bite or appropriate exposure history; erythema chronicum migrans skin rash; arthritis, radiculopathy, Bell's palsy, meningoencephalitis–multiple sclerosis-like syndrome
Syphilis (secondary, tertiary) *Treponema pallidum*	Mononuclear cells; elevated protein	CSF VDRL; serum VDRL (or RPR); fluorescent treponemal antibody-absorbed (FTA) or MHA-TP; serum VDRL may be negative in tertiary syphilis	Appropriate exposure history; HIV-seropositive individuals at increased risk of aggressive infection; "dementia"; cerebral infarction due to endarteritis
Uncommon Bacterial Causes			
Actinomyces	Polymorphonuclear cells	Anaerobic culture	Parameningeal abscess or sinus tract (oral or dental focus); pneumonitis
Nocardia	Polymorphonuclear; occasionally mononuclear cells; often low glucose	Isolation may require weeks; weakly acid fast	Associated brain abscess may be present
Brucella	Mononuclear cells (rarely polymorphonuclear); elevated protein; often low glucose	CSF antibody detection; serum antibody detection	Intake of unpasteurized dairy products; exposure to goats, sheep, cows; fever, arthralgia, myalgia, vertebral osteomyelitis
Whipple's disease *Tropheryma whipplei*	Mononuclear cells	Biopsy of small bowel or lymph node; CSF PCR for *T. whipplei;* brain and meningeal biopsy (with PAS stain and EM examination)	Diarrhea, weight loss, arthralgias, fever; dementia, ataxia, paresis, ophthalmoplegia, oculomasticatory myoclonus
Rare Bacterial Causes			
Leptospirosis (occasionally if left untreated may last 3–4 weeks)			

(*Continued*)

TABLE 134-2 Infectious Causes of Chronic Meningitis (Continued)

CAUSATIVE AGENT	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Fungal Causes			
Cryptococcus neoformans and var. gatti	Mononuclear cells; count not elevated in some patients with AIDS	India ink or fungal wet mount of CSF (budding yeast); blood and urine cultures; antigen detection in CSF	AIDS and immune suppression; pigeon exposure for neoformans, decaying wood exposure for var. gatti; skin and other organ involvement due to disseminated infection
Coccidioides immitis	Mononuclear cells (sometimes 10–20% eosinophils); often low glucose	Antibody detection in CSF and serum, antigen detection in CSF	Exposure history—southwestern United States; increased virulence in dark-skinned races
Candida sp.	Polymorphonuclear or mononuclear	Fungal stain and culture of CSF	IV drug abuse; postsurgery; prolonged IV therapy; disseminated candidiasis, recent epidural injection
Histoplasma capsulatum	Mononuclear cells; low glucose	Fungal stain and culture of large volumes of CSF; antigen detection in CSF, serum, and urine; antibody detection in serum, CSF	Exposure history—Ohio and central Mississippi River Valley; AIDS; mucosal lesions
Blastomyces dermatitidis	Mononuclear cells	Fungal stain and culture of CSF; biopsy and culture of skin, lung lesions; antibody detection in serum	Midwestern and southeastern United States; usually systemic infection; abscesses, draining sinus, ulcers
Aspergillus sp.	Mononuclear or polymorphonuclear	CSF culture	Sinusitis; granulocytopenia or immunosuppression
Sporothrix schenckii	Mononuclear cells	Antibody detection in CSF and serum; CSF culture	Traumatic inoculation; IV drug use; ulcerated skin lesion
Rare Fungal Causes			
Xylohypha (formerly *Cladosporium*) *trichoides* and other dark-walled (dematiaceous) fungi such as *Curvularia; Drechslera; Mucor*; and, after water aspiration, *Pseudallescheria boydii;* iatrogenic *Exserohilum rostratum* infection following spinal blocks			
Protozoal Causes			
Toxoplasma gondii	Mononuclear cells	Biopsy or response to empirical therapy in clinically appropriate context (including presence of antibody in serum)	Usually with intracerebral abscesses; common in HIV-seropositive patients
Trypanosomiasis *Trypanosoma gambiense*, *T. rhodesiense*	Mononuclear cells; elevated protein	Elevated CSF IgM; identification of trypanosomes in CSF and blood smear	Endemic in Africa; chancre, lymphadenopathy; prominent sleep disorder
Rare Protozoal Causes			
Acanthamoeba sp. causing granulomatous amebic encephalitis and meningoencephalitis in immunocompromised and debilitated individuals. *Balamuthia mandrillaris* causing chronic meningoencephalitis in immunocompetent hosts.			
Helminthic Causes			
Cysticercosis (infection with cysts of *Taenia solium*)	Mononuclear cells; may have eosinophils; glucose level may be low	Indirect hemagglutination assay in CSF; ELISA immunoblotting in serum	Usually with multiple cysts in basal meninges and hydrocephalus; cerebral cysts, muscle calcification
Gnathostoma spinigerum	Eosinophils, mononuclear cells	Peripheral eosinophilia	History of eating raw fish; common in Thailand and Japan; subarachnoid hemorrhage; painful radiculopathy
Angiostrongylus cantonensis	Eosinophils, mononuclear cells	Recovery of worms from CSF	History of eating raw shellfish; common in tropical Pacific regions; often benign
Baylisascaris procyonis (raccoon ascarid)	Eosinophils, mononuclear cells		Infection follows accidental ingestion of *B. procyonis* eggs from raccoon feces; fatal meningoencephalitis
Rare Helminthic Causes			
Trichinella spiralis (trichinosis); *Fasciola hepatica* (liver fluke), *Echinococcus* cysts; *Schistosoma* sp. The former may produce a lymphocytic pleocytosis whereas the latter two may produce an eosinophilic response in CSF associated with cerebral cysts (*Echinococcus*) or granulomatous lesions of brain or spinal cord			
Viral Causes			
Mumps	Mononuclear cells	Antibody in serum	No prior mumps or immunization; may produce meningoencephalitis; may persist for 3–4 weeks
Lymphocytic choriomeningitis	Mononuclear cells; may have low glucose	Antibody in serum; PCR for LCMV in CSF	Contact with rodents or their excreta; may persist for 3–4 weeks
Echovirus	Mononuclear cells; may have low glucose	Virus isolation from CSF	Congenital hypogammaglobulinemia; history of recurrent meningitis
HIV (acute retroviral syndrome)	Mononuclear cells	PCR for HIV in blood and CSF	HIV risk factors; rash, fever, lymphadenopathy; lymphopenia in peripheral blood; syndrome may persist long enough to be considered as "chronic meningitis"; or chronic meningitis may develop in later stages (AIDS) due to HIV
Human herpes viruses	Mononuclear cells	PCR for HSV, CMV DNA; CSF antibody for HSV, EBV	Recurrent meningitis due to HSV-2 (rarely HSV-1) often associated with genital recurrences; EBV associated with myeloradiculopathy, CMV with polyradiculopathy

Abbreviations: AFB, acid-fast bacillus; CMV, cytomegalovirus; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ELISA, enzyme-linked immunosorbent assay; EM, electron microscopy; FTA, fluorescent treponemal antibody absorption test; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay–*T. pallidum*; MRI, magnetic resonance imaging; PAS, periodic acid–Schiff; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TB, tuberculosis; VDRL, Venereal Disease Research Laboratories test.

TABLE 134-3 Noninfectious Causes of Chronic Meningitis

CAUSATIVE AGENTS	CSF FORMULA	HELPFUL DIAGNOSTIC TESTS	RISK FACTORS AND SYSTEMIC MANIFESTATIONS
Malignancy	Mononuclear cells; elevated protein; low glucose	Repeated cytologic examination of large volumes of CSF; CSF exam by polarizing microscopy; clonal lymphocyte markers; deposits on nerve roots or meninges seen on myelogram or contrast-enhanced MRI; meningeal biopsy	Metastatic cancer of breast, lung, stomach, or pancreas; melanoma, lymphoma, leukemia; meningeal gliomatosis; sarcoma; cerebral dysgerminoma
Chemical compounds (may cause recurrent meningitis)	Mononuclear or PMNs; low glucose, elevated protein; xanthochromia from subarachnoid hemorrhage in week prior to presentation with "meningitis"	Contrast-enhanced CT scan or MRI; cerebral angiogram to detect aneurysm. Enhancement and clumping of nerve roots of the cauda equina in arachnoiditis/pachymeningitis	History of recent injection into the subarachnoid space; history of sudden onset of headache; recent resection of acoustic neuroma or craniopharyngioma; epidermoid tumor of brain or spine, sometimes with dermoid sinus tract; pituitary apoplexy
Primary Inflammation			
CNS sarcoidosis	Mononuclear cells; elevated protein; often low glucose	Serum and CSF angiotensin-converting enzyme levels; biopsy of extraneural affected tissues or brain lesion/ meningeal biopsy	CN palsy, especially CN VII; hypothalamic dysfunction, especially diabetes insipidus; abnormal chest radiograph; peripheral neuropathy or myopathy
Vogt-Koyanagi-Harada syndrome (recurrent meningitis)	Mononuclear cells		Recurrent meningoencephalitis with uveitis, retinal detachment, alopecia, lightening of eyebrows and lashes, dysacousia, cataracts, glaucoma
Isolated granulomatous angiitis of the nervous system	Mononuclear cells; elevated protein	Angiography; meningeal biopsy may be necessary if confined to small vessels. VZV PCR in blood and biopsy tissue	Subacute dementia; multiple cerebral infarctions; recent zoster ophthalmicus
Systemic lupus erythematosus	Mononuclear or PMNs	Anti-DNA antibody, antinuclear antibodies	Encephalopathy; seizures; stroke; transverse myelopathy; rash; arthritis
Behçet's syndrome (recurrent meningitis)	Mononuclear or PMNs; elevated protein		Oral and genital aphthous ulcers; iridocyclitis; retinal hemorrhages; pathergic lesions at site of skin puncture
Chronic benign lymphocytic meningitis	Mononuclear cells		Recovery in 2–6 months, diagnosis by exclusion
Mollaret's meningitis (recurrent meningitis)	Large endothelial cells and PMNs in first hours, followed by mononuclear cells	PCR for herpes; MRI/CT to rule out epidermoid tumor or dural cyst	Recurrent meningitis; exclude HSV-2; rare cases due to HSV-1; occasional case associated with dural cyst
Drug hypersensitivity	PMNs; occasionally mononuclear cells or eosinophils	Complete blood count (eosinophilia)	Exposure to nonsteroidal anti-inflammatory agents, sulfonamides, isoniazid, tolmetin, ciprofloxacin, penicillin, carbamazepine, lamotrigine, IV immunoglobulin, OKT3 antibodies, phenazopyridine; improvement after discontinuation of drug; recurrence with repeat exposure
Granulomatosis with polyangiitis (Wegener's)	Mononuclear cells	Chest and sinus radiographs; urinalysis; ANCA antibodies in serum	Associated sinus, pulmonary, or renal lesions; CN palsies; skin lesions; peripheral neuropathy
Neonatal-Onset Multisystem Inflammatory Disorder	Mononuclear and PMNs	Gain of function mutation in NLRP3 gene leading to elevated IL-1β	Recurrent fever, urticaria, arthralgia, sensorineural hearing loss, papilledema, increased ICP
IgG4-Related Hypertrophic Pachymeningitis	Mild lymphocytic pleocytosis in some cases; normal to mildly increased protein; normal glucose	Serum IgG4 levels frequently elevated; ESR and C-reactive protein; meningeal biopsy shows swirling "storiform" fibrosis with lymphocytic infiltrates, obliterative phlebitis and IgG4+ plasma cells	Headache; seizures; focal symptoms from dural involvement in spinal cord/nerve roots, clivus, periorbital, vestibular and brainstem structures. Systemic IgG4-related disease can involve many tissues including pancreas, thyroid, lungs, and retroperitoneum
Other: multiple sclerosis, Sjögren's syndrome, and rarer forms of vasculitis (e.g., Cogan's syndrome)			

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; CN, cranial nerve; CSF, cerebrospinal fluid; CT, computed tomography; HSV, herpes simplex virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PMNs, polymorphonuclear cells.

symptoms, signs, and CSF parameters of meningeal inflammation resolve completely between episodes either spontaneously or in response to a specific therapy. In such patients, the likely etiologies include Mollaret's meningitis which is most often due to herpes simplex virus (HSV) type 2; chemical meningitis due to episodic leakage from an epidermoid tumor, craniopharyngioma, or cholesteatoma into CSF; primary autoimmune inflammatory conditions, including Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, IgG4-related disease and drug hypersensitivity with repeated administration of the offending agent.

The epidemiologic history is of considerable importance in diagnosis of chronic meningitis and may provide direction for selection of laboratory studies. Pertinent features include a history of tuberculosis or exposure; recent epidural injection that led to epidemic of fungal meningitis by *Exserohilum rostratum*; past travel to areas endemic for fungal infections (the San Joaquin Valley in California and southwestern states for coccidioidomycosis, midwestern states for histoplasmosis, southeastern states for blastomycosis); travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (*Brucella*); time spent in wooded areas endemic for Lyme disease; exposure to sexually transmitted disease (syphilis); exposure of an immunocompromised host to pigeons and their droppings (*Cryptococcus neoformans*); exposure to decaying wood in Vancouver Island, South Africa, and Australia (*Cryptococcus neoformans var. gatti*); gardening (*Sporothrix schenckii*); ingestion of poorly cooked meat or contact with a household cat (*Toxoplasma gondii*); residence in Thailand or Japan (*Gnathostoma spinigerum*), Latin America

(*Paracoccidioides brasiliensis*), or the South Pacific (*Angiostrongylus cantonensis*); rural residence and raccoon exposure (*Baylisascaris procyonis*); and residence in Latin America, the Philippines, sub-Saharan Africa, or Southeast Asia (*Taenia solium/cysticercosis*).

The presence of focal cerebral signs in a patient with chronic meningitis suggests the possibility of a brain abscess, parameningeal infection or infarct; identification of a potential source of infection (chronic draining ear, sinusitis, right-to-left cardiac or pulmonary shunt, chronic pleuropulmonary infection) supports this diagnosis. In some cases, diagnosis may be established by recognition and biopsy of unusual skin lesions (Behçet's syndrome, SLE, cryptococcosis, blastomycosis, Lyme disease, sporotrichosis, trypanosomiasis, IV drug use) or enlarged lymph nodes (lymphoma, sarcoid, tuberculosis, HIV, secondary syphilis, or Whipple's disease). A careful ophthalmologic examination may reveal uveitis (Vogt-Koyanagi-Harada syndrome, sarcoid, or central nervous system [CNS] lymphoma), keratoconjunctivitis sicca (Sjögren's syndrome), or iridocyclitis (Behçet's syndrome) and is essential to assess visual loss from papilledema. Aphthous oral lesions, genital ulcers, and hypopyon suggest Behçet's syndrome. Hepatosplenomegaly suggests lymphoma, sarcoid, tuberculosis, or brucellosis. Herpetic lesions in the genital area or on the thighs suggest HSV-2 infection. A breast nodule, a suspicious hyperpigmented skin lesion, focal bone pain, hard, fixed lymph nodes, or an abdominal mass directs attention to possible carcinomatous meningitis.

IMAGING

Once the clinical syndrome is recognized as a potential manifestation of chronic meningitis, proper analysis of the CSF is essential. However, if the possibility of raised ICP exists, a brain imaging study should be performed before lumbar puncture. If ICP is elevated because of a mass lesion, brain swelling, or a block in ventricular CSF outflow (obstructive hydrocephalus), then lumbar puncture carries the potential risk of brain herniation. Obstructive hydrocephalus usually requires direct ventricular drainage. In patients with open CSF flow pathways, elevated ICP can still occur due to impaired resorption of CSF by arachnoid villi. In such patients, lumbar puncture is usually safe and may be therapeutic, but repetitive or continuous lumbar drainage may be necessary to prevent abrupt deterioration and death from raised ICP. In some patients, especially those with cryptococcal meningitis, fatal levels of raised ICP can occur without enlarged ventricles.

Contrast-enhanced MRI or CT studies of the brain and spinal cord can identify meningeal enhancement, parameningeal infections (including brain abscess), encasement of the spinal cord (malignancy, inflammation or infection), or nodular deposits on the meninges or nerve roots (malignancy or sarcoidosis) **(Fig. 134-1)**. Imaging studies are also useful to guide biopsy of affected meninges.

Angiographic studies can identify evidence of cerebral arteritis in patients with chronic meningitis and stroke.

CEREBROSPINAL FLUID ANALYSIS

The CSF pressure should be measured and samples sent for bacterial, fungal, and tuberculous culture; Venereal Disease Research Laboratories (VDRL) test; cell count and differential; Gram's stain; and measurement of glucose and protein. Wet mount for fungus and parasites, india ink preparation, culture for fastidious bacteria and fungi, assays for cryptococcal antigen and oligoclonal immunoglobulin bands, and cytology should be performed. Other specific CSF tests (Tables 134-2 and 134-3) or blood tests and cultures should be ordered as indicated on the basis of the history, physical examination, or preliminary CSF results (i.e., eosinophilic, mononuclear, or polymorphonuclear meningitis). Rapid diagnosis may be facilitated by serologic tests and polymerase chain reaction (PCR) testing to identify DNA sequences in the CSF that are specific for the suspected pathogen. 16s ribosomal RNA (rRNA) PCR can be used to detect a broad range of bacterial causes of meningitis and can be particularly useful in partially treated meningitis when the yield of culture is low. 18s and 28s rRNA can similarly be useful for detecting a broad range of fungal species. In patients with suspected fungal infections, when other tests are negative, assays for beta-glucans may be a useful adjunct in establishing the diagnosis. Building on progress in parallel deep sequencing and informatics, unbiased metagenomic next-generation sequencing is becoming generally available, representing an efficient and powerful method for diagnosis of challenging diagnostic cases.

In most categories of chronic (not recurrent) meningitis, mononuclear cells predominate in the CSF. When neutrophils predominate after 3 weeks of illness, the principal etiologic considerations are *Nocardia asteroides*, *Actinomyces israelii*, *Brucella*, *Mycobacterium tuberculosis* (5–10% of early cases only), various fungi (*Blastomyces dermatitidis*, *Candida albicans*, *Histoplasma capsulatum*, *Aspergillus* spp., *Pseudallescheria boydii*, *Cladophialophora bantiana*), and noninfectious causes (SLE, exogenous chemical meningitis). When eosinophils predominate or are present in limited numbers in a primarily mononuclear cell response in the CSF, the differential diagnosis includes parasitic diseases (*A. cantonensis*, *G. spinigerum*, *B. procyonis*, or *Toxocara canis* infection, cysticercosis, schistosomiasis, echinococcal disease, *T. gondii* infection), fungal infections (6–20% eosinophils along with a predominantly lymphocyte pleocytosis, particularly with coccidioidal meningitis), neoplastic disease (lymphoma, leukemia, metastatic carcinoma), or other inflammatory processes (sarcoidosis, hypereosinophilic syndrome).

It is often necessary to broaden the number of diagnostic tests if the initial workup does not reveal the cause. In addition, repeated samples (three or more) of large volumes of lumbar CSF may be required to diagnose certain infectious and malignant causes of chronic meningitis. Lymphomatous or carcinomatous meningitis may be diagnosed by examination of sections cut from a cell block formed by spinning down the sediment from a large volume of CSF. Flow cytometry for malignant cells may also be useful in patients with suspected carcinomatous meningitis. The diagnosis of fungal meningitis may also require large volumes of CSF for culture of sediment. If standard lumbar puncture is unrewarding, a cervical cisternal tap to sample CSF near to the basal meninges may be fruitful. Ventricular fluid may appear sterile in cases with active infection in the lower lumbar space.

LABORATORY INVESTIGATION

In addition to the CSF examination, an attempt should be made to uncover pertinent underlying illnesses. Tuberculin skin test, chest radiograph, urine analysis and culture, blood count and differential, renal and liver function tests, alkaline phosphatase, sedimentation rate, antinuclear antibody, anti-Ro antibody, anti-La antibody, rheumatoid factor, and IgG4 level are often indicated. In some cases, a thorough search for a systemic site of infection is indicated. Pulmonary foci of infection may be present, particularly with fungal or tuberculous disease. Hence a CT or MRI of the chest and a sputum examination may be helpful. Abnormalities can be pursued by bronchoscopy or transthoracic needle biopsy. A tuberculin skin test is often placed, although the test has limited specificity and sensitivity for diagnosis of active disease. Where available gamma interferon release assays may be used to diagnose latent tuberculosis. Liver, bone marrow, or lymph node biopsy may be diagnostic in some cases of miliary tuberculosis, disseminated fungal infection, sarcoidosis, or metastatic malignancy. Positron emission tomography with fluorodeoxyglucose may be useful in identifying a systemic site for biopsy in patients with suspected carcinomatous meningitis or sarcoidosis when other tests are unrevealing. Genetic testing can identify mutations that cause rare monogenic autoinflammatory disorders.

MENINGEAL BIOPSY

If CSF is not diagnostic then a meningeal biopsy should be strongly considered in patients who are severely disabled, who need chronic ventricular decompression, or whose illness is progressing rapidly. The activities of the surgeon, pathologist, microbiologist, and

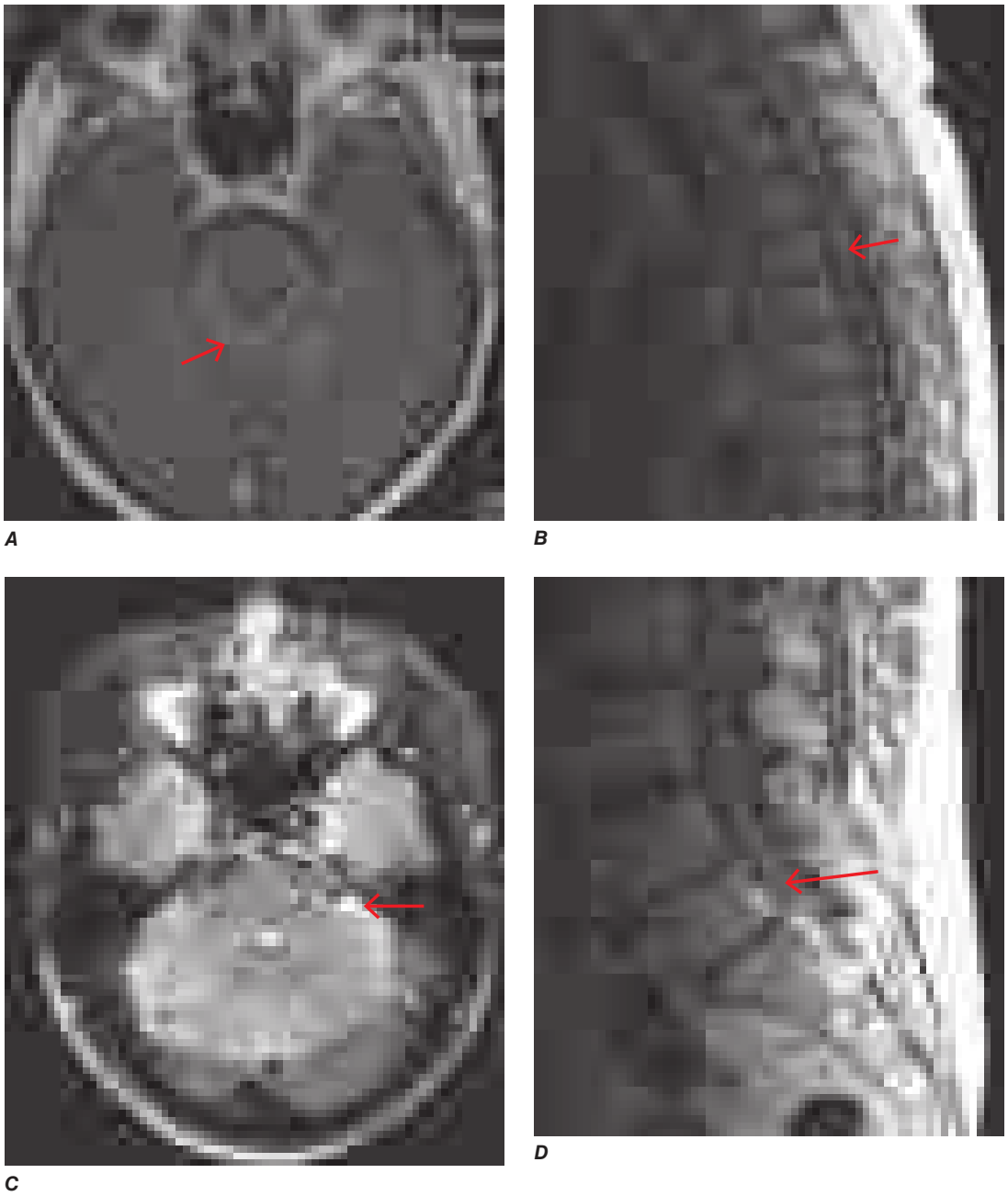

FIGURE 134-1 Chronic meningitis illustrating meningeal enhancement on contrast MRI scan. ***A*** and ***B*** are images from a patient with chronic meningitis due to carcinoma. ***C*** and ***D*** are from a patient with chronic meningitis due to Cryptococcus infection. *Arrows* point to the most prominent areas of meningeal inflammation around the brainstem and cerebellar folia (***A***), cerebellum (***C***), along the dorsal spinal cord (***B***), and clumping of roots in the cauda equina (***D***).

cytologist should be coordinated so that a large enough sample is obtained and the appropriate cultures and histologic and molecular studies, including electron-microscopic and PCR studies, are performed. The diagnostic yield of meningeal biopsy can be increased by targeting regions that enhance with contrast on MRI or CT. With current microsurgical techniques, most areas of the basal meninges can be accessed for biopsy via a limited craniotomy. In one series, MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy; biopsy of an enhancing region was diagnostic in 80% of cases, biopsy of nonenhancing regions was diagnostic in only 9%, and sarcoid (31%) and metastatic adenocarcinoma (25%) were the most common conditions identified. Tuberculosis is the most common condition identified in many reports from outside the United States.

APPROACH TO THE ENIGMATIC CASE

In approximately one-third of cases, the diagnosis is not known despite careful evaluation of CSF and potential extraneural sites of disease. A number of the organisms that cause chronic meningitis may take weeks to be identified by cultures. In enigmatic cases, several options are available, determined by the extent of the clinical deficits and rate of progression. It is prudent to wait until cultures are finalized if the patient is asymptomatic or symptoms are mild and not progressive. Unfortunately, in many cases progressive neurologic deterioration occurs, and rapid treatment is required. Ventricular-peritoneal shunts may be placed to relieve hydrocephalus, but the risk of disseminating the undiagnosed inflammatory process into the abdomen must be considered.

Empirical Treatment Diagnosis of the causative agent is essential because effective therapies exist for many etiologies of chronic meningitis, but if the condition is left untreated, progressive damage to the CNS and cranial nerves and roots is likely to occur. Occasionally, empirical therapy must be initiated when all attempts at diagnosis fail. In general, empirical therapy in the United States consists of antimycobacterial agents, amphotericin for fungal infection,

and/or glucocorticoids for noninfectious inflammatory causes. It is important to direct empirical therapy of lymphocytic meningitis at tuberculosis, particularly if the condition is associated with low CSF glucose, since untreated disease can be devastating within weeks. Prolonged anti-tumor necrosis factor therapy and anti-programmed death-1 (PD-1) inhibitors can cause reactivation of TB, and such patients who develop chronic meningitis should be treated empirically with antituberculous therapy if the etiology is uncertain. In the Mayo Clinic series, the most useful empirical therapy was administration of glucocorticoids rather than antituberculous therapy. When proceeding with empiric glucocorticoids, caution should be maintained whenever a transient response to treatment is noted, as some infectious (e.g., tuberculosis and cysticercosis) and non-infectious (e.g., lymphoma) etiologies may temporarily respond to glucocorticoid monotherapy. Carcinomatous or lymphomatous meningitis may be difficult to diagnose initially, but the diagnosis becomes evident with time.

THE IMMUNOSUPPRESSED PATIENT

Chronic meningitis is not uncommon in the course of HIV infection. Pleocytosis and mild meningeal signs often occur at the onset of HIV infection, and occasionally low-grade meningitis persists. Toxoplasmosis commonly presents as intracranial abscesses and also may be associated with meningitis. Other important causes of chronic meningitis in AIDS include infection with *Cryptococcus*, *Nocardia*, *Candida*, or other fungi; syphilis; and lymphoma (Fig. 134-1). Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiologic considerations in individuals with immunodeficiency states other than AIDS, including those due to immunosuppressive medications. Because of the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal irritation in immunosuppressed individuals, CSF examination should be performed for any persistent headache or unexplained change in mental state.

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135 Brain Abscess and Empyema

Karen L. Roos, Kenneth L. Tyler

BRAIN ABSCESS

DEFINITION

A brain abscess is a focal, suppurative infection within the brain parenchyma, typically surrounded by a vascularized capsule. The term *cerebritis* is often employed to describe a nonencapsulated brain abscess.

EPIDEMIOLOGY

A bacterial brain abscess is a relatively uncommon intracranial infection, with an incidence of ~0.3–1.3:100,000 persons per year. Predisposing conditions include otitis media and mastoiditis, paranasal sinusitis, pyogenic infections in the chest or other body sites, penetrating head trauma or neurosurgical procedures, and dental infections. In immunocompetent individuals the most important pathogens are *Streptococcus* spp. (anaerobic, aerobic, and viridans [40%]), Enterobacteriaceae (*Proteus* spp., *E. coli* sp., *Klebsiella* spp. [25%]), anaerobes (e.g., *Bacteroides* spp., *Fusobacterium* spp. [30%]), and staphylococci (10%). In immunocompromised hosts with underlying HIV infection, organ transplantation, cancer, or immunosuppressive therapy, most brain abscesses are caused by *Nocardia* spp., *Toxoplasma gondii, Aspergillus* spp., *Candida* spp., and *C. neoformans*. In Latin America and in immigrants from Latin America, the most common cause of brain abscess is *Taenia solium* (neurocysticercosis). In India and East Asia, mycobacterial infection (tuberculoma) remains a major cause of focal CNS mass lesions.

ETIOLOGY

A brain abscess may develop (1) by direct spread from a contiguous cranial site of infection, such as paranasal sinusitis, otitis media, mastoiditis, or dental infection; (2) following head trauma or a neurosurgical procedure; or (3) as a result of hematogenous spread from a remote site of infection. In up to 25% of cases, no obvious primary source of infection is apparent (cryptogenic brain abscess).

Approximately one-third of brain abscesses are associated with otitis media and mastoiditis, often with an associated cholesteatoma. Otogenic abscesses occur predominantly in the temporal lobe (55–75%) and cerebellum (20–30%). In some series, up to 90% of cerebellar abscesses are otogenic. Common organisms include streptococci, *Bacteroides* spp., *Pseudomonas* spp., *Haemophilus* spp., and Enterobacteriaceae. Abscesses that develop as a result of direct spread of infection from the frontal, ethmoidal, or sphenoidal sinuses and those that occur due to dental infections are usually located in the frontal lobes. Approximately 10% of brain abscesses are associated with paranasal sinusitis, and this association is particularly strong in young males in their second and third decades of life. The most common pathogens in brain abscesses associated with paranasal sinusitis are streptococci (especially *Streptococcus milleri*), *Haemophilus* spp., *Bacteroides* spp., *Pseudomonas* spp., and *Staphylococcus aureus*. Dental infections are associated with ~2% of brain abscesses, although it is often suggested that many "cryptogenic" abscesses are in fact due to dental infections. The most common pathogens in this setting are streptococci, staphylococci, *Bacteroides* spp., and *Fusobacterium* spp.

Hematogenous abscesses account for ~25% of brain abscesses. Hematogenous abscesses are often multiple, and multiple abscesses often (50%) have a hematogenous origin. These abscesses show a predilection for the territory of the middle cerebral artery (i.e., posterior frontal or parietal lobes). Hematogenous abscesses are often located at the junction of the gray and white matter and are often poorly encapsulated. The microbiology of hematogenous abscesses is dependent on the primary source of infection. For example, brain abscesses that develop as a complication of infective endocarditis are often due to viridans streptococci or *S. aureus*. Abscesses associated with pyogenic lung infections such as lung abscess or bronchiectasis are often due to streptococci, staphylococci, *Bacteroides* spp., *Fusobacterium* spp., or Enterobacteriaceae. Abscesses that follow penetrating head trauma or neurosurgical procedures are frequently due to methicillin-resistant *S. aureus* (MRSA), *S. epidermidis*, Enterobacteriaceae, *Pseudomonas* spp., and *Clostridium* spp. Enterobacteriaceae and *P. aeruginosa* are important causes of abscesses associated with urinary sepsis. Congenital cardiac malformations that produce a right-to-left shunt, such as tetralogy of Fallot, patent ductus arteriosus, and atrial and ventricular septal defects, allow bloodborne bacteria to bypass the pulmonary capillary bed and reach the brain. Similar phenomena can occur with pulmonary arteriovenous malformations. The decreased arterial oxygenation and saturation from the right-to-left shunt and polycythemia may cause focal areas of cerebral ischemia, thus providing a nidus for microorganisms that bypassed the pulmonary circulation to multiply and form an abscess. Streptococci are the most common pathogens in this setting.

PATHOGENESIS AND HISTOPATHOLOGY

Results of experimental models of brain abscess formation suggest that for bacterial invasion of brain parenchyma to occur, there must be preexisting or concomitant areas of ischemia, necrosis, or hypoxemia

in brain tissue. The intact brain parenchyma is relatively resistant to infection. Once bacteria have established infection, brain abscess frequently evolves through a series of stages, influenced by the nature of the infecting organism and by the immunocompetence of the host. The early cerebritis stage (days 1–3) is characterized by a perivascular infiltration of inflammatory cells, which surround a central core of coagulative necrosis. Marked edema surrounds the lesion at this stage. In the late cerebritis stage (days 4–9), pus formation leads to enlargement of the necrotic center, which is surrounded at its border by an inflammatory infiltrate of macrophages and fibroblasts. A thin capsule of fibroblasts and reticular fibers gradually develops, and the surrounding area of cerebral edema becomes more distinct than in the previous stage. The third stage, early capsule formation (days 10–13), is characterized by the formation of a capsule that is better developed on the cortical than on the ventricular side of the lesion. This stage correlates with the appearance of a ring-enhancing capsule on neuroimaging studies. The final stage, late capsule formation (day 14 and beyond), is defined by a well-formed necrotic center surrounded by a dense collagenous capsule. The surrounding area of cerebral edema has regressed, but marked gliosis with large numbers of reactive astrocytes has developed outside the capsule. This gliotic process may contribute to the development of seizures as a sequela of brain abscess.

CLINICAL PRESENTATION

A brain abscess typically presents as an expanding intracranial mass lesion rather than as an infectious process. Although the evolution of signs and symptoms is extremely variable, ranging from hours to weeks or even months, most patients present to the hospital 11–12 days following onset of symptoms. The classic clinical triad of headache, fever, and a focal neurologic deficit is present in <50% of cases. The most common symptom in patients with a brain abscess is headache, occurring in >75% of patients. The headache is often characterized as a constant, dull, aching sensation, either hemicranial or generalized, and it becomes progressively more severe and refractory to therapy. Fever is present in only 50% of patients at the time of diagnosis, and its absence should not exclude the diagnosis. The new onset of focal or generalized seizure activity is a presenting sign in 15–35% of patients. Focal neurologic deficits including hemiparesis, aphasia, or visual field defects are part of the initial presentation in >60% of patients.

The clinical presentation of a brain abscess depends on its location, the nature of the primary infection if present, and the level of the ICP. Hemiparesis is the most common localizing sign of a frontal lobe abscess. A temporal lobe abscess may present with a disturbance of language (dysphasia) or an upper homonymous quadrantanopia. Nystagmus and ataxia are signs of a cerebellar abscess. Signs of raised ICP—papilledema, nausea and vomiting, and drowsiness or confusion—can be the dominant presentation of some abscesses, particularly those in the cerebellum. Meningismus is not present unless the abscess has ruptured into the ventricle or the infection has spread to the subarachnoid space.

DIAGNOSIS

Diagnosis is made by neuroimaging studies. MRI **(Fig. 135-1)** is better than CT for demonstrating abscesses in the early (cerebritis) stages and is superior to CT for identifying abscesses in the posterior fossa. Cerebritis appears on MRI as an area of low-signal intensity on T1-weighted images with irregular postgadolinium enhancement and as an area of increased signal intensity on T2-weighted images. Cerebritis is often not visualized by CT scan, but when present, appears as an area of hypodensity. On a contrast-enhanced CT scan, a mature brain abscess appears as a focal area of hypodensity surrounded by ring enhancement with surrounding edema (hypodensity). On contrast-enhanced T1-weighted MRI, a mature brain abscess has a capsule that enhances surrounding a hypodense center and surrounded by a hypodense area of edema. On T2-weighted MRI, there is a hyperintense central area of pus surrounded by a well-defined hypointense capsule and a hyperintense surrounding area of edema. It is important to recognize that the CT and MRI appearance, particularly of the capsule, may be altered by treatment with glucocorticoids. The distinction between a brain abscess and other focal CNS lesions such as primary or metastatic tumors may be facilitated by the use of diffusion-weighted imaging sequences on which a brain abscess typically shows increased signal due to restricted diffusion of the abscess cavity with corresponding low signal on apparent diffusion coefficient images.

Microbiologic diagnosis of the etiologic agent is most accurately determined by Gram's stain and culture of abscess material obtained by CT-guided stereotactic needle aspiration. Aerobic and anaerobic bacterial cultures and mycobacterial and fungal cultures should be obtained. Up to 10% of patients will also have positive blood cultures. LP should not be performed in patients with known or suspected focal intracranial infections such as abscess or empyema; CSF analysis contributes nothing to diagnosis or therapy, and LP increases the risk of herniation.

Additional laboratory studies may provide clues to the diagnosis of brain abscess in patients with a CNS mass lesion. About 50% of patients have a peripheral leukocytosis, 60% an elevated ESR, and 80% an elevated C-reactive protein. Blood cultures are positive in ~10% of cases overall but may be positive in >85% of patients with abscesses due to *Listeria*.

DIFFERENTIAL DIAGNOSIS

Conditions that can cause headache, fever, focal neurologic signs, and seizure activity include brain abscess, subdural empyema, bacterial meningitis, viral meningoencephalitis, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. When fever is absent,

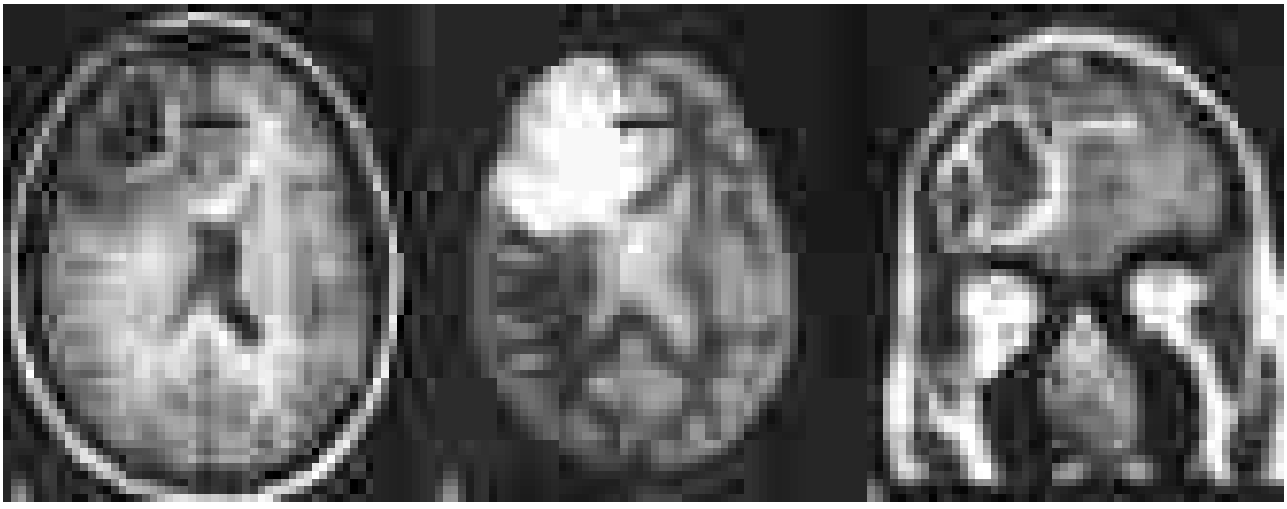

FIGURE 135-1 Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted magnetic resonance imaging (MRI) (***A***, *black arrow*), hypointense signal on the axial proton density images (***B***, *black arrow*), and enhances prominently after gadolinium administration on the coronal T1-weighted image (***C***). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (***C***, *white arrow*). (*Courtesy of Joseph Lurito, MD; with permission.*)

primary and metastatic brain tumors become the major differential diagnosis. Less commonly, cerebral infarction or hematoma can have an MRI or CT appearance resembling brain abscess.

TREATMENT

Brain Abscess

Optimal therapy of brain abscesses involves a combination of high-dose parenteral antibiotics and neurosurgical drainage. Empirical therapy of community-acquired brain abscess in an immunocompetent patient typically includes a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, or cefepime) and metronidazole **(see Table 133-1 for antibiotic dosages)**. In patients with penetrating head trauma or recent neurosurgical procedures, treatment should include ceftazidime as the third-generation cephalosporin to enhance coverage of *Pseudomonas* spp. and vancomycin for coverage of staphylococci. Meropenem plus vancomycin also provides good coverage in this setting.

Aspiration and drainage of the abscess under stereotactic guidance are beneficial for both diagnosis and therapy. Empirical antibiotic coverage should be modified based on the results of Gram's stain and culture of the abscess contents. Complete excision of a bacterial abscess via craniotomy or craniectomy is generally reserved for multiloculated abscesses or those in which stereotactic aspiration is unsuccessful.

Medical therapy alone is not optimal for treatment of brain abscess and should be reserved for patients whose abscesses are neurosurgically inaccessible, for patients with small (<2–3 cm) or nonencapsulated abscesses (cerebritis), and for patients whose condition is too tenuous to allow performance of a neurosurgical procedure. All patients should receive a minimum of 6–8 weeks of parenteral antibiotic therapy. The role, if any, of supplemental oral antibiotic therapy following completion of a standard course of parenteral therapy has never been adequately studied.

In addition to surgical drainage and antibiotic therapy, patients should receive prophylactic anticonvulsant therapy because of the high risk (~35%) of focal or generalized seizures. Anticonvulsant therapy is continued for at least 3 months after resolution of the abscess, and decisions regarding withdrawal are then based on the EEG. If the EEG is abnormal, anticonvulsant therapy should be continued. If the EEG is normal, anticonvulsant therapy can be slowly withdrawn, with close follow-up and repeat EEG after the medication has been discontinued.

Glucocorticoids should not be given routinely to patients with brain abscesses. Intravenous dexamethasone therapy (10 mg every 6 h) is usually reserved for patients with substantial periabscess edema and associated mass effect and increased ICP. Dexamethasone should be tapered as rapidly as possible to avoid delaying the natural process of encapsulation of the abscess.

Serial MRI or CT scans should be obtained on a monthly or twice-monthly basis to document resolution of the abscess. More frequent studies (e.g., weekly) are probably warranted in the subset of patients who are receiving antibiotic therapy alone. A small amount of enhancement may remain for months after the abscess has been successfully treated.

PROGNOSIS

The mortality rate of brain abscess has declined in parallel with the development of enhanced neuroimaging techniques, improved neurosurgical procedures for stereotactic aspiration, and improved antibiotics. In modern series, the mortality rate is typically <15%. Significant sequelae, including seizures, persisting weakness, aphasia, or mental impairment, occur in ≥20% of survivors.

NONBACTERIAL CAUSES OF INFECTIOUS FOCAL CNS LESIONS

ETIOLOGY

Neurocysticercosis is the most common parasitic disease of the CNS worldwide. Humans acquire cysticercosis by the ingestion of food contaminated with the eggs of the parasite *T. solium*. Toxoplasmosis is a parasitic disease caused by *T. gondii* and acquired from the ingestion of undercooked meat and from handling cat feces.

CLINICAL PRESENTATION

The most common manifestation of neurocysticercosis is new-onset partial seizures with or without secondary generalization. Cysticerci may develop in the brain parenchyma and cause seizures or focal neurologic deficits. When present in the subarachnoid or ventricular spaces, cysticerci can produce increased ICP by interference with CSF flow. Spinal cysticerci can mimic the presentation of intraspinal tumors. When the cysticerci first lodge in the brain, they frequently cause little in the way of an inflammatory response. As the cysticercal cyst degenerates, it elicits an inflammatory response that may present clinically as a seizure. Eventually the cyst dies, a process that may take several years and is typically associated with resolution of the inflammatory response and, often, abatement of seizures.

Primary *Toxoplasma* infection is often asymptomatic. However, during this phase parasites may spread to the CNS, where they become latent. Reactivation of CNS infection is almost exclusively associated with immunocompromised hosts, particularly those with HIV infection. During this phase patients present with headache, fever, seizures, and focal neurologic deficits.

DIAGNOSIS

The lesions of neurocysticercosis are readily visualized by MRI or CT scans. Lesions with viable parasites appear as cystic lesions. The scolex can often be visualized on MRI. Lesions may appear as contrast-enhancing lesions surrounded by edema. A very early sign of cyst death is hypointensity of the vesicular fluid on T2-weighted images when compared with CSF. Parenchymal brain calcifications are the most common finding and evidence that the parasite is no longer viable. MRI findings of toxoplasmosis consist of multiple lesions in the deep white matter, the thalamus, and basal ganglia and at the gray-white junction in the cerebral hemispheres. With contrast administration, the majority of the lesions enhance in a ringed, nodular, or homogeneous pattern and are surrounded by edema. In the presence of the characteristic neuroimaging abnormalities of *T. gondii* infection, serum IgG antibody to *T. gondii* should be obtained and, when positive, the patient should be treated.

TREATMENT

Infectious Focal CNS Lesions

Anticonvulsant therapy is initiated when the patient with neurocysticercosis presents with a seizure. There is controversy about whether or not anthelmintic therapy should be given to all patients, and recommendations are based on the stage of the lesion. Cysticerci appearing as cystic lesions in the brain parenchyma with or without pericystic edema or in the subarachnoid space at the convexity of the cerebral hemispheres should be treated with anticysticidal therapy. Cysticidal drugs accelerate the destruction of the parasites, resulting in a faster resolution of the infection. Albendazole and praziquantel are used in the treatment of neurocysticercosis. Approximately 85% of parenchymal cysts are destroyed by a single course of albendazole, and ~75% are destroyed by a single course of praziquantel. The dose of albendazole is 15 mg/kg per day in two doses for 8 days. The dose of praziquantel is 50 mg/kg per day for 15 days, although a number of other dosage regimens are also frequently cited. Prednisone or dexamethasone is given with anticysticidal therapy to reduce the host inflammatory response to degenerating parasites. Only cysts in the vesicular stage, where the cyst contains living larva (scolex seen on CT or MRI), and cysts in the colloidal stage as the larva degenerates (edema surrounds the lesion), are treated with anticysticidal therapy. Some, but not all, experts recommend anticysticidal therapy for lesions that are in the "granulo-nodular" stage (surrounded by a contrast-enhancing ring). There is universal agreement that calcified lesions do not need to be treated with anticysticidal therapy. Antiepileptic therapy can be stopped once the follow-up CT scan shows resolution of the lesion.

Long-term antiepileptic therapy is recommended when seizures occur after resolution of edema and resorption or calcification of the degenerating cyst.

CNS toxoplasmosis is treated with a combination of sulfadiazine, 1.5–2.0 g orally qid, plus pyrimethamine, 100 mg orally to load, then 75–100 mg orally qd, plus folinic acid, 10–15 mg orally qd. Folinic acid is added to the regimen to prevent megaloblastic anemia. Therapy is continued until there is no evidence of active disease on neuroimaging studies, which typically takes at least 6 weeks, and then the dose of sulfadiazine is reduced to 2–4 g/d and pyrimethamine to 50 mg/d. Clindamycin plus pyrimethamine is an alternative therapy for patients who cannot tolerate sulfadiazine, but the combination of pyrimethamine and sulfadiazine is more effective.

SUBDURAL EMPYEMA

A subdural empyema (SDE) is a collection of pus between the dura and arachnoid membranes **(Fig. 135-2)**.

EPIDEMIOLOGY

SDE is a rare disorder that accounts for 15–25% of focal suppurative CNS infections. Sinusitis is the most common predisposing condition and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis-associated empyema has a striking predilection for young males, possibly reflecting sex-related differences in sinus anatomy and development. It has been suggested that SDE may complicate 1–2% of cases of frontal sinusitis severe enough to require hospitalization. As a consequence of this epidemiology, SDE shows an ~3:1 male/female predominance, with 70% of cases occurring in the second and third decades of life. SDE may also develop as a complication of head trauma or neurosurgery. Secondary infection of a subdural effusion may also result in empyema, although secondary infection of hematomas, in the absence of a prior neurosurgical procedure, is rare.

ETIOLOGY

Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobic bacteria are the most common causative organisms of sinusitis-associated SDE. Staphylococci and gram-negative bacilli are often the etiologic organisms when SDE follows neurosurgical procedures or head trauma. Up to one-third of cases are culture-negative, possibly reflecting difficulty in obtaining adequate anaerobic cultures.

PATHOPHYSIOLOGY

Sinusitis-associated SDE develops as a result of either retrograde spread of infection from septic thrombophlebitis of the mucosal veins draining the sinuses or contiguous spread of infection to the brain from osteomyelitis in the posterior wall of the frontal or other sinuses. SDE may also develop from direct introduction of bacteria into the subdural space as a complication of a neurosurgical procedure. The evolution of SDE can be extremely rapid because the subdural space is a large compartment that offers few mechanical barriers to the spread of infection. In patients with sinusitis-associated SDE, suppuration typically begins in the upper and anterior portions of one cerebral hemisphere and then extends posteriorly. SDE is often associated with other intracranial infections, including epidural empyema (40%), cortical thrombophlebitis (35%), and intracranial abscess or cerebritis (>25%). Cortical venous infarction produces necrosis of underlying cerebral cortex and subcortical white matter, with focal neurologic deficits and seizures (see below).

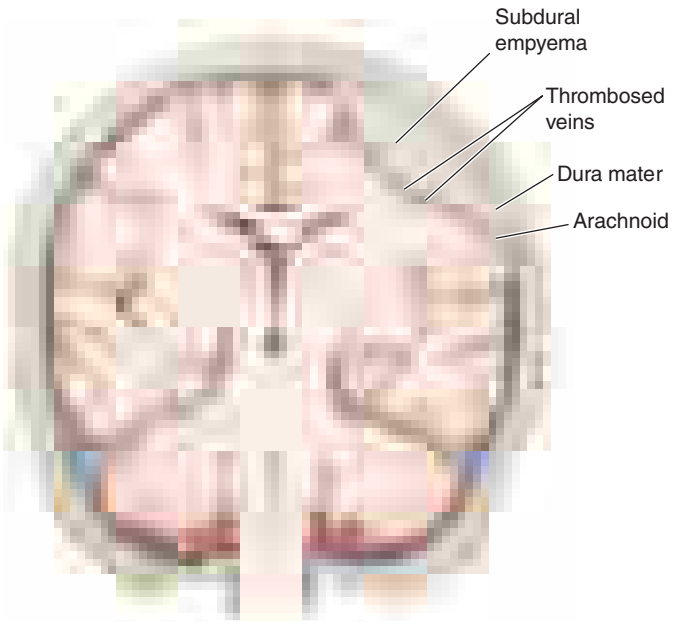

FIGURE 135-2 Subdural empyema.

CLINICAL PRESENTATION

A patient with SDE typically presents with fever and a progressively worsening headache. The diagnosis of SDE should always be suspected in a patient with known sinusitis who presents with new CNS signs or symptoms. Patients with underlying sinusitis frequently have symptoms related to this infection. As the infection progresses, focal neurologic deficits, seizures, nuchal rigidity, and signs of increased ICP commonly occur. Headache is the most common complaint at the time of presentation; initially it is localized to the side of the subdural infection, but then it becomes more severe and generalized. Contralateral hemiparesis or hemiplegia is the most common focal neurologic deficit and can occur from the direct effects of the SDE on the cortex or as a consequence of venous infarction. Seizures begin as partial motor seizures that then become secondarily generalized. Seizures may be due to the direct irritative effect of the SDE on the underlying cortex or result from cortical venous infarction (see above). In untreated SDE, the increasing mass effect and increase in ICP cause progressive deterioration in consciousness, leading ultimately to coma.

DIAGNOSIS

MRI **(Fig. 135-3)** is superior to CT in identifying SDE and any associated intracranial infections. The administration of gadolinium greatly improves diagnosis by enhancing the rim of the empyema and allowing the empyema to be clearly delineated from the underlying brain parenchyma. Cranial MRI is also extremely valuable in identifying sinusitis, other focal CNS infections, cortical venous infarction, cerebral edema, and cerebritis. CT may show a crescent-shaped hypodense lesion over one or both hemispheres or in the interhemispheric fissure. Frequently the degree of mass effect, exemplified by midline shift, ventricular compression, and sulcal effacement, is far out of proportion to the mass of the SDE.

CSF examination should be avoided in patients with known or suspected SDE because it adds no useful information and is associated with the risk of cerebral herniation.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the combination of headache, fever, focal neurologic signs, and seizure activity that progresses rapidly to an altered level of consciousness includes subdural hematoma, bacterial meningitis, viral encephalitis, brain abscess, superior sagittal sinus thrombosis, and acute disseminated encephalomyelitis. The presence of nuchal rigidity is unusual with brain abscess or epidural empyema and should suggest the possibility of SDE when associated with significant focal neurologic signs and fever. Patients with bacterial meningitis also have nuchal rigidity but do not typically have focal deficits of the severity seen with SDE.

TREATMENT

Subdural Empyema

SDE is a medical emergency. Emergent neurosurgical evacuation of the empyema, either through craniotomy, craniectomy, or burr-hole drainage, is the definitive step in the management of this infection. Empirical antimicrobial therapy for community-acquired SDE should include a combination of a third-generation cephalosporin

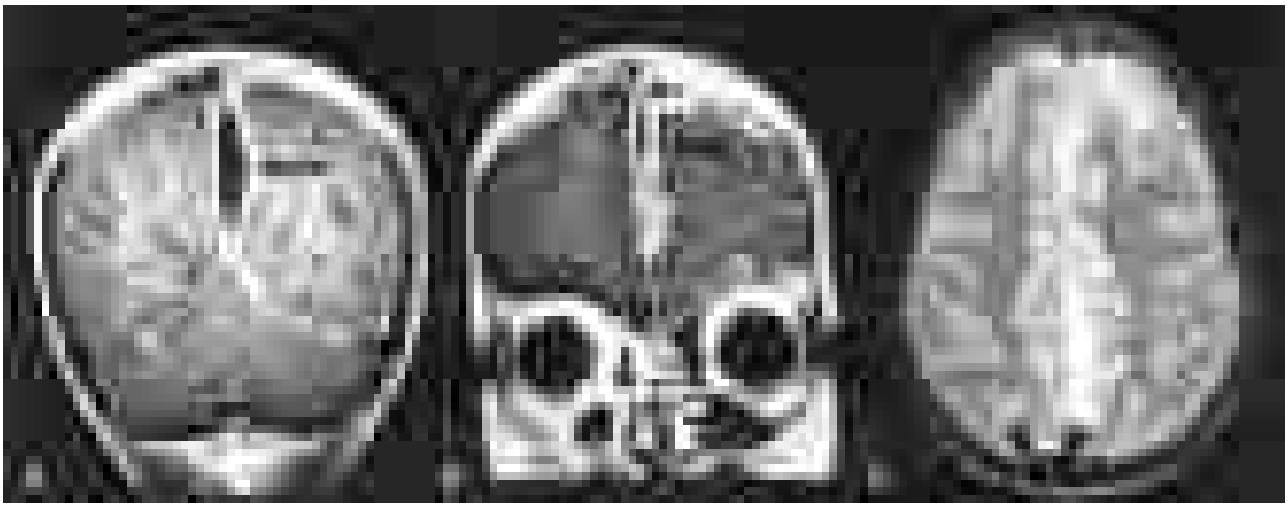

FIGURE 135-3 Subdural empyema. There is marked enhancement of the dura and leptomeninges (***A***, ***B***, *straight arrows*) along the left medial hemisphere. The pus is hypointense on T1-weighted images (***A***, ***B***) but markedly hyperintense on the proton density–weighted (***C***, *curved arrow*) image. *(Courtesy of Joseph Lurito, MD; with permission.)*

(e.g., cefotaxime or ceftriaxone), vancomycin, and metronidazole **(see Table 133-1 for dosages)**. Patients with hospital-acquired SDE may have infections due to *Pseudomonas* spp. or MRSA and should receive coverage with a carbapenem (e.g., meropenem) and vancomycin. Metronidazole is not necessary for antianaerobic therapy when meropenem is being used. Parenteral antibiotic therapy should be continued for a minimum of 3–4 weeks after SDE drainage. Patients with associated cranial osteomyelitis may require longer therapy. Specific diagnosis of the etiologic organisms is made based on Gram's stain and culture of fluid obtained via either burr holes or craniotomy; the initial empirical antibiotic coverage can be modified accordingly.

PROGNOSIS

Prognosis is influenced by the level of consciousness of the patient at the time of hospital presentation, the size of the empyema, and the speed with which therapy is instituted. Long-term neurologic sequelae, which include seizures and hemiparesis, occur in up to 50% of cases.

CRANIAL EPIDURAL ABSCESS

Cranial epidural abscess is a suppurative infection occurring in the potential space between the inner skull table and dura **(Fig. 135-4)**.

ETIOLOGY AND PATHOPHYSIOLOGY

Cranial epidural abscess is less common than either brain abscess or SDE and accounts for <2% of focal suppurative CNS infections. A cranial epidural abscess develops as a complication of a craniotomy or compound skull fracture or as a result of spread of infection from the frontal sinuses, middle ear, mastoid, or orbit. An epidural abscess may develop contiguous to an area of osteomyelitis, when craniotomy is complicated by infection of the wound or bone flap, or as a result of direct infection of the epidural space. Infection in the frontal sinus, middle ear, mastoid, or orbit can reach the epidural space through retrograde spread of infection from septic thrombophlebitis in the emissary veins that drain these areas or by way of direct spread of infection through areas of osteomyelitis. Unlike the subdural space, the epidural space is really a potential rather than an actual compartment. The dura is normally tightly adherent to the inner skull table, and infection must dissect the dura away from the skull table as it spreads. As a result, epidural abscesses are often smaller than SDEs. Cranial epidural abscesses, unlike brain abscesses, only rarely result from hematogenous spread of infection from extracranial primary sites. The bacteriology of a cranial epidural abscess is similar to that of SDE (see above). The etiologic organisms of an epidural abscess that arises from frontal sinusitis, middle-ear infections, or mastoiditis are usually streptococci or anaerobic organisms. Staphylococci or gram-negative organisms are the usual cause of an epidural abscess that develops as a complication of craniotomy or compound skull fracture.

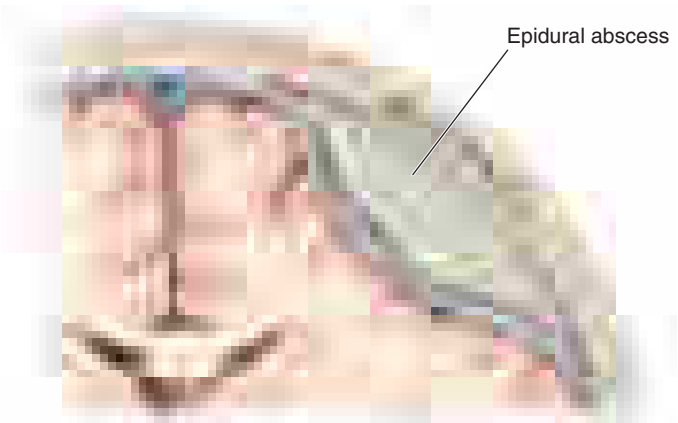

FIGURE 135-4 Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

CLINICAL PRESENTATION

Patients present with fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%). Development of symptoms may be insidious, as the empyema usually enlarges slowly in the confined anatomic space between the dura and the inner table of the skull. Periorbital edema and Pott's puffy tumor, reflecting underlying associated frontal bone osteomyelitis, are present in ~40%. In patients with a recent neurosurgical procedure, wound infection is invariably present, but other symptoms may be subtle and can include altered mental status (45%), fever (35%), and headache (20%). The diagnosis should be considered when fever and headache follow recent head trauma or occur in the setting of frontal sinusitis, mastoiditis, or otitis media.

DIAGNOSIS

Cranial MRI with gadolinium enhancement is the procedure of choice to demonstrate a cranial epidural abscess. The sensitivity of CT is limited by the presence of signal artifacts arising from the bone of the inner skull table. The CT appearance of an epidural empyema is that of a lens or crescent-shaped hypodense extraaxial lesion. On MRI, an epidural empyema appears as a lentiform or crescent-shaped fluid collection that is hyperintense compared to CSF on T2-weighted images. On T1-weighted images, the fluid collection may be either isointense or hypointense compared to brain. Following the administration of gadolinium, there is linear enhancement of the dura on T1-weighted images. In distinction to subdural empyema, signs of mass effect or other parenchymal abnormalities are uncommon.

TREATMENT

Epidural Abscess

Immediate neurosurgical drainage is indicated. Empirical antimicrobial therapy, pending the results of Gram's stain and culture of the purulent material obtained at surgery, should include a combination of a third-generation cephalosporin, vancomycin, and metronidazole **(see Table 133-1).** Ceftazidime or meropenem should be substituted for ceftriaxone or cefotaxime in neurosurgical patients. Metronidazole is not necessary for antianaerobic coverage in patients receiving meropenem. When the organism has been identified, antimicrobial therapy can be modified accordingly. Antibiotics should be continued for 3–6 weeks after surgical drainage. Patients with associated osteomyelitis may require additional therapy.

PROGNOSIS

The mortality rate is <5% in modern series, and full recovery is the rule in most survivors.

SUPPURATIVE THROMBOPHLEBITIS

DEFINITION

Suppurative intracranial thrombophlebitis is septic venous thrombosis of cortical veins and sinuses. This may occur as a complication of bacterial meningitis; SDE; epidural abscess; or infection in the skin of the face, paranasal sinuses, middle ear, or mastoid.

ANATOMY AND PATHOPHYSIOLOGY

The cerebral veins and venous sinuses have no valves; therefore, blood within them can flow in either direction. The superior sagittal sinus is the largest of the venous sinuses **(Fig. 135-5)**. It receives blood from the frontal, parietal, and occipital superior cerebral veins and the diploic veins, which communicate with the meningeal veins. Bacterial meningitis is a common predisposing condition for septic thrombosis of the superior sagittal sinus. The diploic veins, which drain into the superior sagittal sinus, provide a route for the spread of infection from the meninges, especially in cases where there is purulent exudate near areas of the superior sagittal sinus. Infection can also spread to the superior sagittal sinus from nearby SDE or epidural abscess. Dehydration from vomiting, hypercoagulable states, and immunologic abnormalities, including the presence of circulating antiphospholipid antibodies, also contribute to cerebral venous sinus thrombosis. Thrombosis may extend from one sinus to another, and at autopsy, thrombi of different histologic ages can often be detected in several sinuses. Thrombosis of the superior sagittal sinus is often associated with thrombosis of superior cortical veins and small parenchymal hemorrhages.

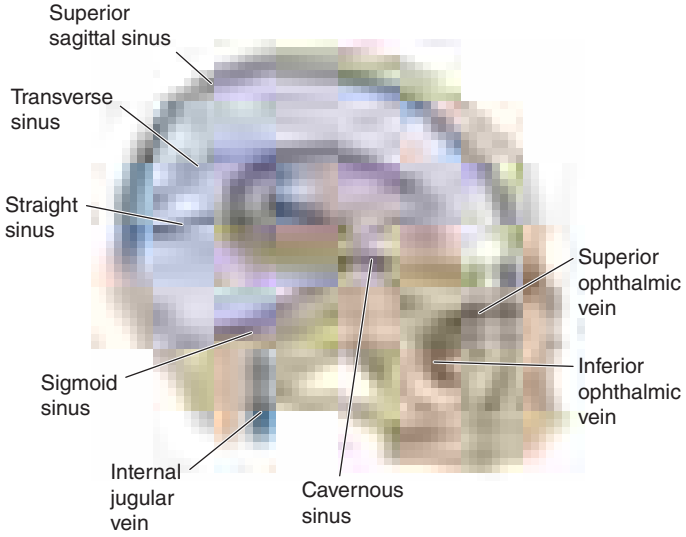

FIGURE 135-5 Anatomy of the cerebral venous sinuses.

The superior sagittal sinus drains into the transverse sinuses (Fig. 135-5). The transverse sinuses also receive venous drainage from small veins from both the middle ear and mastoid cells. The transverse sinus becomes the sigmoid sinus before draining into the internal jugular vein. Septic transverse/sigmoid sinus thrombosis can be a complication of acute and chronic otitis media or mastoiditis. Infection spreads from the mastoid air cells to the transverse sinus via the emissary veins or by direct invasion. The cavernous sinuses are inferior to the superior sagittal sinus at the base of the skull. The cavernous sinuses receive blood from the facial veins via the superior and inferior ophthalmic veins. Bacteria in the facial veins enter the cavernous sinus via these veins. Bacteria in the sphenoid and ethmoid sinuses can spread to the cavernous sinuses via the small emissary veins. The sphenoid and ethmoid sinuses are the most common sites of primary infection resulting in septic cavernous sinus thrombosis.

CLINICAL MANIFESTATIONS

Septic thrombosis of the superior sagittal sinus presents with headache, fever, nausea and vomiting, confusion, and focal or generalized seizures. There may be a rapid development of stupor and coma. Weakness of the lower extremities with bilateral Babinski's signs or hemiparesis is often present. When superior sagittal sinus thrombosis occurs as a complication of bacterial meningitis, nuchal rigidity and Kernig's and Brudzinski's signs may be present.

The oculomotor nerve, the trochlear nerve, the abducens nerve, the ophthalmic and maxillary branches of the trigeminal nerve, and the internal carotid artery all pass through the cavernous sinus **(see Fig. 433-4)**. The symptoms of *septic cavernous sinus thrombosis* are fever, headache, frontal and retroorbital pain, and diplopia. The classic signs are ptosis, proptosis, chemosis, and extraocular dysmotility due to deficits of cranial nerves III, IV, and VI; hyperesthesia of the ophthalmic and maxillary divisions of the fifth cranial nerve and a decreased corneal reflex may be detected. There may be evidence of dilated, tortuous retinal veins and papilledema.

Headache and earache are the most frequent symptoms of *transverse sinus thrombosis*. A transverse sinus thrombosis may also present with otitis media, sixth nerve palsy, and retroorbital or facial pain (*Gradenigo's syndrome*). Sigmoid sinus and internal jugular vein thrombosis may present with neck pain.

DIAGNOSIS

The diagnosis of septic venous sinus thrombosis is suggested by an absent flow void within the affected venous sinus on MRI and confirmed by magnetic resonance venography, CT angiogram, or the venous phase of cerebral angiography. The diagnosis of thrombophlebitis of intracerebral and meningeal veins is suggested by the presence of intracerebral hemorrhage but requires cerebral angiography for definitive diagnosis.

TREATMENT

Suppurative Thrombophlebitis

Septic venous sinus thrombosis is treated with antibiotics, hydration, and removal of infected tissue and thrombus in septic lateral or cavernous sinus thrombosis. The choice of antimicrobial therapy is based on the bacteria responsible for the predisposing or associated condition. Optimal duration of therapy is unknown, but antibiotics are usually continued for 6 weeks or until there is radiographic evidence of resolution of thrombosis. Anticoagulation with dose-adjusted intravenous heparin is recommended for aseptic venous sinus thrombosis and in the treatment of septic venous sinus thrombosis complicating bacterial meningitis in patients who have progressive neurologic deterioration despite antimicrobial therapy and intravenous fluids. The presence of a small intracerebral hemorrhage from septic thrombophlebitis is not an absolute contraindication to heparin therapy. Successful management of aseptic venous sinus thrombosis has been reported with surgical thrombectomy, catheter-directed urokinase therapy, and a combination of

intrathrombus recombinant tissue plasminogen activator (rtPA) and intravenous heparin, but there are not enough data to recommend these therapies in septic venous sinus thrombosis.

FURTHER READING

Baird A et al: Evidence-based guideline: Treatment of parenchymal neurocysticerosis. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 80:1424, 2013.

Garcia HH et al: Clinical symptoms, diagnosis and treatment of neurocysticercosis. Lancet Neurol 13:1202, 2014.

136 Infectious Complications of Bites

Sandeep S. Jubbal, Florencia Pereyra, Lawrence C. Madoff

The skin is an essential component of nonspecific immunity, protecting the host from potential pathogens in the environment. Breaches in this protective barrier thus represent a form of immunocompromise that predisposes the patient to infection. Bites and scratches from animals and humans allow the inoculation of microorganisms past the skin's protective barrier into deeper, susceptible host tissues.

Each year in the United States, millions of animal-bite wounds are sustained. The vast majority are inflicted by pet dogs and cats, which number >100 million; the annual incidence of dog and cat bites has been reported as 300 bites per 100,000 population. Other bite wounds are a consequence of encounters with animals in the wild or in occupational settings. While many of these wounds require minimal or no therapy, a significant number result in infection, which may be life-threatening. The microbiology of bite-wound infections in general reflects the oropharyngeal flora of the biting animal, although organisms from the soil, the skin of the animal and the victim, and the animal's feces may also be involved.

DOG BITES

In the United States, dogs bite >4.7 million people each year and are responsible for 80% of all animal-bite wounds, an estimated 15–20% of which become infected. Each year, 800,000 Americans seek medical attention for dog bites; of those injured, 386,000 require treatment in an emergency department, with >1000 emergency department visits each day and ~30 deaths per year. Most dog bites are provoked and are inflicted by the victim's pet or by a dog known to the victim. These bites are frequently sustained during efforts to break up a dogfight. Children are more likely than adults to sustain canine bites, with the highest incidence of 6 bites per 1000 population among boys 5–9 years old. Victims are more often male than female, and bites most often involve an upper extremity. Among children <4 years old, two-thirds of all these injuries involve the head or neck. Infection typically manifests 8–24 h after the bite as pain at the site of injury with cellulitis accompanied by purulent, sometimes foul-smelling discharge. Septic arthritis and osteomyelitis may develop if a canine tooth penetrates synovium or bone. Systemic manifestations (e.g., fever, lymphadenopathy, and lymphangitis) also may occur. The microbiology of dog-bite wound infections is usually mixed and includes *Pasteurella* species, β-hemolytic streptococci, *Staphylococcus* species (including methicillin-resistant *Staphylococcus aureus* [MRSA] and *Staphylococcus intermedius*), *Neisseria* species (commonly *Neisseria weaveri*, formerly known as CDC group M-5), *Eikenella corrodens*, and *Capnocytophaga canimorsus*. Many wounds also include anaerobic bacteria such as *Actinomyces, Fusobacterium, Prevotella*, and *Porphyromonas* species.

While most infections resulting from dog-bite injuries are localized to the area of injury, many of the microorganisms involved are capable of causing systemic infection, including bacteremia, meningitis, brain abscess, endocarditis, and chorioamnionitis. These infections are particularly likely in hosts with edema or compromised lymphatic drainage in the involved extremity (e.g., after a bite on the arm in a woman who has undergone mastectomy) and in patients who are immunocompromised by medication or disease (e.g., glucocorticoid use, systemic lupus erythematosus, acute leukemia, or hepatic cirrhosis). In addition, dog bites and scratches may result in systemic illnesses such as rabies (Chap. 203) and tetanus (Chap. 147).

Infection with *C. canimorsus* following dog-bite wounds (or licking of preexisting wounds) may result in fulminant sepsis, disseminated intravascular coagulation, and renal failure, particularly in hosts who have impaired hepatic function, who have undergone splenectomy, or who are immunosuppressed. This thin gram-negative rod is difficult to culture on most solid media but grows in a variety of liquid media. It may require up to 14 days of incubation to grow on blood cultures. The bacteria are occasionally seen within polymorphonuclear leukocytes on Wright-stained smears of peripheral blood from septic patients. Tularemia (Chap. 165) also has been reported to follow dog bites.

CAT BITES

Although less common than dog bites, cat bites and scratches result in infection in more than half of all cases. Because the cat's narrow, sharp canine teeth penetrate deeply into tissue, cat bites are more likely than dog bites to cause septic arthritis and osteomyelitis; the development of these conditions is particularly likely when punctures are located over or near a joint, especially in the hand. Women sustain cat bites more frequently than do men. These bites most often involve the hands and arms. Both bites and scratches from cats are prone to infection from organisms in the cat's oropharynx. *Pasteurella multocida*, a normal component of the feline oral flora, is a small gram-negative coccobacillus implicated in the majority of cat-bite wound infections. Like that of dog-bite wound infections, however, the microflora of cat-bite wound infections is usually mixed. Other microorganisms causing infection after cat bites are similar to those causing dog-bite wound infections.

The same risk factors for systemic infection following dog-bite wounds apply to cat-bite wounds. *Pasteurella* infections tend to advance rapidly, often within hours, causing severe inflammation accompanied by purulent drainage with adenitis; *Pasteurella* may also be spread by respiratory droplets from animals, resulting in pneumonia or bacteremia. Like dog-bite wounds, cat-bite wounds may result in the transmission of rabies or in the development of tetanus. Infection with *Bartonella henselae* causes cat-scratch disease (Chap. 167) and is an important late consequence of cat bites and scratches. Tularemia (Chap. 165) also has been reported to follow cat bites. Occasionally, sporotrichosis (Chap. 214) has been associated with scratches or bites by animals, especially domestic cats.

OTHER ANIMAL BITES

Infections have been attributed to bites from many animal species. Often these bites are sustained as a consequence of occupational exposure (farmers, laboratory workers, veterinarians) or recreational exposure (hunters and trappers, wilderness campers, owners of exotic pets). Generally, the microflora of bite wounds reflects the oral flora of the biting animal. Most members of the cat family, including feral cats, harbor *P. multocida*. Bite wounds from aquatic animals such as alligators or piranhas may contain *Aeromonas hydrophila*. Shark, moray eel, and barracuda bites, like other injuries sustained in saltwater, are often associated with infections with marine *Vibrio* species. Venomous snakebites (Chap. 451) result in severe inflammatory responses and tissue necrosis—conditions that render these injuries prone to infection. The snake's oral flora includes many species of aerobes and anaerobes, such as *Pseudomonas aeruginosa, Serratia marcescens, Proteus* species, *Staphylococcus epidermidis, Bacteroides fragilis*, and *Clostridium* species. Bites from nonhuman primates are highly susceptible to infection with pathogens similar to those isolated from human bites (see below). Bites from Old World monkeys (*Macaca*) may also result in the transmission of B virus (*Macacine herpesvirus 1, Herpesvirus simiae, Cercopithecine herpesvirus*), a cause of serious infection of the human central nervous

system. *Actinobacillus lignieresii* has often been reported in infected wounds of humans bitten by horses, pigs, and sheep. Bites of seals, walruses, and polar bears may cause a chronic suppurative infection known as *seal finger*, which is probably due to one or more species of *Mycoplasma* colonizing these animals.

Small rodents, including rats, mice, and gerbils, as well as animals that prey on rodents may transmit *Streptobacillus moniliformis* (a microaerophilic, pleomorphic gram-negative rod) or *Spirillum minor* (a spirochete); these organisms cause a clinical illness known as *rat-bite fever*. The vast majority of cases in the United States are streptobacillary, whereas *Spirillum* infection occurs mainly in Asia.

In the United States, the risk of rodent bites is usually greatest among laboratory workers or inhabitants of rodent-infested dwellings (particularly children). Rat-bite fever is distinguished from acute bite-wound infection by its typical manifestation after the initial wound has healed. Streptobacillary disease follows an incubation period of 3–10 days. Fever, chills, myalgias, headache, and severe migratory arthralgias are usually followed by a maculopapular rash, which characteristically involves the palms and soles and may become confluent or purpuric. Complications include endocarditis, myocarditis, meningitis, pneumonia, and abscesses in many organs. *Haverhill fever* is an *S. moniliformis* infection acquired from contaminated milk or drinking water and has similar manifestations. Streptobacillary rat-bite fever was frequently fatal in the preantibiotic era. The differential diagnosis includes Rocky Mountain spotted fever, Lyme disease, leptospirosis, and secondary syphilis. The diagnosis is made by direct observation of the causative organisms in tissue or blood, by culture of the organisms on enriched media, or by serologic testing with specific agglutinins.

Spirillum infection (referred to in Japan as *sodoku*) causes pain and purple swelling at the site of the initial bite, with associated lymphangitis and regional lymphadenopathy, after an incubation period of 1–4 weeks. The systemic illness includes fever, chills, and headache. The original lesion may eventually progress to an eschar. The infection is diagnosed by direct visualization of the spirochetes in blood or tissue or by animal inoculation.

Finally, NO-1 (CDC nonoxidizer group 1) is a bacterium associated with dog- and cat-bite wounds. Infections in which NO-1 has been isolated have tended to manifest locally (i.e., as abscess and cellulitis). These infections have occurred in healthy persons with no underlying illness and in some instances have progressed from localized to systemic illnesses. The phenotypic characteristics of NO-1 are similar to those of asaccharolytic *Acinetobacter* species; i.e., NO-1 is oxidase-, indole-, and urease-negative. To date, all strains identified have been shown to be susceptible to aminoglycosides, β-lactam antibiotics, tetracyclines, quinolones, and sulfonamides.

HUMAN BITES

Human bites may be self-inflicted; may be sustained by medical personnel caring for patients; or may take place during fights, domestic abuse, or sexual activity. Human-bite wounds become infected more frequently (~10–15% of the time) than do bites inflicted by other animals. These infections reflect the diverse oral microflora of humans, which includes multiple species of aerobic and anaerobic bacteria. Common aerobic isolates include viridans streptococci, *S. aureus, E. corrodens* (which is particularly common in clenched-fist injury; see below), and *Haemophilus influenzae*. Anaerobic species, including *Fusobacterium nucleatum* and *Prevotella, Porphyromonas*, and *Peptostreptococcus* species, are isolated from 50% of wound infections due to human bites; many of these isolates produce β-lactamases. The oral flora of hospitalized and debilitated patients often includes Enterobacteriaceae in addition to the usual organisms. Hepatitis B, hepatitis C, herpes simplex virus infection, syphilis, tuberculosis, actinomycosis, and tetanus have been reported to be transmitted by human bites; it is biologically possible to transmit HIV through human bites, although this event is quite unlikely.

Human bites are categorized as either *occlusional* injuries, which are inflicted by actual biting, or *clenched-fist* injuries, which are sustained when the fist of one individual strikes the teeth of another, causing traumatic laceration of the hand. For several reasons, clenched-fist injuries, which are sometimes referred to as "fight bite" and which are more common than occlusional injuries, result in particularly serious infections. The deep spaces of the hand, including the bones, joints, and tendons, are frequently inoculated with organisms in the course of such injuries. The clenched position of the fist during injury, followed by extension of the hand, may further promote the introduction of bacteria as contaminated tendons retract beneath the skin's surface. Moreover, medical attention is often sought only after frank infection develops.

APPROACH TO THE PATIENT

Animal or Human Bites

A careful history should be elicited, including the type of biting animal, the type of attack (provoked or unprovoked), and the amount of time elapsed since injury. Local and regional public-health authorities should be contacted to determine whether an individual species could be rabid and/or to locate and observe the biting animal when rabies prophylaxis may be indicated **(Chap. 203)**. Suspicious human-bite wounds should provoke careful questioning regarding domestic or child abuse. Details on antibiotic allergies, immunosuppression, splenectomy, liver disease, mastectomy, and immunization history should be obtained. The wound should be inspected carefully for evidence of infection, including redness, exudate, and foul odor. The type of wound (puncture, laceration, or scratch); the depth of penetration; and the possible involvement of joints, tendons, nerves, and bones should be assessed. It is often useful to include a diagram or photograph of the wound in the medical record. In addition, a general physical examination should be conducted and should include an assessment of vital signs as well as an evaluation for evidence of lymphangitis, lymphadenopathy, dermatologic lesions, and functional limitations. Injuries to the hand warrant consultation with a hand surgeon for the assessment of tendon, nerve, and muscular damage. Radiographs should be obtained when bone may have been penetrated or a tooth fragment may be present. Culture and Gram's staining of all infected wounds are essential; anaerobic cultures should be undertaken if abscesses, devitalized tissue, or foul-smelling exudate is present. A small-tipped swab may be used to culture deep punctures or small lacerations. It is also reasonable to culture samples from apparently uninfected wounds due to bites inflicted by animals other than dogs and cats, since the microorganisms causing disease are less predictable in these cases. The white blood cell count should be determined and the blood cultured if systemic infection is suspected.

TREATMENT

Bite-Wound Infections

WOUND MANAGEMENT

Wound closure is controversial in bite injuries. Many authorities prefer not to attempt primary closure of wounds that are or may become infected, choosing instead to irrigate these wounds copiously, debride devitalized tissue, remove foreign bodies, and approximate the wound edges. Delayed primary closure may be undertaken after the risk of infection is over. Small uninfected wounds may be allowed to close by secondary intention. Puncture wounds due to cat bites should be left unsutured because of the high rate at which they become infected. Facial wounds are usually sutured after thorough cleaning and irrigation because of the importance of a good cosmetic result in this area and because anatomic factors such as an excellent blood supply and the absence of dependent edema lessen the risk of infection. In general, wounds >12 h old (for bites to the arm or leg) or >24 h old (for bites to the face) should not be closed primarily and may require prophylactic antibiotics (see below).

ANTIBIOTIC THERAPY

Established Infection Antibiotics should be administered for all established bite-wound infections and should be chosen in light

TABLE 136-1 Management of Wound Infections Following Animal and Human Bites

BITING SPECIES	COMMONLY ISOLATED PATHOGENS	PREFERRED ANTIBIOTIC(S)[a]	ALTERNATIVE IN PENICILLIN-ALLERGIC PATIENT	PROPHYLAXIS ADVISED FOR EARLY UNINFECTED WOUNDS	OTHER CONSIDERATIONS
Dog	*Staphylococcus aureus*, *Pasteurella multocida*, anaerobes, *Capnocytophaga canimorsus*	Amoxicillin/clavulanate (250–500 mg PO tid) or ampicillin/sulbactam (1.5–3.0 g IV q6h)	Clindamycin (150–300 mg PO qid) plus either TMP-SMX (1 DS tablet PO bid) or ciprofloxacin (500 mg PO bid)	Sometimes[b]	Consider rabies prophylaxis.
Cat	*P. multocida*, *S. aureus*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Usually	Consider rabies prophylaxis. Carefully evaluate for joint/bone penetration.
Human, occlusional	Viridans streptococci, *S. aureus*, *Haemophilus influenzae*, anaerobes	Amoxicillin/clavulanate or ampicillin/sulbactam as above	Erythromycin (500 mg PO qid) or a fluoroquinolone	Always	
Human, clenched-fist	As for occlusional, plus *Eikenella corrodens*	Ampicillin/sulbactam as above or imipenem (500 mg q6h)	Cefoxitin[c]	Always	Examine for tendon, nerve, or joint involvement.
Monkey	As for human bite	As for human bite	As for human bite	Always	For macaque monkeys, consider B virus prophylaxis with acyclovir.
Snake	*Pseudomonas aeruginosa*, *Proteus* spp., *Bacteroides fragilis*, *Clostridium* spp.	Ampicillin/sulbactam as above	Clindamycin plus TMP-SMX as above or a fluoroquinolone	Sometimes, especially with venomous snakes	Administer antivenin for venomous snakebite.
Rodent	*Streptobacillus moniliformis*, *Leptospira* spp., *P. multocida*	Penicillin VK (500 mg PO qid)	Doxycycline (100 mg PO bid)	Sometimes	
Aquatic animal (alligator, piranha, shark, moray eel, barracuda)	*Aeromonas hydrophila*, marine *Vibrio* spp. *(Vibrio vulnificus)*	Third-generation cephalosporin (e.g., ceftriaxone, 1 g IV q24h) plus doxycycline (100 mg PO bid)	Clindamycin plus levofloxacin (750 mg PO qd) plus doxycycline	Always	Obtain prompt surgical consultation, as risk for necrotizing infection is high with *Aeromonas* and *Vibrio* spp.

[a]Antibiotic choices should be based on culture data when available. These suggestions for empirical therapy need to be tailored to individual circumstances and local conditions. IV regimens should be used for hospitalized patients. A single IV dose of antibiotics may be given to patients who will be discharged after initial management. [b]Prophylactic antibiotics are suggested for severe or extensive wounds, facial wounds, and crush injuries; when bone or joint may be involved; and when comorbidity is present (see text). [c]May be hazardous in patients with immediate-type hypersensitivity to penicillin.

Abbreviations: DS, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole.

of the most likely potential pathogens, as indicated by the biting species and by Gram's stain and culture results **(Table 136-1)**. For dog and cat bites, antibiotics should be effective against *S. aureus, Pasteurella* species, *C. canimorsus*, streptococci, and oral anaerobes. For human bites, agents with activity against *S. aureus, H. influenzae,* and β-lactamase-positive oral anaerobes should be used. The combination of an extended-spectrum penicillin with a β-lactamase inhibitor (amoxicillin/clavulanic acid, ticarcillin/clavulanic acid, ampicillin/sulbactam) appears to offer the most reliable coverage for these pathogens. Second- and third-generation cephalosporins (cefuroxime, cefoxitin, cefpodoxime) also offer substantial coverage when given in conjunction with a drug that provides anaerobic coverage (clindamycin or metronidazole). The choice of antibiotics for penicillin-allergic patients (particularly those in whom immediate-type hypersensitivity makes the use of cephalosporins hazardous) is more difficult and is based primarily on in vitro sensitivity since data on clinical efficacy are inadequate. The combination of an antibiotic active against gram-positive cocci and anaerobes (such as clindamycin) with trimethoprim-sulfamethoxazole or a fluoroquinolone, which is active against many of the other potential pathogens, would appear reasonable. In vitro data suggest that azithromycin alone provides coverage against most commonly isolated bite-wound pathogens; however, this agent has variable activity against *P. multocida*, *E. corrodens,* and fusobacteria and thus should be avoided unless no alternative agent is available. As MRSA becomes more common in the community and evidence of its transmission between humans and their animal contacts increases, empirical use of agents active against MRSA should be considered in high-risk situations while culture results are awaited.

Antibiotics are generally given for 10–14 days, but the response to therapy must be carefully monitored. Failure to respond should prompt a consideration of diagnostic alternatives and surgical evaluation for possible drainage or debridement. Complications such as osteomyelitis or septic arthritis mandate a longer duration of therapy.

Management of *C. canimorsus* sepsis requires a 2-week course of IV penicillin G (2 million units IV every 4 h) and supportive measures. Alternative agents for the treatment of *C. canimorsus* infection include cephalosporins and fluoroquinolones. Serious infection with *P. multocida* (e.g., pneumonia, sepsis, or meningitis) also should be treated with IV penicillin G. Alternative agents include a second- or third-generation cephalosporin or ciprofloxacin.

Bites by venomous snakes **(Chap. 451)** may not require antibiotic treatment. Because it is often difficult to distinguish signs of infection from tissue damage caused by the envenomation, many authorities continue to recommend treatment directed against the snake's oral flora—i.e., the administration of broadly active agents such as ceftriaxone (1–2 g IV every 12–24 h) or ampicillin/sulbactam (1.5–3.0 g IV every 6 h).

Seal finger appears to respond to doxycycline (100 mg twice daily for a duration guided by the response to therapy).

Presumptive or Prophylactic Therapy The use of antibiotics for patients presenting early (within 8 h) after bite injury is controversial. Although symptomatic infection frequently will not yet have manifested at this point, many early wounds will harbor pathogens, and many will become infected. Studies of antibiotic prophylaxis for wound infections are limited and have often included only small numbers of cases in which various types of wounds have been managed according to various protocols. A meta-analysis of eight randomized trials of prophylactic antibiotics in patients with dog-bite wounds demonstrated a reduction in the rate of infection by 50% with prophylaxis. However, in the absence of sound clinical trials, many clinicians base the decision to treat bite wounds

with empirical antibiotics on the species of the biting animal; the location, severity, and extent of the bite wound; and the existence of comorbid conditions in the host. All human- and monkey-bite wounds should be treated presumptively because of the high rate of infection. Most cat-bite wounds, particularly those involving the hand, should be treated. Other factors favoring treatment for bite wounds include severe injury, as in crush wounds; potential bone or joint involvement; involvement of the hands or genital region; host immunocompromise, including that due to diabetes mellitus, liver disease, or splenectomy; involvement of extremities with underlying venous and/or lymphatic compromise; and prior mastectomy on the side of an involved upper extremity. When prophylactic antibiotics are administered, they are usually given for 3–5 days.

Rabies and Tetanus Prophylaxis Rabies prophylaxis, consisting of both passive administration of rabies immune globulin (with as much of the dose as possible infiltrated into and around the wound) and active immunization with rabies vaccine, should be given in consultation with local and regional public-health authorities for some animal bites and scratches as well as for certain nonbite exposures **(Chap. 203)**. Rabies is endemic in a variety of animals, including dogs and cats in many areas of the world. In the United States, although the majority (90%) of rabid animals reported each year are wild (including raccoons, skunks, foxes, and bats), most people receive rabies prophylaxis because of close contact with domestic animals. Furthermore, more cats than dogs are reported rabid each year. Many local health authorities require the reporting of all animal bites.

A tetanus booster immunization should be given if the patient has undergone primary immunization but has not received a booster dose in the past 5 years. Patients who have not previously completed primary immunization should be immunized and should also receive tetanus immune globulin. Elevation of the site of injury is an important adjunct to antimicrobial therapy. Immobilization of the infected area, especially the hand, also is beneficial.

Hepatitis B Prophylaxis Hepatitis B virus can be transmitted, albeit rarely, by exposure of non-intact skin to blood-free saliva. The mainstay of postexposure prophylaxis is active immunization with hepatitis B vaccine, but, in certain circumstances, hepatitis B immune globulin is recommended in addition to vaccine for added protection **(Chap. 332)**.

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137 Infections Acquired in Health Care Facilities

Robert A. Weinstein

Health care–associated infections affect as many as 1.7 million patients at a cost of ~$10–33 billion and up to 99,000 lives in U.S. hospitals annually. Although efforts to lower infection risks are challenged by numbers of immunocompromised patients, antibiotic-resistant bacteria, and fungal and viral superinfections, a prevailing viewpoint—"zero tolerance"—is that health care–associated infections are avoidable with strict application of evidence-based prevention guidelines **(Table 137-1)**. In fact, rates of most device-related infections—historically, the largest drivers of risk—have fallen steadily over the past few years. Unfortunately, at the same time, antimicrobial-resistant pathogens have risen in number and are estimated to contribute to ~23,000 deaths annually. This chapter reviews health care–associated and device-related infections as well as basic surveillance, prevention, control, and treatment activities.

ORGANIZATION, RESPONSIBILITIES, AND SCRUTINY OF HEALTH CARE–ASSOCIATED INFECTION PROGRAMS

The standards of the Joint Commission require accredited hospitals to have active programs for surveillance, prevention, and control of nosocomial infections. Concerns over patient safety have led to federal legislation that prevents U.S. hospitals from upgrading Medicare charges to pay for hospital costs resulting from at least 14 specific nosocomial events, including some health care–associated infections (*www.cms.gov/hospitalacqcond*), and have prompted public reporting on processes of patient care (e.g., timely administration and appropriateness of perioperative antibiotic prophylaxis) and patient outcomes (e.g., surgical wound infection rates). Recommendations for ensuring a culture of safety continue to evolve (e.g., *www.npsf.org/free-from-harm*), but neither the carrot (pay-for-performance) nor the stick (nonpayment for preventable infections) appears to have had a major impact on infection rates. The effect of public attention may be more positive (*https://www.cdc.gov/hai/pdfs/stateplans/factsheets/us.pdf*) **(Fig. 137-1)**; the U.S. Department of Health and Human Services has updated its interagency Action Plan to Prevent Health Care–Associated Infections, with a good-progress midpoint 2014 evaluation and targets for the year 2020 **(Table 137-2)**.

SURVEILLANCE

Traditionally, infection preventionists have surveyed inpatients for infections acquired in hospitals (defined as those neither present nor incubating at the time of admission). However, many infection-control programs have replaced manual surveillance of microbiology laboratory results and "shoe-leather" epidemiology on nursing wards with computerized algorithm-driven electronic surveillance of hospital databases (e.g., vascular catheter or surgical wound infections inferred from clinical microbiology data). Such approaches provide "house-wide" surveillance, remove observer bias, and display the potential power of newer computer techniques like machine learning algorithms. Although infection surveillance in many nursing homes and some long-term acute-care hospitals (LTACHs) is still in its formative stage, the role of these facilities in the transmission of antimicrobial-resistant pathogens puts a premium on their increased attention to surveillance and control.

In the spirit of "what is measured improves," most states require public reporting of processes for prevention of health care–associated infection and/or patient outcomes. As a result, the surveillance pendulum

TABLE 137-1 Sources of Infection Control Guidelines and Oversight

ORGANIZATION	ROLE	MAJOR CONSTITUENTS	WEBSITE
Joint Commission	Regulatory	Hospitals, long-term-care facilities, laboratories	*www.jointcommission.org*
CAP	Regulatory	Laboratories	*www.cap.org*
OSHA	Regulatory	Workers	*www.osha.gov*
CMS	Regulatory	Medicare/Medicaid providers	*www.cms.hhs.gov*
PQRI	Regulatory and advisory	Eligible professionals	*www.cms.hhs.gov/pqri/*
HHS Action Plan	Advisory and national action plan	Health care and infection prevention personnel	*www.health.gov/hcq/prevent-hai.asp; https://health.gov/hcq/pdfs/hai-action-plan-acute-care-hospitals.pdf*
CDC			
DHQP	Advisory	Health care facilities and personnel	*www.cdc.gov/ncezid/dhqp/*
NHSN	Surveillance	Health care facilities and personnel	*https://www.cdc.gov/nhsn/index.html*
HICPAC	Advisory	Health care facilities and personnel	*www.cdc.gov/hicpac/*
NIOSH	Advisory	Workers	*www.cdc.gov/niosh/*
AHRQ	Advisory	Broad (e.g., health care personnel)	*www.ahrq.gov; https://www.ahrq.gov/research/data/hcup/index.html*
NQF	Advisory	Broad (e.g., health care personnel)	*www.qualityforum.org*
National Academies	Advisory	Broad (e.g., health care personnel)	*www.nationalacademies.org*
Federal Influenza Planning	Advisory	Health care and public health personnel	*www.flu.gov/planning-preparedness/hospital*
Trust for America's Health	Advisory	Broad (e.g., the public)	*www.healthyamericans.org*
PACCARB	Advisory	Health care and public health personnel	*www.hhs.gov/ash/advisory-committees/paccarb*
National Action Plan on CARB	Action plan	Health care and public health personnel	*www.hhs.gov/ash/advisory-committees/paccarb/working-groups/national-action-plan*
CSTE	Advisory and professional society	Public health personnel	*www.cste.org*
IDSA	Professional society	Infectious disease physicians/ researchers	*www.idsociety.org*
SHEA	Professional society	Health care epidemiologists	*www.shea-online.org*
HIS	Professional society	Health care epidemiologists	*www.his.org.uk*
APIC	Professional society	Infection preventionists	*www.apic.org*
BSAC	Professional society	Medical microbiologists	*www.bsac.org.uk*
MedQIC	Quality improvement	Broad (e.g., health care personnel)	*www.qualitynet.org*
IHI	Quality improvement	Broad (e.g., health care personnel)	*www.ihi.org*
Leapfrog Group	Quality improvement	Broad (payers, consumers, employers, and health care personnel)	*www.leapfroggroup.org*
NSQIP	Quality improvement	Surgery services	*www.facs.org/quality-programs/acs-nsqip*

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; APIC, Association for Professionals in Infection Control and Epidemiology; BSAC, British Society for Antimicrobial Chemotherapy; CAP, College of American Pathologists; CARB, combating antibiotic-resistant bacteria; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare & Medicaid Services; CSTE, Council of State and Territorial Epidemiologists; DHQP, Division of Healthcare Quality Promotion; HHS, Health and Human Services; HICPAC, Healthcare Infection Control Practices Advisory Committee; HIS, Hospital Infection Society; IDSA, Infectious Diseases Society of America; IHI, Institute for Healthcare Improvement; IOM, Institute of Medicine; MedQIC, Medicare Quality Improvement Community; NHSN, National Healthcare Safety Network; NIOSH, National Institute for Occupational Safety and Health; NQF, National Quality Forum; NSQIP, National Surgical Quality Improvement Program; OSHA, Occupational Safety & Health Administration; PACCARB, Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria; PQRI, Physician Quality Reporting Initiative; SHEA, Society for Healthcare Epidemiology of America.

is swinging back to use of "house-wide" surveillance, facilitated by computerized surveillance systems, and many states now require that hospitals use the Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN) reporting system to provide uniform definitions and to facilitate transmission of data. Increasing reliance on the NHSN by states to facilitate public reporting has led to participation by >20,000 facilities (~5000 of the ~5700 acute-care hospitals in the United States, ~540 LTACHs, ~1340 inpatient rehabilitation facilities, ~6800 outpatient dialysis facilities, ~4800 ambulatory surgery centers, and ~1900 long-term-care facilities). This level of participation provides a nationwide view of health care–associated infections and potential access to national rates of antimicrobial use and resistance.

Results of surveillance are expressed as rates, qualified when possible by duration of risk, site of infection, patient population, and exposure to risk factors. To account for some of these variables, the CDC now uses a standardized infection ratio (SIR; *www.cdc.gov/hai/national-annual-sir/*) as part of NHSN rate reporting. Meaningful denominators for infection rates include the number of patients exposed to a specific risk or the number of intervention days (e.g., 1000 patient-days on a ventilator). As use of invasive devices such as indwelling bladder catheters has purposely been decreased, the denominators have become smaller, but patients who still require such devices often are at intrinsically higher risk (potential numerators)—a situation that may paradoxically increase rates when device-days account for the denominator. Temporal trends in rates should be reviewed, and rates should be compared with regional and national benchmarks that incorporate the SIR. Interhospital comparisons still may be misleading because of the wide range in risk factors and severity of underlying illnesses. Process measures (e.g., adherence to hand hygiene) usually do not require risk adjustment, and major morbidity and cost outcome measures (e.g., cardiac surgery wound-infection rates) can identify hospitals with outlier infection rates (e.g., in the top deciles) for further evaluation. Most importantly, temporal analysis of a hospital's infection rates—comparison to self over time—can help to determine whether control measures are succeeding and where increased efforts should be focused.

FIGURE 137-1 Progress in control of selected common health care–associated infections in U.S. acute-care hospitals.

EPIDEMIOLOGIC BASIS AND GENERAL MEASURES FOR PREVENTION AND CONTROL

Nosocomial infections follow basic epidemiologic patterns that can help to direct prevention and control measures. Nosocomial pathogens have reservoirs, are transmitted by largely predictable routes, and require susceptible hosts. Reservoirs and sources exist in the inanimate environment (e.g., residual *Clostridium difficile* spores on frequently touched surfaces in patients' rooms) and in the animate environment (e.g., infected or colonized patients and hospital visitors). The mode of transmission usually is either cross-infection (e.g., indirect spread of pathogens from one patient to another on the inadequately cleaned hands of hospital personnel) or autoinoculation (e.g., aspiration of oropharyngeal flora into the lungs along an endotracheal tube). Occasionally, pathogens (e.g., group A streptococci and many respiratory viruses) are spread from person to person via large infectious droplets released by coughing or sneezing. Much less common—but often devastating in terms of epidemic risk—is true airborne spread of small or droplet nuclei (as in nosocomial chickenpox) or common-source spread (e.g., by contaminated IV fluids). Factors that increase host susceptibility include diabetes, renal insufficiency, and other underlying

TABLE 137-2 Summary of Progress Toward the National 2020 Targets for Elimination of Health Care–Associated Infections (U.S. Department of Health and Human Services) and Midpoint Evaluation

METRIC (SOURCE)	ORIGINAL TARGET FOR 2013[a] (FROM 2009 BASELINE)	PROGRESS MADE BY 2014	2020 TARGET (FROM 2015 BASELINE)
Central line–associated bloodstream infections (NHSN)	50% reduction	50% reduction	50% reduction
Catheter-associated urinary tract infections (NHSN)	25% reduction	No change	25% reduction
Invasive MRSA infections (NHSN)	50% reduction	36% reduction	50% reduction
Facility-onset MRSA infections (NHSN)	25% reduction	13% reduction	50% reduction
Clostridium difficile infections (NHSN)	30% reduction	8% reduction	30% reduction
Surgical-site infections (NHSN)	25% reduction	18% reduction	30% reduction
Clostridium difficile hospitalizations (HCUP)	30% reduction	18% reduction	30% reduction

[a]Examples of changes as of 2013: Catheter-related bloodstream infections decreased to ~1.7/1000 catheter-days; *C. difficile* infections increased to ~11.2 cases/10,000 discharges; catheter-related urinary tract infections decreased to ~3.1/1000 catheter-days; and hospital-onset MRSA invasive infections decreased to ~4.5/100,000 persons.

Abbreviations: HCUP, Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project; MRSA, methicillin-resistant *Staphylococcus aureus*; NHSN, National Healthcare Safety Network (Centers for Disease Control and Prevention).

Source: Adapted from *www.health.gov/hcq/prevent-hai-measures.asp* (last accessed January 31, 2017).

conditions; extremes of age; abnormalities of innate defense (e.g., due to genetic polymorphisms; see Chap. 456); and medical–surgical interventions that compromise host defenses.

Hospitals' infection-control programs must determine general and specific control measures. Given the prominence of cross-infection, hand hygiene is cited traditionally as the most important preventive measure. Health care workers' rates of adherence to hand-hygiene recommendations are abysmally low (often <50%). Reasons cited include inconvenience, time pressures, and skin damage from frequent washing. Sinkless alcohol rubs are quick and highly effective and may improve hand condition since they contain emollients and allow the retention of natural protective oils that would be removed with repeated rinsing. Use of alcohol hand rubs between patient contacts is recommended for all health care workers except when hands are visibly soiled or after care of a patient who is part of a health care facility outbreak of infection with *C. difficile*, whose spores resist killing by alcohol and require mechanical removal. In these cases, washing with soap and running water is recommended. A number of innovative electronic monitoring systems have been developed to track hand-hygiene adherence and to provide real-time feedback; although this approach is exciting, sustained improvements in rates remain to be seen.

NOSOCOMIAL AND DEVICE-RELATED INFECTIONS

The percentage of nosocomial infections that is due to invasive devices—25–50%—has fallen toward the lower end of that range in recent years; this decline reflects the marked improvements in the use and design of such devices. Intensive education, bundling of evidence-based interventions (Table 137-3), and use of checklists to facilitate adherence have reduced infection rates (Table 137-2), largely through improved asepsis in handling and earlier removal of invasive devices. This progress demonstrates both the effectiveness of infection-control programs and the need to focus current surveillance and interventions on control of the other 50–75% of health care–associated infections.

URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) account for ~14% of nosocomial infections; up to 3% of bacteriuric patients develop bacteremia. Although UTIs contribute marginally to prolongation of hospital stay and may have an attributable cost in the range of only $900, these infections are sources for spread of antibiotic-resistant bacteria. Most nosocomial UTIs are associated with preceding instrumentation or indwelling bladder catheters, which create a 3–7% risk of infection each day. UTIs generally are caused by pathogens that spread up the periurethral space from the patient's perineum or gastrointestinal tract—the most common pathogenesis in women—or via intraluminal contamination of urinary catheters, usually due to cross-infection by caregivers who are emptying drainage bags. Pathogens come occasionally from inadequately disinfected equipment and rarely from contaminated supplies.

A U.S. national demonstration project has shown that, with organized control programs, rates of catheter use and UTI can be reduced. Hospitals should monitor performance measures (Table 137-3). Prompts to clinicians to assess a patient's need for continued use of an indwelling bladder catheter can improve removal rates and lessen the risk of UTI. Guidelines for managing postoperative urinary retention (e.g., with bladder scanners) may limit use or duration of catheterization. Other prevention strategies have included the use of topical meatal antimicrobial agents, drainage bag disinfectants, and anti-infective catheters. None of the latter three measures is considered routine.

Irrigation of catheters, with or without antimicrobial agents, may actually increase the risk of infection. A condom catheter for men without bladder obstruction may be more acceptable than an indwelling catheter and may lessen the risk of UTI if maintained carefully. The role of suprapubic catheters in preventing infection is not well defined.

Treatment of UTIs is based on the results of quantitative urine cultures (Chap. 130). The most common pathogens are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and *Candida*. Several caveats apply in the treatment of institutionally acquired infection. First, in patients with chronic indwelling bladder catheters, especially those in long-term-care facilities, the catheter flora—microorganisms living on encrustations within the catheter lumen—may differ from actual urinary tract pathogens. Therefore, for suspected UTI in the setting of chronic catheterization (especially in women), it is useful to replace the bladder catheter and to obtain a freshly voided urine specimen. Second, as in all nosocomial infections, at the time treatment is initiated on the basis of a positive culture, it is useful to repeat the culture to verify the persistence of infection. Third, the frequency with which UTIs occur may lead to the erroneous assumption that the urinary tract alone is the source of infection in a febrile hospitalized patient. Fourth, recovery of *Staphylococcus aureus* from urine cultures may result from hematogenous seeding and indicate an occult systemic infection. Finally, although *Candida* is now the most common pathogen in nosocomial UTIs among patients on intensive care units (ICUs), treatment of candiduria is often unsuccessful and is recommended only when there is upper-pole or bladder-wall invasion, obstruction, neutropenia, or immunosuppression.

TABLE 137-3 Examples of Selected Components of Evidence-Based Bundled Interventions to Prevent Common Health Care–Associated Infections and Other Adverse Events[a]

Prevention of Central Venous Catheter Infections
Catheter insertion bundle
• Educate personnel about catheter insertion and care.
• Use chlorhexidine to prepare the insertion site.
• Use maximal barrier precautions and asepsis during catheter insertion.
• Consolidate insertion supplies (e.g., in an insertion kit or cart).
• Use a checklist to enhance adherence to the insertion bundle.
• Empower nurses to halt insertion if asepsis is breached.
Catheter maintenance bundle
• Cleanse patients daily with chlorhexidine.
• Maintain clean, dry dressings.
• Enforce hand hygiene among health care workers.
Ask daily: Is the catheter needed? Remove catheter if not needed or used.
Prevention of Ventilator-Associated Events
• Avoid mechanical ventilation whenever possible.
• Elevate head of bed to 30–45°.
• Decontaminate oropharynx regularly with chlorhexidine (controversial).
• Give "sedation vacation" and assess readiness to extubate daily.
• Use deep-vein thrombosis prophylaxis (unless contraindicated).
Prevention of Surgical-Site Infections
• Choose a surgeon wisely.
• Administer prophylactic antibiotics within 1 h before surgery; discontinue within 24 h.
• Limit any hair removal to the time of surgery; use clippers or do not remove hair at all.
• Prepare surgical site with chlorhexidine-alcohol.
Prevention of Urinary Tract Infections
• Place bladder catheters only when absolutely needed (e.g., to relieve obstruction), not solely for the provider's convenience.
• Use aseptic equipment and technique for catheter insertion and urinary tract instrumentation.
• Minimize manipulation or opening of drainage systems.
• Ask daily: Is the bladder catheter needed? Remove catheter if not needed.
Prevention of Pathogen Cross-Transmission
• Cleanse hands with alcohol hand rub before and after all contacts with patients or their environments.

[a]See text for additional interventions to prevent device- and procedure-associated infections; checklists and personnel education have been recommended as management tools for each of the prevention bundles.

Source: Adapted from information presented at the following websites: *www.cdc.gov/hicpac/pubs.html; www.cdc.gov/HAI/index.html; www.ihi.org*.

PNEUMONIA

Pneumonia accounts for ~24% of nosocomial infections; ventilator-associated pneumonia (VAP) occurs in ~10% of patients on ventilators, and these infections are reported as responsible for 12–14 extra hospital days and ~$40,000 in extra costs per episode. Most cases of bacterial nosocomial pneumonia are caused by aspiration of endogenous or hospital-acquired oropharyngeal (and occasionally gastric) flora. Nosocomial pneumonias have been associated with more deaths than have infections at any other body site. However, attributable mortality rates suggest that the risk of dying from nosocomial pneumonia is affected greatly by other factors, including comorbidities, inadequate antibiotic treatment, and the involvement of specific pathogens (particularly *Pseudomonas aeruginosa* or *Acinetobacter*). Surveillance and accurate diagnosis of pneumonia have been problematic in hospitals because many patients, especially those in the ICU, have abnormal chest roentgenographs, fever, and leukocytosis potentially attributable to multiple causes. This diagnostic uncertainty has led to questions about the reliability of surveillance data and a refocus from VAP to ventilator-associated events (VAEs), conditions, and complications, for which worsening physiologic parameters, such as oxygenation, are key metrics. VAEs occur in as many as 5–10% of patients using mechanical ventilators.

There is increasing interest in health care–associated pneumonia in patients who are on general medical and surgical wards and are not receiving mechanical ventilation. Viral pneumonias, which are particularly important in pediatric and immunocompromised patients, are discussed in the virology section and in **Chap. 121**.

Risk factors for nosocomial pneumonia include those events that increase colonization by potential pathogens (e.g., prior antimicrobial therapy, contaminated ventilator circuits or equipment, or decreased gastric acidity); those that facilitate aspiration of oropharyngeal contents into the lower respiratory tract (e.g., intubation, decreased levels of consciousness, or presence of a nasogastric tube); and those that reduce host defense mechanisms in the lung and permit overgrowth of aspirated pathogens (e.g., chronic obstructive pulmonary disease or upper abdominal surgery).

Control measures for pneumonia (Table 137-3) are aimed at frequent testing of readiness for extubation, which also can shorten ICU lengths of stay; remediation of risk factors in patient care (e.g., minimizing aspiration-prone supine positioning); and aseptic care of respirator equipment. Although the benefits of selective decontamination of the oropharynx and gut with nonabsorbable antimicrobial agents—a practice avoided in the United States because of concerns about antibiotic resistance—have been controversial, a randomized multicenter Dutch trial demonstrated lowered ICU mortality rates among patients on mechanical ventilation who underwent oropharyngeal decontamination.

Among the logical preventive measures that require further investigation are placement of endotracheal tubes that provide channels for subglottic drainage of secretions, which has been associated with reduced infection risks during short-term postoperative use, and noninvasive mechanical ventilation whenever feasible. It is noteworthy that reducing the rate of VAP often has not reduced overall ICU mortality; this fact suggests inadequacies of surveillance and indicates that this infection at times is a marker for patients with an otherwise-heightened risk of death.

The most likely pathogens for nosocomial pneumonia and treatment options are discussed in **Chap. 121**. Several considerations regarding diagnosis and treatment are worth emphasizing. First, clinical criteria for diagnosis (e.g., fever, leukocytosis, development of purulent secretions, new or changing radiographic infiltrates, and changes in oxygen requirement or ventilator settings) have high sensitivity but relatively low specificity. These criteria are useful for selecting patients for bronchoscopic or nonbronchoscopic procedures that yield lower respiratory tract samples protected from upper-tract contamination; quantitative cultures of such specimens have diagnostic sensitivities in the range of 80%. Second, early-onset nosocomial pneumonia, which manifests within the first 4 days of hospitalization, is most often caused by community-acquired pathogens such as *Streptococcus pneumoniae* and *Haemophilus* species, although some studies have challenged this view. Late-onset pneumonias most commonly are due to *S. aureus*, *P. aeruginosa*, *Enterobacter* species, *Klebsiella pneumoniae*, or *Acinetobacter*. Third, one multicenter study suggested that 8 days is an appropriate duration of therapy for nosocomial pneumonia and lessened emergence of resistant pathogens. Fourth, a controversial study of health care–associated pneumonia suggested that therapy based on guidelines from professional societies did not improve patient outcomes. Finally, in febrile patients (particularly those who have tubes inserted through the nares), occult bacterial sinusitis and otitis media should be considered.

SURGICAL WOUND INFECTIONS

Wound infections occur in 280,000 or more patients each year, account for ~24% of nosocomial infections, contribute up to 11 extra postoperative hospital days, and result in $3000–29,000 in extra costs, depending on the operative procedure and pathogen(s). The average wound infection has an incubation period of 5–7 days—longer than many postoperative stays. For this reason and because many procedures are now performed on an outpatient basis, the incidence of wound infections has become more difficult to assess. These infections usually are caused by the patient's endogenous or hospital-acquired skin and mucosal flora and occasionally are due to airborne spread of skin squames that may be shed into the wound from members of the operating-room team. True airborne spread of infection through droplet nuclei is rare in operating rooms unless there is a disseminator (e.g., of group A streptococci or staphylococci) among the staff. In general, the common risks for postoperative wound infection are related to the surgeon's technical skill, the patient's underlying conditions (e.g., diabetes mellitus, obesity) or advanced age, and inappropriate timing of antibiotic prophylaxis. Additional risks include the presence of drains, prolonged preoperative hospital stays, shaving of operative sites by razor the day before surgery, long duration of surgery, and infection at remote sites (e.g., untreated UTI).

The substantial global morbidity and costs associated with these infections have led to international guidelines (*http://www.who.int/gpsc/ssi-guidelines/en/*) in addition to existing national prevention programs and recommendations for bundling of preventive measures (Table 137-3). Other measures include attention to technical surgical issues (e.g., avoiding open or prophylactic drains), operating-room asepsis, and preoperative therapy for active infection. Reporting surveillance results to surgeons has been associated with reductions in infection rates. Preoperative administration of intranasal mupirocin to patients colonized with *S. aureus*, preoperative antiseptic bathing, intra- and postoperative oxygen supplementation, and attention to patients' blood glucose levels and body temperature have been controversial because of conflicting study results, but evidence seems mostly to favor these interventions.

The process of diagnosing and treating wound infections begins with a careful assessment of the surgical site. Diagnosis of infections of prosthetic devices, such as orthopedic implants, may be complicated when pathogens are cloistered in prosthesis-adherent biofilms; cultures of sonicates from explanted prosthetic joints have been more sensitive.

The most common pathogens in postoperative wound infections are *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria. In rapidly progressing postoperative infections manifesting within 24–48 h of a surgical procedure, the level of suspicion regarding group A streptococcal or clostridial infection **(Chaps. 143 and 149)** should be high. Treatment of postoperative wound infections requires adequate source control—i.e., drainage or surgical excision of infected or necrotic material—and antibiotic therapy aimed at the most likely or laboratory-confirmed pathogens.

INFECTIONS RELATED TO VASCULAR ACCESS AND MONITORING

Intravascular device–related bacteremias cause ~10–15% of nosocomial infections; central vascular catheters (CVCs) account for most of these bloodstream infections, although peripheral catheters may be under-appreciated as a source of nosocomial bacteremia. National estimates have indicated that ~72,000 primary bloodstream infections

occur in the United States each year. CVC infections have had estimated attributable mortality rates of 12–25%, an excess length of hospital stay of 7–15 days, and an estimated cost of $31,000–65,000 per episode; one-third to one-half of these episodes occurred in ICUs. However, infection rates have dropped steadily (Table 137-2) since the publication of guidelines by the Healthcare Infection Control Practices Advisory Committee (HICPAC) in 2002. With increasing care of seriously ill patients in the community, vascular catheter–associated bloodstream infections acquired in outpatient settings are becoming more frequent. Broader surveillance for infections—outside ICUs and even outside hospitals—is more routine.

Catheter-related bloodstream infections derive largely from the cutaneous microflora of the insertion site, with pathogens migrating extraluminally to the catheter tip, usually during the first week after insertion—a risk that has been lessened greatly by use of bundled catheter-insertion guidelines. In addition, contamination of the hubs of CVCs or of the ports of needle-less systems may lead to intraluminal infection over longer periods, particularly with surgically implanted or cuffed catheters. Intrinsic (during the manufacturing process) or extrinsic (on-site in a health care facility) contamination of infusate, although rare, is the most common cause of epidemic device-related bloodstream infection. The most common pathogens isolated from vascular device–associated bacteremias include coagulase-negative staphylococci, *S. aureus* (with ≥50% of U.S. isolates resistant to methicillin), enterococci, nosocomial gram-negative bacilli, and *Candida*. Many pathogens, especially staphylococci, produce extracellular polysaccharide biofilms that facilitate attachment to catheters and provide sanctuary from antimicrobial agents.

Evidence-based bundles of control measures (Table 137-3) have been strikingly effective, eliminating almost all CVC-associated infections in some ICUs. In a systematic review prompted by the global problem of CVC-associated infections in ICUs, prevention bundles were shown to be effective in low-income and middle-income, as well as in high-income, countries. Additional control measures for infections associated with vascular access include use of a chlorhexidine-impregnated patch at the skin-catheter junction; daily bathing of ICU patients with chlorhexidine; application of semitransparent access-site dressings (for ease of bathing and site inspection and protection of the site from secretions); avoidance of the femoral site for catheterization because of a higher risk of infection (most likely related to the density of the skin flora); rotation of peripheral catheters—an under-recognized cause of staphylococcal bacteremia—to a new site at specified intervals (e.g., every 72–96 h) rather than as clinically indicated (a controversial recommendation that may be facilitated by use of an IV therapy team); and use of aseptic technique when accessing pressure transducers or other vascular ports.

Unresolved issues include the role of gut translocation rather than vascular-access sites as a cause of primary bacteremia in immunocompromised patients and the implications for surveillance definitions; the best frequency for rotation of CVC sites (given that guidewire-assisted catheter changes at the same site do not lessen and can even increase infection risk); the relative risk posed by peripherally inserted central catheters (PICC lines); and the risk–benefit of prophylactic use of vancomycin, alcohol, or other solutions as catheter "locks"—i.e., concentrated anti-infective solutions instilled into the catheter lumen—for high-risk patients.

Vascular device–related infection is suspected on the basis of the appearance of the catheter site or the presence of fever or bacteremia without another source in patients with vascular catheters. The diagnosis is confirmed by the recovery of the same species of microorganism from peripheral-blood cultures (preferably two samples drawn from peripheral veins by separate venipunctures) and from semiquantitative or quantitative cultures of the vascular catheter tip. Potential complications of drawing cultures from the CVC for diagnostic purposes include false-positive results (e.g., due to catheter hub contamination) and increased risk of CVC infection as a result of interrupting a closed system. When infusion-related sepsis is considered (e.g., because of the abrupt onset of fever or shock temporally related to infusion therapy), a sample of the infusate or blood product should be retained for culture.

Therapy for vascular access–related infection is directed at the pathogen recovered from the blood and/or infected site. Important considerations in treatment are the need for an echocardiogram (to evaluate the patient for endocarditis), the duration of therapy, and the need to remove potentially infected catheters. In one report, approximately one-fourth of patients with intravascular catheter–associated *S. aureus* bacteremia who were studied by transesophageal echocardiography had evidence of endocarditis; this test may be useful in determining the appropriate duration of treatment.

Detailed consensus guidelines for the management of intravascular catheter–related infections have been published and recommend catheter removal in most cases of bacteremia or fungemia due to nontunneled CVCs. When attempting to salvage a potentially infected catheter, some clinicians use the "antibiotic lock" technique, which may facilitate penetration of infected biofilms, in addition to systemic antimicrobial therapy (see *www.idsociety.org/Other_Guidelines/*).

ISOLATION TECHNIQUES

Written policies for the isolation of infectious patients are standard for infection-control programs. The CDC has basic isolation guidelines for all components of health care, including acute-care hospitals and long-term, ambulatory, and home-care settings (see *www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf*), as well as recommendations for the control of multidrug-resistant organisms.

Standard precautions are designed for the care of all patients in hospitals and aim to reduce the risk of transmission of microorganisms from both recognized and unrecognized sources. These precautions include gloving and hand cleansing for potential contact with (1) blood; (2) all other body fluids, secretions, and excretions, whether or not they contain visible blood; (3) nonintact skin; and (4) mucous membranes. Depending on exposure risks, standard precautions also include use of masks, eye protection, and gowns.

Precautions for the care of patients with potentially contagious clinical syndromes (e.g., acute diarrhea) or with suspected or diagnosed colonization or infection by transmissible pathogens are based on probable routes of transmission: *airborne*, *droplet*, or *contact*, for which personnel don, at a minimum, N95 respirators, surgical face masks, or glove and gown, respectively. Sets of precautions may be combined for diseases that have more than one route of transmission (e.g., contact and airborne isolation for varicella).

Some prevalent antibiotic-resistant pathogens, particularly those that colonize the gastrointestinal tract (e.g., vancomycin-resistant enterococci [VRE] and even multidrug-resistant gram-negative bacilli such as strains of *K. pneumoniae* and other Enterobacteriaceae that produce carbapenemases [carbapenem-resistant Enterobacteriaceae, or CRE]), may be present on *intact* skin of patients in hospitals (the "fecal patina"). This issue has led some experts to recommend gloving for all contact with patients who are acutely ill and/or in high-risk units, such as ICUs or LTACHs, and daily bathing of all ICU and LTACH patients with chlorhexidine to remove this veneer of antibiotic-resistant bacteria. Wearing gloves does not replace the need for hand hygiene because hands sometimes (in up to 20% of interactions) become contaminated during wearing or removal of gloves. To further lessen the risk of self-contamination, some personnel shun ties and long-sleeves, a practice that is understandable although not scientifically supported as a means of reducing the spread of resistant bacteria.

EPIDEMIC AND EMERGING PROBLEMS

Full-blown epidemics probably account for <5% of nosocomial infections, but mini-clusters of a few infections that result from time-limited gaps in asepsis may be more common. The investigation and control of nosocomial epidemics require that infection control personnel (1) develop a case definition, (2) confirm that an outbreak really exists (since apparent epidemics may actually be pseudo-outbreaks due to surveillance or laboratory artifacts), (3) review aseptic practices and disinfectant use, (4) determine the extent of the outbreak, (5) perform an epidemiologic investigation, which may require a case–control study to determine sources and modes of transmission, (6) work closely with microbiology personnel to culture for common sources or

personnel carriers as appropriate and to provide molecular typing—by pulsed-field gel electrophoresis (PFGE) or whole-genome sequencing (WGS)—of epidemiologically important isolates, and (7) heighten surveillance to judge the effect of control measures. Control measures generally include reinforcing routine aseptic practices and hand hygiene, ensuring appropriate isolation of cases (and instituting cohort isolation and nursing if needed), and implementing further controls on the basis of the investigation's findings. Examples of some emerging and potential epidemic problems follow.

VIRAL RESPIRATORY INFECTIONS: PANDEMIC INFLUENZA

Infections caused by the severe acute respiratory syndrome (SARS)–associated coronavirus challenged health care systems globally in 2003 **(Chap. 194)**, and in 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) emerged as a more geographically localized problem **(Chap. 194)**. For SARS, basic infection-control measures helped to keep the worldwide case and death counts at ~8000 and ~800, respectively. The epidemiology of SARS—spread largely in households once patients were ill or in hospitals—contrasts markedly with that of influenza **(Chap. 195)**, which is often contagious a day before symptom onset; can spread rapidly in the community among nonimmune persons; and, even in its seasonal variety, kills as many as 35,000 persons in the United States each year.

Control of seasonal influenza has depended on (1) the use of effective vaccines, with increasingly broad evidence-based recommendations for vaccination of children, the general public, and health care workers; (2) the use of antiviral medications for early treatment and for prophylaxis as part of outbreak control, especially for high-risk patients and in high-risk settings like nursing homes or hospitals; and (3) infection control (surveillance and droplet precautions) for symptomatic patients. Controversial infection-control issues have been the questionable role of airborne spread of influenza and the historical embarrassingly low rates of vaccination among health care workers, which have now markedly improved, in part as a result of mandated vaccination policies in many hospitals.

With the occurrence of localized outbreaks of avian influenza (due to H5N1 and other strains) in Asia over the past few years, concerns about potential pandemic influenza led to (1) recommendations for universal respiratory hygiene and cough etiquette (basically, "cover your cough"), as described and promoted in the CDC's *Guideline for Isolation Precautions*, and for source containment (e.g., use of face masks and spatial separation) for outpatients with potentially infectious respiratory illnesses; (2) re-examinations of the value in the 1918–1919 influenza pandemic of nonpharmacologic interventions, such as social distancing (e.g., closing of schools and community venues); and (3) debate about the level of respiratory protection required for health care workers (i.e., whether to use the higher-efficiency N95 respirators recommended for airborne isolation rather than the surgical masks used for droplet precautions).

In the spring of 2009, a novel strain of influenza virus—H1N1 (swine flu) virus—caused the first influenza pandemic in four decades. Recombinant events that create new strains (e.g., H7N9) continue to challenge global efforts at infection control and vaccine development **(Chap. 195)**.

EMERGING VIRAL PATHOGENS

The re-emergence of Ebola virus in West Africa has had a global impact on infection-control preparedness and isolation techniques, on situational awareness, and on vaccine development **(Chap. 205)**. The emergence of epidemic Zika virus disease in Brazil and its spread throughout Latin America to the United States has created a major threat to pregnant women and has added to the list yet another potential blood-borne pathogen that requires blood-bank screening **(Chap. 204)**.

NOSOCOMIAL DIARRHEA

Overall rates of *C. difficile*–associated diarrhea **(Chap. 129)** have increased, especially among older patients in U.S. hospitals during the past few years. This increase is related in part to a new, more virulent strain, NAP1/BI/027. There are ~250,000 incident cases, with 14,000 deaths, from *C. difficile*–associated diarrhea in the United States annually. In a CDC multistate survey, *C. difficile* was the most common nosocomial pathogen, causing 12% of health care–associated infections. Use of WGS is improving our understanding of *C. difficile* epidemiology. For now, control measures include judicious use of all antibiotics, especially fluoroquinolone antibiotics that have been implicated in driving outbreaks; heightened suspicion for atypical presentations (e.g., toxic megacolon or leukemoid reaction without diarrhea); enhanced disinfection of isolation rooms with sporicidal agents, such as bleach; and early diagnosis, treatment, and contact precautions. To improve diagnosis, use of more sensitive polymerase chain reaction–based rather than enzyme immunoassay–based testing of diarrheal stool is now recommended, with resultant artificial doubling of infection rates (as patients who are colonized but not clinically infected with *C. difficile* are being detected) in some hospitals. Preliminary data suggest a role for probiotics in the prevention of diarrhea in patients in whom systemic antibiotic therapy is being initiated. Fecal transplantation has had dramatic results in the treatment of relapsing cases of *C. difficile*–associated diarrhea **(Chap. 129)**. Successes with fecal transplants and probiotics have called attention to the potential role of manipulation of the intestinal microbiome as a broader infection-control strategy (e.g., to eliminate carriage of antibiotic-resistant gram-negative bacilli).

Reports of outbreaks of norovirus infection **(Chap. 198)** in U.S. and European health care facilities appear to continue to increase, with the virus often introduced by ill visitors or staff. This pathogen should be suspected when nausea and vomiting are prominent aspects of bacterial culture–negative diarrheal syndromes. Contact precautions may need to be augmented by aggressive environmental cleaning (given the persistence of norovirus on inanimate objects), prevention of secondary cases in members of the cleaning staff through an emphasis on the use of personal protective equipment and hand hygiene, and active exclusion of ill staff and visitors.

CHICKENPOX

Infection-control practitioners institute a varicella exposure investigation and control plan whenever health care workers have been exposed to chickenpox **(Chap. 188)** or have worked while having or during the 24 h before developing chickenpox. Fortunately, routine varicella vaccination of children and susceptible health care employees has made nosocomial spread less common.

MYCOBACTERIA

Important measures for the control of pulmonary tuberculosis **(Chap. 173)** include prompt recognition, isolation, and treatment of cases; recognition of atypical presentations (e.g., lower-lobe infiltrates without cavitation); use of negative-pressure, 100% exhaust, private isolation rooms with closed doors and at least 6–12 air changes per hour; use of N95 respirators by caregivers entering isolation rooms; possible use of high-efficiency particulate air-filter units and/or ultraviolet lights for disinfecting air when other engineering controls are not feasible or reliable; and follow-up testing of susceptible personnel who have been exposed to infectious patients before isolation. The use of serologic tests, rather than skin tests, in the diagnosis of latent tuberculosis for infection control purposes has become common, mostly for logistic reasons. As tuberculosis once again is on the decline in the United States, we need to remember that the price of freedom—in this instance, from a communicable disease—is eternal vigilance.

An unprecedented multicountry outbreak of postoperative invasive *Mycobacterium chimaera* infections has been traced to commercially contaminated heater–cooler devices used commonly during cardiac surgery. The implicated devices are manufactured by a single company that sells the majority of such devices used globally. Guidelines for diagnosis, treatment, and prevention are being formulated.

GROUP A STREPTOCOCCAL INFECTIONS

The potential for an outbreak of group A streptococcal infection **(Chap. 143)** should be considered when even one or two nosocomial cases occur. Most outbreaks involve surgical wounds and are due to the presence of an asymptomatic carrier in the operating room.

Investigation can be confounded by carriage at extrapharyngeal sites such as the rectum and vagina.

FUNGAL INFECTIONS

When dusty areas—common sources of fungal spores—are disturbed during hospital repairs or renovation, the spores become airborne. Inhalation of spores by immunosuppressed (especially neutropenic) patients creates a risk of pulmonary and/or paranasal sinus infection and disseminated aspergillosis **(Chap. 212)**. Routine surveillance among neutropenic patients for infections with filamentous fungi, such as *Aspergillus* and *Fusarium*, helps hospitals to assess environmental risks. As a matter of routine, hospitals should inspect and clean air-handling equipment; review all planned renovations with infection-control personnel and construct appropriate barriers; remove immunosuppressed patients from renovation sites; and consider the use of high-efficiency particulate air-intake filters for rooms housing immunosuppressed patients.

A major multistate iatrogenic outbreak of meningitis, localized spinal or paraspinal infection, and arthritis due to *Exserohilum rostratum* was recognized in 2012 and traced to contamination of an injectable preservative-free steroid product produced by a single compounding pharmacy **(Chap. 212)**.

Candida auris, a pathogen first identified in Japan in 2009, is emerging globally as a cause of invasive health care–associated infections. The international strains are closely related within regions, often multidrug-resistant, and difficult to identify by routine laboratory testing.

LEGIONELLOSIS

Nosocomial *Legionella* pneumonia **(Chap. 154)** is most often due to contamination of potable water or of water used in decorative fountains. This disease predominantly affects immunosuppressed patients, particularly those receiving glucocorticoid medications. The risk varies greatly within and among geographic regions, depending on the extent of hospital water contamination and on specific hospital practices (e.g., the presence of decorative fountains in hospital lobbies or inappropriate use of nonsterile water in respiratory therapy equipment). The diagnosis of legionellosis should probably be considered more often than it is. If nosocomial cases are detected, environmental samples (e.g., tap water) should be cultured. If cultures yield *Legionella* and if typing of clinical and environmental isolates reveals a correlation, eradication measures should be pursued. An alternative approach is to periodically culture tap water in wards housing high-risk patients. If *Legionella* is found, a concerted effort should be made to culture samples from all patients with nosocomial pneumonia for *Legionella* and to introduce engineering controls to reduce or eliminate water-borne *Legionella* within the facility.

ANTIBIOTIC-RESISTANT BACTERIA: SURVEILLANCE, CONTROL, AND ANTIBIOTIC STEWARDSHIP

Emerging multidrug-resistant bacteria like CRE are harbingers of a potential postantibiotic era. Control of resistance depends on close laboratory surveillance, with early detection of problems; on aggressive reinforcement of routine asepsis; on implementation of barrier precautions for all colonized and/or infected patients; on use of patient-surveillance cultures to more fully ascertain the extent of patient colonization; on antimicrobial stewardship in humans and animals to lessen ecologic pressures; and on timely initiation of an epidemiologic investigation when rates increase. Advanced molecular diagnostics (e.g., PFGE and, most recently, WGS) can help differentiate an outbreak due to a single strain (which necessitates an emphasis on hand hygiene and an evaluation of potential common-source exposures) from a polyclonal outbreak (which requires an emphasis on antibiotic prudence and device bundles; Table 137-3). Continuing emergence of multidrug-resistant organisms suggests that control efforts have been insufficient and that heightened interventions and global strategies are needed urgently (see *www.cdc.gov/drugresistance/threat-report-2013/* and *https://www.cdc.gov/vitalsigns/protect-patients/index.html*); this need is highlighted by the creation of the U.S. Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria and by the U.N. General Assembly's 2016 Declaration (see *https://www.hhs.gov/ash/advisory-committees/paccarb*, *http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/*, and *www.gov.uk/government/publications/uk-5-year-antimicrobial-resistance-strategy-2013-to-2018/*).

To facilitate tracking of resistance problems, the CDC's innovative, interactive online Antibiotic Resistance Patient Safety Atlas allows users to search state-level resistance data (*http://www.cdc.gov/hai/surveillance/ar-patient-safety-atlas.html*). The European Centre for Disease Prevention and Control also has online resistance reporting (*http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial_resistance/EARS-Net/Pages/EARS-Net.aspx*).

Currently, several antibiotic resistance problems are of particular concern. First, over the past decade or so, the emergence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) has been dramatic in many countries, with as many as 50% of community-acquired "staph infections" in some U.S. cities now caused by strains resistant to β-lactam antibiotics **(Chap. 142)**. The incursion of CA-MRSA into hospitals is well documented and has impacted surveillance and control of nosocomial MRSA infections.

Second, in the global emergence of multidrug-resistant gram-negative bacilli, new problems include plasmid-mediated resistance to fluoroquinolones, metallo-β-lactamase-mediated resistance to carbapenems, CRE, and pan-resistant strains of *Acinetobacter*. The problematic plasmid-mediated New Delhi metallo-β-lactamase (NDM) has been highly successful in inter-genus transmission and quickly has become a threat worldwide. Many multidrug-resistant gram-negative bacilli are susceptible only to colistin, a drug that is consequently being "re-discovered," or to no available agents. The potential dependence on colistin has led to increased colistin susceptibility testing and recognition of plasmid-mediated resistance to colistin in *E. coli*—first in swine-associated strains from China and now in strains from many countries, including the United States.

Transmission of CRE has been traced in a number of outbreaks to exposure to duodenoscopes used for endoscopic retrograde cholangiopancreatography. The duodenoscope is more intricate than other endoscopes and has an "elevator mechanism" that can be difficult to clean and disinfect. In some—though not all—of these outbreaks, investigators identified breaches of approved cleaning protocols.

Third, there has been renewed recognition of the role of nursing homes, and now LTACHs, in the spread of resistant gram-negative bacilli such as CRE. In some LTACHs, as many as 30–50% of patients may be colonized with CREs. The frequent transfer of patients who are colonized or infected with antibiotic-resistant bacteria between long-term and acute-care facilities has led to studies of the regional spread of antibiotic resistance and the proposal of regional infection-control interventions (see *www.cdc.gov/vitalsigns/stop-spread*).

Fourth, there has been increasing community-based spread of *E. coli* strains harboring an enzyme, CTX-M, that renders them broadly resistant to β-lactam antibiotics. Given the community focus of spread, these strains may be seen as a gram-negative version of CA-MRSA.

Fifth, as a consequence of going abroad, international travelers, especially to Latin America, Asia, and Africa, may become gastrointestinal carriers of multidrug-resistant Enterobacteriaceae that express extended-spectrum β-lactamases (ESBLs) and encode resistance to many commonly used antibiotics. In one study, 34% of returning Dutch travelers had newly acquired resistant strains and were colonized for as long as 6–12 months until their pretravel gastrointestinal microbiomes rebounded. The frequency of clinical consequences—e.g., the emergence of antibiotic-resistant UTIs or local spread of resistant strains—is not yet known.

Finally, clinical infections with MRSA strains exhibiting high-level vancomycin resistance due to VRE-derived plasmids have been reported in a few patients—almost all in the United States and most in Michigan—in the setting of prolonged or repeated treatment with vancomycin and/or VRE colonization.

Colonized personnel who are implicated in nosocomial transmission of multidrug-resistant pathogens and patients who pose a threat may be decontaminated, depending on the pathogen and available

decontamination regimens. In a few ICUs, nonabsorbed antimicrobial agents for gastrointestinal decontamination of patients have been used as a temporary emergency control measure for outbreaks of infection due to gram-negative bacilli. Manipulation of patients' intestinal microbiomes may prove to be a more durable strategy to control outbreaks of multidrug-resistant pathogens that have a gastrointestinal reservoir.

In several cluster-randomized controlled trials over the past ~15 years, source control—i.e., removal of patients' fecal patinas—by daily bathing with chlorhexidine has reduced the risk of bacteremia in ICU patients. "Search-and-destroy" methods—i.e., active surveillance cultures to detect and isolate the "resistance iceberg" of patients colonized with MRSA—are credited with elimination of nosocomial MRSA in the Netherlands and Denmark. In a multicenter trial in the United States, universal source control with chlorhexidine and nasal mupirocin was significantly more effective in controlling MRSA than was a search-and-destroy approach and led to control of other pathogens as well, providing a broad (horizontal) rather than a narrower (vertical) intervention (see *www.ahrq.gov/professionals/systems/hospital/universal_icu_decolonization*). For some pathogens, such as VRE, enforcement of environmental cleaning also reduces cross-transmission risk.

Because the excessive use of broad-spectrum antibiotics underlies many resistance problems, antibiotic stewardship programs will be mandatory in acute care hospitals (see *https://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html*) and are being promulgated actively for long-term care and outpatient facilities (see *https://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html* and *https://www.cdc.gov/mmwr/volumes/65/rr/rr6506a1.htm*). The main tenets are to restrict the use of particular agents to narrowly defined indications in order to limit selective pressure on the nosocomial flora; to treat with the shortest efficacious courses; and, when broad-spectrum therapy is begun empirically in critically ill patients, to de-escalate treatment as soon as possible on the basis of the results of culture and susceptibility tests.

From a broader perspective, the One Health movement cites what many would call the overriding role of antimicrobial use in animal husbandry as a driver of resistance. This concern has led to recommendations for eliminating the use of antibiotics for growth promotion and as prophylaxis for feed animals. The United States lags behind some European countries in control of veterinary use of antimicrobial drugs.

Key to an understanding of the success of antibiotic stewardship initiatives is better surveillance of antibiotic use among humans and other animals at regional and national levels.

BIOTERRORISM AND OTHER SURGE-EVENT PREPAREDNESS

The horrific attack on the World Trade Center in New York City on September 11, 2001; subsequent mailings of anthrax spores in the United States; the Boston Marathon bombing in 2013; and ongoing terrorist activities globally have made bioterrorism a prominent source of concern to hospital infection-control programs **(Chap. S2)**. The essentials for hospital preparedness entail education, internal and external communication, and situational awareness. Up-to-date information is available from the CDC (see *www.emergency.cdc.gov/bioterrorism*).

EMPLOYEE HEALTH SERVICE ISSUES

An institution's employee health service is critical for infection control. New employees should be processed through the service, where a contagious-disease history can be taken; evidence of immunity to a variety of diseases, such as hepatitis B, chickenpox, measles, mumps, and rubella, can be sought; immunizations for hepatitis B, measles, mumps, rubella, varicella, and pertussis can be given as needed (an especially important step with the resurgence in the United States of vaccine-preventable diseases such as pertussis, mumps, and measles); baseline tuberculosis testing can be performed; and education about personal responsibility for infection control can be initiated.

The employee health service must have protocols for dealing with workers exposed to contagious diseases (e.g., influenza) and those percutaneously or mucosally exposed to the blood of patients infected with HIV or hepatitis B or C virus. Protocols are also needed for dealing with caregivers who have common contagious diseases (such as chickenpox, group A streptococcal infection, influenza or another respiratory infection, or infectious diarrhea) and for those who have less common but high-visibility public health problems (such as chronic hepatitis B or C or HIV infection) for which exposure-control guidelines have been published by the CDC and by the Society for Healthcare Epidemiology of America.

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138 Infections in Transplant Recipients

Robert W. Finberg, Joyce D. Fingeroth

This chapter considers aspects of infection unique to patients receiving transplanted tissue. The evaluation of infections in transplant recipients involves consideration of both the donor and the recipient of the transplanted cells or organ. Two central issues are of paramount importance: (1) infectious agents (particularly viruses, but also bacteria, fungi, and parasites) can be introduced into the recipient by the donor; and (2) treatment of the recipient with medicine to prevent rejection can suppress normal immune responses, greatly increasing susceptibility to infection. Thus, what might have been a latent or asymptomatic infection in an immunocompetent donor or in the recipient prior to therapy can become a life-threatening problem when the recipient becomes immunosuppressed. The pretransplantation evaluation of each patient should be guided by an analysis of both (1) what infections the recipient is currently harboring, since organisms that exist in a state of latency or dormancy before the procedure may cause fatal disease when the patient receives immunosuppressive treatment; and (2) what organisms are likely to be transmitted by the donor, particularly those to which the recipient may be naïve.

PRETRANSPLANTATION EVALUATION

THE DONOR

A variety of organisms have been transmitted by organ transplantation. Transmission of infections that may have been latent or not clinically apparent in the donor has resulted in the development of specific donor-screening protocols. Results from routine blood-bank studies, including those for antibodies to *Treponema pallidum*

(syphilis), *Trypanosoma cruzi*, hepatitis B and C viruses, HIV-1 and -2, and human T-lymphotropic virus types 1 and 2 (HTLV-1 and -2), should be documented. Serologic studies should be ordered to identify latent infection with viruses such as herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Kaposi's sarcoma–associated herpesvirus (KSHV, also known as human herpesvirus type 8); acute infection with hepatitis A virus; and infection with the common parasite *Toxoplasma gondii*. Donors should be screened for parasites such as *Strongyloides stercoralis, T. cruzi*, and *Schistosoma* species if they have lived in endemic areas. Clinicians caring for prospective organ donors should examine chest radiographs for evidence of granulomatous disease (e.g., caused by mycobacteria or fungi) and should perform skin testing or obtain blood for immune cell-based assays that detect active or latent *Mycobacterium tuberculosis* infection. An investigation of the donor's dietary habits (e.g., consumption of raw meat or fish or of unpasteurized dairy products), occupations or avocations (e.g., gardening or spelunking), and travel history (e.g., travel to areas with endemic fungi causing infections such as blastomycosis, coccidioidomycosis, and histoplasmosis) also is indicated and may mandate additional testing. A number of unusual parasites (including *Balamuthia mandrillaris*) have been transplanted in kidneys. Uncommonly diagnosed viruses, including lymphocytic choriomeningitis virus (LCMV), West Nile virus, Zika virus, dengue virus, and rabies virus, can be transplanted in organs and are likely to be difficult to diagnose in recipients. If an unusual parasite or uncommon virus is identified in a transplant recipient, the organ-donor organization and caregivers for recipients of other organs isolated from the same donor should be notified immediately.

Creutzfeldt-Jakob disease has been transmitted through corneal transplants; however, to what degree it can be transmitted by transfused blood is not known. Variant Creutzfeldt-Jakob disease can be transmitted with transfused non-leukodepleted blood, posing a theoretical risk to transplant recipients.

THE RECIPIENT

It is expected that the recipient will have been even more comprehensively assessed than the donor. Additional studies recommended for the recipient include evaluation for acute respiratory viruses and gastrointestinal pathogens in the immediate pretransplantation period. An important caveat is that, because of immune dysfunction resulting from chemotherapy or underlying chronic disease, serologic testing of the recipient may prove less reliable than usual.

THE DONOR CELLS/ORGAN

Careful attention to the sterility of the medium used to process the donor organ, combined with meticulous microbiologic evaluation, reduces rates of transmission of bacteria (or, rarely, yeasts) that may be present or grow in the organ culture medium. From 2 to >20% of donor kidneys are estimated to be contaminated with bacteria—in most cases, with the organisms that colonize the skin or grow in the tissue culture medium used to bathe the donor organ while it awaits implantation. The reported rate of bacterial contamination of transplanted stem cells (bone marrow, peripheral blood, cord blood) is as high as 17% but most commonly is ~1%. The use of enrichment columns and monoclonal antibody depletion procedures results in a higher incidence of contamination. In some cases, because of the clinical situation, contaminated cells have been infused, usually with concomitant administration of antimicrobial agents. In one series of patients receiving contaminated stem cells, 14% had fever or bacteremia, but none died. Results of cultures performed at the time of cryopreservation and at the time of thawing were helpful in guiding therapy for the recipient.

INFECTIONS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Transplantation of hematopoietic stem cells (HSCs) from bone marrow or from peripheral or cord blood for cancer, immunodeficiency, or autoimmune disease is marked by a transient state of complete immunologic incompetence. Immediately after myeloablative chemotherapy and transplantation, both innate immune cells (phagocytes, dendritic cells, natural killer cells) and adaptive immune cells (T and B cells) are absent, and the host is extremely susceptible to infection. The reconstitution that follows transplantation has been likened to maturation of the immune system in neonates. The analogy does not entirely predict infections seen in HSC transplant recipients, however, because the stem cells mature in an old host who has several latent infections already. The choice among the current variety of methods for obtaining stem cells is determined by availability and by the need to optimize the chances of a cure for an individual recipient. One strategy is autologous HSC transplantation, in which the donor and the recipient are the same. After chemotherapy, stem cells are collected and are purged (ex vivo) of residual neoplastic populations. Allogeneic HSC transplantation has the advantage of providing a graft-versus-tumor effect. In this case, the recipient is matched to varying degrees for human leukocyte antigens (HLAs) with a donor who may be related or unrelated. In some individuals, nonmyeloablative therapy (mini-allotransplantation) is used and permits recipient cells to persist for some time after transplantation while preserving the graft-versus-tumor effect and sparing the recipient intense myeloablative therapy. Cord-blood transplantation is increasingly used in adults; two independent cord-blood units are typically required for suitable neutrophil engraftment early after transplantation, even though only one of the units is likely to provide long-term engraftment. In each circumstance, a different balance is struck among the toxicity of conditioning therapy, the need for a maximal graft-versus-target effect, short-term and long-term infectious complications, and the risk of graft-versus-host disease (GVHD; acute versus chronic). The various approaches differ in terms of reconstitution speed, cell lineages introduced, and likelihood of GVHD—all factors that can produce distinct effects on the risk of infection after transplantation **(Table 138-1)**. Despite these caveats, most infections occur in a predictable time frame after transplantation **(Table 138-2)**.

BACTERIAL INFECTIONS

In the first month after HSC transplantation, infectious complications are similar to those in granulocytopenic patients receiving chemotherapy for acute leukemia **(Chap. 70)**. Because of the anticipated 1- to 4-week duration of neutropenia and the high rate of bacterial infection in this population, many centers give prophylactic antibiotics to patients upon initiation of myeloablative therapy. Quinolones decrease the incidence of gram-negative bacteremia among these patients. Bacterial infections are common in the first few days after HSC transplantation. The organisms involved are predominantly those found on skin, mucosa, or IV catheters (*Staphylococcus aureus*, coagulase-negative staphylococci, streptococci) or aerobic bacteria that colonize the bowel (*Escherichia coli, Klebsiella, Pseudomonas*). *Bacillus cereus*, although rare, has emerged as a pathogen early after transplantation and can cause meningitis, which is unusual in these patients. Chemotherapy, use of broad-spectrum antibiotics, and delayed reconstitution of humoral immunity place HSC transplant patients at risk for diarrhea and colitis caused by *Clostridium difficile* overgrowth and toxin production. Reconstitution of the bowel with microbial flora from donors ("fecal transplantation") has been successful in drug-resistant cases **(Chap. 129)**.

Beyond the first few days of neutropenia, infections with nosocomial pathogens (e.g., vancomycin-resistant enterococci, *Stenotrophomonas maltophilia*, *Acinetobacter* species, and extended-spectrum β-lactamase-producing gram-negative bacteria) as well as with filamentous bacteria (e.g., *Nocardia* species) become more common. Vigilance is indicated, particularly for patients with a history of active or known latent tuberculosis, even when they have been appropriately pretreated. A form of bacterial colitis among cord-blood recipients has occurred 90–300 days after transplantation, responds to antimicrobial agents such as metronidazole, and—as determined by polymerase chain reaction (PCR) testing of biopsy specimens—may be attributed to the common bacterium *Bradyrhizobium enterica* (related to *B. japonicum*). Episodes of bacteremia due to encapsulated organisms mark the late posttransplantation period (>6 months after HSC reconstitution); patients who have undergone splenectomy and those with persistent hypogammaglobulinemia are at particular risk.

TABLE 138-1 Risk of Infection, by Type of Hematopoietic Stem Cell Transplant

TYPE OF HEMATOPOIETIC STEM CELL TRANSPLANT	SOURCE OF STEM CELLS	RISK OF EARLY INFECTION: NEUTROPHIL DEPLETION	RISK OF LATE INFECTION: IMPAIRED T AND B CELL FUNCTION	RISK OF ONGOING INFECTION: GVHD AND IATROGENIC IMMUNOSUPPRESSION	GRAFT VS TUMOR EFFECT
Autologous	Recipient (self)	High risk; neutrophil recovery sometimes prolonged	~1 year	Minimal to no risk of GVHD and late-onset severe infection	None (–)
Syngeneic (genetic twin)	Identical twin	Low risk; 1–2 weeks for neutrophil recovery	~1 year	Minimal risk of GVHD and late-onset severe infection	+/–
Allogeneic related	Sibling	Low risk; 1–2 weeks for neutrophil recovery	~1 year	Minimal to moderate risk of GVHD and late-onset severe infection	++
Allogeneic related	Child/parent (haploidentical)	Intermediate risk; 2–3 weeks for neutrophil recovery	1–2 years	Moderate risk of GVHD and late-onset severe infection	++++
Allogeneic unrelated adult	Unrelated donor	Intermediate risk; 2–3 weeks for neutrophil recovery	1–2 years	High risk of GVHD and late-onset severe infection	++++
Allogeneic unrelated cord blood	Unrelated cord-blood units (×2)	Intermediate to high risk; neutrophil recovery sometimes prolonged	Prolonged	Minimal to moderate risk of GVHD and late-onset severe infection	++++
Allogeneic mini (nonmyeloablative)	Donor (transiently coexisting with recipient cells)	Low risk; neutrophil counts close to normal	1–2+ years	Variable risk of GVHD and late-onset severe infection[a]	++++ (but develops slowly)

[a]Depending on the disparity of the match (major and minor histocompatibility antigens), GVHD may be severe or mild, the requirement for immunosuppression intense or minimal, and the risk of severe late infections coordinate with the degree of immunosuppression.

Abbreviation: GVHD, graft-versus-host disease.

FUNGAL INFECTIONS

Beyond the first week after HSC transplantation, fungal infections become increasingly common, particularly among patients who have received broad-spectrum antibiotics. As in most granulocytopenic patients, *Candida* infections are most commonly seen in this setting. However, with increased use of prophylactic fluconazole, infections with *Candida albicans* resistant to fluconazole and naturally fluconazole-resistant fungi—in particular, *Aspergillus* and other non-*Aspergillus* molds (*Rhizopus*, *Fusarium*, *Scedosporium*, *Penicillium*)—have become more common, prompting some centers to replace fluconazole with agents such as micafungin, voriconazole, isavuconazole, or posaconazole. Identification of *Candida auris* as a pathogen has made prophylaxis and treatment of fungal infections more difficult as these organisms are often resistant to most antifungal agents. The role of antifungal prophylaxis with these different agents, in contrast to empirical treatment for suspected infection that is based on a positive β-D-glucan assay or galactomannan antigen test, remains controversial (Chap. 70). Documented infection should be aggressively treated, ideally with agents of proven activity. In patients with GVHD who require prolonged or indefinite courses of glucocorticoids and other immunosuppressive agents (e.g., cyclosporine, tacrolimus [FK506, Prograf], mycophenolate mofetil [CellCept], rapamycin [sirolimus, Rapamune], antithymocyte globulin, or anti-CD52 antibody [alemtuzumab, Campath—an antilymphocyte and antimonocyte monoclonal antibody]), there is a high risk of fungal infection (usually with *Candida* or *Aspergillus*) even after engraftment and resolution of neutropenia. These patients are also at high risk for reactivation of latent fungal infection (histoplasmosis, coccidioidomycosis, or blastomycosis) in areas where endemic fungi reside and after involvement in activities such as gardening or caving. Prolonged use of central venous catheters for parenteral nutrition (lipids) increases the risk of fungemia with *Malassezia*. Some centers administer prophylactic antifungal agents to these patients. Because of the high and prolonged risk of *Pneumocystis jirovecii* pneumonia (especially among patients being treated for hematologic malignancies), most patients receive maintenance prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) starting after engraftment and continuing for at least 1 year.

PARASITIC INFECTIONS

The regimen just described for the fungal pathogen *Pneumocystis* may also protect patients seropositive for the parasite *T. gondii*, which can cause pneumonia, visceral disease (occasionally), and central nervous system (CNS) lesions (more commonly). The advantages of maintaining HSC transplant recipients on daily TMP-SMX for 1 year after transplantation include some protection against *Listeria monocytogenes*

TABLE 138-2 Common Sources of Infection after Hematopoietic Stem Cell Transplantation

	PERIOD AFTER TRANSPLANTATION		
INFECTION SITE	EARLY (<1 MONTH)	MIDDLE (1–4 MONTHS)	LATE (>6 MONTHS)
Disseminated	Aerobic bacteria (gram-negative, gram-positive)	*Candida*, *Aspergillus*, EBV	Encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*)
Skin and mucous membranes	HSV	HHV-6	VZV, HPV (warts)
Lungs	Aerobic bacteria (gram-negative, gram-positive), *Candida*, *Aspergillus*, other molds, HSV	CMV, seasonal respiratory viruses, *Pneumocystis*, *Toxoplasma*	*Pneumocystis*, *Nocardia*, *S. pneumoniae*
Gastrointestinal tract	*Clostridium difficile*	CMV, adenovirus	EBV, CMV
Kidney		BK virus, adenovirus	
Brain		HHV-6, *Toxoplasma*	*Toxoplasma*, JC virus (rare)
Bone marrow		CMV, HHV-6	CMV, HHV-6

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV-6, human herpesvirus type 6; HPV, human papillomavirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

and nocardiosis as well as late infections with *Streptococcus pneumoniae* and *Haemophilus influenzae* that stem from the inability of the immature immune system to respond to polysaccharide antigens.

With increasing international travel, parasitic diseases typically restricted to particular environmental niches may pose a risk of reactivation in certain patients after HSC transplantation. Thus, in recipients with an appropriate history who were not screened and/or treated before transplantation or in patients with recent exposures, evaluation for infection with *Strongyloides, Leishmania*, schistosomes, trypanosomes, or various parasitic causes of diarrheal illness (*Giardia, Entamoeba, Cryptosporidium*, microsporidia) may be warranted.

VIRAL INFECTIONS

HSC transplant recipients are susceptible to infection with a variety of viruses, including primary and reactivation syndromes caused by most human herpesviruses **(Table 138-3)** and acute infections caused by viruses that circulate in the community.

Herpes Simplex Virus Within the first 2 weeks after transplantation, most patients who are seropositive for HSV-1 excrete the virus from the oropharynx. The ability to isolate HSV declines with time. Administration of prophylactic acyclovir (or valacyclovir) to seropositive HSC transplant recipients has been shown to reduce mucositis and prevent HSV pneumonia (a rare condition reported almost exclusively in allogeneic HSC transplant recipients). Both esophagitis (usually due to HSV-1) and anogenital disease (commonly caused by HSV-2) may be prevented with acyclovir prophylaxis. **For further discussion, see Chap. 187.**

Varicella-Zoster Virus Reactivation of VZV manifests as herpes zoster and may occur within the first month but more commonly occurs several months after transplantation. Reactivation rates are ~40% for allogeneic HSC transplant recipients and 25% for autologous recipients. Localized zoster can spread rapidly in an immunosuppressed patient. Fortunately, disseminated disease can usually be controlled with high doses of acyclovir. Because of frequent VZV dissemination among patients with skin lesions, acyclovir is given prophylactically in many centers to prevent severe disease. Low doses of acyclovir appear to be effective in preventing reactivation of VZV. However, acyclovir can also suppress the development of VZV-specific immunity. Thus, its administration for only 6 months after transplantation does not prevent zoster from occurring when treatment is stopped. Administration of low doses of acyclovir for an entire year after transplantation is effective and may eliminate most cases of posttransplantation zoster, even among cord-blood recipients. **For further discussion, see Chap. 188.**

TABLE 138-3 Herpesvirus Syndromes in Transplant Recipients

VIRUS	REACTIVATION DISEASE
Herpes simplex virus type 1	Oral lesions Esophageal lesions Pneumonia (primarily HSC transplant recipients) Hepatitis (rare)
Herpes simplex virus type 2	Anogenital lesions Hepatitis (rare)
Varicella-zoster virus	Zoster (can disseminate)
Cytomegalovirus	Associated with graft rejection Fever and malaise Bone marrow failure Pneumonitis Gastrointestinal disease
Epstein-Barr virus	B cell lymphoproliferative disease/lymphoma Oral hairy leukoplakia (rare)
Human herpesvirus type 6	Fever Delayed monocyte/platelet engraftment Encephalitis (rare)
Human herpesvirus type 7	Undefined
Kaposi's sarcoma–associated virus (human herpesvirus type 8)	Kaposi's sarcoma Primary effusion lymphoma (rare) Multicentric Castleman's disease (rare) Marrow aplasia (rare)

Abbreviation: HSC, hematopoietic stem cell.

Cytomegalovirus The onset of CMV disease (interstitial pneumonia, bone marrow suppression, graft failure, hepatitis/colitis) usually begins 30–90 days after HSC transplantation, when the granulocyte count is adequate but immunologic reconstitution has not occurred. CMV disease rarely develops earlier than 14 days after transplantation and may become evident as late as 4 months or more after the procedure. It is of greatest concern in the second month after transplantation, particularly in allogeneic HSC transplant recipients. In cases in which the donor marrow is depleted of T cells (to prevent GVHD or eliminate a T cell tumor) and in cord-blood recipients, the disease may manifest earlier. The use of alemtuzumab to prevent GVHD in nonmyeloablative transplantation has been associated with an increase in CMV disease. Patients who receive ganciclovir for prophylaxis, preemptive treatment, or treatment (see below) may develop recurrent CMV infection even later than 4 months after transplantation, as treatment appears to delay the development of an effective immune response to CMV infection. Although CMV disease may present as isolated fever, granulocytopenia, thrombocytopenia, or gastrointestinal disease, the foremost cause of death from CMV infection in the setting of HSC transplantation is pneumonia.

With the standard use of CMV-negative or filtered blood products, CMV infection should be a major risk in allogeneic transplantation only when the recipient is CMV-seropositive and the donor is CMV-seronegative. This situation is the reverse of that in solid organ transplant recipients. CMV reactivates from latent reservoirs present in the recipient at a time when donor T cells (especially cord-blood T cells) are too immature to control CMV replication. If the T cells from the donor have never encountered CMV and the recipient carries the virus, the patient is at maximal risk of severe disease. Reactivation disease or superinfection with another strain from the donor also can occur in CMV-positive recipients, but clinical manifestations are typically less severe, presumably because of CMV-specific memory in transplanted donor T cells. Most patients infected with CMV who undergo HSC transplantation excrete virus, with or without clinical findings. Serious CMV disease is much more common among allogeneic than autologous recipients and is often associated with GVHD. In addition to pneumonia and marrow suppression (and, less often, graft failure), manifestations of CMV disease in HSC transplant recipients include fever with or without arthralgias, myalgias, hepatitis, and esophagitis. CMV ulcerations occur in both the lower and the upper gastrointestinal tract, and it may be difficult to distinguish diarrhea due to GVHD from that due to CMV infection. The finding of CMV in the liver of a patient with GVHD does not necessarily mean that CMV is responsible for hepatic enzyme abnormalities. It is interesting that ocular and neurologic manifestations of CMV infections are common in patients with AIDS but uncommon in patients who develop CMV disease after transplantation.

Management of CMV disease in HSC transplant recipients includes strategies directed at prophylaxis, preemptive therapy (suppression of silent replication), and treatment of disease. Prophylaxis results in a lower incidence of disease at the cost of treating many patients who otherwise would not require therapy. Because of the high fatality rate associated with CMV pneumonia in these patients and the difficulty of early diagnosis of CMV infection, prophylactic IV ganciclovir or oral valganciclovir has been used in some centers and has been shown to prevent CMV disease during the period of maximal vulnerability (from engraftment to day 120 after transplantation). Ganciclovir also prevents HSV reactivation and reduces the risk of VZV reactivation; thus acyclovir prophylaxis should be discontinued when ganciclovir is administered. The foremost problem with the administration of ganciclovir relates to adverse effects, which include dose-related bone marrow suppression (thrombocytopenia, leukopenia, anemia, and pancytopenia). Because the frequency of CMV pneumonia is lower among autologous HSC transplant recipients (2–7%) than among allogeneic

HSC transplant recipients (10–40%), prophylaxis in the former group will not become the rule until a less toxic oral antiviral agent becomes available. Several such agents are under study.

Preemptive treatment of CMV—that is, initiation of therapy with drugs only after CMV is detected in blood by a nucleic acid amplification test (NAAT)—is used at most centers. To limit variability between tests, the World Health Organization (WHO) has developed an international reference standard for measurement of CMV load by NAAT-based assays. Because of toxic drug side effects (e.g., neutropenia and bone marrow suppression), the preemptive approach has supplanted prophylactic therapy; it has also replaced treatment of all seropositive (recipient and/or donor) HSC transplants with an antiviral agent (typically ganciclovir). A positive test (or increasing viral load) prompts the initiation of preemptive therapy with ganciclovir. Preemptive approaches that target patients who have quantitative NAAT evidence of CMV infection can still lead to unnecessary treatment of many individuals with drugs that have adverse effects on the basis of a laboratory test that is not highly predictive of disease; however, invasive disease, particularly in the form of pulmonary infection, is difficult to treat and is associated with high mortality rates. When prophylaxis or preemptive therapy is stopped, late manifestations of CMV replication may occur, although by then the HSC transplant patient is often equipped with improved graft function and is better able to combat disease. Cord-blood transplant recipients are especially vulnerable to disease caused by members of the human herpesvirus family, including CMV. Implementation of the WHO standard for CMV load measurement will facilitate large-scale comparative studies and thus the establishment of optimal guidelines for distinct patient subsets.

CMV pneumonia in HSC transplant recipients (unlike that in other clinical settings) is often treated with both IV immunoglobulin (IVIg) and ganciclovir. In patients who cannot tolerate ganciclovir, foscarnet is a useful alternative, although it may produce nephrotoxicity and electrolyte imbalance. When neither ganciclovir nor foscarnet is clinically tolerated, cidofovir can be used; however, its efficacy is less well established, and its side effects include nephrotoxicity. A lipid-conjugate form of cidofovir, brincidofovir, appears to have more activity and less toxicity than cidofovir and is in clinical trials. Transfusion of CMV-specific T cells from the donor has decreased viral load in a small series of patients; this result suggests that immunotherapy (e.g., banked T cells) may play a role in the management of this disease in the future. **For further discussion, see Chap. 190.**

Human Herpesviruses 6 and 7 Human herpesvirus type 6 (HHV-6), the cause of roseola in children, is a ubiquitous herpesvirus that is reactivated (as determined by quantitative plasma PCR) in ~50% of HSC transplant recipients 2–4 weeks after transplantation. Reactivation is more common among patients requiring glucocorticoids for GVHD and among those receiving second transplants. Reactivation of HHV-6, primarily type B, may be associated with delayed monocyte and platelet engraftment. Limbic encephalitis developing after transplantation has been associated with HHV-6 in cerebrospinal fluid (CSF). The causality of the association is not well defined; in several cases, plasma viremia was detected long before the onset of encephalitis. Nevertheless, most patients with encephalitis had very high viral loads in plasma at the time of CNS illness, and viral antigen has been detected in hippocampal astrocytes. HHV-6 DNA is sometimes found in lung samples after transplantation. However, its role in pneumonitis is unclear, as co-pathogens are frequently present. While HHV-6 is susceptible to foscarnet or cidofovir (and possibly to ganciclovir) in vitro, the efficacy of antiviral treatment has not been well studied. Little is known about the related herpesvirus HHV-7 or its role in posttransplantation infection. **For further discussion, see Chap. 190.**

Epstein-Barr Virus Primary EBV infection can be fatal to HSC transplant recipients; EBV reactivation can cause EBV B cell lymphoproliferative disease (EBV-LPD), which may also be fatal to patients taking immunosuppressive drugs. Latent EBV infection of B cells leads to several interesting phenomena in HSC transplant recipients. The marrow ablation that occurs as part of the HSC transplantation procedure may sometimes eliminate latent EBV from the host. Infection can then be reacquired immediately after transplantation by transfer of infected donor B cells. Rarely, transplantation from a seronegative donor may result in a cure. The recipient is then at risk for a second primary infection.

EBV-LPD can develop in the recipient's B cells (if any survive marrow ablation) but is more likely to be a consequence of outgrowth of infected donor cells. Both lytic replication and latent replication of EBV are more likely during immunosuppression (e.g., they are associated with GVHD and the use of antibodies to T cells). Although less likely in autologous transplantation, reactivation can occur in T cell–depleted autologous recipients (e.g., patients being given antibodies to T cells for the treatment of T cell lymphoma with marrow depletion). EBV-LPD, which can become apparent as early as 1–3 months after engraftment, can cause high fevers and cervical adenopathy resembling the symptoms of infectious mononucleosis but more commonly presents as an extranodal mass. The incidence of EBV-LPD among allogeneic HSC transplant recipients is 0.6–1%, which contrasts with figures of ~5% for renal transplant recipients and up to 20% for cardiac transplant patients. In all cases, EBV-LPD is more likely to occur with high-dose, prolonged immunosuppression, especially that caused by the use of antibodies to T cells, glucocorticoids, and calcineurin inhibitors (e.g., cyclosporine, tacrolimus). Cord-blood recipients constitute another high-risk group because of delayed T cell function. Ganciclovir, administered to preempt CMV disease, may reduce EBV lytic replication and thereby diminish the pool of B cells that can become newly infected and give rise to LPD. Increasing evidence indicates that replacement of calcineurin inhibitors with mTOR inhibitors (e.g., rapamycin) exerts an antiproliferative effect on EBV-infected B cells that decreases the likelihood of development of LPD or unrelated proliferative disorders associated with transplant-related immunosuppression.

PCR can be used to monitor EBV production after HSC transplantation. High or increasing viral loads predict an enhanced likelihood of EBV-LPD development and should prompt rapid reduction of immunosuppression and a search for nodal or extranodal disease. If reduction of immunosuppression does not have the desired effect, administration of a monoclonal antibody to CD20 (e.g., rituximab) for the treatment of B-cell lymphomas that express this surface protein has elicited dramatic responses and currently constitutes first-line therapy for CD20-positive EBV-LPD. However, long-term suppression of new antibody responses accompanies therapy, and recurrences are common. Additional B cell–directed antibodies, including anti-CD22, are under study. The role of antiviral drugs is uncertain because no available agents have been documented to have activity against the different forms of latent EBV infection. Diminishing lytic replication and virion production in these patients would theoretically produce a statistical decrease in the frequency of latent disease by decreasing the number of virions available to cause additional infection. In case reports and animal studies, ganciclovir and/or high-dose zidovudine, together with other agents, has been used to eradicate EBV-LPD and CNS lymphomas, another EBV-associated complication of transplantation. Both interferon and retinoic acid have been employed in the treatment of EBV-LPD, as has IVIg, but no large-scale prospective studies have assessed the efficacy of any of these agents. Several additional drugs are undergoing preclinical evaluation. Standard chemotherapeutic regimens are used if disease persists after reduction of immunosuppressive agents and administration of antibodies. EBV-specific T cells generated from the donor have been used experimentally to prevent and treat EBV-LPD in allogeneic recipients, and efforts are under way to increase the activity and specificity of ex vivo–generated T cells. **For further discussion, see Chap. 189.**

Human Herpesvirus 8 (KSHV) The EBV-related gammaherpesvirus KSHV, which is causally associated with Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease, has rarely resulted in disease in HSC transplant recipients, although some cases of virus-associated marrow aplasia have been reported in the peritransplantation period. The relatively low seroprevalence of KSHV in the population and the limited duration of profound T cell suppression after HSC transplantation provide a plausible explanation

for the currently low incidence of KSHV disease compared with that in recipients of solid organ transplants and patients with HIV infection. **For further discussion, see Chap. 190.**

Other (Non-Herpes) Viruses The diagnosis of pneumonia in HSC transplant recipients poses special problems. Because patients have undergone treatment with multiple chemotherapeutic agents and sometimes irradiation, their differential diagnosis should include—in addition to bacterial and fungal pneumonia—CMV pneumonitis, pneumonia of other viral etiologies, parasitic pneumonia, diffuse alveolar hemorrhage, and chemical- or radiation-associated pneumonitis. Since fungi and viruses (e.g., influenza A and B viruses, respiratory syncytial virus [RSV], parainfluenza virus types 1–4, adenovirus, enterovirus, bocavirus, human metapneumovirus, coronavirus, and rhinovirus [increasingly detected by multiplex PCR]) also can cause pneumonia in this setting, it is important to obtain a specific diagnosis. Diagnostic modalities include Gram's stain, microbiologic culture, antigen testing, and—increasingly—multipathogen PCR and mass spectrometry assays.

GLOBAL CONSIDERATIONS

M. tuberculosis has been an uncommon cause of pneumonia among HSC transplant recipients in Western countries (accounting for <0.1–0.2% of cases) but is common in Hong Kong (5.5%) and in countries where the prevalence of tuberculosis is high. The recipient's exposure history is clearly critical in an assessment of posttransplantation infections.

Both RSV and parainfluenza viruses, particularly type 3, can cause severe or even fatal pneumonia in HSC transplant recipients. Infections with both of these agents sometimes occur as disastrous nosocomial epidemics. Therapy with palivizumab or ribavirin for RSV infection remains controversial. New agents, some host-directed, are under study. Influenza also occurs in HSC transplant recipients and generally mirrors the presence of infection in the community. Progression to pneumonia is more common when infection occurs early after transplantation and when the recipient is lymphopenic. The neuraminidase inhibitors oseltamivir (oral) and zanamivir (aerosolized) are active against both influenza A virus and influenza B virus and are a reasonable treatment option. Parenteral forms of neuraminidase inhibitors such as peramivir (intravenous) are available in some countries, and several new oral agents are still being assessed in trials. An important preventive measure is immunization of household members, hospital staff members, and other frequent contacts. Adenoviruses can be isolated from HSC transplant recipients at rates varying from 5 to ≥18%. Like CMV infection, adenovirus infection usually occurs in the first to third month after transplantation and is often asymptomatic, although pneumonia, hemorrhagic cystitis/nephritis, severe gastroenteritis with hemorrhage, and fatal disseminated infection have been reported and may be strain-specific. Banked virus-specific T cell therapy is under study for adenovirus infection (as well as for CMV and EBV infections).

Although diverse respiratory viruses can sometimes cause severe pneumonia and respiratory failure in HSC transplant recipients, mild or even asymptomatic infection may be more common. For example, rhinoviruses and coronaviruses are frequent co-pathogens in HSC transplant recipients; however, whether they independently contribute to significant pulmonary infection is not known. At present, the overall contribution of these viral respiratory pathogens to the burden of lower respiratory tract disease in HSC transplant recipients requires further study. Infections with parvovirus B19 (presenting as anemia or occasionally as pancytopenia) and disseminated enteroviruses (sometimes fatal) can occur. Parvovirus B19 infection can be treated with IVIg **(Chap. 192)**.

Rotaviruses, a cause of gastroenteritis in HSC transplant recipients, cause disease more frequently in children. Norovirus is a common cause of vomiting and diarrhea, and symptoms can be prolonged in HSC recipients. The BK virus (a polyomavirus) is found at high titers in the urine of patients who are profoundly immunosuppressed. BK viruria may be associated with hemorrhagic cystitis in these patients. In contrast to its incidence among patients with impaired T cell function due to AIDS (4–5%), progressive multifocal leukoencephalopathy caused by the related JC virus is relatively rare among HSC transplant recipients **(Chap. 133)**. When transmitted by mosquitoes or by blood transfusion, West Nile virus (WNV) can cause encephalitis and death after HSC transplantation.

INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS

Rates of morbidity and mortality among recipients of solid organ transplants (SOTs) are reduced by the use of effective antibiotics. The organisms that cause acute infections in recipients of SOTs are different from those that infect HSC transplant recipients because SOT recipients do not go through a period of neutropenia. As the transplantation procedure involves major surgery, however, SOT recipients are subject to infections at anastomotic sites and to wound infections. Compared with HSC transplant recipients, SOT patients are immunosuppressed for longer periods (often permanently). Thus they are susceptible to many of the same organisms as patients with chronically impaired T cell immunity (**Chap. 70**, especially **Table 70-1**). Moreover, the persistent HLA mismatch between recipient immune cells (e.g., effector T cells) and the donor organ (allograft) places the organ at permanently increased risk of infection.

During the early period (<1 month after transplantation; **Table 138-4**), infections are most commonly caused by extracellular bacteria (staphylococci, streptococci, enterococci, and *E. coli* and other gram-negative organisms, including nosocomial organisms with broad antibiotic resistance), which often originate in surgical-wound or anastomotic sites. The type of transplant largely determines the spectrum of infection. In subsequent weeks, the consequences of the administration of agents that suppress cell-mediated immunity become apparent, and acquisition—or, more commonly, reactivation—of viruses, mycobacteria, endemic fungi, and parasites (from the recipient or from the transplanted organ) can occur. CMV infection is often a problem, particularly in the first 6 months after transplantation, and may present as severe systemic disease or as infection of the transplanted organ. HHV-6 reactivation (assessed by plasma PCR) occurs within the first 2–4 weeks after transplantation and may be associated with fever, leukopenia, and very rare cases of encephalitis. Data suggest that replication of HHV-6 and HHV-7 may exacerbate CMV-induced disease. CMV is associated not only with generalized immunosuppression but also with organ-specific, rejection-related syndromes: glomerulopathy in kidney transplant recipients, bronchiolitis obliterans in lung transplant recipients, vasculopathy in heart transplant recipients, and the vanishing bile duct syndrome in liver transplant recipients. A complex interplay between increased CMV replication and enhanced graft rejection is well established: elevated immunosuppression leads to increased CMV replication, which is associated with graft rejection. For this reason, considerable attention has been focused on the diagnosis, prophylaxis, and treatment of CMV infection in SOT recipients. Early transmission of WNV to transplant recipients from a donated organ or transfused blood has been reported; however, the risk of WNV acquisition has been reduced by implementation of screening procedures. In rare instances, rabies virus and lymphocytic choriomeningitis virus also have been acutely transmitted in this setting; although accompanied by distinct clinical syndromes, both viral infections have resulted in fatal encephalitis. As screening for unusual viruses is not routine, only vigilant assessment of the prospective donor is likely to prevent the use of an infected organ.

Beyond 6 months after transplantation, infections characteristic of patients with defects in cell-mediated immunity—e.g., infections with *Listeria, Nocardia, Rhodococcus*, mycobacteria, various fungi, and other intracellular pathogens—may be a problem. International patients and global travelers may experience reactivation of dormant infections with trypanosomes, *Leishmania*, *Plasmodium*, *Strongyloides*, and other parasites. Reactivation of latent *M. tuberculosis* infection, while rare in Western nations, is far more common among persons from developing countries. The recipient is typically the source, although reactivation and spread from the donor organ can occur. While pulmonary disease remains most common, atypical sites can be involved and mortality rates can be high (up to 30%). Vigilance, prophylaxis/preemptive

TABLE 138-4 Common Infections after Solid Organ Transplantation, by Site of Infection

	PERIOD AFTER TRANSPLANTATION		
INFECTED SITE	EARLY (<1 MONTH)	MIDDLE (1–4 MONTHS)	LATE (>6 MONTHS)
Donor organ	Bacterial and fungal infections of the graft, anastomotic site, and surgical wound	CMV infection	EBV infection (may present in allograft organ)
Systemic	Bacteremia and candidemia (often resulting from central venous catheter colonization)	CMV infection (fever, bone marrow suppression)	CMV infection, especially in patients given early posttransplantation prophylaxis; EBV proliferative syndromes (may occur in donor organs)
Lung	Bacterial aspiration pneumonia with prevalent nosocomial organisms associated with intubation and sedation (highest risk in lung transplantation)	*Pneumocystis* infection; CMV pneumonia (highest risk in lung transplantation); *Aspergillus* infection (highest risk in lung transplantation)	*Pneumocystis* infection; granulomatous lung diseases (nocardial and reactivated fungal and mycobacterial diseases)
Kidney	Bacterial and fungal (*Candida*) infections (cystitis, pyelonephritis) associated with urinary tract catheters (highest risk in kidney transplantation)	Kidney transplantation: BK virus infection (associated with nephropathy); JC virus infection	Kidney transplantation: bacterial infections (late urinary tract infections, usually not associated with bacteremia); BK virus infection (nephropathy, graft failure, generalized vasculopathy)
Liver and biliary tract	Cholangitis	CMV hepatitis	CMV hepatitis
Heart		*Toxoplasma gondii* infection (highest risk in heart transplantation); endocarditis (*Aspergillus* and gram-negative organisms more common than in general population)	*T. gondii* (highest risk in heart transplantation)
Gastrointestinal tract	Peritonitis, especially after liver transplantation	Colitis secondary to *Clostridium difficile* infection (risk can persist)	Colitis secondary to *C. difficile* infection (risk can persist)
Central nervous system		*Listeria* infection (meningitis); *T. gondii* infection; CMV infection	Listerial meningitis; cryptococcal meningitis; nocardial abscess; JC virus-associated PML

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; PML, progressive multifocal leukoencephalopathy.

therapy (when indicated), and rapid diagnosis and treatment of infections can be lifesaving in SOT recipients, who, unlike most HSC transplant recipients, continue to be immunosuppressed.

SOT recipients are susceptible to EBV-LPD from as early as 2 months to many years after transplantation. The prevalence of this complication is increased by potent and prolonged use of T cell–suppressive drugs. Decreasing the degree of immunosuppression may in some cases reverse the condition. Among SOT patients, those with heart and lung transplants—who receive the most intensive immunosuppressive regimens—are most likely to develop EBV-LPD, particularly in the lungs. Although the disease usually originates in recipient B cells, several cases of donor origin, particularly in the transplanted organ, have been noted. High organ-specific content of B lymphoid tissues (e.g., bronchus-associated lymphoid tissue in the lung), anatomic factors (e.g., lack of access of host T cells to the transplanted organ because of disturbed lymphatics), and differences in major histocompatibility loci between the host T cells and the organ (e.g., lack of cell migration or lack of effective T cell/macrophage/dendritic cell cooperation) may result in defective elimination of EBV-infected B cells. SOT recipients are also highly susceptible to the development of Kaposi's sarcoma and, less frequently, to the B cell–proliferative disorders associated with KSHV, such as primary effusion lymphoma and multicentric Castleman's disease. Kaposi's sarcoma is 550–1000 times more common among SOT recipients than in the general population, can develop very rapidly after transplantation, and can also occur in the allograft. However, because the seroprevalence of KSHV is very low in Western countries, Kaposi's sarcoma is not common. Recipients (or donors) from Iceland, the Middle East, Mediterranean countries, and Africa are at highest risk of disease. Data suggest that a switch of immunosuppressive agents—from calcineurin inhibitors (cyclosporine, tacrolimus) to mTOR pathway–active agents (sirolimus, everolimus)—after adequate wound healing may significantly reduce the likelihood of development of Kaposi's sarcoma and perhaps of EBV-LPD and certain other posttransplantation malignancies.

KIDNEY TRANSPLANTATION

See Table 138-4.

Early Infections Bacteria often cause infections that develop in the period immediately after kidney transplantation. There is a role for perioperative antibiotic prophylaxis, and many centers give cephalosporins to decrease the risk of postoperative complications. Urinary tract infections developing soon after transplantation are usually related to anatomic alterations resulting from surgery. Such early infections may require prolonged treatment (e.g., 6 weeks of antibiotic administration for pyelonephritis). Urinary tract infections that occur >6 months after transplantation may be treated for shorter periods because they do not seem to be associated with the high rate of pyelonephritis or relapse seen with infections that occur during the first 3 months.

Prophylaxis with TMP-SMX for the first 4–6 months after transplantation decreases the incidence of early and middle-period infections (see below, Table 138-4, and **Table 138-5**).

Middle-Period Infections Because of continuing immunosuppression, kidney transplant recipients are predisposed to lung infections characteristic of those in patients with T-cell deficiency (i.e., infections with intracellular bacteria, mycobacteria, nocardiae, fungi, viruses, and parasites). A high mortality rate associated with *Legionella pneumophila* infection **(Chap. 154)** led to the closing of renal transplant units in hospitals with endemic legionellosis.

About 50% of all renal transplant recipients presenting with fever 1–4 months after transplantation have evidence of CMV disease; CMV itself accounts for the fever in more than two-thirds of cases and thus is the predominant pathogen during this period. CMV infection **(Chap. 190)** may also present as arthralgias, myalgias, or organ-specific symptoms. During this period, this infection may represent primary disease (in the case of a seronegative recipient of a kidney from a seropositive donor) or may represent reactivation disease or superinfection. Patients may have atypical lymphocytosis. Unlike immunocompetent patients, however, they rarely have lymphadenopathy or splenomegaly. Therefore, clinical suspicion and laboratory confirmation are necessary for diagnosis. The clinical syndrome may be accompanied by bone marrow suppression (particularly leukopenia). CMV also causes glomerulopathy and is associated with an increased incidence of other opportunistic infections. Because of the frequency and severity of disease, a considerable effort has been made to prevent and treat CMV infection in renal transplant recipients. An immune globulin preparation enriched with antibodies to CMV was used by many centers in the past in an effort to protect the group at highest risk for severe infection (seronegative recipients of seropositive kidneys). However,

TABLE 138-5 Prophylactic Regimens Commonly Used to Decrease Risk of Infection in Transplant Recipients[a]

RISK FACTOR	ORGANISM	PROPHYLACTIC DRUG	EXAMINATION(S)[b]
Travel to or residence in area with known risk of endemic fungal infection	*Histoplasma*, *Blastomyces*, *Coccidioides*	Triazoles considered in context of clinical and laboratory assessment	Chest radiography, antigen testing, serology
Latent herpesviruses	HSV, VZV, CMV, EBV	Acyclovir after HSC transplantation to prevent HSV and VZV infection or reactivation; ganciclovir to prevent CMV infection, with possible effect on EBV/KSHV (HHV-8)/HHV-6 infections in some settings	Serologic tests for HSV, VZV, CMV, HHV-6, EBV, KSHV (HHV-8); PCR
Latent fungi and parasites	*Pneumocystis jirovecii*, *Toxoplasma gondii*	Trimethoprim-sulfamethoxazole (or alternatives)	Serologic test for *Toxoplasma*
History of exposure to active or latent tuberculosis	*Mycobacterium tuberculosis*	Isoniazid in patients with recent seroconversion or positive chest imaging and/or no previous treatment	Chest imaging; TST and/or cell-based assay

[a]For information on latent infection with hepatitis B or C virus, see **Chap. 334**. [b]Serologic examination, tuberculin skin test, and interferon assays may be less reliable after transplantation.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSC, hematopoietic stem cell; HSV, herpes simplex virus; KSHV, Kaposi's sarcoma–associated herpesvirus; PCR, polymerase chain reaction; TST, tuberculin skin test; VZV, varicella-zoster virus.

with the development of effective oral antiviral agents, CMV immune globulin is no longer used. Ganciclovir (or valganciclovir) is beneficial for prophylaxis (when indicated) and for the treatment of serious CMV disease. The availability of valganciclovir has allowed most centers to move to oral prophylaxis for transplant recipients. Infection with the other herpesviruses may become evident within 6 months after transplantation or later. Early after transplantation, HSV may cause either oral or anogenital lesions that are usually responsive to acyclovir. Large ulcerating lesions in the anogenital area may lead to bladder and rectal dysfunction and may predispose the patient to bacterial infection. VZV may cause fatal disseminated infection in nonimmune kidney transplant recipients, but in immune patients reactivation zoster usually does not disseminate outside the dermatome; thus disseminated VZV infection is a less fearsome complication in kidney transplantation than in HSC transplantation. HHV-6 reactivation may take place and (although usually asymptomatic) may be associated with fever, rash, marrow suppression, or rare instances of renal impairment, hepatitis, colitis, or encephalitis.

EBV disease is more serious; it may present as an extranodal proliferation of B cells that invade the CNS, nasopharynx, liver, small bowel, heart, and other organs, including the transplanted kidney. The disease is diagnosed by the finding of a mass of proliferating EBV-positive B cells. The incidence of EBV-LPD is elevated among patients who acquire EBV infection from the donor and among patients given high doses of cyclosporine, tacrolimus, glucocorticoids, and anti–T cell antibodies. Disease may regress once immunocompetence is restored. KSHV infection can be transmitted with the donor kidney and result in the development of Kaposi's sarcoma, although it more often represents reactivation of latent infection in the recipient. Kaposi's sarcoma often appears within 1 year after transplantation, although the time of onset ranges widely (1 month to ~20 years). Avoidance of immunosuppressive agents that inhibit calcineurin has been associated with less Kaposi's sarcoma, less EBV disease, and even less CMV replication. The use of rapamycin (sirolimus) has independently led to regression of Kaposi's sarcoma.

The polyomaviruses BK virus and JC virus (polyomavirus hominis types 1 and 2) have been cultured from the urine of kidney transplant recipients (as they have from that of HSC transplant recipients) in the setting of profound immunosuppression. High levels of BK virus replication detected by PCR in urine and blood are predictive of pathology, especially in the setting of renal transplantation. JC virus may rarely cause similar disease in kidney transplantation. Urinary excretion of BK virus and BK viremia are associated with the development of ureteral strictures, polyomavirus-associated nephropathy (1–10% of renal transplant recipients), and (less commonly) generalized vasculopathy. Timely detection and early reduction of immunosuppression are critical and can reduce rates of graft loss related to polyomavirus-associated nephropathy from 90 to 10–30%. Therapeutic responses to IVIg, quinolones, leflunomide, and cidofovir have been reported, but the efficacy of these agents has not been substantiated through adequate clinical study. Most centers approach the problem by reducing immunosuppression in an effort to enhance host immunity and decrease viral titers. JC virus is associated with rare cases of progressive multifocal leukoencephalopathy. Adenoviruses may persist and cause hemorrhagic nephritis/cystitis with continued immunosuppression in these patients, but disseminated disease, like that seen in HSC transplant recipients, is much less common.

Kidney transplant recipients are also subject to infections with other intracellular organisms. These patients may develop pulmonary infections with *Mycobacterium, Aspergillus*, and *Mucor* species as well as infections with other pathogens in which the T cell/macrophage axis plays an important role. *L. monocytogenes* is a common cause of bacteremia ≥1 month after renal transplantation and should be seriously considered in renal transplant recipients presenting with fever and headache. Kidney transplant recipients may develop *Salmonella* bacteremia, which can lead to endovascular infections and require prolonged therapy. Pulmonary infections with *Pneumocystis* are common unless the patient is maintained on TMP-SMX prophylaxis. Acute interstitial nephritis caused by TMP-SMX is rare. However, because transient increases in creatinine (artifactual) and hyperkalemia (manageable) can occur, early discontinuation of prophylaxis, especially after kidney transplantation, is recommended by some groups. Although additional monitoring is indicated, the benefits of TMP-SMX in kidney transplant recipients may outweigh the risks; otherwise, second-line prophylactic agents should be used. *Nocardia* infection **(Chap. 169)** may present in the skin, bones, and lungs or in the CNS, where it usually takes the form of single or multiple brain abscesses. Nocardiosis generally occurs ≥1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. Pulmonary manifestations most commonly consist of localized disease with or without cavities, but the disease may be disseminated. The diagnosis is made by culture of the organism from sputum or from the involved nodule. As it is for *P. jirovecii* infection, prophylaxis with TMP-SMX is often efficacious in the prevention of nocardiosis.

Toxoplasmosis can occur in seropositive patients but is less common than in other transplantation settings, usually developing in the first few months after kidney transplantation. Again, TMP-SMX is helpful in prevention. In endemic areas, histoplasmosis, coccidioidomycosis, and blastomycosis may cause pulmonary infiltrates or disseminated disease.

Late Infections Late infections (>6 months after kidney transplantation) may involve the CNS and include CMV retinitis as well as other CNS manifestations of CMV disease. Patients (particularly those whose immunosuppression has been increased) are at risk for subacute meningitis due to *Cryptococcus neoformans*. Cryptococcal disease may present in an insidious manner (sometimes as a skin infection before the development of clear CNS findings). *Listeria* meningitis may have

an acute presentation and requires prompt therapy to avoid a fatal outcome. TMP-SMX prophylaxis may reduce the frequency of *Listeria* infections.

Patients who continue to take glucocorticoids are predisposed to ongoing infection. "Transplant elbow," a recurrent bacterial infection in and around the elbow that is thought to result from a combination of poor tensile strength of the skin of steroid-treated patients and steroid-induced proximal myopathy, requires patients to push themselves up with their elbows to get out of chairs. Bouts of cellulitis (usually caused by *S. aureus*) recur until patients are provided with elbow protection.

Kidney transplant recipients are susceptible to invasive fungal infections, including those due to *Aspergillus* and *Rhizopus*, which may present as superficial lesions before dissemination. Mycobacterial infection (particularly that with *Mycobacterium marinum*) can be diagnosed by skin examination. Infection with *Prototheca wickerhamii* (an achlorophyllic alga) has been diagnosed by skin biopsy. Warts caused by human papillomaviruses (HPVs) are a late consequence of persistent immunosuppression; imiquimod or other forms of local therapy are usually satisfactory. Merkel cell carcinoma, a rare and aggressive neuroendocrine skin tumor whose frequency is increased fivefold in elderly SOT (especially kidney) recipients, is causally linked to a novel polyomavirus, Merkel cell polyomavirus.

Notably, although BK virus replication and virus-associated disease can be detected far earlier, polyomavirus-associated nephropathy is clinically diagnosed at a median of ~300 days and thus qualifies as a late-onset disease. With the establishment of better screening procedures (e.g., urine cytology, urine nucleic acid load, plasma PCR), disease onset is being detected earlier (see "Middle-Period Infections," above), and preemptive strategies (decrease or modification of immunosuppression) are being instituted more promptly, as the efficacy of antiviral therapy is not well established.

HEART TRANSPLANTATION

Early Infections Sternal wound infection and mediastinitis are early complications of heart transplantation. An indolent course is common, with fever or a mildly elevated white blood cell count preceding the development of site tenderness or drainage. Clinical suspicion based on evidence of sternal instability and failure to heal may lead to the diagnosis. Common microbial residents of the skin (e.g., *S. aureus*, including methicillin-resistant strains, and *Staphylococcus epidermidis*) as well as gram-negative organisms (e.g., *Pseudomonas aeruginosa*) and fungi (e.g., *Candida*) are often involved. In rare cases, mediastinitis in heart transplant recipients can also be due to *Mycoplasma hominis* **(Chap. 183)**; since this organism requires an anaerobic environment for growth and may be difficult to see on conventional medium, the laboratory should be alerted that its involvement is suspected. *M. hominis* mediastinitis has been cured with a combination of surgical debridement (sometimes requiring muscle-flap placement) and the administration of clindamycin and tetracycline. Organisms associated with mediastinitis may sometimes be cultured from pericardial fluid.

Middle-Period Infections *T. gondii* **(Chap. 223)** residing in the heart of a seropositive donor may be transmitted to a seronegative recipient. Thus serologic screening for *T. gondii* infection is important before and in the months after cardiac transplantation. Rarely, active disease can be introduced at the time of transplantation. The overall incidence of toxoplasmosis is so high in the setting of heart transplantation that some prophylaxis is always warranted. Although alternatives are available, the most frequently used agent is TMP-SMX, which prevents infection with *Pneumocystis* as well as with *Nocardia* and several other bacterial pathogens. CMV also has been transmitted by heart transplantation. *Toxoplasma*, *Nocardia*, and *Aspergillus* can cause CNS infections. *L. monocytogenes* meningitis should be considered in heart transplant recipients with fever and headache.

CMV infection is associated with poor outcomes after heart transplantation. The virus is usually detected 1–2 months after transplantation, causes early signs and laboratory abnormalities (usually fever and atypical lymphocytosis or leukopenia and thrombocytopenia) at 2–3 months, and can produce severe disease (e.g., pneumonia) at 3–4 months. An interesting observation is that seropositive recipients usually develop viremia faster than patients whose primary CMV infection is a consequence of transplantation. Between 40 and 70% of patients develop symptomatic CMV disease in the form of (1) CMV pneumonia, the form most likely to be fatal; (2) CMV esophagitis and gastritis, sometimes accompanied by abdominal pain with or without ulcerations and bleeding; and (3) the CMV syndrome, consisting of CMV in the bloodstream along with fever, leukopenia, thrombocytopenia, and hepatic enzyme abnormalities. Ganciclovir is efficacious in the treatment of CMV infection; prophylaxis with ganciclovir or possibly with other antiviral agents may reduce the overall incidence of CMV-related disease.

Late Infections EBV infection usually presents as a lymphoma-like proliferation of B cells late after heart transplantation, particularly in patients maintained on intense immunosuppressive therapy. A subset of heart and heart–lung transplant recipients may develop early fulminant EBV-LPD (within 2 months). Treatment includes the reduction of immunosuppression (if possible), the use of glucocorticoid and calcineurin inhibitor–sparing regimens, and the consideration of therapy with anti–B cell antibodies (rituximab and possibly others). Immunomodulatory and antiviral agents continue to be studied. Ganciclovir prophylaxis for CMV disease may indirectly reduce the risk of EBV-LPD through reduced spread of replicating EBV to naïve B cells. Aggressive chemotherapy is a last resort, as discussed earlier for HSC transplant recipients. KSHV-associated disease, including Kaposi's sarcoma and primary effusion lymphoma, has been reported in heart transplant recipients. GVHD prophylaxis with sirolimus may decrease the risk of both rejection and outgrowth of KSHV-infected cells. Antitumor therapy is discussed in **Chap. 69**. Prophylaxis for *Pneumocystis* infection is required for these patients (see "Lung Transplantation, Late Infections," below).

LUNG TRANSPLANTATION

Early Infections It is not surprising that lung transplant recipients are predisposed to the development of pneumonia. The combination of ischemia and the resulting mucosal damage, together with accompanying denervation and lack of lymphatic drainage, probably contributes to the high rate of pneumonia (66% in one series). The prophylactic use of high doses of broad-spectrum antibiotics for the first 3–4 days after surgery may decrease the incidence of pneumonia. Gram-negative pathogens (Enterobacteriaceae and *Pseudomonas* species) are troublesome in the first 2 weeks after surgery (the period of maximal vulnerability). Pneumonia can also be caused by *Candida* (including drug-resistant strains of *C. auris*), possibly as a result of colonization of the donor lung, and by *Aspergillus* and *Cryptococcus.* Many centers use antifungal prophylaxis (typically fluconazole or liposomal amphotericin B) for the first 1–2 weeks.

Mediastinitis may occur at an even higher rate among lung transplant recipients than among heart transplant recipients and most commonly develops within 2 weeks of surgery. In the absence of prophylaxis, pneumonitis due to CMV (which may be transmitted as a consequence of transplantation) usually presents between 2 weeks and 3 months after surgery, with primary disease occurring later than reactivation disease.

Middle-Period Infections The incidence of CMV infection, either reactivated or primary, is 75–100% if either the donor or the recipient is seropositive for CMV. CMV-induced disease after solid organ transplantation appears to be most severe in recipients of lung and heart–lung transplants. Whether this severity relates to the mismatch in lung antigen presentation and host immune cells or is attributable to nonimmunologic factors is not known. More than half of lung transplant recipients with symptomatic CMV disease have pneumonia. Difficulty in distinguishing the radiographic picture of CMV infection from that of other infections or from organ rejection further complicates therapy. CMV can also cause bronchiolitis obliterans in lung transplants. The development of pneumonitis related to HSV

has led to the prophylactic use of acyclovir. Such prophylaxis may also decrease rates of CMV disease, but ganciclovir is more active against CMV and is also active against HSV. The prophylaxis of CMV infection with IV ganciclovir—or increasingly with valganciclovir, the oral alternative—is recommended for lung transplant recipients. Antiviral alternatives are discussed in the earlier section on HSC transplantation. Although the overall incidence of serious disease is decreased during prophylaxis, late disease may occur when prophylaxis is stopped—a pattern observed increasingly in recent years. With recovery from peritransplantation complications and, in many cases, a decrease in immunosuppression, the recipient is often better equipped to combat late infection.

Late Infections The incidence of *Pneumocystis* infection (which may present with a paucity of findings) is high among lung and heart–lung transplant recipients. Some form of prophylaxis for *Pneumocystis* pneumonia is indicated in all organ transplant situations (Table 138-5). Prophylaxis with TMP-SMX for 12 months after transplantation may be sufficient to prevent *Pneumocystis* disease in patients whose immunosuppression is not increased.

As in other transplant recipients, EBV infection in lung and heart–lung recipients may cause either a mononucleosis-like syndrome or EBV-LPD. The tendency of the B cell blasts to present in the lung appears to be greater after lung transplantation than after the transplantation of other organs, possibly because of a rich source of B cells in bronchus-associated lymphoid tissue. Reduction of immunosuppression and switching of regimens, as discussed in earlier sections, cause remission in some cases, but mTOR inhibitors such as rapamycin may contribute to lung toxicity. Airway compression can be fatal, and rapid intervention may, therefore, become necessary. The approach to EBV-LPD is similar to that described in other sections.

LIVER TRANSPLANTATION

Early Infections As in other transplantation settings, early bacterial infections are a major problem after liver transplantation. Many centers administer systemic broad-spectrum antibiotics for the first 24 h or sometimes longer after surgery, even in the absence of documented infection. However, despite prophylaxis, infectious complications are common and correlate with the duration of the surgical procedure and the type of biliary drainage. An operation lasting >12 h is associated with an increased likelihood of infection. Patients who have a choledochojejunostomy with drainage of the biliary duct to a Roux-en-Y jejunal bowel loop have more fungal infections than those whose bile is drained via anastomosis of the donor common bile duct to the recipient common bile duct. Overall, liver transplant patients have a high incidence of fungal infections, and the occurrence of fungal (often candidal) infection in the setting of choledochojejunostomy correlates with re-transplantation, elevated creatinine levels, long procedures, transfusion of >40 units of blood, reoperation, preoperative use of glucocorticoids, prolonged treatment with antibacterial agents, and fungal colonization 2 days before and 3 days after surgery. Many centers give antifungal agents prophylactically in this setting.

Peritonitis and intraabdominal abscesses are common complications of liver transplantation. Bacterial peritonitis or localized abscesses may result from biliary leaks. Early leaks are especially common with live-donor liver transplants. Peritonitis in liver transplant recipients is often polymicrobial, frequently involving enterococci, aerobic gram-negative bacteria, staphylococci, anaerobes, or *Candida* and sometimes involving other invasive fungi. Only one-third of patients with intraabdominal abscesses have bacteremia. Abscesses within the first month after surgery may occur not only in and around the liver but also in the spleen, pericolic area, and pelvis. Treatment includes antibiotic administration and drainage as necessary. Not surprisingly, *C. difficile* colitis is also a problem in this setting **(Chap. 129)**.

Middle-Period Infections The development of postsurgical biliary stricture predisposes patients to cholangitis. The incidence of strictures is increased in live-donor liver transplantation. Transplant recipients who develop cholangitis may have high spiking fevers and rigors but often lack the characteristic signs and symptoms of classic cholangitis, including abdominal pain and jaundice. Although these findings may suggest graft rejection, rejection is typically accompanied by marked elevation of liver function enzymes. In contrast, in cholangitis in transplant recipients, results of liver function tests (with the possible exception of alkaline phosphatase levels) are often within the normal range. Definitive diagnosis of cholangitis in liver transplant recipients requires demonstration of aggregated neutrophils in bile duct biopsy specimens. Unfortunately, invasive studies of the biliary tract (either T-tube cholangiography or endoscopic retrograde cholangiopancreatography) may themselves lead to cholangitis. For this reason, many clinicians recommend an empirical trial of therapy with antibiotics covering gram-negative organisms and anaerobes before these procedures are undertaken as well as antibiotic coverage if procedures are eventually performed.

Reactivation of viral hepatitis is a common complication of liver transplantation **(Chap. 332)**. Recurrent hepatitis B and C infections, for which transplantation may be performed, are problematic. To prevent hepatitis B virus reinfection, prophylaxis with an optimal antiviral agent or combination of agents (lamivudine, adefovir, entecavir) and hepatitis B immune globulin is currently recommended, although the optimal dose, route, and duration of therapy remain controversial. Success in preventing reinfection with hepatitis B virus has increased in recent years. Complications related to hepatitis C infection are the most common reason for liver transplantation in the United States. Without treatment, reinfection of the graft with hepatitis C virus occurs in all patients, with a variable time frame. Recent studies employing direct-acting antivirals have provided impressive results in both the treatment of existing infections before transplantation and the prevention of infections after transplantation in patients with hepatitis C **(Chap. 332)**.

As in other transplantation settings, reactivation disease with herpesviruses is common (Table 138-3). Herpesviruses can be transmitted in donor organs. Although CMV hepatitis occurs in ~4% of liver transplant recipients, it is usually not so severe as to require re-transplantation. Without prophylaxis, CMV disease develops in the majority of seronegative recipients of organs from CMV-positive donors, but fatality rates are lower among liver transplant recipients than among lung or heart–lung transplant recipients. Disease due to CMV has also been associated with the vanishing bile duct syndrome after liver transplantation. Liver transplant recipients with high levels of CMV respond to treatment with ganciclovir; prophylaxis with oral forms of ganciclovir or valganciclovir decreases the frequency of disease. A role for HHV-6 reactivation in early posttransplantation fever and leukopenia has been proposed, although the more severe sequelae described in HSC transplantation are unusual. HHV-6 and HHV-7 appear to exacerbate CMV disease in this setting. EBV-LPD after liver transplantation shows a propensity for involvement of the liver, and such disease may be of donor origin. See previous sections for discussion of EBV infections in solid organ transplantation.

PANCREAS TRANSPLANTATION

Pancreas transplantation is most frequently performed together with or after kidney transplantation, although it may be performed alone. Transplantation of the pancreas can be complicated by early bacterial and yeast infections. Most pancreatic transplants are drained into the bowel, and the rest are drained into the bladder. A cuff of duodenum is used in the anastomosis between the pancreatic graft and either the gut or the bladder. Bowel drainage poses a risk of early intraabdominal and allograft infections with enteric bacteria and yeasts. These infections can result in loss of the graft. Bladder drainage causes a high rate of urinary tract infection and sterile cystitis; however, such infection can usually be cured with appropriate antimicrobial agents. In both procedures, prophylactic antimicrobial agents are commonly used at the time of surgery. Aggressive immunosuppression, especially when the patient receives a kidney and a pancreas from different donors, is associated with late-onset systemic fungal and viral infections; thus, many centers administer an antifungal drug and an antiviral agent (ganciclovir or a congener) for extended prophylaxis.

Issues related to the development of CMV infection, EBV-LPD, and infections with opportunistic pathogens in patients receiving a pancreatic transplant are similar to those in other SOT recipients.

COMPOSITE-TISSUE TRANSPLANTATION

Composite-tissue allotransplantation (CTA) is a new field in which, rather than a single organ, multiple tissue types composing a major body part are transplanted. The sites involved have included hands, feet, arms, legs, face, trachea, and abdominal wall. The numbers of recipients are limited. The different procedures and the associated infectious complications vary. Nevertheless, some early trends related to infectious complications have become apparent, as very intense and prolonged immunosuppression is typically required to prevent rejection. For example, in the early postoperative period, bacterial infections are especially frequent in facial transplant recipients. Perioperative prophylaxis is tailored to the organisms likely to complicate the different procedures. As in SOT recipients, complicated CMV infections have been observed in several CTA settings, particularly when the recipient is seronegative and the donor is seropositive. In some patients, anti-CMV immune globulin in addition to ganciclovir (as used in HSC transplant recipients with CMV pneumonia) was needed to control disease, and ganciclovir resistance requiring alternative therapies developed in several patients. Infectious complications from reactivation of other members of the human herpesvirus family and other latent viruses also caused significant morbidity, as discussed for SOT recipients. Prophylaxis for CMV infection, *P. jirovecii* infection, toxoplasmosis, and fungal infection is administered for several months on the basis of the limited studies available.

MISCELLANEOUS INFECTIONS IN SOLID ORGAN TRANSPLANTATION

Indwelling IV Catheter Infections The prolonged use of indwelling IV catheters for administration of medications, blood products, and nutrition is common in diverse transplantation settings and poses a risk of local and bloodstream infections. Exit-site infection is most commonly caused by staphylococcal species. Bloodstream infection most frequently develops within 1 week of catheter placement or in patients who become neutropenic. Coagulase-negative staphylococci are the most common isolates from blood. Although infective endocarditis in HSC transplant recipients is uncommon, the incidence of endocarditis among SOT recipients has been estimated to be as high as 1%, and this infection is associated with excessive high mortality in this population. Although staphylococci predominate, the involvement of fungal and gram-negative organisms may be more common than in the general population. **For further discussion of differential diagnosis and therapeutic options, see Chap. 70.**

Tuberculosis The incidence of tuberculosis within the first 12 months after solid organ transplantation is greater than that observed after HSC transplantation (0.23–0.79%) and ranges broadly worldwide (1.2–15%), reflecting the prevalence of tuberculosis in local populations. Lesions suggesting prior tuberculosis on chest radiography, older age, diabetes, chronic liver disease, GVHD, and intense immunosuppression are predictive of tuberculosis reactivation and development of disseminated disease in a host with latent disease. Tuberculosis has rarely been transmitted from the donor organ. In contrast to the low mortality rate among HSC transplant recipients, mortality rates among SOT recipients are reported to be as high as 30%. Vigilance is indicated, as the presentation of disease is often extrapulmonary (gastrointestinal, genitourinary, central nervous, endocrine, musculoskeletal, laryngeal) and atypical; tuberculosis in this setting sometimes manifests as fever of unknown origin. Careful elicitation of a history and direct evaluation of both the recipient and the donor prior to transplantation are optimal. Skin testing of the recipient with purified protein derivative may be unreliable because of chronic disease and/or immunosuppression. Cell-based assays that measure interferon γ and/or cytokine production may prove more sensitive in the future. Isoniazid toxicity has not been a significant problem except in the setting of liver transplantation. Therefore, appropriate prophylaxis should be used (see recommendations from the Centers for Disease Control and Prevention [CDC] at *www.cdc.gov/tb/topic/treatment/ltbi.htm*). An assessment of the need to treat latent disease should include careful consideration of the possibility of a false-negative test result. Pending final confirmation of suspected tuberculosis, aggressive multidrug treatment in accordance with the guidelines of the CDC, the Infectious Diseases Society of America, and the American Thoracic Society is indicated because of the high mortality rates among these patients. Altered drug metabolism (e.g., upon coadministration of antituberculous medications and certain immunosuppressive agents) can be managed with careful monitoring of drug levels and appropriate dose adjustment. Close follow-up of hepatic enzymes is warranted. Drug-resistant tuberculosis is especially problematic in these individuals **(Chap. 173)**.

Virus-Associated Malignancies In addition to malignancy associated with gammaherpesvirus infection (EBV, KSHV) and simple warts (HPV), other tumors that are virus-associated or suspected of being virus-associated are more likely to develop in transplant recipients, particularly those who require long-term immunosuppression, than in the general population. The interval to tumor development is usually >1 year. Transplant recipients develop nonmelanoma skin or lip cancers that, in contrast to de novo skin cancers, have a high ratio of squamous cells to basal cells. HPV may play a major role in these lesions. Cervical and vulvar carcinomas, which are quite clearly associated with HPV, develop with increased frequency in female transplant recipients. The frequency of Merkel cell carcinoma associated with Merkel cell polyomavirus is also increased among transplant recipients; however, it is unclear whether recipients infected with HTLV-1 are at increased risk of leukemia. Among renal transplant recipients, rates of melanoma are modestly increased and rates of cancers of the kidney and bladder are increased. Recommendations for dealing with these problems include vaccination against HPV, a switch from calcineurin inhibitors to mTOR inhibitors (see above), and reduction of immunosuppression to the lowest level possible without graft rejection.

VACCINATION OF TRANSPLANT RECIPIENTS

(See also Chap. 118) In addition to receiving antibiotic prophylaxis, transplant recipients should be vaccinated against likely pathogens **(Table 138-6)**. In the case of HSC transplant recipients, optimal responses cannot be achieved until after immune reconstitution, despite previous immunization of both donor and recipient. Recipients of an allogeneic HSC transplant must be reimmunized if they are to be protected against pathogens. The situation is less clear-cut in the case of autologous transplantation. T and B cells in the peripheral blood may reconstitute the immune response if they are transferred in adequate numbers. However, cancer patients (particularly those with Hodgkin's disease, in whom vaccination has been extensively studied) who are undergoing chemotherapy do not respond normally to immunization, and titers of antibodies to infectious agents fall more rapidly than in healthy individuals. Therefore, even immunosuppressed patients who have not undergone HSC transplantation may need booster vaccine injections. If memory cells are specifically eliminated as part of a stem cell "cleanup" procedure, it will be necessary to reimmunize the recipient with a new primary series. Optimal times for immunizations of different transplant populations are being evaluated. Yearly immunization of household and other contacts (including health care personnel) against influenza benefits the patient by preventing local spread.

In the absence of compelling data as to optimal timing, it is reasonable to administer the pneumococcal and *H. influenzae* type b conjugate vaccines to both autologous and allogeneic HSC transplant recipients beginning 12 months after transplantation. A series that includes both the 13-valent pneumococcal conjugate vaccine (Prevnar®) and the 23-valent pneumococcal polysaccharide vaccine (Pneumovax®) is now recommended (according to CDC guidelines). The pneumococcal and *H. influenzae* type b vaccines are particularly important for patients who have undergone splenectomy. The *Neisseria meningitidis* polysaccharide conjugate vaccine (Menactra® or Menveo®) also is recommended. In addition, diphtheria, tetanus, acellular pertussis, and inactivated polio

TABLE 138-6 Vaccination of Hematopoietic Stem Cell Transplant (HSCT) and Solid Organ Transplant (SOT) Recipients

VACCINE	TYPE OF TRANSPLANTATION	
	HSCT	SOT[a]
Streptococcus pneumoniae, *Haemophilus influenzae*, *Neisseria meningitidis*	Immunize after transplantation with *H. influenzae* conjugate vaccine and *N. meningitidis* conjugate vaccine. *S. pneumoniae* vaccine is given in two steps.[b]	Immunize before transplantation with *H. influenzae* conjugate and *N. meningitidis* conjugate vaccines. *S. pneumoniae* vaccine is given in two steps.[b]
Influenza	Vaccinate in the fall. Vaccinate close contacts.	Vaccinate in the fall. Vaccinate close contacts.
Polio	Administer inactivated vaccine.	Administer inactivated vaccine.
Measles/mumps/rubella	Immunize 24 months after transplantation if GVHD is absent.	Immunize before transplantation.
Diphtheria, pertussis, tetanus	Reimmunize after transplantation with primary series, DTaP. See IDSA 2013 recommendations (*www.idsociety.org/Other_Guidelines/#immunizationFortheCompromisedHost).*	Immunize or boost before transplantation with Tdap; give Td boosters at 10-year intervals or as required.
Hepatitis B and A	Reimmunize after transplantation. See recommendations.	Immunize before transplantation.
Human papillomavirus	3 doses for persons 9–26 years of age[c]	3 doses for persons 9–26 years of age[c]

[a]Immunizations should be given before SOT whenever possible. [b]Step 1: Administer one dose of the pneumococcal conjugate vaccine Prevnar® (13-valent pneumococcal vaccine, PCV13) to all transplant candidates. If a candidate has previously been vaccinated with Pneumovax® (23-valent pneumococcal vaccine, PPSV23), at least 6 months should have elapsed before Prevnar is administered. Step 2: Administer one dose of Pneumovax at least 8 weeks after vaccination with PCV13; follow with a booster dose of Pneumovax 5 years later. If the patient has previously been vaccinated with Pneumovax (i.e., before receiving Prevnar), at least 3 years should have elapsed before the second dose of Pneumovax is administered. [c]The second and third doses should follow the first dose after 1–2 months and 6 months, respectively. Centers for Disease Control (CDC) current recommendations: *https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm*. Some authorities recommend vaccination of all transplant recipients because of the risk of new sexual contacts later in life and the potential for human papillomavirus replication in immunocompromised patients.

Note: Recommendations from the CDC should be checked regularly as they frequently change upon receipt of new clinical information and new formulations of specific vaccines.

Abbreviations: DTaP, full-level diphtheria and tetanus toxoids and acellular pertussis, adsorbed; GVHD, graft-versus-host disease; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; IDSA, Infectious Diseases Society of America.

vaccines can all be given at these same intervals (12 months and, as required, 24 months after transplantation). Some authorities recommend a new primary series for tetanus/diphtheria/pertussis and inactivated poliovirus vaccines beginning 12 months after transplantation. Vaccination to prevent hepatitis B and hepatitis A (both killed vaccines) also seems advisable. HPV vaccination, which can prevent genital warts as well as specific cancers, is recommended through age 26 for healthy young adults who previously have not been vaccinated or have not received the full series. Live-virus measles/mumps/rubella (MMR) vaccine can be given to autologous HSC transplant recipients 24 months after transplantation and to most allogeneic HSC transplant recipients at 24 months if they are not receiving maintenance therapy with immunosuppressive drugs and do not have ongoing GVHD. The risk of spread from a household contact is low for MMR vaccine. In parts of the world where live poliovirus vaccine is used, patients as well as contacts should be advised to receive only the killed vaccine. In the rare setting where both donor and recipient are VZV naïve and the recipient is no longer receiving acyclovir or ganciclovir prophylaxis, the patient should be counseled to receive varicella-zoster immune globulin (VariZIG®) up to 10 days after exposure to a person with chickenpox or uncovered zoster; such patients should avoid close contact with persons recently vaccinated with Varivax®. Neither patients nor their household contacts should receive vaccinia vaccine unless they have been exposed to smallpox virus. Among patients who have active GVHD and/or are taking high maintenance doses of glucocorticoids, it may be prudent to avoid all live-virus vaccines.

In the case of SOT recipients, administration of all the usual vaccines and of the indicated booster doses should be completed before immunosuppression, if possible, to maximize responses. For patients taking immunosuppressive agents, the administration of pneumococcal vaccine should be repeated every 5 years. No data are available for the meningococcal vaccine, but it is probably reasonable to administer it along with the pneumococcal vaccine. *H. influenzae* conjugate vaccine is safe and should be efficacious in this population; therefore, its administration before transplantation is recommended. Booster doses of this vaccine are not recommended for adults. SOT recipients who continue to receive immunosuppressive drugs should not receive live-virus vaccines. A person in this group who is exposed to measles should be given measles immune globulin. Similarly, an immunocompromised patient who is seronegative for varicella and who comes into contact with a person who has chickenpox should be given varicella-zoster immune globulin as soon as possible (optimally within 96 h; up to 10 days after contact); if this is not possible, a 10- to 14-day course of acyclovir therapy should be started immediately. Upon the discontinuation of treatment, clinical disease may still occur in a small number of patients; thus vigilance is indicated. Rapid re-treatment with acyclovir should limit the symptoms of disease. Household contacts of transplant recipients can receive live attenuated VZV vaccine, but vaccinees should avoid direct contact with the patient if a rash develops. Virus-like particle vaccines have been licensed for the prevention of infection with several HPV serotypes most commonly implicated in cervical and anal carcinomas and in anogenital and laryngeal warts. These vaccines are not live; current CDC recommendations are for three doses in immunocompromised hosts.

Immunocompromised patients who travel may benefit from some but not all vaccines **(Chaps. 118 and 119)**. In general, these patients should receive any killed or inactivated vaccine preparation appropriate to the area they are visiting; this recommendation includes the vaccines for Japanese encephalitis, hepatitis A and B, poliomyelitis, meningococcal infection, and typhoid. Live typhoid vaccines are not recommended for use in most immunocompromised patients, but an inactivated or purified polysaccharide typhoid vaccine can be used. Live yellow fever vaccine should not be administered, nor should live cholera vaccine. On the other hand, primary immunization or boosting with the purified-protein hepatitis B vaccine is indicated. Inactivated hepatitis A vaccine should also be used in the appropriate setting **(Chap. 118)**. A vaccine is now available that provides dual protection against hepatitis A and hepatitis B. If hepatitis A vaccine is not administered, travelers should consider receiving passive protection with immune globulin (the dose depending on the duration of travel in the high-risk area).

FURTHER READING

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139 Treatment and Prophylaxis of Bacterial Infections

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Antimicrobial agents have had a major impact on human health. Together with vaccines, they have contributed to reduced mortality, extended lifespan, and enhanced quality of life. Among drugs used in human medicine, however, they are distinctive in that their use promotes the occurrence of drug resistance in the pathogens they are designed to treat as well as in other "bystander" organisms. Indeed, the history of antimicrobial development has been driven in large part by the medical need engendered by the emergence of resistance to each generation of agents. Thus, the careful and appropriate use of antimicrobial drugs is particularly important not only for optimizing efficacy and minimizing adverse effects but also for minimizing the risk of resistance and preserving the value of existing agents. Although this chapter focuses on antibacterial agents, the optimal use of all antimicrobials depends on an understanding of each drug's mechanism of action, spectrum of activity, mechanisms of resistance, pharmacology, and adverse effect profile. This information is applied in the context of the patient's clinical presentation, underlying conditions, and epidemiology to define the site and likely nature of the infection or other condition and thus to choose the best therapy. Gathering of microbiologic information is important for refining therapeutic choices on the basis of documented pathogen and susceptibility data whenever possible; this information also makes it possible to choose more targeted therapy, thereby reducing the risk of selection of resistant bacteria. Durations of therapy are chosen according to the nature of the infection and the patient's response to treatment and are informed by clinical studies when they are available, with the understanding that shorter courses are less likely than longer ones to promote the emergence of resistance. This chapter and the one that follows provide specific information that is necessary for making informed choices among antibacterial agents. The mechanisms of action of antibacterial agents are discussed in detail in the text of this chapter, and mechanisms of resistance are discussed in detail in Chap. 140. Both types of mechanisms are summarized for the most commonly used groups of agents in Table 139-1. A schematic of antibacterial targets is provided in Fig. 139-1.

MECHANISMS OF ACTION

Multiple essential components of bacterial cell structures and metabolism have been the targets of antibacterial agents used in clinical medicine, and the interaction of an agent with its target results in either inhibition of bacterial growth and replication (*bacteriostatic effect*) or bacterial killing (*bactericidal effect*). In general, targets have been chosen because they either do not exist in mammalian cells and physiology or are sufficiently different from their bacterial counterparts to allow selective bacterial targeting. Treatment with bacteriostatic agents is effective when the patient's host defenses are sufficient to contribute to eradication of the infecting pathogen. In patients with impaired host defenses (e.g., neutropenia) or infections at body sites with impaired or limited host defenses (e.g., meningitis and endocarditis), bactericidal agents are generally preferred.

INHIBITION OF CELL WALL SYNTHESIS

The bacterial cell wall, which is external to the cytoplasmic membrane and has no counterpart in mammalian cells, protects bacterial cells from lysis under low osmotic conditions. The cell wall is a cross-linked peptidoglycan composed of a polymer of alternating units of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM), four-amino-acid stem peptides linked to each NAM, and a peptide cross-bridge that links adjacent stem peptides to form a netlike structure. Several steps in peptidoglycan synthesis are targets of antibacterial agents. Inhibition of cell wall synthesis generally results in a bactericidal effect that is linked to cell lysis. This effect results not only from the blocking of new cell-wall formation but from the uninhibited action of cell wall–remodeling enzymes called *autolysins*, which cleave peptidoglycan as part of normal cell-wall growth.

In gram-positive bacteria the peptidoglycan is the most external cell structure, but in gram-negative bacteria an asymmetric lipid outer membrane is external to the peptidoglycan and contains diffusion channels called *porins*. The space between the cytoplasmic membrane peptidoglycan and the outer membrane is referred to as the *periplasmic space*. Most antibacterial drugs enter the gram-negative bacterial cell through a porin channel, since the outer membrane is a major diffusion barrier. Although the peptidoglycan layer is thicker in gram-positive (20–80 nm) than in gram-negative (1 nm) bacteria, peptidoglycan itself constitutes only a limited diffusion barrier for antibacterial agents.

β-Lactams The β-lactam drugs, including penicillins, cephalosporins, monobactams, and carbapenems, target transpeptidase enzymes (also called *penicillin-binding proteins* or PBPs) involved in the stem-peptide cross-linking step. Inhibitors of β-lactamases—enzymes that can degrade β-lactams—are used in combination with some β-lactams to expand their spectrum of activity.

Glycopeptides and Lipoglycopeptides The glycopeptides, including vancomycin and teicoplanin, and the lipoglycopeptides, including telavancin, dalbavancin, and oritavancin, bind the two terminal D-alanine residues of the stem peptide, hindering the glycosyltransferase involved in polymerizing NAG–NAM units as well as transpeptidases. Vancomycin also binds to the lipid II intermediate that delivers cell wall precursor subunits. The additional binding of teicoplanin, telavancin, dalbavancin, and oritavancin to the bacterial cytoplasmic membrane contributes to their increased potency. Both β-lactams and glycopeptides interact with their targets external to the cytoplasmic membrane.

Bacitracin (Topical) and Fosfomycin These agents interrupt enzymatic steps in the production of peptidoglycan precursors in the cytoplasm.

INHIBITION OF PROTEIN SYNTHESIS

Most inhibitors of bacterial protein synthesis target bacterial ribosomes, whose difference from eukaryotic ribosomes allows selective antibacterial action. Some inhibitors bind to the 30S ribosomal subunit and others to the 50S subunit. Most protein synthesis–inhibiting agents are bacteriostatic; aminoglycosides are an exception and are bactericidal.

Aminoglycosides Aminoglycosides (amikacin, gentamicin, kanamycin, netilmicin, streptomycin, and tobramycin) bind irreversibly to 16S ribosomal RNA (rRNA) of the 30S ribosomal subunit, blocking the translocation of peptidyl transfer RNA (tRNA) from the A (aminoacyl) to the P (peptidyl) site and, at low concentrations, causing misreading of messenger RNA (mRNA) codons and thus causing the introduction of incorrect amino acids into the peptide chain; at higher concentrations, translocation of the peptide chain is blocked. Cellular uptake of aminoglycosides is dependent on the electrochemical gradient across the bacterial membrane. Under anaerobic conditions, this gradient is reduced, with a consequent reduction in the uptake and activity of the aminoglycosides. Spectinomycin is a related aminocyclitol antibiotic that also binds to 16S rRNA of the 30S ribosomal subunit but at a different site. This drug inhibits translocation of the growing peptide chain but does not trigger codon misreading and produces only a bacteriostatic effect.

Tetracyclines and Glycylcyclines Tetracyclines (doxycycline, minocycline, and tetracycline) bind reversibly to the 16S rRNA of the 30S ribosomal subunit and block the binding of aminoacyl tRNA to the ribosomal A site, thereby inhibiting peptide elongation. Active transport of tetracyclines into bacterial but not mammalian cells contributes to the selectivity of these agents. Tigecycline, a derivative

TABLE 139-1 Mechanisms of Action of and Resistance to Antibacterial Agents

ANTIBACTERIAL AGENT(S)	MAJOR TARGET	MECHANISM(S) OF ACTION	MECHANISM(S) OF RESISTANCE
β-Lactams (penicillins, cephalosporins, monobactams, carbapenems)	Cell wall synthesis	Bind cell wall cross-linking enzymes (PBPs, transpeptidases)	1. Drug inactivation by β-lactamases 2. Altered PBP targets 3. Reduced diffusion through porin channels
Glycopeptides (vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin)	Cell wall synthesis	Block cell wall glycosyltransferases by binding D-Ala-D-Ala stem-peptide terminus Teicoplanin, telavancin, dalbavancin, and oritavancin: affect membrane function	1. Altered D-Ala-D-Ala target (D-Ala-D-Lac) 2. Increased D-Ala-D-Ala target binding at sites distant from cell wall synthesis enzymes
Bacitracin	Cell wall synthesis	Blocks lipid carrier of cell wall precursors	Active drug efflux
Fosfomycin	Cell wall synthesis	Blocks linkage of stem peptide to NAG by enoyltransferase	1. Target enzyme overexpression 2. Drug-modifying enzymes
Aminoglycosides (gentamicin, tobramycin, amikacin)	Protein synthesis	Bind 30S ribosomal subunit Block translocation of peptide chain Cause misreading of mRNA	1. Drug-modifying enzymes 2. Methylation at ribosome binding site 3. Decreased permeation to target due to active efflux
Tetracyclines (tetracycline, doxycycline, minocycline)	Protein synthesis	Bind 30S ribosomal subunit Inhibit peptide elongation	1. Active drug efflux 2. Ribosomal protection proteins
Tigecycline	Protein synthesis	Same as tetracyclines	Active drug efflux (pumps different from those affecting tetracyclines)
Macrolides (erythromycin, clarithromycin, azithromycin) and ketolide (telithromycin)	Protein synthesis	Bind 50S ribosomal subunit Block peptide chain exit	1. Methylation at ribosome binding site 2. Active drug efflux
Lincosamides (clindamycin)	Protein synthesis	Bind 50S ribosomal subunit Block peptide bond formation	Methylation at ribosome binding site
Streptogramins (quinupristin, dalfopristin)	Protein synthesis	Same as macrolides	1. Same as macrolides 2. Drug-modifying enzymes
Chloramphenicol	Protein synthesis	Binds 50S ribosomal subunit Blocks aminoacyl tRNA positioning	Drug-modifying enzymes
Oxazolidinones (linezolid, tedizolid)	Protein synthesis	Bind 50S ribosomal subunit Inhibit initiation of peptide synthesis	1. Altered rRNA binding site 2. Methylation of ribosome binding site
Mupirocin	Protein synthesis	Blocks isoleucyl tRNA synthetase	1. Acquired resistant tRNA synthetase (drug bypass) 2. Altered native tRNA synthetase target
Sulfonamides (sulfadiazine, sulfisoxazole, and sulfamethoxazole)	Folate synthesis	Inhibit dihydropteroate synthetase	Acquired resistant dihydropteroate synthetase (drug bypass)
Trimethoprim	Folate synthesis	Inhibits DHFR	Acquired resistant DHFR (drug bypass)
Quinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, delafloxacin)	DNA synthesis	Inhibit DNA gyrase and DNA topoisomerase IV Enzyme–DNA–drug complex: block DNA replication apparatus	1. Altered target(s) 2. Active efflux 3. Protection of target from drug 4. Drug-modifying enzyme (ciprofloxacin)
Rifamycins (rifampin, rifabutin, rifapentine)	RNA synthesis	Inhibit RNA polymerase	Altered target
Nitrofurantoin	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	Altered drug-activating enzymes
Metronidazole	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	1. Altered drug-activating enzyme 2. Acquired detoxifying enzymes 3. Active efflux
Polymyxins (polymyxin B and polymyxin E [colistin])	Cell membrane	Bind LPS and disrupt both outer and cytoplasmic membranes	Altered cell membrane charge with reduced drug binding
Daptomycin	Cell membrane	Produces membrane channel and membrane leakage	Altered cell membrane with reduced drug binding

Abbreviations: DHFR, dihydrofolate reductase; LPS, lipopolysaccharide; NAG, *N*-acetylglucosamine; PBP, penicillin-binding protein.

of minocycline and the only available glycylcycline, acts similarly to the tetracyclines but is distinctive for its ability to circumvent the most common mechanisms of resistance to the tetracyclines.

Macrolides and Ketolides In contrast to the aminoglycosides and tetracyclines, the macrolides (azithromycin, clarithromycin, and erythromycin) and ketolides (telithromycin) bind to the 23S rRNA of the 50S ribosomal subunit. These agents block translocation of the growing peptide chain by binding to the tunnel from which the chain exits the ribosome.

Lincosamides Clindamycin is the only lincosamide in clinical use. It binds to the 23S rRNA of the 50S ribosomal subunit, interacting with both the ribosomal A and P sites and blocking peptide bond formation.

Streptogramins The only streptogramin in clinical use is a combination of quinupristin, a group B streptogramin, and dalfopristin, a group A streptogramin. Both components bind to 23S rRNA of the 50S ribosome: dalfopristin binds to both the A and P sites of the peptidyl transferase center, and quinupristin binds to a site that overlaps the macrolide-binding site, blocking the emergence of nascent peptide from the ribosome. The combination is bactericidal, but macrolide-resistant bacteria exhibit cross-resistance to quinupristin, and the remaining activity of dalfopristin alone is only bacteriostatic.

Chloramphenicol Chloramphenicol binds reversibly to the 23S rRNA of the 50S subunit in a manner that interferes with the proper positioning of the aminoacyl component of tRNA in the A site. This site of binding is near those of the macrolides and lincosamides.

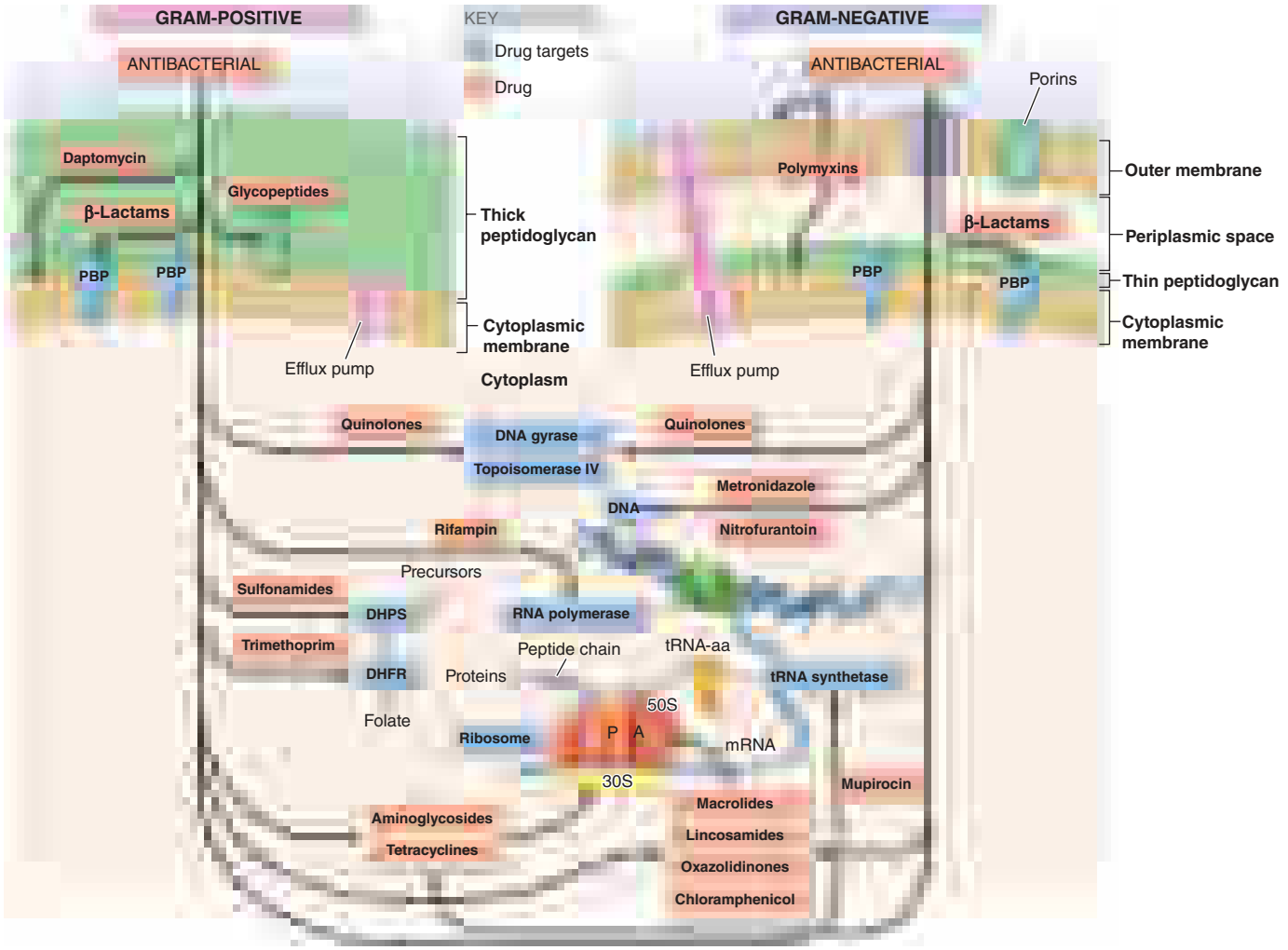

FIGURE 139-1 Antibacterial targets. A, aminoacyl site; DHFR, dihydrofolate reductase; DHPS, dihydropteroate synthetase; P, peptidyl site; PBP, penicillin-binding protein; tRNA-aa, aminoacyl tRNA.

Oxazolidinones Linezolid and tedizolid are the only oxazolidinones in clinical use. They bind directly to the A site in the 23S rRNA of the 50S ribosomal subunit and block binding of aminoacyl tRNA, inhibiting the initiation of protein synthesis.

Mupirocin Mupirocin (pseudomonic acid) is used topically. It competes with isoleucine for binding to isoleucyl tRNA synthetase, depleting stores of isoleucyl tRNA and thereby inhibiting protein synthesis.

INHIBITION OF BACTERIAL METABOLISM

Available inhibitors (antimetabolites) target the pathway for synthesis of folate, which is a cofactor in a number of one-carbon transfer reactions involved in the synthesis of some nucleic acids, including the pyrimidine thymidine and all purines (adenine and guanine), as well as some amino acids (methionine and serine) and acetyl coenzyme A. Two sequential steps in folate synthesis are targeted. The selective antibacterial effect stems from the inability of mammalian cells to synthesize folate; they depend instead on exogenous sources. Antibacterial activity, however, may be reduced in the presence of high exogenous concentrations of the end products of the folate pathway (e.g., thymidine and purines) that may occur in some infections, resulting from local breakdown of leukocytes and host tissues.

Sulfonamides Sulfonamides, including sulfadiazine, sulfisoxazole, and sulfamethoxazole, inhibit dihydropteroate synthetase (DHPS), which adds *p*-aminobenzoic acid (PABA) to pteridine, producing dihydropteroate. Sulfonamides are structural analogues of PABA and act as competing enzyme substrates.

Trimethoprim Subsequent steps in folate synthesis are catalyzed by dihydrofolate synthase, which adds glutamate to dihydropteroate, and dihydrofolate reductase (DHFR), which then generates the final product, tetrahydrofolate. Trimethoprim is a structural analogue of pteridine and inhibits DHFR. Trimethoprim is available alone but is most often used in combination products that also contain sulfamethoxazole and thus block two sequential steps in folate synthesis.

INHIBITION OF DNA AND RNA SYNTHESIS OR ACTIVITY

A variety of antibacterial agents act on these processes.

Quinolones The quinolones include nalidixic acid, the first agent in the class, and newer, more widely used fluorinated derivatives (fluoroquinolones), including norfloxacin, ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin. The quinolones are synthetic compounds that inhibit bacterial DNA synthesis by interacting with the DNA complexes of two essential enzymes, DNA gyrase and DNA topoisomerase IV, which alter DNA topology. Quinolones trap enzyme–DNA complexes in such a way that they block movement of the DNA replication apparatus and can generate lethal double-strand breaks in DNA, resulting in bactericidal activity. Although mammalian cells also have type II DNA topoisomerases related to gyrase and topoisomerase IV, the structures of the mammalian enzymes are sufficiently different from those of the bacterial enzymes that quinolones have substantially selective antibacterial activity.

Rifamycins Rifampin, rifabutin, and rifapentine are semisynthetic derivatives of rifamycin B and bind the β subunit of bacterial

RNA polymerase, thereby blocking elongation of mRNA. Their action is highly selective for the bacterial enzyme over mammalian RNA polymerases.

Nitrofurantoin The reduction of nitrofurantoin, a nitrofuran compound, by bacterial enzymes produces highly reactive derivatives that are thought to cause DNA strand breakage. Nitrofurantoin is used only for the treatment of lower urinary tract infections.

Metronidazole Metronidazole is a synthetic nitroimidazole with activity limited to anaerobic bacteria and certain anaerobic protozoa. Reduction of its nitro group by the electron-transport system in anaerobic bacteria produces reactive intermediates that damage DNA and result in bactericidal activity. Both nitrofurantoin and metronidazole have selective antibacterial activity because the reducing activity needed to produce active derivatives is generated only by bacterial and not mammalian enzymes.

DISRUPTION OF MEMBRANE INTEGRITY

The integrity of the bacterial cytoplasmic membrane—and, in gram-negative bacteria, the outer membrane—is important for bacterial viability. Two bactericidal drugs have membrane targets.

Polymyxins The polymyxins, including polymyxin B and polymyxin E (colistin), are cationic cyclic polypeptides that disrupt the cytoplasmic membrane and the outer membrane (the latter by binding lipopolysaccharide, which is negatively charged).

Daptomycin Daptomycin is a lipopeptide that binds the cytoplasmic membrane of gram-positive bacteria in the presence of calcium, generating a channel that leads to leakage of cytoplasmic potassium ions and membrane depolarization.

PHARMACOKINETICS AND PHARMACODYNAMICS

The term *pharmacokinetics* describes the disposition of a drug in the body, whereas *pharmacodynamics* describes the determinants of drug action on the pathogen in relation to pharmacokinetic factors. An understanding of the principles governing these two areas is required for effective drug selection and dosing and for prevention of toxicities.

PHARMACOKINETICS

The process of drug disposition has four principal phases: absorption, distribution, metabolism, and excretion. These components determine the time course of drug concentrations in serum and subsequently the concentrations in other tissues and body fluids.

Absorption When a drug is given by a particular route, *absorption* is defined as the percentage of the dose that reaches the systemic circulation. For example, since IV administration provides direct access to the systemic circulation, 100% of a drug dose given IV is usually absorbed. The level of absorption becomes more relevant when non-IV routes are used—e.g., the oral, IM, SC, and topical routes. The percentage of a drug that is absorbed is termed its *bioavailability*. Examples of antibacterial agents with a high oral bioavailability include metronidazole, levofloxacin, and linezolid. IV administration and oral dosing for highly bioavailable agents usually give equivalent results. Many factors can affect a drug's oral bioavailability, including the timing of food consumption relative to drug administration, drug-metabolizing enzymes, efflux transporters, concentration-dependent solubility, and acid degradation. Underlying conditions such as diarrhea or ileus can also affect the site of drug absorption and thereby alter bioavailability. Certain orally administered drugs have lower bioavailability because of the *first-pass effect*—the process by which drugs are absorbed in the small intestine through the portal circulation and then directly transported to the liver for metabolism.

Distribution *Distribution* describes the process by which a drug transfers reversibly between the general circulation and the tissues. After absorption into the general circulation and the central compartment (the extensively perfused organs), the drug will also distribute into the peripheral compartment (less well-perfused tissues). The volume of distribution (Vd) is a pharmacokinetic parameter that describes the amount of drug in the body at a given time relative to the measured serum concentration. Properties such as the drug's lipophilicity, partition coefficient within different body tissues, and protein binding; blood flow; and pH can affect the Vd. Drugs with a small Vd are limited to certain areas within the body (typically extracellular fluid), whereas those with a higher Vd penetrate extensively into tissues throughout the body. Antibacterial drugs can bind to serum proteins, and a given drug is usually described as either poorly or highly protein bound. Only the unbound (free) drug is active and available to exert antibacterial effects. For example, because tigecycline is highly protein bound and also has a large Vd, concentrations of free drug in the serum are low.

Metabolism *Metabolism* is the chemical transformation of a drug by the body. This modification can occur within several areas; the liver is the organ most commonly involved. Drugs are metabolized by enzymes, but enzyme systems have a finite capacity to metabolize a substrate drug. If a drug is given in a dose at which the concentration does not exceed the rate of metabolism, then the metabolic process is generally linear. If the dose exceeds the amount that can be metabolized, drug accumulation and potential toxicity may occur. Drugs are metabolized through phase I or phase II reactions. In phase I reactions, the drug is made more polar through dealkylation, hydroxylation, oxidation, and deamination. Polarity facilitates drug removal from the body. Phase II reactions, which include glucuronidation, sulfation, and acetylation, result in compounds larger and more polar than the parent drug. Both phases usually inactivate the parent drug, but some drugs are rendered more active. The cytochrome P450 (CYP) enzyme system is responsible for phase I reactions and is generally found in the liver. CYP3A4 is a common subfamily within this system that is responsible for the majority of drug metabolism. Antibacterial drugs can be substrates, inhibitors, or inducers of a particular CYP enzyme. Inducers, such as rifampin, can increase the production of CYP enzymes and consequently increase the metabolism of other drugs. Inhibitors, such as quinupristin-dalfopristin, cause a decrease in enzyme activity (or competition for CYP substrate) and therefore an increase in the concentration of the interacting drug.

Excretion *Excretion* describes the body's mechanisms of drug elimination. Drugs can be eliminated through more than one mechanism. Renal clearance is the most common route and includes elimination through glomerular filtration, tubular secretion, and/or passive diffusion. Some agents have nonrenal clearance and rely on the biliary tree or the intestine for excretion. Excretion affects the half-life of a drug—i.e., the time it takes for the blood concentration of a drug to decrease by one-half. This value can range from minutes to days. Approximately five to seven half-lives are required for a drug to reach steady state when multiple doses are given in a time frame shorter than the half-life itself. Drug half-life and overall clearance can be extended if the organ responsible for clearance is impaired. Patients with renal or hepatic impairment may require dose adjustments that take delayed clearance into account and prevent toxicities from drug accumulation. For example, imipenem is cleared predominantly through glomerular filtration, and in the presence of renal impairment the dosing interval is typically increased to account for the increased half-life.

PHARMACODYNAMICS

The term *pharmacodynamics* describes the relationship between the serum concentrations that determine the efficacy of the drug and the serum concentrations that produce the toxic effects of the drug. For an antibacterial agent, the pharmacodynamic focus is the type of drug exposure needed for optimal antibacterial effect in relation to the minimal inhibitory concentration (MIC)—the lowest drug concentration that inhibits the growth of a microorganism under standardized laboratory conditions. Antibacterial effect usually correlates with one of the following parameters: (1) ratio of peak serum concentration to the MIC (C_{max}/MIC), (2) ratio of the area under the concentration–time curve to the MIC (AUC/MIC), or (3) duration of concentrations above the MIC (T > MIC) **(Fig. 139-2)**.

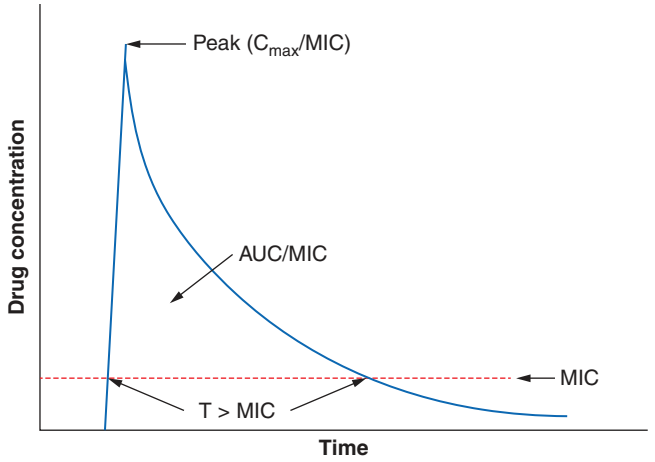

FIGURE 139-2 Pharmacokinetic and pharmacodynamic model predicting efficacy of antibacterial drugs. AUC, area under the time–concentration curve; C_{max}, peak serum concentration of drug; MIC, minimal inhibitory concentration; T > MIC, duration of drug concentrations above the MIC.

For *concentration-dependent* killing agents, as the designation implies, the higher the drug concentration, the higher the rate and extent of bacterial killing. Aminoglycosides fit into the C_{max}/MIC model of pharmacodynamics activity, and a particular peak serum concentration is often targeted to achieve optimal killing. Fluoroquinolones exemplify antibacterial agents for which the AUC/MIC is a predictor of efficacy. For example, studies have found that an AUC/MIC ratio of >30 will maximize killing of *S. pneumoniae* by fluoroquinolones. In contrast, *time-dependent* killing agents reach a ceiling at which higher concentrations do not result in increased effect. Instead, these agents are active against bacteria only when the drug concentration is above the MIC. The T > MIC predicts clinical efficacy for all β-lactams. The longer the concentration of the β-lactam remains above the MIC for an infecting pathogen during the dosing interval, the greater the killing effect. For some drug classes, such as aminoglycosides, a *postantibiotic effect*—the delayed regrowth of surviving bacteria after exposure to an antibiotic—supports less frequent dosing.

APPROACH TO THERAPY

The approach to antibiotic therapy is driven by host factors, site of infection, and local resistance profiles of suspected or known pathogens. Further, national and local drug shortages and formulary restrictions can affect available therapies. Regular monitoring of the patient and collection of laboratory data should be undertaken to streamline antibacterial therapy as appropriate and to investigate the possibility of treatment failure if the patient fails to respond appropriately.

EMPIRICAL AND DIRECTED THERAPY

Therapy is considered *empirical* when the causative agent has yet to be determined and therapeutic decisions are based on the severity of illness, the clinician's assessment of likely pathogens in light of the clinical syndrome, the patient's medical conditions and prior therapy, and relevant epidemiologic factors. For patients with severe illness, empirical therapy often takes the form of an antibacterial combination that provides broad coverage of diverse agents and thus ensures adequate treatment of possible pathogens while additional data are being collected. *Directed* therapy is predicated on identification of the pathogen, determination of its susceptibility profile, and establishment of the extent of the infection. Directed therapy generally allows the use of more targeted and narrower-spectrum antibacterial agents than does empirical therapy.

Information on epidemiology, exposures, and local antibacterial susceptibility patterns can help guide empirical therapy. When empirical treatment is clinically appropriate, care should be taken to obtain clinical specimens for microbiologic analysis before the initiation of therapy and to de-escalate therapy as new information is obtained about the patient's clinical condition and the causal pathogens. De-escalation to the point of directed therapy can limit unnecessary risks to the patient as well as the risk of emergence of antibacterial resistance.

SITE OF INFECTION

The site of infection is a consideration in antibacterial therapy, largely because of the differing abilities of drugs to penetrate and achieve adequate concentrations at particular body sites. For example, to be effective in the treatment of meningitis, an agent must (1) be able to cross the blood–brain barrier and reach adequate concentrations in the cerebrospinal fluid (CSF) and (2) be active against the relevant pathogen(s). Dexamethasone, administered with or 15–20 min before the first dose of an antibacterial drug, has been shown to improve outcomes in patients with some types of acute bacterial meningitis, but its use may reduce penetration of some antibacterial agents, such as vancomycin, into the CSF. In this case, rifampin is added because its penetration is not reduced by dexamethasone. Infections at other sites where either pathogens are protected from normal host defenses or penetration of an antibacterial drug is suboptimal include osteomyelitis, prostatitis, intraocular infections, and abscesses. In such cases, consideration must be given to the mechanism of drug delivery (e.g., intravitreal injections) as well as to the role of interventions to drain, debride, or otherwise reduce the barriers to effective antibacterial therapy.

HOST FACTORS

Host factors, including immune function, pregnancy, allergies, age, renal and hepatic function, drug–drug interactions, comorbid conditions, and occupational or social exposures, should be considered.

Immune Dysfunction Patients with deficits in immune function that blunt the response to bacterial infection, including neutropenia, deficient humoral immunity, and asplenia (either surgical or functional), are all at increased risk of severe bacterial infection. Such patients should be treated aggressively and often broadly in the early stages of suspected infection pending results of microbiologic tests. For asplenic patients, treatment should include coverage of encapsulated organisms, particularly *Streptococcus pneumoniae*, that may cause rapidly life-threatening infection.

Pregnancy Pregnancy affects decisions regarding antibacterial therapy in two respects. First, pregnancy is associated with an increased risk of particular infections (e.g., those caused by *Listeria*). Second, the potential risks to the fetus that are posed by specific drugs must be considered. As for other drugs, the safety of the vast majority of antibacterial agents in pregnancy has not been established, and such agents are grouped in categories B and C by the U.S. Food and Drug Administration. Drugs in categories D and X are contraindicated in pregnancy or lactation due to established risks. The risks associated with antibacterial use in pregnancy and during lactation are summarized in Table 139-2.

Allergies Allergies to antibiotics are among the most common allergies reported, and an allergy history should be obtained whenever possible before therapy is chosen. A detailed allergy history can shed light on the type of reaction experienced previously and on whether rechallenge with the same or a related medication is advisable (and, if so, under what circumstances). Allergies to the penicillins are most common. Although as many as 10% of patients may report an allergy to penicillin, studies suggest that more than 90% of these patients could tolerate a penicillin or cephalosporin. Adverse effects (Table 139-3) should be distinguished from true allergies to ensure appropriate selection of antibacterial therapy.

Drug–Drug Interactions Patients commonly receive other drugs that may interact with antibacterial agents. A summary of the most common drug–drug interactions, by antibacterial class, is provided in Table 139-4.

Exposures Exposures, both occupational and social, may provide clues to likely pathogens. When relevant, inquiries about exposure to ill contacts, animals, insects, and water should be included in the history, along with sites of residence and travel.

TABLE 139-2 Risks Associated with Use of Antibacterial Drugs in Pregnancy and Lactation

PREGNANCY CATEGORY[a]	ANTIBACTERIAL DRUG	FETAL RISK RECOMMENDATION[b]	BREAST-FEEDING RISK RECOMMENDATION[b]
B	Azithromycin	Limited human data. Animal data suggest low risk.	Limited human data; probably compatible
	Cephalosporins (including cephalexin, cefuroxime, cefixime, cefpodoxime, cefotaxime, ceftriaxone)	Compatible	Compatible
	Ceftazidime-avibactam	No human data; no fetal harm in animal studies	Ceftazidime is excreted into human milk in low concentrations. Avibactam is excreted into the milk of lactating rats; no human studies have been conducted.
	Ceftolozane-tazobactam	Compatible	Unknown
	Clindamycin	Compatible	Compatible
	Ertapenem	No human data; probably compatible	Limited human data; probably compatible
	Erythromycin	Compatible (except for estolate salt)	Compatible
	Meropenem and meropenem-vaborbactam	No human data. Animal data suggest low risk.	No human data; probably compatible
	Metronidazole	Human data suggest low risk.	Interrupt breast-feeding for 12–24 h after single 2-g dose. Limited human data; potential toxicity in divided doses
	Nitrofurantoin	Human data suggest risk in third trimester.	Limited human data; probably compatible. Higher risk associated with younger infants and those with G6PD deficiency
	Penicillins (including amoxicillin, ampicillin, cloxacillin)	Compatible	Compatible
	Quinupristin-dalfopristin	Compatible. Maternal benefit must far outweigh risk to embryo/fetus.	No human data; potential toxicity
	Vancomycin	Compatible	Limited human data; probably compatible
C	Chloramphenicol	Compatible	Limited human data; potential toxicity
	Fluoroquinolones	Human data suggest low risk.	Limited human data; probably compatible
	Clarithromycin	Limited human data. Animal data suggest high risk.	No human data; probably compatible
	Imipenem-cilastatin	Limited human data. Animal data suggest low risk.	Limited human data; probably compatible
	Linezolid	Compatible. Maternal benefit must far outweigh risk to embryo/fetus.	No human data; potential toxicity
	Telavancin	No human data. Animal studies have revealed evidence of teratogenicity.[c]	No human data. Animal studies have revealed evidence of teratogenicity.[c]
	Tedizolid	Limited data. Embryo-fetal studies in mice, rats, and rabbits have demonstrated fetal developmental toxicities. Use only if benefit outweighs risk.	Excreted in the breast milk of rats; unknown in humans; caution use
	Dalbavancin	Limited human data. At high doses in animal studies, delayed fetal maturation, increased embryo and offspring death. Use only if benefit outweighs risk.	Excreted in the breast milk of animals; unknown in humans; caution use
	Oritavancin	Limited human data. Studies in rats and rabbits demonstrated no harm at 25% of recommended human dose. Use only if benefit outweighs risk.	Excreted in the breast milk of rats; unknown in humans; caution use
C/D	Amikacin	Human data suggest low risk.	Compatible
	Gentamicin	Human data suggest low risk.	Compatible
D	Kanamycin	Human data suggest risk.	Limited human data; probably compatible
	Streptomycin	Human data suggest risk.	Compatible
	Sulfonamides	Human data suggest risk in third trimester.	Limited human data; potential toxicity. Avoid in ill, stressed, premature infants and in infants with hyperbilirubinemia or G6PD deficiency.
	Tetracyclines	Contraindicated in second and third trimesters	Compatible
	Tigecycline	Human data suggest risk in second and third trimesters.	No human data; potential toxicity

[a]*Category B: Either* animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; *or* animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. *Category C:* Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. *Category D:* There is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.[b]Fetal risk recommendation and breast-feeding risk recommendation adapted from GG Briggs et al (eds): *Drugs in Pregnancy and Lactation*, 9th ed. Philadelphia, Lippincott Williams and Wilkins, 2011; and the U.S. Food and Drug Administration (Drugs@FDA). [c]A registry has been established to monitor pregnancy outcomes of pregnant women exposed to telavancin. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves by calling 1-855-633-8479.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

TABLE 139-3 Common Adverse Reactions to Antibacterial Agents

ANTIBACTERIAL(S)	POTENTIAL ADVERSE EFFECTS	COMMENTS
β-Lactams	Hypersensitivity reactions	Ranges from rash to anaphylaxis. Cross-reactivity among β-lactams is related to chemical structure and side chain similarity.
	Neurotoxicity	More commonly described with cefepime and imipenem, but likely a class effect. Risk is increased in patients with history of seizures, renal impairment, and advanced age.
	Neutropenia/hematologic reactions	May be related to high doses and prolonged duration
Vancomycin	Nephrotoxicity	Risk increases with vancomycin trough levels >20 μg/mL or concomitant administration with other potentially nephrotoxic agents. The effect is usually reversible.
	"Red man syndrome"	Can be managed with a slower vancomycin infusion and pretreatment with antihistamine
Telavancin	QT prolongation	
	Interference with coagulation tests	May falsely affect INR, PT, aPTT. Perform these tests before the next dose of telavancin (when serum drug levels are at their nadir).
	Taste disturbances	
	Nephrotoxicity	
Oritavancin	Interference with coagulation tests	May falsely affect INR, PT, aPTT. Perform these tests at least 24 h after the dose is administered.
	Gastrointestinal distress	
Dalbavancin	Gastrointestinal distress	
Daptomycin	Myopathy	Monitor CPK levels during therapy. Rhabdomyolysis has been reported but appears to be rare.
	Eosinophilic pneumonia	
Aminoglycosides	Nephrotoxicity	Associated with prolonged use; usually reversible
	Ototoxicity	Can cause both vestibular and cochlear toxicity. Ototoxicity may be irreversible.
Fluoroquinolones	QT_c prolongation	Moxifloxacin appears more likely than other quinolones to exert this effect. Risk of arrhythmia increases when these drugs are given concomitantly with other QT_c-prolonging agents.
	Tendinitis	Risk is greater among the elderly and patients receiving steroids.
	Dysglycemia	
	Exacerbation of myasthenia gravis	
Rifampin	Hepatotoxicity	Risk is greater when drug is given with other antituberculosis agents. When rifampin is given alone, LFT values may be transiently elevated without symptoms.
	Orange discoloration of body fluids	
Tetracyclines and glycylcyclines	Photosensitivity	
	Gastrointestinal distress	High incidence of diarrhea, nausea, vomiting
Macrolides	Gastrointestinal distress	Erythromycin is occasionally used as a therapeutic agent for some gastric motility disorders.
	QT_c prolongation	Azithromycin use is associated with an increased risk of death from cardiovascular causes among patients at high baseline risk.
Metronidazole	Peripheral neuropathy	Associated with prolonged use
Clindamycin	Diarrhea and pseudomembranous colitis	
Linezolid, tedizolid	Myelosuppression	Associated with prolonged use
	Optic and peripheral neuropathy	Associated with prolonged use
	Lactic acidosis	
TMP-SMX	Hypersensitivity reactions	Allergy usually associated with sulfonamide moiety
	Nephrotoxicity	Associated with high doses
	Hematologic effects	Associated with prolonged use
Nitrofurantoin	Pneumonitis and other pulmonary reactions	Associated with prolonged use
	Peripheral neuropathy	Associated with accumulation of nitrofurantoin in renal failure. Avoid use in renal impairment.
Fosfomycin	Gastrointestinal effects	
Polymyxins	Nephrotoxicity	Associated with high dose
	Neurotoxicity	Neuromuscular blockade and muscle weakness are well described and usually reversible.
Quinupristin-dalfopristin	Arthralgias and myalgias	
Chloramphenicol	Bone marrow suppression	Aplastic anemia or hematopoietic toxicity

Note: All systemic antibiotics have the potential to alter abdominal flora and induce *Clostridium difficile* infection.

Abbreviations: aPTT, activated partial thromboplastin time; CPK, creatine phosphokinase; INR, international normalized ratio; LFT, liver function test; PT, prothrombin time; TMP-SMX, trimethoprim-sulfamethoxazole.

Other Host Factors Age, renal and hepatic function, and comorbid conditions are all considerations in the choice of and schedule for therapy. Dose adjustments should be made accordingly. In patients with decreased or unreliable oral absorption, IV therapy may be preferred to ensure adequate blood levels of drug and delivery of the antibacterial agent to the site of infection.

DURATION OF THERAPY

Whether empirical or directed, the duration of therapy should be determined in most clinical situations. Guidelines that synthesize available literature and expert opinion provide recommendations on therapy duration that are based on infecting organism, organ system, and patient factors. For example, the American Heart Association has

TABLE 139-4 Significant Antibacterial Drug Interactions

ANTIBACTERIAL(S)	INTERACTING AGENT(S)	POTENTIAL EFFECT AND MANAGEMENT
Nafcillin	Warfarin, cyclosporine, tacrolimus	Decreased levels of warfarin, cyclosporine via CYP3A4 induction. Monitor levels of affected drug closely if drugs are given concomitantly.
Ceftriaxone	Calcium-containing IV solutions	Concomitant use is contraindicated in neonates (<28 days); the combination can lead to precipitation of ceftriaxone-calcium particulate. Ceftriaxone and calcium-containing solutions can be given to infants >28 days of age provided they are given sequentially and the lines are thoroughly flushed between infusions.
Carbapenems	Valproic acid	Decreased levels of valproic acid. Monitor valproic acid levels closely if drugs are given concomitantly.
Linezolid, tedizolid	Serotonergic and adrenergic agents (e.g., SSRIs, vasopressors)	Increased levels of serotonergic and adrenergic agents. Monitor for serotonin syndrome. Tedizolid may have less potential than linezolid to cause this drug interaction.
Quinupristin-dalfopristin	Substrates of CYP3A4 (e.g., warfarin, ritonavir, cyclosporine, diazepam, verapamil)	Can result in increased levels of interacting drug
Fluoroquinolones	Theophylline[a]	Can result in theophylline toxicity
	Sucralfate; antacids containing aluminum, calcium, or magnesium; ferrous sulfate– and zinc-containing multivitamins	Can result in subtherapeutic fluoroquinolone levels. Administer fluoroquinolone 2 h before or 6 h after interacting drug.
	Tizanidine[a]	Can result in increased levels of tizanidine and hypotensive, sedative effects. Monitor for side effects if drugs are given concomitantly.
Rifampin	Substrates of CYP3A4 (e.g., warfarin, ritonavir, cyclosporine, diazepam, verapamil, protease inhibitors, voriconazole)	Can result in decreased levels of interacting drug. Avoid concomitant use if possible. If giving drugs concomitantly, monitor drug levels if possible.
	Substrates of CYP2C19 (e.g., omeprazole, lansoprazole)	
	Substrates of CYP2C9 (e.g., warfarin, tolbutamide)	
	Substrates of CYP2C8 (e.g., repaglinide, rosiglitazone)	
	Substrates of CYP2B6 (e.g., efavirenz)	
	Hormone therapy (e.g., norethindrone)	Can result in decreased levels of hormone. If oral contraceptive and rifampin are given concomitantly, use alternative form of birth control.
Tetracyclines	Antacids or drugs containing calcium, magnesium, iron, or aluminum	Can result in decreased absorption of tetracyclines. Administer tetracycline 2 h before or 6 h after interacting drug.
	Warfarin	Increased effect of warfarin. Monitor levels closely if drugs are given concomitantly.
Macrolides[b]	Substrates of CYP3A4 (e.g., warfarin, ritonavir, cyclosporine, diazepam, verapamil)	Avoid concomitant administration if possible.
	QT_c-prolonging agents (e.g., fluoroquinolones, sotalol)	Increased risk of cardiotoxicity and arrhythmias. Monitor QT_c.
	Protease inhibitors (e.g., ritonavir)	Can result in increased levels of both macrolides and protease inhibitors. Avoid concomitant use if possible.
	Cimetidine	Cimetidine can increase levels of macrolides.
Metronidazole	Ethanol	Can result in disulfiram-like reaction. Ethanol may be present in some formulations of oral drug suspensions (e.g., ritonavir).
	Warfarin	Can increase warfarin levels. Monitor INR closely if drugs are given concomitantly.
TMP-SMX	Warfarin	Increased effect of warfarin. Monitor levels closely if drugs are given concomitantly.
	Phenytoin	Increased levels of phenytoin. Monitor levels closely if drugs are given concomitantly.
	Methotrexate	Increased levels of methotrexate. Monitor levels closely if drugs are given concomitantly.
Oritavancin	Substrates of CYP3A4 (e.g., cyclosporine, warfarin) and CYP2D6 (e.g., aripiprazole) Substrates of CYP2C19 (e.g., omeprazole) and CYP2C9 (e.g., warfarin)	Can result in decreased levels of interacting drug. Avoid concomitant use if possible. If giving drugs concomitantly, monitor drug levels if possible.

[a]Drug reaction described with ciprofloxacin only. [b]Clarithromycin and erythromycin are potent CYP3A4 inhibitors; the probability of a drug interaction with azithromycin is lower.

Abbreviations: INR, international normalized ratio; SSRI, selective serotonin-reuptake inhibitor; TMP-SMX, trimethoprim-sulfamethoxazole.

published guidelines endorsed by the Infectious Diseases Society of America (IDSA) on diagnosis, antibacterial therapy, and management of complications of infective endocarditis. Similar guidelines from the IDSA exist for bacterial meningitis, urinary tract infections (including those that are catheter-associated), intraabdominal infections, community- and hospital-acquired pneumonia, skin and soft tissue infections, and other infections.

FAILURE OF THERAPY

If a patient does not respond to therapy, investigations often should include the collection of additional specimens for microbiologic testing and imaging as indicated. Failure to respond can be the result of an antibacterial regimen that does not address the underlying causative organism, the development of resistance during therapy, or the existence of a focus of infection at a site poorly penetrated by systemic

therapy. Some infections may also require surgical interventions (e.g., large abscesses, myonecrosis). Fever due to allergic drug reactions can sometimes complicate assessment of the patient's response to antibacterial treatment.

EXPERT GUIDANCE

Selected websites with the most up-to-date information and guidance for the clinician include the following:

- Johns Hopkins ABX Guide (*www.hopkins-abxguide.org*)
- IDSA Practice Guidelines (*http://www.idsociety.org/PracticeGuidelines/*)
- Center for Disease Dynamics, Economics and Policy Resistance Map (*https://resistancemap.cddep.org/*)
- Centers for Disease Control and Prevention Antibiotic/Antimicrobial Resistance (*www.cdc.gov/drugresistance/*)

CLINICAL USE OF ANTIBACTERIAL AGENTS

The clinical application of antibacterial therapy is guided by the spectrum of the agent and the suspected or known target pathogen. Infections for which specific antibacterial agents are among the drugs of choice are listed, along with associated pathogens and susceptibility data, in **Table 139-5**. Resistance rates of specific organisms are dynamic and should be taken into account in the approach to antibacterial therapy. While national resistance rates can serve as a reference, the most useful reference for the clinician is the most recent local laboratory antibiogram, which provides details on local resistance patterns, often on an annual or semiannual basis.

β-LACTAMS

The β-lactam class of antibiotics consists of penicillins, cephalosporins, carbapenems, and monobactams. The term *β-lactam* reflects the drugs' four-membered lactam ring, which is their core structure. The differing side chains among the agents of this family determine the spectrum of activity. All β-lactams exert a bactericidal effect by inhibiting bacterial cell-wall synthesis. The β-lactams are classified as time-dependent killing agents; therefore, their clinical efficacy is best correlated with the proportion of the dosing interval during which drug levels remain above the MIC for the pathogenic organism.

Penicillins and β-Lactamase Inhibitors Penicillin, the first β-lactam, was discovered in 1928 by Alexander Fleming. Natural penicillins, such as penicillin G, are active against non-β-lactamase-producing gram-positive and gram-negative bacteria, anaerobes, and some gram-negative cocci. Penicillin G is used for penicillin-susceptible streptococcal infections, pneumococcal and meningococcal meningitis, enterococcal endocarditis, and syphilis. The antistaphylococcal penicillins, which have potent activity against methicillin-susceptible *Staphylococcus aureus* (MSSA), include nafcillin, oxacillin, dicloxacillin,

TABLE 139-5 Drug Indications for Specific Infections, Associated Pathogens, and Sample Susceptibility Rates

ANTIMICROBIAL(S)	INFECTIONS	COMMON PATHOGENS (% SUSCEPTIBLE); RESISTANCE AS NOTED[a]
Penicillin G	Syphilis; yaws; leptospirosis; streptococcal infections; pneumococcal infections; actinomycosis; oral and periodontal infections; meningococcal meningitis and meningococcemia; viridans streptococcal endocarditis; clostridial myonecrosis; tetanus; rat-bite fever; *Pasteurella multocida* infections; erysipeloid (*Erysipelothrix rhusiopathiae*)	*Neisseria meningitidis*; viridans streptococci (69%); *Streptococcus pneumoniae* (96% nonmeningitis; 68% meningitis)
Ampicillin, amoxicillin	Salmonellosis; acute otitis media; *Haemophilus influenzae* meningitis and epiglottitis; *Listeria monocytogenes* meningitis; *Enterococcus faecalis* UTI	*Escherichia coli* (51%); *H. influenzae* (70%); *Salmonella* spp. (85%)
Nafcillin, oxacillin	MSSA bacteremia and endocarditis	*Staphylococcus aureus* (72%); coagulase-negative staphylococci (49%)
Piperacillin-tazobactam	Intraabdominal infections (facultative enteric gram-negative bacilli and obligate anaerobes); infections caused by mixed flora (aspiration pneumonia, diabetic foot ulcers); infections caused by *Pseudomonas aeruginosa*	*P. aeruginosa* (88%)[b]
Cefazolin	*E. coli* UTI; surgical prophylaxis; MSSA bacteremia and endocarditis	*E. coli* (82%)
Cefoxitin, cefotetan	Intraabdominal infections and pelvic inflammatory disease	*Bacteroides fragilis* (60%)[c]
Ceftriaxone	Gonococcal infections; pneumococcal meningitis; viridans streptococcal endocarditis; salmonellosis and typhoid fever; hospital-acquired infections caused by nonpseudomonal facultative gram-negative enteric bacilli	*S. pneumoniae* (93%);[d] *E. coli* (91%); *Klebsiella pneumoniae* (89%)
Ceftazidime, cefepime	Hospital-acquired infections caused by facultative gram-negative bacilli and *Pseudomonas* spp.	*P. aeruginosa* (90%)
Ceftaroline	CAP caused by *S. pneumoniae*, MSSA, *H. influenzae, K. pneumoniae, Klebsiella oxytoca*, and *E. coli*; acute bacterial skin and skin-structure infections caused by MSSA, MRSA, *Streptococcus pyogenes, Streptococcus agalactiae, E. coli, K. pneumoniae*, and *Klebsiella oxytoca*	Mostly susceptible; four strains of MRSA with ceftaroline MICs >4 μg/mL reported in isolates from a single Greek hospital[e]
Ceftazidime-avibactam, meropenem-vaborbactam	Complicated UTIs (ceftazidime-avibactam and meropenem-vaborbactam) and complicated intraabdominal infections (ceftazidime-avibactam in combination with metronidazole) caused by resistant gram-negative organisms, including *Pseudomonas*, and some anaerobes	*P. aeruginosa* (84–97%)[f] MDR Enterobacteriaceae, including carbapenem-resistant Enterobacteriaceae that produce KPCs No activity against metallo-β-lactamases (e.g., NDM)
Ceftolozane-tazobactam	Complicated UTIs and complicated intraabdominal infections (in combination with metronidazole) caused by resistant gram-negative organisms, including *Pseudomonas*, and some anaerobes	*P. aeruginosa* (>86% overall; 60–80% of ceftazidime- and meropenem-resistant strains)[f] MDR Enterobacteriaceae No activity against KPC-producing organisms
Imipenem, meropenem	Intraabdominal infections, infections caused by *Enterobacter* spp. and ESBL-producing gram-negative bacilli	*P. aeruginosa* (84%); *Acinetobacter calcoaceticus-baumannii* complex (93%) (meropenem susceptibilities reported)
Ertapenem	CAP; complicated UTIs, including pyelonephritis; acute pelvic infections; complicated intraabdominal infections; complicated skin and skin-structure infections, excluding diabetic foot infections accompanied by osteomyelitis or caused by *P. aeruginosa*	*Enterobacter cloacae* (88%); *K. pneumoniae* (99%)

(*Continued*)

TABLE 139-5 Drug Indications for Specific Infections, Associated Pathogens, and Sample Susceptibility Rates (Continued)

ANTIMICROBIAL(S)	INFECTIONS	COMMON PATHOGENS (% SUSCEPTIBLE); RESISTANCE AS NOTED[a]
Aztreonam	HAIs caused by facultative gram-negative bacilli and *Pseudomonas* in penicillin-allergic patients	*P. aeruginosa* (74%)
Vancomycin	Bacteremia, endocarditis, and other invasive disease caused by MRSA; pneumococcal meningitis; oral formulation for CDAD	*S. aureus* (100%); *E. faecalis* (96%); *E. faecium* (33%)
Telavancin	Hospital- and ventilator-associated pneumonia or skin and soft tissue infections caused by MRSA	*S. aureus*: none reported
Dalbavancin, oritavancin	Complicated skin and soft tissue infections	*S. aureus*: rarely reported for dalbavancin,[g] none reported for oritavancin
Daptomycin	VRE infections; MRSA bacteremia	*E. faecalis* (99.9%);[h] *E. faecium* (99.7%);[h] *S. aureus* (99.9%)[g]
Gentamicin, tobramycin, amikacin	Combined with penicillin for staphylococcal, enterococcal, or streptococcal endocarditis; combined with β-lactam for gram-negative bacteremia; pyelonephritis	*E. coli* (gentamicin, 90%); *P. aeruginosa* (amikacin, 91%; gentamicin, 87%); *A. calcoaceticus-baumannii* complex (gentamicin, 94%)
Azithromycin, clarithromycin, erythromycin	*Legionella, Campylobacter*, and *Mycoplasma* infections; CAP; GAS pharyngitis in penicillin-allergic patients; bacillary angiomatosis; gastric infections due to *Helicobacter pylori*; MAI infections	*S. pneumoniae* (60%); group A streptococci (82%); *H. pylori* (75%)[i]
Clindamycin	Severe, invasive GAS infections (with β-lactam); infections caused by obligate anaerobes; infections caused by susceptible staphylococci	*S. aureus* (69%)
Doxycycline, minocycline	Acute bacterial exacerbations of chronic bronchitis; granuloma inguinale; brucellosis (with streptomycin); tularemia; glanders; melioidosis; spirochetal infections caused by *Borrelia* (Lyme disease and relapsing fever; doxycycline); infections caused by *Vibrio vulnificus*; some *Aeromonas* infections; infections due to *Stenotrophomonas* (minocycline); plague; ehrlichiosis; chlamydial infections (doxycycline); granulomatous infections due to *Mycobacterium marinum* (minocycline); rickettsial infections; mild CAP; skin and soft tissue infections caused by gram-positive cocci (e.g., CA-MRSA infections); leptospirosis; syphilis; and actinomycosis in the penicillin-allergic patient	*S. pneumoniae* (68%); *S. aureus* (94%)
Tigecycline	CAP caused by *S. pneumoniae, H. influenzae*, or *Legionella pneumophila*; complicated skin infections caused by *E. coli*, MRSA, MSSA, *S. pyogenes, Streptococcus anginosus, S. agalactiae, B. fragilis*; complicated intraabdominal infections caused by *E. coli*, vancomycin-susceptible *E. faecalis, Citrobacter freundii, Enterobacter cloacae, K. pneumoniae, K. oxytoca, Bacteroides* spp., *Clostridium perfringens*, and *Peptostreptococcus* spp.	Mostly susceptible, although case reports of resistance in *A. baumannii* and *K. pneumoniae*
TMP-SMX	Community-acquired UTI; CA-MRSA skin and soft tissue infections	*E. coli* (71%); *S. aureus* (95%)
Sulfonamides	Nocardial infections; leprosy (dapsone); toxoplasmosis (sulfadiazine)	Unknown
Ciprofloxacin, levofloxacin, moxifloxacin, delafloxacin	CAP (levofloxacin and moxifloxacin); UTI; bacterial gastroenteritis; hospital-acquired gram-negative enteric infections; *Pseudomonas* infections (ciprofloxacin and levofloxacin); skin and skin-structure infections (delafloxacin)	*S. pneumoniae* (99%); *E. coli* (80%); *P. aeruginosa* (ciprofloxacin, 77%; levofloxacin, 77%); *Salmonella* spp. (ciprofloxacin, 88%; levofloxacin, 98%)
Rifampin	Staphylococcal foreign body infections (in combination with other antistaphylococcal agents); *Legionella* pneumonia; *Mycobacterium tuberculosis*; atypical nontuberculous mycobacterial infection; pneumococcal meningitis when organisms are susceptible or response is delayed	*S. aureus* (99%), although staphylococci rapidly develop resistance with monotherapy
Metronidazole	Obligate anaerobic gram-negative bacteria (e.g., *Bacteroides* spp); abscess in lung, brain, or abdomen; bacterial vaginosis; CDAD	Mostly susceptible; resistance very rare
Linezolid, tedizolid	VRE; uncomplicated and complicated skin and soft tissue infections caused by MSSA and MRSA; CAP with concurrent bacteremia; hospital-acquired pneumonia	Mostly susceptible; resistance occasionally seen in VRE
Chloramphenicol	HAI due to gram-positive and gram-negative organisms resistant to standard alternatives (e.g., *Burkholderia*)	Unknown
Colistin	HAI due to gram-negative bacilli resistant to all other chemotherapy (e.g., *P. aeruginosa, Acinetobacter* spp., and *Stenotrophomonas maltophilia*)	*P. aeruginosa* (case reports, outbreaks)
Quinupristin-dalfopristin	VRE; complicated skin and skin-structure infections due to MSSA and *S. pyogenes*	*E. faecalis* (<20%);[j] *E. faecium* (>90%)[j]
Mupirocin	Topical application to nares for *S. aureus* decolonization	*S. aureus* (74–100%)[k]
Nitrofurantoin	UTI caused by most gram-negative bacilli and some gram-positive organisms; prophylaxis in recurrent cystitis	*E. coli* (95%); *E. faecalis* (99%)
Fosfomycin	UTI caused by most gram-negative bacilli and some gram-positive organisms; prophylaxis in recurrent cystitis	Unknown

[a]Unless otherwise noted, susceptibility rates are based on isolates from the Massachusetts General Hospital Clinical Microbiology Laboratory collected between January and December 2012. Local rates will vary. [b]Center for Disease Dynamics, Economics and Policy Resistance Map, Washington, DC. [c]JA Karlowsky et al: Antimicrob Agents Chemother 56:1247, 2012. [d]GV Doern et al: Clin Infect Dis 41:139, 2005. [e]RE Mendes et al: J Antimicrob Chemother 67:1321, 2012. [f]D Van Duin, RA Bonomo: Clin Infect Dis 63:234, 2016. [g]SP McCurdy et al: Antimicrob Agents Chemother 59:5007, 2015. [h]HS Sader et al: J Chemother 23:200, 2011. [i]J Torres et al: J Clin Microbiol 39:2677, 2001. [j]WS Oh et al: Antimicrob Agents Chemother 49:5176, 2005. [k]AE Simor et al: Antimicrob Agents Chemother 51:3880, 2007.

Abbreviations: CA-MRSA, community-acquired MRSA; CAP, community-acquired pneumonia; CA-UTI, community-acquired UTI; CDAD, *Clostridium difficile*–associated diarrhea; ESBL, extended-spectrum β-lactamase; GAS, group A streptococcal; HAI, hospital-acquired infection; KPCs, *Klebsiella pneumoniae* carbapenemases; MAI, *Mycobacterium avium-intracellulare*; MDR, multidrug-resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NDM, New Delhi metallo-β-lactamase; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection; VRE, vancomycin-resistant *Enterococcus*.

and flucloxacillin. Aminopenicillins, such as ampicillin and amoxicillin, provide added coverage beyond penicillin against gram-negative cocci, such as *Haemophilus influenzae*, and some Enterobacteriaceae, including *Escherichia coli*, *Proteus mirabilis*, *Salmonella*, and *Shigella.* The aminopenicillins are hydrolyzed by many common β-lactamases. These drugs are commonly used for infections caused by susceptible enterococcal and streptococcal species. IV ampicillin is commonly used in meningitis and endocarditis. Oral amoxicillin may be an option for otitis media, respiratory tract infections, and urinary tract infections. The antipseudomonal penicillins include ticarcillin and piperacillin. These penicillin groups generally offer adequate anaerobic coverage; the exceptions are *Bacteroides* species (such as *Bacteroides fragilis*), which produce β-lactamases and are generally resistant. The rising prevalence of β-lactamase-producing bacteria has led to the increased use of β-lactam–β-lactamase inhibitor combinations, such as ampicillin-sulbactam, amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, ceftolozane-tazobactam, ceftazidime-avibactam, and meropenem-vaborbactam. The β-lactamase inhibitors themselves do not have antibacterial activity (with the exception of sulbactam, which has activity against *Acinetobacter baumannii*) but typically inhibit the *S. aureus* class A β-lactamase, β-lactamases of *H. influenzae* and *Bacteroides* species, and a number of plasmid-encoded β-lactamases. These combination agents are typically used when broader-spectrum coverage is needed—e.g., in pneumonia and intraabdominal infections. Piperacillin-tazobactam is a useful agent for broad coverage in febrile neutropenic patients. Avibactam and vaborbactam inhibit a broader spectrum of β-lactamases than the other inhibitors, including extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases, and some carbapenemases **(see Chap. 140)**.

Cephalosporins The cephalosporin drug class encompasses several generations determined by spectrum of antibacterial activity. The first generation (cefazolin, cefadroxil, and cephalexin) largely has activity against gram-positive bacteria, with some additional activity against *E. coli*, *P. mirabilis*, and *Klebsiella pneumoniae*. First-generation cephalosporins are commonly used for infections caused by MSSA and streptococci (e.g., skin and soft tissue infections). Cefazolin is a popular choice for surgical prophylaxis against skin organisms. The second generation (cefamandole, cefuroxime, cefaclor, cefprozil, cefuroxime axetil, cefoxitin, and cefotetan) has additional activity against *H. influenzae* and *Moraxella catarrhalis*. Cefoxitin and cefotetan have potent activity against anaerobes as well. Second-generation cephalosporins are used to treat community-acquired pneumonia because of their activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. They are also used for other mild or moderate infections, such as acute otitis media and sinusitis. The third-generation cephalosporins are characterized by greater potency against gram-negative bacilli and reduced potency against gram-positive cocci. These cephalosporins, which include cefoperazone, cefotaxime, ceftazidime, ceftriaxone, cefdinir, cefixime, and cefpodoxime, are used for infections caused by Enterobacteriaceae, although resistance is an increasing concern. Ceftriaxone penetrates the CSF and can be used to treat meningitis caused by *H. influenzae*, *N. meningitidis*, and susceptible strains of *S. pneumoniae*. It is also used for the treatment of later-stage Lyme disease, gonococcal infections, and streptococcal endocarditis. It is noteworthy that ceftazidime is the only third-generation cephalosporin with activity against *Pseudomonas aeruginosa* but lacks activity against gram-positive bacteria. This drug is frequently used for pulmonary infections in cystic fibrosis, postneurosurgical meningitis, and febrile neutropenia. The fourth generation of cephalosporins includes cefepime and cefpirome, broad-coverage agents with potent activity against both gram-negative bacilli, including *P. aeruginosa*, and gram-positive cocci. The fourth generation has clinical applications similar to those of the third generation and may offer additional activity over the first, second, and third generations in the presence of certain β-lactamases. These agents can be used in bacteremia, febrile neutropenia, and intraabdominal and urinary tract infections. Ceftaroline, a fifth-generation cephalosporin, differs from the other cephalosporins in its added activity against MRSA, which is resistant to all other β-lactams. Ceftaroline's gram-negative activity is similar to that of the third-generation cephalosporins but does not include *P. aeruginosa*. Ceftaroline may be used in community -acquired pneumonia and skin infections, and emerging data support its use in more severe infections such as bacteremia. Adverse reactions to ceftaroline have included hypersensitivity reactions and neutropenia. Ceftolozane-tazobactam and ceftazidime-avibactam are novel cephalosporin–β-lactamase inhibitor combinations with activity against gram-negative bacteria, including *Pseudomonas*, and some anaerobes. Both agents have been studied in complicated intraabdominal infections and complicated urinary tract infections. Ceftolozane-tazobactam is thought to be stable against many ESBL-producing organisms because of the tazobactam component. The addition of avibactam to ceftazidime yields a combination agent with activity against AmpC-, ESBL-, and KPC-producing organisms. These cephalosporin–β-lactamase inhibitor combinations may be of clinical benefit in multidrug-resistant gram-negative infections.

Carbapenems Carbapenems, including doripenem, imipenem, meropenem, and ertapenem, offer the most reliable coverage for strains containing ESBLs. All carbapenems have broad activity against gram-positive cocci, gram-negative bacilli, and anaerobes. None is active against methicillin-resistant *S. aureus* (MRSA), but all are active against MSSA, *Streptococcus* species, and Enterobacteriaceae. Ertapenem is the only carbapenem that has poor activity against *P. aeruginosa* and *Acinetobacter*. Imipenem is active against penicillin-susceptible *Enterococcus faecalis* but not *Enterococcus faecium*. Carbapenems are not active against Enterobacteriaceae containing carbapenemases. *Stenotrophomonas maltophilia* and some *Bacillus* species are intrinsically resistant to carbapenems because of a zinc-dependent carbapenemase. Addition of vaborbactam to meropenem results in inhibition of AmpC β-lactamases, ESBLs, and *K. pneumoniae* carbapenemases (KPCs).

Monobactams Aztreonam is the sole monobactam. Its activity is limited to gram-negative bacteria and includes *P. aeruginosa* and most other Enterobacteriaceae. This drug is inactivated by ESBLs and carbapenemases. The principal use for aztreonam is as an alternative to penicillins, cephalosporins, or carbapenems in patients with a serious β-lactam allergy. Aztreonam is structurally related to ceftazidime and should be used cautiously in individuals with a serious ceftazidime allergy. It is commonly used in febrile neutropenia and intraabdominal infections.

Adverse Reactions to β-Lactam Drugs Agents within the β-lactam class are known for several adverse effects. Gastrointestinal side effects, mainly diarrhea, are common, but hypersensitivity reactions constitute the most common adverse effect of β-lactams. The reactions' severity can range from rash to anaphylaxis, but the rate of true anaphylactic reactions is only 0.05%. An individual with an accelerated IgE-mediated reaction to one β-lactam agent may still receive another agent within the class, but caution should be used in choosing a β-lactam that has a dissimilar side chain and a low level of cross-reactivity. For example, the second-, third-, and fourth-generation cephalosporins and the carbapenems display very low cross-reactivity in patients with penicillin allergy. Aztreonam is the only β-lactam that has no cross-reactivity with the penicillin group. In cases of severe allergy, desensitization (a graded challenge) to the indicated β-lactam, with close monitoring, may be warranted if other antibacterial options are not suitable.

β-Lactams can rarely cause serum sickness, Stevens-Johnson syndrome, nephropathy, hematologic reactions, and neurotoxicity. Neutropenia appears to be related to high doses or prolonged use. Neutropenia and interstitial nephritis caused by β-lactams generally resolve upon discontinuation of the agent. Imipenem and cefepime are associated with an increased risk of seizure, but this risk is likely a class effect and related to high doses or doses that are not adjusted in renal impairment.

GLYCOPEPTIDES AND LIPOGLYCOPEPTIDES

Vancomycin is a glycopeptide antibiotic with activity against staphylococci (including MRSA and coagulase-negative staphylococci), streptococci (including *S. pneumoniae*), and enterococci. It is not active

against gram-negative organisms. Vancomycin also displays activity against *Bacillus* species, *Corynebacterium jeikeium*, *Listeria monocytogenes*, and gram-positive anaerobes such as *Peptostreptococcus*, *Actinomyces*, *Clostridium*, and *Propionibacterium* species. Vancomycin has several important clinical uses. It is used for serious infections caused by MRSA, including health care–associated pneumonia, bacteremia, osteomyelitis, and endocarditis. It is also commonly used for skin and soft tissue infections. Oral vancomycin is not absorbed systemically and is reserved for the treatment of *Clostridium difficile* infection. Vancomycin is also an alternative for the treatment of infections caused by MSSA in patients who cannot tolerate β-lactams. Resistance to vancomycin is a rising concern. Strains of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant enterococci (VRE) are not uncommon. Vancomycin appears to be a concentration-dependent killer, with the AUC/MIC ratio being the best predictor of efficacy (Fig. 139-2). Guidelines recommend targeting a vancomycin trough level of 15–20 μg/mL in MRSA infections in order to maintain an AUC/MIC ratio >400. When using vancomycin, clinicians should monitor for nephrotoxicity. The risk increases when trough levels are >20 μg/mL. Concomitant therapy with other nephrotoxic agents, such as aminoglycosides, also increases the risk of nephrotoxicity. Ototoxicity was reported with early formulations of vancomycin but is currently uncommon because purer formulations are available. Both of these adverse effects are reversible upon discontinuation of vancomycin. Clinicians should be aware of the "red man syndrome," a common reaction that presents as a rapid onset of erythematous rash or pruritus on the head, face, neck, and upper trunk. This reaction is caused by histamine release from basophils and mast cells and can be treated with diphenhydramine and slowing of the vancomycin infusion.

Telavancin, dalbavancin, and oritavancin are structurally similar to vancomycin and are referred to as *lipoglycopeptides*. They have antibacterial activity against *S. aureus* (including MRSA and some strains of VISA and vancomycin-resistant *S. aureus* [VRSA]), streptococci, and enterococci. Oritavancin may have activity against some strains of VRE. These lipoglycopeptide agents also provide coverage against anaerobic gram-positive organisms except for *Lactobacillus* and some *Clostridium* species. The clinical efficacy of telavancin has been demonstrated in both skin and soft tissue infections and nosocomial pneumonia, and the efficacy of dalbavancin and oritavancin has been shown in skin and soft tissue infections. The vancomycin resistance phenotype may reduce the potency of all three lipoglycopeptides, but the rate of resistance to these drugs among *S. aureus* and enterococcal isolates has been low. Adverse effects of telavancin include nephrotoxicity, metallic taste, and gastrointestinal side effects. Clinicians should be aware of the potential for electrocardiographic QT_c prolongation that can increase the risk of cardiac arrhythmias when telavancin is used concomitantly with other QT_c-prolonging agents. Telavancin may interfere with certain coagulation tests (e.g., causing false elevations in prothrombin time). Dalbavancin and oritavancin have safety profiles similar to that of vancomycin, with common effects reported as headache and gastrointestinal side effects. These glycolipopeptides should be used cautiously in patients with hypersensitivity reactions to vancomycin, as cross-allergy may be possible.

LIPOPEPTIDES

Daptomycin is a lipopeptide antibiotic with activity against a broad range of gram-positive organisms. This drug is active against staphylococci (including MRSA and coagulase-negative staphylococci), streptococci, and enterococci. Daptomycin remains active against enterococci that are resistant to vancomycin. In addition, it exhibits activity against *Bacillus*, *Corynebacterium*, *Peptostreptococcus*, and *Clostridium* species. Daptomycin's pharmacodynamic parameter for efficacy is concentration-dependent killing. Resistance to daptomycin is rare, but MICs may be higher for VISA strains. Daptomycin can be used in skin and soft tissue infections, bacteremia, endocarditis, and osteomyelitis. It is an important alternative for MRSA and other gram-positive infections when bactericidal therapy is needed and vancomycin cannot be used. Daptomycin is generally well tolerated, and its main toxicity consists of elevation of creatine phosphokinase (CPK) levels and myopathy. CPK should be monitored during daptomycin treatment, and the drug should be discontinued if muscular toxicities occur. There have also been case reports of reversible eosinophilic pneumonia associated with daptomycin use.

AMINOGLYCOSIDES

The aminoglycosides are a class of antibacterial agents with concentration-dependent activity against most gram-negative organisms. The most commonly used aminoglycosides are gentamicin, tobramycin, and amikacin, although others, such as streptomycin, kanamycin, neomycin, and paromomycin, may be used in special circumstances. Aminoglycosides have a significant dose-dependent postantibiotic effect; i.e., they have an antibacterial effect even after serum drug levels are undetectable. The postantibiotic effect and concentration-dependent killing form the rationale behind extended-interval aminoglycoside dosing, in which a larger dose is given once daily rather than smaller doses multiple times daily. Aminoglycosides are active against gram-negative bacilli, such as Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter*. They also enhance the activity of cell wall–active agents such as β-lactams or vancomycin against some gram-positive bacteria, including staphylococci and enterococci. This combination therapy is termed *synergistic* because the effect of both agents provides a killing effect greater than would be predicted from the effects of either agent alone. Amikacin and streptomycin have activity against *Mycobacterium tuberculosis*, and amikacin has activity against *Mycobacterium avium-intracellulare*. The aminoglycosides do not have activity against anaerobes, *S. maltophilia*, or *Burkholderia cepacia*. Aminoglycosides are used in clinical practice in a variety of infections caused by gram-negative organisms, including bacteremia and urinary tract infections. They are frequently used alone or in combination for the treatment of *P. aeruginosa* infection. When used in combination with a cell wall–active agent, gentamicin and streptomycin are also important for the treatment of gram-positive bacterial endocarditis. All aminoglycosides can cause nephrotoxicity and ototoxicity. The risk of nephrotoxicity is not well defined; however, some studies have indicated that the effect may be related to the duration of therapy as well as to the concomitant use of other nephrotoxic agents. Nephrotoxicity is usually reversible, but ototoxicity can be irreversible.

MACROLIDES AND KETOLIDES

The macrolides (azithromycin, clarithromycin, and erythromycin) and ketolides (telithromycin) are classes of antibiotics that inhibit protein synthesis. Compared with erythromycin (the older antibiotic), azithromycin and clarithromycin have better oral absorption and tolerability. Azithromycin, clarithromycin, and telithromycin all have broader spectra of activity than erythromycin, which is less frequently used. These agents are commonly used in the treatment of upper and lower respiratory tract infections caused by *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and atypical organisms (e.g., *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*); group A streptococcal pharyngitis in penicillin-allergic patients; and nontuberculous mycobacterial infections (e.g., caused by *Mycobacterium marinum* and *Mycobacterium chelonae*) as well as in the prophylaxis and treatment of *M. avium-intracellulare* infection in patients with HIV/AIDS and in combination therapy for *Helicobacter pylori* infection and bartonellosis. Enterobacteriaceae, *Pseudomonas* species, and *Acinetobacter* species are intrinsically resistant to macrolides as a result of decreased membrane permeability, although azithromycin is active against gram-negative diarrheal pathogens. The major adverse effects of this drug class include nausea, vomiting, diarrhea and abdominal pain, prolongation of QT_c interval, exacerbation of myasthenia gravis, and tinnitus. Azithromycin specifically has been associated with an increased risk of death, especially among patients with underlying heart disease, because of the risk of QT_c interval prolongation and torsades de pointes. Erythromycin, clarithromycin, and telithromycin inhibit the CYP3A4 hepatic drug-metabolizing enzyme and can result in increased levels of coadministered drugs, including benzodiazepines, statins, warfarin, cyclosporine, and tacrolimus. Azithromycin does not inhibit CYP3A4 and therefore does not interact with these drugs.

CLINDAMYCIN

Clindamycin is a lincosamide antibiotic and is bacteriostatic against some organisms and bactericidal against others. It is used most often to treat bacterial infections caused by anaerobes (e.g., *B. fragilis*, *Clostridium perfringens*, *Fusobacterium* species, *Prevotella melaninogenicus*, and *Peptostreptococcus* species) and susceptible staphylococci and streptococci. Clindamycin is used for treatment of dental infections, anaerobic lung abscess, and skin and soft tissue infections. It is used together with bactericidal agents (penicillins or vancomycin) to inhibit new toxin synthesis in the treatment of streptococcal or staphylococcal toxic shock syndrome. Other uses include treatment of infections caused by *Capnocytophaga canimorsus*, combination therapy for malaria and babesiosis, and therapy for toxoplasmosis. Clindamycin has excellent oral bioavailability. Adverse effects include nausea, vomiting, diarrhea, *C. difficile*–associated diarrhea and pseudomembranous colitis, maculopapular rash, and (rarely) Stevens-Johnson syndrome.

TETRACYCLINES AND GLYCYLCYCLINES

The tetracyclines (doxycycline, minocycline, and tetracycline) and the glycylcyclines (tigecycline) inhibit protein synthesis and are bacteriostatic. These drugs have wide clinical uses. They are used in the treatment of skin and soft tissue infections caused by gram-positive cocci (including MRSA), spirochetal infections (e.g., Lyme disease, syphilis, leptospirosis, and relapsing fever), rickettsial infections (e.g., Rocky Mountain spotted fever), atypical pneumonia, sexually transmitted infections (e.g., *Chlamydia trachomatis* infection, lymphogranuloma venereum, and granuloma inguinale), infections with *Nocardia* and *Actinomyces*, brucellosis, tularemia, Whipple's disease, and malaria. Tigecycline, the only approved agent in the glycylcycline class, is a derivative of minocycline and is indicated in the treatment of complicated skin and soft tissue infections, complicated intraabdominal infections, and community-acquired bacterial pneumonia in adults. Tigecycline has activity against MRSA, vancomycin-sensitive enterococci, many Enterobacteriaceae, and *Bacteroides* species; it has no activity against *P. aeruginosa*. This drug has been used in combination with colistin for the treatment of serious infections with multidrug-resistant gram-negative organisms. A pooled analysis of 13 clinical trials found an increased risk of death and treatment failure among patients given tigecycline alone; as a result, the U.S. Food and Drug Administration mandated a black box warning. Tetracyclines have reduced absorption when orally coadministered with calcium- and iron-containing compounds, including milk, and doses should be spaced at least 2 h apart. The major adverse reactions to both of these classes are nausea, vomiting, diarrhea, and photosensitivity. Tetracyclines have been associated with fetal bone-growth abnormalities and should be avoided during pregnancy and in the treatment of children <8 years old.

TRIMETHOPRIM-SULFAMETHOXAZOLE

Trimethoprim-sulfamethoxazole (TMP-SMX) is an antibiotic with two components that inhibit folate synthesis and produce antibacterial activity. TMP-SMX is active against gram-positive bacteria such as staphylococci and streptococci; however, its use against MRSA is usually limited to community-acquired infections, and its activity against *Streptococcus pyogenes* may not be reliable. This drug is also active against many gram-negative bacteria, including *H. influenzae*, *E. coli*, *P. mirabilis*, *Neisseria gonorrhoeae*, and *S. maltophilia*. TMP-SMX is not active against anaerobes or *P. aeruginosa*. It has many uses because of its wide spectrum of activity and high oral bioavailability. Urinary tract infections, skin and soft tissue infections, and respiratory tract infections are among the common uses. Another important indication is for both prophylaxis and treatment of *Pneumocystis jirovecii* infections in immunocompromised patients. Resistance to TMP-SMX has limited its use against many Enterobacteriaceae. Resistance rates among urinary isolates of *E. coli* are almost 25% in the United States. The most common adverse reactions associated with TMP-SMX are gastrointestinal effects such as nausea, vomiting, and diarrhea. In addition, rash is a common allergic reaction and may preclude the subsequent use of other sulfonamides. With prolonged use, leukopenia, thrombocytopenia, and granulocytopenia can develop. TMP-SMX can also cause nephrotoxicity, hyperkalemia, and hyponatremia, which are more common at high doses. TMP-SMX has several important interactions with other drugs (Table 139-4), including warfarin, phenytoin, and methotrexate.

FLUOROQUINOLONES

The fluoroquinolones include norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin. Ciprofloxacin and levofloxacin have the broadest spectrum of activity against gram-negative bacteria, including *P. aeruginosa* (similar to that of third-generation cephalosporins). Because of the risk of selection of resistance during fluoroquinolone treatment of serious pseudomonal infections, these agents are usually used in combination with an antipseudomonal β-lactam. Levofloxacin, moxifloxacin, gemifloxacin, and delafloxacin have additional gram-positive activity, including that against *S. pneumoniae* and some strains of MSSA, and, with the exception of delafloxacin, these agents are used for treatment of community-acquired pneumonia. Strains of MRSA are commonly resistant to all fluoroquinolones except delafloxacin. Moxifloxacin is used as one component of second-line regimens for multidrug-resistant tuberculosis. Fluoroquinolones exhibit concentration-dependent killing, are well absorbed orally, and have elimination half-lives that usually support once- or twice-daily dosing. Oral coadministration with compounds containing high concentrations of aluminum, magnesium, or calcium can reduce fluoroquinolone absorption. The penetration of fluoroquinolones into prostate tissue supports their use for bacterial prostatitis. Fluoroquinolones are generally well tolerated but can cause central nervous system (CNS) stimulatory effects, including seizures; peripheral neuropathy; glucose dysregulation; and tendinopathy associated with Achilles tendon rupture, particularly in older patients, organ transplant recipients, and patients taking glucocorticoids. Other potential effects on connective tissues include an association with increased risk of aortic aneurysm. Worsening of myasthenia gravis also has been associated with quinolone use. Moxifloxacin causes modest prolongation of the QT_c interval and should be used with caution in patients receiving other QT_c-prolonging drugs.

RIFAMYCINS

The rifamycins include rifampin, rifabutin, and rifapentine. Rifampin is the most commonly used rifamycin. For almost all therapeutic indications, it is used in combination with other agents to reduce the likelihood of selection of high-level rifampin resistance. Rifampin is used foremost in the treatment of mycobacterial infections—specifically, as a mainstay of combination therapy for *M. tuberculosis* infection or as a single agent in the treatment of latent *M. tuberculosis* infection. In addition, it is often used in the treatment of nontuberculous mycobacterial infection. Rifampin is used in combination regimens for the treatment of staphylococcal infections, particularly prosthetic-valve endocarditis and bone infections with retained hardware. It is a component of combination therapy for brucellosis (with doxycycline) and leprosy (with dapsone for tuberculoid leprosy and with dapsone and clofazimine for lepromatous disease). Rifampin can be used alone for prophylaxis in close contacts of patients with *H. influenzae* or *N. meningitidis* meningitis. The drug has high oral bioavailability, which is further enhanced when it is taken on an empty stomach. Rifampin has several adverse effects, including elevated aminotransferase levels (14%), rash (1–5%), and gastrointestinal events such as nausea, vomiting, and diarrhea (1–2%). Its many clinically relevant interactions with other drugs (Table 139-4) mandate the clinician's careful review of the patient's medications before rifampin initiation to assess safety and the need for additional monitoring, including monitoring of drug levels.

METRONIDAZOLE

Metronidazole is used in the treatment of anaerobic bacterial infections as well as infections caused by protozoa (e.g., amebiasis, giardiasis, trichomoniasis). It is the agent of choice as a component of combination therapy for polymicrobial abscesses in the lung, brain, or abdomen, the etiology of which often includes anaerobic bacteria, and for bacterial vaginosis, pelvic inflammatory disease, and anaerobic infections, such as those due to *Bacteroides*, *Fusobacterium*, and

Prevotella species. This drug is an alternative agent for treatment of mild to moderate *C. difficile*–associated diarrhea. Metronidazole is bactericidal against anaerobic bacteria and exhibits concentration-dependent killing. It has high oral bioavailability and tissue penetration, including penetration of the blood–brain barrier. The majority of *Actinomyces*, *Propionibacterium*, and *Lactobacillus* species are intrinsically resistant to metronidazole. The major adverse effects include nausea, diarrhea, and a metallic taste. Concomitant ingestion of alcohol may result in a disulfiram-like reaction, and patients are usually instructed to avoid alcohol during treatment. Long-term treatment carries the risk of leukopenia, neutropenia, peripheral neuropathy, and CNS toxicity manifesting as confusion, dysarthria, ataxia, nystagmus, and ophthalmoparesis. Through metronidazole's effect on the CYP2C9 drug-metabolizing enzyme, its coadministration with warfarin can result in decreased metabolism and enhanced anticoagulant effects that require close monitoring. Concomitant administration of metronidazole with lithium can result in increased serum levels of lithium and associated toxicity; coadministration with phenytoin can result in phenytoin toxicity and possibly decreased levels of metronidazole.

OXAZOLIDINONES

Linezolid is a bacteriostatic agent and is indicated for serious infections due to resistant gram-positive bacteria, such as MRSA and VRE. The intrinsic resistance of gram-negative bacteria is mediated primarily by endogenous efflux pumps. Linezolid has excellent oral bioavailability. Adverse effects include myelosuppression and ocular and peripheral neuropathy with prolonged therapy. Peripheral neuropathy may be irreversible. Linezolid is a weak, reversible monoamine oxidase inhibitor, and coadministration with sympathomimetics and foods rich in tyramine should be avoided. Linezolid has been associated with serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors. Tedizolid has properties similar to those of linezolid, but with lower dosing it may be less likely to cause adverse hematologic and neuropathic effects.

NITROFURANTOIN

Nitrofurantoin's antibacterial activity results from the drug's conversion to highly reactive intermediates that can damage DNA and other macromolecules. Nitrofurantoin is bactericidal, and its action is concentration dependent. It displays activity against a range of gram-positive bacteria, including *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *E. faecalis*, *Streptococcus agalactiae*, group D streptococci, viridans streptococci, and corynebacteria, as well as gram-negative organisms, including *E. coli* and *Enterobacter*, *Neisseria*, *Salmonella*, and *Shigella* species. Nitrofurantoin is used primarily in the treatment of urinary tract infections and is preferred in the treatment of such infections in pregnancy. It may be used for the prevention of recurrent cystitis. Recently, there has been interest in the use of nitrofurantoin for treatment of urinary tract infections caused by ESBL-producing Enterobacteriaceae such as *E. coli*, although resistance has been growing in Latin America and parts of Europe. Coadministration with magnesium should be avoided because of decreased absorption, and patients should be encouraged to take the drug with food to increase its bioavailability and decrease the risk of adverse effects, which include nausea, vomiting, and diarrhea. Nitrofurantoin may also cause pulmonary fibrosis and drug-induced hepatitis. Because the risk of adverse reactions increases with age, the use of nitrofurantoin in elderly patients is not recommended. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at elevated risk for nitrofurantoin-associated hemolytic anemia.

POLYMYXINS

Colistin and polymyxin B act by disrupting bacterial cell membrane integrity and are active against the nonenteric pathogens *P. aeruginosa* and *A. baumannii* but not against *Burkholderia*. These drugs also exhibit activity against many Enterobacteriaceae, with the exceptions of *Proteus*, *Providencia*, and *Serratia* species. They lack activity against gram-positive bacteria. Polymyxins are bactericidal and are available in IV formulations. Colistimethate is converted to the active form (colistin) in plasma. Polymyxins are most often used for infections due to pathogens resistant to multiple other antibacterial agents, including urinary tract infections, hospital-acquired pneumonia, and bloodstream infections. Nebulized formulations have been used for adjunctive treatment of refractory ventilator-associated pneumonia. The most important adverse effect is dose-dependent reversible nephrotoxicity. Neurotoxicity, including paresthesias, muscle weakness, and confusion, is reversible and less common than nephrotoxicity.

QUINUPRISTIN-DALFOPRISTIN

Quinupristin-dalfopristin is a member of the streptogramin class of antibiotics and kills bacteria by inhibiting protein synthesis. The antibacterial spectrum of quinupristin-dalfopristin includes staphylococci (including MRSA), streptococci, and *E. faecium* (but not *E. faecalis*). This drug is also active against *Corynebacterium* species and *L. monocytogenes*. Quinupristin-dalfopristin is not reliably active against gram-negative organisms. It exhibits concentration-dependent killing, with an AUC/MIC ratio predicting efficacy. The clinical use of quinupristin-dalfopristin is largely for infections due to vancomycin-resistant *E. faecium* and other gram-positive bacterial infections. The drug has demonstrated efficacy in a variety of infections, including urinary tract infections, bone and joint infections, and bacteremia. Adverse effects associated with quinupristin-dalfopristin include infusion-related reactions, arthralgias, and myalgias. The arthralgias and myalgias may be severe enough to warrant drug discontinuation. Quinupristin-dalfopristin inhibits the CYP3A4 drug-metabolizing enzyme, with consequent drug interactions (Table 139-4).

FOSFOMYCIN

Fosfomycin is a phosphonic acid antibiotic that has greater activity in acidic environments and is excreted in its active form in the urine. Thus, its use is primarily for prophylaxis and treatment of uncomplicated cystitis and should be avoided if there is concern about pyelonephritis. The drug is administered as a single 3-g dose that results in high urine concentrations for up to 48 h. Fosfomycin is active against *S. aureus*, vancomycin-susceptible enterococci and VRE, and a wide range of gram-negative organisms, including *E. coli*, *Enterobacter* species, *Serratia marcescens*, *P. aeruginosa*, and *K. pneumoniae*. Notably, the vast majority of ESBL-producing Enterobacteriaceae are susceptible to fosfomycin. *A. baumannii* and *Burkholderia* species are resistant. The emergence of resistance to fosfomycin has not been observed during treatment of cystitis but has been documented during treatment of respiratory tract infections and osteomyelitis. The few adverse effects that have been reported include nausea and diarrhea.

CHLORAMPHENICOL

The use of chloramphenicol is limited by its potentially serious toxicities. When other agents are contraindicated or ineffective, chloramphenicol represents an alternative treatment for infections, including meningitis caused by susceptible bacteria such as *N. meningitidis*, *H. influenzae*, and *S. pneumoniae*. It has also been used for the treatment of anthrax, brucellosis, *Burkholderia* infections, chlamydial infections, clostridial infections, erlichiosis, rickettsial infections, and typhoid fever. Adverse reactions include aplastic anemia, myelosuppression, and gray baby syndrome. Chloramphenicol inhibits the CYP2C19 and CYP3A4 drug-metabolizing enzymes and consequently increases levels of many classes of drugs.

APPROACH TO PROPHYLAXIS OF INFECTION

Antibacterial prophylaxis is indicated only in selected circumstances **(Table 139-6)** and should be supported by well-designed studies or expert panel recommendations. In all cases, the risk or severity of the infection to be prevented should be greater than the adverse consequences of antibacterial therapy, including the potential for selection of resistance. In addition, the timing and duration of antibacterial treatment should be targeted for maximal effect and minimal required exposure. Prophylaxis of surgical-site infections targets bacteria that may contaminate the wound during the surgical procedure, including the skin flora of the patient or operating team and the air in the

TABLE 139-6 Prophylaxis of Bacterial Infections in Adults

CONDITION	ANTIBACTERIAL AGENTS[a]	TIMING OR DURATION OF PROPHYLAXIS
Surgical		
Clean (cardiac, thoracic, neurologic, orthopedic, vascular, plastic)	Cefazolin (vancomycin,[b] clindamycin)	1 h before incision; re-dose with long procedures
Clean (ophthalmic)	Topical neomycin–polymyxin B–gramicidin, topical moxifloxacin	Every 5–15 min for 5 doses immediately prior to procedure
Clean-contaminated (head and neck)	Cefazolin + metronidazole, ampicillin-sulbactam[c] (clindamycin)	1 h before incision; re-dose with long procedures
Clean-contaminated (hysterectomy, gastroduodenal, biliary, unobstructed small intestine, urologic)	Cefazolin, ampicillin-sulbactam[c] (clindamycin + aminoglycoside, aztreonam, or fluoroquinolone)	1 h before incision; re-dose with long procedures
Clean-contaminated (colorectal, appendectomy)	Cefazolin + metronidazole, ampicillin-sulbactam,[c] ertapenem (clindamycin + aminoglycoside, aztreonam, or fluoroquinolone)	1 h before incision; re-dose with long procedures
Dirty (ruptured viscus)	Therapeutic regimen directed at anaerobes and gram-negative bacteria (e.g., ceftriaxone + metronidazole)	1 h before incision; re-dose with long procedures; continue for 3–5 days after procedure
Dirty (traumatic wound)	Therapeutic regimen: cefazolin (clindamycin ± aminoglycoside, aztreonam, or fluoroquinolone)	1 h before incision; re-dose with long procedures; continue for 3–5 days after procedure
Nonsurgical		
Dental, oral, or upper respiratory procedures in patients with high-risk cardiac lesions (prosthetic valves, congenital heart defects, prior endocarditis)	Amoxicillin PO, ampicillin IM (clindamycin PO, IV)	Oral agents 1 h before procedure; injection 30 min before procedure
Recurrent *S. aureus* skin infections[d]	Mupirocin[e]	Intranasal application for 5 days
Recurrent cellulitis associated with lymphatic disruption[d]	Benzathine penicillin IM monthly, oral penicillin or erythromycin twice daily	Undefined
Recurrent cystitis in women[d]	Nitrofurantoin, TMP-SMX, fluoroquinolone	After sexual intercourse *or* 3 times weekly for up to 1 year
Bite wounds	Amoxicillin-clavulanate (doxycycline, moxifloxacin)	3–5 days
Recurrent spontaneous bacterial peritonitis in cirrhotic patients[d]	Fluoroquinolone[f]	Undefined
Recurrent pneumococcal meningitis in patient with CSF leak or humoral immune defect[d]	Penicillin	Undefined
Exposure to patient with meningococcal meningitis	Rifampin, ciprofloxacin	2 days (rifampin), single dose (ciprofloxacin)
High-risk neutropenia (ANC, ≤100/μL for >7 days)[d]	Levofloxacin or ciprofloxacin[f]	Until neutropenia resolves or fever dictates use of other antibacterials

[a]Regimens in parentheses are alternatives for patients allergic to β-lactams. [b]Vancomycin may be given together with cefazolin to patients known to be colonized with methicillin-resistant *Staphylococcus aureus*. [c]Cefoxitin or cefotetan may also be considered. [d]Not considered routine for all patients, but an acceptable consideration among alternative approaches. [e]Usually coupled with bathing with chlorhexidine-containing skin antiseptic. [f]Choice of fluoroquinolone prophylaxis must be balanced against the risk of selection of resistance.

Abbreviations: ANC, absolute neutrophil count; CSF, cerebrospinal fluid; TMP-SMX, trimethoprim-sulfamethoxazole.

operating room. Delivery of the antibacterial drug within 1 h before the surgical incision is most effective. For prolonged procedures, redosing may be necessary to maintain effective blood and tissue levels until the wound is closed. Additional dosing is not recommended after the incision is closed. In patients with nasal carriage of *S. aureus*, preoperative decolonization with nasal mupirocin reduces the rate of *S. aureus* surgical-site infections and is generally recommended for high-risk procedures such as cardiac surgery and orthopedic implantation of prosthetic devices. For dental procedures, preprocedure antibacterial drugs are given to prevent transient bacteremia and the seeding of certain high-risk cardiac lesions. Prophylaxis is also used in nonprocedural settings in certain patients who have recurrent infections or who are at risk of serious infection from a specific exposure (e.g., close contact with a patient with meningococcal meningitis). Extension of prophylaxis beyond the period of infection risk (24 h in the case of surgical procedures) does not add further benefit and may increase the risk of resistance selection or *C. difficile* disease.

ANTIMICROBIAL STEWARDSHIP

In an era of increasing prevalence of multidrug-resistant bacteria and with a substantial amount of inappropriate antimicrobial use, the need for rational antimicrobial prescribing has never been greater **(Chap. 140)**. *Antimicrobial stewardship* describes the practice of promoting the selection of the appropriate drug, dosage, route, and duration of antimicrobial therapy. Antimicrobial stewardship programs implement a variety of strategies to (1) improve patient care through appropriate antimicrobial use; (2) decrease the development of resistance within patients and populations; (3) reduce the incidence of adverse effects; and (4) control costs.

Infections caused by resistant pathogens result in significant morbidity and mortality as well as increased health care costs. Antimicrobial stewardship programs are typically multidisciplinary and often include infectious disease physicians, clinical pharmacists (usually with special training in infectious disease), clinical microbiologists, information systems specialists, infection prevention and control practitioners, and epidemiologists. These teams employ a variety of approaches to achieving the program's goals.

Established strategies of antimicrobial stewardship programs include (1) prospective audit of antimicrobial use, with intervention and feedback; (2) formulary restriction; and (3) preauthorization. *Prospective audit and feedback* are usually undertaken by an infectious disease physician or a pharmacist. In this process, orders for broad-spectrum antimicrobials (e.g., carbapenems) or agents for which more cost-effective alternatives may exist (e.g., daptomycin, ceftazidime-avibactam) are reviewed on a regular basis for appropriateness. In circumstances in which an antimicrobial is used in the absence of an appropriate indication, the stewardship program team intervenes and recommends an alternative to the primary team caring for the patient. This process has been successful in several quasi-experimental studies, resulting in declines in use of broad-spectrum drugs and decreases in adverse events, such as *C. difficile* infection. *Formulary restriction* is the inclusion of a limited set of antimicrobial agents in a hospital formulary for the purpose of limiting indiscriminant use of antimicrobials in the absence of demonstrated benefit. Such restriction coincidentally serves to reduce

costs. *Preauthorization* is the practice of requiring clinicians to obtain approval before using selected antimicrobials. Approval may be provided electronically with sophisticated Computerized Provider Order Entry (CPOE) software, after specific criteria for use are met, or after communication with an infectious disease specialist as designated by the stewardship program. These strategies have led to a decrease in *C. difficile* infections and to improvements in drug susceptibility patterns.

Additional strategies used in specific health care settings are guidelines and pathways, dose optimization, parenteral-to-oral conversion, antibiotic time-out, and de-escalation of therapy. Documentation of the indication for which each antimicrobial is prescribed is also encouraged. Antimicrobial stewardship is an evolving area and an increasingly active area of research aimed at identifying the best practices. The IDSA, in collaboration with several other professional organizations, has published guidelines for developing institutional antimicrobial stewardship programs (*www.idsociety.org/Antimicrobial_Agents/*).

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140 Bacterial Resistance to Antimicrobial Agents

David C. Hooper

DEFINITION OF RESISTANCE

The action of antimicrobial agents on a range of targets within the bacterial cell can result in inhibition of bacterial growth or in killing of the bacterial cell **(Chap. 139)**. Reduction in or loss of an agent's antibacterial effect is referred to as *resistance*, and the properties of or alterations in the bacterium that result in reduced antimicrobial activity are termed *resistance mechanisms*. Bacteria can be resistant to single or multiple antimicrobials, as detailed in the sections that follow. The occurrence and magnitude of resistance are often assessed in clinical microbiology laboratories by measurement of the lowest drug concentration that inhibits growth of a bacterium (minimal inhibitory concentration, or MIC) with a standardized inoculum and growth conditions. MIC values are generally interpreted as representing bacterial susceptibility, intermediate susceptibility, or resistance; the interpretation is based on correlations of the MIC values with the pharmacokinetics and delivery of a drug to the site of infection in the body as well as with data from clinical trials. Thus, a clinical laboratory result of "susceptible" for a bacterium predicts a likely clinical response to an appropriately dosed antimicrobial drug by a patient infected with that organism, whereas a result of "resistant" predicts poor or no clinical response to that drug. Breakpoint MIC values for categorization of bacteria as susceptible, intermediate, or resistant are generally developed by regulatory and advisory groups and are often based on the distribution of MIC values from a large collection of recent clinical bacterial isolates. Research studies on the mechanisms and epidemiology of resistance may in some cases use different and less rigid definitions of resistance based on determination of a reproducible increase in an MIC value relative to a baseline reference MIC, independent of clinical breakpoints.

MECHANISMS OF RESISTANCE

Bacteria use a wide variety of mechanisms to block or circumvent the activity of antibacterial agents **(Table 140-1** and **Fig. 140-1)**. Although myriad, these mechanisms can generally be grouped into three categories: (1) alteration or bypassing of targets that exhibit reduced binding of the drug, (2) altered access of the drug to its target by reductions in uptake or increases in active efflux, and (3) a modification of the drug that reduces its activity. These mechanisms result from either mutations in bacterial chromosomal genes occurring spontaneously during bacterial DNA replication or the acquisition of new genes by DNA transfer from other bacteria or uptake of exogenous DNA. New genes are most often acquired on self-replicating plasmids or other DNA elements transferred from other bacteria. However, some bacteria, such as *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*, can also take up fragments of environmental DNA from related bacterial species and recombine that DNA directly into their own chromosomes, a process called *transformation*. Not uncommonly, resistant bacteria have combinations of resistance mechanisms either within one category or among categories, and many plasmids contain more than one resistance gene. Thus, plasmid acquisition itself can in many cases confer resistance to multiple antibacterial agents. Resistance to multiple, structurally unrelated antibiotics can also occur by mutations that cause increased expression of certain bacterial efflux pumps, some of which have broad substrate profiles.

Many antibacterial drugs are derived from natural products of environmental microbial species. Some genes encoding resistance to these drugs originate in the drug-producer organism to protect it from its product and have then been mobilized onto plasmids that spread into other organisms. Surviving non-producer bacteria in the exposed natural environment may also have evolved resistance under selection pressure that adds to the reservoir of resistance mechanisms. Exposure to antibacterial agents either in nature or during human or animal use then results in the selection of resistant strains within an otherwise susceptible bacterial population. In some cases, resistance mechanisms may confer disadvantages that render bacterial growth or survival fitness inferior to that of susceptible strains. In a number of examples, however, fitness defects are often mitigated over time by compensatory mutational mechanisms that make the bacteria both resistant and fit and thereby more likely to persist in a reservoir even in the absence of continued antimicrobial selection pressures. Discussed below are the major classes of antimicrobial agents currently in clinical use and the most important mechanisms of resistance encountered in clinical infections.

β-Lactams β-lactams, the largest class of antibiotics, inhibit bacterial cell-wall synthesis by binding to cell wall transpeptidases, cross-linking enzymes that are also called penicillin-binding proteins (PBPs); PBPs are targets that are unique to bacteria and have no mammalian counterpart. The most common mechanism of resistance to β-lactams, particularly in gram-negative bacteria, is their degradation by β-lactamases, enzymes that break down the core β-lactam ring and destroy drug activity. β-Lactamases differ in the spectrum of β-lactams they can degrade. Some β-lactamases are encoded on the bacterial chromosome, and their activity contributes to the susceptibility profile of a particular species. Chromosomally encoded β-lactamases can be produced in varying amounts that affect the degree of resistance. In some cases, enzyme expression is physiologically induced by exposure to certain β-lactams; in other cases, enzyme expression can become constant or constitutive through mutations in genes that encode the regulators of expression of a β-lactamase gene. Other β-lactamases are

TABLE 140-1 The Most Common Mechanisms of Resistance to Antibacterial Agents

ANTIBACTERIAL AGENT(S)	MAJOR TARGET	MECHANISM(S) OF ACTION	MECHANISM(S) OF RESISTANCE
β-Lactams (penicillins, cephalosporins, monobactams, carbapenems)	Cell wall synthesis	Bind cell-wall cross-linking enzymes (PBPs, transpeptidases)	1. Drug inactivation by β-lactamases 2. Altered PBP targets 3. Reduced diffusion through porin channels
Glycopeptides and lipoglycopeptides (vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin)	Cell wall synthesis	Block cell wall glycosyltransferases by binding D-Ala-D-Ala stem-peptide terminus Teicoplanin, telavancin, dalbavancin, and oritavancin: affect membrane function	1. Altered D-Ala-D-Ala target (D-Ala-D-Lac) 2. Increased D-Ala-D-Ala target binding at sites distant from cell wall synthesis enzymes
Bacitracin	Cell wall synthesis	Blocks lipid carrier of cell wall precursors	Active drug efflux
Fosfomycin	Cell wall synthesis	Blocks linkage of stem peptide to NAG by enoyltransferase	1. Target enzyme overexpression 2. Drug-modifying enzymes
Aminoglycosides (gentamicin, tobramycin, amikacin)	Protein synthesis	Bind 30S ribosomal subunit Block translocation of peptide chain Cause misreading of mRNA	1. Drug-modifying enzymes 2. Methylation at ribosome binding site 3. Decreased permeation to target due to active efflux
Tetracyclines (tetracycline, doxycycline, minocycline)	Protein synthesis	Bind 30S ribosomal subunit Inhibit peptide elongation	1. Active drug efflux 2. Ribosomal protection proteins
Tigecycline	Protein synthesis	Same as tetracyclines	Active drug efflux (pumps different from those affecting tetracyclines)
Macrolides (erythromycin, clarithromycin, azithromycin) and the ketolide telithromycin	Protein synthesis	Bind 50S ribosomal subunit Block peptide chain exit	1. Methylation at ribosome binding site 2. Active drug efflux
Lincosamides (clindamycin)	Protein synthesis	Bind 50S ribosomal subunit Block peptide bond formation	Methylation at ribosome binding site
Streptogramins (quinupristin, dalfopristin)	Protein synthesis	Same as macrolides	1. Same as macrolides 2. Drug-modifying enzymes
Chloramphenicol	Protein synthesis	Binds 50S ribosomal subunit Blocks aminoacyl tRNA positioning	Drug-modifying enzymes
Oxazolidinones (linezolid, tedizolid)	Protein synthesis	Bind 50S ribosomal subunit Inhibit initiation of peptide synthesis	1. Altered rRNA binding site 2. Methylation of ribosome binding site
Mupirocin	Protein synthesis	Blocks isoleucyl tRNA synthetase	1. Acquired resistant tRNA synthetase (drug bypass) 2. Altered native tRNA synthetase target
Sulfonamides (sulfadiazine, sulfisoxazole, and sulfamethoxazole)	Folate synthesis	Inhibit dihydropteroate synthetase	Acquired resistant dihydropteroate synthetase (drug bypass)
Trimethoprim	Folate synthesis	Inhibits dihydrofolate reductase	Acquired resistant dihydrofolate reductase (drug bypass)
Quinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gemifloxacin, delafloxacin)	DNA synthesis	Inhibit DNA gyrase and DNA topoisomerase IV Enzyme–DNA–drug complex: blocks DNA replication apparatus	1. Altered target(s) 2. Active efflux 3. Protection of target from drug 4. Drug-modifying enzyme (ciprofloxacin)
Rifamycins (rifampin, rifabutin, rifapentine)	RNA synthesis	Inhibit RNA polymerase	Altered target
Nitrofurantoin	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	Altered drug-activating enzymes
Metronidazole	Nucleic acid synthesis	Reduces reactive drug derivatives that damage DNA	1. Altered drug-activating enzyme 2. Acquired detoxifying enzymes 3. Active efflux
Polymyxins (polymyxin B and polymyxin E [colistin])	Cell membrane	Bind LPS and disrupt both outer and cytoplasmic membranes	Altered cell-membrane charge with reduced drug binding
Daptomycin	Cell membrane	Produces membrane channel and membrane leakage	Altered cell-membrane charge with reduced drug binding

Abbreviations: LPS, lipopolysaccharide; NAG, *N*-acetylglucosamine; PBP, penicillin-binding protein.

encoded by genes on acquired plasmids and are usually constitutively expressed. The resistance profiles due to plasmids may be present in some strains of a species but not others, depending on which plasmids the strain has acquired. In gram-positive bacteria β-lactamases are secreted into the extracellular environment, whereas in gram-negative bacteria these enzymes are secreted into the periplasmic space between the cytoplasmic and outer membranes—a limited space that permits the presence of high concentrations of β-lactamase. Thus, in gram-negative bacteria, access of β-lactams both to their target PBPs and to β-lactamases requires diffusion across the outer membrane, generally through the porin diffusion channels. Reductions in outer-membrane diffusion channels due to mutation can further augment the efficiency of β-lactamase degradation of β-lactams: slow diffusion acts together with the high enzyme concentrations in the periplasmic space to enhance drug degradation and resistance.

Most strains of *Staphylococcus aureus* produce a plasmid-encoded β-lactamase that degrades penicillin but not semisynthetic penicillins, such as oxacillin and nafcillin. The greatest diversity among β-lactamases, however, is found in gram-negative bacteria. The most common and earliest identified plasmid-encoded β-lactamases of gram-negative

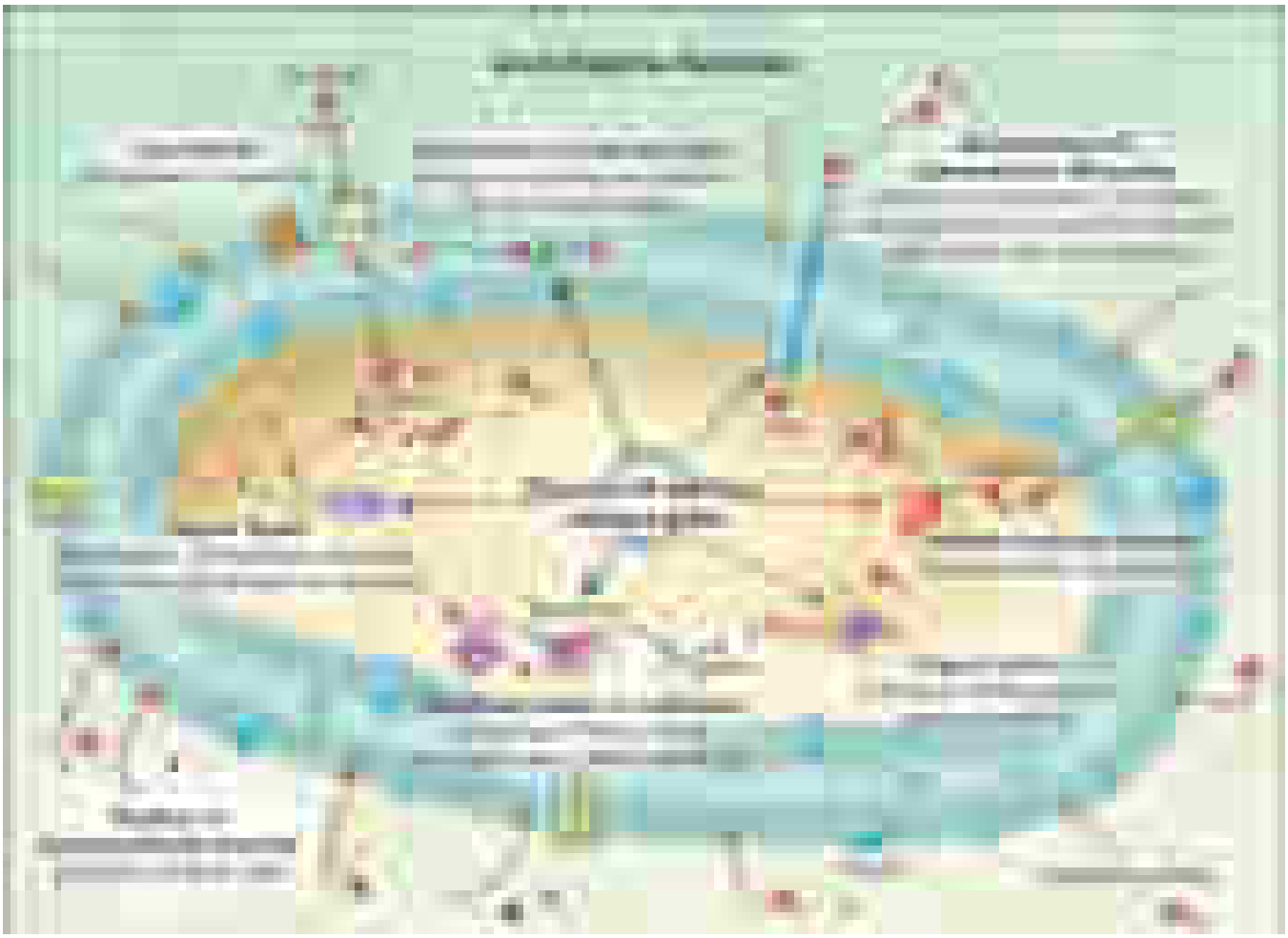

FIGURE 140-1 Mechanisms of resistance to antibacterial agents, as illustrated in a gram-negative bacterium. Similar mechanisms are found in gram-positive bacteria, but their lack of an outer membrane causes β-lactamases to be excreted outside the cell, rather than into the periplasmic space between the inner and outer membranes, and reduces the efficiency of efflux pumps because exported drugs can re-enter the cell after crossing a single membrane, rather than the two membranes in gram-negative bacteria. Red spheres indicate antibiotics. *(From Peleg AY, Hooper DC: Hospital-acquired infections due to gram-negative bacteria. N Engl J Med 362:1084, 2010. © 2010 Massachusetts Medical Society. Reprinted with permission.)*

bacteria can inactivate all penicillins and most early-generation cephalosporins. Multiple extended-spectrum β-lactamase (ESBL) variants of these early enzymes have emerged and are now widely disseminated. These ESBLs can degrade later-generation cephalosporins (ceftriaxone, cefotaxime, ceftazidime) as well as the monobactam aztreonam, and some ESBLs also degrade the fourth-generation cephalosporin cefepime. Carbapenems (imipenem, meropenem, ertapenem, doripenem) generally are not degraded by ESBLs, but additional β-lactamases, called *carbapenemases*, which degrade carbapenems and most if not all other β-lactams, have emerged and are increasing in prevalence. In the United States, *Klebsiella pneumoniae* carbapenemases (KPCs), which are usually found in strains of *Escherichia coli* and *K. pneumoniae*, are most widespread, but New Delhi metallo-β-lactamases (NDM carbapenemases), which were found initially on the Indian subcontinent, have now appeared in several areas in the United States, as has an OXA group carbapenemase, OXA-48. In some cases, high levels of expression of an ESBL or an AmpC enzyme (see below), together with reduced porin diffusion channels, can also result in resistance to carbapenems. In *Pseudomonas aeruginosa*, resistance to carbapenems can occur by mutations that cause reductions in the OprD diffusion channel for imipenem or increased expression of efflux pumps that can remove meropenem from the bacterial cell.

The chromosomal β-lactamase of *K. pneumoniae* preferentially degrades penicillins but not cephalosporins. In contrast, the chromosomal β-lactamase of *Enterobacter* and related genera, AmpC, can degrade almost all cephalosporins but is normally expressed in only small amounts. Mutations in regulatory genes that cause increased amounts of AmpC to be produced confer full resistance to penicillins and cephalosporins; the exceptions are cefoxitin and cefepime, which are relatively stable to AmpC. Resistance to cefepime can develop, however, through the combined effects of increased AmpC production and decreased porin diffusion channels. Genes encoding AmpC have also been found on plasmids but are less common than plasmid-encoded ESBLs.

Inhibitors of β-lactamases such as clavulanate, sulbactam, tazobactam, avibactam, and vaborbactam have been developed and paired with amoxicillin and ticarcillin (clavulanate), ampicillin (sulbactam), piperacillin and ceftolozane (tazobactam), ceftazidime (avibactam), or meropenem (vaborbactam). These inhibitors have little or no antibacterial activity of their own but inhibit plasmid-mediated β-lactamases, including ESBLs. Only avibactam and vaborbactam inhibit AmpC enzymes and some carbapenemases (KPCs but not metallo-carbapenemases, such as NDM).

Resistance to β-lactams also occurs through alterations in the drugs' target transpeptidase enzymes (PBPs) involved in cross-linking of the bacterial cell-wall peptidoglycan structure. In *S. pneumoniae*, *N. gonorrhoeae*, and *Neisseria meningitidis*, resistance to penicillin occurs by recombination of transformed DNA from related species that results in mosaic PBPs with lower affinity for penicillin. A combination of increased expression of an efflux pump and a porin mutation also causes penicillin resistance in *N. gonorrhoeae*. In staphylococci, resistance to methicillin and other β-lactams occurs by acquisition of the *mec* gene, which encodes PBP2a with reduced drug affinity. PBP2a is a bypass target that can function in the presence of β-lactams, bypassing their effect on other PBPs. Ceftaroline is the only β-lactam that has an affinity for PBP2a and is thus active against methicillin-resistant staphylococcal strains. Resistance

to ceftaroline can occur, however, by mutations in the gene encoding PBP2a that reduce its affinity for the drug.

Glycopeptides and Lipoglycopeptides Glycopeptides and lipoglycopeptides inhibit bacterial cell-wall synthesis by binding to the terminal two D-alanine amino acids on the cell-wall peptidoglycan stem peptides, which are involved in peptidoglycan cross-links. In doing so, these drugs block the transpeptidase cross-linking enzymes and glycosyl transferases necessary for cell wall synthesis. Resistance to vancomycin in enterococci is due to the acquisition of a set of *van* genes that result in (1) the production of D-alanine-D-lactate—instead of the normal D-alanine-D-alanine—at the end of the peptidoglycan stem peptide and (2) the reduction of existing D-alanine-D-alanine–terminated peptides. Vancomycin binds D-alanine-D-lactate with a 1000-fold lower affinity than D-alanine-D-alanine. The *van* genes originated in the organisms that naturally produce vancomycin and have been mobilized and reorganized in transposon mobile genetic elements and onto plasmids, which can be transferred between enterococci. In rare cases, the *van* gene cassettes have been transferred from enterococci to *S. aureus*, with the consequent generation of full vancomycin resistance. In *S. aureus*, intermediate resistance to vancomycin is more common than full vancomycin resistance and is due to a different mechanism that results from a series of several chromosomal mutations leading to a thickened and poorly cross-linked cell wall. This modified cell wall contains additional D-alanine-D-alanine–terminated stem peptides that bind vancomycin at a site distant from the cell membrane, adjacent to which new peptidoglycan is synthesized and where vancomycin binding blocks transpeptidase and transglycosylase enzymes. Thus, vancomycin's binding to these distant termini impedes its access to the proximal binding sites that result in inhibition of peptidoglycan synthesis. This intermediate-resistance phenotype was first recognized in patients receiving prolonged courses of vancomycin that created an opportunity for selection of the multiple mutations needed to produce the modified cell wall. Because of the energy costs of a thickened cell wall, this intermediate-resistance phenotype may be unstable, with strains returning to susceptibility in the absence of vancomycin selection pressure. Susceptibility to telavancin, dalbavancin, and oritavancin is also reduced in strains that exhibit resistance or intermediate susceptibility to vancomycin, although in some cases the drugs remain sufficiently active that the strains may still be classified as susceptible on the basis of standard clinical laboratory interpretive criteria.

Aminoglycosides Aminoglycosides are one of several classes of antimicrobials that inhibit protein synthesis by binding to either the 30S or the 50S bacterial ribosomal subunit (both of which differ from eukaryotic ribosomal subunits), with consequent selective antibacterial activity. The aminoglycosides bind to the 30S subunit of the bacterial ribosome. The most common mechanism of resistance to aminoglycosides in gram-negative bacteria is due to acquisition of plasmid genes encoding transferase enzymes that modify aminoglycosides by the addition of acetyl, adenyl, or phosphate groups; these added groups decrease the drugs' binding affinity to their ribosomal target site. Transferases differ in which aminoglycosides they modify, and amikacin resistance occurs less often than resistance to gentamicin or tobramycin by these mechanisms. Another recently found mechanism of plasmid-mediated resistance is due to methylase enzymes that can methylate the site of aminoglycoside binding on the 16S ribosomal RNA of the 30S ribosomal subunit and reduce drug binding to its ribosome target, resulting in resistance to all aminoglycosides. For streptomycin, a single ribosomal protein mutation may also cause resistance. In *P. aeruginosa*, resistance can occur through mutations in regulatory genes causing increased expression of a chromosomally encoded efflux pump, MexXY, which reduces intracellular drug concentrations.

Tetracyclines and Glycylcyclines These antibiotics bind the 16S ribosomal RNA of the 30S ribosomal subunit at a site distinct from the binding site of the aminoglycosides and inhibit bacterial protein synthesis. For tetracyclines, resistance is often plasmid mediated and attributable either to active efflux pumps, which are generally specific for tetracyclines, or to proteins that protect the ribosome from tetracycline action. A number of broad-spectrum, chromosomally encoded efflux pumps may also include tetracyclines among their substrates, and regulatory mutations that cause pump overexpression may confer tetracycline resistance together with resistance to other agents. Resistance to the glycylcycline tigecycline, which is not affected by the usual tetracycline resistance mechanisms, can occur through mutations that cause overexpression of some broad-spectrum efflux pumps, particularly in *Proteus* species. Plasmid-encoded tetracycline modification as a resistance mechanism has been described in *Bacteroides* species but is uncommon.

Macrolides, Ketolides, Lincosamides, and Streptogramins These antibiotics are also inhibitors of bacterial protein synthesis, in this case through their binding to the 23S RNA of the 50S ribosomal subunit. They are generally active against gram-positive bacteria. Resistance to macrolides, clindamycin, and quinupristin is most often due to acquired Erm methylases that modify the drug-binding site on the ribosome, reducing binding. Resistance to quinupristin by this mechanism renders the quinupristin-dalfopristin combination bacteriostatic rather than bactericidal. Telithromycin, a ketolide structurally related to macrolides, has an additional binding site on the ribosome and remains active in the presence of some methylases. Methylase gene expression can be induced by exposure to most macrolides but generally not ketolides (e.g., telithromycin); however, bacterial strains constitutively expressing methylase genes can display resistance to both macrolides and ketolides. Acquired genes encoding active efflux pumps also can contribute to resistance to macrolides in streptococci and to resistance to macrolides, clindamycin, and dalfopristin in staphylococci. Plasmid-acquired, drug-modifying enzymes in staphylococci can also cause resistance to quinupristin and dalfopristin. Macrolide resistance due to 23S rRNA mutations at the site of drug binding is uncommon in staphylococci and streptococci because of the multiple copies of the rRNA genes on the chromosomes of these species; such resistance may occur more frequently, however, in mycobacteria, *Helicobacter pylori*, and *Treponema* species, which have only one or two chromosomal copies of these rRNA genes. Among gram-negative bacteria, many of which are not susceptible to current macrolides because of inadequate drug permeation, some strains with acquired genes for macrolide-modifying enzymes have been described.

Chloramphenicol Chloramphenicol inhibits bacterial protein synthesis by binding to the 23S rRNA of the 50S subunit at a site that overlaps the macrolide-binding site. Chloramphenicol is uncommonly used in human medicine because of infrequent but potentially severe bone marrow toxicity. Resistance to chloramphenicol is most often due to plasmid-encoded, drug-modifying acetyltransferases that have been found in both gram-positive and gram-negative bacteria and whose expression can be induced by drug exposure. Among staphylococci, some resistant strains have been found to have a plasmid-encoded ribosomal methylase that confers resistance to chloramphenicol, clindamycin, and oxazolidinones. As is the case for macrolides, ribosomal mutations causing resistance to chloramphenicol are uncommon because of multiple copies of rRNA genes in most human pathogens. Plasmid-encoded efflux pumps affecting chloramphenicol specifically have been found in gram-negative bacteria, and other pumps affecting chloramphenicol and oxazolidinones have been found in gram-positive bacteria.

Oxazolidinones Linezolid and tedizolid are the only members of the oxazolidinone class of antimicrobials in clinical use, and both are active against gram-positive bacteria only; lack of sufficient activity in gram-negative bacteria results from the ability of native efflux pumps in these bacteria to limit drug access to their cytoplasmic ribosome targets. Oxazolidinones target the bacterial ribosome and inhibit protein synthesis by binding to 23S rRNA of the 50S subunit at a distinct site that overlaps with the chloramphenicol-binding site. Resistance has been seen in enterococci more often than in staphylococci and, in both organisms, is most often due to mutations in multiple copies of the 23S rRNA genes that reduce drug binding to the ribosome. A plasmid-acquired ribosomal methylase gene that enables ribosomal alteration at a site that

confers resistance to both linezolid and chloramphenicol has also been found in some strains of both *S. aureus* and coagulase-negative staphylococci but is not yet widespread. A plasmid-encoded active efflux pump conferring resistance to oxazolidinones (both linezolid and tedizolid) and chloramphenicol has been described in animal isolates and a small number of human isolates of *Enterococcus faecalis*.

Mupirocin Mupirocin is used only in topical formulations, most often for elimination of nasal carriage of *S. aureus*. It targets bacterial leucyl-tRNA synthetase and inhibits protein synthesis. Resistance to mupirocin occurs by either mutation in the target leucyl-tRNA synthetase (low-level resistance) or the acquisition of a plasmid-encoded resistant tRNA synthetase (high-level resistance), which bypasses drug inhibition of the native, sensitive synthetase.

Sulfonamides and Trimethoprim These agents inhibit the folate biosynthesis pathway at different steps. Sulfonamides are structurally similar to *para*-aminobenzoic acid (PABA) and competitively inhibit dihydropteroate synthetase, which, in an early step in the pathway, uses PABA to synthesize dihydropteroate, a precursor of dihydrofolate. Trimethoprim inhibits dihydrofolate reductase at a later step in the pathway that generates tetrahydrofolate. Clinical use of folate pathway inhibitors most often consists of the combination of sulfamethoxazole and trimethoprim; on occasion, however, trimethoprim or various sulfonamides are used individually. Resistance to both of these antimetabolites can result from mutation in their target enzymes or can be due to plasmid-acquired genes encoding resistant enzymes that bypass the inhibition of the native sensitive enzymes—a resistant dihydropteroate synthetase in the case of sulfonamides and a resistant dihydrofolate reductase in the case of trimethoprim. Resistance to the combination of sulfamethoxazole and trimethoprim requires that the bacterial strain have resistance mechanisms for both agents and yet is not uncommon. Resistance due to drug efflux or drug modification has not been problematic for either sulfonamides or trimethoprim.

Quinolones Quinolones are synthetic inhibitors of bacterial DNA synthesis. They bind to two enzymes required for DNA synthesis: DNA gyrase and DNA topoisomerase IV. In addition to inhibiting the enzymes' catalytic functions of altering DNA topology, they stabilize enzyme–DNA complexes that form a barrier to the DNA replication machinery and are a precursor to lethal double-strand DNA breaks. Although related topoisomerase enzymes are involved in mammalian DNA synthesis, the mammalian and bacterial enzymes are sufficiently different from each other for quinolones to have selective activity against bacteria. Resistance to quinolones is most often due either to chromosomal mutations altering the target enzymes DNA gyrase and DNA topoisomerase IV, with consequent reduction in drug binding, or to mutations that increase the expression of native broad-spectrum efflux pumps for which quinolones (among other compounds) are substrates. In addition, three types of acquired genes can confer reduced susceptibility or low-level resistance by either protecting the target enzymes, modifying some quinolones (particularly ciprofloxacin and norfloxacin) to reduce their activity, or generating an efflux of quinolones. These genes are usually located on multidrug-resistance plasmids that have spread worldwide. Their presence can promote higher levels of quinolone resistance by enhancing selection of the mutations in chromosomal target genes with exposure to quinolones and can then link quinolone resistance to resistance to other antibacterial drugs that are encoded on the same plasmid.

Rifampin and Rifabutin Antimicrobials of the rifamycin class target bacterial RNA polymerase and thereby inhibit transcription of messenger RNA and gene expression. Their activity is generally limited to gram-positive bacteria because native efflux pumps in most gram-negative bacteria reduce drug access to the cytoplasmic enzyme target. Single mutations in the β subunit of RNA polymerase constitute the principal mechanism of acquired rifampin resistance, which is high level. Thus, rifampin and other rifamycins are used for treatment of infections only in combination with other antibacterial drugs in order to reduce the likelihood of selection of high-level resistance.

Metronidazole Metronidazole is actively taken up by most anaerobic bacteria and then converted to reactive drug derivatives that nonspecifically damage cytoplasmic proteins and nucleic acids. Thus, metronidazole lacks a specific cellular target. Acquired resistance to metronidazole in *Bacteroides* species is rare. Such resistance has been reported in strains that lack the endogenous activating nitroreductase or that have acquired *nim* genes responsible for further reduction of DNA-damaging nitroso intermediates to an inactive derivative. Active efflux and enhanced DNA repair mechanisms also have been associated with resistance.

Nitrofurantoin Nitrofurantoin is used only for treatment of lower urinary tract infections because adequate drug concentrations are found only in urine. Its mechanism of action is not fully understood but is thought to involve generation of reactive derivative molecules (as occurs with metronidazole) that damage DNA and ribosomes. Resistance to nitrofurantoin in *E. coli* can emerge through a series of mutations that progressively decrease the nitroreductase activity required for generating active nitrofuran metabolites. These mutants are also impaired in growth; this impairment possibly explains the infrequent occurrence of resistance with clinical use of nitrofurantoin.

Polymyxins Because of emerging multidrug resistance in gram-negative bacteria, colistin and polymyxin B are being used increasingly for infections due to resistant Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* species. Polymyxins are cationic cyclic peptide molecules that bind negatively charged lipopolysaccharides on the gram-negative bacterial outer membrane, with subsequent disruption and permeabilization of both outer-membrane and cytoplasmic-membrane structure. Thus, the polymyxins are bactericidal. Resistance is so far uncommon but can emerge during therapy through mutations that cause reductions in the negative charge of the gram-negative bacterial cell surface, thereby reducing binding of the positively charged colistin. Recently transferable plasmid-mediated colistin resistance has also been found to be due to *mcr-1*, a gene encoding a phosphoethanolamine transferase that also reduces the negative charge on the cell surface. *mcr-1*-containing enteric bacteria have now been identified in Asia, Europe, and the United States.

Daptomycin Daptomycin is active against gram-positive bacteria and interacts with and disrupts the cytoplasmic membrane in a calcium-dependent manner, resulting in bactericidal activity. The mechanisms of resistance to daptomycin are complex and involve mutations in several genes that can alter cell membrane charge and structure and reduce daptomycin binding. Resistance to daptomycin is relatively infrequent but has emerged in some *S. aureus* strains with intermediate vancomycin susceptibility from patients treated with vancomycin and not exposed to daptomycin. In some strains of methicillin-resistant *S. aureus*, daptomycin resistance has been linked to acquired susceptibility to β-lactams; combinations of daptomycin with nafcillin or ceftaroline have been successful for treatment of patients infected with resistant strains when daptomycin alone or in combination with other agents has failed. The mechanism of this effect is not yet clear but may involve alteration in surface charge and increased daptomycin binding in the presence of β-lactams. Daptomycin resistance has also been reported in enterococci.

EPIDEMIOLOGY OF RESISTANCE AND REDUCTION OF ITS OCCURRENCE

Multidrug resistance in human bacterial infections has been increasing overall in recent years, substantially limiting the number of antibiotics that can be used to treat some infections. The prevalence of resistance to various antimicrobials among human pathogens can, however, vary greatly in different geographic areas and even at different institutions in the same area. Thus, specific local data on the occurrence of various types of resistance are an important component of the choice of antimicrobials for empirical treatment of infection until the responsible pathogen is identified and its specific susceptibilities are determined by the clinical microbiology laboratory. Prompt adjustment of the initially chosen antimicrobial on the basis of species and susceptibility data to

best target therapy is equally important. These principles emphasize the importance of obtaining appropriate samples for culture or other diagnostic modalities and susceptibility testing—whenever possible, prior to administration of antimicrobials. They also highlight the importance of rapid and sensitive diagnostic methods and the prompt communication of their results to clinicians to inform best choices of antimicrobials.

The overall prevalence of resistance can be affected by a number of factors, including (1) the extent of resistance reservoirs in the patient population; (2) the selection pressures from use of antimicrobials that favor resistant strains over susceptible ones; and (3) the extent by which resistance is amplified by transmission of resistant strains to patients from their environment or other persons, either directly or indirectly via the contaminated hands of health care workers when hand hygiene and other infection control practices are inadequately followed. The likelihood that an individual patient will be infected with a resistant pathogen is likewise affected by his or her history. Studies have shown that prior antibiotic treatment, prior infection with resistant pathogens, and prior hospitalizations all increase this likelihood.

These factors emphasize the importance of the appropriate use of antimicrobials (particularly, the avoidance of their use in clinical conditions in which they are not needed), the use of the shortest courses of therapy sufficient for a successful clinical outcome, and the implementation of antimicrobial stewardship programs **(Chap. 139)** as well as careful and consistent infection control practices in short- and long-term-care institutions. Antimicrobial agents are distinct among drug classes in human medicine in that—despite their clear clinical value when used appropriately—the extent of their use can compromise their future utility because of resistance. The remarkable ability of pathogens to acquire resistance is inherent in their biology and emphasizes the necessity for clinicians and institutions to pay careful attention to those factors that can be controlled through judicious antimicrobial use and rigorous infection control and prevention practices.

Efforts to address the problems caused by resistance are now being made worldwide. The U.S. Centers for Disease Control and Prevention (CDC) has recently estimated that >2 million resistant bacterial infections occur in the United States each year, with 23,000 deaths, and has identified particular resistant pathogens that are of greatest concern because of their overall effects on public health **(Table 140-2)**. Enteric bacteria (such as *E. coli*, *K. pneumoniae*, and *Enterobacter* species) that are resistant to carbapenems are included in the "urgent" category because of their increasing occurrence worldwide and because they are often highly resistant to multiple drugs, with few if any active antimicrobials available for treatment. Resistant *N. gonorrhoeae* is included in this category as well because of the ease with which gonorrhea can be spread from person to person and because few active agents are now available. Other resistances are common and also affect clinical care, often requiring use of alternatives to first-line agents that can be less effective and less well tolerated. To address the problems posed by resistance, the CDC has emphasized a set of four core actions. (1) *Preventing infections and preventing spread:* These efforts focus on implementation of evidence-based activities to reduce the risks and incidence of device-related infections overall and on improvement of compliance with infection control practices that prevent transmission of resistant pathogens from one person to another, such as hand hygiene and isolation precautions in health care and long-term-care settings. (2) *Tracking resistance patterns:* Efforts aim to increase the reporting and sharing of the occurrence of resistance to enhance epidemiologic data and inform targeting of preventive interventions. (3) *Improving use of existing antimicrobials:* Antimicrobial stewardship programs with specific components to track usage and educate clinicians on appropriate use have become required in hospitals, and the CDC has implemented efforts to reduce inappropriate use in outpatient settings, with particular attention to upper respiratory illnesses that often do not require antimicrobials because of their common self-limited viral causes. (4) *Developing new antimicrobials and diagnostic tests:* The U.S. Congress and the U.S. Food and Drug Administration have recently developed incentives and enhanced regulatory pathways for drug approval that pharmaceutical companies can use for development of antimicrobials that specifically address particular resistant pathogens. Both small and large companies have undertaken efforts in this area. New technologies for rapid detection of resistance and susceptibility are also being developed by multiple diagnostics companies in order to facilitate the appropriate choice of antimicrobials earlier in the course of illness, providing an important tool for antimicrobial stewardship programs.

TABLE 140-2 Antibiotic Resistance Threats in the United States, 2013

THREAT CATEGORY	ORGANISMS
Urgent	*Clostridium difficile*
	Carbapenem-resistant Enterobacteriaceae
	Drug-resistant *Neisseria gonorrhoeae*
Serious	Multidrug-resistant *Acinetobacter*
	Drug-resistant *Campylobacter*
	Extended-spectrum β-lactamase–producing Enterobacteriaceae
	Vancomycin-resistant *Enterococcus*
	Multidrug-resistant *Pseudomonas aeruginosa*
	Drug-resistant nontyphoidal *Salmonella*
	Drug-resistant *Salmonella* Typhi
	Drug-resistant *Shigella*
	Methicillin-resistant *Staphylococcus aureus*
	Drug-resistant *Streptococcus pneumoniae*
	Drug-resistant *Mycobacterium tuberculosis*
Concerning	Vancomycin-resistant *S. aureus*
	Erythromycin-resistant group A *Streptococcus*
	Clindamycin-resistant group B *Streptococcus*

Source: U.S. Centers for Disease Control and Prevention.

FURTHER READING

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Section 5 Diseases Caused by Gram-Positive Bacteria

141 Pneumococcal Infections

David Goldblatt, Katherine L. O'Brien

In the late nineteenth century, pairs of micrococci were first recognized in the blood of rabbits injected with human saliva by both Louis Pasteur, working in France, and George Sternberg, an American army physician. The important role of these micrococci in human disease was not appreciated at that time. By 1886, when the organism was designated "pneumokokkus" and *Diplococcus pneumoniae*, it had been isolated by many independent investigators, and its role in the etiology of pneumonia was well known. In the 1930s, pneumonia was the third leading cause of death in the United States (after heart disease and cancer) and was responsible for ~7% of all deaths both in the United States and in

Europe. While pneumonia was caused by a host of pathogens, lobar pneumonia—a pattern more likely to be caused by the pneumococcus—accounted for approximately one-half of all pneumonia deaths in the United States in 1929. In 1974, the organism was reclassified as *Streptococcus pneumoniae*.

MICROBIOLOGY

Etiologic Agent Pneumococci are spherical gram-positive bacteria of the genus *Streptococcus*. Within this genus, cell division occurs along a single axis, and bacteria grow in chains or pairs—hence the name *Streptococcus*, from the Greek *streptos*, meaning "twisted," and *kokkos*, meaning "berry." At least 22 streptococcal species are recognized and are divided further into groups based on their hemolytic properties. *S. pneumoniae* belongs to the α-hemolytic group that characteristically produces a greenish color on blood agar because of the reduction of iron in hemoglobin **(Fig. 141-1)**. The bacteria are fastidious and grow best in 5% CO_2 but require a source of catalase (e.g., blood) for growth on agar plates, where they develop mucoid (smooth/shiny) colonies. Pneumococci without a capsule produce colonies with a rough surface. Unlike that of other α-hemolytic streptococci, their growth is inhibited in the presence of optochin (ethylhydrocupreine hydrochloride), and they are bile soluble.

In common with other gram-positive bacteria, pneumococci have a cell membrane beneath a cell wall, which in turn is covered by a polysaccharide capsule. Pneumococci are divided into serogroups or serotypes based on capsular polysaccharide structure, as distinguished with rabbit polyclonal antisera; capsules swell in the presence of specific antiserum (the Quellung reaction). The most recently discovered serotypes—6C, 6D, 6F, 6G, 6H, 11E, 20A, and 20B—have been identified with monoclonal antibodies and by serologic, genetic, and biochemical means. The currently recognized 98 serotypes fall into 21 serogroups, and each serogroup contains two to eight serotypes with closely related capsules. In the absence of type-specific antibody, the capsule protects the bacteria from phagocytosis by host cells and is arguably the most important determinant of pneumococcal virulence. Unencapsulated variants are occasionally identified in cases of invasive pneumococcal disease; however, when their genotype is assessed, they often contain capsular genes. Thus it is likely that they were encapsulated in vivo and have stopped producing capsule during the laboratory steps of pathogen isolation.

FIGURE 141-1 Pneumococci growing on blood agar, illustrating α hemolysis and optochin sensitivity (zone around optochin disk). *Inset:* Gram's stain, illustrating gram-positive diplococci. *(Photographs courtesy of Paul Turner, University of Oxford, United Kingdom.)*

Virulence Factors Within the cytoplasm, cell membrane, and cell wall, many molecules that may play a role in pneumococcal pathogenesis and virulence have been identified **(Fig. 141-2)**. These proteins are often involved in direct interactions with host tissues or in concealment of the bacterial surface from host defense mechanisms. Pneumolysin is a secreted cytotoxin thought to result in cytolysis of cells and tissues, and LytA enhances pathogenesis. A number of cell wall proteins interfere with the complement pathway, thus inhibiting complement deposition and preventing lysis and/or opsonophagocytosis. The pneumococcal H inhibitor (Hic) impedes the formation of C3 convertase, while pneumococcal surface protein C (PspC), also known as choline-binding protein A (CbpA), binds factor H and is thought to accelerate the breakdown of C3. PspA and CbpA inhibit the deposition of or degrade C3b. The numerous pneumococcal proteins thought to be involved in adhesion include the ubiquitous surface-anchored sialidase (neuraminidase) NanA, which cleaves sialic acid on host cells and proteins, and pneumococcal surface adhesin A (PsaA). Pili recently recognized by electron microscopy also may play an important role in binding to cells. Some of the antigens mentioned above are potential vaccine candidates (see "Prevention," below). Biofilm production by pneumococci is now well recognized and is likely to be an important mechanism aiding survival of pneumococci in the upper respiratory tract and contributing to local disease manifestations such as otitis media.

Although the capsule surrounding the cell wall of *S. pneumoniae* is the basis for categorization by serotype, the behavior and pathogenic potential of a serotype may also be related to the genetic origin of the strain. Molecular typing is therefore of considerable interest. Initially, techniques such as pulsed-field gel electrophoresis were used to determine genetic relatedness; such techniques have been superseded by sequencing of housekeeping genes to define a clone (multilocus sequence typing, MLST). For *S. pneumoniae*, alleles at each of the loci *aroE*, *gdh*, *gki*, *recP*, *spi*, *xpt*, and *ddl* are sequenced and compared with all of the known alleles at that locus. Sequences identical to a known allele are assigned the same allele number, whereas those differing from any known allele—even at a single nucleotide site—are assigned new numbers. Software for assignment of alleles at each locus is available on the pneumococcal MLST website (*pubmlst.org/spneumoniae/*), and the allelic profile of each isolate and its consequent sequence type are generated. With the advent of high-throughput and relatively inexpensive sequencing techniques, whole-genome sequencing will soon supersede MLST. The first pneumococcal genome was sequenced in 2001 (a serotype 4 strain known as TIGR4), and to date more than 10,000 pneumococcal strains have been sequenced. The pneumococcal genome has ~2.2 million base pairs containing 2236 predicted coding regions. Genome sequence analysis has made major contributions to the understanding of pneumococcal biology and diversity.

EPIDEMIOLOGY

(See also "Global Health," below.) Pneumococcal infections remain a significant global cause of morbidity and death, particularly among children and the elderly. Rapid and dramatic changes in the epidemiology of this disease during the past 15 years in several developed countries followed the licensure and routine childhood administration of pneumococcal polysaccharide–protein conjugate vaccine (PCV). With PCV introduction in underdeveloped and middle-income countries, additional profound changes in pneumococcal ecology and disease epidemiology are occurring. The disease burden and serotype distribution in the PCV era are influenced not only by the reduction in disease caused by serotypes included in PCV but also by serotype replacement as a result of reductions in vaccine serotypes, concomitant secular trends in pneumococcal strains unrelated to vaccine use, the impact of antibiotic use on pneumococcal strain ecology, and surveillance system attributes that can themselves affect analysis of epidemiologic features of pneumococcal strains and disease.

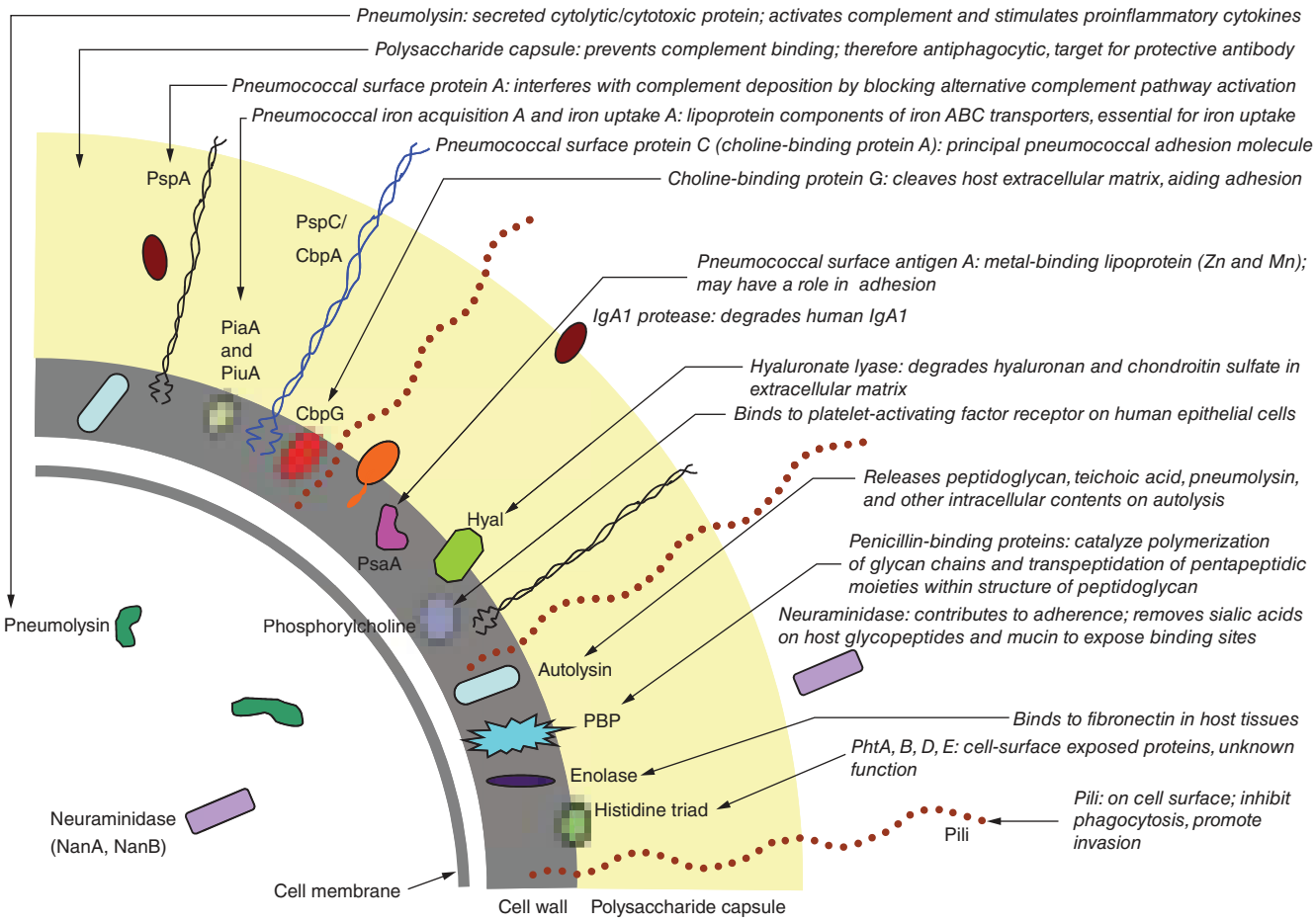

FIGURE 141-2 Schematic diagram of the pneumococcal cell surface, with key antigens and their roles highlighted.

Serotype Distribution Not all pneumococcal serotypes are equally likely to cause disease; observed serotype distributions vary by age category, disease syndrome, and geography. Geographic differences may be driven by variations in the relative prevalence of syndromes causing disease rather than by true serotype distribution differences since certain serotypes are more common causes of some syndromes than others (e.g., pneumonia and meningitis). Most data on serotype distribution come from pediatric invasive pneumococcal disease (IPD, defined as infection of a normally sterile site); much less information on global or regional serotype distributions is available for disease in adults. In the era before PCV use, five to seven serotypes caused >60% of IPD cases among children <5 years of age in most parts of the world; seven serotypes (1, 5, 6A, 6B, 14, 19F, and 23F) accounted for ~60% of such cases in all areas of the world, but in any given region these seven serotypes may not all rank as the most common disease strains (Fig. 141-3). Some serotypes (e.g., types 1 and 5) not only tend to cause disease in areas with a high disease burden but also cause waves of disease in lower-burden areas (e.g., Europe) or outbreaks (e.g., in military barracks; meningitis in sub-Saharan Africa). The broader range of serotypes causing disease among adults than among children is apparent from a comparison of the coverage of existing multiserotype vaccines in different age groups. For example, data from the United States for 2013–2014 on the serotypes causing IPD indicated that a polysaccharide vaccine containing 23 serotypes (PPSV23) would include the serotypes causing 59% of cases among children <5 years of age, 70% of those among persons 18–64 years of age, and 57% of those among persons ≥65 years of age.

Nasopharyngeal Carriage Pneumococci are intermittent inhabitants of the healthy human nasopharynx and are transmitted by respiratory droplets. In children, pneumococcal nasopharyngeal ecology varies by geographic region, socioeconomic status, climate, degree of crowding, and particularly intensity of exposure to other children, with children in day-care settings having higher rates of colonization. In developed-world settings, children serve as the major vectors of

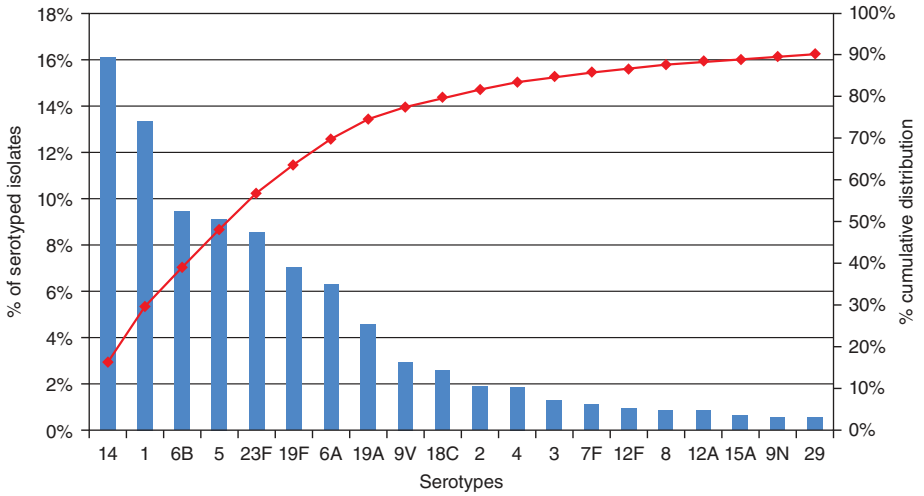

FIGURE 141-3 Meta-analysis of available global pneumococcal serotype data, adjusted for regional disease incidence. The red line shows cumulative incidence, as indicated on the right-hand Y axis. *(Source: Global Serotype Project Report for the Pneumococcal Advance Market Commitment Target Product Profile; available at www.gavi.org/library/gavi-documents/amc/tpp-codebook/.)*

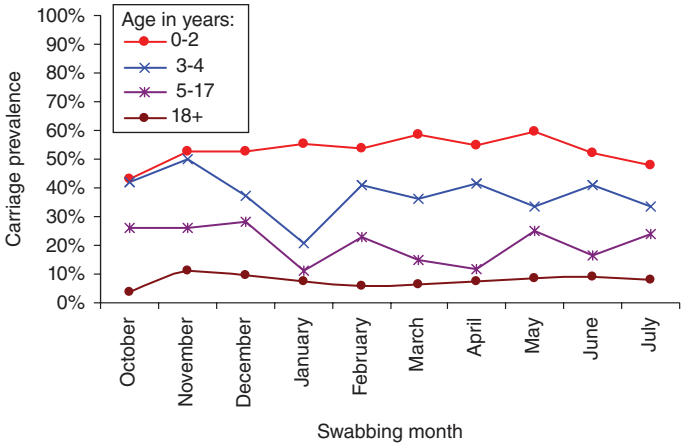

FIGURE 141-4 Prevalence of pneumococcal carriage in adults and children resident in the United Kingdom who had nasopharyngeal swabs collected monthly for 10 months (no seasonal trend; *t* test trend, >.05). *(Data adapted from D Goldblatt et al: J Infect Dis 192:387, 2005.)*

pneumococcal transmission. By 1 year of age, ~50% of children have had at least one episode of pneumococcal colonization. Cross-sectional prevalence data show rates of pneumococcal carriage ranging from 20% to 50% among children <5 years of age and from 5% to 15% among young and middle-aged adults; Fig. 141-4 shows relevant data from the United Kingdom. Data on colonization rates among healthy elderly individuals are limited. In developing-world settings, pneumococcal acquisition occurs much earlier, sometimes within the first few days after birth, and nearly all infants have had at least one episode of colonization by 2 months of age. Cross-sectional studies show that up to the age of 5 years, 70–90% of children carry *S. pneumoniae* in the nasopharynx, and a significant proportion of adults (sometimes >40%) also are colonized. Their high rates of colonization make adults an important source of transmission and may affect community transmission dynamics.

Invasive Disease and Pneumonia IPD develops when *S. pneumoniae* invades the bloodstream and seeds other organs or directly reaches the cerebrospinal fluid (CSF) by local extension. Pneumonia may follow aspiration of pneumococci, although only 10–30% of pneumococcal pneumonia cases are associated with a positive blood culture (and thus contribute to the measured burden of IPD). The substantial variation of IPD rates with age is illustrated by data from the United States for 1998–1999, a period prior to PCV introduction. Rates of IPD were highest among children <2 years of age and among adults ≥65 years of age (188 and 60 cases/100,000, respectively; Fig. 141-5). Since the introduction of PCV, IPD rates among infants and children in the United States have fallen by >75%, a decrease driven by the near elimination of vaccine-serotype IPD. A similar impact of PCV on vaccine-serotype IPD rates has been consistently observed

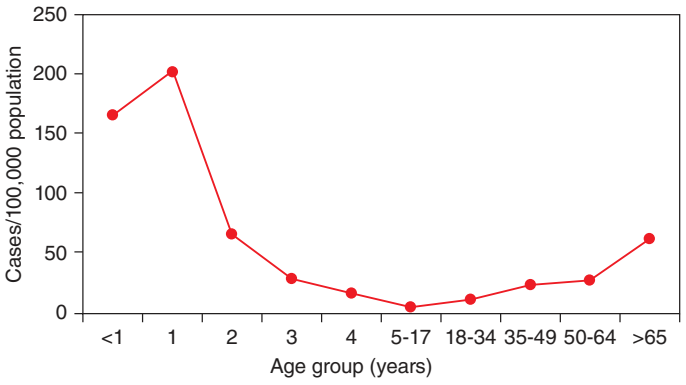

FIGURE 141-5 Rates of invasive pneumococcal disease before the introduction of pneumococcal conjugate vaccine, by age group: United States, 1998. *(Source: CDC, Active Bacterial Core Surveillance/Emerging Infectious Program Network, 2000. Data adapted from MMWR 49[RR-9], 2000.)*

in countries where PCV has been introduced into the routine pediatric vaccination schedule. However, the magnitudes of change in the non-vaccine-serotype IPD rate in various countries have been heterogeneous; the interpretation of this heterogeneity is a complex issue. In the United States, Canada, and Australia, rates of non-vaccine-serotype IPD have increased but the magnitude of the increase is generally small relative to the substantial reductions in vaccine-serotype IPD. In contrast, in other settings (e.g., Alaska Native communities and the United Kingdom), the reduction in vaccine-serotype IPD has been offset by notable increases in rates of disease caused by non-vaccine serotypes. Explanations for the heterogeneity of findings include replacement disease resulting from vaccine pressure, changes in clinical case investigation, secular trends unrelated to PCV use, antibiotic pressure selecting for resistant organisms, changes in surveillance or reporting systems, rapidity of PCV introduction, and inclusion of a catch-up campaign. A recent systematic review concludes that serotype replacement in IPD follows the use of PCV7 but that the magnitude of this phenomenon is small relative to the reduction in disease from vaccine serotypes. Furthermore, much of the replacement disease has been caused by serotype 19A. In contrast to the changes seen following implementation of PCV7, the replacing serotypes are more diverse and a single serotype is not dominant with the use of expanded-valency PCV products (i.e., PCV10 and PCV13, the latter of which includes serotype 19A). In spite of some serotype replacement in disease, the net effect of PCV is to reduce the rate of pneumococcal disease both in the age group targeted for vaccination and in unvaccinated age groups.

Pneumonia is the most common of the serious pneumococcal disease syndromes and poses special challenges from a clinical and public health perspective. Most cases of pneumococcal pneumonia are not associated with bacteremia, and in these cases a definitive etiologic diagnosis is difficult or impossible. As a result, estimates of disease burden focus primarily on IPD rates and fail to include the major portion of the burden of serious pneumococcal disease. Among children, PCV trials designed to collect efficacy data on syndrome-based outcomes (e.g., radiographically confirmed pneumonia, clinically diagnosed pneumonia) have revealed the burden of culture-negative pneumococcal pneumonia. These trials have provided the means to infer that only ~5–20% of pneumococcal pneumonia cases result in bacteremia. An important randomized controlled trial of PCV among the elderly in the Netherlands (the Capita trial) has revealed the small fraction of adult pneumococcal pneumonia patients who also have bacteremia. Use of high-quality sputum specimens and, in the case of adults with a low likelihood of colonization absent disease, urine antigen detection both contribute to the diagnosis of nonbacteremic pneumococcal pneumonia. Furthermore, evidence continues to accrue that pneumococcal pneumonia events are often the result of co-infection with viral or other bacterial pathogens. Thus a pneumonia case resulting from a pulmonary infection with a single pathogen is probably an uncommon event; rather, most cases of pneumonia likely result from the sequential or contemporaneous co-infection of a host with multiple pathogens, often both viruses and bacteria.

The case–fatality ratios (CFRs) for pneumococcal pneumonia and IPD vary by age, underlying medical condition, and access to care. In addition, the CFR for pneumococcal pneumonia varies with the severity of disease at presentation (rather than according to whether the pneumonia episode is associated with bacteremia) and with the patient's age (from <5% among hospitalized patients 18–44 years old to >12% among those >65 years old, even when appropriate and timely management is available). Notably, the likelihood of death in the first 24 h of hospitalization did not change substantially with the introduction of antibiotics; this surprising observation highlights the fact that the pathophysiology of severe pneumococcal pneumonia among adults reflects a rapidly progressive cascade of events that often unfolds irrespective of antibiotic administration. Management in an intensive care unit can provide critical support for the patient through the acute period, with lower CFRs, while antibiotics address the underlying infection.

Rates of pneumococcal disease vary by season, with higher rates in colder than in warmer months in temperate climates; by sex, with males

TABLE 141-1 Clinical Risk Groups for Pneumococcal Infection

CLINICAL RISK GROUP	EXAMPLES
Asplenia or splenic dysfunction	Sickle cell disease, celiac disease
Chronic respiratory disease	Chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, bronchopulmonary dysplasia, aspiration risk, neuromuscular disease (e.g., cerebral palsy), severe asthma
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic renal failure, renal transplantation
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis
Diabetes mellitus	Diabetes mellitus requiring insulin or oral hypoglycemic drugs
Immunocompromise/ immunosuppression	HIV infection, common variable immunodeficiency, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chemotherapy, organ or bone marrow transplantation, systemic glucocorticoid treatment for >1 month at a dose equivalent to ≥20 mg/d (children, ≥1 mg/kg per day)
Cochlear implants	…
Cerebrospinal fluid leaks	…
Miscellaneous	Infancy and old age; prior hospitalization; alcoholism; malnutrition; cigarette smoking; day-care center attendance; residence in military training camps, prisons, homeless shelters

Note: Groups for whom pneumococcal vaccines are recommended by the Advisory Committee on Immunization Practices can be found at *www.cdc.gov/vaccines/schedules/*.

more often affected than females; and by risk group, with risk factors including underlying medical conditions, behavioral issues (e.g., smoking), and ethnic group. In the United States, some Native American populations (including Alaska Natives) and African Americans have higher rates of disease than the general population; the increased risk is probably attributable to socioeconomic conditions and the prevalence of underlying risk factors for pneumococcal disease. Medical conditions that increase the risk of pneumococcal infection are listed in Table 141-1. Outbreaks of disease are well recognized in crowded settings with susceptible individuals, such as infant day-care facilities, military barracks, and nursing homes. Furthermore, there is a clear association between preceding viral respiratory disease (especially but not exclusively influenza) and risk of secondary pneumococcal infections. The significant role of pneumococcal pneumonia in the morbidity and mortality associated with seasonal and pandemic influenza is increasingly well recognized.

Antibiotic Resistance Reduced pneumococcal susceptibility to penicillin was first noted in 1967, but not until the 1990s did reduced antibiotic susceptibility emerge as a significant clinical and public health issue, with an increasing prevalence of pneumococcal isolates resistant to single or multiple classes of antibiotics and a rising absolute magnitude of minimal inhibitory concentrations (MICs). Strains with reduced susceptibility to penicillin G, cefotaxime, ceftriaxone, macrolides, and other antibiotics are now found worldwide and account for a significant proportion of disease-causing strains in many locations, especially among children. Vancomycin resistance has not yet been observed in clinical pneumococcal strains. Lack of antimicrobial susceptibility is clearly related to a subset of serotypes, many of which disproportionately cause disease among children. Resistance phenotypes are based on a diverse array of mutational events and inter- and intraspecies gene-transfer phenomena carried out by several types of mobile genetic elements, with consequent dissemination of successful resistant clones. The vicious cycle of antibiotic exposure, selection of resistant organisms in the nasopharynx, and transmission of these organisms within the community, leading to difficult-to-treat infections and increased antibiotic exposure, has been interrupted to some extent by the introduction and routine use of PCV. The clinical implications of pneumococcal antimicrobial nonsusceptibility are addressed below in the section on treatment.

PATHOGENESIS

Pneumococci colonize the human nasopharynx from an early age; colonization acquisition events are generally described as asymptomatic, but evidence exists to associate acquisition with mild respiratory symptoms, especially in the very young. Bacteria survive in the nasopharynx protected by a variety of factors, including their bacterial capsule and the formation of a biofilm. From the nasopharynx, the bacteria spread either via the bloodstream to distant sites (e.g., brain, joint, bones, peritoneal cavity) or locally to mucosal surfaces where they can cause otitis media or pneumonia. Direct spread from the nasopharynx to the central nervous system (CNS) can occur in rare cases of skull-base fracture, although most cases of pneumococcal meningitis are secondary to hematogenous spread. The pneumococcus is not a static bacterium; rather, it modifies its expression of capsule in adaptation to the external environment. In the nasopharynx, the pneumococcus downregulates capsular expression, averting protective immunologic mechanisms that recognize capsule; the phenotype on culture are rough colonies. Upon invasion by traversal of the epithelium, the pneumococcus upregulates its capsular expression, transforming its appearance on culture to smooth colonies—a change illustrating the dynamic nature of the organism in response to the local environment. Pneumococci can cause disease in almost any organ or part of the body; however, otitis media, pneumonia, bacteremia, and meningitis are most common. Colonization is a relatively frequent event, yet disease is rare. In the nasopharynx, pneumococci survive in mucus secreted by epithelial cells and in a biofilm they create, where they can avoid local immune factors such as leukocytes and complement. The mucus itself is a component of local defense mechanisms, and the flow of mucus (driven in part by cilia in what is known as the *mucociliary escalator*) effects mechanical clearance of pneumococci. While many colonization episodes are of short duration, longitudinal studies in adults and children have revealed persistent colonization with a specific serotype over many months. Colonization eventually results in the development of capsule- and protein-specific serum IgG antibodies, which are thought to play a role in mediating clearance of bacteria from the nasopharynx. IgG antibodies to surface-exposed cell-wall or secreted proteins also appear in the circulation in an age-dependent fashion or after colonization; the biologic role of these antibodies is less clear. Recent acquisition of a new colonizing serotype is more likely to be associated with subsequent invasion, presumably as a result of the absence of type-specific immunity. Intercurrent viral infections make the host more susceptible to pneumococcal colonization, and pneumococcal disease in a colonized individual often follows perturbation of the nasopharyngeal mucosa by such infections. Local cytokine production after a viral infection is thought to upregulate adhesion factors in the respiratory epithelium, allowing pneumococci to adhere via a variety of surface adhesin molecules, including PsaA, PspA, CbpA, PspC, Hyl, pneumolysin, and the neuraminidases (Fig. 141-2). Adhesion coupled with inflammation induced by pneumococcal factors such as peptidoglycans and teichoic acids results in invasion. It is the inflammation induced by various bacterium-derived factors that is responsible for the pathology associated with pneumococcal infection. Pneumococcal cell wall–derived teichoic acids and peptidoglycans induce a variety of cytokines, including the proinflammatory cytokines interleukin (IL) 1, IL-6, and tumor necrosis factor, and activate complement via the alternative pathway. Polymorphonuclear leukocytes are thus attracted, and an intense inflammatory response is initiated. Pneumolysin also is important in local pathology, inducing proinflammatory cytokine production by local monocytes.

The pneumococcal capsule, consisting of polysaccharides with antiphagocytic properties (i.e., the capacity to resist complement deposition in the absence of type-specific antibody), plays an important role in pathogenesis. While most capsular types can cause human disease, certain capsular types are more commonly isolated from sites of infection. The reason for the dominance of some serotypes over others in IPD, as depicted in Fig. 141-3, is unclear.

HOST DEFENSE MECHANISMS

Innate Immunity As described above, intact respiratory epithelium and a host of nonspecific or innate immune factors (e.g., mucus, splenic function, complement, neutrophils, and macrophages) constitute the first line of defense against pneumococci. Physical factors such as the cough reflex and the mucociliary escalator are important in clearing bacteria from the lungs. Immunologic factors are critical as well: C-reactive protein (CRP) binds phosphorylcholine in the pneumococcal cell wall, inducing complement activation and leading to bacterial clearance; Toll-like receptor 2 (TLR2) recognizes both pneumococcal lipoteichoic acid and cell wall peptidoglycan; and in animal models, the absence of host TLR2 leads to more severe infection and impaired clearance of nasopharyngeal colonization. TLR4 appears to be necessary for the proinflammatory effect of pneumolysin on macrophages. The importance of TLR recognition is underlined by descriptions of an inherited deficiency of human IL-1 receptor–associated kinase 4 (IRAK-4) that manifests as an unusual susceptibility to infection with bacteria, including *S. pneumoniae*. IRAK-4 is essential for the normal functioning of several TLRs. Other factors that interfere with these nonspecific mechanisms (e.g., viral infections, cystic fibrosis, bronchiectasis, complement deficiency, and chronic obstructive pulmonary disease) all predispose to the development of pneumococcal pneumonia. Patients who lack a spleen or have abnormal splenic function (e.g., persons with sickle cell disease) are at high risk of developing overwhelming pneumococcal disease.

Acquired Immunity Acquired immunity induced following colonization or through exposure to cross-reactive antigens rests largely on the development of serum IgG antibody specific for the pneumococcal capsular polysaccharide. Nearly all polysaccharides are T cell–independent antigens; B cells can make antibodies to such antigens without T cell help. However, in children <1–2 years old, such B cell responses are poorly developed. This delayed ontogeny of capsule-specific IgG in young children is associated with susceptibility to pneumococcal infection (Fig. 141-5). The extremely high risk of pneumococcal infection in the absence of serum immunoglobulin (i.e., in conditions such as agammaglobulinemia) highlights the important role of capsular antibody in protection against disease. Each serotype's capsule is chemically distinct, even though for some serotypes the chemical distinction from another type may be a minor one; thus immunity tends to be serotype specific, although some cross-immunity exists. For example, conjugate vaccine–induced antibodies to serotype 6B prevent infection due to serotype 6A. However, cross-protection against serotypes within serogroups is not universal; for instance, antibodies to serotype 19F induced by some vaccines do not appear to confer protection against disease caused by serotype 19A. Antibodies to surface-exposed or secreted pneumococcal proteins (such as pneumolysin, PsaA, and PspA) also appear in the circulation with increasing age of the host, but their functional significance remains unclear. Data from murine models suggest that CD4+ T cells may play a role in preventing pneumococcal colonization and disease, and experimental data derived from humans suggest that IL-17-secreting CD4+ T cells may be relevant.

APPROACH TO THE PATIENT

Pneumococcal Infections

There is no pathognomonic presentation of pneumococcal disease; patients may present with one or more clinical syndromes (e.g., pneumonia, meningitis, sepsis). *S. pneumoniae* can infect nearly any body tissue, manifesting as disease ranging in severity from mild and self-limited to life-threatening. The differential diagnosis of common clinical syndromes such as pneumonia, otitis media, fever of unknown origin, and meningitis should always include pneumococcal infection. A microbiologically confirmed diagnosis is made in only a minority of pneumococcal cases since, in most circumstances (and especially in pneumonia and otitis media), fluid from the site of infection is not available for etiologic determination, and infection of body fluids distant from the site of infection (e.g., blood in the case of pneumonia) occurs in only a minority of true pneumococcal cases. Empirical therapy that includes appropriate treatment for *S. pneumoniae* is often indicated.

Algorithms for assessment and management of ill children (IMCI; Integrated Management of Childhood Illness) have been developed for use in the developing world or in other settings where evaluation by a trained physician may not be feasible. No such algorithms for the management of adults with suspected disease exist. Children who present with signs associated with increased risk of serious disease, such as an inability to drink, convulsions, lethargy, and severe malnutrition, are categorized as having very severe disease without further evaluation by the community health care worker; are given antibiotics; and are immediately referred to a hospital for diagnosis and management. Children who present with cough and tachypnea (the latter defined according to specific age strata) are further stratified into severity categories based on the presence or absence of lower chest wall indrawing and are managed accordingly either with antibiotics alone or with antibiotics and referral to a hospital facility. Children with cough but no tachypnea are categorized as having a nonpneumonia respiratory illness.

CLINICAL MANIFESTATIONS

The clinical manifestations of pneumococcal disease depend on the site of infection and the duration of illness. Clinical syndromes are classified as noninvasive (e.g., otitis media) or invasive (e.g., bacteremic pneumonia, meningitis) according to whether a normally sterile site is infected. The pathogenesis of noninvasive illness involves contiguous spread from the nasopharynx or skin; invasive disease involves infection of a normally sterile body fluid or follows bacteremia. Regardless of the mechanism, all pneumococcal infections result from nasopharyngeal acquisition of the organism.

Pneumonia Pneumonia is the most common serious pneumococcal syndrome and is considered invasive when associated with a positive blood culture. Whether to categorize nonbacteremic pneumococcal pneumonia as invasive or noninvasive remains debatable.

Pneumococcal pneumonia can present as a mild community-acquired infection at one extreme and as a life-threatening disease requiring intubation and intensive support at the other.

PRESENTING MANIFESTATIONS The presentation of pneumococcal pneumonia does not reliably distinguish it from pneumonia of other etiologies. In a subset of cases, pneumococcal pneumonia is recognized at the outset as associated with a viral upper respiratory infection and is characterized by the abrupt onset of cough and dyspnea accompanied by fever, shaking chills, and myalgias. The cough evolves from nonpurulent to productive of sputum that is purulent and sometimes tinged with blood. Patients may describe stabbing pleuritic chest pain and significant dyspnea indicating involvement of the parietal pleura. Among the elderly, the presenting clinical symptoms may be less specific, with confusion or malaise but without fever or cough. In such cases, a high index of suspicion is required because failure to treat pneumococcal pneumonia promptly in an elderly patient is likely to result in rapid evolution of the infection, with increased severity, morbidity, and risk of death.

FINDINGS ON PHYSICAL EXAMINATION The clinical signs associated with pneumococcal pneumonia among adults include tachypnea (defined as >30 breaths/min) and tachycardia, hypotension in severe cases, and fever in most cases (although not in all elderly patients). Respiratory signs are varied, including dullness to percussion in areas of the chest with significant consolidation, crackles on auscultation, reduced expansion of the chest in some cases as a result of splinting to reduce pain, bronchial breathing in a minority of cases, pleural rub in occasional cases, and cyanosis in cases with significant hypoxemia. Among infants with severe pneumonia, chest wall indrawing and nasal flaring are common. Nonrespiratory findings can include upper abdominal pain if the diaphragmatic pleura is involved as well as mental status changes, particularly confusion in elderly patients.

DIFFERENTIAL DIAGNOSIS The differential diagnosis of pneumococcal pneumonia includes cardiac conditions such as myocardial infarction and heart failure with atypical pulmonary edema; pulmonary conditions such as atelectasis; and pneumonia caused by viral pathogens, mycoplasmas, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Legionella*, or (in HIV-infected and otherwise immunocompromised hosts) *Pneumocystis*. In cases with abdominal symptoms, the differential diagnosis includes cholecystitis, appendicitis, perforated peptic ulcer disease, and subphrenic abscesses. The challenge in cases with abdominal symptoms is to remember to include pneumococcal pneumonia—a nonabdominal process—in the differential diagnosis.

DIAGNOSIS Some authorities advocate treating uncomplicated, nonsevere, community-acquired pneumonia without determining the microbiologic etiology, given that this information is unlikely to alter clinical management. However, efforts to identify the cause of pneumonia are important when the disease is more severe and when the diagnosis of pneumonia is not clearly established. The gold standard for etiologic diagnosis of pneumococcal pneumonia is pathologic examination of lung tissue. In lieu of that procedure, evidence of an infiltrate on chest radiography warrants a diagnosis of pneumonia. However, cases of pneumonia without radiographic evidence do occur. An infiltrate can be absent either early in the course of the illness or with dehydration; upon rehydration, an infiltrate usually appears. The radiographic appearance of pneumococcal pneumonia is varied; it classically consists of lobar or segmental consolidation **(Fig. 141-6)** but in some cases is patchy. More than one lobe is involved in ~30% of cases. Consolidation may be associated with a small pleural effusion or empyema in complicated cases. In children, "round pneumonia," a distinctly spherical consolidation on chest radiography, is associated with a pneumococcal etiology. Round pneumonia is uncommon in adults. *S. pneumoniae* is not the only cause of such lesions; other causes, especially cancer, should be considered.

Blood drawn from patients with suspected pneumococcal pneumonia can be used for supportive or definitive diagnostic tests. Blood cultures are positive for pneumococci in a minority (<30%) of cases of pneumococcal pneumonia, as evidenced especially by vaccine clinical trials, which provide an independent method to reveal the contribution of the pneumococcus to pneumonia cases. Nonspecific findings include an elevated polymorphonuclear leukocyte count (>15,000/μL in most cases and upward of 40,000/μL in some), leukopenia in <10% of cases (a poor prognostic sign associated with a fatal outcome), and elevated values in liver function tests (e.g., both conjugated and unconjugated hyperbilirubinemia). Anemia, low serum albumin levels, hyponatremia, and elevated serum creatinine levels are all found in ~20–30% of patients.

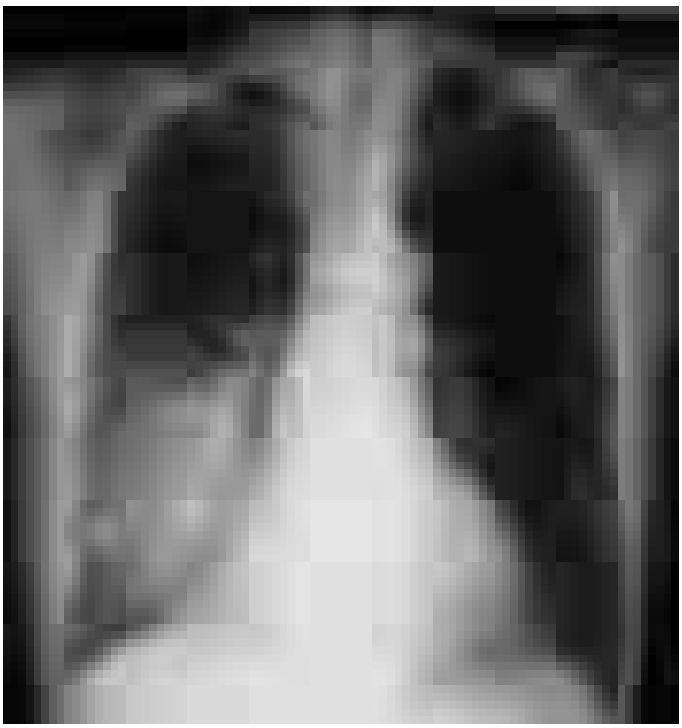

FIGURE 141-6 Chest radiograph depicting classic lobar pneumococcal pneumonia in the right lower lobe of an elderly patient's lung.

Urinary pneumococcal antigen assays have facilitated etiologic diagnosis, but the application of the results is confounded by the fact that nasopharyngeal colonization with the pneumococcus, in the absence of disease, also results in a positive test. In adults, therefore, a positive pneumococcal urinary antigen test has a high predictive value for etiologic attribution of pneumonia because the prevalence of pneumococcal nasopharyngeal colonization is relatively low. In communities, particularly those in low-income countries, where colonization rates among adults are high, urine antigen assays may be less useful. The same issue holds for children, in whom a positive urinary antigen test is usually uninformative for etiologic attribution of their pneumonia illness because colonization rates are generally high. A recent advance is the development of quantitative serotype-specific urinary antigen detection assays; their application for adults and children holds promise, especially in detecting serotypes that are rarely identified in asymptomatic carriage (e.g., serotype 1), even among children.

Most cases of pneumococcal pneumonia in adults are diagnosed by Gram's staining and culture of sputum. The utility of a sputum specimen is directly related to its quality and the patient's antibiotic treatment status.

COMPLICATIONS Empyema is the most common focal complication of pneumococcal pneumonia, occurring in <5% of cases. When fluid in the pleural space is accompanied by fever and leukocytosis (even low-grade) after 4–5 days of appropriate antibiotic treatment for pneumococcal pneumonia, empyema should be considered. Parapneumonic effusions are more common than empyema, representing a self-limited inflammatory response to pneumonia. Pleural fluid with frank pus, bacteria (detected by microscopic examination), or a pH of ≤7.1 indicates empyema and demands aggressive and complete drainage, usually through chest tube insertion.

Meningitis Pneumococcal meningitis usually presents as a pyogenic condition that is clinically indistinguishable from meningitis of other bacterial etiologies. Meningitis can be the primary presenting pneumococcal syndrome or a complication of other conditions such as skull fracture, otitis media, bacteremia, or mastoiditis. Now that *H. influenzae* type b vaccine is routinely used in children, *S. pneumoniae* and *Neisseria meningitidis* are the most common bacterial causes of meningitis in both adults and children. Pyogenic meningitis, including that due to *S. pneumoniae*, is associated clinically with findings that include severe, generalized, gradual-onset headache, fever, and nausea as well as specific CNS manifestations such as stiff neck, photophobia, seizures, and confusion. Clinical signs include a toxic appearance, altered consciousness, bradycardia, and hypertension indicative of increased intracranial pressure. A small proportion of adult patients have Kernig's or Brudzinski's sign or cranial nerve palsies (particularly of the third and sixth cranial nerves).

A definitive diagnosis of pneumococcal meningitis rests on the examination of CSF for (1) evidence of turbidity (visual inspection); (2) elevated protein level, elevated white blood cell count, and reduced glucose concentration (quantitative measurement); and (3) specific identification of the etiologic agent (culture, Gram's staining, antigen testing, or polymerase chain reaction [PCR]). A blood culture positive for *S. pneumoniae* in conjunction with clinical manifestations of meningitis also is considered confirmatory. As discussed in the section on pneumonia, among adults, detection of pneumococcal antigen in urine is considered highly specific because of the low prevalence of nasopharyngeal colonization in this age group.

The mortality rate for pneumococcal meningitis is ~20%. In addition, up to 50% of survivors experience acute or chronic complications, including deafness, hydrocephalus, and mental retardation in children and diffuse brain swelling, subarachnoid bleeding, hydrocephalus, cerebrovascular complications, and hearing loss in adults.

Other Invasive Syndromes *S. pneumoniae* can cause other invasive syndromes involving virtually any body site. These syndromes include primary bacteremia without other sites of infection (bacteremia without a source; occult bacteremia), osteomyelitis, septic arthritis, endocarditis, pericarditis, and peritonitis. The essential diagnostic approach is collection of fluid from the site of infection by sterile technique and examination by Gram's staining, culture, and—when relevant—capsular antigen assay or PCR. Hemolytic-uremic syndrome can complicate invasive pneumococcal disease.

Noninvasive Syndromes The two major noninvasive syndromes caused by *S. pneumoniae* are sinusitis and otitis media; the latter is the most common pneumococcal syndrome and most often affects young children. The manifestations of otitis media include the acute onset of severe pain, fever, deafness, and tinnitus, most frequently in the setting of a recent upper respiratory tract infection. Clinical signs include a red, swollen, often bulging tympanic membrane with reduced movement on insufflation or tympanography. Redness of the tympanic membrane is not sufficient for the diagnosis of otitis media.

Pneumococcal sinusitis is also a complication of upper respiratory tract infections and presents with facial pain, congestion, fever, and—in many cases—persistent nighttime cough. A definitive diagnosis is made by aspiration and culture of sinus material; however, presumptive treatment is most commonly initiated after application of a strict set of clinical diagnostic criteria.

TREATMENT

Pneumococcal Infections

Historically, the activity of penicillin against pneumococci made parenteral penicillin G the drug of choice for disease caused by susceptible organisms, including community-acquired pneumonia. For susceptible strains, penicillin G remains the most commonly used agent, with daily doses ranging from 50,000 U/kg for minor infections to 300,000 U/kg for meningitis. Other parenteral β-lactam drugs, such as ampicillin, cefotaxime, ceftriaxone, and cefuroxime, can be used against penicillin-susceptible strains but offer little advantage over penicillin. Macrolides and cephalosporins are alternatives for penicillin-allergic patients. While agents such as clindamycin, tetracycline, and trimethoprim-sulfamethoxazole exhibit some activity against pneumococci, resistance to these agents is frequently encountered in different parts of the world.

Penicillin-resistant pneumococci were first described in the mid-1960s, at which point tetracycline- and macrolide-resistant strains had already been reported. Multidrug-resistant strains were first described in the 1970s, but it was during the 1990s that pneumococcal drug resistance reached pandemic proportions. The use of antibiotics selects for resistant pneumococci, and strains resistant to β-lactam agents and to multiple drugs are now found all over the world. The emergence of high rates of macrolide and fluoroquinolone resistance also has been described.

The molecular basis of penicillin resistance in *S. pneumoniae* is the alteration of penicillin-binding protein (PBP) genes by transformation and horizontal transfer of DNA from related streptococcal species. Such alteration of PBPs results in lower affinity for penicillins. Depending on the specific PBP(s) and the number of PBPs altered, the level of resistance ranges from intermediate to high. For many years, penicillin susceptibility breakpoints have been defined by MICs as follows: susceptible, ≤0.06 μg/mL; intermediate, 0.12–1.0 μg/mL; and resistant, ≥2.0 μg/mL. However, in vitro results often were not predictive of the response of a patient to treatment for pneumococcal diseases other than meningitis. Revised recommendations have been based on the penicillin G breakpoints established in 2008 by the Clinical and Laboratory Standards Institute. For IV treatment of meningitis with at least 24 million units per day in 8 divided doses, the susceptibility breakpoint remains ≤0.06 μg/mL, and MICs of ≥0.12 μg/mL indicate resistance. For IV treatment of nonmeningeal infections with 12 million units per day in 6 divided doses, the breakpoints are ≤2 μg/mL for susceptible organisms, 4 μg/mL for intermediate organisms, and ≥8 μg/mL for resistant organisms; a dosage of 18–24 million units per day is recommended for strains with MICs in the intermediate category. The original breakpoints remain the same for oral treatment of nonmeningeal infections with penicillin V.

Although guidelines for antibiotic therapy should be driven in part by local patterns of resistance, guidelines from national organizations in many countries (e.g., the Infectious Diseases Society of America/American Thoracic Society, the British Thoracic Society, and the European Respiratory Society) lay out evidence-based approaches. The following guidelines for the treatment of individual sepsis syndromes are based on those advocated by the American Academy of Pediatrics and published in the 2015 *Red Book*.

MENINGITIS LIKELY OR PROVEN TO BE DUE TO *S. PNEUMONIAE*

As a result of the increased prevalence of resistant pneumococci, first-line therapy for persons ≥1 month of age is a combination of vancomycin (adults, 30–60 mg/kg per day; infants and children, 60 mg/kg per day) and cefotaxime (adults, 8–12 g/d in 4–6 divided doses; children, 225–300 mg/kg per day in 1 dose or 2 divided doses) or ceftriaxone (adults, 4 g/d in 1 dose or 2 divided doses; children, 100 mg/kg per day in 1 dose or 2 divided doses). If children are hypersensitive to β-lactam agents (penicillins and cephalosporins), rifampin (adults, 600 mg/d; children, 20 mg/d in 1 dose or 2 divided doses) can be substituted for cefotaxime or ceftriaxone. A repeat lumbar puncture should be considered after 48 h if the organism is not susceptible to penicillin and information on cephalosporin sensitivity is not yet available, if the patient's clinical condition does not improve or deteriorates, or if dexamethasone has been administered and may be compromising clinical evaluation. When antibiotic sensitivity data become available, treatment should be modified accordingly. If the isolate is sensitive to penicillin, vancomycin can be discontinued and penicillin can replace the cephalosporin, or cefotaxime or ceftriaxone can be continued alone. If the isolate displays any resistance to penicillin but is susceptible to the cephalosporins, vancomycin can be discontinued and cefotaxime or ceftriaxone continued. If the isolate exhibits any resistance to penicillin and is not susceptible to cefotaxime and ceftriaxone, vancomycin and high-dose cefotaxime or ceftriaxone can be continued; rifampin may be added as well if the isolate is susceptible and the patient's clinical condition is worsening, if the CSF remains positive for bacteria, or if the MIC of the cephalosporin in question against the infecting strain is high. Some physicians advocate the use of glucocorticoids in children >6 months old, but this recommendation remains controversial and is not universally considered the standard of care. Glucocorticoids significantly reduce rates of mortality, severe hearing loss, and neurologic sequelae in adults and should be administered to those with community-acquired bacterial meningitis. If dexamethasone is given to either adults or children, it should be administered before or in conjunction with the first antibiotic dose.

INVASIVE INFECTIONS (EXCLUDING MENINGITIS)

In previously well children with noncritical illness, therapy with a recommended antibiotic should be instigated at the following dosages: penicillin G, 250,000–400,000 units/kg per day (in divided doses 4–6 h apart); cefotaxime, 75–100 mg/d (doses 8 h apart); or ceftriaxone, 50–75 mg/d (doses 12–24 h apart). For critically ill children, including those who have myocarditis or multilobular pneumonia with hypoxia or hypotension, vancomycin may be added if the isolate may possibly be resistant to β-lactam drugs, with its use reviewed once susceptibility data become available. If the organism is resistant to β-lactam agents, therapy should be modified on the basis of clinical response and susceptibility to other antibiotics. Clindamycin or vancomycin can be used as a first-line agent for children with severe β-lactam hypersensitivity, but vancomycin should not be continued if the organism is shown to be sensitive to other non-β-lactam antibiotics.

For outpatient management, amoxicillin (1 g every 8 h) provides effective treatment for virtually all cases of pneumococcal

pneumonia. Neither cephalosporins nor quinolones, which are far more expensive, offer advantages over amoxicillin. Levofloxacin (500–750 mg/d as a single dose) and moxifloxacin (400 mg/d as a single dose) also are highly likely to be effective in the United States except in patients who come from closed populations where these drugs are used widely or who have themselves been treated recently with a quinolone. Clindamycin (600–1200 mg/d every 6 h) is effective in 90% of cases and azithromycin (500 mg on day 1 followed by 250–500 mg/d) or clarithromycin (500–750 mg/d as a single dose) in 80% of cases. Treatment failure resulting in bacteremic disease due to macrolide-resistant isolates has been amply documented in patients given azithromycin empirically. As noted above, rates of resistance to all these antibiotics are relatively low in some countries and much higher in others; high-dose amoxicillin remains the best option worldwide.

The optimal duration of treatment for pneumococcal pneumonia is uncertain, but its continuation for at least 5 days once the patient becomes afebrile appears to be a prudent approach. Cases with a second focus of infection (e.g., empyema or septic arthritis) require longer therapy.

ACUTE OTITIS MEDIA

Amoxicillin (80–90 mg/kg per day) is recommended for children with acute otitis media except in situations where observation and symptom-based treatment without antibiotics are advocated. These situations include nonsevere illness and an uncertain diagnosis in children 6 months to 2 years of age and nonsevere illness (even if the diagnosis seems certain) in children >2 years of age. Although the optimal duration of therapy has not been conclusively established, a 10-day course is recommended for younger children and for children with severe disease at any age. For children >6 years old who have mild or moderate disease, a course of 5–7 days is considered adequate. Patients whose illness fails to respond should be reassessed at 48–72 h. If acute otitis media is confirmed and antibiotic treatment has not been started, administration of amoxicillin should be commenced. If antibiotic therapy fails, a change is indicated. Failure to respond to second-line antibiotics as well indicates that myringotomy or tympanocentesis may need to be undertaken in order to obtain samples for culture.

The above recommendations can also be followed for the treatment of sinusitis. Detailed information on the further management of these conditions in children has been published by the American Academy of Pediatrics and the American Academy of Family Physicians.

PREVENTION

Measures to prevent pneumococcal disease include vaccination against *S. pneumoniae* and influenza viruses, reduction of comorbidities that increase the risk of pneumococcal disease, and prevention of antibiotic overuse, which fuels pneumococcal resistance.

Capsular Polysaccharide Vaccines The 23-valent pneumococcal polysaccharide vaccine (PPSV23), containing 25 μg of each capsular polysaccharide, has been licensed for use since 1983. Recommendations for its use vary by country. The U.S. Advisory Committee on Immunization Practices recommends PPSV23 for all persons ≥65 years of age and for those 2–64 years of age who have underlying medical conditions that put them at increased risk for pneumococcal disease or, if infected, disease of increased severity (Table 141-1; see also *www.cdc.gov/vaccines/schedules*). The committee updated their recommendations to include the combined use of PPSV23 and pneumococcal conjugate vaccine in at-risk individuals (see "Polysaccharide–Protein Conjugate Vaccines," below). Revaccination 5 years after the first dose is recommended for persons >2 years of age who have underlying medical conditions but not routinely for those whose only indication is an age of ≥65 years. PPSV23 does not induce an anamnestic response, and antibody concentrations wane over time; thus revaccination is particularly important for individuals with conditions resulting in loss of antibody. Concerns about repeated revaccination have focused on safety (i.e., local reactions) and the induction of immune hyporesponsiveness. Neither the clinical relevance nor the biologic basis of hyporesponsiveness is clear, but, given the possibility of its occurrence, more than one revaccination has not been recommended.

The effectiveness of PPSV23 against IPD, pneumococcal pneumonia, all-cause pneumonia, and death is controversial, with wide variation in observations. The many published meta-analyses of PPSV efficacy have often reached opposing conclusions with regard to a given clinical entity. Generally, observational studies cite greater effectiveness than do controlled clinical trials. The consensus is that PPSV is effective against IPD but is less effective or ineffective against nonbacteremic pneumococcal pneumonia. However, the results of some published trials, observational studies, and meta-analyses contradict this view. Effectiveness is often lower in the elderly and in immunodeficient patients whose condition is associated with reduced antibody responses to vaccines than in younger, healthier populations. When PPSV is effective, the duration of protection following a single dose of vaccine is estimated to be ~5 years.

What is not disputed is that improved pneumococcal vaccines are needed for adults. Even in the setting of routine pneumococcal conjugate vaccination of infants (which indirectly protects adults from vaccine-serotype strains), disease caused by serotypes not represented in the conjugate vaccine continues to be a significant burden among adults.

Polysaccharide–Protein Conjugate Vaccines Infants and young children respond poorly to PPSV, which contains T cell–independent antigens. Consequently, another class of pneumococcal vaccines, the PCVs, were developed specifically for infants and young children. The first product, a 7-valent PCV, was licensed in 2000 in the United States. Two PCV products—containing 10 and 13 serotypes, respectively—are currently (2017) commercially available. The serotypes included in these PCV formulations are important causes of IPD and antibiotic resistance among young children. Randomized controlled trials have demonstrated a high degree of efficacy of PCVs against vaccine-serotype IPD as well as efficacy against pneumonia, otitis media, nasopharyngeal colonization, and all-cause mortality. PCVs are recommended by the World Health Organization for inclusion in routine childhood immunization schedules worldwide, especially in countries with high infant mortality rates.

The United States was the first country to introduce PCV (in 2000) and therefore has the longest experience with its community-wide effects. The introduction of PCV in the United States has resulted in a >90% reduction in vaccine-serotype IPD among the whole population **(Fig. 141-7)**. This decline has been noted not only in those age groups immunized but also in adults and is attributable to the near elimination of vaccine-serotype nasopharyngeal colonization in immunized infants, which reduces spread to adults. This protection of unimmunized community members through vaccination of a subset of the community is termed *the indirect effect*. Increases in colonization with—and concomitantly in disease due to—non-vaccine-serotype strains (i.e., replacement colonization and disease) have been seen; however, the absolute rate increases in IPD caused by non-vaccine serotypes are generally small, especially relative to decreases in vaccine-serotype IPD (see "Epidemiology," above). Since vaccine-serotype strains are more commonly resistant to antibiotics than are non-vaccine serotypes, use of PCV has also resulted in substantial declines in the proportion and absolute rates of drug-resistant pneumococcal disease. The recommendations of the Advisory Committee on Immunization Practices for the use of conjugate vaccines can be found at *www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html*. PCV has been shown to prevent pneumococcal infection in HIV-infected adults. In the United States, PCV13 followed by a dose of PPSV23 is now recommended for all immunocompromised children and adults. PCV13 is also effective in preventing vaccine sero type pneumococcal pneumonia in healthy adults over 65 years of age and is recommended for routine use in that age group (followed by a dose of PPSV23) in the United States (*www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a4.htm*). This recent policy change will be reviewed in 2018 in light of ongoing and rapid changes in pneumococcal epidemiology with widespread PCV13 use in infants.

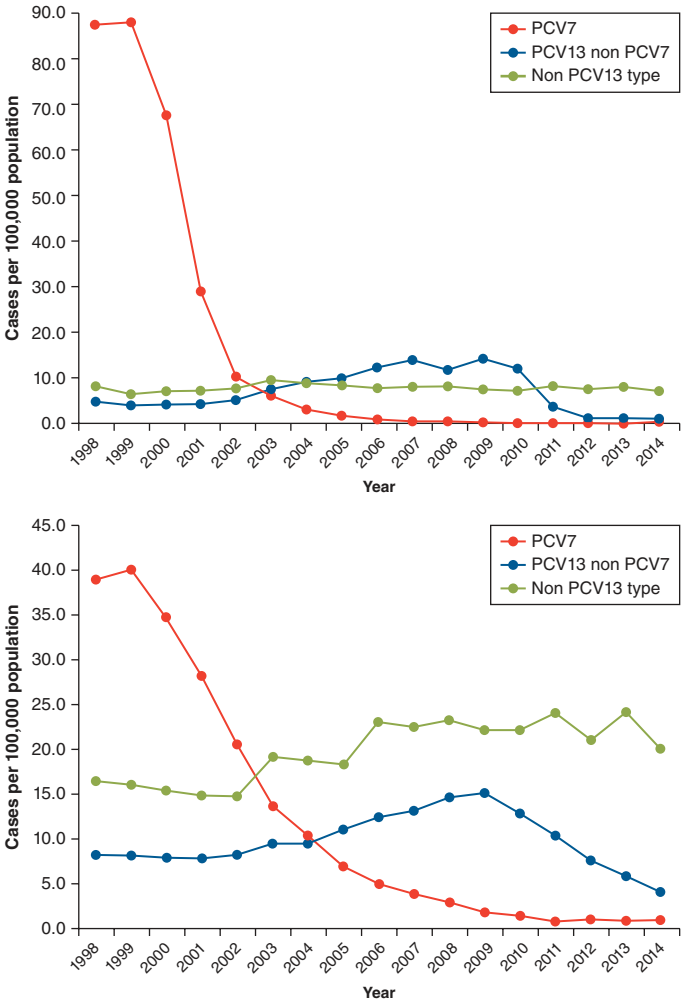

FIGURE 141-7 Changes in invasive pneumococcal disease incidence, by serotype group, among children <5 years old (top) and adult ≥65 years old (bottom), 1998–2014. 7-Valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine administration to infants and young children during the second half of 2000, while PCV13 was introduced in 2010. PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F as well as cross-reactive serotype 6A. PCV13 includes the PCV7 serotypes as well as serotypes 1, 3, 5, 6A, 7F, and 19A. *(Reprinted with permission from Dr. T. Pilishvili, Centers for Disease Control and Prevention.)*

Other Prevention Strategies Pneumococcal disease can be averted through the prevention of illnesses that predispose individuals to pneumococcal infections. Relevant measures include influenza vaccination and improved management and control of diabetes, HIV infection, heart disease, and lung disease. Finally, the reduction of antibiotic misuse is a strategy for the prevention of pneumococcal disease in that antimicrobial resistance directly and indirectly perpetuates organism transmission and disease in the community.

GLOBAL HEALTH

Pneumococcal infections are estimated to cause ~330,000 annual deaths worldwide among children 1–59 months of age, accounting for 11% of the 3.2 million all-cause deaths in this age group in 2015. Reliable estimates of adult cases and deaths globally are more difficult to establish because of limited data from parts of the world where most disease occurs. Rates of pneumococcal disease and mortality vary substantially across geographic settings, with the highest rates in selected countries of sub-Saharan Africa and southern Asia, where risk factors for pneumococcal disease—including HIV infection, lack of breast feeding of infants and children, malnutrition, sickle cell disease, and limited access to medical care—are prevalent. Serotypes causing disease exhibit some heterogeneity across geographic settings, but a small number of serotypes universally account for the preponderance of disease in the absence of vaccination; accordingly, vaccine development and vaccination programs are globally relevant. Reductions in disease from pneumococcal infections are anchored in prevention through the inclusion of pneumococcal vaccines in infant immunization programs, timely assessment and appropriate treatment of persons with pneumococcal infections, and reduction of risk factors for pneumococcal disease. The availability of vaccines for the prevention of adult pneumococcal disease, particularly among the elderly, is currently restricted to high-income countries, with virtually no availability in low-income countries where most cases of disease exist.

FURTHER READING

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American Academy of Pediatrics RED BOOK: The report of the Committee on Infectious Diseases: *aapredbook.aappublications.org*.

Pneumococcal Regional Serotype Distribution for Pneumococcal AMC TPP: *www.gavialliance.org/library/documents/amc/tpp-codebook/*.

142 Staphylococcal Infections

Franklin D. Lowy

Staphylococcus aureus, the most virulent of the many staphylococcal species, has demonstrated its versatility by remaining a major cause of morbidity and mortality worldwide despite the availability of numerous effective antistaphylococcal antibiotics. *S. aureus* is a pluripotent pathogen, causing disease through both toxin- and non-toxin-mediated mechanisms. It is responsible for numerous nosocomial and community-based infections that range from relatively minor skin and soft tissue infections (SSTIs) to life-threatening systemic infections.

The "other" staphylococci, collectively designated coagulase-negative staphylococci (CoNS), are considerably less virulent than *S. aureus* but remain important pathogens in select settings, such as infections that involve prosthetic devices.

MICROBIOLOGY AND TAXONOMY

Staphylococci, gram-positive cocci in the family Micrococcaceae, form grapelike clusters on Gram's stain (Fig. 142-1). These organisms (~1 μm in diameter) are catalase-positive (unlike streptococcal species), nonmotile, aerobic, and facultatively anaerobic. They are capable of prolonged survival on environmental surfaces under varying conditions. Some species have a relatively broad host range, including mammals and birds, whereas the host range for others is quite narrow—i.e., limited to one or two closely related animals.

More than 30 staphylococcal species are pathogenic. Identification of the more clinically important species has generally relied on a series of biochemical tests. Automated diagnostic systems, kits for biochemical characterization, and DNA-based assays are available for species identification. With few exceptions, *S. aureus* is distinguished from other staphylococcal species by its production of coagulase, a surface enzyme that converts fibrinogen to fibrin. Latex kits that detect both protein A and clumping factor also distinguish *S. aureus* from most other

FIGURE 142-1 Gram's stain of *S. aureus* in a sputum sample, illustrating staphylococcal clusters. *(From ASM MicrobeLibrary.org. © Pfizer, Inc.)*

staphylococcal species. *S. aureus* ferments mannitol, is positive for protein A, and produces DNAse. On blood agar plates, *S. aureus* tends to form golden β-hemolytic colonies; in contrast, CoNS form small white nonhemolytic colonies. Newer methods such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) are increasingly being used for staphylococcal speciation in some clinical microbiology laboratories.

Determining whether multiple staphylococcal isolates from different patients are the same or different is often relevant when there is concern that a nosocomial outbreak is due to a common point source (e.g., a contaminated medical instrument). Molecular typing methods, such as pulsed-field gel electrophoresis and sequence-based techniques (e.g., staphylococcal protein A [SpA] typing), have increasingly been used for this purpose. More recently, whole-genome sequencing has dramatically enhanced the ability to discriminate among clinical isolates.

S. AUREUS INFECTIONS

EPIDEMIOLOGY

S. aureus is both a commensal and an opportunistic pathogen. Approximately 20–40% of healthy persons are colonized with *S. aureus*, with a smaller percentage (~10%) persistently colonized with the same strain. The rate of colonization is elevated among insulin-dependent diabetics, HIV-infected patients, patients undergoing hemodialysis, injection drug users, and individuals with skin damage. The anterior nares and oropharynx are frequent sites of human colonization, although the skin (especially when damaged), vagina, axilla, and perineum are also often colonized. These colonization sites serve as potential reservoirs for future infections.

Most individuals who develop *S. aureus* infections become infected with a strain that is already a part of their own commensal flora. Breaches of the skin or mucosal membrane allow *S. aureus* to initiate infection. Person-to-person transmission of *S. aureus* also occurs, most frequently from direct personal contact with a colonized body site. Spread of staphylococci in aerosols of respiratory or nasal secretions from heavily colonized individuals also has been reported.

Some diseases increase the risk of *S. aureus* infection; diabetes, for example, combines an increased rate of *S. aureus* colonization and the use of injectable insulin with the possibility of impaired leukocyte function. Individuals with congenital or acquired qualitative or quantitative defects of polymorphonuclear leukocytes (PMNs) are at increased risk of *S. aureus* infections; this group includes neutropenic patients (e.g., those receiving chemotherapeutic agents), those with chronic granulomatous disease, and those with Job (autosomal dominant hyperimmunoglobulin E syndrome) or Chédiak-Higashi syndrome. Other groups at risk include individuals with end-stage renal disease, HIV infection, skin abnormalities, or prosthetic devices.

S. aureus is a leading cause of health care–associated infections **(Chap. 137)**. It is the most common cause of surgical wound infections and is second only to CoNS as a cause of primary bacteremia. These isolates are often resistant to multiple antibiotics; thus available therapeutic options may be limited. In the community, *S. aureus* remains an important cause of SSTIs, respiratory infections, and (among injection drug users) infective endocarditis. The increasing use of home infusion therapy also poses a risk of community-acquired staphylococcal infections.

In the past three decades, there has been a dramatic change in the epidemiology of infections due to methicillin-resistant *S. aureus* (MRSA). In addition to its major role as a nosocomial pathogen, MRSA has become an established community-based pathogen. Numerous outbreaks of community-associated MRSA (CA-MRSA) infections have been reported in both rural and urban settings in widely separated regions throughout the world. This trend appears to be due in part to the dramatic increase in MRSA colonization found in the community in different parts of the world. Outbreaks of CA-MRSA infections have occurred among such diverse groups as children, prisoners, athletes, Native Americans, and drug users. Risk factors common to these outbreaks include poor hygienic conditions, close contact, contaminated material, and damaged skin. In some geographic regions of the world, the infections have been caused by a single CA-MRSA strain, while in others a variety of CA-MRSA strains have been responsible. In the United States, strain USA300 (defined by pulsed-field gel electrophoresis) has been the predominant clone. Although the majority of infections caused by these strains have involved the skin and soft tissue, 5–10% have been invasive and potentially life-threatening. CA-MRSA strains have also been responsible for an increasing number of nosocomial infections. Of concern has been the apparently enhanced capacity of CA-MRSA to cause disease in immunocompetent individuals.

PATHOGENESIS

General Concepts *S. aureus* is a pyogenic pathogen known for its capacity to induce abscess formation at sites of both local and metastatic infections. This classic pathologic response to *S. aureus* defines the framework within which the infection will progress. The bacteria elicit an inflammatory response characterized by an initial intense infiltration of PMNs and a subsequent infiltration of macrophages and fibroblasts. Either the host cellular response (including the deposition of fibrin and collagen) contains the infection, or infection spreads to the adjoining tissue or into the bloodstream.

In toxin-mediated staphylococcal disease, infection is not invariably present. For example, once the heat-stable enterotoxin has been elaborated into food, staphylococcal food poisoning can develop in the absence of viable bacteria. In staphylococcal toxic shock syndrome (TSS), conditions allowing toxin elaboration at colonization sites (e.g., the presence of a superabsorbent tampon) suffice for initiation of clinical illness.

The *S. aureus* Genome The complete genomes of *S. aureus* strains are now readily sequenced. Among the interesting revelations are (1) the high degree of nucleotide sequence similarity of the core genomes of different strains; (2) the acquisition of a relatively large amount of genetic information by horizontal transfer from other bacterial species; and (3) the presence of unique "pathogenicity" or "genomic" islands—mobile genetic elements that contain clusters of enterotoxin and exotoxin genes and/or antimicrobial resistance determinants. Among the genes in these islands is *mecA*, the gene responsible for methicillin resistance. Methicillin resistance–containing islands have been designated staphylococcal cassette chromosome *mec* (SCC*mec*) types and range in size from ~20 to 60 kb. Among the more common SCC*mec* types, types 1–3 are traditionally associated with nosocomial MRSA isolates, whereas types 4–6 have been associated with epidemic CA-MRSA strains.

A relatively limited number of MRSA clones have been responsible for most community- and hospital-associated infections worldwide. A comparison of these strains with those from earlier outbreaks (e.g., the phage 80/81 strains from the 1950s) has revealed preservation of the nucleotide sequence over time.

This observation suggests that these strains possess determinants that facilitate survival and spread.

Regulation of Virulence Gene Expression In both toxin-mediated and non-toxin-mediated diseases due to *S. aureus*, the expression of virulence determinants associated with infection depends on a series of regulatory genes (e.g., accessory gene regulator [*agr*] and staphylococcal accessory regulator [*sar*]) that coordinately control the expression of many virulence genes. The regulatory gene *agr* is part of a quorum-sensing signal transduction pathway that senses and responds to bacterial density. Staphylococcal surface proteins are synthesized during the bacterial exponential growth phase in vitro. In contrast, many secreted proteins, such as α toxin, the enterotoxins, and assorted enzymes, are released during the postexponential growth phase in response to transcription of the effector molecule of *agr*, RNAIII.

It has been hypothesized that these regulatory genes serve a similar function in vivo. Successful invasion requires the sequential expression of these different bacterial elements. Bacterial adhesins are needed to initiate colonization of host tissue surfaces. The subsequent release of various enzymes enables the colony to obtain nutritional support and permits bacteria to spread to adjacent tissues. Studies with strains in which these regulatory genes are inactivated show reduced virulence in several animal models of *S. aureus* infection.

Pathogenesis of Invasive *S. aureus* Infection Staphylococci are opportunists. For these organisms to invade the host and cause infection, some or all of the following steps are necessary: contamination and colonization of host tissue surfaces, breach of cutaneous or mucosal barriers, establishment of a localized infection, invasion, evasion of the host response, and metastatic spread. Colonizing strains or strains transferred from other individuals are introduced into damaged skin, a wound, or the bloodstream. Recurrences of *S. aureus* infections are common, apparently because of the capacity of these pathogens to survive, to persist in a quiescent state in various tissues, and then to cause recrudescent infections when suitable conditions arise.

***S. AUREUS* COLONIZATION OF BODY SURFACES** The anterior nares are a primary site of staphylococcal colonization in humans. Colonization appears to involve the attachment of *S. aureus* to keratinized epithelial cells found in the anterior nares. Other factors that contribute to colonization include the influence of other resident nasal flora and their bacterial density, host factors, and nasal mucosal damage (e.g., that resulting from inhalational drug use). Other colonized body sites, such as damaged skin, the groin, and the oropharynx, may be particularly important reservoirs for CA-MRSA strains.

INOCULATION AND COLONIZATION OF TISSUE SURFACES Staphylococci may be introduced into tissue as a result of minor abrasions (e.g., mosquito bites), administration of medications such as insulin, or establishment of IV access with catheters. After their introduction into a tissue site, bacteria replicate and colonize the host tissue surface. A family of structurally related *S. aureus* surface proteins referred to as MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) plays an important role in mediating adherence to these different sites. By adhering to exposed matrix molecules (e.g., fibrinogen, fibronectin), MSCRAMMs, such as clumping factor and collagen-binding protein, enable the bacteria to colonize different host tissue surfaces; these proteins contribute to the pathogenesis of invasive infections such as endocarditis and septic arthritis by facilitating the adherence of *S. aureus* to surfaces with exposed fibrinogen or collagen.

Although CoNS are classically known for their ability to elaborate biofilms and to colonize prosthetic devices, *S. aureus* also possesses the genes responsible for biofilm formation, such as the intercellular adhesion (*ica*) locus. Binding to these devices occurs in a stepwise fashion, involving staphylococcal adherence to serum constituents that have coated the device surface and subsequent biofilm elaboration. *S. aureus* is thus a frequent cause of biomedical device–related infections.

INVASION After colonization, staphylococci replicate at the initial site of infection, elaborating enzymes that include serine proteases, hyaluronidases, thermonucleases, and lipases. These enzymes facilitate bacterial survival and local spread across tissue surfaces. The lipases may facilitate survival in lipid-rich areas such as the hair follicles, where *S. aureus* infections are often initiated. MSCRAMMs also appear to play an important role in the ability of *S. aureus* to spread and cause disease at other tissue sites.

Constitutional findings may result from either localized or systemic infections. The staphylococcal cell wall—consisting of alternating *N*-acetyl muramic acid and *N*-acetyl glucosamine units in combination with an additional cell wall component, lipoteichoic acid—can initiate an inflammatory response that includes the sepsis syndrome. Staphylococcal α toxin is a critical staphylococcal toxin. It causes pore formation in various eukaryotic cells and can also initiate an inflammatory response with findings suggestive of sepsis. The *S. aureus* toxin Panton-Valentine leukocidin is cytolytic to PMNs, macrophages, and monocytes. Strains elaborating this toxin have been epidemiologically linked with cutaneous and more serious infections caused by strains of CA-MRSA.

EVASION OF HOST DEFENSE MECHANISMS Staphylococci have many immune evasion strategies that are crucial to their survival. They possess an antiphagocytic polysaccharide microcapsule. Most human *S. aureus* infections are due to strains with capsular types 5 and 8. The zwitterionic (both negatively and positively charged) *S. aureus* capsule also plays a critical role in the induction of abscess formation. Protein A, an MSCRAMM unique to *S. aureus*, acts as an Fc receptor, binding the Fc portion of IgG subclasses 1, 2, and 4 and preventing opsonophagocytosis by PMNs. Both chemotaxis inhibitory protein of staphylococci (CHIPS, a secreted protein) and extracellular adherence protein (EAP, a surface protein) interfere with PMN migration to sites of infection.

An additional potential mechanism of *S. aureus* evasion is its capacity for intracellular survival. Both professional and nonprofessional phagocytes internalize staphylococci. Internalization by these cells may provide a sanctuary that protects bacteria against the host's defenses. This phenomenon appears to be especially relevant for hepatic Kupffer cells during staphylococcal bacteremias. The intracellular environment favors the phenotypic expression of *S. aureus* small-colony variants, which are found in patients receiving antimicrobial therapy (e.g., with aminoglycosides) and in those with cystic fibrosis or osteomyelitis. These variants, whether intra- or extracellular, may facilitate prolonged staphylococcal survival in different tissue sites and enhance the likelihood of recurrences. Finally, *S. aureus* can survive within PMNs and may use these cells to spread and seed other tissue sites.

PATHOGENESIS OF COMMUNITY-ACQUIRED MRSA INFECTIONS A number of virulence determinants have been identified that contribute to the pathogenesis of CA-MRSA infections. A strong epidemiologic association links the presence of the gene for the Panton-Valentine leukocidin with SSTIs and with necrotizing post-influenza pneumonia. Other determinants that play a role in the pathogenesis of these infections include the arginine catabolic mobile element (ACME), a cluster of unique genes that may facilitate evasion of host defense mechanisms; phenol-soluble modulins, a family of cytolytic peptides; and α toxin.

Host Response to *S. aureus* Infection The primary host response to *S. aureus* infection is the recruitment of PMNs. These cells are attracted to infection sites by bacterial components such as formylated peptides or peptidoglycan as well as by the cytokines tumor necrosis factor (TNF) and interleukins (ILs) 1 and 6, which are released by activated macrophages and endothelial cells.

Although most individuals have antibodies to staphylococci, it is not clear that antibody levels are qualitatively or quantitatively sufficient to protect against infection. Anticapsular and anti-MSCRAMM antibodies facilitate opsonization in vitro and have been protective against infection in several animal models; however, they have not yet successfully prevented staphylococcal infections in clinical trials.

Pathogenesis of Toxin-Mediated Disease *S. aureus* produces three types of toxin: cytotoxins, pyrogenic toxin superantigens, and exfoliative toxins. Both epidemiologic data and studies in animals

suggest that antitoxin antibodies are protective against illness in TSS, staphylococcal food poisoning, and staphylococcal scalded-skin syndrome (SSSS). Illness develops after toxin synthesis and absorption and the subsequent toxin-initiated host response.

ENTEROTOXIN AND TOXIC SHOCK SYNDROME TOXIN 1 (TSST-1) The pyrogenic toxin superantigens are a family of small-molecular-size, structurally similar proteins that are responsible for two diseases: TSS and food poisoning. TSS results from the ability of TSST-1 and enterotoxins to function as T cell mitogens. In the normal process of antigen presentation, the antigen is first processed within the cell, and peptides are then presented in the major histocompatibility complex (MHC) class II groove, initiating a measured T cell response. In contrast, enterotoxins bind directly to the invariant region of MHC—outside the MHC class II groove. The enterotoxins can then bind T cell receptors via the vβ chain; this binding results in a dramatic overexpansion of T cell clones (up to 20% of the total T cell population). The consequence of this T cell expansion is a "cytokine storm," with the release of inflammatory mediators that include interferon γ, IL-1, IL-6, TNF-α, and TNF-β. The resulting multisystem disease produces a constellation of findings that mimic those found in endotoxin shock; however, the pathogenic mechanisms differ. The release of endotoxin from the gastrointestinal tract may synergistically enhance the toxin's effects.

A different region of the enterotoxin molecule is responsible for the symptoms of food poisoning. The enterotoxins are heat stable and can survive conditions that kill the bacteria. Illness results from the ingestion of preformed toxin. As a result, the incubation period is short (1–6 h). The toxin stimulates the vagus nerve and the vomiting center of the brain. It also appears to stimulate intestinal peristaltic activity.

EXFOLIATIVE TOXINS AND SSSS The exfoliative toxins are responsible for SSSS, most commonly seen in newborns. The toxins that produce disease in humans are of two serotypes: ETA and ETB. These toxins are serine proteases, which cleave desmosomal cadherins in the superficial layer of the skin, triggering exfoliation. The result is a split in the epidermis at the granular level, which is responsible for the superficial desquamation of the skin that typifies this illness.

DIAGNOSIS

Staphylococcal infections are readily diagnosed by Gram's stain (Fig. 142-1) and microscopic examination of abscess contents or of infected tissue. Routine culture of infected material usually yields positive results, and blood cultures are sometimes positive even when infections are localized to extravascular sites. *S. aureus* is rarely a blood culture contaminant. Polymerase chain reaction (PCR)–based assays are now often used for the rapid diagnosis of *S. aureus* infection. A number of point-of-care tests are now available to screen patients for colonization with MRSA. Determining whether patients with documented *S. aureus* bacteremia also have infective endocarditis or a metastatic focus of infection remains a diagnostic challenge. Uniformly positive cultures of blood collected over time suggest an endovascular infection such as endocarditis (see "Bacteremia, Sepsis, and Infective Endocarditis," below).

CLINICAL SYNDROMES

(Table 142-1)

TABLE 142-1 Common Illnesses Caused by *Staphylococcus aureus*

Skin and Soft Tissue Infections
Folliculitis
Abscess, furuncle, carbuncle
Cellulitis
Impetigo
Mastitis
Surgical wound infections
Musculoskeletal Infections
Septic arthritis
Osteomyelitis (hematogenous or contiguous spread)
Pyomyositis
Psoas abscess
Respiratory Tract Infections
Ventilator-associated or nosocomial pneumonia
Septic pulmonary emboli
Postviral pneumonia (e.g., influenza)
Empyema
Bacteremia and Its Complications
Sepsis, septic shock
Metastatic foci of infection (kidney, joints, bone, lung)
Infective endocarditis
Infective Endocarditis
Injection drug use–associated
Native-valve
Prosthetic-valve
Nosocomial
Device-Related Infections (e.g., intravascular catheters, prosthetic joints)
Toxin-Mediated Illnesses
Toxic shock syndrome
Food poisoning
Staphylococcal scalded-skin syndrome
Invasive Infections Associated with Community-Acquired Methicillin-Resistant *S. aureus*
Necrotizing fasciitis
Waterhouse-Friderichsen syndrome
Necrotizing pneumonia
Purpura fulminans

Skin and Soft Tissue Infections *S. aureus* causes a variety of cutaneous infections, many of which may also be caused by group A streptococci or (less commonly) other streptococcal species. Common factors predisposing to *S. aureus* cutaneous infection include chronic skin conditions (e.g., eczema), skin damage (e.g., insect bites, minor trauma), injections (e.g., in diabetes, injection drug use), and poor personal hygiene. These infections are characterized by the formation of pus-containing blisters, which often begin in hair follicles and spread to adjoining tissues. *Folliculitis* is a superficial infection that involves the hair follicle, with a central area of purulence (pus) surrounded by induration and erythema. *Furuncles* (boils) are more extensive, painful lesions that tend to occur in hairy, moist regions of the body and extend from the hair follicle to become a true abscess with an area of central purulence. *Carbuncles* are most often located in the lower neck and are even more severe and painful, resulting from the coalescence of other lesions that extend to a deeper layer of the subcutaneous tissue. In general, furuncles and carbuncles are readily apparent, with pus often expressible or discharging from the abscess. Other cutaneous *S. aureus* infections include impetigo and cellulitis. *S. aureus* is one of the most common causes of surgical wound infection.

Mastitis develops in 1–3% of nursing mothers. This infection of the breast, which generally presents within 2–3 weeks after delivery, is characterized by findings that range from cellulitis to abscess formation. Systemic signs, such as fever and chills, are often present in more severe cases.

Musculoskeletal Infections *S. aureus* is among the most common causes of bone infections—both those resulting from hematogenous dissemination and those arising from contiguous spread from a soft tissue site. *Hematogenous osteomyelitis* in children most often involves the long bones. Infections present with fever and bone pain or with a child's reluctance to bear weight. The white blood cell count and erythrocyte sedimentation rate are often elevated. Blood cultures are positive in ~50% of cases. When necessary, bone biopsies for culture and histopathologic examination are usually diagnostic.

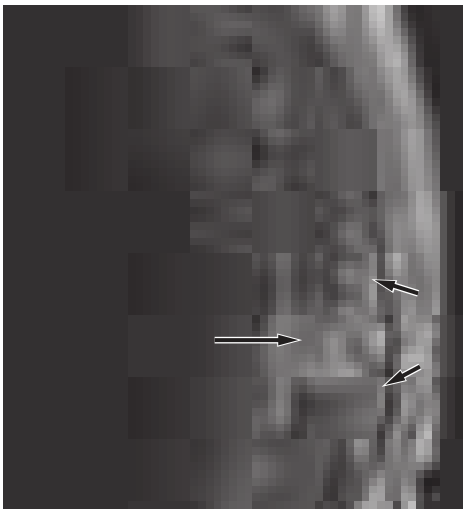

FIGURE 142-2 *S. aureus* vertebral osteomyelitis and epidural abscess involving the thoracic disk between T9 and T10. Sagittal post-contrast MRI of the spine illustrates destruction of the T9–T10 intervertebral space with enhancement (*long arrow*). There is impingement on the thoracic cord and an epidural collection extending from T9 through T11 (*short arrows*).

In adults, hematogenous osteomyelitis involving the long bones is less common. However, *vertebral osteomyelitis* is among the more common clinical presentations. Vertebral bone infections are most often seen in patients with endocarditis, those undergoing hemodialysis, diabetics, and injection drug users. These infections may present as intense back pain with fever but may also be clinically occult, presenting as chronic back pain with low-grade fever. *S. aureus* is the most common cause of epidural abscess, a complication that can result in neurologic compromise. Patients report difficulty voiding or walking and radicular pain in addition to the symptoms associated with their osteomyelitis. Surgical intervention in this setting often constitutes a medical emergency.

MRI is the most reliable imaging modality to help establish the diagnosis of osteomyelitis. **(Fig. 142-2)**. Routine x-rays are an appropriate first step, but findings may be normal for up to 14 days after the onset of symptoms. If an MRI is not possible, CT is an acceptable alternative.

Bone infections that result from contiguous spread tend to develop from soft tissue infections, such as those associated with diabetic or vascular ulcers, surgery, or trauma. Exposure of bone, a draining fistulous tract, failure to heal, or continued drainage suggests involvement of underlying bone. Bone involvement is established by bone culture and histopathologic examination (revealing evidence of PMN infiltration). Contamination of culture material from adjacent tissue can make the diagnosis of osteomyelitis difficult in the absence of pathologic confirmation. Samples obtained during surgery are more reliable. In addition, it is sometimes hard to distinguish radiologically between osteomyelitis and overlying soft tissue infection with underlying osteitis.

In both children and adults, *S. aureus* is the most common cause of *septic arthritis* in native joints. This infection is rapidly progressive and may be associated with extensive joint destruction if left untreated. It presents with intense pain on motion of the affected joint, swelling, and fever. Aspiration of the joint reveals turbid fluid, with >50,000 PMNs/μL and gram-positive cocci in clusters on Gram's stain (Fig. 142-1). In adults, septic arthritis may result from trauma, surgery, or hematogenous dissemination. The most commonly involved joints include the knees, shoulders, hips, and phalanges. Infection frequently develops in joints previously damaged by osteoarthritis or rheumatoid arthritis. Iatrogenic infections resulting from aspiration or injection of agents into the joint also occur. In these settings, the patient experiences increased pain and swelling in the involved joint in association with fever.

Pyomyositis is an unusual infection of skeletal muscles that is seen primarily in tropical climates but also occurs in immunocompromised and HIV-infected patients. It is believed to arise from occult bacteremia. Pyomyositis presents as fever, swelling, and pain overlying the involved muscle. Aspiration of fluid from the involved tissue yields pus. Although a history of trauma may be associated with the infection, its pathogenesis is poorly understood.

Respiratory Tract Infections Respiratory tract infections caused by *S. aureus* occur in selected clinical settings. *S. aureus* is a cause of serious respiratory tract infections in newborns and infants; these infections present with shortness of breath, fever, and respiratory failure. Chest x-ray may reveal pneumatoceles (shaggy, thin-walled cavities). Pneumothorax and empyema are recognized complications.

In adults, nosocomial *S. aureus* pulmonary infections are common among intubated patients in intensive care units. Nasally colonized patients are at increased risk of these infections. The clinical presentation is no different from that encountered in pulmonary infections caused by other bacterial pathogens. Patients produce increased volumes of purulent sputum and develop respiratory distress, fever, and new pulmonary infiltrates. Distinguishing bacterial pneumonia from respiratory failure or other causes of new pulmonary infiltrates in critically ill patients is difficult and relies on a constellation of clinical, radiologic, and laboratory findings.

Community-acquired respiratory tract infections due to *S. aureus* often follow viral infections—most commonly influenza. Patients may present with fever, bloody sputum production, and midlung-field pneumatoceles or multiple, patchy pulmonary infiltrates. Diagnosis is made by sputum Gram's stain and culture. Blood cultures, although useful, are usually negative.

Bacteremia, Sepsis, and Infective Endocarditis *S. aureus* bacteremia may be complicated by sepsis, endocarditis, vasculitis, or metastatic seeding (establishment of suppurative collections at other tissue sites). Among the more commonly seeded tissue sites are bones, joints, kidneys, and lungs. The frequency of metastatic seeding during bacteremia has been estimated to be as high as 31%. The incidence of complications increases with the duration of the bacteremia.

Recognition of these complications by clinical and laboratory diagnostic methods alone is often difficult. Comorbid conditions that are frequently seen in association with *S. aureus* bacteremia and that increase the risk of complications include diabetes, HIV infection, and renal insufficiency. Other host factors associated with an increased risk of complications include presentation with community-acquired *S. aureus* bacteremia (except in injection drug users), lack of an identifiable primary focus of infection, and the presence of prosthetic devices or material.

Clinically, *S. aureus* sepsis presents in a manner similar to that documented for sepsis due to other bacteria. The well-described progression of hemodynamic changes—beginning with respiratory alkalosis and clinical findings of hypotension and fever—is commonly seen. The microbiologic diagnosis is established by positive blood cultures.

The overall incidence of *S. aureus* endocarditis has increased over the past 20 years. *S. aureus* is now the leading cause of endocarditis worldwide, accounting for 25–35% of cases. This increase is due, at least in part, to the increased use of intravascular devices. Studies using transesophageal echocardiography found an endocarditis incidence of ~25% among patients with intravascular catheter–associated *S. aureus* bacteremia. Other factors associated with an increased risk of endocarditis are injection drug use, hemodialysis, the presence of intravascular prosthetic devices at the time of bacteremia, and immunosuppression. Patients with implantable cardiac devices (e.g., permanent pacemakers) are at increased risk of endocarditis or device-related infections. Despite the availability of effective antibiotics, mortality rates from these infections continue to range from 20% to 40%, depending on both the host and the nature of the infection. Complications of *S. aureus* endocarditis include cardiac valvular insufficiency, peripheral emboli, metastatic seeding, vasculitis, and central nervous system (CNS) involvement (e.g., mycotic aneurysms, embolic strokes).

S. aureus endocarditis is encountered in four clinical settings: (1) right-sided endocarditis in association with injection drug use, (2)

left-sided native-valve endocarditis, (3) prosthetic-valve endocarditis, and (4) nosocomial endocarditis. In each of these settings, the diagnosis is suspected from the patient's history and the recognition of clinical stigmata suggestive of endocarditis. These findings include cardiac manifestations, such as new or changing cardiac valvular murmurs; cutaneous evidence, such as vasculitic lesions, Osler's nodes, or Janeway lesions; evidence of right- or left-sided embolic disease; and a history suggesting a risk for *S. aureus* bacteremia. In the absence of antecedent antibiotic therapy, blood cultures are almost uniformly positive. Transthoracic echocardiography, while less sensitive than transesophageal echocardiography, is less invasive and identifies valvular vegetations. The Duke criteria **(see Table 123-3)** are now commonly used to help establish the likelihood of this diagnosis.

Acute right-sided tricuspid valvular *S. aureus* endocarditis is most often seen in injection drug users. The classic presentation includes a high fever, a toxic clinical appearance, pleuritic chest pain, and the production of purulent (sometimes bloody) sputum. Chest x-rays or CT scans reveal evidence of septic pulmonary emboli (small, peripheral, circular lesions that may cavitate with time) **(Fig. 142-3)**. A high percentage of affected patients have no history of antecedent valvular damage. At the outset of their illness, patients may present with fever alone, without cardiac or other localizing findings. As a result, a high index of clinical suspicion is essential for diagnosis.

Individuals with antecedent cardiac valvular damage more commonly present with left-sided native-valve endocarditis involving the damaged valve. These patients tend to be older than those with right-sided endocarditis, their prognosis is worse, and their incidence of complications (including peripheral emboli, cardiac decompensation, and metastatic seeding) is higher.

S. aureus is one of the more common causes of prosthetic-valve endocarditis. This infection is especially fulminant in the early postoperative period and is associated with a high mortality rate. In most instances, medical therapy alone is not sufficient and urgent valve replacement is necessary. Patients are prone to develop valvular insufficiency or myocardial abscesses originating from the region of valve implantation.

The increased frequency of nosocomial endocarditis (15–30% of cases, depending on the series) reflects in part the increased use of intravascular devices. This form of endocarditis is most commonly caused by *S. aureus*. Because patients often are critically ill, are receiving antibiotics for various other indications, and have comorbid conditions, the diagnosis is often missed.

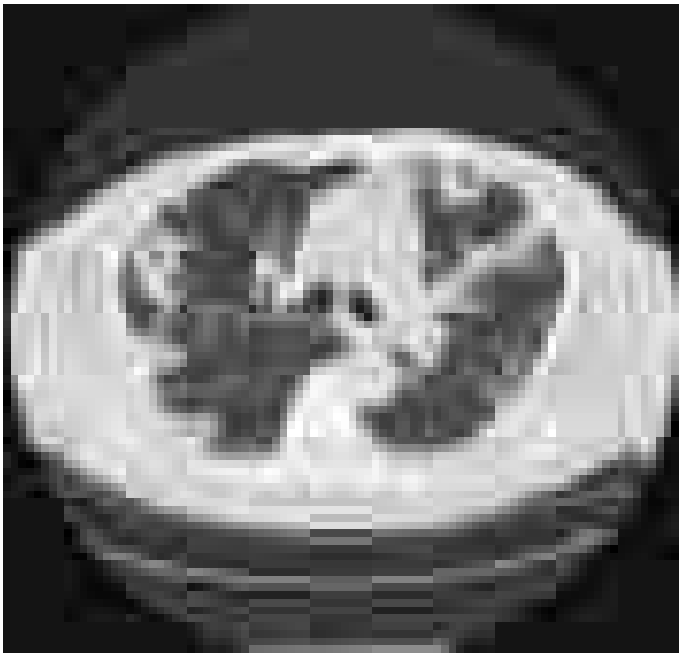

FIGURE 142-3 CT scan illustrating septic pulmonary emboli in a patient with methicillin-resistant *Staphylococcus aureus* bacteremia.

Prosthetic Device–Related Infections *S. aureus* accounts for a large proportion of prosthetic device–related infections. These infections may involve intravascular catheters, prosthetic valves, orthopedic devices, peritoneal catheters, pacemakers, left-ventricular-assist devices, or vascular grafts. In contrast with the more indolent presentation of CoNS infections, *S. aureus* device-related infections are more acute, have both local and systemic manifestations, and tend to progress more rapidly. It is relatively common for a pyogenic collection to be present at the device site. Aspiration of these collections and performance of blood cultures are important components in establishing a diagnosis. *S. aureus* infections tend to occur more commonly soon after implantation unless the device is used for access (e.g., intravascular or hemodialysis catheters). In the latter instance, infections can occur at any time. As in most prosthetic-device infections, successful therapy usually involves removal of the device. Left in place, the device serves as a potential nidus for either persistent or recurrent infections.

Urinary Tract Infections Urinary tract infections (UTIs) are infrequently caused by *S. aureus*. The presence of *S. aureus* in the urine generally suggests hematogenous dissemination. Ascending *S. aureus* infections occasionally result from instrumentation of the genitourinary tract.

Infections Associated with Community-Acquired MRSA Although the skin and soft tissues are by far the most common sites of infection associated with CA-MRSA, 5–10% of these infections are invasive and can be life-threatening. The latter unique infections, including necrotizing fasciitis, necrotizing pneumonia, and sepsis with Waterhouse-Friderichsen syndrome or purpura fulminans, were rarely associated with *S. aureus* prior to the emergence of CA-MRSA. These life-threatening infections reflect the increased virulence of CA-MRSA strains.

Toxin-Mediated Diseases • **FOOD POISONING** *S. aureus* is among the most common causes of foodborne outbreaks in the United States. Staphylococcal food poisoning results from the inoculation of toxin-producing *S. aureus* into food by colonized food handlers. Toxin is then elaborated in such growth-promoting food as custards, potato salad, or processed meats. Even if the bacteria are killed by warming, the heat-stable toxin is not destroyed. The onset of illness is rapid, occurring within 1–6 h of ingestion. The illness is characterized by nausea and vomiting, although diarrhea, hypotension, and dehydration also may occur. The differential diagnosis includes diarrhea of other etiologies, especially that caused by similar toxins (e.g., the toxins elaborated by *Bacillus cereus*). The rapidity of onset, the absence of fever, and the epidemic nature of the presentation (without secondary spread) should arouse suspicion of staphylococcal food poisoning. Symptoms generally resolve within 8–10 h. The diagnosis can be established by the demonstration of bacteria or the documentation of enterotoxin in the implicated food. Treatment is entirely supportive.

TOXIC SHOCK SYNDROME TSS gained attention in the early 1980s, when a nationwide outbreak occurred in the United States among young, otherwise healthy, menstruating women. Epidemiologic investigation demonstrated that these cases were associated with the use of a highly absorbent tampon that had recently been introduced to the market. Subsequent studies established the role of TSST-1 in these illnesses. Withdrawal of the tampon from the market resulted in a rapid decline in the incidence of this disease. However, menstrual and nonmenstrual cases continue to be reported. Nonmenstrual cases are frequently seen in patients with surgical or postpartum wound infections, especially when packing of the wound occurs.

The clinical presentation is similar in menstrual and nonmenstrual TSS. Evidence of clinical *S. aureus* infection is not a prerequisite. TSS results from the elaboration of an enterotoxin or the structurally related enterotoxin-like TSST-1. More than 90% of menstrual cases are caused by TSST-1, whereas a high percentage of nonmenstrual cases are caused by enterotoxins (e.g., enterotoxin B). TSS begins with relatively nonspecific flulike symptoms. In menstrual cases, the onset usually comes 2 or 3 days after the start of menstruation. Patients present with

TABLE 142-2 Case Definition of *Staphylococcus aureus* Toxic Shock Syndrome

Clinical Criteria
An illness with the following clinical manifestations:
• Fever: temperature ≥102.0°F (≥38.9°C)
• Rash: diffuse macular erythroderma
• Desquamation: 1–2 weeks after rash onset
• Hypotension: systolic blood pressure ≤90 mmHg for adults or less than the fifth percentile, by age, for children <16 years old
• Multisystem involvement (≥3 of the following organ systems)
◦ Gastrointestinal: vomiting or diarrhea at illness onset
◦ Muscular: severe myalgia or creatine phosphokinase level at least twice ULN
◦ Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
◦ Renal: blood urea nitrogen or creatinine level at least twice ULN for laboratory or urinary sediment with pyuria (≥5 leukocytes per high-power field) in the absence of urinary tract infection
◦ Hepatic: total bilirubin or aminotransferase level at least twice ULN for laboratory
◦ Hematologic: platelet count $<10^5$/μL
◦ Central nervous system: disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension
Laboratory Criteria
Negative results in the following tests, if obtained:
• Blood or cerebrospinal fluid cultures for another pathogen[a]
• Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles
Case Classification
Probable: a case that meets the laboratory criteria and in which four of the five clinical criteria are fulfilled
Confirmed: a case that meets the laboratory criteria and in which all five of the clinical criteria are fulfilled, including desquamation (unless the patient dies before desquamation occurs)

[a]Blood cultures may be positive for *S. aureus*.

Abbreviation: ULN, upper limit of normal.

Source: Centers for Disease Control and Prevention (*https://www.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/*).

fever, hypotension, and erythroderma of variable intensity. Mucosal involvement is common (e.g., conjunctival hyperemia). The illness can rapidly progress to symptoms that include vomiting, diarrhea, confusion, myalgias, and abdominal pain. These symptoms reflect the multisystemic nature of the disease, with involvement of the liver, kidneys, gastrointestinal tract, and/or CNS. Desquamation of the skin occurs during convalescence, usually 1–2 weeks after the onset of illness. Laboratory findings may include azotemia, leukocytosis, hypoalbuminemia, thrombocytopenia, and liver function abnormalities.

Diagnosis of TSS still depends on a constellation of findings rather than one specific finding and on a lack of evidence of other possible infections **(Table 142-2)**. Other diagnoses to be considered are drug toxicities, viral exanthems, Rocky Mountain spotted fever, sepsis, and Kawasaki disease. Illness occurs only in persons who lack antibody to TSST-1. Recurrences are possible if antibody fails to develop after the illness.

STAPHYLOCOCCAL SCALDED-SKIN SYNDROME SSSS primarily affects newborns and children. The illness may vary from a localized blister to exfoliation of much of the skin surface. The skin is usually fragile and often tender, with thin-walled, fluid-filled bullae. Gentle pressure results in rupture of the lesions, leaving denuded underlying skin. The mucous membranes are usually spared. In more generalized infection, there are often constitutional symptoms, including fever, lethargy, and irritability with poor feeding. Significant amounts of fluid can be lost in more extensive cases. Illness usually follows localized infection at one of a number of possible sites. SSSS is much less common among adults but can follow infections caused by exfoliative toxin–producing strains.

COAGULASE-NEGATIVE STAPHYLOCOCCAL INFECTIONS

Although considerably less virulent than *S. aureus*, CoNS are among the most common causes of prosthetic-device infections, including endocarditis. They also are increasingly a cause of native-valve endocarditis and life-threatening infections in neonates and in neutropenic patients. Approximately half of the identified CoNS species have been associated with human infections. Of these species, *Staphylococcus epidermidis* is the most common human pathogen. It is part of the normal human flora and is found on the skin (where it is the most abundant bacterial species) as well as in the oropharynx and vagina. *Staphylococcus saprophyticus*, a novobiocin-resistant species, is a common pathogen in UTIs.

PATHOGENESIS

S. epidermidis is the CoNS species most often associated with prosthetic-device infections. Infection is a two-step process, with initial adhesion to the device followed by colonization. *S. epidermidis* is uniquely adapted to colonize these devices because of its capacity to elaborate the extracellular polysaccharide (glycocalyx or slime) that facilitates formation of a protective biofilm on the device surface.

Implanted prosthetic material is rapidly coated with host serum or tissue constituents such as fibrinogen or fibronectin. These molecules serve as potential bridging ligands, facilitating initial bacterial attachment to the device surface. A number of staphylococcal surface-associated proteins, such as autolysin (AtlE), fibrinogen-binding protein, and accumulation-associated protein (AAP), appear to play a role in attachment to either modified or unmodified prosthetic surfaces. The polysaccharide intercellular adhesin facilitates subsequent staphylococcal colonization and accumulation on the device surface. Intercellular adhesin (*ica*) genes are more commonly found in strains of *S. epidermidis* that are associated with device infections than in strains associated with colonization of mucosal surfaces. Biofilm acts as a barrier, protecting bacteria from host defense mechanisms as well as from antibiotics while providing a suitable environment for bacterial maturation, survival, and potentially spread to other tissue sites.

Two additional CoNS species, *Staphylococcus lugdunensis* and *Staphylococcus schleiferi*, produce more serious infections (native-valve endocarditis and osteomyelitis) than do other CoNS. The basis for this enhanced virulence is not known, although both species appear to share more virulence determinants with *S. aureus* (e.g., clumping factor and lipase) than do other CoNS.

The capacity of *S. saprophyticus* to cause UTIs in young women appears to be related to its enhanced capacity to adhere to uroepithelial cells. A 160-kDa hemagglutinin/adhesin may contribute to this affinity.

DIAGNOSIS

Although the detection of CoNS at sites of infection or in the bloodstream by standard microbiologic culture methods is not difficult, interpretation of these results is frequently problematic. Because these organisms are present in large numbers on the skin, they often contaminate cultures. It has been estimated that only 10–20% of blood cultures positive for CoNS reflect true bacteremia. Similar problems arise with cultures obtained from other sites. Among the clinical findings suggestive of true bacteremia are fever, evidence of local infection (e.g., erythema or purulent drainage at the IV catheter site), leukocytosis, and systemic signs of sepsis. Laboratory findings suggestive of true bacteremia include repeated isolation of the same strain (i.e., the same species with the same antibiogram or with a closely related DNA fingerprint) from separate cultures, growth of the strain within 48 h, and bacterial growth in both aerobic and anaerobic bottles.

CLINICAL SYNDROMES

CoNS cause a diverse array of prosthetic device–related infections, including those that involve prosthetic cardiac valves and joints, vascular grafts, intravascular devices, and CNS shunts. In all of these settings, the clinical presentation is similar. The signs of localized infection are often subtle, the rate of disease progression is slow, and

the systemic findings are often limited. Signs of infection, such as purulent drainage, pain at the site, or loosening of prosthetic implants, are sometimes evident. Fever is frequently but not always present, and there may be mild leukocytosis. Acute-phase reactant levels, the erythrocyte sedimentation rate, and the C-reactive protein concentration may be elevated.

Infections that are not associated with prosthetic devices include, as noted, native-valve endocarditis due to CoNS, which accounts for ~5% of cases. Infections in preterm infants and neutropenic patients are often associated with the need for intravascular devices. *S. lugdunensis* appears to be a more aggressive pathogen in this setting, causing greater mortality and rapid valvular destruction with abscess formation.

TREATMENT

Staphylococcal Infections

GENERAL PRINCIPLES OF THERAPY

Source control (e.g., incision and drainage of suppurative collections or removal of infected prosthetic devices), coupled with rapid institution of appropriate antimicrobial therapy, is essential for the management of all staphylococcal infections. The emergence of MRSA in the community has increased the importance of culturing all collections in order to determine antimicrobial susceptibility.

DURATION OF ANTIMICROBIAL THERAPY

Therapy for *S. aureus* bacteremia is generally prolonged (4–6 weeks) because of the high risk of complications (e.g., endocarditis, metastatic foci of infection). Among the findings associated with complicated bacteremias are (1) persistently positive blood cultures 96 h after institution of therapy, (2) acquisition of the infection in the community, (3) failure to promptly remove or drain an identified focus of infection (i.e., an intravascular catheter), and (4) the presence of deep-seated infections. Patients with uncomplicated bacteremias are generally defined by a removable focus of infection, prompt response to antimicrobial therapy (i.e., no fever or positive blood cultures after 3–4 days), no evidence of metastatic foci of infection, and no implanted prostheses. In these infections, short-course therapy (2 weeks) can be given. Transesophageal echocardiography to rule out endocarditis is generally necessary because neither clinical nor laboratory findings can reliably detect cardiac involvement. A thorough radiologic investigation to identify potential metastatic collections is also indicated. All symptomatic body sites must be carefully evaluated.

CHOICE OF ANTIMICROBIAL AGENTS

The choice of antimicrobial agents to treat both coagulase-positive and coagulase-negative staphylococcal infections is often problematic because of the prevalence of multidrug-resistant strains and the absence of comparative clinical trials. Staphylococcal resistance to most antibiotic families, including β-lactams, aminoglycosides, fluoroquinolones, and (to a lesser extent) glycopeptides, has increased. This trend is even more apparent with CoNS; >80% of nosocomial isolates are resistant to methicillin, and these methicillin-resistant strains are often resistant to many other antibiotics. Because the selection of antimicrobial agents for *S. aureus* infections is similar to that for CoNS infections, treatment options for these pathogens are discussed together and are summarized in **Table 142-3**.

As a result of the widespread dissemination of plasmids containing the enzyme penicillinase, few strains of staphylococci (≤5%) remain susceptible to penicillin. Penicillin-resistant isolates are treated with semisynthetic penicillinase-resistant penicillins (SPRPs), such as oxacillin or nafcillin. Methicillin, the first of the SPRPs, is no longer used. Cephalosporins are alternative therapeutic agents for these infections. Second- and third-generation cephalosporins offer no therapeutic advantage over first-generation cephalosporins for the treatment of staphylococcal infections, and some third-generation cephalosporins (e.g., ceftazidime) have considerably less activity. The carbapenems also have excellent activity against methicillin-sensitive *S. aureus* but not against MRSA.

The isolation of MRSA was reported within 1 year of the introduction of methicillin. Since then, the prevalence of MRSA has steadily increased. In many U.S. hospitals, 40–50% of *S. aureus* isolates are resistant to methicillin. This trend has also been observed in many other countries. Resistance to methicillin indicates resistance to all SPRPs as well as to all cephalosporins (except ceftaroline). Production of a novel penicillin-binding protein (PBP2a) is responsible for methicillin resistance. This protein is synthesized by the *mecA* gene, which (as stated above) is part of a large mobile genetic element—a pathogenicity or genomic island—called SCC*mec*. It is hypothesized that this genetic material was acquired via horizontal transfer from *Staphylococcus sciuri*, a related staphylococcal species. Phenotypic expression of methicillin resistance may be constitutive (i.e., expressed in all cells in a population) or heterogeneous (i.e., displayed by only a proportion of the total cell population). Detection of methicillin resistance is enhanced by growth of cultures at reduced temperatures (≤35°C for 24 h) and with increased concentrations of salt in the medium. Culture techniques are increasingly being replaced by PCR-based or other methods (e.g., latex agglutination) that allow the rapid detection of methicillin resistance.

Vancomycin or daptomycin is recommended as the drug of choice for the treatment of invasive MRSA infections. MRSA susceptibility to vancomycin has decreased in many areas of the world. It is important to note that vancomycin is less effective than SPRPs for the treatment of infections due to methicillin-susceptible strains. In patients with a history of serious β-lactam allergies, alternatives to SPRPs for the treatment of invasive infections should be used only after careful consideration. Desensitization to β-lactams remains an option for life-threatening infections.

Three types of staphylococcal resistance to vancomycin have emerged. (1) Minimal inhibitory concentration (MIC; an in vitro measure of susceptibility) "creep" refers to the incremental increase in vancomycin MICs that has been detected in various geographic areas. Studies suggest that morbidity and mortality are increased in infections due to *S. aureus* strains with vancomycin MICs of ≥1.5 μg/mL. (2) In 1997, an *S. aureus* strain with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]) was reported from Japan. Subsequently, additional VISA clinical isolates were reported. These strains were resistant to methicillin and many other antimicrobial agents. The VISA strains appear to evolve (under vancomycin selective pressure) from strains that are susceptible to vancomycin but are heterogeneous, with a small proportion of the bacterial population expressing the resistance phenotype. The mechanism of VISA resistance is in part due to an abnormally thick cell wall. Vancomycin is trapped by the abnormal peptidoglycan cross-linking and is unable to gain access to its target site. Regulatory genes involved in cell wall metabolism appear to play an important role in this type of resistance. (3) In 2002, the first clinical isolate of fully vancomycin-resistant *S. aureus* (VRSA) was reported. Resistance in this and several additional clinical isolates was due to the presence of *vanA*, the gene responsible for expression of vancomycin resistance in enterococci. This observation suggested that resistance was acquired as a result of horizontal conjugal transfer from a vancomycin-resistant strain of *Enterococcus faecalis*. Several patients had both MRSA and vancomycin-resistant enterococci cultured from infection sites. The *vanA* gene is responsible for the synthesis of the dipeptide D-Ala-D-Lac in place of D-Ala-D-Ala. Vancomycin cannot bind to the altered peptide. While isolates with MICs of ≥1.5 μg/mL have been relatively common in some areas, VISA and VRSA isolates remain rare.

Daptomycin, a parenteral bactericidal agent with antistaphylococcal activity, is approved for the treatment of bacteremia (including right-sided endocarditis) and complicated skin infections. It is not effective in respiratory infections. This drug has a unique mechanism of action: it disrupts the cytoplasmic membrane.

TABLE 142-3 Antimicrobial Therapy for Staphylococcal Infections[a]

SENSITIVITY/RESISTANCE OF ISOLATE	DRUG OF CHOICE	ALTERNATIVE(S)	COMMENTS
Parenteral Therapy for Serious Infections			
Sensitive to penicillin	Penicillin G (4 mU q4h)	Nafcillin or oxacillin (2 g q4h), cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8h[b])	Fewer than 5% of isolates are sensitive to penicillin. The clinical microbiology laboratory must verify that the strain is not a β-lactamase producer.
Sensitive to methicillin	Nafcillin or oxacillin (2 g q4h)	Cefazolin (2 g q8h), vancomycin (15–20 mg/kg q8h[b])	Patients with a penicillin allergy can be treated with a cephalosporin if the allergy does not involve an anaphylactic or accelerated reaction; desensitization to β-lactams may be indicated in selected cases of serious infection when maximal bactericidal activity is needed (e.g., prosthetic-valve endocarditis[c]). Type A β-lactamase may rapidly hydrolyze cefazolin and reduce its efficacy in endocarditis. Vancomycin is a less effective option than a β-lactam.
Resistant to methicillin	Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6–10 mg/kg IV q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	Linezolid (600 mg q12h PO or IV), ceftaroline (600 mg IV q8–12h), telavancin (7.5–10 mg/kg IV q24h)[b], TMP-SMX (5 mg [based on TMP]/kg IV q8–12h)[f] Newer agents include tedizolid (200 mg once daily IV or PO), oritavancin (single dose of 1200 mg), and dalbavancin (single dose of 1500 mg). These drugs are approved only for the treatment of skin and soft tissue infections.[g]	Sensitivity testing is necessary before an alternative drug is selected. The efficacy of adjunctive therapy is not well established in many settings. Linezolid, ceftaroline, and telavancin have in vitro activity against most VISA and VRSA strains. See footnote for treatment of prosthetic-valve endocarditis.[c]
Resistant to methicillin with intermediate or complete resistance to vancomycin[e]	Daptomycin (6–10 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	Same as for methicillin-resistant strains (check antibiotic susceptibilities) *or* Ceftaroline (600 mg IV q8–12h) Newer agents include tedizolid (200 mg once daily IV or PO), oritavancin (single dose of 1200 mg), and dalbavancin (single dose of 1500 mg). These drugs are approved only for the treatment of skin and soft tissue infections.	Same as for methicillin-resistant strains; check antibiotic susceptibilities. Ceftaroline is used either alone or in combination with daptomycin.
Not yet known (i.e., empirical therapy)	Vancomycin (15–20 mg/kg q8–12h[b]), daptomycin (6–10 mg/kg q24h[b,d]) for bacteremia, endocarditis, and complicated skin infections	—	Empirical therapy is given when the susceptibility of the isolate is not known. Vancomycin with or without a β-lactam is recommended for suspected community- or hospital-acquired *Staphylococcus aureus* infections because of the increased frequency of methicillin-resistant strains in the community. If isolates with an elevated MIC to vancomycin (≥1.5 μg/ml) are common in the community, daptomycin may be preferable.
Oral Therapy for Skin and Soft Tissue Infections			
Sensitive to methicillin	Dicloxacillin (500 mg qid), cephalexin (500 mg qid), or cefadroxil (1 g q12h)	Minocycline or doxycycline (100 mg q12h[b]), TMP-SMX (1 or 2 ds tablets bid), clindamycin (300–450 mg tid), linezolid (600 mg PO q12h), tedizolid (200 mg PO q24h)	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained and drainage should be cultured.
Resistant to methicillin	Clindamycin (300–450 mg tid), TMP-SMX (1 or 2 ds tablets bid), minocycline or doxycycline (100 mg q12h[b]), linezolid (600 mg bid), or tedizolid (200 mg once daily)	Same options as under "Drug of Choice"	It is important to know the antibiotic susceptibility of isolates in the specific geographic region. All collections should be drained and drainage should be cultured.

[a]Recommended dosages are for adults with normal renal and hepatic function. [b]The dosage must be adjusted for patients with reduced creatinine clearance. [c]For the treatment of prosthetic-valve endocarditis, the addition of gentamicin (1 mg/kg q8h) and rifampin (300 mg PO q8h) is recommended, with adjustment of the gentamicin dosage if the creatinine clearance rate is reduced. [d]Daptomycin cannot be used for the treatment of pneumonia. [e]Vancomycin-resistant *S. aureus* isolates from clinical infections have been reported. [f]TMP-SMX may be less effective than vancomycin. [g]Limited data are available on the efficacy of dalbavancin, oritavancin, and tedizolid for the treatment of invasive infections.

Abbreviations: ds, double-strength; TMP-SMX, trimethoprim-sulfamethoxazole; VISA, vancomycin-intermediate *S. aureus;* VRSA, vancomycin-resistant *S. aureus.*

Source: Modified from C Liu et al: Clin Infect Dis 52:285, 2011; DL Stevens et al: Clin Infect Dis 59:148, 2014; DL Stevens et al: Med Lett Drugs Ther 56:39, 2014; and LM Baddour et al: Circulation 132:1435, 2015.

Staphylococcal resistance to daptomycin has been reported. Resistance can emerge during therapy; patients previously treated with vancomycin may have elevated MICs of daptomycin. Patients need to be monitored for rhabdomyolysis with creatine phosphokinase measurement and for eosinophilic pneumonia.

Linezolid—the first oxazolidinone—is bacteriostatic against staphylococci; it offers the advantage of comparable bioavailability after oral or parenteral administration. Cross-resistance with other inhibitors of protein synthesis has not been detected. Resistance to linezolid has been increasingly reported. Serious adverse reactions to linezolid include thrombocytopenia, occasional cases of neutropenia, and rare instances of lactic acidosis or peripheral and optic neuropathy. These reactions tend to occur after a relatively prolonged course of therapy.

Tedizolid, a second oxazolidinone released in 2014, is available as both oral and parenteral preparations. It exhibits enhanced in vitro activity against antibiotic-resistant gram-positive bacteria, including staphylococci. Tedizolid is administered once a day. Data on its efficacy for the treatment of deep-seated infections are limited.

Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA (including strains with reduced susceptibility to vancomycin and daptomycin). It is generally well tolerated. Ceftaroline is approved for use in nosocomial pneumonias and for SSTIs.

Telavancin is a parenteral lipoglycopeptide derivative of vancomycin that is approved for the treatment of complicated SSTIs and for nosocomial pneumonias. The drug has two targets: the cell wall and the cell membrane. It remains active against VISA strains. Because of its potential nephrotoxicity, telavancin should be avoided in patients with renal disease.

The parenteral streptogramin antibiotic quinupristin/dalfopristin displays bactericidal activity against all staphylococci, including VISA strains. This drug, although infrequently used because of toxicity (infusion reactions), has been used successfully to treat serious MRSA infections. In cases of resistance to erythromycin or clindamycin, quinupristin/dalfopristin is bacteriostatic against staphylococci.

Dalbavancin and oritavancin are long-acting, parenterally administered lipoglycopeptides that have been used to treat complicated SSTIs. Because of their long half-lives, they can be administered on a weekly basis. Both have been used as single-dose regimens for the treatment of SSTIs. Data on their use for the treatment of invasive staphylococcal infections are limited.

Although the quinolones are active against staphylococci in vitro, the frequency of staphylococcal resistance to these agents has increased, especially among methicillin-resistant isolates. Of particular concern in MRSA is the possible emergence of quinolone resistance during therapy. Therefore, quinolones are not recommended for the treatment of MRSA infections. Resistance to the quinolones is most commonly chromosomal and results from mutations of the topoisomerase IV or DNA gyrase genes, although multidrug efflux pumps may also contribute. Although the newer quinolones exhibit increased in vitro activity against staphylococci, it is uncertain whether this increase translates into enhanced in vivo activity.

Tigecycline, a broad-spectrum minocycline analogue, has bacteriostatic activity against MRSA and is approved for use in SSTIs as well as intraabdominal infections caused by *S. aureus*. It is not recommended for the treatment of invasive infections. Other older antibiotics, such as minocycline, doxycycline, clindamycin, and trimethoprim-sulfamethoxazole, have been used successfully to treat MRSA infections.

Combinations of antistaphylococcal agents have been used to enhance bactericidal activity in the treatment of deep-seated infections, to shorten the duration of therapy (e.g., for right-sided endocarditis), or to optimize empirical therapy when the susceptibility of the isolate to methicillin is not yet known (e.g., using a β-lactam plus vancomycin). Among the additional antimicrobial agents often used are rifampin, gentamicin, or fusidic acid (not available in the United States). To date, clinical studies have not documented a therapeutic benefit from these different combinations; recent reports have raised concern about the potential nephrotoxicity of gentamicin and adverse reactions to/interactions with rifampin. As a result, the use of gentamicin in combination with β-lactams or other antimicrobial agents is no longer routinely recommended for the treatment of native-valve endocarditis. Rifampin continues to be used for the treatment of prosthetic device–related infections and for osteomyelitis.

ANTIMICROBIAL THERAPY FOR SELECTED SETTINGS

Empirical Therapy Empirical coverage for MRSA is generally indicated. Addition of a β-lactam to vancomycin provides more effective initial therapy should the isolate prove to be methicillin susceptible and may offer synergy in MRSA infections. It remains uncertain at present whether daptomycin is preferable when elevated vancomycin MICs (>1.5 μg/mL) are common in a specific locale.

Salvage Therapy Salvage therapy for complicated *S. aureus* infections is sometimes needed when the bacteremia persists (i.e., for more than 3 or 4 days) despite appropriate treatment. There is little high-quality evidence to serve as a guide to salvage therapy. The combination of daptomycin or vancomycin with a β-lactam antibiotic (e.g., ceftaroline) has been successfully used to treat patients with persistent MRSA bacteremia, even those with isolates displaying reduced susceptibility to these antimicrobial agents. This combination appears to enhance the bactericidal activity of daptomycin by reducing the bacterial cell-surface charge and thus allowing more daptomycin binding. For vancomycin, the combination may allow more strategic binding to the target site with reduced cell-wall thickness. Other combinations have included trimethoprim-sulfamethoxazole or rifampin combined with daptomycin. Linezolid or ceftaroline has also been used as a single alternative agent.

Endocarditis *S. aureus* endocarditis is usually an acute, life-threatening infection. Thus, prompt collection of blood for cultures should be followed by immediate institution of empirical antimicrobial therapy. For native-valve endocarditis, therapy with a β-lactam is recommended. If a MRSA strain is isolated, vancomycin (15–20 mg/kg every 8–12 h, given in equal doses up to a total of 2 g, with the dose adjusted in the case of renal disease) or daptomycin (6–10 mg/kg every 24 h) is recommended. The vancomycin dose should be adjusted on the basis of trough drug levels. Patients are generally treated for 6 weeks. For prosthetic-valve endocarditis, surgery in addition to antibiotic therapy is often necessary. The combination of a β-lactam agent—or, if the isolate is β-lactam-resistant, vancomycin or daptomycin—with an aminoglycoside (gentamicin, 1 mg/kg IV every 8 h) for 2 weeks and rifampin (300 mg orally or IV every 8 h) for ≥6 weeks is recommended.

Bone and Joint Infections For hematogenous osteomyelitis or septic arthritis in children, a 4-week course of therapy is usually adequate. In adults, treatment is often more prolonged. For chronic forms of osteomyelitis, surgical debridement is necessary in combination with antimicrobial therapy. For joint infections, a critical component of therapy is the repeated aspiration or arthroscopy of the affected joint to prevent damage from leukocytes. The combination of rifampin with ciprofloxacin has been used successfully to treat or suppress prosthetic-joint infections, especially when the device cannot be removed. The efficacy of this combination may reflect enhanced activity against staphylococci in biofilms as well as the attainment of effective intracellular concentrations.

Skin and Soft Tissue Infections The increase in SSTIs caused by CA-MRSA has drawn attention to the need for initiation of appropriate empirical therapy. Many of these infections respond to incision and drainage alone without antibiotics. Antibiotics are selected depending on local antibiotic susceptibility data; a number of oral agents have been used to treat these infections, including clindamycin, trimethoprim-sulfamethoxazole, doxycycline, linezolid, and tedizolid. Parenteral therapy is reserved for more complicated infections.

Toxic Shock Syndrome Supportive therapy with reversal of hypotension is the mainstay of therapy for TSS. Both fluids and

pressors may be necessary. Tampons or other packing material should be promptly removed. Some investigators recommend therapy with a combination of clindamycin and a semisynthetic penicillin or (if the isolate is resistant to methicillin) vancomycin. Clindamycin is advocated because, as a protein synthesis inhibitor, it reduces toxin synthesis in vitro. Linezolid also appears to be effective. A semisynthetic penicillin or a glycopeptide is recommended to eliminate any potential focus of infection as well as to eradicate persistent carriage that might increase the likelihood of recurrent illness. Anecdotal reports document the successful use of IV immunoglobulin to treat TSS. Glucocorticoids are not recommended for the treatment of this disease.

Other Toxin-Mediated Diseases Therapy for staphylococcal food poisoning is entirely supportive. For SSSS, antistaphylococcal therapy targets the primary site of infection.

PREVENTION

Primary prevention of *S. aureus* infections in the hospital setting involves hand washing and careful attention to appropriate isolation procedures. Through careful screening for MRSA carriage and strict isolation practices, several Scandinavian countries have been remarkably successful at preventing the introduction and dissemination of MRSA in hospitals.

Decolonization strategies, using both universal and targeted approaches with topical agents (e.g., mupirocin) to eliminate nasal colonization and/or chlorhexidine to eliminate colonization of additional body sites with *S. aureus*, have been successful in some clinical settings where the risk of infection is high (e.g., intensive care units). An analysis of clinical trials suggests that the incidence of postsurgical infections may be reduced among persons who are nasally colonized with *S. aureus*.

"Bundling" (the application of selected medical interventions in a sequence of prescribed steps) has reduced rates of nosocomial infections related to such procedures as the insertion of intravenous catheters, in which staphylococci are among the most common pathogens **(see Table 137-3)**. A number of immunization strategies to prevent *S. aureus* infections—both active (e.g., capsular polysaccharide–protein conjugate vaccine) and passive (e.g., clumping factor antibody)—have been investigated. However, none has been successful for either prophylaxis or therapy in clinical trials.

Strategies to prevent recurrent *S. aureus* infections in the community have had limited success. Decolonization with intranasal mupirocin and chlorhexidine washes of the infected individual and the additional decolonization of household members combined with environmental cleaning of surfaces and personal items have all been studied. For individuals with extensive skin disease and recurrent infections, the use of bleach baths (e.g., one-half cup of bleach in a one-quarter-filled bathtub) may be useful.

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143 Streptococcal Infections

Michael R. Wessels

Many varieties of streptococci are found as part of the normal flora colonizing the human respiratory, gastrointestinal, and genitourinary tracts. Several species are important causes of human disease. Group A *Streptococcus* (GAS, *Streptococcus pyogenes*) is responsible for streptococcal pharyngitis, one of the most common bacterial infections of school-age children, and for the postinfectious syndromes of acute rheumatic fever (ARF) and poststreptococcal glomerulonephritis (PSGN). Group B *Streptococcus* (GBS, *Streptococcus agalactiae*) is the leading cause of bacterial sepsis and meningitis in newborns and a major cause of endometritis and fever in parturient women. Viridans streptococci are the most common cause of bacterial endocarditis. Enterococci, which are morphologically similar to streptococci, are now considered a separate genus on the basis of DNA homology studies. Thus, the species previously designated as *Streptococcus faecalis* and *Streptococcus faecium* have been renamed *Enterococcus faecalis* and *Enterococcus faecium*, respectively. **The enterococci are discussed in Chap. 144.**

Streptococci are gram-positive, spherical to ovoid bacteria that characteristically form chains when grown in liquid media. Most streptococci that cause human infections are facultative anaerobes, although some are strict anaerobes. Streptococci are relatively fastidious organisms, requiring enriched media for growth in the laboratory. Clinicians and clinical microbiologists identify streptococci by several classification systems, including hemolytic pattern, Lancefield group, species name, and common or trivial name. Many streptococci associated with human infection produce a zone of complete (β) hemolysis around the bacterial colony when cultured on blood agar. The β-hemolytic streptococci that form large (≥0.5-mm) colonies on blood agar can be classified by the Lancefield system, a serologic grouping based on the reaction of specific antisera with bacterial cell-wall carbohydrate antigens. With rare exceptions, organisms belonging to Lancefield groups A, B, C, and G are all β-hemolytic, and each is associated with characteristic patterns of human infection. Other streptococci produce a zone of partial (α) hemolysis, often imparting a greenish appearance to the agar. These α-hemolytic streptococci are further identified by biochemical testing and include *Streptococcus pneumoniae* **(Chap. 141)**, an important cause of pneumonia, meningitis, and other infections, and the several species referred to collectively as the *viridans streptococci*, which are part of the normal oral flora and are important agents of subacute bacterial endocarditis. Finally, some streptococci are nonhemolytic, a pattern sometimes called γ *hemolysis*. Among the organisms classified serologically as group D streptococci, the enterococci are classified as a distinct genus **(Chap. 144)**. The classification of the major streptococcal groups causing human infections is outlined in **Table 143-1**.

GROUP A STREPTOCOCCI

Lancefield's group A consists of a single species, *S. pyogenes*. As its species name implies, this organism is associated with a variety of suppurative infections. In addition, GAS can trigger the postinfectious syndromes of ARF (which is uniquely associated with *S. pyogenes* infection; **Chap. 352**) and PSGN **(Chap. 308)**.

Worldwide, GAS infections and their postinfectious sequelae (primarily ARF and rheumatic heart disease) account for an estimated 500,000 deaths per year. Although data are incomplete, the incidence of all forms of GAS infection and that of rheumatic heart disease are thought to be tenfold higher in resource-limited countries than in developed countries **(Fig. 143-1)**.

PATHOGENESIS

GAS elaborates a number of cell-surface components and extracellular products important in both the pathogenesis of infection and the human immune response. The cell wall contains a carbohydrate antigen that may be released by acid treatment. The reaction of such acid extracts with group A–specific antiserum is the basis for definitive

TABLE 143-1 Classification of Streptococci

LANCEFIELD GROUP	REPRESENTATIVE SPECIES	HEMOLYTIC PATTERN	TYPICAL INFECTIONS
A	*S. pyogenes*	β	Pharyngitis, impetigo, cellulitis, scarlet fever
B	*S. agalactiae*	β	Neonatal sepsis and meningitis, puerperal infection, urinary tract infection, diabetic ulcer infection, endocarditis
C, G	*S. dysgalactiae* subsp. *equisimilis*	β	Cellulitis, bacteremia, endocarditis
D	Enterococci[a]: *E. faecalis*, *E. faecium*	Usually nonhemolytic	Urinary tract infection, nosocomial bacteremia, endocarditis
	Nonenterococci: *S. gallolyticus* (formerly *S. bovis*)	Usually nonhemolytic	Bacteremia, endocarditis
Variable or nongroupable	Viridans streptococci: *S. sanguis*, *S. mitis*	α	Endocarditis, dental abscess, brain abscess
	Intermedius or *milleri* group: *S. intermedius*, *S. anginosus*, *S. constellatus*	Variable	Brain abscess, visceral abscess
	Anaerobic streptococci[b]: *Peptostreptococcus magnus*	Usually nonhemolytic	Sinusitis, pneumonia, empyema, brain abscess, liver abscess

[a]See Chap. 144. [b]See Chap. 172.

identification of a streptococcal strain as *S. pyogenes*. The major surface protein of GAS is M protein, which is the basis for the serotyping of strains with specific antisera. The M protein molecules are fibrillar structures anchored in the cell wall of the organism that extend as hair-like projections away from the cell surface. The amino acid sequence of the distal or amino-terminal portion of the M protein molecule is variable, accounting for the antigenic variation of the different M types, while more proximal regions of the protein are relatively conserved. A newer technique for assignment of M type to GAS isolates uses the polymerase chain reaction to amplify the variable region of the *emm* gene, which encodes M protein. DNA sequence analysis of the amplified gene segment can be compared with an extensive database (developed at the Centers for Disease Control and Prevention [CDC]) for assignment of *emm* type. Use of *emm* typing has increased the number of identified *emm* types to more than 200. This method eliminates the need for typing sera, which are available in only a few reference laboratories. The presence of M protein on a GAS isolate correlates with its capacity to resist phagocytic killing in fresh human blood. This phenomenon appears to be due, at least in part, to the binding of plasma fibrinogen to M protein molecules on the streptococcal surface, which interferes with complement activation and deposition of opsonic complement fragments on the bacterial cell. This resistance to phagocytosis may be overcome by M protein–specific antibodies; thus individuals with antibodies to a given M type acquired as a result of prior infection are protected against subsequent infection with organisms of the same M type but not against that with different M types.

GAS also elaborates, to varying degrees, a polysaccharide capsule composed of hyaluronic acid. While most clinical isolates of GAS produce a hyaluronic acid capsule, strains of M type 4 or 22 lack a capsule, as do some isolates of M type 89. The fact that acapsular strains have been associated with pharyngitis and invasive infection implies that the capsule is not essential for virulence. The production of large amounts of capsule by certain strains imparts a characteristic mucoid appearance to the colonies. The capsular polysaccharide plays an important role in protecting GAS from ingestion and killing by phagocytes. In contrast to M protein, the hyaluronic acid capsule is a weak immunogen, and antibodies to hyaluronate have not been shown to be important in protective immunity. The presumed explanation is the apparent structural identity between streptococcal hyaluronic acid and the hyaluronic acid of mammalian connective tissues. The capsular polysaccharide may also play a role in GAS colonization of the pharynx by binding to CD44, a hyaluronic acid–binding protein expressed on human pharyngeal epithelial cells.

GAS produces a large number of extracellular products that may be important in local and systemic toxicity and in the spread of infection through tissues. These products include streptolysins S and O, toxins that damage cell membranes and account for the hemolysis produced by the organisms; streptokinase; DNAses; SpyCEP, a serine protease

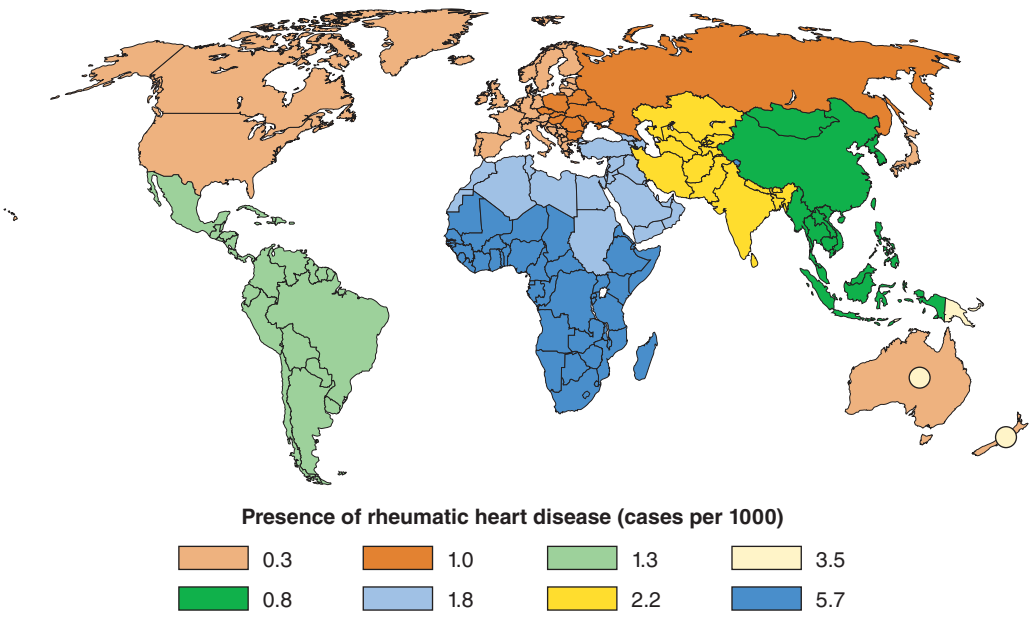

FIGURE 143-1 Prevalence of rheumatic heart disease in children 5–14 years old. The *circles* within Australia and New Zealand represent indigenous populations (and also Pacific Islanders in New Zealand). *(From JR Carapetis et al: Lancet Infect Dis 5:685, 2005, with permission.)*

that cleaves and inactivates the chemoattractant cytokine interleukin 8, thereby inhibiting neutrophil recruitment to the site of infection; and several pyrogenic exotoxins. Previously known as erythrogenic toxins, the pyrogenic exotoxins cause the rash of scarlet fever. Since the mid-1980s, pyrogenic exotoxin–producing strains of GAS have been linked to unusually severe invasive infections, including necrotizing fasciitis and the streptococcal toxic shock syndrome (TSS). Several extracellular products stimulate specific antibody responses useful for serodiagnosis of recent streptococcal infection. Tests for antibodies to streptolysin O and DNase B are used most commonly for detection of preceding streptococcal infection in cases of suspected ARF or PSGN.

CLINICAL MANIFESTATIONS

Pharyngitis Although seen in patients of all ages, GAS pharyngitis is one of the most common bacterial infections of childhood, accounting for 20–40% of all cases of exudative pharyngitis in children; it is rare among those under the age of 3. Younger children may manifest streptococcal infection with a syndrome of fever, malaise, and lymphadenopathy without exudative pharyngitis. Infection is acquired through contact with another individual carrying the organism. Respiratory droplets are the usual mechanism of spread, although other routes, including food-borne outbreaks, have been well described. The incubation period is 1–4 days. Symptoms include sore throat, fever and chills, malaise, and sometimes abdominal complaints and vomiting, particularly in children. Both symptoms and signs are quite variable, ranging from mild throat discomfort with minimal physical findings to high fever and severe sore throat associated with intense erythema and swelling of the pharyngeal mucosa and the presence of purulent exudate over the posterior pharyngeal wall and tonsillar pillars. Enlarged, tender anterior cervical lymph nodes commonly accompany exudative pharyngitis.

The differential diagnosis of streptococcal pharyngitis includes the many other bacterial and viral etiologies (Table 143-2). Streptococcal infection is an unlikely cause when symptoms and signs suggestive of viral infection are prominent (conjunctivitis, coryza, cough, hoarseness, or discrete ulcerative lesions of the buccal or pharyngeal mucosa). Because of the range of clinical presentations of streptococcal pharyngitis and the large number of other agents that can produce the same clinical picture, diagnosis of streptococcal pharyngitis on clinical grounds alone is not reliable. The throat culture remains the diagnostic gold standard. Culture of a throat specimen that is properly collected (i.e., by vigorous rubbing of a sterile swab over both tonsillar pillars) and properly processed is the most sensitive and specific means of definitive diagnosis. A rapid diagnostic kit for latex agglutination or enzyme immunoassay of swab specimens is a useful adjunct to throat culture. While precise figures on sensitivity and specificity vary, rapid diagnostic kits generally are >95% specific. Thus a positive result can be relied upon for definitive diagnosis and eliminates the need for throat culture. However, because rapid diagnostic tests are less sensitive than throat culture (relative sensitivity in comparative studies, 55–90%), a negative result should be confirmed by throat culture.

TABLE 143-2 Infectious Etiologies of Acute Pharyngitis

ORGANISM	ASSOCIATED CLINICAL SYNDROME(S)
Viruses	
Rhinovirus	Common cold
Coronavirus	Common cold
Adenovirus	Pharyngoconjunctival fever
Influenza virus	Influenza
Parainfluenza virus	Cold, croup
Coxsackievirus	Herpangina, hand-foot-and-mouth disease
Herpes simplex virus	Gingivostomatitis (primary infection)
Epstein-Barr virus	Infectious mononucleosis
Cytomegalovirus	Mononucleosis-like syndrome
HIV	Acute (primary) infection syndrome
Bacteria	
Group A streptococci	Pharyngitis, scarlet fever
Group C or G streptococci	Pharyngitis
Mixed anaerobes	Vincent's angina
Arcanobacterium haemolyticum	Pharyngitis, scarlatiniform rash
Neisseria gonorrhoeae	Pharyngitis
Treponema pallidum	Secondary syphilis
Francisella tularensis	Pharyngeal tularemia
Corynebacterium diphtheriae	Diphtheria
Yersinia enterocolitica	Pharyngitis, enterocolitis
Yersinia pestis	Plague
Chlamydiae	
Chlamydia pneumoniae	Bronchitis, pneumonia
Chlamydia psittaci	Psittacosis
Mycoplasmas	
Mycoplasma pneumoniae	Bronchitis, pneumonia

TREATMENT

GAS Pharyngitis

In the usual course of uncomplicated streptococcal pharyngitis, symptoms resolve after 3–5 days. The course is shortened little by treatment, which is given primarily to prevent suppurative complications and ARF. Prevention of ARF depends on eradication of the organism from the pharynx, not simply on resolution of symptoms, and requires 10 days of penicillin treatment (Table 143-3). A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever).

Alternative agents are erythromycin and azithromycin. Azithromycin is more expensive but offers the advantages of better gastrointestinal tolerability, once-daily dosing, and a 5-day treatment course. Resistance to erythromycin and other macrolides is common among isolates from several countries, including Spain, Italy, Finland, Japan, and Korea. Macrolide resistance may be becoming more prevalent elsewhere with the increasing use of this class of antibiotics. In areas with resistance rates exceeding 5–10%, macrolides should be avoided unless results of susceptibility testing are known.

TABLE 143-3 Treatment of Group A Streptococcal Infections

INFECTION	TREATMENT[a]
Pharyngitis	Benzathine penicillin G (1.2 mU IM) *or* penicillin V (250 mg PO tid or 500 mg PO bid) × 10 days (Children <27 kg: Benzathine penicillin G [600,000 units IM] *or* penicillin V [250 mg PO bid or tid] × 10 days)
Impetigo	Same as pharyngitis
Erysipelas/cellulitis	Severe: Penicillin G (1–2 mU IV q4h) Mild to moderate: Procaine penicillin (1.2 mU IM bid)
Necrotizing fasciitis/ myositis	Surgical debridement *plus* penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h)
Pneumonia/empyema	Penicillin G (2–4 mU IV q4h) *plus* drainage of empyema
Streptococcal toxic shock syndrome	Penicillin G (2–4 mU IV q4h) *plus* clindamycin[b] (600–900 mg IV q8h) *plus* IV immunoglobulin[b] (2 g/kg as a single dose)

[a]Penicillin allergy: A first-generation cephalosporin, such as cephalexin or cefadroxil, may be substituted for penicillin in cases of penicillin allergy if the nature of the allergy is not an immediate hypersensitivity reaction (anaphylaxis or urticaria) or another potentially life-threatening manifestation (e.g., severe rash and fever). Alternative agents for oral therapy are erythromycin (10 mg/kg PO qid, up to a maximum of 250 mg per dose) and azithromycin (a 5-day course at a dose of 12 mg/kg once daily, up to a maximum of 500 mg/d). Vancomycin is an alternative for parenteral therapy. [b]Efficacy unproven, but recommended by several experts. See text for discussion.

Follow-up culture after treatment is no longer routinely recommended but may be warranted in selected cases, such as those involving patients or families with frequent streptococcal infections or those occurring in situations in which the risk of ARF is thought to be high (e.g., when cases of ARF have recently been reported in the community).

COMPLICATIONS Suppurative complications of streptococcal pharyngitis have become uncommon with the widespread use of antibiotics for most symptomatic cases. These complications result from the spread of infection from the pharyngeal mucosa to deeper tissues by direct extension or by the hematogenous or lymphatic route and may include cervical lymphadenitis, peritonsillar or retropharyngeal abscess, sinusitis, otitis media, meningitis, bacteremia, endocarditis, and pneumonia. Local complications, such as peritonsillar or parapharyngeal abscess formation, should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance. Nonsuppurative complications include ARF **(Chap. 351)** and PSGN **(Chap. 308)**, both of which are thought to result from immune responses to streptococcal infection. Penicillin treatment of streptococcal pharyngitis reduces the likelihood of ARF but not that of PSGN.

BACTERIOLOGIC TREATMENT FAILURE AND THE ASYMPTOMATIC CARRIER STATE Surveillance cultures have shown that up to 20% of individuals in certain populations may have asymptomatic pharyngeal colonization with GAS. There are no definitive guidelines for management of these asymptomatic carriers or of asymptomatic patients who still have a positive throat culture after a full course of treatment for symptomatic pharyngitis. A reasonable course of action is to give a single 10-day course of penicillin for symptomatic pharyngitis and, if positive cultures persist, not to re-treat unless symptoms recur. Studies of the natural history of streptococcal carriage and infection have shown that the risk both of developing ARF and of transmitting infection to others is substantially lower among asymptomatic carriers than among individuals with symptomatic pharyngitis. Therefore, overly aggressive attempts to eradicate carriage probably are not justified under most circumstances. An exception is the situation in which an asymptomatic carrier is a potential source of infection to others. Outbreaks of foodborne infection and nosocomial puerperal infection have been traced to asymptomatic carriers who may harbor the organisms in the throat, vagina, or anus or on the skin.

TREATMENT

Asymptomatic Pharyngeal Colonization with GAS

When a carrier is transmitting infection to others, attempts to eradicate carriage are warranted. Data are limited on the best regimen to clear GAS after penicillin alone has failed. Regimens reported to have efficacy superior to that of penicillin alone for eradication of carriage include (1) a first-generation cephalosporin such as cephalexin (30 mg/kg; 500 mg maximum) twice daily for 10 days or (2) oral clindamycin (7 mg/kg; 300 mg maximum) three times daily for 10 days. A 10-day course of oral vancomycin (250 mg four times daily) and rifampin (600 mg twice daily) has eradicated rectal colonization.

Scarlet Fever Scarlet fever consists of streptococcal infection, usually pharyngitis, accompanied by a characteristic rash **(Fig. 143-2)**. The rash arises from the effects of one of several toxins, currently designated *streptococcal pyrogenic exotoxins* and previously known as *erythrogenic* or *scarlet fever toxins*. In the past, scarlet fever was thought to reflect infection of an individual lacking toxin-specific immunity with a toxin-producing strain of GAS. Susceptibility to scarlet fever was correlated with results of the Dick test, in which a small amount of erythrogenic toxin injected intradermally produced local erythema in susceptible individuals but elicited no reaction in those with specific immunity. Subsequent studies have suggested that development of the scarlet fever rash may reflect a hypersensitivity reaction requiring prior exposure to the toxin. For reasons that are not clear, scarlet fever has become less common in recent years, although large outbreaks have occurred recently in China and the United Kingdom. The symptoms of scarlet fever are the same as those of pharyngitis alone. The rash typically begins on the first or second day of illness over the upper trunk, spreading to involve the extremities but sparing the palms and soles. The rash is made up of minute papules, giving a characteristic "sandpaper" feel to the skin. Associated findings include circumoral pallor, "strawberry tongue" (enlarged papillae on a coated tongue, which later may become denuded), and accentuation of the rash in skinfolds (*Pastia's lines*). Subsidence of the rash in 6–9 days is followed after several days by desquamation of the palms and soles. The differential diagnosis of scarlet fever includes other causes of fever and generalized rash, such as measles and other viral exanthems, Kawasaki disease, TSS, and systemic allergic reactions (e.g., drug eruptions).

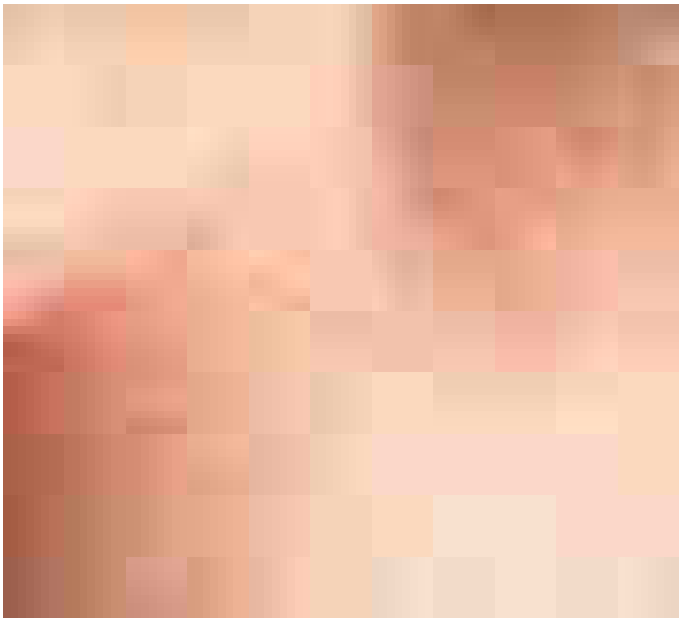

FIGURE 143-2 Scarlet fever exanthem. Finely punctate erythema has become confluent (scarlatiniform); petechiae can occur and have a linear configuration within the exanthem in body folds (Pastia's lines). *(From Fitzpatrick, Johnson, Wolff: Color Atlas and Synopsis of Clinical Dermatology, 4th ed, New York, McGraw-Hill, 2001, with permission.)*

Skin and Soft Tissue Infections GAS—and occasionally other streptococcal species—can cause a variety of infections involving the skin, subcutaneous tissues, muscles, and fascia. While several clinical syndromes offer a useful means for classification of these infections, not all cases fit exactly into one category. The classic syndromes are general guides to predicting the level of tissue involvement in a particular patient, the probable clinical course, and the likelihood that surgical intervention or aggressive life support will be required.

IMPETIGO (PYODERMA) Impetigo, a superficial infection of the skin, is caused primarily by GAS and occasionally by other streptococci or *Staphylococcus aureus*. Impetigo is seen most often in young children, tends to occur during warmer months, and is more common in semitropical or tropical climates than in cooler regions. Infection is more common among children living under conditions of poor hygiene. Prospective studies have shown that colonization of unbroken skin with GAS precedes clinical infection. Minor trauma, such as a scratch or an insect bite, may then serve to inoculate organisms into the skin. Impetigo is best prevented, therefore, by attention to adequate hygiene. The usual sites of involvement are the face (particularly around the nose and mouth) and the legs, although lesions may occur at other locations. Individual lesions begin as red papules, which evolve quickly into vesicular and then pustular lesions that break down and coalesce to form characteristic honeycomb-like crusts **(Fig. 143-3)**. Lesions generally are not painful, and patients do not appear ill. Fever

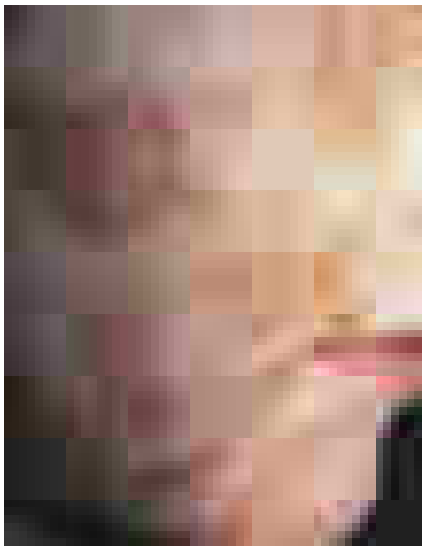

FIGURE 143-3 Impetigo is a superficial streptococcal or *Staphylococcus aureus* infection consisting of honey-colored crusts and erythematous weeping erosions. Occasionally, bullous lesions may be seen. *(Courtesy of Mary Spraker, MD; with permission.)*

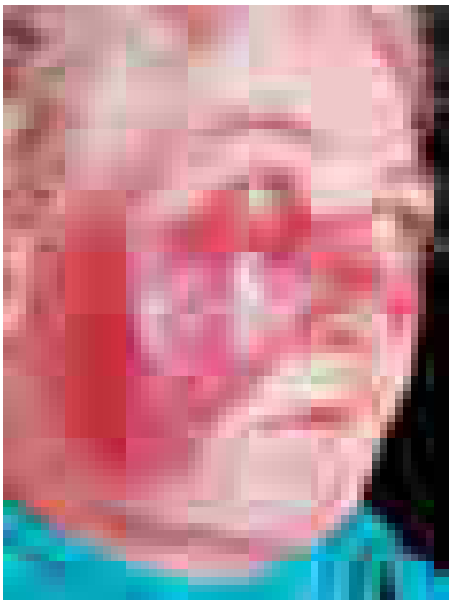

FIGURE 143-4 Erysipelas is a streptococcal infection of the superficial dermis and consists of well-demarcated, erythematous, edematous, warm plaques.

is not a feature of impetigo and, if present, suggests either infection extending to deeper tissues or another diagnosis. The classic presentation of impetigo usually poses little diagnostic difficulty. Cultures of impetiginous lesions often yield *S. aureus* as well as GAS. In almost all cases, streptococci are isolated initially and staphylococci appear later, presumably as secondary colonizing flora. In the past, penicillin was nearly always effective against these infections. However, an increasing frequency of penicillin treatment failure suggests that *S. aureus* may have become more prominent as a cause of impetigo. *Bullous impetigo* due to *S. aureus* is distinguished from typical streptococcal infection by more extensive, bullous lesions that break down and leave thin paper-like crusts instead of the thick amber crusts of streptococcal impetigo. Other skin lesions that may be confused with impetigo include herpetic lesions—either those of orolabial herpes simplex or those of chickenpox or zoster. Herpetic lesions can generally be distinguished by their appearance as more discrete, grouped vesicles and by a positive Tzanck test. In difficult cases, cultures of vesicular fluid should yield GAS in impetigo and the responsible virus in herpesvirus infections.

TREATMENT

Streptococcal Impetigo

Treatment of streptococcal impetigo is the same as that for streptococcal pharyngitis. In view of evidence that *S. aureus* has become a relatively frequent cause of impetigo, empirical regimens should cover both streptococci and *S. aureus*. For example, either dicloxacillin or cephalexin can be given at a dose of 250 mg four times daily for 10 days. Topical mupirocin ointment is also effective. Culture may be indicated to rule out methicillin-resistant *S. aureus*, especially if the response to empirical treatment is unsatisfactory. ARF is not a sequela to streptococcal skin infections, although PSGN may follow either skin or throat infection. The reason for this difference is not known. One hypothesis is that the immune response necessary for development of ARF occurs only after infection of the pharyngeal mucosa. In addition, the strains of GAS that cause pharyngitis are generally of different M protein types than those associated with skin infections; thus the strains that cause pharyngitis may have rheumatogenic potential, while the skin-infecting strains may not.

CELLULITIS Inoculation of organisms into the skin may lead to *cellulitis*: infection involving the skin and subcutaneous tissues. The portal of entry may be a traumatic or surgical wound, an insect bite, or any other break in skin integrity. Often, no entry site is apparent. One form of streptococcal cellulitis, *erysipelas*, is characterized by a bright red appearance of the involved skin, which forms a plateau sharply demarcated from surrounding normal skin **(Fig. 143-4)**. The lesion is warm to the touch, may be tender, and appears shiny and swollen. The skin often has a *peau d'orange* texture, which is thought to reflect involvement of superficial lymphatics; superficial blebs or bullae may form, usually 2–3 days after onset. The lesion typically develops over a few hours and is associated with fever and chills. Erysipelas tends to occur on the malar area of the face (often with extension over the bridge of the nose to the contralateral malar region) or on the lower extremities. After one episode, recurrence at the same site—sometimes years later—is not uncommon. Classic cases of erysipelas, with typical features, are almost always due to β-hemolytic streptococci, usually GAS and occasionally group C or G. Often, however, the appearance of streptococcal cellulitis is not sufficiently distinctive to permit a specific diagnosis on clinical grounds. The anatomic area involved may not be typical for erysipelas, the lesion may be less intensely red than usual and may fade into surrounding skin, and/or the patient may appear only mildly ill. In such cases, it is prudent to broaden the spectrum of empirical antimicrobial therapy to include other pathogens, particularly *S. aureus*, that can produce cellulitis with the same appearance. Staphylococcal infection should be suspected if cellulitis develops around a wound or an ulcer.

Streptococcal cellulitis tends to develop at anatomic sites in which normal lymphatic drainage has been disrupted, such as sites of prior cellulitis, the arm ipsilateral to a mastectomy and axillary lymph node dissection, a lower extremity previously involved in deep venous thrombosis or chronic lymphedema, or the leg from which a saphenous vein has been harvested for coronary artery bypass grafting. The organism may enter via a dermal breach some distance from the eventual site of clinical cellulitis. For example, some patients with recurrent leg cellulitis following saphenous vein removal stop having recurrent episodes only after treatment of tinea pedis on the affected extremity. Fissures in the skin presumably serve as a portal of entry for streptococci, which then produce infection more proximally in the leg at the site of previous injury. Streptococcal cellulitis may also involve recent surgical wounds. GAS is among the few bacterial pathogens that typically produce signs of wound infection and surrounding cellulitis within the first 24 h after surgery. These wound infections are usually associated with a thin exudate and may spread rapidly, either as cellulitis in the skin and subcutaneous tissue or as a deeper tissue infection (see below). Streptococcal wound infection or localized cellulitis may also be associated with *lymphangitis*, manifested by red streaks extending proximally along superficial lymphatics from the infection site.

TREATMENT

Streptococcal Cellulitis

See Table 143-3 and Chap. 124.

DEEP SOFT-TISSUE INFECTIONS *Necrotizing fasciitis* (*hemolytic streptococcal gangrene*) involves the superficial and/or deep fascia investing the muscles of an extremity or the trunk. The source of the infection is either the skin, with organisms introduced into tissue through trauma (sometimes trivial), or the bowel flora, with organisms released during abdominal surgery or from an occult enteric source, such as a diverticular or appendiceal abscess. The inoculation site may be inapparent and is often some distance from the site of clinical involvement; e.g., the introduction of organisms via minor trauma to the hand may be associated with clinical infection of the tissues overlying the shoulder or chest. Cases associated with the bowel flora are usually polymicrobial, involving a mixture of anaerobic bacteria (such as *Bacteroides fragilis* or anaerobic streptococci) and facultative organisms (usually gram-negative bacilli). Cases unrelated to contamination from bowel organisms are most commonly caused by GAS alone or in combination with other organisms (most often *S. aureus*). Overall, GAS is implicated in ~60% of cases of necrotizing fasciitis. The onset of symptoms is usually quite acute and is marked by severe pain at the site of involvement, malaise, fever, chills, and a toxic appearance. The physical findings, particularly early on, may not be striking, with only minimal erythema of the overlying skin. Pain and tenderness are usually severe. In contrast, in more superficial cellulitis, the skin appearance is more abnormal, but pain and tenderness are only mild or moderate. As the infection progresses (often over several hours), the severity and extent of symptoms worsen, and skin changes become more evident, with the appearance of dusky or mottled erythema and edema. The marked tenderness of the involved area may evolve into anesthesia as the spreading inflammatory process produces infarction of cutaneous nerves.

Although myositis is more commonly due to *S. aureus* infection, GAS occasionally produces abscesses in skeletal muscles (*streptococcal myositis*), with little or no involvement of the surrounding fascia or overlying skin. The presentation is usually subacute, but a fulminant form has been described in association with severe systemic toxicity, bacteremia, and a high mortality rate. The fulminant form may reflect the same basic disease process seen in necrotizing fasciitis, but with the necrotizing inflammatory process extending into the muscles themselves rather than remaining limited to the fascial layers.

TREATMENT

Deep Soft-Tissue Streptococcal Infections

Once necrotizing fasciitis is suspected, early surgical exploration is both diagnostically and therapeutically indicated. Surgery reveals necrosis and inflammatory fluid tracking along the fascial planes above and between muscle groups, without involvement of the muscles themselves. The process usually extends beyond the area of clinical involvement, and extensive debridement is required. Drainage and debridement are central to the management of necrotizing fasciitis; antibiotic treatment is a useful adjunct (Table 143-3), but surgery is life-saving. Treatment for streptococcal myositis consists of surgical drainage—usually by an open procedure that permits evaluation of the extent of infection and ensures adequate debridement of involved tissues—and high-dose penicillin (Table 143-3).

Pneumonia and Empyema GAS is an occasional cause of pneumonia, generally in previously healthy individuals. The onset of symptoms may be abrupt or gradual. Pleuritic chest pain, fever, chills, and dyspnea are the characteristic manifestations. Cough is usually present but may not be prominent. Approximately one-half of patients with GAS pneumonia have an accompanying pleural effusion. In contrast to the sterile parapneumonic effusions typical of pneumococcal pneumonia, those complicating streptococcal pneumonia are almost always infected. The empyema fluid is usually visible by chest radiography on initial presentation, and its volume may increase rapidly. These pleural collections should be drained early, as they tend to become loculated rapidly, resulting in a chronic fibrotic reaction that may require thoracotomy for removal.

Bacteremia, Puerperal Sepsis, and Streptococcal Toxic Shock Syndrome In adults, GAS bacteremia is usually associated with an identifiable local infection, whereas children may have bacteremia without an associated focal infection. Bacteremia occurs rarely with otherwise uncomplicated pharyngitis, occasionally with cellulitis or pneumonia, and relatively frequently with necrotizing fasciitis. Bacteremia without an identified source raises the possibility of endocarditis, an occult abscess, or osteomyelitis. A variety of focal infections may arise secondarily from streptococcal bacteremia, including endocarditis, meningitis, septic arthritis, osteomyelitis, peritonitis, and visceral abscesses. GAS is occasionally implicated in infectious complications of childbirth, usually endometritis and associated bacteremia. In the preantibiotic era, puerperal sepsis was commonly caused by GAS; currently, it is more often caused by GBS. Several nosocomial outbreaks of puerperal GAS infection have been traced to an asymptomatic carrier, usually someone present at delivery. The site of carriage may be the skin, throat, anus, or vagina.

Beginning in the late 1980s, several reports described patients with GAS infections associated with shock and multisystem organ failure. This syndrome was called *streptococcal TSS* because it shares certain features with staphylococcal TSS. In 1993, a case definition for streptococcal TSS was formulated (Table 143-4). The general features of the illness include fever, hypotension, renal impairment, and respiratory distress syndrome. Various types of rash have been described, but rash usually does not develop. Laboratory abnormalities include a marked shift to the left in the white blood cell differential, with many immature granulocytes; hypocalcemia; hypoalbuminemia; and thrombocytopenia, which usually becomes more pronounced on the second or third day of illness. In contrast to patients with staphylococcal TSS, the majority with streptococcal TSS are bacteremic. The most common associated infection is a soft tissue infection—necrotizing fasciitis, myositis, or cellulitis—although a variety of other associated local infections have been described, including pneumonia, peritonitis, osteomyelitis, and myometritis. Streptococcal TSS is associated with a mortality rate of ≥30%, with most deaths secondary to shock and respiratory failure. Because of its rapidly progressive and lethal course, early recognition of the syndrome is essential. Patients should receive aggressive supportive care (fluid resuscitation, pressors, and mechanical ventilation) in addition to antimicrobial therapy and, in cases associated with necrotizing fasciitis, should undergo surgical debridement. Exactly why certain patients develop this fulminant syndrome is not known. Early studies of the streptococcal strains isolated from these patients demonstrated a strong association with the production of pyrogenic

TABLE 143-4 Proposed Case Definition for the Streptococcal Toxic Shock Syndrome[a]

- I. Isolation of group A streptococci (*Streptococcus pyogenes*)
  - A. From a normally sterile site
  - B. From a nonsterile site
- II. Clinical signs of severity
  - A. Hypotension *and*
  - B. ≥2 of the following signs
    1. Renal impairment
    2. Coagulopathy
    3. Liver function impairment
    4. Adult respiratory distress syndrome
    5. A generalized erythematous macular rash that may desquamate
    6. Soft tissue necrosis, including necrotizing fasciitis or myositis; *or* gangrene

[a]An illness fulfilling criteria IA, IIA, and IIB is defined as a *definite* case. An illness fulfilling criteria IB, IIA, and IIB is defined as a *probable* case if no other etiology for the illness is identified.

Source: Modified from Working Group on Severe Streptococcal Infections: JAMA 269:390, 1993.

exotoxin A. This association has been inconsistent in subsequent case series. Pyrogenic exotoxin A and several other streptococcal exotoxins act as superantigens to trigger release of inflammatory cytokines from T lymphocytes. Fever, shock, and organ dysfunction in streptococcal TSS may reflect, in part, the systemic effects of superantigen-mediated cytokine release.

TREATMENT

Streptococcal Toxic Shock Syndrome

In light of the possible role of pyrogenic exotoxins or other streptococcal toxins in streptococcal TSS, treatment with clindamycin has been advocated by some authorities (Table 143-3), who argue that, through its direct action on protein synthesis, clindamycin is more effective in rapidly terminating toxin production than is penicillin—a cell-wall agent. Support for this view comes from studies of an experimental model of streptococcal myositis, in which mice given clindamycin had a higher rate of survival than those given penicillin. Comparable data on the treatment of human infections are not available, although retrospective analysis has suggested a better outcome when patients with invasive soft-tissue infection are treated with clindamycin rather than with cell wall–active antibiotics. Although clindamycin resistance in GAS is uncommon among U.S. isolates (<2%), resistance rates as high as 23% have been documented in Finland. Thus, if clindamycin is used for initial treatment of a critically ill patient, penicillin should be given as well until the antibiotic susceptibility of the streptococcal isolate is known. IV immunoglobulin has been used as adjunctive therapy for streptococcal TSS (Table 143-3). Pooled immunoglobulin preparations contain antibodies capable of neutralizing the effects of streptococcal toxins. Anecdotal reports and case series have suggested favorable clinical responses to IV immunoglobulin, but no adequately powered, prospective, controlled trials have been reported.

PREVENTION

No vaccine against GAS is commercially available. A formulation that consists of recombinant peptides containing epitopes of 26 M-protein types has undergone phase 1 and 2 testing in volunteers. Early results indicate that the vaccine is well tolerated and elicits type-specific antibody responses. Vaccines based on a conserved region of M protein or on a mixture of other conserved GAS protein antigens are in earlier stages of development.

Household contacts of individuals with invasive GAS infection (e.g., bacteremia, necrotizing fasciitis, or streptococcal TSS) are at greater risk of invasive infection than the general population. Asymptomatic pharyngeal colonization with GAS has been detected in up to 25% of persons with >4 h/d of same-room exposure to an index case. However, the CDC does not recommend antibiotic prophylaxis routinely for contacts of patients with invasive disease because such an approach (if effective) would require treatment of hundreds of contacts to prevent a single case. Prophylaxis may be considered for contacts of unusually severe cases or for individuals at increased risk for invasive infection.

STREPTOCOCCI OF GROUPS C AND G

Group C and group G streptococci are β-hemolytic bacteria that occasionally cause human infections similar to those caused by GAS. Strains that form small colonies on blood agar (<0.5 mm) are generally members of the *Streptococcus milleri* group (*Streptococcus intermedius*, *Streptococcus anginosus*; see "Viridans Streptococci," below). Large-colony group C and G streptococci of human origin are now considered a single species, *Streptococcus dysgalactiae* subspecies *equisimilis*. These organisms have been associated with pharyngitis, cellulitis and soft tissue infections, pneumonia, bacteremia, endocarditis, and septic arthritis. Puerperal sepsis, meningitis, epidural abscess, intraabdominal abscess, urinary tract infection, and neonatal sepsis have also been reported. Group C or G streptococcal bacteremia most often affects elderly or chronically ill patients and, in the absence of obvious local infection, is likely to reflect endocarditis. Septic arthritis, sometimes involving multiple joints, may complicate endocarditis or develop in its absence. Distinct streptococcal species of Lancefield group C cause infections in domesticated animals, especially horses and cattle; some human infections are acquired through contact with animals or consumption of unpasteurized milk. These zoonotic organisms include *Streptococcus equi* subspecies *zooepidemicus* and *S. equi* subspecies *equi*.

TREATMENT

Group C or G Streptococcal Infection

Penicillin is the drug of choice for treatment of group C or G streptococcal infections. Antibiotic treatment is the same as for similar syndromes due to GAS (Table 143-3). Patients with bacteremia or septic arthritis should receive IV penicillin (2–4 mU every 4 h). All group C and G streptococci are sensitive to penicillin; nearly all are inhibited in vitro by concentrations of ≤0.03 μg/mL. Occasional isolates exhibit tolerance: although inhibited by low concentrations of penicillin, they are killed only by significantly higher concentrations. The clinical significance of tolerance is unknown. Because of the poor clinical response of some patients to penicillin alone, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) is recommended by some authorities for treatment of endocarditis or septic arthritis due to group C or G streptococci; however, combination therapy has not been shown to be superior to penicillin treatment alone. Patients with joint infections often require repeated aspiration or open drainage and debridement for cure; the response to treatment may be slow, particularly in debilitated patients and those with involvement of multiple joints. Infection of prosthetic joints almost always requires prosthesis removal in addition to antibiotic therapy.

GROUP B STREPTOCOCCI

Identified first as a cause of mastitis in cows, streptococci belonging to Lancefield's group B have since been recognized as a major cause of sepsis and meningitis in human neonates. GBS is also a frequent cause of peripartum fever in women and an occasional cause of serious infection in nonpregnant adults. Since the widespread institution of prenatal screening for GBS in the 1990s, the incidence of neonatal infection per 1000 live births has fallen from ~2–3 cases to ~0.6 case. During the same period, GBS infection in adults with underlying chronic illnesses has become more common; adults now account for a larger proportion of invasive GBS infections than do newborns. Lancefield group B consists of a single species, *S. agalactiae*, which is definitively identified with specific antiserum to the group B cell wall–associated carbohydrate antigen. A streptococcal isolate can be classified presumptively as GBS on the basis of biochemical tests, including hydrolysis of sodium hippurate (in which 99% of isolates are positive), hydrolysis of bile esculin (in which 99–100% are negative), bacitracin susceptibility (in which 92% are resistant), and production of CAMP factor (in which 98–100% are positive). CAMP factor is a phospholipase produced by GBS that causes synergistic hemolysis with β lysin produced by certain strains of *S. aureus*. Its presence can be demonstrated by cross-streaking of the test isolate and an appropriate staphylococcal strain on a blood agar plate. GBS organisms causing human infections are encapsulated by one of ten antigenically distinct polysaccharides. The capsular polysaccharide is an important virulence factor. Antibodies to the capsular polysaccharide afford protection against GBS of the same (but not of a different) capsular type.

INFECTION IN NEONATES

Two general types of GBS infection in infants are defined by the age of the patient at presentation. *Early-onset infections* occur within the first week of life, with a median age of 20 h at onset. Approximately half of these infants have signs of GBS disease at birth. The infection is acquired during or shortly before birth from the colonized maternal genital tract. Surveillance studies have shown that 5–40% of women are vaginal or rectal carriers of GBS. Approximately 50% of infants delivered vaginally by carrier mothers become colonized, although only 1–2% develop

clinically evident infection. Prematurity, prolonged labor, obstetric complications, and maternal fever are risk factors for early-onset infection. The presentation of early-onset infection is the same as that of other forms of neonatal sepsis. Typical findings include respiratory distress, lethargy, and hypotension. Essentially all infants with early-onset disease are bacteremic, one-third to one-half have pneumonia and/or respiratory distress syndrome, and one-third have meningitis.

Late-onset infections occur in infants 1 week to 3 months old and, in rare instances, in older infants (mean age at onset, 3–4 weeks). The infecting organism may be acquired during delivery (as in early-onset cases) or during later contact with a colonized mother, nursery personnel, or another source. Meningitis is the most common manifestation of late-onset infection and in most cases is associated with a strain of capsular type III. Infants present with fever, lethargy or irritability, poor feeding, and seizures. The various other types of late-onset infection include bacteremia without an identified source, osteomyelitis, septic arthritis, and facial cellulitis associated with submandibular or preauricular adenitis.

TREATMENT

Group B Streptococcal Infection in Neonates

Penicillin is the agent of choice for all GBS infections. Empirical broad-spectrum therapy for suspected bacterial sepsis, consisting of ampicillin and gentamicin, is generally administered until culture results become available. If cultures yield GBS, many pediatricians continue to administer gentamicin, along with ampicillin or penicillin, for a few days until clinical improvement becomes evident. Infants with bacteremia or soft tissue infection should receive penicillin at a dosage of 200,000 units/kg per day in divided doses. For meningitis, infants ≤7 days of age should receive 250,000–450,000 units/kg per day in three divided doses; infants >7 days of age should receive 450,000–500,000 units/kg per day in four divided doses. Meningitis should be treated for at least 14 days because of the risk of relapse with shorter courses.

Prevention The incidence of GBS infection is unusually high among infants of women with risk factors: preterm delivery, early rupture of membranes (>24 h before delivery), prolonged labor, fever, or chorioamnionitis. Because the usual source of the organisms infecting a neonate is the mother's birth canal, efforts have been made to prevent GBS infections by the identification of high-risk carrier mothers and their treatment with various forms of antibiotic prophylaxis or immunoprophylaxis. Prophylactic administration of ampicillin or penicillin to such patients during delivery reduces the risk of infection in the newborn. This approach has been hampered by logistical difficulties in identifying colonized women before delivery; the results of vaginal cultures early in pregnancy are poor predictors of carrier status at delivery. The CDC recommends screening for anogenital colonization at 35–37 weeks of pregnancy by a swab culture of the lower vagina and anorectum; intrapartum chemoprophylaxis is recommended for culture-positive women and for women who, regardless of culture status, have previously given birth to an infant with GBS infection or have a history of GBS bacteriuria during pregnancy. Women whose culture status is unknown and who develop premature labor (<37 weeks), prolonged rupture of membranes (>18 h), or intrapartum fever or who have a positive intrapartum nucleic acid amplification test for GBS should also receive intrapartum chemoprophylaxis. The recommended regimen for chemoprophylaxis is a loading dose of 5 million units of penicillin G followed by 2.5 million units every 4 h until delivery. Cefazolin is an alternative for women with a history of penicillin allergy who are thought not to be at high risk for anaphylaxis. For women with a history of immediate hypersensitivity, clindamycin may be substituted, but only if the colonizing isolate has been demonstrated to be susceptible. If susceptibility testing results are not available or indicate resistance, vancomycin should be used in this situation.

Treatment of all pregnant women who are colonized or have risk factors for neonatal infection will result in exposure of up to one-third of pregnant women and newborns to antibiotics, with the attendant risks of allergic reactions and selection for resistant organisms. Although still in the developmental stages, a GBS vaccine may ultimately offer a better solution to prevention. Because transplacental passage of maternal antibodies produces protective antibody levels in newborns, efforts are under way to develop a vaccine against GBS that can be given to childbearing-age women before or during pregnancy. Results of phase 1 clinical trials of GBS capsular polysaccharide–protein conjugate vaccines suggest that a multivalent conjugate vaccine would be safe and highly immunogenic.

INFECTION IN ADULTS

The majority of GBS infections in otherwise healthy adults are related to pregnancy and parturition. Peripartum fever, the most common manifestation, is sometimes accompanied by symptoms and signs of endometritis or chorioamnionitis (abdominal distention and uterine or adnexal tenderness). Blood and vaginal swab cultures are often positive. Bacteremia is usually transitory but occasionally results in meningitis or endocarditis. Infections in adults that are not associated with the peripartum period generally involve individuals who are elderly or have an underlying chronic illness, such as diabetes mellitus or a malignancy. Among the infections that develop with some frequency in adults are cellulitis and soft tissue infection (including infected diabetic skin ulcers), urinary tract infection, pneumonia, endocarditis, and septic arthritis. Other reported infections include meningitis, osteomyelitis, and intraabdominal or pelvic abscesses. Relapse or recurrence of invasive infection weeks to months after a first episode is documented in ~4% of cases.

TREATMENT

Group B Streptococcal Infection in Adults

GBS is less sensitive to penicillin than GAS, requiring somewhat higher doses. Adults with serious localized infections (pneumonia, pyelonephritis, abscess) should receive doses of ~12 million units of penicillin G daily; patients with endocarditis or meningitis should receive 18–24 million units per day in divided doses. Vancomycin is an acceptable alternative for penicillin-allergic patients.

NONENTEROCOCCAL GROUP D STREPTOCOCCI

The main nonenterococcal group D streptococci that cause human infections were previously considered a single species, *Streptococcus bovis*. The organisms encompassed by *S. bovis* have been reclassified into two species, each of which has two subspecies: *Streptococcus gallolyticus* subspecies *gallolyticus*, *S. gallolyticus* subspecies *pasteurianus*, *Streptococcus infantarius* subspecies *infantarius*, and *S. infantarius* subspecies *coli.* Endocarditis caused by these organisms is often associated with neoplasms of the gastrointestinal tract—most frequently, a colon carcinoma or polyp—but is also reported in association with other bowel lesions. When occult gastrointestinal lesions are carefully sought, abnormalities are found in >60% of patients with endocarditis due to *S. gallolyticus* or *S. infantarius*. In contrast to the enterococci, nonenterococcal group D streptococci like these organisms are reliably killed by penicillin as a single agent, and penicillin is the agent of choice for the infections they cause.

VIRIDANS AND OTHER STREPTOCOCCI

VIRIDANS STREPTOCOCCI

Consisting of multiple species of α-hemolytic streptococci, the viridans streptococci are a heterogeneous group of organisms that are important agents of bacterial endocarditis **(Chap. 123)**. Several species of viridans streptococci, including *Streptococcus salivarius*, *Streptococcus mitis*, *Streptococcus sanguis*, and *Streptococcus mutans*, are part of the normal flora of the mouth, where they live in close association with the teeth and gingiva. Some species contribute to the development of dental caries.

Previously known as *Streptococcus morbillorum*, *Gemella morbillorum* has been placed in a separate genus, along with *Gemella haemolysans*,

on the basis of genetic-relatedness studies. These species resemble viridans streptococci with respect to habitat in the human host and associated infections.

The transient viridans streptococcal bacteremia induced by eating, toothbrushing, flossing, and other sources of minor trauma, together with adherence to biologic surfaces, is thought to account for the predilection of these organisms to cause endocarditis **(see Fig. 123-1)**. Viridans streptococci are also isolated, often as part of a mixed flora, from sites of sinusitis, brain abscess, and liver abscess.

Viridans streptococcal bacteremia occurs relatively frequently in neutropenic patients, particularly after bone marrow transplantation or high-dose chemotherapy for cancer. Some of these patients develop a sepsis syndrome with high fever and shock. Risk factors for viridans streptococcal bacteremia include chemotherapy with high-dose cytosine arabinoside, prior treatment with trimethoprim-sulfamethoxazole or a fluoroquinolone, treatment with antacids or histamine antagonists, mucositis, and profound neutropenia.

The *S. milleri* group (also referred to as the *S. intermedius* or *S. anginosus* group) includes three species that cause human disease: *S. intermedius*, *S. anginosus*, and *Streptococcus constellatus*. These organisms are often considered viridans streptococci, although they differ somewhat from other viridans streptococci in both their hemolytic pattern (they may be α-, β-, or nonhemolytic) and the disease syndromes they cause. This group commonly produces suppurative infections, particularly abscesses of brain and abdominal viscera, and infections related to the oral cavity or respiratory tract, such as peritonsillar abscess, lung abscess, and empyema.

TREATMENT

Infection with Viridans Streptococci

Isolates from neutropenic patients with bacteremia are often resistant to penicillin; thus these patients should be treated presumptively with vancomycin until the results of susceptibility testing become available. Viridans streptococci isolated in other clinical settings usually are sensitive to penicillin. Susceptibility testing should be performed to guide treatment of serious infections.

ABIOTROPHIA AND *GRANULICATELLA* SPECIES (NUTRITIONALLY VARIANT STREPTOCOCCI)

Occasional isolates cultured from the blood of patients with endocarditis fail to grow when subcultured on solid media. These *nutritionally variant streptococci* require supplemental thiol compounds or active forms of vitamin B_6 (pyridoxal or pyridoxamine) for growth in the laboratory. The nutritionally variant streptococci are generally grouped with the viridans streptococci because they cause similar types of infections. However, they have been reclassified on the basis of 16S ribosomal RNA sequence comparisons into two separate genera: *Abiotrophia*, with a single species (*Abiotrophia defectiva*), and *Granulicatella*, with three species associated with human infection (*Granulicatella adiacens*, *Granulicatella para-adiacens*, and *Granulicatella elegans*).

TREATMENT

Infection with Nutritionally Variant Streptococci

Treatment failure and relapse appear to be more common in cases of endocarditis due to nutritionally variant streptococci than in those due to the usual viridans streptococci. Thus the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) to the penicillin regimen is recommended for endocarditis due to the nutritionally variant organisms.

OTHER STREPTOCOCCI

Streptococcus suis is an important pathogen in swine and has been reported to cause meningitis in humans, usually in individuals with occupational exposure to pigs. *S. suis* has been reported to be the most common cause of bacterial meningitis in Vietnam, and it has been responsible for outbreaks in China. Strains of *S. suis* associated with human infections have generally reacted with Lancefield group R typing serum and sometimes with group D typing serum as well. Isolates may be α- or β-hemolytic and are sensitive to penicillin. *Streptococcus iniae*, a pathogen of fish, has been associated with infections in humans who have handled live or freshly killed fish. Cellulitis of the hand is the most common form of human infection, although bacteremia and endocarditis have been reported. *Anaerobic streptococci*, or *peptostreptococci*, are part of the normal flora of the oral cavity, bowel, and vagina. **Infections caused by the anaerobic streptococci are discussed in Chap. 172.**

FURTHER READING

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144 Enterococcal Infections

Cesar A. Arias, Barbara E. Murray

Enterococci have been recognized as potential human pathogens for more than a century, but only in recent years have these organisms acquired prominence as important causes of nosocomial infections. The ability of enterococci to survive and/or disseminate in the hospital environment and to acquire antibiotic resistance determinants makes the treatment of some enterococcal infections in critically ill patients a difficult challenge. Enterococci were first mentioned in the French literature in 1899; the "entérocoque" was found in the human gastrointestinal tract. The first pathologic description of an enterococcal infection dates to the same year. A clinical isolate from a patient who died as a consequence of endocarditis was initially designated *Micrococcus zymogenes*, was later named *Streptococcus faecalis* subspecies *zymogenes*, and would now be classified as *Enterococcus faecalis*. The ability of this isolate to cause severe disease in both rabbits and mice illustrated its potential lethality in the appropriate settings.

MICROBIOLOGY AND TAXONOMY

Enterococci are gram-positive organisms. In clinical specimens, they are usually observed as single cells, diplococci, or short chains **(Fig. 144-1)**, although long chains are noted with some strains. Enterococci were originally classified as streptococci because organisms of the two genera share many morphologic and phenotypic characteristics, including a generally negative catalase reaction. Only DNA hybridization studies and later 16S rRNA sequencing clearly demonstrated that enterococci should be grouped as a genus distinct from the streptococci. Nonetheless, unlike the majority of streptococci, enterococci hydrolyze esculin in the presence of 40% bile salts and grow at high salt concentrations (e.g., 6.5%) and at high temperatures (46°C). Enterococci are usually reported by the clinical laboratory to be nonhemolytic on the basis of their inability to lyse the ovine or bovine red blood cells (RBCs) commonly used in agar plates; however, some strains of *E. faecalis* do

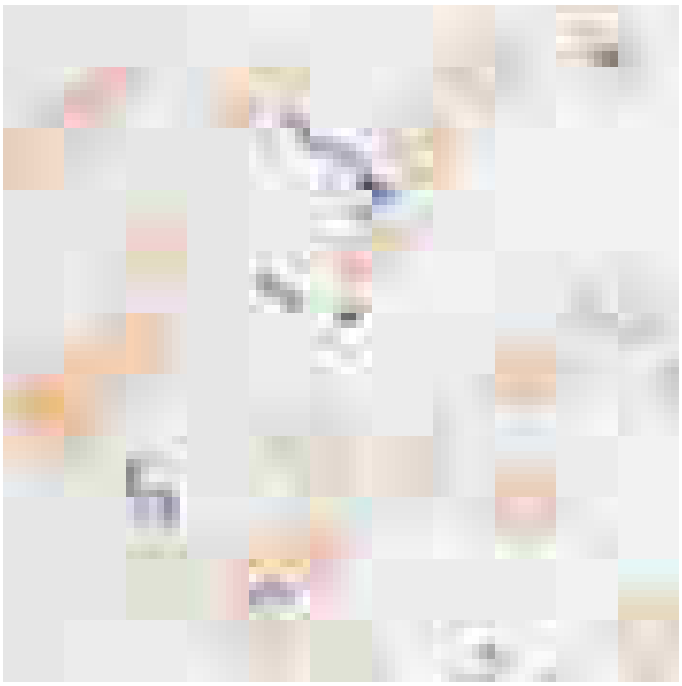

FIGURE 144-1 Gram's stain of cultured blood from a patient with enterococcal bacteremia. Oval gram-positive bacterial cells are arranged as diplococci and short chains. *(Courtesy of Audrey Wanger, PhD.)*

lyse RBCs from humans, horses, and rabbits. The majority of clinically relevant enterococcal species hydrolyze pyrrolidonyl-β-naphthylamide (PYR); this characteristic is helpful in differentiating enterococci from organisms of the *Streptococcus gallolyticus* group (formerly known as *S. bovis*), which includes *S. gallolyticus*, *S. pasteurianus*, and *S. infantarius*) and from *Leuconostoc* species. Although at least 18 species of enterococci have been isolated from human infections, the overwhelming majority of cases are caused by two species, *E. faecalis* and *E. faecium*. Less frequently isolated species include *E. gallinarum*, *E. durans*, *E. hirae*, and *E. avium*.

PATHOGENESIS

Enterococci are normal inhabitants of the large bowel of human adults, although they usually make up <1% of the culturable intestinal microbiota. In the healthy human host, enterococci are typical symbionts that coexist with other gastrointestinal bacteria; in fact, the utility of certain enterococcal strains as probiotics in the treatment of diarrhea suggests their possible role in maintaining the homeostatic equilibrium of the bowel. One of the most important factors that disrupts this equilibrium and promotes increased gastrointestinal colonization by enterococci is the administration of antimicrobial agents since enterococci are intrinsically resistant to a variety of commonly used antibacterial drugs. In particular, antibiotics that are excreted in the bile and have broad-spectrum activity (e.g., certain cephalosporins that target anaerobes and gram-negative bacteria) are usually associated with the recovery of higher numbers of enterococci from feces. In the absence of antibiotics, hospital-associated lineages of *E. faecium* seem to be less adapted for survival in the gastrointestinal tract than are commensal *E. faecium* strains. However, in the presence of antimicrobial agents, the increased colonization by hospital-associated strains of *E. faecium* appears to be due not only to the simple filling of a "biological niche" after the eradication of competing components of the microbiota, but also (at least in mice) to the suppression—upon reduction of the gram-negative microflora by antibiotics—of important immunologic signals (e.g., by the lectin RegIIIγ) that contribute to the control of enterococcal counts in the normal human bowel. Several studies have shown that a higher level of gastrointestinal colonization is a critical factor in the pathogenesis of enterococcal infections. However, the mechanisms by which enterococci successfully colonize the bowel and gain access to the lymphatics and/or bloodstream remain incompletely understood. Recent data suggest that vancomycin-resistant enterococci (VRE) occupy distinct biological niches within the colonic lumen that fulfill their in vivo metabolic needs. Another factor that may contribute to enterococcal survival in the gastrointestinal tract is the production of bacteriocins (molecules that kill competing bacteria). Indeed, strains of *E. faecalis* harboring pheromone-producing plasmids that code for bacteriocins are capable of outcompeting enterococci lacking such plasmids. Furthermore, in vivo transfer of these plasmids occurs by conjugation, enhancing the survival of the recipients.

Several vertebrate, worm, and insect models have been developed to study the role of possible pathogenic determinants in both *E. faecalis* and *E. faecium*. Three main groups of virulence factors may increase the ability of enterococci to colonize the gastrointestinal tract and/or cause disease. The first group, *enterococcal secreted factors*, are molecules released outside the bacterial cell that contribute to the process of infection. The best-studied of these molecules include enterococcal hemolysin/cytolysin and two enterococcal proteases (gelatinase and serine protease). Enterococcal cytolysin is a heterodimeric toxin produced by some strains of *E. faecalis* that is capable of lysing human RBCs as well as polymorphonuclear leukocytes and macrophages. *E. faecalis* gelatinase and serine protease are thought to mediate virulence by several mechanisms, including the degradation of host tissues and the modification of critical components of the immune system. Mutants lacking the genes corresponding to these proteins are highly attenuated in experimental peritonitis, endocarditis, and endophthalmitis.

A second group of virulence factors, *enterococcal surface components*, includes adhesins and is thought to contribute to bacterial attachment to extracellular matrix molecules in the human host. Several molecules on the surface of enterococci have been characterized and shown to play a role in the pathogenesis of enterococcal infections. Among the characterized adhesins is *aggregation substance* of *E. faecalis*, which mediates the attachment of bacterial cells to each other, thereby facilitating conjugative plasmid exchange. Several lines of evidence indicate that aggregation substance and enterococcal cytolysin act synergistically to increase the virulence potential of *E. faecalis* strains in experimental endocarditis. The surface protein adhesin of collagen of *E. faecalis* (Ace) and its *E. faecium* homologue (Acm) are microbial surface components adhering to matrix molecules (MSCRAMMS); they recognize adhesive matrix molecules involved in bacterial attachment to host proteins such as collagen, fibronectin, and fibrinogen. Both Ace and Acm are important in the pathogenesis of experimental endocarditis. Pili of gram-positive bacteria are important mediators of attachment to and invasion of host tissues and are considered potential targets for immunotherapy. Both *E. faecalis* and *E. faecium* have surface pili. Mutants of *E. faecalis* lacking pili are attenuated in biofilm production, experimental endocarditis, and urinary tract infections (UTIs). Other surface proteins that share structural homology with MSCRAMMs and appear to play a role in enterococcal attachment to the host and in virulence include the *E. faecalis* surface protein Esp and its *E. faecium* homologue Esp_{fm}, the second collagen adhesin of *E. faecium* (Scm), the surface proteins of *E. faecium* (Fms), SgrA (which binds to components of the basal lamina), and EcbA (which binds to collagen type V). Additional surface components apparently associated with pathogenicity include the Erl protein (a protein from the WxL family) and polysaccharides, which are thought to interfere with phagocytosis of the organism by host immune cells. Some *E. faecalis* strains appear to harbor at least three distinct classes of capsular polysaccharide; some of these polysaccharides play a role in virulence and are potential targets for immunotherapy. Teichoic acids on the enterococcal surface appear to be immunogenic, and antibodies to these molecules are protective in some animal models.

The third group of virulence factors has not been well characterized but includes the *E. faecalis* stress protein Gls24, which has been associated with enterococcal resistance to bile salts and appears to be important in the pathogenesis of endocarditis, and the hyl_{Efm}-containing plasmids of *E. faecium*, which are transferable between strains and increase gastrointestinal colonization by *E. faecium*. In mouse peritonitis, acquisition of these plasmids increased the lethality of a commensal strain of *E. faecium* and enhanced colonization of the uroepithelium.

A gene encoding a regulator of oxidative stress (AsrR) has been identified as an important virulence factor of *E. faecium*.

The ability to sequence bacterial genomes has increased our understanding of bacterial diversity, evolution, pathogenesis, and mechanisms of antibiotic resistance. The genome sequences of more than 1000 enterococcal strains are currently available, and some have been entirely closed and annotated. Sequence analysis has shown that the genetic diversity of enterococci is related in large part to the acquisition of exogenous DNA and the mobilization of large chromosomal regions, resulting in recombination of the "core" genomes. In addition, analyses indicate that *E. faecium* harbors a malleable *accessory genome* incorporating a substantial content of exogenous elements, including DNA from phages. Indeed, a hospital-associated *E. faecium* clade that contains most clinical and outbreak-associated strains is the predominant genetic lineage circulating in hospitals around the world. This clade appears to be evolving rapidly, and genomic comparisons suggest that this lineage emerged 75–80 years ago—a time point that coincides with the introduction of antimicrobial drugs—and evolved, perhaps continuously, from animal strains, not from human commensal isolates. An initial genomic separation within *E. faecium* into human and animal commensals appears to have occurred ~3000 years ago, simultaneous with urbanization and domestication of animals. This genomic information provides new clues with regard to the evolution of enterococci from commensal organisms to important nosocomial pathogens.

EPIDEMIOLOGY

According to the National Healthcare Safety Network of the Centers for Disease Control and Prevention, enterococci are the second most common isolates (after staphylococci) from hospital-associated infections in the United States. Although *E. faecalis* remains the predominant species recovered from nosocomial infections, the isolation of *E. faecium* has increased substantially in the past 15–20 years. In fact, *E. faecium* is now almost as common as *E. faecalis* as an etiologic agent of hospital-associated infections. This point is important, since *E. faecium* is by far the most resistant and challenging enterococcal species to treat; indeed, more than 80% of *E. faecium* isolates recovered in U.S. hospitals are resistant to vancomycin, and more than 90% are resistant to ampicillin (historically the most effective β-lactam agent against enterococci). Resistance to vancomycin and ampicillin in *E. faecalis* isolates is much less common.

The dynamics of enterococcal transmission and dissemination in the hospital environment have been extensively studied, with a focus on VRE. These studies have revealed that VRE colonization of the gastrointestinal tract is a critical step in the development of enterococcal disease and that a substantial proportion of patients colonized with VRE remain colonized for prolonged periods (sometimes >1 year) and are more likely than patients without VRE colonization to develop an *Enterococcus*-related illness (e.g., bacteremia). Important factors associated with VRE colonization and persistence in the gut include prolonged hospitalization; long courses of antibiotic therapy; hospitalization in long-term-care facilities, surgical units, and/or intensive care units; organ transplantation; renal failure (particularly in patients undergoing hemodialysis) and/or diabetes; high APACHE scores; and physical proximity to patients infected or colonized with VRE or these patients' rooms. Once a patient becomes colonized with VRE, several key factors are involved in the organisms' dissemination in the hospital environment. VRE can survive exposure to heat and certain disinfectants and have been found on numerous inanimate objects in the hospital, including bed rails, medical equipment, doorknobs, gloves, telephones, and computer keyboards. Thus health care workers and the environment play pivotal roles in enterococcal transmission from patient to patient, and infection control measures are crucial in breaking the chain of transmission. Moreover, two meta-analyses have found that, independent of the patient's clinical status, VRE infection increases the risk of death over that among individuals infected with a glycopeptide-susceptible enterococcal strain.

The epidemiology of enterococcal disease and the emergence of VRE have followed slightly different trends in other parts of the world than in the United States. In Europe, the emergence of VRE in the mid-1980s was seen primarily in isolates recovered from animals and healthy humans rather than from hospitalized patients. The presence of VRE was associated with the use of the glycopeptide avoparcin as a growth promoter in animal feeds; this association prompted the European Union to ban the use of this compound in animal husbandry in 1996. However, after an initial decrease in the isolation of VRE from animals and humans, the prevalence of hospital-associated VRE infections has slowly increased in certain European countries, with important regional differences. For example, rates of vancomycin resistance among *E. faecium* clinical isolates in Europe are highest in Greece, the United Kingdom, and Portugal (10–30%), whereas rates in the Scandinavian countries and the Netherlands are <1%. These regional differences have been attributed in part to the implementation of aggressive "search-and-destroy" infection-control policies in countries such as the Netherlands; these policies have kept the frequency of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE very low. In spite of regional differences, rates of VRE continue to be much lower in Europe than in the United States. The reasons are not totally understood, although it has been postulated that this difference is related to the higher levels of human antibiotic use in the United States. Rates of enterococcal resistance to vancomycin in some Latin American countries are also lower (~4%) than those in the United States. Conversely, in Asia, rates of vancomycin resistance among enterococci appear to be similar to those in U.S. hospitals.

As mentioned above, genomic analyses of vancomycin-resistant *E. faecium* in different parts of the world suggest that the emergence and dissemination of these organisms in the hospital environment worldwide are due to the success of hospital-associated genetic lineages that acquired the genes responsible for vancomycin resistance as well as other antibiotic resistance determinants.

CLINICAL SYNDROMES

Urinary Tract Infection and Prostatitis Enterococci are well-known causes of nosocomial UTI—the most common infection caused by these organisms **(Chap. 130)**. Enterococcal UTIs are usually associated with indwelling catheterization, instrumentation, or anatomic abnormalities of the genitourinary tract, and it is often challenging to differentiate between true infection and colonization (particularly in patients with chronic indwelling catheters). The presence of leukocytes in the urine in conjunction with systemic manifestations (e.g., fever) or local signs and symptoms of infection with no other explanation and a positive urine culture ($\geq 10^5$ CFU/mL) suggests the diagnosis. Moreover, enterococcal UTIs often occur in critically or chronically ill patients whose comorbidities may obscure the diagnosis. In many cases, removal of the indwelling catheter may suffice to eradicate the organism without specific antimicrobial therapy. In rare circumstances, UTIs caused by enterococci may run a complicated course, with the development of pyelonephritis and perinephric abscesses that may be a portal of entry for bloodstream infections (see below). Enterococci are also known causes of chronic prostatitis, particularly in men whose urinary tract has been manipulated surgically or endoscopically. These infections can be difficult to treat since the agents most potent against enterococci (i.e., aminopenicillins and glycopeptides) penetrate prostatic tissue poorly. Chronic prostatic infection can be a source of recurrent enterococcal bacteremia.

Bacteremia and Endocarditis Bacteremia without endocarditis is one of the most common presentations of enterococcal disease. Intravascular catheters and other devices are commonly associated with these bacteremic episodes **(Chap. 137)**. Other well-known sources of enterococcal bacteremia include the gastrointestinal and hepatobiliary tracts; pelvic and intraabdominal foci; and, less frequently, wound infections, UTIs, and bone infections. In the United States, enterococci are ranked second (after coagulase-negative staphylococci) as etiologic agents of central line–associated bacteremia. Patients with enterococcal bacteremia usually have comorbidities and have been in the hospital for prolonged periods; they commonly have received several courses of antibiotics. Several studies indicate that the isolation of *E. faecium* from the blood may lead to worse outcomes and higher mortality

rates than when other enterococcal species are isolated; this finding may be related to the higher prevalence of vancomycin and ampicillin resistance in *E. faecium* than in other enterococcal species, with the consequent reduction of therapeutic options. In some cases (usually when the gastrointestinal tract is the source), enterococcal bacteremia may be polymicrobial, with gram-negative organisms isolated at the same time. In addition, several cases have been documented in which enterococcal bacteremia was associated with *Strongyloides stercoralis* hyperinfection syndrome in immunocompromised patients.

Enterococci are important causes of community- and health care–associated endocarditis, ranking second after staphylococci in the latter infections. The presumed initial source of bacteremia leading to endocarditis is the gastrointestinal or genitourinary tract—e.g., in patients who have malignant and inflammatory conditions of the gut or have undergone procedures in which these tracts are manipulated. The affected patients tend to be male and elderly and to have other debilitating diseases and heart conditions. Both prosthetic and native valves can be involved; mitral and aortic valves are affected most often. Community-associated endocarditis (usually caused by *E. faecalis*) also occurs in patients with no apparent risk factors or cardiac abnormalities. Endocarditis in women of childbearing age has been well described. The typical presentation of enterococcal endocarditis is a subacute course of fever, weight loss, malaise, and cardiac murmur; typical stigmata of endocarditis (e.g., petechiae, Osler's nodes, Roth's spots) are found in only a minority of patients. Atypical manifestations include arthralgias and manifestations of metastatic disease (splenic abscesses, hiccups, pain in the left flank, pleural effusion, and spondylodiscitis). Embolic complications are variable and can affect the brain. Heart failure is a common complication of enterococcal endocarditis, and valve replacement may be critical in curing this infection, particularly when multidrug-resistant organisms or major complications are involved. A recent clinical score (designated NOVA) has been proposed to help differentiate enterococcal bacteremia from true endocarditis. The duration of therapy is usually 4–6 weeks, with more prolonged courses suggested for multidrug-resistant isolates in the absence of valvular replacement.

Meningitis Enterococcal meningitis is an uncommon disease (accounting for only ~4% of meningitis cases) that is usually associated with neurosurgical interventions and conditions such as shunts, central nervous system (CNS) trauma, and cerebrospinal fluid (CSF) leakage. In some instances—usually in patients with a debilitating condition, such as cardiovascular or congenital heart disease, chronic renal failure, malignancy, receipt of immunosuppressive therapy, or HIV/AIDS—presumed hematogenous seeding of the meninges is seen in infections such as endocarditis or bacteremia. Fever and changes in mental status are common, whereas overt meningeal signs are less so. CSF findings are consistent with bacterial infection—i.e., pleocytosis, with a predominance of polymorphonuclear leukocytes (average, ~500/μL), an elevated serum protein level (usually >100 mg/dL), and a decreased glucose concentration (average, 28 mg/dL). Gram's staining yields a positive result in about half of cases, with a high rate of organism recovery from CSF cultures; the most common species isolated are *E. faecalis* and *E. faecium*. Complications include hydrocephalus, brain abscesses, and stroke. As mentioned before for bacteremia, an association with *Strongyloides* hyperinfection has also been documented.

Intraabdominal, Pelvic, and Soft Tissue Infections As mentioned earlier, enterococci are part of the commensal microbiota of the gastrointestinal tract and can produce spontaneous peritonitis in cirrhotic individuals and in patients undergoing chronic ambulatory peritoneal dialysis **(Chap. 127)**. These organisms are commonly found (usually along with other bacteria, including enteric gram-negative species and anaerobes) in clinical samples from intraabdominal and pelvic collections. The presence of enterococci in intraabdominal infections is sometimes considered to be of little clinical relevance. Several studies have shown that the role of enterococci in intraabdominal infections originating in the community and involving previously healthy patients is minor, since surgery and broad-spectrum antimicrobial drugs that do not target enterococci are often sufficient to treat these infections successfully. In the last few decades, however, these organisms have become prominent as a cause of intraabdominal infections in hospitalized patients because of the emergence and spread of vancomycin resistance among enterococci and the increase in rates of nosocomial infections due to multidrug-resistant *E. faecium* isolates. In fact, several studies have now documented treatment failures due to enterococci, with consequently increased rates of postoperative complications and death among patients with intraabdominal infections. Thus, anti-enterococcal therapy is recommended for nosocomial peritonitis in immunocompromised and severely ill patients who have had a prolonged hospital stay, have undergone multiple procedures, have persistent abdominal sepsis and collections, or have risk factors for the development of endocarditis (e.g., prosthetic or damaged heart valves). Conversely, specific treatment for enterococci in the first episode of intraabdominal infection originating in the community and affecting previously healthy patients with no important cardiac risk factors for endocarditis does not appear to be beneficial.

Enterococci are commonly isolated from soft tissue infections **(Chap. 124)**, particularly those involving surgical wounds **(Chap. 137)**. In fact, these organisms rank third as agents of nosocomial surgical-site infections, with *E. faecalis* the most frequently isolated species. The clinical relevance of enterococci in some of these infections—as in intraabdominal infections—is a matter of debate; differentiating between colonization and true infection is sometimes challenging, although in some cases enterococci have been recovered from lung, liver, and skin abscesses. Diabetic foot and decubitus ulcers are often colonized with enterococci and may be the portal of entry for bone infections.

Other Infections Enterococci are well-known causes of neonatal infections, including sepsis (mostly late-onset), bacteremia, meningitis, pneumonia, and UTI. Outbreaks of enterococcal sepsis in neonatal units have been well documented. Risk factors for enterococcal disease in newborns include prematurity, low birth weight, indwelling devices, and abdominal surgery. Enterococci have also been described as etiologic agents of bone and joint infections, including vertebral osteomyelitis, usually in patients with underlying conditions such as diabetes or endocarditis. Similarly, enterococci have been isolated from bone infections in patients who have undergone arthroplasty or reconstruction of fractures with the placement of hardware. Since enterococci can produce a biofilm that is likely to alter the efficacy of anti-enterococcal agents, treatment of infections that involve foreign material is challenging, and removal of the hardware may be necessary to eradicate the infection. Rare cases of enterococcal pneumonia, lung abscess, and spontaneous empyema have been described.

TREATMENT

Enterococcal Infections

GENERAL PRINCIPLES

Enterococci are intrinsically resistant and/or tolerant to several antimicrobial agents. (*Tolerance* is defined as lack of killing by drug concentrations 32 times higher than the minimal inhibitory concentration [MIC].) Monotherapy for endocarditis with a β-lactam antibiotic (to which many enterococci are tolerant) has produced disappointing results, with high relapse rates after the end of therapy. However, the addition of an aminoglycoside to a cell wall–active agent (a β-lactam or a glycopeptide) increases cure rates and eradicates the organisms; moreover, this combination is synergistic and bactericidal in vitro. Therefore, for many decades, combination therapy with a cell wall–active agent and an aminoglycoside was the standard of care for endovascular infections caused by enterococci. This synergistic effect can be explained, at least in part, by the increased penetration of the aminoglycoside into the bacterial cell, presumably as a result of cell wall alterations produced by the β-lactam (or glycopeptide). Nonetheless, attaining synergistic bactericidal activity in the treatment of severe enterococcal infections—particularly those caused by *E. faecium*—has become increasingly

difficult because of the development of resistance to virtually all antibiotics available for this purpose.

The treatment of *E. faecalis* differs substantially from that of *E. faecium* **(Tables 144-1 and 144-2)**, mainly because of differences in resistance profiles (see below). For example, resistance to ampicillin and vancomycin is rare in *E. faecalis*, whereas these antibiotics are only infrequently useful against current isolates of *E. faecium*. Moreover, as a consequence of the challenges and therapeutic limitations posed by the emergence of drug resistance in enterococci, valve replacement may need to be considered in the treatment of endocarditis caused by multidrug-resistant enterococci. Less severe infections are often related to indwelling intravascular catheters; removal of the catheter increases the likelihood of enterococcal eradication by a subsequent short course of appropriate antimicrobial therapy.

TABLE 144-1 Suggested Regimens for the Management of Infections Caused by *Enterococcus faecalis*

CLINICAL SYNDROME	SUGGESTED THERAPEUTIC OPTIONS[a]
Endovascular infections (including endocarditis)	• Ampicillin[b] (12 g/d IV in divided doses q4h or by continuous infusion) or penicillin (18–30 mU/d IV in divided doses q4h or by continuous infusion) *plus* an aminoglycoside[c] • Ampicillin[b] (12 g/d IV in divided doses q4h) plus ceftriaxone (2 g IV q12h) • Vancomycin[d] (15 mg/kg IV per dose) plus an aminoglycoside[c] • High-dose daptomycin[e] ± another active agent[f] • Ampicillin[b] plus imipenem
Non-endovascular bacteremia[g]	• Ampicillin (12 g/d IV in divided doses q4h) or penicillin (18 mU/d IV in divided doses q4h) ± an aminoglycoside[c] or ceftriaxone • Vancomycin[d] (15 mg/kg IV per dose) • High-dose daptomycin[e] ± another active agent[f] • Linezolid (600 mg IV/PO q12h)
Meningitis	• Ampicillin (20–24 g/d IV in divided doses q4h) or penicillin (24 mU/d IV in divided doses q4h) *plus* an aminoglycoside[c,h] and consider adding ceftriaxone (2 g IV q12h) • Vancomycin (500–750 mg IV q6h)[d] *plus* an aminoglycoside[c] or rifampin • Linezolid • High-dose daptomycin[e] (plus intrathecal daptomycin) ± another active agent[f]
Urinary tract Infections (uncomplicated)	• Fosfomycin (3 g PO, one dose)[i] • Ampicillin (500 mg IV or PO q6h) • Nitrofurantoin (100 mg PO q6h)

[a]Authors' preferences are underlined for each category; many of the regimens are off-label. [b]In rare cases, β-lactamase-producing isolates may be present. Because these isolates are not detected by conventional determination of the minimal inhibitory concentration, additional tests (e.g., the nitrocefin disk) are recommended for isolates from endocarditis. The use of ampicillin/sulbactam (12–24 g/d) is suggested in these cases. [c]Only if the organism does not exhibit high-level resistance (HLR) to aminoglycosides. This test is performed by the clinical microbiology laboratory only for gentamicin or streptomycin (growth of enterococci on agar containing gentamicin [500 μg/mL] or streptomycin [2000 μg/mL]). If HLR is documented, the aminoglycoside will not act synergistically with the other agent in the combination. However, HLR to one of these aminoglycosides does not indicate resistance to the other agent (as reported individually). HLR to gentamicin implies lack of synergism with tobramycin and with amikacin. Gentamicin (1–1.5 mg/kg IV q8h) and streptomycin (15 mg/kg per day IV/IM in two divided doses) are the only two recommended aminoglycosides. [d]Vancomycin is recommended only as an alternative to β-lactam agents in cases of allergy or toxicity plus the inability to desensitize. Cerebrospinal fluid (CSF) concentrations in meningitis should be determined. Vancomycin-resistant strains of *E. faecalis* have been reported. [e]Consider doses of 10–12 mg/kg once daily if used in combination and 10–12 mg/kg day if used alone. Monitoring of creatine phosphokinase levels is recommended throughout therapy because of possible rhabdomyolysis. [f]Potentially active agents may include an aminoglycoside (if HLR is not detected), ampicillin, ceftaroline, tigecycline, or a fluoroquinolone (which, if the isolate is susceptible, may be favored in meningitis). The presence of mutations in *liaFSR* seems to increase susceptibility to ampicillin and ceftaroline, and combinations of daptomycin with these compounds are bactericidal in vitro against such strains. [g]In selected cases of catheter-associated bacteremia, removal of the catheter and a short course of therapy (~5–7 days) may be sufficient. A single positive blood culture that is likely to be associated with a catheter in a patient who is otherwise doing well may not require therapy after removal of the catheter. Patients at high risk for endovascular infections or with severe disease may benefit from synergistic combination therapy. [h]The addition of intrathecal or intraventricular therapy with gentamicin (2–10 mg/d) if the organism does not exhibit HLR or with vancomycin (10–20 mg/d) when the isolate is susceptible has been suggested by some authorities. The addition of systemic rifampin (a good CSF-penetrating agent) may be considered. The combination of ampicillin and ceftriaxone may have clinical benefit (by analogy with endocarditis), but no cases treated with this combination have been reported; the authors would use this combination. [i]Approved by the U.S. Food and Drug Administration only for uncomplicated urinary tract infections caused by vancomycin-susceptible *E. faecalis*.

TABLE 144-2 Suggested Regimens for the Management of Infections Caused by Vancomycin- and Ampicillin-Resistant *Enterococcus faecium*

CLINICAL SYNDROME	SUGGESTED THERAPEUTIC OPTIONS[a]
Endovascular infections (including endocarditis)	• High-dose daptomycin[b] plus another agent[c] ± an aminoglycoside[d] • Linezolid (600 mg IV q12h) • High-dose ampicillin (if MIC is ≤64 μg/mL) ± an aminoglycoside[d] • Ampicillin plus imipenem (if the ampicillin MIC is ≤32 μg/mL) • Q/D[e] (22.5 mg/kg per day in divided doses q8h) ± another active agent[f]
Non-endovascular bacteremia[g]	• High-dose daptomycin[b] ± another agent[c] ± an aminoglycoside[d] • Linezolid (600 mg IV q12h) • Q/D (22.5 mg/kg per day in divided doses q8h) ± another active agent[f]
Meningitis	• Linezolid (600 mg IV q12h) ± another CSF-penetrating active agent[h] • High-dose daptomycin[b] (plus intraventricular daptomycin) ± another CSF-penetrating active agent[h,j] • Q/D (22.5 mg/kg per day in divided doses q8h plus intraventricular Q/D)[i] ± another active agent[h]
Urinary tract infections	• Fosfomycin (3 g PO, one dose)[k] • Nitrofurantoin (100 mg PO q6h) • Ampicillin or amoxicillin (2 g IV/PO q4–6h)[l]

[a]Authors' preferences are underlined for each category; many of these regimens are off-label. [b]Daptomycin at doses of 10–12 mg/kg once daily is suggested (off-label). Close monitoring of creatine phosphokinase levels is recommended throughout therapy because of possible rhabdomyolysis. [c]Potentially active agents may include ampicillin or ceftaroline (even if the infecting strain is resistant in vitro) or tigecycline. In vitro synergism of daptomycin with ampicillin or ceftaroline has been observed against some isolates that subsequently become nonsusceptible to daptomycin during therapy. The synergism of daptomycin and β-lactams is associated with mutations in *liaFSR*. Consider combination therapy if the minimal inhibitory concentration (MIC) of daptomycin is ≥3 μg/mL. [d]Only if the organism does not exhibit high-level resistance to aminoglycosides (see Table 144-1, footnote *c*). [e]Quinupristin-dalfopristin (Q/D) lost U.S. Food and Drug Administration (FDA) approval for endocarditis due to VRE. [f]Agents that may be useful in combination with Q/D (if the isolate is susceptible to each agent) include doxycycline with rifampin (one reported case) or fluoroquinolones (one reported case). [g]In selected cases of catheter-associated bacteremia, removal of the catheter and a short course of therapy (~5–7 days) may be sufficient. A single positive blood culture that is likely to be associated with a catheter in a patient who is otherwise doing well may not require therapy after removal of the catheter. [h]Fluoroquinolones (e.g., moxifloxacin) and rifampin (if the isolate is susceptible to each agent) reach therapeutic levels in the cerebrospinal fluid. [i]Intrathecal Q/D (1–5 mg/d) has been used in combination with Q/D systemic therapy in meningitis. If Q/D is chosen, simultaneous use of both systemic and intrathecal therapy is suggested. [j]Intrathecal gentamicin (2–10 mg/d) if high-level resistance is not detected. Intraventricular daptomycin has been used in two cases of meningitis. [k]Approved by the FDA only for uncomplicated urinary tract infections caused by vancomycin-susceptible *E. faecalis*. [l]Concentrations of amoxicillin and ampicillin in urine far exceed those in serum and may be potentially effective even against isolates with high MICs. Doses up to 12 g/d are suggested for isolates with MICs of ≥64 μg/mL.

CHOICE OF ANTIMICROBIAL AGENTS

Among the β-lactams, the most active are the aminopenicillins (ampicillin, amoxicillin) and ureidopenicillins (i.e., piperacillin); next most active are penicillin G and imipenem. For *E. faecium*, a combination of high-dose ampicillin (up to 30 g/d) plus an aminoglycoside has been suggested—even for ampicillin-resistant strains

if the MIC is ≤64 µg/mL—since a plasma ampicillin concentration higher than this value can be achieved at high doses. The only two aminoglycosides recommended for synergistic therapy in severe enterococcal infections are gentamicin and streptomycin. The use of amikacin is strongly discouraged, tobramycin should never be used for the treatment of *E. faecium* infection, and aminoglycoside monotherapy should not be employed. Vancomycin is an alternative to β-lactam drugs for the treatment of *E. faecalis* infections but is less useful against *E. faecium* because resistance is common.

As mentioned above, use of the aminoglycoside–ampicillin combination for *E. faecalis* infections has become increasingly problematic because of toxicity in critically ill patients and increased rates of high-level resistance to aminoglycosides. An observational, nonrandomized, comparative study encompassing a multicenter cohort was conducted in 17 Spanish hospitals and one Italian hospital; the results indicated that a 6-week course of ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin in the treatment of *E. faecalis* endocarditis, with less risk of toxicity. Therefore, this regimen should be considered in patients at risk for aminoglycoside toxicity and is now recommended as first-line therapy.

Linezolid is the only agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of VRE infections (Table 144-2). (A prior approval for quinupristin/dalfopristin has been withdrawn.) Linezolid is not bactericidal, and its use in severe endovascular infections has produced mixed results; therefore, it is recommended only as an alternative to other agents for such infections. In addition, linezolid may cause significant toxicities (thrombocytopenia, peripheral neuropathy, and optic neuritis) when used in regimens given for >2 weeks. Nonetheless, linezolid may play a role in the treatment of enterococcal meningitis and other CNS infections, although clinical data are limited.

The lipopeptide daptomycin is a bactericidal antibiotic with potent in vitro activity against all enterococci. Although daptomycin is not approved by the FDA for the treatment of VRE or *E. faecium* infections, it has been used alone (at high dosage) or in combination with other agents (ampicillin, ceftaroline, and tigecycline) with apparent success against multidrug-resistant enterococcal infections (Tables 144-1 and 144-2). The main adverse reactions to daptomycin are elevated creatine phosphokinase levels and eosinophilic pneumonitis (rare). Daptomycin is not useful against pulmonary infections because the pulmonary surfactant inhibits its antibacterial activity.

The glycylcycline drug tigecycline is active in vitro against all enterococci, regardless of the isolates' vancomycin susceptibility. However, its use as monotherapy for endovascular or severe enterococcal infections is not recommended because of low attainable blood levels.

Telavancin, a lipoglycopeptide approved by the FDA for the treatment of skin and soft-tissue infections as well as hospital-associated pneumonia, is active against vancomycin-susceptible enterococci but not VRE. Oritavancin, a novel glycopeptide with activity against VRE, has been approved for the treatment of acute bacterial skin and soft-tissue infections caused by susceptible organisms, including vancomycin-susceptible *E. faecalis*. The MICs of oritavancin against VRE are low, and this compound may be a promising drug for VRE treatment in the future.

Lastly, tedizolid—a new oxazolidinone now available for clinical use—is approved only for the treatment of *E. faecalis* infections. Tedizolid is more potent than linezolid in vitro against VRE strains; however, its role in severe VRE infections remains to be determined.

ANTIMICROBIAL RESISTANCE

Resistance to β-lactam agents continues to be observed only infrequently in *E. faecalis* but is characteristic of *E. faecium*. The mechanism of ampicillin resistance in *E. faecium* is related to a penicillin-binding protein (PBP) designated PBP5, which is the target of β-lactam antibiotics. PBP5 exhibits low affinity for ampicillin and can synthesize cell wall in the presence of this antibiotic, even when other PBPs are inhibited. The version of this protein found in ampicillin-resistant hospital-associated strains has multiple amino-acid differences that even further decrease the affinity of PBP5 for ampicillin; these changes and/or hyperproduction of PBP5 are the two most common mechanisms of high-level ampicillin resistance (e.g., MIC, >32 µg/mL) in clinical strains.

Vancomycin is a glycopeptide antibiotic that inhibits cell-wall peptidoglycan synthesis in susceptible enterococci and has been widely used against enterococcal infections in clinical practice when the utility of β-lactams is limited by resistance, allergy, or adverse reactions. This effect is mediated by binding of the antibiotic to peptidoglycan precursors (UDP-MurNAc-pentapeptides) upon their exit from the bacterial cell cytoplasm. The interaction of vancomycin with the peptidoglycan is specific and involves the last two D-alanine residues of the precursor. The first isolates of VRE were documented in 1986, and vancomycin resistance (particularly in *E. faecium*) has since increased considerably around the world. The mechanism involves the replacement of the last D-alanine residue of peptidoglycan precursors with D-lactate or D-serine, with consequent high- and low-level resistance, respectively. There is significant heterogeneity among isolates, but either substitution substantially decreases the affinity of vancomycin for the peptidoglycan; with the D-lactate substitution, the MIC is increased up to 1000-fold. Vancomycin-resistant organisms also produce enzymes that destroy the D-alanine-D-alanine ending precursors, ensuring that additional binding sites for vancomycin are not available.

High-level resistance to aminoglycosides (of which gentamicin and streptomycin are the only two tested by clinical laboratories) abolishes the synergism observed between cell wall–active agents and the aminoglycoside. This important phenotype is routinely sought by the clinical laboratory in isolates from serious infections (Tables 144-1 and 144-2). Genes encoding aminoglycoside-modifying enzymes are usually the cause of high-level resistance to these compounds and are widely disseminated among enterococci, decreasing the options for the treatment of severe enterococcal infections.

Resistance to daptomycin has now been well documented in both *E. faecalis* and *E. faecium*. This resistance seems to be related to activation of the cell-membrane stress response that, in enterococci, is mainly regulated by a three-component system designated LiaFSR, although other systems have also been implicated. In addition, changes in the enzymes responsible for phospholipid metabolism are involved. Most important, activation of the LiaFSR system leads to tolerance to daptomycin and minor increases in MICs. Therefore, isolates with MICs of 3–4 µg/mL (close to the breakpoint of 4 µg/mL) should be judged to be potentially resistant, and alternative therapies (including combinations of daptomycin with ß-lactams; see above) should be considered.

Resistance to linezolid is usually due to mutations in the 23S rRNA genes or the presence of an rRNA methylase (designated *cfr*). A novel transferable gene (*optrA*) encoding a putative efflux pump has been implicated in linezolid resistance in enterococcal strains of human and animal origin.

Tigecycline resistance has been documented and appears to be related to changes in the S10 ribosomal protein.

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145 Diphtheria and Other Corynebacterial Infections

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DIPHTHERIA

Diphtheria is a nasopharyngeal and skin infection caused by *Corynebacterium diphtheriae*. Toxigenic strains of *C. diphtheriae* produce a protein toxin that causes systemic toxicity, myocarditis, and polyneuropathy. The toxin is associated with the formation of pseudomembranes in the pharynx during respiratory diphtheria. While toxigenic strains most frequently cause pharyngeal diphtheria, nontoxigenic strains commonly cause cutaneous disease.

ETIOLOGY

C. diphtheriae is a gram-positive bacillus that is unencapsulated, nonmotile, and nonsporulating. The organism was first identified microscopically in 1883 by Klebs and a year later was isolated in pure culture by Löffler in Robert Koch's laboratory. The bacteria have a characteristic club-shaped bacillary appearance and typically form clusters of parallel rays, or *palisades*, that are referred to as "Chinese characters." The specific laboratory media recommended for the cultivation of *C. diphtheriae* rely upon tellurite, colistin, or nalidixic acid for the organism's selective isolation from other autochthonous pharyngeal microbes. *C. diphtheriae* may be isolated from individuals with both nontoxigenic (*tox*$^-$) and toxigenic (*tox*$^+$) phenotypes. Uchida and Pappenheimer demonstrated that corynebacteriophage beta carries the structural gene *tox*, which encodes diphtheria toxin, and that a family of closely related corynebacteriophages are responsible for toxigenic conversion of *tox*$^-$ *C. diphtheriae* to the *tox*$^+$ phenotype. Moreover, lysogenic conversion from a nontoxigenic to a toxigenic phenotype has been shown to occur in situ. Growth of toxigenic strains of *C. diphtheriae* under iron-limiting conditions leads to the optimal expression of diphtheria toxin and is believed to be a pathogenic mechanism during human infection. Less commonly, diphtheria-like disease may be caused by *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*, which express the same toxin and are considered members of the *C. diphtheriae* group (discussed below).

EPIDEMIOLOGY

While in many regions diphtheria has been controlled in recent years with effective vaccination, there have been sporadic outbreaks in the United States and Europe. Diphtheria is still common in the Caribbean, Latin America, and the Indian subcontinent, where mass immunization programs are not enforced. Large-scale epidemics of diphtheria have occurred in the post–Soviet Union independent states. Additional outbreaks have recently been reported in Africa and Asia. In temperate regions, respiratory diphtheria occurs year-round but is most common during winter months.

C. diphtheriae is transmitted via the aerosol route, usually during close contact with an infected person. There are no significant reservoirs other than humans. The incubation period for respiratory diphtheria is 2–5 days, but disease onset has occurred as late as 10 days after exposure. Prior to the vaccination era, most individuals over the age of 10 were immune to *C. diphtheriae*; infants were protected by maternal IgG antibodies but became susceptible after ~6 months of age. Thus, the disease primarily affected children and nonimmune young adults.

The development of diphtheria antitoxin in 1898 by von Behring and of the diphtheria toxoid vaccine in 1924 by Ramon led to the near-elimination of diphtheria in Western countries. The annual incidence rate in the United States peaked in 1921, with 206,000 cases (191 cases per 100,000) and 15,520 deaths. In contrast, since 1980, the annual figure in the United States has been fewer than 5 cases per 100,000, with only two cases reported from 2004 through 2015. Nevertheless, pockets of colonization persist in North America, and groups or individuals who resist vaccination remain at risk. Immunity to diphtheria induced by childhood vaccination gradually decreases in adulthood. An estimated 30% of men 60–69 years old have antitoxin titers below the protective level. In addition to older age and lack of vaccination, risk factors for diphtheria outbreaks include alcoholism, low socioeconomic status, crowded living conditions, and Native American ethnic background. An outbreak of diphtheria in Seattle, Washington, between 1972 and 1982 comprised 1100 cases, most of which were cutaneous. During the 1990s in the states of the former Soviet Union, a much larger diphtheria epidemic included more than 140,000 cases and more than 4000 deaths; at its peak in 1995, more than 50,412 cases were reported. Clonally related toxigenic *C. diphtheriae* strains of the ET8 complex were associated with this outbreak. Beginning in 1998, this epidemic was controlled by mass vaccination programs, and between 2000 and 2009 the diphtheria incidence fell by >95%, with high-burden countries such as Latvia reporting fewer than 10 cases. During the epidemic, the incidence rate was high among individuals between 16 and 50 years of age. The epidemic was attributed to multiple factors, including socioeconomic instability, migration, deteriorating public health programs, unnecessary contraindications to vaccination, low-dose vaccine formulations, frequent vaccine and antitoxin shortages, delayed implementation of vaccination and treatment in response to cases, public mistrust, and lack of awareness.

Since 2010, significant outbreaks of diphtheria and diphtheria-related mortality have continued to be reported from many developing countries, including the Dominican Republic, Nigeria, India, Laos, Thailand, Indonesia, and Brazil. Statistics collected by the World Health Organization indicated that 7321 diphtheria cases were reported in 2014, but many more cases are likely to have gone unreported. Although 86% of the global population has been adequately vaccinated, only 28% of countries have successfully vaccinated >80% of individuals in all districts.

Cutaneous diphtheria is usually a secondary infection that follows a primary skin lesion due to trauma, allergy, or autoimmunity. Most often, these isolates lack the *tox* gene and thus do not express diphtheria toxin. In tropical latitudes, cutaneous diphtheria is more common than respiratory diphtheria. In contrast to respiratory disease, cutaneous diphtheria is not reportable in the United States. Nontoxigenic strains of *C. diphtheriae* have been associated with pharyngitis in Europe, causing outbreaks among men who have sex with men and persons who use illicit IV drugs.

PATHOGENESIS AND IMMUNOLOGY

Diphtheria toxin produced by *tox*$^+$ strains of *C. diphtheriae* is the primary virulence factor in clinical disease. The toxin is synthesized in precursor form; is released as a 535-amino-acid, single-chain protein; and, in sensitive species (e.g., guinea pigs and humans, but not mice or rats), has a 50% lethal dose of ~100 ng/kg of body weight. The toxin is produced in the pseudomembranous lesion and is taken up in the bloodstream, from which it is distributed to all organ systems in the body. Once bound to its cell surface receptor (a heparin-binding epidermal growth factor–like precursor), the toxin is internalized by receptor-mediated endocytosis and enters the cytosol from an acidified early endosomal compartment. In vitro, the toxin may be separated into two chains by digestion with serine proteases: the N-terminal A fragment and the C-terminal B fragment. Delivery of the A fragment into the eukaryotic cell cytosol results in irreversible inhibition of protein synthesis by NAD^+-dependent ADP-ribosylation of elongation factor 2. The eventual result is the death of the cell.

In 1926, Ramon at the Institut Pasteur found that formalinization of diphtheria toxin resulted in the production of a nontoxic but highly immunogenic diphtheria toxoid. Subsequent studies showed that immunization with diphtheria toxoid elicited antibodies that neutralized the toxin and prevented most disease manifestations. In the 1930s, mass immunization of children and susceptible adults with diphtheria toxoid commenced in the United States and Europe.

Individuals with a diphtheria antitoxin titer of >0.01 U/mL are at low risk of disease. In populations where a majority of individuals have protective antitoxin titers, the carrier rate for toxigenic strains of *C. diphtheriae* decreases and the overall risk of diphtheria among

susceptible individuals is reduced. Nevertheless, individuals with nonprotective titers may contract diphtheria through either travel or exposure to individuals who have recently returned from regions where the disease is endemic.

Characteristic pathologic findings of diphtheria include mucosal ulcers with a pseudomembranous coating composed of an inner band of fibrin and a luminal band of neutrophils. Initially white and firmly adherent, in advanced diphtheria the pseudomembranes turn gray or even green or black as necrosis progresses. Mucosal ulcers result from toxin-induced necrosis of the epithelium accompanied by edema, hyperemia, and vascular congestion of the submucosal base. A significant fibrinosuppurative exudate from the ulcer develops into the pseudomembrane. Ulcers and pseudomembranes in severe respiratory diphtheria may extend from the pharynx into medium-sized bronchial airways. Expanding and sloughing membranes may result in fatal airway obstruction.

APPROACH TO THE PATIENT

Diphtheria

Diphtheria, although rare in the United States and other developed countries, should be considered when a patient has severe pharyngitis, particularly when there is difficulty swallowing, respiratory compromise, or signs of systemic disease (e.g., myocarditis or generalized weakness). The leading causes of pharyngitis are respiratory viruses (rhinoviruses, influenza viruses, parainfluenza viruses, coronaviruses, adenoviruses; ~25% of cases), group A streptococci (15–30%), group C streptococci (~5%), atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (15–20% in some series), and other viruses such as herpes simplex virus (~4%) and Epstein-Barr virus (<1% in infectious mononucleosis). Less common causes are acute HIV infection, gonorrhea, fusobacterial infection (e.g., Lemierre's syndrome), thrush due to *Candida albicans* or other *Candida* species, and diphtheria. The presence of a pharyngeal pseudomembrane or an extensive exudate should prompt consideration of diphtheria **(Figure 145-1)**.

CLINICAL MANIFESTATIONS

Respiratory Diphtheria The clinical diagnosis of diphtheria is based on the constellation of sore throat; adherent tonsillar, pharyngeal, or nasal pseudomembranous lesions; and low-grade fever. In addition, diagnosis requires the isolation of *C. diphtheriae* or histopathologic isolation of compatible gram-positive organisms. The Centers for Disease Control and Prevention (CDC) recognizes *confirmed* respiratory diphtheria (laboratory proven or epidemiologically linked to a culture-confirmed case) and *probable* respiratory diphtheria (clinically compatible but not laboratory proven or epidemiologically linked). Carriers are defined as individuals who have positive cultures for *C. diphtheriae* and who either are asymptomatic or have symptoms but lack pseudomembranes. Most patients seek medical care for sore throat and fever several days into the illness. Occasionally, weakness, dysphagia, headache, and voice change are the initial manifestations. Neck edema and difficulty breathing are evident in more advanced cases and carry a poor prognosis.

The systemic manifestations of diphtheria stem from the effects of diphtheria toxin and include weakness as a result of neurotoxicity and cardiac arrhythmias or congestive heart failure due to myocarditis. Most commonly, the pseudomembranous lesion is located in the tonsillopharyngeal region. Less commonly, the lesions are located in the larynx, nares, and trachea or bronchial passages. Large pseudomembranes are associated with severe disease and a poor prognosis. A few patients develop massive swelling of the tonsils and present with "bull-neck" diphtheria, which results from edema of the submandibular and paratracheal region and is further characterized by foul breath, thick speech, and stridorous breathing. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis, the pseudomembrane in diphtheria is tightly adherent to the underlying tissues. Attempts to dislodge the membrane may cause bleeding. Hoarseness suggests laryngeal diphtheria, in which laryngoscopy may be diagnostically helpful.

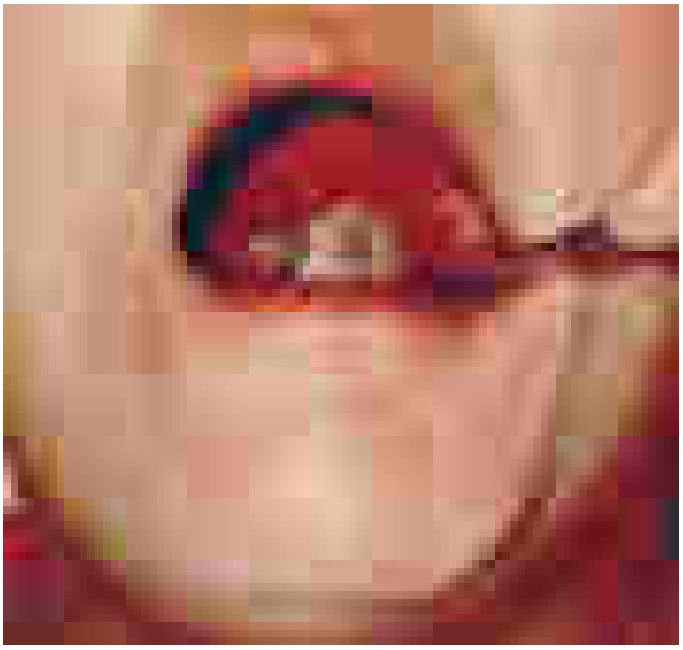

FIGURE 145-1 Respiratory diphtheria due to toxigenic *C. diphtheriae* producing exudative pharyngitis in a 47-year-old woman displaying neck edema and a pseudomembrane extending from the uvula to the pharyngeal wall. The characteristic white pseudomembrane is caused by diphtheria toxin–mediated necrosis of the respiratory epithelial layer, producing a fibrinous coagulative exudate. Submucosal edema adds to airway narrowing. The pharyngitis is acute in onset, and respiratory obstruction from the pseudomembrane may occur in severe cases. Inoculation of pseudomembrane fragments or submembranous swabs onto Löffler's or tellurite selective medium reveals *C. diphtheriae*. *(Photograph by P Strebel, MD, used by permission. From R Kadirova et al: J Infect Dis 181:S110, 2000. With permission of Oxford University Press.)*

Cutaneous Diphtheria This dermatosis is characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation **(Figure 145-2)**. The diagnosis requires cultivation of *C. diphtheriae* from lesions, which most commonly occur on the lower and upper extremities, head, and trunk.

Infections Due to Non-*diphtheriae Corynebacterium* Species and Nontoxigenic *C. diphtheriae* Non-*diphtheriae* species of *Corynebacterium* and related genera (discussed below) as well as nontoxigenic strains of *C. diphtheriae* itself have been found in bloodstream

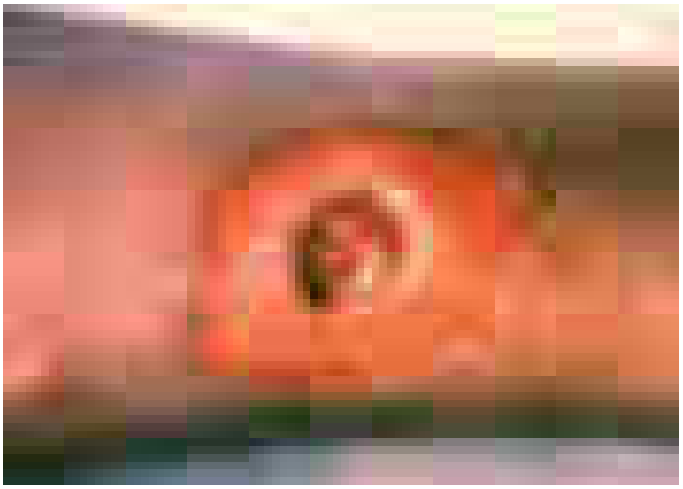

FIGURE 145-2 Cutaneous diphtheria due to nontoxigenic *C. diphtheriae* on the lower extremity. *(From the Centers for Disease Control and Prevention, Public Health Image Library [PHIL]. #1941.)*

and respiratory infections, often in individuals with immunosuppression or chronic respiratory disease. These organisms can cause disease manifestations and should not necessarily be dismissed as colonizers.

Other Clinical Manifestations *C. diphtheriae* causes rare cases of endocarditis and septic arthritis, most often in patients with preexisting risk factors, such as abnormal cardiac valves, injection drug use, or cirrhosis.

COMPLICATIONS

Airway obstruction poses a significant early risk in patients presenting with advanced diphtheria. Pseudomembranes may slough and obstruct the airway or may advance to the larynx or into the tracheobronchial tree. Children are particularly prone to obstruction because of their small airways.

Polyneuropathy and myocarditis are late toxic manifestations of diphtheria. During a diphtheria outbreak in the Kyrgyz Republic in 1999, myocarditis was found in 22% and neuropathy in 5% of 676 hospitalized patients. The mortality rate was 7% among patients with myocarditis as opposed to 2% among those without myocardial manifestations. The median time to death in hospitalized patients was 4.5 days. Myocarditis is typically associated with arrhythmias and dilated cardiomyopathy.

Polyneuropathy is seen 3–5 weeks after the onset of diphtheria and has a slow indolent course. However, patients may develop severe and prolonged neurologic abnormalities. The disorders typically occur in the mouth and neck, with lingual or facial numbness as well as dysphonia, dysphagia, and cranial nerve paresthesias. More ominous signs include weakness of respiratory and abdominal muscles and paresis of the extremities. Sensory manifestations and sensory ataxia also are observed. Cranial nerve dysfunction typically precedes disturbances of the trunk and extremities because of proximity to the site of infection. Autonomic dysfunction also is associated with polyneuropathy and can lead to hypotension. Polyneuropathy is typically reversible in patients who survive the acute phase.

Other complications of diphtheria include pneumonia, renal failure, encephalitis, cerebral infarction, pulmonary embolism, and serum sickness from antitoxin therapy.

DIAGNOSIS

The diagnosis of diphtheria is based on clinical signs and symptoms plus laboratory confirmation. Respiratory diphtheria should be considered in patients with sore throat, pharyngeal exudates, and fever. Other symptoms may include hoarseness, stridor, or palatal paralysis. The presence of a pseudomembrane should prompt strong consideration of diphtheria. Once a clinical diagnosis of diphtheria is made, diphtheria antitoxin should be obtained and administered as rapidly as possible.

Laboratory diagnosis of diphtheria is based either on cultivation of *C. diphtheriae* or toxigenic *C. ulcerans* from the site of infection or on the demonstration of local lesions with characteristic histopathology. *Corynebacterium pseudodiphtheriticum*, a nontoxigenic organism, is a common component of the normal throat flora and does not pose a significant risk. Throat samples should be submitted to the laboratory for culture with the notation that diphtheria is being considered. This information should prompt cultivation on special selective medium and subsequent biochemical testing to differentiate *C. diphtheriae* from other nasopharyngeal commensal corynebacteria. All laboratory isolates of *C. diphtheriae,* including nontoxigenic strains, should be submitted to the CDC.

A diagnosis of cutaneous diphtheria requires laboratory confirmation since the lesions are not characteristic and are indistinguishable from other dermatoses. Diphtheritic ulcers occasionally—but not consistently—have a punched-out appearance (Fig. 145-2). Patients in whom cutaneous diphtheria is identified should have the nasopharynx cultured for *C. diphtheriae*. The laboratory medium for cutaneous diphtheria specimens is the same as that used for respiratory diphtheria: Löffler's or Tinsdale's selective medium in addition to nonselective medium such as blood agar. As has been mentioned, respiratory diphtheria remains a notifiable disease in the United States, whereas cutaneous diphtheria is not.

TREATMENT

Diphtheria

DIPHTHERIA ANTITOXIN

Prompt administration of diphtheria antitoxin is critical in the management of respiratory diphtheria. Diphtheria antitoxin, a horse antiserum, is effective in reducing the extent of local disease as well as the risk of complications of myocarditis and neuropathy. Rapid institution of antitoxin therapy is also associated with a significant reduction in mortality risk. Because diphtheria antitoxin cannot neutralize cell-bound toxin, prompt initiation is important. This product, which is no longer commercially available in the United States, can be obtained from the CDC Emergency Operations Center at 770-488-7100 (website: *www.cdc.gov/diphtheria/dat.html*) after first contacting the state health department. The current protocol for the use of diphtheria antitoxin involves a test dose to rule out immediate hypersensitivity. Patients who demonstrate hypersensitivity require desensitization before a full therapeutic dose of antitoxin is administered.

Given that the world supply of equine anti–diphtheria toxin is limited, a human monoclonal antibody with the potential to provide a safer alternative to equine antitoxin therapy is being developed.

ANTIMICROBIAL THERAPY

Antibiotics are used in the management of diphtheria primarily to prevent transmission to susceptible contacts. Antibiotics also prevent further toxin production and reduce the severity of local infection. Recommended treatment options for patients with respiratory diphtheria are as follows:

- Procaine penicillin G, 600,000 U IM q12h (for children: 12,500–25,000 U/kg IM q12h) until the patient can swallow comfortably; then oral penicillin V, 125–250 mg qid to complete a 14-day course
- Erythromycin, 500 mg IV q6h (for children: 40–50 mg/kg per day IV in two or four divided doses) until the patient can swallow comfortably; then 500 mg PO qid to complete a 14-day course

A clinical study in Vietnam found that penicillin was associated with a more rapid resolution of fever and a lower rate of bacterial resistance than erythromycin; however, relapses were more common in the penicillin group. Erythromycin therapy targets protein synthesis and thus offers the presumed benefit of stopping toxin synthesis more quickly than a cell wall–active β-lactam agent. Alternative therapeutic agents for patients who are allergic to penicillin or cannot take erythromycin include rifampin and clindamycin. Other reasonable antibiotics are clarithromycin, azithromycin, linezolid, and vancomycin, although they have not been studied in comparison to the agents above.

Eradication of *C. diphtheriae* should be documented after antimicrobial therapy is complete. A repeat throat culture 2 weeks later is recommended. For patients in whom the organism is not eradicated after a 14-day course of erythromycin or penicillin, an additional 10-day course followed by repeat culture is recommended. Drug-resistant strains of *C. diphtheriae* exist, and several reports have described multidrug-resistant strains, predominantly in Southeast Asia. Drug resistance should be considered when efforts at pathogen eradication fail.

Cutaneous diphtheria should be treated as described above for respiratory disease. Individuals infected with toxigenic strains should receive antitoxin. It is important to treat the underlying cause of the dermatoses in addition to the superinfection with *C. diphtheriae*.

Patients who recover from respiratory or cutaneous diphtheria should have antitoxin levels measured. If diphtheria antitoxin has been administered, this test should be performed 6 months later. Patients who recover from respiratory or cutaneous diphtheria should receive the appropriate vaccine to ensure the development of protective antibody titers.

MANAGEMENT STRATEGIES

Patients in whom diphtheria is suspected should be hospitalized in respiratory isolation rooms, with close monitoring of cardiac and respiratory function. A cardiac workup is recommended to assess the possibility of myocarditis. In patients with extensive pseudomembranes, an anesthesiology or an ear, nose, and throat consultation is recommended because of the possible need for tracheostomy or intubation. In some settings, pseudomembranes can be removed surgically. Treatment with glucocorticoids has not been shown to reduce the risk of myocarditis or polyneuropathy.

PROGNOSIS

The mortality rate for diphtheria is 5–10% but may approach 20% among children <5 years old and adults >40 years of age. Fatal pseudomembranous diphtheria typically occurs in patients with nonprotective antibody titers and in unimmunized patients. The pseudomembrane may actually increase in size from the time it is first noted. Risk factors for death include bullneck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudomembrane elongation; and laryngeal, tracheal, or bronchial involvement. Another important predictor of fatal outcome is the interval between the onset of local disease and the administration of antitoxin. Cutaneous diphtheria has a low mortality rate and is rarely associated with myocarditis or peripheral neuropathy.

PREVENTION

Vaccination Sustained campaigns for vaccination of children and adequate boosting vaccination of adults are responsible for the exceedingly low incidence of diphtheria in most developed nations. Currently, diphtheria toxoid vaccine is coadministered with tetanus vaccine (with or without acellular pertussis). DTaP (full-level diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine) is currently recommended for children up to the age of 6; DTaP replaced the earlier whole-cell pertussis vaccine DTP in 1997. Tdap is a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine formulated for adolescents and adults. Tdap was licensed for use in the United States in 2005 and is recommended for children ≥7 years old and for adults. It is recommended that all adults (i.e., persons >19 years old) receive a single dose of Tdap if they have not received it previously, regardless of the interval since the last dose of Td (tetanus and reduced-dose diphtheria toxoids, adsorbed). Tdap vaccination is a priority for health care workers, pregnant women, adults anticipating contact with infants, and adults not previously vaccinated for pertussis. Adults who have received acellular pertussis vaccine should continue to receive decennial Td booster vaccinations. **The vaccine schedule is detailed in Chap. 118.**

Prophylaxis Administration to Contacts Close contacts of diphtheria patients should undergo throat culture to determine whether they are carriers. After samples for throat culture are obtained, antimicrobial prophylaxis should be considered for all contacts, even those whose cultures are negative. The options are 7–10 days of oral erythromycin or one dose of IM benzathine penicillin G (1.2 million units for persons ≥6 years of age or 600,000 units for children <6 years of age).

Contacts of diphtheria patients whose immunization status is uncertain should receive the appropriate diphtheria toxoid–containing vaccine. The Tdap vaccine (rather than Td) is now the booster vaccine of choice for adults who have not recently received an acellular pertussis–containing vaccine. Carriers of *C. diphtheriae* in the community should be treated and vaccinated when identified.

OTHER CORYNEBACTERIAL AND *RHODOCOCCUS* INFECTIONS

Nondiphtherial corynebacteria, referred to as *diphtheroids* or *coryneforms*, are frequently considered colonizers or contaminants; however, they have been associated with invasive disease, particularly in immunocompromised patients. These organisms have been isolated from the bloodstream, especially in association with catheter infection, endocarditis, prosthetic valve infection, meningitis, brain abscess, osteomyelitis, and peritonitis. Risk factors include indwelling intravenous or peritoneal catheters and neurosurgical shunts. Patients infected with these organisms are often immunosuppressed or have significant medical comorbidities. The nondiphtherial coryneforms are a collection of bacteria that are taxonomically grouped together in the genus *Corynebacterium* on the basis of their 16S rDNA signature nucleotides. Despite the shared rDNA signatures, these isolates are quite diverse. For example, their guanine-cytosine content ranges from 45 to 70%. Several nondiphtheroid corynebacteria, including *Corynebacterium jeikeium* and *Corynebacterium urealyticum*, are associated with resistance to multiple antibiotics. *Rhodococcus equi* is associated with necrotizing pneumonia and granulomatous infection, particularly in immunocompromised individuals.

MICROBIOLOGY AND LABORATORY DIAGNOSIS

These organisms are non-acid-fast, catalase-positive, aerobic or facultatively anaerobic rods. Their colonial morphologies on blood agar vary widely; some species are small and α-hemolytic (similar to lactobacilli), whereas others form large white colonies (similar to yeasts). Many nondiphtherial coryneforms require special media, such as Löffler's, Tinsdale's, or tellurite medium. These cultivation idiosyncrasies have led to a complex taxonomic categorization of the organisms.

EPIDEMIOLOGY

Humans are the natural reservoirs for several nondiphtherial coryneforms, including *C. xerosis*, *C. pseudodiphtheriticum*, *C. striatum*, *C. minutissimum*, *C. jeikeium*, *C. urealyticum*, and *Arcanobacterium haemolyticum*. Animal reservoirs are responsible for carriage of *Arcanobacterium pyogenes*, *C. ulcerans*, and *C. pseudotuberculosis*. Soil is the natural reservoir for *R. equi*.

C. pseudodiphtheriticum is a component of the normal flora of the human pharynx and skin. *C. xerosis* is found on the skin, nasopharynx, and conjunctiva; *C. auris* in the external auditory canal; and *C. striatum* in the anterior nares and on the skin. *C. jeikeium* and *C. urealyticum* are found in the axilla, groin, and perineum, particularly in hospitalized patients. Infections with *C. ulcerans* and *C. pseudotuberculosis* have been associated with the consumption of raw milk from infected cattle.

C. ulcerans This organism causes a diphtheria-like illness and produces both diphtheria toxin and a dermonecrotic toxin. The organism is a commensal in horses and cattle and has been isolated from cow's milk. In contrast to diphtheria, this infection is considered a zoonosis, and cases have been traced to contact with animal carriers, including dogs and pigs. *C. ulcerans* causes exudative pharyngitis, primarily during summer months, in rural areas, and among individuals exposed to animals. Treatment with antitoxin and antibiotics should be initiated when respiratory *C. ulcerans* is identified, and a contact investigation (including throat cultures to determine the need for antimicrobial prophylaxis and, in unimmunized contacts, administration of the appropriate diphtheria toxoid–containing vaccine) should be conducted. The organism grows on Löffler's, Tinsdale's, and telluride agars as well as blood agar. In addition to exudative pharyngitis, cutaneous disease due to *C. ulcerans* has been reported. *C. ulcerans* is susceptible to a wide panel of antibiotics. Erythromycin and macrolides appear to be the first-line agents.

C. pseudotuberculosis (ovis) Infection caused by *C. pseudotuberculosis* is rare and is reported predominantly from Australia. *C. pseudotuberculosis* causes suppurative granulomatous lymphadenitis and an eosinophilic pneumonia syndrome among individuals who handle sheep; horses, cattle, goats, deer, and raw milk have also been implicated. The organism is an important veterinary pathogen, causing suppurative lymphadenitis, abscesses, and pneumonia, but is rarely a human pathogen. Surgical excision of affected lymph nodes should be performed when feasible, and successful treatment with erythromycin or tetracycline has been reported. Some strains express diphtheria toxin and produce a diphtheria-like disease, which should be treated with antitoxin.

***C. jeikeium* (Group JK)** Originally described in American hospitals, *C. jeikeium* infection was subsequently reported in Europe. After a 1976 survey of diseases caused by nondiphtherial corynebacteria, CDC group JK emerged as an important opportunistic pathogen among neutropenic and HIV-infected patients. The organism has now been designated a separate species. *C. jeikeium* forms small, gray to white, glistening, nonhemolytic colonies on blood agar. It lacks urease and nitrate reductase and does not ferment most carbohydrates. The predominant syndrome associated with *C. jeikeium* is sepsis, sometimes with associated pneumonia, endocarditis, meningitis, osteomyelitis, or epidural abscess. Risk factors for *C. jeikeium* infection include hematologic malignancy, neutropenia from comorbid conditions, prolonged hospitalization, exposure to multiple antibiotics, and skin disruption. There is evidence that *C. jeikeium* is part of the inguinal, axillary, genital, and perirectal flora of hospitalized patients.

Broad-spectrum antimicrobial therapy appears to select for colonization. The organisms appear as gram-positive coccobacillary forms slightly resembling streptococci. *C. jeikeium* is resistant to the majority of antibiotic classes except oxazolidinones (e.g., linezolid) and glycopeptides (e.g., vancomycin). Effective therapy involves removal of the infectious source, whether a catheter, prosthetic joint, or prosthetic valve. Efforts have been made to prevent *C. jeikeium* infection with strict institution of infection control protocols for high-risk patients, particularly those in intensive care units.

***C. urealyticum* (Group D2)** Identified as a urease-positive nondiphtherial *Corynebacterium* in 1972, *C. urealyticum* is an opportunistic pathogen causing sepsis and urinary tract infection. *C. urealyticum* appears to be the etiologic agent of a severe urinary tract syndrome known as *alkaline-encrusted cystitis*, a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phosphate on the surface and walls of ulcerating lesions in the bladder. In addition, *C. urealyticum* has been associated with pneumonia, peritonitis, endocarditis, osteomyelitis, and wound infection. It is similar to *C. jeikeium* in its resistance to most antibiotics except oxazolidinones and glycopeptides. Vancomycin therapy has been used successfully in severe infections.

***C. minutissimum* (Erythrasma)** Erythrasma is a cutaneous infection producing reddish-brown, macular, scaly, pruritic intertriginous patches. The dermatologic presentation under the Wood's lamp is of coral red fluorescence. *C. minutissimum* appears to be a common cause of erythrasma, although there is evidence for a polymicrobial etiology in certain settings. This microbe has also been associated with bacteremia in patients with hematologic malignancy. Erythrasma responds to topical erythromycin, clarithromycin, clindamycin, or fusidic acid, although more severe infections may require oral macrolide therapy.

Other Nondiphtherial Corynebacterial *C. xerosis* is a human commensal found in the conjunctiva, nasopharynx, and skin. This nontoxigenic organism is occasionally identified as a source of invasive infection in immunocompromised or postoperative patients and prosthetic joint recipients. *C. striatum* is found in the anterior nares, skin, face, and upper torso of healthy individuals. Also nontoxigenic, this organism has been associated with invasive opportunistic infections in severely ill or immunocompromised patients. *C. amycolatum* is isolated from human skin and is identified on the basis of a unique 16S ribosomal RNA sequence associated with opportunistic infection. *C. glucuronolyticum* is a nonlipophilic species that causes male genitourinary tract infections such as prostatitis and urethritis. These infections may be successfully treated with a wide variety of antibacterial agents, including β-lactams, rifampin, aminoglycosides, or vancomycin; however, the organism appears to be resistant to fluoroquinolones, macrolides, and tetracyclines. *C. imitans* has been identified in eastern Europe as a nontoxigenic cause of pharyngitis. *C. auris* has been identified in children with otitis media; it is susceptible to fluoroquinolones, rifampin, tetracycline, and vancomycin but resistant to penicillin G and variably susceptible to macrolides. *C. pseudodiphtheriticum* (*C. hoffmannii*) is a nontoxigenic species that is part of the normal human flora. Human infections—particularly endocarditis of either prosthetic or natural valves and invasive pneumonia—have been reported only rarely. Although *C. pseudodiphtheriticum* may be isolated from the nasopharynx of patients with suspected diphtheria, it is part of the normal flora and does not produce diphtheria toxin. *C. propinquum*, a close relative of *C. pseudodiphtheriticum*, is part of CDC group ANF-3 and has been isolated from the human respiratory tract and blood. *C. afermentans* subspecies *lipophilum* belongs to CDC group ANF-1 and has been isolated from human blood and abscesses. *C. accolens* has been isolated from wound drainage, throat swabs, and sputum and is typically identified as a satellite of staphylococcal organisms; this species has been associated with endocarditis. *C. bovis* is a veterinary commensal that has not been clearly associated with human disease. *C. aquaticum* is a water-dwelling organism that is occasionally isolated from patients using medical devices (e.g., for chronic ambulatory peritoneal dialysis or venous access).

Rhodococcus *Rhodococcus* species are phylogenetically related to the corynebacteria. These gram-positive coccobacilli have been associated with tuberculosis-like infections in humans with granulomatous pathology. While *R. equi* is best known, other species have been identified, including *R.* (*Gordonia*) *bronchialis*, *R.* (*Tsukamurella*) *aurantiacus*, *R. luteus*, *R. erythropolis*, *R. rhodochrous*, and *R. rubropertinctus*.

R. equi has been recognized as a cause of pneumonia in horses since the 1920s and as a cause of related infections in cattle, sheep, and swine. It is found in soil as an environmental microbe. The organisms vary in length; appear as spherical to long, curved, clubbed rods; and produce large irregular mucoid colonies. *R. equi* cannot ferment carbohydrates or liquefy gelatin and is often acid fast. An intracellular pathogen of macrophages, *R. equi* can cause granulomatous necrosis and caseation. This organism has most commonly been identified in pulmonary infection, but infections of brain, bone, and skin also have been reported. Most commonly, *R. equi* disease manifests as nodular cavitary pneumonia of the upper lobe—a picture similar to that seen in tuberculosis or nocardiosis. Most patients are immunocompromised, often by HIV infection. Subcutaneous nodular lesions have also been identified. The involvement of *R. equi* should be considered when any patient presents with a tuberculosis-like syndrome.

Infection due to *R. equi* has been treated successfully with antibiotics that penetrate intracellularly, including macrolides, clindamycin, rifampin, and trimethoprim-sulfamethoxazole. β-Lactam antibiotics have not been useful. The organism is routinely susceptible to vancomycin, which is considered the drug of choice.

Other Related Species • ***ACTINOMYCES PYOGENES*** This organism, a well-known pathogen of cattle, sheep, goats, and pigs, causes seasonal leg ulcers in rural Thailand. A few human cases of sepsis, endocarditis, septic arthritis, pneumonia, meningitis, and empyema have been reported. This species is susceptible to β-lactams, tetracyclines, aminoglycosides, and fluoroquinolones.

ARCANOBACTERIUM HAEMOLYTICUM *A. haemolyticum* was identified as an agent of wound infections in U.S. soldiers in the South Pacific during World War II. It appears to be a human commensal of the nasopharynx and skin, but has also been implicated in pharyngitis and chronic skin ulcers. In contrast to the much more common pharyngitis caused by *Streptococcus pyogenes*, *A. haemolyticum* pharyngitis is associated with a scarlatiniform rash on the trunk and proximal extremities in about half of cases; this illness is occasionally confused with toxic shock syndrome. Because *A. haemolyticum* pharyngitis primarily affects teenagers, it has been postulated that the rash–pharyngitis syndrome may represent co-pathogenicity, synergy, or opportunistic secondary infection with Epstein-Barr virus. *A. haemolyticum* has also been reported as a cause of bacteremia, soft tissue infections, osteomyelitis, and cavitary pneumonia, predominantly in the setting of underlying diabetes mellitus. The organism is susceptible to β-lactams, macrolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. Penicillin resistance has been reported.

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146 *Listeria monocytogenes* Infections

Elizabeth L. Hohmann, Daniel A. Portnoy

Listeria monocytogenes is a food-borne pathogen that can cause serious infections, particularly in pregnant women and immunocompromised individuals. A ubiquitous saprophytic environmental bacterium, *L. monocytogenes* is also a facultative intracellular pathogen with a broad host range. Humans are probably accidental hosts for this microorganism. *L. monocytogenes* is of interest not only to clinicians but also to basic scientists as a model intracellular pathogen that is used to study basic mechanisms of microbial pathogenesis and host immunity.

MICROBIOLOGY

L. monocytogenes is a facultatively anaerobic, nonsporulating, gram-positive rod that grows over a broad temperature range, including refrigeration temperatures. This organism is motile during growth at low temperatures but much less so at 37°C. The vast majority of cases of human listerial disease can be traced to serotypes 1/2a, 1/2b, and 4. *L. monocytogenes* is weakly β-hemolytic on blood agar, and (as detailed below) its β-hemolysin is an essential determinant of its pathogenicity.

PATHOGENESIS

Infections with *L. monocytogenes* follow ingestion of contaminated food that contains the bacteria at high concentrations. The conversion from environmental saprophyte to pathogen involves the coordinate regulation of bacterial determinants of pathogenesis that mediate entry into cells, intracellular growth, and cell-to-cell spread. Many of the organism's pathogenic strategies can be examined experimentally in tissue culture models of infection **(Fig. 146-1)**. Like other enteric pathogens, *L. monocytogenes* induces its own internalization by cells that are not normally phagocytic. Its entry into cells is mediated by host surface proteins classified as internalins. Internalin-mediated entry is important in the crossing of intestinal, blood–brain, and fetoplacental barriers, although how *L. monocytogenes* traffics from the intestine to the brain or fetus is only beginning to be investigated. In a pregnant guinea pig model of infection, *L. monocytogenes* was shown to traffic from maternal organs to the placenta; surprisingly, however, it also trafficked from the placenta back to maternal organs. These data are consistent with a model in which miscarriage can be viewed as a host defense strategy to eliminate a nidus of infection.

An essential determinant of the pathogenesis of *L. monocytogenes* is its β-hemolysin, listeriolysin O (LLO). LLO is a pore-forming, cholesterol-dependent cytolysin. (Related cytolysins include streptolysin O, pneumolysin, and perfringolysin O, all of which are produced by extracellular pathogens.) LLO is largely responsible for mediating rupture of the phagosomal membrane that forms after phagocytosis of *L. monocytogenes*. LLO probably acts by insertion into an acidifying phagosome, which prevents the vesicle's maturation. In addition, LLO acts as a translocation pore for one or both of the *L. monocytogenes* phospholipases that also contribute to vacuolar lysis by blocking host cell autophagy. LLO synthesis and activity are controlled at multiple levels to ensure that its lytic activity is limited to acidic vacuoles and does not affect the cytosol. Mutations in LLO that influence its synthesis, cytosolic half-life, or pH optimum cause premature toxicity to infected cells. There is an inverse relationship between toxicity and virulence—i.e., the more cytotoxic the strain, the less virulent it is in animals. This relationship may seem paradoxical, but, as an intracellular pathogen, *L. monocytogenes* benefits from leaving its host cell unharmed.

Shortly after exposure to the mammalian-cell cytosol, *L. monocytogenes* expresses a surface protein, ActA, that mediates the nucleation of host actin filaments to propel the bacteria intra- and intercellularly. ActA mimics host proteins of the Wiskott-Aldrich syndrome protein (WASP) family by promoting the actin nucleation properties of the Arp2/3 complex. Thus, *L. monocytogenes* can enter the cytosol of almost any eukaryotic cell or cell extract and can exploit a conserved and essential actin-based motility system. Other pathogens as diverse as certain *Shigella*, *Mycobacterium*, *Rickettsia*, and *Burkholderia* species use a related pathogenic strategy that allows cell-to-cell spread without exposure to the extracellular milieu.

IMMUNE RESPONSE

The innate and acquired immune responses to *L. monocytogenes* have been studied extensively in mice. Shortly after IV injection, most bacteria are found in liver macrophages, with some organisms in splenic dendritic cells and macrophages. Listeriae that survive the bactericidal activity of initially infected macrophages grow in the cytosol and spread from cell to cell. *L. monocytogenes* triggers three innate immune pathways: a MyD88-dependent pathway that leads to inflammatory cytokine production; a STING/IRF3 pathway that is triggered by secreted bacterial cyclic di-adenosine monophosphate and leads to a type I interferon response; and low-level inflammasome activation that is triggered by DNA from infrequent bacteriolysis. Neutrophils

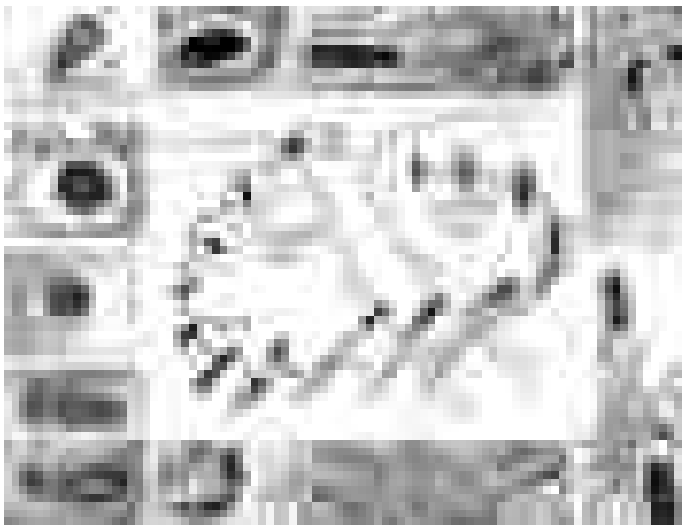

FIGURE 146-1 Stages in the intracellular life cycle of *Listeria monocytogenes*. The central diagram depicts cell entry, escape from a vacuole, actin nucleation, actin-based motility, and cell-to-cell spread. Surrounding the diagram are representative electron micrographs from which it was derived. ActA, surface protein mediating nucleation of host actin filaments to propel bacteria intra- and intercellularly; LLO, listeriolysin O; PLCs, phospholipases C; Inl, internalin. See text for further details. *(Adapted with permission from LG Tilney, DA Portnoy: J Cell Biol 109:1597, 1989. © Rockefeller University Press.)*

are crucial to host defense during the first 24 h of infection, whereas an influx of activated macrophages from the bone marrow is critical subsequently. Mice that survive sublethal infection clear the organisms within a week, with consequent sterile immunity. Studies with knockout mice have been instrumental in dissecting the roles played by chemokines and cytokines during infection. For example, interferon γ, tumor necrosis factor, and CCR2 are essential in controlling infection. While innate immunity is sufficient to control infection, the acquired immune response is required for sterile immunity. Immunity is cell mediated; antibody plays no measurable role. The critical effector cells are cytotoxic (CD8+) T cells that recognize and lyse infected cells; the resulting extracellular bacteria are killed by circulating activated phagocytes.

A hallmark of the *L. monocytogenes* model is that killed vaccines do not provide protective immunity. The explanation for this fundamental observation is multifactorial, involving the generation of appropriate cytokines and the compartmentalization of bacterial proteins for antigen processing and presentation. Because the organism has the capacity to induce a robust cell-mediated immune response, attenuated strains have been engineered to express foreign antigens and are undergoing clinical studies as therapeutic vaccines for cancer.

EPIDEMIOLOGY

L. monocytogenes usually enters the body via the gastrointestinal tract in foods. Listeriosis is most often sporadic, although outbreaks do occur. No evidence supports person-to-person transmission (other than vertical transmission from mother to fetus) or waterborne infection. In line with its survival and multiplication at refrigeration temperatures, *L. monocytogenes* is commonly found in processed and unprocessed foods of animal and plant origin, especially soft cheeses, delicatessen meats, hot dogs, milk, and cold salads; fresh fruits and vegetables also can transmit the organism. Because food supplies are increasingly centralized and normal hosts tolerate the organism well, outbreaks may not be immediately apparent.

DIAGNOSIS

Symptoms of listerial infection overlap greatly with those of other infectious diseases. Timely diagnosis requires that the illness be considered in groups at risk: pregnant women; elderly persons; neonates; individuals immunocompromised by organ transplantation, cancer, or treatment with tumor necrosis factor antagonists or glucocorticoids; and patients with a variety of chronic medical conditions, including alcoholism, diabetes, renal disease, and rheumatologic and hepatic illnesses. Meningitis in older adults (especially with parenchymal brain involvement or subcortical brain abscess) should trigger consideration of *L. monocytogenes* infection and treatment. Listeriosis occasionally affects healthy, young, nonpregnant individuals. HIV-infected patients are at risk; however, listeriosis seems to be prevented by trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis targeting other AIDS-related infections. The diagnosis is typically made by culture of blood, cerebrospinal fluid (CSF), or amniotic fluid. *L. monocytogenes* may be confused with "diphtheroids" or pneumococci in Gram-stained CSF or may be gram-variable and confused with *Haemophilus* species. Polymerase chain reaction diagnostics have been described but are not widely available, and serology is not clinically useful.

CLINICAL MANIFESTATIONS

Listerial infections present as several clinical syndromes, of which meningitis and septicemia are most common.

Gastroenteritis Listerial gastroenteritis typically develops within 48 h of ingestion of a large inoculum of bacteria in contaminated foods. *L. monocytogenes* is neither sought nor found in routine fecal cultures, but its involvement should be considered in outbreaks when cultures for other likely pathogens are negative. Manifestations include fever, diarrhea, headache, and constitutional symptoms. The largest reported outbreak occurred in an Italian school system and included 1566 individuals; ~20% of patients were hospitalized, but only one person had a positive blood culture. Isolated gastrointestinal illness does not require antibiotic treatment. Surveillance studies show that 0.1–5% of healthy asymptomatic adults may have stool cultures positive for the organism.

Bacteremia *L. monocytogenes* septicemia presents with fever, chills, and myalgias/arthralgias and cannot be differentiated from septicemia involving other organisms. Meningeal symptoms, focal neurologic findings, or mental status changes may suggest the diagnosis. Bacteremia is documented in 70–90% of cancer patients with listeriosis. A nonspecific flulike illness with fever is a common presentation in pregnant women. A lumbar puncture is often prudent, although not necessary, in pregnant women without central nervous system (CNS) symptoms.

Meningitis *L. monocytogenes* causes ~5–10% of all cases of community-acquired bacterial meningitis in adults in the United States. Case–fatality rates are reported to be 15–26% and do not appear to have changed over time. This diagnosis should be considered in all older or chronically ill adults with "aseptic" meningitis. The presentation is more frequently subacute (with illness developing over several days) than in meningitis of other bacterial etiologies, and nuchal rigidity and meningeal signs are less common. Photophobia is infrequent. Focal findings and seizures are common in some but not all series. The CSF profile in listerial meningitis most often shows white blood cell counts in the range of 100–5000/μL (rarely higher); 75% of patients have counts below 1000/μL, usually with a neutrophil predominance more modest than that in other bacterial meningitides. Low glucose levels and positive results on Gram's staining are found ~30–40% of the time. Hydrocephalus can occur.

Meningoencephalitis and Focal CNS Infection *L. monocytogenes* can directly invade the brain parenchyma, producing either cerebritis or focal abscess. Approximately 10% of cases of CNS infection are macroscopic abscesses resulting from bacteremic seeding; the affected patients often have positive blood cultures. Concurrent meningitis can exist, but the CSF may appear normal. Abscesses can be misdiagnosed as metastatic or primary tumors and, in rare instances, occur in the cerebellum and the spinal cord. Invasion of the brainstem results in a characteristic severe rhombencephalitis, usually in otherwise healthy older adults (although there are numerous other infectious and noninfectious causes of this syndrome). The presentation may be biphasic, with a prodrome of fever and headache followed by neurologic decline and focal findings. The subacute course and the often minimally abnormal CSF findings may delay the diagnosis, which may be suggested by MRI showing ring-enhancing lesions after gadolinium contrast. A pattern of multiple brain abscesses along white-matter fiber tracts may represent intra-axonal spread and suggest the diagnosis. MRI is superior to CT for the diagnosis of these infections.

Infection in Pregnant Women and Neonates Listeriosis in pregnancy is a severe and important infection that can cause miscarriage and stillbirth. The usual presentation is a nonspecific acute or subacute febrile illness with myalgias, arthralgias, backache, and headache. Pregnant women with listeriosis are usually bacteremic. This syndrome should prompt blood cultures, especially if there is no other reasonable explanation. Involvement of the CNS is uncommon in pregnant women. Preterm delivery is a common complication, and the diagnosis may be made only postpartum. As many as 70–90% of fetuses from infected women can become infected. Prepartum treatment of bacteremic women enhances the chances of delivery of a healthy infant. Women usually do well after delivery: maternal deaths are very rare, even when the diagnosis is made late in pregnancy or postpartum. Overall mortality rates for fetuses infected in utero approach 50% in some series; among live-born neonates treated with antibiotics, mortality rates are much lower (~20%). *Granulomatosis infantiseptica* is an overwhelming listerial fetal infection with miliary microabscesses and granulomas, most often in the skin, liver, and spleen. Less severe neonatal infection acquired in utero presents at birth. "Late-onset" neonatal illness typically develops ~10–30 days postpartum. Mothers of infants with late-onset disease are not ill. It is hypothesized that peripartum antibiotic prophylaxis for group B streptococcal infection may be decreasing the rates of neonatal listeriosis.

TREATMENT

Infections Caused by *Listeria monocytogenes*

ANTIBIOTICS

No clinical trials have compared antimicrobial agents for the treatment of *L. monocytogenes* infections. Data from studies conducted in vitro and in animals as well as observational clinical data indicate that ampicillin is the drug of choice, although penicillin also is highly active. Adults should receive IV ampicillin at high doses (2 g every 6 h). Many experts recommend the addition of gentamicin for synergy (1.0–1.7 mg/kg every 8 h); retrospective uncontrolled trials are not conclusive, but one study suggests that gentamicin may not help. TMP-SMX, given IV, is the best alternative for the penicillin-allergic patient (15–20 mg of TMP/kg per day in divided doses every 6–8 h). The dosages recommended cover CNS infection and bacteremia (see below for duration); dosages must be reduced for patients with renal insufficiency. One small nonrandomized study supports a combination of ampicillin and TMP-SMX. Case reports document success with vancomycin, imipenem, meropenem, linezolid, tetracycline, and macrolides, although there are also reports of clinical failure or disease development with some of these agents. None of these agents has been demonstrated to be superior to ampicillin. Although not rigorously studied, adjunctive dexamethasone has not been shown to be advantageous in CNS infection. Acquired resistance to antimicrobial agents has been sought but not found in large strain collections. Cephalosporins are *not* effective and should not be used. Neonates should receive ampicillin and gentamicin at doses based on weight.

DURATION

The duration of therapy depends on the syndrome: 2 weeks for bacteremia, 3 weeks for meningitis, 6–8 weeks for brain abscess/encephalitis, and 4–6 weeks for endocarditis in both neonates and adults. Early-onset neonatal disease may be more severe and should be treated for >2 weeks.

COMPLICATIONS AND PROGNOSIS

Many individuals who are promptly diagnosed and treated recover fully, but permanent neurologic sequelae are common in patients with brain abscess or rhombencephalitis. Endocarditis and focal infections of visceral organs; the eye; the pleural, peritoneal, and pericardial spaces; the bones; and both native and prosthetic joints and endovascular grafts have all been reported. Of 100 live-born, treated neonates in one series, 60% recovered fully, 24% died, and 13% had long-term neurologic or other complications.

PREVENTION

Healthy persons should take standard precautions to prevent foodborne illness: fully cooking meats, washing fresh vegetables, carefully cleaning utensils, and avoiding unpasteurized dairy products. In addition, persons at risk for listeriosis, including pregnant women, should avoid soft cheeses (hard cheeses and yogurt are not problematic) and should avoid or thoroughly reheat ready-to-eat and delicatessen foods. Entirely well pregnant women who report exposure to foods recalled for possible listerial contamination may be educated and followed expectantly.

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147 Tetanus

C. Louise Thwaites, Lam Minh Yen

Tetanus is an acute disease manifested by skeletal muscle spasm and autonomic nervous system disturbance. It is caused by a powerful neurotoxin produced by the bacterium *Clostridium tetani* and is completely preventable by vaccination. *C. tetani* is found throughout the world, and tetanus commonly occurs where the vaccination coverage rate is low. In developed countries, the disease is seen occasionally in individuals who are incompletely vaccinated. In any setting, established tetanus is a severe disease with a high mortality rate.

DEFINITION

Tetanus is diagnosed on clinical grounds (sometimes with supportive laboratory confirmation of the presence of *C. tetani*; see "Diagnosis," below), and case definitions are often used to facilitate clinical and epidemiologic assessments. The Centers for Disease Control and Prevention (CDC) defines probable tetanus as "an acute illness with muscle spasms or hypertonia in the absence of a more likely diagnosis." *Neonatal* tetanus is defined by the World Health Organization (WHO) as "an illness occurring in a child who has the normal ability to suck and cry in the first 2 days of life but who loses this ability between days 3 and 28 of life and becomes rigid and has spasms." Given the unique presentation of neonatal tetanus, the history generally permits accurate classification of the illness with a high degree of probability. *Maternal* tetanus is defined by the WHO as tetanus occurring during pregnancy or within 6 weeks after the conclusion of pregnancy (whether with birth, miscarriage, or abortion).

ETIOLOGY

C. tetani is an anaerobic, gram-positive, spore-forming rod whose spores are highly resilient and can survive readily in the environment throughout the world. Spores resist boiling and many disinfectants. In addition, *C. tetani* spores and bacilli survive in the intestinal systems of many animals, and fecal carriage is common. The spores or bacteria enter the body through abrasions, wounds, or (in the case of neonates) the umbilical stump. Once in a suitable anaerobic environment, the organisms grow, multiply, and release tetanus toxin, an exotoxin that enters the nervous system and causes disease. Very low concentrations of this highly potent toxin can result in tetanus (minimal lethal human dose, 2.5 ng/kg).

In 20–30% of cases of tetanus, no puncture entry wound is found. Superficial abrasions to the limbs are the most common infection sites in adults. Deeper infections (e.g., attributable to open fracture, abortion, or drug injection) are associated with more severe disease and worse outcomes. In neonates, infection of the umbilical stump can result from inadequate umbilical-cord care; in some cultures, for example, the cord is cut with grass or animal dung is applied to the stump. Circumcision or ear-piercing also can result in neonatal tetanus.

EPIDEMIOLOGY

Tetanus is a rare disease in the developed world. Two cases of neonatal tetanus have occurred in the United States since 1989. In 2013, 26 cases of tetanus were reported to the U.S. national surveillance system. Most cases occur in incompletely vaccinated or unvaccinated individuals. Vaccination status is known in 50% of cases reported in the United States between 1972 and 2009; among these cases, only 16% of patients had had three or more doses of tetanus toxoid.

Persons >60 years of age are at greater risk of tetanus because antibody levels decrease over time. One-third of recent cases in the United States were in persons >65 years old. People who inject drugs—particularly those injecting heroin subcutaneously ("skin-popping")—are increasingly recognized as a high-risk group (15% of all cases in 2001–2008). In 2004, an outbreak of tetanus occurred in the United Kingdom, which had

previously reported low rates among drug users. The reasons for this outbreak remain unclear but are thought to involve a combination of heroin contamination, skin-popping, and incomplete vaccination. Since then, only sporadic cases have been reported in the United Kingdom.

The global incidence of tetanus among older children and adults is unknown, as few countries have good surveillance systems.

PATHOGENESIS

Genome sequencing of *C. tetani* has allowed identification of several exotoxins and virulence factors. Only those bacteria producing tetanus toxin (tetanospasmin) can cause tetanus. Although closely related to the botulinum toxins in structure and mode of action, tetanus toxin undergoes retrograde transport into the central nervous system (CNS) and thus produces clinical effects different from those caused by the botulinum toxins, which remain at the neuromuscular junction.

Tetanus toxin is intra-axonally transported to motor nuclei of the cranial nerves or ventral horns of the spinal cord. This toxin is produced as a single 150-kDa protein that is cleaved to produce heavy (100-kDa) and light (50-kDa) chains linked by a disulfide bond and noncovalent forces. The carboxy terminal of the heavy chain binds to specific membrane components in presynaptic α-motor nerve terminals; evidence suggests binding to both polysialogangliosides and membrane proteins. This binding results in toxin internalization and uptake into the nerves. Once inside the neuron, the toxin enters a retrograde transport pathway, whereby it is carried proximally to the motor neuron body in what appears to be a highly specific process. Unlike other components of the endosomal contents, which undergo acidification following internalization, tetanus toxin is transported in a carefully regulated pH-neutral environment that prevents an acid-induced conformational change that would result in light-chain expulsion into the surrounding cytosol.

The next stage in toxin trafficking is less clearly understood but involves tetanus toxin's escaping normal lysosomal degradation processes and undergoing translocation across the synapse to the GABA-ergic presynaptic inhibitory interneuron terminals. Here the light chain, which is a zinc-dependent endopeptidase, cleaves vesicle-associated membrane protein 2 (VAMP2, also known as *synaptobrevin*). This molecule is necessary for presynaptic binding and release of neurotransmitter; thus tetanus toxin prevents transmitter release and effectively blocks inhibitory interneuron discharge. The result is unregulated activity in the motor nervous system. Similar activity in the autonomic system accounts for the characteristic features of skeletal muscle spasm and autonomic system disturbance. The increased circulating catecholamine levels in severe tetanus are associated with cardiovascular complications.

Relatively little is known about the processes of recovery from tetanus. Recovery can take several weeks. Peripheral nerve sprouting is involved in recovery from botulism, and similar CNS sprouting may occur in tetanus. Other evidence suggests toxin degradation as a mechanism of recovery.

APPROACH TO THE PATIENT

Tetanus

The clinical manifestations of tetanus occur only after tetanus toxin has reached presynaptic inhibitory nerves. Once these effects become apparent, there may be little that can be done to affect disease progression. Treatment should not be delayed while the results of laboratory tests are awaited. Management strategies aim to neutralize remaining unbound toxin and support vital functions until the effects of the toxin have worn off. Recent interest has focused on intrathecal methods of antitoxin administration to neutralize toxin within the CNS and limit disease progression (see "Treatment," below).

CLINICAL MANIFESTATIONS

Tetanus produces a wide spectrum of clinical features that are broadly divided into generalized (including neonatal) and local. In the usually mild form of local tetanus, only isolated areas of the body are affected and only small areas of local muscle spasm may be apparent. If the cranial nerves are involved in localized cephalic tetanus, the pharyngeal or laryngeal muscles may spasm, with consequent aspiration or airway obstruction, and the prognosis may be poor. In the typical progression of generalized tetanus **(Fig. 147-1)**, muscles of the face and jaw often are affected first, presumably because of the shorter distances toxin must travel up motor nerves to reach presynaptic terminals. Neonates typically present with an inability to suck.

In assessing prognosis, the speed at which tetanus develops is important. The incubation period (time from wound to first symptom) and the period of onset (time from first symptom to first generalized

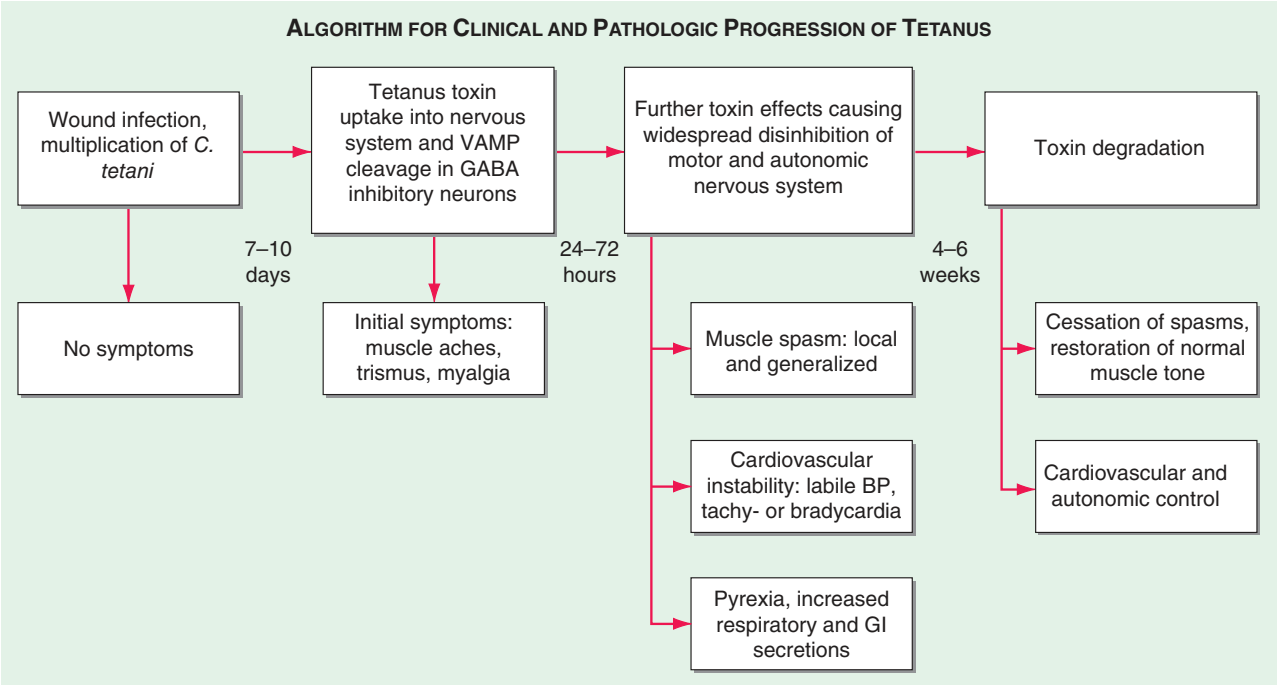

FIGURE 147-1 Clinical and pathologic progression of tetanus. BP, blood pressure; GABA, γ-aminobutyric acid; GI, gastrointestinal; VAMP, vesicle-associated membrane protein (synaptobrevin).

spasm) are of particular significance; shorter times are associated with worse outcome. In neonatal tetanus, the younger the infant is when symptoms occur, the worse the prognosis.

The most common initial symptoms are trismus (lockjaw), muscle pain and stiffness, back pain, and difficulty swallowing. In neonates, difficulty in feeding is the usual presentation. As the disease progresses, muscle spasm develops. Generalized muscle spasm can be very painful. Commonly, the laryngeal muscles are involved early or even in isolation. This is a life-threatening event as complete airway obstruction may ensue. Spasm of the respiratory muscles results in respiratory failure. Without ventilatory support, respiratory failure is the most common cause of death in tetanus. Spasms strong enough to produce tendon avulsions and crush fractures have been reported, but this outcome is rare.

Autonomic disturbance is maximal during the second week of severe tetanus, and death due to cardiovascular events becomes the major risk. Blood pressure is usually labile, with rapid fluctuations from high to low accompanied by tachycardia. Episodes of bradycardia and heart block also can occur. Autonomic involvement is evidenced by gastrointestinal stasis, sweating, increased tracheal secretions, and acute (often high-output) renal failure.

DIAGNOSIS

The diagnosis of tetanus is based on clinical findings. As stated above, treatment should not be delayed while laboratory tests are conducted. Culture of *C. tetani* from a wound provides supportive evidence. Serum anti-tetanus immunoglobulin G also may be measured in a sample taken before the administration of antitoxin or immunoglobulin; levels >0.1 IU/mL (measured by standard ELISA) are deemed protective and do not support the diagnosis of tetanus. If levels are below this threshold, a bioassay for serum tetanus toxin may be helpful, but a negative result does not exclude the diagnosis and these levels are not generally performed. Polymerase chain reaction also has been used for detection of tetanus toxin, but its sensitivity is unknown.

The few conditions that mimic generalized tetanus include strychnine poisoning and dystonic reactions to antidopaminergic drugs. Abdominal muscle rigidity is characteristically continuous in tetanus but is episodic in the latter two conditions. Cephalic tetanus can be confused with trismus of other etiologies, such as oropharyngeal infection. Hypocalcemia and meningoencephalitis are included in the differential diagnosis of neonatal tetanus.

TREATMENT

Tetanus

If possible, the entry wound should be identified, cleaned, and debrided of necrotic material in order to remove anaerobic foci of infection and prevent further toxin production. Metronidazole (400 mg rectally or 500 mg IV every 6 h for 7 days) is preferred for antibiotic therapy. An alternative is penicillin (100,000–200,000 IU/kg per day), although this drug theoretically may exacerbate spasms and in one study was associated with increased mortality. Failure to remove pockets of ongoing infection may result in recurrent or prolonged tetanus.

Antitoxin should be given early in an attempt to deactivate any circulating tetanus toxin and prevent its uptake into the nervous system. Two preparations are available: human tetanus immune globulin (TIG) and equine antitoxin. TIG is the preparation of choice, as it is less likely to be associated with anaphylactoid reactions. A single IM dose (3000–5000 IU) is given, with a portion injected around the wound. Equine-derived antitoxin is available widely and is used in low-income countries; after hypersensitivity testing, 10,000–20,000 U is administered IM as a single dose or as divided doses. Some evidence indicates that intrathecal administration of TIG inhibits disease progression and leads to a better outcome. The results of relevant studies have been supported by a meta-analysis of trials involving both adults and neonates, with TIG doses of 50–1500 IU administered intrathecally.

Spasms are controlled by heavy sedation with benzodiazepines. Chlorpromazine and phenobarbital are commonly used worldwide, and IV magnesium sulfate has been used as a muscle relaxant. A significant problem with all these treatments is that the doses necessary to control spasms also cause respiratory depression; thus, in resource-limited settings without mechanical ventilators, controlling spasms while maintaining adequate ventilation is problematic, and respiratory failure is a common cause of death. In locations with ventilation equipment, severe spasms are best controlled with a combination of sedatives or magnesium and relatively short-acting, cardiovascularly inert, nondepolarizing neuromuscular blocking agents that allow titration against spasm intensity. Infusions of propofol also have been used successfully to control spasms and provide sedation.

It is important to establish a secure airway early in severe tetanus. Ideally, patients should be nursed in calm, quiet environments because light and noise can trigger spasms. Tracheal secretions are increased in tetanus, and dysphagia due to pharyngeal involvement combined with hyperactivity of laryngeal muscles makes endotracheal intubation difficult. Patients may need ventilator support for several weeks. Thus tracheostomy is the usual method of securing the airway in severe tetanus.

Cardiovascular instability in severe tetanus is notoriously difficult to treat. Rapid fluctuations in blood pressure and heart rate can occur. Cardiovascular stability is improved by increasing sedation with IV magnesium sulfate (plasma concentration, 2–4 mmol/L or titrated against disappearance of the patella reflex), morphine, fentanyl, or other sedatives. In addition, drugs acting specifically on the cardiovascular system (e.g., esmolol, calcium antagonists, and inotropes) may be required. Short-acting drugs that allow rapid titration are preferred; particular care should be taken when longer-acting β antagonists are administered, as their use has been associated with hypotensive cardiac arrest.

Complications arising from treatment are common and include thrombophlebitis associated with diazepam injection, ventilator-associated pneumonia, central-line infections, and septicemia. In some centers, prophylaxis against deep-vein thrombosis and thromboembolism is routine.

Recovery from tetanus may take 4–6 weeks. Patients must be given a full primary course of immunization, as tetanus toxin is poorly immunogenic and the immune response following natural infection is inadequate.

PROGNOSIS

Rapid development of tetanus is associated with more severe disease and poorer outcome; it is important to note time of onset and length of incubation period. More sophisticated modeling has revealed other important predictors of prognosis **(Table 147-1)**. Few studies have formally addressed long-term outcomes of tetanus. However, it is generally accepted that recovery is typically complete unless periods of hypoventilation have been prolonged or other complications have ensued. Studies of children and neonates have suggested a higher incidence of neurologic sequelae. Neonates may be at increased risk of learning disabilities, behavioral problems, cerebral palsy, and deafness.

TABLE 147-1 Factors Associated with a Poor Prognosis in Tetanus

ADULT TETANUS	NEONATAL TETANUS
Age >70 years	Younger age, premature birth
Incubation period <7 days	Incubation period <6 days
Short time from first symptom to admission	Delay in hospital admission
Puerperal, IV, postsurgery, burn entry site	Grass used to cut cord
Period of onset[a] <48 h	Low birth weight
Heart rate >140 beats/min[b]	Fever on admission
Systolic blood pressure >140 mmHg[b]	
Severe disease or spasms[b]	
Temperature >38.5°C[b]	

[a]Time from first symptom to first generalized spasm. [b]At hospital admission.

PREVENTION

Tetanus is prevented by good wound care and immunization (Chap. 118). In neonates, use of safe, clean delivery and cord-care practices as well as maternal vaccination are essential. The WHO guidelines for tetanus vaccination consist of a primary course of three doses in infancy, boosters at 4–7 and 12–15 years of age, and one booster in adulthood. In the United States, the CDC suggests an additional dose at 15–18 months with boosters every 10 years. "Catch-up" schedules recommend a three-dose primary course with 4 weeks between doses, followed by two boosters 6 months apart. For persons who have received a complete primary course in childhood but no further boosters, two doses at least 4 weeks apart are recommended.

Standard WHO recommendations for prevention of maternal and neonatal tetanus call for administration of two doses of tetanus toxoid at least 4 weeks apart to previously unimmunized pregnant women. However, in high-risk areas, a more intensive approach has been successful, with all women of childbearing age receiving a primary course along with education on safe delivery and postnatal practices.

Individuals sustaining tetanus-prone wounds should be immunized if their vaccination status is incomplete or unknown or if their last booster was given >10 years earlier. Patients with an inadequate vaccine status who sustain wounds not classified as clean or minor should also undergo passive immunization with TIG. It is recommended that tetanus toxoid be given in conjunction with diphtheria toxoid in a preparation with or without acellular pertussis: DTaP for children <7 years old, Td for 7- to 9-year-olds, and Tdap for children >9 years old and adults.

In the early 1980s, tetanus caused more than 1 million deaths a year, accounting for an estimated 5% of maternal deaths and 14% of all neonatal deaths. In 1989, the World Health Assembly adopted a resolution to eliminate neonatal tetanus by the year 2000; elimination was defined as <1 case/1000 live births in every district in every country. By 1999, elimination was still to be achieved in 57 countries and the deadline was extended until 2005, with the additional target of eliminating maternal tetanus (tetanus occurring during pregnancy or within 6 weeks of its end). Ratification of the Millennium Development Goals, in particular goal 4 (achieving a two-thirds reduction in the mortality rate among children under 5 by 2015), has further focused attention on reducing deaths from vaccine-preventable disease, particularly in the first 4 weeks of life.

Because vaccination reduces the incidence of neonatal tetanus by an estimated 94%, immunization of pregnant women with two doses of tetanus toxoid at least 4 weeks apart has been the primary method of maternal and neonatal tetanus elimination. In some areas, all women of childbearing age have been targeted as a means of increasing vaccination coverage. In addition, educational programs have focused on improving hygiene during the birth process, an intervention that in itself is estimated to reduce neonatal tetanus deaths by up to 40%.

The latest available data show that significant progress has been made: in recent years, 40 countries have achieved maternal and neonatal tetanus elimination, including China, India, and Indonesia. Worldwide, deaths from neonatal tetanus fell by 94% between 1990 and 2014; in the latter year, with 82% of newborns protected from the disease by maternal vaccination, there were an estimated 49,000 neonatal tetanus deaths, mainly in Africa and Southeast Asia. Despite this relative success, immunization programs need to be ongoing as there is no herd immunity effect for tetanus and *C. tetani* contamination of soil and feces is widespread.

The rate of primary vaccination coverage in infancy (three doses of DTP) is 84%, but rates for the subsequent boosters necessary for long-term protection are unknown. Dedicated public health initiatives are lacking, and the continuing reports of sizable case series in the medical literature suggest that tetanus continues to pose a significant global health burden.

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148 Botulism

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Botulism, recognized at least since the eighteenth century, is a neuroparalytic disease caused by botulinum toxin, one of the most toxic substances known. While initially thought to be caused only by the ingestion of botulinum toxin in contaminated food (food-borne botulism), three additional forms caused by in situ toxin production after germination of spores in either a wound or the intestine are now recognized worldwide: wound botulism, infant botulism, and adult intestinal-colonization botulism. In addition to occurring in these recognized natural forms of the disease, botulism symptoms have been reported in patients receiving higher than recommended doses of botulinum toxin (iatrogenic botulism) for therapeutic or cosmetic purposes. Moreover, botulism was once reported after possible inhalation of botulinum toxin in a laboratory setting. Botulism manifests as a clinical syndrome of bilateral cranial-nerve palsies that may progress to respiratory compromise, a descending bilateral flaccid paralysis of voluntary muscles, and even death. Patients exposed to the same contaminated food may have a varying constellation of cranial nerve palsies and varying illness severity. Cases are known to be misdiagnosed or suspected late in a hospital course. The mainstays of therapy are meticulous intensive care and treatment with antitoxin early in the clinical course while alternative diagnoses are still being worked up. Early suspicion of botulism and empirical treatment are critical to favorable clinical outcomes.

ETIOLOGY AND PATHOGENESIS

Seven serologically distinct serotypes of botulinum toxin (A through G) have been confirmed. Botulinum toxin is produced by four recognized species of clostridia: *Clostridium botulinum* and rare strains of *Clostridium argentinense, Clostridium baratii*, and *Clostridium butyricum*. All these species are anaerobic gram-positive spore-forming organisms. The spores survive environmental conditions and ordinary cooking procedures. Toxin production, however, requires a rare confluence of product storage conditions: an anaerobic environment, a pH of >4.5, low salt and sugar concentrations, and temperatures of >3°C. Although commonly ingested, spores do not normally germinate and produce toxin in the adult human intestine.

Food-borne botulism is caused by consumption of foods contaminated with botulinum toxin; no confirmed host-specific factors are involved in the disease. *Wound botulism* is caused by toxin produced from germinating *C. botulinum* spores that contaminate an abscess or a wound. *Infant botulism* is caused by toxin produced in situ by toxigenic clostridia colonizing the intestine of children <1 year of age.

Colonization is thought to occur because the normal bowel microbiota is not yet fully established; this theory is supported by studies in animals. *Adult intestinal-colonization botulism*, a rare form that is poorly understood, is believed to have a pathology similar to that of infant botulism but occurs in adults; typically, patients have some anatomic or functional bowel abnormality or have recently used antibiotics that may help toxigenic clostridia compete more successfully against the normal bowel microbiota. Despite antitoxin treatment, relapse due to intermittent intraluminal production of toxin may be observed in patients with adult intestinal-colonization botulism. Relapse is a theoretical concern in wound botulism but has never been reported.

Regardless of how exposure occurs, botulinum neurotoxin enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. Botulinum toxin is a zinc-endopeptidase protein of ~150 kDa, consisting of a 100-kDa heavy chain and a 50-kDa light chain. Steps in neurotoxin activity include (1) heavy-chain binding to nerve terminals, (2) internalization in endocytic vesicles, (3) translocation of the light chain to cytosol, and (4) light-chain serotype-specific cleavage of one of several proteins involved in the release of the neurotransmitter acetylcholine. Inhibition of acetylcholine release by any of the seven toxin serotypes results in characteristic flaccid paralysis.

All botulinum toxin serotypes have been demonstrated to cause botulism in nonhuman primates. Human cases associated with serotypes A, B, E, and F are reported each year. Serotype A produces the most severe syndrome, with the greatest proportion of patients requiring mechanical ventilation. Serotype B causes milder disease. Serotype E, most often associated with foods of aquatic origin (e.g., uneviscerated fish and seal oil), produces a syndrome of variable severity. Illnesses caused by toxin serotype F are infrequent and are characterized by rapid progression to quadriplegia and respiratory failure but also by relatively rapid recovery. Studies have shown that at least some serotypes can be differentiated into subtypes through neurotoxin gene sequencing; however, the impact of these subtype differences on clinical illness is not yet known.

EPIDEMIOLOGY

Botulism occurs worldwide, but the number of cases reported varies among countries and regions. The variation may be due not only to actual differences in incidence but also to underreporting as a result of (1) limited awareness of the clinical presentation on which diagnosis depends; (2) lack of local specialized laboratory facilities to confirm botulism; (3) differences in requirements for disease reporting by physicians to public health agencies; and (4) lack of formal surveillance for botulism within a country. There is no universal surveillance system to capture worldwide botulism incidence. However, 30 countries currently participate in voluntary reporting of botulism cases to the European Union through an established surveillance system that includes standardized case definitions similar to those used in the United States and Canada. Some countries (e.g., the United States, Canada, Argentina, and Japan) maintain independent botulism surveillance, and some countries (e.g., Ethiopia) have no botulism surveillance.

Food-Borne Botulism From 1899 to 2014, 1246 food-borne botulism events (single cases or outbreaks) were reported in the United States; from 1990 to 2014, a median of 20 cases were reported annually. Most such events (~80%) involve vegetables or fish/aquatic animals, usually home-preserved (canned, jarred). Native communities in both the United States (Alaska) and Canada have a high incidence of food-borne botulism due to traditional food-preparation practices; 85% of all cases in Canada occur in Native communities. Outbreaks typically involve three or four cases; however, one restaurant-associated outbreak in 1977 affected 59 persons. Worldwide, the highest incidence rate is reported from Georgia and Armenia in the southern Caucasus region, where illness is also associated with home-canning practices. Outbreaks in Asia are attributable to consumption of home-preserved fish or vegetable products such as bean curd and bamboo shoots. In parts of Europe, including Poland, France, and Germany, illness is often associated with home-preserved meat such as ham or sausage. Since 1950, commercial products have rarely been implicated in botulism in the United States and, when they have been implicated, cases have most often been attributed to consumer error in storage or cooking. However, manufacturer deficiencies do occur. In 2007, botulism developed in eight persons in the United States who consumed a widely distributed commercially canned hot-dog chili sauce. Significant deficiencies discovered by regulatory authorities involved 91 different products and resulted in the recall of 111 million cans of food. Lack of barriers to toxin production in commercially produced, non-canned products has also been documented. In 2006, commercially produced and internationally distributed carrot juice was implicated in six cases of botulism in the United States and Canada; inappropriate refrigeration in the setting of a lack of barriers to botulinum toxin production was believed to be the cause.

Wound Botulism This form of disease was first recognized in 1951 as a result of a review of the clinical records on an accidental injury in 1943. Between 1943 and 2011, 491 cases of wound botulism were reported in the United States; 97% of cases reported after 1990 were associated with injection drug use. In the early 2000s, wound botulism associated with injection drug use emerged in Europe, and case clusters have been reported. The typical patient in the United States is a 30- to 50-year-old resident of the western United States with a long history of drug injection—specifically, of black-tar heroin. Some cases of wound botulism are due to contamination of traumatic wounds with *C. botulinum* spores. This category of botulism has been reported after injuries sustained during motor vehicle accidents.

Infant Botulism More than 4400 infant botulism cases have been reported worldwide (80% of them in the United States) since this form of the disease was first recognized in 1976; ~80–100 cases (commonly caused by serotypes A and B) are reported annually in the United States.

Adult Intestinal-Colonization Botulism This form of botulism is difficult to confirm because it is poorly understood. No clear criteria are available to differentiate cases of adult intestinal-colonization botulism from other adult botulism cases. Often these cases are caused by *C. baratii* type F, but the involvement of both *C. botulinum* type A and *C. butyricum* type E have been reported. Botulism following abdominal surgery or antibiotic use has sometimes been considered to be adult intestinal-colonization botulism.

Iatrogenic Botulism Paralysis of variable severity has followed injection of high doses of licensed botulinum toxin products for treatment of refractory conditions involving hypertonicity of large muscle groups. Although some patients had symptoms consistent with botulism, no cases were laboratory-confirmed. Injection of approved doses of licensed products for cosmetic purposes has not been associated with botulism. However, four cases of laboratory-confirmed botulism in the United States resulted from illegal injection of a highly concentrated preparation of botulinum toxin that was not intended for clinical use; this preparation was privately administered for cosmetic purposes in 2004.

Inhalational Botulism Inhalational botulism does not occur naturally. One report from Germany described botulism resulting from possible inhalational exposure to botulinum toxin in a laboratory incident.

Intentional Botulism Botulinum toxin has been "weaponized" by governments and terrorist organizations. An attack might entail aerosolization of toxin or contamination of foods or beverages ranging in scope from small-scale tampering to contamination of a widely distributed food item. An unnatural event may be suggested by a very large number of ill persons, an unusual relationship between patients (e.g., a visit to the same building), exposure to foods not typically associated with botulism, or the involvement of atypical toxin serotypes (i.e., those not usually associated with human illness).

CLINICAL MANIFESTATIONS

The clinical syndrome of botulism consists of bilateral cranial-nerve palsies that may progress to respiratory compromise, a bilateral descending flaccid paralysis of voluntary muscles, and even death. The incubation period from ingestion of contaminated food to onset of symptoms in food-borne botulism is usually 8–36 h but can be as long as 10 days and is dose dependent. Incubation periods of 4–17 days have been documented in wound botulism associated with accidental injury. Estimation is difficult in cases involving injection drug users because patients may inject drugs several times daily. Similarly, the incubation period for infant botulism has not been established, but the fact that the illness has affected infants <3 days old suggests that this interval may be very short.

Cranial nerve deficits may manifest as some of the following: diplopia, dysarthria, dysphonia, ptosis, ophthalmoplegia, facial paralysis, and impaired gag reflex **(Fig. 148-1)**. Pupillary reflexes may be depressed, and fixed or dilated pupils are sometimes noted. Autonomic symptoms such as dizziness, dry mouth, and "sore throat" are common. Dysphagia may lead to increased pooling of secretions and the need for suctioning despite dry mouth. Constipation due to paralytic ileus is often noted in the days after illness onset, and urinary retention is also common. Patients are afebrile and remain alert and oriented, but dysarthria, ptosis, and paresis have sometimes led physicians to believe incorrectly that a patient's mental status is altered (Fig. 148-1). Either late or early in the illness, respiratory failure due either to paralysis of the diaphragm and accessory breathing muscles or to pharyngeal collapse secondary to cranial nerve paralysis may occur. Because of skeletal muscle paralysis, patients experiencing respiratory distress may appear placid and detached even as they near respiratory arrest.

Weakness descends from the head, often rapidly, to involve the neck, arms, thorax, and legs; weakness and some cranial nerve deficits can be asymmetric. Deep tendon reflexes typically are normal or may progressively disappear. Paresthesias, while rare, have been reported. Ataxia, which has sometimes been reported, manifests not as cerebellar ataxia but rather as gait problems due to weakness or visual issues. The absence of cranial nerve palsies makes botulism highly unlikely, as does a lack of cranial nerve deficits at the onset of illness. Nausea, vomiting, and abdominal pain may precede or follow the onset of paralysis in food-borne botulism. Infants with botulism typically present with a reduced ability to suck and swallow, constipation, weakened voice, ptosis, sluggish pupils, hypotonia, lethargic appearance, and floppy neck; as in adults, illness can progress to generalized flaccidity and respiratory compromise.

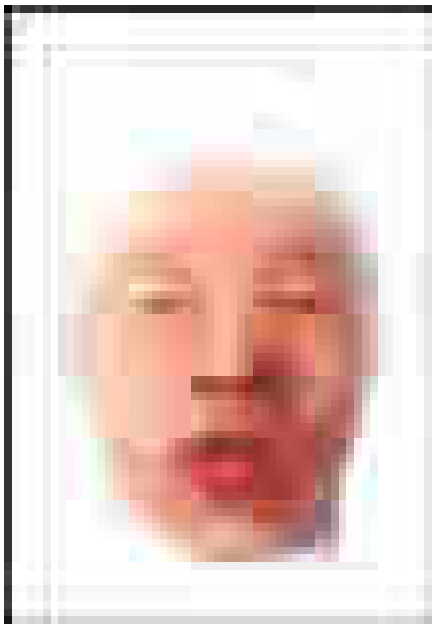

FIGURE 148-1 Artist's rendition of an adult with mild botulism. The patient has ptosis and facial paralysis manifested as lethargy and expressionless facies. The patient is fully alert. *(Illustrator, James K. Archer; reprinted from J Sobel: Clin Infect Dis 41:1170, 2005.)*

Even when intubated, patients can sometimes respond to questions by moving their fingers or toes unless paralysis has affected the digits. Clinical improvement follows sprouting of new nerve terminals and may take weeks to months. Patients often require outpatient rehabilitation therapy and may experience residual deficits. Death in untreated botulism is usually due to airway obstruction from pharyngeal muscle paralysis and inadequate tidal volume resulting from paralysis of diaphragmatic and accessory respiratory muscles. Death can also result from hospital-associated infections and other sequelae of long-term paralysis, hospitalization, and mechanical ventilation.

A history of preparing improperly home-canned foods may assist with the diagnosis. Patients with wound botulism may or may not have a discernible wound or abscess. A history of injection drug use or the presence of track marks should prompt suspicion for the diagnosis. In a substantial number of cases, no epidemiologic clue is discerned at the time of clinical presentation.

DIAGNOSIS

Botulism is diagnosed primarily on clinical grounds, with laboratory confirmation by specific tests performed only in specialized public-health laboratories. In the setting of an outbreak in which multiple patients present to the same treatment facility, the diagnosis can still be challenging; patients in a case cluster may have different cranial nerve deficits, chief manifestations, illness severity, and signs and symptoms. Patients sometimes present with respiratory failure as their chief manifestation, and neurologic signs and symptoms are not immediately appreciated. The temporal occurrence of two or more cases with botulism-compatible symptoms is essentially pathognomonic because other illnesses that resemble botulism do not usually occur in clusters. Because of the rarity of this disease, few physicians in the United States have seen or will see botulism; this potential unfamiliarity contributes to delays in diagnosis.

A food history over the 10 days before illness onset, with emphasis on the 48 h before illness onset, is critical to the public health response. The names of contacts who may have shared foods should be obtained before illness progresses to respiratory failure. Specific questions should address the consumption of improperly home-canned foods, home-preserved and/or exotic foods, and products requiring refrigeration that have been left at room temperature in sealed plastic containers or bags. A history of recent consumption of home-canned food substantially enhances the probability of food-borne botulism.

Ascertainment of the patient's behavioral history related to injection drug use or the sustaining of a traumatic wound is important to the diagnosis of wound botulism. Caretakers' observations up to and including the onset of symptoms are vital to the diagnosis of infant botulism. A history of recent abdominal surgery or antibiotic use may be important in the diagnosis of adult intestinal-colonization botulism.

DIFFERENTIAL DIAGNOSIS

The illnesses most commonly considered in the differential diagnosis of adult botulism cases include Guillain-Barré syndrome (GBS), myasthenia gravis, stroke syndromes, Eaton-Lambert syndrome, and tick paralysis. Less likely considerations are tetrodotoxin poisoning, shellfish poisoning, diphtheria, and tetanus. Botulism is sometimes confused with other illnesses because a neurologic examination is not adequately performed, particularly when a patient presents with symptoms that do not immediately indicate a neurologic illness—e.g., respiratory symptoms. A thorough history and a meticulous physical examination can effectively eliminate many alternative diagnoses, but a workup for other diagnoses should not delay treatment with botulinum antitoxin.

GBS, a rare autoimmune demyelinating polyneuropathy that often follows an acute infection, presents most often as an ascending paralysis. Case clusters are rare. Occasional GBS cases present as the Miller Fisher variant, which is a descending paralysis. The characteristic triad of ophthalmoplegia, ataxia, and areflexia in Miller Fisher variant GBS is easily mistaken for botulism. Protein levels in cerebrospinal fluid (CSF) can be elevated in GBS. In contrast, CSF findings are generally

normal in botulism, although marginally elevated CSF protein concentrations have been reported. In experienced hands, electromyography may differentiate GBS from botulism but is limited by technical and interpretive expertise. The edrophonium (Tensilon) test is sometimes of value in distinguishing botulism (usually a negative result) from myasthenia gravis (usually a positive result), but results have been positive in botulism cases. In most cerebrovascular accidents, physical examination reveals unilateral paralysis and upper motor neuron signs. Brain imaging can reveal the rare basilar stroke that produces bilateral bulbar palsies. Eaton-Lambert syndrome usually manifests as proximal limb weakness in a patient already debilitated by cancer. Tick paralysis is a rare flaccid condition closely resembling botulism and caused by neurotoxins of certain ticks.

BOTULISM-SPECIFIC LABORATORY TESTS

Botulism is confirmed in specialized public health laboratories by demonstration of toxin in clinical specimens (e.g., serum, stool, gastric aspirate, and sterile-water enema samples) or in samples of ingested foods. Isolation of toxigenic clostridia from stool also provides evidence of botulism. Wound cultures yielding the organism are highly suggestive in symptomatic cases. The universally accepted method for confirmation of botulism is the mouse bioassay; no testing available in hospital or other clinical laboratories (e.g., a blood culture or culture-independent diagnostic test) can detect botulinum toxin or *C. botulinum*. Specific guidance about what specimens to collect should be obtained from the testing laboratory because the requirements vary with the form of botulism suspected. The earlier in the course of illness specimens are collected, the likelier they are to yield positive results, allowing confirmation of botulism. Clinical specimens collected early in the hospital admission process should be submitted for testing; toxin results are usually negative with specimens collected >7 days after symptom onset but have been positive weeks after illness onset in high-level toxin exposures. Because of the extreme potency of botulinum toxin, serum toxin concentrations below the laboratory detection threshold can cause illness in a patient whose test yields a negative result; thus, a negative result does not rule out botulism. New laboratory tests for botulism are being developed but remain experimental. Standard blood work and radiologic studies are not useful in diagnosing botulism.

TREATMENT

Botulism

The cornerstones of treatment for botulism are meticulous intensive care and administration of botulinum antitoxin. Because antitoxin is most beneficial early in the course of clinical illness, it should be administered empirically and before the time-consuming workup for other illnesses or laboratory confirmation is complete. Persons of all ages in whom botulism is suspected should be hospitalized immediately so that signs of respiratory failure—the usual cause of death—can be detected and managed. Vital capacity should be monitored frequently and mechanical ventilation provided as needed. Botulinum antitoxin can limit the progression of illness because it neutralizes toxin molecules in the circulation that have not yet bound to nerve endings. However, antitoxin does not reverse existing paralysis, which may take weeks to improve. In the United States, there are two licensed antitoxin products. Botulism Antitoxin Heptavalent® (BAT; Emergent Biosolutions, Rockville, MD) is an equine-derived heptavalent (A through G) product enzymatically de-speciated for treatment of all forms of adult botulism and for infant botulism not involving serotypes A and B. Botulism Immune Globulin Intravenous (BabyBIG®; California Department of Public Health, Sacramento, CA) is a human-derived product for treating infant botulism caused by serotype A and/or B only. Alternative antitoxins are available in some countries. Aminoglycosides and other medications that block the neuromuscular junction may potentiate botulism and should be avoided.

In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly. The role of penicillin and metronidazole in treatment and decolonization is unclear. It has been hypothesized that antimicrobial agents may increase circulating botulinum toxin from lysis of bacterial cells.

Person-to-person transmission of botulism does not occur. Universal precautions are the only infection-control measures required during inpatient care. Patients with botulism can acquire health care–associated infections, deep venous thromboses, and other ailments that occur among patients who are hospitalized and immobile for long periods.

NOTIFICATION, EXPERT CONSULTATION, AND ANTITOXIN PROVISION

Every botulism case is a public health emergency. Some countries maintain stockpiles of antitoxin for immediate response, whereas others must access supplies from other nations or commercial manufacturers when a suspected case occurs.

In the United States, clinicians must report every suspected case, regardless of form, on an emergency basis to their state health departments. The state health department may put the physician in contact with the 24/7 botulism consultation service at the Centers for Disease Control and Prevention (CDC) through the CDC Emergency Operations Center (770-488-7100) or a locally available service. The botulism consultant will review the case with the physician, and they will collaboratively determine whether botulism is likely. If indicated, the consultant will coordinate laboratory confirmation at appropriate testing facilities and facilitate emergency shipment of antitoxin for all adult cases and for infant cases not involving serotypes A and B. In the United States, botulinum antitoxin for non-infant cases is available exclusively from the CDC. Physicians who see suspected infant botulism cases should contact the California Department of Public Health Infant Botulism Treatment and Prevention Program (510-231-7600), which provides 24-h consultation and distributes antitoxin (BabyBIG®) for the treatment of infant botulism nationwide. Except in cases involving infants who reside in California, laboratory-testing requests must still be authorized by the state health department where the infant is located or by the CDC.

PREVENTION

No prophylaxis or licensed vaccine against botulism is available. Home-canning instructions and equipment have changed over the years. Up-to-date canning instructions from reliable sources (e.g., the U.S. Department of Agriculture or the U.S. Food and Drug Administration) should be followed to ensure food safety. Processed food should be stored properly and heated thoroughly before consumption. Because of the possible presence of spores, honey should not be given to infants (<12 months of age). Injection of illicit drugs increases the risk of botulism. All traumatic wounds should be meticulously cleaned to eliminate possible contamination with bacterial spores.

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149 Gas Gangrene and Other Clostridial Infections

Amy E. Bryant, Dennis L. Stevens

The genus *Clostridium* encompasses >60 species that may be commensals of the gut microflora or may cause a variety of infections in humans and animals through the production of a plethora of proteinaceous exotoxins. *C. tetani* and *C. botulinum*, for example, cause specific clinical disease by elaborating single but highly potent toxins. In contrast, *C. perfringens* and *C. septicum* cause aggressive necrotizing infections that are attributable to multiple toxins, including bacterial proteases, phospholipases, and cytotoxins.

ETIOLOGIC AGENT

Vegetative cells of *Clostridium* species are pleomorphic, rod-shaped, and arranged singly or in short chains **(Fig. 149-1)**; the cells have rounded or sometimes pointed ends. Although clostridia stain gram-positive in the early stages of growth, they may appear to be gram-negative or gram-variable later in the growth cycle or in infected tissue specimens. Most strains are motile by means of peritrichous flagella; *C. septicum* swarms on solid media. Nonmotile species include *C. perfringens*, *C. ramosum*, and *C. innocuum*. Most species are obligately anaerobic, although clostridial tolerance to oxygen varies widely; some species (e.g., *C. septicum*, *C. tertium*) will grow but will not sporulate in air.

Clostridia produce more protein toxins than any other bacterial genus, and >25 clostridial toxins lethal to mice have been identified. These proteins include neurotoxins, enterotoxins, cytotoxins, collagenases, permeases, necrotizing toxins, lipases, lecithinases, hemolysins, proteinases, hyaluronidases, DNases, ADP-ribosyltransferases, and neuraminidases. Botulinum and tetanus neurotoxins are the most potent toxins known, with lethal doses of 0.2–10 ng/kg for humans. Epsilon toxin, a 33-kDa protein produced by *C. perfringens* types B and D, causes edema and hemorrhage in the brain, heart, spinal cord, and kidneys of animals. It is among the most lethal of the clostridial toxins and is considered a potential agent of bioterrorism. The genomic sequences of some pathogenic clostridia are now available and are likely to facilitate a comprehensive approach to understanding the virulence factors involved in clostridial pathogenesis.

FIGURE 149-1 Scanning electron micrograph of *C. perfringens*.

EPIDEMIOLOGY AND TRANSMISSION

Clostridium species are widespread in nature, forming endospores that are commonly found in soil, feces, sewage, and marine sediments. The ecology of *C. perfringens* in soil is greatly influenced by the degree and duration of animal husbandry in a given location and is relevant to the incidence of gas gangrene caused by contamination of war wounds with soil. For example, the incidence of clostridial gas gangrene is higher in agricultural regions of Europe than in the Sahara Desert of Africa. Similarly, the incidences of tetanus and food-borne botulism are clearly related to the presence of clostridial spores in soil, water, and many foods. Clostridia are present in large numbers in the indigenous microbiota of the intestinal tract of humans and animals, in the female genital tract, and on the oral mucosa. It should be noted that not all commensal clostridia are toxigenic.

Clostridial infections remain a serious public-health concern worldwide. In developing nations, food poisoning, necrotizing enterocolitis, and gas gangrene are common because large portions of the population are poor and have little or no immediate access to health care. These infections remain prevalent in developed countries as well. Gas gangrene commonly follows knife or gunshot wounds or vehicular accidents or develops as a complication of surgery or gastrointestinal carcinoma. Severe clostridial infections have emerged as a health threat to injection drug users and to women undergoing childbirth or abortion. Historically, clostridial gas gangrene has been the scourge of the battlefield. The global political situation portends another possible scenario involving mass casualties of war or terrorism, with extensive injuries conducive to gas gangrene. Thus there is an ongoing need to develop novel strategies to prevent or attenuate the course of clostridial infections in both civilians and military personnel. Vaccination against exotoxins important in pathogenesis would be of great benefit in developing nations and could also be used safely in at-risk populations such as the elderly, patients with diabetes who may require lower-limb surgery due to trauma or poor circulation, and those undergoing intestinal surgery. Moreover, a hyperimmune globulin would be a valuable tool for prophylaxis in victims of acute traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene.

CLINICAL SYNDROMES

Life-threatening clostridial infections range from intoxications (e.g., food poisoning, tetanus) to necrotizing enteritis/colitis, bacteremia, myonecrosis, and toxic shock syndrome (TSS). **Tetanus and botulism are discussed in Chaps. 147 and 148, respectively. Colitis due to *C. difficile* is discussed in Chap. 129.**

CLOSTRIDIAL WOUND CONTAMINATION

Of open traumatic wounds, 30–80% reportedly are contaminated with clostridial species. In the absence of devitalized tissue, the presence of clostridia does not necessarily lead to infection. In traumatic injuries, clostridia are isolated with equal frequency from both suppurative and well-healing wounds. Thus, diagnosis and treatment of clostridial infection should be based on clinical signs and symptoms and not solely on bacteriologic findings.

POLYMICROBIAL INFECTIONS INVOLVING CLOSTRIDIA

Clostridial species may be found in polymicrobial infections also involving microbial components of the indigenous flora. In these infections, clostridia often appear in association with non-spore-forming anaerobes and facultative or aerobic organisms. Head and neck infections, conjunctivitis, brain abscess, sinusitis, otitis, aspiration pneumonia, lung abscess, pleural empyema, cholecystitis, septic arthritis, and bone infections all may involve clostridia. These conditions are often associated with severe local inflammation but may lack the characteristic systemic signs of toxicity and rapid progression seen

in other clostridial infections. In addition, clostridia are isolated from ~66% of intraabdominal infections in which the mucosal integrity of the bowel or respiratory system has been compromised. In this setting, *C. ramosum*, *C. perfringens*, and *C. bifermentans* are the most commonly isolated species. Their presence does not invariably lead to a poor outcome. Clostridia have been isolated from suppurative infections of the female genital tract (e.g., ovarian or pelvic abscess) and from diseased gallbladders. Although the most frequently isolated species is *C. perfringens*, gangrene is not typically observed; however, gas formation in the biliary system can lead to emphysematous cholecystitis, especially in diabetic patients. *C. perfringens* in association with mixed aerobic and anaerobic microbes can cause aggressive life-threatening type I necrotizing fasciitis or Fournier's gangrene.

The treatment of mixed aerobic/anaerobic infection of the abdomen, perineum, or gynecologic organs should be based on Gram's staining, culture, and antibiotic sensitivity information. Reasonable empirical treatment consists of ampicillin or ampicillin/sulbactam combined with either clindamycin or metronidazole **(Table 149-1)**. Broader gram-negative coverage may be necessary if the patient has recently been hospitalized or treated with antibiotics. Such coverage can be obtained by substituting ticarcillin/clavulanic acid, piperacillin/sulbactam, or a penem antibiotic for ampicillin or by adding a fluoroquinolone or an aminoglycoside to the regimen. Empirical treatment should be given for 10–14 days or until the patient's clinical condition improves.

ENTERIC CLOSTRIDIAL INFECTIONS

C. perfringens type A is one of the most common bacterial causes of food-borne illness in the United States and Canada. The foods typically implicated include improperly cooked meat and meat products (e.g., gravy) in which residual spores germinate and proliferate during slow cooling or insufficient reheating. Illness results from the ingestion of food containing at least ~10^8 viable vegetative cells, which sporulate in the alkaline environment of the small intestine, producing *C. perfringens* enterotoxin in the process. The diarrhea that develops within 7–30 h of ingestion of contaminated food is generally mild and self-limiting; however, in the very young, the elderly, and the immunocompromised, symptoms are more severe and occasionally fatal. Enterotoxin-producing *C. perfringens* has been implicated as an etiologic agent of persistent diarrhea in elderly patients in nursing homes and tertiary-care institutions and has been considered to play a role in antibiotic-associated diarrhea without pseudomembranous colitis.

C. perfringens strains associated with food poisoning possess the gene (*cpe*) coding for enterotoxin, which acts by forming pores in host cell membranes. *C. perfringens* strains isolated from non-food-borne diseases, such as antibiotic-associated and sporadic diarrhea, carry *cpe* on a plasmid that may be transmitted to other strains. Several methods have been described for the detection of *C. perfringens* enterotoxin in feces, including cell culture assay (Vero cells), enzyme-linked immunosorbent assay, reversed-phase latex agglutination, and polymerase chain reaction (PCR) amplification of *cpe*. Each method has its advantages and limitations.

Enteritis necroticans (gas gangrene of the bowel) is a fulminating clinical illness characterized by extensive necrosis of the intestinal mucosa and wall. Cases can occur sporadically in adults or as epidemics in people of all ages. Enteritis necroticans is caused by α toxin– and β toxin–producing strains of *C. perfringens* type C; β toxin is located on a plasmid and is mainly responsible for pathogenesis. This life-threatening infection causes ischemic necrosis of the jejunum. In Papua New Guinea during the 1960s, enteritis necroticans (known in that locale as *pigbel*) was found to be the most common cause of death in childhood; it was associated with pig feasts and occurred both sporadically and in outbreaks. Intramuscular immunization against the β toxin resulted in a decreased incidence of the disease in Papua New Guinea, although the condition remains common. Enteritis necroticans has also been recognized in the United States, the United Kingdom, Germany (where it is known as *darmbrand*), and other developed nations; especially affected are adults who are malnourished or who have diabetes, alcoholic liver disease, or neutropenia.

Necrotizing enterocolitis, a disease resembling enteritis necroticans but associated with *C. perfringens* type A, has been found in North America in previously healthy adults. It is also a serious gastrointestinal disease of low-birth-weight (premature) infants hospitalized in neonatal intensive care units. The etiology and pathogenesis of this disease have remained enigmatic for more than four decades. Pathologic similarities between necrotizing enterocolitis and enteritis necroticans include the pattern of small-bowel necrosis involving the submucosa, mucosa, and muscularis; the presence of gas dissecting the tissue planes; and the degree of inflammation. In contrast to enteritis necroticans, which most commonly involves the jejunum, necrotizing enterocolitis affects the ileum and frequently the ileocecal valve. Both diseases may manifest as intestinal gas cysts, although this feature is more common in necrotizing enterocolitis. The sources of the gas, which contains hydrogen, methane, and carbon dioxide, are probably the fermentative activities of intestinal bacteria, including clostridia. Epidemiologic data support an important role for *C. perfringens* or other gas-producing microorganisms (e.g., *C. neonatale*, certain other clostridia, or *Klebsiella* species) in the pathogenesis of necrotizing enterocolitis.

Patients with suspected clostridial enteric infection should undergo nasogastric suction and receive IV fluids. Pyrantel is given by mouth, and the bowel is rested by fasting. Benzylpenicillin (1 mU) is given IV every 4 h, and the patient is observed for complications requiring

TABLE 149-1 Treatment of Clostridial Infections

CONDITION	ANTIBIOTIC TREATMENT	PENICILLIN ALLERGY	ADJUNCTIVE TREATMENT/NOTE
Wound contamination	None	—	Treatment should be based on clinical signs and symptoms as listed below and not solely on bacteriologic findings.
Polymicrobial anaerobic infections involving clostridia (e.g., abdominal wall, gynecologic)	Ampicillin (2 g IV q4h) ***plus*** Clindamycin (600–900 mg IV q6–8h) ***plus*** Ciprofloxacin (400 mg IV q6–8 h)	Vancomycin (1 g IV q12h) ***plus*** Metronidazole (500 mg IV q6h) ***plus*** Ciprofloxacin (400 mg IV q6–8h)	Empirical therapy should be initiated. Therapy should be based on Gram's stain and culture results and on sensitivity data when available. Add gram-negative coverage if indicated (see text).
Clostridial sepsis	Penicillin (3–4 mU IV q4–6h) ***plus*** Clindamycin (600–900 mg IV q6–8h)	Clindamycin alone ***or*** Metronidazole (as above) ***or*** Vancomycin (as above)	Transient bacteremia without signs of systemic toxicity may be clinically insignificant.
Gas gangrene[a]	Penicillin G (4 mU IV q4–6 h) ***plus*** Clindamycin (600–900 mg IV q6–8h)	Cefoxitin (2 g IV q6h) ***plus*** Clindamycin (600–900 mg IV q6–8h)	Emergent surgical exploration and thorough debridement are extremely important. Hyperbaric oxygen therapy may be considered after surgery and antibiotic initiation.

[a]*C. tertium* is resistant to penicillin, cephalosporins, and clindamycin. Appropriate antibiotic therapy for *C. tertium* infection is vancomycin (1 g q12h IV) or metronidazole (500 mg q8h IV).

surgery. Patients with mild cases recover without surgical intervention. However, if surgical indications are present (gas in the peritoneal cavity, absent bowel sounds, rebound tenderness, abdominal rigidity), the mortality rate ranges from 35 to 100%; a fatal outcome is due in part to perforation of the intestine.

As pigbel continues to be a common disease in Papua New Guinea, consideration should be given to the use of a *C. perfringens* type C β toxoid vaccine in local areas. Two doses given 3–4 months apart are preventive.

CLOSTRIDIAL BACTEREMIA

Clostridium species are important causes of bloodstream infections. Molecular epidemiologic studies of anaerobic bacteremia have identified *C. perfringens* and *C. tertium* as the two most frequently isolated species; these organisms cause up to 79 and 5%, respectively, of clostridial bacteremias. Occasionally, *C. perfringens* bacteremia occurs in the absence of an identifiable infection at another site. When associated with myonecrosis, bacteremia has a grave prognosis.

C. septicum is also commonly associated with bacteremia. This species is isolated only rarely from the feces of healthy individuals but may be found in the normal appendix. More than 50% of patients whose blood cultures are positive for this organism have some gastrointestinal anomaly (e.g., diverticular disease) or underlying malignancy (e.g., carcinoma of the colon). In addition, a clinically important association of *C. septicum* bacteremia with neutropenia of any origin—and, more specifically, with neutropenic enterocolitis involving the terminal ileum or cecum—has been observed. Patients with diabetes mellitus, severe atherosclerotic cardiovascular disease, or anaerobic myonecrosis (gas gangrene) also may develop *C. septicum* bacteremia. *C. septicum* has been recovered from the bloodstream of cirrhotic patients, as have *C. perfringens*, *C. bifermentans*, and other clostridia. Infections of the bloodstream by *C. sordellii* and *C. perfringens* have been associated with TSS.

Bloodstream infection by *C. tertium*, either alone or in combination with *C. septicum* or *C. perfringens*, can be found in patients with serious underlying disease such as malignancy or acute pancreatitis, with or without neutropenic enterocolitis; the frequency has not been systematically studied. *C. tertium* may present special problems in terms of both identification and treatment. This organism may stain gram-negative; is aerotolerant; and is resistant to metronidazole, clindamycin, and cephalosporins.

Other clostridia from the *C. clostridioforme* group (including *C. clostridioforme*, *C. hathewayi*, and *C. bolteae*) can cause bacteremia.

The clinical importance of recognizing clostridial bacteremia—especially that due to *C. septicum*—and starting appropriate treatment immediately (Table 149-1) cannot be overemphasized. Patients with this condition usually are gravely ill, and infection may metastasize to distant anatomic sites, resulting in spontaneous myonecrosis (see next section). Alternative methods to identify bacteremia-causing clostridial species, such as PCR or other rapid diagnostic tests, are not currently available. Anaerobic blood cultures and Gram's stain interpretation remain the best diagnostic tests at this point.

CLOSTRIDIAL SKIN AND SOFT-TISSUE INFECTIONS

Histotoxic clostridial species such as *C. perfringens*, *C. histolyticum*, *C. septicum*, *C. novyi*, and *C. sordellii* cause aggressive necrotizing infections of the skin and soft tissues. These infections are attributable in part to the elaboration of bacterial proteases, phospholipases, and cytotoxins. Necrotizing clostridial soft-tissue infections are rapidly progressive and are characterized by marked tissue destruction, gas in the tissues, and shock; they frequently end in death. Severe pain, crepitus, brawny induration with rapid progression to skin sloughing, violaceous bullae, and marked tachycardia are characteristics found in the majority of patients.

Clostridial Myonecrosis (Gas Gangrene)

• **TRAUMATIC GAS GANGRENE** *C. perfringens* myonecrosis (gas gangrene) is one of the most fulminant gram-positive bacterial infections of humans. Even with appropriate antibiotic therapy and management in an intensive care unit, tissue destruction can progress rapidly. Gas gangrene is accompanied by bacteremia, hypotension, and multiorgan failure and is invariably fatal if untreated. Gas gangrene is a true emergency and requires immediate surgical debridement.

The development of gas gangrene requires an anaerobic environment and contamination of a wound with spores or vegetative organisms. Devitalized tissue, foreign bodies, and ischemia reduce locally available oxygen levels and favor outgrowth of vegetative cells and spores. Thus conditions predisposing to traumatic gas gangrene include crush-type injury, laceration of large or medium-sized arteries, and open fractures of long bones that are contaminated with soil or bits of clothing containing the bacterial spores. Gas gangrene of the abdominal wall and flanks follows penetrating injuries such as knife or gunshot wounds that are sufficient to compromise intestinal integrity, with resultant leakage of the bowel contents into the soft tissues. Proximity to fecal sources of bacteria is a risk factor for cases following hip surgery, adrenaline injections into the buttocks, or amputation of the leg for ischemic vascular disease. In the last decade, cutaneous gas gangrene caused by *C. perfringens*, *C. novyi*, and *C. sordellii* has been described in the United States and northern Europe among persons injecting black-tar heroin subcutaneously.

The incubation period for traumatic gas gangrene can be as short as 6 h and is usually <4 days. The infection is characterized by the sudden onset of excruciating pain at the affected site and the rapid development of a foul-smelling wound containing a thin serosanguineous discharge and gas bubbles. Brawny edema and induration develop and give way to cutaneous blisters containing bluish to maroon-colored fluid. Such tissue later may become liquefied and slough. The margin between healthy and necrotic tissue often advances several inches per hour despite appropriate antibiotic therapy, and radical amputation remains the single best life-saving intervention. Shock and organ failure frequently accompany gas gangrene; when patients become bacteremic, the mortality rate exceeds 50%.

Diagnosis of traumatic gas gangrene is not difficult because the infection always begins at the site of significant trauma, is associated with gas in the tissue, and is rapidly progressive. Gram's staining of drainage or tissue biopsy is usually definitive, demonstrating large gram-positive (or gram-variable) rods, an absence of inflammatory cells, and widespread soft-tissue necrosis.

SPONTANEOUS (NONTRAUMATIC) GAS GANGRENE Spontaneous gas gangrene generally occurs via hematogenous seeding of normal muscle with histotoxic clostridia—principally *C. perfringens*, *C. septicum*, and *C. novyi* and occasionally *C. tertium*—from a gastrointestinal tract portal of entry (as in colonic malignancy, inflammatory bowel disease, diverticulitis, necrotizing enterocolitis, cecitis, or distal ileitis or after gastrointestinal surgery, including colonoscopic polypectomy). These gastrointestinal pathologies permit bacterial access to the bloodstream; consequently, aerotolerant *C. septicum* can proliferate in normal tissues. Patients surviving bacteremia or spontaneous gangrene due to *C. septicum* should undergo aggressive diagnostic studies to rule out gastrointestinal pathology.

Additional predisposing host factors include leukemia, lymphoproliferative disorders, cancer chemotherapy, radiation therapy, and AIDS. Cyclic, congenital, or acquired neutropenia also is strongly associated with an increased incidence of spontaneous gas gangrene due to *C. septicum*; in such cases, necrotizing enterocolitis, cecitis, or distal ileitis is common, particularly among children.

The first symptom of spontaneous gas gangrene may be confusion followed by the abrupt onset of excruciating pain in the absence of trauma. These findings, along with fever, should heighten suspicion of spontaneous gas gangrene. However, because of the lack of an obvious portal of entry, the correct diagnosis is frequently delayed or missed. The infection is characterized by rapid progression of tissue destruction with demonstrable gas in the tissue **(Fig. 149-2)**. Swelling increases, and bullae filled with clear, cloudy, hemorrhagic, or purplish fluid appear. The surrounding skin has a purple hue, which may reflect vascular compromise resulting from the diffusion of bacterial toxins into surrounding tissues. Invasion of healthy tissue rapidly ensues, with quick progression to shock and multiple-organ failure. Mortality rates

FIGURE 149-2 Radiograph of patient with spontaneous gas gangrene due to *C. septicum*, demonstrating gas in the affected arm and shoulder.

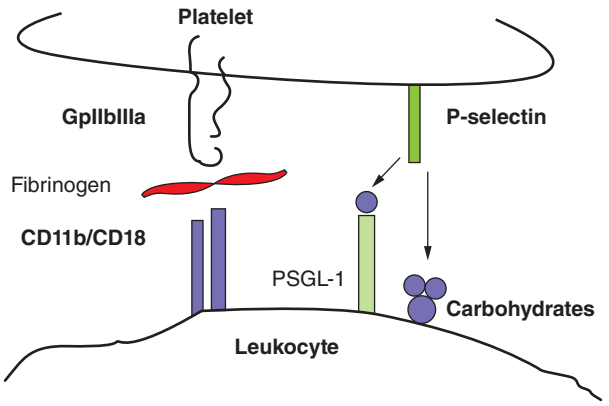

FIGURE 149-3 Schematic illustration of the molecular mechanisms of *C. perfringens* α toxin–induced platelet/neutrophil aggregates. Homotypic aggregates of platelets (not shown) and heterotypic aggregates of platelets and leukocytes are due to α toxin–induced activation of the platelet fibrinogen receptor gpIIb/IIIa and upregulation of leukocyte CD11b/CD18. Binding of fibrinogen (*red*) bridges the connection between these adhesion molecules on adjacent cells. An auxiliary role for α toxin–induced upregulation of platelet P-selectin and its binding to leukocyte P-selectin glycoprotein ligand 1 (PSGL-1) or other leukocyte surface carbohydrates also has been demonstrated.

in this setting range from 67 to 100% among adults; among children, the mortality rate is 59%, with the majority of deaths occurring within 24 h of onset.

PATHOGENESIS OF GAS GANGRENE In traumatic gas gangrene, organisms are introduced into devitalized tissue. It is important to recognize that, for *C. perfringens* and *C. novyi*, trauma must be sufficient to interrupt the blood supply and thereby to establish an optimal anaerobic environment for growth of these species. These conditions are not strictly required for the more aerotolerant species such as *C. septicum* and *C. tertium*, which can seed normal tissues from gastrointestinal lesions. Once introduced into an appropriate niche, the organisms proliferate locally and elaborate exotoxins.

The major *C. perfringens* extracellular toxins implicated in gas gangrene are α toxin and θ toxin. A lethal hemolysin that has both phospholipase C and sphingomyelinase activities, α toxin has been implicated as the major virulence factor of *C. perfringens*: immunization of mice with the C-terminal domain of α toxin provides protection against lethal challenge with *C. perfringens*, and isogenic α toxin–deficient mutant strains of *C. perfringens* are not lethal in a murine model of gas gangrene. Recently, a human single-chain recombinant antibody to α toxin that has significant preventive and therapeutic efficacy in mice has been developed.

It has been shown in experimental models that the severe pain, rapid progression, marked tissue destruction, and absence of neutrophils in *C. perfringens* gas gangrene are attributable in large part to α toxin–induced occlusion of blood vessels by heterotypic aggregates of platelets and neutrophils. The formation of these aggregates, which occurs within minutes, is largely mediated by α toxin's ability to activate the platelet adhesion molecule gpIIb/IIIa **(Fig. 149-3)**; the implication is that platelet glycoprotein inhibitors (e.g., eptifibatide, abciximab) may be therapeutic for maintaining tissue blood flow.

C. perfringens θ toxin (*perfringolysin*) is a member of the thiol-activated cytolysin family known as cholesterol-dependent cytolysins, which includes streptolysin O from group A *Streptococcus*, pneumolysin from *Streptococcus pneumoniae*, and several other toxins. Cholesterol-dependent cytolysins bind as oligomers to cholesterol in host cell membranes. At high concentrations, these toxins form ring-like pores resulting in cell lysis. At sub-lytic concentrations, θ toxin hyperactivates phagocytes and vascular endothelial cells.

Cardiovascular collapse and end-organ failure occur late in the course of *C. perfringens* gas gangrene and are largely attributable to both direct and indirect effects of α and θ toxins. In experimental models, θ toxin causes markedly reduced systemic vascular resistance but increased cardiac output (i.e., "warm shock"), probably via induction of endogenous mediators (e.g., prostacyclin, platelet-activating factor) that cause vasodilation. This effect is similar to that observed in gram-negative sepsis. In sharp contrast, α toxin directly suppresses myocardial contractility; the consequence is profound hypotension due to a sudden reduction in cardiac output. The roles of other endogenous mediators, such as cytokines (e.g., tumor necrosis factor, interleukin 1, interleukin 6) and vasodilators (e.g., bradykinin) have not been fully elucidated.

C. septicum produces three main toxins—α toxin (lethal, hemolytic, necrotizing activity), β toxin (DNase), and γ toxin (hyaluronidase)—as well as a protease and a neuraminidase. Unlike the α toxin of *C. perfringens*, that of *C. septicum* does not possess phospholipase activity. The mechanisms remain to be fully elucidated, but it is likely that each of these toxins contributes uniquely to *C. septicum* gas gangrene.

TREATMENT

Gas Gangrene

Patients with suspected gas gangrene (either traumatic or spontaneous) should undergo prompt surgical inspection of the infected site. Direct examination of a Gram-stained smear of the involved tissues is of major importance. Characteristic histologic findings in clostridial gas gangrene include widespread tissue destruction, a paucity of leukocytes in infected tissues in conjunction with an accumulation of leukocytes in adjacent vessels **(Fig. 149-4)**, and the presence of gram-positive rods (with or without spores). CT and MRI are invaluable for determining whether the infection is localized or is spreading along fascial planes, and needle aspiration or punch biopsy may provide an etiologic diagnosis in at least 20% of cases. However, these techniques should not replace surgical exploration, Gram's staining, and histopathologic examination. When spontaneous gas gangrene is suspected, blood should be cultured since bacteremia usually precedes cutaneous manifestations by several hours.

For patients with evidence of clostridial gas gangrene, thorough emergent surgical debridement is of extreme importance. All devitalized tissue should be widely resected back to healthy viable muscle and skin so as to remove conditions that allow anaerobic

FIGURE 149-4 Histopathology of experimental gas gangrene due to *C. perfringens*, demonstrating widespread muscle necrosis, a paucity of leukocytes in infected tissues, and accumulation of leukocytes in adjacent vessels (*arrows*). These features are due to the effects of α and θ toxins on muscle cells, platelets, leukocytes, and endothelial cells.

organisms to continue proliferating. Closure of traumatic wounds or compound fractures should be delayed for 5–6 days until it is certain that these sites are free of infection.

Except for infection caused by *C. tertium* (see below), antibiotic treatment of traumatic or spontaneous gas gangrene (Table 149-1) consists of the administration of penicillin and clindamycin for 10–14 days. Penicillin is recommended on the basis of in vitro sensitivity data; clindamycin is recommended because of its superior efficacy over penicillin in animal models of *C. perfringens* gas gangrene and in some clinical reports. Controlled clinical trials comparing the efficacy of these agents in humans have not been performed. In the penicillin-allergic patient, clindamycin may be used alone. The superior efficacy of clindamycin is probably due to its ability to inhibit bacterial protein toxin production, its insensitivity to the size of the bacterial load or the stage of bacterial growth, and its ability to modulate the host's immune response.

C. tertium is resistant to penicillin, cephalosporins, and clindamycin. Appropriate antibiotic therapy for *C. tertium* infection is vancomycin (1 g every 12 h IV) or metronidazole (500 mg every 8 h IV).

The value of adjunctive treatment with hyperbaric oxygen (HBO) for gas gangrene remains controversial. Basic-science studies suggest that HBO can inhibit the growth of *C. perfringens* but not that of the more aerotolerant *C. septicum*. In vitro, blood and macerated muscle inhibit the bactericidal potential of HBO. Numerous studies in animals demonstrate little efficacy of HBO alone, whereas antibiotics alone—especially those that inhibit bacterial protein synthesis—confer marked benefits. Addition of HBO to the therapeutic regimen provides some additional benefit, but only if surgery and antibiotic administration precede HBO treatment.

In conclusion, gas gangrene is a rapidly progressive infection whose outcome depends on prompt recognition, emergent surgery, and timely administration of antibiotics that inhibit toxin production. Gas gangrene associated with bacteremia probably represents a later stage of illness and is associated with the worst outcomes. Emergent surgical debridement is crucial to ensure survival, and ancillary procedures (e.g., CT or MRI) or transport to HBO units should not delay this intervention. Some trauma centers associated with HBO units may have special expertise in managing these aggressive infections, but proximity and speed of transfer must be carefully weighed against the need for haste.

PROGNOSIS OF GAS GANGRENE The prognosis for patients with gas gangrene is more favorable when the infection involves an extremity rather than the trunk or visceral organs, since debridement of the latter sites is more difficult. Gas gangrene is most likely to progress to shock and death in patients with associated bacteremia and intravascular hemolysis. Mortality rates are highest for patients in shock at the time of diagnosis. Mortality rates are relatively high among patients with spontaneous gas gangrene, especially that due to *C. septicum*. Survivors of gas gangrene may undergo multiple debridements and face long periods of hospitalization and rehabilitation.

PREVENTION OF GAS GANGRENE Initial aggressive debridement of devitalized tissue can reduce the risk of gas gangrene in contaminated deep wounds. Interventions to be avoided include prolonged application of tourniquets and surgical closure of traumatic wounds; patients with compound fractures are at significant risk for gas gangrene if the wound is closed surgically. Vaccination against α toxin is protective in experimental animal models of *C. perfringens* gas gangrene but has not been investigated in humans. In addition, as mentioned above, a hyperimmune globulin would represent a significant advance for prophylaxis in victims of acute traumatic injury or for attenuation of the spread of infection in patients with established gas gangrene.

Toxic Shock Syndrome

Clostridial infection of the endometrium, particularly that due to *C. sordellii*, can develop after gynecologic procedures, childbirth, or abortion (spontaneous or elective, surgical or medical) and, once established, proceeds rapidly to TSS and death. Systemic manifestations, including edema, effusions, profound leukocytosis, and hemoconcentration, are followed by the rapid onset of hypotension and multiple-organ failure. Elevation of the hematocrit to 75–80% and leukocytosis of 50,000–200,000 cells/μL, with a left shift, are characteristic of *C. sordellii* infection. Pain may not be a prominent feature, and fever is typically absent. In one series, 18% of 45 cases of *C. sordellii* infection were associated with normal childbirth, 11% with medically induced abortion, and 0.4% with spontaneous abortion; the case–fatality rate was 100% in these groups. Of the infections in this series that were not related to gynecologic procedures or childbirth, 22% occurred in injection drug users, and 50% of these patients died. Other infections followed trauma or surgery (42%), mostly in healthy persons, and 53% of these patients died. Overall, the mortality rate was 69% (31 of 45 cases). Of patients who succumbed, 85% died within 2–6 days after infection onset or following procedures. Rapidly fatal, spontaneous *C. bifermentans* necrotizing endometritis with toxic shock, leukemoid reaction, and capillary leak has also been described.

Early diagnosis of *C. sordellii* infections often proves difficult for several reasons. First, the prevalence of these infections is low. Second, the initial symptoms are nonspecific and frankly misleading. Early in the course, the illness resembles any number of infectious diseases, including viral syndromes. Given these vague symptoms and an absence of fever, physicians usually do not aggressively pursue additional diagnostic tests. The absence of local evidence of infection and the lack of fever make early diagnosis of *C. sordellii* infection particularly problematic in patients who develop deep-seated infection following childbirth, therapeutic abortion, gastrointestinal surgery, or trauma. Such patients are frequently evaluated for pulmonary embolization, gastrointestinal bleeding, pyelonephritis, or cholecystitis. Unfortunately, such delays in diagnosis increase the risk of death, and, as in most necrotizing soft-tissue infections, patients are hypotensive with evidence of organ dysfunction by the time local signs and symptoms become apparent. In contrast, infection is more readily suspected in injection drug users presenting with local swelling, pain, and redness at injection sites; early recognition probably contributes to the lower mortality rates in this group.

Physicians should suspect *C. sordellii* infection in patients who present within 2–7 days after injury, surgery, drug injection, childbirth, or abortion and who report pain, nausea, vomiting, and diarrhea but are afebrile. There is little information regarding appropriate treatment for *C. sordellii* infections. In fact, the interval between onset of symptoms and death is often so short that there is little time to initiate empirical antimicrobial therapy. Indeed, anaerobic cultures of blood and wound aspirates are time-consuming, and many hospital laboratories do not routinely perform antimicrobial sensitivity testing on anaerobes. Antibiotic susceptibility data from older studies suggest that *C. sordellii*,

like most clostridia, is susceptible to β-lactam antibiotics, clindamycin, tetracycline, and chloramphenicol but is resistant to aminoglycosides and sulfonamides. Antibiotics that suppress toxin synthesis (e.g., clindamycin) may possibly prove useful as therapeutic adjuncts since they are effective in necrotizing infections due to other toxin-producing gram-positive organisms.

Other Clostridial Skin and Soft-Tissue Infections *Crepitant cellulitis* (also called *anaerobic cellulitis*) occurs principally in diabetic patients and characteristically involves subcutaneous tissues or retroperitoneal tissues, whereas the muscle and fascia are not involved. This infection can progress to fulminant systemic disease.

Cases of *C. histolyticum* infection with cellulitis, abscess formation, or endocarditis have also been documented in injection drug users. Endophthalmitis due to *C. sordellii* or *C. perfringens* has been described. *C. ramosum* is also isolated frequently from clinical specimens, including blood and both intraabdominal and soft tissues. This species may be resistant to clindamycin and multiple cephalosporins.

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Section 6 Diseases Caused by Gram-Negative Bacteria

150 Meningococcal Infections

Andrew J. Pollard

DEFINITION

Infection with *Neisseria meningitidis* most commonly manifests as asymptomatic colonization in the nasopharynx of healthy adolescents and adults. Invasive disease occurs rarely, usually presenting as either bacterial meningitis or meningococcal septicemia. Patients may also present with occult bacteremia, pneumonia, septic arthritis, conjunctivitis, and chronic meningococcemia.

ETIOLOGY AND MICROBIOLOGY

N. meningitidis is a gram-negative aerobic diplococcus that colonizes humans only and that causes disease after transmission to a susceptible individual. Several related neisserial organisms have been recognized, including the pathogen *N. gonorrhoeae* and the commensals *N. lactamica*, *N. flavescens*, *N. mucosa*, *N. sicca*, and *N. subflava*. *N. meningitidis* is a catalase- and oxidase-positive organism that utilizes glucose and maltose to produce acid.

TABLE 150-1 Structure of the Polysaccharide Capsule of Common Disease-Causing Meningococci

MENINGOCOCCAL CAPSULAR GROUP	CHEMICAL STRUCTURE OF OLIGOSACCHARIDE	CURRENT DISEASE EPIDEMIOLOGY
A	2-Acetamido-2-deoxy-D-mannopyranosyl phosphate	Epidemic disease mainly in sub-Saharan Africa; sporadic cases worldwide
B	α-2,8-*N*-acetylneuraminic acid	Sporadic cases worldwide; propensity to cause hyperendemic disease
C	α-2,9-O-acetylneuraminic acid	Small outbreaks and sporadic disease
Y	4-O-α-D-glucopyranosyl-*N*-acetylneuraminic acid	Sporadic disease and occasional small institutional outbreaks
W	4-O-α-D-galactopyranosyl-*N*-acetylneuraminic acid	Sporadic disease; outbreaks of disease associated with mass gatherings; epidemics in sub-Saharan Africa
X	(α1→4) *N*-acetyl-D-glucosamine-1-phosphate	Sporadic disease and large outbreaks in the meningitis belt of Africa

Meningococci associated with invasive disease are usually encapsulated with polysaccharide, and the antigenic nature of the capsule determines an organism's capsular group (serogroup) **(Table 150-1)**. In total, 12 capsular groups have been identified (A–C, X–Z, 29E, W, H–J, and L), but just six of these—A, B, C, X, Y, and W (formerly W135)—account for the majority of cases of invasive disease. Group D is often listed as the thirteenth capsular group but has recently been identified as an unencapsulated variant of group C. Meningococci are commonly isolated from the nasopharynx in studies of carriage; the lack of capsule often is a result of phase variation of capsule expression, but as many as 16% of isolates lack the genes for capsule synthesis and assembly. These "capsule-null" meningococci and those that express capsules other than A, B, C, X, Y, and W are only rarely associated with invasive disease and are most commonly identified in the nasopharynx of asymptomatic carriers.

Beneath the capsule, meningococci are surrounded by an outer phospholipid membrane containing lipopolysaccharide (LPS, endotoxin) and multiple outer-membrane proteins **(Figs. 150-1 and 150-2)**. Antigenic variability in porins expressed in the outer membrane defines the serotype (PorB) and serosubtype (PorA) of the organism, and structural differences in LPS determine the immunotype. Serologic methods for typing of meningococci are restricted by the limited availability of serologic reagents that can distinguish among the organisms' highly variable surface proteins. Where available, high-throughput antigen gene sequencing has superseded serology for meningococcal typing. A large database of antigen gene sequences for the outer-membrane proteins PorA, PorB, FetA, Opa, and factor H–binding protein is available online (*www.neisseria.org*). The number of specialized iron-regulated proteins found in the meningococcal outer membrane (e.g., FetA and transferrin-binding proteins) highlights the organisms' dependence on iron from human sources. A thin peptidoglycan cell wall separates the outer membrane from the cytoplasmic membrane.

The structure of meningococcal populations involved in local and global spread has been studied with multilocus enzyme electrophoresis (MLEE), which characterizes isolates according to differences in the electrophoretic mobility of cytoplasmic enzymes. However, this technique was replaced by multilocus sequence typing (MLST), in which meningococci are characterized by sequence types assigned on the basis of sequences of internal fragments of seven housekeeping

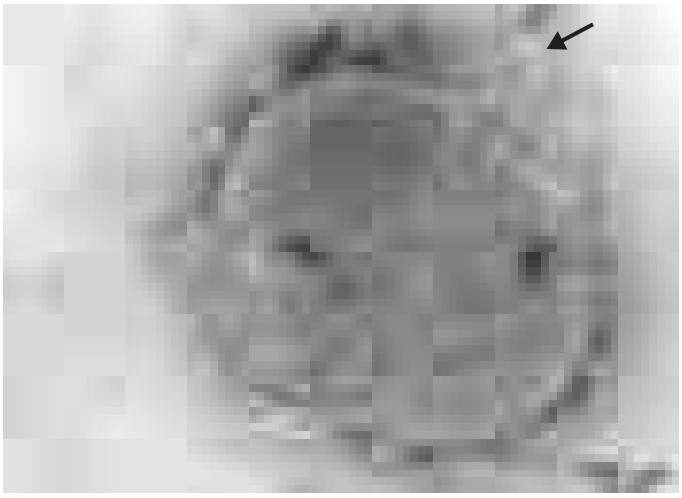

FIGURE 150-1 Electron micrograph of *Neisseria meningitidis*. Black dots are gold-labeled polyclonal antibodies binding surface opacity proteins. Blebs of outer membrane can be seen being released from the bacterial surface (*arrow*). *(Photo courtesy of D. Ferguson, Oxford University.)*

genes. The online MLST database currently includes more than 12,000 unique *Neisseria* sequence types *(pubmlst.org/neisseria/)*. A limited number of hyperinvasive lineages of *N. meningitidis* have been recognized and are responsible for the majority of cases of invasive meningococcal disease worldwide. Hyperinvasive lineages may be associated with more than one capsular group. The apparent genetic stability of these meningococcal clones over decades and during wide geographic spread indicates that they are well adapted to the nasopharyngeal environment of the host and to efficient transmission. While MLST has become established as the main method for meningococcal genotyping in many reference laboratories over the past 15 years, whole-genome sequencing is gradually replacing this approach, with almost 3153 genomes already available in the United Kingdom's national library (*www.meningitis.org/genome-library*).

The group B meningococcal genome is >2 megabases in length and contains 2158 coding regions. Many genes undergo phase variation that makes it possible to control their expression; this capacity is likely to be important in meningococcal adaptation to the host environment and evasion of the immune response. Meningococci can obtain DNA from their environment and can acquire new genes—including the capsular operon—such that *capsule switching* from one capsular group to another can occur.

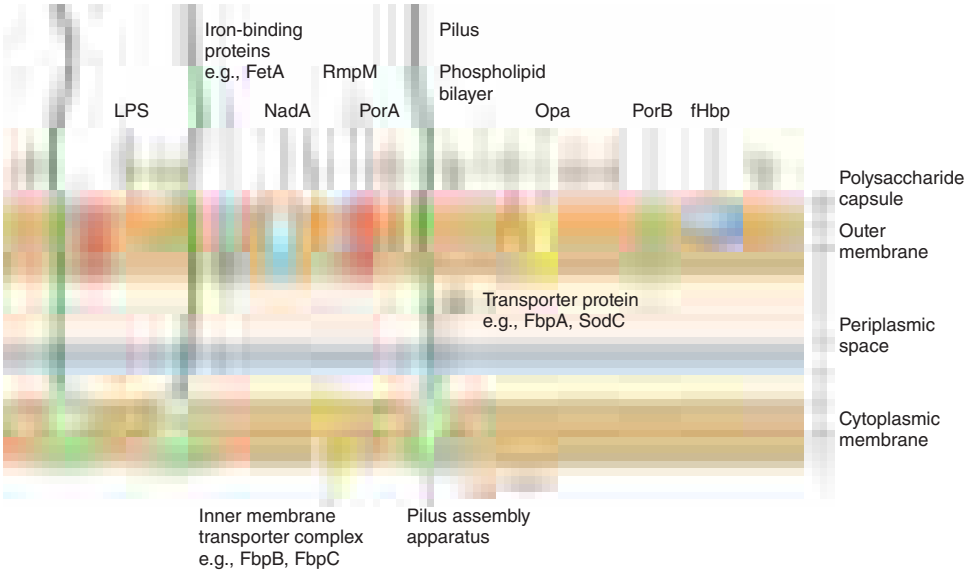

FIGURE 150-2 Cross-section through surface structures of *Neisseria meningitidis*. LPS, lipopolysaccharide. *(Reprinted with permission from M Sadarangani, AJ Pollard: Lancet Infect Dis 10:112, 2010.)*

EPIDEMIOLOGY

Patterns of Disease Up to 500,000 cases of meningococcal disease are thought to occur worldwide each year, though the numbers have been declining recently as a result of both immunization programs and secular trends. About 10% of the individuals affected die. There are several patterns of disease: epidemic, outbreak (small clusters of cases), hyperendemic, and sporadic or endemic.

Epidemics have continued since the original descriptions of meningococcal disease, especially affecting the sub-Saharan meningitis belt of Africa, where tens to hundreds of thousands of cases (caused mainly by capsular group A but also by capsular groups W and X) may be reported over a season and rates may be as high as 1000 cases per 100,000 population. Capsular group A epidemics took place in Europe and North America after the First and Second World Wars, and capsular group A outbreaks have been documented over the past 30 years in New Zealand, China, Nepal, Mongolia, India, Pakistan, Poland, and Russia. However, 81% of cases reported in the meningitis belt in 2014 were caused by capsular group W meningococci and followed an immunization campaign to control capsular group A outbreaks.

Clusters of cases occur where there is an opportunity for increased transmission—i.e., in closed or semi-closed communities such as schools, colleges, universities, military training centers, and refugee camps. Recently, such clusters have been especially strongly linked with a particular clone (sequence type 11) that is mainly associated with capsular group C or W but was first described in association with capsular group B. Clusters of capsular group W disease associated with the Hajj pilgrimage in 2000/2001 led to a requirement for vaccination against meningococcal disease for travel to Saudi Arabia. Wider and more prolonged community outbreaks (hyperendemic disease) due to single clones of capsular group B meningococci account for ≥10 cases per 100,000. Regions affected in the past decade include the U.S. Pacific Northwest, New Zealand (both islands), and the province of Normandy in France.

Most countries now experience predominantly sporadic cases (0.3–5 cases per 100,000 population), with many different disease-causing clones involved and usually no clear epidemiologic link between one case and another. The disease rate and the distribution of meningococcal strains vary in different regions of the world and also in any one location over time. For example, in the United States, the rate of meningococcal disease fell from 1.2 cases per 100,000 population in 1997 to <0.15 case per 100,000 in 2012 **(Fig. 150-3)**. Meningococcal disease in the United States was previously dominated by capsular groups B and C; however, capsular group Y emerged during the 1990s and became more common than capsular group C in 2007 **(Fig. 150-4)**. In contrast, rates of disease in England and Wales rose to >5 cases per 100,000 during the 1990s because of an increase in cases caused by the ST11 capsular group C clone. As a result of a mass immunization program against capsular group C in 1999, the majority of cases in the United Kingdom are now attributed to capsular group B (Fig. 150-4). Over the last decade, most industrialized nations have seen a general decrease in meningococcal disease; this decrease is linked to immunization against capsular group C meningococci in Europe, Canada, and Australia and to adolescent immunization programs for capsular groups A, C, Y, and W in the United States. However, other factors, including changes in population immunity and prevalent clones of meningococci (factors that, in combination, probably explain the cyclic nature of meningococcal disease rates) as well as a reduction in smoking and passive exposure to tobacco smoke (driven by bans on

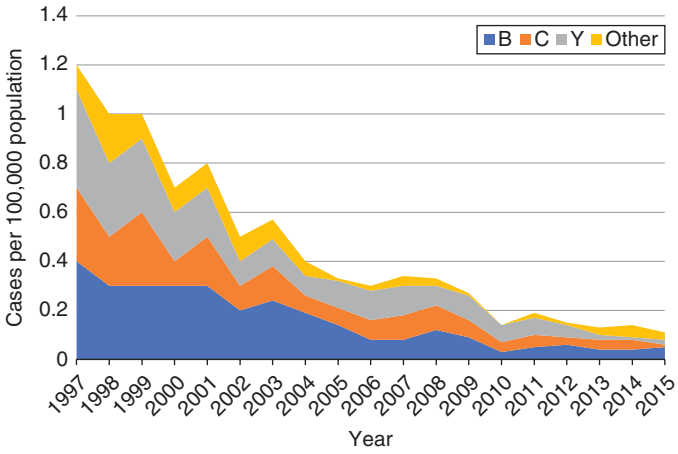

FIGURE 150-3 Meningococcal disease in the United States over time. ABCs, active bacterial cores. *(Adapted from ABC Surveillance data, Centers for Disease Control and Prevention; www.cdc.gov.)*

smoking in buildings and public spaces) across wealthy countries, are likely to have contributed to the fall in cases. Recently, a hyperinvasive ST11 clone bearing a W capsule has emerged in South America and spread to the United Kingdom and has also emerged in other countries in Europe and in Australia, leading to a considerable increase in capsular group W cases. Increases in capsular group Y disease have also been noted in various countries in Europe, Canada, and South Africa.

Factors Associated with Disease Risk and Susceptibility

The principal determinant of disease susceptibility is age, with the peak incidence in the first year of life **(Fig. 150-5)**. The susceptibility of the very young presumably results from an absence of specific adaptive immunity in combination with very close contact with colonized individuals, including parents. Compared with other age groups, infants appear to be particularly susceptible to capsular group B disease: >30% of capsular group B cases in the United States occur during the first year of life. In the early 1990s in North America, the median ages for patients with disease due to capsular groups B, C, Y, and W were 6, 17, 24, and 33 years, respectively.

After early childhood, a second peak of disease occurs among adolescents and young adults (15–25 years of age) in Europe and North America. It is thought that this peak relates to social behaviors and environmental exposures in this age group, as discussed below. Most cases of infection with *N. meningitidis* in developed countries today are sporadic, and the rarity of the disease suggests that individual susceptibility may be important. A number of factors probably contribute to individual susceptibility, including the host's genetic constitution, environment, and contact with a carrier or a case.

The best-documented genetic association with meningococcal disease is complement deficiency, chiefly of the terminal complement components (C5–9), properdin, or factor D; such a deficiency increases the risk of disease by up to 600-fold and may result in recurrent attacks. Complement components are believed to be important for the bactericidal activity of serum, which is considered the principal mechanism of immunity against invasive meningococcal disease. However, when investigated, complement deficiency is found in only a very small proportion of individuals with meningococcal disease (0.3%). Conversely, 7–20% of persons whose disease is caused by the less common capsular groups (W, X, Y, Z, 29E) have a complement deficiency. Complement deficiency appears to be associated with capsular group B disease only rarely. Individuals with recurrences of meningococcal disease, particularly those caused by non-B capsular groups, should be assessed for complement deficiency by measurement of total hemolytic complement activity. There is also limited evidence that hyposplenism (through reduction in phagocytic capacity) and hypogammaglobulinemia (through absence of specific antibody) increase the risk of meningococcal disease. Genetic studies have revealed various associations with disease susceptibility, including complement and mannose-binding lectin deficiency, single-nucleotide polymorphisms in Toll-like receptor (TLR) 4 and complement factor H, and variants of Fc gamma receptors.

Factors that increase the chance of a susceptible individual's acquiring *N. meningitidis* via the respiratory route also increase the risk of meningococcal disease. Acquisition occurs through close contact with carriers as a result of overcrowding (e.g., in poor socioeconomic settings, in refugee camps, during the Hajj pilgrimage to Mecca, and during freshman-year residence in college dormitories) and certain social behaviors (e.g., attendance at bars and nightclubs, kissing). Secondary cases may occur in close contacts of an index case (e.g., household members and persons kissing the infected individual); the

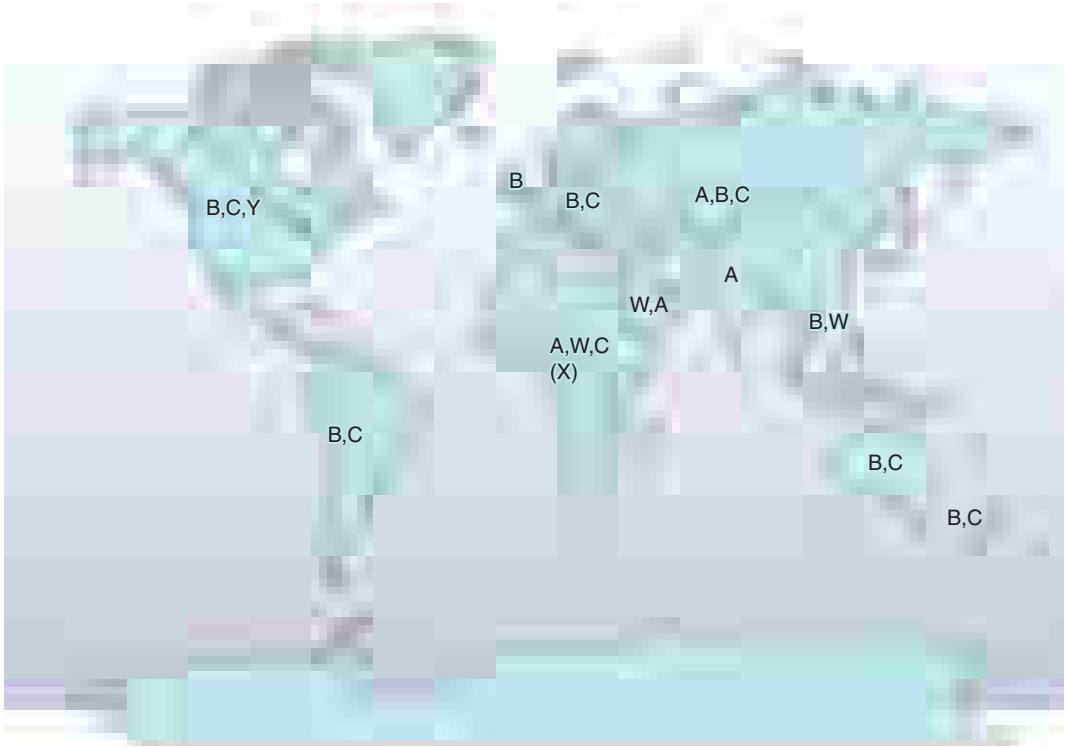

FIGURE 150-4 Global distribution of meningococcal capsular groups, 1999–2009.

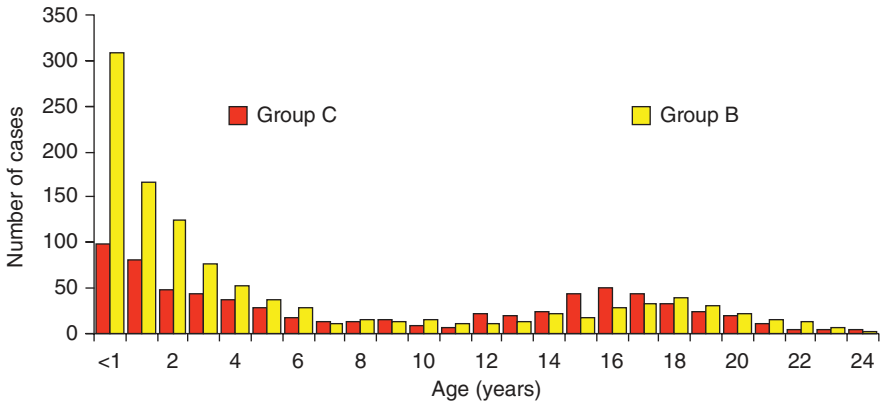

FIGURE 150-5 Age distribution of capsular groups B and C meningococcal disease in England and Wales, 1998–1999. *(Health Protection Agency, UK; www.hpa.org.uk.)*

risk to these contacts may be as high as 1000 times the background rate in the population. Factors that damage the nasopharyngeal epithelium also increase the risk of both colonization with *N. meningitidis* and invasive disease. The most important of these factors are cigarette smoking (odds ratio, 4.1) and passive exposure to cigarette smoke. In addition, recent viral respiratory tract infection, infection with *Mycoplasma* species, and winter or the dry season have been associated with meningococcal disease; all of these factors presumably either increase the expression of adhesion molecules in the nasopharynx, thus enhancing meningococcal adhesion, or facilitate meningococcal invasion of the bloodstream.

PATHOGENESIS

N. meningitidis has evolved as an effective colonizer of the human nasopharynx, with asymptomatic infection rates of >25% described in some series of adolescents and young adults and among residents of crowded communities. Point-prevalence studies reveal widely divergent rates of carriage for different types of meningococci. This variation suggests that some types may be adapted to a short duration of carriage with frequent transmission to maintain the population, while others may be less efficiently transmitted but may overcome this disadvantage by colonizing for a long period. Despite the high rates of carriage among adolescents and young adults, only ~10% of adults carry meningococci, and colonization is very rare in early childhood. Many of the same factors that increase the risk of meningococcal disease also increase the risk of carriage. Colonization of the nasopharynx involves a series of interactions of meningococcal adhesins (e.g., Opa proteins and pili) with their ligands on the epithelial mucosa. *N. meningitidis* produces an IgA1 protease that is likely to reduce interruption of colonization by mucosal IgA.

Colonization should be considered the normal state of meningococcal infection, with an increased risk of invasion being the unfortunate consequence (for both host and organism) of adaptations of hyperinvasive meningococcal lineages. The meningococcal capsule is an important virulence factor: acapsular strains only very rarely cause invasive disease. The capsule provides resistance to phagocytosis and may be important in preventing desiccation during transmission between hosts. Antigenic diversity in surface structures and an ability to vary levels of their expression have probably evolved as important factors in maintaining meningococcal populations within and between individual hosts.

Invasion through the mucosa into the bloodstream occurs rarely, usually within a few days of acquisition of an invasive strain by a susceptible individual. Only occasional cases of prolonged colonization prior to invasion have been documented. Once the organism is in the bloodstream, its growth may be limited if the individual is partially immune, although bacteremia may allow seeding of another site, such as the meninges or the joints. Alternatively, unchecked proliferation may continue, resulting in high bacterial counts in the circulation. During growth, meningococci release blebs of outer membrane (Fig. 150-1) containing outer-membrane proteins and LPS. Endotoxin binds cell-bound CD14 in association with TLR4 to initiate an inflammatory cascade with the release of high levels of various mediators, including tumor necrosis factor (TNF) α, soluble TNF receptor, interleukin (IL) 1, IL-1 receptor antagonist, IL-1β, IL-6, IL-8, IL-10, plasminogen-activator inhibitor 1 (PAI-1), and leukemia inhibitory factor. Soluble CD14-bound endotoxin acts as a mediator of endothelial activation. The severity of meningococcal disease is related both to the levels of endotoxin in the blood and to the magnitude of the inflammatory response. The latter is determined to some extent by polymorphisms in the inflammatory response genes (and their inhibitors), and the release of the inflammatory cascade heralds the development of meningococcal septicemia (meningococcemia). Endothelial injury is central to many clinical features of meningococcemia, including increased vascular permeability, pathologic changes in vascular tone, loss of thromboresistance, intravascular coagulation, and myocardial dysfunction. Endothelial injury leads to increased vascular permeability (attributed to loss of glycosaminoglycans and endothelial proteins), with subsequent gross proteinuria. Leakage of fluid and electrolytes into the tissues from capillaries ("capillary leak syndrome") leads to hypovolemia, tissue edema, and pulmonary edema. Initial compensation results in vasoconstriction and tachycardia, although cardiac output eventually falls. While resuscitation fluids may restore circulating volume, tissue edema will continue to increase, and, in the lung, the consequence may be respiratory failure.

Intravascular thrombosis (caused by activation of procoagulant pathways in association with upregulation of tissue factor on the endothelium) occurs in some patients with meningococcal disease and results in purpura fulminans and infarction of areas of skin or even of whole limbs. At the same time, multiple anticoagulant pathways are downregulated through loss of endothelial thrombomodulin and protein C receptors and decreases in levels of antithrombin III, protein C, protein S, and tissue factor pathway inhibitor. Thrombolysis is also profoundly impaired in meningococcal sepsis through the release of high levels of PAI-1.

Shock in meningococcal septicemia appears to be attributable to a combination of factors, including hypovolemia, which results from the capillary leak syndrome secondary to endothelial injury, and myocardial depression, which is driven by hypovolemia, hypoxia, metabolic derangements (e.g., hypocalcemia), and cytokines (e.g., IL-6). Decreased perfusion of tissues as a result of intravascular thrombosis, vasoconstriction, tissue edema, and reduced cardiac output in meningococcal septicemia can cause widespread organ dysfunction, including renal impairment and—later in the disease—a decreased level of consciousness due to central nervous system involvement.

Bacteria that reach the meninges cause a local inflammatory response—with release of a spectrum of cytokines similar to that seen in septicemia—that presents clinically as meningitis and is thought to determine the severity of neuronal injury. Local endothelial injury may result in cerebral edema and rapid onset of raised intracranial pressure in some cases.

CLINICAL MANIFESTATIONS

As discussed above, the most common form of infection with *N. meningitidis* is asymptomatic carriage of the organism in the nasopharynx. Despite the location of infection in the upper airway, meningococcal pharyngitis is rarely reported; however, upper respiratory tract symptoms are common prior to presentation with invasive disease. It is not clear whether these symptoms relate to preceding viral infection (which may promote meningococcal acquisition) or to meningococcal acquisition itself. After acquiring the organism, susceptible individuals develop disease manifestations in 1–10 days (usually <4 days, although colonization for 11 weeks has been documented).

Along the spectrum of presentations of meningococcal disease, the most common clinical syndromes are meningitis and meningococcal

septicemia. In fulminant cases, death may occur within hours of the first symptoms. Occult bacteremia is also recognized and, if untreated, progresses in two-thirds of cases to focal infection, including meningitis or septicemia. Meningococcal disease may also present as pneumonia, pyogenic arthritis or osteomyelitis, purulent pericarditis, endophthalmitis, conjunctivitis, primary peritonitis, or (rarely) urethritis. Perhaps because it is difficult to diagnose, pneumococcal pneumonia is not commonly reported but is associated with capsular groups Y, W, and Z and appears most often to affect individuals >10 years of age.

Rash A nonblanching rash (petechial or purpuric) develops in >80% of cases of meningococcal disease; however, the rash is often absent early in the illness. Usually initially blanching in nature (macules, maculopapules, or urticaria) and indistinguishable from more common viral rashes, the rash of meningococcal infection becomes petechial or frankly purpuric over the hours after onset. In the most severe cases, large purpuric lesions develop (purpura fulminans; **Fig. A1-41**). Some patients (including those with overwhelming sepsis) may have no rash. While petechial rash and fever are important signs of meningococcal disease, fewer than 10% of children (and, in some clinical settings, fewer than 1% of patients) with this presentation are found to have meningococcal disease. Most patients presenting with a petechial or purpuric rash have a viral infection **(Table 150-2)**. The skin lesions exhibit widespread endothelial necrosis and occlusion of small vessels in the dermis and subcutaneous tissues, with a neutrophilic infiltrate.

Meningitis Meningococcal meningitis commonly presents as nonspecific manifestations, including fever, vomiting, and (especially in infants and young children) irritability, and is indistinguishable from other forms of bacterial meningitis unless there is an associated petechial or purpuric rash, which occurs in two-thirds of cases. Headache is rarely reported in early childhood but is more common in later childhood and adulthood. When headache is present, the following features, in association with fever or a history of fever, are suggestive of bacterial meningitis: neck stiffness, photophobia, decreased level of consciousness, seizures or status epilepticus, and focal neurologic signs. Classic signs of meningitis, such as neck stiffness and photophobia, are often absent in infants and young children with bacterial meningitis, who more usually present with fever and irritability and may have a bulging fontanelle.

While 30–50% of patients present with a meningitis syndrome alone, up to 40% of meningitis patients also present with some features of septicemia. Most deaths from meningococcal meningitis alone (i.e., without septicemia) are associated with raised intracranial pressure presenting as a reduced level of consciousness, relative bradycardia and hypertension, focal neurologic signs, abnormal posturing, and signs of brainstem involvement—e.g., unequal, dilated, or poorly reactive pupils; abnormal eye movement; and impaired corneal responses **(Chap. 300)**.

Septicemia Meningococcal septicemia alone accounts for up to 20% of cases of meningococcal disease. The condition may progress from early nonspecific symptoms to death within hours. Mortality rates among children with this syndrome have been high (25–40%), but early aggressive management (as discussed below) may reduce the figure to <10%. Early symptoms are nonspecific and suggest an influenza-like illness with fever, headache, and myalgia accompanied by vomiting and abdominal pain. As discussed above, the rash, if present, may appear to be viral early in the course until petechiae or purpuric lesions develop. Purpura fulminans occurs in severe cases **(Fig. A1-41)**, with multiple large purpuric lesions and signs of peripheral ischemia. Surveys of patients have indicated that limb pain, pallor (including a mottled appearance and cyanosis), and cold hands and feet may be prominent. Shock is manifested by tachycardia, poor peripheral perfusion, tachypnea, and oliguria. Decreased cerebral perfusion leads to confusion, agitation, or decreased level of consciousness. With progressive shock, multiorgan failure ensues; hypotension is a late sign in children, who more commonly present with compensated shock (tachycardia, poor peripheral perfusion, and normal blood pressure). Poor outcome is associated with an absence of meningism, hypotension, young age, coma, relatively low temperature (<38°C), leukopenia, and thrombocytopenia. Spontaneous hemorrhage (pulmonary, gastric, or cerebral) may result from consumption of coagulation factors and thrombocytopenia.

TABLE 150-2 Common Causes of Petechial or Purpuric Rashes

Enteroviruses
Influenza and other respiratory viruses
Measles virus
Epstein-Barr virus
Cytomegalovirus
Parvovirus
Deficiency of protein C or S (including postvaricella protein S deficiency)
Platelet disorders (e.g., idiopathic thrombocytopenic purpura, drug effects, bone marrow infiltration)
Henoch-Schönlein purpura, connective tissue disorders, trauma (including nonaccidental injuries in children)
Pneumococcal, streptococcal, staphylococcal, or gram-negative bacterial sepsis

Chronic Meningococcemia Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash **(Fig. A1-42)** associated with fever, joint pain, features of arthritis, and splenomegaly that may progress to acute meningococcal septicemia if untreated. During the relapsing course, bacteremia characteristically clears without treatment and then recurs. The differential diagnosis includes bacterial endocarditis, acute rheumatic fever, Henoch-Schönlein purpura, infectious mononucleosis, disseminated gonococcal infection, and immune-mediated vasculitis. This condition has been associated with complement deficiencies in some cases and with inadequate sulfonamide therapy in others.

A study from the Netherlands found that half of isolates from patients with chronic meningococcemia had an underacylated lipid A (part of the surface LPS molecule) due to an *lpxL1* gene mutation, which markedly reduces the inflammatory response to endotoxin.

Postmeningococcal Reactive Disease In a small proportion of patients, an immune complex disease develops ~4–10 days after the onset of meningococcal disease, with manifestations that include a maculopapular or vasculitic rash (2% of cases), arthritis (up to 8% of cases), iritis (1%), pericarditis, and/or polyserositis associated with fever. The immune complexes involve meningococcal polysaccharide antigen and result in immunoglobulin and complement deposition with an inflammatory infiltrate. These features resolve spontaneously without sequelae. It is important to recognize this condition since a new onset of fever and rash can lead to concerns about relapse of meningococcal disease and unnecessarily prolonged antibiotic treatment.

DIAGNOSIS

Like other invasive bacterial infections, meningococcal disease may produce elevations of the white blood cell (WBC) count and of values for inflammatory markers (e.g., C-reactive protein and procalcitonin levels or the erythrocyte sedimentation rate). Values may be normal or low in rapidly progressive disease, and a lack of rise in these laboratory test values does not exclude the diagnosis. However, in the presence of fever and a petechial rash, these elevations are suggestive of meningococcal disease. In patients with severe meningococcal septicemia, common laboratory findings include hypoglycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy.

Although meningococcal disease is often diagnosed on clinical grounds, in suspected meningococcal meningitis or meningococcemia, blood should routinely be sent for culture to confirm the diagnosis and to facilitate public health investigations; blood cultures are positive in up to 75% of cases. Culture media containing sodium polyanethol sulfonate, which may inhibit meningococcal growth, should be avoided. Meningococcal viability is reduced if there is a delay in transport of the specimen to the microbiology laboratory for culture or in plating of

cerebrospinal fluid (CSF) samples. In countries where treatment with antibiotics before hospitalization is recommended for meningococcal disease, the majority of clinically suspected cases are culture negative. Real-time polymerase chain reaction (PCR) analysis of whole-blood samples increases the diagnostic yield by >40%, and results obtained with this method may remain positive for several days after administration of antibiotics. Indeed, in the United Kingdom, more than half of clinically suspected cases are currently identified by PCR.

Unless contraindications exist (raised intracranial pressure, uncorrected shock, disordered coagulation, thrombocytopenia, respiratory insufficiency, local infection, ongoing convulsions), lumbar puncture should be undertaken to identify and confirm the etiology of suspected meningococcal meningitis, whose presentation cannot be distinguished from that of meningitis of other bacterial causes. Some authorities have recommended a CT brain scan prior to lumbar puncture because of the risk of cerebral herniation in patients with raised intracranial pressure. However, a normal CT scan is not uncommon in the presence of raised intracranial pressure in meningococcal meningitis, and the decision to perform a lumbar puncture should be made on clinical grounds. CSF features of meningococcal meningitis (elevated protein level and WBC count, decreased glucose level) are indistinguishable from those of other types of bacterial meningitis unless a gram-negative diplococcus is identified. (Gram's staining is up to 80% sensitive for meningococcal meningitis.) CSF should be submitted for culture (sensitivity, 90%) and (where available) PCR analysis. CSF antigen testing with latex agglutination is insensitive and should be replaced by molecular diagnosis when possible.

Lumbar puncture should generally be avoided in meningococcal septicemia, as positioning for the procedure may critically compromise the patient's circulation in the context of hypovolemic shock. Delayed lumbar puncture may still be useful when the diagnosis is uncertain, particularly if molecular diagnostic technology is available.

In other types of focal infection, culture and PCR analysis of normally sterile body fluids (e.g., synovial fluid) may aid in the diagnosis. Although some authorities have recommended cultures of scrapings or aspirates from skin lesions, this procedure adds little to the diagnostic yield when compared with a combination of blood culture and PCR analysis. Urinary antigen testing also is insensitive, and serologic testing for meningococcal infection has not been adequately studied. Because *N. meningitidis* is a component of the normal human nasopharyngeal flora, identification of the organism on throat swabs has limited diagnostic value, but strains identified in the nasopharynx in the context of a probable case are likely to be those responsible for disease.

TREATMENT

Meningococcal Infections

Death from meningococcal disease is associated most commonly with hypovolemic shock (meningococcemia) and occasionally with raised intracranial pressure (meningococcal meningitis). Therefore, management should focus on the treatment of these urgent clinical issues in addition to the administration of specific antibiotic therapy. Delayed recognition of meningococcal disease or its associated physiologic derangements, together with inadequate emergency management, is associated with poor outcome. Since the disease is rare, protocols for emergency management have been developed (see *www.meningitis.org*).

Airway patency may be compromised if the level of consciousness is depressed as a result of shock (impaired cerebral perfusion) or raised intracranial pressure; this situation may require intervention. In meningococcemia, pulmonary edema and pulmonary oligemia (presenting as hypoxia) require oxygen therapy or elective endotracheal intubation. In cases with shock, aggressive fluid resuscitation (with replacement of the circulating volume several times in severe cases) and inotropic support may be necessary to maintain cardiac output. If shock persists after volume resuscitation at 40 mL/kg, the risk of pulmonary edema is high, and elective intubation is recommended to improve oxygenation and decrease the work of breathing. Metabolic derangements, including hypoglycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy, should be anticipated and corrected. In the presence of raised intracranial pressure, management includes correction of coexistent shock and neurointensive care to maintain cerebral perfusion.

Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per day [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to cover the various other (potentially penicillin-resistant) bacteria that may produce an indistinguishable clinical syndrome. Although unusual in most isolates, reduced meningococcal sensitivity to penicillin (a minimal inhibitory concentration of 0.12–1.0 μg/mL) has been reported widely.

Both meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days, although courses of 3–5 days may be equally effective. Furthermore, a single dose of ceftriaxone or an oily suspension of chloramphenicol has been used successfully in resource-poor settings. No data are available to guide the duration of treatment for meningococcal infection at other foci (e.g., pneumonia, arthritis); antimicrobial therapy is usually continued until clinical and laboratory evidence of infection has resolved. Cultures usually become sterile within 24 h of initiation of appropriate antibiotic chemotherapy.

The use of glucocorticoids for adjunctive treatment of meningococcal meningitis remains controversial since no relevant studies have had sufficient power to determine true efficacy. One large study in adults did indicate a trend toward benefit, and in clinical practice a decision to use glucocorticoids usually must precede a definite microbiologic diagnosis. Therapeutic doses of glucocorticoids are not recommended in meningococcal septicemia, but many intensivists recommend replacement glucocorticoid doses for patients who have refractory shock in association with impaired adrenal gland responsiveness.

Various other adjunctive therapies for meningococcal disease have been considered, but few have been subjected to clinical trials and none can currently be recommended. An antibody to LPS (HA1A) failed to confer a demonstrable benefit. Recombinant bactericidal/permeability-increasing protein (which is not currently available) was tested in a study that had inadequate power to show an effect on mortality rates; however, there were trends toward lower mortality rates among patients who received a complete infusion, and this group also had fewer amputations, fewer blood-product transfusions, and a significantly improved functional outcome. Given that protein C concentrations are reduced in meningococcal disease, the use of activated protein C has been considered. A survival benefit was demonstrated in adult sepsis trials; however, trials in pediatric sepsis (of particular relevance for meningococcal disease) found no benefit and indicated a potential risk of bleeding complications with use of activated protein C.

The postmeningococcal immune-complex inflammatory syndrome has been treated with nonsteroidal anti-inflammatory agents until spontaneous resolution occurs.

COMPLICATIONS

About 10% of patients with meningococcal disease die despite the availability of antimicrobial therapy and other intensive medical interventions. The most common complication of meningococcal disease (10% of cases) is scarring after necrosis of purpuric skin lesions, for which skin grafting may be necessary. The lower limbs are most often affected; next in frequency are the upper limbs, the trunk, and the face. On average, 13% of the skin surface area is involved. Amputations are necessary in 1–2% of survivors of meningococcal disease because of a loss of tissue viability after peripheral ischemia or compartment syndromes. Unless there is local infection, amputation should usually be delayed to allow the demarcation between viable and nonviable tissue to become apparent. Approximately 5% of patients with meningococcal

disease suffer hearing loss, and 7% have neurologic complications. In one study pain was reported by 21% of survivors, and in a recent analysis of capsular group B meningococcal disease (the MOSAIC study) as many as one-quarter of survivors had psychological disorders. In some investigations, the rate of complications is higher for capsular group C disease (mostly associated with the ST11 clone) than for capsular group B disease. In patients with severe hypovolemic shock, renal perfusion may be impaired and prerenal failure is common, but permanent renal replacement therapy is rarely needed.

Several studies suggest adverse psychosocial outcomes after meningococcal disease, with reduced quality of life, lowered self-esteem, and poorer neurologic development, including increased rates of attention deficit/hyperactivity disorder and special educational needs. Other studies have not found evidence of such outcomes.

PROGNOSIS

Several prognostic scoring systems have been developed to identify patients with meningococcal disease who are least likely to survive. Factors associated with a poorer prognosis are shock; young age (infancy), old age, and adolescence; coma; purpura fulminans; disseminated intravascular coagulation; thrombocytopenia; leukopenia; absence of meningitis; metabolic acidosis; low plasma concentrations of antithrombin and proteins S and C; high blood levels of PAI-1; and a low erythrocyte sedimentation rate or C-reactive protein level. The Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) performs well and may be clinically useful for severity assessment in meningococcal disease. However, scoring systems do not direct the clinician to specific interventions, and the priority in management should be recognition of compromised airways, breathing, or circulation and direct, urgent intervention. Most patients improve rapidly with appropriate antibiotics and supportive therapy. Fulminant meningococcemia is more likely to result in death or ischemic skin loss than is meningitis; optimal emergency management may reduce mortality rates among the most severely affected patients.

PREVENTION

Since mortality rates in meningococcal disease remain high despite improvements in intensive care management, immunization is the only rational approach to prevention at a population level. Secondary cases are common among household and "kissing" contacts of cases, and secondary prophylaxis with antibiotics is widely recommended for these contacts (see below).

Polysaccharide Vaccines Purified meningococcal capsular polysaccharide has been used for immunization since the 1960s. Meningococcal polysaccharide vaccines are currently formulated as either bivalent (capsular groups A and C) or quadrivalent (capsular groups A, C, Y, and W), with 50 μg of each polysaccharide per dose. Local reactions (erythema, induration, and tenderness) may occur in up to 40% of vaccinees, but serious adverse events (including febrile convulsions in young children) are very rarely reported. In adults, the vaccines are immunogenic, but immunity appears to be relatively short-lived (with antibody levels above baseline for only 2–10 years), and booster doses do not induce a further rise in antibody concentration. Indeed, a state of immunologic hyporesponsiveness has been widely reported to follow booster doses of plain polysaccharide vaccines. The repeating units of these vaccines cross-link B cell receptors to drive specific memory B cells to become plasma cells and produce antibody. Because meningococcal polysaccharides are T cell–independent antigens, no memory B cells are produced after immunization, and the memory B cell pool is depleted such that fewer polysaccharide-specific cells are available to respond to a subsequent dose of vaccine **(Fig. 150-6)**. The clinical relevance of hyporesponsiveness is unknown. Plain polysaccharide vaccines generally are not immunogenic in early childhood, possibly because marginal-zone B cells are involved in polysaccharide responses and maturation of the splenic marginal zone is not complete until 18 months to 2 years of age. The efficacy of the meningococcal capsular group C component is >90% in young adults; no efficacy data are available for the capsular group Y and W polysaccharides in this age group.

Group A meningococcal polysaccharides are exceptional in that they are effective in preventing disease at all ages. Two doses administered 2–3 months apart to children 3–18 months of age or a single dose administered to older children or adults has a protective efficacy rate of >95%. The vaccine was previously used widely in the control of outbreaks of meningococcal disease in the African meningitis belt. The duration of protection appears to be only 3–5 years. The plain polysaccharide vaccines have largely been superseded by protein–polysaccharide conjugate vaccines.

There is no meningococcal capsular group B plain polysaccharide vaccine because α-2,8-*N*-acetylneuraminic acid is expressed on the surface of neural cells in the fetus such that the B polysaccharide is perceived as "self" and therefore is not immunogenic in humans.

Conjugate Vaccines The poor immunogenicity of plain polysaccharide vaccines in infancy has been overcome by chemical conjugation of the polysaccharides to a carrier protein (CRM_{197}, tetanus toxoid, or diphtheria toxoid). Conjugates that contain monovalent capsular group C polysaccharide and quadrivalent vaccines with A, C, Y, and W polysaccharides have been developed, as have vaccines including various other antigen combinations (e.g., tetanus conjugates with capsular group C and/or Y polysaccharide and *Haemophilus influenzae* type b polysaccharide). After immunization, peptides from the carrier protein are conventionally thought to be presented by polysaccharide-specific B cells to peptide-specific T cells in association with major histocompatibility complex (MHC) class II molecules. (Some recent data suggest that carrier protein peptide may actually be presented in association with an oligosaccharide and MHCII.) The result is a T cell–dependent immune response that allows production of antibody and generation of an expanded B cell memory pool. Unlike responses to booster doses of plain polysaccharides, responses to booster doses of conjugate vaccines have the characteristics of memory responses. Indeed, conjugate vaccines overcome the hyporesponsiveness induced by plain polysaccharides by replenishing the memory pool. The reactogenicity of conjugate vaccines is similar to that of plain polysaccharide vaccines.

The first widespread use of capsular group C meningococcal conjugate vaccine (MenC) came in 1999 in the United Kingdom after a rise in capsular group C disease. A mass vaccination campaign involving all individuals <19 years of age was undertaken, and the number of laboratory-confirmed capsular group C cases fell from 955 in 1998–1999 to just 29 in 2011–2012. The effectiveness of the immunization program was attributed both to direct protection of immunized persons and to reduced transmission of the organism in the population as a result of decreased rates of colonization among the immunized (i.e., herd immunity). Data on immunogenicity and effectiveness have shown that the duration of protection is short when the vaccine is administered in early childhood; thus booster doses are needed to maintain population immunity. In contrast, immunity after a dose of vaccine given in adolescence appears to be more prolonged.

In 2005, the first quadrivalent conjugate meningococcal vaccine containing A, C, Y, and W polysaccharides conjugated to diphtheria toxoid was initially recommended for all children >11 years of age in the United States and for persons 2–55 years of age in Canada. Such vaccines are now recommended by the Advisory Committee on Immunization Practices (ACIP) for routine administration to individuals 11–18 years of age, with a booster dose 3 years later; only a single dose is given to persons >16 years of age. These vaccines are also recommended for high-risk persons from 2 months to 55 years of age (see *www.cdc.gov/mmwr/preview/mmwrhtml/mm6324a2.htm*).

Uptake was slow initially, but current U.S. data suggest an efficacy rate of 82% in the first year after vaccination, with waning to 59% at 3–6 years after vaccination. Limited early data from the U.S. Vaccine Adverse Events Reporting System indicated that there might be a short-term increase in the risk of Guillain-Barré syndrome after immunization with the diphtheria conjugate vaccine; however, further investigation has not confirmed this finding. Quadrivalent conjugate vaccines with tetanus or CRM_{197} as carrier protein are now available in many countries and are used for high-risk groups and in routine programs for toddlers and adolescents.

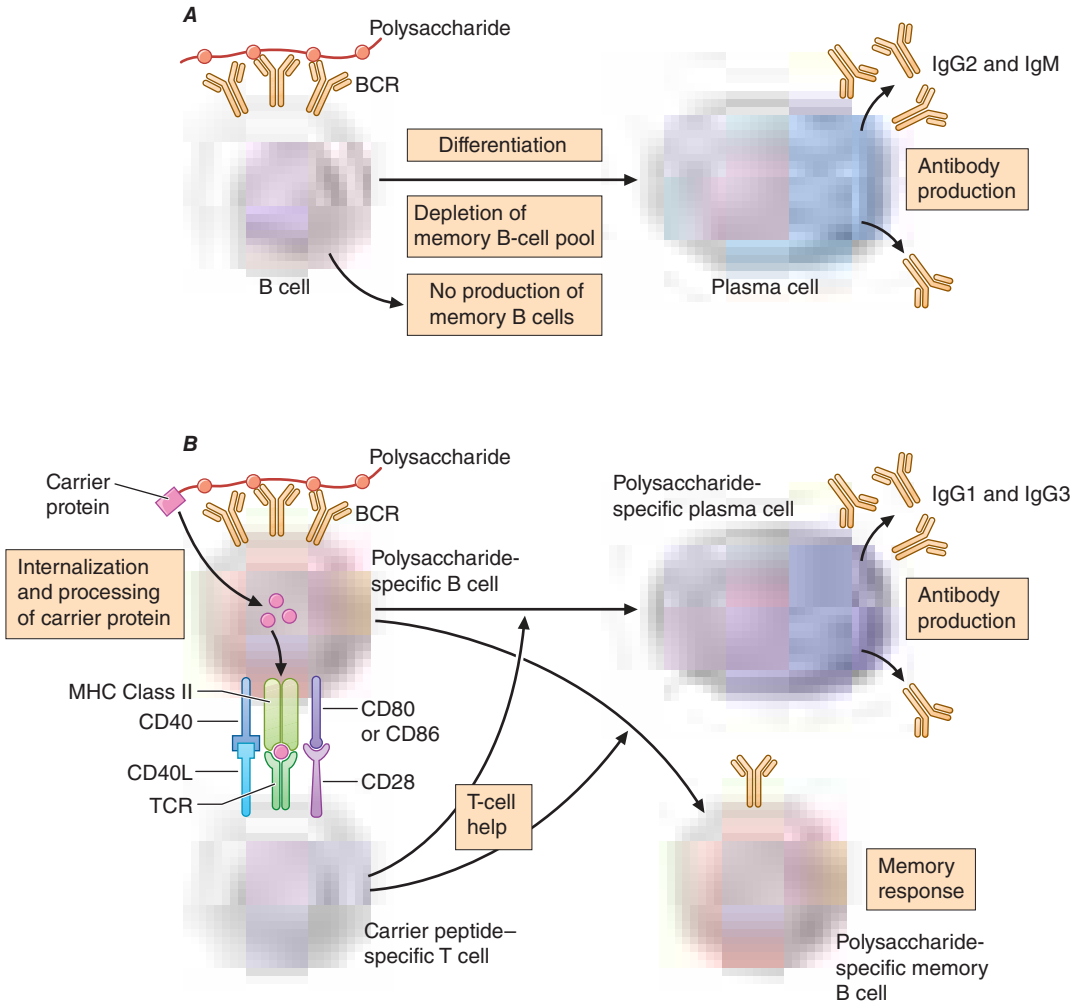

FIGURE 150-6 ***A.*** Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B cells by cross-linking the B cell receptor (BCR) and driving the production of immunoglobulins. There is no production of memory B cells, and the B cell pool may be depleted by this process such that subsequent immune responses are decreased. ***B.*** The carrier protein from protein–polysaccharide conjugate vaccines is processed by the polysaccharide-specific B cell, and peptides are presented to carrier peptide–specific T cells, with the consequent production of both plasma cells and memory B cells. MHC, major histocompatibility complex; TCR, T cell receptor. *(Reprinted from AJ Pollard et al: Nat Rev Immunol 9:213, 2009.)*

A monovalent capsular group A vaccine, manufactured in India, was licensed in 2010 and rolled out to countries in the sub-Saharan African meningitis belt in a mass immunization campaign. There is strong evidence that this vaccine has been highly effective in controlling epidemic meningococcal disease in the region, with some evidence of a >90% reduction in disease in vaccinated populations. However, disease caused by capsular groups C, X, and W persists, and new-generation vaccines with wider coverage are being developed.

Vaccines Based on Subcapsular Antigens The lack of immunogenicity of the group B capsule has led to the development of vaccines based on subcapsular antigens. Various surface components have been studied in early-phase clinical trials. Outer-membrane vesicles (OMVs) containing outer-membrane proteins, phospholipid, and LPS can be extracted from cultures of *N. meningitidis* by detergent treatment (Fig. 150-7). OMVs prepared in this way were used in efficacy trials with a Norwegian outbreak strain and reduced the incidence of group B disease among 14- to 16-year-old schoolchildren by 53%. Similarly, OMV vaccines constructed from local outbreak strains in Cuba and New Zealand have had reported efficacy rates of >70%. These OMV vaccines appear to produce strain-specific immune responses, with only limited cross-protection, and are therefore best suited to clonal outbreaks (e.g., those in Cuba and New Zealand as well as others in Norway and the province of Normandy in France).

Several purified surface proteins have been evaluated in phase 1 clinical trials but have not yet been developed further because of antigenic variability or poor immunogenicity (e.g., transferrin-binding proteins, neisserial surface protein A). Other vaccine candidates have been identified since sequencing of the meningococcal genome. The combination vaccine 4CMenB, which includes the New Zealand OMV vaccine and three recombinant proteins (neisserial adhesin A, factor H–binding protein, and neisserial heparin-binding antigen), is immunogenic from infancy and has been licensed for use in the United States, Canada, Europe, and Australia. This vaccine has been used with apparent success in the control of several university outbreaks in the United States and in a community outbreak in an area of Quebec, Canada. 4CMenB vaccine has an acceptable safety profile, with fever prominent among infants and injection-site pain frequently reported among older children and adults. The vaccine is also being used in many countries for immunization of high-risk groups. In September 2015, 4CMenB was recommended for routine use in the United Kingdom for all infants born from May 2015 onward; a preliminary analysis has found an effectiveness rate of 82.9% (95% confidence interval, 24.1–95.2) against all capsular group B strains among infants receiving two or more doses, with a 50% reduction in cases below the number anticipated from comparison with trends in other age groups. Because the disease is so rare, the cost-effectiveness of capsular group B vaccine in infant immunization programs, as assessed with conventional thresholds, is borderline. Since infants are not commonly colonized with capsular group B meningococci, any impact on the total population burden of carried organisms will be small. It is therefore unlikely that an infant immunization program will provide additional value through induction of

FIGURE 150-7 Illustration of meningococcal outer-membrane vesicle containing outer-membrane structures.

herd immunity. Rates of capsular group B carriage are higher among teenagers and young adults. Studies estimating the potential effect of 4CMenB on carriage of capsular group B meningococci among adolescents indicate that there is likely to be some impact. However, because these studies lack power, it remains uncertain whether the vaccine would have the substantial and sustained herd effects in this age group that could support widespread routine administration.

An immunogenic vaccine based on two variants of the lipoprotein factor H–binding protein (fHbp2) has been developed for use in adolescents and is licensed in the United States and Europe. The vaccine is immunogenic against representative indicator strains, inducing fourfold rises in bactericidal antibody titer in 50–92% of individuals. fHbp2 has an acceptable safety profile, with pain at the injection site, fatigue, and headache commonly reported. This vaccine can be used with a range of vaccines routinely administered in adolescence, including Tdap (tetanus–diphtheria–acellular pertussis), human papillomavirus, and MenACWY vaccines. fHbp2 has been used to control outbreaks of meningococcal disease in educational institutions in the United States, but no formal studies of its effectiveness have yet been undertaken.

Both of the new capsular group B meningococcal vaccines are licensed for use in the United States for persons 10–25 years of age. In addition, ACIP recommends their administration to individuals at high risk of capsular group B disease, with 4CMenB administered as two doses (1–2 months apart) and fHbp2 as three doses on a 0/1/6-month schedule.

MANAGEMENT OF CONTACTS

Close (household and kissing) contacts of individuals with meningococcal disease are at increased risk for developing secondary disease (up to 1000 times the rate for the general population); a secondary case follows as many as 3% of sporadic cases. About one-fifth of secondary cases are actually co-primary cases—i.e., cases that occur soon after the primary case and in which transmission is presumed to have originated from the same third party. The rate of secondary cases is highest during the week after presentation of the index case. The risk falls rapidly but remains above baseline for up to 1 year after the index case; 30% of secondary cases occur in the first week, 20% in the second week, and most of the remainder over the next 6 weeks. In outbreaks of meningococcal disease, mass prophylaxis has been used; however, limited data support population intervention, and significant concerns have arisen about adverse events and the development of resistance. For these reasons, prophylaxis is usually restricted to (1) persons at greatest risk who are intimate and/or household contacts of the index case and (2) health care workers who have been directly exposed to respiratory secretions. In most cases, members of wider communities (e.g., at schools or colleges) are not offered prophylaxis.

The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease in the index case. Prophylaxis should be given to all contacts at the same time to avoid recolonization by meningococci transmitted from untreated contacts and should also be used as soon as possible to treat early disease in secondary cases. If the index patient is treated with an antibiotic that does not reliably clear colonization (e.g., penicillin), he or she should be given a prophylactic agent at the end of treatment to prevent relapse or onward transmission. Although rifampin has been most widely used and studied, it is not the optimal agent because it fails to eradicate carriage in 15–20% of cases, rates of adverse events have been high, compliance is affected by the need for four doses, and emerging resistance has been reported. Ceftriaxone as a single IM or IV injection is highly (97%) effective in carriage eradication and can be used at all ages and in pregnancy. Reduced susceptibility of isolates to ceftriaxone has occasionally been reported. Ciprofloxacin or ofloxacin is preferred in some countries; these agents are highly effective and can be administered by mouth but are not recommended in pregnancy. Resistance to fluoroquinolones has been reported in some meningococci in North America, Europe, and Asia.

In documented capsular group A, B, C, Y, or W disease, contacts may be offered immunization (with either the MenACWY conjugate vaccine or the MenB vaccine, as appropriate) in addition to chemoprophylaxis to provide protection beyond the duration of antibiotic therapy. Mass vaccination has been used successfully to control disease during outbreaks in closed communities (educational and military establishments) as well as during epidemics in open communities.

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151 Gonococcal Infections

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DEFINITION

Gonorrhea is a sexually transmitted infection (STI) of epithelium and commonly manifests as cervicitis, urethritis, proctitis, and conjunctivitis. If untreated, infections at these sites can lead to local complications such as endometritis, salpingitis, tuboovarian abscess, bartholinitis, peritonitis, and perihepatitis in female patients; periurethritis and

epididymitis in male patients; and ophthalmia neonatorum in newborns. Disseminated gonococcemia is an uncommon event whose manifestations include skin lesions, tenosynovitis, arthritis, and (in rare cases) endocarditis or meningitis.

MICROBIOLOGY

Neisseria gonorrhoeae is a gram-negative, nonmotile, non-spore-forming organism that grows singly and in pairs (i.e., as monococci and diplococci, respectively). Exclusively a human pathogen, the gonococcus contains, on average, three genome copies per coccal unit; this polyploidy permits a high level of antigenic variation and the survival of the organism in its host. Gonococci, like all other *Neisseria* species, are oxidase positive. They are distinguished from other neisseriae by their ability to grow on selective media and to use glucose but not maltose, sucrose, or lactose.

EPIDEMIOLOGY

The incidence of gonorrhea had been declining steadily in the United States, but in 2016 there were ~450,000 newly reported cases—up 46% since 2011. With 80 million cases estimated by the World Health Organization to have occurred globally in 2014, gonorrhea remains a major public health problem worldwide, is a significant cause of morbidity in developing countries, and may play a role in enhancing transmission of HIV.

Gonorrhea predominantly affects young, nonwhite, unmarried, less educated members of urban populations. The number of reported cases probably represents half of the true number of cases—a discrepancy resulting from under-reporting, self-treatment, and nonspecific treatment without a laboratory-proven diagnosis. The number of reported new cases of gonorrhea in the United States rose from ~250,000 in the early 1960s to a high of 1.01 million in 1978. The recorded incidence of gonorrhea in modern times peaked in 1975, with 468 reported new cases per 100,000 population in the United States. This peak was attributable to the interaction of several variables, including improved accuracy of diagnosis, changes in patterns of contraceptive use, and changes in sexual behavior. A decline in the overall incidence of gonorrhea in the United States over the past quarter-century may reflect increased condom use resulting from public health efforts to curtail HIV transmission. Nevertheless, in 2016, 146 new cases per 100,000 population were reported in this country, representing a 1-year increase of 19%; this figure is the highest among industrialized countries. Simultaneously, antibiotic resistance is increasing in the United States and other countries, prompting the U.S. Centers for Disease Control and Prevention (CDC) to name antibiotic-resistant *N. gonorrhoeae* as one of the three most urgent threats of its kind. At present, the attack rate in the United States is highest among 15- to 24-year-old women and 20- to 29-year-old men; more than 70% of all reported cases occur in these two groups. From the standpoint of ethnicity, rates are highest among African Americans and lowest among persons of Asian descent.

The incidence of gonorrhea is higher in developing countries than in industrialized nations. The exact incidence of any STI is difficult to ascertain in developing countries because of limited surveillance and variable diagnostic criteria. Extremely high rates of gonorrhea have been reported among aboriginal populations in Namibia and Australia. Studies in Africa have clearly demonstrated that nonulcerative STIs such as gonorrhea (in addition to ulcerative STIs) are an independent risk factor for the transmission of HIV (Chap. 197).

Gonorrhea is transmitted from males to females more efficiently than in the opposite direction. The rate of transmission to a woman during a single unprotected sexual encounter with an infected man is ~50–70%. Oropharyngeal gonorrhea occurs in ~20% of women who practice fellatio with infected partners. Transmission in either direction by cunnilingus is rare.

In any population, there exists a small minority of individuals who have high rates of new-partner acquisition. These "core-group members" or "high-frequency transmitters" are vital in sustaining STI transmission at the population level. Another instrumental factor in sustaining gonorrhea in the population is the large number of infected individuals who are asymptomatic or have minor symptoms that are ignored. These persons, unlike symptomatic individuals, may not cease sexual activity and therefore may continue to transmit the infection. This situation underscores the importance of contact tracing and empirical treatment of the sex partners of index cases.

PATHOGENESIS, IMMUNOLOGY, AND ANTIMICROBIAL RESISTANCE

Outer-Membrane Proteins • **PILI** Fresh clinical isolates of *N. gonorrhoeae* initially form piliated (fimbriated) colonies distinguishable on translucent agar. Pilus expression is rapidly switched off with unselected subculture because of rearrangements in pilus genes. This change is a basis for antigenic variation of gonococci. Piliated strains adhere better to cells derived from human mucosal surfaces and are more virulent in organ culture models and human inoculation experiments than nonpiliated variants. In a fallopian tube explant model, pili mediate gonococcal attachment to nonciliated columnar epithelial cells. This event initiates gonococcal phagocytosis and transport through these cells to intercellular spaces near the basement membrane or directly into the subepithelial tissue. Pili are also essential for genetic competence and transformation of *N. gonorrhoeae*, which permit horizontal transfer of genetic material between different gonococcal lineages in vivo.

OPACITY-ASSOCIATED PROTEIN Another gonococcal surface protein that is important in adherence to epithelial cells is opacity-associated protein (Opa, formerly called protein II). Opa contributes to intergonococcal adhesion, which is responsible for the opaque nature of gonococcal colonies on translucent agar and the organism's adherence to a variety of eukaryotic cells, including polymorphonuclear leukocytes (PMNs). Certain Opa variants promote invasion of epithelial cells, and this effect has been linked with the ability of Opa to bind vitronectin, glycosaminoglycans, and several members of the carcinoembryonic antigen–related cell adhesion molecule (CEACAM) receptor family. CEACAM5-binding gonococci prevent exfoliation of epithelium and may interfere with bacterial clearance. *N. gonorrhoeae* Opa proteins that bind CEACAM1, which is expressed by primary CD4+ T lymphocytes, suppress the activation and proliferation of these lymphocytes. Select Opa proteins can engage CEACAM3, which is expressed on neutrophils, with consequent nonopsonic phagocytosis (i.e., phagocytosis independent of antibody and complement) and killing of bacteria.

PORIN Porin (previously designated protein I) is the most abundant gonococcal surface protein. Porin molecules exist as trimers that provide anion-transporting aqueous channels through the otherwise hydrophobic outer membrane. Porin exhibits stable interstrain antigenic variation and forms the basis for gonococcal serotyping. Two main serotypes have been identified; PorB.1A strains are often associated with disseminated gonococcal infection (DGI), whereas PorB.1B strains usually cause local genital infections only. DGI strains are generally resistant to the killing action of normal human serum and do not incite a significant local inflammatory response; therefore, they may not cause symptoms at genital sites. These characteristics may be related to the ability of PorB.1A strains to bind to complement-inhibitory molecules, resulting in a diminished inflammatory response. Porin can translocate to the cytoplasmic membrane of host cells—a process that could initiate gonococcal endocytosis and invasion.

OTHER OUTER-MEMBRANE PROTEINS Other notable outer-membrane proteins include H.8, a lipoprotein that is present in high concentration on the surface of all gonococcal strains and is an excellent target for antibody-based diagnostic testing. Transferrin-binding proteins (Tbp1 and Tbp2) and lactoferrin-binding protein are required for scavenging iron from transferrin and lactoferrin in vivo. Transferrin and iron have been shown to enhance the attachment of iron-deprived *N. gonorrhoeae* to human endometrial cells. IgA1 protease is produced by *N. gonorrhoeae* and may protect the organism from the action of mucosal IgA.

Lipooligosaccharide Gonococcal lipooligosaccharide (LOS) consists of a lipid A and a core oligosaccharide that lacks the repeating O-carbohydrate antigenic side chain seen in other gram-negative

bacteria (Chap. 116). Gonococcal LOS possesses marked endotoxic activity and contributes to the local cytotoxic effect in a fallopian tube model. LOS core sugars undergo a high degree of phase variation under different conditions of growth; this variation reflects genetic regulation and expression of glycotransferase genes that dictate the carbohydrate structure of LOS. These phenotypic changes may affect interactions of *N. gonorrhoeae* with elements of the humoral immune system (antibodies and complement) and may also influence direct binding of organisms to both professional phagocytes and nonprofessional phagocytes (epithelial cells). For example, gonococci that are sialylated at their LOS sites inhibit the classic pathway of complement by reducing binding of IgG and also bind complement factor H to inhibit the alternative pathway of complement. LOS sialylation may also decrease nonopsonic Opa-mediated association with neutrophils and inhibit the oxidative burst in PMNs. The binding of the unsialylated terminal lactosamine residue of LOS to an asialoglycoprotein receptor on male epithelial cells facilitates adherence and subsequent gonococcal invasion of these cells. Moreover, oligosaccharide structures in LOS can modulate host immune responses. For example, the terminal monosaccharide expressed by LOS determines the C-type lectin receptor on dendritic cells that is targeted by the bacteria. In turn, the specific C-type lectin receptor engaged influences whether a T_H1- or T_H2-type response is elicited; the latter response may be less favorable for clearance of gonococcal infection.

Host Factors In addition to gonococcal structures that interact with epithelial cells, host factors seem to be important in mediating entry of gonococci into nonphagocytic cells. Activation of phosphatidylcholine-specific phospholipase C and acidic sphingomyelinase by *N. gonorrhoeae*, which results in the release of diacylglycerol and ceramide, is a requirement for the entry of *N. gonorrhoeae* into epithelial cells. Ceramide accumulation within cells leads to apoptosis, which may disrupt epithelial integrity and facilitate entry of gonococci into subepithelial tissue. Release of chemotactic factors as a result of complement activation contributes to inflammation, as does the toxic effect of LOS in provoking the release of inflammatory cytokines.

The importance of humoral immunity in host defenses against neisserial infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to have recurrent bacteremic gonococcal infections and recurrent meningococcal meningitis or meningococcemia. Gonococcal porin induces T cell–proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin (IL) 4–producing CD4+ as well as CD8+ T lymphocytes is seen in individuals with mucosal gonococcal disease. A portion of these lymphocytes that show a porin-specific T_H2-type response could traffic to mucosal surfaces and play a role in immune protection against the disease. Few data clearly indicate that protective immunity is acquired from a previous gonococcal infection, although bactericidal and opsonophagocytic antibodies to porin and LOS may offer partial protection. On the other hand, women who are infected and acquire high levels of antibody to another outer-membrane protein, Rmp (reduction modifiable protein, formerly called protein III), may be especially likely to become reinfected with *N. gonorrhoeae* because Rmp antibodies block the effect of bactericidal antibodies to porin and LOS. Rmp shows little, if any, interstrain antigenic variation; therefore, Rmp antibodies potentially may block antibody-mediated killing of all gonococci. The mechanism of blocking has not been fully characterized, but Rmp antibodies may noncompetitively inhibit binding of porin and LOS antibodies because of the proximity of these structures in the gonococcal outer membrane. In male volunteers who have no history of gonorrhea, the net effect of these events may influence the outcome of experimental challenge with *N. gonorrhoeae*. Because Rmp bears extensive homology to enterobacterial OmpA and meningococcal class 4 proteins, it is possible that these blocking antibodies result from prior exposure to cross-reacting proteins from these species and also play a role in first-time infection with *N. gonorrhoeae*.

Gonococcal Resistance to Antimicrobial Agents It is no surprise that *N. gonorrhoeae*, with its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment, has become resistant to numerous antibiotics. The first effective agents against gonorrhea were the sulfonamides, which were introduced in the 1930s and became ineffective within a decade. Penicillin was then used as the drug of choice for the treatment of gonorrhea. By 1965, 42% of gonococcal isolates had developed low-level resistance to penicillin G. Resistance due to the production of penicillinase arose later.

Gonococci become fully resistant to antibiotics either by chromosomal mutations or by acquisition of R factors (plasmids). Two types of chromosomal mutations have been described. The first type, which is drug specific, is a single-step mutation leading to high-level resistance. The second type involves mutations at several chromosomal loci that combine to determine the level as well as the pattern of resistance. Strains with mutations in chromosomal genes were first observed in the late 1950s. As recently as 2007, chromosomal mutations accounted for resistance to penicillin, tetracycline, or both in ~16% of strains surveyed in the United States.

β-Lactamase (penicillinase)–producing strains of *N. gonorrhoeae* (PPNG) carrying β-lactamase plasmids had rapidly spread worldwide by the early 1980s. *N. gonorrhoeae* strains with plasmid-borne tetracycline resistance (TRNG) can mobilize some β-lactamase plasmids, and PPNG and TRNG occur together, sometimes along with strains exhibiting chromosomally mediated resistance (CMRNG). Penicillin, ampicillin, and tetracycline are no longer reliable for the treatment of gonorrhea and should not be used.

Quinolone-containing regimens also were recommended for treatment of gonococcal infections; the fluoroquinolones offered the advantage of antichlamydial activity when administered for 7 days. However, quinolone-resistant *N. gonorrhoeae* (QRNG) appeared soon after these agents were first used to treat gonorrhea. QRNG is particularly common in the Pacific Islands (including Hawaii) and Asia, where, in certain areas, all gonococcal strains are now resistant to quinolones. At present, QRNG is also common in parts of Europe and the Middle East. In the United States, QRNG has been identified in all areas but predominantly in states on the Pacific coast, where resistant strains were first seen. Alterations in DNA gyrase and topoisomerase IV have been implicated as mechanisms of fluoroquinolone resistance.

Resistance to spectinomycin, which has been used in the past as an alternative agent, has been reported. Because this agent usually is not associated with resistance to other antibiotics, spectinomycin can be reserved for use against multidrug-resistant strains of *N. gonorrhoeae*. Nevertheless, outbreaks caused by strains resistant to spectinomycin have been documented in Korea and England when the drug has been used for primary treatment of gonorrhea.

Third-generation cephalosporins have remained highly effective as single-dose therapy for gonorrhea, but the recent isolation of strains highly resistant to ceftriaxone (minimal inhibitory concentrations [MICs], 2 μg/mL) in Japan and some European countries is cause for concern. Even though the MICs of ceftriaxone against certain strains may reach 0.015–0.125 μg/mL (higher than the MICs of 0.0001–0.008 μg/mL for fully susceptible strains), these levels are greatly exceeded in the blood, the urethra, and the cervix when the routinely recommended parenteral dose of ceftriaxone is administered. The rising MICs of oral cefixime (the previously recommended alternative oral third-generation cephalosporin) against *N. gonorrhoeae*, combined with this drug's limited capacity to reach levels sufficiently higher than MICs in the blood, the urethra, the cervix, and especially the pharynx, have resulted in the removal of cefixime from the list of first-line agents for treatment of uncomplicated gonorrhea. *N. gonorrhoeae* strains with reduced susceptibility to ceftriaxone and cefixime (i.e., cephalosporin-intermediate/resistant strains) contain mutations in (1) the *penA* allele, which is the principal resistance determinant and encodes a penicillin-binding protein (PBP2) whose sequence can differ in up to 60–70 amino acids from that of wild-type PBP2; (2) the *m*ultiple *t*ransferable *r*esistance *r*egulator (*mtrR*) gene that results in increased drug efflux through the MtrCDE efflux pump; and (3) *penB*, which decreases drug influx through PorB.

Resistance to azithromycin can result from alterations of the ribosomal binding target by azithromycin and—as with cephalosporins—the

over- and under-expression of efflux and influx systems. Combined resistance to cephalosporins and azithromycin could contribute to the failure of the currently recommended dual therapy for gonorrhea with these two antimicrobial agents. Indeed, clinical failures caused by organisms resistant to these agents have been reported on two occasions in infected heterosexual men treated with both agents.

CLINICAL MANIFESTATIONS

Gonococcal Infections in Men Acute urethritis is the most common clinical manifestation of gonorrhea in male patients. The usual incubation period after exposure is 2–7 days, although the interval can be longer and most men remain asymptomatic. Strains of the PorB.1A serotype tend to cause a greater proportion of cases of mild and asymptomatic urethritis than do PorB.1B strains. When they occur, urethral discharge and dysuria, usually without urinary frequency or urgency, are the major symptoms. The discharge initially is scant and mucoid but becomes profuse and purulent within a day or two. Gram's staining of the urethral discharge may reveal PMNs and gram-negative intracellular monococci and diplococci **(Fig. 151-1)**. The clinical manifestations of gonococcal urethritis are usually more severe and overt than those of nongonococcal urethritis, including urethritis caused by *Chlamydia trachomatis* **(Chap. 184)**; however, exceptions are common, and it is often impossible to differentiate the causes of urethritis on clinical grounds alone. The majority of cases of urethritis seen in the United States today are not caused by *N. gonorrhoeae* and/or *C. trachomatis*. Although a number of other organisms may be responsible, many cases do not have a specific etiologic agent identified. Certain clones of *Neisseria meningitidis*, the second member of the pathogenic *Neisseria* species, have been associated with urethritis in men who have sex with men (MSM) in Europe and in heterosexual men in the southern and midwestern United States.

Most symptomatic men with gonorrhea seek treatment and cease to be infectious. The remaining men, who are largely asymptomatic, accumulate in number over time and constitute about two-thirds of all infected men at any point in time; together with men incubating the organism who shed the organism but are asymptomatic, they serve as the source of spread of infection. Before the antibiotic era, symptoms of urethritis persisted for ~8 weeks. Epididymitis is now an uncommon complication, and gonococcal prostatitis occurs rarely, if at all. Other unusual local complications of gonococcal urethritis include edema of the penis due to dorsal lymphangitis or thrombophlebitis, submucous inflammatory "soft" infiltration of the urethral wall, periurethral abscess or fistula, inflammation or abscess of Cowper's gland, and seminal vesiculitis. Balanitis may develop in uncircumcised men.

Gonococcal Infections in Women • **GONOCOCCAL CERVICITIS** Mucopurulent cervicitis is a common STI diagnosis in American women and may be caused by *N. gonorrhoeae, C. trachomatis*, and other organisms, including *Mycoplasma genitalium* **(Chap. 183)**. Cervicitis may coexist with candidal or trichomonal vaginitis. *N. gonorrhoeae* primarily infects the columnar epithelium of the cervical os. Bartholin's glands occasionally become infected.

FIGURE 151-1 Gram's stain of urethral discharge from a male patient with gonorrhea shows gram-negative intracellular monococci and diplococci. *(From the Public Health Agency of Canada.)*

Women infected with *N. gonorrhoeae* usually develop symptoms. However, women who either remain asymptomatic or have only minor symptoms may delay in seeking medical attention. These minor symptoms may include scant vaginal discharge issuing from the inflamed cervix (without vaginitis or vaginosis per se) and dysuria (often without urgency or frequency) that may be associated with gonococcal urethritis. Although the incubation period of gonorrhea is less well defined in women than in men, symptoms usually develop within 10 days of infection and are more acute and intense than those of chlamydial cervicitis.

The physical examination reveals a mucopurulent discharge (mucopus) issuing from the cervical os or a reddened (inflamed) cervix even in the absence of reported symptoms. Because Gram's stain is not sensitive for the diagnosis of gonorrhea in women, specimens should be submitted for culture or a nonculture assay (see "Laboratory Diagnosis," below). Edematous and friable cervical ectopy and endocervical bleeding induced by gentle swabbing are more often seen in chlamydial infection. Gonococcal infection may extend deep enough to produce dyspareunia and lower abdominal or back pain. In such cases, it is imperative to consider a diagnosis of pelvic inflammatory disease (PID) and to administer treatment for that disease **(Chaps. 131 and 184)**.

N. gonorrhoeae may also be recovered from the urethra and rectum of women with cervicitis, but these are rarely the only infected sites. Urethritis in women may produce symptoms of internal dysuria, which is often attributed to "cystitis." Pyuria in the absence of bacteriuria visible on Gram's stain of unspun urine, accompanied by urine cultures that fail to yield $>10^2$ colonies of bacteria usually associated with urinary tract infection, signifies the possibility of urethritis due to *C. trachomatis*. Urethral infection with *N. gonorrhoeae* also may occur in this context, but in this instance urethral cultures are usually positive.

GONOCOCCAL VAGINITIS The vaginal mucosa of healthy women is lined by stratified squamous epithelium and is rarely infected by *N. gonorrhoeae*. However, gonococcal vaginitis can occur in anestrogenic women (e.g., prepubertal girls and postmenopausal women), in whom the vaginal stratified squamous epithelium is often thinned down to the basilar layer, which can be infected by *N. gonorrhoeae*. The intense inflammation of the vagina makes the physical (speculum and bimanual) examination extremely painful. The vaginal mucosa is red and edematous, and an abundant purulent discharge is often present. Infection in the urethra and in Skene's and Bartholin's glands often accompanies gonococcal vaginitis. Inflamed cervical erosion or abscesses in nabothian cysts may also occur. Coexisting cervicitis may result in pus in the cervical os.

Anorectal Gonorrhea Because the female anatomy permits the spread of cervical exudate to the rectum, *N. gonorrhoeae* is sometimes recovered from the rectum of women with uncomplicated gonococcal cervicitis. The rectum is the sole site of infection in only 5% of women with gonorrhea. Such women are usually asymptomatic but occasionally have acute proctitis manifested by anorectal pain or pruritus, tenesmus, purulent rectal discharge, and rectal bleeding. Among MSM, the frequency of gonococcal infection, including rectal infection, fell by ≥90% throughout the United States in the early 1980s, but a resurgence of gonorrhea among MSM has been documented in several cities since the 1990s. Gonococcal isolates from the rectum of MSM tend to be more resistant to antimicrobial agents than are gonococcal isolates from other sites. Gonococcal isolates with a mutation in *mtrR* or in the promoter region of the gene that encodes for this transcriptional regulator develop increased resistance to antimicrobial hydrophobic agents such as bile acids and fatty acids in feces and thus are found with increased frequency in MSM. This situation may have been responsible for higher rates of failure of treatment for rectal gonorrhea with older regimens consisting of penicillin or tetracyclines.

Pharyngeal Gonorrhea Pharyngeal gonorrhea is usually mild or asymptomatic, although symptomatic pharyngitis does occasionally occur with cervical lymphadenitis. The mode of acquisition is oral–genital sexual exposure, with fellatio being a more efficient means of transmission than cunnilingus. In certain female adolescent populations in the United States, pharyngeal gonorrhea has become as

common as genital gonorrhea. Most cases resolve spontaneously, and transmission from the pharynx to sexual contacts is rare. Pharyngeal infection almost always coexists with genital infection. Swabs from the pharynx should be plated directly onto gonococcal selective media. Pharyngeal colonization with *N. meningitidis* needs to be differentiated from that with other *Neisseria* species.

Ocular Gonorrhea in Adults Ocular gonorrhea in an adult usually results from autoinoculation of *N. gonorrhoeae* from an infected genital site. As in genital infection, the manifestations range from severe to occasionally mild or asymptomatic disease. The variability in clinical manifestations may be attributable to differences in the ability of the infecting strain to elicit an inflammatory response. Infection may result in a markedly swollen eyelid, severe hyperemia and chemosis, and a profuse purulent discharge. The massively inflamed conjunctiva may be draped over the cornea and limbus. Lytic enzymes from the infiltrating PMNs occasionally cause corneal ulceration and rarely cause perforation.

Prompt recognition and treatment of this condition are of paramount importance. Gram's stain and culture of the purulent discharge establish the diagnosis. Genital cultures also should be performed.

Gonorrhea in Pregnant Women, Neonates, and Children Gonorrhea in pregnancy can have serious consequences for both the mother and the infant. Recognition of gonorrhea early in pregnancy also identifies a population at risk for other STIs, particularly chlamydial infection, syphilis, and trichomoniasis. The risks of salpingitis and PID—conditions associated with a high rate of fetal loss—are highest during the first trimester. Pharyngeal infection, most often asymptomatic, may be more common during pregnancy because of altered sexual practices. Prolonged rupture of the membranes, premature delivery, chorioamnionitis, funisitis (infection of the umbilical cord stump), and sepsis in the infant (with *N. gonorrhoeae* detected in the newborn's gastric aspirate during delivery) are common complications of maternal gonococcal infection at term. Other conditions and microorganisms, including *Mycoplasma hominis*, *Ureaplasma urealyticum*, *C. trachomatis*, and bacterial vaginosis (often accompanied by infection with *Trichomonas vaginalis*), have been associated with similar complications.

The most common form of gonorrhea in neonates is ophthalmia neonatorum, which results from exposure to infected cervical secretions during parturition. Ocular neonatal instillation of a prophylactic agent (e.g., 1% silver nitrate eye drops or ophthalmic preparations containing erythromycin or tetracycline) prevents ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics. The clinical manifestations are acute and usually begin 2–5 days after birth. An initial nonspecific conjunctivitis with a serosanguineous discharge is followed by tense edema of the eyelids, chemosis, and a profuse, thick, purulent discharge. Corneal ulcerations that result in nebulae or perforation may lead to anterior synechiae, anterior staphyloma, panophthalmitis, and blindness. Infections described at other mucosal sites in infants, including vaginitis, rhinitis, and anorectal infection, are likely to be asymptomatic. Pharyngeal colonization has been demonstrated in 35% of infants with gonococcal ophthalmia, and coughing is the most prominent symptom in these cases. Septic arthritis (see below) is the most common manifestation of systemic infection or DGI in the newborn. The onset usually comes at 3–21 days of age, and polyarticular involvement is common. Sepsis, meningitis, and pneumonia are seen in rare instances.

Any STI in children beyond the neonatal period raises the possibility of sexual abuse. Gonococcal vulvovaginitis is the most common manifestation of gonococcal infection in children beyond infancy. Anorectal and pharyngeal infections are common in these children and are frequently asymptomatic. The urethra, Bartholin's and Skene's glands, and the upper genital tract are rarely involved. All children with gonococcal infection should also be evaluated for chlamydial infection, syphilis, and possibly HIV infection.

Gonococcal Arthritis (DGI) DGI (gonococcal arthritis) results from gonococcal bacteremia. In the 1970s, DGI occurred in ~0.5–3% of persons with untreated gonococcal mucosal infection. The lower incidence of DGI at present is probably attributable to a decline in the prevalence of particular strains that are likely to disseminate. DGI strains resist the bactericidal action of human serum and generally do not incite inflammation at genital sites, probably because of limited generation of chemotactic factors. Strains recovered from DGI cases in the 1970s were often of the PorB.1A serotype, were highly susceptible to penicillin, and had special growth requirements—including arginine, hypoxanthine, and uracil—that made the organism more fastidious and more difficult to isolate.

Menstruation is a risk factor for dissemination, and approximately two-thirds of cases of DGI are in women. In about half of affected women, symptoms of DGI begin within 7 days of onset of menses. Complement deficiencies, especially of the components involved in the assembly of the membrane attack complex (C5 through C9), predispose to neisserial bacteremia, and persons with more than one episode of DGI should be screened with an assay for total hemolytic complement activity.

The clinical manifestations of DGI have sometimes been classified into two stages: a bacteremic stage, which is less common today, and a joint-localized stage with suppurative arthritis. A clear-cut progression usually is not evident. Patients in the bacteremic stage have higher temperatures, and chills more frequently accompany their fever. Painful joints are common and often occur together with tenosynovitis and skin lesions. Polyarthralgias usually include the knees, elbows, and more distal joints; the axial skeleton is generally spared. Skin lesions are seen in ~75% of patients and include papules and pustules, often with a hemorrhagic component **(Fig. 151-2; see also Fig. A1-43)**. Other manifestations of noninfectious dermatitis, such as nodular lesions, urticaria, and erythema multiforme, have been described. These lesions are usually on the extremities and number between 5 and 40. The differential diagnosis of the bacteremic stage of DGI includes reactive arthritis, acute rheumatoid arthritis, sarcoidosis, erythema nodosum, drug-induced arthritis, and viral infections (e.g., hepatitis B and acute HIV infection). The distribution of joint symptoms in reactive arthritis differs from that in DGI **(Fig. 151-3)**, as do the skin and genital manifestations **(Chap. 355)**.

Suppurative arthritis involves one or two joints, most often the knees, wrists, ankles, and elbows (in decreasing order of frequency); other joints occasionally are involved. Most patients who develop gonococcal septic arthritis do so without prior polyarthralgias or skin lesions; in the absence of symptomatic genital infection, this disease cannot be distinguished from septic arthritis caused by other pathogens. The differential diagnosis of acute arthritis in young adults is discussed in **Chap. 125**. Rarely, osteomyelitis complicates septic arthritis involving small joints of the hand.

Gonococcal endocarditis, although rare today, was a relatively common complication of DGI in the preantibiotic era, accounting for about one-quarter of reported cases of endocarditis. Another unusual complication of DGI is meningitis.

Gonococcal Infections in HIV-Infected Persons The association between gonorrhea and the acquisition of HIV has been demonstrated in several well-controlled studies, mainly in Kenya and Zaire. The nonulcerative STIs enhance the transmission of HIV three- to fivefold; transmission of HIV-infected immune cells and increased viral shedding by persons with urethritis or cervicitis may contribute **(Chap. 197)**. HIV has been detected by polymerase chain reaction (PCR) more commonly in ejaculates from HIV-positive men with gonococcal urethritis than in those from HIV-positive men with nongonococcal urethritis. PCR positivity diminishes twofold after appropriate therapy for urethritis. Not only does gonorrhea enhance the transmission of HIV, but it may also increase the individual's risk for acquisition of HIV. A proposed mechanism is the significantly greater number of CD4+ T lymphocytes and dendritic cells that can be infected by HIV in endocervical secretions from women with nonulcerative STIs than in those from women with ulcerative STIs.

LABORATORY DIAGNOSIS

A rapid diagnosis of gonococcal infection in men may be obtained by Gram's staining of urethral exudates (Fig. 151-1). The detection of

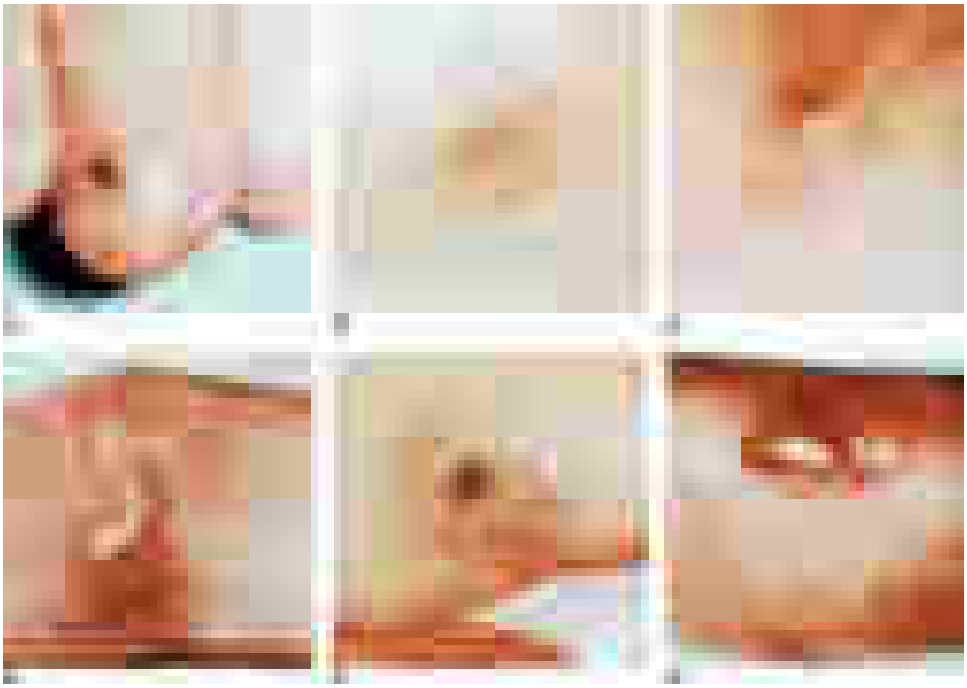

FIGURE 151-2 Characteristic skin lesions in patients with proven gonococcal bacteremia. The lesions are in various stages of evolution. ***A.*** Very early petechia on finger. ***B.*** Early papular lesion, 7 mm in diameter, on lower leg. ***C.*** Pustule with central eschar resulting from early petechial lesion. ***D.*** Pustular lesion on finger. ***E.*** Mature lesion with central necrosis (black) on hemorrhagic base. ***F.*** Bullae on anterior tibial surface. *(Reprinted with permission from KK Holmes et al: Disseminated gonococcal infection. Ann Intern Med 74:979, 1971.)*

gram-negative intracellular monococci and diplococci is usually highly specific and sensitive in diagnosing gonococcal urethritis in symptomatic males but is only ~50% sensitive in diagnosing gonococcal cervicitis. Samples should be collected with Dacron or rayon swabs. Part of the sample should be inoculated onto a plate of modified Thayer-Martin or other gonococcal selective medium for culture. It is important to process all samples immediately because gonococci do not tolerate drying. If plates cannot be incubated immediately, they can be held safely for several hours at room temperature in candle extinction jars prior to incubation. If processing is to occur within 6 h, transport of specimens may be facilitated by the use of nonnutritive swab transport systems such as Stuart or Amies medium. For longer holding periods (e.g., when specimens for culture are to be mailed), culture media with self-contained CO_2-generating systems (such as the JEMBEC or Gono-Pak systems) may be used. Specimens should also be obtained for the diagnosis of chlamydial infection **(Chap. 184)**.

PMNs are often seen in the endocervix on a Gram's stain, and an abnormally increased number (≥30 PMNs per field in five 1000× oil-immersion microscopic fields) establishes the presence of an inflammatory discharge. Unfortunately, the presence or absence of gram-negative intracellular monococci or diplococci in cervical smears does not accurately predict which patients have gonorrhea, and the diagnosis in this setting should be made by culture or another suitable nonculture diagnostic method. The sensitivity of a single endocervical culture is ~80–90%. If a history of rectal sex is elicited, a rectal wall swab (uncontaminated with feces) should be cultured. A presumptive diagnosis of gonorrhea cannot be made on the basis of gram-negative diplococci in smears from the pharynx, where other *Neisseria* species are components of the normal flora.

Several nucleic acid amplification tests (NAATs), including the Roche COBAS AMPLICOR, Gen-Probe Aptima Combo 2, and BD ProbeTec ET, are now widely available on semiautomated or fully automated platforms and are the most commonly employed diagnostic tests for gonorrhea. These tests also detect *C. trachomatis* and are more sensitive than culture for identification of either *N. gonorrhoeae* or *C. trachomatis*. The Gen-Probe and BD tests offer the advantage that urine samples can be tested with a sensitivity similar to or greater than that obtained when urethral or cervical swab samples are assessed by other non-NAATs or culture, respectively. A disadvantage of non-culture-based assays is that *N. gonorrhoeae* cannot be grown from the transport systems. Thus a culture-confirmatory test and formal antimicrobial susceptibility testing, if needed, cannot be performed.

Because of the legal implications, the preferred method for the diagnosis of gonococcal infection in children is a standardized culture. Two positive NAATs, each targeting a different nucleic acid sequence, may be substituted for culture of the cervix or the urethra as legal evidence of infection in children. Although nonculture tests for gonococcal infection have not been approved by the U.S. Food and Drug Administration for use with specimens obtained from the pharynx and rectum of infected children, NAATs from these sites are preferred for diagnostic evaluation in adult victims of suspected sexual abuse, especially if the NAATs have been evaluated by the local laboratory and found to be superior. Cultures should be obtained from the pharynx and anus of both girls and boys, the urethra of boys, and the vagina of girls; cervical specimens are not recommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen of the discharge is adequate for culture. Presumptive colonies of *N. gonorrhoeae* should be identified definitively by at least two independent methods.

Blood should be cultured in suspected cases of DGI. The use of Isolator blood culture tubes may enhance the yield. The probability of positive blood cultures decreases after 48 h of illness. Synovial fluid should be inoculated into blood culture broth medium and plated onto chocolate agar rather than selective medium because this fluid is not likely to be contaminated with commensal bacteria. Gonococci are infrequently recovered from early joint effusions containing <20,000 leukocytes/μL but may be recovered from effusions containing >80,000 leukocytes/μL. The organisms are seldom recovered from blood and synovial fluid of the same patient.

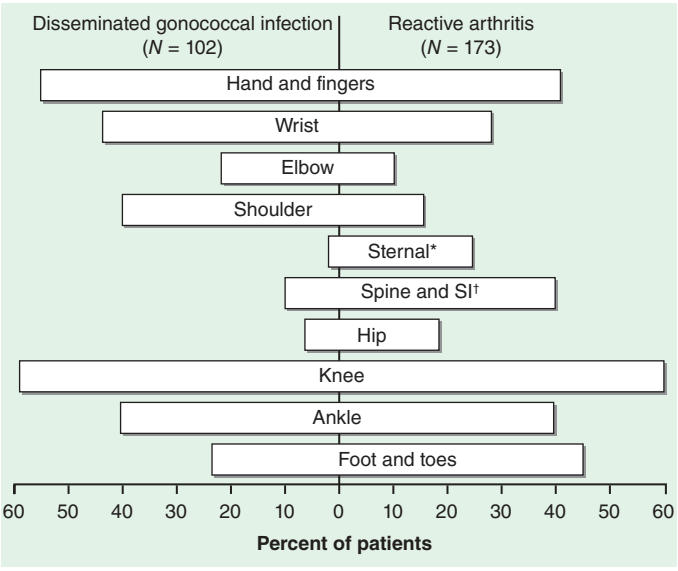

FIGURE 151-3 Distribution of joints with arthritis in 102 patients with disseminated gonococcal infection and 173 patients with reactive arthritis. *Includes the sternoclavicular joints. †SI, sacroiliac joint.

Gonococcal Infections

Treatment failure can lead to continued transmission and the emergence of antibiotic resistance. The importance of adequate treatment with a regimen that the patient will adhere to cannot be overemphasized. Thus highly effective single-dose regimens have been developed for uncomplicated gonococcal infections. The 2015 treatment guidelines for gonococcal infections from the CDC are summarized in Table 151-1. Rising MICs of cefixime worldwide have led the CDC to discontinue its recommendation of this agent as first-line treatment for uncomplicated gonorrhea. The third-generation cephalosporin ceftriaxone in combination with azithromycin is recommended as treatment; dual therapy against gonorrhea could slow the development of resistance to either of these antimicrobial agents. Azithromycin, which also treats nongonococcal urethritis, is preferred to doxycycline because of its superior activity against gonorrhea and ease of use. The recommendations for uncomplicated gonorrhea apply to HIV-infected as well as HIV-uninfected patients.

TABLE 151-1 Recommended Treatment for Gonococcal Infections: Adapted from the 2015 Guidelines of the Centers for Disease Control and Prevention

DIAGNOSIS	TREATMENT OF CHOICE[a]
Uncomplicated gonococcal infection of the cervix, urethra, pharynx[b], or rectum	
First-line regimen	Ceftriaxone (250 mg IM, single dose)
	plus
	Azithromycin (1 g PO, single dose)
Alternative regimens[c]	Cefixime (400 mg PO, single dose) *or* ceftizoxime (500 mg IM, single dose) *or* cefotaxime (500 mg IM, single dose) *or* spectinomycin (2 g IM, single dose)[d,e] *or* cefotetan (1 g IM, single dose) plus probenecid (1 g PO, single dose)[d] *or* cefoxitin (2 g IM, single dose) plus probenecid (1 g PO, single dose)[d]
	plus
	Azithromycin (1 g PO, single dose)
Epididymitis	**See Chap. 131**
Pelvic inflammatory disease	**See Chap. 131**
Gonococcal conjunctivitis in an adult	Ceftriaxone (1 g IM, single dose)[f]
Ophthalmia neonatorum[g]	Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg)
Disseminated gonococcal infection[h]	
Initial therapy[i]	
Patient tolerant of β-lactam drugs	Ceftriaxone (1 g IM or IV q24h; recommended) *or* cefotaxime (1 g IV q8h) *or* ceftizoxime (1 g IV q8h)
Patients allergic to β-lactam drugs	Spectinomycin (2 g IM q12h)[d]
Continuation therapy[i]	Cefixime (400 mg PO bid)
Meningitis or endocarditis	See text for specific recommendations[j]

[a]True failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis. [b]Ceftriaxone and azithromycin are the only agents recommended for treatment of pharyngeal infection. [c]See text for follow-up of persons with infection who are treated with alternative regimens. [d]Spectinomycin, cefotetan, and cefoxitin, which are alternative agents, currently are unavailable or in short supply in the United States. [e]Spectinomycin may be ineffective for the treatment of pharyngeal gonorrhea. [f]Plus lavage of the infected eye with saline solution (once). [g]Prophylactic regimens are discussed in the text. [h]Hospitalization is indicated if the diagnosis is uncertain, if the patient has frank arthritis with an effusion, or if the patient cannot be relied on to adhere to treatment. [i]All initial regimens should also include azithromycin (1 g PO, single dose) and should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week. [j]Hospitalization is indicated to exclude suspected meningitis or endocarditis.

The currently recommended regimen for the treatment of uncomplicated gonococcal infection of the urethra, cervix, rectum, or pharynx (a single IM dose of ceftriaxone plus a single dose of azithromycin taken orally) almost always results in an effective cure. Quinolone-containing regimens are no longer recommended in the United States as first-line treatment because of widespread resistance. A multicenter trial of treatment for uncomplicated gonorrhea in the United States showed ≥99.5% efficacy of two combination regimens: (1) gemifloxacin (320 mg, single oral dose) plus azithromycin (2 g, single oral dose) or (2) azithromycin (2 g, single oral dose) plus gentamicin (a single IM dose of 240 mg or, in individuals who weigh ≤45 kg, 5 mg/kg). At this time, however, neither of these regimens is recommended as first-line treatment.

Co-infection with *C. trachomatis* occurs frequently; treatment of gonorrhea with ceftriaxone that also includes a single 1-g dose of azithromycin is effective against chlamydial infection. However, a 1-g dose of azithromycin used alone as treatment for gonorrhea in penicillin-allergic persons results in an unacceptably low cure rate (93%) for gonococcal infections and should not be used. A single 2-g dose of azithromycin, particularly in the extended-release microsphere formulation, delivers azithromycin to the lower gastrointestinal tract, thereby improving tolerability. Azithromycin is effective against sensitive strains, but this drug is expensive, causes gastrointestinal distress, and is not recommended for routine or first-line treatment of gonorrhea. Spectinomycin has been used as an alternative agent for the treatment of uncomplicated gonococcal infections in penicillin-allergic persons outside the United States but is not currently available in this country. Of note, the limited effectiveness of spectinomycin for the treatment of pharyngeal infection reduces its utility in populations among whom such infection is common, such as MSM.

Persons with uncomplicated infections who receive ceftriaxone and azithromycin do not need a test of cure; however, cultures for *N. gonorrhoeae* should be performed if symptoms persist after therapy with an established regimen, and any gonococci isolated should be tested for antimicrobial susceptibility. Persons given an alternative regimen should return for a test of cure targeting the infected anatomic site. This test ideally should be a culture. If culture is not readily available and NAAT is positive, every effort should be made to perform a confirmatory culture. All isolates from test-of-cure cultures should undergo antimicrobial susceptibility testing. Because of high rates of reinfection with *N. gonorrhoeae* and *C. trachomatis* within 6 months, repeat testing is recommended 3 months after treatment.

Symptomatic gonococcal pharyngitis is more difficult to eradicate than genital infection. Persons who cannot tolerate ceftriaxone and those in whom quinolones are contraindicated may be treated with spectinomycin if it is available, but this agent results in a cure rate of ≤52%. Persons given spectinomycin should have a pharyngeal sample cultured 3–5 days after treatment as a test of cure. A single 2-g dose of azithromycin may be used in areas where rates of resistance to azithromycin are low.

Treatments for gonococcal epididymitis and PID are discussed in Chap. 131. Ocular gonococcal infections in older children and adults should be managed with a single dose of ceftriaxone combined with saline irrigation of the conjunctivae (both undertaken expeditiously), and patients should undergo a careful ophthalmologic evaluation that includes a slit-lamp examination.

DGI may require higher dosages and longer durations of therapy (Table 151-1). Hospitalization is indicated if the diagnosis is uncertain, if the patient has localized joint disease that requires aspiration, or if the patient cannot be relied on to comply with treatment. Open drainage is necessary only occasionally—e.g., for management of hip infections that may be difficult to drain percutaneously. Nonsteroidal anti-inflammatory agents may be indicated to alleviate pain and hasten clinical improvement of affected joints.

Gonococcal meningitis and endocarditis should be treated in the hospital with high-dose IV ceftriaxone (1–2 g IV every 12–24 h);

therapy should continue for 10–14 days for meningitis and for at least 4 weeks for endocarditis. All persons who experience more than one episode of DGI should be evaluated for complement deficiency.

PREVENTION AND CONTROL

Condoms, if properly used, provide effective protection against the transmission and acquisition of gonorrhea as well as other infections that are transmitted to and from genital mucosal surfaces. Spermicidal preparations used with a diaphragm or cervical sponges impregnated with nonoxynol-9 offer some protection against gonorrhea and chlamydial infection. However, the frequent use of preparations that contain nonoxynol-9 is associated with mucosal disruption that paradoxically may enhance the risk of HIV infection in the event of exposure. All patients should be instructed to refer sex partners for evaluation and treatment. All sex partners of persons with gonorrhea should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last contact with the patient took place within 60 days before the onset of symptoms or the diagnosis of infection in the patient. If the patient's last sexual encounter was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated. Partner-delivered medications or prescriptions for medications to treat gonorrhea and chlamydial infection diminish the likelihood of reinfection (or relapse) in the infected patient. In states where it is not prohibited, this approach is an option for partner management. Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms. Greater emphasis must be placed on prevention by public health education, individual patient counseling, and behavior modification, particularly the use of condoms. Sexually active persons, especially adolescents, should be offered screening for STIs. For male patients, NAAT of urine or a urethral swab may be used for screening. Preventing the spread of gonorrhea may help reduce the transmission of HIV. No effective vaccine for gonorrhea is yet available, but efforts to test several candidates are underway.

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152 *Haemophilus* and *Moraxella* Infections

Timothy F. Murphy

HAEMOPHILUS INFLUENZAE

MICROBIOLOGY

Haemophilus influenzae was first recognized in 1892 by Pfeiffer, who erroneously concluded that the bacterium was the cause of influenza. *H. influenzae* is a small (1- × 0.3-μm) gram-negative organism of variable shape; thus, it is often described as a pleomorphic coccobacillus. In clinical specimens such as cerebrospinal fluid (CSF) and sputum, *H. influenzae* frequently stains only faintly with safranin and therefore can easily be overlooked.

H. influenzae grows both aerobically and anaerobically. Its aerobic growth requires two factors: hemin (X factor) and nicotinamide adenine dinucleotide (V factor). These requirements are used in the clinical laboratory to identify the bacterium. Caution must be used to distinguish *H. influenzae* from *Haemophilus haemolyticus*, a respiratory tract commensal that has identical growth requirements. *H. haemolyticus* has classically been distinguished from *H. influenzae* by the hemolysis of the former species on horse blood agar. However, a significant proportion of isolates of *H. haemolyticus* have now been recognized as nonhemolytic. Analysis of various genotypic and phenotypic markers, including16S ribosomal sequences, superoxide dismutase, outer-membrane protein P6, protein D, and fuculose kinase, can be used to distinguish these two species.

Six major serotypes of *H. influenzae* have been identified; designated *a* through *f*, they are based on antigenically distinct polysaccharide capsules. In addition, some strains lack a polysaccharide capsule and are referred to as *nontypable* strains. Type b and nontypable strains are the most relevant strains clinically **(Table 152-1)**, although encapsulated strains other than type b can cause disease. *H. influenzae* was the first free-living organism to have its entire genome sequenced.

The antigenically distinct type b capsule is a linear polymer composed of ribosyl-ribitol phosphate. Strains of *H. influenzae* type b (Hib) cause disease primarily in infants and children <6 years of age. Nontypable strains are primarily mucosal pathogens but occasionally cause invasive disease.

TABLE 152-1 Characteristics of Type b and Nontypable Strains of *Haemophilus influenzae*

FEATURE	TYPE b STRAINS	NONTYPABLE STRAINS
Capsule	Ribosyl-ribitol phosphate	Unencapsulated
Pathogenesis	Invasive infections due to hematogenous spread	Mucosal infections due to contiguous spread
Clinical manifestations	Meningitis and invasive infections in incompletely immunized infants and children	Otitis media in infants and children; lower respiratory tract infections in adults with chronic bronchitis
Evolutionary history	Basically clonal	Genetically diverse
Vaccine	Highly effective conjugate vaccines	Under development

EPIDEMIOLOGY AND TRANSMISSION

H. influenzae, an exclusively human pathogen, is spread by airborne droplets or by direct contact with secretions or fomites. Colonization with nontypable *H. influenzae* is a dynamic process; new strains are acquired and other strains are replaced periodically.

The widespread use of Hib conjugate vaccines in many industrialized countries has resulted in striking decreases in the rate of nasopharyngeal colonization by Hib and in the incidence of Hib infection **(Fig. 152-1)**. Worldwide, invasive Hib disease occurs predominantly in unimmunized children and in those who have not completed the primary immunization series. Of 194 World Health Organization member countries, 99% have introduced Hib conjugate vaccination, but a large number of the world's children remain unimmunized. Certain groups have a higher incidence of invasive Hib disease than the general population, including African-American and Australian Aboriginal children and Native American groups. Although this increased incidence has not yet been accounted for, several factors may be relevant, including age at exposure to the bacterium, socioeconomic conditions, and genetic differences.

PATHOGENESIS

Hib strains cause systemic disease by invasion and hematogenous spread from the respiratory tract to distant sites such as the meninges,

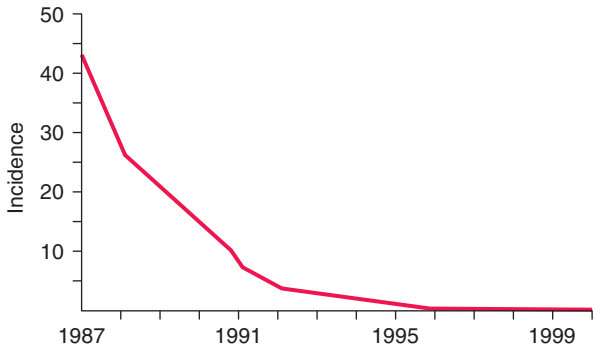

FIGURE 152-1 Estimated incidence (rate per 100,000) of invasive disease due to *Haemophilus influenzae* type b among children <5 years of age: 1987–2000. Fewer than 40 cases per year have been reported since 2000. *(Data from the Centers for Disease Control and Prevention.)*

bones, and joints. The type b polysaccharide capsule is an important virulence factor affecting the bacterium's ability to avoid opsonization and cause systemic disease.

Nontypable strains cause disease by local invasion of mucosal surfaces. Otitis media results when bacteria reach the middle ear by way of the eustachian tube. Adults with chronic bronchitis experience recurrent lower respiratory tract infection due to nontypable strains. In addition, persistent nontypable *H. influenzae* colonization of the lower airways of adults with chronic obstructive pulmonary disease (COPD) contributes to the airway inflammation that is a hallmark of the disease. Nontypable strains that cause infection in adults with COPD differ in pathogenic potential and genome content from strains that cause otitis media. In the middle ear, nontypable strains form biofilms. More resistant to host clearance mechanisms and to antibiotics than are planktonic bacteria, biofilms are associated with chronic and recurrent otitis media. The incidence of invasive disease caused by nontypable strains is low. Strains that cause invasive disease are genetically and phenotypically diverse.

IMMUNE RESPONSE

Antibody to the capsule is important in protection from infection by Hib strains. The level of (maternally acquired) serum antibody to the capsular polysaccharide, which is a polymer of polyribitol ribose phosphate (PRP), declines from birth to 6 months of age and, in the absence of vaccination, remains low until ~2 or 3 years of age. The age at the antibody nadir correlates with that of the peak incidence of type b disease. Antibody to PRP then appears partly as a result of exposure to Hib or cross-reacting antigens. Systemic Hib disease is unusual after the age of 6 years because of the presence of protective antibody. Vaccines in which PRP is conjugated to protein carrier molecules have been developed and are now used widely. These vaccines generate an antibody response to PRP in infants and effectively prevent invasive infections in infants and children.

Since nontypable strains lack a capsule, the immune response to infection is directed at noncapsular antigens. These antigens have generated considerable interest as immune targets and potential vaccine components. The human immune response to nontypable strains appears to be strain-specific, a characteristic that accounts in part for the propensity of these strains to cause recurrent otitis media and recurrent exacerbations of chronic bronchitis in immunocompetent hosts.

CLINICAL MANIFESTATIONS

Hib The most serious manifestation of infection with Hib is *meningitis* **(Chap. 133)**, which primarily affects children <2 years of age. The clinical manifestations of Hib meningitis are similar to those of meningitis caused by other bacterial pathogens. Fever and altered central nervous system function are the most common features at presentation. Nuchal rigidity may or may not be evident. Subdural effusion, the most common complication, is suspected when, despite 2 or 3 days of appropriate antibiotic therapy, the infant has seizures, hemiparesis, or continued obtundation. The overall mortality rate from Hib meningitis is ~5%, and the morbidity rate is high. Of survivors, 6% have permanent sensorineural hearing loss, and about one-fourth have a significant handicap of some type. If more subtle handicaps are sought, up to half of survivors are found to have some neurologic sequelae, such as partial hearing loss and delayed language development.

Epiglottitis **(Chap. 31)** is a life-threatening Hib infection involving cellulitis of the epiglottis and supraglottic tissues. It can lead to acute upper-airway obstruction. Its unique epidemiologic features are its occurrence in an older age group (2–7 years old) than other Hib infections and its absence among Navajo Native Americans and Alaskan Eskimos. Sore throat and fever rapidly progress to dysphagia, drooling, and airway obstruction. Epiglottitis also occurs in adults.

Cellulitis **(Chap. 124)** due to Hib occurs in young children. The most common location is on the head or neck, and the involved area sometimes takes on a characteristic bluish-red color. Most patients have bacteremia, and 10% have an additional focus of infection.

Hib causes *pneumonia* in infants. The infection is clinically indistinguishable from other types of bacterial pneumonia (e.g., pneumococcal pneumonia) except that Hib is more likely to involve the pleura. Several less common invasive conditions can be important clinical manifestations of Hib infection in children. These include osteomyelitis, septic arthritis, pericarditis, orbital cellulitis, endophthalmitis, urinary tract infection, abscesses, and bacteremia without an identifiable focus.

Non–type b encapsulated strains of *H. influenzae* (types a, c, d, e, and f) are unusual causes of invasive infection manifested predominantly by bacteremia and pneumonia. *H. influenzae* type a infections are seen with increased frequency in indigenous populations of North America. Most infections due to non–type b encapsulated strains occur in the setting of underlying conditions.

Nontypable *H. influenzae* Nontypable *H. influenzae* is the most common bacterial cause of exacerbations of COPD; these exacerbations are characterized by increased cough, sputum production, and shortness of breath. Fever is low-grade, and no infiltrates are evident on chest x-ray. Nontypable strains also cause community-acquired bacterial pneumonia in adults, especially among patients with COPD or AIDS. The clinical features of *H. influenzae* pneumonia are similar to those of other types of bacterial pneumonia, including pneumococcal pneumonia.

Nontypable *H. influenzae* is one of the three most common causes of childhood otitis media (the other two being *Streptococcus pneumoniae* and *Moraxella catarrhalis*) **(Chap. 31)**. Infants are febrile and irritable, while older children report ear pain. Symptoms of viral upper-respiratory infection often precede otitis media. The diagnosis is made by pneumatic otoscopy. An etiologic diagnosis, although not routinely sought, can be established by tympanocentesis and culture of middle-ear fluid. Clinical features associated with *H. influenzae* otitis media include a history of recurrent episodes, treatment failure, concomitant conjunctivitis, bilateral otitis media, and recent antimicrobial therapy. The increasing use of pneumococcal polysaccharide conjugate vaccines in infants is resulting in a relative increase in the proportion of otitis media cases that are caused by *H. influenzae*.

Nontypable *H. influenzae* also causes puerperal sepsis and is an important cause of neonatal bacteremia. These nontypable strains, which are closely related to *H. haemolyticus*, tend to be of biotype IV and cause invasive disease after colonizing the female genital tract.

Nontypable *H. influenzae* causes sinusitis **(Chap. 31)** in adults and children. In addition, the bacterium is a less common cause of various invasive infections. These infections include empyema, adult epiglottitis, pericarditis, cellulitis, septic arthritis, osteomyelitis, endocarditis, cholecystitis, intraabdominal infections, urinary tract infections, mastoiditis, aortic graft infection, and bacteremia without a detectable focus. While most *H. influenzae* invasive infections in countries where Hib vaccines are used widely are caused by nontypable strains, there is no convincing evidence of an increased incidence of infection by nontypable *H. influenzae* as a result of the use of Hib vaccines. Continued monitoring will be important. Many patients with *H. influenzae* bacteremia have an underlying condition, such as HIV infection, cardiopulmonary disease, alcoholism, or cancer.

DIAGNOSIS

The most reliable method for establishing a diagnosis of Hib infection is recovery of the organism in culture. The presence of gram-negative coccobacilli in Gram-stained CSF is strong evidence for Hib meningitis. Recovery of the organism from CSF confirms the diagnosis. Cultures of other normally sterile body fluids, such as blood, joint fluid, pleural fluid, pericardial fluid, and subdural effusion, are confirmatory in other infections.

Detection of PRP is an important adjunct to culture in rapid diagnosis of Hib meningitis. Immunoelectrophoresis, latex agglutination, coagglutination, and enzyme-linked immunosorbent assay are effective in detecting PRP. These assays are particularly helpful when patients have received prior antimicrobial therapy and thus are especially likely to have negative cultures.

Because nontypable *H. influenzae* is primarily a mucosal pathogen, it is a component of a mixed flora; thus etiologic diagnosis is challenging. Nontypable *H. influenzae* infection is strongly suggested by the predominance of gram-negative coccobacilli among abundant polymorphonuclear leukocytes in a Gram-stained sputum specimen from a patient in whom pneumonia is suspected. Although bacteremia is detectable in a small proportion of patients with pneumonia due to nontypable *H. influenzae*, most such patients have negative blood cultures.

A diagnosis of otitis media is based on the detection by pneumatic otoscopy of fluid in the middle ear. An etiologic diagnosis requires tympanocentesis but is not routinely sought. An invasive procedure is also required to determine the etiology of sinusitis; thus, treatment is often empirical once the diagnosis is suspected in light of clinical symptoms and sinus radiographs.

TREATMENT

Haemophilus influenzae

Initial therapy for meningitis due to Hib should consist of a cephalosporin such as ceftriaxone or cefotaxime. For children, the dosage of ceftriaxone is 75–100 mg/kg daily given in two doses 12 h apart. The pediatric dosage of cefotaxime is 200 mg/kg daily given in four doses 6 h apart. Adult dosages are 2 g every 12 h for ceftriaxone and 2 g every 4–6 h for cefotaxime. An alternative regimen for initial therapy is ampicillin (200–300 mg/kg daily in four divided doses) plus chloramphenicol (75–100 mg/kg daily in four divided doses). Therapy should continue for a total of 1–2 weeks.

Administration of glucocorticoids to patients with Hib meningitis reduces the incidence of neurologic sequelae. The presumed mechanism is reduction of the inflammation induced by bacterial cell-wall mediators of inflammation when cells are killed by antimicrobial agents. Dexamethasone (0.6 mg/kg per day intravenously in four divided doses for 2 days) is recommended for the treatment of Hib meningitis in children >2 months of age.

Invasive infections other than meningitis are treated with the same antimicrobial agents. For epiglottitis, the dosage of ceftriaxone is 50 mg/kg daily, and the dosage of cefotaxime is 150 mg/kg daily, given in three divided doses 8 h apart. Epiglottitis constitutes a medical emergency, and maintenance of an airway is critical. The duration of therapy is determined by the clinical response. A course of 1–2 weeks is usually appropriate.

Many infections caused by nontypable strains of *H. influenzae*, such as otitis media, sinusitis, and exacerbations of COPD, can be treated with oral antimicrobial agents. Approximately 20–35% of nontypable strains produce β-lactamase (with the exact proportion depending on geographic location), and these strains are resistant to ampicillin. Several agents have excellent activity against nontypable *H. influenzae*, including amoxicillin/clavulanic acid, various extended-spectrum cephalosporins, and the macrolides azithromycin and clarithromycin. Fluoroquinolones are highly active against *H. influenzae* and are useful in adults with exacerbations of COPD. However, fluoroquinolones are not currently recommended for the treatment of children or pregnant women because of possible effects on articular cartilage.

In addition to β-lactamase production, alteration of penicillin-binding proteins—a second mechanism of ampicillin resistance—has been detected in isolates of *H. influenzae*. Although rare in the United States, these β-lactamase-negative ampicillin-resistant strains are common in Japan and are increasing in prevalence in Europe. Resistance to macrolides is also being observed with increasing frequency in many regions of the world. Continued monitoring of the evolving antimicrobial susceptibility patterns of *H. influenzae* will be important.

PREVENTION

Vaccination (See also Chap. 118) Three conjugate vaccines that prevent invasive infections with Hib in infants and children are licensed in the United States. In addition to eliciting protective antibody, these vaccines prevent disease by reducing rates of pharyngeal colonization with Hib. The widespread use of conjugate vaccines has dramatically reduced the incidence of Hib disease in developed countries. Even though the manufacture of Hib vaccines is costly, vaccination is cost-effective. The Global Alliance for Vaccines and Immunizations has recognized the underuse of Hib conjugate vaccines.

The disease burden has been reduced in developing countries that have implemented routine vaccination (e.g., The Gambia, Chile). An important obstacle to more widespread vaccination is the lack of data on the epidemiology and burden of Hib disease in many developing countries.

All children should be immunized with an Hib conjugate vaccine, receiving the first dose at ~2 months of age, the rest of the primary series at 2–6 months of age, and a booster dose at 12–15 months of age. Specific recommendations vary for the different conjugate vaccines. The reader is referred to the recommendations of the American Academy of Pediatrics (Chap. 118 and *www.cispimmunize.org*).

Currently, no vaccines are available specifically for the prevention of disease caused by nontypable *H. influenzae*. However, a vaccine that contains protein D—a surface protein of *H. influenzae*—conjugated to pneumococcal polysaccharides is licensed in other countries and is used widely throughout the world. The vaccine has shown partial efficacy in preventing *H. influenzae* otitis media in clinical trials. Additional progress in the development of vaccines against nontypable *H. influenzae* is anticipated.

Chemoprophylaxis The risk of secondary disease is greater than normal among household contacts of patients with Hib disease. Therefore, all children and adults (except pregnant women) in households with an index case and at least one incompletely immunized contact <4 years of age should receive prophylaxis with oral rifampin. When two or more cases of invasive Hib disease have occurred within 60 days at a child-care facility attended by incompletely vaccinated children, administration of rifampin to all attendees and personnel is indicated, as it is for household contacts. Chemoprophylaxis is not indicated in nursery and child-care contacts of a single index case. The reader is referred to the recommendations of the American Academy of Pediatrics.

HAEMOPHILUS DUCREYI

Haemophilus ducreyi is the etiologic agent of chancroid (Chap. 131), a sexually transmitted disease characterized by genital ulceration and inguinal adenitis. In addition to being a cause of morbidity in itself, chancroid is associated with HIV infection because of the role played by genital ulceration in HIV transmission. Chancroid increases the efficiency of transmission of and the degree of susceptibility to HIV infection. *H. ducreyi* has also been recognized as an important cause of non-sexually transmitted cutaneous ulcers.

MICROBIOLOGY

H. ducreyi is a highly fastidious coccobacillary gram-negative bacterium whose growth requires X factor (hemin). Although, in light of this requirement, the bacterium has been classified in the genus *Haemophilus*, DNA homology and chemotaxonomic studies have established substantial differences between *H. ducreyi* and other *Haemophilus*

species. Taxonomic reclassification of the organism is likely in the future but awaits further study. Ulcers contain predominantly T cells. The fact that patients who have had chancroid may have repeated infections indicates that infection does not confer protection.

EPIDEMIOLOGY AND PREVALENCE

The prevalence of chancroid has declined in the United States and worldwide. However, prevalence data must be interpreted with caution because of the difficulty of establishing a diagnosis. The infection appears to be more common in developing countries. Transmission is predominantly heterosexual, and cases in males have outnumbered those in females by ratios of 3:1 to 25:1 during outbreaks. Contact with commercial sex workers and illicit drug use are strongly associated with chancroid.

H. ducreyi has emerged as a major cause of cutaneous ulcers in the South Pacific and Africa. Strains that cause cutaneous ulcers have genome sequences that are nearly identical to class I strains (of two related classes) of *H. ducreyi* that cause genital ulcers.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Infection is acquired as the result of a break in the epithelium during sexual contact with an infected individual. After an incubation period of 4–7 days, the initial lesion—a papule with surrounding erythema—appears. In 2 or 3 days, the papule evolves into a pustule, which spontaneously ruptures and forms a sharply circumscribed ulcer that generally is not indurated **(Fig. 152-2)**. The ulcers are painful and bleed easily; little or no inflammation of the surrounding skin is evident. Approximately half of patients develop enlarged, tender inguinal lymph nodes, which frequently become fluctuant and spontaneously rupture. Patients usually seek medical care after 1–3 weeks of painful symptoms.

The presentation of chancroid does not usually include all of the typical clinical features and is sometimes atypical. Multiple ulcers can coalesce to form giant ulcers. Ulcers can appear and then resolve, with inguinal adenitis (Fig. 152-2) and suppuration following 1–3 weeks later; this clinical picture can be confused with that of lymphogranuloma venereum **(Chap. 184)**. Multiple small ulcers can resemble folliculitis. Other differential diagnostic considerations include the various infections causing genital ulceration, such as primary syphilis, secondary syphilis (condyloma latum), genital herpes, and donovanosis. In rare cases, chancroid lesions become secondarily infected with bacteria; the result is extensive inflammation.

Non-sexually transmitted cutaneous ulcers caused by *H. ducreyi* resemble those of yaws caused by *Treponema pallidum* subspecies *pertenue*, which is endemic in regions where *H. ducreyi* cutaneous ulcers are seen. Ulcers caused by *H. ducreyi* are less likely than those of yaws to show central granulating tissue and less likely to have indurated edges, but substantial overlap in clinical characteristics exists.

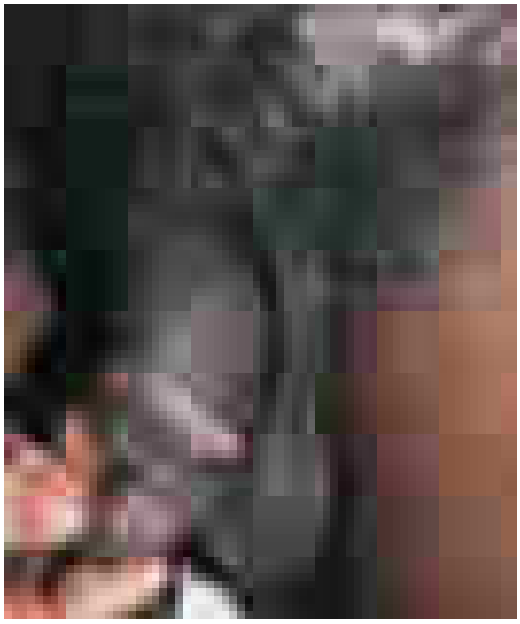

FIGURE 152-2 Chancroid with characteristic penile ulcers and associated left inguinal adenitis (bubo).

DIAGNOSIS

Clinical diagnosis of chancroid is often inaccurate, and laboratory confirmation should be attempted in suspected cases. An accurate diagnosis of chancroid relies on culture of *H. ducreyi* from the lesion or from an aspirate of suppurative lymph nodes. Since the organism can be difficult to grow, the use of selective and supplemented media is necessary. No polymerase chain reaction (PCR) assay for *H. ducreyi* is commercially available; such tests can be performed by Clinical Laboratory Improvement Amendment (CLIA)–certified clinical laboratories that have developed their own assays.

A probable diagnosis of chancroid can be made when the following criteria are met: (1) one or more painful genital ulcers; (2) no evidence of *T. pallidum* infection by dark-field examination of ulcer exudate or by a negative serologic test for syphilis performed at least 7 days after ulcer onset; (3) a typical clinical presentation for chancroid; and (4) a negative test for herpes simplex virus in the ulcer exudate.

A serologic test for syphilis does not distinguish cutaneous ulcers due to *H. ducreyi* from those due to yaws. A PCR assay has been used in clinical studies to establish an *H. ducreyi* etiology, but, as stated above, no such assay is commercially available.

TREATMENT

Haemophilus ducreyi

Treatment regimens recommended by the Centers for Disease Control and Prevention include (1) a single 1-g oral dose of azithromycin; (2) ceftriaxone (250 mg intramuscularly in a single dose); (3) ciprofloxacin (500 mg by mouth twice a day for 3 days); and (4) erythromycin base (500 mg by mouth three times a day for 7 days). Isolates from patients who do not respond promptly to treatment should be tested for antimicrobial resistance. In patients with HIV infection, healing may be slow and longer courses of treatment may be necessary. Clinical treatment failure in HIV-seropositive patients may reflect co-infection, especially with herpes simplex virus. Contacts of patients with chancroid should be identified and treated, whether or not symptoms are present, if they have had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

MORAXELLA CATARRHALIS

MICROBIOLOGY

M. catarrhalis is an unencapsulated gram-negative diplococcus whose ecologic niche is the human respiratory tract. The organism was initially designated *Micrococcus catarrhalis*. Its name was changed to *Neisseria catarrhalis* in 1970 because of phenotypic similarities to commensal *Neisseria* species. On the basis of more rigorous analysis of genetic relatedness, *Moraxella catarrhalis* is now the widely accepted name for this species.

EPIDEMIOLOGY

Nasopharyngeal colonization by *M. catarrhalis* is common in infancy, with colonization rates ranging between 33% and 100% and depending on geographic location. Several factors probably account for this geographic variation, including living conditions, day-care attendance, hygiene, household smoking, and population genetics. The prevalence of colonization decreases steadily with age.

The widespread use of pneumococcal conjugate vaccines in some countries has resulted in alterations in patterns of nasopharyngeal colonization in resident populations. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypable *H. influenzae*, and *M. catarrhalis* has occurred. These changes in colonization patterns

may be altering the distribution of pathogens of both otitis media and sinusitis in children.

PATHOGENESIS

M. catarrhalis causes mucosal infections of the respiratory tract by contiguous spread from its colonizing site in the upper airway. A preceding viral upper respiratory tract infection is a common inciting event for otitis media. In exacerbations of COPD, the acquisition of new strains is critical for pathogenesis. Strains exhibit substantial genetic diversity and differences in virulence properties.

The expression of several adhesin molecules with differing specificities for various host cell receptors reflects the importance of adherence to the respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* invades multiple cell types. Its intracellular residence in lymphoid tissue provides a potential reservoir for persistence in the human respiratory tract. Like many gram-negative bacteria, *M. catarrhalis* sheds vesicles into the surrounding environment. The vesicles are internalized by host cells and mediate several virulence mechanisms, including induction of inflammation and delivery of β-lactamase, that can promote the survival of co-pathogens.

CLINICAL MANIFESTATIONS

In children, *M. catarrhalis* causes predominantly mucosal infections when the bacterium migrates from the nasopharynx to the middle ear or the sinuses **(Chap. 31)**. The inciting event for both otitis media and sinusitis is often a preceding viral infection. Overall, cultures of middle-ear fluid obtained by tympanocentesis indicate that *M. catarrhalis* causes 15–20% of cases of acute otitis media. Acute otitis media caused by *M. catarrhalis* or nontypable *H. influenzae* is clinically milder than otitis media caused by *S. pneumoniae*, with less fever and a lower prevalence of a red bulging tympanic membrane. However, substantial overlap makes it impossible to predict etiology in an individual child on the basis of clinical features.

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. Cultures of sinus puncture aspirates show that *M. catarrhalis* accounts for ~20% of cases of acute bacterial sinusitis in children and for a smaller proportion in adults.

M. catarrhalis is a common cause of exacerbations in adults with COPD. The bacterium has been overlooked in this clinical setting because it has long been considered to be a commensal and because it is easily mistaken for commensal *Neisseria* species in cultures of respiratory secretions (see "Diagnosis," below). Several independent lines of evidence have established *M. catarrhalis* as a pathogen in COPD. These include (1) the demonstration of *M. catarrhalis* in the lower airways during exacerbations, (2) the association of exacerbation with acquisition of new strains, (3) elevations of inflammatory markers in association with *M. catarrhalis*, and (4) the development of specific immune responses following infection. *M. catarrhalis* is the second most common bacterial cause of COPD exacerbations (after *H. influenzae*), as shown in a 10-year prospective study; the distribution of exacerbations associated with new-strain acquisitions is shown in **Fig. 152-3**. Not included are culture-negative cases or cases from which a pathogen had been previously isolated. With the application of rigorous clinical criteria for defining the etiology of exacerbations (both culture-positive and culture-negative), ~10% of all exacerbations in the same study were caused by *M. catarrhalis*. The clinical features of an exacerbation due to *M. catarrhalis* are similar to those of exacerbations due to other bacterial pathogens, including *H. influenzae* and *S. pneumoniae*. The cardinal symptoms are cough with increased sputum production, sputum purulence, and dyspnea in comparison with baseline symptoms.

Pneumonia due to *M. catarrhalis* occurs in the elderly, particularly in the setting of underlying cardiopulmonary disease, but is infrequent. Invasive infections, such as bacteremia, endocarditis, neonatal meningitis, and septic arthritis, are rare.

DIAGNOSIS

Tympanocentesis is required for etiologic diagnosis of otitis media, but this procedure is not performed routinely. Therefore, treatment of otitis media is generally empirical. Similarly, an etiologic diagnosis of sinusitis requires an invasive procedure and thus is usually not available to the clinician. Isolation of *M. catarrhalis* from an expectorated sputum sample from an adult experiencing clinical symptoms of an exacerbation is suggestive, but not diagnostic, of *M. catarrhalis* as the cause.

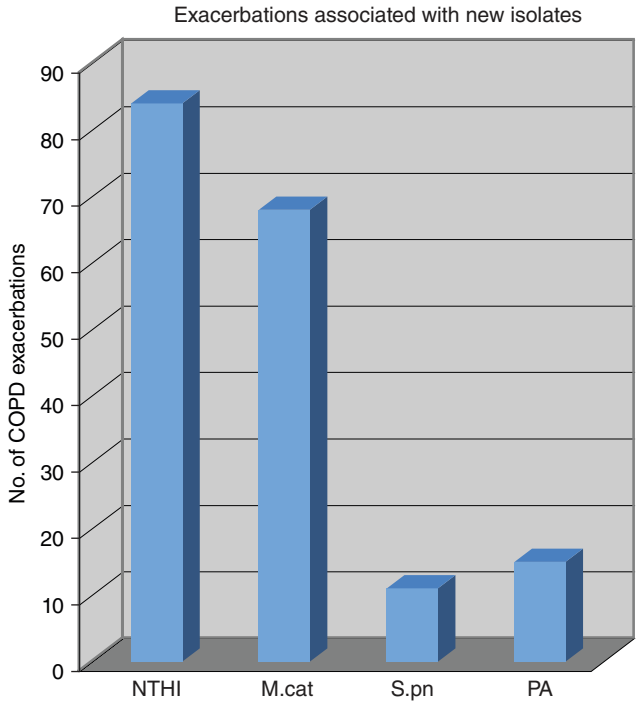

FIGURE 152-3 Cumulative results of a prospective study (1994–2004) of bacterial infection in chronic obstructive pulmonary disease (COPD) showing etiology of exacerbations. The numbers of exacerbations shown indicate the acquisition of a new strain simultaneous with clinical symptoms of an exacerbation. NTHI, nontypable *H. influenzae*; M.cat, *M. catarrhalis*; S.pn, *Streptococcus pneumoniae*; PA, *Pseudomonas aeruginosa*. *(Adapted from TF Murphy, GI Parameswaran: Clin Infect Dis 49:124, 2009, with permission. © 2009 Infectious Diseases Society of America.)*

Upon culture, colonies of *M. catarrhalis* resemble those of commensal neisseriae that are part of the normal upper airway flora. As mentioned above, the difficulty in distinguishing colonies of *M. catarrhalis* from neisserial colonies in cultures of respiratory secretions explains in part why *M. catarrhalis* has been overlooked as a pathogen. In contrast to these *Neisseria* species, *M. catarrhalis* colonies can be slid across the agar surface without disruption (the "hockey puck sign"). In addition, after 48 h of growth, *M. catarrhalis* colonies take on a pink color and tend to be larger than neisserial colonies. A variety of biochemical tests can distinguish *M. catarrhalis* from neisseriae. Kits that rely on these biochemical reactions are commercially available.

TREATMENT

Moraxella catarrhalis

M. catarrhalis rapidly acquired β-lactamases during the 1970s and 1980s; antimicrobial susceptibility patterns have remained relatively stable since that time, with >90% of strains now producing β-lactamase and thus resistant to amoxicillin. Otitis media in children and exacerbations of COPD in adults are generally managed empirically with antimicrobial agents that are active against *S. pneumoniae, H. influenzae*, and *M. catarrhalis*. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, newer macrolides (azithromycin, clarithromycin), trimethoprim-sulfamethoxazole, and fluoroquinolones. However, recent reports from several centers in Asia show substantial resistance to macrolides and fluoroquinolones, indicating emerging resistance. Continued monitoring of global antimicrobial susceptibility patterns of *M. catarrhalis* will be critical.

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153 Infections Due to the HACEK Group and Miscellaneous Gram-Negative Bacteria

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THE HACEK GROUP

HACEK organisms are a group of fastidious, slow-growing, gram-negative bacteria whose growth requires an atmosphere of carbon dioxide. These organisms do not grow on media routinely used for enteric bacteria (e.g., MacConkey agar). Species belonging to this group include several *Haemophilus* species, *Aggregatibacter* (formerly *Actinobacillus*) species, *Cardiobacterium* species, *Eikenella corrodens*, and *Kingella kingae*. HACEK bacteria normally reside in the oral cavity and have been associated with local infections in the mouth. They are also known to cause severe systemic infections—most often bacterial endocarditis, which can develop on either native or prosthetic valves **(Chap. 123)**. HACEK bacteremia is strongly predictive of underlying infective endocarditis (overall positive predictive value, 60%). However, this association varies significantly by organism. For example, in one study, infective endocarditis was diagnosed in 100% of patients with *Aggregatibacter actinomycetemcomitans* bacteremia but in no patients with *Eikenella* bacteremia.

In large series, 0.8–6% of cases of infective endocarditis are attributable to HACEK organisms, most often *Aggregatibacter* species, *Haemophilus* species, and *Cardiobacterium hominis*. Invasive infection typically occurs in patients with a history of cardiac valvular disease or prosthetic valves, often in the setting of a recent dental procedure or nasopharyngeal infection. The aortic and mitral valves are most commonly affected. The clinical course of HACEK endocarditis tends to be subacute, particularly with *Aggregatibacter* or *Cardiobacterium*. However, *K. kingae* endocarditis may have a more aggressive presentation. Compared with non-HACEK endocarditis, HACEK endocarditis occurs in younger patients and is more frequently associated with embolic, vascular, and immunologic manifestations. Systemic embolization is common. The overall prevalence of major emboli associated with HACEK endocarditis ranges from 28 to 71% in different series. On echocardiography, valvular vegetations are seen in up to 85% of patients. *Aggregatibacter* and *Haemophilus* species cause mitral valve vegetations most often; *Cardiobacterium* is associated with aortic valve vegetations.

The microbiology laboratory should be alerted when a HACEK organism is being considered. Most cultures that ultimately yield a HACEK organism become positive within the first week, especially with improved culture systems such as BACTEC. Studies have not shown that prolonged incubation increases laboratory recovery of clinically significant HACEK isolates. Polymerase chain reaction (PCR) techniques, such as gene amplification of 16S rRNA, can facilitate the diagnosis of HACEK infection of blood or cardiac valves. Other tools, such as matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry performed directly on agar colonies, can increase the accuracy and speed of diagnosis of HACEK infections.

Because of HACEK organisms' slow growth, antimicrobial susceptibility testing may be difficult, and β-lactamase production may not be detected. Resistance is most commonly noted in *Haemophilus* and *Aggregatibacter* species. Etest methodology may increase the accuracy of susceptibility testing. In recent studies, ceftriaxone and levofloxacin have been active against all isolates. The overall prognosis in both native-valve and prosthetic-valve HACEK endocarditis is excellent and is significantly better than that in endocarditis caused by non-HACEK pathogens.

***Haemophilus* Species** *Haemophilus parainfluenzae* is the most common *Haemophilus* species isolated from cases of HACEK endocarditis. Of patients with HACEK endocarditis due to *Haemophilus* species, 60% have been ill for <2 months before presentation, and 19–50% develop congestive heart failure. Mortality rates as high as 30–50% were reported in older series; however, more recent studies have documented mortality rates of <5%. *H. parainfluenzae* has been isolated from other infections, such as meningitis; brain, dental, pelvic, and liver abscess; pneumonia; urinary tract infection; and septicemia.

***Aggregatibacter* Species** *Aggregatibacter* species are the most common cause of HACEK endocarditis; the species most frequently involved are *A. actinomycetemcomitans*, *A.* (formerly *Haemophilus*) *aphrophilus*, and *A. paraphrophilus*. *Aggregatibacter* is associated with prosthetic-valve endocarditis more often than are *Haemophilus* species. *A. actinomycetemcomitans* can be isolated from soft tissue infections and abscesses in association with *Actinomyces israelii*. Typically, patients who develop *Aggregatibacter* endocarditis have periodontal disease or have recently undergone dental procedures in the setting of underlying cardiac valvular damage. The disease is insidious; patients may be sick for several months before diagnosis. Frequent complications include embolic phenomena, congestive heart failure, and renal failure.

A. actinomycetemcomitans has been isolated from patients with brain abscess, meningitis, endophthalmitis, parotitis, osteomyelitis, urinary tract infection, pneumonia, and empyema, among other infections. *A. aphrophilus* is often associated with bone and joint infection and is an important cause of brain abscess. In one series, *A. aphrophilus* was isolated from brain abscesses in 10% of cases—a rate that is disproportionate to its isolation from oral flora. This species has also been described as a cause of abscess in other organ systems.

***Cardiobacterium* Species** *Cardiobacterium* species, most often *C. hominis*, cause endocarditis primarily in patients with underlying valvular heart disease or with prosthetic valves. These organisms most frequently affect the aortic valve. Many patients have signs and symptoms of long-standing infection before diagnosis, with evidence of arterial embolization, vasculitis, cerebrovascular accidents, immune complex glomerulonephritis, or arthritis at presentation. Embolization, mycotic aneurysms, and congestive heart failure are common complications. A second species, *C. valvarum*, has been described in association with endocarditis.

Eikenella corrodens *E. corrodens* is most frequently recovered from sites of infection in conjunction with other bacterial species. Clinical sources of *E. corrodens* include sites of human bite wounds (clenched-fist injuries), endocarditis, soft tissue infections, osteomyelitis, head and neck infections, respiratory infections, chorioamnionitis, gynecologic infections associated with intrauterine devices, meningitis, brain abscesses, and visceral abscesses. This organism is the least common cause of HACEK endocarditis.

Kingella kingae More than half of cases of *K. kingae* infection are bone and joint infections; the majority of the remaining infections are infective endocarditis, bacteremia, and meningitis. Invasive *K. kingae* infections with bacteremia are associated with upper respiratory tract infections and stomatitis in 80% of cases. Rates of oropharyngeal colonization with *K. kingae* are highest in the first 3 years of life (detected in

~10% of children); colonization coincides with an increased incidence of skeletal infections and other invasive infections due to this organism from the age of 6 months to 4 years. *K. kingae* can be transmitted from child to child and has been the cause of outbreaks among young children. *K. kingae* bacteremia can present with a petechial rash similar to that seen in *Neisseria meningitidis* sepsis.

Because of improved microbiologic methodology and molecular methods such as real-time PCR, the isolation of *K. kingae* is increasingly common. Inoculation of clinical specimens (e.g., synovial fluid) into aerobic blood culture bottles enhances recovery of this organism. PCR studies of blood or joint fluid can identify *K. kingae* in culture-negative cases. Some studies have demonstrated that *K. kingae* has surpassed *Staphylococcus aureus* as the leading cause of septic arthritis and osteomyelitis in children.

Infective endocarditis, unlike other infections with *K. kingae*, occurs in older children and adults. The majority of patients have preexisting valvular disease. There is a high incidence of complications, including arterial emboli, cerebrovascular accidents, tricuspid insufficiency, and congestive heart failure with cardiovascular collapse.

TREATMENT

HACEK Endocarditis

(Table 153-1) Ceftriaxone (2 g/d) is first-line therapy for HACEK endocarditis. Data on the use of levofloxacin (750 mg/d) for HACEK endocarditis remain limited, but this drug can be considered an alternative for treatment of patients intolerant of β-lactam therapy. Of note, *Eikenella* is resistant to clindamycin, metronidazole, and aminoglycosides.

Native-valve endocarditis should be treated for 4 weeks with antibiotics, whereas prosthetic-valve endocarditis requires 6 weeks of therapy. The cure rates for HACEK prosthetic-valve endocarditis appear to be high. Unlike prosthetic-valve endocarditis caused by other gram-negative organisms, HACEK endocarditis is often cured with antibiotic treatment alone—i.e., without surgical intervention.

OTHER FASTIDIOUS GRAM-NEGATIVE BACTERIA

***Capnocytophaga* Species** Like HACEK organisms, this genus of fastidious, fusiform, gram-negative coccobacilli is facultatively anaerobic and requires an atmosphere enriched in carbon dioxide for optimal growth. *Capnocytophaga* species such as *C. ochracea*, *C. gingivalis*, *C. haemolytica*, and *C. sputigena* are part of the oral flora; most infections are contiguous with the oropharynx (e.g., periodontal disease, respiratory tract infections, cervical abscesses, endophthalmitis). These organisms have also been associated with sepsis in immunocompromised hosts, particularly neutropenic patients with oral ulcerations, meningitis, endocarditis, cellulitis, osteomyelitis, and septic arthritis. *Capnocytophaga* species have been isolated from many other sites as well, usually as part of a polymicrobial infection. There is a high prevalence of resistance to β-lactams and macrolides in *Capnocytophaga*; the oral cavity serves as a reservoir for resistance genes to those agents.

C. canimorsus and *C. cynodegmi* are endogenous to the canine and feline mouth **(Chap. 136)**. Patients infected with these species frequently have a history of dog or cat bites or of exposure without scratches or bites. Asplenia, glucocorticoid therapy, and alcohol abuse are predisposing conditions that can be associated with severe sepsis with shock and disseminated intravascular coagulation. Patients typically have a petechial rash that can progress from purpuric lesions to gangrene.

TREATMENT

Capnocytophaga Infections

(Table 153-1) Because of increasing β-lactamase production, a penicillin derivative plus a β-lactamase inhibitor—such as ampicillin/sulbactam (1.5–3.0 g of ampicillin every 6 h)—is currently recommended for empirical treatment of infections caused by *Capnocytophaga* species. If the isolate is known to be susceptible, infections with *C. canimorsus* should be treated with penicillin (12–18 million units every 4 h). *Capnocytophaga* is also susceptible to clindamycin (600–900 mg every 6–8 h) and third-generation cephalosporins such as ceftriaxone (2 g every 12–24 h). Antibiotics should be given prophylactically to asplenic patients who have sustained dog-bite injuries.

Pasteurella multocida *P. multocida* is a fastidious, bipolar-staining, gram-negative coccobacillus that colonizes the respiratory and gastrointestinal tracts of domestic animals; oropharyngeal colonization rates are 70–90% in cats and 50–65% in dogs. *P. multocida* can be transmitted to humans through bites or scratches, via the respiratory tract from contact with contaminated dust or infectious droplets, or via deposition of the organism on injured skin or mucosal surfaces during licking. Most human infections affect skin and soft tissue; almost two-thirds of these infections are caused by cats. Patients at the extremes of age or with serious underlying disorders (e.g., cirrhosis, diabetes) are at increased risk for systemic manifestations, including meningitis, peritonitis, osteomyelitis and septic arthritis, endocarditis, septic shock, and purpura fulminans, and are more likely not to have evidence of an animal bite. However, cases have also occurred in healthy individuals of all ages. If inhaled, *P. multocida* can cause acute respiratory tract infection, particularly in patients with underlying sinus and pulmonary disease.

TREATMENT

Pasteurella multocida Infections

(Table 153-1) *P. multocida* is susceptible to penicillin, ampicillin, ampicillin/sulbactam, second- and third-generation cephalosporins, tetracyclines, and fluoroquinolones. β-Lactamase-producing strains have been reported.

TABLE 153–1 Treatment of Infections Caused by HACEK-Group and Other Fastidious Gram–Negative Organisms

ORGANISMS	PREFERRED THERAPY	ALTERNATIVE AGENTS	COMMENTS
Haemophilus spp. *Aggregatibacter* spp. *Cardiobacterium* spp. *Eikenella corrodens* *Kingella kingae*	Ceftriaxone (2 g/d)	Ampicillin/sulbactam (3 g of ampicillin q6h) Levofloxacin (750 mg/d)	Ampicillin/sulbactam resistance has been described in *Haemophilus* and *Aggregatibacter* spp. Data on use of levofloxacin for endocarditis therapy are limited. Fluoroquinolones are not recommended for treatment of patients <18 years of age. Penicillin (16–18 million units q4h) or ampicillin (2 g q4h) can be used if the organism is susceptible. However, because of the slow growth of HACEK bacteria, antimicrobial testing may be difficult, and β-lactamase production may not be detected.
Capnocytophaga spp.	Ampicillin/sulbactam (1.5–3 g of ampicillin q6h)	Ceftriaxone (2 g/d q12–24h)	Penicillin (12–18 million units q4h) should be used if the isolate is known to be susceptible.
Pasteurella multocida	Ampicillin/sulbactam (1.5–3 g of ampicillin q6h)	Ceftriaxone (1–2 g/d q12–24h)	Penicillin should be used if the isolate is known to be susceptible. *P. multocida* is also susceptible to tetracyclines and fluoroquinolones.

Achromobacter xylosoxidans *Achromobacter* (previously *Alcaligenes*) *xylosoxidans* is an aerobic nonfermenting gram-negative organism that is probably part of the endogenous intestinal flora. It has been isolated from a variety of water sources, including well water, IV fluids, and humidifiers. Immunocompromised hosts, including patients with cancer and postchemotherapy neutropenia, cirrhosis, chronic renal failure, and cystic fibrosis, are at increased risk for infection. Nosocomial outbreaks and pseudo-outbreaks of *A. xylosoxidans* infection have been attributed to contaminated fluids, and clinical illness has been associated with isolates from many sites, including blood (often in the setting of intravascular devices). Community-acquired *A. xylosoxidans* bacteremia usually occurs in the setting of pneumonia. Metastatic skin lesions are present in one-fifth of cases. The reported mortality rate is as high as 67%—a figure similar to rates for other bacteremic gram-negative pneumonias.

TREATMENT

Achromobacter xylosoxidans Infections

(Table 153-2) Treatment is based on in vitro susceptibility testing of all clinically relevant isolates; multidrug resistance is common. Carbapenems, tigecycline, and colistin are typically the most active agents.

***Aeromonas* Species** *Aeromonas* is a facultative anaerobic gram-negative bacterium. *Aeromonas* infections are most often caused by *A. hydrophila*, *A. caviae*, *A. veronii*, and *A. dhakensis*. *Aeromonas* proliferates in potable water, freshwater, and soil. It remains controversial whether *Aeromonas* is a cause of bacterial gastroenteritis; asymptomatic colonization of the intestinal tract with *Aeromonas* occurs frequently, and no clonally related diarrheal outbreak has been documented. However, rare cases of hemolytic-uremic syndrome following bloody diarrhea have been shown to be secondary to the presence of *Aeromonas*.

Aeromonas causes health care–associated sepsis and bacteremia in infants with multiple medical problems and in immunocompromised hosts, particularly those with cancer or hepatobiliary disease, including cirrhosis. *A. caviae* is associated with health care–related bacteremia. Community-acquired infections include bacteremia, spontaneous bacterial peritonitis, biliary tract infections, and skin and soft tissue infections. Severe soft tissue infections such as necrotizing fasciitis are more common in Taiwan than in Western countries; *Aeromonas* was the most common pathogen associated with skin and soft tissue infections after the tsunami in Thailand. *Aeromonas* infection and sepsis can occur in patients with trauma (including severe trauma with myonecrosis), patients with seawater-contaminated wounds, and burn patients exposed to the organism by environmental (freshwater or soil) wound contamination. Reported mortality rates range from 25% among immunocompromised adults with sepsis to >90% among patients with myonecrosis. Patients with *A. dhakensis* bacteremia have higher 14-day mortality rates than do those whose bacteremia is attributable to other species. *Aeromonas* can produce ecthyma gangrenosum (hemorrhagic vesicles surrounded by a rim of erythema with central necrosis and ulceration; see Fig. A1-34) resembling the lesions seen in *Pseudomonas aeruginosa* infection. This organism causes nosocomial infections related to catheters, surgical incisions, or use of leeches. Other manifestations include meningitis, peritonitis, pneumonia, and ocular infections.

TABLE 153-2 Treatment Options for Other Selected Gram-Negative Bacteria[a]

ORGANISM	TREATMENT OPTIONS
Achromobacter xylosoxidans	Carbapenems, tigecycline, colistin
Aeromonas spp.	Fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems, aminoglycosides
Elizabethkingia/Chryseobacterium spp.	Fluoroquinolones, minocycline, tigecycline, piperacillin/tazobactam
Rhizobium radiobacter	Fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems
Shewanella spp.	Fluoroquinolones, third- and fourth-generation cephalosporins, β-lactam/β-lactamase inhibitors, carbapenems, aminoglycosides
Chromobacterium violaceum	Carbapenems, fluoroquinolones, trimethoprim-sulfamethoxazole

[a]Treatment should be based on in vitro susceptibility testing; multidrug resistance is common among these organisms.

TREATMENT

Aeromonas Infections

(Table 153-2) *Aeromonas* species are generally susceptible to fluoroquinolones (e.g., ciprofloxacin at a dosage of 500 mg every 12 h PO or 400 mg every 12 h IV), third- and fourth-generation cephalosporins, carbapenems, and aminoglycosides, but resistance to all those agents has been described. Because *Aeromonas* can produce various β-lactamases, including carbapenemases, susceptibility testing must be used to guide therapy. Antibiotic prophylaxis (e.g., with ciprofloxacin) is indicated when medicinal leeches are used.

***Elizabethkingia/Chryseobacterium* Species** *Elizabethkingia meningoseptica* (formerly *Chryseobacterium meningosepticum*), a nonfastidious aerobic nonfermentative gram-negative bacillus, is an important cause of nosocomial infections, including outbreaks due to contaminated fluids (e.g., contaminated sinks, disinfectants, and aerosolized antibiotics) and sporadic infections due to indwelling devices, feeding tubes, and other fluid-associated apparatuses. Outbreaks due to this organism have persisted until extensive cleaning of environmental surfaces and equipment has been performed. Most published reports have originated from Taiwan. Nosocomial *E. meningoseptica* infection usually involves preterm neonates, patients with underlying immunosuppression (e.g., related to malignancy or diabetes), or patients exposed to antibiotics in intensive care. *E. meningoseptica* has been reported to cause meningitis (primarily in neonates), pneumonia, sepsis, endocarditis, bacteremia, eye infections, and soft tissue infections.

Chryseobacterium indologenes has caused bacteremia, sepsis, and pneumonia, typically in immunocompromised patients with indwelling devices. Mortality rates have been as high as 50% in some reports; it is unclear whether a poor prognosis is related to underlying comorbidities or to the multidrug-resistant phenotype of the organism.

TREATMENT

Elizabethkingia/Chryseobacterium Infections

(Table 153-2) These organisms are often susceptible to fluoroquinolones, minocycline, tigecycline, and rifampin. They may be susceptible to β-lactam/β-lactamase inhibitor combinations such as piperacillin/tazobactam but can possess extended-spectrum β-lactamases and metallo-β-lactamases. In vitro susceptibility testing often indicates activity of agents used against gram-positive bacteria (e.g., vancomycin), but it is unclear that those agents are reliable clinically. Combination therapy may be needed for successful treatment. Susceptibility testing should be performed to guide the choice of optimal agents.

MISCELLANEOUS ORGANISMS

Rhizobium (formerly *Agrobacterium) radiobacter* has usually been associated with infection in the presence of medical devices, including intravascular catheter–related infections, prosthetic-joint and prosthetic-valve infections, and peritonitis caused by dialysis catheters. Cases of endophthalmitis after cataract surgery also have been described. Most *R. radiobacter* infections occur in immunocompromised hosts, especially individuals with malignancy or HIV infection. Strains are usually susceptible to fluoroquinolones, third- and fourth-generation cephalosporins, and carbapenems (Table 153-2).

Shewanella species are ubiquitous nonfermentative gram-negative organisms found in seawater and marine environments. Human disease is caused primarily by *S. putrefaciens* and *S. algae*; *S. algae* may be the more virulent species. Most infections involve skin and soft tissue, ranging from impetigo to necrotizing fasciitis. Patients are exposed to the organism through contact of bites, open wounds, or devitalized tissue with seawater, marine animals, or fresh seafood or through ingestion of seawater or of raw or undercooked seafood, especially shellfish. *Shewanella* species also cause chronic ulcers of the lower extremities, osteomyelitis, biliary tract infections, pneumonia, bacteremia, sepsis, and potentially chronic otitis media. A fulminant course is associated with cirrhosis, hemochromatosis, diabetes mellitus, malignancy, or other severe underlying conditions. In one series of cases from Martinique, 13% of infections were fatal. These organisms are often susceptible to fluoroquinolones, third- and fourth-generation cephalosporins, β-lactam/β-lactamase inhibitors, carbapenems, and aminoglycosides (Table 153-2).

Chromobacterium violaceum is a facultative anaerobic organism found in soil and water in tropical or subtropical regions. After exposure, it can cause rare but serious—often fatal—skin and soft tissue infections of limbs. Life-threatening infections with severe sepsis and metastatic abscesses occur most often in patients with underlying illness, particularly in children with defective neutrophil function (e.g., those with chronic granulomatous disease). *C. violaceum* is frequently resistant to multiple drugs; carbapenems are most often used empirically. Fluoroquinolones and trimethoprim-sulfamethoxazole also can be active (Table 153-2).

Ochrobactrum anthropi causes infections related to central venous catheters in compromised hosts; other invasive infections such as bacteremia have been described. *Pseudomonas* (formerly *Flavimonas*) *oryzihabitans* can cause catheter-related bloodstream infections in immunocompromised patients. *Sphingobacterium* is a rare cause of human infection in immunocompromised hosts. It can colonize hospital water systems, respiratory tract equipment, and laboratory instruments. *Ralstonia* species also can contaminate water supplies, including hospital water systems. Cases of bacteremia, osteomyelitis, pneumonia, and meningitis have been described. Other organisms implicated in human infections include *Weeksella* species; various CDC groups, such as Ve-1 and Ve-2; and *Oligella urethralis*. The reader is advised to consult subspecialty texts and references for further guidance on these organisms.

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154 *Legionella* Infections

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Legionellosis refers to the two clinical syndromes caused by bacteria of the genus *Legionella*. *Pontiac fever* is an acute, febrile, self-limited illness that has been serologically linked to *Legionella* species, whereas *Legionnaires' disease* is the designation for pneumonia caused by these species. Legionnaires' disease was first recognized in 1976, when an outbreak of pneumonia took place at a Philadelphia hotel during an American Legion convention.

MICROBIOLOGY

The family Legionellaceae comprises more than 50 species with more than 70 serogroups. The species *Legionella pneumophila* causes 80–90% of human infections and includes at least 16 serogroups; serogroups 1, 4, and 6 are most commonly implicated in human infections. To date, 18 species other than *L. pneumophila* have been associated with human infections, among which *L. micdadei* (Pittsburgh pneumonia agent), *L. bozemanii*, *L. dumoffii*, and *L. longbeachae* are the most common. Members of the Legionellaceae are aerobic gram-negative bacilli that do not grow on routine microbiologic media. Buffered charcoal yeast extract (BCYE) agar is the medium used to grow *Legionella*.

ECOLOGY AND TRANSMISSION

The natural habitats for *L. pneumophila* are aquatic bodies, including lakes and streams. *L. longbeachae* has been isolated from natural soil. Commercial potting soil has been suggested as the reservoir for *L. longbeachae* infections in Australia and New Zealand. *Legionella* can survive under a wide range of environmental conditions; for example, the organisms can live for years in refrigerated water samples. Natural bodies of water contain only small numbers of legionellae. However, once the organisms enter human-constructed aquatic reservoirs (such as drinking-water systems), they can grow and proliferate. Factors known to enhance colonization by and amplification of *Legionella* include warm temperatures (25–42°C) and the presence of scale and sediment. *L. pneumophila* can form microcolonies within biofilms; its eradication from drinking-water systems requires disinfectants that can penetrate the biofilm. The presence of symbiotic microorganisms, including algae, amebas, ciliated protozoa, and other water-dwelling bacteria, promotes the growth of *Legionella*. The organisms can invade and multiply within free-living protozoa.

Heavy rainfall and flooding can result in the entry of high numbers of legionellae into water-distribution systems, leading to an upsurge of cases. Climate change may be a factor in the apparent increase in incidence of Legionnaires' disease worldwide.

Large buildings over three stories high are commonly colonized with *Legionella*. Sporadic community-acquired Legionnaires' disease has been linked to colonization of hotels, office buildings, factories, and even private homes. Drinking-water systems in hospitals and extended-care facilities have been the source for health care–associated Legionnaires' disease.

In contrast, cooling towers and evaporative condensers have been overestimated as sources of *Legionella* causing human illness. Early investigations that implicated cooling towers antedated the discovery that the organism could also exist in drinking water. In many outbreaks attributed to cooling towers, cases of Legionnaires' disease continued to occur despite disinfection of the cooling towers; drinking water was found to be the actual source. Koch's postulates have never been fulfilled for *Legionella* links to cooling tower–associated outbreaks as they have been for hospital-acquired Legionnaires' disease. Nevertheless, cooling towers have, in rare instances, been implicated in community-acquired outbreaks, including outbreaks in Murcia, Spain, and Bronx, New York. As mentioned above, *L. longbeachae* infections have been linked to potting soil, but the mode of transmission remains to be clarified.

Multiple modes of transmission of *Legionella* to humans exist, including aerosolization, aspiration, and direct instillation into the lungs during respiratory tract manipulations. Aspiration is now known to be the predominant mode of transmission, but it is unclear whether *Legionella* enters the lungs via oropharyngeal colonization or directly via the drinking of contaminated water. Oropharyngeal colonization with *Legionella* has been demonstrated in patients undergoing transplantation. Nasogastric tubes have been linked to hospital-acquired Legionnaires' disease; microaspiration of contaminated water was the hypothesized mode of transmission. Surgery with general anesthesia is a known risk factor that is consistent with aspiration. The incidence of postoperative Legionnaires' disease was 30% among patients

undergoing head and neck surgery at a hospital with a contaminated water supply; aspiration is a recognized postoperative complication in such cases. Patients with hospital-acquired Legionnaires' disease underwent endotracheal intubation significantly more often and for a significantly longer duration than patients with hospital-acquired pneumonias of other etiologies.

Aerosolization of *Legionella* by devices filled with tap water, including whirlpools, nebulizers, and humidifiers, have been linked to cases in patients. An ultrasonic mist machine in the produce section of a grocery store was the source in a community outbreak. Pontiac fever has been linked to *Legionella*-containing aerosols from water-using machinery, a cooling tower, air conditioners, and whirlpools.

EPIDEMIOLOGY

Community-Acquired Pneumonia The incidence of Legionnaires' disease depends on the degree of contamination of the aquatic reservoir, the immune status of the persons exposed to water from that reservoir, the intensity of exposure, and the availability and use of specialized laboratory tests on which the correct diagnosis can be based. *Legionella* is an underestimated cause of community-acquired pneumonia; on the basis of a multihospital study of community-acquired pneumonia in Ohio, the Centers for Disease Control and Prevention (CDC) estimated that only 3% of community-acquired Legionnaires' disease cases are diagnosed. Observational studies of community-acquired pneumonia showed that Legionnaires' disease went largely unrecognized unless *Legionella* diagnostic testing was routinely applied to all patients with pneumonia; such studies in Spain, Germany, and Taiwan stimulated an upsurge in the detection of cases throughout Europe and Asia.

Hospital-Acquired Pneumonia *Legionella* is responsible for 10–50% of cases of nosocomial pneumonia when a hospital's water system is colonized with the organisms. The incidence of hospital-acquired Legionnaires' disease depends on the degree of contamination of drinking water, as defined by the rate of positivity of distal water sites; in contrast, the use of quantitative criteria of the number of colony-forming units per milliliter has proven useless.

Proactive culture of the hospital water supply has increased the detection of hospital-acquired Legionnaires' disease and simultaneously allowed expeditious diagnosis resulting in early administration of antibiotic therapy. In the early years after its recognition, Legionnaires' disease was documented primarily in the United States. As diagnostic modalities (especially the urinary antigen test) became more widely used, cases subsequently appeared worldwide.

Risk factors for Legionnaires' disease include cigarette smoking, chronic lung disease, advanced age, and prior hospitalization with discharge within 10 days before onset of pneumonia symptoms. Immunosuppressive conditions that predispose to Legionnaires' disease include transplantation and treatment with glucocorticoids or tumor necrosis factor α antagonists. However, in a large prospective study of community-acquired pneumonia, 28% of patients with Legionnaires' disease did not have these classic risk factors. Hospital-acquired cases are now being recognized among neonates and immunosuppressed children.

Pneumonia in Transplant Recipients Transplant recipients appear to be at unusually high risk of *Legionella* pneumonia. This elevated risk may be due to diagnostic bias, given the extensive workup for opportunistic pathogens as well as long-standing immunosuppression. Legionnaires' disease usually occurs during the 3 months after transplantation. Cavitation on chest radiograph is seen more frequently in transplant recipients, and mortality rates are higher.

Pontiac Fever Pontiac fever occurs in epidemics. The high attack rate (>90%) reflects airborne transmission.

PATHOGENESIS AND IMMUNITY

Legionella enters the lungs through aspiration or direct inhalation. Attachment to host cells is mediated by bacterial type IV pili, heat-shock proteins, a major outer-membrane protein, and complement. Because the organism possesses pili that mediate adherence to respiratory tract epithelial cells, conditions that impair mucociliary clearance, including cigarette smoking, lung disease, or alcoholism, predispose to Legionnaires' disease.

Both innate and adaptive immune responses play a role in host defense. Toll-like receptors mediate recognition of *L. pneumophila* in alveolar macrophages and enhance early neutrophil recruitment to the site of infection. After phagocytosis, *L. pneumophila* evades intracellular killing by inhibiting phagosome–lysosome fusion. Although many legionellae are killed, some proliferate intracellularly until the cells rupture; the bacteria are then phagocytosed again by newly recruited phagocytes, and the cycle begins anew. The role of neutrophils in immunity appears to be minimal: neutropenic patients are not predisposed to Legionnaires' disease. Although *L. pneumophila* is susceptible to oxygen-dependent microbiologic systems in vitro, it resists killing by neutrophils. The humoral immune system is active against *Legionella*. Type-specific IgM and IgG antibodies are measurable within weeks of infection. In vitro, antibodies promote killing of *Legionella* by phagocytes (neutrophils, monocytes, and alveolar macrophages). Immunized animals develop a specific antibody response, with subsequent resistance to *Legionella* challenge. However, antibodies neither enhance lysis by complement nor inhibit intracellular multiplication within phagocytes.

The genome of *L. pneumophila* has been sequenced. A broad range of membrane transporters within the genome are thought to optimize the use of nutrients in water and soil. Some *L. pneumophila* strains are clearly more virulent than others, although the precise factors mediating virulence remain uncertain. For example, although multiple strains may colonize water-distribution systems, only a few cause disease in patients exposed to water from these systems. At least one surface epitope of *L. pneumophila* serogroup 1 is associated with virulence. Monoclonal antibody subtype mAb2 has been linked to virulence. *L. pneumophila* serogroup 6 is more commonly involved in hospital-acquired Legionnaires' disease and is especially likely to be associated with a poor outcome.

CLINICAL AND LABORATORY FEATURES

Pontiac Fever Pontiac fever is an acute, self-limiting, flu-like illness with an incubation period of 24–48 h. Pneumonia does not develop. Malaise, fatigue, and myalgias are the most common symptoms, occurring in 97% of cases. Fever (usually with chills) develops in 80–90% of cases and headache in 80%. Other symptoms (seen in <50% of cases) include arthralgias, nausea, cough, abdominal pain, and diarrhea. Modest leukocytosis with a neutrophilic predominance is sometimes detected. Complete recovery occurs within a few days; antibiotic therapy is unnecessary. A few patients may experience lassitude for some weeks after recovery. The diagnosis is established by antibody seroconversion. Pontiac fever due to *L. longbeachae* has also been reported in individuals exposed to potting soil.

Legionnaire's Disease (Pneumonia) Legionnaires' disease is often included in the differential diagnosis of "atypical pneumonia," along with pneumonia due to *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, and some viruses. The clinical similarities among "atypical" pneumonias include a nonproductive cough with a low frequency of grossly purulent sputum. The clinical manifestations of Legionnaires' disease are usually more severe than those of most "atypical" pneumonias. The course and prognosis of *Legionella* pneumonia more closely resemble those of bacteremic pneumococcal pneumonia than those of pneumonia due to other "atypical" pathogens. Patients with community-acquired Legionnaires' disease are significantly more likely than patients with pneumonia of other etiologies to be admitted to an intensive care unit on presentation.

The incubation period for Legionnaires' disease is usually 2–10 days, although slightly longer incubation periods have been documented. The presence of fever is almost universal. Temperatures in excess of 40°C (104°F) were seen in 20% of patients in one observational study. The symptoms and signs may range from a mild cough and a slight

TABLE 154-1 Clinical Clues Suggestive of Legionnaires' Disease

Diarrhea
High fever (>40°C; >104°F)
Numerous neutrophils but no organisms revealed by Gram's staining of respiratory secretions
Hyponatremia (serum sodium level <131 mg/dL)
Failure to respond to β-lactam drugs (penicillins or cephalosporins) and aminoglycoside antibiotics
Occurrence of illness in an environment in which the potable water supply is known to be contaminated with *Legionella*
Onset of symptoms within 10 days after discharge from the hospital (hospital-acquired legionellosis manifesting after discharge or transfer)

fever to stupor with widespread pulmonary infiltrates and multisystem failure. The mild cough of Legionnaires' disease is only slightly productive. Sometimes the sputum is streaked with blood. Chest pain—either pleuritic or nonpleuritic—can be a prominent feature and, when coupled with hemoptysis, can lead to an incorrect diagnosis of pulmonary embolism. Shortness of breath is reported by one-third to one-half of patients. Gastrointestinal difficulties are often pronounced; abdominal pain, nausea, and vomiting affect 10–20% of patients. Diarrhea (watery rather than bloody) is reported in 25–50% of cases. The most common neurologic abnormalities are confusion or changes in mental status; however, the multitudinous neurologic symptoms reported range from headache and lethargy to encephalopathy. Nonspecific symptoms—malaise, fatigue, anorexia, and headache—are seen early in the illness. Myalgias and arthralgias are uncommon but are prominent in a few patients. Upper respiratory symptoms, including coryza, are rare.

Relative bradycardia has been overemphasized as a useful diagnostic finding; it occurs primarily in older patients with severe pneumonia. Chest examination reveals rales early in the course and evidence of consolidation as the disease progresses. Abdominal examination may reveal generalized or local tenderness.

Although the clinical manifestations often considered classic for Legionnaires' disease may suggest the diagnosis **(Table 154-1)**, prospective comparative studies have shown that clinical manifestations are generally nonspecific and that Legionnaires' disease is not readily distinguishable from pneumonia of other etiologies. In a review of 13 studies of community-acquired pneumonia, clinical manifestations that occurred significantly more often in Legionnaires' disease included diarrhea, neurologic findings (including confusion), and a temperature of >39°C (>102.2°F). Hyponatremia, elevated values in liver function tests, and hematuria also occurred more frequently in Legionnaires' disease. Other laboratory abnormalities include creatine phosphokinase elevation, hypophosphatemia, serum creatinine elevation, and proteinuria.

Sporadic cases of Legionnaires' disease appear to be more severe than outbreak-associated and hospital-acquired cases, presumably because their diagnosis is delayed. Results of the German CAPNETZ Study showed that, among cases of community-acquired *Legionella* pneumonia, ambulatory patients were as common as hospitalized patients.

Extrapulmonary Legionellosis Since the portal of entry for *Legionella* is the lung in virtually all cases, extrapulmonary manifestations usually result from bloodborne dissemination from the lung. *Legionella* has been identified in lymph nodes, spleen, liver, or kidneys in autopsied cases. Sinusitis, peritonitis, pyelonephritis, skin and soft-tissue infection, septic arthritis, and pancreatitis have developed predominantly in immunosuppressed patients. The most severe sequela, neurologic dysfunction, is rare but can be debilitating. The most common neurologic deficits in the long term—ataxia and speech difficulties—result from cerebellar dysfunction.

Cardiac abnormalities may occur without pneumonia; *Legionella*-contaminated water can enter through an IV injection site, chest tube, or surgical wound, with subsequent seeding of a prosthetic valve, the myocardium, or the pericardium.

Chest Radiography Virtually all patients with Legionnaires' disease have abnormal chest radiographs showing pulmonary infiltrates at the time of clinical presentation. In a few cases of hospital-acquired disease, fever and respiratory tract symptoms have preceded the radiographic appearance of the infiltrate. Radiologic findings are nonspecific. Pleural effusion is evident in 28–63% of patients on hospital admission. In immunosuppressed patients, especially those receiving glucocorticoids, distinctive rounded nodular opacities may be seen; these lesions may expand and cavitate **(Fig. 154-1)**. Likewise, abscesses can occur in immunosuppressed hosts. The progression of infiltrates and pleural effusion on chest radiography despite appropriate antibiotic therapy within the first week is common, and radiographic improvement lags behind clinical improvement by several days. Complete clearing of infiltrates requires 1–4 months. CT scan is more sensitive than chest radiography and may show more extensive disease. A CT scan should be obtained if fever persists during treatment with presumably effective antibiotics **(Fig. 154-2)**.

DIAGNOSIS

Given the nonspecific clinical manifestations of Legionnaires' disease and the high mortality rates for untreated Legionnaires' disease, the use of *Legionella* testing—especially the *Legionella* urinary antigen test—is recommended for all patients with community-acquired pneumonia, including patients with ambulatory pneumonia and hospitalized children. *Legionella* cultures should be made more widely available since the urinary antigen test can diagnose only *L. pneumophila* serogroup 1. Hospitals in which the drinking water is known to be colonized with *Legionella* species should have *Legionella* cultures routinely available.

The diagnosis of Legionnaires' disease requires special microbiologic tests **(Table 154-2)**. The sensitivity of bronchoscopy specimens is similar to that of sputum samples for culture on selective media; if

FIGURE 154-1 Chest radiographic findings in a 52-year-old man who presented with pneumonia subsequently diagnosed as Legionnaires' disease. The patient was a cigarette smoker with chronic obstructive pulmonary disease and alcoholic cardiomyopathy; he had received glucocorticoids. *Legionella pneumophila* was identified by direct fluorescent antibody staining and culture of sputum. ***Left:*** Baseline chest radiograph showing long-standing cardiomegaly. ***Center:*** Admission chest radiograph showing new rounded opacities. ***Right:*** Chest radiograph taken 3 days after admission, during treatment with erythromycin.

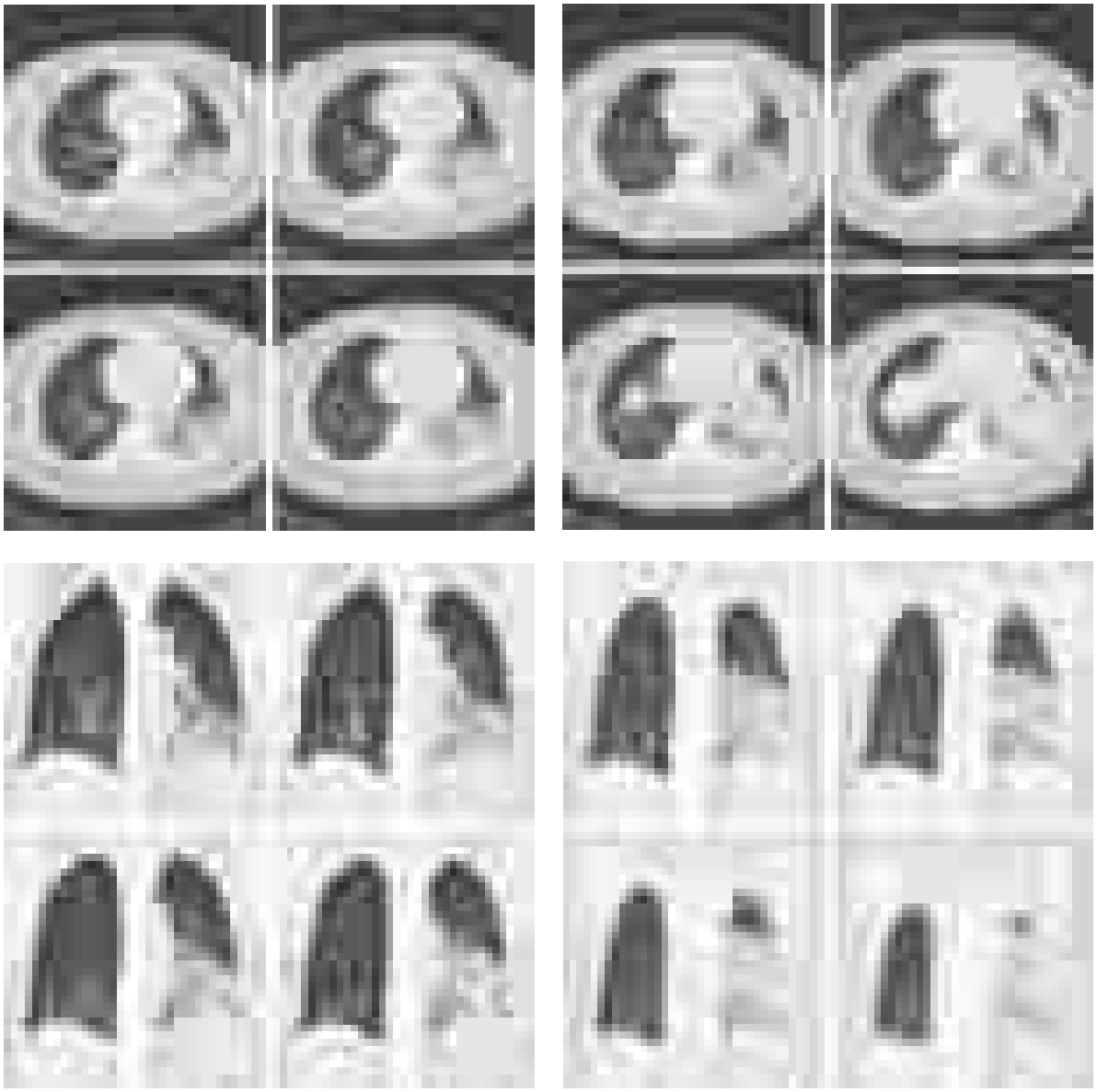

FIGURE 154-2 CT findings in a 49-year-old woman with no underlying conditions who presented with community-acquired pneumonia. CT revealed multilobar infiltrates, some of which were not as prominent on chest x-ray. Cultures of both the patient's sputum and her home water supply yielded *Legionella pneumophila* serogroup 1. *(Images courtesy of Dr. Wen-Chien Ko, National Cheng Kung University Hospital, Tainan, Taiwan.)*

sputum is not available, bronchoscopy specimens may yield the organism. Bronchoalveolar lavage fluid gives higher yields than bronchial wash specimens. Thoracentesis should be performed if pleural effusion is found, and the fluid should be evaluated by direct fluorescent antibody (DFA) staining, culture, and the antigen assay designed for use with urine.

TABLE 154-2 Utility of Special Laboratory Tests for the Diagnosis of Legionnaires' Disease

TEST	SENSITIVITY, %	SPECIFICITY, %
Culture		
Sputum[a]	80	100
Transtracheal aspirate	90	100
Direct fluorescent antibody staining of sputum	50–70	96–99
Urinary antigen testing[b]	70	100
Antibody serology[c]	40–60	96–99

[a]Use of multiple selective media with dyes. [b]Reliable only for *L. pneumophila* serogroup 1. [c]IgG and IgM testing of both acute- and convalescent-phase sera. A single titer of ≥1:256 is considered presumptive, while a fourfold rise in titer between the acute and convalescent phases is considered definitive. Titers peak at 3 months.

Stains Gram's staining of material from normally sterile sites, such as pleural fluid or lung tissue, occasionally suggests the diagnosis; efforts to detect *Legionella* in sputum by Gram's staining typically reveal numerous leukocytes but no organisms. When they are visualized, the organisms appear as small, pleomorphic, faint, gram-negative bacilli. *L. micdadei* organisms can be detected as weakly or partially acid-fast bacilli in clinical specimens.

The DFA stain is rapid and highly specific but is less sensitive than culture because large numbers of organisms are required for microscopic visualization. This test is more likely to be positive in advanced than in early disease.

Culture The "gold-standard" method for diagnosis of *Legionella* infection is isolation of the organism from respiratory secretions, although culture for 3–5 days—and sometimes up to 2 weeks for non-*pneumophila* species—is required. Antibiotics added to the medium suppress the growth of competing flora from nonsterile sites, and dyes color the colonies and assist in identification. The use of multiple selective BCYE media is necessary for maximal sensitivity. When culture

plates are overgrown with other microflora, pretreatment of the specimen with acid or heat can markedly improve the yield. *L. pneumophila* is often isolated from sputum that is not grossly or microscopically purulent; sputum containing more than 25 epithelial cells per high-power field (a finding that classically suggests contamination) may still yield *L. pneumophila*.

Antibody Detection Antibody testing of both acute- and convalescent-phase sera is necessary. A fourfold rise in titer is diagnostic; 12 weeks are often required for the detection of an antibody response. A single titer of 1:128 in a patient with pneumonia constitutes circumstantial evidence for Legionnaires' disease; a single titer of 1:256 constitutes presumptive evidence. The specificity of serology for *Legionella* species other than *L. pneumophila* is uncertain; there is cross-reactivity within *Legionella* species and some gram-negative bacilli. Positive serology serves as the criterion for the diagnosis of Pontiac fever.

Although serology has its limitations, it can still be useful for confirmation of Legionnaires' disease when isolation of the agent is impossible, and it can serve as a corroborating test. Serology is also useful for retrospective epidemiologic investigations and general seroprevalence determinations.

Urinary Antigen The detection of *Legionella* soluble antigen in urine, which is often easier to collect than sputum, is a relatively low-cost test and is easy to perform. Urinary antigen can be detected shortly after clinical symptoms appear and for up to 10 months thereafter, even during antibiotic treatment. The test's specificity is 95–100%, and its sensitivity ranges from 70 to 90%. Its drawback is that it is reliable only for *L. pneumophila* serogroup 1, which causes ~80% of *Legionella* infections. Cross-reactivity with other *L. pneumophila* serogroups and other *Legionella* species has been detected in up to 22% of urine samples from patients with culture-proven cases.

Molecular Methods Nucleic acid–based detection of *Legionella* offers advantages over serology and cultures because of its sensitivity and speed. DNA detection with the polymerase chain reaction (PCR) in both conventional and real-time thermal cyclers is highly specific (almost 100%) and sensitive. The sensitivity of DNA detection may be superior to that of culture in milder cases of Legionnaires' disease. DFA stains can identify a number of *Legionella* species. Both polyclonal and monoclonal antibody stains are commercially available. Procalcitonin can be used as an indicator of severity of illness in ICU patients. In addition, the clinical response to antibiotics can be monitored by procalcitonin levels.

TREATMENT

Legionella Infection

Because *Legionella* is an intracellular pathogen, antibiotics that reach high intracellular concentrations are more likely to be effective. The dosages for various drugs used in the treatment of *Legionella* infection are listed in Table 154-3.

The macrolides (especially azithromycin) and the quinolones (especially levofloxacin or ciprofloxacin) are the antibiotics of choice and are effective as monotherapy. Compared with erythromycin, the newer macrolides have superior in vitro activity, display greater intracellular activity, reach higher concentrations in respiratory secretions and lung tissue, and have fewer adverse effects. Quinolones are the preferred antibiotics for transplant recipients because both macrolides and rifampin interact pharmacologically with cyclosporine and tacrolimus. Retrospective uncontrolled studies have shown that complications of pneumonia are fewer and clinical response is more rapid in patients receiving quinolones than in those receiving macrolides.

Alternative agents include tetracycline and its analogues: doxycycline and minocycline. Tigecycline is active in vitro, but clinical experience with this drug is minimal. Anecdotal reports have described both successes and failures with trimethoprim-sulfamethoxazole, imipenem, and clindamycin.

TABLE 154-3 Antibiotic Therapy for *Legionella* Infection

ANTIMICROBIAL AGENT	DOSAGE[a]
Macrolides	
Azithromycin	500 mg[b] PO or IV[c] q24h
Clarithromycin	500 mg PO or IV[c] q12h
Quinolones	
Levofloxacin	750 mg IV q24h
	500 mg[b] PO q24h
Ciprofloxacin	400 mg IV q8h
	750 mg PO q12h
Moxifloxacin	400 mg[b] PO q24h
Ketolide	
Telithromycin	800 mg PO q24h
Tetracyclines	
Doxycycline	100 mg[b] PO or IV q12h
Minocycline	100 mg[b] PO or IV q12h
Tetracycline	500 mg PO or IV q6h
Tigecycline	100-mg IV load, then 50 mg IV q12h
Others	
Trimethoprim-sulfamethoxazole	160/800 mg IV q8h
Rifampin[d]	160/800 mg PO q12h
	300–600 mg PO or IV q12h

[a]Dosages are derived from clinical experience. [b]The authors recommend doubling the first dose. [c]The IV formulation is not available in some countries. [d]Rifampin should be used only in combination with a macrolide or a quinolone, and the duration of therapy should be limited to 3–5 days.

For treatment of critically ill patients, we use combinations of azithromycin, a quinolone, and/or rifampin. This practice is empirical and is not supported by comparative studies. Rifampin is highly active in vitro and in cell models. Adverse effects of rifampin can be minimized by limiting the duration of therapy to 3–5 days.

Initial antibiotic therapy should be given by the IV route because gastrointestinal symptoms are common in Legionnaires' disease. A clinical response usually occurs within 3–5 days, after which oral therapy can be substituted. The total duration of therapy in the immunocompetent host is 10–14 days; a longer course (3 weeks) may be appropriate for immunosuppressed patients. For azithromycin, with its long half-life, a 5- to 10-day course is sufficient.

Pontiac fever requires only symptom-based treatment, not antimicrobial therapy.

PROGNOSIS

Mortality rates for Legionnaires' disease vary with the patient's underlying disease, the patient's immune status, the severity of pneumonia, and the timing of administration of appropriate antimicrobial therapy. Mortality rates are highest (80%) among immunosuppressed patients who do not receive appropriate antimicrobial therapy early in the course of illness. With timely antibiotic treatment, mortality rates from community-acquired Legionnaires' disease among immunocompetent patients range from 3 to 11%; without treatment, the figure may be as high as 31%. In a study of survivors of an outbreak of community-acquired Legionnaires' disease, sequelae of fatigue, neurologic symptoms, and weakness were found in 63–75% of patients 17 months after receipt of antibiotics.

PREVENTION

Routine environmental culture of hospital water supplies for *Legionella* is recommended as an approach to the prevention of hospital-acquired Legionnaires' disease. Guidelines mandating this proactive approach have been adopted throughout Europe, in Taiwan, and in several U.S. states. The presence of *Legionella* in the water supply mandates the use of specialized laboratory tests (especially culture on selective

media and the urinary antigen test) for patients with hospital-acquired pneumonia. A 30% cutoff for the presence of *Legionella* in water from multiple sites in a hospital has been used as a prompt for an increased index of suspicion and consideration of empirical therapy for Legionnaires' disease. When the 30% cutoff is exceeded, *Legionella* diagnostic tests need to be performed for all patients with hospital-acquired pneumonia, and measures directed at the water supply may be considered. Quantitative criteria at a water site (CFU/mL) have proven unreliable and inconsistent in predicting disease.

Studies have shown that neither a high degree of outward cleanliness of the water system nor routine application of maintenance measures decreases the frequency or intensity of *Legionella* contamination. Thus, engineering guidelines and building codes, although routinely advocated as preventive measures, have little impact on the presence of *Legionella*.

Environmental cultures for *Legionella* from water taps, the hot-water recirculating line, and water storage tanks will reveal the source of hospital-acquired infections. Disinfection of hospital drinking-water systems is an effective preventive measure for hospital-acquired cases of Legionnaires' disease since these systems serve as the reservoir for *Legionella*. In geographic areas where the weather is semitropical, the cold-water lines also may be colonized by *Legionella*.

Copper–silver ionization has been shown to be a reliable and efficacious method for eradicating *Legionella* in hospitals worldwide. Unlike that of chlorine dioxide treatment and chlorination, the efficacy of ionization is not affected by high water temperatures. Ionization systems are easy to install, and the ions are odorless with minimal adverse effects. A comprehensive review of 10 published studies concluded that copper–silver ionization is effective in controlling *Legionella* as long as ion levels are monitored. If cold-water colonization by *Legionella* is the source of an outbreak, chlorine dioxide and monochloramine treatment is advantageous. Chlorine dioxide treatment is often the least expensive method, offers superior penetration into biofilms, and has less corrosive effects than chlorine. The major disadvantage of chlorine dioxide is the necessity for maintaining an effective residual throughout the drinking-water system, especially in the hot-water system. Eradication of *Legionella* by chlorine dioxide may require several months—a drawback in outbreak situations. Monochloramine appears to be effective. Hyperchlorination is no longer recommended because of its expense, carcinogenicity, corrosive effects on piping, and unreliable efficacy.

Point-of-use disposable water filters (pore size, 0.2 μm) may be an economical and effective option in high-risk areas (e.g., ICUs and transplant units). These filters can be used in an outbreak situation for a limited period.

Ineffective yet expensive methods of prevention are often promulgated. These methods include removal of stagnation (e.g., in dead-legs) within the water distribution system and replacement or disinfection/cleaning of distal outlets. Infection control personnel should oversee the selection of disinfection technology and apply evidence-based criteria for their selection. Health care facility managers should not be given the primary responsibility for selection and subsequent monitoring.

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155 Pertussis and Other *Bordetella* Infections

Karina A. Top, Scott A. Halperin

Pertussis is an acute infection of the respiratory tract caused by *Bordetella pertussis*. The word *pertussis* means "violent cough," which aptly describes the most consistent and prominent feature of the illness. The inspiratory sound made at the end of an episode of paroxysmal coughing gives rise to the common name for the illness, "whooping cough." However, this feature is variable: it is uncommon among infants ≤6 months of age and is frequently absent in older children and adults. The Chinese name for pertussis is "the 100-day cough," which accurately describes the clinical course of the illness. The identification of *B. pertussis* was first reported by Bordet and Gengou in 1906, and vaccines were produced over the following two decades.

MICROBIOLOGY

Of the 10 identified species in the genus *Bordetella*, only four are of major medical significance. *B. pertussis* infects only humans and is the most important *Bordetella* species causing human disease. *B. parapertussis* causes an illness in humans that is similar to pertussis but is typically milder; co-infections with *B. parapertussis* and *B. pertussis* have been documented. With improved polymerase chain reaction (PCR) diagnostic methodology, up to 20% of patients with a pertussis-like syndrome have been found to be infected with *B. holmesii*, formerly thought to be an unusual cause of bacteremia. *B. bronchiseptica* is an important pathogen of domestic animals that causes kennel cough in dogs, atrophic rhinitis and pneumonia in pigs, and pneumonia in cats. Both respiratory infection and opportunistic infection due to *B. bronchiseptica* are reported occasionally in humans. *B. petrii*, *B. hinzii*, and *B. ansorpii* have been isolated from patients who are immunocompromised.

Bordetella species are gram-negative pleomorphic aerobic bacilli that share common genotypic characteristics. *B. pertussis* and *B. parapertussis* are the most similar of the species, but *B. parapertussis* does not express the gene coding for pertussis toxin. *B. pertussis* is a slow-growing fastidious organism that requires selective medium and forms small, glistening, bifurcated colonies. Suspicious colonies are presumptively identified as *B. pertussis* by direct fluorescent antibody testing or by agglutination with species-specific antiserum. *B. pertussis* is further differentiated from other *Bordetella* species by biochemical and motility characteristics.

B. pertussis produces a wide array of toxins and biologically active products that are important in its pathogenesis and in immunity. Most of these virulence factors are under the control of a single genetic locus that regulates their production, resulting in antigenic modulation and phase variation. Although these processes occur both in vitro and in vivo, their importance in the pathobiology of the organism is unknown; they may play a role in intracellular persistence and person-to-person spread. The organism's most important virulence factor is *pertussis toxin*, which is composed of a B oligomer–binding subunit and an enzymatically active A protomer that ADP-ribosylates a guanine nucleotide–binding regulatory protein (G protein) in target cells, producing a variety of biologic effects. Pertussis toxin has important mitogenic activity, affects the circulation of lymphocytes, and serves as an adhesin for bacterial binding to respiratory ciliated cells. Other important virulence factors and adhesins are *filamentous hemagglutinin*, a component of the cell wall, and *pertactin*, an outer-membrane protein. *Fimbriae*, bacterial appendages that play a role in bacterial attachment, are the major antigens against which agglutinating antibodies are directed. These agglutinating antibodies have historically been the primary means of serotyping *B. pertussis* strains. Other virulence factors include tracheal cytotoxin, which causes respiratory epithelial damage; adenylate cyclase toxin, which impairs host immune-cell function; dermonecrotic toxin, which may contribute to respiratory mucosal

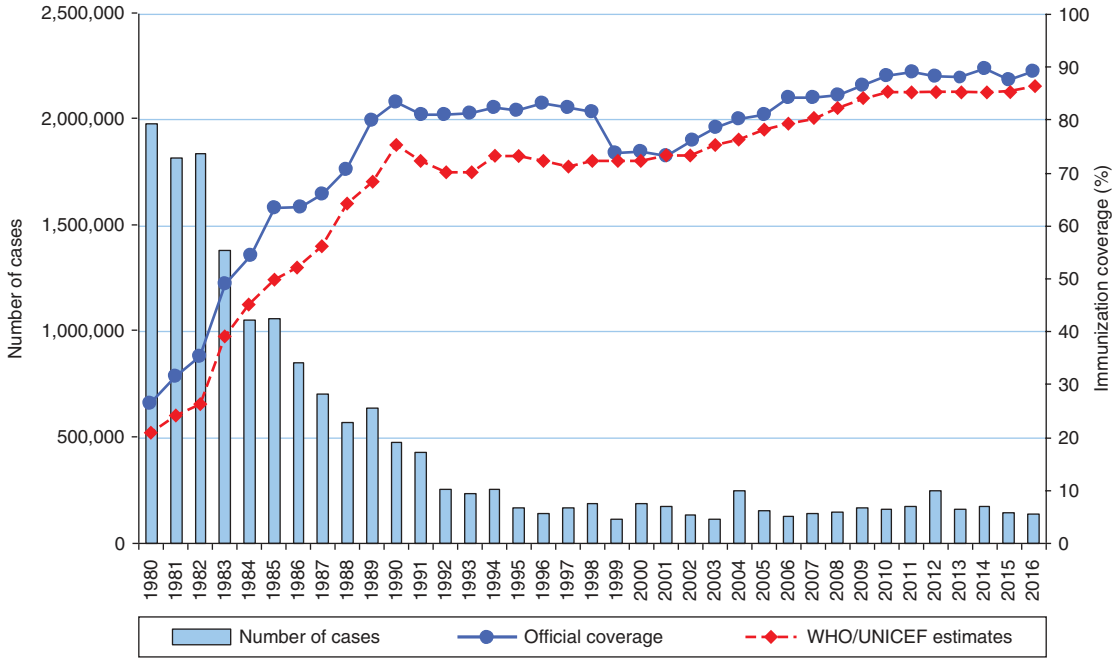

FIGURE 155-1 Global annual reported cases of pertussis and rate of coverage with DTP3 (diphtheria toxoid, tetanus toxoid, and pertussis vaccine; 3 doses), 1980–2016. *(© World Health Organization, 2017. All rights reserved. From http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis_coverage.jpg?ua=1. Source: WHO/IVB database, 2017. Accessed January 8, 2018.)*

damage; and lipooligosaccharide, which has properties similar to those of other gram-negative bacterial endotoxins.

EPIDEMIOLOGY

Pertussis is a highly communicable disease, with attack rates of 80–100% among unimmunized household contacts and 20% within households in well-immunized populations. The infection has a worldwide distribution, with cyclical outbreaks every 3–5 years (a pattern that has persisted despite widespread immunization). Pertussis occurs in all months; however, in North America, its activity peaks in autumn and winter.

In developing countries, pertussis remains an important cause of infant morbidity and death. The reported incidence of pertussis worldwide has decreased as a result of improved vaccine coverage (Fig. 155-1). However, coverage rates are still <60% in many developing nations; the World Health Organization (WHO) estimates that 90% of the burden of pertussis is in developing regions. In addition, over-reporting of immunization coverage and under-reporting of disease result in substantial underestimation of the global burden of pertussis. The WHO estimates that there were 63,000 deaths from pertussis among children <5 years of age in 2013.

Before the institution of widespread immunization programs in the developed world, pertussis was one of the most common infectious causes of morbidity and death. In the United States before the 1940s, between 115,000 and 270,000 cases of pertussis were reported annually, with an average yearly rate of 150 cases per 100,000 population. With universal childhood immunization, the number of reported cases fell by >95%, and mortality rates decreased even more dramatically. Only 1010 cases of pertussis were reported in 1976 (Fig. 155-2). After that historic low, rates of pertussis slowly increased. In recent years, pertussis epidemics have been reported with increasing frequency in several developed countries, including Australia, the United Kingdom, and the United States. The United States experienced widespread outbreaks of pertussis in 2005, 2010, 2012, and 2014 at levels not seen in 40–50 years (>40,000 reported cases in 2012).

Although thought of as a disease of childhood, pertussis can affect people of all ages and is increasingly being identified as a cause of prolonged coughing illness in adolescents and adults. In unimmunized populations, pertussis incidence peaks during the preschool years, and well over half of children have the disease before reaching adulthood. In highly immunized populations such as those in North America, the peak incidence is among infants <1 year of age who have not completed the three-dose primary immunization series. An increase in pertussis incidence among adolescents and adults began in the late 1990s and led to the introduction of an adolescent booster dose across North America by 2006. While the disease burden among adolescents has started to decrease, children 7–10 years of age have recently emerged as a high-risk group. In major outbreaks in 2010 and 2012, the incidence of pertussis among children 10 years of age, most of whom were fully immunized, was as high as that among infants <6 months of age. Although adults contribute a smaller proportion of reported cases of pertussis than do children and adolescents, this difference may be related to a greater degree of under-recognition and under-reporting. A number of studies of prolonged coughing illness suggest that *B. pertussis* may be the etiologic agent in 12–30% of adults with cough that does not improve within 2 weeks. In one study of the efficacy of an acellular pertussis vaccine in adolescents and adults, the incidence of pertussis in the placebo group was 3.7–4.5 cases per 1000 person-years. Although this prospective cohort study yielded a lower estimate than the studies of cough illness, its results still translate to 600,000–800,000 cases of pertussis annually among adults in the United States.

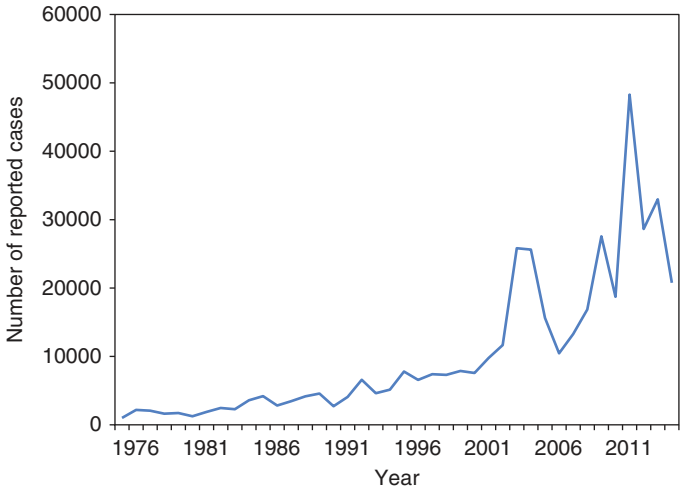

FIGURE 155-2 Reported cases of pertussis by year—United States, 1976–2015. *(From the Centers for Disease Control and Prevention, www.cdc.gov/pertussis/surv-reporting/cases-by-year.html. Accessed January 8, 2018.)*

Severe morbidity and high mortality rates, however, are restricted almost entirely to infants. In the United States between 1993 and 2004, all pertussis deaths and 86% of hospitalizations for pertussis involved infants ≤3 months of age. Although school-age children are the source of infection for most households, adults are often the source for cases in high-risk infants and may serve as the reservoir of infection between epidemic years.

PATHOGENESIS

Infection with *B. pertussis* is initiated by attachment of the organism to the ciliated epithelial cells of the nasopharynx. Attachment is mediated by surface adhesins (e.g., pertactin and filamentous hemagglutinin), which bind to the integrin family of cell-surface proteins, probably in conjunction with pertussis toxin. The role of fimbriae in adhesion and in maintenance of infection has not been fully delineated. At the site of attachment, the organism multiplies, producing a variety of other toxins that cause local mucosal damage (tracheal cytotoxin, dermonecrotic toxin). Impairment of host defense by *B. pertussis* is mediated by pertussis toxin and adenylate cyclase toxin. There is local cellular invasion, with intracellular bacterial persistence; however, systemic dissemination does not occur. Systemic manifestations (lymphocytosis) result from the effects of the toxins.

The pathogenesis of the clinical manifestations of pertussis is poorly understood. It is not known what causes the hallmark paroxysmal cough. A pivotal role for pertussis toxin has been proposed. Proponents of this position point to the efficacy of preventing clinical symptoms with a vaccine containing only pertussis toxoid. Detractors counter that pertussis toxin is not the critical factor because paroxysmal cough also occurs in patients infected with *B. parapertussis*, which does not produce pertussis toxin. It is thought that neurologic events in pertussis, such as seizures and encephalopathy, are due to hypoxia from coughing paroxysms or apnea rather than to the effects of specific bacterial products. *B. pertussis* pneumonia, which occurs in up to 10% of infants with pertussis, is usually a diffuse bilateral primary infection. In older children and adults with pertussis, pneumonia is often due to secondary bacterial infection with streptococci or staphylococci. Deaths from pertussis among young infants are frequently associated with very high levels of leukocytosis and pulmonary hypertension.

IMMUNITY

Both humoral and cell-mediated immunity are thought to be important in pertussis. Antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae are all protective in animal models. Pertussis agglutinins were correlated with protection in early studies of whole-cell pertussis vaccines. Serologic correlates of protection conferred by acellular pertussis vaccines have not been established, although antibody to pertactin, fimbriae, and (to a lesser degree) pertussis toxin correlated best with protection in two efficacy trials. The duration of immunity after whole-cell pertussis vaccination is short-lived, with little protection remaining after 10–12 years. Studies have demonstrated early waning of immunity—i.e., within 2–4 years after the fifth dose of acellular pertussis vaccine in children who received acellular pertussis vaccine for their primary series in infancy. These data suggest that boosters may be needed more frequently than every 10 years, as previously thought. Although immunity after natural infection was thought to be lifelong, seroepidemiologic evidence demonstrates that it clearly is not and that subsequent episodes of clinical pertussis are prevented by intermittent subclinical infection.

CLINICAL MANIFESTATIONS

Pertussis is a prolonged coughing illness with clinical manifestations that vary by age **(Table 155-1)**. Although not uncommon among adolescents and adults, classic pertussis is most often seen in preschool and school-age children. After an incubation period averaging 7–10 days, an illness develops that is indistinguishable from the common cold and is characterized by coryza, lacrimation, mild cough, low-grade fever, and malaise. After 1–2 weeks, this *catarrhal phase* evolves into the *paroxysmal phase*: the cough becomes more frequent and spasmodic with repetitive bursts of 5–10 coughs, often within a single expiration. Post-tussive vomiting is frequent, with a mucous plug occasionally expelled at the end of an episode. The episode may be terminated by an audible whoop, which occurs upon rapid inspiration against a closed glottis at the end of a paroxysm. During a spasm, there may be impressive neck-vein distension, bulging eyes, tongue protrusion, and cyanosis. Paroxysms may be precipitated by noise, eating, or physical contact. Between attacks, the patient's appearance is normal but increasing fatigue is evident. The frequency of paroxysmal episodes varies widely, from several per hour to 5–10 per day. Episodes are often worse at night and interfere with sleep. Most complications occur during the paroxysmal stage. Fever is uncommon and suggests bacterial superinfection.

TABLE 155-1 Clinical Features of Pertussis, by Age Group and Diagnostic Status

FEATURE	PERCENTAGE OF PATIENTS		
	ADOLESCENTS AND ADULTS		
	LABORATORY CONFIRMATION	NO LABORATORY CONFIRMATION	CHILDREN
Cough	95–100	95–100	95–100
Prolonged	60–80	60–80	60–95
Paroxysmal	60–90	50–90	80–95
Sleep-disturbing	50–80	50–80	90–100
Whoop	10–40	5–30	40–80
Post-tussive vomiting	20–50	5–30	80–90

After 2–4 weeks, the coughing episodes become less frequent and less severe—changes heralding the onset of the *convalescent phase*. This phase can last 1–3 months and is characterized by gradual resolution of coughing episodes. For 6–12 months, intercurrent viral infections may be associated with a recrudescence of paroxysmal cough.

Not all individuals who develop pertussis have classic disease. The clinical manifestations in adolescents and adults are more often atypical. In a German study of pertussis in adults, more than two-thirds had paroxysmal cough and more than one-third had whoop. Adult illness in North America differs from this experience: the cough may be severe and prolonged but is less frequently paroxysmal, and a whoop is uncommon. Vomiting with cough is the best predictor of pertussis as the cause of prolonged cough in adults. Other predictive features are a cough at night, sweating episodes between paroxysms of coughing, and exposure to other individuals with a prolonged coughing illness.

COMPLICATIONS

Complications are frequently associated with pertussis and are more common among infants than among older children or adults. Subconjunctival hemorrhages, abdominal and inguinal hernias, pneumothoraces, and facial and truncal petechiae can result from increased intrathoracic pressure generated by severe fits of coughing. Weight loss can follow decreased caloric intake. Urinary incontinence, rib fracture, carotid artery aneurysm, and cough syncope have also been reported in adolescents and adults with pertussis. In a series of more than 1100 children <2 years of age who were hospitalized with pertussis, 27.1% had apnea, 9.4% had pneumonia, 2.6% had seizures, and 0.4% had encephalopathy; 10 children (0.9%) died. Pneumonia is reported in <5% of adolescents and adults and increases in frequency after 50 years of age. In contrast to the primary *B. pertussis* pneumonia that develops in infants, pneumonia in adolescents and adults with pertussis is usually caused by a secondary infection with encapsulated organisms such as *Streptococcus pneumoniae* or *Haemophilus influenzae*.

DIAGNOSIS

If the classic symptoms of pertussis are present, clinical diagnosis is not difficult. However, particularly in older children and adults, it is difficult to differentiate infections caused by *B. pertussis* and *B. parapertussis* from other respiratory tract infections on clinical grounds. Therefore, laboratory confirmation should be attempted in all cases. Lymphocytosis (absolute lymphocyte count, $>10^8$–10^9/L) is common among young children, in whom it is unusual with other infections, but not among adolescents and adults. Culture of nasopharyngeal secretions remains

the gold standard of diagnosis, although DNA detection by PCR has replaced culture in many laboratories because of increased sensitivity and quicker results. Appropriate PCR methodology must include primers to differentiate among *B. pertussis*, *B. parapertussis*, and *B. holmesii*. The best specimen is collected by nasopharyngeal aspiration, in which a fine flexible plastic catheter attached to a 10-mL syringe is passed into the nasopharynx and withdrawn while gentle suction is applied. Since *B. pertussis* is highly sensitive to drying, secretions for culture should be inoculated without delay onto appropriate medium (Bordet-Gengou or Regan-Lowe), or the catheter should be flushed with a phosphate-buffered saline solution for culture and/or PCR. An alternative to the aspirate is a Dacron or rayon nasopharyngeal swab; again, inoculation of culture plates should be immediate or an appropriate transport medium (e.g., Regan-Lowe charcoal medium) should be used. Results of PCR can be available within hours; cultures become positive by day 5 of incubation. *B. pertussis* and *B. parapertussis* can be differentiated by agglutination with specific antisera or by direct immunofluorescence.

Nasopharyngeal cultures in untreated pertussis remain positive for a mean of 3 weeks after the onset of illness; these cultures become negative within 5 days of the institution of appropriate antimicrobial therapy. The duration of a positive PCR in untreated pertussis or after therapy is not known but exceeds that of positive cultures. Since much of the period during which the organism can be recovered from the nasopharynx falls into the catarrhal phase, when the etiology of the infection is not suspected, there is only a small window of opportunity for culture-proven diagnosis. Cultures from infants and young children are more frequently positive than those from older children and adults; this difference may reflect earlier presentation of the former age group for medical care. Direct fluorescent antibody tests of nasopharyngeal secretions for direct diagnosis may still be available in some laboratories but should not be used because of poor sensitivity and specificity. Pseudo-outbreaks of pertussis have been reported as a result of false-positive PCR results. Greater standardization of PCR methodology can alleviate this problem.

As a result of the difficulties with laboratory diagnosis of pertussis in adolescents, adults, and patients who have been symptomatic for >4 weeks, increasing attention is being given to serologic diagnosis. Enzyme immunoassays detecting IgA and IgG antibodies to pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae have been developed and assessed for reproducibility. Two- or fourfold increases in antibody titer are suggestive of pertussis, although cross-reactivity of some antigens (such as filamentous hemagglutinin and pertactin) among *Bordetella* species makes it difficult to depend diagnostically on seroconversion involving a single type of antibody. Late presentation for medical care and prior immunization also complicate serologic diagnosis because the first sample obtained may in fact be a convalescent-phase specimen. Criteria for serologic diagnosis based on comparison of results for a single serum specimen with established population values are gaining acceptance, and serologic measurement of antibody to pertussis toxin is becoming more widely standardized and available for diagnostic purposes, particularly in outbreak settings and for surveillance.

DIFFERENTIAL DIAGNOSIS

A child presenting with paroxysmal cough, post-tussive vomiting, and whoop is likely to have an infection caused by *B. pertussis* or *B. parapertussis*; lymphocytosis increases the likelihood of a *B. pertussis* etiology. Viruses such as respiratory syncytial virus and adenovirus have been isolated from patients with clinical pertussis but probably represent co-infection.

In adolescents and adults, who often do not have paroxysmal cough or whoop, the differential diagnosis of a prolonged coughing illness is more extensive. Pertussis should be suspected when any patient has a cough that does not improve within 14 days, a paroxysmal cough of any duration, a cough followed by vomiting (adolescents and adults), or any respiratory symptoms after contact with a laboratory-confirmed case of pertussis. Other etiologies to consider include infections caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, adenovirus, influenza virus, and other respiratory viruses. Use of angiotensin-converting enzyme (ACE) inhibitors, reactive airway disease, and gastroesophageal reflux disease are well-described noninfectious causes of prolonged cough in adults.

TREATMENT

Pertussis

ANTIBIOTICS

The purpose of antibiotic therapy for pertussis is to eradicate the infecting bacteria from the nasopharynx; therapy does not substantially alter the clinical course unless given early in the catarrhal phase. Macrolide antibiotics are the drugs of choice for treatment of pertussis **(Table 155-2)**; macrolide-resistant *B. pertussis* strains have been reported but are rare. Trimethoprim-sulfamethoxazole is recommended as an alternative for individuals allergic to macrolides.

SUPPORTIVE CARE

Young infants have the highest rates of complication and death from pertussis; therefore, most infants (and older children with severe disease) should be hospitalized. A quiet environment may decrease the stimulation that can trigger paroxysmal episodes. Use of β-adrenergic agonists and/or glucocorticoids has been advocated by some authorities but has not been proven to be effective. Cough suppressants are not effective and play no role in the management of pertussis.

INFECTION CONTROL MEASURES

Hospitalized patients with pertussis should be placed in respiratory isolation, with the use of precautions appropriate for pathogens spread by large respiratory droplets. Isolation should continue for 5 days after initiation of macrolide therapy or, in untreated patients, for 3 weeks (i.e., until nasopharyngeal cultures are consistently negative).

PREVENTION

Chemoprophylaxis Because the risk of transmission of *B. pertussis* within households is high, chemoprophylaxis is widely recommended for household contacts of pertussis cases. The effectiveness of chemoprophylaxis, although unproven, is supported by several epidemiologic studies of institutional and community outbreaks. In the only randomized, placebo-controlled study, erythromycin estolate (50 mg/kg per day in three divided doses; maximum dose, 1 g/d) was effective in reducing the incidence of bacteriologically confirmed pertussis by 67%; however, there was no decrease in the incidence of clinical disease. Despite these disappointing results, many authorities continue to recommend chemoprophylaxis, particularly in households

TABLE 155-2 Antimicrobial Therapy for Pertussis

DRUG	ADULT DAILY DOSE	FREQUENCY	DURATION, DAYS	COMMENTS
Erythromycin estolate	1–2 g	3 divided doses	7–14	Frequent gastrointestinal side effects
Clarithromycin	500 mg	2 divided doses	7	—
Azithromycin	500 mg on day 1250 mg subsequently	1 daily dose	5	—
Trimethoprim-sulfamethoxazole	160 mg of trimethoprim, 800 mg of sulfamethoxazole	2 divided doses	14	For patients allergic to macrolides; data on effectiveness limited

with members at high risk of severe disease (children <1 year of age, pregnant women). Data on the use of the newer macrolides for chemoprophylaxis are not available, but these drugs are commonly used because of their increased tolerability and their effectiveness.

Immunization **(See also Chap. 118)** The mainstay of pertussis prevention is active immunization. Pertussis vaccine became widely used in North America after 1940; the reported number of pertussis cases subsequently fell by >90%. Whole-cell pertussis vaccines are prepared through the heating, chemical inactivation, and purification of whole *B. pertussis* organisms. Despite their efficacy (average estimate, 85%; range for different products, 30–100%), whole-cell pertussis vaccines are associated with adverse events—both common (fever; injection-site pain, erythema, and swelling; irritability) and uncommon (febrile seizures, hypotonic-hyporesponsive episodes). Alleged associations of whole-cell pertussis vaccine with encephalopathy, sudden infant death syndrome, and autism, although not substantiated, have spawned an active anti-immunization lobby. The development of acellular pertussis vaccines, which are effective and less reactogenic, has greatly alleviated concerns about the inclusion of pertussis vaccine in the combined infant immunization series.

Although a wide variety of acellular pertussis vaccines were developed, only a few are still marketed widely; all contain pertussis toxoid and filamentous hemagglutinin. One acellular pertussis vaccine also contains pertactin, and another contains pertactin and two types of fimbriae. In phase 3 efficacy studies, multicomponent acellular pertussis vaccines were more efficacious than one- or two-component vaccines. However, epidemiologic studies in countries using one- and two-component acellular pertussis vaccines demonstrated high vaccine effectiveness against pertussis. Adult formulations of acellular pertussis vaccines have been shown to be safe, immunogenic, and efficacious in clinical trials in adolescents and adults and are now recommended for routine immunization of these groups in several countries.

Although whole-cell vaccines are still used extensively in developing regions of the world, acellular pertussis vaccines are used exclusively for childhood immunization in much of the developed world. In light of evidence of early waning of immunity among children who received acellular pertussis vaccine in infancy, the WHO Strategic Advisory Group of Experts (SAGE) now recommends using whole-cell pertussis vaccine for the primary infant immunization series. In countries using acellular pertussis vaccines in infancy, additional booster immunizations in older children, adolescents, and adults are recommended to prevent pertussis in high-risk infants. In North America, acellular pertussis vaccines for children are given as a three-dose primary series at 2, 4, and 6 months of age, with a reinforcing dose at 15–18 months of age and a booster dose at 4–6 years of age. Adolescents (11–18 years of age) and all unvaccinated adults should receive a dose of the adult-formulation diphtheria–tetanus–acellular pertussis vaccine. In addition, several countries, including the United States and the United Kingdom, recommend pertussis immunization specifically for health care workers and for women in the third trimester of pregnancy to increase passive transfer of maternal antibodies to the fetus. In a study from the United Kingdom, immunization of pregnant women ≥7 days prior to delivery was 91–93% effective at preventing pertussis in infants ≤3 months of age. Pertussis vaccine coverage among U.S. adolescents was 84.6% in 2012, and coverage among pregnant women is increasing (from 12.7% in 2010 to 41.7% in 2013 in a cohort of privately insured women). Nevertheless, coverage among adults remains low (14.2% in 2012). Further improvements in adult vaccine coverage may permit better control of pertussis across the age spectrum, with collateral protection of infants too young to be immunized. However, more effective vaccines with longer-lasting protection will ultimately be needed to control this disease.

FURTHER READING

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156 Diseases Caused by Gram-Negative Enteric Bacilli

Thomas A. Russo, James R. Johnson

GENERAL FEATURES AND PRINCIPLES

The post-antibiotic era has begun. For most people, this is the first time in their lives that an effective treatment for a bacterial infection may not exist. The Enterobacteriaceae are at the forefront of this evolving public health crisis. For example, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have designated carbapenem-resistant Enterobacteriaceae as representing a threat level of "urgent" and "priority one, critical," respectively. Enterobacteriaceae are responsible for a significant proportion of the deaths attributed to resistant bacteria, the number of which has been estimated at 23,000 and 25,000 annually in the United States and the European Union, respectively, with numbers three- to fivefold greater (per capita) in low- and middle-income countries (e.g., Thailand). These pathogens cause a wide variety of infections involving diverse anatomic sites in both healthy and compromised hosts. Therefore, a thorough knowledge of clinical presentations and appropriate therapeutic choices is necessary for optimal outcomes. *Escherichia coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are enteric gram-negative bacilli (GNB) that are members of the family Enterobacteriaceae. *Salmonella*, *Shigella*, and *Yersinia*, also in the family Enterobacteriaceae, are discussed in **Chaps. 160, 161, and 166**, respectively.

EPIDEMIOLOGY

E. coli, *Klebsiella*, *Proteus*, *Enterobacter*, *Serratia*, *Citrobacter*, *Morganella*, *Providencia*, *Cronobacter*, and *Edwardsiella* are components of the normal animal and human colonic microbiota and/or the microbiota in various environmental habitats, including long-term-care facilities (LTCFs) and hospitals. As a result, except for certain pathotypes of intestinal pathogenic *E. coli*, these genera are global pathogens. The incidence of infection due to these agents is increasing because of the combination of an aging population and increasing antimicrobial resistance. In healthy humans, *E. coli* is the predominant species of GNB in the colonic microbiota; *Klebsiella* and *Proteus* are less prevalent. GNB (primarily *E. coli*, *Klebsiella*, and *Proteus*) colonize the oropharynx and skin of healthy individuals only transiently. By contrast, in LTCFs and hospital settings, a variety of GNB emerge as the dominant colonizers of both mucosal and skin surfaces, particularly in association with antimicrobial use, severe illness, and extended length of stay. LTCFs are emerging as an important reservoir for resistant GNB. This colonization may lead to subsequent infection; for example, oropharyngeal colonization may lead to pneumonia, and colonic/perineal colonization may lead to urinary tract infection (UTI). The use of ampicillin or amoxicillin was associated with an increased risk of subsequent infection due to the hypervirulent pathotype of *Klebsiella pneumoniae* in Taiwan; this association suggests that changes in the quantity or prevalence of colonizing bacteria may significantly influence the risk of infection. *Serratia* and *Enterobacter* infection may be acquired directly through a variety of infusates (e.g., medications, blood products). *Edwardsiella* infections are acquired through freshwater

and marine environment exposures and are most common in Southeast Asia.

STRUCTURE AND FUNCTION

Enteric GNB possess an extracytoplasmic outer membrane consisting of a lipid bilayer with associated proteins, lipoproteins, and polysaccharides (capsule, lipopolysaccharide). The outer membrane interfaces with the external environment, including the human host. A variety of components of the outer membrane are critical determinants in pathogenesis (e.g., capsule) and antimicrobial resistance (e.g., permeability barrier, efflux pumps). In addition, secreted products play an important role in both host infection (e.g., iron acquisition molecules) and environmental niche survival and colonization (e.g., type VI secretion systems).

PATHOGENESIS

Multiple bacterial virulence factors are required for the pathogenesis of infections caused by GNB. Possession of specialized virulence genes defines pathogens and enables them to infect the host efficiently. Hosts and their cognate pathogens have been co-adapting throughout evolutionary history. During the host–pathogen "chess match" over time, various and redundant strategies have emerged in both the pathogens and their hosts **(Table 156-1)**.

Intestinal pathogenic (diarrheagenic) mechanisms are discussed below. The members of the Enterobacteriaceae family that cause extraintestinal infections are primarily extracellular pathogens and therefore share certain pathogenic features. The principal components of host defense against Enterobacteriaceae, regardless of species, are innate immunity (including intact skin and mucosal barriers; the withholding of nutrients; and the activities of complement, antimicrobial peptides, and professional phagocytes) and humoral immunity. Both susceptibility to and severity of infection are increased with dysfunction or deficiencies of these host components. By contrast, the virulence traits of intestinal pathogenic *E. coli*—i.e., the distinctive strains that can cause diarrheal disease—are for the most part different from those of extraintestinal pathogenic *E. coli* (ExPEC) and other GNB that cause extraintestinal infections. This distinction reflects site-specific differences in host environments and defense mechanisms.

A given enterobacterial strain usually possesses multiple adhesins for binding to a variety of host cells (e.g., in *E. coli*: type 1, S, and F1C fimbriae; P pili). Nutrient acquisition (e.g., of iron via siderophores) requires many genes that are necessary but not sufficient for pathogenesis. The ability to resist the bactericidal activity of complement and phagocytes in the absence of antibody (e.g., as conferred by capsule or the O antigen component of lipopolysaccharide) is one of the defining traits of an extracellular pathogen. Tissue damage (e.g., as mediated by *E. coli* hemolysin) may facilitate nutrient acquisition and spread within the host. Without doubt, many important virulence genes await identification **(Chap. 116)**.

The ability to induce septic shock is another defining feature of these genera. GNB are the most common causes of this potentially lethal syndrome. Pathogen-associated molecular pattern molecules (PAMPs; e.g., the lipid A moiety of lipopolysaccharide) stimulate a proinflammatory host response via pattern recognition receptors (e.g., Toll-like or C-type lectin receptors) that activate host defense signaling pathways; if overly exuberant, this response results in shock **(Chap. 297)**. Direct bacterial damage of host tissue (e.g., by toxins) or collateral damage from the host response can result in the release of damage-associated molecular pattern molecules (DAMPs; e.g., HMGB1) that can propagate a detrimental proinflammatory host response.

Many antigenic variants (serotypes) exist in most genera of GNB. For example, *E. coli* has more than 150 O (somatic) antigens, 80 K (capsular) antigens, and 53 H (flagellar) antigens. This antigenic variability, which permits immune evasion and allows recurrent infection by different strains of the same species, has impeded vaccine development **(Chap. 118)**.

TABLE 156-1 Interactions of Extraintestinal Pathogenic *Escherichia coli* with the Human Host: A Paradigm for Extracellular, Extraintestinal Gram-Negative Bacterial Pathogens

BACTERIAL GOAL	HOST OBSTACLE	BACTERIAL SOLUTION
Extraintestinal attachment	Flow of urine, mucociliary escalator	Multiple adhesins (e.g., type 1, S, and F1C fimbriae; P pili)
Nutrient acquisition for growth	Nutrient sequestration (e.g., iron via intracellular storage and extracellular scavenging via lactoferrin and transferrin)	Cellular lysis (e.g., hemolysin), multiple mechanisms for competing for iron (e.g., siderophores) and other nutrients
Initial avoidance of host bactericidal activity	Complement, phagocytic cells, antimicrobial peptides	Capsular polysaccharide, lipopolysaccharide
Dissemination (within host and between hosts)	Intact tissue barriers	Irritant tissue damage resulting in increased excretion (e.g., toxins such as hemolysin), invasion of brain endothelium
Late avoidance of host bactericidal activity	Acquired immunity (e.g., specific antibodies), treatment with antibiotics	Cell entry, acquisition of antimicrobial resistance

INFECTIOUS SYNDROMES

Depending on both the host and the pathogen, GNB can infect nearly every organ or body cavity. *E. coli* can cause either intestinal or extraintestinal infection, depending on the particular pathotype, and *Edwardsiella tarda* can cause both intestinal and extraintestinal infection. *Klebsiella* causes primarily extraintestinal infection, but a toxin-producing variant of *Klebsiella oxytoca* has been associated with hemorrhagic colitis.

E. coli and—to a lesser degree—*Klebsiella* account for most extraintestinal infections due to GNB. These species (for *K. pneumoniae*, primarily its hypervirulent pathotype) are the most virulent pathogens within this group, as demonstrated by their ability to cause severe infections in healthy, ambulatory hosts from the community. However, the other genera of GNB are also important extraintestinal pathogens, especially among LTCF residents and hospitalized patients, in large part because of the intrinsic or acquired antimicrobial resistance of these organisms and the increasing number of individuals with compromised host defenses. The mortality rate is substantial in many GNB infections and correlates with severity of illness and underlying host status. Especially problematic are pneumonia, sepsis, and septic shock (arising from any site of infection), for which the associated mortality rates are 20–60%.

DIAGNOSIS

Isolation of GNB from sterile sites almost always implies infection, whereas their isolation from nonsterile sites, particularly from open wounds and the respiratory tract, requires clinical correlation to differentiate colonization from infection. Clinical microbiology laboratories are increasingly incorporating newer molecular-based methodologies (e.g., matrix-assisted laser desorption–ionization–time-of-flight mass spectrometry [MALDI-TOF-MS] and polymerase chain reaction [PCR]) to enhance the sensitivity, accuracy, and rapidity of reporting on pathogen identification and resistance genes (e.g., *bla*KPC, NDM, OXA, CTX). This information can be used to increase the timeliness of initiation and/or the accurate selection of empirical antimicrobial therapy, thereby improving outcomes.

TREATMENT

Infections Caused by Gram-Negative Enteric Bacilli

(See also Chap. 139) Initiation of appropriate empirical antimicrobial therapy early in the course of GNB infections (particularly serious ones) leads to improved outcomes. The ever-increasing prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) GNB; the lag between published and current resistance rates; and variations in antimicrobial susceptibility by species, geographic location, regional antimicrobial use,

and hospital site (e.g., intensive care units [ICUs] versus wards) necessitate familiarity with evolving patterns of antimicrobial resistance for the selection of appropriate empirical therapy. Factors predictive of resistance in a given isolate include recent antimicrobial use, a health care association (e.g., recent or ongoing hospitalization, dialysis, residence in an LTCF), or international travel (e.g., to Asia, Latin America, Africa, Eastern Europe). Resistance rates will almost certainly increase over time and will likely be higher than shown here by the time this chapter is published. Data for 2008–2014 from the U.S. National Healthcare Safety Network indicates that the prevalence of the extended-spectrum β-lactamase (ESBL) phenotype among Enterobacteriaceae isolates varied by health care setting—i.e., 16% for short-term care, 38.6% for long-term care, and 10.7% for inpatient rehabilitation facilities—as did the prevalence of carbapenem resistance (2.8%, 12%, and 1.9%, respectively). Global ESBL rates for Enterobacteriaceae isolates from hospitalized patients were roughly similar in North America, Western Europe, Australia, and New Zealand and were higher in Latin America, Eastern Europe, and Asia. Perhaps even more concerning is the reported isolation of carbapenem-resistant Enterobacteriaceae (mediated primarily by New Delhi metallo-β-lactamase [NDM]) from ambulatory patients without known risk factors.

For appropriately selected patients, it may be prudent initially, pending antimicrobial susceptibility results, to use two potentially active agents as a way to increase the likelihood that at least one agent will be active against the patient's organism. If broad-spectrum treatment has been initiated, it is important to switch to the most appropriate narrower-spectrum agent once antimicrobial susceptibility results become available. Such responsible antimicrobial stewardship should help disrupt the ever-escalating cycle of selection for increasingly resistant bacteria, decrease the likelihood of *Clostridium difficile* infection, decrease costs, and maximize the useful longevity of available antimicrobial agents. Likewise, it is important to avoid treatment of patients who are colonized but not infected (e.g., who have a positive sputum culture without evidence of pneumonia or a positive urine culture without clinical manifestations of UTI).

At present, the most reliably active antimicrobial agents against GNB are the carbapenems (e.g., meropenem); the aminoglycoside amikacin; the fourth-generation cephalosporin cefepime; the β-lactamase inhibitor combination agents piperacillin-tazobactam, ceftolozane-tazobactam, and ceftazidime-avibactam; and the polymyxins (colistin and polymyxin B). However, it should be noted that *Proteus*, *Serratia*, *Morganella*, and *Providencia* are intrinsically resistant to the polymyxins. The number of antimicrobial agents effective against certain Enterobacteriaceae is shrinking, and truly pan-resistant GNB exist. Accordingly, the currently available antimicrobial drugs must be used judiciously.

β-Lactamases, which inactivate β-lactam agents, are the most important mediators of β-lactam resistance in GNB. Decreased permeability and/or active efflux of β-lactam agents, although less important and less potent, may occur alone or in combination with β-lactamase-mediated resistance.

Broad-spectrum β-lactamases (e.g., TEM, SHV), which mediate resistance to many penicillins and first-generation cephalosporins, are frequently expressed in enteric GNB. These enzymes are inhibited by β-lactamase inhibitors (e.g., clavulanate, sulbactam, tazobactam, avibactam). In their wild-type form, they do not hydrolyze third- and fourth-generation cephalosporins or cephamycins (e.g., cefoxitin). However, molecular variants of TEM and SHV that have amino acid replacements at certain critical positions in the peptide do exhibit such hydrolytic capability and thus are referred to as ESBLs, as discussed below.

ESBLs (e.g., CTX-M, SHV, TEM) are modified broad-spectrum enzymes that hydrolyze third-generation cephalosporins, aztreonam, and (in some instances) fourth-generation cephalosporins in addition to the drugs hydrolyzed by broad-spectrum β-lactamases. GNB that express ESBLs may also possess porin mutations that result in decreased uptake of cephalosporins, β-lactam/β-lactamase inhibitor combinations, and carbapenems, thereby further reducing susceptibility to these β-lactam agents. The prevalence of acquired ESBL production, particularly of CTX-M-type enzymes, is increasing in GNB worldwide, in large part as a result of the presence of the corresponding genes on transferable (conjugal) plasmids variably linked to or associated with resistance to fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, tetracyclines, and (more recently) fosfomycin.

To date, ESBLs are most prevalent in *E. coli*, *K. pneumoniae*, and *K. oxytoca*, but these enzymes can occur in all Enterobacteriaceae. The approximate regional prevalence of ESBL-producing GNB currently follows a descending gradient as follows: China > Eastern Europe > other parts of Asia > Latin America and Africa > Western Europe, the United States, Canada, and Australia. International travel to high-prevalence regions increases the likelihood of colonization with these strains.

ESBL-producing GNB were described initially in hospitals (ICUs > wards) and LTCFs, where outbreaks occurred in association with extensive use of third-generation cephalosporins. However, over the last decade, the incidence of UTI due to CTX-M ESBL-producing *E. coli* has increased worldwide (including in the United States), even among healthy ambulatory women without health care or antimicrobial exposure. Antimicrobial use in food animals has also been implicated in the rise of ESBLs.

Carbapenems are the most reliably active β-lactam agents against ESBL-expressing strains. Clinical experience with alternatives is more limited, but, for organisms susceptible to piperacillin-tazobactam (minimal inhibitory concentration [MIC], ≤4 μg/mL), this agent—dosed at 4.5 g q6h—may offer a carbapenem-sparing alternative, as may ceftazidime-avibactam and ceftolozane-tazobactam.

The role of tigecycline is unclear despite its excellent in vitro activity; *Proteus*, *Morganella*, and *Providencia* are inherently resistant, and attainable serum and urine levels are low. Therefore, caution is advisable, especially with serious infections, until more clinical data become available.

Oral options for the treatment of strains expressing ESBLs are limited. Fosfomycin and nitrofurantoin (for *E. coli*) and perhaps pivmecillinam (not available in the United States) are the most reliably active agents.

AmpC β-lactamases, when induced or stably derepressed to high levels of expression, confer resistance to the same substrates as do ESBLs as well as to the cephamycins (e.g., cefoxitin and cefotetan). The genes encoding these enzymes are primarily chromosomal and therefore may not exhibit the linked or associated resistance to fluoroquinolones, TMP-SMX, aminoglycosides, and tetracyclines that is common with ESBLs. These enzymes are problematic for the clinician: resistance may develop during therapy with third-generation cephalosporins and result in clinical failure, particularly in the setting of bacteremia.

Although chromosomal AmpC β-lactamases are present in nearly all members of the Enterobacteriaceae family, the risk of clinically significant induction of high-level expression or selection of stably derepressed mutants with cephalosporin treatment is greatest with *Enterobacter cloacae* and *Enterobacter aerogenes*, lower with *Serratia marcescens* and *Citrobacter freundii*, and lowest with *Providencia* and *Morganella morganii.* In addition, rare strains of *E. coli*, *K. pneumoniae*, and other Enterobacteriaceae have acquired plasmids containing inducible AmpC β-lactamase genes.

For AmpC-expressing strains, carbapenems are an appropriate treatment option. Ceftazidime-avibactam and ceftolozane-tazobactam are active in vitro, but clinical data are limited. The fourth-generation cephalosporin cefepime may be an appropriate option if the concomitant presence of an ESBL can be excluded (a task that currently exceeds the capability of most clinical microbiology laboratories) and source control is achieved. Although clinical data are limited, other carbapenem-sparing alternatives to consider if isolates are susceptible in vitro include fluoroquinolones, piperacillin-tazobactam, TMP-SMX, tigecycline, and aminoglycosides.

Carbapenemases—e.g., class A (*Klebsiella pneumoniae* carbapenemase [KPC]); class B (NDM; Verona integron–encoded metallo-β-lactamase [VIM]; and imipenemase metallo-β-lactamase [IMP]); and class D [OXA-48])—confer resistance to the same drugs as do ESBLs as well as to cephamycins and carbapenems. As with ESBLs, carbapenemase-encoding genes may be present on transferable plasmids, which often encode linked resistance to fluoroquinolones, TMP-SMX, tetracyclines, and aminoglycosides. Transposon-mediated spread (e.g., TN4401 for KPC) is also important. Unfortunately, carbapenemase-producing Enterobacteriaceae are becoming increasingly common, particularly in Asia. Asymptomatic intestinal carriage may facilitate spread.

Carbapenemase production by Enterobacteriaceae is most prevalent in *K. pneumoniae* and, secondarily, in *E. coli*, but has been described in nearly all members of the family. Carbapenem resistance may also occur in the absence of carbapenemase production, mediated by production of an AmpC β-lactamase and/or ESBL along with modifications in permeability/efflux. Resistance to any carbapenem should prompt assessment for carbapenemase production via either genotypic or phenotypic tests, if available; the exception to this rule is isolated resistance to imipenem in *M. morganii*, *Proteus*, and *Providencia*, which exhibit intrinsic low-level resistance. Although the modified Hodge test is used widely for phenotypic confirmation of carbapenemase production, its limitations include false-positive results with *Enterobacter* species and false-negative results with NDM.

For treatment of infections due to carbapenem-resistant Enterobacteriaceae, tigecycline and colistin are the most reliably active parenteral agents in vitro. However, because tigecycline reaches only low serum and urine concentrations, caution is warranted in using it to treat bacteremia and perhaps UTI, although a few case reports describe some success with tigecycline therapy for UTI. Colistin has nephrotoxic and neurotoxic potential. The recent emergence of the colistin resistance gene *mcr-1* on a stable transferable plasmid is extremely concerning since polymyxins (polymyxin B and polymyxin E [colistin]) currently constitute a last line of defense against strains that produce metallo-carbapenemases (e.g., NDM-1). In addition, in a recent study, 13% of carbapenem-resistant *K. pneumoniae* isolates were co-resistant to colistin independent of *mcr-1*.

Ceftazidime-avibactam is active in vitro against the serine carbapenemases (e.g., KPC, OXA-48) but not the metallo-carbapenemases (e.g., NDM, VIM, IMP). However, limited clinical data from an uncontrolled retrospective study of ceftazidime-avibactam for the treatment of infection with carbapenem-resistant Enterobacteriaceae demonstrated suboptimal efficacy and development of resistance in 8% of the cohort. Aminoglycosides may have some utility for combination therapy if they are active in vitro. Fosfomycin is often active in vitro, but clinical data are limited. Furthermore, resistance may develop with monotherapy and increased use, plasmid-mediated resistance (via *fosA3*) has been described (raising concern about rapid dissemination), resistance is generally more prevalent among XDR strains, susceptibility testing may not be readily available, and no parenteral formulation is available in the United States. Aztreonam is active against the problematic metallo-carbapenemases but is hydrolyzed by ESBLs and AmpC β-lactamases, which often co-exist in XDR strains. Ongoing studies are assessing aztreonam plus avibactam, a promising combination for the treatment of pan-drug-resistant strains.

Extensive resistance to available agents may leave the clinician with few or no ideal therapeutic options. However, use of a regimen that takes into account the site of infection, achievable drug levels at that site (e.g., higher concentrations of many agents in urine), and pharmacodynamic factors (e.g., prolonged infusion of β-lactam agents to maintain drug levels above the MIC) may increase the chance for a successful outcome. Likewise, observational data suggest that combination therapy may be beneficial against carbapenem-resistant Enterobacteriaceae; randomized controlled trials are in progress.

Resistance to fluoroquinolones usually is due to alterations in or protection of the target sites in DNA gyrase and topoisomerase IV, with or without decreased permeability and active efflux. Fluoroquinolone resistance is increasingly prevalent among GNB and is associated with resistance to other antimicrobial classes; for example, 20–80% of ESBL-producing enteric GNB are also resistant to fluoroquinolones. At present, fluoroquinolones should be considered unreliable as empirical therapy for GNB infections in critically ill patients.

In this era of increasing antimicrobial resistance, it is critical to culture the primary site of infection before initiating antimicrobial therapy and, for systemically ill patients, to obtain blood cultures. In vitro testing may not always detect antimicrobial resistance; therefore, it is important to assess the patient's clinical response to treatment. Moreover, as discussed above, resistance may emerge during therapy through the induction or stable derepression of AmpC β-lactamases. In addition, drainage of abscesses, resection of necrotic tissue, and removal of infected foreign bodies, sometimes referred to collectively as "source control," are often required for cure.

GNB are commonly involved in polymicrobial infections, in which the role of each individual pathogen is uncertain **(Chap. 172)**. Although some GNB are more pathogenic than others, it is usually prudent, if possible, to design an antimicrobial regimen active against all of the GNB identified, because each is capable of pathogenicity in its own right. Lastly, for patients treated initially with a broad-spectrum empirical regimen, the regimen should be de-escalated as expeditiously as possible once susceptibility results are known and the patient has responded to therapy.

PREVENTION

(See also Chap. 137) Certain measures are broadly applicable for decreasing infection risk. Antimicrobial stewardship programs should be instituted to facilitate appropriate antimicrobial use, which will minimize the development of resistance. Diligent adherence to hand-hygiene protocols by health care personnel and cleaning/disinfection or single-patient use of objects that come into contact with patients (e.g., stethoscopes and blood pressure cuffs) are essential. Indwelling devices (e.g., urinary and intravascular catheters) should be used only when necessary and inserted according to an appropriate protocol; protocols for daily-use evaluation and prompt removal should be implemented. Multi-use medication vials should be avoided if possible. Oral application of chlorhexidine decreases the incidence of pneumonia among patients on ventilators. Increasing data support the implementation of universal decolonization (e.g., chlorhexidine bathing) to prevent infection in ICU patients. The public health threat from carbapenem-resistant Enterobacteriaceae has resulted in additional recommendations, especially for carbapenemase-producing carbapenem-resistant Enterobacteriaceae, which are an even greater concern. These recommendations include contact precautions for patients colonized or infected with carbapenem-resistant Enterobacteriaceae, notification to the receiving facility from facilities transferring a patient colonized or infected with these organisms, and daily environmental cleaning. Screening of contacts and active surveillance for these bacteria may also be appropriate.

ESCHERICHIA COLI INFECTIONS

All *E. coli* strains share a core genome of ~2000 genes. In contrast, an *E. coli* strain's ability to cause infection and the nature of such infections are defined largely by accessory (i.e., non-core, non-essential) genes that encode various virulence factors. The composition of the *E. coli* accessory genome is fluid and ongoing, as demonstrated by the recent evolution of Shiga toxin–producing enteroaggregative *E. coli*.

COMMENSAL STRAINS

Commensal *E. coli* variants are an important constituent of the normal intestinal microbiota that confer benefits to the host (e.g., resistance to colonization with pathogenic organisms). Such strains generally lack the specialized virulence traits that enable extraintestinal and intestinal pathogenic *E. coli* strains to cause disease outside and within the gastrointestinal tract, respectively. However, even commensal *E. coli* strains can be involved in extraintestinal infections in the presence of

an aggravating factor, such as a foreign body (e.g., a urinary catheter), host compromise (e.g., local anatomic or functional abnormalities [including urinary or biliary tract obstruction] or systemic immunocompromise), or an inoculum that is large or contains a mixture of bacterial species (e.g., fecal contamination of the peritoneal cavity).

EXTRAINTESTINAL PATHOGENIC STRAINS

ExPEC strains are the most common enteric GNB to cause community-acquired and health care–associated bacterial infections. The emerging propensity of these strains to acquire new mechanisms of antimicrobial resistance (e.g., ESBLs and carbapenemases) poses novel challenges in managing ExPEC infection. Several ExPEC clonal groups (e.g., ST131, ST95, ST69, and ST73) are recognized to have undergone global dissemination. The mechanisms underlying the epidemiologic success of such disseminated lineages presumably include superior biological fitness and acquisition of antimicrobial resistance, as demonstrated by members of the ST131 subclone *H*30-Rx, which are resistant to fluoroquinolones and usually express the ESBL CTX-M-15. Reservoirs and transmission pathways are an active area of study, but human-to-human, food-to-human (e.g., pork, turkey, and chicken), and perhaps environment-to-human are most likely.

Like commensal *E. coli* (but unlike intestinal pathogenic *E. coli*), ExPEC strains are often found in the intestinal microbiota of healthy individuals and do not cause gastroenteritis in humans. Entry from their site of colonization (e.g., the colon, vagina, or oropharynx) into a normally sterile extraintestinal site (e.g., the urinary tract, peritoneal cavity, or lungs) is the rate-limiting step for infection. ExPEC strains have acquired accessory genes encoding diverse extraintestinal virulence factors that enable the bacteria to cause infections outside the gastrointestinal tract in both normal and compromised hosts (Table 156-1). These virulence genes define ExPEC and, for the most part, are distinct from the virulence genes that enable intestinal pathogenic strains to cause diarrheal disease **(Table 156-2)**. All age groups, all types of hosts, and nearly all organs and anatomic sites are susceptible to infection by ExPEC. Even previously healthy hosts can become severely ill or die when infected with ExPEC; however, adverse outcomes are more common among hosts with comorbid illnesses and host defense abnormalities. The diversity and the medical and economic impact of ExPEC infections are evident from consideration of the following specific syndromes.

Extraintestinal Infectious Syndromes • **URINARY TRACT INFECTION** The urinary tract is the site most frequently infected by ExPEC. UTI is an exceedingly common infection among ambulatory patients, accounting for 1% of ambulatory care visits in the United States and second only to lower respiratory tract infection among infections responsible for hospitalization. UTIs are best considered by clinical syndrome (e.g., cystitis, pyelonephritis, and catheter-associated UTI) and within the context of specific hosts (e.g., premenopausal women, compromised hosts; **Chap. 130**). *E. coli* is the single most common pathogen for all UTI syndrome/host group combinations. Each year in the United States, *E. coli* causes 80–90% of the estimated 6–8 million episodes of cystitis that occur in ambulatory, premenopausal women with an anatomically and functionally normal urinary tract (i.e., uncomplicated cystitis). Furthermore, 20% of women with an initial cystitis episode develop frequent recurrences.

Uncomplicated cystitis, the most common acute UTI syndrome, is characterized by dysuria, urinary frequency and urgency, and suprapubic pain. Fever and/or back pain suggests progression to pyelonephritis. Even when pyelonephritis is treated effectively, fever may take 5–7 days to resolve completely. Persistently elevated or increasing fever and neutrophil counts should prompt evaluation for intrarenal or perinephric abscess and/or obstruction. Pyelonephritis uncommonly causes renal parenchymal damage and loss of renal function, primarily in association with urinary obstruction, which can be preexisting or, rarely, occurs de novo in diabetic patients who develop renal papillary necrosis as a result of kidney infection. Pregnant women are at unusually high risk for developing pyelonephritis, which can adversely affect the outcome of pregnancy. As a result, prenatal screening for and treatment of asymptomatic bacteriuria during pregnancy are standard. Prostatic infection (prostatitis), a potential complication of UTI in men, can present in either an acute (severe) or a chronic (recurrent cystitis) manner. Acute pyelonephritis, acute prostatitis, and other systemic illnesses due to UTI can be designated collectively as *urosepsis*, *febrile UTI*, or *systemic UTI*. The diagnosis and treatment of UTI, as detailed in **Chap. 130**, should be tailored to the individual host, the nature and site of infection, and local patterns of antimicrobial susceptibility.

ABDOMINAL AND PELVIC INFECTION The abdomen/pelvis is the second most common site of extraintestinal infection due to *E. coli*. A wide variety of clinical syndromes occur in this location, including acute peritonitis secondary to fecal contamination, spontaneous bacterial peritonitis, dialysis-associated peritonitis, diverticulitis, appendicitis, intraperitoneal or visceral abscesses (hepatic, pancreatic, splenic), infected pancreatic pseudocysts, and septic cholangitis and/or cholecystitis. In intraabdominal infections, *E. coli* can be isolated either alone or, as occurs more often, in combination with other facultative and/or anaerobic members of the intestinal microbiota **(Chap. 127)**.

PNEUMONIA *E. coli* is not usually considered an important cause of pneumonia **(Chap. 121)**. Indeed, enteric GNB account for only 1–3% of cases of community-acquired pneumonia, in part because these organisms colonize the oropharynx only transiently in a minority of healthy individuals. However, rates of oral colonization with *E. coli* and other GNB increase with severity of illness and antibiotic use. Consequently, GNB are a more common cause of pneumonia among residents of

TABLE 156-2 Intestinal Pathogenic *E. coli*

PATHOTYPE	EPIDEMIOLOGY	CLINICAL SYNDROME[a]	DEFINING MOLECULAR TRAIT	RESPONSIBLE GENETIC ELEMENT[b]
STEC/EHEC/ST-EAEC	Food, water, person-to-person; all ages, industrialized countries	Hemorrhagic colitis, hemolytic-uremic syndrome	Shiga toxin	Lambda-like Stx1- or Stx2-encoding bacteriophage
ETEC	Food, water; young children in and travelers to developing countries	Traveler's diarrhea	Heat-stable and labile enterotoxins, colonization factors	Virulence plasmid(s)
EPEC	Person-to-person; young children and neonates in developing countries	Watery diarrhea, persistent diarrhea	Localized adherence, attaching and effacing lesion on intestinal epithelium	EPEC adherence factor plasmid pathogenicity island (locus for enterocyte effacement [LEE])
EIEC	Food, water; children in and travelers to developing countries	Watery diarrhea, occasionally dysentery	Invasion of colonic epithelial cells, intracellular multiplication, cell-to-cell spread	Multiple genes contained primarily in a large virulence plasmid
EAEC	?Food, water; children in and travelers to developing countries; all ages, industrialized countries	Traveler's diarrhea, acute diarrhea, persistent diarrhea	Aggregative/diffuse adherence, virulence factors regulated by AggR	Chromosomal or plasmid-associated adherence and toxin genes

[a]Classic syndromes; see text for details on disease spectrum. [b]Pathogenesis involves multiple genes, including genes in addition to those listed.

Abbreviations: EAEC, enteroaggregative *E. coli*; EHEC, enterohemorrhagic *E. coli*; EIEC, enteroinvasive *E. coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; ST-EAEC, Shiga toxin–producing enteroaggregative *E. coli*; STEC, Shiga toxin–producing *E. coli*.

LTCFs and are the most common cause (60–70% of cases) of hospital-acquired pneumonia **(Chap. 137)**, particularly among postoperative and ICU patients (e.g., ventilator-associated pneumonia).

Pulmonary infection is usually acquired by small-volume aspiration but occasionally occurs via hematogenous spread, in which case multifocal nodular infiltrates can be seen. Tissue necrosis, probably due to bacterial cytotoxins, is common. Despite significant institutional variation, *E. coli* is generally the third or fourth most commonly isolated type of GNB in hospital-acquired pneumonia, accounting for 5–8% of episodes in both U.S.-based and Europe-based studies. Regardless of the host, pneumonia due to ExPEC is a serious disease, with high crude and attributable mortality rates (20–60% and 10–20%, respectively).

MENINGITIS **(See also Chap. 133)** *E. coli* is one of the two leading causes of neonatal meningitis, together with group B *Streptococcus*. Most *E. coli* strains that cause neonatal meningitis possess the K1 capsular antigen and derive from a limited number of meningitis-associated clonal groups. Ventriculomegaly occurs commonly. After the first month of life, *E. coli* meningitis is uncommon, occurring predominantly in the setting of surgical or traumatic disruption of the meninges or hepatic cirrhosis. In patients with cirrhosis who develop meningitis, the meninges are presumably seeded as a result of poor hepatic clearance of portal vein bacteremia.

CELLULITIS/MUSCULOSKELETAL INFECTION *E. coli* contributes frequently to infections of decubitus ulcers and occasionally to infections of lower-extremity ulcers and wounds in diabetic patients and other hosts with neurovascular compromise. Osteomyelitis secondary to contiguous spread can occur in these settings. *E. coli* also causes cellulitis or infections of burn sites and surgical wounds (accounting for ~10% of surgical site infections), particularly when the infection originates close to the perineum. *E. coli* causes hematogenously acquired osteomyelitis, especially of vertebral discs and bodies, accounting for up to 10% of cases in some series **(Chap. 126)**. *E. coli* occasionally causes orthopedic device–associated infection or septic arthritis and rarely causes hematogenous myositis. Myositis or fasciitis of the thigh due to *E. coli* should prompt an evaluation for an abdominal source with contiguous spread.

ENDOVASCULAR INFECTION Despite being one of the most common causes of bacteremia, *E. coli* rarely seeds native heart valves. When the organism does infect native valves, it usually does so in the setting of prior valvular disease. *E. coli* infections of aneurysms, the portal vein (*pylephlebitis*), and vascular grafts are quite uncommon.

MISCELLANEOUS INFECTIONS *E. coli* can cause infection in nearly every organ and anatomic site. It occasionally causes postoperative mediastinitis or complicated sinusitis and uncommonly causes endophthalmitis, ecthyma gangrenosum, or brain abscess.

BACTEREMIA *E. coli* bacteremia can arise from infection at any extraintestinal site. In addition, *E. coli* bacteremia can arise from percutaneous intravascular devices or transrectal prostate biopsy or from the increased intestinal mucosal permeability seen in neonates and in the settings of neutropenia, chemotherapy-induced mucositis, trauma, and burns. Roughly equal proportions of *E. coli* bacteremia cases originate in the community and in health care settings. Isolation of *E. coli* from the blood is almost always clinically significant and may be accompanied by the sepsis syndrome (dysfunction of at least one organ or system) or septic shock **(Chap. 297)**.

The urinary tract is the most common source for *E. coli* bacteremia, accounting for one-half to two-thirds of episodes. Bacteremia from a urinary tract source is particularly common among patients with pyelonephritis, urinary tract obstruction, or urinary instrumentation in the presence of infected urine. The abdomen is the second most common source, accounting for ~25% of episodes. Although many of these episodes result from biliary obstruction (stones, tumor) and overt bowel disruption, which typically are readily apparent, some abdominal sources (e.g., abscesses) are remarkably silent clinically and require identification via imaging studies (e.g., computed tomography). Therefore, especially given the high prevalence of asymptomatic bacteriuria among elderly and functionally compromised individuals, the physician should be cautious in attributing *E. coli* bacteremia to a urinary source in the absence of characteristic signs and symptoms of UTI. Soft tissue, bone, pulmonary, and intravascular catheter infections are other sources of *E. coli* bacteremia.

Diagnosis Strains of *E. coli* that cause extraintestinal infections usually grow both aerobically and anaerobically within 24 h on standard diagnostic media and are identified readily by the clinical microbiology laboratory according to routine biochemical criteria. More than 90% of ExPEC strains are rapid lactose fermenters and are indole-positive.

TREATMENT

Extraintestinal *E. coli* Infections

In the past, most *E. coli* isolates were highly susceptible to a broad range of antimicrobial agents. Unfortunately, this situation has changed. Although geographic differences exist, in general, the prevalence of resistance is >20% for ampicillin, amoxicillin-clavulanate, cefazolin, TMP-SMX, and fluoroquinolones, even in community-acquired infections. This resistance precludes empirical use of these agents for serious infections. Travel outside of the United States, prior exposure to an antimicrobial agent, or exposure to a health care setting increases the likelihood of resistance. Fortunately, >90% of isolates that cause uncomplicated cystitis remain susceptible to nitrofurantoin and fosfomycin.

ESBL-producing strains are increasingly prevalent (8–60%), with the highest prevalences in Eastern Europe, Asia, and health care settings. A growing number of reports describe community-acquired UTIs caused by *E. coli* strains that produce CTX-M ESBLs. Data suggest that in some locales acquisition of CTX-M-producing, fluoroquinolone-resistant strains may result from consumption of meat products from food animals treated with third- and fourth-generation cephalosporins and fluoroquinolones. Oral treatment options for such strains are limited; however, in vitro and limited clinical data indicate that fosfomycin, pivmecillinam, and nitrofurantoin often can be used for cystitis. Carbapenems, amikacin, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam are the most predictably active agents overall. Carbapenemase-producing strains are also on the rise, but prevalences in most locales are <5%. Tigecycline and the polymyxins, with or without a second agent, have been used most frequently against these XDR isolates; however, the *mcr-1* polymyxin resistance gene has already been described in *E. coli*, and its presence calls into question the future reliability of polymyxins. Ceftazidime-avibactam is active in vitro against strains that produce serine carbapenemases such as KPC but not against those that produce metalloenzymes such as NDM-1; however, relevant clinical data are limited.

This evolving antimicrobial resistance—a source of serious concern—necessitates not only the increasing use of broad-spectrum agents for empirical therapy but also the use of appropriate narrower-spectrum agents for definitive therapy whenever possible as well as the avoidance of treatment of patients who are colonized but not infected.

INTESTINAL PATHOGENIC STRAINS

Pathotypes Certain strains of *E. coli* are capable of causing diarrheal disease. **(Other important intestinal pathogens are discussed in Chaps. 128, 129, and 160–163.)** At least in the industrialized world, intestinal pathogenic *E. coli* strains are rarely encountered in the fecal flora of healthy persons and instead appear to be essentially obligate pathogens. These strains have evolved a special ability to cause enteritis, enterocolitis, and colitis when ingested in sufficient quantities by a naive host. At least five distinct pathotypes of intestinal pathogenic *E. coli* exist: (1) Shiga toxin–producing *E. coli* (STEC), which includes the subsets enterohemorrhagic *E. coli* (EHEC) and the recently evolved Shiga toxin–producing enteroaggregative *E. coli* (ST-EAEC); (2) enterotoxigenic *E. coli* (ETEC); (3) enteropathogenic *E. coli* (EPEC); (4) enteroinvasive *E. coli* (EIEC); and (5) enteroaggregative *E. coli* (EAEC). Diffusely adherent *E. coli* (DAEC) and cytodetaching

E. coli are additional putative pathotypes. Lastly, a variant termed adherent invasive *E. coli* (AIEC) has been associated with Crohn's disease (although a causal role remains unproven) but does not cause acute diarrheal disease.

Contaminated food and water are the primary transmission vehicles for ETEC, STEC/EHEC/ST-EAEC, EIEC, and EAEC, whereas person-to-person spread (direct or indirect) is the primary transmission route for EPEC and a secondary transmission route for STEC/EHEC/ST-EAEC. Gastric acidity confers some protection against infection; therefore, persons with decreased stomach acid levels are especially susceptible. Humans are the major reservoir for such strains (except for STEC/EHEC, for which bovines are the main carriers); host range appears to be dictated by species-specific attachment factors. Although there is some overlap, each pathotype possesses a distinctive combination of virulence traits that results in a pathotype-specific pathogenic mechanism (Table 156-2). With rare exceptions, these strains are largely incapable of causing disease outside the intestinal tract. Whereas disease due to STEC/EHEC/ST-EAEC occurs primarily in high-income countries, disease due to ETEC, EPEC, and EIEC occurs primarily in low- and middle-income countries in Asia, Africa, and Latin America, and disease due to EAEC occurs globally.

SHIGA TOXIN–PRODUCING *E. COLI* STEC/EHEC/ST-EAEC strains constitute an emerging group of pathogens that can cause hemorrhagic colitis and the hemolytic-uremic syndrome (HUS). In contrast to other intestinal pathotypes, STEC/EHEC/ST-EAEC causes infections more frequently in industrialized countries than in developing regions. Several large outbreaks resulting from the consumption of fresh produce (e.g., lettuce, spinach, sprouts) and of undercooked ground beef have received significant media attention. In addition, a dramatic 2011 outbreak—mainly in Germany—involved an EAEC strain that acquired a Shiga toxin–encoding phage, resulting in a novel genotype, ST-EAEC (O104:H4). This strain was transmitted to the primary cases by sprouted fenugreek seeds, with subsequent human-to-human transmission, and resulted in >4000 cases and 54 deaths.

STEC strains are the fourth most commonly reported cause of bacterial diarrhea in the United States (after *Campylobacter*, *Salmonella*, and *Shigella*). O157:H7 is the most prominent serotype, but many other serogroups have been described, including O6, O26, O45, O55, O91, O103, O111, O113, O121, and O145. Domesticated ruminant animals, particularly cattle and young calves, serve as the major reservoir for STEC/EHEC. Ground or mechanically tenderized beef—the most common food source of STEC/EHEC strains—is often contaminated during processing. Furthermore, manure from cattle or other animals (including in the form of fertilizer) can contaminate produce (potatoes, lettuce, spinach, sprouts, fallen fruits, nuts, strawberries), and fecal runoff from these sources can contaminate water systems. Dairy products and petting zoos are additional sources of infection.

It is estimated that $<10^2$ colony-forming units (CFU) of STEC/EHEC/ST-EAEC can cause disease. Therefore, not only can low levels of food or environmental contamination (e.g., in water swallowed while swimming) result in disease, but person-to-person transmission (e.g., at day-care centers and in institutions) is an important route for secondary spread. Laboratory-associated infections also occur. Illness due to this group of pathogens occurs both as outbreaks and as sporadic cases, with a peak incidence in the summer months.

For STEC/EHEC/ST-EAEC, production of Shiga toxin (Stx2a-g and/or Stx1a,c,d) is a critical factor for occurrence of clinical disease, as demonstrated by the 2011 ST-EAEC outbreak. The *stx* gene is present on chromosomally integrated prophages, and various combinations of *stx* types and subtypes can occur in a given strain. *Shigella dysenteriae* strains that produce the closely related Shiga toxin Stx can also cause hemorrhagic colitis and HUS. Stx2 (especially Stx2a,c,d) appears to be more important than Stx1 in the development of HUS. All Shiga toxins studied to date are multimers comprising one A subunit that is enzymatically active and five identical B subunits that mediate binding to globosyl ceramides, which are membrane-associated glycolipids expressed on certain host cells. As in ricin, the Stx A subunit cleaves an adenine from the host cell's 28S rRNA, thereby irreversibly inhibiting ribosomal function (i.e., protein synthesis) and potentially leading to apoptosis.

For full pathogenicity, STEC strains require additional properties such as acid tolerance and epithelial cell adherence. Most disease-causing isolates possess the chromosomal locus for enterocyte effacement (LEE). This pathogenicity island was first described in EPEC strains and contains genes that mediate adherence to intestinal epithelial cells and a system that subverts host cells by the translocation of bacterial proteins (type III secretion system). EHEC strains make up the subgroup of STEC strains that possess stx_1 and/or stx_2 as well as LEE. In contrast, the 2011 ST-EAEC outbreak strain lacked LEE, yet was associated with a higher proportion of patients developing HUS (22%) than the historical average for STEC/EHEC outbreaks (2–8%). Data support the essential role of the 2011 outbreak strain's EAEC-associated virulence factors (e.g., AAF/I fimbriae, serine proteases SigA, SepA) in adherence, increased inflammation, and disruption of the intestinal epithelial barrier, which in turn increased the systemic translocation of Stx2a.

After exposure to STEC/EHEC/ST-EAEC and a 3- to 4-day incubation period, colonization of the colon and perhaps the ileum results in symptoms. Colonic edema and an initial non-bloody secretory diarrhea may progress to the hallmark syndrome of grossly bloody diarrhea (identified by history or examination). Significant abdominal pain and fecal leukocytes are common (70% of cases), whereas fever is not; absence of fever can incorrectly lead to consideration of noninfectious conditions (e.g., intussusception and inflammatory or ischemic bowel disease). Occasionally, infections caused by *C. difficile*, *K. oxytoca* (see "*Klebsiella* Infections," below), *Campylobacter*, and *Salmonella* present in a similar fashion. STEC/EHEC disease is usually self-limited, lasting 5–10 days.

An uncommon but feared complication of infection with STEC/EHEC strains is HUS, which occurs 2–14 days after diarrhea, most often in very young or elderly patients; in contrast, with ST-EAEC strains, HUS occurs more commonly among non-elderly adults, especially young women. It is estimated that in the United States >50% of all HUS cases—and 90% of HUS cases in children—are caused by STEC/EHEC. HUS is mediated by the systemic translocation of Shiga toxins. Erythrocytes may serve as carriers of Stx to endothelial cells located in the small vessels of the kidney and brain. The subsequent development of thrombotic microangiopathy (perhaps with direct toxin-mediated effects on various nonendothelial cells) commonly produces some combination of fever, thrombocytopenia, renal failure, and encephalopathy. Stx-mediated complement activation may also play a role in the development of HUS. Although with dialysis support the mortality rate of HUS is <10%, survivors often have persisting renal and neurologic dysfunction.

ENTEROTOXIGENIC *E. COLI* ETEC is a major cause of endemic diarrhea in low- and middle-income countries; it is responsible for an estimated 800 million cases annually. After weaning, children in these locales commonly experience several episodes of ETEC infection during the first 3 years of life. The incidence of disease diminishes with age, a pattern that correlates with the development of mucosal immunity to colonization factors (i.e., adhesins). In industrialized countries, infection usually follows travel to endemic areas, although occasional food-borne outbreaks occur.

ETEC is the most common agent of traveler's diarrhea, causing 25–75% of cases. The incidence of infection may be decreased by prudent avoidance of potentially contaminated fluids and foods, particularly items that are poorly cooked, unpeeled, or unrefrigerated **(Chap. 119)**. ETEC infection is uncommon in the United States, but outbreaks secondary to consumption of food products imported from endemic areas have occurred. A large inoculum (10^6–10^8 CFU) is needed to produce disease, which usually develops after an incubation period of 12–72 h.

After adherence of ETEC via colonization factors (e.g., CFA/I, CS), disease is mediated primarily by a heat-labile toxin (LT) and/or a heat-stable toxin (STa). Disease is less severe with strains that produce only LT. Both LT and STa cause net fluid secretion via activation of adenylate

cyclase and/or guanylate cyclase C (STa) in the jejunum and ileum. The result is watery diarrhea accompanied by cramps.

LT consists of an A and a B subunit and is structurally and functionally similar to cholera toxin. Strong binding of the B subunit to the GM_1 ganglioside on intestinal epithelial cells leads to the intracellular translocation of the A subunit, which functions as an ADP-ribosyltransferase. Mature STa is an 18- or 19-amino-acid secreted peptide that leads to increased intracellular concentrations of cGMP. Characteristically absent in ETEC-mediated disease are histopathologic changes within the small bowel; mucus, blood, and inflammatory cells in stool; and fever.

The disease spectrum of ETEC infection ranges from mild illness to a life-threatening cholera-like syndrome. Although symptoms are usually self-limited (typically lasting for 3–5 days), infection may result in significant morbidity and mortality (>250,000 deaths annually, mostly from profound volume depletion) when access to health care or suitable rehydration fluids is limited and when small and/or undernourished children are affected.

ENTEROPATHOGENIC *E. COLI* EPEC causes disease primarily in young children, including neonates. The first *E. coli* pathotype recognized as an agent of diarrheal disease, EPEC was responsible for outbreaks of infantile diarrhea (including in hospital nurseries) in industrialized countries in the 1940s and 1950s. At present, EPEC infection is uncommon in high-income countries, but among infants in low- and middle-income countries is an important cause of diarrhea (both sporadic and epidemic), often accompanied by vomiting and fever. Breast-feeding diminishes the incidence of EPEC infection. Rapid person-to-person spread may occur.

Symptoms develop after colonization of the small bowel and a brief incubation period (1 or 2 days). Initial localized adherence to enterocytes via type IV bundle-forming pili leads to a characteristic effacement of microvilli, with the formation of cuplike, actin-rich pedestals mediated by factors in the LEE. Diarrhea production is a complex and regulated process in which host cell modulation by a type III secretion system plays an important role. Strains lacking bundle-forming pili have been categorized as atypical EPEC (aEPEC); increasing data support a role for these strains as intestinal pathogens in all age groups and among HIV-infected individuals. Diarrheal stool often contains mucus but not blood. Although EPEC diarrhea is usually self-limited (lasting 5–15 days), it may persist for weeks.

ENTEROINVASIVE *E. COLI* EIEC, a relatively uncommon (or perhaps under-recognized) cause of diarrhea, is rarely identified in the United States, although a few food-related outbreaks have been described. In low- and middle-income countries, sporadic disease is recognized infrequently in children and travelers.

EIEC shares many genetic and clinical features, as well as a common ancestor, with *Shigella*. Both are intracellular pathogens whose virulence is mediated by the presence of specific factors and by the loss or inactivation of other factors (antivirulence genes), which presumably occurred during these organisms' transition from an extracellular to an intracellular lifestyle.

Colonization and invasion of the colonic mucosa, followed by replication therein and cell-to-cell spread (in part via a type III secretion system), result in the development of inflammatory colitis. However, unlike *Shigella*, EIEC produces disease only with a large inoculum (10^8–10^{10} CFU) and is less virulent, typically causing only mild, self-limited (7–10 days), watery diarrhea. Onset generally follows an incubation period of 1–3 days. Occasionally, EIEC can cause a shigellosis-like (dysentery) syndrome characterized by fever, abdominal pain, tenesmus, and scant stool containing mucus, blood, and inflammatory cells.

ENTEROAGGREGATIVE AND DIFFUSELY ADHERENT *E. COLI* EAEC has been described primarily in low- and middle-income countries and in young children. However, recent studies indicate that it also may be a relatively common cause of diarrhea in all age groups in industrialized countries. EAEC has been recognized increasingly as an important cause of traveler's diarrhea. It is highly adapted to humans—the probable reservoir. A large inoculum is required for infection, which usually manifests as watery and sometimes persistent diarrhea in healthy, malnourished, and HIV-infected hosts.

In vitro, EAEC cells exhibit a diffuse or "stacked-brick" pattern of adherence to small-intestine epithelial cells. Virulence factors that probably are necessary for disease are regulated in large part by the transcriptional activator AggR. The pathogenesis of EAEC disease begins with intestinal adherence, which results from stimulation of epithelial mucus production and bacterial biofilm formation, the latter mediated by fimbriae (AAF/I-III) and possibly the mucinase Pic and dispersin. Inflammation ensues, resulting in epithelial cell exfoliation, as does intestinal secretion mediated by the enterotoxins Pet, EAST-1, ShET1, and HlyE.

Some DAEC strains are capable of causing diarrheal disease, primarily in children 2–6 years of age in some developing countries, and may cause traveler's diarrhea. The Afa/Dr adhesins may contribute to the pathogenesis of such infections.

Diagnosis Acute infectious diarrhea can be classified as noninflammatory (most commonly viral) or inflammatory (usually bacterial); the latter is suggested by grossly bloody or mucoid stools or a positive test for fecal leukocytes or lactoferrin **(Chap. 128)**. ETEC, EPEC, DAEC, and EAEC cause noninflammatory diarrhea. Identification of these agents requires specialized assays (e.g., PCR-based tests for pathotype-specific genes) that are not routinely available; however, it is rarely necessary to identify the organisms because the associated diseases are self-limited. ETEC causes the majority and EAEC a minority of cases of noninflammatory traveler's diarrhea; here again, however, definitive diagnosis generally is not necessary for management (as discussed below). If diarrhea persists for >10 days despite treatment, *Giardia* or *Cryptosporidium* (or, in immunocompromised hosts, certain opportunistic pathogens) should be sought. The diagnosis of infection with EIEC, a rare cause of inflammatory diarrhea in the United States, also requires specialized assays.

Because of the considerable public-health importance of STEC/EHEC/ST-EAEC infections, including the threat of HUS, the CDC now recommends that all patients with community-acquired diarrhea, whether inflammatory or not, be evaluated for these pathogens by simultaneous culture (to provide an isolate for strain typing and for outbreak detection and control) and detection of Shiga toxin or its associated genes. The rationale for testing all cases of community-acquired diarrhea, regardless of clinical features, is that bloody stool and fecal white blood cells (or lactoferrin) are not reliably present with STEC/EHEC/ST-EAEC infection. In addition, the use of both tests increases diagnostic sensitivity over that with either test alone.

O157 STEC/EHEC may be identified via culture by screening for *E. coli* strains that do not ferment sorbitol, with subsequent serotyping and testing for Shiga toxin. Selective or screening media are not available for culture-based detection of non-O157 STEC/EHEC/ST-EAEC strains. Detection of Shiga toxins or toxin genes via DNA-based, enzyme-linked immunosorbent, and cytotoxicity assays offers the advantages of rapidity and detection of non-O157 STEC/EHEC/ST-EAEC strains. Specimens positive for toxin but culture-negative for O157 should be forwarded to the local or state public-health laboratory for specialized testing.

TREATMENT

Intestinal *E. coli* Infections

The mainstay of treatment for all diarrheal syndromes is replacement of water and electrolytes. This measure is especially important for STEC/EHEC/ST-EAEC infection because appropriate volume expansion may decrease renal damage and improve outcome.

The use of prophylactic antibiotics to prevent traveler's diarrhea generally should be discouraged, especially in light of high rates of antimicrobial resistance. However, in selected patients (e.g., those who cannot afford a brief illness or are predisposed to infection), the use of rifaximin, which is nonabsorbable and is well tolerated, is reasonable.

When stools are free of mucus and blood, early patient-initiated treatment of traveler's diarrhea with a fluoroquinolone or azithromycin decreases the duration of illness, and the use of loperamide may halt symptoms within a few hours. Although dysentery caused by EIEC is self-limited, treatment hastens the resolution of symptoms, particularly in severe cases. In contrast, antimicrobial therapy for STEC/EHEC/ST-EAEC infection (the presence of which is suggested by grossly bloody diarrhea without fever) should be avoided because antibiotics may increase the incidence of HUS (possibly via increased production/release of Stx). In the treatment of HUS, plasmapheresis has no benefit and the value of inhibition of C5 (via eculizumab) is unresolved.

KLEBSIELLA INFECTIONS

K. pneumoniae is the most important *Klebsiella* species from a medical standpoint, causing community-acquired, LTCF-acquired, and nosocomial infections. *K. oxytoca* is primarily a pathogen in LTCFs and hospitals. *Klebsiella* species are broadly prevalent in the environment and colonize the mucosal surfaces of mammals. In healthy humans, the prevalence of *K. pneumoniae* colonization is 5–35% in the colon and 1–5% in the oropharynx; skin is usually colonized only transiently.

Most *Klebsiella* infections in Western countries are caused by "classic" *K. pneumoniae* (cKP) and occur in hospitals and LTCFs. The most common clinical syndromes due to cKP are pneumonia, UTI, abdominal infection, intravascular device infection, surgical site infection, soft tissue infection, and secondary bacteremia. cKP strains have gained notoriety because their propensity for acquiring antimicrobial resistance determinants makes treatment challenging. Clonal group ST258, many members of which produce KPC, is undergoing international dissemination. The spread of NDM-1-producing strains from India in association with medical tourism has captured the attention of physicians and the lay press.

In addition, hypervirulent *K. pneumoniae* (hvKP) strains that are phenotypically and clinically distinct from cKP have emerged recently, having initially been recognized in Taiwan in 1986. Although hvKP infections have occurred globally in all ethnic groups, most cases have been reported in individuals of Asian ethnicity, mainly from the Asian Pacific Rim but also from other locales. Affected individuals often have diabetes mellitus. These demographics raise the possibility of a locale-specific distribution of the organism or an increased susceptibility of Asian hosts, especially those who are diabetic. In contrast to the usual health care–associated context for cKP infections in the West, hvKP is capable of causing serious life- and organ-threatening infections in younger, healthy individuals from the community and can spread metastatically to the eyes, central nervous system, and lungs from the primary site of infection.

hvKP infection initially was characterized and distinguished from traditional infections caused by cKP strains by its (1) presentation as community-acquired pyogenic liver abscess **(Fig. 156-1, *top*)**, (2) occurrence in patients lacking a history of hepatobiliary disease, and (3) propensity for metastatic spread to distant sites (11–80% of cases). More recently, the hvKP pathotype has been recognized as the cause of a variety of serious community-acquired extrahepatic abscesses and infections without liver involvement, including pneumonia, meningitis, endophthalmitis **(Fig. 156-1, *middle*)**, splenic abscess, and necrotizing fasciitis. Survivors often suffer catastrophic morbidity, such as vision loss and major neurologic sequelae.

K. pneumoniae subspecies *rhinoscleromatis* is the causative agent of rhinoscleroma, a granulomatous mucosal upper-respiratory infection that progresses slowly (over months or years) and causes necrosis and occasionally obstruction of the nasal passages. *K. pneumoniae* subspecies *ozaenae* has been implicated as a cause of chronic atrophic rhinitis and rarely of invasive disease in compromised hosts. *K.* (*Calymmatobacterium*) *granulomatis* is sexually transmitted and is the causative agent of granuloma inguinale (donovanosis) that results in chronic genital ulcers **(Chap. 168)**. These *Klebsiella* pathotypes are usually isolated from patients in tropical climates and are genomically distinct from both cKP and hvKP.

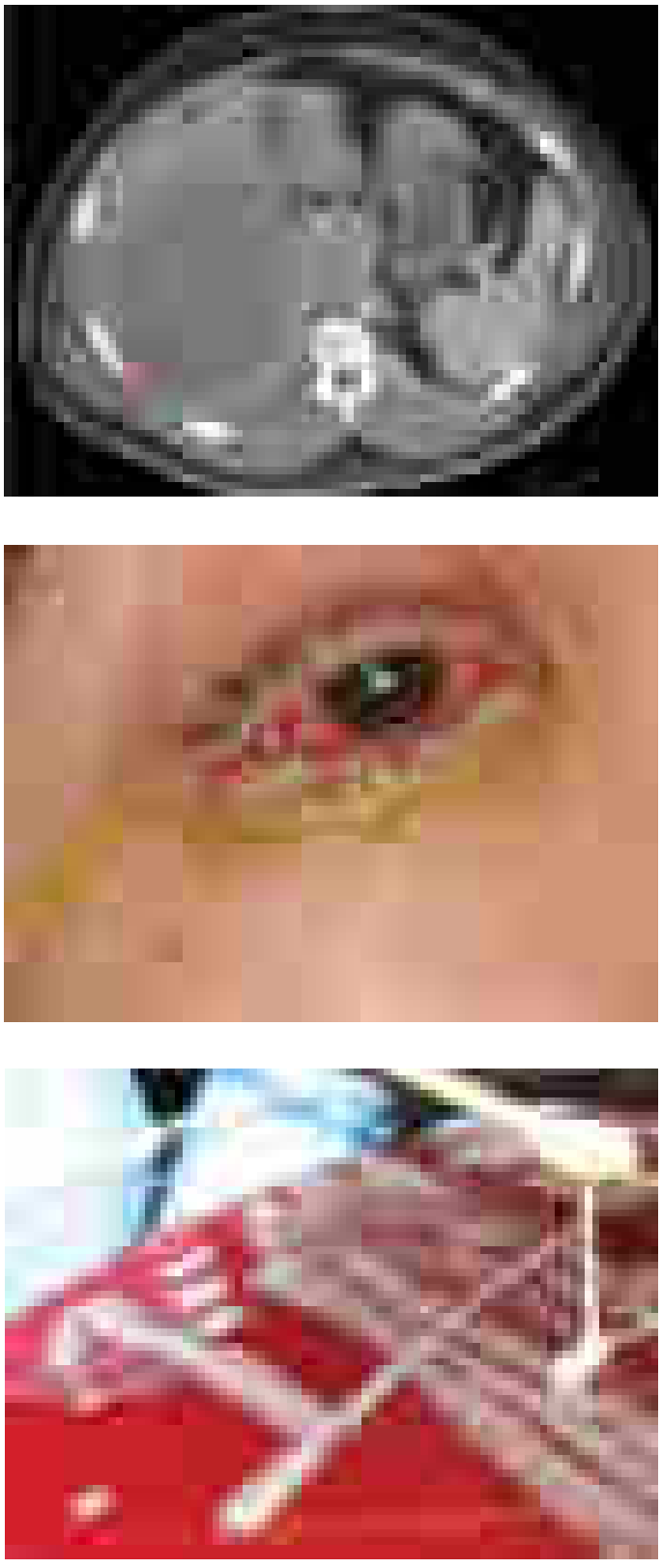

FIGURE 156-1 Hypervirulent pathotype of *K. pneumoniae* (hvKP). ***Top:*** Abdominal CT scan of a previously healthy 24-year-old Vietnamese man shows a primary liver abscess (*red arrow*) with metastatic spread to the spleen (*black arrow*). *(Courtesy of Drs. Chiu-Bin Hsaio and Diana Pomakova.)* ***Middle:*** A previously healthy 33-year-old Chinese man presented with endophthalmitis. *(From AS Shon et al: Virulence 4:107, 2013.)* ***Bottom:*** A hypermucoviscous phenotype (which does not necessarily equate with a mucoid phenotype) has been associated with hvKP strains. A positive string test is shown. However, this test is not optimally sensitive or specific. A more sensitive and specific marker is needed.

INFECTIOUS SYNDROMES

Pneumonia Although cKP accounts for only a small proportion of cases of community-acquired pneumonia in Western countries (Chap. 121), cKP and *K. oxytoca* are common causes of pneumonia among LTCF residents and hospitalized patients because of increased rates of oropharyngeal colonization in such individuals. Mechanical ventilation is an important risk factor. In Asia and South Africa, community-acquired pneumonia due to hvKP is becoming increasingly common and often occurs in younger patients with no underlying disease. *Klebsiella* is also a common cause of pneumonia in severely malnourished children in developing countries.

As in all pneumonias due to enteric GNB, typical manifestations include production of purulent sputum and evidence of airspace disease. Presentation with earlier, less extensive infection is now more common than is the classically described lobar infiltrate, bulging fissure, and currant jelly sputum. Pulmonary infection due to hvKP that has spread metastatically (e.g., from a hepatic abscess) usually includes nodular bilateral densities, more commonly in the lower lobes. Pulmonary necrosis, pleural effusion, and empyema can occur with disease progression.

UTI cKP accounts for only 1–2% of UTI episodes among otherwise healthy adults but for 5–17% of episodes of UTI in patients with anatomical and functional abnormalities of the urinary tract, including indwelling urinary catheter use (complicated UTI). UTI due to hvKP presents more commonly as renal or prostatic abscess due to bacteremic spread than as ascending infection from the urethra and bladder.

Abdominal Infection cKP causes a spectrum of abdominal infections similar to that caused by *E. coli* but is less frequently isolated from such infections than is *E. coli*. hvKP is a common cause of monomicrobial community-acquired pyogenic liver abscess; in the Asian Pacific Rim, it has been recovered with steadily increasing frequency over the past two decades, replacing *E. coli* as the most common pathogen causing this syndrome. hvKP also is increasingly described as a cause of spontaneous bacterial peritonitis and splenic abscess.

Other Infections When cKP and *K. oxytoca* cause cellulitis or soft tissue infection, it most frequently involves devitalized tissue (e.g., decubitus and diabetic ulcers, burn wounds) and immunocompromised hosts. cKP and *K. oxytoca* cause some cases of surgical site infection and nosocomial sinusitis as well as occasional cases of osteomyelitis contiguous to soft tissue infection, nontropical myositis, and meningitis (during the neonatal period and after neurosurgery). By contrast, hvKP has become an important cause of community-acquired monomicrobial necrotizing fasciitis, meningitis, endophthalmitis (Fig. 156-1, *middle*), and abscesses within the brain, subdural space, and epidural space, particularly in the Asian Pacific Rim but also globally. Cytotoxin-producing strains of *K. oxytoca* have been implicated as a cause of non–*C. difficile* antibiotic-associated hemorrhagic colitis.

Bacteremia *Klebsiella* infection at any site can produce bacteremia. Infections of the urinary tract, respiratory tract, and abdomen (especially hepatic abscess) each account for 15–30% of episodes of *Klebsiella* bacteremia. Intravascular device–related infections account for another 5–15% of episodes, and surgical site and miscellaneous infections account for the rest. *Klebsiella* is an occasional cause of sepsis in neonates and of bacteremia in neutropenic patients. However, like enteric GNB in general, *Klebsiella* rarely causes endocarditis or other endovascular infections.

DIAGNOSIS

Klebsiellae are readily isolated and identified in the laboratory. These organisms usually ferment lactose, although the subspecies *rhinoscleromatis* and *ozaenae* are nonfermenters and are indole-negative. hvKP usually possesses a hypermucoviscous phenotype (Fig. 156-1, *bottom*), although the sensitivity and specificity of the string test is less than optimal. A better diagnostic test for hvKP is needed.

TREATMENT

Klebsiella Infections

cKP and *K. oxytoca* have similar antibiotic resistance profiles. These species are intrinsically resistant to ampicillin and ticarcillin and are inconsistently susceptible to nitrofurantoin. The prevalence of resistance to amoxicillin-clavulanate, fluoroquinolones, and TMP-SMX is generally >20%. Increasing resistance is mediated primarily by plasmid-encoded ESBLs (6–70%) and carbapenemases (1–18%), with the highest prevalences in Eastern Europe and Asia and among health care–associated isolates. Furthermore, isolates of cKP that produce CTX-M ESBLs have been obtained from ambulatory patients with no recent health care contact. Oral treatment for infection due to ESBL-producing *Klebsiella* is more challenging than that for infection due to *E. coli* because of the poor activity of nitrofurantoin, the lesser activity—and perhaps lesser efficacy—of fosfomycin, and limited data on pivmecillinam. Empirical treatment of serious cKP and *K. oxytoca* infections with amikacin or a carbapenem may be prudent, depending on local susceptibility patterns and patient-specific risk factors.

Predictably, however, the ESBL-driven use of carbapenems has selected for strains of cKP and *K. oxytoca* that express carbapenemases. The limited treatment options for carbapenem-resistant *Klebsiella* are similar to those described for *E. coli*. Tigecycline, the polymyxins (e.g., colistin), and ceftazidime-avibactam are the most active agents in vitro. However, ceftazidime-avibactam is not active against metallo-carbapenemases (e.g., NDM), and resistance to polymyxins is emerging (e.g., *mcr-1*-mediated colistin resistance). A lethal infection due to a pan-resistant *K. pneumoniae* isolate has already been described in the United States. Combination therapy is often used in this setting, and consultation with relevant experts is advised.

PROTEUS INFECTIONS

Proteus species are part of the colonic flora of a wide variety of mammals, birds, fish, and reptiles. The ability of these GNB to generate histamine from contaminated fish has implicated them in the pathogenesis of scombroid (fish) poisoning (Chap. 451).

Proteus mirabilis causes 90% of *Proteus* infections, which occur in the community, LTCFs, and hospitals. *Proteus vulgaris* and *Proteus penneri* are associated primarily with infections acquired in LTCFs or hospitals. *P. mirabilis* colonizes healthy humans (prevalence, 50%), whereas *P. vulgaris* and *P. penneri* are isolated primarily from individuals with underlying disease. By far the most common site of *Proteus* infection is the urinary tract, where the principal known urovirulence factors of *Proteus* include adhesins, flagella, IgA-IgG protease, iron acquisition systems, and urease. *Proteus* less commonly causes infection at a variety of other extraintestinal sites.

INFECTIOUS SYNDROMES

UTI *P. mirabilis* causes only 1–2% of UTIs in healthy women, and *Proteus* species collectively cause only 5% of hospital-acquired UTIs. However, *Proteus* is responsible for 10–15% of cases of complicated UTI, primarily those associated with catheterization; indeed, *Proteus* accounts for 20–45% of urine isolates from chronically catheterized patients. This high prevalence is due in part to bacterial production of urease, which hydrolyzes urea to ammonia and results in alkalization of the urine. Alkalization of urine, in turn, leads to precipitation of organic and inorganic compounds, which contributes to formation of struvite and carbonate–apatite crystals, formation of biofilms on catheters, and/or development of frank calculi. *Proteus* becomes associated with the stones and biofilms; thereafter, it usually cannot be eradicated without removal of the stones or catheter. Over time, staghorn calculi may form within the renal pelvis and lead to obstruction and renal failure. Although biologically plausible, clinical support is lacking for the concept that urine samples exhibiting unexplained alkalinity should

be cultured, and isolation of a *Proteus* species (or other urea-splitting organism) should prompt consideration of an evaluation for urolithiasis.

Other Infections *Proteus* occasionally causes pneumonia (primarily in LTCF residents or hospitalized patients), nosocomial sinusitis, intraabdominal abscesses, biliary tract infection, surgical site infection, soft tissue infection (especially decubitus and diabetic ulcers), and osteomyelitis (primarily contiguous); in rare cases, it causes nontropical myositis. In addition, *Proteus* uncommonly causes neonatal meningitis, with the umbilicus frequently implicated as the source; this disease is often complicated by development of a cerebral abscess. Otogenic brain abscess also occurs.

Bacteremia Most episodes of *Proteus* bacteremia originate from the urinary tract; however, intravascular devices and any of the less common sites of *Proteus* infection are also potential sources. Endovascular infection is rare, but when endocarditis occurs it can be persistent and destructive. *Proteus* species are occasional agents of sepsis in neonates and of bacteremia in neutropenic patients.

DIAGNOSIS

Proteus is readily isolated and identified in the laboratory. Most strains are lactose-negative, produce H_2S, and demonstrate characteristic swarming motility on agar plates. *P. mirabilis* and *P. penneri* are indole-negative, whereas *P. vulgaris* is indole-positive. The inability to produce ornithine decarboxylase differentiates *P. penneri* from *P. mirabilis*.

TREATMENT

Proteus Infections

The intrinsic resistance of *P. mirabilis* to tetracyclines, cefazolin, nitrofurantoin, polymyxins, and tigecycline renders treatment of XDR isolates problematic. Acquired resistance to ampicillin (prevalence range, 15–60%), fluoroquinolones (11–55%), and TMP-SMX (20–50%) is common. Ampicillin-sulbactam tends to be more active, with resistance prevalences of 6–18%. In the United States and Canada, the prevalence of ESBL production by *P. mirabilis* remains low (generally <5%). However, rates as high as 60% have been reported from Asia. Isolates of *P. mirabilis* that produce CTX-M ESBLs have been recovered from ambulatory patients with no recent health-care contact (see the section on the treatment of extraintestinal *E. coli* infections for treatment considerations). *P. vulgaris* and *P. penneri* exhibit more extensive drug resistance than does *P. mirabilis*, and induction or selection of *P. vulgaris* variants with stable derepression of chromosomal AmpC β-lactamase may occur. For critically ill patients, carbapenems, fourth-generation cephalosporins (e.g., cefepime), ceftazidime-avibactam, ceftolozane-tazobactam, and amikacin generally display excellent activity against *Proteus* species (90–100% of isolates susceptible).

ENTEROBACTER AND *CRONOBACTER* INFECTIONS

E. cloacae and *E. aerogenes* are responsible for most *Enterobacter* infections (65–75% and 15–25%, respectively); *Cronobacter sakazakii*, *Cronobacter malonaticus* (formerly *Enterobacter sakazakii*), and *Enterobacter gergoviae* are less commonly isolated (1% for each). *Enterobacter* species cause primarily health care–related infections. The organisms are widely prevalent in foods, environmental sources (including equipment at health care facilities), and a variety of animals.

These organisms colonize few healthy humans, but the percentage colonized increases significantly with LTCF residence or hospitalization. Although colonization is an important prelude to infection, direct introduction via IV lines (e.g., contaminated IV fluids or pressure monitors) also occurs. Extensive antibiotic resistance has developed in *Enterobacter* species and probably has contributed to the emergence of the organisms as prominent nosocomial pathogens. Individuals who have previously received antibiotic treatment, have comorbid disease, and are ICU residents are at greatest risk for infection. *Enterobacter* causes a spectrum of extraintestinal infections similar to that described for other GNB.

INFECTIOUS SYNDROMES

Pneumonia, UTI (particularly catheter-related), intravascular device–related infection, surgical site infection, and abdominal infection (primarily postoperative or related to devices such as biliary stents) are the most common syndromes encountered. Nosocomial sinusitis, meningitis related to neurosurgical procedures (including use of intracranial pressure monitors), osteomyelitis, and endophthalmitis after eye surgery are less frequent. Neonates (particularly those of low birth weight) are at risk for *C. sakazakii* infection, including neonatal bacteremia, necrotizing enterocolitis, and meningitis (often complicated by brain abscess or ventriculitis). Contaminated powdered infant formula has been implicated as a source for such neonatal infections. The WHO recommends that, to reduce the initial number of bacteria, powdered infant formula should be reconstituted with hot water (>70°C) and, to limit replication of residual bacteria, the reconstituted formula should be stored at <5°C or its storage time minimized.

Enterobacter bacteremia can result from primary infection at any anatomic site. In bacteremia of unclear origin, the contamination of IV fluids or medications, blood components or plasma derivatives, catheter-flushing fluids, pressure monitors, and dialysis equipment should be considered, particularly in an outbreak setting. *Enterobacter* can also cause bacteremia in neutropenic patients. *Enterobacter* endocarditis is rare, occurring primarily in association with illicit IV drug use or prosthetic valves.

DIAGNOSIS

Enterobacter is readily isolated and identified in the laboratory. Most strains are lactose-positive and indole-negative.

TREATMENT

Enterobacter Infections

Significant antimicrobial resistance exists among *Enterobacter* strains. Ampicillin, ampicillin-sulbactam, and first- and second-generation cephalosporins have little or no activity. Extensive use of third-generation cephalosporins can induce or select for variants with stable derepression of AmpC β-lactamase, which confers resistance to these agents, to monobactams (e.g., aztreonam), and—in many cases—to β-lactam/β-lactamase inhibitor combinations. Resistance may emerge during therapy; in one study, this phenomenon was documented in 20% of clinical isolates. De novo resistance should be considered when clinical deterioration follows initial improvement, and third-generation cephalosporins should be avoided in the treatment of serious *Enterobacter* infections.

Cefepime is stable in the presence of AmpC β-lactamases; thus, it is a suitable option for treatment of *Enterobacter* infections so long as no coexistent ESBL is present. Detection of ESBLs in *Enterobacter* is difficult because of the presence of AmpC β-lactamase; nonetheless, their prevalence (particularly in *E. cloacae*) is known to be variable worldwide but is generally increasing and is now 5–50% overall. This increase is evidenced by 2014 data from the National Healthcare Safety Network, which documented resistance to third- and fourth-generation cephalosporins in 36.1% of *Enterobacter* isolates from central line–associated bloodstream infections in the United States. The prevalence of resistance has ranged from 15 to 40% for piperacillin-tazobactam and from 5 to 15% for colistin; it is more variable but generally higher for the fluoroquinolones. Fortunately, carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, amikacin, and tigecycline have generally retained excellent activity (90–99% of isolates susceptible). Once susceptibility data for a patient's isolate become available, it is advisable to de-escalate the antimicrobial regimen whenever possible.

SERRATIA INFECTIONS

S. marcescens causes the great majority (>90%) of *Serratia* infections, with other species isolated only occasionally. Serratiae are found primarily in the environment (including in health care institutions), particularly in moist settings. Serratiae have been isolated from a variety of animals, insects, and plants but only infrequently from healthy humans. In LTCFs or hospitals, reservoirs for the organisms include the hands and fingernails of health care personnel, food, milk (on neonatal units), sinks, medical equipment or devices, IV solutions or parenteral medications (particularly those generated by compounding pharmacies), prefilled syringes and multiple-access medication vials (e.g., heparin, saline), blood products (e.g., platelets), hand soaps and lotions, irrigation solutions, and even disinfectants.

Infection results from either direct inoculation (e.g., via contaminated IV fluid or injected medications or recreational drugs) or colonization (primarily of the respiratory tract). Sporadic infection is most common, but outbreaks (often involving MDR strains in adult and neonatal ICUs) also occur. Hygiene, medication-compounding standards, sterile technique, and infection control programs are critical measures to prevent infection.

The spectrum of extraintestinal infections caused by *Serratia* is similar to that for other GNB. *Serratia* species are usually considered causative agents of health care–associated infection and account for 1–3% of hospital-acquired infections. However, population-based laboratory surveillance studies in Canada and Australia have demonstrated that community-acquired *Serratia* infections occur more commonly than was previously appreciated. *Serratia* also is one of the pathogens associated with chronic granulomatous disease.

INFECTIOUS SYNDROMES

The respiratory tract, the genitourinary tract, intravascular devices, the eye (contact lens–associated keratitis and other ocular infections), surgical wounds, and the bloodstream (from contaminated infusions) are the most common sites of *Serratia* infection; the former five sites are the most common sources of *Serratia* bacteremia. Soft tissue infections (including myositis, fasciitis, mastitis), osteomyelitis, abdominal and biliary tract infections (postprocedural), and septic arthritis (primarily from intraarticular injections) occur less commonly. Serratiae are uncommon causes of neonatal or postsurgical meningitis and of bacteremia in neutropenic patients. Endocarditis is rare.

DIAGNOSIS

Serratiae are readily cultured and identified by the laboratory and are usually lactose- and indole-negative. The red pigmentation of some *S. marcescens* strains and *Serratia rubidaea* can produce distinctive clinical findings (e.g., pink breast milk or hypopyon; pseudohemoptysis).

TREATMENT

Serratia Infections

Most *Serratia* strains (>80%) are resistant to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, first-generation cephalosporins, cephamycins, nitrofurantoin, and colistin. Induction or selection of variants with stable derepression of chromosomal AmpC β-lactamases may develop during therapy. Both in the United States and globally, the prevalence of ESBL-producing isolates is generally low (<5%), but rates of 20–30% have been reported in Asia and Latin America. Acquisition of carbapenemase-encoding genes is uncommon but increasing. For critically ill patients, carbapenems, amikacin, ceftazidime-avibactam, and ceftolozane-tazobactam are most reliably active (>90% susceptible).

CITROBACTER INFECTIONS

C. freundii and *Citrobacter koseri* cause most human *Citrobacter* infections, which are epidemiologically and clinically similar to *Enterobacter* infections. *Citrobacter* species are commonly present in water, food, soil, and certain animals. *Citrobacter* is part of the normal fecal microbiota in a minority of healthy humans, but colonization rates are higher in LTCFs and hospitals—the settings in which nearly all *Citrobacter* infections occur. *Citrobacter* species account for 1–2% of nosocomial infections. The affected hosts are usually immunocompromised and/or have comorbid disease or disruption of skin or mucosal barriers. *Citrobacter* causes extraintestinal infections similar to those described for other GNB.

INFECTIOUS SYNDROMES

The urinary tract accounts for 40–50% of *Citrobacter* infections. Less commonly involved sites include the biliary tree (particularly with stones or obstruction), the respiratory tract, surgical sites, soft tissue (e.g., decubitus ulcers), the peritoneum, and intravascular devices. Osteomyelitis (usually from a contiguous focus), adult central nervous system infection (from neurosurgical or other types of meningeal disruption), and myositis occur rarely. *Citrobacter* (primarily *C. koseri*) also causes 1–2% of neonatal meningitis cases, of which 50–80% are complicated by brain abscess. Further, case reports in adults suggest that *C. koseri* infection has a predilection for abscess formation. Bacteremia is most often due to UTI, biliary/abdominal infection, or intravascular device infection. *Citrobacter* occasionally causes bacteremia in neutropenic patients. Endocarditis and endovascular infections are rare.

DIAGNOSIS

Citrobacter species are readily isolated and identified; 35–50% of isolates are lactose-positive, and 100% are oxidase-negative. *C. freundii* is indole-negative, whereas *C. koseri* is indole-positive.

TREATMENT

Citrobacter Infections

C. freundii is more extensively antibiotic-resistant than is *C. koseri*. More than 90% of isolates are resistant to ampicillin and to first- and second-generation cephalosporins, and >50% of strains are resistant to ampicillin-sulbactam. *Citrobacter* species (except *C. koseri*) possess AmpC β-lactamases; induction or selection of variants with stable derepression may occur during therapy. The prevalence of resistance generally ranges from 15 to 35% for third-generation cephalosporins, from 5 to 15% for piperacillin-tazobactam and fluoroquinolones, and from 5 to 20% for TMP-SMX. The prevalence of ESBL production is <5%. Carbapenems, amikacin, cefepime, tigecycline, ceftazidime-avibactam, ceftolozane-tazobactam, fosfomycin, and colistin are most active (>90% of isolates susceptible).

MORGANELLA AND *PROVIDENCIA* INFECTIONS

M. morganii, *Providencia stuartii*, and (less frequently) *Providencia rettgeri* are the members of their respective genera that cause human infections. The epidemiologic associations, pathogenic properties, and clinical manifestations of these organisms resemble those of *Proteus* species. *Morganella* and *Providencia* occur more commonly among LTCF residents than among hospitalized patients, largely resulting from chronic urinary-catheter use. In settings with extensive use of polymyxins and tigecycline, these organisms may become increasingly common because of their intrinsic resistance to these agents.

INFECTIOUS SYNDROMES

These species are primarily urinary tract pathogens, causing UTIs that are most often associated with long-term (>30-day) catheterization. Such infections commonly lead to biofilm formation and catheter encrustation (sometimes causing catheter obstruction) or the development of struvite bladder or renal stones (sometimes causing renal obstruction and serving as foci for relapse). *Morganella* is also commonly isolated from snakebite infection.

Other, less common infectious syndromes include surgical site infection, soft tissue infection (primarily involving decubitus and diabetic ulcers), burn site infection, pneumonia (particularly ventilator-associated), intravascular device infection, and intraabdominal infection. Rarely, the other extraintestinal infections described for GNB also

occur. Bacteremia is uncommon; when it does occur, any infected site can serve as the source, but the urinary tract accounts for most cases, with the next most common sources being surgical site, soft tissue, and hepatobiliary infections.

DIAGNOSIS

M. morganii and *Providencia* are readily isolated and identified. Nearly all isolates are lactose-negative and indole-positive.

TREATMENT

Morganella and *Providencia* Infections

Morganella and *Providencia* may be extensively resistant to antibiotics. Most (or all) isolates are resistant to ampicillin, ampicillin-sulbactam, first-generation cephalosporins, nitrofurantoin, fosfomycin, tigecycline, and the polymyxins; treatment of XDR strains is especially challenging. The β-lactamase inhibitor tazobactam increases susceptibility to β-lactam agents, but sulbactam and clavulanic acid do not. *Morganella* and *Providencia* possess inducible AmpC β-lactamases; clinically significant induction or selection of stably derepressed mutants may develop during therapy. The prevalence of resistance generally ranges from 10 to 30% for the third-generation cephalosporins, from 10 to 40% for fluoroquinolones, and from 20 to 40% for TMP-SMX; the prevalence is more widely variable for piperacillin-tazobactam. The prevalence of ESBL-producing isolates is <5%. Carbapenems, amikacin, cefepime, ceftazidime-avibactam, and ceftolozane-tazobactam are the most active agents (>90% of isolates susceptible). Removal of a colonized urinary catheter or stone is critical for eradication of UTI.

EDWARDSIELLA INFECTIONS

E. tarda is the only member of the genus *Edwardsiella* that is associated with human disease. This organism is found predominantly in freshwater and marine environments and in the associated aquatic animal species. Human acquisition occurs primarily from interaction with these reservoirs or ingestion of inadequately cooked aquatic animals. *E. tarda* infection is rare in the United States, where acquisition occurs mainly along the Gulf of Mexico; recently reported cases are mostly from Asia. This pathogen shares clinical features with *Salmonella* species (as an intestinal pathogen; **Chap. 160**), *Vibrio vulnificus* (as an extraintestinal pathogen; **Chap. 163**), and *Aeromonas hydrophila* (as both an intestinal and an extraintestinal pathogen; **Chap. 153**).

INFECTIOUS SYNDROMES

Gastroenteritis is the predominant infectious syndrome (50–80% of infections). Self-limiting watery diarrhea is most common, but severe colitis also occurs. The most common extraintestinal infection is wound infection due to direct inoculation, which is often associated with freshwater, marine, or snakebite injuries. Other infectious syndromes result from invasion of the gastrointestinal tract and subsequent bacteremia. Most afflicted hosts have comorbidities (e.g., hepatobiliary disease, iron overload, cancer, or diabetes mellitus). A primary bacteremic syndrome, sometimes complicated by meningitis, has a 40% case–fatality rate. Visceral (primarily hepatic) and intraperitoneal abscesses also occur, as do endocarditis and empyema.

DIAGNOSIS

Although *E. tarda* can readily be isolated and identified, most laboratories do not routinely seek to identify it in stool samples. Production of hydrogen sulfide is a characteristic biochemical property.

TREATMENT

Edwardsiella Infections

E. tarda is susceptible to most antimicrobial agents appropriate for use against GNB. Gastroenteritis is generally self-limiting, but treatment with a fluoroquinolone may hasten resolution. In the setting of severe sepsis, fluoroquinolones, third- and fourth-generation cephalosporins, carbapenems, and amikacin—either alone or in combination—are the safest choices pending susceptibility data.

INFECTIONS CAUSED BY MISCELLANEOUS GENERA

Species of *Hafnia*, *Kluyvera*, *Cedecea*, *Pantoea*, *Ewingella*, *Leclercia*, *Raoultella*, and *Photorhabdus* are occasionally isolated from diverse clinical specimens, including blood, sputum, urine, cerebrospinal fluid, joint fluid, bile, and wounds. These organisms are rare and usually cause infection in compromised hosts or in association with an invasive procedure or foreign body. Cephalosporinases from *Kluyvera* have been implicated as the progenitors of CTX-M ESBLs. *Kluyvera* and *Raoultella* may produce carbapenemases.

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157 *Acinetobacter* Infections

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DEFINITION

Acinetobacter species were first described in 1911 and named *Micrococcus calcoaceticus*. Thereafter, the genus was renamed multiple times; since 1950, it has been known as *Acinetobacter*. *Acinetobacter* species are gram-negative, oxidase-negative, nonmotile, nonfermenting coccobacilli that are easily recovered on standard culture media. Differentiation among *Acinetobacter* species on the basis of phenotypic characteristics alone is very difficult. Molecular-based methods such as matrix-assisted laser desorption–ionization–time-of-flight mass spectrometry (MALDI-TOF-MS) and quantitative real-time polymerase chain reaction (PCR) are usually necessary to identify *Acinetobacter baumannii*, the most clinically relevant species of the genus.

ETIOLOGY AND EPIDEMIOLOGY

Acinetobacter species are naturally encountered in water and soil and have also been recovered from fruits and vegetables. In humans, *Acinetobacter* can be found on the skin and in the respiratory and gastrointestinal tracts. *A. baumannii* is capable of surviving environmental

desiccation for weeks; this characteristic is important from an infection-control perspective as it allows this organism to persist in the hospital environment and on equipment.

Acinetobacter was historically considered a pathogen of hot and humid climates. In recent years, however, hospital outbreaks caused by *A. baumannii* have been reported worldwide, even in temperate climates. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that 12,000 *Acinetobacter* infections occur every year, 7300 of which are caused by multidrug-resistant strains, with 500 attributable deaths. The increase in the number of infections with *A. baumannii* is suspected to be due to the rapid spread of certain genetically distinct lineages; of the three international clonal lineages (ICLs), ICL I and ICL II are multidrug resistant. The predominance of these lineages remains unexplained, although it has been proposed that this population structure is the result of two waves of expansion. The first wave followed a bottleneck (possibly linked to a restricted ecologic niche) that occurred in the distant past. The second wave is ongoing and is being driven by the rapid expansion of a limited number of multidrug-resistant clones.

Analysis of the *A. baumannii* pangenome (the sum of the core and dispensable genomes) has shown that its organization is characterized by a small core genome and a large accessory or disposable genome. This organization reflects *A. baumannii's* high plasticity, which enables it to acquire exogenous genetic material. With few exceptions, gene functions associated with virulence are found in the core genome; this observation suggests a limited role for the acquisition of new virulence traits in the recent nosocomial expansion of *A. baumannii* clones. Genes associated with resistance to antimicrobial agents are found in both the species core genome and the accessory genome. In the accessory genome, these genes have been found in alien islands, often flanked by integrases, transposases, or insertion sequences. This pattern suggests possible acquisition by horizontal gene transfer from other *Acinetobacter* strains or even from different bacterial species present in the immediate environment. Acquisition of these antimicrobial resistance genes is hypothesized to have led to the recent rapid expansion of highly homogeneous clonal lineages, whose main difference from nonclonal *A. baumannii* appears to be their antimicrobial resistance.

Health Care–Associated Infections Infections caused by *A. baumannii* occur frequently among patients admitted to intensive care units (ICUs). Risk factors for colonization and infection with this pathogen include nursing home residence, prolonged ICU stay, central venous catheterization, tracheostomy, mechanical ventilation, enteral feedings, and treatment with third-generation cephalosporins, fluoroquinolones, and carbapenems. Acquisition of carbapenem-resistant *A. baumannii* is most common among patients exposed to carbapenems. Spread of *A. baumannii* across different regions is facilitated by the movement of patients between health care systems and throughout the continuum of health care. Within the hospital, environmental spread of *A. baumannii* occurs as a result of inappropriate hand hygiene among workers providing health care for infected or colonized patients and the contamination of hospital equipment, such as respiratory therapy and ventilation equipment. The air surrounding the patient may also play a role in environmental colonization with *A. baumannii*, especially in inpatient areas without physical barriers between patients and with an inadequate number of air exchanges.

A. baumannii strains identified during hospital outbreaks are typically resistant to more antibiotic classes than strains from the community. The prevalence of colonization with *A. baumannii* at the time of admission or during a stay in a long-term acute-care hospital (LTACH) or nursing home is variable and depends on regional flora. Outbreaks of *A. baumannii* in acute-care hospitals and LTACHs that "share" patients have been described in Ohio, Michigan, Illinois, and Indiana.

Community-Acquired Infections Community-acquired infections caused by *Acinetobacter* have been described in Australia and Asia. Few cases have been reported in regions with a temperate climate, and even those few cases have taken place during warm and humid months. Risk factors for community-acquired pneumonia due to this organism include a history of alcohol abuse, diabetes mellitus, smoking, and chronic lung disease.

War Zone–Associated Infections Infections caused by *Acinetobacter* in war zones include skin and soft tissue infections associated with traumatic injuries and bloodstream infections. Outbreak investigations of *A. baumannii* infections among military personnel returning from Iraq and Afghanistan suggested the acquisition of *A. baumannii* in field hospitals rather than colonization of the skin before an injury. This view is supported by the recovery of *A. baumannii* isolates with similar genetic characteristics from inanimate surfaces in field hospitals and from patients.

Disaster Medicine *A. baumannii* is linked to infections among victims of trauma during tsunamis, earthquakes, and terrorist attacks. The types of infections most frequently observed in these settings are soft tissue injuries, but bloodstream infections and pneumonia have also been reported. In addition, outbreaks of *A. baumannii* infection in ICUs caring for disaster victims have been described.

PATHOGENESIS

Mechanisms of pathogenesis and virulence in *Acinetobacter* species have not been fully elucidated. However, *A. baumannii* seems to have greater virulence potential than other *Acinetobacter* species, as evidenced by its ability to grow at 37°C and to resist uptake by macrophages.

Initial *A. baumannii* colonization of the host and the environment is facilitated by the organism's ability to adhere to surfaces and human cells and to create biofilms. The ability to form a biofilm is phenotypically associated with exopolysaccharide production and pilus formation. A quorum-sensing molecule encoded by the *abaI* autoinducer synthase gene has been implicated in *A. baumannii* biofilm formation on abiotic surfaces. Outer-membrane porins appear to mediate cell apoptosis. *A. baumannii* can survive in harsh environments within the host and on inanimate surfaces by modifying the structure of its lipid A, with a consequent decrease in susceptibility to antibiotics and antimicrobial peptides and an increase in survival upon desiccation.

Acinetobacter species produce an extracellular capsule that protects the bacteria from external threats, including complement-mediated killing. Studies of mouse models showed that *Acinetobacter* species can increase capsule production in the presence of subinhibitory levels of antibiotic—an ability that leads to increased resistance to complement-mediated killing and a hypervirulent phenotype.

Phospholipase C and phospholipase D have been identified as virulence factors in *A. baumannii.* These enzymes exert cytotoxic effects on epithelial cells and facilitate their invasion.

Iron-acquisition systems are also important virulence mechanisms in *A. baumannii*. Through secretion of siderophores (low-molecular-mass ferric-binding compounds), *A. baumannii* is able to grow despite iron deficiencies in the surrounding environment (e.g., in the human host).

Several protein-secretion systems have been identified in *A. baumannii*. The most recently described is a type II secretion system. The substrate for this system, the LipA lipase, is required for growth on medium containing lipids as a sole carbon source. Mutants lacking the genes for the type II secretion system or its substrate exhibit defective in vivo growth in a neutropenic murine model of bacteremia. *A. baumannii* also has a type VI secretion system whose primary function seems to be to secrete antibacterial toxins that kill competing bacteria, including other strains in the same species.

The type V autotransporter system has been characterized in *A. baumannii.* In a murine systemic model of *Acinetobacter* infection, the *Acinetobacter* trimeric autotransporter mediates biofilm formation and maintenance; adherence to extracellular matrix components such as collagen I, II, and IV; and virulence.

Outer-membrane vesicles (OMVs) play a special role in protein secretion. Many *A. baumannii* strains secrete OMVs containing various virulence factors, including outer-membrane protein A (OmpA), proteases, and phospholipases. The membrane proteins in OMVs are responsible for eliciting a potent innate immune response. Several studies have shown that *A. baumannii* OMVs could be used as an acellular vaccine to effectively control *A. baumannii* infections.

Nosocomial strains of *Acinetobacter* can deploy multiple mechanisms of resistance, including alterations in porins and efflux pumps and expression of β-lactamases. More specifically, *Acinetobacter* species can reduce the expression of porins, thus hindering the passage of β-lactam antibiotics into the periplasmic space. These species can overexpress bacterial efflux pumps and decrease the concentration of β-lactam antibiotics in the periplasmic space. Efflux pumps can also actively remove quinolones, tetracyclines, chloramphenicol, disinfectants, and tigecycline. *Acinetobacter* species possess chromosomally encoded cephalosporinases and are capable of acquiring β-lactamases, including serine and metallo-β-lactamases. AmpC β-lactamases are class C β-lactamases intrinsic to all *A. baumannii* strains. Although these enzymes are expressed at low levels and are not inducible, the addition of the insertion sequence *ISAba1* next to the AmpC gene increases β-lactamase production, with resulting resistance to cephalosporins.

Carbapenem resistance in *Acinetobacter* species is mostly tied to the emergence of Ambler class D oxacillinases of group 2d, some of which are intrinsic and chromosomal (e.g., OXA-51-like) while others are acquired and are found in plasmids or are chromosomally encoded (e.g., OXA-23-like, 24 [33-like, 40-like], 58-like, 143-like, and 235-like).

CLINICAL MANIFESTATIONS

Pneumonia *A. baumannii* is a notorious cause of nosocomial pneumonia, most frequently among patients requiring prolonged mechanical ventilation. The onset of disease tends to be later than that caused by other gram-negative bacilli; however, clinical symptoms of hospital-acquired or ventilator-associated pneumonia due to *A. baumannii* are similar to those of nosocomial or ventilator-associated pneumonia due to other nosocomial pathogens. Thus, the most common indicators of infection include fever and increased sputum production. The positivity of respiratory cultures in most cases may present a challenge for the clinician, since airway colonization with *A. baumannii* is a risk factor for infection itself. Radiologic findings are nonspecific and can include lobar consolidations and pleural effusions, but cavitations are rarely seen. The crude mortality rates associated with nosocomial pneumonia due to *A. baumannii* are reported to be as high as 65%. However, since these infections occur in debilitated patients, their attributable mortality has been difficult to establish.

Community-acquired pneumonia due to *A. baumannii* is a relatively rare entity. Its clinical presentation is characterized by fever, severe respiratory symptoms, and multiple-organ dysfunction. Patients frequently have a cough productive of purulent sputum, shortness of breath, and chest pain. Imaging studies usually show lobar consolidation. Mortality rates associated with this process are >50%.

Bloodstream Infections Bloodstream infections due to *A. baumannii* are most frequent among ICU patients and usually occur in the presence of a central venous catheter or as a secondary complication of hospital-acquired or ventilator-associated pneumonia. Polymicrobial growth has been reported in 20–36% of bacteremia episodes. Fever is the most common sign of infection (developing in >95% of cases), and presentation with septic shock and disseminated intravascular coagulopathy has been described in as many as 25 and 30% of patients, respectively. *A. baumannii* bloodstream infections often result in higher hospitalization costs and longer ICU stays. Crude mortality rates from this infection are as high as 40%; however, rates can be as high as 70% from infections caused by carbapenem-resistant isolates. In patients with infections caused by extremely drug-resistant strains, poor outcomes are thought to be driven by delays in the initiation of adequate antimicrobial therapy.

Skin and Soft Tissue Infections *Acinetobacter* species have been described as part of the skin flora, yet the majority of the organisms from this genus that colonize the skin are not those associated with nosocomial infections. Discerning infection from wound colonization is challenging. Gunshot wounds and the presence of orthopedic external-fixation devices are common among patients with combat trauma–associated *A. baumannii* skin and soft tissue infections. The report on a case series of eight U.S. military patients described the clinical presentation of their infections as evolving from an edematous *peau d'orange* appearance to a sandpaper appearance with overlying vesicles and then to a necrotizing process with hemorrhagic bullae. Other case series have also included necrotizing fasciitis. *A. baumannii* is an important pathogen in burn units worldwide. Large burns provide ideal conditions for *A. baumannii* and facilitate patient-to-patient transmission. The presence of *A. baumannii* in wounds contributes to healing delays and graft loss. In addition, wound colonization is a risk factor for bloodstream infections among patients with extensive burn injuries.

A. baumannii infections resulting from trauma to soft tissues in the setting of natural disasters, such as tsunamis and earthquakes, have been reported. The implication is that *A. baumannii* should be considered in the differential diagnosis of soft tissue infections following exposure to tropical and subtropical environments.

Urinary Tract Infections *A. baumannii* is an infrequent cause of urinary tract infections. The majority of cases reported are catheter-associated infections, reflecting the ability of *A. baumannii* to form biofilms on these devices. A few reports have described community-acquired infections occurring in the setting of nephrolithiasis and after renal transplantation.

Meningitis Central nervous system infections with *A. baumannii* have been reported in the context of outbreaks, traumatic injuries, neurosurgical procedures, and external ventricular drains. One case series described a petechial rash in up to 30% of patients. *Acinetobacter* species may look similar to *Neisseria meningitidis* on a Gram's stain of cerebrospinal fluid; both appear as gram-negative paired cocci.

Other Miscellaneous Infections A few cases of *A. baumannii* keratitis associated with the use of contact lenses have been reported. Cases of native- and prosthetic-valve endocarditis have also been described.

TREATMENT

Acinetobacter Infections

Treatment of *Acinetobacter* infections is challenging because *Acinetobacter* can develop resistance to most available antibiotics. Therefore, the choice of empirical therapy should be based on local epidemiology and the patient's colonization status. Definitive therapy should be determined by antimicrobial susceptibility testing. Antimicrobial options for the management of infections caused by *A. baumannii* are displayed in **Table 157-1**.

Acinetobacter species possess intrinsic β-lactamases that inactivate first- and second-generation cephalosporins. Through acquisition of extended-spectrum β-lactamases, the organisms can also become resistant to third- and fourth-generation cephalosporins. Nevertheless, when the isolate is susceptible, β-lactam agents are the drugs of choice for the treatment of *A. baumannii*. Among β-lactamase inhibitors, sulbactam is active against *A. baumannii* and is as effective as carbapenems and polymyxins.

Carbapenems have been the preferred drugs for treatment of invasive or hospital-acquired infections. Unfortunately, surveillance data from U.S. hospitals show that up to 50% of *A. baumannii* isolates recovered from ICUs are carbapenem resistant, and rates of carbapenem resistance are even higher around the world.

Aminoglycosides are of limited utility against *A. baumannii* because of toxicity and lack of lung penetration. Inhaled formulations of tobramycin have been used with variable success.

Polymyxins are cationic detergents that fell out of use as a result of nephrotoxicity and neurotoxicity. In vitro, they are the most active agents against carbapenem-resistant *A. baumannii*. Colistin has been used in both intravenous and inhaled formulations, although the optimal dosage has not yet been determined.

Tigecycline is a glycylcycline with clinical activity against *A. baumannii*. It reaches only low serum concentrations and therefore cannot be used for bloodstream infections. The susceptibility of isolates is variable, especially in outbreak settings, and the emergence of resistance during treatment has been reported.

TABLE 157-1 Therapeutic Options for the Management of Multidrug-Resistant *Acinetobacter baumannii* Infections

ANTIBIOTIC	DOSING[a]	COMMENTS
Sulbactam	3–9 g/d (9–27 g/d if given in combination with ampicillin)	Unavailable as single drug in many countries (including the United States)
Meropenem	2 g q8h	Prolonged infusion (3–4 h) has been used; limited data
Imipenem	500 mg q6h	Prolonged infusion (3–4 h) has been used; limited data
Colistin	Loading dose of 5 mg/kg followed by 2.5–5.0 mg/kg per day of colistin base given in 2–4 divided doses	Optimal dosing regimen unknown Inhaled formulation has been used as adjunct treatment in lung infections.
Polymyxin B	1.5–3 mg/kg q12h	
Tigecycline	100-mg loading dose followed by 50 mg q12h	Low serum concentrations and bacteriostatic activity limit use in bacteremia.
Minocycline	100 mg q12h	Loading dose of 200 mg IV has been used.
Amikacin	15 mg/kg qd	Inhaled formulation of tobramycin has been used as adjunct treatment in lung infections.
Rifampin	600 mg qd or 600 mg q12h	Use in combination therapy
Fosfomycin	4 g q12h PO	Use in combination therapy IV formulation not available in the United States

[a]All drugs are given by the IV route unless otherwise stated.

Minocycline is a tetracycline that has a bacteriostatic effect on *A. baumannii*. Synergistic and bactericidal activity has been noted when minocycline is used in combination with colistin or a carbapenem.

Fosfomycin is an inhibitor of peptidoglycan synthesis that has no direct activity against *A. baumannii* but has been observed to be synergistic in vitro in combination with colistin or sulbactam. Clinical data have shown higher rates of microbiologic cure, but no differences in clinical response, with combinations of fosfomycin and colistin.

In vitro data favor combination therapy with colistin in many different regimens containing a carbapenem (imipenem, meropenem), rifampin, minocycline, ceftazidime, azithromycin, doxycycline, trimethoprim-sulfamethoxazole, or ampicillin-sulbactam. However, clinical data have not shown such combination therapy to be superior to colistin alone.

COMPLICATIONS AND PROGNOSIS

Infections caused by *A. baumannii* can be associated with high mortality rates. Factors contributing to higher mortality are thought to include severity of the patient's underlying illness and drug resistance in the infecting strain.

INFECTION CONTROL AND PREVENTION

Acinetobacter species are capable of surviving on hospital surfaces for prolonged periods. In the hospital environment, *A. baumannii* has been associated with establishment of a *fecal patina*; this term refers to a coating of enteric organisms that can cover the skin of colonized patients and extend to their surrounding environment. Concentrations of enteric organisms are highest in the colonized patient's rectum, with spread in a target-like concentric pattern covering the patient's body and the surrounding environment. High-frequency touch areas in rooms occupied by patients colonized with *A. baumannii* are more likely to be contaminated. The hands, gloves, and gowns of health care workers can be contaminated after entry into the room of a patient colonized with *A. baumannii* **(Fig. 157-1)**.

Outbreaks caused by *A. baumannii* are frequently mono- or oligoclonal. A common source of infection has been identified in ~50% of outbreaks. These sources include respiratory therapy equipment, the hands of health care workers, bedside humidifiers, warm bathwater, hospital-prepared distilled water, bedpans, urine jugs, heparinized saline solution, mattresses, reusable pressure transducers in arterial lines, and fluids used for pressure lavage of wounds.

Control of multidrug-resistant *Acinetobacter* outbreaks starts with early recognition, with subsequent halting of the spread of infection throughout a facility and prevention of the establishment of an endemic strain. It is important to identify the outbreak strain and differentiate it from non-outbreak strains so that infection control activities can be better targeted. Traditionally, the strain was identified with phenotypic typing systems (biotyping) or by determination of

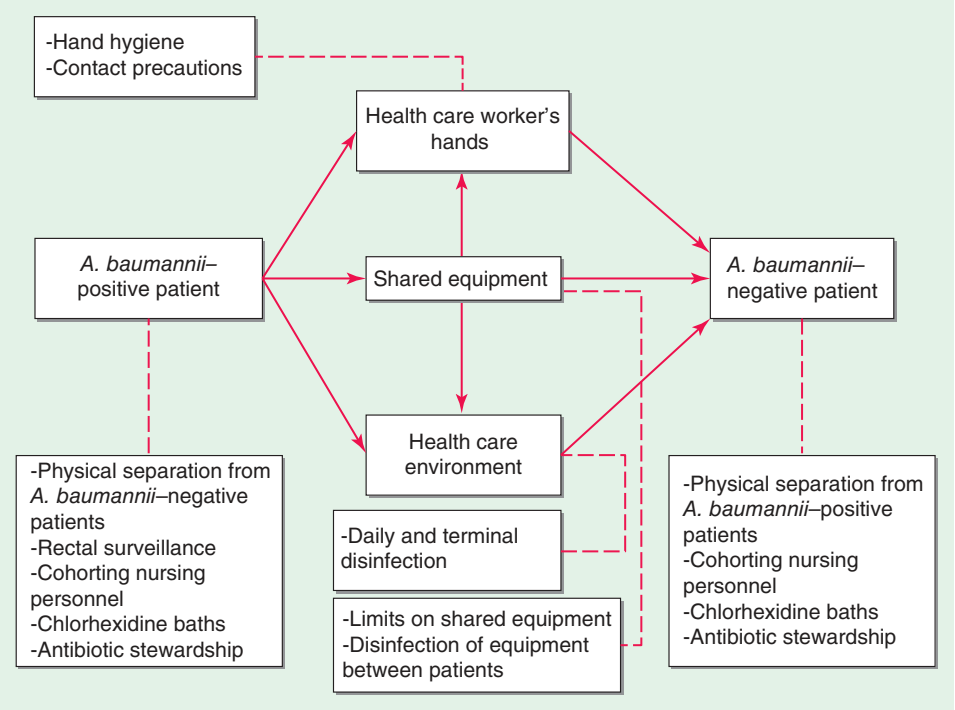

FIGURE 157-1 Strategies for the prevention of dissemination of *Acinetobacter baumannii* in health care facilities.

antimicrobial susceptibility patterns. Molecular typing systems have ushered in an era of molecular epidemiology that allows more precise identification of outbreak strains through use of techniques such as ribotyping, pulse-field gel electrophoresis, repetitive sequence-based PCR, and multilocus sequence testing.

During outbreaks, the simultaneous introduction of multiple ("bundled") measures makes it difficult to assess the impact of each individual measure. These interventions include aggressive cleaning of the general environment, active surveillance, contact isolation of colonized or infected patients, cohorting of medical staff, reinforcement of compliance with hand hygiene by health care workers, and use of aseptic care devices.

Colonization with *A. baumannii* is a strong predictor of subsequent clinical infection by this organism. Exposure to carbapenems is a risk factor for initial acquisition of this pathogen; therefore, efforts to curtail unnecessary use of antibiotics are fundamental to the prevention of *A. baumannii* colonization of patients and the organism's establishment in health care facilities.

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158 *Helicobacter pylori* Infections

John C. Atherton, Martin J. Blaser

Helicobacter pylori colonizes the stomach in ~50% of the world's human population, essentially for life unless eradicated by antibiotic treatment. Colonization with this organism is the main risk factor for peptic ulceration **(Chap. 317)** as well as for gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma **(Chap. 76)**. Treatment for *H. pylori* has revolutionized the management of peptic ulcer disease, providing a permanent cure in most cases. Such treatment also represents first-line therapy for patients with low-grade gastric MALT lymphoma. Treatment of *H. pylori* is of no benefit in the treatment of gastric adenocarcinoma, but prevention of *H. pylori* colonization or eradicative treatment could potentially prevent gastric malignancy and peptic ulceration. In contrast, increasing evidence indicates that lifelong *H. pylori* colonization may offer some protection against complications of gastroesophageal reflux disease (GERD), including esophageal adenocarcinoma. Recent research has focused on whether *H. pylori* colonization is also a risk factor for some extragastric diseases and whether it is protective against some recently emergent medical problems, such as childhood-onset asthma and other allergic and metabolic conditions.

ETIOLOGIC AGENT

Helicobacter pylori *H. pylori* is a gram-negative bacillus that has naturally colonized humans for at least 100,000 years, and probably throughout human evolution. It lives in gastric mucus, with a proportion of the bacteria adherent to the mucosa and possibly a very small number of the organisms entering cells or penetrating the mucosa; the organism's distribution is never systemic. Its spiral shape and flagella render *H. pylori* motile in the mucus environment. The organism has several acid-resistance mechanisms, most notably a highly expressed urease that catalyzes urea hydrolysis to produce buffering ammonia. *H. pylori* is microaerophilic (i.e., requires low levels of oxygen), is slow-growing, and requires complex growth media in vitro.

Other *Helicobacter* Species A very small proportion of gastric *Helicobacter* infections are due to species other than *H. pylori*, possibly acquired as zoonoses. These non-*pylori* gastric helicobacters are associated with low-level inflammation and occasionally with disease. In immunocompromised hosts, several nongastric (intestinal) *Helicobacter* species can cause disease with clinical features resembling those of *Campylobacter* infections; these species are covered in **Chap. 162**.

EPIDEMIOLOGY

Prevalence and Risk Factors The prevalence of *H. pylori* among adults is <30% in most parts of the United States and in other developed countries as opposed to >80% in some developing countries. In the United States, prevalence varies with age: up to 50% of 60-year-old persons, ~20% of 30-year-old persons, and <10% of children are colonized. *H. pylori* is usually acquired in childhood. The age association is due mostly to a birth-cohort effect whereby current 60-year-olds were more commonly colonized as children than are current children. Spontaneous acquisition or loss of *H. pylori* in adulthood is uncommon. Childhood acquisition explains why the main risk factors for infection are markers of crowding and social deprivation in childhood.

Transmission Humans are the only important reservoir of *H. pylori*. Children may acquire the organism from their parents (most often the primary caregiver) or from other children. The former is more common in developed countries and the latter in less developed countries. Whether transmission takes place more often by the fecal–oral or the oral–oral route is unknown, but *H. pylori* is easily cultured from vomitus and gastroesophageal refluxate and is less easily cultured from stool.

PATHOLOGY AND PATHOGENESIS

H. pylori colonization induces *chronic superficial gastritis*, a tissue response in the stomach that includes infiltration of the mucosa by both mononuclear and polymorphonuclear cells. (The term *gastritis* should be used specifically to describe histologic features; it has also been used to describe endoscopic appearances and even symptoms, but these features do not correlate with microscopic findings or even with the presence of *H. pylori*.) Although *H. pylori* is capable of numerous adaptations that prevent excessive stimulation of the immune system, colonization is accompanied by a considerable persistent local and systemic immune response, including the production of antibodies and cell-mediated responses. However, these responses are ineffective in clearing the bacterium. This inefficient clearing appears to be due in part to *H. pylori*'s downregulation of the immune system, which fosters its own persistence.

Most *H. pylori*–colonized persons do not develop clinical sequelae. That some persons develop overt disease whereas others do not is related to a combination of factors: bacterial strain differences, host susceptibility to disease, and environmental factors.

Bacterial Virulence Factors Several *H. pylori* virulence factors are more common among strains that are associated with disease than among those that are not. The *cag* island is a group of genes that encodes a bacterial type IV secretion system. Through this system, an effector protein, CagA, is translocated into epithelial cells, where it may be activated by phosphorylation and induces host cell signal transduction; proliferative, cytoskeletal, and inflammatory changes in the cell result. The protein at the tip of the secretory apparatus, CagL, binds to integrins on the cell surface, transducing further signaling. Finally, soluble components of the peptidoglycan cell wall enter the cell, mediated by the same secretory system. These components are recognized by the intracellular bacterial receptor Nod1, which stimulates a proinflammatory cytokine response resulting in an enhanced tissue response. Carriage of *cag*-positive strains increases the risk of peptic ulcer or gastric adenocarcinoma. A second major host-interaction factor is the vacuolating cytotoxin VacA, which forms pores in cell membranes. VacA is polymorphic, and carriage of more active forms also increases the risk of ulcer disease and gastric cancer. Other bacterial factors that are associated with increased disease risk include adhesins, such as BabA (which binds to blood group antigens on epithelial cells).

Host Genetic and Environmental Factors The best-characterized host determinants of disease are genetic polymorphisms leading to enhanced activation of the innate immune response, including polymorphisms in cytokine genes and in genes encoding bacterial recognition proteins such as Toll-like receptors. For example, colonized people with polymorphisms in the interleukin 1 gene that increase the production of this cytokine in response to *H. pylori* infection are at increased risk of gastric adenocarcinoma. In addition, environmental cofactors are important in pathogenesis. Smoking increases the risks of duodenal ulcers and gastric cancer in *H. pylori*–positive individuals. Diets high in salt and preserved foods increase cancer risk, whereas diets high in antioxidants and vitamin C are modestly protective.

Distribution of Gastritis and Differential Disease Risk The pattern of gastric tissue response is associated with disease risk: antral-predominant gastritis is most closely linked with duodenal ulceration, whereas pan-gastritis and corpus-predominant gastritis are linked with gastric ulceration and adenocarcinoma. This difference probably explains why patients with duodenal ulceration are not at high risk of developing gastric adenocarcinoma later in life, despite being colonized by *H. pylori*.

PATHOGENESIS OF DUODENAL ULCERATION How gastric colonization causes duodenal ulceration is now becoming clearer. *H. pylori*–induced tissue responses in the gastric antrum diminish the number of somatostatin-producing D cells. Because somatostatin inhibits gastrin release, gastrin levels are higher than in *H. pylori*–negative persons, and these higher levels lead to increased meal-stimulated acid secretion from the relatively spared gastric corpus. How this situation increases duodenal ulcer risk remains controversial, but the increased acid secretion may contribute to the formation of the potentially protective gastric metaplasia found in the duodenum of duodenal ulcer patients. Gastric metaplasia in the duodenum may become colonized by *H. pylori* and subsequently inflamed and ulcerated.

PATHOGENESIS OF GASTRIC ULCERATION AND GASTRIC ADENOCARCINOMA The pathogenesis of these conditions is less well understood, although both arise in association with pan- or corpus-predominant gastritis. The hormonal changes described above still occur, but the tissue responses in the gastric corpus mean that it produces less acid (hypochlorhydria) despite hypergastrinemia. Gastric ulcers commonly occur at the junction of antral and corpus-type mucosa, an area that is often particularly inflamed. Gastric cancer probably stems from progressive DNA damage and the survival of abnormal epithelial cell clones. The DNA damage is thought to be due principally to reactive oxygen and nitrogen species arising from inflammatory cells, perhaps in relation to other bacteria that survive in a hypochlorhydric stomach. Longitudinal analyses of gastric biopsy specimens taken years apart from the same patient show that the common *intestinal* type of gastric adenocarcinoma follows stepwise changes from simple gastritis to gastric atrophy, metaplasia, and dysplasia. A second, *diffuse* type of gastric adenocarcinoma found more commonly in younger adults may arise directly from chronic gastritis without atrophic changes.

CLINICAL MANIFESTATIONS

Essentially all *H. pylori*–colonized persons have histologic gastritis, but only ~10–15% develop associated illnesses such as peptic ulceration, gastric adenocarcinoma, or gastric lymphoma **(Fig. 158-1)**. Despite similar rates of *H. pylori* colonization, rates of these diseases among women are less than half of those among men.

Peptic Ulcer Disease Worldwide, ~70% of duodenal ulcers and ~50% of gastric ulcers are related to *H. pylori* colonization **(Chap. 317)**. However, in particular, the proportion of gastric ulcers caused by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing, and in many developed countries these drugs have overtaken *H. pylori* as a cause of gastric ulceration. The main lines of evidence supporting an ulcer-promoting role for *H. pylori* are that (1) the presence of the organism is a risk factor for the development of ulcers, (2) non-NSAID-induced ulcers rarely develop in the absence of *H. pylori*, (3) eradication of *H. pylori* virtually abolishes long-term ulcer relapse, and (4) experimental *H. pylori* infection of gerbils can cause gastric ulceration.

Gastric Adenocarcinoma and Lymphoma Prospective nested case–control studies have shown that *H. pylori* colonization is

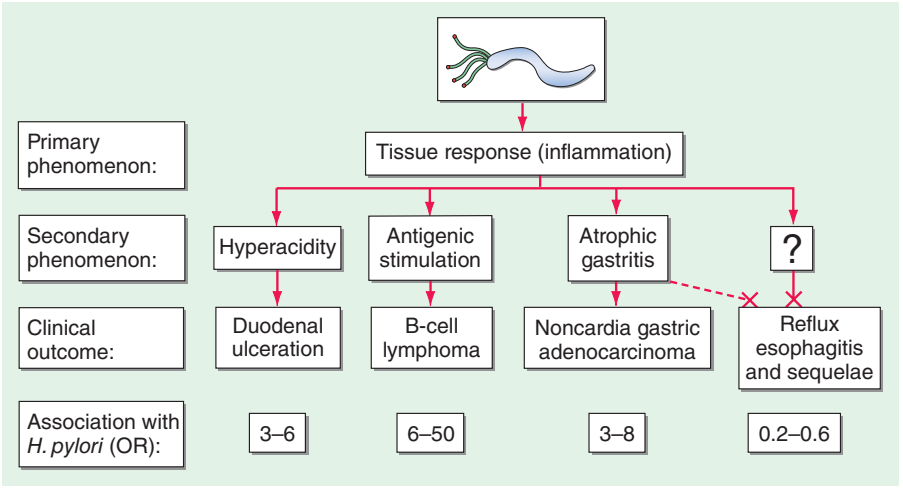

FIGURE 158-1 Schematic of the relationships between colonization with *Helicobacter pylori* and diseases of the upper gastrointestinal tract. Essentially all persons colonized with *H. pylori* develop a host response, which is generally termed *chronic gastritis*. The nature of the host's interaction with the particular bacterial population determines the clinical outcome. *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, noncardia gastric cancer, and B-cell non-Hodgkin's gastric lymphoma (odds ratios [ORs] for all, >3). In contrast, a growing body of evidence indicates that *H. pylori* colonization (especially with *cagA*$^+$ strains) protects against adenocarcinoma of the esophagus (and the sometimes related gastric cardia) and premalignant lesions such as Barrett's esophagus (OR, <1). Although the incidences of peptic ulcer disease (cases not due to nonsteroidal anti-inflammatory drugs) and noncardia gastric cancer are declining in developed countries, the incidence of adenocarcinoma of the esophagus is increasing. *(Adapted from MJ Blaser: Hypothesis: The changing relationships of Helicobacter pylori and humans: Implications for health and disease. J Infect Dis 179:1523, 1999, with permission.)*

a risk factor for adenocarcinomas of the distal (noncardia) stomach (Chap. 76). Long-term experimental infection of gerbils also may result in gastric adenocarcinoma. Moreover, *H. pylori* may induce primary gastric lymphoma, although this condition is much less common. Many low-grade gastric B-cell lymphomas are dependent on *H. pylori* for continuing growth and proliferation, and these tumors may regress either fully or partially after *H. pylori* eradication. However, they require careful short- and long-term monitoring; any that are not confined to the superficial mucosa (and, indeed, some that are) require additional treatment with chemotherapeutic agents.

Functional Dyspepsia Many patients have upper gastrointestinal symptoms but have normal results on upper gastrointestinal endoscopy (so-called functional or non-ulcer dyspepsia; Chap. 317). Because *H. pylori* is common, some of these patients will be colonized with the organism. *H. pylori* eradication leads to symptom resolution up to 15% more commonly than does placebo treatment. Whether such patients have peptic ulcers in remission at the time of endoscopy or whether a small subgroup of patients with "true" functional dyspepsia respond to *H. pylori* treatment is unclear. Either way, because functional dyspepsia is often persistent and difficult to treat, most guidelines recommend *H. pylori* eradication in these patients. If this advice is followed, it is important to realize that only a small subgroup of patients who are treated will benefit.

Protection Against Peptic Esophageal Disease, Including Esophageal Adenocarcinoma Much interest has focused on a protective role for *H. pylori* against GERD (Chap. 316), Barrett's esophagus (Chap. 316), and adenocarcinoma of the esophagus and gastric cardia (Chap. 76). The main lines of evidence for this role are (1) that there is a temporal relationship between a falling prevalence of gastric *H. pylori* colonization and a rising incidence of these conditions; (2) that, in most studies, the prevalence of *H. pylori* colonization (especially with proinflammatory *cagA*$^+$ strains) is significantly lower among patients with these esophageal diseases than among control participants; and (3) that, in prospective nested studies (see above), the presence of *H. pylori* is inversely related to these cancers. The mechanism underlying this protective effect is likely *H. pylori*–induced hypochlorhydria. Because, at the individual level, GERD severity may decrease, worsen, or remain unchanged after *H. pylori* treatment, concerns about GERD should not affect decisions about whether to treat *H. pylori* in an individual patient when a clear-cut indication exists.

Other Pathologies *H. pylori* has an increasingly recognized role in other gastric pathologies. It may predispose some patients to iron deficiency through occult blood loss and/or hypochlorhydria and reduced iron absorption. In addition, several extra-gastrointestinal pathologies have been linked with *H. pylori* colonization, although evidence of causality is less strong. Studies of *H. pylori* treatment in idiopathic thrombocytopenic purpura have consistently described improvement in or even normalization of platelet counts. Potentially important but even more controversial (protective) associations are with ischemic heart disease and cerebrovascular disease. However, the strength of the latter associations is reduced if confounding factors are taken into account, and our present knowledge is incomplete. Most authorities consider the associations to be non-causal. An increasing number of studies have shown an inverse association of *cagA*$^+$ *H. pylori* with childhood-onset asthma, hay fever, and atopic disorders. These associations have been shown to be causal in animal models, but causality in humans and the size of any effect have not been established.

DIAGNOSIS

Tests for *H. pylori* fall into two groups: tests that require upper-gastrointestinal endoscopy and simpler tests that can be performed in the clinic (Table 158-1).

TABLE 158-1 Tests Commonly Used to Detect *Helicobacter pylori*

TEST	ADVANTAGES	DISADVANTAGES
Tests Based on Endoscopic Biopsy		
Biopsy urease test	Quick, simple	Some commercial tests not fully sensitive before 24 h
Histology	May give additional histologic information	Sensitivity dependent on experience and use of special stains
Culture	Permits determination of antibiotic susceptibility	Sensitivity dependent on experience
Noninvasive Tests		
Serology	Inexpensive and convenient; not affected by recent antibiotics or proton pump inhibitors to the same extent as breath and stool tests	Cannot be used to monitor treatment success; some commercial kits inaccurate, and most less accurate than urea breath test
^{13}C urea breath test	Inexpensive and simpler than endoscopy; useful for follow-up after treatment	Requires fasting; not as convenient as blood or stool tests
Stool antigen test	Inexpensive and convenient; useful for follow-up after treatment; may be particularly useful in children	Stool-based tests disliked by people from some cultures

Endoscopy-Based Tests Endoscopy is usually unnecessary in the initial management of young patients with simple dyspepsia but is commonly used to exclude malignancy and make a positive diagnosis in older patients or those with "alarm" symptoms. If endoscopy is performed, the most convenient biopsy-based test is the biopsy urease test, in which one large or two small gastric biopsy specimens are placed into a gel containing urea and an indicator. The presence of *H. pylori* urease leads to a pH alteration and therefore to a color change, which often occurs within minutes but can require up to 24 h. Histologic examination of biopsy specimens for *H. pylori* also is accurate, provided that a special stain (e.g., a modified Giemsa, silver, or immuno-stain) permitting optimal visualization of the organism is used. If biopsy specimens are obtained from both antrum and corpus, histologic study yields additional information, including the degree and pattern of inflammation and the presence of any atrophy, metaplasia, or dysplasia. Microbiologic culture is most specific but may be insensitive because of difficulty with *H. pylori* isolation. Once the organism is cultured, its identity as *H. pylori* can be confirmed by its typical appearance on Gram's stain and its positive reactions in oxidase, catalase, and urease tests. Moreover, the organism's susceptibility to antibiotics can be determined, and this information can be clinically useful in difficult cases. The occasional biopsy specimens containing the less common non-*pylori* gastric helicobacters give weakly positive results in the biopsy urease test. Positive identification of these bacteria requires visualization of the characteristic long, tight spirals in histologic sections; they cannot easily be cultured.

Noninvasive Tests Noninvasive *H. pylori* testing is the norm if gastric cancer does not need to be excluded by endoscopy. The best-established test (and a very accurate one) is the *urea breath test*. In this simple test, the patient drinks a solution of urea labeled with the nonradioactive isotope ^{13}C and then blows into a tube. If *H. pylori* urease is present, the urea is hydrolyzed, and labeled carbon dioxide is detected in breath samples. The *stool antigen test*, a simple and accurate test using monoclonal antibodies specific for *H. pylori* antigens, is more convenient and potentially less expensive than the urea breath test, but some patients dislike sampling stool. The simplest tests for ascertaining *H. pylori* status are *serologic assays* measuring specific IgG levels in serum by enzyme-linked immunosorbent assay or immunoblot. The best of these tests are as accurate as other diagnostic methods, but many commercial tests—especially rapid office tests—do not perform well.

Use of Tests to Assess Treatment Success The urea breath test, the stool antigen test, and biopsy-based tests can all be used to assess the success of treatment (Fig. 158-2). However, because these tests are dependent on *H. pylori* load, their use <4 weeks after treatment may yield false-negative results. Early suppression of bacterial

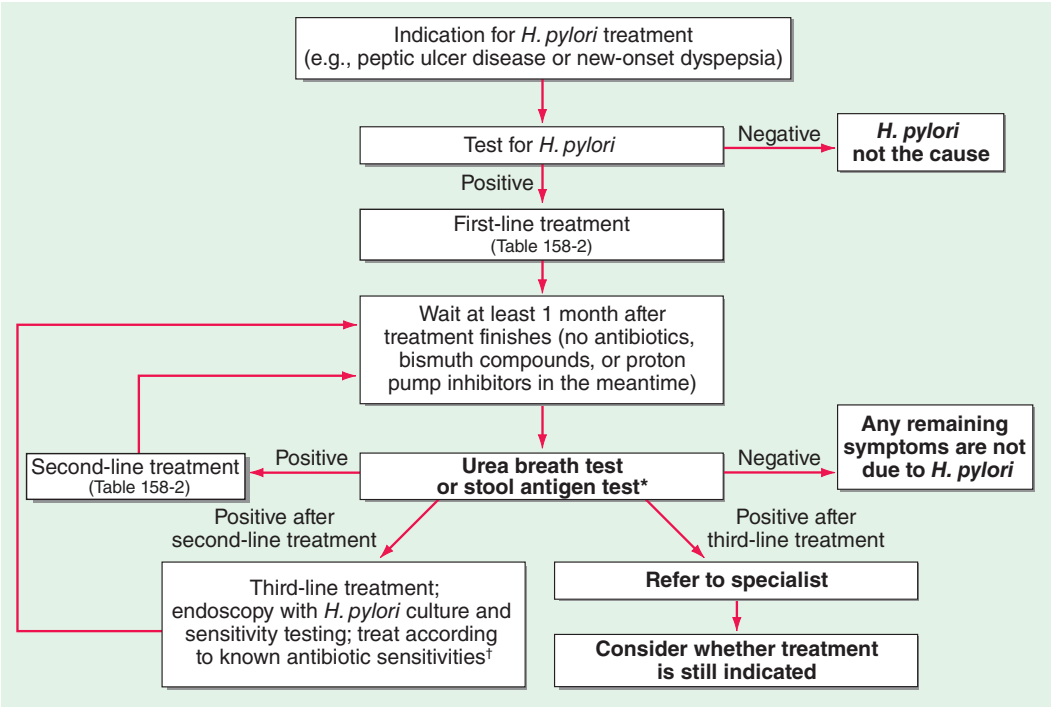

FIGURE 158-2 Algorithm for the management of *Helicobacter pylori* infection. *Note that either the urea breath test or the stool antigen test can be used in this algorithm. Occasionally, endoscopy and a biopsy-based test are used instead of either of these tests in follow-up after treatment. The main indication for these invasive tests is gastric ulceration; in this condition, as opposed to duodenal ulceration, it is important to check healing and to exclude underlying gastric adenocarcinoma. However, even in this situation, patients undergoing endoscopy may still be receiving proton pump inhibitor therapy, which precludes *H. pylori* testing. Thus, a urea breath test or a stool antigen test is still required at a suitable interval after the end of therapy to determine whether treatment has been successful (see text). †Some authorities use empirical third-line regimens, of which several have been described.

numbers may lead to false-negative results, since regrowth of the organism can result in its detection weeks later. For the same reason, these tests are unreliable if performed within 4 weeks of intercurrent treatment with antibiotics or bismuth compounds or within 2 weeks of the discontinuation of proton pump inhibitor (PPI) treatment. In the assessment of treatment success, noninvasive tests are normally preferred. However, after gastric ulceration, endoscopy should be repeated to ensure healing and to exclude gastric carcinoma by further histologic sampling; if PPIs have been stopped for at least 2 weeks and no antibiotics or bismuth compounds have been given for at least 4 weeks, there is an opportunity to assess treatment success with biopsy-based tests. Serologic tests are not used to monitor treatment success, as the gradual drop in titer of *H. pylori*–specific antibodies is too slow to be of practical use.

TREATMENT

Helicobacter pylori Infection

INDICATIONS

The most clear-cut indications for treatment are *H. pylori*–related duodenal or gastric ulceration or low-grade gastric B-cell lymphoma. Whether or not the ulcers are currently active, *H. pylori* should be eradicated in patients with documented ulcer disease to prevent relapse (Fig. 158-2). Guidelines have recommended *H. pylori* treatment for colonized patients with functional dyspepsia in case they are among the ~10% who will benefit from such therapy (beyond placebo effects). *H. pylori* eradication in the treatment of conditions not definitively known to respond has also been recommended but is not universally supported; such conditions include idiopathic thrombocytopenic purpura, vitamin B_{12} deficiency, and iron-deficiency anemia where other causes have been carefully excluded. For individuals with a strong family history of gastric cancer, treatment to eradicate *H. pylori* in the hope of reducing cancer risk is reasonable but of unproven value. For older dyspeptic patients in the community or those who have "alarm" symptoms (e.g., weight loss) associated with their dyspepsia, upper-gastrointestinal endoscopy is indicated to seek a diagnosis and test for *H. pylori*; the decision over whether to eradicate the organism can then be based on indication. Endoscopy is usually considered unnecessary for young dyspeptic patients in the community who have no alarm symptoms (with the precise age cutoff dependent on local guidelines). If the community prevalence of *H. pylori* is below ~20%, such patients are treated with a short course of acid suppression using a PPI. If these patients do not respond or relapse when treatment is stopped, or if the *H. pylori* community prevalence is >20%, all national guidelines recommend a strategy of testing for *H. pylori* noninvasively and eradicating it if it is found. This strategy will benefit patients who have peptic ulcers and the 10% of patients who have functional dyspepsia responsive to *H. pylori* eradication, but most patients will be treated unnecessarily. Currently, widespread community screening for and treatment of *H. pylori* as primary prophylaxis for gastric cancer and peptic ulcers are not recommended in most countries, mainly because the extent of the consequent reduction in cancer risk is not known. Several studies have found a modestly reduced cancer risk after treatment, but the period of follow-up is still fairly short, and the size of the effect in different populations remains unclear. Other reasons not to treat *H. pylori* in asymptomatic populations at present include (1) the adverse side effects (which are common and can be severe in rare cases) of the multiple-antibiotic regimens used; (2) antibiotic resistance, which may emerge in *H. pylori* or other incidentally carried bacteria; (3) the anxiety that may arise in otherwise healthy people, especially if treatment is unsuccessful; and (4) the existence of a subset of people who will develop GERD symptoms after treatment, although in most cases *H. pylori* treatment does not affect GERD symptoms or severity. Despite the absence of screening strategies, many doctors treat *H. pylori* if it is known to be present (particularly in children and younger adults), even when the patient is asymptomatic. The rationale is that it reduces patient concern and may reduce future gastric cancer risk and that any reduction in risk is likely to be greater in younger patients. However, such practices do not factor in any potential benefits of *H. pylori* colonization.

TABLE 158-2 Commonly Recommended Treatment Regimens for *Helicobacter pylori*

REGIMEN[a] (DURATION)	DRUG 1	DRUG 2	DRUG 3	DRUG 4
Regimen 1: OCM (14 days)[b]	Omeprazole (20 mg bid[c])	Clarithromycin (500 mg bid)	Metronidazole (500 mg bid)	—
Regimen 2: OCA (14 days)[b]	Omeprazole (20 mg bid[c])	Clarithromycin (500 mg bid)	Amoxicillin (1 g bid)	—
Regimen 3: OBTM (14 days)[d]	Omeprazole (20 mg bid[c])	Bismuth subsalicylate (2 tabs qid)	Tetracycline HCl (500 mg qid)	Metronidazole (500 mg tid)
Regimen 4: concomitant (14 days)[e]	Omeprazole (20 mg bid[c])	Amoxicillin (1 g bid)	Clarithromycin (500 mg bid)	Tinidazole (500 mg bid[f])
Regimen 5: OAL (10 days)[g]	Omeprazole (20 mg bid[c])	Amoxicillin (1 g bid)	Levofloxacin (500 mg bid)	—

[a]The recommended first-line regimens for most of the world are shown in **bold** type. [b]This regimen should be used only for populations in which the prevalence of clarithromycin-resistant strains is known to be <20%. In practice, this restriction limits the regimens' appropriate range mainly to northern Europe. [c]Many authorities and some guidelines recommend doubling this dose of omeprazole, as trials show resultant increased efficacy with some antibiotic combinations. Omeprazole may be replaced with any proton pump inhibitor at an equivalent dosage. Because extensive metabolizers of PPIs are prevalent among Caucasian populations, many authorities recommend esomeprazole (40 mg bid) or rabeprazole (20 mg bid), particularly for regimens 4 and 5. [d]Data supporting this regimen come mainly from Europe and are based on the use of bismuth subcitrate (1 tablet qid) and metronidazole (400 mg tid). This is a recommended first-line regimen in most countries and is the recommended second-line regimen in northern Europe. [e]This regimen may be used as an alternative to regimen 3. [f]Metronidazole (500 mg bid) may be used as an alternative. [g]This regimen is used as second-line treatment in many countries (particularly where quadruple or concomitant therapy is used as the first-line regimen) and as third-line treatment in others. It may be less effective where rates of fluoroquinolone use are high and is more likely to be ineffective if there is a personal history of fluoroquinolone use for previous treatment of other infections.

Overall, despite widespread clinical activity in this area, most treatment of persons with asymptomatic *H. pylori* carriage is given without a firm evidence base.

REGIMENS

Although *H. pylori* is susceptible to a wide range of antibiotics in vitro, monotherapy is not usually successful, probably because of inadequate active antibiotic delivery to the colonization niche. Clinical failure of monotherapy prompted the development of multidrug regimens. Current regimens consist of a PPI and two or three antimicrobial agents given for 10–14 days **(Table 158-2)**. The optimal regimens vary in different parts of the world, depending on the known rates of primary antibiotic resistance in most *H. pylori* strains in a particular locale. For this reason, guidelines on optimal regimens for *H. pylori* eradication in individual countries are evolving, and physicians should refer to the most up-to-date local guideline.

The two most important factors in successful *H. pylori* treatment are the patient's close compliance with the regimen and the use of drugs to which the patient's strain of *H. pylori* has not acquired resistance. Treatment failure following minor lapses in compliance is common and often leads to acquired resistance. To stress the importance of compliance, written instructions should be given to the patient, and minor side effects of the regimen should be explained. Increasing levels of primary *H. pylori* resistance to clarithromycin, levofloxacin, and—to a lesser extent—metronidazole are of growing concern. In most parts of the world (the main exception being northwestern Europe), the rate of primary clarithromycin resistance is sufficiently high that regimens containing clarithromycin plus one other antibiotic often fail; regimens with clarithromycin and two other antibiotics remain an option as the other two antibiotics are likely to eradicate *H. pylori* even if the strain is clarithromycin resistant. When a patient is known to have been exposed—even distantly—to clarithromycin or a fluoroquinolone, these antibiotics usually should be avoided. Resistance to amoxicillin or tetracycline is unusual, even if these antibiotics have been given previously, and resistance to metronidazole is only partial; thus there is no need to avoid using these antibiotics whether or not they have been previously prescribed. Assessment of antibiotic susceptibilities before treatment would be optimal but is not usually undertaken because endoscopy and mucosal biopsy are necessary to obtain *H. pylori* for culture and because most microbiology laboratories are inexperienced in *H. pylori* culture. If initial *H. pylori* treatment fails, the usual approach is empirical re-treatment with another drug regimen (Table 158-2). The third-line approach ideally should be endoscopy, biopsy, and culture plus treatment based on documented antibiotic sensitivities. However, empirical third-line therapies are often used.

Non-*pylori* gastric helicobacters are treated in the same way as *H. pylori*. However, in the absence of trials, it is unclear whether a positive outcome always represents successful treatment or whether it is sometimes due to natural clearance of the bacteria.

PREVENTION

Carriage of *H. pylori* has considerable public health significance in developed countries, where it is associated with peptic ulcer disease and gastric adenocarcinoma, and in developing countries, where gastric adenocarcinoma may be an even more common cause of cancer death late in life. If mass prevention were contemplated, vaccination would be the most obvious method: experimental immunization of animals has given promising results, and the first reported trial in humans has shown some efficacy. Further trials are ongoing. However, given that *H. pylori* has co-evolved with its human host over millennia, preventing or eliminating colonization on a population basis may have biological and clinical costs. For example, lifelong absence of *H. pylori* is a risk factor for GERD complications, including esophageal adenocarcinoma. We have speculated that the disappearance of *H. pylori* may also be associated with an increased risk of other emergent diseases reflecting aspects of the current Western lifestyle, such as childhood-onset asthma and allergy.

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159 Infections Due to *Pseudomonas*, *Burkholderia*, and *Stenotrophomonas* Species

Reuben Ramphal

The pseudomonads are a heterogeneous group of gram-negative bacteria that have in common an inability to ferment lactose. Formerly classified in the genus *Pseudomonas*, the members of this group have been assigned to three medically important genera—*Pseudomonas*, *Burkholderia*, and *Stenotrophomonas*—whose biologic behaviors encompass both similarities and marked differences and whose genetic repertoires differ in many respects. The pathogenicity of most pseudomonads is based on opportunism; the exceptions are *Burkholderia pseudomallei* and *Burkholderia mallei*, which are primary pathogens.

Pseudomonas aeruginosa, the major pathogen of the group, is a significant cause of infections in hospitalized patients and in patients with cystic fibrosis (CF; **Chap. 285**). Cytotoxic chemotherapy, mechanical ventilation, and broad-spectrum antibiotic therapy set up conditions that predispose to colonization and infection of increasing numbers of hospitalized patients by this pathogen. The other members of the genus *Pseudomonas*—*Pseudomonas putida*, *Pseudomonas fluorescens*, and *Pseudomonas stutzeri*—infect humans infrequently.

The genus *Burkholderia* comprises >40 species, of which *Burkholderia cepacia* is most frequently encountered in Western countries. Like *P. aeruginosa*, *B. cepacia* is both a nosocomial pathogen and a cause of infection in CF. The other medically important members of this genus are *B. pseudomallei* and *B. mallei*, the etiologic agents of melioidosis and glanders, respectively.

The genus *Stenotrophomonas* contains one species of medical significance, *Stenotrophomonas maltophilia* (previously classified in the genera *Pseudomonas* and *Xanthomonas*). This organism is strictly an opportunist that "overgrows" in the setting of potent broad-spectrum antibiotic use.

PSEUDOMONAS AERUGINOSA

EPIDEMIOLOGY

P. aeruginosa is found in most moist environments. Soil, plants, vegetables, tap water, and countertops are all potential reservoirs for this microbe, as it has simple nutritional needs. Given the ubiquity of *P. aeruginosa*, it is clear that simple contact with the organism is not sufficient for colonization or infection. Clinical and experimental observations suggest that infection by *P. aeruginosa* occurs concomitantly with compromised host defenses, mucosal trauma, physiologic derangement, and antibiotic-mediated suppression of normal flora. Thus, it comes as no surprise that the majority of *P. aeruginosa* infections occur in intensive care units (ICUs), where these factors frequently converge. The organism is initially acquired from environmental sources, but patient-to-patient spread also occurs in clinics and families.

In the past, burned patients appeared to be unusually susceptible to *P. aeruginosa*. For example, in 1959–1963, *Pseudomonas* burn-wound sepsis was the principal cause of death in 60% of burned patients dying at the U.S. Army Institute of Surgical Research. For reasons that are unclear, *P. aeruginosa* infection in burns is no longer the major problem that it was during the 1950s and 1960s. Similarly, in the 1960s, *P. aeruginosa* appeared as a common pathogen in patients receiving cytotoxic chemotherapy at many institutions in the United States, but it has subsequently diminished in importance. Despite this subsidence, *P. aeruginosa* remains one of the most feared pathogens in this population because of its high attributable mortality.

In some parts of Asia and Latin America, *P. aeruginosa* continues to be the most common cause of gram-negative bacteremia in neutropenic patients.

In contrast to the trends for burned patients and neutropenic patients in the United States, the incidence of *P. aeruginosa* infections among patients with CF has not changed. *P. aeruginosa* remains the most common contributing factor to respiratory failure in CF and is responsible for the majority of deaths among CF patients.

LABORATORY FEATURES

P. aeruginosa is a nonfastidious, motile, gram-negative rod that grows on most common laboratory media, including blood and MacConkey agars. It is easily identified in the laboratory on primary-isolation agar plates by pigment production that confers a yellow to dark green or even bluish appearance. Colonies have a shiny "gun-metal" appearance and a characteristic fruity odor. Two of the identifying biochemical characteristics of *P. aeruginosa* are an inability to ferment lactose on MacConkey agar and a positive reaction in the oxidase test. Most strains are identified on the basis of these readily detectable laboratory features even before extensive biochemical testing is done. Some isolates from CF patients are easily identified by their mucoid appearance, which is due to the production of large amounts of the mucoid exopolysaccharide or alginate.

PATHOGENESIS

Unraveling the mechanisms that underlie disease caused by *P. aeruginosa* has proved challenging. Of the common gram-negative bacteria, no other species produces such a large number of putative virulence factors **(Table 159-1)**. Yet *P. aeruginosa* rarely initiates an infectious process in the absence of host injury or compromise, and few of its putative virulence factors have been shown definitively to be involved in disease in humans. Despite its metabolic versatility and possession of multiple colonizing factors, *P. aeruginosa* exhibits no competitive advantage over enteric bacteria in the human gut; it is not a normal inhabitant of the human gastrointestinal tract, despite the host's continuous environmental exposure to the organism.

Virulence Attributes Involved in Acute *P. aeruginosa* Infections • **MOTILITY AND COLONIZATION** A general tenet of bacterial pathogenesis is that most bacteria must adhere to surfaces or colonize a host niche in order to initiate disease. Most gram-negative bacteria examined thus far possess adherence factors called *adhesins*. *P. aeruginosa* is no exception. Among its many adhesins are its pili, which demonstrate adhesive properties for a variety of cells and adhere best to injured cell surfaces. In the organism's flagellum, the flagellin molecule binds to cells, and the flagellar cap attaches to mucins through the recognition of glycan chains. Other *P. aeruginosa* adhesins include the outer core of the lipopolysaccharide (LPS) molecule, which binds to the cystic fibrosis transmembrane conductance regulator (CFTR) and aids in internalization of the organism, and the alginate coat of mucoid strains, which enhances adhesion to cells and mucins. In addition, membrane proteins and lectins have been proposed as colonization factors. The deletion of any given adhesin is not sufficient to abrogate the ability of *P. aeruginosa* to colonize surfaces. Motility is important in host invasion via mucosal surfaces in some animal models; however, nonmotile strains are not uniformly avirulent.

EVASION OF HOST DEFENSES The transition from bacterial colonization to disease requires the evasion of host defenses followed by invasion

TABLE 159-1 Main Putative Virulence Factors of *Pseudomonas aeruginosa*

SUBSTANCE/ ORGANELLE	FUNCTION	VIRULENCE IN ANIMAL DISEASE
Pili	Adhesion to cells	?
Flagella	Adhesion, motility, inflammation	Yes
Lipopolysaccharide	Antiphagocytic activity, inflammation	Yes
Type III secretion system	Toxic activity (ExoU, ExoS)	Yes
Type II secretion system	Toxic activity	Yes
Proteases	Proteolytic activity	?
Phospholipases	Cytotoxicity	?
Exotoxin A	Cytotoxicity	?

by the microorganism. *P. aeruginosa* appears to be well equipped for evasion. Attached bacteria inject four known toxins (ExoS or ExoU, ExoT, and ExoY) via a type III secretion system that allows the bacteria to evade phagocytic cells either by direct cytotoxicity or by inhibition of phagocytosis. Clinical studies suggest that the mortality rate is higher among patients infected by strains that secrete the ExoU toxin. Another secretion system—the type II system—secretes toxins that can kill animals, and some of its secreted toxins, such as exotoxin A, have the potential to kill phagocytic cells. Multiple proteases secreted by this system may degrade host effector molecules, such as cytokines and chemokines, that are released in response to infection.

TISSUE INJURY Among gram-negative bacteria, *P. aeruginosa* probably produces the largest number of substances that are toxic to cells and thus have the potential to injure tissues. The toxins secreted by the organism's type III secretion system are capable of injuring tissue. However, their delivery requires the adherence of the organism to cells. Thus, the effects of these toxins are likely to be local or to depend on the presence of vast numbers of bacteria. On the other hand, diffusible toxins, secreted by the organism's type II secretion system, can act freely wherever they come into contact with cells. Possible effectors include exotoxin A, at least four different proteases, and at least two phospholipases; in addition to these secreted toxins, rhamnolipids, pyocyanin, and hydrocyanic acid are produced by *P. aeruginosa* and are all capable of causing host injury.

INFLAMMATORY COMPONENTS The inflammatory responses to the lipid A component of *Pseudomonas* LPS and to its flagellin, mediated through the Toll-like receptor (TLR) system (principally TLR4 and TLR5, respectively), are thought to represent important factors in disease causation. Although these inflammatory responses are required for successful defense against *P. aeruginosa* (i.e., in their absence, animals are defenseless against *P. aeruginosa* infection), florid responses are likely to result in disease. Thus, when the sepsis syndrome and septic shock develop in *P. aeruginosa* infection, they are probably the result of the host response to one or both of these substances, but injury to the lung by *Pseudomonas* toxins may also result in sepsis syndromes, possibly by causing cell death and the release of cellular components (e.g., heat-shock proteins) that may activate the TLR or another proinflammatory system.

Chronic *P. aeruginosa* Infections Chronic infection due to *P. aeruginosa* occurs mainly in the lungs in the setting of structural pulmonary diseases. The classic example is CF; others include bronchiectasis and chronic relapsing panbronchiolitis, a disease seen in Japan and some Pacific Islands. A hallmark of these illnesses is altered mucociliary clearance leading to mucus stasis and mucus accumulation in the lungs. There is probably a common factor that selects for *P. aeruginosa* colonization in these lung diseases—perhaps the adhesiveness of *P. aeruginosa* for mucus, a phenomenon that is not noted for most other common gram-negative bacteria, and/or the ability of *P. aeruginosa* to evade host defenses in mucus. Furthermore, *P. aeruginosa* seems to evolve in ways that allow its prolonged survival in the lung without an early fatal outcome for the host. The strains found in CF patients exhibit minimal production of virulence factors. Many strains lose the ability to produce pili and flagella, and most become complement-sensitive because of the loss of the O side chain of their LPS molecules. In addition, most strains found in CF patients overproduce a mucoid exopolysaccharide. These changes probably dampen the host response, allowing the organism to survive in CF mucus. *P. aeruginosa* is also believed to lose its ability to secrete many of its injectable toxins during growth in mucus. Although the alginate coat is thought to play a role in the organism's survival, alginate is not essential, as nonmucoid strains may predominate for long periods. In short, virulence in chronic infections may be mediated by the chronic but attenuated host inflammatory response, which injures the lungs over decades.

CLINICAL MANIFESTATIONS

P. aeruginosa causes infections at almost all sites in the body but shows a rather strong predilection for the lungs. The infections encountered most commonly in hospitalized patients are described below.

Bacteremia Crude mortality rates exceeding 50% have been reported among patients with *P. aeruginosa* bacteremia. Consequently, this clinical entity has been much feared, and its management has been attempted with the use of multiple antibiotics. Recent publications report attributable mortality rates of 28–44%, with the precise figure depending on the adequacy of treatment and the seriousness of the underlying disease. In the past, the patient with *P. aeruginosa* bacteremia classically was neutropenic or had a burn injury. Today, however, a minority of such patients have bacteremic *P. aeruginosa* infections. Rather, *P. aeruginosa* bacteremia is seen most often in patients in ICUs.

The clinical presentation of *P. aeruginosa* bacteremia rarely differs from that of sepsis in general **(Chap. 297)**. Patients are usually febrile, but those who are most severely ill may be in shock or even hypothermic. The only point differentiating this entity from gram-negative sepsis of other causes may be the distinctive skin lesions (ecthyma gangrenosum) of *Pseudomonas* infection, which occur almost exclusively in markedly neutropenic patients and patients with AIDS. These small or large, painful, reddish, maculopapular lesions have a geographic margin; they are initially pink, then darken to purple, and finally become black and necrotic **(Fig. 159-1)**. Histopathologic studies indicate that the lesions are due to vascular invasion and are teeming with bacteria. Although similar lesions may occur in aspergillosis and mucormycosis, their presence suggests *P. aeruginosa* bacteremia as the most likely diagnosis.

TREATMENT

P. aeruginosa Bacteremia

(Table 159-2) Antimicrobial treatment of *P. aeruginosa* bacteremia has been controversial. Before 1971, the outcome of *Pseudomonas* bacteremia in febrile neutropenic patients treated with the available agents—gentamicin and the polymyxins—was dismal. However, treatment with carbenicillin, with or without an aminoglycoside, significantly improved outcomes. Concurrently, several retrospective analyses suggested that the use of two agents that were synergistic against gram-negative pathogens in vitro resulted in better outcomes in neutropenic patients. Thus, combination therapy became the standard of care—first for *P. aeruginosa* bacteremia in febrile neutropenic patients and then for all *P. aeruginosa* infections in neutropenic or nonneutropenic patients.

With the introduction of newer antipseudomonal drugs, a number of studies have revisited the choice between combination treatment and monotherapy for *Pseudomonas* bacteremia. Although many experts still favor combination therapy, most recent observational studies indicate that a single modern antipseudomonal β-lactam agent to which the isolate is sensitive is as efficacious as a combination. Even in patients at greatest risk of early death from *P. aeruginosa* bacteremia (i.e., those with fever and neutropenia), empirical antipseudomonal monotherapy is deemed to be as efficacious as empirical combination therapy by the practice guidelines of the Infectious Diseases Society of America (IDSA). One firm conclusion is that monotherapy with an aminoglycoside is not optimal.

There are, of course, institutions and countries where rates of susceptibility of *P. aeruginosa* to first-line antibiotics are <80%. Thus, when a septic patient with a high probability

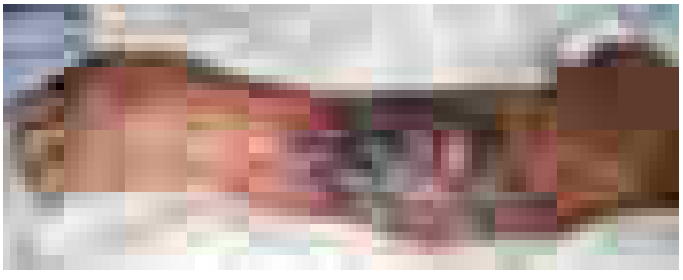

FIGURE 159-1 **Ecthyma gangrenosum** in a neutropenic patient 3 days after onset.

TABLE 159-2 Antibiotic Treatment of Infections Due to *Pseudomonas aeruginosa* and Related Species

INFECTION	ANTIBIOTICS AND DOSAGES	OTHER CONSIDERATIONS
Bacteremia		
Nonneutropenic host	Ceftazidime (2 g q8h IV) *or* cefepime (2 g q8h IV) *or* piperacillin/tazobactam (3.375 g q4h IV) *or* imipenem (500 mg q6h IV) *or* meropenem (1 g q8h IV) *or* doripenem (500 mg q8h IV) ***Optional:*** Amikacin (7.5 mg/kg q12h or 15 mg/kg q24h IV)	Add an aminoglycoside for patients in shock and in regions or hospitals where rates of resistance to the primary β-lactam agents are high. Tobramycin may be used instead of amikacin (susceptibility permitting). The duration of therapy is 7 days for nonneutropenic patients. Neutropenic patients should be treated until no longer neutropenic.
Neutropenic host	Cefepime (2 g q8h IV) *or* all the other agents above (except doripenem) in the above dosages	
Endocarditis	Antibiotic regimens as for bacteremia for 6–8 weeks	Resistance during therapy is common. Surgery is required for relapse.
Pneumonia	Drugs and dosages as for bacteremia, except that the available carbapenems should not be the sole primary drugs because of high rates of resistance during therapy.	IDSA guidelines recommend the addition of an aminoglycoside or ciprofloxacin. The duration of therapy is 7 days.
Bone infection, malignant otitis externa	Cefepime or ceftazidime at the same dosages as for bacteremia; aminoglycosides not a necessary component of therapy; ciprofloxacin (500–750 mg q12h PO) may be used	Duration of therapy varies with the drug used (e.g., 6 weeks for a β-lactam agent; at least 3 months for oral therapy except in puncture-wound osteomyelitis, for which the duration should be 2–4 weeks).
Central nervous system infection	Ceftazidime or cefepime (2 g q8h IV) *or* meropenem (1 g q8h IV)	Abscesses or other closed-space infections may require drainage. The duration of therapy is ≥2 weeks.
Eye infection		
Keratitis/ulcer	Topical therapy with tobramycin/ciprofloxacin/levofloxacin eyedrops	Use maximal strengths available or compounded by pharmacy. Therapy should be administered for 2 weeks or until the resolution of eye lesions, whichever is shorter.
Endophthalmitis	Ceftazidime or cefepime as for central nervous system infection ***plus*** Topical therapy	
Urinary tract infection	Ciprofloxacin (500 mg q12h PO) *or* levofloxacin (750 mg q24h) *or* any aminoglycoside (total daily dose given once daily)	Relapse may occur if an obstruction or a foreign body is present. The duration of therapy for complicated UTI is 7–10 days (up to 2 weeks for pyelonephritis).
Multidrug-resistant *P. aeruginosa* infection	Ceftazidime/avibactam (2.5 g q8h, infused over 2 h) *or* ceftolozane/tazobactam (1.5 g q8h) *or* colistin (100 mg q12h IV for the shortest possible period to obtain a clinical response)	Higher doses of ceftolozane/tazobactam may be required for pneumonias. The colistin doses used have varied. Dosage adjustment for colistin is required in renal failure. Inhaled colistin may be added for pneumonia (100 mg q12h).
Burkholderia cepacia infection	Meropenem (1 g q8h IV) *or* TMP-SMX (1600/320 mg q12h IV) for 14 days	Resistance to both agents is increasing. Do not use them in combination because of possible antagonism.
Melioidosis (*B. pseudomallei*), glanders (*B. mallei*)	Ceftazidime (2 g q6h) *or* meropenem (1 g q8h) *or* imipenem (500 mg q6h) for 2 weeks ***followed by*** TMP-SMX (1600/320 mg q12h PO) for 3 months	
Stenotrophomonas maltophilia infection	TMP-SMX (1600/320 mg q12h IV) *plus* ticarcillin/clavulanate (3.1 g q4h IV) for 14 days	Resistance to all agents is increasing. Levofloxacin or tigecycline may be alternatives, but there is little published clinical experience with these agents.

Abbreviations: IDSA, Infectious Diseases Society of America; TMP-SMX, trimethoprim-sulfamethoxazole.

of *P. aeruginosa* infection is encountered in such settings, empirical combination therapy should be administered until the pathogen is identified and susceptibility data become available. Thereafter, whether one or two agents should be continued remains a matter of individual preference. Recent studies suggest that extended infusions of β-lactams such as cefepime, piperacillin/tazobactam, or meropenem may result in better outcomes of *Pseudomonas* bacteremia and possibly of *Pseudomonas* pneumonia.

Acute Pneumonia Respiratory infections are the most common of all infections caused by *P. aeruginosa*. This organism appears first or second among the causes of ventilator-associated pneumonia (VAP). However, much debate centers on the actual role of *P. aeruginosa* in VAP. Many of the relevant data are based on cultures of sputum or endotracheal tube aspirates and may represent nonpathogenic colonization of the tracheobronchial tree, biofilms on the endotracheal tube, or simple tracheobronchitis.

Older reports of *P. aeruginosa* pneumonia described patients with an acute clinical syndrome of fever, chills, cough, and necrotizing pneumonia indistinguishable from other gram-negative bacterial pneumonias. The traditional accounts described a fulminant infection. Chest radiographs demonstrated bilateral pneumonia, often with nodular densities with or without cavities. This picture is now remarkably rare. Today, the typical patient is on a ventilator, has a slowly progressive infiltrate, and has been colonized with *P. aeruginosa* for days. While some cases may progress rapidly over 48–72 h, they are the exceptions. Nodular densities are not commonly seen. However, infiltrates may go on to necrosis. Necrotizing pneumonia has also been seen in the community (e.g., after inhalation of hot-tub water contaminated with *P. aeruginosa*). The typical patient has fever, leukocytosis, and purulent sputum, and the chest radiograph shows a new infiltrate or the expansion of a preexisting infiltrate. A sputum Gram's stain showing mainly polymorphonuclear leukocytes (PMNs) in conjunction with a culture positive for *P. aeruginosa* in this setting suggests a diagnosis of acute *P. aeruginosa* pneumonia. There is no consensus about whether an invasive procedure (e.g., bronchoalveolar lavage or protected-brush sampling of the distal airways) is superior to tracheal aspiration in obtaining samples for lung cultures in order to substantiate the occurrence of *P. aeruginosa* pneumonia and prevent antibiotic overuse.

TREATMENT

Acute Pneumonia

(Table 159-2) Therapy for *P. aeruginosa* pneumonia has been unsatisfactory. Reports suggest mortality rates of 40–80%, but how many of these deaths are attributable to underlying disease remains unknown. The drugs of choice for *P. aeruginosa* pneumonia are similar to those given for bacteremia. A potent antipseudomonal β-lactam drug is the mainstay of therapy. Failure rates were high when aminoglycosides were used as single agents, possibly because of their poor penetration into the airways and their binding to airway secretions. Nonetheless, for the treatment of patients at high risk of death, some experts suggest the combination of a β-lactam agent and an antipseudomonal fluoroquinolone or aminoglycoside. As for the duration of therapy, recent IDSA/American Thoracic Society (ATS) guidelines recommend 7 days of treatment for hospital-acquired pneumonia or VAP, even when *P. aeruginosa* is the offending organism.

Chronic Respiratory Tract Infections *P. aeruginosa* is responsible for chronic infections of the airways associated with a number of underlying or predisposing conditions—most commonly CF **(Chap. 285)**. A state of chronic colonization beginning early in childhood is seen in some Asian populations with chronic or diffuse panbronchiolitis, a disease of unknown etiology. *P. aeruginosa* is one of the organisms that colonizes damaged bronchi in bronchiectasis, a disease secondary to multiple causes in which profound structural abnormalities of the airways result in mucus stasis.

TREATMENT

Chronic Respiratory Tract Infections

Optimal management of chronic *P. aeruginosa* lung infection has not been determined. Patients respond clinically to antipseudomonal therapy, but the organism is rarely eradicated. Because eradication is unlikely, the aim of treatment for chronic infection is to quell exacerbations of inflammation. The regimens used are similar to those used for pneumonia, but an aminoglycoside is almost always added because resistance is common in chronic disease. However, it may be appropriate to use an inhaled aminoglycoside preparation in order to maximize airway drug levels.

Endovascular Infections Infective endocarditis due to *P. aeruginosa* is a disease of IV drug users whose native valves are involved. This organism has also been reported to cause prosthetic-valve endocarditis. Sites of prior native-valve injury due to the injection of foreign material such as talc or fibers probably serve as niduses for bacterial attachment to the heart valve. The manifestations of *P. aeruginosa* endocarditis resemble those of other forms of endocarditis in IV drug users except that the disease is more indolent than *Staphylococcus aureus* endocarditis. While most disease involves the right side of the heart, left-sided involvement is not rare and multivalvular disease is common. Fever is a common manifestation, as is pulmonary involvement (due to septic emboli to the lungs). Thus, patients may also experience chest pain and hemoptysis. Involvement of the left side of the heart may lead to signs of cardiac failure, systemic emboli, and local cardiac involvement with sinus of Valsalva abscesses and conduction defects. Skin manifestations are rare in this disease, and ecthyma gangrenosum is not seen. The diagnosis is based on positive blood cultures along with clinical signs of endocarditis.

TREATMENT

Endovascular Infections

(Table 159-2) It has been customary to use synergistic antibiotic combinations in treating *P. aeruginosa* endocarditis because of the development of resistance during therapy with a single antipseudomonal β-lactam agent. Which combination therapy is preferable is unclear, as all combinations have failed. Cases of *P. aeruginosa* endocarditis that relapse during or fail to respond to therapy are often caused by resistant organisms and may require surgical therapy. Other considerations for valve replacement are similar to those in other forms of endocarditis **(Chap. 123)**.

Bone and Joint Infections *P. aeruginosa* is an infrequent cause of bone and joint infections. However, *Pseudomonas* bacteremia or infective endocarditis caused by the injection of contaminated illicit drugs has been documented to result in vertebral osteomyelitis and sternoclavicular joint arthritis. The clinical presentation of vertebral *P. aeruginosa* osteomyelitis is more indolent than that of staphylococcal osteomyelitis. The duration of symptoms in IV drug users with vertebral osteomyelitis due to *P. aeruginosa* varies from weeks to months. Fever is not uniformly present; when present, it tends to be low grade. There may be mild tenderness at the site of involvement. Blood cultures are usually negative unless there is concomitant endocarditis. The erythrocyte sedimentation rate (ESR) is generally elevated. Vertebral osteomyelitis due to *P. aeruginosa* has also been reported in the elderly, in whom it originates from urinary tract infections (UTIs). The infection generally involves the lumbosacral area because of a shared venous drainage (Batson's plexus) between the lumbosacral spine and the pelvis. Sternoclavicular septic arthritis due to *P. aeruginosa* is seen almost exclusively in IV drug users. This disease may occur with or without endocarditis, and a primary site of infection often is not found. Plain radiographs show joint or bone involvement. Treatment of these forms of disease is generally successful.

Pseudomonas osteomyelitis of the foot most often follows puncture wounds through sneakers and mostly affects children. The main manifestation is pain in the foot, sometimes with superficial cellulitis around the puncture wound and tenderness on deep palpation of the wound. Multiple joints or bones of the foot may be involved. Systemic symptoms are generally absent, and blood cultures are usually negative. Radiographs may or may not be abnormal, but the bone scan is usually positive, as are MRI studies. Needle aspiration usually yields a diagnosis. Prompt surgery, with exploration of the nail puncture tract and debridement of the involved bones and cartilage, is generally recommended in addition to antibiotic therapy.

Central Nervous System (CNS) Infections CNS infections due to *P. aeruginosa* are relatively rare. Involvement of the CNS is almost always secondary to a surgical procedure or head trauma. The entity seen most often is postoperative or posttraumatic meningitis. Subdural or epidural infection occasionally results from contamination of these areas. Embolic disease arising from endocarditis in IV drug users and leading to brain abscesses has also been described. The cerebrospinal fluid (CSF) profile of *P. aeruginosa* meningitis is no different from that of pyogenic meningitis of any other etiology.

TREATMENT

Central Nervous System Infections

(Table 159-2) Treatment of *Pseudomonas* meningitis is difficult; little information has been published. However, the general principles involved in the treatment of meningitis apply, including the need for high doses of bactericidal antibiotics to attain high drug levels in the CSF. The agent with which there is the most published experience in *P. aeruginosa* meningitis is ceftazidime, but other antipseudomonal β-lactam drugs that reach reasonable CSF concentrations, such as cefepime, piperacillin/tazobactam, and meropenem, have also been used successfully. Other forms of *P. aeruginosa* CNS infection, such as brain abscesses and epidural and subdural empyema, generally require surgical drainage in addition to antibiotic therapy.

Eye Infections Eye infections due to *P. aeruginosa* occur mainly as a result of direct inoculation into the tissue during trauma or surface injury by contact lenses. Keratitis and corneal ulcers are the most

common types of eye disease and are often associated with contact lenses (especially the extended-wear variety). Keratitis can be slowly or rapidly progressive, but the classic description is disease progressing over 48 h to involve the entire cornea, with opacification and sometimes perforation. *P. aeruginosa* keratitis should be considered a medical emergency because of the rapidity with which it can progress to loss of sight. *P. aeruginosa* endophthalmitis secondary to bacteremia is the most devastating of *P. aeruginosa* eye infections. The disease is fulminant, with severe pain, chemosis, decreased visual acuity, anterior uveitis, vitreous involvement, and panophthalmitis.

TREATMENT

Eye Infections

(Table 159-2) The usual therapy for keratitis is the administration of topical antibiotics. Therapy for endophthalmitis includes the use of high-dose local and systemic antibiotics (to achieve higher drug concentrations in the eye) and vitrectomy.

Ear Infections *P. aeruginosa* infections of the ears vary from mild swimmer's ear to serious life-threatening infections with neurologic sequelae. Swimmer's ear is common among children and results from infection of moist macerated skin of the external ear canal. Most cases resolve with treatment, but some patients develop chronic drainage. Swimmer's ear is managed with topical antibiotic agents (otic solutions). The most serious form of *Pseudomonas* infection involving the ear has been given various names: two of these designations, *malignant otitis externa* and *necrotizing otitis externa*, are now used for the same entity. This disease was originally described in elderly diabetic patients, in whom the majority of cases still occur. However, it has also been described in patients with AIDS and in elderly patients without underlying diabetes or immunocompromise. The usual presenting symptoms are decreased hearing and ear pain, which may be severe and lancinating. The pinna is usually painful, and the external canal may be tender. The ear canal almost always shows signs of inflammation, with granulation tissue and exudate. Tenderness anterior to the tragus may extend as far as the temporomandibular joint and mastoid process. A small minority of patients have systemic symptoms. Patients in whom the diagnosis is made late may present with cranial nerve palsies or even with cavernous venous sinus thrombosis. The ESR is invariably elevated (≥100 mm/h). The diagnosis is made on clinical grounds in severe cases; however, the "gold standard" is a positive technetium-99 bone scan in a patient with otitis externa due to *P. aeruginosa*. In diabetic patients, a positive bone scan constitutes presumptive evidence for this diagnosis and should prompt biopsy or empirical therapy.

TREATMENT

Ear Infections

(Table 159-2) Given the infection of the ear cartilage, sometimes with mastoid or petrous ridge involvement, patients with malignant (necrotizing) otitis externa are treated as for osteomyelitis.

Urinary Tract Infections UTIs due to *P. aeruginosa* generally occur as a complication of a foreign body in the urinary tract, an obstruction in the genitourinary system, or urinary tract instrumentation or surgery. However, UTIs caused by *P. aeruginosa* have been described in pediatric outpatients without stones or evident obstruction.

TREATMENT

Urinary Tract Infections

(Table 159-2) Most *P. aeruginosa* UTIs are considered complicated infections that must be treated longer than uncomplicated cystitis. In general, a 7- to 10-day course of treatment suffices, with up to 2 weeks of therapy in cases of pyelonephritis. Urinary catheters, stents, or stones should be removed to prevent relapse, which is common and may be due not to resistance but rather to factors such as a foreign body that has been left in place or an ongoing obstruction.

Skin and Soft Tissue Infections Besides pyoderma gangrenosum in neutropenic patients, folliculitis and other papular or vesicular lesions due to *P. aeruginosa* have been extensively described and are collectively referred to as *dermatitis*. Multiple outbreaks have been linked to whirlpools, spas, and swimming pools. To prevent such outbreaks, the growth of *P. aeruginosa* in the home and in recreational environments must be controlled by proper chlorination of water. Most cases of hot-tub folliculitis are self-limited, requiring only the avoidance of exposure to the contaminated source of water.

Toe-web infections occur especially often in the tropics, and the "green-nail syndrome" is caused by *P. aeruginosa* paronychia, which results from frequent submersion of the hands in water. In the latter entity, the green discoloration results from diffusion of pyocyanin into the nail bed. *P. aeruginosa* remains a prominent cause of burn wound infections in some parts of the world. The management of these infections is best left to specialists in burn wound care.

Infections in Febrile Neutropenic Patients In febrile neutropenia, *P. aeruginosa* has historically been the organism against which empirical coverage is always essential. Although in Western countries these infections are now less common, their importance has not diminished because of persistently high mortality rates. In other parts of the world, *P. aeruginosa* continues to be a significant problem in febrile neutropenia, causing a larger proportion of infections in febrile neutropenic patients than any other single organism. For example, *P. aeruginosa* was responsible for 28% of documented infections in 499 febrile neutropenic patients in one study from the Indian subcontinent and for 31% of such infections in another. In a large study of infections in leukemia patients from Japan, *P. aeruginosa* was the most frequently documented cause of bacterial infection. In studies performed in North America, northern Europe, and Australia, the incidence of *P. aeruginosa* bacteremia in febrile neutropenia was quite variable. In a review of 97 reports published between 1987 and 1994, the incidence was reported to be 1–2.5% among febrile neutropenic patients given empirical therapy and 5–12% among patients with microbiologically documented infections. The most common clinical syndromes encountered were bacteremia, pneumonia, and soft tissue infections manifesting mainly as ecthyma gangrenosum.

TREATMENT

Infections in Febrile Neutropenic Patients

(Table 159-2) Compared with rates three decades ago, improved rates of response to antibiotic therapy have been reported in many studies. A study of 127 patients demonstrated a reduction in the mortality rate from 71 to 25% with the introduction of ceftazidime and imipenem. Because neutrophils—the normal host defenses against this organism—are absent in febrile neutropenic patients, maximal doses of antipseudomonal β-lactam antibiotics should be used for the management of *P. aeruginosa* bacteremia in this setting.

Infections in Patients with AIDS *P. aeruginosa* infections were documented in patients with AIDS before the advent of antiretroviral therapy. Since the introduction of protease inhibitors, *P. aeruginosa* infections in AIDS patients have been seen less frequently but still occur, particularly in the form of sinusitis. The clinical presentation of *Pseudomonas* infection (especially pneumonia and bacteremia) in AIDS patients is remarkable in that, although the illness may appear not to be severe, the infection may nonetheless be fatal. Patients with bacteremia may have only a low-grade fever and may present with ecthyma gangrenosum. Pneumonia, with or without bacteremia, is

perhaps the most common type of *P. aeruginosa* infection. Patients with *P. aeruginosa* pneumonia exhibit the classic clinical signs and symptoms of pneumonia, such as fever, productive cough, and chest pain. The infection may be lobar or multilobar and shows no predisposition for any particular location. The most striking feature is the high frequency of cavitary disease.

TREATMENT

Infections in Patients with AIDS

Therapy for any of these conditions in AIDS patients is no different from that in other patients. However, relapse is the rule unless the patient's CD4+ T cell count rises to >50/μL or suppressive antibiotic therapy is given. In attempts to achieve cures and prevent relapses, therapy tends to be more prolonged than in the case of an immunocompetent patient.

Gastrointestinal Infections A poorly understood syndrome caused by *P. aeruginosa* has been described in the Far East and has been called *Shanghai fever* and *Pseudomonas enterocolitis*. This syndrome occurs in young children; its occurrence in adults appears to be rare. Shanghai fever manifests as severe enteric disease, sepsis with invasive disease, and complications, whereas *Pseudomonas* enterocolitis is characterized by prolonged fever with bloody or mucoid diarrhea mimicking bacterial enterocolitis. The mortality rate ranges between 23 and 89%, with ecthyma gangrenosum occurring in >50% of cases. Early recognition and treatment have led to a reduction in the mortality rate. There is an above-average occurrence of the *exoU* gene among *Pseudomonas* isolates from patients with this syndrome.

Multidrug-Resistant Infections (Table 159-2) *P. aeruginosa* has a notorious propensity to develop antibiotic resistance. During three decades, the impact of resistance was minimized by the rapid development of several potent antipseudomonal agents. However, the situation has changed, with the worldwide emergence of strains carrying determinants that mediate resistance to multiple β-lactams, fluoroquinolones, and aminoglycosides. Physicians now resort to drugs such as colistin and polymyxin B, which were discarded decades ago. These alternative approaches to the management of multidrug-resistant *P. aeruginosa* infections were first used some time ago in CF patients, who receive colistin (polymyxin E) IV and by aerosol despite its renal toxicity. The clinical outcome of multidrug-resistant *P. aeruginosa* infections treated with colistin or polymyxin B is difficult to judge from case reports, especially given the many drugs used in the complicated management of these infections. Although earlier reports described marginal efficacy and serious nephrotoxicity and neurotoxicity, recent reports have been more encouraging as physicians learn how these agents should be dosed. Ceftolozane/tazobactam and ceftazidime/avibactam are welcome additions in the fight against multidrug-resistant *P. aeruginosa* strains as both agents are active against >50–80% of these strains in vitro. However, clinical data showing in vivo efficacy against multidrug-resistant strains are sparse at this time. The use of these agents will likely be restricted to certain niches because of cost constraints. A caveat is that these are β-lactam drugs, and *P. aeruginosa* has shown a remarkable ability to evade this class of antibiotics.

BURKHOLDERIA SPECIES

BURKHOLDERIA CEPACIA

The *B. cepacia* complex gained notoriety as the cause of a rapidly fatal syndrome of respiratory distress and septicemia (the "cepacia syndrome") in CF patients. Previously, it had been recognized as an antibiotic-resistant nosocomial pathogen (then designated *Pseudomonas cepacia*) in ICU patients. Patients with chronic granulomatous disease are also predisposed to *B. cepacia* lung disease. The organism has been reclassified into nine subgroups, only some of which are common in CF. *B. cepacia* is an environmental organism that inhabits moist environments and is found in the rhizosphere. This organism possesses multiple virulence factors that may play roles in disease as well as colonizing factors that are capable of binding to lung mucus—an ability that may explain the predilection of *B. cepacia* for the lungs in CF. *B. cepacia* secretes elastase and possesses components of an injectable toxin-secretion system like that of *P. aeruginosa*; its LPS is among the most potent of all LPSs in stimulating an inflammatory response in the lungs. Inflammation may be the major cause of the lung disease seen in the cepacia syndrome. Besides infecting the lungs in CF, *B. cepacia* appears as an airway colonizer during broad-spectrum antibiotic therapy and is a cause of VAP, catheter-associated infections, and wound infections.

TREATMENT

B. cepacia Infections

B. cepacia is intrinsically resistant to many antibiotics. Therefore, treatment must be tailored according to sensitivities. Trimethoprim-sulfamethoxazole (TMP-SMX), meropenem, and doxycycline are the most effective agents in vitro and may be started as first-line agents (Table 159-2). Some strains are susceptible to third-generation ureidopenicillins, advanced cephalosporins, and fluoroquinolones, and these agents may be used against isolates known to be susceptible. Combination therapy for serious pulmonary infection (e.g., in CF) is suggested when multidrug-resistant strains are implicated; the combination of meropenem and TMP-SMX may be antagonistic, however. Resistance to all agents used has been reported during therapy.

BURKHOLDERIA PSEUDOMALLEI

B. pseudomallei is the causative agent of melioidosis, a disease of humans and animals that is geographically restricted to Southeast Asia and northern Australia, with occasional cases in countries such as India and China. This organism may be isolated from individuals returning directly from these endemic regions and from military personnel who have served in endemic regions. Symptoms of this illness may develop only at a later date because of the organism's ability to cause latent infections. *B. pseudomallei* is found in soil and water. Humans and animals are infected by inoculation, inhalation, or ingestion; only rarely is the organism transmitted from person to person. Humans are not colonized without being infected. Among the pseudomonads, *B. pseudomallei* is perhaps the most virulent. Host compromise is not an essential prerequisite for disease, although many patients have common underlying medical diseases (e.g., diabetes or renal failure). *B. pseudomallei* is a facultative intracellular organism whose replication in PMNs and macrophages may be aided by the possession of a polysaccharide capsule. The organism also possesses elements of a type III secretion system that plays a role in its intracellular survival. During infection, there is a florid inflammatory response whose role in disease is unclear.

B. pseudomallei causes a wide spectrum of conditions, ranging from asymptomatic infection to abscesses, pneumonia, and disseminated disease. It is a significant cause of fatal community-acquired pneumonia and septicemia in endemic areas, with mortality rates as high as 44% reported in Thailand. Acute pulmonary infection is the most commonly diagnosed form of melioidosis. Pneumonia may be asymptomatic (with routine chest radiographs showing mainly upper-lobe infiltrates) or may present as severe necrotizing disease. *B. pseudomallei* also causes chronic pulmonary infections with systemic manifestations that mimic those of tuberculosis, including chronic cough, fever, hemoptysis, night sweats, and cavitary lung disease. Besides pneumonia, the other principal form of *B. pseudomallei* disease is skin ulceration with associated lymphangitis and regional lymphadenopathy. Spread from the lungs or skin, which is most often documented in debilitated individuals, gives rise to septicemic forms of melioidosis that carry a high mortality rate.

TREATMENT

B. pseudomallei Infections

B. pseudomallei is susceptible to advanced penicillins and cephalosporins and to carbapenems (Table 159-2). Treatment is divided into two stages: an intensive 2-week phase of therapy with ceftazidime or a carbapenem followed by at least 12 weeks of oral TMP-SMX to eradicate the organism and prevent relapse. The recognition of this bacterium as a potential agent of biologic warfare has stimulated interest in the development of a vaccine.

BURKHOLDERIA MALLEI

B. mallei causes the equine disease glanders in Africa, Asia, and South America. The organism was eradicated from Europe and North America decades ago. The last case seen in the United States occurred in 2001 in a laboratory worker; before that, *B. mallei* had last been seen in this country in 1949. In contrast to the other organisms discussed in this chapter, *B. mallei* is not an environmental organism and does not persist outside its equine hosts. Consequently, *B. mallei* infection is an occupational risk for handlers of horses, equine butchers, and veterinarians in areas of the world where it still exists. The polysaccharide capsule is a critical virulence determinant; diabetics are thought to be especially susceptible to infection by this organism. The organism is transmitted from animals to humans by inoculation into the skin, where it causes local infection with nodules and lymphadenitis. Regional lymphadenopathy is common. Respiratory secretions from infected horses are extremely infectious. Inhalation results in clinical signs of typical pneumonia but may also cause an acute febrile illness with ulceration of the trachea. The organism may disseminate from the skin or lungs to cause septicemia with signs of sepsis. The septicemic form is frequently associated with shock and a high mortality rate. The infection may also enter a chronic phase and present as disseminated abscesses. *B. mallei* infection may present as early as 1–2 days after inhalation or (in cutaneous disease) may not become evident for months.

TREATMENT

B. mallei Infections

The antibiotic susceptibility pattern of *B. mallei* is similar to that of *B. pseudomallei*; in addition, the organism is susceptible to the macrolides azithromycin and clarithromycin. *B. mallei* infection should be treated with the same drugs and for the same duration as melioidosis.

STENOTROPHOMONAS MALTOPHILIA

S. maltophilia is the only potential human pathogen among a genus of ubiquitous organisms found in the rhizosphere (i.e., the soil that surrounds the roots of plants). The organism is an opportunist that is acquired from the environment but is even more limited than *P. aeruginosa* in its ability to colonize patients or cause infections. Immunocompromise is not sufficient to permit these events; rather, major perturbations of the human flora are usually necessary for the establishment of *S. maltophilia*. Accordingly, most cases of human infection occur in the setting of very broad-spectrum antibiotic therapy with agents such as advanced cephalosporins and carbapenems, which eradicate the normal flora and other pathogens. The remarkable ability of *S. maltophilia* to resist virtually all classes of antibiotics is attributable to the possession of antibiotic efflux pumps and of two β-lactamases (L1 and L2) that mediate β-lactam resistance, including that to carbapenems. It is fortunate that the virulence of *S. maltophilia* appears to be limited. Although a serine protease is present in some strains, virulence is probably a result of the host's inflammatory response to components of the organism such as LPS and flagellin. *S. maltophilia* is most commonly found in the respiratory tract of ventilated patients, where the distinction between its roles as a colonizer and as a pathogen is often difficult to make. However, *S. maltophilia* does cause pneumonia and bacteremia in such patients, and these infections have led to septic shock. Also common is central venous line–associated infection (with or without bacteremia), which has been reported most often in patients with cancer. *S. maltophilia* is a rare cause of ecthyma gangrenosum in neutropenic patients. It has been isolated from ~5% of CF patients but is not believed to be a significant pathogen in this setting.

TREATMENT

S. maltophilia Infections

The intrinsic resistance of *S. maltophilia* to most antibiotics renders infection difficult to treat. The antibiotics to which it is most often (although not uniformly) susceptible are TMP-SMX, ticarcillin/clavulanate, levofloxacin, and tigecycline (Table 159-2). Consequently, a combination of TMP-SMX and ticarcillin/clavulanate is recommended for initial therapy pending susceptibility testing. Catheters must be removed in the treatment of bacteremia. The treatment of VAP due to *S. maltophilia* is much more difficult than that of bacteremia, with frequent development of resistance during therapy.

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160 Salmonellosis

David A. Pegues, Samuel I. Miller

Bacteria of the genus *Salmonella* are highly adapted for growth in both humans and animals and cause a wide spectrum of diseases. The growth of serotypes *Salmonella* Typhi and *Salmonella* Paratyphi is restricted to human hosts, in whom these organisms cause enteric (typhoid) fever. The remaining serotypes (nontyphoidal *Salmonella*, or NTS) can colonize the gastrointestinal tracts of a broad range of animals, including mammals, reptiles, birds, and insects. More than 200 serotypes of *Salmonella* are pathogenic to humans, in whom they often cause gastroenteritis and can be associated with localized infections and/or bacteremia.

ETIOLOGY

This large genus of gram-negative bacilli within the family Enterobacteriaceae consists of two species: *Salmonella enterica*, which contains six subspecies, and *Salmonella bongori*. *S. enterica* subspecies I includes almost all the serotypes pathogenic for humans. Members of the seven *Salmonella* subspecies are classified into >2500 serotypes (serovars); for

simplicity, *Salmonella* serotypes (most of which are named for the city where they were identified) are often used as the species designation. For example, the full taxonomic designation *S. enterica* subspecies *enterica* serotype Typhimurium can be shortened to *Salmonella* serotype Typhimurium or simply *S.* Typhimurium. Serotyping is based on the somatic O antigen (lipopolysaccharide cell-wall components), the surface Vi antigen (restricted to *S.* Typhi and *S.* Paratyphi C), and the flagellar H antigen.

Salmonellae are gram-negative, non-spore-forming, facultatively anaerobic bacilli that measure 2–3 μm by 0.4–0.6 μm. The initial identification of salmonellae in the clinical microbiology laboratory is based on growth characteristics. Salmonellae, like other Enterobacteriaceae, produce acid on glucose fermentation, reduce nitrates, and do not produce cytochrome oxidase. In addition, all salmonellae except *Salmonella* Gallinarum-Pullorum are motile by means of peritrichous flagella, and all but *S.* Typhi produce gas (H_2S) on sugar fermentation. Notably, only 1% of clinical isolates ferment lactose; a high level of suspicion must be maintained to detect these rare clinical lactose-fermenting isolates.

Although serotyping of all surface antigens can be used for formal identification, most laboratories perform a few simple agglutination reactions that define specific O-antigen serogroups, designated A, B, C_1, C_2, D, and E. Strains in these six serogroups cause ~99% of *Salmonella* infections in humans and other warm-blooded animals. Molecular typing methods, including pulsed-field gel electrophoresis, multiple-locus variable-number tandem repeat analysis, and whole-genome sequencing, are used in epidemiologic investigations to differentiate *Salmonella* strains of a common serotype.

PATHOGENESIS

All *Salmonella* infections begin with ingestion of organisms, most commonly in contaminated food or water. The infectious dose ranges from 200 colony-forming units (CFU) to 10^6 CFU, and the ingested dose is an important determinant of incubation period and disease severity. Conditions that decrease either stomach acidity (an age of <1 year, acid suppression therapy, or achlorhydric disease) or intestinal integrity (inflammatory bowel disease, cytotoxic chemotherapy, prior gastrointestinal surgery, or alteration of the intestinal microbiome by antibiotic administration) increase susceptibility to *Salmonella* infection.

Once *S.* Typhi and *S.* Paratyphi reach the small intestine, they penetrate the mucus layer of the gut and traverse the intestinal layer through phagocytic microfold (M) cells that reside within Peyer's patches. Salmonellae can trigger the formation of membrane ruffles in normally nonphagocytic epithelial cells. These ruffles reach out and enclose adherent bacteria within large vesicles by *bacterium-mediated endocytosis*. This process is dependent on the direct delivery of *Salmonella* proteins into the cytoplasm of epithelial cells by the specialized bacterial type III secretion system. These bacterial proteins mediate alterations in the actin cytoskeleton that are required for *Salmonella* uptake.

After crossing the epithelial layer of the small intestine, *S.* Typhi and *S.* Paratyphi, which cause enteric (typhoid) fever, are phagocytosed by macrophages. These salmonellae survive the antimicrobial environment of the macrophage by sensing environmental signals that trigger alterations in regulatory systems of the phagocytosed bacteria. For example, PhoP/PhoQ (the best-characterized regulatory system) triggers the alteration of the outer membrane by increasing the synthesis and transport of different outer-membrane proteins, lipopolysaccharides, and glycerophospholipids, so that the altered bacterial surface can resist microbicidal activities and potentially alter host cell signaling. In addition, salmonellae encode a second type III secretion system that directly delivers bacterial proteins across the phagosome membrane into the macrophage cytoplasm. This secretion system functions to remodel the *Salmonella*-containing vacuole, promoting bacterial survival and replication.

Once phagocytosed, typhoidal salmonellae disseminate throughout the body in macrophages via the lymphatics and colonize reticuloendothelial tissues (liver, spleen, lymph nodes, and bone marrow). Patients have relatively few or no signs and symptoms during this initial incubation stage. Signs and symptoms, including fever and abdominal pain, probably result from secretion of cytokines by macrophages and epithelial cells in response to bacterial products that are recognized by innate immune receptors when a critical number of organisms have replicated. Over time, the development of hepatosplenomegaly is likely to be related to the recruitment of mononuclear cells and the development of a specific acquired cell-mediated immune response to *S.* Typhi colonization. The recruitment of additional mononuclear cells and lymphocytes to Peyer's patches during the several weeks after initial colonization/infection can result in marked enlargement and necrosis of the Peyer's patches, which may be mediated by bacterial products that promote cell death as well as the inflammatory response. In the case of *S.* Typhi, many strains produce a toxin, which probably contributes to systemic symptoms as well as the unusual neuropsychiatric states that can be seen in severe typhoidal illness.

In contrast to enteric fever, which is characterized by an infiltration of mononuclear cells into the small-bowel mucosa, NTS gastroenteritis is characterized by massive polymorphonuclear leukocyte infiltration into both the large- and small-bowel mucosa. This response appears to depend on the induction of interleukin 8, a strong neutrophil chemotactic factor, which is secreted by intestinal cells as a result of nontyphoidal *Salmonella* colonization and translocation of bacterial proteins into host cell cytoplasm. The degranulation and release of toxic substances by neutrophils may result in damage to the intestinal mucosa, causing the inflammatory diarrhea observed with nontyphoidal gastroenteritis. An additional important factor in the persistence of NTS in the intestinal tract and the organism's capacity to compete with endogenous flora is the ability to utilize the sulfur-containing compound tetrathionate for metabolism in a microaerophilic environment. In the presence of intestinal inflammation, tetrathionate is generated from thiosulfate produced by epithelial cells through inflammatory cell production of reactive oxygen species.

ENTERIC (TYPHOID) FEVER

Enteric (typhoid) fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *S.* Typhi or *S.* Paratyphi. The disease was initially called *typhoid fever* because of its clinical similarity to typhus. In the early 1800s, typhoid fever was clearly defined pathologically as a unique illness on the basis of its association with enlarged Peyer's patches and mesenteric lymph nodes. In 1869, given the anatomic site of infection, the term *enteric fever* was proposed as an alternative designation to distinguish typhoid fever from typhus. However, to this day, the two designations are used interchangeably.

EPIDEMIOLOGY

In contrast to other *Salmonella* serotypes, the etiologic agents of enteric fever—*S.* Typhi and *S.* Paratyphi serotypes A, B, and C—have no known hosts other than humans. Most commonly, food-borne or waterborne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures.

With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. Worldwide, however, there are an estimated 21–27 million cases of enteric fever, with 200,000–600,000 deaths annually. The annual incidence is highest (>100 cases/100,000 population) in South-Central and Southeast Asia; medium (10–100 cases/100,000) in the rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand); and low in other parts of the world **(Fig. 160-1)**. A high incidence of enteric fever correlates with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents than among other age groups. Risk factors include contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced gastric acidity). It is estimated that there is one case of paratyphoid fever for every four cases of typhoid fever, but

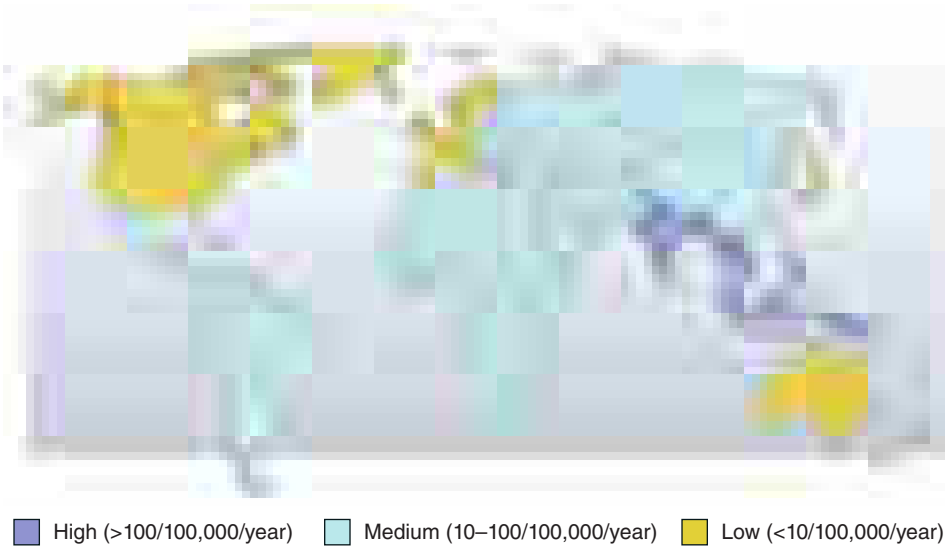

FIGURE 160-1 Annual incidence of typhoid fever per 100,000 population. *(Adapted from JA Crump et al: The global burden of typhoid fever. Bull World Health Organ 82:346, 2004.)*

the incidence of infection associated with *S.* Paratyphi A appears to be increasing, especially in India; this increase may be a result of vaccination for *S.* Typhi.

Multidrug-resistant (MDR) strains of *S.* Typhi emerged in the 1980s in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim—antibiotics long used to treat enteric fever. With the increased use of fluoroquinolones to treat MDR enteric fever in the 1990s, MDR strains of *S.* Typhi and *S.* Paratyphi with decreased susceptibility to ciprofloxacin (DSC; minimal inhibitory concentration [MIC], 0.125–0.5 μg/mL) or ciprofloxacin resistance (MIC, ≥1 μg/mL) have emerged on the Indian subcontinent and have spread with human migration to southern Asia and now to eastern and southern Africa. These strains represent clone H58, which increasingly has been associated with clinical failure of quinolone treatment. Testing of isolates for resistance to the first-generation quinolone nalidixic acid detects many but not all strains with reduced susceptibility to ciprofloxacin and is no longer recommended. Strains of *S.* Typhi and *S.* Paratyphi producing extended-spectrum β-lactamases have emerged, primarily in India and Nepal.

Approximately 300 cases of typhoid and 150 cases of paratyphoid fever are reported annually in the United States. Of 3499 cases of *S.* Typhi–associated enteric fever reported to the Centers for Disease Control and Prevention in 1999–2010, 82% were associated with recent international travel, most commonly to India, Pakistan, and Bangladesh, and occurred predominantly in young to middle-aged adults. Only 6% of travelers diagnosed with enteric fever had received *S.* Typhi vaccine. Overall, 15% of recent *S.* Typhi isolates in the United States were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX), whereas 60% of isolates exhibited DSC. Infection with DSC *S.* Typhi was associated with travel to the Indian subcontinent. During this period, 18% of reported cases of enteric fever in the United States were domestically acquired, and these cases were less often due to MDR or DSC strains than were travel-associated cases. Most cases of domestically acquired enteric fever are sporadic, but outbreaks linked to contaminated food products and previously unrecognized chronic carriers continue to occur.

CLINICAL COURSE

Enteric fever is a misnomer, in that the hallmark features of this disease—fever and abdominal pain—are variable. While fever is documented at presentation in >75% of cases, abdominal pain is reported in only 30–40%. Thus, a high index of suspicion for this potentially fatal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

The incubation period for *S.* Typhi averages 10–14 days but ranges from 5 to 21 days, depending on the inoculum size and the host's health and immune status. The most prominent symptom is prolonged fever (38.8°–40.5°C; 101.8°–104.9°F), which can continue for up to 4 weeks if untreated. *S.* Paratyphi A is thought to cause milder disease than *S.* Typhi, with predominantly gastrointestinal symptoms. However, a prospective study of 669 consecutive cases of enteric fever in Kathmandu, Nepal, found that the infections caused by these organisms were clinically indistinguishable. In this series, symptoms reported on initial medical evaluation included headache (80%), chills (35–45%), cough (30%), sweating (20–25%), myalgias (20%), malaise (10%), and arthralgia (2–4%). Gastrointestinal manifestations included anorexia (55%), abdominal pain (30–40%), nausea (18–24%), vomiting (18%), and diarrhea (22–28%) more commonly than constipation (13–16%). Physical findings included coated tongue (51–56%), splenomegaly (5–6%), and abdominal tenderness (4–5%).

Early physical findings of enteric fever include rash ("rose spots"; 30%), hepatosplenomegaly (3–6%), epistaxis, and relative bradycardia at the peak of high fever (<50%). Rose spots **(Fig. 160-2; see also Fig. A1-9)** make up a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest. The rash is evident in ~30% of patients at the end of the first week and resolves without a trace after 2–5 days. Patients can have two or three crops of lesions, and *Salmonella* can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in highly pigmented patients.

The development of severe disease (which occurs in ~10–15% of patients) depends on host factors (host genetics, immunosuppression, acid suppression therapy, previous exposure, and vaccination), strain virulence and inoculum, and choice of antibiotic therapy. Gastrointestinal bleeding (10–20%) and intestinal perforation (1–3%) most commonly occur in the third and fourth weeks of illness and result from hyperplasia, ulceration, and necrosis of the ileocecal Peyer's patches at the initial site of *Salmonella* infiltration **(Fig. 160-3)**. Both complications are life-threatening and require immediate fluid resuscitation and surgical intervention, with broadened antibiotic coverage for polymicrobial peritonitis **(Chap. 127)** and treatment of gastrointestinal

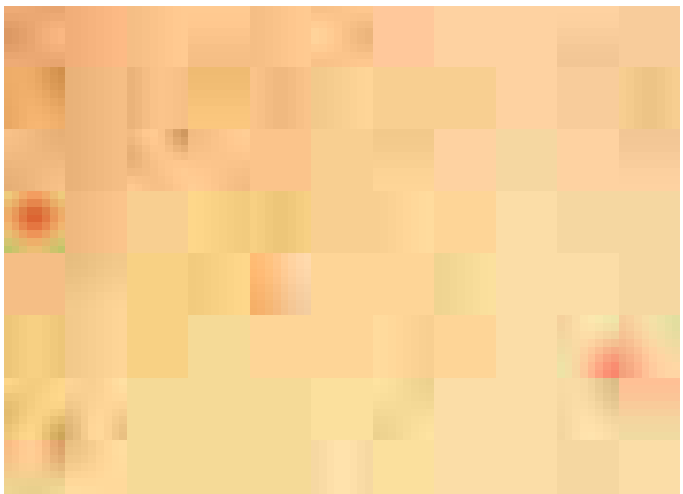

FIGURE 160-2 "Rose spots," the rash of enteric fever due to *Salmonella* Typhi or *Salmonella* Paratyphi.

FIGURE 160-3 Typical ileal perforation associated with *Salmonella* Typhi infection. *(From JM Saxe, R Cropsey: Is operative management effective in treatment of perforated typhoid? Am J Surg 189:342, 2005.)*

hemorrhages, including bowel resection. Neurologic manifestations occur in 2–40% of patients and include meningitis, Guillain-Barré syndrome, neuritis, and neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects.

Rare complications whose incidences are reduced by prompt antibiotic treatment include disseminated intravascular coagulation, hematophagocytic syndrome, pancreatitis, hepatic and splenic abscesses and granulomas, endocarditis, pericarditis, myocarditis, orchitis, hepatitis, glomerulonephritis, pyelonephritis and hemolytic-uremic syndrome, severe pneumonia, arthritis, osteomyelitis, endophthalmitis, and parotitis. Up to 10% of patients develop mild relapse, usually within 2–3 weeks of fever resolution and in association with the same strain type and susceptibility profile.

Up to 10% of untreated patients with typhoid fever excrete *S.* Typhi in the feces for up to 3 months, and 2–5% develop chronic asymptomatic carriage, shedding *S.* Typhi in either urine or stool for >1 year. Chronic carriage is more common among women, infants, and persons who have biliary abnormalities or concurrent bladder infection with *Schistosoma haematobium*. *S.* Typhi and other salmonellae are adapted to survive in the gallbladder environment by forming biofilms on gallstones and invading gallbladder epithelial cells. Chronic carriage is associated with an increased risk of gallbladder cancer, which is much more common in locales where *S.* Typhi is common, such as the Indian subcontinent.

DIAGNOSIS

Because the clinical presentation of enteric fever is relatively nonspecific, the diagnosis needs to be considered in any febrile traveler returning from a developing region, especially the Indian subcontinent, the Philippines, or Latin America. Other diagnoses that should be considered in these travelers include malaria, hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amebic liver abscesses, and acute HIV infection **(Chap. 119)**. Other than a positive culture, no specific laboratory test is diagnostic for enteric fever. In 15–25% of cases, leukopenia and neutropenia are detectable. Leukocytosis is more common among children, during the first 10 days of illness, and in cases complicated by intestinal perforation or secondary infection. Other nonspecific laboratory findings include moderately elevated values in liver function tests and muscle enzyme levels.

The definitive diagnosis of enteric fever requires the isolation of *S.* Typhi or *S.* Paratyphi from blood, bone marrow, other sterile sites, rose spots, stool, or intestinal secretions. The sensitivity of blood culture is only 40–80%, probably because of high rates of antibiotic use in endemic areas and the small number of *S.* Typhi organisms (i.e., <15/mL) typically present in the blood. Because almost all *S.* Typhi organisms in blood are associated with the mononuclear cell/platelet fraction, centrifugation of blood and culture of the buffy coat can substantially reduce the time to isolation of the organism but do not increase sensitivity.

Bone marrow culture is >80% sensitive, and, unlike that of blood culture, its yield is not reduced by up to 5 days of prior antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield is >90%. Stool cultures, although negative in 60–70% of cases during the first week, can become positive during the third week of infection in untreated patients.

The classic Widal serologic test for "febrile agglutinins" is simple and rapid but has limited sensitivity and specificity, especially in endemic regions. Rapid point-of-care tests that detect antibodies to outer-membrane proteins or to Vi or O:9 antigen are available for detection of *S.* Typhi; they are moderately sensitive and specific, but their cost and accuracy have limited their routine use in developing countries. More sensitive and highly specific nucleic acid amplification tests have been developed to detect *S.* Typhi and *S.* Paratyphi in blood, but they do not detect antibiotic resistance and remain impractical in many areas where enteric fever is endemic.

TREATMENT

Enteric (Typhoid) Fever

Prompt administration of appropriate antibiotic therapy prevents severe complications of enteric fever and results in a case–fatality rate of <1%. The initial choice of antibiotics depends on the susceptibility of the *S.* Typhi and *S.* Paratyphi strains in the area of residence or travel **(Table 160-1)**. For treatment of drug-susceptible typhoid fever, fluoroquinolones are the most effective class of agents, with cure rates of ~98% and relapse and fecal carriage rates of <2%. Experience is most extensive with ciprofloxacin. Short-course ofloxacin therapy is similarly successful against infection caused by quinolone-susceptible strains. However, the

TABLE 160-1 Antibiotic Therapy for Enteric Fever in Adults

INDICATION	AGENT	DOSAGE (ROUTE)	DURATION, DAYS
Empirical Treatment			
	Ceftriaxone[a]	2 g/d (IV)	10–14
	Azithromycin[b]	1 g/d (PO)	5
Fully Susceptible			
Optimal treatment	Ciprofloxacin[c]	500 mg bid (PO) or 400 mg q12h (IV)	5–7
	Azithromycin	1 g/d (PO)	5
Alternative treatment	Amoxicillin	1 g tid (PO) or 2 g q6h (IV)	14
	Chloramphenicol	25 mg/kg tid (PO or IV)	14–21
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	7–14
Multidrug-Resistant			
Optimal treatment	Ceftriaxone[a]	2 g/d (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Alternative treatment	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	5–14
Quinolone-Resistant			
Optimal treatment	Ceftriaxone	2 g/d (IV)	10–14
	Azithromycin	1 g/d (PO)	5
Alternative treatment	High-dose ciprofloxacin[d]	750 mg bid (PO) or 400 mg q8h (IV)	10–14

[a]Or another third-generation cephalosporin (e.g., cefotaxime, 2 g q8h IV; or cefixime, 400 mg bid PO). [b]Or 1 g on day 1 followed by 500 mg/d PO for 6 days. [c]Or ofloxacin, 400 mg bid PO for 2–5 days. [d]High-dose ciprofloxacin is an alternative for strains with reduced susceptibility to ciprofloxacin (MIC, 0.125–0.5 μg/mL) but should not be used for fully resistant strains (MIC, ≥1 μg/mL).

high prevalence of DSC and ciprofloxacin-resistant *S.* Typhi and *S.* Paratyphi on the Indian subcontinent, in Nepal, and in some locales in Africa suggests that fluoroquinolones should no longer be used for empirical treatment of enteric fever in these regions. Patients infected with DSC strains of *S.* Typhi or *S.* Paratyphi should be treated with ceftriaxone or azithromycin. Alternatively, high-dose ciprofloxacin (750 mg twice daily for 10–14 days) can be used to treat DSC strains but should not be used to treat ciprofloxacin-resistant enteric fever (MIC, ≥1 μg/mL) because of high failure rates.

Ceftriaxone, cefotaxime, and (oral) cefixime are effective for treatment of MDR enteric fever, including that caused by DSC and fluoroquinolone-resistant strains. These agents clear fever in ~1 week, with failure rates of ~5–10%, fecal carriage rates of <3%, and relapse rates of 3–6%. Oral azithromycin results in defervescence in 4–6 days, with rates of relapse and convalescent stool carriage of <3%. Against DSC strains, azithromycin is associated with lower rates of treatment failure and shorter durations of hospitalization than are fluoroquinolones. Despite efficient in vitro killing of *Salmonella*, first- and second-generation cephalosporins as well as aminoglycosides are ineffective in the treatment of clinical infections.

Most patients with uncomplicated enteric fever can be managed at home with oral antibiotics and antipyretics. Patients with persistent vomiting, diarrhea, and/or abdominal distension should be hospitalized and given supportive therapy as well as a parenteral third-generation cephalosporin or a fluoroquinolone, depending on the susceptibility profile. Therapy should be administered for at least 10 days or for 5 days after fever resolution.

In a randomized, prospective, double-blind study of critically ill patients with enteric fever (i.e., those with shock and obtundation) in Indonesia in the early 1980s, the administration of dexamethasone (an initial dose of 3 mg/kg followed by eight doses of 1 mg/kg every 6 h) with chloramphenicol was associated with a substantially lower mortality rate than was treatment with chloramphenicol alone (10% vs 55%). Although this study has not been repeated in the "post-chloramphenicol era," severe enteric fever remains one of the few indications for glucocorticoid treatment of an acute bacterial infection.

The 2–5% of patients who develop chronic carriage of *Salmonella* can be treated for 4 weeks with oral ciprofloxacin or other fluoroquinolones, with an eradication rate of ~80%. Treatment with oral amoxicillin or TMP-SMX is no longer recommended because of lower eradication rates than for fluoroquinolones and the high prevalence of MDR strains. In cases of anatomic abnormality (e.g., biliary or kidney stones), eradication often requires both antibiotic therapy and surgical correction.

PREVENTION AND CONTROL

Theoretically, it is possible to eliminate the salmonellae that cause enteric fever because they survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack adequate sewage disposal and water treatment, this goal is currently unrealistic. Thus, travelers to developing countries should be advised to monitor their food and water intake carefully and to strongly consider immunization against *S.* Typhi.

Two typhoid vaccines are commercially available: (1) Ty21a, an oral live attenuated *S.* Typhi vaccine (given on days 1, 3, 5, and 7, with revaccination with a full 4-dose series every 5 years); and (2) Vi CPS, a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in a single dose, with a booster every 2 years). The old parenteral whole-cell typhoid/paratyphoid A and B vaccine is no longer licensed, largely because of significant side effects, especially fever. An acetone-killed whole-cell vaccine is available only for use by the U.S. military. The minimal age for vaccination is 6 years for Ty21a and 2 years for Vi CPS. In a recent meta-analysis of vaccines for preventing typhoid fever in populations in endemic areas, the cumulative efficacy was 58% for Ty21a at 2 years and 55% for Vi CPS at 3 years. Although data on typhoid vaccines in travelers are limited, recent evidence suggests moderate efficacy (80%) in U.S. travelers. Currently, there is no licensed vaccine for paratyphoid fever.

Vi CPS typhoid vaccine is poorly immunogenic in children <5 years of age because of T cell–independent properties. In the more recently developed Vi-rEPA vaccine, Vi is bound to a nontoxic recombinant protein that is identical to *Pseudomonas aeruginosa* exotoxin A. In 2- to 4-year-olds, two injections of Vi-rEPA induced stronger T cell responses and higher levels of serum IgG antibody to Vi than did Vi CPS in 5- to 14-year-olds. In a two-dose trial in 2- to 5-year-old children in Vietnam, Vi-rEPA provided 91% efficacy at 27 months and 89% efficacy at 46 months and was very well tolerated. This vaccine is not yet commercially available in the United States. Efforts to improve the immunogenicity and reduce the number of doses of live attenuated oral vaccines are ongoing.

Typhoid vaccine is not required for international travel, but it is recommended for travelers to areas where there is a moderate to high risk of exposure to *S.* Typhi, especially those who are traveling to southern Asia and other developing regions of Asia, Africa, the Caribbean, and Central and South America and who will be exposed to potentially contaminated food and drink. Typhoid vaccine should be considered even for persons planning <2 weeks of travel to high-risk areas. In addition, laboratory workers who deal with *S.* Typhi and household contacts of known *S.* Typhi carriers should be vaccinated. Because the protective efficacy of vaccine can be overcome by the high inocula that are commonly encountered in food-borne exposures, immunization is an adjunct and not a substitute for the avoidance of high-risk foods and beverages. Immunization is not recommended for adults residing in typhoid-endemic areas or for the management of persons who may have been exposed in a common-source outbreak.

Enteric fever is a notifiable disease in the United States. Individual health departments have their own guidelines for allowing ill or colonized food handlers or health care workers to return to their jobs. The reporting system enables public health departments to identify potential source patients and to treat chronic carriers in order to prevent further outbreaks. In addition, because 1–4% of patients with *S.* Typhi infection become chronic carriers, it is important to monitor patients (especially child-care providers and food handlers) for chronic carriage and to treat this condition if indicated.

NONTYPHOIDAL SALMONELLOSIS

EPIDEMIOLOGY

Worldwide, NTS causes ~93 million enteric infections and 155,000 deaths annually. In the United States, NTS causes ~12 million illnesses annually, and the incidence has remained relatively unchanged during the past two decades. In 2014, the incidence of NTS infection in the United States was 14.45 cases per 100,000 persons—the highest rate among the 10 food-borne enteric pathogens under active surveillance. Four serotypes accounted for more than half of U.S. infections in 2014: Enteritidis (21%), Typhimurium (12%), Newport (11%), and Javiana (10%).

The incidence of nontyphoidal salmonellosis is highest during the rainy season in tropical climates and during the warmer months in temperate climates—a pattern coinciding with the peak in food-borne outbreaks. Rates of morbidity and mortality associated with NTS are highest among the elderly, infants, and immunocompromised individuals, including those with hemoglobinopathies, HIV infection, or infections that cause blockade of the reticuloendothelial system (e.g., bartonellosis, malaria, schistosomiasis, histoplasmosis). NTS account for a significant majority of illnesses and hospitalizations associated with U.S. multistate food-borne outbreaks.

Unlike *S.* Typhi and *S.* Paratyphi, whose only reservoir is humans, NTS can be acquired from multiple animal reservoirs. Transmission is most commonly associated with food products of animal origin (especially eggs, poultry, undercooked ground meat, and dairy products), fresh produce contaminated with animal waste, and contact with animals or their environments.

S. Enteritidis infection associated with chicken eggs emerged as a major cause of food-borne disease during the 1980s and 1990s. *S.* Enteritidis infection of the ovaries and upper oviduct tissue of hens results

in contamination of egg contents before shell deposition. Infection is spread to egg-laying hens from breeding flocks and through contact with rodents and manure. The number of *S.* Enteritidis outbreaks and the proportion attributable to egg-containing foods have continued to decline since the mid-1990s; these declines have coincided with interventions in the egg-producing and food service industries. Despite these control efforts, outbreaks of *S.* Enteritidis infection associated with shell eggs continue to occur. In 2010, a national outbreak of *S.* Enteritidis infection resulted in more than 1900 reported illnesses and the recall of 500 million eggs. Transmission via contaminated eggs can be prevented by cooking eggs until the yolk is solidified and pasteurizing egg products. However, a 2010 survey found that 44% of respondents reported consuming undercooked or runny eggs in the previous 12 months, suggesting that adherence to safe food-preparation practices has lagged in the home.

In the last 10 years in Europe (and to a lesser degree in the United States), nontyphoidal strains related to *S.* Typhimurium have emerged and are termed Serotype 4,5,12:i:-. These strains are genetically identical to serotype Typhimurium strains, but a mutation in the *fljA* and *fljB* genes encoding one of the flagellar antigens results in a different serotype that lacks flagellar phase 2 antigen. In Europe, these strains have been associated with pigs and their products, and the reason for their emergence is unknown.

Centralization of food processing and widespread food distribution have contributed to the increased incidence of NTS in developed countries. Manufactured foods to which recent multistate *Salmonella* outbreaks have been traced include peanut butter; milk products, including infant formula; and various processed foods, including packaged breakfast cereal, salsa, frozen prepared meals, and snack foods. Large outbreaks also have been linked to fresh produce, including alfalfa sprouts, nuts and seeds, cantaloupe, mangoes, papayas, and tomatoes; these items become contaminated by manure or water at a single site and then are widely distributed.

An estimated 6% of sporadic *Salmonella* infections in the United States are attributed to contact with reptiles or amphibians, especially iguanas, snakes, turtles, and lizards. Reptile-associated *Salmonella* infection more commonly leads to hospitalization and more frequently involves children, including infants, than do other *Salmonella* infections. Other pets, including hedgehogs, birds, rodents, baby chicks, ducklings, dogs, and cats, also are potential sources of NTS.

Increasing antibiotic resistance in NTS species is a global problem and has been linked to the widespread use of antimicrobial agents in food animals and especially in animal feed. In the early 1990s, *S.* Typhimurium definitive phage type 104 (DT104), characterized by resistance to at least five antibiotics (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines; R-type ACSSuT), emerged worldwide. In 2014, resistance to at least ACSSuT was reported in 3.1% of U.S. NTS isolates, including 14.5% of *S.* Typhimurium isolates. Acquisition is associated with exposure to ill farm animals and to various meat products, including uncooked or undercooked ground beef. Although probably no more virulent than susceptible *S.* Typhimurium strains, DT104 strains are associated with an increased risk of bloodstream infection and hospitalization. DSC and trimethoprim-resistant DT104 strains are emerging, especially in the United Kingdom.

Because of increased resistance to conventional antibiotics such as ampicillin and TMP-SMX, extended-spectrum cephalosporins and fluoroquinolones have emerged as the agents of choice for the treatment of MDR NTS infections. In 2014, 2.4% of all U.S. NTS strains were resistant to ceftriaxone. Most ceftriaxone-resistant isolates were from children <18 years of age, in whom ceftriaxone is the antibiotic of choice for treatment of invasive NTS infection. These strains contained plasmid -encoded AmpC β-lactamases that were probably acquired by horizontal genetic transfer from *Escherichia coli* strains in food-producing animals—an event linked to the widespread use of the veterinary cephalosporin ceftiofur. Most recently, carbapenemase-resistant NTS strains have been reported in Europe, North Africa, and southern Asia.

Over the last decade, strains of DSC NTS (MIC, 0.125–0.5 μg/mL) have emerged and have been associated with delayed response and treatment failure. In 2014, 4.3% of NTS isolates in the United States displayed decreased susceptibility or resistance to ciprofloxacin (MIC, ≥1 μg/mL), and the proportion is higher in Europe (~6%). These strains have diverse resistance mechanisms, including single and multiple mutations in the DNA gyrase genes *gyr*A and *gyr*B, mutations in the chromosomally encoded quinolone resistance–determining region, and plasmid-encoded quinolone resistance genes that are not reliably detected by nalidixic acid susceptibility testing or standard ciprofloxacin disk diffusion. In 2012, the U.S. Clinical Laboratory Standards Institute proposed a lower ciprofloxacin susceptibility breakpoint (≥0.06 μg/mL) for all *Salmonella* species to address this issue. Because commercial test systems do not contain ciprofloxacin concentrations low enough to allow use of this breakpoint, laboratories need to determine the ciprofloxacin MIC by Etest or another alternative method.

CLINICAL MANIFESTATIONS

Gastroenteritis Infection with NTS most often results in gastroenteritis indistinguishable from that caused by other enteric pathogens. Nausea, vomiting, and diarrhea occur 6–48 h after the ingestion of contaminated food or water. Patients often experience abdominal cramping and fever (38–39°C; 100.5–102.2°F). Diarrheal stools are usually loose, nonbloody, and of moderate volume. However, large-volume watery stools, bloody stools, or symptoms of dysentery may occur. Rarely, NTS causes pseudoappendicitis or an illness that mimics inflammatory bowel disease.

Gastroenteritis caused by NTS is usually self-limited. Diarrhea resolves within 3–7 days and fever within 72 h. Stool cultures remain positive for 4–5 weeks after infection and—in rare cases of chronic carriage (<1%)—for >1 year. Persistent NTS infection and relapsing diarrhea have been described in a small fraction of patients and were associated with in-host single-nucleotide mutations in key virulence regulators. For acute NTS gastroenteritis, antibiotic treatment usually is not recommended and may prolong fecal carriage. Neonates, the elderly, and immunosuppressed patients (e.g., transplant recipients, HIV-infected persons) with NTS gastroenteritis are especially susceptible to dehydration and invasive infection and may require hospitalization and antibiotic therapy. Acute NTS gastroenteritis was associated with a threefold increased risk of dyspepsia and irritable bowel syndrome at 1 year in a study from Spain.

Bacteremia and Endovascular Infections Up to 8% of patients with NTS gastroenteritis develop bacteremia; of these, 5–10% develop localized infections. Bacteremia and metastatic infection are most common with *Salmonella* Choleraesuis and *Salmonella* Dublin and among infants, the elderly, and immunocompromised patients, especially those with HIV infection. NTS endovascular infection should be suspected in high-grade or persistent bacteremia, especially with preexisting valvular heart disease, atherosclerotic vascular disease, prosthetic vascular graft, or aortic aneurysm. Arteritis should be suspected in elderly patients with prolonged fever and back, chest, or abdominal pain developing after an episode of gastroenteritis. Endocarditis and arteritis are rare (<1% of cases) but are associated with potentially fatal complications, including valve perforation, endomyocardial abscess, infected mural thrombus, pericarditis, mycotic aneurysms, aneurysm rupture, aortoenteric fistula, and vertebral osteomyelitis.

In some areas of sub-Saharan Africa, NTS is among the most common causes of bacteremia in children. NTS bacteremia among these children is not associated with diarrhea and has been associated with poor nutritional status, malaria, and HIV infection. The responsible strains form a specific clade that is associated with genome reduction; they also exhibit reduced resistance to oxidative and nitrogenous stress, and they have lost the ability to produce catalase and a flavohemoprotein involved in these processes.

Localized Infections • **INTRAABDOMINAL INFECTIONS** Intraabdominal infections due to NTS are rare and usually manifest as hepatic or splenic abscesses or as cholecystitis. Risk factors include hepatobiliary anatomic abnormalities (e.g., gallstones), abdominal malignancy, and sickle cell disease (especially with splenic abscesses). Eradication

of the infection often requires surgical correction of abnormalities and percutaneous drainage of abscesses.

CENTRAL NERVOUS SYSTEM INFECTIONS NTS meningitis most commonly develops in infants 1–4 months of age and in adults with HIV infection. It often results in severe sequelae (including seizures, hydrocephalus, brain infarction, and mental retardation), with death in up to 60% of cases. Other rare central nervous system infections include ventriculitis, subdural empyema, and brain abscesses.

PULMONARY INFECTIONS NTS pulmonary infections usually present as lobar pneumonia, and complications include lung abscess, empyema, and bronchopleural fistula formation. The majority of cases occur in patients with lung cancer, structural lung disease, sickle cell disease, or glucocorticoid use.

URINARY AND GENITAL TRACT INFECTIONS Urinary tract infections caused by NTS present as either cystitis or pyelonephritis. Risk factors include malignancy, urolithiasis, structural abnormalities, HIV infection, and renal transplantation. NTS genital infections are rare and include ovarian and testicular abscesses, prostatitis, and epididymitis. Like other focal infections, both genital and urinary tract infections can be complicated by abscess formation.

BONE, JOINT, AND SOFT TISSUE INFECTIONS *Salmonella* osteomyelitis most commonly affects the femur, tibia, humerus, or lumbar vertebrae and is most often seen in association with sickle cell disease, hemoglobinopathies, or preexisting bone disease (e.g., fractures). Prolonged antibiotic treatment is recommended to decrease the risk of relapse and chronic osteomyelitis. Septic arthritis occurs in the same patient population as osteomyelitis and usually involves the knee, hip, or shoulder joints. Reactive arthritis can follow NTS gastroenteritis and is seen most frequently in persons with the HLA-B27 histocompatibility antigen. NTS rarely can cause soft tissue infections, usually at sites of local trauma in immunosuppressed patients.

DIAGNOSIS

The diagnosis of NTS infection is based on isolation of the organism from freshly passed stool or from blood or another ordinarily sterile body fluid. All salmonellae isolated in clinical laboratories should be sent to local public health departments for serotyping. Blood cultures should be done whenever a patient has prolonged or recurrent fever. Endovascular infection should be suspected if there is high-grade bacteremia (>50% of three or more blood cultures positive). Echocardiography, CT, and indium-labeled white cell scanning are used to identify localized infection. When another localized infection is suspected, joint fluid, abscess drainage, or cerebrospinal fluid should be cultured, as clinically indicated.

TREATMENT

Nontyphoidal Salmonellosis

Antibiotics should not be used routinely to treat uncomplicated NTS gastroenteritis. The symptoms are usually self-limited, and the duration of fever and diarrhea is not significantly decreased by antibiotic therapy. In addition, antibiotic treatment has been associated with increased rates of relapse, prolonged gastrointestinal carriage, and adverse drug reactions. Dehydration secondary to diarrhea should be treated with fluid and electrolyte replacement.

Preemptive antibiotic treatment (Table 160-2) should be considered for patients at increased risk for invasive NTS infection, including neonates (probably up to 3 months of age); persons >50 years of age with known or suspected atherosclerosis; and patients with immunosuppression, cardiac valvular or endovascular abnormalities, or significant joint disease. Treatment should consist of an oral or IV antibiotic administered for 48–72 h or until the patient becomes afebrile. Immunocompromised persons may require up to 7–14 days of therapy. The <1% of persons who develop chronic carriage of NTS should receive a prolonged antibiotic course, as described above for chronic carriage of *S.* Typhi.

TABLE 160-2 Antibiotic Therapy for Nontyphoidal *Salmonella* Infection in Adults

INDICATION	AGENT	DOSAGE (ROUTE)	DURATION, DAYS
Preemptive Treatment[a]			
	Ciprofloxacin[b]	500 mg bid (PO)	2–3
Severe Gastroenteritis[c]			
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	3–7
	Trimethoprim-sulfamethoxazole	160/800 mg bid (PO)	
	Amoxicillin	1 g tid (PO)	
	Ceftriaxone	1–2 g/d (IV)	
Bacteremia			
	Ceftriaxone[d]	2 g/d (IV)	7–14
	Ciprofloxacin	400 mg q12h (IV), then 500 mg bid (PO)	
Endocarditis or Arteritis			
	Ceftriaxone	2 g/d (IV)	42
	Ciprofloxacin	400 mg q8h (IV), then 750 mg bid (PO)	
	Ampicillin	2 g q4h (IV)	
Meningitis			
	Ceftriaxone	2 g q12 h (IV)	14–21
	Ampicillin	2 g q4h (IV)	
Other Localized Infection			
	Ceftriaxone	2 g/d (IV)	14–28
	Ciprofloxacin	500 mg bid (PO) or 400 mg q12h (IV)	
	Ampicillin	2 g q6h (IV)	

[a]Consider for neonates; persons >50 years of age with possible atherosclerotic vascular disease; and patients with immunosuppression, endovascular graft, or joint prosthesis. [b]Or ofloxacin, 400 mg bid (PO). [c]Consider on an individualized basis for patients with severe diarrhea and high fever who require hospitalization. [d]Or cefotaxime, 2 g q8h (IV).

Because of the increasing prevalence of antibiotic resistance, empirical therapy for life-threatening NTS bacteremia or focal NTS infection should include a third-generation cephalosporin or a fluoroquinolone (Table 160-2). If the bacteremia is low-grade (<50% of blood cultures positive), the patient should be treated for 7–14 days. Patients with HIV/AIDS and NTS bacteremia should receive 1–2 weeks of IV antibiotic therapy followed by 4 weeks of oral therapy with a fluoroquinolone. Patients whose infections relapse after this regimen should receive long-term suppressive therapy with a fluoroquinolone or TMP-SMX, as indicated by bacterial sensitivities.

If the patient has endocarditis or arteritis, treatment for 6 weeks with an IV β-lactam antibiotic (such as ceftriaxone or ampicillin) is indicated. IV ciprofloxacin followed by prolonged oral therapy is an option. Early surgical resection of infected aneurysms or other infected endovascular sites is recommended. Patients with infected prosthetic vascular grafts that cannot be resected have been maintained successfully on chronic suppressive oral therapy. For extraintestinal nonvascular infections, a 2- to 4-week course of antibiotic therapy (depending on the infection site) is usually recommended. In chronic osteomyelitis, abscess, or urinary or hepatobiliary infection associated with anatomic abnormalities, surgical resection or drainage may be required in addition to prolonged antibiotic therapy for eradication of infection.

PREVENTION AND CONTROL

Despite widespread efforts to prevent or reduce bacterial contamination of animal-derived food products and to improve food-safety education and training, recent declines in the incidence of NTS in

the United States have been modest compared with those of other food-borne pathogens. This observation probably reflects the complex epidemiology of NTS. Identifying effective risk-reduction strategies requires monitoring of every step of food production, from handling of raw animal or plant products to preparation of finished foods. Contaminated food can be made safe for consumption by pasteurization, irradiation, or proper cooking. All cases of NTS infection should be reported to local public health departments because tracking and monitoring of these cases can identify the source(s) of infection and help authorities anticipate large outbreaks. Lastly, the prudent use of antimicrobial agents in both humans and animals is needed to limit the emergence of MDR *Salmonella*.

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161 Shigellosis

Philippe J. Sansonetti, Jean Bergounioux

The discovery of *Shigella* as the etiologic agent of dysentery—a clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools—is attributed to the Japanese microbiologist Kiyoshi Shiga, who isolated the Shiga bacillus (now known as *Shigella dysenteriae* type 1) from patients' stools in 1897 during a large and devastating dysentery epidemic. *Shigella* cannot be distinguished from *Escherichia coli* by DNA hybridization and remains a separate species only on historical and clinical grounds.

ETIOLOGIC AGENT

Shigella is a non-spore-forming, gram-negative bacterium that, unlike *E. coli*, is nonmotile and does not produce gas from sugars, decarboxylate lysine, or hydrolyze arginine. Some serovars produce indole, and occasional strains utilize sodium acetate. *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei* (serogroups A, B, C, and D, respectively) can be differentiated on the basis of biochemical and serologic characteristics.

Genome sequencing of *E. coli* K12, *S. flexneri* 2a, *S. sonnei*, *S. dysenteriae* type 1, and *S. boydii* has revealed that these species have ~93% of genes in common. The three major genomic "signatures" of *Shigella* are (1) a 215-kb virulence plasmid that carries most of the genes required for pathogenicity (particularly invasive capacity); (2) the lack or alteration of genetic sequences encoding products (e.g., lysine decarboxylase) that, if expressed, would attenuate pathogenicity; and (3) in *S. dysenteriae* type 1, the presence of genes encoding Shiga toxin, a potent cytotoxin.

EPIDEMIOLOGY

The human intestinal tract represents the major reservoir of *Shigella*, which is also found (albeit rarely) in the higher primates. Because excretion of shigellae is greatest in the acute phase of disease, the bacteria are transmitted most efficiently by the fecal–oral route via hand carriage; however, some outbreaks reflect foodborne or waterborne transmission. In impoverished areas, *Shigella* can be transmitted by flies. The high-level infectivity of *Shigella* is reflected by the very small inoculum required for experimental infection of volunteers (100 colony-forming units [CFU]), by the very high attack rates during outbreaks in day-care centers (33–73%), and by the high rates of secondary cases among family members of sick children (26–33%). Shigellosis can also be transmitted sexually.

Throughout history, *Shigella* epidemics have often occurred in settings of human crowding under conditions of poor hygiene—e.g., among soldiers in campaigning armies, inhabitants of besieged cities, groups on pilgrimages, and refugees in camps. Epidemics follow a cyclical pattern in areas such as the Indian subcontinent and sub-Saharan Africa. These devastating epidemics, which are most often caused by *S. dysenteriae* type 1, are characterized by high attack and mortality rates. In Bangladesh, for instance, an epidemic caused by *S. dysenteriae* type 1 was associated with a 42% increase in mortality rate among children 1–4 years of age. Apart from these epidemics, shigellosis is mostly an endemic disease, with 99% of cases occurring in the developing world and the highest prevalences in the most impoverished areas, where personal and general hygiene is below standard. *S. flexneri* isolates predominate in the least developed areas, whereas *S. sonnei* is more prevalent in economically emerging countries and in the industrialized world.

Prevalence in the Developing World In a review published under the auspices of the World Health Organization (WHO), the total annual number of cases in 1966–1997 was estimated at 165 million, and 69% of these cases occurred in children <5 years of age. In this review, the annual number of deaths was calculated to range between 500,000 and 1.1 million. More recent data (2000–2004) from six Asian countries indicate that, even though the incidence of shigellosis remains stable, mortality rates associated with this disease may have decreased significantly, possibly as a result of improved nutritional status. However, extensive and essentially uncontrolled use of antibiotics, which may also account for declining mortality rates, has increased the rate of emergence of multidrug-resistant *Shigella* strains. A 2013 prospective matched case–control study of children <5 years of age emphasizes the importance of *Shigella* in the burden and etiology of diarrheal diseases in developing countries. *Shigella* is one of the top four pathogens associated with moderate to severe diarrhea and is now ranked first among children 12–59 months of age. These moderate to severe cases account for an 8.5-fold increase in mortality incidence over the average diarrheal disease–related mortality. The study's authors conclude that *Shigella* remains a major pathogen to be targeted by health care programs.

An often-overlooked complication of shigellosis is the short- and long-term impairment of the nutritional status of infected children in endemic areas. Combined with anorexia, the exudative enteropathy resulting from mucosal abrasions contributes to rapid deterioration of the patient's nutritional status. Shigellosis is thus a major contributor to stunted growth among children in developing countries.

Peaking in incidence in the pediatric population, endemic shigellosis is rare among young and middle-aged adults, probably because of naturally acquired immunity. Incidence then increases again in the elderly population.

Prevalence in the Industrialized World In pediatric populations, local outbreaks occur when proper and adapted hygiene policies are not implemented in group facilities like day-care centers and institutions for the mentally retarded. In adults, as in children, sporadic cases occur among travelers returning from endemic areas, and rare outbreaks of varying size can follow waterborne or foodborne infections.

PATHOGENESIS AND PATHOLOGY

Shigella infection occurs essentially through oral contamination via direct fecal–oral transmission, the organism being poorly adapted to survive in the environment. Resistance to low-pH conditions allows shigellae to survive passage through the gastric barrier, an ability that may explain in part why a small inoculum (as few as 100 CFU) is sufficient to cause infection.

The watery diarrhea that usually precedes the dysenteric syndrome is attributable to active secretion and abnormal water reabsorption—a secretory effect at the jejunal level described in experimentally infected

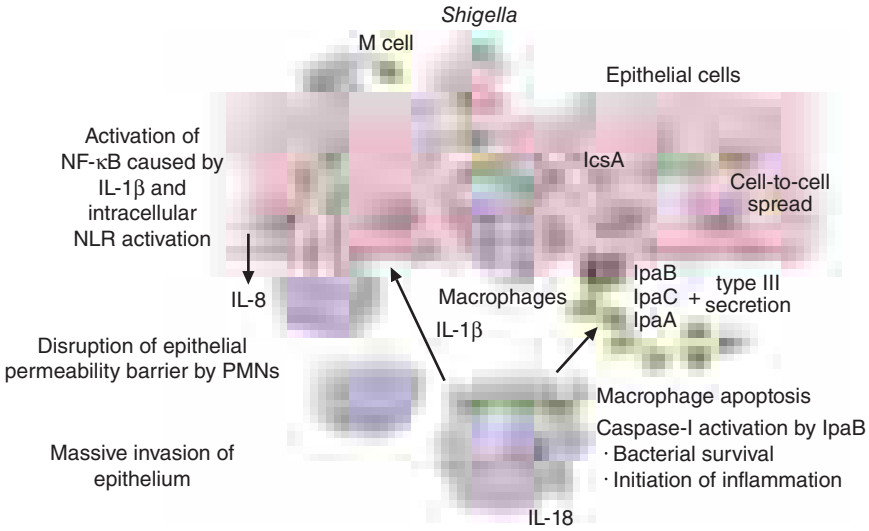

FIGURE 161-1 Invasive strategy of *Shigella flexneri*. IL, interleukin; NF-κB, nuclear factor κB; NLR, NOD-like receptor; PMN, polymorphonuclear leukocyte.

rhesus monkeys. This initial purge is probably due to the combined action of an enterotoxin (ShET-1) and mucosal inflammation. The dysenteric syndrome, manifested by bloody and mucopurulent stools, reflects invasion of the mucosa.

The pathogenesis of *Shigella* is essentially determined by a large virulence plasmid of 214 kb comprising ~100 genes, of which 25 encode a type III secretion system that inserts into the membrane of the host cell to allow effectors to transit from the bacterial cytoplasm to the host cell cytoplasm **(Fig. 161-1)**. Bacteria are thereby able to invade intestinal epithelial cells by inducing their own uptake after the initial crossing of the epithelial barrier through M cells (the specialized translocating epithelial cells in the follicle-associated epithelium that covers mucosal lymphoid nodules). The organisms induce apoptosis of subepithelial resident macrophages. Once inside the cytoplasm of intestinal epithelial cells, *Shigella* effectors trigger the cytoskeletal rearrangements necessary to direct uptake of the organism into the epithelial cell. The *Shigella*-containing vacuole is then quickly lysed, releasing bacteria into the cytosol.

Intracellular shigellae next use cytoskeletal components to propel themselves inside the infected cell; when the moving organism and the host cell membrane come into contact, cellular protrusions form and are engulfed by neighboring cells. This series of events permits bacterial cell-to-cell spread.

Cytokines released by a growing number of infected intestinal epithelial cells attract increased numbers of immune cells (particularly polymorphonuclear leukocytes [PMNs]) to the infected site, thus further destabilizing the epithelial barrier, exacerbating inflammation, and leading to the acute colitis that characterizes shigellosis. Evidence indicates that some type III secretion system–injected effectors can control the extent of inflammation, thus facilitating bacterial survival.

Shiga toxin produced by *S. dysenteriae* type 1 increases disease severity. This toxin belongs to a group of A1-B5 protein toxins whose B subunit binds to the receptor globotriaosylceramide on the target cell surface and whose catalytic A subunit is internalized by receptor-mediated endocytosis and interacts with the subcellular machinery to inhibit protein synthesis by expressing RNA *N*-glycosidase activity on 28S ribosomal RNA. This process leads to inhibition of binding of the amino-acyl-tRNA to the 60S ribosomal subunit and thus to a general shutoff of cell protein biosynthesis. Shiga toxins are translocated from the bowel into the circulation. After binding of the toxins to target cells in the kidney, pathophysiologic alterations may result in hemolytic-uremic syndrome (HUS; see below).

CLINICAL MANIFESTATIONS

The presentation and severity of shigellosis depend to some extent on the infecting serotype but even more on the age and the immunologic and nutritional status of the host. Poverty and poor standards of hygiene are strongly related to the number and severity of diarrheal episodes, especially in children <5 years old who have been weaned.

Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the postinfectious phase. The incubation period usually lasts 1–4 days but may be as long as 8 days. Typical initial manifestations are transient fever, limited watery diarrhea, malaise, and anorexia. Signs and symptoms may range from mild abdominal discomfort to severe cramps, diarrhea, fever, vomiting, and tenesmus. The manifestations are usually exacerbated in children, with temperatures up to 40°–41°C (104.0°–105.8°F) and more severe anorexia and watery diarrhea. This initial phase may represent the only clinical manifestation of shigellosis, especially in developed countries. Otherwise, dysentery follows within hours or days and is characterized by uninterrupted excretion of small volumes of bloody mucopurulent stools with increased tenesmus and abdominal cramps. At this stage, *Shigella* produces acute colitis involving mainly the distal colon and the rectum. Unlike most diarrheal syndromes, dysenteric syndromes rarely present with dehydration as a major feature. Endoscopy shows an edematous and hemorrhagic mucosa, with ulcerations and possibly overlying exudates resembling pseudomembranes. The extent of the lesions correlates with the number and frequency of stools and with the degree of protein loss by exudative mechanisms. Most episodes are self-limited and resolve without treatment in 1 week. With appropriate treatment, recovery takes place within a few days to a week, with no sequelae.

Acute life-threatening complications are seen most often in children <5 years of age (particularly those who are malnourished) and in elderly patients. Risk factors for death in a clinically severe case include nonbloody diarrhea, moderate to severe dehydration, bacteremia, absence of fever, abdominal tenderness, and rectal prolapse. Major complications are predominantly intestinal (e.g., toxic megacolon, intestinal perforations, rectal prolapse) or metabolic (e.g., hypoglycemia, hyponatremia, dehydration). Bacteremia is rare and is reported most frequently in severely malnourished and HIV-infected patients. Alterations of consciousness, including seizures, delirium, and coma, may occur, especially in children <5 years old, and are associated with a poor prognosis; fever and severe metabolic alterations are more often the major causes of altered consciousness than is meningitis or the Ekiri syndrome (toxic encephalopathy associated with bizarre posturing, cerebral edema, and fatty degeneration of viscera), which has been reported mostly in Japanese children. Pneumonia, vaginitis, and keratoconjunctivitis due to *Shigella* are rarely reported. In the absence of serious malnutrition, severe and very unusual clinical manifestations, such as meningitis, may be linked to genetic defects in innate immune functions (i.e., deficiency in interleukin 1 receptor–associated kinase 4 [IRAK-4]) and may require genetic investigation.

Two complications of particular importance are toxic megacolon and HUS. Toxic megacolon is a consequence of severe inflammation extending to the colonic smooth-muscle layer and causing paralysis and dilation. The patient presents with abdominal distention and tenderness, with or without signs of localized or generalized peritonitis. The abdominal x-ray characteristically shows marked dilation of the transverse colon (with the greatest distention in the ascending and descending segments); thumbprinting caused by mucosal inflammatory edema; and loss of the normal haustral pattern associated with pseudopolyps, often extending into the lumen. Pneumatosis coli is an occasional finding. If perforation occurs, radiographic signs of pneumoperitoneum may be apparent. Predisposing factors (e.g., hypokalemia and use of opioids, anticholinergics, loperamide, psyllium seeds, and antidepressants) should be investigated.

Shiga toxin produced by *S. dysenteriae* type 1 has been linked to HUS in developing countries but rarely in industrialized countries, where enterohemorrhagic *E. coli* (EHEC) predominates as

the etiologic agent of this syndrome. HUS is an early complication that most often develops after several days of diarrhea. Clinical examination shows pallor, asthenia, and irritability and, in some cases, bleeding of the nose and gums, oliguria, and increasing edema. HUS is a nonimmune (Coombs test–negative) hemolytic anemia defined by a diagnostic triad: microangiopathic hemolytic anemia (hemoglobin level typically <80 g/L [<8 g/dL]), thrombocytopenia (mild to moderate in severity; typically <60,000 platelets/μL), and acute renal failure due to thrombosis of the glomerular capillaries (with markedly elevated creatinine levels). Anemia is severe, with fragmented red blood cells (*schizocytes*) in the peripheral smear, high serum concentrations of lactate dehydrogenase and free circulating hemoglobin, and elevated reticulocyte counts. Acute renal failure occurs in 55–70% of cases; however, renal function recovers in most of these cases (up to 70% in various series). Leukemoid reactions, with leukocyte counts of 50,000/μL, are sometimes noted in association with HUS.

The postinfectious immunologic complication known as *reactive arthritis* can develop weeks or months after shigellosis, especially in patients expressing the histocompatibility antigen HLA-B27. About 3% of patients infected with *S. flexneri* later develop this syndrome, with arthritis, ocular inflammation, and urethritis—a condition that can last for months or years and can progress to difficult-to-treat chronic arthritis. Postinfectious arthropathy occurs only after infection with *S. flexneri* and not after infection with the other *Shigella* serotypes.

LABORATORY DIAGNOSIS

The differential diagnosis in patients with a dysenteric syndrome depends on the clinical and environmental context. In developing areas, infectious diarrhea caused by other invasive pathogenic bacteria (*Salmonella*, *Campylobacter jejuni*, *Clostridium difficile*, *Yersinia enterocolitica*) or parasites (*Entamoeba histolytica*) should be considered. Only bacteriologic and parasitologic examinations of stool can truly differentiate among these pathogens. A first flare of inflammatory bowel disease, such as Crohn's disease or ulcerative colitis **(Chap. 319)**, should be considered in patients in industrialized countries. Despite the similarity in symptoms, anamnesis discriminates between shigellosis, which usually follows recent travel in an endemic zone, and these other conditions.

Microscopic examination of stool smears shows erythrophagocytic trophozoites with very few PMNs in *E. histolytica* infection, whereas bacterial enteroinvasive infections (particularly shigellosis) are characterized by high PMN counts in each microscopic field. However, because shigellosis often manifests only as watery diarrhea, systematic attempts to isolate *Shigella* are necessary.

The "gold standard" for the diagnosis of *Shigella* infection remains the isolation and identification of the pathogen from fecal material. One major difficulty, particularly in endemic areas where laboratory facilities are not immediately available, is the fragility of *Shigella* and its common disappearance during transport, especially with rapid changes in temperature and pH. In the absence of a reliable enrichment medium, buffered glycerol saline or Cary-Blair medium can be used as a holding medium, but prompt inoculation onto isolation medium is essential. The probability of isolation is higher if the portion of stools that contains bloody and/or mucopurulent material is directly sampled. Rectal swabs can be used, as they offer the highest rate of successful isolation during the acute phase of disease. Blood cultures are positive in fewer than 5% of cases but should be done when a patient presents with a clinical picture of severe sepsis.

In addition to quick processing, the use of several media increases the likelihood of successful isolation: a nonselective medium such as bromocresol-purple agar lactose; a low-selectivity medium such as MacConkey or eosin-methylene blue; and a high-selectivity medium such as Hektoen, *Salmonella-Shigella*, or xylose-lysine-deoxycholate agar. After incubation on these media for 12–18 h at 37°C (98.6°F), shigellae appear as non-lactose-fermenting colonies that measure 0.5–1 mm in diameter and have a convex, translucent, smooth surface. Suspected colonies on nonselective or low-selectivity medium can be subcultured on a high-selectivity medium before being specifically identified or can be identified directly by standard commercial systems on the basis of four major characteristics: glucose positivity (usually without production of gas), lactose negativity, H_2S negativity, and lack of motility. The four *Shigella* serogroups (A–D) can then be differentiated by additional characteristics. This approach adds time and difficulty to the identification process; however, after presumptive diagnosis, the use of serologic methods (e.g., slide agglutination, with group- and then type-specific antisera) should be considered. Group-specific antisera are widely available; in contrast, because of the large number of serotypes and subserotypes, type-specific antisera are rare and more expensive and thus are often restricted to reference laboratories.

TREATMENT

Shigellosis

ANTIBIOTIC SUSCEPTIBILITY OF *SHIGELLA*

As an enteroinvasive disease, shigellosis requires antibiotic treatment. Since the mid-1960s, however, increasing resistance to multiple drugs has been a dominant factor in treatment decisions. Resistance rates are highly dependent on the geographic area. Clonal spread of particular strains and horizontal transfer of resistance determinants, particularly via plasmids and transposons, contribute to multidrug resistance. The current global status—i.e., high rates of resistance to classic first-line antibiotics such as amoxicillin—has led to a rapid switch to quinolones such as nalidixic acid. However, resistance to such early-generation quinolones has also emerged and spread quickly as a result of chromosomal mutations affecting DNA gyrase and topoisomerase IV; this resistance has necessitated the use of later-generation quinolones as first-line antibiotics in many areas. For instance, a review of the antibiotic resistance history of *Shigella* in India found that, after their introduction in the late 1980s, the second-generation quinolones norfloxacin, ciprofloxacin, and ofloxacin were highly effective in the treatment of shigellosis, including cases caused by multidrug-resistant strains of *S. dysenteriae* type 1. However, investigations of subsequent outbreaks in India and Bangladesh detected resistance to norfloxacin, ciprofloxacin, and ofloxacin in 5% of isolates. The incidence of multidrug resistance parallels the widespread, uncontrolled use of antibiotics and calls for the rational use of effective drugs.

ANTIBIOTIC TREATMENT OF SHIGELLOSIS (TABLE 161-1)

Because of the ready transmissibility of *Shigella*, current public health recommendations in the United States are that every case be treated with antibiotics. Ciprofloxacin is recommended as first-line treatment. A number of other drugs have been tested and shown to be effective, including ceftriaxone, azithromycin, pivmecillinam, and some fifth-generation quinolones. Whereas infections caused by non-*dysenteriae Shigella* in immunocompetent individuals are routinely treated with a 3-day course of antibiotics, it is recommended that *S. dysenteriae* type 1 infections be treated for 5 days and that *Shigella* infections in immunocompromised patients be treated for 7–10 days.

Treatment for shigellosis must be adapted to the clinical context, with the recognition that the most fragile patients are children <5 years old, who represent two-thirds of all cases worldwide. There are few data on the use of quinolones in children, but *Shigella*-induced dysentery is a well-recognized indication for their use. The half-life of ciprofloxacin is longer in infants than in older individuals. The ciprofloxacin dose generally recommended for children is 30 mg/kg per day in two divided doses. Adults living in areas with high standards of hygiene are likely to develop milder, shorter-duration disease, whereas infants in endemic areas can develop severe, sometimes fatal, dysentery. In the former setting, treatment will remain minimal and bacteriologic proof of infection will often come after symptoms have resolved; in

TABLE 161-1 Recommended Antimicrobial Therapy for Shigellosis

ANTIMICROBIAL AGENT	TREATMENT SCHEDULE: CHILDREN	TREATMENT SCHEDULE: ADULTS	LIMITATIONS
First Line			
Ciprofloxacin	15 mg/kg	500 mg	
	2 times per day for 3 days, PO		
Second Line			
Pivmecillinam	20 mg/kg	100 mg	Cost
	4 times per day for 5 days PO		No pediatric formulation
			Frequent administration
			Emerging resistance
Ceftriaxone	50–100 mg/kg	–	Efficacy not validated
	Once a day IM for 2–5 days		Must be injected
Azithromycin	6–20 mg/kg	1–1.5 g	Cost
	Once a day for 1–5 days PO		Efficacy not validated
			Minimum inhibitory concentration near serum concentration
			Rapid emergence of resistance and spread to other bacteria

Source: WHO Library Cataloguing-in-Publication Data: Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae* type 1 (*www.who.int/cholera/publications/shigellosis/en/*).

the latter setting, antibiotic treatment and more aggressive measures, possibly including resuscitation, are often required.

REHYDRATION AND NUTRITION

Shigella infection rarely causes significant dehydration. Cases requiring aggressive rehydration (particularly in industrialized countries) are uncommon. In developing countries, malnutrition remains the primary indicator for diarrhea-related death, highlighting the importance of nutrition in early management. Rehydration should be oral unless the patient is comatose or presents in shock. Because of the improved effectiveness of reduced-osmolarity oral rehydration solution (especially for children with acute noncholera diarrhea), the WHO and UNICEF now recommend a standard solution of 245 mOsm/L (sodium, 75 mmol/L; chloride, 65 mmol/L; glucose [anhydrous], 75 mmol/L; potassium, 20 mmol/L; citrate, 10 mmol/L). In shigellosis, the coupled transport of sodium and glucose may be variably affected, but oral rehydration therapy remains the easiest and most efficient form of rehydration, especially in severe cases.

Nutrition should be started as soon as possible after completion of initial rehydration. Early refeeding is safe, well tolerated, and clinically beneficial. Because breast-feeding reduces diarrheal losses and the need for oral rehydration in infants, it should be maintained in the absence of contraindications (e.g., maternal HIV infection).

NONSPECIFIC, SYMPTOM-BASED THERAPY

Antimotility agents have been implicated in prolonged fever in volunteers with shigellosis. These agents are suspected of increasing the risk of toxic megacolon and are thought to have been responsible for HUS in children infected by EHEC strains. For safety reasons, it is better to avoid antimotility agents in bloody diarrhea.

TREATMENT OF COMPLICATIONS

There is no consensus regarding the best treatment for toxic megacolon. The patient should be assessed frequently by both medical and surgical teams. Anemia, dehydration, and electrolyte deficits (particularly hypokalemia) may aggravate colonic atony and should be actively treated. Nasogastric aspiration helps to deflate the colon. Parenteral nutrition has not been proven to be beneficial. Fever persisting beyond 48–72 h raises the possibility of local perforation or abscess. Most studies recommend colectomy if, after 48–72 h, colonic distention persists. However, some physicians recommend continuation of medical therapy for up to 7 days if the patient seems to be improving clinically despite persistent megacolon without free perforation. Intestinal perforation, either isolated or complicating toxic megacolon, requires surgical treatment and intensive medical support.

Rectal prolapse must be treated as soon as possible. With the health care provider using surgical gloves or a soft warm wet cloth and the patient in the knee-chest position, the prolapsed rectum is gently pushed back into place. If edema of the rectal mucosa is evident (rendering reintegration difficult), it can be osmotically reduced by the application of gauze impregnated with a warm solution of saturated magnesium sulfate. Rectal prolapse often relapses but usually resolves along with the resolution of dysentery.

HUS must be treated by water restriction, including discontinuation of oral rehydration solution and potassium-rich alimentation. Hemofiltration is usually required.

PREVENTION

Hand washing after defecation or handling of children's feces and before handling of food is recommended. Stool decontamination (e.g., with sodium hypochlorite), together with a cleaning protocol for medical staff as well as for patients, has proven useful in limiting the spread of infection during *Shigella* outbreaks. Ideally, patients should have a negative stool culture before their infection is considered cured. Recurrences are rare if therapeutic and preventive measures are correctly implemented.

Although several live attenuated oral and subunit parenteral vaccine candidates have been produced and are undergoing clinical trials, no vaccine against shigellosis is currently available. Especially given the rapid progression of antibiotic resistance in *Shigella*, a vaccine is urgently needed.

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162 Infections Due to *Campylobacter* and Related Organisms

Beth D. Kirkpatrick, Martin J. Blaser

DEFINITION

Bacteria of the genus *Campylobacter* and of the related genera *Arcobacter* and *Helicobacter* **(Chap. 158)** cause a variety of inflammatory conditions. Although acute diarrheal illnesses are most common, these organisms may cause infections in virtually all parts of the body, especially in compromised hosts, and these infections may have late nonsuppurative sequelae. The designation *Campylobacter* comes from the Greek for "curved rod" and refers to the organism's vibrio-like morphology.

ETIOLOGY

Campylobacters are motile, non-spore-forming, curved, gram-negative rods. Originally known as *Vibrio fetus*, these bacilli were reclassified as a new genus in 1973 after their dissimilarity to other vibrios was recognized. More than 20 species have since been identified. These species are currently divided into three genera: *Campylobacter*, *Arcobacter,* and *Helicobacter*. Not all of the species are pathogens of humans. The human pathogens fall into two major groups: those that primarily cause diarrheal disease and those that cause extraintestinal infection. The principal diarrheal pathogen is *Campylobacter jejuni*, which accounts for 80–90% of all cases of recognized illness due to campylobacters and related genera. Other organisms that cause diarrheal disease include *Campylobacter coli, Campylobacter upsaliensis, Campylobacter lari, Campylobacter hyointestinalis, Campylobacter fetus, Arcobacter butzleri, Arcobacter cryaerophilus, Helicobacter cinaedi,* and *Helicobacter fennelliae.* The two *Helicobacter* species causing diarrheal disease, *H. cinaedi* and *H. fennelliae*, are intestinal rather than gastric organisms; in terms of the clinical features of the illnesses they cause, these species most closely resemble *Campylobacter* rather than *Helicobacter pylori* **(Chap. 158)** and thus are considered in this chapter. The pathogenic roles of *Campylobacter concisus, Campylobacter ureolyticus, Campylobacter troglodytis,* and *Campylobacter pyloridis* are uncertain. A new subspecies—*C. fetus* subspecies *testudinum*—has been described, chiefly in Asian patients; its close resemblance to strains isolated from reptiles suggests a food source.

The major species causing extraintestinal illnesses is *C. fetus*. However, any of the diarrheal agents listed above may cause systemic or localized infection as well, especially in compromised hosts. Neither aerobes nor strict anaerobes, these microaerophilic organisms are adapted for survival in the gastrointestinal mucous layer. This chapter focuses on *C. jejuni* and *C. fetus* as the major pathogens in and prototypes for their groups. The key features of infection are listed by species (excluding *C. jejuni*, described in detail in the text below) in **Table 162-1**.

EPIDEMIOLOGY

Campylobacters are found in the gastrointestinal tract of many animals used for food (including poultry, cattle, sheep, and swine) and many household pets (including birds, dogs, and cats). These microorganisms usually do not cause illness in their animal hosts. In most cases, campylobacters are transmitted to humans in raw or undercooked food products or through direct contact with infected animals. In the United States and other developed countries, ingestion of contaminated poultry that has not been sufficiently cooked is the most common mode of acquisition (30–70% of cases). Other modes include ingestion of raw (unpasteurized) milk or untreated water, contact with infected household pets, travel to developing countries (campylobacters being a leading cause of traveler's diarrhea; **Chaps. 119 and 128**), oral–anal sexual contact, cross-contamination from any of these sources, and (occasionally) contact with an index case who is incontinent of stool.

Campylobacter infections are common. Active surveillance of foodborne infections in the United States estimates the incidence of diarrheal disease due to campylobacters at 11.8 cases per 100,000 persons—similar in incidence to *Salmonella* and more common than *Shigella*. Infections occur throughout the year, but the incidence peaks during summer and early autumn. Persons of all ages are affected; however, attack rates for *C. jejuni* are highest among young children and young adults, whereas those for *C. fetus* are highest at the extremes of age. Systemic infections due to *C. fetus* (and to other *Campylobacter* and related species) are most common among compromised hosts. Persons at increased risk include those with AIDS, hypogammaglobulinemia, neoplasia, liver disease, diabetes mellitus, and generalized atherosclerosis as well as neonates and pregnant women.

TABLE 162-1 Clinical Features Associated with Infection Due to "Atypical" *Campylobacter* and Related Species Implicated as Causes of Human Illness

SPECIES	COMMON CLINICAL FEATURES	LESS COMMON CLINICAL FEATURES	ADDITIONAL INFORMATION
Campylobacter coli	Fever, diarrhea, abdominal pain	Bacteremia[a]	Clinically indistinguishable from *C. jejuni*
Campylobacter fetus	Bacteremia,[a] sepsis, meningitis, vascular infections	Diarrhea, relapsing fevers	Not usually isolated from media containing cephalothin or incubated at 42°C
Campylobacter upsaliensis	Watery diarrhea, low-grade fever, abdominal pain	Bacteremia, abscesses	Difficult to isolate because of cephalothin susceptibility
Campylobacter lari	Abdominal pain, diarrhea	Colitis, appendicitis	Seagulls frequently colonized; organism often transmitted to humans via contaminated water
Campylobacter hyointestinalis	Watery or bloody diarrhea, vomiting, abdominal pain	Bacteremia	Causes proliferative enteritis in swine
Helicobacter fennelliae	Chronic mild diarrhea, abdominal cramps, proctitis	Bacteremia[a]	Best treated with fluoroquinolones
Helicobacter cinaedi	Chronic mild diarrhea, abdominal cramps, proctitis	Bacteremia[a]	Best treated with fluoroquinolones; identified in healthy hamsters
Campylobacter jejuni subspecies *doylei*	Diarrhea	Chronic gastritis, bacteremia[b]	Uncertain role as human pathogen
Arcobacter cryaerophilus	Diarrhea	Bacteremia	Cultured under aerobic conditions
Arcobacter butzleri	Fever, diarrhea, abdominal pain, nausea	Bacteremia, appendicitis	Cultured under aerobic conditions; enzootic in nonhuman primates
Campylobacter sputorum	Pulmonary, perianal, groin, and axillary abscesses; diarrhea	Bacteremia	Three clinically relevant biovars: *sputorum*, *faecalis*, and *paraureolyticus*

[a]In immunocompromised hosts, especially HIV-infected persons. [b]In children.

Source: Adapted from BM Allos, MJ Blaser: Clin Infect Dis 20:1092, 1995.

However, apparently healthy nonpregnant persons occasionally develop transient *Campylobacter* bacteremia as part of a gastrointestinal illness (0.1–1% of cases).

In contrast, in many developing countries, *C. jejuni* infections are hyperendemic, with the highest rates among children <2 years old. According to large prospective cohort studies in low- to middle-income countries, *Campylobacter* infections—even when asymptomatic—are associated with growth shortfalls (stunting). Rates of clinically apparent infection fall with age, as does the illness-to-infection ratio.

PATHOLOGY AND PATHOGENESIS

C. jejuni infections may be subclinical, especially in hosts in developing countries who have had multiple prior infections and may be partially immune. Symptomatic infections mostly occur within 2–4 days (range, 1–7 days) of exposure to the organism. The sites of tissue injury include the jejunum, ileum, and colon. Biopsies show an acute nonspecific inflammatory reaction, with neutrophils, monocytes, and eosinophils in the lamina propria, as well as damage to the epithelium, including loss of mucus, glandular degeneration, and crypt abscesses. Biopsy findings may be consistent with Crohn's disease or ulcerative colitis, but these "idiopathic" chronic inflammatory diseases should not be diagnosed unless infectious colitis, *specifically including* that due to infection with *Campylobacter* species and related organisms, has been ruled out.

The components of protective immunity to *Campylobacter* in humans are poorly understood. The high frequency of *C. jejuni* infections and their severity and recurrence among hypogammaglobulinemic patients suggest that antibodies are important in protective immunity. Experience from field studies and human experimental infection models suggests that immune protection may be short-lived or incomplete in the absence of continuous exposure. Knowledge of the pathogenesis of infection is also incomplete. Both the motility of the strain and its capacity to adhere to host tissues appear to favor disease, but classic enterotoxins and cytotoxins (including cytolethal distending toxin) appear not to play substantial roles in tissue injury or disease production. The organisms have been visualized within the epithelium, albeit in low numbers. The documentation of a significant tissue response and occasionally of *C. jejuni* bacteremia further suggests that tissue invasion is clinically significant, and in vitro studies are consistent with this pathogenic feature.

The pathogenesis of *C. fetus* infections is better defined. Virtually all clinical isolates of *C. fetus* possess a proteinaceous capsule-like structure (an S-layer) that renders the organisms resistant to complement-mediated killing and opsonization. As a result, *C. fetus* can cause bacteremia and can seed sites beyond the intestinal tract. The ability of the organism to switch the S-layer proteins expressed—a phenomenon that results in antigenic variability—may contribute to the chronicity and high rate of recurrence of *C. fetus* infections in compromised hosts.

CLINICAL MANIFESTATIONS

The clinical features of infections due to *Campylobacter* and the related *Arcobacter* and intestinal *Helicobacter* species causing enteric disease appear to be highly similar. *C. jejuni* can be considered the prototype, in part because it is by far the most common enteric pathogen in the group. A prodrome of fever, headache, myalgia, and/or malaise often occurs 12–48 h before the onset of diarrheal symptoms. The most common signs and symptoms of the intestinal phase are diarrhea, abdominal pain, and fever. The degree of diarrhea varies from several loose watery stools to visibly bloody stools (~10% of cases in adults); most patients presenting for medical attention have ≥10 bowel movements on the worst day of illness. Abdominal pain usually consists of cramping and may be the most prominent symptom. Pain is usually generalized but may become localized; *C. jejuni* infection may cause pseudoappendicitis. Fever may be the only initial manifestation of *C. jejuni* infection, a situation mimicking the early stages of typhoid fever. Febrile young children may develop convulsions. *Campylobacter* enteritis is generally self-limited; however, symptoms persist for >1 week in 10–20% of patients seeking medical attention, and clinical relapses occur in 5–10% of untreated patients. Studies of common-source epidemics indicate that milder illnesses or asymptomatic infections may commonly occur.

C. fetus may cause a diarrheal illness similar to that due to *C. jejuni*, especially in immunocompetent hosts. This organism also may cause either intermittent diarrhea or nonspecific abdominal pain without localizing signs. Sequelae are uncommon, and the outcome is benign. *C. fetus* may also cause a prolonged relapsing systemic illness (with fever, chills, and myalgias) that has no obvious primary source; this manifestation is especially common among compromised hosts. Secondary seeding of an organ (e.g., meninges, brain, bone, urinary tract, or soft tissue) complicates the course, which may be fulminant. *C. fetus* infections have a tropism for vascular sites: endocarditis, mycotic aneurysm, and septic thrombophlebitis may all occur. Infection during pregnancy often leads to fetal death. A variety of *Campylobacter* species and *H. cinaedi* can cause recurrent cellulitis with fever and bacteremia in immunocompromised hosts.

COMPLICATIONS

Except in infection with *C. fetus*, bacteremia is uncommon, developing most often in immunocompromised hosts and at the extremes of age. Three patterns of extraintestinal infection have been noted: (1) transient bacteremia in a normal host with enteritis (benign course, no specific treatment needed); (2) sustained bacteremia or focal infection in a normal host (bacteremia originating from enteritis, with patients responding well to antimicrobial therapy); and (3) sustained bacteremia or focal infection in a compromised host. Enteritis may not be clinically apparent. Antimicrobial therapy, possibly prolonged, is necessary for suppression or cure of the infection.

Campylobacter, Arcobacter, and intestinal *Helicobacter* infections in patients with AIDS or hypogammaglobulinemia may be severe, persistent, and extraintestinal; relapse after cessation of therapy is common. Hypogammaglobulinemic patients also may develop osteomyelitis and an erysipelas-like rash or cellulitis.

Local suppurative complications of infection include cholecystitis, pancreatitis, and cystitis; distant complications include meningitis, endocarditis, arthritis, peritonitis, cellulitis, and septic abortion. All these complications are rare, except in immunocompromised hosts. Hepatitis, interstitial nephritis, and the hemolytic-uremic syndrome occasionally complicate acute infection. The two most common postinfectious sequelae are reactive arthritis and the Guillain-Barré syndrome. Reactive arthritis has been reported in up to 2.5% of cases, although nonspecific rheumatologic symptoms are more common (~10%). Reactive arthritis may develop several weeks after infection, especially in persons with the HLA-B27 phenotype. The knees are most frequently involved, but involvement of the ankles, wrists, and small joints of the hands is common, with an average of 3.2 joints affected. Guillain-Barré syndrome or its Miller Fisher (cranial polyneuropathy) variant follows symptomatic or asymptomatic *Campylobacter* infections uncommonly—i.e., in 1 of every 1000–2000 cases or, for certain *C. jejuni* serotypes (such as O19), in 1 of every 100–200 cases. Despite the low frequency of this complication, it is estimated that *Campylobacter* infections, because of their high incidence, may trigger 20–40% of all cases of Guillain-Barré syndrome. The presence of sialylated lipopolysaccharides on *C. jejuni* strains prompts a form of molecular mimicry that promotes autoimmune recognition of sialylated cell-surface molecules on axons. Immunoproliferative small-intestinal disease (*alpha chain disease*), a form of lymphoma that originates in small-intestinal mucosa-associated lymphoid tissue, has been associated with *C. jejuni*; antimicrobial therapy has led to marked clinical improvement.

DIAGNOSIS

In patients with *Campylobacter* enteritis, peripheral leukocyte counts reflect the severity of the inflammatory process. In addition, stools from nearly all *Campylobacter*-infected patients presenting for medical attention in the United States contain leukocytes or erythrocytes. Gram- or Wright-stained fecal smears should be examined in all suspected cases. When the diagnosis of *Campylobacter* enteritis is suspected on the basis of findings indicating inflammatory diarrhea (fever, fecal leukocytes), clinicians can ask the microbiology laboratory to attempt

the visualization of organisms with characteristic vibrioid morphology by direct microscopic examination of stools with Gram's staining or to use phase-contrast or dark-field microscopy to identify the organisms' characteristic "darting" motility. Confirmation of the diagnosis of *Campylobacter* infection is based on identification of an isolate from cultures of stool, blood, or another site. *Campylobacter*-specific media should be used to culture stools from all patients with inflammatory or bloody diarrhea. Because all *Campylobacter* species are fastidious, they will not be isolated unless selective media or other selective techniques are used. Failure to isolate campylobacters from stool by culture does not entirely rule out their presence. Although culture remains the diagnostic gold standard, species-specific real-time polymerase chain reaction (PCR) techniques appear more sensitive than culture; although PCR techniques may detect nonviable bacteria, they are now used frequently to diagnose infection with *Campylobacter* and other enteric bacteria in clinical microbiology laboratories. The detection of the organisms in stool in the United States almost always implies active or recent infection. In contrast, *Campylobacter sputorum* and related organisms found in the oral cavity are commensals that only rarely have pathogenic significance. Because of the low levels of metabolic activity of *Campylobacter* species in standard blood culture media, *Campylobacter* bacteremia is difficult to detect.

DIFFERENTIAL DIAGNOSIS

The symptoms of *Campylobacter* enteritis are not sufficiently unusual to distinguish this illness from that due to *Salmonella, Shigella, Yersinia*, and other pathogens. The combination of fever and fecal leukocytes or erythrocytes is indicative of inflammatory diarrhea, and definitive diagnosis is based on culture, real-time PCR, or demonstration of the characteristic organisms on stained fecal smears. Similarly, extraintestinal *Campylobacter* illness is diagnosed by culture. Infection due to *Campylobacter* should be suspected in the setting of septic abortion, and that due to *C. fetus* should be suspected specifically in the setting of septic thrombophlebitis. It is important to reiterate that (1) the presentation of *Campylobacter* enteritis may mimic that of ulcerative colitis or Crohn's disease, (2) *Campylobacter* enteritis is much more common than either of the latter (especially among young adults), and (3) biopsy may not distinguish among these entities. Thus, a diagnosis of inflammatory bowel disease should not be made until *Campylobacter* infection has been ruled out, especially in persons with a history of foreign travel, significant animal contact, immunodeficiency, or exposure incurring a high risk of transmission.

TREATMENT

Campylobacter Infection

Fluid and electrolyte replacement is central to the treatment of diarrheal illnesses **(Chap. 128)**. Even among patients presenting for medical attention with *Campylobacter* enteritis, not all clearly benefit from specific antimicrobial therapy. Indications for therapy include high fever, bloody diarrhea, severe diarrhea, persistence for >1 week, and worsening of symptoms. A 3-day course of azithromycin (500 mg once daily) is the regimen of choice. A 1-day regimen of azithromycin (1000 mg given as two 500-mg tablets) can also be used. Alternative regimens for adults consist of fluoroquinolones—ciprofloxacin (500 mg by mouth twice daily for 3 days) or levofloxacin (750 mg daily for 3 days)—but resistance to this class of agents as well as to tetracyclines is substantial; ~27% of U.S. human isolates of *Campylobacter* in 2014 were resistant to ciprofloxacin. Because macrolide resistance usually is much less common (<10%), these drugs are the empirical agents of choice. Patients infected with antibiotic-resistant strains are at increased risk of adverse outcomes. Use of antimotility agents, which may prolong the duration of symptoms and have been associated with toxic megacolon and with death, is not recommended. Of note, *C. jejuni* and *C. coli* are resistant to trimethoprim and β-lactam antibiotics, including penicillin and most cephalosporins.

For patients with immunocompromising conditions and uncomplicated enteritis caused by *C. jejuni*, therapy duration should be extended to 7–14 days. For systemic infections, treatment with a carbapenem (imipenem, 500 mg IV every 6 h; or meropenem, 1–2 g IV every 8 h) should be started empirically, and susceptibility testing should always be performed. For life-threatening illness, gentamicin (1.0–1.7 mg/kg IV every 8 h after a loading dose of 1.5–2 mg/kg) can be added. In the absence of endovascular involvement, therapy for systemic infections should be administered for 7–14 days. For immunocompromised patients with systemic infections due to *C. fetus* and for patients with endovascular infections due to any species, prolonged therapy (up to 4 weeks) is usually necessary. For recurrent infections in immunocompromised hosts, lifelong therapy/prophylaxis is sometimes necessary.

PROGNOSIS

Nearly all patients recover fully from *Campylobacter* enteritis, either spontaneously or after antimicrobial therapy. Volume depletion probably contributes to the few deaths that are reported. As stated above, occasional patients develop reactive arthritis or Guillain-Barré syndrome or its variants. Systemic infection with *C. fetus* is much more often fatal than that due to related species; this higher mortality rate reflects in part the population affected. Prognosis depends on the rapidity with which appropriate therapy is begun. Otherwise healthy hosts usually survive *C. fetus* infections without sequelae. Compromised hosts often have recurrent and/or life-threatening infections due to a variety of *Campylobacter* species.

FURTHER READING

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163 Cholera and Other Vibrioses

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Members of the genus *Vibrio* cause a number of important infectious syndromes. Classic among them is cholera, a devastating diarrheal disease caused by *Vibrio cholerae* that has been responsible for seven global pandemics and much suffering over the past two centuries. Epidemic cholera remains a significant public-health concern in the developing world today. Other vibrioses caused by other *Vibrio* species include syndromes of diarrhea, soft tissue infection, or primary sepsis. All *Vibrio* species are highly motile, facultatively anaerobic, curved gram-negative rods with one or more flagella. In nature, vibrios most commonly reside in tidal rivers and bays under conditions of moderate salinity. They proliferate in the summer months when water temperatures exceed 20°C. As might be expected, the illnesses they cause also increase in frequency during the warm months.

CHOLERA

DEFINITION

Cholera is an acute diarrheal disease that can, in a matter of hours, result in profound, rapidly progressive dehydration and death. Accordingly, *cholera gravis* (the severe form) is a much-feared disease, particularly in its epidemic presentation. Fortunately, prompt aggressive fluid repletion and supportive care can obviate the high mortality that is historically associated with cholera. Although the term *cholera* has occasionally been applied to any severely dehydrating secretory diarrheal illness, whether infectious in etiology or not, it now refers to disease caused by *V. cholerae* serogroup O1 or O139—i.e., the serogroups with epidemic potential.

MICROBIOLOGY AND EPIDEMIOLOGY

The species *V. cholerae* is classified into >200 serogroups based on the carbohydrate determinants of their lipopolysaccharide (LPS) O antigens. Although some non-O1 *V. cholerae* serogroups (strains that do not agglutinate in antisera to the O1 group antigen) have occasionally caused sporadic outbreaks of diarrhea, serogroup O1 was, until the emergence of serogroup O139 in 1992 (see below), the exclusive cause of epidemic cholera. Two biotypes of *V. cholerae* O1, classical and El Tor, are distinguished. Each biotype is further subdivided into two serotypes, termed *Inaba* and *Ogawa*.

The natural habitat of *V. cholerae* is coastal salt water and brackish estuaries, where the organism lives in close relation to plankton. *V. cholerae* can also exist in freshwater in the presence of adequate nutrients and warmth. Humans become infected incidentally but, once infected, can act as vehicles for spread. Ingestion of water contaminated by human feces is the most common means of acquisition of *V. cholerae*. Consumption of contaminated food also can contribute to spread. There is no known animal reservoir. Although the infectious dose is relatively high, it is markedly reduced in hypochlorhydric persons, in those using antacids, and when gastric acidity is buffered by a meal. Cholera is predominantly a pediatric disease in endemic areas, but it affects adults and children equally when newly introduced into a population. In endemic areas, the burden of disease is often greatest during "cholera seasons" associated with high temperatures, heavy rainfall, and flooding, but cholera can occur year-round. For unexplained reasons, susceptibility to cholera is significantly influenced by ABO blood group status; persons with type O blood are at greatest risk of severe disease if infected, whereas those with type AB are at least risk.

Cholera is native to the Ganges delta on the Indian subcontinent. Since 1817, seven global pandemics have occurred. The current (seventh) pandemic—the first due to the El Tor biotype—began in Indonesia in 1961 and spread in serial waves throughout Asia as *V. cholerae* El Tor displaced the endemic classical biotype, which is thought to have caused the previous six pandemics. In the early 1970s, El Tor cholera erupted in Africa, causing major epidemics before becoming a persistent endemic problem. Currently, >40% of cholera cases reported annually to the World Health Organization (WHO) are from Africa, >35% are from Asia, and >20% are from the Americas **(Fig. 163-1)**, but the true burden and distribution of cholera are unknown because the diagnosis is often syndromic and because many countries with endemic cholera do not report cholera to the WHO. It is possible that >2–3 million cases of cholera occur yearly (of which only ~200,000 are reported to the WHO) and that these cases result in >50,000–100,000 deaths annually (of which <2000 are reported to the WHO).

After a century without cholera in Latin America, the current cholera pandemic reached Central and South America in 1991. Following an initial explosive spread that affected millions, the burden of disease has markedly decreased in Latin America. In 2010, a severe cholera outbreak began in Haiti, a country with no recorded history of this disease. Several lines of evidence indicate that cholera was likely introduced into Haiti by United Nations security forces from Asia, raising the possibility that asymptomatic carriers of *V. cholerae* play an important role in transmitting cholera over long distances. To date, the outbreak has involved >800,000 individuals, resulting in thousands of deaths. The recent history of cholera has been punctuated by such severe outbreaks, especially among impoverished or displaced persons. These outbreaks are often precipitated by war or other circumstances that lead to the breakdown of public health measures. Such was the case in the camps for Rwandan refugees set up in 1994 around Goma, Zaire; in 2008–2009 in Zimbabwe; in 2015 in South Sudan and the Democratic Republic of the Congo; and in 2017 in Yemen.

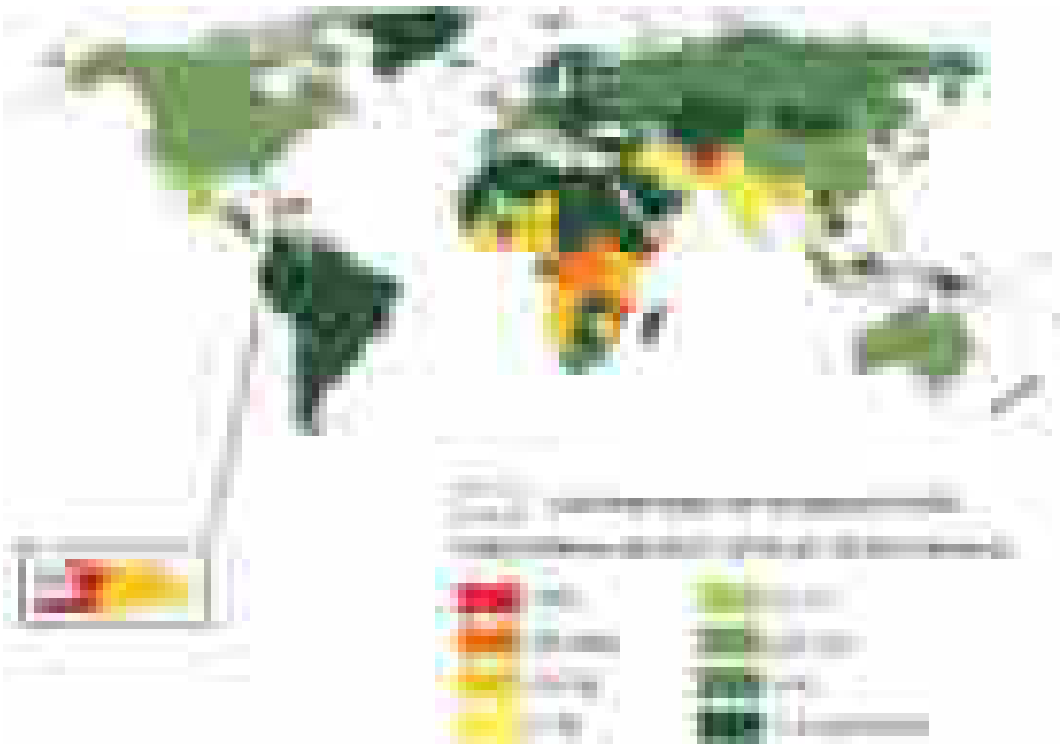

FIGURE 163-1 World distribution of cholera in 2013–2015. WHO, World Health Organization. *(Courtesy of Drs. M. and R. Piarroux, Université de la Méditerranée, France, with permission; map generated with Philcarto [http://philcarto.free.fr].)*

Sporadic endemic infections due to *V. cholerae* O1 strains related to the seventh-pandemic strain have been recognized along the U.S. Gulf Coast of Louisiana and Texas. These infections are typically associated with the consumption of contaminated, locally harvested shellfish. Occasionally, cases in U.S. locations remote from the Gulf Coast have been linked to shipped-in Gulf Coast seafood.

In October 1992, a large-scale outbreak of clinical cholera caused by a new serogroup, O139, occurred in southeastern India. The organism appears to be a derivative of El Tor O1 but has a distinct LPS and an immunologically related O-antigen polysaccharide capsule. (O1 organisms are not encapsulated.) After an initial spread across 11 Asian countries, *V. cholerae* O139 has once again been almost entirely replaced by O1 strains. The clinical manifestations of disease caused by *V. cholerae* O139 are indistinguishable from those of O1 cholera. Immunity to one, however, is not protective against the other.

PATHOGENESIS

In the final analysis, cholera is a toxin-mediated disease. The watery diarrhea characteristic of cholera is due to the action of cholera toxin, a potent protein enterotoxin elaborated by the organism in the small intestine. The toxin-coregulated pilus (TCP), so named because its synthesis is regulated in parallel with that of cholera toxin, is essential for *V. cholerae* to survive and multiply in (colonize) the small intestine. Cholera toxin, TCP, and several other virulence factors are coordinately regulated by ToxR. This protein modulates the expression of genes coding for virulence factors in response to environmental signals via a cascade of regulatory proteins. Additional regulatory processes, including bacterial responses to the density of the bacterial population (in a phenomenon known as *quorum sensing*), modulate the virulence of *V. cholerae*.

Once established in the human small bowel, the organism produces cholera toxin, which consists of a monomeric enzymatic moiety (the A subunit) and a pentameric binding moiety (the B subunit). The B pentamer binds to GM_1 ganglioside, a glycolipid on the surface of epithelial cells that serves as the toxin receptor and makes possible the delivery of the A subunit to its cytosolic target. The activated A subunit (A_1) irreversibly transfers ADP-ribose from nicotinamide adenine dinucleotide to its specific target protein, the GTP-binding regulatory component of adenylate cyclase. The ADP-ribosylated G protein upregulates the activity of adenylate cyclase; the result is the intracellular accumulation of high levels of cyclic adenosine monophosphate (AMP). In intestinal epithelial cells, cyclic AMP inhibits the absorptive sodium-transport system in villus cells and activates the secretory chloride-transport system in crypt cells, and these events lead to the accumulation of sodium chloride in the intestinal lumen. Because water moves passively to maintain osmolality, isotonic fluid accumulates in the lumen. When the volume of that fluid exceeds the capacity of the rest of the gut to resorb it, watery diarrhea results. Unless the wasted fluid and electrolytes are adequately replaced, shock (due to profound dehydration) and acidosis (due to loss of bicarbonate) follow. Although perturbation of the adenylate cyclase pathway is the primary mechanism by which cholera toxin causes excess fluid secretion, cholera toxin also enhances intestinal secretion via prostaglandins and/or neural histamine receptors.

The *V. cholerae* genome comprises two circular chromosomes. Lateral gene transfer has played a key role in the evolution of epidemic *V. cholerae*. The genes encoding cholera toxin (*ctxAB*) are part of the genome of a bacteriophage, CTXΦ. The receptor for this phage on the *V. cholerae* surface is the intestinal colonization factor TCP. Because *ctxAB* is part of a mobile genetic element (CTXΦ), horizontal transfer of this bacteriophage may account for the emergence of new toxigenic *V. cholerae* serogroups. Many of the other genes important for *V. cholerae* pathogenicity, including the genes encoding the biosynthesis of TCP, those encoding accessory colonization factors, and those regulating virulence gene expression, are clustered together in the *V. cholerae* pathogenicity island. Similar clustering of virulence genes is found in other bacterial pathogens. It is believed that pathogenicity islands are acquired by horizontal gene transfer. *V. cholerae* O139 is probably derived from an El Tor O1 strain that acquired the genes for O139 O-antigen synthesis by horizontal gene transfer.

CLINICAL MANIFESTATIONS

Individuals infected with *V. cholerae* O1 or O139 exhibit a range of clinical manifestations. Some individuals are asymptomatic or have only mild diarrhea; others present with the sudden onset of explosive and life-threatening diarrhea (*cholera gravis*). The reasons for the range in signs and symptoms of disease are incompletely understood but include the level of preexisting immunity, blood type, and nutritional status. In a nonimmune individual, after a 24- to 48-h incubation period, cholera characteristically begins with the sudden onset of painless watery diarrhea that may quickly become voluminous. Patients often vomit. In severe cases, volume loss can exceed 250 mL/kg in the first 24 h. If fluids and electrolytes are not replaced, hypovolemic shock and death may ensue. Fever is usually absent. Muscle cramps due to electrolyte disturbances are common. The stool has a characteristic appearance: a nonbilious, gray, slightly cloudy fluid with flecks of mucus, no blood, and a somewhat fishy, inoffensive odor. It has been called "rice-water" stool because of its resemblance to the water in which rice has been washed **(Fig. 163-2)**. Clinical symptoms parallel volume contraction: at losses of <5% of normal body weight, thirst develops; at 5–10%, postural hypotension, weakness, tachycardia, and decreased skin turgor are documented; and at >10%, oliguria, weak or absent pulses, sunken eyes (and, in infants, sunken fontanelles), wrinkled ("washerwoman") skin, somnolence, and coma are characteristic. Complications derive exclusively from the effects of volume and electrolyte depletion and include renal failure due to acute tubular necrosis. Thus, if the patient is adequately treated with fluid and electrolytes, complications are averted and the process is self-limited, resolving in a few days.

Laboratory data usually reveal an elevated hematocrit (due to hemoconcentration) in nonanemic patients; mild neutrophilic leukocytosis; elevated levels of blood urea nitrogen and creatinine consistent with prerenal azotemia; normal sodium, potassium, and chloride levels; a markedly reduced bicarbonate level (<15 mmol/L); and an elevated anion gap (due to increases in serum lactate, protein, and phosphate). Arterial pH is usually low (~7.2).

DIAGNOSIS

Cholera should be suspected when a patient ≥5 years of age develops acute watery diarrhea in an area known to have cholera or develops severe dehydration or dies from acute watery diarrhea, even in an area where cholera is not known to be present. The clinical suspicion

FIGURE 163-2 Rice-water cholera stool. Note floating mucus and gray watery appearance. *(Courtesy of Dr. A. S. G. Faruque, International Centre for Diarrhoeal Disease Research, Dhaka; with permission.)*

of cholera can be confirmed by the identification of *V. cholerae* in stool; however, the organism must be specifically sought. With experience, it can be detected directly by dark-field microscopy on a wet mount of fresh stool, and its serotype can be discerned by immobilization with specific antiserum. Laboratory isolation of the organism requires the use of a selective medium such as taurocholate–tellurite–gelatin (TTG) agar or thiosulfate–citrate–bile salts–sucrose (TCBS) agar. If a delay in sample processing is expected, Carey-Blair transport medium and/or alkaline-peptone water-enrichment medium may be used as well. In endemic areas, there is little need for biochemical confirmation and characterization, although these tasks may be worthwhile in places where *V. cholerae* is an uncommon isolate. Standard microbiologic biochemical testing for Enterobacteriaceae will suffice for identification of *V. cholerae*. All vibrios are oxidase-positive. A point-of-care antigen-detection cholera dipstick assay is now commercially available for use in the field or where laboratory facilities are lacking.

TREATMENT

Cholera

Death from cholera is due to hypovolemic shock; thus treatment of individuals with cholera first and foremost requires fluid resuscitation and management. In light of the level of dehydration **(Table 163-1)** and the patient's age and weight, euvolemia should first be rapidly restored, and adequate hydration should then be maintained to replace ongoing fluid losses **(Table 163-2)**. Administration of oral rehydration solution (ORS) takes advantage of the hexose-Na^+ co-transport mechanism to move Na^+ across the gut mucosa together with an actively transported molecule such as glucose (or galactose). Cl^- and water follow. This transport mechanism remains intact even when cholera toxin is active. ORS may be made by adding safe water to prepackaged sachets containing salts and sugar or by adding 0.5 teaspoon (i.e., a small spoonful) of table salt and 6 level teaspoons (i.e., 6 small spoonfuls) of table sugar to 1 L of safe water. Potassium intake in bananas or green coconut water should be encouraged. A number of ORS formulations are available, and the WHO now recommends "low-osmolarity" ORS for treatment of individuals with dehydrating diarrhea of any cause **(Table 163-3)**. If available, rice-based ORS is considered superior to standard ORS in the treatment of cholera. ORS can be administered via a nasogastric tube to individuals who cannot ingest fluid; however, optimal management of individuals with severe dehydration includes the administration of IV fluid and electrolytes. Because profound acidosis (pH <7.2) is common in this group, Ringer's lactate is the best choice among commercial products **(Table 163-4)**; it must be used with additional potassium supplements, preferably given by mouth. The total fluid deficit in severely dehydrated patients (>10% of body weight) can be replaced safely within the first 3–4 h of therapy, half within the first hour. Transient muscle cramps and tetany are common. Thereafter, oral therapy can usually be initiated, with the goal of maintaining fluid intake equal to fluid output. However, patients with continued large-volume diarrhea may require prolonged IV treatment to match gastrointestinal fluid losses. Severe hypokalemia can develop but will respond to potassium given either IV or orally. In the absence of adequate staff to monitor the patient's progress, the oral route of rehydration and potassium replacement is safer than the IV route.

Although not necessary for cure, the use of an antibiotic to which the organism is susceptible diminishes the duration and volume of fluid loss and hastens clearance of the organism from the stool. Adjunctive antibiotics should therefore be administered to patients with moderate or severe dehydration due to cholera. In many areas, macrolides such as erythromycin (adults, 250 mg orally four times a day for 3 days; children, 12.5 mg/kg per dose four times a day for 3 days) or azithromycin (adults, a single 1-g dose; children, a single 20-mg/kg dose) are the agents of choice. Increasing resistance to tetracyclines is widespread; however, in areas with confirmed susceptibility, tetracycline (nonpregnant adults, 500 mg orally four times a day for 3 days; children >8 years old, 12.5 mg/kg per dose four times a day for 3 days) or doxycycline (nonpregnant adults, a 300-mg single dose; children >8 years old, a single dose of 4–6 mg/kg) may be used. Similarly, increasing resistance to fluoroquinolones is being reported, but in areas with confirmed susceptibility, a fluoroquinolone such as ciprofloxacin may be used (adults,

TABLE 163-1 Assessing the Degree of Dehydration in Patients with Cholera

DEGREE OF DEHYDRATION	CLINICAL FINDINGS
None or mild, but diarrhea	Thirst in some cases; <5% loss of total body weight
Moderate	Thirst, postural hypotension, weakness, tachycardia, decreased skin turgor, dry mouth/tongue, no tears; 5–10% loss of total body weight
Severe	Unconsciousness, lethargy, or "floppiness"; weak or absent pulse; inability to drink; sunken eyes (and, in infants, sunken fontanelles); >10% loss of total body weight

TABLE 163-2 Treatment of Cholera, Based on Degree of Dehydration[a]

DEGREE OF DEHYDRATION, PATIENT'S AGE (WEIGHT)	TREATMENT[b]
None or Mild, but Diarrhea[c]	
<2 years	1/4–1/2 cup (50–100 mL) of ORS, to a maximum of 0.5 L/d
2–9 years	1/2–1 cup (100–200 mL) of ORS, to a maximum of 1 L/d
≥10 years	As much ORS as desired, to a maximum of 2 L/d
Moderate[c,d]	
<4 months (<5 kg)	200–400 mL of ORS
4–11 months (5–<8 kg)	400–600 mL of ORS
12–23 months (8–<11 kg)	600–800 mL of ORS
2–4 years (11–<16 kg)	800–1200 mL of ORS
5–14 years (16–<30 kg)	1200–2200 mL of ORS
≥15 years (≥30 kg)	2200–4000 mL of ORS
Severe[c]	
All ages and weights	Undertake IV fluid replacement with Ringer's lactate (or, if not available, normal saline). Give 100 mL/kg in the first 3-h period (or the first 6-h period for children <12 months old); start rapidly, then slow down. Give a total of 200 mL/kg in the first 24 h. Continue until the patient is awake, can ingest ORS, and no longer has a weak pulse.

[a]Adapted from World Health Organization: First steps for managing an outbreak of acute diarrhoea. Global Task Force on Cholera Control, 2009 (updated 2010; *http://www.who.int/cholera/publications/firststeps/en/*). [b]Continue normal feeding during treatment. [c]Reassess regularly; monitor stool and vomit output. [d]Volumes of ORS listed should be given within the first 4 h.

Abbreviation: ORS, oral rehydration solution.

TABLE 163-3 Composition of World Health Organization Reduced-Osmolarity Oral Rehydration Solution (ORS)[a,b]

CONSTITUENT	CONCENTRATION, mmol/L
Na^+	75
K^+	20
Cl^-	65
Citrate[c]	10
Glucose	75
Total osmolarity	245

[a]Contains (per package, to be added to 1 L of drinking water): NaCl, 2.6 g; $Na_3C_6H_5O_7 \cdot 2H_2O$, 2.9 g; KCl, 1.5 g; and glucose (anhydrous), 13.5 g. [b]If prepackaged ORS is unavailable, a simple homemade alternative can be prepared by combining 3.5 g (~1/2 teaspoon) of NaCl with either 50 g of precooked rice cereal or 6 teaspoons of table sugar (sucrose) in 1 L of drinking water. In that case, potassium must be supplied separately (e.g., in orange juice or coconut water). [c]10 mmol of citrate per liter, which supplies 30 mmol of HCO_3/L.

TABLE 163-4 Electrolyte Composition of Cholera Stool and of Intravenous Rehydration Solution

SUBSTANCE	CONCENTRATION, mmol/L			
	NA^+	K^+	CL^-	BASE
Stool				
Adult	135	15	100	45
Child	100	25	90	30
Ringer's lactate	130	4[a]	109	28

[a]Potassium supplements, preferably administered by mouth, are required to replace the usual potassium losses from stool.

500 mg twice a day for 3 days; children, 15 mg/kg twice a day for 3 days). Oral administration of supplemental zinc is associated with decreased volume and severity of diarrhea in young children, including in those with cholera. Children <6 months of age with cholera should be treated with 10 mg of zinc daily for 10 days; children from 6 to <60 months of age should be treated with 20 mg of oral zinc daily for 10 days.

PREVENTION

Provision of safe water and of facilities for sanitary disposal of feces, improved nutrition, and attention to food preparation and storage in the household can significantly reduce the incidence of cholera. In addition, precautions should be taken to prevent the spread of cholera via infected and potentially asymptomatic persons from endemic to nonendemic regions of the world (as was probably the case in the ongoing outbreak in Haiti; see "Microbiology and Epidemiology," above).

Much effort has been devoted to the development of an effective cholera vaccine over the past few decades, with a particular focus on oral vaccine strains. In an attempt to maximize mucosal responses, two types of oral cholera vaccine have been developed: oral killed vaccines and live attenuated vaccines. Currently, three oral killed cholera vaccines have been prequalified by the WHO and are available internationally. BivWC (Shanchol™; Shantha Biotechnics, Hyderabad, India) contains several biotypes and serotypes of *V. cholerae* O1 and *V. cholerae* O139 without supplemental cholera toxin B subunit. A related vaccine is produced in South Korea (Euvichol™; Eubiologics, Seoul). WC-rBS (Dukoral®; Valneva, Lyon, France) contains several biotypes and serotypes of *V. cholerae* O1 supplemented with 1 mg of recombinant cholera toxin B subunit per dose. The vaccines are administered as a two- or three-dose regimen, with doses usually separated by 14 days. They provide ~60–85% protection for the first few months. Booster immunizations of WC-rBS are recommended after 2 years for individuals ≥6 years of age and after 6 months for children 2–5 years of age. For BivWC, which was developed more recently, no formal recommendation regarding booster immunizations exists. However, BivWC was associated with ~60% protection over 5 years among recipients of all ages in a study in Kolkata, India; the rate of protection among children ≤5 years of age approximated 40%. Models predict significant herd immunity when vaccination coverage rates exceed 50%. The killed vaccines have been safely administered among populations with high rates of HIV infection.

Oral live attenuated vaccines for *V. cholerae* O1 are also in development. These strains have in common their lack of the genes encoding cholera toxin. One such vaccine, CVD 103-HgR (Vaxchora™; PaxVax, Redwood City, CA), was approved in 2016 by the U.S. Food and Drug Administration for use in travelers to cholera-endemic regions. The vaccine was 90 and 80% efficacious against severe cholera after experimental infection of North American volunteers 10 days and 90 days after vaccination, respectively. Vaxchora is approved for use in adults 18–64 years of age; no recommendations concerning the timing or need for booster vaccinations are currently available. Other live attenuated vaccine candidate strains have been prepared from El Tor and O139 *V. cholerae* and have been tested in studies of volunteers. An advantage of live attenuated cholera vaccines is that they may induce protection after a single oral dose; evaluation of single-dose regimens of oral killed cholera vaccines is underway. Conjugate and subunit cholera vaccines are also being developed. Recognizing that it may be decades before safe water and adequate sanitation become a reality for those most at risk of cholera, the WHO has recommended incorporation of cholera vaccination into comprehensive control strategies and has established an international stockpile of oral killed cholera vaccine to assist in outbreak responses. One million doses of oral killed cholera vaccine were released from this stockpile for use in Haiti following Hurricane Matthew in 2016. Since its inception in 2017, more than 5 million doses of oral cholera vaccine have been released from the global stockpile.

OTHER *VIBRIO* SPECIES

The genus *Vibrio* includes several human pathogens that do not cause cholera. Abundant in coastal waters throughout the world, noncholera vibrios can reach high concentrations in the tissues of filter-feeding mollusks. As a result, human infection commonly follows the ingestion of seawater or of raw or undercooked shellfish **(Table 163-5)**. Most noncholera vibrios can be cultured on blood or MacConkey agar, which contains enough salt to support the growth of these halophilic species. In the microbiology laboratory, the species of noncholera vibrios are distinguished by standard biochemical tests. The most important of these organisms are *Vibrio parahaemolyticus* and *Vibrio vulnificus*.

The two major types of syndromes for which these noncholera vibrios are responsible are gastrointestinal illness (due to *V. parahaemolyticus*, non-O1/O139 *V. cholerae*, *Vibrio mimicus*, *Vibrio fluvialis*, *Vibrio hollisae*, and *Vibrio furnissii*) and soft tissue infections (due to *V. vulnificus*, *Vibrio alginolyticus*, and *Vibrio damselae*). *V. vulnificus* is also a cause of primary sepsis in some compromised individuals.

SPECIES ASSOCIATED PRIMARILY WITH GASTROINTESTINAL ILLNESS

V. parahaemolyticus Widespread in marine environments, the halophilic *V. parahaemolyticus* is the leading seafood-borne bacterial cause of enteritis worldwide. This species was originally implicated in enteritis in Japan in 1953, accounting for 24% of reported cases in one study—a rate that presumably was due to the common practice of eating raw seafood in that country. In the United States, common-source outbreaks of diarrhea caused by this organism have been linked to the consumption of undercooked or improperly

TABLE 163-5 Features of Selected Noncholera Vibrioses

ORGANISM	VEHICLE OR ACTIVITY	HOST AT RISK	SYNDROME
Vibrio parahaemolyticus	Shellfish, seawater	Normal	Gastroenteritis
	Seawater	Normal	Wound infection
Non-O1/O139 *Vibrio cholerae*	Shellfish, travel	Normal	Gastroenteritis
	Seawater	Normal	Wound infection, otitis media
Vibrio vulnificus	Shellfish	Immunosuppressed[a]	Sepsis, secondary cellulitis
	Seawater	Normal, immunosuppressed[a]	Wound infection, cellulitis
Vibrio alginolyticus	Seawater	Normal	Wound infection, cellulitis, otitis
	Seawater	Burned, other immunosuppressed	Sepsis

[a]Especially with liver disease or hemochromatosis.

Source: Table 161-3 in *Harrison's Principles of Internal Medicine*, 14th edition.

handled seafood or of other foods contaminated by seawater. Since the mid-1990s, the incidence of *V. parahaemolyticus* infections has increased in several countries, including the United States. Serotypes O3:K6, O4:K68, and O1:K-untypable, which are genetically related to one another, account in part for this increase. The enteropathogenicity of *V. parahaemolyticus* is linked to its ability to cause hemolysis on Wagatsuma agar (i.e., the *Kanagawa phenomenon*) via a thermostable direct hemolysin (Vp-TDH). Although the mechanisms by which the organism causes diarrhea are not fully defined, the genome sequence of *V. parahaemolyticus* contains two type III secretion systems, which directly inject toxic bacterial proteins into host cells. The activity of one of these secretion systems is required for intestinal colonization and virulence in animal models. *V. parahaemolyticus* should be considered a possible etiologic agent in all cases of diarrhea that can be linked epidemiologically to seafood consumption or to the sea itself. The incidence of *V. parahaemolyticus* infection in the United States may be increasing, with this species accounting for almost half of all *Vibrio* isolates reported in this country in 2014.

Infections with *V. parahaemolyticus* can result in two distinct gastrointestinal presentations. The more common of the two presentations (including nearly all cases in North America) is characterized by watery diarrhea, usually occurring in conjunction with abdominal cramps, nausea, and vomiting and accompanied in ~25% of cases by fever and chills. After an incubation period of 4 h to 4 days, symptoms develop and persist for a median of 3 days. Dysentery, the less common presentation, is characterized by severe abdominal cramps, nausea, vomiting, and bloody or mucoid stools. *V. parahaemolyticus* also causes rare cases of wound infection and otitis and very rare cases of sepsis.

Most cases of *V. parahaemolyticus*–associated gastrointestinal illness, regardless of the presentation, are self-limited. Fluid replacement should be stressed. The role of antimicrobial agents is uncertain, but they may be of benefit in moderate or severe disease. Doxycycline, fluoroquinolones, macrolides, or third-generation cephalosporins are usually used. Deaths are extremely rare among immunocompetent individuals. Severe infections are associated with underlying diseases, including diabetes, preexisting liver disease, iron-overload states, or immunosuppression.

Non-O1/O139 (Noncholera) *V. cholerae* The heterogeneous non-O1/O139 *V. cholerae* organisms cannot be distinguished from *V. cholerae* O1 or O139 by routine biochemical tests but do not agglutinate in O1 or O139 antiserum. Non-O1/O139 strains have caused several well-studied food-borne outbreaks of gastroenteritis and have also been responsible for sporadic cases of otitis media, wound infection, and bacteremia; non-O1/O139 *V. cholerae* strains do not cause epidemics of cholera. Like other vibrios, non-O1/O139 *V. cholerae* organisms are widely distributed in marine environments. In most instances, recognized cases in the United States have been associated with the consumption of raw oysters or with recent travel. The broad clinical spectrum of diarrheal illness caused by these organisms is probably due to the group's heterogeneous virulence attributes.

In the United States, about half of all non-O1/O139 *V. cholerae* isolates are from stool samples. The typical incubation period for gastroenteritis due to these organisms is <2 days, and the illness lasts for ~2–7 days. Patients' stools may be copious and watery or may be partly formed, less voluminous, and bloody or mucoid. Diarrhea can result in severe dehydration. Many cases include abdominal cramps, nausea, vomiting, and fever. Like those with cholera, patients who are seriously dehydrated should receive oral or IV fluids; the value of antibiotics is not clear.

Extraintestinal infections due to non-O1/O139 *V. cholerae* commonly follow occupational or recreational exposure to seawater. Around 10% of non-O1/O139 *V. cholerae* isolates come from cases of wound infection, 10% from cases of otitis media, and 20% from cases of bacteremia (which is particularly likely to develop in patients with liver disease). Extraintestinal infections should be treated with antibiotics. Information to guide antibiotic selection and dosing is limited, but most strains are sensitive in vitro to tetracycline, ciprofloxacin, and third-generation cephalosporins.

SPECIES ASSOCIATED PRIMARILY WITH SOFT TISSUE INFECTION OR BACTEREMIA

(See also Chap. 124)

V. vulnificus Infection with *V. vulnificus* is rare, but this organism is the most common cause of severe *Vibrio* infections in the United States. Like most vibrios, *V. vulnificus* proliferates in the warm summer months and requires a saline environment for growth. In the United States, infections in humans typically occur in coastal states between May and October and most commonly affect men >40 years of age. *V. vulnificus* has been linked to two distinct syndromes: primary sepsis, which usually occurs in patients with underlying liver disease, and primary wound infection, which generally affects people without underlying disease. (*Vulnificus* is Latin for "wound maker.") Some authors have suggested that *V. vulnificus* also causes gastroenteritis independent of other clinical manifestations. *V. vulnificus* is endowed with a number of virulence attributes, including a capsule that confers resistance to phagocytosis and to the bactericidal activity of human serum as well as a cytolysin. Measured as the 50% lethal dose in mice, the organism's virulence is considerably increased under conditions of iron overload; this observation is consistent with the propensity of *V. vulnificus* to infect patients who have hemochromatosis.

Primary sepsis most often develops in patients who have cirrhosis or hemochromatosis. However, *V. vulnificus* bacteremia can also affect individuals who have hematopoietic disorders or chronic renal insufficiency, those who are using immunosuppressive medications or alcohol, or (in rare instances) those who have no known underlying disease. After a median incubation period of 16 h, the patient develops malaise, chills, fever, and prostration. One-third of patients develop hypotension, which is often apparent at admission. Cutaneous manifestations develop in most cases (usually within 36 h of onset) and characteristically involve the extremities (the lower more often than the upper). In a common sequence, erythematous patches are followed by ecchymoses, vesicles, and bullae. In fact, sepsis and hemorrhagic bullous skin lesions suggest the diagnosis in appropriate settings. Necrosis and sloughing may also be evident. Laboratory studies reveal leukopenia more often than leukocytosis, thrombocytopenia, or elevated levels of fibrin-split products. *V. vulnificus* can be cultured from blood or cutaneous lesions. The mortality rate approaches 50%, with most deaths due to uncontrolled sepsis (Chap. 297). Accordingly, prompt treatment is critical and should include empirical antibiotic administration, aggressive debridement, and general supportive care. *V. vulnificus* is sensitive in vitro to a number of antibiotics, including tetracycline, fluoroquinolones, and third-generation cephalosporins. Data from animal models suggest that either a fluoroquinolone or the combination of a tetracycline and a third-generation cephalosporin should be used in the treatment of *V. vulnificus* septicemia.

V. vulnificus–associated soft tissue infection can complicate either a fresh or an old wound that comes into contact with seawater; the patient may or may not have underlying disease. After a short incubation period (4 h to 4 days; mean, 12 h), the disease begins with swelling, erythema, and (in many cases) intense pain around the wound. These signs and symptoms are followed by cellulitis, which spreads rapidly and is sometimes accompanied by vesicular, bullous, or necrotic lesions. Metastatic events are uncommon. Most patients have fever and leukocytosis. *V. vulnificus* can be cultured from skin lesions and occasionally from the blood. Prompt antibiotic therapy and debridement are usually curative.

V. alginolyticus First identified as a pathogen of humans in 1973, *V. alginolyticus* occasionally causes eye, ear, and wound infections. This species is the most salt-tolerant of the vibrios and can grow in salt concentrations of >10%. Most clinical isolates come from superinfected wounds that presumably become contaminated at the beach. Although its severity varies, *V. alginolyticus* infection tends not to be serious and generally responds well to antibiotic therapy and drainage. A few cases of otitis externa, otitis media, and conjunctivitis due to this pathogen have been described. Tetracycline treatment usually results in cure. *V. alginolyticus* is a rare cause of bacteremia in immunocompromised hosts.

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164 Brucellosis

Nicholas J. Beeching

DEFINITION

Brucellosis is a bacterial zoonosis transmitted directly or indirectly to humans from infected animals, predominantly domesticated ruminants and swine. The disease is known colloquially as *undulant fever* because of its remittent character. Although brucellosis commonly presents as an acute febrile illness, its clinical manifestations vary widely, and definitive signs indicative of the diagnosis may be lacking. Thus the clinical diagnosis usually must be supported by the results of bacteriologic and/or serologic tests.

ETIOLOGIC AGENTS

Human brucellosis is caused by strains of *Brucella*, a bacterial genus that was previously suggested, on genetic grounds, to comprise a single species, *B. melitensis*, with a number of biologic variants exhibiting particular host preferences. This view was challenged on the basis of detailed differences in chromosomal structure and host preference. The traditional classification into nomen species is now favored both because of these differences and because this classification scheme closely reflects the epidemiologic patterns of the infection. The nomen system recognizes *B. melitensis*, which is the most common cause of symptomatic disease in humans and for which the main sources are sheep, goats, and camels; *B. abortus*, which is usually acquired from cattle or buffalo; *B. suis*, which is generally acquired from swine but has one variant enzootic in reindeer and caribou and another in rodents; and *B. canis*, which is acquired most often from dogs. *B. ovis*, which causes reproductive disease in sheep, has not been clearly implicated in human disease, while rare human infections have been reported with *B. neotomae*, which is found in desert rodents. Two relatively new species, *B. ceti* and *B. pinnipedialis*, have been identified in marine mammals, including seals and dolphins. At least one case of laboratory-acquired human disease due to one of these species has been described, and several cases of natural human infection have been reported. As infections in marine mammals appear to be widespread, more cases of zoonotic infection in humans may be identified. Other newly reported species include *B. microti* (isolated from field voles), *B. papionis* (from baboons), *B. vulpis* (from foxes), and *B. inopinata* (from a patient with a breast implant). Additional novel strains have been described in diverse species, including frogs, bats, and various rodents, and the genus likely will expand further in forthcoming years. Moreover, it has become apparent that *Brucella* is closely related to the genus *Ochrobactrum*, which includes environmental bacteria sometimes associated with opportunistic infections. Genomics-based studies are beginning to elucidate the pathway of evolution from free-living soil bacteria to highly successful intracellular pathogens.

All brucellae are small, gram-negative, unencapsulated, nonsporulating rods or coccobacilli. They grow aerobically on peptone-based medium incubated at 37°C; the growth of some types is improved by supplementary CO_2. In vivo, brucellae behave as facultative intracellular parasites. The organisms are sensitive to sunlight, ionizing radiation, and moderate heat; they are killed by boiling and pasteurization but are resistant to freezing and drying. Their resistance to drying renders brucellae stable in aerosol form, facilitating airborne transmission. The organisms can survive for up to 2 months in soft cheeses made from goat's or sheep's milk; for at least 6 weeks in dry soil contaminated with infected urine, vaginal discharge, or placental or fetal tissues; and for at least 6 months in damp soil or liquid manure kept in cool dark conditions. Brucellae are easily killed by a wide range of common disinfectants used under optimal conditions but are likely to be much more resistant at low temperatures or in the presence of heavy organic contamination.

EPIDEMIOLOGY

Brucellosis is a zoonosis whose occurrence and control are closely related to its prevalence in domesticated animals. Its distribution is worldwide apart from the few countries where it has been eradicated from the animal reservoir. The true global prevalence of human brucellosis is unknown because of the imprecision of diagnosis and the inadequacy of reporting and surveillance systems in many countries. Recently, there has been increased recognition of the high incidence of brucellosis in India and parts of China and of importations to countries in Oceania, such as Fiji, and in Asia, such as Thailand and Vietnam. In Europe, the incidence of brucellosis in a country is inversely related to gross domestic product, and, in both developed and less well-resourced settings, human brucellosis is related to rural poverty and inadequate access to medical care. Failure of veterinary control programs due to conflicts or for economic reasons contributes further to the emergence and re-emergence of disease, as seen currently in some eastern Mediterranean countries.

Even in well-resourced settings, the true incidence of brucellosis in domesticated animals may be 10–20 times higher than the reported figures. Bovine brucellosis has been the target of control programs in many parts of the world and has been eradicated from the cattle populations of much of northern Europe, Australia, New Zealand, and Canada, among other nations. Its incidence has been reduced to a low level in the United States and most Western European countries, with a varied picture in other parts of the world. Efforts to eradicate *B. melitensis* infection from sheep and goat populations have been much less successful. These efforts have relied heavily on vaccination programs, which have tended to fluctuate with changing economic and political conditions. In some countries (e.g., Israel), *B. melitensis* has caused serious outbreaks in cattle. Infections with *B. melitensis* still pose a major public health problem in Mediterranean countries; in western, central, and southern Asia; and in parts of Africa and South and Central America. Infections with *B. abortus* are common in cattle-rearing communities in African countries such as Kenya and Uganda.

Human brucellosis is usually associated with occupational or domestic exposure to infected animals or their products. Farmers, shepherds, goatherds, veterinarians, and employees in slaughterhouses and meat-processing plants in endemic areas are occupationally exposed to infection. Feral pig hunters are at risk of infection with *B. suis* in several countries, including Australia. Family members of individuals involved in animal husbandry may be at risk, although it is often difficult to differentiate food-borne infection from environmental contamination under these circumstances. Laboratory workers who handle cultures or infected samples also are at risk. Travelers and urban residents usually acquire the infection through consumption of contaminated foods. In countries that have eradicated the disease, new cases are most commonly acquired abroad. Dairy products, especially soft cheeses, unpasteurized milk, and ice cream, are the most frequently implicated sources of infection; raw meat and bone marrow may be sources under exceptional circumstances. Infections acquired through cosmetic treatments using materials of fetal origin have been reported. Person-to-person transmission is extremely rare, as is

transfer of infection by blood or tissue donation. Although brucellosis is a chronic intracellular infection, there is no evidence for increased prevalence or severity among individuals with HIV infection or with immunodeficiency or immunosuppression of other etiologies.

Brucellosis may be acquired by ingestion, inhalation, or mucosal or percutaneous exposure. Accidental injection or ingestion of the live vaccine strains of *B. abortus* (S19 and RB51) and *B. melitensis* (Rev 1) can cause disease. *B. melitensis* and *B. suis* have historically been developed as biological weapons by several countries and could be exploited for bioterrorism **(Chap. S2)**. This possibility should be borne in mind in the event of sudden unexplained outbreaks.

IMMUNITY AND PATHOGENESIS

Exposure to brucellosis elicits both humoral and cell-mediated immune responses. The mechanisms of protective immunity against human brucellosis are presumed to be similar to those documented in laboratory animals, but such generalizations must be interpreted with caution. The response to infection and its outcome are influenced by the virulence, phase, and species of the infecting strain. Differences have been reported between *B. abortus* and *B. suis* in modes of cellular entry and subsequent compartmentalization and processing. Antibodies promote clearance of extracellular brucellae by bactericidal action and by facilitation of phagocytosis by polymorphonuclear and mononuclear phagocytes; however, antibodies alone cannot eradicate infection. Organisms taken up by macrophages and other cells can establish persistent intracellular infections. The key target cell is the macrophage, and bacterial mechanisms for suppressing intracellular killing and apoptosis result in very large intracellular populations. Opsonized bacteria are actively phagocytosed by neutrophilic granulocytes and by monocytes. In these and other cells, initial attachment takes place via specific receptors, including Fc, C3, fibronectin, and mannose-binding proteins. Opsonized—but not unopsonized—bacteria trigger an oxidative burst inside phagocytes. Unopsonized bacteria are internalized via similar receptors but at much lower efficiency. Smooth strains enter host cells via lipid rafts. Smooth lipopolysaccharide (LPS), β-cyclic glucan, and possibly an invasion–attachment protein (IalB) are involved in this process. Tumor necrosis factor α (TNF-α) produced early in the course of infection stimulates cytotoxic lymphocytes and activates macrophages, which can kill intracellular brucellae (probably mainly through production of reactive oxygen and nitrogen intermediates) and may clear infection. However, virulent *Brucella* cells can suppress the TNF-α response, and control of infection in this situation depends on macrophage activation and interferon γ (IFN-γ) responses. Cytokines such as interleukin (IL) 12 promote production of IFN-γ, which drives T_H1-type responses and stimulates macrophage activation. Inflammatory cytokines, including IL-4, IL-6, and IL-10, downregulate the protective response. As in other types of intracellular infection, it is assumed that initial replication of brucellae takes place within cells of the lymph nodes draining the point of entry. Subsequent hematogenous spread may result in chronic localizing infection at almost any site, although the reticuloendothelial system, musculoskeletal tissues, and genitourinary system are most frequently targeted. Both acute and chronic inflammatory responses develop in brucellosis, and the local tissue response may include granuloma formation with or without necrosis and caseation. Abscesses may also develop, especially in chronic localized infection.

The determinants of pathogenicity of *Brucella* have not been fully characterized, and the mechanisms underlying the manifestations of brucellosis are incompletely understood. The organism is a "stealth" pathogen whose survival strategy is centered on several processes that avoid triggering innate immune responses and that permit survival within monocytic cells. These processes include evasion of intracellular destruction by restricting the fusion of type IV secretion system–dependent *Brucella*-containing vacuoles with lysosomal compartments, inhibition of apoptosis of infected mononuclear cells, and prevention of dendritic cell maturation, antigen presentation, and activation of naïve T cells. The smooth *Brucella* LPS, which has an unusual O-chain and core-lipid composition, has relatively low endotoxin activity and plays a key role in pyrogenicity and in resistance to phagocytosis and serum killing in the nonimmune host. In addition, LPS is believed to play a role in suppressing phagosome–lysosome fusion and diverting the internalized bacteria into vacuoles located in endoplasmic reticulum, where intracellular replication takes place. Specific exotoxins have not been isolated, but a type IV secretion system (VirB) that regulates intracellular survival and trafficking has been identified. In *B. abortus* this system can be activated extracellularly, but in *B. suis* it is activated (by low pH) only during intracellular growth. Brucellae then produce acid-stable proteins that facilitate the organisms' survival in phagosomes and may enhance their resistance to reactive oxygen intermediates. A type III secretion system based on modified flagellar structures also has been inferred, although not yet confirmed. Virulent brucellae are resistant to defensins and produce a Cu-Zn superoxide dismutase that increases their resistance to reactive oxygen intermediates. A hemolysin-like protein may trigger the release of brucellae from infected cells.

CLINICAL FEATURES

Brucellosis almost invariably causes fever, which may be associated with profuse sweats, especially at night. In endemic areas, brucellosis may be difficult to distinguish from the many other causes of fever. However, two features recognized in the nineteenth century distinguish brucellosis from other tropical fevers, such as typhoid and malaria: (1) Left untreated, the fever of brucellosis shows an undulating pattern that persists for weeks before the commencement of an afebrile period that may be followed by relapse. (2) The fever of brucellosis is associated with musculoskeletal symptoms and signs in about one-half of all patients.

The clinical syndromes caused by the different nomen species are similar, although *B. melitensis* tends to be associated with a more acute and aggressive presentation and *B. suis* with focal abscess induction. *B. abortus* infections may be more insidious in onset and more likely to become chronic. *B. canis* infections are reported to present frequently with acute gastrointestinal symptoms.

The incubation period varies from 1 week to several months, and the onset of fever and other symptoms may be abrupt or insidious. In addition to experiencing fever and sweats, patients become increasingly apathetic and fatigued; lose appetite and weight; and have nonspecific myalgia, headache, and chills. Overall, the presentation of brucellosis often fits one of three patterns: febrile illness that resembles typhoid but is less severe; fever and acute monoarthritis, typically of the hip or knee, in a young child; and long-lasting fever, misery, and low-back or hip pain in an older man. In an endemic area (e.g., much of the Middle East), a patient with fever and difficulty walking into the clinic would be regarded as having brucellosis until it was proven otherwise.

Diagnostic clues in the patient's history include travel to an endemic area, employment in a diagnostic microbiology laboratory, consumption of unpasteurized milk products (including soft cheeses), contact with animals, accidental inoculation with veterinary *Brucella* vaccines, and—in an endemic setting—a history of similar illness in the family (documented in almost 50% of cases). Focal features are present in the majority of patients. The most common are musculoskeletal pain and physical findings in the peripheral and axial skeleton (~40% of cases). Osteomyelitis more commonly involves the lumbar and low thoracic vertebrae than the cervical and high thoracic spine. Individual joints that are most commonly affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints; the pattern may be one of monoarthritis or polyarthritis. Osteomyelitis may also accompany septic arthritis.

In addition to the usual causes of vertebral osteomyelitis or septic arthritis, the most important disease in the differential diagnosis is tuberculosis. This point influences the therapeutic approach as well as the prognosis, given that several antimicrobial agents used to treat brucellosis are also used to treat tuberculosis. Septic arthritis in brucellosis progresses slowly, starting with small pericapsular erosions. In the vertebrae, anterior erosions of the superior end plate are typically the first features to become evident, with eventual involvement and sclerosis of the whole vertebra. Anterior osteophytes eventually develop, but vertebral destruction or impingement on the spinal cord is rare and usually suggests tuberculosis **(Table 164-1)**.

TABLE 164-1 Radiology of the Spine: Differentiation of Brucellosis from Tuberculosis

	BRUCELLOSIS	TUBERCULOSIS
Site	Lumbar and others	Dorsolumbar
Vertebrae	Multiple or contiguous	Contiguous
Diskitis	Late	Early
Body	Intact until late	Morphology lost early
Canal compression	Rare	Common
Epiphysitis	Anterosuperior (Pom's sign)	General: upper and lower disk regions, central, subperiosteal
Osteophyte	Anterolateral (parrot beak)	Unusual
Deformity	Wedging uncommon	Anterior wedge, gibbus
Recovery	Sclerosis, whole-body	Variable
Paravertebral abscess	Small, well-localized	Common and discrete loss, transverse process
Psoas abscess	Rare	More likely

Other systems may be involved in a manner that resembles typhoid. About one-quarter of patients have a dry cough, usually with few changes visible on the chest x-ray, although pneumonia, empyema, intrathoracic adenopathy, or lung abscess can occur. Sputum or pleural effusion cultures are rarely positive in such cases, which respond well to standard brucellosis treatment. One-quarter of patients have hepatosplenomegaly, and 10–20% have significant lymphadenopathy; the differential diagnosis includes glandular fever–like illness such as that caused by Epstein-Barr virus, *Toxoplasma*, cytomegalovirus, HIV, or *Mycobacterium tuberculosis*. Up to 10% of men have acute epididymo-orchitis, which must be distinguished from mumps and from surgical problems such as torsion. Prostatitis, inflammation of the seminal vesicles, salpingitis, and pyelonephritis all occur. There is an increased incidence of fetal loss among infected pregnant women, although teratogenicity has not been described and the tendency toward abortion is much less pronounced in humans than in farm animals.

Neurologic involvement is common, with depression and lethargy whose severity may not be fully appreciated by either the patient or the physician until after treatment. A small proportion of patients develop lymphocytic meningoencephalitis that mimics neurotuberculosis, atypical leptospirosis, or noninfectious conditions and that may be complicated by intracerebral abscess, a variety of cranial nerve deficits, or ruptured mycotic aneurysms.

Endocarditis occurs in ~1% of cases, most often affecting the aortic valve (natural or prosthetic). Any site in the body may be involved in metastatic abscess formation or inflammation; the female breast and the thyroid gland are affected particularly often. Nonspecific maculopapular rashes and other skin manifestations are uncommon and are rarely noticed by the patient even if they develop.

DIAGNOSIS

Because the clinical picture of brucellosis is not distinctive, the diagnosis must be based on a history of potential exposure, a presentation consistent with the disease, and supporting laboratory findings. Results of routine biochemical assays are usually within normal limits, although serum levels of hepatic enzymes and bilirubin may be elevated. Peripheral leukocyte counts are usually normal or low, with relative lymphocytosis. Mild anemia may be documented. Thrombocytopenia and disseminated intravascular coagulation with raised levels of fibrinogen degradation products can develop. The erythrocyte sedimentation rate and C-reactive protein levels are often normal but may be raised.

In body fluids such as cerebrospinal fluid (CSF) or joint fluid, lymphocytosis and low glucose levels are the norm. Elevated CSF levels of adenosine deaminase cannot be used to distinguish tubercular meningitis, as they may also be found in brucellosis. Biopsied samples of tissues such as lymph node or liver may show noncaseating granulomas without acid/alcohol-fast bacilli. The radiologic features of bony disease develop late and are much more subtle than those of tuberculosis or septic arthritis of other etiologies, with less bone and joint destruction. Isotope scanning is more sensitive than plain x-ray and continues to give positive results long after successful treatment.

Isolation of brucellae from blood, CSF, bone marrow, or joint fluid or from a tissue aspirate or biopsy sample is definitive, and attempts at isolation are usually successful in 50–70% of cases. Duplicate cultures should be incubated for up to 6 weeks (in air and 10% CO_2, respectively). Concentration and lysis of buffy coat cells before culture may increase the isolation rate. Cultures in modern nonradiometric or similar signaling systems (e.g., Bactec) usually become positive within 7–10 days but should be maintained for at least 3 weeks before the results are declared negative. All cultures should be handled under containment conditions appropriate for dangerous pathogens. *Brucella* species may be misidentified as *Agrobacterium*, *Ochrobactrum*, or *Psychrobacter (Moraxella) phenylpyruvicus* by the gallery identification strips commonly used in the diagnostic laboratory. In recent years, matrix-assisted laser desorption ionization time-of-flight spectrometry (MALDI-TOF MS) has emerged as a powerful tool in bacterial identification. The relative homogeneity of classical *Brucella* species makes identification beyond the genus level by routine approaches challenging, although further improvements may facilitate discrimination at the species level, particularly in reference laboratories. The place of this technique in routine diagnostic practice will depend on further refinements. Meanwhile, the author is aware of cases in which blood culture isolates have been identified incorrectly using MALDI-TOF MS.

The peripheral blood–based polymerase chain reaction has enormous potential to detect bacteremia, to predict relapse, and to exclude "chronic brucellosis." This method is probably more sensitive and is certainly quicker than blood culture, and it does not carry the attendant biohazard risk posed by culture. Nucleic acid amplification techniques are now quite widely used, although no single standardized procedure has been adopted. Primers for the spacer region between the genes encoding the 16S and 23S ribosomal RNAs (*rrs-rrl),* various outer-membrane protein–encoding genes, the insertion sequence *IS711*, and the protein BCSP31 are sensitive and specific. Blood and other tissues are the most suitable samples for analysis.

Serologic examination often provides the only positive laboratory findings in brucellosis. In acute infection, IgM antibodies appear early and are followed by IgG and IgA. All these antibodies are active in agglutination tests, whether performed by tube, plate, or microagglutination methods. The majority of patients have detectable agglutinins at this stage. As the disease progresses, IgM levels decline, and the avidity and subclass distribution of IgG and IgA change. The result is reduced or undetectable agglutinin titers. However, the antibodies are detectable by alternative tests, including the complement fixation test, Coomb's antiglobulin test, and enzyme-linked immunosorbent assay. There is no clear cutoff value for a diagnostic titer. Rather, serology results must be interpreted in the context of exposure history and clinical presentation. In endemic areas or in settings of potential occupational exposure, agglutinin titers of 1:320–1:640 or higher are considered diagnostic; in nonendemic areas, a titer of ≥1:160 is considered significant. Repetition of tests after 2–4 weeks may demonstrate a rising titer.

In most centers, the standard agglutination test (or derivatives such as the microagglutination test) is still the mainstay of serologic diagnosis. Some investigators rely on the Rose Bengal test, which has been only partially validated for human diagnostic use. Dipstick assays for anti-*Brucella* IgM are useful for the diagnosis of acute infection but are less sensitive for infection with symptoms of several months' duration. In an endemic setting, >90% of patients with acute bacteremia have standard agglutination titers of at least 1:320. Other screening tests are used in some centers.

Antibody to the *Brucella* LPS O chain—the dominant antigen—is detected by all the conventional tests that employ smooth *B. abortus* cells as antigen. Since *B. abortus* cross-reacts with *B. melitensis* and *B. suis*, there is no advantage in replicating the tests with these antigens. Cross-reactions also occur with the O chains of some other gram-negative bacteria, including *Yersinia enterocolitica* O:9, *Escherichia coli* O157, *Francisella tularensis*, *Salmonella enterica* group N, *Stenotrophomonas*

maltophilia, and *Vibrio cholerae*. Cross-reactions do not occur with the cell-surface antigens of rough *Brucella* strains such as *B. canis* or *B. ovis*; serologic tests for these nomen species must employ an antigen prepared from either one. The live *B. abortus* vaccine strain RB51 does not elicit antibody responses in serologic tests that use smooth antigens, and this fact must be taken into account if serologic tests are employed in attempts to identify or follow the course of infections in persons accidentally exposed to the vaccine.

TREATMENT

Brucellosis

The broad aims of antimicrobial therapy are to treat and relieve the symptoms of current infection and to prevent relapse. Focal disease presentations may require specific intervention in addition to more prolonged and tailored antibiotic therapy. In addition, tuberculosis must always be excluded, or—to prevent the emergence of resistance—therapy must be tailored to specifically exclude drugs active against tuberculosis (e.g., rifampin used alone) or to include a full antituberculous regimen.

Early experience with streptomycin monotherapy showed that relapse was common; thus dual therapy with tetracyclines became the norm. This is still the most effective combination, but alternatives may be used, with the options depending on local or national policy about the use of rifampin for the treatment of nonmycobacterial infection. For the several antimicrobial agents that are active in vivo, efficacy can usually be predicted by in vitro testing. However, numerous *Brucella* strains show in vitro sensitivity to a whole range of antimicrobials that are therapeutically ineffective, including assorted β-lactams. Moreover, the use of fluoroquinolones remains controversial despite the good in vitro activity and white-cell penetration of most agents of this class. Low intravacuolar pH is probably a factor in the poor performance of these drugs.

For adults with acute nonfocal brucellosis (duration, <1 month), a 6-week course of therapy incorporating at least two antimicrobial agents is required. Complex or focal disease may necessitate ≥3 months of therapy. Adherence to the therapeutic regimen is very important, and poor adherence underlies almost all cases of apparent treatment failure; such failure is rarely due to the emergence of drug resistance, although increasing resistance to trimethoprim-sulfamethoxazole (TMP-SMX) has been reported at one center. There is good retrospective evidence that a 3-week course of two agents is as effective as a 6-week course for treatment and prevention of relapse in children, but this point has not yet been proven in prospective studies.

The gold standard for the treatment of brucellosis in adults is IM streptomycin (0.75–1 g daily for 14–21 days) together with doxycycline (100 mg twice daily for 6 weeks). In both clinical trials and observational studies, relapse follows such treatment in 5–10% of cases. The usual alternative regimen (and the current World Health Organization recommendation) is rifampin (600–900 mg/d) plus doxycycline (100 mg twice daily) for 6 weeks. The relapse/failure rate is ~10% in trial conditions but rises to >20% in many non-trial situations, possibly because doxycycline levels are reduced and clearance rates increased by concomitant rifampin administration. Patients who cannot tolerate or receive tetracyclines (children, pregnant women) can be given high-dose TMP-SMX instead (two or three standard-strength tablets twice daily for adults, depending on weight).

Increasing evidence supports the use of an aminoglycoside such as gentamicin (5–6 mg/kg per day for at least 2 weeks) instead of streptomycin. Shorter courses have been associated with high failure rates in adults. A 5- to 7-day course of therapy with gentamicin and a 3-week course of TMP-SMX may be adequate for children with uncomplicated disease, but prospective trials are still needed to support this recommendation. Early experience with fluoroquinolone monotherapy was disappointing, although it was suggested that ofloxacin or ciprofloxacin, given together with rifampin for 6 weeks, might be an acceptable alternative to the other 6-week regimens for adults. A substantial meta-analysis did not support the use of fluoroquinolones in first-line treatment regimens, and these drugs are not recommended by an expert consensus group (Ioannina) except in the context of well-designed clinical trials. However, a more recent meta-analysis is more supportive of the efficacy of these drugs, and an adequately powered prospective study will be needed to resolve their role in standard combination therapy. A triple-drug regimen—doxycycline and rifampin combined with an initial course of an aminoglycoside—was superior to double-drug regimens in a meta-analysis. The triple-drug regimen should be considered for all patients with complicated disease and for those for whom treatment adherence is likely to be a problem.

Significant neurologic disease due to *Brucella* species requires prolonged treatment (i.e., for 3–6 months), usually with ceftriaxone supplementation of a standard regimen. *Brucella* endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin), and many experts add ceftriaxone and/or a fluoroquinolone to reduce the need for valve replacement. Treatment is usually given for at least 4–6 months, and clinical end points for its discontinuation are often difficult to define. Surgery is still required for the majority of cases of infection of prosthetic heart valves and prosthetic joints.

There is no evidence base to guide prophylaxis after exposure to *Brucella* organisms (e.g., in the laboratory), inadvertent immunization with live vaccine intended for use in animals, or exposure to deliberately released brucellae. Most authorities have recommended the administration of rifampin plus doxycycline for 3 weeks after a low-risk exposure (e.g., an unspecified laboratory accident) and for 6 weeks after a major exposure to aerosol or injected material. However, such regimens are poorly tolerated, and doxycycline monotherapy of the same duration may be substituted. (Monotherapy is the standard recommendation in the United Kingdom but not in the United States.) Rifampin should be omitted after exposure to vaccine strain RB51, which is resistant to rifampin but sensitive to doxycycline. After significant brucellosis exposure, expert consultation is advised for women who are (or may be) pregnant.

PROGNOSIS AND FOLLOW-UP

Relapse occurs in up to 30% of poorly compliant patients. Thus patients should ideally be followed clinically for up to 2 years to detect relapse, which responds to a prolonged course of the same therapy used originally. The general well-being and the body weight of the patient are more useful guides than serology to lack of relapse. IgG antibody levels detected by the standard agglutination test and its variants can remain in the diagnostic range for >2 years after successful treatment. Complement fixation titers usually fall to normal within 1 year of cure. Immunity is not solid; patients can be reinfected after repeated exposures. Fewer than 1% of patients die of brucellosis. When the outcome is fatal, death is usually a consequence of cardiac involvement; more rarely, it results from severe neurologic disease. Despite the low mortality rate, recovery from brucellosis is slow, and the illness can cause prolonged inactivity, with domestic and economic consequences.

The existence of a prolonged chronic brucellosis state after successful treatment remains controversial. Evaluation of patients in whom this state is considered (often those with work-related exposure to brucellae) includes careful exclusion of malingering, nonspecific chronic fatigue syndromes, and other causes of excessive sweating, such as alcohol abuse and obesity. In the future, the availability of more sensitive assays to detect *Brucella* antigen or DNA may help to identify patients with ongoing infection.

PREVENTION

Vaccines based on live attenuated *Brucella* strains, such as *B. abortus* strain 19BA or 104M, have been used in some countries to protect high-risk populations but have displayed only short-term efficacy and high reactogenicity. Subunit vaccines have been developed but are of uncertain value and cannot be recommended at present. Research in this area has been stimulated by interest in biodefense (Chap. S2) and may

eventually yield new products. The mainstay of veterinary prevention is a national commitment to testing and slaughter of infected herds/flocks (with compensation for owners), control of animal movement, and active immunization of animals. These measures are usually sufficient to control human disease as well. In their absence, pasteurization of all milk products before consumption is sufficient to prevent nonoccupational animal-to-human transmission. All cases of brucellosis in animals and humans should be reported to the appropriate public health authorities.

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165 Tularemia

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DEFINITION

Tularemia is a zoonotic disease caused by the bacterium *Francisella tularensis*. Human infection is rare but widespread and can be life-threatening. Sources of human infection include arthropod bites, agricultural aerosols, contaminated food or water, and contact with tissues of infected animals. Clinical diagnosis of tularemia can be challenging as the disease manifestations are diverse, with up to six distinct clinical syndromes. The prognosis is favorable when effective antimicrobial treatment is initiated early; however, complications are common if treatment is delayed.

ETIOLOGY

F. tularensis is a small (0.2 × 0.2–0.7 μm), aerobic, nonmotile, nonspore-forming, gram-negative coccobacillus. The bacterium is dependent on the invasion of host cells in vivo to multiply and cause disease. Genetically, it is not closely related to other known human pathogens. *F. tularensis* can enter the human body through the skin, mucous membranes, or respiratory tract. The infectious dose is low, with inhalation of 25 or fewer organisms sufficient to cause illness. Historically, *F. tularensis* was developed as a biological weapon and is currently classified as a Tier 1 select agent **(Chap. S2)**. Two subspecies of *F. tularensis*, subsp. *tularensis* (hereafter referred to as type A) and subsp. *holarctica* (hereafter referred to as type B) cause human tularemia in the United States.

EPIDEMIOLOGY

Tularemia occurs widely throughout the Northern Hemisphere. The disease is nationally notifiable in the United States, and cases have been reported in all U.S. states except Hawaii **(Fig. 165-1)**. States located in the south-central and midwestern regions—specifically, Arkansas, Kansas, Missouri, and Oklahoma—account for a disproportionate number of cases. Despite a substantial decrease during the mid-twentieth century, U.S. case counts have remained relatively stable since 1970 **(Fig. 165-2)**. During the 10-year period from 2006 through 2015, 93–314 cases were reported annually (average, 147 cases). The year 2015 marked a substantial increase in cases in Colorado, Wyoming, South Dakota, and Nebraska, with >100 cases reported among residents of these four states. The incidence was highest in Wyoming (35.8 cases per 1 million population), far higher than the national average of 1 case per 1 million population in 2015.

In nature, *F. tularensis* is maintained by arthropod and animal hosts. The bacterium is transmitted among animal hosts by arthropod bite or by direct exposure to contaminated materials in the environment. *F. tularensis* can infect and cause illness in an exceedingly broad variety of animals, having been isolated from >100 species, including domestic animals (cats and dogs). However, lagomorphs (wild hares and cottontail rabbits), terrestrial rodents (voles and meadow mice), aquatic rodents (muskrats and beavers), and ticks are thought to play a particularly significant role in propagating the organism in nature.

Humans are infected incidentally through various exposure routes—i.e., via the skin, mouth, lungs, or eyes **(Table 165-1).** Most commonly, *F. tularensis* enters through the skin by tick or deerfly bite or during handling of infected wildlife (e.g., while hunting or skinning). Domestic cats can transmit the bacterium by bite. The organism can be ingested by consumption of undercooked infected meat from wild

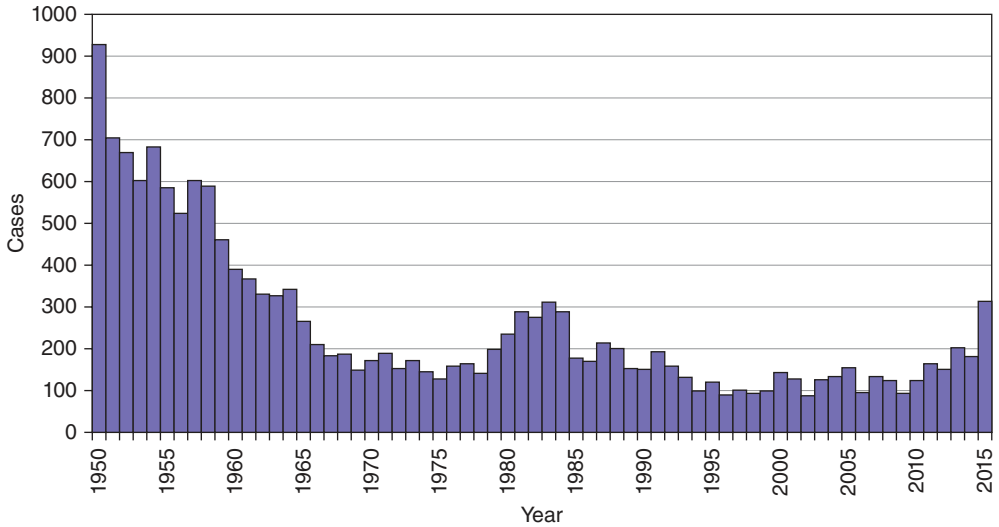

FIGURE 165-1 Yearly reported tularemia cases in the United States, 1950–2015.

FIGURE 165-2 Map displaying reported U.S. tularemia cases in 2000–2015. One dot was plotted randomly within the county of residence for each reported case.

animals or by drinking of untreated natural water contaminated by infected animals. It can directly enter the lungs upon inhalation of contaminated aerosols or dusts during farming or landscaping activities, especially when infected animals or carcasses are mowed over. Rarely, cases can occur by direct inoculation of contaminated materials into the mucous membranes of the eye. Person-to-person transmission of *F. tularensis* has not been reported. As in other zoonotic diseases, the risk of infection is associated with outdoor and occupational activities. Hunters, wildlife specialists, hikers, campers, veterinarians, and others with animal or arthropod exposure are at increased risk of infection. Laboratorians who handle cultures of *F. tularensis* without using personal protective equipment such as biosafety cabinets and N-95 respirators are also at elevated risk because of the high concentration of organisms being manipulated and the low infectious inhalation dose.

Tularemia cases are more common in the temperate months of May through September. Infections due to bites from infected ticks (*Dermacentor* and *Amblyomma* species) or deerflies (*Chrysops* species) occur during these months, whereas illness due to animal handling and hunting can develop at any time of the year. The principal animal sources of infection are the cottontail rabbit (*Sylvilagus* species), wild hares, and rodents (muskrats, beavers, voles). Human cases are most often sporadic and widespread; outbreaks are rare. Tularemia occurs more frequently in males than in females. Healthy persons of all ages are susceptible, with a higher incidence reported among children <10 years of age and middle-aged men. In children, the head and neck

TABLE 165-1 Clinical Manifestations of Tularemia

CLINICAL FORM	PORTAL OF ENTRY	TRANSMISSION SOURCE(S)	SYMPTOMS[a]	ALTERNATIVE DIAGNOSES
Ulceroglandular/glandular	Skin	Tick or deerfly bite; handling of infected animals	Fever; regional lymphadenopathy, with (ulceroglandular) or without (glandular) ulcer at site of entry	Cat-scratch disease, streptococcal or staphylococcal lymphadenitis, bubonic plague, lymphoma
Oropharyngeal	Mouth	Ingestion of contaminated food (undercooked game) or untreated water contaminated by infected animals	Fever; sore throat; marked unilateral cervical adenopathy; pharyngitis (which may be exudative)	Streptococcal infection, infectious mononucleosis, adenoviral infection
Oculoglandular	Eyes	Direct inoculation of contaminated materials into conjunctiva	Fever; unilateral conjunctivitis with mucopurulent discharge; eyelid swelling; regional lymphadenopathy	Cat-scratch disease
Pneumonic/respiratory[b]	Lungs	Inhalation of contaminated aerosols or agricultural dusts	Fever; dry paroxysmal cough; pleuritic or retrosternal pain and dyspnea	Mycoplasmal pneumonia, chlamydial pneumonia, Legionnaires' disease, pneumocystosis, histoplasmosis, tuberculosis, Q fever

[a]All clinical forms may also be marked by chills, headache, malaise, fatigue, myalgias, and arthralgias. [b]Pneumonia is also a secondary complication of other clinical forms of tularemia, in which the organism can spread to the lungs after initial replication at the entry site.

are often the primary sites of infection; ulcers or enlarged lymph nodes may be less obvious at these sites. The incidence of tularemia is roughly tenfold higher among some Native American populations, presumably because of higher rates of exposure.

The severity of clinical disease is influenced by the infecting strain, the route of exposure, and the length of delay before administration of effective treatment. Infections due to *F. tularensis* type A strains are typically more severe than those caused by type B strains. Although both of these subspecies cause tularemia throughout the United States, infections due to type B seem to predominate in the Pacific Northwest and along tributaries of the Mississippi, whereas infections due to type A prevail along the Atlantic seaboard and in south-central states. Virulence and geographic distribution differ among type A strains; subpopulations of strains localized in the eastern United States are associated with more severe disease.

GLOBAL CONSIDERATIONS

The distribution of *F. tularensis* type A is restricted to North America. In contrast, type B strains are widely dispersed throughout the Northern Hemisphere. *F. tularensis* type B, associated with opossums, has also been identified recently in Australia. Among Eurasian type B strains, a subpopulation displays natural resistance to erythromycin, whereas type B strains originating from the United States are uniformly susceptible to erythromycin. In Sweden, mosquito bite is a primary route of infection. This route of transmission is occasionally reported in other areas of northern and central Europe as well, but there is no evidence of mosquito-borne transmission of *F. tularensis* in North America. Water-borne cases of tularemia occur primarily in regions of the world where chlorinated municipal water systems are lacking, and water is an uncommon route of infection in the United States. A third subspecies of *F. tularensis*, subsp. *mediasiatica,* is localized to regions of central Asia, where it has been described in animals and ticks.

PATHOGENESIS

F. tularensis is an obligate intracellular pathogen that enters and replicates within the cytoplasm of various host cells, including (but not limited to) macrophages, dendritic cells, and polymorphonuclear neutrophils. Upon entry into the human body, the organism multiplies locally, producing a skin ulcer after skin entry or destruction of bronchial tissues after inhalation and then spreading to local lymph nodes. Systemic spread can follow, with infected cells disseminating throughout the host to the liver, spleen, and lungs. Uncontrolled replication of *F. tularensis* leads to cell death, substantial tissue damage, and impairment of vital organs.

The ability of *F. tularensis* to survive and replicate within host cells is essential for the development of tularemia. The bacterium does not produce toxins. By evading recognition by the innate immune system, *F. tularensis* can enter and proliferate within host cells. The atypical lipopolysaccharide of *F. tularensis* plays a key role in this process, exhibiting reduced endotoxicity and therefore failing to stimulate the host's innate immunity. Rapid bacterial growth within host cells, followed by cell death, triggers a systemic inflammatory reaction that overwhelms the host defense system, culminating in extensive tissue injury.

Inflammatory cell infiltration and various degrees of necrosis are histopathologic hallmarks of lymph node involvement. In the early stages of disease, infected lymph nodes may be characterized by follicular hyperplasia and inflammatory cell infiltration, whereas granulomatous lesions with areas of focal caseous necrosis, which may resemble tuberculous nodes (granulomatous form), are detected later in disease. Histopathologic findings on autopsied tissues include granulomas and microabscesses in the liver and pyogranulomatous foci, often with central necrosis, in the spleen and lungs.

CLINICAL MANIFESTATIONS

Primary clinical manifestations of tularemia vary with the portal of entry, which may be through the skin (ulceroglandular, glandular), the eye (oculoglandular), the mouth (oropharyngeal), or the lung (pneumonic or respiratory) (Table 165-1). Systemic disease can follow entry by virtually any route. The incubation period for tularemia is typically 3–7 days (range, 1–14 days). A sudden onset of fever, with temperatures as high as 41°C (106°F), is characteristic in all forms of tularemia. All clinical forms of disease may also be marked by chills, headache, malaise, fatigue, myalgias, and arthralgias. Blood chemistries are of limited value in diagnosis, as infection is not commonly associated with distinctive changes. The white blood cell count may be normal or elevated, and the differential count usually shows a relative increase of mononuclear cells. A slight increase in C-reactive protein levels and liver enzymes may be observed.

Ulceroglandular/Glandular Tularemia The most commonly reported clinical form is ulceroglandular tularemia, which follows a tick or deerfly bite or direct inoculation of the bacteria into the skin via handling of or biting by an infected animal. Initially, a small papule occurs at the site of organism entry, at or shortly after the onset of fever, and advances into an ulcer accompanied by painful regional lymphadenopathy in one or more adjacent lymph nodes. In ~30% of ulceroglandular tularemia cases, skin manifestations, including papular and maculopapular rash and erythema nodosum, are observed. Symptoms of glandular tularemia are similar to those of ulceroglandular tularemia, but without an ulcer. In both forms, suppuration of lymph nodes may occur in up to 40% of cases if there is a delay of >2 weeks in administration of an effective antibiotic. Children more often present with glandular disease, probably because of the increased frequency in this age group of the head and neck as the primary sites of infection; at these sites, ulcers may easily be overlooked or may resolve by the time tularemia is diagnosed.

Oropharyngeal and Oculoglandular Tularemia Oropharyngeal infection occurs after ingestion of *F. tularensis* in contaminated water or inadequately cooked game meat and occasionally after inhalation of the organism. Patients present with fever, sore throat, marked cervical adenopathy (most often unilateral), and pharyngitis, which may be exudative or accompanied by a small ulcer. Oculoglandular tularemia results from entry of the organism into the eye, either by touching of the conjunctival sac with contaminated fingers or possibly by exposure to infectious aerosols. The patient typically presents with fever, unilateral conjunctivitis with mucopurulent discharge, eyelid swelling, and ulcers or pustules on the palpebral conjunctivae. Preauricular, submandibular, or cervical lymph nodes appear enlarged, red, and tender. In both clinical forms, lymph node suppuration may ensue if treatment is delayed.

Pneumonic Tularemia Primary pneumonic tularemia develops from direct inhalation of *F. tularensis* and is the most severe form of the disease. Pneumonia is also a secondary complication of other clinical forms of tularemia in which the organism can spread to the lungs after initial replication at the entry site. Symptoms include dry paroxysmal cough, pleuritic or retrosternal pain, and dyspnea. Radiographic findings may include lobar and multilobar infiltrates, lung abscesses, and hilar adenopathy. Pleural effusions occur in ~20–30% of cases and appear to be exudative.

Typhoidal Tularemia *Typhoidal tularemia* is a term that was originally used to designate those patients with systemic infections for which the portal of entry into the body was unclear. This designation dates back to the time when ingestion and inhalation were not recognized as routes of exposure to *F. tularensis*. The term is outdated and infrequently used.

APPROACH TO THE PATIENT

Tularemia

As with many other rare diseases, failure to consider the diagnosis is the greatest obstacle to recognition and proper management. A careful history that reveals recent exposure to ticks or biting flies, hunting activity, or contact with secretions of domestic animals (e.g., cat bites, facial licking by dogs) is suggestive. Exposure to agricultural aerosols (i.e., during mowing or haying) should invariably trigger

consideration of the diagnosis in patients with pneumonic involvement. Human cases often occur in the setting of an epizootic in which excess mortality among rabbits or rodents may have been noticed by the patient or a family member.

The differential diagnosis for tularemia is broad and reflects the diverse clinical forms of the infection (Table 165-1). In persons with glandular or ulceroglandular tularemia, alternative diagnoses include cat-scratch fever, streptococcal or staphylococcal lymphadenitis, bubonic plague, cutaneous anthrax, sporotrichosis, lymphoma, toxoplasmosis, mycobacterial infection, tick typhus, and viral infections such as herpetic whitlow or poxvirus infection. Involvement of the groin should lead to consideration of lymphogranuloma venereum, chancre, and chancroid. Oropharyngeal tularemia may be confused with stomatitis, pharyngitis, and cervical adenitis of other bacterial and viral etiologies, including infectious mononucleosis, streptococcal infection, adenoviral infection, mycobacterial infection, and diphtheria. Pneumonic tularemia can be severe but generally follows the pattern of atypical community-acquired pneumonia with scant sputum production and causes that include mycoplasmal and chlamydial pneumonia, Legionnaires' disease, Q fever, secondary pneumonic plague, pneumocystosis, histoplasmosis, and tuberculosis. Exudative pleural effusion is common, and cultures of pleural fluid can be helpful in confirming the diagnosis. Indolent cases presenting as weight loss, night sweats, and hilar adenopathy have been mistaken for malignancy. Conditions mimicking typhoidal tularemia include bacterial endocarditis, disseminated mycobacterial and fungal infection, typhoid fever, brucellosis, listeriosis, Q fever, and sepsis of other etiologies.

LABORATORY DIAGNOSIS

Confirmation of tularemia cases is based on recovery of an isolate from a clinical specimen or a rise in antibody titer between paired acute- and convalescent-phase serum specimens. The optimal specimen for diagnostic testing depends on the clinical form of disease, the duration of illness, and the treatment history. Serology is valuable for diagnosing all forms of tularemia, although it is of limited utility in acute illness because host immunologic responses to *F. tularensis* are not typically detectable until ~10 days after illness onset. Nonetheless, the diagnosis of tularemia may rely on serologic testing of convalescent-phase samples, as the slow-growing, fastidious characteristics of the organism reduce the likelihood of its recovery from clinical specimens. The primary serologic testing method used is an agglutination assay (micro- or tube), which detects total *F. tularensis* immunoglobulins.

For isolation of live bacteria in culture, collection of clinical specimens before antibiotic treatment is necessary. The appropriate specimens for culture are respiratory secretions, particularly pleural fluid or bronchial washes/aspirates (pneumonic disease); swabs of visible lesions or affected areas (ulceroglandular and oculoglandular disease); aspirates or biopsy samples of lymph nodes or lesions (ulceroglandular, glandular, oculoglandular, and oropharyngeal disease); and blood (all clinical forms). *F. tularensis* grows aerobically and requires cysteine-supplemented medium for optimal growth. Relevant media available in clinical laboratories include buffered charcoal yeast extract, Thayer-Martin, and chocolate agars. For growth of blood cultures, automated systems can be useful, with the caveat that the results may often be negative. If *F. tularensis* is suspected as the source of a patient's illness, the laboratory should be alerted so that cultures can be incubated for 7–10 days in order to maximize the chance of organism recovery. Notification of the laboratory that tularemia is suspected on clinical grounds is also critical for minimizing the risk to laboratory staff posed by aerosol exposure during the handling of cultures containing high concentrations of organisms. Because of the rarity of the organism, it often is not easily identified when it is cultured. On Gram's stain, it appears as a tiny gram-negative coccobacillus that counterstains faintly with safranin. Available *F. tularensis*–specific assays include the direct fluorescence assay (antigen detection) and polymerase chain reaction (PCR).

Misidentification of *F. tularensis* can occur, particularly when tularemia is not suspected. Commercial automated biochemical identification systems are not ideal for classification of *F. tularensis* because of the organism's slow growth and lack of biochemical reactivity. Some molecular methods may erroneously classify *Francisella novicida* as *F. tularensis* because of the high degree of genetic relatedness between the two organisms. In contrast to *F. tularensis*, *F. novicida* is an opportunistic pathogen, primarily causing illness in patients with an underlying compromising condition. Results from diagnostic testing should be interpreted in conjunction with the patient's symptoms and exposures.

TREATMENT

Tularemia

Drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of tularemia include streptomycin, doxycycline, and tetracycline. Among these, streptomycin is the drug of choice on the basis of experience and lower relapse rates. Nevertheless, because streptomycin is difficult to obtain, gentamicin is often used as an acceptable alternative. Aminoglycosides are recommended for management of severe cases of tularemia; the primary drawback to their use is the potential for oto- and nephrotoxicity. The streptomycin dose is 1 g IM twice daily for adults and 15 mg/kg twice daily (up to a maximal daily dose of 2 g) for children; the drug is given for 10 days. Gentamicin is given IV to adults in an initial dose of 1.5–2 mg/kg followed by 1–1.7 mg/kg IV or IM every 8 h or 5–7 mg/kg IV every 24 h for 10–14 days, depending on the nature and severity of the infection.

If aminoglycosides are contraindicated or are not readily available, tetracyclines are alternatives to streptomycin and gentamicin. Primary treatment failure and relapse occur at higher rates with tetracyclines, given their bacteriostatic mode of action; these agents are therefore recommended only for mild cases of tularemia. Tetracyclines should be administered for at least 14 days. For adults, the doxycycline dose is 100 mg by mouth twice daily and the tetracycline dose is 500 mg by mouth every 6 h.

Ciprofloxacin and other fluoroquinolones are not approved by the FDA for the treatment of tularemia. Nonetheless, they have displayed good efficacy for this indication in published case series, they are bactericidal, they are effective at low concentrations in vitro, and they have reasonably good tissue penetration. The Infectious Diseases Society of America's guidelines for treatment of skin and soft tissue infections due to *F. tularensis* recommend treatment with oral levofloxacin (500 mg daily) or ciprofloxacin (750 mg twice daily) for at least 14 days for mild to moderate cases.

Consensus-based treatment recommendations have been developed by the Working Group on Civilian Biodefense for use in the event that tularemia is used as a biological weapon. For postexposure prophylaxis, doxycycline and ciprofloxacin are the preferred choices and are administered for 14 days. Adults and children weighing >45 kg take 100 mg of doxycycline by mouth twice daily; children weighing <45 kg take 2.2 mg/kg by mouth twice daily. The oral dosages for ciprofloxacin in adults and children are 500 mg and 15 mg/kg twice daily, respectively.

β-Lactam antibiotics are ineffective for treatment of tularemia because of β-lactamase production by *F. tularensis* strains. Although the third-generation β-lactam ceftriaxone is active against *F. tularensis* in vitro, it is not used for management of tularemia cases because therapeutic failures are common. Likewise, macrolides are not used for treatment of tularemia because some Eurasian *F. tularensis* type B strains are naturally resistant to this class of antimicrobials.

Antimicrobial susceptibility testing of *F. tularensis* isolates worldwide indicates uniform susceptibility to antibiotics used for treatment of tularemia, including aminoglycosides, tetracyclines, and fluoroquinolones. Naturally occurring resistance to antibiotics used for treatment of tularemia has never been demonstrated in *F. tularensis*.

PROGNOSIS

Cases diagnosed early after illness onset respond rapidly to appropriate therapy, and fever most often abates within 24–72 h. Factors

associated with poor outcome include a lack of timeliness in dispensing effective treatment, an underlying medical condition, the route of infection, and the infecting strain type. Prior to the advent of effective antimicrobials, mortality rates >60% were reported for primary pneumonic cases occurring via direct inhalation of *F. tularensis* type A strains. Among type A infections in the United States, those that occur along the Atlantic seaboard and in regions of the eastern United States are associated with the highest mortality rates. In Eurasia, where only *F. tularensis* type B causes tularemia, fatal cases are exceedingly rare, with or without antibiotic therapy. Overall, the expected mortality rate in the United States among appropriately treated patients is estimated at <1% overall and <5% for patients with pneumonic tularemia.

COMPLICATIONS

Complications of tularemia most often result from a delay in the initiation of treatment. Such a delay can be due to a failure to seek medical care until the later stages of disease progression, to a lack of clinical suspicion of tularemia, or to treatment with antibiotics ineffective against *F. tularensis*. Clinical chart review of 87 tularemia cases in Missouri (one of four states accounting for ~50% of U.S. cases) in 2000–2007 found that the disease was not suspected in more than half of cases until after the incidental isolation of *F. tularensis*.

The most commonly reported complication is suppuration of infected lymph nodes requiring surgical drainage(s). Other complications include hepatic abscesses, hepatitis, renal failure, rhabdomyolysis, adult respiratory distress syndrome, and loculated empyema requiring surgical decortication. Meningitis is a rare complication that can arise from untreated bacteremia, with only ~20 cases reported in the published literature; in two cases, cerebral microabscesses and brain lesions were documented. Other rare complications include endocarditis, pericarditis, and infections of prosthetic joints. Corneal edema and glaucoma have been reported as complications of oculoglandular tularemia.

TREATMENT FAILURES

Relapses are most often associated with the use of bacteriostatic antibiotics for shorter periods of treatment. The duration of treatment with a bacteriostatic agent needs to be sufficient to allow the development of a bactericidal cell-mediated host immune response to *F. tularensis*, which usually takes 2 weeks. Nonresponsiveness to antibiotics is most likely when there is a delay in the initiation of treatment after symptom onset. Poor antibiotic penetration of and accumulation in tissues, especially in the intracellular environment where *F. tularensis* multiplies, can also affect treatment efficacy. Lymph node suppuration, which is nonresponsive to all classes of antibiotics, occurs when disease progresses without the initiation of effective treatment; this nonresponsiveness to otherwise effective antibiotics is not due to resistance. For management of these cases, incision and surgical drainage or removal are often required for clinical cure. As stated above, treatment failure due to resistance of *F. tularensis* to the antibiotics recommended for therapy has never been demonstrated.

PREVENTION

The most effective methods for preventing tularemia are based on the likely source of infection. Use of insect repellents (20–30% DEET [N,N-diethyl-meta-toluamide]) and the wearing of long pants, long sleeves, and long socks can reduce the risk of tick and deerfly bites. Arthropod exposure may be further reduced by the use of permethrin-treated clothing. If attached ticks are found on the body, they should be promptly removed with tweezers. During handling of potentially infected animals (carcasses, game), gloves should be worn to avoid bacterial invasion through cuts or abrasions on the hands. Game meat should be cooked thoroughly before eating and care taken to avoid cross-contamination from uncooked meat. Exclusion of rodents from food and water supplies and chlorination of drinking water can reduce the risk of oral ingestion. To limit the risk of inhalation of infectious aerosols, sick or dead animals should not be mowed over and the area should be checked for carcasses prior to mowing. Use of masks during mowing and other landscaping activities may also reduce the risk of inhaling the bacteria, but this measure has not been studied. To reduce the risk of laboratory-acquired infections, laboratory staff should be notified whenever tularemia is suspected. For management of patients with tularemia, standard hospital infection precautions are considered adequate, given that person-to-person transmission has not been documented. Bodies of patients who die of tularemia should be handled with standard precautions. Autopsy procedures likely to produce aerosols or droplets should be avoided. No vaccine is currently available for *F. tularensis*.

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166 Plague and Other *Yersinia* Infections

Michael B. Prentice

PLAGUE

Plague is a systemic zoonosis caused by *Yersinia pestis*. It predominantly affects small rodents in rural areas of Africa, Asia, and the Americas and is usually transmitted to humans by an arthropod vector (the flea). Less often, infection follows contact with animal tissues or respiratory droplets. Plague is an acute febrile illness that is treatable with antimicrobial agents, but mortality rates among untreated patients are high. Ancient DNA studies have confirmed that both the fourteenth-century Black Death and the sixth-century Plague of Justinian in Europe were due to *Y. pestis* infection. Patients can present with the bubonic, septicemic, or pneumonic form of the disease. Although there is concern about epidemic spread of plague by the respiratory route, this is not the most common route of plague transmission, and established infection-control measures for respiratory plague exist. However, the fatalities associated with plague and the capacity for infection via the respiratory tract mean that *Y. pestis* fits the profile of a potential agent of bioterrorism **(Chap. S2)**. Consequently, measures have been taken to restrict access to the organism, including legislation affecting diagnostic and research procedures in some countries (e.g., the United States).

ETIOLOGY

The genus *Yersinia* comprises gram-negative bacteria of the family Enterobacteriaceae (gamma proteobacteria). Overwhelming taxonomic evidence showing *Y. pestis* strains as a clonal group within *Yersinia pseudotuberculosis* suggests recent evolution from the latter organism—an enteric pathogen of mammals that is spread by the fecal–oral route and thus has a phenotype distinctly different from that of *Y. pestis*. When grown in vivo or at 37°C, *Y. pestis* forms an amorphous capsule made from a plasmid-specified fimbrial protein, Caf or fraction 1 (F1) antigen, which is an immunodiagnostic marker of infection.

EPIDEMIOLOGY

Human plague generally follows an outbreak in a host rodent population (epizootic). Mass deaths among the rodent primary hosts lead to a search by fleas for new hosts, with consequent incidental infection of other mammals. The precipitating cause for an epizootic may ultimately be related to climate or other environmental factors. The reservoir for *Y. pestis* causing enzootic plague in natural endemic foci between epizootics (i.e., when the organism may be difficult to detect in rodents or fleas) is a topic of ongoing research and may not be the same in all regions. The enzootic/epizootic pattern may be the result of complex dynamic interactions of host rodents that have different plague susceptibilities with different flea vectors; alternatively, an environmental reservoir may be important.

GLOBAL FEATURES

In general, the enzootic areas for plague are lightly populated regions of Africa, Asia, and the Americas **(Fig. 166-1)**. Between January 2010 and December 2015, 3248 cases of plague with a global case–fatality rate of 18% were recorded by the World Health Organization (WHO); these figures were based on cases notified under the International Health Regulations and on data from national surveillance programs and publications. More than 96% of these cases were in Africa. The majority of cases were reported from the island of Madagascar, which additionally in 2017 experienced an outbreak of more than 2300 cases (76% pneumonic), with a case–fatality rate of 8.6%. A decline in reports from the Democratic Republic of the Congo (DRC) may reflect ongoing conflict in that country affecting surveillance rather than a true decrease. In the past decade, outbreaks of pneumonic plague have been recorded in the DRC, Uganda, Algeria, Madagascar, China, and Peru.

Plague was introduced into North America via the port of San Francisco in 1900 as part of the Third Pandemic, which spread around the world from Hong Kong. The disease is presently enzootic on the western side of the continent from southwestern Canada to Mexico. Most human cases in the United States occur in two regions: "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and southern Colorado; and further west in California, southern Oregon, and western Nevada *(http://www.cdc.gov/plague/maps/index.html)*. From 1990 to 2015, 185 cases of plague were reported in the United States, a mean of seven cases per year. Most cases occurred from May to October—the time of year when people are outdoors and rodents and their fleas are most plentiful. Infection is most often acquired by flea-bite in peridomestic environments. Infection can also be transmitted during the handling of living or dead small mammals (e.g., rabbits, hares, and prairie dogs) or wild carnivores (e.g., wildcats, coyotes, or mountain lions). Dogs and cats may bring plague-infected fleas into the home, and infected cats or dogs may transmit plague directly to humans by the respiratory route. In 2014, an outbreak of nonfatal pneumonic plague in Colorado affected four people exposed to an infected dog, with possible interhuman transmission in one case. The most recent case of person-to-person transmission in the United States before this occurred in the Los Angeles pneumonic plague outbreak of 1924.

Plague most often develops in areas with poor sanitary conditions and infestations of rats—in particular, the widely distributed roof rat *Rattus rattus* and the brown rat *Rattus norvegicus* (which serves as a laboratory model of plague). Rat control in warehouses and shipping facilities has been recognized as important in preventing the spread of plague since the early twentieth century and features in the current WHO International Health Regulations. Urban rodents acquire infection from wild rodents, and the proximity of the former to humans increases the risk of transmission. The oriental rat flea *Xenopsylla cheopis* is the most efficient vector for transmission of plague among rats and onward to humans in Asia, Africa, and South America.

Worldwide, bubonic plague is the predominant form reported (80–95% of suspected cases), with mortality rates of 10–20%. The mortality rate is higher (22%) in the small proportion of patients (10–20%) with primary septicemic plague (i.e., systemic *Y. pestis* sepsis with no bubo; see "Clinical Manifestations," below) and is highest with primary pulmonary plague. The latter is generally the least common of the main plague presentations, but, as in the 2017 Madagascar outbreak, it is occasionally predominant. Mortality rates of 50% or more for primary pulmonary plague are reported with delayed antimicrobial treatment in small case series from the older literature. Rare outbreaks of pharyngeal plague following consumption of raw or undercooked camel or goat meat have been reported.

A total of 744 (82%) of the 913 plague cases with clinically documented features (out of 1006 cases reported in total) in the United States from 1900 to 2012 were bubonic disease, 87 (10%) were septicemic disease, and 74 (8%) were pneumonic disease; 6 cases (1%) were pharyngeal. Sixteen percent of cases were fatal in the postantibiotic era from 1942 onward compared with 66% in the period 1900–1941.

PATHOGENESIS

As mentioned earlier, genetic evidence suggests that *Y. pestis* is a clone derived from the enteric pathogen *Y. pseudotuberculosis* in the recent evolutionary past (9000–20,000 years ago). The change from infection by the fecal–oral route to a two-stage life cycle, with alternate parasitization of arthropod and mammalian hosts, followed the acquisition of two plasmids—pFra and pPst—and the inactivation of remarkably few *Y. pseudotuberculosis* genes in conjunction with preexisting properties

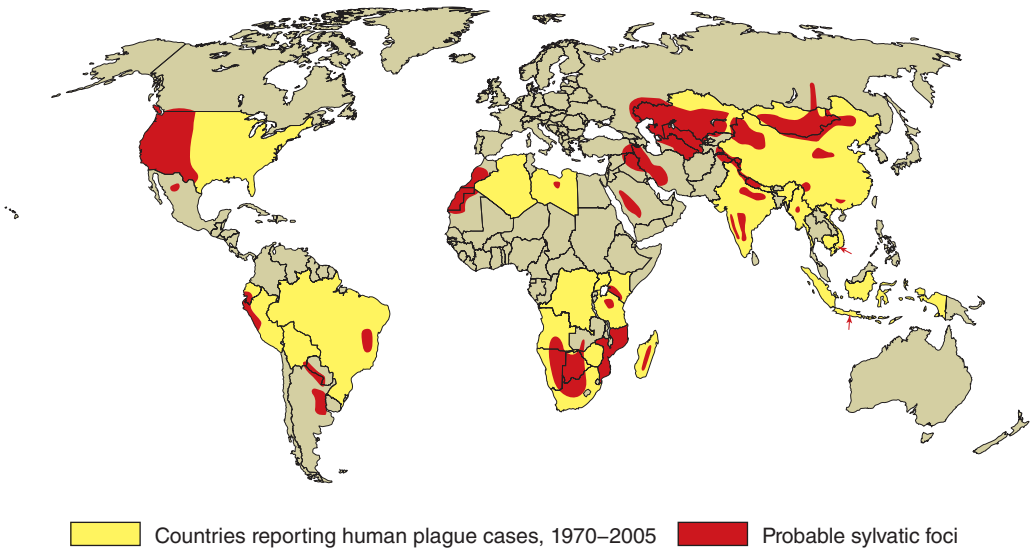

FIGURE 166-1 Approximate global distribution of *Yersinia pestis*. *(Compiled from WHO, CDC, and country sources. Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

of the *Y. pseudotuberculosis* ancestor, including the presence of a third plasmid, pYV, and the capacity to cause septicemia. In the arthropod-parasitizing portion of its life cycle, *Y. pestis* multiplies and forms biofilm-embedded aggregates in the flea midgut after ingestion of a blood meal containing bacteria. In some fleas, biofilm-embedded bacteria eventually fill the proventriculus (a valve connecting the esophagus to the midgut) and block normal blood feeding. Both "blocked" fleas and those containing masses of biofilm-embedded *Y. pestis* without complete blockage inoculate *Y. pestis* into each bite site. The ability of *Y. pestis* to colonize and multiply in the flea requires phospholipase D encoded by the *ymt* gene on the pFra plasmid, and biofilm synthesis requires the chromosomal *hms* locus shared with *Y. pseudotuberculosis.* However, three *Y. pseudotuberculosis* genes inhibiting biofilm formation or promoting its degradation are inactivated in *Y. pestis*, together with urease, which causes acute flea gastrointestinal toxicity. Blockage takes days or weeks to come about after initial infection of the flea and is followed by the flea's death. Many flea vectors (including *X. cheopis*) are also able to transmit plague in an early-phase unblocked state for up to a week after feeding, but 10 fleas in this state are required to infect a mammalian host (mass transmission).

Y. pestis disseminates from the site of inoculation in the mammalian host in a process initially dependent on plasminogen activator Pla, which is encoded by the small pPst plasmid. This surface protease activates mammalian plasminogen, degrades complement, and adheres to the extracellular matrix component laminin. Pla is essential for the high-level virulence of *Y. pestis* in mice by subcutaneous or intradermal injection (laboratory proxies for fleabites) and for the development of primary pneumonic plague. When actual fleabite inoculation is used in mouse models, the fimbrial capsule-forming protein (Ca1 or fraction 1; F1 antigen) encoded on pFra increases the efficiency of transmission, and plasminogen activator is required for the formation of buboes. Macrophages, neutrophils, and dendritic cells are all involved in the innate immune response to flea-transmitted *Y. pestis*. The organism is taken up by macrophages but avoids being killed by autophagy and can also survive and replicate in neutrophils. Rapid transport of the bacteria to regional lymph nodes occurs. *Y. pestis* then undergoes extracellular replication with full expression of its antiphagocytic systems: the type III secretion machines and their effectors encoded by pYV as well as the F1 capsule. These factors prevent neutrophil uptake, and the type III secretion effectors also block extrusion of microbicidal DNA by neutrophils and trigger apoptotic cell death. Overproduction of the type III secretion substrate and translocation protein LcrV exerts an anti-inflammatory effect, reducing host immune responses. Likewise, *Y. pestis* lipopolysaccharide is modified to minimize stimulation of host Toll-like receptor 4, thereby reducing protective host inflammatory responses during peripheral infection and prolonging host survival with high-grade bacteremia—an effect that probably enhances the pathogen's subsequent transmission by fleabite.

Replication of *Y. pestis* in a regional lymph node results in the local swelling of the lymph node and periglandular region known as a *bubo*. On histology, the node is found to be hemorrhagic or necrotic, with thrombosed blood vessels, and the lymphoid cells and normal architecture are replaced by large numbers of bacteria and fibrin. Periglandular tissues are inflamed and also contain large numbers of bacteria in a serosanguineous, gelatinous exudate.

Continued spread through the lymphatic vessels to contiguous lymph nodes produces second-order primary buboes. Infection is initially contained in the infected regional lymph nodes, although transient bacteremia can be detected. As the infection progresses, spread via efferent lymphatics to the thoracic duct produces high-grade bacteremia. Hematogenous spread to the spleen, liver, and secondary buboes follows, with subsequent uncontrolled septicemia, endotoxic shock, and disseminated intravascular coagulation leading to death. In some patients, this septicemic phase occurs without obvious prior bubo development or lung disease (septicemic plague). Hematogenous spread to the lungs results in secondary plague pneumonia, with bacteria initially more prominent in the interstitium than in the air spaces (the reverse being the case in primary plague pneumonia). Hematogenous spread to other organs, including the meninges, can occur.

CLINICAL MANIFESTATIONS

Bubonic Plague After an incubation period of 2–6 days, the onset of bubonic plague is sudden and is characterized by fever (>38°C), malaise, myalgia, dizziness, and increasing pain due to progressive lymphadenitis in the regional lymph nodes near the fleabite or other inoculation site. Lymphadenitis manifests as a tense, tender swelling (bubo) that, when palpated, has a boggy consistency with an underlying hard core. Generally, there is one painful and erythematous bubo with surrounding periganglionic edema. The bubo is most commonly inguinal but can also be crural, axillary **(Fig. 166-2)**, cervical, or submaxillary, depending on the site of the bite. Abdominal pain from intraabdominal node involvement can occur without other visible signs. Children are most likely to present with cervical or axillary buboes.

The differential diagnosis includes acute focal lymphadenopathy of other etiologies, such as streptococcal or staphylococcal infection, tularemia, cat-scratch disease, tick typhus, infectious mononucleosis, or lymphatic filariasis. These infections do not progress as rapidly, are not as painful, and are associated with visible cellulitis or ascending lymphangitis—both of which are absent in plague.

Without treatment, *Y. pestis* dissemination occurs and causes serious illness, including pneumonia (secondary pneumonic plague) and meningitis. Secondary pneumonic plague can be the source of person-to-person transmission of respiratory infection by productive cough (droplet infection), with the consequent development of primary plague pneumonia. Appropriate treatment of bubonic plague results in fever resolution within 2–5 days, but buboes may remain enlarged for >1 week after initial treatment and can become fluctuant.

Primary Septicemic Plague A minority (10–25%) of infections with *Y. pestis* present as gram-negative septicemia (hypotension, shock) without preceding lymphadenopathy. Septicemic plague occurs in all age groups, but persons >40 years of age are at elevated risk. Some chronic conditions may predispose to septicemic plague: in 2009 in the United States, a fatal laboratory-acquired infection with an attenuated *Y. pestis* strain manifested as septicemic plague in a 60-year-old researcher with diabetes mellitus and undiagnosed hemochromatosis. These conditions also carry an increased risk of septicemia with other pathogenic *Yersinia* species. The term *septicemic plague* can be confusing

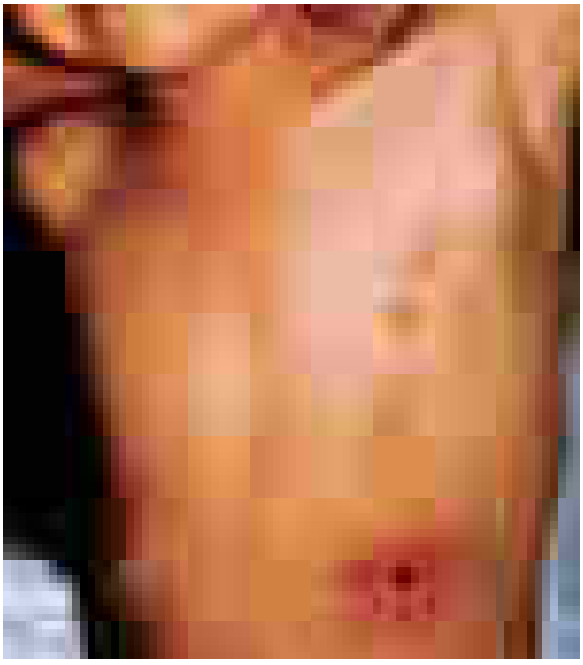

FIGURE 166-2 Plague patient in the southwestern United States with a left axillary bubo and an unusual plague ulcer and eschar at the site of the infective flea bite. *(Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

FIGURE 166-3 Sequential chest radiographs of a patient with fatal primary plague pneumonia. ***Left:*** Upright posteroanterior film taken at admission to hospital emergency department on third day of illness, showing segmental consolidation of right upper lobe. ***Center:*** Portable anteroposterior film taken 8 h after admission, showing extension of pneumonia to right middle and right lower lobes. ***Right:*** Portable anteroposterior film taken 13 h after admission (when patient had clinical acute respiratory distress syndrome), showing diffuse infiltration throughout right lung and patchy infiltration of left lower lung. A cavity later developed at the site of initial right-upper-lobe consolidation. *(Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed. AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

since most patients with buboes have detectable bacteremia at some stage, with or without systemic signs of sepsis. In laboratory experiments, however, septicemic disease without histologic changes in lymph nodes is seen in a minority of mice infected via fleabites.

Pneumonic Plague Primary pneumonic plague results from inhalation of infectious bacteria in droplets expelled from another person or an animal with primary or secondary plague pneumonia. This syndrome has a short incubation period, averaging from a few hours to 2–3 days (range, 1–7 days), and is characterized by a sudden onset of fever, headache, myalgia, weakness, nausea, vomiting, and dizziness. Respiratory signs—cough, dyspnea, chest pain, and sputum production with hemoptysis—typically arise after 24 h. Progression of initial segmental pneumonitis to lobar pneumonia and then to bilateral lung involvement may occur **(Fig. 166-3)**. The possible release of aerosolized *Y. pestis* bacteria in a bioterrorist attack, manifesting as an outbreak of primary pneumonic plague in nonendemic regions or in an urban setting where plague is rarely seen, has been a source of public health concern. Secondary pneumonic plague is a consequence of bacteremia occurring in ~10–15% of patients with bubonic plague. Bilateral alveolar infiltrates are seen on chest x-ray, and diffuse interstitial pneumonitis with scanty sputum production is typical.

Meningitis Meningeal plague is uncommon, occurring in ≤6% of plague cases reported in the United States. Presentation with headache and fever typically occurs >1 week after the onset of bubonic or septicemic plague and may be associated with suboptimal antimicrobial therapy (delayed therapy, penicillin administration, or low-dose tetracycline treatment) and cervical or axillary buboes.

Pharyngitis Symptomatic plague pharyngitis can follow the consumption of contaminated meat from an animal dying of plague or contact with persons or animals with pneumonic plague. This condition can resemble tonsillitis, with peritonsillar abscess and cervical lymphadenopathy. Asymptomatic pharyngeal carriage of *Y. pestis* can also occur in close contacts of patients with pneumonic plague.

LABORATORY DIAGNOSIS

Because of the scarcity of laboratory facilities in regions where human *Y. pestis* infection is most common, and because of the potential significance of *Y. pestis* isolation in a nonendemic area or an area from which human plague has been absent for many years, the WHO recommends an initial presumptive diagnosis followed by reference laboratory confirmation **(Table 166-1)**. In the United States, comprehensive national diagnostic facilities for plague have been in place since a federal Laboratory Response Network (LRN; *https://emergency.cdc.gov/lrn/index.asp*) was set up in 1999 to detect possible use of biological terrorism agents, including *Y. pestis*. Routine diagnostic clinical microbiology laboratories that are included in this network as sentinel-level laboratories use joint protocols from the Centers for Disease Control and Prevention (CDC) and the American Society for Microbiology to identify suspected *Y. pestis* isolates and to refer these specimens to LRN reference laboratories for confirmatory tests (*https://www.asm.org/index.php/guidelines/sentinel-guidelines*). *Y. pestis* is designated a "Tier 1 select agent" under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and subsequent executive orders; the provisions of this act, the Patriot Act of 2001, and related executive orders apply to all U.S. laboratories and individuals working with *Y. pestis*. Details of the applicable regulations are available from the CDC.

TABLE 166-1 World Health Organization Case Definitions of Plague

Suspected Case
Compatible clinical presentation
and
Consistent epidemiologic features, such as exposure to infected animals or humans and/or evidence of fleabites and/or residence in or travel to a known endemic focus within the previous 10 days
Presumptive Case
Meeting the definition of a suspected case
plus
Putative new or reemerging focus: ≥2 of the following tests positive
• Microscopy: gram-negative coccobacilli in material from bubo, blood, or sputum; bipolar appearance of Wayson or Wright-Giemsa staining
• F1 antigen detected in bubo aspirate, blood, or sputum
• A single anti-F1 serology without evidence of previous *Yersinia pestis* infection or immunization
• PCR detection of *Y. pestis* in bubo aspirate, blood, or sputum
Known endemic focus: ≥1 of the following tests positive
• Microscopic evidence of gram-negative or bipolar (Wayson, Wright-Giemsa) coccobacilli from bubo, blood, or sputum
• A single anti-F1 serology without evidence of previous plague infection or immunization
• F1 antigen detected in bubo aspirate, blood, or sputum
Confirmed Case
Meeting the definition of a suspected case
plus
• Identification of an isolate from a clinical sample as *Y. pestis* (colonial morphology and 2 of the following 4 tests positive: phage lysis of cultures at 20–25°C and 37°C; F1 antigen detection; PCR; *Y. pestis* biochemical profile)
or
• A fourfold rise in anti-F1 titer in paired serum samples
or
• In endemic areas when no other confirmatory test can be performed, a positive rapid diagnostic test with immunochromatography to detect F1 antigen

Abbreviation: PCR, polymerase chain reaction.

Source: Interregional Meeting on Prevention and Control of Plague, Antananarivo, Madagascar, 7–11 April 2006 *(www.who.int/entity/csr/resources/publications/WHO_HSE_EPR_2008_3w.pdf).*

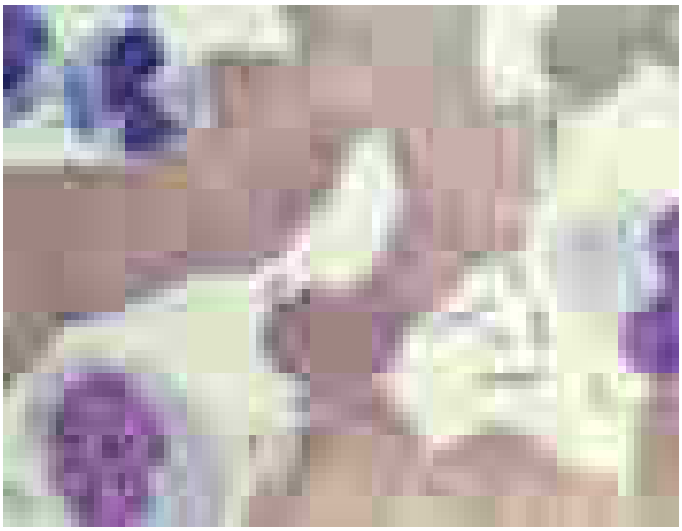

FIGURE 166-4 Peripheral-blood smear from a patient with fatal plague septicemia and shock, showing characteristic bipolar-staining *Yersinia pestis* bacilli (Wright's stain, oil immersion). *(Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

Yersinia species are gram-negative coccobacilli (short rods with rounded ends) 1–3 μm in length and 0.5–0.8 μm in diameter. *Y. pestis* in particular appears bipolar (with a "closed safety pin" appearance) and pleomorphic when stained with a polychromatic stain (Wayson or Wright-Giemsa; Fig. 166-4). Its lack of motility distinguishes *Y. pestis* from other *Yersinia* species, which are motile at 25°C and nonmotile at 37°C. Transport medium (e.g., Cary-Blair medium) preserves the viability of *Y. pestis* if transport is delayed.

The appropriate specimens for diagnosis of bubonic, pneumonic, and septicemic plague are bubo aspirate, bronchoalveolar lavage fluid or sputum, and blood, respectively. Culture of postmortem organ biopsy samples can also be diagnostic. A bubo aspirate is obtained by injection of 1 mL of sterile normal saline into a bubo under local anesthetic and aspiration of a small amount of (usually blood-stained) fluid. The WHO has provided interim guidance on how to aspirate buboes and collect sputum from patients with suspected pneumonic plague (*http://www.who.int/csr/disease/plague/collecting-pus-samples.PDF?ua=1*; *http://www.who.int/csr/disease/plague/collecting-sputum-samples.PDF?ua=1*). Gram's staining of these specimens may reveal gram-negative rods, which are shown by Wayson or Wright-Giemsa staining to be bipolar. These bacteria may even be visible in direct blood smears in septicemic plague (Fig. 166-4); this finding indicates very high numbers of circulating bacteria and a poor prognosis.

Y. pestis grows on nutrient agar and other standard laboratory media but forms smaller colonies than do other Enterobacteriaceae. Specimens should be inoculated onto nutrient-rich media such as sheep blood agar (SBA), into nutrient-rich broth such as brain-heart infusion broth, and onto selective agar such as MacConkey or eosin methylene blue (EMB) agar. *Yersinia*-specific CIN (cefsulodin, triclosan [Irgasan], novobiocin) agar can be useful for culture of contaminated specimens, such as sputum. Blood should be cultured in a standard blood culture system. The optimal growth temperature is <37°C (25–29°C), with pinpoint colonies only on SBA at 24 h. Slower growth occurs at 37°C. *Y. pestis* is oxidase-negative, catalase-positive, urea-negative, indole-negative, and lactose-negative. Automated biochemical identification systems can misidentify *Y. pestis* as *Y. pseudotuberculosis* or other bacterial species.

Reference laboratory tests for definitive identification of isolates include direct immunofluorescence for F1 antigen; specific polymerase chain reaction (PCR) for targets such as F1 antigen, the pesticin gene, and the plasminogen activator gene; and specific bacteriophage lysis. PCR can also be applied to diagnostic specimens, as can direct immunofluorescence for F1 antigen (produced in large amounts by *Y. pestis*) by slide microscopy. An immunochromatographic test strip for F1 antigen detection by monoclonal antibodies in clinical specimens has been devised in Madagascar. This method is effective for both laboratory and near-patient use and is now widely used in endemic countries. A similar test strip for Pla antigen has been developed and could be used to detect wild-type or engineered F1-negative virulent strains. Many other rapid diagnostic kits for possible bioterrorism pathogens, including *Y. pestis*, have been described in recent years, but none is widely used for primary or reference laboratory identification, and only one (a field real-time PCR for a range of potential bioterrorism agents) is approved by the U.S. Food and Drug Administration (FDA). Detailed phylogeographic DNA sequence data based on culture collections have been accumulated to trace plague evolution, and this approach could be adapted in the future to real-time clinical plague epidemiology.

In the absence of other positive laboratory diagnostic tests, a retrospective serologic diagnosis may be made on the basis of rising titers of hemagglutinating antibody to F1 antigen. Enzyme-linked immunosorbent assays (ELISAs) for IgG and IgM antibodies to F1 antigen are also available.

The white blood cell (WBC) count is generally raised (to 10,000–20,000/μL) in plague, with neutrophilic leukocytosis and a left shift (numerous immature neutrophils); in some cases, however, the WBC count is normal or leukopenia develops. WBC counts are occasionally very high, especially in children (>100,000/μL). Levels of fibrinogen degradation products are elevated in a majority of patients, but platelet counts are usually normal or low-normal. However, disseminated intravascular coagulation, with low platelet counts, prolonged prothrombin times, reduced fibrinogen, and elevated fibrinogen degradation product levels, occurs in a significant minority of patients.

TREATMENT

Plague

Guidelines for the treatment of plague are given in Table 166-2. A 10- to 14-day course of antimicrobial therapy (or a course continued until 2 days after fever subsides) is recommended. Streptomycin has historically been the parenteral treatment of choice for plague and is approved for this indication by the FDA. Although not yet approved by the FDA for plague, gentamicin has proven safe and effective in clinical trials in Tanzania and Madagascar and in retrospective reviewed cases in the United States. In view of streptomycin's adverse-reaction profile and limited availability, some experts now recommend gentamicin over streptomycin. The FDA has approved levofloxacin, moxifloxacin, and ciprofloxacin for prophylaxis and treatment of plague (including septicemic and pneumonic plague) under a regulatory approach based on animal studies alone, known as the Animal Rule. Levofloxacin has more efficacy than ciprofloxacin in postexposure prophylaxis of inhalational anthrax in animal models and has also received FDA approval for this indication (Chap. S2); thus it is a suitable agent for prophylaxis against two diseases in possible bioterrorism exposures.

While systemic chloramphenicol therapy is available in the resource-poor countries primarily affected by plague, it is less likely to be available or used in high-income countries because of its adverse-effect profile. Tetracyclines are also effective and can be given by mouth but are not generally recommended for children age <7 years because of tooth discoloration. Doxycycline is the tetracycline of choice; at an oral dosage of 100 mg twice daily, this drug was as effective as intramuscular gentamicin (2.5 mg/kg twice daily) in a trial in Tanzania. There is recent evidence that doxycycline does not cause dental staining in children because it binds calcium less readily than other tetracyclines.

Although *Y. pestis* is sensitive to β-lactam drugs in vitro and these drugs have been efficacious against plague in some animal models, the response to penicillins has been poor in some clinical cases; thus β-lactams and macrolides are not generally recommended as first-line therapy. Chloramphenicol, alone or in combination, is

TABLE 166-2 Guidelines for the Treatment of Plague

DRUG	DAILY DOSE	DOSING INTERVAL, h	ROUTE
Gentamicin			
Adult	5 mg/kg[a]	24	IM/IV
	5 mg/kg	8[b]	IM/IV
Child	5 mg/kg[a]	24	IM/IV
	7.5 mg/kg	8[c]	IM/IV
Streptomycin			
Adult	2 g	12	IM
Child	30 mg/kg	12	IM
Levofloxacin			
Adult and child >50 kg	500 mg	24	PO/IV
Child <50 kg and ≥6 months of age	16 mg/kg (maximum, 250 mg/dose)	12	PO/IV
Ciprofloxacin			
Adult	1000–1500 mg	12	PO
	800–1200 mg	8–12	IV
Child	40 mg/kg (maximum, 500 mg/dose)	12	PO
	30 mg/kg (maximum, 400 mg/dose)	12	IV
Moxifloxacin			
Adult	400 mg	24	PO/IV
Doxycycline			
Adult and child ≥45 kg	200 mg	12 or 24	PO/IV
Child <45 kg	4.4 mg/kg (maximum, 100 mg/dose)	12	PO/IV
Tetracycline			
Adult	2 g	6	PO/IV
Child >8 yr	25–50 mg/kg	6	PO/IV
Chloramphenicol			
Adult	100 mg/kg	6	PO/IV
Child >2 yr	100 mg/kg (maximum, 4 g)	6	PO/IV

[a]Aminoglycoside dose is adjusted with impaired renal function. No trial data have been published for once-daily gentamicin therapy for plague in adults or children, but this regimen is efficacious in gram-negative sepsis of other etiologies and has been successful in a recent outbreak of pneumonic plague in the Democratic Republic of the Congo. Neonates (up to 1 week of age) and premature infants should receive gentamicin at 2.5 mg/kg IV twice daily. [b]A 2-mg/kg loading dose followed by 1.7 mg/kg 3 times daily, reduced. [c]2.5 mg/kg 3 times daily.

Source: TV Inglesby et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281, 2000; and *https://www.cdc.gov/plague/healthcare/clinicians.html*.

recommended for some focal complications of plague (e.g., meningitis, endophthalmitis, myocarditis) because of its tissue penetration properties. Fluoroquinolones, effective in vitro and in animal models, are recommended in guidelines for possible bioterrorism-associated pneumonic plague and are increasingly used in plague therapy.

PREVENTION

In endemic areas, the control of plague in humans is based on reduction of the likelihood of being bitten by infected fleas or exposed to infected droplets from either humans or animals with plague pneumonia. In the United States, residence and outdoor activity in rural areas of western states where epizootics occur are the main risk factors for infection. To assess potential risks to humans in specific areas, surveillance for *Y. pestis* infection among animal plague hosts and vectors is carried out regularly as well as in response to observed animal die-offs. Personal protective measures include avoidance of areas where a plague epizootic has been identified and publicized (e.g., by warning signs or closure of campsites). Sick or dead animals should not be handled by the general public. Hunters and zoologists should wear gloves when handling wild-animal carcasses in endemic areas. General measures to avoid rodent fleabite during outdoor activity are appropriate and include the use of insect repellant, insecticide, and protective clothing. General measures to reduce peridomestic and occupational human contact with rodents are advised and include rodent-proofing of buildings and food-waste stores and removal of potential rodent habitats (e.g., woodpiles and junk heaps). Flea control by insecticide treatment of wild rodents is an effective means of minimizing human contact with plague if an epizootic is identified in an area close to human habitation. Any attempt to reduce rodent numbers must be preceded by flea suppression to reduce the migration of infected fleas to human hosts. An oral F1-V subunit vaccine using raccoon poxvirus (RCN) as a vector (sylvatic plague vaccine) is partially protective against plague when administered to wild prairie dogs in field trials and may in the future provide a means of reducing the risk of human exposure to *Y. pestis*.

Patients in whom pneumonic plague is suspected should be managed in isolation (with negative pressure, if available), with droplet precautions observed until pneumonia is excluded or effective antimicrobial therapy has been given for 48 h. Review of the literature published before the advent of antimicrobial agents suggests that the main infective risk is posed by patients in the final stages of disease who are coughing up sputum with plentiful visible blood and/or pus. Cotton and gauze masks were protective in these circumstances. Current surgical masks capable of barrier protection against droplets, including large respiratory particles, are probably protective, but the differential diagnosis of fever and hemoptysis in plague-endemic areas includes aerosol-transmitted infections such as tuberculosis. In addition, WHO guidance recommends that personal protective equipment for potential aerosol-generating procedures (e.g., collection of respiratory samples from patients with suspected or confirmed plague) should include a fit-tested N95 face mask, a gown, gloves, and a face shield or goggles.

Antimicrobial Prophylaxis Postexposure antimicrobial prophylaxis lasting 7 days is recommended following household, hospital, or other close contact with persons with untreated pneumonic plague. (*Close contact* is defined as contact with a patient at <2 m.) In animal aerosol-infection studies, levofloxacin and ciprofloxacin are associated with higher survival rates than doxycycline **(Table 166-3)**.

Immunization Studies with candidate plague vaccines in animal models show that neutralizing antibody provides protection against exposure but that cell-mediated immunity is critical for protection and clearance of *Y. pestis* from the host. A killed whole-cell vaccine used in humans required multiple doses, caused significant local and systemic reactions, and was not protective against pneumonic plague; this vaccine is not currently available in the United States. A live attenuated vaccine based on strain EV76 is still used in countries of the former Soviet Union and China but has significant side effects. The vaccines closest to licensing are subunit vaccines comprising recombinant F1 (rF1) and various recombinant V (rV) proteins produced in *Escherichia coli*, combined either as a fusion protein or as a mixture, purified, and adsorbed to aluminum hydroxide for injection. This combination protects mice and various nonhuman primates in laboratory models of bubonic and pneumonic plague and has been evaluated in phase 2 clinical trials. Special ethical considerations with controlled clinical studies involving plague in humans make prelicensing field-efficacy studies unlikely. In the United States, the FDA is therefore prepared to assess plague vaccines for human use under the Animal Rule, using efficacy data and other results from animal studies and antibodies and other correlates of immunity from human vaccinees *(www.fda.gov/emergencypreparedness/counterterrorism/medicalcountermeasures/mcmregulatoryscience/ucm391604.htm)*. Live attenuated *Y. pseudotuberculosis* and *Salmonella* strains expressing *Y. pestis*–specific antigens have been shown to be protective in laboratory animal models of bubonic and pneumonic plague and could be delivered by the oral route. A wide

TABLE 166-3 Guidelines for Plague Prophylaxis

DRUG	DAILY DOSE	DOSING INTERVAL, h	ROUTE
Doxycycline			
Adult	200 mg	12 or 24	PO
Child ≥8 y	≥45 kg: adult dose	12	PO
	≤45 kg: 2.2 mg/kg bid (maximum, 200 mg)	12	PO
Tetracycline			
Adult	1–2 g	6 or 12	PO
Child ≥8 y	25–50 mg/kg	6 or 12	PO
Levofloxacin			
Adult and child >50 kg)	500 mg	24	PO
Child <50 kg and ≥6 months of age	16 mg/kg (maximum, 250 mg/dose)	12	PO
Ciprofloxacin			
Adult	1 g	12	PO
Child	40 mg/kg	12	PO

Source: TV Inglesby et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281, 2000; FDA Drug Product Label Reference ID:3382318; *https://www.cdc.gov/plague/healthcare/clinicians.html*; *www.accessdata.fda.gov/drugsatfda_docs/label/2013/020634s065,020635s071,021721s032lbl.pdf*.

variety of other delivery mechanisms for *Y. pestis* antigens are being explored. Antigens other than F1 and V that could be added to subunit vaccines are being investigated. Providing impetus for exploration of these antigens are the recovery of F1-negative *Y. pestis* strains from natural sources and the observation that F1 antigen is not required for virulence in primate models of pneumonic plague.

YERSINIOSIS

Yersiniosis is a zoonotic infection with an enteropathogenic *Yersinia* species, usually *Y. enterocolitica* or *Y. pseudotuberculosis*. The usual hosts for these organisms are pigs and other wild and domestic animals; humans are usually infected by the oral route, and outbreaks from contaminated food occur. Yersiniosis is most common in childhood and in colder climates. Patients present with abdominal pain and sometimes with diarrhea (which may not occur in up to 50% of cases). *Y. enterocolitica* is more closely associated with terminal ileitis and *Y. pseudotuberculosis* with mesenteric adenitis, but both organisms may cause mesenteric adenitis and symptoms of abdominal pain and tenderness that result in pseudoappendicitis, with the surgical removal of a normal appendix. Diagnosis is based on culture of the organism or convalescent serology. *Y. pseudotuberculosis* and some rarer strains of *Y. enterocolitica* are especially likely to cause systemic infection, which is also more likely in patients with diabetes or iron overload. Systemic sepsis is treatable with antimicrobial agents, but postinfective arthropathy responds poorly to such therapy. Fourteen other *Yersinia* species lacking the virulence plasmid pYV common to *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica* are now recognized. These are, at most, opportunistic pathogens of humans (*Y. aldovae*, *Y. aleksiciae*, *Y. bercovieri*, *Y. entomophaga*, *Y. frederiksenii*, *Y. intermedia*, *Y. kristensenii*, *Y. massiliensis*, *Y. mollaretii*, *Y. nurmii*, *Y. pekkanenii*, *Y. rohdei*, *Y. similis*, and *Y. ruckeri*). Molecular phylogeny shows that *Y. enterocolitica* is more distantly related to *Y. pseudotuberculosis* than these other *Yersinia* species, and the similar virulence plasmid they share has probably been acquired independently by at least one of the two since the species diverged.

EPIDEMIOLOGY

Y. enterocolitica *Y. enterocolitica* is found worldwide and has been isolated from a wide variety of wild and domestic animals and environmental samples, including samples of food and water. In vitro, *Y. enterocolitica* is resistant to predation by the protozoon *Acanthamoeba castellani* and can survive inside it, suggesting a possible mode of environmental persistence. Strains are differentiated by combined biochemical reactions (biovar) and serogroup. Most clinical infections are associated with serogroups O:3, O:9, and O:5,27, with a declining number of O:8 infections in North America. Some O:8 infections, previously confined to North America, have been reported from Europe and Japan in recent years, and O:8 infections caused a high percentage of yersiniosis cases in Poland in 2008–2011, with a subsequent decline. Yersiniosis, mostly due to *Y. enterocolitica*, is the third commonest zoonosis reported in Europe; most reports come from northern Europe, especially Germany and Scandinavia. The incidence is highest among children; children <4 years of age are more likely to present with diarrhea than are older children. Abdominal pain with mesenteric adenitis and terminal ileitis is more prominent among older children and adults. Septicemia is more likely in patients with preexisting conditions such as diabetes mellitus, liver disease, any condition involving iron overload (including thalassemia and hemochromatosis), advanced age, malignancy, or HIV/AIDS. As in enteritis of other bacterial etiologies, postinfective complications such as reactive arthritis occur mainly in individuals who are HLA-B27 positive. Erythema nodosum **(Fig. A1-39)** following *Yersinia* infection is not associated with HLA-B27 and is more common among women than among men.

Consumption or preparation of raw pork products (such as chitterlings) and some processed pork products is strongly linked with infection because a high percentage of pigs carry pathogenic *Y. enterocolitica* strains. Outbreaks of *Y. enterocolitica* infection have been associated with consumption of milk (pasteurized, unpasteurized, and chocolate-flavored) and various foods contaminated with springwater. Person-to-person transmission is suspected in a few cases (e.g., in nosocomial and familial outbreaks) but is much less likely with *Y. enterocolitica* than with other causes of gastrointestinal infection, such as *Salmonella*. A multivariate analysis indicates that contact with companion animals is a risk factor for *Y. enterocolitica* infection among children in Sweden, and low-level colonization of dogs and cats with *Y. enterocolitica* has been reported. Transfusion-associated septicemia due to *Y. enterocolitica*, while recognized as a very rare but frequently fatal event for >30 years, has been difficult to eradicate.

Y. pseudotuberculosis *Y. pseudotuberculosis* is less frequently reported as a cause of human disease than *Y. enterocolitica*, and infection with *Y. pseudotuberculosis* is more likely to present as fever and abdominal pain due to mesenteric lymphadenitis. This organism is associated with wild mammals (rodents, rabbits, and deer), birds, and domestic pigs. Although outbreaks are generally rare, several have recently occurred in Finland in association with consumption of lettuce, raw carrots, or unpasteurized milk. Strains have historically been differentiated by combined biochemical reactions (biovar) and serogroup. Multilocus sequence typing and other phenotypic typing have revealed that some strains previously assigned to *Y. pseudotuberculosis* belong to the closely related but distinct species now called *Yersinia wautersii* (pathogenic) and *Yersinia similis* (nonpathogenic).

PATHOGENESIS

The usual route of infection is oral. Studies with both *Y. enterocolitica* and *Y. pseudotuberculosis* in animal models suggest that initial replication in the small intestine is followed by invasion of Peyer's patches of the distal ileum via M cells, with onward spread to mesenteric lymph nodes. The liver and spleen can also be involved after oral infection. The characteristic histologic appearance of enteropathogenic *Yersinia* after invasion of host tissues is as extracellular microabscesses surrounded by an epithelioid granulomatous lesion.

Experiments involving oral infection of mice with tagged *Y. enterocolitica* show that only a very small proportion of bacteria in the gut invade tissues. Individual bacterial clones from an orally inoculated pool give rise to each microabscess in a Peyer's patch, and the host restricts the invasion of previously infected Peyer's patches. A prior model positing progressive bacterial spread from Peyer's patches and mesenteric lymph nodes to the liver and spleen appears to be inaccurate: spread of *Y. pseudotuberculosis* and *Y. enterocolitica* to the liver and

spleen of mice occurs independently of regional lymph node colonization and in mice lacking Peyer's patches.

Invasion requires the expression of several nonfimbrial adhesins, such as invasin (Inv) and—in *Y. pseudotuberculosis*—*Yersinia* adhesin A (YadA). Inv interacts directly with β1 integrins, which are expressed on the apical surfaces of M cells but not enterocytes. YadA of *Y. pseudotuberculosis* interacts with extracellular matrix proteins such as collagen and fibronectin to facilitate host cell integrin association and invasion. YadA of *Y. enterocolitica* lacks a crucial N-terminal region and binds collagen and laminin but not fibronectin and does not cause invasion. Inv is chromosomally encoded, whereas YadA is encoded on the virulence plasmid pYV. YadA also helps to confer serum resistance in *Y. enterocolitica* by binding host complement regulators such as factor H and C4-binding protein. Another chromosomal gene, *ail* (attachment and invasion locus), encodes the extracellular protein Ail, which is the main factor conferring serum resistance in *Y. pseudotuberculosis* by binding these complement regulators.

By binding to host cell surfaces, YadA allows targeting of immune effector cells by the pYV plasmid–encoded type III secretion system (injectisome). As a consequence, the host's innate immune response is altered; toxins (*Yersinia* outer proteins, or Yops) are injected into host macrophages, neutrophils, and dendritic cells, affecting signal transduction pathways, resulting in reduced phagocytosis and inhibited production of reactive oxygen species by neutrophils, and triggering apoptosis of macrophages. Other factors functional in invasive disease include yersiniabactin (Ybt), a siderophore produced by some strains of *Y. pseudotuberculosis* and *Y. enterocolitica* as well as other Enterobacteriaceae. Ybt allows bacteria to access iron from saturated lactoferrin during infection and reduces production of reactive oxygen species by innate immune effector cells, thereby decreasing bacterial killing. *Y. pseudotuberculosis* and *Y. pestis* make other siderophores apart from Ybt.

CLINICAL MANIFESTATIONS

Self-limiting diarrhea is the most common reported presentation in infection with pathogenic *Y. enterocolitica*, especially in children <4 years of age, who form the single largest group in most case series. Blood may be detected in diarrheal stool. Older children and adults are more likely than younger children to present with abdominal pain, which can be localized to the right iliac fossa—a situation that often leads to laparotomy for presumed appendicitis (pseudoappendicitis). Appendectomy is not indicated for *Yersinia* infection causing pseudoappendicitis. Thickening of the terminal ileum and cecum is seen on endoscopy and ultrasound, with elevated round or oval lesions that may overlie Peyer's patches. Mesenteric lymph nodes are enlarged. Ulcerations of the mucosa are noted on endoscopy. Gastrointestinal complications include granulomatous appendicitis, a chronic inflammatory condition affecting the appendix that is responsible for ≤2% of cases of appendicitis; *Yersinia* is involved in a minority of cases. *Y. enterocolitica* infection can present as acute pharyngitis with or without other gastrointestinal symptoms. Fatal *Y. enterocolitica* pharyngitis has been recorded. Mycotic aneurysm can follow *Y. enterocolitica* bacteremia, as can focal infection (abscess) in many other sites and body compartments (liver, spleen, kidney, bone, meninges, endocardium).

In all age groups, *Y. pseudotuberculosis* infection is more likely to present as abdominal pain and fever than as diarrhea. A superantigenic toxin—*Y. pseudotuberculosis* mitogen (YPM)—is produced by strains seen in eastern Russia in association with Far Eastern scarlet-like fever, a childhood illness with desquamating rash, arthralgia, and toxic shock. A similar illness is recognized in Japan (Izumi fever) and Korea. Similarities have been noted with Kawasaki disease, the idiopathic acute systematic vasculitis of childhood. There is an epidemiologic link between exposure of populations to superantigen-positive *Y. pseudotuberculosis* and an elevated incidence of Kawasaki disease.

Y. enterocolitica or *Y. pseudotuberculosis* septicemia presents as a severe illness with fever and leukocytosis, often without localizing features, and is significantly associated with predisposing conditions such as diabetes mellitus, liver disease, and iron overload. Hemochromatosis combines several of these risk factors. Administration of iron chelators like desferrioxamine, which provide iron accessible to *Yersinia* (and have an inhibitory effect on neutrophil function), may result in *Yersinia* septicemia in patients with iron overload who presumably have an otherwise mild gastrointestinal infection. HIV/AIDS has been associated with *Y. pseudotuberculosis* septicemia. The unusual phenomenon of transfusion-associated septicemia is linked to the ability of *Y. enterocolitica* to multiply at refrigerator temperature (psychrotrophy). Typically, the transfused unit has been stored for >20 days, and it is believed that small numbers of yersiniae from an apparently healthy donor with subclinical bacteremia are amplified to very high numbers by growth inside the bag at ≤4°C, with consequent septic shock after transfusion. A method for preventing this very rare event (i.e., a range of 1 case in 500,000 to 1 case in several million transfused units in countries such as the United States and France) without unacceptable restriction in the blood supply has not yet been devised.

POSTINFECTIVE PHENOMENA

As in other invasive intestinal infections (salmonellosis, shigellosis), reactive arthritis (articular arthritis of multiple joints developing within 2–4 weeks of a preceding infection) occurs as a result of autoimmune activity initiated by the deposition of bacterial components (not viable bacteria) in joints in combination with the immune response to invading bacteria. The majority of individuals affected by reactive arthritis due to *Yersinia* are HLA-B27 positive. Myocarditis with electrocardiographic ST-segment abnormalities may occur with *Yersinia*-associated reactive arthritis. Most *Yersinia*-associated cases follow *Y. enterocolitica* infection (presumably because it is more common than infection with other species), but *Y. pseudotuberculosis*–associated reactive arthritis is also well documented in Finland, where sporadic and outbreak infections with *Y. pseudotuberculosis* are more common than in other countries. Of infected individuals identified in a recent *Y. pseudotuberculosis* serotype O:3 outbreak in Finland, 12% developed reactive arthritis affecting the small joints of the hands and feet, knees, ankles, and shoulders and lasting >6 months in most cases. Erythema nodosum **(Fig. A1-39)** occurs after *Yersinia* infection (more commonly in women) with no evidence of HLA-B27 linkage.

There is a long-standing association between antithyroid and anti-*Yersinia* antibodies. Antibody evidence of prior *Y. enterocolitica* infection in Graves' disease and increased levels of antithyroid antibody in patients with *Y. enterocolitica* antibodies were first noted in the 1970s. *Y. enterocolitica* contains a thyroid-stimulating hormone (TSH)–binding site that is recognized by antibodies to TSH from Graves' disease patients. Raised titers of antibodies to *Y. enterocolitica* whole cells and Yops have been found in some series of Graves' disease patients but not in others. One Danish study of twins found no evidence of an association between asymptomatic *Yersinia* infection (as evidenced by titers of Yop antibody) and antithyroid antibodies in euthyroid individuals, while another Danish study of twins with and without Graves' disease found that increased titers of Yop antibody were associated with Graves' disease. It remains unclear whether this cross-reactivity is significant in the etiology of Graves' disease.

LABORATORY DIAGNOSIS

Standard laboratory culture methods can be used to isolate enteropathogenic *Yersinia* species from sterile samples, including blood and cerebrospinal fluid. Culture on specific selective media (CIN agar), with or without pre-enrichment in broth or phosphate-buffered saline at either 4°C or 16°C, is the basis of most schema for isolation of yersiniae from stool or other nonsterile samples. Outside known high-incidence areas, specific culture may be carried out by laboratories only upon request. Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry systems can speciate isolates of *Y. enterocolitica* and *Y. pseudotuberculosis*. Virulence plasmid–negative strains of *Y. enterocolitica* can be isolated from cultures of stool from asymptomatic individuals, especially after cold enrichment. These strains usually differ in biotype (typically biovar 1a) from virulence plasmid–possessing strains; although some display apparent pathogenicity in a mouse model and all are pathogenic in an insect model, virulence plasmid–negative strains are not commonly accepted as

human pathogens. Because of the frequency with which the virulence plasmid is lost on laboratory subculture, combined biochemical identification (with biotyping according to a standard schema) and serologic identification are usually required to interpret the significance of an isolate of *Y. enterocolitica* from a nonsterile site. Most pathogenic *Y. enterocolitica* strains currently isolated from humans are of serogroup O:3/biovar 4 or serogroup O:9/biovar 2; this pattern holds even in the United States, where serogroup O:8/biovar 1B strains were previously predominant. Several CE-marked, FDA-approved multiplex real-time PCR kits now include *Y. enterocolitica* as one of the pathogens detectable in human feces; the precise assay targets are not disclosed. A standard for PCR detection of pathogenic *Y. enterocolitica* and *Y. pseudotuberculosis* in food samples is available from the International Organization for Standardization.

Agglutinating or ELISA antibody titers to specific O-antigen types are used in the retrospective diagnosis of both *Y. enterocolitica* and *Y. pseudotuberculosis* infections. IgA and IgG antibodies persist in patients with reactive arthritis. Serologic cross-reactions between *Y. enterocolitica* serogroup O:9 and *Brucella* are due to the similarity of their lipopolysaccharide structures. Multiple assays are required to cover even the predominant serogroups (*Y. enterocolitica* O:3, O5,27, and O:9; *Y. pseudotuberculosis* O:1a, O:1b, and O:3), and these assays are generally available only in reference laboratories. ELISA and western blot tests for antibodies to Yops, which are expressed by all pathogenic strains of *Y. enterocolitica* and *Y. pseudotuberculosis*, are also available; most of the positivity in these assays probably relates to previous infection with *Y. enterocolitica*.

TREATMENT

Yersiniosis

Most cases of diarrhea caused by enteropathogenic *Yersinia* are self-limiting. Data from clinical trials do not support antimicrobial treatment for adults or children with *Y. enterocolitica* diarrhea. Systemic infections with bacteremia or focal infections outside the gastrointestinal tract generally require antimicrobial therapy. Infants <3 months of age with documented *Y. enterocolitica* infection may require antimicrobial treatment because of the increased likelihood of bacteremia in this age group. *Y. enterocolitica* strains nearly always express β-lactamases. Because of the relative rarity of systemic *Y. enterocolitica* infection, there are no clinical trial data to guide antimicrobial choice or to suggest the optimal dose and duration of therapy. On the basis of retrospective case series and in vitro sensitivity data, fluoroquinolone therapy is effective for bacteremia in adults; for example, ciprofloxacin is given at a typical dose of 500 mg twice daily by mouth or 400 mg twice daily IV for at least 2 weeks (longer if positive blood cultures persist). A third-generation cephalosporin is an alternative—e.g., cefotaxime (typical dose, 6–8 g/d in 3 or 4 divided doses) or ceftriaxone. In children, third-generation cephalosporins are effective; for example, cefotaxime is given to children ≥1 month of age at a typical dose of 75–100 mg/kg per day in 3 or 4 divided doses, with an increase to 150–200 mg/kg per day in severe cases (maximal daily dose, 8–10 g). Amoxicillin and amoxicillin/clavulanate have shown poor efficacy in case series. Trimethoprim-sulfamethoxazole, gentamicin, and imipenem are all active in vitro. *Y. pseudotuberculosis* strains do not express β-lactamase but are intrinsically resistant to polymyxin. Because human infection with *Y. pseudotuberculosis* is less common than that with *Y. enterocolitica*, less case information is available; however, studies in mice suggest that ampicillin is ineffective. Drugs similar to those used against *Y. enterocolitica* should be used. The best results have been obtained with a quinolone.

Some trials of treatment for reactive arthritis (with a large proportion of cases due to *Yersinia*) found that 3 months of oral ciprofloxacin therapy did not affect outcome. One trial in which the same therapy was given specifically for *Y. enterocolitica*–reactive arthritis found that, while outcome indeed was not affected, there was a trend toward faster remission of symptoms in the treated group. Follow-up 4–7 years after initial antibiotic treatment of reactive arthritis (predominantly following *Salmonella* and *Yersinia* infections) demonstrated apparent efficacy in the prevention of chronic arthritis in HLA-B27-positive individuals. A trial showing that azithromycin therapy did not affect outcome in reactive arthritis included cases thought to have followed yersiniosis, although no breakdown of cases was provided.

PREVENTION AND CONTROL

Current control measures are similar to those used against other enteric pathogens like *Salmonella* and *Campylobacter*, which colonize the intestine of food animals. The focus is on safe handling and processing of food. No vaccine is effective in preventing intestinal colonization of food animals by enteropathogenic *Yersinia*. Consumption of food made from raw pork (which is popular in Germany and Belgium) should be discouraged at present because it is not possible to eliminate contamination with the enteropathogenic *Yersinia* strains found worldwide in pigs. Exposure of infants to raw pig intestine during domestic preparation of chitterlings is inadvisable. Modification of abattoir technique in Scandinavian countries from the 1990s onward included the removal of pig intestines in a closed plastic bag; levels of carcass contamination with *Y. enterocolitica* were reduced, but such contamination was not eliminated. Experimental pig herds free of pathogenic *Y. enterocolitica* O:3 (and also of *Salmonella*, *Campylobacter*, *Toxoplasma*, and *Trichinella*) have been established by selective breeding in Norway but remain rare. In the food industry, vigilance is required because of the potential for large outbreaks if small numbers of enteropathogenic yersiniae contaminate any ready-to-eat food whose safe preservation is based on refrigeration before consumption.

The rare phenomenon of contamination of blood for transfusion has proved impossible to eradicate. However, leukodepletion is now practiced in most blood transfusion centers, primarily to prevent nonhemolytic febrile transfusion reactions and alloimmunization against HLA antigens. This measure reduces but does not eliminate the risk of *Yersinia* blood contamination.

Notification of yersiniosis is now obligatory in some countries.

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167 *Bartonella* Infections, Including Cat-Scratch Disease

Michael Giladi, Moshe Ephros

Bartonella species are fastidious, facultative intracellular, slow-growing, gram-negative bacteria that cause a broad spectrum of diseases in humans. This genus includes ~40 distinct species or subspecies, of which at least 16 have been recognized as confirmed or potential human pathogens; *Bartonella bacilliformis*, *Bartonella quintana*, and *Bartonella henselae* are most commonly identified **(Table 167-1)**. Most *Bartonella* species have successfully adapted to survival in specific domestic or wild mammals. Prolonged intraerythrocytic infection in these animals creates a niche where the bacteria are protected from both innate and adaptive immunity and which serves as a reservoir for human infections. *Bartonella* characteristically evades the host immune system by modification of its virulence factors (e.g., lipopolysaccharides or flagella) and by attenuation of the immune response. *B. bacilliformis* and *B. quintana*, which are not zoonotic, are exceptions. Arthropod vectors are often involved. Isolation and characterization of *Bartonella* species are difficult and require special techniques. Clinical presentation generally depends on both the infecting *Bartonella* species and the immune status of the infected individual. *Bartonella* species are susceptible to many antibiotics in vitro; however, clinical responses to therapy and studies in animal models suggest that the minimal inhibitory concentrations of many antimicrobial agents correlate poorly with the drugs' in vivo efficacies in patients with *Bartonella* infections.

CAT-SCRATCH DISEASE

DEFINITION AND ETIOLOGY

Usually a self-limited illness, cat-scratch disease (CSD) has two general clinical presentations. *Typical* CSD, the more common, is characterized by subacute regional lymphadenopathy; *atypical* CSD is the collective designation for numerous extranodal manifestations involving various organs. *B. henselae* is the principal etiologic agent of CSD. Rare cases have been associated with *Afipia felis* and other *Bartonella* species.

EPIDEMIOLOGY

CSD occurs worldwide, favoring warm and humid climates. In temperate climates, incidence peaks during fall and winter; in the tropics, disease occurs year-round. Adults are affected nearly as frequently as children. Intrafamilial clustering is rare, and person-to-person transmission does not occur. Apparently healthy cats constitute the major reservoir of *B. henselae*, and cat fleas (*Ctenocephalides felis*) may be responsible for cat-to-cat transmission. CSD usually follows contact with cats (especially kittens), but other animals (e.g., dogs) have been implicated as possible reservoirs in rare instances. In the United States, the estimated annual disease incidence is ~4–10 cases per 100,000 population. About 5–10% of patients are hospitalized.

PATHOGENESIS

Inoculation of *B. henselae*, possibly via contaminated flea feces, usually results from a cat scratch or bite. Infection of mucous membranes or conjunctivae via droplets or licking may occur as well. With lymphatic drainage to one or more regional lymph nodes in immunocompetent hosts, a T_H1 response can result in necrotizing granulomatous lymphadenitis. Dendritic cells, along with their associated chemokines, play a role in the host inflammatory response and granuloma formation.

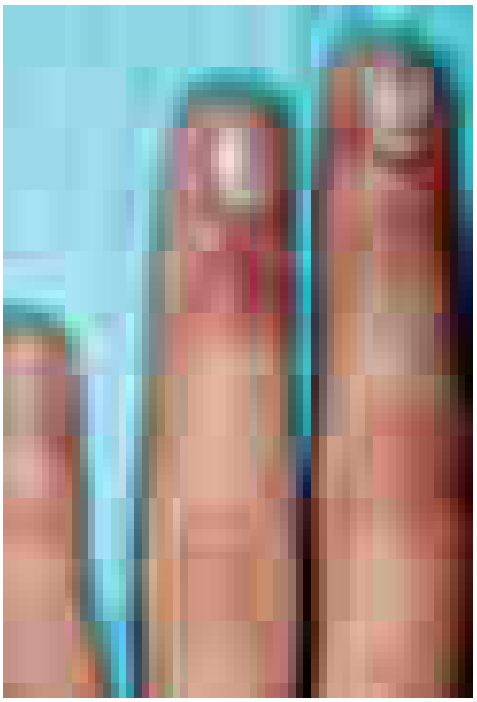
CLINICAL MANIFESTATIONS AND PROGNOSIS

Of patients with CSD, 85–90% have *typical* disease. The primary lesion, a small (0.3- to 1-cm) painless erythematous papule or pustule, develops at the inoculation site within days to 2 weeks in about one-third to two-thirds of patients **(Fig. 167-1*A, B*)**. Lymphadenopathy develops 1–3 weeks or longer after cat contact. The affected lymph node(s) are enlarged and usually painful, sometimes have overlying erythema, and suppurate in 10–15% of cases **(Fig. 167-1*C, D,* and *E*)**. Axillary/epitrochlear nodes are most commonly involved; next in frequency are head/neck nodes and then inguinal/femoral nodes. Approximately 50% of patients have fever, malaise, and anorexia. A smaller proportion experience weight loss and night sweats mimicking the presentation of lymphoma. Fever is usually low-grade but infrequently rises to ≥39°C.

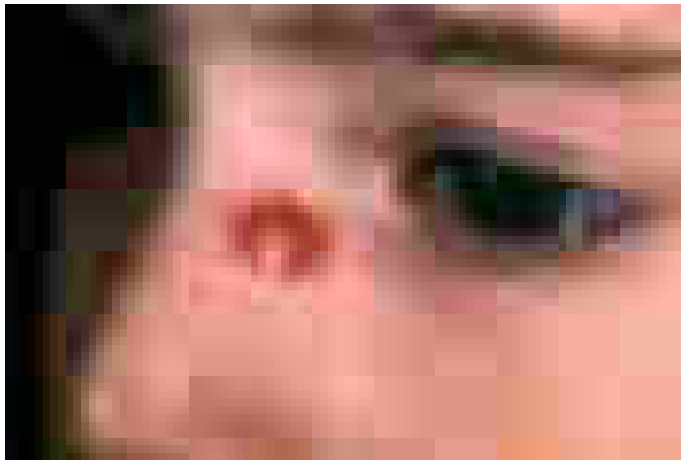
TABLE 167-1 *Bartonella* Species Known or Suspected to Be Human Pathogens

BARTONELLA SPECIES[a]	DISEASE(S)[b]	RESERVOIR HOST(S)[c]	ARTHROPOD VECTOR
B. henselae	Cat-scratch disease, bacillary angiomatosis, bacillary peliosis, bacteremia, endocarditis	Cats, other felines	Cat fleas (*Ctenocephalides felis*): associated with cat-to-cat, but not with cat-to-human, transmission
B. quintana	Trench fever, chronic bacteremia, bacillary angiomatosis, endocarditis	Humans	Human body lice (*Pediculus humanus corporis*)
B. bacilliformis	Carrión's disease	Humans	Sandflies (*Lutzomyia verrucarum*)
B. elizabethae	Endocarditis	Rats, dogs	Unknown
B. grahamii[d]	Lymphadenopathy	Mice, voles	Fleas
B. vinsonii subsp. *arupensis*	Endocarditis, febrile illness	Mice, dogs	Ticks
B. vinsonii subsp. *berkhoffii*	Endocarditis	Domestic dogs, coyotes, gray foxes	Ticks
B. washoensis	Myocarditis, meningitis	Squirrels, possibly other rodents	Fleas
B. alsatica	Endocarditis, lymphadenitis	Rabbits	Fleas
B. koehlerae	Endocarditis	Cats	Unknown
B. clarridgeiae	Possibly cat-scratch disease	Cats	Unknown
B. rochalimae	Bacteremia, fever, splenomegaly	Unknown	Possibly fleas
B. tamiae	Bacteremia, fever, myalgia, rash	Unknown	Unknown
B. melophagi	Various clinical manifestations	Sheep	Sheep keds
B. ancashensis	Verruga peruana	Unknown	Unknown
Candidatus B. mayotimonensis[e]	Endocarditis	Bats	Unknown

[a]Many other *Bartonella* species exist but are not recognized as human pathogens. [b]Animal-associated *Bartonella* species (*B. henselae, B. doshiae, B. schoenbuchensis*, and *B. tribocorum*) were isolated from blood of patients who reported tick bites and chronic symptoms such as fatigue and myalgia. DNA of *B. henselae, B. vinsonii* subsp. *berkhoffii, B. koehlerae*, or *B. melophagi* or co-infection with more than one *Bartonella* species was detected by PCR in blood samples from patients with extensive arthropod and animal exposure who presented with chronic neurologic or neurocognitive syndromes. The causal relationship between bacteremia with these pathogens, tick bites, and clinical manifestations needs to be established. [c]Animals are implicated when existing evidence supports their infection with *Bartonella* species. Data supporting animal-to-human transmission may be lacking. [d]Retinitis may also be associated with *B. grahamii*. [e]*Candidatus* is a taxonomic status for bacteria that cannot be described in sufficient detail to warrant establishment of a novel taxon or cannot be cultured or propagated in culture media. The phylogenetic relatedness of these bacteria has been determined by gene amplification and sequence analysis.

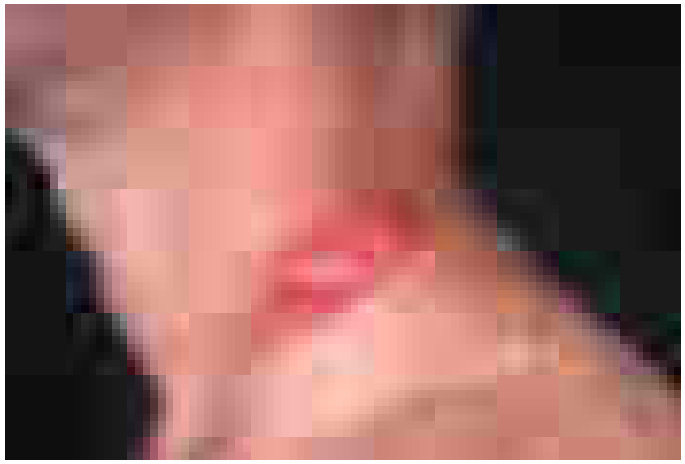


A

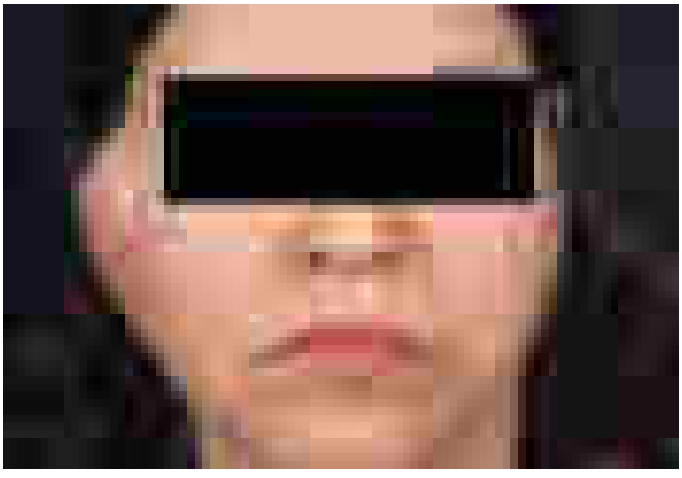


B

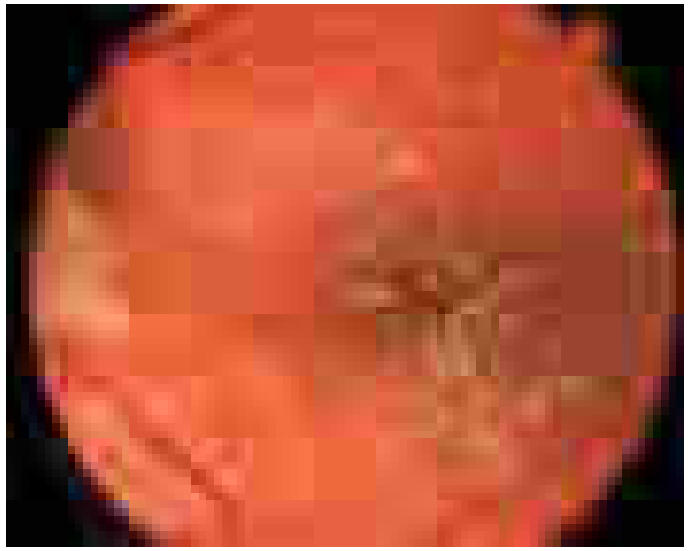
C



D



E



F

FIGURE 167-1 Manifestations of cat-scratch disease. ***A.*** Primary inoculation lesion. Axillary and epitrochlear lymphadenitis appeared 2 weeks later. ***B.*** Primary inoculation lesion. Submental lymphadenitis appeared 10 days later. ***C.*** Axillary lymphadenopathy of 2 weeks' duration. The overlying skin appears normal. ***D.*** Cervical lymphadenopathy of 6 weeks' duration. The overlying skin is red. Thick, odorless pus (12 mL) was aspirated. ***E.*** Preauricular lymphadenopathy. ***F.*** Left-eye neuroretinitis. Note papilledema and stellate macular exudates ("macular star").

Resolution is slow, requiring weeks (for fever, pain, and accompanying signs and symptoms) to months (for node shrinkage).

Atypical CSD occurs in 10–15% of patients as extranodal or complicated disease in the absence or presence of lymphadenopathy. Atypical disease includes Parinaud's oculoglandular syndrome (granulomatous conjunctivitis with ipsilateral preauricular lymphadenitis; Fig. 167-1*E*), granulomatous hepatitis/splenitis, neuroretinitis (often presenting as unilateral deterioration of vision; **Fig. 167-1*F***), and other ophthalmologic manifestations. In addition, neurologic involvement (encephalopathy, seizures, myelitis, radiculitis, cerebellitis, facial and other cranial or peripheral palsies), fever of unknown origin, debilitating myalgia, arthritis or arthralgia (affecting mostly women >20 years old), osteomyelitis (including multifocal disease), tendinitis, neuralgia, and dermatologic manifestations (including erythema nodosum **[see Fig. A1-39]**, sometimes accompanying arthropathy) occur. Other manifestations and syndromes (pneumonitis, pleural effusion, idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, erythema multiforme **[see Fig. A1-24]**, hypercalcemia, glomerulonephritis, myocarditis) have also been associated with CSD. In elderly patients (>60 years old), lymphadenopathy is more often absent but encephalitis and fever of unknown origin are more common than in younger patients. In immunocompetent individuals, CSD—whether typical or atypical—usually resolves without treatment and without sequelae, although some of the ophthalmologic manifestations may occasionally result in moderate to severe vision loss. Lifelong immunity is the rule.

DIAGNOSIS

Routine laboratory tests usually yield normal or nonspecific results. Histopathology initially shows lymphoid hyperplasia and later demonstrates stellate granulomata with necrosis, coalescing microabscesses, and occasional multinucleated giant cells—findings that, although nonspecific, may narrow the differential diagnosis. Serologic testing (immunofluorescence or enzyme immunoassay) is the most commonly used laboratory diagnostic approach, with variable sensitivity and specificity. CSD serodiagnosis is often based on the presence of IgG alone (i.e., in the absence of IgM), and seroconversion may take a few weeks; these two factors may pose difficulties in the interpretation of serologic results. Other tests are of low sensitivity (culture, Warthin-Starry silver staining), of low specificity (cytology, histopathology), or of limited availability in routine diagnostic laboratories (polymerase chain reaction [PCR], immunohistochemistry). PCR of pus aspirated from lymph nodes or the primary inoculation lesion is highly sensitive and specific and is particularly useful for definitive and rapid diagnosis in seronegative patients. PCR of a lymph node biopsy specimen may be less sensitive, perhaps because of sampling error.

APPROACH TO THE PATIENT

Cat-Scratch Disease

A history of cat contact, a primary inoculation lesion, and regional lymphadenopathy—especially axillary/epitrochlear lymphadenopathy—are highly suggestive of CSD. A characteristic clinical course and corroborative laboratory tests make the diagnosis very likely. Conversely, when acute- and convalescent-phase sera are negative (as is the case in 10–20% of CSD patients), when spontaneous regression of lymph node size does not occur, and particularly when constitutional symptoms persist, malignancy must be ruled out. Pyogenic lymphadenitis, mycobacterial infection, brucellosis, syphilis, tularemia, plague, toxoplasmosis, sporotrichosis, and histoplasmosis should also be considered. In clinically suspected CSD in a seronegative individual, fine-needle aspiration may be adequate and PCR can confirm the diagnosis. When data are less supportive of CSD, lymph node biopsy rather than fine-needle aspiration is preferred. In seronegative CSD patients with lymphadenopathy and severe complications (e.g., encephalitis or neuroretinitis), early biopsy is important to establish a specific diagnosis.

TABLE 167-2 Antimicrobial Therapy for Disease Caused by *Bartonella* Species in Adults

DISEASE	ANTIMICROBIAL THERAPY
Typical cat-scratch disease	Not routinely indicated; for patients with extensive lymphadenopathy, consider azithromycin (500 mg PO on day 1, then 250 mg PO once a day for 4 days)
Cat-scratch disease neuroretinitis	Value of systemic antibiotics is controversial, particularly when visual acuity is not significantly compromised. For more severe cases, doxycycline (100 mg PO bid) *plus* rifampin (300 mg PO bid) for 4–6 weeks is given. Consider adding systemic glucocorticoids.
Other atypical cat-scratch disease manifestations[a]	As per neuroretinitis. Treatment duration should be individualized.
Trench fever or chronic bacteremia with *B. quintana*	Gentamicin (3 mg/kg IV once a day for 14 days) *plus* doxycycline (200 mg PO once a day or 100 mg PO bid for 6 weeks)
Suspected *Bartonella* endocarditis	Gentamicin[b] (1 mg/kg IV q8h for ≥14 days) *plus* doxycycline (100 mg PO/IV bid for 6 weeks[c]) *plus* ceftriaxone (2 g IV once a day for 6 weeks)
Confirmed *Bartonella* endocarditis	As for suspected *Bartonella* endocarditis *minus* ceftriaxone
Bacillary angiomatosis	Erythromycin[d] (500 mg PO qid for 3 months) *or* Doxycycline (100 mg PO bid for 3 months)
Bacillary peliosis	Erythromycin[d] (500 mg PO qid for 4 months) *or* Doxycycline (100 mg PO bid for 4 months)
Carrión's disease	
Oroya fever	Chloramphenicol (500 mg PO/IV qid for 14 days) *plus* another antibiotic (β-lactam preferred) *or* Ciprofloxacin (500 mg PO bid for 10 days)
Verruga peruana	Rifampin (10 mg/kg PO once a day, to a maximum of 600 mg, for 14 days) *or* Streptomycin (15–20 mg/kg IM once a day for 10 days)

[a]Data on treatment efficacy for encephalitis and hepatosplenic cat-scratch disease are lacking. Therapy similar to that given for neuroretinitis is reasonable. [b]Some experts recommend gentamicin at 3 mg/kg IV once a day. If gentamicin is contraindicated, rifampin (300 mg PO bid) can be added to doxycycline for documented *Bartonella* endocarditis. [c]Some experts recommend extending oral doxycycline therapy for 3–6 months. [d]Other macrolides are probably effective and may be substituted for erythromycin or doxycycline.

Source: Recommendations are modified from JM Rolain et al: Antimicrob Agents Chemother 48:1921, 2004.

TREATMENT

Cat-Scratch Disease

(Table 167-2) Treatment regimens are based on only minimal data. Suppurative nodes should be drained by large-bore needle aspiration and not by incision and drainage in order to avoid chronic draining tracts. Immunocompromised patients must always be treated with systemic antimicrobials.

PREVENTION

Avoiding cats (especially kittens) and instituting flea control are options for immunocompromised patients and for patients with valvular heart disease.

TRENCH FEVER AND CHRONIC BACTEREMIA

DEFINITION AND ETIOLOGY

Trench fever, also known as *5-day fever* or *quintan fever*, is a febrile illness caused by *B. quintana*. It was first described as an epidemic in

the trenches of World War I; however, recent paleomicrobiologic studies have provided evidence that *B. quintana* has been associated with human infection for 4000 years. This infection recently reemerged as chronic bacteremia seen most often in homeless people, also referred to as *urban* or *contemporary trench fever*.

EPIDEMIOLOGY

In addition to epidemics during World Wars I and II, sporadic outbreaks of trench fever have been reported in many regions of the world. The human body louse has been identified as the vector and humans as the only known reservoir. After a hiatus of several decades during which trench fever was almost forgotten, small clusters of cases of *B. quintana* chronic bacteremia were reported sporadically, primarily from the United States and France, in HIV-uninfected homeless people. Alcoholism and louse infestation were identified as risk factors.

CLINICAL MANIFESTATIONS

The typical incubation period is 15–25 days (range, 3–38 days). "Classical" trench fever, as described in 1919, ranges from a mild febrile illness to a recurrent or protracted and debilitating disease. Onset may be abrupt or preceded by a prodrome of several days. Fever is often periodic, lasting 4–5 days with 5-day (range, 3- to 8-day) intervals between episodes. Other symptoms and signs include headache, back and limb pain, profuse sweating, shivering, myalgia, arthralgia, splenomegaly, a maculopapular rash in occasional cases, and nuchal rigidity in some cases. Untreated, the disease usually lasts 4–6 weeks. Death is rare. The clinical spectrum of *B. quintana* bacteremia in homeless people ranges from asymptomatic infection to a febrile illness with headache, severe leg pain, and thrombocytopenia. Endocarditis sometimes develops.

DIAGNOSIS

Definitive diagnosis requires isolation of *B. quintana* by blood culture. Some patients have positive blood cultures for several weeks. Patients with acute trench fever typically develop significant titers of antibody to *Bartonella*, whereas those with chronic *B. quintana* bacteremia may be seronegative. Patients with high titers of IgG antibodies should be evaluated for endocarditis. In epidemics, trench fever should be differentiated from epidemic louse-borne typhus and relapsing fever, which occur under similar conditions and share many features.

TREATMENT

B. quintana Bacteremia

(Table 167–2) In a small, randomized, placebo-controlled trial involving homeless people with *B. quintana* bacteremia, therapy with gentamicin and doxycycline was superior to administration of placebo in eradicating bacteremia. Treatment of bacteremia is important, even in clinically mild cases, to prevent endocarditis. Optimal therapy for trench fever without documented bacteremia is uncertain.

BARTONELLA ENDOCARDITIS

DEFINITION AND ETIOLOGY

Coxiella burnetii **(Chap. 182)** and *Bartonella* species are the most common pathogens in culture-negative endocarditis **(Chap. 123)**. In France, for example, *Bartonella* species were identified as the etiologic agents in 28% of 348 cases of culture-negative endocarditis. Prevalence, however, varies by geographic location and epidemiologic setting. In addition to *B. quintana* and *B. henselae* (the most common *Bartonella* species implicated in endocarditis, the former more commonly than the latter), other *Bartonella* species have reportedly caused rare cases (Table 167-1).

EPIDEMIOLOGY

Bartonella endocarditis has been reported worldwide. Most patients are adults; more are male than female. Risk factors associated with *B. quintana* endocarditis include homelessness, alcoholism, and body louse infestation; however, individuals with no risk factors have had *Bartonella* endocarditis diagnosed as well. *B. henselae* endocarditis is associated with exposure to cats. Most cases involve native rather than prosthetic valves; the aortic valve accounts for ~60% of cases. Patients with *B. henselae* endocarditis usually have preexisting valvulopathy, whereas *B. quintana* often infects normal valves.

CLINICAL MANIFESTATIONS

Clinical manifestations are usually characteristic of subacute endocarditis of any etiology. However, a substantial number of patients have a prolonged, minimally febrile or even afebrile indolent illness, with mild nonspecific symptoms lasting weeks or months before the diagnosis is made. Initial echocardiography may not show vegetations. Acute, aggressive disease is rare.

DIAGNOSIS

Blood cultures, even with use of special techniques (lysis centrifugation or EDTA-containing tubes), are positive in only ~25% of cases—mostly those caused by *B. quintana* and only rarely those caused by *B. henselae*. Prolonged incubation of cultures (up to 6 weeks) is required. Serologic tests—either immunofluorescence or enzyme immunoassay—usually demonstrate high-titer IgG antibodies to *Bartonella*. Because of cross-antigenicity, routine serology does not distinguish between *B. quintana* and *B. henselae* and may also be low-titer cross-reactive with other pathogens, such as *C. burnetii* and *Chlamydia* species. Identification of *Bartonella* to the species level is usually accomplished by application of PCR and DNA sequencing methods to valve tissue.

TREATMENT

Bartonella Endocarditis

(Table 167-2) For patients with culture-negative endocarditis suspected to be due to *Bartonella* species, empirical treatment consists of gentamicin, doxycycline, and ceftriaxone; the major role of ceftriaxone in this regimen is to adequately treat other potential causes of culture-negative endocarditis, including members of the HACEK group **(Chap. 153)**. Once a diagnosis of *Bartonella* endocarditis has been established, ceftriaxone is discontinued. Aminoglycosides, the only antibiotics known to be bactericidal against *Bartonella*, should be included in the regimen for ≥2 weeks. Indications for valvular surgery are the same as in subacute endocarditis due to other pathogens; however, the proportion of patients who undergo surgery (~60%) is high, probably as a consequence of delayed diagnosis.

BACILLARY ANGIOMATOSIS AND PELIOSIS

DEFINITION AND ETIOLOGY

Bacillary angiomatosis (sometimes called *bacillary epithelioid angiomatosis* or *epithelioid angiomatosis*) is a disease of severely immunocompromised patients, is caused by *B. henselae* or *B. quintana*, and is characterized by neovascular proliferative lesions involving the skin and other organs. Both species cause cutaneous lesions; hepatosplenic lesions are caused only by *B. henselae*, whereas subcutaneous and lytic bone lesions are more frequently associated with *B. quintana*. Bacillary peliosis is a closely related angioproliferative disorder caused by *B. henselae* and involving primarily the liver (peliosis hepatis) but also the spleen and lymph nodes. Bacillary peliosis is characterized by blood-filled cystic structures whose size ranges from microscopic to several millimeters.

EPIDEMIOLOGY

Bacillary angiomatosis and bacillary peliosis occur primarily in HIV-infected persons **(Chap. 197)** with CD4+ T cell counts of <100/μL but also affect other immunosuppressed patients and, in rare instances, immunocompetent patients. The incidence has decreased since the introduction of effective antiretroviral therapy and the routine use of rifabutin and macrolides to prevent *Mycobacterium avium* complex infection in AIDS patients. Contact with cats or cat fleas increases the risk of *B. henselae* infection. Risk factors for *B. quintana* infection are low income, homelessness, and body louse infestation.

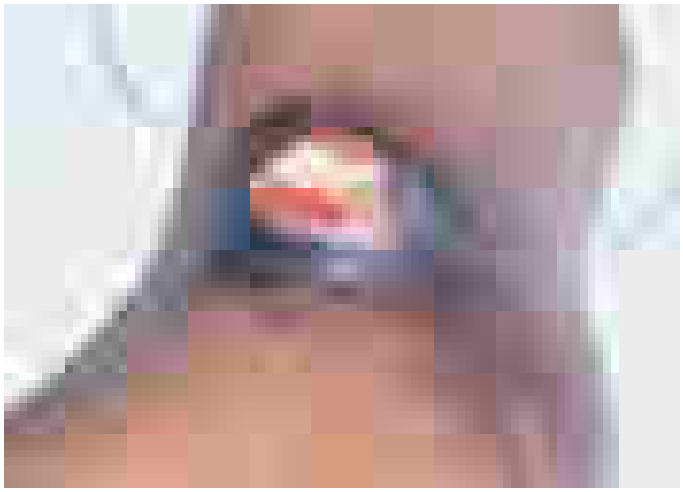


FIGURE 167-2 Nodular lesion of bacillary angiomatosis with superficial ulceration in an AIDS patient with advanced immunodeficiency. *(Reprinted with permission from DH Spach and E Darby: Bartonella Infections, Including Cat-Scratch Disease, in Harrison's Principles of Internal Medicine, 17th ed, AF Fauci et al [eds]. New York, McGraw-Hill, 2008, p 989.)*

CLINICAL MANIFESTATIONS

Bacillary angiomatosis presents most commonly as one or more cutaneous lesions that are not painful and that may be tan, red, or purple in color. Subcutaneous masses or nodules, superficial ulcerated plaques **(Fig. 167-2)**, and verrucous growths are also seen. Nodular forms resemble those seen in fungal or mycobacterial infections. Subcutaneous nodules are often tender. Painful osseous lesions, most often involving long bones, may underlie cutaneous lesions and occasionally develop in their absence. In rare cases, other organs are involved in bacillary angiomatosis. Patients usually have constitutional symptoms, including fever, chills, malaise, headache, anorexia, weight loss, and night sweats. In osseous disease, lytic lesions are generally seen on radiography, and technetium scan shows focal uptake. The differential diagnosis of cutaneous bacillary angiomatosis includes Kaposi's sarcoma, pyogenic granuloma, subcutaneous tumors, and verruga peruana. In bacillary peliosis, hypodense hepatic areas are usually evident on imaging. In patients with advanced immunodeficiency, *B. henselae* and *B. quintana* are important causes of fever of unknown origin. Intermittent bacteremia with positive blood cultures can occur with or without endocarditis.

PATHOLOGY

Bacillary angiomatosis consists of lobular proliferations of small blood vessels lined by enlarged endothelial cells interspersed with mixed infiltrates of neutrophils and lymphocytes, with predominance of the former. Histologic examination of organs with bacillary peliosis reveals small blood-filled cystic lesions partially lined by endothelial cells that can be several millimeters in size. Peliotic lesions are surrounded by fibromyxoid stroma containing inflammatory cells, dilated capillaries, and clumps of granular material. Warthin-Starry silver staining of bacillary angiomatosis and peliosis lesions reveals clusters of bacilli. Cultures are usually negative.

DIAGNOSIS

Bacillary angiomatosis and bacillary peliosis are diagnosed on histologic grounds. Blood cultures may be positive.

TREATMENT

Bacillary Angiomatosis and Peliosis

(Table 167-2) Prolonged therapy with a macrolide or doxycycline is recommended for both bacillary angiomatosis and bacillary peliosis.

PREVENTION

Reasonable strategies for HIV-infected persons consist of control of cat-flea infestation and avoidance of cat scratches (for prevention of *B. henselae*) and avoidance and treatment of body louse infestation (for prevention of *B. quintana*). Primary prophylaxis is not recommended, but suppressive therapy with a macrolide or doxycycline is indicated in HIV-infected patients with bacillary angiomatosis or bacillary peliosis until CD4+ T cell counts are >200/μL. Relapse may necessitate lifelong suppressive therapy in individual cases.

CARRIÓN'S DISEASE (OROYA FEVER AND VERRUGA PERUANA)

DEFINITION AND ETIOLOGY

Carrión's disease is a biphasic disease caused by *B. bacilliformis*. *Oroya fever* is the initial, bacteremic, systemic form, and *verruga peruana* is its late-onset, eruptive manifestation.

EPIDEMIOLOGY AND PREVENTION

Infection is endemic to the geographically restricted Andes valleys of Peru, Ecuador, and Colombia (~500–3200 m above sea level). Sporadic epidemics occur. The disease is transmitted by the phlebotomine sandfly *Lutzomyia verrucarum*. Humans are the only known reservoir of *B. bacilliformis*. Sandfly control measures (e.g., insecticides) and personal protection measures (e.g., repellents, screening, bed nets) may decrease the risk of infection.

PATHOGENESIS

After inoculation by the sandfly, bacteria invade the blood vessel endothelium and proliferate; the reticuloendothelial system and various organs may also be involved. Upon reentry into blood vessels, *B. bacilliformis* invades, replicates, and ultimately destroys erythrocytes, with consequent massive hemolysis and sudden, severe anemia. Microvascular thrombosis results in end-organ ischemia. Survivors sometimes develop cutaneous hemangiomatous lesions characterized by various inflammatory cells, endothelial proliferation, and the presence of *B. bacilliformis*.

CLINICAL MANIFESTATIONS

The incubation period is 3 weeks (range, 2–14 weeks). Oroya fever may present as a nonspecific bacteremic febrile illness without anemia or as an acute, severe hemolytic anemia with hepatomegaly and jaundice of rapid onset leading to vascular collapse and clouded sensorium. Myalgia, arthralgia, lymphadenopathy, and abdominal pain may develop. Temperature is elevated but not extremely so; high fever may suggest intercurrent infection. Subclinical asymptomatic infection also occurs. In verruga peruana, red, hemangioma-like, cutaneous vascular lesions of various sizes appear either weeks to months after systemic illness or with no previous suggestive history. These lesions persist for months up to 1 year. Mucosal and internal lesions may also develop.

DIAGNOSIS AND APPROACH TO THE PATIENT

Systemic illness (with or without anemia) or the development of cutaneous lesions in a person who has been to an endemic area raises the possibility of *B. bacilliformis* infection. Severe anemia with exuberant reticulocytosis—and sometimes thrombocytopenia—can occur. In systemic illness, Giemsa-stained blood films may show typical intraerythrocytic bacilli, and blood and bone marrow cultures are positive. Serologic assays may be helpful. Biopsy may be required to confirm the diagnosis of verruga peruana. Differential diagnosis includes the spectrum of coendemic systemic febrile illnesses (e.g., typhoid fever, malaria, brucellosis) as well as diseases producing cutaneous vascular lesions (e.g., hemangiomata, bacillary angiomatosis, Kaposi's sarcoma).

TREATMENT

Carrión's Disease

(Table 167-2) Antibiotic therapy for systemic *B. bacilliformis* infection usually results in rapid defervescence. Additional antibiotic

treatment of intercurrent infection (particularly salmonellosis) is often required. Blood transfusion may be necessary. Treatment of verruga peruana usually is not required, although large lesions or those interfering with function may require excision. Patients with numerous lesions, especially lesions that have been present for only a short period, may respond well to antibiotic therapy.

COMPLICATIONS AND PROGNOSIS

Mortality rates associated with Oroya fever have been reported to be as high as 40% without treatment but are considerably lower (~10%) with treatment. Complications such as bacterial superinfection and neurologic and cardiac manifestations occur frequently. Generalized massive edema (anasarca) and petechiae are associated with poor outcome. Permanent immunity usually develops.

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168 Donovanosis

Nigel O'Farrell

Donovanosis is a chronic, progressive bacterial infection that usually involves the genital region. The condition is generally regarded as a sexually transmitted infection of low infectivity. This infection has been known by many other names, the most common being *granuloma inguinale*.

ETIOLOGY

The causative organism has been reclassified as *Klebsiella granulomatis comb nov* on the basis of phylogenetic analysis, although there is ongoing debate about this decision. Some authorities consider the original nomenclature (*Calymmatobacterium granulomatis*) to be more appropriate in light of analysis of 16S rRNA gene sequences.

Donovanosis was first described in Calcutta in 1882, and the causative organism was recognized by Charles Donovan in Madras in 1905. He identified the characteristic Donovan bodies, measuring 1.5 × 0.7 µm, in macrophages and the stratum malpighii. The organism was not reproducibly cultured until the mid-1990s, when its isolation in peripheral-blood monocytes and human epithelial cell lines was reported.

EPIDEMIOLOGY

Donovanosis has an unusual geographic distribution that includes Papua New Guinea, parts of southern Africa, India, the Caribbean, French Guyana, Brazil, and Aboriginal communities in Australia. In Australia, donovanosis has been almost entirely eliminated through a sustained program backed by strong political commitment and resources at the primary health care level. Although few cases are now reported in the United States, donovanosis was once prevalent in this country, with 5000–10,000 cases recorded in 1947. The largest epidemic recorded was in Dutch South Guinea, where 10,000 cases were identified in a population of 15,000 (the marind-anim people) between 1922 and 1952.

Donovanosis is associated with poor hygiene and is more common in lower socioeconomic groups than in those who are better off and in men than in women. Infection in sexual partners of index cases occurs to a limited extent. Donovanosis is a risk factor for HIV infection **(Chap. 197)**.

Globally, the incidence of donovanosis has decreased significantly in recent times. This decline probably reflects a greater focus on effective management of genital ulcers because of their role in facilitating HIV transmission.

CLINICAL FEATURES

A lesion starts as a papule or subcutaneous nodule that later ulcerates after trauma. The incubation period is uncertain, but experimental infections in humans indicate a duration of ~50 days. Four types of lesions have been described: (1) the classic ulcerogranulomatous lesion **(Fig. 168-1)**, a beefy red ulcer that bleeds readily when touched; (2) a hypertrophic or verrucous ulcer with a raised irregular edge; (3) a necrotic, offensive-smelling ulcer causing tissue destruction; and (4) a sclerotic or cicatricial lesion with fibrous and scar tissue.

The genitals are affected in 90% of patients and the inguinal region in 10%. The most common sites of infection are the prepuce, coronal sulcus, frenum, and glans in men and the labia minora and fourchette in women. Cervical lesions may mimic cervical carcinoma. In men, lesions are associated with lack of circumcision. Lymphadenitis is uncommon. Extragenital lesions occur in 6% of cases and may involve the lip, gums, cheek, palate, pharynx, larynx, and chest. Hematogenous spread with involvement of liver and bone has been reported. During pregnancy, lesions tend to develop more quickly and respond more slowly to treatment. Polyarthritis and osteomyelitis are rare complications. In newborn infants, donovanosis may present with ear infection. Cases in children have been attributed to sitting on the laps of infected adults. As the incidence of donovanosis has decreased, the number of unusual case reports has appeared to be increasing.

Complications include neoplastic changes, pseudoelephantiasis, and stenosis of the urethra, vagina, or anus.

DIAGNOSIS

A clinical diagnosis of donovanosis made by an experienced practitioner on the basis of the lesion's appearance usually has a high positive predictive value. The diagnosis is confirmed by microscopic identification of Donovan bodies **(Fig. 168-2)** in tissue smears. Preparation of a good-quality smear is important. If donovanosis is suspected on clinical grounds, the smear for Donovan bodies should be taken before swab samples are collected to be tested for other causes of genital ulceration so that enough material can be collected from the ulcer.

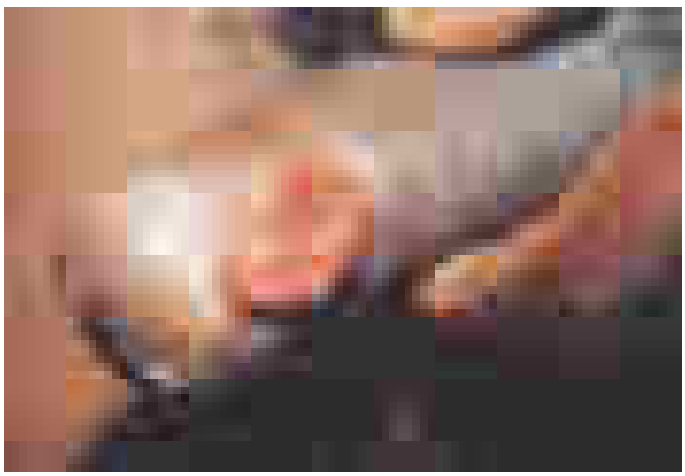

FIGURE 168-1 Ulcerogranulomatous penile lesion of donovanosis, with some hypertrophic features.

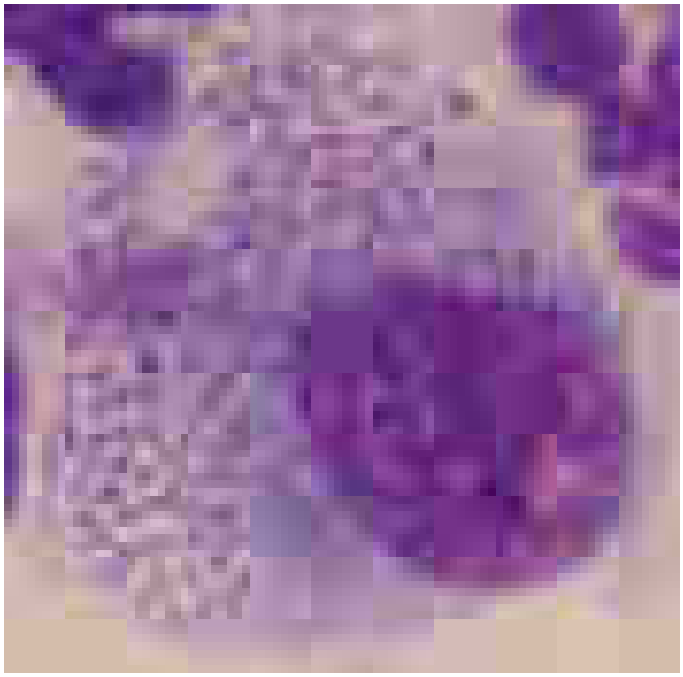

FIGURE 168-2 Pund cell stained by rapid Giemsa (RapiDiff) technique. Numerous Donovan bodies are visible.

A swab should be rolled firmly over an ulcer previously cleaned with a dry swab to remove debris. Smears can be examined in a clinical setting by direct microscopy with a rapid Giemsa or Wright's stain. Alternatively, a piece of granulation tissue crushed and spread between two slides can be used. Donovan bodies can be seen in large, mononuclear (Pund) cells as gram-negative intracytoplasmic cysts filled with deeply staining bodies that may have a safety-pin appearance. These cysts eventually rupture and release the infective organisms. Histologic changes include chronic inflammation with infiltration of plasma cells and neutrophils. Epithelial changes include ulceration, microabscesses, and elongation of rete ridges.

A diagnostic polymerase chain reaction (PCR) test was based on the observation that two unique base changes in the *phoE* gene eliminate Hae111 restriction sites, enabling differentiation of *K. granulomatis comb nov* from related *Klebsiella* species. PCR analysis with a colorimetric detection system can now be used in routine diagnostic laboratories. A genital ulcer multiplex PCR that includes *K. granulomatis* has been developed. Serologic tests are only poorly specific and are not currently used.

The differential diagnosis of donovanosis includes primary syphilitic chancres, secondary syphilis (condylomata lata), chancroid, lymphogranuloma venereum, genital herpes, neoplasm, and amebiasis. Mixed infections are common. Histologic appearances should be distinguished from those of rhinoscleroma, leishmaniasis, and histoplasmosis.

TREATMENT

Donovanosis

Many patients with donovanosis present quite late with extensive ulceration. They may be embarrassed and have low self-esteem related to their disease. Reassurance that they have a treatable condition is important, as are the administration of antibiotics and the monitoring of patients for an adequate interval (see below). Epidemiologic treatment of sexual partners and advice about how to improve genital hygiene are recommended.

The recommended drug regimens for donovanosis are shown in Table 168-1. Gentamicin can be added if the response is slow. Ceftriaxone, chloramphenicol, and norfloxacin are also effective. Patients treated for 14 days should be monitored until lesions have healed completely. Those treated with azithromycin probably do not need such rigorous follow-up.

Surgery may be indicated for very advanced lesions.

TABLE 168-1 Effective Antibiotics for the Treatment of Donovanosis

ANTIBIOTIC	ORAL DOSE
Azithromycin	1 g on day 1, then 500 mg daily for 7 days or 1 g weekly for 4 weeks
Trimethoprim-sulfamethoxazole	960 mg bid for 14 days
Doxycycline	100 mg bid for 14 days
Erythromycin	500 mg qid for 14 days (in pregnant women)
Tetracycline	500 mg qid for 14 days

CONTROL AND PREVENTION

Donovanosis is probably the cause of genital ulceration that is most readily recognizable clinically. Donovanosis is now limited to a few specific locations, and its global eradication is a distinct possibility.

FURTHER READING

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Section 7 Miscellaneous Bacterial Infections

169 Nocardiosis

Gregory A. Filice

Nocardiosis results from infection with bacteria in the genus *Nocardia*, saprophytic aerobic actinomycetes that commonly reside in soil worldwide and contribute to the decay of organic matter. Nocardiae are relatively inactive in standard biochemical tests, and speciation with traditional biochemical methods is difficult. Since the year 2000, molecular phylogenetic techniques, primarily based on 16S rRNA gene sequences, have identified more than 100 *Nocardia* species, many of which are implicated in human disease.

In the past, the majority of isolates associated with pneumonia and systemic disease were identified biochemically as *Nocardia asteroides*, but the lineage of the type strain was muddled and most human isolates in fact belong to other species. Nine species or species complexes are commonly associated with human disease (Table 169-1). Most systemic disease involves *N. cyriacigeorgica*, *N. farcinica*, *N. pseudobrasiliensis*, and species in the *N. transvalensis* and *N. nova* complexes. *N. brasiliensis* is usually associated with disease limited to the skin. Actinomycetoma—an indolent, slowly progressive disease of skin and underlying tissues with nodular swellings and draining sinuses—is often associated with *N. brasiliensis*, *N. otitidiscaviarum*, *N. transvalensis* complex strains, or other actinomycetes. *N. asteroides* sensu stricto is rarely associated with human disease. However, most clinical laboratories cannot speciate isolates accurately and may identify them simply as *N. asteroides* or *Nocardia* species.

EPIDEMIOLOGY

Pulmonary and/or systemic nocardiosis occurs worldwide. The annual incidence, estimated on three continents (North America, Europe, and Australia), is ~0.375 case per 100,000 persons and may be increasing. There is some geographic variation in species frequencies; for example, *N. asiatica* infections and

TABLE 169-1 *Nocardia* Species Most Commonly Associated with Human Disease and Their In Vitro Susceptibility Patterns

SPECIES	SUSCEPTIBLE TO[a]	RESISTANT TO[b]
N. abscessus	Amikacin, amoxicillin/clavulanate, ampicillin, ceftriaxone, gentamicin, linezolid, minocycline, tigecycline, tobramycin, TMP-SMX	Ciprofloxacin, clarithromycin (v), imipenem (v), moxifloxacin
N. brevicatena/paucivorans complex (*N. brevicatena*, *N. paucivorans*, *N. carnea*, others)	Amikacin, ampicillin, ceftriaxone, ciprofloxacin, clarithromycin (v), gentamicin, imipenem, linezolid, minocycline (v), moxifloxacin, tigecycline, tobramycin, TMP-SMX	Amoxicillin/clavulanate (v)
N. nova complex (*N. nova*, *N. veterana*, *N. africana*, *N. kruczakiae*, *N. elegans*, others)	Amikacin, ampicillin (v), ceftriaxone (v), clarithromycin, gentamicin (v), imipenem, linezolid, tigecycline (v), TMP-SMX	Amoxicillin/clavulanate, ciprofloxacin, minocycline, moxifloxacin, tobramycin
N. transvalensis complex (*N. blacklockiae*, *N. wallacei*, others)	Ceftriaxone (v), ciprofloxacin (v), linezolid, moxifloxacin, TMP-SMX (v)	Amikacin (v), amoxicillin/clavulanate (v), ampicillin, clarithromycin, gentamicin, imipenem, minocycline (v), tobramycin
N. farcinica	Amikacin, amoxicillin/clavulanate (v), linezolid, moxifloxacin (v), TMP-SMX	Ampicillin, ceftriaxone, ciprofloxacin (v), clarithromycin, gentamicin, imipenem (v), minocycline, tigecycline (v), tobramycin
N. cyriacigeorgica	Amikacin, ceftriaxone, gentamicin, linezolid, tigecycline, tobramycin, TMP-SMX	Amoxicillin/clavulanate, ampicillin, ciprofloxacin, clarithromycin, imipenem (v), minocycline, moxifloxacin
N. brasiliensis	Amikacin, amoxicillin/clavulanate, linezolid, tigecycline, tobramycin, TMP-SMX	Ampicillin, ceftriaxone (v), ciprofloxacin, clarithromycin, imipenem, minocycline (v), moxifloxacin
N. pseudobrasiliensis	Amikacin (v), ciprofloxacin, clarithromycin, linezolid, tobramycin, TMP-SMX (v)	Amoxicillin/clavulanate, ampicillin, ceftriaxone, imipenem, minocycline
N. otitidiscaviarum complex	Amikacin, gentamicin (v), linezolid, tobramycin (v), TMP-SMX	Amoxicillin/clavulanate, ampicillin, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, minocycline (v), moxifloxacin (v)

[a]From 85 to 100% of isolates are susceptible unless the drug name is followed by (v), in which case 50–84% are susceptible. [b]From 0 to 15% of isolates are susceptible unless the drug name is followed by (v), in which case 16–49% are susceptible.

Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole; v, variable.

Source: Adapted from multiple sources.

N. beijingensis infections appear to be more commonly involved in cases from eastern Asia. However, exact species prevalences are difficult to determine precisely since nocardial infections are not reportable and most publications consist of case reports or case series.

Actinomycetoma occurs mainly in tropical and subtropical regions. Most cases are reported from Sudan, Mexico, and India. The most important risk factors are lower socioeconomic status and frequent contact with soil or vegetable matter; accordingly, many patients are laborers.

Pulmonary and/or systemic nocardiosis is more common among adults than among children and more common among males than among females. Nearly all cases are sporadic, but outbreaks have been associated with contamination of the hospital environment, cosmetic procedures, and parenteral illicit drug use. Person-to-person spread is not well documented. There is no known seasonality. In regions of the world where tuberculosis is relatively common, nocardiosis is diagnosed in 1–5% of patients in whom pulmonary tuberculosis is suspected, and tuberculosis and nocardiosis can occur in the same patient.

The majority of cases of pulmonary or disseminated disease occur in people with a host defense defect. Most have deficient cell-mediated immunity, especially that associated with lymphoma, transplantation, glucocorticoid therapy, or AIDS. The incidence is ~140-fold greater among patients with AIDS and ~340-fold greater among bone marrow transplant recipients than in general populations. In AIDS, nocardiosis usually affects persons with <250 CD4+ T lymphocytes/μL. Nocardiosis has also been associated with pulmonary alveolar proteinosis, tuberculosis and other mycobacterial diseases, chronic granulomatous disease, interleukin 12 deficiency, and autoantibodies to granulocyte-macrophage colony-stimulating factor (GM-CSF). Any child with nocardiosis and no known cause of immunosuppression should undergo tests to determine the adequacy of the phagocytic respiratory burst. Many cases have been associated with newer immunomodulating drugs—initially with tumor necrosis factor inhibitors and subsequently with a much broader array of these agents. *Nocardia* is frequently isolated from respiratory secretions of patients with cystic fibrosis and may be associated with deterioration of lung function, but this association has not been convincingly established.

PATHOLOGY AND PATHOGENESIS

Pneumonia and disseminated disease are both thought to follow inhalation of fragmented bacterial mycelia. The characteristic histologic feature of nocardiosis is an abscess with extensive neutrophil infiltration and prominent necrosis. Granulation tissue usually surrounds the lesions, but extensive fibrosis or encapsulation is uncommon.

Actinomycetoma is characterized by suppurative inflammation with sinus tract formation. Granules—microcolonies composed of dense masses of bacterial filaments extending radially from a central core—are occasionally observed in histologic preparations. The granules are frequently found in discharges from lesions of actinomycetoma but almost never in discharges from lesions in other forms of nocardiosis.

Nocardiae have evolved a number of properties that enable them to survive within phagocytes, including neutralization of oxidants, prevention of phagosome–lysosome fusion, and prevention of phagosome acidification. Neutrophils phagocytose the organisms and limit their growth but do not kill them efficiently. Cell-mediated immunity is important for definitive control and elimination of nocardiae. Nocardiae stimulate the production of GM-CSF in phagocytes in vitro, and nocardial infection has recently been observed in several patients with autoantibodies to GM-CSF. Antibodies to GM-CSF have been found in the majority of patients with alveolar proteinosis and appear to be central to the pathogenesis of this disease. These antibodies may explain the long-standing association of nocardiosis and alveolar proteinosis.

CLINICAL MANIFESTATIONS

Respiratory Tract Disease Pneumonia, the most common form of nocardial disease in the respiratory tract, is typically subacute; symptoms have usually been present for days or weeks at presentation. The onset is occasionally more acute in immunosuppressed patients. Cough is prominent and produces small amounts of thick, purulent sputum that is not malodorous. Fever, anorexia, weight loss, and malaise are common; dyspnea, pleuritic pain, and hemoptysis are less common. Remissions and exacerbations over several weeks are frequent. Roentgenographic patterns vary, but some are highly suggestive of nocardial pneumonia. Infiltrates vary in size and are typically dense. Single or multiple nodules are common **(Figs. 169-1 and 169-2)**, sometimes suggesting tumors or metastases. Infiltrates and nodules tend to cavitate (Fig. 169-2). Empyema is present in one-quarter of cases.

Nocardiosis may spread directly from the lungs to adjacent tissues. Pericarditis, mediastinitis, and the superior vena cava syndrome have all been reported. Nocardial laryngitis, tracheitis, bronchitis, and sinusitis are much less common than pneumonia. In the major airways, disease often presents as a nodular or granulomatous mass. Nocardiae are sometimes isolated from respiratory secretions of persons without

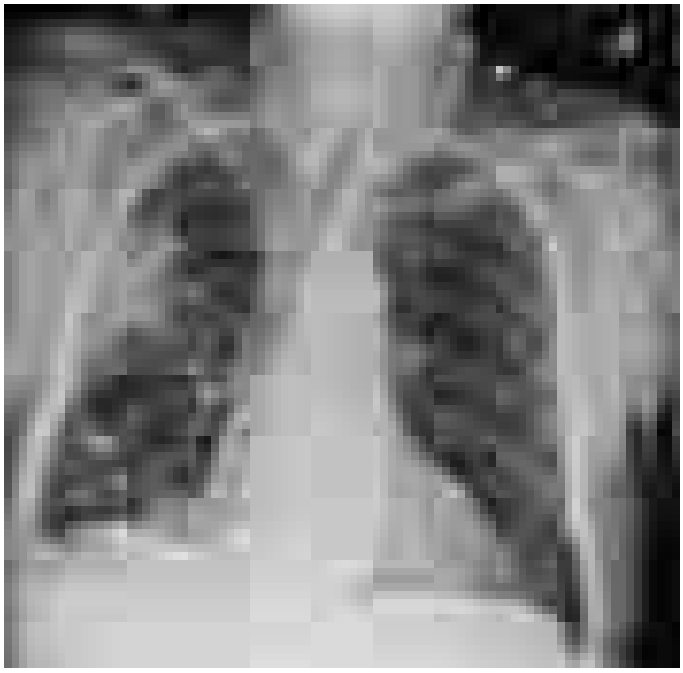

FIGURE 169-1 Nocardial pneumonia. A dense infiltrate with a possible cavity and several nodules are apparent in the right lung.

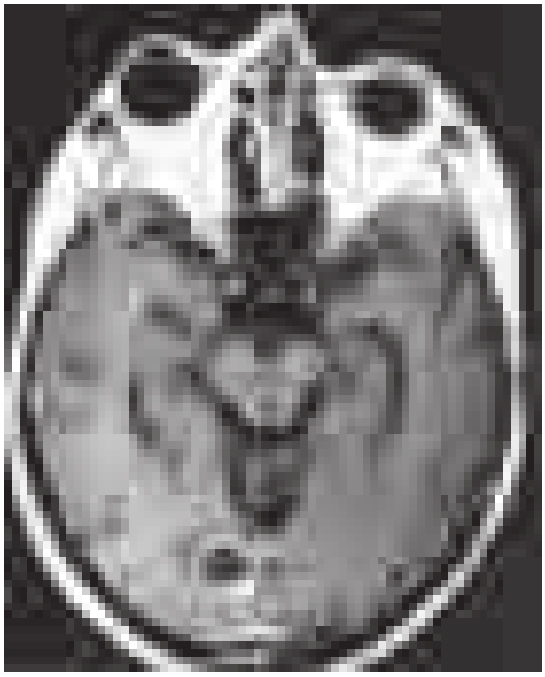

FIGURE 169-3 Nocardial abscesses in the right occipital lobe.

apparent nocardial disease, usually individuals who have underlying lung or airway abnormalities.

Extrapulmonary Disease In half of all cases of pulmonary nocardiosis, disease appears outside the lungs. In one-fifth of cases of disseminated disease, lung disease is not apparent. The most common site of dissemination is the brain. Other common sites include the skin and supporting structures, kidneys, bones, muscles, and eyes, but almost any organ can be involved. Peritonitis has been reported in patients undergoing peritoneal dialysis. Nocardiae have been recovered from blood in a few cases of pneumonia, disseminated disease, or central venous catheter infection. Nocardial endocarditis occurs rarely and can affect either native or prosthetic valves.

The typical manifestation of extrapulmonary dissemination is a subacute abscess. A minority of abscesses outside the lungs or central nervous system (CNS) form fistulas and discharge small amounts of pus. In CNS infections, brain abscesses are usually supratentorial, are often multiloculated, and may be single or multiple **(Fig. 169-3)**. Cases in the posterior fossa and spinal cord have been reported, but they are less common. Brain abscesses tend to burrow into the ventricles or extend out into the subarachnoid space. The symptoms and signs are somewhat more indolent than those of other types of bacterial brain abscess. Meningitis is uncommon and is usually due to spread from a nearby brain abscess. Nocardiae are not easily recovered from cerebrospinal fluid (CSF).

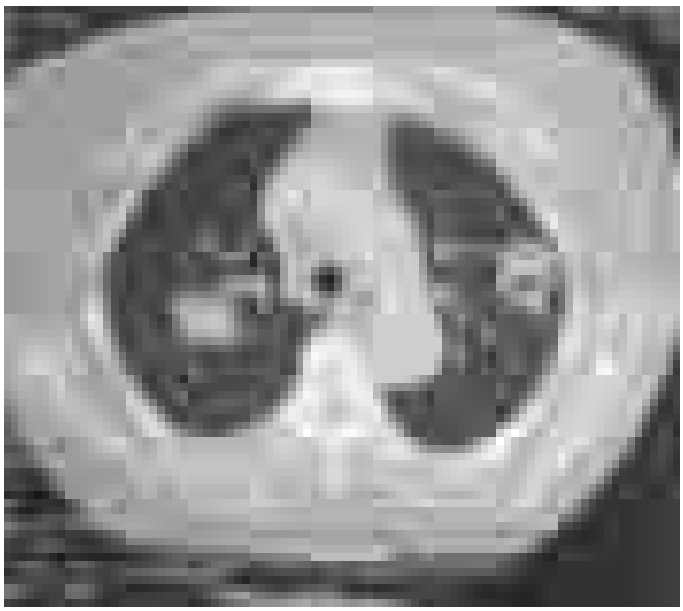

FIGURE 169-2 Nocardial pneumonia. A computed tomography scan shows bilateral nodules, with cavitation in the nodule in the left lung.

Disease Following Transcutaneous Inoculation Disease that follows transcutaneous nocardial inoculation usually takes one of three forms: cellulitis, lymphocutaneous syndrome, or actinomycetoma.

Cellulitis generally begins 1–3 weeks after a recognized breach of the skin, often with soil contamination. Subacute cellulitis, with pain, swelling, erythema, and warmth, develops over days to weeks. The lesions are usually firm and not fluctuant. Disease may progress to involve underlying muscles, tendons, bones, or joints. Dissemination is rare. *N. brasiliensis* and species in the *N. otitidiscaviarum* complex are most common in cellulitis cases.

Lymphocutaneous disease usually begins as a pyodermatous nodule at the site of inoculation, with central ulceration and purulent or honey-colored drainage. Subcutaneous nodules often appear along lymphatics that drain the primary lesion. Most cases of nocardial lymphocutaneous syndrome are associated with *N. brasiliensis*. Similar disease occurs with other pathogens, most notably *Sporothrix schenckii* **(Chap. 214)** and *Mycobacterium marinum* **(Chap. 175)**.

Actinomycetoma usually begins with a nodular swelling, sometimes at a site of local trauma. Lesions **(Fig. 169-4*A*)** typically develop on the feet or hands but may involve the posterior part of the neck, the upper back, the head, and other sites. The nodule eventually breaks down, and a fistula appears, typically followed by others. The fistulas tend to come and go, with new ones forming as old ones disappear. The discharge is serous or purulent, may be bloody, and often contains 0.1- to 2-mm white granules consisting of masses of mycelia **(Figs. 169-4*C* and 169-4*D*)**. The lesions spread slowly along fascial planes to involve adjacent areas of skin, subcutaneous tissue, and bone. Over months or years, there may be extensive deformation of the affected part. Lesions involving soft tissues are only mildly painful; those affecting bones or joints are more so **(Fig. 169-4*B*)**. Systemic symptoms are absent or minimal. Infection rarely disseminates from actinomycetoma, and lesions on the hands and feet usually cause only local disability. Lesions on the head, neck, and trunk can invade locally to involve deep organs, with consequent severe disability or death.

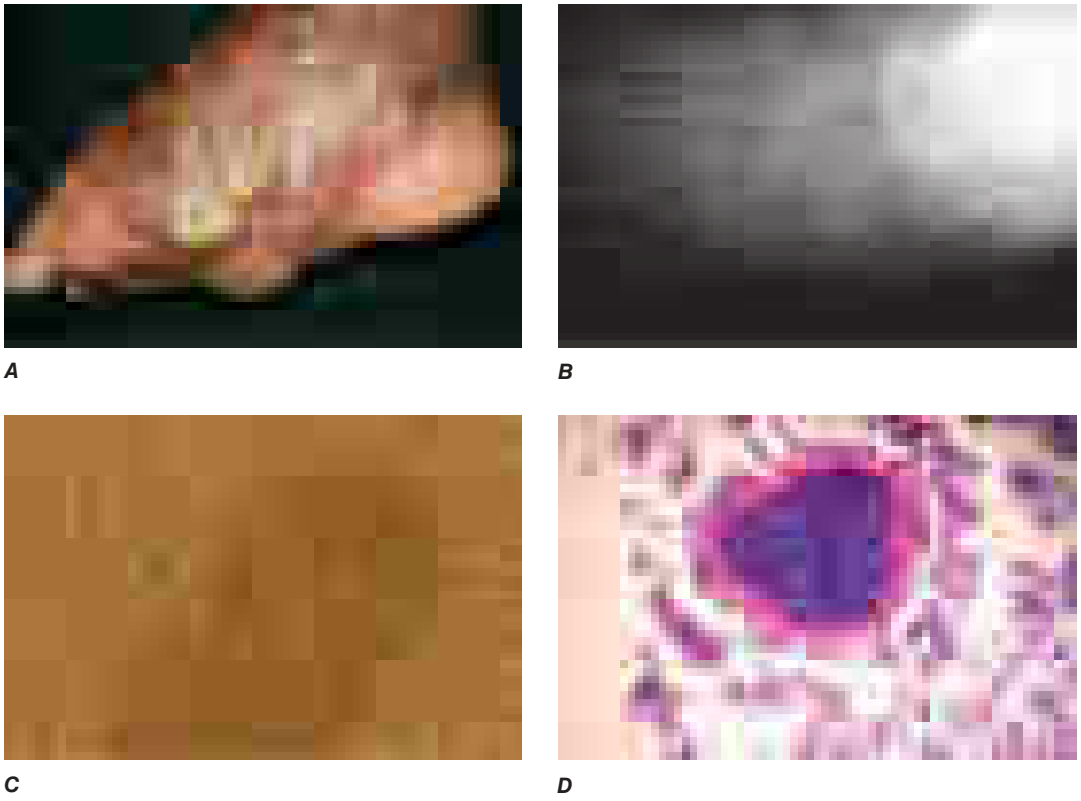

FIGURE 169-4 ***Nocardia brasiliensis* mycetoma. *A.*** Draining sinuses and giant white grains with a seropurulent discharge. ***B.*** Radiography of the foot showing marked soft tissue enlargement and bony lytic lesions. ***C.*** Direct microscopy of grains stained with Lugol's iodine (×40). ***D.*** Periodic acid–Schiff stain of skin biopsy (×40). *(Images provided by Roberto Arenas and Mahreen Ameen, St. John's Institute of Dermatology, Guy's & St Thomas' NHS Trust, London, UK. Reprinted from R Arenas, M Ameen: Lancet Infect Dis 10:66, 2010, with permission from Elsevier.)*

Eye Infections Nocardia species are uncommon causes of subacute keratitis, usually following eye trauma. Nocardial endophthalmitis can develop after eye surgery. In one series, nocardiae accounted for more than half of culture-proved cases of endophthalmitis after cataract surgery. Endophthalmitis can also occur during disseminated disease. Nocardial infection of lachrymal glands has been reported.

DIAGNOSIS

The first step in diagnosis is examination of sputum or pus for crooked, branching, beaded, gram-positive filaments 1 µm wide and up to 50 µm long **(Fig. 169-5)**. Most nocardiae are acid-fast in direct smears if a weak acid is used for decolorization (e.g., in the modified Kinyoun, Ziehl-Neelsen, and Fite-Faraco methods). The organisms often take up silver stains. Recovery from specimens containing a mixed flora can be improved with selective media (colistin–nalidixic acid agar, modified Thayer-Martin agar, or buffered charcoal–yeast extract agar). Nocardiae grow well on most fungal and mycobacterial media, but procedures used for decontamination of specimens for mycobacterial culture can kill nocardiae and should not be used when nocardiae are suspected.

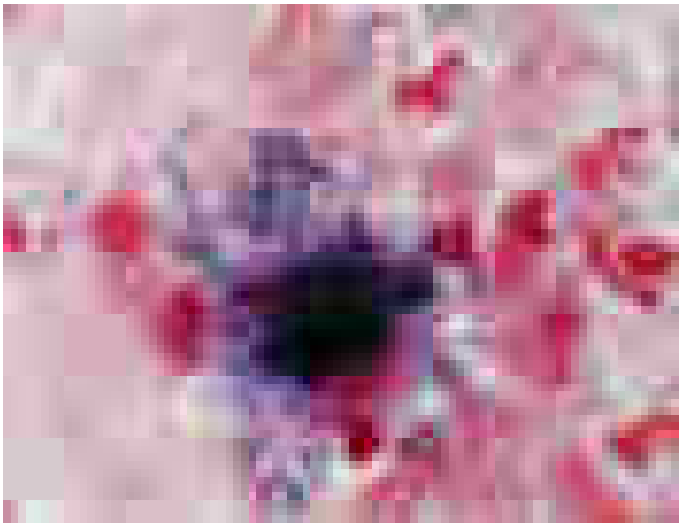

FIGURE 169-5 **Gram-stained sputum** from a patient with nocardial pneumonia. *(Image provided by Charles Cartwright and Susan Nelson, Hennepin County Medical Center, Minneapolis, MN.)*

Nocardiae grow relatively slowly; colonies may take up to 2 weeks to appear and may not develop their characteristic appearance—white, yellow, or orange, with aerial mycelia and delicate, dichotomously branched substrate mycelia—for up to 4 weeks. Several blood culture systems support nocardial growth, although nocardiae may not be detected for up to 2 weeks. The growth of nocardiae is so different from that of more common pathogens that the laboratory should be alerted when nocardiosis is suspected in order to maximize the likelihood of isolation.

In nocardial pneumonia, sputum smears are often negative. Unless the diagnosis can be made in smear-negative cases by sampling lesions in more accessible sites, bronchoscopy or lung aspiration is usually necessary. To evaluate the possibility of dissemination in patients with nocardial pneumonia, a careful history should be obtained and a thorough physical examination performed. Suggestive symptoms or signs should be pursued with further diagnostic tests. Some authorities recommend brain imaging in all cases of pulmonary or disseminated disease. When clinically indicated, CSF or urine should be concentrated and then cultured. Actinomycetoma, eumycetoma (cases involving fungi; **Chap. 214**), and botryomycosis (cases involving cocci or bacilli, often *Staphylococcus aureus*) are difficult to distinguish clinically but are readily distinguished with microbiologic testing or biopsy. Granules should be sought in any discharge. Suspect particles should be washed in saline, examined microscopically, and cultured. Granules in actinomycetoma cases are usually white, pale yellow, pink, or red. Viewed microscopically, they consist of tight masses of fine filaments (0.5–1 µm wide) radiating outward from a central core (Fig. 169-5). Granules from

eumycetoma cases are white, yellow, brown, black, or green; under the microscope, they appear as masses of broader filaments (2–5 μm wide) encased in a matrix. Granules of botryomycosis consist of loose masses of cocci or bacilli. Organisms can also be seen in wound discharge or histologic specimens. The most reliable way to differentiate among the various organisms associated with mycetoma is by culture.

Isolation of nocardiae from sputum or blood occasionally represents colonization, transient infection, or contamination. In typical cases of respiratory tract colonization, Gram-stained specimens are negative and cultures are only intermittently positive. A positive sputum culture in an immunosuppressed patient usually reflects disease. When nocardiae are isolated from sputum of an immunocompetent patient without apparent nocardial disease, the patient should be observed carefully without treatment. A patient with a host-defense defect that increases the risk of nocardiosis should usually receive antimicrobial treatment.

Species are definitively determined by molecular techniques. In recent comparisons, the results were similar for species identification by molecular testing and matrix-assisted laser desorption/ionization/time-of-flight (MALDI-TOF) mass spectrometry. MALDI-TOF is much more practical for clinical laboratories and is becoming common in laboratories in high-resource countries.

Because nocardiosis is uncommon, data on the relation between susceptibility test results for specific drugs and clinical outcomes in patients treated with these drugs are meager. Careful clinical monitoring is essential, and consultation with clinicians who have experience with nocardiosis is often needed. Susceptibility to antimicrobial agents in vitro can be determined with a Clinical Laboratory Standards Institute (CLSI)–approved broth dilution test. Determination of susceptibility by Etest and BACTEC radiometric methods appears to correlate well with that by broth microdilution. Nocardial growth is slower than the growth of most clinically important bacteria, and nocardiae tend to clump in suspension so that susceptibility-test end points are difficult to read; thus experience is necessary for reliable reading of results. If an isolate can be accurately speciated, its susceptibility to antimicrobial drugs can be predicted with a high degree of accuracy.

Speciation by molecular methods or MALDI-TOF is not practical in many resource-poor countries. As a result, therapy for nocardiosis is often initiated without definitive speciation or knowledge of susceptibility results. For mild or moderate cases, therapy with drugs known to be effective against most isolates is usually adequate. For severe cases or cases that do not respond promptly to antimicrobial therapy, isolates should be sent to a laboratory experienced with *Nocardia* for identification and susceptibility testing whenever possible.

TREATMENT

Nocardiosis

Trimethoprim-sulfamethoxazole (TMZ-SMX) is the drug of choice for most cases **(Tables** 169-1 and **169-2)**. Reported rates of TMP-SMX susceptibility have varied widely, and controversy has ensued about the reliability of sulfonamides for therapy. However, clinical responses to appropriate sulfonamide treatment around the world are nearly always satisfactory. At the outset, 10–20 mg/kg of TMP and 50–100 mg/kg of SMX are given each day in two divided doses. Later, daily doses can be decreased to as little as 5 mg/kg and 25 mg/kg, respectively. In persons with sulfonamide allergies, desensitization usually allows continuation of therapy with these effective and inexpensive drugs.

Clinical experience with other oral drugs is limited. Minocycline (100–200 mg twice a day) is often effective; other tetracyclines are usually less effective. Linezolid is the most consistently active antimicrobial agent, but adverse effects become common and limiting in many patients after 2–3 weeks. Amoxicillin (875 mg) combined with clavulanate (125 mg), given twice a day, has been effective but should be avoided in cases involving strains of the *N. nova* complex, in which clavulanate induces β-lactamase production. Among the quinolones, moxifloxacin and gemifloxacin appear to be most active.

TABLE 169-2 Treatment Duration for Nocardiosis

DISEASE	DURATION
Pulmonary or systemic	
Intact host defenses	6–12 months
Deficient host defenses	12 months[a]
CNS disease	12 months[b]
Cellulitis, lymphocutaneous syndrome	2 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Actinomycetoma	6–12 months after clinical cure
Keratitis	Topical: until apparent cure Systemic: until 2–4 months after apparent cure

[a]In some patients with AIDS and CD4+ T lymphocyte counts of <200/μL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely. [b]If all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.

Amikacin, the best-established parenteral drug except in cases involving the *N. transvalensis* complex, is given in doses of 5–7.5 mg/kg every 12 h or 15 mg/kg every 24 h. Serum drug levels should be monitored during prolonged therapy in patients with diminished renal function and in the elderly. Ceftriaxone and imipenem are usually effective except as indicated in Table 169-1. Tigecycline appears to be active in vitro against some species, but little clinical experience has been reported.

Patients with severe disease are initially treated with a combination including TMP-SMX, amikacin, and ceftriaxone or imipenem. Clinical improvement is usually noticeable after 1–2 weeks of therapy but may take longer, especially with CNS disease. After definite clinical improvement, therapy can be continued with a single oral drug, usually TMP-SMX. Some experts use two or more drugs for the entire course of therapy, but whether multiple drugs are better than a single agent is not known, and additional drugs increase the risk of toxicity. In patients with nocardiosis who need immunosuppressive therapy for an underlying disease or prevention of transplant rejection, immunosuppressive therapy should be continued.

Use of SMX and TMP in high-risk populations to prevent *Pneumocystis* disease or urinary tract infections appears to reduce but not eliminate the risk of nocardiosis. The incidence of nocardiosis is low enough that prophylaxis solely to prevent this disease is not recommended.

Surgical management of nocardial disease is similar to that of other bacterial diseases. Brain abscesses should be aspirated, drained, or excised if the diagnosis is unclear, if an abscess is large and accessible, or if an abscess fails to respond to chemotherapy. Small or inaccessible brain abscesses should be treated medically; clinical improvement should be noticeable within 1–2 weeks. Brain imaging should be repeated to document the resolution of lesions, although abatement on images often lags behind clinical improvement.

Antimicrobial therapy usually suffices for nocardial actinomycetoma. In deep or extensive cases, drainage or excision of heavily involved tissue may facilitate healing, but structure and function should be preserved whenever possible. Keratitis is treated with a topical sulfonamide or amikacin drops plus a sulfonamide or an alternative drug given by mouth.

Nocardial infections tend to relapse (particularly in patients with chronic granulomatous disease), and long courses of antimicrobial therapy are necessary (Table 169-2). If disease is unusually extensive or if the response to therapy is slow, the recommendations in Table 169-2 should be exceeded.

With appropriate treatment, the mortality rate for pulmonary or disseminated nocardiosis outside the CNS should be <5%. CNS disease carries a higher mortality rate. Patients should be followed carefully for at least 6 months after therapy has ended.

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170 Actinomycosis

Thomas A. Russo

Actinomycosis is uncommon, and most physicians' personal experience with its clinical presentations is limited. Laboratory identification of the etiologic agents from the order Actinomycetales is not routine. Thus actinomycosis remains a diagnostic challenge, even for a skilled clinician. However, this infection is usually curable with medical therapy alone. Therefore, an awareness of the full spectrum of clinical syndromes can expedite diagnosis and treatment and minimize unnecessary surgical interventions, morbidity, and mortality.

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily of the genus *Actinomyces*, that colonize the mouth, colon, and vagina. Mucosal disruption may lead to infection at virtually any site in the body. In vivo growth of actinomycetes usually results in the formation of characteristic clumps called *grains* or *sulfur granules*. The clinical presentations of actinomycosis are myriad. Common in the preantibiotic era, actinomycosis has diminished in incidence, as has its timely recognition. Actinomycosis has been called the most misdiagnosed disease, and it has been said that no disease is so often missed by experienced diagnosticians.

Three "classic" clinical presentations that should prompt consideration of this unique infection are (1) the combination of chronicity, progression across tissue boundaries, and mass-like features (mimicking malignancy, with which it is often confused); (2) the development of a sinus tract, which may spontaneously resolve and recur; and (3) a refractory or relapsing infection after a short course of therapy, since cure of established actinomycosis requires prolonged treatment.

ETIOLOGIC AGENTS

Actinomycosis is most commonly caused by *A. israelii, A. naeslundii, A. odontolyticus, A. viscosus, A. meyeri, A. graevenitzii*, and *A. gerencseriae*. Most if not all actinomycotic infections are polymicrobial. *Aggregatibacter (Actinobacillus) actinomycetemcomitans, Eikenella corrodens*, Enterobacteriaceae, and species of *Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus*, and *Streptococcus* are commonly isolated with actinomycetes in various combinations, depending on the site of infection. Their contribution to the pathogenesis of actinomycosis is uncertain.

Comparative 16S rRNA gene sequencing has led to the identification of an ever-expanding list of *Actinomyces* species and a reclassification of some species to other genera. At present, 47 species and 2 subspecies have been recognized (*http://www.bacterio.net/actinomyces.html*), with 25 species implicated as causes of human disease. *A. europaeus, A. neuii, A. radingae, A. turicensis, A. cardiffensis, A. urogenitalis, A. hongkongensis, A. georgiae, A. massiliensis, A. timonensis*, and *A. funkei* as well as two former *Actinomyces* species—*Trueperella* (*Arcanobacterium*) *pyogenes* and *Trueperella* (*Arcanobacterium*) *bernardiae*—and *Propionibacterium propionicum* are additional causes of human actinomycosis, albeit not always with a "classic" presentation.

EPIDEMIOLOGY

Actinomycosis has no geographic boundaries and occurs throughout life, with a peak incidence in the middle decades. Males have a threefold higher incidence than females, possibly because of poorer dental hygiene and/or more frequent trauma. Improved dental hygiene and the initiation of antimicrobial treatment before actinomycosis fully develops have probably contributed to a decrease in incidence since the advent of antibiotics. Individuals who do not seek or have access to health care, those who have an intrauterine contraceptive device (IUCD) in place for a prolonged period (see "Pelvic Disease," below), and those who receive bisphosphonate treatment (see "Oral–Cervicofacial Disease," below) are probably at higher risk.

PATHOGENESIS AND PATHOLOGY

The etiologic agents of actinomycosis are members of the normal oral flora and are often cultured from the bronchi, the gastrointestinal tract, and the female genital tract. The critical step in the development of actinomycosis is disruption of the mucosal barrier. Local infection may ensue. Once established, actinomycosis spreads contiguously in a slow, progressive manner, ignoring tissue planes. Although acute inflammation may initially develop at the infection site, the hallmark of actinomycosis is the characteristic chronic, indolent phase manifested by lesions that usually appear as single or multiple indurations. Central necrosis consisting of neutrophils and sulfur granules develops and is virtually diagnostic. The fibrotic walls of the mass are typically described as "wooden." The responsible bacterial and/or host factors have not been identified. Over time, sinus tracts to the skin, adjacent organs, or bone may develop. In rare instances, distant hematogenous seeding may occur; lymphatic spread and associated lymphadenopathy are uncommon. As mentioned above, these unique features of actinomycosis mimic malignancy, with which it is often confused.

Foreign bodies appear to facilitate infection. This association most frequently involves IUCDs. Reports have described an association of actinomycosis with HIV infection; transplantation; common variable immunodeficiency; chronic granulomatous disease; treatment with anti–tumor necrosis factor α agents, glucocorticoids, or bisphosphonates; and radio- or chemotherapy. Ulcerative mucosal infections (e.g., by herpes simplex virus or cytomegalovirus) may facilitate disease development.

CLINICAL MANIFESTATIONS

Oral–Cervicofacial Disease Actinomycosis occurs most frequently at an oral, cervical, or facial site, usually as a soft tissue swelling, abscess, mass, or ulcerative lesion that is often mistaken for a neoplasm. Dental diseases or procedures are common precipitating factors. The angle of the jaw is generally involved, but a diagnosis of actinomycosis should be considered with any mass lesion or relapsing infection in the head and neck **(Chap. 31)**. Radiation therapy and especially bisphosphonate treatment have been recognized as contributing to an increasing incidence of actinomycotic infection of the mandible and maxilla **(Fig. 170-1)**. Canaliculitis (commonly due to *P. propionicum*), otitis, sinusitis, and laryngeal disease also can develop. Pain, fever, and leukocytosis are variably reported. Contiguous extension to the cranium, cervical spine, or thorax is a potential sequela.

FIGURE 170-1 Bisphosphonate-associated maxillary osteomyelitis due to *Actinomyces viscosus*. A sulfur granule is seen within the bone. *(Reprinted with permission from NH Naik, TA Russo: Bisphosphonate related osteonecrosis of the jaw: The role of Actinomyces. Clin Infect Dis 49:1729, 2009. © 2009 Oxford University Press.)*

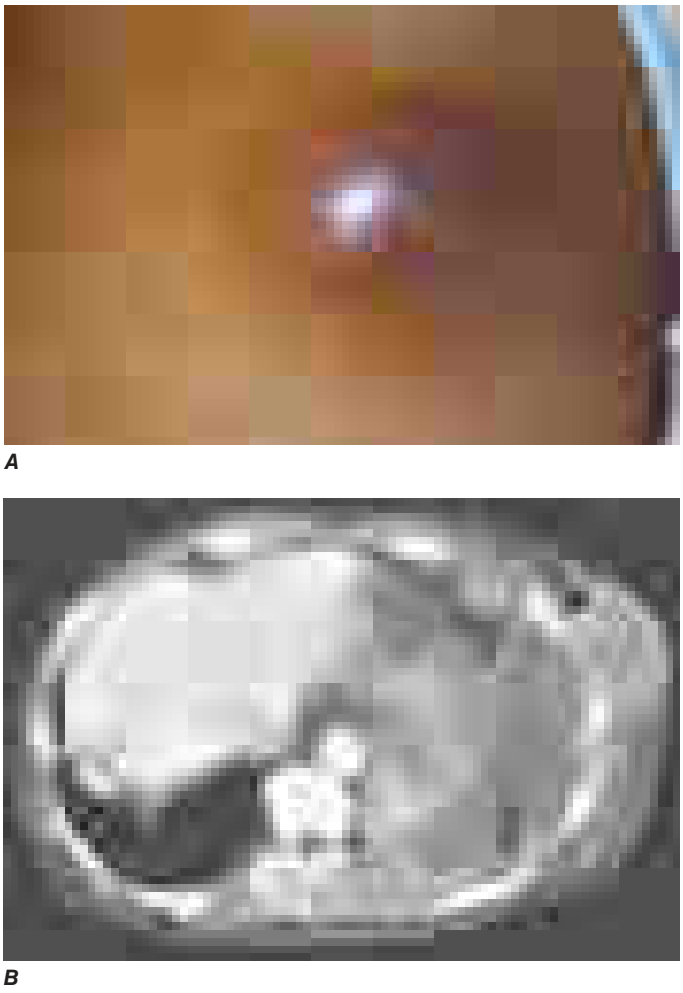

FIGURE 170-2 Thoracic actinomycosis. *A.* A chest wall mass from extension of pulmonary infection. ***B.*** Pulmonary infection is complicated by empyema (*open arrow*) and extension to the chest wall (*closed arrow*). *(Courtesy of Dr. C. B. Hsiao, Division of Infectious Diseases, Department of Medicine, State University of New York at Buffalo.)*

Thoracic Disease Thoracic actinomycosis, which may be facilitated by aspirated foreign material, usually follows an indolent progressive course, with involvement of the pulmonary parenchyma and/or the pleural space. Chest pain, fever, and weight loss are common. A cough, when present, is variably productive. The usual radiographic finding is either a mass lesion or pneumonia. On CT, central areas of low attenuation and ring-like rim enhancement may be seen; cavitary disease may develop. More than 50% of cases include pleural thickening, effusion, or empyema **(Fig. 170-2)**. Rarely, pulmonary nodules or endobronchial lesions occur. Lesions suggestive of actinomycosis include those that cross fissures or pleura; extend into the mediastinum, contiguous bone, or chest wall (*empyema necessitatis*); or are associated with a sinus tract. In the absence of these findings, thoracic actinomycosis is usually mistaken for a neoplasm or pneumonia due to more usual causes.

Mediastinal infection is uncommon, usually arising from thoracic extension but rarely from perforation of the esophagus, trauma, or extension of head and neck or abdominal disease. The structures within the mediastinum and the heart can be involved in various combinations; consequently, the possible presentations are diverse. Primary endocarditis (in which *A. neuii* has been increasingly described), esophageal infection, and isolated disease of the breast occur.

Abdominal Disease Abdominal actinomycosis poses a great diagnostic challenge. Months or years usually pass from the inciting event (e.g., appendicitis, diverticulitis, peptic ulcer disease, spillage of gall stones or bile during cholecystectomy, foreign-body perforation, bowel surgery, or ascension from IUCD-associated pelvic disease) to clinical recognition. Because of the flow of peritoneal fluid and/or the direct extension of primary disease, virtually any abdominal organ, region, or space can be involved. The disease usually presents as an abscess, a mass, or a mixed lesion that is often fixed to underlying tissue and mistaken for a tumor. On CT, enhancement is most often heterogeneous and adjacent bowel is thickened. Sinus tracts to the abdominal wall, to the perianal region, or between the bowel and other organs may develop and mimic inflammatory bowel disease **(Chap. 319)**. Recurrent disease or a wound or fistula that fails to heal suggests actinomycosis.

Hepatic infection usually presents as one or more abscesses or masses **(Fig. 170-3)**. Isolated disease presumably develops via hematogenous seeding from cryptic foci. Imaging and percutaneous techniques have resulted in improved diagnosis and treatment.

All levels of the urogenital tract can be infected. Renal disease usually presents as pyelonephritis and/or renal and perinephric abscess. Bladder involvement, usually due to extension of pelvic disease, may result in ureteral obstruction or fistulas to bowel, skin, or uterus. *Actinomyces* can be detected in urine with appropriate stains and cultures.

Pelvic Disease Actinomycotic involvement of the pelvis occurs most commonly in association with an IUCD but can also be associated with other foreign bodies, such as surgical mesh. When an IUCD is in place or has been used but removed, pelvic symptoms should prompt consideration of actinomycosis. The risk, although not quantified, appears small. The disease rarely develops when the IUCD has been in place for <1 year, but the risk increases with time. Symptoms are typically indolent; fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge are the most common. The earliest stage of disease—often endometritis—commonly progresses to pelvic masses or a tuboovarian abscess **(Fig. 170-4)**. Unfortunately, because the diagnosis is often delayed, a "frozen pelvis" mimicking malignancy or endometriosis can develop by the time of recognition, which may lead to unnecessary surgery. Cancer antigen 125 levels may be elevated, further contributing to misdiagnosis. In contrast to malignancy and tuberculosis, pelvic actinomycosis only uncommonly includes ascites and lymphadenopathy.

Actinomyces-like organisms (ALOs), which are identified in Papanicolaou-stained specimens in (on average) 7% of women using an IUCD, have a low positive predictive value for diagnosis. The detection of ALOs in an asymptomatic patient warrants education and close follow-up but not removal of the IUCD unless a suitable contraceptive alternative is agreed on. In the presence of symptoms that cannot be accounted for, it seems prudent to remove the IUCD and—if advanced

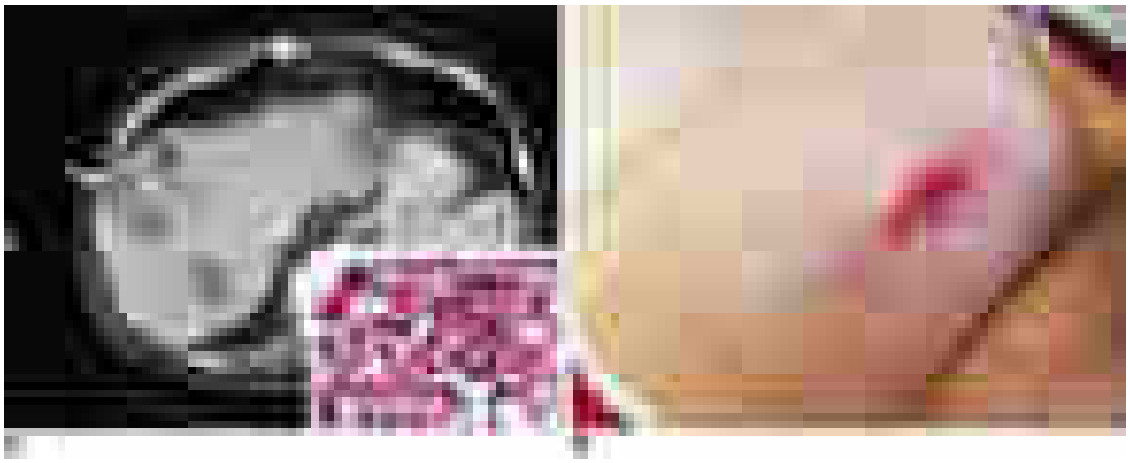

FIGURE 170-3 Hepatic–splenic actinomycosis. *A.* Computed tomogram showing multiple hepatic abscesses and a small splenic lesion due to *Actinomyces israelii*. Arrow indicates extension outside the liver. *Inset:* Gram's stain of abscess fluid demonstrating beaded filamentous gram-positive rods. ***B.*** Subsequent formation of a sinus tract. *(Reprinted with permission from Saad M: Actinomyces hepatic abscess with cutaneous fistula. N Engl J Med 353:e16, 2005. © 2005 Massachusetts Medical Society. All rights reserved.)*

disease is excluded—to initiate a 14-day course of empirical treatment for possible early endometritis.

Central Nervous System Disease Actinomycosis of the central nervous system (CNS) is rare. Single or multiple brain abscesses are most common. Individuals with hereditary hemorrhagic telangiectasia are at increased risk for brain abscess with *Actinomyces* as the potential etiologic agent. An abscess usually appears on CT as a ring-enhancing lesion with a thick wall that may be irregular or nodular. Magnetic resonance perfusion and spectroscopy findings have also been described, as have primary meningitis, epidural or subdural space infection, and cavernous sinus syndrome.

Musculoskeletal and Soft Tissue Infection Actinomycotic infection of bones and joints is usually due to adjacent soft-tissue infection but may be associated with trauma, injections, surgery (e.g., prostheses), osteoradionecrosis and bisphosphonate osteonecrosis (limited to mandibular and maxillary bones), or hematogenous spread. Because of slow disease progression, new bone formation and bone destruction can be seen concomitantly. Infection of soft tissue is uncommon and is usually a result of trauma. An actinomycetoma results from progression over months to years with the development of granulation tissue and tumor-like features. The foot is most commonly involved. Skin, subcutaneous tissue, muscle, and bone are affected in various combinations, and cutaneous sinus tracts frequently develop.

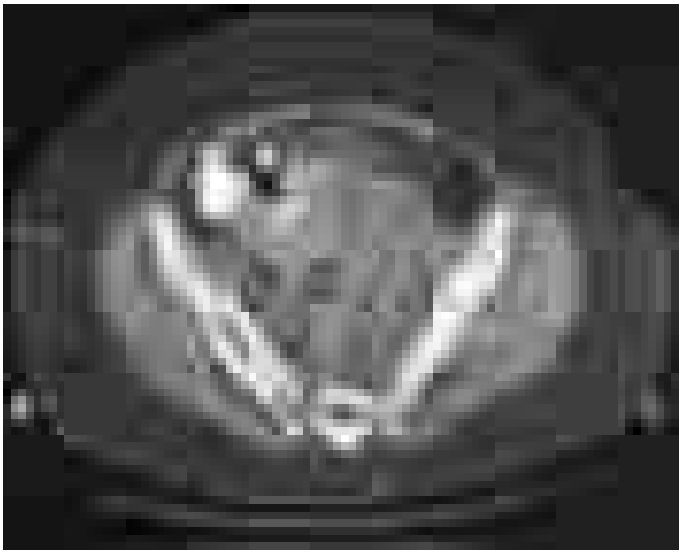

FIGURE 170-4 Computed tomogram showing pelvic actinomycosis associated with an intrauterine contraceptive device. The device is encased by endometrial fibrosis (*solid arrow*); also visible are paraendometrial fibrosis (*open triangular arrowhead*) and an area of suppuration (*open arrow*).

Disseminated Disease Hematogenous dissemination of disease from any location rarely results in multiple-organ involvement. *A. meyeri* is most commonly involved. The lungs and liver are most often affected, with the presentation of multiple nodules mimicking disseminated malignancy. The clinical presentation may be surprisingly indolent given the extent of disease.

DIAGNOSIS

The diagnosis of actinomycosis is rarely considered. All too often, actinomycosis is first mentioned by the pathologist after extensive surgery. Since medical therapy alone is frequently sufficient for cure, the challenge for the clinician is to consider the possibility of actinomycosis, to diagnose it in the least invasive fashion, and to avoid unnecessary surgery. The clinical and radiographic presentations that suggest actinomycosis are discussed above. Of note, hypermetabolism has been demonstrated by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in actinomycotic disease. Aspirations and biopsies (with or without CT or ultrasound guidance) are being used successfully to obtain clinical material for diagnosis, although surgery may be required. The microscopic identification of sulfur granules (an in vivo matrix of bacteria, calcium phosphate, and host material) in pus or tissues, which increases with the examination of additional histopathologic sections and the use of positively charged slides to optimize adhesion, is the most common means of diagnosis. Occasionally, these granules are identified grossly from draining sinus tracts or pus. Although sulfur granules are a defining characteristic of actinomycosis, granules also are found in mycetoma **(Chaps. 169 and 214)** and botryomycosis (a chronic suppurative bacterial infection of soft tissue or, in rare cases, visceral tissue that produces clumps of bacteria resembling granules). These entities can easily be differentiated from actinomycosis with appropriate histopathologic and microbiologic studies. Microbiologic identification of actinomycetes is often precluded by prior antimicrobial therapy or failure to perform appropriate microbiologic cultures. For optimal yield, the avoidance of even a single dose of antibiotics is mandatory. Although some species can grow aerobically, isolation is maximized under anaerobic conditions, usually requiring 5–7 days but potentially up to 2–4 weeks. The use of 16S rRNA gene amplification and sequencing by clinical microbiology laboratories is increasing and is enhancing diagnostic sensitivity and specificity. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) holds similar promise, but databases are still being optimized. Because actinomycetes are components of the normal oral and genital-tract flora, their identification in the absence of sulfur granules in sputum, bronchial washings, and cervicovaginal secretions is of little significance.

TREATMENT

Actinomycosis

Decisions about treatment are based on the collective clinical experience of the past 70 years. Actinomycosis requires prolonged treatment with high doses of antimicrobial agents; suitable antimicrobial agents and those deemed unreliable are listed in Table 170-1. The need for intensive treatment is presumably due to the drugs' poor penetration of the thick-walled masses common in this infection and/or the sulfur granules themselves, which may represent a biofilm. Although therapy must be individualized, the IV administration of 18–24 million units of penicillin daily for 2–6 weeks, followed by oral therapy with penicillin or amoxicillin (total duration, 6–12 months), is a reasonable guideline for serious infections and bulky disease. For penicillin-allergic patients, tetracyclines, ceftriaxone, or carbapenems are reasonable alternatives. Less extensive disease, particularly that involving the oral–cervicofacial region or the isolation of *Actinomyces* in the absence of tissue changes associated with actinomycosis, may be cured with a shorter course. If therapy is extended beyond the resolution of measurable disease, the risk of relapse—a clinical hallmark of this infection—will be minimized; CT and MRI are generally the most sensitive and objective techniques by which to accomplish this goal. A similar approach is reasonable for immunocompromised patients, although refractory disease has been described in HIV-infected individuals. While the role played by "companion" microbes in actinomycosis is unclear, many isolates are pathogens in their own right, and a regimen covering these organisms during the initial treatment course is reasonable. Isolation of *Actinomyces* from blood cultures in the absence of defined infection may represent contamination or transient bacteremia from a mucosal site of colonization, in which case treatment may not be necessary.

Combined medical–surgical therapy is still advocated in some reports. However, an increasing body of literature now supports an initial attempt at cure with medical therapy alone, even in extensive disease. CT and MRI should be used to monitor the response to therapy. In most cases, either surgery can be avoided or a less extensive procedure can be used. This approach is particularly valuable in sparing critical organs, such as the bladder or the reproductive organs in women of childbearing age. For a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach. When a critical location is involved (e.g., the epidural space, the CNS), when there is significant hemoptysis, or when suitable medical therapy fails, surgical intervention may be appropriate. In the absence of optimal data, the combination of a prolonged course of antimicrobial therapy and resection—at least of necrotic bone for bisphosphonate-related osteonecrosis of the jaw (BRONJ)—is a reasonable approach.

TABLE 170-1 Appropriate and Inappropriate Antibiotic Therapy for Actinomycosis[a]

CATEGORY	AGENT
Extensive successful clinical experience[b]	Penicillin: 3–4 million units IV q4h[c,d]
	Amoxicillin: 500 mg PO q6h
	Erythromycin: 500–1000 mg IV q6h or 500 mg PO q6h[c]
	Tetracycline: 500 mg PO q6h
	Doxycycline: 100 mg IV or PO q12h
	Minocycline: 100 mg IV or PO q12h
	Clindamycin: 900 mg IV q8h or 300–450 mg PO q6h[c]
Anecdotal successful clinical experience	Ceftriaxone[d]
	Ceftizoxime
	Imipenem-cilastatin
	Piperacillin-tazobactam
Agents that should be avoided	Metronidazole
	Aminoglycosides
	Oxacillin, dicloxacillin
	Cephalexin
	Fluoroquinolones
Agents predicted to be efficacious on the basis of in vitro activity	Vancomycin
	Linezolid
	Quinupristin-dalfopristin
	Rifampin
	Ertapenem[d]
	Tigecycline[d]
	Azithromycin[d]

[a]Additional coverage for concomitant "companion" bacteria may be required. [b]Controlled evaluations have not been performed. Dose and duration require individualization depending on the host, site, and extent of infection. As a general rule, a maximal parenteral antimicrobial dose for 2–6 weeks followed by oral therapy, for a total duration of 6–12 months, is required for serious infections and bulky disease, whereas a shorter course may suffice for less extensive disease, particularly in the oral–cervicofacial region. Monitoring the impact of therapy with CT or MRI is advisable when appropriate. [c]Recent in vitro data have demonstrated resistance in up to 33% of isolates. [d]This agent can be considered for at-home parenteral therapy; penicillin requires a continuous infusion pump.

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171 Whipple's Disease

Thomas A. Russo

Whipple's disease, described by George Whipple in 1907, is a chronic infection caused by *Tropheryma whipplei*. Most commonly, years pass from the onset of symptoms to the recognition of the disease because of its rarity, its various manifestations mimicking other conditions, and the need to perform nonroutine diagnostic tests. The long-held belief that Whipple's disease is an infection was supported by observations on its responsiveness to antimicrobial therapy in the 1950s and the identification of bacilli via electron microscopy in small-bowel biopsy specimens in the 1960s. This hypothesis was finally confirmed by amplification and sequencing of a partial 16S rRNA polymerase chain reaction (PCR)–generated amplicon from duodenal tissue in 1991. The subsequent successful cultivation of *T. whipplei* enabled whole-genome sequencing and the development of additional diagnostic tests. The development of PCR-based diagnostics has broadened our understanding of both the epidemiology of and the clinical syndromes attributable to *T. whipplei*. Exposure to *T. whipplei*, which appears to be much more common than has been appreciated, can be followed by asymptomatic carriage, acute disease, or chronic infection. Chronic infection—Whipple's disease—is a rare development after exposure. "Classic" Whipple's disease is manifested by some combination of arthralgias/arthritis, weight loss, chronic diarrhea, abdominal pain, and fever. Variable involvement at other sites also occurs; neurologic and cardiac disease are most common. Acute infection and chronic

organ disease in the absence of intestinal involvement (see "Isolated Infection," below) are described with increasing frequency. Since untreated Whipple's disease is often fatal and delayed diagnosis may lead to irreparable organ damage (e.g., in the central nervous system [CNS]), knowledge of the clinical scenarios in which Whipple's should be considered and of an appropriate diagnostic strategy is mandatory.

ETIOLOGIC AGENT

T. whipplei is a weakly staining gram-positive bacillus. Genomic sequence data have revealed that the organism has a small (<1-megabase) chromosome, with many biosynthetic pathways absent or incomplete. This finding is consistent with a host-dependent intracellular pathogen or a pathogen that requires a nutritionally rich extracellular environment. It is one of the slowest growing human pathogens, with a doubling time of 18 days. A genotyping scheme based on a variable region has disclosed >100 genotypes to date. All genotypes appear to be capable of causing similar clinical syndromes.

EPIDEMIOLOGY

Whipple's disease is rare but has been increasingly recognized since the advent of PCR-based diagnostic tools. It occurs in all parts of the globe, with a prevalence estimated at 1–3 cases per 1 million population. Seroprevalence studies indicate that ~50% of Western Europeans and ~75% of Africans from rural Senegal have been exposed to *T. whipplei*. A predilection for chronic disease has been observed in middle-aged Caucasian men, who develop disease five to eight times more frequently than middle-aged women. Humans are the only known host. To date, no clear animal or environmental reservoir has been demonstrated. However, the organism has been identified by PCR in sewage water and human feces. Workers with direct exposure to sewage are more likely to be asymptomatically colonized than controls, a pattern suggesting fecal–oral spread. Fecal PCR detection rates of 38% among family members of carriers or patients with infection support oral–oral or fecal–oral spread, although a common environmental exposure cannot be excluded. Further, the development of acute *T. whipplei* pneumonia in children raises the possibility of droplet or airborne transmission.

PATHOGENESIS AND PATHOLOGY

Since rates of exposure to *T. whipplei*, as defined by seroprevalence, appear to be much higher than rates of chronic disease development (0.00001%), it has been hypothesized that chronically infected individuals possess a subtle host-defense abnormality. The human leukocyte antigen (HLA) alleles DRB1*13 and DQB1*06 are associated with an increased risk of infection. Chronic infection results in a general state of immunosuppression characterized by an impaired T_H1 response, enhanced production of anti-inflammatory cytokines, increased activity of regulatory T cells, M2 polarization of macrophages with diminished antimicrobial activity and impaired phagosome–lysosome fusion and ensuing apoptosis, and blunted development of *T. whipplei*–specific T cells. Immunosuppressive glucocorticoid treatment or anti–tumor necrosis factor α (anti-TNF-α) therapy appears to accelerate progression of chronic disease and perhaps enables infection in colonized individuals. Asymptomatic HIV-infected individuals have been found to have significantly higher levels of *T. whipplei* sequence in bronchoalveolar lavage fluid (BALF) than do non-HIV-infected individuals, and these levels decrease with antiretroviral therapy. A weak humoral response, perhaps due to bacterial glycosylation in patients with chronic disease, appears to differentiate persons who clear the bacillus from asymptomatic carriers. In the initiation of chronic infection, the relative importance of the host's genetic background versus the modulation of the host response by *T. whipplei* is unknown.

T. whipplei has a tropism for myeloid cells, which it invades and in which it can avoid being killed. Infiltration of infected tissue by large numbers of foamy macrophages containing periodic acid–Schiff (PAS)–staining inclusions (representing ingested bacteria) is a characteristic and most common finding. With disease progression, villus atrophy, lymphangiectasia, crypt hyperplasia, and apoptosis of surface epithelial cells are observed in the small intestine, with resultant diarrhea due to decreased absorption and increased leak flux of water and solutes. Occasionally, involvement of lymphatic or hepatic tissue may manifest as noncaseating granulomas that can mimic sarcoid.

CLINICAL MANIFESTATIONS

Asymptomatic Colonization/Carriage Studies using primarily PCR have detected *T. whipplei* sequence in stool, saliva, duodenal tissue, and (rarely) blood in the absence of symptoms. Although prevalence rates are still being defined, in Western European countries, detection in saliva (0.2%) is less common than that in stool (1–11%) and appears to occur only with concomitant fecal carriage. The prevalence of fecal carriage is elevated among individuals with exposure to waste water or sewage (12–26%) and among children living in tropical Africa and Asia (20–48%). A duration of carriage of 7 years for the same strain has been described in a sewer worker. Evolution of the carrier state into chronic disease is uncommon. Bacterial loads are lighter in asymptomatic carriage than in active disease.

Acute Infection *T. whipplei* has been implicated as a cause of acute gastroenteritis in children. It was also detected via PCR in the blood of 4.6% of febrile patients (75% of whom were <15 years of age) from two rural villages in Senegal as opposed to 0.25% of healthy controls. Further, *T. whipplei* has been implicated as a cause of acute pneumonia. These data suggest that primary acquisition may result in symptomatic pulmonary or intestinal infection or a febrile syndrome, which perhaps are more common than is generally appreciated.

Chronic Infection • **"CLASSIC" WHIPPLE'S DISEASE** So-called classic Whipple's disease was the initial clinical syndrome recognized, with consequent identification of *T. whipplei*. This chronic infection is defined by involvement of the duodenum and/or jejunum that develops over years. In most individuals, the initial phase of disease manifests primarily as intermittent, occasionally chronic, and rarely destructive migratory oligo- or polyarthralgias/seronegative arthritis involving the knees, wrists, and ankles most commonly. Less frequently, spondylitis, sacroiliitis, discitis, and prosthetic hip infection also have been described. Intermittent fever, myalgias, and skin nodules may accompany joint symptoms. Tests for rheumatoid factor and antinuclear antibody are usually negative. This initial stage is often confused with a variety of rheumatologic disorders and, on average, lasts 6–8 years before gastrointestinal symptoms commence. Treatment of presumed inflammatory arthritis with immunosuppressive agents (e.g., glucocorticoids, anti-TNF-α) can accelerate progression of the disease process; thus screening for Whipple's disease prior to initiation of immunosuppressant therapy may be appropriate, depending on the clinical scenario. Alternatively, antimicrobial therapy for another indication may reduce symptoms, and this situation should also prompt consideration of Whipple's disease. The intestinal symptoms that develop in the majority of cases are characterized by diarrhea with accompanying weight loss and may be associated with fever and abdominal pain. Occult gastrointestinal blood loss, hepatosplenomegaly (10–15%), and ascites (10%) are less common. Anemia and hypereosinophilia may be detected. The most common finding on abdominal CT is mesenteric and/or retroperitoneal lymphadenopathy (usually raising concern about lymphoma). The endoscopic or video-capsule observation of pale, yellow, or shaggy mucosa with erythema or ulceration past the first portion of the duodenum suggests Whipple's disease **(Fig. 171-1)**. When endoscopy with duodenal biopsy is nondiagnostic, a video-capsule study may assist in identifying more distal lesions for subsequent biopsy. Diagnostic misdirection can be caused by coinfection with *Giardia lamblia*, which is occasionally identified. The intestinal phase can also be confused with Crohn's or celiac disease. In addition to rheumatologic and intestinal disease, neurologic (6–63%), cardiac (17–55%), pulmonary (10–50%), lymphatic (10–55%), ocular (5–10%), dermal (5–30%), and less commonly other sites are variably involved in classic Whipple's disease.

Neurologic Disease CNS disease, defined by PCR-based detection of *T. whipplei* in cerebrospinal fluid (CSF), develops in ~50% of patients,

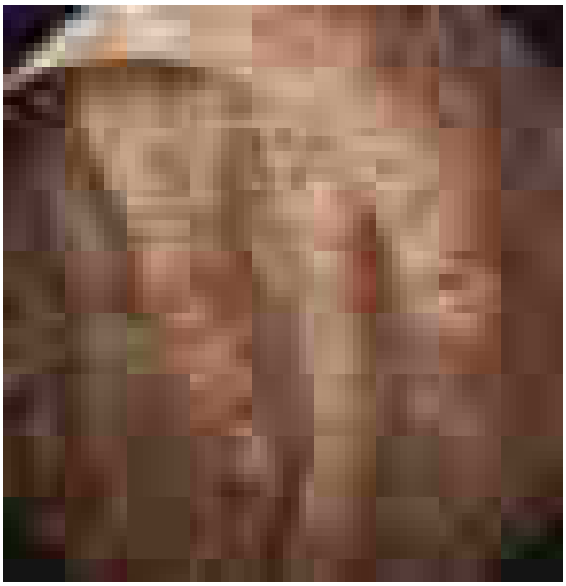

FIGURE 171-1 Endoscopic view of the jejunal mucosa demonstrating a thickened, granular mucosa and "white spots" due to dilated lacteals. *(Reprinted with permission from J Bureš et al: Whipple's disease: Our own experience and review of the literature. Gastroenterol Res Pract, 2013. http://dx.doi.org/10.1155/2013/478349.)*

many of whom are asymptomatic. A variety of neurologic manifestations have been reported and portend a poor prognosis. The most common are cognitive changes progressing to dementia, personality and mood alterations, hypothalamic involvement (e.g., polyuria/polydipsia, sleep-cycle disorders), and supranuclear ophthalmoplegia. In addition, neuro-ophthalmologic manifestations of Whipple's disease include supranuclear gaze palsy (usually vertical), oculomasticatory and oculofacial myorhythmia (highly suggestive of Whipple's), nystagmus, and retrobulbar neuritis. Focal neurologic presentations (dependent on lesion location), seizures, ataxia, meningitis, encephalitis, hydrocephalus, myelopathy, myoclonus, choreiform movements, and distal polyneuropathy also have been described. Neurologic sequelae occur with CNS disease, and the mortality risk is significant.

MRI results may be normal. Identified lesions (solitary or multifocal) are usually T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense and may enhance with gadolinium. All sites can be involved, and the nature of lesions is variable (e.g., nodular, infiltrative, tumor-like). Although imaging findings are myriad and are not diagnostic, the median temporal lobe, midbrain, hypothalamus, and thalamus are commonly affected. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) may reveal increased uptake. CSF analysis may be normal; when abnormal, leukocytosis (generally lymphocyte-predominant) and an elevated protein concentration are common. A low CSF glucose level has been reported.

Cardiac Disease Endocarditis, which is increasingly recognized in Whipple's disease, presents as culture-negative infection and/or congestive heart failure; hypotension occurs rarely. Embolic events or various arrhythmias or conduction defects may also be noted. Fever is often absent, and the Duke clinical criteria are rarely met. Vegetations are identified by echocardiography in 50–75% of cases. All valves, alone or in combination, can be affected; most commonly involved are the aortic and mitral valves. Preexisting valvular disease is found in only a minority of cases, although infection of bioprosthetic valves has been described. Mural, myocardial, or pericardial disease also occurs alone or in combination with valvular involvement. Constrictive pericarditis develops infrequently. Diagnosis of cardiac disease is rarely made prior to surgical intervention.

Pulmonary Disease Some combination of interstitial disease, nodules, parenchymal infiltrate, and pleural effusion is observed. An association with pulmonary hypertension has also been reported. The clinical significance of *T. whipplei* sequence identified in BALF from asymptomatic HIV-infected individuals or in a case of interstitial lung disease is unresolved but suggests caution in diagnosing "isolated" pneumonia on the basis of sequence alone.

Lymphatic Disease Mesenteric and retroperitoneal lymphadenopathy are common with intestinal disease, and mediastinal adenopathy may be associated with pulmonary infection. Peripheral adenopathy is less common.

Ocular Disease (Non-neuro-Ophthalmologic) Uveitis is the most common form of ocular disease, usually presenting as a change in vision or "floaters." Anterior (anterior chamber), intermediate (vitreous), and posterior (retina/choroid) uveitis can occur alone or in combination. Treatment with glucocorticoids alone can worsen uveitis and unmask extraocular disease. Likewise, use of local or systemic glucocorticoids after ocular surgery can precipitate ocular infection, likely as a result of asymptomatic or subclinical disease. Keratitis, crystalline keratopathy, and optic neuritis also have been reported. Patients may be misdiagnosed with sarcoid or Behçet's disease prior to the recognition of Whipple's.

Dermatologic Disease Skin hyperpigmentation, particularly in light-exposed areas in the absence of adrenal dysfunction, is suggestive of Whipple's disease. A variety of other cutaneous manifestations have been described, including erythematous macular lesions, nonthrombocytopenic purpura, subcutaneous nodules, and hyperkeratosis.

Miscellaneous Sites Thyroid, renal, testicular, epididymal, gallbladder, skeletal muscle, and bone marrow involvement have all been described. In fact, almost any organ can be involved in classic Whipple's disease, with varying frequency, variable combinations, and myriad signs and symptoms. As a result, Whipple's disease should be considered in the setting of a chronic multisystemic process. Despite its rarity, the combination of rheumatologic and intestinal disease with weight loss, with or without neurologic and cardiac involvement, warrants heightened suspicion.

ISOLATED INFECTION This entity has been defined as infection in the absence of intestinal symptoms, although an occasional small-bowel biopsy may be PCR-positive in this setting. "Isolated infection" is something of a misnomer since multiple nonintestinal sites of *T. whipplei* infection are not uncommon. Infection at the same nonintestinal sites (single or multiple) that are variably involved in classic Whipple's disease may also present as "isolated infection." Further, intestinal disease can subsequently develop. Endocarditis, neurologic disease, uveitis, rheumatologic manifestations, and pulmonary involvement are most commonly described. Signs and symptoms are similar to those described for *T. whipplei* infection of these sites in classic Whipple's disease. With enhanced PCR-based diagnostic capabilities, *T. whipplei* infection without concomitant intestinal involvement (of which endocarditis is the best example) will probably be diagnosed increasingly often.

REINFECTION/RELAPSING DISEASE/IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) It has been suggested that, if an underlying host immune defect places an individual at risk for chronic infection, then that person may be at risk for reinfection due to occupational exposure or contact with family members who are asymptomatically colonized. One case of apparent reinfection that was due to a different genotype supports this contention.

Optimal treatment regimens and durations are still being defined. However, it is clear, especially in the setting of occult or overt CNS disease, that treatment with oral tetracycline or trimethoprim-sulfamethoxazole (TMP-SMX) alone may result in disease relapse. Relapses or perhaps reinfections occurring years to decades after initial therapy have been described.

As in patients treated for HIV or mycobacterial disease, IRIS has been described in up to 17% of patients treated for *T. whipplei* infection. Prior immunosuppressive therapy increases the likelihood of IRIS, in which inflammation recurs after an initial clinical response to treatment and loss of PCR detection of *T. whipplei*. Manifestations include the development of fever, arthritis, skin lesions, subcutaneous nodules, pleuritis, uveitis, and orbital and periorbital inflammation; some cases have been fatal.

DIAGNOSIS

Considering *T. whipplei* infection and ensuring that the appropriate tests are performed are the critical steps in making the diagnosis, which otherwise will likely be missed. Serology is of little value since patients with active infection usually mount a poor IgM/IgG response to *T. whipplei* and a positive result most likely reflects prior exposure and clearance. The clinical presentation will in part dictate which clinical specimens are most likely to enable the diagnosis. In the presence (and perhaps the absence) of gastrointestinal symptoms, postbulbar duodenal biopsies should be performed, although a normal macroscopic appearance is common. As a general rule, diagnostic yield is greater for tissue specimens than for body fluids. Biopsy of normal-appearing skin may detect *T. whipplei* in the setting of classic Whipple's disease and serve as a minimally invasive means to establish the diagnosis. It is prudent to collect CSF even in the absence of CNS symptoms; asymptomatic disease is common, the CNS is the most common site for relapse, and thus the information gained by CSF examination could influence the design and duration of the treatment regimen.

The diagnosis of classic Whipple's disease was originally based on histologic findings in intestinal biopsy specimens, and this diagnostic procedure remains important. Infiltration of the lamina propria with macrophages containing PAS-positive inclusions that are resistant to diastase is observed. However, PAS is nonspecific, also yielding positive results with mycobacteria (which can be differentiated with Ziehl–Neelsen stain and culture), *Rhodococcus equi*, *Bacillus cereus*, *Corynebacterium* species, and *Histoplasma* species. *T. whipplei* can be detected by silver stain, Brown-Brenn (weakly positive), or acridine orange and is not stained by calcofluor. Staining of other tissues or fluids (e.g., ocular aspirations) for PAS-positive inclusions in macrophages can be performed to support the diagnosis. The sensitivity of identification of PAS-positive inclusions in Whipple's disease may be decreased by anti-TNF-α therapy. Electron microscopy can be used to identify the trilaminar cell wall of *T. whipplei*.

The development and implementation of PCR-based diagnostics have significantly increased the sensitivity and specificity of *T. whipplei* identification. PCR can be applied to affected tissues (with greater sensitivity for non-formalin-fixed than for formalin-fixed tissue) and to various body fluids (e.g., CSF; aqueous or vitreous humor; joint, pericardial, or pleural fluid; BALF; blood; feces). In some clinical scenarios, a generic 16S rRNA bacterial assay combined with amplicon sequencing can be used to detect and identify *T. whipplei* sequence. Delineation of the *T. whipplei* genomic sequence has enabled the development and broad availability of more sensitive and specific PCR-based assays. The interpretation of a PCR-based diagnostic approach must take into account limitations such as false-positive results due to sample contamination and false-negative results due to low organism load, poor sample quality, and inadequate DNA extraction. As with all diagnostic tests, consideration of pretest probability is critical for interpretation.

When available, immunohistochemistry has greater specificity and sensitivity than PAS staining and can be performed on archived fixed tissue. *T. whipplei* has been successfully cultured from blood, CSF, synovial fluid, BALF, valve tissue, duodenal tissue, skeletal muscle, and lymph nodes, but culture is not practical since it takes months to obtain a positive result.

Although histologic or cytologic detection of *T. whipplei* is less specific and sensitive than PCR, a positive result is strongly supportive within the appropriate clinical context and is definitive when combined with a second, more specific test (e.g., PCR, immunohistochemistry).

TREATMENT

Whipple's Disease

Data on treatment are emerging, but questions persist regarding the optimal regimen and duration for chronic infection, which may depend on the sites involved (e.g., CNS and heart valve). Appropriate treatment usually results in a rapid—and at times remarkable—clinical response (e.g., in CNS disease), but eradication requires prolonged treatment. Maintenance of a durable response has been more challenging because of both relapse and host predisposition to reinfection.

Rates of relapse, particularly of CNS disease, were unacceptable with oral tetracycline or TMP-SMX monotherapy. Sequence data now indicate that TMP is not active against *T. whipplei* (given the absence of dihydrofolate reductase in *T. whipplei*) and that resistance to SMX and sulfadiazine can occur. However, a randomized controlled trial in 40 patients, who received either ceftriaxone (2 g IV q24h) or meropenem (1 g IV q8h) for 2 weeks followed by oral TMP-SMX (160/800 mg) twice a day for 1 year, demonstrated outstanding efficacy. The only case in which therapy failed—an asymptomatic CNS infection that was not eradicated by either regimen—was subsequently cured with oral minocycline and chloroquine (250 mg/d after a loading dose). A follow-up trial reported similar efficacy with a regimen of ceftriaxone (2 g IV q24h) for 2 weeks followed by oral TMP-SMX for 3 months. One issue in these trials was that the doses—and perhaps the duration of ceftriaxone and meropenem treatment as well—were not optimal for CNS infection. By contrast, in a small retrospective series, outcome was better in patients treated with oral doxycycline (100 mg twice a day) plus hydroxychloroquine (200 mg three times a day; to raise phagosome pH and increase drug activity in vitro) than in patients initially treated with TMP-SMX. A randomized trial comparing oral doxycycline/hydroxychloroquine with a TMP-SMX-based regimen is ongoing and may resolve these discrepancies. Until more data become available, it seems prudent—at least in asymptomatic/symptomatic CNS disease or cardiac infection—first to administer CNS-optimized doses of IV ceftriaxone (2 g q12h) or meropenem (2 g q8h) for 2–4 weeks and then to treat with oral doxycycline or minocycline plus hydroxychloroquine or chloroquine for at least 1 year, if tolerated. Although data on the use of PCR to guide therapy do not exist, it seems reasonable that continued *T. whipplei* detection by PCR, especially in the CSF, should dictate at least continuation of therapy and perhaps consideration of an alternative regimen. Data on isolated infection and certain site-specific treatment issues are even more limited. Anecdotal reports describe successful treatment of uveitis with oral TMP-SMX with or without rifampin, whereas treatment with tetracycline alone has resulted in relapse. Although a role for adjunctive intraocular therapy has been reported, the data are unclear on this point. Surgery may be needed in the setting of endocarditis with significant valve dysfunction or myocardial abscess; however, timely recognition can result in cure with medical management alone. Although data on the treatment of foreign body-associated infection are virtually nonexistent, medical treatment for a prosthetic hip infection was apparently successful; however, follow-up was limited.

The occurrence of a Jarisch-Herxheimer reaction within 24 h of treatment initiation has been described, with rapid resolution. The addition of glucocorticoids may be beneficial in the management of IRIS, and thalidomide has been used in steroid-refractory cases.

Although data are completely lacking, lifelong suppressive therapy with doxycycline after completion of the initial treatment regimen has been advocated to prevent the occurrence of late relapse or reinfection. Regardless of the therapeutic approach chosen, an effort to ensure compliance and close follow-up for potential relapse or reinfection, which can occur many years after an apparent cure, will maximize the chances for a good outcome.

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172 Infections Due to Mixed Anaerobic Organisms

Neeraj K. Surana, Dennis L. Kasper

Anaerobes comprise the predominant class of bacteria of the normal human microbiota that reside on mucous membranes and predominate in many infectious processes, particularly those arising from mucosal surfaces. These organisms generally cause disease subsequent to the breakdown of mucosal barriers and the leakage of the microbiota into normally sterile sites. Infections resulting from contamination by the microbiota are usually polymicrobial and involve both aerobic and anaerobic bacteria. However, the difficulties encountered in handling specimens in which anaerobes may be important and the technical challenges entailed in cultivating and identifying these organisms in clinical microbiology laboratories continue to leave the anaerobic etiology of an infectious process unproven in many cases. Therefore, an understanding of the types of infections in which anaerobes can play a role is crucial in selecting appropriate microbiologic tools to identify the organisms in clinical specimens and in choosing the most appropriate treatment, including antibiotics and surgical drainage or debridement of the infected site. This chapter focuses on infections caused by anaerobic bacteria other than *Clostridium* species, which are covered elsewhere **(Chaps. 129 and 149)**.

HISTORICAL PERSPECTIVE

Anaerobic organisms were first identified by Antonie van Leeuwenhoek in 1680—nearly a century before oxygen itself was discovered. Leeuwenhoek set up culture medium (crushed pepper powder and clean rainwater) in two glass tubes—one open to ambient air and the other sealed closed—that he incubated for several days. Although he did not expect to observe anything in the sealed tube, he was surprised to find "animalcules" in both tubes. He noted that these bacteria in the sealed tube were "bigger than the biggest sort" in the tube left open to air. It was not until the mid- to late nineteenth century that Leeuwenhoek's findings were confirmed by Pasteur and others. However, these principles described by Leeuwenhoek underlie the basic pathogenesis of anaerobic infections: development of an anaerobic environment in a closed space is due to consumption of oxygen by aerobic organisms and results in the outgrowth of anaerobic organisms.

DIFFERENCES BETWEEN ANAEROBIC AND AEROBIC ORGANISMS

Anaerobic bacteria can be categorized as *obligate anaerobes* (killed in the presence of ≥0.5% oxygen), *aerotolerant organisms* (can tolerate the presence of oxygen but cannot use it for growth), and *facultative anaerobes* (can grow in the presence or absence of oxygen). Most clinically relevant anaerobes, such as *Bacteroides fragilis, Prevotella melaninogenica,* and *Fusobacterium nucleatum*, are relatively aerotolerant. These organisms contrast with *obligate aerobes*, which require high concentrations of oxygen for growth, and *microaerophilic organisms*, which are damaged by atmospheric concentrations of oxygen (~21%) but require low concentrations of oxygen (typically 2–10%) for growth. Given that molecular oxygen can reduce to superoxide (O_2^-) and hydrogen peroxide (H_2O_2), which are damaging to cells, the ability to tolerate the presence of oxygen is due, in part, to the expression of superoxide dismutase and catalase. The variation in anaerobic organisms tolerating anywhere from <0.5 to 8% O_2 may reflect the amount of these enzymes that is produced.

Furthermore, aerobic and anaerobic organisms differ in their energy metabolism. Cellular respiration requires establishment of an electrochemical gradient across the membrane, resulting in an electric potential (often related to a proton gradient) across the membrane. In aerobic respiration, electrons are shuttled through an electron transport chain, with oxygen as the final electron acceptor. Anaerobic organisms can metabolize energy by either anaerobic respiration or fermentation. Given that the final electron acceptor in anaerobic respiration (e.g., sulfate, nitrate, carbon dioxide, or fumarate) is not as highly oxidizing as oxygen, this pathway is less efficient than aerobic respiration and produces less ATP per glucose molecule. In contrast, fermentation does not use an electrochemical gradient. Rather, it releases energy from an organic molecule (e.g., pyruvate and its derivatives) via substrate-level phosphorylation and is therefore a less efficient process than either aerobic or anaerobic respiration; for comparison, fermentation results in ~5% of the energy released by aerobic respiration. For these reasons, facultative anaerobes will preferentially utilize oxygen if it is available; in oxygen-limiting situations, organisms will use anaerobic respiration rather than fermentative processes, if possible.

ANAEROBES OF THE HUMAN MICROBIOTA

Most human mucocutaneous surfaces harbor a rich indigenous normal microbiota composed of aerobic and anaerobic bacteria. These surfaces are dominated by anaerobic bacteria, which often account for 99.0–99.9% of the cultivable microbiota and range in concentration from 10^3/mL in the nose to 10^{12}/mL in gingival scrapings and the colon **(Table 172-1)**. It is interesting that anaerobes inhabit many areas of the body that are exposed to air: skin, nose, mouth, and throat. Anaerobes are thought to reside in the portions of these sites that either are relatively well protected from oxygen (e.g., gingival crevices) or have a local anaerobic environment conferred by neighboring aerobic organisms (e.g., tooth surfaces). The ability to cultivate these organisms is improving, and—with strict attention to anaerobic conditions—more than 80% of the microscopic counts in fecal samples can be cultured. However, culture-independent approaches (e.g., sequencing of the 16S rDNA gene) show that the overwhelmingly diverse low-abundance

TABLE 172-1 The Anaerobic Human Microbiota: An Overview

ANATOMIC SITE	TOTAL BACTERIA[a]	ANAEROBIC/AEROBIC RATIO	POTENTIAL PATHOGEN(S)
Nose	10^3–10^4	2:1	*Peptostreptococcus* spp., *Prevotella* spp.
Oral cavity			
Saliva	10^8–10^9	10:1	*Fusobacterium nucleatum, Prevotella melaninogenica, Prevotella oralis* group, *Bacteroides ureolyticus* group, *Peptostreptococcus* spp.
Tooth surface	10^{10}–10^{11}	1:1	
Gingival crevices	10^{11}–10^{12}	10^3:1	
Gastrointestinal tract			
Stomach	0–10^5	1:1	*Bacteroides* spp. (principally members of the *B. fragilis* group), *Prevotella* spp., *Clostridium* spp., *Peptostreptococcus* spp.
Jejunum/ileum	10^4–10^7	1:1	
Cecum and colon	10^{11}–10^{12}	10^3:1	
Female genital tract	10^7–10^9	10:1	*Peptostreptococcus* spp., *Bacteroides* spp., *Prevotella bivia*
Skin	10^4–10^6	100:1	*Cutibacterium acnes*

[a]Per gram or milliliter.

bacterial species present in the microbiota remain uncultivated. Several projects, including the Human Microbiome Project (funded by the U.S. National Institutes of Health) and MetaHIT (financed by the European Commission), have characterized the normal microbiota of healthy individuals and have demonstrated the presence of >10,000 different bacterial species in the collective human microbiota. The human gut alone harbors >1000 bacterial species, with 100–200 species present in any given individual.

The major reservoir of anaerobic bacteria is the lower gastrointestinal tract, but these organisms are also present in considerable numbers in the oral cavity, skin, and female genital tract (Table 172-1). In the oral cavity, the ratio of anaerobic to aerobic bacteria ranges from 1:1 on the surface of a tooth to 1000:1 in the gingival crevices. *Prevotella* and *Porphyromonas* species make up much of the indigenous oral anaerobic microbiota. *Fusobacterium* and *Bacteroides* (non–*B. fragilis* group) are present in lower numbers. Anaerobic bacteria are not found in appreciable numbers in the normal stomach and proximal small intestine. In the distal ileum, the microbiota begins to resemble that of the colon, where the ratio of anaerobes to aerobic species is high (~1000:1). The predominant anaerobes in the human intestine belong to the phyla Bacteroidetes and Firmicutes and include a number of *Prevotella* and *Bacteroides* species (e.g., members of the *B. fragilis* group, such as *B. fragilis, B. thetaiotaomicron, B. ovatus, B. vulgatus, B. uniformis*, and *Parabacteroides distasonis*) as well as various *Clostridium, Peptostreptococcus, Blautia*, and *Fusobacterium* species. In the female genital tract, there are ~10^9 organisms/mL of secretions, with an anaerobe-to-aerobe ratio of ~10:1. The predominant anaerobes in the female genital tract are *Prevotella, Bacteroides, Fusobacterium, Clostridium*, and the anaerobic *Lactobacillus* species. The skin microbiota contains anaerobes as well; *Cutibacterium acnes* (which was previously *Propionibacterium acnes* and will be considered as one of the *Propionibacterium* species for the remainder of this chapter) is the predominant species, and other species of propionibacteria and peptostreptococci are present in lower numbers.

ANAEROBES AND HUMAN HEALTH

Commensal anaerobes have been implicated as crucial mediators of physiologic, metabolic, and immunologic functions in the mammalian host. The intestinal microbiota is essential for fermenting dietary carbohydrates into forms that are more usable by the host, among which polysaccharides are the most abundant biological source of energy. Of the organisms found within the intestines, *Bacteroides* species express the widest array of polysaccharide-degrading enzymes, providing important nutrients for both the host and other commensal organisms. For example, *B. thetaiotaomicron* expresses 172 glycosyl hydrolases. The anaerobic intestinal microbiota is also responsible for the production of secreted products that promote human health (e.g., vitamin K and bile acids useful in fat absorption and cholesterol regulation).

One of the most important roles that anaerobes serve as components of the normal colonic microbiota is the promotion of resistance to colonization. The presence of commensal bacteria effectively interferes with colonization by potentially pathogenic bacterial species through the depletion of oxygen and nutrients, the production of enzymes and toxic end products, and the modulation of the host's intestinal innate immune response. For example, the normal intestinal microbiota plays an important role in protection against enteric infections, including those due to *Salmonella enterica* serotype Typhimurium and *Clostridium difficile*.

The anaerobic intestinal microbiota also has immunomodulatory properties that help regulate the immune system. The first example of this role was demonstrated with *B. fragilis*, which can balance the effector functions of T cells in the peripheral immune system and induce colonic regulatory T cells via expression of polysaccharide A (PSA). Moreover, *B. fragilis* expresses a glycosphingolipid that regulates the number of colonic invariant natural killer T cells. There are now numerous examples of commensal anaerobes that can modulate different aspects of the intestinal and extraintestinal immune system—everything from specific effector T cells to dendritic cells to antimicrobial peptides.

Clearly, the gut microbiota confers many benefits, and its dysregulation may play a role in the pathogenesis of diseases characterized by inflammation and aberrant immune responses, such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, asthma, and type 1 diabetes. Furthermore, the gut microbiota has been associated with obesity and metabolic syndrome. A more complete discussion of the intersection between the microbiota and human health is covered elsewhere **(Chap. 459)**.

ETIOLOGY

There are >10,000 species of bacteria—the overwhelming majority of which are anaerobes—in the human microbiota, with each individual colonized by hundreds of species. Anaerobic infections occur when the harmonious relationship between the host and the host's microbiota is disrupted. Any site in the body is susceptible to infection with these indigenous organisms if they are introduced into otherwise sterile tissue, either through disruption of mucosal surfaces (e.g., intestinal perforation, ischemia, surgery) or via direct inoculation of organisms into tissue (e.g., bite wounds, trauma). Because the sites that are colonized by anaerobes contain many species of bacteria, the resulting infections are often polymicrobial, involving multiple species of anaerobes in combination with synergistically acting facultative and/or microaerophilic organisms.

Despite the complex array of bacteria in the normal microbiota, relatively few genera are isolated commonly from human infections **(Fig. 172-1)**. While the specific organisms identified vary with the site and source of infection, the etiologic agents typically reflect the neighboring microbiota. For example, organisms normally found in the oro- and nasopharyngeal microbiota (e.g., *P. melaninogenica, Fusobacterium necrophorum, F. nucleatum, Peptostreptococcus* species, *Porphyromonas gingivalis, Porphyromonas asaccharolytica*, and *Actinomyces* species) can cause disease in contiguous areas, including odontogenic infections, peripharyngeal space infections, chronic sinusitis, and pleuropulmonary infections. In female genital tract infections, organisms normally colonizing the vagina (e.g., *Prevotella bivia* and *Prevotella disiens*) are the most common isolates. *Escherichia coli* and *B. fragilis*, both of which are components of the intestinal microbiota, are the most commonly identified isolates from intraabdominal abscesses. Indeed, the *B. fragilis* group, which encompasses 28 species and includes *B. thetaiotaomicron, B. vulgatus, B. uniformis*, and *B. ovatus*, contains the anaerobic organisms most frequently isolated from clinical infections.

It is useful to think about anaerobic infectious etiologies with regard not only to their anatomic location but also to their microbiologic features. While many anaerobic gram-negative bacilli cause disease (e.g., *Prevotella, Bacteroides, Fusobacterium*, and *Porphyromonas* species), *Veillonella* species, which are part of the oral and intestinal microbiota, are among the few anaerobic gram-negative cocci that have been implicated in human disease. Similarly, the peptostreptococci (e.g., *P. micros, P. asaccharolyticus*, and *P. anaerobius*) and *Finegoldia magnus* (which was previously *Peptostreptococcus magnus* and will be considered as part of the peptostreptococci for the remainder of this chapter) are the chief anaerobic gram-positive cocci that have pathogenic potential. *Clostridium* species are the primary anaerobic spore-forming gram-positive rods that produce human disease **(Chap. 149)**. Uncommonly, anaerobic

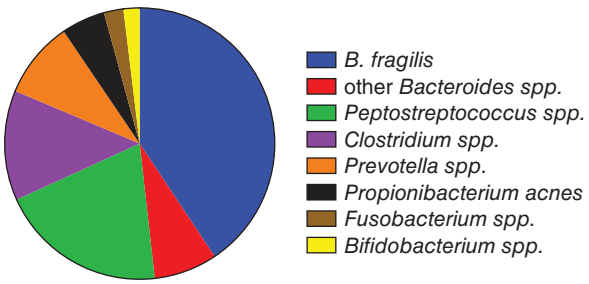

FIGURE 172-1 Distribution of all anaerobic organisms identified at a single hospital over a 7-year period. *(Data from Y Park et al: Clinical features and prognostic factors of anaerobic infections: A 7-year retrospective study. Korean J Intern Med 24:13, 2009.)*

gram-positive non-spore-forming bacilli cause infection; *P. acnes*, a component of the skin microbiota and a cause of foreign-body infections, and *Actinomyces* species are relevant examples.

PATHOGENESIS

First and foremost, anaerobic infections require an anaerobic environment with a lowered oxidation-reduction potential. In some circumstances, this environment can occur directly—e.g., in tissue ischemia, trauma, surgery, or a perforated viscus. In many other situations, the infection is polymicrobial, and the facultative organisms maintain a lowered oxidation-reduction potential in the local microenvironment that allows for the propagation of obligate anaerobes. Once the proper anaerobic environment is established, the organisms must still contend with the host's immune defenses. Similar to aerobic organisms, anaerobes express an array of virulence factors that help evade host defenses, they can form abscesses as a protective measure, and they can act synergistically with other bacteria to better persist in the host.

Virulence factors associated with anaerobes typically confer the ability to evade host defenses, adhere to cell surfaces, produce toxins and/or enzymes, or display surface structures such as capsular polysaccharides and lipopolysaccharide that contribute to pathogenic potential. The ability of an organism to adhere to host tissues is often critical to the establishment of infection. Some oral species adhere to the epithelium in the oral cavity. *P. gingivalis*, a common isolate in periodontal disease, has fimbriae that facilitate attachment. In supragingival plaque, many oral anaerobes are able to attach directly to aerobic bacteria (e.g., *Streptococcus* species) that are adherent to the tooth's surface. *F. nucleatum* is a notable example of these secondary colonizers: it expresses receptors to which almost all oral bacteria can bind and serves as an important bridge between the primary colonizers and subsequent layers of bacteria. *B. fragilis* synthesizes pili, fimbriae, and hemagglutinins that aid in attachment to host cell surfaces in the intestine.

Anaerobic bacteria produce a number of exoproteins that can enhance the organisms' virulence. *P. gingivalis* produces a collagenase that enhances tissue destruction. Exotoxins produced by clostridial species, including botulinum toxins, tetanus toxin, *C. difficile* toxins A and B, and five toxins produced by *Clostridium perfringens*, are among the most virulent bacterial toxins in mouse lethality assays. Anaerobic gram-negative bacteria, such as *B. fragilis, P. gingivalis*, and *Prevotella intermedia*, possess lipid A molecules (endotoxins) that are 100–1000 times less biologically potent than endotoxins associated with aerobic gram-negative bacteria; these differences may relate to variations in acylation status, length of fatty acids, and number of phosphate groups. This relative biologic inactivity may account for the lower frequency of disseminated intravascular coagulation and purpura in anaerobic gram-negative bacteremia than in facultative and aerobic gram-negative bacillary bacteremia. An exception is the lipopolysaccharide from *Fusobacterium*, which may account for the severity of Lemierre syndrome (see "Complications of Anaerobic Head and Neck Infections," below).

The most extensively studied virulence factor of the nonsporulating anaerobes is the capsular polysaccharide complex of *B. fragilis*. This organism is unique among anaerobes in its potential for virulence during growth at normally sterile sites. Although it constitutes only 0.5–1% of the normal colonic microbiota, *B. fragilis* is the anaerobe most commonly isolated from intraabdominal infections and bacteremia. In an animal model of intraabdominal sepsis, the capsular polysaccharide was identified as the major virulence factor of *B. fragilis*; this polymer plays a specific, central role in the induction of abscesses. A series of detailed biologic and molecular studies of this virulence factor showed that *B. fragilis* produces at least eight distinct capsular polysaccharides, far more than the number reported for any other encapsulated bacterium. *B. fragilis* can exhibit distinct surface polysaccharides either alone or in combination by regulating the expression of these different capsules in an on–off manner through a reversible inversion of DNA segments within the promoters for operons containing the genes required for polysaccharide synthesis. Structural analysis of two of these polysaccharides, PSA and polysaccharide B (PSB), revealed that each polymer consists of repeating units with positively charged free amino groups and negatively charged groups. This structural feature is rare among bacterial polysaccharides, and the ability of PSA—and, to a lesser extent, PSB—to induce abscesses in animals depends on this zwitterionic charge motif. Intraabdominal abscess induction is related to the capacity of PSA to stimulate macrophages to release cytokines and chemokines—in particular, interleukin (IL) 8, IL-17, and tumor necrosis factor α (TNF-α)—from resident peritoneal cells through a Toll-like receptor 2–dependent mechanism. The release of cytokines and chemokines results in the chemotaxis of polymorphonuclear neutrophils (PMNs) into the peritoneum, where they adhere to mesothelial cells induced by TNF-α to upregulate their expression of intercellular adhesion molecule 1 (ICAM-1). PMNs adherent to ICAM-1-expressing cells probably represent the nidus for an abscess. PSA also activates T cells to produce certain cytokines, including IL-17 and interferon γ, that are necessary for abscess formation.

These virulence factors not only promote persistence of the anaerobe that produces them but also aid in the survival of bystander organisms and result in bacterial synergies. Clinically, these synergies are evidenced by the fact that anaerobic infections typically involve three to six different organisms. Examples of this synergistic pathogenesis include creation of a favorable environment for growth (e.g., establishment and maintenance of an anaerobic environment by facultative organisms), inhibition of host defenses (e.g., production of short-chain fatty acids and succinic acid that inhibit the ability of phagocytes to clear facultative organisms), provision of necessary growth factors for other organisms (e.g., oral diphtheroids that produce vitamin K, which is needed by *P. melaninogenica*), and creation of tissue damage that promotes spread of the infection. In these ways, facultative and obligate anaerobes synergistically potentiate abscess formation.

APPROACH TO THE PATIENT

Infections Due to Anaerobic Bacteria

The physician must consider several points when approaching the patient with a possible infection due to anaerobic bacteria.

1. The organisms colonizing mucosal sites are commensals, very few of which typically cause disease. When these organisms do cause disease, it often occurs in proximity to the mucosal site they colonize.
2. For anaerobes to cause tissue infection, they must spread beyond the normal mucosal barriers.
3. Conditions favoring the propagation of anaerobic bacteria, particularly a lowered oxidation-reduction potential, are necessary. These conditions exist at sites of trauma, tissue destruction, compromised vascular supply, and necrosis.
4. Frequently, a complex array of infecting microbes can be found, occasionally with >10 different species isolated from a suppurative site.
5. Anaerobic organisms tend to be found in abscess cavities or in necrotic tissue. The failure of an abscess to yield organisms on routine culture is a clue that the abscess is likely to contain anaerobic bacteria. Often smears of this "sterile pus" are found to be teeming with bacteria when Gram's stain is applied. Although some facultative organisms (e.g., *Staphylococcus aureus*) are also capable of causing abscesses, abscesses in organs or deeper body tissues should call anaerobic infection to mind.
6. Gas is found in many anaerobic infections of deep tissues but is not diagnostic because it can be produced by aerobic bacteria as well.
7. Although a putrid-smelling infection site or discharge is considered diagnostic for anaerobic infection, this manifestation usually develops late in the course and is present in only 30–50% of cases.
8. Some species (the best example being the *B. fragilis* group) require specific therapy. However, many synergistic infections can be cured with antibiotics directed at some but not all of the organisms involved. Antibiotic therapy, combined with

debridement and drainage, disrupts the interdependent relationship among the bacteria, and some species that are resistant to the antibiotic do not survive without the co-infecting organisms.
9. Manifestations of severe sepsis and disseminated intravascular coagulation are unusual in patients with purely anaerobic infection.

EPIDEMIOLOGY

Difficulties in the performance of appropriate cultures, contamination of cultures by components of the normal microbiota, and the lack of readily available, reliable culture techniques have made it challenging to obtain accurate data on the incidence or prevalence of anaerobic infections. However, anaerobic infections are encountered frequently, with anaerobes comprising 7–8% and 13–15% of bacteria isolated from inpatients and outpatients, respectively. Bacteremia and soft tissue infections are the most common types of anaerobic infection **(Fig. 172-2)**. Typically, anaerobic bacteria account for <1% of all cases of bacteremia.

CLINICAL MANIFESTATIONS

Although anaerobes can cause infection anywhere in the body, certain clinical findings and characteristics are commonly found. These include abscess formation, putrid purulence (due to volatile fatty acid byproducts), septic thrombophlebitis, tissue necrosis, and failure to respond clinically to broad-spectrum antibiotics that lack activity against anaerobes.

Anaerobic Infections of the Mouth, Head, and Neck

Anaerobic bacteria are commonly involved in infections of the mouth, head, and neck **(Chap. 31)**. The predominant isolates are components of the normal microbiota of the upper airways—mainly *Prevotella* species, *P. asaccharolytica*, *Fusobacterium* species, peptostreptococci, and microaerophilic streptococci.

OROFACIAL INFECTIONS The most common oral infections are odontogenic and include dental caries and periodontal disease (gingivitis and periodontitis). While dental caries usually manifest with pain, sensitivity, and discoloration of the tooth, periodontal disease involves inflammation of the gums and underlying tissue. In its more severe forms, periodontitis can result in difficulty chewing, loose teeth, and occasionally tooth loss. Severe orofacial infections typically develop as a consequence of dental infection, and the infection can spread from the tooth to different anatomic areas that provide the least resistance, resulting in periapical, periodontal, or pericoronal infections. If the dental surface is completely breached, an endodontic infection (pulpitis) can occur. In late stages of pulpitis, the tooth is generally very sensitive to heat, but cold stimuli may provide relief. Left untreated, pulpitis can progress to invade the alveolar bone and develop into a periapical abscess. The abscesses, particularly those involving the second and third molars, can occasionally extend into the submandibular, sublingual, and submental spaces (*Ludwig's angina*). This infection results in marked local swelling of tissues, with pain, trismus, and superior and posterior displacement of the tongue. Submandibular swelling of the neck and obstruction by the tongue can impair swallowing and cause respiratory obstruction. In some cases, tracheotomy is lifesaving.

Microbiologically, dental caries begin with the binding of *Streptococcus mutans* and *Streptococcus sanguis* to the tooth surface, with subsequent further colonization by anaerobes. In contrast, periodontitis is typically associated with *P. gingivalis, Tannerella forsythensis, Aggregatibacter actinomycetemcomitans*, and *Treponema denticola*. *Fusobacterium*, *Actinomyces*, *Peptostreptococcus*, and *Bacteroides* species (other than *B. fragilis*) are the organisms most commonly isolated from periapical abscesses.

ACUTE NECROTIZING ULCERATIVE GINGIVITIS Gingivitis may become a necrotizing infection (*trench mouth*, *Vincent's stomatitis*) **(Chap. 31)**. The onset of disease is usually sudden and is associated with painful bleeding gums, foul breath, and a bad taste. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a yellowish-white or gray "pseudomembrane," which is removable with gentle pressure. Patients may become systemically ill, developing fever, malaise, cervical lymphadenopathy, and leukocytosis. The infection can sometimes extend into the pharynx, resulting in an extremely sore throat, foul breath, and tonsillar pillars that are swollen, red, ulcerated, and covered by a pseudomembrane. *Prevotella*, *Treponema*, and *Fusobacterium* species have been implicated.

In some cases, acute necrotizing gingivitis can rapidly progress to noma (*cancrum oris*), a gangrenous infection that destroys the soft and hard tissues related to the oral cavity. Noma occurs most frequently in young children (1–4 years of age) who have immune dysfunction related to malnutrition and endemic infections (particularly measles). This infection occurs worldwide but is most common in sub-Saharan Africa, where the incidence is 1–7 cases per 1000 children. Although the pathogenesis is not fully understood, infection with *F. necrophorum* and *P. intermedia* are thought to be key drivers of this disease. Without treatment, the mortality rate is 70–90%.

PERIPHARYNGEAL SPACE INFECTIONS These infections arise from the spread of organisms from the upper airways to potential spaces formed by the fascial planes of the head and neck. The etiology is typically polymicrobial and represents the normal microbiota of the mucosa of the originating site.

Peritonsillar abscess (*quinsy*) is the most common peripharyngeal infection and occurs as a complication of acute tonsillitis. Consistent with its association with tonsillitis, adolescents are most commonly affected. Patients present with a sore throat, dysphagia, peritonsillar swelling, muffled voice, and uvular deviation to the contralateral side. The abscess material typically grows group A *Streptococcus* in conjunction with obligate anaerobes (e.g., *Bacteroides*, *Prevotella*, and *Peptostreptococcus* species) **(Chap. 31)**. Retropharyngeal abscesses typically occur in children 2–4 years of age, although they can occur at any age. Although a suppurative infection of the retropharyngeal lymph nodes is the usual precursor to these abscesses in children, foreign-body ingestion and/or local trauma is more commonly the inciting factor in adults. The clinical presentation shares many features with peritonsillar abscesses, but difficulty extending the neck and torticollis are more common with retropharyngeal abscesses. The etiologic agents are the same as in peritonsillar abscesses, with additional aerobic organisms (e.g., *S. aureus*, viridans streptococci) also playing a role.

SINUSITIS AND OTITIS Anaerobic bacteria have been implicated in chronic sinusitis but play little role in acute sinusitis. Numerous studies related to the microbiology of chronic sinusitis have been conducted; on average, anaerobic bacteria have been found in two-thirds of patients, with many studies demonstrating their presence in >90% of patients. Anaerobic bacteria represent ~40% of all bacteria cultured, with *Peptostreptococcus*, *Prevotella*, and *Porphyromonas* species the most commonly isolated anaerobes. *S. aureus* and Enterobacteriaceae are the aerobes most commonly recovered in chronic sinusitis. Anaerobic bacteria have been isolated in ~60% of cases of chronic suppurative otitis media in children, but they are not involved in acute otitis media.

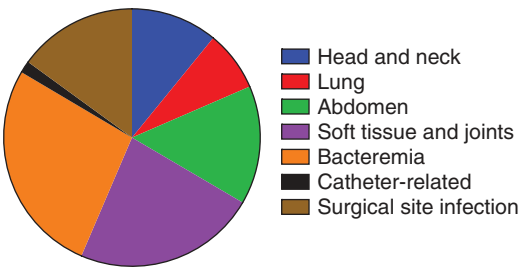

FIGURE 172-2 Distribution of types of infection from which anaerobic organisms were cultured at a single hospital over a 7-year period. Head and neck infections included sinusitis, otitis media, and retropharyngeal abscess; abdominal infections included liver abscess, biliary tract infection, bowel obstruction, and intraabdominal abscess; catheter-related infections included those related to peritoneal dialysis catheters and ventriculoperitoneal shunts. *(Data from Y Park et al: Clinical features and prognostic factors of anaerobic infections: A 7-year retrospective study. Korean J Intern Med 24:13, 2009.)*

COMPLICATIONS OF ANAEROBIC HEAD AND NECK INFECTIONS Direct extension of these infections into contiguous areas can result in additional disease manifestations. Cranial spread of these infections can result in osteomyelitis of the skull or mandible or in intracranial infections, such as brain abscess and subdural empyema. Caudal spread can produce mediastinitis or pleuropulmonary infection. Hematogenous complications can also result from anaerobic infections of the head and neck. Bacteremia, which occasionally is polymicrobial, can lead to endocarditis or other distant infections. Lemierre syndrome **(Chap. 31)**, which is usually due to *F. necrophorum*, is an acute oropharyngeal infection with secondary septic thrombophlebitis of the internal jugular vein and frequent septic emboli, most commonly to the lung. This infection typically begins with pharyngitis, which is followed by local invasion in the lateral pharyngeal space, with resultant internal jugular vein thrombophlebitis.

Central Nervous System (CNS) Infections CNS infections associated with anaerobic bacteria are brain abscess, epidural abscess, and subdural empyema, in which anaerobes are recovered in up to 30, 20, and 10% of cases, respectively. The frequency with which anaerobes are recovered depends in large part on the underlying reason for the infection. For example, brain abscesses are typically due to hematogenous seeding, contiguous spread, penetrating head trauma, or recent surgical intervention. Anaerobic bacteria are most commonly associated with brain abscesses resulting from contiguous spread (related to otogenic, odontogenic, and sinus infections), and the pathogens recovered are the same as in these antecedent infections. Facultative or microaerophilic streptococci and coliforms are often part of a mixed infecting flora in brain abscesses. The location of the abscess may also provide insight into the pathogens. Abscesses in the frontal lobe (often associated with sinusitis) are due to anaerobes, streptococci, and staphylococci; temporal lobe and cerebellar abscesses are often related to the oral microbiota and middle-ear pathogens.

Obligate anaerobes rarely cause meningitis. Only one obligate anaerobe was identified in a seminal study of 188 bacterial meningitis isolates, and a U.S. national surveillance study of 18,642 such isolates collected between 1977 and 1981 found only five obligate anaerobes. This low incidence may be due, in part, to the fact that many clinical microbiology laboratories do not routinely culture cerebrospinal fluid (CSF) for anaerobes.

Pleuropulmonary Infections The lungs are constantly seeded with organisms from the oral microbiota via subclinical microaspiration that normally occurs in all people. Even though the lung is the site of oxygen exchange and is therefore an overwhelmingly aerobic environment, the organisms most abundant in the lower respiratory tract (as assessed by culture-independent methods) include anaerobes such as *Prevotella* and *Veillonella* species, with oral microaerophilic streptococcal species (e.g., the *Streptococcus milleri* group) also present in significant abundances. In patients who have impaired bacterial clearance (due to decreased cough, dysfunctional mucociliary transport, or alcohol intoxication) and/or increased rates of aspiration (due to neurologic disorders, impaired consciousness, or swallowing dysfunction), these anaerobic bacteria can establish an infection and result in aspiration pneumonia, lung abscess, or empyema. These anaerobic infections have an indolent course that may serve as a clinical clue differentiating them from conditions with other etiologies (e.g., chemical pneumonitis, pneumococcal pneumonia) that often present more acutely.

ASPIRATION PNEUMONIA Bacterial aspiration pneumonia must be distinguished from two other clinical syndromes associated with aspiration that are not of bacterial etiology. One syndrome results from aspiration of food or, rarely, other foreign bodies. Obstruction of major airways typically results in difficulty breathing, atelectasis, and moderate nonspecific inflammation. Therapy consists of removal of the foreign body. The second aspiration syndrome relates to chemical pneumonitis caused by inhalation or aspiration of alveolar irritants. Perhaps the most common cause of chemical pneumonitis is *Mendelson syndrome*, which results from regurgitation and aspiration of acidic gastric juices. Pulmonary inflammation—including the destruction of the alveolar lining, with transudation of fluid into the alveolar space—occurs with remarkable rapidity. This syndrome typically develops within 4–6 h, often following anesthesia when the gag reflex is depressed. The patient becomes tachypneic, tachycardic, and hypoxic, often in the absence of fever. The leukocyte count may rise, and the chest x-ray may evolve from normal to a complete bilateral "whiteout" within 8–24 h. Sputum production is minimal. The pulmonary signs and symptoms often resolve quickly with symptom-based therapy, but this condition can culminate in respiratory failure due, in part, to pulmonary edema. Antibiotic therapy is not indicated unless bacterial superinfection occurs.

In contrast to these syndromes, bacterial aspiration pneumonia develops over a period of several days or weeks rather than hours. The pathogenesis includes some combination of an increased bacterial burden, increased virulence of the organisms aspirated, and potential airway damage related to aspiration of gastric fluid. Patients generally report fever, malaise, and sputum production. In some patients, weight loss and anemia reflect a more chronic process. Usually the history reveals factors predisposing to aspiration, such as significant alcohol consumption or neurologic impairment due to a previous stroke. Severe dental disease is often associated with aspiration pneumonia, but it is not clear whether this association relates to an increased number of oral microbes and/or the presence of organisms with increased virulence. Sputum characteristically is not malodorous unless the process has been ongoing for at least a week. Chest x-rays show consolidation in dependent pulmonary segments: in the basilar segments of the lower lobes if the patient has aspirated while upright and in either the posterior segment of the upper lobe (usually on the right side, given that the right mainstem bronchus has a more vertical orientation) or the superior segment of the lower lobe if the patient has aspirated while supine.

A mixed bacterial population with many PMNs is evident on Gram's staining of sputum. Expectorated sputum is unreliable for anaerobic cultures because of inevitable contamination by the normal oral microbiota. Reliable specimens for culture can be obtained by transtracheal or transthoracic aspiration—techniques that are rarely used at present. Although the culture of protected-brush specimens or bronchoalveolar lavage fluid obtained by bronchoscopy is controversial, more recent data suggest that these approaches can be used without oropharyngeal contamination and can recover anaerobic organisms from the lower respiratory tract in a site-directed manner. Further research is needed to determine how these approaches compare with the previous gold standards.

ANAEROBIC LUNG ABSCESSES **(See also Chap. 122)** These abscesses result from subacute anaerobic pulmonary infection. The clinical presentation typically involves a history of constitutional signs and symptoms (including malaise, weight loss, fever, night sweats, and foul-smelling sputum) that have typically persisted for 1–3 weeks prior to hospitalization. Patients who develop lung abscesses often, but not always, have an antecedent dental infection. Abscess cavities may be single or multiple and generally occur in dependent pulmonary segments **(Fig. 172-3)**. The differential diagnosis for lung abscesses includes pneumonia (including necrotizing pneumonia), a purulent pleural effusion with a bronchopleural fistula, and a pneumatocele. Of note, infection with some aerobic organisms, particularly *S. aureus*, can develop into a lung abscess without an anaerobic component. Approximately 90% of cases have an anaerobe identified—usually three to six isolates per sample—if careful attention is paid to handling and processing of the abscess sample. The most common isolates include peptostreptococci, *Prevotella* and *Porphyromonas* species, and *F. nucleatum*. An important finding is that ~90% of cultures also demonstrate the presence of aerobic organisms, such as *S. aureus*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*. Consistent with the notion that anaerobes are contributing to disease, patients often do not improve clinically until they receive an antibiotic regimen that includes anaerobic coverage.

EMPYEMA Empyema is a manifestation of long-standing anaerobic pulmonary infection and manifests with thick, purulent material in the pleural space, often in association with a bronchopleural fistula. Alternatively, a subdiaphragmatic infection may extend into the pleural

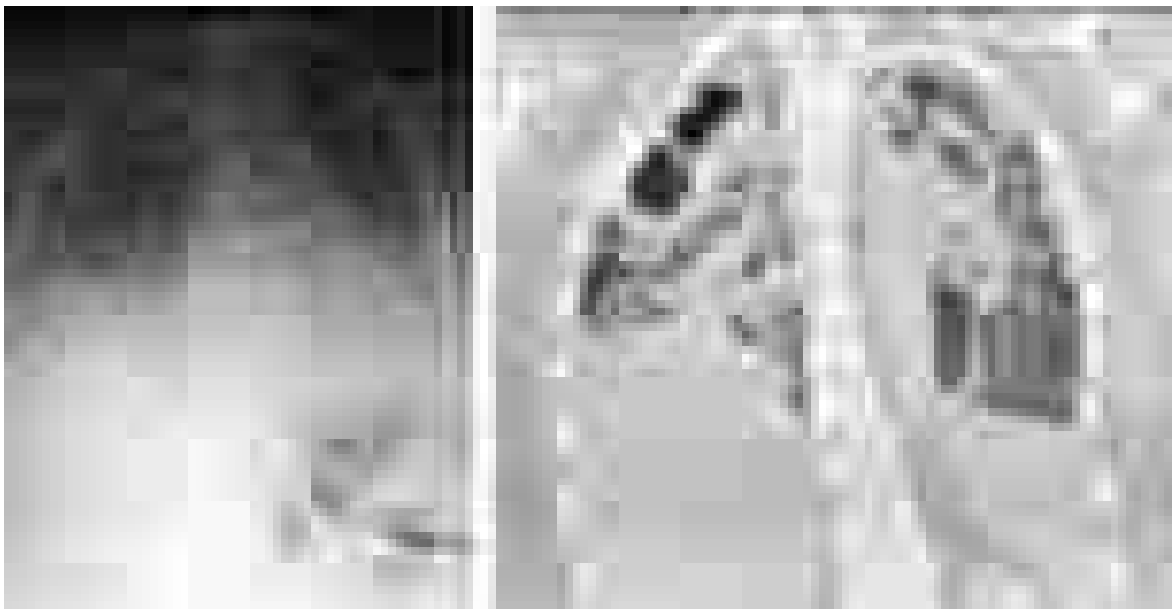

FIGURE 172-3 Chest radiograph (*left*) and CT image (*right*) of a lung abscess. The patient aspirated while supine and developed an abscess in the posterior segment of the right upper lobe. Cultures were pretreated and grew only *Klebsiella pneumoniae*. *(Images provided by Gita N. Mody, MD, MPH, Division of Thoracic Surgery, Brigham and Women's Hospital, Boston.)*

space and similarly result in an empyema. The clinical presentation resembles that of other anaerobic pulmonary infections and may include foul-smelling sputum, pleuritic chest pain, and marked chest-wall tenderness. This disease process must be differentiated from a parapneumonic effusion resulting from more routine causes of pneumonia (e.g., *S. pneumoniae*). In the latter instance, the fluid is a thin exudate that has a mean white blood cell (WBC) count of ~5000 cells/mL, a lactate dehydrogenase level of >200 IU/L, and a pH of ~7.4. In contrast, empyema is characterized by foul-smelling thick pus with a mean WBC count of ~55,000 cells/mL, a lactate dehydrogenase level of >1000 IU/L, and a pH of <7.2 as well as loculations and a thick pleural peel on imaging. Drainage and occasionally decortication of the visceral and parietal pleura are required. Defervescence, a return to a feeling of well-being, and resolution of the process may require several months, particularly in the absence of surgical intervention.

Intraabdominal Infections Breach of the gut mucosal surface (e.g., due to trauma, intestinal perforation, or malignancy) allows members of the microbiota to enter the normally sterile peritoneum. Accordingly, the offending organisms reflect the microbiota in the affected intestinal region. For example, recovery of *Candida* species from intraabdominal infections should prompt evaluation of the stomach and proximal small bowel for potential perforation. Furthermore, a study of patients with perforated and gangrenous appendicitis demonstrated that virtually all samples yielded *E. coli* and members of the *B. fragilis* group; peptostreptococci and *Bilophila wadsworthia*—additional components of the appendiceal and colonic microbiota—were also recovered from >50% of samples. Notably, some studies have identified an average of 10 different bacterial species, with an anaerobe-to-aerobe ratio of ~3:1. Given that >1000 bacterial species are present in the colonic microbiota, the dominance of such a limited repertoire of bacterial genera and species recovered in intraabdominal infections reflects a combination of two factors: the increased propensity of these organisms to result in intraabdominal abscesses and the difficulty faced by clinical microbiology laboratories in culturing the diverse organisms present in these samples. **See Chap. 127 for a complete discussion of intraabdominal infections.**

Neutropenic enterocolitis (typhlitis) involves marked thickening of the bowel wall (typically >4 mm) in the setting of neutropenia, abdominal pain, and fever. This condition most commonly affects the cecum and may extend to the neighboring terminal ileum and/or proximal colon, but any intestinal region may be involved. Typhlitis generally occurs after 1–2 weeks of chemotherapy-induced neutropenia associated with treatment of hematologic or, less commonly, solid tumor malignancies, but it can occur regardless of the cause of neutropenia. At least 5% of adults hospitalized for malignancy are thought to develop typhlitis, but this is likely an underestimate. Although the right lower quadrant is the most common location of abdominal pain and tenderness, these symptoms are absent in nearly half of cases; moreover, some patients, particularly those taking glucocorticoids, may not experience abdominal pain at all. Given the weakened integrity of the bowel wall and the associated neutropenia, patients often develop bacteremia due to one or more organisms related to the microbiota of the affected intestinal segment. Patients who develop bacteremia due to *Clostridium septicum* often have relatively severe disease, and identification of this organism is highly associated with the presence of malignancy—notably, colon cancer. Medical management including bowel rest, intestinal decompression, and broad-spectrum antibiotic administration is generally successful, although surgical intervention may be required in cases of persistent intestinal bleeding, necrotic bowel, or clinical deterioration suggestive of an ongoing intestinal process.

Pelvic Infections Anaerobes are frequently encountered in pelvic inflammatory disease, pelvic abscess, endometritis, tubo-ovarian abscess, septic abortion, and postoperative or postpartum infections. These infections are often of mixed etiology, involving both anaerobes and coliforms; pure anaerobic infections without coliform or other facultative bacterial species occur more often in pelvic than in intraabdominal sites. The major anaerobic pathogens in pelvic abscesses are *P. bivia*, *P. disiens*, and the *B. fragilis* group, but many other anaerobes have also been implicated. **See Chap. 131 for a complete discussion of pelvic inflammatory disease.**

Anaerobic bacteria have been thought to be contributing factors in bacterial vaginosis. This syndrome of unknown etiology is characterized by a profuse malodorous discharge and a change in bacterial ecology that results in replacement of the *Lactobacillus*-dominated normal microbiota with an overgrowth of anaerobic bacterial species. Culture-based and culture-independent approaches have identified numerous organisms, including *Gardnerella vaginalis*, peptostreptococci, genital mycoplasmas, and species within the genera *Prevotella*, *Mobiluncus*, *Atopobium*, *Leptotrichia*, *Megasphaera*, and *Eggerthella*. This wide array of implicated bacteria may reflect differences in the overall disease spectrum of bacterial vaginosis and/or a shared physiologic response to these different organisms.

Skin and Soft Tissue Infections Similar to other anatomic sites, skin or soft tissue injured by trauma, ischemia, or surgery creates a

suitable environment for anaerobic infections. The infecting bacteria either are introduced directly (e.g., wounds associated with intestinal surgery, decubitus ulcers, or human bites) or originate in contiguous areas (e.g., cutaneous abscesses, rectal abscesses, and axillary sweat gland infections [*hidradenitis suppurativa*]). Anaerobes also are often cultured from foot ulcers of diabetic patients. The most common locations for anaerobic cellulitis include the neck, trunk, groin (including the genitalia), and legs. The deep soft-tissue infections associated with anaerobic bacteria are gas gangrene, synergistic cellulitis (both progressive and necrotizing), necrotizing fasciitis, and myositis **(Chaps. 124 and 149)**.

Gas gangrene (crepitus cellulitis) is most often due to *C. perfringens*, although other clostridial species have been implicated as well. This infection involves extensive gas formation in the tissue leading to crepitus and a thin, dark, occasionally malodorous discharge. True gas gangrene typically presents with fever and tenderness around the lesion and can rapidly spread; in contrast, there are somewhat more indolent forms of anaerobic cellulitis that may involve some gas formation but often present without fever or extensive local pain and can spread over the course of days rather than minutes.

Progressive bacterial synergistic gangrene (*Meleney gangrene*) is characterized by an area of exquisite pain, redness, and swelling followed by ulceration. As the ulcer enlarges, it is surrounded by a violaceous ring that fades into a pink edematous border. If it is not promptly treated, the ulcer continues to enlarge, and new, distant ulcers may emerge. Symptoms are limited to pain; fever is not typical. Peptostreptococci and microaerophilic streptococci are commonly found in the leading edge of the lesions, and *S. aureus* and *Proteus* species can be isolated from the ulcerated lesion. Treatment includes surgical removal of necrotic tissue and antimicrobial administration. In contrast, synergistic necrotizing cellulitis involves the deep fascia and occurs near the point of bacterial entry. Pain, fever, and systemic symptoms are common. If this form of cellulitis involves the scrotum, perineum, and anterior abdominal wall, it is referred to as *Fournier gangrene*. *S. aureus*, the *B. fragilis* group, *Peptostreptococcus* species, *Clostridium* species, *Fusobacterium* species, and members of the family Enterobacteriaceae are the predominant organisms identified.

Necrotizing fasciitis, a rapidly spreading destructive disease of the fascia, is usually attributed to group A streptococci **(Chap. 143)** but can also be a mixed infection involving anaerobes and aerobes. Polymicrobial necrotizing fasciitis differs from stereotypical group A streptococcal necrotizing fasciitis in that the initial erythematous, swollen, tender lesions progress over 3–5 days (as opposed to 1–3 days), with consequent skin breakdown and cutaneous gangrene. Fever, subcutaneous gas, development of anesthesia (often before skin necrosis), and a foul-smelling discharge are common. The particular clinical findings sometimes suggest the causative agent: regional lymphadenopathy suggests the *B. fragilis* group; necrosis and gangrene suggest *Clostridium* species, peptostreptococci, the *B. fragilis* group, and Enterobacteriaceae; bullous lesions suggest Enterobacteriaceae; a foul-smelling odor suggests *Bacteroides* and *Clostridium* species; and subcutaneous gas suggests peptostreptococci, *Clostridium* species, and the *B. fragilis* group. Moreover, diabetic infections are often associated with *Bacteroides* species, Enterobacteriaceae, and *S. aureus*, and infections related to trauma are associated with *Clostridium* species.

Although *S. aureus* is the typical cause of myositis, anaerobes—particularly *C. perfringens*—are often recovered from patients with pyogenic myositis. In anaerobic streptococcal myonecrosis, peptostreptococci are often identified along with group A streptococci or *S. aureus*. Patients typically present with fever, muscle pain, fatigue, and an elevated creatinine kinase level suggestive of muscle inflammation.

Bone and Joint Infections A comprehensive review of the world literature on anaerobic bone infections included >650 cases. Of these, ~400 cases were caused by *Actinomyces* species; anaerobic cocci and *Bacteroides*, *Fusobacterium*, and *Clostridium* species were most commonly identified in the remaining cases. Actinomycotic involvement of the jaw was the most common bone infection, with the mandible involved four times as frequently as the maxilla. Patients with cervicofacial actinomycosis **Chap. 170)** are often described as having a "lumpy jaw" because of the prominent soft-tissue swelling that is sometimes mistaken for malignancy or granulomatous disease. These infections can be chronic in nature, can include the development of sinus tracts, can progress across normal tissue boundaries, and can require prolonged antibiotic treatment to prevent relapse. The vertebrae are the second most common location for *Actinomyces* infection; involvement of the thorax, abdomen, or pelvis is much less frequent.

Osteomyelitis involving anaerobes other than *Actinomyces* species most commonly develops by extension of an adjacent infection (e.g., soft tissue, paranasal sinus, or middle-ear infection). For example, diabetic foot ulcers and decubitus ulcers may be complicated by mixed aerobic–anaerobic osteomyelitis **(Chap. 126)**. Hematogenous seeding of bone by anaerobes is uncommon and is thought to occur in fewer than 10% of cases. The most common sites of anaerobic osteomyelitis are the head (skull and jaw) and the extremities. Fusobacteria have been isolated in pure culture from infections of the mastoid, mandible, and maxilla. *Clostridium* species have been reported as anaerobic pathogens in cases of osteomyelitis of the long bones following trauma. Anaerobic and microaerophilic cocci are most frequently isolated from infections involving the skull or mastoid; usually, these organisms are present in mixed cultures.

In contrast to anaerobic osteomyelitis, anaerobic arthritis **(Chap. 125)** is uncommon, typically involving a single isolate, and most cases are secondary to hematogenous spread. Although *Fusobacterium* species accounted for nearly one-third of cases in the pre-antibiotic era, *P. acnes*, peptostreptococci, and *B. fragilis* are now among the more frequent causes of anaerobic septic arthritis. Peptostreptococci and *P. acnes* are often found in association with prosthetic joints, *Fusobacterium* species have a predilection for the sternoclavicular and sacroiliac joints, and clostridial arthritis is especially common after trauma. As a frequent cause of bacteremia, *B. fragilis* is a common cause of anaerobic septic arthritis; however, arthritis occurs in fewer than 5% of patients with *B. fragilis* bacteremia.

Bacteremia *B. fragilis* is the anaerobe most commonly isolated from blood cultures. Although the frequency of positive cultures appeared to be decreasing in the 1980s, more recent evidence suggests that the rate is now increasing and that the increase may be related to changing demographics, with more patients who are elderly, immunocompromised, and/or receiving medications that may disrupt the mucosal barrier (e.g., chemotherapy). The source of bacteremia is most often an abscess in the abdomen, female genital tract, or soft tissue. At a large tertiary-care U.S. hospital, 0.8% of all positive blood cultures yielded an anaerobic gram-negative bacillus, with 0.5% yielding *B. fragilis*. A similar study in France revealed that 0.6% of all positive blood cultures yielded an anaerobic organism; 60% of these isolates were *Bacteroides* species, and 22% were *Clostridium* species. *Peptostreptococcus* and *Fusobacterium* species are also recovered with significant frequency.

Once the organism in the blood has been identified, both the portal of bloodstream entry and the underlying problem that probably led to seeding of the bloodstream can often be deduced from an understanding of the organism's normal site of residence. For example, mixed anaerobic bacteremia including *B. fragilis* usually implies a colonic pathology, with mucosal disruption from neoplasia, diverticulitis, or some other inflammatory lesion. The initial manifestations are determined by the portal of entry and reflect the localized condition. Although the clinical manifestations of *B. fragilis* bacteremia (e.g., rigors, hectic fevers) are similar to those of aerobic gram-negative bacillary bacteremia, the incidence of septic shock is lower with *B. fragilis*. This difference may be due to differences in the immunostimulatory effects of the different endotoxin structures.

In virtually all cases, isolation of a member of the *B. fragilis* group from blood indicates underlying infection that is associated with a mortality rate of 60% if untreated. It has been suggested that the mortality rate depends in part on the species recovered (*B. thetaiotaomicron* > *P. distasonis* > *B. fragilis*), but it is unclear whether differences in mortality rates relate to intrinsic differences in the virulence of these organisms, in their antimicrobial susceptibility profiles, and/or in the host's immune response. Case–fatality rates appear to increase with the increasing age

of the patient (with reported rates of >66% among patients >60 years old), with the isolation of multiple species from the bloodstream, and with the failure to surgically remove a focus of infection.

Endocarditis (See also Chap. 123) Although gram-negative anaerobic bacteria only rarely cause endocarditis, their involvement is associated with significant mortality rates (21–43%). Members of the *B. fragilis* group are the most commonly identified gram-negative anaerobes in endocarditis. Anaerobic streptococci, which are often classified incorrectly, are likely responsible for this disease more frequently than is generally appreciated. Compared to aerobic bacterial endocarditis, endocarditis due to *Bacteroides* species is less likely to be associated with a history of cardiovascular disease and more likely to involve thromboembolic complications.

DIAGNOSIS

There are three critical steps in the diagnosis of anaerobic infection: (1) proper collection of specimens; (2) rapid transport of the specimens to the microbiology laboratory, preferably in anaerobic transport media; and (3) proper handling of the specimens by the laboratory. Specimens must be collected by meticulous sampling of infected sites, with avoidance of contamination by the normal microbiota. Samples from sites known to harbor numerous anaerobes (e.g., the mouth, nose, vagina, feces) are not acceptable for anaerobic culture as the presence of the normal microbiota will complicate interpretation of the results in a clinically meaningful manner. In contrast, samples from normally sterile locations (e.g., blood, pleural fluid, peritoneal fluid, CSF, and aspirates or biopsy samples from normally sterile sites) are appropriate for anaerobic culture in clinical microbiology laboratories. As a general rule, liquid or tissue specimens are preferred; if swab specimens must be used, special anaerobic swab systems should be used to help maintain persistence of anaerobes. Liquid samples should be collected in an air-free syringe that is then capped, injected into anaerobic transport bottles, or quickly transported to the clinical microbiology laboratory for immediate culture.

Because of the time and difficulty involved in the isolation of anaerobic bacteria, the diagnosis of anaerobic infections must frequently be based on presumptive evidence. As mentioned previously, anaerobic infections are sometimes suggested by specific clinical factors, such as origins from a site with an anaerobic-rich microbiota (e.g., the intestinal tract, oropharynx), the presence of an abscess, involvement of sites with lowered oxidation-reduction potential (e.g., avascular necrotic tissues), a foul odor, and the presence of gas in tissues. None of these features is necessarily pathognomonic or required for the diagnosis of an anaerobic infection, but these are helpful clues to keep in mind when constructing a differential diagnosis.

When cultures of obviously infected sites or purulent material yield no growth, streptococci only, or a single aerobic species (such as *E. coli*) and Gram's staining reveals a mixed bacterial population, the involvement of anaerobes should be suspected; the implication is that the anaerobic microorganisms have failed to grow because of inadequate transport and/or culture techniques. It is also important to remember that prior antibiotic therapy reduces the cultivability of these bacteria. Failure of an infection to respond to antibiotics that are not active against anaerobes (e.g., aminoglycosides and—in some circumstances—penicillin, cephalosporins, or tetracyclines) suggests an anaerobic etiology.

TREATMENT

Anaerobic Infections

Similar to successful therapy for other types of infection, treatment for anaerobic infections requires the administration of appropriate antibiotics, surgical debridement of devitalized tissues, and drainage of any large abscess. Any mucosal breach must be closed promptly to prevent ongoing infection.

ANTIBIOTIC THERAPY AND RESISTANCE

The antibiotics used to treat anaerobic infections should be active against both aerobic and anaerobic organisms because many of these infections are of mixed etiology. Antibiotic regimens can usually be selected empirically on the basis of the location of infection (which provides insight into the likely species involved), the severity of infection, and knowledge of local antimicrobial resistance patterns. Other factors influencing the selection of antibiotics include need for penetration into certain organs (such as the brain) and associated toxicity (Chap. 139). As with all infections, the general maxim is to use the least broad-spectrum agent(s) possible so as to minimize the impact on the normal microbiota and the development of resistance.

Because of the slow growth rate of many anaerobes, the lack of standardized testing methods and of clinically relevant standards for resistance, and the generally good results obtained with empirical therapy, the role of antibiotic susceptibility testing of these organisms has been limited in most clinical microbiology laboratories. Instead, isolates are sent to reference laboratories for susceptibility testing when an infection is serious (e.g., brain abscess, meningitis, joint infection), is refractory, or requires prolonged therapy (e.g., osteomyelitis, prosthetic joint infection, endocarditis). Such testing should also be considered when a patient is not responding to antimicrobial therapy as expected; multidrug-resistant anaerobes have been reported. Antimicrobial susceptibility testing is also helpful in monitoring the activity of new drugs and recording current resistance patterns among anaerobic pathogens.

The need for susceptibility testing of anaerobic organisms is highlighted by increasing rates of antimicrobial resistance, geographic and institutional differences in susceptibility profiles, species-specific antibiograms, and the potential for worse clinical outcomes when ineffective antibiotics are used. These differences preclude making any sweeping generalizations regarding antibiotic therapy for anaerobic infections. For example, rates of resistance to piperacillin-tazobactam have remained low (≤1%) for all *Bacteroides* species in the United States, but *B. thetaiotaomicron* isolates in Korea have a notably higher resistance rate (17%). Clindamycin was historically effective against members of the *B. fragilis* group, but rates of resistance have increased to 30–43% in the United States and are >80% in some parts of the world. Furthermore, metronidazole is effective against many different anaerobic organisms and is considered a first-line agent for many anaerobic infections worldwide, but, in a population of Colombian patients with refractory periodontitis, 45% of *Fusobacterium* isolates and 25% of *Prevotella* and *Porphyromonas* strains were resistant to metronidazole; this finding underscores the importance of understanding the local antibiogram and of assessing susceptibility profiles in refractory disease.

Empirical Therapy Not every anaerobe isolated must be specifically targeted by the antibiotic regimen. Given that infections involving anaerobes are typically polymicrobial, that the cultivation and identification of anaerobes are challenging (i.e., not all organisms may be recovered), and that organisms often depend on one another for persistence, clinical resolution of the infection is often achieved with empirical antibiotics targeting the bulk of the organisms recovered. Antibiotics that demonstrate no useful activity against anaerobes include aminoglycosides, monobactams, and trimethoprim-sulfamethoxazole. With the caveat that susceptibility profiles may change with time and geography, the antibiotics that are commonly used as empirical therapy against anaerobic bacteria include metronidazole, β-lactam/β-lactamase inhibitor combinations, clindamycin, carbapenems, and chloramphenicol (Table 172-2).

Metronidazole is active against gram-negative anaerobes, including nearly all isolates of *Bacteroides* species, and gram-positive spore-forming organisms, such as *C. difficile* (Chap. 129) and other *Clostridium* species. Given intrinsically reduced susceptibility, metronidazole is clinically unreliable against gram-positive non-spore-forming organisms, such as *Actinomyces*, *Propionibacterium*, *Lactobacillus*, *Bifidobacterium*, *Eubacterium*, and *Peptostreptococcus*. Of note, a few metronidazole-resistant *Bacteroides* isolates have been identified in the United States, and rates of such resistance have been increasing in Europe. Moreover, the rate of resistance to metronidazole has probably been greatly underestimated in some countries

TABLE 172-2 Antimicrobial Therapy That Is Typically Active Against Commonly Encountered Anaerobes

ANTIBIOTIC(S)	CAVEATS
Metronidazole	This drug is clinically unreliable against gram-positive non-spore-forming anaerobes (e.g., *Actinomyces* spp., *Propionibacterium* spp., *Peptostreptococcus* spp.).
β-Lactam/β-lactamase inhibitor combinations (ampicillin-sulbactam, ticarcillin–clavulanic acid, piperacillin-tazobactam)	Rates of resistance are increasing in some gram-negative anaerobes. The newer cephalosporin/β-lactamase combinations have limited anaerobic activity.
Clindamycin	Rates of resistance are increasing in *Bacteroides* spp.
Carbapenems (meropenem, imipenem, ertapenem, doripenem)	Rates of resistance are currently very low (<5%), although some carbapenemase-producing strains have been identified.
Chloramphenicol	Some clinical failures have been noted, even when the isolate is found to be susceptible by in vitro testing.

(e.g., the United Kingdom) that use metronidazole susceptibility to discriminate between obligate and facultative anaerobes (with obligate anaerobes defined by their susceptibility). Although the majority of metronidazole-resistant isolates have been identified in patients who have been exposed to the drug, resistant organisms have also been found in metronidazole-naïve patients.

More than 90% of clinical isolates from the *B. fragilis* group produce β-lactamases that are predominantly active against cephalosporins and that are highly active, cell associated, and produced constitutively. Thus, members of the *B. fragilis* group are presumed to be resistant to penicillin and ampicillin but may remain susceptible to extended-spectrum penicillins, particularly in combination with a β-lactamase inhibitor (e.g., ampicillin-sulbactam, piperacillin-tazobactam). Rates of resistance to ampicillin-sulbactam are increasing, particularly in *P. distasonis*, which has a reported resistance rate of 21% in the United States. Because β-lactamase production is not common in *Clostridium* species, these combination agents are usually effective. Of note, the newer cephalosporin/β-lactamase inhibitors (e.g., ceftolozane-tazobactam, ceftazidime-avibactam) have limited anaerobic activity.

Clindamycin is active against many anaerobes. However, rates of resistance to clindamycin among *Bacteroides* species increased in the United States from 7% in 1981 to 35% in 2008–2009. Resistance to clindamycin among non-*Bacteroides* gram-negative anaerobes is much less common (<10%). Some *Clostridium* species are resistant to clindamycin, although *C. perfringens* typically is not.

Carbapenems (ertapenem, doripenem, meropenem, and imipenem) are active against anaerobes, with fewer than 5% of *Bacteroides* species resistant. There is little difference among resistance rates for specific species, and, of the carbapenems, imipenem typically has the lowest resistance rate. Although the β-lactamase produced by most *Bacteroides* species is unable to inactivate carbapenems, rare *B. fragilis* strains have been reported to produce a carbapenemase.

Resistance to chloramphenicol is rare in *Bacteroides* species. Nationwide surveys in the United States have identified no resistant organisms, but some isolates with elevated minimal inhibitory concentrations (MICs)—i.e., 16 μg/mL—have been noted. Although chloramphenicol has excellent in vitro activity against all clinically relevant anaerobes, some clinical failures have been documented. Therefore, this drug may be less preferable if other active agents are available.

Other antibiotics with more variable activity against anaerobes include the fluoroquinolones and tigecycline. Although many fluoroquinolones (e.g., ciprofloxacin, levofloxacin, ofloxacin) display reasonable activity against anaerobic organisms other than *Bacteroides* species, these agents exhibit poor activity against the *B. fragilis* group. Rates of resistance to moxifloxacin are relatively high (39–83%) among *Bacteroides* isolates obtained in the United States but are much lower among *B. fragilis* and *B. thetaiotaomicron* isolates collected in Korea (8 and 2%, respectively) or Taiwan (8 and 15%, respectively). Tigecycline is active against most anaerobic bacteria, although MICs are somewhat higher for *Clostridium* species. Tigecycline's efficacy for treatment of complicated intraabdominal infections is comparable to that of imipenem, and it is therefore recommended as single-agent therapy for these infections.

Infections at Specific Sites In clinical situations, specific antibiotic regimens and durations must be tailored to the initial site of infection; the reader is referred to specific chapters on infections at specific sites for recommendations. In general, anaerobic infections are often broadly categorized as originating above or below the diaphragm. This distinction is clinically useful in that the predominant pathogens—and therefore the empirical antibiotic regimens—differ between these two categories of infection.

Infections above the diaphragm usually reflect the orodental microbiota, which includes *Prevotella*, *Porphyromonas*, *Fusobacterium*, and *Bacteroides* species other than the *B. fragilis* group along with streptococci (both aerobic and microaerophilic). Accordingly, antibiotic regimens should cover both aerobic and anaerobic bacteria. Given that >70% of these infections include a β-lactamase-producing organism, β-lactam drugs (penicillins and cephalosporins) are poor options as monotherapy. The recommended regimens include clindamycin, a β-lactam/β-lactamase inhibitor combination, or metronidazole in combination with a drug active against microaerophilic and aerobic streptococci (e.g., penicillin).

Anaerobic infections arising below the diaphragm (e.g., colonic and intraabdominal infections) must be treated specifically with agents active against *Bacteroides* species, including *B. fragilis*. Single agents suitable for this purpose include cefoxitin, moxifloxacin, a β-lactam/β-lactamase inhibitor combination, or a carbapenem. A two-drug regimen is an alternative, with one drug active against anaerobes and the other against coliforms (e.g., metronidazole with either a cephalosporin or a fluoroquinolone). In addition, if the clinician suspects that gram-positive facultative organisms such as enterococci are involved, therapeutic regimens should include ampicillin or vancomycin. Although clindamycin and cefotetan were previously considered acceptable options for intraabdominal infections involving anaerobes, these drugs are no longer recommended because of escalating rates of resistance in the *B. fragilis* group. Ampicillin-sulbactam is not recommended because of high rates of resistance among community-acquired strains of *E. coli* rather than because of resistance in anaerobic bacteria.

CNS infections involving anaerobic organisms may be treated with metronidazole, a carbapenem, chloramphenicol, or—if only gram-positive anaerobes are involved—penicillin. Clindamycin and cefoxitin have poor penetration into the CSF and should not be used. Cases of osteomyelitis in which a polymicrobial infection is identified from a bone biopsy specimen should be treated with a regimen that covers both aerobes and anaerobes, as some organisms that are often regarded as a contaminant (e.g., *P. acnes*) may have a pathogenic role. When an anaerobic organism is recognized as a major or sole pathogen infecting a joint, the duration of treatment should be similar to that used for arthritis caused by aerobic bacteria **(Chap. 125)**.

Although not every anaerobe needs to be covered with pathogen-directed therapy in most polymicrobial infections, several studies of *Bacteroides* bacteremia have clearly demonstrated that patients receiving effective therapy have lower mortality rates and more rapid sterilization of blood cultures than patients receiving ineffective therapy.

FAILURE OF THERAPY

Anaerobic infections that fail to respond to treatment or that relapse should be reassessed. Potential causes include an uncontrolled source of infection (e.g., ongoing intestinal leak into the peritoneum), superinfection with a new organism, and/or antibiotic failure. Additional imaging may be useful to discern whether surgical drainage or debridement is warranted. Obtaining additional culture

specimens will help identify whether an organism resistant to the antibiotics being used is present. Strong consideration should be given to obtaining susceptibility profiles for the isolates.

Acknowledgment

The authors thank Ronit Cohen-Poradosu for her contributions to this chapter in previous editions.

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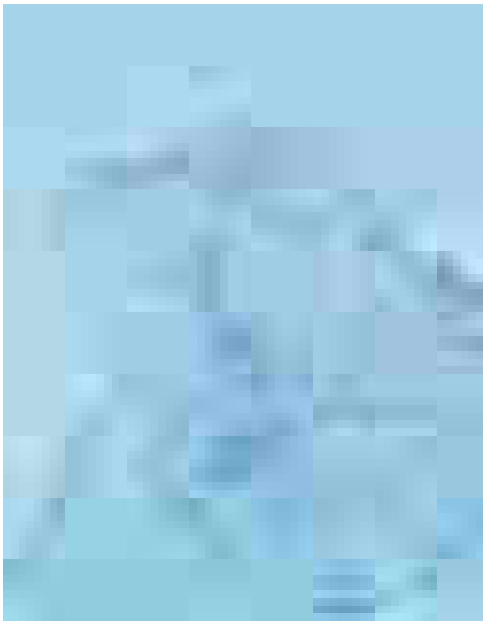

FIGURE 173-1 Acid-fast bacillus smear showing *M. tuberculosis* bacilli. *(Courtesy of the Centers for Disease Control and Prevention, Atlanta.)*

Section 8 Mycobacterial Diseases

173 Tuberculosis

Mario C. Raviglione

Tuberculosis (TB), which is caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and the top cause of infectious death worldwide. Population genomic studies suggest that *M. tuberculosis* may have emerged ~70,000 years ago in Africa and subsequently disseminated along with anatomically modern humans, expanding globally during the Neolithic Age as human density started to increase. Progenitors of *M. tuberculosis* are likely to have affected prehominids. This disease most often affects the lungs, although other organs are involved in up to one-third of cases. If properly treated, TB caused by drug-susceptible strains is curable in the vast majority of cases. If untreated, the disease may be fatal within 5 years in 50–65% of cases. Transmission usually takes place through the airborne spread of droplet nuclei produced by patients with infectious pulmonary TB.

ETIOLOGIC AGENT

Mycobacteria belong to the family Mycobacteriaceae and the order Actinomycetales. Of the pathogenic species belonging to the *M. tuberculosis* complex, which comprises eight distinct subgroups, the most common and important agent of human disease by far is *M. tuberculosis* (*sensu stricto*). A closely related organism isolated from cases in West, Central, and East Africa is *M. africanum.* The complex includes some zoonotic members, such as *M. bovis* (the bovine tubercle bacillus—characteristically resistant to pyrazinamide, once an important cause of TB transmitted by unpasteurized milk, and currently responsible for ~150,000 human cases worldwide, half of them in Africa) and *M. caprae* (related to *M. bovis*). In addition, other organisms that have been reported rarely as causing TB include *M. pinnipedii* (a bacillus infecting seals and sea lions in the Southern Hemisphere and recently isolated from humans), *M. mungi* (isolated from banded mongooses in southern Africa), *M. orygis* (described in oryxes and other Bovidae in Africa and Asia and a potential cause of infection in humans), and *M. microti* (the "vole" bacillus, a less virulent organism). Finally, *M. canetti* is a rare isolate from East African cases that produces unusual smooth colonies on solid media and is considered closely related to a supposed progenitor type. There is no known environmental reservoir for any of these organisms.

M. tuberculosis is a rod-shaped, non-spore-forming, thin aerobic bacterium measuring 0.5 µm by 3 µm. Mycobacteria, including *M. tuberculosis*, are often neutral on Gram's staining. However, once stained, the bacilli cannot be decolorized by acid alcohol; this characteristic justifies their classification as acid-fast bacilli (AFB; **Fig. 173-1**). Acid fastness is due mainly to the organisms' high content of mycolic acids, long-chain cross-linked fatty acids, and other cell-wall lipids. Microorganisms other than mycobacteria that display some acid fastness include species of *Nocardia* and *Rhodococcus*, *Legionella micdadei*, and the protozoa *Isospora* and *Cryptosporidium*. In the mycobacterial cell wall, lipids (e.g., mycolic acids) are linked to underlying arabinogalactan and peptidoglycan. This structure results in very low permeability of the cell wall, thus reducing the effectiveness of most antibiotics. Another molecule in the mycobacterial cell wall, lipoarabinomannan, is involved in the pathogen–host interaction and facilitates the survival of *M. tuberculosis* within macrophages.

The complete genome sequence of *M. tuberculosis* comprises 4.4 million base pairs, 4043 genes encoding 3993 proteins, and 50 genes encoding RNAs; its high guanine-plus-cytosine content (65.6%) is indicative of an aerobic "lifestyle." A large proportion of genes are devoted to the production of enzymes involved in cell wall metabolism. Substantial genetic variability exists among strains from different parts of the world.

EPIDEMIOLOGY

In 2016, 6.3 million new cases of TB (all forms, both pulmonary and extrapulmonary) were reported to the World Health Organization (WHO) by its member states; 95% of cases were reported from developing countries. However, because of insufficient case detection and incomplete notification, reported cases may represent only about two-thirds of the total estimated cases. As a result, the WHO estimated that 10.4 million (range, 8.8–12.2 million) new (incident) cases of TB occurred worldwide in 2016, 95% of them in developing countries of Asia (6.5 million), Africa (2.6 million), the Middle East (0.77 million), and Latin America (0.26 million). Seven countries accounted for 64% of all new cases: India, Indonesia, China, the Philippines, Pakistan, Nigeria, and South Africa. Two-thirds of cases typically occur in male patients, and 1.04 million children are affected every year. It is further estimated that 1.7 million (range, 1.5–1.8 million) deaths from TB,

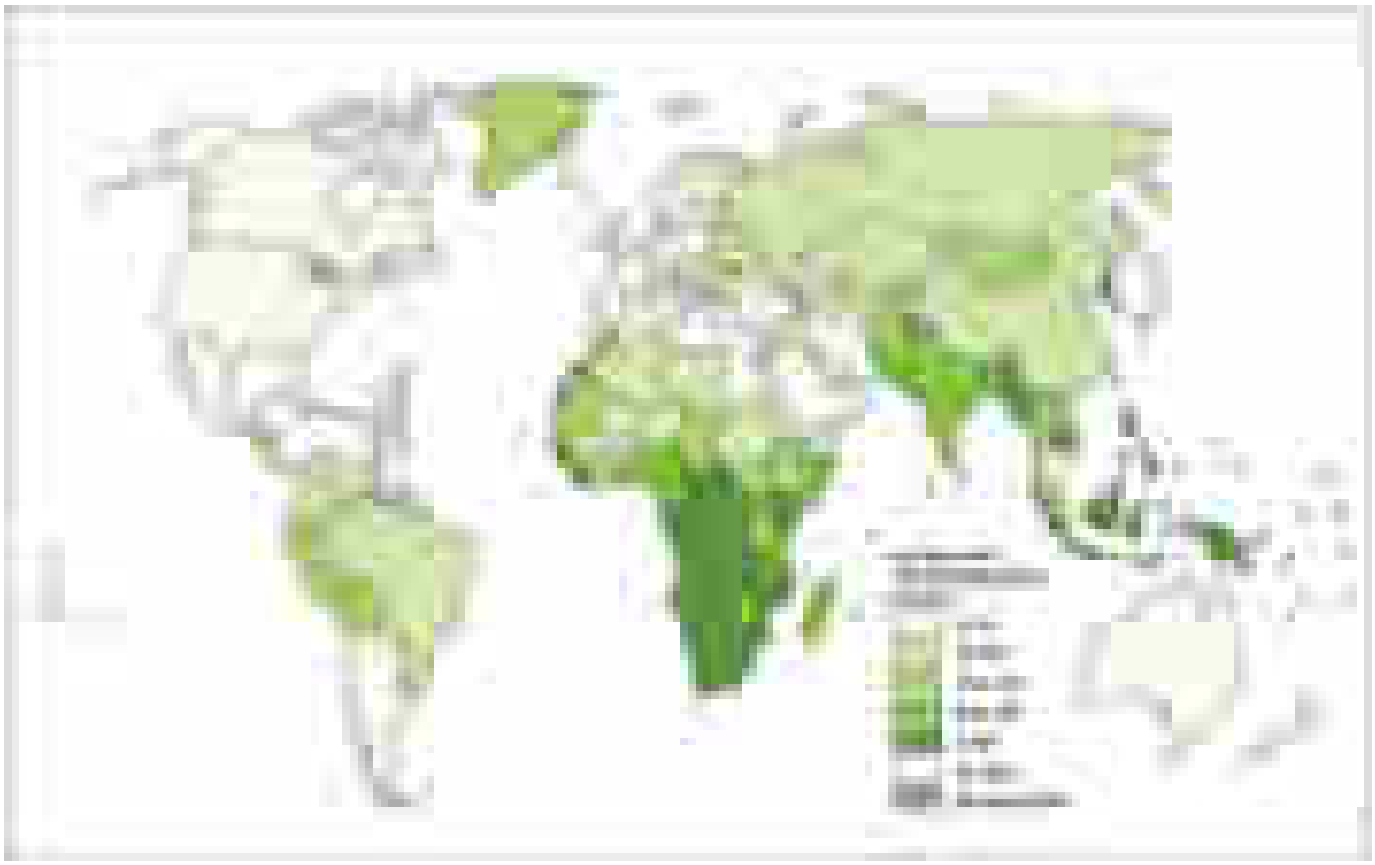

FIGURE 173-2 Estimated tuberculosis (TB) incidence rates (per 100,000 population) in 2016. The designations used and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city, or area or of its authorities or concerning the delimitation of its frontiers or boundaries. *Dotted*, *dashed*, and *white lines* represent approximate border lines for which there may not yet be full agreement. *(Courtesy of the Global TB Programme, WHO; with permission.)*

including 0.37 million among people with HIV infection, occurred in 2016; 96% of these deaths were in developing countries. Estimates of TB incidence rates (per 100,000 population) and numbers of TB-related deaths in 2016 are depicted in **Figs. 173-2 and 173-3**, respectively. During the late 1980s and early 1990s, numbers of reported cases of TB increased in industrialized countries. These increases were related largely to immigration from countries with a high incidence of TB; the spread of the HIV epidemic; social problems, such as increased urban poverty, homelessness, and drug abuse; and dismantling of TB services. During the past few years, numbers of reported cases have begun to decline again or have stabilized in most industrialized nations. In the United States, with the re-establishment of stronger control programs, the decline resumed in 1993 and had since been maintained until 2015, when numbers increased over the previous year for the first time in more than two decades; in that year, 9557 cases of TB (3.0 cases/100,000 population) were reported to the U.S. Centers for Disease Control and Prevention (CDC). However, in 2016 a slight decline from 2015 was observed in incidence (2.9 cases/100,000 population) and number of cases (9287).

In the United States, TB is uncommon among young adults of European descent, who have only rarely been exposed to *M. tuberculosis* infection during recent decades. In contrast, because of a high risk of transmission in the past, the prevalence of latent *M. tuberculosis* infection (LTBI) is relatively high among elderly whites. In general, adults ≥65 years of age have the highest incidence rate per capita (4.8 cases/100,000 population in 2016) and children <14 years of age the lowest (0.7 case/100,000 population). Among U.S.-born persons, blacks account for the highest proportion of cases (36%; 1062 cases in 2016). TB in the United States is also a disease of adult members of the HIV-infected population, the foreign-born population (68.5% of all cases in 2016), and disadvantaged/marginalized populations. Of the 6307 cases reported among foreign-born persons in the United States in 2016, 31% occurred in persons from the Americas and 47% in persons born in Asia. Overall, the highest rates per capita were among Asian Americans (18 cases/100,000 population). A total of 493 deaths were caused by TB in the United States in 2015. In Canada in 2015, 1639 TB cases were reported (4.6 cases/100,000 population); 71% (1169) of these cases occurred in foreign-born persons, and 17% (470 cases) occurred in members of the Canadian aboriginal peoples, whose per capita rate is disproportionately high (17.1 cases/100,000 population). The highest rate was found in the territory of Nunavut, at 119 cases/100,000 population—a rate similar to that in many highly endemic countries. Similarly, in Europe, TB has reemerged as an important public health problem, mainly as a result of cases among immigrants from high-incidence countries and among marginalized populations, often in large urban settings like London. In 2015, 39.4% of all cases reported from England occurred in London, and the rate per capita (26 cases/100,000 population) was similar to that in some middle-income countries. In most Western European countries, there are more cases annually among foreign-born than native populations.

Recent data on global trends indicate that in 2015 the TB incidence was stable or falling in most regions; this trend began in the early 2000s and appears to have continued, with an average annual decline of 1.5% globally. This global decrease is explained largely by the simultaneous reduction in TB incidence in sub-Saharan Africa, where rates had risen steeply since the 1980s as a result of the HIV epidemic and the lack of capacity of health systems and services to deal with the problem effectively, and in Eastern Europe, where incidence increased rapidly during the 1990s because of a deterioration in socioeconomic conditions and the health care infrastructure (although, after peaking in 2001, incidence in Eastern Europe has since declined slowly).

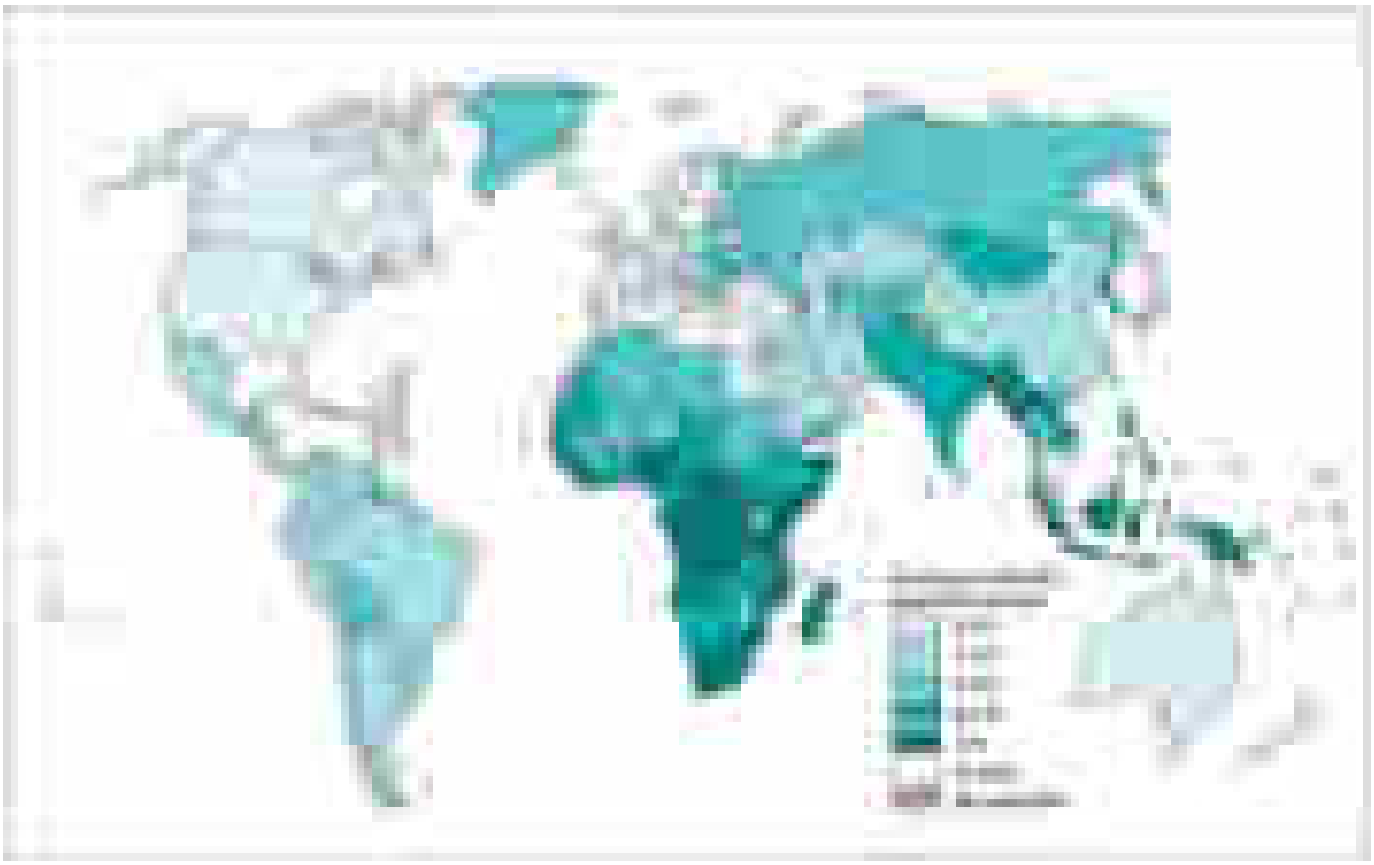

FIGURE 173-3 Estimated tuberculosis mortality rates, excluding tuberculosis-related deaths among HIV-positive people, in 2016. *(See disclaimer in Fig. 173-2. Courtesy of the Global TB Programme, WHO; with permission.)*

Of the estimated 10.4 million new cases of TB in 2016, 10% (1.03 million) were associated with HIV infection, and 74% of these HIV-associated cases occurred in Africa. An estimated 0.37 million persons with HIV-associated TB died in 2016. Furthermore, an estimated 500,000 cases of multidrug-resistant TB (MDR-TB)—a form of the disease caused by bacilli resistant at least to isoniazid and rifampin—and an additional 100,000 cases of rifampin-resistant TB (RR-TB), which also requires MDR-TB treatment (range for both forms together, 540,000–660,000), occurred in 2016. Only 25% of these cases were diagnosed because of a lack of culture and drug susceptibility testing (DST) capacity in many settings worldwide. As a consequence, 240,000 people with MDR/RR-TB died in 2016. The countries of the former Soviet Union have reported the highest proportions of MDR disease among new TB cases (up to 35% in some regions of Russia and Belarus). Overall, 47% of all MDR-TB cases occur in India, China, and the Russian Federation. Since 2006, 117 countries, including the United States, have reported cases of extensively drug-resistant TB (XDR-TB), in which MDR-TB is compounded by additional resistance to the most powerful second-line anti-TB drugs (fluoroquinolones and at least one of the injectable drugs amikacin, kanamycin, and capreomycin). About 9.5% of the MDR-TB cases worldwide may be XDR-TB, but the vast majority of XDR-TB cases remain undiagnosed because reliable methods for DST are lacking and laboratory capacity is limited. Lately, a few cases deemed resistant to all anti-TB drugs have been reported; however, this information must be interpreted with caution because susceptibility testing for several second-line drugs is neither accurate nor reproducible.

FROM EXPOSURE TO INFECTION

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary TB by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance. The risk of transmission and of subsequent acquisition of *M. tuberculosis* infection is determined mainly by exogenous factors. The probability of contact with a person who has an infectious form of TB, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. Several studies of close-contact situations have clearly demonstrated that TB patients whose sputum contains AFB visible by microscopy (sputum smear–positive cases) are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 10^5–10^7 AFB/mL. Patients with sputum smear–negative/culture-positive TB are less infectious, although they have been responsible for up to 20% of transmission in some studies in the United States. Those with culture-negative pulmonary TB and extrapulmonary TB are essentially noninfectious. Because persons with both HIV infection and TB are less likely to have cavitations, they may be less infectious than persons without HIV co-infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli because it increases the intensity of contact with a case. The virulence of the transmitted organism is also an important factor in establishing infection.

Because of delays in seeking care and in making a diagnosis, it has been estimated that, in high-prevalence settings, up to 20 contacts (or 3–10 people per year) may be infected by each AFB-positive case before the index case is diagnosed.

FROM INFECTION TO DISEASE

Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous

factors, such as the individual's innate immunologic and nonimmunologic defenses and the level at which the individual's cell-mediated immunity is functioning. Clinical illness directly following infection is classified as *primary TB* and is common among children in the first few years of life and among immunocompromised persons. Although primary TB may be severe and disseminated, it generally is not associated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will contain it at least temporarily. Bacilli, however, may persist for years before reactivating to produce *secondary* (or *postprimary*) *TB*, which, because of frequent cavitation, is more often infectious than is primary disease. Overall, it is estimated that up to 10% of infected persons will eventually develop active TB in their lifetime—half of them during the first 18 months after infection. The risk is much higher among HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favor the development of disease. At the height of the TB resurgence in the United States in the early 1990s, molecular typing and comparison of strains of *M. tuberculosis* suggested that up to one-third of cases of active TB in some inner-city communities were due to recent transmission rather than to reactivation of old latent infection. Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of TB is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25–34 years of age. In this age group, rates among women may be higher than those among men, whereas at older ages the opposite is true. The risk increases in the elderly, possibly because of waning immunity and comorbidity.

A variety of diseases and conditions favor the development of active TB **(Table 173-1)**. In absolute terms, the most potent risk factor for TB among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that LTBI will proceed to active disease is directly related to the patient's degree of immunosuppression. In a study of HIV-infected, tuberculin skin test (TST)–positive persons, this risk varied from 2.6 to 13.3 cases/100 person-years and increased as the CD4+ T cell count decreased.

NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis, and >50% died within 5 years. The 5-year mortality rate among sputum smear–positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. However, improper use of anti-TB drugs, while reducing mortality rates, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

TABLE 173-1 Risk Factors for Active Tuberculosis in Persons Who Have Been Infected with Tubercle Bacilli

FACTOR	RELATIVE RISK/ODDS[a]
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidities and iatrogenic causes	
HIV infection	21–>30
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Diabetes	2–4
IV drug use	10–30
Excessive alcohol use	3
Immunosuppressive treatment	10
Tumor necrosis factor α inhibitors	4–5
Gastrectomy	2–5
Jejunoileal bypass	30–60
Post-transplantation period (renal, cardiac)	20–70
Tobacco smoking	2–3
Malnutrition and severe underweight	2

[a]Old infection = 1.

PATHOGENESIS AND IMMUNITY

INFECTION AND MACROPHAGE INVASION

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing viable microorganisms, propelled into the air by infectious patients, are inhaled by a close bystander. Although the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli, a unique immunoregulatory environment. There, alveolar macrophages that have not yet been activated (prototypic alternatively activated macrophages) phagocytose the bacilli. Adhesion of mycobacteria to macrophages results largely from binding of the bacterial cell wall to a variety of macrophage cell-surface molecules, including complement receptors, the mannose receptor, the immunoglobulin G Fcγ receptor, and type A scavenger receptors. Surfactants may also play a role in the early phase of interaction between the host and the pathogen, and surfactant protein D can prevent phagocytosis. Phagocytosis is enhanced by complement activation leading to opsonization of bacilli with C3 activation products such as C3b and C3bi. (Bacilli are resistant to complement-mediated lysis.) Binding of certain receptors, such as the mannose receptor, regulates postphagocytic events such as phagosome–lysosome fusion and inflammatory cytokine production. After a phagosome forms, the survival of *M. tuberculosis* within it seems to depend in part on reduced acidification due to lack of assembly of a complete vesicular proton-adenosine triphosphatase. A complex series of events is generated by the bacterial cell-wall lipoglycan lipoarabinomannan, which inhibits the intracellular increase of Ca^{2+}. Thus, the Ca^{2+}/calmodulin pathway (leading to phagosome–lysosome fusion) is impaired, and the bacilli survive within the phagosomes by blocking fusion. The *M. tuberculosis* phagosome inhibits the production of phosphatidylinositol 3-phosphate, which normally earmarks phagosomes for membrane sorting and maturation (including phagolysosome formation), which would destroy the bacteria. Bacterial factors block the host defense of autophagy, in which the cell sequesters the phagosome in a double-membrane vesicle (*autophagosome*) that is destined to fuse with lysosomes. If the bacilli are successful in arresting phagosome maturation, then replication begins and the macrophage eventually ruptures and releases its bacillary contents. This process is mediated by the ESX-1 secretion system that is encoded by genes contained in the region of difference 1 (RD1). Other uninfected phagocytic cells are then recruited to continue the infection cycle by ingesting dying macrophages and their bacillary content, thus, in turn, becoming infected themselves and expanding the infection.

VIRULENCE OF TUBERCLE BACILLI

M. tuberculosis must be viewed as a complex formed by a multitude of strains that differ in virulence and are capable of producing a variety of manifestations of disease. Since the elucidation of the *M. tuberculosis* genome in 1998, large mutant collections have been generated, and many bacterial genes that contribute to *M. tuberculosis* virulence have been found. Different patterns of virulence defects have been defined in various animal models—predominantly mice but also guinea pigs, rabbits, and nonhuman primates. The *katG* gene encodes for a catalase/peroxidase enzyme that protects against oxidative stress and is required for isoniazid activation and subsequent bactericidal activity. RD1 is a 9.5-kb locus that encodes two key small protein antigens—6-kDa early secretory antigen (ESAT-6) and culture filtrate protein-10 (CFP-10)—as well as a putative secretion apparatus that may facilitate their egress; the absence of this locus in the vaccine strain *M. bovis* bacille Calmette-Guérin (BCG) is a key attenuating mutation. In *M. marinum*, a mutation in the RD1 virulence locus encoding the ESX-1 secretion system impairs the capacity of apoptotic macrophages to recruit uninfected cells for further rounds of infection. The results are

less replication and fewer new granulomas. These observations in *M. marinum* are similar in part to events related to the virulence of *M. tuberculosis*; however, ESX-1, although necessary, is probably insufficient to explain virulence, and other mechanisms may be in play. Mutants lacking key enzymes of bacterial biosynthesis become auxotrophic for the missing substrate and often are totally unable to proliferate in animals; these include the *leuCD* and *panCD* mutants, which require leucine and pantothenic acid, respectively. The isocitrate lyase gene (*icl1*) encodes a key step in the glyoxylate shunt that facilitates bacterial growth on fatty acid substrates; this gene is required for long-term persistence of *M. tuberculosis* infection in mice with chronic TB. *M. tuberculosis* mutants in regulatory genes such as sigma factor C and sigma factor H (*sigC* and *sigH*) are associated with normal bacterial growth in mice, but they fail to elicit full tissue pathology. Finally, the mycobacterial protein CarD (expressed by the *carD* gene) seems essential for the control of rRNA transcription that is required for mycobacterial replication and persistence in the host cell. Its loss exposes mycobacteria to oxidative stress, starvation, DNA damage, and ultimately sensitivity to killing by a variety of host mutagens and defense mechanisms.

INNATE RESISTANCE TO INFECTION

Several observations suggest that genetic factors play a key role in innate nonimmune resistance to infection with *M. tuberculosis* and the development of disease. The existence of this resistance, which is polygenic in nature, is suggested by the differing degrees of susceptibility to TB in different populations. This mechanism of elimination of the pathogen may be accompanied by negative results in the TST and interferon-γ (IFN-γ) release assays (IGRAs). In mice, a gene called *Nramp1* (natural resistance–associated macrophage protein 1) plays a regulatory role in resistance/susceptibility to mycobacteria. The human homologue NRAMP1, which maps to chromosome 2q, may play a role in determining susceptibility to TB, as is suggested by a study among West Africans. Studies of mouse genetics identified a novel host resistance gene, *ipr1*, that is encoded within the *sst1* locus; *ipr1* encodes an IFN-inducible nuclear protein that interacts with other nuclear proteins in macrophages primed with IFNs or infected by *M. tuberculosis*. In addition, polymorphisms in multiple genes, such as those encoding for various major histocompatibility complex alleles, IFN-γ, T cell growth factor β, interleukin (IL) 10, mannose-binding protein, IFN-γ receptor, Toll-like receptor 2, vitamin D receptor, and IL-1, have been associated with susceptibility to TB.

THE HOST RESPONSE, GRANULOMA FORMATION, AND "LATENCY"

In the initial stage of host–bacterium interaction, prior to the onset of an acquired cell-mediated immune (CMI) response, *M. tuberculosis* disseminates widely through the lymph vessels, spreading to other sites in the lungs and other organs, and undergoes a period of extensive growth within naïve unactivated macrophages; additional naïve macrophages are recruited to the early granuloma. How the bacillus accesses the parenchymal tissue remains to be elucidated: it may directly infect epithelial cells or transmigrate through infected macrophages across the epithelium. Infected dendritic cells or monocytes then begin to transport bacilli to the lymphatic system. Studies suggest that *M. tuberculosis* uses specific virulence mechanisms to subvert host cellular signaling and to elicit an early regulated proinflammatory response that promotes granuloma expansion and bacterial growth during this key early phase. A study of *M. marinum* infection in zebrafish has delineated one molecular mechanism by which mycobacteria induce granuloma formation. The mycobacterial protein ESAT-6 induces secretion of matrix metalloproteinase 9 (MMP9) by nearby epithelial cells that are in contact with infected macrophages. MMP9 in turn stimulates recruitment of naïve macrophages, thus inducing granuloma maturation and bacterial growth. Disruption of MMP9 function results in reduced bacterial growth. Another study has shown that *M. tuberculosis*–derived cyclic AMP is secreted from the phagosome into host macrophages, subverting the cell's signal transduction pathways and stimulating an elevation in the secretion of tumor necrosis factor α (TNF-α) as well as further proinflammatory cell recruitment. Ultimately, the chemoattractants and bacterial products released during the repeated rounds of cell lysis and infection of newly arriving macrophages enable dendritic cells to access bacilli; these cells migrate to the draining lymph nodes and present mycobacterial antigens to T lymphocytes. At this point, the development of cell-mediated and humoral immunity begins. These initial stages of infection are usually asymptomatic.

About 2–4 weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating CMI response and a tissue-damaging response. The *macrophage-activating response* is a T cell–mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues (see below). Although both of these responses can inhibit mycobacterial growth, it is the balance between the two that determines the forms of TB that will develop subsequently. With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion, granulomatous lesions (*tubercles*) are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. As stated above, this response, mediated by various bacterial products, not only destroys macrophages but also produces early solid necrosis in the center of the tubercle. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions. Some observations have challenged the traditional view that any encounter between mycobacteria and macrophages results in chronic infection. It is possible that an immune response capable of eradicating early infection may sometimes develop as a consequence, for instance, of disabling mutations in mycobacterial genomes rendering their replication ineffective. Individual granulomas that are formed during this phase of infection can vary in size and cell composition; some can contain the spread of mycobacteria, while others cannot. LTBI ensues as a result of this dynamic balance between the microorganism and the host. It has been speculated that *latency* may not be an accurate term because bacilli may remain active during this "latent" stage, forming biofilms in necrotic areas within which they temporarily hide. Thus, some have proposed the term *persister* as more accurate to indicate the behavior of the bacilli in this phase. It is important to recognize that latent infection and disease represent not a binary state but rather a continuum along which infection will eventually move in the direction of full containment or disease. The ability to predict, through systemic biomarkers, which affected individuals will progress toward disease would be of immense value in devising prophylactic interventions at scale.

MACROPHAGE-ACTIVATING RESPONSE

Cell-mediated immunity is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens processed by macrophages stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize tubercle bacilli without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*)—a phenomenon that may also be observed in other conditions, such as neoplasms. Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for many years. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification.

DELAYED-TYPE HYPERSENSITIVITY

In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified delayed hypersensitivity reactions, which lead to lung tissue destruction.

The lesion tends to enlarge further, and the surrounding tissue is progressively damaged. At the center of the lesion, the caseous material liquefies. Bronchial walls and blood vessels are invaded and destroyed, and cavities are formed. The liquefied caseous material, containing large numbers of bacilli, is drained through bronchi. Within the cavity, tubercle bacilli multiply, spill into the airways, and are discharged into the environment through expiratory maneuvers such as coughing and talking. In the early stages of infection, bacilli are usually transported by macrophages to regional lymph nodes, from which they gain access to the central venous return; from there they reseed the lungs and may also disseminate beyond the pulmonary vasculature throughout the body via the systemic circulation. The resulting extrapulmonary lesions may undergo the same evolution as those in the lungs, although most tend to heal. In young children with poor natural immunity, hematogenous dissemination may result in fatal miliary TB or tuberculous meningitis.

ROLE OF MACROPHAGES AND MONOCYTES

While cell-mediated immunity confers partial protection against *M. tuberculosis*, humoral immunity plays a less well-defined role in protection (although evidence is accumulating on the existence of antibodies to lipoarabinomannan, which may prevent dissemination of infection in children). In cell-mediated immunity, two types of cells are essential: macrophages, which directly phagocytose tubercle bacilli, and T cells (mainly CD4+ T lymphocytes), which induce protection through the production of cytokines, especially IFN-γ. After infection with *M. tuberculosis*, alveolar macrophages secrete various cytokines responsible for a number of events (e.g., the formation of granulomas) as well as systemic effects (e.g., fever and weight loss). However, alternatively activated alveolar macrophages may be particularly susceptible to *M. tuberculosis* growth early on, given their more limited proinflammatory and bactericidal activity, which is related in part to being bathed in surfactant. New monocytes and macrophages attracted to the site are key components of the immune response. Their primary mechanism is probably related to production of oxidants (such as reactive oxygen intermediates or nitric oxide) that have antimycobacterial activity and increase the synthesis of cytokines such as TNF-α and IL-1, which in turn regulate the release of reactive oxygen intermediates and reactive nitrogen intermediates. In addition, macrophages can undergo apoptosis—a defensive mechanism to prevent the release of cytokines and bacilli via their sequestration in the apoptotic cell. Recent work also describes the involvement of neutrophils in the host response, although the timing of their appearance and their effectiveness remain uncertain.

ROLE OF T LYMPHOCYTES

Alveolar macrophages, monocytes, and dendritic cells are also critical in processing and presenting antigens to T lymphocytes, primarily CD4+ and CD8+ T cells; the result is the activation and proliferation of CD4+ T lymphocytes, which are crucial to the host's defense against *M. tuberculosis*. Qualitative and quantitative defects of CD4+ T cells explain the inability of HIV-infected individuals to contain mycobacterial proliferation. Activated CD4+ T lymphocytes can differentiate into cytokine-producing T_H1 or T_H2 cells. T_H1 cells produce IFN-γ—an activator of macrophages and monocytes—and IL-2. T_H2 cells produce IL-4, IL-5, IL-10, and IL-13 and may also promote humoral immunity. The interplay of these various cytokines and their cross-regulation determine the host's response. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely elucidated. IFN-γ may induce the generation of reactive nitrogen intermediates and regulate genes involved in bactericidal effects. TNF-α is also important. Although its precise mechanisms are complex and not yet fully clarified, a model has been suggested that foresees an ideal setting for TNF-α between excessive activation—with consequent worsening of immunopathological reactions—and insufficient activation—with resulting lack of containment—in the control of TB infection. Observations made originally in transgenic knockout mice and more recently in humans suggest that other T cell subsets, especially CD8+ T cells, may play an important role. CD8+ T cells have been associated with protective activities via cytotoxic responses and lysis of infected cells as well as with production of IFN-γ and TNF-α. Finally, natural killer cells act as co-regulators of CD8+ T cell lytic activities, and γδ T cells are increasingly thought to be involved in protective responses in humans.

MYCOBACTERIAL LIPIDS AND PROTEINS

Lipids are involved in mycobacterial recognition by the innate immune system, and lipoproteins (such as 19-kDa lipoprotein) trigger potent signals through Toll-like receptors present in blood dendritic cells. *M. tuberculosis* possesses various protein antigens. Some are present in the cytoplasm and cell wall; others are secreted. That the latter are more important in eliciting a T lymphocyte response is suggested by experiments documenting the appearance of protective immunity in animals after immunization with live, protein-secreting mycobacteria. Among the antigens that may play a protective role are the 30-kDa (or 85B) and ESAT-6 antigens. Protective immunity is probably the result of reactivity to many different mycobacterial antigens. These antigens are being incorporated into newly designed vaccines on various platforms.

SKIN TEST REACTIVITY

Coincident with the appearance of immunity, delayed-type hypersensitivity to *M. tuberculosis* develops. This reactivity is the basis of the TST, which is used primarily for the detection of *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines. Although delayed hypersensitivity is associated with protective immunity (TST-positive persons are less susceptible to a new *M. tuberculosis* infection than TST-negative persons), it by no means guarantees protection against reactivation. In fact, cases of active TB are often accompanied by strongly positive skin-test reactions. There is also evidence of reinfection with a new strain of *M. tuberculosis* in patients previously treated for active disease. This evidence underscores the fact that previous latent or active TB may not confer fully protective immunity.

CLINICAL MANIFESTATIONS

TB is classified as pulmonary, extrapulmonary, or both. Depending on several factors linked to different populations and bacterial strains, extrapulmonary TB may occur in 10–40% of patients. Furthermore, up to two-thirds of HIV-infected patients with TB may have both pulmonary and extrapulmonary TB or extrapulmonary TB alone.

PULMONARY TB

Pulmonary TB is conventionally categorized as primary or postprimary (adult-type, secondary). This distinction has been challenged by molecular evidence from TB-endemic areas indicating that a large percentage of cases of adult pulmonary TB result from recent infection (either primary infection or reinfection) and not from reactivation.

Primary Disease Primary pulmonary TB occurs soon after the initial infection with tubercle bacilli. It may be asymptomatic or may present with fever and occasionally pleuritic chest pain. In areas of high TB transmission, this form of disease is often seen in children. Because most inspired air is distributed to the middle and lower lung zones, these areas are most commonly involved in primary TB. The lesion forming after initial infection (*Ghon focus*) is usually peripheral and accompanied by transient hilar or paratracheal lymphadenopathy, which may or may not be visible on standard chest radiography (CXR) **(Fig. 173-4)**. Some patients develop erythema nodosum on the legs **(see Fig. A1-39)** or phlyctenular conjunctivitis. In the majority of cases, the lesion heals spontaneously and becomes evident only as a small calcified nodule. Pleural reaction overlying a subpleural focus is also common. The Ghon focus, with or without overlying pleural reaction, thickening, and regional lymphadenopathy, is referred to as the *Ghon complex*.

In young children with immature cell-mediated immunity and in persons with impaired immunity (e.g., those with malnutrition or HIV infection), primary pulmonary TB may progress rapidly to clinical illness. The initial lesion increases in size and can evolve in different ways.

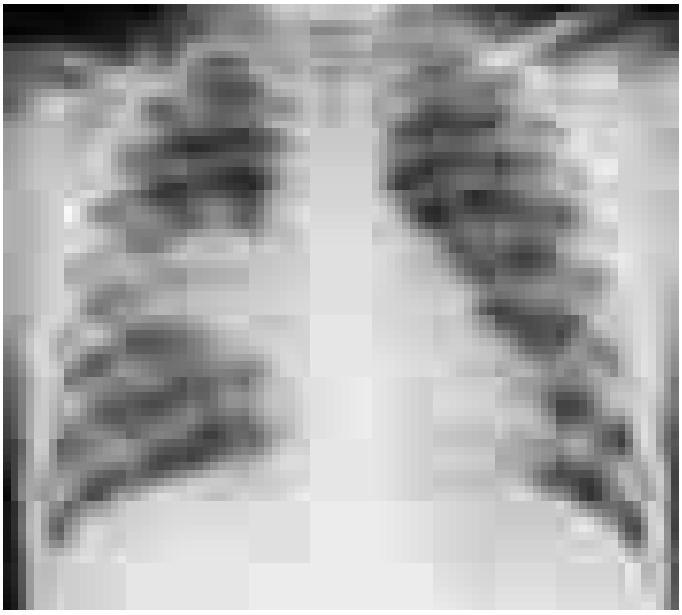

FIGURE 173-4 Chest radiograph showing right hilar lymph node enlargement with infiltration into the surrounding lung tissue in a child with primary tuberculosis. *(Courtesy of Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa; with permission.)*

Pleural effusion, which is found in up to two-thirds of cases, results from the penetration of bacilli into the pleural space from an adjacent subpleural focus. In severe cases, the primary site rapidly enlarges, its central portion undergoes necrosis, and cavitation develops (*progressive primary TB*). TB in young children is almost invariably accompanied by hilar or paratracheal lymphadenopathy due to the spread of bacilli from the lung parenchyma through lymphatic vessels. Enlarged lymph nodes may compress bronchi, causing total obstruction with distal collapse, partial obstruction with large-airway wheezing, or a ball-valve effect with segmental/lobar hyperinflation. Lymph nodes may also rupture into the airway with development of pneumonia, often including areas of necrosis and cavitation, distal to the obstruction. Bronchiectasis **(Chap. 284)** may develop in any segment/lobe damaged by progressive caseating pneumonia. Occult hematogenous dissemination commonly follows primary infection. However, in the absence of a sufficient acquired immune response, which usually contains the infection, disseminated or miliary disease may result **(Fig. 173-5)**. Small granulomatous lesions develop in multiple organs

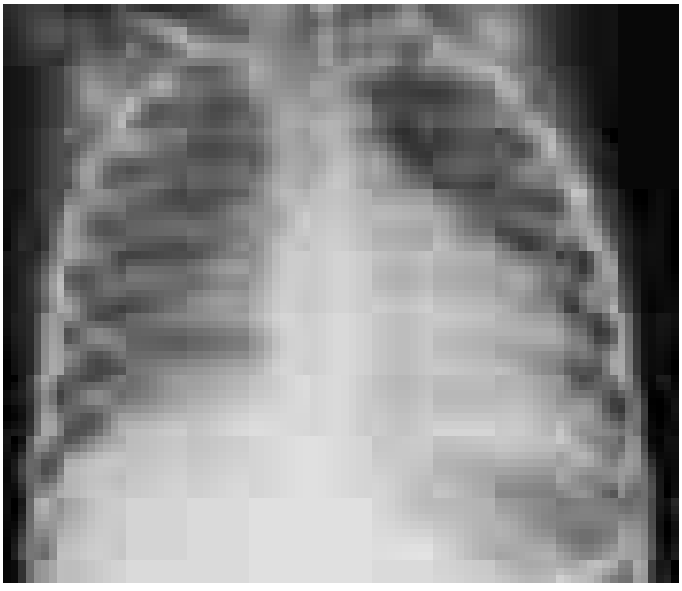

FIGURE 173-5 Chest radiograph showing bilateral miliary (millet-sized) infiltrates in a child. *(Courtesy of Prof. Robert Gie, Department of Paediatrics and Child Health, Stellenbosch University, South Africa; with permission.)*

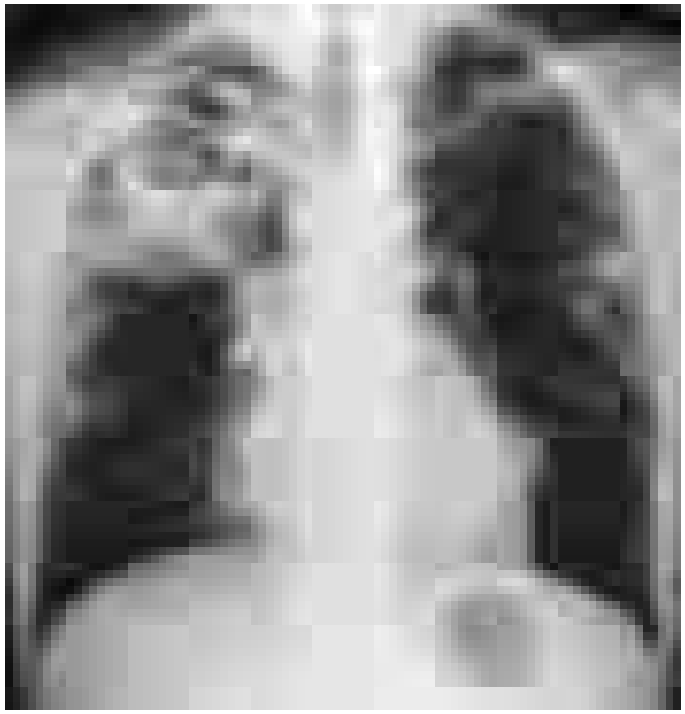

FIGURE 173-6 Chest radiograph showing a right-upper-lobe infiltrate and a cavity with an air-fluid level in a patient with active tuberculosis. *(Courtesy of Dr. Andrea Gori, Department of Infectious Diseases, S. Paolo University Hospital, Milan, Italy; with permission.)*

and may cause locally progressive disease or result in tuberculous meningitis; this is a particular concern in very young children and immunocompromised persons (e.g., patients with HIV infection).

Postprimary (Adult-Type) Disease Also referred to as *reactivation* or *secondary TB*, postprimary TB is probably most accurately termed *adult-type TB* because it may result from endogenous reactivation of distant LTBI or recent infection (primary infection or reinfection). It is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. The superior segments of the lower lobes are also more frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitary disease. With cavity formation, liquefied necrotic contents are ultimately discharged into the airways and may undergo bronchogenic spread, resulting in satellite lesions within the lungs that may in turn undergo cavitation **(Figs. 173-6 and 173-7)**. Massive involvement

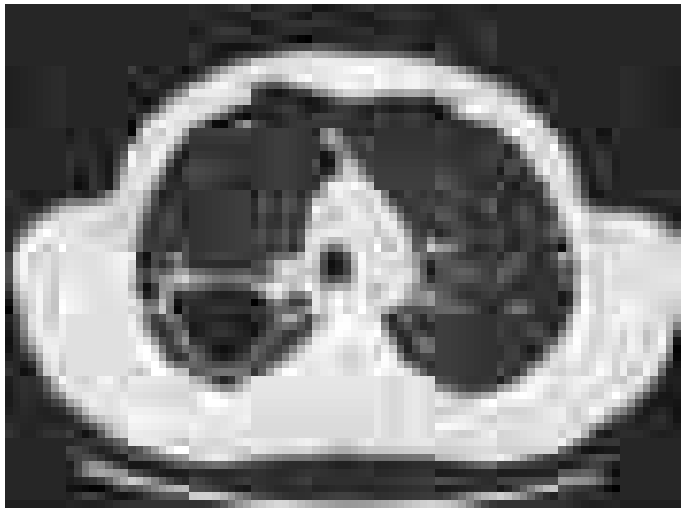

FIGURE 173-7 CT scan showing a large cavity in the right lung of a patient with active tuberculosis. *(Courtesy of Dr. Elisa Busi Rizzi, National Institute for Infectious Diseases, Spallanzani Hospital, Rome, Italy; with permission.)*

of pulmonary segments or lobes, with coalescence of lesions, produces caseating pneumonia. While up to one-third of untreated patients reportedly succumb to severe pulmonary TB within a few months after onset (the classic "galloping consumption" of the past), others may undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course ("consumption" or *phthisis*). Under these circumstances, some pulmonary lesions become fibrotic and may later calcify, but cavities persist in other parts of the lungs. Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment, with defervescence, decreasing cough, weight gain, and a general improvement in well-being within several weeks.

Early in the course of disease, symptoms and signs are often nonspecific and insidious, consisting mainly of diurnal fever and night sweats due to defervescence, weight loss, anorexia, general malaise, and weakness. However, in up to 90% of cases, cough eventually develops—often initially nonproductive and limited to the morning and subsequently accompanied by the production of purulent sputum, sometimes with blood streaking. Hemoptysis develops in 20–30% of cases, and massive hemoptysis may ensue as a consequence of the erosion of a blood vessel in the wall of a cavity. Hemoptysis, however, may also result from rupture of a dilated vessel in a cavity (*Rasmussen's aneurysm*) or from aspergilloma formation in an old cavity. Pleuritic chest pain sometimes develops in patients with subpleural parenchymal lesions or pleural disease. Extensive disease may produce dyspnea and, in rare instances, adult respiratory distress syndrome. Physical findings are of limited use in pulmonary TB. Many patients have no abnormalities detectable by chest examination, whereas others have detectable rales in the involved areas during inspiration, especially after coughing. Occasionally, rhonchi due to partial bronchial obstruction and classic amphoric breath sounds in areas with large cavities may be heard. Systemic features include fever (often low-grade and intermittent) in up to 80% of cases and wasting. Absence of fever, however, does not exclude TB. In some cases, pallor and finger clubbing develop. The most common hematologic findings are mild anemia, leukocytosis, and thrombocytosis with a slightly elevated erythrocyte sedimentation rate and/or C-reactive protein level. None of these findings is consistent or sufficiently accurate for diagnostic purposes. Hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone has also been reported.

EXTRAPULMONARY TB

In descending order of frequency, the extrapulmonary sites most commonly involved in TB are the lymph nodes, pleura, genitourinary tract, bones and joints, meninges, peritoneum, and pericardium. However, virtually any organ system may be affected. As a result of hematogenous dissemination in HIV-infected individuals, extrapulmonary TB is seen more commonly today than in the past in settings of high HIV prevalence.

Lymph Node TB (Tuberculous Lymphadenitis) The most common presentation of extrapulmonary TB in both HIV-seronegative individuals and HIV-infected patients (35% of cases worldwide and >40% of cases in the United States in recent series), lymph node disease is particularly frequent among HIV-infected patients and among children **(Fig. 173-8)**. In the United States, besides children, women (particularly non-Caucasians) seem to be especially susceptible. Once caused mainly by *M. bovis*, tuberculous lymphadenitis today is due largely to *M. tuberculosis*. Lymph node TB presents as painless swelling of the lymph nodes, most commonly at posterior cervical and supraclavicular sites (a condition historically referred to as *scrofula*). Lymph nodes are usually discrete in early disease but develop into a matted nontender mass over time; a fistulous tract draining caseous material may result. Associated pulmonary disease is present in fewer than 50% of cases, and systemic symptoms are uncommon except in HIV-infected patients. The diagnosis is established by fine-needle aspiration biopsy (with a yield of up to 80%) or surgical excision biopsy. Bacteriologic confirmation is achieved in the vast majority of cases, granulomatous lesions with or without visible AFBs are typically seen, and cultures are positive in 70–80% of cases. Among HIV-infected patients, granulomas are less well organized and are frequently absent entirely, but bacterial loads are heavier than in HIV-seronegative patients, with higher yields from microscopy and culture. Differential diagnosis includes a variety of infectious conditions, neoplastic diseases such as lymphomas or metastatic carcinomas, and rare disorders like Kikuchi's disease (necrotizing histiocytic lymphadenitis), Kimura's disease, and Castleman's disease.

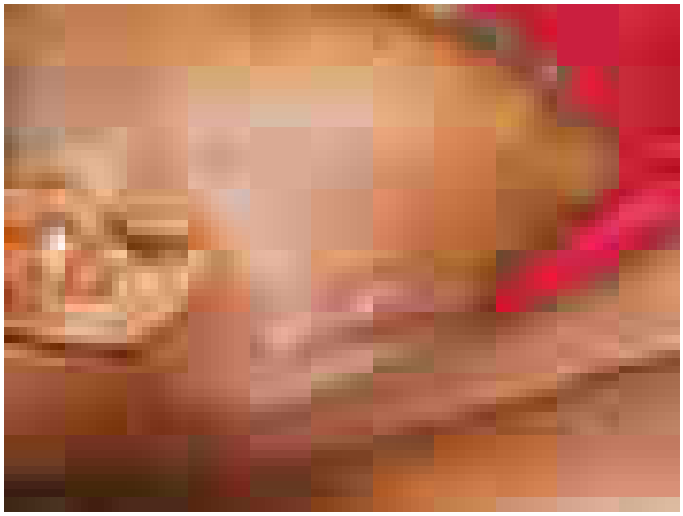

FIGURE 173-8 Tuberculous lymphadenitis affecting the cervical lymph nodes in a 2-year-old child from Malawi. *(Courtesy of Prof. S. Graham, Centre for International Child Health, University of Melbourne, Australia; with permission.)*

Pleural TB Involvement of the pleura accounts for ~20% of extrapulmonary cases in the United States and elsewhere. Isolated pleural effusion usually reflects recent primary infection, and the collection of fluid in the pleural space represents a hypersensitivity response to mycobacterial antigens. Pleural disease may also result from contiguous parenchymal spread, as in many cases of pleurisy accompanying postprimary disease. Depending on the extent of reactivity, the effusion may be small, remain unnoticed, and resolve spontaneously or may be sufficiently large to cause symptoms such as fever, pleuritic chest pain, and dyspnea. Physical findings are those of pleural effusion: dullness to percussion and absence of breath sounds. CXR reveals the effusion and, in up to one-third of cases, also shows a parenchymal lesion. Thoracentesis is required to ascertain the nature of the effusion and to differentiate it from manifestations of other etiologies. The fluid is straw-colored and at times hemorrhagic; it is an exudate with a protein concentration >50% of that in serum (usually ~4–6 g/dL), a normal to low glucose concentration, a pH of ~7.3 (occasionally <7.2), and detectable white blood cells (usually 500–6000/μL). Neutrophils may predominate in the early stage, but lymphocyte predominance is the typical finding later. Mesothelial cells are generally rare or absent. AFBs are rarely seen on direct smear, and cultures often may be falsely negative for *M. tuberculosis*; positive cultures are more common among postprimary cases. Determination of the pleural concentration of adenosine deaminase may be a useful screening test, and TB may be excluded if the value is very low. Lysozyme is also present in the pleural effusion. Measurement of IFN-γ, either directly or through stimulation of sensitized T cells with mycobacterial antigens, can be diagnostically helpful. Needle biopsy of the pleura is often required for diagnosis and is recommended over pleural fluid analysis; it reveals granulomas and/or yields a positive culture in up to 80% of cases. Pleural biopsy can yield a positive result in ~75% of cases when real-time automated nucleic acid amplification is used (the Xpert® MTB/RIF assay [Cepheid, Sunnyvale, CA]; see "Nucleic Acid Amplification Technology," below); testing of pleural fluid with this assay is not recommended because of low sensitivity. This form of pleural TB responds rapidly to chemotherapy and may resolve spontaneously. Concurrent glucocorticoid administration may reduce the duration of fever and/or chest pain but is not of proven benefit.

Tuberculous empyema is a less common complication of pulmonary TB. It is usually the result of the rupture of a cavity, with spillage of a large number of organisms into the pleural space. This process may create a bronchopleural fistula with evident air in the pleural space. CXR shows hydropneumothorax with an air-fluid level. The pleural fluid is purulent and thick and contains large numbers of lymphocytes. Acid-fast smears and mycobacterial cultures are often positive. Surgical drainage is usually required as an adjunct to chemotherapy. Tuberculous empyema may result in severe pleural fibrosis and restrictive lung disease. Removal of the thickened visceral pleura (*decortication*) is occasionally necessary to improve lung function.

TB of the Upper Airways Nearly always a complication of advanced cavitary pulmonary TB, TB of the upper airways may involve the larynx, pharynx, and epiglottis. Symptoms include hoarseness, dysphonia, and dysphagia in addition to chronic productive cough. Findings depend on the site of involvement, and ulcerations may be seen on laryngoscopy. Acid-fast smear of the sputum is often positive, but biopsy may be necessary in some cases to establish the diagnosis. Carcinoma of the larynx may have similar features but is usually painless.

Genitourinary TB Genitourinary TB, which accounts for ~10–15% of all extrapulmonary cases in the United States and elsewhere, may involve any portion of the genitourinary tract. Local symptoms predominate, and up to 75% of patients have abnormalities on CXR suggesting previous or concomitant pulmonary disease. Urinary frequency, dysuria, nocturia, hematuria, and flank or abdominal pain are common presentations. However, patients may be asymptomatic and their disease discovered only after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal results in 90% of cases, revealing pyuria and hematuria. The documentation of culture-negative pyuria in acidic urine should raise the suspicion of TB. IV pyelography, abdominal CT, or MRI **(Fig. 173-9)** may show deformities and obstructions; calcifications and ureteral strictures are suggestive findings. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% of cases. Severe ureteral strictures may lead to hydronephrosis and renal damage. Genital TB is diagnosed more commonly in female than in male patients. In female patients, it affects the fallopian tubes and the endometrium and may cause infertility, pelvic pain, and menstrual abnormalities. Diagnosis requires biopsy or culture of specimens obtained by dilation and curettage. In male patients, genital TB preferentially affects the epididymis, producing a slightly tender mass that may drain externally through a fistulous tract; orchitis and prostatitis may also develop. In almost half of cases of genitourinary TB, urinary tract disease is also present. Genitourinary TB responds well to chemotherapy.

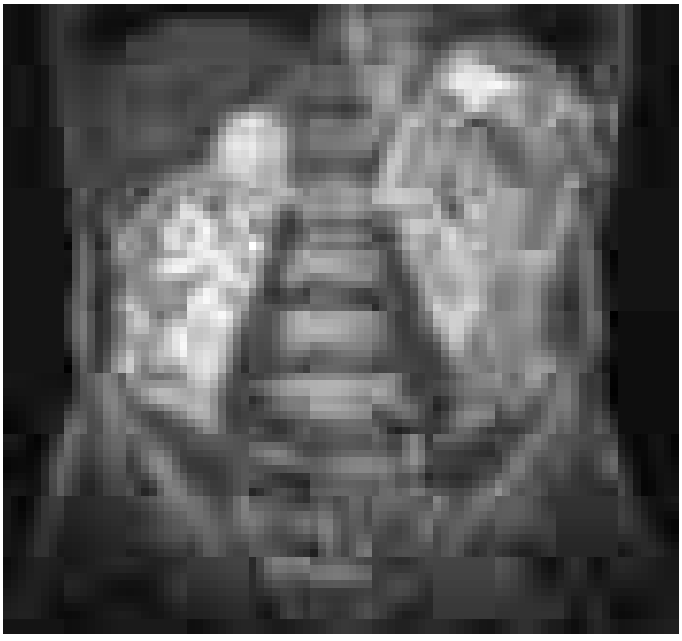

FIGURE 173-9 MRI of culture-confirmed renal tuberculosis. T2-weighted coronary plane: coronal sections showing several renal lesions in both the cortical and the medullary tissues of the right kidney. *(Courtesy of Dr. Alberto Matteelli, Department of Infectious Diseases, University of Brescia, Italy; with permission.)*

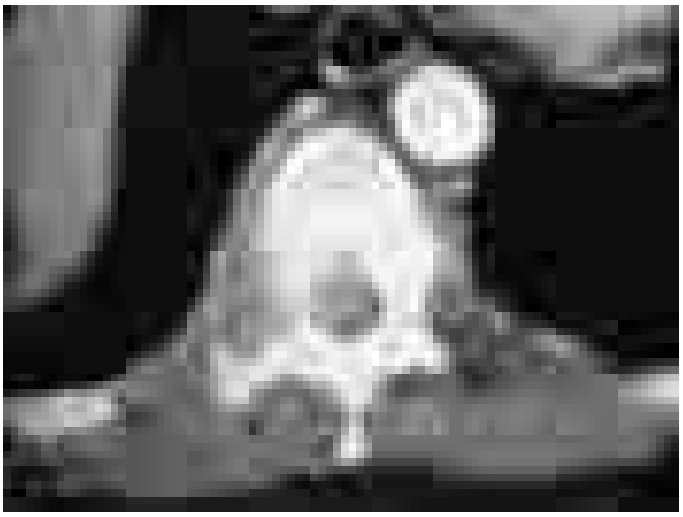

FIGURE 173-10 CT scan demonstrating destruction of the right pedicle of T10 due to Pott's disease. The patient, a 70-year-old Asian woman, presented with back pain and weight loss and had biopsy-proven tuberculosis. *(Courtesy of Charles L. Daley, MD, University of California, San Francisco; with permission.)*

Skeletal TB In the United States, TB of the bones and joints is responsible for ~10% of extrapulmonary cases. In bone and joint disease, pathogenesis is related to reactivation of hematogenous foci or to spread from adjacent paravertebral lymph nodes. Weight-bearing joints (the spine in 40% of cases, the hips in 13%, and the knees in 10%) are most commonly affected. Spinal TB (Pott's disease or tuberculous spondylitis; **Fig. 173-10**) often involves two or more adjacent vertebral bodies. Whereas the upper thoracic spine is the most common site of spinal TB in children, the lower thoracic and upper lumbar vertebrae are usually affected in adults. From the anterior superior or inferior angle of the vertebral body, the lesion slowly reaches the adjacent body, later affecting the intervertebral disk. With advanced disease, collapse of vertebral bodies results in kyphosis (*gibbus*). A paravertebral "cold" abscess may also form. In the upper spine, this abscess may track to and penetrate the chest wall, presenting as a soft tissue mass; in the lower spine, it may reach the inguinal ligaments or present as a psoas abscess. CT or MRI reveals the characteristic lesion and suggests its etiology. The differential diagnosis includes tumors and other infections. Pyogenic bacterial osteomyelitis, in particular, involves the disk very early and produces rapid sclerosis. Aspiration of the abscess or bone biopsy confirms the tuberculous etiology, as cultures are usually positive and histologic findings highly typical. A catastrophic complication of Pott's disease is paraplegia, which is usually due to an abscess or a lesion compressing the spinal cord. Paraparesis due to a large abscess is a medical emergency and requires rapid drainage. TB of the hip joints, usually involving the head of the femur, causes pain; TB of the knee produces pain and swelling. If the disease goes unrecognized, the joints may be destroyed. Diagnosis requires examination of the synovial fluid, which is thick in appearance, with a high protein concentration and a variable cell count. Although synovial fluid culture is positive in a high percentage of cases, synovial biopsy and tissue culture may be necessary to establish the diagnosis. Skeletal TB responds to chemotherapy, but severe cases may require surgery.

Tuberculous Meningitis and Tuberculoma TB of the central nervous system accounts for ~5% of extrapulmonary cases in the United States. It is seen most often in young children but also develops in adults, especially those infected with HIV. Tuberculous meningitis results from the hematogenous spread of primary or postprimary pulmonary TB or from the rupture of a subependymal tubercle into the

subarachnoid space. In more than half of cases, evidence of old pulmonary lesions or a miliary pattern is found on CXR. The disease often presents subtly as headache and slight mental changes after a prodrome of weeks of low-grade fever, malaise, anorexia, and irritability. If not recognized, tuberculous meningitis may evolve acutely with severe headache, confusion, lethargy, altered sensorium, and neck rigidity. Typically, the disease evolves over 1–2 weeks, a course longer than that of bacterial meningitis. Because meningeal involvement is pronounced at the base of the brain, paresis of cranial nerves (ocular nerves in particular) is a frequent finding, and the involvement of cerebral arteries may produce focal ischemia. The ultimate evolution is toward coma, with hydrocephalus and intracranial hypertension.

Lumbar puncture is the cornerstone of diagnosis. In general, examination of cerebrospinal fluid (CSF) reveals a high leukocyte count (up to 1000/μL), usually with a predominance of lymphocytes but sometimes with a predominance of neutrophils in the early stage; a protein content of 1–8 g/L (100–800 mg/dL); and a low glucose concentration. However, any of these three parameters can be within the normal range. AFBs are infrequently seen on direct smear of CSF sediment, and repeated lumbar punctures increase the yield. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard. Real-time automated nucleic acid amplification (the Xpert MTB/RIF assay) has a sensitivity of up to 80% and is the preferred initial diagnostic option. Treatment should be initiated immediately upon a positive Xpert MTB/RIF result. A negative result does not exclude a diagnosis of TB and requires further diagnostic workup. Imaging studies (CT and MRI) may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma. If unrecognized, tuberculous meningitis is uniformly fatal. This disease responds to chemotherapy; however, neurologic sequelae are documented in 25% of treated cases, in most of which the diagnosis has been delayed. Clinical trials have demonstrated that patients given adjunctive glucocorticoids may experience faster resolution of CSF abnormalities and elevated CSF pressure, resulting in lower rates of death or severe disability and relapse. In one study, adjunctive dexamethasone significantly enhanced the chances of survival among persons >14 years of age but did not reduce the frequency of neurologic sequelae. The dexamethasone schedule was (1) 0.4 mg/kg per day given IV with tapering by 0.1 mg/kg per week until the fourth week, when 0.1 mg/kg per day was administered; followed by (2) 4 mg/d given by mouth with tapering by 1 mg per week until the fourth week, when 1 mg/d was administered. The WHO now recommends that adjuvant glucocorticoid therapy with either dexamethasone or prednisolone, tapered over 6–8 weeks, should be used in central nervous system TB.

Tuberculoma, an uncommon manifestation of TB of the central nervous system, presents as one or more space-occupying lesions and usually causes seizures and focal signs. CT or MRI reveals contrast-enhanced ring lesions, but biopsy is necessary to establish the diagnosis.

Gastrointestinal TB Gastrointestinal TB is uncommon, making up only 3.5% of extrapulmonary cases in the United States. Various pathogenetic mechanisms are involved: swallowing of sputum with direct seeding, hematogenous spread, or (largely in developing areas) ingestion of milk from cows affected by bovine TB. Although any portion of the gastrointestinal tract may be affected, the terminal ileum and the cecum are the sites most commonly involved. Abdominal pain (at times similar to that associated with appendicitis) and swelling, obstruction, hematochezia, and a palpable mass in the abdomen are common findings at presentation. Fever, weight loss, anorexia, and night sweats are also common. With intestinal-wall involvement, ulcerations and fistulae may simulate Crohn's disease; the differential diagnosis of this entity is always difficult. Anal fistulae should prompt an evaluation for rectal TB. Because surgery is required in most cases, the diagnosis can be established by histologic examination and culture of specimens obtained intraoperatively.

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intraabdominal organs (e.g., genital TB in women) or hematogenous seeding. Nonspecific abdominal pain, fever, and ascites should raise the suspicion of tuberculous peritonitis. The coexistence of cirrhosis **(Chap. 335)** in patients with tuberculous peritonitis complicates the diagnosis. In tuberculous peritonitis, paracentesis reveals an exudative fluid with a high protein content and leukocytosis that is usually lymphocytic (although neutrophils occasionally predominate). The yield of direct smear and culture is relatively low; culture of a large volume of ascitic fluid can increase the yield, but peritoneal biopsy (with a specimen best obtained by laparoscopy) is often needed to establish the diagnosis.

Pericardial TB (Tuberculous Pericarditis) Due either to direct extension from adjacent mediastinal or hilar lymph nodes or to hematogenous spread, pericardial TB has often been a disease of the elderly in countries with low TB prevalence. However, it also develops frequently in HIV-infected patients. Case–fatality rates are as high as 40% in some series. The onset may be subacute, although an acute presentation, with dyspnea, fever, dull retrosternal pain, and a pericardial friction rub, is possible. An effusion eventually develops in many cases; cardiovascular symptoms and signs of cardiac tamponade may ultimately appear **(Chap. 265)**. In the presence of effusion, TB must be suspected if the patient belongs to a high-risk population (HIV-infected, originating in a high-prevalence country); if there is evidence of previous TB in other organs; or if echocardiography, CT, or MRI shows effusion and thickness across the pericardial space. A definitive diagnosis can be obtained by pericardiocentesis under echocardiographic guidance. The pericardial fluid must be submitted for biochemical, cytologic, and microbiologic evaluation. The effusion is exudative in nature, with a high count of lymphocytes and monocytes. Hemorrhagic effusion is common. Direct smear examination is very rarely positive. Culture of pericardial fluid reveals *M. tuberculosis* in up to two-thirds of cases, whereas pericardial biopsy has a higher yield. High levels of adenosine deaminase, lysozyme, and IFN-γ may suggest a tuberculous etiology.

Without treatment, pericardial TB is usually fatal. Even with treatment, complications may develop, including chronic constrictive pericarditis with thickening of the pericardium, fibrosis, and sometimes calcification, which may be visible on a chest radiograph. Systematic reviews and meta-analyses show a trend toward benefit from glucocorticoid treatment with regard to death and constrictive pericarditis. However, the largest and most recent study—the IMPI study—failed to show such a benefit. Of the patients enrolled in this trial, 67% were infected with HIV, and only a fraction were receiving antiretroviral treatment (ART). A supplemental analysis among HIV-negative people showed a small mortality benefit, as did another small study among HIV-infected people. The WHO currently recommends that, in patients with tuberculous pericarditis, initial adjuvant glucocorticoid therapy may be used. The 2016 guidelines of the American Thoracic Society (ATS), the CDC, and the Infectious Diseases Society of America (IDSA), on the other hand, suggest that glucocorticoid therapy should not be routinely administered.

Caused by direct extension from the pericardium or by retrograde lymphatic extension from affected mediastinal lymph nodes, tuberculous myocarditis is an extremely rare disease. Usually, it is fatal and is diagnosed post-mortem.

Miliary or Disseminated TB Miliary TB is due to hematogenous spread of tubercle bacilli. Although in children it is often the consequence of primary infection, in adults it may be due to either recent infection or reactivation of old disseminated foci. The lesions are usually yellowish granulomas 1–2 mm in diameter that resemble millet seeds (thus the term *miliary*, coined by nineteenth-century pathologists). Clinical manifestations are nonspecific and protean, depending on the predominant site of involvement. Fever, night sweats, anorexia, weakness, and weight loss are presenting symptoms in the majority of cases. At times, patients have a cough and other respiratory symptoms due to pulmonary involvement as well as abdominal symptoms. Physical findings include hepatomegaly, splenomegaly, and lymphadenopathy. Eye examination may reveal choroidal tubercles, which are pathognomonic of miliary TB, in up to 30% of cases. Meningismus occurs in fewer than 10% of cases.

A high index of suspicion is required for the diagnosis of miliary TB. Frequently, CXR (Fig. 173-5) reveals a miliary reticulonodular pattern (more easily seen on underpenetrated film), although no radiographic abnormality may be evident early in the course and among HIV-infected patients. Other radiologic findings include large infiltrates, interstitial infiltrates (especially in HIV-infected patients), and pleural effusion. Sputum-smear microscopy is negative in most cases. Various hematologic abnormalities may be seen, including anemia with leukopenia, lymphopenia, neutrophilic leukocytosis and leukemoid reactions, and polycythemia. Disseminated intravascular coagulation has been reported. Elevation of alkaline phosphatase levels and other abnormal values in liver function tests are detected in patients with severe hepatic involvement. TST results may be negative in up to half of cases, but reactivity may be restored during chemotherapy. Bronchoalveolar lavage and transbronchial biopsy are more likely to provide bacteriologic confirmation, and granulomas are evident in liver or bone-marrow biopsy specimens from many patients. If it goes unrecognized, miliary TB is lethal; with proper early treatment, however, it is amenable to cure. Glucocorticoid therapy has not proved beneficial.

A rare presentation seen in the elderly, *cryptic miliary TB* has a chronic course characterized by mild intermittent fever, anemia, and—ultimately—meningeal involvement preceding death. An acute septicemic form, *nonreactive miliary TB*, occurs very rarely and is due to massive hematogenous dissemination of tubercle bacilli. Pancytopenia is common in this form of disease, which is rapidly fatal. At postmortem examination, multiple necrotic but nongranulomatous ("nonreactive") lesions are detected.

Less Common Extrapulmonary Forms TB may cause chorioretinitis, uveitis, panophthalmitis, and painful hypersensitivity-related phlyctenular conjunctivitis. Tuberculous otitis is rare and presents as hearing loss, otorrhea, and tympanic membrane perforation. In the nasopharynx, TB may simulate granulomatosis with polyangiitis. Cutaneous manifestations of TB include primary infection due to direct inoculation, abscesses and chronic ulcers, scrofuloderma, lupus vulgaris (a smoldering disease with nodules, plaques, and fissures), miliary lesions, and erythema nodosum. Tuberculous mastitis results from retrograde lymphatic spread, often from the axillary lymph nodes. Adrenal TB is a manifestation of disseminated disease presenting rarely as adrenal insufficiency. Finally, congenital TB results from transplacental spread of tubercle bacilli to the fetus or from ingestion of contaminated amniotic fluid. This rare disease affects the liver, spleen, lymph nodes, and various other organs.

Post-TB Complications TB may cause persisting pulmonary damage in patients whose infection has been considered cured on clinical grounds. Chronic impairment of lung functions, bronchiectasis, aspergillomas, and chronic pulmonary aspergillosis have been associated with TB. Chronic pulmonary aspergillosis may manifest as simple aspergilloma (fungal ball) or chronic cavitary aspergillosis. Early studies revealed that, especially in the presence of large residual cavities, *Aspergillus fumigatus* may colonize the lesion and produce symptoms such as respiratory impairment, hemoptysis, persistent fatigue, and weight loss, often resulting in the erroneous diagnosis of TB recurrence. The detection of *Aspergillus* precipitins (IgG) in the blood suggests chronic pulmonary aspergillosis, as do radiographic abnormalities such as thickening of the pleura and cavitary walls or the presence of a fungal ball inside the cavity. Treatment is difficult. Recent preliminary studies on the use of itraconazole for ≥6 months indicate improvement or stabilization of 60–75% of the radiologic and clinical manifestations. Surgical removal of lesions is risky except in simple aspergilloma.

HIV-Associated TB **(See also Chap. 197)** TB is one of the most common diseases among HIV-infected persons worldwide. Responsible for an estimated 20–25% of all HIV-related mortality (some 390,000 deaths per year), TB is likely the main cause of death in this population. In certain urban settings in some African countries, the prevalence of HIV infection among TB patients reaches 70–80%. A person with a positive TST who acquires HIV infection has a 3–13% annual risk of developing active TB, with the exact risk depending on the degree of immunosuppression when observation begins. Furthermore, a new TB infection acquired by an HIV-infected individual may evolve into active disease in a matter of weeks rather than months or years. TB can appear at any stage of HIV infection, and its presentation varies with the stage. When cell-mediated immunity is only partially compromised, pulmonary TB presents in a typical manner (Figs. 173-6 and 173-7), with upper-lobe infiltrates and cavitation and without significant lymphadenopathy or pleural effusion. In late stages of HIV infection, when the CD4+ T cell count is <200/μL, a primary TB–like pattern, with diffuse interstitial and subtle infiltrates, little or no cavitation, pleural effusion, and intrathoracic lymphadenopathy, is more common. However, these forms are becoming less common because of the expanded use of ART. Overall, sputum smears are less frequently positive among TB patients with HIV infection than among those without; thus, the diagnosis of TB with traditional technology may be difficult, especially in view of the variety of HIV-related pulmonary conditions mimicking TB. Extrapulmonary TB is common among HIV-infected patients. In various series, extrapulmonary TB—alone or in association with pulmonary disease—has been documented in 40–60% of all cases in HIV-co-infected individuals. The most common forms are lymphatic, disseminated, pleural, and pericardial. Mycobacteremia and meningitis are also common, particularly in advanced HIV disease. The diagnosis of TB in HIV-infected patients may be complicated not only by the increased frequency of sputum-smear negativity (up to 40% in culture-proven pulmonary cases) but also by atypical radiographic findings, a lack of classic granuloma formation in the late stages, and a negative TST. The Xpert MTB/RIF assay is the preferred initial diagnostic option, and therapy should be started on the basis of a positive result because treatment delays may be fatal. A negative Xpert MTB/RIF result, however, does not exclude a diagnosis of TB. Culture remains the gold standard. Recent assessment of a test based on the detection of mycobacterial lipoarabinomannan antigen in urine has shown favorable results in assisting with the detection of TB in HIV-positive people (see "Additional Diagnostic Procedures," below).

The *immune reconstitution inflammatory syndrome* (IRIS) or *TB immune reconstitution disease* consists of exacerbations in systemic manifestations (lymphadenopathy, fever) or respiratory signs (worsening of pulmonary infiltrations, pleural effusion) as well as laboratory or radiographic manifestations of TB. This syndrome has been associated with the administration of ART and occurs in ~10% of HIV-infected TB patients. Usually developing 1–3 months after initiation of ART, IRIS is more common among patients with advanced immunosuppression and extrapulmonary TB. "Unmasking IRIS" may develop after the initiation of ART in patients with undiagnosed subclinical TB. The earlier ART is started and the lower the baseline CD4+ T cell count, the greater the risk of IRIS. Death due to IRIS is relatively infrequent and occurs mainly among patients who have a high preexisting mortality risk. The presumed pathogenesis of IRIS consists of an immune response that is elicited by antigens released as bacilli are killed during effective chemotherapy and that is temporally associated with improving immune function. There is no diagnostic test for IRIS, and its confirmation relies heavily upon case definitions incorporating clinical and laboratory data; a variety of case definitions have been suggested. The first priority in the management of a possible case of IRIS is to ensure that the clinical syndrome does not represent a failure of TB treatment or the development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment and do not worsen outcomes of treatment for TB. However, IRIS can result in serious neurologic complications or death in patients with central nervous system TB. Therefore, ART should not be initiated during the first 8 weeks of TB treatment in patients with TB meningitis. Glucocorticoids have been used for severe paradoxical reactions; prednisolone given for 4 weeks at a low dosage (1.5 mg/kg per day for 2 weeks and half that dose for the remaining 2 weeks) has reduced the need for hospitalization and therapeutic procedures and has hastened alleviation of symptoms, as reflected by Karnofsky performance scores, quality-of-life assessments, radiographic response, and C-reactive protein levels. The effectiveness of glucocorticoids in alleviating the symptoms of IRIS is probably linked to suppression of proinflammatory cytokine concentrations, as

these medications reduce serum concentrations of IL-6, IL-10, IL-12p40, TNF-α, IFN-γ, and IFN-γ-inducible protein 10. Recommendations for the prevention and treatment of TB in HIV-infected individuals are provided below.

DIAGNOSIS

The key to the early diagnosis of TB is a high index of suspicion. Diagnosis is not difficult in persons belonging to high-risk populations who present with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities (Fig. 173-6). On the other hand, the diagnosis can easily be missed in an elderly nursing-home resident or a teenager with a focal infiltrate. Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 173-6). The longer the delay between the onset of symptoms and the diagnosis, the more likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including those with HIV infection, may have "atypical" findings on CXR—e.g., lower-zone infiltrates without cavity formation.

The several approaches to the diagnosis of TB require, above all, a well-organized laboratory network with an appropriate distribution of tasks at different levels of the health care system. Besides clinical assessment and radiography, screening and referral are the principal tasks at the peripheral and community levels. Diagnosis at a secondary level (e.g., a traditional district hospital in a high-incidence setting) can be accomplished nowadays through real-time automated nucleic acid amplification technology (e.g., the Xpert MTB/RIF assay, which also allows detection of drug resistance) or through traditional AFB microscopy, where new tools have not yet been introduced. At a tertiary level, additional technology is necessary, including molecular tests, rapid culture, and DST.

NUCLEIC ACID AMPLIFICATION TECHNOLOGY

Several test systems based on amplification of mycobacterial nucleic acid have become available in the past few years and are now the preferred first-line diagnostic tests. These tests are progressively replacing smear microscopy, as they ensure rapid confirmation of all types of TB. One system that permits rapid diagnosis of TB with high specificity and sensitivity (approaching that of liquid culture) is the fully automated, real-time nucleic acid amplification technology known as the Xpert MTB/RIF assay. Xpert MTB/RIF can simultaneously detect TB and rifampin resistance in <2 h and has minimal biosafety and training requirements. Therefore, it can be housed in nonconventional laboratory settings as long as a stable and uninterrupted power supply can be assured. The WHO recommends its use worldwide as the first-line diagnostic test in all adults and children with signs or symptoms of active TB. Given the test's high sensitivity, the WHO also recommends its use as the initial diagnostic test for people living with HIV in whom TB is suspected. Likewise, Xpert MTB/RIF should be the initial test applied to CSF from patients in whom TB meningitis is suspected as well as a replacement test (preferable to conventional microscopy, culture, and histopathology) for selected nonrespiratory specimens—those obtained by gastric lavage, fine-needle aspiration, or pleural or other biopsies—from patients in whom extrapulmonary TB is suspected. This test has a sensitivity of 98% among AFB-positive cases and ~70% among AFB-negative specimens. Recently, the new Xpert® MTB/RIF Ultra assay (Ultra), which uses the same GeneXpert® diagnostic platform, has been assessed by the WHO as non-inferior to the Xpert MTB/RIF assay. Overall, its sensitivity is 5% higher, with the greatest increases among smear-negative, culture-positive cases (+17%) and among HIV-infected persons (+12%). However, because of this greater sensitivity, the new Ultra cartridge also detects nonviable bacilli and consequently has 3.2% lower specificity than the original test. In this new assay, "trace calls" (i.e., the "noise" produced by detection of nonviable bacilli or fragments of bacilli) need to be evaluated according to risk/benefit considerations. For instance, trace calls in specimens from HIV-infected patients, children, and persons with extrapulmonary TB should be considered true positives, given the high risk of severe morbidity and premature death, while among other cases they warrant additional tests to confirm the diagnosis of TB and prevent over-treatment. Among patients with a recent history of TB, trace calls may represent false positivity. Accuracy in detection of rifampin resistance by Ultra is similar to that by the Xpert MTB/RIF assay.

Another recently introduced molecular test for detection of *M. tuberculosis* is based on the loop-mediated isothermal amplification (LAMP) temperature-independent technology that amplifies DNA, is relatively simple to use, and is interpreted through a visual display. The new TB-LAMP assay (LoopampTM *M. tuberculosis* complex detection kit; Eiken Chemical Company, Japan) requires minimal laboratory infrastructure and has few biosafety requirements. It may be used as a replacement for sputum-smear microscopy for the diagnosis of adult pulmonary TB and as a follow-up test to smear microscopy for the further investigation of smear-negative specimens from adults with suspected pulmonary TB. The TB-LAMP assay should not replace rapid molecular tests that detect both TB and rifampin resistance, and its usefulness in HIV-infected people in whom TB is suspected remains unclear.

AFB MICROSCOPY

In many low- and middle-income settings, a presumptive diagnosis is still commonly based on the finding of AFB on microscopic examination of a diagnostic specimen, such as a smear of expectorated sputum or of tissue (e.g., a lymph node biopsy). Although inexpensive, AFB microscopy has relatively low sensitivity (40–60%) in culture-confirmed cases of pulmonary TB. The traditional method—light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes—is satisfactory, although time-consuming. Most modern laboratories processing large numbers of diagnostic specimens use auramine–rhodamine staining and fluorescence microscopy; this approach is more sensitive than the Ziehl-Neelsen method. However, it is expensive because it requires high-cost mercury vapor light sources and a dark room. Less expensive light-emitting diode (LED) fluorescence microscopes are now recommended by the WHO as the microscopy tool of choice. They are as sensitive as—or more sensitive than—traditional fluorescence microscopes. As a result, conventional light and fluorescence microscopes are being replaced with this more recent technology, especially in developing countries. For patients with signs or symptoms of pulmonary TB, it has been recommended that one or two sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacterial culture. If tissue is obtained, it is critical that the portion of the specimen intended for culture not be put in preservation fluid such as formaldehyde. The use of AFB microscopy in examining urine or gastric lavage fluid is limited by the low numbers of organisms, which can cause false-negative results, or the presence of commensal mycobacteria, which can cause false-positive results.

MYCOBACTERIAL CULTURE

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a clinical specimen or the identification of specific DNA sequences in a nucleic acid amplification test. Commercial liquid-culture systems such as the mycobacterial growth indicator tube (MGIT) system (Becton Dickinson, Franklin Lakes, NJ) are recommended by the WHO as the reference standard for culture. The MGIT system uses a fluorescent compound sensitive to the presence of oxygen dissolved in the liquid medium. The appearance of fluorescence, detected by fluorometric technology, indicates active growth of mycobacteria. MGIT cultures usually become positive after a period ranging from 10 days to 2–3 weeks; the tubes are read weekly until the eighth week of incubation before the result is declared to be negative. Specimens may also be inoculated onto egg- or agar-based medium (e.g., Löwenstein-Jensen or Middlebrook 7H10 or 7H11) and incubated at 37°C (under 5% CO_2 for Middlebrook medium). Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, 4–8 weeks may be required before growth is detected on these conventional culture media. Although *M. tuberculosis* may be identified presumptively on the basis of growth time and colony pigmentation and morphology, a variety of biochemical tests have traditionally been used to speciate

mycobacterial isolates. In modern, well-equipped laboratories, commercial liquid culture for isolation and species identification by molecular methods or high-pressure liquid chromatography of mycolic acids has replaced isolation on solid media and identification by biochemical tests. A low-cost, rapid immunochromatographic lateral-flow assay based on detection of MTP64 antigen may also be used for species identification of the *M. tuberculosis* complex in culture isolates. These new methods, which are increasingly used in limited-resource settings, have decreased the time required for bacteriologic confirmation of TB to 2–3 weeks.

DRUG SUSCEPTIBILITY TESTING

Universal DST is considered by the WHO as the current standard of care for all TB patients and should consist in DST to at least rifampin for all initial isolates of *M. tuberculosis*, as rifampin resistance is an excellent proxy for MDR-TB. Susceptibility testing is particularly important if one or more risk factors for drug resistance are identified or if the patient either fails to respond to initial therapy or has a relapse after the completion of treatment (see "Treatment Failure and Relapse," below). In addition, expanded and rapid susceptibility testing for isoniazid and key second-line anti-TB drugs (especially the fluoroquinolones and the injectable drugs) is mandatory when RR-TB is found in order to guide selection of the appropriate treatment regimens. Susceptibility testing may be conducted directly (with the clinical specimen) or indirectly (with mycobacterial cultures) on solid or liquid medium. Results are obtained rapidly by direct susceptibility testing on liquid medium, with an average reporting time of 3 weeks. With indirect testing on solid medium, results may not be available for ≥8 weeks. Highly reliable genotypic methods for the rapid identification of genetic mutations in gene regions known to be associated with resistance to rifampin (such as those in *rpo*B) and isoniazid (such as those in *kat*G and *inh*A) have been developed and are being widely implemented for screening of patients at increased risk of drug-resistant TB. Apart from the Xpert MTB/RIF and Xpert MTB/RIF Ultra assays, which, as mentioned above, detect rifampin resistance, the most widely used tests are molecular line probe assays. After extraction of DNA from *M. tuberculosis* isolates or from clinical specimens, the resistance gene regions are amplified by polymerase chain reaction (PCR), and labeled and probe-hybridized PCR products are detected by colorimetric development. This assay reveals the presence of *M. tuberculosis* as well as mutations in target resistance-gene regions. Given the rapidity and accuracy of commercially available line probe assays, the WHO recommends that they (rather than phenotypic culture-based tests) may be used to detect resistance to isoniazid and rifampin when patients have sputum smear–positive specimens or a cultured isolate of *M. tuberculosis*. These recommendations do not eliminate the need for conventional culture-based testing to identify resistance to other drugs and to monitor emergence of additional drug resistance. A similar approach has been developed for second-line anti-TB drugs, such as the fluoroquinolones and the injectable drugs kanamycin, amikacin, and capreomycin. Therefore, second-line line probe assays (instead of phenotypic culture-based DST) are now recommended by the WHO as the initial test for rapid detection of resistance to the fluoroquinolones or the second-line injectable drugs in isolates from patients with confirmed RR-TB or MDR-TB. As with first-line line probe assays, these recommendations do not eliminate the need for conventional phenotypic, culture-based testing to identify resistance to other drugs and to monitor for the emergence of additional resistance. Finally, a few noncommercial, inexpensive culture and susceptibility testing methods (e.g., microscopically observed drug susceptibility, nitrate reductase, and colorimetric redox indicator assays) have been used in resource-limited settings. Their use is restricted to national reference laboratories with proven proficiency and adequate external quality control as an interim solution while genotypic or automated liquid-culture technology is introduced.

RADIOGRAPHIC PROCEDURES

CXR is a rapid imaging technique that has historically been used as a primary tool to detect pulmonary TB. CXR has high sensitivity but poor specificity. Although TB may often present with typical patterns strongly suggesting the disease, some abnormalities seen in TB are also present in several other lung conditions. The initial suspicion of pulmonary TB is often based on abnormal CXR findings in a patient undergoing triage for respiratory symptoms. The presence of lesions suggestive of TB should prompt bacteriologic investigations in all cases, without exception. Although the "classic" picture is that of upper-lobe disease with infiltrates and cavities (Fig. 173-6), virtually any radiographic pattern—from a normal film or a solitary pulmonary nodule to diffuse alveolar infiltrates in a patient with adult respiratory distress syndrome—may be seen. In the era of HIV/AIDS, no radiographic pattern can be considered pathognomonic, but CXR can assist in diagnosing TB or ruling it out before initiation of treatment of latent infection. CXR is also helpful as a screening test used preceding rapid molecular assays (Xpert MTB/RIF and line probe assays) to improve their predictive value. Digital CXR technology, which allows display of images in a digital format on a computer screen instead of on x-ray film, offers several advantages: the procedure time is reduced, the running costs are lower, the imaging is of superior quality, and telemedicine assistance is available, including computer-aided detection and interpretation of findings. However, a recent systematic review of studies using computer-aided detection software that analyzes digital imaging for abnormalities compatible with TB concluded that the diagnostic accuracy of this technology is still limited.

CT (Fig. 173-7) may be useful in interpreting questionable findings on plain CXR and in diagnosing some forms of extrapulmonary TB (e.g., Pott's disease; Fig. 173-10). A recent study has shown the potential of positron emission tomography combined with CT for detection of subclinical disease that may be progressing toward full-blown TB in HIV-infected people. MRI is useful in the diagnosis of intracranial TB.

ADDITIONAL DIAGNOSTIC PROCEDURES

Other diagnostic tests may be used when pulmonary TB is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for molecular testing with the Xpert MTB/RIF assay, mycobacterial culture, and AFB smear. For the diagnosis of primary pulmonary TB in children, who often do not expectorate sputum, induced sputum specimens and specimens from early-morning gastric lavage may yield positive results in the Xpert MTB/RIF assay or on culture.

Invasive diagnostic procedures are indicated for patients with suspected extrapulmonary TB. In addition to testing of specimens from involved sites (e.g., CSF for tuberculous meningitis, pleural fluid and biopsy samples for pleural disease), biopsy and culture of bone marrow and liver tissue have a good diagnostic yield in disseminated (miliary) TB, particularly in HIV-infected patients, who also have a high frequency of positive blood cultures. Xpert MTB/RIF should always be the initial diagnostic test in patients where TB meningitis is suspected; any positive results should prompt immediate treatment initiation, while negative results should be followed up by additional testing. In some cases, the results of culture or Xpert MTB/RIF are negative but a clinical diagnosis of TB is supported by consistent epidemiologic evidence (e.g., a history of close contact with an infectious patient) and a compatible clinical and radiographic response to treatment. In the United States and other industrialized countries with low rates of TB, some patients with limited abnormalities on CXR and sputum positive for AFB are infected with nontuberculous mycobacteria, most commonly organisms of the *M. avium* complex or *M. kansasii* **(Chap. 175)**. Factors favoring the diagnosis of nontuberculous mycobacterial disease over TB include an absence of risk factors for TB and the presence of underlying chronic pulmonary disease.

Patients with HIV-associated TB pose several diagnostic problems (see "HIV-Associated TB," above). HIV-infected patients with sputum

culture–positive, AFB-positive TB may present with a normal chest radiograph. The Xpert MTB/RIF assay is the preferred rapid diagnostic test in this population of patients because of its simplicity and increased sensitivity (~60–70% among AFB-negative, culture-positive cases and 97–98% among AFB-positive cases). With the advent of ART, the occurrence of disseminated *M. avium* complex disease that can be confused with TB has become much less common. A test based on the detection of mycobacterial lipoarabinomannan antigen in urine has emerged as a potentially useful point-of-care test for TB in HIV-infected persons with low CD4+ T cell counts. The lateral-flow urine lipoarabinomannan assay can be performed manually and read by eye. After a systematic review of the evidence, the WHO recommends that this assay be used to assist in the diagnosis of TB in HIV-positive adults who have signs and symptoms of TB and a CD4+ T cell count of ≤100 cells/μL or in HIV-positive patients who are seriously ill regardless of CD4+ T cell count or with an unknown CD4+ count. The WHO also recommends that this test not be used, pending information on recent promising technological test advances, for TB diagnosis or as a screening test for TB in any other patient categories.

SEROLOGIC AND OTHER DIAGNOSTIC TESTS FOR ACTIVE TB

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens have been carefully assessed by the WHO and found not to be useful as diagnostic aids because of their low sensitivity and specificity and their poor reproducibility. In 2011, after a rigorous evaluation of these tests, the WHO issued a "negative" recommendation in order to prevent their abuse in the private sector of many resource-limited countries. Various methods aimed at detection of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determinations of adenosine deaminase and IFN-γ levels in pleural fluid may be useful adjunctive tests in the diagnosis of pleural TB; their utility in the diagnosis of other forms of extrapulmonary TB (e.g., pericardial, peritoneal, and meningeal) is less clear.

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

Two tests currently exist for identification of individuals with LTBI: the TST and IGRAs. Both of these tests have limitations, especially in settings or populations with high TB and/or HIV prevalence.

Tuberculin Skin Testing In 1891, Robert Koch discovered that components of *M. tuberculosis* in a concentrated liquid-culture medium, subsequently named "old tuberculin," were capable of eliciting a skin reaction when injected subcutaneously into patients with TB. In 1932, Seibert and Munday purified this product by ammonium sulfate precipitation to produce an active protein fraction known as *tuberculin purified protein derivative* (PPD). In 1941, PPD-S, developed by Seibert and Glenn, was chosen as the international standard. Later, the WHO and UNICEF sponsored large-scale production of a master batch of PPD (RT23) and made it available for general use. The greatest limitation of PPD is its lack of mycobacterial species specificity, a property due to the large number of proteins in this product that are highly conserved in the various species. In addition, subjectivity of the skin-reaction interpretation, deterioration of the product, and batch-to-batch variations limit the usefulness of PPD.

The skin test with tuberculin PPD (TST) is most widely used in screening for LTBI. It probably measures the response to antigenic stimulation by T cells that reside in the skin rather than the response of recirculating memory T cells. The test is of limited value in the diagnosis of active TB because of its relatively low sensitivity and specificity and its inability to discriminate between LTBI and active disease. False-negative reactions are common in immunosuppressed patients and in those with overwhelming TB. False-positive reactions may be caused by infections with nontuberculous mycobacteria (Chap. 175) and by BCG vaccination. A repeated TST can produce larger reaction sizes due to either boosting or true conversion. The "boosting phenomenon" is a spurious TST conversion resulting from boosting of reactivity on a subsequent TST 1–5 weeks after the initial test. Distinguishing boosting from true conversion is difficult yet important and can be based on clinical and epidemiologic considerations. For instance, true conversions are likely after BCG vaccination in a previously TST-negative person or in a close contact of an infectious patient.

IFN-γ Release Assays Two in vitro assays that measure T cell release of IFN-γ in response to stimulation with the highly TB-specific RD1-encoded antigens ESAT-6 and CFP-10 were introduced in the early 2000s and are commercially available. The T-SPOT®. TB test (Oxford Immunotec, Oxford, United Kingdom) is an enzyme-linked immunospot assay, and the QuantiFERON®-TB Gold test (Qiagen GmbH, Hilden, Germany) is a whole-blood enzyme-linked immunosorbent assay for measurement of IFN-γ. The QuantiFERON®-TB Gold In-Tube assay, which facilitates blood collection and initial incubation, also contains another specific antigen, TB7.7. These tests likely measure the response of recirculating memory T cells—normally part of a reservoir in the spleen, bone marrow, and lymph nodes—to persisting bacilli producing antigenic signals.

In settings or population groups with low TB and HIV burdens, IGRAs have previously been reported to be more specific than the TST as a result of less cross-reactivity with BCG vaccination and sensitization by nontuberculous mycobacteria; i.e., RD1 antigens are not encoded in the genome of either BCG strains or most nontuberculous mycobacteria. Recent studies suggest that IGRAs may not perform well in serial testing (e.g., among health care workers) and that interpretation of results depends on cutoff values used to define positivity. Potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, and the avoidance of somewhat subjective measurements (e.g., skin induration). However, IGRAs require that blood be drawn and then delivered to the laboratory in a timely fashion. IGRAs also require that testing be performed by specially trained technicians in a laboratory setting. These requirements pose challenges similar to those faced with the TST, including cold-chain requirements and batch-to-batch variations. Because of higher specificity and greater availability of resources, IGRAs have usually replaced the TST for LTBI diagnosis in low-incidence, high-income settings. However, in high-incidence TB and HIV settings and population groups, evidence about the performance and usefulness of IGRAs is still limited, and cost considerations may currently limit wider use.

A number of national guidelines on the use of IGRAs for LTBI testing have been issued. In the United States, an IGRA is preferred to the TST for most persons over the age of 5 years who are being screened for LTBI. However, for individuals at high risk of progression to active TB (e.g., HIV-infected persons), either test—or, to optimize sensitivity, both tests—may be used. Because of the paucity of data on the use of IGRAs in children, the TST is preferred for LTBI testing of children aged <5. In Canada and some European countries, a two-step approach for those with positive TSTs—i.e., an initial TST followed by an IGRA—is recommended. However, a TST may boost an IGRA response if the interval between the two tests exceeds 3 days.

In conclusion, both the TST and IGRAs, although useful as diagnostic aids, are imperfect tests for LTBI: while they can identify latently infected persons, they have low predictive value in identifying individuals with the highest risk of progression toward disease, cannot differentiate between active TB and LTBI, cannot distinguish new infections from reinfections, and display reduced sensitivity in immunocompromised patients.

TREATMENT

Tuberculosis

The two main aims of TB treatment are (1) to prevent morbidity and death by curing TB while preventing the emergence of drug resistance and (2) to interrupt transmission by rendering patients noninfectious to others. Chemotherapy for TB became possible with the discovery of streptomycin in 1943. Randomized clinical trials clearly indicated that the administration of streptomycin to patients

with chronic TB reduced mortality rates and led to cure in the majority of cases. However, monotherapy with streptomycin was soon associated with the development of resistance to this drug and the resulting failure of treatment. With the introduction into clinical practice of para-aminosalicylic acid (PAS) and isoniazid, it became axiomatic in the early 1950s that cure of TB required the concomitant administration of at least two agents to which the organism was susceptible. Furthermore, early clinical trials demonstrated that a long period of treatment—i.e., 12–24 months—was required to prevent recurrence. The introduction of rifampin (rifampicin) in the early 1970s heralded the era of effective short-course chemotherapy, with a treatment duration of <12 months. The discovery that pyrazinamide, which was first used in the 1950s, augmented the potency of isoniazid/rifampin regimens led to the use of a 6-month course of this triple-drug regimen as standard therapy. Streptomycin was added as the fourth drug mainly to prevent the emergence of drug resistance. These four drugs (with streptomycin eventually replaced by ethambutol) still form the basis of the optimal treatment regimen for rifampin-susceptible TB. The emergence of drug-resistant TB in the 1990s prompted attempts to standardize the approach to treatment of this condition mainly on the basis of expert opinion. This event has also stimulated research on and development of new anti-TB agents in the past 15 years. In 2013 and 2014, respectively, bedaquiline and delamanid—the first two drugs specifically developed for TB during nearly half a century—received conditional approval by the U.S. Food and Drug Administration (FDA) and other drug-regulatory authorities; approval was based on the results of phase 2b clinical trials in which the drugs were added to the 18- to 24-month WHO-recommended regimen for MDR-TB. Bedaquiline and delamanid are being used increasingly for treatment of MDR-TB under specific conditions.

DRUGS

Four major drugs are considered first-line agents for the treatment of TB: isoniazid, rifampin, pyrazinamide, and ethambutol. **Table 173-2** presents currently recommended dosages in adults and children. Some studies have suggested increased effectiveness when isoniazid, rifampin, and pyrazinamide are given at higher dosage; thus dosages may be revised in the future. These drugs are well absorbed after oral administration, with peak serum levels at 2–4 h and nearly complete elimination within 24 h. Except for ethambutol, these agents are recommended on the basis of their bactericidal activity (i.e., their ability to rapidly reduce the number of viable organisms and render patients noninfectious); in addition, all four agents are recommended in light of their sterilizing activity (i.e., their ability to kill all bacilli and thus sterilize the affected tissues, measured in terms of the ability to prevent relapses) and their low rate of induction of drug resistance by selection of mutant bacilli. Two additional rifamycins, rifapentine and rifabutin, are also available; however, the level of cross-resistance with rifampin is high. For a detailed discussion of the drugs used for the treatment of TB, see **Chap. 176**.

TABLE 173-2 Recommended Dosage[a] for Initial Treatment of Tuberculosis in Adults and Children

DRUG	DAILY DOSE	
	ADULT	PEDIATRIC
Isoniazid	5 mg/kg, max 300 mg	10 (7–15) mg/kg, max 300 mg
Rifampin	10 mg/kg, max 600 mg	15 (10–20) mg/kg, max 600 mg
Pyrazinamide	25 mg/kg, max 2 g	35 (30–40) mg/kg
Ethambutol[b]	15 mg/kg	20 (15–25) mg/kg

[a]The duration of treatment with individual drugs varies by regimen, as detailed in Table 173-3. [b]In certain settings, streptomycin (15 mg/kg daily, with a maximal dose of 1 g; or 25–30 mg/kg thrice weekly, with a maximal dose of 1.5 g) can replace ethambutol in the initial phase of treatment. However, streptomycin generally is no longer considered a first-line drug.

Source: Based on recommendations of the American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention and the World Health Organization.

Because of a lower degree of effectiveness and a higher degree of intolerability and toxicity, several classes of second-line drugs are generally used only for the treatment of patients with drug-resistant TB. These agents are classified at the moment into four groups designated by letters: (A) the fluoroquinolones; (B) the second-line injectable aminoglycosides kanamycin, amikacin, and streptomycin and the injectable polypeptide capreomycin; (C) other oral agents (ethionamide and prothionamide, cycloserine and terizidone, linezolid, and clofazimine); and (D) add-on agents. Group D encompasses three subgroups: D1 (the first-line drugs pyrazinamide, ethambutol, and high-dose isoniazid); D2 (the two new drugs bedaquiline and delamanid); and D3 (PAS, imipenem-cilastatin, meropenem, amoxicillin-clavulanate, and amithiozone [thiacetazone]). Streptomycin, formerly a first-line agent, is now rarely used for drug-resistant TB because resistance levels worldwide are high and it is more toxic than the other drugs in the same class; however, the level of cross-resistance with the other injectable agents is not complete. Of the quinolones, later-generation agents such as levofloxacin (high-dose) and moxifloxacin are recommended; gatifloxacin can be considered as a good alternative with proper selection of patients and careful monitoring of safety. Group D2 includes the novel drugs belonging to two new classes of antituberculosis agents: the diarylquinoline bedaquiline and the nitroimidazole delamanid. These two compounds, which have been shown in phase 2b clinical trials to increase chances of cure among people with MDR-TB, must be used in accordance with international recommendations. However, recent information from the phase 3 clinical trial of delamanid added to an optimized WHO background regimen suggests that treatment success is similar to that of the optimized background regimen with lower than previously observed cardiac toxicity. At the moment, the future role of delamanid in MDR-TB treatment remains to be elucidated. Group D3 agents, the efficacy of which in MDR-TB regimens is not clearly defined, are used in the treatment of patients with TB resistant to most first- and second-line agents. Today, amithiozone is used very rarely because it has been associated with severe and at times fatal skin reactions, including Stevens-Johnson syndrome, among HIV-infected patients.

REGIMENS

Standard regimens are divided into an intensive (bactericidal) phase and a continuation (sterilizing) phase. During the intensive phase, the majority of tubercle bacilli are killed, symptoms resolve, and usually the patient becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse.

The treatment regimen of choice for virtually all forms of drug-susceptible TB in adults consists of a 2-month initial (intensive) phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin **(Table 173-3)**. This regimen can cure TB in >90% of patients. In children, most forms of TB in the absence of HIV infection or suspected isoniazid resistance can be safely treated without ethambutol in the intensive phase. Treatment should be given daily throughout the course. Systematic reviews have demonstrated that the use of an intermittent thrice-weekly regimen in the intensive phase is associated with increased risk of treatment failure, relapse, and acquisition of drug resistance. Furthermore, a thrice-weekly regimen in the continuation phase only has also been associated with increased rates of failure and relapse, while a twice-weekly regimen in the continuation phase increased the risk of acquisition of drug resistance as well as rates of failure and relapse. Therefore, the WHO now recommends that TB treatment in all cases be administered daily. The 2016 guidelines by the ATS, the CDC, and the IDSA, while recommending daily administration of drugs, include a provision for use of intermittent thrice-weekly supervised regimens among patients who are not infected with HIV and are at low risk of relapse (i.e., have pulmonary TB caused by drug-susceptible organisms that, at the start of treatment, is noncavitary and/or sputum smear–negative). The same guidelines suggest that a 4-month regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol may be adequate

TABLE 173-3 Recommended Antituberculosis Treatment Regimens

	INITIAL PHASE		CONTINUATION PHASE	
INDICATION	DURATION, MONTHS	DRUGS	DURATION, MONTHS	DRUGS
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c]
New culture-negative cases	2	HRZE[a]	4	HR[a,d]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default[f]	← Tailored according to rapid drug susceptibility testing →			
Failures[f]	← Tailored according to rapid drug susceptibility testing →			
Resistance (or intolerance) to H	Throughout (6)	RZEQ		
Resistance (or intolerance) to R	← Same as for MDR-TB; see below →			
MDR-TB (resistance to at least H + R)	← See Fig. 173-12 and Table 173-4 →			
XDR-TB	← See Table 173-4 →			
Intolerance to Z	2	HRE	7	HR

[a]All drugs should be given daily. [b]Streptomycin was used in the past in place of ethambutol but is no longer considered a first-line drug. [c]A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase. However, this regimen is rarely used. [d]The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America suggest that a 2-month continuation phase could be used in HIV-seronegative patients with sputum smear–negative and culture-negative TB. [e]The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months. [f]The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment.

Abbreviations: E, ethambutol; H, isoniazid; MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.

for treatment of HIV-negative adults with sputum smear–negative and culture-negative pulmonary TB (i.e., paucibacillary TB).

A continuation phase of once-weekly rifapentine and isoniazid is effective in HIV-seronegative patients without cavitation on CXR. In general, however, this regimen should be used with great caution. Patients with cavitary pulmonary TB and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should be re-tested immediately for drug-resistant TB, and a change of regimen should be considered. A full course of therapy should not include interruptions of >4 weeks. In some developing countries where the ability to ensure adherence to treatment is limited, a continuation-phase regimen of daily isoniazid and ethambutol for 6 months has been used in the past. This regimen is clearly associated with a higher rate of relapse, treatment failure, and death, especially among HIV-infected patients, and is no longer recommended by the WHO. Several studies attempting to reduce treatment duration to 4 months by using fluoroquinolones (with moxifloxacin replacing ethambutol or isoniazid, or gatifloxacin replacing ethambutol) were conducted over the last decade. The main finding was that shorter (4-month) fluoroquinolone-containing regimens are associated with significantly higher rates of relapse at 18 months than the standard 6-month rifampin-containing regimen. In addition, the studies showed no reduction in adverse events with the fluoroquinolone-containing regimen and no difference in all-cause and TB-related mortality rates. Therefore, shortening of the treatment duration to 4 months through the use of fluoroquinolones is not recommended. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 173-3. However, severe side effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon. To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B_6 deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy).

PATIENT CARE AND SUPPORT

Poor adherence to treatment is one of the most important impediments to cure. Moreover, the tubercle bacilli harbored by patients who do not fully adhere to the prescribed regimen are likely to become resistant to the drugs to which they are irregularly exposed. Both patient- and provider-related factors may affect adherence. Patient-related factors include a lack of belief that the illness is worth the cost of adherence; the existence of concomitant medical conditions (notably alcohol or substance abuse); lack of social support; fear of the stigma and discrimination associated with TB; and poverty, with attendant joblessness and homelessness. Provider-related factors that may prevent adherence include lack of support, education, and encouragement of patients and inconvenient clinical services.

A variety of interventions to increase the chances of completion of the months-long treatment course are available. First, a package of social support interventions that are complementary and not mutually exclusive, consisting of educational, psychological, and material goods and services, may enable people with TB to address hurdles to treatment adherence. Health education and counseling on the disease's seriousness and solutions and on the importance of treatment adherence until cure should be provided to all patients at the start of and throughout the course of TB therapy. Psychological support (i.e., counseling sessions or peer-group support) can be particularly relevant in the context of the stigma and discrimination often affecting people with TB and their families. Material support (e.g., food or financial support in forms such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowances, housing incentives, or financial bonuses) reduces indirect costs incurred by patients or their attendants in accessing health services and mitigates the consequences of income loss related to the disease.

Second, it is paramount that health services be arranged to meet the needs and reasonable expectations of patients. Components of optimal health services include a suitable geographic location, a schedule responsive to patients' needs, functional channels of communication between patients and their health care providers (e.g., a telephone short-messaging system, audio/video call capability, home or workplace visits), and a staff willing and competent to care for people with TB, to address their concerns, and to base the care they provide on sound ethical standards.

Third, it is crucial to offer the patient a suitable option for treatment administration that minimizes the chance of non-adherence. Such options traditionally include unsupervised, self-administered therapy; in-person directly observed therapy (DOT); and non-daily DOT (e.g., supervision not for every dose but weekly or a few times per week) at a location mutually agreed on by patient and health care provider, with supervisory responsibility delegated to a qualified person. Direct supervision of adherence is crucial in view of the lack of tools to accurately predict adherence to self-administered treatment and of the public health importance of TB. The WHO, along with the ATS, the CDC, and the IDSA, states that ideally all patients should have their therapy directly supervised, especially during the initial phase, with proper social support

based on a patient-centered approach as described above. In several countries, personnel to supervise therapy are usually available through TB control programs of local public health departments, often involving members of the community who are accepted by the patient and who have been properly trained and educated by health workers to undertake the supervisory role. Direct supervision with social support has been shown to significantly increase the proportion of patients completing treatment in all settings and to lessen the chances of treatment failure, relapse, and default. In general, community- or home-based DOT is recommended over health facility–based DOT or unsupervised treatment; DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members. Recently, comparison of video-observed therapy with in-person DOT has shown similar outcomes. Video-observed therapy can replace DOT when internet access is good and video communication technology (e.g., smartphones, tablets, computers) is available. The system can be appropriately organized and operated by health care providers and patients. Other digital health tools can facilitate the monitoring of adherence, including digital medication monitors; these monitors can register when the pill box is opened, with options to emit audio signals or a short message to remind patients to take medicines. These tools are customized to the needs and preferences of the individual patient and the provider.

In addition to the above measures promoting adherence, provision of fixed-dose combination products that reduce the number of tablets the patient needs to swallow is recommended over separate drug formulations. Various fixed-dose combination products are available (e.g., isoniazid/rifampin, isoniazid/rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ethambutol). Fixed-dose combinations increase patient satisfaction and minimize the likelihood of prescription error or of development of drug resistance resulting from monotherapy if a drug is out of stock or the patient prefers one drug over others. In addition, these combinations facilitate programmatic management of procurement and supply. In the past, the bioavailability of rifampin was found to be substandard in some formulations of fixed-dose combinations. Medical regulatory authorities should ensure that combination products are of good quality; however, top standards for drug quality assurance are not always operative, especially in limited-resource countries. Prescribers should be aware of this potential problem.

MONITORING TREATMENT RESPONSE AND DRUG TOXICITY

Bacteriologic evaluation through commercial liquid-culture systems (or—when liquid-culture capacity is not yet available—through smear microscopy) is essential in monitoring the response to TB treatment. In addition, the patient's weight should be monitored regularly and the drug dosage adjusted with any significant weight change. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative to allow early detection of treatment failure. With the recommended 6-month standard first-line regimen, >80% of drug-susceptible TB patients will have negative sputum cultures at the end of the second month of treatment. By the end of the third month, the sputum of virtually all patients should be culture negative. In some patients, especially those with extensive cavitary disease and large numbers of organisms, AFB smear conversion may lag behind culture conversion as a result of the expectoration and microscopic visualization of dead bacilli. Therefore, as capacity is built, smear microscopy should be progressively abandoned as a monitoring tool in favor of liquid culture. As noted above, patients with cavitary disease in whom sputum culture conversion does not occur by 2 months require immediate testing or re-testing for drug resistance. When a patient's sputum cultures or smears remain positive at ≥3 months despite good adherence, treatment failure caused by drug resistance is likely. The pattern of drug resistance should guide the choice of the best treatment option (see below). A sputum specimen should be collected at the end of treatment to document cure. In settings where mycobacterial cultures are not yet available, monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Bacteriologic monitoring of patients with extrapulmonary TB is more difficult and often is not feasible. In these cases, the response to treatment must be assessed clinically with the help of medical imaging.

Monitoring of the response to chemotherapy by nucleic acid amplification technology, such as the Xpert MTB/RIF assay, is not suitable because these tests can produce positive results due to nonviable bacilli. Likewise, serial chest radiographs are not recommended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor CXR is recommended for routine follow-up purposes. However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes should the patient develop symptoms of recurrent TB months or years later. Patients should be instructed to report promptly for medical assessment if they develop any such symptoms.

During treatment, patients should also be monitored for drug toxicity. The most common adverse reaction of significance among people treated for drug-susceptible TB is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite, nausea) and should be instructed to discontinue treatment promptly and see their health care provider if these manifestations occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and bilirubin). Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases (up to three times the upper limit of normal) in serum levels of aspartate aminotransferase that are not accompanied by symptoms and are of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal. Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regimens available, it usually is not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy. Treatment with second-line agents for drug-resistant TB is associated with a variety of adverse drug reactions that are more frequent and severe than in patients receiving first-line TB regimens (see below). The likelihood of drug–drug interactions is also higher when second-line regimens are used.

TREATMENT FAILURE AND RELAPSE

As stated above, treatment failure should be suspected when a patient's cultures (or sputum smears, when cultures are not available) remain positive after 3 months of treatment. In the management of such patients, it is imperative that the current isolate be urgently re-tested (or tested for the first time if, for some reason, rapid molecular susceptibility testing was not performed at the start of treatment) for susceptibility to first-line agents and, if resistance to rifampin is detected, to second-line agents as well. The treatment approach should start with molecular testing for—at the least—resistance to rifampin and isoniazid. Since results are expected to become available within a few days, changes in the regimen can be

postponed until that time. However, if the patient's clinical condition is deteriorating rapidly, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is always to add more than one drug, preferably two or three, at a time to a failing regimen; in practice, starting an empirical regimen for MDR-TB (see "Drug-Resistant TB," below) is warranted. The patient may continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility tests.

Patients who experience a recurrence after apparently successful treatment (i.e., a relapse) are less likely to harbor drug-resistant strains than are patients in whom treatment has failed. Acquired resistance is uncommon among strains from patients in whom relapse follows the proper completion of a standard 6-month regimen. The treatment decision depends on a general assessment of the risk of drug resistance, the severity of the case, and the results of rapid susceptibility testing. Patients whose treatment has been interrupted and who have a high likelihood of MDR-TB should receive an empirical MDR-TB regimen that includes second-line agents (Table 173-3). Once drug susceptibility results are available, the regimen can be adjusted accordingly.

DRUG-RESISTANT TB

Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome that occur at low but predictable rates (10^{-7}–10^{-10} for the key drugs). Resistance to rifampin is associated with mutations in the *rpo*B gene in 95% of cases; that to isoniazid with mutations mainly in the *kat*G gene (50–95% of cases) and the *inh*A gene promotor region (up to 45%); that to pyrazinamide in the *pnc*A gene (up to 98%); that to ethambutol in the *emb*B gene (50–65%); that to the fluoroquinolones in the *gyr*A–*gyr*B genes (75–95%); and that to the aminoglycosides mainly in the *rrs* gene (up to 80%), with the C-12T mutation as the most common mutation in the *eis* promoter region associated with aminoglycoside resistance, especially in Eastern European countries. Because there is no cross-resistance among the commonly used classes of drugs, the probability that a strain will be resistant to two drug classes is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant TB almost invariably follows monotherapy—i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible; of the patient to absorb or take properly prescribed therapy; or of poor-quality drugs to be adequately bioavailable. Drug-resistant TB may be either primary or acquired. In primary drug resistance, the patient is infected from the start by a drug-resistant strain. Acquired resistance develops in the infecting strain during treatment. In North America, Western Europe, most of Latin America, and the Persian Gulf States, rates of primary resistance are generally low and isoniazid resistance is most common. In the United States, although rates of primary isoniazid resistance have been stable at ~7–8%, the rate of primary MDR-TB has declined from 2.5% in 1993 to <1% since 2000. As described above, MDR-TB is an increasingly serious problem in some regions, especially in the countries of the former Soviet Union and some countries of Asia **(Fig. 173-11)**. Even more serious is the occurrence of XDR-TB due to MDR strains that are also resistant to any fluoroquinolones and to any of three second-line injectable agents (amikacin, kanamycin, and capreomycin). Creation of drug-resistant TB can be prevented by adherence to the principles of sound treatment: inclusion of at least two quality-assured, bactericidal drugs to which the organism is susceptible; use of fixed-dose combination products; supervision of treatment with patient support; and verification that patients complete the prescribed course. Transmission of drug-resistant strains can be prevented by implementation of respiratory infection-control measures (see below) and by early detection of people with active TB followed by immediate initiation of treatment with an effective regimen.

For the treatment of patients with isoniazid-resistant disease, it is recommended to use a combination of rifampin, ethambutol,

FIGURE 173-11 Percentage of new cases of multidrug-resistant/rifampin-resistant TB in all countries surveyed by the World Health Organization (WHO) Global Drug Resistance Surveillance Project during 1994–2016. Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2002 are not shown. *(See disclaimer in Fig. 173-2. Courtesy of the Global TB Programme, WHO; with permission.)*

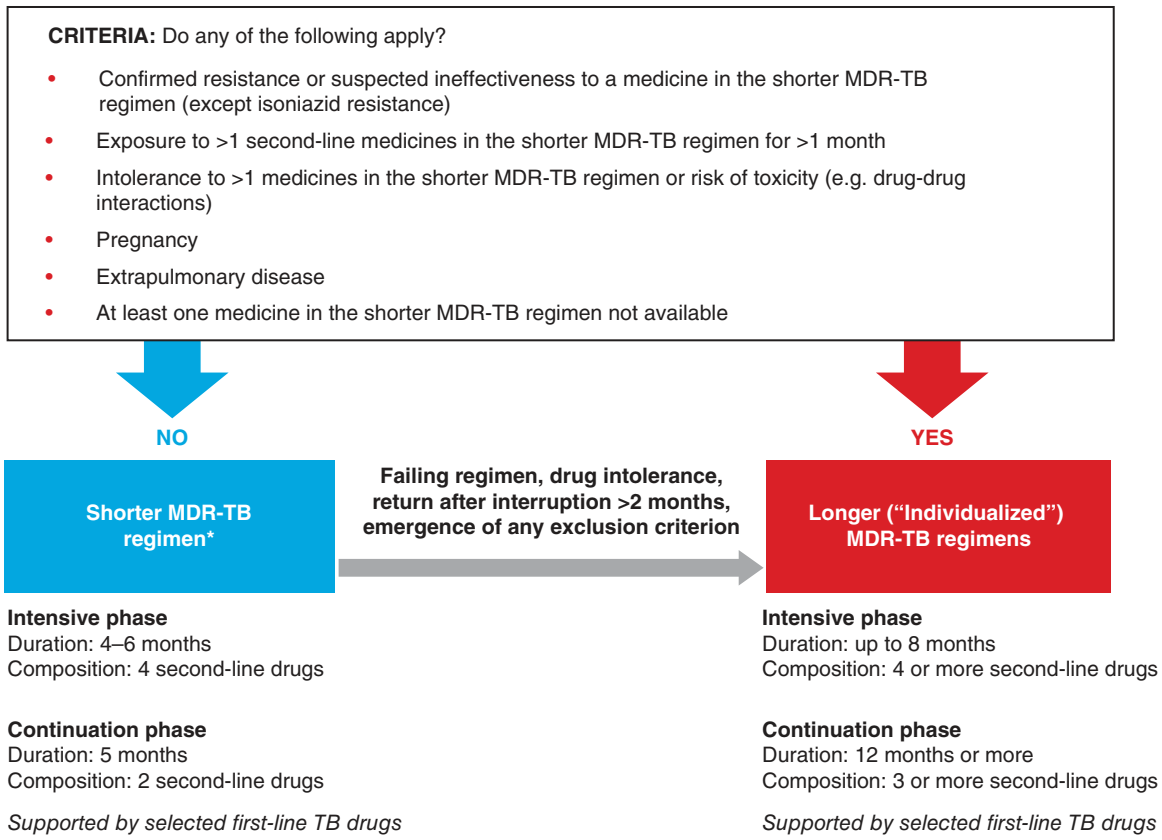

FIGURE 173-12 Choosing the treatment regimen for patients with confirmed rifampin-resistant/multidrug-resistant (RR/MDR) tuberculosis. *The intensive shorter regimen consists of 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol. The shorter continuation regimen consists of 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol. *(Source: World Health Organization.)*

pyrazinamide, and levofloxacin for 6 months. This fluoroquinolone-containing regimen should not be used until rifampin resistance has been excluded by a reliable diagnostic test to avoid inadvertent treatment of MDR-TB with an inadequate regimen. Ideally, a laboratory test for susceptibility should also be done for the fluoroquinolone and pyrazinamide. If the fluoroquinolone is contraindicated because of intolerance or resistance, the patient can be given a 6-month regimen of rifampin, ethambutol, and pyrazinamide. Isoniazid probably does not contribute to a successful outcome in these regimens but may be retained (also to facilitate treatment with the four-drug fixed-dose formulation). Injectable agents, such as streptomycin and kanamycin, are unlikely to play a role in the treatment of most isoniazid-resistant TB cases. MDR-TB, in which bacilli are resistant to (at least) isoniazid and rifampin, is more difficult to manage than is disease caused by drug-susceptible organisms because these two bactericidal drugs are the most potent agents available and because associated resistance to other first-line drugs as well (e.g., ethambutol) is not uncommon. Therapy for MDR-TB is therefore more complex: it is based on limited evidence, is lengthy and potentially toxic, uses drugs of limited efficacy, and is much more expensive than treatment of drug-susceptible disease. For treatment of MDR-TB (and all other rifampin-resistant TB cases in which isoniazid resistance is absent or unknown), two approaches are currently recommended by the WHO: a shorter standardized regimen of 9–12 months' duration and a longer regimen of 18–24 months' duration consisting of an optimal combination of drugs according to a standard design **(Fig. 173-12)**. In patients who have not been treated previously with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, the WHO recommends the use of a shorter MDR-TB regimen comprising seven drugs and given for 9–12 months. The regimen consists of 4–6 months of kanamycin, moxifloxacin, clofazimine, prothionamide, pyrazinamide, high-dose isoniazid (10 mg/kg and up to 15 mg/kg), and ethambutol followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol. This regimen has been tested in observational studies in a number of countries under operational and programmatic conditions and has been successful in a high percentage of cases, with low toxicity; results of an ongoing randomized, controlled clinical trial are expected by the end of 2018. This regimen is the first choice in the majority of MDR-TB cases worldwide, but it should be used only when the criteria shown in Fig. 173-12 are met. As with any anti-TB regimen, the risk of creating additional resistance is high if the regimen is used inappropriately.

In all other patients with MDR-TB or RR-TB, and especially in those presenting with—or presumed to have an infection with—a more complex pattern of resistance (e.g., resistance to the fluoroquinolones, the injectable drugs, or both [XDR-TB]), a regimen with at least five effective TB drugs during the intensive phase is recommended; this regimen should include pyrazinamide and four second-line TB agents—one from group A, one from group B, and at least two from group C (see "Drugs," above, and **Table 173-4**). If the minimal number of these effective TB drugs cannot be incorporated, an agent from subgroup D2 (see below) and other agents from subgroup D3 may be added to bring the total number of drugs to five. The regimen may be further strengthened with high-dose isoniazid and/or ethambutol; Table 173-4 summarizes the steps in designing such a regimen. Although the optimal duration of treatment is not known, a course of at least 20 months is recommended for previously untreated patients, including the initial phase of 5 months with an injectable agent, which is usually discontinued 4 months after culture conversion. In late 2012, the FDA granted accelerated approval of bedaquiline, a diarylquinoline antibiotic included in group D2 (Table 173-4). This drug, when given in addition to an optimized MDR-TB regimen for the first 24 weeks (400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks), accelerated sputum conversion in phase 2B clinical trials. Bedaquiline should be used with caution for people aged >65 years and for HIV-infected

TABLE 173-4 General Steps in Designing a Longer Regimen for the Treatment of Multidrug-Resistant Tuberculosis (MDR-TB)[a]

STEP	DRUG GROUP	OPTIONS
1. Add one later-generation fluoroquinolone.	A[b]	Levofloxacin Moxifloxacin Gatifloxacin
2. Add one second-line injectable agent.	B	Amikacin Capreomycin Kanamycin (Streptomycin[c])
3. Add two or more second-line agents.	C[b]	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
4. Add pyrazinamide and any other first-line agent if they can help strengthen the regimen.	D1	Pyrazinamide Ethambutol High-dose isoniazid
5. Add bedaquiline or delamanid.[d]	D2	Bedaquiline Delamanid
6. Add any of these agents if the regimen cannot be composed otherwise.	D3	*p*-Aminosalicylic acid Imipenem-cilastatin[e] Meropenem[e] Amoxicillin-clavulanate[e] (Thioacetazone[f])

[a]This stepwise approach guides the design of individualized longer regimens for patients who are not eligible for the WHO-recommended shorter regimen. (The composition of the shorter MDR-TB regimen is standardized; see text). The aim is to combine at least five effective agents in the intensive phase; more agents may be included if they can safely increase the chances of cure. The choice of an agent is based on the likelihood of its effectiveness, on reliable information about drug resistance, and on the balance of expected benefits to risk. For instance, in case of nephrotoxicity or hearing loss, an injectable agent may be omitted and additional agents from group C or D2 included. [b]Drugs in groups A and C are shown in decreasing order of usual preference (subject to other considerations). [c]Streptomycin may be substituted for other injectable agents when the other three cannot be used. Resistance to streptomycin alone does not fulfill the definition of extensively drug-resistant TB. [d]Bedaquiline or delamanid may be added to the longer regimen to replace another second-line agent or to strengthen it in accordance with interim policies. [e]Carbapenems and clavulanate are used together. Clavulanate is available only in formulations combined with amoxicillin. [f]HIV status must be tested and confirmed to be negative before thioacetazone treatment is started.

Source: Adapted from D Falzon et al: World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update. Eur Respir J 49:1602308, 2017.

patients; its use is not advised for children and pregnant women. In early 2014, the European Medical Agency granted accelerated approval of another new agent, the nitroimidazole compound delamanid, which is also included in group D2. Data from a phase 2B clinical trial in which delamanid was added to the WHO-recommended longer MDR-TB regimen showed increased rates of culture conversion at 2 months. In 2016, the WHO expanded its recommendation for the use of delamanid to children aged 6–17 years who are not eligible for the shorter regimen. However, recent information from the phase 3 clinical trial of delamanid added to an optimized WHO background regimen shows that, although sputum conversion occurred 1–2 weeks earlier and cardiac toxicity was lower than predicted, treatment success was similar to that of the optimized background regimen. At the moment, therefore, the future role of delamanid in MDR-TB treatment remains to be elucidated. Pending phase 3 trial results and in view of the risk of adverse reactions (including QT interval prolongation), the WHO currently recommends the use of bedaquiline in cases of MDR-TB in which an effective WHO-recommended longer MDR-TB regimen cannot be designed because of known resistance, intolerability, or unavailability of groups A, B, and C second-line drugs. Informed consent should be sought from patients treated with bedaquiline or delamanid, and their treatment should be closely monitored. In particular, the QT interval should be monitored at the start of and during treatment; patients with a QTc interval >500 ms or a history of ventricular arrhythmias should not be given these drugs. Current information about simultaneous use of these two agents is insufficient to make a recommendation; it is therefore prudent to avoid the combination outside of clinical trials.

Patients with XDR-TB have fewer treatment options and a much poorer prognosis. As part of a patient-centered approach, palliative and end-of-life care should be provided to these patients as a priority when all treatment options have been exhausted; respiratory infection-control measures should be observed throughout. The design of XDR-TB regimens follows the same principles outlined in Table 173-4. The use of a novel regimen composed of the nitroimidazole compound pretomanid, bedaquiline, and linezolid recently resulted in a high cure rate among patients with XDR-TB in South Africa. In the future, this promising regimen may become an important therapeutic option. Observational studies have shown that aggressive management of XDR-TB cases, with early DST, rational combination of at least five effective drugs, strict DOT, monthly bacteriologic monitoring, and intensive patient support, may increase the chances of cure and avert death. For patients with localized disease and sufficient pulmonary reserve, lobectomy or wedge resection may be considered as part of treatment. Because the management of patients with MDR- and XDR-TB is complicated by both social and medical factors, care of seriously ill patients is ideally provided in specialized centers or, in their absence, in the context of programs with adequate resources and capacity, including community support. When possible, treatment and care on an ambulatory basis at a decentralized health care facility should be prioritized, as this approach may increase treatment success and reduce loss to follow-up. This approach should not, however, preclude hospitalization when it is necessary.

HIV-ASSOCIATED TB

Several observational studies and randomized controlled trials have shown that treatment of HIV-associated TB with anti-TB drugs and simultaneous use of ART are associated with significant reductions in mortality risk and AIDS-related events. Evidence from randomized controlled trials shows that early initiation of ART during anti-TB treatment is associated with a 34–68% reduction in mortality rates, with especially good results in patients with CD4+ T cell counts of <50/μL. Therefore, the main aim in the management of HIV-associated TB is to initiate anti-TB treatment and to immediately consider initiating or continuing ART. All HIV-infected TB patients, regardless of CD4+ T cell count, are candidates for ART, which optimally is initiated as soon as possible after the diagnosis of TB and within the first 8 weeks of anti-TB therapy; ART should be started within the first 2 weeks of TB treatment for profoundly immunosuppressed patients with CD4+ T cell counts of <50/μL. In general, the standard 6-month daily regimen is equally efficacious in HIV-negative and HIV-positive patients with drug-susceptible TB. However, in the uncommon situation where an HIV-infected patient cannot receive ART, prolongation of the continuation phase of TB treatment by 3 months can be considered. As in any other TB patient, intermittent regimens should not be used in HIV-infected people. As for any other adult living with HIV **(Chap. 197)**, first-line ART for TB patients consists of two nucleoside reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor or an integrase inhibitor. Although TB treatment modalities are similar to those in HIV-negative patients, adverse drug reactions may be more pronounced in HIV-infected patients. In this regard, three important considerations are relevant: an increased frequency of paradoxical reactions, interactions between ART components and rifamycins, and development of rifampin monoresistance with intermittent treatment. IRIS—i.e., the exacerbation of symptoms and signs of TB—has been described above. Rifampin, a potent inducer of enzymes of the cytochrome P450 system, lowers serum levels of many HIV protease inhibitors and some nonnucleoside reverse transcriptase inhibitors—essential drugs used in ART. In such cases, rifabutin, which has much less enzyme-inducing activity,

has been used in place of rifampin. However, dosage adjustments for rifabutin and protease inhibitors are still being assessed. Several clinical trials have found that patients with HIV-associated TB whose degree of immunosuppression is advanced (e.g., CD4+ T cell counts of <100/μL) are prone to treatment failure and relapse with rifampin-resistant organisms when treated with "highly intermittent" (i.e., once- or twice-weekly) rifamycin-containing regimens. Consequently, it is now recommended that all TB patients who are infected with HIV, like all other TB patients with rifampin-susceptible disease, receive a rifampin-containing regimen on a daily basis. Because recommendations are frequently updated, consultation of the following websites is advised: *www.who.int/hiv*, *www.who.int/tb*, *www.cdc.gov/hiv*, and *www.cdc.gov/tb*.

SPECIAL CLINICAL SITUATIONS

Although comparative clinical trials of treatment for extrapulmonary TB are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended for patients with pulmonary disease. For TB meningitis, the ATS, the CDC, and the IDSA recommend extension of the continuation phase for 7–10 months. The WHO and the American Academy of Pediatrics recommend that children with bone and joint TB, tuberculous meningitis, or miliary TB receive up to 12 months of treatment. Treatment for TB may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should not receive aminoglycosides and should receive ethambutol only if serum drug levels can be monitored. Isoniazid, rifampin, and pyrazinamide may be given in the usual doses in cases of mild to moderate renal failure, but the dosages of isoniazid and pyrazinamide should be reduced for all patients with severe renal failure except those undergoing hemodialysis. Patients with hepatic disease pose a special problem because of the hepatotoxicity of isoniazid, rifampin, and pyrazinamide. Patients with severe hepatic disease may be treated with ethambutol, streptomycin, and possibly another drug (e.g., a fluoroquinolone); if required, isoniazid and rifampin may be administered under close supervision. The use of pyrazinamide by patients with liver failure should be avoided. Silicotuberculosis necessitates the extension of therapy by at least 2 months.

The regimen of choice for pregnant women (Table 173-3) is 9 months of treatment with isoniazid and rifampin supplemented by ethambutol for the first 2 months. Although the WHO has recommended routine use of pyrazinamide for pregnant women in combination with isoniazid and rifampin, this drug has not been recommended for pregnant women in the United States because of insufficient data documenting its safety in pregnancy. Streptomycin is contraindicated because it is known to cause eighth-cranial-nerve damage in the fetus. The thioamides, bedaquiline, and delamanid should also be avoided in the treatment of pregnant women with MDR-TB. Treatment for TB is not a contraindication to breast-feeding; most of the drugs administered will be present in small quantities in breast milk, albeit at concentrations far too low to provide any therapeutic or prophylactic benefit to the child.

Medical consultation on difficult-to-manage cases is provided by the U.S. CDC Regional Training and Medical Consultation Centers (*www.cdc.gov/tb/education/rtmc/*).

PREVENTION

The primary way to prevent TB is to diagnose and isolate infectious cases rapidly and to administer appropriate treatment until patients are rendered noninfectious (usually 2–4 weeks after the start of proper treatment) and the disease is cured. Additional strategies include BCG vaccination and treatment of persons with LTBI who are at high risk of developing active disease.

BCG VACCINATION

BCG was derived from an attenuated strain of *M. bovis* and was first administered to humans in 1921. Many BCG vaccines are available worldwide; all are derived from the original strain, but the vaccines vary in efficacy, ranging from 80% to nil in randomized, placebo-controlled trials. A similar range of efficacy was found in observational studies (case–control, historic cohort, and cross-sectional) in areas where infants are vaccinated at birth. These studies and a meta-analysis also found higher rates of efficacy in the protection of infants and young children from serious disseminated forms of childhood TB, such as tuberculous meningitis and miliary TB. BCG vaccine is safe and rarely causes serious complications. The local tissue response begins 2–3 weeks after vaccination, with scar formation and healing within 3 months. Side effects—most commonly, ulceration at the vaccination site and regional lymphadenitis—occur in 1–10% of vaccinated persons. Some vaccine strains have caused osteomyelitis in ~1 case per million doses administered. Disseminated BCG infection ("BCGitis") and death have occurred in 1–10 cases per 10 million doses administered, although this problem is restricted almost exclusively to persons with impaired immunity, such as children with severe combined immunodeficiency syndrome or adults with HIV infection. BCG vaccination induces TST reactivity, which tends to wane with time. The presence or size of TST reactions after vaccination does not predict the degree of protection afforded.

BCG vaccine is recommended for routine use at birth in countries or among populations with high TB prevalence. However, because of the low risk of transmission of TB in the United States and other high-income countries, the variability in protection afforded by BCG, and its impact on the TST, the vaccine is not recommended for general use. HIV-infected adults and children should not receive BCG vaccine. Moreover, infants whose HIV status is unknown but who have signs and symptoms consistent with HIV infection or who are born to HIV-infected mothers should not receive BCG.

Over the past decade, renewed research and development efforts have been made toward a new TB vaccine, and several candidates have been developed and tested. The MVA-85A vaccine (a modified poxvirus-vectored vaccine that expresses the immune-dominant *M. tuberculosis* antigen 85A), developed at the University of Oxford, was the first new TB vaccine to be tested in a phase 2B proof-of-concept trial in infants in South Africa. The aim was to evaluate the efficacy of a new preventive TB vaccine candidate against clinical TB or *M. tuberculosis* infection. Results were published in early 2013: MVA-85A was well tolerated and modestly immunogenic but did not confer significant protection against clinical TB or *M. tuberculosis* infection.

As of late 2017, 12 candidate vaccines were in various stages of clinical trials. They included whole-cell or mycobacterial whole-cell or lysates, viral vector vaccines, and adjuvant recombinant protein vaccines. Several challenges must be faced in the development of a TB vaccine. For instance, the lack of predictive animal models and protection correlates renders trials long and expensive. Furthermore, the decision about whether a candidate vaccine should be developed for prevention of infection (pre-exposure) or prevention of reactivation (post-exposure) without an exact understanding of its precise mechanism of action is complex. Therefore, introduction of a new vaccine on a large scale is not likely in the near future. This step will require an intensified and much larger investment in research and development.

TREATMENT

Latent Tuberculosis Infection

It is estimated that 1.7 billion people—more than one-quarter of the human population—have been infected with *M. tuberculosis*. Although only a small fraction of these infections will progress toward active disease in a lifetime, new active cases will continue to emerge from this pool of "latently" infected individuals. Unfortunately, at present, there is no gold-standard diagnostic test that can confirm true infection (as opposed to immunologic memory of previous exposure) or predict which individuals with LTBI will develop active TB. Therefore, latently infected individuals among persons in defined high-risk groups can only be presumably identified by

TST or IGRA. For skin testing, five tuberculin units of polysorbate-stabilized PPD should be injected intradermally into the volar surface of the forearm (i.e., the Mantoux method). Multipuncture tests are not recommended. Reactions are read at 48–72 h as the transverse diameter (in millimeters) of induration; the diameter of erythema is not considered. In some persons, TST reactivity wanes with time but can be recalled by a second skin test administered ≥1 week after the first (i.e., two-step testing). For persons periodically undergoing the TST, such as health care workers and individuals admitted to long-term-care institutions, initial two-step testing may preclude subsequent misclassification of those who have boosted reactions as TST converters. The cutoff for a positive TST (and thus for treatment) is related both to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop TB. Table 173-5 suggests possible conventional cutoff by risk group. Thus, positive reactions for persons with HIV infection, recent close contacts of infectious cases, organ transplant recipients, previously untreated persons whose chest radiograph shows fibrotic lesions consistent with old TB, and persons receiving drugs that suppress the immune system are defined as an area of induration ≥5 mm in diameter A 10-mm cutoff is used to define positive reactions in most other at-risk persons. For persons with a very low risk of developing TB if infected, a cutoff of 15 mm is used. (Except for employment purposes where longitudinal screening is anticipated, the TST is not indicated for these low-risk persons.) A positive IGRA is based on the manufacturer's recommendations; however, good clinical practice requires that epidemiologic and clinical factors also guide the decision to implement treatment for LTBI and that active TB be definitively excluded before the initiation of chemoprophylaxis. The WHO recommends systematic testing for and treatment of LTBI for the following high-risk groups: people living with HIV, adult and child contacts of patients with infectious pulmonary TB, patients preparing for organ or hematologic transplantation, patients with silicosis, patients starting anti-TNF treatment, and patients on dialysis. Systematic testing for and treatment of LTBI should also be considered for prisoners, health care workers, immigrants from countries with a high TB burden, homeless persons, and illicit drug users.

Some TST- and IGRA-negative individuals are also candidates for treatment. Once an appropriate clinical evaluation has excluded active TB, infants and children who have come into contact with infectious cases should be treated for presumed LTBI. HIV-infected persons who have been exposed to an infectious TB patient should receive treatment regardless of the TST result. Any HIV-infected candidate for LTBI treatment must be screened carefully to exclude active TB, which would necessitate full treatment. The use of a clinical algorithm based on four signs/symptoms (current cough, fever, weight loss, and night sweats) helps to define which HIV-infected person is a candidate for LTBI treatment. The absence of all four symptoms tends to exclude active TB. The presence of one of these four manifestations, on the other hand, warrants further investigation for active TB before treatment of LTBI is started. Although a TST is prudent, this test is not an absolute requirement—given the logistical challenges—among people living with HIV in high-TB-incidence and low-resource settings.

Among people living with HIV and receiving ART, conversion of the TST from negative to positive can occur during the first few months of treatment. Conversions (from negative to positive) and reversions (from positive to negative) are more common with IGRAs than with TSTs among serially tested health care workers in the United States.

Treatment of selected persons with LTBI aims at preventing active disease. Potential candidates for treatment of LTBI are listed in Table 173-5. This intervention (*preventive chemotherapy* or *chemoprophylaxis*) is based on the results of a large number of randomized, placebo-controlled clinical trials demonstrating that a 6- to 9-month course of isoniazid reduces the risk of active TB in infected people by up to 90%. Analysis of available data indicated that the optimal duration of treatment with this drug was ~9 months. In the absence of reinfection, the protective effect is believed to be lifelong. Clinical trials have shown that isoniazid reduces rates of TB among TST-positive persons with HIV infection. Studies in HIV-infected patients have also demonstrated the effectiveness of shorter courses of rifampin-based treatment. Several regimens (Table 173-6) can be used to treat LTBI.

TABLE 173-5 Tuberculin Reaction Size and Treatment of Latent *Mycobacterium tuberculosis* Infection

RISK GROUP	TUBERCULIN REACTION SIZE, mm
HIV-infected persons	≥5
Recent contacts of a patient with TB	≥5[a]
Organ transplant recipients	≥5
Persons with fibrotic lesions consistent with old TB on chest radiography	≥5
Persons who are immunosuppressed—e.g., due to the use of glucocorticoids or tumor necrosis factor α inhibitors	≥5
Persons with high-risk medical conditions[b]	≥5
Recent immigrants (≤5 years) from high-prevalence countries	≥10
Injection drug users	≥10
Mycobacteriology laboratory personnel; residents and employees of high-risk congregate settings[c]	≥10
Children <5 years of age; children and adolescents exposed to adults in high-risk categories	≥10
Low-risk persons[d]	≥15

[a]Tuberculin-negative contacts, especially children, should receive prophylaxis for 2–3 months after contact ends and should then undergo repeat tuberculin skin testing (TST). Those whose results remain negative should discontinue prophylaxis. HIV-infected contacts should receive a full course of treatment regardless of TST results. [b]These conditions include silicosis and end-stage renal disease managed by hemodialysis. [c]These settings include correctional facilities, nursing homes, homeless shelters, and hospitals and other health care facilities. [d]Except for employment purposes where longitudinal TST screening is anticipated, TST is not indicated for these low-risk persons. A decision to treat should be based on individual risk/benefit considerations.

Source: Adapted from Centers for Disease Control and Prevention: TB elimination—treatment options for latent tuberculosis infection (2011). Available at *http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.pdf*.

TABLE 173-6 Recommended Regimens and Drug Dosages for Treatment of Latent *Mycobacterium tuberculosis* Infection[a]

REGIMEN	DOSE	ADVERSE EVENTS
Isoniazid alone for 6 or 9 months	Adults: 5 mg/kg (max, 300 mg) per day Children: 10 mg/kg per day	Drug-induced liver injury, nausea, vomiting, abdominal pain, skin rash, peripheral neuropathy, dizziness, drowsiness, seizure
Rifampin alone for 3–4 months	Adults: 10 mg/kg per day Children: 10 mg/kg (max: <45 kg, 450 mg; >45 kg, 600 mg) per day	Flu-like syndrome, skin rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Isoniazid plus rifampin for 3–4 months	As above	As above
Rifapentine plus isoniazid for 3 months	Adults and children: Isoniazid: 15 mg/kg (900 mg) weekly Rifapentine: 15–30 mg/kg (900 mg) weekly	Hypersensitivity reactions, petechial skin rash, drug-induced liver injury Anorexia, nausea, abdominal pain Hypotensive reactions

[a]See text for full description of evidence on and limitations of these regimens.

Source: World Health Organization.

The most widely used is that based on isoniazid alone at a daily dose of 5 mg/kg (up to 300 mg/d) for 9 months. On the basis of cost–benefit analyses and concerns about feasibility, a 6-month period of treatment is currently recommended by the WHO. Isoniazid can be administered intermittently (twice weekly) at a dose of 15 mg/kg (up to 900 mg) but only as DOT. An alternative regimen for adults is 3–4 months of daily rifampin. A 3- to 4-month regimen of daily isoniazid and rifampin is used in some countries (e.g., the United Kingdom) for both adults and children who are known not to have HIV infection. A previously recommended 2-month regimen of rifampin and pyrazinamide has been associated with serious or even fatal hepatotoxicity and is not recommended. The rifampin-containing regimens should be considered for persons who are likely to have been infected with an isoniazid-resistant strain. A clinical trial showed that a regimen of isoniazid (900 mg) and rifapentine (900 mg), given once weekly for 12 weeks, is as effective as the standard 9-month isoniazid regimen. This regimen was associated with higher rates of treatment completion (82% vs 69%) and less hepatotoxicity (0.4% vs 2.7%) than isoniazid alone, although the rate of permanent discontinuation due to an adverse event was higher (4.9 vs 3.7%).

Currently, the isoniazid–rifapentine regimen is not recommended for children <2 years of age or pregnant women. Rifampin and rifapentine are contraindicated in HIV-infected individuals receiving protease inhibitors and most nonnucleoside reverse transcriptase inhibitors. However, efavirenz can be used for simultaneous administration with a rifamycin. Clinical trials to assess the efficacy of long-term isoniazid administration (i.e., for at least 3 years) among people living with HIV in high-TB-transmission settings have shown that this regimen can be more effective than 9 months of isoniazid and is therefore recommended under those circumstances. Isoniazid should not be given to persons with active liver disease. All isoniazid recipients at increased risk of hepatotoxicity (e.g., those abusing alcohol daily and those with a history of liver disease) should undergo baseline and then monthly assessment of liver function; they should be carefully educated about hepatitis and instructed to discontinue use of the drug immediately should any symptoms develop. Moreover, these patients should be seen and questioned monthly during therapy about adverse reactions and should be given no more than a 1-month supply of drug at each visit.

Treatment of LTBI among persons likely to have been infected by a multidrug-resistant strain is a challenge because no regimens have yet been tested in clinical trials. Close observation for early signs of disease is one option. However, in selected high-risk household contacts of patients with MDR-TB (e.g., children, recipients of immunosuppressive therapy), preventive therapy may be considered on the basis of individualized risk assessment and clinical criteria. In the absence of evidence of efficacy of any regimen, important factors in the decision to treat include intensity of exposure, certainty about a source case, information on the drug resistance pattern of the index case, and potential adverse events. Drug selection should be based on the drug susceptibility profile of the index case. Confirmation of infection with LTBI testing is required.

It may be more difficult to ensure compliance when treating persons with LTBI than when treating those with active TB. If family members of active cases are being treated, compliance and monitoring may be easier. When feasible, supervised therapy may increase the likelihood of completion. As in active cases, the provision of incentives may also be helpful. Currently, no evidence shows that LTBI treatment leads to significant development of drug resistance. However, before treatment of LTBI begins, it is mandatory to carefully exclude active TB in order to prevent the development of resistance.

PRINCIPLES OF TB CONTROL

The highest priority in any TB control program is the prompt detection of cases and the provision of chemotherapy to all TB patients under proper case-management conditions, including DOT and social support. In addition, screening of high-risk groups, including immigrants from high-prevalence countries, migrant workers, prisoners, homeless individuals, substance abusers, and HIV-seropositive persons, is recommended. TST- or IGRA-positive high-risk persons should be treated for LTBI as described above. Contact investigation is an important component of efficient TB control. In the United States and other countries worldwide, a great deal of attention has been given to the transmission of TB (particularly in association with HIV infection) in institutional settings such as hospitals, homeless shelters, and prisons. Measures to limit such transmission include respiratory isolation of persons with suspected TB until they are proven to be noninfectious (at least by sputum AFB smear negativity), proper ventilation in rooms of patients with infectious TB, use of ultraviolet irradiation in areas of increased risk of TB transmission, and periodic screening of personnel who may come into contact with known or unsuspected cases of TB. In the past, radiographic surveys, especially those conducted with portable equipment and miniature films, were advocated for case finding. Today, however, the prevalence of TB in industrialized countries is sufficiently low that "mass miniature radiography" is not cost-effective.

In high-prevalence countries, most TB control programs have made remarkable progress in reducing morbidity and mortality since the mid-1990s by adopting and implementing the standards and strategies internationally promoted by the WHO. Between 2000 and 2016, an estimated 52.5 million lives were saved. The essential elements of good TB care and control were established in the mid-1990s and consist of well-defined interventions that were the basis of the "DOTS strategy": early detection of cases and bacteriologic confirmation of the diagnosis; administration of standardized short-course chemotherapy, with direct supervision to ensure adherence to treatment and the provision of social support to patients; availability of drugs of proven quality, with an effective supply and management system; and a monitoring and evaluation system, including assessment of treatment outcomes—e.g., cure, completion of treatment without bacteriologic proof of cure, death, treatment failure, and default—in all cases registered and notified as well as measurement of the impact of control methods on classical TB indicators such as mortality, incidence, prevalence, and drug resistance. In 2006, the WHO indicated that, besides pursuing these essential elements that remain the fundamental components of any control strategy, additional steps had to be undertaken in order to reach international TB control targets. These steps included addressing HIV-associated TB and MDR-TB with additional measures; operating in harmony with general health services; engaging all care providers beyond the public providers; empowering people with TB and their communities; and enabling and promoting research. Evidence-based International Standards for Tuberculosis Care—focused on diagnosis, treatment, and public health responsibilities—were introduced for wide adoption by medical and professional societies, academic institutions, and all practitioners worldwide.

Care and control of HIV-associated TB are particularly challenging in poor countries because existing interventions require collaboration between HIV/AIDS and TB programs as well as standard services. TB programs must test every patient for HIV in order to provide access to trimethoprim-sulfamethoxazole prophylaxis against common infections and ART. HIV/AIDS programs must regularly screen persons living with HIV/AIDS for active TB, provide treatment for LTBI, and ensure infection control in settings where people living with HIV congregate.

Early and active case detection is considered an important intervention not only among persons living with HIV/AIDS but also among other vulnerable populations, as it reduces transmission in a community and provides early effective care. Additional measures are indicated for the management of MDR-TB, RR-TB, and other forms of drug-resistant TB; they include upgrades of laboratory capacity to perform rapid DST and ensure surveillance of drug resistance; availability of drug regimens that are recommended for RR/MDR-TB, with assured quality of drugs; and infection control measures in all settings where patients with drug-resistant forms of TB may congregate. In

the new era of the United Nations Sustainable Development Goals (2016–2030), the approach to TB control and care needs to evolve further and become multisectoral and more holistic. Engagement beyond dedicated programs and even the health sector is now essential. Therefore, the new "End TB" strategy promoted by WHO since 2016 builds on three pillars and relies on increased investments and efforts by all governments, their national programs, and a multitude of partners within and beyond the health sector: (1) integrated, patient-centered care and prevention; (2) bold policies and supportive systems; and (3) intensified research and innovation. The first pillar incorporates all technological innovations, such as early diagnostic approaches (including universal DST and systematic screening of identified, setting-specific, high-risk groups); well-designed treatment regimens for all forms of TB; proper management of HIV-associated TB and other comorbidities; and preventive treatment of persons at high risk. The second pillar is fundamental and is normally beyond the scope of dedicated programs, relying on policies forged by the highest-level health and governmental authorities: availability of adequate human and financial resources; engagement of civil organizations and all relevant public and private providers to pursue proper care for all patients and prevention for all people at risk; a policy of universal health coverage (which, together with social protection, implies avoidance of catastrophic expenditures caused by TB among the poorest); regulatory frameworks for case notifications, vital registration, quality and rational use of medicines, and infection control; social protection mechanisms as part of poverty alleviation strategies; and promotion of interventions against the broader determinants of TB. Finally, the third pillar of the new strategy emphasizes intensification of research and development on new tools and interventions as well as optimal implementation and rapid adoption of new tools in endemic countries. Besides specific clinical care and control interventions as described in this chapter, elimination of TB in a society ultimately will require control and mitigation of the multitude of direct risk factors (e.g., HIV infection, smoking, alcohol abuse, diabetes) and socioeconomic determinants (e.g., extreme poverty, inadequate living conditions and poor housing, malnutrition, indoor air pollution) with clearly implemented policies within the health sector and other sectors linked to human development and welfare.

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174 Leprosy

Robert H. Gelber

Leprosy, first described in ancient Indian texts from the sixth century B.C., is a nonfatal, chronic infectious disease caused by *Mycobacterium leprae,* the clinical manifestations of which are largely confined to the skin, peripheral nervous system, upper respiratory tract, eyes, and testes. The unique tropism of *M. leprae* for peripheral nerves (from large nerve trunks to microscopic dermal nerves) and certain immunologically mediated reactional states are the major causes of morbidity in leprosy. The propensity of the disease, when untreated, to result in characteristic deformities and the recognition in most cultures that the disease is communicable from person to person have resulted historically in a profound social stigma. Today, with early diagnosis and the institution of appropriate and effective antimicrobial therapy, patients can lead productive lives in the community, and deformities and other visible manifestations can largely be prevented.

ETIOLOGY

M. leprae is an obligate intracellular bacillus (0.3–1 μm wide and 1–8 μm long) that is confined to humans, armadillos in certain locales, and sphagnum moss. The organism is acid-fast, indistinguishable microscopically from other mycobacteria, and ideally detected in tissue sections by a modified Fite stain. Strain variability has been documented in this organism. *M. leprae* produces no known toxins and is well adapted to penetrate and reside within macrophages, yet it may survive outside the body for months. In untreated patients, only ~1% of *M. leprae* organisms are viable. The morphologic index (MI), a measure of the number of acid-fast bacilli (AFB) in skin scrapings that stain uniformly bright, correlates with viability. The bacteriologic index (BI), a logarithmic-scaled measure of the density of *M. leprae* in the dermis, may be as high as 4–6+ in untreated patients and falls by 1 unit per year during effective antimicrobial therapy; the rate of decrease is independent of the relative potency of therapy. A rising MI or BI suggests relapse and perhaps—if the patient is being treated—drug resistance. Drug resistance can be confirmed or excluded in the mouse model of leprosy, and resistance to dapsone and rifampin can be documented by the recognition of mutant genes. However, the availability of these technologies is extremely limited.

As a result of reductive evolution, almost half of the *M. leprae* genome contains nonfunctional genes; only 1605 genes encode for proteins, and 1439 genes are shared with *Mycobacterium tuberculosis*. In contrast, *M. tuberculosis* uses 91% of its genome to encode for 4000 proteins. Among the lost genes in *M. leprae* are those for catabolic and respiratory pathways; transport systems; purine, methionine, and glutamine synthesis; and nitrogen regulation. The genome of *M. leprae* provides a metabolic rationale for its obligate intracellular existence and reliance on host biochemical support, a template for targets of drug development, and ultimately a pathway to cultivation. The finding of strain variability among *M. leprae* isolates has provided a powerful tool with which to address anew the organism's epidemiology and pathobiology and to determine whether relapse represents reactivation or reinfection. The bacterium's complex cell wall contains large amounts of an *M. leprae*–specific phenolic glycolipid (PGL-1), which is detected in serologic tests. The unique trisaccharide of *M. leprae* binds to the basal lamina of Schwann cells; this interaction is probably related to the ability of *M. leprae*—unique among bacteria—to invade peripheral nerves.

Although it was the first bacterium to be etiologically associated with human disease, *M. leprae* remains one of the few bacterial species that still has not been cultivated on artificial medium or tissue culture. The regular multiplication of even a few *M. leprae* organisms in mouse footpads (albeit limited, with a doubling time of ~2 weeks) has provided a sensitive means to evaluate antimicrobial agents, monitor clinical trials, and screen vaccines. Several in vitro methods to assess the

organisms' viability, though promising, are many times less sensitive than the mouse model in detecting viable *M. leprae*. *M. leprae* grows best in cooler tissues (the skin, peripheral nerves, anterior chamber of the eye, upper respiratory tract, and testes), sparing warmer areas of the skin (the axilla, groin, scalp, and midline of the back).

Another distinct and recently discovered mycobacterial species, *M. lepromatosis,* is genetically similar to *M. leprae* and evolved from a common mycobacterial ancestor. *M. lepromatosis* has been identified in tissue from a small number of leprosy patients in Mexico with diffuse lepromatosis/Lucio's phenomenon (see below) and in single leprosy patients from Singapore and Canada. Of six Mexican patients studied, four were infected with *M. leprae* and two with *M. lepromatosis*. Because some new leprosy patients harbor both *M. leprae* and *M. lepromatosis*, it is not entirely clear that the latter organism is, in fact, a causative agent of leprosy. Fortunately, like *M. leprae, M. lepromatosis* is generally sensitive to dapsone, rifampin, and fluoroquinolones.

EPIDEMIOLOGY

Demographics Leprosy is almost exclusively a disease of the developing world, affecting areas of Asia, Africa, Latin America, and the Pacific. While Africa has the highest disease prevalence, Asia has the most cases. More than 80% of the world's cases occur in a few countries: India, China, Myanmar, Indonesia, Brazil, Nigeria, Madagascar, and Nepal. Within endemic locales, the distribution of leprosy is quite uneven, with areas of high prevalence bordering on areas with little or no disease. In Brazil the majority of cases occur in the Amazon basin and two western states, while in Mexico leprosy is mostly confined to the Pacific coast. Except as imported cases, leprosy is largely absent from the United States, Canada, and northwestern Europe. In the United States, ~4000 persons have leprosy and 100–200 new cases are reported annually, most of them in California, Texas, New York, and Hawaii among immigrants from Mexico, Southeast Asia, the Philippines, and the Caribbean.

The comparative genomics of single-nucleotide polymorphisms support the likelihood that four distinct strains exist, having originated in East Africa or Central Asia. A mutation spread to Europe and subsequently underwent two separate mutations that were then followed by spread to West Africa and the Americas.

The global prevalence of leprosy is difficult to assess, given that many of the locales with high prevalence lack a significant medical or public health infrastructure. Estimates range from 0.6 to 8 million affected individuals. The lower estimate includes only persons who have not completed chemotherapy, excluding those who may be physically or psychologically damaged from leprosy and who may yet relapse or develop immune-mediated reactions. The higher figure includes patients whose infections probably are already cured and many who have no leprosy-related deformity or disability. Although the figures on the worldwide prevalence of leprosy are debatable, incidence is not falling; there are still an estimated 500,000 new cases annually.

Leprosy is associated with poverty and rural residence. It appears not to be associated with AIDS, perhaps because of leprosy's long incubation period. Most individuals appear to be naturally immune to leprosy and do not develop disease manifestations after exposure. The time of peak onset is in the second and third decades of life.

The most severe lepromatous form of leprosy is twice as common among men as among women and is rarely encountered in children. The frequency of the polar forms of leprosy in different countries varies widely and may in part be genetically determined; certain human leukocyte antigen (HLA) associations are known for both polar forms of leprosy (see below). Furthermore, variations in immunoregulatory genes are associated with an increased susceptibility to leprosy, particularly the multibacillary form. In India and Africa, 90% of cases are tuberculoid; in Southeast Asia, 50% are tuberculoid and 50% lepromatous; and in Mexico, 90% are lepromatous. (For definitions of disease types, see **Table 174-1** and "Clinical, Histologic, and Immunologic Spectrum," below.)

Transmission The route of transmission of leprosy remains uncertain, and transmission routes may in fact be multiple. Nasal droplet infection, contact with infected soil, and amoeba insect vectors have been considered the prime candidates. Aerosolized *M. leprae* can cause infection in immunosuppressed mice, and a sneeze from an untreated lepromatous patient may contain >10^{10} AFB. Furthermore, both IgA antibody to *M. leprae* and genes of *M. leprae*—demonstrable by polymerase chain reaction (PCR)—have been found in the nose of individuals from endemic areas who have no signs of leprosy and in 19% of occupational contacts of lepromatous patients. Several lines of evidence implicate soil transmission. (1) In endemic countries such as India, leprosy is primarily a rural and not an urban disease. (2) *M. leprae* products reside in soil in endemic locales. (3) Direct dermal inoculation (e.g., during tattooing) may transmit *M. leprae*, and common sites of leprosy in children are the buttocks and thighs, suggesting that microinoculation of infected soil may transmit the disease. Evidence for insect vectors of leprosy includes the demonstration that bedbugs and mosquitoes in the vicinity of leprosaria regularly harbor *M. leprae* and that experimentally infected mosquitoes can transmit the infection to mice.

TABLE 174-1 Clinical, Bacteriologic, Pathologic, and Immunologic Spectrum of Leprosy

FEATURE	TUBERCULOID (TT, BT) LEPROSY	BORDERLINE (BB, BL) LEPROSY	LEPROMATOUS (LL) LEPROSY
Skin lesions	One or a few sharply defined annular asymmetric macules or plaques with a tendency toward central clearing, elevated borders	Intermediate between BT- and LL-type lesions; ill-defined plaques with an occasional sharp margin; few or many in number	Symmetric, poorly marginated, multiple infiltrated nodules and plaques or diffuse infiltration; xanthoma-like or dermatofibroma papules; leonine facies and eyebrow alopecia
Nerve lesions	Skin lesions anesthetic early; nerve near lesions sometimes enlarged; nerve abscesses most common in BT	Hypesthetic or anesthetic skin lesions; nerve trunk palsies, at times symmetric	Hypesthesia a late sign; nerve palsies variable; acral, distal, symmetric anesthesia common
Acid-fast bacilli (BI[a])	0–1+	3–5+	4–6+
Lymphocytes	2+	1+	0–1+
Macrophage differentiation	Epithelioid	Epithelioid in BB; usually undifferentiated but may have foamy changes in BL	Foamy changes the rule; may be undifferentiated in early lesions
Langerhans giant cells	1–3+	—	—
Lepromin skin test	+++	—	—
Lymphocyte transformation test	Generally positive	1–10%	1–2%
CD4+/CD8+ T cell ratio in lesions	1.2	BB: NT; BL: 0.48	0.50
M. leprae PGL-1 antibodies	60%	85%	95%

[a]See text.

Abbreviations: BB, mid-borderline; BL, borderline lepromatous; BT, borderline tuberculoid; TT, polar tuberculoid; LL, polar lepromatous; BI, bacteriologic index; NT, not tested; PGL-1, phenolic glycolipid 1.

Red squirrels from Brownsea Island, England, have recently been found to be commonly infected with a strain of *M. leprae* that circulated in leprosy patients in medieval England. In addition, some red squirrels in England, Scotland, and Ireland have been found to be infected with *M. lepromatosis*. Both of these mycobacterial species have been found in overtly diseased red squirrels and in animals that appeared to be well. It is unclear what role, if any, these zoonoses might play in the propagation of human leprosy. Skin-to-skin contact generally is not considered an important route of transmission.

In endemic countries, ~50% of leprosy patients have a history of intimate contact with an infected person (often a household member), while, for unknown reasons, leprosy patients in nonendemic locales can identify such contact only 10% of the time. Moreover, household contact with an infected lepromatous case carries an eventual risk of disease acquisition of ~10% in endemic areas as opposed to only 1% in nonendemic locales. Contact with a tuberculoid case carries a very low risk. Physicians and nurses caring for leprosy patients and the co-workers of these patients are not at risk for leprosy.

Although multilocus variable-number short-nucleotide tandem-repeat (VNTR) analyses have generally demonstrated considerable variability among isolates, highly similar and even identical VNTR results have been obtained with isolates from a limited number of families with multiple cases. Moreover, VNTR results have been similar for isolates within certain geographic locales and divergent for isolates within others. These findings suggest that genomic analyses may prove useful in the future for defining *M. leprae* transmission patterns.

M. leprae causes disease primarily in humans. However, in Texas and Louisiana, 15% of nine-banded armadillos are infected, and armadillo contact occasionally results in human disease. Armadillos develop disseminated infection after IV inoculation of live *M. leprae*.

CLINICAL, HISTOLOGIC, AND IMMUNOLOGIC SPECTRUM

The incubation period prior to manifestation of clinical disease can vary between 2 and 40 years, although it is generally 5–7 years in duration. This long incubation period is probably, at least in part, a consequence of the extremely long doubling time for *M. leprae* (14 days in mice versus in vitro doubling times of 1 day and 20 min for *M. tuberculosis* and *Escherichia coli*, respectively). Leprosy presents as a spectrum of clinical manifestations that have bacteriologic, pathologic, and immunologic counterparts. The spectrum from polar tuberculoid (TT) to borderline tuberculoid (BT) to mid-borderline (BB, which is rarely encountered) to borderline lepromatous (BL) to polar lepromatous (LL) disease is associated with an evolution from asymmetric localized macules and plaques to nodular and indurated symmetric generalized skin manifestations, an increasing bacterial load, and loss of *M. leprae*–specific cellular immunity (Table 174-1). Distinguishing dermatopathologic characteristics include the number of lymphocytes, giant cells, and AFB as well as the nature of epithelioid cell differentiation. Where a patient presents on the clinical spectrum largely determines prognosis, complications, reactional states, and the intensity of antimicrobial therapy required.

Tuberculoid Leprosy At the less severe end of the spectrum is tuberculoid leprosy, which encompasses TT and BT disease. In general, these forms of leprosy result in symptoms confined to the skin and peripheral nerves. TT/BT leprosy is the most common form encountered in India, and TT is most common in Africa, while TT is virtually absent in Southeast Asia, where BT leprosy is frequent.

The skin lesions of tuberculoid leprosy consist of one or a few hypopigmented macules or plaques **(Fig. 174-1)** that are sharply demarcated and hypesthetic, often have erythematous or raised borders, and are devoid of the normal skin organs (sweat glands and hair follicles) and thus are dry, scaly, and anhidrotic. AFB are generally absent or few in number. Tuberculoid leprosy patients may have asymmetric enlargement of one or a few peripheral nerves. Indeed, leprosy and certain rare hereditary neuropathies are the only human diseases associated with peripheral-nerve enlargement. Although any peripheral nerve may be enlarged (including small digital and supraclavicular nerves), those most commonly affected are the ulnar, posterior auricular, peroneal, and posterior tibial nerves, with associated hypesthesia and myopathy.

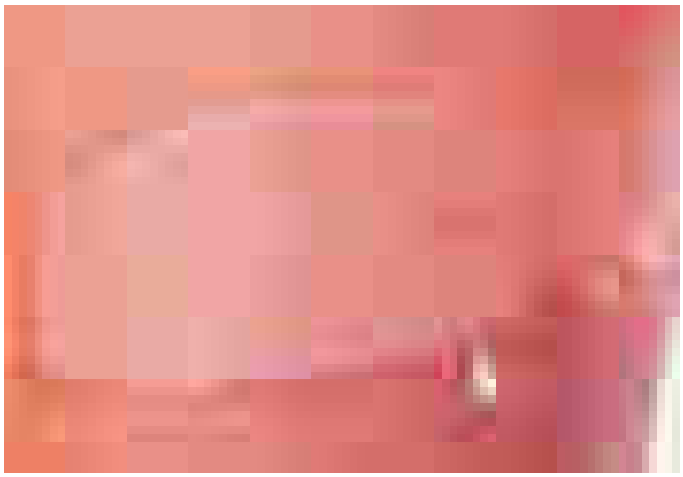

FIGURE 174-1 Tuberculoid (TT) leprosy: a well-defined, hypopigmented, anesthetic macule with anhidrosis and a raised granular margin *(arrowhead)*.

In tuberculoid leprosy, T cells breach the perineurium, and destruction of Schwann cells and axons may be evident, resulting in fibrosis of the epineurium, replacement of the endoneurium with epithelial granulomas, and occasionally caseous necrosis. Such invasion and destruction of nerves in the dermis by T cells are pathognomonic for leprosy.

Circulating lymphocytes from patients with tuberculoid leprosy readily recognize *M. leprae* and its constituent proteins, patients have positive lepromin skin tests (see "Diagnosis," below), and—because of a type 1 cytokine pattern in tuberculoid tissues—strong T cell and macrophage activation results in a localized infection. In tuberculoid leprosy tissue, there is a 2:1 predominance of helper CD4+ over CD8+ T lymphocytes. Tuberculoid tissues are rich in the mRNAs of the proinflammatory T_H1 family of cytokines: interleukin 2 (IL-2), interferon γ (IFN-γ), and IL-12; in contrast, IL-4, IL-5, and IL-10 mRNAs are scarce.

Lepromatous Leprosy Lepromatous leprosy patients present with symmetrically distributed skin nodules **(Fig. 174-2)**, raised plaques, or diffuse dermal infiltration, which, when on the face, results in *leonine facies*. Late manifestations include loss of eyebrows (initially the lateral margins only) and eyelashes, pendulous earlobes, and dry scaling skin, particularly on the feet. In LL leprosy, bacilli are numerous

FIGURE 174-2 Lepromatous (LL) leprosy: advanced nodular lesions.

in the skin (as many as 10^9/g), where they are often found in large clumps (*globi*), and in peripheral nerves, where they initially invade Schwann cells, resulting in foamy degenerative myelination and axonal degeneration and later in Wallerian degeneration. In addition, bacilli are plentiful in circulating blood and in all organ systems except the lungs and the central nervous system. Nevertheless, patients are afebrile, and there is no evidence of major organ system dysfunction.

Found almost exclusively in western Mexico and the Caribbean is a form of lepromatous leprosy without visible skin lesions but with diffuse dermal infiltration and a demonstrably thickened dermis, termed *diffuse lepromatosis*.

In lepromatous leprosy, nerve enlargement and damage tend to be symmetric, result from actual bacillary invasion, and are more insidious but ultimately more extensive than in tuberculoid leprosy. Patients with LL leprosy have acral, distal, symmetric peripheral neuropathy and a tendency toward symmetric nerve-trunk enlargement. They may also have signs and symptoms related to involvement of the upper respiratory tract, the anterior chamber of the eye, and the testes.

In untreated LL patients, lymphocytes regularly fail to recognize either *M. leprae* or its protein constituents, and lepromin skin tests are negative (see "Diagnosis," below). This loss of protective cellular immunity appears to be antigen-specific, as patients are not unusually susceptible to opportunistic infections, cancer, or AIDS and maintain delayed-type hypersensitivity to *Candida*, *Trichophyton*, mumps virus, tetanus toxoid, and even purified protein derivative of tuberculin. At times, *M. leprae*–specific anergy is reversible with effective chemotherapy. In LL tissues, there is a 2:1 ratio of CD8+ to CD4+ T lymphocytes. LL patients have a predominant T_H2 response and hyperglobulinemia, and LL tissues demonstrate a T_H2 cytokine profile, being rich in mRNAs for IL-4, IL-5, and IL-10 and poor in those for IL-2, IFN-γ, and IL-12. It appears that cytokines mediate a protective tissue response in leprosy, as injection of IFN-γ or IL-2 into lepromatous lesions causes a loss of AFB and histopathologic conversion toward a tuberculoid pattern. Macrophages of lepromatous leprosy patients appear to be functionally intact; circulating monocytes exhibit normal microbicidal function and responsiveness to IFN-γ.

Reactional States Lepra reactions comprise several common immunologically mediated inflammatory states that cause considerable morbidity. Some of these reactions precede diagnosis and the institution of effective antimicrobial therapy; indeed, these reactions may precipitate presentation for medical attention and diagnosis. Other reactions follow the initiation of appropriate chemotherapy; these reactions may cause patients to perceive that their leprosy is worsening and to lose confidence in conventional therapy. Only by warning patients of the potential for these reactions and describing their manifestations can physicians treating leprosy patients ensure continued credibility.

TYPE 1 LEPRA REACTIONS (DOWNGRADING AND REVERSAL REACTIONS) Type 1 lepra reactions occur in almost half of patients with borderline forms of leprosy but not in patients with pure lepromatous disease. Manifestations include classic signs of inflammation within previously involved macules, papules, and plaques and, on occasion, the appearance of new skin lesions, neuritis, and (less commonly) fever—generally low-grade. The nerve trunk most frequently involved in this process is the ulnar nerve at the elbow, which may be painful and exquisitely tender. If patients with affected nerves are not treated promptly with glucocorticoids (see below), irreversible nerve damage may result in as little as 24 h. The most dramatic manifestation is footdrop, which occurs when the peroneal nerve is involved.

When type 1 lepra reactions precede the initiation of appropriate antimicrobial therapy, they are termed *downgrading reactions*, and the case becomes histologically more lepromatous; when they occur after the initiation of therapy, they are termed *reversal reactions*, and the case becomes more tuberculoid. Reversal reactions often occur in the first months or years after the initiation of therapy but may also develop several years thereafter.

Edema is the most characteristic microscopic feature of type 1 lepra lesions, whose diagnosis is primarily clinical. Reversal reactions are typified by a T_H1 cytokine profile, with an influx of CD4+ T helper cells and increased levels of IFN-γ and IL-2. In addition, type 1 reactions are associated with large numbers of T cells bearing γ/δ receptors—a unique feature of leprosy.

FIGURE 174-3 Moderately severe skin lesions of erythema nodosum leprosum, some with pustulation and ulceration.

TYPE 2 LEPRA REACTIONS: ERYTHEMA NODOSUM LEPROSUM Erythema nodosum leprosum (ENL) **(Fig. 174-3)** occurs exclusively in patients near the lepromatous end of the leprosy spectrum (BL/LL), affecting nearly 50% of this group. Although ENL may precede leprosy diagnosis and the initiation of therapy (sometimes, in fact, prompting the diagnosis), in 90% of cases it follows the institution of chemotherapy, generally within 2 years. The most common features of ENL are crops of painful erythematous papules that resolve spontaneously in a few days to a week but may recur; malaise; and fever that can be profound. However, patients may also experience neuritis, lymphadenitis, uveitis, orchitis, and glomerulonephritis and may develop anemia, leukocytosis, and abnormal liver function tests (particularly increased aminotransferase levels). Individual patients may have either a single bout of ENL or chronic recurrent manifestations. Bouts may be either mild or severe and generalized; in rare instances, ENL results in death. Skin biopsy of ENL papules reveals vasculitis or panniculitis, sometimes with many lymphocytes but characteristically with polymorphonuclear leukocytes as well.

Elevated levels of circulating tumor necrosis factor (TNF) have been demonstrated in ENL; thus, TNF may play a central role in the pathobiology of this syndrome. ENL is thought to be a consequence of immune complex deposition, given its T_H2 cytokine profile and its high levels of IL-6 and IL-8. However, in ENL tissue, the presence of HLA-DR framework antigen of epidermal cells—considered a marker for a delayed-type hypersensitivity response—and evidence of higher levels of IL-2 and IFN-γ than are usually seen in polar lepromatous disease suggest an alternative mechanism.

LUCIO'S PHENOMENON Lucio's phenomenon is an unusual reaction seen exclusively in patients from the Caribbean and Mexico who have the diffuse lepromatosis form of lepromatous leprosy, most often those who are untreated. Patients with this reaction develop recurrent crops of large, sharply marginated, ulcerative lesions—particularly on the lower extremities—that may be generalized and, when so, are frequently fatal as a result of secondary infection and consequent septic bacteremia. Histologically, the lesions are characterized by ischemic necrosis of the epidermis and superficial dermis, heavy parasitism of endothelial cells with AFB, and endothelial proliferation and thrombus formation in the larger vessels of the deeper dermis. Like ENL, Lucio's phenomenon is probably mediated by immune complexes.

Complications • **THE EXTREMITIES** Complications of the extremities in leprosy patients are primarily a consequence of neuropathy leading to insensitivity and myopathy.

Insensitivity affects fine touch, pain, and heat receptors but generally spares position and vibration appreciation. The most commonly affected nerve trunk is the ulnar nerve at the elbow, whose involvement results in clawing of the fourth and fifth fingers, loss of dorsal interosseous musculature in the affected hand, and loss of sensation in these distributions. Median nerve involvement in leprosy impairs thumb opposition and grasp; radial nerve dysfunction, although rare in leprosy, leads to wrist drop. Tendon transfers can restore hand function but should not be performed until 6 months after the initiation of antimicrobial therapy and the conclusion of episodes of acute neuritis.

Plantar ulceration, particularly at the metatarsal heads, is probably the most common complication of leprous neuropathy. Therapy requires careful debridement; administration of appropriate antibiotics; avoidance of weight-bearing until ulcerations are healed, with slowly progressive ambulation thereafter; and wearing of special shoes to prevent recurrence.

Footdrop as a result of peroneal nerve palsy should be treated with a simple nonmetallic brace in the shoe or with surgical correction attained by tendon transfers. Although uncommon, Charcot's joints, particularly of the foot and ankle, may result from leprosy.

The loss of distal digits in leprosy is a consequence of insensitivity, trauma, secondary infection, and—in lepromatous disease—a poorly understood and sometimes profound osteolytic process. Conscientious protection of the extremities during cooking and work and the early institution of therapy have substantially reduced the frequency and severity of distal digit loss in recent times.

THE NOSE In lepromatous leprosy, bacillary invasion of the nasal mucosa can result in chronic nasal congestion and epistaxis. Saline nose drops may relieve these symptoms. Long-untreated LL leprosy may further result in destruction of the nasal cartilage, with consequent saddle-nose deformity or anosmia (more common in the preantibiotic era than at present). Nasal reconstructive procedures can ameliorate significant cosmetic defects.

THE EYE Arising from cranial nerve palsies, lagophthalmos and corneal insensitivity may complicate leprosy, resulting in trauma, secondary infection, and (without treatment) corneal ulcerations and opacities. For patients with these conditions, eye drops during the day and ointments at night provide some protection from such consequences. Furthermore, in LL leprosy, the anterior chamber of the eye is invaded by bacilli, and ENL may result in uveitis, with consequent cataracts and glaucoma. Thus leprosy is a major cause of blindness in the developing world. Slit-lamp evaluation of LL patients often reveals "corneal beading" that represents globi of *M. leprae*.

THE TESTES *M. leprae* invades the testes, while ENL may cause orchitis. Thus males with lepromatous leprosy often manifest mild to severe testicular dysfunction, with an elevation of luteinizing and follicle-stimulating hormones, decreased testosterone, and aspermia or hypospermia in 85% of LL patients but in only 25% of BL patients. LL patients may become impotent and infertile. Impotence is sometimes responsive to testosterone replacement.

AMYLOIDOSIS Secondary amyloidosis is a complication of LL leprosy and ENL that is encountered infrequently in the antibiotic era. This complication may result in abnormalities of hepatic and particularly renal function.

NERVE ABSCESSES Patients with various forms of leprosy, but especially those with the BT form, may develop abscesses of nerves (most commonly the ulnar), with a cellulitic appearance of adjacent skin. In such conditions, the affected nerve is swollen and exquisitely tender. Although glucocorticoids may reduce signs of inflammation, rapid surgical decompression is necessary to prevent irreversible sequelae.

DIAGNOSIS

Leprosy most commonly presents with both characteristic skin lesions and skin histopathology. Thus the disease should be suspected when a patient from an endemic area has suggestive skin lesions or peripheral neuropathy. The diagnosis should be confirmed by histopathology. In tuberculoid leprosy, lesional areas—preferably the advancing edge—must be biopsied because normal-appearing skin does not have pathologic features. In lepromatous leprosy, nodules, plaques, and indurated areas are optimal biopsy sites, but biopsies of normal-appearing skin also are generally diagnostic. Lepromatous leprosy is associated with diffuse hyperglobulinemia, which may result in false-positive serologic tests (e.g., Venereal Disease Research Laboratory, rheumatoid arthritis, and antinuclear antibody tests) and therefore may cause diagnostic confusion. On occasion, tuberculoid lesions may not (1) appear typical, (2) be hypesthetic, and (3) contain granulomas (instead containing only nonspecific lymphocytic infiltrates). In such instances, two of these three characteristics are considered sufficient for a diagnosis. It is preferable to overdiagnose leprosy rather than to allow a patient to remain untreated.

IgM antibodies to PGL-1 are found in 95% of patients with untreated lepromatous leprosy; the titer decreases with effective therapy. However, in tuberculoid leprosy—the form of disease most often associated with diagnostic uncertainty because of the absence or paucity of AFB—patients have significant antibodies to PGL-1 only 60% of the time; moreover, in endemic locales, exposed individuals without clinical leprosy may harbor antibodies to PGL-1. Thus PGL-1 serology is of little diagnostic utility in tuberculoid leprosy. Heat-killed *M. leprae* (lepromin) has been used as a skin test reagent. It generally elicits a reaction in tuberculoid leprosy patients, may do so in individuals without leprosy, and gives negative results in lepromatous leprosy patients; consequently, it is likewise of little diagnostic value. Unfortunately, PCR of the skin for *M. leprae*, although positive in LL and BL disease, yields negative results in 50% of tuberculoid cases, again offering little diagnostic assistance.

DIFFERENTIAL DIAGNOSIS

Included in the differential diagnosis of lesions that resemble leprosy are sarcoidosis, leishmaniasis, lupus vulgaris, dermatofibroma, histiocytoma, lymphoma, syphilis, yaws, granuloma annulare, and various other disorders causing hypopigmentation (notably pityriasis alba, tinea, and vitiligo). Sarcoidosis may result in perineural inflammation, but actual granuloma formation within dermal nerves is pathognomonic for leprosy. In lepromatous leprosy, sputum specimens may be loaded with AFB—a finding that can be incorrectly interpreted as representing pulmonary tuberculosis.

TREATMENT

Leprosy

ANTIMICROBIAL THERAPY

Active Agents Established agents used to treat leprosy include dapsone (50–100 mg/d), clofazimine (50–100 mg/d, 100 mg three times weekly, or 300 mg monthly), and rifampin (600 mg daily or monthly); see "Choice of Regimens," below. Of these drugs, only rifampin is bactericidal. The sulfones (folate antagonists), the foremost of which is dapsone, were the first antimicrobial agents found to be effective for the treatment of leprosy and are still the mainstays of therapy. With sulfone treatment, skin lesions resolve and numbers of viable bacilli in the skin are reduced. Although primarily bacteriostatic, dapsone monotherapy results in a resistance-related relapse rate of only 2.5%. When dapsone monotherapy was discontinued in lepromatous patients treated for ≥18 years who had been smear-negative for several years, relapses began to occur in the first year after cessation and occurred in ~1% annually thereafter during the next nine years (total, 10%). Dapsone is generally safe and inexpensive. Individuals with glucose-6-phosphate dehydrogenase deficiency who are treated with dapsone may develop severe hemolysis; those without this deficiency also have reduced red cell survival and a hemoglobin decrease averaging 1 g/dL. Dapsone's usefulness is limited occasionally by allergic dermatitis and rarely by the sulfone syndrome (including high fever, anemia, exfoliative dermatitis, and a mononucleosis-type blood picture). When rifampin has been included in finite regimens to treat multibacillary

leprosy (including World Health Organization [WHO] multidrug therapy), several studies have documented double-digit relapse rates, particularly frequently in patients with a high BI. Relapses following the discontinuation of rifampin-containing regimens (unlike those following the discontinuation of dapsone monotherapy) generally begin only after 6 years and most commonly occur after >10 years. It must be remembered that rifampin induces microsomal enzymes, necessitating increased doses of medications such as glucocorticoids and oral birth control regimens. Clofazimine is often cosmetically unacceptable to light-skinned leprosy patients because it causes a red-black skin discoloration that accumulates, particularly in lesional areas, and makes the patient's diagnosis obvious to members of the community.

Other antimicrobial agents active against *M. leprae* in animal models and at the usual daily doses used in clinical trials include ethionamide/prothionamide; the aminoglycosides streptomycin, kanamycin, and amikacin (but not gentamicin or tobramycin); minocycline; clarithromycin; and several fluoroquinolones, particularly ofloxacin and moxifloxacin. After rifampin, the most bactericidal agents against *M. leprae* in mice and patients appear to be minocycline, clarithromycin, and ofloxacin, but these drugs have not been used extensively in leprosy control programs. Most recently, rifapentine and moxifloxacin have been found to be especially potent against *M. leprae* in mice. In a clinical trial in lepromatous leprosy, moxifloxacin was profoundly bactericidal, matched in potency only by rifampin.

Choice of Regimens Antimicrobial therapy for leprosy should be individualized, depending on the clinical/pathologic form of the disease encountered. Tuberculoid leprosy, which is associated with a low bacterial burden and a protective cellular immune response, is the easiest form to treat and can be cured reliably with a finite course of chemotherapy. In contrast, lepromatous leprosy may have a higher bacillary load than any other human bacterial disease, and the absence of a salutary T cell repertoire requires prolonged or even lifelong chemotherapy. Therefore, careful classification of disease prior to therapy is important.

A reasoned approach to the treatment of leprosy is confounded by several issues:

1. Even without therapy, TT leprosy may heal spontaneously, and dapsone monotherapy is generally curative.
2. In tuberculoid disease, it is common for no bacilli to be found in the skin prior to therapy. Thus there is no objective measure of therapeutic success. Furthermore, despite adequate treatment, TT and particularly BT lesions often resolve minimally or incompletely, while relapse and late type 1 lepra reactions can be difficult to distinguish.
3. LL leprosy patients commonly harbor viable *M. leprae* "persisters" that are the source of relapse if therapy is discontinued. Because leprosy may relapse many years after cessation of antibiotic therapy, prolonged follow-up after completion of treatment is recommended in order to prevent further disability and deformity.
4. Even though primary dapsone resistance is exceedingly rare and multidrug therapy is generally recommended (at least for lepromatous leprosy), there is a paucity of information from experimental animals and clinical trials on the optimal combination of antimicrobial agents, dosing schedule, and duration of therapy.

In 1982, the WHO made recommendations for leprosy chemotherapy administered in control programs. These recommendations recognized the limited resources available for leprosy care in the very areas where it is most prevalent and the frustration and discouragement of patients and program managers with the previous requirement for lifelong therapy for many leprosy patients. Thus, for the first time, and without supporting clinical-trial evidence (particularly data on long-term relapse frequency), the WHO advocated a finite duration of therapy for all forms of leprosy and—given the prohibitive cost of daily rifampin treatment in developing countries—encouraged the monthly administration of this agent as part of a multidrug regimen. The WHO treatment regimens were specifically meant for control programs where implementation of a finite regimen for all forms of leprosy would substantially decrease the operational burden of leprosy care; these regimens were not claimed to be optimal in locales where more considerable resources are available. Over the ensuing years, however, the WHO recommendations have been broadly implemented worldwide. For treatment purposes, the WHO originally classified patients with few bacteria in the dermis (BI <2) as paucibacillary and those with many bacteria (BI >2) as multibacillary. The WHO recommended that paucibacillary leprosy in adults be treated with 100 mg of dapsone daily and 600 mg of rifampin monthly (supervised) for 6 months **(Table 174-2)**. As an alternative for patients with single-lesion paucibacillary leprosy, the WHO recommended a single dose of rifampin (600 mg), ofloxacin (400 mg), and minocycline (100 mg). The recommendation for multibacillary leprosy in adults was 100 mg of dapsone plus 50 mg of clofazimine daily (unsupervised) and with 600 mg of rifampin plus 300 mg of clofazimine monthly (supervised). Originally, the WHO recommended that lepromatous patients be treated for 2 years or until smears became negative (generally in ~5 years). In subsequent years, the WHO mandated several modifications to their original multidrug-treatment recommendation, primarily related to leprosy classification criteria and treatment duration (see "The Leprosy Elimination Campaign: Modifications of the Multidrug Regimen and Their Consequences," below).

Several factors have caused many authorities to question the WHO recommendations and to favor a more intensive approach. Among these factors are—for multibacillary patients—a high (double-digit) relapse rate in several locales (reaching 20–40% in one locale, with the rate directly related to the initial bacterial burden) and—for paucibacillary patients—demonstrable lesional activity for years in fully half of patients after the completion of therapy. The more intensive approach (Table 174-2) calls for tuberculoid leprosy to be treated with dapsone (100 mg/d) for 5 years and for lepromatous leprosy to be treated with rifampin (600 mg/d) for 3 years and with dapsone (100 mg/d) throughout life.

With effective antimicrobial therapy, new skin lesions as well as signs and symptoms of peripheral neuropathy cease appearing. Nodules and plaques of lepromatous leprosy noticeably flatten in 1–2 months and resolve in one or a few years, while tuberculoid skin lesions may disappear, ameliorate, or remain relatively unchanged. Although the peripheral neuropathy of leprosy may improve somewhat in the first few months of therapy, rarely is it significantly alleviated by treatment.

Although two of the three recommended drugs (dapsone and clofazimine) are only bacteriostatic against *M. leprae*, and although bactericidal agents have been identified since the WHO formulated its recommendations, significant studies employing the available alternatives in newly designed regimens have not been initiated.

TABLE 174-2 Antimicrobial Regimens Recommended for the Treatment of Leprosy in Adults

FORM OF LEPROSY	MORE INTENSIVE REGIMEN	WHO-RECOMMENDED REGIMEN (1982)
Tuberculoid (paucibacillary)	Dapsone (100 mg/d) for 5 years	Dapsone (100 mg/d, unsupervised) *plus* rifampin (600 mg/month, supervised) for 6 months
Lepromatous (multibacillary)	Rifampin (600 mg/d) for 3 years *plus* dapsone (100 mg/d) indefinitely	Dapsone (100 mg/d) *plus* clofazimine (50 mg/d), unsupervised; *and* rifampin (600 mg) *plus* clofazimine (300 mg) monthly (supervised) for 1–2 years

Note: See text for discussion and comparison of the WHO recommendations with the more intensive approach as well as the alternative WHO regimen for single-lesion paucibacillary leprosy.

Given that moxifloxacin, like rifampin, is profoundly bactericidal in leprosy patients and that short-course chemotherapy for tuberculosis is possible only when two or more bactericidal agents are used, a moxifloxacin/rifamycin-based regimen including either minocycline or clarithromycin (each more potent than either dapsone or clofazimine) appears promising; such a regimen may prove to be more reliably curative than WHO-recommended multidrug therapy for lepromatous leprosy and may allow a considerably shorter course of treatment.

THE LEPROSY ELIMINATION CAMPAIGN: MODIFICATIONS OF THE MULTIDRUG REGIMEN AND THEIR CONSEQUENCES

The World Health Assembly resolution of 1991 proposed to "eliminate leprosy as a public health problem" in all countries by the year 2000, with success defined as <1 in 10,000 persons with leprosy not having completed a course of multidrug therapy. When leprosy elimination appeared not to be occurring in that time frame, several changes were made to WHO multidrug therapy recommendations to simplify leprosy diagnosis and treatment, ease operational requirements for control programs, and facilitate attainment of the elimination target:

1. The duration of treatment of multibacillary leprosy was reduced from 2 years to 1 year in 1995 and to only 6 months in 2002. Neither duration was supported by prior clinical trials, and neither has been demonstrated in trials with prolonged follow-up to provide a reliable cure. However, this reduction in duration of therapy for multibacillary leprosy had the effect of reducing for elimination purposes the number of multibacillary cases by a factor of four.
2. The recommendation for multibacillary treatment was first changed to mandate therapy for any patient whose skin smear was positive. By 1995, skin biopsies and even skin smears were no longer advocated for leprosy diagnosis and classification. For treatment purposes, classification henceforth was to be determined on clinical grounds alone: more than five anesthetic skin lesions or enlarged nerves were to be considered multibacillary and fewer lesions paucibacillary. Unfortunately, such classification often led to under-treatment for some patients and over-treatment for others. Although leprosy often can be diagnosed on clinical grounds alone, it is not infrequently confused with other dermatologic disorders, and the diagnosis not uncommonly remains uncertain even for seasoned leprologists. Skin smears and biopsies often clarify a leprosy diagnosis and earmark those patients most prone to relapse after the completion of therapy. With these diagnostic tests abandoned, leprosy diagnosis has been profoundly compromised.
3. The WHO advocated the integration of leprosy into national general health services. In most countries where leprosy is endemic, those services are already overburdened, and the prospects that their leprosy patients will receive optimal care is most unlikely. Unfortunately, in endemic countries, medical education often ignores leprosy. Therefore, in general health services, a leprosy diagnosis is frequently delayed or missed, and a rise in leprosy disability and deformity has consequently been encountered worldwide.
4. The WHO now promotes "accompanied multidrug therapy," which allows a newly diagnosed patient—if accompanied by a companion who will offer assistance and encourage drug compliance—to receive the full complement of the leprosy regimen at the time of diagnosis; thereafter, the patient is no longer counted as a case and often is no longer entitled to receive further leprosy services. Accompanied multidrug treatment entirely eliminated directly observed therapy—a cornerstone of effective treatment for tuberculosis—from the leprosy treatment regimen. Like that for all chronic diseases, including tuberculosis, compliance with leprosy treatment has proved consistently unreliable. Compliance was previously ameliorated to some extent by the directly observed monthly component of the WHO leprosy regimen.
5. The WHO now encourages "uniform multidrug therapy," whereby all leprosy patients receive the same 6 months of treatment previously reserved for multibacillary cases. This treatment duration for multibacillary cases (or an even longer duration) has not proved reliable in preventing relapse. Moreover, patients whose cases were previously classified as paucibacillary receive clofazimine—a drug whose use is not necessary and is often cosmetically and psychosocially unacceptable, marking patients with a leprosy diagnosis.
6. Since 1995, the WHO went on record as not advocating for patient follow-up after completion of multidrug treatment. Thus, relapse is assuredly underreported, and its impact is not appreciated.
7. A by-product of the elimination campaign and the public perception that leprosy elimination is at hand is the substantial diminution of funding for both patient care and research. An older generation of leprologists is retiring, specialized leprosy facilities are disappearing, and recruitment of professionals for careers as leprosy clinicians and researchers has been substantially reduced. As a consequence, leprosy research has been largely abandoned. In particular, though there are real prospects for improving chemotherapy for leprosy and evaluating new antimicrobial agents both in mice and in clinical trials, almost no such efforts have commenced in the past decade. Furthermore, the mouse footpad laboratories required for such work worldwide are few and lack the capacity to monitor those efforts.

THERAPY FOR REACTIONS

Type 1 Type 1 lepra reactions are best treated with glucocorticoids (e.g., prednisone, initially at doses of 40–60 mg/d). As inflammation subsides, the glucocorticoid dose can be tapered, but steroid therapy must be continued for at least 3–6 months lest recurrence supervene. Because of the myriad toxicities of prolonged glucocorticoid therapy, the indications for its initiation are strictly limited to lesions whose intense inflammation poses a threat of ulceration; lesions at cosmetically important sites, such as the face; and cases in which neuritis is present. Mild to moderate lepra reactions that do not meet these criteria should be tolerated, with glucocorticoid treatment withheld. Thalidomide is ineffective against type 1 lepra reactions. Clofazimine (200–300 mg/d) is of questionable benefit but in any event is far less efficacious than glucocorticoids.

Type 2 Treatment of ENL must be individualized. If ENL is mild (i.e., if it occurs without fever or other organ involvement and with occasional crops of only a few skin papules), it may be treated with antipyretics alone. However, in cases with many skin lesions, fever, malaise, and other tissue involvement, brief courses (1–2 weeks) of glucocorticoid treatment (initially 40–60 mg/d) are often effective. With or without therapy, individual inflamed papules last for <1 week. Successful therapy is defined by the cessation of skin lesion development and the disappearance of other systemic signs and symptoms. If, despite two courses of glucocorticoid therapy, ENL appears to be recurring and persisting, treatment with thalidomide (100–300 mg nightly) should be initiated, with the dose depending on the initial severity of the reaction. Because even a single dose of thalidomide administered early in pregnancy may result in severe birth defects, including phocomelia, the use of this drug in the United States for the treatment of fertile female patients is tightly regulated and requires informed consent, prior pregnancy testing, and maintenance of birth control measures. Although the mechanism of thalidomide's dramatic action against ENL is not entirely clear, the drug's efficacy is probably attributable to its reduction of TNF levels and IgM synthesis and its slowing of polymorphonuclear leukocyte migration. After the reaction is controlled, lower doses of thalidomide (50–200 mg nightly) are effective in preventing relapses of ENL. Clofazimine in high doses (300 mg nightly) has some efficacy against ENL, but its use permits only a modest reduction of the glucocorticoid dose necessary for ENL control.

Lucio's Phenomenon Neither glucocorticoids nor thalidomide is effective against this syndrome. Optimal wound care and therapy for bacteremia are indicated. Ulcers tend to be chronic and heal poorly. In severe cases, exchange transfusion may prove useful.

PREVENTION AND CONTROL

Multidrug Treatment and Leprosy Elimination Between 2000 and 2006, the worldwide annual case-detection rate of leprosy fell from 700,000 to 280,000. Because India alone was estimated to carry 60% of the world's leprosy burden and was slow to reach the elimination goal, additional operational policies were instituted:

1. Single-lesion leprosy, which accounts for one-third of leprosy cases in India, was no longer classified as leprosy at all.
2. A case of leprosy was no longer counted if diagnosed by the treating physician but not verified (as required) by program managers at the district or state level—individuals who were under pressure to produce improved statistics.
3. Active case finding, which had been extensive and successful in India, was discouraged. Because of the stigma of leprosy, self-reporting often does not occur.

In India between 2000 and 2006, the annual leprosy case-detection rate fell from 560,000 to 140,000, and "elimination" was achieved in 2004. However, since the incubation period of leprosy in the large majority of cases is 5–7 years or longer, and since most new cases reported in 2006 were already incubating in 2000, the claim of a dramatic fall in the incidence of leprosy—and, as a consequence, of multidrug therapy—both in India and worldwide is epidemiologically unreasonable. Rather, millions of cases were undiagnosed and untreated, while new leprosy cases, disability, and deformity have been documented to be on the rise.

Vaccination Vaccination at birth with bacille Calmette-Guérin (BCG) has proved variably effective in preventing leprosy: the results have ranged from total inefficacy to 80% efficacy. The addition of heat-killed *M. leprae* to BCG does not increase the effectiveness of the vaccine. Because whole mycobacteria contain large amounts of lipids and carbohydrates that have proved in vitro to be immunosuppressive for lymphocytes and macrophages, *M. leprae* proteins may prove to be superior vaccines. Data from a mouse model support this possibility.

Chemoprophylaxis Chemoprophylaxis with dapsone may reduce the number of tuberculoid leprosy cases but not the number of lepromatous cases and therefore is not recommended, even for household contacts. In addition, single-dose rifampin prophylaxis is of doubtful efficacy.

Isolation Because leprosy transmission appears to require close prolonged household contact, hospitalized patients need not be isolated.

LEPROSY: THE PRESENT SITUATION

During most of the twentieth century, nongovernmental organizations, particularly Christian missionaries, provided a medical infrastructure devoted to the care and treatment of leprosy patients—the envy of those with other medical priorities in the developing world. With the public perception that leprosy is near eradication, resources for patient care are rapidly being diverted, and the burden of patient care is being transferred to nonexistent or overloaded national health services and to health workers who lack the tools and skills needed for the disease's diagnosis and classification and for the selection of nuanced therapy (particularly in cases of reactional neuritis). Furthermore, after the completion of therapy, when a patient is no longer considered to represent a case, half of all patients continue to manifest disease activity for years; relapse rates (at least for multibacillary patients) are unacceptably high; disabilities and deformities go unchecked; and the social stigma of the disease persists. Thus the prerequisites for a salutary outcome increasingly go unmet.

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175 Nontuberculous Mycobacterial Infections

Steven M. Holland

Several terms—nontuberculous mycobacteria (NTM), atypical mycobacteria, mycobacteria other than tuberculosis, and environmental mycobacteria—all refer to mycobacteria other than *Mycobacterium tuberculosis*, its close relatives (*M. bovis, M. caprae, M. africanum, M. pinnipedii, M. canetti*), and *M. leprae*. The number of identified species of NTM is growing and will continue to do so because of the use of DNA sequence typing for speciation. The number of known species currently exceeds 170. NTM are highly adaptable and can inhabit hostile environments, including industrial solvents.

EPIDEMIOLOGY

NTM are ubiquitous in soil and water. Specific organisms have recurring niches, such as *M. simiae* in certain aquifers, *M. fortuitum* in pedicure baths, and *M. immunogenum* in metalworking fluids. Most NTM cause disease in humans only rarely unless some aspect of host defense is impaired, as in bronchiectasis, or breached, as by inoculation (e.g., liposuction, trauma, cardiac surgery). There are few instances of human-to-human transmission of NTM, which occurs almost exclusively in cystic fibrosis. Because infections due to NTM are rarely reported to health agencies and because their identification is sometimes problematic, reliable data on incidence and prevalence are lacking. Disseminated disease denotes significant immune dysfunction (e.g., advanced HIV infection), whereas pulmonary disease, which is much more common, is highly associated with pulmonary epithelial defects but not with systemic immunodeficiency.

In the United States, the incidence and prevalence of pulmonary infection with NTM, mostly in association with bronchiectasis **(Chap. 284)**, have for many years been several-fold higher than the corresponding figures for tuberculosis, and rates of the former are increasing among the elderly as rates of tuberculosis continue to fall. Among patients with cystic fibrosis, who often have bronchiectasis, rates of clinical infection with NTM range from 3 to 15%, with even higher rates among older patients. Although NTM may be recovered from the sputa of many individuals, it is critical to differentiate active disease from commensal harboring of the organisms. A scheme to help with the proper diagnosis of pulmonary infection caused by NTM has been developed by the American Thoracic Society and is widely used. The bulk of nontuberculous mycobacterial disease in North America is due to *M. kansasii*, organisms of the *M. avium* complex (MAC), and *M. abscessus*.

In Europe, Asia, and Australia, the distribution of NTM in clinical specimens is roughly similar to that in North America, with MAC species and rapidly growing organisms such as *M. abscessus* encountered frequently. *M. xenopi* and *M. malmoense* are especially prominent in northern Europe. *M. ulcerans* causes the

distinct clinical entity Buruli ulcer, which occurs throughout tropical zones, especially in western Africa. *M. marinum* is a common cause of cutaneous and tendon infections in coastal regions and among individuals exposed to fish tanks or swimming pools.

The true international epidemiology of infections due to NTM is hard to determine because the isolation of these organisms often is not reported and speciation often is not performed for *M. tuberculosis* or NTM. The latter issue poses an especially important problem during therapy for tuberculosis when smears positive for acid-fast bacilli are considered evidence of treatment failure. The increasing ease of identification and speciation of these organisms is already having a major impact on the description of the dynamic international epidemiology of tuberculosis and NTM infections.

PATHOBIOLOGY

Because exposure to NTM is essentially universal and disease is rare, it can be assumed that normal host defenses against these organisms must be strong and that otherwise healthy individuals in whom significant disease develops are highly likely to have specific susceptibility factors that permit NTM to become established, multiply, and cause disease. At the advent of HIV infection, CD4+ T lymphocytes were recognized as key effector cells against NTM; the development of disseminated MAC disease was highly correlated with a decline in CD4+ T lymphocyte numbers. Such a decrease has also been implicated in disseminated MAC infection in patients with idiopathic CD4+ T lymphocytopenia. Potent inhibitors of tumor necrosis factor α (TNF-α), such as infliximab, adalimumab, certolizumab, golimumab, and etanercept, neutralize this critical cytokine, with consequent inhibition of granuloma formation. The occasional result is severe mycobacterial or fungal infection; these associations indicate that TNF-α is a crucial element in mycobacterial control. However, in cases without the above risk factors, much of the genetic basis of susceptibility to disseminated infection with NTM is accounted for by specific mutations in the interferon γ (IFN-γ)/interleukin 12 (IL-12) synthesis and response pathways.

Mycobacteria are typically phagocytosed by macrophages, which respond with the production of IL-12, a heterodimer composed of IL-12p35 and IL-12p40 moieties that together make up IL-12p70. IL-12 activates T lymphocytes and natural killer cells through binding to its receptor (composed of IL-12Rβ1 and IL-12Rβ2/IL-23R), with consequent phosphorylation of STAT4. IL-12 stimulation of STAT4 leads to secretion of IFN-γ, which activates neutrophils and macrophages to produce reactive oxidants, to increase expression of the major histocompatibility complex and Fc receptors, and to concentrate certain antibiotics intracellularly. Signaling by IFN-γ through its receptor (composed of IFN-γR1 and IFN-γR2) leads to phosphorylation of STAT1, which in turn regulates IFN-γ-responsive genes, such as those coding for IL-12 and TNF-α. TNF-α signals through its own receptor via a downstream complex containing the nuclear factor κB (NF-κB) essential modulator (NEMO). Therefore, the positive feedback loop between IFN-γ and IL-12/IL-23 drives the immune response to mycobacteria and other intracellular infections. These genes are known to be the critical ones in the pathway of mycobacterial control: specific Mendelian mutations have been identified in *IFNGR1, IFNGR2, STAT1, GATA2, ISG15, IRF8, IL-12A, IL-12RB1, IL-12RB2, CYBB* (which encodes the gp91^{phox} protein of the NADPH oxidase), and *IKBKG* (which encodes NEMO) **(Fig. 175-1)**. Despite the identification of genes associated with disseminated disease, only ~70% of cases of disseminated nontuberculous mycobacterial infections that are not associated with HIV infection have a genetic diagnosis; the implication is that more mycobacterial susceptibility genes and pathways remain to be identified.

In contrast to the recognized genes and mechanisms associated with disseminated nontuberculous mycobacterial infection, the best-recognized underlying condition for pulmonary infection with NTM is bronchiectasis **(Chap. 284)**. Most of the well-characterized forms of bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, STAT3-deficient hyper-IgE syndrome, and idiopathic bronchiectasis, have high rates of association with nontuberculous mycobacterial infection. The precise mechanism by which bronchiectasis predisposes to locally destructive but not systemic involvement is unknown.

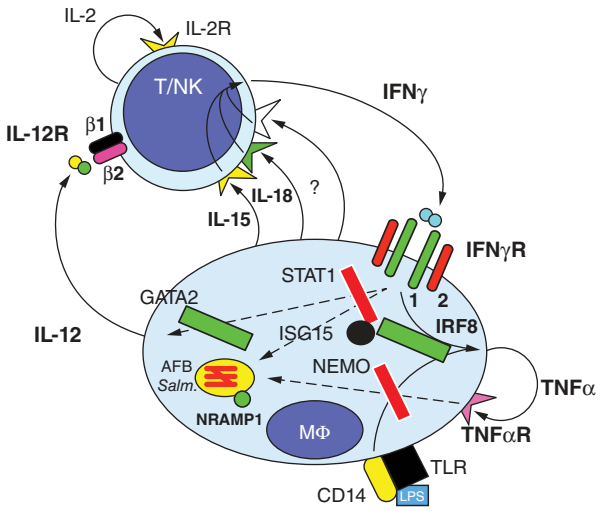

FIGURE 175-1 Cytokine interactions of infected macrophages (MΦ) with T and natural killer (NK) lymphocytes. Infection of macrophages by mycobacteria (AFB) leads to the release of heterodimeric interleukin 12 (IL-12). IL-12 acts on its receptor complex (IL-12R), with consequent STAT4 activation and production of homodimeric interferon γ (IFNγ). Through its receptor (IFNγR), IFNγ activates STAT1, stimulating the production of tumor necrosis factor α (TNFα) and leading to the killing of intracellular organisms such as mycobacteria, salmonellae (*Salm.*), and some fungi. Homotrimeric TNFα acts through its receptor (TNFαR) and requires nuclear factor κB essential modulator (NEMO) to activate nuclear factor κB, which also contributes to the killing of intracellular bacteria. Both IFNγ and TNFα lead to upregulation of IL-12. TNFα-blocking antibodies work either by blocking the ligand (infliximab, adalimumab, certolizumab, golimumab) or by providing soluble receptor (etanercept). Mutations in *IFNGR1, IFNGR2, IL12B, IL12RB1, IL12RB2, STAT1, GATA2, ISG15, IRF8, CYBB,* and *IKBKG* (NEMO) have been associated with predisposition to mycobacterial infections. Other cytokines, such as IL-15 and IL-18, also contribute to IFNγ production. Signaling through the Toll-like receptor (TLR) complex and CD14 also upregulates TNFα production. IRF8, interferon regulatory factor 8; ISG15, interferon-stimulated gene 15; LPS, lipopolysaccharide; NRAMP1, natural resistance-associated macrophage protein 1.

Unlike disseminated or pulmonary infection, "hot-tub lung" represents pulmonary hypersensitivity to NTM—most commonly MAC organisms—growing in underchlorinated water, often in indoor hot tubs.

CLINICAL MANIFESTATIONS

Disseminated Disease Disseminated MAC or *M. kansasii* infections in patients with advanced HIV infection are now uncommon in North America because of effective antimycobacterial prophylaxis and improved treatment of HIV infection. When such mycobacterial disease was common, the portal of entry was the bowel, with spread to bone marrow and the bloodstream. Surprisingly, disseminated infections with rapidly growing NTM (e.g., *M. abscessus, M. fortuitum*) are very rare in HIV-infected patients, even in those with advanced HIV infection. Because these organisms are of low intrinsic virulence and disseminate only in conjunction with impaired immunity, disseminated disease can be indolent and progressive over weeks to months. Typical manifestations of malaise, fever, and weight loss are often accompanied by organomegaly, lymphadenopathy, and anemia. Because special cultures or stains are required to identify the organisms, the most critical step in diagnosis is to suspect infection with NTM. Blood cultures may be negative, but involved organs typically have significant organism burdens, sometimes with a grossly impaired granulomatous response.

In a child, disseminated involvement (i.e., involvement of two or more organs) without an underlying iatrogenic cause should prompt an investigation of the IFN-γ/IL-12 pathway. Recessive mutations in *IFNGR1* and *IFNGR2* typically lead to severe infection with NTM. In contrast, dominant negative mutations in *IFNGR1*, which lead to over-accumulation of a defective interfering mutant receptor on the cell surface, inhibit normal IFN-γ signaling and thus lead to nontuberculous mycobacterial osteomyelitis. Dominant negative mutations in *STAT1* and recessive mutations in *IL-12RB1* can produce variable

phenotypes consistent with their residual capacities for IFN-γ synthesis and response. Male patients who have disseminated nontuberculous mycobacterial infections along with conical, peg, or missing teeth and an abnormal hair pattern should be evaluated for defects in the pathway that activates NF-κB through NEMO (*IKBKG*). These patients may have associated immune globulin defects as well. Patients with myelodysplasia and mycobacterial disease should be investigated for GATA2 deficiency. A recently recognized group of patients who often develop disseminated infections with rapidly growing NTM (predominantly *M. abscessus*) as well as other opportunistic infections have high-titer neutralizing autoantibodies to IFN-γ. Thus far, this syndrome has been reported most frequently in East Asian female patients.

IV catheters can become infected with NTM, usually as a consequence of contaminated water. *M. abscessus* and *M. fortuitum* sometimes infect deep indwelling lines as well as fluids used in eye surgery, subcutaneous injections, and local anesthetics. Infected catheters should be removed.

Pulmonary Disease Lung disease is by far the most common form of nontuberculous mycobacterial infection in North America and the rest of the industrialized world. In North America, rates of NTM lung disease far exceed rates of tuberculosis. The clinical presentation typically consists of months or years of throat clearing, nagging cough, and slowly progressive fatigue. Patients will often have seen physicians multiple times and received symptom-based or transient therapy before the diagnosis is entertained and samples are sent for mycobacterial stains and cultures. Because not all patients can produce sputum, bronchoscopy may be required for diagnosis. The typical lag between onset of symptoms and diagnosis is ~5 years in older women. Predisposing factors include underlying lung diseases such as bronchiectasis **(Chap. 284)**, pneumoconiosis **(Chap. 283)**, chronic obstructive pulmonary disease **(Chap. 286)**, primary ciliary dyskinesia **(Chap. 284)**, α_1 antitrypsin deficiency **(Chap. 286)**, and cystic fibrosis **(Chap. 285)**. Bronchiectasis and nontuberculous mycobacterial infection often coexist and progress in tandem. This situation makes causality difficult to determine in a given index case, but bronchiectasis is certainly among the most critical predisposing factors that are exacerbated by infection.

MAC organisms are the most common causes of pulmonary nontuberculous mycobacterial infection in North America, but rates vary somewhat by region. MAC infection most commonly develops during the sixth or seventh decade of life in women who have had months or years of nagging intermittent cough and fatigue, with or without sputum production or chest pain. The constellation of pulmonary disease due to NTM in a tall and thin woman who may have chest wall abnormalities is often referred to as Lady Windermere syndrome, after an Oscar Wilde character of the same name. In fact, pulmonary MAC infection does afflict older nonsmoking white women more than men, with onset at ~60 years. Patients tend to be taller and thinner than the general population, with high rates of scoliosis, mitral valve prolapse, and pectus anomalies. Whereas male smokers with upper-lobe cavitary disease tend to carry the same single strain of MAC indefinitely, nonsmoking females with nodular bronchiectasis tend to carry several strains of MAC simultaneously, with changes over the course of their disease.

M. kansasii can cause a clinical syndrome that strongly resembles tuberculosis, consisting of hemoptysis, chest pain, and cavitary lung disease. The rapidly growing NTM, such as *M. abscessus*, have been associated with esophageal motility disorders such as achalasia. Patients with pulmonary alveolar proteinosis are prone to pulmonary nontuberculous mycobacterial and *Nocardia* infections; the underlying mechanism may be inhibition of alveolar macrophage function due to the autoantibodies to granulocyte-macrophage colony-stimulating factor found in many of these patients.

Cervical Lymph Nodes The most common form of nontuberculous mycobacterial infection among young children in North America is isolated cervical lymphadenopathy, caused most frequently by MAC organisms but also by other NTM. The cervical swelling is typically firm and relatively painless, with a paucity of systemic signs. Because the differential diagnosis of painless adenopathy includes malignancy, many children have infection with NTM diagnosed inadvertently at biopsy; cultures and special stains may not have been requested because mycobacterial disease was not ranked high in the differential. Local fistulae usually resolve completely with resection and/or antibiotic therapy. Likewise, the entity of isolated pediatric intrathoracic nontuberculous mycobacterial infection, which is probably related to cervical lymph node infection, is usually mistaken for cancer. In neither isolated cervical nor isolated intrathoracic infections with NTM have children with underlying immune defects been commonly identified, nor do the affected children usually go on to develop other opportunistic infections.

Skin and Soft Tissue Disease Cutaneous involvement with NTM usually requires a break in the skin for introduction of the bacteria. Pedicure bath–associated infection with *M. fortuitum* is more likely if skin abrasion (e.g., during leg shaving) has occurred just before the pedicure. Outbreaks of skin infection are often caused by rapidly growing NTM (especially *M. abscessus, M. fortuitum*, and *M. chelonae*) acquired via skin contamination from surgical instruments (especially in cosmetic surgery), injections, and other procedures. These infections are typically accompanied by painful, erythematous, draining subcutaneous nodules, usually without associated fever or systemic symptoms.

M. marinum lives in many water sources and can be acquired from fish tanks, swimming pools, barnacles, and fish scales. This organism typically causes papules or ulcers ("fish-tank granuloma"), but the infection can progress to tendinitis with significant impairment of manual dexterity. Lesions appear days to weeks after inoculation of organisms by a typically minor trauma (e.g., incurred during the cleaning of boats or the handling of fish). Tender nodules due to *M. marinum* can advance up the arm in a pattern also seen with *Sporothrix schenckii* (*sporotricoid spread*). The typical carpal-tendon involvement may be the first presenting manifestation and may lead to surgical exploration or steroid injection. The index of suspicion for *M. marinum* infections must be high to ensure that proper specimens obtained during procedures are sent for culture.

M. ulcerans, another waterborne skin pathogen, is found mainly in the tropics, especially in tropical areas of Africa. Infection follows skin trauma or insect bites that allow admission to contaminated water. The skin lesions are typically painless, clean ulcers that slough and can cause osteomyelitis. The toxin mycolactone accounts for the modest host inflammatory response and the painless ulcerations.

DIAGNOSIS

NTM can be detected on acid-fast or fluorochrome smears of sputum or other body fluids. When the organism burden is high, the organisms may appear as gram-positive beaded rods, but this finding is unreliable. (In contrast, nocardiae may appear as gram-positive and beaded but filamentous bacteria.) Again, the requisite and most sensitive step in the diagnosis of any mycobacterial disease is to think of including it in the differential. In almost all laboratories, mycobacterial sample processing, staining, and culture are conducted separately from routine bacteriologic tests; thus many infections go undiagnosed because of the physician's failure to request the appropriate test. In addition, mycobacteria usually require separate blood culture media. NTM are broadly differentiated into rapidly growing (<7 days) and slowly growing (≥7 days) forms. Because *M. tuberculosis* typically takes ≥2 weeks to grow, many laboratories refuse to consider culture results final until 6 weeks have elapsed. Newer techniques using liquid culture media permit more rapid isolation of mycobacteria from specimens than is possible with traditional media. Species more readily detected with incubation at 30°C include *M. marinum, M. haemophilum*, and *M. ulcerans. M. haemophilum* prefers iron supplementation or blood, whereas *M. genavense* requires supplemented medium with the additive mycobactin J. Bacterial formation of pigment in light conditions (*photochromogenicity*) or dark conditions (*scotochromogenicity*) or a lack of bacterial pigment formation (*nonchromogenicity*) was historically used to help categorize NTM. In contrast to NTM colonies, *M. tuberculosis* colonies are

beige, rough, dry, and flat. Current identification schemes reliably use biochemical, nucleic acid, or cell wall composition, as assessed by high-performance liquid chromatography or mass spectrometry, for speciation. With the remarkable decline in U.S. cases of tuberculosis over recent decades, NTM have become the mycobacteria most commonly isolated from humans in North America. However, not all isolations of NTM, especially from the lung, reflect pathology and require treatment. Whereas identification of an organism in a blood or organ biopsy specimen in a compatible clinical setting is diagnostic, the American Thoracic Society recommends that pulmonary infection due to NTM be diagnosed only when disease is clearly demonstrable—i.e., in an appropriate clinical and radiographic setting (nodules, bronchiectasis, cavities) and with repeated isolation of NTM from expectorated sputum or recovery of NTM from bronchoscopy or biopsy specimens. Given the large number of species of NTM and the importance of accurate diagnosis for the implementation of proper therapy, identification of these organisms is ideally taken to the species level.

The purified protein derivative (PPD) of tuberculin is delivered intradermally to evoke a memory T cell response to mycobacterial antigens. This test is variously referred to as the PPD test, the tuberculin skin test, and the Mantoux test, among other designations. Unfortunately, the cutaneous immune response to these tuberculosis-derived filtrate proteins does not differentiate well between infection with some NTM and that with *M. tuberculosis*. Because intermediate reactions (~10 mm) to PPD in latent tuberculosis and nontuberculous mycobacterial infections can overlap significantly, the progressive decline in active tuberculosis in the United States means that NTM probably account for increasing proportions of PPD reactivity. In addition, *bacille Calmette-Guérin* (BCG) can cause some degree of cross-reactivity, posing problems of interpretation for patients who have received BCG vaccine. Assays to measure the elaboration of IFN-γ in response to the relatively tuberculosis-specific proteins ESAT6 and CFP10 form the basis for IFN-γ-release assays (IGRAs). These assays can be performed with whole blood or on membranes. It is important to note that *M. marinum, M. kansasii*, and *M. szulgai* also have ESAT6 and CFP10 and may cause false-positive reactions in IGRAs. Despite cross-reactivity with NTM, large PPD reactions (>15 mm) most commonly signify tuberculosis.

Isolation of NTM from blood specimens is clear evidence of disease. Whereas rapidly growing mycobacteria may proliferate in routine blood culture media, slow-growing NTM typically do not; thus it is imperative to suspect the diagnosis and to use the correct bottles for cultures. Isolation of NTM from a biopsy specimen constitutes strong evidence for infection, but cases of laboratory contamination do occur. Identification of organisms on stained sections of biopsy material confirms the authenticity of the culture. Certain NTM require lower incubation temperatures (*M. genavense*) or special additives (*M. haemophilum*) for growth. Some NTM (e.g., *M. tilburgii*) remain noncultivable but can be identified molecularly in clinical samples.

The radiographic appearance of nontuberculous mycobacterial disease in the lung depends on the underlying disease, the severity of the infection, and the imaging modality used. The advent and increase in the use of CT have allowed the identification of characteristic changes that are highly consistent with nontuberculous mycobacterial infection, such as the "tree-in-bud" pattern of bronchiolar inflammation **(Fig. 175-2)**. Involvement of the lingual and right-middle lobes is commonly seen on chest CT but is difficult to appreciate on plain film. Severe bronchiectasis and cavity formation are common in more advanced disease. Isolation of NTM from respiratory samples can be confusing. *M. gordonae* is often recovered from respiratory samples but is not usually seen on smear and is almost never a pathogen. Patients with bronchiectasis occasionally have NTM recovered from sputum culture with a negative smear. The American Thoracic Society has developed guidelines for the diagnosis of infection with MAC, *M. abscessus*, and *M. kansasii*. A positive diagnosis requires the growth of NTM from two of three sputum samples, regardless of smear findings; a positive bronchoscopic alveolar sample, regardless of smear findings; or a pulmonary parenchyma biopsy sample with granulomatous inflammation or mycobacteria found on section and NTM found on culture. These guidelines probably apply to other NTM as well.

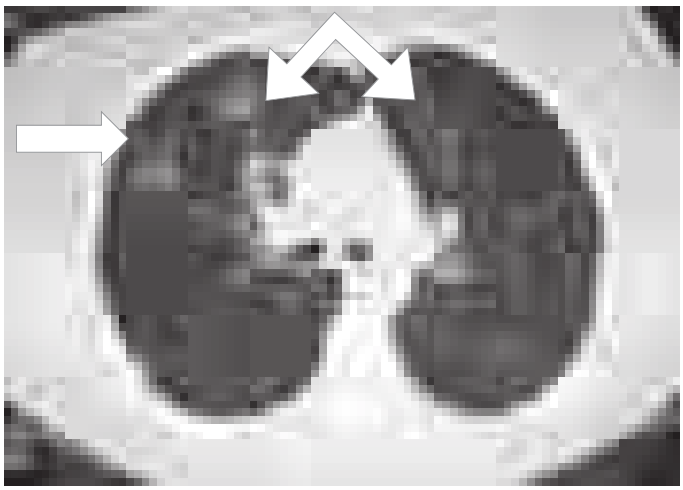

FIGURE 175-2 Chest CT of a patient with pulmonary *Mycobacterium avium* complex infection. *Arrows* indicate the "tree-in-bud" pattern of bronchiolar inflammation (peripheral right lung) and bronchiectasis (central right and left lungs).

Although many laboratories use DNA probes to identify *M. tuberculosis*, MAC, *M. gordonae*, and *M. kansasii*, speciation of NTM helps determine the antimycobacterial therapy to be used. Only testing of MAC organisms for susceptibility to clarithromycin and of *M. kansasii* for susceptibility to rifampin is indicated; few data support other in vitro susceptibility tests, attractive though they appear. MAC isolates that have not been exposed to macrolides are almost always susceptible. NTM that have persisted beyond a course of antimicrobial therapy are often tested for antibiotic susceptibility, but the value and meaning of these tests are undetermined.

PREVENTION

Prophylaxis of MAC disease in patients infected with HIV is started when the CD4+ T lymphocyte count falls to <50/μL. Azithromycin (1200 mg weekly), clarithromycin (1000 mg daily), or rifabutin (300 mg daily) is effective. Macrolide prophylaxis in immunodeficient patients who are susceptible to NTM (e.g., those with defects in the IFN-γ/IL-12 axis) has not been prospectively validated but seems prudent.

TREATMENT

Nontuberculous Mycobacteria

NTM cause chronic infections that evolve relatively slowly over a period of weeks to years. Therefore, it is rarely necessary to initiate treatment on an emergent basis before the diagnosis is clear and the infecting species is known. Treatment of NTM is complex, often poorly tolerated, and potentially toxic. Just as in tuberculosis, inadequate single-drug therapy is almost always associated with the emergence of antimicrobial resistance and relapse.

MAC infection often requires multidrug therapy, the foundation of which is a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). For disseminated nontuberculous mycobacterial disease in HIV-infected patients, the use of rifamycins poses special problems—i.e., rifamycin interactions with protease inhibitors. For pulmonary MAC disease, thrice-weekly administration of a macrolide, a rifamycin, and ethambutol has been successful. Therapy is prolonged, generally continuing for 12 months after culture conversion; typically, a course lasts for at least 18 months. Other drugs with activity against MAC organisms include IV and aerosolized aminoglycosides, fluoroquinolones, and clofazimine. In elderly patients, rifabutin can exert significant toxicity. However, with only modest efforts, most antimycobacterial regimens are well tolerated by most patients. Resection of cavitary lesions or severely bronchiectatic segments has been advocated for some patients, especially those with macrolide-resistant infections. The success of therapy for pulmonary MAC infections depends on

whether disease is nodular or cavitary and on whether it is early or advanced, ranging from 20 to 80%.

M. kansasii lung disease is similar to tuberculosis in many ways and is also effectively treated with isoniazid (300 mg/d), rifampin (600 mg/d), and ethambutol (15 mg/kg per day). Other drugs with very high-level activity against *M. kansasii* include clarithromycin, fluoroquinolones, and aminoglycosides. Treatment should continue until cultures have been negative for at least 1 year. In most instances, *M. kansasii* infection is easily cured. Bulky, severe, necrotizing *M. kansasii* lymphadenopathy, especially in the mediastinum, is strongly associated with GATA2 deficiency.

Rapidly growing mycobacteria pose special therapeutic problems. Extrapulmonary disease in an immunocompetent host is usually due to inoculation (e.g., via surgery, injections, or trauma) or to line infection and is often treated successfully with a macrolide and another drug (with the choice based on in vitro susceptibility), along with removal of the offending focus. In contrast, pulmonary disease, especially that caused by *M. abscessus*, is extremely difficult to cure. Repeated courses of treatment are usually effective in reducing the infectious burden and symptoms. Therapy generally includes a macrolide along with an IV-administered agent such as amikacin, a carbapenem, cefoxitin, or tigecycline. Other oral agents (used according to in vitro susceptibility testing and tolerance) include fluoroquinolones, doxycycline, and linezolid. Because nontuberculous mycobacterial infections are chronic, care must be taken in the long-term use of drugs with neurotoxicities, such as linezolid and ethambutol. Prophylactic pyridoxine has been suggested in these cases. Durations of therapy for *M. abscessus* lung disease are difficult to predict because so many cases are chronic and require intermittent therapy. Expert consultation and management are strongly recommended.

Once recognized, *M. marinum* infection is highly responsive to antimicrobial therapy and is cured relatively easily with any combination of a macrolide, ethambutol, and a rifamycin. Therapy should be continued for 1–2 months after clinical resolution of isolated soft-tissue disease; tendon and bone involvement may require longer courses in light of clinical evolution. Other drugs with activity against *M. marinum* include sulfonamides, trimethoprim-sulfamethoxazole, doxycycline, and minocycline.

Treatment of the other NTM is less well defined, but macrolides and aminoglycosides are usually effective, with other agents added as indicated. Expert consultation is strongly encouraged for difficult or unusual infections due to NTM.

PROGNOSIS

The outcomes of nontuberculous mycobacterial infections are closely tied to the underlying condition (e.g., IFN-γ/IL-12 pathway defect, cystic fibrosis) and can range from recovery to death. With no or inadequate treatment, symptoms and signs can be debilitating, including persistent cough, fever, anorexia, and severe lung destruction. With treatment, patients typically regain strength and energy. The optimal duration of therapy when NTM persist in sputum is unknown, but treatment in this situation can be prolonged. In general, for severe underlying immunodeficiencies, hematopoietic stem cell transplantation is recommended and may be helpful in the resolution of severe mycobacterial disease.

GLOBAL CONSIDERATIONS

In many countries, pulmonary tuberculosis is diagnosed by smear alone, which is also the method used for monitoring of response and relapse. However, examination of mycobacteria from the affected patients shows that a significant proportion of isolates are actually NTM. Overall, as rates of tuberculosis decline, the proportion of positive smears caused by NTM will increase. Advances in speciation will distinguish tuberculosis from nontuberculous mycobacterial infections and thereby affect rates of assumed relapse and resistance, leading to more targeted and appropriate therapy.

FURTHER READING

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176 Antimycobacterial Agents

Divya Reddy, Max R. O'Donnell

Agents used for the treatment of mycobacterial infections, including tuberculosis (TB), leprosy, and infections due to nontuberculous mycobacteria (NTM), are administered in multiple-drug regimens for prolonged courses. Currently, >160 species of mycobacteria have been identified, the majority of which do not cause disease in humans. While the incidence of disease caused by *Mycobacterium tuberculosis* has been declining in the United States, TB remains a leading cause of morbidity and mortality in developing countries—particularly in sub-Saharan Africa and Asia, where the HIV epidemic rages. Not only effective drug regimens are needed; without a well-organized infrastructure for diagnosis and treatment of TB, therapeutic and control efforts are severely hampered **(Chaps. 460 and 462)**. Infections with NTM have gained in clinical prominence in the United States and other developed countries. These largely environmental organisms often establish infection in immunocompromised patients or in persons with structural lung disease.

TUBERCULOSIS

GENERAL PRINCIPLES

The earliest recorded human case of TB dates back 9000 years. Early treatment modalities, such as bloodletting, were replaced by sanatorium regimens in the late nineteenth century. The discovery of streptomycin in 1943 launched the era of antibiotic treatment for TB. Over subsequent decades, the discovery of additional agents and the use of multiple-drug regimens allowed progressive shortening of the treatment course from years to as little as 6 months for drug-susceptible TB. Latent TB infection (LTBI) and active TB disease are diagnosed by history, physical examination, radiographic imaging, tuberculin skin test, interferon γ release assays, acid-fast staining, mycobacterial cultures, and/or new molecular diagnostics. LTBI is treated with isoniazid (optimally daily or weekly for 9 months), rifampin (daily for 4 months), isoniazid plus rifampin (daily for 3 months), or isoniazid plus rifapentine (weekly for 3 months) **(Table 176-1)**.

For active or suspected TB disease, clinical factors, including HIV co-infection, symptom duration, radiographic appearance, and public

TABLE 176-1 Regimens for the Treatment of Latent Tuberculosis Infection in Adults

REGIMEN	SCHEDULE	DURATION	COMMENTS
Isoniazid	300 mg/d (5 mg/kg) Alternative: 900 mg twice weekly (15 mg/kg)	9 months (6 months acceptable)	Supplement with pyridoxine (25–50 mg daily). Twice-weekly regimens require directly observed therapy.
Rifampin	600 mg/d (10 mg/kg)	4 months	Broader efficacy studies are needed.
Isoniazid plus rifampin	300 mg/d (5 mg/kg) plus 600 mg/d (10 mg/kg)	3 months	Broader efficacy studies are needed.
Isoniazid plus rifapentine	900 mg (15 mg/kg) weekly plus 900 mg (for weight >50 kg) weekly	3 months	Directly observed therapy is recommended for once-weekly treatment. This regimen may be supplemented with pyridoxine (25–50 mg/d).

Sources: D Menzies et al: Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: A randomized trial. Ann Intern Med 149:689, 2008; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603, 2003; T Sterling et al: Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 365: 2155, 2011.

health concerns about TB transmission, drive diagnostic testing and treatment initiation. Multiple-drug regimens are used for the treatment of TB disease **(Table 176-2)**. Initially, an intensive phase consisting of four drugs—isoniazid, rifampin, pyrazinamide, and ethambutol—given for 2 months is followed by a continuation phase of isoniazid and rifampin for 4 months, for a total treatment duration of 6 months. The continuation phase is extended to 7 months (for a total treatment duration of 9 months) for patients with cavitary disease; if the 2-month course of pyrazinamide is not completed; or if sputum cultures remain positive beyond 2 months of treatment (delayed culture conversion).

Treatment of TB in patients co-infected with HIV poses significant challenges, but some progress is being made. To improve survival, current recommendations include initiation of antiretroviral therapy (ART) in HIV patients co-infected with *M. tuberculosis* within 2 weeks of the initiation of treatment for TB (except TB meningitis) if the CD4+ T cell count is ≤50/μL and by 8–12 weeks of TB treatment initiation if the CD4+ T cell count is ≥50/μL. Interactions of rifampin with protease inhibitors or non-nucleoside reverse transcriptase inhibitors are significant and require close monitoring and dose adjustments. Rifabutin is the alternative drug of choice in HIV patients co-infected with *M. tuberculosis*. The TB immune reconstitution inflammatory syndrome (IRIS) may appear as early as 1 week after initiation of ART and manifests as paradoxical worsening or unmasking of existing TB infection. Conservative management consists of continued administration of ART and TB medications. However, severe or debilitating IRIS has been treated in reported case series with varying doses of glucocorticoids. Intermittent antimycobacterial therapy in patients infected with HIV and *M. tuberculosis* has been associated with low plasma levels of several key TB drugs and with higher rates of treatment failure or relapse; therefore, intermittent twice-weekly therapy for TB in HIV-co-infected individuals is not recommended.

Adherence to medications is critical in achieving a cure with antimycobacterial therapy. In addition to directly observed therapy (DOT) by trained staff, either in the clinic or at home, case management interventions such as patient education/counseling, field/home visits, and patient reminders are also recommended to improve treatment adherence. Use of mobile health technologies, including video DOT, text messaging, and next-generation electronic pillboxes, shows promise in promoting TB adherence. In drug-susceptible TB, monthly dispensing of TB medications is also advised for all patients to allow essential clinical monitoring for hepatotoxicity due to these medications. Clinical monitoring includes at least monthly assessment for symptoms (nausea, vomiting, abdominal discomfort, and unexplained fatigue) and signs (jaundice, dark urine, light stools, diffuse

TABLE 176-2 Simplified Approach to Treatment of Active Tuberculosis (TB) in Adults

CULTURE RESULTS	INTENSIVE PHASE	CONTINUATION PHASE	EXTENSION OF TOTAL TREATMENT
Culture-positive, drug-susceptible	HRZE for 2 months, daily[a] or 3 times per week (with dose adjustment)	HR for 4 months, daily or 5 days per week *or* HR for 4 months, 3 times per week[b] (with dose adjustment)	Continuation phase extended to 7 months if 2 months of Z is not completed, if the patient is infected with HIV and is not receiving antiretroviral therapy, or if culture conversion is prolonged and/or cavitation is evident on chest radiography[c]
Culture-negative	HRZE for 2 months	HR for 2 months, daily or 2 or 3 times per week[d]	Continuation phase extended to 4 months if the patient is infected with HIV
Extrapulmonary, drug-susceptible	HRZE for 2 months	HR for 4–7 months, daily or 5 days per week[e]	Continuation phase extended to 10 months in TB meningitis; 7 months recommended by some authorities for bone/joint TB
Resistant to H	QRZE[f] (or, less often, RZES) for 6 months	…	Prolonged culture conversion and/or evidence of cavitation on chest radiography
Resistant to R	HZEQ[f] (IA[g]) for 2 months	HEQ(S) for 10–16 months	Prolonged culture conversion, delayed response
Resistant to HR[h]	ZEQ[f] (IA[g]) ± alternative agents[i] for 18–24 months	…	Prolonged culture conversion

[a]Daily treatment is preferred; however, thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are not infected with HIV and are at low risk of relapse (i.e., in pulmonary tuberculosis caused by drug-susceptible organisms that, at the start of treatment, is noncavitary and/or smear negative). [b]Use regimen with caution in HIV patients and/or those with cavitary disease, as missed doses can lead to treatment failure, relapse, and acquired drug resistance. [c]Culture conversion is prolonged if it occurs beyond 2 months. [d]Twice-weekly treatment regimens are not recommended in patients infected with HIV and those with cavitary pulmonary disease suspected to be TB. [e]Standard daily 6-month TB treatment regimen is considered to be adequate for most forms of extrapulmonary TB, including miliary TB. For TB meningitis, the addition of glucocorticoids is recommended. [f]Levofloxacin and moxifloxacin are the preferred fluoroquinolones. Gatifloxacin is associated with dysglycemia but may be an acceptable alternative. Ofloxacin and ciprofloxacin should generally be avoided because of resistance. [g]Injectable agents: streptomycin, amikacin, kanamycin, and capreomycin. [h]Multidrug-resistant TB should be managed by or in close consultation with an expert TB clinician. Surgical management should also be considered. [i]Alternative agents: cycloserine, ethionamide, para-aminosalicylic acid, clarithromycin, linezolid, and amoxicillin-clavulanate.

Abbreviations: E, ethambutol; H, isoniazid; IA, injectable agent; Q, fluoroquinolone; R, rifampin; S, streptomycin; and Z, pyrazinamide.

Sources: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Clinical practice guidelines: Treatment of drug-susceptible tuberculosis. Clin Infect Dis 2016; 63:e147, 2016; C Mitnick et al: Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 359:563, 2008; World Health Organization: 2011 Update: Guidelines for the programmatic management of drug-resistant tuberculosis *(www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/index.html)*.

TABLE 176-3 Monitoring and Clinical Management of Tuberculosis Treatment in Adults[a]

DRUG	ASSESSMENT	MANAGEMENT
LTBI Treatment		
With hepatic risk factors[b], check ALT and bilirubin at baseline. If ALT is ≥3 × ULN or total bilirubin is >2 × ULN, defer treatment and reevaluate.		
Isoniazid	Determine whether hepatic risk factors are present. If so, obtain baseline and periodic ALT and bilirubin values.	If ALT is 5 × ULN (or 3 × ULN with symptoms)[c] or if bilirubin reaches jaundice levels (usually >2 × ULN), interrupt treatment. With normalization, consider an alternative agent.
Rifampin	Same as above	Same as above
TB Treatment		
Check ALT, bilirubin, platelets, creatinine, and hepatitis panel for all patients at baseline. If hepatic risk factors are present, check ALT and bilirubin monthly.		
Isoniazid	If ALT is >5 × ULN (or >3 × ULN with hepatitis symptoms)[c]	Obtain history of alcohol consumption and concomitant drug use. In most instances, discontinue H, Z, R, and other hepatotoxic drugs. Consider alternative agents. Obtain viral hepatitis serologies. Rechallenge: With normalization of liver enzymes, R and H may be sequentially reintroduced. With no recurrence of hepatotoxicity, Z is not resumed in many cases. Alternative rechallenge protocols have been used.
Rifampin	If primary elevation is in bilirubin and alkaline phosphatase, most likely due to rifampin	Discontinue R if total bilirubin reaches jaundice levels (usually >2 × ULN). May try to reintroduce; if not tolerated, may substitute Q
Ethambutol	Decrease in visual acuity or color vision on monthly screening	Discontinue ethambutol and repeat ocular exam. Peripheral neuropathy may be a precursor of ocular toxicity; if it occurs, consider repeat ocular exam.
Pyrazinamide	If ALT is >5 × ULN (or >3 × ULN with symptoms)[c]	Same as for H
Fluoroquinolone	If QTc prolongation is discovered incidentally on ECG	Asymptomatic QTc prolongation should prompt consideration of stopping known QT-prolonging drugs and/or close monitoring, depending on the clinical situation and degree of prolongation. Symptomatic QTc prolongation (e.g., palpitations or arrhythmias) should prompt discontinuation of drugs.
Aminoglycoside	Abnormal results on audiometry testing, BUN, creatinine, electrolytes at baseline or on monthly check	Discontinue aminoglycoside if not MDR-TB. Check audiometry and at least BUN and creatinine monthly. As appropriate, assess renal function, correct electrolytes, or seek ENT consultation.

[a]All regimens require monthly clinical monitoring. [b]Hepatic risk factors: chronic alcohol use, viral hepatitis, preexisting liver disease, pregnancy or ≤3 months postpartum, hepatotoxic medications. [c]Relevant manifestations include nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue.

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; ECG, electrocardiogram; ENT, ear, nose, and throat; H, isoniazid; LTBI, latent tuberculosis infection; MDR-TB, multidrug-resistant tuberculosis; Q, fluoroquinolone; QTc, corrected QT interval; R, rifampin; ULN, upper limit of normal; Z, pyrazinamide.

Sources: JJ Saukkonen et al: An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 174:935, 2006; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603, 2003.

pruritus) of hepatotoxicity, although the latter represent comparatively late manifestations **(Table 176-3)**. The presence of such symptoms and signs mandates provisional discontinuation of potentially hepatotoxic agents; discontinuation at the onset of hepatitis symptoms reduces the risk of progression to fatal hepatitis. Biochemical testing of at least serum alanine aminotransferase (ALT) and total bilirubin levels and exclusion of other causes of these abnormalities are also indicated during treatment for those at risk for hepatotoxicity (Table 176-3). For patients with active TB, monthly mycobacterial cultures of sputum are recommended until it is certain that the organisms have been cleared and the patient has responded to therapy or until no sputum is available for culture.

If significant clinical improvement does not occur or the patient's condition deteriorates over the course of therapy, possibilities include treatment failure due to nonadherence, poor medication absorption, or the development of resistance. For patients co-infected with HIV and *M. tuberculosis*, IRIS, which is a diagnosis of exclusion, should also be a consideration. Drug susceptibility testing should be repeated at this point. If resistance is documented or strongly suspected, at least two efficacious drugs to which the isolate is susceptible or which the patient has not already taken should be added to the therapeutic regimen.

Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by a strain of *M. tuberculosis* that is resistant to both isoniazid and rifampin—the most efficacious of the first-line TB drugs. The risk of MDR-TB is elevated in patients presenting from geographic areas in which ≥5% of incident cases are MDR-TB and in patients previously treated for TB. Treatment regimens for MDR-TB generally include a late-generation fluoroquinolone and an injectable second-line agent (such as capreomycin, amikacin, or kanamycin). Regimens of at least five drugs are recommended for the treatment of MDR-TB. Both standardized and optimized/customized regimens are in use around the world. MDR-TB treatment should be initiated and monitored by clinicians with expertise in drug-resistant TB.

In 2016, the World Health Organization made a provisional recommendation for use of a regimen based on the "Bangladesh regimen" to treat specific patients with MDR-TB **(Table 176-4)**. Unlike a conventional MDR-TB treatment regimen, whose duration may be 18–20 months depending on patient response, the new Bangladesh regimen is 9–12 months in duration. Patients excluded from this short-course regimen include treatment-experienced MDR-TB patients, patients with extrapulmonary TB, and patients with phenotypic or genotypic resistance to pyrazinamide, fluoroquinolones, or second-line injectable agents. This regimen consists of a seven-drug intensive phase (kanamycin, prothionamide, isoniazid, fluoroquinolone, ethambutol, pyrazinamide, and clofazimine) and a four-drug continuation phase (fluoroquinolone, ethambutol, pyrazinamide, and clofazimine). A series of cohort studies in Bangladesh showed favorable outcomes in up to 90% of the treated MDR-TB cases. High-level fluoroquinolone resistance, particularly in the setting of initial pyrazinamide resistance, was the strongest risk factor for an unfavorable treatment outcome in these cohorts. A multicenter randomized control study with sites in South Africa, Ethiopia, Vietnam, and Mongolia is under way and aims to determine the safety and efficacy of a moxifloxacin-based Bangladesh regimen in a setting with diverse HIV and drug resistance prevalences.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with additional resistance to any fluoroquinolone and at least one of the second-line injectable agents. Treatment of XDR-TB is individualized on the basis of complete phenotypic and, if possible, genotypic antimicrobial susceptibility testing. Therapeutic regimens for either MDR-TB or XDR-TB should be constructed with input from experienced clinicians, who should continue the management of the disease.

TABLE 176-4 "Bangladesh Regimen" for the Treatment of Multidrug-Resistant Tuberculosis

TREATMENT PHASE	DRUGS[a]	COMMENTS
Intensive phase	Isoniazid Ethambutol Pyrazinamide Fluoroquinolone[b] Kanamycin Prothionamide Clofazimine	All patients are hospitalized during the intensive phase, which is continued for at least 4 months or until there is sputum conversion or the patient is declared to have bacteriologic treatment failure.
Continuation phase	Fluoroquinolone Ethambutol Pyrazinamide Clofazimine	Patients are closely followed in the outpatient setting, and directly observed therapy is provided. The continuation phase is given for a total of 5 months.

[a]Daily drug doses were based on the patient's weight. [b]Ofloxacin and gatifloxacin have been the most studied fluoroquinolones in this regimen. Ofloxacin-based regimens appear to increase the prevalence of ofloxacin resistance over time from 0 to 10%. This effect was not observed with gatifloxacin-based regimens. Gatifloxacin, however, has been withdrawn from the market because of a high incidence of dysglycemia. A later-generation fluoroquinolone, such as moxifloxacin, is therefore currently preferred.

Sources: A Van Deun et al: Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 182:684, 2010; KJ Augn et al: Successful "9-month Bangladesh regimen" for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 18:1180, 2014; R Moodley, TR Godec: Short-course treatment for multidrug-resistant tuberculosis: The STREAM trials. Eur Respir Rev 25:29, 2016.

FIRST-LINE ANTITUBERCULOSIS DRUGS

The following discussion of individual anti-TB agents focuses on treatment of TB in adults, unless otherwise noted. Several agents are being actively investigated during the current remarkable period of drug development for TB treatment.

Isoniazid Isoniazid is a critical drug for treatment of both TB disease and LTBI. Isoniazid has excellent bactericidal activity against both intracellular and extracellular, actively dividing *M. tuberculosis*. This drug is bacteriostatic against slowly dividing organisms. In treatment of LTBI, isoniazid is considered the first-line agent because it is generally well tolerated, has well-established efficacy, and is inexpensive. In this setting, the drug is taken daily or intermittently (i.e., twice weekly) as DOT for 9 months. The 9-month course is more efficacious than the 6-month course (75–90% vs ≤65%), but extension of treatment to 12 months is not likely to provide further protection. A 6-month course of daily or intermittent isoniazid is considered second-line, but acceptable, therapy. A recent large open-label, multicenter, randomized controlled trial showed that weekly DOT with isoniazid and rifapentine, administered over 3 months, was not inferior to daily isoniazid given for 9 months and had a higher treatment completion rate than the single-drug regimen.

For treatment of TB disease, isoniazid is used in combination with other agents to ensure killing of both actively dividing *M. tuberculosis* and slowly growing "persister" organisms. Unless the organism is resistant, the standard regimen includes isoniazid, rifampin, ethambutol, and pyrazinamide (Table 176-2). Isoniazid is often given together with 25–50 mg of pyridoxine daily to prevent drug-related peripheral neuropathy.

MECHANISM OF ACTION Isoniazid is a prodrug activated by the mycobacterial KatG catalase-peroxidase; isoniazid is coupled with reduced nicotinamide adenine dinucleotide (NADH). The resulting isonicotinic acyl–NADH complex blocks the mycobacterial ketoenoylreductase known as InhA, binding to its substrate and inhibiting fatty acid synthase and ultimately mycolic acid synthesis. Mycolic acids are essential components of the mycobacterial cell wall. KatG activation of isoniazid also results in the release of free radicals that have antimycobacterial activity, including nitric oxide.

The minimal inhibitory concentrations (MICs) of isoniazid for wild-type (untreated) susceptible strains are <0.1 μg/mL for *M. tuberculosis* and 0.5–2 μg/mL for *Mycobacterium kansasii*.

PHARMACOLOGY Isoniazid is the hydrazide of isonicotinic acid, a small, water-soluble molecule. The usual adult oral daily dose of 300 mg results in peak serum levels of 3–5 μg/mL within 30 min to 2 h after ingestion—well in excess of the MICs for most susceptible strains of *M. tuberculosis*. Both oral and IM preparations of isoniazid reach effective levels in the body, although antacids and high-carbohydrate meals may interfere with oral absorption. Isoniazid diffuses well throughout the body, reaching therapeutic concentrations in body cavities and fluids, with concentrations in cerebrospinal fluid (CSF) comparable to those in serum.

Isoniazid is metabolized in the liver via acetylation by *N*-acetyltransferase 2 (NAT2) and hydrolysis. Both fast- and slow-acetylation phenotypes occur; patients who are "fast acetylators" may have lower serum levels of isoniazid, whereas "slow acetylators" may have higher levels and experience more toxicity. Satisfactory isoniazid levels are attained in the majority of homozygous fast NAT2 acetylators given a dose of 6 mg/kg and in the majority of homozygous slow acetylators given only 3 mg/kg. Genotyping is increasingly being used to characterize isoniazid-related pharmacogenomic responses.

Isoniazid's interactions with other drugs are due primarily to its inhibition of the cytochrome P450 system. Among the drugs with significant isoniazid interactions are warfarin, carbamazepine, benzodiazepines, acetaminophen, clopidogrel, maraviroc, dronedarone, salmeterol, tamoxifen, eplerenone, and phenytoin.

DOSING The recommended daily dose of isoniazid for the treatment of TB in the United States is 5 mg/kg for adults and 10–20 mg/kg for children, with a maximal daily dose of 300 mg for both. For intermittent therapy in adults (usually twice per week), the dose is 15 mg/kg, with a maximal daily dose of 900 mg. Isoniazid does not require dosage adjustment in patients with renal disease. When the 12-dose, 3-month weekly LTBI regimen is used, the dose of isoniazid is 15 mg/kg, with a maximal dose of 900 mg, and the drug is coadministered with rifapentine.

RESISTANCE Although isoniazid, along with rifampin, is the mainstay of TB treatment regimens, ~7% of clinical *M. tuberculosis* isolates in the United States are resistant. Rates of primary isoniazid resistance among untreated patients are significantly higher in many populations born outside the United States. Five separate pathways for isoniazid resistance have been elucidated. Most strains have amino acid changes in either the catalase-peroxidase gene (*katG*) or the mycobacterial ketoenoylreductase gene (*inhA*). Less frequently, alterations in *kasA*, the gene for an enzyme involved in mycolic acid elongation, and loss of NADH dehydrogenase 2 activity confers isoniazid resistance. In 20–30% of isoniazid-resistant *M. tuberculosis* isolates, increased expression of efflux pump genes, such as *efpA*, *mmpL7*, *mmr*, *p55*, and the Tap-like gene *Rv1258c*, has been implicated as the underlying mechanism of resistance.

ADVERSE EFFECTS Although isoniazid is generally well tolerated, drug-induced liver injury and peripheral neuropathy are significant adverse effects associated with this agent. Isoniazid may cause asymptomatic transient elevation of aminotransferase levels (often termed *hepatic adaptation*) in up to 20% of recipients. Other adverse reactions include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus–like syndrome, optic atrophy, seizures, and psychiatric symptoms. Symptomatic hepatitis occurs in fewer than 0.1% of persons treated with isoniazid alone for LTBI, and fulminant hepatitis with hepatic failure occurs in fewer than 0.01%. Isoniazid-associated hepatitis is idiosyncratic, but its incidence increases with age, with daily alcohol consumption, and in women who are within 3 months postpartum.

In patients who have liver disorders or HIV infection, who are pregnant or in the 3-month postpartum period, who have a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), who use alcohol regularly, who have multiple medical problems, or who

have other risk factors for chronic liver disease, the risks and benefits of treatment for LTBI should be weighed. If treatment is undertaken, these patients should have serum concentrations of ALT determined at baseline. Routine baseline hepatic ALT testing based solely on an age of >35 years is optional and depends on individual concerns. Monthly biochemical monitoring during isoniazid treatment is indicated for patients whose baseline liver function tests yield abnormal results and for persons at risk for hepatic disease, including the groups just mentioned. Guidelines recommend that isoniazid be discontinued in the presence of hepatitis symptoms or jaundice and an ALT level three times the upper limit of normal or in the absence of symptoms with an ALT level five times the upper limit of normal (Table 176-3).

Peripheral neuropathy associated with isoniazid occurs in up to 2% of patients given 5 mg/kg. Isoniazid appears to interfere with pyridoxine (vitamin B_6) metabolism. The risk of isoniazid-related neurotoxicity is greatest for patients with preexisting disorders that also pose a risk of neuropathy, such as HIV infection; for those with diabetes mellitus, alcohol abuse, or malnutrition; and for those simultaneously receiving other potentially neuropathic medications, such as stavudine. These patients should be given prophylactic pyridoxine (25–50 mg/d).

Rifampin Rifampin is a semisynthetic derivative of *Amycolatopsis rifamycinica* (formerly known as *Streptomyces mediterranei*). The most active antimycobacterial agent available, rifampin is the keystone of first-line treatment for TB. Introduced in 1968, this drug eventually permitted dramatic shortening of the TB treatment course. Rifampin has both sterilizing and bactericidal activity against dividing and nondividing *M. tuberculosis*. The drug is also active against an array of other organisms, including some gram-positive and gram-negative bacteria, *Legionella*, *M. kansasii*, and *Mycobacterium marinum*.

Rifampin, administered for 4 months, is also an alternative agent to isoniazid for the treatment of LTBI, although efficacy data are scant at this time. A 3-month course of rifampin alone has been found to be similar in efficacy to a 6-month course of isoniazid. Although the efficacy of the 4-month regimen of rifampin is still under study, comparison of this regimen with 9 months of isoniazid in randomized safety and tolerability studies suggests fewer adverse events, including hepatotoxicity; less treatment interruption; a higher completion rate; and greater cost-effectiveness with the rifampin regimen.

MECHANISM OF ACTION Rifampin exerts both intracellular and extracellular bactericidal activities. Like other rifamycins, rifampin specifically binds to and inhibits mycobacterial DNA-dependent RNA polymerase, blocking RNA synthesis. Susceptible strains of *M. tuberculosis* as well as *M. kansasii* and *M. marinum* are inhibited by rifampin concentrations of 1 μg/mL.

PHARMACOLOGY Rifampin is a fat-soluble, complex macrocyclic molecule readily absorbed after oral administration. Serum levels of 10–20 μg/mL are achieved 2.5 h after the usual adult oral dose of 10 mg/kg (given without food). Rifampin has a half-life of 1.5–5 h. The drug distributes well throughout most body tissues, including CSF. Rifampin turns body fluids such as urine, saliva, sputum, and tears a reddish-orange color—an effect that offers a simple means of assessing patients' adherence to this medication. Rifampin is excreted primarily through the bile and enters the enterohepatic circulation; <30% of a dose is renally excreted.

As a potent inducer of the hepatic cytochrome P450 system, rifampin can decrease the half-life of some drugs, such as digoxin, warfarin, phenytoin, prednisone, cyclosporine, methadone, oral contraceptives, clarithromycin, azole antifungal agents, quinidine, antiretroviral protease inhibitors, and non-nucleoside reverse transcriptase inhibitors. The Centers for Disease Control and Prevention (CDC) has issued guidelines for the management of drug interactions during treatment of HIV and *M. tuberculosis* co-infection *(www.cdc.gov/tb/)*.

DOSING The daily dosage of rifampin is 10 mg/kg for adults and 10–20 mg/kg for children, with a maximum of 600 mg/d for both. The drug is given once daily, twice weekly, or three times weekly. No adjustments of dose or frequency are necessary in patients with renal insufficiency.

RESISTANCE Resistance to rifampin in *M. tuberculosis, Mycobacterium leprae*, and other organisms is the consequence of spontaneous, mostly missense point mutations in a core region of the bacterial gene coding for the β subunit of RNA polymerase (*rpoB*). RNA polymerase altered in this manner is no longer subject to inhibition by rifampin. Most rapidly and slowly growing NTM harbor intrinsic resistance to rifampin, for which the mechanism has yet to be determined.

ADVERSE EFFECTS Adverse events associated with rifampin are infrequent and generally mild. Hepatotoxicity due to rifampin alone is uncommon in the absence of preexisting liver disease and often consists of isolated hyperbilirubinemia rather than aminotransferase elevation. Other adverse reactions include rash, pruritus, gastrointestinal symptoms, and pancytopenia. Rarely, a hypersensitivity reaction may occur with intermittent therapy, manifesting as fever, chills, malaise, rash, and—in some instances—renal and hepatic failure.

Ethambutol Ethambutol is a bacteriostatic antimycobacterial agent first synthesized in 1961. A component of the standard first-line regimen, ethambutol provides synergy with the other drugs in the regimen and is generally well tolerated. Susceptible species include *M. tuberculosis, M. marinum, M. kansasii*, and organisms of the *Mycobacterium avium* complex (MAC); however, among first-line drugs, ethambutol is the least potent against *M. tuberculosis*. This agent is also used in combination with other agents in the continuation phase of treatment when patients cannot tolerate isoniazid or rifampin or are infected with organisms resistant to either of the latter drugs.

MECHANISM OF ACTION Ethambutol is bacteriostatic against *M. tuberculosis*. Its primary mechanism of action is the inhibition of the arabinosyltransferases involved in cell wall synthesis, which probably inhibits the formation of arabinogalactan and lipoarabinomannan. The MIC of ethambutol for susceptible strains of *M. tuberculosis* is 0.5–2 μg/mL.

PHARMACOLOGY AND DOSING From a single dose of ethambutol, 75–80% is absorbed within 2–4 h of administration. Serum levels peak at 2–4 μg/mL after the standard adult daily dose of 15 mg/kg. Ethambutol is well distributed throughout the body except in the CSF; a dosage of 25 mg/kg is necessary for attainment of a CSF level half of that in serum. For intermittent therapy, the dosage is 25–35 mg/kg thrice weekly. To prevent toxicity, the dosage must be lowered and the frequency of administration reduced for patients with renal insufficiency.

ADVERSE EFFECTS Ethambutol is usually well tolerated and has no significant interactions with other drugs. Optic neuritis, the most serious adverse effect reported, typically presents as reduced visual acuity, central scotoma, and loss of the ability to see green (or, less commonly, red). The cause of this neuritis is unknown, but it may be due to an effect of ethambutol on the amacrine and bipolar cells of the retina. Symptoms typically develop several months after initiation of therapy, but ocular toxicity soon after initiation of ethambutol has been described. The risk of ocular toxicity is dose dependent, with occurrence in 1–5% of patients, and can be increased by renal insufficiency. The routine use of ethambutol in younger children is not recommended because monitoring for visual complications can be difficult. If drug-resistant TB is suspected, ethambutol can be used for treatment of children.

All patients starting therapy with ethambutol should have a baseline test for visual acuity, visual fields, and color vision and should undergo an examination of the optic fundus. Visual acuity and color vision should be monitored monthly or less often as needed. Cessation of ethambutol in response to early symptoms of ocular toxicity usually results in reversal of the deficit within several months. Recovery of all visual function may take up to 1 year. In the elderly and in patients whose symptoms are not recognized early, deficits may be permanent. Some experts think that supplementation with hydroxycobalamin (vitamin B_{12}) is beneficial for patients with ethambutol-related ocular toxicity. Other adverse effects of ethambutol are rare. Peripheral sensory neuropathy occurs in rare instances.

RESISTANCE Ethambutol resistance in *M. tuberculosis* and NTM is associated primarily with missense mutations in the *embB* gene that

encodes for arabinosyltransferase. Mutations have been found in resistant strains at codon 306 in 50–70% of cases. Mutations at *embB*306 can cause significantly increased MICs of ethambutol, resulting in clinical resistance.

Pyrazinamide A nicotinamide analog, pyrazinamide is an important bactericidal drug used in the initial phase of TB treatment. Its administration for the first 2 months of therapy with rifampin and isoniazid allows treatment duration to be shortened from 9 to 6 months and decreases rates of relapse.

MECHANISM OF ACTION Pyrazinamide's antimycobacterial activity is essentially limited to *M. tuberculosis*. The drug is more active against slowly replicating organisms than against actively replicating organisms. Pyrazinamide is a prodrug that is converted by the mycobacterial pyrimidase to the active form, pyrazinoic acid (POA). This agent is active only in acidic environments (pH <6.0), as are found within phagocytes or granulomas. The exact mechanism of action of POA is unclear, but fatty acid synthetase I may be the primary target in *M. tuberculosis*. Susceptible strains of *M. tuberculosis* are inhibited by pyrazinamide concentrations of 16–50 μg/mL at pH 5.5.

PHARMACOLOGY AND DOSING Pyrazinamide is well absorbed after oral administration, with peak serum concentrations of 20–60 μg/mL at 1–2 h after ingestion of the recommended adult daily dose of 15–30 mg/kg (maximum, 2 g/d). It distributes well to various body compartments, including CSF, and is an important component of treatment for tuberculous meningitis. The serum half-life of the drug is 9–11 h with normal renal and hepatic function. Pyrazinamide is metabolized in the liver to POA, 5-hydroxypyrazinamide, and 5-hydroxy-POA. A high proportion of pyrazinamide and its metabolites (~70%) is excreted in the urine. The dosage must be adjusted according to the level of renal function in patients with reduced creatinine clearance.

ADVERSE EFFECTS At the higher dosages used previously, hepatotoxicity was seen in as many as 15% of patients treated with pyrazinamide. However, at the currently recommended dosages, hepatotoxicity now occurs less commonly when this drug is administered with isoniazid and rifampin during the treatment of TB. Older age, active liver disease, HIV infection, and low albumin levels may increase the risk of hepatotoxicity. The use of pyrazinamide with rifampin for the treatment of LTBI is no longer recommended because of unacceptable rates of hepatotoxicity and death in this setting. Hyperuricemia is a common adverse effect of pyrazinamide therapy that usually can be managed conservatively. Clinical gout is rare.

Although pyrazinamide is recommended by international TB organizations for routine use in pregnancy, it is not recommended in the United States because of inadequate teratogenicity data.

RESISTANCE The basis of pyrazinamide resistance in *M. tuberculosis* is a mutation in the *pncA* gene coding for pyrazinamidase, the enzyme that converts the prodrug to active POA. Resistance to pyrazinamide is associated with loss of pyrazinamidase activity, which prevents conversion of pyrazinamide to POA. Of pyrazinamide-resistant *M. tuberculosis* isolates, 72–98% have mutations in *pncA*. Conventional methods of testing for susceptibility to pyrazinamide may produce both false-negative and false-positive results because the high-acidity environment required for the drug's activation also inhibits the growth of *M. tuberculosis*. There is some controversy as to the clinical significance of in vitro pyrazinamide resistance.

OTHER FIRST-LINE DRUGS

Rifabutin Rifabutin, a semisynthetic derivative of rifamycin S, inhibits mycobacterial DNA-dependent RNA polymerase. Rifabutin is recommended in place of rifampin for the treatment of TB in HIV-co-infected individuals who are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors, particularly nevirapine. A recent study in India showed better TB treatment outcomes in HIV-co-infected patients given daily rifabutin plus atazanavir/ritonavir than in those given thrice-weekly rifabutin plus atazanavir/ritonavir. Rifabutin's effect on hepatic enzyme induction is less pronounced than that of rifampin. Protease inhibitors may cause significant increases in rifabutin levels through inhibition of hepatic metabolism. Rifabutin is more active in vitro than rifampin against MAC organisms and other NTM, but its clinical superiority has not been established.

PHARMACOLOGY Like rifampin, rifabutin is lipophilic and is absorbed rapidly after oral administration, reaching peak serum levels 2–4 h after ingestion. Rifabutin distributes best to tissues, reaching levels 5–10 times higher than those in plasma. Unlike rifampin, rifabutin and its metabolites are partially cleared by the hepatic microsomal system. Rifabutin's slow clearance results in a mean serum half-life of 45 h—much longer than the 3- to 5-h half-life of rifampin. Clarithromycin (but not azithromycin) and fluconazole appear to increase rifabutin levels by inhibiting hepatic metabolism.

ADVERSE EFFECTS The most common adverse effects of rifabutin treatment are gastrointestinal; other reactions include rash, headache, asthenia, chest pain, myalgia, and insomnia. Less common adverse reactions include fever, chills, a flu-like syndrome, anterior uveitis, hepatitis, *Clostridium difficile*–associated diarrhea, a diffuse polymyalgia syndrome, and yellow skin discoloration ("pseudo-jaundice"). Laboratory abnormalities include neutropenia, leukopenia, thrombocytopenia, and increased levels of liver enzymes. Rifabutin appears to be better tolerated by the majority (72%) of adult TB patients who have developed rifampin-related adverse effects. Female patients, those co-infected with hepatitis B or hepatitis C, and those with rifampin-related arthralgias, dermatologic reactions, and cholestasis are more likely to develop mild to severe rifabutin-related adverse effects.

RESISTANCE Similar to rifampin resistance, rifabutin resistance is mediated by mutations in *rpoB*.

Rifapentine Rifapentine is a semisynthetic cyclopentyl rifamycin, sharing a mechanism of action with rifampin. Rifapentine is lipophilic and has a prolonged half-life that permits weekly or twice-weekly dosing. Therefore, rifapentine is the subject of intensive clinical investigation aimed at determining optimal dosing and frequency of administration. Currently, it is an alternative to rifampin in the continuation phase of treatment for noncavitary drug-susceptible pulmonary TB in HIV-seronegative patients who have negative sputum smears at completion of the initial phase of treatment. When administered in these specific circumstances, rifapentine (10 mg/kg, up to 600 mg) is given once weekly with isoniazid. Because of higher rates of relapse, this regimen is not recommended for patients with TB disease and HIV co-infection; moreover, it has not been approved for children <12 years of age. In a phase 2 study, substituting daily rifapentine for rifampin yielded higher rates of sputum sterilization after 2 months of intensive treatment. Higher doses of rifapentine (20 mg/kg vs 10 mg/kg) had better results and were safe and well tolerated. Regimens containing high doses of rifapentine are being evaluated to see whether they can shorten the TB treatment course to <6 months.

A large randomized controlled trial demonstrated that, for LTBI, a 12-dose (3-month) regimen of weekly DOT with a weight-based dose of isoniazid and rifapentine was noninferior to daily isoniazid for 9 months. Although the rate of permanent drug discontinuation due to adverse events was higher with rifapentine/isoniazid, this regimen had a higher treatment completion rate than daily isoniazid in this study. The efficacy of this combination regimen in HIV-infected individuals not receiving ART and in children <12 years of age is under study. A recent randomized controlled study of HIV-co-infected patients not receiving ART showed that weekly rifapentine/isoniazid or twice-weekly rifampin/isoniazid for 12 weeks or continuous isoniazid was not superior to 6 months of isoniazid. The regimen is not recommended for pregnant women, for persons with hypersensitivity reactions to isoniazid or rifampin, or for HIV-infected individuals taking ART.

PHARMACOLOGY Rifapentine's absorption is improved when the drug is taken with food. After oral administration, rifapentine reaches peak serum concentrations in 5–6 h and achieves a steady state in 10 days. The half-life of rifapentine and its active metabolite, 25-desacetyl rifapentine, is ~13 h. The administered dose is excreted via the liver (70%).

ADVERSE EFFECTS The adverse-effects profile of rifapentine is similar to that of other rifamycins. Rifapentine is teratogenic in animal models and is relatively contraindicated in pregnancy.

RESISTANCE Rifapentine resistance is mediated by mutations in *rpoB*. Mutations that cause resistance to rifampin also cause resistance to rifapentine.

Streptomycin Streptomycin was the first antimycobacterial agent used for the treatment of TB. Derived from *Streptomyces griseus*, streptomycin is bactericidal against dividing *M. tuberculosis* organisms but has only low-level early bactericidal activity. This drug is administered only by the IM and IV routes. In developed nations, streptomycin is used infrequently because of its toxicity, the inconvenience of injections, and drug resistance. In developing countries, however, streptomycin is used because of its low cost.

MECHANISM OF ACTION Streptomycin inhibits protein synthesis by binding at a site on the 30S mycobacterial ribosome.

PHARMACOLOGY AND DOSING Serum levels of streptomycin peak at 25–45 µg/mL after a 1-g dose. This agent penetrates poorly into the CSF, reaching levels that are only 20% of serum levels. The usual daily dose of streptomycin (given IM either daily or 5 days per week) is 15 mg/kg for adults and 20–40 mg/kg for children, with a maximum of 1 g/d for both. For patients ≥60 years of age, 10 mg/kg is the recommended daily dose, with a maximum of 750 mg/d. Because streptomycin is eliminated almost exclusively by the kidneys, its use in patients with renal impairment should be avoided or implemented with caution, with lower doses and less frequent administration.

ADVERSE EFFECTS Adverse reactions occur frequently with streptomycin (10–20% of patients). Ototoxicity (primarily vestibulotoxicity), neuropathy, and renal toxicity are the most common and the most serious reactions. Renal toxicity, usually manifested as nonoliguric renal failure, is less common with streptomycin than with other frequently used aminoglycosides, such as gentamicin. Manifestations of vestibular toxicity include loss of balance, vertigo, and tinnitus. Patients receiving streptomycin must be monitored carefully for these adverse effects, undergoing audiometry at baseline and monthly thereafter.

RESISTANCE Spontaneous mutations conferring resistance to streptomycin are relatively common, occurring in 1 in 10^6 organisms. In the two-thirds of streptomycin-resistant *M. tuberculosis* strains exhibiting high-level resistance, mutations have been identified in one of two genes: a 16S rRNA gene (*rrs*) or the gene encoding ribosomal protein S12 (*rpsL*). Both targets are believed to be involved in streptomycin ribosomal binding. However, low-level resistance, which is seen in about one-third of resistant isolates, has no associated resistance mutation. A gene (*gidB*) that confers low-level resistance to streptomycin has been identified. Strains of *M. tuberculosis* resistant to streptomycin generally are not cross-resistant to capreomycin or amikacin. Streptomycin is not used for the treatment of MDR-TB or XDR-TB because of (1) the high prevalence of streptomycin resistance among strains resistant to isoniazid and (2) the unreliability of drug susceptibility testing.

SECOND-LINE ANTITUBERCULOSIS DRUGS

Second-line anti-TB agents are indicated for treatment of drug-resistant TB, for patients who are intolerant or allergic to first-line agents, and when first-line supplemental agents are unavailable.

Fluoroquinolones Fluoroquinolones inhibit mycobacterial DNA gyrase and topoisomerase IV, preventing cell replication and protein synthesis, and are bactericidal. They are also being investigated for their potential to shorten the course of treatment for TB. A single randomized trial showed that a regimen of daily moxifloxacin/rifampin/pyrazinamide/ethambutol for 2 months followed by once-weekly 1200 mg rifapentine plus 400 mg of moxifloxacin for 4 continuation-phase months was associated with relapse rates similar to those documented with the standard 6-month regimen given daily in patients with drug-sensitive TB. Gatifloxacin has fallen out of favor because of significant dysglycemia. Ciprofloxacin and ofloxacin are no longer recommended for the treatment of TB because of poor efficacy. Despite documented resistance to early-generation fluoroquinolones (e.g., ofloxacin and ciprofloxacin), use of a later-generation fluoroquinolone in patients with XDR-TB has been associated with favorable outcomes. Fluoroquinolones are also considered safe alternatives for patients who develop treatment-limiting adverse effects from first-line agents. Levofloxacin and moxifloxacin have both been used effectively in the treatment of MDR-TB. The optimal dose of levofloxacin for this indication is being actively studied, but doses of at least 750 mg are commonly used.

The fluoroquinolones are well absorbed orally, reach high serum levels, and distribute well into body tissues and fluids. Their absorption is decreased by co-ingestion with products containing multivalent cations, such as antacids. Adverse effects are relatively infrequent (0.5–10% of patients) and include gastrointestinal intolerance, rashes, dizziness, and headache. Most studies of fluoroquinolone side effects have been based on relatively short-term administration for bacterial infections, but trials have now shown the relative safety and tolerability of fluoroquinolones administered for months during TB treatment in adults. Although the potential to prolong the QTc interval, leading to cardiac arrhythmias, has been a source of concern with fluoroquinolones, cessation of treatment due to this adverse effect is rare. Because the benefits may outweigh the risks in treatment of drug-resistant TB, there is increasing interest in the use of fluoroquinolones in children, which has traditionally been avoided because of the risks of tendon rupture and cartilage damage.

Multiple courses of empirical fluoroquinolone therapy for presumed community-acquired pneumonia are associated with delayed diagnosis of active pulmonary TB and increased fluoroquinolone resistance in *M. tuberculosis*. Mutations in the genes encoding for DNA gyrase (*gyrA* and *gyrB*) are implicated in the majority of cases—but not all cases—of clinical resistance to fluoroquinolones.

Injectable Drugs • **CAPREOMYCIN** Capreomycin, a cyclic peptide antibiotic derived from *Streptomyces capreolus*, is an important second-line agent used for treatment of MDR-TB and XDR-TB. Capreomycin is administered by the IM route; an inhaled preparation is under study. A dose of 15 mg/kg per day is given five to seven times per week (maximal daily dose, 1 g) and results in peak blood levels of 20–40 µg/mL. The dosage may be reduced to 1 g two or three times per week 2–4 months after mycobacterial cultures become negative. For individuals ≥60 years of age, the dose should be reduced to 10 mg/kg per day (maximal daily dose, 750 mg). For patients with renal insufficiency, the drug should be given intermittently and at lower dosage (12–15 mg/kg two or three times per week). A minimal duration of 3 months is recommended for MDR-TB treatment. Penetration of capreomycin into the CSF is believed to be poor.

The mechanism of capreomycin's action is not well understood but involves interference with the mycobacterial ribosome and inhibition of protein synthesis. Resistance to capreomycin is associated with mutations that inactivate a ribosomal methylase (*tlyA*) or that encode genes for the 16S ribosomal subunit (*rrs*). Cross-resistance to kanamycin and amikacin is common with *rrs* but not always with *tylA* mutations. The *rrs* A1401G mutation is now considered a strong predictor of cross-resistance among all three second-line injectable drugs: capreomycin, kanamycin, and amikacin.

Adverse effects of capreomycin are relatively common. Significant hypokalemia and hypomagnesemia as well as oto- and renal toxicity have been reported.

AMIKACIN AND KANAMYCIN Amikacin and kanamycin are aminoglycosides that exert mycobactericidal activity by binding to the 16S ribosomal subunit. The spectrum of antibiotic activity for amikacin and kanamycin includes *M. tuberculosis*, several NTM species, and aerobic gram-negative and gram-positive bacteria. Although amikacin is highly active against *M. tuberculosis*, it is used only infrequently because of its significant side effects. The usual daily adult dosage of both amikacin and kanamycin is 15–30 mg/kg given IM or IV (maximal daily dose, 1 g), with a reduction to 10 mg/kg for patients ≥60 years old. For patients with renal insufficiency, the dose and frequency should be reduced (12–15 mg/kg two or three times per week). Mycobacterial resistance is due to mutations in the genes encoding the

16S ribosomal RNA gene. Cross-resistance among kanamycin, amikacin, and capreomycin is common. Isolates resistant to streptomycin are frequently susceptible to amikacin or kanamycin. Adverse effects of amikacin include ototoxicity (in up to 10% of recipients, with auditory dysfunction occurring more commonly than vestibulotoxicity), nephrotoxicity, and neurotoxicity. Kanamycin has a similar side-effects profile, but adverse reactions are thought to be less frequent and less severe.

Other Second-Line Agents • **ETHIONAMIDE** Ethionamide is a derivative of isonicotinic acid. Its mechanism of action is through inhibition of the *inhA* gene product enoyl–acyl carrier protein (acp) reductase, which is involved in mycolic acid synthesis. Ethionamide is bacteriostatic against metabolically active *M. tuberculosis* and some NTM. It is used in the treatment of drug-resistant TB, but its use is limited by severe gastrointestinal reactions (including abdominal pain, nausea, and vomiting) as well as significant central and peripheral neurologic side effects, reversible hepatitis (in ~5% of recipients), hypersensitivity reactions, and hypothyroidism. Ethionamide should be taken with food to reduce gastrointestinal effects and with pyridoxine (50–100 mg/d) to limit neuropathic side effects.

CYCLOSERINE Cycloserine is an analog of the amino acid D-alanine and prevents bacterial cell-wall synthesis. It inhibits the action of enzymes, including alanine racemase, that are involved in the production of peptidoglycans. Cycloserine is active against a range of bacteria, including *M. tuberculosis*. Mechanisms of mycobacterial resistance are not well understood, but overexpression of alanine racemase can confer resistance in *Mycobacterium smegmatis*. Cycloserine is well absorbed after oral administration and is widely distributed throughout body fluids, including CSF. The usual adult dosage is 250 mg two or three times per day. Serious potential side effects include seizures and psychosis (with suicide in some cases), peripheral neuropathy, headache, somnolence, and allergic reactions. Drug levels are monitored to achieve optimal dosing and to reduce the risk of adverse effects, especially in patients with renal failure. Cycloserine should be administered as DOT only with caution and with support from experienced TB physicians to patients with epilepsy, active alcohol abuse, severe renal insufficiency, or a history of depression or psychosis.

PARA-AMINOSALICYLIC ACID Para-aminosalicylic acid (PAS, 4-aminosalicylic acid) is an oral agent used in the treatment of MDR-TB and XDR-TB. Its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti-TB agent. Adverse effects may include high-level nausea, vomiting, and diarrhea. PAS may cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. The drug should be taken with acidic foods to improve absorption. Enteric-coated PAS granules (4 g orally every 8 h) appear to be better tolerated than other formulations and produce higher therapeutic blood levels. PAS has a short half-life (1 h), and 80% of the dose is excreted in the urine.

CLOFAZIMINE Clofazimine is a fat-soluble riminophenazine dye used primarily in the treatment of leprosy worldwide. It is currently gaining popularity in the management of MDR-TB and XDR-TB because of its low cost and its intracellular and extracellular activity. By increasing reactive oxidant species and causing membrane destabilization, clofazimine may promote killing of antibiotic-tolerant *M. tuberculosis* persister organisms. In addition to antimicrobial activity, the drug has other pharmacologic activities, such as anti-inflammatory, pro-oxidative, and immunopharmacologic properties. Clofazimine has a half-life of ~70 days in humans, and average steady-state concentrations are achieved at ~1 month. Intake with fatty meals can improve its low and variable rates of absorption (45–62%). Common side effects include gastrointestinal intolerance, and reversible orange to brownish discoloration of skin, bodily fluids, and secretions. Dose adjustment may be necessary in patients with severe hepatic impairment. Clofazimine is being studied as part of a regimen developed in Bangladesh (Table 176-4) for potential shortening of the MDR-TB treatment course. A meta-analysis suggested that inclusion of clofazimine in a multidrug regimen for treatment of MDR-TB was associated with a favorable outcome. Newer analogues with improved pharmacokinetics and alternative formulations of clofazimine (liposomal, nanosuspension, inhalational) are being studied.

NEWER ANTITUBERCULOSIS DRUGS

Oxazolidinones Linezolid is an oxazolidinone used primarily for the treatment of drug-resistant gram-positive bacterial infections. However, this drug is active in vitro against *M. tuberculosis* and NTM. Several case series have suggested that linezolid may help clear mycobacteria relatively rapidly when included in a regimen for the treatment of complex cases of MDR-TB and XDR-TB. Linezolid's mechanism of action is disruption of protein synthesis by binding to the 50S bacterial ribosome. Linezolid has nearly 100% oral bioavailability, with good penetration into tissues and fluids, including CSF. Clinical resistance to linezolid has been reported and is typically associated with mutations in the 23S rRNA and in two ribosomal proteins, L3 (*rplC*) and L4 (*rplD*). Adverse effects may include optic and peripheral neuropathy, pancytopenia, and lactic acidosis and are usually associated with higher doses. Linezolid is a weak monoamine oxidase inhibitor and can be associated with the serotonin syndrome when given concomitantly with serotonergic drugs (primarily antidepressants such as selective serotonin-reuptake inhibitors). It has been shown that ~80% of patients with MDR-TB or XDR-TB can be successfully treated with linezolid-containing, individualized anti-TB regimens based on drug sensitivity testing. Replacement of ethambutol with linezolid for 2–4 weeks during the intensive phase of treatment of drug-susceptible TB is currently being evaluated for possible faster sputum conversion and a shorter treatment regimen. For MDR-TB treatment, linezolid is usually administered at a dose of 600 mg (or less in some cases) once daily, which appears to be effective. A single daily dose is associated with fewer adverse events than twice-a-day dosing.

PNU 100480 and AZD 5847, modified versions of oxazolidinones and protein synthesis inhibitors, are undergoing phase 1 trials and appear to have greater efficacy than linezolid against *M. tuberculosis*. However, the adverse-effects profile of these compounds compared with that of linezolid needs further investigation.

Amoxicillin-Clavulanate and Carbapenems β-Lactam agents are largely ineffective for the treatment of *M. tuberculosis* because of resistance conferred by a hydrolyzing class A β-lactamase. Because clavulanate may theoretically inhibit the β-lactamase, amoxicillin-clavulanate has been used in the treatment of MDR-TB; however, it is a comparatively weak agent. Carbapenems are poor substrates for class A β-lactamases found in *M. tuberculosis*. Accordingly, meropenem and imipenem have in vitro activity against *M. tuberculosis*, and their use to treat MDR-TB and XDR-TB has been reported anecdotally. Nevertheless, the need to administer these carbapenems intravenously and the lack of information on the drugs' long-term side effects have restricted their use to certain severe cases only. A newer agent, faropenem, has high oral bioavailability, is more resistant to hydrolysis by β-lactamases, and causes fewer adverse reactions. It is being evaluated in combination with linezolid and moxifloxacin as a first-line therapy for drug-resistant and drug-susceptible TB in children.

Diarylquinolines Bedaquiline (TMC207 or R207910) is a new diarylquinoline with a novel mechanism of action: inhibition of the mycobacterial ATP synthetase proton pump. Bedaquiline is bactericidal for drug-susceptible and MDR strains of *M. tuberculosis*. Resistance has been reported and is due to point mutations in the *atpE* gene encoding for subunit c of ATP synthetase. A phase 2 randomized controlled clinical trial in MDR-TB patients demonstrated substantial improvement in 2-month culture-conversion rates as well as a reduction in acquired resistance to companion drugs. This drug is metabolized by the hepatic cytochrome CYP3A4. Rifampin lowers bedaquiline levels by 50%, and protease inhibitors also interact significantly with this drug. Because efavirenz induces CYP3A4, there is concern about lower bedaquiline levels with coadministration. In a study of co-treatment with bedaquiline and efavirenz in healthy volunteers, bedaquiline levels were reduced by only 20%; however, in a study modeling chronic coadministration of these two drugs, the reduction in bedaquiline levels was

estimated to be 50%, leading many national TB programs to avoid efavirenz coadministration with bedaquiline.

The oral bioavailability of bedaquiline appears to be excellent. The dosage is 400 mg/d for the first 2 weeks and then 200 mg thrice weekly. The elimination half-life is long (>14 days). A single dose of this drug can inhibit the growth of *M. tuberculosis* for up to 1 week through a combination of long plasma half-life, high-level tissue penetration, and long tissue half-life. Bedaquiline added to a background regimen improved the 2-month sputum culture–conversion rate in multicenter, randomized placebo-controlled trials, and these results led to approval by the U.S. Food and Drug Administration (FDA). However, the death rate in one trial was higher in the bedaquiline arm than in the control arm (11.4% vs 2.5%); the result was a "black box" warning from the FDA, which also included QT prolongation. The CDC has made a provisional recommendation for the use of bedaquiline for 24 weeks in adults with laboratory-confirmed pulmonary MDR-TB when no other effective treatment regimen can be provided.

Nitroimidazoles The prodrugs delamanid (OPC-67683) and PA 824 are novel nitro-dihydro-imidazooxazole derivatives that are activated by *M. tuberculosis*–specific flavin-dependent nitroreductases and whose antimycobacterial activity is attributable to inhibition of mycolic acid biosynthesis. These drugs are currently in phase 2 clinical trials and show potential in shortening treatment duration through their activity against nonreplicating drug-susceptible and drug-resistant mycobacteria. Delamanid was shown in a randomized, placebo-controlled, multinational clinical trial to significantly improve the culture-conversion rate at 2 months. QT prolongation occurred significantly more often in delamanid-treated patients, but no clinically relevant events were reported.

Diamines SQ109, an ethambutol analogue with a 1,2-diamine pharmacophore, is the most promising of the diamines for TB treatment. It is activated by mycobacterial cytochrome enzymes and inhibits mycobacterial cell-wall synthesis by an unknown mechanism. It has a high tissue protein-binding capacity with a very long half-life (~61 h) in humans. In vitro studies have demonstrated that SQ109 has low MICs against both susceptible and resistant *M. tuberculosis* strains as well as a synergistic effect when administered with isoniazid and rifampin. The drug is in clinical trials for TB treatment.

Pyrroles LL3858, a pyrrole derivative, has entered clinical trials examining its utility in the treatment of drug-susceptible and drug-resistant TB. The drug's mechanism of action is unknown. However, because it is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs, its target is thought to differ from those of currently used drugs.

NONTUBERCULOUS MYCOBACTERIA

More than 150 species of NTM have been identified. Only a minority of these environmental organisms, which are extensively found in soil and water, are important human pathogens. NTM cause extensive disease primarily in persons with preexisting pulmonary disease or immunocompromise but can also cause nodular/bronchiectatic disease in otherwise seemingly healthy hosts. Disseminated infections with NTM are common in immunocompromised individuals. NTM are also important causes of skin and soft-tissue infections in surgical settings. The two major classes of NTM are the slow-growing and rapidly growing species; subcultures of the latter grow within 1 week. The growth characteristics of NTM have diagnostic, therapeutic, and prognostic implications. The rate of growth can provide useful preliminary information within a specific clinical context, in that growth within 2–3 weeks is much more likely to indicate an NTM than *M. tuberculosis*. When NTM do grow from cultures, colonization should be distinguished from active disease in order to optimize the risk and benefit of prolonged treatment with multiple medications. According to the recommendations of the American Thoracic Society and the Infectious Diseases Society of America, significant clinical manifestations and/or radiographic evidence of progressive disease consistent with NTM infection as well as either reproducible sputum culture results or a single positive culture are required for the diagnosis of NTM pulmonary disease. Isolation of NTM from blood or from an infected-appearing extrapulmonary site, such as soft tissue or bone, is usually indicative of disseminated or local NTM infection (Chap. 175). Treatment of NTM disease is prolonged and requires multiple medications. Side effects of the regimens employed are common, and intermittent therapy is often used to mitigate these adverse events. Treatment regimens depend on the NTM species, the extent or type of disease, and—to some degree—drug susceptibility test results.

THERAPEUTIC CONSIDERATIONS FOR SPECIFIC NTM

Slowly Growing Mycobacteria Slowly growing mycobacteria can be divided into three categories based on their pigment-producing capabilities and—if they do produce pigment—their requirement for light to do so. *Photochromogens*, including *M. marinum* and *M. kansasii*, can produce yellowish-orange pigment only when exposed to light. *Scotochromogens*, including *Mycobacterium gordonae* and *Mycobacterium scrofulaceum*, can make pigment regardless of light exposure. MAC organisms and *Mycobacterium ulcerans* are *nonchromogens*—i.e., are incapable of making pigment irrespective of light exposure.

***MYCOBACTERIUM AVIUM* COMPLEX** Among the NTM, MAC organisms most commonly cause human disease. In immunocompetent hosts, MAC species are most often found in conjunction with underlying significant lung disease, such as chronic obstructive pulmonary disease or bronchiectasis. For patients with nodular or bronchiectatic MAC lung disease, an initial regimen consisting of clarithromycin or azithromycin, rifampin or rifabutin (the latter is preferred for HIV patients receiving ART), and ethambutol is given three times per week. A daily regimen of these three drugs, with consideration of amikacin or streptomycin in the initial treatment phase, is recommended for patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease. Routine initial testing for macrolide resistance is recommended, as is testing at 6 months with a failing regimen (i.e., with cultures persistently positive for NTM).

In immunocompromised individuals, disseminated MAC infection is generally treated with clarithromycin, ethambutol, and rifabutin. Azithromycin may be substituted in patients unable to tolerate clarithromycin. Amikacin and fluoroquinolones are often used in salvage regimens. Treatment for disseminated MAC infection in AIDS patients may be lifelong in the absence of immune reconstitution. Therapy is recommended for at least 12 months after culture conversion and at least 6 months of effective immune reconstitution with ART (CD4+ T cell count, >100/μL).

Surgical resection should be considered for individuals whose infection is localized to one lung, who have adequate lung function to tolerate lung resection, who have had a poor response to medical therapy, and/or who have developed macrolide-resistant MAC disease.

MYCOBACTERIUM KANSASII *M. kansasii* is the second most common NTM causing human disease. It is also the second most common cause of NTM pulmonary disease in the United States, where it is most commonly reported in the southeastern region. *M. kansasii* infection can be treated with isoniazid, rifampin, and ethambutol; therapy continues for at least 18 months or for 12 months after culture conversion. The American Thoracic Society and the Infectious Diseases Society of America recommend routine susceptibility testing to rifampin only. Resistance to isoniazid and ethambutol can be acquired during therapy but is usually associated with rifampin resistance as well. Rifampin-resistant *M. kansasii* is treated with a three-drug regimen of second-line agents such as clarithromycin, ethambutol, rifabutin, ciprofloxacin, amikacin, trimethoprim-sulfamethoxazole, and streptomycin after drug susceptibility testing.

MYCOBACTERIUM MARINUM *M. marinum* is an NTM found in salt water and freshwater, including swimming pools and fish tanks. It is a cause of localized soft-tissue infections, which may require surgical management. Combination regimens include clarithromycin and either ethambutol or rifampin. Other agents with activity against *M. marinum* include doxycycline, minocycline, and trimethoprim-sulfamethoxazole.

Drug susceptibility testing is recommended only if the sputum remains culture positive after 3 months of appropriate therapy.

Rapidly Growing Mycobacteria Rapidly growing mycobacteria causing human disease include *Mycobacterium abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae*. Treatment of these mycobacteria is complex and should be undertaken with input from experienced clinicians. It is important to note that testing rapidly growing mycobacteria for macrolide resistance is tricky, as an inducible *erm* gene may confer in vivo macrolide resistance to isolates that are susceptible in vitro.

M. abscessus is the third most common NTM pathogen in the United States. It is endemic in the southeastern states between Texas and Florida. Skin, soft tissue, and bone infections occur, usually after accidental trauma or surgery. This organism appears to have a predilection to cause lung infections in white nonsmoking women aged >60 who have no preexisting lung disease. *M. abscessus* isolates are usually resistant to standard anti-TB regimens. Skin and soft tissue infections are usually treated for a minimum of 4 months with a macrolide (clarithromycin or azithromycin) and a parenteral agent such as amikacin, cefoxitin, or imipenem. Bone infections are treated for at least 6 months. This regimen can be used for the treatment of lung infections but is often unsuccessful because of drug adverse effects and toxicities. A regimen comprising a combination of parenteral drugs is recommended on the basis of in vitro drug susceptibility testing. Surgical resection should be considered in all patients with good lung reserve and a localized infection.

DRUGS FOR THE TREATMENT OF NTM

Clarithromycin Clarithromycin is a macrolide antibiotic with broad activity against many gram-positive and gram-negative bacteria as well as NTM. This drug is active against MAC organisms and many other NTM species, inhibiting protein synthesis by binding to the 50S mycobacterial ribosomal subunit. NTM resistance to macrolides is probably caused by overexpression of the gene *ermB*, with consequent methylation of the binding site. Clarithromycin is well absorbed orally and distributes well to tissues. It is cleared both hepatically and renally; the dosage should be reduced in renal insufficiency. Clarithromycin is a substrate for and inhibits cytochrome 3A4 and should not be administered with cisapride, pimozide, or terfenadine because cardiac arrhythmias may occur. Numerous drugs interact with clarithromycin through the CYP3A4 metabolic pathway. Rifampin lowers clarithromycin levels; conversely, rifampin levels are increased by clarithromycin. However, the clinical relevance of this interaction does not appear to be great.

For patients with nodular/bronchiectatic MAC infection, the dosage of clarithromycin is 500 mg, given morning and evening three times a week. For the treatment of fibrocavitary or severe nodular/bronchiectatic MAC infection, a dose of 500–1000 mg is given daily. Disseminated MAC infection is treated with 1000 mg daily. Clarithromycin is used in combination regimens that typically include ethambutol and a rifamycin in order to avoid the development of macrolide resistance. Adverse effects include frequent gastrointestinal intolerance, hepatotoxicity, headache, rash, and rare instances of hypoglycemia. Clarithromycin is contraindicated during pregnancy because of its teratogenicity in animal models.

Azithromycin Azithromycin is a derivative of erythromycin. Although technically an azalide and not a macrolide, it works similarly to macrolides, inhibiting protein synthesis through binding to the 50S ribosomal subunit. Resistance to azithromycin is almost always associated with complete cross-resistance to clarithromycin. Azithromycin is well absorbed orally, with good tissue penetration and a prolonged half-life (~48 h). The usual dosage for treatment of MAC infection is 250 mg daily or 500 mg three times per week. Azithromycin is used in combination with other agents to avoid the development of resistance. For prophylaxis against disseminated MAC infection in immunocompromised individuals, a dose of 1200 mg once per week is given. Because azithromycin is not metabolized by cytochrome P450, it interacts with few drugs. Adjustment of the dosage on the basis of renal function is not necessary.

Cefoxitin Cefoxitin is a second-generation parenteral cephalosporin with activity against rapidly growing NTM, particularly *M. abscessus* and *M. chelonae*. Its mechanism of action against NTM is unknown but may involve inactivation of cell-wall synthesis enzymes. High doses are used for treatment of NTM: 200 mg/kg IV three or four times per day, with a maximal daily dose of 12 g. The half-life of cefoxitin is ~1 h, with primarily renal clearance that requires adjustment in renal insufficiency. Adverse effects are uncommon but include gastrointestinal manifestations, rash, eosinophilia, fever, and neutropenia.

Newer Drugs Three newer class of drugs—the oxazolidinones, the glycylcyclines, and the ketolides—are currently being evaluated for possible use in the treatment of NTM infections, especially those caused by *M. abscessus*. Approximately 50% of *M. abscessus* isolates have shown some degree of susceptibility in vitro to linezolid, an oxazolidinone. Tigecycline, which is a glycylcycline and a tetracycline derivative, and telithromycin, a ketolide, also appear to have in vitro activity against *M. abscessus*. These drugs, however, have not yet been clinically tested in patients.

In addition, some anti-TB drugs, including clofazimine and bedaquiline, are being evaluated as alternative agents for the treatment of refractory NTM infections. In particular, clofazimine appears to act synergistically in combination with amikacin, bedaquiline, or tigecycline. Inhaled amikacin has a positive symptomatic and microbiologic impact, but its toxicity is still a problem. The exact role of these agents in the treatment of refractory NTM infections remains unclear. Suppressive therapy with periodic parenteral/oral drugs to limit disease progression and control symptoms may be an appropriate alternative to curative treatment.

CONCLUSION

Treatment of mycobacterial infections requires multiple-drug regimens that often exert significant side effects with the potential to limit tolerability. The prolonged duration of treatment has vastly improved results over those obtained in past decades, but drugs and regimens that will shorten treatment duration and limit adverse drug effects and interactions are needed.

FURTHER READING

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Section 9 Spirochetal Diseases

177 Syphilis

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DEFINITION

Syphilis, a chronic systemic infection caused by *Treponema pallidum* subspecies *pallidum*, is usually sexually transmitted and is characterized by episodes of active disease interrupted by periods of latency. After an incubation period averaging 2–6 weeks, a primary lesion appears—often associated with regional lymphadenopathy—and then resolves

without treatment. The secondary stage, with generalized mucosal and cutaneous lesions and generalized lymphadenopathy, is followed by a latent period of subclinical infection lasting years or decades. Central nervous system (CNS) involvement may occur early in infection and may be symptomatic or asymptomatic. In the preantibiotic era, one-third of untreated patients developed tertiary syphilis, characterized by destructive mucocutaneous, skeletal, or parenchymal lesions; aortitis; or late CNS manifestations.

ETIOLOGY

The Spirochaetales include four genera that are pathogenic for humans and for a variety of other animals: *Leptospira* species (leptospirosis, **Chap. 179**); *Borrelia* species (relapsing fever and Lyme disease, **Chaps. 180 and 181**); *Brachyspira* species (gastrointestinal infections); and *Treponema* species (syphilis and the endemic treponematoses; **see also Chap. 178**). The *Treponema* subspecies include *T. pallidum* subsp. *pallidum* (venereal syphilis); *T. pallidum* subsp. *pertenue* (yaws); *T. pallidum* subsp. *endemicum* (endemic syphilis or bejel); and *T. carateum* (pinta). Until recently, the subspecies were distinguished primarily by the clinical syndromes they produce, but molecular signatures can now differentiate the three *T. pallidum* subspecies when assessed by polymerase chain reaction (PCR) or gene sequencing. The crossing of subspecies boundaries by some gene sequence "signatures" in certain strains demonstrates a genetic "continuum" among strains and subspecies of the pathogenic treponemes. Other *Treponema* species found in the human mouth, genital mucosa, and gastrointestinal tract have been associated with disease (e.g., periodontitis), but their role as primary etiologic agents is unclear.

T. pallidum subspecies are thin spiral organisms, with a cell body surrounded by a trilaminar cytoplasmic membrane, a delicate peptidoglycan layer, and a lipid-rich outer membrane. Endoflagella wind around the cell body in the periplasmic space and are responsible for motility.

The *T. pallidum* subspecies cannot be cultured in vitro. Genome sequencing revealed severely limited metabolic capabilities, including a lack of genes required for de novo synthesis of most amino acids, nucleotides, and lipids. Genes encoding enzymes of the Krebs cycle and oxidative phosphorylation are absent. The organisms contain numerous compensatory genes predicted to encode transporters of amino acids, carbohydrates, and lipids. In addition, genome analyses and other studies have revealed the existence of a 12-member gene family (*tpr*) with similarities to variable outer-membrane antigens of other spirochetes. One member, TprK, has discrete variable regions that undergo antigenic variation during infection, providing a mechanism for immune evasion.

The only known natural host for *T. pallidum* subsp. *pallidum* (referred to hereafter as *T. pallidum*) is the human. *T. pallidum* can infect many mammals, but only humans, higher apes, and a few laboratory animals regularly develop syphilitic lesions. Rabbits are used to propagate virulent strains of *T. pallidum* and serve as the animal model that best reflects human disease and immunopathology.

TRANSMISSION AND EPIDEMIOLOGY

Nearly all cases of syphilis are acquired by sexual contact with infectious lesions (i.e., the chancre, mucous patch, skin rash, or condylomata lata; **see Fig. A1-20**). Less common modes of transmission include nonsexual personal contact, infection in utero, blood transfusion, and organ transplantation.

SYPHILIS IN THE UNITED STATES

With the advent of penicillin therapy in the 1940s, the total number of reported cases of syphilis of all stages in the United States declined 95% from 1943 to a low of 31,575 cases in 2000, with <6000 reported cases of infectious primary and secondary (P&S) syphilis. (P&S cases are a better indicator of disease activity than total syphilis cases.) Since 2000, the number of P&S cases has quadrupled, with 23,872 cases reported in 2015 **(Fig. 177-1)**. Nationally, ~90% of these cases were in men who have sex with men (MSM), ~50% of whom are co-infected with HIV (with exact rates varying by geographic location). From 2014 to 2015, P&S cases also rose among all men (19%) and among women (25%), and increases were seen in all geographic regions in the United States.

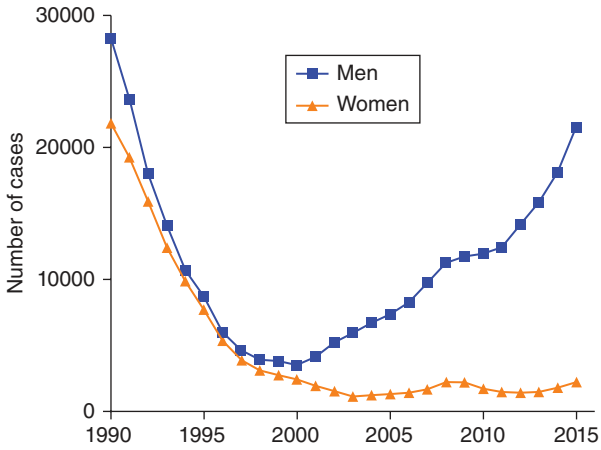

FIGURE 177-1 Primary and secondary syphilis in the United States, 1990–2015, by sex. *(Data from the Centers for Disease Control and Prevention.)*

The incidence of congenital syphilis roughly parallels that of infectious syphilis in women. In 2015, 487 cases in infants <1 year of age were reported, for an increase of 36% in the past 5 years.

The populations at highest risk for acquiring syphilis have changed over time, with outbreaks among MSM in the pre-HIV era of the late 1970s and early 1980s as well as at present. It is speculated that recent increases in syphilis and other sexually transmitted infections in MSM may be due to unprotected sex between persons who are HIV concordant and to disinhibition permitted by highly effective antiretroviral therapies. The syphilis epidemic that peaked in 1990, predominantly among African-American heterosexual men and women, occurred largely in urban areas, where infectious syphilis was correlated with the exchange of sex for crack cocaine. Cases of P&S syphilis among African Americans increased 3.5-fold between 2003 and 2015, and the rate (21.4 per 100,000 population) remains higher than rates for other racial/ethnic groups, even though recent increases have been seen in all racial/ethnic groups.

Of individuals named as sexual contacts of persons with infectious syphilis, many have already developed manifestations of syphilis when they are first seen, and ~30% of asymptomatic contacts examined within 30 days of exposure actually have incubating infection and will later develop infectious syphilis if not treated. Thus, identification and treatment of all recently exposed sexual contacts continue to be important aspects of syphilis control.

GLOBAL SYPHILIS

Syphilis remains a significant health problem globally; the number of new infections is estimated at 11 million per year. The regions that are most affected include sub-Saharan Africa, South America, China, and Southeast Asia. During the past decade, the incidence rate for total syphilis in China reached 30 per 100,000, and rates of infectious syphilis have increased dramatically among MSM in many European countries. Worldwide, there are estimated to be 1.4 million cases of syphilis among pregnant women, with 500,000 adverse pregnancy outcomes annually.

NATURAL COURSE AND PATHOGENESIS OF UNTREATED SYPHILIS

T. pallidum rapidly penetrates intact mucous membranes or microscopic abrasions in skin and, within a few hours, enters the lymphatics and blood to produce systemic infection and metastatic foci long before the appearance of a primary lesion. Blood from a patient with incubating or early syphilis is infectious. The generation time of *T. pallidum* during early active disease in vivo is estimated to be ~30 h, and the incubation period of syphilis is inversely proportional to the number of organisms inoculated. The 50% infectious dose for intradermal inoculation in humans has been calculated to be 57 organisms, and the treponeme concentration generally reaches 10^7/g of tissue before a clinical lesion appears. The median

incubation period in humans (~21 days) suggests an average inoculum of 500–1000 infectious organisms for naturally acquired disease; the incubation period rarely exceeds 6 weeks.

The primary lesion appears at the site of inoculation, usually persists for 4–6 weeks, and then heals spontaneously. Histopathologic examination shows perivascular infiltration, chiefly by CD4+ and CD8+ T lymphocytes, plasma cells, and macrophages, with capillary endothelial proliferation and subsequent obliteration of small blood vessels. The cellular infiltration produces a T_H1-type cytokine profile, consistent with the activation of macrophages. Phagocytosis of opsonized organisms by activated macrophages ultimately causes their destruction, resulting in spontaneous resolution of the chancre.

The generalized parenchymal, constitutional, mucosal, and cutaneous manifestations of secondary syphilis usually appear ~6–12 weeks after infection, although primary and secondary manifestations may occasionally overlap. In contrast, some patients may enter the latent stage without ever recognizing secondary lesions. The histopathologic features of secondary maculopapular skin lesions include hyperkeratosis of the epidermis, capillary proliferation with endothelial swelling in the superficial dermis, dermal papillae with transmigration of polymorphonuclear leukocytes, and—in the deeper dermis—perivascular infiltration by CD8+ T lymphocytes, CD4+ T lymphocytes, macrophages, and plasma cells. Treponemes are found in many tissues, including the aqueous humor of the eye and the cerebrospinal fluid (CSF). *T. pallidum* disseminates during the first weeks of infection, invading many tissues, including the CNS; CSF abnormalities are detected in as many as 40% of patients during the secondary stage. Clinical hepatitis and immune complex–induced glomerulonephritis are relatively rare but are recognized manifestations of secondary syphilis; however, liver function tests reveal the presence of infection and may yield abnormal results in up to one-quarter of cases of early syphilis. Generalized nontender lymphadenopathy is noted in 85% of patients with secondary syphilis. The paradoxical appearance of secondary manifestations, even after the development of an immune response that clears primary lesions, likely results from immune evasion due to antigenic variation of surface antigens. Secondary lesions generally subside within 2–6 weeks, and the infection enters the latent stage, which is detectable only by serologic testing. In the preantibiotic era, up to 25% of untreated patients experienced at least one cutaneous relapse of secondary lesions, usually during the first year. Therefore, identification and examination of sexual contacts are most important for patients with syphilis of <1 year's duration.

In the preantibiotic era, about one-third of patients with untreated latent syphilis developed clinically apparent tertiary disease, the most common types being the gumma (a usually benign granulomatous lesion); cardiovascular syphilis (usually involving the vasa vasorum of the ascending aorta and resulting in aneurysm); and late symptomatic neurosyphilis (tabes dorsalis and paresis). In Western countries today, specific treatment for early and latent syphilis and coincidental therapy (i.e., therapy with antibiotics that are given for other conditions but are active against treponemes) have nearly eliminated tertiary syphilis. Asymptomatic CNS involvement, however, is still demonstrable in up to 40% of persons with early syphilis and 25% of patients with late latent syphilis, and modern cases of general paresis and tabes dorsalis are being reported from China. The factors that contribute to the development and progression of tertiary disease are unknown.

CLINICAL MANIFESTATIONS

PRIMARY SYPHILIS

The typical primary chancre usually begins as a single painless papule that rapidly becomes eroded and usually becomes indurated, with a characteristic cartilaginous consistency on palpation of the edge and base of the ulcer. Multiple primary lesions are seen in a minority of patients. In heterosexual men the chancre is usually located on the penis, where it is readily seen **(Fig. 177-2; see also Fig. A1-17)**, whereas in MSM it may also be found in the anal canal or rectum or in the mouth. Oral sex has been identified as the source of infection in some MSM. In women, common primary sites are the cervix and labia.

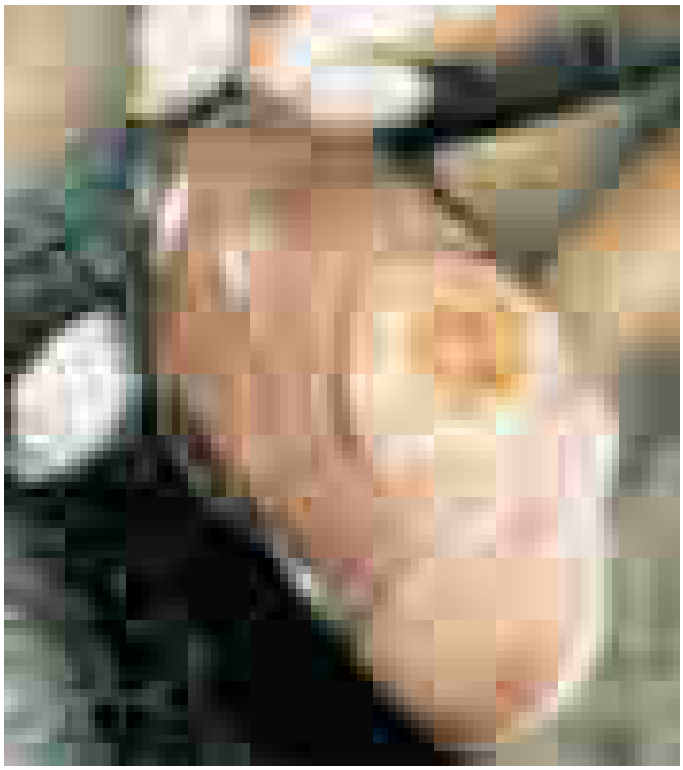

FIGURE 177-2 **Primary syphilis** with a firm, nontender chancre.

Consequently, primary syphilis goes unrecognized in women and MSM more often than in heterosexual men.

Atypical primary lesions are common. A large inoculum produces a dark-field-positive ulcerative lesion in nonimmune volunteers but may produce a small dark-field-negative papule, an asymptomatic but seropositive latent infection, or no response at all in some individuals with a history of syphilis. A small inoculum may produce only a papular lesion, even in nonimmune individuals. Therefore, syphilis should be considered even in the evaluation of trivial or atypical dark-field-negative genital lesions. The lesions that most commonly must be differentiated from those of primary syphilis include those caused by herpes simplex virus infection **(Chap. 187)**, chancroid **(Chap. 152)**, traumatic injury, and donovanosis **(Chap. 168)**. Regional (usually inguinal) lymphadenopathy accompanies the primary syphilitic lesion, appearing within 1 week of lesion onset. The nodes are firm, nonsuppurative, and painless. Inguinal lymphadenopathy is bilateral and may occur with anal as well as with genital chancres. The chancre generally heals within 4–6 weeks (range, 2–12 weeks), but lymphadenopathy may persist for months.

SECONDARY SYPHILIS

The protean manifestations of the secondary stage usually include mucocutaneous or cutaneous lesions and generalized nontender lymphadenopathy. The healing primary chancre may still be present in ~15% of cases—more frequently in persons with concurrent HIV infection. The skin rash consists of macular, papular, papulosquamous, and occasionally pustular syphilides; often more than one form is present simultaneously. The eruption may be very subtle, and 25% of patients with a discernible rash may be unaware that they have dermatologic manifestations. Initial lesions are pale red or pink, nonpruritic, discrete macules distributed on the trunk and extremities; these macules progress to papular lesions that are distributed widely and that frequently involve the palms and soles **(Fig. 177-3; see also Figs. A1-18 and A1-19)**. Rarely, severe necrotic lesions (*lues maligna*) may appear; they are more commonly reported in HIV-infected individuals. Involvement of the hair follicles may result in patchy alopecia of the scalp hair, eyebrows, or beard in up to 5% of cases.

In warm, moist, intertriginous areas (commonly the perianal region, vulva, and scrotum), papules can enlarge to produce broad, moist, pink

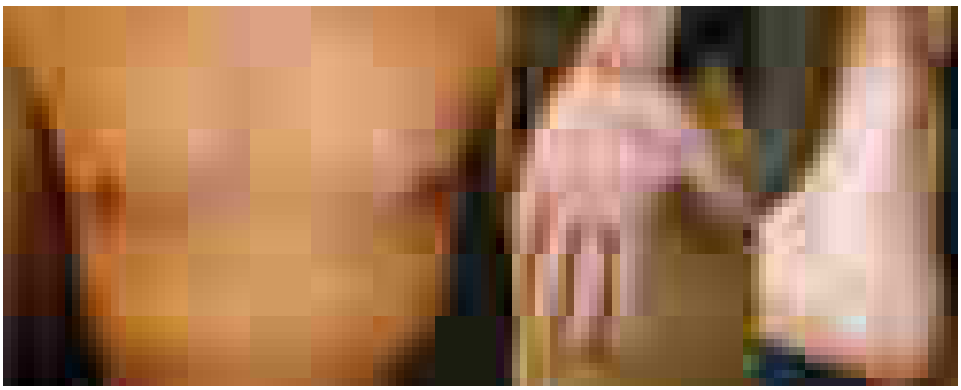

FIGURE 177-3 Secondary syphilis. ***Left:*** Maculopapular truncal eruption. ***Middle:*** Papules on the palms. ***Right:*** Papules on the soles. *(Courtesy of Jill McKenzie and Christina Marra.)*

or gray-white, highly infectious lesions (*condylomata lata*; **see Fig. A1-20**) in 10% of patients with secondary syphilis. Superficial mucosal erosions (*mucous patches*) occur in 10–15% of patients and commonly involve the oral or genital mucosa **(see Fig. A1-21)**. The typical mucous patch is a painless silver-gray erosion surrounded by a red periphery.

Constitutional signs and symptoms that may accompany or precede secondary syphilis include sore throat (15–30%), fever (5–8%), weight loss (2–20%), malaise (25%), anorexia (2–10%), headache (10%), and meningismus (5%). *Acute meningitis* occurs in only 1–2% of cases, but CSF cell and protein concentrations are increased in up to 40% of early syphilis cases, and viable *T. pallidum* organisms have been recovered from CSF during primary and secondary syphilis in 30% of cases; the latter finding is often but not always associated with other CSF abnormalities. Ocular findings associated with secondary (or later/unknown-stage) syphilis include pupillary abnormalities and optic neuritis as well as the classic iritis or uveitis. The diagnosis of ocular syphilis is often considered in affected patients only after they fail to respond to topical steroid therapy. Anterior uveitis has been reported in 5–10% of patients with secondary syphilis, and *T. pallidum* has been demonstrated in aqueous humor from such patients. Permanent blindness may result without prompt diagnosis and treatment. The recent publication of a number of reports of ocular syphilis reminds clinicians to inquire about neurologic manifestations in all stages of syphilis infection. In a recent retrospective study, 7.9% of patients with syphilis, when asked, reported recent vision or hearing changes, and more than half of those reporting these changes had abnormal CSF or ophthalmologic findings consistent with syphilis.

Less common complications of secondary syphilis include hepatitis, nephropathy, gastrointestinal involvement (hypertrophic gastritis, patchy proctitis, or a rectosigmoid mass), arthritis, and periostitis. Hepatic involvement is common in syphilis; although it is usually asymptomatic, up to 25% of patients may have abnormal liver function tests. Frank syphilitic hepatitis may be seen. Renal involvement usually results from immune complex deposition and produces proteinuria associated with an acute nephrotic syndrome. Like those of primary syphilis, most manifestations of the secondary stage resolve spontaneously, usually within 1–6 months.

LATENT SYPHILIS

Positive serologic tests for syphilis, together with a normal CSF examination and the absence of clinical manifestations of syphilis, indicate a diagnosis of latent syphilis in an untreated person. The diagnosis is often suspected on the basis of a history of primary or secondary lesions, a history of exposure to syphilis, or the delivery of an infant with congenital syphilis. A previous nonreactive serologic test or a history of lesions or exposure may help establish the duration of latent infection, which is an important factor in the selection of appropriate therapy. *Early latent* syphilis is limited to the first year after infection, whereas *late latent* syphilis is defined as that of ≥1 year's duration (or of unknown duration). *T. pallidum* may still seed the bloodstream intermittently during the latent stage, and latent syphilis in a pregnant woman may infect the fetus in utero. Moreover, syphilis has been transmitted through blood transfusion or organ donation from patients with latent syphilis. It was previously thought that untreated late latent syphilis had three possible outcomes: (1) persistent lifelong infection; (2) development of late syphilis; or (3) spontaneous cure, with reversion of serologic tests to negative. It is now apparent, however, that the more sensitive treponemal antibody tests rarely, if ever, become nonreactive without treatment. Although progression to clinically evident late syphilis is very rare today, the occurrence of spontaneous microbiologic cure is in doubt.

INVOLVEMENT OF THE CNS

Traditionally, neurosyphilis has been considered a late manifestation of syphilis, but this view is inaccurate. CNS syphilis represents a continuum encompassing early invasion (usually within the first weeks of infection), months to years of asymptomatic involvement, and, in some cases, development of early or late neurologic manifestations.

Asymptomatic Neurosyphilis The diagnosis of asymptomatic neurosyphilis is made in patients who lack neurologic symptoms and signs but who have CSF abnormalities, including mononuclear pleocytosis, increased protein concentrations, or reactivity in the CSF Venereal Disease Research Laboratory (VDRL) test. CSF abnormalities are demonstrated in up to 40% of cases of untreated primary or secondary syphilis and in 25% of cases of untreated latent syphilis. *T. pallidum* has been recovered by inoculation into rabbits of CSF from up to 30% of patients with primary or secondary syphilis but less frequently from patients with latent syphilis. The presence of *T. pallidum* in CSF is often associated with other CSF abnormalities, but organisms can be recovered from patients with otherwise normal CSF. Although the prognostic implications of these findings in early syphilis are uncertain, it may be appropriate to conclude that even patients with early syphilis who have such findings do indeed have asymptomatic neurosyphilis and should be treated for neurosyphilis; such treatment is particularly important in patients with concurrent HIV infection. Before the advent of penicillin, the risk of development of clinical neurosyphilis in untreated asymptomatic persons was roughly proportional to the intensity of CSF changes, with the overall cumulative probability of progression to clinical neurosyphilis ~20% in the first 10 years of infection but increasing with time. Most experts agree that neurosyphilis is more common among HIV-infected persons, while immunocompetent patients with untreated latent syphilis and normal CSF probably run a very low risk of subsequent neurosyphilis. In several large studies, neurosyphilis was associated with a rapid plasma reagin (RPR) titer of ≥1:32, regardless of clinical stage or HIV infection status.

Symptomatic Neurosyphilis The major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. The last category includes general paresis and tabes dorsalis. The onset of symptoms usually occurs <1 year after infection for meningeal syphilis, up to 10 years after infection for meningovascular syphilis, at ~20 years for general paresis, and at 25–30 years for tabes dorsalis. Neurosyphilis is more frequently symptomatic in patients co-infected with HIV, particularly those with low CD4+ T lymphocyte counts. In addition, evidence suggests that syphilis infection worsens the cognitive impairment seen in HIV-infected persons and that this effect persists after treatment for syphilis.

Meningeal syphilis may present as headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status. This condition may be concurrent with or may follow the secondary stage. Patients presenting with uveitis, iritis, or hearing loss often have meningeal syphilis, but these clinical findings can also be seen in patients with normal CSF.

Meningovascular syphilis reflects meningitis together with inflammatory vasculitis of small, medium, or large vessels. The most common

presentation is a stroke syndrome involving the middle cerebral artery of a relatively young adult. However, unlike the usual thrombotic or embolic stroke syndrome of sudden onset, meningovascular syphilis often becomes manifest after a subacute encephalitic prodrome (with headaches, vertigo, insomnia, and psychological abnormalities), which is followed by a gradually progressive vascular syndrome.

The manifestations of *general paresis* reflect widespread late parenchymal damage and include abnormalities corresponding to the mnemonic *paresis: p*ersonality, *a*ffect, *r*eflexes (hyperactive), *e*ye (e.g., Argyll Robertson pupils), *s*ensorium (illusions, delusions, hallucinations), *i*ntellect (a decrease in recent memory and in the capacity for orientation, calculations, judgment, and insight), and *s*peech. *Tabes dorsalis* is a late manifestation of syphilis that presents as symptoms and signs of demyelination of the posterior columns, dorsal roots, and dorsal root ganglia, including ataxia, foot drop, paresthesia, bladder disturbances, impotence, areflexia, and loss of positional, deep-pain, and temperature sensations. The small, irregular Argyll Robertson pupil, a feature of both tabes dorsalis and paresis, reacts to accommodation but not to light. *Optic atrophy* also occurs frequently in association with tabes.

OTHER MANIFESTATIONS OF LATE SYPHILIS

The slowly progressive inflammatory process leading to tertiary disease begins early during infection, although these manifestations may not become clinically apparent for years or decades. Early syphilitic aortitis first becomes evident soon after secondary lesions subside, and treponemes that trigger the development of gummas may have seeded the tissue years earlier.

Cardiovascular Syphilis Cardiovascular manifestations, usually appearing 10–40 years after infection, are attributable to endarteritis obliterans of the vasa vasorum, which provide the blood supply to large vessels; *T. pallidum* DNA has been detected by PCR in aortic tissue. Cardiovascular involvement results in uncomplicated aortitis, aortic regurgitation, saccular aneurysm (usually of the ascending aorta), or coronary ostial stenosis. In the preantibiotic era, symptomatic cardiovascular complications developed in ~10% of persons with untreated late syphilis. Today, cardiovascular syphilis is rarely seen in the developed world.

Late Benign Syphilis (Gumma) Gummas are usually solitary lesions ranging from microscopic to several centimeters in diameter. Histologic examination shows a granulomatous inflammation, with a central area of necrosis due to endarteritis obliterans. *T. pallidum* has been detected by PCR in these lesions, and penicillin treatment results in rapid resolution, confirming the treponemal stimulus for the inflammation. Common sites include the skin and skeletal system; however, any organ (including the brain) may be involved. Gummas of the skin produce indolent, painless, indurated nodular or ulcerative lesions that may resemble other chronic granulomatous conditions. Skeletal gummas may affect any bone or cartilage. Upper respiratory gummas can lead to perforation of the nasal septum or palate.

CONGENITAL SYPHILIS

Transmission of *T. pallidum* across the placenta from a syphilitic woman to her fetus may occur at any stage of pregnancy, but fetal damage generally does not occur until after the fourth month of gestation when fetal immunologic competence begins to develop. This timing suggests that the pathogenesis of congenital syphilis, like that of adult syphilis, depends on the host immune response rather than on a direct toxic effect of *T. pallidum*. The risk of fetal infection during untreated early maternal syphilis is ~75–95%, decreasing to ~35% for maternal syphilis of >2 years' duration. Adequate treatment of the woman before the 16th week of pregnancy should prevent fetal damage, and treatment before the third trimester should adequately treat the infected fetus. Untreated maternal infection may result in a rate of fetal loss of up to 40% with stillbirth (more common than abortion because of the late onset of fetal pathology), prematurity, neonatal death, or nonfatal congenital syphilis. Among infants born alive, only fulminant congenital syphilis is clinically apparent at birth, and these babies have a very poor prognosis. The most common clinical problem is the healthy-appearing baby born to a mother with a positive serologic test.

Routine serologic testing for syphilis in early pregnancy is cost-effective in virtually all populations, even in areas with a low prenatal prevalence of syphilis. Low-tech point-of-care tests have been developed and widely implemented to facilitate antenatal testing in resource-poor settings. Globally, the past 5–8 years have seen a 38% reduction in maternal syphilis and a 39% reduction in congenital syphilis. Progress has been uneven, however, with major advances in Thailand, Cuba, several Baltic States, and India, but continuing high levels in Africa and China. Periodic lack of penicillin availability prevents treatment of seropositive women. Integration of programs to prevent congenital syphilis with programs to prevent maternal transmission of HIV would be highly cost-effective but is hampered by the restrictions placed on HIV-focused funds. Pregnant women should be screened at their first antenatal visit. Where the prevalence of syphilis is high or when the patient is at high risk of reinfection, serologic testing should be repeated in the third trimester and at delivery. Neonatal congenital syphilis must be differentiated from other generalized congenital infections, including rubella, cytomegalovirus or herpes simplex virus infection, and toxoplasmosis, as well as from erythroblastosis fetalis.

Manifestations of congenital syphilis may appear early (within the first 2 years of life, often at 2–10 weeks of age) or late (after 2 years). The earliest manifestations of congenital syphilis include rhinitis, or "snuffles" (23%); mucocutaneous lesions (35–41%); bone changes (61%), including periostitis detectable by x-ray examination of long bones; hepatosplenomegaly (50%); lymphadenopathy (32%); anemia (34%); jaundice (30%); thrombocytopenia; and leukocytosis. CNS invasion by *T. pallidum* is detectable in 22% of infected neonates. Neonatal death is usually due to pulmonary hemorrhage, secondary bacterial infection, or severe hepatitis. Late congenital syphilis (untreated after 2 years of age) is subclinical in 60% of cases; the clinical spectrum in the remainder of cases may include interstitial keratitis (which occurs at 5–25 years of age), eighth-nerve deafness, and recurrent arthropathy. Neurosyphilis was documented in about one-quarter of untreated patients with late congenital syphilis in the preantibiotic era. Gummatous periostitis occurs at 5–20 years of age and, as in nonvenereal endemic syphilis, tends to cause destructive lesions of the palate and nasal septum. Classic stigmata include *Hutchinson's teeth* (centrally notched, widely spaced, peg-shaped upper central incisors), "mulberry" molars (sixth-year molars with multiple, poorly developed cusps), saddle nose, and saber shins.

LABORATORY EXAMINATIONS

DEMONSTRATION OF THE ORGANISM

T. pallidum cannot be detected by culture. Historically, dark-field microscopy and immunofluorescence antibody staining have been used to identify this spirochete in samples from moist lesions such as chancres or condylomata lata, but these tests are rarely available outside of research laboratories. Sensitive and specific PCR tests have been developed but are not commercially available, although a number of laboratories perform in-house validated PCR testing.

T. pallidum can be found in tissue with appropriate silver stains, but these results should be interpreted with caution because artifacts resembling *T. pallidum* are often seen. Tissue treponemes can be demonstrated more reliably in research laboratories by PCR or by immunofluorescence or immunohistochemical methods using specific monoclonal or polyclonal antibodies to *T. pallidum*. *T. pallidum* DNA has been detected by PCR in lesion swabs, tissue samples, blood, CSF, ocular fluid, urine, and oropharyngeal swabs.

SEROLOGIC TESTS FOR SYPHILIS

Treponemal and Lipoidal Tests There are two types of serologic tests for syphilis: lipoidal (so-called nontreponemal) and treponemal. Both are reactive in persons with any treponemal infection, including syphilis, yaws, pinta, and endemic syphilis.

The most widely used lipoidal antibody tests for syphilis are the RPR and VDRL tests, which measure IgG and IgM directed against a

cardiolipin-lecithin-cholesterol antigen complex. The RPR test is easier to perform and uses unheated serum or plasma; it is the test of choice for rapid serologic diagnosis in a clinical setting. The VDRL test remains the standard for examining CSF and is superior to the RPR for this purpose. The RPR and VDRL tests are recommended for screening and for quantitation of serum antibody. The titer reflects disease activity, rising during the evolution of early syphilis, often exceeding 1:32 in secondary syphilis, and declining slowly thereafter without therapy. After treatment for early syphilis, a persistent fall by fourfold or more (e.g., a decline from 1:32 to 1:8) is considered an adequate response. VDRL titers do not correspond directly to RPR titers, and sequential quantitative testing (as for response to therapy) must employ a single test.

Treponemal tests measure antibodies to native or recombinant *T. pallidum* antigens and include the fluorescent treponemal antibody–absorbed (FTA-ABS) test and the *T. pallidum* particle agglutination (TPPA) test, both of which are more sensitive for primary syphilis than the lipoidal tests. When used to confirm reactive lipoidal test results, treponemal tests have a very high positive predictive value for diagnosis of syphilis.

Treponemal enzyme or chemiluminescence immunoassays (EIAs/CIAs), based largely on reactivity to recombinant antigens, are now widely used as screening tests by large laboratories. When used for screening, however, standard treponemal tests give false-positive results at rates as high as 1–2%, but the rate is much higher with the EIA/CIA tests. A high proportion of sera that are reactive by EIA/CIA are nonreactive by lipoidal tests. Such sera should be examined in the TPPA test, which includes different antigens and a different platform. If the TPPA test is nonreactive, the patient is unlikely to have syphilis; if it is reactive, the patient is likely to have current or past syphilis. The rapid immunochromatographic tests described for antenatal screening in resource-poor settings are largely unavailable in the United States.

Both lipoidal and treponemal tests may be nonreactive in early primary syphilis, although treponemal tests are slightly more sensitive (85–90%) during this stage than lipoidal tests (~80%). All tests are reactive during secondary syphilis. (Fewer than 1% of patients with high titers have a lipoidal test that is nonreactive or weakly reactive with undiluted serum but is reactive with diluted serum—the *prozone phenomenon*.) VDRL and RPR sensitivity and titers may decline in untreated persons with late latent syphilis, but treponemal tests remain reactive in late syphilis. After treatment for early syphilis, lipoidal test titers will generally decline or the tests will become nonreactive, whereas treponemal tests often remain reactive after therapy and are not helpful in determining the infection status of persons with past syphilis.

Clinicians need to be familiar with three uses of serologic tests for syphilis recommended by the Centers for Disease Control and Prevention (CDC): (1) screening or diagnosis (RPR or VDRL), (2) quantitative measurement of antibody to assess clinical syphilis activity or to monitor response to therapy (RPR or VDRL), and (3) confirmation of a syphilis diagnosis in a patient with a reactive lipoidal test (FTA-ABS, TPPA, EIA/CIA). Whereas IgM titers appear to decline after therapy, the presence or absence of specific IgM does not strictly correlate with active *T. pallidum* infection. Moreover, no commercially available IgM test is recommended, even for evaluation of infants with suspected congenital syphilis.

False-Positive Serologic Tests for Syphilis The lipid antigens of nontreponemal tests are similar to those found in human tissues, and the tests may be reactive (usually with titers ≤1:8) in persons without treponemal infection. Among patients being screened for syphilis because of risk factors, clinical suspicion, or history of exposure, ~1% of reactive tests are falsely positive. Modern VDRL and RPR tests are highly specific, and false-positive reactions are largely limited to persons with autoimmune conditions or injection drug use. The prevalence of false-positive results increases with advancing age. In a patient with a false-positive nontreponemal test, syphilis is excluded by a nonreactive treponemal test.

False-positive reactions may also occur with treponemal tests, particularly the very sensitive EIA/CIA tests. Screening a low-prevalence population for syphilis with a treponemal test may result in true-positive reactions' being outnumbered by false-positive reactions, leading to unnecessary treatment. Thus screening with lipoidal tests is highly recommended.

EVALUATION FOR NEUROSYPHILIS

Involvement of the CNS is detected by examination of CSF for mononuclear pleocytosis (>5 white blood cells/μL), increased protein concentration (>45 mg/dL), or CSF VDRL reactivity. Elevated CSF cell counts and protein concentrations are not specific for neurosyphilis and may be confounded by HIV co-infection. Because CSF pleocytosis may also be due to HIV, some studies have suggested using a CSF white-cell cutoff of 20 cells/μL as diagnostic of neurosyphilis in HIV-infected patients with syphilis. The CSF VDRL test is highly specific and, when reactive, is considered diagnostic of neurosyphilis; however, this test is insensitive and may be nonreactive even in cases of symptomatic neurosyphilis. The RPR test should not be substituted for the VDRL test for CSF examination. The FTA-ABS test on CSF is reactive far more often than the CSF VDRL test in all stages of syphilis, but reactivity may reflect passive transfer of serum antibody into the CSF. A nonreactive FTA-ABS test on CSF, however, may be used to rule out asymptomatic neurosyphilis. Measuring CXCL13 in CSF has been demonstrated to distinguish between neurosyphilis and HIV-related CSF abnormalities.

All *T. pallidum*–infected patients who have signs or symptoms consistent with neurologic disease (e.g., meningitis, hearing loss) or ophthalmic disease (e.g., uveitis, iritis) should have a CSF examination, regardless of disease stage. The appropriate management of asymptomatic persons is less clear. Lumbar puncture on all asymptomatic patients with untreated syphilis is impractical and unnecessary. Because therapy with penicillin G benzathine fails to result in treponemicidal drug levels in CSF, however, it is important to identify those persons at higher risk for having or developing neurosyphilis so that appropriate therapy may be given. Viable *T. pallidum* has been isolated from the CSF of several patients (with and without HIV infection) after penicillin G benzathine therapy for early syphilis. Large-scale prospective studies have provided evidence-based guidelines for determining which syphilis patients may benefit most from CSF examination. Specifically, patients with RPR titers of ≥1:32 are at higher risk of having neurosyphilis (11-fold and 6-fold higher in HIV-infected and HIV-uninfected persons, respectively), as are HIV-infected patients with CD4+ T cell counts of ≤350/μL. Persons with active tertiary syphilis and those in whom treatment failure is suspected also should have their CSF examined.

EVALUATION OF HIV-INFECTED PATIENTS FOR SYPHILIS

Because persons at highest risk for syphilis are also at increased risk for HIV infection, these two infections frequently coexist. There is evidence that syphilis and other genital ulcer diseases are important risk factors for acquisition and transmission of HIV infection. Some manifestations of syphilis may be altered in patients with concurrent HIV infection, and multiple cases of neurologic relapse after standard therapy have been reported in these patients.

Persons with newly diagnosed HIV infection should be tested for syphilis; conversely, all patients with newly diagnosed syphilis should be tested for HIV infection. Some authorities, persuaded by reports of persistent *T. pallidum* in CSF of HIV-infected persons after standard therapy for early syphilis, recommend CSF examination for evidence of neurosyphilis for all co-infected patients, regardless of the stage of syphilis, with treatment for neurosyphilis if CSF abnormalities are found. Others, on the basis of their own clinical experience, think that standard therapy—without CSF examination—is sufficient for all cases of early syphilis in HIV-infected patients without neurologic signs or symptoms. As described above, RPR titer and CD4+ T cell count can be used to identify patients at higher risk of neurosyphilis for lumbar puncture, although some cases of neurosyphilis will be missed even when these criteria are used. Serologic testing after treatment is important for all patients with syphilis, particularly for those also infected with HIV.

TREATMENT

Syphilis

TREATMENT OF ACQUIRED SYPHILIS

The CDC's 2015 guidelines for the treatment of syphilis are summarized in **Table 177-1** and are discussed below. Penicillin G is the drug of choice for all stages of syphilis. *T. pallidum* is killed by very low concentrations of penicillin G, although a long period of exposure to penicillin is required because of the unusually slow rate of multiplication of the organism. The efficacy of penicillin against syphilis remains undiminished after 70 years of use, and there is no evidence of penicillin resistance in *T. pallidum*. Other antibiotics effective in syphilis include the tetracyclines and the cephalosporins. Aminoglycosides and spectinomycin inhibit *T. pallidum* only in very large doses, and the sulfonamides and most quinolones are inactive. Azithromycin has shown significant promise as an effective oral agent against *T. pallidum*; however, strains harboring 23S rDNA mutations that confer macrolide resistance are widespread. Such strains represent >80–90% of recent isolates from large U.S., European, and Chinese cities, while rates of 23S mutation are much lower in some other locations. The prevalence of resistant strains varies by geographic location, and routine treatment of syphilis with azithromycin is not recommended. Careful follow-up of any patient treated for syphilis with azithromycin must be assured.

Early Syphilis Patients and Their Contacts Penicillin G benzathine is the most widely used agent for the treatment of early syphilis; preventive treatment is also recommended for individuals who have been exposed to infectious syphilis within the previous 3 months.

TABLE 177-1 Recommendations for the Treatment of Syphilis[a]

STAGE OF SYPHILIS	PATIENTS WITHOUT PENICILLIN ALLERGY	PATIENTS WITH CONFIRMED PENICILLIN ALLERGY
Primary, secondary, or early latent	*CSF normal or not examined:* Penicillin G benzathine (single dose of 2.4 mU IM) *CSF abnormal:* Treat as neurosyphilis.	*CSF normal or not examined:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 2 weeks *CSF abnormal:* Treat as neurosyphilis.
Late latent (or latent of unknown duration), cardiovascular, or benign tertiary	*CSF normal or not examined:* Penicillin G benzathine (2.4 mU IM weekly for 3 weeks) *CSF abnormal:* Treat as neurosyphilis.	*CSF normal and patient not infected with HIV:* Tetracycline HCl (500 mg PO qid) or doxycycline (100 mg PO bid) for 4 weeks *CSF normal and patient infected with HIV:* Desensitize and treat with penicillin if compliance cannot be assured. *CSF abnormal:* Treat as neurosyphilis.
Neurosyphilis (asymptomatic or symptomatic)	Aqueous crystalline penicillin G (18–24 mU/d IV, given as 3–4 mU q4h or continuous infusion) for 10–14 days *or* Aqueous procaine penicillin G (2.4 mU/d IM) plus oral probenecid (500 mg qid), both for 10–14 days	Desensitize and treat with penicillin.
Syphilis in pregnancy	According to stage	Desensitize and treat with penicillin.

[a]See text for indications for CSF examination.

Abbreviations: CSF, cerebrospinal fluid; mU, million units.

Source: Adapted from the 2015 Sexually Transmitted Diseases Treatment Guidelines from the Centers for Disease Control and Prevention.

The regimens recommended for prevention are the same as those recommended for early syphilis. Penicillin G benzathine cures >95% of cases of early syphilis, although clinical relapse can follow treatment, particularly in patients with concurrent HIV infection. Because the risk of neurologic relapse may be higher in HIV-infected patients, CSF examination is recommended for HIV-seropositive individuals with syphilis of any stage, particularly those with a serum RPR titer of ≥1:32 or a CD4+ T cell count of ≤350/μL. Therapy appropriate for neurosyphilis should be given if there is any evidence of CNS infection.

Late Latent Syphilis or Syphilis of Unknown Duration If the CSF is normal or is not examined, the recommended treatment is penicillin G benzathine (7.2 million units total; Table 177-1). If CSF abnormalities are found, the patient should be treated for neurosyphilis.

Tertiary Syphilis CSF examination should be performed. If the CSF is normal, the recommended treatment is penicillin G benzathine (7.2 million units total; Table 177-1). If CSF is abnormal, the patient should be treated for neurosyphilis. The clinical response to treatment for benign tertiary syphilis is usually impressive, but responses in cardiovascular syphilis are not dramatic because aortic aneurysm and aortic regurgitation cannot be reversed by antibiotics.

Syphilis in Penicillin-Allergic Patients For penicillin-allergic patients with syphilis, a 2-week (early syphilis) or 4-week (late or late latent syphilis) course of therapy with doxycycline or tetracycline is recommended (Table 177-1). These regimens appear to be effective in early syphilis but have not been tested for late or late latent syphilis, and compliance may be problematic. Limited studies suggest that ceftriaxone (1 g/d, given IM or IV for 8–10 days) is effective for early syphilis. These nonpenicillin regimens have not been carefully evaluated in HIV-infected individuals and should be used with caution. If compliance and follow-up are not assured, penicillin-allergic HIV-infected persons with late latent or late syphilis should be desensitized and treated with penicillin.

Neurosyphilis Penicillin G benzathine, even at high doses, does not produce treponemicidal concentrations of penicillin G in CSF and should not be used for treatment of neurosyphilis. Asymptomatic neurosyphilis may relapse as symptomatic disease after treatment with benzathine penicillin, and the risk of relapse may be higher in HIV-infected patients. Both symptomatic and asymptomatic neurosyphilis should be treated with aqueous penicillin (Table 177-1). Administration either of IV aqueous crystalline penicillin G or of IM aqueous procaine penicillin G plus oral probenecid in recommended doses is thought to ensure treponemicidal concentrations of penicillin G in CSF. The clinical response to penicillin therapy for meningeal syphilis is dramatic, but treatment of neurosyphilis with existing parenchymal damage may only arrest disease progression. No data suggest that additional therapy (e.g., penicillin G benzathine for 3 weeks) is beneficial after treatment for neurosyphilis.

The use of antibiotics other than penicillin G for the treatment of neurosyphilis has not been studied, although limited data suggest that ceftriaxone may be used. In patients with confirmed penicillin allergy, desensitization and treatment with penicillin are recommended.

Management of Syphilis in Pregnancy Every pregnant woman should undergo a lipoidal screening test at her first prenatal visit and, if at high risk of exposure, again in the third trimester and at delivery. In the untreated pregnant patient with presumed syphilis, expeditious treatment appropriate to the stage of the disease is essential. Patients should be warned of the risk of a Jarisch-Herxheimer reaction, which may be associated with mild premature contractions but rarely results in premature delivery.

Penicillin is the only recommended agent for the treatment of syphilis in pregnancy. If the patient has a documented penicillin allergy, desensitization and penicillin therapy should be undertaken according to the CDC's 2015 guidelines. After treatment, a quantitative nontreponemal test should be repeated monthly throughout

pregnancy to assess therapeutic efficacy. Treated women whose antibody titers rise by fourfold or whose titers do not decrease by fourfold over a 3-month period should be re-treated.

EVALUATION AND MANAGEMENT OF CONGENITAL SYPHILIS

Whether or not they are infected, newborn infants of women with reactive serologic tests may themselves have reactive tests because of transplacental transfer of maternal IgG antibodies. For asymptomatic infants born to women treated adequately with penicillin during the first or second trimester of pregnancy, monthly quantitative nontreponemal tests may be performed to monitor for appropriate reduction in antibody titers. Rising or persistent titers indicate infection, and the infant should be treated. Detection of neonatal IgM antibody may be useful, but no commercially available test is currently recommended.

An infant should be treated at birth if the treatment status of the seropositive mother is unknown; if the mother received inadequate or nonpenicillin therapy; if the mother received penicillin therapy in the third trimester; or if the infant may be difficult to follow. The CSF should be examined to obtain baseline values before treatment. Penicillin is the only recommended drug for the treatment of syphilis in infants. Specific recommendations for the treatment of infants and older children are included in the CDC's 2015 treatment guidelines.

JARISCH-HERXHEIMER REACTION

A dramatic although self-limited reaction consisting of fever, chills, myalgia, headache, tachycardia, increased respiratory rate, increased circulating neutrophil count, and vasodilation with mild hypotension may follow the initiation of treatment for syphilis. This reaction is thought to be a response to lipoproteins released by dying *T. pallidum* organisms. The Jarisch-Herxheimer reaction occurs in ~50% of patients with primary syphilis, 90% of those with secondary syphilis, and a lower proportion of persons with later-stage disease. Defervescence takes place within 12–24 h. In secondary syphilis, erythema and edema of the cutaneous lesions may increase. Patients should be warned to expect such developments, which can be managed with symptom-based treatment. Steroid therapy is not required for this mild transient reaction.

FOLLOW-UP EVALUATION OF RESPONSES TO THERAPY

Efficacy of treatment should be assessed by clinical evaluation and monitoring of the quantitative VDRL or RPR titer for a fourfold decline (e.g., from 1:32 to 1:8). Patients with primary or secondary syphilis should be examined 6 and 12 months after treatment, and persons with latent or late syphilis at 6, 12, and 24 months. More frequent clinical and serologic examination (3, 6, 9, 12, and 24 months) is recommended for patients concurrently infected with HIV, regardless of the stage of syphilis.

After successful treatment of seropositive first-episode primary or secondary syphilis, the VDRL or RPR titer progressively declines; the test becomes nonreactive by 12 months in 40–75% of seropositive primary cases and in 20–40% of secondary cases. In patients with HIV infection or a history of prior syphilis, VDRL and RPR tests are less likely to become nonreactive. Rates of decline of serologic titers appear to be slower, and serologically defined treatment failures more common, among HIV-infected patients than among those without HIV co-infection; however, effective antiretroviral therapy may reduce these differences. Re-treatment should be considered if serologic responses are not adequate or if clinical signs persist or recur. Because it is difficult to differentiate treatment failure from reinfection, the CSF should be examined, with treatment for neurosyphilis if CSF is abnormal and treatment for late latent syphilis if CSF is normal. A minority of patients treated for early syphilis may experience a one-dilution titer increase within 14 days after treatment; however, this early elevation does not significantly affect the serologic outcome at 6 months after treatment. Patients treated for late latent syphilis frequently have low initial VDRL or RPR titers and may not have a fourfold decline after therapy with penicillin. In such patients, re-treatment is not warranted unless the titer rises or signs and symptoms of syphilis appear. Because treponemal tests may remain reactive despite treatment for seropositive syphilis, these tests are not useful in following the response to therapy.

The activity of neurosyphilis (symptomatic or asymptomatic) correlates best with CSF pleocytosis, and this measure provides the most sensitive index of response to treatment. Repeat CSF examinations should be performed every 6 months until the cell count is normal. An elevated CSF cell count falls to normal in 3–12 months in adequately treated HIV-uninfected patients. The persistence of mild pleocytosis in HIV-infected patients may be due to the presence of HIV in CSF; this scenario may be difficult to distinguish from treatment failure. Elevated levels of CSF protein fall more slowly, and the CSF VDRL titer declines gradually over several years. In patients treated for neurosyphilis, a fourfold reduction in serum RPR titer has been positively correlated with normalization of CSF abnormalities; this correlation is stronger in HIV-uninfected patients and in HIV-infected patients receiving effective antiretroviral therapy.

IMMUNITY TO SYPHILIS

The rate of development of acquired resistance to *T. pallidum* after natural or experimental infection depends on both the size of the infecting inoculum and the duration of infection before treatment. Both humoral and cellular responses are considered to be of major importance in the healing of early lesions. Cellular infiltration, predominantly by T lymphocytes and macrophages, produces an interferon γ–dominated cytokine milieu and results in the clearance of organisms by activated macrophages. Specific antibodies to surface antigens enhance phagocytosis. Antigenic variation of the TprK protein is thought to contribute to development of subsequent stages of syphilis, persistence of infection, and susceptibility to reinfection with another strain. Comparative genomic studies have revealed genes with sequence variations among *T. pallidum* strains, leading to development of molecular typing methods used to examine syphilis outbreaks. Recent work has demonstrated that immunization with the outer-membrane protein Tp0751 significantly reduces dissemination of *T. pallidum* during syphilis infection in an animal model. Vaccine studies with this and other antigens are underway.

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178 Endemic Treponematoses

Sheila A. Lukehart

The endemic treponematoses are chronic diseases that are transmitted by direct contact, usually during childhood, and, like syphilis, can cause severe late manifestations years after initial infection. These diseases are caused by very close relatives of *Treponema pallidum* subspecies *pallidum*, the etiologic agent of venereal syphilis **(Chap. 177)**. Yaws, pinta, and endemic syphilis (bejel) are traditionally distinguished from venereal syphilis by mode of transmission, age of acquisition, geographic distribution, and clinical features; however, there is some overlap for each of these factors. Our "knowledge" about these infections is based on observations by health care workers who have visited

TABLE 178-1 Comparison of the Treponemes and Associated Diseases

FEATURE	VENEREAL SYPHILIS	YAWS	ENDEMIC SYPHILIS	PINTA
Organism	*T. pallidum* subsp. *pallidum*	*T. pallidum* subsp. *pertenue*	*T. pallidum* subsp. *endemicum*	*T. carateum*
Common modes of transmission	Sexual, transplacental	Skin-to-skin	Mouth-to-mouth or via shared drinking/eating utensils	Skin-to-skin
Usual age of acquisition	Sexual maturity or in utero	Early childhood	Early childhood	Late childhood
Primary lesion	Cutaneous ulcer (chancre)	Papilloma, often ulcerative	Mucosal papule, rarely seen	Nonulcerating papule with satellites, pruritic
Common location	Genital, oral, anal	Extremities	Oral	Extremities, face
Secondary lesions	Cutaneous rash and mucocutaneous lesions; condylomata lata	Cutaneous papillomatous or ulcerative lesions; condylomata lata, osteoperiostitis	Mucocutaneous lesions (mucous patch, split papule, condylomata lata); osteoperiostitis	Pintides, pigmented, pruritic
Infectious relapses	~25%	Common	Unknown	Unknown
Late complications	Gummas, cardiovascular and central nervous system involvement[a]	Destructive gummas of skin, bone, cartilage	Destructive gummas of skin, bone, cartilage	Nondestructive, dyschromic, achromic macules

[a]Central nervous system involvement and congenital infection in the endemic treponematoses have been postulated by some investigators (see text).

endemic areas. Except for recent pilot programs of mass drug administration (MDA) for yaws, virtually no well-designed studies of the natural history, diagnosis, or treatment of these infections have been conducted. The treponemal infections are compared and contrasted in Table 178-1.

EPIDEMIOLOGY

Generally, yaws flourishes in moist tropical areas (Fig. 178-1); endemic syphilis has been found primarily in arid climates of West Africa and the Middle East; and pinta has been found in temperate foci in the Americas. Because no recent data are available for bejel and pinta, the extent of these infections today is unknown. The endemic treponematoses are usually limited to rural areas of developing nations and are seen in developed countries only among recent immigrants from endemic regions.

In a World Health Organization (WHO)–sponsored mass eradication campaign from 1952 to 1969, >160 million people in Africa, Asia, and South America were examined for treponemal infections, and >50 million cases, contacts, and persons with latent infections were treated. This campaign reduced the prevalence of active yaws from >20% to <1% in many areas. In subsequent decades, lack of focused surveillance and diversion of resources resulted in documented resurgence of these infections in some regions. The most recent WHO global estimate (1995) suggested that there are 460,000 new cases per year (mostly yaws) and a prevalence of 2.5 million infected persons. In 2010–2013, a total of 256,000 cases were reported, primarily from countries in which focused yaws detection and treatment trials are ongoing. Areas of resurgent yaws morbidity include West Africa (Ivory Coast, Ghana, Togo, Benin), the Central African Republic, Nigeria, and the Democratic Republic of the Congo. The prevalence of endemic syphilis

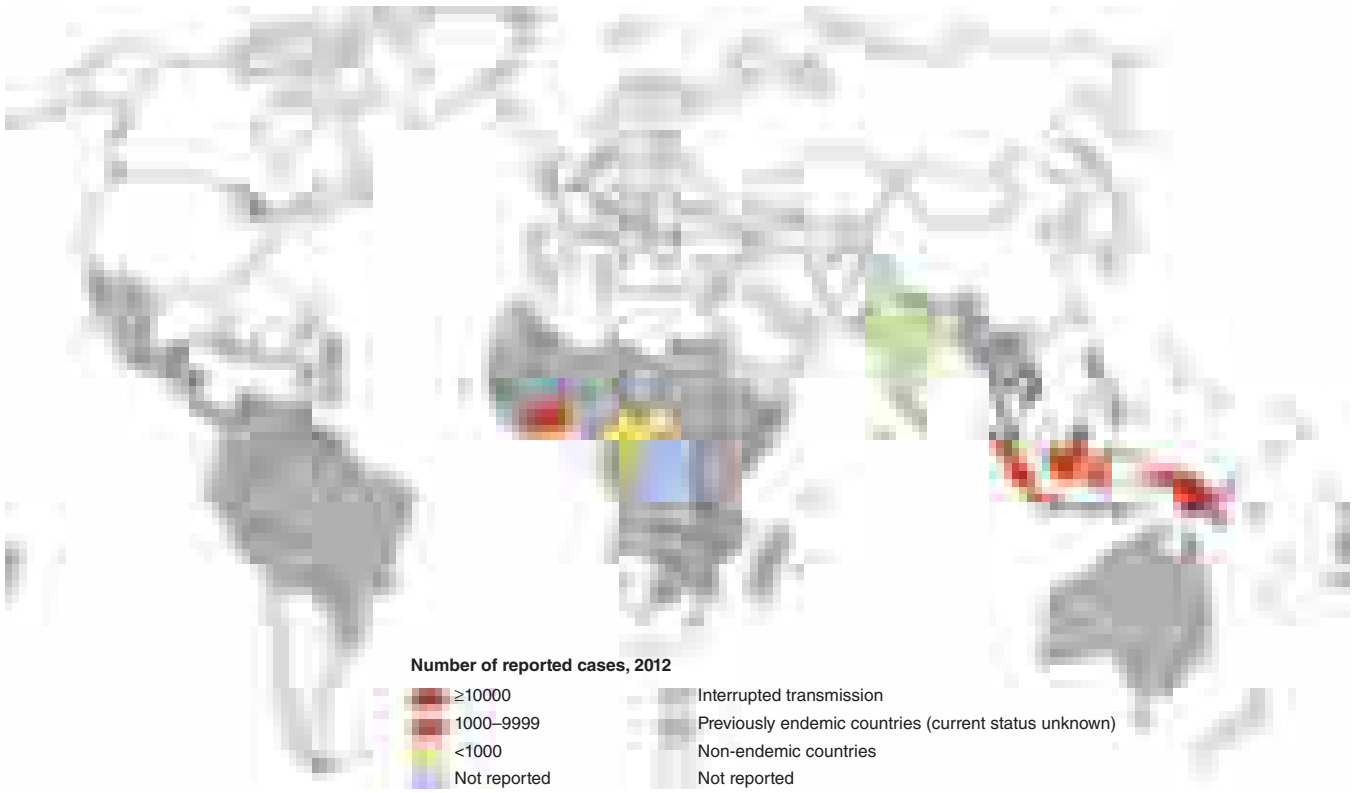


FIGURE 178-1 Geographic distribution of yaws in 2012. *(Reprinted with permission of the World Health Organization; http://www.who.int/yaws/epidemiology/Yaws_map_2012.png?ua=1.)*

is estimated to be >10% in some regions of northern Ghana, Mali, Niger, Burkina Faso, and Senegal, although data are scarce. In Asia and the Pacific Islands, reports document active outbreaks of yaws in Indonesia, Papua New Guinea, the Solomon Islands, East Timor, and Vanuatu. India actively renewed its focus on yaws control in 1996, achieved zero-case status in 2003, declared elimination in 2006, and was declared yaws-free in 2016. In the Americas, foci of yaws had been thought to persist in Haiti and other Caribbean islands, Peru, Colombia, Ecuador, Brazil, Guyana, and Surinam, although recent data are lacking. Pinta is limited to Central America and northern South America, where it is found rarely and only in very remote villages. Evidence of yaws-like and genital manifestations, with treponemal seroreactivity, has been found in wild gorillas and baboons in both West and East Africa and has led to speculation that there may be an animal reservoir for yaws. Organisms very closely related to known *T. pallidum* subspecies *pertenue* isolates have been identified in lesions from affected baboons.

MICROBIOLOGY

The etiologic agents of the endemic treponematoses are listed in Table 178-1. These little-studied organisms are morphologically identical to *T. pallidum* subspecies *pallidum* (the agent of venereal syphilis), and no definitive antigenic differences among them have been identified to date. A controversy has existed about whether the pathogenic treponemes are truly separate organisms, as genome sequencing indicates that yaws and syphilis treponemes are 99.8% identical. Three of the four etiologic agents are classified as subspecies of *T. pallidum*; the fourth (*T. carateum*) remains a separate species simply because no organisms have been available for genetic studies. Based on analysis of the small number of strains currently available, molecular signatures—assessed by restriction fragment length polymorphism and gene sequencing—have been identified that can differentiate the *T. pallidum* subspecies. Whether these genetic differences are related to distinct clinical characteristics of these diseases has not been determined. Full genome sequencing of a previously unclassified *Treponema* strain (Fribourg-Blanc), which was isolated from a baboon in 1966 and can cause experimental infection in humans, shows a very high degree of homology with available strains of *T. pallidum* subspecies *pertenue*. Recent genomic analyses of additional samples from nonhuman primates indicate a very close genetic relationship with known yaws isolates, but the importance of the nonhuman primate reservoir for human infection is not yet known.

CLINICAL FEATURES

All of the treponemal infections, including syphilis, are chronic and are characterized by defined disease stages, with a localized primary lesion, disseminated secondary lesions, periods of latency, and possible late lesions. Primary and secondary stages are more frequently overlapping in yaws and endemic syphilis than in venereal syphilis, and the late manifestations of pinta are very mild relative to the destructive lesions of the other treponematoses. The current preference is to divide the clinical course of the endemic treponematoses into "early" and "late" stages.

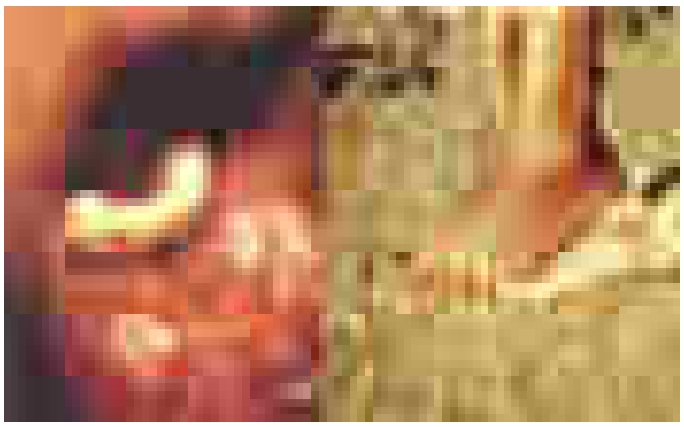
Historically, the major clinical distinctions made between venereal syphilis and the nonvenereal infections are the apparent lack of congenital transmission and of central nervous system (CNS) involvement in the nonvenereal infections. It is not known whether these distinctions are entirely accurate. Because of the high degree of genetic relatedness among the organisms, there is little biological reason to think that *T. pallidum* subspecies *endemicum* and *T. pallidum* subspecies *pertenue* would be unable to cross the blood–brain barrier or to invade the placenta. These organisms are like *T. pallidum* subspecies *pallidum* in that they obviously disseminate from the site of initial infection and can persist for decades. The lack of recognized congenital infection may be due to the fact that childhood infections often reach the latent stage (low bacterial load) before girls reach sexual maturity. Neurologic involvement may go unrecognized because of the lack of trained medical personnel in endemic regions, the delay of many years between infection and possible CNS manifestations, or a low rate of symptomatic CNS disease. Some published evidence supports congenital transmission as well as cardiovascular, ophthalmologic, and CNS involvement in yaws and endemic syphilis. Although the reported studies have been small, have failed to control for other causes of CNS abnormalities, and in some instances have not included serologic confirmation, it may be erroneous to accept unquestioningly the frequently repeated belief that these organisms fail to cause such manifestations.

Yaws Also known as *pian*, *framboesia*, or *bouba*, yaws is characterized by the development of one or several primary lesions ("mother yaw") followed by multiple disseminated skin lesions. All early skin lesions are infectious and may persist for many months; cutaneous relapses are common during the first 5 years. Late manifestations, affecting ~10% of untreated persons, are destructive lesions of skin, bone, and joints.

The infection is transmitted by direct contact with infectious lesions, often during play or group sleeping, and may be enhanced by disruption of the skin by insect bites or abrasions. While *T. pallidum* subspecies *pertenue* DNA has been detected on flies and fomites from endemic regions, there is not yet convincing evidence of insect or fomite transmission of infection. After an average of 3–4 weeks, the first lesion begins as a papule—usually on an extremity—and then enlarges (particularly during moist warm weather) to become ulcerated (Fig 178-2*A*) or papillomatous ("raspberry-like"—thus the name "framboesia"). Notably, recent data indicate that a large proportion of ulcerative lesions in yaws-endemic regions contain *Haemophilus ducreyi*, either as the sole etiologic agent or in combination with *T. pallidum* subspecies *pertenue*. (*H. ducreyi* DNA has also been detected on flies and fomites, as described above for *T. pallidum* subspecies *pertenue*.) Regional lymphadenopathy develops, and the lesion usually heals within 6 months; dissemination is thought to occur during the early weeks of infection. A generalized secondary eruption, accompanied by generalized lymphadenopathy, appears either concurrent with or after the primary lesion; may take several forms—macular, papular, or papillomatous (Fig. 178-2*B*); and may become secondarily infected with other bacteria, including *H. ducreyi*. Painful papillomatous lesions on the soles of

A B C

FIGURE 178-2 Clinical manifestations of early yaws. *A.* Primary ulcer. ***B.*** Secondary papillomata. ***C.*** Periostitis and polydactylitis. *(Photos were taken during a yaws elimination trial in Papua New Guinea and are published with permission from Dr. Oriol Mitjà.)*



A *B*

FIGURE 178-3 Clinical manifestations of endemic syphilis and pinta. ***A.*** Mucous patches of early endemic syphilis. ***B.*** Pigmented macules of early pinta. *(Photos reprinted with permission from the Handbook of Endemic Treponematoses, PL Perine et al, Geneva, World Health Organization, Color Plates 54, 60; 1984.)*

the feet result in a crablike gait ("crab yaws"), and periostitis may result in nocturnal bone pain and polydactylitis **(Fig. 178-2*C*)**. Late yaws is manifested by gummas of the skin and long bones, hyperkeratoses of the palms and soles, osteitis and periostitis, and hydrarthrosis. The late gummatous lesions are characteristically extensive. Destruction of the nose, maxilla, palate, and pharynx is termed *gangosa* and is similar to the destructive lesions seen in leprosy and leishmaniasis.

Endemic Syphilis The early lesions of endemic syphilis (*bejel*, *siti*, *dichuchwa*, *njovera*, *skerljevo*) are localized primarily to mucocutaneous and mucosal surfaces. The infection is reportedly transmitted by direct contact, by kissing, by premastication of food, or by sharing of drinking and eating utensils. A role for insects in transmission has been suggested but is unproven. The initial lesion, usually an intraoral papule, often goes unrecognized and is followed by mucous patches on the oral mucosa **(Fig. 178-3*A*)** and mucocutaneous lesions resembling the condylomata lata of secondary syphilis. This eruption may last for months or even years, and treponemes can readily be demonstrated in early lesions. Periostitis and regional lymphadenopathy are common. After a variable period of latency, late manifestations may appear, including osseous and cutaneous gummas. Destructive gummas, osteitis, and gangosa are more common in endemic syphilis than in yaws.

Pinta Pinta (*mal del pinto*, *carate*, *azul*, *purupuru*) is the most benign of the treponemal infections. This disease has three stages that are characterized by marked changes in skin color **(Fig. 178-3*B*)**, but pinta does not appear to cause destructive lesions or to involve tissues other than the skin. The initial papule is most often located on the extremities or face and is pruritic. After one to many months of infection, numerous disseminated secondary lesions (*pintides*) appear. These lesions are initially red but become deeply pigmented, ultimately turning a dark slate blue. The secondary lesions are infectious and highly pruritic and may persist for years. Late pigmented lesions are called *dyschromic macules* and contain treponemes. Over time, most pigmented lesions show varying degrees of depigmentation, becoming brown and eventually white and giving the skin a mottled appearance. White achromic lesions are characteristic of the late stage.

DIAGNOSIS

Diagnosis of the endemic treponematoses is based on clinical manifestations and, when available, dark-field microscopy and serologic testing. The same serologic tests that are used for venereal syphilis **(Chap. 177)** become reactive during all treponemal infections. Although several targets have been evaluated for specific serodiagnosis, to date there is no antibody test that can discriminate among the different infections. The nonvenereal treponemal infections should be considered in the evaluation of a reactive syphilis serology in any person who has emigrated from an endemic area. Sensitive polymerase chain reaction assays can be used to confirm treponemal infection and to identify the etiologic agent in research laboratories.

TREATMENT

Endemic Treponematoses

The current WHO-recommended therapy for patients and their contacts includes either azithromycin (30 mg/kg, up to a maximum of 2 g) or benzathine penicillin G (1.2 million units IM for adults; 600,000 units for children <10 years old); these two drugs have been shown to be equivalent in a recent study. The recommended dose of benzathine penicillin is half of that recommended for early venereal syphilis, and no controlled efficacy studies have been conducted. Definitive evidence of resistance to penicillin is lacking, although relapsing lesions have been reported after penicillin treatment in Papua New Guinea.

The efficacy of single-dose azithromycin provided the WHO's revitalized yaws eradication program with a much easier regimen for use in mass treatment. Although macrolide resistance has become common in circulating strains of *T. pallidum* subspecies *pallidum* in many parts of the world, analysis of yaws samples from Papua New Guinea has only recently yielded evidence of mutations for resistance to macrolide antibiotics, including azithromycin, in a very small number of patients. Further surveillance is essential. Limited data suggest the efficacy of tetracycline for treatment of yaws, but no data exist for other endemic treponematoses. Solely on the basis of experience with venereal syphilis, it is thought that doxycycline or tetracycline (at doses appropriate for syphilis; **Chap. 177**) are alternatives, in addition to azithromycin, for patients allergic to penicillin. A Jarisch-Herxheimer reaction **(Chap. 177)** may follow treatment of endemic treponematoses. Nontreponemal serologic titers (in the Venereal Disease Research Laboratory [VDRL] slide test or the rapid plasma reagin [RPR] test) usually decline after effective therapy, but patients may not become seronegative.

CONTROL

Buoyed by the successful elimination of yaws in India and the availability of an inexpensive, single-dose oral drug for treatment, in 2012 the WHO renewed its efforts to eradicate yaws globally by 2020. Enthusiasm is high; several pilot programs of MDA have been conducted; and expansion of this approach to other regions is planned. Some caution is warranted: (1) Pilot studies indicate that a very high level of MDA coverage must be achieved, and mathematical modeling suggests that multiple rounds of MDA may be needed. Treatment must be followed by careful case detection and targeted treatment of cases and contacts. (2) The specter of increasing azithromycin resistance looms, and there may be only a short window of time during which countries can successfully use azithromycin for yaws eradication. Antibiotic resistance is of particular concern if multiple rounds of MDA are required. Further, given the ongoing campaigns against trachoma using low-dose azithromycin MDA, often in populations also at high risk for yaws, more widespread macrolide resistance seems inevitable. (3) Lastly, the possible animal reservoir needs be evaluated, particularly in Africa. Yaws elimination will require rapid implementation and scale-up of high-level drug coverage in endemic areas, and continued, careful surveillance by local health centers will be essential for success of this timely and important effort.

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179 Leptospirosis

Jiři F. P. Wagenaar, Marga G. A. Goris

Leptospirosis is a globally important zoonotic disease whose apparent reemergence is illustrated by recent outbreaks on virtually all continents. The disease is caused by pathogenic *Leptospira* species and is characterized by a broad spectrum of clinical manifestations, varying from asymptomatic infection to fulminant, fatal disease. In its mild form, leptospirosis may present as nonspecific symptoms such as fever, headache, and myalgia. Severe leptospirosis, characterized by jaundice, renal dysfunction, and hemorrhagic diathesis, is often referred to as *Weil's syndrome*. With or without jaundice, severe pulmonary hemorrhage is increasingly recognized as an important presentation of severe disease.

ETIOLOGIC AGENT

Leptospira species are spirochetes belonging to the order Spirochaetales and the family Leptospiraceae. Traditionally, the genus *Leptospira* comprised two species: the pathogenic *L. interrogans* and the free-living *L. biflexa*, now designated *L. interrogans* sensu lato and *L. biflexa* sensu lato, respectively. Twenty-two *Leptospira* species with pathogenic (10 species), intermediate (5 species), and nonpathogenic (7 species) status have now been described on the basis of phylogenetic and virulence analyses **(Fig. 179-1)**. Genome sequences of five *Leptospira* species (*L. biflexa*, *L. interrogans*, *L. santarosai*, *L. borgpetersenii*, and *L. licerasiae*) have been published, and the availability of genome sequences of a wide variety of *Leptospira* strains will undoubtedly lead to a better understanding of the pathogenesis of leptospirosis. However, classification based on serologic differences better serves clinical, diagnostic, and epidemiologic purposes. Pathogenic *Leptospira* species are divided into serovars according to their antigenic composition. More than 250 serovars make up the 26 serogroups.

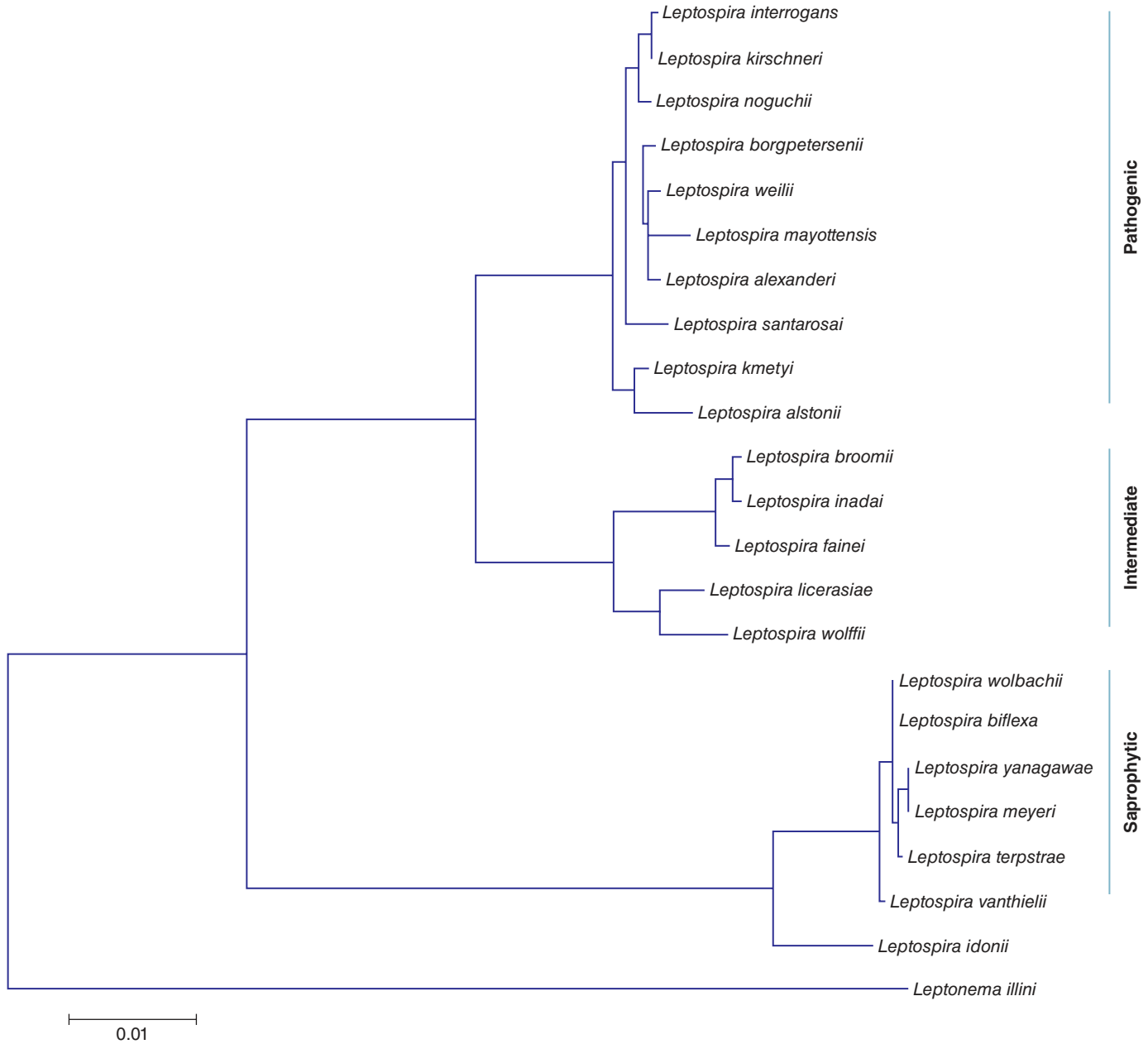

FIGURE 179-1 Differentiation of pathogenic, intermediate, and nonpathogenic (saprophytic) *Leptospira* species by molecular phylogenetic analysis using the *rrs* gene. Scale bar labeled 0.01 indicates the rate of nucleotide substitutions per base pair. *(Figure prepared and provided by Dr. A. Ahmed, Leptospirosis Reference Center, Academic Medical Center, Medical Microbiology, Amsterdam, The Netherlands.)*

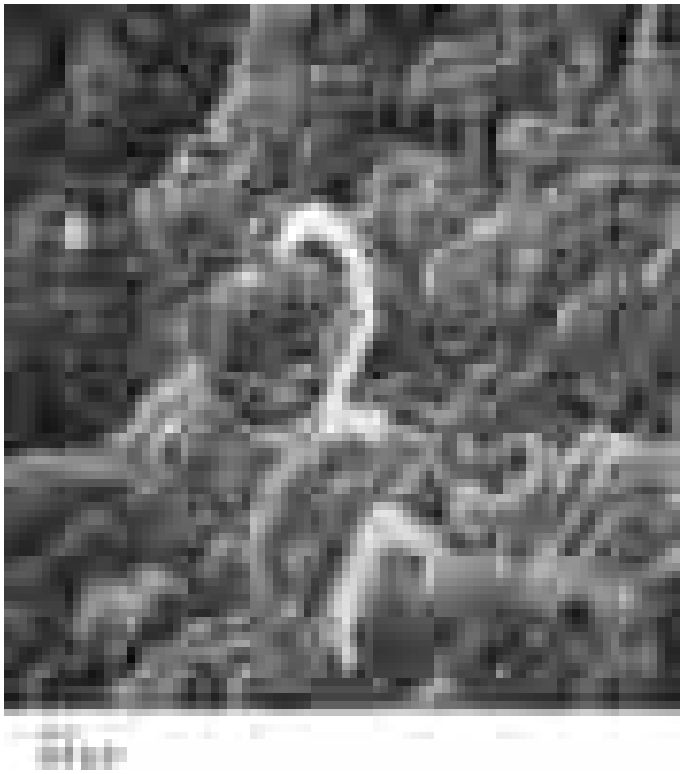

FIGURE 179-2 Transmission electron microscopic image of *Leptospira interrogans* invading equine conjunctival tissue. *(Image kindly provided by Dr. J. E. Nally, National Animal Disease Center, U.S. Department of Agriculture, Ames, IA.)*

Leptospires are coiled, thin, highly motile organisms that have hooked ends and two periplasmic flagella, with polar extrusions from the cytoplasmic membrane that are responsible for motility **(Fig. 179-2)**. These organisms are 6–20 µm long and ~0.1 µm wide; they stain poorly but can be seen microscopically by dark-field examination and after silver impregnation staining of tissues. Leptospires require special media and conditions for growth; it may take weeks to months for cultures to become positive.

EPIDEMIOLOGY

Leptospirosis has a worldwide distribution but occurs most commonly in the tropics and subtropics because the climate and occasionally poor hygienic conditions favor the pathogen's survival and distribution. In most countries, leptospirosis is an underappreciated problem. Most cases occur in men, with a peak incidence during the summer and fall in both the Northern and Southern Hemispheres and during the rainy season in the tropics.

Reliable data on morbidity and mortality from leptospirosis have gradually started to appear. Current information on global human leptospirosis varies but indicates that ~1 million severe cases occur per year, with a mean case–fatality rate of nearly 10%.

As a zoonosis, leptospirosis affects almost all mammalian species and represents a significant veterinary burden. Rodents, especially rats, are the most important reservoir, although other wild mammals as well as domestic and farm animals may also harbor these microorganisms. Leptospires establish a symbiotic relationship with their host and can persist in the urogenital tract for years. Some serovars are generally associated with particular animals—e.g., Icterohaemorrhagiae and Copenhageni with rats, Grippotyphosa with voles, Hardjo with cattle, Canicola with dogs, and Pomona with pigs—but may occur in other animals as well.

Leptospirosis presents as both an endemic and an epidemic disease. Transmission of leptospires may follow direct contact with urine, blood, or tissue from an infected animal or, more commonly, exposure to environmental contamination. The dogma that human-to-human transmission is very rare is challenged by recent findings on household clustering, asymptomatic renal colonization, and prolonged excretion of leptospires. (Both of the latter features imply human infection sources that are not recognized.) Because leptospires can survive in a humid environment for many months, water is an important vehicle in their transmission. Epidemics of leptospirosis are not well understood. Outbreaks may result from exposure to flood waters contaminated by urine from infected animals, as has been reported from several countries. However, it is also true that outbreaks may occur without floods, and floods often occur without outbreaks.

The vast majority of infections with *Leptospira* cause no or only mild disease in humans. A small percentage of infections (~1%) lead to severe, potentially fatal complications. The proportion of leptospirosis cases that are mild is unknown because patients either do not seek or do not have access to medical care or because the nonspecific symptoms are interpreted as an influenza-like illness. Reported cases surely represent a significant underestimation of the total number. Certain occupational groups are at especially high risk, including veterinarians, agricultural workers, sewage workers, slaughterhouse employees, and workers in the fishing industry. Risk factors include direct or indirect contact with animals, including exposure to water and soil contaminated with animal urine. Leptospirosis has also been recognized in deteriorating inner cities and suburban areas where rat populations are expanding.

Recreational exposure and domestic-animal contact are prominent sources of leptospirosis. Recreational freshwater activities, such as canoeing, windsurfing, swimming, and waterskiing, place persons at risk for infection. Several outbreaks have followed sporting events. For example, an outbreak took place in 1998 among athletes after a triathlon in Springfield, Illinois. Ingestion of one or more swallows of lake water during the swimming leg of the triathlon was a prominent risk factor for illness. Heavy rains that preceded the triathlon, with consequent agricultural runoff, are likely to have increased the level of leptospiral contamination in the lake water. In another outbreak, 42% of participants contracted leptospirosis during the 2000 Eco-Challenge-Sabah multisport endurance race in Malaysian Borneo. Swimming in the Segama River was shown to be an independent risk factor.

In addition, leptospirosis is a traveler's disease. Large proportions of patients acquire the infection while traveling in tropical countries, usually during adventurous activities such as whitewater rafting, jungle trekking, and caving. Transmission via laboratory accidents has been reported but is rare. New data indicate that leptospirosis may develop after unanticipated immersion in contaminated water (e.g., in an automobile accident) more frequently than has generally been thought and can also result from an animal bite.

PATHOGENESIS

Transmission occurs through cuts, abraded skin, or mucous membranes, especially the conjunctival and oral mucosa. After entry, the organisms proliferate, cross tissue barriers, and disseminate hematogenously to all organs (*leptospiremic phase*). During this initial incubation period, leptospires can be isolated from the bloodstream **(Fig. 179-3)**. The organisms are able to survive in the nonimmune host: they evade complement-mediated killing by binding factor H, a strong inhibitor of the complement system, on their surface. Moreover, pathogenic leptospires resist ingestion and killing by neutrophils, monocytes, and macrophages. During the *immune phase*, the appearance of antibodies coincides with the disappearance of leptospires from the blood. However, the bacteria persist in various organs, including liver, lung, kidney, heart, and brain. Autopsy findings illustrate the involvement of multiple organ systems in severe disease. Renal pathology shows both acute tubular damage and interstitial nephritis. Acute tubular lesions progress in time to interstitial edema and acute tubular necrosis. Severe nephritis is observed in patients who survive long enough to develop it and seems to be a secondary response to acute epithelial damage. The reported deregulation of the expression of several transporters along the nephron contributes to impaired sodium absorption, tubular potassium wasting, and polyuria. Histopathology of the liver shows focal necrosis (widespread hepatocellular necrosis usually is not found), foci

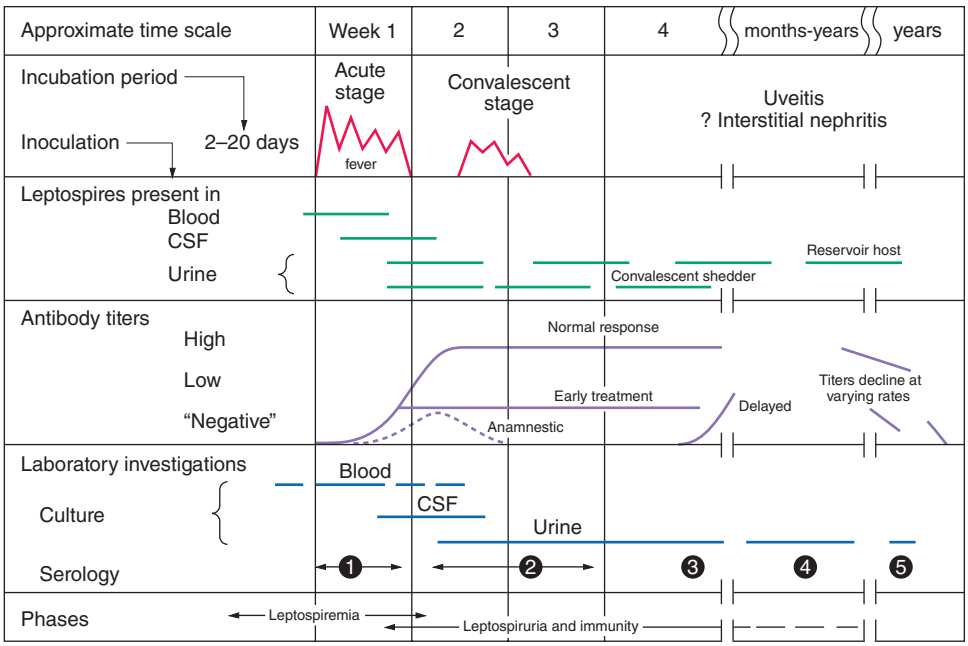

FIGURE 179-3 Biphasic nature of leptospirosis and relevant investigations at different stages of disease. *Note that an incubation period of up to 1 month has now been documented.* Specimens 1 and 2 for serology are acute-phase serum samples; specimen 3 is a convalescent-phase serum sample that may facilitate detection of a delayed immune response; and specimens 4 and 5 are follow-up serum samples that can provide epidemiologic information, such as the presumptive infecting serogroup. CSF, cerebrospinal fluid. *(Reprinted as adapted by PN Levett: Clin Microbiol Rev 14:296, 2001 [from LH Turner: Leptospirosis. BMJ 1:231, 1969] with permission from the American Society for Microbiology and the BMJ Publishing Group.)*

of inflammation, and plugging of bile canaliculi. Hepatocyte apoptosis has also been documented. Experimental work showed infiltration of *Leptospira* in Disse's space and migration between hepatocytes with detachment of the intercellular junctions and disruption of bile canaliculi leading to bile leakage. Petechiae and hemorrhages are observed in the heart, lungs (Fig. 179-4), kidneys (and adrenals), pancreas, liver, gastrointestinal tract (including retroperitoneal fat, mesentery, and omentum), muscles, prostate, testis, and brain (subarachnoid bleeding). Several studies show an association between hemorrhage and thrombocytopenia. Although the underlying mechanisms of thrombocytopenia have not been elucidated, it seems likely that platelet consumption plays an important role. A consumptive coagulopathy may occur, with elevated markers of coagulation activation (thrombin–antithrombin complexes, prothrombin fragments 1 and 2, D-dimer), diminished anticoagulant markers (antithrombin, protein C), and deregulated fibrinolytic activity. Overt disseminated intravascular coagulation (DIC) has been documented in several studies. Elevated plasma levels of soluble E-selectin and von Willebrand factor in patients with leptospirosis reflect endothelial cell activation. Experimental models show that pathogenic leptospires or leptospiral proteins are able to activate endothelial cells in vitro and to disrupt endothelial-cell barrier function, promoting dissemination. Platelets have been shown to aggregate on activated endothelium in the human lung, whereas histology reveals swelling of activated endothelial cells but no evident vasculitis or necrosis. Immunoglobulin and complement deposition have been demonstrated in lung tissue involved in pulmonary hemorrhage.

Leptospira species have a typical double-membrane cell wall structure harboring a variety of membrane-associated proteins, including an unusually high number of lipoproteins. The peptidoglycan layer is located close to the cytoplasmic membrane. The lipopolysaccharide (LPS) in the outer membrane has an unusual structure with relatively low endotoxic potency. Pathogenic leptospires contain a variety of genes coding for proteins involved in motility and in cell and tissue adhesion and invasion that represent potential virulence factors. Many of these are surface-exposed outer-membrane proteins (OMPs). To date, the only leptospiral virulence factor shown to satisfy Koch's molecular postulates is *loa22* encoding a surface-exposed protein with an unknown function. However, the gene is not confined to pathogenic *Leptospira* species.

Immunity to *Leptospira* depends on the production of circulating antibodies to serovar-specific LPS. It is unclear whether other antigens play a significant role in protective humoral immunity. Moreover, immunity may not be confined to antibody responses; involvement of the innate-immune Toll-like receptor 2 (TLR2) and TLR4 activation pathways in controlling infection has been demonstrated, whereas in vaccinated cattle a cell-mediated immune response is correlated with protection. In recent work, the whole-blood transcriptome of patients from Brazil with severe leptospirosis (13 who survived and 3 who died) were studied. In fatal cases, expression of chemokines and the antimicrobial peptide cathelicidin was decreased, whereas transcription of proinflammatory cytokine pathways was more abundant. Previous studies had also highlighted the relation between an exaggerated proinflammatory immune response and death. Moreover, the recent study provided evidence that patients who die of leptospirosis fail to mount an adequate humoral immune response to leptospires.

It is likely that several surface-exposed proteins mediate leptospire–host cell interactions, and these proteins may represent candidate vaccine components. Although animal-model studies have shown various degrees of vaccine efficacy for various putative virulence-associated OMPs, it is not yet clear whether such proteins elicit acceptable levels of sterilizing immunity.

FIGURE 179-4 Severe pulmonary hemorrhage in leptospirosis. ***Left panel:*** Chest x-ray. ***Right panel:*** Gross appearance of right lower lobes of lung at autopsy. This patient, a 15-year-old from the Peruvian Amazonian city of Iquitos, died several days after presentation with acute illness, jaundice, and hemoptysis. Blood culture yielded *Leptospira interrogans* serovar Copenhageni/Icterohaemorrhagiae. *(Adapted with permission from E Segura et al: Clin Infect Dis 40:343, 2005. © 2005 by the Infectious Diseases Society of America.)*

CLINICAL MANIFESTATIONS

Although leptospirosis is a potentially fatal disease with bleeding and multiorgan failure as its clinical hallmarks, the majority of cases are thought to be relatively mild, presenting as the sudden onset of a febrile illness. The incubation period is usually 1–2 weeks but ranges from 1 to 30 days. (Figure 179-3 indicates a slightly different range, but an incubation period of up to 1 month

has now been documented.) Leptospirosis is classically described as biphasic. The acute *leptospiremic phase* is characterized by fever of 3–10 days' duration, during which time the organism can be cultured from blood and detected by polymerase chain reaction (PCR). During the *immune phase*, resolution of symptoms may coincide with the appearance of antibodies, and leptospires can be cultured from the urine. The distinction between the first and second phases is not always clear: milder cases do not always include the second phase, and severe disease may be monophasic and fulminant. The idea that distinct clinical syndromes are associated with specific serogroups has been refuted, although some serovars tend to cause more severe disease than others.

Mild Leptospirosis Most patients are asymptomatic or only mildly ill and do not seek medical attention. Serologic evidence of past inapparent infection is frequently found in persons who have been exposed but have not become ill. Mild symptomatic leptospirosis usually presents as a flu-like illness of sudden onset, with fever, chills, headache, nausea, vomiting, abdominal pain, conjunctival suffusion (redness without exudate), and myalgia. Muscle pain is intense and especially affects the calves, back, and abdomen. The headache is intense, localized to the frontal or retroorbital region (resembling that occurring in dengue), and sometimes accompanied by photophobia. Aseptic meningitis may be present and is more common among children than among adults. Although *Leptospira* can be cultured from the cerebrospinal fluid (CSF) in the early phase, the majority of cases follow a benign course with regard to the central nervous system; symptoms usually disappear within a few days but may persist for weeks.

Physical examination may include any of the following findings, none of which is pathognomonic for leptospirosis: fever, conjunctival suffusion, pharyngeal injection, muscle tenderness, lymphadenopathy, rash, meningismus, hepatomegaly, and splenomegaly. If present, the rash is often transient; may be macular, maculopapular, erythematous, or hemorrhagic (petechial or ecchymotic); and may be misdiagnosed as due to scrub typhus or viral infection. Lung auscultation may reveal crackles. Mild jaundice may be present.

The natural course of mild leptospirosis usually involves spontaneous resolution within 7–10 days, but persistent symptoms have been documented. In the absence of a clinical diagnosis and antimicrobial therapy, the mortality rate in mild leptospirosis is low.

Severe Leptospirosis Although the onset of severe leptospirosis may be no different from that of mild leptospirosis, severe disease is often rapidly progressive and is associated with a case–fatality rate ranging from 1 to 50%. Higher mortality rates are associated with an age >40, altered mental status, acute renal failure, respiratory insufficiency, hypotension, and arrhythmias. The classic presentation, often referred to as *Weil's syndrome*, encompasses the triad of hemorrhage, jaundice, and acute kidney injury.

Patients die of septic shock with multiorgan failure and/or severe bleeding complications that most commonly involve the lungs (pulmonary hemorrhage), gastrointestinal tract (melena, hemoptysis), urogenital tract (hematuria), and skin (petechiae, ecchymosis, and bleeding from venipuncture sites). Pulmonary hemorrhage (with or without jaundice) is now recognized as a widespread public health problem, presenting with cough, chest pain, respiratory distress, and hemoptysis that may not be apparent until patients are intubated.

Jaundice occurs in 5–10% of all patients with leptospirosis; it can be profound and give an orange cast to the skin but usually is not associated with fulminant hepatic necrosis. Physical examination may reveal an enlarged and tender liver.

Acute kidney injury is common in severe disease, presenting after several days of illness, and can be either nonoliguric or oliguric. Typical electrolyte abnormalities include hypokalemia and hyponatremia. Loss of magnesium in the urine is uniquely associated with leptospiral nephropathy. Hypotension is associated with acute tubular necrosis, oliguria, or anuria, requiring fluid resuscitation and sometimes vasopressor therapy. Hemodialysis can be lifesaving, with renal function typically returning to normal in survivors.

In severe leptospirosis, altered mental status may reflect leptospiral meningitis. The diagnosis of leptospiral meningitis may be challenging since patients may be anicteric or lack other diagnostic hallmarks of severe leptospirosis. Without proper antibiotic treatment, a mortality rate of 13% has been reported; in contrast, among patients treated with antibiotics, the mortality rate is 2%. Neurologic sequelae are described until months after acute illness.

Other syndromes include (necrotizing) pancreatitis, cholecystitis, skeletal muscle involvement, and rhabdomyolysis with moderately elevated levels of serum creatine kinase. Cardiac involvement is commonly reflected on the electrocardiogram as nonspecific ST- and T-wave changes. Repolarization abnormalities and arrhythmias are considered poor prognostic factors. Myocarditis has been described. Rare hematologic complications include hemolysis, thrombotic thrombocytopenic purpura, and hemolytic-uremic syndrome.

Long-term symptoms following severe leptospirosis include fatigue, myalgia, malaise, and headache and may persist for years. Autoimmune-associated uveitis, a potentially chronic condition, is a recognized sequela of leptospirosis.

DIAGNOSIS

The clinical diagnosis of leptospirosis should be based on an appropriate exposure history combined with any of the protean manifestations of the disease. Returning travelers from endemic areas usually have a history of recreational freshwater activities or other mucosal or percutaneous contact with contaminated surface waters or soil. For nontravelers, recreational or accidental water/soil contact and occupational hazards that involve direct or indirect animal contact should be explored (see "Epidemiology," above).

Although biochemical, hematologic, and urinalysis findings in acute leptospirosis are nonspecific, certain patterns may suggest the diagnosis. Laboratory results usually show signs of a bacterial infection, including leukocytosis with a left shift and elevated markers of inflammation (C-reactive protein level, procalcitonin level, and erythrocyte sedimentation rate). Thrombocytopenia (platelet count $\leq 100 \times 10^9$/L) is common and is associated with bleeding and renal failure. In severe disease, signs of coagulation activation may be present, varying from borderline abnormalities to a serious derangement compatible with DIC as defined by international criteria. The kidneys are invariably involved in leptospirosis. Related findings range from urinary sediment changes (leukocytes, erythrocytes, and hyaline or granular casts) and mild proteinuria in mild disease to renal failure and azotemia in severe leptospirosis. Nonoliguric hypokalemic renal insufficiency (see "Clinical Manifestations," above) is characteristic of early leptospirosis. Serum bilirubin levels may be high, whereas rises in aminotransferase and alkaline phosphatase levels are usually moderate. Although clinical symptoms of pancreatitis are not a common finding, amylase levels are often elevated. When symptoms of meningitis develop, examination of the CSF shows pleocytosis that can range from a few cells to >1000 cells/μL, with a predominance of lymphocytes. Predominant polymorphonuclear pleocytosis has been reported. This phenomenon may be related to the timing of the lumbar puncture: polymorphonuclear cells are thought to be found in early disease and are later replaced by lymphocytes. Although protein and glucose levels in CSF are usually normal, protein levels may be slightly elevated.

In severe leptospirosis, pulmonary radiographic abnormalities are more common than would be expected on the basis of physical examination (Fig. 179-4). The most common radiographic finding is a patchy bilateral alveolar pattern that corresponds to scattered alveolar hemorrhage. These abnormalities predominantly affect the lower lobes. Other findings include pleura-based densities (representing areas of hemorrhage) and diffuse ground-glass attenuation typical of acute respiratory distress syndrome (ARDS).

A definitive diagnosis of leptospirosis is based on isolation of the organism from the patient, on a positive PCR result, or on seroconversion or a rise in antibody titer. In cases with strong clinical evidence of infection, a single antibody titer of 1:200–1:800 (depending on whether the case occurs in a low- or high-endemic area) in the microscopic agglutination test (MAT) is required. Preferably, a fourfold or greater

rise in titer is detected between acute- and convalescent-phase serum specimens. Antibodies generally do not reach detectable levels until the second week of illness. The antibody response can be affected by early treatment with antibiotics.

The MAT, which uses a battery of live leptospiral strains, and the enzyme-linked immunosorbent assay (ELISA), which uses a broadly reacting antigen, are the standard serologic procedures. The MAT usually is available only in specialized laboratories and is used for determination of the antibody titer and for tentative identification of the involved leptospiral serogroup—and, when epidemiologic background information is available, the putative serovar. This point underscores the importance of testing antigens representative of the serovars prevalent in the particular geographic area. However, cross-reactions occur frequently, and thus definitive identification of the infecting serovar or serogroup is not possible without isolation of the causative organism. Because serologic testing lacks sensitivity in the early acute phase of the disease (up to day 5), it cannot be used as the basis for a timely decision about whether to start treatment.

In addition to the MAT and the ELISA, various rapid tests with diagnostic value have been developed, and some of these are commercially available. These rapid tests mainly apply lateral flow, (latex) agglutination, or ELISA methodology and are reasonably sensitive and specific, although results reported in the literature vary, probably as a consequence of differences in test interpretation, (re)exposure risks, serovar distribution, and the use of biased serum panels. These methods do not require culture or MAT facilities and are useful in settings that lack a strong medical infrastructure. PCR methodologies, notably real-time PCR, have become increasingly widely implemented. Compared with serology, PCR offers a great advantage: the capacity to confirm the diagnosis of leptospirosis with a high degree of accuracy during the first 5 days of illness.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of leptospirosis is broad, reflecting the diverse clinical presentations of the disease. Although leptospirosis transmission is more common in tropical and subtropical regions, the absence of a travel history does not exclude the diagnosis. When fever, headache, and myalgia predominate, influenza and other common and less common viral infections (e.g., dengue and chikungunya) should be considered. Malaria, typhoid fever, ehrlichiosis, viral hepatitis, and acute HIV infection may mimic the early stages of leptospirosis and are important to recognize. Rickettsial diseases as well as dengue and hantavirus infections (hemorrhagic fever with renal syndrome or hantavirus cardiopulmonary syndrome) share epidemiologic and clinical features with leptospirosis. Dual infections have been reported. In this light, it is advisable to conduct serologic testing for rickettsiae, dengue virus, and hantavirus when leptospirosis is suspected. When bleeding is detected, dengue hemorrhagic fever and other viral hemorrhagic fevers, including hantavirus infection, yellow fever, Rift Valley fever, filovirus infections, and Lassa fever, should be considered.

TREATMENT

Leptospirosis

Severe leptospirosis should be treated with IV penicillin (Table 179-1) as soon as the diagnosis is considered. Leptospires are highly susceptible to a broad range of antibiotics, including the β-lactam antibiotics, cephalosporins, aminoglycosides, and macrolides, but are not susceptible to vancomycin, rifampin, metronidazole, and chloramphenicol. Early intervention may prevent the development of major organ-system failure or lessen its severity. Although studies supporting antibiotic therapy have produced conflicting results, clinical trials are difficult to perform in settings where patients frequently present for medical care with late stages of disease. Antibiotics are less likely to benefit patients in whom organ damage has already occurred. Two open-label randomized studies comparing penicillin with parenteral cefotaxime, parenteral ceftriaxone, and doxycycline showed no significant differences among the antibiotics with regard to complications and mortality risk. Thus ceftriaxone, cefotaxime, or doxycycline is a satisfactory alternative to penicillin for the treatment of severe leptospirosis. Antimicrobial susceptibility testing is not routine practice in individual cases of leptospirosis; to date, however, antibiotic resistance has not been reported in isolates from patients or the environment.

TABLE 179-1 Treatment and Chemoprophylaxis of Leptospirosis in Adults[a]

INDICATION	REGIMEN
Treatment	
Mild leptospirosis	Doxycycline[b] (100 mg PO bid) *or* Amoxicillin (500 mg PO tid) *or* Ampicillin (500 mg PO tid)
Moderate/severe leptospirosis	Penicillin (1.5 million units IV or IM q6h) *or* Ceftriaxone (2 g/d IV) *or* Cefotaxime (1 g IV q6h) *or* Doxycycline[b] (loading dose of 200 mg IV, then 100 mg IV q12h)
Chemoprophylaxis[c]	
	Doxycycline[b] (200 mg PO once a week) *or* Azithromycin (250 mg PO once or twice a week)

[a]All regimens are given for 7 days. [b]Doxycycline should not be given to pregnant women or children. [c]The efficacy of doxycycline prophylaxis in endemic or epidemic settings remains unclear. Experiments in animal models and a cost-effectiveness model indicate that azithromycin has a number of characteristics that may make it efficacious in treatment and prophylaxis.

In mild cases, oral treatment with doxycycline, azithromycin, ampicillin, or amoxicillin is recommended. In regions where rickettsial diseases are coendemic, doxycycline or azithromycin is the drug of choice. In rare instances, a Jarisch-Herxheimer reaction develops within hours after the initiation of antimicrobial therapy.

Aggressive supportive care for leptospirosis is essential and can be lifesaving. Patients with nonoliguric renal dysfunction require aggressive fluid and electrolyte resuscitation to prevent dehydration and precipitation of oliguric renal failure. Peritoneal dialysis or hemodialysis should be provided to patients with oliguric renal failure. Rapid initiation of hemodialysis has been shown to reduce mortality risk and typically is necessary only for short periods. Patients with pulmonary hemorrhage may have reduced pulmonary compliance (as seen in ARDS) and may benefit from mechanical ventilation with low tidal volumes to avoid high ventilation pressures. Evidence is contradictory for the use of glucocorticoids and desmopressin as adjunct therapy for pulmonary involvement associated with severe leptospirosis.

PROGNOSIS

Most patients with leptospirosis recover. However, post-leptospirosis symptoms, mainly of a depression-like nature, may occur and persist for years after the acute disease. Mortality rates are highest among patients who are elderly and those who have severe disease (pulmonary hemorrhage, Weil's syndrome). Leptospirosis during pregnancy is associated with high fetal mortality rates. Long-term follow-up of patients with renal failure and hepatic dysfunction has documented good recovery of renal and hepatic function.

PREVENTION

Individuals who may be exposed to *Leptospira* through their occupations or their involvement in recreational freshwater activities should be informed about the risks. Measures for controlling leptospirosis include avoidance of exposure to urine and tissues from infected animals through proper eyewear, footwear, and other protective equipment. Targeted rodent-control strategies could be considered.

Vaccines for agricultural and companion animals are generally available, and their use should be encouraged. The veterinary vaccine used in a given area should contain the serovars known to be present in that area. Unfortunately, some vaccinated animals still excrete leptospires in their urine. Vaccination of humans

against a specific serovar prevalent in an area has been undertaken in some European and Asian countries and has proved effective. Although a large-scale trial of vaccine in humans has been reported from Cuba, no conclusions can be drawn about efficacy and adverse reactions because of insufficient details on study design. The efficacy of chemoprophylaxis with doxycycline (200 mg once a week) or azithromycin (in pregnant women and children) is being disputed, but focused pre- and postexposure administration is indicated in instances of well-defined short-term exposure (Table 179-1).

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180 Relapsing Fever

Alan G. Barbour

Relapsing fever is caused by infection with any of several species of *Borrelia* spirochetes. Physicians in ancient Greece distinguished relapsing fever from other febrile disorders by its characteristic clinical presentation: two or more episodes of fever separated by varying periods of well-being. In the nineteenth century, relapsing fever was one of the first diseases to be associated with a specific microbe by virtue of its characteristic laboratory finding: the presence of large numbers of spirochetes of the genus *Borrelia* in the blood.

The host responds with systemic inflammation that results in an illness ranging from a flu-like syndrome to sepsis. Other manifestations are the consequences of central nervous system (CNS) involvement and coagulopathy. Antigenic variation of the spirochetes' surface proteins accounts for the infection's relapsing course. Acquired immunity follows the serial development of antibodies to each of the several variants appearing during an infection. Treatment with antibiotics results in rapid cure but at the risk of a moderate to severe Jarisch-Herxheimer reaction.

Louse-borne relapsing fever (LBRF) caused large epidemics well into the twentieth century and currently occurs in northeastern Africa and among migrants from that area. At present, however, most cases of relapsing fever are tick-borne in origin. Sporadic cases and small outbreaks are focally distributed on most continents, with Africa and Central Asia most affected. In North America, the majority of reports of relapsing fever have been from the western United States and Canada. Nevertheless, the recent discovery that another species in the relapsing fever group causes human disease in the same geographic distribution as Lyme disease **(Chap. 181)** confounds epidemiologic distinctions between the two infections.

ETIOLOGIC AGENT

Coiled, thin microscopic filaments that swim in one direction and then coil up before heading in another were first observed in the blood of patients with relapsing fever in the 1880s (*www.youtube.com/watch?v=VxDPV2lBd9U*). These microbes were categorized as spirochetes and assigned to the genus *Borrelia*. It was not until the 1960s that the organisms were isolated in pure culture. The breakthrough cultivation medium was rich in ingredients, ranging from simple (e.g., *N*-acetylglucosamine) to more complex (e.g., serum). The limited biosynthetic capacity of *Borrelia* cells is accounted for by a genome content one-quarter that of *Escherichia coli*.

Like other spirochetes, the helix-shaped *Borrelia* cells have two membranes, the outer of which is more loosely secured than in other double-membrane bacteria, such as *E. coli*. As a consequence, fixed organisms with damaged membranes can assume a variety of morphologies in smears and histologic preparations. The flagella of spirochetes run between the two membranes and are not on the cell surface. Although technically gram-negative in their staining properties, the 10- to 20-μm-long *Borrelia* cells, with a diameter of 0.2–0.3 μm, are too narrow to be seen by bright-field microscopy.

EPIDEMIOLOGY

The several species of *Borrelia* that cause relapsing fever have restricted geographic distributions **(Table 180-1)**. The exception is *Borrelia recurrentis*, which is also the only species transmitted by an insect. LBRF is usually acquired from a body louse (*Pediculus humanus corporis*), with humans serving as the reservoir. Acquisition occurs not from the bite itself but from either rubbing of the insect's feces into the bite site with the fingers in response to irritation or inoculation of feces into the conjunctivae or an open wound. Although LBRF transmission is currently limited to Ethiopia and adjacent countries, the disease has had a global distribution in the past, and that potential remains. Epidemics with thousands of cases of LBRF can occur under circumstances of famine, refugee migration, and war. Transmission of LBRF can occur in camps of migrants at a distance from their home countries.

All other known species of relapsing fever agents are tick-borne—in most cases, by soft ticks of the genus *Ornithodoros* **(Fig. 180-1)**. Tick-borne relapsing fever (TBRF) is found on most continents but is absent or rare in tropical, low-desert, or arctic environments. For most species, the reservoirs of infection are small to medium-sized

TABLE 180-1 Relapsing Fever *Borrelia* Species, by Geographic Region, Vector, and Primary Reservoir

SPECIES	REGION(S)	ARTHROPOD VECTOR(S)	PRIMARY RESERVOIR
B. crocidurae	Africa	*Ornithodoros sonrai* (soft ticks)	Mammals
B. duttonii	Africa	*O. moubata*	Humans
B. hermsii	North America	*O. hermsi*	Mammals
B. hispanica	Europe, North Africa	*O. erraticus*	Mammals
B. mazzottii	Mexico, Central America	*O. talaje*	Mammals
B. miyamotoi	Eurasia, North America	*Ixodes* species (hard ticks)	Mammals
B. persica	Eurasia	*O. tholozani*	Mammals
B. recurrentis	Africa, global[a]	*Pediculus humanus corporis* (human body louse)	Humans
B. turicatae	North America	*O. turicata*	Mammals
B. venezuelensis	Central and South America	*O. rudis*	Mammals

[a]Although transmission is currently limited to Ethiopia and adjacent countries, *B. recurrentis* infection has had a global distribution in the past, and that potential remains.

FIGURE 180-1 ***Ornithodoros turicata*** **soft ticks** of different ages.

mammals, usually rodents but sometimes pigs and other domestic animals living in or around human habitats. However, one species, *Borrelia duttonii* in sub-Saharan Africa, is largely maintained by tick transmission between human hosts. In North America, TBRF occurs as single cases or small case clusters through transient exposure of persons to infested buildings or caves in less populated areas where the rodent reservoirs have nests. The two main *Borrelia* species involved in North America are *Borrelia hermsii* (in the mountainous west) and *Borrelia turicatae* (in the southwestern and south-central regions). The soft tick vectors typically feed for no more than 30 min, usually while the victim is sleeping. Transovarial transmission from one generation of ticks to the next means that infection risk may persist in an area long after incriminated mammalian reservoirs have been removed.

A newly recognized pathogen, *Borrelia miyamotoi*, belongs to the same clade as relapsing fever species but is transmitted to humans from other mammals by the hard ticks (e.g., *Ixodes scapularis* in the eastern United States) that also transmit Lyme disease, babesiosis, anaplasmosis, and a viral encephalitis. Similar to *Borreliella* (Borrelia) burgdorferi* **(Chap. 181)**, *B. miyamotoi* is acquired through contact with ticks in forested and shrubby areas during recreation, work, or outdoor activities around the home. In residents of areas where *B. miyamotoi* and *B. burgdorferi* coexist, the prevalence of antibodies to the former is about one-third of that to the latter. In contrast to that of *B. burgdorferi*, the transmission of *B. miyamotoi* to the host begins soon after the tick begins to feed.

PATHOGENESIS AND IMMUNITY

Unlike LBRF spirochetes, TBRF spirochetes enter the body in the tick's saliva with the onset of feeding. From an inoculum of a few cells, the spirochetes proliferate in the blood, doubling every 6 h to numbers of $\geq 10^6$–10^7/mL. *Borrelia* species are extracellular pathogens; their presence inside cells connotes dead bacteria after phagocytosis. Binding of the spirochetes to erythrocytes leads to aggregation of red blood cells, their sequestration in the spleen and liver, and hepatosplenomegaly and anemia. A bleeding disorder is probably the consequence of thrombocytopenia, impaired hepatic production of clotting factors, and/or blockage of small vessels by aggregates of spirochetes, erythrocytes, and platelets. Some species are neurotropic and enter the brain, where they are comparatively sheltered from host immunity. Relapsing fever spirochetes can cross the maternal–fetal barrier and cause placental damage and inflammation, leading to intrauterine growth retardation and congenital infection.

Although *Borrelia* species do not have potent exotoxins or a lipopolysaccharide endotoxin, they have abundant lipoproteins whose binding by Toll-like receptors on host cells can lead to a proinflammatory process similar to that in endotoxemia, with elevations of tumor necrosis factor α, interleukin 6, and interleukin 8 concentrations.

IgM antibodies specific for the serotype-defining surface lipoprotein appear after a few days of infection and soon reach a concentration that causes lysis of bacteria in the blood through either direct bactericidal action or opsonization. The release of lipoproteins and other bacterial products from dying bacteria provokes a "crisis," during which there can be an increase in temperature, hypotension, and other signs of shock. A similar phenomenon occurring in some patients soon after the initiation of antibiotic treatment is characterized by an abrupt worsening of the patient's condition, termed a *Jarisch-Herxheimer reaction*.

**Editors' note:* The nomenclature for the genus causing Lyme disease is currently being reviewed and is in transition. In this chapter, the proposed new genus designation, *Borreliella*, is used.

CLINICAL MANIFESTATIONS

Relapsing fever presents with the sudden onset of fever. Febrile periods are punctuated by intervening afebrile periods of a few days; this pattern occurs at least twice. The patient's temperature is ≥39°C and may be as high as 43°C. The first fever episode often ends in a crisis lasting ~15–30 min and consisting of rigors, a further elevation in temperature, and increases in pulse and blood pressure. The crisis phase is followed by profuse diaphoresis, falling temperature, and hypotension, which usually persist for several hours. In LBRF, the first episode of fever is unremitting for 3–6 days; it is usually followed by a single milder episode. In TBRF, multiple febrile periods last 1–3 days each. In both forms, the interval between fevers ranges from 4 to 14 days, sometimes with symptoms of malaise and fatigue.

The symptoms that accompany the fevers are usually nonspecific. Headache, neck stiffness, arthralgia, myalgia, and nausea may accompany the first and subsequent febrile episodes. An enlarging spleen and liver cause abdominal pain. A nonproductive cough is common during LBRF and—in combination with fever and myalgias—may suggest influenza. Acute respiratory distress syndrome may occur during TBRF.

On physical examination, the patient may be delirious or apathetic. There may be body lice in the patient's clothes or signs of insect bites. In regions with *B. miyamotoi* infection, a hard tick may be embedded in the skin. Epistaxis, petechiae, and ecchymoses are common during LBRF but not during TBRF. Splenomegaly or spleen tenderness is common in both forms of relapsing fever. The majority of patients with LBRF and ~10% of patients with TBRF have discernible hepatomegaly.

Localizing neurologic findings are more common in TBRF than in LBRF. In North America, *B. turicatae* infection has neurologic manifestations more often than *B. hermsii* infection. Meningoencephalitis can result in residual hemiplegia or aphasia. Myelitis and radiculopathy may develop. Unilateral or bilateral Bell's palsy and deafness from seventh or eighth cranial nerve involvement are the most common forms of cranial neuritis and typically present in the second or third febrile episode, not the first. Visual impairment from unilateral or bilateral iridocyclitis or panophthalmitis may be permanent. In LBRF, neurologic manifestations such as altered mental state or stiff neck are thought to be secondary to systemic inflammation rather than to direct invasion of the nervous system.

Myocarditis appears to be common in both forms of relapsing fever and accounts for some deaths. Most commonly, myocarditis is evidenced by gallops on cardiac auscultation, a prolonged QT_c interval, and cardiomegaly and pulmonary edema on chest radiography.

General laboratory studies are not specific. Mild to moderate normocytic anemia is common, but frank hemolysis and hemoglobinuria do not develop. Leukocyte counts are usually in the normal range or only slightly elevated, and leukopenia can occur during the crisis. Platelet counts can fall below 50,000/μL. Laboratory evidence of hepatitis can be found, with elevated serum concentrations of unconjugated bilirubin and aminotransferases; the prothrombin and partial thromboplastin times may be moderately prolonged.

Analysis of the cerebrospinal fluid (CSF) is indicated in cases of suspected relapsing fever with signs of meningitis or meningoencephalitis. The presence of mononuclear pleocytosis and mildly to moderately elevated protein levels justifies intravenous antibiotic therapy in TBRF.

The manifestations and course of *B. miyamotoi* infection remain incompletely characterized. The most common presentation is fever without respiratory symptoms starting 1–2 weeks after a tick bite and recurring once or twice in some cases. Patients have been hospitalized with a presumptive diagnosis of undifferentiated sepsis. Meningoencephalitis, with spirochetes in the CSF, has been documented in immunodeficient adults.

DIAGNOSIS

Relapsing fever should be considered in a patient with the characteristic fever pattern and a history of recent exposure—i.e., within 1–2 weeks before illness onset—to body lice, soft-bodied ticks, or *Ixodes* species hard-bodied ticks in geographic areas with documented current or past transmission. Because of the longevity of the ticks and the transovarial

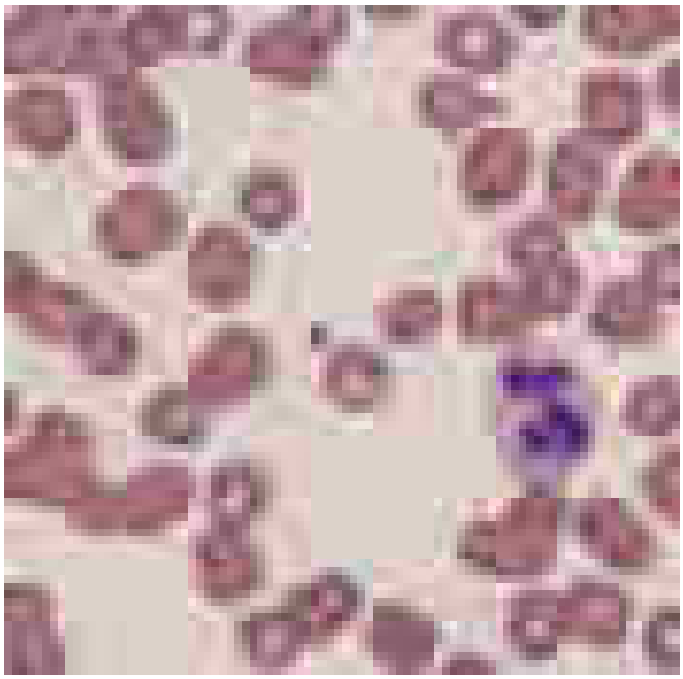

FIGURE 180-2 Photomicrograph of tick-borne relapsing fever spirochete (*Borrelia turicatae*) in a Wright-Giemsa-stained thin blood smear. Included in the figure are a polymorphonuclear leukocyte and two platelets.

transmission of the pathogen in the ticks, a case of relapsing fever may be diagnosed many years after the last case reported in that locale.

The bedrock for laboratory diagnosis remains what it has been for a century: direct detection of the spirochetes by microscopy of the blood. Manual differential counts of white blood cells by Wright or Giemsa stain usually reveal spirochetes in thin blood smears if their concentration is $\geq 10^5$/mL and several oil-immersion fields are examined (Fig. 180-2). The preferred time to obtain a blood specimen is between the fever's onset and its peak. Lower concentrations of spirochetes may be revealed by a thick blood smear that is either directly stained with acridine orange and then examined by fluorescence microscopy or treated with 0.5% acetic acid before Giemsa or Wright staining. An alternative is a wet mount of anticoagulated blood mixed with saline and examined by phase-contrast or dark-field microscopy for motile spirochetes.

Polymerase chain reaction (PCR) and similar DNA amplification procedures are increasingly used for examination of blood or CSF. PCR may reveal spirochetes between febrile episodes, since there are already escape variants in the population when the first wave of bacteria is neutralized.

Culture of blood or CSF in Barbour-Stoenner-Kelly broth medium is an option for isolation of *Borrelia* species. However, few laboratories offer this service. An alternative for tick-borne *Borrelia* species, but not *B. recurrentis*, is inoculation of blood or CSF into immunodeficient mice and examination of the animal's blood after a few days.

Options for serologic confirmation of infection are limited. The few assays that are available commercially or in reference laboratories are based on whole cells of a single *Borrelia* species. These assays may not contain the antigens to which the patient is mainly responding or may yield false-positive results due to antibodies to cross-reactive antigens of related bacteria, including *B. burgdorferi*. The most promising assay is based on GlpQ, a protein antigen of all relapsing fever *Borrelia* species (including *B. miyamotoi*) but not of any Lyme disease species.

DIFFERENTIAL DIAGNOSIS

Depending on the patient's history of residential, occupational, travel, and recreational exposures, the differential diagnosis of relapsing fever includes one or more of the following infections that feature either periodicity in the fever pattern or an extended single febrile period with nonspecific constitutional symptoms: Colorado tick fever (which, along with dengue, can have a "saddleback" fever course); Rocky Mountain spotted fever, ehrlichiosis, anaplasmosis, and other rickettsial diseases; tick-borne arbovirus infection; rat bite fever; and babesiosis in North America, Europe, Russia, and northeastern Asia. Elsewhere in the Americas and Asia and in most of Africa, malaria, typhoid fever, typhus and other rickettsioses, dengue, brucellosis, and leptospirosis may also be considered. Co-infections—malaria, typhus, typhoid, or Lyme disease—may complicate relapsing fever.

TREATMENT

Relapsing Fever

Penicillins and tetracyclines have been the antibiotics of choice for relapsing fever for several decades. Erythromycin has been a long-standing second choice. There is no evidence of acquired resistance to these antibiotics. *Borrelia* species are also susceptible to most cephalosporins and chloramphenicol, but there is less clinical experience with these drugs. Borreliae are relatively resistant to rifampin, sulfonamides, fluoroquinolones, and aminoglycosides. Spirochetes are no longer detectable in the blood within a few hours after the first dose of an effective antibiotic.

A single dose of antibiotic is usually sufficient for the treatment of LBRF (Fig. 180-3). The recurrence rate after antibiotic treatment is ≤5%. For adults, a single dose of oral tetracycline (500 mg), oral doxycycline (200 mg), or intramuscular penicillin G procaine (400,000–800,000 units) is effective. The corresponding doses for children are oral tetracycline at 12.5 mg/kg, oral doxycycline at 5 mg/kg, and intramuscular penicillin G procaine at 200,000–400,000 units. When an adult patient is stuporous or nauseated, the intravenous dose of tetracycline is 250–500 mg. Tetracycline is contraindicated in pregnant and nursing women and in children <9 years old; for individuals in these groups who are allergic to penicillin, oral erythromycin (500 mg for adults and 12.5 mg/kg for children) is an alternative. Tetracycline is marginally superior to penicillin G in terms of time to fever clearance and relapse rate.

The accumulated anecdotal reports on TBRF therapy indicate a recurrence rate of ≥20% after single-dose treatment. This high rate of recurrence plausibly is due to the greater propensity of tick-borne species than of *B. recurrentis* to invade the CNS, from which they can reinvade the bloodstream after antibiotic levels decline. Accordingly,

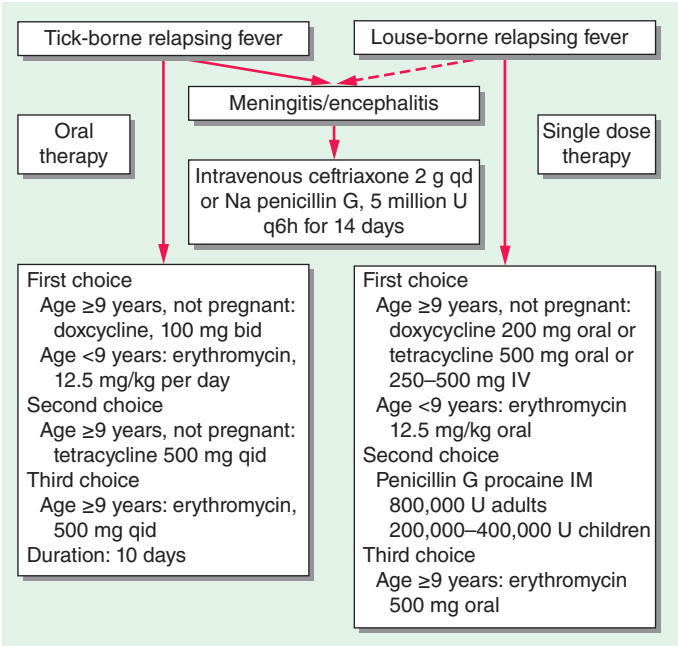

FIGURE 180-3 Algorithm for treatment of relapsing fever. If it is not known whether the patient has tick-borne or louse-borne relapsing fever, the patient should be treated for the tick-borne form. The *dashed line* indicates that central nervous system invasion in louse-borne relapsing fever is uncommon.

multiple antibiotic doses are recommended. The preferred treatment for adults is a 10-day course of tetracycline (500 mg or 12.5 mg/kg orally every 6 h) or doxycycline (100 mg twice daily). When tetracyclines are contraindicated, the alternative is erythromycin (500 mg or 12.5 mg/kg orally every 6 h) for 10 days. If a β-lactam antibiotic is given, it is preferably administered intravenously rather than orally, especially if CNS involvement is confirmed or suspected. For adults, the regimen is penicillin G (5 million units IV every 6 h) or ceftriaxone (2 g IV daily) for 10–14 days. Under conditions of limited resources and when CNS involvement is not suspected, an oral penicillin in divided doses (e.g., penicillin V potassium or penicillin VK at 500 mg or 12.5 mg/kg every 8 h) for 10 days is used.

Experience with the treatment of *B. miyamotoi* infection is limited, but this organism likely has the same antibiotic susceptibilities as other *Borrelia* species. Until more is known about treatment efficacy, therapy for *B. miyamotoi* infection can follow the guidelines for Lyme disease—including parenteral therapy for CNS involvement—because it may be difficult to rule out co-infection.

The Jarisch-Herxheimer reaction during treatment of relapsing fever can be severe or even fatal if precautions are not in place for close monitoring and provision of cardiovascular and volume support as needed. Rigors, fever, and hypotension occur within 2–3 h of initiation of antibiotic treatment. The incidence of this reaction is ~80% in LBRF and ~50% in TBRF. Both penicillin and tetracycline can elicit the Jarisch-Herxheimer reaction.

PROGNOSIS

The mortality rates for untreated LBRF and TBRF are in the ranges of 10–70% and 4–10%, respectively, and are largely determined by coexisting conditions, such as malnutrition, dehydration, or malaria. Death from untreated relapsing fever is most common during the first fever episode. With prompt antibiotic treatment, the mortality rate is 2–5% for LBRF and <2% for TBRF. Features associated with a poor prognosis include concurrence with malaria, typhus, or typhoid; pregnancy; stupor or coma on admission; diffuse bleeding; poor liver function; myocarditis; and bronchopneumonia. The mortality rate from the Jarisch-Herxheimer reaction in LBRF, in the absence of adequate monitoring and resuscitation measures, is ~5%. Some patients have survived the crisis or the reaction only to die suddenly either later that day or on the next day. Relapsing fever during pregnancy frequently leads to abortion or stillbirth, but congenital malformations have not been reported. Although it is possible that spirochetes may persist in the CNS or other sequestered sites after bacteremia has resolved, chronic disability from a persistent infection has not been attributed to relapsing fever, including *B. miyamotoi* infection. Partial immunity against reinfection seems to develop in residents of endemic areas.

PREVENTION

There is no vaccine for either LBRF or TBRF. Reduction of exposure to lice and ticks is the key strategy for prevention. LBRF can be prevented through improved personal hygiene, reduction of crowding, better access to washing facilities, and selected use of pesticides. Infested clothing is an important factor in maintaining body lice. The risk of TBRF can be reduced by construction of houses with concrete or sealed plank floors and without thatched roofs or mud walls. Rustic cabins pose a particular risk in North America when rodents nest in the roof or beneath the house or porch. Buildings infested with *Ornithodoros* ticks can be treated with pesticides and then rodent-proofed. If residing in a high-risk environment, individuals should not sleep on the floor, and beds should be moved away from the wall. With an exposure to TBRF, postexposure treatment with doxycycline (200 mg on day 1 followed by 100 mg/d for 4 days) was efficacious in preventing infection in a placebo-controlled trial.

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181 Lyme Borreliosis

Allen C. Steere

DEFINITION

Lyme borreliosis is caused by a spirochete, *Borrelia burgdorferi sensu lato*, that is transmitted by ticks of the *Ixodes ricinus* complex. The infection usually begins with a characteristic expanding skin lesion, erythema migrans (EM; stage 1, localized infection). After several days or weeks, the spirochete may spread to many different sites (stage 2, disseminated infection). Possible manifestations of disseminated infection include secondary annular skin lesions, meningitis, cranial neuritis, radiculoneuritis, peripheral neuritis, carditis, atrioventricular nodal block, or migratory musculoskeletal pain. Months or years later (usually after periods of latent infection), intermittent or persistent arthritis, chronic encephalopathy or polyneuropathy, or acrodermatitis may develop (stage 3, persistent infection). Most patients experience early symptoms of the illness during the summer, but the infection may not become symptomatic until it progresses to stage 2 or 3.

Lyme disease was recognized as a separate entity in 1976 because of a geographic cluster of children in Lyme, Connecticut, who were thought to have juvenile rheumatoid arthritis. It became apparent that Lyme disease was a multisystemic illness that affected primarily the skin, nervous system, heart, and joints. Epidemiologic studies of patients with EM implicated certain *Ixodes* ticks as vectors of the disease. Early in the twentieth century, EM had been described in Europe and attributed to *I. ricinus* tick bites. In 1982, a previously unrecognized spirochete, now called *Borrelia burgdorferi*, was recovered from *Ixodes scapularis* ticks and then from patients with Lyme disease. The entity is now called Lyme disease or Lyme borreliosis.

ETIOLOGIC AGENT

B. burgdorferi, the causative agent of Lyme disease, is a fastidious microaerophilic bacterium. The spirochete's genome is quite small (~1.5 Mb) and consists of a highly unusual linear chromosome of 950 kb as well as 17–21 linear and circular plasmids. The most remarkable aspect of the *B. burgdorferi* genome is that there are sequences for more than 100 known or predicted lipoproteins—a larger number than in any other organism. The spirochete has few proteins with biosynthetic activity and depends on its host for most of its nutritional requirements. It has no sequences for recognizable toxins.

Currently, 20 closely related borrelial species are collectively referred to as *B. burgdorferi sensu lato* (i.e., "*B. burgdorferi* in the general sense"). The human infection Lyme borreliosis is

caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto* ("*B. burgdorferi* in the strict sense," hereafter referred to simply as *B. burgdorferi*), *Borrelia garinii*, and *Borrelia afzelii*. *B. burgdorferi* is the sole cause of the infection in the United States; all three genospecies are found in Europe, and the latter two species occur in Asia.

Strains of *B. burgdorferi* have been subdivided according to several typing schemes: one based on sequence variation of outer-surface protein C (OspC), a second based on differences in the 16S–23S rRNA intergenic spacer region (RST or IGS), and a third called *multilocus sequence typing*. From these typing systems, it is apparent that strains of *B. burgdorferi* differ in pathogenicity. OspC type A (RST1) strains seem to be particularly virulent and may have played a role in the emergence of Lyme disease in epidemic form in the northeastern United States in the late twentieth century.

EPIDEMIOLOGY

The 20 known genospecies of *B. burgdorferi sensu lato* live in nature in enzootic cycles involving 14 species of ticks that are part of the *I. ricinus* complex. *I. scapularis* **(Fig. 452-1)** is the principal vector in the eastern United States from Maine to Georgia and in the midwestern states of Wisconsin, Minnesota, and Michigan. *I. pacificus* is the vector in the western states of California and Oregon. The disease is acquired throughout Europe (from Great Britain to Scandinavia to European Russia), where *I. ricinus* is the vector, and in Asian Russia, China, and Japan, where *I. persulcatus* is the vector. These ticks may transmit other agents as well. In the United States, *I. scapularis* also transmits *Babesia microti*; *Anaplasma phagocytophilum*; *Ehrlichia* species Wisconsin; *Borrelia miyamotoi*; *Borrelia mayonii*; and, in rare instances, Powassan encephalitis virus (the deer tick virus) (see "Differential Diagnosis," below). In Europe and Asia, *I. ricinus* and *I. persulcatus* also transmit tick-borne encephalitis virus.

Ticks of the *I. ricinus* complex have larval, nymphal, and adult stages. They require a blood meal at each stage. The risk of infection in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts, which have evolved differently in different locations. For *I. scapularis* in the northeastern United States, the white-footed mouse and certain other rodents are the preferred hosts of the immature larvae and nymphs. It is critical that both of the tick's immature stages feed on the same host because the life cycle of the spirochete depends on horizontal transmission: in early summer from infected nymphs to mice and in late summer from infected mice to larvae, which then molt to become the infected nymphs that will begin the cycle again the following year. It is the tiny nymphal tick that is primarily responsible for transmission of the disease to humans, which peaks during the early summer months. White-tailed deer, which are not involved in the life cycle of the spirochete, are the preferred host for the adult stage of *I. scapularis* and seem to be critical to the tick's survival.

Lyme disease is now the most common vector-borne infection in the United States and Europe. Since surveillance was begun by the Centers for Disease Control and Prevention (CDC) in 1982, the number of cases in the United States has increased dramatically. More than 30,000 new cases are now reported each summer, but the actual number of new cases is probably closer to 300,000 annually. In Europe, reported frequencies of the disease are highest in the middle of the continent and in Scandinavia.

PATHOGENESIS AND IMMUNITY

To maintain its complex enzootic cycle, *B. burgdorferi* must adapt to two markedly different environments: the tick and the mammalian host. The spirochete expresses outer-surface protein A (OspA) in the midgut of the tick, whereas OspC is upregulated as the organism travels to the tick's salivary gland. There, OspC binds a tick salivary-gland protein (Salp15), which is required for infection of the mammalian host. The tick usually must be attached for at least 24 h for transmission of *B. burgdorferi*.

After injection into the human skin, the spirochete downregulates OspC and upregulates the VlsE lipoprotein. This protein undergoes extensive antigenic variation, which is necessary for spirochetal survival. After several days to weeks, *B. burgdorferi* may migrate outward in the skin, producing EM, and may spread hematogenously or in the lymph to other organs. The only known virulence factors of *B. burgdorferi* are surface proteins that allow the spirochete to attach to mammalian proteins, integrins, glycosaminoglycans, or glycoproteins. For example, spread through the skin and other tissue matrices may be facilitated by the binding of human plasminogen and its activators to the surface of the spirochete. Some *Borrelia* strains bind complement regulator–acquiring surface proteins (FHL-1/reconectin, or factor H), which help to protect spirochetes from complement-mediated lysis. Dissemination of the organism in the blood is facilitated by binding to the fibrinogen receptor ($\alpha_{IIb}\beta_3$) on activated platelets and the vitronectin receptor ($\alpha_v\beta_3$) on endothelial cells. As the name indicates, spirochetal decorin-binding proteins A and B bind decorin, a glycosaminoglycan on collagen fibrils; this binding may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.

To control and eradicate *B. burgdorferi*, the host mounts both innate and adaptive immune responses, resulting in macrophage- and antibody-mediated killing of the spirochete. As part of the innate immune response, complement may lyse the spirochete in the skin. Cells at affected sites release potent proinflammatory cytokines, including interleukin 6, tumor necrosis factor α, interleukin 1β, and interferon γ. Patients who are homozygous for a Toll-like receptor 1 polymorphism (1805GG), particularly when infected with highly inflammatory *B. burgdorferi* RST1 strains, have exceptionally high levels of proinflammatory cytokines. The purpose of the adaptive immune response appears to be the production of specific antibodies, which opsonize the organism—a step necessary for optimal spirochetal killing. Studies with protein arrays expressing ~1200 *B. burgdorferi* proteins detected antibody responses to a total of 120 spirochetal proteins (particularly outer-surface lipoproteins) in a population of patients with Lyme arthritis. Histologic examination of all affected tissues reveals an infiltration of lymphocytes, macrophages, and plasma cells with some degree of vascular damage, including mild vasculitis or hypervascular occlusion. These findings suggest that the spirochete may have been present in or around blood vessels.

In enzootic infection, *B. burgdorferi* spirochetes must survive this immune assault only during the summer months before returning to larval ticks to begin the cycle again the following year. In contrast, infection of humans is a dead-end event for the spirochete. Within several weeks or months, innate and adaptive immune mechanisms—even without antibiotic treatment—control widely disseminated infection, and generalized systemic symptoms wane. However, without antibiotic therapy, spirochetes may survive in localized niches for several more years. For example, *B. burgdorferi* infection in the United States may cause persistent arthritis or, in rare cases, subtle encephalopathy or polyneuropathy. Thus, immune mechanisms seem to succeed eventually in the near or total eradication of *B. burgdorferi* from selected niches, including the joints or nervous system, and symptoms resolve in most patients.

CLINICAL MANIFESTATIONS

Early Infection: Stage 1 (Localized Infection) Because of the small size of nymphal ixodid ticks, most patients do not remember the preceding tick bite. After an incubation period of 3–32 days, EM usually begins as a red macule or papule at the site of the tick bite that expands slowly to form a large annular lesion **(Fig. 181-1)**. As the lesion increases in size, it often develops a bright red outer border and partial central clearing. The center of the lesion sometimes becomes intensely erythematous and indurated, vesicular, or necrotic. In other instances, the expanding lesion remains an even, intense red; several red rings are found within an outside ring; or the central area turns blue before the lesion clears. Although EM can be located anywhere, the thigh, groin, and axilla are particularly common sites. The lesion is warm but not often painful. Approximately 20% of patients do not exhibit this characteristic skin manifestation.

Early Infection: Stage 2 (Disseminated Infection) In cases in the United States, *B. burgdorferi* often spreads hematogenously to

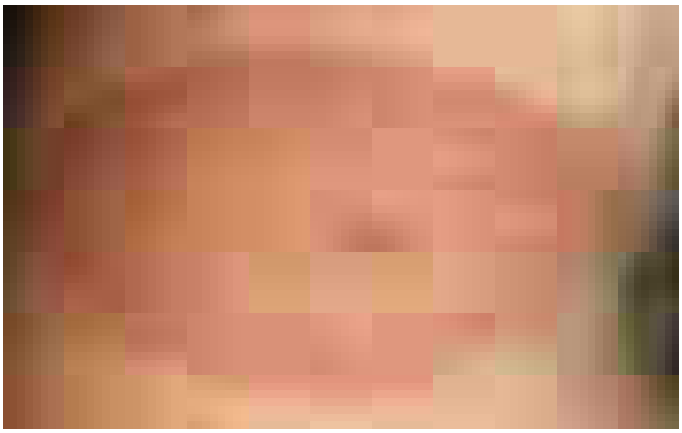

FIGURE 181-1 A classic erythema migrans lesion (9 cm in diameter) is shown near the right axilla. The lesion has partial central clearing, a bright red outer border, and a target center. *(Courtesy of Vijay K. Sikand, MD; with permission.)*

many sites within days or weeks after the onset of EM. In these cases, patients may develop secondary annular skin lesions similar in appearance to the initial lesion. Skin involvement is commonly accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or testicular swelling. Except for fatigue and lethargy, which are often constant, the early signs and symptoms of Lyme disease are typically intermittent and changing. Even in untreated patients, the early symptoms usually become less severe or disappear within several weeks. In ~15% of patients, the infection presents with these nonspecific systemic symptoms.

Symptoms suggestive of meningeal irritation may develop early in Lyme disease when EM is present but usually are not associated with cerebrospinal fluid (CSF) pleocytosis or an objective neurologic deficit. After several weeks or months, ~15% of untreated patients develop frank neurologic abnormalities, including meningitis, subtle encephalitic signs, cranial neuritis (including bilateral facial palsy), motor or sensory radiculoneuropathy, peripheral neuropathy, mononeuritis multiplex, cerebellar ataxia, or myelitis—alone or in various combinations. In children, the optic nerve may be affected because of inflammation or increased intracranial pressure, and these effects may lead to blindness. In the United States, the usual pattern consists of fluctuating symptoms of meningitis accompanied by facial palsy and peripheral radiculoneuropathy. Lymphocytic pleocytosis (~100 cells/μL) is found in CSF, often along with elevated protein levels and normal or slightly low glucose concentrations. In Europe and Asia, the first neurologic sign is characteristically radicular pain, which is followed by the development of CSF pleocytosis (meningopolyneuritis or *Bannwarth's syndrome*); meningeal or encephalitic signs are frequently absent. These early neurologic abnormalities usually resolve completely within months, but in rare cases chronic neurologic disease may occur later.

Within several weeks after the onset of illness, ~8% of patients develop cardiac involvement. The most common abnormality is a fluctuating degree of atrioventricular block (first-degree, Wenckebach, or complete heart block). Some patients have more diffuse cardiac involvement, including electrocardiographic changes indicative of acute myopericarditis, left ventricular dysfunction evident on radionuclide scans, or (in rare cases) cardiomegaly or fatal pancarditis. Cardiac involvement lasts for only a few weeks in most patients but may recur in untreated patients. Chronic cardiomyopathy caused by *B. burgdorferi* has been reported in Europe.

During this stage, musculoskeletal pain is common. The typical pattern consists of migratory pain in joints, tendons, bursae, muscles, or bones (usually without joint swelling) lasting for hours or days and affecting one or two locations at a time.

Late Infection: Stage 3 (Persistent Infection) Months after the onset of infection, ~60% of patients in the United States who have received no antibiotic treatment develop frank arthritis. The typical pattern comprises intermittent attacks of oligoarticular arthritis in large joints (especially the knees), lasting for weeks or months in a given joint. A few small joints or periarticular sites also may be affected, primarily during early attacks. The number of patients who continue to have recurrent attacks decreases each year. However, in a small percentage of cases, involvement of large joints—usually one or both knees—is persistent and may lead to erosion of cartilage and bone.

White cell counts in joint fluid range from 500 to 110,000/μL (average, 25,000/μL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results. Examination of synovial biopsy samples reveals fibrin deposits, villous hypertrophy, vascular proliferation, microangiopathic lesions, and a heavy infiltration of lymphocytes and plasma cells.

Although most patients with Lyme arthritis respond well to antibiotic therapy, a small percentage in the northeastern United States have persistent (*postinfectious, antibiotic-refractory*) arthritis for months or even for several years after receiving oral and IV antibiotic therapy for 2 or 3 months. Although more often these patients are initially infected with RST1 strains of *B. burgdorferi*, this complication is not thought to result from persistent infection. Results of culture and polymerase chain reaction (PCR) for *B. burgdorferi* in synovial tissue obtained in the postantibiotic period have been uniformly negative. Rather, infection-induced autoimmunity, retained spirochetal antigens, or both may play a role in this outcome. Antibiotic-refractory arthritis is associated with a higher frequency of certain class II major histocompatibility complex molecules (particularly HLA-DRBI*0401 or *0101 molecules); the Toll-like receptor 1 polymorphism 1805GG, which leads to exceptionally high levels of cytokines and chemokines in affected joints; and low frequencies of FoxP3+ T regulatory cells in synovial fluid, which correlate with longer posttreatment durations of arthritis. Four autoantigens that are targets of T and B cell responses in patients with Lyme disease, particularly those with antibiotic-refractory arthritis, have now been identified: endothelial cell growth factor, matrix metalloproteinase-10, apolipoprotein B-100, and annexin A2. Additional, yet-to-be identified autoantigens may also have a role in antibiotic-refractory arthritis.

Although rare, chronic neurologic involvement also may become apparent from months to several years after the onset of infection, sometimes after long periods of latent infection. The most common form of chronic central nervous system involvement is subtle encephalopathy affecting memory, mood, or sleep, and the most common form of peripheral neuropathy is an axonal polyneuropathy manifested as either distal paresthesia or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results in CSF analyses. In cases of polyneuropathy, electromyography generally shows extensive abnormalities of proximal and distal nerve segments. Encephalomyelitis or leukoencephalitis, a rare manifestation of Lyme borreliosis associated primarily with *B. garinii* infection in Europe, is a severe neurologic disorder that may include spastic paraparesis, upper motor-neuron bladder dysfunction, and, rarely, lesions in the periventricular white matter.

Acrodermatitis chronica atrophicans, the late skin manifestation of Lyme borreliosis, has been associated primarily with *B. afzelii* infection in Europe and Asia. It has been observed especially often in elderly women. The skin lesions, which are usually found on the acral surface of an arm or leg, begin insidiously with reddish-violaceous discoloration; they become sclerotic or atrophic over a period of years.

The basic patterns of Lyme borreliosis are similar worldwide, but there are regional variations, primarily between the illness found in North America, which is caused exclusively by *B. burgdorferi*, and that found in Europe, which is caused primarily by *B. afzelii* and *B. garinii*. With each of the *Borrelia* species, the infection usually begins with EM. However, *B. burgdorferi* strains in the eastern United States often disseminate widely; they are particularly arthritogenic, and they may cause antibiotic-refractory arthritis. *B. garinii* typically disseminates less widely, but it is especially neurotropic and may cause borrelial encephalomyelitis. *B. afzelii* often infects only the skin but may persist

in that site, where it may cause several different dermatoborrelioses, including acrodermatitis chronica atrophicans.

Post-Lyme Syndrome (Chronic Lyme Disease) Despite resolution of the objective manifestations of the infection with antibiotic therapy, ~10% of patients (although the reported percentages vary widely) continue to have subjective pain, neurocognitive manifestations, or fatigue symptoms. These symptoms usually improve and resolve within months but may last for years. At the far end of the spectrum, the symptoms may be similar to or indistinguishable from chronic fatigue syndrome **(Chap. 442)** and fibromyalgia **(Chap. 366)**. Compared with symptoms of active Lyme disease, post-Lyme symptoms tend to be more generalized or disabling. They include marked fatigue, severe headache, diffuse musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse paresthesias, difficulty with concentration, and sleep disturbances. Patients with this condition lack evidence of joint inflammation, have normal neurologic test results, and may exhibit anxiety and depression. In contrast, late manifestations of Lyme disease, including arthritis, encephalopathy, and neuropathy, are usually associated with minimal systemic symptoms. Currently, no evidence indicates that persistent subjective symptoms after recommended courses of antibiotic therapy are caused by active infection.

DIAGNOSIS

The culture of *B. burgdorferi* in Barbour-Stoenner-Kelly (BSK) medium permits definitive diagnosis, but this method has been used primarily in research studies. Moreover, with a few exceptions, positive cultures have been obtained only early in the illness—particularly from biopsy samples of EM skin lesions, less often from plasma samples, and occasionally from CSF samples. Later in the infection, PCR is greatly superior to culture for the detection of *B. burgdorferi* DNA in joint fluid; this is the major use for PCR testing in Lyme disease. However, because *B. burgdorferi* DNA may persist for at least weeks after spirochetal killing with antibiotics, detection of spirochetal DNA in joint fluid is not an accurate test of active joint infection in Lyme disease and cannot be used reliably to determine the adequacy of antibiotic therapy. The sensitivity of PCR determinations in CSF from patients with neuroborreliosis has been much lower than that in joint fluid. With current methods, there seems to be little if any role for PCR in the detection of *B. burgdorferi* DNA in blood or urine samples, although this is an area of active research. A potential drawback is that PCR must be carefully controlled to prevent contamination.

Because of the problems associated with direct detection of *B. burgdorferi*, Lyme disease is usually diagnosed by the recognition of a characteristic clinical picture accompanied by serologic confirmation. Although serologic testing may yield negative results during the first several weeks of infection, almost all patients have a positive antibody response to *B. burgdorferi* after that time when a two-test approach of enzyme-linked immunosorbent assay (ELISA) and western blot is used. The limitation of serologic tests is that they do not clearly distinguish between active and inactive infection. After antibiotic therapy, the amount of antibody declines but the results of western blot, a nonquantitative test, do not change much. Thus, patients with previous Lyme disease—particularly in cases progressing to late stages—often remain seropositive for years, even after adequate antibiotic therapy. In addition, ~10% of patients are seropositive because of asymptomatic infection. If individuals with past or asymptomatic *B. burgdorferi* infection subsequently develop another illness, the positive serologic test for Lyme disease may cause diagnostic confusion. According to an algorithm published by the American College of Physicians **(Table 181-1)**, serologic testing for Lyme disease is recommended only for patients with at least an intermediate pretest probability of Lyme disease, such as those with oligoarticular arthritis. It should not be used as a screening procedure in patients with pain or fatigue syndromes. In such patients, the probability of a false-positive serologic result is higher than that of a true-positive result.

For serologic analysis of Lyme disease in the United States, the CDC recommends a two-step approach in which samples are first tested by ELISA, and equivocal or positive results are then tested by western blot. During the first weeks of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescent-phase serum samples. Approximately 20–30% of patients have a positive response detectable in acute-phase samples (usually only a positive IgM response), whereas ~70–80% have a positive response during convalescence (2–4 weeks later). After 4–8 weeks of infection (by which time most patients with active Lyme disease have disseminated infection), the sensitivity and specificity of the IgG response to the spirochete are both very high—in the range of 99%—as determined by the two-test approach of ELISA and western blot. At this point and thereafter, a single test (that for IgG) is usually sufficient. In persons with illness of >2 months' duration, a positive IgM test result alone is likely to be false-positive and therefore should not be used to support the diagnosis.

TABLE 181-1 Algorithm for Testing for and Treating Lyme Disease

PRETEST PROBABILITY	EXAMPLE	RECOMMENDATION
High	Patients with erythema migrans	Empirical antibiotic treatment without serologic testing
Intermediate	Patients with oligoarticular arthritis	Serologic testing and antibiotic treatment if test results are positive
Low	Patients with nonspecific symptoms (myalgias, arthralgias, fatigue)	Neither serologic testing nor antibiotic treatment

Source: Adapted from the recommendations of the American College of Physicians (G Nichol et al: Ann Intern Med 128:37, 1998).

According to current criteria adopted by the CDC, an IgM western blot is considered positive if two of the following three bands are present: 23, 39, and 41 kDa. However, the combination of two such bands may still represent a false-positive result. Misuse or misinterpretation of IgM blots has been a factor in the incorrect diagnosis of Lyme disease in patients with other illnesses. An IgG blot is considered positive if 5 of the following 10 bands are present: 18, 23, 28, 30, 39, 41, 45, 58, 66, and 93 kDa. In European cases, no single set of criteria for the interpretation of immunoblots results in high levels of sensitivity and specificity in all countries.

A promising new methodology, particularly for the determination of antibody responses during the first weeks of infection, is a two-test approach using two ELISAs rather than ELISA and western blot. One such method employs a whole–*B. burgdorferi* sonicate ELISA followed by a VlsE C6 peptide IgG ELISA. This approach, which gives simply a positive or a negative result, increases sensitivity during the first several weeks of infection without compromising specificity. For more complex cases, it is still valuable to determine antibody specificities to multiple spirochetal proteins, as is done with western blots. More recently, line immunoblots or other multiplexed antibody platforms have been developed as substitutes for western blots. These assays allow more objective interpretation, and some platforms can provide quantitative data about antibody responses to many spirochetal proteins. After successful antibiotic treatment, antibody titers decline slowly, but responses (including that to the VlsE C6 peptide) may persist for years. Moreover, not only the IgG but also the IgM response may persist for years after therapy. Therefore, even a positive IgM response cannot be interpreted as confirmation of recent infection or reinfection unless the clinical picture is appropriate.

DIFFERENTIAL DIAGNOSIS

Classic EM is a slowly expanding erythema, often with partial central clearing. If the lesion expands little, it may represent the red papule of an uninfected tick bite. If the lesion expands rapidly, it may represent cellulitis (e.g., streptococcal cellulitis) or an allergic reaction, perhaps to tick saliva. Patients with secondary annular lesions may be thought to have erythema multiforme, but neither the development of blistering mucosal lesions nor the involvement of the palms or soles is a feature of *B. burgdorferi* infection. In the eastern United States, an EM-like skin lesion, sometimes with mild systemic symptoms, may be associated with

Amblyomma americanum tick bites. However, the cause of this Southern tick-associated rash illness (STARI) has not yet been identified. This tick may also transmit *Ehrlichia chaffeensis*, a rickettsial agent **(Chap. 182)**.

As stated above, *I. scapularis* ticks in the United States may transmit not only *B. burgdorferi* but also *B. microti*, the red blood cell parasite causing babesiosis **(Chap. 220)**; *A. phagocytophilum*, the agent of human granulocytotropic anaplasmosis **(Chap. 182)**; *B. miyamotoi*, a relapsing fever spirochete **(Chap. 180)**; *B. mayonii* and *Ehrlichia* species Wisconsin, newly recognized species that occur in the upper midwestern United States; or (rarely) Powassan encephalitis virus (the deer tick virus, which is closely related to European tick-borne encephalitis virus) **(Chap. 204)**. Although babesiosis and anaplasmosis are most often asymptomatic, infection with any of these agents may cause nonspecific systemic symptoms, particularly in the young or the elderly, and co-infected patients may have more severe or persistent symptoms than patients infected with a single agent. Standard blood counts may yield clues regarding the presence of co-infection with *Anaplasma* or *Babesia*. Anaplasmosis may cause leukopenia or thrombocytopenia, and babesiosis may cause thrombocytopenia or (in severe cases) hemolytic anemia. IgM serologic responses may confuse the diagnosis. For example, *A. phagocytophilum* may elicit a positive IgM response to *B. burgdorferi*. The frequency of co-infection in different studies has been variable. In one prospective study, 4% of patients with EM had evidence of co-infection.

Facial palsy caused by *B. burgdorferi*, which occurs in the early disseminated phase of the infection (often in July, August, or September), is usually recognized by its association with EM. However, in rare cases, facial palsy without EM may be the presenting manifestation of Lyme disease. In such cases, both the IgM and the IgG responses to the spirochete are usually positive. The most common infectious agents that cause facial palsy are herpes simplex virus type 1 (Bell's palsy; **Chap. 187**) and varicella-zoster virus (Ramsay Hunt syndrome; **Chap. 188**).

Later in the infection, oligoarticular Lyme arthritis most resembles peripheral spondyloarthropathy in an adult or the pauciarticular form of juvenile idiopathic arthritis in a child. Patients with Lyme arthritis usually have the strongest IgG antibody responses seen in Lyme borreliosis, with reactivity to many spirochetal proteins.

The most common problem in diagnosis is to mistake Lyme disease for chronic fatigue syndrome **(Chap. 442)** or fibromyalgia **(Chap. 366)**. This difficulty is compounded by the fact that a small percentage of patients do in fact develop these chronic pain or fatigue syndromes in association with or soon after Lyme disease. Moreover, a counterculture has emerged that ascribes pain and fatigue syndromes to chronic Lyme disease when there is little or no evidence of *B. burgdorferi* infection. In such cases, the term *chronic Lyme disease*, which is equated with chronic *B. burgdorferi* infection, is a misnomer, and the use of prolonged, dangerous, and expensive antibiotic treatment is not warranted.

TREATMENT

Lyme Borreliosis

ANTIBIOTIC TREATMENT

As outlined in the algorithm in **Fig. 181-2**, the various manifestations of Lyme disease can usually be treated successfully with orally administered antibiotics; the exceptions are severe objective neurologic abnormalities and third-degree atrioventricular heart block, which are generally treated with IV antibiotics, and arthritis that does not respond to oral therapy. For early Lyme disease, doxycycline is effective and can be administered to men and nonpregnant women. An advantage of this regimen is that it is also effective against *A. phagocytophilum, B. miyamotoi*, and *B. mayonii*, which are transmitted by the same tick that transmits the Lyme disease agent. Amoxicillin, cefuroxime axetil, and erythromycin or its congeners are second-, third-, and fourth-choice alternatives, respectively, for the treatment of Lyme disease. In children, amoxicillin is effective (not >2 g/d); in cases of penicillin allergy, cefuroxime axetil or erythromycin may be used. In contrast to second- or third-generation cephalosporin

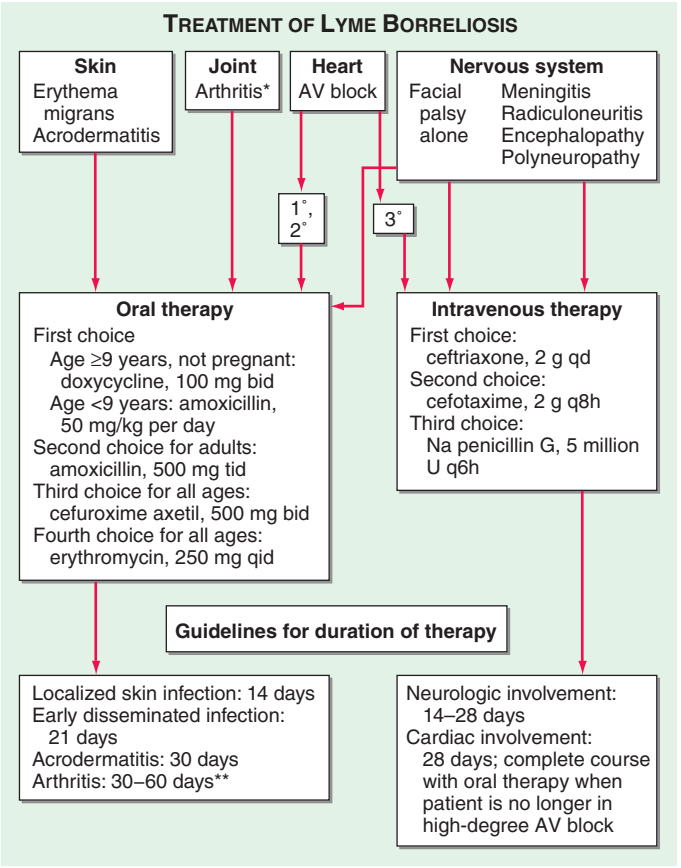

FIGURE 181-2 Algorithm for the treatment of the various early or late manifestations of Lyme borreliosis. AV, atrioventricular. *For arthritis, oral therapy should be tried first; if arthritis is unresponsive, IV therapy should be administered. **For Lyme arthritis, IV ceftriaxone (2 g given once a day for 14–28 days) also is effective and is necessary for patients who do not respond to oral therapy. However, compared with oral treatment, this regimen is less convenient to administer, has more side effects, and is more expensive.

antibiotics, first-generation cephalosporins, such as cephalexin, are not effective. For patients with infection localized to the skin, a 14-day course of therapy is generally sufficient; in contrast, for patients with disseminated infection, a 21-day course is recommended. Approximately 15% of patients experience a Jarisch-Herxheimer-like reaction during the first 24 h of therapy. In multicenter studies, more than 90% of patients whose early Lyme disease was treated with these regimens had satisfactory outcomes. Although some patients reported symptoms after treatment, objective evidence of persistent infection or relapse was rare, and re-treatment was usually unnecessary.

Oral administration of doxycycline or amoxicillin for 30 days is recommended for the initial treatment of Lyme arthritis in patients who do not have concomitant neurologic involvement. Among patients with arthritis who do not respond to oral antibiotics, re-treatment with IV ceftriaxone for 28 days is appropriate. In patients with arthritis in whom joint inflammation persists for months or even several years after both oral and IV antibiotics, treatment with nonsteroidal anti-inflammatory agents, therapy with disease-modifying antirheumatic drugs, or synovectomy may be successful.

In the United States, parenteral antibiotic therapy is usually used for severe objective neurologic abnormalities. Patients with such abnormalities are most commonly treated with IV ceftriaxone for 14–28 days, but IV cefotaxime or IV penicillin G for the same duration also may be effective. In Europe, similar results have been obtained with oral doxycycline and IV antibiotics in the treatment of acute neuroborreliosis. Although systematic trials have not been conducted in the United States, oral doxycycline is now used by some clinicians in this country for the treatment of patients with less severe neurologic abnormalities, such as facial palsy alone or uncomplicated Lyme meningitis. In patients with high-degree

atrioventricular block or a PR interval of >0.3 s, IV therapy for at least part of the course and cardiac monitoring are recommended, but the insertion of a permanent pacemaker is not necessary.

It is unclear how and whether asymptomatic infection should be treated, but patients with such infection are often given a course of oral antibiotics. Because maternal–fetal transmission of *B. burgdorferi* seems to occur rarely (if at all), standard therapy for the manifestations of the illness is recommended for pregnant women. Long-term persistence of *B. burgdorferi* has not been documented in any large series of patients after treatment with currently recommended regimens. Although an occasional patient requires a second course of antibiotics, there is no indication for multiple, repeated antibiotic courses in the treatment of Lyme disease.

CHRONIC LYME DISEASE

After appropriately treated Lyme disease, a small percentage of patients continue to have subjective symptoms, primarily musculoskeletal pain, neurocognitive difficulties, or fatigue. This *chronic Lyme disease* or *post-Lyme syndrome* is sometimes a disabling condition that is similar to chronic fatigue syndrome or fibromyalgia. Five double-blind, placebo-controlled trials conducted in the United States and Europe have failed to show benefit of further antibiotic therapy in these patients. For example, in a large study, one group of patients with post-Lyme syndrome received IV ceftriaxone for 30 days followed by oral doxycycline for 60 days, while another group received IV and oral placebo preparations for the same durations. No significant differences were found between groups in the numbers of patients reporting that their symptoms had improved, become worse, or stayed the same. Such patients are best treated for the relief of symptoms rather than with prolonged courses of antibiotics.

PROPHYLAXIS AFTER A TICK BITE

The risk of infection with *B. burgdorferi* after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if an attached, engorged *I. scapularis* nymph is found or if follow-up is anticipated to be difficult, a single 200-mg dose of doxycycline, which usually prevents Lyme disease when given within 72 h after the tick bite, may be administered.

PROGNOSIS

The response to treatment is best early in the disease. Later treatment of Lyme borreliosis is still effective, but the period of convalescence may be longer. Eventually, most patients recover with minimal or no residual deficits.

REINFECTION

Reinfection may occur after EM when patients are treated with antimicrobial agents. In such cases, the immune response is not adequate to provide protection from subsequent infection. However, patients who develop an expanded immune response to the spirochete over a period of months (e.g., those with Lyme arthritis) have protective immunity for a period of years and rarely, if ever, acquire the infection again.

PREVENTION

Protective measures for the prevention of Lyme disease may include the avoidance of tick-infested areas, the use of repellents and acaricides, tick checks, and modification of landscapes in or near residential areas. Although a vaccine for Lyme disease used to be available, the manufacturer has discontinued its production. Another company is planning testing of a similar vaccine in both the United States and Europe. However, no vaccine is currently available commercially for the prevention of this infection.

FURTHER READING

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Section 10 Diseases Caused by Rickettsiae, Mycoplasmas, and Chlamydiae

182 Rickettsial Diseases

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Rickettsiae are a heterogeneous group of small, obligately intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea, or louse vector. Except in the case of louse-borne typhus, humans are incidental hosts. Among rickettsiae, *Coxiella burnetii*, *Rickettsia prowazekii*, and *Rickettsia typhi* have the well-documented ability to survive for an extended period outside the reservoir or vector and to be extremely infectious: inhalation of a single *Coxiella* microorganism can cause pneumonia. High-level infectivity and severe illness after inhalation make *R. prowazekii*, *R. rickettsii*, *R. typhi*, *R. conorii*, and *C. burnetii* bioterrorism threats **(Chap. S2)**.

Clinical infections with rickettsiae can be classified according to (1) the taxonomy and diverse microbial characteristics of the agents, which belong to seven genera (*Rickettsia*, *Orientia*, *Ehrlichia*, *Anaplasma*, *Neorickettsia*, "*Candidatus* Neoehrlichia," and *Coxiella*); (2) epidemiology; or (3) clinical manifestations. The clinical manifestations of all the acute presentations are similar during the first 5 days: fever, headache, and myalgias with or without nausea, vomiting, and cough. As the course progresses, clinical manifestations—including a macular, maculopapular, or vesicular rash; eschar; pneumonitis; and meningoencephalitis—vary from one disease to another. Given the many etiologic agents with varied mechanisms of transmission, geographic distributions, and associated disease manifestations, the consideration of rickettsial diseases as a single entity poses complex challenges **(Table 182-1)**.

Establishing the etiologic diagnosis of rickettsioses is very difficult during the acute stage of illness, and definitive diagnosis usually requires the examination of serum samples during the acute and convalescent phases of illness. Heightened clinical suspicion is based on epidemiologic data, history of exposure to vectors or reservoir animals, travel to endemic locations, clinical manifestations (sometimes including rash or eschar), and characteristic laboratory findings (including thrombocytopenia, normal or low white blood cell [WBC] counts, elevated hepatic enzyme levels, and hyponatremia). Such suspicion should prompt empirical treatment. Doxycycline is the empirical drug of choice for most of these infections. Only one agent, *C. burnetii*, has been documented to cause chronic illness. One other species, *R. prowazekii*, causes recrudescent illness (Brill-Zinsser disease) when latent infection is reactivated years after resolution of the acute illness.

Rickettsial infections dominated by fever may resolve without further clinical evolution. However, after nonspecific early manifestations,

TABLE 182-1 Features of Selected Rickettsial Infections

DISEASE	ORGANISM	TRANSMISSION	GEOGRAPHIC RANGE	INCUBATION PERIOD, DAYS	DURATION, DAYS	RASH, %	ESCHAR, %	LYMPHADENOPATHY[a]
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor andersoni, D. variabilis*	United States	2–14	10–20	90	<1	+
		Amblyomma cajennense sensu lato, *A. aureolatum*	Central/South America					
		Rhipicephalus sanguineus	Mexico, Brazil, United States					
Mediterranean spotted fever	*R. conorii*	Tick bite: *R. sanguineus, R. pumilio*	Southern Europe, Africa, Middle East, central Asia	5–7	7–14	97	50	+
African tick-bite fever	*R. africae*	Tick bite: *A. hebraeum, A. variegatum*	Sub-Saharan Africa, West Indies	4–10	4–19	50	90	+++
Maculatum disease	*R. parkeri*	Tick bite: *A. maculatum, A. triste, A. tigrinum*	United States, South America	2–10	6–16	88	94	++
Pacific Coast tick fever	*Rickettsia* 364D	Tick bite: *D. occidentalis*	United States	3–9	5–14	14	100	+++
Rickettsialpox	*R. akari*	Mite bite: *Liponyssoides sanguineus*	United States, Ukraine, Turkey, Mexico, Croatia	10–17	3–11	100	90	+++
Tick-borne lymphadenopathy	*R. slovaca*	Tick bite: *D. marginatus, D. reticularis*	Europe	7–9	17–180	5	100	++++
Flea-borne spotted fever	*R. felis*	Flea (mechanism undetermined): *Ctenocephalides felis*	Worldwide	8–16	8–16	80	15	—
Epidemic typhus	*R. prowazekii*	Louse feces: *Pediculus humanus corporis*, fleas and lice of flying squirrels, or recrudescence	Worldwide	7–14	10–18	80	None	—
Murine typhus	*R. typhi*	Flea feces: *Xenopsylla cheopis, C. felis*, others	Worldwide	8–16	9–18	80	None	—
Human monocytotropic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *A. americanum, D. variabilis*	United States	1–21	3–21	26	None	++
Ewingii ehrlichiosis	*E. ewingii*	Tick bite: *A. americanum*	United States	1–21	4–21	0	None	
Unnamed ehrlichiosis	*E. muris eauclairensis*	Tick bite: *Ixodes scapularis*	United States	Unknown	3–14	12	None	
Human granulocytotropic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *I. scapularis, I. ricinus, I. pacificus, I. persulcatus*	United States, Europe, Asia	4–8	3–14	Rare	None	—
Unnamed disease	*A. capra*	*I. persulcatus*	Northeastern China	Unknown	11–21	17	9	+
Neoehrlichiosis	"*Candidatus* Neoehrlichia mikurensis"	Tick bite: *I. ricinus, I. persulcatus, Haemaphysalis concinna*	Europe, China	≥8	11–75	10	None	
Scrub typhus	*Orientia tsutsugamushi*	Mite bite: *Leptotrombidium deliense*, others	Asia, Australia, Pacific and Indian Ocean islands	9–18	6–21	50	35	+++
Q fever	*Coxiella burnetii*	Inhalation of aerosols of infected parturition material (goats, sheep, cattle, cats, others), ingestion of infected milk or milk products	Worldwide except New Zealand, Antarctica	3–30	5–57	<1	None	—

[a]++++, severe; +++, marked; ++, moderate; +, present in a small proportion of cases; —, not a noted feature.

the illnesses can also evolve along one or more of several principal clinical lines: (1) development of a macular or maculopapular rash; (2) development of an eschar at the site of tick or mite feeding; (3) development of a vesicular rash (often in rickettsialpox and African tick-bite fever); (4) development of pneumonitis with chest radiographic opacities and/or rales (Q fever and severe cases of Rocky Mountain spotted fever [RMSF], Mediterranean spotted fever [MSF], louse-borne typhus, human monocytotropic ehrlichiosis [HME], human granulocytotropic anaplasmosis [HGA], scrub typhus, and murine typhus); (5) development of meningoencephalitis (louse-borne typhus and severe cases of RMSF, scrub typhus, HME, murine typhus, MSF, and [rarely] Q fever); and (6) progressive hypotension and multiorgan failure as seen with sepsis or toxic shock syndromes (RMSF, MSF, louse-borne typhus, murine typhus, scrub typhus, HME, HGA, and neoehrlichiosis).

Epidemiologic clues to the transmission of a particular pathogen include (1) environmental exposure to ticks, fleas, or mites during the season of activity of the vector species for the disease in the appropriate geographic region (spotted fever and typhus rickettsioses, scrub typhus, ehrlichiosis, anaplasmosis); (2) travel to or residence in an endemic geographic region during the incubation period (Table 182-1); (3) exposure to

parturient ruminants, cats, and dogs (Q fever); (4) exposure to flying squirrels (*R. prowazekii* infection); and (5) history of previous louse-borne typhus (recrudescent typhus).

Clinical laboratory findings such as thrombocytopenia (particularly in spotted fever and typhus rickettsioses, ehrlichiosis, anaplasmosis, and scrub typhus), normal or low WBC counts, mild to moderate serum elevations of hepatic aminotransferases, and hyponatremia suggest some common pathophysiologic mechanisms.

Application of these clinical, epidemiologic, and laboratory principles requires consideration of a rickettsial diagnosis and knowledge of the individual diseases.

TICK-, MITE-, LOUSE-, AND FLEA-BORNE RICKETTSIOSES

These diseases, caused by organisms of the genera *Rickettsia* and *Orientia* in the family Rickettsiaceae, result from endothelial cell infection and increased vascular permeability. Pathogenic rickettsial species are very closely related, have small genomes (as a result of reductive evolution, which eliminated many genes for biosynthesis of intracellularly available molecules), and are traditionally separated into typhus and spotted fever groups on the basis of lipopolysaccharide antigens. Some diseases and their agents (e.g., *R. africae*, *R. parkeri*, and *R. sibirica*) are too similar to require separate descriptions. Indeed, the similarities among MSF (*R. conorii* [all strains] and *R. massiliae*), North Asian tick typhus (*R. sibirica*), Japanese spotted fever (*R. japonica*), and Flinders Island spotted fever (*R. honei*) far outweigh their minor variations. The Rickettsiaceae that cause life-threatening infections are, in order of decreasing case–fatality rate, *R. rickettsii* (RMSF); *R. prowazekii* (louse-borne typhus); *Orientia tsutsugamushi* (scrub typhus); *R. conorii* (MSF); *R. typhi* (murine typhus); and, in rare cases, other spotted fever–group (SFG) organisms. Some agents (e.g., *R. parkeri*, *R. africae*, *Rickettsia* 364D, *R. akari*, *R. slovaca*, *R. honei*, *R. felis*, *R. massiliae*, *R. helvetica*, *R. heilongjiangensis*, *R. aeschlimannii*, and *R. monacensis*) have never been documented to cause a fatal illness. The most prevalent SFG rickettsia in the United States, *R. amblyommatis*, has been circumstantially associated with asymptomatic seroconversion in most persons and with self-limited illness in others.

ROCKY MOUNTAIN SPOTTED FEVER

Epidemiology RMSF occurs in 47 states (with the highest prevalence in the south-central and southeastern states) as well as in Canada, Mexico, and Central and South America. The infection is transmitted by *Dermacentor variabilis*, the American dog tick, in the eastern two-thirds of the United States and California; by *D. andersoni*, the Rocky Mountain wood tick, in the western United States; by *Rhipicephalus sanguineus*, the brown dog tick, in Mexico, Arizona, and probably Brazil; and by *Amblyomma sculptum*, *A. mixtum*, *A. patinoi*, *A. cajennense*, *A. tonelliae*, and *A. aureolatum* in Central and/or South America. Maintained principally by transovarian transmission from one generation of ticks to the next, *R. rickettsii* can be acquired by uninfected ticks through the ingestion of a blood meal from rickettsemic small mammals or by co-feeding adjacent to an infected tick.

Humans become infected during tick season (in the Northern Hemisphere, from April to September), although some cases occur in winter. The mortality rate was 20–25% in the preantibiotic era and has been reported at ~3–5% in the postantibiotic era, principally because of delayed diagnosis and treatment. Recent reporting of a relatively low mortality rate (0.4%) is likely an artifact related to the abundance of less pathogenic SFG rickettsial species and to a relatively low proportion of diagnostically confirmed cases. Indeed, the reported case–fatality ratios in confirmed cases in the United States and in parts of Arizona, where *R. rickettsii* is the sole infecting SFG species, are 9% and 10%, respectively. The case–fatality ratio is highest among children (<10 years of age) and in the later decades of life (>70 years).

Pathogenesis *R. rickettsii* organisms are inoculated into the dermis along with secretions of the tick's salivary glands after ≥6 h of feeding. The rickettsiae spread lymphohematogenously throughout the body and infect numerous foci of contiguous endothelial cells. The dose-dependent incubation period is ~1 week (range, 2–14 days). Occlusive thrombosis and ischemic necrosis are not the fundamental pathologic bases for tissue and organ injury. Instead, increased vascular permeability, with resulting edema, hypovolemia, and ischemia, is responsible. Consumption of platelets results in thrombocytopenia in 32–52% of patients, but disseminated intravascular coagulation (DIC) with hypofibrinogenemia is rare. Activation of platelets, generation of thrombin, and activation of the fibrinolytic system all appear to be homeostatic physiologic responses to endothelial injury by nonocclusive hemostatic plugs.

Clinical Manifestations Early in the illness, when medical attention usually is first sought, RMSF is difficult to distinguish from many self-limiting viral illnesses. Fever, headache, malaise, myalgia, nausea, vomiting, and anorexia are the most common symptoms during the first 3 days. The patient becomes progressively more ill as vascular infection and injury advance. In one large series, only one-third of patients were diagnosed with presumptive RMSF early in the clinical course and treated appropriately as outpatients. In the tertiary-care setting, RMSF is all too often recognized only when late severe manifestations, developing at the end of the first week or during the second week of illness in patients without appropriate treatment, prompt return to a physician or hospital and admission to an intensive care unit.

The progressive nature of the infection is clearly manifested in the skin. Rash is evident in only 14% of patients on the first day of illness and in only 49% during the first 3 days. Macules (1–5 mm) appear first on the wrists and ankles and then on the remainder of the extremities and the trunk. Later, more severe vascular damage results in frank hemorrhage at the center of the maculopapule, producing a petechia that does not disappear upon compression **(Fig. 182-1)**. This sequence

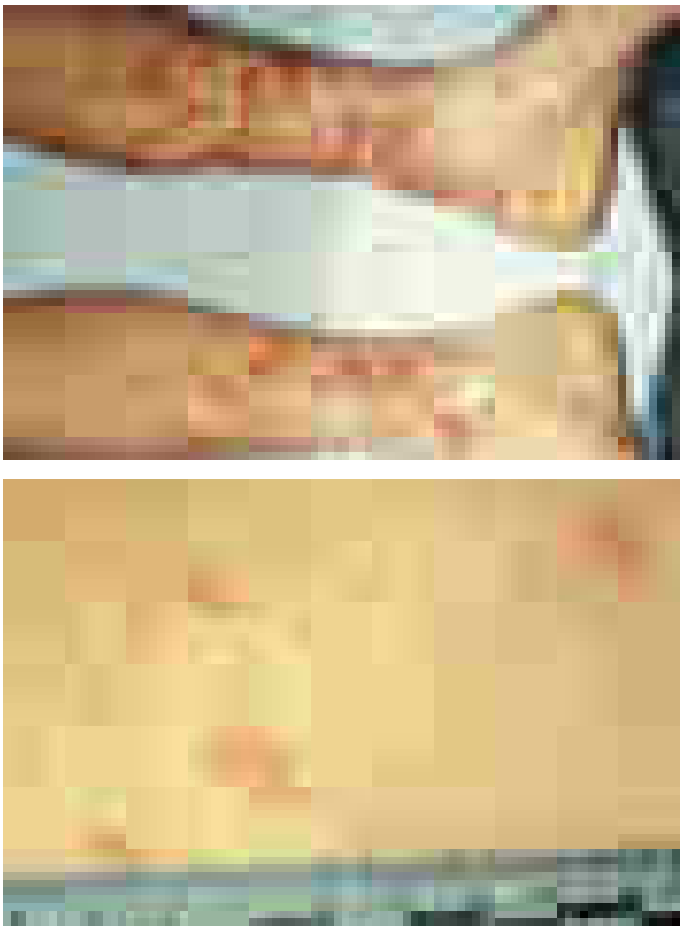

FIGURE 182-1 ***Top:*** Petechial lesions of Rocky Mountain spotted fever on the lower legs and soles of a young, previously healthy patient. ***Bottom:*** Close-up of lesions from the same patient. *(Photos courtesy of Dr. Lindsey Baden; with permission.)*

of events is sometimes delayed or aborted by effective treatment. However, the rash is a variable manifestation, appearing on day 6 or later in 20% of cases and not appearing at all in 9–16% of cases. Petechiae occur in 41–59% of cases, appearing on or after day 6 in 74% of cases that manifest a rash. Involvement of the palms and soles, often considered diagnostically important, usually develops relatively late in the course (after day 5 in 43% of cases) and does not develop at all in 18–64% of cases.

Hypovolemia leads to prerenal azotemia and (in 17% of cases) hypotension. Infection of the pulmonary microcirculation leads to noncardiogenic pulmonary edema; 12% of patients have severe respiratory disease, and 8% require mechanical ventilation. Cardiac involvement manifests as dysrhythmia in 7–16% of cases.

Besides respiratory failure, central nervous system (CNS) involvement is the other important determinant of the outcome of RMSF. Encephalitis, presenting as confusion or lethargy, is apparent in 26–28% of cases. Progressively severe encephalitis manifests as stupor or delirium in 21–26% of cases, ataxia in 18%, coma in 10%, and seizures in 8%. Numerous focal neurologic deficits have been reported. Meningoencephalitis results in cerebrospinal fluid (CSF) pleocytosis in 34–38% of cases; usually there are 10–100 cells/μL and a mononuclear predominance, but occasionally there are >100 cells/μL and a polymorphonuclear predominance. The CSF protein concentration is increased in 30–35% of cases, but the CSF glucose concentration is usually normal.

Renal failure, often reversible with rehydration, is caused by acute tubular necrosis in severe cases with shock. Hepatic injury with increased serum aminotransferase concentrations (38% of cases) is due to focal death of individual hepatocytes without hepatic failure. Jaundice is recognized in 9% of cases and an elevated serum bilirubin concentration in 18–30%.

Life-threatening bleeding is rare. Anemia develops in 30% of cases and is severe enough to require transfusions in 11%. Blood is detected in the stool or vomitus of 10% of patients, and death has followed massive upper-gastrointestinal hemorrhage.

Other characteristic clinical laboratory findings include increased plasma levels of proteins of the acute-phase response (C-reactive protein, fibrinogen, ferritin, and others), hypoalbuminemia, and hyponatremia (in 56% of cases) due to the appropriate secretion of antidiuretic hormone in response to the hypovolemic state. Myositis occurs occasionally, with marked elevations in serum creatine kinase levels and multifocal rhabdomyonecrosis. Ocular involvement includes conjunctivitis in 30% of cases and retinal vein engorgement, flame hemorrhages, arterial occlusion, and papilledema with normal CSF pressure in some instances.

In untreated cases, the patient usually dies 8–15 days after onset. A rare presentation, fulminant RMSF, is fatal within 5 days after onset. This fulminant presentation is seen most often in male black patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and may be related to an undefined effect of hemolysis on the rickettsial infection. Although survivors of RMSF usually return to their previous state of health, permanent sequelae, including neurologic deficits and gangrene necessitating amputation of extremities, may follow severe illness.

Diagnosis The diagnosis of RMSF during the acute stage is more difficult than is generally appreciated. The most important epidemiologic factor is a history of exposure to a potentially tick-infested environment within the 14 days preceding disease onset during a season of possible tick activity. However, only 60% of patients actually recall being bitten by a tick during the incubation period.

The differential diagnosis for early clinical manifestations of RMSF (fever, headache, and myalgia without a rash) includes influenza, enteroviral infection, infectious mononucleosis, viral hepatitis, leptospirosis, typhoid fever, gram-negative or gram-positive bacterial sepsis, HME, HGA, murine typhus, sylvatic flying-squirrel typhus, and rickettsialpox. Enterocolitis may be suggested by nausea, vomiting, and abdominal pain; prominence of abdominal tenderness has resulted in exploratory laparotomy. CNS involvement can masquerade as bacterial or viral meningoencephalitis. Cough, pulmonary signs, and chest radiographic opacities can lead to a diagnostic consideration of bronchitis or pneumonia.

At presentation during the first 3 days of illness, only 3% of patients exhibit the classic triad of fever, rash, and history of tick exposure. When a rash appears, a diagnosis of RMSF should be considered. However, many illnesses considered in the differential diagnosis also can be associated with a rash, including rubeola, rubella, meningococcemia, disseminated gonococcal infection, secondary syphilis, toxic shock syndrome, drug hypersensitivity, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki syndrome, and immune complex vasculitis. Conversely, any person in an endemic area with a provisional diagnosis of one of the above illnesses could have RMSF. Thus, if a viral infection is suspected during RMSF season in an endemic area, it should always be kept in mind that RMSF can mimic viral infection early in the course; if the illness worsens over the next couple of days after initial presentation, the patient should return for reevaluation.

The most common serologic test for confirmation of the diagnosis is the indirect immunofluorescence assay. Not until 7–10 days after onset is a diagnostic titer of ≥64 usually detectable. The sensitivity and specificity of the indirect immunofluorescence IgG assay are 89–100% and 99–100%, respectively. Detection of IgM is no more sensitive in early illness and is subject to nonspecific cross-reactivity. It is important to understand that serologic tests for RMSF are usually negative at the time of presentation for medical care and that treatment should not be delayed while a positive serologic result is awaited.

The only diagnostic test that has proven useful during the acute illness is immunohistologic examination of a cutaneous biopsy sample from a rash lesion for *R. rickettsii*. Examination of a 3-mm punch biopsy from such a lesion is 70% sensitive and 100% specific. Polymerase chain reaction (PCR) amplification for detection of *R. rickettsii* DNA in peripheral blood is not adequately sensitive. Although rickettsiae are present in large quantities in heavily infected foci of endothelial cells, there are relatively low quantities in the circulation. Cultivation of rickettsiae in cell culture is feasible but is seldom undertaken because of biohazard concerns. The recent dramatic increase in the reported incidence of RMSF correlates with the use of single-titer SFG cross-reactive enzyme immunoassay serology. Few cases are specifically determined to be caused by *R. rickettsii*. Currently, many febrile persons who do not have RMSF present with cross-reactive antibodies, possibly because of previous exposure to the highly prevalent SFG rickettsia *R. amblyommatis*.

TREATMENT

Rocky Mountain Spotted Fever

The drug of choice for the treatment of both children and adults with RMSF is doxycycline. Because of the severity of RMSF, immediate empirical administration of doxycycline should be strongly considered for any patient with a consistent clinical presentation in the appropriate epidemiologic setting. Doxycycline is administered orally (or, with coma or vomiting, intravenously) at 100 mg twice daily. For children with suspected RMSF, up to five courses of doxycycline may be administered with minimal risk of dental staining. In patients with allergy to doxycycline, desensitization should be considered. Other regimens include oral tetracycline (500 mg four times daily). Treatment with chloramphenicol, a less effective drug, is advised only for patients who are pregnant. Although available in much of the world, chloramphenicol is difficult to obtain in the United States; when it is unavailable, doxycycline should be used. There is little evidence to support the occurrence of tetracycline-associated adverse events in mothers (hepatotoxicity) and fetuses (staining of deciduous teeth and teratogenicity) who receive doxycycline. The antirickettsial drug should be administered until the patient is afebrile and improving clinically—usually 3–5 days after defervescence. β-Lactam antibiotics, erythromycin, and aminoglycosides have no role in the treatment of RMSF, and sulfa-containing drugs are associated with more adverse outcomes than no treatment at all. There is little clinical experience with fluoroquinolones, clarithromycin, and azithromycin, which are not recommended. The most seriously ill patients are managed in intensive care units, with

careful administration of fluids to achieve optimal tissue perfusion without precipitating noncardiogenic pulmonary edema. In some severely ill patients, hypoxemia requires intubation and mechanical ventilation; oliguric or anuric acute renal failure requires hemodialysis; seizures necessitate the use of antiseizure medication; anemia or severe hemorrhage necessitates transfusions of packed red blood cells; or bleeding with severe thrombocytopenia requires platelet transfusions.

Prevention Avoidance of tick bites is the only available preventive approach. Use of protective clothing and tick repellents, inspection of the body once or twice a day, and removal of ticks before they inoculate rickettsiae reduce the risk of infection. Prophylactic doxycycline treatment of tick bites has no proven role in preventing RMSF.

MEDITERRANEAN SPOTTED FEVER (BOUTONNEUSE FEVER), AFRICAN TICK-BITE FEVER, AND OTHER TICK-BORNE SPOTTED FEVERS

Epidemiology and Clinical Manifestations *R. conorii* is prevalent in southern Europe, Africa, and southwestern and south-central Asia. Regional names for the disease caused by this organism include Mediterranean spotted fever, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever. The disease is characterized by high fever, rash, and—in most geographic locales—an inoculation eschar (*tâche noire*) that appears before the onset of fever at the site of the tick bite. A severe form of the disease (mortality rate, 50%) occurs in patients with diabetes, alcoholism, or heart failure.

African tick-bite fever, caused by *R. africae*, occurs in rural areas of sub-Saharan Africa and in the Caribbean islands and is transmitted by *Amblyomma hebraeum* and *A. variegatum* ticks. The average incubation period is 4–10 days. The mild illness consists of headache, fever, eschar, and regional lymphadenopathy. *Amblyomma* ticks, a high portion of which are infected with *R. africae*, often feed in groups, with the consequent development of multiple eschars. Rash may be vesicular, sparse, or absent altogether. Because of tourism in sub-Saharan Africa, African tick-bite fever is the rickettsiosis most frequently imported into Europe and North America. Maculatum disease, a similar disease caused by the closely related species *R. parkeri*, is transmitted by *A. maculatum* and found in a low percentage of *A. americanum* ticks in the United States. It is also transmitted by *A. triste* in South America and Arizona as well as *A. tigrinum* in South America.

R. japonica causes Japanese spotted fever, which also occurs in Korea and China. Similar diseases in northern Asia are caused by *R. sibirica* and *R. heilongjiangensis.* Queensland tick typhus due to *R. australis* is transmitted by *Ixodes holocyclus* ticks. Flinders Island spotted fever, found on the island for which it is named as well as in Tasmania, mainland Australia, and Asia, is caused by *R. honei*. In Europe, patients infected with *R. slovaca* after a wintertime *Dermacentor* tick bite usually manifest an afebrile illness with an eschar (usually on the scalp) and painful regional lymphadenopathy.

Diagnosis Diagnosis of these tick-borne spotted fevers is based on clinical and epidemiologic findings and is confirmed by serology, immunohistochemical demonstration of rickettsiae in skin biopsy specimens, cell-culture isolation of rickettsiae, or PCR of skin biopsy, eschar biopsy or swab, or blood samples. Serologic diagnosis detects antibodies to antigens shared among SFG rickettsiae, hindering identification of the etiologic species. In an endemic area, a possible diagnosis of rickettsial spotted fevers should be considered when patients present with fever, rash, and/or a skin lesion consisting of a black necrotic lesion or a crust surrounded by erythema.

TREATMENT

Tick-Borne Spotted Fevers

Successful therapeutic agents include doxycycline (100 mg bid orally for 1–5 days) and chloramphenicol (500 mg qid orally for 7–10 days). Pregnant patients may be treated with josamycin (3 g/d orally for 5 days). Data on the efficacy of treatment of mildly ill children with clarithromycin or azithromycin should not be extrapolated to adults or to patients with moderate or severe illness.

RICKETTSIALPOX

R. akari infects mice and their mites (*Liponyssoides sanguineus*), which maintain the organisms by transovarial transmission.

Epidemiology Rickettsialpox is recognized principally in New York City, but cases have also been reported in other urban and rural locations in the United States and in Ukraine, Croatia, Mexico, and Turkey. Investigation of eschars suspected of representing bioterrorism-associated cutaneous anthrax revealed that rickettsialpox occurs more frequently than previously realized.

Clinical Manifestations A papule forms at the site of the mite's feeding, develops a central vesicle, and becomes a 1- to 2.5-cm painless black crusted eschar surrounded by an erythematous halo **(Fig. 182-2)**. Enlargement of the regional lymph nodes draining the eschar suggests initial lymphogenous spread. After an incubation period of 10–17 days, during which the eschar and regional lymphadenopathy frequently go unnoticed, disease onset is marked by malaise, chills, fever, headache, and myalgia. A macular rash appears 2–6 days after onset and usually evolves sequentially into papules, vesicles, and crusts that heal without scarring **(Fig. 182-3)**; in some cases, the rash remains macular or maculopapular. Some patients develop nausea, vomiting, abdominal pain, cough, conjunctivitis, or photophobia. Without treatment, fever lasts 6–10 days.

Diagnosis and Treatment Clinical, epidemiologic, and convalescent serologic data establish the diagnosis of an SFG rickettsiosis that is seldom pursued further. Doxycycline is the drug of choice for treatment.

FLEA-BORNE SPOTTED FEVER

An emerging rickettsiosis caused by *R. felis* occurs worldwide. Maintained transovarially in the geographically widespread cat flea *Ctenocephalides felis*, the infection has been described as moderately severe, with fever, rash, and headache as well as CNS, gastrointestinal, and pulmonary symptoms.

EPIDEMIC (LOUSE-BORNE) TYPHUS

Epidemiology The human body louse (*Pediculus humanus corporis*) lives in clothing under poor hygienic conditions and usually in impoverished cold areas. Lice acquire *R. prowazekii* when they ingest blood from a rickettsemic patient. The rickettsiae multiply in the louse's midgut epithelial cells and are shed in its feces. The infected louse leaves a febrile person and deposits infected feces on its subsequent host during

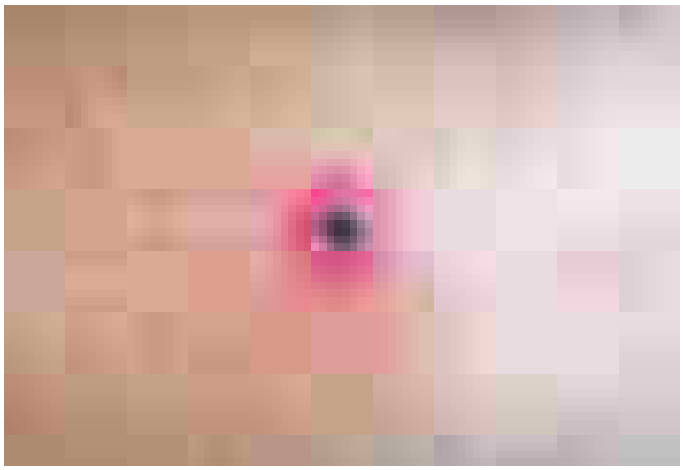

FIGURE 182-2 Eschar at the site of the mite bite in a patient with rickettsialpox. *(Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photo obtained by Dr. Kenneth Kaye.)*

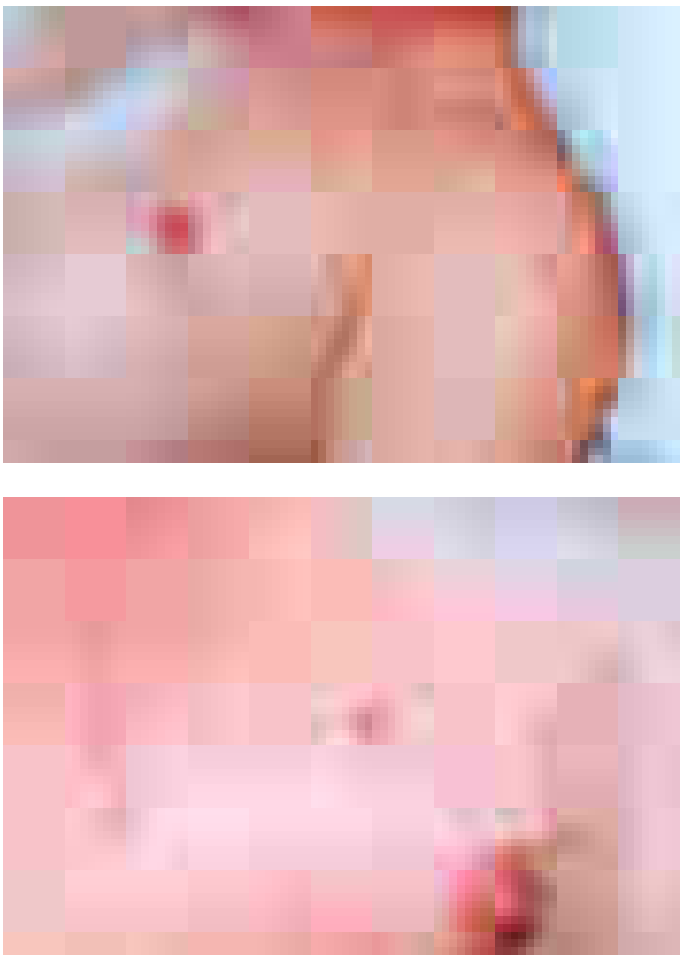

FIGURE 182-3 ***Top:*** Papulovesicular lesions on the trunk of the patient with rickettsialpox shown in Fig. 182-2. ***Bottom:*** Close-up of lesions from the same patient. *(Reprinted from A Krusell et al: Emerg Infect Dis 8:727, 2002. Photos obtained by Dr. Kenneth Kaye.)*

its blood meal; the patient autoinoculates the organisms by scratching. The louse is killed by the rickettsiae and does not pass *R. prowazekii* to its offspring.

Epidemic typhus haunts regions afflicted by wars and disasters. An outbreak involved 100,000 people in refugee camps in Burundi in 1997. A small focus was documented in Russia in 1998, sporadic cases were reported from Algeria, and frequent outbreaks occurred in Peru and Rwanda. Eastern flying squirrels (*Glaucomys volans*) and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle.

Brill-Zinsser disease is a recrudescent illness occurring years after acute epidemic typhus, probably as a result of waning immunity. *R. prowazekii* remains latent for years; its reactivation results in sporadic cases of disease in louse-free populations or in epidemics in louse-infested populations. Recrudescence has been documented after flying squirrel–associated typhus.

Rickettsiae are potential agents of bioterrorism **(Chap. S2)**. Infections with *R. prowazekii* and *R. rickettsii* have high case–fatality ratios. These organisms cause difficult-to-diagnose diseases and are highly infectious when inhaled as aerosols. Organisms resistant to tetracycline or chloramphenicol have been developed in the laboratory.

Clinical Manifestations After an incubation period of ~1–2 weeks, the onset of illness is abrupt, with prostration, severe headache, and fever rising rapidly to 38.8°–40.0°C (102°–104°F). Cough is prominent, developing in 70% of patients. Myalgias are usually severe. A rash begins on the upper trunk, usually on the fifth day, and then becomes generalized, involving the entire body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent. The rash often goes undetected on black skin; 60% of African patients have spotless epidemic typhus. Photophobia, with considerable conjunctival injection and eye pain, is common. The tongue may be dry, brown, and furred. Confusion and coma are common. Skin necrosis and gangrene of the digits as well as interstitial pneumonia may occur in severe cases. Untreated disease is fatal in 7–40% of cases, with outcome depending primarily on the condition of the host. Patients with untreated infections develop renal insufficiency and multiorgan involvement in which neurologic manifestations are frequently prominent. Overall, 12% of patients with epidemic typhus have neurologic involvement. Infection associated with North American flying squirrels is a milder illness; whether this milder disease is due to host factors (e.g., better health status) or attenuated virulence is unknown.

Diagnosis and Treatment Epidemic typhus is sometimes misdiagnosed as typhoid fever in tropical countries **(Chap. 160)**. The means even for serologic studies are often unavailable in settings of louse-borne typhus. Epidemics can be recognized by the serologic or immunohistochemical diagnosis of a single case or by detection of *R. prowazekii* in a louse found on a patient. Doxycycline (100 mg bid) is administered orally or—if the patient is comatose or vomiting—intravenously and continued until 3–5 days after defervescence. Under epidemic conditions, a single 200-mg oral dose can be tried but fails in some cases. Pregnant patients should be evaluated individually and treated with chloramphenicol early in pregnancy or, if necessary, with doxycycline late in pregnancy.

Prevention Prevention of epidemic typhus involves control of body lice. Clothes should regularly be changed and laundered in hot water, and insecticides can be used every 6 weeks to control the louse population.

ENDEMIC MURINE TYPHUS

Epidemiology *R. typhi* is maintained in mammalian host–flea cycles, with rats (*Rattus rattus* and *R. norvegicus*) and the Oriental rat flea (*Xenopsylla cheopis*) as the classic zoonotic niche. Fleas acquire *R. typhi* from rickettsemic rats and carry the organism throughout their life span. Nonimmune rats and humans are infected when rickettsia-laden flea feces contaminate pruritic bite lesions; less frequently, the flea bite transmits the organisms. Transmission can also occur via inhalation of aerosolized rickettsiae from flea feces. Infected rats appear healthy, although they are rickettsemic for ~2 weeks.

Murine typhus occurs mainly in Texas and southern California, where the classic rat–flea cycle is absent and an opossum–cat flea (*C. felis*) cycle is prominent. Globally, endemic typhus occurs mainly in warm (often coastal) areas throughout the tropics and subtropics, where it is highly prevalent though often unrecognized. The incidence peaks from April through July in southern Texas and during the warm months of summer and early fall in other geographic locations. Patients seldom recall exposure to fleas, although exposure to animals such as cats, opossums, and rats is reported in nearly 40% of cases.

Clinical Manifestations The incubation period of experimental murine typhus averages 11 days (range, 8–16 days). Headache, myalgia, arthralgia, nausea, and malaise develop 1–3 days before onset of chills and fever. Patients often experience nausea and vomiting.

The duration of untreated illness averages 12 days (range, 9–18 days). Rash is present in only 13% of patients at presentation for medical care (usually ~4 days after onset of fever), appearing an average of 2 days later in half of the remaining patients and never appearing in the others. The initial macular rash is often detected by careful inspection of the axilla or the inner surface of the arm. Subsequently, the rash becomes maculopapular, involving the trunk more often than the extremities; it is seldom petechial and rarely involves the face, palms, or soles. A rash is detected in only 20% of patients with darkly pigmented skin.

Pulmonary involvement is frequently prominent; 35% of patients have a hacking, nonproductive cough, and 23% of patients who

undergo chest radiography have pulmonary densities due to interstitial pneumonia, pulmonary edema, and pleural effusions. Bibasilar rales are the most common pulmonary sign. Less common clinical manifestations include abdominal pain, confusion, stupor, seizures, ataxia, coma, and jaundice. Clinical laboratory studies frequently reveal anemia and leukopenia early in the course, leukocytosis late in the course, thrombocytopenia, hyponatremia, hypoalbuminemia, increased serum levels of hepatic aminotransferases, and prerenal azotemia. Complications can include respiratory failure, hematemesis, cerebral hemorrhage, and hemolysis. Severe illness necessitates the admission of 10% of hospitalized patients to an intensive care unit. Greater severity is generally associated with old age, underlying disease, and treatment with a sulfonamide; the case–fatality rate is 1%.

Diagnosis and Treatment Serologic studies of acute- and convalescent-phase serum samples can provide a diagnosis, and an immunohistochemical method for identification of typhus group-specific antigens in biopsy samples has been developed. Cultivation is used infrequently and is not widely available. PCR of the blood is not adequately sensitive. When endemic typhus is suspected, patients should be treated empirically with doxycycline (100 mg twice daily by mouth for 7–15 days). Chloramphenicol and ciprofloxacin are less effective alternatives.

SCRUB TYPHUS

Epidemiology *O. tsutsugamushi* differs substantially from *Rickettsia* species both genetically and in cell wall composition (i.e., it lacks lipopolysaccharide). *O. tsutsugamushi* is maintained by transovarial transmission in trombiculid mites. After hatching, infected larval mites (chiggers, the only stage that feeds on a host) inoculate organisms into the skin. Infected chiggers are particularly likely to be found in areas of heavy scrub vegetation during the wet season, when mites lay eggs.

Scrub typhus is endemic and reemerging in eastern and southern Asia, northern Australia, and islands of the western Pacific and Indian Oceans. Infections are prevalent in these regions; in some areas, >3% of the population is infected or reinfected each month. Immunity wanes over 1–3 years, and the organism exhibits remarkable antigenic diversity. Emerging cases in Chile and Africa challenge the classic epidemiology of scrub typhus.

Clinical Manifestations Illness varies from mild and self-limiting to fatal. After an incubation period of 6–21 days, onset is characterized by fever, headache, myalgia, cough, and gastrointestinal symptoms. Some patients recover spontaneously after a few days. The classic case description includes an eschar where the chigger has fed, regional lymphadenopathy, and a maculopapular rash—signs that are seldom seen in indigenous patients. In fact, fewer than 50% of Westerners develop an eschar, and fewer than 40% develop a rash (on day 4–6 of illness). Severe cases typically manifest with encephalitis and interstitial pneumonia due to vascular injury. The case–fatality rate for untreated classic cases is 7% but would probably be lower if all mild cases were diagnosed.

Diagnosis and Treatment Serologic assays (indirect fluorescent antibody, indirect immunoperoxidase, and enzyme immunoassays) are the mainstays of laboratory diagnosis. PCR amplification of *Orientia* genes from eschars and blood also is effective. Patients are treated with oral doxycycline (100 mg twice daily for 7–15 days), azithromycin (500 mg for 3 days), or chloramphenicol (500 mg four times daily for 7–15 days).

Some cases of scrub typhus in Thailand are poorly responsive to doxycycline or chloramphenicol but respond to azithromycin and rifampin.

EHRLICHIOSES AND ANAPLASMOSIS

Ehrlichioses are acute febrile infections caused by members of the family Anaplasmataceae, which is made up of obligately intracellular organisms of five genera: *Ehrlichia*, *Anaplasma*, *Wolbachia*, "*Candidatus* Neoehrlichia," and *Neorickettsia*. The bacteria reside in vertebrate reservoirs and target vacuoles of hematopoietic—and, for some species, endothelial—cells **(Fig. 182-4)**. Four *Ehrlichia* species, two *Anaplasma* species, and one *Neoehrlichia* species are transmitted by ticks to humans and cause infection that can be severe and prevalent. *E. chaffeensis*, the agent of HME, and *E. muris eauclairensis* infect predominantly mononuclear phagocytes; *E. ewingii* and *A. phagocytophilum* infect neutrophils. Infections with "*Candidatus* Neoehrlichia mikurensis" and *A. capra* are less well characterized, but human blood neutrophils and monocytes, respectively, are suspected targets.

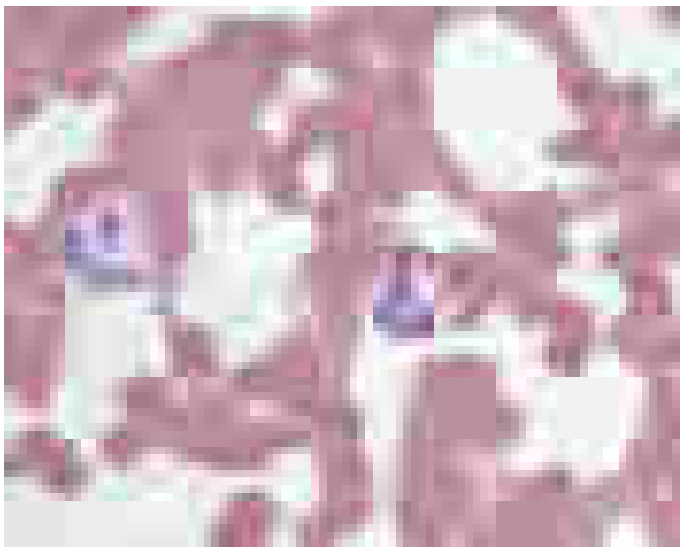

FIGURE 182-4 Peripheral-blood smear from a patient with human granulocytotropic anaplasmosis. A neutrophil contains two morulae (vacuoles filled with *A. phagocytophilum*). *(Photo courtesy of Dr. J. Stephen Dumler.)*

Ehrlichia, "*Candidatus* Neoehrlichia," and *Anaplasma* are maintained by horizontal tick–mammal–tick transmission, and humans are only inadvertently infected. Wolbachiae are associated with human filariasis, since they are important for filarial viability and pathogenicity; antibiotic treatment targeting wolbachiae is a strategy for filariasis control. Neorickettsiae parasitize flukes (trematodes) that in turn parasitize aquatic snails, fish, and insects. Only a single human neorickettsiosis has been described: sennetsu fever, an infectious mononucleosis–like illness first identified in 1953 in association with the ingestion of raw fish containing *N. sennetsu*–infected flukes.

HUMAN MONOCYTOTROPIC EHRLICHIOSIS

Epidemiology More than 14,048 cases of *E. chaffeensis* infection had been reported to the U.S. Centers for Disease Control and Prevention (CDC) as of January 2017. However, active prospective surveillance documented an incidence as high as 414 cases per 100,000 population in some U.S. regions. Most *E. chaffeensis* infections are identified in the south-central, southeastern, and mid-Atlantic states, but cases have also been recognized in California, New York, and Wisconsin. All stages of the Lone Star tick (*A. americanum*) feed on white-tailed deer—a major reservoir. Dogs and coyotes also serve as reservoirs and often lack clinical signs. Tick bites and exposures are frequently reported by patients in rural areas, and 64% of infections occur in May through July. The median age of HME patients is 55 years; however, 11% of infections occur in children ≤19 years of age, and these include severe and fatal infections. Of patients with HME, 59% are male.

E. chaffeensis has been detected in South and Central America, Africa, and Asia.

Clinical Manifestations *E. chaffeensis* disseminates hematogenously from the dermal blood pool created by the feeding tick. After a median incubation period of 8 days, illness develops. Clinical manifestations are undifferentiated and include fever (97% of cases), headache (70%), myalgia (68%), and malaise (77%). Less frequently observed are nausea, vomiting, and diarrhea (28–57%); cough (30%); rash (29% overall, 6% at presentation); and confusion (20%). HME can be severe: 77% of patients with confirmed cases are hospitalized, and

2% die. Life-threatening complications include renal failure, meningoencephalitis, adult respiratory distress syndrome, a DIC-like syndrome, pneumonia, a septic shock–like syndrome, cardiac failure, hepatitis, hemorrhage, and—in immunocompromised patients—overwhelming ehrlichial infection; patients with diabetes, cancer, organ transplantation, asplenia, hepatitis C, or HIV infection have a 2.3 relative risk for death. Laboratory findings are valuable in the differential diagnosis of HME; 66% of patients have leukopenia (initially lymphopenia, later neutropenia), 86% have thrombocytopenia, and 89% have elevated serum levels of hepatic aminotransferases. Despite low blood cell counts, the bone marrow is hypercellular, and noncaseating granulomas can be present. Vasculitis is not a component of HME.

Diagnosis HME can be fatal. If not given empirical doxycycline treatment, 39% and 40% of patients with HME require admission to an intensive care unit and mechanical ventilation, respectively; these measures are necessary in no patients receiving empirical treatment. In addition, hospital stay and illness duration are lengthened in untreated patients by 8 and 12 days, respectively. The diagnosis is suggested by fever, known tick exposure in the preceding 3 weeks, thrombocytopenia and/or leukopenia, and increased serum aminotransferase activities. Morulae are demonstrated in <10% of peripheral-blood smears. HME can be confirmed during active infection by PCR amplification of *E. chaffeensis* nucleic acids in blood obtained before the start of doxycycline therapy. Retrospective serodiagnosis requires a consistent clinical picture and a fourfold increase in *E. chaffeensis* antibody titer to ≥128 in paired serum samples obtained ~3 weeks apart. Separate specific diagnostic tests are necessary for HME and HGA (see below).

EWINGII EHRLICHIOSIS AND *EHRLICHIA MURIS EAUCLAIRENSIS* INFECTIONS

Ehrlichia ewingii resembles *E. chaffeensis* in its tick vector (*A. americanum*) and vertebrate reservoirs (white-tailed deer and dogs). *E. muris eauclairensis* causes human infections after *Ixodes scapularis* tick exposure in Wisconsin and Minnesota. *E. ewingii* and *E. muris* illnesses are similar to but less severe than HME. Many cases occur in immunocompromised patients. Human infections with *E. canis* have been documented as subclinical ehrlichemia. No specific serologic diagnostic tests for these other ehrlichiae are readily available, and *E. chaffeensis* serologic tests can be positive when the infecting agent is actually a different species of *Ehrlichia*.

"*CANDIDATUS* NEOEHRLICHIA MIKURENSIS" INFECTION

"*Candidatus* Neoehrlichia mikurensis," a bacterium in a phylogenetic clade between *Ehrlichia* and *Anaplasma*, was originally identified in *Ixodes ricinus* ticks from the Netherlands and in mice and *Ixodes ovatus* ticks from Japan. By means of broad-range 16S rRNA gene amplification and sequence analysis, this organism was identified as the cause of severe and sometimes prolonged febrile illnesses in European immunocompromised patients with tick bites or exposures and in Chinese patients developing a mild febrile illness after being bitten by *Ixodes persulcatus* and *Haemaphysalis concinna* ticks. The clinical presentation is similar to those of HME and HGA. Specific diagnostic methods have been developed but are not widely available.

TREATMENT

Ehrlichioses

Doxycycline is effective for HME as well as other ehrlichioses; the use of this drug in "*Candidatus* N. mikurensis" infection is associated with disease resolution. Therapy with doxycycline (100 mg given PO or IV twice daily) or tetracycline (250–500 mg given PO every 6 h) lowers hospitalization rates and shortens fever duration. *E. chaffeensis* is not susceptible to chloramphenicol in vitro, and the use of this drug is controversial. While a few reports document *E. chaffeensis* persistence in humans, this finding is rare; most infections are cured by short courses of doxycycline continuing for 3–5 days after defervescence. Although poorly studied for this indication, rifampin may be suitable when doxycycline is contraindicated.

Prevention HME, *E. ewingii* ehrlichiosis, *E. muris* ehrlichiosis, and "*Candidatus* N. mikurensis" infection can be prevented by the avoidance of ticks in endemic areas. The use of protective clothing and tick repellents, careful postexposure tick searches, and prompt removal of attached ticks probably diminish infection risk.

HUMAN GRANULOCYTOTROPIC ANAPLASMOSIS

Epidemiology As of April 2013, 25,288 cases of HGA had been reported to the CDC, most in the upper-midwestern and northeastern United States. The global geographic distribution is similar to that of Lyme disease because of the shared *Ixodes* tick vectors. Natural reservoirs for *A. phagocytophilum* are white-footed mice, squirrels, and white-tailed deer in the United States and red deer in Europe. HGA incidence peaks in May through July, but the disease can occur throughout the year with exposure to *Ixodes* ticks. HGA often affects males (59%) and older persons (median age, 51 years).

Clinical Manifestations Seroprevalence rates are high in endemic regions; thus it seems likely that most individuals develop subclinical infections. The incubation period for HGA is 4–8 days, after which the disease manifests as fever (75–100% of cases), myalgia (75%), headache (83%), and malaise (97%). A minority of patients develop nausea, vomiting, or diarrhea (21–39%); cough (29%); or confusion (17%). A rash in HGA (6%) almost invariably reflects co-infection with *Borrelia*, resulting in erythema migrans. Most patients develop thrombocytopenia (79%) and/or leukopenia (60%) with increased serum hepatic aminotransferase levels (91%).

Life-threatening complications occur most often in the elderly and include renal failure, adult respiratory distress syndrome, a toxic shock–like syndrome, pneumonia, and a DIC- or sepsis-like syndrome. Meningoencephalitis is rare in documented cases of HGA. Other documented neurologic sequelae include brachial plexopathy, cranial nerve involvement, and demyelinating polyneuropathy. Infection of patients with a preexisting immunocompromising condition (diabetes, immunosuppressive medications, asplenia, arthritis) is associated with a 3.0 relative risk for life-threatening complications. Of patients with HGA, 31% are hospitalized and 7% require intensive care. The case–fatality rate is 0.6%, but the relative risk for death is 16 if infection occurs with an immunosuppressive condition. Neither vasculitis nor granulomas are components of HGA. While patients can be co-infected with *Borrelia burgdorferi* and *Babesia microti* (transmitted by the same tick vector[s]), there is little evidence that these infections increase the severity or persistence of HGA. HGA transmitted by transfusion (including the transfusion of leukoreduced blood or platelets) has now been reported in nine cases.

Diagnosis HGA should be included in the differential diagnosis of influenza-like illnesses during seasons with *Ixodes* tick activity (May through December), especially in the context of a known tick bite or exposure. Concurrent thrombocytopenia, leukopenia, or elevated serum levels of alanine or aspartate aminotransferase further increase the likelihood of HGA. Many HGA patients develop Lyme disease antibodies in the absence of clinical findings consistent with that diagnosis. Thus, HGA should be considered in the differential diagnosis of atypical severe Lyme disease presentations. Peripheral-blood film examination for neutrophil morulae can yield a diagnosis in 20–75% of infections. PCR testing of blood from patients with active disease before doxycycline therapy is sensitive and specific. Serodiagnosis is retrospective, requiring a fourfold increase in *A. phagocytophilum* antibody titer (to ≥160) in paired serum samples obtained 1 month apart. Since seroprevalence is high in some regions, a single acute-phase titer should not be used for diagnosis.

***Anaplasma capra* Infection** Human infection by *A. capra*, first isolated from goat blood, was identified in 28 patients from northeastern China. Patients presented with fever, headache, malaise, dizziness, myalgias, and chills, but these manifestations were less severe than in HGA. Hospitalization was recorded for 18% of patients, and 14% had underlying disorders, including hyperglycemia, hypertension, coronary heart disease, diabetes, and cancer. Five patients had severe manifestations, including one with encephalitic signs and *A. capra* DNA present in CSF. *A. capra* is found most often in *I. persulcatus* ticks in this region. All patients responded to doxycycline treatment and survived.

TREATMENT

Human Granulocytotropic Anaplasmosis

No prospective studies of therapy for HGA have been conducted. However, doxycycline (100 mg PO twice daily) is effective. Rifampin therapy is associated with improvement of HGA in pregnant women and children. Most treated patients defervesce within 24–48 h.

Prevention HGA prevention requires tick avoidance. Transmission can be documented as few as 4 h after a tick bite.

Q FEVER

The agent of Q fever is *C. burnetii*, a small intracellular prokaryote that only recently was grown in cell-free medium. *C. burnetii*, a pleomorphic coccobacillus with a gram-negative cell wall, survives in harsh environments; it escapes intracellular killing in macrophages by inhibiting the final step in phagosome maturation (cathepsin fusion) and has adapted to the acidic phagolysosome by producing superoxide dismutase. Infection with *C. burnetii* induces a range of immunomodulatory responses, from immunosuppression in chronic Q fever to the production of autoantibodies, particularly those to smooth muscle and phospholipids.

Q fever encompasses two broad clinical syndromes: acute and chronic infection. The host's immune response (rather than the particular strain) most likely determines whether chronic Q fever develops. *C. burnetii* survives in monocytes from patients with chronic Q fever but not in monocytes from patients with acute Q fever or from uninfected subjects. Impairment of the bactericidal activity of the *C. burnetii*–infected monocyte is associated with overproduction of interleukin 10. The CD4+/CD8+ ratio is decreased in Q fever endocarditis. Very few organisms and a strong cellular response are observed in patients with acute Q fever, while many organisms and a moderate cellular response occur in chronic Q fever. Immune control of *C. burnetii* is T cell–dependent, but 80–90% of bone marrow aspirates obtained years after recovery from Q fever contain *C. burnetii* DNA. *C. burnetii*'s ready multiplication within trophoblasts accounts for the high concentrations it can reach in the placenta.

Epidemiology Q fever is a zoonosis. The primary sources of human infection are infected cattle, sheep, and goats. However, cats, rabbits, pigeons, kangaroos, and dogs also serve as sources for transmission of *C. burnetii* to humans. The wildlife reservoir is extensive and includes ticks, coyotes, gray foxes, skunks, raccoons, rabbits, deer, mice, bears, birds, opossums, and kangaroos. The three-legged sloth is important in the transmission of *C. burnetii* in French Guiana. In female animals, *C. burnetii* localizes to the uterus and mammary glands. Infection is reactivated during pregnancy and after radiotherapy in mouse models. High concentrations of *C. burnetii* are found in the placenta. At the time of parturition, the bacteria are released into the air, and infection follows inhalation of aerosolized organisms by a susceptible host. Windstorms can generate *C. burnetii* aerosols months after soil contamination that occurred during parturition. Individuals up to 18 km from the source have been infected. Because it is easily dispersed as an aerosol, *C. burnetii* is a potential agent of bioterrorism (Chap. S2), with a high infectivity rate and pneumonia as the major manifestation. Treatment with antibody to tumor necrosis factor α is a risk factor for development of Q fever.

Determining the source of an outbreak of Q fever can be challenging. An outbreak of Q fever at a horse-boarding ranch in Colorado in 2005 was due to spread of infection from two herds of goats that had been acquired by the owners. PCR testing confirmed the presence of *C. burnetii* in the soil and among the goats. Of 138 persons who lived within 1 mile of the ranch and who were also tested, 11 (8%) had evidence of *C. burnetii* infection, and 8 of these 11 individuals had no direct contact with the ranch.

Persons at risk for Q fever include abattoir workers, veterinarians, farmers, and other individuals who have contact with infected animals (particularly newborn animals) or products of conception. The organism is shed in milk for weeks to months after parturition. An outbreak of Q fever associated with ingestion of raw milk confirmed the oral route of transmission, although this route is uncommon. In rare instances, person-to-person transmission follows labor and childbirth in an infected woman, autopsy of an infected individual, or blood transfusion. Some evidence suggests that *C. burnetii* can be sexually transmitted among humans. Crushing an infected tick between the fingers has resulted in Q fever; the implication is that percutaneous transmission can occur. Some unusual modes of *C. burnetii* transmission to humans include treatment with live fetal sheep cells in Germany, which was responsible for cases in six persons (five from the United States and one from Canada).

Infections due to *C. burnetii* occur in most geographic locations except New Zealand and Antarctica. Thus Q fever can be associated with travel. The number of reported cases of Q fever in the United States ranges from 28 to 54 per year. More than 70% of these cases occur in males, and April, May, and June are the most common months for acquisition. Q fever continues to be common in Australia, with 30 cases per 1 million population per year. Cases among abattoir workers in Australia declined dramatically as a result of a vaccination program. An outbreak of Q fever began in the Netherlands in 2007, and by 2010 more than 4000 cases had been reported. Pneumonia was a common manifestation in this outbreak. The outbreak was due to a combination of high-density goat farming in areas abutting large urban populations and environmental factors. Farms where spread did not occur had high vegetation densities and lower groundwater concentrations. Q fever is hyperendemic in Cayenne, capital of French Guiana, where it accounts for 24% of all cases of pneumonia.

The primary manifestations of acute Q fever differ geographically (e.g., pneumonia in Nova Scotia and granulomatous hepatitis in Marseille). These differences could reflect the route of infection (i.e., ingestion of contaminated milk for hepatitis and inhalation of contaminated aerosols for pneumonia) or strain differences. In the Netherlands outbreak, sequelae of infection in pregnant women were rare; this was not the case among pregnant women elsewhere.

Young age seems to be protective against disease caused by *C. burnetii*. In a large outbreak in Switzerland, symptomatic infection occurred five times more often among persons >15 years of age than among younger individuals. In many outbreaks, men are affected more commonly than women; the proposed explanation is that female hormones are partially protective.

Clinical Manifestations • **ACUTE Q FEVER** After the usual incubation period of 3–30 days, 1070 patients with acute Q fever in southern France presented with hepatitis (40%), both pneumonia and hepatitis (20%), pneumonia (17%), isolated fever (14%), CNS involvement (2%), and pericarditis or myocarditis (1%). Acalculous cholecystitis, pancreatitis, lymphadenopathy, spontaneous rupture of the spleen, transient hypoplastic anemia, bone marrow necrosis, hemolytic anemia, histiocytic hemophagocytosis, optic neuritis, and erythema nodosum were less common manifestations.

The symptoms of acute Q fever are nonspecific; common among them are fever, extreme fatigue, photophobia, and severe headache that is frequently retro-orbital. Other symptoms include chills, sweats,

nausea, vomiting, and diarrhea, each occurring in 5–20% of cases. Cough develops in about half of patients with Q fever pneumonia. Neurologic manifestations of acute Q fever are uncommon; however, in one outbreak in the United Kingdom, 23% of 102 patients had neurologic signs and symptoms as the major manifestation. A nonspecific rash may be evident in 4–18% of patients, and some patients have urticaria. The WBC count is usually normal. Thrombocytopenia occurs in ~25% of patients, and reactive thrombocytosis (with platelet counts exceeding 10^6/μL) frequently develops during recovery. Chest radiography can show opacities similar to those seen in pneumonia caused by other pathogens, but multiple rounded opacities in patients in endemic areas suggest a diagnosis of Q fever pneumonia.

Acute Q fever occasionally complicates pregnancy. In one series, it resulted in premature birth in 35% of cases and in abortion or neonatal death in 43%. Neonatal death (previous or current) and lower infant birth weight are three times more likely among women seropositive for *C. burnetii*.

POST–Q FEVER FATIGUE SYNDROME Prolonged fatigue can follow Q fever in up to 20% of cases and can be accompanied by a constellation of symptoms, including headaches, sweats, arthralgia, myalgias, blurred vision, muscle fasciculations, and enlarged and painful lymph nodes. Long-term persistence of a noninfective, nonbiodegraded complex of *Coxiella* cell components, with its antigens and specific lipopolysaccharide, has been detected in the affected persons. Patients who develop this syndrome have a higher frequency of carriage of HLA-DRB1*11 and of the 2/2 genotype of the interferon γ intron 1 microsatellite. When patients with Q fever fatigue syndrome were compared with those with chronic fatigue syndrome, the former patients were less likely to be female and less likely to have been treated for depression. Fatigue severity was the same in both groups, and there were no differences in the presence of inflammatory markers in the two groups. Cognitive-based therapy shows some promise in patients with Q fever fatigue syndrome.

CHRONIC Q FEVER Although it has recently been proposed that this entity be renamed *persistent Q fever*, we prefer the term *chronic Q fever*. Chronic Q fever most frequently is manifested as endocarditis and usually occurs in patients with previous valvular heart disease, immunosuppression, or chronic renal insufficiency. Fever is frequently absent or low grade. Valvular vegetations are detected in only 12% of patients with Q fever endocarditis by transthoracic echocardiography, but the rate of detection is higher (21–50%) with transesophageal echocardiography. The vegetations in chronic Q fever endocarditis differ from those in bacterial endocarditis, manifesting as endothelium-covered nodules on the valves. A high index of suspicion is necessary for timely diagnosis. Patients with chronic Q fever are often ill for >1 year before the diagnosis is made. The disease should be suspected in all patients with culture-negative endocarditis. In addition, all patients with valvular heart disease and an unexplained purpuric eruption, renal insufficiency, stroke, and/or progressive heart failure should be tested for *C. burnetii* infection. Patients with chronic Q fever have hepatomegaly and/or splenomegaly, which—in combination with rheumatoid factor, elevated erythrocyte sedimentation rate, high C-reactive protein level, and/or increased γ-globulin concentrations (up to 60–70 g/L)—suggests this diagnosis. Other manifestations of chronic Q fever include infection of vascular prostheses, infection of large-vessel aneurysms, lymphadenitis, bone infection, and chronic sternal wound infection. Unusual manifestations include chronic thrombocytopenia, mixed cryoglobulinemia, and livedo reticularis.

Diagnosis Isolation of *C. burnetii* from buffy-coat blood samples or tissue specimens by a shell-vial technique is easy but requires a biosafety level 3 laboratory. PCR detects *C. burnetii* DNA in tissue specimens, including paraffin-embedded samples. Serology is the most commonly used diagnostic tool. Indirect immunofluorescence is sensitive and specific and is the method of choice. Rheumatoid factor should be adsorbed from the specimen before testing. With chronic infection, the titer to phase I antigen is usually much higher than that to phase II antigen (i.e., *C. burnetii* that has truncated lipopolysaccharide associated with gene deletions during laboratory passages), and the diagnosis should not be based on serology alone. Rather, the entire clinical setting must be taken into consideration. An anti–phase I IgG titer of ≥6400 would be considered a major criterion for the diagnosis of chronic Q fever, while a titer of ≥800 but ≤6400 would be a minor criterion. In acute Q fever, a fourfold rise in titer can be demonstrated between acute- and convalescent-phase serum samples. The phase II antibody titer is higher than the phase I antibody titer in acute Q fever.

Fluorodeoxyglucose positron emission tomography combined with CT (FDG-PET/CT) is useful in localizing the site of infection in chronic Q fever because it can detect not only valvular infection but also intravascular infection elsewhere, osteomyelitis, and lymphadenitis.

TREATMENT

Q Fever

ANTIBIOTICS

Determining the antimicrobial susceptibility of intracellular microorganisms such as *C. burnetii* poses inherent methodologic difficulties. In general, *C. burnetii* is susceptible to tetracyclines, trimethoprim-sulfamethoxazole, and quinolones. In some areas (e.g., French Guiana), all isolates are resistant to erythromycin and azithromycin, and one of six isolates from French Guiana was resistant to telithromycin. There has been one report of the emergence of resistance to doxycycline during therapy for Q fever endocarditis.

Treatment of acute Q fever with doxycycline (100 mg twice daily for 14 days) is usually successful. Quinolones also are effective. When Q fever is diagnosed during pregnancy, treatment with trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for the duration of the pregnancy; because TMP is a folic acid antagonist, folic acid supplementation should be given, especially to pregnant patients in the first trimester. One study showed no intrauterine fetal deaths and substantial reduction of obstetric complications in a group of Q fever patients treated with TMP-SMX.

The treatment of chronic Q fever is difficult and requires careful follow-up. Addition of hydroxychloroquine (to alkalinize the phagolysosome) renders doxycycline bactericidal against *C. burnetii*, and this combination is currently the favored regimen. Treatment for 18 months with doxycycline (100 mg twice daily) and hydroxychloroquine (200 mg three times daily, with the plasma concentration maintained at 0.8–1.2 μg/mL) is superior to a regimen of doxycycline and ofloxacin. Among 21 patients who received doxycycline and hydroxychloroquine, one died of a surgical complication, two were still being treated at the end of the study, one was still being evaluated, and 17 had their infections cured. The mean duration of treatment was 31 months. In the ofloxacin and doxycycline group of 14 patients, one had died, one was still being treated, seven had experienced relapse, and five had been cured by the end of the study. Optimal management of Q fever endocarditis entails determination of the minimal inhibitory concentration (MIC) of doxycycline for the patient's isolate and measurement of serum doxycycline levels. A serum level–to–doxycycline MIC ratio of ≥1 is associated with a rapid decline in phase I antibodies with the doxycycline-hydroxychloroquine regimen. Patients treated with this regimen must be advised about photosensitivity and retinal toxicity risks. The doxycycline-hydroxychloroquine regimen was successful in one patient with HIV infection and Q fever endocarditis. The Jarisch-Herxheimer reaction occasionally complicates the treatment of chronic Q fever. Treatment of *C. burnetii*–infected aortic aneurysms is the same as that for Q fever endocarditis. Surgical intervention is often required.

If doxycycline-hydroxychloroquine cannot be used, the regimen chosen should include at least two antibiotics active against *C. burnetii*. Rifampin (300 mg once daily) combined with doxycycline (100 mg twice daily) or ciprofloxacin (750 mg twice daily) has been used successfully. The management of patients with Q fever

endocarditis is complex and should preferably be undertaken by individuals with experience in managing this illness. Monitoring of antibody titers on a quarterly basis is an essential part of the management of these patients. Thus the laboratory should be contacted and asked to save all serum samples from such patients so that the current sample can be run with the previous one. There is incomplete agreement on the antibody titer at which therapy can be stopped. However, it is reasonable to discontinue treatment if levels of IgG antibody to phase I antigen have decreased by fourfold at 1 year, if IgM antibody to phase II antigen has disappeared, and if the patient is clinically stable.

Patients with acute Q fever and lesions of native heart valves (e.g., the bicuspid aortic valve), prosthetic valves, or prosthetic intravascular material should undergo serologic monitoring every 4 months for 2 years. If the phase I IgG titer is >800, further investigation is warranted. Some authorities recommend that patients with valvulopathy and acute Q fever receive doxycycline and hydroxychloroquine to prevent chronic Q fever. For women who exhibit a serologic profile of chronic Q fever after childbirth, hydroxychloroquine and doxycycline should be given for 1 year.

BIOLOGIC MODIFYING AGENTS

Interferon γ was successful in the treatment of a 3-year-old boy with prolonged fever, abdominal pain, and thrombocytopenia due to *C. burnetii* that had not been eradicated with conventional antibiotic therapy. Many patients with granulomatous hepatitis due to Q fever have a prolonged febrile illness that is unresponsive to antibiotics. For these individuals, treatment with prednisone (0.5 mg/kg) has resulted in defervescence within 2–15 days. After defervescence, the glucocorticoid dose is tapered over the next month.

Prevention A whole-cell vaccine (Q-Vax) licensed in Australia effectively prevents Q fever in abattoir workers. Before administration of the vaccine, skin testing with intradermal diluted *C. burnetii* vaccine is performed, serologic testing is undertaken, and a history of possible Q fever is sought. Vaccine is given only to patients with no history of Q fever and negative results in serologic and skin testing.

Good animal-husbandry practices are important in preventing widespread contamination of the environment by *C. burnetii*. These practices include isolating aborting animals for up to 14 days, raising feed bunks to prevent contamination of feed by excreta, destroying aborted materials (by burning and burying fetal membranes and stillborn animals), and wearing masks and gloves when handling aborted materials. Vaccination of sheep and goats and a culling program were effective in the Netherlands outbreak. Only seronegative pregnant animals should be used in research settings, and only seronegative animals should be permitted in petting zoos.

During an outbreak of Q fever and for 4 weeks after it ceases, blood donations should not be accepted from individuals who live in the affected area.

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183 Infections Due to Mycoplasmas

R. Doug Hardy

Mycoplasmas are prokaryotes of the class Mollicutes. Their size (150–350 nm) is closer to that of viruses than to that of typical bacteria. Unlike viruses, however, mycoplasmas grow in cell-free culture media; in fact, they are the smallest organisms capable of independent replication.

The entire genomes of many *Mycoplasma* species have been sequenced and have been found to be among the smallest of all prokaryotic genomes. Sequencing information for these genomes has helped define the minimal set of genes necessary for cellular life. The absence of genes related to the synthesis of amino acids, fatty acid metabolism, and cholesterol dictates the mycoplasmas' parasitic or saprophytic dependence on a host for exogenous nutrients and necessitates the use of complex fastidious media to culture these organisms. Mycoplasmas lack a cell wall and are bound only by a cell membrane. The absence of a cell wall explains the inactivity of β-lactam antibiotics (penicillins and cephalosporins) against infections caused by these organisms.

At least 13 *Mycoplasma* species, two *Acholeplasma* species and two *Ureaplasma* species have been isolated from humans. Most of these species are thought to be normal inhabitants of oral and urogenital mucous membranes. *M. pneumoniae, M. hominis, M. genitalium, U. urealyticum,* and *U. parvum* have been shown conclusively to be pathogenic in immunocompetent humans. *M. pneumoniae* primarily infects the respiratory tract, while *M. hominis, M. genitalium, U. urealyticum,* and *U. parvum* are associated with a variety of genitourinary tract disorders and neonatal infections. Other mycoplasmas may cause disease in immunocompromised persons.

MYCOPLASMA PNEUMONIAE

PATHOGENESIS

M. pneumoniae is generally thought to act as an extracellular pathogen. Although the organism has been shown to exist and replicate within human cells, it is not known whether these intracellular events contribute to the pathogenesis of disease. *M. pneumoniae* attaches to ciliated respiratory epithelial cells by means of a complex terminal organelle at the tip of one end of the organism. Cytoadherence is mediated by interactive adhesins and accessory proteins clustered on this organelle. After extracellular attachment, *M. pneumoniae* causes injury to host respiratory tissue. The mechanism of injury is thought to be mediated by the production of hydrogen peroxide and of an ADP-ribosylating and vacuolating cytotoxin of *M. pneumoniae* that has many similarities to pertussis toxin. Because mycoplasmas lack a cell wall, they also lack cell wall–derived stimulators of the innate immune system, such as lipopolysaccharide, lipoteichoic acid, and murein (peptidoglycan) fragments. However, lipoproteins from the mycoplasmal cell membrane appear to have inflammatory properties, probably acting through Toll-like receptors (primarily TLR2) on macrophages and other cells. Lung biopsy specimens from patients with *M. pneumoniae* respiratory tract infection reveal an inflammatory process involving the trachea, bronchioles, and peribronchial tissue, with a monocytic infiltrate that coincides with a luminal exudate of polymorphonuclear leukocytes.

Experimental evidence indicates that innate immunity provides most of the host's defense against mycoplasmal infection in the lungs, whereas cellular immunity may actually play an immunopathogenic role, exacerbating mycoplasmal lung disease. Humoral immunity appears to provide protection against dissemination of *M. pneumoniae* infection; patients with humoral immunodeficiencies do not have more severe lung disease than do immunocompetent patients in the early stages of infection but more often develop disseminated infection

resulting in syndromes such as arthritis, meningitis, and osteomyelitis. The immunity that follows severe *M. pneumoniae* infections is more protective and longer-lasting than that following mild infections. Genuine second attacks of *M. pneumoniae* pneumonia have been reported infrequently.

EPIDEMIOLOGY

M. pneumoniae infection occurs worldwide. It is likely that the incidence of upper respiratory illness due to *M. pneumoniae* is up to 20 times that of pneumonia caused by this organism. Infection is spread from one person to another by respiratory droplets expectorated during coughing and results in clinically apparent disease in an estimated 80% of cases. The incubation period for *M. pneumoniae* is 2–4 weeks; therefore, the time-course of infection in a specific population may be several weeks long. Intrafamilial attack rates are as high as 84% among children and 41% among adults. Outbreaks of *M. pneumoniae* illness often occur in institutional settings such as military bases, boarding schools, and summer camps. Infections tend to be endemic, with sporadic epidemics every 4–7 years.

Most significantly, *M. pneumoniae* is a major cause of community-acquired respiratory illness in both children and adults and is often grouped with *Chlamydia pneumoniae* and *Legionella* species as one of the most important bacterial causes of "atypical" community-acquired pneumonia. For community-acquired pneumonia in adults, *M. pneumoniae* is the most frequently detected "atypical" organism. Analysis of 13 studies of community-acquired pneumonia published since 1995 (which included 6207 ambulatory and hospitalized adults) showed that the overall prevalence of *M. pneumoniae* was 22.7%; by comparison, the prevalence of *C. pneumoniae* was 11.7%, and that of *Legionella* species was 4.6%. *M. pneumoniae* pneumonia is also referred to as Eaton agent pneumonia (the organism having first been isolated in the early 1940s by Monroe Eaton), primary atypical pneumonia, and "walking" pneumonia.

CLINICAL MANIFESTATIONS

Upper Respiratory Tract Infections and Pneumonia Acute *M. pneumoniae* infections generally manifest as pharyngitis, tracheobronchitis, reactive airway disease/wheezing, or a nonspecific upper respiratory syndrome. Little evidence supports the commonly held belief that this organism is an important cause of otitis media, with or without bullous myringitis. Pneumonia develops in 3–13% of infected individuals; its onset is usually gradual, occurring over several days, but may be more abrupt. Although *Mycoplasma* pneumonia may begin with a sore throat, the most common presenting symptom is cough. The cough is typically nonproductive, but some patients produce sputum. Headache, malaise, chills, and fever are noted in the majority of patients.

On physical examination, wheezes or rales are detected in ~80% of patients with *M. pneumoniae* pneumonia. In many patients, however, pneumonia can be diagnosed only by chest radiography. The most common radiographic pattern is that of peribronchial pneumonia with thickened bronchial markings, streaks of interstitial infiltration, and areas of subsegmental atelectasis. Segmental or lobar consolidation is not uncommon. While clinically evident pleural effusions are infrequent, lateral decubitus views reveal that up to 20% of patients have pleural effusions.

Overall, the clinical presentation of pneumonia in an individual patient is not useful for differentiating *M. pneumoniae* pneumonia from other types of community-acquired pneumonia. The possibility of *M. pneumoniae* infection deserves particular consideration when community-acquired pneumonia fails to respond to treatment with a penicillin or a cephalosporin—antibiotics that are ineffective against mycoplasmas. Symptoms usually resolve within 2–3 weeks after the onset of illness. Although *M. pneumoniae* pneumonia is generally self-limited, appropriate antimicrobial therapy significantly shortens the duration of clinical illness. Infection uncommonly results in critical illness and only rarely in death. In some patients, long-term recurrent wheezing or reactive airway disease may follow the resolution of acute pneumonia. The significance of chronic infection, especially as it relates to asthma, is an area of active investigation.

Extrapulmonary Manifestations An array of extrapulmonary manifestations may develop during *M. pneumoniae* infection. The most significant are neurologic, dermatologic, cardiac, rheumatologic, and hematologic in nature. Extrapulmonary manifestations can be a result of disseminated infection, especially in patients with humoral immunodeficiencies (e.g., septic arthritis); postinfectious autoimmune phenomena (e.g., Guillain-Barré syndrome); or possibly ADP-ribosylating toxin. Overall, these manifestations are uncommon, given the frequency of *M. pneumoniae* infection. Notably, many patients with extrapulmonary *M. pneumoniae* disease do not have respiratory disease.

Skin eruptions described with *M. pneumoniae* infection include erythematous (macular or maculopapular), vesicular, bullous, petechial, and urticarial rashes. In some reports, 17% of patients with *M. pneumoniae* pneumonia have had an exanthem. Erythema multiforme major (Stevens-Johnson syndrome) is the most clinically significant skin eruption associated with *M. pneumoniae* infection; it appears to occur more commonly with *M. pneumoniae* than with other infectious agents.

A wide spectrum of neurologic manifestations has been reported with *M. pneumoniae* infection. The most common are meningoencephalitis, encephalitis, Guillain-Barré syndrome, and aseptic meningitis. *M. pneumoniae* has been implicated as a likely etiologic agent in 5–7% of cases of encephalitis. Other neurologic manifestations may include cranial neuropathy, acute psychosis, cerebellar ataxia, acute demyelinating encephalomyelitis, cerebrovascular thromboembolic events, and transverse myelitis.

Hematologic manifestations of *M. pneumoniae* infection include hemolytic anemia, aplastic anemia, cold agglutinins, disseminated intravascular coagulation, and hypercoagulopathy. When anemia does occur, it generally develops in the second or third week of illness.

In addition, hepatitis, glomerulonephritis, pancreatitis, myocarditis, pericarditis, rhabdomyolysis, and arthritis (septic and reactive) have been convincingly ascribed to *M. pneumoniae* infection. Septic arthritis has been described most commonly in hypogammaglobulinemic patients.

DIAGNOSIS

Clinical findings, nonmicrobiologic laboratory tests, and chest radiography are not useful for differentiating *M. pneumoniae* pneumonia from other types of community-acquired pneumonia. In addition, since *M. pneumoniae* lacks a cell wall, it is not visible on Gram's stain. Although of historical interest, the measurement of cold agglutinin titers is no longer recommended for the diagnosis of *M. pneumoniae* infection because the findings are nonspecific and assays specific for *M. pneumoniae* are now available.

Acute *M. pneumoniae* infection can be diagnosed by polymerase chain reaction (PCR) detection of the organism in respiratory tract secretions or by isolation of the organism in culture **(Table 183-1)**. Oropharyngeal, nasopharyngeal, and pulmonary specimens are all acceptable for diagnosing *M. pneumoniae* pneumonia. Other bodily fluids, such cerebrospinal fluid, are acceptable for extrapulmonary infection. *M. pneumoniae* culture (which requires special media) is not recommended for routine diagnosis because the organism may take weeks to grow and is often difficult to isolate from clinical specimens. In contrast, PCR allows rapid, specific diagnosis earlier in the course of clinical illness.

The diagnosis can also be established by serologic tests for IgM and IgG antibodies to *M. pneumoniae* in paired (acute- and

TABLE 183-1 Diagnostic Tests for Respiratory *Mycoplasma pneumoniae* Infection[a]

TEST	SENSITIVITY, %	SPECIFICITY, %
Respiratory culture	≤60	100
Respiratory PCR	65–90	90–100
Serologic studies[b]	55–100	55–100

[a]A combination of PCR and serology is suggested for routine diagnosis. If macrolide resistance is suspected, resistance testing by culture and/or PCR is available. [b]Acute- and convalescent-phase serum samples are recommended.

Abbreviation: PCR, polymerase chain reaction.

convalescent-phase) serum samples; enzyme-linked immunoassay is the recommended serologic method. An acute-phase sample alone is not adequate for diagnosis, as antibodies to *M. pneumoniae* may not develop until 2 weeks into the illness; therefore, it is important to test paired samples. In addition, IgM antibody to *M. pneumoniae* can persist for up to 1 year after acute infection. Thus its presence may indicate recent rather than acute infection.

The combination of PCR of respiratory tract secretions and serologic testing constitutes the most sensitive and rapid approach to the diagnosis of *M. pneumoniae* infection.

TREATMENT

Mycoplasma pneumoniae Infections

Although in the majority of untreated cases symptoms resolve within 2–3 weeks without significant associated morbidity, *M. pneumoniae* pneumonia can be a serious illness that responds to appropriate antimicrobial therapy **(Table 183-2)**. Randomized, double-blind, placebo-controlled trials in adults have demonstrated that antimicrobial treatment significantly decreases the duration of fever, cough, malaise, hospitalization, and radiologic abnormalities in *M. pneumoniae* pneumonia. Treatment options for acute *M. pneumoniae* infection include macrolides (e.g., oral azithromycin, 500 mg on day 1, then 250 mg/d on days 2–5), tetracyclines (e.g., oral doxycycline, 100 mg twice daily for 10–14 days), and respiratory fluoroquinolones. However, ciprofloxacin and ofloxacin are *not* recommended because of their high minimal inhibitory concentrations against *M. pneumoniae* isolates and their poor performance in experimental studies. A 10- to 14-day course of quinolone therapy appears adequate.

In Japan and China, very high levels (up to ≥90%) of *M. pneumoniae* resistance to macrolides have been reported. In Europe and to a lesser degree in the United States, macrolide-resistant *M. pneumoniae* is emerging. In investigated outbreaks of respiratory illness due to *M. pneumoniae* in the United States, macrolide resistance has been reported in 8–27% of isolates. Clinical studies have demonstrated that, when treated with macrolides, patients with community-acquired pneumonia due to macrolide-resistant *M. pneumoniae* experience a significantly longer duration of symptoms than do patients infected with macrolide-sensitive organisms; thus macrolide resistance in *M. pneumoniae* does appear to have clinical significance. If macrolide resistance is prominent in a particular geographic locale or is suspected, then a nonmacrolide antibiotic should be considered for treatment; in addition, in these instances, a respiratory sample may be sent to a mycoplasma reference laboratory for the detection of macrolide resistance by culture or PCR.

Clinical observations and experimental data suggest that the addition of glucocorticoids to an antibiotic regimen may be of value for the treatment of severe or refractory *M. pneumoniae* pneumonia. However, relevant clinical experience is limited. Even though appropriate antibiotic therapy significantly reduces the duration of respiratory illness, it does not appear to shorten the duration of detection of *M. pneumoniae* by culture or PCR; therefore, a test of cure or eradication is not suggested.

TABLE 183-2 Antimicrobial Agents of Choice for *Mycoplasma* Infections[a]

ORGANISM(S)	DRUGS
Mycoplasma pneumoniae	Azithromycin, clarithromycin, erythromycin, doxycycline, levofloxacin, moxifloxacin, gemifloxacin (*not* ciprofloxacin or ofloxacin)
Ureaplasma urealyticum, *Ureaplasma parvum*	Azithromycin, clarithromycin, erythromycin, doxycycline
Mycoplasma hominis	Doxycycline, clindamycin
Mycoplasma genitalium	Azithromycin, moxifloxacin

[a]Antimicrobial resistance has been reported in mycoplasmas, as described in the text.

The roles of antimicrobial drugs, glucocorticoids, and IV immunoglobulin in the treatment of neurologic disease due to *M. pneumoniae* remain unknown.

UROGENITAL MYCOPLASMAS (SEE ALSO CHAP. 131)

EPIDEMIOLOGY

M. hominis, *M. genitalium*, *U. urealyticum*, and *U. parvum* can cause urogenital tract disease. The significance of isolation of these organisms in a variety of other syndromes is unknown and in some cases is being investigated. *M. fermentans* has not been shown convincingly to cause human disease.

While urogenital mycoplasmas may be transmitted to a fetus during passage through a colonized birth canal, sexual contact is the major mode of transmission, and the risk of colonization increases dramatically with increasing numbers of sexual partners. In asymptomatic women, these mycoplasmas may be found throughout the lower urogenital tract. The vagina yields the largest number of organisms; next most densely colonized are the periurethral area and the cervix. Ureaplasmas are isolated less often from urine than from the cervix, but *M. hominis* is found with approximately the same frequency at these two sites. Ureaplasmas are isolated from the vagina of 40–80% of sexually active, asymptomatic women and *M. hominis* from 21–70%. The two microorganisms are found concurrently in 31–60% of women. In men, colonization with each organism is less prevalent. Mycoplasmas have been isolated from urine, semen, and the distal urethra of asymptomatic men.

CLINICAL MANIFESTATIONS

Urethritis, Pyelonephritis, and Urinary Calculi In many episodes of *Chlamydia*-negative nongonococcal urethritis, ureaplasmas may be the causative agent. These organisms may also cause chronic voiding symptoms in women. The common presence of ureaplasmas in the urethra of asymptomatic men may suggest either that only certain serovars are pathogenic or that predisposing factors, such as lack of immunity, must exist in persons who develop symptomatic infection. Alternatively, disease may develop only upon initial exposure to ureaplasmas. Ureaplasmas have been implicated in epididymitis. *M. genitalium* also appears to cause urethritis. *M. genitalium* and ureaplasmas do not have a known role in prostatitis. *M. hominis* does not appear to play a primary etiologic role in urethritis, epididymitis, or prostatitis.

Evidence suggests that *M. hominis* causes up to 5% of cases of acute pyelonephritis. Ureaplasmas have not been associated with this disease.

Ureaplasmas play a limited role in the production of urinary calculi. The frequency with which ureaplasmas reach the kidney, the predisposing factors that allow them to do so, and the relative frequency of urinary tract calculi induced by this organism (compared with other organisms) are not known.

Pelvic Inflammatory Disease *M. hominis* can cause pelvic inflammatory disease. In most episodes, *M. hominis* occurs as part of a polymicrobial infection, but the organism may play an independent role in a limited number of cases. Data also support an association of *M. genitalium* with pelvic inflammatory disease. Ureaplasmas are not thought to cause pelvic inflammatory disease.

Postpartum and Postabortal Infection Studies implicate *M. hominis* as the primary pathogen in ~5–10% of women who have postpartum or postabortal fever; ureaplasmas have been implicated to a lesser degree. These infections are generally self-limited; however, if symptoms persist, specific antimicrobial therapy should be given. Ureaplasmas also appear to play a role in occasional postcesarean wound infections.

Nonurogenital Infection In rare instances, *M. hominis* causes nonurogenital infections, such as brain abscess, wound infection, poststernotomy mediastinitis, endocarditis, and neonatal meningitis.

These infections are most common among immunocompromised and hypogammaglobulinemic patients. Ureaplasmas and *M. hominis* can cause septic arthritis in immunodeficient patients. Ureaplasmas probably cause neonatal pneumonitis; their possible causal role in the development of bronchopulmonary dysplasia—the chronic lung disease of premature infants—has been extensively investigated, with most studies indicating at least a significant association. It is unclear whether ureaplasmas and *M. hominis* cause infertility, spontaneous abortion, premature labor, low birth weight, or chorioamnionitis.

DIAGNOSIS

Culture and PCR are both appropriate methods for the isolation of urogenital mycoplasmas. Culture of these organisms, however, requires special techniques and media that generally are available only at larger medical centers and reference laboratories. Serologic testing is not recommended for the clinical diagnosis of urogenital *Mycoplasma* infections.

TREATMENT

Urogenital *Mycoplasma* Infections

Because colonization with urogenital mycoplasmas is common, it appears at present that their isolation from the urogenital tract in the absence of disease generally does not warrant treatment. Macrolides and doxycycline are considered the antimicrobial agents of choice for *Ureaplasma* infections (Table 183-2). *Ureaplasma* resistance to macrolides, doxycycline, quinolones, and chloramphenicol has been reported. *M. hominis* is resistant to macrolides. Doxycycline is generally the drug of choice for *M. hominis* infections, although resistance has been reported. Clindamycin is generally active against *M. hominis*. Quinolones are active in vitro against *M. hominis*. For *M. genitalium*, the initial treatment of choice appears to be azithromycin; moxifloxacin has been successfully used to treat *M. genitalium* resistant to azithromycin.

FURTHER READING

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184 Chlamydial Infections

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Chlamydiae are obligate intracellular bacteria that cause a wide variety of diseases in humans and animals.

ETIOLOGIC AGENTS

The chlamydiae were originally classified as four species in the genus *Chlamydia*: *C. trachomatis*, *C. pneumoniae*, *C. psittaci*, and *C. pecorum* (the last species being found in ruminants). The *C. psittaci* group has been separated into three species: *C. psittaci*, *C. felis*, and *C. abortus*. The mouse pneumonitis strain (MoPn) is now classified as *C. muridarum*, and the guinea pig inclusion conjunctivitis strain (GPIC) is now designated *C. caviae*.

C. trachomatis is divided into two biovars: trachoma and LGV (lymphogranuloma venereum). The trachoma biovar causes two major types of disease in humans: ocular trachoma, the leading infectious cause of preventable blindness in the developing world; and urogenital infections, which are sexually or neonatally transmitted. The 18 serovars of *C. trachomatis* fall into three groups: the trachoma serovars A, B, Ba, and C; the oculogenital serovars D–K; and the LGV serovars L_1–L_3. Serovars can be distinguished by serologic typing with monoclonal antibodies or by molecular gene typing. However, serovar identification usually is not important clinically, since the antibiotic susceptibility pattern is the same for all three groups. The one exception applies when LGV is suspected on clinical grounds; in this situation, serovar determination is important because a longer treatment duration is required for LGV strains.

BIOLOGY, GROWTH CYCLE, AND PATHOGENESIS

BIOLOGY

During their intracellular growth, chlamydiae produce characteristic intracytoplasmic inclusions that can be visualized by direct fluorescent antibody or Giemsa staining of infected clinical material, such as conjunctival scrapings or cervical or urethral epithelial cells. Chlamydiae are nonmotile, gram-negative, obligate intracellular bacteria that replicate within the cytoplasm of host cells, forming the characteristic membrane-bound inclusions that are the basis for some diagnostic tests. Originally considered to be large viruses, chlamydiae differ from viruses in possessing RNA and DNA as well as a cell wall that is quite similar in structure to the cell wall of typical gram-negative bacteria. However, chlamydiae lack peptidoglycan; their structural integrity depends on disulfide binding of outer-membrane proteins.

GROWTH CYCLE

Among the defining characteristics of chlamydiae is a unique growth cycle that involves alternation between two highly specialized morphologic forms **(Figs. 184-1 and 184-2)**: the elementary body, which is the infectious form and is specifically adapted for extracellular survival,

FIGURE 184-1 Chlamydial intracellular inclusions filled with smaller dense elementary bodies and larger reticulate bodies. *(Reprinted with permission from WE Stamm: Chlamydial infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1070.)*

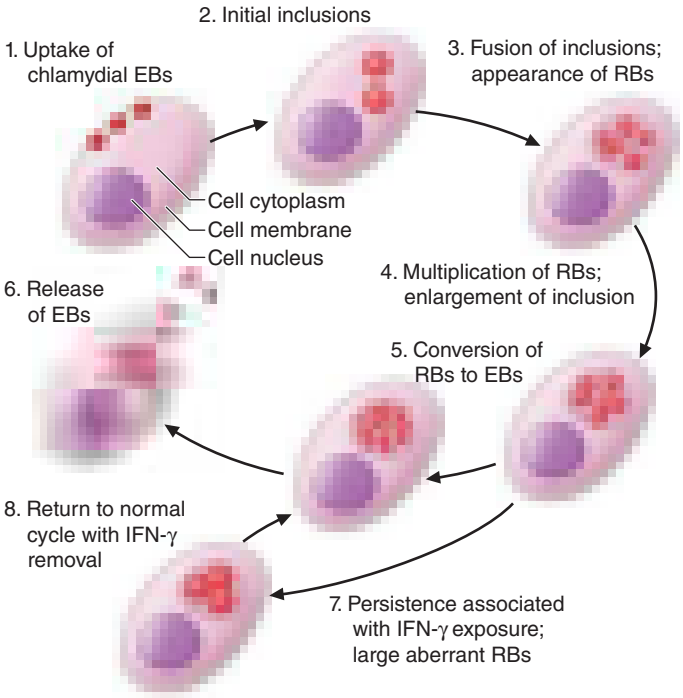

FIGURE 184-2 Chlamydial life cycle. EBs, elementary bodies; RBs, reticulate bodies; IFN-γ, interferon γ. *(Reprinted with permission from WE Stamm: Chlamydial infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, 2008, p 1071.)*

and the metabolically active and replicating reticulate body, which is not infectious, is adapted for an intracellular environment, and does not survive well outside the host cell. The biphasic growth cycle begins with attachment of the elementary body (diameter, 0.25–0.35 μm) at specific sites on the surface of the host cell. The elementary body enters the cell through a process similar to receptor-mediated endocytosis and resides in an inclusion, where the entire growth cycle is completed. The chlamydiae prevent phagosome–lysosome fusion. The inclusion membrane is modified by insertion of chlamydial antigens. Once the elementary body has entered the cell, it reorganizes into a reticulate body, which is larger (0.5–1 μm) and contains more RNA. After ~8 h, the reticulate body starts to divide by binary fission. The intracytoplasmic, membrane-bound inclusion body containing the reticulate bodies increases in size as the reticulate bodies multiply. Approximately 18–24 h after infection of the cell, these reticulate bodies begin to become elementary bodies by a reorganization or condensation process that is poorly understood. After rupture of the inclusion body, the elementary bodies are released to initiate another cycle of infection.

Chlamydiae are susceptible to many broad-spectrum antibiotics and possess a number of enzymes, but they have a very restricted metabolic capacity. None of these metabolic reactions result in the production of energy. Chlamydiae have thus been considered to be energy parasites that use the ATP produced by the host cell for their own metabolic functions. Many aspects of chlamydial molecular biology are not well understood, but the sequencing of several chlamydial genomes and new proteomics research have provided researchers with many relevant tools for elucidating the biology of the life cycle.

PATHOGENESIS

Genital infections are mostly caused by *C. trachomatis* serovars D–K, with serovars D, E, and F involved most often. Molecular typing of the major outer-membrane protein gene (*omp1*) from which serovar differences arise has been used to demonstrate that polymorphisms can occur in isolates from patients who are exposed frequently to multiple infections, while less variation is observed in isolates from less sexually active populations. Polymorphisms in the major outer-membrane protein may provide antigenic variation, and the different forms allow persistence in the community because immunity to one is not protective against the others.

The trachoma biovar is essentially a parasite of squamocolumnar epithelial cells; the LGV biovar is more invasive and involves lymphoid cells. As is typical of chlamydiae, *C. trachomatis* strains are capable of causing chronic, clinically inapparent, asymptomatic infections. Because the duration of the chlamydial growth cycle is ~48–72 h, the incubation period of sexually transmitted chlamydial infections is relatively long—generally 1–3 weeks. *C. trachomatis* causes cell death as a result of its replicative cycle and can induce cell damage whenever it persists. However, few toxic effects are demonstrated, and cell death because of chlamydial replication is not sufficient to account for disease manifestations, the majority of which are due to immunopathologic mechanisms or nonspecific host responses to the organism or its by-products.

In recent years, the entire genomes of various chlamydial species have been sequenced, the field of proteomics has become established, host innate immunity has been more precisely delineated, and innovative host cell–chlamydial interaction studies have been conducted. As a result, many insights have been gained into how chlamydiae adapt and replicate in their intracellular environment and produce disease. These insights into pathogenesis include information on the regulation of gene expression, protein localization, the type III secretion system, the roles of CD4+ and CD8+ T lymphocytes in the host response, and T lymphocyte trafficking.

The chlamydial heat-shock protein, which shares antigenic epitopes with similar proteins of other bacteria and with human heat-shock protein, may sensitize the host, and repeated infections may cause host cell damage. Persistent or recurrent chlamydial infections are associated with fibrosis, scarring, and complications following simple epithelial infections. A common endpoint of these late consequences is scarring of mucous membranes. Genital complications can lead to pelvic inflammatory disease (PID) and its late consequences of infertility, ectopic pregnancy, and chronic pelvic pain, while ocular infections may lead to blinding trachoma. High levels of antibody to human heat-shock protein have been associated with tubal factor infertility and ectopic pregnancy. Without adequate therapy, chlamydial infections may persist for several years, although symptoms—if present—usually abate.

Pathogenic mechanisms of *C. pneumoniae* have yet to be completely elucidated. The same is true for *C. psittaci*, except that this agent infects cells very efficiently and causes disease that may reflect direct cytopathic effects.

C. TRACHOMATIS INFECTIONS

GENITAL INFECTIONS (SEE ALSO CHAP. 131)

Spectrum Although chlamydiae cause a number of human diseases, localized lower genital tract infections caused by *C. trachomatis* and the sequelae of such infections are the most important in terms of medical and economic impact. Oculogenital infections due to *C. trachomatis* serovars D–K are transmitted during sexual contact or from mother to baby during childbirth and are associated with many syndromes, including cervicitis, salpingitis, acute urethral syndrome, endometritis, ectopic pregnancy, infertility, and PID in female patients; urethritis, proctitis, and epididymitis in male patients; and conjunctivitis and pneumonia in infants. Women bear the greatest burden of morbidity because of the serious sequelae of these infections. Untreated infections lead to PID, and multiple episodes of PID can lead to tubal factor infertility and chronic pelvic pain. Studies estimate that up to 80–90% of women and >50% of men with *C. trachomatis* genital infections lack symptoms; other patients have very mild symptoms. Thus, a large reservoir of infected persons continues to transmit infection to sexual partners.

As their designations reflect, the LGV serovars (L_1, L_2, and L_3) cause LGV, an invasive sexually transmitted disease (STD) characterized by acute lymphadenitis with bubo formation and/or acute hemorrhagic proctitis (see "LGV," below).

Epidemiology • **GLOBAL EPIDEMIOLOGY** *C. trachomatis* genital infections are global in distribution. The World Health Organization (WHO) estimated in 2008 that >106.4 million

cases occur annually worldwide. This figure makes chlamydial infection the most prevalent bacterial sexually transmitted infection in the world. The associated morbidity is substantial, and the economic cost is high.

U.S. EPIDEMIOLOGY In the United States, these infections are the most commonly reported of all infectious diseases. In 2015, 1,526,658 cases were reported to the U.S. Centers for Disease Control and Prevention (CDC); however, the CDC estimates that 2–3 million new cases occur per year, with substantial underreporting due to lack of screening in some populations. Rates of infection have increased every year; higher rates among women than among men reflect the focus on expansion of screening programs for women during the past 25 years. Use of increasingly sensitive diagnostic amplification tests, an increased emphasis on case reporting, and improvements in the information systems used have elevated the number of cases reported every year. The CDC and other professional organizations recommend annual screening of all sexually active women <25 years of age as well as rescreening of previously infected individuals at 3 months. The case count corresponds to 478.8 cases per 100,000 population, an increase of 5.9% compared with the rate in 2014. Young women have the highest infection rates (645.5 cases per 100,000)—more than twice the rate among men. Interestingly, with the increased availability of urine testing and extragenital testing, men—including gay, bisexual, and other men who have sex with men (MSM)—are increasingly being tested for chlamydial infection. From 2011 to 2015, rates of chlamydial infection in men increased by 20.0%, whereas rates in women rose by only 0.3% during this period. Chlamydial infection rates vary among different racial and ethnic minority populations. In 2015, rates among African Americans and American Indians/Alaska Natives were 5.9 and 3.8 times that among Caucasians, respectively. These disparities are important reflections of health inequities in the United States.

The aforementioned statistics are based on case reporting. Studies based on screening surveys estimate that the U.S. prevalence of *C. trachomatis* cervical infection is 5% among asymptomatic female college students and prenatal patients, >10% for women seen in family planning clinics, and >20% for women seen in STD clinics. The prevalence of genital *C. trachomatis* infections varies substantially by geographic locale, with the highest rates in the southeastern United States. The prevalence of *C. trachomatis* in the cervix of pregnant women is 5–10 times higher than that of *Neisseria gonorrhoeae*. The prevalence of genital infection with either agent is highest among women who are between the ages of 18 and 24, single, and non-Caucasian. Recurrent infections are common in these same risk groups and are often acquired from untreated sexual partners. The use of oral contraception and the presence of cervical ectopy also confer an increased risk. The proportion of infections that are asymptomatic appears to be higher for *C. trachomatis* than for *N. gonorrhoeae*, and symptomatic *C. trachomatis* infections are clinically less severe. Mild or asymptomatic *C. trachomatis* infections of the fallopian tubes nonetheless cause ongoing tubal damage and infertility. The costs of *C. trachomatis* infections and their complications to the U.S. health care system have recently been estimated to be >$516.7 million annually.

Clinical Manifestations

• NONGONOCOCCAL AND POSTGONOCOCCAL URETHRITIS *C. trachomatis* is the most common cause of nongonococcal urethritis (NGU) and postgonococcal urethritis (PGU). The designation *PGU* refers to NGU developing in men 2–3 weeks after treatment of gonococcal urethritis with single doses of agents such as penicillin or cephalosporins, which lack antimicrobial activity against chlamydiae. Current treatment regimens for gonorrhea have evolved and now include combination therapy with ceftriaxone and azithromycin; this current regimen is effective against concomitant chlamydial infection. Thus both the incidence of PGU and the causative role of *C. trachomatis* in this syndrome have declined.

In the United States, most of the estimated 2 million cases of acute urethritis are NGU, and *C. trachomatis* is implicated in 30–50% of these cases. The cause of most of the remaining cases of NGU is uncertain, but recent evidence suggests that *Mycoplasma genitalium, Trichomonas vaginalis*, and herpes simplex virus (HSV) cause some cases. The rate of involvement of *C. trachomatis* in urethral infection ranges from 3–7% among asymptomatic men to 15–20% among symptomatic men attending STD clinics. One recent multisite study of men in Baltimore, Seattle, Denver, and San Francisco reported an overall chlamydial prevalence of 7% in urine samples assessed by nucleic acid amplification tests (NAATs)—molecular tests that amplify the nucleic acids in clinical specimens. As in women, infection in men is age related, with young age as the greatest risk factor for chlamydial urethritis. The prevalence among men is highest at 20–24 years of age. In STD clinics, urethritis is usually less prevalent among MSM than among heterosexual men and is almost always much more common among black men than among white men. One study reported prevalences of 19 and 9% among nonwhite and white heterosexual men, respectively.

NGU is diagnosed by documentation of a leukocyte urethral exudate and by exclusion of gonorrhea by Gram's staining or culture. *C. trachomatis* urethritis is generally less severe than gonococcal urethritis, although in any individual patient these two forms of urethritis cannot reliably be differentiated solely on clinical grounds. Symptoms include urethral discharge (often whitish and mucoid rather than frankly purulent), dysuria, and urethral itching. Physical examination may reveal meatal erythema and tenderness as well as a urethral exudate that is often demonstrable only by stripping of the urethra.

At least one-third of male patients with *C. trachomatis* urethral infection have no evident signs or symptoms of urethritis. The availability of NAATs for first-void urine specimens has facilitated broader-based testing for asymptomatic infection in male patients. As a result, asymptomatic chlamydial urethritis has been demonstrated in 5–10% of sexually active male adolescents screened at school-based clinics or community centers. Such patients generally have pyuria (≥15 leukocytes per 400× microscopic field in the sediment of first-void urine), a positive leukocyte esterase test, or an increased number of leukocytes on a Gram-stained smear prepared from a urogenital swab inserted 1–2 cm into the anterior urethra. When specific diagnostic tests for chlamydiae are not available, the examination of an endourethral specimen for increased leukocytes is useful in differentiating between true urethritis and functional symptoms in symptomatic patients or in making a presumptive diagnosis of *C. trachomatis* infection in high-risk but asymptomatic men (e.g., male patients in STD clinics, sex partners of women with nongonococcal salpingitis or mucopurulent cervicitis, fathers of children with inclusion conjunctivitis). Alternatively, urethritis can be assayed noninvasively by examination of a first-void urine sample for pyuria, either by microscopy or by the leukocyte esterase test. Urine (or a urethral swab) can also be tested directly for chlamydiae by DNA amplification methods (NAATs), as described below (see "Detection Methods").

EPIDIDYMITIS Chlamydial urethritis may be followed by acute epididymitis, but this condition is rare, generally occurring in sexually active patients <35 years of age; in older men, epididymitis is usually associated with gram-negative bacterial infection and/or instrumentation procedures. An estimated 50–70% of cases of acute epididymitis are caused by *C. trachomatis*. The condition usually presents as unilateral scrotal pain with tenderness, swelling, and fever in a young man, often occurring in association with chlamydial urethritis. The illness may be mild enough to treat with oral antibiotics on an outpatient basis or severe enough to require hospitalization and parenteral therapy. Testicular torsion should be excluded promptly by radionuclide scan, Doppler flow study, or surgical exploration in a teenager or young adult who presents with acute unilateral testicular pain without urethritis. The possibility of testicular tumor or chronic infection (e.g., tuberculosis) should be excluded when a patient with unilateral intrascrotal pain and swelling does not respond to appropriate antimicrobial therapy.

REACTIVE ARTHRITIS Reactive arthritis consists of conjunctivitis, urethritis (or, in female patients, cervicitis), arthritis, and characteristic mucocutaneous lesions. It may develop in 1–2% of cases of NGU and is thought to be the most common type of peripheral inflammatory arthritis in young men. *C. trachomatis* has been recovered from the urethra of 16–44% of patients with reactive arthritis and 69% of men who have

signs of urogenital inflammation at the time of examination. Antibodies to *C. trachomatis* have also been detected in 46–67% of patients with reactive arthritis, and *Chlamydia*-specific cell-mediated immunity has been documented in 72%. In addition, *C. trachomatis* has been isolated from synovial biopsy samples from 15 of 29 patients in a number of small series and from a smaller proportion of synovial fluid specimens. Chlamydial nucleic acids have been identified in synovial membranes and chlamydial elementary bodies in joint fluid. The pathogenesis of reactive arthritis is unclear, but this condition probably represents an abnormal host response to a number of infectious agents, including those associated with bacterial gastroenteritis (e.g., *Salmonella*, *Shigella*, *Yersinia*, or *Campylobacter*), or to infection with *C. trachomatis* or *N. gonorrhoeae*. Since >80% of affected patients have the HLA-B27 phenotype and since other mucosal infections produce an identical syndrome, chlamydial infection is thought to initiate an aberrant hyperreactive immune response that produces inflammation of the involved target organs in these genetically predisposed individuals. Evidence of exaggerated cell-mediated and humoral immune responses to chlamydial antigens in reactive arthritis supports this hypothesis. The finding of chlamydial elementary bodies and DNA in joint fluid and synovial tissue from patients with reactive arthritis suggests that chlamydiae may actually spread from genital to joint tissues in these patients—perhaps in macrophages.

NGU is the initial manifestation of reactive arthritis in 80% of patients, typically occurring within 14 days after sexual exposure. The urethritis may be mild and may even go unnoticed by the patient. Similarly, gonococcal urethritis may precede reactive arthritis, but co-infection with an agent of NGU is difficult to rule out. The urethral discharge may be purulent or mucopurulent, and patients may or may not report dysuria. Accompanying prostatitis, usually asymptomatic, has been described. Arthritis usually begins ~4 weeks after the onset of urethritis but may develop sooner or, in a small percentage of cases, may actually precede urethritis. The knees are most frequently involved; next most commonly affected are the ankles and small joints of the feet. Sacroiliitis, either symmetrical or asymmetrical, is documented in two-thirds of patients. Mild bilateral conjunctivitis, iritis, keratitis, or uveitis is sometimes present but lasts for only a few days. Finally, dermatologic manifestations occur in up to 50% of patients. The initial lesions—usually papules with a central yellow spot—most often involve the soles and palms and, in ~25% of patients, eventually epithelialize and thicken to produce keratoderma blenorrhagicum. Circinate balanitis is usually painless and occurs in fewer than half of patients. The initial episode of reactive arthritis usually lasts 2–6 months.

PROCTITIS Primary anal or rectal infections with *C. trachomatis* have been described in women and MSM who practice anal intercourse. In these infections, rectal involvement is initially characterized by severe anorectal pain, a bloody mucopurulent discharge, and tenesmus. Oculogenital serovars D–K and LGV serovars L_1, L_2, and L_3 have been found to cause proctitis. The LGV serovars are far more invasive and cause much more severely symptomatic disease, including severe ulcerative proctocolitis that can be clinically confused with HSV proctitis. Histologically, LGV proctitis may resemble Crohn's disease in that giant cell formation and granulomas are detected. In the United States and Europe, cases of LGV proctitis occur almost exclusively in MSM, many of whom have HIV infection.

The less invasive non-LGV serovars of *C. trachomatis* cause mild proctitis. Many infected individuals are asymptomatic, and in these cases infection is diagnosed only by routine culture or NAAT of rectal swabs. The number of fecal leukocytes is usually abnormal in both asymptomatic and symptomatic cases. Sigmoidoscopy may yield normal findings or may reveal mild inflammatory changes or small erosions or follicles in the lower 10 cm of the rectum. Histologic examination of rectal biopsies generally shows anal crypts and prominent follicles as well as neutrophilic infiltration of the lamina propria. Chlamydial proctitis is best diagnosed by isolation of *C. trachomatis* from the rectum and documentation of a response to appropriate therapy. NAATs are reportedly more sensitive than culture for diagnosis and are also specific.

MUCOPURULENT CERVICITIS Although most women with chlamydial infections of the cervix have no symptoms, almost half generally have local signs of infection on examination. Cervicitis is usually characterized by the presence of a mucopurulent discharge, with >20 neutrophils per microscopic field visible in strands of cervical mucus in a thinly smeared, gram-stained preparation of endocervical exudate. Hypertrophic ectopy of the cervix may also be evident as an edematous area near the cervical os that is congested and bleeds easily on minor trauma (e.g., when a specimen is collected with a swab). A Papanicolaou smear shows increased numbers of neutrophils as well as a characteristic pattern of mononuclear inflammatory cells, including plasma cells, transformed lymphocytes, and histiocytes. Cervical biopsy shows a predominantly mononuclear cell infiltrate of the subepithelial stroma. Clinical experience and collaborative studies indicate that a cutoff of >30 polymorphonuclear leukocytes (PMNs)/1000× field in a gram-stained smear of cervical mucus correlates best with chlamydial or gonococcal cervicitis.

Clinical recognition of chlamydial cervicitis depends on a high index of suspicion and careful cervical examination. No genital symptoms are specifically correlated with chlamydial cervical infection. The differential diagnosis of a mucopurulent discharge from the endocervical canal in a young, sexually active woman includes gonococcal endocervicitis, salpingitis, endometritis, and intrauterine contraceptive device–induced inflammation. Diagnosis of cervicitis is based on the presence of PMNs on a cervical swab as noted above; the presence of chlamydiae is confirmed by either culture or NAAT.

PELVIC INFLAMMATORY DISEASE Inflammation of sections of the fallopian tube is often referred to as salpingitis or PID. The proportion of acute salpingitis cases caused by *C. trachomatis* varies geographically and with the population studied. It has been estimated that *C. trachomatis* causes up to 50% of PID cases in the United States. PID occurs via ascending intraluminal spread of *C. trachomatis* or *N. gonorrhoeae* from the lower genital tract. Mucopurulent cervicitis is often followed by endometritis, endosalpingitis, and finally pelvic peritonitis. Evidence of mucopurulent cervicitis is often found in women with laparoscopically verified salpingitis. Similarly, endometritis, demonstrated by an endometrial biopsy showing plasma cell infiltration of the endometrial epithelium, is documented in most women with laparoscopy-verified chlamydial (or gonococcal) salpingitis. Chlamydial endometritis can also occur in the absence of clinical evidence of salpingitis. Histologic evidence of endometritis has been correlated with a syndrome consisting of vaginal bleeding, lower abdominal pain, and uterine tenderness in the absence of adnexal tenderness. Chlamydial salpingitis produces milder symptoms than gonococcal salpingitis and may be associated with less marked adnexal tenderness. Thus, mild adnexal or uterine tenderness in a sexually active woman with cervicitis suggests chlamydial PID.

Chronic untreated endometrial and tubal inflammation can result in tubal scarring, impaired tubal function, tubal occlusion, and infertility even among women who report no prior treatment for chlamydial infection. *C. trachomatis* has been particularly implicated in "subclinical" PID on the basis of a lack of history of PID among *Chlamydia*-seropositive women with tubal damage and detection of chlamydial DNA or antigen among asymptomatic women with tubal infertility. These data suggest that the best method to prevent PID and its sequelae is surveillance and control of lower genital tract infections along with diagnosis and treatment of sex partners and prevention of reinfections. Promotion of early symptom recognition and health care presentation may reduce the frequency and severity of sequelae of PID.

PERIHEPATITIS The Fitz-Hugh–Curtis syndrome was originally described as a complication of gonococcal PID. However, studies over the past several decades have suggested that chlamydial infection is more commonly associated with perihepatitis than is *N. gonorrhoeae*. Perihepatitis should be suspected in young, sexually active women who develop right-upper-quadrant pain, fever, or nausea. Evidence of salpingitis may or may not be found on examination. Frequently, perihepatitis is strongly associated with extensive tubal scarring, adhesions, and inflammation observed at laparoscopy, and high titers of

antibody to the 57-kDa chlamydial heat-shock protein have been documented. Culture and/or serologic evidence of *C. trachomatis* is found in three-fourths of women with this syndrome.

URETHRAL SYNDROME IN WOMEN In the absence of infection with uropathogens such as coliforms or *Staphylococcus saprophyticus*, *C. trachomatis* is the pathogen most commonly isolated from college women with dysuria, frequency, and pyuria. Screening studies can recover *C. trachomatis* at both the cervix and the urethra; in up to 25% of infected women, the organism is isolated only from the urethra. The urethral syndrome in women consists of dysuria and frequency in conjunction with chlamydial urethritis, pyuria, and no bacteriuria or urinary pathogens. Although symptoms of the urethral syndrome may develop in some women with chlamydial infection, the majority of women attending STD clinics for urethral chlamydial infection do not have dysuria or frequency. Even in women with chlamydial urethritis causing the acute urethral syndrome, signs of urethritis such as urethral discharge, meatal redness, and swelling are uncommon. However, mucopurulent cervicitis in a woman presenting with dysuria and frequency strongly suggests *C. trachomatis* urethritis. Other correlates of chlamydial urethral syndrome include a duration of dysuria of >7–10 days, lack of hematuria, and lack of suprapubic tenderness. Abnormal urethral Gram's stains showing >10 PMNs/1000× field in women with dysuria but without coliform bacteriuria support the diagnosis of chlamydial urethritis. Other possible diagnoses include gonococcal or trichomonal infection of the urethra.

INFECTION IN PREGNANCY AND THE NEONATAL PERIOD Infections during pregnancy can be transmitted to infants during delivery. Approximately 20–30% of infants exposed to *C. trachomatis* in the birth canal develop conjunctivitis, and 10–15% subsequently develop pneumonia. Consequently, all newborn infants receive ocular prophylaxis at birth to prevent ophthalmia neonatorum. Without treatment, conjunctivitis usually develops at 5–19 days of life and often results in a profuse mucopurulent discharge. Roughly half of infected infants develop clinical evidence of inclusion conjunctivitis. However, it is impossible to differentiate chlamydial conjunctivitis from other forms of neonatal conjunctivitis (e.g., that due to *N. gonorrhoeae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, or HSV) on clinical grounds; thus laboratory diagnosis is required. Inclusions within epithelial cells are often detected in Giemsa-stained conjunctival smears, but these smears are considerably less sensitive than cultures or NAATs for chlamydiae. Gram-stained smears may show gonococci or occasional small gram-negative coccobacilli in *Haemophilus* conjunctivitis, but smears should be accompanied by cultures or NAATs for these agents.

C. trachomatis has also been isolated frequently and persistently from the nasopharynx, rectum, and vagina of infected infants—occasionally for >1 year in the absence of treatment. In some cases, otitis media results from perinatally acquired chlamydial infection. Pneumonia may develop in infants from 2 weeks to 4 months of age. *C. trachomatis* is estimated to cause 20–30% of pneumonia cases in infants <6 months of age. Epidemiologic studies have linked chlamydial pulmonary infection in infants with increased occurrence of subacute lung disease (bronchitis, asthma, wheezing) in later childhood.

LYMPHOGRANULOMA VENEREUM *C. trachomatis* serovars L_1, L_2, and L_3 cause LGV, an invasive systemic STD. The peak incidence of LGV corresponds with the age of greatest sexual activity: the second and third decades of life. The worldwide incidence of LGV is falling, but the disease is still endemic and a major cause of morbidity in parts of Asia, Africa, South America, and the Caribbean. LGV is rare in industrialized countries; for more than a decade, the reported incidence in the United States has been only 0.1 case per 100,000 population. In the Bahamas, an apparent outbreak of LGV was described in association with a concurrent increase in heterosexual infection with HIV. Reports of outbreaks with the newly identified variant L_{2b} in Europe, Australia, and the United States indicate that LGV is becoming more prevalent among MSM. These cases have usually presented as hemorrhagic proctocolitis in HIV-positive men. More widespread use of NAATs for identification of rectal infections may have enhanced case recognition.

LGV begins as a small painless papule that tends to ulcerate at the site of inoculation, often escaping attention. This primary lesion heals in a few days without scarring and is usually recognized as LGV only in retrospect. LGV strains of *C. trachomatis* have occasionally been recovered from genital ulcers and from the urethra of men and the endocervix of women who present with inguinal adenopathy; these areas may be the primary sites of infection in some cases. Proctitis is more common among people who practice receptive anal intercourse, and an elevated white blood cell count in anorectal smears may predict LGV in these patients. Ulcer formation may facilitate transmission of HIV infection and other sexually transmitted and blood-borne diseases.

As NAATs for *C. trachomatis* are being used more often, increasing numbers of cases of LGV proctitis are being recognized in MSM. Such patients present with anorectal pain and mucopurulent, bloody rectal discharge. Sigmoidoscopy reveals ulcerative proctitis or proctocolitis, with purulent exudate and mucosal bleeding. Histopathologic findings in the rectal mucosa include granulomas with giant cells, crypt abscesses, and extensive inflammation. These clinical, sigmoidoscopic, and histopathologic findings may closely resemble those of Crohn's disease of the rectum.

The most common presenting picture in heterosexual men and women is the *inguinal syndrome*, which is characterized by painful inguinal lymphadenopathy beginning 2–6 weeks after presumed exposure; in rare instances, the onset comes after a few months. The inguinal adenopathy is unilateral in two-thirds of cases, and palpable enlargement of the iliac and femoral nodes is often evident on the same side as the enlarged inguinal nodes. The nodes are initially discrete, but progressive periadenitis results in a matted mass of nodes that becomes fluctuant and suppurative. The overlying skin becomes fixed, inflamed, and thin, and multiple draining fistulas finally develop. Extensive enlargement of chains of inguinal nodes above and below the inguinal ligament ("the sign of the groove") is not specific and, although not uncommon, is documented in only a minority of cases. Spontaneous healing usually takes place after several months; inguinal scars or granulomatous masses of various sizes persist for life. Massive pelvic lymphadenopathy may lead to exploratory laparotomy.

Constitutional symptoms are common during the stage of regional lymphadenopathy and, in cases of proctitis, may include fever, chills, headache, meningismus, anorexia, myalgias, and arthralgias. Other systemic complications are infrequent but include arthritis with sterile effusion, aseptic meningitis, meningoencephalitis, conjunctivitis, hepatitis, and erythema nodosum **(Fig. A1-39)**. Complications of untreated anorectal infection include perirectal abscess; anal fistulas; and rectovaginal, rectovesical, and ischiorectal fistulas. Secondary bacterial infection probably contributes to these complications. Rectal stricture is a late complication of anorectal infection and usually develops 2–6 cm from the anal orifice—i.e., at a site within reach on digital rectal examination. A small percentage of cases of LGV in men present as chronic progressive infiltrative, ulcerative, or fistular lesions of the penis, urethra, or scrotum. Associated lymphatic obstruction may produce elephantiasis. When urethral stricture occurs, it usually involves the posterior urethra and causes incontinence or difficulty with urination.

Diagnosis • DETECTION METHODS

Historically, chlamydiae were cultivated in the yolk sac of embryonated eggs. The organisms can be grown more easily in tissue culture, but cell culture—once considered the diagnostic gold standard—has been replaced by nonculture assays **(Table 184-1)**. In general, culture for chlamydiae in clinical specimens is now performed only in specialized laboratories. The first nonculture assays, such as direct fluorescent antibody staining of clinical material and enzyme immunoassay (EIA), have been replaced by NAATs, which are currently recommended by the CDC as the diagnostic assays of choice. At present, five NAAT assays cleared by the U.S. Food and Drug Administration (FDA) are commercially available, some of which are available as high-throughput robotic platforms. Point-of-care diagnostic assays are becoming available; they are of increasing interest since patients can potentially be treated before leaving the clinic.

CHOICE OF SPECIMEN Cervical and urethral swabs have traditionally been used for the diagnosis of STDs in female and male patients,

TABLE 184-1 Diagnostic Tests for Sexually Transmitted and Perinatal *Chlamydia trachomatis* Infection

INFECTION	SUGGESTIVE SIGNS/SYMPTOMS	PRESUMPTIVE DIAGNOSIS[a]	CONFIRMATORY TEST OF CHOICE
Men			
NGU, PGU	Discharge, dysuria	Gram's stain with >4 neutrophils per oil-immersion field; no gonococci	Urine or urethral NAAT for *C. trachomatis*
Epididymitis	Unilateral intrascrotal swelling, pain, tenderness; fever; NGU	Gram's stain with >4 neutrophils per oil-immersion field; no gonococci; urinalysis with pyuria	Urine or urethral NAAT for *C. trachomatis*
Women			
Cervicitis	Mucopurulent cervical discharge, bleeding and edema of the zone of cervical ectopy	Cervical Gram's stain with ≥20 neutrophils per oil-immersion field in cervical mucus	Urine, cervical, or vaginal NAAT for *C. trachomatis*
Salpingitis	Lower abdominal pain, cervical motion tenderness, adnexal tenderness or masses	*C. trachomatis* always potentially present in salpingitis	Urine, cervical, or vaginal NAAT for *C. trachomatis*
Urethritis	Dysuria and frequency without hematuria	MPC; sterile pyuria; negative routine urine culture	Urine or urethral NAAT for *C. trachomatis*
Adults of Either Sex			
Proctitis	Rectal pain, discharge, tenesmus, bleeding; history of receptive anorectal intercourse	Negative gonococcal culture and Gram's stain; at least 1 neutrophil per oil-immersion field in rectal Gram's stain	Rectal NAAT for *C. trachomatis* or culture
Reactive arthritis	NGU, arthritis, conjunctivitis, typical skin lesions	Gram's stain with >4 neutrophils per oil-immersion field; lack of gonococci indicative of NGU	Urine or urethral NAAT for *C. trachomatis*
LGV	Regional adenopathy, primary lesion, proctitis, systemic symptoms	None	Culture of LGV strain from node or rectum, occasionally from urethra or cervix; NAAT for *C. trachomatis* from these sites; LGV CF titer, ≥1:64; MIF titer, ≥1:512
Neonates			
Conjunctivitis	Purulent conjunctival discharge 6–18 days after delivery	Negative culture and Gram's stain for gonococci, *Haemophilus* spp., pneumococci, staphylococci	Conjunctival NAAT for *C. trachomatis*; FA-stained scraping of conjunctival material
Infant pneumonia	Afebrile, staccato cough, diffuse rales, bilateral hyperinflation, interstitial infiltrates	None	Chlamydial culture or NAAT of sputum, pharynx, eye, rectum; MIF antibody to *C. trachomatis*—fourfold change in IgG or IgM antibody titer

[a]A presumptive diagnosis of chlamydial infection is often made in the syndromes listed when gonococci are not found. A positive test for *Neisseria gonorrhoeae* does not exclude the involvement of *C. trachomatis*, which often is present in patients with gonorrhea.

Abbreviations: CF, complement-fixing; FA, fluorescent antibody; LGV, lymphogranuloma venereum; MIF, microimmunofluorescence; MPC, mucopurulent cervicitis; NAAT, nucleic acid amplification test; NGU, nongonococcal urethritis; PGU, postgonococcal urethritis.

Source: Reprinted with permission from WE Stamm: Chlamydial infections, in *Harrison's Principles of Internal Medicine*, 17th ed, AS Fauci et al (eds). New York, McGraw-Hill, 2008, p 1075.

respectively. However, given the greatly increased sensitivity and specificity of NAATs, less invasive samples (e.g., urine for both sexes and vaginal swabs for women) can be used. For screening of asymptomatic women, the CDC now recommends that self-collected or clinician-collected vaginal swabs, which are slightly more sensitive than urine, be used. Urine screening tests are often used in outreach screening programs, however. For symptomatic women undergoing a pelvic examination, cervical swab samples are desirable because they have slightly higher chlamydial counts. For male patients, a urine specimen is the sample of choice, but self-collected penile-meatal swabs have been explored.

ALTERNATIVE SPECIMEN TYPES Ocular samples from babies and adults can be assessed by NAATs. However, since commercial NAATs for this purpose have not yet been approved by the FDA, laboratories must perform their own verification studies. Samples from rectal and pharyngeal sites have been used successfully to detect chlamydiae by NAATs, but laboratories must perform validation studies to verify test performance.

OTHER DIAGNOSTIC ISSUES Because NAATs detect nucleic acids instead of live organisms, they should be used with caution as test-of-cure assays. Residual nucleic acid from cells rendered noninfective by antibiotics may continue to yield a positive result in NAATs for as long as 3 weeks after therapy when viable organisms have actually been eradicated. Therefore, clinicians should not use NAATs for test of cure until after 3 weeks. The CDC currently does not recommend a test of cure after treatment for infection with *C. trachomatis*. However, because incidence studies have demonstrated that previous chlamydial infection increases the probability of becoming reinfected, the CDC does recommend that previously infected individuals be rescreened 3 months after treatment.

SEROLOGY Serologic testing may be helpful in the diagnosis of LGV and neonatal pneumonia caused by *C. trachomatis*. The serologic test of choice is the microimmunofluorescence (MIF) test, in which high-titer purified elementary bodies mixed with embryonated chicken yolk sac material are affixed to a glass microscope slide to which dilutions of sera are applied. After incubation and washing, fluorescein-conjugated IgG or IgM antibody is applied. The test is read with an epifluorescence microscope, with the highest dilution of serum producing visible fluorescence designated as the titer. The MIF test is not widely available except in research laboratories and is highly labor intensive. Although the complement fixation (CF) test can also be used, it employs lipopolysaccharide (LPS) as the antigen and therefore identifies the pathogen only to the genus level. Single-point titers of >1:64 support a diagnosis of LGV, in which it is difficult to demonstrate rising antibody titers—i.e., paired serum samples are difficult to obtain since, by its very nature, the disease results in the patient's being seen by the physician after the acute stage. Any antibody titer of above 1:16 is considered significant evidence of exposure to chlamydiae. However, serologic testing is never recommended for diagnosis of uncomplicated genital infections of the cervix, urethra, and lower genital tract or for *C. trachomatis* screening of asymptomatic individuals.

TREATMENT

C. trachomatis Genital Infections

A 7-day course of tetracycline (500 mg four times daily), doxycycline (100 mg twice daily), erythromycin (500 mg four times daily), or a fluoroquinolone (ofloxacin, 300 mg twice daily; or levofloxacin, 500 mg/d) can be used for treatment of uncomplicated chlamydial infections. A single 1-g oral dose of azithromycin is as effective as a 7-day course of doxycycline for the treatment of uncomplicated genital *C. trachomatis* infections in adults. Azithromycin causes fewer adverse gastrointestinal reactions than do older macrolides such as erythromycin. The single-dose regimen of azithromycin has great appeal for the treatment of patients with uncomplicated chlamydial infection (especially those without symptoms and those with a likelihood of poor compliance) and of the sexual partners of infected patients. These advantages must be weighed against the considerably greater cost of azithromycin. Whenever possible, the single 1-g dose should be given as directly observed therapy. Although not approved by the FDA for use in pregnancy, this regimen appears to be safe and effective for this purpose. However, amoxicillin (500 mg three times daily for 7 days) can also be given to pregnant women. The fluoroquinolones are contraindicated in pregnancy. A 2-week course of treatment is recommended for complicated chlamydial infections (e.g., PID, epididymitis) and at least a 3-week course of doxycycline (100 mg orally twice daily) or erythromycin base (500 mg orally four times daily) for LGV. Failure of treatment with a tetracycline in genital infections usually indicates poor compliance or reinfection rather than involvement of a drug-resistant strain. To date, clinically significant drug resistance has not been observed in *C. trachomatis*.

Treatment or testing for chlamydiae should be considered among *N. gonorrhoeae*–infected patients because of the frequency of coinfection. Systemic treatment with erythromycin has been recommended for ophthalmia neonatorum and for *C. trachomatis* pneumonia in infants. For the treatment of adult inclusion conjunctivitis, a single 1-g dose of azithromycin was as effective as standard 10-day treatment with doxycycline. Recommended treatment regimens for both bubonic and anogenital LGV include tetracycline, doxycycline, or erythromycin for 21 days.

SEX PARTNERS

The continued high prevalence of chlamydial infections in most parts of the United States is due primarily to the failure to diagnose—and therefore treat—patients with symptomatic or asymptomatic infection and their sex partners. Urethral or cervical infection with *C. trachomatis* has been well documented in a high proportion of the sex partners of patients with NGU, epididymitis, reactive arthritis, salpingitis, and endocervicitis. If possible, confirmatory laboratory tests for chlamydiae should be undertaken in these individuals, but even persons without positive tests or evidence of clinical disease who have recently been exposed to proven or possible chlamydial infection (e.g., NGU) should be offered therapy. A novel approach is partner-delivered therapy, in which infected patients receive treatment and are also provided with single-dose azithromycin to give to their sex partner(s).

NEONATES AND INFANTS

In neonates with conjunctivitis or infants with pneumonia, erythromycin ethylsuccinate or estolate can be given orally at a dosage of 50 mg/kg per day, preferably in four divided doses, for 2 weeks. Careful attention must be given to compliance with therapy—a frequent problem. Relapses of eye infection are common after topical treatment with erythromycin or tetracycline ophthalmic ointment and may also follow oral erythromycin therapy. Thus follow-up cultures should be performed after treatment. Both parents should be examined for *C. trachomatis* infection and, if diagnostic testing is not readily available, should be treated with doxycycline or azithromycin.

Prevention Since many chlamydial infections are asymptomatic, effective control and prevention must involve periodic screening of individuals at risk. Selective cost-effective screening criteria have been developed. Among women, young age (generally <25 years) is a critical risk factor for chlamydial infections in nearly all studies. Other risk factors include mucopurulent cervicitis; multiple, new, or symptomatic male sex partners; and lack of barrier contraceptive use. In some settings, screening based on young age may be as sensitive as criteria that incorporate behavioral and clinical measures. Another strategy is universal testing of all patients in high-prevalence clinic populations (e.g., STD clinics, juvenile detention facilities, and family planning clinics).

The effectiveness of selective screening in reducing the prevalence of chlamydial infection among women has been demonstrated in several studies. In the Pacific Northwest, where extensive screening began in family planning clinics in 1998 and in STD clinics in 1993, the prevalence declined from 10% in the 1980s to <5% in 2000. Similar trends have occurred in association with screening programs elsewhere. In addition, screening can effect a reduction in upper genital tract disease. In Seattle, women at a large health maintenance organization who were screened for chlamydial infection on a routine basis had a lower incidence of symptomatic PID than did women who received standard care and underwent more selective screening.

In settings with low to moderate prevalence, the prevalence at which selective screening becomes more cost-effective than universal screening must be defined. Most studies have concluded that universal screening is preferable in settings with a chlamydial prevalence of >3–7%. Depending on the criteria used, selective screening is likely to be more cost-effective when prevalence falls below 3%. Nearly all regions of the United States have now initiated screening programs, particularly in family planning and STD clinics. Along with single-dose therapy, the availability of highly sensitive and specific diagnostic NAATs using urine specimens and self-obtained vaginal swabs makes it feasible to mount an effective nationwide *Chlamydia* control program, with screening of high-risk individuals in traditional health-care settings and in novel outreach and community-based settings. The U.S. Preventive Task Force has named *Chlamydia* screening as a Grade B recommendation, which means that private insurance and Medicare will cover the cost of screening under the Affordable Care Act.

TRACHOMA

Epidemiology Trachoma—a sequela of ocular disease in developing countries—continues to be a leading cause of preventable infectious blindness worldwide. The WHO estimates that ~6 million people have been blinded by trachoma and that ~1.3 million people in developing countries still suffer from preventable blindness due to trachoma; certainly hundreds of millions live in trachoma-endemic areas. Foci of trachoma persist in Australia, the South Pacific, and Latin America. *C. trachomatis* serovars A, B, Ba, and C are isolated from patients with clinical trachoma in areas of endemicity in developing countries in Africa, the Middle East, Asia, and South America.

The trachoma-hyperendemic areas of the world are in northern and sub-Saharan Africa, the Middle East, drier regions of the Indian subcontinent, and Southeast Asia. In hyperendemic areas, the prevalence of trachoma is essentially 100% by the second or third year of life. Active disease is most common among young children, who are the reservoir for trachoma. By adulthood, active infection is infrequent but sequelae result in blindness. In such areas, trachoma constitutes the major cause of blindness.

Trachoma is transmitted through contact with discharges from the eyes of infected patients. Transmission is most common under poor hygienic conditions and most often takes place between family members or between families with shared facilities. Flies can also transfer the mucopurulent ocular discharges, carrying the organisms on their legs from one person to another. The International Trachoma Initiative founded by the WHO in 1998 aims to eliminate blinding trachoma globally by 2020.

Clinical Manifestations Both endemic trachoma and adult inclusion conjunctivitis present initially as conjunctivitis characterized

by small lymphoid follicles in the conjunctiva. In regions with hyperendemic classic blinding trachoma, the disease usually starts insidiously before the age of 2 years. Reinfection is common and probably contributes to the pathogenesis of trachoma. Studies using polymerase chain reaction (PCR) or other NAATs indicate that chlamydial DNA is often present in the ocular secretions of patients with trachoma, even in the absence of positive cultures. Thus, persistent infection may be more common than was previously thought.

The cornea becomes involved, with inflammatory leukocytic infiltrations and superficial vascularization (pannus formation). As the inflammation continues, conjunctival scarring eventually distorts the eyelids, causing them to turn inward so that the lashes constantly abrade the eyeball (trichiasis and entropion); eventually the corneal epithelium is abraded and may ulcerate, with subsequent corneal scarring and blindness. Destruction of the conjunctival goblet cells, lacrimal ducts, and lacrimal gland may produce a "dry-eye" syndrome, with resultant corneal opacity due to drying (xerosis) or secondary bacterial corneal ulcers.

Communities with blinding trachoma often experience seasonal epidemics of conjunctivitis due to *H. influenzae* that contribute to the intensity of the inflammatory process. In such areas, the active infectious process usually resolves spontaneously in affected persons at 10–15 years of age, but conjunctival scars continue to shrink, producing trichiasis and entropion with subsequent corneal scarring in adults. In areas with milder and less prevalent disease, the process may be much slower, with active disease continuing into adulthood; blindness is rare in these cases.

Eye infection with oculogenital *C. trachomatis* strains in sexually active young adults presents as an acute onset of unilateral follicular conjunctivitis and preauricular lymphadenopathy similar to that seen in acute conjunctivitis caused by adenovirus or HSV. If untreated, the disease may persist for 6 weeks to 2 years. It is frequently associated with corneal inflammation in the form of discrete opacities ("infiltrates"), punctate epithelial erosions, and minor degrees of superficial corneal vascularization. Very rarely, conjunctival scarring and eyelid distortion occur, particularly in patients treated for many months with topical glucocorticoids. Recurrent eye infections develop most often in patients whose sexual partners are not treated with antimicrobial agents.

Diagnosis The clinical diagnosis of classic trachoma can be made if two of the following signs are present: (1) lymphoid follicles on the upper tarsal conjunctiva; (2) typical conjunctival scarring; (3) vascular pannus; or (4) limbal follicles or their sequelae, Herbert pits. The clinical diagnosis of endemic trachoma should be confirmed by laboratory tests in children with relatively marked degrees of inflammation. Intracytoplasmic chlamydial inclusions are found in 10–60% of Giemsa-stained conjunctival smears in such populations, but chlamydial NAATs are more sensitive and are often positive when smears or cultures are negative. Follicular conjunctivitis in European or American adults living in trachomatous regions is rarely due to trachoma.

TREATMENT

Trachoma

Adult inclusion conjunctivitis responds well to treatment with the same regimens used in uncomplicated genital infections—namely, azithromycin (a 1-g single oral dose) or doxycycline (100 mg twice daily for 7 days). Simultaneous treatment of all sexual partners is necessary to prevent ocular reinfection and chlamydial genital disease. Topical antibiotic treatment is not required for patients who receive systemic antibiotics.

PSITTACOSIS

Psittacine birds and many other avian species act as natural reservoirs for *C. psittaci*–type organisms, common pathogens in domestic mammals and birds. The species *C. psittaci*, which now includes only avian strains, affects humans only as a zoonosis. (The other strains previously included in this species have been placed into different species that reflect the animals they infect: *C. abortus*, *C. muridarum*, *C. suis*, *C. felis*, and *C. caviae*.) Although all birds are susceptible, pet birds (parrots, parakeets, macaws, and cockatiels) and poultry (turkeys and ducks) are most frequently involved in transmission of *C. psittaci* to humans. Exposure is greatest in poultry-processing workers and in owners of pet birds. Infectious forms of the organisms are shed from both symptomatic and apparently healthy birds and may remain viable for several months. *C. psittaci* can be transmitted to humans by direct contact with infected birds or by inhalation of aerosols from avian nasal discharges and from infectious avian fecal or feather dust. Transmission from person to person has never been demonstrated.

The diagnosis is usually established serologically. Psittacosis in humans may present as acute primary atypical pneumonia (which can be fatal in up to 10% of untreated cases); as severe chronic pneumonia; or as a mild illness or asymptomatic infection in persons exposed to infected birds.

EPIDEMIOLOGY

Fewer than 50 confirmed cases of psittacosis are reported in the United States each year, although many more cases probably occur than are reported. Control of psittacosis depends on control of avian sources of infection. A pandemic of psittacosis was once stopped by banning shipment or importation of psittacine birds. Birds can receive prophylaxis in the form of a tetracycline-containing feed. Imported birds are currently quarantined for 30 days of treatment.

CLINICAL MANIFESTATIONS

Typical symptoms include fever, chills, muscular aches and pains, severe headache, hepato- and/or splenomegaly, and gastrointestinal symptoms. Cardiac complications may involve endocarditis and myocarditis. Fatal cases were common in the preantibiotic era. As a result of quarantine of imported birds and improved veterinary-hygienic measures, outbreaks and sporadic cases of psittacosis are now rare. Severe pneumonia requiring management in an intensive care unit may develop. Endocarditis, hepatitis, and neurologic complications may occur, and fatal cases have been reported. The incubation period is usually 5–19 days but can last as long as 28 days.

DIAGNOSIS

Previously, the most widely used serologic test for diagnosing chlamydial infections was the genus-specific CF test, in which assay of paired serum specimens often shows fourfold or greater increases in antibody titer. The CF test remains useful, but the gold standard of serologic tests is now the MIF test, which is not widely available (see section on diagnosis of *C. trachomatis* genital infection, above). Any antibody titer above 1:16 is considered significant evidence of exposure to chlamydiae, and a fourfold titer rise in paired sera in combination with a clinically compatible syndrome can be used to diagnose psittacosis. Some commercially available serologic tests based on measurement of antibodies to LPS can be useful when the clinical diagnosis is consistent with bird exposure; however, since these tests are reactive for all chlamydiae (i.e., all chlamydiae contain LPS), caution must be used in their interpretation.

TREATMENT

Psittacosis

The antibiotic of choice is tetracycline; the dosage for adults is 250 mg four times a day, continued for at least 3 weeks to avoid relapse. Severely ill patients may need cardiovascular and respiratory support. Erythromycin (500 mg four times a day by mouth) is an alternative therapy.

C. PNEUMONIAE INFECTIONS

C. pneumoniae is a common cause of human respiratory diseases, such as pneumonia and bronchitis. This organism reportedly accounts for as many as 10% of cases of community-acquired pneumonia, most of

which are diagnosed by serology. Serologic studies have linked *C. pneumoniae* to atherosclerosis; isolation and PCR detection in cardiovascular tissues have also been reported. These findings suggest an expanded range of diseases and syndromes for *C. pneumoniae.* Large-scale case–cohort studies have demonstrated some association of *C. pneumoniae* with lung cancer, as evaluated by serology.

EPIDEMIOLOGY

Primary infection occurs mainly in school-aged children and reinfection in adults. Seroprevalence rates of 40–70% show that *C. pneumoniae* is widespread in both industrialized and developing countries. Seropositivity usually is first detected at school age, and rates generally increase by ~10% per decade. About 50% of individuals have detectable antibody at 30 years of age, and most have detectable antibody by the eighth decade of life. Although, as mentioned, serologic evidence suggests that *C. pneumoniae* may be associated with up to 10% of cases of community-acquired pneumonia, most of this evidence is based not on paired serum samples but rather on a single high IgG titer. Some doubt exists about the true prevalence and etiologic role of *C. pneumoniae* in atypical pneumonia, especially since reports of cross-reactivity have raised questions about the specificity of serology when only a single serum sample is used for diagnosis.

PATHOGENESIS

Little is known about the pathogenesis of *C. pneumoniae* infection. It begins in the upper respiratory tract and, in many persons, persists as a prolonged asymptomatic condition of the upper respiratory mucosal surfaces. However, evidence of replication within vascular endothelium and synovial membranes of joints shows that, in at least some individuals, the organism is transported to distant sites, perhaps within macrophages. A *C. pneumoniae* outer-membrane protein may induce host immune responses whose cross-reactivity with human proteins results in an autoimmune reaction.

The role of *C. pneumoniae* in the etiology of atherosclerosis has been discussed since 1988, when Finnish researchers presented serologic evidence of an association of this organism with coronary heart disease and acute myocardial infarction. Subsequently, the organism was identified in atherosclerotic lesions by culture, PCR, immunohistochemistry, and transmission electron microscopy; however, discrepant study results (including those of animal studies) and failure of large-scale treatment studies have raised doubts as to the etiologic role of *C. pneumoniae* in atherosclerosis. Epidemiologic studies have demonstrated an association between serologic evidence of *C. pneumoniae* infection and atherosclerotic disease of the coronary and other arteries. In addition, *C. pneumoniae* has been identified in atherosclerotic plaques by electron microscopy, DNA hybridization, and immunocytochemistry. The organism has been recovered in culture from atheromatous plaques—a result indicating the presence of viable replicating bacteria in vessels. Evidence from animal models supports the hypothesis that *C. pneumoniae* infection of the upper respiratory tract is followed by recovery of the organism from atheromatous lesions in the aorta and that the infection accelerates the process of atherosclerosis, especially in hypercholesterolemic animals. Antimicrobial treatment of the infected animals reverses the increased risk of atherosclerosis. In humans, two small trials in patients with unstable angina or recent myocardial infarction suggested that antibiotics reduce the likelihood of subsequent untoward cardiac events. However, larger-scale trials have not documented an effect of various antichlamydial regimens on the risk of these events.

CLINICAL MANIFESTATIONS

C. pneumoniae was first reported as the etiologic agent of mild atypical pneumonia in military recruits and college students. The clinical spectrum of *C. pneumoniae* infection includes acute pharyngitis, sinusitis, bronchitis, and pneumonitis, primarily in young adults. The clinical manifestations of primary infection appear to be more severe and prolonged than those of reinfection. The pneumonitis of *C. pneumoniae* pneumonia resembles that of *Mycoplasma* pneumonia in that leukocytosis is frequently lacking and patients often have prominent antecedent upper respiratory tract symptoms, fever, nonproductive cough, mild to moderate illness, minimal findings on chest auscultation, and small segmental infiltrates on chest x-ray. In elderly patients, pneumonia due to *C. pneumoniae* can be especially severe and may necessitate hospitalization and respiratory support.

Chronic infection with *C. pneumoniae* has been reported among patients with chronic obstructive pulmonary disease and may also play a role in the natural history of asthma, including exacerbations. The clinical symptoms of respiratory infections caused by *C. pneumoniae* are nonspecific and do not differ from those caused by other agents of atypical pneumonia, such as *Mycoplasma pneumoniae*.

DIAGNOSIS

Serology, PCR amplification, and culture can be used to diagnose *C. pneumoniae* infection. Serology has been the traditional diagnostic method. The gold standard serologic test is the MIF test (see section on diagnosis of *C. trachomatis* genital infection, above). Any antibody titer >1:16 is considered significant evidence of exposure to chlamydiae. According to a CDC-sponsored expert working group, the diagnosis of acute *C. pneumoniae* infection requires demonstration of a fourfold rise in titer in paired serum samples. There are no official recommendations for diagnosis of chronic infections, although many research studies have used high titers of IgA as an indicator. The older CF tests and EIAs for LPS are not recommended, as they are not specific for *C. pneumoniae* but identify the chlamydiae only to the genus level. The organism is very difficult to grow in tissue culture but has been cultivated in HeLa cells, HEp-2 cells, and HL cells. Although NAATs are commercially available for *C. trachomatis*, only research-based PCR assays are available for *C. pneumoniae.*

TREATMENT

C. pneumoniae Infections

Although few controlled trials of treatment have been reported, *C. pneumoniae* is inhibited in vitro by erythromycin, tetracycline, azithromycin, clarithromycin, gatifloxacin, and gemifloxacin. Recommended therapy consists of 2 g/d of either tetracycline or erythromycin for 10–14 days. Other macrolides (e.g., azithromycin) and some fluoroquinolones (e.g., levofloxacin and gatifloxacin) also appear to be effective.

Acknowledgment

The authors acknowledge the late Walter E. Stamm, MD, for his significant contributions to the field of Chlamydia research. Dr. Stamm wrote the chapters on chlamydiae for previous editions of Harrison's Principles of Internal Medicine, and we thank the editors for permission to reproduce Figs. 169-1 and 169-2 and Table 169-1 from his chapter in the 17th edition. Dr. Stamm died on December 14, 2009, and this chapter is dedicated to him.

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Section 11 Viral Diseases: General Considerations

185 Medical Virology

Fred Wang, Elliott Kieff

DEFINING A VIRUS

Viruses are obligate intracellular parasites. They consist of a DNA or RNA genome surrounded by protein. They may also have an outer-membrane lipoprotein envelope. Viruses can replicate only within cells because their nucleic acid does not encode many enzymes necessary for the metabolism of proteins, carbohydrates, or lipids or for the generation of high-energy phosphates. Typically, viral nucleic acids encode messenger RNA (mRNA) and proteins necessary for replicating, packaging, and releasing progeny virus from infected cells.

Viruses differ from virusoids, viroids, and prions. *Virusoids* are nucleic acids that depend on cells and helper viruses for packaging their nucleic acids into virus-like particles. *Viroids* are naked, cyclical, mostly double-strand small RNAs that appear to be restricted to plants, spread from cell to cell, and are replicated by cellular RNA polymerase II. Prions **(Chap. 430)** are abnormal proteins that propagate and cause disease by altering the structure of a normal cell protein. Prions cause neurodegenerative diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straüssler disease, kuru, and human or bovine spongiform encephalopathy ("mad cow disease").

VIRUS STRUCTURE

Viral genomes may consist of single- or double-strand DNA, single- or double-strand RNA, single-strand or segmented antisense RNA, or double-strand segmented RNA. Viral nucleic acids may encode only a few genes or more than 100. Sense-strand viral RNA genomes can be translated directly into protein, whereas antisense RNAs must be copied into translatable RNA. Sense and antisense genomes are also referred to as *positive-strand* and *negative-strand genomes*, respectively. Viral nucleic acid is usually associated with virus-encoded nucleoprotein(s) in the virus core. Viral nucleic acids and nucleoproteins are almost always enclosed in a protein *capsid*. Because of the limited genetic complexity of viruses, their capsids are usually composed of multimers of identical *capsomeres* made up of one or a few proteins. Capsids have icosahedral or helical symmetry. Icosahedral capsid structures approximate spheres and have two-, three-, or fivefold axes of symmetry, whereas helical capsid structures have only a twofold axis of symmetry. The nucleic acid, nucleoprotein(s), and protein capsid together are called a *nucleocapsid*.

Many viruses are composed of a nucleic acid core and a capsid. For these viruses, the outer capsid surface mediates contact with uninfected cells' plasma membranes. Other viruses are more complex and have an outer phospholipid, cholesterol, glycoprotein, and glycolipid envelope that is derived from virus-modified infected cell membranes. Cell nuclear, endoplasmic reticulum, Golgi, or plasma membranes that become parts of the viral envelope have usually been modified during infection by the insertion of virus-encoded glycoproteins, which mediate contact of enveloped virus with uninfected cell surfaces. Matrix or tegument proteins may fill the space between the nucleocapsid and the outer envelope of the virus.

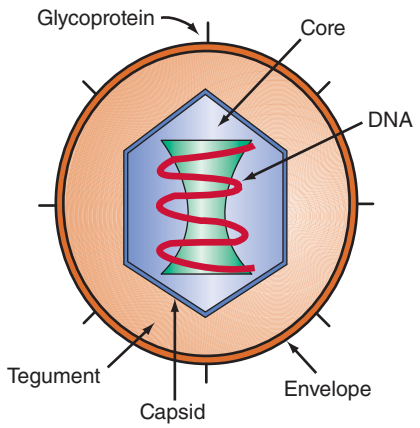

FIGURE 185-1 Schematic diagram of an enveloped herpesvirus with an icosahedral nucleocapsid. The approximate respective dimensions of the nucleocapsid and the enveloped particles are 110 and 180 nm. The capsid is composed of 162 capsomeres: 150 with sixfold and 12 with fivefold axes of symmetry.

Enveloped viruses are usually sensitive to lipid solvents or detergents that can dissolve the envelope, whereas viruses with protein nucleocapsid exteriors may be somewhat detergent resistant. A schematic diagram of large and complex herpesviruses is shown in **Fig. 185-1**. Structures of prototypical pathogenic human viruses are described in **Table 185-1**. The relative sizes and structures of typical pathogenic human viruses are shown in **Fig. 185-2**.

TAXONOMY OF PATHOGENIC HUMAN VIRUSES

As is apparent from Table 185-1 and Fig. 185-2, the classification of viruses into orders and families is based on nucleic acid composition, nucleocapsid size and symmetry, and presence or absence of an envelope. Viruses of a single family have similar structures and may be morphologically indistinguishable in electron micrographs. Subclassification into genera depends on similarity in epidemiology, biologic effects, and nucleic acid sequence.

Most viruses that infect humans have a common name related to their pathologic effects or the circumstances of their discovery. In addition, formal species names—consisting of the name of the host followed by the family or genus of the virus and a number—have been assigned by the International Committee on Taxonomy of Viruses. This dual terminology can cause confusion when viruses are referred to by either name—e.g., varicella-zoster virus (VZV) or human herpesvirus 3 (HHV-3).

VIRAL INFECTION IN VITRO

STAGES OF VIRAL INFECTION OF CELLS IN CULTURE

Viral Interactions with Cell Surfaces and Cell Entry To deliver its nucleic acid payload to the cell cytoplasm or nucleoplasm, a virus must overcome barriers posed by the cell's plasma and cytoplasmic membranes. Infection is frequently initiated by weak electrostatic or hydrophobic interactions with the cell surface. Subsequent stronger, more specific attachment to a cell plasma membrane protein, carbohydrate, glycolipid, heparan sulfate proteoglycan, or sialic acid enables stable binding to a specific cell surface "receptor" that mediates fusion with the cell plasma membrane **(see Table 116-1)**. Receptor binding is often augmented by a viral surface protein interaction with more than one cell surface protein or co-receptor. Receptors and co-receptors are important determinants of the species and cell type that a virus can infect. For example, the HIV envelope glycoprotein binds to the T cell

TABLE 185-1 Virus Families Pathogenic for Humans

FAMILY	REPRESENTATIVE VIRUSES	TYPE OF RNA/DNA	LIPID ENVELOPE
RNA Viruses			
Picornaviridae	Poliovirus Coxsackievirus Echovirus Enterovirus Rhinovirus Hepatitis A virus	(+) RNA	No
Caliciviridae	Norovirus Hepatitis E virus	(+) RNA	No
Togaviridae	Rubella virus Eastern equine encephalitis virus Western equine encephalitis virus	(+) RNA	Yes
Flaviviridae	Yellow fever virus Dengue virus St. Louis encephalitis virus West Nile virus Zika virus Hepatitis C virus Hepatitis G virus	(+) RNA	Yes
Coronaviridae	Coronaviruses[a]	(+) RNA	Yes
Rhabdoviridae	Rabies virus Vesicular stomatitis virus	(–) RNA	Yes
Filoviridae	Marburg virus Ebola virus	(–) RNA	Yes
Paramyxoviridae	Parainfluenza virus Respiratory syncytial virus Newcastle disease virus Mumps virus Rubeola (measles) virus	(–) RNA	Yes
Orthomyxoviridae	Influenza A, B, and C viruses	(–) RNA, 8 segments	Yes
Bunyaviridae	Hantavirus California encephalitis virus Sandfly fever virus	(–) RNA, 3 circular segments	Yes
Arenaviridae	Lymphocytic choriomeningitis virus Lassa fever virus South American hemorrhagic fever virus	(–) RNA, 2 circular segments	Yes
Reoviridae	Rotavirus Reovirus Colorado tick fever virus	ds RNA, 10–12 segments	No
Retroviridae	Human T lymphotropic virus types 1 and 2 Human immunodeficiency virus types 1 and 2	(+) RNA, 2 identical segments	Yes
DNA Viruses			
Hepadnaviridae	Hepatitis B virus	ds DNA with ss portions	Yes
Parvoviridae	Parvovirus B19	ss DNA	No
Papillomaviridae	Human papillomaviruses	ds DNA	No
Polyomaviridae	JC virus BK virus Merkel cell polyoma virus		
Adenoviridae	Human adenoviruses	ds DNA	No
Herpesviridae	Herpes simplex virus types 1 and 2[b] Varicella-zoster virus[c] Epstein-Barr virus[d] Cytomegalovirus[e] Human herpesvirus 6 Human herpesvirus 7 Kaposi's sarcoma–associated herpesvirus[f]	ds DNA	Yes
Poxviridae	Variola (smallpox) virus Orf virus Molluscum contagiosum virus	ds DNA	Yes

[a]Including the coronaviruses causing severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS). [b]Also called human herpesvirus 1 (HHV-1) and HHV-2, respectively. [c]Also called HHV-3. [d]Also called HHV-4. [e]Also called HHV-5. [f]Also called HHV-8.

Abbreviations: ds, double-strand; ss, single-strand.

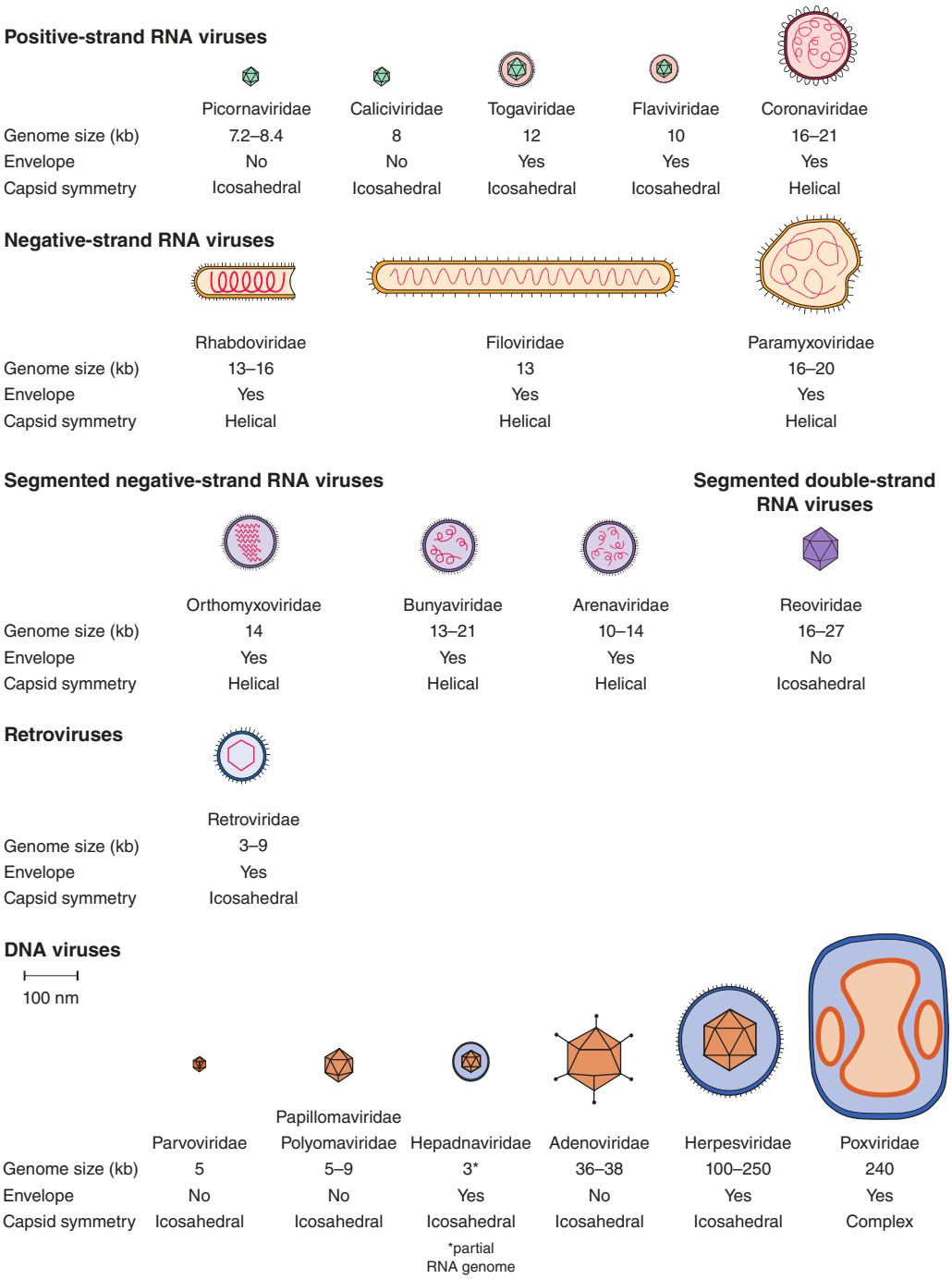

FIGURE 185-2 Schematic diagrams of the major virus families including species that infect humans. The viruses are grouped by genome type and are drawn approximately to scale. Prototype viruses of each family that cause human disease are listed in Table 185-1.

surface protein CD4 and then engages a chemokine receptor that is the definitive co-receptor for the virus and mediates entry into the cell cytoplasm. The Epstein-Barr virus (EBV) glycoprotein gp350 binds to the B lymphocyte complement receptor CD21 and then uses a major histocompatibility complex (MHC) class II molecule as a co-receptor and an integrin for definitive entry.

Viruses have evolved a wide range of strategies to enter cells. Influenza virus has an outer-membrane hemagglutinin glycoprotein that binds to sialic acid on respiratory tract cell plasma membranes. The hemagglutinin mediates adsorption to cell membranes, receptor aggregation, and endocytosis. As the endosome pH decreases in the cell cytoplasm, the influenza hemagglutinin conformation changes, enabling hydrophobic helices, which are initially at the base of the hemagglutinin, to extend, interacting and fusing with the endosome membrane and thereby releasing the viral genome into the cell cytoplasm. The influenza virus M2 membrane channel protein has a key role in lowering endosome pH and permitting virus and cell membrane fusion.

Nonenveloped viruses (e.g., human papillomaviruses [HPVs]) and some enveloped viruses have evolved to partially fuse with cell plasma membrane receptors and be internalized into endosomes. The low pH in an endosome can then trigger virus membrane or capsid fusion with the endocytic membrane, releasing viral DNA into the cytoplasm to initiate infection.

Hydrophobic interactions required for fusion can be susceptible to chemical inhibition or blockade. The HIV envelope glycoprotein gp120 is associated with gp41 on the viral surface. HIV gp120 binding to CD4 and then to specific chemokine receptors results in conformational changes that allow gp41 to initiate cell membrane fusion. The anti-HIV drug enfuvirtide is a small peptide derived from the gp41 structure. Enfuvirtide binds to gp41 and prevents conformational changes required for fusion. In contrast, maraviroc prevents virus entry by

binding to the CCR5 receptor, thereby blocking gp120 binding to CCR5 and preventing gp120 fusion with CCR5.

Viral Gene Expression and Replication After uncoating and release of viral nucleoprotein into the cytoplasm, the viral genome is transported to sites of expression and replication. To produce infectious progeny, viruses must produce proteins necessary for replicating their nucleic acids as well as structural proteins necessary for coating their nucleic acids and for assembling nucleic acids and proteins into progeny virus. Different viruses use different strategies and gene repertoires to accomplish these goals. Most DNA viruses, except for poxviruses, replicate their nucleic acid and assemble into nucleocapsids in the cell nucleus. RNA viruses, except for influenza viruses, transcribe and replicate their RNA and assemble in the cytoplasm before envelopment at the cell plasma membrane. The replication strategies of DNA and RNA viruses and of positive- and negative-strand RNA viruses are presented and discussed separately below. Medically important viruses of each group are used for illustrative purposes.

POSITIVE-STRAND RNA VIRUSES RNA viruses of medical importance include positive-strand picornaviruses, flaviviruses, togaviruses, caliciviruses, and coronaviruses. Genome RNA from positive-strand RNA viruses is released into the cytoplasm without associated enzymes. Cell ribosomes recognize and associate with the viral genome's internal ribosome entry sequence and translate a virus-encoded polyprotein. Proteases within the polyprotein cleave out the viral RNA polymerase and other viral proteins necessary for replication. Antigenomic RNA is next transcribed from the genome RNA template. Positive-strand genomes and mRNAs are then transcribed from the antigenome RNA by the viral RNA polymerase and are translated into capsid proteins. Genomic RNA is encapsidated in the cytoplasm and released as the infected cell undergoes lysis.

NEGATIVE-STRAND RNA VIRUSES Medically important negative-strand RNA viruses include rhabdoviruses, filoviruses, paramyxoviruses, orthomyxoviruses, and bunyaviruses. The genomes of negative-strand viruses are frequently segmented. Negative-strand RNA viral genomes are released into the cytoplasm with an associated RNA polymerase and one or more polymerase accessory proteins. The viral RNA polymerase transcribes mRNAs as well as full-length antigenome RNA, which is the template for genome RNA replication. Viral mRNAs encode the viral RNA polymerase and accessory factors as well as viral structural proteins. Except for influenza virus, which transcribes its mRNAs and antigenome RNAs in the cell nucleus, negative-strand RNA viruses replicate entirely in the cytoplasm. All negative-strand RNA viruses, including influenza viruses, assemble in the cytoplasm.

DOUBLE-STRAND SEGMENTED RNA VIRUSES Double-strand RNA viruses are taxonomically grouped in the family Reoviridae. The medically important viruses in this group are rotaviruses and Colorado tick fever virus. Reovirus genomes have 10–12 RNA segments. Reovirus particles contain an RNA polymerase complex. These viruses replicate and assemble in the cell cytoplasm.

DNA VIRUSES Medically important DNA viruses include parvoviruses, which have small single-strand DNA genomes and cause transient arthritis, and polyomaviruses, including the smaller polyomaviruses such as JC virus, which causes progressive multifocal leukoencephalopathy in immunocompromised patients; BK virus; and Merkel cell polyomavirus. The larger HPVs cause warts as well as cervical, penile, and oral carcinomas. The next larger DNA viruses are adenoviruses, which mostly cause transient respiratory tract and ocular inflammatory disease. The herpesviruses include eight viruses that cause a wide range of inflammatory and malignant diseases in humans. EBV is an important cause of lymphomas and Hodgkin's disease in both immunocompromised and immunocompetent people and of nasopharyngeal carcinoma in southern Chinese and northern African populations. Cytomegalovirus (CMV) is an important cause of transplacental infections and neonatal neurologic impairment. Poxviruses, the largest DNA viruses and the largest viruses that infect humans (barely visible by light microscopy), cause smallpox, monkeypox, and molluscum contagiosum. Aside from those of poxviruses, other DNA virus genomes enter the cell nucleus and are transcribed by cellular RNA polymerase II.

After receptor binding and fusion with plasma membranes or endocytic vesicle membranes, herpesvirus nucleocapsids are released into the cytoplasm with tegument proteins and are transported along microtubules to a nuclear pore. Capsids then release DNA into the nucleus.

DNA virus transcription and mRNA processing depend on both viral and cellular proteins. For herpes simplex virus (HSV), a viral tegument protein enters the nucleus and activates immediate-early genes, the first genes expressed after infection. Transcription of immediate-early genes requires the viral tegument protein and cell transcription factors. HSV becomes nonreplicating, or latent, in neurons because essential cell transcription factors for expression of viral immediate-early genes are docked in the cytoplasm in neurons. Heat shock or other cell stresses can cause these cell factors to enter the nucleus, activate viral gene expression, and initiate replication. This information explains HSV-1 latency in neurons and activation of replicative infection.

For adenoviruses and herpesviruses, transcription of immediate-early genes results in expression of early proteins necessary for viral DNA replication. Viral DNA synthesis is required to turn on late-gene expression and production of viral structural components. The HPVs, polyomaviruses, and parvoviruses are not dependent on transactivators encoded from the viral genome for early-gene transcription. Instead, their early genes have upstream enhancing elements that bind cell transcription factors. The early genes encode proteins that are necessary for viral DNA synthesis and late-gene transcription. DNA virus late genes encode structural proteins necessary for viral assembly and for viral egress from the infected cell. Late-gene transcription is continuously dependent on DNA replication. Therefore, inhibitors of DNA replication also stop late-gene transcription.

Each DNA virus family uses unique mechanisms for replicating its DNA. Adenovirus and herpesvirus DNAs are linear in the virion. Adenovirus DNA remains linear in infected cells and replicates as a linear genome, using an initiator protein–DNA complex. In contrast, herpesvirus DNA circularizes in the infected cell, and genomes replicate into linear concatemers through a "rolling-circle" mechanism. Full-length DNA genomes are cleaved and packaged into virus. Herpesviruses encode a DNA polymerase and at least six other viral proteins necessary for viral DNA replication. Acyclovir and ganciclovir prevent viral DNA synthesis when they are phosphorylated and incorporated into DNA by the viral polymerase. Herpesviruses also encode enzymes that increase the deoxynucleotide triphosphate pools. HPV and polyomavirus DNAs are circular both within the virus and in infected cells. These genomes are reproduced by cellular DNA replication enzymes and remain circular through replication and packaging. HPV and polyomavirus early proteins are necessary for DNA replication in both latent and viral replicative phases. Early viral proteins stimulate cells to remain in cycle, facilitating viral DNA replication.

Parvoviruses have negative single-strand DNA genomes and are the smallest DNA viruses. Their genomes are half the size of HPV genomes and include only two genes. The replication of autonomous parvoviruses, such as B19, depends on cellular DNA replication and requires the virus-encoded Rep protein. Other parvoviruses, such as adeno-associated virus (AAV), are not autonomous and require helper viruses of the adenovirus or herpesvirus family for their replication. AAV is being used as a potentially safe human gene therapy vector because its replication protein causes integration at a single chromosome site. The small genome size limits the range of proteins that can be expressed from AAV vectors.

As stated above, poxviruses are the largest DNA viruses. They are unique among DNA viruses in replicating and assembling in the cytoplasm. To accomplish cytoplasmic replication, poxviruses encode transcription factors, an RNA polymerase II orthologue, enzymes for RNA capping, enzymes for RNA polyadenylation, and enzymes for viral DNA synthesis. Poxvirus DNA also has a unique structure. The double-strand linear DNA is covalently linked at the ends, making a covalently closed

double-strand circular genome. Replication of the circular genomes is initiated by nicking in inverted repeats at the ends of the linear DNA. During DNA replication, the genome is cleaved within the terminal inverted repeats, and the inverted repeats self-prime complementary-strand synthesis by the virus-encoded DNA polymerase. Like herpesviruses, poxviruses encode several enzymes that increase deoxynucleotide triphosphate precursor levels and thus facilitate viral DNA synthesis.

VIRUSES THAT USE BOTH RNA AND DNA GENOMES IN THEIR LIFE CYCLE Retroviruses, including HIV, are RNA viruses that use a DNA intermediate to replicate their genomes. In contrast, hepatitis B virus (HBV) is a DNA virus that uses an RNA intermediate to replicate its genome. Thus these viruses are not purely RNA or DNA viruses. Retroviruses are RNA viruses with two identical sense-strand genomes and associated reverse transcriptase and integrase enzymes. Retroviruses differ from all other viruses in that they reverse-transcribe themselves into partially duplicated double-strand DNA copies and then routinely integrate into the host genome as part of their persistence and replication strategies. Inhibitors of reverse transcriptase (e.g., zidovudine) or integrase (e.g., raltegravir) are now commonly used as antiviral treatments for HIV infection. Integration of remnants and even complete copies of simple retrovirus DNAs into the human genome raises the possibility of replication-competent simple human retroviruses. However, endogenous human retrovirus replication has not been documented or associated with any disease. Integrated, replication-competent retroviral DNAs are also present in many animal species, such as pigs. These porcine retroviruses are a potential cause for concern in xenotransplantation because retrovirus replication could cause disease in humans.

Cellular RNA polymerase II and transcription factors regulate transcription from the integrated provirus DNA genome. Some retroviruses also encode regulators of transcription and RNA processing, such as Tax and Rex in human T lymphotropic virus (HTLV) types 1 and 2. HIV-1 and HIV-2 have orthologous Tat and Rev genes as well as the additional accessory proteins Vpr, Vpu, and Vif, which are important for efficient infection and immune escape. Full-length proviral transcripts are made from a promoter in the viral terminal repeat and serve as both genome RNAs that are packaged in the nucleocapsids and differentially spliced mRNAs that encode for the virus Gag protein, polymerase/integrase protein, and envelope glycoprotein. The Gag protein includes a protease that cleaves it into several components, including a viral matrix protein that coats the viral RNA. Viral RNA polymerase/integrase, matrix protein, and cellular tRNAs are key components in the viral nucleocapsid. Protease inhibitors have been developed as effective agents against infections caused by HIV (e.g., saquinavir) or hepatitis C virus (HCV) (e.g., telaprevir).

HBV replication is unique in several respects. The HBV genome is a partially double-strand DNA genome that is repaired in infected cells to a fully double-strand circular DNA by the virion polymerase. Viral mRNAs are transcribed from the closed circular viral episome by the cellular RNA polymerase II and are translated to yield HBV proteins, including core protein, surface antigen, and polymerase. In addition, a full-genome-length mRNA is packaged into viral core particles in the cytoplasm of infected cells as an intermediate for viral DNA replication. This RNA associates with the viral polymerase, which also has reverse transcriptase activity and converts the full-length encapsidated RNA genome into partially double-strand DNA. Thus, nucleos(t)ide analogs that inhibit reverse transcription (e.g., tenofovir) are commonly used to treat HBV infection. HBV is believed to mature by budding through the cell's plasma membrane, which has been modified by the insertion of viral surface antigen protein.

Viral Assembly and Egress For most viruses, nucleic acid and structural protein synthesis is accompanied by the assembly of protein and nucleic acid complexes. The assembly and egress of mature infectious virus mark the end of the *eclipse phase* of infection, during which infectious virus cannot be recovered from the infected cell. Nucleic acids from RNA viruses and poxviruses assemble into nucleocapsids in the cytoplasm. For all DNA viruses except poxviruses, viral DNA assembles into nucleocapsids in the nucleus. In general, the capsid proteins of viruses with icosahedral nucleocapsids can self-assemble into densely packed and highly ordered capsid structures. Herpesviruses require an assemblin protein as a scaffold for capsid assembly. Viral nucleic acid then spools into the assembled capsid. For herpesviruses, a full unit of the viral DNA genome is packaged into the capsid, and a capsid-associated nuclease cleaves the viral DNA at both ends. In the case of viruses with helical nucleocapsids, the protein component appears to assemble around the nucleic acid, which contributes to capsid organization.

Viruses must egress from the infected cell and not bind back to their receptor(s) on the outer surface of the plasma membrane. Viruses can acquire envelopes from cytoplasmic membranes or by budding through the cell's plasma membrane. Excess viral membrane glycoproteins are synthesized to saturate cell receptors and facilitate separation of the virus from the infected cell. Some viruses encode membrane proteins with enzymatic activity for receptor destruction. Influenza virus, for example, encodes a glycoprotein with neuraminidase activity. Neuraminidase destroys sialic acid on the infected cell's plasma membrane so that newly released virus does not get stuck to the dying cell. Oseltamivir and zanamivir are neuraminidase inhibitors that are used to treat or provide prophylaxis for influenza virus infection. Herpesvirus nucleocapsids acquire an initial envelope by assembling in the nucleus and then budding through the nuclear membrane into the endoplasmic reticular space. The initially enveloped herpesvirus is then de-enveloped and released from the cell either by exocytosis or by re-envelopment at the plasma membrane. Nonenveloped viruses depend on the death and dissolution of the infected cell for their release.

FIDELITY OF VIRAL REPLICATION

Hundreds or thousands of progeny may be produced from a single virus-infected cell. Many particles partially assemble and never mature into virions. Many mature-appearing virions are imperfect and have only incomplete or nonfunctional genomes. Despite the inefficiency of assembly, a typical virus-infected cell releases 10–1000 infectious progeny. Some of these progeny may contain genomes that differ from those of the virus that infected the cell. Smaller, "defective" viral genomes have been noted with the replication of many RNA and DNA viruses. Virions with defective genomes can be produced in large numbers through packaging of incompletely synthesized nucleic acid. Adenovirus packaging is notoriously inefficient, and a high ratio of particle to infectious virus may limit the amount of recombinant adenovirus that can be administered for gene therapy since the immunogenicity of defective particles may contribute to adverse effects.

Changes in viral genomes can lead to mutant viruses of medical significance. In general, viral nucleic acid replication is more error-prone than cellular nucleic acid replication. RNA polymerases and reverse transcriptases are significantly more error-prone than DNA polymerases. Mutations can also be introduced into the HIV genome by APOBEC3G, a cellular protein that is packaged in the virion. APOBEC3G deaminates cytidine in the virion RNA to uridine. When reverse transcriptase subsequently uses the altered virion RNA as a template in the infected cell, a guanosine-to-adenosine mutation is introduced into the proviral DNA. Mutations resulting in less efficient viral growth, or fitness, may be detrimental to the virus. HIV-encoded Vif blocks APOBEC3G activity in the virion, inhibiting the debilitating effects of hypermutation on genetic integrity. Nevertheless, mutations resulting in evasion of the host immune response or resistance to antiviral drugs are preferentially selected in patients, with the consequent perpetuation of infection. Viral genomes can also be altered by recombination or reassortment between two related viruses in a single infected cell. Although this occurrence is unusual under most circumstances of natural infection, the genome changes can be substantial and can significantly alter virulence or epidemiology. Reassortment of the avian or mammalian influenza A hemagglutinin gene into a human influenza background can result in the emergence of new epidemic or pandemic influenza A strains.

VIRAL GENES NOT REQUIRED FOR VIRAL REPLICATION

Viruses frequently have genes encoding proteins that are not directly involved in replication or packaging of the viral nucleic acid, in virion assembly, or in regulation of the transcription of viral genes involved in those processes. Most of these proteins fall into five classes: (1) proteins that directly or indirectly alter cell growth; (2) proteins that inhibit cellular RNA or protein synthesis so that viral mRNA can be efficiently transcribed or translated; (3) proteins that promote cell survival or inhibit apoptosis so that progeny virus can mature and escape from the infected cell; (4) proteins that inhibit the host interferon response; and (5) proteins that downregulate host inflammatory or immune responses so that viral infection can proceed in an infected person to the extent consistent with the survival of the virus and its efficient transmission to a new host. More complex viruses of the poxvirus or herpesvirus family encode many proteins that serve these functions. Some of these viral proteins have motifs similar to those of cellular proteins, while others are quite novel. Virology has increasingly focused on these more sophisticated strategies evolved by viruses to permit the establishment of long-term infection in humans and other animals. These strategies often provide unique insights into the control of cell growth, cell survival, macromolecular synthesis, proteolytic processing, immune or inflammatory suppression, immune resistance, cytokine mimicry, or cytokine blockade.

MicroRNAs (miRNAs) are small noncoding RNAs that can regulate gene expression at the posttranscriptional level by targeting—and usually silencing—mRNAs. miRNAs were initially discovered in plants and plant viruses, where they alter expression of cell defensins. Herpesviruses are especially rich in miRNAs; for example, at least 23 miRNAs have been identified in EBV and 11 in CMV. Adenovirus and polyomavirus miRNAs have also been described. Increasing data indicate that animal viruses encode miRNAs to alter the growth and survival of host cells and the innate and acquired immune responses.

HOST RANGE

The concept of host range was originally based on the cell types in which a virus replicates in tissue culture. For the most part, the host range is limited by specific cell-surface proteins required for viral adsorption or penetration—i.e., to the cell types that express receptors or co-receptors for a specific virus. Another common basis for host-range limitation is the degree of transcriptional activity from viral promoters in different cell types. Most DNA viruses depend not only on cellular RNA polymerase II and the basal components of the cellular transcription complex but also on activated components and transcriptional accessory factors, both of which differ among differentiated tissues, among cells at various phases of the cell cycle, and between resting and cycling cells.

The importance of host-range factors is illustrated by the effects of specific host determinants that limit the replication of influenza virus with avian or porcine hemagglutinins in humans. These viral proteins have adapted to bind avian or porcine sialic acids, and spread of avian or porcine influenza viruses in human populations is limited by their ability to infect human cells.

VIRAL CYTOPATHIC EFFECTS AND INHIBITORS OF APOPTOSIS

The replication of almost all viruses has adverse effects on the infected cell, inhibiting cellular synthesis of DNA, RNA, or proteins through efficient competition for key substrates and enzymatic processes. These general inhibitory effects enable viruses to nonspecifically limit components of innate host resistance, such as interferon (IFN) production. Viruses can specifically inhibit host protein synthesis by attacking a component of the translational initiation complex—frequently, a component that is not required for efficient translation of viral RNAs. Poliovirus protease 2A, for example, cleaves a cellular component of the complex that ordinarily facilitates translation of cellular mRNAs by interacting with their cap structure. Poliovirus RNA is efficiently translated without a cap because it has an internal ribosome entry sequence. Influenza virus inhibits the processing of mRNA by snatching cap structures from nascent cellular RNAs and using them as primers in the synthesis of viral mRNA. HSV has a virion tegument protein that inhibits cellular mRNA translation.

Apoptosis is the expected consequence of virus-induced inhibition of cellular macromolecular synthesis and viral nucleic acid replication. Although the induction of apoptosis may be important for the release of some viruses (particularly nonenveloped viruses), many viruses have acquired genes or parts of genes that enable them to forestall infected-cell death. This delay increases the yield from viral replication. Adenoviruses and herpesviruses encode analogues of the cellular Bc12 protein, which block mitochondrial enhancement of proapoptotic stimuli. Poxviruses and some herpesviruses also encode caspase inhibitors. Many viruses, including HPVs and adenoviruses, encode proteins that inhibit p53 or its downstream proapoptotic effects.

VIRAL INFECTION IN VIVO

TRANSMISSION

The capsid and envelope of a virus protect the genome and enable efficient transmission of the virus from cell to cell and to new prospective hosts. Most common viral infections are spread by direct contact, by ingestion of contaminated water or food, or by inhalation of aerosolized particles. In all these situations, infection begins on an epithelial or mucosal surface and spreads along the mucosa and into deeper tissues. Infection may spread to cells that can enter blood vessels, lymphatics, or neural circuits. HBV, HCV, HTLV, and HIV are dependent on transmission by parenteral inoculation. Some viruses are transmitted only between humans. The dependence of smallpox virus and poliovirus infections on interhuman transmission makes it feasible to eliminate these viruses from human circulation by mass vaccination. Herpesviruses also survive by interhuman transmission but may be more difficult to eliminate because they establish persistent latent infection in humans and continuously reactivate to infect new and naïve generations.

Animals are also important reservoirs and vectors for transmission of viruses causing human disease. Insect vectors can mediate parenteral transfer of viruses that reach high titers in animal or human hosts. Arboviruses are parenterally transmitted from mammalian species to humans by mosquito vectors. Herpes B, monkeypox, rabies, and viral hemorrhagic fevers are other examples of zoonotic infections caused by direct contact with animals, animal tissues, or arthropod vectors.

PRIMARY INFECTION

Initial viral infections usually last for several days or weeks. During this period, the concentration of virus at sites of infection rises and then falls, usually to unmeasurable levels. The rise and fall of viral replication at a given site depend on local innate immune responses and the access of systemic antibody and cell immune effectors to the virus. Typically, primary infections with enteroviruses, mumps virus, measles virus, rubella virus, rotavirus, influenza virus, AAV, adenovirus, HSV, and VZV are cleared from almost all sites within 3–4 weeks. Some viruses are especially proficient in altering or evading innate and acquired immune responses. Primary infection with AAV, EBV, or CMV can last for several months. Characteristically, primary infections due to HBV, HCV, hepatitis D virus (HDV), HIV, HPV, and molluscum contagiosum virus (MCV) extend beyond several weeks. For some of these viruses (e.g., HPV, HBV, HCV, HDV, and MCV), the manifestations of primary infection are almost indistinguishable from the persistent phase.

Disease manifestations usually arise as a consequence of viral replication, infected-cell injury or death, and local inflammatory and innate immune responses. Disease severity may not necessarily correlate with the level of viral replication alone. For example, the clinical manifestations of intense primary infection with poliovirus, enterovirus, rabies virus, measles virus, mumps virus, or HSV at mucosal surfaces may be inapparent or relatively mild, whereas limited replication in neural cells can have dramatic consequences. Similarly, rubella virus or CMV infections in utero or neonatal HSV infections may have much more devastating effects than infections in adults.

Primary infections are cleared by nonspecific innate and specific adaptive immune responses. Thereafter, an immunocompetent host is usually immune to the disease manifestations of reinfection by the same virus. Immunity frequently does not prevent transient surface colonization on reexposure, persistent colonization, or even limited deeper infection.

PERSISTENT AND LATENT INFECTIONS

Relatively few viruses cause persistent or latent infections. HBV, HCV, rabies virus, measles virus, HIV, HTLV, HPV, HHVs, and MCV are notable exceptions. The mechanisms for persistent infection vary. HCV RNA polymerase and HIV reverse transcriptase are error-prone and generate variant genomes. Genome variation can be sufficient to permit evasion of host immune responses, thereby allowing persistent infection. HIV is also directly immunosuppressive, depleting CD4+ T lymphocytes and compromising CD8+ cytotoxic T cell immune responsiveness. Moreover, HIV encodes the Nef protein, which downmodulates MHC class I expression, rendering HIV-infected cells partially resistant to immune CD8+ T cell lysis.

DNA viruses have low mutation rates. Their persistence in human populations usually depends on their ability to establish latent infection in some cells, to reactivate from latency, and then to replicate at epithelial surfaces. *Latency* is defined as a state of infection in which virus is not replicating, viral genes associated with lytic infection are not expressed, and infectious virus is not made. The complete viral genome is present and may be replicated by cellular DNA polymerase in conjunction with replication of the cell's genome. HPVs establish latent infection in basal epithelial cells. The latently infected basal cell replicates, along with the HPV episome, by using cellular DNA polymerase. Some of the progeny cells provide new latently infected basal cells, whereas others go on to squamous differentiation. Infected cells that differentiate to squamous cells become permissive for lytic viral infection. Herpesviruses establish latent infection in nonreplicating neural cells (HSV and VZV) or in replicating cells of hematopoietic lineages (EBV, CMV, HHV-6, HHV-7, and Kaposi's sarcoma–associated herpesvirus [KSHV, also known as HHV-8]). In their latent stage, HPV and herpesvirus genomes are largely hidden from the normal immune response. Reactivated HPV and herpesvirus infections escape immediate and effective immune responses in highly immune hosts by inhibiting host innate immune and inflammatory responses. In addition, HPV, HSV, and VZV are somewhat protected because they replicate in the middle and upper layers of the squamous epithelium—sites not routinely visited by cells that mediate or amplify immune and inflammatory responses. HSV and CMV are also known to encode proteins that downregulate MHC class I expression and antigenic peptide presentation, enabling infected cells to escape recognition by and cytotoxic effects of CD8+ T lymphocytes.

Like other poxviruses, MCV cannot establish latent infection. This virus causes persistent infection in hypertrophic skin lesions that last for months or years. MCV encodes a chemokine homologue that probably blocks inflammatory responses, an MHC class I analogue that blocks cytotoxic T lymphocyte attack, and inhibitors of cell death that prolong infected-cell viability.

PERSISTENT VIRAL INFECTIONS AND CANCER

Persistent viral infection is estimated to be the root cause of as many as 20% of human malignancies. Cancer is an accidental and highly unusual or long-term effect of oncogenic human viral infection. With most "oncogenic viruses," infection is a critical and ultimately determinative early step in carcinogenesis. Latent HPV infection can block cell death and cause cervical cells to proliferate. A virus-infected cell with an integrated HPV genome overexpressing E6 and E7 undergoes subsequent cellular genetic changes that enhance autonomous malignant cell growth.

Most hepatocellular carcinoma is believed to be caused by chronic inflammatory, immune, and regenerative responses to HBV or HCV infection. Epidemiologic data firmly link HBV and HCV infections to hepatocellular carcinoma. These infections elicit repetitive cycles of virus-induced liver injury followed by tissue repair and regeneration. Over decades, chronic viral infection, repetitive tissue regeneration, and acquired chromosomal changes can result in proliferative nodules. Further chromosomal mutations can lead to the degeneration of cells in a proliferating nodule into hepatocellular carcinoma. In rare instances, HBV DNA integrates into cellular DNA, promoting overexpression of a cell gene that can also contribute to oncogenesis.

Most cervical carcinoma is caused by persistent infection with "high-risk" HPV type 16 or 18. In contrast to HBV and HCV infections, which stimulate cell growth as a consequence of virus-induced cell death, HPV type 16 or 18 proteins E6 and E7 destroy p53 and pRB, respectively. Elimination of these key tumor-suppressive cell proteins increases cell growth, cell survival, and cell genome instability. However, like HBV and HCV infections, HPV infection alone is not sufficient for carcinogenesis. Cervical carcinoma is inevitably associated with persistent HPV infection and integration of the HPV genome into chromosomal DNA. Integrations that result in overexpression of E6 and E7 from HPV type 16 or 18 cause more profound changes in cell growth and survival and permit subsequent chromosomal changes that result in cervical carcinoma.

EBV is the most unusual oncogenic virus in that normal B cell infection results in latency with expression of viral proteins that can cause endless B lymphocyte growth. In almost all humans, strong CD4+ and CD8+ T cell immune responses to the antigenic EBV latent-infection nuclear proteins prevent uncontrolled B cell lymphoproliferation. However, when humans are severely immunosuppressed by transplantation-associated medication, HIV infection, or genetic immune deficiencies, EBV-induced B cell malignancies can emerge.

EBV infection also has a role in the long-term development of B lymphocyte and epithelial cell malignancies. Persistent EBV infection with expression of an EBV latency-associated integral membrane protein (LMP1) in latently infected epithelial cells appears to be a critical early step in the evolution of anaplastic nasopharyngeal carcinoma, a common malignancy in populations in southern China and northern Africa. Genomic instability and chromosomal abnormalities also contribute to the development of EBV-associated nasopharyngeal carcinoma. EBV is an important cause of Hodgkin's lymphoma. High-level expression of LMP1 or LMP2 in Reed-Sternberg cells is a hallmark in up to 50% of Hodgkin's lymphoma cases. LMP1-induced nuclear factor κB (NF-κB) activity may prolong the survival of defective B cells that are normally eliminated by apoptosis, thereby allowing other genetic changes leading to the development of malignant Reed-Sternberg cells.

The HTLV-1 Tax and Rex proteins are critical to the initiation of cutaneous adult T cell lymphoma/leukemias that occur long after primary HTLV-1 infection. Tax-induced NF-κB activation may contribute to cytokine production, infected-cell survival, and eventual outgrowth of malignant cells.

Molecular data confirm the presence of KSHV DNA in all Kaposi's tumors, including those associated with HIV infection, transplantation, and familial transmission. KSHV infection is also etiologically implicated in pleural-effusion lymphomas and multicentric Castleman's disease, which are more common among HIV-infected than among HIV-uninfected people. KSHV has a virus-encoded cyclin, an IFN regulatory factor, and a latency-associated nuclear antigen that are implicated in increased cell proliferation and survival.

Evidence supporting a causal role for viral infection in all of these malignancies includes (1) epidemiologic data, (2) the presence of viral DNA in all tumor cells, (3) the ability of the viruses to transform human cells in culture, (4) the results of in vitro cell culture–based assays that reveal transforming effects of specific viral genes on cell growth or survival, (5) pathologic data indicating the expression of transforming viral genes in premalignant or malignant cells in vivo, (6) the demonstration in animal models that these viral genes can cause malignant cell growth, and (7) the ability of virus-specific vaccines to reduce the incidence of virus-associated malignancy.

Virus-related malignancies provide an opportunity to expand our understanding of the biologic mechanisms important in the development of cancer. They also offer unique opportunities to develop diagnostics, vaccines, or therapeutics that could prevent or specifically treat cancers associated with viral infection. Widespread immunization

against hepatitis B has resulted in a decreased prevalence of HBV-associated hepatitis and will probably prevent most HBV-related liver cancers. Current HPV vaccines can reduce rates of colonization with high-risk HPV strains and thereby decrease the risk of cervical cancer. The successful use of in vitro–expanded EBV-specific T cell populations to treat or prevent EBV-associated posttransplantation lymphoproliferative disease demonstrates the potential of immunoprevention or immunotherapy against virus-associated cancers.

RESISTANCE TO VIRAL INFECTIONS

Resistance to viral infections is initially provided by factors that are not virus-specific. Physical protection is afforded by the cornified layers of the skin and by mucous secretions that continuously sweep over mucosal surfaces. Once the first cell is infected, IFNs are induced and confer resistance to RNA virus replication. Viral infection may also trigger the release of other cytokines from infected cells. These cytokines may be chemotactic to inflammatory and immune cells. Viral protein epitopes expressed on the cell surface in the context of MHC class I and II proteins can stimulate the expansion of T cell populations with receptors that can recognize virus-encoded peptides presented on the cell surface by MHC class I proteins. Cytokines and antigens released by virus-induced cell death further attract inflammatory cells, dendritic cells, granulocytes, natural killer (NK) cells, and B lymphocytes to sites of infection and to draining lymph nodes. IFNs and NK cells are particularly important in containing viral infection for the first several days. Granulocytes and macrophages are also important in the phagocytosis and degradation of viruses, especially after an initial antibody response.

By 7–10 days after infection, virus-specific antibody responses, virus-specific human leukocyte antigen (HLA) class II–restricted CD4+ helper T lymphocyte responses, and virus-specific HLA class I–restricted CD8+ cytotoxic T lymphocyte responses develop. These responses, whose magnitude typically increases over the second and third weeks of infection, are important for rapid recovery. Also between the second and third weeks, the antibody type usually changes from IgM to IgG; IgG or IgA antibody can then be detected at infected mucosal surfaces. Antibody may directly neutralize virus by binding to its surface and preventing cell attachment or penetration. Complement can significantly enhance antibody-mediated virus neutralization. Antibody and complement can also lyse virus-infected cells that express viral membrane proteins on the cell surface. Cells infected with a replicating enveloped virus usually express the virus-envelope glycoproteins on the cell plasma membrane. Specific antibodies can bind to the glycoproteins, fix complement, and lyse the infected cell.

Antibody and CD4+/CD8+ T lymphocyte responses to viral infection can remain at high levels for several months after primary infection but usually wane over time. Low-level persistence of antibody-producing B lymphocytes and CD4+ or CD8+ T lymphocyte responses as memory cells can provide a rapid response to a second infection or an early barrier to reinfection with the same virus. Redevelopment of T cell immunity may take longer than secondary antibody responses, particularly when many years have elapsed between primary infection and reexposure. However, persistent infections or frequent reactivations from latency can result in sustained high-level T cell responses. EBV and CMV typically induce high-level CD4+ and CD8+ T cell responses that are maintained for decades after primary infection.

Some viruses have genes that alter innate and acquired host defenses. Adenoviruses encode small RNAs that inhibit IFN-induced, protein kinase R (PKR)–mediated shutoff of infected-cell protein synthesis. Adenovirus E1A can also directly inhibit IFN-mediated changes in cell gene transcription. Moreover, adenovirus E3 proteins prevent tumor necrosis factor (TNF)–induced cytolysis and block HLA class I synthesis by the infected cell. HSV ICP47 and CMV US11 also block class I antigen presentation. EBV encodes an interleukin (IL) 10 homologue that inhibits NK and T cell responses. Vaccinia virus encodes a soluble receptor for IFN-α and binding proteins for IFN-γ, IL-1, IL-18, and TNF, which inhibit host innate and adaptive immune responses. Vaccinia virus also encodes a caspase inhibitor that inhibits the ability of CD8+ cytotoxic T cells to kill virus-infected cells. Some poxviruses and herpesviruses encode chemokine-binding proteins that inhibit cell inflammatory responses. The adoption of these strategies by viruses highlights the importance of the corresponding host resistance factors in containing viral infection and the importance of redundancy in host resistance.

The host inflammatory and immune responses to viral infection do not come without a price. These responses contribute to the symptoms, signs, and other pathophysiologic manifestations of viral infection. Inflammation at sites of viral infection can subvert an effective immune response and induce tissue death and dysfunction. Moreover, immune responses to viral infection could, in principle, result in immune attack upon cross-reactive epitopes on normal cells, with consequent autoimmunity.

INTERFERONS

All human cells can synthesize IFN-α or IFN-β in response to viral infection. These IFN responses are usually induced by the presence of double-strand viral RNA, which can be made by both RNA and DNA viruses and sensed by double-strand RNA binding proteins (e.g., PKR and RIG-I) in the cell cytoplasm. IFN-γ is not closely related to IFN-α or IFN-β and is produced mainly by NK cells and by immune T lymphocytes responding to IL-12. IFN-α and -β bind to the IFN-α receptor, whereas IFN-γ binds to a different but related receptor. Both receptors signal through receptor-associated JAK kinases and other cytoplasmic proteins, including "STAT" proteins, which are tyrosine-phosphorylated by JAK kinases, translocate to the nucleus, and activate promoters for specific cell genes. Three types of antiviral effects are induced by IFN at the transcriptional level. The first effect is attributable to the induction of 2′-5′ oligo(A) synthetases, which require double-strand RNA for their activation. Activated synthetase polymerizes oligo(A) and thereby activates RNAse L, which in turn degrades single-strand RNA. A second effect results from the induction of PKR, a serine and threonine kinase that is also activated by double-strand RNA. PKR phosphorylates and negatively regulates the translational initiation factor eIF2α, shutting down protein synthesis in the infected cell. A third effect is initiated through the induction of Mx proteins, a family of GTPases that is particularly important in inhibiting the replication of influenza virus and vesicular stomatitis virus. These IFN effects are mostly directed against the infected cell, causing virus and cell dysfunction and thereby limiting viral replication.

DIAGNOSTIC VIROLOGY

A wide variety of methods are used to diagnose viral infection. Serology and virus isolation in tissue culture remain important standards. Acute- and convalescent-phase sera with rising titers of antibody to virus-specific antigens and a shift from IgM to IgG antibodies are generally accepted as diagnostic of acute viral infection. Serologic diagnosis is based on a more than fourfold rise in IgG antibody concentration when acute- and convalescent-phase serum samples are analyzed at the same time.

Immunofluorescence, hemadsorption, and hemagglutination assays for antiviral antibodies are labor-intensive and have been replaced by enzyme-linked immunosorbent assays (ELISAs), which generally use the specific viral proteins most frequently targeted by the antibody response. The proteins are purified from virus-infected cells or produced by recombinant DNA technology and are attached to a solid phase, where they can be incubated with serum, washed to eliminate nonspecific antibodies, and allowed to react with an enzyme-linked reagent to detect human IgG or IgM antibody specifically adhering to the viral antigen. The amount of antibody can then be quantitated by the intensity of a color reaction mediated by the linked enzyme. ELISAs can be sensitive and automated. Western blots can simultaneously confirm the presence of antibody to multiple specific viral proteins. The proteins are separated by size and transferred to an inert membrane, where they are incubated with serum antibodies. Western blots have an internal specificity control because the level of reactivity for viral proteins can be compared with that for cellular proteins in the same sample. Western blots require individual evaluation and are inherently difficult to quantitate or automate.

Isolation of virus in tissue culture depends on infection and replication in susceptible cells. Growth of virus in cell cultures can frequently be identified by effects on cell morphology under light microscopy. For example, HSV produces a typical cytopathic effect in rabbit kidney cells within 3 days. Other viral cytopathic effects may not be as diagnostically distinctive. Identification usually requires confirmation by staining with virus-specific monoclonal antibodies. The efficiency and speed of virus identification can be enhanced by combining short-term culture with immune detection. In assays with "shell vials" of tissue culture cells growing on a coverslip, viral infection can be detected by staining with a monoclonal antibody to a specific viral protein expressed early in viral replication. Thus, virus-infected cells can be detected within hours or days of inoculation, whereas several rounds of infection would be required to produce visible cytopathic effects.

Isolation of virus in tissue culture also depends on the collection of specimens from appropriate sites and the rapid transport of these specimens in appropriate medium to the virology laboratory **(Chap. S13)**. Rapid transport maintains viral viability and limits bacterial and fungal overgrowth. Enveloped viruses are generally more sensitive to freezing and thawing than nonenveloped viruses. The most appropriate site for culture depends on the pathogenesis of the virus in question. Nasopharyngeal, tracheal, or endobronchial aspirates are most appropriate for the identification of respiratory viruses. Sputum cultures generally are less appropriate because bacterial contamination and viscosity threaten tissue-culture cell viability. Aspirates of vesicular fluid are useful for isolation of HSV and VZV. Nasopharyngeal aspirates and stool specimens may be useful when the patient has fever and a rash and an enteroviral infection is suspected. Adenoviruses can be cultured from the urine of patients with hemorrhagic cystitis. CMV can frequently be isolated from cultures of urine or buffy coat. Biopsy material can be effectively cultured when viruses infect major organs, as in HSV encephalitis or adenovirus pneumonia.

The isolation of a virus does not necessarily establish disease causality. Viruses can persistently or intermittently colonize normal human mucosal surfaces. Saliva can be positive for herpesviruses, and normal urine samples can be positive for CMV. Isolations from blood, cerebrospinal fluid (CSF), or tissue are more often diagnostic of significant viral infection.

Another method aimed at increasing the speed of viral diagnosis is direct testing for antigen or cytopathic effects. Virus-infected cells from the patient may be detected by staining with virus-specific monoclonal antibodies. For example, epithelial cells obtained by nasopharyngeal aspiration can be stained with a variety of specific monoclonal antibodies to identify the specific infecting respiratory virus. Antigen and serologic assays can be multiplexed to detect multiple analytes simultaneously by coupling of reagents to color-coded beads for each analyte and detection by flow cytometry.

Nucleic acid amplification techniques bring speed, sensitivity, and specificity to diagnostic virology. The ability to directly amplify minute amounts of viral nucleic acids in specimens means that detection no longer depends on viable virus and its replication. For example, amplification and detection of HSV nucleic acids in the CSF of patients with HSV encephalitis is a more sensitive detection method than culture of virus from CSF. The extreme sensitivity of these tests can be a problem, because subclinical infection or contamination can lead to false-positive results. Detection of viral nucleic acids does not necessarily indicate virus-induced disease.

Measurement of the amount of viral RNA or DNA in peripheral blood is an important means for determining whether a patient is at increased risk for virus-induced disease and for evaluating clinical responses to antiviral chemotherapy. Nucleic acid technologies for RNA quantification are routinely used in AIDS patients to evaluate responses to antiviral agents and to detect viral resistance or noncompliance with therapy. Virus-load measurements are also useful for evaluating the treatment of patients with HBV and HCV infections. Nucleic acid testing or direct staining with CMV-specific monoclonal antibodies to quantitate virus-infected cells in the peripheral blood (CMV antigenemia) is useful for identifying immunosuppressed patients who may be at risk for CMV-induced disease.

DRUG TREATMENT FOR VIRAL INFECTIONS

Multiple steps in the life cycles of viruses can be effectively targeted by antiviral drugs **(Chaps. 186 and 197)**. Nucleoside and nonnucleoside reverse transcriptase inhibitors prevent HIV provirus synthesis, whereas protease inhibitors block maturation of the HIV and HCV polyprotein after infection of the cell. Enfuvirtide is a small peptide derived from HIV gp41 that acts before cell infection by preventing a conformational change required for initial fusion of the virus with the cell membrane. Raltegravir is an integrase inhibitor that is approved for use with other anti-HIV drugs. Amantadine and rimantadine inhibit the influenza M2 protein, preventing release of viral RNA early during infection, whereas zanamivir and oseltamivir inhibit the influenza neuraminidase, which is necessary for the efficient release of mature virions from infected cells.

Viral genomes can evolve resistance to drugs by mutation and selection, by recombination with a drug-resistant virus, or (in the case of influenza virus and other segmented RNA viral genomes) by reassortment. The emergence of drug-resistant strains can limit the efficacy of antiviral therapy. As in antibacterial therapy, excessive and inappropriate use of antiviral therapy can select for the emergence of drug-resistant strains. HIV genotyping is a rapid method for identifying drug-resistant viruses. Resistance to reverse transcriptase or protease inhibitors has been associated with specific mutations in the reverse transcriptase or protease genes. Identification of these mutations by polymerase chain reaction amplification and nucleic acid sequencing can be clinically useful for determining which antiviral agents may still be effective. Drug resistance also can arise in herpesviruses but is a less common clinical problem.

IMMUNIZATION FOR THE PREVENTION OF VIRAL INFECTIONS

Viral vaccines are among the outstanding accomplishments of medical science. Smallpox has been eradicated except as a potential weapon of biological warfare or bioterrorism. Poliovirus eradication may soon follow. Measles can be contained or eliminated. Excess mortality due to influenza virus epidemics can be prevented, and the threat of influenza pandemics can be decreased by contemporary killed or live attenuated influenza vaccines. Mumps, rubella, and chickenpox are well controlled by childhood vaccination in the developed world. Reimmunization of mature adults can be used to control herpes zoster. New rotavirus vaccines can have a major impact on this leading cause of gastroenteritis and prominent cause of childhood death worldwide. Widespread HBV vaccination has dramatically lowered the frequency of acute and chronic hepatitis and is expected to lead to a dramatic decrease in the incidence of hepatocellular carcinoma. The HPV vaccine was the first vaccine specifically licensed to prevent virus-induced cancer. Use of purified proteins, genetically engineered live-virus vaccines, and recombinant DNA–based strategies will make it possible to immunize against severe infections with other viruses. The development of effective HIV and HCV vaccines is complicated by the high mutation rate of viral RNA polymerase and reverse transcriptase, the population-based and individual divergence of HIV or HCV genomes, and repeated high-level exposure in some populations. Concerns about the use of smallpox and other viruses as weapons necessitate maintenance of immunity to agents that are not encountered naturally.

VIRUSES AS NOVEL THERAPEUTIC TOOLS OR AGENTS

Viruses are being used experimentally to deliver biotherapeutic agents or novel vaccines. Foreign genes can be inserted into viral nucleic acids, and the recombinant virus vectors can be used to infect the patient or the patient's cells ex vivo. Retrovirus integration into the cell genome has been used to functionally replace the abnormal gene in T cells of patients with severe combined immunodeficiency, thereby restoring immune function. Recombinant adenovirus, AAV, and retroviruses are being explored for use in diseases due to single-gene defects, such as cystic fibrosis and hemophilia. AAV carrying a lipoprotein lipase gene is now being used in Europe to treat a rare lipid-processing disease and is the first gene therapy approved for clinical use. Recombinant poxviruses,

adenoviruses, and influenza viruses are also being used experimentally as vaccine vectors. Viral vectors are being tested experimentally for the expression of cytokines that can enhance immunity against tumor cells or for the expression of proteins that can increase the sensitivity of tumor cells to chemotherapy. HSV deficient for replication in resting cells is being used to selectively kill proliferating glioblastoma cells after injections into CNS tumors. For improved safety, nonreplicating viruses are frequently used in clinical trials. Potential adverse events associated with virus-mediated gene transfer include the induction of inflammatory and antiviral immune responses. Instances of retrovirus-induced human malignancies have raised concerns about the safety of retroviral gene therapy vectors.

FURTHER READING

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186 Antiviral Chemotherapy, Excluding Antiretroviral Drugs

Lindsey R. Baden

The field of antiviral therapy—both the number of antiviral drugs and our understanding of their optimal use—historically has lagged behind that of antibacterial treatment, but significant progress has been made in recent years on new drugs for several viral infections. The development of antiviral drugs poses several challenges. Viruses replicate intracellularly and often use host cell enzymes, macromolecules, and organelles for synthesis of viral particles. Therefore, useful antiviral compounds must discriminate between host and viral functions with a high degree of specificity; agents without such selectivity are likely to be too toxic for clinical use.

Significant progress has also been made in the development of laboratory assays to assist clinicians in the appropriate use of antiviral drugs. Phenotypic and genotypic assays for resistance to antiviral drugs are becoming more widely available, and correlations of laboratory results with clinical outcomes are being better defined. Of particular note has been the development of highly sensitive and specific methods that measure the concentration of virus in blood (*viral load*) and permit direct assessment of the antiviral effect of a given drug regimen in that host site. Viral load measurements have been useful in recognizing the risk of disease progression in patients with viral infections and in identifying patients for whom antiviral chemotherapy might be of greatest benefit. As with any in vitro laboratory test, results are highly dependent on and likely vary with the laboratory techniques used.

Information regarding the pharmacodynamics of antiviral drugs, and particularly the relationship of concentration effects to efficacy, has been slow to develop but is also expanding. However, assays to measure concentrations of antiviral drugs, especially of their active moieties within cells, are still primarily research procedures not widely available to clinicians. Thus, there are limited guidelines for adjusting dosages of antiviral agents to maximize antiviral activity and minimize toxicity. Consequently, clinical use of antiviral drugs must be accompanied by particular vigilance for unanticipated adverse effects.

Like that of other infections, the course of viral infections is profoundly affected by interplay between the pathogen and a complex set of host defenses. The presence or absence of preexisting immunity, the ability to mount humoral and/or cell-mediated immune responses, and the stimulation of innate immunity are important determinants of the outcome of viral infections. The state of the host's defenses needs to be considered when antiviral agents are used or evaluated.

As with any therapy, the optimal use of antiviral compounds requires a specific and timely diagnosis. For some viral infections, such as herpes zoster, the clinical manifestations are so characteristic that a diagnosis can be made on clinical grounds alone. For other viral infections, such as influenza A, epidemiologic information (e.g., the documentation of a community-wide influenza outbreak) can be used to make a presumptive diagnosis with a high degree of accuracy. However, for most of the remaining viral infections, including herpes simplex encephalitis, cytomegalovirus (CMV) infections other than retinitis, and enterovirus infections, diagnosis on clinical grounds alone cannot be accomplished with certainty. For such infections, rapid viral diagnostic techniques are of great importance. Considerable progress has been made in recent years in the development of such tests, which are now widely available for a number of viral infections.

Despite these complexities, the efficacy of a number of antiviral compounds has been clearly established in rigorously conducted and controlled studies. As summarized in **Table 186-1**, this chapter reviews the antiviral drugs that are currently approved or are likely to be considered for approval in the near future for use against viral infections other than those caused by HIV. **Antiretroviral drugs are reviewed in Chap. 197.**

ANTIVIRAL DRUGS ACTIVE AGAINST RESPIRATORY INFECTIONS (SEE ALSO CHAPS. 194 AND 195)

ZANAMIVIR, OSELTAMIVIR, PERAMIVIR, AND LANINAMIVIR

Zanamivir and oseltamivir are inhibitors of the influenza virus neuraminidase enzyme, which is essential for release of virus from infected cells and for its subsequent spread throughout the respiratory tract of the infected host. The enzyme cleaves terminal sialic acid residues and thus destroys the cellular receptors to which the viral hemagglutinin attaches. Zanamivir and oseltamivir are sialic acid transition-state analogues and are highly active and specific inhibitors of the neuraminidases of both influenza A and B viruses. The antineuraminidase activity of the two drugs is similar, although zanamivir has somewhat greater in vitro activity against influenza B virus. Zanamivir may also be active against certain strains of influenza A virus that are resistant to oseltamivir. Both zanamivir and oseltamivir act through competitive and reversible inhibition of the active site of influenza A and B viral neuraminidases and have relatively little effect on mammalian cell enzymes.

Oseltamivir phosphate is an ethyl ester prodrug that is converted to oseltamivir carboxylate by esterases in the liver. Orally administered oseltamivir has a bioavailability of >60% and a plasma half-life of 7–9 h. The drug is excreted unmetabolized, primarily by the kidneys. Zanamivir has low oral bioavailability and is administered orally via a handheld inhaler. By this route, ~15% of the dose is deposited in the lower respiratory tract, and low plasma levels of the drug are detected. The toxicities most frequently encountered with orally administered oseltamivir are nausea, gastrointestinal discomfort, and (less commonly) vomiting. Gastrointestinal discomfort is usually transient and is less likely if the drug is administered with food. Neuropsychiatric events (delirium, self-injury) have been reported in children who have been taking oseltamivir, primarily in Japan. Zanamivir is orally inhaled and is generally well tolerated, although exacerbations of asthma may occur.

TABLE 186-1 Antiviral Chemotherapy and Chemoprophylaxis

INFECTION(S)	DRUG	ROUTE	DOSAGE	COMMENT
Influenza A and B: treatment	Oseltamivir	Oral	Adults: 75 mg bid × 5 d Children 1–12 years: 30–75 mg bid, depending on weight,[a] × 5 d	When started within 2 days of onset in uncomplicated disease, zanamivir and oseltamivir reduce symptom duration by 1.0–1.5 and 1.3 days, respectively. Their effectiveness in prevention or treatment of complications is unclear, although some analyses suggest that oseltamivir may reduce the frequency of respiratory tract complications and hospitalizations. Oseltamivir's side effects of nausea and vomiting can be reduced in frequency by drug administration with food. Zanamivir may exacerbate bronchospasm in patients with asthma. Amantadine and rimantadine are not recommended for routine use unless antiviral susceptibilities are known because of widespread resistance in A/H3N2 viruses since 2005–2006 and in pandemic A/H1N1 viruses in 2009–2010. Their efficacy in treatment of uncomplicated disease caused by sensitive viruses has been similar to that of neuraminidase inhibitors.
	Zanamivir	Inhaled orally	Adults and children ≥7 years: 10 mg bid × 5 d	
Influenza A: treatment	Amantadine[b]	Oral	Adults: 100 mg qd or bid × 5–7 d Children 1–9 years: 5 mg/kg per day (maximum, 150 mg/d) × 5–7 d	
	Rimantadine[b]	Oral	100 mg qd or bid × 5–7 d in adults	
Influenza A and B: prophylaxis	Oseltamivir	Oral	Adults: 75 mg/d Children ≥1 year: 30–75 mg/d, depending on weight[a]	Prophylaxis must be continued for the duration of exposure and can be administered simultaneously with inactivated vaccine. Unless the sensitivity of isolates is known, neither amantadine nor rimantadine is currently recommended for prophylaxis or therapy.
	Zanamivir	Inhaled orally	Adults and children ≥5 years: 10 mg/d	
Influenza A: prophylaxis	Amantadine[b] or rimantadine[b]	Oral	Adults: 200 mg/d Children 1–9 years: 5 mg/kg per day (maximum, 150 mg/d)	
RSV infection	Ribavirin	Small-particle aerosol	Administered 12–18 h/d from a reservoir containing 20 mg/mL × 3–6 d	Use of ribavirin is to be considered for treatment of infants and young children hospitalized with RSV pneumonia and bronchiolitis, according to the American Academy of Pediatrics.
CMV disease	Ganciclovir	IV	5 mg/kg bid × 14–21 d; then 5 mg/kg per day as maintenance dose	Ganciclovir, valganciclovir, foscarnet, and cidofovir are approved for treatment of CMV retinitis in patients with AIDS. They are also used for colitis, pneumonia, or "wasting" syndrome associated with CMV and for prevention of CMV disease in transplant recipients.
	Valganciclovir	Oral	900 mg bid × 21 d; then 900 mg/d as maintenance dose	Valganciclovir has largely supplanted oral ganciclovir and is frequently used in place of IV ganciclovir.
	Foscarnet	IV	60 mg/kg q8h × 14–21 d; then 90–120 mg/kg per day as maintenance dose	Foscarnet is not myelosuppressive and is active against acyclovir- and ganciclovir-resistant herpesviruses.
	Cidofovir	IV	5 mg/kg once weekly × 2 weeks, then once every other week; given with probenecid and hydration	—
	Fomivirsen	Intravitreal	330 mg on days 1 and 15 followed by 330 mg monthly as maintenance	Fomivirsen has reduced the rate of progression of CMV retinitis in patients in whom other regimens have failed or have not been well tolerated. The major form of toxicity is ocular inflammation.
Varicella: immunocompetent host	Acyclovir	Oral	20 mg/kg (maximum, 800 mg) 4 or 5 times daily × 5 d	Treatment confers modest clinical benefit when administered within 24 h of rash onset.
	Valacyclovir	Oral	Children 2–18 years: 20 mg/kg tid (not to exceed 1 g tid) × 5 d	
Varicella: immunocompromised host	Acyclovir	IV	10 mg/kg q8h × 7 d	A change to oral valacyclovir can be considered once fever has subsided if there is no evidence of visceral involvement.
Herpes simplex encephalitis	Acyclovir	IV	10 mg/kg q8h × 14–21 d	Results are optimal when therapy is initiated early. Some authorities recommend treatment for 21 d to prevent relapses.
Neonatal herpes simplex	Acyclovir	IV	20 mg/kg q8h × 14–21 d	Serious morbidity is common despite therapy. Prolonged oral administration after initial IV therapy has been suggested because of long-term sequelae associated with cutaneous recurrences of HSV infection.
Genital herpes simplex, primary: treatment	Acyclovir	IV	5 mg/kg q8h × 5–10 d	The IV route is preferred for infections severe enough to warrant hospitalization or with neurologic complications.
		Oral	400 mg tid or 200 mg 5 times daily × 7–10 d	The oral route is preferred for patients whose condition does not warrant hospitalization. Adequate hydration must be maintained.
		Topical	5% ointment; 4–6 applications daily × 7–10 d	Topical use—largely supplemented by oral therapy—may obviate systemic administration to pregnant women. Systemic symptoms and untreated areas are not affected.
	Valacyclovir	Oral	1 g bid × 7–10 d	Valacyclovir appears to be as effective as acyclovir but can be administered less frequently.
	Famciclovir	Oral	250 mg tid × 7–10 d[c]	Famciclovir appears to be similar in effectiveness to acyclovir.

(*Continued*)

TABLE 186-1 Antiviral Chemotherapy and Chemoprophylaxis (Continued)

INFECTION(S)	DRUG	ROUTE	DOSAGE	COMMENT
Genital herpes simplex, recurrent: treatment	Acyclovir	Oral	400 mg tid × 5 d or 800 mg tid × 2 d	The clinical effect is modest and is enhanced if therapy is initiated early. Treatment does not affect recurrence rates.
	Famciclovir	Oral	125 mg bid × 5 d, 1000 mg bid × 1 d, or 500 mg once, then 250 mg PO bid × 3 doses	
	Valacyclovir	Oral	500 mg bid × 3 d or 1 g once a day × 5 d	
Genital herpes simplex, recurrent: suppression	Acyclovir	Oral	400 mg bid	Suppressive therapy is recommended only for patients with at least 6–10 recurrences per year. "Breakthrough" occasionally takes place, and asymptomatic shedding of virus occurs. The need for suppressive therapy should be reevaluated after 1 year. Suppression with valacyclovir reduces transmission of genital HSV among virus-discordant couples.
	Valacyclovir	Oral	500–1000 mg/d or 250–500 mg bid	
	Famciclovir	Oral	250 mg bid	
Mucocutaneous herpes simplex in immunocompromised host: treatment	Acyclovir	IV	5 mg/kg q8h × 7–14 d	The choice of the IV or oral route and the duration of therapy depend on the severity of infection and the patient's ability to take oral medication. Oral or IV treatment has supplanted topical therapy except for small, easily accessible lesions. Foscarnet is used for acyclovir-resistant viruses.
		Oral	400 mg 5 times daily × 10–14 d	
		Topical	5% ointment; 4–6 applications daily × 7 d or until healed	
	Valacyclovir	Oral	1 g tid × 7–10 d[c]	
	Famciclovir	Oral	500 mg bid × 7–10 d[d]	
Mucocutaneous herpes simplex in immunocompromised host: prevention of recurrence during intense immunosuppression	Acyclovir	Oral	400 mg 2–5 times daily or 800 mg bid	Treatment is administered during periods when intense immunosuppression is expected—e.g., during antitumor chemotherapy or after transplantation—and is usually continued for 2–3 months.
		IV	5 mg/kg q12h	
	Valacyclovir	Oral	500 mg to 1 g bid or tid	
	Famciclovir	Oral	500 mg bid[c]	
Herpes simplex orolabialis, recurrent[e]	Penciclovir	Topical	1.0% cream applied q2h during waking hours × 4 d	Treatment shortens healing time and symptom duration by 0.5–1.0 d (versus placebo).
	Valacyclovir	Oral	2 g q12h × 1 d	Therapy begun at earliest symptom reduces disease duration by 1 d.
	Famciclovir[c]	Oral	1500 mg once or 750 mg bid × 1 d	Therapy begun within 1 h of prodrome decreases time to healing by 1.8–2.2 d.
	Docosanol[f]	Topical	10% cream 5 times daily until healed	Application at initial symptoms reduces healing time by 1 d.
Herpes simplex keratitis	Trifluridine	Topical	1 drop of 1% ophthalmic solution q2h while awake (maximum, 9 drops daily)	Therapy should be undertaken in consultation with an ophthalmologist.
	Vidarabine	Topical	0.5-in. ribbon of 3% ophthalmic ointment 5 times daily	
Herpes zoster: immunocompetent host	Valacyclovir	Oral	1 g tid × 7 d	Valacyclovir may be more effective than acyclovir for pain relief; otherwise, it has a similar effect on cutaneous lesions and should be given within 72 h of rash onset.
	Famciclovir	Oral	500 mg q8h × 7 d	The duration of postherpetic neuralgia is shorter than with placebo. Famciclovir showed overall efficacy similar to that of acyclovir in a comparative trial. It should be given ≤72 h after rash onset.
	Acyclovir	Oral	800 mg 5 times daily × 7–10 d	Acyclovir causes faster resolution of skin lesions than placebo and provides some relief of acute symptoms if given within 72 h of rash onset. Combined with tapering doses of prednisone, acyclovir improves quality-of-life outcomes.
Herpes zoster: immunocompromised host	Acyclovir	IV	10 mg/kg q8h × 7 d	Effectiveness in localized zoster is most marked when treatment is given early. Foscarnet may be used for acyclovir-resistant VZV infections.
		Oral	800 mg 5 times daily × 7 d	
	Valacyclovir	Oral	1 g tid × 7 d[c]	
	Famciclovir	Oral	500 mg tid × 10 d[c]	
Herpes zoster ophthalmicus	Acyclovir	Oral	600–800 mg 5 times daily × 10 d	Treatment reduces ocular complications, including ocular keratitis and uveitis.
	Valacyclovir	Oral	1 g tid × 7 d	
	Famciclovir	Oral	500 mg tid × 7 d	
Condyloma acuminatum	IFN-α2b	Intralesional	1 million units per wart (maximum of 5) thrice weekly × 3 weeks	Intralesional treatment frequently results in regression of warts, but lesions often recur. Parenteral administration may be useful if lesions are numerous.
	IFN-αn3	Intralesional	250,000 units per wart (maximum of 10) twice weekly × up to 8 weeks	
Chronic hepatitis B	IFN-α2b	SC	5 million units daily or 10 million units thrice weekly × 16–24 weeks	HBeAg and DNA are eliminated in 33–37% of cases. Histopathologic improvement is also seen.
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	ALT levels return to normal in 39% of patients, and histologic improvement occurs in 38%.

(*Continued*)

TABLE 186-1 Antiviral Chemotherapy and Chemoprophylaxis (Continued)

INFECTION(S)	DRUG	ROUTE	DOSAGE	COMMENT
	Lamivudine	Oral	100 mg/d × 12–18 months; 150 mg bid as part of therapy for HIV infection	Lamivudine monotherapy is well tolerated and effective in reduction of HBV DNA levels, normalization of ALT levels, and improvement in histopathology. However, resistance develops in 24% of recipients when lamivudine is used as monotherapy for 1 year.
	Adefovir dipivoxil	Oral	10 mg/d × 48 weeks	A return of ALT levels to normal is documented in 48–72% of recipients and improved liver histopathology in 53–64%. Adefovir is effective in lamivudine-resistant hepatitis B. Renal function including proteinuria should be monitored.
	Entecavir	Oral	0.5 mg/d × 48 weeks (1 mg/d if HBV is resistant to lamivudine)	Normalization of ALT is seen in 68–78% of recipients and loss of HBeAg in 21%. Entecavir is active against lamivudine-resistant HBV.
	Telbivudine	Oral	600 mg/d × 52 weeks	HBV DNA is reduced by >5 $\log_{10}$ copies/mL along with normalization of ALT levels in 74–77% of patients and improved histopathology in 65–67%. Resistance develops in 9–22% of patients after 2 years of therapy. Elevated CPK levels and myopathy may occur.
	Tenofovir disoproxil	Oral	300 mg/d × 48 weeks	ALT levels return to normal in 68–76% of patients, and liver histopathology improves in 72–74%. Resistance is uncommon with up to 2 years of therapy. Initial data suggest a better safety profile (renal and bone) for tenofovir alafenamide than for tenofovir disoproxil.
	Tenofovir alafenamide	Oral	25 mg/d × 48 weeks	
Chronic hepatitis C	Sofosbuvir[g]/ pegylated IFN-α2a or IFN-α2b/ ribavirin	Oral/SC	HCV genotypes 1, 4, 5, and 6: sofosbuvir (400 mg qd) with daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) and weekly pegylated IFN (180 μg per week) for 12 weeks Genotypes 2 and 3: sofosbuvir (400 mg qd) with daily weight-based ribavirin for 12 and 24 weeks, respectively	Sofosbuvir is generally well tolerated, and most common side effects have been attributable to concomitantly administered IFN and ribavirin. Sofosbuvir is recommended in triple combination with pegylated IFN and ribavirin for genotypes 1, 4, 5, and 6, with SVRs in 89–97% of treatment-naïve patients.
	Simeprevir[g]/ pegylated IFN-α2b/ ribavirin	Oral/SC/oral	Alternative regimen for genotypes 1 and 4: simeprevir (50 mg qd) for 12 weeks plus daily ribavirin and weekly pegylated IFN for 24–28 weeks, respectively	Simeprevir has supplanted the first-generation protease inhibitors boceprevir and telaprevir. Its metabolism by cytochrome CYP3A can result in interactions with other drugs. Photosensitivity and reversible hyperbilirubinemia are associated toxicities. Testing for the Q80K-resistant variant should be carried out since this variant is present in one-third of HCV genotype 1a infections. Triple combinations of simeprevir with pegylated IFN and ribavirin result in SVRs in 80% of genotype 1 infections without Q80K. Combination therapy results in SVR in up to 40–50% of recipients.
	IFN-α2a or IFN-α2b	SC	9 million units thrice weekly × 12 months	The overall efficacy and the optimal regimen and duration of therapy are not fully established. Sustained SVRs have been seen in 25–30% of patients for IFN-α and in 17–43% for pegylated IFN-α. The slower clearance of pegylated IFNs than of standard IFNs permits once-weekly administration. Pegylated formulations appear to be superior to standard IFNs in efficacy, both as monotherapy and in combination with ribavirin, and have largely supplanted standard IFNs in treatment of hepatitis C. SVRs were seen in 42–51% of patients infected with HCV genotype 1 and in 76–82% of those infected with genotype 2 or 3.
	Pegylated IFN-α2b	SC	1.5 μg weekly × 48 weeks	
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	
	Pegylated IFN-α2b/ ribavirin	SC (IFN)/oral (ribavirin)	1.5 μg/kg weekly (IFN)/ 800–1400 mg daily (ribavirin) × 24–48 weeks	
	Pegylated IFN-α2a/ ribavirin	SC (IFN)/oral (ribavirin)	180 μg weekly (IFN)/800–1200 mg daily (ribavirin) × 24–48 weeks	
	IFN-alfacon	SC	9–15 μg thrice weekly × 6–12 months	Doses of 9 and 15 μg are equivalent to IFN-α2a and IFN-α2b doses of 3 million units and 5 million units, respectively.
	Sofosbuvir[g]	Oral	HCV genotypes 1, 4, 5, and 6: 400 mg qd with daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) and weekly pegylated IFN for 12 weeks Genotypes 2 and 3: 400 mg qd with daily weight-based ribavirin for 12 and 24 weeks, respectively	Sofosbuvir is generally well tolerated, and most common side effects have been attributable to concomitantly administered IFN and ribavirin. Sofosbuvir is recommended in triple combination with pegylated IFN and ribavirin for genotypes 1, 4, 5, and 6, with SVRs in 89–97% of treatment-naïve patients, and in double combination with ribavirin for genotypes 2 and 3.
	Simeprevir[g]	Oral	Alternative regimen for genotypes 1 and 4: 150 mg qd for 12 weeks plus daily ribavirin and weekly pegylated IFN for 24 weeks and for 24–48 weeks, respectively	Simeprevir has supplanted the first-generation protease inhibitors boceprevir and telaprevir. Its metabolism by cytochrome CYP3A can result in interactions with other drugs. Photosensitivity and reversible hyperbilirubinemia are associated toxicities. Testing for the Q80K-resistant variant should be carried out since this variant is present in one-third of HCV genotype 1a infections. Triple combinations with pegylated IFN and ribavirin result in SVRs in 80% of genotype 1 infections without Q80K.

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TABLE 186-1 Antiviral Chemotherapy and Chemoprophylaxis (Continued)

INFECTION(S)	DRUG	ROUTE	DOSAGE	COMMENT
	Sofosbuvir/ledipasvir	Oral	Active against genotypes 1, 4, 5	These DAA regimens have largely supplanted prior HCV treatments because of their ease of administration, excellent tolerability, and high efficacy. Various durations of regimens—from 8 to 24 weeks—have been studied, depending on regimen, cirrhosis, genotype, and prior HCV treatment. These highly active regimens are IFN and ribavirin free. Monitoring for HBV reactivation is warranted. Please access *http://www.hcvguidelines.org/* for the latest recommendations.
	Sofosbuvir/daclatasvir	Oral	Active against genotypes 1, 2, 3	
	Sofosbuvir/velpatasvir	Oral	Active against genotypes 1, 2, 3, 4, 5	
	Elbasvir/grazoprevir	Oral	Active against genotypes 1, 4	
	Paritaprevir/ritonavir/ombitasvir +/- dasabuvir	Oral	Active against genotypes 1, 4	
Chronic hepatitis D	IFN-α2a or IFN-α2b	SC	9 million units thrice weekly × 12 months	The overall efficacy and the optimal regimen and duration of therapy are not fully established. Sustained SVRs have been seen in 25–30% of patients for IFN-α and in 17–43% for pegylated IFN-α.
	Pegylated IFN-α2b	SC	1.5 μg weekly × 48 weeks	
	Pegylated IFN-α2a	SC	180 μg weekly × 48 weeks	

[a]For detailed weight recommendations and for children <1 year of age, see *www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm*. [b]Amantadine and rimantadine are not recommended for routine use because of widespread resistance in currently circulating A/H3N2 and pandemic A/H1N1 viruses. Their use may be reconsidered if sensitivities become reestablished. [c]Not approved for this indication by the U.S. Food and Drug Administration (FDA). [d]Approved by the FDA for treatment of HIV-infected individuals. [e]Acyclovir suspension (15 mg/kg PO, to a maximum of 200 mg/dose) given for 7 days has been reported to be effective in the treatment of primary herpetic gingivostomatitis in children. [f]Active ingredient: benzyl alcohol. Available without prescription. [g]Consult *www.hcvguidelines.org* for recommendations regarding treatment of null or partial responders to IFN regimens or of patients ineligible to receive IFN.

Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; CPK, creatine phosphokinase; DAA, direct-acting antiviral agent; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; IFN, interferon; RSV, respiratory syncytial virus; SVR, sustained virologic response; VZV, varicella-zoster virus.

An IV formulation of zanamivir is under development and is available from GlaxoSmithKline as part of clinical trials.

Inhaled zanamivir and orally administered oseltamivir have been effective in the treatment of naturally occurring, uncomplicated influenza A or B in otherwise healthy adults. In placebo-controlled studies, illness has been shortened by 1.0–1.5 days of therapy with either of these drugs when treatment is administered within 2 days of onset of symptoms. Pooled analyses of clinical studies of oseltamivir suggest that treatment may reduce the likelihood of hospitalizations and of certain respiratory tract complications associated with influenza, and observational studies suggest that oseltamivir may reduce mortality rates associated with influenza A outbreaks **(Chap. 195)**. Once-daily inhaled zanamivir or once-daily orally administered oseltamivir can provide prophylaxis against laboratory-documented influenza A– and influenza B–associated illness.

Resistance to the neuraminidase inhibitors may develop by changes in the viral neuraminidase enzyme, by changes in the hemagglutinin that make it more resistant to the actions of the neuraminidase, or by both mechanisms. Isolates that are resistant to oseltamivir—most commonly through the H275Y mutation, which leads to a change from histidine to tyrosine at that residue in the neuraminidase—remain sensitive to zanamivir. Certain mutations impart resistance to both oseltamivir and zanamivir (e.g., I223R, which leads to a change from isoleucine to arginine). Because the mechanisms of action of the neuraminidase inhibitors differ from those of the adamantanes (see below), zanamivir and oseltamivir are active against strains of influenza A virus that are resistant to amantadine and rimantadine.

Appropriate use of antiviral agents against influenza viruses depends on a knowledge of the resistance patterns of circulating viruses. As of this writing, currently circulating influenza A/H1N1 and H3N2 viruses (2013–2014) were sensitive to zanamivir and oseltamivir, with a few exceptions for oseltamivir. Up-to-date information on patterns of resistance to antiviral drugs is available from the Centers for Disease Control and Prevention (CDC) at *www.cdc.gov/flu*.

Zanamivir and oseltamivir have been approved by the U.S. Food and Drug Administration (FDA) for treatment of influenza in adults and in children (those ≥7 years old for zanamivir and those ≥1 year old for oseltamivir) who have been symptomatic for ≤2 days. Oseltamivir is approved for prophylaxis of influenza in individuals ≥1 year of age and zanamivir for those ≥5 years of age (Table 186-1). Guidelines for the use of oseltamivir in children <1 year of age can be accessed through the CDC website (*www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm*).

Peramivir (BCX-1812) is a neuraminidase inhibitor that can be administered intravenously. It has been approved in Japan, China, and South Korea but not in the United States, where it has been available in clinical trials through BioCryst Pharmaceuticals and previously as part of an emergency use authorization in response to the influenza A(H1N1) pdm09 virus pandemic in 2009–2010. Oseltamivir-resistant viruses generally exhibit reduced sensitivity to peramivir.

Laninamivir octanoate is a neuraminidase that has been approved in Japan for the treatment and prevention of influenza A and B. It is the prodrug of laninamivir, which is administered by oral inhalation and has a prolonged half-life of ~3 days. In limited studies, it has been investigated as single-dose therapy for influenza; its effects were similar to those obtained with multiple doses of zanamivir or oseltamivir.

AMANTADINE AND RIMANTADINE

Amantadine and the closely related compound rimantadine are primary symmetric amines that have antiviral activity limited to influenza A viruses. Amantadine and rimantadine have a long history of efficacy in the prophylaxis and treatment of influenza A infections in humans. However, high frequencies of resistance to these drugs were noted among influenza A/H3N2 viruses in the 2005–2006 influenza season and continued to be seen in 2013–2014. The pandemic A/H1N1 viruses that circulated in 2009–2010 were also resistant to amantadine and rimantadine, and circulating influenza A/H1N1 viruses in the 2013–2014 season were largely resistant. Therefore, these agents are no longer recommended unless the sensitivity of the particular isolate of influenza A virus is known, in which case their use may be considered. Amantadine and rimantadine act through inhibition of the ion channel function of the influenza A M2 matrix protein, on which uncoating of the virus depends. A substitution of a single amino acid at critical sites in the M2 protein can result in a virus that is resistant to amantadine and rimantadine.

Amantadine and rimantadine have been shown to be effective in the prophylaxis of influenza A in large-scale studies of young adults and in less extensive studies of children and elderly persons. In such studies, efficacy rates of 55–80% in the prevention of influenza-like illness were noted, and even higher rates were reported when virus-specific

attack rates were calculated. Amantadine and rimantadine have also been found to be effective in the treatment of influenza A infection in studies involving predominantly young adults and, to a lesser extent, children. Administration of these compounds within 24–72 h after the onset of illness has resulted in a reduction of the duration of signs and symptoms by ~50% compared with that in placebo recipients. The effect on signs and symptoms of illness is superior to that of commonly used antipyretic–analgesic agents. Only anecdotal reports are available concerning the efficacy of amantadine or rimantadine in the prevention or treatment of complications of influenza (e.g., pneumonia).

Amantadine and rimantadine are available only in oral formulations and are ordinarily administered to adults once or twice daily, with a dosage of 100–200 mg/d. Despite their structural similarities, the two compounds have different pharmacokinetics. Amantadine is not metabolized and is excreted almost entirely by the kidneys, with a half-life of 12–17 h and peak plasma concentrations of 0.4 μg/mL. In contrast, rimantadine is extensively metabolized to hydroxylated derivatives and has a half-life of 30 h. Only 30–40% of an orally administered dose of rimantadine is recovered in the urine. The peak plasma levels of rimantadine are approximately half those of amantadine, but rimantadine is concentrated in respiratory secretions to a greater extent than amantadine. For prophylaxis, the compounds must be administered daily for the period at risk (i.e., duration of the exposure). For therapy, amantadine or rimantadine is generally administered for 5–7 days.

Although these compounds are generally well tolerated, 5–10% of amantadine recipients experience mild central nervous system side effects consisting primarily of dizziness, anxiety, insomnia, and difficulty in concentrating. These effects are rapidly reversible upon cessation of the drug's administration. At a dose of 200 mg/d, rimantadine is better tolerated than amantadine; in a large-scale study of young adults, adverse effects were no more frequent among rimantadine recipients than among placebo recipients. Seizures and worsening of congestive heart failure have also been reported in patients treated with amantadine, although a causal relationship has not been established. The dosage of amantadine should be reduced to 100 mg/d in patients with renal insufficiency—i.e., a creatinine clearance rate (Cr_{Cl}) of <50 mL/min—and in the elderly. A rimantadine dose of 100 mg/d should be used for patients with a Cr_{Cl} of <10 mL/min and for the elderly.

RIBAVIRIN

Ribavirin is a synthetic nucleoside analogue that inhibits a wide range of RNA and DNA viruses. The mechanism of action of ribavirin is not completely defined and may be different for different groups of viruses. Ribavirin-5′-monophosphate blocks the conversion of inosine-5′-monophosphate to xanthosine-5′-monophosphate and interferes with the synthesis of guanine nucleotides as well as with that of both RNA and DNA. Ribavirin-5′-monophosphate also inhibits capping of virus-specific messenger RNA in certain viral systems.

Ribavirin administered as a small-particle aerosol to young children hospitalized with respiratory syncytial virus (RSV) infection has been clinically beneficial and has improved oxygenation in some studies (7 of 11). Although ribavirin has been approved for treatment of infants hospitalized with RSV infection, the American Academy of Pediatrics has recommended that it be considered on an individual basis rather than used routinely in that setting. Aerosolized ribavirin has also been administered to older children and adults (including immunosuppressed patients) with severe RSV and parainfluenza virus infections and to older children and adults with influenza A or B infection, but the benefit of this treatment, if any, is unclear. In RSV infections in immunosuppressed patients, ribavirin has been given in combination with anti-RSV immunoglobulins.

Orally administered ribavirin has not been effective in the treatment of influenza A virus infections. IV or oral ribavirin has reduced mortality rates among patients with Lassa fever; it is thought to be more effective in this regard when given within the first 6 days of illness. IV ribavirin has been reported to be of clinical benefit in the treatment of hemorrhagic fever with renal syndrome caused by Hantaan virus and as therapy for Argentinean hemorrhagic fever. Oral ribavirin has also been recommended for the treatment and prophylaxis of Congo-Crimean hemorrhagic fever. Use of IV ribavirin in patients with hantavirus pulmonary syndrome in the United States has not been associated with clear-cut benefits.

Oral administration of ribavirin reduces serum aminotransferase levels in patients with chronic hepatitis C virus (HCV) infection; because it appears not to reduce serum HCV RNA levels, the mechanism of this effect is unclear. The drug provides added benefit when given by mouth in doses of 800–1200 mg/d in combination with interferon (IFN) α2b or α2a (see below), and the triple combination of ribavirin, IFN, and sofosbuvir or simeprevir has been approved for the treatment of patients with chronic HCV infection (see below). Recent data suggest that oral ribavirin may be beneficial in resolution of chronic hepatitis E infection (largely genotype 3) associated with organ transplantation. Larger oral doses of ribavirin (800–1000 mg/d) have been associated with reversible hematopoietic toxicity. This effect has not been observed with aerosolized ribavirin, apparently because little drug is absorbed systemically. Aerosolized administration of ribavirin is generally well tolerated but occasionally is associated with bronchospasm, rash, or conjunctival irritation. It should be administered under close supervision—particularly in the setting of mechanical ventilation, where precipitation of the drug is possible. Health care workers exposed to the drug have experienced minor toxicity, including eye and respiratory tract irritation. Because ribavirin is mutagenic, teratogenic, and embryotoxic, its use is generally contraindicated in pregnancy. Its administration as an aerosol poses a risk to pregnant health care workers. Because clearance of ribavirin is primarily renal, dose reduction is required in the setting of significant renal dysfunction.

AGENTS OF INVESTIGATIVE INTEREST

Favipiravir (T-705) is a viral RNA–dependent RNA polymerase inhibitor active against influenza viruses, including neuraminidase inhibitor–resistant strains. It is approved in Japan for the treatment of influenza. Given favipiravir's in vitro activity against a broad range of viruses, including arenaviruses, phleboviruses (e.g., Rift Valley Fever virus), hantaviruses, flaviviruses, and filoviruses (e.g., Ebola virus), its use has been considered in the context of outbreaks of disease caused by these viruses even though their clinical activity remains uncertain. DAS181 is an investigational antiviral agent with activity against influenza A and B and parainfluenza viruses. A sialidase fusion protein, DAS181 cleaves the terminal sialic acid residues on human respiratory cells, reducing the binding of influenza and parainfluenza viruses. It is interesting to note that this agent targets host cellular rather than microbial protein. DAS181 is administered by oral inhalation and is being evaluated in the treatment of parainfluenza type 3 infections in recipients of lung and stem cell transplants. Three investigational agents with activity against RSV are being studied: (1) GS-5806, a small molecule that blocks fusion of the viral envelope with the host cell membrane, thus inhibiting viral entry, and has shown promising activity in human challenge studies; (2) ALS-008176, a prodrug of a cytidine nucleoside analogue that inhibits RSV replication by means of chain termination; and (3) ALN-RSV01, which works via RNA interference and is directed against the conserved region encoding the nucleocapsid (N) protein.

ANTIVIRAL DRUGS ACTIVE AGAINST HERPESVIRUS INFECTIONS

ACYCLOVIR AND VALACYCLOVIR

Acyclovir is a highly potent and selective inhibitor of the replication of certain herpesviruses, including herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV). This drug is relatively ineffective in the treatment of human CMV infections; however, some studies have indicated effectiveness (at higher doses) in the prevention of CMV-associated disease in immunosuppressed patients. Valacyclovir, the L-valyl ester of acyclovir, is converted almost entirely to acyclovir by intestinal and hepatic hydrolysis after oral administration. Valacyclovir offers pharmacokinetic advantages over orally administered acyclovir: it exhibits significantly greater oral

bioavailability, results in higher blood levels, and can be given less frequently than acyclovir (two or three rather than five times daily).

The high degree of selectivity of acyclovir is related to its mechanism of action, which requires that the compound first be phosphorylated to acyclovir monophosphate. This phosphorylation occurs efficiently in herpesvirus-infected cells by means of a virus-coded thymidine kinase. In uninfected mammalian cells, little phosphorylation of acyclovir occurs, and the drug is therefore concentrated in herpesvirus-infected cells. Acyclovir monophosphate is subsequently converted by host cell kinases to a triphosphate that is a potent inhibitor of virus-induced DNA polymerase but has relatively little effect on host cell DNA polymerase. Acyclovir triphosphate can also be incorporated into viral DNA, with early chain termination.

Acyclovir is available in IV, oral, and topical forms, while valacyclovir is available in an oral formulation. IV acyclovir is effective in the treatment of mucocutaneous HSV infections in immunocompromised hosts, in whom it reduces time to healing, duration of pain, and virus shedding. When administered prophylactically during periods of intense immunosuppression (e.g., related to chemotherapy for leukemia or transplantation) and before the development of lesions, IV acyclovir reduces the frequency of HSV-associated disease. After prophylaxis is discontinued, HSV lesions recur. IV acyclovir is also effective in the treatment of HSV encephalitis.

Because VZV is generally less sensitive to acyclovir than is HSV, higher doses of acyclovir must be used to treat VZV infections. In immunocompromised patients with herpes zoster, IV acyclovir reduces the frequency of cutaneous dissemination and visceral complications and—in one comparative trial—was more effective than vidarabine. Acyclovir, administered at oral doses of 800 mg five times a day, had a modest beneficial effect on localized herpes zoster lesions in both immunocompromised and immunocompetent patients. Combination of acyclovir with a tapering regimen of prednisone appeared to be more effective than acyclovir alone in terms of quality-of-life outcomes in immunocompetent patients aged >50 years with herpes zoster. A comparative study of acyclovir (800 mg PO five times daily) and valacyclovir (1 g PO three times daily) in immunocompetent patients with herpes zoster indicated that the latter drug may be more effective in eliciting the resolution of zoster-associated pain. Orally administered acyclovir (600 mg five times a day) reduced complications of herpes zoster ophthalmicus in a placebo-controlled trial.

In chickenpox, a modest overall clinical benefit is attained when oral acyclovir therapy is begun within 24 h of the onset of rash in otherwise healthy children (20 mg/kg, up to a maximum of 800 mg, four times a day) or adults (800 mg five times a day). IV acyclovir has also been reported to be effective in the treatment of immunocompromised children with chickenpox.

A common use of acyclovir is in the treatment of genital HSV infections. IV or oral acyclovir or oral valacyclovir has shortened the duration of symptoms, reduced virus shedding, and accelerated healing when used for the treatment of primary genital HSV infections. Oral acyclovir and valacyclovir have also had a modest effect in treatment of recurrent genital HSV infections. However, the failure of treatment of either primary or recurrent disease to reduce the frequency of subsequent recurrences has indicated that acyclovir is ineffective in eliminating latent infection. Documented chronic oral administration of acyclovir for up to 6 years or of valacyclovir for up to 1 year has reduced the frequency of recurrences markedly during therapy; once the drug is discontinued, lesions recur. In one study, suppressive therapy with valacyclovir (500 mg once daily for 8 months) reduced transmission of HSV-2 genital infections among discordant couples by 50%. A modest effect on herpes labialis (i.e., a reduction of disease duration by 1 day) was seen when valacyclovir was administered upon detection of the first symptom of a lesion at a dose of 2 g every 12 h for 1 day. In AIDS patients, chronic or intermittent administration of acyclovir has been associated with the development of HSV and VZV strains resistant to the action of the drug and with clinical failures. The most common mechanism of resistance is a deficiency of the virus-induced thymidine kinase. Patients with HSV or VZV infections resistant to acyclovir have frequently responded to foscarnet.

With the availability of the oral and IV forms, there are few indications for topical acyclovir, although treatment with this formulation has been modestly beneficial in primary genital HSV infections and in mucocutaneous HSV infections in immunocompromised hosts.

Overall, acyclovir is remarkably well tolerated and is generally free of toxicity. The most frequently encountered form of toxicity is renal dysfunction because of drug crystallization (which is pH dependent), particularly after rapid IV administration or with inadequate hydration. Central nervous system changes, including lethargy and tremors, are occasionally reported, primarily in immunosuppressed patients. However, whether these changes are related to acyclovir, to concurrent administration of other therapy, or to underlying infection remains unclear. Acyclovir is excreted primarily unmetabolized by the kidneys via both glomerular filtration and tubular secretion. Approximately 15% of a dose of acyclovir is metabolized to 9-Carboxymethoxymethylguanine or other minor metabolites. Reduction in dosage is indicated in patients with a Cr_{Cl} of <50 mL/min. The half-life of acyclovir is ~3 h in normal adults, and the peak plasma concentration after a 1-h infusion of a dose of 5 mg/kg is 9.8 μg/mL. Approximately 22% of an orally administered acyclovir dose is absorbed, and peak plasma concentrations of 0.3–0.9 μg/mL are attained after administration of a 200-mg dose. Acyclovir penetrates relatively well into the cerebrospinal fluid (CSF), with concentrations approaching half of those found in plasma.

Acyclovir causes chromosomal breakage at high doses, but its administration to pregnant women has not been associated with fetal abnormalities. Nonetheless, the potential risks and benefits of acyclovir should be carefully assessed before the drug is used in pregnancy.

Valacyclovir exhibits three to five times greater bioavailability than acyclovir. The concentration–time curve for valacyclovir, given as 1 g PO three times daily, is similar to that for acyclovir, given as 5 mg/kg IV every 8 h. The safety profiles of valacyclovir and acyclovir are similar, although thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome has been reported in immunocompromised patients who have received high doses of valacyclovir (8 g/d). Valacyclovir is approved for the treatment of herpes zoster, of initial and recurrent episodes of genital HSV infection, and of herpes labialis in immunocompetent adults as well as for suppressive treatment of genital herpes. Although it has not been extensively studied in other clinical settings involving HSV or VZV infections, many consultants use valacyclovir rather than oral acyclovir in settings where only the latter has been approved because of valacyclovir's superior pharmacokinetics and more convenient dosing schedule.

CIDOFOVIR

Cidofovir is a phosphonate nucleotide analogue of cytosine. Its major use is in CMV infections, but it is active against a broad range of herpesviruses, including HSV, human herpesvirus (HHV) types 6A and 6B, HHV-8, and certain other DNA viruses such as polyomaviruses, papillomaviruses, adenoviruses, and poxviruses, including variola (smallpox) and vaccinia. Cidofovir does not require initial phosphorylation by virus-induced kinases; the drug is phosphorylated by host cell enzymes to cidofovir diphosphate, which is a competitive inhibitor of viral DNA polymerases and, to a lesser extent, of host cell DNA polymerases. Incorporation of cidofovir diphosphate slows or terminates nascent DNA chain elongation. Cidofovir is active against HSV isolates that are resistant to acyclovir because of absent or altered thymidine kinase and against CMV isolates that are resistant to ganciclovir because of UL97 phosphotransferase mutations. CMV isolates resistant to ganciclovir on the basis of UL54 mutations are usually resistant to cidofovir as well. Cidofovir is usually active against foscarnet-resistant CMV, although cross-resistance to foscarnet has been described, typically in the UL54 polymerase.

Cidofovir has poor oral availability and is administered intravenously. It is excreted primarily by the kidney and has a plasma half-life of 2.6 h. Cidofovir diphosphate's intracellular half-life of >48 h is the basis for the recommended dosing regimen of 5 mg/kg once a week for the initial 2 weeks and then 5 mg/kg every other week. The major toxic effect of cidofovir is proximal renal tubular injury, as manifested by elevated serum creatinine levels and proteinuria. The risk

of nephrotoxicity can be reduced by vigorous saline hydration and by concomitant oral administration of probenecid. Neutropenia, rashes, and gastrointestinal tolerance may also occur.

IV cidofovir has been approved for the treatment of CMV retinitis in AIDS patients who are intolerant of ganciclovir or foscarnet or in whom those drugs have failed. In a controlled study, a maintenance dosage of 5 mg/kg per week administered to AIDS patients reduced the progression of CMV retinitis from that seen at 3 mg/kg. Intravitreal cidofovir has been used to treat CMV retinitis but has been associated with significant toxicity. IV cidofovir has been reported anecdotally to be effective for treatment of acyclovir-resistant mucocutaneous HSV infections. Likewise, topically administered cidofovir is reportedly beneficial against mucocutaneous HSV infections in HIV-infected patients. Anecdotal use of IV cidofovir has been described in disseminated adenoviral infections in immunosuppressed patients and in genitourinary infections with BK virus in renal transplant recipients; however, its efficacy, if any, in these circumstances is not established.

CMX-001 (brincidofovir) is an ester prodrug of cidofovir that can be administered orally and may be less nephrotoxic than IV cidofovir. It has not shown efficacy in the prevention of CMV infection in stem cell transplant recipients but is being studied for treatment of BK nephropathy and adenovirus infections.

FOMIVIRSEN

Fomivirsen is the first antisense oligonucleotide approved by the FDA for therapy in humans. This phosphorothioate oligonucleotide, 21 nucleotides in length, inhibits CMV replication through interaction with CMV messenger RNA. Fomivirsen is complementary to messenger transcripts of the major immediate early region 2 of CMV, which codes for proteins regulating viral gene expression. In addition to its antisense mechanism of action, fomivirsen may exert activity against CMV through inhibition of viral adsorption to cells as well as direct inhibition of viral replication. Because of its different mechanism of action, fomivirsen is active against CMV isolates that are resistant to nucleoside or nucleotide analogues, such as ganciclovir, foscarnet, or cidofovir.

Fomivirsen has been approved for intravitreal administration in the treatment of CMV retinitis in AIDS patients who have failed to respond to other treatments or cannot tolerate them. Injection of two doses of 330 mg 2 weeks apart, followed by maintenance doses of 330 mg monthly, significantly reduces the rate of progression of CMV retinitis. The major toxicity is ocular inflammation, including vitritis and iritis, which usually responds to topically administered glucocorticoids.

GANCICLOVIR AND VALGANCICLOVIR

An analogue of acyclovir, ganciclovir is active against HSV and VZV and is markedly more active than acyclovir against CMV. Ganciclovir triphosphate inhibits CMV DNA polymerase and can be incorporated into CMV DNA, whose elongation it eventually terminates. In HSV- and VZV-infected cells, ganciclovir is phosphorylated by virus-encoded thymidine kinases; in CMV-infected cells, it is phosphorylated by a viral kinase encoded by the UL97 gene. Ganciclovir triphosphate is present in tenfold higher concentrations in CMV-infected cells than in uninfected cells. Ganciclovir is approved for the treatment of CMV retinitis in immunosuppressed patients and for the prevention of CMV disease in transplant recipients. It is widely used for the treatment of other CMV-associated syndromes, including pneumonia, esophagogastrointestinal infections, hepatitis, and "wasting" illness.

Ganciclovir is available for IV or oral administration. Because its oral bioavailability is low (5–9%), relatively large doses (1 g three times daily) must be administered by this route. Oral ganciclovir has largely been supplanted by valganciclovir, which is the L-valyl ester of ganciclovir. Valganciclovir is well absorbed orally, with a bioavailability of 60%, and is rapidly hydrolyzed to ganciclovir in the intestine and liver. The area under the curve for a 900-mg dose of valganciclovir is equivalent to that for 5 mg/kg of IV ganciclovir, although peak serum concentrations are ~40% lower for valganciclovir. The serum half-life is 3.5 h after IV administration of ganciclovir and 4.0 h after PO administration of valganciclovir. Ganciclovir is excreted primarily by the kidneys in an unmetabolized form, and its dosage should be reduced in cases of renal failure. Ganciclovir therapy at the most commonly used initial IV dosage—i.e., 5 mg/kg every 12 h for 14–21 days—can be changed to valganciclovir (900 mg PO twice daily) when the patient can tolerate oral therapy. The maintenance dose is 5 mg/kg IV daily or five times per week for ganciclovir and 900 mg by mouth once a day for valganciclovir. Dose adjustment in patients with renal dysfunction is required. Intraocular ganciclovir, given by either intravitreal injection or intraocular implantation, has also been used to treat CMV retinitis.

Ganciclovir is effective as prophylaxis against CMV-associated disease in organ and bone marrow transplant recipients. Oral ganciclovir administered prophylactically to AIDS patients with CD4+ T cell counts of <100/μL has provided protection against the development of CMV retinitis. However, the long-term benefits of this approach to prophylaxis in AIDS patients have not been established, and most experts do not recommend the use of oral ganciclovir for this purpose. As already mentioned, valganciclovir has supplanted oral ganciclovir in settings where oral prophylaxis or therapy is considered.

The administration of ganciclovir has been associated with bone marrow suppression, particularly neutropenia, which significantly limits the drug's use in many patients. Bone marrow toxicity is potentiated in the setting of renal dysfunction and when other bone marrow suppressants, such as zidovudine or mycophenolate mofetil, are used concomitantly. This toxicity is typically dose and duration sensitive and is reversible with cessation of ganciclovir use.

Resistance has been noted in CMV isolates obtained after therapy with ganciclovir, especially those from patients with AIDS or from patients receiving prolonged ganciclovir therapy after organ transplantation. Such resistance may develop through a mutation in either the viral UL97 gene or the viral DNA polymerase. Ganciclovir-resistant isolates are usually sensitive to foscarnet (see below) or may be sensitive to cidofovir, depending on the mechanism of resistance (see above).

FAMCICLOVIR AND PENCICLOVIR

Famciclovir is the diacetyl 6-deoxyester of the guanosine analogue penciclovir. This agent is well absorbed orally, has a bioavailability of 77%, and is rapidly converted to penciclovir by deacetylation and oxidation in the intestine and liver. Penciclovir's spectrum of activity and mechanism of action are similar to those of acyclovir. Thus, penciclovir usually is not active against acyclovir-resistant viruses. However, some acyclovir-resistant viruses with altered thymidine kinase or DNA polymerase substrate specificity may be sensitive to penciclovir. This drug is phosphorylated initially by a virus-encoded thymidine kinase and subsequently by cellular kinases to penciclovir triphosphate, which inhibits HSV-1, HSV-2, VZV, and EBV as well as hepatitis B virus (HBV). The serum half-life of penciclovir is 2 h, but the intracellular half-life of penciclovir triphosphate is 7–20 h—markedly longer than that of acyclovir triphosphate. The latter is the basis for the less frequent (twice-daily) dosing schedule for famciclovir than for acyclovir. Penciclovir is eliminated primarily in the urine by both glomerular filtration and tubular secretion. The usually recommended dosage interval should be adjusted for renal insufficiency.

Clinical trials involving immunocompetent adults with herpes zoster showed that famciclovir was superior to placebo in eliciting the resolution of skin lesions and virus shedding and in shortening the duration of postherpetic neuralgia; moreover, administered at 500 mg every 8 h, famciclovir was at least as effective as acyclovir administered at an oral dose of 800 mg five times daily. Famciclovir was also effective in the treatment of herpes zoster in immunosuppressed patients. Clinical trials have demonstrated its effectiveness in the suppression of genital HSV infections for up to 1 year and in the treatment of initial and recurrent episodes of genital herpes. Famciclovir is effective as therapy for mucocutaneous HSV infections in HIV-infected patients. Application of a 1% penciclovir cream reduces the duration of signs and symptoms of herpes labialis in immunocompetent patients (by 0.5–1 day) and has been approved for that purpose by the FDA. Famciclovir is generally well tolerated, with occasional headache, nausea, and diarrhea reported in frequencies similar to those among placebo recipients.

 The administration of high doses of famciclovir for 2 years was associated with an increased incidence of mammary adenocarcinomas in female rats, but the clinical significance of this effect is unknown.

FOSCARNET

Foscarnet (phosphonoformic acid) is a pyrophosphate-containing compound that potently inhibits herpesviruses, including CMV. This drug inhibits DNA polymerases at the pyrophosphate binding site at concentrations that have relatively little effect on cellular polymerases. Foscarnet does not require phosphorylation to exert its antiviral activity and is therefore active against HSV and VZV isolates that are resistant to acyclovir because of deficiencies in thymidine kinase as well as against most ganciclovir-resistant strains of CMV. Foscarnet also inhibits the reverse transcriptase of HIV and is active against HIV in vivo.

Foscarnet is poorly soluble and must be administered intravenously via an infusion pump in a dilute solution over 1–2 h. The plasma half-life of foscarnet is 3–5 h and increases with decreasing renal function because the drug is eliminated primarily by the kidneys. It has been estimated that 10–28% of a dose may be deposited in bone, where it can persist for months. The most common initial dosage of foscarnet is 60 mg/kg every 8 h for CMV and 40 mg/kg every 8 h for HSV. Once the infection is controlled, a maintenance dose of 90–120 mg/kg once a day has been used by some.

Foscarnet is approved for the treatment of CMV retinitis in patients with AIDS and of acyclovir-resistant mucocutaneous HSV infections. In a comparative clinical trial, the drug appeared to be about as efficacious as ganciclovir against CMV retinitis but was associated with a longer survival period, possibly because of its activity against HIV. Intraocular foscarnet has been used to treat CMV retinitis. In addition, foscarnet has been employed to treat acyclovir-resistant HSV and VZV infections as well as ganciclovir-resistant CMV infections, although resistance to foscarnet has been reported in CMV isolates obtained during therapy. Foscarnet has also been used to treat HHV-6B infections in immunosuppressed patients.

The major form of toxicity associated with foscarnet is renal impairment. Thus renal function should be monitored closely, particularly during the initial phase of therapy. Because foscarnet binds divalent metal ions, hypocalcemia, hypomagnesemia, hypokalemia, and hypo- or hyperphosphatemia can develop. Saline hydration and slow infusion appear to protect the patient against nephrotoxicity and electrolyte disturbances. Although hematologic abnormalities have been documented (most commonly anemia), foscarnet is not generally myelosuppressive and can be administered concomitantly with myelosuppressive medications.

TRIFLURIDINE

Trifluridine is a pyrimidine nucleoside active against HSV-1, HSV-2, and CMV. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and trifluridine triphosphate inhibits viral and, to a lesser extent, cellular DNA polymerases. Because of systemic toxicity, trifluridine's use is limited to topical therapy. Trifluridine is approved for treatment of HSV keratitis, against which trials have shown that it is more effective than topical idoxuridine but similar in efficacy to topical vidarabine. The drug has benefited some patients with HSV keratitis who have failed to respond to idoxuridine or vidarabine. Topical application of trifluridine to sites of acyclovir-resistant HSV mucocutaneous infection has also been beneficial in some cases.

VIDARABINE

Vidarabine is a purine nucleoside analogue with activity against HSV-1, HSV-2, VZV, and EBV. Vidarabine inhibits viral DNA synthesis through its 5′-triphosphorylated metabolite, although its precise molecular mechanisms of action are not completely understood. IV-administered vidarabine has been shown to be effective in the treatment of herpes simplex encephalitis, mucocutaneous HSV infections, herpes zoster in immunocompromised patients, and neonatal HSV infections. Its use has been supplanted by that of IV acyclovir, which is more effective and easier to administer. Production of the IV preparation has been discontinued by the manufacturer, but vidarabine is available as an ophthalmic ointment, which is effective in the treatment of HSV keratitis.

AGENTS OF INVESTIGATIVE INTEREST

Maribavir is a benzimidazole that inhibits CMV and EBV. This drug inhibits the CMV UL97 kinase and does not require intracellular phosphorylation for its antiviral activity. Its mechanism of action involves blocking viral DNA synthesis and virion egress. Maribavir is orally administered and has been associated with taste disturbance and diarrhea. In phase 3 studies, it was not efficacious in the prevention of CMV infection in recipients of hematopoietic stem cell and adult liver transplants. However, when used at somewhat higher doses, it may be efficacious for the treatment of refractory or resistant CMV infections in transplant recipients.

Letermovir is an investigational drug with activity against CMV. It is a dihydroquinazoline that acts through inhibition of the viral terminase enzyme complex. This mechanism of action differs from that of ganciclovir, foscarnet, and cidofovir, which inhibit viral DNA polymerase; therefore, letermovir is active against CMV isolates that are resistant to those drugs. It is orally administered and is reportedly well tolerated. Letermovir demonstrated significant activity in preventing CMV reactivation in a recent phase 3 trial in adults undergoing hematopoietic stem cell transplantation and may be clinically available soon.

Inhibition of the helicase–primase heterotrimeric complex of HSV-1 and HSV-2 represents a novel mechanism of action of amenamevir and pritelivir. These drugs are being assessed for prevention and treatment of HSV genital infection. The efficacy of amenamevir, administered as a single oral dose of 1200 mg for recurrent genital herpes, was comparable to that of valacyclovir given for 3 days. Pritelivir has a longer half-life (up to 80 h) and was studied in a placebo-controlled trial of suppression of genital HSV infections. Compared with placebo, pritelivir—a loading dose followed by either a daily oral dose of 75 mg for 4 weeks or a weekly dose of 400 mg for 4 weeks—reduced HSV shedding and days of genital lesions. Additional clinical studies of the helicase–primase inhibitors of HSV are planned.

ANTIVIRAL DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

LAMIVUDINE

Lamivudine is a pyrimidine nucleoside analogue that is used primarily in combination therapy against HIV infection (Chap. 197). Its activity against HBV is attributable to inhibition of the viral DNA polymerase. This drug has also been approved for the treatment of chronic HBV infection. At doses of 100 mg/d given for 1 year to patients positive for hepatitis B e antigen (HBeAg), lamivudine is well tolerated and results in suppression of HBV DNA levels, normalization of serum aminotransferase levels in 40–75% of patients, and reduction of hepatic inflammation and fibrosis in 50–60% of patients. Loss of HBeAg occurs in 30% of patients. Lamivudine also appears to be useful in the prevention or suppression of HBV infection associated with liver transplantation. Resistance to lamivudine develops in 24% of patients treated for 1 year and is associated with changes in the YMDD motif of HBV DNA polymerase. Because of the frequency of development of resistance, lamivudine has been largely supplanted by less-resistance-prone drugs for the treatment of HBV infection.

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is the oral prodrug of adefovir, an acyclic nucleotide analogue of adenosine monophosphate that is active against HBV, HIV, HSV, CMV, and poxviruses. It is phosphorylated by cellular kinases to the active triphosphate moiety, which is a competitive inhibitor of HBV DNA polymerase and results in chain termination after incorporation into nascent viral DNA. Adefovir is administered orally and is eliminated primarily by the kidneys, with a plasma half-life of 5–7.5 h. In clinical studies, therapy with adefovir at a dose of 10 mg/d for 48 weeks resulted in normalization of serum alanine aminotransferase (ALT) levels in 48–72% of patients and improved liver histology in 53–64%; it also resulted in a 3.5- to 3.9-$\log_{10}$ reduction in the number

of HBV DNA copies per milliliter of plasma. Adefovir was effective in treatment-naïve patients as well as in those infected with lamivudine-resistant HBV. Resistance to adefovir appears to develop less readily than that to lamivudine, but adefovir resistance rates of 15–18% have been reported after 192 weeks of treatment and may reach 30% after 5 years. This agent is generally well tolerated. Significant nephrotoxicity attributable to adefovir is uncommon at the dose used in the treatment of HBV infections (10 mg/d) but is a treatment-limiting adverse effect at the higher doses used in therapy for HIV infections (30–120 mg/d). In any case, renal function should be monitored in patients taking adefovir, even at the lower dose. Adefovir is approved only for treatment of chronic HBV infection.

TENOFOVIR

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, a nucleotide analogue of adenosine monophosphate with activity against both retroviruses and hepadnaviruses. In both immunocompetent and immunocompromised patients (including those co-infected with HIV and HBV), tenofovir given at a dose of 300 mg/d for 48 weeks reduced HBV replication by 4.6–6 $\log_{10}$, normalized ALT levels in 68–76% of patients, and improved liver histopathology in 72–74% of patients. Resistance develops uncommonly during ≥2 years of therapy, and tenofovir is active against lamivudine-resistant HBV. The safety profile of tenofovir is similar to that of adefovir, but nephrotoxicity has not been encountered at the dose used for HBV therapy. Tenofovir is approved for the treatment of HIV and chronic HBV infections. Tenofovir alafenamide (TAF) has recently been approved for use in the treatment of HIV and chronic HBV infections. TAF is dosed at 25 mg orally per day and has better renal and bone safety than TDF. Lactic acidosis is an important side effect associated with tenofovir use. **For a more detailed discussion of tenofovir, see Chap. 197.**

ENTECAVIR

Entecavir is a cyclopentyl 2′-deoxyguanosine analogue that inhibits HBV through interaction of entecavir triphosphate with several HBV DNA polymerase functions. At a dose of 0.5 mg/d given for 48 weeks, entecavir reduced HBV DNA copies by 5.0–6.9 $\log_{10}$, normalized serum aminotransferase levels in 68–78% of patients, and improved histopathology in 70–72% of patients. Entecavir inhibits lamivudine-resistant viruses that have M550I or M550V/L526M mutations but only at serum concentrations twenty- or thirtyfold higher than those obtained with the 0.5-mg/d dose. Thus, higher doses of entecavir (1 mg/d) are recommended for the treatment of patients infected with lamivudine-resistant HBV. Development of resistance to entecavir is uncommon in treatment-naïve patients but does occur at unacceptably high rates (43% after 4 years) in patients previously infected with lamivudine-resistant virus. Entecavir-resistant strains appear to be sensitive to adefovir and tenofovir.

Entecavir is highly bioavailable but should be taken on an empty stomach because food interferes with its absorption. The drug is eliminated primarily in unchanged form by the kidneys, and its dosage should be adjusted for patients with Cr_{Cl} values of <50 mL/min. Overall, entecavir is well tolerated, with a safety profile similar to that of lamivudine. As with other anti-HBV treatments, exacerbation of hepatitis may occur when entecavir therapy is stopped. Entecavir is approved for treatment of chronic hepatitis B, including infection with lamivudine-resistant viruses, in adults. Entecavir has some activity against HIV-1 (median effective concentration, 0.026 to >10 μM) but should not be used as monotherapy in HIV-positive patients because of the potential for development of HIV resistance due to the M184V mutation.

TELBIVUDINE

Telbivudine is a β-L enantiomer of thymidine and is a potent, selective inhibitor of HBV. Its active form is telbivudine triphosphate, which inhibits HBV DNA polymerase and causes chain termination but has little or no activity against human DNA polymerase. Administration of telbivudine at an oral dose of 600 mg/d for 52 weeks to patients with chronic hepatitis B resulted in reduction of HBV DNA by 5.2–6.4 $\log_{10}$ copies/mL along with normalization of ALT levels in 74–77% of recipients and improved histopathology in 65–67% of patients. Telbivudine-resistant HBV is generally cross-resistant with lamivudine-resistant virus but is usually susceptible to adefovir. After 2 years of therapy, resistance to telbivudine was noted in isolates from 22% of HBeAg-positive patients and in those from 9% of HBeAg-negative patients.

Orally administered telbivudine is rapidly absorbed; because it is eliminated primarily by the kidneys, its dosage should be reduced in patients with a Cr_{Cl} value of <50 mL/min. Telbivudine is generally well tolerated, but increases in serum levels of creatinine kinases as well as fatigue and myalgias have been observed. As with other anti-HBV drugs, hepatitis may be exacerbated in patients who discontinue telbivudine therapy. Telbivudine has been approved for the treatment of adults with chronic hepatitis B who have evidence of viral replication and either persistently elevated serum aminotransferase levels or histopathologically active disease, but it has not been widely used because of the frequency of development of resistance, as noted above.

INTERFERONS

IFNs are cytokines that exhibit a broad spectrum of antiviral activities as well as immunomodulating and antiproliferative properties. IFNs are not available for oral administration but must be given IM, SC, or IV. Early studies with human leukocyte IFN demonstrated an effect in the prophylaxis of experimentally induced rhinovirus infections in humans and in the treatment of VZV infections in immunosuppressed patients. DNA recombinant technology has made available highly purified α, β, γ, and λ IFNs that have been evaluated in a variety of viral infections. Results of such trials have confirmed the effectiveness of intranasally administered IFN in the prophylaxis of rhinovirus infections, although its use has been associated with nasal mucosal irritation. Studies have also demonstrated a beneficial effect of intralesionally or systemically administered IFNs on genital warts. The effect of systemic administration consists primarily of a reduction in the size of the warts, and this mode of therapy may be useful in persons who have numerous warts that cannot easily be treated by individual intralesional injections. However, lesions frequently recur after either intralesional or systemic IFN therapy is discontinued.

IFNs have undergone extensive study in the treatment of chronic HBV infection. The administration of standard IFN-α2b (5 million units daily or 10 million units three times a week for 16–24 weeks) to patients with stable chronic HBV infection resulted in loss of markers of HBV replication, such as HBeAg and HBV DNA, in 33–37% of cases; 8% of patients also became negative for hepatitis B surface antigen. In most patients who lose HBeAg and HBV DNA markers, serum aminotransferases return to normal levels, and both short- and long-term improvements in liver histopathology have been described. Predictors of a favorable response to standard IFN therapy include low pretherapy levels of HBV DNA, high pretherapy serum levels of ALT, a short duration of chronic HBV infection, and active inflammation in liver histopathology. Poor responses are seen in immunosuppressed patients, including those with HIV infection.

In pegylated IFNs, IFN alphas are linked to polyethylene glycol. This linkage results in slower absorption, decreased clearance, and more sustained serum concentrations, thereby permitting a more convenient, once-weekly dosing schedule; in many instances, pegylated IFN has supplanted standard IFN. After 48 weeks of treatment with 180 μg of pegylated IFN-α2a, HBV DNA was reduced by 4.1–4.5 $\log_{10}$ copies/mL, with normalization of serum ALT levels in 39% of patients and improved histology in 38%. Response rates were somewhat higher when lamivudine was administered with pegylated IFN-α2a. Adverse effects of IFN are common and include fever, chills, myalgia, fatigue, neurotoxicity (manifested primarily as somnolence, depression, anxiety, and confusion), and leukopenia. Autoantibodies (e.g., antithyroid antibodies) can also develop. IFN-α2b and pegylated IFN-α2a are approved for the treatment of patients with chronic hepatitis B. Data supporting the therapeutic efficacy of pegylated interferon-α2b in HBV infection have been published; the drug has not been approved for this indication in the United States but has been approved for treatment of chronic HBV infection in other countries.

Several IFN preparations, including IFN-α2a, IFN-α2b, IFN-alfacon-1, and IFN-αm1 (lymphoblastoid), have been studied as therapy for chronic HCV infections. A variety of monotherapy regimens have been studied, of which the most common for standard IFN is IFN-α2b or -α2a at 3 million units three times per week for 12–18 months. The addition of oral ribavirin to IFN-α2b—either as initial therapy or after failure of IFN therapy alone—results in significantly higher rates of sustained virologic and/or serum ALT responses (40–50%) than are obtained with monotherapy. Comparative studies indicate that pegylated IFN-α2b or -α2a therapy is more effective than standard IFN treatment against chronic HCV infection. The combination of SC pegylated IFN and oral ribavirin results in sustained virologic responses (SVRs) in 42–51% of patients with HCV genotype 1 infection and in 76–82% of patients with genotype 2 or 3 infection. Ribavirin appears to have a small antiviral effect in HCV infection but may also be working through an immunomodulatory effect in combination with IFN. Optimal results with ribavirin appear to be associated with weight-based dosing. Prognostic factors for a favorable response include an age of <40 years, a short duration of infection, low levels of HCV RNA, a lesser degree of liver histopathology, and infection with HCV genotypes other than 1. IFN-alfacon, a synthetic "consensus" α interferon, appears to produce response rates similar to those elicited by standard IFN-α2a or -α2b alone. In 2014, the approval of a polymerase inhibitor, sofosbuvir, and a second-generation protease inhibitor, simeprevir, as well as the successful development of other direct-acting antiviral agents (DAAs) active against HCV led to revised recommendations for treatment of hepatitis C with DAA regimens not requiring IFN or ribavirin in most cases. DAA regimens have been developed that are active against all HCV genotypes (see below and Table 186-1).

IFN-α and pegylated IFN-α are active against hepatitis D, but high doses are required (9 million units three times per week for 48 weeks). IFN-α elicited an SVR in 25–30% of patients, whereas pegylated IFN-α had a variable effect, evoking an SVR in 17–43% of patients. However, long-term biochemical and histologic improvements have been seen, even in the absence of sustained inhibition of viral replication.

POLYMERASE INHIBITORS

Sofosbuvir is the prodrug of a uridine nucleoside inhibitor of HCV RNA NS5B polymerase. Its metabolism to the active uridine nucleoside triphosphate results in chain termination. Sofosbuvir is active against all HCV genotypes (1–6) and has a median effective concentration (EC_{50}) of 0.7–2.6 μM against NS5B. Resistance to sofosbuvir is conferred by an S282T substitution in NS5B, but clinically expressed resistance to treatment has only rarely been encountered in patients who receive sofosbuvir.

Sofosbuvir is administered orally and is unaffected by food. After oral administration, plasma concentrations of sofosbuvir and of its active metabolite peak in 0.5–2 h and 2–4 h, respectively. Approximately 61–65% of sofosbuvir is bound in plasma proteins, but very little of the active metabolite is bound. Both sofosbuvir and its active metabolite are cleared renally, with $t_{1/2}$ values of 0.4 and 27 h, respectively. Sofosbuvir is relatively free from clinically significant drug interactions, although P-glycoprotein inducers can reduce sofosbuvir concentrations.

Sofosbuvir is generally well tolerated and has not been associated with significant toxicity. The most common side effects in recipients of sofosbuvir have been attributable to concomitant administration of IFN and ribavirin in combination clinical trials (see below).

Sofosbuvir has been studied in a variety of controlled and open-label clinical trials. In late 2013, the results of these trials led to its recommendation—in triple combination with pegylated IFN and ribavirin—as first-line treatment for chronic hepatitis due to HCV genotypes 1, 4, 5, and 6, in which SVR rates among treatment-naïve patients were 89–97%. For HCV genotypes 2 and 3, IFN-free regimens consisting of sofosbuvir and ribavirin have been recommended, with SVR rates among treatment-naïve patients of 93% for genotype 2 and 61% for genotype 3.

PROTEASE INHIBITORS

BOCEPREVIR, TELAPREVIR

This drug class is specifically designed to inhibit the 3/4A (NS3/4A) HCV protease. These agents resemble the HCV polypeptide and, when processed by the viral protease, form a covalent bond with the catalytic NS3 serine residues, block further activity, and prevent proteolytic cleavage of the HCV polyprotein into NS4A, NS4B, NS5A, and NS5B proteins. Boceprevir and telaprevir are linear ketoamide compounds that are active against HCV genotype 1 (1b > 1a) and much less so against genotypes 2 and 3. These first-generation protease inhibitors received approval for combination therapy (with IFN and ribavirin) for genotype 1 infection. Neither boceprevir nor telaprevir is now recommended for the treatment of hepatitis C. These drugs have been supplanted by sofosbuvir and by simeprevir, a second-generation protease inhibitor with improved pharmacokinetic properties, fewer drug–drug interactions, and less overall toxicity (see below).

SIMEPREVIR

Simeprevir is a second-generation NS3/4A protease inhibitor with antiviral activity against HCV genotype 1 (1b > 1a); the EC_{50} is 9.4 nM in an HCV genotype 1b replicon. The NS3 polymorphism Q80K, which is present in approximately one-third of patients carrying HCV genotype 1b, increases the EC_{50} by elevenfold and results in clinical resistance to simeprevir. Thus testing for Q80K should be carried out if treatment with simeprevir is being considered. Cross-resistance occurs between simeprevir and the first-generation protease inhibitors boceprevir and telaprevir.

Simeprevir is orally administered as a 150-mg capsule, and its bioavailability is increased by administration with food. The serum concentration peaks 4–6 h after oral administration. The drug's elimination half-life is 10–13 h in healthy individuals and 41 h in patients with hepatitis C. Simeprevir is nearly entirely bound by plasma proteins and cleared by biliary excretion. Because there is no renal excretion, dose adjustments are not required in the presence of renal dysfunction. Simeprevir is metabolized by hepatic CYP3A and therefore should not be administered to patients with decompensated liver function.

Because of its metabolism by cytochrome P450 3A (CYP3A), simeprevir interacts with drugs that induce or inhibit CYP3A, and these interactions may concomitantly increase or reduce plasma concentrations of simeprevir. Administration of simeprevir may also increase plasma concentrations of drugs that are substrates for hepatic organic anion-transporting polypeptide 1B1 or 1B3 or for P glycoprotein transporters.

Toxicity observed during clinical trials with simeprevir included photosensitivity (usually mild or moderate) in 28% of recipients and reversible hyperbilirubinemia (both conjugated and unconjugated), which was generally mild to moderate. Most of the other adverse effects seen in clinical trials with simeprevir were attributable to concomitant administration of IFN and ribavirin.

Simeprevir has been recommended as a component of alternative treatment—in combination with pegylated IFN and ribavirin—of chronic infection with HCV genotypes 1 and 4. Daily simeprevir, daily ribavirin, and weekly pegylated IFN for 12 weeks followed by another 12 weeks of pegylated IFN and ribavirin resulted in an SVR of 80% in the absence of the Q80K variant. In general, simeprevir-based triple therapy appeared to be 10% less likely to yield an SVR than sofosbuvir-based therapy and more likely to cause adverse effects. However, for prior nonresponders or partial responders to pegylated IFN, the IFN-free regimen of simeprevir, sofosbuvir, and ribavirin shows promise.

PARITAPREVIR/RITONAVIR AND GRAZOPREVIR

These drugs are more recently developed NS3/4A protease inhibitors. Paritaprevir is used with ritonavir and ombitasvir (an NS5A inhibitor; see below) as a fixed-dose combination and may be used with dasabuvir and ribavirin. This combination is active against HCV genotypes 1a and 1b. Ritonavir is used to increase the levels of paritaprevir. Ritonavir is a potent CYP3A inhibitor and may impact the metabolism of other

medications handled by this pathway. Grazoprevir is used with elbasvir (an NS5A inhibitor; see below) in a fixed-dose combination and is approved by the FDA for treatment of HCV genotypes 1 and 4.

NS5A INHIBITORS

NS5A is a membrane-associated phosphoprotein that is part of the HCV RNA replication complex and is essential for viral replication and assembly. Ledipasvir, velpatasvir, daclatasvir, elbasvir, and ombitasvir are all NS5A inhibitors. Each of these agents has largely been developed and studied with specific partner drugs as noted above (Table 186-1).

Treatment of HCV has been associated with flaring of chronic HBV infection. Monitoring for HBV activation in this context is warranted. In the setting of significant renal dysfunction (Cr_{Cl}, <30 mL/min), few data are available to guide use of these newer DAAs. However, studies are ongoing to assess elbasvir/grazoprevir in this context, as these agents are eliminated through the feces and are not renally handled. Emergence of HCV resistance-associated substitutions to the DAAs have been documented. The impact on treatment is under active investigation and at this time is relevant mostly to those patients in whom prior treatment has failed.

These newer DAA regimens allow shorter courses of therapy, improved tolerability, and reduced resistance. For updated information, readers should consult *http://www.hcvguidelines.org/*.

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Section 12 Infections Due to DNA Viruses

187 Herpes Simplex Virus Infections

Lawrence Corey

DEFINITION

Herpes simplex viruses (HSV-1, HSV-2; *Herpesvirus hominis*) produce a variety of infections involving mucocutaneous surfaces, the central nervous system (CNS), and—on occasion—visceral organs. Prompt recognition and treatment reduce the morbidity and mortality rates associated with HSV infections.

ETIOLOGIC AGENT

The genome of HSV is a 152-kb linear, double-stranded DNA molecule (molecular weight, ~100 × 10^6) that encodes >90 transcription units with 84 identified proteins. The genomic structures of the two HSV subtypes are similar. The overall genomic sequence homology between HSV-1 and HSV-2 is ~50%, whereas the proteome homology is >80%. The homologous sequences are distributed over the entire genome map, and most of the polypeptides specified by one viral type are antigenically related to polypeptides of the other viral type. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, however, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic assays that distinguish between the two viral subtypes. Either restriction endonuclease analysis or sequencing of viral DNA can be used to distinguish between the two subtypes and among strains of each subtype. Recombinant viruses (HSV-1/HSV-2) do circulate in nature. The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns or genomic sequences. Moreover, epidemiologically related sources, such as sexual partners, mother–infant pairs, or persons involved in a common-source outbreak, can be inferred from such patterns. Deep sequencing of sequential isolates suggests that more than one variant of HSV-1 or HSV-2 can be found in a single individual.

The viral genome is packaged in a regular icosahedral protein shell (capsid) composed of 162 capsomeres **(see Fig. 185-1)**. The outer covering of the virus is a lipid-containing membrane (envelope) acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Between the capsid and lipid bilayer of the envelope is the tegument. Viral replication has both nuclear and cytoplasmic phases. Initial attachment to the cell membrane involves interactions of viral glycoproteins C and B with several cellular heparan sulfate–like surface receptors. Subsequently, viral glycoprotein D binds to cellular co-receptors that belong to the tumor necrosis factor receptor family of proteins, the immunoglobulin superfamily (nectin family), or both. The ubiquity of these receptors contributes to the wide host range of herpesviruses. HSV replication is highly regulated. After fusion and entry, the nucleocapsid enters the cytoplasm and several viral proteins are released from the virion. Some of these viral proteins shut off host protein synthesis (by increasing cellular RNA degradation), whereas others "turn on" the transcription of early genes of HSV replication. These early gene products, designated *α genes*, are required for synthesis of the subsequent polypeptide group: the β polypeptides, many of which are regulatory proteins and enzymes required for DNA replication. Most current antiviral drugs interfere with β proteins, such as viral DNA polymerase. The third (γ) class of HSV genes requires viral DNA replication for expression and encodes most structural proteins specified by the virus. New antiviral drugs directed at viral assembly and release are under development.

After viral genome replication and structural protein synthesis, nucleocapsids are assembled in the cell's nucleus. Envelopment occurs as the nucleocapsids bud through the inner nuclear membrane into the perinuclear space. In some cells, viral replication in the nucleus forms two types of inclusion bodies: type A basophilic Feulgen-positive bodies that contain viral DNA and eosinophilic inclusion bodies that are devoid of viral nucleic acid or protein and represent a "scar" of viral infection. Enveloped virions are then transported via the endoplasmic reticulum and the Golgi apparatus to the cell surface.

Viral genomes are maintained by some neuronal cells in a repressed state called *latency*. Latency, which is associated with transcription of only a limited number of virus-encoded RNAs, accounts for the presence of viral DNA and RNA in neural tissue at times when infectious virus cannot be isolated. Maintenance and growth of neural cells from latently infected ganglia in tissue culture result in production of infectious virions (*explantation*) and in subsequent permissive infection

of susceptible cells (*co-cultivation*). Activation of the viral genome may then occur, resulting in *reactivation*—the normal pattern of regulated viral gene expression and replication and HSV release. The release of virions from the neuron follows a complex process of anterograde transport down the length of neuronal axons. In experimental animals, ultraviolet light, systemic and local immunosuppression, and trauma to the skin or ganglia are associated with reactivation.

Three noncoding RNA latency-associated transcripts (LATs) are found in the nuclei of latently infected neurons. Microdissection plus real-time polymerase chain reaction (PCR) of individual neurons from cadaveric trigeminal ganglia explants revealed that many more neurons (2–10%) harbor HSV than would be predicted by in situ hybridization studies for LATs. Viral copy number is highly variable between neurons, with extremely high levels in certain neurons, and HSV DNA copy numbers are similar in LAT-positive and LAT-negative neurons. These findings add to the uncertainty about the role that LATs play in preventing reactivation. Deletion mutants of the LAT region exhibit reduced efficiency in their later reactivation. Substitution of HSV-1 LATs for HSV-2 LATs induces an HSV-1 reactivation pattern. These data indicate that LATs apparently maintain—rather than establish—latency. HSV-1 LATs promote the survival of acutely infected neurons, perhaps by inhibiting apoptotic pathways. LAT transcript abundance and low genome-copy number correlate with subnuclear positioning of HSV genomes around the centromere. Indeed, chromatization of HSV DNA appears to play a vital role in silencing expression of lytic replication genes. While the mechanism of latency and reactivation remains elusive, data suggest that viral micro-RNA appears to silence expression of the key neurovirulence factor infected-cell protein 34.5 (ICP34.5) and to bind in an antisense configuration to the immediate-early protein ICP0 messenger RNA to prevent expression, which is vital to HSV reactivation. Although certain viral transcripts are known to be necessary for reactivation from latency, the molecular mechanisms of HSV latency are not fully understood, and strategies to interrupt or maintain latency in neurons are in developmental stages.

While latency is the predominant state of virus on a per-neuron basis, the high frequency of oral and genital tract reactivation for HSV-1 and HSV-2 suggests that the viruses are rarely quiescent within the entire biomass of ganglionic tissue. There is increasing recognition that HSV infection of the autonomic ganglia plays an important role in both initial and reactivation infections. In fact, deaths of animals from HSV-2 infection appear to be related to autonomic dysfunction of the bowel. Both HSV-1 and HSV-2 are shed subclinically. Most persons infected with HSV-2 and HSV-1 have frequent subclinical bursts of reactivation lasting 2–4 h, and the host tissue-based immune system can contain viral reactivation in the tissue before the development of clinical reactivation.

PATHOGENESIS

Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus into cells of the epidermis and dermis and initiation of viral replication therein. HSV infections are usually acquired subclinically. Whether clinical or subclinical, HSV acquisition is associated with sufficient viral replication to permit infection of sensory and/or autonomic nerve endings. On entry into the neuronal cell, the virus—or, more likely, the nucleocapsid—is transported intra-axonally to the nerve cell bodies in ganglia. Viral particles tether onto cellular proteins that motor along microtubules from axon tips (neurite endings) to neuronal cell bodies. In humans, the transit interval of spread to the ganglia after virus inoculation into peripheral tissue is unknown. During the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue. Virus then spreads to other mucocutaneous surfaces through centrifugal migration of infectious virions via peripheral sensory nerves. This mode of spread helps explain the large surface area involved, the high frequency of new lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral–labial HSV infection, and the ability to recover virus from neural tissue distant from neurons innervating the inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease. Recent studies have demonstrated HSV viremia—another mechanism for extension of infection throughout the body—in ~30–40% of persons with primary HSV-2 infection; latent infection with both viral subtypes in both sensory and autonomic ganglia has been demonstrated. For HSV-1 infection, trigeminal ganglia are most commonly infected, although extension to the inferior and superior cervical ganglia also occurs. With genital infection, sacral nerve root ganglia (S2–S5) are most commonly affected. Autonomic ganglia, pelvic nerves, and vaginal nerve roots are commonly infected.

After resolution of primary disease, infectious HSV can no longer be cultured from the ganglia; however, neuronal infection, as defined by the presence of viral DNA, persists in ganglionic cells in the anatomic regions of the initial infection. The mechanism of reactivation from latency is unknown, although increasingly evidence of limited viral genes or microRNAs is identified in latently infected neurons. Evidence exists for viral antigen and activated host T cells at the ganglia and periphery, and immune responses in ganglia as well as peripheral tissue appear to influence the frequency and severity of HSV reactivation. HSV-specific T cells have been recovered from peripheral-nerve root ganglia. Many of these resident CD8+ T cells are juxtaposed with latently HSV-1-infected neurons in the trigeminal ganglia and can block reactivation with both interferon (IFN) γ release and granzyme B–mediated degradation of the immediate-early protein ICP4. In addition, there appears to be a latent viral load in the ganglia that correlates positively with the number of neurons infected and the rate of reactivation but inversely with the number of T cells present. It is not known whether reactivating stimuli transiently suppress these immune cells, independently upregulate transcription of lytic genes, or both. Moreover, host containment in the mucosa has been demonstrated. Once virus reaches the dermal–epidermal junction, there are three possible outcomes: (1) rapid host containment of infection near the site of reactivation; (2) spread of small amounts of virus into the epidermis, with a micro-ulceration associated with low-titer subclinical shedding; and (3) widespread replication and necrosis of epithelial cells and subsequent clinical recurrence (the latter defined clinically by a skin blister and ulceration). Histologically, herpetic lesions involve a thin-walled vesicle or ulceration in the basal region, multinucleated cells that may include intranuclear inclusions, necrosis, and an acute inflammatory infection. Re-epithelialization occurs once viral replication is restricted, almost always in the absence of a scar.

Analysis of the DNA from sequential isolates of HSV or from isolates from multiple infected ganglia in any one individual has revealed similar, if not identical, restriction endonuclease or DNA sequence patterns in most persons. As more sensitive genomic technologies are developed, evidence of multiple strains of the same subtype is increasingly being reported. For example, infection of individual neurons with multiple strains of drug-susceptible and drug-resistant virus in severely immunosuppressed patients indicates that ganglia can be reseeded during chronic infection. Because exposure to mucosal shedding is relatively common during a person's lifetime, current data suggest that exogenous infection with different strains of the same subtype does occur.

IMMUNITY

Host responses influence the acquisition of HSV disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experimental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce titers of virus in neural tissue. Some clinical manifestations of HSV appear to be related to the host immune response (e.g., stromal opacities associated with recurrent herpetic keratitis). The surface viral glycoproteins have been shown to be targets of antibodies that mediate neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity). Monoclonal antibodies to HSV viral glycoproteins have,

in experimental infections, conferred protection against subsequent neurologic disease or ganglionic latency. In humans, however, subunit glycoprotein vaccines have been largely ineffective in reducing acquisition of infection. Multiple cell populations, including neutrophils, macrophages, and a variety of T lymphocytes, play a role in host defenses against HSV infections, as do lymphokines generated by T lymphocytes. In animals, passive transfer of primed lymphocytes confers protection from subsequent HSV challenge. Maximal protection usually requires the activation of multiple T-cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter may confer protection by the antigen-stimulated release of lymphokines (e.g., IFNs), which in turn have a direct antiviral effect and both activate and enhance a variety of specific and nonspecific effector cells. The HSV virion contains a variety of genes that are directed at the inhibition of host responses. These include gene no. 12 (*US-12*), which can bind to the cellular transporter-activating protein TAP-1 and reduce the ability of this protein to bind HSV peptides to human leukocyte antigen class I, thereby reducing recognition of viral proteins by cytotoxic T cells of the host. This effect can be overcome by the addition of IFN-γ, but this reversal requires 24–48 h; thus, the virus has time to replicate and invade other host cells. Entry of infectious HSV-1 and HSV-2 inhibits several signaling pathways of both CD4+ and CD8+ T cells, leading to their functional impairment in killing and influencing the spectrum of their cytokine secretion.

HSV-specific CD8+ T-cell responses appear to be an important component in viral clearance from lesions. Immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. HSV-specific CD8+ T cells have been shown to persist in the genital skin at the dermal–epidermal junction contiguous to neuronal endings for months after lesion resolution. Even during clinical quiescence, these CD8+ T cells make both antiviral and cytotoxic proteins indicative of immune surveillance. These resident memory CD8+ T cells appear to be "first responders" capable of controlling viral reactivation at the site of viral release into the dermis. This rapid "on and off" interplay between the virus and the host helps explain the variability in clinical disease severity between episodes in any single individual. Differences of 30–60 min in host responses can result in 100- to 1000-fold differences in viral levels and can determine whether an episode of disease is subclinical or clinical.

There is a strong association between the magnitude of the CD8+ T lymphocyte response and the clearance of virus from genital lesions. The location, effectiveness, and longevity of the T lymphocytes (and perhaps of other immune effector cells) may be important in the expression of disease and the likelihood of transmission over time.

EPIDEMIOLOGY

Seroepidemiologic studies have documented HSV infections worldwide. The past 15 years have shown that the prevalence of HSV-2 is even higher in the developing than in the developed world. In sub-Saharan Africa, HSV-2 seroprevalence among pregnant women may approach 60%, and annual acquisition rates among teenage girls may verge on 20%. The global incidence has been estimated at ~23.6 million infections per year, with >400 million infected persons worldwide. As in the developed world, the rate of HSV-2 coital acquisition as well as the serologic prevalence is higher among women than among men. Most of this HSV-2 acquisition is preceded by acquisition of HSV-1; the frequency of genital HSV-1 in the developing world is low at present.

Infection with HSV-1 is acquired more frequently and earlier in life than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life. Antibodies to HSV-2 are not detected routinely until puberty. Antibody prevalence rates correlate with past sexual activity and vary greatly among different population groups. There is evidence that the prevalence of HSV-2 has decreased slightly over the past decade or so in the United States. Serosurveys indicate that 15–20% of the U.S. population has antibodies to HSV-2. In most routine obstetric and family planning clinics, 25% of women have HSV-2 antibodies, although only 10% of those who are seropositive for HSV-2 report a history of genital lesions. As many as 50% of heterosexual adults attending sexually transmitted disease clinics have antibodies to HSV-2. A wide variety of serologic surveys has catalogued the widespread epidemic of HSV-2 in Central America, South America, and Africa. In Africa, HSV-2 seroprevalence has ranged from 40 to 70% in obstetric and other sexually experienced populations. Antibody prevalence rates average ~5–10% higher among women than among men.

Many studies continue to show that both incident and—more important—prevalent HSV-2 infection enhances the acquisition rate of HIV-1. More specifically, HSV-2 infection is associated on a population basis with a two- to fourfold increase in HIV-1 acquisition. This association has been amply demonstrated in heterosexual men and women in both the developed and the developing worlds. Epidemiologically, regions of the world with high HSV-2 prevalence and selected populations within such regions have a higher population-based incidence of HIV-1.

An important observation is that HSV-2 facilitates the spread of HIV into low-risk populations; prevalent HSV-2 appears to increase the risk of HIV infection by seven- to ninefold on a per-coital basis. Mathematical models suggest that ~33–50% of HIV-1 infections may be attributable to HSV-2 both in men who have sex with men (MSM) and in sub-Saharan Africa. In addition, HSV-2 is more frequently reactivated in and transmitted by persons co-infected with HIV-1 than in persons not co-infected. Thus, most areas of the world with a high HIV-1 prevalence also have a high HSV-2 prevalence. The shedding of HIV-1 virions from herpetic lesions in the genital region facilitates the spread of HIV through sexual contact. HSV-2 reactivation is associated with a localized persistent inflammatory response consisting of high concentrations of CCR5-enriched CD4+ T cells as well as inflammatory dendritic cells in the submucosa of the genital skin. These cells can support HIV infection and replication and thus are likely to account for the increased risk of HIV acquisition among persons with genital herpes. Unfortunately, antiviral therapy does not reduce this subclinical postreactivation inflammation, probably because of the inability of current antiviral agents to prevent the release of small amounts of HSV antigen into the genital mucosa.

Several studies suggest that many cases of "asymptomatic" genital HSV-2 infection are, in fact, simply unrecognized or confined to anatomic regions of the genital tract that are not easily visualized. Asymptomatic seropositive persons shed virus on mucosal surfaces almost as frequently as do those with symptomatic disease. This large reservoir of unidentified carriers of HSV-2 and the frequent asymptomatic reactivation of the virus from the genital tract have fostered the continued spread of genital herpes throughout the world.

HSV infections occur throughout the year. Transmission can result from contact with persons who have active ulcerative lesions or with persons who have no clinical manifestations of infection but who are shedding HSV from mucocutaneous surfaces. HSV reactivation on genital skin and mucosal surfaces is common. In fact, recent studies indicate that most HSV-1 and HSV-2 episodes last <4–6 h; thus, replication of the virus and clearance by the host are rapid. Even with once-daily sampling, HSV DNA can be detected on 20–30% of days by PCR. Corresponding figures for HSV-1 in oral secretions are similar. Rates of shedding are highest during the initial years after acquisition, with viral shedding occurring on as many as 30–50% of days during this period. Immunosuppressed patients shed HSV from mucosal sites at an even higher frequency (20–80% of days). These high rates of mucocutaneous reactivation suggest that exposure to HSV from sexual or other close contact (kissing, sharing of glasses or silverware) is common and help explain the continuing spread and high seroprevalence of HSV infections worldwide. Reactivation rates vary widely among individuals. Among HIV-positive patients, a low CD4+ T-cell count and a high HIV-1 load are associated with increased rates of HSV reactivation. Daily antiviral chemotherapy for HSV-2 infection can reduce shedding rates but does not eliminate shedding, as measured by PCR or culture.

CLINICAL SPECTRUM

HSV has been isolated from nearly all visceral and mucocutaneous sites. The clinical manifestations and course of HSV infection depend on the anatomic site involved, the age and immune status of the host,

and the antigenic type of the virus. Primary HSV infections (i.e., first infections with either HSV-1 or HSV-2 in which the host lacks HSV antibodies in acute-phase serum) are frequently accompanied by systemic signs and symptoms. Compared with recurrent episodes, primary infections, which involve both mucosal and extramucosal sites, are characterized by a longer duration of symptoms and virus isolation from lesions. The incubation period ranges from 1 to 26 days (median, 6–8 days). Both viral subtypes can cause genital and oral–facial infections, and the infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation of infection is influenced by anatomic site and virus type. Genital HSV-2 infection is twice as likely to reactivate and recurs 8–10 times more frequently than genital HSV-1 infection. Conversely, oral–labial HSV-1 infection recurs more frequently than oral–labial HSV-2 infection. Asymptomatic shedding rates follow the same pattern.

Oral–Facial Infections Gingivostomatitis and pharyngitis are the most common clinical manifestations of first-episode HSV-1 infection, whereas recurrent herpes labialis is the most common clinical manifestation of reactivation HSV-1 infection. HSV pharyngitis and gingivostomatitis usually result from primary infection and are most common among children and young adults. Clinical symptoms and signs, which include fever, malaise, myalgias, inability to eat, irritability, and cervical adenopathy, may last 3–14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and facial area. HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. Lesions of the tongue, buccal mucosa, or gingiva may occur later in the course in one-third of cases. Fever lasting 2–7 days and cervical adenopathy are common. It can be difficult to differentiate HSV pharyngitis clinically from bacterial pharyngitis, *Mycoplasma pneumoniae* infections, and pharyngeal ulcerations of noninfectious etiologies (e.g., Stevens-Johnson syndrome). No substantial evidence suggests that reactivation of oral–labial HSV infection is associated with symptomatic recurrent pharyngitis.

Reactivation of HSV from the trigeminal ganglia may be associated with asymptomatic virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50–70% of seropositive patients undergoing trigeminal nerve-root decompression and 10–15% of those undergoing dental extraction develop oral–labial HSV infection a median of 3 days after these procedures. Clinical differentiation of intraoral mucosal ulcerations due to HSV from aphthous, traumatic, or drug-induced ulcerations is difficult.

In immunosuppressed patients, HSV infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. The lesions of HSV mucositis are clinically similar to mucosal lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infections. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. HSV and *Candida* infections often occur concurrently. Systemic antiviral therapy speeds the rate of healing and relieves the pain of mucosal HSV infections in immunosuppressed patients. The frequency of HSV reactivation during the early phases of transplantation or induction chemotherapy is high (50–90%), and prophylactic systemic antiviral agents such as IV acyclovir and penciclovir or the oral congeners of these drugs are used to reduce reactivation rates. Patients with atopic eczema may also develop severe oral–facial HSV infections (*eczema herpeticum*), which may rapidly involve extensive areas of skin and occasionally disseminate to visceral organs. Extensive eczema herpeticum has resolved promptly with the administration of IV acyclovir. Erythema multiforme may also be associated with HSV infections **(see Figs. 52-9 and A1-24)**; some evidence suggests that HSV infection is the precipitating event in ~75% of cases of cutaneous erythema multiforme. HSV antigen has been demonstrated both in circulatory immune complexes and in skin lesion biopsy samples from these cases. Patients with severe HSV-associated erythema multiforme are candidates for chronic suppressive oral antiviral therapy.

HSV-1 and varicella-zoster virus (VZV) have been implicated in the etiology of Bell's palsy (flaccid paralysis of the mandibular portion of the facial nerve). Some but not all trials have documented quicker resolution of facial paralysis with the prompt initiation of antiviral therapy, with or without glucocorticoids. However, other trials have shown little benefit. A recent Cochrane review indicates that there are advantages to the use of both antiviral drugs and glucocorticoids for moderate to severe Bell's palsy. Glucocorticoids alone are preferred for mild disease.

Genital Infections First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms. Widely spaced bilateral lesions of the external genitalia are characteristic **(Fig. 187-1)**. Lesions may be present in varying stages, including vesicles, pustules, or painful erythematous ulcers. The cervix and urethra are involved in >80% of women with first-episode infections. First episodes of genital herpes in patients who have had prior HSV-1 infection are associated with systemic symptoms in a few cases and with faster healing than primary genital herpes. Subclinical DNAemia has been found in ~30% of cases of true primary genital herpes. The clinical courses of acute first-episode genital herpes are similar for HSV-1 and HSV-2 infection. However, the recurrence rates of genital disease differ with the viral subtype: the 12-month recurrence rates among patients with first-episode HSV-2 and HSV-1 infections are ~90 and ~55%, respectively (median number of recurrences, 4 and <1, respectively). Recurrence rates for genital HSV-2 infections vary greatly among individuals and over time within the same individual. HSV has been isolated from the urethra and urine of men and women without external genital lesions. A clear mucoid discharge and dysuria are characteristics of symptomatic HSV urethritis. HSV has been isolated from the urethra of 5% of women with the dysuria–frequency syndrome. Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and by prostatitis in men. About 15% of cases of HSV-2 acquisition are associated with nonlesional clinical syndromes, such as aseptic meningitis, cervicitis, or urethritis. A more complete discussion of the differential diagnosis of genital herpes is presented in **Chap. 131**.

Both HSV-1 and HSV-2 can cause symptomatic or asymptomatic rectal and perianal infections. HSV proctitis is usually associated with rectal intercourse. However, subclinical perianal shedding of HSV is detected in women and men who report no rectal intercourse. This phenomenon is due to the establishment of latency in the sacral

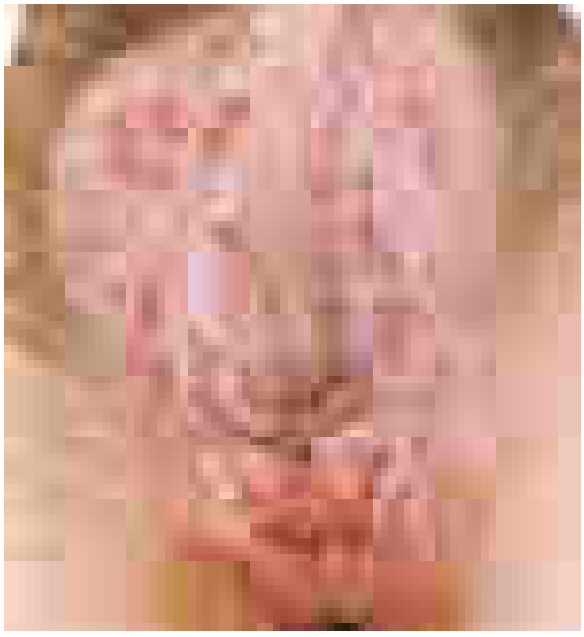

FIGURE 187-1 Genital herpes: primary vulvar infection, with multiple, extremely painful, punched-out, confluent, shallow ulcers on the edematous vulva and perineum. Micturition is often very painful. Associated inguinal lymphadenopathy is common. *(Reprinted with permission from K Wolff et al: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 5th ed. New York, McGraw-Hill, 2005.)*

dermatome from prior genital tract infection, with subsequent reactivation in epithelial cells in the perianal region. Such reactivations are often subclinical. Symptoms of HSV proctitis include anorectal pain, anorectal discharge, tenesmus, and constipation. Sigmoidoscopy reveals ulcerative lesions of the distal 10 cm of the rectal mucosa. Rectal biopsies show mucosal ulceration, necrosis, polymorphonuclear and lymphocytic infiltration of the lamina propria, and (in occasional cases) multinucleated intranuclear inclusion-bearing cells. Perianal herpetic lesions are also found in immunosuppressed patients receiving cytotoxic therapy. Extensive perianal herpetic lesions and/or HSV proctitis is common among patients with HIV infection.

Herpetic Whitlow Herpetic whitlow—HSV infection of the finger—may occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface or by direct introduction of virus into the hand through occupational or some other type of exposure. Clinical signs and symptoms include abrupt-onset edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy and/or transmission) is essential. Antiviral chemotherapy is usually recommended (see below).

Herpes Gladiatorum HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during wrestling. Several recent outbreaks have illustrated the importance of prompt diagnosis and therapy to contain the spread of this infection.

Eye Infections HSV infection of the eye is the most common cause of corneal blindness in the United States. HSV keratitis presents as an acute onset of pain, blurred vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea. Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye. Debridement, topical antiviral treatment, and/or IFN therapy hastens healing. However, recurrences are common, and the deeper structures of the eye may sustain immunopathologic injury. Stromal keratitis due to HSV appears to be related to T cell–dependent destruction of deep corneal tissue. An HSV-1 epitope that is autoreactive with T cell–targeting corneal antigens has been postulated to be a factor in this infection. Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection. HSV and VZV can cause acute necrotizing retinitis as an uncommon but severe manifestation.

Central and Peripheral Nervous System Infections HSV accounts for 10–20% of all cases of sporadic viral encephalitis in the United States. The estimated incidence is ~2.3 cases per 1 million persons per year. Cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5–30 and >50 years of age. HSV-1 causes >95% of cases.

The pathogenesis of HSV encephalitis varies. In children and young adults, primary HSV infection may result in encephalitis; presumably, exogenously acquired virus enters the CNS by neurotropic spread from the periphery via the olfactory bulb. However, most adults with HSV encephalitis have clinical or serologic evidence of mucocutaneous HSV-1 infection before the onset of CNS symptoms. In ~25% of the cases examined, the HSV-1 strains from the oropharynx and brain tissue of the same patient differ; thus some cases may result from reinfection with another strain of HSV-1 that reaches the CNS. Two theories have been proposed to explain the development of actively replicating HSV in localized areas of the CNS in persons whose ganglionic and CNS isolates are similar. Reactivation of latent HSV-1 infection in trigeminal or autonomic nerve roots may be associated with extension of virus into the CNS via nerves innervating the middle cranial fossa. HSV DNA has been demonstrated by DNA hybridization in brain tissue obtained at autopsy—even from healthy adults. Thus, reactivation of long-standing latent CNS infection may be another mechanism for the development of HSV encephalitis.

Recent studies have identified genetic polymorphisms among families with a high frequency of HSV encephalitis. Peripheral-blood mononuclear cells from these patients (predominantly children) appear to secrete reduced levels of IFN in response to HSV. Genetic mutations in *TLR3* documented in patients with HSV encephalitis suggest that some cases of sporadic HSV encephalitis may be related to host genetic determinants.

The clinical hallmark of HSV encephalitis has been the acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe **(Fig. 187-2)**. Clinical differentiation of HSV encephalitis from other viral encephalitides, focal infections, or noninfectious processes is difficult. Elevated cerebrospinal fluid (CSF) protein levels, leukocytosis (predominantly lymphocytes), and red blood cell counts due to hemorrhagic necrosis are common. While brain biopsy has been the gold standard for defining HSV encephalitis, a highly sensitive and specific PCR for detection of HSV DNA in CSF has largely replaced biopsy for defining CNS infection. Although titers of antibody to HSV in CSF and serum increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and therefore, although useful in retrospect, generally are not helpful in establishing an early clinical diagnosis. In rare cases, demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive; examination of such tissue also provides the opportunity to identify alternative, potentially treatable causes of encephalitis. Antiviral chemotherapy with acyclovir reduces the rate of death from HSV encephalitis. Most authorities recommend the administration of IV acyclovir to patients with presumed HSV encephalitis until the diagnosis is confirmed or an alternative diagnosis is made. All confirmed cases should be treated with IV acyclovir (30 mg/kg per day in three divided doses for 14–21 days). After the completion of therapy, the clinical recurrence

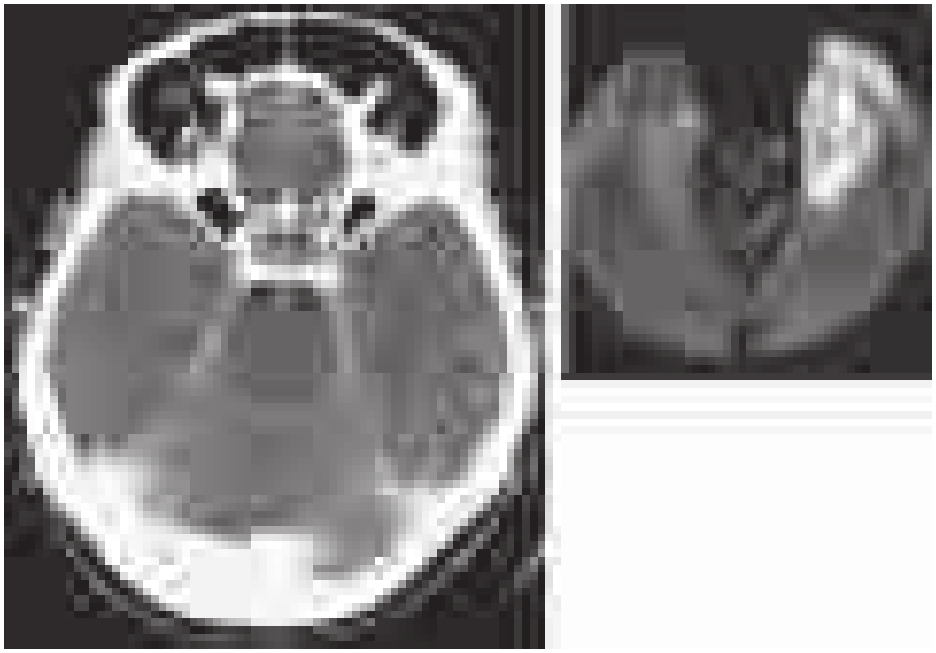

FIGURE 187-2 Computed tomography and diffusion-weighted magnetic resonance imaging scans of the brain of a patient with left-temporal-lobe herpes simplex virus encephalitis.

of encephalitis requiring more treatment has been reported. For this reason, some authorities prefer to treat initially for 21 days, and many continue therapy until HSV DNA has been eliminated from the CSF. Even with therapy, neurologic sequelae are common, especially among persons >50 years of age.

HSV DNA has been detected in CSF from 3 to 15% of persons presenting to the hospital with aseptic meningitis. HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute, self-limited disease manifested by headache, fever, and mild photophobia and lasting 2–7 days. Lymphocytic pleocytosis in the CSF is characteristic. Neurologic sequelae of HSV meningitis are rare. HSV is the most commonly identified cause of recurrent lymphocytic meningitis (*Mollaret's meningitis*). Demonstration of HSV antibodies in CSF or persistence of HSV DNA in CSF can establish the diagnosis. For persons with frequent recurrences of HSV meningitis, daily antiviral therapy has reduced the frequency of recurrent episodes of symptomatic meningitis.

Autonomic nervous system dysfunction, especially of the sacral region, has been reported in association with both HSV and VZV infections. Numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, CSF pleocytosis, and (in males) impotence may occur. Symptoms appear to resolve slowly over days or weeks. Occasionally, hypoesthesia and/or weakness of the lower extremities persists for many months. Transitory hypoesthesia of the area of skin innervated by the trigeminal nerve and vestibular system dysfunction (as measured by electronystagmography) are the predominant signs of disease. Whether antiviral chemotherapy can abort these signs or reduce their frequency and severity is not yet known. Rarely, transverse myelitis, manifested by a rapidly progressive symmetric paralysis of the lower extremities or Guillain-Barré syndrome, follows HSV infection. Similarly, peripheral nervous system involvement (Bell's palsy) or cranial polyneuritis may be related to reactivation of HSV-1 infection.

Visceral Infections HSV infection of visceral organs usually results from viremia, and multiple-organ involvement is common. Occasionally, however, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oral–pharyngeal HSV infection into the esophagus or may occur de novo by reactivation and spread of HSV to the esophageal mucosa via the vagus nerve. The predominant symptoms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. Multiple oval ulcerations appear on an erythematous base with or without a patchy white pseudomembrane. The distal esophagus is most commonly involved. With extensive disease, diffuse friability may spread to the entire esophagus. Neither endoscopic nor barium examination can reliably differentiate HSV esophagitis from *Candida* esophagitis or from esophageal ulcerations due to thermal injury, radiation, or corrosives. Endoscopically obtained secretions—for cytologic examination and culture or DNA detection by PCR—provide the most useful material for diagnosis. Systemic antiviral chemotherapy usually reduces the severity and duration of symptoms and heals esophageal ulcerations.

HSV pneumonitis is uncommon except in severely immunosuppressed patients and may result from extension of herpetic tracheobronchitis into lung parenchyma. Focal necrotizing pneumonitis usually ensues. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease may also occur, producing bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic pathogens are commonly present in HSV pneumonitis. The mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (>80%). HSV has also been isolated from the lower respiratory tract of persons with acute respiratory distress syndrome and prolonged intubation. Most authorities believe that the presence of HSV in tracheal aspirates in such settings is due to reactivation of HSV in the tracheal region and localized tracheitis in persons with long-term intubation. Such patients should be evaluated for extension of HSV infection into the lung parenchyma. Controlled trials assessing the role of antiviral agents used against HSV in morbidity and mortality associated with acute respiratory distress syndrome have not been conducted. The role of lower respiratory tract HSV infection in overall rates of morbidity and mortality associated with these conditions is unclear. HSV is an uncommon cause of hepatitis in immunocompetent patients. HSV infection of the liver is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (<4000 white blood cells/μL). Disseminated intravascular coagulation may also develop.

Other reported complications of HSV infection include monarticular arthritis, adrenal necrosis, idiopathic thrombocytopenia, and glomerulonephritis. Disseminated HSV infection in immunocompetent patients is rare. In immunocompromised patients, burn patients, or malnourished individuals, HSV occasionally disseminates to other visceral organs, such as the adrenal glands, pancreas, small and large intestines, and bone marrow. Rarely, primary HSV infection in pregnancy disseminates and may be associated with the death of both mother and fetus. This uncommon event is usually related to the acquisition of primary infection in the third trimester. Disseminated HSV infection is best detected by the presence of HSV DNA in plasma or blood.

Neonatal HSV Infections Of all HSV-infected populations, neonates (infants <6 weeks) have the highest frequency of visceral and/or CNS infection. Without therapy, the overall rate of death from neonatal herpes is 65%; <10% of neonates with CNS infection develop normally. Although skin lesions are the most commonly recognized features of disease, many infants do not develop lesions at all or do so only well into the course of disease. Neonatal infection is usually acquired perinatally from contact with infected genital secretions at delivery. Congenitally infected infants have been reported. Of neonatal HSV infections, 30–50% are due to HSV-1 and 50–70% to HSV-2. The risk of developing neonatal HSV infection is 10 times higher for an infant born to a mother who has recently acquired HSV than for other infants. Neonatal HSV-1 infections may also be acquired through postnatal contact with immediate family members who have symptomatic or asymptomatic oral–labial HSV-1 infection or through nosocomial transmission within the hospital. All neonates with presumed herpes should be treated with IV acyclovir and then placed on maintenance oral antiviral therapy for the first 6–12 months of life. Antiviral chemotherapy with high-dose IV acyclovir (60 mg/kg per day) has reduced the mortality rate from neonatal herpes to ~15%. However, rates of morbidity, especially among infants with HSV-2 infection involving the CNS, are still very high.

HSV in Pregnancy In the United States, 22% of all pregnant women and 55% of non-Hispanic black pregnant women are seropositive for HSV-2. However, the risk of mother-to-child transmission of HSV in the perinatal period is highest when the infection is acquired near the time of labor—that is, in previously HSV-seronegative women. The clinical manifestations of recurrent genital herpes—including the frequency of subclinical versus clinical infection, the duration of lesions, pain, and constitutional symptoms—are similar in pregnant and nonpregnant women. Recurrences increase in frequency over the course of pregnancy. However, when women are seropositive for HSV-2 at the outset of pregnancy, no effect on neonatal outcomes (including birth weight and gestational age) is seen. First-episode infections in pregnancy have more severe consequences for mother and infant. Maternal visceral dissemination during the third trimester occasionally occurs, as does premature birth or intrauterine growth retardation. The acquisition of primary disease in pregnancy, whether related to HSV-1 or HSV-2, carries the risk of transplacental transmission of virus to the neonate and can result in spontaneous abortion, although this outcome is relatively uncommon. For newly acquired genital HSV infection during pregnancy, most authorities recommend treatment with acyclovir (400 mg three times daily) or valacyclovir (500–1000 mg twice daily) for 7–10 days. However, the impact of this intervention on transmission is unknown. The high HSV-2 prevalence rate in pregnancy and the low incidence of neonatal disease (1 case per 6000–20,000 live births) indicate that only a few infants are at risk of acquiring HSV. Therefore, cesarean section is not warranted for all women with recurrent genital disease. Because intrapartum transmission of infection accounts for

the majority of cases, abdominal delivery need be considered only for women who are shedding HSV at delivery. Several studies have shown no correlation between recurrence of viral shedding before delivery and viral shedding at term. Hence, weekly virologic monitoring and amniocentesis are not recommended.

The frequency of transmission from mother to infant is markedly higher among women who acquire HSV near term (30–50%) than among those in whom HSV-2 infection is reactivated at delivery (<1%). Although maternal antibody to HSV-2 is protective, antibody to HSV-1 offers little or no protection against neonatal HSV-2 infection. Primary genital infection with HSV-1 leads to a particularly high risk of transmission during pregnancy and accounts for an increasing proportion of neonatal HSV cases. Moreover, during reactivation, HSV-1 appears more transmissible to the neonate than HSV-2. Only 2% of women who are seropositive for HSV-2 have HSV-2 isolated from cervical secretions at delivery, and only 1% of infants exposed in this manner develop infection, presumably because of the protective effects of maternally transferred antibodies and perhaps lower viral titers during reactivation. Despite the low frequency of transmission of HSV in this setting, 30–50% of infants with neonatal HSV are born to mothers with established genital herpes.

Isolation of HSV by cervicovaginal swab at the time of delivery is the greatest risk factor for intrapartum HSV transmission (relative risk = 346); however, culture-negative, PCR-positive cases of intrapartum transmission are well described. New acquisition of HSV (odds ratio [OR] = 49), isolation of HSV-1 versus HSV-2 (OR = 35), cervical versus vulvar HSV detection (OR = 15), use of fetal scalp electrodes (OR = 3.5), and young maternal age confer further risk of transmission, whereas cesarean delivery is protective (OR = 0.14). Physical examination poorly predicts the absence of shedding, and PCR far exceeds culture in terms of sensitivity and speed. Therefore, PCR detection at the onset of labor should be used to aid clinical decision-making for women with HSV-2 antibody. Because cesarean section appears to be an effective means of reducing maternal–fetal transmission, patients with recurrent genital herpes should be encouraged to come to the hospital early at the time of delivery for careful examination of the external genitalia and cervix as well as collection of a swab sample for viral isolation. Women who have no evidence of lesions can have a vaginal delivery. The presence of active lesions on the cervix or external genitalia is an indication for cesarean delivery.

If first-episode exposure has occurred (e.g., if HSV serologies show that the mother is seronegative or if the mother is HSV-1-seropositive and the isolate at delivery is found to be HSV-2), many authorities would initiate antiviral therapy for the infant with IV acyclovir. At a minimum, samples for viral cultures and PCR should be obtained from the throat, nasopharynx, eyes, and rectum of these infants immediately and at 5- to 10-day intervals. Lethargy, skin lesions, or fever should be evaluated promptly. All infants from whom HSV is isolated 24 h after delivery should be treated with IV acyclovir at recommended doses.

DIAGNOSIS

Both clinical and laboratory criteria are useful for diagnosing HSV infections. A clinical diagnosis can be made accurately when characteristic multiple vesicular lesions on an erythematous base are present. However, herpetic ulcerations may resemble skin ulcerations of other etiologies. Mucosal HSV infections may also present as urethritis or pharyngitis without cutaneous lesions. Thus, laboratory studies to confirm the diagnosis and to guide therapy are recommended. While staining of scrapings from the base of the lesions with Wright's, Giemsa's (Tzanck preparation), or Papanicolaou's stain to detect giant cells or intranuclear inclusions of *Herpesvirus* infection is a well-described procedure, few clinicians are skilled in this technique, the sensitivity of staining is low (<30% for mucosal swabs), and these cytologic methods do not differentiate between HSV and VZV infections.

HSV infection is best confirmed in the laboratory by detection of virus, viral antigen, or viral DNA in scrapings from lesions. HSV DNA detection by PCR is the most sensitive laboratory technique for detecting mucosal or visceral HSV infections and is the recommended test for laboratory confirmation of a diagnosis. HSV causes a discernible cytopathic effect in a variety of cell culture systems, and this effect can be identified within 48–96 h after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time needed to identify HSV to <24 h. Culture is indicated when antiviral sensitivity testing is required. The sensitivity of all detection methods depends on the stage of the lesions (with higher sensitivity for vesicular than for ulcerative lesions), on whether the patient has a first or a recurrent episode of the disease (with higher sensitivity in first than in recurrent episodes), and on whether the sample is from an immunosuppressed or an immunocompetent patient (with more antigen or DNA in immunosuppressed patients). Laboratory confirmation permits subtyping of the virus; information on subtype may be useful epidemiologically and may help to predict the frequency of reactivation after first-episode oral–labial or genital HSV infection.

Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Serologic assays with whole-virus antigen preparations, such as complement fixation, neutralization, indirect immunofluorescence, passive hemagglutination, radioimmunoassay, and enzyme-linked immunosorbent assay, are useful for differentiating uninfected (seronegative) persons from those with past HSV-1 or HSV-2 infection, but they do not reliably distinguish between the two viral subtypes. Serologic assays that identify antibodies to the type-specific glycoprotein G of the two viral subtypes (G1 and G2) are available commercially and can distinguish reliably between the human antibody responses to HSV-1 and HSV-2. Point-of-care assays that provide results from capillary blood or serum during a clinic visit are available. A western blot assay that can detect several HSV type-specific proteins can also be used. The presence of type-specific HSV-2 antibody implies past HSV-2 infection—i.e., latent infection and likely subclinical reactivation.

Acute- and convalescent-phase serum samples can be useful in demonstrating seroconversion during primary HSV-1 or HSV-2 infection. However, few available tests report titers, and increases in index values do not reflect first episodes in all patients. Serologic assays based on type-specific proteins should be used to identify asymptomatic carriers of HSV-1 or HSV-2. No reliable IgM method for defining acute HSV infection is available.

Several studies have shown that persons with previously unrecognized HSV-2 infection can be taught to identify symptomatic reactivations. Individuals seropositive for HSV-2 should be told about the high frequency of subclinical reactivation on mucosal surfaces that are not visible to the eye (e.g., cervix, urethra, perianal skin) or in microscopic ulcerations that may not be clinically symptomatic. Transmission of infection during such episodes is well established. HSV-2-seropositive persons should be educated about the high likelihood of subclinical shedding and the role that condoms (male or female) may play in reducing transmission. Antiviral therapy with valacyclovir (500 mg once daily) has been shown to reduce the transmission of HSV-2 between sexual partners.

TREATMENT

Herpes Simplex Virus Infections

Many aspects of mucocutaneous and visceral HSV infections are amenable to antiviral chemotherapy. For mucocutaneous infections, acyclovir and its congeners famciclovir and valacyclovir have been the mainstays of therapy. Several antiviral agents are available for topical use in HSV eye infections: idoxuridine, trifluorothymidine, topical vidarabine, and cidofovir. For HSV encephalitis and neonatal herpes, IV acyclovir is the treatment of choice.

All licensed antiviral agents for use against HSV inhibit the viral DNA polymerase. One class of drugs, typified by the drug acyclovir, is made up of substrates for the HSV enzyme thymidine kinase (TK). Acyclovir, ganciclovir, famciclovir, and valacyclovir are all selectively phosphorylated to the monophosphate form in virus-infected cells. Cellular enzymes convert the monophosphate form of the drug to the triphosphate, which is then incorporated into the viral DNA chain. Acyclovir is the agent most frequently used

for the treatment of HSV infections and is available in IV, oral, and topical formulations. Valacyclovir, the valyl ester of acyclovir, offers greater bioavailability than acyclovir and thus can be administered less frequently. Famciclovir, the oral formulation of penciclovir, is clinically effective in the treatment of a variety of HSV-1 and HSV-2 infections. Ganciclovir is active against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famciclovir and generally is not recommended for the treatment of HSV infections. Anecdotal case reports suggest that ganciclovir may also be less effective than acyclovir for the treatment of HSV infections. All three recommended compounds—acyclovir, valacyclovir, and famciclovir—have proved effective in shortening the duration of symptoms and lesions of mucocutaneous HSV infections in both immunocompromised and immunocompetent patients **(Table 187-1)**. IV and oral formulations prevent reactivation of HSV in seropositive immunocompromised patients during induction chemotherapy or

TABLE 187-1 Antiviral Chemotherapy for Herpes Simplex Virus (HSV) Infection

I. Mucocutaneous HSV infections

A. *Infections in immunosuppressed patients*

1. *Acute symptomatic first or recurrent episodes:* IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg bid or tid), or valacyclovir (500 mg bid) is effective. Treatment duration may vary from 7 to 14 days. IV therapy may be given for 2–7 days until clinical improvement and followed by oral therapy.
2. *Suppression of reactivation disease (genital or oral–labial):* IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in reducing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral acyclovir (400–800 mg bid), valacyclovir (500 mg bid), or famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

B. *Infections in immunocompetent patients*

1. *Genital herpes*
   a. *First episodes:* Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 7–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.
   b. *Symptomatic recurrent genital herpes:* Short-course (1- to 3-day) regimens are preferred because of low cost, likelihood of adherence, and convenience. Oral acyclovir (800 mg tid for 2 days), valacyclovir (500 mg bid for 3 days), or famciclovir (750 or 1000 mg bid for 1 day, a 1500-mg single dose, or 500 mg stat followed by 250 mg q12h for 2 days) effectively shortens lesion duration. Other options include oral acyclovir (200 mg 5 times per day), valacyclovir (500 mg bid), and famciclovir (125 mg bid for 5 days).
   c. *Suppression of recurrent genital herpes:* Oral acyclovir (400–800 mg bid) or valacyclovir (500 mg daily) is given. Patients with >9 episodes per year should take oral valacyclovir (1 g daily or 500 mg bid) or famciclovir (250 mg bid or 500 mg bid).
2. *Oral–labial HSV infections*
   a. *First episode:* Oral acyclovir is given (200 mg 5 times per day or 400 mg tid); an oral acyclovir suspension can be used (600 mg/m^2 qid). Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically. The duration of therapy is 5–10 days.
   b. *Recurrent episodes:* If initiated at the onset of the prodrome, single-dose or 1-day therapy effectively reduces pain and speeds healing. Regimens include oral famciclovir (a 1500-mg single dose or 750 mg bid for 1 day) or valacyclovir (a 2-g single dose or 2 g bid for 1 day). Self-initiated therapy with 6-times-daily topical penciclovir cream effectively speeds healing of oral–labial HSV infection. Topical acyclovir cream has also been shown to speed healing.
   c. *Suppression of reactivation of oral–labial HSV:* If started before exposure and continued for the duration of exposure (usually 5–10 days), oral acyclovir (400 mg bid) prevents reactivation of recurrent oral–labial HSV infection associated with severe sun exposure.
3. *Surgical prophylaxis of oral or genital HSV infection:* Several surgical procedures, such as laser skin resurfacing, trigeminal nerve-root decompression, and lumbar disk surgery, have been associated with HSV reactivation. IV acyclovir (3–5 mg/kg q8h) or oral acyclovir (800 mg bid), valacyclovir (500 mg bid), or famciclovir (250 mg bid) effectively reduces reactivation. Therapy should be initiated 48 h before surgery and continued for 3–7 days.
4. *Herpetic whitlow:* Oral acyclovir (200 mg) is given 5 times daily (alternative: 400 mg tid) for 7–10 days.
5. *HSV proctitis:* Oral acyclovir (400 mg 5 times per day) is useful in shortening the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.
6. *Herpetic eye infections:* In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required. Topical steroids may worsen disease.

II. Central nervous system HSV infections

A. *HSV encephalitis:* IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) is given for 10 days or until HSV DNA is no longer detected in cerebrospinal fluid.

B. *HSV aseptic meningitis:* No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.

C. *Autonomic radiculopathy:* No studies are available. Most authorities recommend a trial of IV acyclovir.

III. Neonatal HSV infections: IV acyclovir (60 mg/kg per day, divided into 3 doses) is given. The recommended duration of IV treatment is 21 days. Monitoring for relapse should be undertaken. Continued suppression with oral acyclovir suspension should be given for 3–4 months.

IV. Visceral HSV infections

A. *HSV esophagitis:* IV acyclovir (15 mg/kg per day) is given. In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

B. *HSV pneumonitis:* No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

V. Disseminated HSV infections: No controlled studies exist. IV acyclovir (5 mg/kg q8h) should be tried. Adjustments for renal insufficiency may be needed. No definite evidence indicates that therapy will decrease the risk of death.

VI. Erythema multiforme associated with HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) will suppress erythema multiforme.

VII. Infections due to acyclovir-resistant HSV: IV foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 1% cidofovir gel, both of which must be compounded at a pharmacy. These preparations should be applied once daily for 5–7 days. Topical imiquimod can be considered. The helicase primase inhibitor pritelivir is being studied for treatment of acyclovir-resistant HSV infection. IV cidofovir (5 mg/kg weekly) may be considered.

VIII. Acyclovir and pregnancy: No adverse effects to the fetus or newborn have been attributable to acyclovir. Acyclovir can be used in all stages of pregnancy and among women who are breastfeeding (the drug can be found in breast milk). Suppressive acyclovir treatment in late pregnancy reduces the frequency of cesarean delivery among women with recurrent genital herpes. Such treatment may not protect against transmission to neonates.

in the period immediately after bone marrow or solid organ transplantation. Chronic daily suppressive therapy reduces the frequency of reactivation disease among patients with frequent genital or oral–labial herpes. Only valacyclovir has been subjected to clinical trials that demonstrated reduced transmission of HSV-2 infection between sexual partners. IV acyclovir (30 mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is effective in reducing rates of death and morbidity from HSV encephalitis. Early initiation of therapy is a critical factor in outcome. The major side effect associated with IV acyclovir is transient renal insufficiency, usually due to crystallization of the compound in the renal parenchyma. This adverse reaction can be avoided if the medication is given slowly over 1 h and the patient is well hydrated. Because CSF levels of acyclovir average only 30–50% of plasma levels, the dosage of acyclovir used for treatment of CNS infection (30 mg/kg per day) is double that used for treatment of mucocutaneous or visceral disease (15 mg/kg per day). Even higher doses of IV acyclovir are used for neonatal HSV infection (60 mg/kg per day in three divided doses). Antiviral drugs neither eradicate latent infection nor affect the risk, frequency, or severity of subclinical or clinical recurrence after the drug is discontinued.

Increasingly, shorter courses of therapy are being used for recurrent mucocutaneous infection with HSV-1 or HSV-2 in immunocompetent patients. One-day courses of famciclovir and valacyclovir are clinically effective, more convenient, and generally less costly than longer courses of therapy (Table 187-1). These short-course regimens should be reserved for immunocompetent hosts.

SUPPRESSION OF MUCOCUTANEOUS HERPES

Recognition of the high frequency of subclinical reactivation provides a well-accepted rationale for the use of daily antiviral therapy to suppress reactivations of HSV, especially in persons with frequent clinical reactivations (e.g., those with recently acquired genital HSV infection). Immunosuppressed persons, including those with HIV infection, may also benefit from daily antiviral therapy. Daily acyclovir and valacyclovir reduce the frequency of HSV reactivations among HIV-positive persons. Regimens used include acyclovir (400–800 mg twice daily), famciclovir (500 mg twice daily), and valacyclovir (500 mg twice daily); valacyclovir at a dose of 4 g/d was associated with thrombotic thrombocytopenic purpura in one study of HIV-infected persons. Daily acyclovir therapy is associated with a modest reduction in the titer of HIV RNA in plasma (0.5-$\log_{10}$ reduction) and in the genital mucosa (0.33-$\log_{10}$ reduction).

REDUCED HSV TRANSMISSION TO SEXUAL PARTNERS

Once-daily valacyclovir (500 mg) has been shown to reduce transmission of HSV-2 between sexual partners. Transmission rates are higher from males to females and among persons with frequent HSV-2 reactivation. Serologic screening can be used to identify at-risk couples. Daily valacyclovir appears to be more effective at reducing subclinical shedding than daily famciclovir.

ACYCLOVIR RESISTANCE

Clinically relevant acyclovir-resistant strains of HSV do occur. Most of these strains have an altered substrate specificity for phosphorylating acyclovir. Thus, cross-resistance to famciclovir and valacyclovir is usually found. Occasionally, an isolate with altered TK specificity arises and is sensitive to famciclovir but not to acyclovir. In some patients infected with TK-deficient virus, higher doses of acyclovir are associated with clearing of lesions. In others, clinical disease progresses despite high-dose therapy. Almost all clinically significant acyclovir resistance has been seen in immunocompromised patients, and HSV-2 isolates are more often resistant than HSV-1 strains. A study by the Centers for Disease Control and Prevention indicated that ~5% of HSV-2 isolates from HIV-positive persons exhibit some degree of in vitro resistance to acyclovir. Of HSV-2 isolates from immunocompetent patients attending sexually transmitted disease clinics, <0.5% show reduced in vitro sensitivity to acyclovir. The lack of appreciable change in the frequency of detection of such isolates in the past 30 years probably reflects the reduced transmission of TK-deficient mutants. Isolation of HSV from lesions persisting despite adequate dosages and blood levels of acyclovir should raise the suspicion of acyclovir resistance. Clinical management of acyclovir resistance is challenging. Therapy with the antiviral drug foscarnet (40–80 mg/kg IV every 8 h until clinical resolution) is useful in acyclovir-resistant cases **(Chap. 186)**. Because of its toxicity and cost, this drug is usually reserved for patients with extensive mucocutaneous infections. Cidofovir is a nucleotide analogue and exists as a phosphonate or monophosphate form. Most TK-deficient strains of HSV are sensitive to cidofovir. Cidofovir ointment speeds healing of acyclovir-resistant lesions. No well-controlled trials of systemic cidofovir have been reported. Occasional cases may respond to topical imiquimod. True TK-negative variants of HSV appear to have a reduced capacity to spread because of altered neurovirulence—a feature important in the relatively infrequent presence of such strains in immunocompetent populations, even with increasing use of antiviral drugs. A new class of drugs that inhibit HSV-specific helicase/primase activity (pritelivir) is under clinical investigation and may offer a better toxicity profile for the treatment of acyclovir-resistant strains of HSV.

ACYCLOVIR EFFICACY IN THE DEVELOPING WORLD

Initial studies of acyclovir-like drugs were performed solely in the developed world. While acyclovir, valacyclovir, and famciclovir are effective in the developing world, their clinical and virologic benefits, especially in reducing the frequency of genital lesions among patients in Africa, seem reduced from those in European and U.S. populations. The mechanism of this phenomenon is uncertain. Acyclovir therapy does not reduce the rate of HIV acquisition; however, HIV load among MSM in the United States decreased by 1.3 $\log_{10}$ in contrast to 0.9 $\log_{10}$ among Peruvian MSM and 0.5 $\log_{10}$ among African women. Curiously, the anti-HIV drug tenofovir reduces HSV-2 acquisition among women in Africa although it has no demonstrable clinical benefit or antiviral effects among persons with established HSV-2 infection in studies in the United States. The reasons for these disparate results are unclear.

PREVENTION

Efforts to control HSV disease on a population basis through suppressive antiviral chemotherapy and/or educational programs have been limited. Barrier forms of contraception (especially condoms) decrease the likelihood of transmission of HSV infection, particularly during periods of asymptomatic viral excretion. When lesions are present, HSV infection may be transmitted by skin-to-skin contact despite the use of a condom. Nevertheless, the available data suggest that consistent condom use is an effective means of reducing the risk of genital HSV-2 transmission. Chronic daily antiviral therapy with valacyclovir can also be partially effective in reducing acquisition of HSV-2, especially among susceptible women. There are no comparative efficacy studies of valacyclovir versus condom use. Most authorities suggest both approaches. The need for a vaccine to prevent acquisition of HSV infection is great, especially in light of the role HSV-2 plays in enhancing the acquisition and transmission of HIV-1.

A substantial portion of neonatal HSV cases could be prevented by reducing the acquisition of HSV by women in the third trimester of pregnancy. Neonatal HSV infection can result from either the acquisition of maternal infection near term or the reactivation of infection at delivery in the already-infected mother. Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known to have or suspected of having genital herpes. Some authorities have recommended that antiviral therapy with acyclovir or valacyclovir be given to HSV-2-infected women in late pregnancy as a means of reducing reactivation of HSV-2 at term. Data are not available to support the efficacy of this approach, and the high treatment-to-prevention ratio makes this a difficult if not dubious public health strategy, even though it can reduce the frequency of HSV-associated cesarean delivery.

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188 Varicella-Zoster Virus Infections

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DEFINITION

Varicella-zoster virus (VZV) causes two distinct clinical syndromes: varicella (chickenpox) and herpes zoster (shingles). Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash. With reactivation of latent VZV (which is most common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash and is usually associated with severe pain.

ETIOLOGY

Early in the twentieth century, similarities in the histopathologic features of skin lesions resulting from varicella and herpes zoster were demonstrated. Viral isolates from patients with both of these diseases produced similar pathology in tissue culture—specifically, the appearance of eosinophilic intranuclear inclusions and multinucleated giant cells. These results suggested that the viruses were biologically similar. Restriction endonuclease analyses of viral DNA from a patient with chickenpox who subsequently developed herpes zoster verified the molecular identity of the two viruses responsible for these different clinical presentations.

VZV is a member of the family Herpesviridae, sharing with other members such structural characteristics as a lipid envelope surrounding a nucleocapsid with icosahedral symmetry, a total diameter of ~180–200 nm, and centrally located double-stranded DNA that is ~125,000 bp in length.

PATHOGENESIS AND PATHOLOGY

Primary Infection Transmission occurs readily by the respiratory route; the subsequent localized replication of the virus at an undefined site (presumably the nasopharynx) leads to seeding of the lymphatic/reticuloendothelial system and ultimately to the development of viremia. Viremia in patients with chickenpox is reflected in the diffuse and scattered nature of the skin lesions and can be confirmed in selected cases by the recovery of VZV from the blood or routinely by the detection of viral DNA in either blood or lesions by polymerase chain reaction (PCR). Vesicles involve the corium and dermis, with degenerative changes characterized by ballooning, the presence of multinucleated giant cells, and eosinophilic intranuclear inclusions. Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage. With the evolution of disease, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin. Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed.

Recurrent Infection The mechanism of reactivation of VZV that results in herpes zoster is unknown. The virus infects dorsal root ganglia during chickenpox, where it remains latent until reactivated. Histopathologic examination of representative dorsal root ganglia during active herpes zoster demonstrates hemorrhage, edema, and lymphocytic infiltration. Latent virus been detected in sensory (dorsal, cranial, and enteric) ganglia.

Active replication of VZV in other organs, such as the lung or the brain, can occur during either chickenpox or herpes zoster but is uncommon in the immunocompetent host. Pulmonary involvement is characterized by interstitial pneumonitis, multinucleated giant cell formation, intranuclear inclusions, and pulmonary hemorrhage. Central nervous system (CNS) infection leads to histopathologic evidence of perivascular cuffing similar to that encountered in measles and other viral encephalitides. Focal hemorrhagic necrosis of the brain, characteristic of herpes simplex virus (HSV) encephalitis, develops infrequently in VZV infection.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

Chickenpox Humans are the only known reservoir for VZV. Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals. Persons of both sexes and all races are infected equally. The virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal peaks—namely, late winter and early spring in the temperate zone. Much of our knowledge of the disease's natural history and incidence predates the licensure of the chickenpox vaccine in 1995. Historically, children 5–9 years old were most commonly affected, accounting for 50% of all cases. Most other cases involved children 1–4 and 10–14 years old. Approximately 10% of the population of the United States over the age of 15 was susceptible to infection. VZV vaccination during the second year of life has dramatically changed the epidemiology of infection, causing a significant decrease in the annualized incidence of chickenpox, as noted below.

The incubation period of chickenpox ranges from 10 to 21 days but is usually 14–17 days. Secondary attack rates in susceptible siblings within a household are 70–90%. Patients are infectious ~48 h before the onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4–5 days), and until all vesicles are crusted.

Clinically, chickenpox presents as a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1–2 days before onset of the exanthem. In the immunocompetent patient, chickenpox is usually a benign illness associated with lassitude and with body temperatures of 37.8°–39.4°C (100°–103°F) of 3–5 days' duration. The skin lesions—the hallmark of the infection—include maculopapules, vesicles, and scabs in various stages of evolution **(Fig. 188-1; see also Fig. A1-30)**. These lesions, which evolve from maculopapules to vesicles over hours to days, appear on the trunk and face and rapidly spread to involve other areas of the body. Most are small and have an erythematous base with a diameter of 5–10 mm. Successive crops appear over a 2- to 4-day period. Lesions can also be found on the mucosa of the pharynx and/or the vagina. Their severity varies from one person to another. Some individuals have very few lesions, while others have as many as 2000. Younger children tend to have fewer vesicles than older individuals. Within families, secondary and tertiary cases are associated with a larger number of vesicles than the first case. Immunocompromised patients—both children and adults, particularly those with leukemia—have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompetent patients. Immunocompromised individuals are also at greater risk for visceral complications, which occur in 30–50% of cases and are fatal 15% of the time in the absence of antiviral therapy.

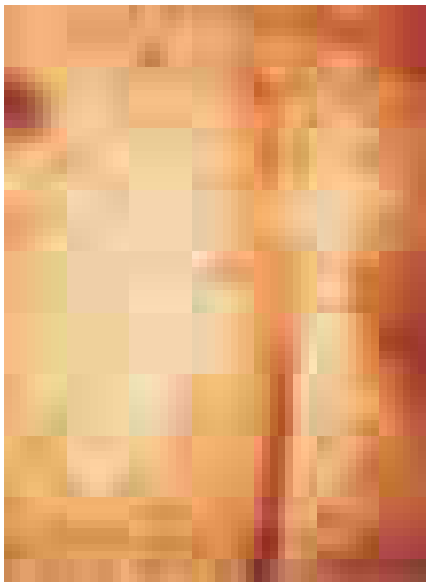

FIGURE 188-1 Varicella lesions at various stages of evolution: vesicles on an erythematous base, umbilical vesicles, and crusts.

The most common infectious complication of varicella is secondary bacterial superinfection of the skin, which is usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus,* including strains that are methicillin-resistant. Skin infection results from excoriation of lesions after scratching. Gram's staining of skin lesions should help clarify the etiology of unusually erythematous and pustulated lesions.

The most common extracutaneous site of involvement in children is the CNS. The syndrome of acute cerebellar ataxia and meningeal inflammation generally appears ~21 days after onset of the rash and rarely develops in the pre-eruptive phase. The cerebrospinal fluid (CSF) contains lymphocytes and elevated levels of protein. CNS involvement is a benign complication of VZV infection in children and generally does not require hospitalization. Aseptic meningitis, encephalitis, transverse myelitis, and Guillain-Barré syndrome also can occur. Encephalitis is reported in 0.1–0.2% of children with chickenpox. Reye's syndrome can occur in children concomitantly treated with aspirin, which therefore is no longer used. Other than supportive care, no specific therapy (e.g., acyclovir administration) has proved efficacious for patients with CNS involvement.

Varicella pneumonia, the most serious complication following chickenpox, develops more often in adults (up to 20% of cases) than in children and is particularly severe in pregnant women. Pneumonia due to VZV usually has its onset 3–5 days into the illness and is associated with tachypnea, cough, dyspnea, and fever. Cyanosis, pleuritic chest pain, and hemoptysis are frequently noted. Roentgenographic evidence of disease consists of nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash; however, patients may have persistent fever and compromised pulmonary function for weeks.

Other complications of chickenpox include myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses, acute glomerulonephritis, and hepatitis. Hepatic involvement, distinct from Reye's syndrome and usually asymptomatic, is common in chickenpox and is generally characterized by elevated levels of liver enzymes, particularly aspartate and alanine aminotransferases.

Perinatal varicella is associated with mortality rates as high as 30% when maternal disease develops within 5 days before delivery or within 48 h thereafter. Illness in this setting is unusually severe because the newborn does not receive protective transplacental antibodies and has an immature immune system. *Congenital varicella*, with clinical manifestations of limb hypoplasia, cicatricial skin lesions, and microcephaly at birth, is extremely uncommon.

Herpes Zoster Herpes zoster (shingles) is a sporadic disease that results from reactivation of latent VZV from dorsal root ganglia. Most patients with shingles have no history of recent exposure to other individuals with VZV infection. Herpes zoster occurs at all ages, but its incidence is highest (5–10 cases per 1000 persons) among individuals in the sixth decade of life and beyond. Data suggest that at least 1.2 million cases occur annually in the United States. Recurrent herpes zoster is exceedingly rare except in immunocompromised hosts, especially those with AIDS.

Herpes zoster is characterized by a unilateral vesicular dermatomal eruption, often associated with severe pain. The dermatomes from T3 to L3 are most frequently involved. If the ophthalmic branch of the trigeminal nerve is involved, *zoster ophthalmicus* results. The factors responsible for the reactivation of VZV are not known. In children, reactivation is usually benign; in adults, it can be debilitating because of pain. The onset of disease is heralded by pain within the dermatome, which may precede lesions by 48–72 h; an erythematous maculopapular rash evolves rapidly into vesicular lesions **(Fig. 188-2)**. In the normal host, these lesions may remain few in number and continue to form for only 3–5 days. The total duration of disease is generally 7–10 days; however, it may take as long as 2–4 weeks for the skin to return to normal. Patients with herpes zoster can transmit infection to seronegative individuals, with resulting chickenpox. In a few patients, characteristic localization of pain to a dermatome with serologic evidence of herpes zoster has been reported in the absence of skin lesions, an entity known as *zoster sine herpetica*. When branches of the trigeminal nerve are involved, lesions may appear on the face, in the mouth, in the eye, or on the tongue. *Zoster ophthalmicus* is usually a debilitating condition that can result in blindness in the absence of antiviral therapy. In *Ramsay Hunt syndrome*, pain and vesicles appear in the external auditory canal, and patients lose their sense of taste in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved.

In both normal and immunocompromised hosts, the most debilitating complication of herpes zoster is pain associated with acute neuritis and postherpetic neuralgia. Postherpetic neuralgia is uncommon in young individuals; however, at least 50% of patients over age 50 report some degree of pain in the involved dermatome for months after the resolution of cutaneous disease. Changes in sensation in the dermatome, resulting in either hypo- or hyperesthesia, are common.

CNS involvement may follow localized herpes zoster. Many patients without signs of meningeal irritation have CSF pleocytosis and

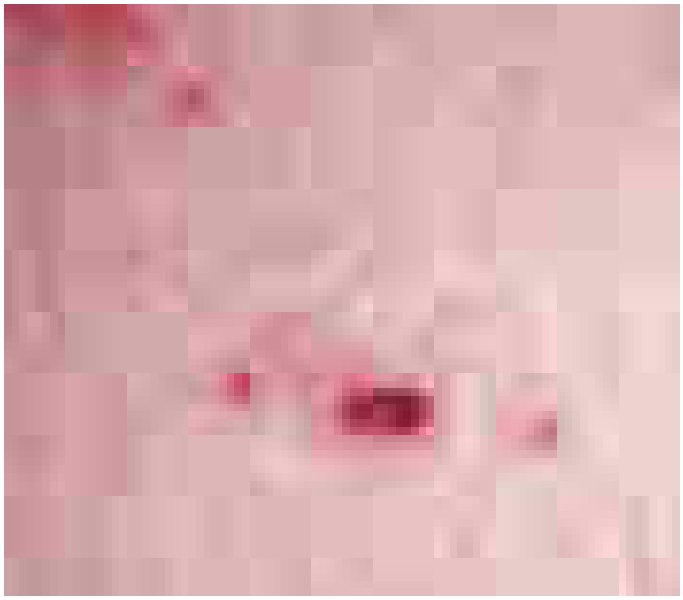

FIGURE 188-2 Close-up of lesions of disseminated zoster. Note lesions at different stages of evolution, including pustules and crusting. *(Photo courtesy of Lindsey Baden; with permission.)*

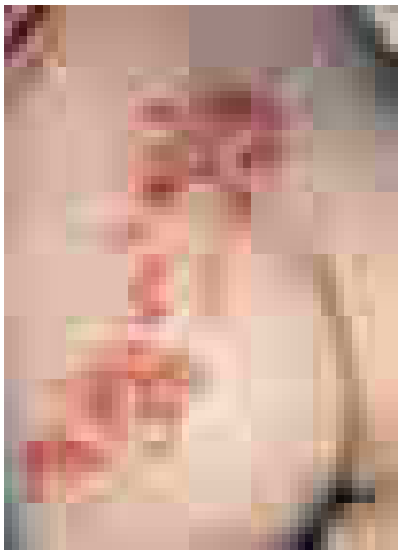

FIGURE 188-3 Herpes zoster in an HIV-infected patient is seen as hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution.

moderately elevated levels of CSF protein. Symptomatic meningoencephalitis is characterized by headache, fever, photophobia, meningitis, and vomiting. A rare manifestation of CNS involvement is granulomatous angiitis with contralateral hemiplegia, which can be diagnosed by cerebral arteriography. Other neurologic manifestations include transverse myelitis with or without motor paralysis.

Like chickenpox, herpes zoster is more severe in immunocompromised than immunocompetent individuals. Lesions continue to form for >1 week, and scabbing is not complete in most cases until 3 weeks into the illness. Patients with Hodgkin's disease and non-Hodgkin's lymphoma are at greatest risk for progressive herpes zoster. Cutaneous dissemination **(Fig. 188-3)** develops in ~40% of immunocompromised patients. Among patients with cutaneous dissemination, the risk of pneumonitis, meningoencephalitis, hepatitis, and other serious complications is increased by 5–10%. However, even in immunocompromised patients, disseminated zoster is rarely fatal.

Recipients of hematopoietic stem cell transplants are at particularly high risk of VZV infection. Of all cases of post-transplantation VZV infection, 30% occur within 1 year (50% of these within 9 months); 45% of the patients involved have cutaneous or visceral dissemination. The mortality rate in this situation is 10%. Postherpetic neuralgia, scarring, and bacterial superinfection are especially common in VZV infections occurring within 9 months of transplantation. Among infected patients, concomitant graft-versus-host disease increases the chance of dissemination and/or death.

DIFFERENTIAL DIAGNOSIS

The diagnosis of chickenpox is not difficult. The characteristic rash and a history of recent exposure should lead to a prompt diagnosis. Other viral infections that can mimic chickenpox include disseminated HSV infection in patients with atopic dermatitis and the disseminated vesiculopapular lesions sometimes associated with coxsackievirus infection, echovirus infection, or atypical measles. However, these rashes are more commonly morbilliform with a hemorrhagic component rather than vesicular or vesiculopustular. Rickettsialpox **(Chap. 182)** is sometimes confused with chickenpox; however, rickettsialpox can be distinguished easily by detection of the "herald spot" at the site of the mite bite and the development of a more pronounced headache. Serologic testing is also useful in differentiating rickettsialpox from varicella and can confirm susceptibility in adults unsure of their chickenpox history. Monkeypox can be considered in travelers returning from endemic areas **(Chap. 191)**. Concern about smallpox has recently increased because of the threat of bioterrorism **(Chap. S2)**. The lesions of smallpox are larger than those of chickenpox and are all at the same stage of evolution at any given time.

Unilateral vesicular lesions in a dermatomal pattern should lead rapidly to the diagnosis of herpes zoster, although the occurrence of shingles without a rash has been reported. Both HSV and coxsackievirus infections can cause dermatomal vesicular lesions. Supportive diagnostic virology and fluorescent staining of skin scrapings with monoclonal antibodies are helpful in ensuring the proper diagnosis. In the prodromal stage of herpes zoster, the diagnosis can be exceedingly difficult and may be made only after lesions have appeared or by retrospective serologic assessment.

LABORATORY FINDINGS

Unequivocal confirmation of the diagnosis is possible only through the isolation of VZV in susceptible tissue-culture cell lines, the demonstration of either seroconversion or a fourfold or greater rise in antibody titer between acute-phase and convalescent-phase serum specimens, or the detection of VZV DNA by PCR. Specimens for detection of VZV DNA by PCR include lesions, blood, and saliva. A rapid impression can be obtained by a Tzanck smear, with scraping of the base of the lesions in an attempt to demonstrate multinucleated giant cells; however, the sensitivity of this method is low (~60%). PCR technology for the detection of viral DNA in vesicular fluid is available in many diagnostic laboratories. Direct immunofluorescent staining of cells from the lesion base or detection of viral antigens by other assays (such as the immunoperoxidase assay) also is useful, although these tests are not commercially available. The most frequently employed serologic tools for assessing host response are the immunofluorescent detection of antibodies to VZV membrane antigens, the fluorescent antibody to membrane antigen (FAMA) test, immune adherence hemagglutination, and enzyme-linked immunosorbent assay (ELISA). The FAMA test and the ELISA appear to be most sensitive.

TREATMENT

Varicella-Zoster Virus Infections

Medical management of chickenpox in the immunologically normal host is directed toward the prevention of avoidable complications. Obviously, good hygiene includes daily bathing and soaks. Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fingernails. Pruritus can be decreased with topical dressings or the administration of antipruritic drugs. Tepid water baths and wet compresses are better than drying lotions for the relief of itching. Administration of aspirin to children with chickenpox should be avoided because of the association of aspirin derivatives with the development of Reye's syndrome. Acyclovir (800 mg by mouth five times daily), valacyclovir (1 g three times daily), or famciclovir (250 mg three times daily) for 5–7 days is recommended for adolescents and adults with chickenpox of ≤24 h duration. (Valacyclovir is licensed for use in children and adolescents. Famciclovir is recommended but not licensed for varicella.) Likewise, acyclovir therapy may be of benefit to children <12 years of age if initiated early in the disease (<24 h) at a dose of 20 mg/kg every 6 h. The advantages (i.e., pharmacokinetics) of the second-generation agents valacyclovir and famciclovir are described in **Chap. 186**.

Aluminum acetate soaks for the management of herpes zoster can be both soothing and cleansing. Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Acyclovir is administered at a dosage of 800 mg five times daily for 7–10 days. However, valacyclovir and famciclovir are superior in terms of pharmacokinetics and pharmacodynamics and should be used preferentially. Famciclovir, the prodrug of penciclovir, is at least as effective as acyclovir and perhaps more so; the dose is 500 mg by mouth three times daily for 7 days.

Valacyclovir, the prodrug of acyclovir, accelerates healing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5–7 days. Compared with acyclovir, both famciclovir and valacyclovir offer the advantage of less frequent administration. All three of these drugs are now available as generic products.

In severely immunocompromised hosts (e.g., transplant recipients, patients with lymphoproliferative malignancies), both chickenpox and herpes zoster (including disseminated disease) should be treated, at least at the outset, with IV acyclovir, which reduces the occurrence of visceral complications but has no effect on healing of skin lesions or pain. The dose is 10 mg/kg every 8 h for 7 days. For low-risk immunocompromised hosts, oral therapy with valacyclovir or famciclovir appears beneficial. If medically feasible, it is desirable to decrease immunosuppressive treatment concomitant with the administration of IV acyclovir.

Patients with varicella pneumonia typically require ventilatory support. Persons with zoster ophthalmicus should be referred immediately to an ophthalmologist. Therapy for this condition consists of the administration of analgesics for severe pain and the use of atropine. Acyclovir, valacyclovir, and famciclovir all accelerate healing. Decisions about the use of glucocorticoids should be made by the ophthalmologist.

The management of acute neuritis and/or postherpetic neuralgia can be particularly difficult. In addition to the judicious use of analgesics ranging from non-narcotics to narcotic derivatives, drugs such as gabapentin, pregabalin, amitriptyline hydrochloride, lidocaine (patches), and fluphenazine hydrochloride are reportedly beneficial for pain relief. In one study, glucocorticoid therapy administered early in the course of localized herpes zoster significantly accelerated such quality-of-life improvements as a return to usual activity and termination of analgesic medications. The dose of prednisone administered orally was 60 mg/d on days 1–7, 30 mg/d on days 8–14, and 15 mg/d on days 15–21. This regimen is appropriate only for relatively healthy elderly persons with moderate or severe pain at presentation. Patients with osteoporosis, diabetes mellitus, glycosuria, or hypertension may not be appropriate candidates. Glucocorticoids should not be used without concomitant antiviral therapy.

PREVENTION

Three methods are used for the prevention of VZV infections. First, a live attenuated varicella vaccine (Oka) is recommended for all children >1 year of age (up to 12 years of age) who have not had chickenpox and for adults known to be seronegative for VZV. Two doses are recommended for all children: the first at 12–15 months of age and the second at ~4–6 years of age. VZV-seronegative persons >13 years of age should receive two doses of vaccine at least 1 month apart. The vaccine is both safe and efficacious. Breakthrough cases are mild and may result in spread of the vaccine virus to susceptible contacts. The universal vaccination of children has resulted in a decreased incidence of chickenpox in sentinel communities. Furthermore, inactivation of the vaccine virus significantly decreases the occurrence of herpes zoster after hematopoietic stem-cell transplantation.

In individuals >50 years of age, a VZV vaccine with 18 times the viral content of the Oka vaccine (ZostaVax) decreased the incidence of shingles by 51%, the burden of illness by 61%, and the incidence of postherpetic neuralgia by 66%. The Advisory Committee on Immunization Practices has therefore recommended that persons in this age group be offered this vaccine in order to reduce the frequency of shingles and the severity of postherpetic neuralgia. Of note, vaccine immunity wanes over time, and reassessment of current recommendations or the use of a promising inactivated vaccine in development will be required.

A second approach is to administer varicella-zoster immune globulin (VZIG) to individuals who are susceptible, are at high risk for developing complications of varicella, and have had a significant exposure. This product should be given within 96 h (preferably within 72 h) of the exposure. Indications for administration of VZIG appear in Table 188-1.

TABLE 188-1 Recommendations for VZIG Administration

Exposure Criteria
1. Significant exposure to a person with chickenpox or zoster
a. Household: residence in the same household
b. Playmate: face-to-face indoor play
c. Hospital
Varicella: same 2- to 4-bed room or adjacent beds in a large ward, face-to-face contact with an infectious staff member or patient, visit by a person deemed contagious
Zoster: intimate contact (e.g., touching or hugging) with a person deemed contagious
d. Newborn infant: onset of varicella in the mother ≤5 days before delivery or ≤48 h after delivery; VZIG not indicated if the mother has zoster
2. Patient should receive VZIG as soon as possible but not >96 h after exposure.
Candidates (Provided They Have Significant Exposure) Include
1. Immunocompromised susceptible children without a history of varicella or varicella immunization
2. Susceptible pregnant women
3. Newborn infants whose mother had onset of chickenpox within 5 days before or within 48 h after delivery
4. Hospitalized premature infant (≥28 weeks of gestation) whose mother lacks a reliable history of chickenpox or serologic evidence of protection against varicella
5. Hospitalized premature infant (<28 weeks of gestation or ≤1000-g birth weight), regardless of maternal history of varicella or VZV serologic status

Note: Table is adapted from the American Academy of Pediatrics *Red Book.*

Lastly, antiviral therapy can be given as prophylaxis to individuals at high risk who are ineligible for vaccination or who are beyond the 96-h window after direct contact. While the initial studies have used acyclovir, similar benefit can be anticipated with either valacyclovir or famciclovir. Therapy is instituted 7 days after intense exposure. At this time, the host is midway into the incubation period. This approach significantly decreases disease severity, if not totally preventing disease.

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189 Epstein-Barr Virus Infections, Including Infectious Mononucleosis

Jeffrey I. Cohen

DEFINITION

Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several tumors, including nasopharyngeal and gastric carcinoma, Burkitt's lymphoma, Hodgkin's disease, T cell lymphoma, and (in patients with immunodeficiencies) B cell lymphoma and smooth muscle tumors. The virus is a member of the family Herpesviridae. The two types of EBV that are widely prevalent in nature are not distinguishable by conventional serologic tests.

EPIDEMIOLOGY

EBV infections occur worldwide. These infections are most common in early childhood, with a second peak during late adolescence. By adulthood, more than 90% of individuals have been infected and have antibodies to the virus. IM is usually a disease of young adults. In lower socioeconomic groups and in areas of the world with deficient standards of hygiene (e.g., developing regions), EBV tends to infect children at an early age, and IM is uncommon. In areas with higher standards of hygiene, infection with EBV is often delayed until adulthood, and IM is more prevalent.

EBV is spread by contact with oral secretions. The virus is frequently transmitted from asymptomatic adults to infants and among young adults by transfer of saliva during kissing. Transmission by less intimate contact is rare. EBV has been transmitted by blood transfusion and by bone marrow transplantation. More than 90% of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions. Shedding is increased in immunocompromised patients and those with IM.

PATHOGENESIS

EBV is transmitted by salivary secretions. The virus infects the epithelium of the oropharynx and the salivary glands and is shed from these cells. While B cells may become infected after contact with epithelial cells, studies suggest that lymphocytes in the tonsillar crypts can be infected directly. The virus then spreads through the bloodstream. The proliferation and expansion of EBV-infected B cells along with reactive T cells during IM result in enlargement of lymphoid tissue. Polyclonal activation of B cells leads to the production of antibodies to host-cell and viral proteins. During the acute phase of IM, up to 1 in every 100 B cells in the peripheral blood is infected by EBV; after recovery, 1–50 in every 1 million B cells is infected. During IM, there is an inverted CD4+/CD8+ T cell ratio. The percentage of CD4+ T cells decreases, while there are large clonal expansions of CD8+ T cells; up to 40% of CD8+ T cells are directed against EBV antigens during acute infection. Memory B cells, not epithelial cells, are the reservoir for EBV in the body. When patients are treated with acyclovir, shedding of EBV from the oropharynx stops but the virus persists in B cells.

The EBV receptor (CD21) on the surface of B cells is also the receptor for the C3d component of complement. Another EBV receptor (CD35) on B cells binds to CD21. Human leukocyte antigen class II serves as a co-receptor for EBV entry into B cells. EBV infection of epithelial cells occurs by virus binding to integrins and results in viral replication and production of virions. When B cells are infected by EBV in vitro, they become transformed and can proliferate indefinitely. During latent infection of B cells, the EBV nuclear antigens (EBNAs), latent membrane proteins (LMPs), multiple microRNAs, and small EBV RNAs (EBERs) are expressed in vitro. EBV-transformed B cells secrete immunoglobulin; only a small fraction of these cells produce virus.

Cellular immunity is more important than humoral immunity in controlling EBV infection. In the initial phase of infection, suppressor T cells, natural killer cells, and nonspecific cytotoxic T cells are important in controlling the proliferation of EBV-infected B cells. Levels of markers of T cell activation and serum interferon γ are elevated. Later in infection, human leukocyte antigen–restricted cytotoxic T cells that recognize EBNAs and LMPs and destroy EBV-infected cells are generated.

If T cell immunity is compromised, EBV-infected B cells may begin to proliferate. When EBV is associated with lymphoma in immunocompetent persons, virus-induced proliferation is but one step in a multistep process of neoplastic transformation. In many EBV-containing tumors, LMP-1 mimics members of the tumor necrosis factor receptor family (e.g., CD40), transmitting growth-proliferating signals.

CLINICAL MANIFESTATIONS

Signs and Symptoms Most EBV infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis. In contrast, ~75% of infections in adolescents present as IM. IM in the elderly often presents with nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise. In contrast, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients.

The incubation period for IM in young adults is ~4–6 weeks. A prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, sore throat, and lymphadenopathy. Fever is usually low-grade and is most common in the first 2 weeks of the illness; however, it may persist for >1 month. Common signs and symptoms are listed along with their frequencies in **Table 189-1**. Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks. Lymphadenopathy most often affects the posterior cervical nodes but may be generalized. Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place. Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis. A morbilliform or papular rash, usually on the arms or trunk, develops in ~5% of cases **(Fig. 189-1)**. Earlier studies reported that many patients treated with penicillin derivatives develop a macular rash; penicillin-associated rashes are not predictive of future adverse reactions to penicillins. More recent studies suggest that EBV-associated rashes may occur with similar frequency in those exposed to penicillin derivatives and those not taking these drugs. Erythema nodosum **(Fig. A1-39)** and erythema multiforme **(Fig. A1-24)** also have been described **(Chap. 54)**. The severity of the disease correlates with the levels of CD8+ T cells and EBV DNA in the blood. Most patients

TABLE 189-1 Signs and Symptoms of Infectious Mononucleosis

MANIFESTATION	MEDIAN PERCENTAGE OF PATIENTS (RANGE)
Symptoms	
Sore throat	75 (50–87)
Malaise	47 (42–76)
Headache	38 (22–67)
Abdominal pain, nausea, or vomiting	17 (5–25)
Chills	10 (9–11)
Signs	
Lymphadenopathy	95 (83–100)
Fever	93 (60–100)
Pharyngitis or tonsillitis	82 (68–90)
Splenomegaly	51 (43–64)
Hepatomegaly	11 (6–15)
Rash	10 (0–25)
Periorbital edema	13 (2–34)
Palatal enanthem	7 (3–13)
Jaundice	5 (2–10)

FIGURE 189-1 Rash in a patient with infectious mononucleosis due to Epstein-Barr virus. *(Courtesy of Maria Turner, MD; with permission.)*

have symptoms for 2–4 weeks, but nearly 10% have fatigue that persists for ≥6 months.

Laboratory Findings The white blood cell count is usually elevated and peaks at 10,000–20,000/μL during the second or third week of illness. Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes. The latter cells are enlarged lymphocytes that have abundant cytoplasm, vacuoles, and indentations of the cell membrane **(Fig. 189-2)**. CD8+ T cells predominate among the atypical lymphocytes. Low-grade neutropenia and thrombocytopenia are common during the first month of illness. Liver function is abnormal in >90% of cases. Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated. The serum concentration of bilirubin is elevated in ~40% of cases.

Complications Most cases of IM are self-limited. Deaths are very rare and are most often due to central nervous system (CNS) complications, splenic rupture, upper-airway obstruction, or bacterial superinfection.

When CNS complications develop, they usually do so during the first 2 weeks of EBV infection; in some patients, especially children, they are the only clinical manifestations of acute infection. Heterophile antibodies and atypical lymphocytes may be absent. Meningitis and encephalitis are the most common neurologic abnormalities, and patients may present with headache, meningismus, or cerebellar ataxia. Acute hemiplegia and psychosis also have been described. The cerebrospinal fluid contains mainly lymphocytes, with occasional atypical lymphocytes. Most cases resolve without neurologic sequelae. Acute EBV infection has also been associated with cranial nerve palsies (especially those involving cranial nerve VII), Guillain-Barré syndrome, acute transverse myelitis, and peripheral neuritis.

Autoimmune hemolytic anemia occurs in ~2% of cases during the first 2 weeks. In most cases, the anemia is Coombs-positive, with cold agglutinins directed against the red blood cell antigen. Most patients with hemolysis have mild anemia that lasts for 1–2 months, but some patients have severe disease with hemoglobinuria and jaundice. Nonspecific antibody responses may also include rheumatoid factor, antinuclear antibodies, anti–smooth muscle antibodies, antiplatelet antibodies, and cryoglobulins. IM has been associated with red-cell aplasia, severe granulocytopenia, thrombocytopenia, pancytopenia, and hemophagocytic lymphohistiocytosis. The spleen ruptures in <0.5% of cases. Splenic rupture is more common among male than female patients and may manifest as abdominal pain, referred shoulder pain, or hemodynamic compromise.

Hypertrophy of lymphoid tissue in the tonsils or adenoids can result in upper-airway obstruction, as can inflammation and edema of the epiglottis, pharynx, or uvula. About 10% of patients with IM develop streptococcal pharyngitis after their initial sore throat resolves.

Other rare complications associated with acute EBV infection include hepatitis (which can be fulminant), myocarditis or pericarditis, pneumonia with pleural effusion, interstitial nephritis, genital ulcerations, and vasculitis.

EBV-Associated Diseases Other Than IM EBV-associated lymphoproliferative disease has been described in patients with congenital or acquired immunodeficiency, including those with severe combined immunodeficiency, patients with AIDS, and recipients of bone marrow or organ transplants who are receiving immunosuppressive drugs (especially cyclosporine). Proliferating EBV-infected B cells infiltrate lymph nodes and multiple organs, and patients present with fever and lymphadenopathy or gastrointestinal symptoms. Pathologic studies show B cell hyperplasia or poly- or monoclonal lymphoma.

X-linked lymphoproliferative disease is a recessive disorder of young boys who have a normal response to childhood infections but develop fatal lymphoproliferative disorders after infection with EBV. The protein associated with most cases of this syndrome (SAP) binds to a protein that mediates interactions of B and T cells. Most patients with this syndrome die of acute IM. Others develop hypogammaglobulinemia, malignant B cell lymphomas, aplastic anemia, or agranulocytosis. Disease resembling X-linked lymphoproliferative disease, but with more prominent hemophagocytosis, has also been associated with mutations in XIAP. Mutations in *ITK*, *MAGT1*, *CORO1A*, or *CD27* are associated with inability to control EBV and lymphoma. Mutations in other genes, such as *GATA2*, *PIK3CD*, *CTPS1*, and several genes associated with severe combined immunodeficiency, also can predispose to severe or fatal EBV disease as well as other infections. Moreover, IM has proved fatal to some patients with no obvious preexisting immune abnormality.

Oral hairy leukoplakia **(Fig. 189-3)** is an early manifestation of infection with HIV in adults **(Chap. 197)**. Most patients present with

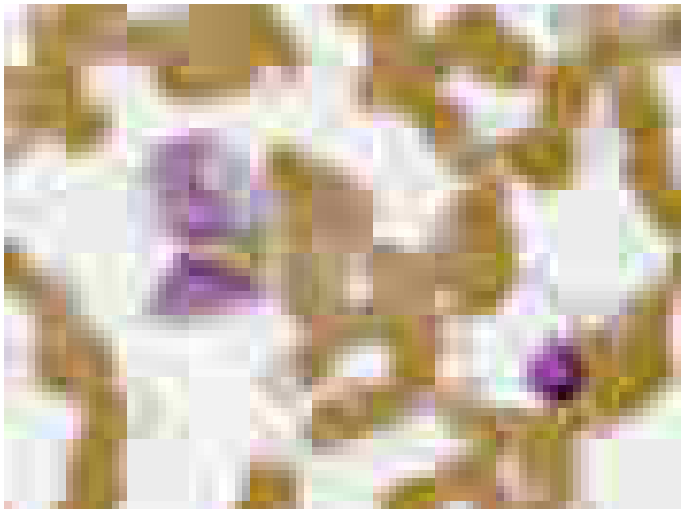

FIGURE 189-2 Atypical lymphocytes from a patient with infectious mononucleosis due to Epstein-Barr virus.

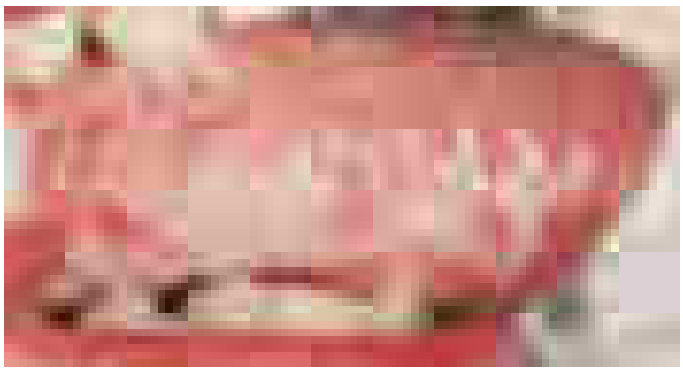

FIGURE 189-3 Oral hairy leukoplakia often presents as white plaques on the lateral surface of the tongue and is associated with Epstein-Barr virus infection.

raised, white corrugated lesions on the tongue (and occasionally on the buccal mucosa) that contain EBV DNA. Children infected with HIV can develop lymphoid interstitial pneumonitis; EBV DNA is often found in lung tissue from these patients.

Patients with chronic fatigue syndrome may have titers of antibody to EBV that are elevated but are not significantly different from those in healthy EBV-seropositive adults. While some patients have malaise and fatigue that persist for weeks or months after IM, persistent EBV infection is not a cause of chronic fatigue syndrome. Chronic active EBV infection is very rare and is distinct from chronic fatigue syndrome. The affected patients have an illness lasting >6 months, with elevated levels of EBV DNA in the blood (in T cells, NK cells, or B cells); high titers of antibody to EBV; and evidence of organ involvement, including hepatosplenomegaly, lymphadenopathy, and pneumonitis, uveitis, or neurologic disease.

EBV is associated with several malignancies. About 15% of cases of Burkitt's lymphoma in the United States and ~90% of those in Africa are associated with EBV **(Chap. 104)**. African patients with Burkitt's lymphoma have high levels of antibody to EBV, and their tumor tissue usually contains viral DNA. Malaria in African patients may impair cellular immunity to EBV and induce polyclonal B cell activation with an expansion of EBV-infected B cells. In addition, malaria may target B cells and result in expansion of germinal centers, with consequently increased activity of activation-induced cytidine deaminase, which can mutate DNA. These changes may enhance the proliferation of B cells with elevated EBV DNA in the bloodstream, thereby increasing the likelihood of a *c-myc* translocation—the hallmark of Burkitt's lymphoma. EBV-containing Burkitt's lymphoma also occurs in patients with AIDS.

Anaplastic nasopharyngeal carcinoma is common in southern China and is uniformly associated with EBV; the affected tissues contain viral DNA and antigens. Patients with nasopharyngeal carcinoma often have elevated titers of antibody to EBV **(Chap. 73)**. High levels of EBV plasma DNA before treatment or detectable levels of EBV DNA after radiation therapy correlate with lower rates of overall survival and relapse-free survival among patients with nasopharyngeal carcinoma.

Worldwide, the most common EBV-associated malignancy is gastric carcinoma. About 9% of these tumors are EBV-positive **(Chap. 76)**.

EBV has been associated with Hodgkin's disease, especially the mixed-cellularity type **(Chap. 105)**. Patients with Hodgkin's disease often have elevated titers of antibody to EBV. In about half of cases in the United States, viral DNA and antigens are found in Reed-Sternberg cells. The risk of EBV-positive Hodgkin's disease is significantly increased in young adults for several years after EBV-seropositive IM. About 50% of non-Hodgkin's lymphomas in patients with AIDS are EBV-positive.

EBV is present in B cells of lesions from patients with lymphomatoid granulomatosis. In some cases, EBV DNA has been detected in tumors from immunocompetent patients with angiocentric nasal NK/T cell lymphoma, T cell lymphoma, and CNS lymphoma. Studies have demonstrated viral DNA in leiomyosarcomas from AIDS patients and in smooth-muscle tumors from organ transplant recipients. Virtually all CNS lymphomas in AIDS patients are associated with EBV. Studies have found that a history of IM and higher levels of antibodies to EBV before the onset of disease is more common in persons with multiple sclerosis than in the general population; additional research on a possible causal relationship is needed.

DIAGNOSIS

Serologic Testing (Fig. 189-4) The heterophile test is used for the diagnosis of IM in children and adults. In the test for this antibody, human serum is absorbed with guinea pig kidney, and the heterophile titer is defined as the greatest serum dilution that agglutinates sheep, horse, or cow erythrocytes. The heterophile antibody does not interact with EBV proteins. A titer of ≥40 is diagnostic of acute EBV infection in a patient who has symptoms compatible with IM and atypical lymphocytes. Tests for heterophile antibodies are positive in 40% of patients with IM during the first week of illness and in 80–90% during the third week. Therefore, repeated testing may be necessary, especially if the initial test is performed early. Tests usually remain positive for 3 months after the onset of illness, but heterophile antibodies can persist for up to 1 year. These antibodies usually are not detectable in children <5 years of age, in the elderly, or in patients presenting with symptoms not typical of IM. The commercially available monospot test for heterophile antibodies is somewhat more sensitive than the classic heterophile test. The monospot test is ~75% sensitive and ~90% specific compared with EBV-specific serologies (see below). False-positive monospot results are more common among persons with connective tissue disease, lymphoma, viral hepatitis, and malaria.

EBV-specific antibody testing is used for patients with suspected acute EBV infection who lack heterophile antibodies and for patients with atypical infections. Titers of IgM and IgG antibodies to viral capsid antigen (VCA) are elevated in the serum of more than 90% of patients at the onset of disease. IgM antibody to VCA is most useful for the diagnosis of acute IM because it is present at elevated titers only during the first 2–3 months of the disease; in contrast, IgG antibody to VCA usually is not useful for diagnosis of IM but often is used to assess past exposure to EBV because it persists for life. Seroconversion to EBNA positivity also is useful for the diagnosis of acute infection with EBV. Antibodies to EBNA become detectable relatively late (3–6 weeks after the onset of symptoms) in nearly all cases of acute EBV infection and persist for the lifetime of the patient. These antibodies may be lacking in immunodeficient patients and in those with chronic active EBV infection.

Titers of other antibodies also may be elevated in IM; however, these elevations are less useful for diagnosis. Antibodies to early antigens are detectable 3–4 weeks after the onset of symptoms in patients with IM. About 70% of individuals with IM have antibodies to early antigen diffuse (EA-D) during the illness; the presence of EA-D antibodies is especially likely in patients with relatively severe disease. These antibodies usually persist for only 3–6 months. Levels of EA-D antibodies are also elevated in patients with nasopharyngeal carcinoma or chronic active EBV infection. Antibodies to early antigen restricted (EA-R) are only occasionally detected in patients with IM but are often found at elevated titers in patients with African Burkitt's lymphoma or chronic active EBV infection. IgA antibodies to EBV antigens have proved useful for the identification of patients with nasopharyngeal carcinoma and of persons at high risk for the disease.

Other Studies Detection of EBV DNA, RNA, or proteins has been valuable in demonstrating the association of the virus with various malignancies. The polymerase chain reaction has been used to detect EBV DNA in the cerebrospinal fluid of some AIDS patients with CNS lymphomas and to monitor the amount of EBV DNA in the blood of patients with lymphoproliferative disease. Detection of high

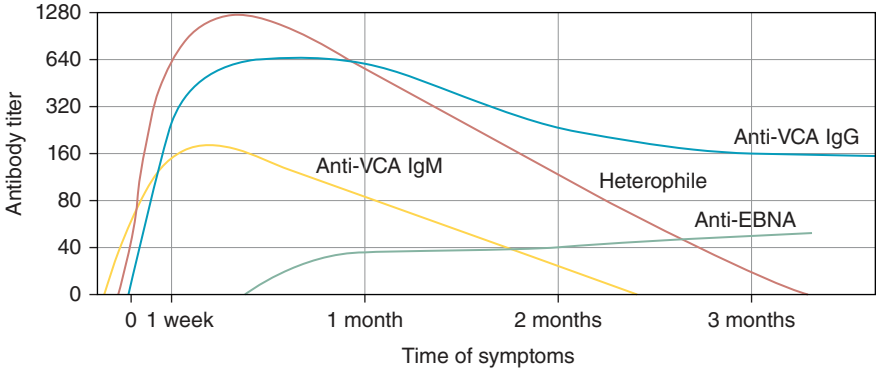

FIGURE 189-4 Pattern of Epstein-Barr virus (EBV) serology during acute infection. EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen. *(From JI Cohen, in NS Young et al [eds]: Clinical Hematology. Philadelphia, Mosby, 2006.)*

TABLE 189-2 Differential Diagnosis of Infectious Mononucleosis

ETIOLOGY	SIGN OR SYMPTOM				DIFFERENCES FROM EBV MONONUCLEOSIS
	FEVER	ADENOPATHY	SORE THROAT	ATYPICAL LYMPHOCYTES	
EBV infection	+	+	+	+	—
CMV infection	+	±	±	+	Older age at presentation, longer duration of fever
HIV infection	+	+	+	±	Diffuse rash, oral/genital ulcers, aseptic meningitis
Toxoplasmosis	+	+	±	±	Less splenomegaly, exposure to cats or raw meat
HHV-6 infection	+	+	+	+	Older age at presentation
Streptococcal pharyngitis	+	+	+	–	No splenomegaly, less fatigue
Viral hepatitis	+	±	–	±	Higher aminotransferase levels
Rubella	+	+	±	±	Maculopapular rash, no splenomegaly
Lymphoma	+	+	+	+	Fixed, nontender lymph nodes
Drugs[a]	+	+	–	±	Occurs at any age

[a]Most commonly phenytoin, carbamazepine, sulfonamides, or minocycline.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus.

levels of EBV DNA in blood for a few days to several weeks after the onset of IM may be useful if serologic studies yield equivocal results. Culture of EBV from throat washings or blood is not helpful in the diagnosis of acute infection, since EBV persists in the oropharynx and in B cells for the lifetime of the infected individual.

Differential Diagnosis Whereas ~90% of cases of IM are due to EBV, 5–10% of cases are due to cytomegalovirus (CMV) **(Chap. 190)**. CMV is the most common cause of heterophile-negative mononucleosis; less common causes of IM and differences from IM due to EBV are shown in **Table 189-2**.

TREATMENT

EBV-Associated Disease

Therapy for IM consists of supportive measures, with rest and analgesia. Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture, which often necessitates splenectomy. Glucocorticoid therapy is not indicated for uncomplicated IM and in fact may predispose to bacterial superinfection. Prednisone (40–60 mg/d for 2–3 days, with subsequent tapering of the dose over 1–2 weeks) has been used for the prevention of airway obstruction in patients with severe tonsillar hypertrophy, for autoimmune hemolytic anemia, for hemophagocytic lymphohistiocytosis, and for severe thrombocytopenia. Glucocorticoids have also been administered to rare patients with severe malaise and fever and to patients with severe CNS or cardiac disease.

Acyclovir has had no significant clinical impact on IM in controlled trials. In one study, the combination of acyclovir and prednisolone had no significant effect on the duration of symptoms of IM.

Acyclovir, at a dosage of 400–800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses). Post-transplantation EBV lymphoproliferative disease **(Chap. 138)** generally does not respond to antiviral therapy. When possible, therapy should be directed toward reduction of immunosuppression. Antibody to CD20 (rituximab) has been effective in some cases. Infusions of donor lymphocytes are often effective for stem cell transplant recipients, although graft-versus-host disease can occur. Infusions of EBV-specific cytotoxic T cells have been used to prevent EBV lymphoproliferative disease in high-risk settings as well as to treat the disease. Interferon α administration, cytotoxic chemotherapy, and radiation therapy (especially for CNS lesions) also have been used. Infusion of autologous EBV-specific cytotoxic T lymphocytes has shown promise in small studies of patients with nasopharyngeal carcinoma and Hodgkin's disease. Treatment of several cases of X-linked lymphoproliferative disease with antibody to CD20 resulted in a successful outcome of what otherwise would probably have been fatal acute EBV infection.

PREVENTION

The isolation of patients with IM is unnecessary. A vaccine directed against the major EBV glycoprotein reduced the frequency of IM but did not affect the rate of asymptomatic infection in a phase 2 trial. Additional vaccines are under development.

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190 Cytomegalovirus and Human Herpesvirus Types 6, 7, and 8

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CYTOMEGALOVIRUS

DEFINITION

Cytomegalovirus (CMV), which was initially isolated from patients with congenital cytomegalic inclusion disease, is now recognized as an important pathogen in all age groups. In addition to inducing severe birth defects, CMV causes a wide spectrum of disorders in older children and adults, ranging from an asymptomatic subclinical infection to a mononucleosis syndrome in healthy individuals to disseminated disease in immunocompromised patients. Human CMV is one of several related species-specific viruses that cause similar diseases in various animals. All are associated with the production of characteristic enlarged cells—hence the name *cytomegalovirus*.

CMV, a β-herpesvirus, has double-stranded DNA, four species of mRNA, a protein capsid, and a lipoprotein envelope. Like other herpesviruses, CMV demonstrates icosahedral symmetry, replicates in the cell nucleus, and can cause either a lytic and productive or a latent infection. CMV can be distinguished from other herpesviruses by certain biologic properties, such as host range and type of cytopathology. Viral replication is associated with the production of large intranuclear inclusions and smaller cytoplasmic inclusions. CMV appears to

replicate in a variety of cell types in vivo; in tissue culture it grows preferentially in fibroblasts. Although there is little evidence that CMV is oncogenic in vivo, it does transform fibroblasts in rare instances, and genomic transforming fragments have been identified.

EPIDEMIOLOGY

CMV has a worldwide distribution. In many regions of the world, nearly all adults are seropositive for CMV, whereas only half of adults in the United States and Canada are seropositive. In regions where the prevalence of CMV antibody is high, immunocompromised adults are more likely to undergo reactivation disease rather than primary infection. Data generated in specific regions should be considered in the context of local seropositivity rates, when appropriate.

Of newborns in the United States, ~1% are infected with CMV; the percentages are higher in less developed regions. Communal living and poor personal hygiene facilitate spread. Perinatal and early childhood infections are common. CMV may be present in breast milk, saliva, feces, and urine. Transmission has occurred among young children in day-care centers and has been traced from infected toddler to pregnant mother to developing fetus. When an infected child introduces CMV into a household, 50% of susceptible family members seroconvert within 6 months.

CMV is not readily spread by casual contact but rather requires repeated or prolonged intimate exposure for transmission. In late adolescence and young adulthood, CMV is often transmitted sexually, and asymptomatic carriage in semen or cervical secretions is common. Antibody to CMV is present at detectable levels in a high proportion of sexually active men and women, who may harbor several strains simultaneously. Transfusion of blood products containing viable leukocytes may transmit CMV, with a frequency of 0.14–10% per unit transfused. Transfusion of leukocyte-reduced or CMV-seronegative blood significantly decreases the risk of CMV transmission.

Once infected, an individual generally carries CMV for life. The infection usually remains silent. CMV reactivation syndromes develop more frequently, however, when T lymphocyte–mediated immunity is compromised—for example, after organ transplantation, with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, HIV infection; **Chap. 197**), or during critical illness in intensive care units. Most primary CMV infections in organ transplant recipients **(Chap. 138)** result from transmission via the graft. In CMV-seropositive transplant recipients, infection results from reactivation of latent virus or from infection by a new strain from the donor. CMV infection may also be associated with diseases as diverse as coronary artery stenosis and malignant gliomas, although these associations require further validation.

PATHOGENESIS

Congenital CMV infection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is related largely to primary maternal infection **(Table 190-1)**. The major factors determining the severity of congenital infection are unclear, although a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Primary infection with CMV in late childhood or adulthood is often associated with a vigorous T lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to the sequelae of infection with Epstein-Barr virus **(Chap. 189)**. The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8+ T lymphocytes. Polyclonal activation of B cells by CMV contributes to the development of rheumatoid factors and other autoantibodies during mononucleosis.

Once acquired, CMV persists indefinitely in host tissues. The sites of persistent infection may include multiple cell types and various organs. Transmission via blood transfusion or organ transplantation is due primarily to silent infections in these tissues. If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can reactivate to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, after organ transplantation) appears to be an ideal setting for CMV activation and CMV disease. Certain particularly potent suppressants of T cell immunity (e.g., antithymocyte globulin, alemtuzumab) are associated with a high rate of clinical CMV syndromes. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens such as bacteria, molds, and *Pneumocystis*.

PATHOLOGY

Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10-μm intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an "owl's eye" appearance. Smaller granular cytoplasmic inclusions are demonstrated occasionally. Cytomegalic cells are found in a wide variety of organs, including the salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and central nervous system.

The cellular inflammatory response to infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute to CMV disease. Immune complexes have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has also been observed in some CMV-infected patients after renal transplantation.

CLINICAL MANIFESTATIONS

Congenital CMV Infection Fetal infections range from subclinical to severe and disseminated. CMV seroconversion rates during pregnancy range from 1% to 7%. Of infants born to mothers with primary CMV infections during pregnancy, 5–20% will develop clinical manifestations, with a mortality rate of ~5%. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60–80% of cases). Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30–50% of

TABLE 190-1 CMV Disease in the Immunocompromised Host

POPULATION	RISK FACTORS	PRINCIPAL SYNDROME(S)	TREATMENT	PREVENTION
Fetus	Primary maternal infection/early pregnancy	Cytomegalic inclusion disease	Ganciclovir followed by valganciclovir for symptomatic neonates	Avoidance of exposure; possible maternal treatment with CMV immunoglobulin during pregnancy
Organ transplant recipient	Seropositivity of donor and/or recipient; potent immunosuppressive regimen; treatment of rejection	Febrile leukopenia; gastrointestinal disease; pneumonia	Ganciclovir or valganciclovir	Prophylaxis with ganciclovir or valganciclovir or preemptive therapy
Hematopoietic stem cell transplant recipient	Graft-vs-host disease; older age of recipient; seropositive recipient; viremia	Pneumonia; gastrointestinal disease	Ganciclovir or valganciclovir or foscarnet, ± CMV immunoglobulin	Prophylaxis with letermovir, ganciclovir, or valganciclovir or preemptive therapy
Person with HIV	<50 CD4+ T cells/μL; CMV seropositivity	Retinitis; gastrointestinal disease; neurologic disease	Ganciclovir, valganciclovir, foscarnet, or cidofovir	Oral valganciclovir

cases. Inguinal hernias and chorioretinitis are less common. Laboratory abnormalities include elevated alanine aminotransferase levels in serum, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated protein levels in cerebrospinal fluid. The prognosis for severely infected infants is poor, and few survivors escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, toxoplasmosis, bacterial sepsis, and infection with a variety of viruses, including rubella, Zika, or herpes simplex virus.

Most congenital CMV infections are clinically inapparent at birth. Of asymptomatically infected infants, 5–25% develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

Perinatal CMV Infection The newborn may acquire CMV at delivery by passage through an infected birth canal or by postnatal contact with infected breast milk or other maternal secretions. Of infants who are breast-fed for >1 month by seropositive mothers, 40–60% become infected. Iatrogenic transmission can result from blood transfusion; use of leukocyte-reduced or CMV-seronegative blood products for transfusion into low-birth-weight seronegative infants or seronegative pregnant women decreases risk.

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquired CMV infection, particularly in premature infants, and occasionally has been accompanied by infection with *Chlamydia trachomatis*, *Pneumocystis*, or *Ureaplasma urealyticum*. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for months or years.

CMV Mononucleosis The most common clinical manifestation of CMV infection in immunocompetent hosts beyond the neonatal period is a heterophile antibody–negative mononucleosis syndrome, which may develop spontaneously or follow transfusion of leukocyte-containing blood products. Although the syndrome occurs at all ages, it most often involves sexually active young adults. With incubation periods of 20–60 days, the illness generally lasts for 2–6 weeks. Prolonged high fevers, sometimes with chills, profound fatigue, and malaise, characterize this disorder. Myalgias, headache, and splenomegaly are common, but in CMV mononucleosis (as opposed to Epstein-Barr virus mononucleosis), exudative pharyngitis and cervical lymphadenopathy are rare. Occasional patients develop rubelliform rashes, often after exposure to ampicillin or certain other antibiotics. Less common are interstitial or segmental pneumonia, myocarditis, pleuritis, arthritis, and encephalitis. In rare cases, Guillain-Barré syndrome complicates CMV mononucleosis. The characteristic laboratory abnormality of CMV mononucleosis is relative lymphocytosis in peripheral blood, with >10% atypical lymphocytes. Total leukocyte counts may be low, normal, or markedly elevated. Although significant jaundice is uncommon, serum aminotransferase and alkaline phosphatase levels are often moderately elevated. Heterophile antibodies are absent; however, transient immunologic abnormalities are common and may include the presence of cryoglobulins, rheumatoid factors, cold agglutinins, and antinuclear antibodies. Hemolytic anemia, thrombocytopenia, and granulocytopenia complicate recovery in rare instances.

Most patients recover without sequelae, although postviral asthenia may persist for months. The excretion of CMV in urine, genital secretions, and/or saliva often continues for months or years. Rarely, CMV infection is fatal in immunocompetent hosts; survivors can have recurrent episodes of fever and malaise, sometimes associated with autonomic nervous system dysfunction (e.g., attacks of sweating or flushing).

CMV Infection in the Immunocompromised Host (Table 190-1) CMV is the most common viral pathogen complicating organ transplantation **(Chap. 138)**. In recipients of kidney, heart, lung, liver, pancreas, and vascularized composite (hand, face, other) transplants, CMV infection may result in a variety of clinical manifestations, including fever and leukopenia, hepatitis, colitis, pneumonitis, esophagitis, gastritis, and retinitis. CMV disease is an independent risk factor for both graft loss and death. Without prophylaxis, the period of maximal risk is between 1 and 4 months after transplantation. Disease likelihood and viral replication levels generally are greater after primary infection than after reactivation. Molecular studies indicate that seropositive organ transplant recipients are susceptible to infection with donor-derived, genotypically variant CMV. Reactivation infection, although common, is less likely than primary infection to be clinically significant. The overall risk of clinical disease is related to various factors, such as serologic mismatch (donor seropositive, recipient seronegative), degree of immunosuppression, use of antilymphocyte antibodies, lack of anti-CMV prophylaxis, and co-infection with other pathogens. The transplanted organ is particularly vulnerable as a target for CMV infection; thus there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation.

CMV viremia occurs in roughly one-third of hematopoietic stem cell transplant recipients; the risk of severe disease may be reduced by prophylaxis or preemptive therapy with antiviral drugs. The risk is greatest in the first 100 days after transplantation, and identified risk factors include certain types of immunosuppressive therapy, an allogeneic (rather than an autologous) graft, acute graft-versus-host disease, older age, and pretransplantation recipient seropositivity.

CMV is an important pathogen in patients with advanced HIV infection **(Chap. 197)**, in whom it may cause retinitis or disseminated disease, particularly when peripheral-blood CD4+ T cell counts fall below 50/μL. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. During the first few weeks after institution of highly active antiretroviral therapy, however, acute flare-ups of CMV retinitis may occur secondary to an immune reconstitution inflammatory syndrome.

Syndromes produced by CMV in immunocompromised hosts ("CMV syndrome") often begin with fatigue, fever, malaise, anorexia, night sweats, and arthralgias or myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. Without treatment, CMV infection may progress to more severe end-organ disease. The development of tachypnea, hypoxemia, and nonproductive cough signals respiratory involvement. Radiologic examination of the lung often shows bilateral interstitial or reticulonodular infiltrates that begin in the periphery of the lower lobes and spread centrally and superiorly; localized segmental, nodular, or alveolar patterns are less common. The differential diagnosis includes *Pneumocystis* infection; other viral, bacterial, or fungal infections; pulmonary hemorrhage; and injury secondary to irradiation or to treatment with cytotoxic drugs.

Gastrointestinal CMV involvement may be localized or extensive and almost exclusively affects immunocompromised hosts. Colitis is the most common clinical manifestation in organ transplant recipients. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. Clinicians should be aware that blood tests such as CMV antigenemia and viral load testing may yield negative results in the setting of intestinal disease. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly after liver transplantation. Acalculous cholecystitis and adrenalitis also have been described.

CMV rarely causes meningoencephalitis in otherwise healthy individuals. Two forms of CMV encephalitis are seen in people with HIV. One resembles HIV encephalitis and presents as progressive dementia; the other is a ventriculoencephalitis characterized by cranial-nerve deficits, nystagmus, disorientation, lethargy, and ventriculomegaly. In immunocompromised patients, CMV can also cause subacute progressive polyradiculopathy, which is often reversible if recognized and treated promptly.

CMV retinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS **(Chap. 197)**. Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema **(Fig. 190-1)**. CMV retinopathy must be distinguished from that due to other

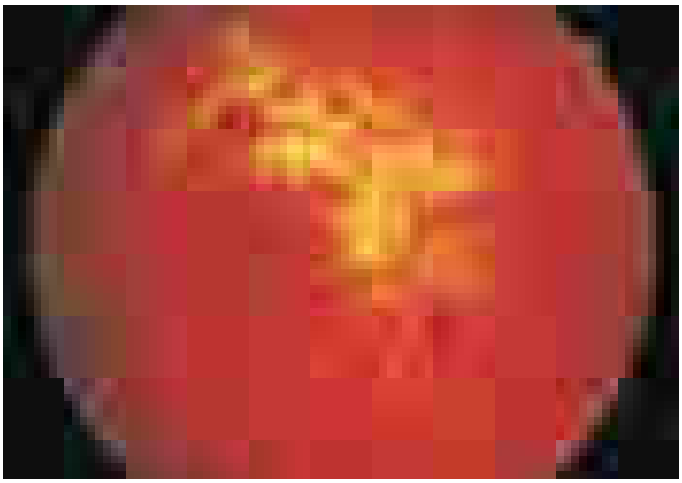

FIGURE 190-1 Cytomegalovirus infection in a patient with AIDS may appear as an arcuate zone of retinitis with hemorrhages and optic disk swelling. Often CMV is confined to the retinal periphery, beyond view of the direct ophthalmoscope.

conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection.

Fatal CMV infections are often associated with persistent viremia and the involvement of multiple organ systems. Progressive pulmonary infiltrates, pancytopenia, hyperamylasemia, and hypotension are characteristic features that are frequently found in conjunction with a terminal bacterial, fungal, or protozoan superinfection. Extensive adrenal necrosis with CMV inclusions is often documented at autopsy, as is CMV involvement of many other organs.

DIAGNOSIS

CMV infection usually cannot be diagnosed reliably on clinical grounds alone. Isolation of CMV or detection of its antigens or DNA in appropriate clinical specimens is the preferred approach. The most common method of detection is quantitative nucleic acid testing (QNAT) for CMV by polymerase chain reaction (PCR) technology, for which blood or other specimens can be used; some centers use a CMV antigenemia test, an immunofluorescence assay that detects CMV antigens (pp65) in peripheral-blood leukocytes. Such assays may yield a positive result several days earlier than culture methods. QNAT may predict the risk for disease progression, particularly in immunocompromised hosts. CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy. Recent introduction of an international testing standard has helped reduce variation in viral load test results.

Virus excretion and/or viremia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If CMV titers are high, as is common in congenital disseminated infection and in AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations (e.g., CMV mononucleosis), viral titers are low, and cytopathic effects may take several weeks to appear. Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of virus from urine, stool, or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of viremia by QNAT or antigenemia testing is a better predictor of acute infection.

A variety of serologic assays detect antibody to CMV. An increased level of IgG antibody to CMV may not be detectable for up to 4 weeks after primary infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; however, circulating rheumatoid factors may result in occasional false-positive IgM tests. Serology is more helpful when used to predict risk of CMV infection and disease in transplant recipients rather than to diagnose acute disease.

PREVENTION

Prevention of CMV infection and disease in organ and hematopoietic stem cell transplant recipients is usually based on one of two methods: universal prophylaxis or preemptive therapy. With universal prophylaxis, antiviral drugs are used for a defined period, often 3 or 6 months. One clinical trial demonstrated that, in CMV-seronegative kidney transplant recipients with seropositive donors, prophylaxis with (val)ganciclovir was more effective at prevention when given for 200 days rather than 100 days. With preemptive therapy, patients are monitored weekly for CMV viremia, and antiviral treatment is initiated once viremia is detected. Because of the bone marrow–suppressive effects of universal prophylaxis, preemptive therapy has been more commonly employed in hematopoietic stem cell transplant recipients; letermovir, which has recently been approved, allows prophylaxis in higher-risk patients. For patients with HIV infection, CMV end-organ disease is best prevented by using antiretroviral therapy sufficient to maintain CD4+ T cell counts above 100/μL. Primary prophylaxis with ganciclovir or valganciclovir is not recommended.

Several additional measures are useful for the prevention of CMV transmission to CMV-naïve, high-risk patients. The use of CMV-seronegative or leukocyte-depleted blood significantly decreases the rate of transfusion-associated transmission. In a placebo-controlled trial, a CMV glycoprotein B vaccine reduced infection rates among 464 CMV-seronegative women; this outcome raises the possibility that this experimental vaccine will reduce rates of congenital infection, but further studies must validate this approach. A CMV glycoprotein B vaccine with MF59 adjuvant appeared effective in reducing the risk and duration of viremia in both seropositive and seronegative renal transplant recipients at risk for CMV infection. CMV immune globulin has been studied in a variety of clinical situations (primary CMV infection in pregnancy, hematopoietic stem cell transplantation, solid organ transplantation), with conflicting results.

Prophylactic acyclovir or valacyclovir at high doses may reduce rates of CMV infection and disease in renal transplant recipients; neither drug is effective in the treatment of active CMV disease.

TREATMENT

Cytomegalovirus Infection

Ganciclovir is a guanosine derivative that has considerably more activity against CMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70–90% among people with HIV who are given ganciclovir for the treatment of CMV retinitis or colitis. In severe infections (e.g., CMV pneumonia in hematopoietic stem cell transplant recipients), ganciclovir is sometimes combined with CMV immune globulin. Prophylactic or suppressive ganciclovir may be useful in high-risk hematopoietic stem cell or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation). In many people with HIV, persistently low CD4+ T cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is more common among patients treated for >3 months and is usually related to mutations in the CMV UL97 gene (or, less commonly, the UL54 gene). The advent of CMV genotyping for resistance mutations has made it possible to rapidly obtain information regarding optimal treatment approaches against clinically resistant virus.

Valganciclovir is an orally bioavailable prodrug that is rapidly metabolized to ganciclovir in intestinal tissues and the liver. Approximately 60–70% of an oral dose of valganciclovir is absorbed. An oral valganciclovir dose of 900 mg results in ganciclovir blood levels similar to those obtained with an IV ganciclovir dose of 5 mg/kg. Valganciclovir appears to be as effective as IV ganciclovir for both CMV induction (treatment) and maintenance regimens, also offering

the advantage of oral dosing. Furthermore, the adverse-event profiles and rates of resistance for the two drugs are similar.

Ganciclovir or valganciclovir therapy for CMV disease consists of a 14- to 21-day induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg PO twice daily for valganciclovir), sometimes followed by maintenance therapy (e.g., valganciclovir, 900 mg/d). Peripheral-blood neutropenia develops in roughly one-quarter of treated patients but may be ameliorated by granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Whether to use maintenance therapy should depend on the overall level of immunocompromise and the risk of recurrent disease. Discontinuation of maintenance therapy should be considered in people with HIV who, while receiving antiretroviral therapy, have a sustained (3- to 6-month) increase in CD4+ T cell counts to >100/μL. Compared with shorter (6-week) courses, prolonged (6-month) courses of valganciclovir had beneficial effects on hearing and developmental outcomes in infants with congenital CMV infection.

For treatment of CMV retinitis, some clinicians prefer intravitreal injections of ganciclovir or foscarnet (see below) plus oral valganciclovir to intravenous ganciclovir, although no clinical trials have compared these approaches. *Foscarnet* (sodium phosphonoformate) inhibits CMV DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant isolates. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiomyopathy). The approved induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90–120 mg/kg once daily. No oral preparation is available. Foscarnet-resistant virus may emerge during extended therapy. This drug is used more frequently after hematopoietic stem cell transplantation than in other situations to avoid the myelosuppressive effects of ganciclovir; in general, foscarnet is also the first choice for infections with ganciclovir-resistant CMV.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent IV administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by maintenance regimens of 3–5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be tempered somewhat by saline hydration and probenecid. Cidofovir is used primarily for ganciclovir-resistant virus.

HUMAN HERPESVIRUS (HHV) TYPES 6, 7, AND 8

HHV-6 AND HHV-7

HHV-6 and -7 seropositivity rates are generally high throughout the world. HHV-6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. Two genetically distinct variants (HHV-6A and HHV-6B) are now recognized. HHV-6 appears to be transmitted by saliva and possibly by genital secretions.

Infection with HHV-6 frequently occurs during infancy as maternal antibody wanes. The peak age of acquisition is 9–21 months; by 24 months, seropositivity rates approach 80%. Older siblings appear to serve as a source of transmission. In addition, congenital infection may occur, and ~1% of newborns are infected with HHV-6; placental infection with HHV-6 has been described. Congenital infection is generally asymptomatic, although subtle neurologic defects have been described. Most postnatally infected children develop symptoms (fever, fussiness, and diarrhea). A minority develop exanthem subitum (roseola infantum; see Fig. A1-5), a common illness characterized by fever with subsequent rash. In addition, ~10–20% of febrile seizures without rash during infancy are caused by HHV-6. After initial infection, HHV-6 persists in peripheral-blood mononuclear cells as well as in the central nervous system, salivary glands, and female genital tract.

In older age groups, HHV-6 has been associated with mononucleosis syndromes; in immunocompromised hosts, encephalitis, pneumonitis, syncytial giant-cell hepatitis, and disseminated disease are seen. In transplant recipients, HHV-6 infection may also be associated with graft dysfunction. Acute HHV-6-associated limbic encephalitis has been reported in hematopoietic stem cell transplant recipients and is characterized by memory loss, confusion, seizures, hyponatremia, and abnormal electroencephalographic and MRI results. High plasma loads of HHV-6 DNA in hematopoietic stem cell transplant recipients are associated with allelic-mismatched donors, use of glucocorticoids, delayed monocyte and platelet engraftment, development of limbic encephalitis, and increased all-cause mortality rates. Mesial temporal lobe epilepsy has been associated with HHV-6 infections, and, like many other viruses, HHV-6 has been implicated in the pathogenesis of multiple sclerosis, although further study is needed to distinguish between association and etiology.

HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. The virus is frequently acquired during childhood, albeit at a later age than HHV-6. HHV-7 is commonly present in saliva, which is presumed to be the principal source of infection; breast milk and cervical secretions may also carry the virus. Viremia can be associated with either primary or reactivation infection. The most common clinical manifestations of childhood HHV-7 infections are fever and seizures. Some children present with respiratory or gastrointestinal signs and symptoms. An association has been made between HHV-7 and pityriasis rosea, but evidence is insufficient to indicate a causal relationship.

Clustering of HHV-6, HHV-7, and CMV infections in transplant recipients can make it difficult to sort out the roles of the various agents in individual clinical syndromes. HHV-6 and HHV-7 appear to be susceptible to ganciclovir and foscarnet, although definitive evidence of clinical response is lacking.

HHV-8

Unique herpesvirus-like DNA sequences were reported during 1994 and 1995 in tissues derived from Kaposi's sarcoma (KS) and body cavity–based lymphoma occurring in people with HIV. The virus from which these sequences were derived is designated HHV-8 or Kaposi's sarcoma–associated herpesvirus (KSHV). HHV-8, which infects B lymphocytes, macrophages, and both endothelial and epithelial cells, appears to be causally related not only to KS and a subgroup of AIDS-related B cell body cavity–based lymphomas (primary effusion lymphomas) but also to multicentric Castleman disease, a lymphoproliferative disorder of B cells. The association of HHV-8 with several other diseases has been reported but not confirmed.

HHV-8 seropositivity occurs worldwide, with areas of high endemicity influencing rates of disease. Unlike other herpesvirus infections, HHV-8 infection is much more common in some geographic areas (e.g., central and southern Africa) than in others (North America, Asia, northern Europe). In high-prevalence areas, infection occurs in childhood, seropositivity is associated with having a seropositive mother or (to a lesser extent) older sibling, and HHV-8 may be transmitted in saliva. In low-prevalence areas, infections typically occur in adults, probably with sexual transmission. Concurrent epidemics of HIV-1 and HHV-8 infections among certain populations (e.g., men who have sex with men) in the late 1970s and early 1980s appear to have resulted in the frequent association of AIDS and KS. Transmission of HHV-8 may also be associated with organ transplantation, injection drug use, and blood transfusion; however, transmission via organ transplantation or blood transfusion in the United States appears to be quite rare.

Primary HHV-8 infection in immunocompetent children may manifest as fever and maculopapular rash. Among individuals with intact immunity, chronic asymptomatic infection is the rule, and neoplastic disorders generally develop only after subsequent immunocompromise.

Immunocompromised persons with primary infection may present with fever, splenomegaly, lymphoid hyperplasia, pancytopenia, or rapid-onset KS. Quantitative analysis of HHV-8 DNA suggests a predominance of latently infected cells in KS lesions and frequent lytic replication in multicentric Castleman disease. The KS-associated herpesvirus inflammatory cytokine syndrome (KICS)—consisting of fever and high levels of HHV-8, human and viral interleukin 6, and human interleukin 10—has been described in some HIV-infected patients and is associated with a high mortality rate.

Effective antiretroviral therapy for HIV-infected individuals has led to a marked reduction in rates of KS among persons dually infected with HHV-8 and HIV in resource-rich areas. HHV-8 itself is susceptible in vitro to ganciclovir, foscarnet, and cidofovir. A small, randomized, double-blind, placebo-controlled, crossover trial suggested that oral valganciclovir administered once daily reduced HHV-8 replication. However, clinical benefits of valganciclovir or other drugs in HHV-8 infection have not yet been demonstrated. Sirolimus inhibits the progression of dermal KS in kidney transplant recipients while providing effective immunosuppression.

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191 Molluscum Contagiosum, Monkeypox, and Other Poxvirus Infections

Fred Wang

The poxvirus family includes a large number of related DNA viruses that infect various vertebrate hosts. The poxviruses responsible for infections in humans, the geographic locations in which these infections are found, the host reservoirs, and the main manifestations are listed in Table 191-1. Infections with orthopoxviruses—e.g., smallpox (variola major) virus (Chap. S2) or the zoonotic monkeypox virus—can result in systemic, potentially lethal human disease. Other poxvirus infections cause primarily localized skin disease in humans.

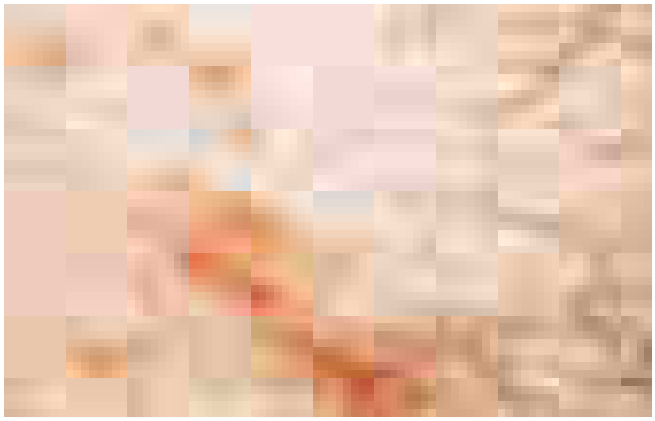

FIGURE 191-1 Molluscum contagiosum is a cutaneous poxvirus infection characterized by multiple umbilicated flesh-colored or hypopigmented papules.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum virus is an obligate human pathogen that causes distinctive proliferative skin lesions. These lesions measure 2–5 mm in diameter and are pearly, flesh-colored, and umbilicated, with a characteristic dimple at the center (Fig. 191-1). A relative lack of inflammation and necrosis distinguishes these proliferative lesions from other poxvirus lesions. Lesions may be found—singly or in clusters—anywhere on the body except on the palms and soles and may be associated with an eczematous rash.

Molluscum contagiosum is highly prevalent among children and is the most common human disease resulting from poxvirus infection. Swimming pools are a common vector for transmission. Atopy and compromise of skin integrity increase the risk of infection. Genital lesions are more common in adults, to whom the virus may be transmitted by sexual contact. The incubation period ranges from 2 weeks to 6 months, with an average of 2–7 weeks. In most cases, the disease is self-limited and regresses spontaneously after 3–4 months in immunocompetent hosts. There are no systemic complications, but skin lesions may persist for 3–5 years. Molluscum contagiosum can be associated with immunosuppression and is frequently seen among HIV-infected patients (Chap. 197). The disease can be more generalized, severe, and persistent in AIDS patients than in other groups. Moreover, molluscum contagiosum can be exacerbated in the immune reconstitution inflammatory syndrome (IRIS) associated with the initiation of antiretroviral therapy.

TABLE 191-1 Poxviruses and Human Infections

GENUS	SPECIES	GEOGRAPHIC LOCATION	HOST RESERVOIR	HUMAN DISEASE
Orthopoxvirus	Variola[a]	Extinct	Humans	Smallpox, systemic
	Monkeypox	Africa	Rodents	Smallpox-like, systemic
	Cowpox	Europe	Rodents	Local pox lesion, occasionally systemic
	Buffalopox	Indian subcontinent	Water buffalo	Local pox lesion, mild illness
	Cantagalo and Araçatuba	South America	Cattle	Local pox lesion, mild illness
	Vaccinia	—	—	Local pox lesions (smallpox vaccine)
Molluscipoxvirus	Molluscum contagiosum	Worldwide	Humans	Multiple cutaneous lesions
Parapoxvirus	Orf	Worldwide	Sheep, goats	Local pox lesions (contagious pustular dermatitis)
	Pseudocowpox (paravaccinia)	Worldwide	Cattle	Local pox lesions (milker's nodule)
	Bovine papular stomatitis	Worldwide	Cattle	Local pox lesions
	Deerpox	Deer herds	Deer	Local pox lesions
	Sealpox	Seal colonies	Seals	Local pox lesions
Yatapoxvirus	Tanapox	Africa	Monkeys	Local pox lesions

[a]See Chap. S2.

The diagnosis of molluscum contagiosum is typically based on its clinical presentation and can be confirmed by histologic demonstration of the cytoplasmic eosinophilic inclusions (*molluscum bodies*) that are characteristic of poxvirus replication. Molluscum contagiosum virus cannot be propagated in vitro, but electron microscopy and molecular studies can be used for its identification.

There is no specific systemic treatment for molluscum contagiosum, and lesions are likely to resolve spontaneously. Treatment may be more pressing in HIV-positive patients, but initiation of effective antiretroviral therapy may still be the best option. Regardless of the patient's HIV status, strong clinical-trial evidence of superiority for physical ablation or drugs is lacking.

MONKEYPOX

Although monkeypox virus was named after the animal from which it was originally isolated, rodents are the primary viral reservoir. Human infections with monkeypox virus typically occur in Africa when humans come into direct contact with infected animals. Human-to-human transmission of monkeypox infection has been rare; however, such transmission may increase as cross-reactive immunity from smallpox vaccination wanes. Such an increase was observed during a 2013 monkeypox outbreak in the Democratic Republic of the Congo. Human disease is characterized by a systemic illness and vesicular rash similar to those of variola. The clinical presentation of monkeypox can be confused with that of the more common varicella-zoster virus infection **(Chap. 188)**. Compared with the lesions of this herpesvirus infection, monkeypox lesions tend to be more uniform (i.e., in the same stage of development), diffuse, and peripheral in distribution. Lymphadenopathy is a prominent feature of monkeypox infection.

The first outbreak of human monkeypox infection in the Western Hemisphere occurred during 2003, when more than 70 cases were reported in the midwestern United States. The outbreak was linked to contact with pet prairie dogs that had become infected while being housed with rodents imported from Ghana. Patients presented most frequently with fever, rash, and lymphadenopathy ~14 days after exposure. The risk of human disease from animal orthopoxvirus infections is increasing as cross-reactive smallpox immunity wanes in the general population and exposure to wild animals in the rainforest and to exotic animals as household pets grows.

OTHER ZOONOTIC POXVIRUS INFECTIONS

Cowpox and buffalopox are rare zoonotic infections characterized by cutaneous poxlike lesions and mild systemic illness. Outbreaks of similar poxlike lesions among cattle and farm workers in Brazil have been due to Cantagalo and Araçatuba viruses, which are virtually identical to vaccinia virus and may have become established in cattle during smallpox vaccination programs.

Parapoxviruses are widely scattered among animal species, but only a few are known to cause human disease via direct contact with infected animals. Parapoxviruses are antigenically distinct from orthopoxviruses and share no cross-immunity. *Tanapox* virus belongs to a separate, antigenically distinct genus and usually causes a single nodular lesion on the exposed area after contact with infected monkeys.

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192 Parvovirus Infections

Kevin E. Brown

Parvoviruses, members of the family Parvoviridae, are small (diameter, ~22 nm), nonenveloped, icosahedral viruses with a linear single-strand DNA genome of ~5000 nucleotides. These viruses are dependent on either rapidly dividing host cells or helper viruses for replication. At least five groups of parvoviruses infect humans: parvovirus B19 (B19V), dependoparvoviruses (adeno-associated viruses; AAVs), human tetraparvoviruses (PARV4 and PARV5), human bocaparvoviruses (HBoVs), and human protoparvoviruses (bufavirus and tusavirus). Human dependoparvoviruses are nonpathogenic and will not be considered further in this chapter.

PARVOVIRUS B19

DEFINITION

B19V is the type member of the genus *Erythroparvovirus*. On the basis of viral sequence, B19V is divided into three genotypes (designated 1, 2, and 3), but only a single B19V antigenic type has been described. Genotype 1 is predominant in most parts of the world; genotype 2 is rarely associated with active infection; and genotype 3 appears to predominate in parts of western Africa.

EPIDEMIOLOGY

B19V exclusively infects humans, and infection is endemic in virtually all parts of the world. Transmission occurs predominantly via the respiratory route and is followed by the onset of rash and arthralgia. By the age of 15 years, ~50% of children have detectable IgG antibody to B19V; this figure rises to >90% among the elderly. In pregnant women, the estimated annual seroconversion rate is ~1%. Within households, secondary infection rates approach 50%.

Detection of high-titer B19V in blood is not unusual (see "Pathogenesis," below). Transmission can occur as a result of transfusion, most commonly of pooled components. To reduce the risk of transmission, plasma pools are screened by nucleic acid amplification technology, and high-titer pools are discarded. B19V is resistant to both heat and solvent-detergent inactivation.

PATHOGENESIS

B19V replicates primarily in erythroid progenitors. This specificity is due in part to the limited tissue distribution of the primary B19V receptor, blood group P antigen (globoside). Infection leads to high-titer viremia, with $>10^{12}$ virus particles (or IU)/mL detectable in the blood at the apex **(Fig. 192-1)**, and virus-induced cytotoxicity results in cessation of red cell production. In immunocompetent individuals, viremia and arrest of erythropoiesis are transient and resolve as the IgM and IgG antibody response is mounted. In individuals with normal erythropoiesis, there is only a minimal drop in hemoglobin levels; however, in those with increased erythropoiesis (especially with hemolytic anemia), this cessation of red cell production can induce a transient crisis with severe anemia (Fig. 192-1). Similarly, if an individual (or, after maternal infection, a fetus) does not mount a neutralizing antibody response and halt the lytic infection, erythroid production is compromised and chronic anemia develops (Fig. 192-1).

The immune-mediated phase of illness, which begins 2–3 weeks after infection as the IgM response peaks, manifests as the rash of fifth disease together with arthralgia and/or frank arthritis. Low-level B19V DNA can be detected by polymerase chain reaction (PCR) in blood and tissues for months to years after acute infection. The B19V receptor is found in a variety of other cells and tissues, including megakaryocytes, endothelial cells, placenta, myocardium, and liver. Infection of these tissues by B19V may be responsible for some of the more unusual presentations of the infection. Rare individuals who lack P antigen are naturally resistant to B19V infection.

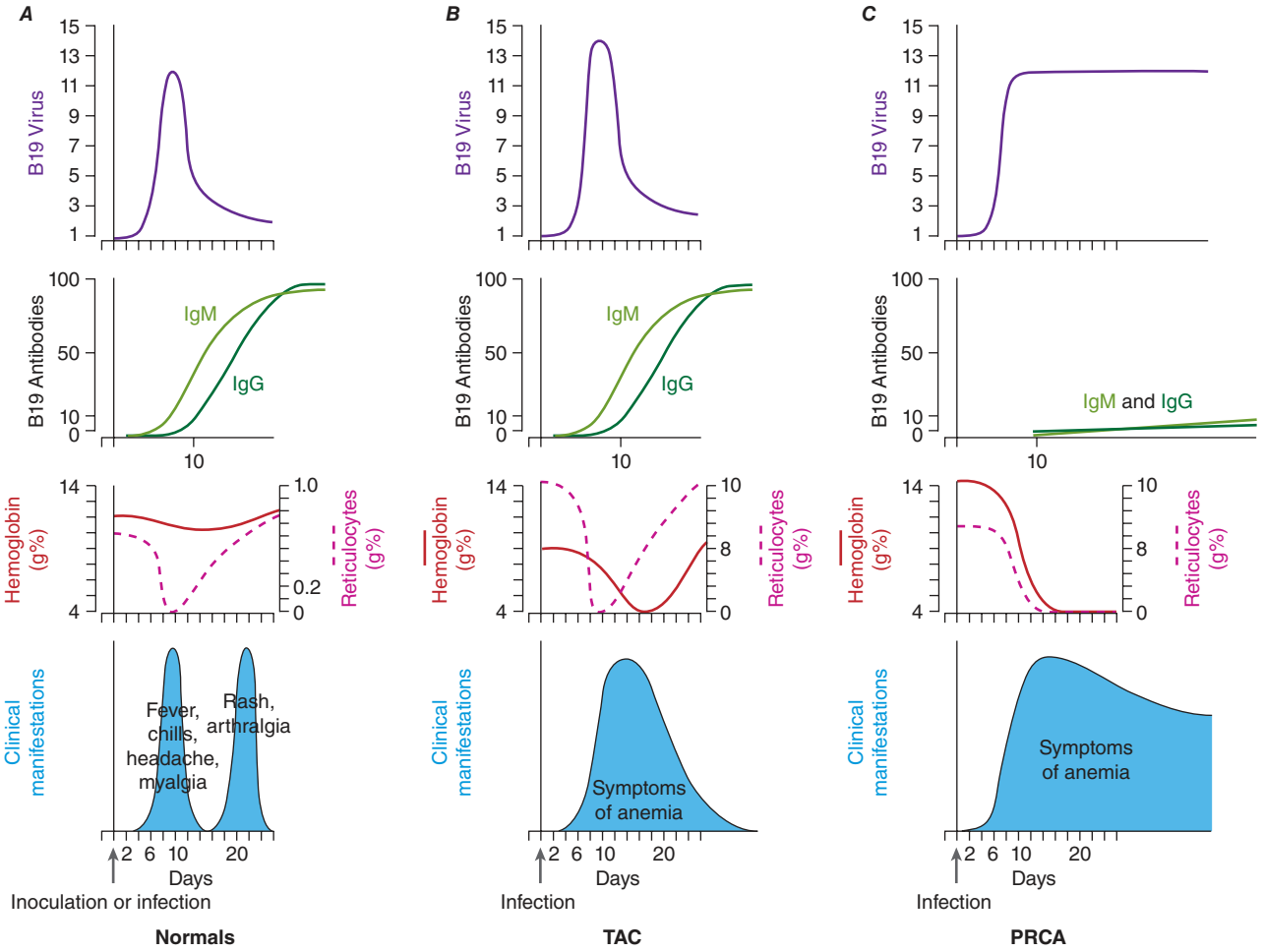

FIGURE 192-1 Schematic of the time course of parvovirus B19 infection in (***A***) normals (erythema infectiosum), (***B***) transient aplastic crisis (TAC), and (***C***) chronic anemia/pure red-cell aplasia (PRCA). *(Reprinted with permission from NS Young, KE Brown: N Engl J Med 350:586, 2004. © 2004 Massachusetts Medical Society. All rights reserved.)*

CLINICAL MANIFESTATIONS

Erythema Infectiosum Most B19V infections are asymptomatic or are associated with only a mild nonspecific illness. The main manifestation of symptomatic B19V infection is erythema infectiosum, also known as *fifth disease* or *slapped-cheek disease* **(Figs. 192-2 and A1-1*A*)**. Infection begins with a minor febrile prodrome ~7–10 days after exposure, and the classic facial rash develops several days later; after 2–3 days, the erythematous macular rash may spread to the extremities in a lacy reticular pattern. However, its intensity and distribution vary, and B19V-induced rash is difficult to distinguish from other viral exanthems. Adults typically do not exhibit the "slapped-cheek" phenomenon but present with arthralgia, with or without the macular rash.

Polyarthropathy Syndrome Although uncommon among children, arthropathy occurs in ~50% of adults and is more common among women than among men. The distribution of the affected joints is often symmetrical, with arthralgia affecting the small joints of the hands and occasionally the ankles, knees, and wrists. Resolution usually occurs within a few weeks, but recurring symptoms can continue for months. The illness may mimic rheumatoid arthritis, and rheumatoid factor can often be detected in serum. B19V infection may trigger rheumatoid disease in some patients and has been associated with juvenile idiopathic arthritis.

Transient Aplastic Crisis Asymptomatic transient reticulocytopenia occurs in most individuals with B19V infection. However, in patients who depend on continual rapid production of red cells, infection can cause transient aplastic crisis (TAC). Affected individuals include those with hemolytic disorders, hemoglobinopathies, red

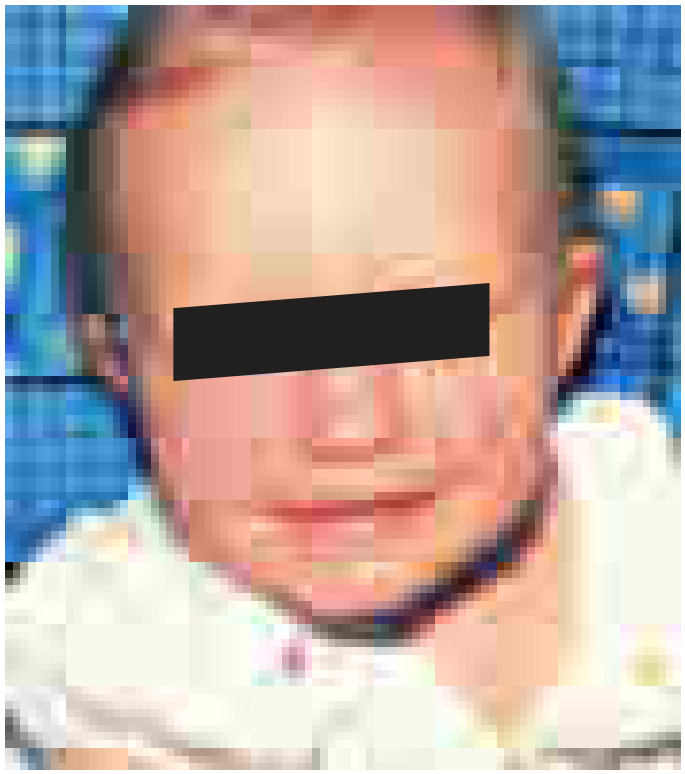

FIGURE 192-2 Young child with erythema infectiosum, or fifth disease, showing typical "slapped-cheek" appearance.

cell enzymopathies, and autoimmune hemolytic anemias. Patients present with symptoms of severe anemia (sometimes life-threatening) and a low reticulocyte count, and bone marrow examination reveals an absence of erythroid precursors and characteristic giant pronormoblasts. As its name indicates, the illness is transient, and anemia resolves with the cessation of cytopathic infection in the erythroid progenitors.

Pure Red-Cell Aplasia/Chronic Anemia Chronic B19V infection has been reported in a wide range of immunosuppressed patients, including those with congenital immunodeficiency, AIDS **(Chap. 197)**, lymphoproliferative disorders (especially acute lymphocytic leukemia), and transplantation **(Chap. 138)**. Patients have persistent anemia with reticulocytopenia, absent or low levels of B19V IgG, high titers of B19V DNA in serum, and—in many cases—scattered giant pronormoblasts in bone marrow. Rarely, nonerythroid hematologic lineages also are affected. Transient neutropenia, lymphopenia, and thrombocytopenia (including idiopathic thrombocytopenic purpura) have been observed. B19V occasionally causes a hemophagocytic syndrome.

Studies in Papua New Guinea, Gabon, and Ghana, where malaria is endemic, suggest that co-infection with *Plasmodium* and B19V plays a major role in the development of severe anemia in young children. Further studies must determine whether B19V infection contributes to severe anemia in other malarial regions.

Hydrops Fetalis B19V infection during pregnancy can lead to hydrops fetalis and/or fetal loss. The risk of transplacental fetal infection is ~30%, and the risk of fetal loss (predominantly early in the second trimester) is ~9%. The risk of congenital infection is <1%. Although B19V does not appear to be teratogenic, anecdotal cases of eye damage and central nervous system (CNS) abnormalities have been reported. Cases of congenital anemia have also been described. B19V probably causes 10–20% of all cases of nonimmune hydrops.

Unusual Manifestations B19V infection may rarely cause hepatitis, vasculitis, myocarditis, glomerulosclerosis, or meningitis. A variety of other cardiac manifestations, CNS diseases, and autoimmune infections have also been reported. However, B19V DNA can be detected by PCR for years in many tissues; this finding is of no known clinical significance, but its interpretation may cause confusion regarding B19V disease association.

DIAGNOSIS

Diagnosis of B19V infection in immunocompetent individuals is generally based on detection of B19V IgM antibodies **(Table 192-1)**. IgM can be detected at the time of rash in erythema infectiosum and by the third day of TAC in patients with hematologic disorders; these antibodies remain detectable for ~3 months. B19V IgG is detectable by the seventh day of illness and persists throughout life. Quantitative detection of B19V DNA should be used for the diagnosis of early TAC or chronic anemia. Although B19V levels fall rapidly with the development of the immune response, DNA can be detectable by PCR for months or even years after infection, even in healthy individuals; therefore, quantitative PCR should be used. In acute infection at the height of viremia, >10^{12} B19V DNA IU/mL of serum can be detected; however, titers fall rapidly within 2 days. Patients with aplastic crisis or B19V-induced chronic anemia generally have >10^5 B19V DNA IU/mL.

TREATMENT

Parvovirus B19 Infection

No antiviral drug effective against B19V is available, and treatment of B19V infection often targets symptoms only. TAC precipitated by B19V infection frequently necessitates symptom-based treatment with blood transfusions. In patients receiving chemotherapy, temporary cessation of treatment may result in an immune response and resolution. If this approach is unsuccessful or not applicable, commercial immune globulin (IVIg; Gammagard, Sandoglobulin) from healthy blood donors can cure or ameliorate persistent B19V infection in immunosuppressed patients. Generally, the dose used is 400 mg/kg daily for 5–10 days. Like patients with TAC, immunosuppressed patients with persistent B19V infection should be considered infectious. Administration of IVIg is not beneficial for erythema infectiosum or B19V-associated polyarthropathy. Intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops.

PREVENTION

No vaccine has been approved for the prevention of B19V infection, although vaccines based on B19V virus-like particles expressed in insect cells are known to be highly immunogenic. Phase 1 trials of a putative vaccine were discontinued because of adverse side effects.

HUMAN TETRAPARVOVIRUSES (PARV4/5)

DEFINITION

The PARV4 viral sequence was initially detected in a patient with an acute viral syndrome. Similar sequences, including the related PARV5 sequence, have been detected in pooled plasma collections. The DNA sequence of PARV4/5 is distinctly different from that of all other parvoviruses, and this virus is now classified as a member of the newly described genus *Tetraparvovirus.*

EPIDEMIOLOGY

PARV4 DNA is commonly found in plasma pools but at lower concentrations than the levels of B19V DNA found before in plasma pools prior to screening. The higher levels of PARV4 DNA and IgG antibody in tissues (bone marrow and lymphoid tissue) and sera from IV drug users than in the corresponding specimens from control patients suggest that the virus is transmitted predominantly by parenteral means in the United States and Europe. Evidence for nonparenteral transmission in other parts of the world is limited.

CLINICAL MANIFESTATIONS

To date, PARV4/5 infection has been associated only with mild clinical disease (rash and/or transient aminotransferase elevation).

TABLE 192-1 Diseases Associated with Human Parvovirus B19 Infection and Methods of Diagnosis

DISEASE	HOSTS	IgM	IgG	PCR	QUANTITATIVE PCR
Fifth disease	Healthy children	Positive	Positive	Positive	>10^4 IU/mL
Polyarthropathy syndrome	Healthy adults (more often women)	Positive within 3 months of onset	Positive	Positive	>10^4 IU/mL
Transient aplastic crisis	Patients with increased erythropoiesis	Negative/positive	Negative/positive	Positive	Often >10^{12} IU/mL, but rapidly decreases
Persistent anemia/pure red-cell aplasia	Immunodeficient or immunocompetent patients	Negative/weakly positive	Negative/weakly positive	Positive	Often >10^{12} IU/mL, but should be >10^6 in the absence of treatment
Hydrops fetalis/ congenital anemia	Fetuses (<20 weeks)	Negative/positive	Positive	Positive amniotic fluid or tissue	n/a

Abbreviations: IU, international units (1 IU equals ~1 genome); n/a, not applicable; PCR, polymerase chain reaction.

HUMAN BOCAPARVOVIRUSES

DEFINITION

Animal bocaparvoviruses are associated with mild respiratory symptoms and enteritis in young animals. Human bocavirus 1 (HBoV1) was originally identified in the respiratory tract of young children with lower respiratory tract infections. More recently, HBoV1 and the related viruses HBoV2, HBoV3, and HBoV4 have all been identified in human fecal samples.

EPIDEMIOLOGY

Seroepidemiologic studies with HBoV virus-like particles suggest that HBoV infection is common. Worldwide, most individuals are infected before the age of 5 years.

CLINICAL MANIFESTATIONS

HBoV1 DNA is found in respiratory secretions from 2–20% of children with acute respiratory infection, often in the presence of other pathogens; in these circumstances, the role of HBoV1 in disease pathogenesis is unknown. Clinical disease due to HBoV1 is associated with evidence of primary infection (IgG seroconversion or the presence of IgM), HBoV1 DNA in serum, or high-titer HBoV1 DNA (>10^4 genome copies/mL) in respiratory secretions. Symptoms are not dissimilar from those of other viral respiratory infections, and cough and wheezing are commonly reported. There is no specific treatment for HBoV infection. The role of HBoVs in childhood gastroenteritis remains to be established.

HUMAN PROTOPARVOVIRUSES

DEFINITION

Bufavirus and tusavirus were both identified in clinical samples by a metagenomics approach used for identifying new pathogens. These viruses are classified as members of the protoparvovirus group along with the original prototype member of the Parvoviridae, minute virus of mice.

EPIDEMIOLOGY

Little is known about the epidemiology of either virus, but bufavirus DNA has been found in 0.2–4% of stools from children and adults with diarrhea in many countries; tusavirus has been identified in only a single patient with diarrhea in Tunisia.

CLINICAL MANIFESTATIONS

Although bufavirus DNA is found in patients with diarrhea, often it is detected in conjunction with other viruses. The role of bufavirus in childhood gastroenteritis remains to be confirmed.

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193 Human Papillomavirus Infections

Darron R. Brown, Aaron Ermel

Interest in human papillomavirus (HPV) infection began in earnest in the 1980s after Harold zur Hausen postulated that infection with these viruses was associated with cervical cancer. It is now recognized that HPV infection of the human genital tract is extremely common and causes clinical conditions ranging from asymptomatic infection to genital warts (condylomata acuminata); dysplastic lesions and invasive cancers of the anus, penis, vulva, vagina, and cervix; and a subset of oropharyngeal cancers. This chapter describes the epidemiology of HPV as a virus and a pathogen, the natural history of HPV infections and associated cancers, strategies to prevent infection and HPV-associated disease, and treatment modalities for some conditions caused by HPV.

PATHOGENESIS

Overview HPV is an icosahedral, nonenveloped, 8000-base-pair, double-stranded DNA virus with a diameter of 55 nm. Like the genomes of other papillomaviruses, HPV's genome consists of an early (E) gene region, a late (L) gene region, and a noncoding region, which contains regulatory elements. The E1, E2, E5, E6, and E7 proteins are expressed early in the growth cycle and are necessary for viral replication and cellular transformation. The E6 and E7 proteins are responsible for malignant transformation, targeting the human cell-cycle regulatory molecules p53 and Rb (retinoblastoma protein) for degradation, respectively. Translation of the L1 and L2 transcripts and splicing of an E1^E4 transcript occur later. The L1 gene encodes the 54-kDa major capsid protein that makes up the majority of the virus shell; the 77-kDa L2 minor protein contributes a smaller percentage of the capsid mass.

More than 125 HPV types have been identified and are numerically designated on the basis of a unique L1 gene sequence. Approximately 40 HPV types are regularly identified in the anogenital tract; these types are subdivided into high-risk and low-risk categories depending on the associated risk of cervical cancer. For example, HPV types 6 and 11 cause genital warts and ~10% of low-grade cervical lesions and are thus designated low risk. HPV types 16 and 18 cause dysplastic lesions and a high percentage of invasive cancers of the cervix and are therefore considered high risk.

HPV targets basal keratinocytes after microtrauma allows exposure of these cells to the virus. The HPV replication cycle is completed as keratinocytes undergo differentiation. Virions are assembled in the nuclei of differentiated keratinocytes and can be detected by electron microscopy. Infection is transmitted by contact with virus contained in these desquamated keratinocytes (or with free virus) from an infected individual.

The Immune Response to HPV Infection Unlike many viral infections, HPV infection has no viremic phase. This lack of viremia may account for the incomplete antibody response to HPV infection. Natural HPV infection of the genital tract gives rise to a serum antibody response in 60–70% of individuals. Significant, although incomplete, protection against type-specific reinfection is associated with the presence of neutralizing antibodies. Serum antibodies likely reach the cervical epithelium and secretions by transudation and exudation. Therefore, protection against infection relates to the amount of neutralizing antibody at the site of infection and lasts as long as sufficient levels of neutralizing antibodies are present.

A cell-mediated immune response plays an important role in controlling progression of HPV infection. Histologic examination of lesions in individuals who experience regression of genital warts demonstrates infiltration by T cells and macrophages. CD4+ T cell regulation is

particularly important in controlling HPV infections, as evidenced by the higher rates of infection and disease in immunosuppressed individuals, particularly those who are infected with HIV. Specific T-cell responses may be measured against HPV proteins, the most important of which appear to be the E2 and E6 proteins. In women with HPV type 16 cervical infection, a strong T-cell response to type 16–derived E2 protein is associated with a lack of progression of cervical disease. However, measurable changes occur in the innate and adaptive immune systems of patients with HPV-associated cancers. There is suppression of the antigen-presentation process as well as suppression of antitumor activity. The end result is a reduction of HPV-specific antitumor immune responses and an increase in immunosuppressive cellular responses.

THE NATURAL HISTORY OF HPV-ASSOCIATED MALIGNANCY

HPV is transmitted by vaginal or anal intercourse, oral sex, and probably by touching a partner's genitalia. In cross-sectional and longitudinal studies, ~40% of young women demonstrate evidence of HPV infection, with peaks during the teens and early twenties, soon after first coital experience. The number of lifetime sexual partners correlates with the likelihood of HPV infection and the subsequent risk of HPV-associated malignancy. HPV infection may occur in a monogamous person if that person's partner is infected.

Most HPV infections become undetectable after 6–9 months, a phenomenon known as "clearance." However, with prolonged follow-up and frequent sampling, the same HPV types may again be detected months or even years later. It is still debated whether such episodic detection indicates viral latency followed by reactivation or represents reinfection with an identical HPV type.

While HPV is the causative agent of several cancers, most attention has focused on cervical cancer, which is the second most common cancer in women worldwide. More than 500,000 women are diagnosed and 275,000 die from invasive cervical cancer annually. More than 85% of all cervical cancer cases, as well as deaths, occur in women living in low-income countries, especially countries in sub-Saharan Africa, Asia, and South and Central America.

Twenty-five years of evidence shows that HPV causes nearly 100% of cervical cancers. Persistent HPV infection is the most significant risk factor for cervical cancer; relative risks range from 10 to 20 and exceed 100 in prospective and case–control studies, respectively. The time from HPV infection to cervical cancer may exceed 20 years. Cervical cancer peaks in the fifth and sixth decades of life for women living in developed countries and as much as a decade earlier for women living in resource-poor countries. Persistent carriers of oncogenic HPV types are at greatest risk for high-grade cervical dysplasia and cancer.

Why HPV infections in some women but not others eventually lead to malignancy is not clear. Although oncogenic HPV infection is necessary for the development of cervical malignancy, only ~3–5% of infected women will ever develop this cancer, even in the absence of cytologic screening. Biomarkers that can predict which women will develop cervical cancer are not available. Immunosuppression in general plays a significant role in redetection/reactivation of HPV infections, while other factors, such as smoking, hormonal changes, chlamydial infection, and nutritional deficits, have an impact on viral persistence and cancer.

The International Agency for Research on Cancer has concluded that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are carcinogenic in the uterine cervix. HPV type 16 is particularly virulent and causes 50% of cervical cancers. Worldwide, HPV types 16 and 18 cause at least 70% of cervical squamous cell carcinomas and 85% of cervical adenocarcinomas. Oncogenic types other than 16 or 18 cause the remaining 30% of cervical cancers. HPV types 16 and 18 also cause nearly 90% of anal cancers worldwide.

In addition to cervical and anal cancer, other HPV-associated cancers include vulvar and vaginal cancer (caused by HPV in 50–70% of cases), penile cancer (caused by HPV in 50% of cases), and at least 65% of oropharyngeal squamous cell carcinomas (OPSCCs). Over the past two decades, an epidemic of OPSCC related to oncogenic HPV infection, primarily HPV type 16, has developed. Rates of OPSCC in the United States have been increasing in men from a low of 0.27 case per 100,000 in 1973 to 0.57 case per 100,000 per year in 2004; rates in women have remained relatively stable at ~0.17 per 100,000 per year. The greatest increase in the incidence of OPSCC is among white men 40–50 years of age. Nearly 14,000 new cases were diagnosed in the United States in 2013. OPSCCs of the base of the tongue and tonsil cancer have increased annually by rates of 1.3 and 0.6%, respectively. Few data are available from developing countries about OPSCC.

THE EFFECTS OF HIV ON HPV-ASSOCIATED DISEASE

HIV infection accelerates the natural history of HPV infections. HIV-infected individuals are more likely than other individuals to develop genital warts, and their lesions are more recalcitrant to treatment. HIV infection has been consistently associated with precancerous cervical lesions, including low-grade cervical intraepithelial lesions (CIN) and CIN 3, the immediate precursor to cervical cancer. Women with HIV/AIDS have significantly higher rates of cervical cancer as well as subsets of some vulvar, vaginal, and oropharyngeal tumors than women in the general population. Studies indicate a direct relationship between low CD4+ T lymphocyte count and the risk of cervical cancer. Some studies show a reduced likelihood of HPV infection and precancerous lesions of the cervix in HIV-infected women given antiretroviral therapy (ART). However, the incidence of cervical cancer in HIV-infected women has not changed significantly since ART was introduced, possibly because of preexisting oncogenic HPV infections that occurred before ART was initiated.

The burden of HPV-associated cancers is expected to increase in HIV-infected patients, given the prolonged life expectancies provided with ART. For women living in developing countries where cervical cancer screening is not widely available, this trend will have significant consequences. Thus, elucidating the interactions of HIV infection and cervical cancer with cofactors such as diet, other sexually transmitted infections, and environmental exposures is an important focus of research that impacts women living in low- and middle-income countries.

Similar to that of cervical cancer, the incidence of anal cancer is strongly influenced by HIV infection. HIV-infected men who have sex with men (MSM) and HIV-infected women have much higher rates of anal cancer than HIV-uninfected populations. Specifically, the incidence among HIV-infected MSM has been found to be as high as 130 cases per 100,000, as opposed to 5 cases per 100,000 among HIV-negative MSM. The advent of ART has not impacted the incidence of anal cancer and high-grade anal intraepithelial neoplasia in the HIV-infected patient population.

More information regarding screening, prevention, and treatment in the HIV-infected population can be found at the Department of Health and Human Services website (*aidsinfo.nih.gov/guidelines*).

CLINICAL MANIFESTATIONS OF HPV INFECTION

HPV infects the male urethra, penis, and scrotum and the female vulva, vagina, and cervix. Perianal, anal, and oropharyngeal infections occur in both genders. Genital warts are caused primarily by HPV type 6 or 11 and appear as soft sessile growths with a surface that is either smooth or rough with multiple finger-like projections. Penile genital warts are usually 2–5 mm in diameter and often occur in groups. A second type of penile lesion, the keratotic plaque, is slightly raised above normal epithelium and has a rough, often pigmented surface. **Figs. 193-1–193-3** show vulvar and vaginal, penile, and perianal warts, respectively.

Vulvar warts are soft, whitish papules that are either sessile or have multiple fine, finger-like projections. These lesions are most often located in the introitus and labia. In nonmucosal areas, vulvar lesions are similar in appearance to those in men: dry and keratotic. Vulvar lesions can appear as smooth, sometimes pigmented papules that may coalesce. Vaginal lesions appear as multiple areas of elongated papillae. Biopsy of vulvar or vaginal lesions may reveal malignancy; differentiation based on clinical exam is not always reliable.

Subclinical cervical HPV infections are common, and the cervix may appear normal on examination. Cervical lesions often appear as

FIGURE 193-1 Warts of the vulva and vagina caused by human papillomavirus. *(Reprinted with permission from K Wolff et al: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7th ed. New York: McGraw-Hill, 2013.)*

FIGURE 193-3 Perianal warts caused by human papillomavirus. *(Reprinted with permission from K Wolff et al: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7th ed. New York: McGraw-Hill, 2013.)*

papillary proliferations near the transformation zone. Irregular vascular loops are present beneath the surface epithelium. Patients who develop cervical cancer from HPV infection may present with a variety of symptoms. Early carcinomas appear eroded and bleed easily. More advanced carcinomas present as ulcerated lesions or as an exophytic cervical mass. Some cervical carcinomas are located in the cervical canal and may be difficult to see. Bleeding, symptoms of a mass lesion in late stages, and metastatic disease that may manifest as bowel or bladder obstruction due to direct extension of the tumor have also been described.

Patients with squamous cell cancer of the anus have more variable presentations. The most common presentations include rectal bleeding and pain or a mass sensation. Twenty percent of patients who are diagnosed with anal cancer may not present with any specific symptoms at the time of diagnosis, and the lesion is found fortuitously.

PREVENTION OF HPV INFECTION AND DISEASE

Behaviors That Can Reduce Exposure to HPV HPV infections are transmitted through direct contact with infected genital skin or mucosal surfaces and secretions. Does abstinence reduce HPV infections? For both men and women, numerous studies indicate that HPV infection and HPV-associated diseases correlate with the number of lifetime sexual partners, and people with no history of sexual intercourse have a lower detection rate of HPV. Fewer studies look at nonpenetrative sex and the risk of HPV infection and disease, but several studies indicate that HPV can be spread by *any* sexual intimacy, including touching, oral sex, or use of sex toys. It is therefore possible that individuals who have not partaken in penetrative sex can become infected.

Use of latex condoms reduces the risk of HPV infection and HPV-associated disease, such as genital warts and cervical precancers. Correct and consistent condom use has also been associated with regression of CIN in women and regression of HPV-associated penile lesions in men. As a preventive measure, condom use should be considered partially effective at best, not a substitute for cervical cancer screening or vaccination against HPV.

FIGURE 193-2 Penile genital warts caused by human papillomavirus. *(Reprinted with permission from K Wolff et al: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 7th ed. New York: McGraw-Hill, 2013.)*

HPV Vaccines The development of HPV vaccines effective in preventing infection and HPV-associated disease represents a major development in the last decade. The vaccines use virus-like particles (VLPs) that consist of the HPV L1 major capsid protein. The L1 protein self-assembles into VLPs when expressed in eukaryotic cells (i.e., yeast for the Merck vaccine or insect cells for the GlaxoSmithKline vaccine). These VLPs contain the same epitopes as the HPV virion. However, they do not contain genetic material and cannot transmit infection. The immunogenicity of the HPV vaccines relies on development of conformational neutralizing antibodies to epitopes displayed on viral capsids.

Several large vaccine trials have been completed and demonstrate the high degree of safety and efficacy of HPV vaccines. The evidence to date shows high and sustained efficacy against disease caused by those HPV types represented in the vaccines (HPV types 6, 11, 16, and 18 in the Merck vaccine and HPV types 16 and 18 in the GlaxoSmithKline vaccine). However, no therapeutic effect of either vaccine against active infection or disease has been documented.

BIVALENT VACCINE (CERVARIX) The bivalent L1 VLP vaccine (HPV types 16 and 18) marketed under the name Cervarix (GlaxoSmithKline) is administered by intramuscular injection at months 0, 1, and 6. This vaccine was tested in 18,644 women 15–25 years of age who resided in the United States, South America, Europe, and Asia. The primary endpoints of the study included vaccine efficacy against persistent infections with HPV types 16 and 18. Investigators also assessed

vaccine efficacy against CIN grade 2 or higher due to HPV 16 and 18 in women who had no evidence of HPV 16 or 18 infection at baseline. Vaccine efficacy related to HPV type 16 or 18 was 94.9% (95% confidence interval [CI], 87.7–98.4) against CIN 2 or worse; 91.7% (95% CI, 66.6–99.1) against CIN 3 or worse; and 100% (95% CI, –8.6 to 100) against adenocarcinoma in situ (AIS). Adverse events associated with the bivalent vaccine were evaluated in phase 3 trials in a subset of 3077 women who received vaccine and 3080 women who received hepatitis A vaccine. Injection-site adverse events (pain, redness, and swelling) and systemic adverse events (fatigue, headache, and myalgia) were reported more frequently in the HPV vaccine group than in the control group. Serious adverse events, new-onset chronic disease, or medically significant conditions occurred in the same proportion (3.5%) of HPV vaccine recipients and control vaccine recipients. The bivalent vaccine is approved in the United States for prevention of cervical cancer, CIN 2 or worse, AIS, and CIN 1 caused by HPV types 16 and 18. This vaccine is approved for females 9–25 years of age.

QUADRIVALENT VACCINE (GARDASIL) The quadrivalent L1 VLP vaccine (HPV types 6, 11, 16, and 18) marketed under the name Gardasil (Merck) is administered intramuscularly at months 0, 2, and 6. A combined efficacy analysis based on data from four randomized double-blind clinical studies including >20,000 participants was performed; results demonstrated that vaccine efficacy against external genital warts was 98.9% (95% CI, 93.7–100). Vaccine protective efficacy was 95.2% (95% CI, 87.2–98.7) against CIN; 100% (95% CI, 92.9–100) against type 16– or 18–related CIN 2/3 or AIS; and 100% (95% CI, 55.5–100.0) against type 16– or 18–related vulvar intraepithelial neoplasia (VIN) grades 2 and 3 and against vaginal intraepithelial neoplasia (VaIN) grades 2 and 3.

Safety data on the quadrivalent HPV vaccine are available from seven clinical trials including nearly 12,000 women 9–26 years of age who received the vaccine and ~10,000 women who received aluminum-containing or saline placebo. A larger proportion of young women reported injection-site adverse events in the vaccine groups than in the placebo groups. Systemic adverse events were reported by similar proportions of vaccine and placebo recipients and were described as mild or moderate for most participants. The types of serious adverse events reported were similar for the two groups. Ten persons who received the quadrivalent vaccine and seven persons who received placebo died during the trials; no deaths were considered to be vaccine related.

During the course of studies on the quadrivalent vaccine, surveillance data on the development of new medical conditions were collected for up to 4 years after vaccination. No statistically significant differences in the incidence of any medical conditions between vaccine and placebo recipients were demonstrated; this result indicated a very high safety profile for the vaccine. A recent safety review by the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) examined events related to Gardasil that had been reported to the Vaccine Adverse Events Reporting System (VAERS). The adverse events were consistent with what was seen in previous safety studies of the vaccine. Of note, rates of syncope and venous thrombotic events were higher with Gardasil than those usually observed with other vaccines.

The quadrivalent vaccine is approved for (1) vaccination of girls and women ages 9–26 years of age to prevent genital warts and cervical cancer caused by HPV types 6, 11, 16, and 18; (2) vaccination of the same population to prevent precancerous or dysplastic lesions, including cervical AIS, CIN 2/3, VIN 2/3, VaIN 2/3, and CIN 1; (3) vaccination of boys and men 9–26 years of age to prevent genital warts caused by HPV types 6 and 11; and (4) vaccination of people 9–26 years of age to prevent anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18. While the duration of protection has not been established, no evidence of waning protection has been found after a three-dose series of quadrivalent HPV vaccine, even after 10 years of follow-up from clinical trials.

NINE-VALENT VACCINE (GARDASIL-9) HPV types 16 and 18 together cause up to 80% of all cervical cancers worldwide, and worldwide data show that HPV types 31, 33, 35, 45, 52, and 58 are the next most frequently detected types in invasive cervical cancers. In 2014, the FDA approved a new nine-valent L1 VLP vaccine that targets HPV types 6, 11, 16, and 18 (the types also targeted by the quadrivalent HPV vaccine) as well as five additional oncogenic HPV types (31, 33, 45, 52, and 58). The nine-valent vaccine is marketed under the name Gardasil-9 (Merck) and is administered intramuscularly at months 0, 2, and 6.

In clinical studies of girls and women 16–26 years of age, the nine-valent HPV vaccine generated a noninferior antibody response to HPV types 6, 11, 16, and 18 compared to the quadrivalent vaccine. Bridging immunologic studies in male and female vaccine recipients 9–15 years of age and in boys and men 16–26 years of age indicated that the lower bound of the 95% CIs of the geometric mean titer ratio and seroconversion rates met criteria for noninferiority for all HPV types represented in the vaccine. In female recipients 16–26 years of age, vaccine efficacy against the combined endpoint of high-grade cervical, vulvar, or vaginal disease caused by any of the five additional oncogenic HPV types was 96.7% (95% CI, 80.9–99.8%). Like the other available HPV vaccines, the nine-valent HPV vaccine is safe and extremely well tolerated.

Mathematical models estimate that the level of protection conferred by the nine-valent HPV vaccine against all HPV-associated squamous cell cancers worldwide could be raised to 90%. However, the true impact will depend on vaccine uptake, especially in poor countries where cervical cancer is common and the vaccine is currently prohibitively expensive.

CROSS-PROTECTION OF HPV VACCINES Women who receive any of the available HPV vaccines produce neutralizing antibodies to virus types that are closely related to type 16 or 18. Analyses of data from clinical trials suggest that the HPV vaccines may offer limited cross-protection against nonvaccine virus types. Over short periods, the bivalent vaccine appears more efficacious against HPV types 31, 33, and 45 than the quadrivalent vaccine, but differences in study design make direct comparisons difficult, if not impossible. In addition, in the bivalent vaccine trials, vaccine efficacy against persistent infections with HPV types 31 and 45 waned over time, whereas efficacy against persistent infection with HPV type 16 or 18 remained stable. These results suggest that cross-protection is likely to be shorter lived than efficacy against infection and disease caused by vaccine types.

TWO-DOSE VERSUS THREE-DOSE SCHEDULE FOR HPV VACCINATION In an effort to simplify the dosing schedule and potentially reduce costs and improve vaccine uptake, a two-dose schedule has been considered. In several randomized vaccine trials among adolescent girls, geometric mean concentrations (GMCs) of antibodies to HPV types 16 and 18 were shown to be noninferior up to 24 months after a two-dose schedule to GMCs after a three-dose schedule. Numerous countries have adopted a two-dose HPV vaccination schedule. In the United States, the CDC now recommends two doses of HPV vaccine (at 0 and 6–12 months) for persons starting the vaccination series before the 15th birthday, as the immunologic response is rigorous in this age group. Three doses of HPV vaccine (at 0, 1–2, and 6 months) are recommended for persons starting the vaccination series on or after the fifteenth birthday and for persons with certain immunocompromising conditions, including HIV/AIDS.

RECOMMENDATIONS FOR HPV VACCINATION The most recent guidelines for HPV vaccination from the Advisory Committee on Immunization Practices (ACIP) are summarized below and provided in detail at *https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm.*

For both girls and boys, the ACIP recommends that routine HPV vaccination be initiated at age 11 or 12 years, although the vaccination series can be started beginning at age 9 years. An individual can begin a vaccines series with one HPV vaccine and then complete the series with another.

For female recipients, vaccination is recommended through 26 years of age with the bivalent, quadrivalent (if still available), or nine-valent HPV vaccine. Papanicolaou (Pap) smear testing and screening for HPV DNA are not recommended before vaccination. After vaccination, cervical cancer screening should be conducted according to age-specific guidelines (see below).

For male recipients, vaccination with either the bivalent vaccine or (as long as this formulation is available) the nine-valent vaccine is recommended through 21 years of age to those who have not been vaccinated previously or who have not completed the three-dose series. Men 22–26 years of age may also be vaccinated.

SCREENING FOR HPV-ASSOCIATED CANCER

Once HPV infection occurs, prevention of HPV-associated disease relies on screening. At present, screening for cervical cancer is widely accepted as cost-effective in preventing cervical cancer, and anal screening is accepted for screening in high-risk groups. In resource-rich countries, the primary method of cervical cancer screening is cytology via Pap smear. The American Society of Colposcopy and Cervical Pathology guidelines recommend initiation of cervical cancer screening at age 21, no matter the age of sexual debut. Women 21–29 years old should have a Pap smear every 3 years if their initial and subsequent Pap smears are normal. Although adolescent and young women often test positive for HPV DNA, they are at very low risk of cervical cancer. Because the presence of HPV DNA does not correlate with the presence of high-grade squamous intraepithelial neoplasia, co-testing (testing for HPV DNA at the time of Pap smear) is not recommended for women in this age group.

As a method of determining the need for colposcopy, HPV DNA co-testing is recommended for women 25–29 years of age in whom cytology detects abnormal squamous cells of undetermined significance. Women 30–65 years of age should have a Pap smear every 3 years if testing for HPV DNA is not performed. The screening interval for women in this age group can be extended to every 5 years if HPV DNA co-testing is performed and results are negative. HPV testing is not recommended for partners of women with HPV or for screening of conditions other than cervical cancer.

The role of HPV DNA testing as a primary screen for cervical cancer is changing. In 2014, the FDA approved the Roche Cobas HPV test for primary screening of cervical cancer. This test can be used to detect HPV DNA in specimens obtained from the cervix without cervical cytology for women ≥25 years of age. A positive result for HPV type 16 or 18 has a high enough positive predictive value in the general population that these women should have colposcopy performed. If high-risk HPV types other than 16 or 18 are detected, then cytology can be used. Ongoing studies of other HPV DNA testing methods are evaluating their use as a primary screening tool. The complete set of algorithms for appropriate age-specific screening guidelines, HPV DNA testing, and the management of abnormal Pap smears is available through the American Society of Colposcopy and Cervical Pathology at *http://www.asccp.org/asccp-guidelines*.

For women ≤30 years of age who are infected with HIV, cervical cytology is the preferred method of cervical cancer screening, and HPV DNA co-testing is not recommended. Cervical cancer screening should begin within 1 year of diagnosis of HIV infection, regardless of the mode of HIV transmission. If the first Pap smear is normal, then subsequent Pap smears should be performed annually until three negative tests are obtained. Cytology can then be conducted every 3 years. For women >30 years old, Pap testing is performed in the same manner as for younger women. However, HPV DNA co-testing can be used in women of this age group. If cytology and HPV DNA co-testing are negative, the next exam can be performed in 3 years. Positive results of HPV DNA co-testing are treated in the same manner as in HIV-uninfected women.

Women residing in developing countries with a lack of access to cervical screening programs have a higher rate of cervical cancer and poorer cancer-specific survival. Approximately 75% of women living in developed countries have been screened in the past 5 years, as opposed to ~5% of women living in developing countries. Economic and logistic obstacles likely impede routine cervical cancer screening for these populations. Many poor countries rely on an alternative method—visual inspection with acetic acid (VIA)—for cervical cancer screening. While some studies show a reduction in cervical cancer mortality in communities where VIA is widely used, other studies do not. In addition, the low specificity of VIA is problematic. As newer methods that use detection of oncogenic HPV DNA become available, even resource-limited countries may be able to replace VIA with these methods and achieve a reduction in cervical cancers as a result.

Currently, there is no broad consensus regarding screening for anal cancer and its precursors, including high-grade anal intraepithelial lesions. The reason is a lack of understanding of optimal treatment for low- or high-grade anal dysplasia found during cytologic screening. Current HIV treatment guidelines suggest that there may be a benefit to screening, but an effect on the associated morbidity and mortality of anal squamous cell cancer has not been consistently demonstrated.

TREATMENT

HPV-Associated Disease

A variety of treatment modalities are available for various HPV infections, but none has been proven to eliminate HPV from tissue adjacent to the destroyed and infected tissue. Treatment efficacies are limited by frequent recurrences, presumably due to reinfection from an infected partner, reactivation of latent virus, or autoinoculation from nearby infected cells. The goals of treatment include prevention of viral transmission, eradication of premalignant lesions, and reduction of symptoms.

Therapies are generally successful in eliminating visible lesions and grossly diseased tissue. Different therapies are indicated for genital warts, vaginal and cervical disease, and perianal and anal disease.

THERAPEUTIC OPTIONS

Imiquimod Imiquimod (5 or 3.75% cream) is a patient-applied topical immunomodulatory agent thought to activate immune cells by binding to a Toll-like receptor that leads to an inflammatory response. Imiquimod 5% cream is applied to genital warts at bedtime three times per week for up to 16 weeks. Warts are cleared in ~56% of patients, more often in women than in men; recurrence rates approach 13%. Local inflammatory side effects are common. Rates of clearance of genital warts are not as high with the 3.75% formulation as with the 5% preparation, but the duration of treatment is shorter (daily application required for a maximum of 8 weeks) and fewer local and systemic adverse reactions occur. Imiquimod should not be used to treat vaginal, cervical, or anal lesions. The safety of imiquimod during pregnancy has not been established.

Interferon Recombinant interferon α is used for intralesional treatment of genital warts, including perianal lesions. The recommended dosage is 1.0×10^6 IU of interferon into each lesion three times weekly for 3 weeks. Interferon therapy causes clearance of infected cells by immune-boosting effects. Adverse events include headache, nausea, vomiting, fatigue, and myalgia. Interferon therapy is costly and should be reserved for severe cases that do not respond to less expensive treatments. Interferon should not be used to treat vaginal, cervical, or anal lesions.

Cryotherapy Cryotherapy (liquid nitrogen treatment) for HPV-associated lesions causes cellular death. Genital warts usually disappear after two or three weekly sessions but often recur. Cryotherapy, which is nontoxic and is not associated with significant adverse reactions, can also be used for diseased cervical tissue. Local pain occurs frequently.

Surgical Methods Exophytic lesions can be surgically removed after intradermal injection of 1% lidocaine. This treatment is well tolerated but can cause scarring and requires hemostasis. Genital warts can also be destroyed by electrocautery, in which no additional hemostasis is required.

Laser Therapy Laser treatment affords destruction of exophytic lesions and other HPV-infected tissue while preserving normal tissue. Local anesthetics are generally adequate. Efficacy for genital lesions is at least equal to that of other therapies (60–90%), with low

TABLE 193-1 Recommended Treatments for Genital Warts Caused by Human Papillomavirus[a]

TREATMENT	IMIQUIMOD	CRYOTHERAPY	INTERFERON	SURGICAL REMOVAL	LASER
Effectiveness	Good	Good	Good	Excellent	Excellent
Recurrence	Frequent	Frequent	Frequent	Frequent	Frequent
Adverse effects	Frequent, mild to moderate	Mild, well tolerated	Frequent, moderately severe	Mild, well tolerated	Mild to moderate, well tolerated
Availability	Fair	Good	Fair	Good	Fair
Cost	Expensive	Inexpensive	Very expensive	Moderately expensive	Very expensive

[a]Imiquimod can be self-administered. All other treatments must be administered by a clinician.

recurrence rates (5–10%). Complications include local pain, vaginal discharge, periurethral swelling, and penile or vulvar swelling. Laser therapy has also been used successfully for cervical dysplasia and anal disease caused by HPV.

Therapeutic Vaccines The innate and adaptive immune systems are altered in patients with HPV-associated cancers. Antitumor immune responses are blunted by specific viral mechanisms. Numerous therapeutic vaccines that are being developed are designed to enhance the cell-mediated response to the HPV E6 and E7 oncoproteins, which are expressed in HPV-associated cancers. Such vaccines would enhance the ability to treat HPV-associated cancers, conditions that are very difficult to treat with current modalities. However, while progress has been made, no HPV vaccine is currently available for treatment of HPV infection or HPV-associated disease.

Other Therapies Both trichloroacetic acid and bichloroacetic acid are caustic agents that destroy warts by coagulation of proteins. Neither of these agents is recommended for treatment. Sinecatechins (15% ointment) and podophyllotoxin (0.05% solution or gel and 0.15% cream) are occasionally used for external genital warts, but other modalities listed above are as or more effective and are better tolerated.

RECOMMENDATIONS FOR TREATMENT

Table 193-1 lists available treatments for genital warts. An optimal therapy for HPV-related genital tract disease that combines high efficacy, low toxicity, low cost, and low recurrence is not available. For genital warts of the penis or vulva, cryotherapy is the safest, least expensive, and most effective modality. However, all available modalities for treatment of genital warts carry high rates of recurrence. Guidelines for the treatment of genital warts can be found on the CDC website (*http://www.cdc.gov/std/treatment/2010/genital-warts.htm*).

Women with vaginal lesions should be referred to a gynecologist experienced in colposcopy and treatment of these lesions. Treatment of cervical disease involves careful inspection, biopsy, and histopathologic grading to determine the severity and extent of disease. Women with evidence of HPV-associated cervical disease should be referred to a gynecologist familiar with HPV and experienced in colposcopy. Optimal follow-up of these patients includes colposcopic examination of the cervix and vagina on a yearly basis. Guidelines from the American College of Obstetricians and Gynecologists are available for the treatment of cervical dysplasia and cancer.

For anal or perianal lesions, cryotherapy or surgical removal is safest and most effective. Anoscopy and/or sigmoidoscopy should be performed in patients with perianal lesions, and suspicious lesions should be biopsied to rule out malignancy.

COUNSELING PATIENTS REGARDING HPV DISEASE

Most sexually active adults will be infected with HPV during their lives. The only way to avoid acquiring an HPV infection is to abstain from sexual activity, including intimate touching and oral sex. Practicing safe sex (partner reduction, use of condoms) may help reduce HPV transmission. Most HPV infections will be controlled by the immune system and cause no symptoms or disease. Some infections lead to genital warts and cervical precancers. Genital warts can be treated for cosmetic reasons and to prevent spread of infection to others. Even after resolution of genital warts, latent HPV may persist in normal-appearing skin or mucosa and thus theoretically may be transmitted to uninfected partners. Precancerous cervical lesions should be treated to prevent progression to cancer.

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Section 13 Infections Due to DNA and RNA Respiratory Viruses

194 Common Viral Respiratory Infections

James E. Crowe, Jr.

The most common and frequent infections in humans are respiratory virus infections. Some classical respiratory viruses (e.g., rhinoviruses) enter the body through the respiratory tract, replicating and causing disease only in cells of the respiratory epithelium. Other, more systemic viruses (e.g., measles virus and severe acute respiratory syndrome [SARS] coronavirus) spread via the bloodstream and cause systemic disease; however, they also may enter through and cause disease in the respiratory tract. Although infections with systemic viruses often induce lifelong immunity against disease, respiratory viruses that do not cause viremia usually can reinfect the same host many times throughout life. Reinfection with the same virus is common because

of incomplete or waning immunity after natural infection. Hundreds of different viruses cause infection of the respiratory tract, and within each virus type there can be a nearly unlimited diversity of field strains that vary antigenically, geographically, and over time (e.g., antigenically drifting influenza viruses). Specific antiviral treatment options are limited, and only a few licensed vaccines are available. **For further discussion of common respiratory virus infections, see Chap. 31 and syndrome-specific chapters.**

Common viral respiratory infections can be categorized in several ways, including by site of anatomic involvement, disease syndrome, or etiologic agent.

ANATOMIC SITES IN THE HUMAN RESPIRATORY TRACT

The type of respiratory disease that develops during virus infection is dictated to a large degree by the cell types and tissue organization in the respiratory tract. The vocal cords mark the transition between the upper and lower respiratory tracts. The upper respiratory tract is a complex anatomic system with interconnected structures, including the sinuses, middle-ear spaces, Eustachian tubes, conjunctiva, nasopharynx, oropharynx, and larynx. The tonsils and the adenoids are large collections of lymphoid tissue in the pharynx that participate in immunity but also are susceptible to infections. The lower respiratory tract structures include the trachea, bronchi, bronchioles, alveolar spaces, and lung tissue, including epithelial cells and blood vessels. The epithelial cell types that line the respiratory tract are varied in morphology and function, and their susceptibility to different virus infections varies. The principal types of cells in the major airways are ciliated or nonciliated epithelial cells, goblet cells, and Clara cells. Smooth-muscle cells form major tissue structures around the epithelial structures of the large airways of the lower respiratory tract down to the level of the bronchioles, and these cells are reactive to intrinsic and extrinsic signals, including viral infection or exposure to allergens or pollutants. The pathologic process of wheezing is driven by smooth-muscle contraction and obstruction of airways caused by mucous accumulation and epithelial sloughing in the lumen. Reactive airways causing wheezing are most often due to constriction of lumen size at the level of the bronchioles (which have the narrowest lumen diameter of the airways). The lung does not have smooth-muscle or ciliated cells, but instead possesses pneumocytes of types I and II. Pneumonia **(Chap. 121)** is an infection of the pneumocytes in the lung tissue and the alveolar spaces. The alveolar spaces also contain cells of the monocyte lineage, such as macrophages, which patrol the air spaces.

DISEASE SYNDROMES

Since different respiratory viruses tend to have a predilection for replication in differing cells or regions of the respiratory tract, it is possible for the well-trained clinician with epidemiologic information to understand the most likely associations of viruses with clinical syndromes. The clinical diagnoses for virus infections in the upper respiratory tract are rhinitis or the common cold, sinusitis, otitis media, conjunctivitis, pharyngitis, tonsillitis, and laryngitis. In reality, some upper respiratory tract infections affect more than one upper respiratory tract anatomic site during a single infection, such as the classical pattern of pharyngoconjunctival fever during adenovirus infection. Lower respiratory tract syndromes also can be associated easily with anatomic region, including tracheitis, bronchitis, bronchiolitis, pneumonia, and exacerbations of reactive airway disease or asthma. Bronchiolitis is a disease condition characterized by trapping of air in the lungs with difficulty in expiration (i.e., wheezing); it is caused by inflammation or infection of the bronchioles, the smallest and most highly resistant airways. Again, mixed syndromes occur, such as laryngotracheitis, usually termed croup. Croup, a disease condition characterized by difficulty in inspiration associated with a barky cough, is caused by inflammation or infection of the larynx, trachea, and bronchi. When respiratory symptoms occur in the context of a respiratory viral illness with significant systemic signs, infection with particular agents can be suspected (e.g., influenza, measles, SARS, or hantavirus pulmonary syndrome [HPS]), with exposure history taken into account.

ETIOLOGIC AGENTS

RESPIRATORY VIRUSES CAUSING DISEASE IN IMMUNOCOMPETENT HOSTS

Children have more frequent respiratory virus infections than adults; thus it was natural that many early discoveries about the viral causes of respiratory infections came from pediatric studies. The principal causes of acute viral respiratory infections were determined in large epidemiologic studies in the 1960s and 1970s, when cell culture of infectious agents became available. More recently, studies of viral epidemiology have been conducted in adults, especially in special populations such as the elderly, nursing home residents, and immunocompromised individuals. Rapid antigen detection tests (based on immunoassays for detection of viral proteins) became available for respiratory syncytial virus (RSV) and influenza virus in the 1980s. With the availability of sensitive and specific molecular tests, such as reverse transcription combined with the polymerase chain reaction (RT-PCR), studies in the past two decades have greatly increased the extent to which we understand the causes of viral respiratory infections. Multiplex panels of RT-PCR tests capable of detecting a dozen or more viruses are commonly available for clinical testing of respiratory secretions. These sensitive tests have been especially helpful in studies of infection in adults, who often shed much lower concentrations of virus in secretions than do children. Influenza viruses, RSV, and human metapneumovirus (hMPV) are the most common causes of serious lower respiratory tract disease in otherwise healthy subjects; parainfluenza viruses (PIVs) and adenoviruses also cause substantial disease. Rhinoviruses (the most common cause of the common cold syndrome) have been increasingly associated with lower respiratory tract syndromes. Rhinovirus infection is so common, even in asymptomatic individuals, that it has been hard to establish clear figures for the role of rhinovirus in lower respiratory disease. Generally, about two-thirds of cases of respiratory illness in a research setting can be associated with a specific viral agent. Besides the viruses mentioned above (and discussed below), a number of additional viruses identified with molecular tools have been associated with respiratory illness. Still, it is fair to say that our diagnostic tools remain suboptimal since a specific infectious agent is not identified in approximately one-third of clinical respiratory illnesses in large surveillance studies. It is likely that in most of these cases pathogens are not detected because of the very low titers of virus in patient samples at the time of clinical presentation, which may occur after the period of peak virus shedding. It is also possible that novel agents are yet to be identified. As emerging tools for microbiome and "virome" studies (with sequencing of all nucleic acids in a sample) are applied in these settings in coming years, new agents and new associations with disease will probably be discovered.

RESPIRATORY VIRUSES CAUSING DISEASE IN IMMUNOCOMPROMISED HOSTS

Special populations of patients are susceptible not only to the conventional respiratory viruses discussed above but also to agents causing symptoms during reactivation of latent viruses or new infections with opportunistic agents. Most prominently, reactivating latent viruses, such as herpes simplex virus (HSV) and cytomegalovirus (CMV) and adenoviruses, cause disease in immunocompromised humans. Patients at most risk are those with hematopoietic stem cell or solid organ transplantation, leukopenia caused by chemotherapy, or advanced HIV-AIDS. In immunosuppressed patients with pneumonia, CMV is the virus recovered most frequently during deep respiratory tract diagnostic procedures such as bronchoalveolar lavage. These patients also are highly susceptible to more frequent and more severe disease caused by common respiratory viruses, including RSV, hMPV, PIVs, influenza viruses, rhinoviruses, and adenoviruses. Conventional acute respiratory viruses can cause chronic and sometimes fatal infections in these populations. Nosocomial transmission of respiratory viruses occurs in hematopoietic stem cell transplantation units, and the frequency of transmission can be high, with entire units affected.

SPECIFIC VIRAL CAUSES OF RESPIRATORY DISEASE

Orthomyxoviridae: Influenza Viruses (See also Chap. 195)

Influenza virus infection and influenza syndrome usually are associated with fever, myalgias, fatigue, sore throat, headache, and cough. Influenza causes severe and even fatal pneumonia, particularly in elderly patients, nursing home residents, immunocompromised persons, and very young children. Influenza pneumonia has an unusually high rate of complication by bacterial superinfection, with staphylococcal and streptococcal bacterial pneumonia occurring in as many as 10% of cases in some clinical series.

Influenza is a single-stranded, segmented, negative-sense, RNA genome virus of the family Orthomyxoviridae. There are three (sero)types of influenza viruses: A, B, and C. Influenza A and C viruses infect multiple species, while influenza B virus infects humans almost exclusively. Type A viruses appear to be the most virulent for humans and most commonly cause severe disease manifestations, although type B viruses cause substantial morbidity. On the basis of antibody response, influenza A viruses can be subdivided into 18 different hemagglutinin (H) surface protein subtypes and 11 neuraminidase (N) surface protein subtypes. The subtypes that have caused major pandemics in humans are H1N1, which caused the 1918 pandemic; H2N2, which caused the 1957 pandemic; H3N2, which caused the 1968 pandemic; and H1N1pdm2009, which caused the 2009 pandemic. Currently, type A subtypes H1N1 and H3N2 and type B viruses cause annual seasonal epidemics.

Major pandemics caused by new influenza viruses are always possible. Many highly pathogenic influenza viruses circulate in aquatic birds. Occasionally, avian viruses infect humans directly after close contact with infected wild birds or poultry. Co-housing of pigs (which have both avian and human influenza virus receptors) with poultry may increase the risk of reassortment of human and animal or bird viruses; reassortment can make the zoonotic viruses more fit for replication in humans. Several outbreaks of avian influenza have occurred in limited numbers of humans to date, and there is the risk of a worldwide pandemic with avian influenza viruses if a strain acquires the potential to spread efficiently from human to human. H5N1 influenza virus infection of humans, predominantly by direct chicken-to-human transmission, occurred during an epizootic in Hong Kong's poultry population in 1997. The disease affected many types of wild and domestic birds and caused a high rate of systemic disease and death in infected humans. This virus, carried in the gastrointestinal tract of wild birds, has spread throughout Asia and beyond and continues to evolve antigenically. Avian H7N7 and H7N9 viruses also have caused zoonotic outbreaks. A significant outbreak of H7N9 virus infection began in China in March 2013, with high mortality, and seasonal outbreaks that have subsequently occurred nearly yearly threaten to cause a pandemic. H1N2 virus is endemic in pigs and affects humans with close contact. An H3N2 variant virus that differs antigenically from seasonal human viruses is endemic in pigs and occasionally infects children who have close contact with pigs in the United States. Rare human cases caused by H6, H7, H9, and H10 viruses have been reported. Type B influenza viruses co-circulate in humans during seasonal epidemics. Type B viruses mutate less frequently than type A viruses, and there is only one influenza B subtype. The slower evolution of type B viruses is probably linked to the fact that they are almost exclusively human pathogens. There is some antigenic diversity in these strains, however, and two major lineages have been designated B/Shanghai-like and B/Fujian-like strains.

Paramyxoviridae • RESPIRATORY SYNCYTIAL VIRUS

RSV is a single-stranded, negative-sense, nonsegmented, RNA genome virus of the genus *Pneumovirus* in the family Paramyxoviridae. Infection is ubiquitous, affecting most humans in the first several years of life and causing reinfections throughout life. RSV is among the most transmissible viruses of humans. Disease epidemics occur yearly, typically between October or November and March in temperate regions. RSV is one of the most common viral causes of severe lower respiratory tract illness in the elderly and in children; it is among the most important causes of hospitalization of elderly and infant patients throughout the world. There is only one serotype of RSV, but antigenic variability does occur in circulating field strains. In immune serum reciprocal cross-neutralization studies, the two antigenic subgroups, A and B, appear to be ~25% antigenically related; this relatedness may partially explain the susceptibility of humans to reinfection, which is very common and can be caused by viruses of the same subgroup or even the same strain. However, reinfection in otherwise healthy adults usually is associated with mild disease confined to the upper respiratory tract. Severe lower respiratory tract disease is common in the elderly, especially in frail institutionalized elderly populations. Immunocompromised patients of any age also are at risk of severe or prolonged disease, especially recipients of hematopoietic stem cell transplants. Wheezing is common with primary infection in children (bronchiolitis), and there is a strong association of RSV infection early in life and subsequent asthma, although it is unclear whether severe childhood RSV causes asthma or is the first manifestation of reactive airway disease. RSV causes exacerbations of asthma and is associated with acute exacerbations of chronic obstructive pulmonary disease (COPD), also referred to as acute exacerbations of chronic bronchitis (AECB).

HUMAN PARAINFLUENZA VIRUSES The human PIVs are a group of four distinct serotypes (designated 1–4) of single-stranded, negative-sense RNA viruses belonging to the family Paramyxoviridae. PIV3 most commonly causes severe disease, and repeated infection is common throughout life, although secondary infections often are mild or asymptomatic. Primary infections in children manifest as laryngotracheitis (croup), while subsequent infections typically are limited to the upper respiratory tract. PIVs are detected with sensitive RT-PCR tests or, more classically, by cell culture with immunofluorescent microscopy or hemadsorption in reference laboratories.

HUMAN METAPNEUMOVIRUS hMPV was discovered only in 2001 but probably has always been present in human populations. Infection occurs first in early childhood, and reinfections are common throughout life. This virus is similar in many respects to RSV. It belongs to the family Paramyxoviridae and is a member of the genus *Pneumovirus*. It causes both upper and lower respiratory disease. It appears to be somewhat less virulent than RSV, causing about half as much severe lower respiratory tract disease, probably because it does not possess the nonstructural genes that RSV expresses in infected cells to abrogate the effect of host innate immune effectors like interferons. The clinical features of lower respiratory tract infections caused by hMPV are similar to those of such infections caused by other paramyxoviruses, most often including cough, coryza, and wheezing. Like RSV, hMPV plays an important role in exacerbations of asthma or COPD and causes pneumonia or wheezing in frail and institutionalized elderly individuals and immunocompromised patients.

MEASLES VIRUS (See also Chap. 200) Measles virus is also a paramyxovirus but of the genus *Morbillivirus*. This virus causes a systemic infection known as rubeola but also can manifest with respiratory symptoms. Measles virus probably is the most contagious respiratory virus infection of humans: it is transmitted efficiently not only by direct contact with infected persons or fomites (like other respiratory viruses) but also by small-particle aerosols. Measles virus infection is preventable by vaccination but is so infectious that cases are inevitable—even in the United States—whenever vaccination rates fall below 90–95% in a population. The virus causes systemic illness, sometimes including severe pneumonia, when primary infection occurs in an unvaccinated adult or an immunocompromised person of any age. Therefore, vigilance in maintaining high vaccination rates is critical. With primary infection, the illness in children is typically milder; however, mortality rates in lower-resource countries are high, especially among persons with underlying risk factors, including malnutrition.

Symptoms of measles include ≥3 days of high fever and a classical set of upper and lower respiratory tract symptoms sometimes termed "the 3 Cs": cough, coryza, and conjunctivitis. Unlike most respiratory viruses, measles virus circulates in the bloodstream and thus causes disseminated infection with systemic manifestations. Usually, a characteristic diffuse maculopapular rash appears within days of fever onset.

TABLE 194-1 Enterovirus, Rhinovirus, and Parechovirus Species Name Changes Made in Order to Remove References to Host Species Names and Approved by the International Committee on Taxonomy of Viruses in February 2013

GENUS	CURRENT SPECIES NAME	FORMER SPECIES NAME
Enterovirus (now 13 species)	Enterovirus A: consists of 25 serotypes, including coxsackieviruses and some non-polio enteroviruses that cause respiratory disease	Human enterovirus A
	Enterovirus B: consists of 63 serotypes, including some coxsackieviruses, echoviruses, and non-polio enteroviruses	Human enterovirus B
	Enterovirus C: consists of 23 serotypes, including the polioviruses	Human enterovirus C
	Enterovirus D: consists of 5 serotypes and includes enterovirus D68	Human enterovirus D
	Rhinoviruses A–C	Human rhinoviruses A–C
Parechovirus (2 species)	Parechovirus A: consists of 19 types (1–19). Human parechoviruses (HPeVs) 1 and 2 are common human pathogens.	HPeV-1 and HPeV-2 were formerly classified in the genus *Enterovirus* as echoviruses 22 and 23, respectively.

Koplik's spots **(see Fig. A1-2)**—typical mucosal lesions in the mouth that appear briefly—are considered diagnostic of measles infection in the setting of the typical rash and fever.

Picornaviridae A wide variety of picornaviruses cause respiratory disease, including non-polio enteroviruses, rhinoviruses, and parechoviruses **(Chap. 199)**. The designations of these viruses can be confusing: the enterovirus, rhinovirus, and parechovirus species names were changed (with the approval of the International Committee on Taxonomy of Viruses in February 2013) to remove references to host species names. These changes are summarized in **Table 194-1**. The genus *Enterovirus* consists of 13 species, including enteroviruses A through D and rhinoviruses A through C. The genus *Parechovirus* contains two species, one of which—Parechovirus A—encompasses 19 types: human parechovirus (HPeV) 1 through 19. These viruses exhibit seasonal patterns that differ from those of most other acute respiratory viruses. Rhinovirus infections occur year-round. Enterovirus infections occur most commonly in the summer months in temperate areas.

RHINOVIRUSES Rhinoviruses have single-stranded, positive-sense RNA genomes. Rhinoviruses A through C represent species in the *Enterovirus* genus of the family Picornaviridae. Rhinoviruses are the most common viral infective agents in humans and the most frequent cause of the common cold. Field isolates of rhinovirus are exceptionally diverse; they can be classified by serotyping into more than 100 serotypes or alternatively by genotyping into a large number of genotypes that cause cold symptoms. At the time of writing in 2017, the species Rhinovirus A contained 80 types, Rhinovirus B had 32 types, and Rhinovirus C had 55 types. The viral particles are icosahedral in structure and are non-enveloped. Rhinoviruses are responsible for at least half of all cases of the common cold. Rhinovirus-induced common colds may be complicated in children by otitis media and in adults by sinusitis. Most adults, in fact, have radiographic evidence of sinusitis during the common cold, which resolves without therapy. Therefore, the primary disease is probably best termed *rhinosinusitis*. Rhinovirus infection is associated with exacerbations of reactive airway disease in children and asthma in adults. It is not clear whether rhinovirus is restricted to the upper respiratory tract and only indirectly induces inflammatory responses that affect the lower respiratory tract or whether the viruses spread to the lower respiratory tract. In the past, it was thought that these viruses did not often replicate or cause disease in the lower respiratory tract. However, recent studies have discerned strong epidemiologic associations of rhinoviruses with wheezing and asthma exacerbations, including episodes severe enough to require hospitalization. Rhinoviruses likely can infect the lower airways to some degree, inducing a local inflammatory response. Another possibility is that significant local infection of the upper respiratory tract may induce regional elaboration of mediators that causes lower airway disease. The association of rhinovirus infection with lower respiratory tract illness is difficult to study because diagnosis by cell culture is not sensitive. RT-PCR diagnostic tests are difficult to interpret because they are often positive for prolonged periods and even asymptomatic individuals may have a positive test. Comprehensive serologic studies to confirm infection are difficult because of the large number of serotypes. Nevertheless, most experts believe rhinoviruses are a common cause of serious lower respiratory tract illness.

ENTEROVIRUSES Non-polio enteroviruses are common and distributed worldwide. Although infection often is asymptomatic, these viruses cause outbreaks of clinical respiratory disease, sometimes with fatal consequences. The species Enterovirus A consists of 25 serotypes, including coxsackieviruses and some non-polio enteroviruses that cause respiratory disease. Coxsackieviruses cause oral lesions and often are associated in children with hand-foot-and-mouth disease. The pharyngitis associated with this infection characteristically manifests with herpangina, a clinical syndrome of ulcers or small vesicles on the palate that often involves the tonsillar fossa and is associated with fever, difficulty swallowing, and throat pain. Outbreaks commonly occur in young children during the summer. Enterovirus A71 also causes large outbreaks of hand-foot-and-mouth disease, especially in Asia, sometimes leading to neurologic complications and even death. The species Enterovirus B consists of 63 serotypes, including the echoviruses (*echo* being an acronym for *e*nteric *c*ytopathic *h*uman *o*rphan, which may be an archaic notion since most echoviruses are associated with human diseases, most commonly in children). Echoviruses can be isolated from many children with upper respiratory tract infections during the summer months. Echovirus 11 has been associated with laryngotracheitis or croup. Epidemiologic studies also have associated echoviruses with epidemic pleurodynia, an acute illness characterized by sharp chest pain and fever. The species Enterovirus C consists of 23 serotypes, including the polioviruses. The species Enterovirus D consists of five serotypes, including enterovirus D68, which has been associated with wheezing and some severe syndromes in children.

PARECHOVIRUSES The genus *Parechovirus* comprises two species, one of which is Parechovirus A. The most common member of the genus *Parechovirus*, human parechovirus 1, is a frequent human pathogen. The genus also includes the closely related human parechovirus 2. Human parechoviruses usually cause mild respiratory or gastrointestinal illness. Most infections occur in young children. The seroprevalence of parechoviruses 1 and 2 is high among adults.

Adenoviridae Viruses of the family Adenoviridae infect both humans and animals. As their designation indicates, adenoviruses were first isolated in human lymphoid tissues from surgically removed adenoids. In fact, some serotypes establish persistent asymptomatic infections in tonsil and adenoid tissues, and virus shedding can occur for months or years. These double-stranded DNA viruses are <100 nm in diameter and have non-enveloped icosahedral morphology. The large double-stranded DNA genome is linear and nonsegmented. The seven major human adenovirus species (designated A through G) fall into 57 immunologically distinct serotypes. Human respiratory tract infections are caused mainly by the B and C species. Adenovirus infections can occur throughout the year. Many serotypes cause sporadic outbreaks, while others appear to be endemic in particular locations. Respiratory illnesses include mild disease such as the common cold and lower respiratory tract illnesses including croup, bronchiolitis, and pneumonia. Conjunctivitis is associated with infection by the B and D species. A particular constellation of symptoms referred to as pharyngoconjunctival fever is frequently associated with acute adenovirus infection. In contrast, gastroenteritis has been associated most frequently with serotypes 40 and 41 virus of species F.

Immunocompromised patients are highly susceptible to severe disease during infection with respiratory adenoviruses. The syndrome of acute respiratory disease (ARD), especially common in stressful or crowded living conditions, was first recognized among military recruits during World War II and has continued to be a problem when vaccination has been suspended temporarily because of lapses in vaccine supply. ARD is most often associated with adenovirus types 4 and 7.

Coronaviridae Members of the genus *Coronavirus* also contribute to respiratory illness, including severe disease. Dozens of coronaviruses affect animals. In the twentieth century, only two representative strains of human coronaviruses were known to cause disease: 229E (HCoV-229E) and OC43 (HCoV-OC43). An outbreak of infection with SARS-associated coronavirus (SARS-CoV) showed that animal coronaviruses have the potential to cross from other species to humans, with devastating effects. The one major epidemic to date (November 2002 through July 2003) encompassed more than 8000 cases, with mortality rates approaching 10%. SARS-CoV causes a systemic illness with a respiratory route of entry. SARS is a unique form of viral pneumonia. In contrast to most other viral pneumonias, SARS lacks upper respiratory symptoms, although cough and dyspnea occur in most patients. Typically, patients present with a nonspecific illness manifesting as fever, myalgia, malaise, and chills or rigors; watery diarrhea may occur as well. Investigators have reported the identification of a fourth human coronavirus, HCoV-NL63. Evidence is emerging that this new group 1 coronavirus is a common respiratory pathogen of humans, causing both upper and lower respiratory tract illness. HCoV-HKU1 was first described in January 2005 after its detection in a patient with pneumonia. Several cases of respiratory illness have been associated with this virus, but its infrequent identification suggests that this putative group 2 coronavirus has caused a low incidence of illness to date. The Middle East respiratory syndrome coronavirus (MERS-CoV), first isolated in 2012, causes severe disease in humans, with 35% mortality. MERS-CoV is a zoonotic virus (transmitted between animals and people). The virus may have emerged from bats in the Middle East. Studies have shown that humans are infected through direct or indirect contact with infected dromedary camels.

Herpesviridae Several herpesviruses cause upper respiratory infections, especially infection of the oral cavity. Herpes simplex pharyngitis is associated with characteristic clinical findings, such as acute ulcerative stomatitis and ulcerative pharyngitis. HSV types 1 and 2—also called human herpesvirus (HHV) 1 and 2, respectively—both cause oral lesions (Chap. 187), although >90% of oral infections are caused by HSV-1. Primary oral disease can be severe, especially in young children, who sometimes are admitted for rehydration therapy as a result of poor oral intake. A significant proportion of individuals suffer recurrences of symptomatic disease consisting of vesicles on the lips. Epstein-Barr virus (EBV) mononucleosis syndrome (Chap. 189) is often marked by acute or subacute exudative pharyngitis; in some cases, tonsillar swelling in EBV pharyngitis is so severe that airway occlusion appears imminent. Most of the viruses in the family Herpesviridae—including CMV (Chap. 190); EBV; varicella-zoster virus (VZV; Chap. 188); and HHV-6, -7, and -8 (Chap. 190)—can cause severe disease in immunocompromised patients, especially hematopoietic stem cell transplant recipients.

Parvoviridae: Human Bocavirus A new virus was recently identified in respiratory samples from children with lower respiratory tract disease in Sweden. Sequence analysis of the genome revealed that the virus is highly related to canine minute virus and bovine parvovirus and is a member of the genus *Bocavirus* (subfamily Parvovirinae, family Parvoviridae). This virus, tentatively named human bocavirus (HBoV), has been identified as the sole agent in a limited number of respiratory samples from children hospitalized with respiratory tract disease. Whether the virus causes or is merely associated with disease remains controversial.

Retroviridae: HIV Pharyngitis occurs with primary HIV infection and may be associated with mucosal erosions and lymphadenopathy.

Papovaviridae: Polyomaviruses Polyomaviruses are small, double-stranded, DNA-genome, non-enveloped icosahedral viruses that may be oncogenic. Two major polyomaviruses, JC and BK viruses, are known to infect humans. Of adults in the United States, ≥80% are seropositive for these viruses. JC virus can infect the respiratory system, kidneys, or brain. BK virus infection causes a mild respiratory infection or pneumonia and can involve the kidneys of immunosuppressed transplant recipients.

EPIDEMIOLOGY

AGE

Age (along with the associated factor of prior exposure history) is a major determinant of risk for symptomatic disease during respiratory virus infection. Primary infection with most of the acute respiratory viruses often is more severe than secondary infection. Indeed, reinfection with most of these viruses occurs throughout life, but primary infection is much more likely to be associated with severe lower respiratory tract disease, while secondary infection typically is asymptomatic or associated with upper respiratory tract symptoms only. As these infections are ubiquitous, most primary infections (and thus many of the severe cases) occur during the first few years of life. Later, exposure to young children (in populations such as parents of young children and daycare workers) is a risk factor for frequent reinfection. Despite a lifetime of previous exposures, the risk of severe disease increases with age in the elderly, probably because of immune senescence and general medical decline.

SEASON

Infections with most of the conventional respiratory viruses (e.g., influenza virus, RSV, and hMPV) occur in winter. Typically, there is one dominant virus sweeping through a local community at any one time, a pattern that suggests some population-level interference with transmission. However, outbreaks can be closely spaced, and co-circulation of different viruses or antigenically diverse strains of one virus does occur. In the United States, some regional differences in seasonality have been noted; for example, RSV often appears in Florida and other southeastern states first. Seasons are, of course, reversed in the Northern and Southern hemispheres, so that winter epidemics occur roughly from November to March in the United States but from April to August in Australia; therefore, "winter" epidemics are almost always occurring somewhere in the world. Seasonal variances differ in the tropics, where acute respiratory viral infections are more common in the rainy season.

RISK FACTORS FOR DISEASE

Infection with these viruses is nearly universal, but disease expression varies among individuals infected with identical viruses. Therefore, investigators have sought to identify risk factors for severe disease. Most single risk factors identified have a moderate effect on the incidence of severe disease, but an accumulation of factors is associated with high risk. Underlying lung disease is a major factor, especially diseases associated with the need for chronic oxygen supplementation. COPD is one of the most profound risk factors. Other severe underlying medical conditions, especially cardiovascular disease, also enhance risk. Smoking (or exposure to wood smoke), low socioeconomic status, and male gender all contribute to a minor increase in the risk of lower respiratory tract illness. Close exposure to infected people is a major factor. For instance, living in close quarters (e.g., housing for military trainees, college dormitories, or nursing homes) puts groups of individuals at risk for rapid outbreaks. The U.S. military has instituted an adenovirus vaccination program to prevent severe or fatal adenovirus respiratory infections that can occur during outbreaks when new recruits are brought together. A breakdown in isolation and hand-washing compliance procedures can lead to cycles of nosocomial transmission of infection in hospital inpatient wards and intensive care units. In assessments of severe lower respiratory tract illness, a history of travel to an area with unusual agents should be considered carefully (e.g., exposure to avian influenza outbreaks in Asia, exposure to MERS-CoV in the Middle East).

TRANSMISSION

Respiratory viruses are transmitted by two principal modes: fomites or large-particle aerosols of respiratory droplets spread directly from person to person by coughing or sneezing. Fomite transmission occurs indirectly when infected respiratory droplets are deposited on the hands or on inanimate objects and surfaces, with subsequent transfer of secretions to a susceptible person's nose or conjunctiva. Most respiratory viruses do not spread by small-particle aerosols across rooms or down halls, although measles virus and VZV do spread in this manner. Therefore, contact and droplet precautions are sufficient to prevent transmission in most settings; hand washing is especially critical in health care settings during the winter.

APPROACH TO THE PATIENT

Common Viral Respiratory Infections

The principal interventions that make a difference in the care of patients with acute respiratory virus infections are supportive, and these factors should be managed meticulously. Hypoxia is managed with supplemental oxygen and respiratory failure with mechanical ventilation. Because the tachypnea and fever that often accompany pneumonia and wheezing frequently result in dehydration, fluid management is important. The astute clinician can narrow the etiologic possibilities on the basis of epidemiologic knowledge; information about viruses circulating in the community (widely available from local reference laboratories, county and state health departments, and the U.S. Centers for Disease Control and Prevention [CDC]); and the patient's exposure history, age, and immunologic status, including vaccination status. Proper use of rapid diagnostic tests is important. When diagnostic tests are applied only to samples from individuals at high risk of exposure to an infectious agent in the appropriate season, the positive predictive value of the test is increased. A central medical decision is whether or not to use a specific antibacterial or antiviral agent to treat a respiratory infection. Antibiotics do not improve the outcome of uncomplicated respiratory virus infections in otherwise healthy subjects. Some viral infections, especially influenza, can be complicated by secondary bacterial infection. There are only a limited number of licensed antiviral drugs, which should be used when a specific viral etiology is determined. Antiviral treatment generally is effective only when administered early in the course of illness.

CLINICAL MANIFESTATIONS

The common cold is characterized by nasal congestion, sneezing, rhinorrhea, cough, and sore throat. Laryngitis is accompanied by hoarseness or dysphonia. Acute bronchitis is characterized by a dry or productive cough of <3 weeks' duration (most prevalent in winter) in the absence of signs and symptoms of pneumonia and of evidence of pneumonia on chest radiography and is primarily caused by viruses. Bacteria play a more prominent role in chronic bronchitis. Bronchiolitis is an acute illness with wheezing and evidence of upper respiratory infection, most commonly seen in the winter in infants and young children. The typical clinical manifestations of acute pneumonia include cough, sputum production, dyspnea, and chest pain. More systemic signs and symptoms also occur in pneumonia, including fever, fatigue, sweats, headache, myalgia, and occasionally nausea, abdominal pain, and diarrhea.

DIAGNOSIS

The clinical diagnosis of a respiratory syndrome and the anatomic location of infection is based on history, physical examination, and radiography. A specific viral etiology can be determined by specific diagnostic tests. The gold standard for diagnosing a respiratory viral infection is virus isolation, performed by inoculation of cell cultures with fresh secretions and use of multiple cell types in a reference laboratory staffed by experienced technologists. Direct or indirect fluorescent antibody detection can be used to visualize virus-infected cells in nasal secretions. Rapid antigen-based diagnostic tests are used to detect influenza virus or RSV proteins in nasopharyngeal secretions. The most sensitive tests typically are RT-PCR molecular diagnostic tests that amplify and detect the presence of viral genomic RNA or DNA in respiratory secretions. Multiplex panels assaying a sample for a dozen or more common respiratory viruses are available. These tests must be used and interpreted carefully because of their extreme sensitivity. If care is not taken, it is relatively easy to contaminate a PCR test in the laboratory with small amounts of DNA from a previous reaction. In addition, because a viral genome can sometimes persist in nasal secretions for weeks after an infection resolves, a positive test may indicate a recently resolved rather than a currently acute infection. Despite these limitations, PCR tests generally are considered the most sensitive and specific tests available. Chest radiographs should be obtained for all patients with suspected pneumonia.

TREATMENT

Common Viral Respiratory Infections

NFLUENZA (SEE ALSO CHAP. 195)

A number of drugs are licensed in the United States for the treatment or prophylaxis of influenza. Neuraminidase inhibitors act on both influenza A and B viruses by serving as transition-state analogs of the viral neuraminidase that is needed to release newly budded virion progeny from the surface of infected cells. The cell surface normally is coated heavily with the viral receptor sialic acid. Oseltamivir is administered orally and is effective for the prevention or treatment of uncomplicated influenza in otherwise healthy adults. Observational studies indicate that oseltamivir also may be beneficial during serious illness. The drug is generally well tolerated, with primarily gastrointestinal toxicity. Zanamivir, a powder that is administered through oral inhalation, exhibits effectiveness similar to that of oseltamivir. Moreover, zanamivir is active against some influenza virus strains that are resistant to oseltamivir. Inhalation of zanamivir powder may cause bronchospasm in patients with COPD or asthma. Peramivir is a newer drug that is administered intravenously as a single 600-mg dose. It is efficacious in acute, uncomplicated influenza and is approved for treatment of individuals who cannot take oral or inhaled medications. Its efficacy in severe influenza requiring hospitalization has not yet been demonstrated. Laninamivir is a new drug that is approved in Japan for prophylaxis and treatment of influenza. It is a polymeric zanamivir conjugate that is delivered by oral inhalation, and it exhibits greater potency and longer retention times than conventional zanamivir. The adamantanes amantadine and rimantidine have been used for the treatment of influenza A infection. These drugs interfere with the ion channel activity caused by the M2 protein of influenza A viruses, which is needed for viral particle uncoating after endocytosis. These agents were commonly used in the past, but widespread resistance has been found in many currently circulating influenza A viruses. Therefore, the adamantanes should not be used unless isolate sensitivity is demonstrated, and, in many influenza seasons, the CDC advises against their use. When they are used, they are administered orally and display efficacy against uncomplicated influenza A caused by susceptible strains. The effectiveness of these drugs in serious illness has not been established. Toxicity with rimantadine generally manifests as gastrointestinal intolerance. Toxicity with amantadine is primarily associated with central nervous system symptoms.

RSV INFECTION

Ribavirin is a nucleoside antimetabolite prodrug whose activation by kinases in the cell results in a 5′-triphosphate nucleotide form that inhibits RNA replication. The drug was licensed in an aerosol formula in the United States in 1986 for treatment of children with severe RSV-induced lower respiratory tract infection. The efficacy of aerosolized ribavirin therapy remains uncertain despite a number of clinical trials. Most centers use it infrequently, if ever, in otherwise healthy infants with severe RSV disease. Intravenous ribavirin has been used for adenovirus, hantavirus, measles virus, PIV, and influenza virus infections, although a good risk/benefit profile has not been clearly established for any of these uses.

OTHER VIRAL TARGETS

Pleconaril, an oral drug with good bioavailability for treatment of infections caused by picornaviruses, has been tested for treatment of rhinovirus infection. This drug acts by binding to a hydrophobic pocket in the VP1 protein and stabilizing the protein capsid, preventing release of viral RNA into the cell. Pleconaril reduces mucus secretions and other symptoms and is being further examined for this indication. Acyclovir and related compounds are guanine-analog antiviral drugs used in the treatment of herpesvirus infections. HSV stomatitis in immunocompromised patients is treated with famciclovir or valacyclovir, and immunocompetent patients with severe oral disease compromising oral intake are sometimes treated with these agents. These compounds have also been used prophylactically to prevent the recurrence of outbreaks, with mixed results. Intravenous acyclovir is effective against HSV or VZV pneumonia in immunocompromised patients. Ganciclovir, given together with human immunoglobulin, may reduce the mortality rates associated with CMV pneumonia in hematopoietic stem cell transplant recipients and has been used as monotherapy in other patient groups. Cidofovir is a nucleotide analog with activity against a large number of viruses, including adenoviruses. Intravenous cidofovir has been effective in the management of severe adenoviral infection in immunocompromised patients but may cause serious nephrotoxicity.

COMPLICATIONS: CO-INFECTIONS

Co-infections with two or more viruses can occur because of the overlap in the winter season of these viruses in temperate areas. In general, in careful studies using cell culture techniques for virus isolation, two or more viruses were isolated from respiratory secretions of otherwise healthy adults with acute respiratory illness in ~5–10% of cases. There is little evidence that more severe disease occurs during co-infections. The incidence of positive results in two molecular diagnostic tests (generally RT-PCR for these RNA viruses) is expected to be higher than that of culture because, as discussed above, molecular tests can remain positive for an extended period after shedding of infectious virus has ended.

PREVENTION

VACCINES

Numerous vaccines against influenza viruses have been licensed. In the United States, trivalent and quadrivalent inactivated intramuscular vaccines (covering H3N2, H1N1, and one or two B antigens) and a live attenuated trivalent vaccine for intranasal administration are available, although in 2017 the CDC stopped recommending the latter vaccine. Vaccines are effective when the vaccine strains chosen for inclusion are highly related antigenically to the epidemic strain, but occasional antigenic mismatches cause negligible efficacy of a vaccine component. Antigenic drift caused by point mutations in the H and N molecules leads to antigenic divergence, requiring the production of new vaccines each year. The segmented influenza genome allows reassortment of two viruses during co-infection of one individual or animal; sometimes the consequence is a major antigenic shift resulting in a pandemic. On average, pandemics occur every 20–30 years. There is current concern about the potential for an H5N1 or H7N9 pandemic, and experimental vaccines are being tested for these viruses.

Vaccines were developed for adenovirus serotypes 4 and 7 and were approved for prevention of epidemic respiratory illness among military recruits. Essentially, these vaccines consisted of unmodified viruses given by the enteric route in capsules instead of by the respiratory route—the natural route of infection leading to disease. Inoculation by the altered route resulted in an immunizing asymptomatic infection. Most U.S. military recruits are vaccinated against adenovirus, and epidemic disease recurs in the absence of vaccination.

Live attenuated and subunit vaccine candidates against RSV are under development and are being tested in clinical trials. Subunit RSV vaccines are being tested for maternal immunization and in the elderly. There are no licensed vaccines against rhinoviruses; as there is little or no cross-protection between serotypes, it will be challenging to develop a vaccine covering >100 serotypes. Efforts to develop coronavirus vaccines are in the preclinical stage.

PASSIVE PROTECTION WITH IMMUNOTHERAPY

Palivizumab, a humanized mouse monoclonal antibody to the F protein of RSV, is licensed for prevention of RSV hospitalization in high-risk infants, in half or more of whom it is effective. Experimental treatment of both immunocompetent and immunocompromised RSV-infected individuals has been reported, but the efficacy of this approach has not been established. Next-generation antibodies with higher potency and an extended half-life of ~90 days are being tested.

ISOLATION PROCEDURES, PERSONAL PROTECTIVE EQUIPMENT, AND HAND WASHING

Most respiratory viruses are spread by direct contact—i.e., body-surface to body-surface contact and physical transfer of microorganisms between a susceptible person and an infected person. Poor hand hygiene is probably the most common cause of contact transmission of viruses, which occurs often in family, school, and workplace settings. Transmission between health care workers and patients also takes place when hand-washing compliance is low. Fomites (objects or substances capable of carrying infectious organisms), including instruments, stethoscopes, and other objects in medical environments, can contribute to transmission. Airborne transmission can occur but is probably not the dominant mode of transmission for most respiratory viruses. Particle size affects the epidemiology of airborne pathogens. The composition and size distribution of the generated particles affect the duration of suspension of the infectious agents in the air, the distance across which they can be transported, the interval during which the virus remains infectious, and the site of deposition in the airway of a susceptible host. Direct exposure to large-particle aerosols (e.g., exposure at close range—up to 3 ft—to a cough or sneeze) causes some transmission. Particles of small size can remain suspended in the air for long periods; for instance, particles of ~1 μm can remain suspended for hours. However, in general, only a few respiratory viruses are thought to be transmitted by small-particle aerosols. Protection from transmission in health care environments can be achieved by proper implementation of and adherence to established procedures for the appropriate level of precaution.

Standard and Contact Precautions Standard precautions, the basic level of infection control that is used in the care of all patients at all times, reduces the risk of transmission of viruses from respiratory tract secretions and mucous membranes. Contact precautions, the second level, require a single room for the patient when possible and the use of additional personal protective equipment, including the wearing of clean, nonsterile gloves when touching a patient or coming into contact with secretions. Fluid-resistant nonsterile gowns are used to protect skin and clothing during activities where contact with secretions is anticipated, and providers should wear each gown for the care of only one patient. A face mask is used when there is potential for direct contact with respiratory secretions. Eye protection (goggles or face shields) is worn in anticipation of potential splashing of respiratory secretions. Good hand hygiene should always follow any patient contact, including washing for 20 seconds with soap and warm water or cleaning with an alcohol-based hand rub. Providers should attempt to avoid the contamination of clothing and the transfer of microorganisms to other patients, surfaces, or environments.

Droplet Precautions Large-particle droplets are generated during sneezing and coughing and during the performance of some medical procedures, such as airway suctioning in critical care units or bronchoscopy. Such droplets may contain viruses, but their range is usually limited to about 3 ft. Transmission of large-particle droplets occurs when they are deposited on the nasal mucosa or conjunctivae. To prevent transmission in these settings, providers should implement droplet precautions. They should wear a face mask, such as a surgical mask, for close contact (within 3 ft of the patient). Patients also should wear a face mask when exiting the examination room and should avoid coming into close contact with other patients.

Airborne Precautions Airborne transmission occurs through the dissemination of airborne droplet nuclei (particles of ≤5 μm) or evaporated droplets containing viruses that can remain suspended in the air for long periods. Certain viruses that are carried by the airborne route can be inhaled by a susceptible host in the same room or over a long distance from the source patient, depending on environmental factors such as temperature and ventilation. Viruses transmitted by this route are SARS-CoV, measles virus, and VZV. Patients with these infections should be managed with personal respiratory protection and special ventilation and air handling. Providers should wear an N95 respirator selected with fit-testing, which must be repeated annually. Powered air-purifying respirators (PAPRs) are used in some cases. The patient should be housed in an airborne-infection isolation room—a negative-pressure room that has a minimum of six air exchanges per hour and exhausts through high-efficiency particulate air (HEPA) filtration or directly to the outside.

GLOBAL CONSIDERATIONS

HENDRA AND NIPAH VIRUSES

These emerging paramyxoviruses, which are grouped in their own new genus (*Henipavirus*), may not be respiratory pathogens in a conventional sense, but they probably infect humans by the respiratory route. Nipah virus is a newly recognized zoonotic virus, named after the location in Malaysia where it was first identified in 1999. It has caused disease in humans who have had contact with infectious animals. Hendra virus (formerly called equine morbillivirus) is another closely related zoonotic paramyxovirus and was first isolated in Australia in 1994. The viruses have caused only a few localized outbreaks, but their wide host range and ability to cause high mortality raise concerns for the future. The natural host of these viruses is thought to be a certain species of fruit bat present in Australia and the Pacific. Pigs may be an intermediate host for transmission to humans in Nipah infection and horses in Hendra infection. Although the mode of transmission from animals to humans is not defined, inoculation of infected materials onto the respiratory tract probably plays a role. The clinical presentation usually appears to be an influenza-like syndrome that progresses to encephalitis, includes respiratory illness, and causes death in about half of identified cases.

BUNYAVIRIDAE: HANTAVIRUS

Intermittent outbreaks of hantavirus infection occur in South America and cause a severe lung infection: HPS. In addition, more than 400 cases of HPS have been reported in the United States. The disease was first recognized during an outbreak in 1993. About one-third of recognized cases end in death. The Four Corners outbreak (at the intersection of the northwestern corner of New Mexico, the northeastern corner of Arizona, the southeastern corner of Utah, and the southwestern corner of Colorado) is well known; however, cases now have been reported in a total of 32 states. Patients with HPS usually present with an influenza-like illness, including fever. Findings on physical examination are nonspecific, often consisting only of fever and elevated respiratory and heart rates. In addition to respiratory symptoms, abdominal pain is common. Diagnosis is often delayed until illness becomes severe, at which point intubation and mechanical ventilation may be required for respiratory support.

SUMMARY

Viruses are the leading causes of acute lower respiratory tract infection in most populations. Influenza virus and RSV are the most common pathogens; hMPV, PIV3, and rhinoviruses account for most other acute viral respiratory infections. Infection in otherwise healthy adults generally leads to partial immunity to these pathogens, with protection against severe lower respiratory disease. However, reinfection, with upper respiratory tract illness, is common throughout life. Special populations such as immunocompromised patients, institutionalized frail elderly patients, and patients with COPD are at highest risk for severe disease.

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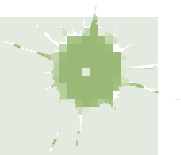
195 Influenza

Peter F. Wright



DEFINITION

The term *influenza* represents both a clinically defined respiratory illness accompanied by systemic symptoms of fever, malaise, and myalgia and the name of the orthomyxoviruses that cause this syndrome. Although this term is sometimes used more generally to denote any viral respiratory illness, many features distinguish influenza from these other illnesses, most particularly its systemic symptoms, its propensity to cause sharply peaked winter epidemics, and its capacity to spread rapidly among close contacts. The morbidity and mortality associated with influenza epidemics are documented closely in the United States by the Centers for Disease Control and Prevention (CDC), which records clinical cases of influenza-like illness, cases of virologically documented influenza, and excess deaths due to pneumonia and influenza combined.

ETIOLOGIC AGENTS

Three influenza viruses occur in humans: A, B, and C. These viruses are irregularly circular in shape, measure 80–120 nm in diameter, and have a lipid envelope and prominent spikes that are formed by the two surface glycoproteins, hemagglutinin (H) and neuraminidase (N) **(Fig. 195-1)**. The hemagglutinin functions as the viral attachment protein, binding to sialic acid receptors on the cells that line the superficial epithelium of the respiratory tract. The neuraminidase cleaves the virus from the cell membrane to facilitate its release from the cell and prevents self-aggregation of viruses. Influenza A viruses have eight single-strand negative-sense RNA segments in their genomes that encode hemagglutinin and neuraminidase as well as internal genes, including polymerase, matrix, nucleoprotein, and nonstructural genes. The segmented nature of the genome allows gene *reassortment*; an analogy for reassortment is the shuffling of a deck of cards. Reassortment takes place when a single cell is infected with two different strains.

Among the influenza viruses, the A viruses are of paramount importance for several reasons: (1) the plasticity of their genomes, which enables them to react to the prevailing immunity in the community by modifying their immunogenic epitopes, particularly on the

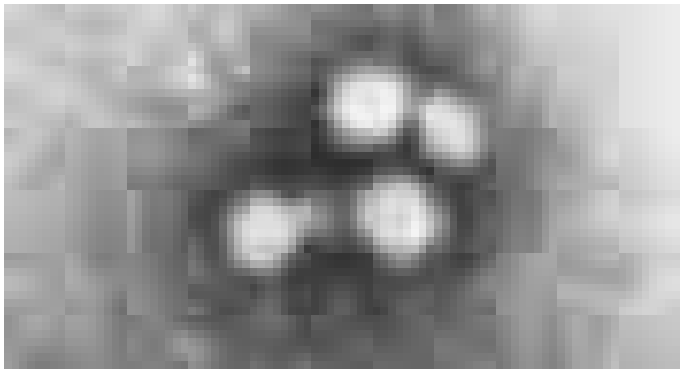


FIGURE 195-1 An electron micrograph of influenza A virus (x40,000). *(Reprinted with permission from YZ Cohen, R Dolin: Influenza, in Harrison's Principles of Internal Medicine, 19th ed. DL Kasper et al [eds]. New York: McGraw-Hill, 2015, p 1209.)*

TABLE 195-1 Emergence of Antigenic Subtypes of Influenza A Virus Associated with Pandemic or Epidemic Disease

YEARS	SUBTYPE	EXTENT OF OUTBREAK
1889–1890	H2N8[a]	Severe pandemic
1900–1903	H3N8[a]	? Moderate epidemic
1918–1919	H1N1[b] (formerly HswN1)	Severe pandemic
1933–1935	H1N1[b] (formerly H0N1)	Mild epidemic
1946–1947	H1N1	Mild epidemic
1957–1958	H2N2	Severe pandemic
1968–1969	H3N2	Moderate pandemic
1977–1978[c]	H1N1	Mild pandemic
2009–2010[d]	H1N1	Pandemic

[a]As determined by retrospective serologic survey of individuals alive during those years ("seroarchaeology"). [b]Hemagglutinins formerly designated as Hsw and H0 are now classified as variants of H1. [c]From this time until 2016–2017, viruses of the H1N1 and H3N2 subtypes circulated in alternating years or concurrently. [d]A novel influenza A/H1N1 virus emerged to cause this pandemic.

Source: Adapted from YZ Cohen, R Dolin: Influenza, in *Harrison's Principles of Internal Medicine*, 19th ed. DL Kasper et al (eds). New York, McGraw-Hill, 2015, p 1209.

hemagglutinin surface protein (*antigenic drift*); (2) the segmentation of their genomes, which allows genes coding both surface and internal proteins to be reassorted between influenza A variants (*antigenic shift*); and (3) their extensive mammalian and avian reservoirs, in which multiple variants with distinct hemagglutinin and neuraminidase genes lie in wait. As a result of all of these factors, influenza A virus has the ability, particularly after an antigenic shift, to cause a worldwide epidemic (*pandemic*). The most severe influenza A pandemic in modern history took place in 1918; ~50 million deaths were attributed to the culpable influenza A H1N1 virus in the years surrounding 1918.

The influenza A viruses are further classified by their surface glycoproteins (H and N), the geographic location of their isolation, their sequential number among isolated viruses, and their year of isolation. Thus, the influenza vaccine for the 2017–2018 season in the Northern Hemisphere was formulated to provide protection against influenza A/Michigan/45/2015 (H1N1)pdm09–like virus, influenza A/Hong Kong/4801/2014 (H3N2)–like virus, and two lineages in the influenza B family: B/Brisbane/60/2008–like virus (Victoria lineage) and B/Phuket/3073/2013–like virus (Yamagata lineage).

EPIDEMIOLOGY

Influenza virus causes outbreaks during the cooler months of the year and thus has a mirror-image season in the antipodes compared with that in the Northern Hemisphere. The circulation of strains in the Southern Hemisphere has some predictive value for vaccine composition in the Northern Hemisphere, and vice versa. This information is important as the degree of antigenic drift is one determinate of vaccine efficacy. Vaccine composition typically must change in at least one component yearly in anticipation of the predicted circulating strains.

A typical outbreak begins in early winter and lasts 4–5 weeks in a given community, although its impact on the country as a whole will be of considerably longer duration. When excess mortality occurs, an influenza outbreak is classified as an *epidemic*. Influenza's impact is reflected in increased school and work absenteeism, increased visits to emergency rooms and primary care physicians, and increased hospitalizations, particularly of elderly patients and individuals with underlying cardiopulmonary disease. The impact often is most easily recognized in the pediatric population, whose school absenteeism quickly peaks. Despite efforts to limit influenza spread through vaccination, cohorting, use of masks, and hand washing, long-term-care facilities house another sentinel population, including many elderly patients who are at increased risk of complicated disease.

Influenza is largely spread by small- and large-particle droplets; spread is undoubtedly facilitated by the coughing and sneezing that accompany the illness. Within families, the illness is often introduced by a preschool or school-aged child.

Influenza's global spread and causative strain(s) in a given year are well documented by the surveillance networks of the World Health Organization (WHO) and the CDC. The severity of an epidemic depends on the transmissibility and virulence of the viral strain, the susceptibility of the population, the adaptation of the virus to its human host, and the degree of antigenic match to the recommended vaccine. None of these parameters is totally predictable for influenza A.

Influenza A Viruses When a major shift in the hemagglutinin and/or the neuraminidase occurs, with introduction of a new serotype from an animal or avian reservoir, an influenza A strain has the potential to cause a pandemic. In modern influenza history, such shifts occurred in 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), 1977 (H1N1), and 2009 (H1N1pdm) **(Table 195-1)**. On the basis of seroarchaeology (the analysis of serum antibody profiles in the elderly), epidemics that took place in the 1890s have been attributed to H3N2 and H2N2 viruses. Epidemics typical of influenza have been documented throughout recorded history.

In some epidemics, a younger age group proves especially susceptible. This is the case with current H1N1 epidemics, where individuals born before 1968 had likely been exposed to related viral strains and thus were relatively protected against the current strain. The 1918 epidemic was striking in this regard: the most severely infected individuals were infants and previously healthy young adults—the latter being a group not typically found to have high influenza mortality **(Fig. 195-2)**. The 1918 epidemic increased all-cause mortality and led to more deaths than all military losses in World War I. In spite of the attention paid to the risk and impact of pandemic disease, it is generally appreciated that—with the exception of 1918—cumulatively more illness occurs during yearly epidemics combined than in pandemics.

All of the annual influenza A epidemics in the past 50 years have been caused by H1N1 and/or H3N2 strains. H2N2 strains circulated between 1957 and 1968, and H1N1 strains circulated prior to that, including in 1918. However, potentially pandemic viruses continue to emerge, mostly in Asia, with higher-numbered hemagglutinins (e.g., H5, H6, H7, H9) reflecting some of the 16 distinct H and 9 distinct N subtypes in avian reservoirs. Most cases of these potentially pandemic illnesses have occurred in individuals who have had direct contact with domesticated birds or who have visited live-bird markets, which are common in Asia. In addition to the global aeronautic movement of infected people, bird migration is one mechanism for rapid global spread. It is not clear why higher-numbered avian hemagglutinin strains have not acquired the degree of transmissibility necessary to cause pandemic disease.

Avian and Swine Influenza Viruses The full panoply of influenza viruses is found in domestic and migratory wild birds. It is postulated that epithelial cells in the swine respiratory tract may play a specific role as a "mixing vessel," allowing the reassortment of genes from avian and human sources and thereby permitting the transition of avian viruses to humans. The nature of the sialic acid receptors for

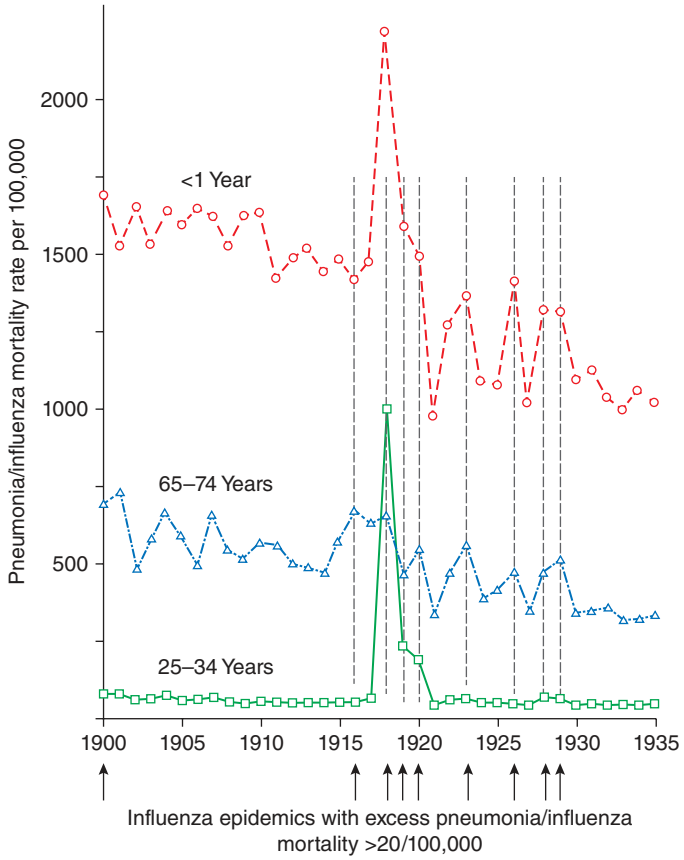


FIGURE 195-2 Excess pneumonia/influenza deaths in 1900–1953, demonstrating the dramatic peaks of deaths among young infants and young adults (25–34 years of age). *(Data are from public health records collated by the author.)*

influenza virus hemagglutinin partially accounts for host preference. Humans have largely α-2,6-galactose receptors, while birds have α-2,3-galactose receptors. Swine have both types of receptors on their respiratory epithelial cells—hence their postulated role in facilitating reassortment and host adaptation of avian strains to growth in humans. Strains such as 2009 H1N1pdm (pandemic) had genes of avian, swine, and human origin. Some avian strains—notably H5 strains—are highly pathogenic in humans, as was the 1918 strain. The reasons for the high pathogenicity of certain strains are not entirely clear. Virulence and transmissibility often appear to be separate genetic traits.

After the sequencing of the 1918 virus recovered from the lungs of bodies buried in the Arctic permafrost, the virus was genetically reconstructed under carefully controlled isolation conditions. In animal studies of this viable 1918 virus, both the hemagglutinin and the ribonucleoprotein contributed to high levels of replication accompanied by an abnormally enhanced innate immune response characterized by proinflammatory cytokines. Perhaps this "cytokine storm" is the best explanation for the enhanced illness occurring in young, immunologically vigorous individuals in the 1918 pandemic. Sequencing demonstrated that the 1918 virus was of avian origin. Although the 1918 virus was first identified in military camps in the United States, its impact cannot be attributed to the disruption of war: the illness was well documented in countries such as Iceland that were not directly involved in World War I.

The same concerns about a "cytokine storm" have been raised with regard to the H5N1 viruses that first emerged in Hong Kong in 1996. These viruses exhibited high pathogenicity in individuals who had direct contact with domestic fowl, with mortality rates close to 50%, but also displayed poor human-to-human transmissibility. Pathogenicity appears to be a function not just of the viruses' surface proteins, but also of an optimal gene constellation including all eight segmented influenza genes. However, unlike the 1918 strain, the H5N1 viruses have, to date, caused only sporadic disease, as have other limited clusters of a highly pathogenic H7N9 virus.

Influenza B and C Viruses The influenza B viruses are more genetically stable than the influenza A viruses and have no animal reservoirs. Two lineages of influenza B have circulated for the past 40 years (B/Yamagata-like and B/Victoria-like viruses), and it has proven very difficult to predict which strain will be dominant in a given year. This issue has led to the incorporation of representatives of both influenza B lineages plus influenza A/H1N1 and H3N2 viruses into a quadrivalent vaccine.

Influenza C viruses cause intermittent mild disease and have attracted little attention. These viruses have been the subject of fewer than 10 publications annually since the year 2000.

Influenza-Associated Morbidity and Mortality Although epidemics vary in severity and in the age groups most affected, certain high-risk groups are seen in all epidemics **(Table 195-2)**. These groups are assigned the highest priority for vaccination and other preventive and therapeutic measures. Their caregivers and close contacts are also prioritized targets of interventions. A generalization is that the relative impact of an epidemic is seen in the youngest age group with the least prior exposure—and therefore the least immunity—to influenza. The impact of influenza can be depicted as a pyramid of illnesses, medical visits, hospitalizations, and deaths **(Fig. 195-3)**.

Pneumonia and influenza mortality, reported as excess over the anticipated sine-wave curve of deaths during the year, is seen in the CDC's data for 2012–2017 **(Fig. 195-4)**. In addition to excess respiratory deaths directly attributed to influenza, an increase in circulatory deaths also occurs during an influenza epidemic.

PATHOGENESIS AND IMMUNITY

At a cellular level, influenza virus binds to sialic acid receptors and enters the epithelial cell through receptor-mediated endocytosis. The virus then enters an endosome, where acidification promotes proteolytic cleavage of the hemagglutinin, exposing a fusion domain. The influenza hemagglutinin undergoes a marked structural reorganization in this cleavage step. Hemagglutinin cleavage may be one of the factors that restrict viral growth to epithelial cells, as a unique protease in the respiratory milieu is required for this cleavage to occur. The fusion domain allows the viral RNA to enter the cytoplasm. The nucleoprotein is transported into the nucleus of the cell, where transcription to a positive-sense

TABLE 195-2 High-Risk Groups Who Should Be Assigned a High Priority for Influenza Immunization and Treatment[a]

High-Risk Group
Children 6–59 months of age
Adults ≥50 years of age
Persons with chronic pulmonary (including asthma), cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
Persons who are immunocompromised (any cause, including medications or HIV infection)
Women who are or plan to be pregnant during the influenza season
Children and adolescents (6 months through 18 years of age) who are receiving aspirin- or salicylate-containing medications and who might be at risk for Reye syndrome
Residents of nursing homes and other long-term-care facilities
Native Americans, including Alaska Natives
Persons who are extremely obese (BMI ≥40)
Contacts and Caregivers
Caregivers and contacts of those at risk: health care personnel in inpatient and outpatient care settings, medical emergency-response workers, employees of nursing home and long-term-care facilities who have contact with patients or residents, and students in these professions who have contact with patients
Household contacts and caregivers of children ≤59 months (i.e., <5 years) of age (particularly contacts of infants <6 months old) and adults ≥50 years of age
Household contacts and caregivers of persons who are in a high-risk group

[a]No hierarchy is implied by order of listing.

Source: Centers for Disease Control and Prevention 2017–2018 summary of recommendations for influenza vaccine (*https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html*).

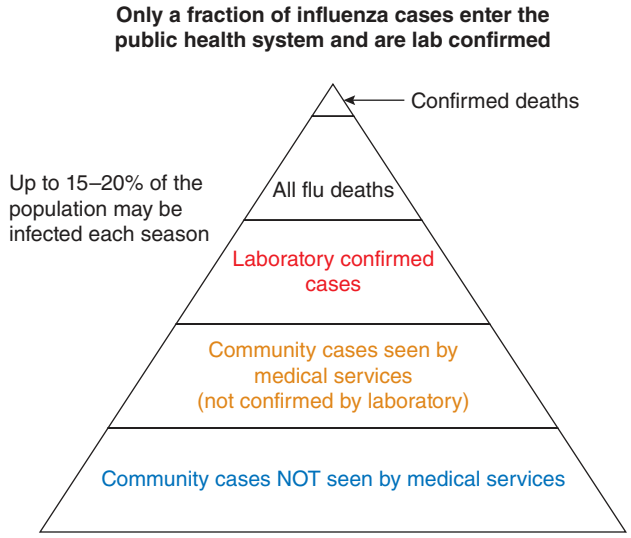


FIGURE 195-3 Pyramid of impact of influenza illness. *(From http://4.bp.blogspot.com/-ZjKKbq-d5O4/VClasJsjOGI/AAAAAAAADVo/UdpfdzH1JYc/s1600/WHO-flu-pyramid.jpg; accessed October 15, 2017.)*

RNA and replication take place. Viral proteins then assemble on the apical surface of the infected cell and, after incorporation of cellular membrane, bud from the membrane back into the mucosal milieu.

Influenza infection is initiated in the upper respiratory tract via aerosolized virus. The cells infected with influenza virus are primarily the ciliated cells of the respiratory tract. Denudation of the superficial epithelium probably accounts for much of the symptomatology and may predispose to secondary bacterial infections. The onset of symptoms follows an incubation period that, for a viral illness, is very short: 48–72 h. The infection spreads to the lungs but, even there, remains confined to the epithelial layer.

Uniquely among respiratory viruses, influenza virus is associated with systemic symptoms of fever, malaise, and myalgia. These manifestations are presumed to be mediated by cytokines, and excess cytokine production has been implicated in the acute toxicity of H5N1 and other highly pathogenic influenza viruses.

The immune response to influenza virus occurs at the systemic and mucosal levels and involves both T and B cells. The B cell responses are directed primarily toward antigenic epitopes on the two surface glycoproteins—i.e., hemagglutinin and neuraminidase. At a structural level, the four recognized epitopes on the hemagglutinin are largely confined to the globular head of the protein, which collectively constitute the targets for hemagglutination inhibition (HAI) antibodies. HAI and neutralizing antibodies are highly correlated; HAI antibody levels are used as a measure of susceptibility to clinical infection and thus as a measure of vaccine-induced protection. In a child or an adult without prior vaccination or with the emergence of a distinctly new strain, serum HAI antibody is a surrogate for protection. However, in individuals with both vaccine-induced and natural immunity, the protective efficacy of a vaccine based on serum HAI antibody is more difficult to predict.

Studies with improved collection methods and assays that more sensitively and reproducibly measure mucosal antibody suggest that mucosal neutralizing IgA antibody more accurately reflects susceptibility to infection. Perhaps the patterns of immune protection are best shown in a murine model, in which passively administered IgA antibody to influenza virus protects animals from initiation of infection and epithelial damage in the upper respiratory tract, while infused IgG antibody to the virus is protective in the lungs.

There is now considerable research interest in the induction and protective role of broadly neutralizing antibodies that recognize less antigenically variable regions on the stalk of the hemagglutinin. The results of these studies have led to talk of a universal influenza vaccine, although no such vaccines are yet available in clinical practice.

The role of T-cell immunity, which primarily recognizes internal protein epitopes, remains unclear in humans. However, T-cell immunity is thought to play a role in clearance of an influenza infection that quite reproducibly develops 8–10 days after exposure. A role for T cells in protection against acquisition of infection has also been proposed.

CLINICAL MANIFESTATIONS

Influenza is primarily a respiratory illness causing rhinorrhea, sore throat, conjunctivitis, and cough. The illness has a sudden onset and is epidemiologically linked to close contact with persons who have similar symptoms and often to community-wide respiratory illness. What distinguishes influenza from other respiratory illnesses is the degree of accompanying fever, fatigue, myalgia, and malaise. The symptoms typically begin within 48–72 h of exposure. The constellation of symptoms caused by an H3N2 viral strain, A/Port Chalmers 1/73, was followed

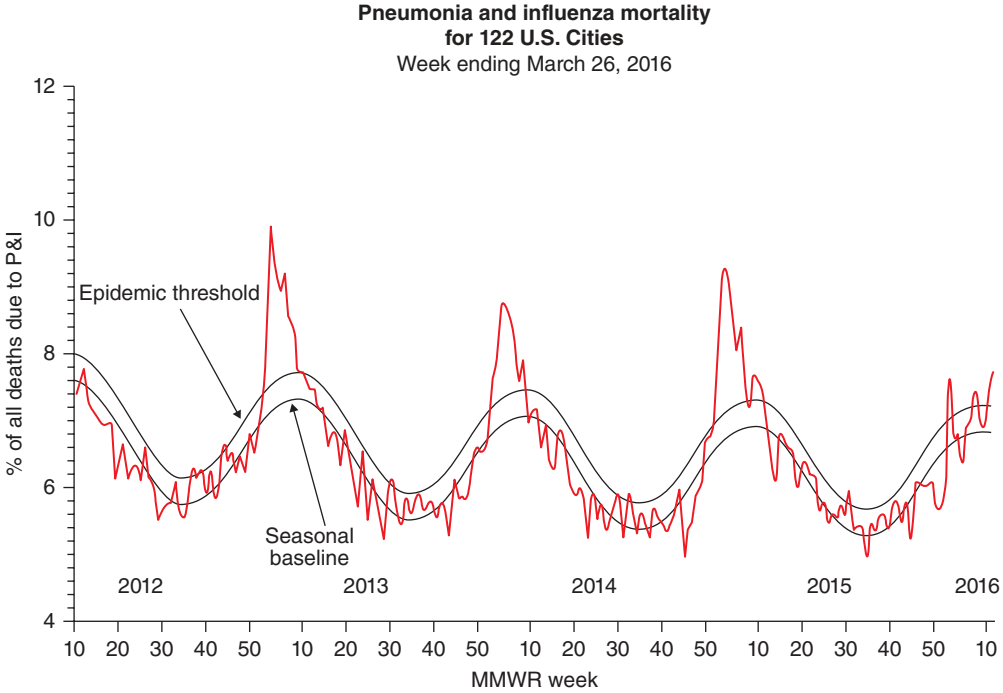


FIGURE 195-4 Morbidity and mortality attributable to influenza. P&I, pneumonia and influenza; MMWR, *Morbidity and Mortality Weekly Report*. *(From https://www.cdc.gov/flu/weekly/weeklyarchives2015-2016/images/122CMRS12_small.gif; accessed February 13, 2018.)*

TABLE 195-3 Clinical Observations in 24 Seronegative Children Examined during Influenza A/Port Chalmers Infection

CONDITION/EVENT	NO. OF PATIENTS
Coryza	22
Fever (temperature >38.4°C [>101°F])	21
Cough	21
Pharyngitis	20
Irritability	20
Fever (temperature >39.5°C [>103°F])	13
Anorexia	12
Tonsillitis	8
Vomiting	7
Otitis	6
Pneumonia	6
Diarrhea	6
Hoarseness	4
Croup	1

prospectively in young seronegative children. Although these data involve children and a viral strain circulating 45 years ago, they present a representative picture of influenza today except that irritability in a young child is more specifically recognized as malaise, myalgia, and headache in an adult **(Table 195-3)**.

Respiratory symptoms, particularly recurrent cough, persist well beyond the 2–5 days of systemic symptoms. There is a postinfectious delay in return to normal levels of activity. Pulmonary function is persistently decreased after acute influenza. Persons with a regular exercise routine (e.g., runners) note a decrease from their prior level of performance that typically lasts for a month or more. In the elderly, the respiratory presentation may be less prominent, but there is often a decline in baseline activity and a loss of appetite.

The variation among epidemics in symptom severity must be stressed. The circulation of an early H1N1 virus, A/USSR/77, in young children followed prospectively was detected only by comparison of pre- and post-season serum samples, which documented that 31% of 195 children had experienced infection with this virus without developing associated clinical illness. In the same population in the same year, influenza A/Texas/H3N2 virus infected 37% of children and was clearly associated with a typical influenza illness. In recent years, when H1N1 and H3N2 viruses have co-circulated, the latter has caused more severe epidemics.

On physical examination, the patient with influenza appears ill and rheumy, with sweating, coughing, nonpurulent conjunctivitis, and diffuse pharyngeal erythema. Pulmonary examination typically reveals nonlocalizing scattered rales, rhonchi, and wheezes. When present, localized pulmonary findings suggest relatively complicated pneumonia with a bacterial component. Muscle pain may be elicited by pressure, particularly in the calves and thighs. There are rare gastrointestinal findings. No rash is associated with influenza.

COMPLICATIONS

Complications of influenza occur most commonly in persons >65 years of age, those with underlying cardiopulmonary disease, those with immunosuppression, and women who are in the second or third trimester of pregnancy. In recent years, there has been mortality attributable to influenza among often previously healthy children <5 years of age in the United States, with ~100 deaths per year.

Respiratory Complications Pneumonia characterized by progressive air hunger, localized pulmonary findings on physical examination, and radiographic findings of infiltrates and consolidation is the most common complication of influenza. Pneumonia in influenza can be primary influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia. Primary viral pneumonia is characterized by increasing dyspnea, persistent fever, and—in more severe cases—cyanosis. Primary influenza pneumonia was typical in the 1918 pandemic and occurs with H5N1 virus, as initially described in Hong Kong in 1997. Pathologically, a marked inflammatory reaction in the alveolar septa is characterized by infiltration of monocytes, lymphocytes, and macrophages, with variable numbers of neutrophils. Destruction and hemorrhage are seen in the respiratory epithelium. Large amounts of virus can be recovered from the lungs.

In secondary bacterial pneumonia or mixed viral and bacterial pneumonia, illness may be biphasic, with evidence of recovery from the primary influenza illness followed by recrudescence of fever and pulmonary symptoms. Localizing findings may be detected on pulmonary examination and/or x-ray. The development of secondary bacterial infection is not surprising, as influenza de-epithelializes the airways and destroys ciliary function, allowing bacterial contamination. Another proposed mechanism for bacterial/viral enhancement is the production by *Staphylococcus* and *Pseudomonas* of proteases that enhance cleavage of the influenza hemagglutinin and thereby facilitate viral replication. The risk of secondary bacterial disease is greatest in elderly patients and those with chronic obstructive pulmonary disease.

Some influenza strains cause laryngotracheobronchitis or croup in children. Otitis media—a common accompaniment to influenza in children—may also be due to a combination of influenza virus and bacteria.

Extrapulmonary Complications Although influenza is believed to spread only rarely beyond the respiratory epithelial cells, where unique endogenous proteases facilitate hemagglutinin cleavage and productive infection, this disease causes not only prominent systemic complaints but also a variety of extrapulmonary manifestations. The most common extrapulmonary manifestation of influenza is myositis, which is seen more often in influenza B and is characterized by severe muscle pain, elevated creatinine phosphokinase levels, and myoglobinuria that can lead to renal failure. The muscles are extremely tender to touch. Myo/pericarditis is seen less frequently and has been reported only in selected epidemics, notably the pandemic of 1918. However, a consistent epidemiologic link exists between influenza epidemics and excess cardiovascular hospitalizations.

Postinfectious acute demyelinating encephalomyelitis can follow influenza as well as other viral infections. The literature is mixed on the benefit and reliability of efforts to establish a polymerase chain reaction (PCR)–based diagnosis in this condition. MRI shows distinctive multifocal, symmetric brain lesions affecting the thalamus, brainstem tegmentum, cerebral periventricular white matter, and cerebellar medulla. Encephalitis and transverse myelitis may accompany influenza infection. Guillain-Barré syndrome can develop after influenza and was reported after a widespread influenza vaccination effort in the fall of 1976 that was undertaken in anticipation of a swine influenza epidemic (which never materialized). Until aspirin was recognized as a co-factor in its precipitation, Reye syndrome, an acute hepatic decompensation, was seen commonly in children and adolescents with influenza, particularly those infected with influenza B virus. Subsequently, the use of aspirin for fever control and symptom relief in children with viral infections was strongly discouraged, and Reye syndrome has virtually disappeared from clinical practice.

LABORATORY FINDINGS AND DIAGNOSIS

There is a strong argument for establishing a microbiologic diagnosis from both an individual-patient and a public-health perspective. This information is particularly valuable early in the season, when the extent of influenza and the precise circulating strain(s) are uncertain; in the management of complicated cases in hospitalized patients; and in settings such as long-term-care facilities and hospitals, where the institution of specific infection-control measures is appropriate.

Influenza virus is most easily recovered from nasopharygeal specimens. These samples are most effectively collected with a flocked swab that is inserted 1–2 inches into the nose (following the course of the inferior meatus), twirled, placed in viral transport medium that supports viral viability, and transported on ice to the laboratory as promptly as possible. The available rapid tests based on antigen detection vary in complexity and cost. Some are point-of-care tests, and others require laboratory support. These tests are highly specific but have

a sensitivity of only 50–70%. Their sensitivity is strongly dependent on sample collection early in the course of illness—ideally within 48 h of the onset of symptoms. Traditionally, viruses have been isolated in tissue culture or with the use of embryonated eggs, and infection has been confirmed with hemadsorption or hemagglutination.

The most useful clinical approach today is to use a PCR-based molecular probe that amplifies specific segments of the influenza genome. Not only is this the most sensitive and specific method; it also provides opportunities to identify the strain with some specificity. Testing by multiplex PCR can simultaneously identify multiple respiratory pathogens—an advantage in the ill hospitalized patient. Serologic confirmation of infection is also possible but requires paired serum samples, with the convalescent-phase sample obtained 2 weeks after infection. Mucosal antibody assays that are now being developed can detect strain-specific antibodies in paired mucosal specimens and yield insights into the importance of mucosal immunity in protection against influenza.

Other laboratory tests are of limited value. Mild leukopenia is seen in influenza, and a white blood cell count above 15,000/μL suggests a secondary bacterial component in influenzal pneumonia.

DIFFERENTIAL DIAGNOSIS

The distinctive nature of influenza is such that clinical diagnoses by experienced pediatric physicians are 85% concordant with microbiologic etiologic confirmation. Respiratory syncytial virus often co-circulates with influenza virus; it particularly affects the youngest children, causing bronchiolitis, but it can also infect the elderly, leading to an influenza-like nonspecific respiratory illness and a decline in mobility, nutrition, and pulmonary function, with resultant hospitalization.

PROPHYLAXIS

The major intervention to limit influenza illness is vaccination, which is conducted on a yearly basis because of variation in the predicted circulating strains for the coming year and which enhances existing immunity in advance of the influenza season. The decision about vaccine composition must be made ~10 months before the seasonal peak in influenza virus circulation; this decision is made by committees at the WHO and the CDC. This timing can result in a mismatch of vaccine composition with the viral strains that are actually prevalent in the upcoming season. The overall accuracy of the prediction is at least 70% for all strains in the recommended vaccine. Influenza vaccine is unique in being given seasonally in the months immediately preceding an outbreak. In the United States, vaccine is typically available from September.

The currently available vaccines are all based on purified subunit inactivated virus produced in eggs, in tissue culture, or through a baculovirus-expressed hemagglutinin protein. They are all calibrated to hemagglutinin content. Depending on the vaccine, they are administered intramuscularly or intradermally. Some influenza vaccines include MF-59 as an adjuvant or have elevated hemagglutinin content for enhanced immunogenicity in the elderly. The recommendations for use, the approved age range of each product, the route of administration, and the anticipated side effects are published annually by the CDC (*https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html*). The protection (and licensure) of all influenza vaccines depend on their stimulation of antibodies to the hemagglutinin; all are 50–75% effective at preventing clinical influenza. No effort is made to standardize the neuraminidase content. The contraindications to inactivated influenza vaccine administration are limited to individuals who have experienced a Guillain-Barré reaction within 6 weeks of a prior influenza vaccination. Egg allergy is not considered a contraindication to vaccination.

In recent years, a live, attenuated, intranasally administered vaccine (LAIV) has been used in children and has exhibited an efficacy exceeding that of injected inactivated vaccines. However, beginning in 2014–2015 and continuing in the following season, LAIV had no demonstrable efficacy assignable to the vaccine's H1N1 component. This change led advisory committees in the United States not to recommend the use of LAIV despite its prior effectiveness, ease of administration, and theoretical advantage of stimulating mucosal immunity by the topical route. Active research is aimed at discerning the reason(s) for this lack of efficacy.

In the United States, the recommendation is that all individuals >6 months of age receive inactivated influenza vaccine yearly and that two doses of vaccine be given to children <9 years of age who are getting their first or second yearly vaccination. Groups at special risk of experiencing or transmitting influenza for whom influenza immunization is a particularly high priority are listed in Table 195-2.

Especially in hospital settings, considerable attention is paid to hand washing and the use of masks by persons with respiratory symptoms and those who are at particular risk of acquisition (typically, immunocompromised patients). Studies have demonstrated the benefit of face masks and hand hygiene in the hospital setting.

TREATMENT

Influenza

Antiviral therapy for influenza has been limited by the paucity of available drugs, the short duration of symptoms in uncomplicated influenza, and the changing patterns of drug resistance in influenza viral strains. In the past, influenza A infection could be treated with the M-2 channel blockers amantadine and rimantadine. Widespread resistance has currently relegated these compounds to historical interest only.

The currently available class of drugs for treatment of influenza A and B viruses consists of neuraminidase inhibitors. As their name implies, these drugs act by inhibiting the influenza neuraminidase and thus limiting the egress of influenza virus from an infected cell. They are most effective in patients whose influenza illness is recognized early and confirmed by rapid antigen detection or on the basis of clinical and epidemiologic evidence. In experimental trials, these drugs hasten the resolution of symptoms if given within 48 h of infection. There are indications for their use both prophylactically—either throughout the season or, when a case is recognized in a close contact, in the short term—and therapeutically. The anticipated effect of early administration is the resolution of symptoms 1–2 days sooner than without treatment. The use of neuraminidase inhibitors is recommended for complicated influenza infections in hospitalized patients in the absence of formal proof of efficacy and when diagnosis may have been delayed. All the available neuraminidase inhibitors carry a risk of development of resistance, particularly with prolonged administration (e.g., to an immunodeficient individual with persistent recovery of influenza virus). Resistance to neuraminidase inhibitors is not widespread among currently circulating influenza A or B strains, but its development has been demonstrated in the laboratory, and clinical resistance could influence the utility of these drugs.

The defined risk groups who can benefit from neuraminidase inhibitors include children <2 years of age, adults >65 years of age, patients with chronic conditions, immunosuppressed individuals, pregnant women, women who have delivered infants ≤2 weeks previously, patients <19 years old who are receiving long-term aspirin treatment, Native Americans (including Alaska Natives), morbidly obese individuals, and residents of nursing homes or chronic-care facilities. This list resembles that of candidates whose vaccination is a high priority (Table 195-2). Use of neuraminidase inhibitors should be considered in selected high-risk cases despite a history of vaccination.

The available neuraminidase inhibitors are oral oseltamivir, nasal-spray zanamivir, and intravenous peramivir and zanamivir. Oseltamivir, which is most widely used, is an orally absorbed drug that is converted to its active component, oseltamivir carboxylate, in the liver. Gastrointestinal symptoms, especially nausea, may accompany the administration of oseltamivir. Because zanamivir is not orally bioavailable, it is given as an inhaled dry powder dispersed through a Diskhaler device.

The usual duration of therapy with either oral oseltamivir or intranasal zanamivir is 5 days, with twice-a-day dosing. Oseltamivir is preferred for treatment of pregnant women and is approved for children ≥1 year of age. Poor oral intake or absorption is a contraindication to the use of oseltamivir, although this drug can also be given by oro/nasal tube. Asthma and chronic obstructive pulmonary disease are relative contraindications to the use of intranasal

zanamivir; this agent is approved for children ≥5 years of age. The use of the intravenous preparations of peramivir and zanamivir is indicated in severely ill patients. Peramivir is licensed for individuals >18 years of age, and intravenous zanamivir may be available through the manufacturer via an individual Emergency Investigational New Drug request. The most current recommendations and details on influenza antiviral drug use and release are available through the CDC (*https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm*).

Other critical aspects of treatment include maintenance of fluid and electrolyte balance, oxygen supplementation, fever control with nonsteroidal anti-inflammatory drugs, and treatment of suspected secondary bacterial complications with antibiotics. Appropriate respiratory isolation of patients should be practiced in accordance with local hospital guidelines.

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Section 14 Infections Due to Human Immunodeficiency Virus and Other Human Retroviruses

196 The Human Retroviruses

Dan L. Longo, Anthony S. Fauci

The retroviruses, which make up a large family (Retroviridae), infect mainly vertebrates. These viruses have a unique replication cycle whereby their genetic information is encoded by RNA rather than DNA. Retroviruses contain an RNA-dependent DNA polymerase (a reverse transcriptase) that directs the synthesis of a DNA form of the viral genome after infection of a host cell. The designation *retrovirus* denotes that information in the form of RNA is transcribed into DNA in the host cell—a sequence that overturned a central dogma of molecular biology: that information passes unidirectionally from DNA to RNA to protein. The observation that RNA was the source of genetic information in the causative agents of certain animal tumors led to a number of paradigm-shifting biologic insights regarding not only the direction of genetic information passage but also the viral etiology of certain cancers and the concept of oncogenes as normal host genes scavenged and altered by a viral vector.

TABLE 196-1 Classification of Retroviruses: The Family Retroviridae

GENUS	EXAMPLE(S)	FEATURE
Alpharetrovirus	Rous sarcoma virus	Contains *src* oncogene
Betaretrovirus	Mouse mammary tumor virus	Exogenous or endogenous
Gammaretrovirus	Abelson murine leukemia virus	Contains *abl* oncogene
Deltaretrovirus	HTLV-1	Causes T-cell lymphoma and neurologic disease
Epsilonretrovirus	Walleye dermal sarcoma virus	Not known to be pathogenic in humans
Lentivirus	HIV-1, HIV-2	Causes AIDS
Spumavirus	Simian foamy virus	Not known to be pathogenic in humans

The family Retroviridae includes seven subfamilies **(Table 196-1)**. Members of two of the families infect humans with pathologic consequences: the deltaretroviruses, of which human T-cell lymphotropic virus (HTLV) type 1 is the most important in humans; and the lentiviruses, of which HIV is the most important in humans.

The wide variety of interactions of a retrovirus with its host range from completely benign events (e.g., silent carriage of endogenous retroviral sequences in the germline genome of many animal species) to rapidly fatal infections (e.g., exogenous infection with an oncogenic virus such as Rous sarcoma virus in chickens). The ability of retroviruses to acquire and alter the structure and function of host cell genetic sequences has revolutionized our understanding of molecular carcinogenesis. The viruses can insert into the germline genome of the host cell and behave as a transposable or movable genetic element. They can activate or inactivate genes near the site of integration into the genome. They can rapidly alter their own genome by recombination and mutation under selective environmental stimuli.

Most human viral diseases occur as a consequence of tissue destruction either directly by the virus itself or indirectly by the host's response to the virus. Although these mechanisms are operative in retroviral infections, retroviruses have additional mechanisms of inducing disease, including the malignant transformation of an infected cell and the induction of an immunodeficiency state through selective destruction or dysfunction of immune-competent cells that renders the host susceptible to opportunistic diseases (infections and neoplasms; **Chap. 197**).

STRUCTURE AND LIFE CYCLE

All retroviruses are similar in structure, genome organization, and mode of replication. Retroviruses are 70–130 nm in diameter and have a lipid-containing envelope surrounding an icosahedral capsid with a dense inner core. The core contains two identical copies of the single-strand RNA genome. The RNA molecules are 8–10 kb long and are complexed with reverse transcriptase and tRNA. Other viral proteins, such as integrase, are also components of the virion particle. The RNA has features usually found in mRNA: a cap site at the 5′ end of the molecule, which is important in the initiation of mRNA translation, and a polyadenylation site at the 3′ end, which influences mRNA turnover (i.e., messages with shorter polyA tails turn over faster than messages with longer polyA tails). However, the retroviral RNA is not translated; instead it is transcribed into DNA. The DNA form of the retroviral genome is called a *provirus*.

The replication cycle of retroviruses proceeds in two phases **(Fig. 196-1)**. In the first phase, the virus enters the cytoplasm after binding to one or more specific cell-surface receptors; the viral RNA and reverse transcriptase synthesize a double-strand DNA version of the RNA template; and the provirus moves into the nucleus and integrates into the host cell genome. This proviral integration is permanent. Although some animal retroviruses integrate into a single specific site of the host genome in every infected cell, the human retroviruses integrate randomly. This first phase of replication depends entirely on gene products in the virus. The second phase includes the synthesis and processing of viral genomes, mRNAs, and proteins using host cell machinery, often under the influence of viral gene products. Virions are

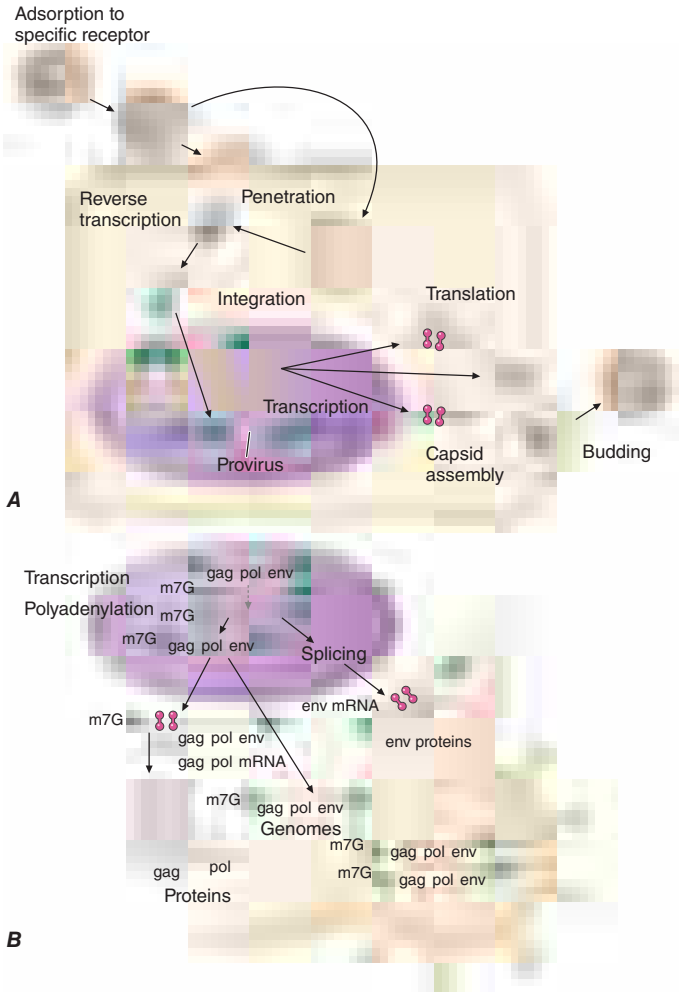

FIGURE 196-1 The life cycle of retroviruses. ***A.*** Overview of virus replication. The retrovirus enters a target cell by binding to a specific cell-surface receptor; once the virus is internalized, its RNA is released from the nucleocapsid and is reverse-transcribed into proviral DNA. The provirus is inserted into the genome and then transcribed into RNA; the RNA is translated; and virions assemble and are extruded from the cell membrane by budding. ***B.*** Overview of retroviral gene expression. The provirus is transcribed, capped, and polyadenylated. Viral RNA molecules then have one of three fates: they are exported to the cytoplasm, where they are packaged as the viral RNA in infectious viral particles; they are spliced to form the message for the envelope polyprotein; or they are translated into Gag and Pol proteins. Most of the messages for the Pol protein fail to initiate Pol translation because of a stop codon before its initiation; however, in a fraction of the messages, the stop codon is missed and the Pol proteins are translated. *(Modified from JM Coffin, in BN Fields, DM Knipe [eds]: Fields Virology. New York, Raven, 1990; with permission.)*

assembled and released from the cell by budding from the membrane; host cell membrane proteins are frequently incorporated into the envelope of the virus. Proviral integration occurs during the S-phase of the cell cycle; thus, in general, nondividing cells are resistant to retroviral infection. Only the lentiviruses are able to infect nondividing cells. Once a host cell is infected, it is infected for the life of the cell.

Retroviral genomes include both coding and noncoding sequences **(Fig. 196-2)**. In general, noncoding sequences are important recognition signals for DNA or RNA synthesis or processing events and are located in the 5′ and 3′ terminal regions of the genome. All retroviral genomes are terminally redundant, containing identical sequences called *long terminal repeats* (LTRs). The ends of the retroviral RNA genome differ slightly in sequence from the integrated retroviral DNA. In the latter, the LTR sequences are repeated in both the 5′ and the 3′ terminus of the virus. The LTRs contain sequences involved in initiating the expression of the viral proteins, the integration of the provirus, and the polyadenylation of viral RNAs. The primer binding site, which is critical for the initiation of reverse transcription, and the viral packaging sequences are located outside the LTR sequences. The coding regions include the *gag* (group-specific antigen, core protein), *pol* (RNA-dependent DNA polymerase), and *env* (envelope) genes. The *gag* gene encodes a precursor polyprotein that is cleaved to form three to five capsid proteins; a fraction of the Gag precursor proteins also contain a protease responsible for cleaving the Gag and Pol polyproteins. A Gag-Pol polyprotein gives rise to the protease that is responsible for cleaving the Gag-Pol polyprotein. The *pol* gene encodes three proteins: the reverse transcriptase, the integrase, and the protease. The reverse transcriptase copies the viral RNA into the double-strand DNA provirus, which inserts itself into the host cell DNA via the action of integrase. The protease cleaves the Gag-Pol polyprotein into smaller protein products. The *env* gene encodes the envelope glycoproteins: one protein that binds to specific surface receptors and determines what cell types can be infected and a smaller transmembrane protein that anchors the complex to the envelope. **Fig. 196-3** shows how the retroviral gene products make up the virus structure.

HTLVs have a region between *env* and the 3′ LTR that encodes several proteins and transcripts in overlapping reading frames (Fig. 196-2). Tax is a 40-kDa protein that does not bind to DNA but induces the expression of host cell transcription factors that alter host cell gene expression and is capable of inducing cell transformation under certain circumstances. Rex is a 27-kDa protein that regulates the expression of viral mRNAs. Other transcripts from this region (p12, p13, and p30) tend to restrict expression of viral genes and diminish the immunogenicity of infected cells. The protein of *HBZ*, a product of the complementary proviral DNA strand, interacts with many cellular transcription factors and signaling proteins. It stimulates proliferation of infected cells and is the only viral product universally expressed in HTLV-1-infected tumor cells. These proteins are produced from messages that are similar but that are spliced differently from overlapping but distinct exons.

The lentiviruses in general, and HIV-1 and -2 in particular, contain a larger genome than other pathogenic retroviruses. They contain an untranslated region between *pol* and *env* that encodes portions of several proteins, varying with the reading frame into which the mRNA is spliced. Tat is a 14-kDa protein that augments the expression of virus from the LTR. The Rev protein of HIV-1, similar to the Rex protein of HTLV, regulates RNA splicing and/or RNA transport. The Nef protein downregulates CD4, the cellular receptor for HIV; alters host T cell–activation pathways; and enhances viral infectivity. The Vif protein is necessary for the proper assembly of the HIV nucleoprotein core in many types of cells; without Vif, proviral DNA is not efficiently produced in these infected cells. In addition, the Vif protein targets APOBEC (apolipoprotein B mRNA-editing enzyme catalytic polypeptide, a cytidine deaminase that mutates the viral sequence) for proteasomal degradation, thus blocking its virus-suppressing effect. Vpr, Vpu (HIV-1 only), and Vpx (HIV-2 only) are viral proteins encoded by translation of the same message in different reading frames. As noted above, oncogenic retroviruses depend on cell proliferation for their replication; lentiviruses can infect nondividing cells, largely through effects mediated by Vpr. Vpr facilitates transport of the provirus into the nucleus and can induce other cellular changes, such as G_2 growth arrest and differentiation of some target cells. Vpx is structurally related to Vpr, but its functions are not fully defined. Vpu promotes the degradation of CD4 in the endoplasmic reticulum and stimulates the release of virions from infected cells.

Retroviruses can be either exogenously acquired (by infection with an infected cell or a free virion capable of replication) or transmitted in the germline as endogenous virus. Endogenous retroviruses are often replication defective. The human genome contains endogenous retroviral sequences, but there are no known replication-competent endogenous retroviruses in humans.

In general, viruses that contain only the *gag*, *pol*, and *env* genes either are not pathogenic or take a long time to induce disease; these observations indicate the importance of the other regulatory genes in viral disease pathogenesis. The pathogenesis of neoplastic transformation by retroviruses relies on the chance integration of the provirus at a spot in the genome resulting in the expression of a cellular gene (protooncogene) that becomes transforming by virtue of its unregulated

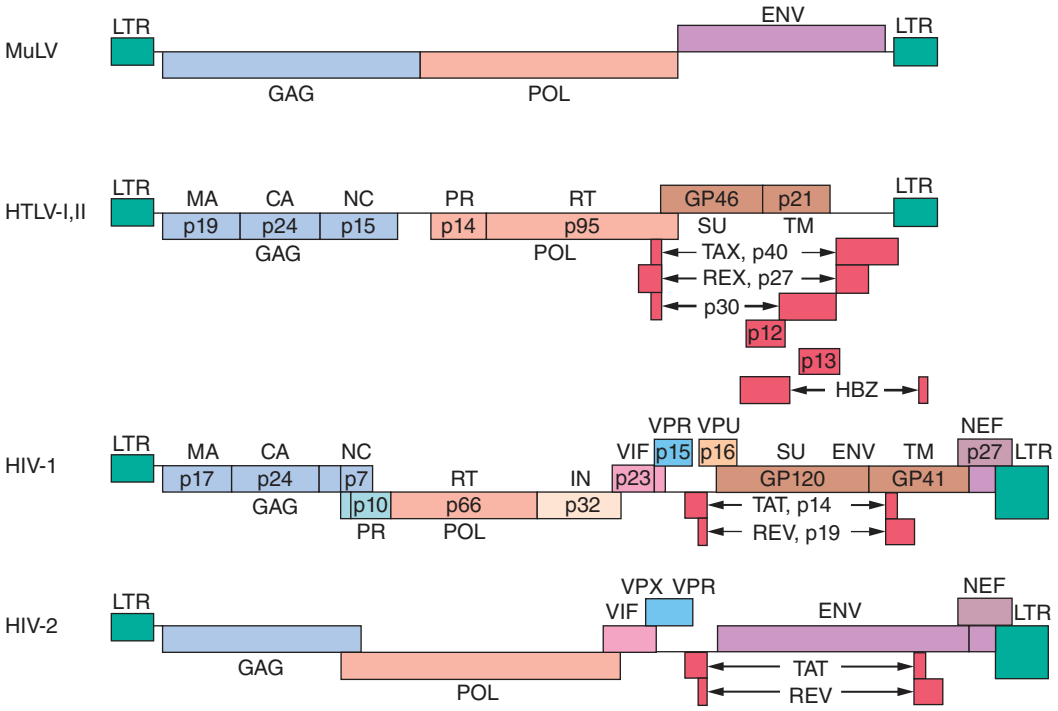

FIGURE 196-2 Genomic structure of retroviruses. The murine leukemia virus MuLV has the typical three structural genes: *gag*, *pol*, and *env*. The *gag* region gives rise to three proteins: matrix (MA), capsid (CA), and nucleic acid-binding (NC) proteins. The *pol* region encodes both a protease (PR) responsible for cleaving the viral polyproteins and a reverse transcriptase (RT). In addition, HIV *pol* encodes an integrase (IN). The *env* region encodes a surface protein (SU) and a small transmembrane protein (TM). The human retroviruses have additional gene products translated in each of the three possible reading frames. HTLV-1 and HTLV-2 have *tax* and *rex* genes with exons on either side of the *env* gene. HIV-1 and HIV-2 have six accessory gene products: *tat*, *rev*, *vif*, *nef*, *vpr*, and either *vpu* (in HIV-1) or *vpx* (in HIV-2). The genes for these proteins are located mainly between the *pol* and *env* genes. GP, glycoprotein; HBZ, HTLV-1 basic leucine zipper domain–containing protein; LTR, long terminal repeat.

expression. For example, avian leukosis virus causes B-cell leukemia by inducing the expression of *myc*. Some retroviruses possess captured and altered cellular genes near their integration site, and these viral oncogenes can transform the infected host cell. Viruses that have oncogenes often have lost a portion of their genome that is required for replication. Such viruses need helper viruses to reproduce, a feature that may explain why these acute transforming retroviruses are rare in nature. All human retroviruses identified to date are exogenous and are not acutely transforming (i.e., they lack a transforming oncogene).

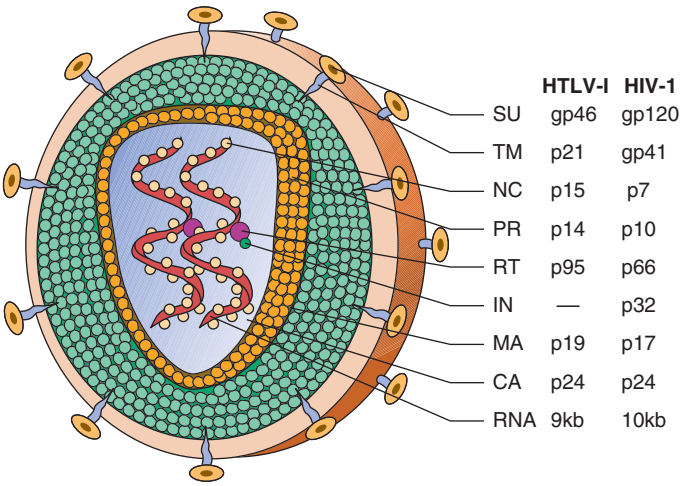

FIGURE 196-3 Schematic structure of human retroviruses. The surface glycoprotein (SU) is responsible for binding to receptors of host cells. The transmembrane protein (TM) anchors SU to the virus. NC is a nucleic acid–binding protein found in association with the viral RNA. A protease (PR) cleaves the polyproteins encoded by the *gag*, *pol*, and *env* genes into their functional components. RT is reverse transcriptase, and IN is an integrase present in some retroviruses (e.g., HIV-1) that facilitates insertion of the provirus into the host genome. The matrix protein (MA) is a Gag protein closely associated with the lipid of the envelope. The capsid protein (CA) forms the major internal structure of the virus, the core shell.

These remarkable properties of retroviruses have led to experimental efforts to use them as vectors to insert specific genes into particular cell types, a process known as *gene therapy* or *gene transfer*. The process could be used to repair a genetic defect or to introduce a new property that could be used therapeutically; for example, a gene (e.g., thymidine kinase) that would make a tumor cell susceptible to killing by a drug (e.g., ganciclovir) could be inserted. One source of concern about the use of retroviral vectors in humans is that replication-competent viruses might rescue endogenous retroviral replication, with unpredictable results. This concern is not merely hypothetical: the detection of proteins encoded by endogenous retroviral sequences on the surface of cancer cells implies that the genetic events leading to the cancer were able to activate the synthesis of these usually silent genes.

HUMAN T-CELL LYMPHOTROPIC VIRUS

HTLV-1 was isolated in 1980 from a T-cell lymphoma cell line from a patient originally thought to have cutaneous T-cell lymphoma. Later it became clear that the patient had a distinct form of lymphoma (originally reported in Japan) called *adult T-cell leukemia/lymphoma* (ATL). Serologic data have determined that HTLV-1 is the cause of at least two important diseases: ATL and tropical spastic paraparesis, also called *HTLV-1-associated myelopathy* (HAM). HTLV-1 may also play a role in infective dermatitis, arthritis, uveitis, and Sjögren's syndrome.

Two years after the isolation of HTLV-1, HTLV-2 was isolated from a patient with an unusual form of hairy-cell leukemia that affected T cells. Epidemiologic studies of HTLV-2 failed to reveal a consistent disease association. Similarly, HTLV-3 and HTLV-4 have been identified but have no known disease association.

BIOLOGY AND MOLECULAR BIOLOGY

Because the biology of HTLV-1 and that of HTLV-2 are similar, the following discussion will focus on HTLV-1.

Human glucose transporter protein 1 (GLUT-1) functions as a receptor for HTLV-1, probably acting together with neuropilin-1 (NRP1) and heparan sulfate proteoglycans. Generally, only T cells are productively infected, but infection of B cells and other cell types is occasionally

detected. The most common outcome of HTLV-1 infection is latent carriage of randomly integrated provirus in CD4+ T cells. HTLV-1 does not contain an oncogene and does not insert into a unique site in the genome. Indeed, most infected cells express no viral gene products. The only viral gene product that is routinely expressed in tumor cells transformed by HTLV-1 in vivo is *hbz*. The *tax* gene is thought to be critical to the transformation process but is not expressed in the tumor cells of many ATL patients, possibly because of the immunogenicity of *tax*-expressing cells. Cells transformed in vitro, by contrast, actively transcribe HTLV-1 RNA and produce infectious virions. Most HTLV-1-transformed cell lines are the result of the infection of a normal host T cell in vitro. It is difficult to establish cell lines derived from authentic ATL cells.

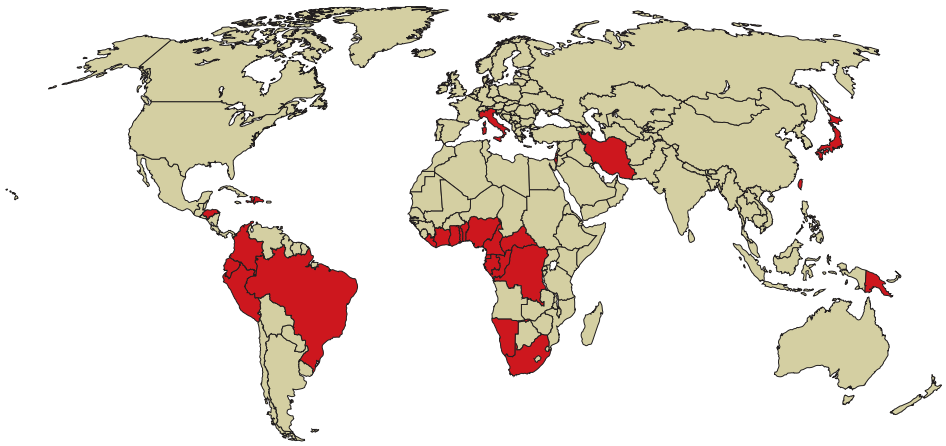

FIGURE 196-4 Global distribution of HTLV-1 infection. Countries with a prevalence of HTLV-1 infection of 1–5% are shaded darkly. Note that the distribution of infected patients is not uniform in endemic countries. For example, the people of southwestern Japan and northeastern Brazil are more commonly affected than those in other regions of those countries.

Although *tax* does not itself bind to DNA, it does induce the expression of a wide range of host cell gene products, including transcription factors (especially c-rel/nuclear factor κB [NF-κB], ets-1 and -2, and members of the fos/jun family), cytokines (e.g., interleukin [IL] 2, granulocyte-macrophage colony-stimulating factor, and tumor necrosis factor), membrane proteins and receptors (major histocompatibility [MHC] molecules and IL-2 receptor α), and chromatin remodeling complexes. The genes activated by *tax* are generally controlled by transcription factors of the c-rel/NF-κB and cyclic AMP response element binding (CREB) protein families. It is unclear how this induction of host gene expression leads to neoplastic transformation; *tax* can interfere with G_1 and mitotic cell-cycle checkpoints, block apoptosis, inhibit DNA repair, and promote antigen-independent T-cell proliferation. Induction of a cytokine-autocrine loop has been proposed; however, IL-2 is not the crucial cytokine. The involvement of IL-4, IL-7, and IL-15 has been proposed.

In light of the irregular expression of *tax* in ATL cells, it has been suggested that *tax* is important in the early phases of transformation but is not essential for the maintenance of the transformed state. The maintenance role is thought to be due to *hbz* expression. As is clear from the epidemiology of HTLV-1 infection, transformation of an infected cell is a rare event and may depend on heterogeneous second, third, or fourth genetic hits. No consistent chromosomal abnormalities have been described in ATL; however, aneuploidy is common, and individual cases with p53 mutations and translocations involving the T-cell receptor genes on chromosome 14 have been reported. *Tax* may repress certain DNA repair enzymes, permitting the accumulation of genetic damage that would normally be repaired. However, the molecular pathogenesis of HTLV-1-induced neoplasia is not fully understood.

FEATURES OF HTLV-1 INFECTION

Epidemiology HTLV-1 infection is transmitted in at least three ways: from mother to child, especially via breast milk; through sexual activity, more commonly from men to women; and through the blood—via contaminated transfusions or contaminated needles. The virus is most commonly transmitted perinatally. Compared with HIV, which can be transmitted in cell-free form, HTLV-1 is less infectious, and its transmission usually requires cell-to-cell contact.

HTLV-1 is endemic in southwestern Japan and Okinawa, where >1 million persons are infected. Antibodies to HTLV-1 are present in the serum of up to 35% of Okinawans, 10% of residents of the Japanese island of Kyushu, and <1% of persons in nonendemic regions of Japan. Despite this high prevalence of infection, only ~500 cases of ATL are diagnosed in this area each year. Clusters of infection have been noted in other areas of eastern Asia, such as Taiwan; in the Caribbean basin, including northeastern South America; in northwestern South America; in central and southern Africa; in Italy, Israel, Iran, and Papua New Guinea; in the Arctic; and in the southeastern part of the United States **(Fig. 196-4)**. An estimated 5–10 million persons have HTLV-1 infection worldwide.

Progressive spastic or ataxic myelopathy developing in an individual who is HTLV-1 positive (i.e., who has serum antibodies to HTLV-1) may be due to direct infection of the nervous system with the virus, but destruction of the pyramidal tracts appears to involve HTLV-1-infected CD4+ T cells; a similar disorder may result from infection with HIV or HTLV-2. In rare instances, patients with HAM are seronegative but have detectable antibody to HTLV-1 in cerebrospinal fluid (CSF).

The cumulative lifetime risk of developing ATL is 3% among HTLV-1-infected patients, with a threefold greater risk among men than among women; a similar cumulative risk is projected for HAM (4%), but with women more commonly affected than men. The distribution of these two diseases overlaps the distribution of HTLV-1, with >95% of affected patients showing serologic evidence of HTLV-1 infection. The latency period between infection and the emergence of disease is 20–30 years for ATL. For HAM, the median latency period is ~3.3 years (range, 4 months to 30 years). The development of ATL is rare among persons infected by blood products; however, ~20% of patients with HAM acquire HTLV-1 from contaminated blood. ATL is more common among perinatally infected individuals, whereas HAM is more common among persons infected via sexual transmission.

Associated Diseases • **ATL** Four clinical types of HTLV-1-induced neoplasia have been described: acute, lymphomatous, chronic, and smoldering. All of these tumors are monoclonal proliferations of CD4+ postthymic T cells with clonal proviral integrations and clonal T-cell receptor gene rearrangements.

ACUTE ATL About 60% of patients who develop malignancy have classic acute ATL, which is characterized by a short clinical prodrome (~2 weeks between the first symptoms and the diagnosis) and an aggressive natural history (median survival period, 6 months). The clinical picture is dominated by rapidly progressive skin lesions, pulmonary involvement, hypercalcemia, and lymphocytosis with cells containing lobulated or "flower-shaped" nuclei **(see Fig. 104-10)**. The malignant cells have monoclonal proviral integrations and express CD4, CD3, and CD25 (low-affinity IL-2 receptors) on their surface. Serum levels of CD25 can be used as a tumor marker. Anemia and thrombocytopenia are rare. The skin lesions may be difficult to distinguish from those in mycosis fungoides. Lytic bone lesions, which are common, do not contain tumor cells but rather are composed of osteolytic cells, usually without osteoblastic activity. Despite the leukemic picture, bone marrow involvement is patchy in most cases.

The hypercalcemia of ATL is multifactorial; the tumor cells produce osteoclast-activating factors (tumor necrosis factor α, IL-1, lymphotoxin) and can also produce a parathyroid hormone–like molecule. Affected patients have an underlying immunodeficiency that makes

them susceptible to opportunistic infections similar to those seen in patients with AIDS (Chap. 197). The pathogenesis of the immunodeficiency is unclear. Pulmonary infiltrates in ATL patients reflect leukemic infiltration half the time and opportunistic infections with organisms such as *Pneumocystis* and other fungi the other half. Gastrointestinal symptoms are nearly always related to opportunistic infection. *Strongyloides stercoralis* is a gastrointestinal parasite that has a pattern of endemic distribution similar to that of HTLV-1. HTLV-1-infected persons also infected with this parasite may develop ATL more often or more rapidly than those without *Strongyloides* infections. Serum concentrations of lactate dehydrogenase and alkaline phosphatase are often elevated in ATL. About 10% of patients have leptomeningeal involvement leading to weakness, altered mental status, paresthesia, and/or headache. Unlike other forms of central nervous system (CNS) lymphoma, ATL may be accompanied by normal CSF protein levels. The diagnosis depends on finding ATL cells in the CSF (Chap. 104).

LYMPHOMATOUS ATL The lymphomatous type of ATL occurs in ~20% of patients and is similar to the acute form in its natural history and clinical course, except that circulating abnormal cells are rare and lymphadenopathy is evident. The histology of the lymphoma is variable but does not influence the natural history. In general, the diagnosis is suspected on the basis of the patient's birthplace (see "Epidemiology," above) and the presence of skin lesions and hypercalcemia. The diagnosis is confirmed by the detection of antibodies to HTLV-1 in serum.

CHRONIC ATL Patients with the chronic form of ATL generally have normal serum levels of calcium and lactate dehydrogenase and no involvement of the CNS, bone, or gastrointestinal tract. The median duration of survival for these patients is 2 years. In some cases, chronic ATL progresses to the acute form of the disease.

SMOLDERING ATL Fewer than 5% of patients have the smoldering form of ATL. In this form, the malignant cells have monoclonal proviral integration; <5% of peripheral-blood cells exhibit typical morphologic abnormalities; hypercalcemia, adenopathy, and hepatosplenomegaly do not develop; the CNS, the bones, and the gastrointestinal tract are not involved; and skin lesions and pulmonary lesions may be present. The median survival period for this small subset of patients appears to be ≥5 years.

HAM (TROPICAL SPASTIC PARAPARESIS) In contrast to ATL, in which there is a slight predominance of male patients, HAM affects female patients disproportionately. HAM resembles multiple sclerosis in certain ways (Chap. 436). The onset is insidious. Symptoms include weakness or stiffness in one or both legs, back pain, and urinary incontinence. Sensory changes are usually mild, but peripheral neuropathy may develop. The disease generally takes the form of slowly progressive and unremitting thoracic myelopathy; one-third of patients are bedridden within 10 years of diagnosis, and one-half are unable to walk unassisted by this point. Patients display spastic paraparesis or paraplegia with hyperreflexia, ankle clonus, and extensor plantar responses. Cognitive function is usually spared; cranial nerve abnormalities are unusual.

MRI reveals lesions in both the white matter and the paraventricular regions of the brain as well as in the spinal cord. Pathologic examination of the spinal cord shows symmetric degeneration of the lateral columns, including the corticospinal tracts; some cases involve the posterior columns as well. The spinal meninges and cord parenchyma contain an inflammatory infiltrate that includes CD8+ T cells with myelin destruction.

HTLV-1 is not usually found in cells of the CNS but may be detected in a small population of lymphocytes present in the CSF. In general, HTLV-1 replication is greater in HAM than in ATL, and patients with HAM have a stronger immune response to the virus. Antibodies to HTLV-1 are present in the serum and appear to be produced in the CSF of HAM patients, where titers are often higher than in the serum. The pathophysiology of HAM may involve the induction of autoimmune destruction of neural cells by T cells with specificity for viral components such as Tax or Env proteins. One theory is that susceptibility to HAM may be related to the presence of human leukocyte antigen (HLA) alleles capable of presenting viral antigens in a fashion that leads to autoimmunity. Insufficient data are available to confirm an HLA association. However, antibodies in the sera of HAM patients have been shown to bind a neuron-specific antigen (heteronuclear ribonuclear protein A1 [hnRNP A1]) and to interfere with neurotransmission in vitro.

It is unclear what factors influence whether HTLV-1 infection will cause disease and, if it does, whether it will induce a neoplasm (ATL) or an autoimmune disorder (HAM). Differences in viral strains, the susceptibility of particular MHC haplotypes, the route of HTLV-1 infection, the viral load, and the nature of the HTLV-1-related immune response are putative factors, but few definitive data are available.

OTHER PUTATIVE HTLV-1-RELATED DISEASES Even in the absence of the full clinical picture of HAM, bladder dysfunction is common in HTLV-1-infected women. In areas where HTLV-1 is endemic, diverse inflammatory and autoimmune diseases have been attributed to the virus, including uveitis, dermatitis, pneumonitis, rheumatoid arthritis, and polymyositis. However, a causal relationship between HTLV-1 and these illnesses has not been established.

Prevention Women in endemic areas should not breast-feed their children, and blood donors should be screened for serum antibodies to HTLV-1. As in the prevention of HIV infection, the practice of safe sex and the avoidance of needle sharing are important.

TREATMENT

HTLV-1 Infection

For the small number of patients who develop HTLV-1-related disease, therapies are not curative. In patients with the acute and lymphomatous types of ATL, the disease progresses rapidly. Hypercalcemia is generally controlled by glucocorticoid administration and cytotoxic therapy directed against the neoplasm. The tumor is highly responsive to combination chemotherapy that is used against other forms of lymphoma; however, patients are susceptible to overwhelming bacterial and opportunistic infections, and ATL relapses within 4–10 months after remission in most cases. The combination of interferon α and zidovudine may extend survival. Because viral replication is not clearly associated with ATL progression, zidovudine is probably effective through its cytotoxic effects (as a chain-terminating thymidine analogue) rather than its antiviral effects. Selected series have reported high rates of response and a 40% rate of 5-year survival; however, this level of response has not been universal. LSG15, a multidrug chemotherapy program developed in Japan, induces complete responses in about one-third of patients, about half of whom survive for >2 years; however, the median survival time is about 13 months. High-dose therapy with bone marrow transplantation has been widely tested in Japan. Median survival has not been influenced by this treatment; however, up to 25% of patients survive free of disease for 4 years. Lenalidomide has been reported to have a 42% response rate in patients with relapsed ATL, extending median survival to 20 months despite a short 4-month progression-free survival period. A pilot trial suggested that treatment with mogamulizumab, an antibody to CCR4 (a receptor for a number of chemokines, including RANTES and TARC), improved response rates when added to chemotherapy. An experimental approach using an yttrium 90-labeled or toxin-conjugated antibody to the IL-2 receptor appears promising but is not widely available. Patients with the chronic or smoldering form of ATL may be managed with an expectant approach: treat any infections, and watch and wait for signs of progression to acute disease.

Patients with HAM may obtain some benefit from the use of glucocorticoids to reduce inflammation. Antiretroviral regimens have not been effective. In one study, danazol (200 mg three times daily) produced significant neurologic improvement in five of six treated patients, with resolution of urinary incontinence in two

cases, decreased spasticity in three, and restoration of the ability to walk after confinement to a wheelchair in two. Antibody to IL-15 receptor β chain has been tested with some promising clinical effects in small numbers of patients. Physical therapy and rehabilitation are important components of management.

FEATURES OF HTLV-2 INFECTION

Epidemiology HTLV-2 is endemic in certain Native American tribes and in Africa. It is generally considered to be a New World virus that was brought from Asia to the Americas 10,000–40,000 years ago during the migration of infected populations across the Bering land bridge. The mode of transmission of HTLV-2 is probably the same as that of HTLV-1 (see above). HTLV-2 may be less readily transmitted sexually than HTLV-1.

Studies of large cohorts of injection drug users with serologic assays that reliably distinguish HTLV-1 from HTLV-2 indicated that the vast majority of HTLV-positive cohort members were infected with HTLV-2. The seroprevalence of HTLV in a cohort of 7841 injection drug users from drug treatment centers in Baltimore, Chicago, Los Angeles, New Jersey (Asbury Park and Trenton), New York City (Brooklyn and Harlem), Philadelphia, and San Antonio was 20.9%, with >97% of cases due to HTLV-2. The seroprevalence of HTLV-2 was higher in the Southwest and the Midwest than in the Northeast. In contrast, the seroprevalence of HIV-1 was higher in the Northeast than in the Southwest or the Midwest. Approximately 3% of the cohort members were infected with both HTLV-2 and HIV-1. The seroprevalence of HTLV-2 increased linearly with age. Women were significantly more likely than men to be infected with HTLV-2; the virus is thought to be more efficiently transmitted from male to female than from female to male.

Associated Diseases Although HTLV-2 was isolated from a patient with a T-cell variant of hairy-cell leukemia, this virus has not been consistently associated with a particular disease and in fact has been thought of as "a virus searching for a disease." However, evidence is accumulating that HTLV-2 may play a role in certain neurologic, hematologic, and dermatologic diseases. These data require confirmation, particularly in light of the previous confusion regarding the relative prevalences of HTLV-1 and HTLV-2 among injection drug users.

Prevention Avoidance of needle sharing, adherence to safe-sex practices, screening of blood (by assays for HTLV-1, which also detect HTLV-2), and avoidance of breast-feeding by infected women are important principles in the prevention of spread of HTLV-2.

HUMAN IMMUNODEFICIENCY VIRUS

HIV-1 and HIV-2 are members of the lentivirus subfamily of Retroviridae and are the only lentiviruses known to infect humans. The lentiviruses are slower-acting than viruses that cause acute infection (e.g., influenza virus) but not than other retroviruses. The features of acute primary infection with HIV resemble those of more classic acute infections. The characteristic chronicity of HIV disease is consistent with the designation *lentivirus*. **For a detailed discussion of HIV, see Chap. 197.**

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197 Human Immunodeficiency Virus Disease: AIDS and Related Disorders

Anthony S. Fauci, Gregory K. Folkers, H. Clifford Lane

AIDS was first recognized in the United States in the summer of 1981, when the U.S. Centers for Disease Control and Prevention (CDC) reported the unexplained occurrence of *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia in five previously healthy homosexual men in Los Angeles and of Kaposi's sarcoma (KS) with or without *P. jirovecii* pneumonia and other opportunistic infections in 26 previously healthy homosexual men in New York, San Francisco, and Los Angeles. The disease was soon recognized in male and female injection drug users; in hemophiliacs and blood transfusion recipients; among female sexual partners of men with AIDS; and among infants born to mothers with AIDS. In 1983, human immunodeficiency virus (HIV) was isolated from a patient with lymphadenopathy, and by 1984 it was demonstrated clearly to be the causative agent of AIDS. In 1985, a sensitive enzyme-linked immunosorbent assay (ELISA) was developed; this led to an appreciation of the scope and evolution of the HIV epidemic at first in the United States and other developed nations and ultimately among developing nations throughout the world (see "HIV Infection and AIDS Worldwide," below). The staggering worldwide evolution of the HIV pandemic has been matched by an explosion of information in the areas of HIV virology, pathogenesis (both immunologic and virologic), treatment of HIV disease, treatment and prophylaxis of the opportunistic diseases associated with HIV infection, and prevention of HIV infection. The information flow related to HIV disease is enormous and continues to expand, and it has become almost impossible for the health care generalist to stay abreast of the literature. The purpose of this chapter is to present the most current information available on the scope of the pandemic; on its pathogenesis, treatment, and prevention; and on prospects for vaccine development. Above all, the aim is to provide a solid scientific basis and practical clinical guidelines for a state-of-the-art approach to the HIV-infected patient.

DEFINITION

The current CDC classification system for HIV infection and AIDS categorizes patients based on clinical conditions associated with HIV infection together with the level of the CD4+ T lymphocyte count. A confirmed HIV case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown). If there was a negative HIV test within 6 months of the first HIV infection diagnosis, the stage is 0, and remains 0 until 6 months after diagnosis. Advanced HIV disease (AIDS) is classified as stage 3 if one or more specific opportunistic illness has been diagnosed **(Table 197-1)**. Otherwise, the stage is determined by CD4+ T lymphocyte test results and immunologic criteria **(Table 197-2)**. If none of these criteria apply (e.g., because of missing information on CD4+ T lymphocyte test results), the stage is U (unknown).

The definition and staging criteria of AIDS are complex and comprehensive and were established for surveillance purposes rather than for the practical care of patients. Thus, the clinician should not focus on whether the patient fulfills the strict definition of AIDS, but should view HIV disease as a spectrum ranging from primary infection, with or without the acute syndrome, to the relatively asymptomatic stage, to advanced stages associated with opportunistic diseases (see "Pathophysiology and Pathogenesis," below).

ETIOLOGIC AGENT

HIV is the etiologic agent of AIDS; it belongs to the family of human retroviruses (Retroviridae) and the subfamily of lentiviruses **(Chap. 196)**. Nononcogenic lentiviruses cause disease in other animal

TABLE 197-1 CDC Stage 3 (AIDS)-Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent[a]
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive[b]
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,[b] disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent[b]
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV

[a]Only among children age <6 years. [b]Only among adults, adolescents, and children age ≥6 years.

Source: MMWR 63(RR-03), April 11, 2014.

species, including sheep, horses, goats, cattle, cats, and monkeys. The four retroviruses known to cause human disease belong to two distinct groups: the human T lymphotropic viruses (HTLV)-1 and HTLV-2, which are transforming retroviruses; and the human immunodeficiency viruses, HIV-1 and HIV-2, which cause cytopathic effects either directly or indirectly **(Chap. 196)**. The most common cause of HIV disease throughout the world, and certainly in the United States, is HIV-1, which comprises several subtypes with different geographic distributions (see "Molecular Heterogeneity of HIV-1," below). HIV-2 was first identified in 1986 in West African patients and was originally confined to West Africa. However, cases traced to West Africa or to sexual contacts with West Africans have been identified throughout the world. The currently defined groups of HIV-1 (M, N, O, P) and

TABLE 197-2 CDC HIV Infection Stages 1–3 Based on Age-Specific CD4+ T Lymphocyte Count or CD4+ T Lymphocyte Percentage of Total Lymphocytes[a]

	AGE ON DATE OF CD4 T+ LYMPHOCYTE TEST					
	<1 YEAR		1–5 YEARS		6 YEARS THROUGH ADULT	
STAGE[a]	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1500	≥34	≥1000	≥30	≥500	≥26
2	750–1499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a]The stage is based primarily on the CD4+ T lymphocyte count; the CD4+ T lymphocyte count takes precedence over the CD4+ T lymphocyte percentage, and the percentage is considered only if the count is missing.

Source: MMWR 63(RR-03), April 11, 2014.

the HIV-2 groups A through H each are likely derived from a separate transfer to humans from a nonhuman primate reservoir. HIV-1 viruses likely came from chimpanzees and/or gorillas, and HIV-2 from sooty mangabeys. The AIDS pandemic is primarily caused by the HIV-1 M group viruses. Although HIV-1 group O and HIV-2 viruses have been found in numerous countries, including those in the developed world, they have caused much more localized epidemics. The taxonomic relationship between primate lentiviruses is shown in **Fig. 197-1**.

MORPHOLOGY OF HIV

Electron microscopy shows that the HIV virion is an icosahedral structure **(Fig. 197-2)** containing numerous external spikes formed by the two major envelope proteins, the external gp120 and the transmembrane gp41. The HIV envelope exists as a trimeric heterodimer. The virion buds from the surface of the infected cell (Fig. 197-2***A***) and incorporates a variety of host cellular proteins into its lipid bilayer. The structure of HIV-1 is schematically diagrammed in Fig. 197-2***B***.

REPLICATION CYCLE OF HIV

HIV is an RNA virus whose hallmark is the reverse transcription of its genomic RNA to DNA by the enzyme *reverse transcriptase*. The replication cycle of HIV begins with the high-affinity binding via surface-exposed residues within the gp120 protein to its receptor on the host cell surface, the CD4 molecule **(Fig. 197-3)**. The CD4 molecule is a 55-kDa protein found predominantly on a subset of T lymphocytes that are responsible for helper function in the immune system **(Chap. 342)**. Once it binds to CD4, the gp120 protein undergoes a conformational change that facilitates binding to one of two major co-receptors. The two major co-receptors for HIV-1 are CCR5 and CXCR4. Both receptors belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors, and the use of one or the other or both receptors by the virus for entry into the cell is an important determinant of the cellular tropism of the virus. Cell-to-cell spread is also facilitated by accessory molecules such as the C-type lectin receptor *DC-SIGN* expressed on certain dendritic cells (DCs) that bind to the HIV gp120 envelope protein, allowing virus captured on DCs to spread to CD4+ T cells. Following binding of the envelope protein to the CD4 molecule associated with the above-mentioned conformational change in the viral envelope gp120, fusion with the host cell membrane occurs via the newly exposed gp41 molecule penetrating the plasma membrane of the target cell and then coiling upon itself to bring the virion and target cell together **(Fig. 197-4)**. Following fusion, uncoating of the capsid protein shell is initiated—a step that facilitates reverse transcription and leads to formation of the preintegration complex, composed of viral RNA, enzymes, and accessory proteins and surrounded by capsid and matrix proteins (Fig. 197-3). As the preintegration complex traverses the cytoplasm to reach the nucleus, the viral reverse transcriptase enzyme catalyzes the reverse transcription of the genomic RNA into DNA, resulting in the formation of double-stranded proviral HIV DNA. At several steps of the replication cycle, the virus is vulnerable to various cellular factors that can block the progression of infection. The cytoplasmic tripartite motif-containing protein 5-α (TRIM5-α) is a host restriction factor that interacts with retroviral capsids, causing their premature disassembly and induction of innate immune responses. While early studies with laboratory strains found the HIV-1 capsid bound weakly to the human form of TRIM5-α, capsids of primary isolates appear to be more susceptible to TRIM5-α-mediated disassembly. The apolipoprotein B mRNA editing enzyme (catalytic polypeptide-like 3 [APOBEC3]) family of cellular proteins also inhibits progression of virus infection after virus has entered the cell and prior to entering the nucleus. APOBEC3 proteins, which are incorporated into virions and released into the cytoplasm of a newly infected cell, bind to the single minus-strand DNA intermediate and deaminate viral cytidine, causing hypermutation of retroviral genomes. HIV has evolved a powerful strategy to protect itself from APOBEC. The viral protein Vif targets

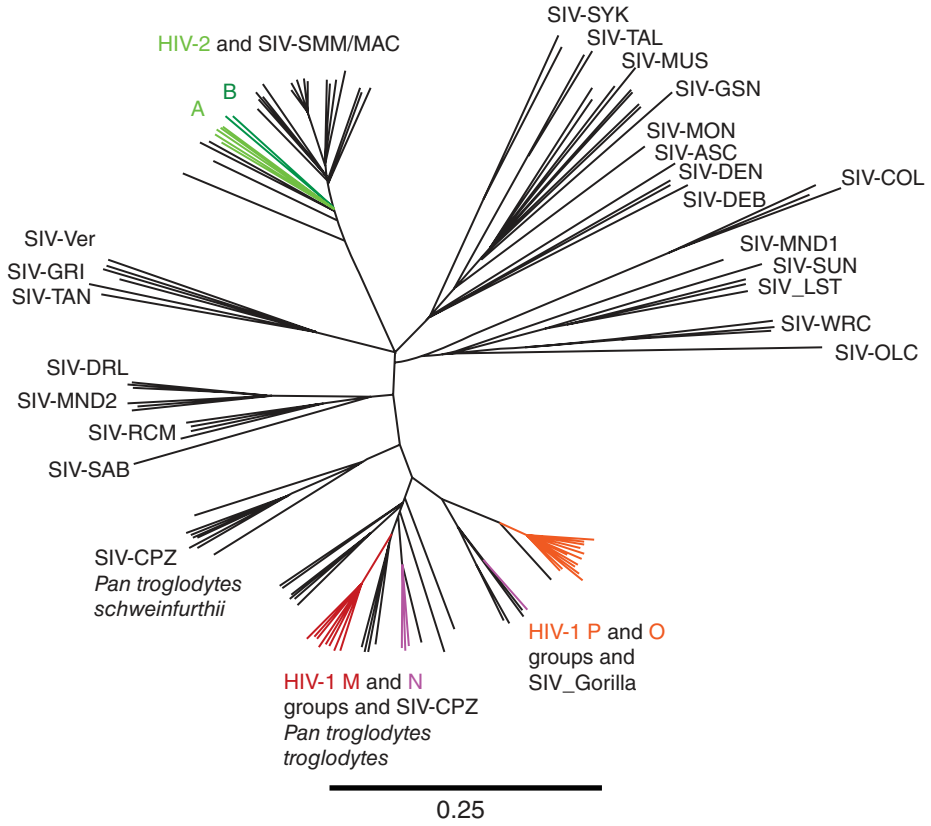


FIGURE 197-1 A phylogenetic tree based on the nearly complete genomes (*gag* through *nef* genes) of primate immunodeficiency viruses. The scale (0.25) indicates a 25% phylogenetically corrected genetic distance at the nucleotide level. Clades in color represent viruses (HIV-1, HIV-2) identified in humans after relatively recent transfers from chimpanzee, gorilla, and sooty mangabey reservoirs. *(Prepared by Brian Foley, PhD, of the HIV Sequence Database, Theoretical Biology and Biophysics Group, Los Alamos National Laboratory; additional information at www.hiv.lanl.gov/content/sequence/HelpDocs/subtypes.html.)*

APOBEC3 for proteasomal degradation. SAMHD1 is another post-entry host factor that prevents reverse transcription by depleting pools of deoxynucleotides (dNTPs). The type I interferon (IFN)-induced myxovirus resistance protein 2 (MX2) is another restriction factor associated with innate immunity that inhibits HIV-1 nuclear entry.

With activation of the cell, the viral DNA accesses the nuclear pore and is transferred from the cytoplasm to the nucleus, where it is integrated into the host cell chromosomes through the action of another virally encoded enzyme, *integrase* (Fig. 197-3). HIV proviral DNA integrates into the host genomic DNA preferentially in regions of active transcription and regional hotspots. This provirus may remain transcriptionally inactive (latent) or it may manifest varying levels of gene expression, up to active transcription and production of virus depending on the metabolic state of the infected cell.

Cellular activation plays an important role in the replication cycle of HIV and is critical to the pathogenesis of HIV disease (see "Pathogenesis and Pathophysiology," below). Following initial binding, fusion, and internalization of the nucleic acid contents of virions into the target cell, incompletely reverse-transcribed DNA intermediates are labile in quiescent cells and do not integrate efficiently into the host cell genome unless cellular activation occurs shortly after infection. Furthermore, some degree of activation of the host cell is required for the initiation of transcription of the integrated proviral DNA into either genomic RNA or mRNA. This latter process may not necessarily be associated with the detectable expression of the classic cell-surface markers of activation. In this regard, activation of HIV expression from the latent state depends on the interaction of a number of cellular and viral factors. Following transcription, HIV mRNA is translated into proteins that undergo modification through glycosylation, myristoylation, phosphorylation, and cleavage. The viral particle is formed by the assembly of HIV proteins, enzymes, and genomic RNA at the plasma membrane of the cells. Budding of the progeny virion through the lipid bilayer of the host cell membrane is the point at which the core acquires its external envelope and where the host restriction factor tetherin can inhibit the release of budding particles. Tetherin is an IFN-induced type II transmembrane protein that interferes with virion detachment, although the HIV accessory protein Vpu counteracts this effect through direct interactions with tetherin. During or soon after budding, the virally encoded protease catalyzes the cleavage of the gag-pol precursor to yield the mature virion. Progression through the virus replication cycle is profoundly influenced by a variety of viral regulatory gene products. Likewise, each point in the replication cycle of HIV is a real or potential target for therapeutic intervention. Thus far, the reverse transcriptase, protease, and integrase enzymes as well as the process of virus–target cell binding and fusion have proved to be susceptible to pharmacologic disruption.

HIV GENOME

Figure 197-5 illustrates schematically the arrangement of the HIV genome. Like other retroviruses, HIV-1 has genes that encode the structural proteins of the virus: *gag* encodes the proteins that form the core of the virion (including p24 antigen); *pol* encodes the enzymes responsible for protease processing of viral proteins, reverse transcription, and integration; and *env* encodes the envelope glycoproteins. However, HIV-1 is more complex than other retroviruses, particularly those of the nonprimate group, in that it also contains at least six other regulatory genes (*tat*, *rev*, *nef*, *vif*, *vpr*, and *vpu*), which code for proteins involved in the modification of the host cell to enhance virus growth and the regulation of viral gene expression. Several of these proteins are thought to play a role in the pathogenesis of HIV disease; their various functions are listed in Fig. 197-5. Flanking these genes are the long terminal repeats (LTRs), which contain regulatory elements involved in gene expression (Fig. 197-5). The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the *vpu* gene and has a *vpx* gene not contained in HIV-1.

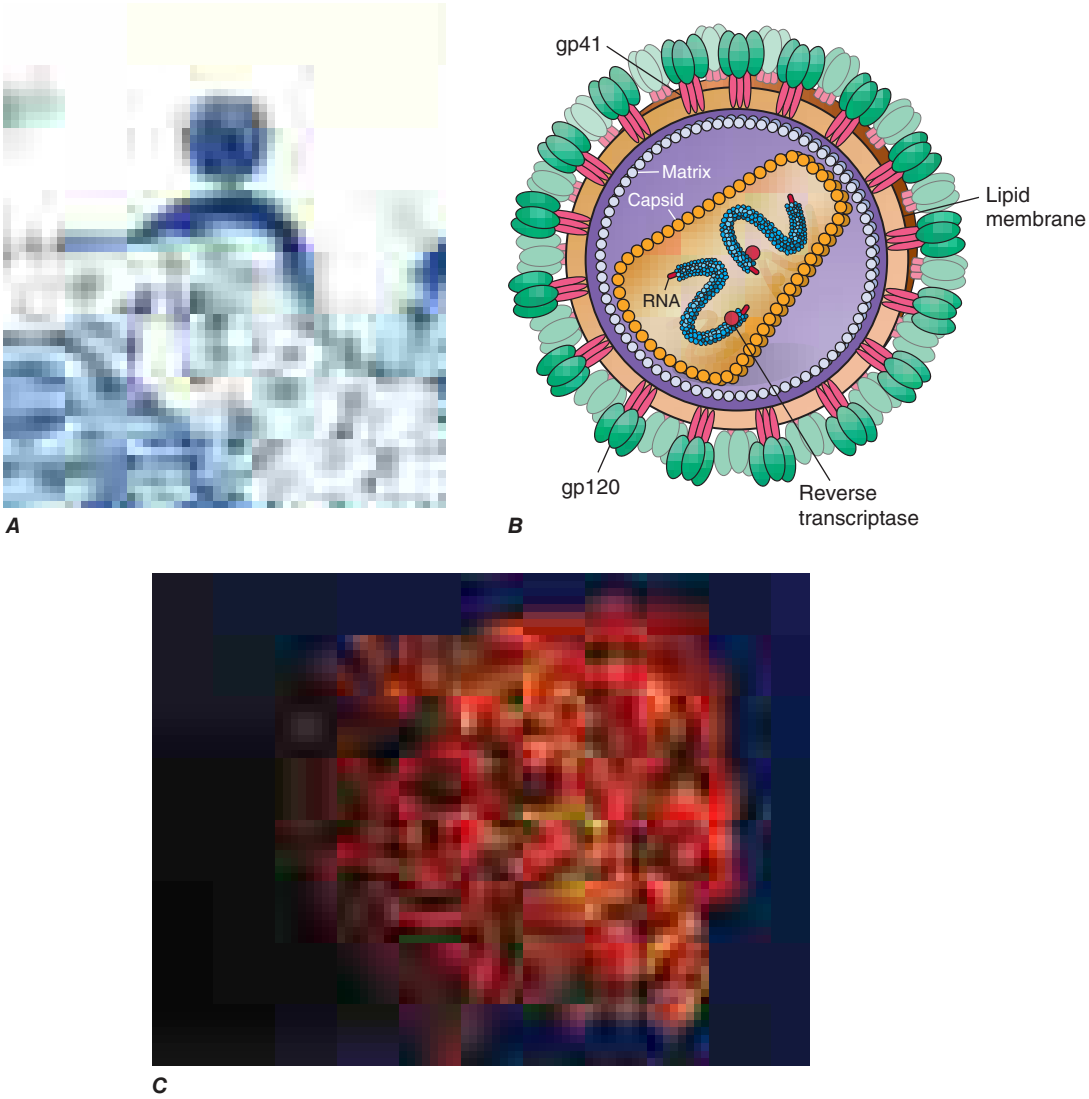


FIGURE 197-2 ***A.*** Electron micrograph of HIV. Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. ***B.*** Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). *(Copyright by George V. Kelvin.) (Adapted from RC Gallo: Sci Am 256:46, 1987.)* ***C.*** Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 20,000× magnification. Cell is approximately 10 microns in diameter, and the HIV particles are approximately 120 nanometers. *(Courtesy of Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases; with permission.)*

MOLECULAR HETEROGENEITY OF HIV-1

Molecular analyses of HIV isolates reveal varying levels of sequence diversity over all regions of the viral genome. For example, the degree of difference in the coding sequences of the viral envelope protein ranges from a few percent (very close, among isolates from the same infected individual) to more than 50% (extreme diversity, between isolates from the different groups of HIV-1: M, N, O, and P). The changes tend to cluster in hypervariable regions. HIV can evolve by several means, including simple base substitution, insertions and deletions, recombination, and gain and loss of glycosylation sites. HIV sequence diversity arises directly from the limited fidelity of the reverse transcriptase, i.e., a tendency toward copying errors. The balance of immune pressure and functional constraints on proteins influences the regional level of variation within proteins. For example, Envelope, which is exposed on the surface of the virion and is under immune selective pressure from both antibodies and cytolytic T lymphocytes, is extremely variable, with clusters of mutations in hypervariable domains. In contrast, reverse transcriptase, with important enzymatic functions, is relatively conserved, particularly around the active site. The extraordinary variability of HIV-1 contrasts markedly with the relative stability of HTLV-1 and 2.

The four groups (M, N, O and P) of HIV-1 are the result of four separate chimpanzee-to-human (or possibly gorilla-to-human for groups O and P) transfers. Group M (major), which is responsible for most of the infections in the world, has diversified into subtypes and intersubtype recombinant forms, due to "sub-epidemics" within humans after one of those transfers.

Among primate lentiviruses, HIV-1 is most closely related to viruses isolated from chimpanzees and gorillas (Fig. 197-1). The chimpanzee subspecies *Pan troglodytes troglodytes* has been established to be the natural reservoir of the HIV-1 M and N groups. The rare viruses of the HIV-1 O and P groups are most closely related to viruses found in Cameroonian gorillas. The M group comprises nine subtypes, or *clades*, designated A, B, C, D, F, G, H, J, and K, as well as more than 90 known circulating recombinant forms (CRFs) and numerous unique recombinant forms. Intersubtype recombinants are generated by infection of an individual with two subtypes that then recombine and create a virus with a selective advantage. These CRFs range from highly prevalent forms such as CRF01_AE, common in southeast Asia, and CRF02_AG from west and central Africa, to a large number of CRFs that are relatively rare, either because they are of a more recent origin (newly recombined) or because they have not broken out into a major population. The subtypes and CRFs create the major lineages of the M group of HIV-1. HIV-1 M group subtype C dominates the global pandemic, and although there is much speculation that it is more transmissible than other subtypes, solid data on variations in transmissibility

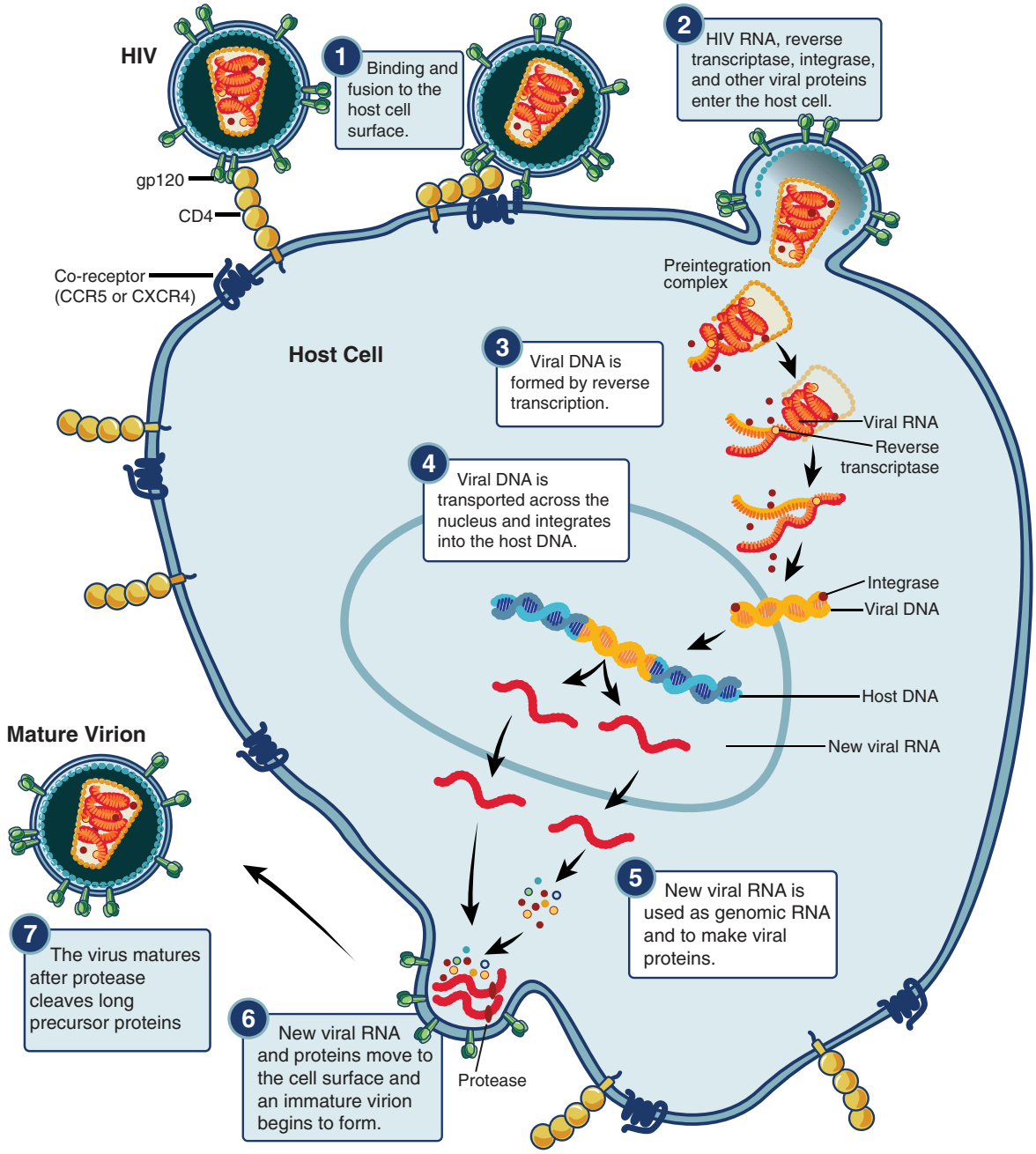


FIGURE 197-3 The replication cycle of HIV. See text for description. *(From the National Institute of Allergy and Infectious Diseases.)*

between subtypes are lacking. Human population densities, access to prevention and treatment, prevalence of genital ulcers, iatrogenic transmissions, and other confounding host factors are all possible reasons why one subtype has spread more than another.

Figure 197-6 schematically diagrams the worldwide distribution of HIV-1 subtypes by region. Nine strains account for the vast majority of HIV infections globally: HIV-1 subtypes A, B, C, D, F, G and three of the CRFs, CRF01_AE, CRF02_AG, and CRF07_BC. Subtype C viruses (of the M group) are by far the most common form worldwide, likely accounting for ~50% of prevalent infections worldwide. In sub-Saharan Africa, home to approximately two-thirds of all individuals living with HIV/AIDS, most infections are caused by subtype C, with smaller proportions of infections caused by subtype A, subtype D, CRF02_AG, and other subtypes and recombinants. In South Africa, the country with the largest number of prevalent infections (7.1 million in 2016), >98% of the HIV-1 isolates sequenced are of subtype C. In Asia, HIV-1 isolates of the CRF01_AE lineage and subtypes B and C predominate. CRF01_AE accounts for most infections in south and southeast Asia, while >95% of infections in India, home to an estimated 2.1 million HIV-infected individuals, are of subtype C (see "HIV Infection and AIDS Worldwide," below). Subtype B viruses are the overwhelmingly predominant viruses seen in the United States, Canada, certain countries in South America, western Europe, and Australia. It is thought that, purely by chance, subtype B was seeded into the United States and Europe in the late 1970s, thereby establishing an overwhelming founder effect. Many countries have co-circulating viral subtypes that are giving rise to new CRFs. Sequence analyses of HIV-1 isolates from infected individuals indicate that recombination among viruses of different clades likely occurs when an individual is infected with viruses of more than one subtype, particularly in geographic areas where subtypes overlap, and more often in sub-epidemics driven by IV drug use than in those driven by sexual transmission.

The extraordinary diversity of HIV, reflected by the presence of multiple subtypes, circulating recombinant forms, and continuous viral evolution, has implications for possible differential rates of transmission, rates of disease progression, and the development of resistance to antiretroviral drugs. This diversity may also prove to be a formidable obstacle to HIV vaccine development, as a broadly useful vaccine would need to induce protective responses against a wide range of viral strains.

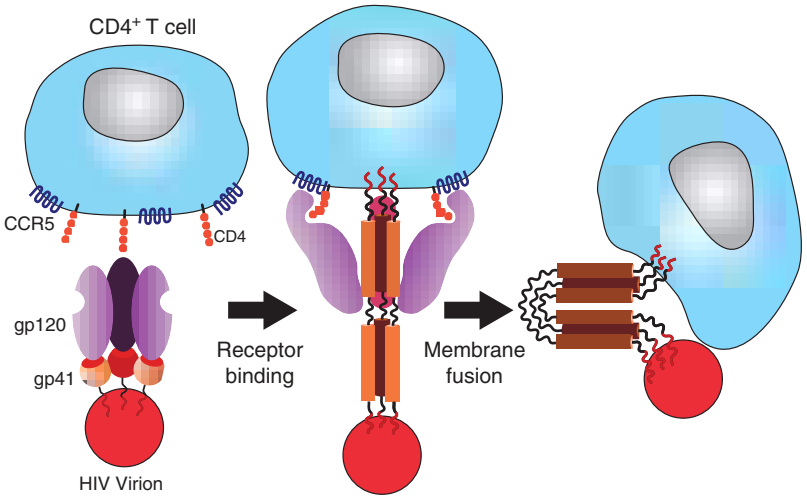


FIGURE 197-4 Binding and fusion of HIV-1 with its target cell. HIV-1 binds to its target cell via the CD4 molecule, leading to a conformational change in the gp120 molecule that allows it to bind to the co-receptor CCR5 (for R5-using viruses). The virus then firmly attaches to the host cell membrane in a coiled-spring fashion via the newly exposed gp41 molecule. Virus-cell fusion occurs as the transitional intermediate of gp41 undergoes further changes to form a hairpin structure that draws the two membranes into close proximity (see text for details). *(Adapted from D Montefiori, JP Moore: Science 283:336, 1999; with permission.)*

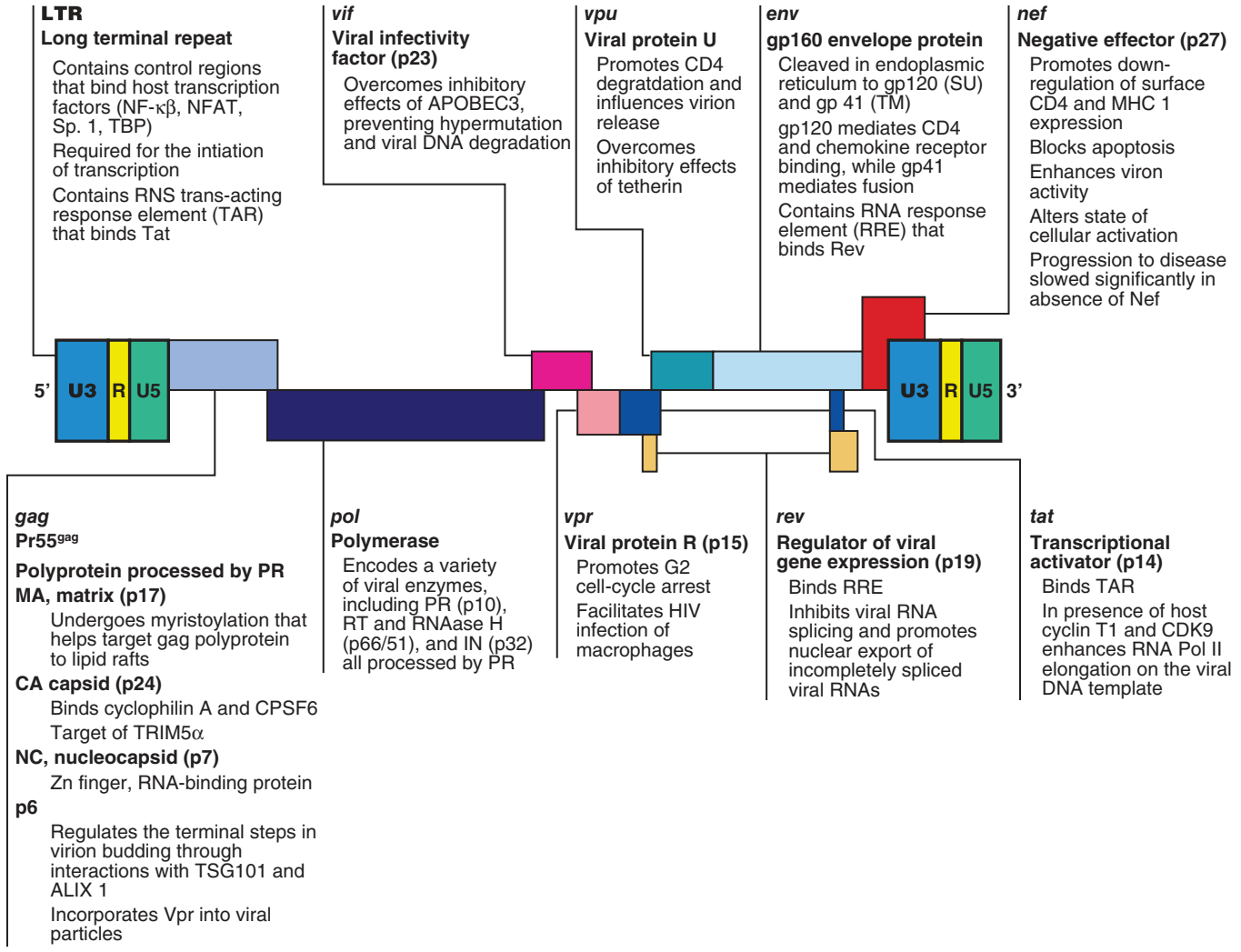


FIGURE 197-5 Organization of the genome of the HIV provirus together with a summary description of its 9 genes encoding 15 proteins. *(Adapted from WC Greene, BM Peterlin: Nat Med 8:673, 2002.)*

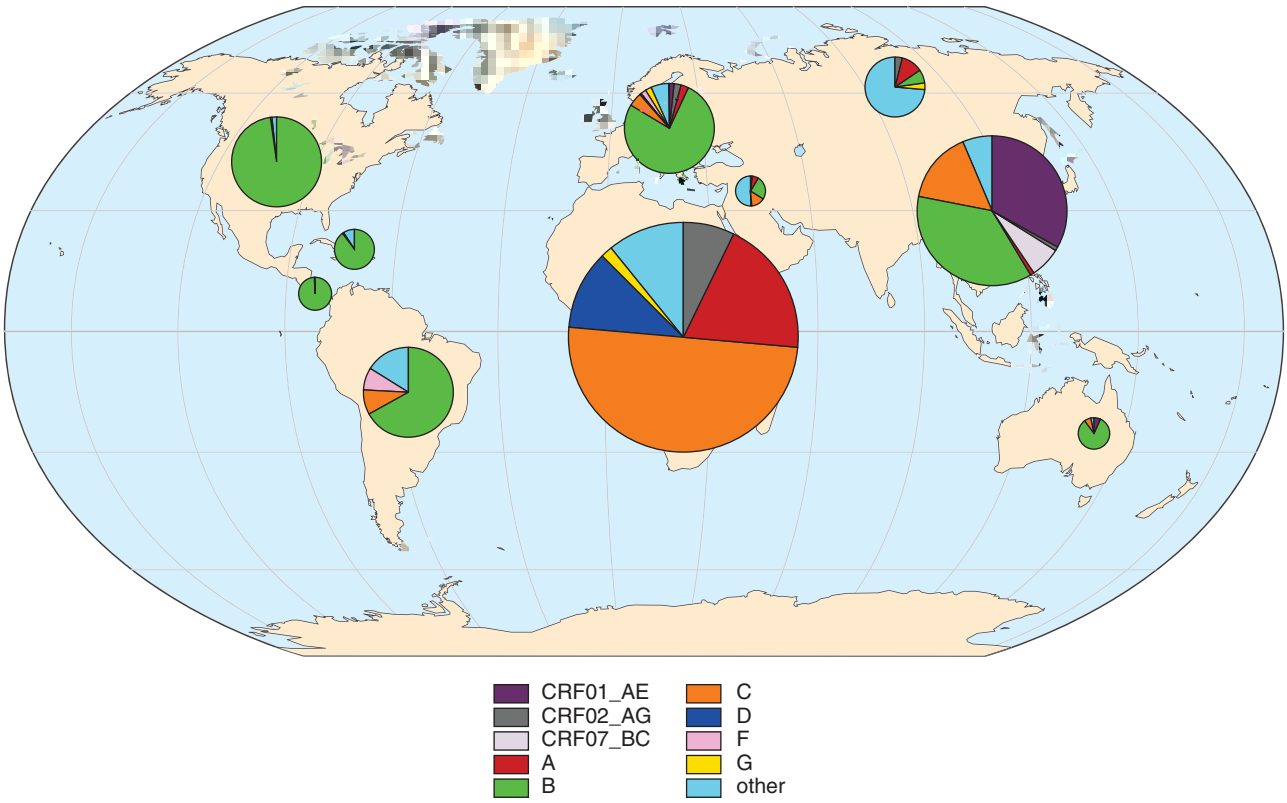


FIGURE 197-6 Global geographic distribution of HIV-1 subtypes and recombinant forms. Distributions derived from relative frequency of subtypes among >710,000 HIV genomic sequences in the Los Alamos National Laboratory HIV Sequence Database. (Additional information available at *www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp*.)

TRANSMISSION

HIV is transmitted primarily by sexual contact (both heterosexual and male to male); by blood and blood products; and by infected mothers to infants intrapartum, perinatally, or via breast milk. After more than 35 years of experience and observations, there is no evidence that HIV is transmitted by any other modality. Table 197-3 lists the estimated risk of HIV transmission for various types of exposures.

TABLE 197-3 Estimated Per-Act Probability of Acquiring HIV From an Infected Source, By Exposure Act

TYPE OF EXPOSURE	RISK PER 10,000 EXPOSURES
Parenteral	
Blood transfusion	9250
Needle-sharing during injection drug use	63
Percutaneous (needle-stick)	23
Sexual	
Receptive anal intercourse	138
Insertive anal intercourse	11
Receptive penile-vaginal intercourse	8
Insertive penile-vaginal intercourse	4
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Other[a]	
Biting	Negligible
Spitting	Negligible
Throwing body fluids (including semen or saliva)	Negligible
Sharing sex toys	Negligible

[a]HIV transmission through these exposure routes is technically possible but unlikely and not well documented.

Sources: CDC, *www.cdc.gov/hiv/risk/estimates/riskbehaviors.html*; P Patel: AIDS 28:1509, 2014.

SEXUAL TRANSMISSION

HIV infection is predominantly a sexually transmitted infection (STI) worldwide. By far the most common mode of infection, particularly in developing countries, is heterosexual transmission, although in many western countries male-to-male sexual transmission dominates. Although a wide variety of factors including viral load and the presence of ulcerative genital diseases influence the efficiency of heterosexual transmission of HIV, such transmission is generally inefficient. A recent systemic review found a low per-act risk of heterosexual transmission in the absence of antiretrovirals: 0.04% for female-to-male transmission and 0.08% for male-to-female transmission during vaginal intercourse in the absence of antiretroviral therapy or condom use (Table 197-3).

HIV has been demonstrated in seminal fluid both within infected mononuclear cells and in cell-free material. The virus appears to concentrate in the seminal fluid, particularly in situations where there are increased numbers of lymphocytes and monocytes in the fluid, as seen in genital inflammatory states such as urethritis and epididymitis, conditions closely associated with other STIs. The virus has also been demonstrated in cervical smears and vaginal fluid. There is an elevated risk of HIV transmission associated with unprotected receptive anal intercourse (URAI) among both men and women compared to the risk associated with unprotected receptive vaginal intercourse. Although data are limited, the per-act risk for HIV transmission via URAI has been estimated to be ~1.4% (Table 197-3). The risk of HIV acquisition associated with URAI is higher than that seen in penile-vaginal intercourse probably because only a thin, fragile rectal mucosal membrane separates the deposited semen from potentially susceptible cells in and beneath the mucosa, and micro-trauma of the mucosal membrane has been associated with anal intercourse. Anal douching and sexual practices that traumatize the rectal mucosa also increase the likelihood of infection. It is likely that anal intercourse provides at least two modalities of infection: (1) direct inoculation into blood in cases of traumatic tears in the mucosa; and (2) infection of susceptible target

cells, such as Langerhans cells, in the mucosal layer in the absence of trauma. Insertive anal intercourse also confers an increased risk of HIV acquisition compared to insertive vaginal intercourse in the receptive partner since the vaginal mucosa is several layers thicker than the rectal mucosa and less likely to be traumatized during intercourse. Nonetheless, the virus can be transmitted to either partner through vaginal intercourse. As noted in Table 197-3, male-to-female HIV transmission is more efficient than female-to-male transmission. The differences in reported transmission rates between men and women may be due in part to the prolonged exposure to infected seminal fluid of the vaginal and cervical mucosa, as well as the endometrium (when semen enters through the cervical os). By comparison, the penis and urethral orifice of the uninfected male partner are exposed relatively briefly to infected vaginal fluid. Among various cofactors examined in studies of heterosexual HIV transmission, the presence of other STIs has been strongly associated with HIV transmission. In this regard, there is a close association between genital ulcerations and transmission, owing to both susceptibility to infection and infectivity. Infections with microorganisms such as *Treponema pallidum* **(Chap. 177)**, *Haemophilus ducreyi* **(Chap. 152)**, and herpes simplex virus (HSV; **Chap. 187**) are important causes of genital ulcerations linked to transmission of HIV. In addition, pathogens responsible for non-ulcerative inflammatory STIs such as those caused by *Chlamydia trachomatis* **(Chap. 184)**, *Neisseria gonorrhoeae* **(Chap. 151)**, and *Trichomonas vaginalis* **(Chap. 224)** also are associated with an increased risk of transmission of HIV infection. Bacterial vaginosis, an infection related to sexual behavior, but not strictly an STI, also may be linked to an increased risk of transmission of HIV infection. Several studies suggest that treating other STIs and genital tract syndromes may help prevent transmission of HIV. This effect is most prominent in populations in which the prevalence of HIV infection is relatively low. It is noteworthy that this principle may not apply to the treatment of HSV infections since it has been shown that even following anti-HSV therapy with resulting healing of HSV-related genital ulcers, HIV acquisition is not reduced. Biopsy studies revealed that the likely explanation is that HIV receptor–positive inflammatory cells persisted in the genital tissue despite the healing of ulcers, and so HIV-susceptible targets remained at the site.

The quantity of HIV-1 in plasma (viral load) is a primary determinant of the risk of HIV-1 transmission. In a cohort of heterosexual couples in Uganda discordant for HIV infection and not receiving antiretroviral therapy, the mean serum HIV RNA level was significantly higher among HIV-infected subjects whose partners seroconverted than among those whose partners did not seroconvert. In fact, transmission was rare when the infected partner had a plasma level of <1700 copies of HIV RNA per milliliter, even when genital ulcer disease was present **(Fig. 197-7)**. The rate of HIV transmission per coital act was highest during the early stage of HIV infection when plasma HIV RNA levels were high and in advanced disease with high viral set points.

Antiretroviral therapy dramatically reduces plasma viremia in most HIV-infected individuals (see "Treatment," below) and is associated with a dramatic reduction in risk of transmission. In a large study of serodiscordant couples, earlier treatment of the HIV-infected partner with antiretroviral therapy rather than treatment delayed until the CD4+ T cell counts fell below 250 cells per μL was associated with a 96% reduction in HIV transmission to the uninfected partner. This approach has been widely referred to as *treatment as prevention* or TasP. Recent cohort studies have indicated that if the viral load of the infected partner is decreased to below detectable levels by antiretroviral therapy, there is essentially no chance of sexual transmission to the uninfected partner.

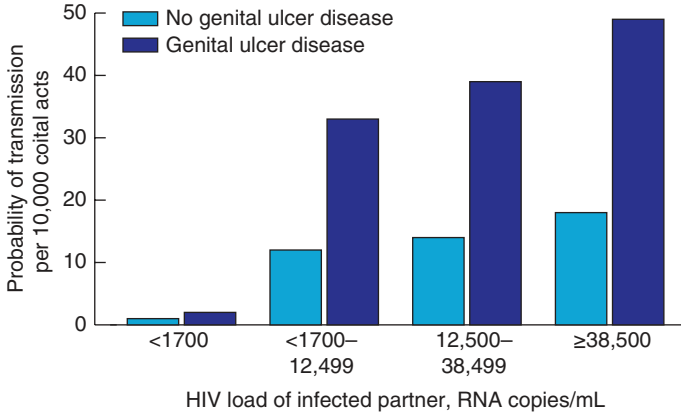


FIGURE 197-7 Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. *(From RH Gray et al: Lancet 357:1149, 2001.)*

A number of studies including large, randomized, controlled trials clearly have indicated that male *circumcision* is associated with a lower risk of acquisition of HIV infection for heterosexual men. Studies also suggest that circumcision is protective in those men who have sex with men who are insertive only. The benefit of circumcision may be due to increased susceptibility of uncircumcised men to ulcerative STIs, as well as to other factors such as microtrauma to the foreskin and glans penis. In addition, the highly vascularized inner layer of foreskin tissue contains a high density of Langerhans cells as well as increased numbers of CD4+ T cells, macrophages, and other cellular targets for HIV. Finally, the moist environment under the foreskin may promote the presence or persistence of microbial flora that, via inflammatory changes, may lead to even higher concentrations of target cells for HIV in the foreskin. In addition, randomized clinical trials have demonstrated that male circumcision also reduces herpes simplex virus (HSV) type 2, human papillomavirus virus (HPV), and genital ulcer disease in men as well as HPV, genital ulcer disease, bacterial vaginosis, and *Trichomonas vaginalis* infections among female partners of circumcised men. Thus, there may be an added indirect benefit of diminution of risk for HIV acquisition to the female sexual partners of circumcised men.

In some studies the use of oral contraceptives was associated with an increase in incidence of HIV infection over and above that which might be expected by not using a condom for birth control. This phenomenon may be due to drug-induced changes in the cervical mucosa, rendering it more vulnerable to penetration by the virus. Adolescent girls might also be more susceptible to infection upon exposure due to the properties of an immature genital tract with increased cervical ectopy or exposed columnar epithelium.

Oral sex is a much less efficient mode of transmission of HIV than is anal intercourse or vaginal intercourse (Table 197-3). A number of studies have reported that the incidence of transmission of infection by oral sex among couples discordant for HIV was extremely low. However, there have been well-documented reports of HIV transmission that likely resulted from fellatio or cunnilingus. Therefore, the assumption that oral sex is completely safe is not warranted.

The association of alcohol consumption and illicit drug use with unsafe sexual behavior, both homosexual and heterosexual, leads to an increased risk of sexual transmission of HIV. Methamphetamine and other so-called club drugs (e.g., MDMA, ketamine, and gamma hydroxybutyrate), sometimes taken in conjunction with PDE-5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra), have been associated with risky sexual practices and increased risk of HIV infection, particularly among men who have sex with men.

TRANSMISSION THROUGH INJECTION DRUG USE

HIV can be transmitted to injection drug users (IDUs) who are exposed to HIV while sharing injection paraphernalia such as needles, syringes, the water in which drugs are mixed, or the cotton through which drugs are filtered. Parenteral transmission of HIV during injection drug use does not require IV puncture; subcutaneous ("skin popping") or intramuscular ("muscling") injections can transmit HIV as well, even though these behaviors are sometimes erroneously perceived as low-risk. Among IDUs, the risk of HIV infection increases with the duration of injection drug use; the frequency of needle sharing; the number of partners with whom paraphernalia are shared, particularly in the setting of "shooting galleries" where drugs are sold and large numbers of IDUs may share a limited number of "works"; comorbid psychiatric conditions such as antisocial personality disorder; the use of cocaine in

injectable form or smoked as "crack"; and the use of injection drugs in a geographic location with a high prevalence of HIV infection. As noted in Table 197-3, the per-act risk of transmission from injection drug use with a contaminated needle has been estimated to be approximately 0.6%.

TRANSMISSION BY TRANSFUSED BLOOD AND BLOOD PRODUCTS

HIV can be transmitted to individuals who receive HIV-contaminated blood transfusions, blood products, or transplanted tissue. The vast majority of HIV infections acquired via contaminated blood transfusions, blood components, or transplanted tissue in resource-rich countries occurred prior to the spring of 1985, when mandatory testing of donated blood for HIV-1 was initiated. It is estimated that >90% of individuals exposed to HIV-contaminated blood products become infected (Table 197-3). Transfusions of whole blood, packed red blood cells, platelets, leukocytes, and plasma are all capable of transmitting HIV infection. In contrast, hyperimmune gamma globulin, hepatitis B immune globulin, plasma-derived hepatitis B vaccine, and Rh_o immune globulin have not been associated with transmission of HIV infection. The procedures involved in processing these products either inactivate or remove the virus.

Currently, in the United States and in most developed countries, the following measures have made the risk of transmission of HIV infection by transfused blood or blood products extremely small: the screening of blood donations for antibodies to HIV-1 and HIV-2 and determination of the presence of HIV nucleic acid usually in minipools of several specimens; the careful selection of potential blood donors with health history questionnaires to exclude individuals with risk behavior; and opportunities for self-deferral and the screening out of HIV-negative individuals with serologic testing for infections that have shared risk factors with HIV, such as hepatitis B and C and syphilis. The chance of infection of a hemophiliac via clotting factor concentrates has essentially been eliminated because of standard screening of blood together with the added layer of safety resulting from heat treatment of the concentrates. It is currently estimated that the risk of infection with HIV in the United States via transfused screened blood is approximately 1 in 1.5 million units. Therefore, since nearly 21 million blood components are transfused in the United States each year, despite the best efforts of science, one cannot completely eliminate the risk of transfusion-related transmission of HIV. In this regard, a case of transfusion-related transmission of HIV was reported in the United States in 2010, which was tracked to a blood donation in 2008; this was the first such reported case since 2002 and only the third in that decade. Transmission of HIV (both HIV-1 and HIV-2) by blood or blood products is still an ongoing threat in certain developing countries where routine screening of blood is not universally practiced. In 2013, 108 out of 167 countries (65%) had specific legislation covering the safety and quality of blood transfusion, including 79% of high-income countries, 64% of middle-income countries, and 41% of low-income countries. Furthermore, there have been reports in certain countries of sporadic breakdowns in routinely available screening procedures in which contaminated blood was allowed to be transfused, resulting in small clusters of patients becoming infected.

OCCUPATIONAL TRANSMISSION OF HIV: HEALTH CARE WORKERS, LABORATORY WORKERS, AND THE HEALTH CARE SETTING

There is a small but definite occupational risk of HIV transmission to health care workers and laboratory personnel and potentially others who work with HIV-containing materials, particularly when sharp objects are used. An estimated 600,000 to 800,000 health care workers are stuck with needles or other sharp medical instruments in the United States each year. The global number of HIV infections among health care workers attributable to sharps injuries has been estimated to be 1000 cases (range, 200–5000) per year. In the United States, 58 documented cases of occupational HIV transmission to health care workers, and 150 possible transmissions have been reported by the CDC. There have been no confirmed cases reported since 1999.

Exposures that place a health care worker at potential risk of HIV infection are percutaneous injuries (e.g., a needle stick or cut with a sharp object) or contact of mucous membrane or nonintact skin (e.g., exposed skin that is chapped, abraded, or afflicted with dermatitis) with blood, tissue, or other potentially infectious body fluids. Large, multi-institutional studies have indicated that the risk of HIV transmission following skin puncture from a needle or a sharp object that was contaminated with blood from a person with documented HIV infection is ~0.23% and after a mucous membrane exposure it is 0.09% (see "HIV and the Health Care Worker," below) if the injured and/or exposed person is not treated within 24 h with antiretroviral drugs. The risk of hepatitis B virus (HBV) infection following a similar type of exposure is ~6–30% in nonimmune individuals; if a susceptible worker is exposed to HBV, postexposure prophylaxis with hepatitis B immune globulin and initiation of HBV vaccine is >90% effective in preventing HBV infection. The risk of HCV infection following percutaneous injury is ~1.8% **(Chap. 332)**.

Rare HIV transmission after nonintact skin exposure has been documented, but the average risk for transmission by this route has not been precisely determined; however, it is estimated to be less than the risk for mucous membrane exposure. Transmission of HIV through intact skin has not been documented. Currently in developed countries, virtually all puncture wounds and mucous membrane exposures in health care workers involving blood from a patient with documented HIV infection are treated prophylactically with combination antiretroviral therapy (cART). This practice, referred to as *postexposure prophylaxis* or PEP, has dramatically reduced the occurrence of puncture-related transmissions of HIV to health care workers.

In addition to blood and visibly bloody body fluids, semen and vaginal secretions also are considered potentially infectious; however, they have not been implicated in occupational transmission from patients to health care workers. The following fluids also are considered potentially infectious: cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid. The risk for transmission after exposure to fluids or tissues other than HIV-infected blood also has not been quantified, but it is probably considerably lower than the risk after blood exposures. Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered potentially infectious for HIV unless they are visibly bloody. Rare cases of HIV transmission via human bites have been reported, but not in the setting of occupational exposure.

An increased risk for HIV infection following percutaneous exposures to HIV-infected blood is associated with exposures involving a relatively large quantity of blood, as in the case of a device visibly contaminated with the patient's blood, a procedure that involves a hollow-bore needle placed directly in a vein or artery, or a deep injury. Factors that might be associated with mucocutaneous transmission of HIV include exposure to an unusually large volume of blood and prolonged contact. In addition, the risk increases for exposures to blood from untreated patients with high levels of HIV in the blood. Since the beginning of the HIV epidemic, there have been rare instances where transmission of infection from a health care worker to patients seemed highly probable. Despite these small number of documented cases, the risk of HIV transmission involving health care workers (infected or not) to patients is extremely low in developed countries—in fact, too low to be measured accurately. In this regard, several retrospective epidemiologic studies have been performed tracing thousands of patients of HIV-infected dentists, physicians, surgeons, obstetricians, and gynecologists, and no other cases of HIV transmission that could be linked to the health care providers were identified.

Breaches in infection control and the reuse of contaminated syringes, failure to properly sterilize surgical instruments, and/or hemodialysis equipment also have resulted rarely in the transmission of HIV from patient to patient in hospitals, nursing homes, and outpatient settings. Finally, these very rare occurrences of transmission of HIV as well as HBV and HCV to and from health care workers in the workplace underscore the importance of the use of universal precautions when caring for all patients (see below and **Chap. 137**).

MOTHER-TO-CHILD TRANSMISSION OF HIV

HIV infection can be transmitted from an infected mother to her fetus during pregnancy, during delivery, or by breast-feeding. This remains an important form of transmission of HIV infection in some developing countries. Virologic analyses of aborted fetuses indicate that HIV can be transmitted to the fetus during the first or second trimesters of pregnancy. However, maternal transmission to the fetus occurs most commonly in the perinatal period. Two studies performed in Rwanda and the Democratic Republic of Congo (then called Zaire) indicated that among all mother-to-child transmissions of HIV, the relative proportions were 23–30% before birth, 50–65% during birth, and 12–20% via breast-feeding.

In the absence of antiretroviral therapy for the mother during pregnancy, labor, and delivery, and for the fetus prophylactically following birth, the probability of transmission of HIV from mother to infant/fetus ranges from 15% to 25% in industrialized countries and from 25% to 35% in developing countries. These differences may relate to the adequacy of prenatal care as well as to the stage of HIV disease and the general health of the mother during pregnancy. Higher rates of transmission have been reported to be associated with many factors—the best documented of which is the presence of high maternal levels of plasma viremia, with the risk increasing linearly with the level of maternal plasma viremia. It is very unlikely that mother-to-child transmission will occur if the mother's level of plasma viremia is <1000 copies of HIV RNA/mL of blood and extremely unlikely if the level is undetectable (i.e., <50 copies/mL). However, there may not be a lower "threshold" below which transmission never occurs, since certain studies have reported rare transmission by women with viral RNA levels <50 copies/mL. Increased mother-to-child transmission is also correlated with closer human leukocyte antigen (HLA) match between mother and child. A prolonged interval between membrane rupture and delivery is another well-documented risk factor for transmission. Other conditions that are potential risk factors, but that have not been consistently demonstrated, are the presence of chorioamnionitis at delivery; STIs during pregnancy; illicit drug use during pregnancy; cigarette smoking; preterm delivery; and obstetric procedures such as amniocentesis, amnioscopy, fetal scalp electrodes, and episiotomy. Today, the rate of mother-to-child transmission has fallen to 1% or less in pregnant women who are receiving cART for their HIV infection. Such treatment, combined with cesarean section delivery, has rendered mother-to-child transmission of HIV an unusual event in the United States and other developed nations. In this regard, both the United States Public Health Service and the World Health Organization guidelines recommend that all pregnant HIV-infected women should receive life-long cART for the health of the mother and to prevent perinatal transmission regardless of plasma HIV RNA copy number or CD4+ T cell counts.

Breast-feeding is an important modality of transmission of HIV infection in certain developing countries, particularly where mothers continue to breast-feed for prolonged periods. The risk factors for mother-to-child transmission of HIV via breast-feeding include detectable levels of HIV in breast milk, the presence of mastitis, low maternal CD4+ T cell counts, and maternal vitamin A deficiency. The risk of HIV infection via breast-feeding is highest in the early months of breast-feeding. In addition, exclusive breast-feeding has been reported to carry a lower risk of HIV transmission than mixed feeding. In developed countries, breast feeding of babies by an HIV-infected mother is contraindicated since alternative forms of adequate nutrition, i.e., formulas, are readily available. In developing countries, where breast-feeding may be essential for the overall health of the infant, the continuation of cART in the infected mother during the period of breastfeeding markedly diminishes the risk of transmission of HIV to the infant. In fact, once cART has been initiated in a pregnant woman, it should be continued for life.

TRANSMISSION OF HIV BY OTHER BODY FLUIDS

Although HIV can be isolated typically in low titers from saliva of a small proportion of infected individuals, there is no convincing evidence that saliva can transmit HIV infection, either through kissing or through other exposures, such as occupationally to health care workers. Saliva contains endogenous antiviral factors; among these factors, HIV-specific immunoglobulins of IgA, IgG, and IgM isotypes are detected readily in salivary secretions of infected individuals. It has been suggested that large glycoproteins such as mucins and thrombospondin 1 sequester HIV into aggregates for clearance by the host. In addition, a number of soluble salivary factors inhibit HIV to various degrees in vitro, probably by targeting host cell receptors rather than the virus itself. Perhaps the best studied of these, secretory leukocyte protease inhibitor (SLPI), blocks HIV infection in several cell culture systems, and it is found in saliva at levels that approximate those required for inhibition of HIV in vitro. In this regard, higher salivary levels of SLPI in breast-fed infants were associated with a decreased risk of HIV transmission through breast milk. It has also been suggested that submandibular saliva reduces HIV infectivity by stripping gp120 from the surface of virions, and that saliva-mediated disruption and lysis of HIV-infected cells occurs because of the hypotonicity of oral secretions. There have been outlier cases of suspected transmission by saliva, but these have probably been blood-to-blood transmissions. Transmission of HIV by a human bite can occur but is a rare event. Although virus can be identified, if not isolated, from virtually any body fluid, there is no evidence that HIV transmission can occur as a result of exposure to tears, sweat, or urine. However, there have been isolated cases of transmission of HIV infection by body fluids that may or may not have been contaminated with blood. Most of these situations occurred in the setting of a close relative providing intensive nursing care for an HIV-infected person without observing universal precautions, underscoring the importance of adhering to such precautions in the handling of body fluids and wastes from HIV-infected individuals.

EPIDEMIOLOGY

HIV INFECTION AND AIDS WORLDWIDE

HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. At the end of 2016, an estimated 36.7 million individuals were living with HIV infection, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). An estimated 95% of people living with HIV/AIDS reside in low- and middle-income countries; ~50% are female, and 2.1 million are children <15 years. The regional distribution of these cases is illustrated in **Fig. 197-8**. The estimated number of people living with HIV—i.e., the global prevalence—has increased more than fourfold since 1990, reflecting the combined effects of continued high rates of new HIV infections and the life-prolonging impact of antiretroviral therapy **(Fig. 197-9)**. In 2016, the global prevalence of HIV infection among people aged 15–49 years was 0.8%, with rates varying widely by country and region as illustrated in **Fig. 197-10**.

In 2016, an estimated 1.8 million new cases of HIV infection occurred worldwide, including 160,000 among children <15 years; about one-third of new infections were among people age 15–24 years. Globally, the majority of new HIV infections are due to heterosexual transmission. Members of certain high-risk populations are disproportionately affected. Sex workers, people who inject drugs, transgender people, prisoners, gay men, other men who have sex with men, and their sexual partners accounted for 34% of all new HIV infections in 2015 **(Fig. 197-11)**.

Between 2000 and 2016, the estimated annual number of new HIV infections globally fell by 40% (Fig. 197-9). These reductions in global HIV incidence likely reflect progress with HIV prevention efforts and the increased provision to HIV-infected people of antiretroviral therapy, which makes them much less likely to transmit the virus to sexual partners. Among adults, the estimated incidence declined by 11% from 2010 to 2016. From 2010 to 2016 there was a ~47% reduction in HIV infections among children <15 years, progress that is due largely to the increasing availability of antiretroviral medications to prevent the transmission of HIV from mother to infant.

In 2016, global AIDS deaths totaled 1.0 million (including 120,000 children <15 years), a 48% decrease since 2005 that coincides with a

FIGURE 197-8 Estimated number of adults and children living with HIV infection as of December, 2016. Total: 36.7 million (30.8 million–42.9 million). *(From Joint United Nations Programme on HIV/AIDS [UNAIDS].)*

rapid expansion of access to antiretroviral therapy **(Fig. 197-12)**. Since the beginning of the pandemic, an estimated 35 million people have died of an AIDS-related illness.

The HIV epidemic has occurred in "waves" in different regions of the world, each wave having somewhat different characteristics depending on the demographics of the country and region in question and the timing of the introduction of HIV into the population. Although the AIDS epidemic was first recognized in the United States and shortly thereafter in Western Europe, it very likely began in sub-Saharan Africa (see above), which has been particularly devastated by the epidemic. East and Southern Africa is the region hardest hit by HIV. The region is home to 6.2% of the world's population but has 19.4 million people living with HIV, >50% of the global total (Fig. 197-8). In eight countries in the region, >10% of the adult population age 15–49 is HIV-infected (Fig. 197-10). South Africa has the highest number of people living with HIV in the world (7.1 million); Swaziland has the highest adult HIV prevalence in the world (27.2%). Among high-risk individuals, rates are much higher than in the general population. HIV prevalence among sex workers varies between 50% and 70% in several countries in the region. Recent data offer promising signs of declining HIV incidence and prevalence in many countries in the region, although frequently at levels that remain high. Heterosexual exposure is the primary mode of HIV transmission in most countries in sub-Saharan Africa. Women and girls account for ~60 percent of all HIV infections in that region.

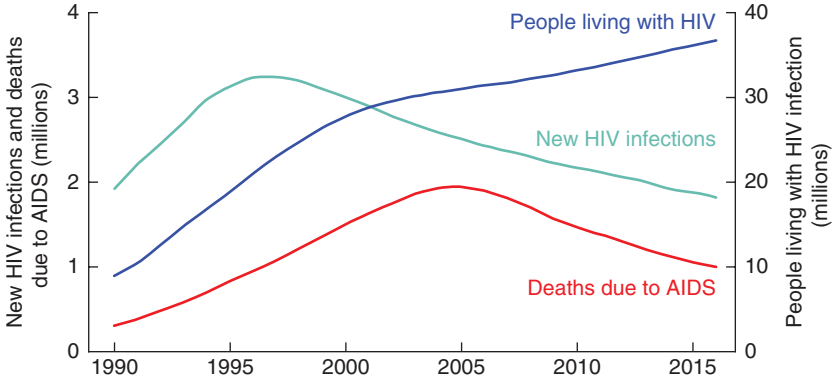


FIGURE 197-9 Global estimates of HIV incidence, AIDS deaths, and HIV prevalence 1990–2016. *(From UNAIDS.)*

The 25 countries of West and Central Africa are home to 6.1 million people living with HIV, of whom half a million are children. HIV prevalence in most of the countries is relatively low compared with East and Southern Africa. HIV prevalence among adults across the region overall stands at 2.2% although there is wide variation between countries, ranging from 0.5% in Niger and Senegal to 4.9% in Equatorial Guinea. An estimated 60% of new infections in the region in 2015 occurred in Nigeria. As in East and Southern Africa, heterosexual transmission accounts for most HIV transmission West and Central Africa.

The Middle East and North Africa region has one of the lowest HIV prevalence rates in the world (0.1%). In 2016, an estimated 230,000 people were living with HIV in the region. Cases are largely concentrated among IDUs, men who have sex with men, and sex workers and their clients.

In Asia and the Pacific, an estimated 5.1 million people were living with HIV at the end of 2016. In this region of the world, HIV prevalence is highest in southeast Asian countries, with wide variation in trends between different countries. Among countries in Asia, only Thailand has an adult seroprevalence rate of >1%. However, the populations of many Asian nations are so large that even low infection and seroprevalence rates result in large numbers of people living with HIV. In this regard, three populous countries—China, India and Indonesia—account for around three-quarters of all people living with HIV in the region. Although the HIV epidemic in Asia has long been concentrated among specific populations—sex workers and their clients, men who have sex with men, and IDUs—it is expanding to the heterosexual partners of those most at risk.

Eastern Europe and Central Asia is the only region in the world where the HIV epidemic continues to expand rapidly, with a >60% increase in annual new HIV infections between 2010 and 2016. The Russian Federation and Ukraine account for the majority of HIV cases in the region, where the epidemic has been driven by injection drug use and increasingly by heterosexual transmission.

Approximately 2.1 million people were living with HIV/AIDS in Latin America and the Caribbean at the end of 2016. The rate of new HIV infections in the region held steady from 2010 to 2016. Brazil is home to the largest number of HIV-infected persons (830,00) in the region, and the Bahamas has the region's highest prevalence (3.3%). Men who have sex with men

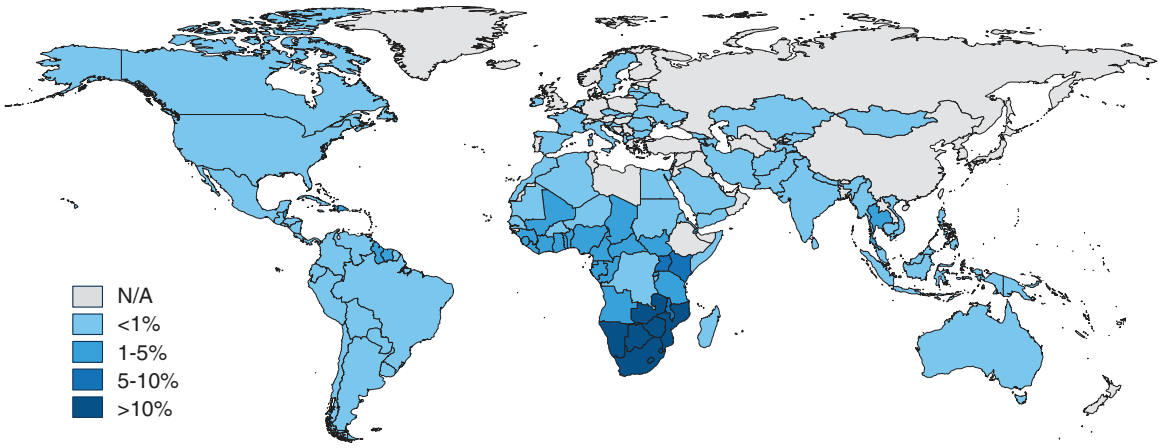


FIGURE 197-10 Adult HIV prevalence rates by country, 2016. Data are estimates for adults age 15–49 years. *(From UNAIDS.)*

account for the largest proportion of HIV infections in Central and South America. In the Caribbean, heterosexual transmission, often tied to sex work, is the main driver of transmission.

Approximately 2.1 million people were living with HIV/AIDS in North America and western and central Europe at the end of 2016. While modes of transmission vary greatly by country, HIV disproportionately affects men who have sex with men. Over the past decade, the number of HIV diagnoses decreased dramatically in all risk groups in western Europe but increased slightly in central Europe. North America saw a decrease in HIV diagnoses overall but a small increase among gay and bisexual men.

HIV INFECTION AND AIDS IN THE UNITED STATES

About 1.8 million people have been infected with HIV in the United States since the beginning of the epidemic, of whom ~693,000 have died. Approximately 1.1 million individuals in the United States are living with HIV infection, ~15% of whom are unaware of their infection, according to recent estimates. As illustrated in **Fig. 197-13**, only about half of HIV-infected people in the United States have been able to negotiate the steps in the HIV "care continuum," from diagnosis, to entering into care and receiving antiretroviral therapy, and ultimately to achieving a suppressed viral load (see "Treatment," below).

More than 60% of people living with HIV in the United States are Black/African American or Hispanic/Latino, and more than half are men who have sex with men. The estimated HIV seroprevalence rate among all individuals age 13 years or older in the United States is ~0.5%. Approximately 2% of Black/African-American adults are HIV-infected in the United States, higher than any other group.

The number of new HIV infections in the United States, *HIV incidence*, peaked at about 130,000 per year in the late 1980s, followed by declines. After remaining stable since the mid-1990s, the estimated number of annual HIV infections in the United States fell ~15% between 2008 and 2015 (from 45,200 to 38,500). The distribution of incident HIV cases in 2015 is shown in **Fig. 197-14**. Gay and bisexual men account for more than two-thirds of incident infections and were the only group that did not experience an overall decline in annual HIV infections from 2008 to 2015. While infections among white gay and bisexual men and men age 15–24 years fell during that period, these declines were offset by increases among 25- to 34-year-old gay and bisexual men, and among Hispanic/Latino gay and bisexual males.

In the United States, the burden of HIV and AIDS is not evenly distributed across states and regions. In most areas of the country, HIV is concentrated in urban areas. In the southern United States, larger percentages of diagnoses are in smaller metropolitan and nonmetropolitan areas. HIV infection and AIDS have disproportionately affected minority populations in the United States in both urban and rural areas. Among those diagnosed with HIV (regardless of stage of infection) in 2016, 44% percent were Blacks/African Americans, a group that constitutes only 12% of the U.S. population. The estimated rate of new HIV diagnoses in 2016 by race/ethnicity per 100,000 population in the United States is shown in **Fig. 197-15**.

Perinatal HIV transmission, from an HIV-infected mother to her baby, has declined significantly in the United States, largely due to the implementation of guidelines for the universal counseling and voluntary HIV testing of pregnant women and the use of antiretroviral therapy for pregnant women and newborn infants to prevent infection. In 2016, 122 children were newly diagnosed with HIV infection in the United States, down from a peak of ~1750 in 1991.

The rate of HIV-related deaths in the United States rose steadily through the 1980s and peaked in 1995. Since then, the HIV death rate has fallen fourfold **(Fig. 197-16)**. This trend is likely due to several factors, including improved prophylaxis and treatment of opportunistic infections, growing experience among the health professions in caring for HIV-infected individuals, improved access to health care, and a decrease in new infections. However, the most influential factor clearly has been the increased use of potent antiretroviral drugs, generally administered in a combination of three or four agents.

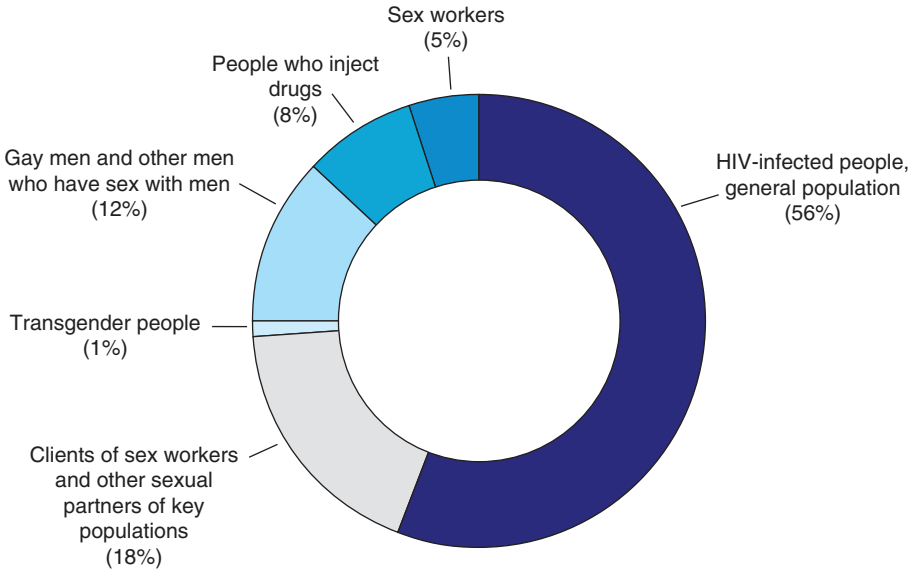


FIGURE 197-11 Global distribution of new HIV infections by population. Data for 2015. *(From UNAIDS.)*

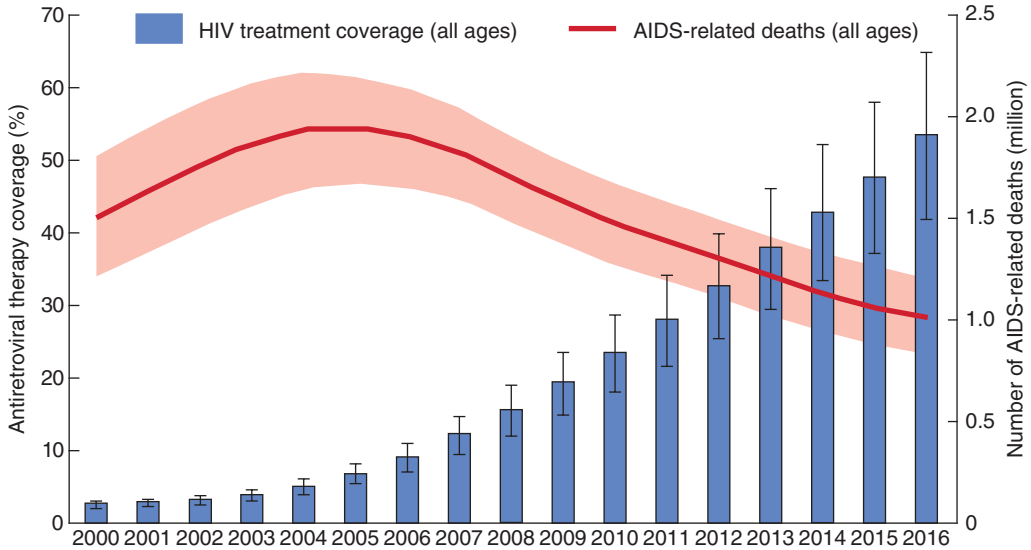


FIGURE 197-12 Global antiretroviral therapy coverage and number of AIDS-related deaths, 2000–2016. *(From UNAIDS).*

PATHOPHYSIOLOGY AND PATHOGENESIS

The hallmark of HIV disease is a profound immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of the subset of T lymphocytes referred to as *helper T cells* occurring in a setting of polyclonal immune activation. The *helper* subset of T cells is defined phenotypically by the presence on its surface of the CD4 molecule **(Chap. 342)**, which serves as the primary cellular receptor for HIV. A co-receptor also must be present together with CD4 for efficient binding, fusion, and entry of HIV-1 into its target cells (Figs. 197-3 and 197-4). HIV-1 uses two major co-receptors, CCR5 and CXCR4, for fusion and entry; these co-receptors are also the primary receptors for certain chemoattractive cytokines termed *chemokines* and belong to the seven-transmembrane-domain G protein–coupled family of receptors. A number of mechanisms responsible for cellular depletion and/or immune dysfunction of CD4+ T cells have been demonstrated in vitro; these include direct infection and destruction of these cells by HIV, as well as indirect effects such as immune clearance of infected cells, cell death associated with aberrant immune activation, and immune exhaustion due to aberrant cellular activation with resulting cellular dysfunction. Patients with CD4+ T cell levels below certain thresholds are at high risk of developing a variety of opportunistic diseases, particularly the infections and neoplasms that are AIDS-defining illnesses. Some features of AIDS, such as Kaposi's sarcoma and certain neurologic abnormalities, cannot be explained completely by the immunodeficiency caused by HIV infection, since these complications may occur prior to the development of severe immunologic impairment.

The combination of viral pathogenic and immunopathogenic events that occurs during the course of HIV disease from the moment of initial (primary) infection through the development of advanced-stage disease is complex and varied. It is important to appreciate that the pathogenic mechanisms of HIV disease are multifactorial and multiphasic and are different at different stages of the disease. Therefore, it is essential to consider the typical clinical course of an untreated HIV-infected individual in order to more fully appreciate these pathogenic events **(Fig. 197-17)**.

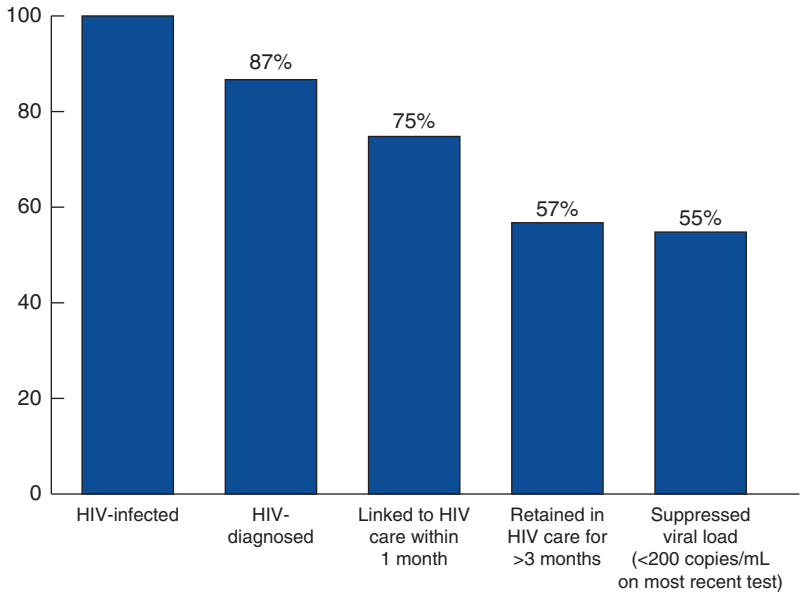


FIGURE 197-13 Estimated percentage of HIV-infected people engaged at selected stages of the continuum of HIV care in the United States. *(From Centers for Disease Control and Prevention [CDC]: HIV Surveillance Supplemental Report 21[No. 7], 2016.)*

EARLY EVENTS IN HIV INFECTION: PRIMARY INFECTION AND INITIAL DISSEMINATION OF VIRUS

Using rectal or vaginal mucosal transmission in nonhuman primates as a model, the earliest events (within hours) that occur following exposure of HIV to the mucosal surface determine whether an infection will be established or aborted as well as the subsequent course of events following infection. Although the mucosal barrier is relatively effective in limiting access of HIV to susceptible targets in the submucosal tissue, the virus can cross the barrier by transport on Langerhans cells, an epidermal type of DC, just beneath the surface or through microscopic rents in the mucosa. Significant disruptions in the mucosal barrier as seen in ulcerative genital disease facilitate viral entry and increase the efficiency of infection. Virus then seeks susceptible targets, which are primarily CD4+ T cells that are spatially dispersed in the mucosa. This spatial dispersion of targets provides a significant obstacle to the establishment of infection. Such obstacles account for the low efficiency of sexual transmission of HIV (see "Sexual Transmission," above). Both "partially" resting CD4+ T cells and activated CD4+ T cells serve as early amplifiers of infection. Resting CD4+ T cells are more abundant; however, activated CD4+ T cells produce larger amounts of virus. In order for infection to become established, the basic reproductive rate (R_0) must become equal to or greater than 1, i.e., each infected cell would infect at least one other cell. Once infection is established, the virus replicates in lymphoid cells in the mucosa, the submucosa, and to some extent the lymphoreticular tissues that drain the gut or genital tissues. For a variable period

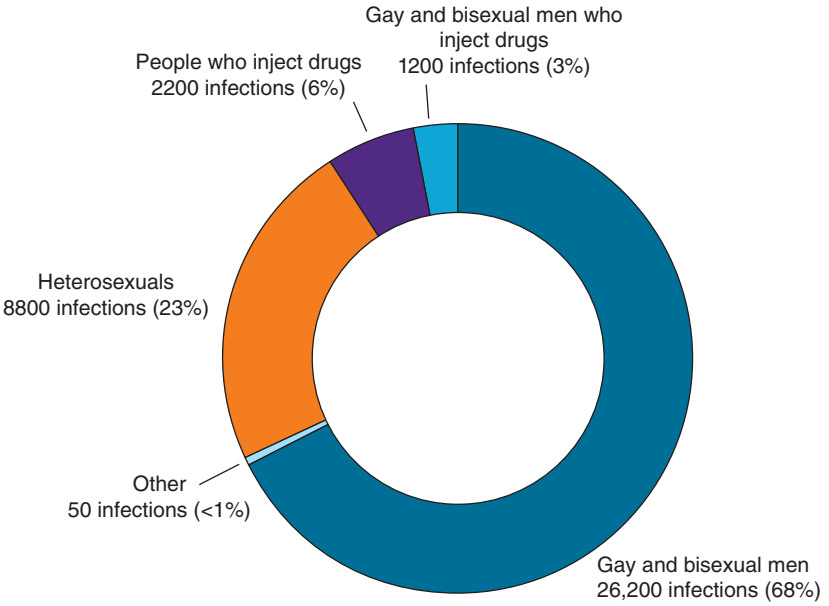


FIGURE 197-14 Estimated distribution of new HIV infections in the United States. Total: 38,500. Incidence estimate for 2015. *(From CDC.)*

of time ranging from a few to several days, the virus cannot yet be detected in the plasma. This period is referred to as the "eclipse" phase of infection. As more virus is produced within several days to weeks, it is disseminated, first to the draining lymph nodes and then to other lymphoid compartments where it has easy access to dense concentrations of CD4+ T cell targets, allowing for a burst of high-level viremia that is readily detectable by currently available assays **(Fig. 197-18)**. The gut-associated lymphoid tissue (GALT) is a major target of HIV infection and the location where large numbers of CD4+ T cells (usually memory cells) are infected and depleted, both by direct viral effects and by activation-associated apoptosis. Once virus replication reaches this threshold and virus is widely disseminated, infection is firmly established throughout the lymphoid tissues of the body and the process is irreversible. It is important to point out that the initial infection of susceptible cells may vary somewhat with the route of infection. Virus that enters directly into the bloodstream via infected blood or blood products (i.e., transfusions, use of contaminated needles for injection drugs, sharp-object injuries, maternal-to-fetal transmission either intrapartum or perinatally, or sexual intercourse where there is enough trauma to cause bleeding) is likely first cleared from the circulation to the spleen and other lymphoid organs, where primary focal infections begin, followed by wider dissemination throughout other lymphoid tissues as described above.

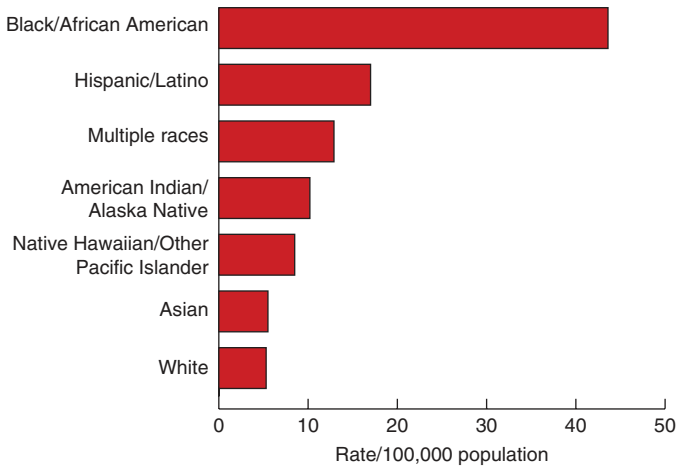


FIGURE 197-15 Estimated rate of HIV infections (including children) diagnosed during 2016 in the United States, by race/ethnicity (per 100,000 population). *(From CDC.)*

It has been demonstrated that sexual transmission of HIV is the result of a single infectious event and that a viral genetic bottleneck exists for transmission with selective transmission of certain viruses. In this regard, certain characteristics of the HIV envelope glycoprotein have a major influence on transmission, at least in subtype A and C viruses. Transmitting viruses, often referred to as "founder viruses," are usually underrepresented in the circulating viremia of the transmitting partner and are less-diverged viruses with signature sequences including shorter V1–V2 loop sequences and fewer predicted N-linked glycosylation sites relative to the major circulating variants. These viruses are almost exclusively R5 strains and are usually sensitive to neutralizing antibody. Once replication proceeds in the newly infected partner, the founder virus diverges and accumulates glycosylation sites, becoming progressively more resistant to neutralization **(Fig. 197-19)**.

The acute burst of viremia and wide dissemination of virus in primary HIV infection may be associated with an *acute HIV syndrome*, which occurs to varying degrees in ~50% of individuals within 2 to 4 weeks of initial infection (see below). This syndrome is usually associated with high levels of viremia measured in millions of copies of HIV RNA per milliliter of plasma that last for several weeks. Acute mononucleosis-like symptoms are well correlated with the presence of viremia. Virtually all patients develop some degree of viremia during primary infection, which contributes to virus dissemination throughout the lymphoid tissue, even though they may remain asymptomatic or not recall experiencing symptoms. The initial level of plasma viremia in primary HIV infection does not necessarily determine the rate of disease progression; however, the set point of the level of steady-state plasma viremia after ~1 year seems to correlate with the slope of disease progression in the untreated patient. The strikingly high levels of viremia observed in many patients with acute HIV infection is felt to be associated with a higher likelihood of transmission of the virus to others by a variety of routes including sexual transmission, shared needles and syringes, and mother-to-child transmission intrapartum, perinatally, or via breast milk.

ESTABLISHMENT OF CHRONIC AND PERSISTENT INFECTION

Persistence of Virus Replication HIV infection is unique among human viral infections. Despite the robust cellular and humoral immune responses that are mounted following primary infection (see "Immune Response to HIV," below), once infection has been established the virus succeeds in escaping complete immune-mediated clearance, paradoxically seems to thrive on immune activation, and is never eliminated completely from the body. Rather, a chronic infection develops and persists with varying degrees of continual virus replication in the untreated patient for a median of ~10 years before the patient becomes clinically ill (see "Advanced HIV Disease," below). It is this establishment of a chronic, persistent infection that is the hallmark of HIV disease. Throughout the often-protracted course of chronic infection, virus replication can invariably be detected in untreated patients by widely available assays that measure copies of virion-associated HIV RNA in plasma (copies per milliliter). Levels of virus vary greatly in most untreated patients, usually ranging from several thousand to a few million copies of HIV RNA per milliliter of plasma. Studies using highly sensitive molecular techniques have demonstrated that even in certain patients in whom plasma viremia is suppressed to below detection (lower limit, 20–50 copies of HIV RNA per milliliter depending on assay kit manufacturer) by cART, there is a continual low level of virion production in the majority of infected patients. In other human viral infections, with very few exceptions, if the host survives, the virus is completely cleared from the body and a state of immunity against subsequent infection develops. HIV infection very rarely kills the host during primary infection. Certain viruses, such as HSV **(Chap. 187)**, are

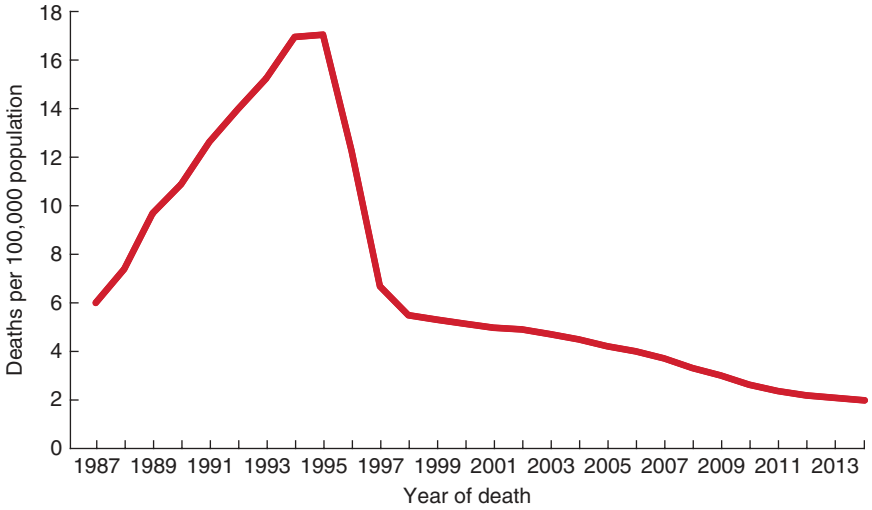


FIGURE 197-16 Trends in annual age-adjusted rates of death due to HIV infection, United States, 1987–2014. Age distribution based on 2000 population. *(From CDC.)*

not completely cleared from the body after infection, but instead enter a latent state; in these cases, clinical latency is accompanied by microbiologic latency. This is not the case with HIV infection as described above. Chronicity associated with persistent virus replication can also be seen in certain cases of HBV and HCV infections **(Chap. 334)**; however, in these infections the immune system is not a target of the virus.

Escape of HIV from Effective Immune System Control

Inherent to the establishment of chronicity of HIV infection is the ability of the virus to evade adequate control and elimination by both the cellular and humoral immune responses. There are a number of mechanisms whereby the virus accomplishes this evasion. Paramount among these is the establishment of a sustained level of replication associated with the generation of viral diversity via mutation and recombination. The selection of mutants that escape control by CD8+ cytolytic T lymphocytes (CTLs) is critical to the propagation and progression of HIV infection. The high rate of virus replication associated with inevitable mutations also contributes to the inability of antibody to clear the autologous virus. Furthermore, for reasons that remain unclear, the humoral immune system does not readily produce classic neutralizing antibodies against the HIV envelope and does so only after years of persistent virus replication and after the infection is firmly established (see below). Extensive analyses of sequential HIV isolates and host responses have demonstrated that viral escape from B cell and CD8+ T cell responses occurs early after infection and allows the virus to stay one step ahead of effective immune responses. Virus-specific CD8+ CTLs expand greatly during primary HIV infection, and they likely represent the high-affinity responses that would be expected to be most efficient in eliminating virus-infected cells; however, viral control is generally incomplete as viral replication persists at relatively high levels in the majority of individuals. In addition to viral escape from CTLs through high rates of mutation, it is thought that the initially strong response becomes qualitatively dysfunctional owing to the overwhelming immune activation associated with persistent viral replication, leading to immune "exhaustion" that affects both arms of adaptive immunity. Several studies have indicated that exhaustion of HIV-specific CD8+ T cells during prolonged immune activation is associated with upregulation of several inhibitory receptors, such as programmed death (PD) 1 molecule (of the B7-CD28 family of molecules), T cell immunoreceptor with Ig and ITIM domains (TIGIT), T cell immunoglobulin and mucin-domain containing molecule 3 (Tim-3), and lymphocyte activating gene 3 (Lag-3), collectively referred to as *immune-checkpoint receptors*. Upregulation of these surface proteins restricts polyreactivity and proliferative capacity, functional attributes of CD8+ T cells that are essential for effective killing of pathogens. Another mechanism contributing to the evasion by HIV of immune system control is the downregulation of HLA class I molecules on the surface of HIV-infected cells by the viral proteins Nef, Tat, and Vpu, resulting in the lack of ability of CD8+ CTLs to recognize and kill infected target cells. Although this downregulation of HLA class I molecules would seem to favor elimination of HIV-infected cells by natural killer (NK) cells, this latter mechanism does not remove HIV-infected cells effectively (see below). Another potential means of escape of HIV-infected cells from elimination by CD8+ CTLs is the sequestration of infected cells in immunologically privileged sites such as the central nervous system (CNS), as well as the low frequency of virus-specific

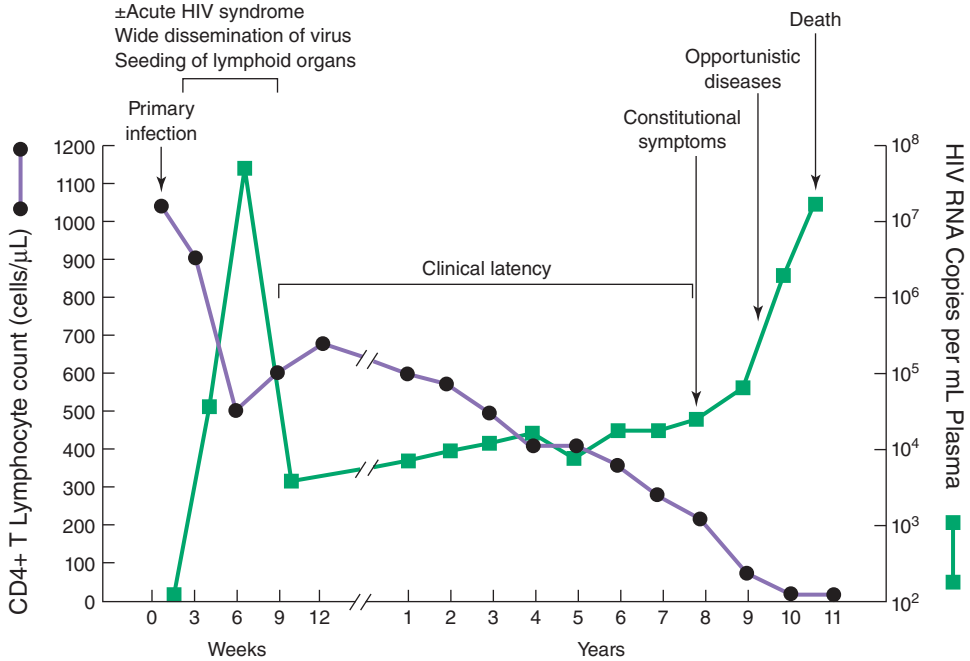


FIGURE 197-17 Typical course of an untreated HIV-infected individual. See text for detailed description. *(From G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.)*

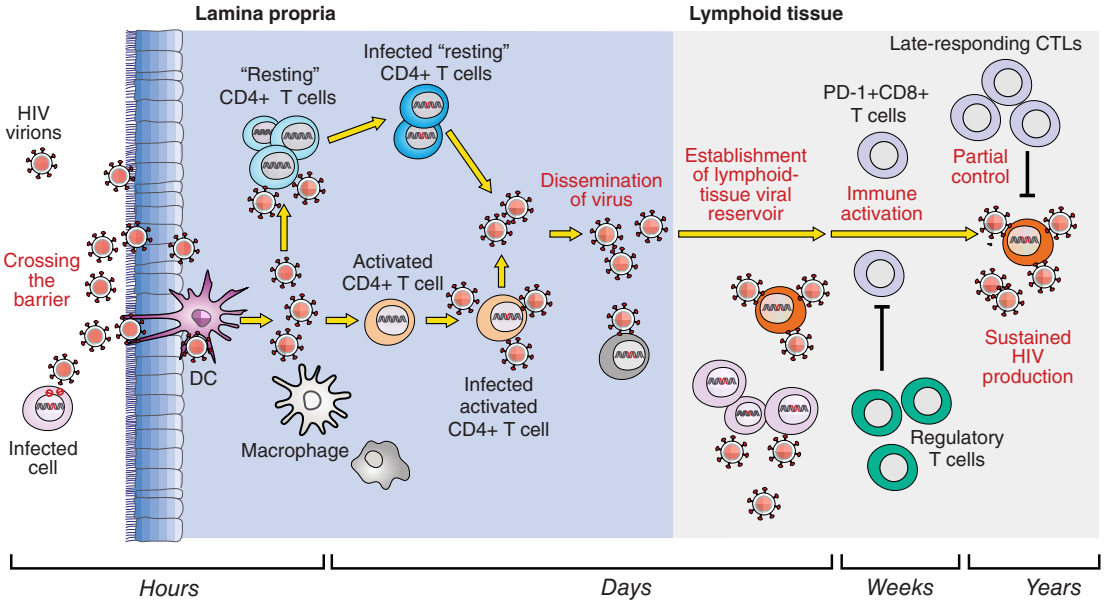


FIGURE 197-18 Summary of early events in HIV infection. See text for detailed description. CTLs, cytolytic T lymphocytes; HIV, human immunodeficiency virus. *(Adapted from AT Haase: Nat Rev Immunol 5:783, 2005.)*

CD8+ CTLs in areas of lymphoid tissues, namely germinal centers, where HIV actively replicates.

The principal targets of neutralizing antibodies against HIV are the envelope proteins gp120 and gp41. HIV employs at least three mechanisms to evade neutralizing antibody responses: hypervariability in the primary sequence of the envelope, extensive glycosylation of the envelope, and conformational masking of neutralizing epitopes. Several studies that have followed the evolution of the humoral immune response to HIV from the earliest points after primary infection indicate that the virus continually mutates to escape the emerging antibody response such that the sequential antibodies that are induced do not neutralize the currently autologous virus. *Broadly neutralizing antibodies* capable of neutralizing a wide range of primary HIV isolates in vitro occur in only about 20% of HIV-infected individuals, and, when they do occur, 2 to 3 years of infection with continual virus replication are generally required to drive the affinity maturation of the antibodies. Unfortunately, by the time these broadly neutralizing antibodies are formed, they are ineffective in containing the virus currently replicating in the patient. Persistent viremia also results in exhaustion of B cells similar to the exhaustion reported for CD8+ T cells, adding to the defects in the humoral response to HIV.

CD4+ T cell help is essential for the integrity of antigen-specific immune responses, both humoral and cell-mediated. HIV preferentially infects activated CD4+ T cells including HIV-specific CD4+ T cells, and so this loss of viral-specific helper T cell responses has profoundly negative consequences for the immunologic control of HIV replication. Furthermore, this loss occurs early in the course of infection, and animal studies indicate that 40–70% of all memory CD4+ T cells in the GALT are eliminated during acute infection. During chronic HIV viremia, CD4+ T cells also exhibit evidence of exhaustion, including by upregulation of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), also a member of the B7-CD28 family.

Finally, the escape of HIV from immune-mediated elimination during primary infection allows the formation of a pool of latently infected cells, referred to as the *viral reservoir*, that may not be recognized or completely eliminated by virus-specific CTLs or by ART (see below). Thus, despite a potent immune response and the marked downregulation of virus replication following primary HIV infection, HIV succeeds in establishing a state of chronic infection with a variable degree of persistent virus replication. During this period most patients make the clinical transition from acute primary infection to variable periods of clinical latency or smoldering disease activity (see below).

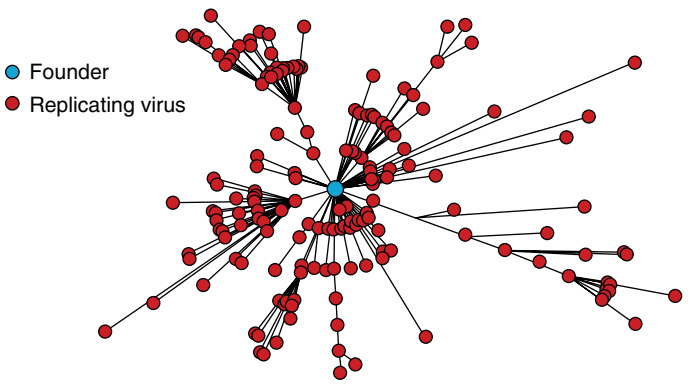


FIGURE 197-19 As HIV diverges from founder to chronically replicating virus, it accumulates N-linked glycosylation sites. See text for detailed description. *(Adapted from CA Derdeyn et al: Science 303:2019, 2004; B Chohan et al: J Virol 79:6528, 2005; and BF Keele et al: Proc Natl Acad Sci USA 105:7552, 2008.)*

The HIV Reservoir: Obstacles to the Eradication of Virus A pool of latently infected, resting CD4+ T cells that serves as at least one component of the persistent reservoir of virus exists in virtually all HIV-infected individuals, including those who are receiving cART. Such cells carry an integrated form of HIV DNA in the genome of the host and can remain in this state until an activation signal drives the expression of HIV transcripts. Only a small fraction of the latently infected cells in the viral reservoir contain replication-competent virus with the overwhelming majority of cells containing defective proviruses incapable of a full replication cycle. However, upon activation of the reservoir variable degrees of sustained virus replication invariably occur. This form of latency is to be distinguished from preintegration latency, in which HIV enters a resting CD4+ T cell and, in the absence of an activation signal, reverse transcription of the HIV genome occurs to a certain extent but the resulting proviral DNA fails to integrate into the host genome. This period of preintegration latency may last hours to days, and if no activation signal is delivered to the cell, the proviral DNA loses its capacity to initiate a productive infection. If these cells do become activated prior to decay of the preintegration complex, reverse transcription proceeds to completion and the virus continues along its replication cycle (see above and Fig. 197-20). The pool of cells that are in the postintegration state of latency is established early during the course of primary HIV infection. Despite the suppression of plasma viremia to undetectable levels by potent regimens of cART administered over several years, this pool of latently infected cells persists and can give rise to replication-competent virus upon cellular activation ex

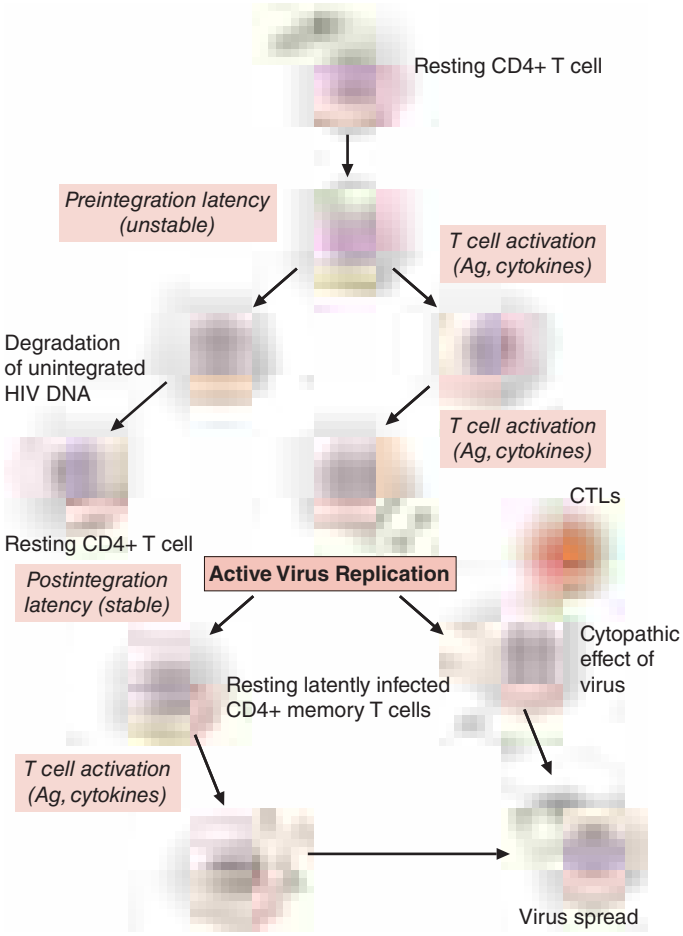


FIGURE 197-20 Generation of latently infected, resting CD4+ T cells in HIV-infected individuals. See text for details. Ag, antigen; CTLs, cytolytic T lymphocytes. *(Courtesy of TW Chun; with permission.)*

vivo. Modeling studies built on projections of decay curves have estimated that in such a setting of prolonged viral suppression, it would require a few to several years for the pool of latently infected cells to be completely eliminated. This has not been documented to occur spontaneously in any patients very likely because the latent viral reservoir is long-lived and is continually replenished by the low levels of persistent virus replication that may remain below the limits of detection of current assays (see below) as well as by the expansion by proliferation of the pool of latently infected cells (Fig. 197-20), even in patients who for the most part are treated successfully. Reservoirs of HIV-infected cells, latent or otherwise, can exist in a number of compartments including the lymphoid tissue, peripheral blood, and the CNS (likely in cells of the monocyte/macrophage lineage) as well as in other unidentified locations. Over the past several years attempts have been made to eliminate HIV in the latent viral reservoir using agents that activate resting CD4+ T cells during the course of cART; however, such attempts, referred to as "shock and kill," have been unsuccessful. Thus, this persistent reservoir of infected cells and/or low levels of persistent virus replication remain major obstacles to the goal of eradication of virus from infected individuals and hence a "cure," despite the favorable clinical outcomes that have resulted from cART.

Viral Dynamics The dynamics of viral production and turnover have been quantified using mathematical modeling in the setting of the administration of reverse transcriptase and protease inhibitors to HIV-infected individuals in clinical studies. Treatment with these drugs resulted in a precipitous decline in the level of plasma viremia, which typically fell by well over 90% within 2 weeks. It was determined on the basis of modeling the kinetics of viral decline and the emergence of resistant mutants during therapy that 93–99% of the circulating virus originated from recently infected, rapidly turning over CD4+ T cells and that ~1–7% of circulating virus originated from longer-lived cells, likely monocytes/macrophages. A negligible amount of circulating virus originated from the pool of latently infected cells **(Fig. 197-21)**. It was also determined that the half-life of a circulating virion was ~30–60 min and that of productively infected cells was 1 day. Given the relatively steady level of plasma viremia and of infected cells, it appears that extremely large amounts of virus (~10^{10}–10^{11} virions) are produced and cleared from the circulation each day. In addition, data suggest that the minimal duration of the HIV-1 replication cycle in vivo is ~2 days. Other studies have demonstrated that the decrease in plasma viremia that results from cART correlates closely with a decrease in virus replication in lymph nodes, further confirming that lymphoid tissue is the main site of HIV replication and the main source of plasma viremia.

The level of steady-state viremia, called the viral *set point*, at ~1 year following acquisition of HIV infection has important prognostic implications for the progression of HIV disease in the untreated patient. It has been demonstrated that, as a group, untreated HIV-infected individuals who have a low set point at 6 months to 1 year following infection progress to AIDS much more slowly than do individuals whose set point is very high at that time **(Fig. 197-22)**.

Clinical Latency versus Microbiologic Latency With the exception of certain long-term nonprogressors and "elite controllers" of HIV replication, the level of CD4+ T cells in the blood inevitably decreases progressively in viremic HIV-infected individuals in the absence of cART. The decline in CD4+ T cells may be gradual or abrupt, the latter usually reflecting a significant spike in the level of plasma viremia. Most patients are relatively asymptomatic while this progressive decline is taking place (see below) and are often described as being in a state of *clinical latency*. However, this term is misleading; it does not mean disease latency, since progression, although slow in many cases and often without symptoms, is generally relentless during this period. Furthermore, clinical latency should not be confused with microbiologic latency, since varying levels of virus replication inevitably occur during this period of clinical latency. Even in those rare patients who have <50 copies of HIV RNA per milliliter in the absence of therapy, there is virtually always some degree of low-level ongoing virus replication.

ADVANCED HIV DISEASE

In untreated patients or in patients in whom therapy has not adequately controlled virus replication, after a variable period, usually measured in years, the CD4+ T cell count falls below a critical level (<200/μL) and the patient becomes highly susceptible to opportunistic

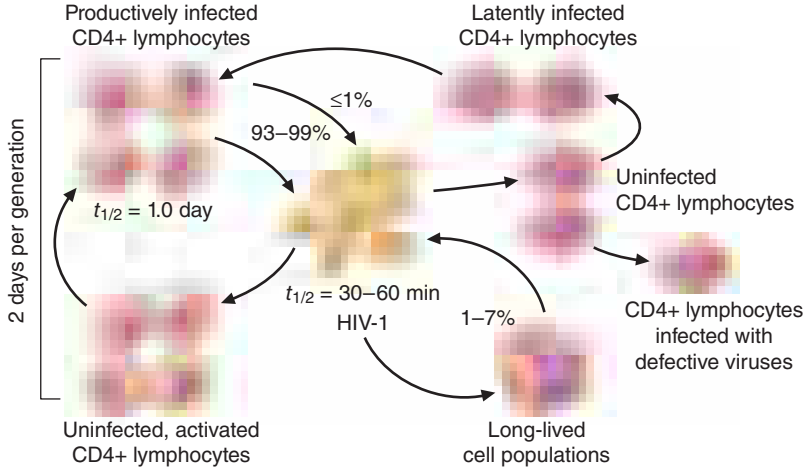


FIGURE 197-21 Dynamics of HIV infection in vivo. See text for detailed description. *(From AS Perelson et al: Science 271:1582, 1996.)*

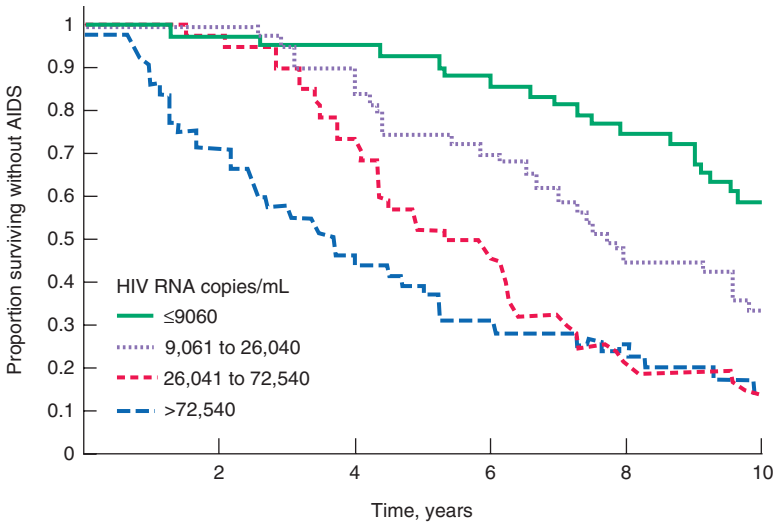


FIGURE 197-22 Relationship between levels of virus and rates of disease progression. Kaplan-Meier curves for AIDS-free survival stratified by baseline HIV-1 RNA categories (copies per milliliter). *(From JW Mellors et al: Science 272:1167, 1996.)*

disease (Fig. 197-17). For this reason, the CDC case definition of AIDS includes all HIV-infected individuals >5 years of age with CD4+ T cell counts below this level (Table 197-2). Patients may experience constitutional signs and symptoms or may develop an opportunistic disease abruptly without any prior symptoms. The depletion of CD4+ T cells continues to be progressive and unrelenting in this phase. It is not uncommon for CD4+ T cell counts in the untreated patient to drop to as low as 10/μL or even to zero. In countries where cART and prophylaxis and treatment for opportunistic infections are readily accessible to such patients, survival is increased dramatically even in those patients with advanced HIV disease. In contrast, untreated patients who progress to this severest form of immunodeficiency usually succumb to opportunistic infections or neoplasms (see below).

LONG-TERM SURVIVORS, LONG-TERM NONPROGRESSORS, AND ELITE CONTROLLERS

It is important to distinguish between the terms *long-term survivor* and *long-term nonprogressor*. Long-term nonprogressors are by definition long-term survivors; however, the reverse is not always true. Predictions from one study that antedated the availability of effective cART estimated that ~13% of homosexual/bisexual men who were infected at an early age may remain free of clinical AIDS for >20 years. Many of these individuals may have progressed in their degree of immune deficiency; however, they certainly survived for a considerable period of time. With the advent of effective cART, the survival of HIV-infected individuals has dramatically increased. Early in the AIDS epidemic, prior to the availability of therapy, if a patient presented with a life-threatening opportunistic infection, the median survival was 26 weeks from the time of presentation. Currently, an HIV-infected 20-year-old individual in a high-income country who is appropriately treated with cART can expect to live at least 50 years according to mathematical model projections. In the face of cART, long-term survival is becoming commonplace. Definitions of long-term nonprogressors have varied considerably over the years, and so such individuals constitute a heterogeneous group. Long-term nonprogressors were first described in the 1990s. Originally, individuals were considered to be long-term nonprogressors if they had been infected with HIV for a long period (≥10 years), their CD4+ T cell counts were in the normal range, and they remained stable over years without receiving cART. Approximately 5–15% of HIV-infected individuals fell into this broader nonprogressor category. However, this group was rather heterogenous and over time a significant proportion of these individuals progressed and ultimately required therapy. From this broader group, a much smaller subgroup of "elite" controllers or nonprogressors was identified, and they constituted a fraction of 1% of HIV-infected individuals. These elite controllers, by definition, have extremely low levels of plasma viremia that is often undetectable by standard assays and normal CD4+ T cell counts. It is noteworthy that certain of their HIV-specific immune responses are robust and clearly superior to those of HIV-infected progressors. In this group of elite controllers certain HLA class I haplotypes are overrepresented, particularly HLA-B57-01 and HLA-B27-05. Outside of the subgroup of elite controllers, a number of other genetic factors have been shown to be involved to a greater or lesser degree in the control of virus replication and thus in the rate of HIV disease progression (see "Genetic Factors in HIV-1 and AIDS Pathogenesis," below).

LYMPHOID ORGANS AND HIV PATHOGENESIS

Regardless of the portal of entry of HIV, lymphoid tissues are the major anatomic sites for the establishment and propagation of HIV infection. Despite the use of measurements of plasma viremia to determine the level of disease activity, virus replication occurs mainly in lymphoid tissue and not in blood; indeed, the level of plasma viremia directly reflects virus production in lymphoid tissue.

Some patients experience progressive generalized lymphadenopathy early in the course of the infection; others experience varying degrees of transient lymphadenopathy. Lymphadenopathy reflects the cellular activation and immune response to the virus in the lymphoid tissue, which is generally characterized by follicular or germinal center hyperplasia. Lymphoid tissue involvement is a common denominator of virtually all patients with HIV infection, even those without easily detectable lymphadenopathy.

Examinations of lymph tissue and peripheral blood in patients and monkeys during various stages of HIV and SIV infection, respectively, have led to substantial insight into the pathogenesis of HIV disease. In most of the original human studies, peripheral lymph nodes have been used predominantly as the source of lymphoid tissue. More recent studies in monkeys and humans have also focused on the GALT, where the earliest burst of virus replication occurs associated with marked depletion of CD4+ T cells. In detailed studies of peripheral lymph node tissue that utilized a variety of molecular techniques to measure the level of HIV DNA and RNA and imaging techniques to visualize virus and cells, the following picture has emerged. During acute HIV infection resulting from mucosal transmission, virus replication progressively amplifies from scattered lymphoid cells in the lamina propria of the gut to draining lymphoid tissue, leading to high levels of plasma viremia. The GALT plays a major role in the amplification of virus replication, and virus is disseminated from replication in the GALT to peripheral lymphoid tissue. A profound degree of cellular activation occurs within lymphoid tissue (see below) and is reflected in follicular or germinal center hyperplasia. At this time copious amounts of extracellular virions (both infectious and defective) are trapped on the processes of the follicular dendritic cells (FDCs) in the germinal centers of the lymph nodes. Virions that have bound complement components on their surfaces attach to the surface of FDCs via interactions with complement receptors and likely via Fc receptors that bind to antibodies that are attached to the virions. In situ hybridization reveals expression of virus in individual cells of the paracortical area and, to a lesser extent, the germinal center **(Fig. 197-23)**. The persistence of trapped virus likely reflects a steady state whereby trapped virus turns over and is replaced by fresh virions that are continually produced. The trapped virus, either as whole virion or shed envelope, serves as a continual activator of CD4+ T cells, thus driving further virus replication.

During the early stages of HIV disease, the architecture of lymphoid tissues is generally preserved and may even be hyperplastic owing to an increased presence of B cells and specialized CD4+ T cells called follicular helper CD4+ T cells (TF_H) in prominent germinal centers. Extracellular virions can be seen by electron microscopy attached to FDC processes. The trapping of antigen is a physiologically normal function for the FDCs, which present antigen to B cells and, along with stimulatory factors produced by TF_H cells, contribute to the generation of B cell memory. However, in the case of HIV, persistent cellular

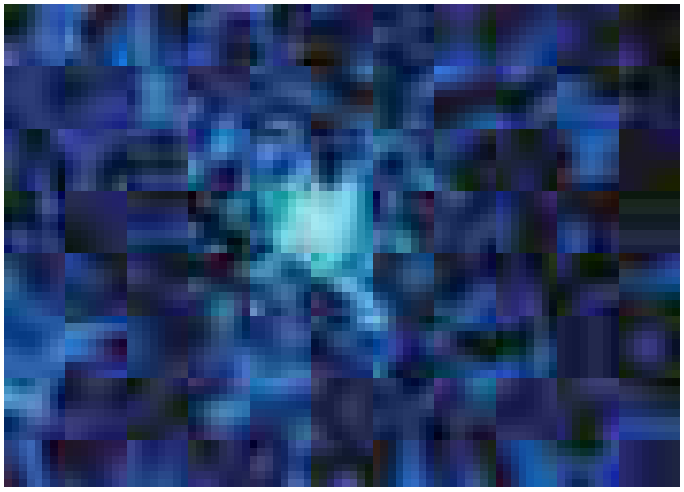


FIGURE 197-23 HIV in the lymph node of an HIV-infected individual. An individual cell infected with HIV shown expressing HIV RNA by in situ hybridization using a radiolabeled molecular probe. Original ×500. *(Adapted from G Pantaleo, AS Fauci et al: Nature 362:355, 1993.)*

activation, resulting in a shift to secretion of proinflammatory cytokines such as interleukin (IL) 1β, tumor necrosis factor (TNF) α, IFN-γ, and IL-6, can induce viral replication (see below) and diminish the effectiveness of the immune response against the virus. In addition, the CD4+ TF_H cells that are recruited into the germinal center to provide help to B cells in the generation of an HIV-specific immune response are highly susceptible to infection and may be an important component of the HIV reservoir. Thus, in HIV infection, a normal physiologic function of the immune system that contributes to the clearance of virus, as well as to the generation of a specific immune response, can also have deleterious consequences.

As HIV disease progresses, the architecture of lymphoid tissues begins to show disruption. Confocal microscopy reveals destruction of the fibroblastic reticular cell (FRC) and FDC networks in the T cell zone and B cell follicles, respectively. The mechanisms of destruction are not completely understood, but they are thought to be associated with collagen deposition causing fibrosis and loss of production of cytokines such as IL-7 and lymphotoxin-α, which are critical to the maintenance of lymphoid tissues and their lymphocyte constituents. As the disease progresses to an advanced stage, there is complete disruption of the architecture of the lymphoid tissues, accompanied by dissolution of the FRC and FDC networks. At this point, the lymph nodes are "burnt out." This destruction of lymphoid tissue compounds the immunodeficiency of HIV disease and contributes both to the inability to control HIV replication and to the inability to mount adequate immune responses against opportunistic pathogens. The events from primary infection to the ultimate destruction of the immune system are illustrated in Fig. 197-24. More recently, nonhuman primate studies and some human studies have examined GALT at various stages of HIV disease. Within the GALT, the basal level of cellular activation combined with virus-mediated activation results in the infection and elimination of an estimated 50–90% of CD4+ T cells in the gut. The extent of this early damage to GALT, which constitutes a major component of lymphoid tissue in the body, may play a role in determining the potential for immunologic recovery of the memory cell subset.

THE ROLE OF IMMUNE ACTIVATION AND INFLAMMATION IN HIV PATHOGENESIS

Activation of the immune system and variable degrees of inflammation are essential components of any appropriate immune response to a foreign antigen. However, immune activation and inflammation, which can be considered aberrant in HIV-infected individuals, play a critical role in the pathogenesis of HIV disease as well as other chronic conditions associated with HIV infection. Immune activation and inflammation in the HIV-infected individual contribute substantially to (1) the replication of HIV, (2) the induction of immune dysfunction, and (3) the increased incidence of chronic conditions such as premature cardiovascular disease (Table 197-4).

INDUCTION OF HIV REPLICATION BY ABERRANT IMMUNE ACTIVATION The immune system is normally in a state of homeostasis, awaiting perturbation by foreign antigenic stimuli. Once the immune response deals with and clears the antigen, the system returns to relative quiescence (Chap. 342). This is generally not the case in HIV infection where, in the untreated patient, virus replication is invariably persistent with very few exceptions and immune activation is persistent. HIV replicates most efficiently in activated CD4+ T cells; in HIV infection, chronic activation provides the cell substrates necessary for persistent virus replication throughout the course of HIV disease, particularly in the untreated patient. Even in certain patients receiving cART whose levels of plasma viremia are suppressed to below the level of detection by standard assays, there are low but detectable degrees of virus replication that drives persistent immune activation. From a virologic standpoint, although quiescent CD4+ T cells can be infected, albeit inefficiently, with HIV, reverse transcription, integration, and virus spread are much more efficient in activated cells. Furthermore, cellular activation induces expression of virus in cells latently infected with HIV. In essence, immune activation and inflammation provide the engine that drives HIV replication. In addition to endogenous factors such as cytokines, a number of exogenous factors such as other microbes that are associated with heightened cellular activation can enhance HIV replication and thus may play a role in HIV pathogenesis. Co-infection with a range of viruses, such as HSV types 1 and 2, cytomegalovirus (CMV), human herpesvirus (HHV) 6, Epstein-Barr virus (EBV), HBV, HCV, adenovirus, and HTLV-1 have been shown to upregulate HIV expression. In addition, infestation with nematodes has been shown to be associated with a heightened state of immune activation that facilitates HIV replication; in certain studies deworming of the infected host has resulted in a decrease in plasma viremia.

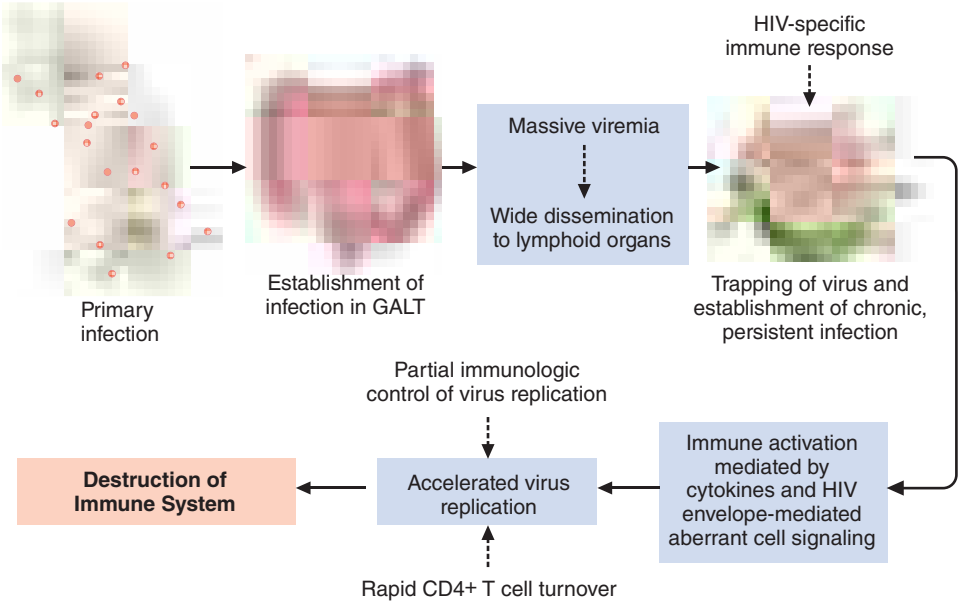


FIGURE 197-24 Events that transpire from primary HIV infection through the establishment of chronic persistent infection to the ultimate destruction of the immune system. See text for details. CTLs, cytolytic T lymphocytes; GALT, gut-associated lymphoid tissue.

TABLE 197-4 Conditions Associated with Persistent Immune Activation and Inflammation in Patients with HIV Infection

Accelerated aging syndrome
Bone fragility
Cancers
Cardiovascular disease
Diabetes
Kidney disease
Liver disease
Neurocognitive dysfunction

Two diseases of extraordinary global health significance, malaria and tuberculosis (TB), have been shown to increase HIV viral load in dually infected individuals. Globally, *Mycobacterium tuberculosis* is the most common opportunistic infection in HIV-infected individuals **(Chap. 173)**. In addition to the fact that HIV-infected individuals are more likely to develop active TB after exposure and to reactivate latent TB, it has been demonstrated that active TB can accelerate the course of HIV infection. It has also been shown that levels of plasma viremia are greatly elevated in HIV-infected individuals with active TB who are not receiving cART, compared with pre-TB levels and levels of viremia after successful treatment of the active TB. The situation is similar in the interaction between HIV and malaria parasites **(Chap. 219)**. Acute infection of HIV-infected individuals with *Plasmodium falciparum* increases HIV viral load, and the increased viral load is reversed by effective treatment of malaria.

MICROBIAL TRANSLOCATION AND PERSISTENT IMMUNE ACTIVATION One proposed mechanism of persistent immune activation involves the disruption of the mucosal barrier in the gut due to HIV replication in submucosal lymphoid tissue. As a result of this disruption, there is an increase in the products, particularly lipopolysaccharide (LPS), of bacteria that translocate from the bowel lumen through the damaged mucosa to the circulation, leading to persistent systemic immune activation and inflammation. This effect can persist even after the HIV viral load is brought to <50 copies/mL by cART. Depletion in the GALT of IL-17–producing T cells, which are responsible for defense against extracellular bacteria and fungi, also is thought to contribute to HIV pathogenesis.

PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION INDUCE IMMUNE DYSFUNCTION The immune activated state in HIV infection is reflected by hyperactivation of B cells leading to hypergammaglobulinemia; increased lymphocyte turnover; activation of monocytes; expression of activation markers and immune checkpoint receptors on CD4+ and CD8+ T cells; increased activation-associated cellular apoptosis; lymph node hyperplasia, particularly early in the course of disease; increased secretion of proinflammatory cytokines, particularly IL-6; elevated levels of high-sensitivity C-reactive protein, fibrinogen, D-dimer, neopterin, β_2-microglobulin, acid-labile interferon, soluble (s) IL-2 receptors (R), sTNFR, sCD27, and sCD40L; and autoimmune phenomena (see "Autoimmune Phenomena," below). Even in the absence of direct infection of a target cell, HIV envelope proteins can interact with cellular receptors (CD4 molecules and chemokine receptors) to deliver potent activation signals resulting in calcium flux, the phosphorylation of certain proteins involved in signal transduction, co-localization of cytoplasmic proteins including those involved in cell trafficking, immune dysfunction, and, under certain circumstances, apoptosis. From an immunologic standpoint, chronic exposure of the immune system to a particular antigen over an extended period of time may ultimately lead to an inability to sustain an adequate immune response to the antigen in question. In many chronic viral infections, including HIV infection, persistent viremia is associated with "functional exhaustion" of virus-specific T cells, decreasing their capacity to proliferate and perform effector functions. It has been demonstrated that this phenomenon of immune exhaustion may be mediated, at least in part, by the upregulation of inhibitory receptors on HIV-specific T cells, such as PD-1 and Tim-3 that are shared by both CD4+ and CD8+ T cells, as well as CTLA-4 on CD4+ and 2B4 and CD106 on CD8+ T cells. Furthermore, the ability of the immune system to respond to a broad spectrum of non-HIV antigens may be compromised if immunocompetent bystander cells are maintained in a state of chronic activation.

The deleterious effects of chronic immune activation on the progression of HIV disease are well established. As in most conditions of persistent antigen exposure, the host must maintain sufficient activation of antigen (HIV)-specific responses but must also prevent excessive activation and potential immune-mediated damage to tissues. Certain studies suggest that normal immunoregulatory mechanisms that act to keep hyperimmune activation in check, particularly CD4+, FoxP3+, and CD25+ regulatory T cells (T-regs), may be dysfunctional or depleted in the context of advanced HIV disease.

Apoptosis Apoptosis is a form of programmed cell death that is a normal mechanism for the elimination of effete cells in organogenesis as well as in the cellular proliferation that occurs during a normal immune response **(Chap. 342)**. Apoptosis can occur by intrinsic or extrinsic pathways, the latter of which is largely dependent on cellular activation, and the aberrant cellular activation associated with HIV disease is correlated with a heightened state of apoptosis. HIV can trigger activation-induced cell death through the upregulation of the death receptors, such as Fas/CD95, TNFR1, or TNF-related apoptosis-inducing ligand (TRAIL) receptors 1 and 2. Their corresponding ligands FasL, TNF, and TRAIL also are upregulated in HIV disease. HIV-induced stress and alterations in homeostasis also can trigger intrinsic apoptosis due to the downregulation of antiapoptotic proteins such as Bcl-2. Other mechanisms of HIV-induced cell death have been described, including autophagy, necrosis, necroptosis, and pyroptosis. The phenomenon of pyroptosis, an inflammatory form of cell death involving the upregulation of the proinflammatory enzyme caspase 1 and release of the proinflammatory cytokines IL-1β and IL-18, has been linked to a bystander effect of HIV replication on CD4+ T cells. The process of pyroptosis generates multimeric complexes called inflammasomes, which can also be activated by LPS. Certain viral gene products have been associated with enhanced susceptibility to apoptosis; these include Env, Tat, and Vpr. In contrast, Nef has been shown to possess antiapoptotic properties. The intensity of apoptosis correlates with the general state of activation of the immune system and not with the stage of disease or with viral burden. A number of studies, including those examining lymphoid tissue, have demonstrated that the rate of apoptosis is elevated in HIV infection and that apoptosis is seen in "bystander" cells such as CD8+ T cells and B cells as well as in uninfected CD4+ T cells. It is likely that this bystander apoptosis of immunocompetent cells related to immune activation contributes to the general immune abnormalities in HIV disease.

MEDICAL CONDITIONS ASSOCIATED WITH PERSISTENT IMMUNE ACTIVATION AND INFLAMMATION IN HIV DISEASE It has become clear, as the survival of HIV-infected individuals has increased, that a number of previously unrecognized medical complications are associated with HIV disease—and that these complications relate to chronic immune activation and inflammation (Table 197-4). These complications can appear even after patients have experienced years of adequate control of viral replication (plasma viremia below detectable levels) for several years. Of particular note are endothelial cell dysfunction and its relationship to cardiovascular disease. Other chronic conditions that have been reported include bone fragility, certain cancers, diabetes, kidney and liver disease, and neurocognitive dysfunction, thus presenting an overall picture of accelerated aging.

Autoimmune Phenomena Autoimmune phenomena are commonly observed in HIV-infected individuals and they reflect, at least in part, chronic immune activation and the dysregulation of B and T cells. Although these phenomena usually occur in the absence of autoimmune disease, a wide spectrum of clinical manifestations that may be associated with autoimmunity have been described (see "Immunologic and Rheumatologic Diseases," below). Autoimmune phenomena include antibodies against autoantigens expressed on intact lymphocytes and other cells, or against proteins released from dying cells. Antiplatelet antibodies have some clinical relevance in that they may contribute to

the thrombocytopenia of HIV disease (see below). Antibodies to nuclear and cytoplasmic components of cells have been reported, as have antibodies to cardiolipin and phospholipids; CD4 molecules; CD43 molecules; C1q-A; variable regions of the T cell receptor α, β, and γ chains; Fas; denatured collagen; and IL-2. In addition, autoantibodies to a range of serum proteins, including albumin, immunoglobulin, and thyroglobulin, have been reported. Molecular mimicry, either from opportunistic pathogens or from HIV itself, also is a trigger or cofactor in autoimmunity. Antibodies against the HIV envelope proteins, especially gp41, often cross-react with host proteins; the best known examples are antibodies directed against the membrane-proximal external region (MPER) of gp41 that also react with phospholipids and cardiolipin. The phenomenon of polyreactive HIV-specific antibodies may be beneficial to the host (see "Immune Response to HIV," below).

The increased occurrence and/or exacerbation of certain autoimmune diseases have been reported in HIV infection; these diseases include psoriasis, idiopathic thrombocytopenic purpura, Graves' disease, antiphospholipid syndrome, and primary biliary cirrhosis. The majority of these manifestations were described prior to the advent of cART and have decreased in frequency since its widespread use. However, with increasing availability of cART, an *immune reconstitution inflammatory syndrome* (IRIS) has been increasingly observed in infected individuals, particularly those with low CD4+ T cell counts (see below). IRIS is an autoimmune-like phenomenon characterized by a paradoxical deterioration of clinical condition, which is usually compartmentalized to a particular organ system, in individuals in whom cART has recently been initiated. It is associated with a decrease in viral load and at least partial recovery of immune competence, which is usually associated with increases in CD4+ T cell counts. The immunopathogenesis of this syndrome is felt to be related to an increase in immune response against the presence of residual antigens that are usually microbial and is most commonly seen with underlying *Mycobacterium tuberculosis* and cryptococcosis. This syndrome is discussed in more detail below.

CYTOKINES AND OTHER SOLUBLE FACTORS IN HIV PATHOGENESIS

The immune system is homeostatically regulated by a complex network of immunoregulatory cytokines, which are pleiotropic and redundant and operate in an autocrine and paracrine manner. They are expressed continuously, even during periods of apparent quiescence of the immune system. On perturbation of the immune system by antigenic challenge, the expression of cytokines increases to varying degrees **(Chap. 342)**. Cytokines that are important components of this immunoregulatory network are thought to play major roles in HIV disease, during both the early and chronic phases of infection. A potent proinflammatory "cytokine storm" is induced during the acute phase of HIV infection, likely a response by inflammatory cells to virus replicating at very high levels. Cytokines that are induced during this early phase include IFN-α, IL-15, and the CXC chemokine IP-10 (CXCL10), followed by IL-6, IL-12, and TNF-α, and a delayed peak of the anti-inflammatory cytokine IL-10. Soluble factors of innate immunity also are induced shortly after infection, including neopterin and β-microglobulin. Several of these early-expressed cytokines and factors are not downregulated following the early phase of HIV infection, as seen in other self-resolving viral infections, and persist during the chronic phase of infection and contribute to maintaining high levels of immune activation. Among the cytokines and factors associated with early innate immune responses, they are intended to contain viral replication, although paradoxically most are potent inducers of HIV expression/replication because of their ability to induce immune activation that leads to enhanced viral production and an increase in readily available target cells for HIV (activated CD4+ T cells). The induction of IFN-α, one of the first cytokines induced during primary HIV infection and an important element of innate immune sensing, is thought to play a particularly important role in HIV pathogenesis by inducing a large number of IFN-associated genes that activate the immune system, alter the homeostasis of CD4+ T cells, and influence the virus variants that are selected during the HIV transmission bottleneck. Other cytokines that are elevated during the chronic phase of HIV infection and linked to immune activation include IFN-γ, the *CC-chemokine* RANTES (CCL5), macrophage inflammatory protein (MIP)-1β (CCL4), and IL-18.

Several specific cytokines and soluble factors have been associated with HIV pathogenesis at various stages of disease, in various tissues or organs, and in the regulation of HIV replication. Plasma levels of IP-10 are predictive of disease progression, whereas the proinflammatory cytokine IL-6, soluble CD14 (sCD14), and coagulation marker D-dimer are associated with increased risk of all-cause mortality in HIV-infected individuals. In particular, IL-6, sCD14, and D-dimer are associated with increased risk of cardiovascular disease and other causes of death, even in individuals receiving cART. IL-18 has also been shown to play a role in the development of the HIV-associated lipodystrophy syndrome, whereas increased levels of transforming growth factor (TGF)-β are associated with the induction of collagen deposition in lymph nodes (see above). Elevated levels of TNF-α and IL-6 have been demonstrated in plasma and cerebrospinal fluid (CSF), and increased expression of TNF-α, IL-1β, IFN-γ, and IL-6 has been demonstrated in the lymph nodes of HIV-infected individuals. RANTES, MIP-1α (CCL3), and MIP-1β (CCL4) **(Chap. 342)** inhibit infection by and spread of R5 HIV-1 strains, while *stromal cell–derived factor* (SDF) 1 inhibits infection by and spread of X4 strains. The mechanisms whereby the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) inhibit infection of R5 strains of HIV, or SDF-1 blocks X4 strains of HIV, involve blocking of the binding of the virus to its co-receptors, the CC-chemokine receptor CCR5 and the CXC-chemokine receptor CXCR4, respectively. Other soluble factors that have not yet been fully characterized, such as soluble CD8 antiviral factor (CAF), also have been shown to suppress HIV replication, independent of co-receptor usage.

LYMPHOCYTE TURNOVER IN HIV INFECTION

The immune systems of patients with HIV infection are characterized by a profound increase in lymphocyte turnover that is immediately reduced with effective cART. Studies utilizing in vivo or in vitro labeling of lymphocytes in the S-phase of the cell cycle have demonstrated a tight correlation between the degree of lymphocyte turnover and plasma levels of HIV RNA. This increase in turnover is seen in CD4+ and CD8+ T lymphocytes as well as B lymphocytes and can be observed in peripheral blood and lymphoid tissue. Mathematical models derived from these data suggest that one can view the lymphoid pool as consisting of dynamically distinct subpopulations of cells that are differentially affected by HIV infection. A major consequence of HIV infection appears to be a shift in cells from a more quiescent pool to a pool with a higher turnover rate. It is likely that a consequence of a higher rate of turnover is a higher rate of cell death. It has been suggested that the more rapid decline in CD4+ compared with CD8+ T cells may be linked to alterations in inflammatory and homeostatic cytokines that cause increased activation-induced death without replenishment of CD4+ but not CD8+ T cells. (See **Table 197-5** for additional mechanisms of depletion.)

THE ROLE OF VIRAL RECEPTORS AND CO-RECEPTORS IN HIV PATHOGENESIS

CCR5 AND CXCR4 As mentioned above, HIV-1 utilizes two major co-receptors along with CD4 to bind to, fuse with, and enter target cells; these co-receptors are CCR5 and CXCR4, which are also receptors for certain endogenous chemokines. Strains of HIV that utilize CCR5 as a co-receptor are referred to as *R5 viruses*. Strains of HIV that utilize CXCR4 are referred to as *X4 viruses*. Many virus strains are *dual tropic* in that they utilize both CCR5 and CXCR4; these are referred to as *R5X4 viruses*.

The natural chemokine ligands for the major HIV co-receptors can readily block entry of HIV. For example, the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4), which are the natural ligands for CCR5, block entry of R5 viruses, whereas SDF-1, the natural ligand for CXCR4, blocks entry of X4 viruses. The mechanism of inhibition of viral entry is a steric inhibition of binding that is not dependent on signal transduction **(Fig. 197-25)**.

The transmitting virus is almost invariably an R5 virus that predominates during the early stages of HIV disease. In the absence of cART

TABLE 197-5 Proposed Mechanisms of CD4+ T Cell Dysfunction and Depletion

DIRECT MECHANISMS	INDIRECT MECHANISMS
Loss of plasma membrane integrity due to viral budding	Aberrant intracellular signaling events
Accumulation of unintegrated viral DNA Activation of DNA-dependent protein kinase during viral integration into host genome	Autoimmunity
Interference with cellular RNA processing	Innocent bystander killing of viral antigen–coated cells
Intracellular gp120-CD4 autofusion events	Apoptosis, pyroptosis (caspase-1 associated inflammation), autophagy
Syncytia formation	Inhibition of lymphopoiesis from reduced survival cytokines and lymphoid tissue integrity Activation-induced cell death Elimination of HIV-infected cells by virus-specific immune responses

or in cases of therapy failure, there is a transition to a predominantly X4 virus in approximately half of individuals infected with subtype B. The transition is often preceded by dual R5X4 strains, and detection of X4 variants is associated with a relatively rapid decline in CD4+ T cell counts, increased HIV plasma viremia, and progression of disease. However, the other half of infected individuals progress in their disease while maintaining predominance of an R5 virus, and individuals infected with subtype C rarely switch from CCR5 tropism to CXCR4 tropism. The reason for this difference is unclear.

The basis for the tropism of different envelope glycoproteins for either CCR5 or CXCR4 relates to the ability of the HIV envelope, including the third variable region (V3 loop) of gp120, to interact with these co-receptors. In this regard, binding of gp120 to CD4 induces a conformational change in gp120 that increases its affinity for the relevant co-receptor. Finally, R5 viruses are more efficient in infecting monocytes/macrophages and microglial cells of the brain (see "Neuropathogenesis in HIV Disease," below).

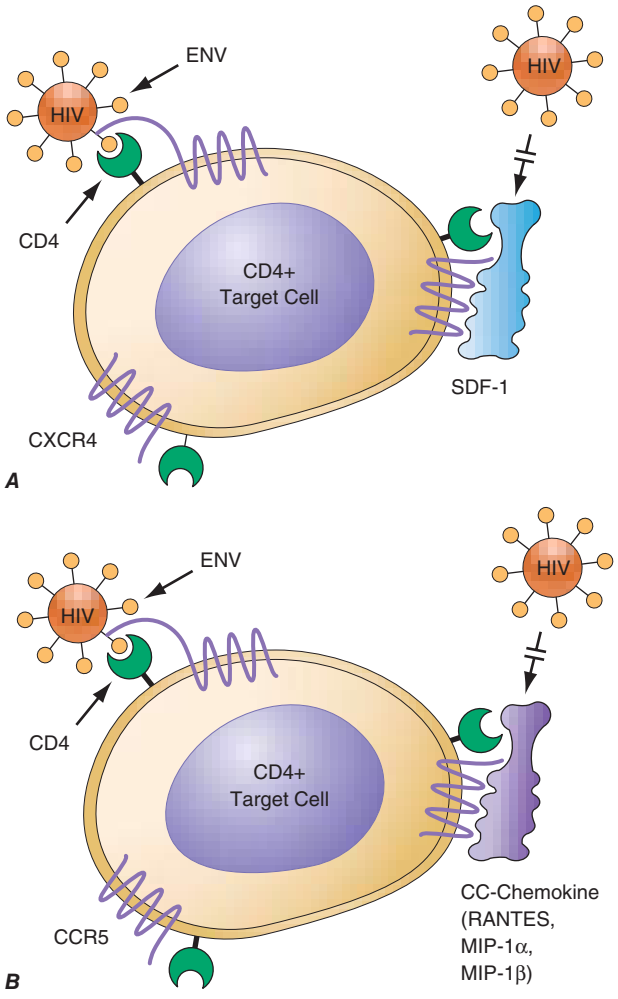


FIGURE 197-25 Model for the role of co-receptors CXCR4 and CCR5 in the efficient binding and entry of X4 (***A***) and R5 (***B***) strains of HIV-1, respectively, into CD4+ target cells. Blocking of this initial event in the virus life cycle can be accomplished by inhibition of binding to the co-receptor by the normal ligand for the receptor in question. The ligand for CXCR4 is stromal cell–derived factor (SDF-1); the ligands for CCR5 are RANTES, MIP-1α, and MIP-1β.

THE INTEGRIN α4β7 The integrin α4β7 is an accessory receptor for HIV. It is not essential for the binding and infection of a CD4+ T cell by HIV; however, it likely plays an important role in the transmission of HIV at mucosal surfaces such as the genital tract and gut and contributes somewhat to the pathogenesis of HIV disease. The integrin α4β7, which is the gut homing receptor for peripheral T cells, binds in its activated form to a specific tripeptide in the V2 loop of gp120, resulting in rapid activation of leukocyte function–associated antigen 1 (LFA-1), the central integrin in the establishment of virologic synapses, which facilitate efficient cell-to-cell spread of HIV. It has been demonstrated that $\alpha4\beta7^{high}$ CD4+ T cells are more susceptible to productive infection than are $\alpha4\beta7^{low-neg}$ CD4+ T cells because this cellular subset is enriched with metabolically active CD4+ T cells that are $CCR5^{high}$. These cells are present at the gut and genital tract mucosal surfaces. Importantly, it has been demonstrated that the virus that is transmitted during sexual exposure binds much more efficiently to α4β7 than does the virus that diversifies from the transmitting virus over time by mutation, particularly involving the accumulation of glycogens on the surface of the HIV envelope (see "Early Events in HIV Infection: Primary Infection and Initial Dissemination of Virus," above).

CELLULAR TARGETS OF HIV

CD4+ T lymphocytes and to a lesser extent CD4+ cells of the myeloid lineage are the principal targets of HIV and are the only cells that can be productively infected with HIV. Circulating DCs have been reported to express low levels of CD4, although high expression of the restriction factor SAMHD1 in myeloid (mDC) and plasmacytoid (pDC) DCs limits HIV replication in these cells by depleting intracellular pools of dNTPs and directly degrading viral RNA. Epidermal Langerhans cells express CD4 and have been infected by HIV in vivo, although, they too restrict replication by high expression of the host restriction factor, langerin. As has been shown in vivo for DCs, FDCs, and B cells, Langerhans cells are more likely to bind and transfer virus to activated CD4+ T cells than to be productively infected themselves.

Of potential clinical relevance is the demonstration that thymic precursor cells, which were assumed to be negative for CD3, CD4, and CD8 molecules, actually do express low levels of CD4 and can be infected with HIV in vitro. In addition, human thymic epithelial cells transplanted into an immunodeficient mouse can be infected with HIV by direct inoculation of virus into the thymus. Since these cells may play a role in the normal regeneration of CD4+ T cells, it is possible that their infection and depletion contribute, at least in part, to the impaired ability of the CD4+ T cell pool to completely reconstitute itself in certain infected individuals in whom cART has suppressed plasma viremia to below the level of detection (see below). In addition, CD34+ monocyte precursor cells have been shown to be infected in vivo in patients with advanced HIV disease. It is likely that these cells express low levels of CD4, and therefore it is not essential to invoke CD4-independent mechanisms to explain the infection. The clinical relevance of this finding is unclear.

QUALITATIVE AND QUANTITATIVE ABNORMALITIES OF MONONUCLEAR CELLS

CD4+ T Cells The primary immunopathogenic lesion in HIV infection involves CD4+ T cells, and the range of CD4+ T cell abnormalities in advanced HIV infection is broad. The defects are both

quantitative and qualitative and ultimately impact virtually every limb of the immune system, indicating the critical dependence of the integrity of the immune system on the inducer/helper function of CD4+ T cells. In advanced HIV disease, most of the observed immune defects can ultimately be explained by the quantitative depletion of CD4+ T cells. However, T cell dysfunction can be demonstrated in patients early in the course of infection, even when the CD4+ T cell count is in the low-normal range. The degree and spectrum of dysfunctions increase as the disease progresses, reflecting the range of CD4+ T cell functional heterogeneity, especially in lymphoid tissues. One of the first sites of intense HIV replication is in the GALT where CD4+ T_H17 cells reside; they are important for host defense against extracellular pathogens in the intestinal mucosa and help maintain the integrity of the gut epithelium. In HIV infection, they are depleted by direct and indirect effects of viral replication and cause loss of gut homeostasis and integrity, as well as a shift toward a T_H1 phenotype. Studies have shown that even after many years of cART, normalization of the CD4+ T cells in the GALT remains incomplete. In lymph nodes, HIV perturbs another important subset of the CD4+ helper T lineage, namely TF_H cells (see "Lymphoid Organs and HIV Pathogenesis," above). TF_H cells, which are derived either directly from naïve CD4+ T cells or from other T_H precursors, migrate into B follicles during germinal center reactions and provide help to antigen-specific B cells through cell–cell interactions and secretion of cytokines to which B cells respond, the most important of which is IL-21. As with T_H17 cells, TF_H cells are highly susceptible to HIV infection. However, in contrast to T_H17 and most other CD4+ T cell subsets, the number of TF_H cells is increased in lymph nodes of HIV-infected individuals, especially those who are viremic. It is unclear whether this increase is helpful to responding B cells, although the likely outcome is that the increase in numbers is detrimental to the quality of the humoral immune response against HIV (see "Immune Response to HIV," below). In addition, defects of central memory cells are a critical component of HIV immunopathogenesis. The progressive loss of antigen-specific CD4+ T cells has important implications for the control of HIV infection. In this regard, there is a correlation between the maintenance of HIV-specific CD4+ T cell proliferative responses and improved control of infection. Essentially every T cell function has been reported to be abnormal at some stage of HIV infection. Loss of polyfunctional HIV-specific CD4+ T cells, especially those that produce IL-2, occurs early in disease, whereas IFN-producing CD4+ T cells are maintained longer and do not correlate with control of HIV viremia. Other abnormalities include impaired expression of IL-2 receptors, defective IL-2 production, reduced expression of the IL-7 receptor (CD127), and a decreased proportion of CD4+ T cells that express CD28, a major co-stimulatory molecule necessary for the normal activation of T cells, which is also depleted as a result of aging. Cells lacking expression of CD28 do not respond normally to activation signals and may express markers of terminal activation including HLA-DR, CD38, and CD45RO. As mentioned above ("The Role of Immune Activation and Inflammation in HIV Pathogenesis"), a subset of CD4+ T cells referred to as *T regulatory cells*, or T-regs, may be involved in damping aberrant immune activation that propagates HIV replication. The presence of these T-reg cells correlates with lower viral loads and higher CD4+/CD8+ T cell ratios. A loss of this T-reg capability with advanced disease may be detrimental to the control of virus replication.

It is difficult to explain completely the profound immunodeficiency noted in HIV-infected individuals solely on the basis of direct infection and quantitative depletion of CD4+ T cells. This is particularly apparent during the early stages of HIV disease, when CD4+ T cell numbers may be only marginally decreased. In this regard, it is likely that CD4+ T cell dysfunction results from a combination of depletion of cells due to direct infection of the cell and a number of virus-related but indirect effects on the cell such as elimination of "innocent bystander cells" (Table 197-5). Several of these effects have been demonstrated ex vivo and/or by the analysis of cells isolated from the peripheral blood. Soluble viral proteins, particularly gp120, can bind with high affinity to the CD4 molecules on uninfected T cells and monocytes; in addition, virus and/or viral proteins can bind to DCs or FDCs. HIV-specific antibody can recognize these bound molecules and potentially collaborate in the elimination of the cells by ADCC. HIV envelope glycoproteins gp120 and gp160 manifest high-affinity binding to the CD4 molecule as well as to various chemokine receptors. Intracellular signals transduced by gp120 through both CD4 and CCR5/CXCR4 have been associated with a number of immunopathogenic processes including anergy, apoptosis, and abnormalities of cell trafficking. The molecular mechanisms responsible for these abnormalities include dysregulation of the T cell receptor–phosphoinositide pathway, p56lck activation, phosphorylation of focal adhesion kinase, activation of the MAP kinase and ras signaling pathways, and downregulation of the co-stimulatory molecules CD40 ligand and CD80.

The inexorable decline in CD4+ T cell counts that occurs in most HIV-infected individuals may result in part from the inability of the immune system to regenerate over an extended period of time the rapidly turning over CD4+ T cell pool efficiently enough to compensate for both HIV-mediated and naturally occurring attrition of cells. In this regard, the degree and duration of decline of CD4+ T cells at the time of initiation of therapy is an important predictor of the restoration of these cells. A person who maintains a very low CD4+ T cell count for a considerable period of time before the initiation of cART almost invariably has an incomplete reconstitution of such cells. At least two major mechanisms may contribute to the failure of the CD4+ T cell pool to reconstitute itself adequately over the course of HIV infection. The first is the destruction of lymphoid precursor cells, including thymic and bone marrow progenitor cells; the other is the gradual disruption of the lymphoid tissue architecture and microenvironment, which is essential for efficient regeneration of immunocompetent cells. Finally, during the advanced stages of CD4+ T lymphopenia, there are increased serum levels of the homeostatic cytokine IL-7. It was initially felt that this elevation was a homeostatic response to the lymphopenia; however, recent findings suggest that the increase in serum IL-7 was a result of reduced utilization of the cytokine related to the loss of cells expressing the IL-7 receptor, CD127, which serves as a normal physiologic regulator of IL-7 production.

CD8+ T Cells A relative CD8+ T lymphocytosis is generally associated with high levels of HIV plasma viremia and likely reflects an immune response to the virus as well as dysregulated homeostasis associated with generalized immune activation. During the late stages of HIV infection, there may be a significant reduction in the numbers of CD8+ T cells despite the presence of high levels of viremia. HIV-specific CD8+ CTLs have been demonstrated in HIV-infected individuals early in the course of disease, and their emergence often coincides with a decrease in plasma viremia—an observation that is a factor in the proposal that virus-specific CTLs can control HIV disease for a finite period of time in a certain percentage of infected individuals. However, emergence of HIV escape mutants that ultimately evade these HIV-specific CD8+ T cells has been described in the majority of HIV-infected individuals who are not receiving cART. In addition, as the disease progresses, the functional capability of these cells gradually decreases, at least in part due to the persistent nature of HIV infection that causes functional exhaustion via the upregulation of inhibitory receptors such as PD-1 and TIGIT on HIV-specific CD8+ T cells (see "The Role of Immune Activation and Inflammation in HIV Pathogenesis," above). As chronic immune activation persists, there are also systemic effects on CD8+ T cells, such that as a population they assume an abnormal phenotype characterized by expression of activation markers such as HLA-DR and CD38 with an absence of expression of the IL-2 receptor (CD25) and a reduced expression of the IL-7 receptor (CD127). In addition, CD8+ T cells lacking CD28 expression are increased in HIV disease, reflecting a skewed expansion of a less differentiated CD8+ T cell subset. This skewing of subsets is also associated with diminished polyfunctionality, a qualitative difference that distinguishes elite controllers from progressors. Elite controllers can also be distinguished from progressors by the maintenance in the former of a high proliferative capacity of their HIV-specific CD8+ T cells coupled to increases in perforin expression and elimination of infected targets, characteristics that are markedly diminished in advanced HIV disease. It has been

reported that the phenotype of CD8+ T cells in HIV-infected individuals may be of prognostic significance. Those individuals whose CD8+ T cells developed a phenotype of HLA-DR+/CD38– following seroconversion had stabilization of their CD4+ T cell counts, whereas those whose CD8+ T cells developed a phenotype of HLA-DR+/CD38+ had a more aggressive course and a poorer prognosis. In addition to the defects in HIV-specific CD8+ CTLs, functional defects in other MHC-restricted CTLs, such as those directed against influenza and CMV, have been demonstrated. CD8+ T cells secrete a variety of soluble factors that inhibit HIV replication, including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4) as well as potentially a number of as yet unidentified factors. The presence of high levels of HIV viremia in vivo as well as exposure of CD8+ T cells in vitro to HIV envelope, both of which are associated with aberrant immune activation, have been shown to be associated with a variety of cellular functional abnormalities. Furthermore, since the integrity of CD8+ T cell function depends in part on adequate inductive signals from CD4+ T cells, the defect in CD8+ CTLs is likely compounded by the quantitative loss and qualitative dysfunction of CD4+ T cells.

B Cells The predominant defect in B cells from HIV-infected individuals is one of aberrant cellular activation, which is reflected by increased propensity to terminal differentiation and immunoglobulin secretion, as well as increased expression of markers of activation and exhaustion. As a result of activation and differentiation in vivo, B cells from HIV viremic patients manifest a decreased capacity to mount a proliferative response to ligation of the B cell antigen receptor and other B cell stimuli in vitro. B cells from HIV-infected individuals manifest enhanced spontaneous secretion of immunoglobulins in vitro, a process that reflects their highly differentiated state in vivo. There is also an increased incidence of EBV-related B cell lymphomas in HIV-infected individuals that are likely due to combined effects of defective T cell immune surveillance and increased B cell turnover that increases the risk of oncogenesis. Untransformed B cells cannot be infected with HIV, although HIV or its products can activate B cells directly. B cells from patients with high levels of viremia bind virions to their surface via the CD21 complement receptor. It is likely that in vivo activation of B cells by replication-competent or defective virus as well as viral products during the viremic state accounts at least in part for their activated phenotype. B cell subpopulations from HIV-infected individuals undergo a number of changes over the course of HIV disease, including the attrition of resting memory B cells and replacement with several aberrant memory and differentiated B cell subpopulations that collectively express reduced levels of CD21 and either increased expression of activation markers or inhibitory receptors associated with functional exhaustion. The more activated and differentiated B cells are also responsible for increased secretion of immunoglobulins and increased susceptibility to Fas-mediated apoptosis. In more advanced disease, there is also the appearance of immature B cells associated with CD4+ T cell lymphopenia. Despite increased frequencies of germinal center B cells and CD4+ TF_H cells, both of which are required for effective humoral immunity, cognate B cell–CD4+ T cell interactions in lymphoid tissues are perturbed in HIV-infected individuals, especially those with persistent viremia. In vivo, the aberrant activated state of B cells manifests itself by hypergammaglobulinemia and by the presence of circulating immune complexes and autoantibodies. HIV-infected individuals respond poorly to primary and secondary immunizations with protein and polysaccharide antigens. Using immunization with influenza vaccine, it has been demonstrated that there is a memory B cell defect in HIV-infected individuals, particularly those with high levels of HIV viremia. There is also evidence that responses to HIV and non-HIV antigens in infected individuals, especially those who remain viremic, are enriched in abnormal subsets of B cells that either are highly prone to apoptosis or show signs of functional exhaustion. Taken together, these B cell defects are likely responsible at least in part for the inadequate humoral response to HIV as well as to decreased response to vaccinations and the increase in certain bacterial infections seen in advanced HIV disease in adults. In addition, they likely contribute to the inadequacy of host defenses against bacterial infections that play a role in the increased morbidity and mortality of HIV-infected children. The absolute number of circulating B cells also may be depressed in HIV infection; this phenomenon likely reflects increased activation-induced apoptosis as well as a redistribution of cells out of the circulation and into the lymphoid tissue—phenomena that are associated with ongoing viral replication.

Monocytes/Macrophages Circulating monocytes are generally normal in number in HIV-infected individuals; however, there is evidence of increased activation within this lineage. The increased level of sCD14 and other biomarkers (see above) reported in HIV-infected individuals is an indirect marker of monocyte activation in vivo. A number of other abnormalities of circulating monocytes have been reported in HIV-infected individuals, many of which may be related directly or indirectly to aberrant in vivo immune activation. In this regard, increased levels of lipopolysaccharide (LPS) are found in the sera of HIV-infected individuals due, at least in part, to translocation across the gut mucosal barrier (see above). LPS is a highly inflammatory bacterial product that preferentially binds to macrophages through CD14 and Toll-like receptors, resulting in cellular activation. Functional abnormalities of monocyte/macrophages in HIV disease include decreased secretion of IL-1 and IL-12; increased secretion of cytokines such as IL-10 and IL-18 and markers of coagulation such as D-dimer; defects in antigen presentation and induction of T cell responses due to decreased MHC class II expression; and abnormalities of Fc receptor function, C3 receptor–mediated clearance, oxidative burst responses, and certain cytotoxic functions such as ADCC, possibly related to low levels of expression of Fc and complement receptors. Monocytes express the CD4 molecule and several co-receptors for HIV on their surface, and thus are potential targets of HIV infection. However, in vivo infection of circulating monocytes is difficult to demonstrate, although infection of tissue macrophages and macrophage-lineage cells in the brain (infiltrating macrophages or resident microglial cells) and lung (pulmonary alveolar macrophages) can be demonstrated easily. Tissue macrophages are an important source of HIV during the inflammatory response associated with opportunistic infections and can serve as persistent reservoirs of HIV infection, thus representing an obstacle to the eradication of HIV by antiretroviral drugs. Infection of monocyte precursors in the bone marrow may directly or indirectly be responsible for certain of the hematologic abnormalities in HIV-infected individuals. However, as with DCs, monocytes and macrophages express high levels of host restriction factors that likely help explain the low contribution of myeloid cells to the overall viral burden in HIV-infected individuals.

Dendritic and Langerhans Cells DCs and Langerhans cells are not productively infected with HIV, but they are thought to play an important role in the initiation of HIV infection by virtue of the ability of HIV to bind to cell-surface C-type lectin receptors, particularly DC-SIGN (see above) and langerin. However, while langerin provides a host barrier for replication by trafficking HIV to acidic compartments for degradation, DC-SIGN retains HIV in early endosomal compartments. This allows efficient presentation of intact virus to CD4+ T cell targets that become infected; complexes of infected CD4+ T cells and DCs provide an optimal microenvironment for virus replication. Furthermore, pDCs secrete large amounts of IFN-α in response to viral infections and as such play an important role in innate sensing of HIV during early phase of infection. The numbers of circulating pDCs are decreased in HIV infection through mechanisms that remain unclear, although several studies have shown increased lymphoid tissue recruitment of DCs associated with lymphoid hyperplasia and inflammation. The mDCs or conventional DCs are also involved in the initiation of adaptive immunity in draining lymph nodes by presenting antigen to T cells and B cells, as well as by secreting cytokines such as IL-12, IL-15, and IL-18 that activate other immune cells. There are also indications that the relatively low infectibility of DCs may be associated with the expression of host restriction factors, including APOBEC3G and SAMHD1 (see above).

Natural Killer Cells The role of NK cells is to provide immunosurveillance against virus-infected cells, certain tumor cells, and

allogeneic cells **(Chap. 342)**. There are no convincing data that HIV productively infects NK cells in vivo; however, functional abnormalities in NK cells have been observed throughout the course of HIV disease, and the severity of these abnormalities increases as disease progresses. NK cells are part of the innate immune system and act by direct killing of infected cells and secretion of antiviral cytokines and chemokines. In early HIV infection there is an increase in the activation of NK cells, and the capacity to secrete IFN-γ is maintained, although they manifest reduced cytotoxic function. During chronic HIV infection, both NK cell cytotoxicity and cytokine secretion become impaired. Given that HIV infection of target cells downregulates HLA-A and B, but not HLA-C and D molecules, this may explain in part the relative inability of NK cells to kill HIV-infected target cells. However, the NK cell impairments, especially in patients with high levels of virus replication, are associated with an expansion of an "anergic" CD56–/CD16+ NK cell subset. This abnormal subset of NK cells manifests an increased expression of inhibitory NK cell receptors (iNKRs) and a substantial decrease in expression of natural cytotoxicity receptors (NCRs) and shows a markedly impaired lytic activity. The overrepresentation of this abnormal subset of NK cells may explain in part the observed defects in NK cell function in HIV-infected individuals and likely begins to occur during primary infection. The relative expression of iNKRs and NCRs—as well as their ligands, which include HLA class I molecules—has an impact on the antiviral functions associated with NK cells, including direct killing and ADCC. Polymorphisms in iNKR and NCR alleles have been linked to HIV-1 disease outcomes. NK cells also serve as important sources of HIV-inhibitory CC-chemokines. NK cells isolated from HIV-infected individuals constitutively produce high levels of MIP-1α (CCL3), MIP-1β (CCL4), and RANTES (CCL5), although the impact of these chemokines on HIV replication in vivo is unclear. Finally, NK cell–DC interactions are important for normal immune function. NK cells and DCs reciprocally modulate each other's activation and maturation. These interactions are markedly impaired in HIV-infected individuals with high levels of plasma viremia.

GENETIC FACTORS IN HIV-1 AND AIDS PATHOGENESIS

Candidate gene approaches and genome-wide association studies (GWAS) have identified polymorphisms in host genes that contribute to inter-individual variation in (1) the risk of acquiring HIV, (2) the steady-state levels of HIV that are established soon after infection (virologic set point), (3) the rate at which untreated HIV-infected patients progress to AIDS as well as risk of developing specific AIDS-defining illnesses (e.g., renal and neurologic diseases), and (4) the level of immune reconstitution (e.g., CD4+ counts) achieved after initiation of virally suppressive ART. The key polymorphisms that influence these four traits are summarized in **Table 197-6**, and their identification has greatly advanced our understanding of the genes that influence HIV-AIDS pathogenesis. Of particular interest are polymorphisms in two chromosomal regions, as they are associated with consistent effects on HIV acquisition, virologic set point, and/or rates of HIV disease progression: the region in chromosome 3 that includes the gene that encodes the HIV co-receptor *CC chemokine receptor 5* (*CCR5*) and the *major histocompatibility locus* (MHC) in chromosome 6 **(Fig. 197-26)**.

GENETICS OF CCR5: FROM BENCH TO BEDSIDE While the discovery of CCR5 as a major co-receptor for cell entry of HIV-1 was established by in vitro studies, genetic association studies were required to establish its seminal role in HIV pathogenesis. Initial in vitro studies revealed that a 32-bp deletion (*Δ32*) in the coding region of CCR5 contributes to resistance to CCR5-using R5 strains of HIV. The *CCR5 Δ32* allele encodes a truncated protein that is not expressed on the cell surface. Congruently, genotype-phenotype association studies in large cohorts demonstrated that individuals homozygous for the *CCR5 Δ32* allele (*Δ32/Δ32*) lack CCR5 surface expression and are highly resistant to acquiring HIV infection; heterozygosity for the *CCR5 Δ32* allele is associated with a lower risk of acquiring HIV.

The distribution of the *CCR5 Δ32* allele is population specific. Approximately 1% of individuals of European ancestry are homozygous for the *CCR5 Δ32* allele. Depending on the geographic region in Europe, up to 18% of individuals are heterozygous for the *CCR5 Δ32* allele. The *CCR5 Δ32* allele is rare in other populations. The evolutionary pressure that resulted in the emergence of the *CCR5 Δ32* allele in the European population remains unknown and has been speculated to be secondary to an ancestral pandemic, such as the plague.

Subsequent studies identified single nucleotide polymorphisms (SNPs) in the promoter (regulatory) region of *CCR5* that influence gene expression levels. Alleles bearing specific cassettes of linked polymorphisms (haplotypes) were identified and designated as human haplogroups A to G*2 (HHA to HHG*2) (Fig. 197-26). The *CCR5 Δ32* polymorphism is found on the HHG*2 haplotype. *CCR5* haplotypes A–D vs. E–G*2 differ by bearing GT versus AC at polymorphic sites rs1799987 and rs1799988 (Fig. 197-26). *CCR5-HHA* haplotype represents the ancestral haplotype (found in chimpanzees) and is associated with lower CCR5 gene expression, whereas the *CCR5-HHE* haplotype is associated with higher CCR5 expression. Methylation of DNA is a common epigenetic signaling mechanism that cells use to lock genes in the "off" position, and polymorphisms in *CCR5* haplotypes may mediate their effects by influencing DNA methylation levels in the *CCR5* locus. The *CCR5-HHE* and *CCR5-HHA* haplotypes are more sensitive and resistant, respectively, to T cell activation–induced demethylation of the *CCR5* locus.

In worldwide populations, HHE and HHC are more prevalent, whereas the ancestral HHA haplotype is more common in persons of African ancestry. The associations of *CCR5* haplotypes with HIV acquisition and/or HIV disease course are largely consistent with their effects on *CCR5* gene expression. For example, homozygosity for the *CCR5-HHE* haplotype is associated with an increased risk of acquiring HIV, progressing rapidly to AIDS, and reduced immune recovery while the patient is on ART. The HHA haplotype is associated with slower disease progression in African populations and has been speculated to be a basis for why chimpanzees (who all carry the ancestral *CCR5* HHA haplotype) naturally infected with simian immunodeficiency virus (SIV) may resist disease progression. The pairing of the HHC and *CCR5 Δ32*-bearing HHG*2 haplotypes (HHC/HHG*2 genotype) is associated with a lower risk of acquiring HIV infection and slower rate of HIV disease progression, whereas the pairing of the HHE haplotype with the HHG*2 haplotype is associated with the opposite effects. The *CCR2*-64I-bearing HHF*2 haplotype is associated with a slower HIV disease course.

Consistent with these genetic associations, polymorphisms in genes encoding ligands for CCR5 have also been demonstrated to associate with variable HIV susceptibility and disease progression rates. Examples include copy number variations of *CCL3L1* and SNPs in *CCL5*. The sum of these studies established a pivotal role of CCR5 and its ligands in HIV-AIDS pathogenesis and, potentially, immune recovery.

The discovery that the *CCR5 Δ32/Δ32* genotype is associated with strong resistance to HIV infection, and that uninfected Caucasians bearing this genotype did not appear to have impaired immunity, led to the development of two kinds of novel therapies. First, it spurred the development of a new class of therapies approved by the U.S. Food and Drug Administration (FDA), i.e., entry inhibitors (e.g., maraviroc) that block the interaction of CCR5 with the HIV envelope. Second, it led to the evaluation of novel experimental cellular therapies. An HIV-infected patient with acute myelogenous leukemia was given an allogeneic stem cell transplantation from an HLA-compatible person whose cells lacked expression of CCR5 due to the *Δ32/Δ32* genotype. There has been no evidence of HIV-1 infection in the patient who underwent the transplant thus far (~10 years). This observation provided a "proof of concept" for an HIV cure and led to the development of additional novel cellular therapies involving autologous transplantation of CD4+ T cells in which the *CCR5* gene is inactivated ex vivo using new gene editing procedures.

DISCOVERY OF HLA CLASS I ALLELES THAT ASSOCIATE WITH VIROLOGIC CONTROL OF HIV INFECTION There is a strong association between variations within the *HLA-B* gene with protective (e.g., HLA-B*57 and B*27 alleles) or detrimental (e.g., HLA-B*35 allele) outcomes during

TABLE 197-6 Host Genetic Factors That Influence Risk of HIV-1 Acquisition and Rates of HIV-1 Disease Progression

GENE[a]	GENETIC VARIATION	MECHANISMS[b]	GENETIC EFFECT ON HIV-AIDS[c]
Genes in MHC Locus			
HLA-B	B*27 and B*57	Presentation of specific HIV antigens	Slower progression to AIDS; lower viral load
	B*35	Restriction of specific HIV peptide presentation	Faster progression to AIDS; higher viral load
	HLA-Bw4	Providing ligands for activating KIR	Slower progression to AIDS
HLA class I allele	Homozygosity of *HLA*-class I alleles	Reduced repertoire for epitope recognition	Faster progression to AIDS; increased risk of mother-to-child transmission
	Shared donor-recipient *HLA* alleles	Preadaptation of HIV strains	Faster disease progression to AIDS
	Rare *HLA* alleles	Limited adaptation of HIV strains; less frequent escape mutants	Protection against HIV infection
HLA class II allele	*HLA-DRB1* alleles	Influencing protein specificity of CD4+ T cell responses to HIV Gag and Nef proteins	HLA-DRB1*15:02—lower viral load HLA-DRB1*03:01—higher viral load
HLA extended haplotype	A1-B8-DR3-DQ2 (AH 8.1)	Increased proinflammatory responses; higher TNF-α production	Faster progression to AIDS
HLA-C	35 kb upstream, rs9264942-C	Increased expression of HLA-C	Decreased viral load set point
HCP5	rs2395029-G	Linkage disequilibrium with HLA-B*57:01	Lower viral load
MICA	Noncoding SNP near *MICA*, rs4418214-T	May affect HLA class I peptide presentation—linkage with protective *HLA-B* alleles	Enriched in HIV-1 controllers
PSORS1C3	rs3131018-A	May affect HLA class I peptide presentation	Enriched in HIV-1 controllers
ZNRD1	rs9261174-C	Possible interference in processing of HIV transcripts; influencing ZNRD1 expression; linkage disequilibrium with *HLA-A10*	Slower disease progression to AIDS
Chemokine Receptors			
CCR5	32-bp deletion in the ORF (Δ32), rs333	Truncated CCR5 protein	Δ32/Δ32: resistance to acquiring HIV infection Δ32/wild type: delays AIDS onset; improves immune reconstitution during ART
	Promoter SNPs, haplotypes (HHA to HHG*2)	Altered CCR5 expression, e.g., HHE haplotype correlates with high CCR5 expression	HHE/HHE: increased HIV/AIDS susceptibility
CCR2	SNP in ORF (64 V→I), rs1799864	Possibly due to linkage with polymorphism in *CCR5* promoter	64I: delayed AIDS onset
CCRL2	Coding SNP (167 Y→F) rs3204849	Possibly due to linkage with *CCR5* haplotype	167F is associated with accelerated progression to AIDS and more rapid development of PCP
	rs1015164	Possibly due to linkage with *CCR5* haplotype	Associated with high viral load set point
CXCR6	rs2234358 G→T in the 3'UTR	Trafficking of effector T cells and activation of NK T cells; minor HIV co-receptor	Prevalence of rs2234358-T was lower in long-term nonprogressors and viremic controllers
CX3CR1	SNPs in ORF (249 V→I, rs3732379; and 280 T→M, rs3732378)	280M reduces receptor expression and binding of fractalkine, the CX3CR1 ligand	249I and 280M associated with faster AIDS onset in some Caucasian cohorts; inconsistent effects detected in other cohorts
DARC	African-specific promoter SNP (–46T→C), rs2814778	–46C/C associates with low neutrophil counts; influences circulating chemokine levels; alters HIV binding to RBCs and transinfection of HIV-1	–46C/C: increased risk of acquiring HIV but slower HIV disease progression; Duffy-null-associated low neutrophil trait associated with increased HIV risk in persons of African descent
Chemokines			
CCL3L, CCL4L	Gene copy number of *CCL3L* and *CCL4L*	High numbers of *CCL3L* and *CCL4L* gene-containing segmental duplications correlate with high CCL3L and CCL4L levels	Gene copy number lower than population median associated with increased HIV/AIDS susceptibility and reduced immune reconstitution during ART
CCL5	Promoter SNPs	Altered gene expression	Altered HIV-AIDS susceptibility
CCL2	Promoter SNP (–2578 T→G), rs1024611	–2578G allele: increased CCL2 expression and monocyte recruitment	–2578G/G associated with increased risk of developing HIV-1-associated dementia and rapid AIDS onset
Cytokines			
IL-6	Promoter SNP (–174 G→C), rs1800795	–174G/G associated with increased IL-6 and CRP levels	–174G/G associated with high risk of KS development and variable recovery of CD4 cells during ART
IL-7RA	Coding SNP (244 T→I), rs6897932	244 I/I associated with increased signal transduction and proliferation in response to IL-7	244 I/I associated with faster CD4+ T cell recovery after ART initiation
IL-10	Promoter SNP (–592 C→A), rs1800872	–592A results in decreased IL-10 levels	–592A associated with increased HIV-AIDS susceptibility

(*Continued*)

TABLE 197-6 Host Genetic Factors That Influence Risk of HIV-1 Acquisition and Rates of HIV-1 Disease Progression (Continued)

GENE[a]	GENETIC VARIATION	MECHANISMS[b]	GENETIC EFFECT ON HIV-AIDS[c]
Innate Immunity Genes			
MBL	Coding alleles (O)	Low plasma concentration and structural variation of MBL protein	Slow progression to AIDS in heterozygous subjects (A/O)
	X allele (promoter SNP –221)	Decreased levels of MBL protein	Faster progression to AIDS in homozygous X/X subjects
Apobec-3G	ORF SNP (186 H→R), rs8177832	Reduced anti-HIV-1 activity	186R associated with rapid AIDS onset in African Americans
Apobec-3F	Haplotype tagged by ORF SNP (231 I→V), rs2076101	231V variant may influence Vif-mediated Apobec-3F degradation	231V associated with lower VL, slower progression to AIDS and delayed progression to PCP
TLR7	ORF SNP (Gln11Leu), rs179008	Decreased expression of TLR7 leading to lack of recognition of HIV-infected cells	Leu-containing protein associated with higher viral load and faster progression to AIDS
PARD3B	rs11884476 (C→G), near exon 20	Direct interaction with HIV, signaling through SMAD family of proteins	rs11884476-G associated with slower progression to AIDS
IFNL4	Frameshift mutation (TT→ΔG), rs368234815	Functional polymorphism in *IFNL4* gene, possibly in linkage with IL28B variant and regulates IL-28B levels	rs368234815-ΔG associated with higher prevalence of AIDS-defining illnesses and potentially increased HIV-1 infection risk
Others			
ApoE	E4 allele	E4 enhances HIV cell entry in vitro	ApoE4/E4 associated with rapid AIDS onset and dementia
ApoL1/ MYH9	Several risk haplotypes, including G1	Unknown	Increased risk for HIV-associated nephropathy
RYR3	ORF SNP (A →G), rs2229116	Unknown, potential impact on calcium signaling and homeostasis	rs2229116-G associated with subclinical atherosclerosis
PROX1	rs17762192-G, 36kb upstream of *PROX1*	Unknown, presumably due to its impact on PROX1 expression, which is a negative regulator of IFN-γ	rs17762192-G: reduced rate of disease progression
Gene–Gene Interaction			
KIR+HLA	KIR3DS1 + HLA-Bw4-80Ile	Altered NK cell activity required to eliminate HIV-infected cells	KIR3DS1 associated with HLA-Bw4-80Ile; +: delayed AIDS onset
	HLA-C1 + KIR2DL3	Reduction of inhibitory KIR likely results in increased immune activation; impaired killing of latently infected cells; and a higher proviral burden	HLA-C1+/KIR2DL3+: better immune recovery after viral load suppression on ART
LILRB2+HLA	LILRB2 + HLA class I	Regulation of dendritic cells by LILRB2-HLA engagement	Control of HIV-1
CCL3L1+ CCR5	Low *CCL3L1* gene copies + detrimental *CCR5* genotypes	Low CCL3L1 and high CCR5 expression	Increased HIV/AIDS susceptibility and reduced immune reconstitution during ART

[a]Representative genes and polymorphisms and [b]possible mechanisms are listed. [c]Some of the associations are population specific and may display cohort-specific effects.

Note: Apobec, apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like; ApoE, apolipoprotein E; ART, antiretroviral therapy; CCL, CC ligand; CCL3L, CCL3-like; CCR5, CC chemokine receptor 5; CCRL2: CC chemokine receptor like 2; CRP, C-reactive protein; CXCR6, chemokine (C-X-C motif) receptor 6; DARC, Duffy antigen receptor for chemokines; HCP5, HLA class I histocompatibility antigen protein P5; HHE, human haplogroup E; HLA, human leukocyte antigen; IFN, interferon; IFNL4, interferon λ4 gene; IL, interleukin; IL-7RA, interleukin 7 receptor-α; KIR, killer cell immunoglobulin-like receptors; KS, Kaposi's sarcoma; LILRB2, leukocyte immunoglobulin-like receptor B2; MBL, mannose-binding lectin; MHC, major histocompatibility complex; MICA, MHC class I polypeptide-related sequence A; NK, natural killer; ORF, open reading frame; PARD3B, par-3 family cell polarity regulator beta; PCP, *Pneumocystis* pneumonia; PROX1, prospero homeobox 1; PSORS1C3, psoriasis susceptibility 1 candidate 3; SMAD, Mothers against decapentaplegic homolog; SNP, single nucleotide polymorphism; rs#, SNP identification number; TNF-α, tumor necrosis factor-α; UTR, untranslated region; VL, viral load; ZNRD1, zinc ribbon domain containing 1; +, present, –, absent.

Sources: Sunil K. Ahuja, MD, Weijing He, MD, Kristen Rogers, MS. Reviews for additional information: P An et al: Trends Genet 26:119, 2010; J Fellay: Antivir Ther 14:731, 2009; RA Kaslow et al: J Infect Dis 191:S68, 2005; D van Manen et al: Retrovirology 9:70, 2012; MP Martin et al: Immunol Rev 254:245, 2013; S Limou et al: Front Immunol 4:118, 2013; PJ McLaren et al: Curr Opin HIV AIDS 10:110, 2015; PJ McLaren et al: Proc Natl Acad Sci USA 112:14658, 2015; PJ McLaren, M Carrington: Nat Immunol 16:577, 2015; P An et al: PLoS Genet 12:e1005921, 2016; F Pereyra et al: Science 330:1551, 2010; I Bartha et al: PLoS Comput Biol 13:e1005339, 2017.

HIV infection. Carriage of the HLA-B*57 and/or HLA-B*27 alleles is associated with slower disease progression. The beneficial effects of these alleles may relate in part to their consistent associations with a lower virologic set point as well as to higher cell-mediated immunity in HIV-infected persons. The protective effect of the HLA-B*57 and B*27 alleles on the HIV disease course is underscored by the finding that the prevalence of these alleles is higher among long-term nonprogressors and persons who control HIV replication spontaneously (elite controllers). In contrast, the HLA-B*35 allele has been associated with faster progression to AIDS and higher viral load. The prevalence of the *HLA-B* alleles differs between populations. HLA-B*57:01 in Europeans and HLA-B*57:03 in African Americans are the protective alleles. In some populations (e.g., Japanese) where the HLA-B*57/-B*27 alleles are absent, HLA-B*51 is associated with a protective phenotype.

Possession of the protective *HLA-B* alleles is associated with broader and stronger CD8+ T cell responses to HIV epitopes. The mechanisms underlying the differential effects of the *HLA-B* alleles on the course of HIV disease may relate to differences in the ability of antigen-presenting cells to present immunodominant HIV epitopes to T helper or cytotoxic T lymphocytes in the context of MHC-encoded molecules. This may result in differential immune responses that influence viral replication. In this regard, the *HLA-B* alleles that impact the course of HIV disease differ in their amino acid residues in the HLA-B peptide-binding groove; this may play a critical role in virologic control.

Investigators have also examined the influence of extended *HLA* haplotypes (linked alleles) on the course of HIV disease. The extended *HLA* ancestral haplotype (AH) 8.1 is defined by the presence of HLA-A1, HLA-B8, and HLA-DR3 alleles. AH 8.1 is the most common ancestral haplotype in Caucasians (present in 10%) and is associated with multiple autoimmune diseases in HIV-uninfected persons. These associations of AH 8.1 are thought to be due to a genetically determined hyperresponsiveness characterized by high TNF-α production

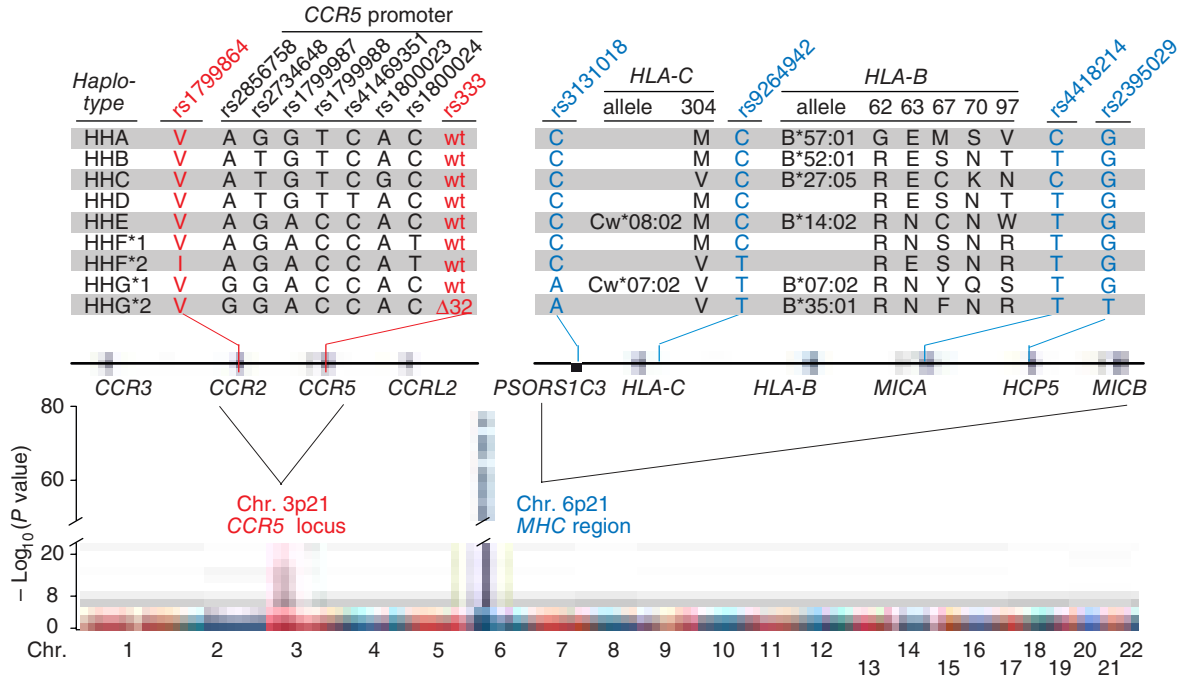


FIGURE 197-26 CCR5 and MHC loci: two key regions that influence HIV-AIDS pathogenesis. ***Bottom:*** Manhattan plot of genome-wide association from >6000 HIV-infected Europeans. *(Adapted from PJ McLaren et al: Proc Acad Natl Acad Sci 112:14658, 2015.)* ~8 million common variants were tested for their association with HIV viral load set point using linear regression. Genome-wide signals of association ($p < 5 \times 10^{-8}$, dotted line) were observed on chromosomes (Chr.) 6p21 in the MHC region and 3p21 in the *CCR5* locus. ***Upper left:*** schema depicting composition of *CCR5* haplotypes. *(Adapted from E Gonzalez et al: Proc Natl Acad Sci USA 96:12004, 1999.)* The 9 human haplotypes (HH) designated as HHA to HHG*2 were derived from the coding polymorphism of CCR2 64 V → I; 7 single nucleotide polymorphisms (SNPs) in the *CCR5* promoter region as well as the Δ32 coding mutation in *CCR5*; wt, wild type. Carrington and colleagues refer to the *CCR5-HHE* haplotype as the P1 haplotype (*MP Martin et al: Science 282:1907, 1998*). ***Upper right:*** Representative haplotypes at Chr. 6p21 MHC region in Europeans. *(Adapted from F Pereyra et al: Science 330:1551, 2010.)* Haplotypes defined by the SNPs identified by genome-wide association studies, classic HLA alleles and amino acids in HLA-B and HLA-C that are associated with HIV viral control. Figure is not to scale and full references are in Table 197-6.

and lack of complement C4A. Strong epidemiologic data indicate that carriage of AH 8.1 in HIV-infected persons is associated with a rapid decline in CD4+ T cells and faster progression to AIDS development. Gene–gene interactions between HLA alleles and other genes (e.g., killer cell immunoglobulin-like receptors) also may influence HIV disease progression rates.

POLYMORPHISMS IDENTIFIED BY GWAS THAT ASSOCIATE WITH HIV-1 ACQUISITION AND VIROLOGIC CONTROL GWAS have not identified additional genetic variations that associate with risk of HIV-1 acquisition. By contrast, large-scale GWAS have identified SNPs, especially in the MHC, that influence HIV viral load, including in a large group of individuals termed "HIV controllers" who spontaneously (without ART) control viral replication. GWAS in HIV-infected persons of European ancestry identified four SNPs in genes in the HLA class I loci that associated with virologic control. These SNPs are within or in the vicinity of *PSORS1C3*, *HLA-C*, *MICA*, and *HCP5* genes (Fig. 197-26). As noted in this figure, the individual effects of these alleles are difficult to discern because of linkage disequilibrium. The protective effects of the SNPs in *HCP5* and *MICA* may relate to their linkage with known protective *HLA-B* alleles. The protective *HCP5* allele is in linkage disequilibrium with the HLA-B*57:01 allele, and the protective *MICA* allele tags with the HLA-B*57:01 and B*27:05 alleles. The protective *HLA-C* SNP is associated with higher HLA-C expression, and this effect is thought to be due to the altered binding of a microRNA to the *HLA-C* mRNA. Higher HLA-C expression has been associated with beneficial HIV phenotypes. The mechanism associated with the SNP in *PSORS1C3* is unknown. GWAS in African Americans identified a SNP that tags the HLA-B*57:03 allele that is known to associate with a lower virologic set point and slower disease course. Together, these GWAS data underscore the importance of variations in HLA class I loci in control of viral replication. A recent GWAS study suggested that an allele in the gene encoding *CCRL2* influences the HIV viral load set point. *CCRL2* is on chromosome 3p21 and resides ~30 kb downstream of the *CCR5* loci; its effect could potentially be due to its linkage with the *CCR5* haplotypes. Mathematical modeling revealed that variations in host genes may explain about 10% of the observed variability in HIV viral load, whereas viral genetic diversity may explain 29% of the variability.

GENETIC ASSOCIATIONS WITH SPECIFIC AIDS AND NON-AIDS CONDITIONS

Carotid artery disease Many of the non-AIDS events in HIV-infected individuals resemble those related to immune senescence and those found in the HIV-uninfected aging population. A functional SNP in the ryanodine receptor 3 (*RYR3*) gene was found to be associated with an increased risk of common carotid intima–media thickness (cIMT), which is a surrogate for subclinical atherosclerosis. Functional studies on *RYR3* and its isoforms demonstrate a major role of these receptors in modulating endothelial function and atherogenesis via calcium signaling pathways, providing a biologically plausible mechanism by which the SNP in *RYR3* may associate with increased cIMT risk.

Renal disease HIV-1-associated nephropathy (HIVAN) is a form of focal sclerosing glomerulonephritis caused by direct infection of kidney epithelial cells with HIV. HIVAN is more common in persons of African descent. There is evidence that polymorphisms in the *MYH9* gene and in the neighboring *APOL1* gene are a strong determinant of susceptibility to HIVAN in African Americans. The effect of carrying two *APOL1* risk alleles explains nearly 35% of HIVAN. The mechanisms by which *MYH9*/*APOL1* variants predispose to HIVAN are currently unknown.

HIV-associated neurocognitive disorder HIV-associated neurocognitive disorder (HAND) comprises a spectrum of neurocognitive deficits due to HIV infection. Variations in the apolipoprotein E (ApoE) gene have strong associations with Alzheimer's disease in the HIV-uninfected population. In HIV-infected persons, possession of the *ApoE4* allele has been associated with several cognitive outcomes, including dementia, peripheral neuropathy, and impairment in cognition and immediate and delayed verbal memory. Macrophage recruitment and activation play a central role in the development of many of the HAND syndromes. Variations in chemokines that play

an influential role in macrophage activation and recruitment, namely *CCL2* (MCP-1) and *CCL3* (MIP-1α), have been shown to alter the risk of developing HAND. Variations in mitochondrial genes also have been associated with risk of AIDS and HAND. A GWAS identified a polymorphism in chromosome 14 in the T cell receptor α locus that may influence neurocognitive outcomes.

HIV-1 associated Pneumocystis pneumonia Human Apobec3 cytidine deaminases are intrinsic resistance factors to HIV-1. However, HIV-1 encodes a viral infectivity factor (Vif) that degrades Apobec3 proteins. Association studies suggest a role of the genetic variation in the Apobec3 family in HIV disease. A common haplotype derived from 6 SNPs in the *Apobec-3F* gene and tagged by a codon-changing variant is associated with significantly lower viral load set point, slower rate of progression to AIDS, and delayed development of *Pneumocystis* pneumonia (PCP). In addition, a coding SNP in the *CCRL2* gene is associated with accelerated progression to AIDS and more rapid development of PCP.

ASSOCIATIONS WITH ART-RELATED ADVERSE EVENTS Abacavir, an effective antiretroviral agent, is associated with significant risk of hypersensitivity reactions (2–9% of cases). Interestingly, while the *HLA-B*57:01* allele is associated with a slower HIV disease course, possession of this allele is associated with a higher risk of abacavir-associated hypersensitivity. Pharmacogenetic screening for the *HLA-B*57:01* allele is recommended before initiation of abacavir treatment.

NEUROPATHOGENESIS IN HIV DISEASE

While there has been a remarkable decrease in the incidence of the severe forms of HIV encephalopathy among those with access to treatment in the era of effective cART, HIV-infected individuals can still experience milder forms of neurocognitive impairment despite adequate cART. Factors that contribute to the neurocognitive decline include lack of complete control of HIV replication in the brain; production of HIV proteins that may be neurotoxic; low CD4+ T cell nadir; chronic immune activation; comorbidities such as drug abuse, microvascular disease, older age, and diabetes; and the potential for neurotoxicity of certain antiretroviral drugs. HIV has been demonstrated in the brain and CSF of infected individuals with and without neuropsychiatric abnormalities. As opposed to lymphoid tissues, there are no resident lymphocytes in the brain. The main cell types that are infected in the brain in vivo are the perivascular macrophages and the microglial cells, which can sometimes form syncytia resulting in multinucleated giant cells; low-level viral replication is also seen in perivascular astrocytes. It has been proposed that monocytes that have already been infected in the blood can migrate into the brain, where they then reside as macrophages, or macrophages can be directly infected while residing within the brain. The precise mechanisms whereby HIV enters the brain are unclear; however, they are thought to relate, at least in part, to the ability of virus-infected and immune-activated macrophages to induce adhesion molecules such as E-selectin and vascular cell adhesion molecule 1 (VCAM-1) on brain endothelium. Other studies have demonstrated that HIV gp120 enhances the expression of intercellular adhesion molecule 1 (ICAM-1) in glial cells and HIV Tat protein can disrupt the tight junctions of the brain endothelial cells to facilitate entry of HIV-infected cells into the CNS. Virus isolates from the brain are preferentially R5 strains as opposed to X4 strains; in this regard, HIV-infected individuals who are heterozygous for *CCR5-Δ32* appear to be relatively protected against the development of HIV encephalopathy. Once HIV enters the brain due to pressures of the local environment, it evolves to develop distinct sequences in the env, tat, and LTR genes. These unique sequences have been associated with neurocognitive dysfunction; however, it is unclear if they are causal (see below).

HIV-infected individuals may manifest white matter lesions as well as neuronal loss. The white matter lesions are due to axonal injury and a disruption of the blood-brain barrier and not due to demyelination. Given the absence of evidence of HIV infection of neurons, HIV-mediated effects on neurons are thought to involve indirect pathways whereby viral proteins, particularly gp120 and Tat, trigger the release of endogenous neurotoxins from macrophages and to a lesser extent from astrocytes. In addition, it has been demonstrated that both HIV-1 Nef and Tat can induce chemotaxis of leukocytes, including monocytes, into the CNS. Neurotoxins can be released from monocytes as a consequence of infection and/or immune activation. Monocyte-derived neurotoxic factors have been reported to kill neurons via a variety of mechanisms including activation of the *N*-methyl-D-aspartate (NMDA) receptors and induction of oxidative stress. In addition, HIV gp120 shed by virus-infected monocytes could cause neurotoxicity by antagonizing the function of vasoactive intestinal peptide (VIP), by elevating intracellular calcium levels, and by decreasing neurotrophic factor levels in the cerebral cortex. A variety of monocyte-derived cytokines can contribute directly or indirectly to the neurotoxic effects in HIV infection; these include TNF-α, IL-1, IL-6, TGF-β, IFN-γ, platelet-activating factor, and endothelin. Furthermore, among the CC-chemokines, elevated levels of monocyte chemotactic protein-1 (MCP-1 or CCL-2) in the brain and CSF have been shown to correlate best with the presence and degree of HIV encephalopathy in ART-naïve patients. In addition, infection and/or activation of monocyte-lineage cells can result in increased production of eicosanoids, quinolinic acid, nitric oxide, excitatory amino acids such as L-cysteine and glutamate, arachidonic acid, platelet activating factor, free radicals, TNF-α, and TGF-β, which may contribute to neurotoxicity. Astrocytes may play diverse roles in HIV neuropathogenesis. Reactive gliosis or astrocytosis has been demonstrated in the brains of HIV-infected individuals, and TNF-α and IL-6 have been shown to induce astrocyte proliferation. In addition, astrocyte-derived IL-6 can induce HIV expression in infected cells in vitro. Furthermore, it has been suggested that astrocytes may downregulate macrophage-produced neurotoxins. Evidence of neuronal injury can be demonstrated by measuring neurofilament levels in CSF. Treatment with cART leads to improvement in neuropsychiatric manifestations and a decrease in these cytokine levels in CSF, suggesting that they are driven by the virus or by its products. However, even in patients on long-term cART, there may be evidence of persistently activated lymphocytes in the CSF. It is unclear if these lymphocytes may contribute to neuronal injury in the brain or are critical for controlling the CNS viral reservoir. However, some individuals may develop a subacute encephalitis due to an IRIS reaction (see below). This often occurs weeks or a few months after initiation of cART in individuals with low CD4+ T cell counts. It is thought that the recovery of CD4+ T cells causes a lymphocyte response to the CNS HIV reservoir. The contribution of host genetic factors to development of neuropsychiatric manifestations of HIV infection has not been well studied. However, evidence supports the role of several genetic factors including the E4 allele for apoE in an increased risk of HIV-associated neurocognitive disorders and peripheral neuropathy.

It has also been suggested that the CNS may serve as a relatively sequestered site for a reservoir of latently infected cells that might be a barrier for the eradication of virus by cART (see "The HIV Reservoir: Obstacles to the Eradication of Virus," above).

PATHOGENESIS OF KAPOSI'S SARCOMA

There are at least four distinct epidemiologic forms of KS: (1) the classic form that occurs in older men of predominantly Mediterranean or eastern European Jewish backgrounds with no recognized contributing factors; (2) the equatorial African form that occurs in all ages, also without any recognized precipitating factors; (3) the form associated with organ transplantation and its attendant iatrogenic immunosuppressed state; and (4) the form associated with HIV-1 infection. In the latter two forms, KS is an opportunistic disease; in HIV-infected individuals, unlike typical opportunistic infections, its occurrence is not strictly related to the level of depression of CD4+ T cell counts. The pathogenesis of KS is complex; fundamentally, it is an angioproliferative disease that is not a true neoplastic sarcoma, at least not in its early stages. It is a manifestation of excessive proliferation of spindle cells that are believed to be of vascular origin and have features in common with endothelial and smooth-muscle cells. In HIV disease the development of KS is dependent on the interplay of a variety of factors including HIV-1 itself, human herpes virus 8 (HHV-8), immune activation, and

cytokine secretion. A number of epidemiologic and virologic studies have clearly linked HHV-8, which is also referred to as *Kaposi's sarcoma–associated herpesvirus* (KSHV), to KS not only in HIV-infected individuals but also in individuals with the other forms of KS. HHV-8 is a γ-herpesvirus related to EBV and *herpesvirus saimiri*. It encodes a homologue to human IL-6 and, in addition to KS, has been implicated in the pathogenesis of body cavity lymphoma, multiple myeloma, and monoclonal gammopathy of undetermined significance. Sequences of HHV-8 are found universally in the lesions of KS, and patients with KS are virtually all seropositive for HHV-8. HHV-8 DNA sequences can be found in the B cells of 30–50% of patients with KS and 7% of patients with AIDS without clinically apparent KS.

Between 1% and 2% of eligible blood donors are positive for antibodies to HHV-8, while the prevalence of HHV-8 seropositivity in HIV-infected men is 30–35%. The prevalence of HHV-8 seropositivity in HIV-infected women is ~4%. This finding is reflective of the lower incidence of KS in women. It has been debated whether HHV-8 is actually the transforming agent in KS; the bulk of the cells in the tumor lesions of KS are not neoplastic cells. However, it has been demonstrated that endothelial cells can be transformed in vitro by HHV-8. In this regard, HHV-8 possesses a number of genes, including homologues of the IL-8 receptor, Bcl-2, and cyclin D, that can potentially transform the host cell. Despite the complexity of the pathogenic events associated with the development of KS in HIV-infected individuals, HHV-8 is the etiologic agent of this disease. The initiation and/or propagation of KS requires an activated state and is mediated, at least in part, by cytokines. A number of factors, including TNF-α, IL-1β, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), basic fibroblast growth factor, and oncostatin M, function in an autocrine and paracrine manner to sustain the growth and chemotaxis of the KS spindle cells. In this regard, KSHV-derived IL-6 has been demonstrated to induce proliferation of lymphoma cells and to inhibit the cytostatic effects of IFN-α on KSHV-infected lymphoma cells.

IMMUNE RESPONSE TO HIV

As detailed above and below, following the initial burst of viremia during primary infection, HIV-infected individuals mount robust immune responses that in most cases substantially curtail the levels of plasma viremia and likely contribute to delaying the ultimate development of clinically apparent disease for a median of 10 years in untreated individuals. This immune response contains elements of both humoral and cell-mediated immunity involving both adaptive and innate immune responses (**Table 197-7**; **Fig. 197-27**). It is directed against multiple antigenic determinants of the HIV virion as well as against viral proteins expressed on the surface of infected cells. Ironically, those CD4+ T cells with T cell receptors specific for HIV are theoretically those CD4+ T cells most likely to be activated—and thus to serve as early targets for productive HIV infection and the cell death or dysfunction associated with infection. Thus, an early consequence of HIV infection is interference with and decrease of the helper T cell population needed to generate an effective immune response.

Although a great deal of investigation has been directed toward delineating and better understanding the components of this immune response, it remains unclear which immunologic effector mechanisms are most important in delaying progression of infection and which, if any, play a role in the pathogenesis of HIV disease. This lack of knowledge has also hampered the ability to develop an effective vaccine for HIV disease.

HUMORAL IMMUNE RESPONSE

Antibodies to HIV usually appear within 3–6 weeks and almost invariably within 12 weeks of primary infection (**Fig. 197-28**); rare exceptions are in individuals who have defects in the ability to produce HIV-specific antibodies. Detection of these antibodies forms the basis of most diagnostic screening tests for HIV infection. The appearance of HIV-binding antibodies detected by ELISA and western blot assays occurs prior to the appearance of neutralizing antibodies; the latter generally appear following the initial decreases in plasma viremia and are more closely related to the appearance of HIV-specific

TABLE 197-7 Elements of the Immune Response to HIV

Humoral immunity
Binding antibodies
Neutralizing antibodies
Type specific
Group specific
Broadly neutralizing
Antibodies participating in antibody-dependent cellular cytotoxicity (ADCC)
Protective
Pathogenic (bystander killing)
Enhancing antibodies
Complement
Cell-mediated immunity
Helper CD4+ T lymphocytes
Class I MHC–restricted cytotoxic CD8+ T lymphocytes
CD8+ T cell–mediated inhibition (noncytolytic)
ADCC
Natural killer cells

Abbreviation: MHC, major histocompatibility complex.

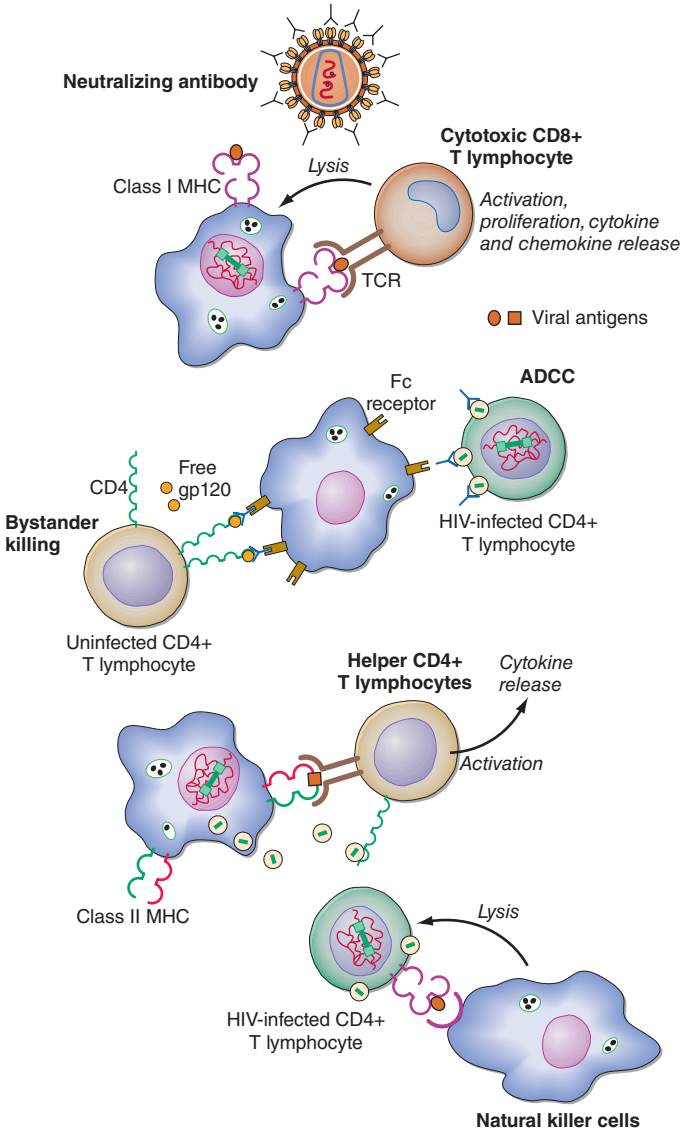


FIGURE 197-27 Schematic representation of the different immunologic effector mechanisms thought to be active in the setting of HIV infection. Detailed descriptions are given in the text. ADCC, antibody-dependent cellular cytotoxicity; MHC, major histocompatibility complex; TCR, T cell receptor.

CD8+ T lymphocytes. The first antibodies detected are those directed against the immunodominant region of the envelope gp41, followed by the appearance of antibodies to the structural or gag protein p24 and the gag precursor p55. Antibodies to p24 gag are followed by the appearance of antibodies to the outer envelope glycoprotein (gp120), the gag protein p17, and the products of the *pol* gene (p31 and p66). In addition, one may see antibodies to the low-molecular-weight regulatory proteins encoded by the HIV genes *vpr*, *vpu*, *vif*, *rev*, *tat*, and *nef*. On rare occasion, levels of HIV-specific antibodies may decline during treatment of acute HIV infection.

While antibodies to multiple antigens of HIV are produced, the precise functional significance of these different antibodies is unclear. The only viral proteins that elicit neutralizing antibodies are the envelope proteins gp120 and gp41. Antibodies directed toward the envelope proteins of HIV have been characterized both as being protective and as possibly contributing to the pathogenesis of HIV disease. Among the protective antibodies are those that function to neutralize HIV directly and prevent the spread of infection to additional cells, as well as those that participate in ADCC. The first neutralizing antibodies are directed against the autologous infecting virus and appear after approximately 12 to 24 weeks of infection. Due to its high rate of mutation the virus is usually able to quickly escape these (and subsequent) neutralizing antibodies. One important mechanism of immune escape is the addition of N-linked glycosylation sites, forming a glycan shield that interferes with envelope recognition by these initial antibodies.

A number of broad and potent HIV-neutralizing envelope-specific antibodies have been isolated from HIV-infected individuals in studies designed to better understand the host response to HIV infection. Approximately 20% of patients develop antibodies capable of neutralizing highly diverse strains. These usually appear 2 or more years following infection in the face of continual viremia. These studies have revealed at least five major sites within the HIV envelope trimer that are able to elicit broadly neutralizing antibodies. These sites include antibodies directed toward the CD4 binding site (CD4bs) of gp120, those binding glycan-dependent epitopes in the V1/V2 region of gp120, those near the base of the V3 region of gp120, those binding to the gp120/gp41 bridge, and those binding to the membrane-proximal region of gp41 **(Fig. 197-29)**. Several of these antibodies contain unique features including high levels of somatic hypermutation, selective germline gene usage (especially for CD4bs antibodies), and long heavy chain complementary determining regions (especially CDRH3). Of note, while these antibodies are broadly neutralizing in vitro, their precise in vivo significance is unclear and the patients from whom they were derived demonstrate evidence of ongoing viral replication unless treated with cART.

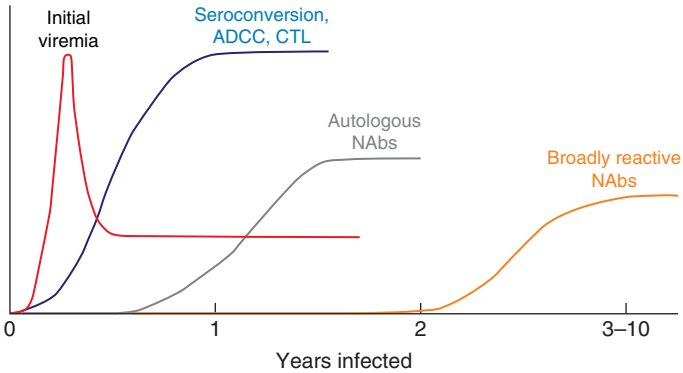


FIGURE 197-28 Relationship between initial HIV viremia and the development of antibodies to HIV. Within 3 to 6 weeks of initial HIV infection, non-neutralizing antibodies to HIV appear. These antibodies are capable of mediating antibody-dependent cellular cytotoxicity (ADCC). The decline in plasma viremia generally correlates with the appearance of cytotoxic T lymphocytes (CTL). After approximately 3 months, autologous neutralizing antibodies (NAbs) capable of neutralizing prior circulating strains of HIV appear. After 2 or more years, broadly reactive NAbs appear. *(Adapted from JT Mascola, DC Montefiori: Annu Rev Immunol 28:413, 2010.)*

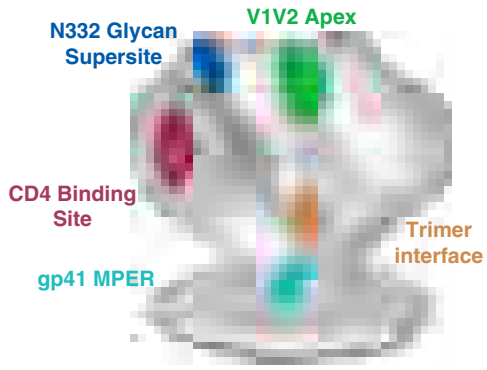


FIGURE 197-29 Known targets of broadly neutralizing antibodies against HIV-1. *(Adapted from PD Kwong, JR Mascola: Immunity 37:412, 2012.)*

The other major class of protective antibodies are those that participate in ADCC, a form of cell-mediated immunity **(Chap. 342)** in which NK cells that bear Fc receptors are armed with specific anti-HIV antibodies that bind to the NK cells via their Fc portion. These armed NK cells then bind to and destroy cells expressing HIV antigens. The levels of anti-envelope antibodies capable of mediating ADCC are highest in the earlier stages of HIV infection. Antibodies to both gp120 and gp41 have been shown to participate in ADCC-mediated killing of HIV-infected cells. In vitro, IL-2 can augment ADCC-mediated killing.

In addition to playing a role in host defense, HIV-specific antibodies have also been implicated in disease pathogenesis. Antibodies directed to gp41, when present in low titer, have been shown in vitro to be capable of facilitating infection of cells through an Fc receptor–mediated mechanism known as *antibody enhancement*. Thus, the same regions of the envelope protein of HIV that give rise to antibodies capable of mediating ADCC can also elicit the production of antibodies that can facilitate infection of cells in vitro. In addition, it has been postulated that anti-gp120 antibodies that participate in the ADCC killing of HIV-infected cells might also kill uninfected CD4+ T cells if the uninfected cells had bound free gp120, a phenomenon referred to as *bystander killing*.

One of the most primitive components of the humoral immune system is the complement system **(Chap. 342)**. This element of innate immunity consists of ~30 proteins that are found circulating in blood or associated with cell membranes. While HIV alone is capable of directly activating the complement cascade, the resulting lysis is weak due to the presence of host cell regulatory proteins captured in the virion envelope during budding. It is possible that complement-opsonized HIV virions have increased infectivity in a manner analogous to antibody-mediated enhancement.

CELLULAR IMMUNE RESPONSE

Given that T cell–mediated immunity is known to play a major role in host defense against most viral infections **(Chap. 342)**, it is generally thought to be an important component of the host immune response to HIV. T cell immunity can be divided into two major categories: that mediated by *helper/inducer CD4+ T cells* and that mediated by *cytotoxic/immunoregulatory CD8+ T cells*.

HIV-specific CD4+ T cells can be detected in the majority of HIV-infected patients through the use of flow cytometry to measure intracellular cytokine production in response to MHC class II tetramers pulsed with HIV peptides or through lymphocyte proliferation assays utilizing HIV antigens such as p24. These cells likely play a critical role in the orchestration of the immune response to HIV by providing help to HIV-specific B cells and CD8+ T cells. They may also be capable of directly killing HIV-infected cells. HIV-specific CD4+ T cells may be preferential targets of HIV infection by HIV-infected antigen-presenting cells during the generation of an immune response to HIV (Fig. 197-27). However, they also are likely to undergo clonal expansions in response to HIV antigens and thus survive as a population of cells. No clear correlations exist between levels of HIV-specific CD4+ T lymphocytes and plasma HIV RNA levels; however, in the setting

of high viral loads, CD4+ T cell responses to HIV antigens appear to shift from one of proliferation and IL-2 production to one of IFN-γ production. Thus, while a reverse correlation exists between the level of p24-specific proliferation and levels of plasma HIV viremia, the nature of the causal relationship between these parameters is unclear.

MHC class I–restricted, HIV-specific CD8+ T cells have been identified in the peripheral blood of patients with HIV-1 infection. These cells include CTLs that produce perforins and T cells that can be induced by HIV antigens to express an array of cytokines such as IFN-γ, IL-2, MIP-1β, and TNF-α. CTLs have been identified in the peripheral blood of patients within weeks of HIV infection and prior to the appearance of plasma virus. The selective pressure they exert on the evolution of the population of circulating viruses reflects their potential role in control of HIV infection. These CD8+ T lymphocytes, through their HIV-specific antigen receptors, bind to and cause the lytic destruction of target cells bearing autologous MHC class I molecules presenting HIV antigens. Two types of CTL activity can be demonstrated in the peripheral blood or lymph node mononuclear cells of HIV-infected individuals. The first type directly lyses appropriate target cells in culture without prior in vitro stimulation (*spontaneous CTL activity*). The other type of CTL activity reflects the *precursor frequency of CTLs* (CTLp); this type of CTL activity can be demonstrated by stimulation of CD8+ T cells in vitro with a mitogen such as phytohemagglutinin or anti-CD3 antibody.

In addition to CTLs, CD8+ T cells capable of being induced by HIV antigens to express cytokines such as IFN-γ also appear in the setting of HIV-1 infection. It is not clear whether these are the same or different effector pools compared with those cells mediating cytotoxicity; in addition, the relative roles of each in host defense against HIV are not fully understood. It does appear that these CD8+ T cells are driven to in vivo expansion by HIV antigen. There is a direct correlation between levels of CD8+ T cells capable of producing IFN-γ in response to HIV antigens and plasma levels of HIV-1 RNA. Thus, while these cells are clearly induced by HIV-1 infection, their overall ability to control infection remains unclear. Multiple HIV antigens, including Gag, Env, Pol, Tat, Rev, and Nef, can elicit CD8+ T cell responses. Among patients who control viral replication in the absence of antiretroviral drugs are a subset of patients referred to as *elite nonprogressors* (see "Long-Term Survivors, Long-Term Nonprogressors, and Elite Controllers," above) whose peripheral blood contains a population of CD8+ T cells that undergo substantial in vitro proliferation and perforin expression in response to HIV antigens. It is possible that these cells play an important role in HIV-specific host defense.

At least three other forms of cell-mediated immunity to HIV have been described: non-cytolytic CD8+ T cell–mediated suppression of HIV replication, ADCC, and NK cell activity. *Non-cytolytic CD8+ T cell–mediated suppression of HIV replication* refers to the ability of CD8+ T cells from an HIV-infected patient to inhibit the replication of HIV in tissue culture without killing infected targets. There is no requirement for HLA compatibility between the CD8+ T cells and the HIV-infected cells. This effector mechanism is thus nonspecific and appears to be mediated by soluble factor(s) including the CC-chemokines RANTES (CCL5), MIP-1α (CCL3), and MIP-1β (CCL4). These CC-chemokines are potent suppressors of HIV replication and operate at least in part via blockade of the HIV co-receptor (*CCR5*) for R5 (macrophage-tropic) strains of HIV-1 (see above). *ADCC*, as described above in relation to humoral immunity, involves the killing of HIV-expressing cells by NK cells armed with specific antibodies directed against HIV antigens. Finally, *NK cells* alone have been shown to be capable of killing HIV-infected target cells in tissue culture. This primitive cytotoxic mechanism of host defense is directed toward nonspecific surveillance for neoplastic transformation and viral infection through recognition of altered class I MHC molecules.

DIAGNOSIS AND LABORATORY MONITORING OF HIV INFECTION

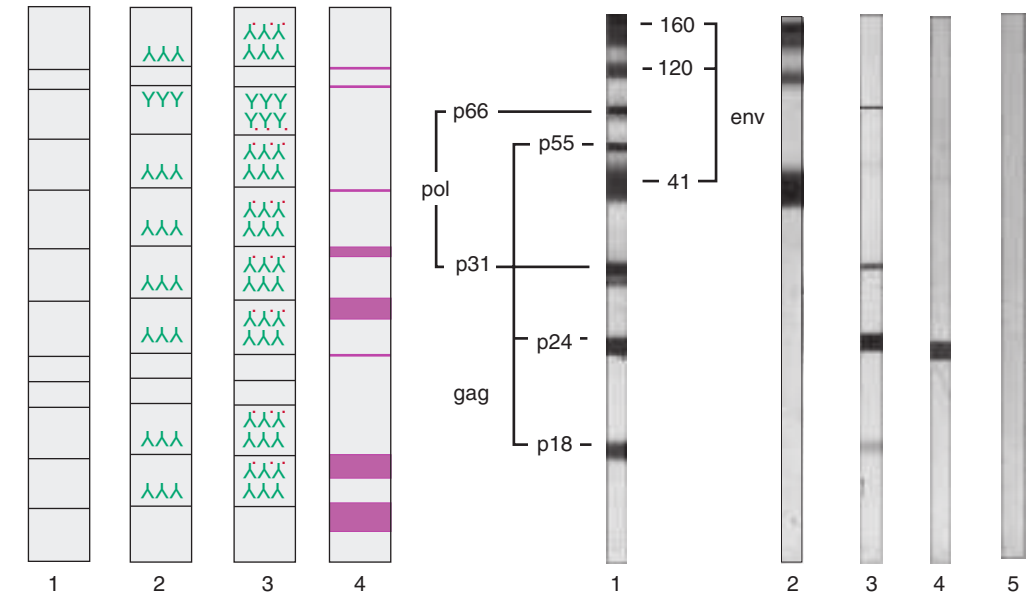
The establishment of HIV as the causative agent of AIDS and related syndromes early in 1984 was followed by the rapid development of sensitive screening tests for HIV infection. By March 1985, blood donors in the United States were routinely screened for antibodies to HIV. In 1996, blood banks in the United States added the p24 antigen capture assay to the screening process to help identify the rare infected individuals who were donating blood in the time (up to 3 months) between infection and the development of antibodies. In 2002, the ability to detect early infection with HIV was further enhanced by the licensure of nucleic acid testing (NAT) as a routine part of blood donor screening. These refinements decreased the interval between infection and detection (window period) from 22 days for antibody testing to 16 days with p24 antigen testing and subsequently to 12 days with NAT. The development of sensitive assays for monitoring levels of plasma viremia ushered in a new era of being able to monitor the progression of HIV disease more closely. Utilization of these tests, coupled with the measurement of levels of CD4+ T lymphocytes in peripheral blood, is essential in the management of patients with HIV infection.

DIAGNOSIS OF HIV INFECTION

The CDC has recommended that screening for HIV infection be performed as a matter of routine health care. The diagnosis of HIV infection depends on the demonstration of antibodies to HIV and/or the direct detection of HIV or one of its components. As noted above, antibodies to HIV generally appear in the circulation 3–12 weeks following infection.

The standard blood screening tests for HIV infection are based on the detection of antibodies to HIV. A common platform is the ELISA, also referred to as an *enzyme immunoassay* (EIA). This solid-phase assay is an extremely good screening test with a sensitivity of >99.5%. Most diagnostic laboratories use commercial kits that contain antigens from both HIV-1 and HIV-2 and thus are able to detect antibodies to either. These kits use both natural and recombinant antigens and are continuously updated to increase their sensitivity to newly discovered species, such as group O viruses (Fig. 197-1). The fourth-generation EIA tests combine detection of antibodies to HIV with detection of the p24 antigen of HIV. EIA tests are generally scored as positive (highly reactive), negative (nonreactive), or indeterminate (partially reactive). While the EIA is an extremely sensitive test, it is not optimal with regard to specificity. This is particularly true in studies of low-risk individuals, such as volunteer blood donors. In this latter population, only 10% of EIA-positive individuals are subsequently confirmed to have HIV infection. Among the factors associated with false-positive EIA tests are antibodies to class II antigens (such as may be seen following pregnancy, blood transfusion, or transplantation), autoantibodies, hepatic disease, recent influenza vaccination, and acute viral infections. For these reasons, anyone suspected of having HIV infection based on a positive or inconclusive fourth-generation EIA result should have the result confirmed with a more specific assay such as an HIV-1- or HIV-2-specific antibody immunoassay, a western blot, or a plasma HIV RNA level. One can estimate whether an individual has a recent infection with HIV-1 by comparing the results on a standard EIA test that will score positive for all infected individuals with the results on an assay modified to be less sensitive ("detuned assay") that will score positive for individuals with established HIV infection and negative for individuals with recent infection. In rare instances, an HIV-infected individual treated early in the course of infection may revert to a negative EIA. This does *not* indicate clearing of infection; rather, it signifies levels of ongoing exposure to virus or viral proteins insufficient to maintain a measurable antibody response. When these individuals have discontinued therapy, viruses and antibodies have reappeared.

While current CDC recommendations indicate that a positive fourth-generation assay confirmed by a second HIV-1- or HIV-2-specific immunoassay is adequate for diagnosis, many feel it is prudent to confirm diagnosis with a second platform test such as the western blot or HIV plasma RNA level. The western blot **(Fig. 197-30)** assay takes advantage of the fact that multiple HIV antigens of different, well-characterized molecular weights elicit the production of specific antibodies. These antigens can be separated on the basis of molecular weight, and antibodies to each component can be detected as discrete bands on the western blot. A negative western blot is one in which no bands are present at molecular weights corresponding to HIV gene products. In a patient with a positive or indeterminate EIA



A

1. Virus digested: digest separated into components by molecular weight
2. Proteins transferred to filter paper: reaction with test serum
3. Enzyme-conjugated antihuman antibody added
4. Substrate added and color noted

B

1. Positive HIV-1 infection
2. gp 160 immunization
3. Indeterminate (HIV-2 infection)
4. Indeterminate (cross-reacting antibody to p24)
5. Negative

FIGURE 197-30 Western blot assay for detection of antibodies to HIV. *A.* Schematic representation of how a western blot is performed. ***B.*** Examples of patterns of western blot reactivity. In each instance the western blot strip contains antigens to HIV-1. The serum from the patient immunized to the HIV-1 envelope gp160 contains only antibodies to the HIV-1 envelope proteins. The serum from the patient with HIV-2 infection cross-reacts with both *reverse transcriptase* and *gag* gene products of HIV-1.

and a negative western blot, one can conclude with certainty that the EIA reactivity was a false positive. On the other hand, a western blot demonstrating antibodies to products of all three of the major genes of HIV (*gag*, *pol*, and *env*) is conclusive evidence of infection with HIV. Criteria established by the FDA in 1993 state that a western blot result is considered positive if antibodies exist to two of the three HIV proteins: p24, gp41, and gp120/160. Using these criteria, ~10% of all blood donors deemed positive for HIV-1 infection lacked an antibody band to the *pol* gene product p31. Some 50% of these blood donors were subsequently found to be false positives. Thus, the absence of the p31 band should increase the suspicion that one may be dealing with a false-positive test result. In this setting it is prudent to obtain additional confirmation with an RNA-based test for HIV-1 and/or a follow-up western blot. By definition, western blot patterns of reactivity that do not fall into the positive or negative categories are considered "indeterminate." There are two possible explanations for an indeterminate western blot result. The most likely explanation in a low-risk individual is that the patient being tested has antibodies that cross-react with one of the proteins of HIV. The most common patterns of cross-reactivity are antibodies that react with p24 and/or p55. The least likely explanation in this setting is that the individual is infected with HIV and is in the process of mounting a classic antibody response. In either instance, the western blot should be repeated in 1 month to determine whether the indeterminate pattern is a pattern in evolution. In addition, one may attempt to confirm a diagnosis of HIV infection with one of the tests for HIV RNA (discussed below). While the western blot is an excellent confirmatory test for HIV infection in patients with a positive or indeterminate EIA, it is a poor screening test. Among individuals with a negative EIA and PCR for HIV, 20–30% may show one or more bands on western blot. While these bands are usually faint and represent cross-reactivity, their presence creates a situation in which other diagnostic modalities (such as DNA PCR, RT-PCR, or p24 antigen capture) must be employed to ensure that the bands do not indicate early HIV infection.

A guideline for the use of these serologic tests in attempting to make a diagnosis of HIV infection is depicted in **Fig. 197-31**. In patients in whom HIV infection is suspected, the appropriate initial test is the EIA. If the result is negative, unless there is strong reason to suspect early HIV infection (as in a patient exposed within the previous 3 months), the diagnosis is ruled out and retesting should be performed only as clinically indicated. If the EIA is indeterminate or positive, the test should be repeated. If the repeat is negative on two occasions, one can assume that the initial positive reading was due to a technical error in the performance of the assay and that the patient is negative. If the repeat is indeterminate or positive, one should proceed to the HIV-1 western blot. If the western blot is positive, the diagnosis is HIV-1 infection. If the western blot is negative, the EIA can be assumed to have been a false positive for HIV-1 and the diagnosis of HIV-1 infection is ruled out. It would also be prudent at this point to perform specific serologic testing for HIV-2 following the same type of algorithm. If the western blot for HIV-1 is indeterminate, it should be repeated in 4–6 weeks; in addition, one may proceed to a specific HIV-1 or HIV-2 antibody differentiation assay, HIV-1 RNA assay, or HIV-1 DNA PCR. If the HIV RNA assays are negative and there is no progression in the western blot, a diagnosis of HIV-1 is ruled out. If either HIV-1 RNA assay is positive and/or the HIV-1 western blot shows progression, a tentative diagnosis of HIV-1 infection can be made and later confirmed with a follow-up western blot demonstrating a positive pattern. In addition to these standard laboratory-based assays for detecting antibodies to HIV, a series of point-of-care tests can provide results in 1–60 min. Among the most popular of these is the OraQuick Rapid HIV-1 antibody test that can be run on blood, plasma, or saliva. The sensitivity and specificity of this test is ~99% when run on whole blood. Specificity remains the same but sensitivity drops to 98% when the test is run on saliva. While negative results from this test are adequate to rule out a diagnosis of HIV infection, a positive finding should be considered preliminary and confirmed with standard serologic testing, as described above. Two rapid test kits are licensed for home use. They are the OraQuick HIV test and the Home Access HIV-1 test system. A positive result with either of these tests should be followed with confirmatory testing by a healthcare professional.

A variety of laboratory tests are available for the direct detection of HIV or its components **(Table 197-8)**. These tests may be of

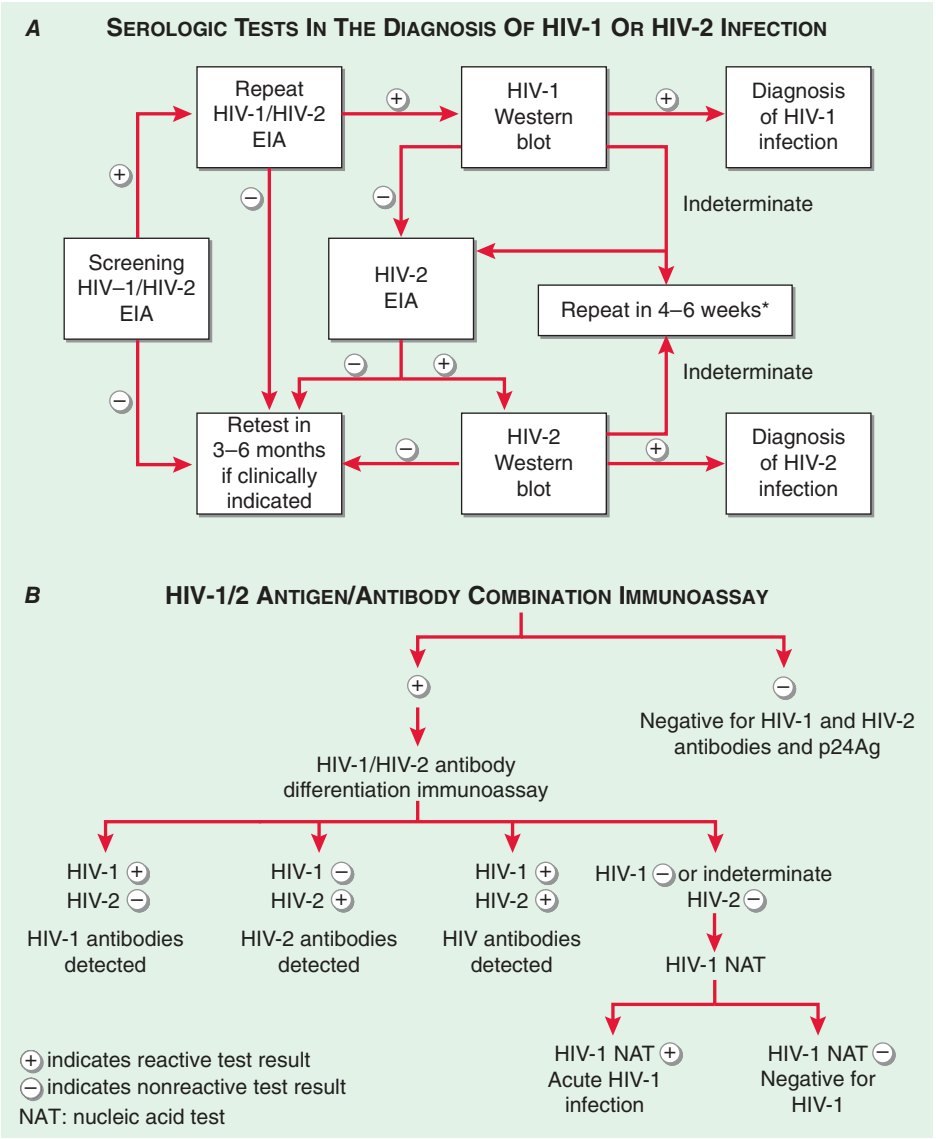


FIGURE 197-31 Serologic tests for the diagnosis of HIV-1 or HIV-2 infection. *A.* Algorithm including the use of a western blot. *Stable indeterminate western blot 4–6 weeks later makes HIV infection unlikely. However, it should be repeated twice at 3-month intervals to rule out HIV infection. Alternatively, one may test for HIV-1 p24 antigen or HIV RNA. EIA, enzyme immunoassay. ***B.*** CDC algorithm not including the use of a western blot. *(Adapted from stacks.cdc.gov/view/cdc/23446.)*

considerable help in making a diagnosis of HIV infection when the antibody determination assays or western blot results are indeterminate. In addition, the tests detecting levels of HIV RNA can be used to determine prognosis and to assess the response to antiretroviral therapies. The simplest, least expensive, and most rarely used of the direct detection tests is the *p24 antigen capture assay*. This is an EIA-type assay in which the solid phase consists of antibodies to the p24 antigen of HIV. It detects the viral protein p24 in the blood of HIV-infected individuals where it exists either as free antigen or complexed to anti-p24 antibodies. Overall, ~30% of individuals with untreated HIV infection have detectable levels of free p24 antigen. This increases to ~50% when samples are treated with a weak acid to dissociate antigen-antibody complexes. Throughout the course of HIV infection, an equilibrium exists between p24 antigen and anti-p24 antibodies. During the first

TABLE 197-8 Characteristics of Tests for Direct Detection of HIV

TEST	TECHNIQUE	SENSITIVITY[a]	COST/TEST[b]
Immune complex–dissociated p24 antigen capture assay	Measurement of levels of HIV-1 core protein in an EIA-based format following dissociation of antigen-antibody complexes by weak acid treatment	Positive in 50% of patients; detects down to 15 pg/mL of p24 protein	$1–2
HIV RNA by PCR	Target amplification of HIV-1 RNA via reverse transcription followed by PCR	Reliable to 40 copies/mL of HIV RNA	$75–150
HIV RNA by bDNA	Measurement of levels of particle-associated HIV RNA in a nucleic acid capture assay employing signal amplification	Reliable to 50 copies/mL of HIV RNA	$75–150
HIV RNA by TMA	Target amplification of HIV-1 RNA via reverse transcription followed by T7 RNA polymerase	Reliable to 100 copies/mL of HIV RNA	$225
HIV RNA by NASBA	Isothermal nucleic acid amplification with internal controls	Reliable to 80 copies/mL of HIV RNA	$75–150

[a]Sensitivity figures refer to those approved by the U.S. Food and Drug Administration. [b]Prices may be lower in large-volume settings.

Abbreviations: bDNA, branched DNA; cDNA, complementary DNA; EIA, enzyme immunoassay; NASBA, nucleic acid sequence–based amplification; PCR, polymerase chain reaction; TMA, transcription-mediated amplification.

few weeks of infection, before an immune response develops, there is a brisk rise in p24 antigen levels. After the development of anti-p24 antibodies, these levels decline. Late in the course of infection, when circulating levels of virus are high, p24 antigen levels also increase, particularly when detected by techniques involving dissociation of antigen-antibody complexes. The p24 antigen capture assay has its greatest use as a screening test for HIV infection in patients suspected of having the acute HIV syndrome (see below), as high levels of p24 antigen are present prior to the development of antibodies. Its use as a stand-alone test for routine blood donor screening for HIV infection has been replaced by use of NAT or "fourth-generation" assays that combine antigen and antibody testing. The ability to measure and monitor levels of HIV RNA in the plasma of patients with HIV infection has been of extraordinary value in furthering our understanding of the pathogenesis of HIV infection, in monitoring the response to cART, and in providing a diagnostic tool in settings where measurements of anti-HIV antibodies may be misleading, such as in acute infection and neonatal infection. Four assays are predominantly used for this purpose. They are reverse transcriptase PCR (*RT-PCR*; Amplicor and RealTime); branched DNA (*bDNA*; VERSANT); transcription-mediated amplification (*TMA*; APTIMA); and nucleic acid sequence–based amplification (*NASBA*; NucliSENS). These tests are of value in making a diagnosis of HIV infection, in establishing initial prognosis, and in monitoring the effects of therapy. In addition to the commercially available tests for measuring HIV RNA, *DNA PCR* assays are also employed by research laboratories for making a diagnosis of HIV infection by amplifying HIV proviral DNA from peripheral blood mononuclear cells. The commercially available RNA detection tests have a sensitivity of 40–80 copies of HIV RNA per milliliter of plasma. Research laboratory–based RNA assays can detect as few as one HIV RNA copy per milliliter, while the DNA PCR tests can detect proviral DNA at a frequency of one copy per 10,000–100,000 cells. Thus, these tests are extremely sensitive. One frequent consequence of a high degree of sensitivity is some loss of specificity, and false-positive results have been reported with each of these techniques. For this reason, a positive EIA with a confirmatory western blot or HIV RNA assay remains the "gold standard" for a diagnosis of HIV infection, and the interpretation of other test results must be done with this in mind.

In the RT-PCR technique, following DNAse treatment, a cDNA copy is made of all RNA species present in plasma. Because HIV is an RNA virus, this will result in the production of DNA copies of the HIV genome in amounts proportional to the amount of HIV RNA present in plasma. This cDNA is then amplified and characterized using standard PCR techniques, employing primer pairs that can distinguish genomic cDNA from messenger cDNA. The bDNA assay involves the use of a solid-phase nucleic acid capture system and signal amplification through successive nucleic acid hybridizations to detect small quantities of HIV RNA. Both tests can achieve a tenfold increase in sensitivity to 40–50 copies of HIV RNA per milliliter with a preconcentration step in which plasma undergoes ultracentrifugation to pellet the viral particles. In the TMA assay, a cDNA copy of viral RNA is made using primers that contain a promoter sequence for T7 RNA polymerase. T7 polymerase is then added to produce multiple copies of RNA amplicon from the DNA template. It is qualified at 100 copies/mL. The NASBA technique involves the isothermal amplification of a sequence within the gag region of HIV in the presence of internal standards and employs the production of multiple RNA copies through the action of T7-RNA polymerase. The resulting RNA species are quantitated through hybridization with a molecular beacon DNA probe that is quenched in the absence of hybridization. The lower limit of detection for the NucliSENS assay is 80 copies/mL.

In addition to being a diagnostic and prognostic tool, RT-PCR and DNA-PCR are also useful for amplifying defined areas of the HIV genome for sequence analysis and have become an important technique for studies of sequence diversity and microbial resistance to antiretroviral agents. In patients with a positive or indeterminate EIA test and an indeterminate western blot, and in patients in whom serologic testing may be unreliable (such as patients with hypogammaglobulinemia or advanced HIV disease), these tests for quantitating HIV RNA in plasma or detecting proviral DNA in peripheral blood mononuclear cells are valuable tools for making a diagnosis of HIV infection; however, they should be used for diagnosis only when standard serologic testing has failed to provide a definitive result.

LABORATORY MONITORING OF PATIENTS WITH HIV INFECTION

The epidemic of HIV infection and AIDS has provided the clinician with new challenges for integrating clinical and laboratory data to effect optimal patient management. The close relationship between clinical manifestations of HIV infection and CD4+ T cell count has made measurement of CD4+ T cell numbers a routine part of the evaluation of HIV-infected individuals. The discovery of HIV as the cause of AIDS led to the development of sensitive tests that allow one to monitor the levels of HIV in the blood. Determinations of peripheral blood CD4+ T cell counts and measurements of the plasma levels of HIV RNA provide a powerful set of tools for determining prognosis and monitoring response to therapy.

CD4+ T Cell Counts The CD4+ T cell count is the laboratory test generally accepted as the best indicator of the immediate state of immunologic competence of the patient with HIV infection. This measurement, which can be made directly or calculated as the product of the percentage of CD4+ T cells (determined by flow cytometry) and the total lymphocyte count (determined by the white blood cell count [WBC] multiplied by the lymphocyte differential percentage), has been shown to correlate very well with the level of immunologic competence. Patients with CD4+ T cell counts <200/μL are at high risk of disease from *P. jirovecii*, while patients with CD4+ T cell counts <50/μL are also at high risk of disease from CMV, mycobacteria of the *M. avium* complex (MAC), and/or *T. gondii* **(Fig. 197-32)**. Once the CD4+ T cell count is <200/μL, patients should be placed on a regimen for *P. jirovecii* prophylaxis, and once the count is <50/μL, primary prophylaxis for MAC infection is indicated. As with any laboratory measurement, one may wish to obtain two determinations prior to any significant changes in patient management based on CD4+ T cell count alone. Patients with HIV infection should have CD4+ T cell measurements performed at the time of diagnosis and every 3–6 months thereafter. More frequent measurements should be made if a declining trend is noted. For patients who have been on cART for at least 2 years with HIV RNA levels persistently <50 copies/mL and CD4 counts >500/μl, the monitoring of the CD4 count is felt by many to be optional. There are a handful of clinical situations in which the CD4+ T cell count may be misleading. Patients with HTLV-1/HIV co-infection may have elevated CD4+ T cell counts that do not accurately reflect their degree of immune competence. In patients with hypersplenism or those who have undergone splenectomy, and in patients receiving medications that suppress the bone marrow such as IFN-α, the CD4+ T cell percentage may be a more reliable indication of immune function than the CD4+ T cell count. A CD4+ T cell percentage of 15 is comparable to a CD4+ T cell count of 200/μL.

HIV RNA Determinations Facilitated by highly sensitive techniques for the precise quantitation of small amounts of nucleic acids, the measurement of serum or plasma levels of HIV RNA has become an essential component in the monitoring of patients with HIV infection. As discussed in "Diagnosis of HIV Infection," above, the most commonly used technique is the RT-PCR assay. This assay generates data in the form of number of copies of HIV RNA per milliliter of serum or plasma and can reliably detect as few as 40 copies of HIV RNA per milliliter of plasma. Research-based assays can detect down to one copy per milliliter. While it is common practice to describe levels of HIV RNA below these cut-offs as "undetectable," this is a term that should be avoided as it is imprecise and leaves the false impression that the level of virus is 0. By utilizing more sensitive, nested PCR techniques and by studying tissue levels of virus as well as plasma levels, HIV RNA can be detected in virtually every patient with HIV infection. The one notable exception to this is a patient who underwent cytoreductive therapy followed by a bone marrow transplant from a *CCR5Δ32* homozygous donor.

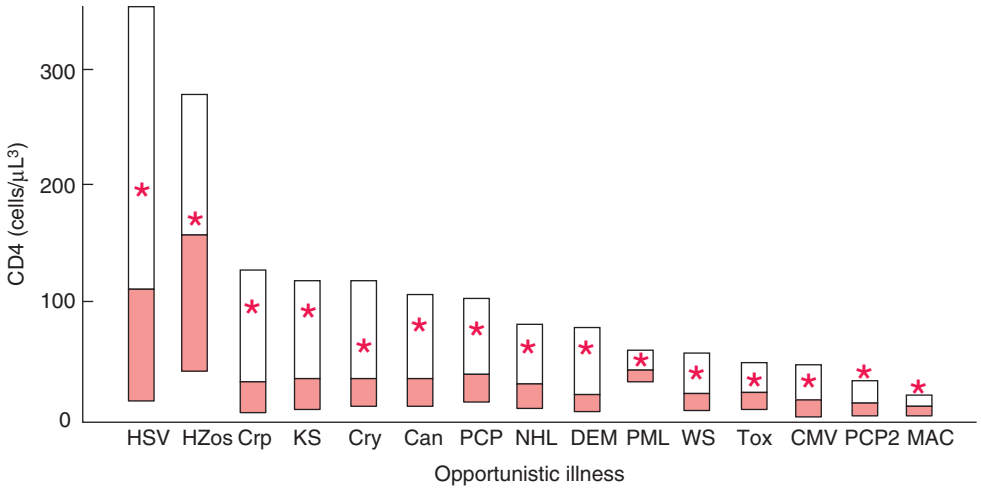


FIGURE 197-32 Relationship between CD4+ T cell counts and the development of opportunistic diseases. Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, *Mycobacterium avium* complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary *Pneumocystis jirovecii* pneumonia; PCP2, secondary *P. jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, *Toxoplasma gondii* encephalitis; WS, wasting syndrome. *(From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.)*

Measurements of changes in HIV RNA levels over time have been of great value in delineating the relationship between levels of virus and rates of disease progression (Fig. 197-22), the rates of viral turnover, the relationship between immune system activation and viral replication, and the time to development of drug resistance. HIV RNA measurements are greatly influenced by the state of activation of the immune system and may fluctuate greatly in the setting of secondary infections or immunization. For these reasons, decisions based on HIV RNA levels should never be made on a single determination. Measurements of plasma HIV RNA levels should be made at the time of HIV diagnosis and every 3–6 months thereafter in the untreated patient. Following the initiation of therapy or any change in therapy, plasma HIV RNA levels should be monitored approximately every 4 weeks until the effectiveness of the therapeutic regimen is determined by the development of a new steady-state level of HIV RNA. In most instances of effective antiretroviral therapy the plasma level of HIV RNA will drop to <50 copies/mL within 6 months of the initiation of treatment. During therapy, levels of HIV RNA should be monitored every 3–6 months to evaluate the continuing effectiveness of therapy.

HIV Resistance Testing The availability of multiple antiretroviral drugs as treatment options has generated a great deal of interest in the potential for measuring the sensitivity of an individual's HIV viral quasispecies to different antiretroviral agents. HIV resistance testing can be done through either genotypic or phenotypic measurements. In the genotypic assays, sequence analyses of the HIV genomes obtained from patients are compared with sequences of viruses with known antiretroviral resistance profiles. In the phenotypic assays, the in vivo growth of viral isolates obtained from the patient is compared with the growth of reference strains of the virus in the presence or absence of different antiretroviral drugs. A modification of this phenotypic approach utilizes a comparison of the enzymatic activities of the reverse transcriptase, protease, or integrase genes obtained by molecular cloning of patients' isolates to the enzymatic activities of genes obtained from reference strains of HIV in the presence or absence of different drugs targeted to these genes. These tests are quite good in identifying those antiretroviral agents that have been utilized in the past and suggesting agents that may be of future value in a given patient. Resistance testing is recommended at the time of initial diagnosis and, if therapy is not initiated at that time, at the time of initiation of cART. Drug resistance testing is also indicated in the setting of virologic failure and should be performed while the patient is still on the failing regimen because of the propensity for the pool of HIV quasispecies to rapidly revert to wild-type in the absence of the selective pressures of cART. In the hands of experts, resistance testing enhances the short-term ability to decrease viral load by ~0.5 log compared with changing drugs merely on the basis of drug history. In addition to the use of resistance testing to help in the selection of new drugs in patients with virologic failure, it may also be of value in selecting an initial regimen for treatment of therapy-naïve individuals. This is particularly true in geographic areas with a high level of background resistance. The patient needs to have an HIV-1 RNA level above 500–1000 copies/mL for an accurate resistance determination. Resistance assays lose their consistency at lower levels of plasma viremia.

Co-Receptor Tropism Assays Following the licensure of maraviroc as the first CCR5 antagonist for the treatment of HIV infection (see below), it became necessary to be able to determine whether a patient's virus was likely to respond to this treatment. Patients tend to have CCR5-tropic virus early in the course of infection, with a trend toward CXCR4 viruses later in disease. The antiretroviral agent maraviroc is effective only against CCR5-tropic viruses. Because the genotypic determinants of cellular tropism are poorly defined, a phenotypic assay is necessary to determine this property of HIV. Two commercial assays, the Trofile assay (Monogram Biosciences) and the Phenoscript assay (VIRalliance), are available to make this determination. These assays clone the envelope regions of the patient's virus into an indicator virus that is then used to infect target cells expressing either CCR5 or CXCR4 as their co-receptor. These assays take weeks to perform and are expensive. Another, less costly option is to obtain a genotypic assay of the V3 region of HIV-1 and then employ a computer algorithm to predict viral tropism from the sequence. While this approach is less expensive than the classic phenotypic assay, there are fewer data to validate its predictive value.

Other Tests A variety of other laboratory tests have been studied as potential markers of HIV disease activity. Among these are quantitative culture of replication-competent HIV from plasma, peripheral blood mononuclear cells, or resting memory CD4+ T cells; circulating levels of β_2-microglobulin, soluble IL-2 receptor, IgA, acid-labile endogenous IFN, or TNF-α; and the presence or absence of activation markers such as CD38, HLA-DR, and PD-1 on CD4+ or CD8+ T cells. Nonspecific serologic markers of inflammation and/or coagulation such as IL-6, D-dimer, and sCD14 have been shown to have a high correlation with all-cause mortality **(Table 197-9)**. While these measurements have value as markers of disease activity and help to increase our understanding of the pathogenesis of HIV disease, they do not currently play a major role in the monitoring of patients with HIV infection.

TABLE 197-9 Association Between High-Sensitivity CRP, Il-6, and D-Dimer with All-Cause Mortality in Patients with HIV Infection

MARKER	UNADJUSTED		ADJUSTED	
	ODDS RATIO (FOURTH/FIRST)	*P*	ODDS RATIO (FOURTH/FIRST)	*P*
Hs-CRP	2.0	.05	2.8	.03
IL-6	8.3	<.0001	11.8	<.0001
D-dimer	12.4	<.0001	26.5	<.0001

Abbreviations: Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6.

Source: From LH Kuller et al: PLoS Med 5:e203, 2008.

TABLE 197-10 Clinical Findings in the Acute HIV Syndrome

General	Neurologic
Fever	Meningitis
Pharyngitis	Encephalitis
Lymphadenopathy	Peripheral neuropathy
Headache/retroorbital pain	Myelopathy
Arthralgias/myalgias	Dermatologic
Lethargy/malaise	Erythematous maculopapular rash
Anorexia/weight loss	Mucocutaneous ulceration
Nausea/vomiting/diarrhea	

Source: From B Tindall, DA Cooper: AIDS 5:1, 1991.

CLINICAL MANIFESTATIONS

The clinical consequences of HIV infection encompass a spectrum ranging from an acute syndrome associated with primary infection to a prolonged asymptomatic state to advanced disease. It is best to regard HIV disease as beginning at the time of primary infection and progressing through various stages. As mentioned above, active virus replication and progressive immunologic impairment occur throughout the course of HIV infection in most patients. With the exception of the rare, true, "elite" virus controllers or long-term nonprogressors (see "Long-Term Survivors, Long-Term Nonprogressors, and Elite Controllers," above), HIV disease in untreated patients inexorably progresses even during the clinically latent stage. Since the mid-1990s, cART has had a major impact on preventing and reversing the progression of disease over extended periods of time in a substantial proportion of adequately treated patients. Today, a person diagnosed with HIV infection and treated with cART has a close to normal life expectancy.

ACUTE HIV INFECTION

It is estimated that 50–70% of individuals with HIV infection experience an acute clinical syndrome ~3–6 weeks after primary infection (Fig. 197-33). Varying degrees of clinical severity have been reported, and although it has been suggested that symptomatic seroconversion leading to the seeking of medical attention indicates an increased risk for an accelerated course of disease, there does not appear to be a correlation between the level of the initial burst of viremia in acute HIV infection and the subsequent course of disease. The typical clinical findings in the acute HIV syndrome are listed in Table 197-10; they occur along with a burst of plasma viremia. It has been reported that several symptoms of the acute HIV syndrome (fever, skin rash, pharyngitis, and myalgia) occur less frequently in those infected by injection drug use compared with those infected by sexual contact. The syndrome is typical of an acute viral syndrome and has been likened to acute infectious mononucleosis. Symptoms usually persist for one to several weeks and gradually subside as an immune response to HIV develops and the levels of plasma viremia decrease. Opportunistic infections have been reported during this stage of infection, reflecting the immunodeficiency that results from reduced numbers of CD4+ T cells and likely also from the dysfunction of CD4+ T cells owing to viral protein and endogenous cytokine-induced perturbations of cells (Table 197-5) associated with the extremely high levels of plasma viremia. The Fiebig staging system has been used to describe the different stages of acute HIV infection, ranging from Stage 1 (HIV RNA positive alone) to Stage VI (HIV RNA and full western blot positive). A number of immunologic abnormalities accompany the acute HIV syndrome, including multiphasic perturbations of the numbers of circulating lymphocyte subsets. The number of total lymphocytes and T cell subsets (CD4+ and CD8+) are initially reduced. An inversion of the CD4+/CD8+ T cell ratio occurs later because of a rise in the number of CD8+ T cells. In fact, there may be a selective and transient expansion of CD8+ T cell subsets, as determined by T cell receptor analysis (see above). The total circulating CD8+ T cell count may remain elevated or return to normal; however, CD4+ T cell levels usually remain somewhat depressed, although there may be a slight rebound toward normal. Lymphadenopathy occurs in ~70% of individuals with primary HIV infection. Most patients recover spontaneously from this syndrome and many are left with only a mildly depressed CD4+ T cell count that remains stable for a variable period before beginning its progressive decline; in some individuals, the CD4+ T cell count returns to the normal range. Approximately 10% of patients manifest a fulminant course of immunologic and clinical deterioration after primary infection, even after the disappearance of initial symptoms. In most patients, primary infection with or without the acute syndrome is followed by a prolonged period of clinical latency or smoldering low disease activity.

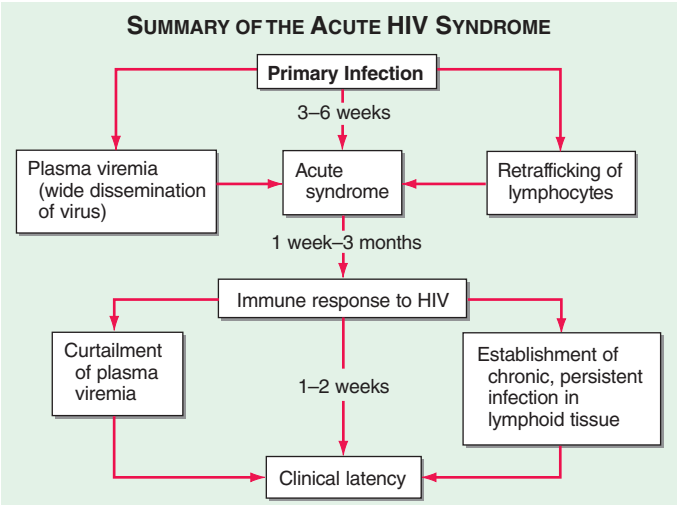


FIGURE 197-33 The acute HIV syndrome. See text for detailed description. *(Adapted from G Pantaleo et al: N Engl J Med 328:327, 1993. Copyright 1993 Massachusetts Medical Society. All rights reserved.)*

THE ASYMPTOMATIC STAGE—CLINICAL LATENCY

Although the length of time from initial infection to the development of clinical disease varies greatly, the median time for untreated patients is ~10 years. As emphasized above, HIV disease with active virus replication is ongoing and progressive during this asymptomatic period. The rate of disease progression is directly correlated with HIV RNA levels. Patients with high levels of HIV RNA in plasma progress to symptomatic disease faster than do patients with low levels of HIV RNA (Fig. 197-22). Some patients referred to as *long-term nonprogressors* show little if any decline in CD4+ T cell counts over extended periods of time. These patients generally have extremely low levels of HIV RNA; a subset, referred to as *elite nonprogressors*, exhibits HIV RNA levels <50 copies/mL. Certain other patients remain entirely asymptomatic despite the fact that their CD4+ T cell counts show a steady progressive decline to extremely low levels. In these patients, the appearance of an opportunistic disease may be the first manifestation of HIV infection. During the asymptomatic period of HIV infection, the average rate of CD4+ T cell decline is ~50/μL per year in an untreated patient. When the CD4+ T cell count falls to <200/μL, the resulting state of immunodeficiency is severe enough to place the patient at high risk for opportunistic infections and neoplasms and, hence, for clinically apparent disease.

SYMPTOMATIC DISEASE

Symptoms of HIV disease can appear at any time during the course of HIV infection. Generally speaking, the spectrum of illnesses that one observes changes as the CD4+ T cell count declines. The more severe

and life-threatening complications of HIV infection occur in patients with CD4+ T cell counts <200/μL. A diagnosis of AIDS is made in any individual age 6 years and older with HIV infection and a CD4+ T cell count <200/μL (Stage 3, Table 197-2) and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity (Table 197-1). While the causative agents of the secondary infections are characteristically opportunistic organisms such as *P. jirovecii*, atypical mycobacteria, CMV, and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include several common bacterial and mycobacterial pathogens. Following the widespread use of cART and implementation of guidelines for the prevention of opportunistic infections **(Table 197-11)**, the incidence of these secondary infections has decreased dramatically **(Fig. 197-34)**. Overall, the clinical spectrum of HIV disease is constantly changing as patients live longer and new and better approaches to treatment and prophylaxis are developed. In addition to the classic AIDS-defining illnesses, patients with HIV infection also have an increase in several serious non-AIDS illnesses, including non-AIDS related cancers and cardiovascular, renal, and hepatic disease. Non-AIDS events dominate the disease burden for patients with HIV infection receiving cART (Table 197-4). In developed countries, AIDS-related illnesses are responsible for only ~25% of deaths in patients with HIV infection. A similar percentage of deaths are due to non-AIDS-defining malignancies, with cardiovascular disease and liver disease each accounting for approximately 15% of deaths. The physician providing care to a patient with HIV infection must be well versed in general internal medicine as well as HIV-related opportunistic diseases. In general, it should be stressed that a key element of treatment of symptomatic complications of HIV disease, whether they are primary or secondary, is achieving good control of HIV replication through the use of cART and instituting primary and secondary prophylaxis for opportunistic infections as indicated.

Diseases of the Respiratory System Acute bronchitis and sinusitis are prevalent during all stages of HIV infection. The most severe cases tend to occur in patients with lower CD4+ T cell counts. Sinusitis presents as fever, nasal congestion, and headache. The diagnosis is made by CT or MRI. The maxillary sinuses are most commonly involved; however, disease is also frequently seen in the ethmoid, sphenoid, and frontal sinuses. While some patients may improve without antibiotic therapy, radiographic improvement is quicker and more pronounced in patients who have received antimicrobial therapy. It is postulated that this high incidence of sinusitis results from an increased frequency of infection with encapsulated organisms such as *H. influenzae* and *Streptococcus pneumoniae*. In patients with low CD4+ T cell counts one may see mucormycosis infections of the sinuses. In contrast to the course of this infection in other patient populations, mucormycosis of the sinuses in patients with HIV infection may progress more slowly. In this setting aggressive, frequent local debridement in addition to local and systemic amphotericin B may result in effective treatment.

Pulmonary disease is one of the most frequent complications of HIV infection. The most common manifestation of pulmonary disease is pneumonia. Three of the 10 most common AIDS-defining illnesses are recurrent bacterial pneumonia, tuberculosis, and pneumonia due to the unicellular fungus *P. jirovecii*. Other major causes of pulmonary infiltrates include other mycobacterial infections, other fungal infections, nonspecific interstitial pneumonitis, KS, and lymphoma.

Bacterial pneumonia is seen with an increased frequency in patients with HIV infection, with 0.8–2.0 cases per 100 person-years. Patients with HIV infection are particularly prone to infections with encapsulated organisms. *S. pneumoniae* **(Chap. 141)** and *H. influenzae* **(Chap. 152)** are responsible for most cases of bacterial pneumonia in patients with AIDS. This may be a consequence of altered B cell function and/or defects in neutrophil function that may be secondary to HIV disease (see above). Pneumonias due to *S. aureus* **(Chap. 142)** and *P. aeruginosa* **(Chap. 159)** also are reported to occur with an increased frequency in patients with HIV infection. *S. pneumoniae* (pneumococcal) infection may be the earliest serious infection to occur in patients with HIV disease. This can present as pneumonia, sinusitis, and/or bacteremia. Patients with untreated HIV infection have a sixfold increase in the incidence of pneumococcal pneumonia and a 100-fold increase in the incidence of pneumococcal bacteremia. Pneumococcal disease may be seen in patients with relatively intact immune systems. In one study, the baseline CD4+ T cell count at the time of a first episode of pneumococcal pneumonia was ~300/μL. Of interest is the fact that the inflammatory response to pneumococcal infection appears proportional to the CD4+ T cell count. Due to this high risk of pneumococcal disease, immunization with the conjugated pneumococcal vaccine followed by booster immunization with the 23-valent pneumococcal polysaccharide vaccine is one of the generally recommended prophylactic measures for patients with HIV infection. This is likely most effective if given while the CD4+ T cell count is >200/μL and, if given to patients with lower CD4+ T cell counts, should be repeated once the count has been above 200 for 6 months. Although clear guidelines do not exist, it also makes sense to repeat immunization every 5 years. The incidence of bacterial pneumonia is cut in half when patients quit smoking.

Pneumocystis pneumonia (PCP), once the hallmark of AIDS, has dramatically declined in incidence following the development of effective prophylactic regimens and the widespread use of cART. It is, however, still the single most common cause of pneumonia in patients with HIV infection in the United States and can be identified as a likely etiologic agent in 25% of cases of pneumonia in patients with HIV infection, with an incidence in the range of 2–3 cases per 100 person-years. Approximately 30% of cases of HIV-associated PCP occur in patients who are unaware of their HIV status. The risk of PCP is greatest among those who have experienced a previous bout of PCP and those who have CD4+ T cell counts of <200/μL. Overall, 79% of patients with PCP have CD4+ T cell counts <100/μL and 95% of patients have CD4+ T cell counts <200/μL. Recurrent fever, night sweats, thrush, and unexplained weight loss also are associated with an increased incidence of PCP. For these reasons, it is strongly recommended that all patients with CD4+ T cell counts <200/μL (or a CD4 percentage <15) receive some form of PCP prophylaxis. The incidence of PCP is approaching zero in patients with known HIV infection receiving appropriate cART and prophylaxis. In the United States, primary PCP is now occurring at a median CD4+ T cell count of 36/μL, while secondary PCP is occurring at a median CD4+ T cell count of 10/μL. Patients with PCP generally present with fever and a cough that is usually nonproductive or productive of only scant amounts of white sputum. They may complain of a characteristic retrosternal chest pain that is worse on inspiration and is described as sharp or burning. HIV-associated PCP may have an indolent course characterized by weeks of vague symptoms and should be included in the differential diagnosis of fever, pulmonary complaints, or unexplained weight loss in any patient with HIV infection and <200 CD4+ T cells/μL. The most common finding on chest x-ray is either a normal film, if the disease is suspected early, or a faint bilateral interstitial infiltrate. The classic finding of a dense perihilar infiltrate is unusual in patients with AIDS. In patients with PCP who have been receiving aerosolized pentamidine for prophylaxis, one may see an x-ray picture of upper lobe cavitary disease, reminiscent of TB. Other less common findings on chest x-ray include lobar infiltrates and pleural effusions. Thin-section CT may demonstrate a patchy ground-glass appearance. Routine laboratory evaluation is usually of little help in the differential diagnosis of PCP. A mild leukocytosis is common, although this may not be obvious in patients with prior neutropenia. Elevation of lactate dehydrogenase is common. Arterial blood-gases may indicate hypoxemia with a decline in Pao_2 and an increase in the arterial-alveolar (a–A) gradient. Arterial blood-gas measurements not only aid in making the diagnosis of PCP but also provide important information for staging the severity of the disease and directing treatment (see below). A definitive diagnosis of PCP requires demonstration of the organism in samples obtained from induced sputum, bronchoalveolar lavage, transbronchial biopsy, or open-lung biopsy. PCR has been used to detect specific DNA sequences for *P. jirovecii* in clinical specimens where histologic examinations have failed to make a diagnosis.

In addition to pneumonia, a number of other clinical problems have been reported in HIV-infected patients as a result of infection

TABLE 197-11 NIH/CDC/IDSA 2013 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Recommended as Standard of Care for Primary and Secondary Prophylaxis			
Pneumocystis jirovecii	CD4+ T cell count <200/μL *or* Oropharyngeal candidiasis *or* Prior bout of PCP	Trimethoprim-sulfamethoxazole (TMP-SMX), 1 DS tablet qd PO *or* TMP-SMX, 1 SS tablet qd PO	Dapsone 50 mg bid PO or 100 mg/d PO *or* Dapsone 50 mg/d PO + Pyrimethamine 50 mg/week PO + Leucovorin 25 mg/week PO *or* (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg weekly PO) *or* Aerosolized pentamidine, 300 mg via Respirgard II nebulizer every month *or* Atovaquone 1500 mg/d PO *or* TMP-SMX 1 DS tablet 3×/week PO
	May stop prophylaxis if CD4+ T cell count >200/μL for ≥3 months		
Mycobacterium tuberculosis Isoniazid sensitive	Skin test >5 mm *or* Positive IFN-γ release assay *or* Prior positive test without treatment *or* Close contact with case of active pulmonary TB Same with high probability of exposure to drug-resistant TB	(Isoniazid 300 mg PO + Pyridoxine 25 mg PO) qd × 9 months *or* Isoniazid 900 mg PO twice weekly + Pyridoxine 25 mg PO daily × 9 months	Rifabutin (dose adjusted based on cART regimen) or rifampin 600 mg PO qd × 4 months
Drug resistant	Consult local public health authorities		
Mycobacterium-avium complex	CD4+ T cell count <50/μL	Azithromycin 1200 mg weekly PO or 600 mg twice weekly PO *or* Clarithromycin 500 mg bid PO	Rifabutin (dose adjusted based on cART regimen)
	Prior documented disseminated disease	Clarithromycin 500 mg bid PO + Ethambutol 15 (mg/kg)/d PO	Azithromycin 500–600 mg/d PO + Ethambutol 15 (mg/kg)/d PO
	May stop prophylaxis if CD4+ T cell count >100/μL for ≥6 months		
Toxoplasma gondii	TOXO IgG antibody positive and CD4+ T cell count <100/μL	TMP-SMX 1 DS tablet PO qd	TMP-SMX 1 DS 3× weekly PO *or* TMP-SMX, 1 SS PO daily *or* Dapsone 50 mg/d PO + Pyrimethamine 50 mg weekly PO + Leucovorin 25 mg weekly PO *or* (Dapsone 200 mg PO + Pyrimethamine 75 mg PO + Leucovorin 25 mg PO) weekly *or* Atovaquone 1500 mg PO daily ± (Pyrimethamine 25 mg PO + Leucovorin 10 mg PO) daily
	Prior toxoplasmic encephalitis and CD4+ T cell count <200/μL	Sulfadiazine 2000–4000 mg in 2–4 divided doses daily PO + Pyrimethamine 25–50 mg/d PO + Leucovorin 10–25 mg/d PO	Clindamycin 600 mg q8h PO + Pyrimethamine 25–50 mg/d PO + Leucovorin 10–25 mg/d PO *or* TMP-SMX 1 DS tablet bid *or* Atovaquone 750–1500 mg PO bid ± (Pyrimethamine 25 mg/d PO + Leucovorin 10 mg/d PO) or Sulfadiazine 2000–4000 mg/d (in 2–4 divided doses) PO

(*Continued*)

TABLE 197-11 NIH/CDC/IDSA 2013 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV (Continued)

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Toxoplasma gondii	May stop prophylaxis if CD4+ T cell count >200/μL for ≥3 months		
Varicella zoster virus	Significant exposure to chickenpox or shingles in a patient with no history of immunization or prior exposure to either	Varicella zoster immune globulin, IM, within 10 d of exposure (800-843-7477)	Acyclovir 800 mg PO 5 × day for 5–7 days *or* Valacyclovir 1 g PO tid for 5–7 days
Cryptococcus neoformans	Prior documented disease	Fluconazole 200 mg/d PO	Itraconazole 200 mg/d PO
	May stop prophylaxis if CD4+ T cell count >100/μL, no evidence of active fungal infection, and HIV RNA levels <500 copies/mL for >3 months		
Histoplasma capsulatum	Prior documented disease or CD4+ T cell count <150μL and high risk (endemic area or occupational exposure)	Itraconazole 200 mg bid PO	Fluconazole 400 mg/d PO
	May stop prophylaxis after 1 year if CD4+ T cell count >150/μL and patient on cART for ≥6 months		
Coccidioides immitis	Prior documented disease *or* positive serology and CD4+ T cell count <250/μL if from a disease endemic area. (For this indication prophylaxis can be stopped if CD4+ T cell count ≥250 for 6 months.)	Fluconazole 400 mg/d PO	
Penicillium marneffei	Prior documented disease Patients with CD4+T cell counts <100 who live or stay in northern Thailand, Southern China, or Vietnam	Itraconazole 200 mg/d PO	Fluconazole 400 mg PO once weekly
	May stop secondary prophylaxis in patients on ARV therapy with CD4+ T cell count >100/μL for ≥6 months		
Salmonella species	Prior recurrent bacteremia	Ciprofloxacin 500 mg bid PO for ≥6 months	
Bartonella	Prior infection	Doxycycline 200 mg/d PO *or* Azithromycin 1200 mg weekly PO *or* Clarithromycin 500 mg bid PO	
	May stop if CD4+ T cell count >200/μL for >3 months		
Cytomegalovirus	Prior end-organ disease	Valganciclovir 900 mg bid PO	Cidofovir 5 mg/kg every other week IV + Probenecid *or* Foscarnet 90–120 (mg/kg)/d IV
	May stop prophylaxis if CD4+ T cell count >100/μL for 6 months and no evidence of active CMV disease Restart if prior retinitis and CD4+ T cells <100/μL		
Immunizations Generally Recommended			
Hepatitis B virus	All susceptible (anti-HBc- and anti-HBs-negative) patients	Hepatitis B vaccine: 3 doses	
Hepatitis A virus	All susceptible (anti-HAV-negative) patients	Hepatitis A vaccine: 2 doses	
Influenza virus	All patients annually	Inactivated trivalent influenza virus vaccine 1 dose yearly	Oseltamivir 75 mg PO qd *or* Rimantadine or amantadine 100 mg PO bid (influenza A only)
Streptococcus pneumoniae	All patients, preferably before CD4+ T cell count ≤200/μL	Pneumococcal conjugated vaccine (13) 0.5 mL IM × 1 followed in 8 weeks or more by pneumococcal polysaccharide vaccine (23) if CD4+ T cell count >200/μL	
	Patients initially immunized at a CD4+ T cell count <100/μL whose CD4+ T cell count then increases to>200/μL	Reimmunize	
Human papillomavirus	All patients 13–26 years of age	HPV vaccine; 3 doses	

(*Continued*)

TABLE 197-11 NIH/CDC/IDSA 2013 Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV (Continued)

PATHOGEN	INDICATIONS	FIRST CHOICE(S)	ALTERNATIVES
Recommended for Prevention of Severe or Frequent Recurrences			
Herpes simplex	Frequent/severe recurrences	Valacyclovir 500 mg bid PO *or* Acyclovir 400 mg bid PO *or* Famciclovir 500 mg bid PO	
Candida	Frequent/severe recurrences	Fluconazole 100–200 mg/d PO	Posaconazole 400 mg bid PO

Abbreviations: ARV, antiretroviral; bid, twice daily; cART, combination antiretroviral therapy; DS, double-strength; IM, intramuscular; PCP, *Pneumocystis jirovecii* pneumonia; PO, by mouth; qd, daily; SS, single-strength; TB, tuberculosis; tid, three times a day.

with *P. jirovecii*. Otic involvement may be seen as a primary infection, presenting as a polypoid mass involving the external auditory canal. In patients receiving aerosolized pentamidine for prophylaxis against PCP, one may see a variety of extrapulmonary manifestations of *P. jirovecii*. These include ophthalmic lesions of the choroid, a necrotizing vasculitis that resembles Buerger disease, bone marrow hypoplasia, and intestinal obstruction. Other organs that have been involved include lymph nodes, spleen, liver, kidney, pancreas, pericardium, heart, thyroid, and adrenals. Organ infection may be associated with cystic lesions that may appear calcified on CT or ultrasound.

The standard treatment for PCP or disseminated pneumocystosis is trimethoprim-sulfamethoxazole (TMP-SMX). A high (20–85%) incidence of side effects, particularly skin rash and bone marrow suppression, is seen with TMP-SMX in patients with HIV infection. Alternative treatments for mild to moderate PCP include dapsone/trimethoprim, clindamycin/primaquine, and atovaquone. IV pentamidine is the treatment of choice for severe disease in the patient unable to tolerate TMP-SMX. For patients with a Pa_{o2} <70 mmHg or with an a–A gradient >35 mmHg, adjunct glucocorticoid therapy should be used in addition to specific antimicrobials. Overall, treatment should be continued for 21 days and followed by secondary prophylaxis. Prophylaxis for PCP is indicated for any HIV-infected individual who has experienced a prior bout of PCP, any patient with a CD4+ T cell count of <200/μL or a CD4 percentage <15, any patient with unexplained fever for >2 weeks, and any patient with a recent history of oropharyngeal candidiasis. The preferred regimen for prophylaxis is TMP-SMX, one double-strength tablet daily. This regimen also provides protection against toxoplasmosis and some bacterial respiratory pathogens. For patients who cannot tolerate TMP-SMX, alternatives for prophylaxis include dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine administered by the Respirgard II nebulizer, and atovaquone. Primary or secondary prophylaxis for PCP can be discontinued in those patients treated with cART who maintain good suppression of HIV (<50 copies/mL) and CD4+ T cell counts >200/μL for at least 3 months.

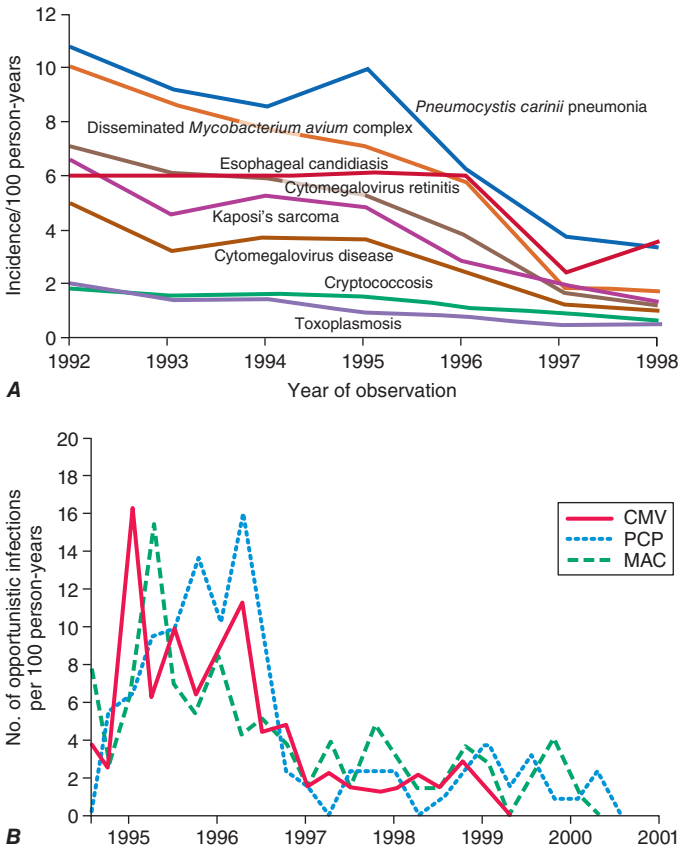


FIGURE 197-34 **A.** Decrease in the incidence of opportunistic infections and Kaposi's sarcoma in HIV-infected individuals with CD4+ T cell counts <100/μL from 1992 through 1998. *(Adapted and updated from FJ Palella et al: N Engl J Med 338:853, 1998, and JE Kaplan et al: Clin Infect Dis 30[S1]:S5, 2000, with permission.)* **B.** Quarterly incidence rates of cytomegalovirus (CMV), *Pneumocystis jirovecii* pneumonia (PCP), and *Mycobacterium avium* complex (MAC) from 1995 to 2001. *(From FJ Palella et al: AIDS 16:1617, 2002.)*

M. tuberculosis, once thought to be on its way to extinction in the United States, experienced a resurgence associated with the HIV epidemic **(Chap. 173)**. Worldwide, approximately one-third of all AIDS-related deaths are associated with TB, and TB is the primary cause of death for 10–15% of patients with HIV infection. In the United States ~5% of AIDS patients have active TB. Patients with HIV infection are more likely to have active TB by a factor of 100 when compared with an HIV-negative population. For an asymptomatic HIV-negative person with a positive purified protein derivative (PPD) skin test, the risk of reactivation TB is around 1% per year. For the patient with untreated HIV infection, a positive PPD skin test, and no signs or symptoms of TB, the rate of reactivation TB is 7–10% per year. Untreated TB can accelerate the course of HIV infection. Levels of plasma HIV RNA increase in the setting of active TB and decline in the setting of successful TB treatment. Active TB is most common in patients 25–44 years of age, in African Americans and Hispanics, in patients in New York City and Miami, and in patients in developing countries. In these demographic groups, 20–70% of the new cases of active TB are in patients with HIV infection. The epidemic of TB embedded in the epidemic of HIV infection probably represents the greatest health risk to the general public and the health care profession associated with the HIV epidemic. In contrast to infection with atypical mycobacteria such as MAC, active TB often develops relatively early in the course of HIV infection and may be an early clinical sign of HIV disease. In one study, the median CD4+ T cell count at presentation of TB was 326/μL. The clinical manifestations of TB in HIV-infected patients are quite varied and generally show different patterns as a function of the CD4+ T cell count. In patients with relatively high CD4+ T cell counts, the typical pattern of pulmonary reactivation occurs: patients present with fever, cough, dyspnea on exertion, weight loss, night sweats, and a chest x-ray revealing cavitary apical disease of the upper lobes. In patients with lower CD4+ T cell counts, disseminated disease is more common. In these patients the chest x-ray may reveal diffuse or lower-lobe bilateral reticulonodular infiltrates consistent with miliary spread, pleural effusions, and hilar and/or mediastinal adenopathy. Infection may be present in bone, brain, meninges, GI tract, lymph nodes (particularly cervical lymph nodes), and viscera. Some patients with advanced HIV infection and active TB may have no symptoms of illness, and thus screening for TB should be part of the initial evaluation of every patient with HIV infection. Approximately 60–80% of HIV-infected patients

with TB have pulmonary disease, and 30–40% have extrapulmonary disease. Respiratory isolation and a negative-pressure room should be used for patients in whom a diagnosis of pulmonary TB is being considered. This approach is critical to limit nosocomial and community spread of infection. Culture of the organism from an involved site provides a definitive diagnosis. Blood cultures are positive in 15% of patients. This figure is higher in patients with lower CD4 +T cell counts. In the setting of fulminant disease one cannot rely on the accuracy of a negative PPD skin test to rule out a diagnosis of TB. In addition, IFN-γ release assays may be difficult to interpret due to high backgrounds as a consequence of HIV-associated immune activation. TB is one of the conditions associated with HIV infection for which cure is possible with appropriate therapy. Therapy for TB is generally the same in the HIV-infected patient as in the HIV-negative patient **(Chap. 173)**. Due to the possibility of multidrug-resistant or extensively drug-resistant TB, drug susceptibility testing should be performed to guide therapy. Due to pharmacokinetic interactions, adjusted doses of rifabutin and/or changes in cART are required when treating TB in the setting of HIV infection. Treatment is most effective in programs that involve directly observed therapy. Initiation of cART and/or anti-TB therapy may be associated with clinical deterioration due to immune reconstitution inflammatory syndrome (IRIS) reactions. These are most common in patients initiating both treatments at the same time, may occur as early as 1 week after initiation of cART therapy, and are seen more frequently in patients with advanced HIV disease. For these reasons it is recommended that initiation of cART be delayed in antiretroviral-naïve patients with CD4 counts >50 cells/μL until 2–4 weeks following the initiation of treatment for TB. For patients with lower CD4 counts the benefits of more immediate cART outweigh the risks of IRIS, and cART should be started as soon as possible in those patients. Effective prevention of active TB can be a reality if the health care professional is aggressive in looking for evidence of latent or active TB by making sure that all patients with HIV infection receive a PPD skin test or evaluation with an IFN-γ release assay. Anergy testing is not of value in this setting. Since these tests rely on the host mounting an immune response to *M. tuberculosis*, patients with CD4+ T cell counts <200 cells/μL should be retested if their CD4+ T cell counts rise to persistently above 200. Patients at risk of continued exposure to TB should be tested annually. HIV-infected individuals with a skin-test reaction of >5 mm, those with a positive IFN-γ release assay, or those who are close household contacts of persons with active TB should receive treatment with 9 months of isoniazid and pyridoxine.

Atypical mycobacterial infections are also seen with an increased frequency in patients with HIV infection. Infections with at least 12 different mycobacteria have been reported, including *M. bovis* and representatives of all four Runyon groups. The most common atypical mycobacterial infection is with *M. avium* or *M. intracellulare* species—the *Mycobacterium avium* complex (MAC). Infections with MAC are seen mainly in patients in the United States and are rare in Africa. It has been suggested that prior infection with *M. tuberculosis* decreases the risk of MAC infection. MAC infections probably arise from organisms that are ubiquitous in the environment, including both soil and water. There is little evidence for person-to-person transmission of MAC infection. The presumed portals of entry are the respiratory and GI tracts. MAC infection is a late complication of HIV infection, occurring predominantly in patients with CD4+ T cell counts of <50/μL. The average CD4+ T cell count at the time of diagnosis is 10/μL. The most common presentation is disseminated disease with fever, weight loss, and night sweats. At least 85% of patients with MAC infection are mycobacteremic, and large numbers of organisms can often be demonstrated on bone marrow biopsy. The chest x-ray is abnormal in ~25% of patients, with the most common pattern being that of a bilateral, lower-lobe infiltrate suggestive of miliary spread. Alveolar or nodular infiltrates and hilar and/or mediastinal adenopathy also can occur. Other clinical findings include endobronchial lesions, abdominal pain, diarrhea, and lymphadenopathy. Anemia and elevated liver alkaline phosphatase are common. The diagnosis is made by the culture of blood or involved tissue. The finding of two consecutive sputum samples positive for MAC is highly suggestive of pulmonary infection. Cultures may take 2 weeks to turn positive. Therapy consists of a macrolide, usually clarithromycin, with ethambutol. Some physicians elect to add a third drug from among rifabutin, ciprofloxacin, or amikacin in patients with extensive disease. Therapy is continued until resolution of clinical signs and symptoms, negative cultures, and CD4+ T cell counts >100/μL for 3–6 months in the setting of cART. Primary prophylaxis for MAC is indicated in patients with HIV infection and CD4+ T cell counts <50/μL (Table 197-11). This may be discontinued in patients in whom cART induces a sustained suppression of viral replication and an increase in CD4+ T cell count to >100/μL for ≥6 months.

Rhodococcus equi is a gram-positive, pleomorphic, acid-fast, nonspore-forming bacillus that can cause pulmonary and/or disseminated infection in patients with advanced HIV infection. Fever and cough are the most common presenting signs. Radiographically one may see cavitary lesions and consolidation. Blood cultures are often positive. Treatment is based on antimicrobial sensitivity testing.

Fungal infections of the lung, in addition to PCP, can be seen in patients with AIDS. Patients with pulmonary cryptococcal disease present with fever, cough, dyspnea, and, in some cases, hemoptysis. A focal or diffuse interstitial infiltrate is seen on chest x-ray in >90% of patients. In addition, one may see lobar disease, cavitary disease, pleural effusions, and hilar or mediastinal adenopathy. More than half of patients are fungemic, and 90% of patients have concomitant CNS infection. *Coccidioides immitis* is a mold that is endemic in the southwest United States. It can cause a reactivation pulmonary syndrome in patients with HIV infection. Most patients with this condition will have CD4+ T cell counts <250/μL. Patients present with fever, weight loss, cough, and extensive, diffuse reticulonodular infiltrates on chest x-ray. One may also see nodules, cavities, pleural effusions, and hilar adenopathy. While serologic testing is of value in the immunocompetent host, serologies are negative in 25% of HIV-infected patients with coccidioidal infection. Invasive aspergillosis is not an AIDS-defining illness and is generally not seen in patients with AIDS in the absence of neutropenia or administration of glucocorticoids. When it does occur, *Aspergillus* infection may have an unusual presentation in the respiratory tract of patients with AIDS, where it gives the appearance of a pseudomembranous tracheobronchitis. Primary pulmonary infection of the lung may be seen with *histoplasmosis*. The most common pulmonary manifestation of histoplasmosis, however, is in the setting of disseminated disease, presumably due to reactivation. In this setting respiratory symptoms are usually minimal, with cough and dyspnea occurring in 10–30% of patients. The chest x-ray is abnormal in ~50% of patients, showing either a diffuse interstitial infiltrate or diffuse small nodules, and the urine will often be positive for *Histoplasma* antigen.

Two forms of *idiopathic interstitial pneumonia* have been identified in patients with HIV infection: lymphoid interstitial pneumonitis (LIP) and nonspecific interstitial pneumonitis (NIP). LIP, a common finding in children, is seen in about 1% of adult patients with untreated HIV infection. This disorder is characterized by a benign infiltrate of the lung and is thought to be part of the polyclonal activation of lymphocytes seen in the context of HIV and EBV infections. Transbronchial biopsy is diagnostic in 50% of the cases, with an open-lung biopsy required for diagnosis in the remainder of cases. This condition is generally self-limited and no specific treatment is necessary. Severe cases have been managed with brief courses of glucocorticoids. Although rarely a clinical problem since the use of cART, evidence of NIP may be seen in up to half of all patients with untreated HIV infection. Histologically, interstitial infiltrates of lymphocytes and plasma cells in a perivascular and peribronchial distribution are present. When symptomatic, patients present with fever and nonproductive cough occasionally accompanied by mild chest discomfort. Chest x-ray is usually normal or may reveal a faint interstitial pattern. Similar to LIP, NIP is a self-limited process for which no therapy is indicated other than appropriate management of the underlying HIV infection. HIV-related pulmonary arterial hypertension (HIV-PAH) is seen in ~0.5% of HIV-infected individuals. Patients may present with an array of symptoms including shortness of breath, fatigue, syncope, chest pain, and signs of right-sided heart failure. Chest x-ray reveals dilated pulmonary vessels and right-sided cardiomegaly with right ventricular hypertrophy seen on electrocardiogram. cART

does not appear to be of clear benefit, and the prognosis is quite poor with a median survival in the range of 2 years.

Neoplastic diseases of the lung including KS and lymphoma are discussed below in the section on neoplastic diseases.

Diseases of the Cardiovascular System Heart disease is a relatively common postmortem finding in HIV-infected patients (25–75% in autopsy series). The most common form of heart disease is coronary heart disease. In one large series the overall rate of myocardial infarction (MI) was 3.5/1000 patient-years, 28% of these events were fatal, and MI was responsible for 7% of all deaths in the cohort. In patients with HIV infection, cardiovascular disease may be associated with classic risk factors such as smoking, a direct consequence of HIV infection, or a complication of cART. Patients with HIV infection have higher levels of triglycerides, lower levels of high-density lipoprotein cholesterol, and a higher prevalence of smoking than cohorts of individuals without HIV infection. The finding that the rate of cardiovascular disease events was lower in patients on antiretroviral therapy than in those randomized to undergo a treatment interruption identified a clear association between HIV replication and risk of cardiovascular disease. In one study, a baseline CD4+ T cell count of <500/μL was found to be an independent risk factor for cardiovascular disease comparable in magnitude to that attributable to smoking. While the precise pathogenesis of this association remains unclear, it is likely related to the immune activation and increased propensity for coagulation seen as a consequence of HIV replication. Exposure to HIV protease inhibitors and certain reverse transcriptase inhibitors has been associated with increases in total cholesterol and/or risk of MI. Any increases in the risk of death from MI resulting from the use of certain antiretrovirals must be balanced against the marked increases in overall survival brought about by these drugs.

Another form of heart disease associated with HIV infection is a dilated cardiomyopathy associated with congestive heart failure (CHF) referred to as *HIV-associated cardiomyopathy*. This generally occurs as a late complication of HIV infection and, histologically, displays elements of myocarditis. For this reason some have advocated treatment with IV immunoglobulin (IVIg). HIV can be directly demonstrated in cardiac tissue in this setting, and there is debate over whether it plays a direct role in this condition. Patients present with typical findings of CHF including edema and shortness of breath. Patients with HIV infection may also develop cardiomyopathy as side effects of IFN-α or nucleoside analogue therapy. These are reversible once therapy is stopped. KS, cryptococcosis, Chagas' disease, and toxoplasmosis can involve the myocardium, leading to cardiomyopathy. In one series, most patients with HIV infection and a treatable myocarditis were found to have myocarditis associated with toxoplasmosis. Most of these patients also had evidence of CNS toxoplasmosis. Thus, MRI or double-dose contrast CT scan of the brain should be included in the workup of any patient with advanced HIV infection and cardiomyopathy.

A variety of other cardiovascular problems are found in patients with HIV infection. Pericardial effusions may be seen in the setting of advanced HIV infection. Predisposing factors include TB, CHF, mycobacterial infection, cryptococcal infection, pulmonary infection, lymphoma, and KS. While pericarditis is quite rare, in one series 5% of patients with HIV disease had pericardial effusions that were considered to be moderate or severe. Tamponade and death have occurred in association with pericardial KS, presumably owing to acute hemorrhage. Nonbacterial thrombotic endocarditis has been reported and should be considered in patients with unexplained embolic phenomena. IV pentamidine, when given rapidly, can result in hypotension as a consequence of cardiovascular collapse.

Diseases of the Oropharynx and Gastrointestinal System Oropharyngeal and GI diseases are common features of HIV infection. They are most frequently due to secondary infections. In addition, oral and GI lesions may occur with KS and lymphoma.

Oral lesions, including *thrush*, *hairy leukoplakia*, and *aphthous ulcers* **(Fig. 197-35)**, are particularly common in patients with untreated HIV infection. Thrush, due to *Candida* infection, and oral hairy leukoplakia, presumed due to EBV, are usually indicative of fairly advanced immunologic decline; they generally occur in patients with CD4+ T cell counts of <300/μL. In one study, 59% of patients with oral candidiasis went on to develop AIDS in the next year. Thrush appears as a white, cheesy exudate, often on an erythematous mucosa in the posterior oropharynx. While most commonly seen on the soft palate, early lesions are often found along the gingival border. The diagnosis is made by direct examination of a scraping for pseudohyphal elements. Culturing is of no diagnostic value, as patients with HIV infection may have a positive throat culture for *Candida* in the absence of thrush. Oral hairy leukoplakia presents as white, frondlike lesions, generally along the lateral borders of the tongue and sometimes on the adjacent buccal mucosa (Fig. 197-35). Despite its name, oral hairy leukoplakia is not considered a premalignant condition. Lesions are associated with florid replication of EBV. While usually more disconcerting as a sign of HIV-associated immunodeficiency than a clinical problem in need of treatment, severe cases have been reported to respond to topical podophyllin or systemic therapy with anti-herpesvirus agents. Aphthous ulcers of the posterior oropharynx also are seen with regularity in patients with untreated HIV infection (Fig. 197-35). These lesions are of unknown etiology and can be quite painful and interfere with swallowing. Topical anesthetics provide immediate symptomatic relief of short duration. The fact that thalidomide is an effective treatment for this condition suggests that the pathogenesis may involve the action of tissue-destructive cytokines. Palatal, glossal, or gingival ulcers may also result from cryptococcal disease or histoplasmosis.

Esophagitis **(Fig. 197-36)** may present with odynophagia and retrosternal pain. Upper endoscopy is generally required to make an accurate diagnosis. Esophagitis may be due to *Candida*, CMV, or HSV. While CMV tends to be associated with a single large ulcer, HSV infection is more often associated with multiple small ulcers. The esophagus may also be the site of KS and lymphoma. Like the oral mucosa, the esophageal mucosa may have large, painful ulcers of unclear etiology that may respond to thalidomide. While achlorhydria is a common problem in patients with HIV infection, other gastric problems are generally rare. Among the neoplastic conditions involving the stomach are KS and lymphoma.

Infections of the small and large intestine leading to diarrhea, abdominal pain, and occasionally fever are among the most significant GI problems in HIV-infected patients. They include infections with bacteria, protozoa, and viruses.

Bacteria may be responsible for secondary infections of the GI tract. Infections with enteric pathogens such as *Salmonella*, *Shigella*, and *Campylobacter* are more common in men who have sex with men and are often more severe and more apt to relapse in patients with HIV infection. Patients with untreated HIV have approximately a 20-fold increased risk of infection with *S. typhimurium*. They may present with a variety of nonspecific symptoms including fever, anorexia, fatigue, and malaise of several weeks' duration. Diarrhea is common but may be absent. Diagnosis is made by culture of blood and stool. Long-term therapy with ciprofloxacin is the recommended treatment. HIV-infected patients also have an increased incidence of *S. typhi* infection in areas of the world where typhoid is a problem. *Shigella* spp., particularly *S. flexneri*, can cause severe intestinal disease in HIV-infected individuals. Up to 50% of patients will develop bacteremia. *Campylobacter* infections occur with an increased frequency in patients with HIV infection. While *C. jejuni* is the strain most frequently isolated, infections with many other strains have been reported. Patients usually present with crampy abdominal pain, fever, and bloody diarrhea. Infection may also present as proctitis. Stool examination reveals the presence of fecal leukocytes. Systemic infection can occur, with up to 10% of infected patients exhibiting bacteremia. Most strains are sensitive to erythromycin. Abdominal pain and diarrhea may be seen with MAC infection.

Fungal infections may also be a cause of diarrhea in patients with HIV infection. Histoplasmosis, coccidioidomycosis, and penicilliosis have all been identified as a cause of fever and diarrhea in patients with HIV infection. Peritonitis has been seen with *C. immitis*.

Cryptosporidia, microsporidia, and *Isospora belli* **(Chap. 224)** are the most common opportunistic protozoa that infect the GI tract and cause diarrhea in HIV-infected patients. Cryptosporidial infection may present in a variety of ways, ranging from a self-limited or intermittent

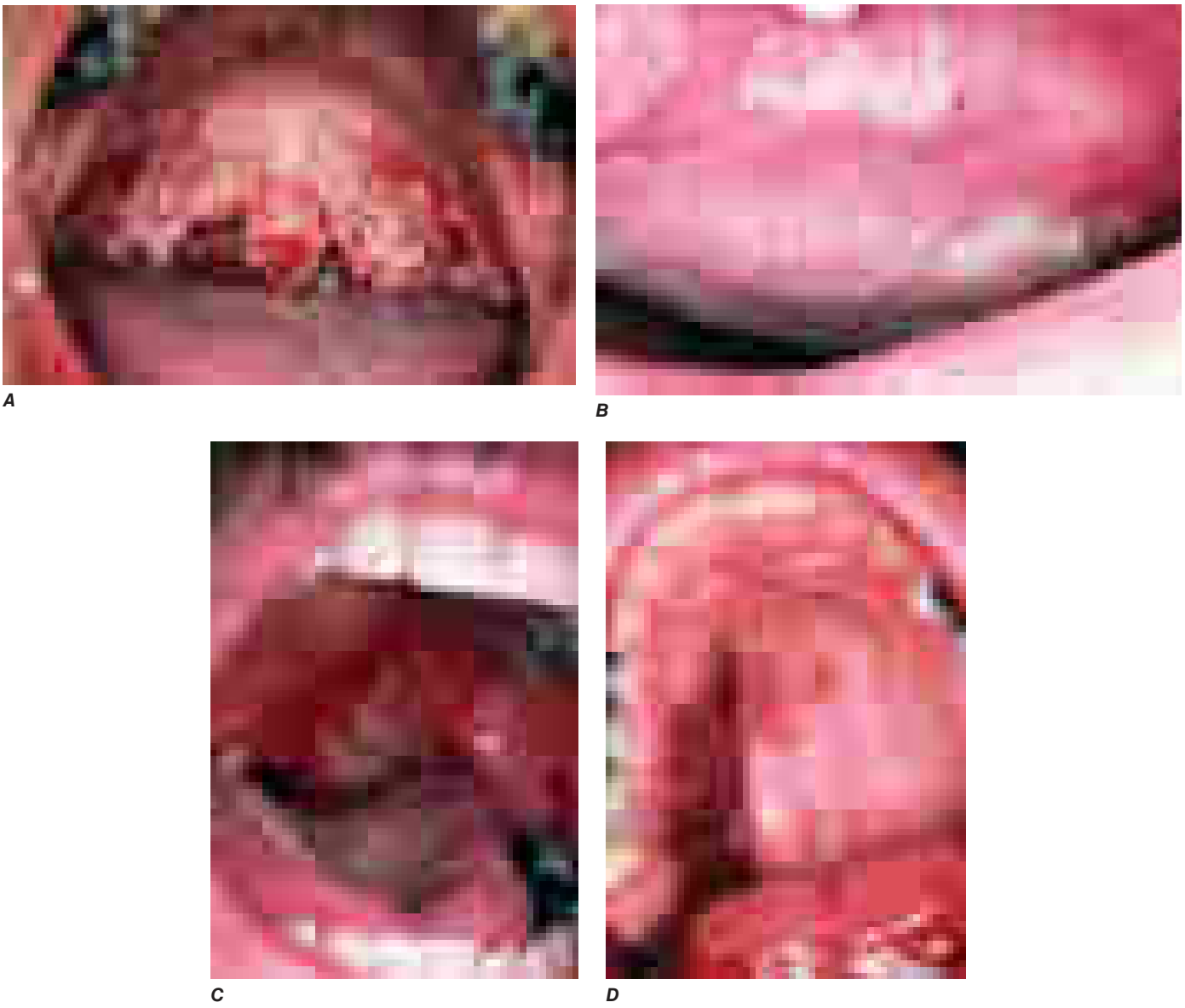


FIGURE 197-35 Various oral lesions in HIV-infected individuals. *A.* Thrush. ***B.*** Hairy leukoplakia. ***C.*** Aphthous ulcer. ***D.*** Kaposi's sarcoma.

diarrheal illness in patients in the early stages of HIV infection to a severe, life-threatening diarrhea in severely immunodeficient individuals. In patients with untreated HIV infection and CD4+ T cell counts of <300/μL, the incidence of cryptosporidiosis is ~1% per year. In 75% of cases the diarrhea is accompanied by crampy abdominal pain, and 25% of patients have nausea and/or vomiting. Cryptosporidia may also cause biliary tract disease in the HIV-infected patient, leading to cholecystitis with or without accompanying cholangitis and pancreatitis secondary to papillary stenosis. The diagnosis of cryptosporidial diarrhea is made by stool examination or biopsy of the small intestine. The diarrhea is noninflammatory, and the characteristic finding is the presence of oocysts that stain with acid-fast dyes. Therapy is predominantly supportive, and marked improvements have been reported in the setting of effective cART. Treatment with up to 2000 mg/d of nitazoxanide (NTZ) is associated with improvement in symptoms or a decrease in shedding of organisms in about half of patients. Its overall role in the management of this condition remains unclear. Patients can minimize their risk of developing cryptosporidiosis by avoiding contact with human and animal feces, by not drinking untreated water from lakes or rivers, and by not eating raw shellfish.

Microsporidia are small, unicellular, obligate intracellular parasites that reside in the cytoplasm of enteric cells **(Chap. 224)**. The main species causing disease in humans is *Enterocytozoon bieneusi*. The clinical manifestations are similar to those described for cryptosporidia and include abdominal pain, malabsorption, diarrhea, and cholangitis. The small size of the organism may make it difficult to detect; however, with the use of chromotrope-based stains, organisms can be identified in stool samples by light microscopy. Definitive diagnosis generally depends on electron-microscopic examination of a stool specimen, intestinal aspirate, or intestinal biopsy specimen. In contrast to cryptosporidia, microsporidia have been noted in a variety of extraintestinal locations, including the eye, brain, sinuses, muscle, and liver, and they have been associated with conjunctivitis and hepatitis. The most effective way to deal with microsporidia in a patient with HIV infection is to restore the immune system by treating the HIV infection with cART. Albendazole, 400 mg bid, has been reported to be of benefit in some patients.

I. belli is a coccidian parasite **(Chap. 224)** most commonly found as a cause of diarrhea in patients from tropical and subtropical regions. Its cysts appear in the stool as large, acid-fast structures that can be differentiated from those of cryptosporidia on the basis of size, shape, and number of sporocysts. The clinical syndromes of *Isospora* infection are identical to those caused by cryptosporidia. The important distinction is that infection with *Isospora* is generally relatively easy to treat with TMP-SMX. While relapses are common, a thrice-weekly regimen of TMP-SMX appears adequate to prevent recurrence.

CMV colitis was once seen as a consequence of advanced immunodeficiency in 5–10% of patients with AIDS. It is much less common with

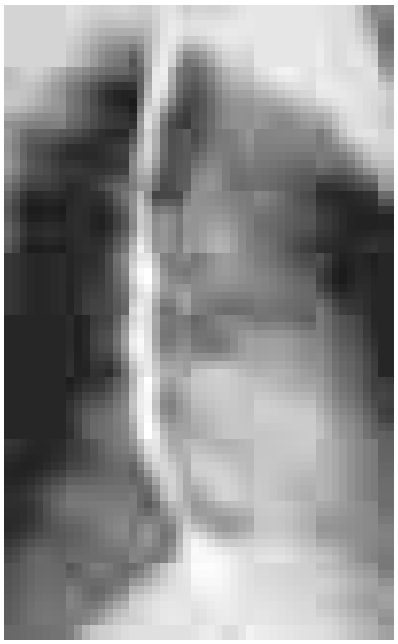


FIGURE 197-36 Barium swallow of a patient with *Candida* esophagitis. The flow of barium along the mucosal surface is grossly irregular.

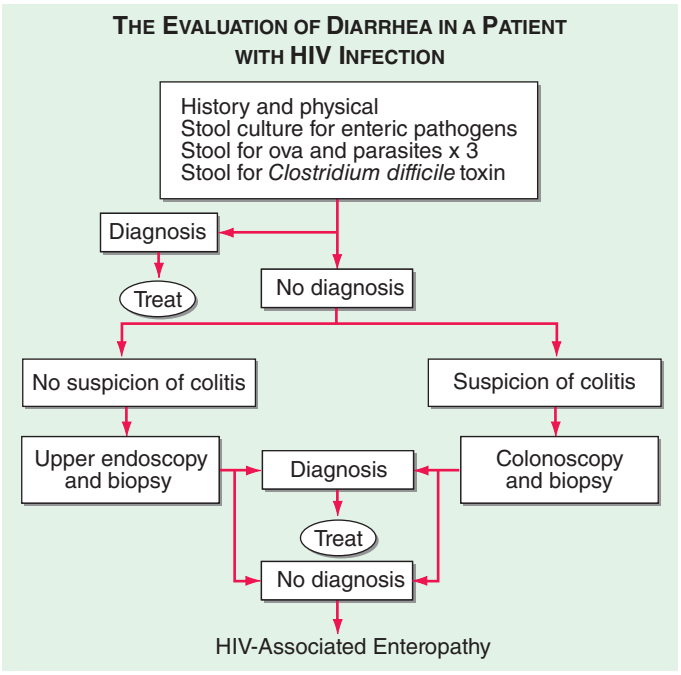


FIGURE 197-37 Algorithm for the evaluation of diarrhea in a patient with HIV infection. HIV-associated enteropathy is a diagnosis of exclusion and can be made only after other, generally treatable, forms of diarrheal illness have been ruled out.

the advent of cART. CMV colitis presents as diarrhea, abdominal pain, weight loss, and anorexia. The diarrhea is usually nonbloody, and the diagnosis is achieved through endoscopy and biopsy. Multiple mucosal ulcerations are seen at endoscopy, and biopsies reveal characteristic intranuclear and cytoplasmic inclusion bodies. Secondary bacteremias may result as a consequence of thinning of the bowel wall. Treatment is with either ganciclovir or foscarnet for 3–6 weeks. Relapses are common, and maintenance therapy is typically necessary in patients whose HIV infection is poorly controlled. Patients with CMV disease of the GI tract should be carefully monitored for evidence of CMV retinitis.

In addition to disease caused by specific secondary infections, patients with HIV infection may also experience a chronic diarrheal syndrome for which no etiologic agent other than HIV can be identified. This entity is referred to as *AIDS enteropathy* or *HIV enteropathy*. It is most likely a direct result of HIV infection in the GI tract. Histologic examination of the small bowel in these patients reveals low-grade mucosal atrophy with a decrease in mitotic figures, suggesting a hyporegenerative state. Patients often have decreased or absent small-bowel lactase and malabsorption with accompanying weight loss.

The initial evaluation of a patient with HIV infection and diarrhea should include a set of stool examinations, including culture, examination for ova and parasites, and examination for *Clostridium difficile* toxin. Approximately 50% of the time this workup will demonstrate infection with pathogenic bacteria, mycobacteria, or protozoa. If the initial stool examinations are negative, additional evaluation, including upper and/or lower endoscopy with biopsy, will yield a diagnosis of microsporidial or mycobacterial infection of the small intestine ~30% of the time. In patients for whom this diagnostic evaluation is nonrevealing, a presumptive diagnosis of HIV enteropathy can be made if the diarrhea has persisted for >1 month. An algorithm for the evaluation of diarrhea in patients with HIV infection is given in Fig. 197-37.

Rectal lesions are common in HIV-infected patients, particularly the perirectal ulcers and erosions due to the reactivation of HSV (Fig. 197-38). These lesions may appear quite atypical, as denuded skin without vesicles. They typically respond well to treatment with valacyclovir, famciclovir, or foscarnet. Other rectal lesions encountered in patients with HIV infection include condylomata acuminata, KS, and intraepithelial neoplasia (see below).

Hepatobiliary Diseases Diseases of the hepatobiliary system are a major problem in patients with HIV infection. It has been estimated that approximately 15% of the deaths of patients with HIV infection are related to liver disease. While this is predominantly a reflection of the problems encountered in the setting of co-infection with hepatitis B or C, it is also a reflection of the hepatic injury, ranging from hepatic steatosis to hypersensitivity reactions to immune reconstitution, that can be seen in the context of cART.

The prevalence of co-infection with HIV and hepatitis viruses varies by geographic region. In the United States, ~90% of HIV-infected individuals have evidence of infection with HBV; 6–14% have chronic HBV infection; 5–50% of patients are co-infected with HCV; and co-infections with hepatitis D, E, and/or G viruses are common. Among IV drug users with HIV infection, rates of HCV infection range from 70% to 95%. HIV infection has a significant impact on the course of hepatitis virus infection. It is associated with approximately a

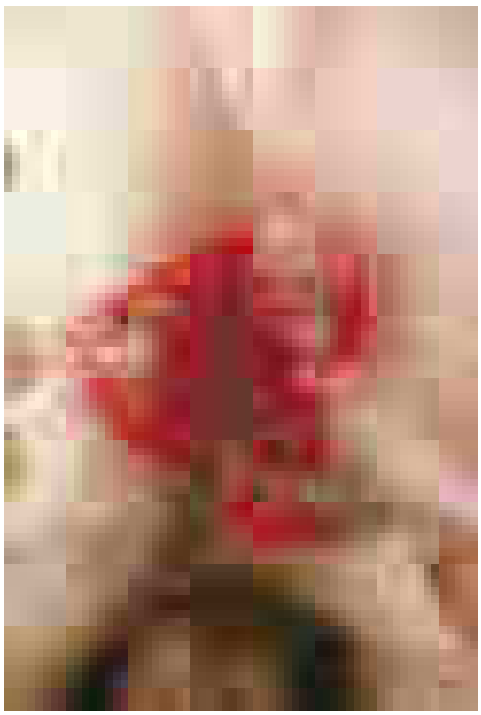


FIGURE 197-38 Severe, erosive perirectal herpes simplex in a patient with AIDS.

threefold increase in the development of persistent hepatitis B surface antigenemia. Patients infected with both HBV and HIV have decreased evidence of inflammatory liver disease. The presumption that this is due to the immunosuppressive effects of HIV infection is supported by the observations that this situation can be reversed, and one may see the development of more severe hepatitis following the initiation of effective cART. In studies of the impact of HIV on HBV infection, four- to tenfold increases in liver-related mortality rates have been noted in patients with HIV and active HBV infection compared to rates in patients with either infection alone. There is, however, only a slight increase in overall mortality rate in HIV-infected individuals who are also hepatitis B surface antigen (HBsAg)–positive. IFN-α is less successful as treatment for HBV in patients with HIV co-infection. Lamivudine, emtricitabine, adefovir/tenofovir/entecavir, and telbivudine alone or in combination are useful in the treatment of hepatitis B in patients with HIV infection. It is important to remember that all the above-mentioned drugs also have activity against HIV and should not be used alone in patients with HIV infection, in order to avoid the emergence of quasispecies of HIV resistant to these drugs. For this reason, the treatment of hepatitis B infection in a patient with HIV infection should always be done in the setting of cART. HCV infection is more severe in the patient with HIV infection; it does not appear to affect overall mortality rates in HIV-infected individuals when other variables such as age, baseline CD4+ T cell count, and use of cART are taken into account. In the setting of HIV and HCV co-infection, levels of HCV are approximately tenfold higher than in the HIV-negative patient with HCV infection. There is a 50% higher overall mortality rate with a five-fold increased risk of death due to liver disease in patients chronically infected with both HCV and HIV. Use of directly acting agents for the treatment of HCV leads to cure rates approaching 100%, even in patients with HIV co-infection. Successful treatment of HCV in HIV-infected patients decreases mortality. Hepatitis A virus infection is not seen with an increased frequency in patients with HIV infection. It is recommended that all patients with HIV infection who have not experienced natural infection be immunized with hepatitis A and/or hepatitis B vaccines. Infection with hepatitis G virus, also known as GB virus C, is seen in ~50% of patients with HIV infection. For reasons that are currently unclear, there are data to suggest that patients with HIV infection co-infected with this virus have a decreased rate of progression to AIDS.

A variety of other infections also may involve the liver. Granulomatous hepatitis may be seen as a consequence of mycobacterial or fungal infections, particularly MAC infection. Hepatic masses may be seen in the context of TB, peliosis hepatis, or fungal infection. Among the fungal opportunistic infections, *C. immitis* and *Histoplasma capsulatum* are those most likely to involve the liver. Biliary tract disease in the form of papillary stenosis or sclerosing cholangitis has been reported in the context of cryptosporidiosis, CMV infection, and KS. When no diagnosis can be made, the term *AIDS cholangiopathy* is used. Hemophagocytic lymphohistiocytosis of the liver has been seen in the setting of Hodgkin's disease and may occur prior to diagnosis of the underlying neoplasm.

Many of the drugs used to treat HIV infection are metabolized by the liver and can cause liver injury. Fatal hepatic reactions have been reported with a wide array of antiretrovirals including nucleoside analogues, nonnucleoside analogues, and protease inhibitors. Nucleoside analogues work by inhibiting DNA synthesis. This can result in toxicity to mitochondria, which can lead to disturbances in oxidative metabolism. This may manifest as hepatic steatosis and, in severe cases, lactic acidosis and fulminant liver failure. It is important to be aware of this condition and to watch for it in patients with HIV infection receiving nucleoside analogues. It is reversible if diagnosed early and the offending agent(s) discontinued. Nevirapine has been associated with at times fatal fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. Indinavir may cause mild to moderate elevations in serum bilirubin in 10–15% of patients in a syndrome similar to Gilbert's syndrome. A similar pattern of hepatic injury may be seen with atazanavir. In the patient receiving cART with an unexplained increase in hepatic transaminases, strong consideration should be given to drug toxicity.

Pancreatic injury is most commonly a consequence of drug toxicity, notably that secondary to pentamidine or dideoxynucleosides. While up to half of patients in some series have biochemical evidence of pancreatic injury, <5% of patients show any clinical evidence of pancreatitis that is not linked to a drug toxicity.

Diseases of the Kidney and Genitourinary Tract Diseases of the kidney or genitourinary tract may be a direct consequence of HIV infection, due to an opportunistic infection or neoplasm, or related to drug toxicity. Overall, microalbuminuria is seen in ~20% of untreated HIV-infected patients; significant proteinuria is seen in closer to 2%. The presence of microalbuminuria has been associated with an increase in all-cause mortality rate. *HIV-associated nephropathy* (HIVAN) was first described in IDUs and was initially thought to be IDU nephropathy in patients with HIV infection; it is now recognized as a true direct complication of HIV infection. Although the majority of patients with this condition have CD4+ T cell counts <200/μL, HIV-associated nephropathy can be an early manifestation of HIV infection and is also seen in children. Over 90% of reported cases have been in African-American or Hispanic individuals; the disease is not only more prevalent in these populations but also more severe and is the third leading cause of end-stage renal failure among African Americans age 20–64 in the United States. Proteinuria is the hallmark of this disorder. Edema and hypertension are rare. Ultrasound examination reveals enlarged, hyperechogenic kidneys. A definitive diagnosis is obtained through renal biopsy. Histologically, focal segmental glomerulosclerosis is present in 80%, and mesangial proliferation in 10–15% of cases. Prior to effective antiretroviral therapy, this disease was characterized by relatively rapid progression to end-stage renal disease. Patients with HIV-associated nephropathy should be treated for their HIV infection. Treatment with angiotensin-converting enzyme (ACE) inhibitors and/or prednisone, 60 mg/d, also has been reported to be of benefit in some cases. The incidence of this disease in patients receiving adequate cART has not been well defined; however, the impression is that it has decreased in frequency and severity. It is the leading cause of end-stage renal disease in patients with HIV infection.

Among the drugs commonly associated with renal damage in patients with HIV disease are pentamidine, amphotericin, adefovir, cidofovir, tenofovir, and foscarnet. TMP-SMX may compete for tubular secretion with creatinine and cause an increase in the serum creatinine level. The pharmacokinetic booster cobicistat, a component of several fixed-drug cART formulations, inhibits renal tubular secretion of creatinine leading to increased serum creatinine levels without a true decline in glomerular filtration rate. Sulfadiazine may crystallize in the kidney and result in an easily reversible form of renal shutdown, while indinavir or atazanavir may form renal calculi. Adequate hydration is the mainstay of treatment and prevention for these latter two conditions.

Genitourinary tract infections are seen with a high frequency in patients with HIV infection; they present with skin lesions, dysuria, hematuria, and/or pyuria and are managed in the same fashion as in patients without HIV infection. Infections with HSV are covered below ("Dermatologic Diseases"). Infections with *T. pallidum*, the etiologic agent of *syphilis*, play an important role in the HIV epidemic. In HIV-negative individuals, genital syphilitic ulcers as well as the ulcers of chancroid are major predisposing factors for heterosexual transmission of HIV infection. While most HIV-infected individuals with syphilis have a typical presentation, a variety of formerly rare clinical problems may be encountered in the setting of dual infection. Among them are *lues maligna*, an ulcerating lesion of the skin due to a necrotizing vasculitis; unexplained fever; nephrotic syndrome; and neurosyphilis. The most common presentation of syphilis in the HIV-infected patient is that of *condylomata lata*, a form of secondary syphilis. Neurosyphilis may be asymptomatic or may present as acute meningitis, neuroretinitis, deafness, or stroke. The rate of neurosyphilis may be as high as 1% in patients with HIV infection, and one should consider a lumbar puncture to look for neurosyphilis in all patients with HIV infection and secondary syphilis. As a consequence of the immunologic abnormalities seen in the setting of HIV infection, diagnosis of syphilis

through standard serologic testing may be challenging. On the one hand, a significant number of patients have false-positive Venereal Disease Research Laboratory (VDRL) tests due to polyclonal B cell activation. On the other hand, the development of a new positive VDRL may be delayed in patients with new infections, and the anti–fluorescent treponemal antibody (anti-FTA) test may be negative due to immunodeficiency. Thus, dark-field examination of appropriate specimens should be performed in any patient in whom syphilis is suspected, even if the patient has a negative VDRL. Similarly, any patient with a positive serum VDRL test, neurologic findings, and an abnormal spinal fluid examination should be considered to have neurosyphilis and treated accordingly, regardless of the CSF VDRL result. In any setting, patients treated for syphilis need to be carefully monitored to ensure adequate therapy. Approximately one-third of patients with HIV infection will experience a Jarisch-Herxheimer reaction upon initiation of therapy for syphilis.

Vulvovaginal candidiasis is a common problem in women with HIV infection. Symptoms include pruritus, discomfort, dyspareunia, and dysuria. Vulvar infection may present as a morbilliform rash that may extend to the thighs. Vaginal infection is usually associated with a white discharge, and plaques may be seen along an erythematous vaginal wall. Diagnosis is made by microscopic examination of the discharge for pseudohyphal elements in a 10% potassium hydroxide solution. Mild disease can be treated with topical therapy. More serious disease can be treated with fluconazole. Other causes of vaginitis include *Trichomonas* and mixed bacteria.

Diseases of the Endocrine System and Metabolic Disorders A variety of endocrine and metabolic disorders are seen in the context of HIV infection. These may be a direct consequence of HIV infection, secondary to opportunistic infections or neoplasms, or related to medication side effects. Between 33% and 75% of patients with HIV infection receiving thymidine analogues or protease inhibitors as a component of cART develop a syndrome often referred to as *lipodystrophy*, consisting of elevations in plasma triglycerides, total cholesterol, and apolipoprotein B, as well as hyperinsulinemia and hyperglycemia. Many of the patients have been noted to have a characteristic set of body habitus changes associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting **(Fig. 197-39)**. Truncal obesity is apparent as an increase in abdominal girth related to increases in mesenteric fat, a dorsocervical fat pad ("buffalo hump") reminiscent of patients with Cushing's syndrome, and enlargement of the breasts. The peripheral wasting, or lipoatrophy, is particularly noticeable in the face and buttocks and by the prominence of the veins in the legs. These changes may develop at any time ranging from ~6 weeks to several years following the initiation of cART. Approximately 20% of the patients with HIV-associated lipodystrophy meet the criteria for the *metabolic syndrome* as defined by The International Diabetes Federation or The U.S. National Cholesterol Education Program Adult Treatment Panel III. The lipodystrophy syndrome has been reported in association with regimens containing a variety of different drugs, and while initially reported in the setting of protease inhibitor therapy, it appears that similar changes can also be induced by protease-sparing regimens. It has been suggested that the lipoatrophy changes are particularly severe in patients receiving the thymidine analogues stavudine and zidovudine. Current treatment guidelines avoid these drugs and recommend drugs with fewer of these side effects. National Cholesterol Education Program (NCEP) guidelines should be followed in the management of these lipid abnormalities **(Chap. 400)**, and consideration should be given to changing the components of cART with avoidance of thymidine analogues (azidothymidine and stavudine) and offending protease inhibitors. Due to concerns regarding drug interactions, the most commonly utilized lipid-lowering agents in this setting are gemfibrozil and atorvastatin. In addition, lactic acidosis is associated with cART. This is most commonly seen with nucleoside analogue reverse transcriptase inhibitors and can be fatal.

Patients with advanced HIV disease may develop hyponatremia due to the syndrome of inappropriate antidiuretic hormone (vasopressin) secretion (SIADH) as a consequence of increased free-water intake and decreased free-water excretion. SIADH is usually seen in conjunction with pulmonary or CNS disease. Low serum sodium may also be due to adrenal insufficiency; a concomitant high serum potassium should alert one to this possibility. Hyperkalemia may be secondary to adrenal insufficiency; HIV nephropathy; or medications, particularly trimethoprim and pentamidine. Hypokalemia may be seen in the setting of tenofovir or amphotericin therapy. Adrenal gland disease may be due to mycobacterial infections, CMV disease, cryptococcal disease, histoplasmosis, or ketoconazole toxicity. Iatrogenic Cushing's syndrome with suppression of the hypothalamic-pituitary-adrenal axis may be seen with the use of local glucocorticoids (injected or inhaled) in patients receiving ritonavir. This is due to inhibition of the hepatic

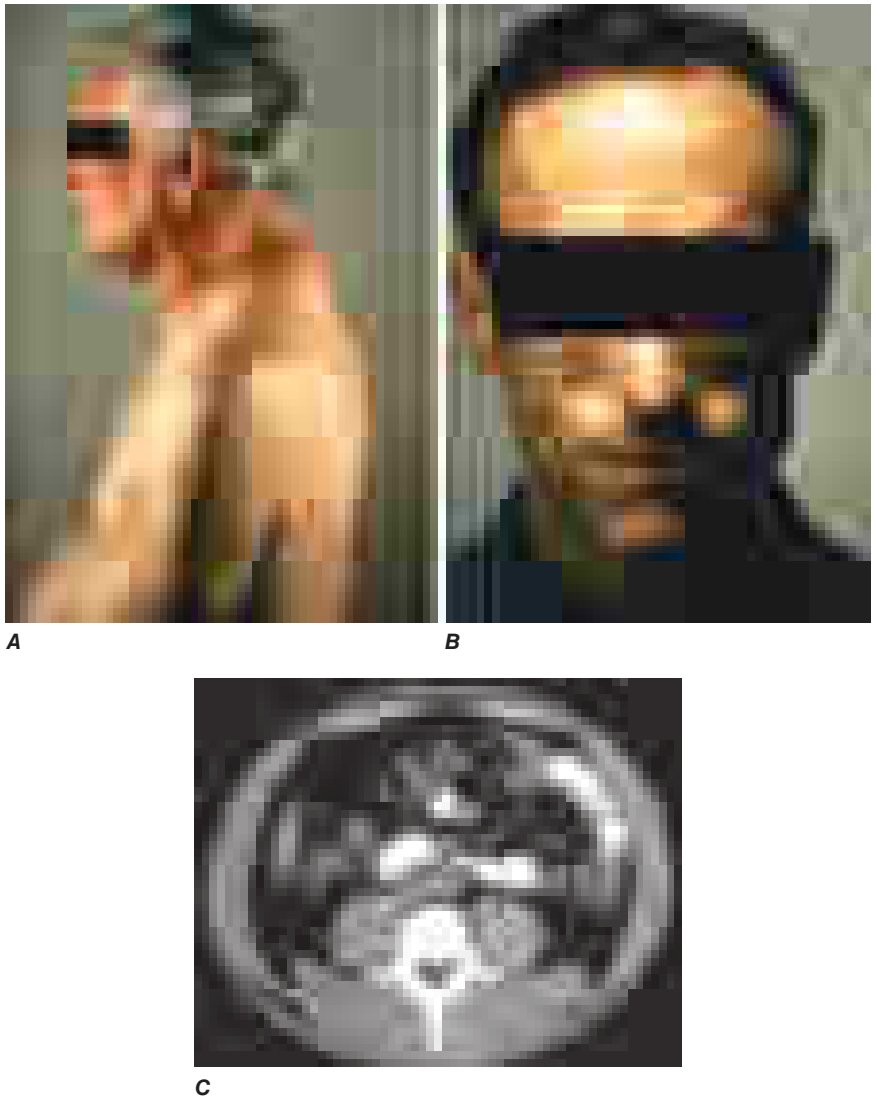


FIGURE 197-39 Characteristics of lipodystrophy. *A.* Truncal obesity and buffalo hump. ***B.*** Facial wasting. ***C.*** Accumulation of intraabdominal fat on CT scan.

enzyme CYP3A4 by ritonavir leading to prolongation of the glucocorticoid half-life.

Thyroid function may be altered in 10–15% of patients with HIV infection. Both hypo- and hyperthyroidism may be seen. The predominant abnormality is subclinical hypothyroidism. In the setting of cART, up to 10% of patients have been noted to have elevated thyroid-stimulating hormone levels, suggesting that this may be a manifestation of immune reconstitution. Immune-reconstitution Graves' disease may occur as a late (9–48 months) complication of cART. In advanced HIV disease, infection of the thyroid gland may occur with opportunistic pathogens, including *P. jirovecii*, CMV, mycobacteria, *Toxoplasma gondii*, and *Cryptococcus neoformans*. These infections are generally associated with a nontender, diffuse enlargement of the thyroid gland. Thyroid function is usually normal. Diagnosis is made by fine-needle aspirate or open biopsy.

Depending on the severity of disease, HIV infection is associated with *hypogonadism* in 20–50% of men. While this is generally a complication of underlying illness, testicular dysfunction may also be a side effect of ganciclovir therapy. In some surveys, up to two-thirds of patients report decreased libido and one-third complain of erectile dysfunction. Androgen-replacement therapy should be considered in patients with symptomatic hypogonadism. HIV infection does not seem to have a significant effect on the menstrual cycle outside the setting of advanced disease.

Immunologic and Rheumatologic Diseases Immunologic and rheumatologic disorders are common in patients with HIV infection and range from excessive immediate-type hypersensitivity reactions **(Chap. 347)** to an increase in the incidence of reactive arthritis **(Chap. 355)** to conditions characterized by a diffuse infiltrative lymphocytosis. The occurrence of these phenomena is an apparent paradox in the setting of the profound immunodeficiency and immunosuppression that characterizes HIV infection and reflects the complex nature of the immune system and its regulatory mechanisms.

Drug allergies are the most significant allergic reactions occurring in HIV-infected patients and appear to become more common as the disease progresses. They occur in up to 65% of patients who receive therapy with TMP-SMX for PCP. In general, these drug reactions are characterized by erythematous, morbilliform eruptions that are pruritic, tend to coalesce, and are often associated with fever. Nonetheless, ~33% of patients can be maintained on the offending therapy, and thus these reactions are not an immediate indication to stop the drug. Anaphylaxis is extremely rare in patients with HIV infection, and patients who have a cutaneous reaction during a single course of therapy can still be considered candidates for future treatment or prophylaxis with the same agent. The one exception to this is the nucleoside analogue abacavir, where fatal hypersensitivity reactions have been reported with rechallenge. This hypersensitivity is strongly associated with the HLA-B5701 haplotype, and a hypersensitivity reaction to abacavir is an absolute contraindication to future therapy. For other agents, including TMP-SMX, desensitization regimens are moderately successful. While the mechanisms underlying these allergic-type reactions remain unknown, patients with HIV infection have been noted to have elevated IgE levels that increase as the CD4+ T cell count declines. The numerous examples of patients with multiple drug reactions suggest that a common pathway is involved.

HIV infection shares many similarities with a variety of autoimmune diseases, including a substantial polyclonal B cell activation that is associated with a high incidence of antiphospholipid antibodies, such as anticardiolipin antibodies, VDRL antibodies, and lupus-like anticoagulants. In addition, HIV-infected individuals have an increased incidence of antinuclear antibodies. Despite these serologic findings, there is no evidence that HIV-infected individuals have an increase in two of the more common autoimmune diseases, i.e., systemic lupus erythematosus and rheumatoid arthritis. In fact, it has been observed that these diseases may be somewhat ameliorated by the concomitant presence of HIV infection, suggesting that an intact CD4+ T cell limb of the immune response plays an integral role in the pathogenesis of these conditions. Similarly, there are anecdotal reports of patients with common variable immunodeficiency **(Chap. 344)**, characterized by hypogammaglobulinemia, who have had a normalization of Ig levels following the development of HIV infection, suggesting a possible role for overactive CD4+ T cell immunity in certain forms of that syndrome. The one autoimmune disease that may occur with an increased frequency in patients with HIV infection is a variant of primary Sjögren's syndrome **(Chap. 354)**. Patients with HIV infection may develop a syndrome consisting of parotid gland enlargement, dry eyes, and dry mouth that is associated with lymphocytic infiltrates of the salivary gland and lung. One also can see peripheral neuropathy, polymyositis, renal tubular acidosis, and hepatitis. In contrast to Sjögren's syndrome, in which the lymphocytic infiltrates are composed predominantly of CD4+ T cells, in patients with HIV infection the infiltrates are composed predominantly of CD8+ T cells. In addition, while patients with Sjögren's syndrome are mainly women who have autoantibodies to Ro and La and who frequently have HLA-DR3 or B8 MHC haplotypes, HIV-infected individuals with this syndrome are usually African-American men who do not have anti-Ro or anti-La and who most often are HLA-DR5. This syndrome appears to be less common with the increased use of effective cART. The term *diffuse infiltrative lymphocytosis syndrome* (DILS) is used to describe this entity and to distinguish it from Sjögren's syndrome.

Approximately one-third of HIV-infected individuals experience arthralgias; furthermore, 5–10% are diagnosed as having some form of reactive arthritis, such as Reiter's syndrome or psoriatic arthritis as well as undifferentiated spondyloarthropathy **(Chap. 355)**. These syndromes occur with increasing frequency as the competency of the immune system declines. This association may be related to an increase in the number of infections with organisms that may trigger a reactive arthritis with progressive immunodeficiency or to a loss of important regulatory T cells. Reactive arthritides in HIV-infected individuals generally respond well to standard treatment; however, therapy with methotrexate has been associated with an increase in the incidence of opportunistic infections and should be used with caution and only in severe cases.

HIV-infected individuals also experience a variety of joint problems without obvious cause that are referred to generically as *HIV-* or *AIDS-associated arthropathy*. This syndrome is characterized by subacute oligoarticular arthritis developing over a period of 1–6 weeks and lasting 6 weeks to 6 months. It generally involves the large joints, predominantly the knees and ankles, and is nonerosive with only a mild inflammatory response. X-rays are nonrevealing. Nonsteroidal anti-inflammatory drugs are only marginally helpful; however, relief has been noted with the use of intraarticular glucocorticoids. A second form of arthritis also thought to be secondary to HIV infection is called *painful articular syndrome*. This condition, reported as occurring in as many as 10% of AIDS patients, presents as an acute, severe, sharp pain in the affected joint. It affects primarily the knees, elbows, and shoulders; lasts 2–24 h; and may be severe enough to require narcotic analgesics. The cause of this arthropathy is unclear; however, it is thought to result from a direct effect of HIV on the joint. This condition is reminiscent of the fact that other lentiviruses, in particular the caprine arthritis-encephalitis virus, are capable of directly causing arthritis.

A variety of other immunologic or rheumatologic diseases have been reported in HIV-infected individuals, either de novo or in association with opportunistic infections or drugs. Using the criteria of widespread musculoskeletal pain of at least 3 months' duration and the presence of at least 11 of 18 possible tender points by digital palpation, 11% of an HIV-infected cohort containing 55% IDUs were diagnosed as having *fibromyalgia* **(Chap. 366)**. While the incidence of frank arthritis was less in this population than in other studied populations that consisted predominantly of men who have sex with men, these data support the concept that there are musculoskeletal problems that occur as a direct result of HIV infection. In addition there have been reports of leukocytoclastic vasculitis in the setting of zidovudine therapy. CNS angiitis and polymyositis also have been reported in HIV-infected individuals. Septic arthritis is surprisingly rare, especially given the increased incidence of staphylococcal bacteremias seen in this population. When septic arthritis has been reported, it has usually been due

to *Staphylococcus aureus*, systemic fungal infection with *C. neoformans*, *Sporothrix schenckii*, or *H. capsulatum* or to systemic mycobacterial infection with *M. tuberculosis*, *M. haemophilum*, *M. avium*, or *M. kansasii*.

Patients with HIV infection treated with cART have been found to have an increased incidence of osteonecrosis or avascular necrosis of the hip and shoulders. In a study of asymptomatic patients, 4.4% were found to have evidence of osteonecrosis on MRI. While precise cause-and-effect relationships have been difficult to establish, this complication has been associated with the use of lipid-lowering agents, systemic glucocorticoids, and testosterone; bodybuilding exercise; alcohol consumption; and the presence of anticardiolipin antibodies. Osteoporosis has been reported in 7% of women with HIV infection, with 41% of women demonstrating some degree of osteopenia. Several studies have documented decreases in bone mineral density of 2–6% in the first 2 years following the initiation of cART. This may be particularly apparent with tenofovir-containing regimens.

Immune Reconstitution Inflammatory Syndrome (IRIS) Following the initiation of effective cART, a paradoxical worsening of preexisting, untreated, or partially treated opportunistic infections may be noted. One may also see exacerbations of pre-existing autoimmune conditions or the development of new autoimmune conditions following the initiation of antiretrovirals **(Table 197-12)**. IRIS related to a known pre-existing infection or neoplasm is referred to as *paradoxical IRIS*, while IRIS associated with a previously undiagnosed condition is referred to as *unmasking IRIS*. The term *immune reconstitution disease (IRD)* is sometimes used to distinguish IRIS manifestations related to opportunistic diseases from IRIS manifestations related to autoimmune diseases. IRD is particularly common in patients with underlying untreated mycobacterial or fungal infections. Some form of IRIS is seen in 10–30% of patients, depending on the clinical setting, and is most common in patients starting therapy with CD4+ T cell counts <50 cells/μL who have a precipitous drop in HIV RNA levels following the initiation of cART. Signs and symptoms may appear anywhere from 2 weeks to 2 years after the initiation of cART and can include localized lymphadenitis, prolonged fever, pulmonary infiltrates, hepatitis, increased intracranial pressure, uveitis, sarcoidosis, and Graves' disease. The clinical course can be protracted, and severe cases can be fatal. The underlying mechanism appears to be related to a phenomenon similar to type IV hypersensitivity reactions and reflects the immediate improvements in immune function that occur as levels of HIV RNA drop and the immunosuppressive effects of HIV infection are controlled. In severe cases, the use of immunosuppressive drugs such as glucocorticoids may be required to blunt the inflammatory component of these reactions while specific antimicrobial therapy takes effect.

Diseases of the Hematopoietic System Disorders of the hematopoietic system including lymphadenopathy, anemia, leukopenia, and/or thrombocytopenia are common throughout the course of HIV infection and may be the direct result of HIV, manifestations of secondary infections and neoplasms, or side effects of therapy **(Table 197-13)**. Direct histologic examination and culture of lymph node or bone marrow tissue are often diagnostic. A significant percentage of bone marrow aspirates from patients with HIV infection have been reported to contain lymphoid aggregates, the precise significance of which is unknown. Initiation of cART will lead to reversal of most hematologic complications that are the direct result of HIV infection.

TABLE 197-12 Characteristics of Immune Reconstitution Inflammatory Syndrome (IRIS)

Paradoxical worsening of an existing clinical condition or abrupt appearance of a new clinical finding (unmasking) is seen following the initiation of antiretroviral therapy
Occurs weeks to months following the initiation of antiretroviral therapy
Is most common in patients starting therapy with a CD4+ T cell count <50/μL who experience a precipitous drop in viral load
Is frequently seen in the setting of tuberculosis; particularly when cART is starting soon after initiation of anti-TB therapy
Can be fatal

TABLE 197-13 Causes of Bone Marrow Suppression in Patients with HIV Infection

HIV infection	Medications
Mycobacterial infections	Zidovudine
Fungal infections	Dapsone
B19 parvovirus infection	Trimethoprim/sulfamethoxazole
Lymphoma	Pyrimethamine
	5-Flucytosine
	Ganciclovir
	Interferon α
	Trimetrexate
	Foscarnet

Some patients, otherwise asymptomatic, may develop *persistent generalized lymphadenopathy* as an early clinical manifestation of HIV infection. This condition is defined as the presence of enlarged lymph nodes (>1 cm) in two or more extrainguinal sites for >3 months without an obvious cause. The lymphadenopathy is due to marked follicular hyperplasia in the node in response to HIV infection. The nodes are generally discrete and freely movable. This feature of HIV disease may be seen at any point in the spectrum of immune dysfunction and is not associated with an increased likelihood of developing AIDS. Paradoxically, a loss in lymphadenopathy or a decrease in lymph node size outside the setting of cART may be a prognostic marker of disease progression. In patients with CD4+ T cell counts >200/μL, the differential diagnosis of lymphadenopathy includes KS, TB, Castleman's disease, and lymphoma. In patients with more advanced disease, lymphadenopathy may also be due to atypical mycobacterial infection, toxoplasmosis, systemic fungal infection, or bacillary angiomatosis. While indicated in patients with CD4+ T cell counts <200/μL, lymph node biopsy is not indicated in patients with early-stage disease unless there are signs and symptoms of systemic illness, such as fever and weight loss, or unless the nodes begin to enlarge, become fixed, or coalesce. Monoclonal gammopathy of unknown significance (MGUS) **(Chap. 107)**, defined as the presence of a serum monoclonal IgG, IgA, or IgM in the absence of a clear cause, has been reported in 3% of patients with HIV infection. The overall clinical significance of this finding in patients with HIV infection is unclear, although it has been associated with other viral infections, non-Hodgkin's lymphoma, and plasma cell malignancy.

Anemia is the most common hematologic abnormality in HIV-infected patients and, in the absence of a specific treatable cause, is independently associated with a poor prognosis. While generally mild, anemia can be quite severe and require chronic blood transfusions. Among the specific reversible causes of anemia in the setting of HIV infection are drug toxicity, systemic fungal and mycobacterial infections, nutritional deficiencies, and parvovirus B19 infections. Zidovudine may block erythroid maturation prior to its effects on other marrow elements. A characteristic feature of zidovudine therapy is an elevated mean corpuscular volume (MCV). Another drug used in patients with HIV infection that has a selective effect on the erythroid series is dapsone. This drug can cause a serious hemolytic anemia in patients who are deficient in glucose-6-phosphate dehydrogenase and can create a functional anemia in others through induction of methemoglobinemia. Folate levels are usually normal in HIV-infected individuals; however, vitamin B_{12} levels may be depressed as a consequence of achlorhydria or malabsorption. True autoimmune hemolytic anemia is rare, although ~20% of patients with HIV infection may have a positive direct antiglobulin test as a consequence of polyclonal B cell activation. Infection with parvovirus B19 may also cause anemia. It is important to recognize this possibility given the fact that it responds well to treatment with IVIg. Erythropoietin levels in patients with HIV infection and anemia are generally lower than expected given the degree of anemia. Treatment with erythropoietin may result in an increase in hemoglobin levels. An exception to this is a subset of patients with

zidovudine-associated anemia in whom erythropoietin levels may be quite high.

During the course of HIV infection, neutropenia may be seen in approximately half of patients. In most instances it is mild; however, it can be severe and can put patients at risk of spontaneous bacterial infections. This is most frequently seen in patients with severely advanced HIV disease and in patients receiving any of a number of potentially myelosuppressive therapies. In the setting of neutropenia, diseases that are not commonly seen in HIV-infected patients, such as aspergillosis or mucormycosis, may occur. Both granulocyte colony-stimulating factor (G-CSF) and GM-CSF increase neutrophil counts in patients with HIV infection regardless of the cause of the neutropenia. Earlier concerns about the potential of these agents to also increase levels of HIV were not confirmed in controlled clinical trials.

Thrombocytopenia may be an early consequence of HIV infection. Approximately 3% of patients with untreated HIV infection and CD4+ T cell counts ≥400/μL have platelet counts <150,000/μL. For untreated patients with CD4+ T cell counts <400/μL, this incidence increases to 10%. In patients receiving antiretrovirals, thrombocytopenia is associated with hepatitis C, cirrhosis, and ongoing high-level HIV replication. Thrombocytopenia is rarely a serious clinical problem in patients with HIV infection and generally responds well to successful cART. Clinically, it resembles the thrombocytopenia seen in patients with idiopathic thrombocytopenic purpura **(Chap. 111)**. Immune complexes containing anti-gp120 antibodies and anti-anti-gp120 antibodies have been noted in the circulation and on the surface of platelets in patients with HIV infection. Patients with HIV infection have also been noted to have a platelet-specific antibody directed toward a 25-kDa component of the surface of the platelet. Other data suggest that the thrombocytopenia in patients with HIV infection may be due to a direct effect of HIV on megakaryocytes. Whatever the cause, it is very clear that the most effective medical approach to this problem has been the use of cART. For patients with platelet counts <20,000/μL, a more aggressive approach combining IVIg or anti-Rh Ig for an immediate response and cART for a more lasting response is appropriate. Rituximab has been used with some success in otherwise refractory cases. Splenectomy is a rarely needed option and is reserved for patients refractory to medical management. Because of the risk of serious infection with encapsulated organisms, all patients with HIV infection about to undergo splenectomy should be immunized with pneumococcal polysaccharide. It should be noted that, in addition to causing an increase in the platelet count, removal of the spleen will result in an increase in the peripheral blood lymphocyte count, making CD4+ T cell counts unreliable markers of immunocompetence. In this setting, the clinician should rely on the CD4+ T cell percentage for making diagnostic decisions with respect to the likelihood of opportunistic infections. A CD4+ T cell percentage of 15 is approximately equivalent to a CD4+ T cell count of 200/μL. In patients with early HIV infection, thrombocytopenia has also been reported as a consequence of classic thrombotic thrombocytopenic purpura **(Chap. 111)**. This clinical syndrome, consisting of fever, thrombocytopenia, hemolytic anemia, and neurologic and renal dysfunction, is a rare complication of early HIV infection. As in other settings, the appropriate management is the use of salicylates and plasma exchange. Other causes of thrombocytopenia include lymphoma, mycobacterial infections, and fungal infections.

The incidence of venous thromboembolic disease such as deep-vein thrombosis or pulmonary embolus is approximately 1% per year in patients with HIV infection. This is approximately 10 times higher than that seen in an age-matched population. Factors associated with an increased risk of clinical thrombosis include age over 45, history of an opportunistic infection, lower CD4 count, and estrogen use. Abnormalities of the coagulation cascade, including decreased protein S activity, increases in factor VIII, anticardiolipin antibodies, PAR-1 expression on T cells, or lupus-like anticoagulant, have been reported in more than 50% of patients with HIV infection. The clinical significance of this increased propensity toward thromboembolic disease is likely reflected in the observation that elevations in D-dimer are strongly associated with all-cause mortality in patients with HIV infection (Table 197-9).

Dermatologic Diseases Dermatologic problems occur in >90% of patients with HIV infection. From the macular, roseola-like rash seen with the acute seroconversion syndrome to extensive end-stage KS, cutaneous manifestations of HIV disease can be seen throughout the course of HIV infection. Among the more common nonneoplastic problems are seborrheic dermatitis, folliculitis, and opportunistic infections. Extrapulmonary pneumocystosis may cause a necrotizing vasculitis. Neoplastic conditions are covered in a separate section below.

Seborrheic dermatitis occurs in 3% of the general population and in up to 50% of patients with HIV infection. Seborrheic dermatitis increases in prevalence and severity as the CD4+ T cell count declines. In HIV-infected patients, seborrheic dermatitis may be aggravated by concomitant infection with *Pityrosporum*, a yeastlike fungus; use of topical antifungal agents has been recommended in cases refractory to standard topical treatment.

Folliculitis is among the most prevalent dermatologic disorders in patients with HIV infection and is seen in ~20% of patients. It is more common in patients with CD4+ T cell counts <200 cells/μL. *Pruritic papular eruption* is one of the most common pruritic rashes in patients with HIV infection. It appears as multiple papules on the face, trunk, and extensor surfaces and may improve with cART. *Eosinophilic pustular folliculitis* is a rare form of folliculitis that is seen with increased frequency in patients with HIV infection. It presents as multiple, urticarial perifollicular papules that may coalesce into plaquelike lesions. Skin biopsy reveals an eosinophilic infiltrate of the hair follicle, which in certain cases has been associated with the presence of a mite. Patients typically have an elevated serum IgE level and may respond to treatment with topical anthelmintics. Pruritus is a common symptom in patients with HIV infection and can lead to *prurigo nodularis*. Patients with HIV infection have also been reported to develop a severe form of *Norwegian scabies* with hyperkeratotic psoriasiform lesions.

Both *psoriasis* and *ichthyosis*, although they are not reported to be increased in frequency, may be particularly severe when they occur in patients with HIV infection. Preexisting psoriasis may become guttate in appearance and more refractory to treatment in the setting of HIV infection.

Reactivation herpes zoster (*shingles*) is seen in 10–20% of patients with HIV infection. This reactivation syndrome of varicella-zoster virus indicates a modest decline in immune function and may be the first indication of clinical immunodeficiency. In one series, patients who developed shingles did so an average of 5 years after HIV infection. In a cohort of patients with HIV infection and localized zoster, the subsequent rate of the development of AIDS was 1% per month. In that study, AIDS was more likely to develop if the outbreak of zoster was associated with severe pain, extensive skin involvement, or involvement of cranial or cervical dermatomes. The clinical manifestations of reactivation zoster in HIV-infected patients, although indicative of immunologic compromise, are not as severe as those seen in other immunodeficient conditions. Thus, while lesions may extend over several dermatomes, involve the spinal cord, and/or be associated with frank cutaneous dissemination, visceral involvement has not been reported. In contrast to patients without a known underlying immunodeficiency state, patients with HIV infection tend to have recurrences of zoster with a relapse rate of ~20%. Valacyclovir, acyclovir, or famciclovir is the treatment of choice. Foscarnet may be of value in patients with acyclovir-resistant virus.

Infection with *herpes simplex virus* in HIV-infected individuals is associated with recurrent orolabial, genital, and perianal lesions as part of recurrent reactivation syndromes **(Chap. 187)**. As HIV disease progresses and the CD4+ T cell count declines, these infections become more frequent and severe. Lesions often appear as beefy red, are exquisitely painful, and have a tendency to occur high in the gluteal cleft (Fig. 197-37). Perirectal HSV may be associated with proctitis and anal fissures. HSV should be high in the differential diagnosis of any HIV-infected patient with a poorly healing, painful perirectal lesion. In addition to recurrent mucosal ulcers, recurrent HSV infection in the form of *herpetic whitlow* can be a problem in patients with HIV infection, presenting with painful vesicles or extensive cutaneous erosion. Valacyclovir, acyclovir, or famciclovir is the treatment of

choice in these settings. It is noteworthy that even subclinical reactivation of herpes simplex may be associated with increases in plasma HIV RNA levels.

Diffuse skin eruptions due to *Molluscum contagiosum* may be seen in patients with advanced HIV infection. These flesh-colored, umbilicated lesions resemble those of *Penicillium marnefei* or *Cryptococcosis.* They tend to regress with effective cART and can also be treated with local therapy. Similarly, *condyloma acuminatum* lesions may be more severe and more widely distributed in patients with low CD4+ T cell counts. Imiquimod cream may be helpful in some cases. Atypical mycobacterial infections may present as erythematous cutaneous nodules, as may fungal infections, *Bartonella*, *Acanthamoeba*, and KS. Cutaneous infections with *Aspergillus* have been noted at the site of IV catheter placement.

The skin of patients with HIV infection is often a target organ for drug reactions **(Chap. 56)**. Although most skin reactions are mild and not necessarily an indication to discontinue therapy, patients may have particularly severe cutaneous reactions, including erythroderma, *Stevens-Johnson syndrome*, and toxic epidermal necrolysis, as a reaction to drugs—particularly sulfa drugs, nonnucleoside reverse transcriptase inhibitors, abacavir, amprenavir, darunavir, fosamprenavir, and tipranavir. Similarly, patients with HIV infection are often quite photosensitive and burn easily following exposure to sunlight or as a side effect of radiation therapy **(Chap. 57)**.

HIV infection and its treatment may be accompanied by cosmetic changes of the skin that are not of great clinical importance but may be troubling to patients. Yellowing of the nails and straightening of the hair, particularly in African-American patients, have been reported as a consequence of HIV infection. Zidovudine therapy has been associated with elongation of the eyelashes and the development of a bluish discoloration to the nails, again more common in African-American patients. Therapy with clofazimine may cause a yellow-orange discoloration of the skin and urine.

Neurologic Diseases Clinical disease of the nervous system accounts for a significant degree of morbidity in a high percentage of patients with HIV infection **(Table 197-14)**. The neurologic problems that occur in HIV-infected individuals may be either primary to the pathogenic processes of HIV infection or secondary to opportunistic infections or neoplasms. Among the more frequent opportunistic diseases that involve the CNS are toxoplasmosis, cryptococcosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Other less common problems include mycobacterial infections; syphilis; and infection with CMV, herpes zoster, HTLV-1, *Trypanosoma cruzi*, or *Acanthamoeba*. Overall, secondary diseases of the CNS have been reported to occur in approximately one-third of patients with AIDS. These data antedate the widespread use of cART, and this frequency is considerably lower in patients receiving effective antiretroviral drugs.

TABLE 197-14 Neurologic Diseases in Patients with HIV Infection

Opportunistic infections	HIV-1 infection
Toxoplasmosis	Aseptic meningitis
Cryptococcosis	HIV-associated neurocognitive disorders (HAND), including HIV encephalopathy/ AIDS dementia complex
Progressive multifocal leukoencephalopathy	Myelopathy
Cytomegalovirus	Vacuolar myelopathy
Syphilis	Pure sensory ataxia
Mycobacterium tuberculosis	Paresthesia/dysesthesia
HTLV-1 infection	Peripheral neuropathy
Amebiasis	Acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome)
Neoplasms	Chronic inflammatory demyelinating polyneuropathy (CIDP)
Primary CNS lymphoma	Mononeuritis multiplex
Kaposi's sarcoma	Distal symmetric polyneuropathy
	Myopathy

Primary processes related to HIV infection of the nervous system are reminiscent of those seen with other lentiviruses, such as the maedivisna virus of sheep.

Neurologic problems directly attributable to HIV occur throughout the course of infection and may be inflammatory, demyelinating, or degenerative in nature. The term *HIV-associated neurocognitive disorders* (HAND) is used to describe a spectrum of disorders that range from asymptomatic neurocognitive impairment (ANI) to minor neurocognitive disorder (MND) to clinically severe dementia. The most severe form, *HIV-associated dementia* (HAD), also referred to as the *AIDS dementia complex*, or *HIV encephalopathy*, is considered an AIDS-defining illness. Most HIV-infected patients have some neurologic problem during the course of their disease. Even in the setting of suppressive cART, approximately 50% of HIV-infected individuals can be shown to have mild to moderate neurocognitive impairment using sensitive neuropsychiatric testing. As noted in the section on pathogenesis, damage to the CNS may be a direct result of viral infection of the CNS macrophages or glial cells or may be secondary to the release of neurotoxins and potentially toxic cytokines such as IL-1β, TNF-α, IL-6, and TGF-β. It has been reported that HIV-infected individuals with the E4 allele for apoE are at increased risk for AIDS encephalopathy and peripheral neuropathy. Virtually all patients with HIV infection have some degree of nervous system involvement with the virus. This is evidenced by the fact that CSF findings are abnormal in ~90% of untreated patients, even during the asymptomatic phase of HIV infection. CSF abnormalities include pleocytosis (50–65% of patients), detection of viral RNA (~75%), elevated CSF protein (35%), and evidence of intrathecal synthesis of anti-HIV antibodies (90%). It is important to point out that evidence of infection of the CNS with HIV does not imply impairment of cognitive function. The neurologic function of an HIV-infected individual should be considered normal unless clinical signs and symptoms suggest otherwise.

Aseptic meningitis may be seen in any but the very late stages of HIV infection. In the setting of acute primary infection, patients may experience a syndrome of headache, photophobia, and meningismus. Rarely, an acute encephalopathy due to encephalitis may occur. Cranial nerve involvement may be seen, predominantly cranial nerve VII but occasionally V and/or VIII. CSF findings include a lymphocytic pleocytosis, elevated protein level, and normal glucose level. This syndrome, which cannot be clinically differentiated from other viral meningitides **(Chap. 134)**, usually resolves spontaneously within 2–4 weeks; however, in some patients, signs and symptoms may become chronic. Aseptic meningitis may occur any time in the course of HIV infection; however, it is rare following the development of AIDS. This suggests that clinical aseptic meningitis in the context of HIV infection is an immune-mediated disease.

Cryptococcus is the leading infectious cause of meningitis in patients with AIDS **(Chap. 210)**. While the vast majority of these are due to *C. neoformans*, up to 12% may be due to *C. gattii*. Cryptococcal meningitis is the initial AIDS-defining illness in ~2% of patients and generally occurs in patients with CD4+ T cell counts <100/μL. Cryptococcal meningitis is particularly common in untreated patients with AIDS in Africa, occurring in ~5% of patients. Most patients present with a picture of subacute meningoencephalitis with fever, nausea, vomiting, altered mental status, headache, and meningeal signs. The incidence of seizures and focal neurologic deficits is low. The CSF profile may be normal or may show only modest elevations in WBC or protein levels and decreases in glucose. The opening pressure in the CSF is usually elevated. In addition to meningitis, patients may develop cryptococcomas and cranial nerve involvement. Approximately one-third of patients also have pulmonary disease. Uncommon manifestations of cryptococcal infection include skin lesions that resemble *molluscum contagiosum*, lymphadenopathy, palatal and glossal ulcers, arthritis, gastroenteritis, myocarditis, and prostatitis. The prostate gland may serve as a reservoir for smoldering cryptococcal infection. The diagnosis of cryptococcal meningitis is made by identification of organisms in spinal fluid with india ink examination or by the detection of cryptococcal antigen. Blood cultures for fungus are often positive. A biopsy may be needed to make a diagnosis of CNS cryptococcoma. Treatment is with

IV amphotericin B 0.7 mg/kg daily, or liposomal amphotericin 4–6 mg/kg daily, with flucytosine 25 mg/kg qid for at least 2 weeks if possible, continuing with amphotericin alone ideally until the CSF culture turns negative. Decreases in renal function in association with amphotericin can lead to increases in flucytosine levels and subsequent bone marrow suppression. Amphotericin is followed by fluconazole 400 mg/d PO for 8 weeks, and then fluconazole 200 mg/d until the CD4+ T cell count has increased to >200 cells/μL for 6 months in response to cART. Repeated lumbar puncture may be required to manage increased intracranial pressure. Symptoms may recur with initiation of cART as an immune reconstitution syndrome (see above). Other fungi that may cause meningitis in patients with HIV infection are *C. immitis* and *H. capsulatum*. Meningoencephalitis has also been reported due to *Acanthamoeba* or *Naegleria*.

HIV-associated dementia consists of a constellation of signs and symptoms of CNS disease. While this is generally a late complication of HIV infection that progresses slowly over months, it can be seen in patients with CD4+ T cell counts >350 cells/μL. A major feature of this entity is the development of dementia, defined as a decline in cognitive ability from a previous level. It may present as impaired ability to concentrate, increased forgetfulness, difficulty reading, or increased difficulty performing complex tasks. Initially these symptoms may be indistinguishable from findings of situational depression or fatigue. In contrast to "cortical" dementia (such as Alzheimer's disease), aphasia, apraxia, and agnosia are uncommon, leading some investigators to classify HIV encephalopathy as a "subcortical dementia" characterized by defects in short-term memory and executive function (see below). In addition to dementia, patients with HIV encephalopathy may also have motor and behavioral abnormalities. Among the motor problems are unsteady gait, poor balance, tremor, and difficulty with rapid alternating movements. Increased tone and deep tendon reflexes may be found in patients with spinal cord involvement. Late stages may be complicated by bowel and/or bladder incontinence. Behavioral problems include apathy, irritability, and lack of initiative, with progression to a vegetative state in some instances. Some patients develop a state of agitation or mild mania. These changes usually occur without significant changes in level of alertness. This is in contrast to the finding of somnolence in patients with dementia due to toxic/metabolic encephalopathies.

HIV-associated dementia is the initial AIDS-defining illness in ~3% of patients with HIV infection and thus only rarely precedes clinical evidence of immunodeficiency. Clinically significant encephalopathy eventually develops in ~25% of untreated patients with AIDS. As immunologic function declines, the risk and severity of HIV-associated dementia increases. Autopsy series suggest that 80–90% of patients with HIV infection have histologic evidence of CNS involvement. Several classification schemes have been developed for grading HIV encephalopathy; a commonly used clinical staging system is outlined in **Table 197-15**.

TABLE 197-15 Clinical Staging of Hand According to Frascati Criteria

STAGE	NEUROCOGNITIVE STATUS[a]	FUNCTIONAL STATUS[b]
Asymptomatic	1 SD below mean in 2 cognitive domains	No impairments in activities of daily living
Mild neurocognitive disorder	1 SD below mean in 2 cognitive domains	Impairments in activities of daily living
HIV-associated dementia	2 SD below mean in 2 cognitive domains	Notable impairments in activities of daily living

[a]Neurocognitive testing should include assessment of at least 5 domains, including attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory (including learning and recall), simple motor skills, or sensory perceptual skills. Appropriate norms must be available to establish the number of domains in which performance is below 1 SD. [b]Functional status is typically assessed by self-reporting but might be corroborated by a collateral source. No agreed measures exist for HIV-associated neurocognitive disorder criteria. Note that, for diagnosis of HIV-associated neurocognitive disorder, other causes of dementia must be ruled out and potential confounding effects of substance use or psychiatric illness should be considered.

Source: Adapted from A Antinori et al: Neurology 69:1789, 2007.

The precise cause of HIV-associated dementia remains unclear, although the condition is thought to be a result of a combination of direct effects of HIV on the CNS and associated immune activation. HIV has been found in the brains of patients with HIV encephalopathy by Southern blot, in situ hybridization, PCR, and electron microscopy. Multinucleated giant cells, macrophages, and microglial cells appear to be the main cell types harboring virus in the CNS. Histologically, the major changes are seen in the subcortical areas of the brain and include pallor and gliosis, multinucleated giant cell encephalitis, and vacuolar myelopathy. Less commonly, diffuse or focal spongiform changes occur in the white matter. Areas of the brain involved in motor function, language, and judgment are most severely affected.

There are no specific criteria for a diagnosis of HIV-associated dementia, and this syndrome must be differentiated from a number of other diseases that affect the CNS of HIV-infected patients (Table 197-14). The diagnosis of dementia depends on demonstrating a decline in cognitive function. This can be accomplished objectively with the use of a Mini-Mental Status Examination (MMSE) in patients for whom prior scores are available. For this reason, it is advisable for all patients with a diagnosis of HIV infection to have a baseline MMSE. However, changes in MMSE scores may be absent in patients with mild HIV encephalopathy. Imaging studies of the CNS, by either MRI or CT, often demonstrate evidence of cerebral atrophy **(Fig. 197-40)**. MRI may also reveal small areas of increased density on T2-weighted images. Lumbar puncture is an important element of the evaluation of patients with HIV infection and neurologic abnormalities. It is generally most helpful in ruling out or making a diagnosis of opportunistic infections. In HIV encephalopathy, patients may have the nonspecific findings of an increase in CSF cells and protein level. While HIV RNA can often be detected in the spinal fluid and HIV can be cultured from the CSF, this finding is not specific for HIV encephalopathy. There appears to be no correlation between the presence of HIV in the CSF and the presence of HIV encephalopathy. Elevated levels of macrophage chemoattractant protein (MCP-1), β_2-microglobulin, neopterin, and quinolinic acid (a metabolite of tryptophan reported to cause CNS injury) have been noted in the CSF of patients with HIV encephalopathy. These findings suggest that these factors as well as inflammatory cytokines may be involved in the pathogenesis of this syndrome.

Combination antiretroviral therapy is of benefit in patients with HIV-associated dementia. Improvement in neuropsychiatric test scores has been noted for both adult and pediatric patients treated with antiretrovirals. The rapid improvement in cognitive function noted with the initiation of cART suggests that at least some component of this

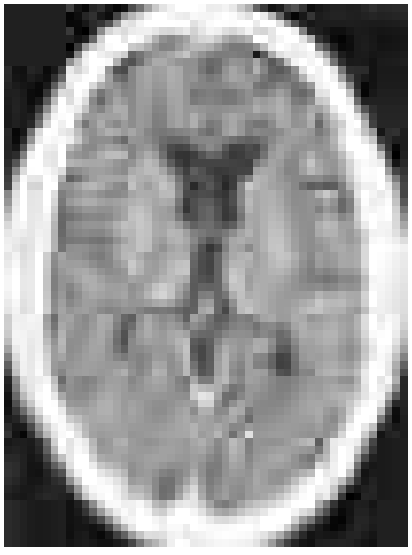


FIGURE 197-40 AIDS dementia complex. Postcontrast CT scan through the lateral ventricles of a 47-year-old man with AIDS, altered mental status, and dementia. The lateral and third ventricles and the cerebral sulci are abnormally prominent. Mild white matter hypodensity is seen adjacent to the frontal horns of the lateral ventricles.

TABLE 197-16 Causes of Seizures in Patients with HIV Infection

DISEASE	OVERALL CONTRIBUTION TO FIRST SEIZURE, %	FRACTION OF PATIENTS WHO HAVE SEIZURES, %
HIV encephalopathy	24–47	7–50
Cerebral toxoplasmosis	28	15–40
Cryptococcal meningitis	13	8
Primary central nervous system lymphoma	4	15–30
Progressive multifocal leukoencephalopathy	1	20

Source: From DM Holtzman et al: Am J Med 87:173, 1989.

problem is quickly reversible, again supporting at least a partial role of soluble mediators in the pathogenesis. It should also be noted that these patients have an increased sensitivity to the side effects of neuroleptic drugs. The use of these drugs for symptomatic treatment is associated with an increased risk of extrapyramidal side effects; therefore, patients with HIV encephalopathy who receive these agents must be monitored carefully. It is felt by many physicians that the decrease in the prevalence of severe cases of HAND brought about by cART has resulted in an increase in the prevalence of milder forms of this disorder.

Seizures may be a consequence of opportunistic infections, neoplasms, or HIV encephalopathy **(Table 197-16)**. The seizure threshold is often lower than normal in patients with advanced HIV infection due in part to the frequent presence of electrolyte abnormalities. Seizures are seen in 15–40% of patients with cerebral toxoplasmosis, 15–35% of patients with primary CNS lymphoma, 8% of patients with cryptococcal meningitis, and 7–50% of patients with HIV encephalopathy. Seizures may also be seen in patients with CNS tuberculosis, aseptic meningitis, and progressive multifocal leukoencephalopathy. Seizures may be the presenting clinical symptom of HIV disease. In one study of 100 patients with HIV infection presenting with a first seizure, cerebral mass lesions were the most common cause, responsible for 32 of the 100 new-onset seizures. Of these 32 cases, 28 were due to toxoplasmosis and 4 to lymphoma. HIV encephalopathy accounted for an additional 24 new-onset seizures. Cryptococcal meningitis was the third most common diagnosis, responsible for 13 of the 100 seizures. In 23 cases, no cause could be found, and it is possible that these cases represent a subcategory of HIV encephalopathy. Of these 23 cases, 16 (70%) had 2 or more seizures, suggesting that anticonvulsant therapy is indicated in all patients with HIV infection and seizures unless a rapidly correctable cause is found. Due to a variety of drug-drug interactions between antiseizure medications and antiretrovirals, drug levels need to be monitored carefully.

Patients with HIV infection may present with *focal neurologic deficits* from a variety of causes. The most common causes are toxoplasmosis, progressive multifocal leukoencephalopathy, and CNS lymphoma. Other causes include cryptococcal infections (discussed above; also **Chap. 210**), stroke, and reactivation of Chagas' disease.

Toxoplasmosis has been one of the most common causes of secondary CNS infections in patients with AIDS, but its incidence is decreasing in the era of cART. It is most common in patients from the Caribbean and from France, where the seroprevalence of *T. gondii* is around 50%. This figure is closer to 15% in the United States. Toxoplasmosis is generally a late complication of HIV infection and usually occurs in patients with CD4+ T cell counts <200/μL. Cerebral toxoplasmosis is thought to represent a reactivation of latent tissue cysts. It is 10 times more common in patients with antibodies to the organism than in patients who are seronegative. Patients diagnosed with HIV infection should be screened for IgG antibodies to *T. gondii* during the time of their initial workup. Those who are seronegative should be counseled about ways to minimize the risk of primary infection including avoiding the consumption of undercooked meat and careful hand washing after contact with soil or changing the cat litter box. The most common clinical presentation of cerebral toxoplasmosis in patients with HIV infection is fever, headache, and focal neurologic deficits. Patients may present with seizure, hemiparesis, or aphasia as a manifestation of these focal

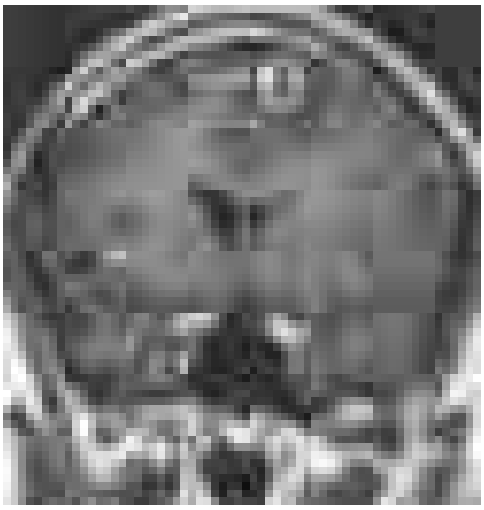


FIGURE 197-41 Central nervous system toxoplasmosis. A coronal postcontrast T1-weighted MRI scan demonstrates a peripheral enhancing lesion in the left frontal lobe, associated with an eccentric nodular area of enhancement (*arrow*); this so-called eccentric target sign is typical of toxoplasmosis.

deficits or with a picture more influenced by the accompanying cerebral edema and characterized by confusion, dementia, and lethargy, which can progress to coma. The diagnosis is usually suspected on the basis of MRI findings of multiple lesions in multiple locations, although in some cases only a single lesion is seen. Pathologically, these lesions generally exhibit inflammation and central necrosis and, as a result, demonstrate ring enhancement on contrast MRI **(Fig. 197-41)** or, if MRI is unavailable or contraindicated, on double-dose contrast CT. There is usually evidence of surrounding edema. In addition to toxoplasmosis, the differential diagnosis of single or multiple enhancing mass lesions in the HIV-infected patient includes primary CNS lymphoma and, less commonly, TB or fungal or bacterial abscesses. The definitive diagnostic procedure is brain biopsy. However, given the morbidity rate that can accompany this procedure, it is usually reserved for the patient who has failed 2–4 weeks of empiric therapy for toxoplasmosis. If the patient is seronegative for *T. gondii*, the likelihood that a mass lesion is due to toxoplasmosis is <10%. In that setting, one may choose to be more aggressive and perform a brain biopsy sooner. Standard treatment is sulfadiazine and pyrimethamine with leucovorin as needed for a minimum of 4–6 weeks. Alternative therapeutic regimens include clindamycin in combination with pyrimethamine; atovaquone plus pyrimethamine; and azithromycin plus pyrimethamine plus rifabutin. Relapses are common, and it is recommended that patients with a history of prior toxoplasmic encephalitis receive maintenance therapy with sulfadiazine, pyrimethamine, and leucovorin as long as their CD4+ T cell counts remain <200 cells/μL. Patients with CD4+ T cell counts <100/μL and IgG antibody to *Toxoplasma* should receive primary prophylaxis for toxoplasmosis. Fortunately, the same daily regimen of a single double-strength tablet of TMP-SMX used for *P. jirovecii* prophylaxis provides adequate primary protection against toxoplasmosis. Secondary prophylaxis/maintenance therapy for toxoplasmosis may be discontinued in the setting of effective cART and increases in CD4+ T cell counts to >200/μL for 6 months.

JC virus, a human polyomavirus that is the etiologic agent of *progressive multifocal leukoencephalopathy* (PML), is an important opportunistic pathogen in patients with AIDS **(Chap. 133)**. While ~80% of the general adult population has antibodies to JC virus, indicative of prior infection, <10% of healthy adults show any evidence of ongoing viral replication. PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~1–4% of patients with AIDS. The lesions of PML begin as small foci of demyelination in subcortical white matter that eventually coalesce. The cerebral hemispheres, cerebellum, and brainstem may all be involved. Patients typically have a protracted course with multifocal neurologic deficits, with or without changes in mental status. Approximately 20% of patients experience seizures. Ataxia, hemiparesis, visual field

defects, aphasia, and sensory defects may occur. Headache, fever, nausea, and vomiting are rarely seen. Their presence should suggest another diagnosis. MRI typically reveals multiple, nonenhancing white matter lesions that may coalesce and have a predilection for the occipital and parietal lobes. The lesions show signal hyperintensity on T2-weighted images and diminished signal on T1-weighted images. The measurement of JC virus DNA levels in CSF has a diagnostic sensitivity of 76% and a specificity of close to 100%. Prior to the availability of cART, the majority of patients with PML died within 3–6 months of the onset of symptoms. Paradoxical worsening of PML has been seen with initiation of cART as an immune reconstitution syndrome. There is no specific treatment for PML; however, a median survival of 2 years and survival of >15 years have been reported in patients with PML treated with cART for their HIV disease. Despite having a significant impact on survival, only ~50% of patients with HIV infection and PML show neurologic improvement with cART. Studies with other antiviral agents such as cidofovir have failed to show clear benefit. Factors influencing a favorable prognosis for PML in the setting of HIV infection include a CD4+ T cell count >100/μL at baseline and the ability to maintain an HIV viral load of <500 copies/mL. Baseline HIV-1 viral load does not have independent predictive value of survival. PML is one of the few opportunistic infections that continues to occur with some frequency despite the widespread use of cART.

Reactivation American trypanosomiasis may present as acute meningoencephalitis with focal neurologic signs, fever, headache, vomiting, and seizures. Accompanying cardiac disease in the form of arrhythmias or heart failure should increase the index of suspicion. The presence of antibodies to *T. cruzi* supports the diagnosis. In South America, reactivation of *Chagas' disease* is considered to be an AIDS-defining condition and may be the initial AIDS-defining condition. The majority of cases occur in patients with CD4+ T cell counts <200 cells/μL. Lesions appear radiographically as single or multiple hypodense areas, typically with ring enhancement and edema. They are found predominantly in the subcortical areas, a feature that differentiates them from the deeper lesions of toxoplasmosis. *T. cruzi* amastigotes, or trypanosomes, can be identified from biopsy specimens or CSF. Other CSF findings include elevated protein and a mild (<100 cells/μL) lymphocytic pleocytosis. Organisms can also be identified by direct examination of the blood. Treatment consists of benzimidazole (2.5 mg/kg bid) or nifurtimox (2 mg/kg qid) for at least 60 days, followed by maintenance therapy for the duration of immunodeficiency with either drug at a dose of 5 mg/kg three times a week. As is the case with cerebral toxoplasmosis, successful therapy with antiretrovirals may allow discontinuation of therapy for Chagas' disease.

Stroke may occur in patients with HIV infection. In contrast to the other causes of focal neurologic deficits in patients with HIV infection, the symptoms of a stroke are sudden in onset. Patients with HIV infection have an increased prevalence of many classic risk factors associated with stroke, including smoking and diabetes. It has been reported that HIV infection itself can lead to an increase in carotid artery stiffness. The relative increase in risk for stroke as a consequence of HIV infection is more pronounced in women and in individuals between the ages of 18 and 29. Among the secondary infectious diseases in patients with HIV infection that may be associated with stroke are vasculitis due to cerebral varicella zoster or neurosyphilis and septic embolism in association with fungal infection. Other elements of the differential diagnosis of stroke in the patient with HIV infection include atherosclerotic cerebral vascular disease, thrombotic thrombocytopenic purpura, and cocaine or amphetamine use.

Primary CNS lymphoma is discussed below in the section on neoplastic diseases.

Spinal cord disease, or myelopathy, is present in ~20% of patients with AIDS, often as part of HIV-associated neurocognitive disorder. In fact, 90% of the patients with HIV-associated myelopathy have some evidence of dementia, suggesting that similar pathologic processes may be responsible for both conditions. Three main types of spinal cord disease are seen in patients with AIDS. The first of these is a vacuolar myelopathy, as mentioned above. This condition is pathologically similar to subacute combined degeneration of the cord, such as that occurring with pernicious anemia. Although vitamin B_{12} deficiency can be seen in patients with AIDS as a primary complication of HIV infection, it does not appear to be responsible for the majority of the cases of myelopathy seen in patients with HIV infection. Vacuolar myelopathy is characterized by a subacute onset and often presents with gait disturbances, predominantly ataxia and spasticity; it may progress to include bladder and bowel dysfunction. Physical findings include evidence of increased deep tendon reflexes and extensor plantar responses. The second form of spinal cord disease involves the dorsal columns and presents as a pure sensory ataxia. The third form is also sensory in nature and presents with paresthesias and dysesthesias of the lower extremities. In contrast to the cognitive problems seen in patients with HIV encephalopathy, these spinal cord syndromes do not respond well to antiretroviral drugs, and therapy is mainly supportive.

One important disease of the spinal cord that also involves the peripheral nerves is a *myelopathy* and *polyradiculopathy* seen in association with CMV infection. This entity is generally seen late in the course of HIV infection and is fulminant in onset, with lower extremity and sacral paresthesias, difficulty in walking, areflexia, ascending sensory loss, and urinary retention. The clinical course is rapidly progressive over a period of weeks. CSF examination reveals a predominantly neutrophilic pleocytosis, and CMV DNA can be detected by CSF PCR. Therapy with ganciclovir or foscarnet can lead to rapid improvement, and prompt initiation of foscarnet or ganciclovir therapy is important in minimizing the degree of permanent neurologic damage. Combination therapy with both drugs should be considered in patients who have been previously treated for CMV disease. Other diseases involving the spinal cord in patients with HIV infection include HTLV-1-associated myelopathy (HAM) **(Chap. 196)**, neurosyphilis **(Chap. 177)**, infection with herpes simplex **(Chap. 187)** or varicella-zoster **(Chap. 188)**, TB **(Chap. 173)**, and lymphoma **(Chap. 104)**.

Peripheral neuropathies are common in patients with HIV infection. They occur at all stages of illness and take a variety of forms. Early in the course of HIV infection, an acute inflammatory demyelinating polyneuropathy resembling Guillain-Barré syndrome may occur **(Chap. 439)**. In other patients, a progressive or relapsing-remitting inflammatory neuropathy resembling chronic inflammatory demyelinating polyneuropathy (CIDP) has been noted. Patients commonly present with progressive weakness, areflexia, and minimal sensory changes. CSF examination often reveals a mononuclear pleocytosis, and peripheral nerve biopsy demonstrates a perivascular infiltrate suggesting an autoimmune etiology. Plasma exchange or IVIg has been tried with variable success. Because of the immunosuppressive effects of glucocorticoids, they should be reserved for severe cases of CIDP refractory to other measures. Another autoimmune peripheral neuropathy seen in patients with AIDS is mononeuritis multiplex **(Chaps. 439 and 356)** due to a necrotizing arteritis of peripheral nerves. The most common peripheral neuropathy in patients with HIV infection is a *distal sensory polyneuropathy* (DSPN) also referred to as painful sensory neuropathy (HIV-SN), predominantly sensory neuropathy, or distal symmetric peripheral neuropathy. This condition may be a direct consequence of HIV infection or a side effect of dideoxynucleoside therapy. It is more common in taller individuals, older individuals, and those with lower CD4 counts. Two-thirds of patients with AIDS may be shown by electrophysiologic studies to have some evidence of peripheral nerve disease. Presenting symptoms are usually painful burning sensations in the feet and lower extremities. Findings on examination include a stocking-type sensory loss to pinprick, temperature, and touch sensation and a loss of ankle reflexes. Motor changes are mild and are usually limited to weakness of the intrinsic foot muscles. Response of this condition to antiretrovirals has been variable, perhaps because antiretrovirals are responsible for the problem in some instances. When due to dideoxynucleoside therapy, patients with lower extremity peripheral neuropathy may complain of a sensation that they are walking on ice. Other entities in the differential diagnosis of peripheral neuropathy include diabetes mellitus, vitamin B_{12} deficiency, and side effects from metronidazole or dapsone. For distal symmetric polyneuropathy that fails to resolve following the discontinuation of dideoxynucleosides, therapy is symptomatic; gabapentin, carbamazepine, tricyclics, or

analgesics may be effective for dysesthesias. Treatment-naïve patients may respond to cART.

Myopathy may complicate the course of HIV infection; causes include HIV infection itself, zidovudine, and the generalized wasting syndrome (discussed below). HIV-associated myopathy may range in severity from an asymptomatic elevation in creatine kinase levels to a subacute syndrome characterized by proximal muscle weakness and myalgias. Quite pronounced elevations in creatine kinase may occur in asymptomatic patients, particularly after exercise. The clinical significance of this as an isolated laboratory finding is unclear. A variety of both inflammatory and noninflammatory pathologic processes have been noted in patients with more severe myopathy, including myofiber necrosis with inflammatory cells, nemaline rod bodies, cytoplasmic bodies, and mitochondrial abnormalities. Profound muscle wasting, often with muscle pain, may be seen after prolonged zidovudine therapy. This toxic side effect of the drug is dose-dependent and is related to its ability to interfere with the function of mitochondrial polymerases. It is reversible following discontinuation of the drug. Red ragged fibers are a histologic hallmark of zidovudine-induced myopathy.

Ophthalmologic Diseases Ophthalmologic problems occur in ~50% of patients with advanced HIV infection. The most common abnormal findings on funduscopic examination are cotton-wool spots. These are hard white spots that appear on the surface of the retina and often have an irregular edge. They represent areas of retinal ischemia secondary to microvascular disease. At times they are associated with small areas of hemorrhage and thus can be difficult to distinguish from CMV retinitis. In contrast to CMV retinitis, however, these lesions are not associated with visual loss and tend to remain stable or improve over time.

One of the most devastating consequences of HIV infection is CMV retinitis. Patients at high risk of CMV retinitis (CD4+ T cell count <100/μL) should undergo an ophthalmologic examination every 3–6 months. The majority of cases of CMV retinitis occur in patients with a CD4+ T cell count <50/μL. Prior to the availability of cART, this CMV reactivation syndrome was seen in 25–30% of patients with AIDS. In the cART era this has dropped to close to 2%. CMV retinitis usually presents as a painless, progressive loss of vision. Patients may also complain of blurred vision, "floaters," and scintillations. The disease is usually bilateral, although typically it affects one eye more than the other. The diagnosis is made on clinical grounds by an experienced ophthalmologist. The characteristic retinal appearance is that of perivascular hemorrhage and exudate. In situations where the diagnosis is in doubt due to an atypical presentation or an unexpected lack of response to therapy, vitreous or aqueous humor sampling with molecular diagnostic techniques may be of value. CMV infection of the retina results in a necrotic inflammatory process, and the visual loss that develops is irreversible. CMV retinitis may be complicated by rhegmatogenous retinal detachment as a consequence of retinal atrophy in areas of prior inflammation. Therapy for CMV retinitis consists of oral valganciclovir, IV ganciclovir, or IV foscarnet, with cidofovir as an alternative. Combination therapy with ganciclovir and foscarnet has been shown to be slightly more effective than either ganciclovir or foscarnet alone in the patient with relapsed CMV retinitis. A 3-week induction course is followed by maintenance therapy with oral valganciclovir. If CMV disease is limited to the eye, intravitreal injections of ganciclovir or foscarnet may be considered. Intravitreal injections of cidofovir are generally avoided due to the increased risk of uveitis and hypotony. Maintenance therapy is continued until the CD4+ T cell count remains >100 μL for >6 months. The majority of patients with HIV infection and CMV disease develop some degree of uveitis with the initiation of cART. The etiology of this is unknown; however, it has been suggested that this may be due to the generation of an enhanced immune response to CMV as an IRIS (see above). In some instances this has required the use of topical glucocorticoids.

Both HSV and varicella zoster virus can cause a rapidly progressing, bilateral, necrotizing retinitis referred to as the *acute retinal necrosis syndrome*, or *progressive outer retinal necrosis* (PORN). This syndrome, in contrast to CMV retinitis, is associated with pain, keratitis, and iritis. It is often associated with orolabial HSV or trigeminal zoster. Ophthalmologic examination reveals widespread pale gray peripheral lesions. This condition is often complicated by retinal detachment. It is important to recognize and treat this condition with IV acyclovir as quickly as possible to minimize the loss of vision.

Several other secondary infections may cause ocular problems in HIV-infected patients. *P. jirovecii* can cause a lesion of the choroid that may be detected as an incidental finding on ophthalmologic examination. These lesions are typically bilateral, are from half to twice the disc diameter in size, and appear as slightly elevated yellow-white plaques. They are usually asymptomatic and may be confused with cotton-wool spots. Chorioretinitis due to toxoplasmosis can be seen alone or, more commonly, in association with CNS toxoplasmosis. KS may involve the eyelid or conjunctiva, while lymphoma may involve the retina. Syphilis may lead to a uveitis that is highly associated with the presence of neurosyphilis.

Additional Disseminated Infections and Wasting Syndrome Infections with species of the small, gram-negative, *Rickettsia*-like organism *Bartonella* **(Chap. 167)** are seen with increased frequency in patients with HIV infection. While it is not considered an AIDS-defining illness by the CDC, many experts view infection with *Bartonella* as indicative of a severe defect in cell-mediated immunity. It is usually seen in patients with CD4+ T cell counts <100/μL and is a significant cause of unexplained fever in patients with advanced HIV infection. Among the clinical manifestations of *Bartonella* infection are bacillary angiomatosis, cat-scratch disease, and trench fever. *Bacillary angiomatosis* is usually due to infection with *B. henselae* and is linked to exposure to flea-infested cats. It is characterized by a vascular proliferation that leads to a variety of skin lesions that have been confused with the skin lesions of KS. In contrast to the lesions of KS, the lesions of bacillary angiomatosis generally blanch, are painful, and typically occur in the setting of systemic symptoms. Infection can extend to the lymph nodes, liver (peliosis hepatis), spleen, bone, heart, CNS, respiratory tract, and GI tract. *Cat-scratch disease* also is due to *B. henselae* and generally begins with a papule at the site of inoculation. This is followed several weeks later by the development of regional adenopathy and malaise. Infection with *B. quintana* is transmitted by lice and has been associated with case reports of trench fever, endocarditis, adenopathy, and bacillary angiomatosis. The organism is quite difficult to culture, and diagnosis often relies on identifying the organism in biopsy specimens using the Warthin-Starry or similar stains. Treatment is with either doxycycline or erythromycin for at least 3 months.

Histoplasmosis is an opportunistic infection that is seen most frequently in patients in the Mississippi and Ohio River valleys, Puerto Rico, the Dominican Republic, and South America. These are all areas in which infection with *H. capsulatum* is endemic **(Chap. 207)**. Because of this limited geographic distribution, the percentage of AIDS cases in the United States with histoplasmosis is only ~0.5. Histoplasmosis is generally a late manifestation of HIV infection; however, it may be the initial AIDS-defining condition. In one study, the median CD4+ T cell count for patients with histoplasmosis and AIDS was 33/μL. While disease due to *H. capsulatum* may present as a primary infection of the lung, disseminated disease, presumably due to reactivation, is the most common presentation in HIV-infected patients. Patients usually present with a 4- to 8-week history of fever and weight loss. Hepatosplenomegaly and lymphadenopathy are each seen in about 25% of patients. CNS disease, either meningitis or a mass lesion, is seen in 15% of patients. Bone marrow involvement is common, with thrombocytopenia, neutropenia, and anemia occurring in 33% of patients. Approximately 7% of patients have mucocutaneous lesions consisting of a maculopapular rash and skin or oral ulcers. Respiratory symptoms are usually mild, with chest x-ray showing a diffuse infiltrate or diffuse small nodules in ~50% of cases. The gastrointestinal tract may be involved. Diagnosis is made by silver staining of tissue, by culturing the organisms from blood, bone marrow, or tissue, or by detecting antigen in blood or urine. Treatment is typically with liposomal amphotericin B followed by maintenance therapy with oral itraconazole until the serum histoplasma antigen is <2 units, the patient has been on antiretrovirals for at least 6 months, and the CD4 count is >150 cells/μL. In the setting of mild infection, it may be appropriate to initiate therapy with itraconazole alone.

Following the spread of HIV infection to southeast Asia, disseminated infection with the fungus *Penicillium marneffei* was recognized as a complication of HIV infection and is considered an AIDS-defining condition in those parts of the world where it occurs. *P. marneffei* is the third most common AIDS-defining illness in Thailand, following TB and cryptococcosis. It is more frequently diagnosed in the rainy than the dry season. Clinical features include fever, generalized lymphadenopathy, hepatosplenomegaly, anemia, thrombocytopenia, and papular skin lesions with central umbilication resembling the lesions of *Molluscum contagiosum*. Treatment is with amphotericin B followed by itraconazole until the CD4+ T cell count is >100 cells/μL for at least 6 months.

Visceral leishmaniasis **(Chap. 221)** is recognized with increasing frequency in patients with HIV infection who live in or travel to areas endemic for this protozoal infection transmitted by sandflies. The clinical presentation is one of hepatosplenomegaly, fever, and hematologic abnormalities. Lymphadenopathy and other constitutional symptoms may be present. A chronic, relapsing course is seen in two-thirds of co-infected patients. Organisms can be isolated from cultures of bone marrow aspirates. Histologic stains may be negative, and antibody titers are of little help. Patients with HIV infection usually respond well initially to standard therapy with amphotericin B or pentavalent antimony compounds. Eradication of the organism is difficult, however, and relapses are common.

Patients with HIV infection are at a slightly increased risk of clinical malaria. This is particularly true for patients from nonendemic areas and thus at risk for primary infection and in patients with lower CD4+ T cell counts. HIV-positive individuals with CD4+ T cell counts <300 cells/μL have a poorer response to malaria treatment than others. Co-infection with malaria is associated with a modest increase in HIV viral load. The risk of malaria may be decreased with TMP-SMX prophylaxis.

Generalized wasting is an AIDS-defining condition; it is defined as involuntary weight loss of >10% associated with intermittent or constant fever and chronic diarrhea or fatigue lasting >30 days in the absence of a defined cause other than HIV infection. Prior to the widespread use of cART it was the initial AIDS-defining condition in ~10% of patients with AIDS in the United States. Generalized wasting is rarely seen today with the earlier initiation of antiretrovirals. A constant feature of this syndrome is severe muscle wasting with scattered myofiber degeneration and occasional evidence of myositis. Glucocorticoids may be of some benefit; however, this approach must be carefully weighed against the risk of compounding the immunodeficiency of HIV infection. Androgenic steroids, growth hormone, and total parenteral nutrition have been used as therapeutic interventions with variable success.

Neoplastic Diseases The neoplastic diseases considered to be AIDS-defining conditions are Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical carcinoma. In addition, there is also an increase in the incidence of a variety of non-AIDS-defining malignancies including Hodgkin's disease; multiple myeloma; leukemia; melanoma; and cervical, brain, testicular, oral, lung, gastric, liver, renal, and anal cancers. Since the introduction of potent cART, there has been a marked reduction in the incidence of KS (Fig. 197-34). The non-AIDS-defining malignancies now account for more morbidity and mortality in patients with HIV infection than the AIDS-defining malignancies and are responsible for approximately 25% of the deaths in patients with HIV infection. Rates of non-Hodgkin's lymphoma have declined; however, this decline has not been as dramatic as the decline in rates of KS. In contrast, cART has had little effect on human papillomavirus (HPV)-associated malignancies. As patients with HIV infection live longer, a wider array of cancers is seen in this population. While some may only reflect known risk factors (e.g., smoking, alcohol consumption, co-infection with other viruses such as hepatitis B) that are increased in patients with HIV infection, some may be a direct consequence of HIV and are clearly increased in patients with lower CD4+ T cell counts.

Kaposi's sarcoma is a multicentric neoplasm consisting of multiple vascular nodules appearing in the skin, mucous membranes, and viscera. The clinical course of KS ranges from indolent, with only minor skin or lymph node involvement, to fulminant, with extensive cutaneous and visceral involvement. In the initial period of the AIDS epidemic, KS was a prominent clinical feature of the first cases of AIDS, occurring in 79% of the patients diagnosed in 1981. By 1989 it was seen in only 25% of cases, by 1992 the number had decreased to 9%, and by 1997 the number was <1%. HHV-8 (KSHV) has been strongly implicated as a viral cofactor in the pathogenesis of KS.

Clinically, KS has varied presentations and may be seen at any stage of HIV infection, even in the presence of a normal CD4+ T cell count. The initial lesion may be a small, raised reddish-purple nodule on the skin **(Fig. 197-42)**, a discoloration on the oral mucosa (Fig. 197-34*D*), or a swollen lymph node. Lesions often appear in sun-exposed areas, particularly the tip of the nose, and have a propensity to occur in areas of trauma (Koebner phenomenon). Because of the vascular nature of the tumors and the presence of extravasated red blood cells in the lesions, their colors range from reddish to purple to brown and often take the appearance of a bruise, with yellowish discoloration and tattooing. Lesions range in size from a few millimeters to several centimeters in diameter and may be either discrete or confluent. KS lesions most commonly appear as raised macules; however, they can also be papular, particularly in patients with higher CD4+ T cell counts. Confluent lesions may give rise to surrounding lymphedema and may be disfiguring when they involve the face and disabling when they involve the lower extremities or the surfaces of joints. Apart from skin, the lymph nodes, GI tract, and lung are the organ systems most commonly affected by KS. Lesions have been reported in virtually every organ, including the heart and the CNS. In contrast to most malignancies, in which lymph node involvement implies metastatic spread and a poor prognosis, lymph node involvement may be seen very early in KS and is of no special clinical significance. In fact, some patients may present with disease limited to the lymph nodes. These are generally patients with relatively intact immune function and thus the patients with the best prognosis. Pulmonary involvement with KS generally presents with shortness of breath. Some 80% of patients with pulmonary KS also have cutaneous lesions. The chest x-ray characteristically shows bilateral lower lobe infiltrates that obscure the margins of the mediastinum and diaphragm **(Fig. 197-43)**. Pleural effusions are seen in 70% of cases of pulmonary KS, a fact that is often helpful in the differential diagnosis. GI involvement is seen in 50% of patients with

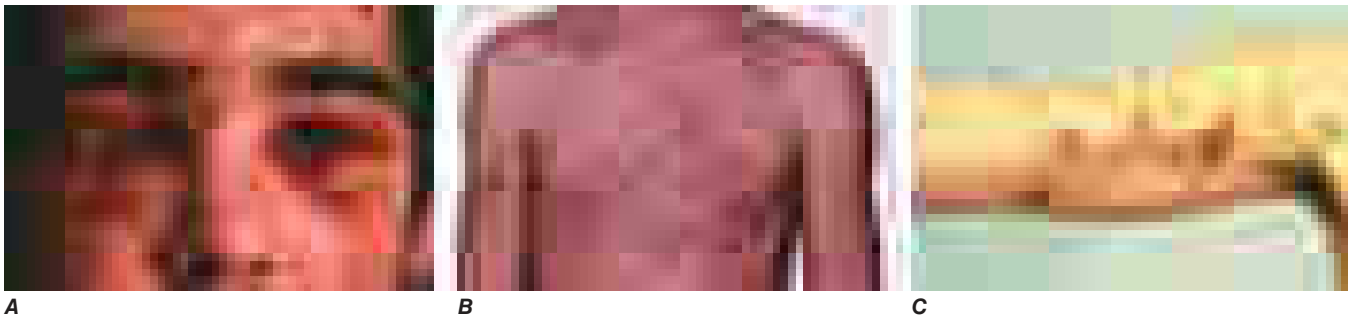


FIGURE 197-42 Kaposi's sarcoma in three patients with AIDS demonstrating (***A***) periorbital edema and bruising; (***B***) classic truncal distribution of lesions; and (***C***) upper extremity lesions.

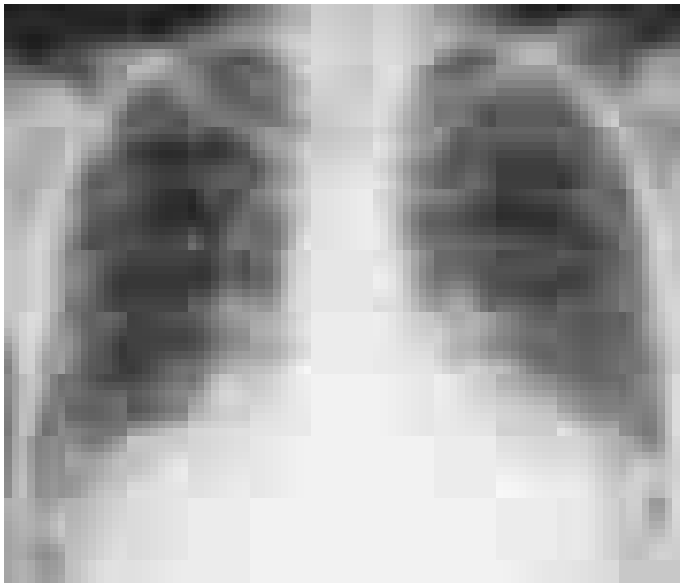


FIGURE 197-43 Chest x-ray of a patient with AIDS and pulmonary Kaposi's sarcoma. The characteristic findings include dense bilateral lower lobe infiltrates obscuring the heart borders and pleural effusions.

KS and usually takes one of two forms: (1) mucosal involvement, which may lead to bleeding that can be severe; these patients sometimes also develop symptoms of GI obstruction if lesions become large; and (2) biliary tract involvement. KS lesions may infiltrate the gallbladder and biliary tree, leading to a clinical picture of obstructive jaundice similar to that seen with sclerosing cholangitis. Several staging systems have been proposed for KS. One in common use was developed by the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group; it distinguishes patients on the basis of tumor extent, immunologic function, and presence or absence of systemic disease **(Table 197-17)**.

A diagnosis of KS is based on biopsy of a suspicious lesion. Histologically one sees a proliferation of spindle cells and endothelial cells, extravasation of red blood cells, hemosiderin-laden macrophages, and, in early cases, an inflammatory cell infiltrate. Included in the differential diagnosis are lymphoma (particularly for oral lesions), bacillary angiomatosis, and cutaneous mycobacterial infections.

Management of KS **(Table 197-18)** should be carried out in consultation with an expert since definitive treatment guidelines do not exist. In the majority of cases, effective cART will go a long way in achieving control. Antiretroviral therapy has been associated with the spontaneous regression of KS lesions. Paradoxically, it has also been associated with the initial appearance of KS as a form of IRIS. For

TABLE 197-17 National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group TIS Staging System For Kaposi's Sarcoma

PARAMETER	GOOD RISK (STAGE 0): ALL OF THE FOLLOWING	POOR RISK (STAGE 1): ANY OF THE FOLLOWING
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease	Tumor-associated edema or ulceration Extensive oral lesions GI lesions Nonnodal visceral lesions
Immune system (I)	CD4+ T cell count ≥200/μL	CD4+ T cell count <200/μL
Systemic illness (S)	No B symptoms[a]	B symptoms[a] present
	Karnofsky performance status ≥70	Karnofsky performance status <70
	No history of opportunistic infection, neurologic disease, lymphoma, or thrush	History of opportunistic infection, neurologic disease, lymphoma, or thrush

[a]Defined as unexplained fever, night sweats, >10% involuntary weight loss, or diarrhea persisting for more than 2 weeks.

TABLE 197-18 Management of AIDS-Associated Kaposi's Sarcoma

- Observation and optimization of antiretroviral therapy
- Single or limited number of lesions
  - Radiation
  - Intralesional vinblastine
  - Cryotherapy
- Extensive disease
  - Initial therapy
    - Interferon α (if CD4+ T cells >150/μL)
    - Liposomal daunorubicin
  - Subsequent therapy
    - Liposomal doxorubicin
    - Paclitaxel
- Combination chemotherapy with low-dose doxorubicin, bleomycin, and vinblastine (ABV)
- Targeted radiation

patients in whom tumor persists or is compromising vital functions or in whom control of HIV replication is not possible, a variety of options exist. In some cases, lesions remain quite indolent, and many of these patients can be managed with no specific treatment. Fewer than 10% of AIDS patients with KS die as a consequence of their malignancy, and death from secondary infections is considerably more common. Thus, whenever possible one should avoid treatment regimens that may further suppress the immune system and increase susceptibility to opportunistic infections. Treatment is indicated under two main circumstances. The first is when a single lesion or a limited number of lesions are causing significant discomfort or cosmetic problems, such as with prominent facial lesions, lesions overlying a joint, or lesions in the oropharynx that interfere with swallowing or breathing. Under these circumstances, treatment with localized radiation, intralesional vinblastine, topical 9-*cis*-retinoic acid, or cryotherapy may be helpful. It should be noted that patients with HIV infection are particularly sensitive to the side effects of radiation therapy. This is especially true with respect to the development of radiation-induced mucositis; doses of radiation directed at mucosal surfaces, particularly in the head and neck region, should be adjusted accordingly. The use of systemic therapy, either IFN-α or chemotherapy, should be considered in patients with a large number of lesions or in patients with visceral involvement. The single most important determinant of response appears to be the CD4+ T cell count. This relationship between response rate and baseline CD4+ T cell count is particularly true for IFN-α. The response rate to IFN-α for patients with CD4+ T cell counts >600/μL is ~80%, while the response rate for patients with counts <150/μL is <10%. In contrast to the other systemic therapies, IFN-α provides an added advantage of having antiretroviral activity; thus, it may be the appropriate first choice for single-agent systemic therapy for early patients with disseminated disease. A variety of chemotherapeutic agents also have been shown to have activity against KS. Four of them—liposomal daunorubicin, liposomal doxorubicin, vinblastine, and paclitaxel—have been approved by the FDA for this indication. Liposomal daunorubicin is approved as first-line therapy for patients with advanced KS. It has fewer side effects than conventional chemotherapy. In contrast, liposomal doxorubicin and paclitaxel are approved only for KS patients who have failed standard chemotherapy. Response rates vary from 23% to 88%, appear to be comparable to what had been achieved earlier with combination chemotherapy regimens, and are greatly influenced by CD4+ T cell count.

Lymphomas occur with an increased frequency in patients with congenital or acquired T cell immunodeficiencies **(Chap. 344)**. AIDS is no exception; at least 6% of all patients with AIDS develop lymphoma at some time during the course of their illness. This is a 120-fold increase in incidence compared with the general population. In contrast to the situation with KS, primary CNS lymphoma, and most opportunistic infections, the incidence of AIDS-associated systemic lymphomas has not experienced a dramatic decrease as a consequence of the widespread use of effective cART. Lymphoma occurs in all risk groups,

with the highest incidence in patients with hemophilia and the lowest incidence in patients from the Caribbean or Africa with heterosexually acquired infection. Lymphoma is a late manifestation of HIV infection, generally occurring in patients with CD4+ T cell counts <200/μL. As HIV disease progresses, the risk of lymphoma increases. The attack rate for lymphoma increases exponentially with increasing duration of HIV infection and decreasing level of immunologic function. At 3 years following a diagnosis of HIV infection, the risk of lymphoma is 0.8% per year; by 8 years after infection, it is 2.6% per year. As individuals with HIV infection live longer as a consequence of improved cART and better treatment and prophylaxis of opportunistic infections, it is anticipated that the incidence of lymphomas may increase.

Three main categories of lymphoma are seen in patients with HIV infection: grade III or IV immunoblastic lymphoma, Burkitt's lymphoma, and primary CNS lymphoma. Approximately 90% of these lymphomas are B cell in phenotype; more than half contain EBV DNA. Some are associated with KSHV. These tumors may be either monoclonal or oligoclonal in nature and are probably in some way related to the pronounced polyclonal B cell activation seen in patients with AIDS.

Immunoblastic lymphomas account for ~60% of the cases of lymphoma in patients with AIDS. The majority of these are diffuse large B cell lymphomas (DLBCL). They are generally high grade and would have been classified as diffuse histiocytic lymphomas in earlier classification schemes. This tumor is more common in older patients, increasing in incidence from 0% in HIV-infected individuals <1 year old to >3% in those >50 years of age. Two variants of immunoblastic lymphoma that are seen primarily in HIV-infected patients are primary effusion lymphoma (PEL) and its solid variant, plasmacytic lymphoma of the oral cavity. PEL, also referred to as body cavity lymphoma, presents with lymphomatous pleural, pericardial, and/or peritoneal effusions in the absence of discrete nodal or extranodal masses. The tumor cells do not express surface markers for B cells or T cells and are felt to represent a preplasmacytic stage of differentiation. While both HHV-8 and EBV DNA sequences have been found in the genomes of the malignant cells from patients with body cavity lymphoma, KSHV is felt to be the driving force behind the oncogenesis (see above).

Small noncleaved cell lymphoma (*Burkitt's lymphoma*) accounts for ~20% of the cases of lymphoma in patients with AIDS. It is most frequent in patients 10–19 years old and usually demonstrates characteristic c-*myc* translocations from chromosome 8 to chromosome 14 or 22. Burkitt's lymphoma is not commonly seen in the setting of immunodeficiency other than HIV-associated immunodeficiency, and the incidence of this particular tumor is more than 1000-fold higher in the setting of HIV infection than in the general population. In contrast to African Burkitt's lymphoma, where 97% of the cases contain EBV genome, only 50% of HIV-associated Burkitt's lymphomas are EBV-positive.

Primary CNS lymphoma accounts for ~20% of the cases of lymphoma in patients with HIV infection. In contrast to HIV-associated Burkitt's lymphoma, primary CNS lymphomas are usually positive for EBV. In one study, the incidence of Epstein-Barr positivity was 100%. This malignancy does not have a predilection for any particular age group. The median CD4+ T cell count at the time of diagnosis is ~50/μL. Thus, CNS lymphoma generally presents at a later stage of HIV infection than does systemic lymphoma. This may explain, at least in part, the poorer prognosis for this subset of patients.

The clinical presentation of lymphoma in patients with HIV infection is quite varied, ranging from focal seizures to rapidly growing mass lesions in the oral mucosa **(Fig. 197-44)** to persistent unexplained fever. At least 80% of patients present with extranodal disease, and a similar percentage have B-type symptoms of fever, night sweats, or weight loss. Virtually any site in the body may be involved. The most common extranodal site is the CNS, which is involved in approximately one-third of all patients with lymphoma. Approximately 60% of these cases are primary CNS lymphoma. Primary CNS lymphoma generally presents with focal neurologic deficits, including cranial nerve findings, headaches, and/or seizures. MRI or CT generally reveals a limited number (one to three) of 3- to 5-cm lesions **(Fig. 197-45)**. The lesions often show ring enhancement on contrast administration and may occur in any location. Contrast enhancement is usually less

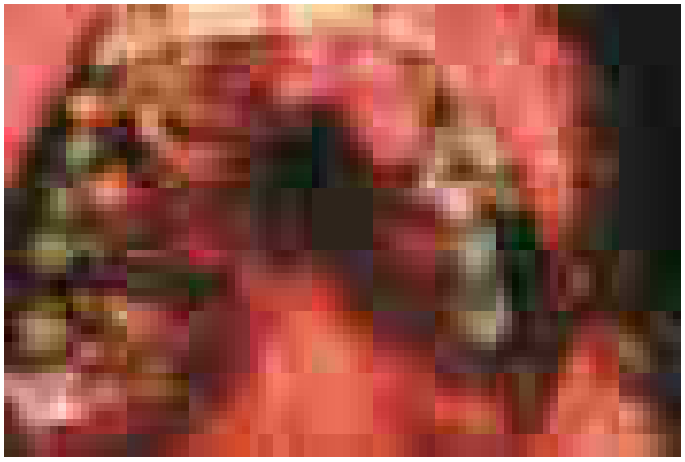


FIGURE 197-44 Immunoblastic lymphoma involving the hard palate of a patient with AIDS.

pronounced than that seen with toxoplasmosis. Locations that are most commonly involved with CNS lymphoma are deep in the white matter. The main diseases in the differential diagnosis are cerebral toxoplasmosis and cerebral Chagas' disease. In addition to the 20% of lymphomas in HIV-infected individuals that are primary CNS lymphomas, CNS disease is also seen in HIV-infected patients with systemic lymphoma. Approximately 20% of patients with systemic lymphoma have CNS disease in the form of leptomeningeal involvement. This fact underscores the importance of lumbar puncture in the staging evaluation of patients with systemic lymphoma.

Systemic lymphoma is seen at earlier stages of HIV infection than primary CNS lymphoma. In one series the mean CD4+ T cell count was 226/μL. In addition to lymph node involvement, systemic lymphoma may commonly involve the GI tract, bone marrow, liver, and lung. GI tract involvement is seen in ~25% of patients. Any site in the GI tract may be involved, and patients may complain of difficulty swallowing or abdominal pain. The diagnosis is usually suspected on the basis of CT or MRI of the abdomen. Bone marrow involvement is seen in ~20% of patients and may lead to pancytopenia. Liver and lung involvement are each seen in ~10% of patients. Pulmonary disease may present as a mass lesion, multiple nodules, or an interstitial infiltrate.

Both conventional and unconventional approaches have been employed in an attempt to treat HIV-related lymphomas. Systemic lymphoma is generally treated by the oncologist with combination chemotherapy. Earlier disappointing figures are being replaced with

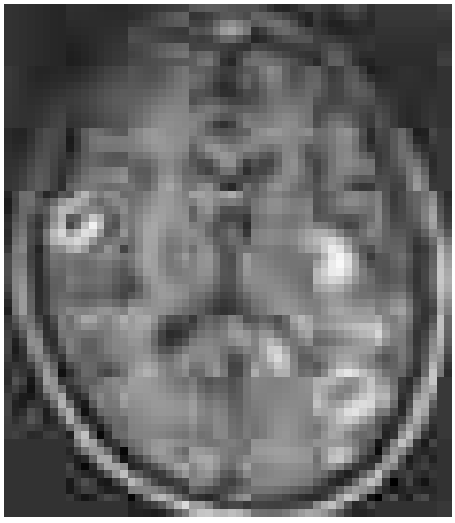


FIGURE 197-45 Central nervous system lymphoma. Postcontrast T1-weighted MRI scan in a patient with AIDS, altered mental status, and hemiparesis. Multiple enhancing lesions, some ring-enhancing, are present. The left sylvian lesion shows gyral and subcortical enhancement, and the lesions in the caudate and splenium (*arrowheads*) show enhancement of adjacent ependymal surfaces.

more optimistic results for the treatment of systemic lymphoma following the availability of more effective cART and the use of rituximab in CD20+ tumors. While there is some controversy regarding the use of antiretrovirals during chemotherapy, there is no question that their use overall in patients with HIV lymphoma has improved survival. Concerns regarding synergistic bone marrow toxicities with chemotherapy and cART are mitigated with the use of cART regimens that avoid bone marrow–toxic antiretrovirals. As in most situations in patients with HIV disease, those with higher CD4+ T cell counts tend to fare better. Response rates as high as 72% with a median survival of 33 months and disease-free intervals up to 9 years have been reported. Treatment of primary CNS lymphoma remains a significant challenge. Treatment is complicated by the fact that this illness usually occurs in patients with advanced HIV disease. Palliative measures such as radiation therapy provide some relief. The prognosis remains poor in this group, with a 2-year survival of 29%.

Multicentric Castleman's disease is a KSHV-associated lymphoproliferative disorder that is seen with an increased frequency in patients with HIV infection. While not a true malignancy, it shares many features with lymphoma including generalized lymphadenopathy, hepatosplenomegaly, and systemic symptoms of fever, fatigue, and weight loss. Pulmonary symptoms may be seen in ~50% of patients. KS is present in 75–82% of cases. Lymph node biopsies reveal a predominance of interfollicular plasma cells and/or germinal centers with vascularization and an "onionskin" (hyaline vascular) appearance. Prior to the availability of cART, HIV-infected patients with multicentric Castleman's disease had a 15-fold increased risk of developing non-Hodgkin's lymphoma compared with HIV-infected patients in general. Treatment typically involves chemotherapy. Anecdotal reports of success with rituximab suggest that more specific treatment may be successful, although, in one series treatment with rituximab was associated with worsening of coexisting KS. The median survival of patients with treated multicentric Castleman's disease pre-cART was initially reported as 14 months. This has increased to a 2-year survival of more than 90% in the era of cART.

Evidence of infection with *human papillomavirus* (HPV), associated with *intraepithelial dysplasia of the cervix* or *anus*, is approximately twice as common in HIV-infected individuals as in the general population and can lead to intraepithelial neoplasia and eventually invasive cancer. In a series of studies, HIV-infected men were examined for evidence of anal dysplasia, and Papanicolaou (Pap) smears were found to be abnormal in 20–80%. These changes tend to persist and are generally not affected by cART, raising the possibility of a subsequent transition to a more malignant condition. While the incidence of an abnormal Pap smear of the cervix is ~5% in otherwise healthy women, the incidence of abnormal cervical smears in women with HIV infection is 30–60%, and *invasive cervical cancer* is included as an AIDS-defining condition. While only small increases in the absolute numbers of cervical or anal cancers have been seen as a consequence of HIV infection, the relative risk of these conditions when one compares HIV-infected to noninfected men and women is on the order of 10- to 100-fold. Given the high rates of dysplasia and relative risks for cervical and anal cancer, a comprehensive gynecologic and rectal examination, including Pap smear, is indicated at the initial evaluation and 6 months later for all patients with HIV infection. If these examinations are negative at both time points, the patient should be followed with yearly evaluations. If an initial or repeat Pap smear shows evidence of severe inflammation with reactive squamous changes, the next Pap smear should be performed at 3 months. If, at any time, a Pap smear shows evidence of squamous intraepithelial lesions, colposcopic examination with biopsies as indicated should be performed. The 2-year survival rate for HIV-infected patients with invasive cervical cancer is 64% compared with 79% in non-HIV-infected patients. In addition to rectal and cervical lesions, HPV can also lead to head and neck cancers. In one study of men who have sex with men, 25% were found to have oral HPV; high-risk HPV genotypes were three times more common in the HIV-infected men. The most common HPV genotypes in the general population and the genotypes upon which current HPV vaccines are based are 6, 11, 16, and 18. This is not the case in the HIV-infected population, where other genotypes such as 58 and 53 also are prominent. This raises concerns about the level of effectiveness of the current HPV vaccines for HIV-infected patients. Despite this, it is recommended that patients with HIV infection be vaccinated against HPV.

IDIOPATHIC CD4+ T LYMPHOCYTOPENIA

A syndrome was recognized in 1992 characterized by an absolute CD4+ T cell count of <300/μL or <20% of total T cells on a minimum of two occasions at least 6 weeks apart; no evidence of HIV-1, HIV-2, HTLV-1, or HTLV-2 on testing; and the absence of any defined immunodeficiency or therapy associated with decreased levels of CD4+ T cells. By mid-1993, ~100 patients had been described. After extensive multicenter investigations, a series of reports were published in early 1993, which together allowed a number of conclusions. Idiopathic CD4+ lymphocytopenia (ICL) is a very rare syndrome, as determined by studies of blood donors and cohorts of HIV-seronegative men who have sex with men. Cases were clearly identified as early as 1983 and were remarkably similar to the clinical features of ICL that had been identified decades earlier. The definition of ICL based on CD4+ T cell counts coincided with the ready availability of testing for CD4+ T cells in patients suspected of being immunodeficient. Although, as a result of immune deficiency, certain patients with ICL develop some of the opportunistic diseases (particularly cryptococcosis, nontuberculous mycobacterial infections, and cervical dysplasia) seen in HIV-infected patients, the syndrome is demographically, clinically, and immunologically unlike HIV infection and AIDS. Fewer than half of the reported ICL patients had risk factors for HIV infection, and there were wide geographic and age distributions. The fact that a significant proportion of patients did have risk factors probably reflects a selection bias, in that physicians who take care of HIV-infected patients are more likely to monitor CD4+ T cells. Approximately half of the patients are women, compared with approximately one-third among HIV-infected individuals in the United States. Many patients with ICL remained clinically stable, and their condition did not deteriorate progressively as is common with seriously immunodeficient HIV-infected patients. Approximately 15% of patients with ICL experience spontaneous reversal of the CD4+ T lymphocytopenia. Immunologic abnormalities in ICL are somewhat different from those of HIV infection. ICL patients often have increases in CD4+ T cell activation with decreases in CD8+ T cells and B cells. Furthermore, immunoglobulin levels are either normal or, more commonly, decreased in patients with ICL, compared with the usual hypergammaglobulinemia of HIV-infected individuals. Virologic studies of these patients have revealed no evidence of HIV-1, HIV-2, HTLV-1, or HTLV-2 or of any other mononuclear cell–tropic virus. Furthermore, there has been no epidemiologic evidence to suggest that a transmissible microbe was involved. The cases of ICL have been widely dispersed, with no clustering. Close contacts and sexual partners who were studied were clinically well and were serologically, immunologically, and virologically negative for HIV. ICL is a heterogeneous syndrome, and it is highly likely that there is no common cause; however, there may be common causes among subgroups of patients that are currently unrecognized.

Patients who present with laboratory data consistent with ICL should be worked up for underlying diseases that could be responsible for the immune deficiency. If no underlying cause is detected, no specific therapy should be initiated. However, if opportunistic diseases occur, they should be treated appropriately (see above). Depending on the level of the CD4+ T cell count, patients should receive prophylaxis for the commonly encountered opportunistic infections.

TREATMENT

AIDS and Related Disorders

GENERAL PRINCIPLES OF PATIENT MANAGEMENT

The CDC guidelines call for the testing for HIV infection to be a part of routine medical care. It is recommended that the patient be informed of the intention to test, as is the case with other routine laboratory determinations, and be given the opportunity to "opt

out." Such an approach is critical to the goal of identifying as many infected individuals as possible since 15% of the 1.1 million individuals in the United States who are HIV-infected are not aware of their status. Under these circumstances of routine testing, although it is desirable, pretest counseling may not always be built into the testing process. However, no matter how well prepared a patient is for adversity, the discovery of a diagnosis of HIV infection is a devastating event. Thus, physicians should be sensitive to this fact and, where possible, execute some degree of pretest counseling to at least partially prepare the patient should the results demonstrate the presence of HIV infection. Following a diagnosis of HIV infection, the health care provider should be prepared to immediately activate support systems for the newly diagnosed patient and initiate cART therapy. These supports should include individuals who can spend time talking to the newly diagnosed person and ensuring that he or she is emotionally stable and ready to begin therapy. Most communities have HIV support centers that can be of great help in these difficult situations.

The treatment of patients with HIV infection requires not only a comprehensive knowledge of the possible disease processes that may occur and up-to-date knowledge of and experience with cART, but also the ability to deal with the problems of a chronic, potentially life-threatening illness. A comprehensive knowledge of internal medicine is required to deal with the changing spectrum of illnesses associated with HIV infection, many of which are similar to a state of accelerated aging. Great advances have been made in the treatment of patients with HIV infection. The appropriate use of potent cART and other treatment and prophylactic interventions are of critical importance in providing each patient with the best opportunity to live a long and healthy life with HIV infection. In contrast to the earlier days of this epidemic, a diagnosis of HIV infection need no longer be equated with having an inevitably fatal disease. In addition to medical interventions, the health care provider has a responsibility to provide each patient with appropriate counseling and education concerning their disease as part of a comprehensive care plan. Patients must be educated about the potential transmissibility of their infection and about the fact that while health care providers may refer to levels of the virus as "undetectable," this is only a reflection of the sensitivity of the assay being used to measure the virus, rather than a comment on the presence or absence of the virus. It is important for patients to be aware that the virus is still present in virtually all patients who have ever been diagnosed with HIV infection and capable of being transmitted at all stages of HIV disease. Thus, there must be frank discussions concerning sexual practices and the sharing of syringes and other paraphernalia used in illicit drug use. The treating physician not only must be aware of the latest medications available for patients with HIV infection but also must educate patients concerning the natural history of their illness and listen and be sensitive to their fears and concerns. As with other diseases, therapeutic decisions should be made in consultation with the patient, when possible, and with the patient's proxy if the patient is incapable of making decisions. In this regard, it is recommended that all patients with HIV infection, and in particular those with CD4+ T cell counts <200/μL, designate a trusted individual with durable power of attorney to make medical decisions on their behalf, if necessary.

Following a diagnosis of HIV infection, there are several examinations and laboratory studies that should be performed to help determine the extent of disease and provide baseline standards for future reference **(Table 197-19)**. In addition to routine chemistry, fasting lipid profile, aspartate aminotransferase, alanine aminotransferase, total and direct bilirubin, fasting glucose and hematology screening panels, Pap smear, urinalysis, and chest x-ray, one should also obtain a CD4+ T cell count, a plasma HIV RNA level, an HIV resistance test, a rapid plasma reagin or VDRL test, an anti-*Toxoplasma* antibody titer, and serologies for hepatitis A, B, and C. A PPD test or IFN-γ release assay should be done and an MMSE performed and recorded. A pregnancy test should be done in women in whom the drug efavirenz is being considered, and HLA-B5701 testing should be done in all patients in whom the drug abacavir is being considered. Patients should be immunized with pneumococcal polysaccharide, with annual influenza shots, and, if seronegative for these viruses, with HPV, hepatitis A, and hepatitis B vaccines. The status of hepatitis C infection should be determined. In addition, patients should be counseled with regard to sexual practices and needle sharing, and counseling should be offered to those whom the patient knows or suspects may also be infected. Once these baseline activities are performed, short- and long-term medical management strategies should be developed based on the most recent information available and modified as new information becomes available. The field of HIV medicine is changing rapidly, and it is difficult to remain fully up-to-date. Fortunately there are a series of excellent sites on the Internet that are frequently updated, and they provide the most recent information on a variety of topics, including consensus panel reports on treatment **(Table 197-20)**.

TABLE 197-19 Initial Evaluation of the Patient with HIV Infection

History and physical examination
Routine chemistry and hematology
AST, ALT, alkaline phosphatase, direct and indirect bilirubin
Lipid profile and fasting glucose
CD4+ T lymphocyte count
Plasma HIV RNA level
HIV resistance testing
HLA-B5701 screening
RPR or VDRL test
Anti-*Toxoplasma* antibody titer
Urinalysis
PPD skin test or IFN-γ release assay
Mini-Mental Status Examination
Serologies for hepatitis A, hepatitis B, and hepatitis C
Immunization with pneumococcal polysaccharide; influenza; HPV as indicated
Immunization with hepatitis A and hepatitis B if seronegative
Counseling regarding natural history and transmission
Help contacting others who might be infected

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPD, purified protein derivative; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

ANTIRETROVIRAL THERAPY

Combination antiretroviral therapy (cART), also referred to as highly active antiretroviral therapy (HAART), is the cornerstone of management of patients with HIV infection. Following the initiation of widespread use of cART in the United States in 1995–1996, marked declines were noted in the incidence of most AIDS-defining conditions (Fig. 197-34). Suppression of HIV replication is an important component in prolonging life as well as in improving the quality of life in patients with HIV infection. Adequate suppression requires strict adherence to prescribed regimens of antiretroviral drugs. This has been facilitated by the coformulations of antiretrovirals and the development of once-daily regimens. Unfortunately, many of the most important questions related to the treatment of HIV disease currently lack definitive answers. Among the decisions that need to be made in the context of prescribing cART are when therapy should be started, selection of the best initial regimen, when a given regimen should be changed, and what it

TABLE 197-20 HIV Disease Resources Available on the World Wide Web

www.aidsinfo.nih.gov	AIDSinfo, a service of the U.S. Department of Health and Human Services, posts federally approved treatment guidelines for HIV and AIDS; provides information on federally funded and privately funded clinical trials and CDC publications and data
www.cdcnpin.org	Updates on epidemiologic data and prevention information from the CDC

Abbreviation: CDC, Centers for Disease Control and Prevention.

should be changed to when a change is made. The care provider and patient must come to a mutually agreeable plan based on the best available data. In an effort to facilitate this process, the U.S. Department of Health and Human Services makes available on the Internet (*www.aidsinfo.nih.gov*) a series of periodically updated guidelines, including "*Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents*" and "*Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus*." At present, an extensive clinical trials network, involving both clinical investigators and patient advocates, is in place attempting to develop improved approaches to therapy. Consortia comprising representatives of academia, industry, independent foundations, and the federal government are involved in the process of drug development, including a wide-ranging series of clinical trials. As a result, new therapies and new therapeutic strategies are continually emerging. New drugs are often available through expanded-access programs prior to official licensure. Given the complexity of this field, decisions regarding cART are best made in consultation with experts.

Currently available drugs for the treatment of HIV infection as part of a combination regimen fall into four categories: those that inhibit the viral reverse transcriptase enzyme (nucleoside and nucleotide reverse transcriptase inhibitors; nonnucleoside reverse transcriptase inhibitors), those that inhibit the viral protease enzyme (protease inhibitors), those that inhibit the viral integrase enzyme (integrase inhibitors), and those that interfere with viral entry (fusion inhibitors; CCR5 antagonists) **(Table 197-21; Fig. 197-46)**. Numerous formulations combining two or more of these antiretroviral drugs have been licensed **(Table 197-22)**. Prior to initiation of therapy and at any time a change in therapy due to treatment failure is being considered, drug resistance testing should be performed to help guide the selection of drugs to be used in combination. A summary of known resistance mutations for antiretroviral drugs is shown in **Fig. 197-47**.

The FDA-approved reverse transcriptase inhibitors include the *nucleoside analogues* zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, and emtricitabine; the *nucleotide analogues* tenofovir disoproxil and tenofovir alafenamide; and the *nonnucleoside reverse transcriptase inhibitors* nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine (Table 197-21). These represent the first class of drugs licensed for the treatment of HIV infection. They are indicated for this use as part of combination regimens. It should be stressed that none of these drugs should be used as monotherapy for HIV infection due to the relative ease with which drug resistance may develop under such circumstances. Thus, when lamivudine, emtricitabine, or tenofovir is used to treat hepatitis B infection in the setting of HIV infection, one should ensure that the patient is also on additional antiretroviral medication. The reverse transcriptase inhibitors block the HIV replication cycle at the point of RNA-dependent DNA synthesis, the reverse transcription step. While the nonnucleoside reverse transcriptase inhibitors are quite selective for the HIV-1 reverse transcriptase, the nucleoside and nucleotide analogues inhibit a variety of DNA polymerases in addition to those of the HIV-1 reverse transcriptase. For this reason, serious side effects are more varied with the nucleoside analogues and include mitochondrial damage that can lead to hepatic steatosis and lactic acidosis as well as peripheral neuropathy and pancreatitis. The use of either of the thymidine analogues zidovudine and stavudine has been associated with a syndrome of hyperlipidemia, glucose intolerance/insulin resistance, and fat redistribution often referred to as *lipodystrophy syndrome* (discussed in "Diseases of the Endocrine System and Metabolic Disorders," above). The reverse transcriptase inhibitors preferred for use in combination regimens according to the DHHS Panel on the use of antiretroviral drugs are lamivudine, emtricitabine, abacavir, tenofovir disoproxil, and tenofovir alafenamide.

The HIV-1 protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, lopinavir/ritonavir, atazanavir, tipranavir, and darunavir) are an important part of the therapeutic armamentarium of antiretrovirals. While possessing antiviral properties of its own, ritonavir is typically used as a pharmacokinetic enhancer due to its high affinity for several isoforms of cytochrome P450 (3A4, 2D6) leading to large increases in the plasma concentrations of co-administered drugs metabolized by these pathways As in the case of reverse transcriptase inhibitors, resistance to protease inhibitors can develop rapidly in the setting of monotherapy, and thus these agents should be used only as part of combination therapeutic regimens. Based upon superior efficacy and side-effect profile, ritonavir-boosted darunavir in combination with emtricitabine and tenofovir disoproxil or tenofovir alafenamide is the protease inhibitor strategy preferred for initial therapy according to the DHHS Panel on the use of antiretroviral drugs.

Integrase inhibitors act by blocking the action of the HIV integrase enzyme and thus preventing integration of the HIV provirus into the host cell genome. They are among the most potent and safest of the antiretroviral drugs and frequently part of initial combination regimens. The four licensed integrase inhibitors are raltegravir, elvitegravir, dolutegravir, and bictegravir. Elvitegravir is always given in combination with cobicistat, which acts to boost the concentrations of elvitegravir. Cobicistat also inhibits tubular secretion of creatinine, resulting in increases in serum creatinine, and is not recommended for patients with estimated creatinine clearances <70 mL/min. Bictegravir is available only in combination with tenofovir alafenamide and emtricitabine.

TABLE 197-21 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Nucleoside or Nucleotide Reverse Transcriptase Inhibitors					
Zidovudine (AZT, azidothymidine, *Retrovir, 3'azido-3'-deoxythymidine)	Licensed	Treatment of HIV infection in combination with other antiretroviral agents	200 mg q8h or 300 mg bid	19 vs 1 death in original placebo-controlled trial in 281 patients with AIDS or ARC	Anemia, granulocytopenia, myopathy, lactic acidosis, hepatomegaly with steatosis, headache, nausea, nail pigmentation, lipid abnormalities, lipoatrophy, hyperglycemia
		Prevention of maternal-fetal HIV transmission		In pregnant women with CD4+ T cell count ≥200/μL, AZT PO beginning at weeks 14–34 of gestation plus IV drug during labor and delivery plus PO AZT to infant for 6 weeks decreased transmission of HIV by 67.5% (from 25.5% to 8.3%); n = 363	

(*Continued*)

TABLE 197-21 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection (Continued)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Lamivudine (Epivir, 2'3'-dideoxy-3'-thiacytidine, 3TC)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	150 mg bid 300 mg qd	In combination with AZT superior to AZT alone with respect to changes in CD4+ T cell counts in 495 patients who were zidovudine-naïve and 477 patients who were zidovudine-experienced; overall CD4+ T cell counts for the zidovudine group were at baseline by 24 weeks, while in the group treated with zidovudine plus lamivudine, they were 10–50 cells/μL above baseline; 54% decrease in progression to AIDS/death compared with AZT alone	Flare of hepatitis in HBV-co-infected patients who discontinue drug
Emtricitabine (FTC, Emtriva)	Licensed	In combination with other antiretroviral agents for the treatment of HIV infection	200 mg qd	Comparable to lamivudine in combination with stavudine and nevirapine/efavirenz	Hepatotoxicity in HBV-co-infected patients who discontinue drug, skin discoloration
Abacavir (Ziagen)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	300 mg bid	Abacavir + AZT + 3TC equivalent to indinavir + AZT + 3TC with regard to viral load suppression (~60% in each group with <400 HIV RNA copies/mL plasma) and CD4+ T cell increase (~100/μL in each group) at 24 weeks	Hypersensitivity reaction In HLA-B5701+ individuals (can be fatal); fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite
Tenofovir disoproxil fumarate (Viread)	Licensed	For use in combination with other antiretroviral agents when treatment is indicated	300 mg qd	Reduction of ~0.6 log in HIV-1 RNA levels when added to background regimen in treatment-experienced patients	Renal, osteomalacia, flare of hepatitis in HBV-co-infected patients who discontinue drug
Tenofovir alafenamide (Vemlidy)	Licensed	In combination with emtricitabine and other antiretroviral agents for treatment of HIV-1 infection	25 mg qd	92% of patients treated in combination with emtricitabine, elvitegravir, and cobicistat had HIV-1 RNA levels <50 copies/mL	Nausea, less renal toxicity than tenofovir disoproxil fumarate
Non-Nucleoside Reverse Transcriptase Inhibitors					
Nevirapine (Viramune)	Licensed	In combination with other antiretroviral agents for treatment of progressive HIV infection	200 mg/d × 14 days then 200 mg bid *or* 400 mg extended release qd	Increase in CD4+ T cell count, decrease in HIV RNA when used in combination with nucleosides	Skin rash, hepatotoxicity
Efavirenz (Sustiva)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	600 mg qhs	Efavirenz + AZT + 3TC comparable to indinavir + AZT + 3TC with regard to viral load suppression (a higher percentage of the efavirenz group achieved viral load <50 copies/mL, but the discontinuation rate in the indinavir group was unexpectedly high, accounting for most treatment "failures"); CD4 cell increase (~140/μL in each group) at 24 weeks	Rash, dysphoria, elevated liver function tests, drowsiness, abnormal dreams, depression, lipid abnormalities, potentially teratogenic
Etravirine (Intelence)	Licensed	In combination with other antiretroviral agents in treatment-experienced patients whose HIV is resistant to nonnucleoside reverse transcriptase inhibitors and other antiretroviral medications	200 mg bid	Higher rates of HIV RNA suppression to <50 copies/mL (56% vs 39%); greater increases in CD4+ T cell count (89 vs 64 cells) compared to placebo when given in combination with an optimized background regimen	Rash, nausea, hypersensitivity reactions
Rilpivirine (Edurant)	Licensed	In combination with other drugs in previously untreated patients when treatment is indicated.	25 mg qd	Noninferior to efavirenz with respect to suppression at week 48 in 1368 treatment-naive individuals, except in patients with pretherapy HIV RNA levels >100,000 where it was inferior	Nausea, dizziness, somnolence, vertigo, less CNS toxicity and rash than efavirenz
Protease Inhibitors					
Ritonavir (Norvir)	Licensed	In combination with other antiretroviral agents for treatment of HIV infection when treatment is warranted	600 mg bid (also used in lower doses as pharmacokinetic booster)	Reduction in the cumulative incidence of clinical progression or death from 34% to 17% in patients with CD4+ T cell count <100/μL treated for a median of 6 months	Nausea, abdominal pain, hyperglycemia, fat redistribution, lipid abnormalities, may alter levels of many other drugs, paresthesias, hepatitis

(*Continued*)

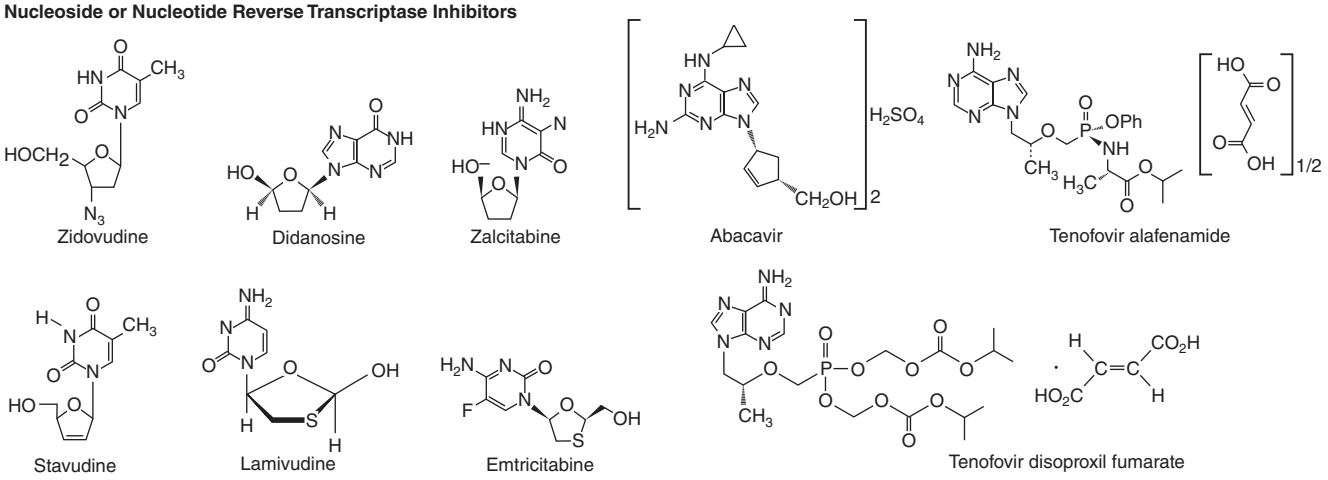
TABLE 197-21 Antiretroviral Drugs Most Commonly Used in the Treatment of HIV Infection (Continued)

DRUG	STATUS	INDICATION	DOSE IN COMBINATION	SUPPORTING DATA	TOXICITY
Atazanavir (Reyataz)	Licensed	For treatment of HIV infection in combination with other antiretroviral agents	400 mg qd or 300 mg qd + ritonavir 100 mg qd when given with efavirenz	Comparable to efavirenz when given in combination with AZT + 3TC in a study of 810 treatment-naïve patients; comparable to nelfinavir when given in combination with stavudine + 3TC in a study of 467 treatment-naïve patients	Hyperbilirubinemia, PR prolongation, nausea, vomiting, hyperglycemia, fat maldistribution, rash transaminase elevations, renal stones
Darunavir (Prezista)	Licensed	In combination with 100 mg ritonavir for combination therapy in treatment-experienced adults	600 mg + 100 mg ritonavir twice daily with food	At 24 weeks, patients with prior extensive exposure to antiretrovirals treated with a new combination including darunavir showed a –1.89-log change in HIV RNA levels and a 92-cell increase in CD4+ T cells compared with –0.48 log and 17 cells in the control arm	Diarrhea, nausea, headache, skin rash, hepatotoxicity, hyperlipidemia, hyperglycemia
Entry Inhibitors					
Enfuvirtide (Fuzeon)	Licensed	In combination with other agents in treatment-experienced patients with evidence of HIV-1 replication despite ongoing anti-retroviral therapy	90 mg SC bid	In treatment of experienced patients, superior to placebo when added to new optimized background (37% vs 16% with <400 HIV RNA copies/mL at 24 weeks; + 71 vs + 35 CD4+ T cells at 24 weeks)	Local injection reactions, hypersensitivity reactions, increased rate of bacterial pneumonia
Maraviroc (Selzentry)	Licensed	In combination with other antiretroviral agents in adults infected with only CCR5-tropic HIV-1	150–600 mg bid depending on concomitant medications (see text)	At 24 weeks, among 635 patients with CCR5-tropic virus and HIV-1 RNA >5000 copies/mL despite at least 6 months of prior therapy with at least 1 agent from 3 of the 4 antiretroviral drug classes, 61% of patients randomized to maraviroc achieved HIV RNA levels <400 copies/mL compared with 28% of patients randomized to placebo	Hepatotoxicity, nasopharyngitis, fever, cough, rash, abdominal pain, dizziness, musculoskeletal symptoms
Ibalizumab (Trogarzo)	Licensed	In combination with other antiretroviral agents in patients with multidrug-resistant HIV-1	Single loading dose of 2000 mg followed by a maintenance dose of 800 mg every 2 weeks	At 25 weeks, 50% of patients with multi-drug resistant HIV-1 with HIV-1 RNA >1000 copies/mL treated with an optimized background of 1 active drug and ibalizumab achieved HIV RNA levels <200 copies/mL	Rash, diarrhea, nausea
Integrase Inhibitor					
Raltegravir (Isentress)	Licensed	In combination with other antiretroviral agents	400 mg bid	At 24 weeks, among 436 patients with 3-class drug resistance, 76% of patients randomized to receive raltegravir achieved HIV RNA levels <400 copies/mL compared with 41% of patients randomized to receive placebo	Nausea, headache, diarrhea, CPK elevation, muscle weakness, rhabdomyolysis
Elvitegravir (Available only in combination with cobicistat, tenofovir, and emtricitabine [Stribild])	Licensed	Fixed-dose combination	1 tablet daily	Noninferior to raltegravir or atazanavir/ritonavir in treatment-experienced patients.	Diarrhea, nausea, upper respiratory infections, headache
Dolutegravir (Tivicay)	Licensed	In combination with other antiretroviral agents	50 mg daily for treatment-naïve patients 50 mg twice daily for treatment-experienced patients or those also receiving efavirenz or rifampin	Noninferior to raltegravir, superior to efavirenz or darunavir/ritonavir	Insomnia, headache, hypersensitivity reactions, hepatotoxicity
Bictegravir (Available only in combination with tenofovir alafenamide and emtricitabine [Biktarvy]	Licensed	For treatment of HIV infection in adults	50 mg bictegravir/ 25 mg tenofovir alafenamide/ 200 mg emtricitabine qd	Non-inferior to dolutegravir/tenofovir/ emtricitabine and non-inferior to dolutegravir/abacavir/lamivudine	Nausea, diarrhea, headache

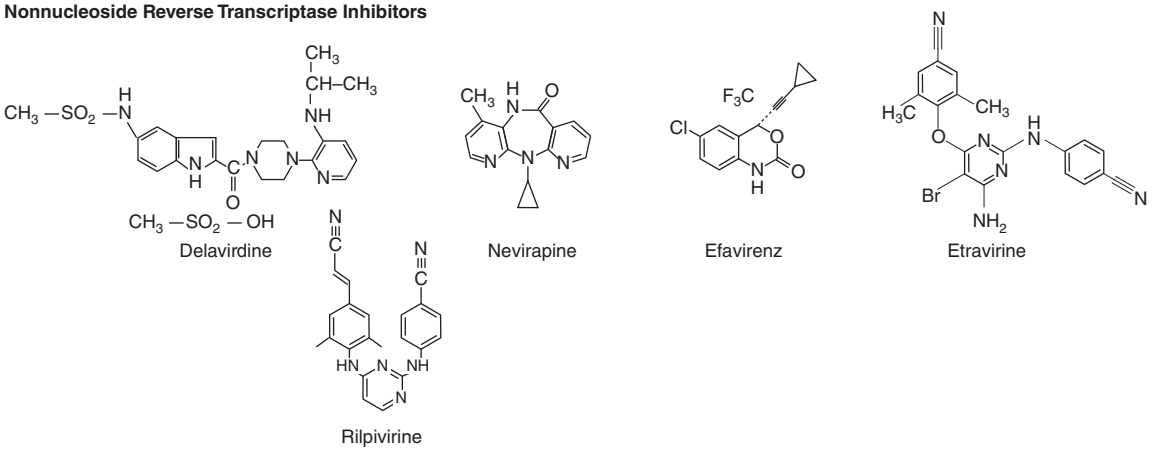
*Initial trade names are provided. Generic forms may be available.

Abbreviations: ARC, AIDS-related complex; NRTIs, nonnucleoside reverse transcriptase inhibitors.

Nucleoside or Nucleotide Reverse Transcriptase Inhibitors



Nonnucleoside Reverse Transcriptase Inhibitors



Protease Inhibitors

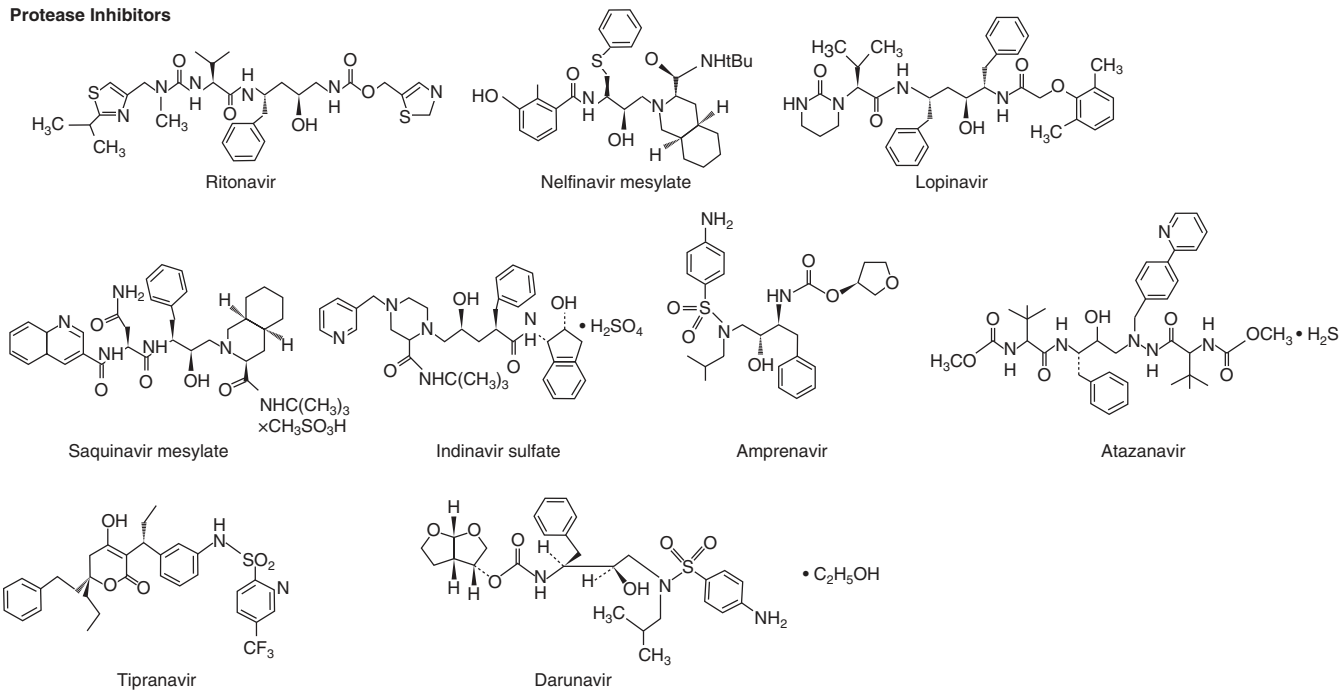
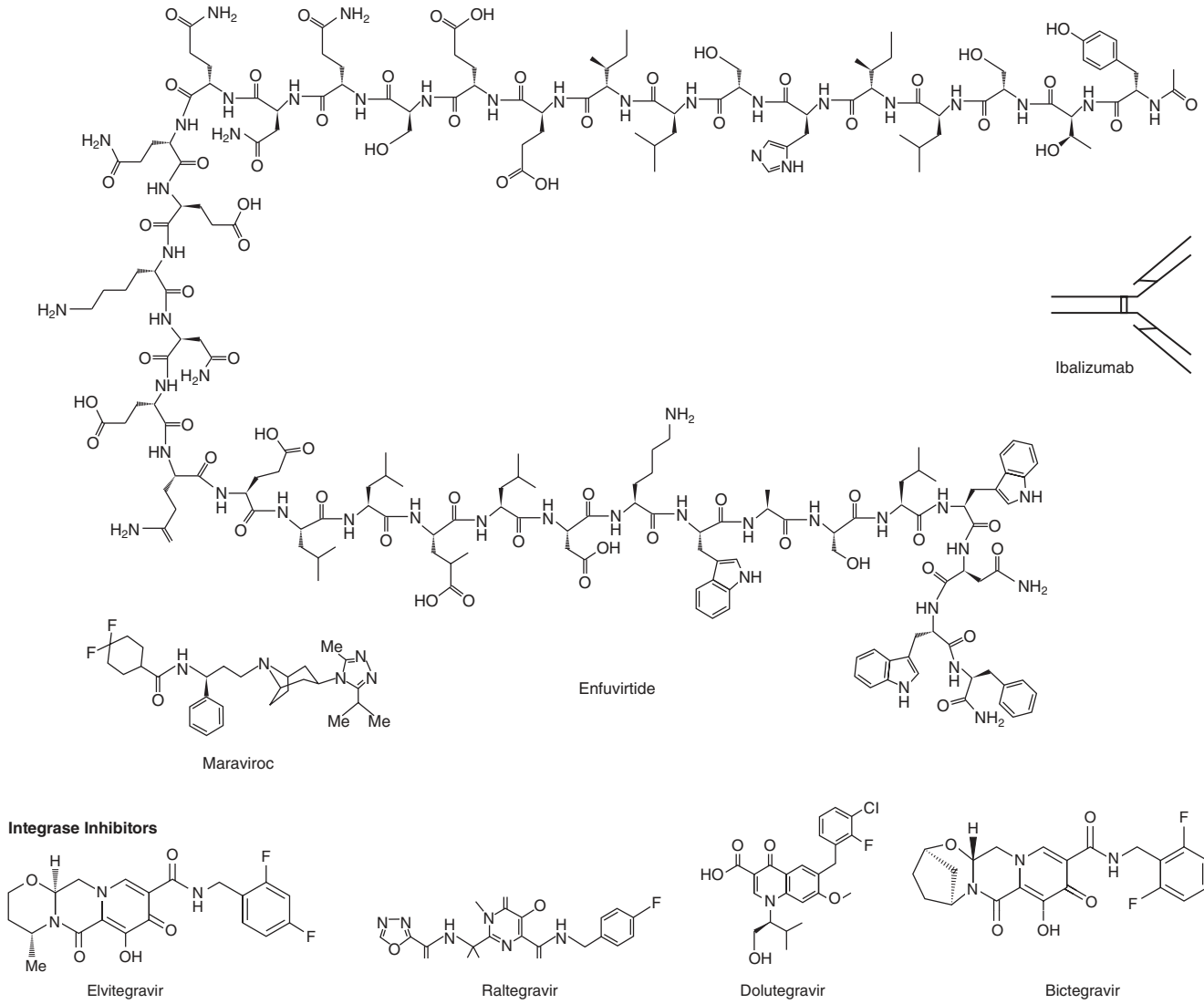


FIGURE 197-46 Molecular structures of antiretroviral agents.



Integrase Inhibitors

FIGURE 197-46 (*Continued*)

Entry inhibitors act by interfering with the binding of HIV to its receptor or co-receptor or by interfering with the process of fusion (see above). The first drug in this class to be licensed was the fusion inhibitor *enfuvirtide*, or T-20, followed by the CCR5 antagonist *maraviroc*. The anti-CD4 monoclonal antibody ibalizumab was licensed in 2018, and a variety of additional small molecules that bind to HIV-1 co-receptors are currently in clinical trials.

PRINCIPLES OF THERAPY

The principles of therapy for HIV infection have been articulated by a panel sponsored by the U.S. Department of Health and Human Services as a working group of the NIH Office of AIDS Research Advisory Council. These principles are summarized in **Table 197-23**. As noted in these guidelines, cART of HIV infection does not lead to eradication or cure of HIV. The single possible exception to this is an individual with HIV infection who received an allogeneic stem cell transplant for treatment of acute myelogenous leukemia. His conditioning regimen included cytotoxic chemotherapy, total-body irradiation, and antithymocyte immunoglobulin. The donor cells were homozygous for the *CCR5Δ32* mutation (see above) and thus resistant to HIV infection. Despite cART being stopped the day of the transplant, the patient has exhibited no signs of active HIV infection for more than 8 years.

Treatment decisions must take into account the fact that one is dealing with a chronic infection that requires daily therapy. Patients initiating antiretroviral therapy must be willing to commit to lifelong treatment and understand the importance of adherence to their prescribed regimen. The importance of adherence is illustrated by the observation that treatment interruption is associated with rapid increases in HIV RNA levels, rapid declines in CD4+ T cell counts, and an increased risk of clinical progression. While it seems reasonable to assume that the complications associated with cART could be minimized by intermittent treatment regimens designed to minimize exposure to the drugs in question, all efforts to do so have paradoxically been associated with an increase in serious adverse events in the patients randomized to intermittent therapy, suggesting that some "non-AIDS-associated" serious adverse events such as heart attack and stroke may be linked to HIV replication. Thus, unless contraindicated for reasons of toxicity, patients started on cART should remain on cART.

At present, the U.S. Department of Health and Human Services Guidelines panel recommends that everyone with HIV infection be treated with cART and that therapy be initiated a soon as possible after diagnosis. Therapy has been associated with a decrease in disease progression in patients at all stages of HIV infection and leads to a decrease in the risk of transmission of infection. In addition, one may wish to administer a 6-week course of therapy to uninfected individuals immediately following a high-risk exposure to HIV. The combination of tenofovir and emtricitabine is also indicated for pre-exposure prophylaxis in individuals at high risk of HIV

TABLE 197-22 Combination Formulations of Antiretroviral Drugs

NAME	COMBINATION
Atripla*	Tenofovir disoproxil fumarate + emtricitabine + efavirenz
Biktarvy*	Tenofovir alafenamide + emtricitabine + bictegravir
Cimduo	Tenofovir disoproxil fumarate + lamivudine
Combivir	Zidovudine + lamivudine
Complera*	Tenofovir disoproxil fumarate+ emtricitabine + rilpivirine
Descovy	Tenofovir alafenamide + emtricitabine
Dutrebis	Raltegravir + lamivudine
Epzicom	Abacavir + lamivudine
Evotaz	Atazanavir + cobicistat
Genvoya*	Tenofovir alafenamide + emtricitabine + elvitegravir + cobicistat
Juluca	Dolutegravir + rilpivirine
Kaletra	Lopinavir + ritonavir
Odefsey*	Tenofovir alafenamide +emtricitabine + rilpivirine
Prezcobix	Darunavir + cobicistat
Stribild*	Tenofovir disoproxil fumarate + emtricitabine + elvitegravir + cobicistat
Symfi*	Tenofovir disoproxil fumarate + lamivudine + efavirenz (600 mg)
Symfi Lo*	Tenofovir disoproxil fumarate + lamivudine + efavirenz (400 mg)
Triumeq*	Abacavir + lamivudine + dolutegravir
Truvada	Tenofovir disoproxil fumarate + emtricitabine
Trizivir	Zidovudine + lamivudine + abacavir

*Complete, once-daily, single tablet regimens.

infection. For patients diagnosed with an opportunistic infection and HIV infection at the same time, one may consider a 2- to 4-week delay in the initiation of antiretroviral therapy during which time treatment is focused on the opportunistic infection. This delay may decrease the severity of any subsequent immune reconstitution inflammatory syndrome by lowering the antigenic burden of the opportunistic infection. This is particularly true for patients with TB or cryptococcal infections. For patients with advanced HIV infection (CD4+ <50 cells/μL), however, cART should be initiated as soon as possible.

Once the decision has been made to initiate therapy, the health care provider must decide which drugs to use as the first regimen. The decision regarding choice of drugs not only will affect the immediate response to therapy but also will have implications regarding options for future therapeutic regimens. The initial regimen is usually the most effective insofar as the virus has yet to develop significant resistance. HIV is capable of rapidly developing resistance to any single agent, and therapy must be given as a multidrug combination. Given that patients can be infected with viruses that harbor drug resistance mutations, it is recommended that a viral genotype be done prior to the initiation of therapy to optimize the selection of antiretroviral agents. The combination regimens currently recommended for initial therapy in most treatment-naïve patients are listed in **Table 197-24**. It is currently debated whether treatment-naïve individuals with <50 copies/mL of HIV RNA benefit from cART. While these individuals are at low risk of disease progression in the short term, they do have evidence of persistent immune activation that may have long-term consequences. Following the initiation of therapy one should expect a rapid, at least 1-log (tenfold) reduction in plasma HIV RNA levels within 1–2 months and then a slower decline in plasma HIV RNA levels to <50 copies/mL within 6 months. During this same time there should be a rise in the CD4+ T cell count of 100–150/cells μL that is also particularly brisk during the first month of therapy. Subsequently, one should anticipate a CD4+ T cell count increase of 50–100 cells/year until numbers approach normal. Many clinicians feel that failure to achieve these endpoints is an indication for a change in therapy. Other reasons for a change in therapy include a persistently declining CD4+ T cell count, a consistent increase in HIV RNA levels to >200 copies/mL, clinical deterioration, or drug toxicity **(Table 197-25)**. As in the case of initiating therapy, changing therapy may have a lasting impact on future therapeutic options. When changing therapy because of treatment failure (clinical progression or worsening laboratory parameters), it is important to attempt to provide a regimen with at least two new active drugs. This decision can be guided by resistance testing (see below). In the patient in whom a change is made for reasons of drug toxicity, a simple replacement of one drug is reasonable. It should be stressed that in attempting to sort out a drug toxicity it may be advisable to hold all therapy for a period of time to distinguish between drug toxicity and disease progression. Drug toxicity will usually begin to show signs of reversal within 1–2 weeks. Prior to changing a treatment regimen because of drug failure, it is important to ensure that the patient has been adherent to the prescribed regimen. As in the case of initial therapy, the simpler the new therapeutic regimen, the easier it is for the patient to be compliant. Plasma HIV RNA levels should be monitored every 3–6 months during therapy and more frequently if one is contemplating a change in regimen due to an increase in viral load or immediately following a change in regimen.

In order to determine an optimal therapeutic regimen for initial therapy or for a patient on a failing regimen, one may attempt to measure antiretroviral drug susceptibility through genotyping or phenotyping of HIV quasispecies and to determine adequacy of dosing through measurement of drug levels. Genotyping may be done through cDNA sequencing. Phenotypic assays typically measure the enzymatic activity of viral enzymes in the presence or absence of different concentrations of different drugs and have also been used to determine co-receptor tropism. These assays will generally detect quasispecies present at a frequency of ≥10%. Next-generation sequencing may allow detection of quasispecies at frequencies down to 1%. It is generally recommended that resistance testing be used in selecting initial therapy in settings where the risk of transmission of resistant virus is high (such as the United States and Europe) and in determining new regimens for patients experiencing virologic failure while on therapy. Resistance testing may be of particular value in distinguishing drug-resistant virus from poor patient compliance. Due to the rapid rate at which drug-resistant viruses revert to wild-type, it is recommended that resistance testing performed in the setting of drug failure be carried out while the patient is still on the failing regimen. Measurement of plasma drug levels can also be used to tailor an individual treatment. The inhibitory quotient, defined as the trough blood level/IC_{50} of the patient's virus, is used by some to determine the adequacy of dosing of a given treatment regimen. Despite the best of efforts there will still be patients with ongoing high levels of HIV replication while receiving the best available therapy. These patients will receive benefit from remaining on antiretroviral therapy even though it is not fully suppressive.

In addition to the licensed medications discussed above, a large number of experimental agents are being evaluated as possible therapies for HIV infection. Therapeutic strategies are being developed to interfere with virtually every step of the replication cycle of the virus (Fig. 197-3) and in an attempt to eliminate the reservoir of infected cells to "cure" HIV infection. In addition to directly acting antiviral drugs, other strategies, generically referred to as "immune-based therapies," are being developed as a complement to antiviral therapy. Among the antiviral agents in early clinical trials are additional nucleoside and nucleotide analogues, protease inhibitors, fusion inhibitors, receptor and co-receptor antagonists, and integrase inhibitors—as well as new antiviral strategies including antisense nucleic acids and maturation inhibitors. Among the immune-based therapies being evaluated are monoclonal antibodies, IFN-α, bone marrow transplantation, adoptive transfer of lymphocytes genetically modified to resist infection or enhance HIV-specific immunity, active immunotherapy with inactivated HIV or its components, IL-7, and IL-15. Strategies directed toward cure are examining the role of latency-reversing agents such as histone-deacetylase inhibitors.

HIV AND THE HEALTH CARE WORKER

Health care workers, especially those who deal with large numbers of HIV-infected patients, have a small but definite risk of becoming infected with HIV as a result of professional activities (see "Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting," above).

In the United States 58 health care workers for whom case investigations have been completed have had documented seroconversions to HIV following occupational exposures. Only one of these has occurred since 1999. Approximately 85% of the exposures resulting in infection have been due to percutaneous (puncture/cut injury) exposures to HIV-infected blood. The individuals with documented seroconversions included 19 laboratory workers (16 of whom were clinical laboratory workers), 24 nurses, 16 clinical laboratory technicians, 6 physicians, 4 nonclinical laboratory technicians, 2 housekeepers, 2 surgical technicians, 1 dialysis technician, 1 respiratory therapist, 1 health aide, 1 embalmer/morgue technician, and 1 unknown. In addition, at least 150 possible cases of occupationally acquired HIV infection have been reported among

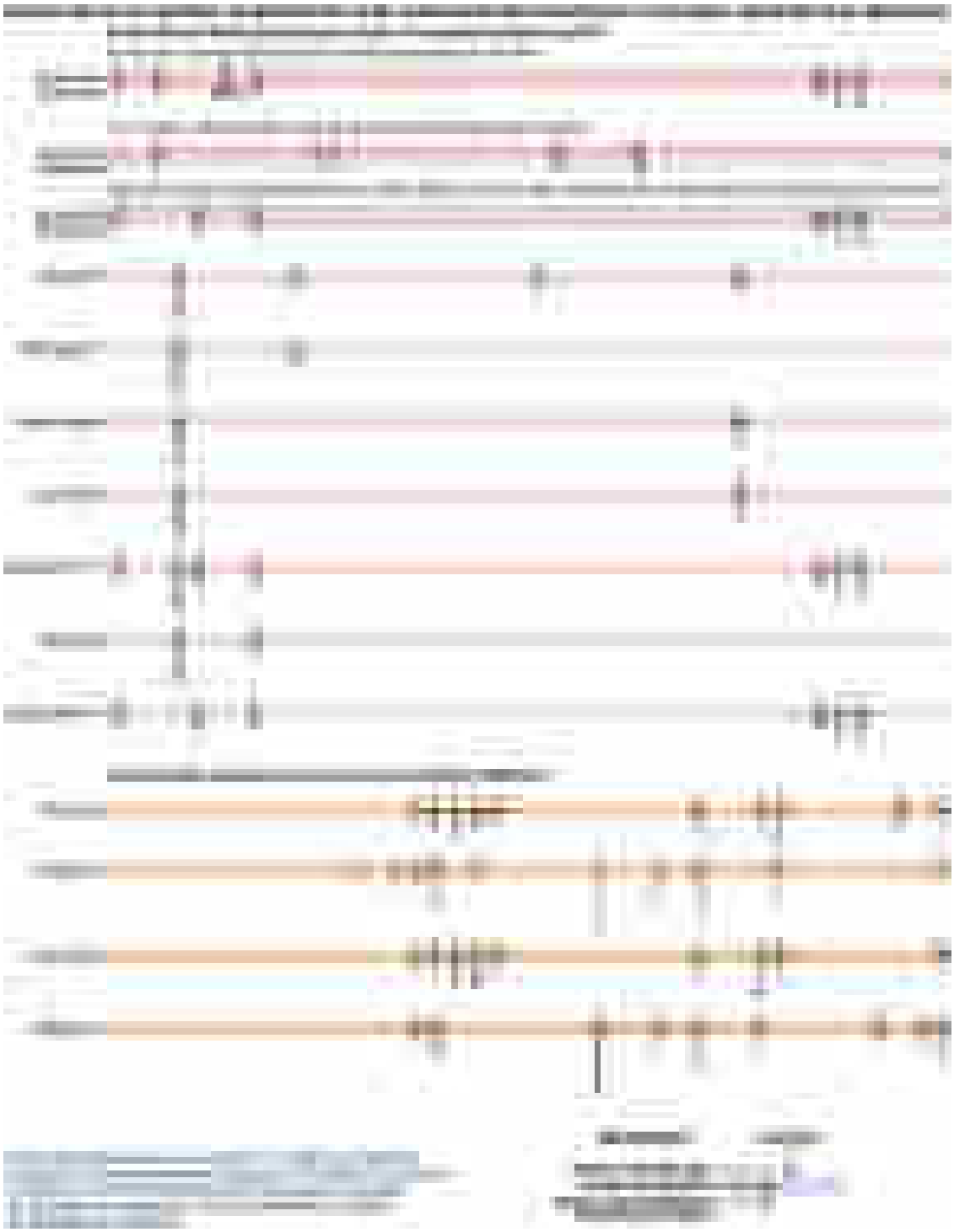


FIGURE 197-47 Amino acid substitutions conferring resistance to antiretroviral drugs. For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed. HR1, first heptad repeat; NAMs, nRTI-associated mutations; nRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor. Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine. *(Reprinted with permission from the International Antiviral Society—USA. AM Wensing, V Calvez, HR Günthard et al: 2014 Update of the Drug Resistance Mutations in HIV-1. Top Antivir Med 22:642, 2014. Updated information [and thorough explanatory notes] available at www.iasusa.org.)*

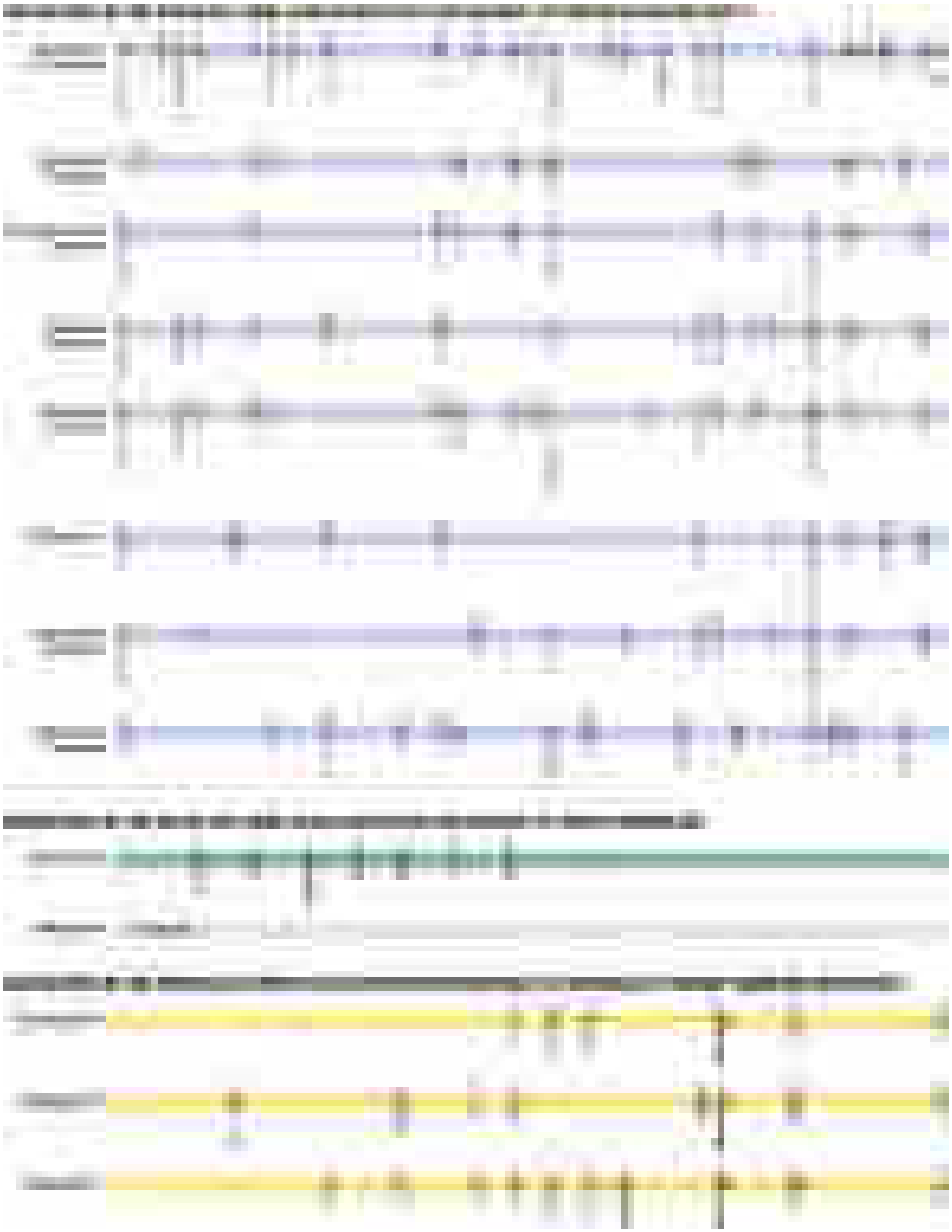


FIGURE 197-47 (*Continued*)

health care personnel in the United States. The number of these workers who actually acquired their infection through occupational exposures is not known. Taken together, data from several large studies suggest that the risk of HIV infection following a percutaneous exposure to HIV-contaminated blood is ~0.2323%, and after a mucous membrane exposure, ~0.09%. Although episodes of HIV transmission after nonintact skin exposure have been documented, the average risk for transmission by this route has not been precisely quantified but is estimated to be less than the risk for mucous membrane exposures. The risk for transmission after exposure to body fluids or tissues other than HIV-infected blood also has not been quantified but is probably considerably lower than for blood exposures. A seroprevalence survey of 3420 orthopedic surgeons, 75% of whom practiced in an area with a relatively high prevalence of HIV infection and 39% of whom reported percutaneous exposure to patient blood, usually through an accident involving a suture needle, failed to reveal any cases of possible occupational infection, suggesting that the risk of infection with a suture needle may be considerably less than that with a blood-drawing (hollow-bore) needle.

Most cases of health care worker seroconversion occur as a result of needle-stick injuries. When one considers the circumstances that result in needle-stick injuries, it is immediately obvious that adhering to the standard guidelines for dealing with sharp objects would result in a significant decrease in this type of accident. In one study, 27% of needle-stick injuries resulted from improper disposal of the needle (over half of these were due to recapping the needle), 23% occurred during attempts to start an IV line, 22% occurred during blood drawing, 16% were associated with an IM or SC injection, and 12% were associated with giving an IV infusion.

TABLE 197-23 Principles of Therapy of HIV Infection

1. Ongoing HIV replication leads to immune system damage, progression to AIDS, and systemic immune activation.
2. Plasma HIV RNA levels indicate the magnitude of HIV replication and the rate of CD4+ T cell destruction. CD4+ T cell counts indicate the current level of competence of the immune system.
3. Maximal suppression of viral replication is a goal of therapy; the greater the suppression the less likely the appearance of drug-resistant quasispecies.
4. The most effective therapeutic strategies involve the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents that the patient has already received.
5. The antiretroviral drugs used in combination regimens should be used according to optimum schedules and dosages.
6. The number of available drugs is limited. Any decisions on antiretroviral therapy have a long-term impact on future options for the patient.
7. Women should receive optimal antiretroviral therapy regardless of pregnancy status.
8. The same principles apply to children and adults. The treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
9. Compliance is an important part of ensuring maximal effect from a given regimen. The simpler the regimen, the easier it is for the patient to be compliant.

Source: Modified from *Principles of Therapy of HIV Infection*, USPHS, and the Henry J. Kaiser Family Foundation.

Occupational exposures to HIV should be considered as a medical emergency to ensure timely postexposure management and administration of postexposure antiretroviral prophylaxis (PEP). Recommendations regarding PEP must take into account that a variety of circumstances determine the risk of transmission of HIV following occupational exposure. In this regard, several factors have been associated with an increased risk for occupational transmission of HIV infection, including deep injury, the presence of visible blood on the instrument causing the exposure, injury with a device that had been placed in the vein or artery of the source patient, and advanced HIV disease in the source patient. Other important considerations when considering PEP in the health care worker include known or suspected pregnancy or breast-feeding, the possibility of exposure to drug-resistant virus, and the toxicities of different PEP regimens. Regardless of the decision to use PEP, the wound should be cleansed immediately and antiseptic applied. If a decision is made to offer PEP, U.S. Public Health Service guidelines recommend that PEP regimens contain 3 (or more) antiretroviral drugs administered for a 4-week duration for all occupational exposures to HIV. Detailed guidelines are available from the *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis* (CDC, 2013). The report emphasizes the importance of adherence to PEP when it is indicated, and close follow-up of exposed workers should be provided including counseling, baseline and follow-up HIV testing, and monitoring for drug toxicity. Follow-up appointments should begin within 72 h of an HIV exposure, and if newer fourth-generation combination HIV p24 antigen-HIV antibody test is utilized for follow-up HIV testing of the exposed health care worker, HIV testing may be concluded 4 months after exposure; if a newer testing platform is not available, follow-up HIV testing is typically concluded 6 months after an HIV exposure. For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEPline) at 888-448-4911. This service is available 24 hours a day at no charge. (Additional information on the Internet is available at *www.nccc.ucsf.edu*.) PEPline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or the health care worker is pregnant.

TABLE 197-24 Initial Combination Regimens Recommended for Most Treatment-Naïve Patients Regardless of HIV RNA Level or CD4 Count

Dolutegravir + tenofovir* + emtricitabine**
Raltegravir + tenofovir* + emtricitabine**
Bictegravir + tenofovir*+ emtricitabine**
Elvitegravir + cobicistat + tenofovir* + emtricitabine**
Dolutegravir + abacavir + lamivudine** (only for those HLA-B*5701 negative)

*Tenofovir alafenamide and tenofovir disoproxil fumarate are two forms of tenofovir approved by FDA. Tenofovir alafenamide has fewer bone and renal toxicities while tenofovir disoproxil fumarate is associated with lower lipid levels. **Lamivudine may substitute for emtricitabine and vice versa.

Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS.

TABLE 197-25 Indications for Changing Antiretroviral Therapy in Patients with HIV Infection[a]

Less than a 1-log drop in plasma HIV RNA by 4 weeks following the initiation of therapy
A reproducible significant increase (defined as threefold or greater) from the nadir of plasma HIV RNA level not attributable to intercurrent infection, vaccination, or test methodology
Persistently declining CD4+ T cell numbers
Clinical deterioration
Side effects

[a]Generally speaking, a change should involve the initiation of at least two drugs felt to be effective in the given patient. The exception to this is when change is being made to manage toxicity, in which case a single substitution is reasonable.

Source: Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, USPHS.

Health care workers can minimize their risk of occupational HIV infection by following the CDC guidelines of June 2015, which include adherence to universal precautions, assuming that blood and other body fluids from all patients are potentially infectious. Therefore, the following infection control precautions should be adhered to at all times: (1) routinely use barriers (such as gloves and/or goggles) when anticipating contact with blood or body fluids; (2) immediately wash hands and other skin surfaces after contact with blood or body fluids; and (3) carefully handle and dispose of sharp instruments during and after use. For further information contact the CDC at 800-CDC-INFO (232-4636) or see *www.cdc.gov/info*. In attempting to put this small but definite occupational risk of HIV infection to the health care worker in perspective, it is important to point out that ~200 health care workers die each year as a result of occupationally acquired hepatitis B infection. The tragedy in this instance is that these infections and deaths due to HBV could be greatly decreased by more extended use of the HBV vaccine. The risk of HBV infection following a needle-stick injury from a hepatitis antigen–positive patient is much higher than the risk of HIV infection (see "Transmission," above). There are multiple examples of needle-stick injuries where the patient was positive for both HBV and HIV and the health care worker became infected only with HBV. For these reasons, it is advisable, given the high prevalence of HBV infection in HIV-infected individuals, that all health care workers dealing with HIV-infected patients be immunized with the HBV vaccine.

TB is another infection common to HIV-infected patients that can be transmitted to the health care worker. For this reason, all health care workers should know their PPD status, have it checked yearly, and, where appropriate, receive 6 months of isoniazid treatment if their skin test converts to positive. In addition, all patients in whom a diagnosis of pulmonary TB is being entertained should be placed immediately in respiratory isolation, pending results of the diagnostic evaluation. The emergence of drug-resistant organisms, including extensively drug-resistant TB strains, has made TB an increasingly important problem for health care workers. This is particularly true for the health care worker with preexisting HIV infection.

One of the most charged issues ever to come between health care workers and patients is that of transmission of infection from HIV-infected health care workers to their patients. This is discussed in "Occupational Transmission of HIV: Health Care Workers, Laboratory Workers, and the Health Care Setting," above. Theoretically, the same universal precautions that are used to protect the health care worker

from the HIV-infected patient will also protect the patient from the HIV-infected health care worker.

VACCINE FOR THE PREVENTION OF HIV INFECTION

There is currently no safe and effective vaccine that has been approved for the prevention of HIV infection. Successful vaccines are predicated on the assumptions that the body can mount an adequate immune response to the microbe or virus in question during natural infection and that the vaccine will mimic the natural response to infection. Even with serious diseases, such as smallpox, poliomyelitis, measles, and influenza among others, the body in the vast majority of cases clears the infectious agent and provides protection, which is usually life-long against future exposure against the same pathogen. Unfortunately, this is not the case with HIV infection since the natural immune response to HIV infection is unable to clear the virus from the body and cases of superinfection are not uncommon. Some of the factors that contribute to the problematic nature of development of a preventive HIV vaccine are (1) the high mutability of the virus; (2) the fact that the infection can be transmitted by cell-free or cell-associated virus; (3) the fact that the HIV provirus integrates itself into the genome of the target cell and may remain in a latent form unexposed to the immune system; (4) the likely need for the development of effective mucosal immunity; and (5) the fact that it has been difficult to establish the precise correlates of protective immunity to HIV infection. A fraction of a percent of HIV-infected individuals are "elite controllers" in that they maintain extremely low and even undetectable levels of viremia in the absence of cART, and a number of individuals have been exposed to HIV multiple times but remain uninfected; these facts suggest that there are elements of host defense or an HIV-specific immune response that have the potential to be protective against acquisition of infection. Early attempts to develop a vaccine with the envelope protein gp120 aimed at inducing neutralizing antibodies in humans were unsuccessful; the elicited antisera failed to neutralize primary isolates of HIV cultured and tested in fresh peripheral blood mononuclear cells. In this regard, two phase 3 trials were undertaken in the United States and Thailand using soluble gp120, and the vaccines failed to protect human volunteers from HIV infection. In addition, two separate vaccine trials aimed at eliciting CD8+ T cell responses to prevent infection and, if unsuccessful in preventing infection, to control postinfection viremia, also failed at both goals. In 2009, a vaccine using a poxvirus vector prime expressing various viral proteins followed by an envelope protein boost was tested in a 16,000-person clinical trial (RV144) conducted in Thailand among predominantly low-HIV-prevalence heterosexuals. The vaccine provided the first positive, albeit very modest, signal ever reported in an HIV vaccine trial, showing 31% protection against acquisition of infection. Such a result is certainly not sufficient justification for clinical use of the vaccine, but it served as an important first step in the direction of the development of a safe and effective vaccine against HIV infection. Follow-up studies of RV144 indicate that nonneutralizing or weakly neutralizing antibody responses against certain constant epitopes in the otherwise highly variable V1-V2 region of the HIV envelope may be associated with the modest degree of protection observed in that clinical trial. Additional similar studies are being conducted in high-HIV-prevalence countries in sub-Saharan Africa in attempts to improve on the results of RV144 by a variety of approaches, including increasing the number of vaccine boosts with envelope protein and the addition of adjuvant.

An area of HIV vaccine research that is currently being actively pursued is the attempt to induce broadly neutralizing antibodies by developing as immunogens for vaccination certain epitopes on the HIV envelope that are the targets of naturally occurring broadly neutralizing antibodies during HIV infection. It is curious that only about 20% of HIV-infected individuals develop broadly neutralizing antibodies in response to natural infection and they do so only after 2–3 years of ongoing infection. By the time these antibodies appear, they can neutralize a broad range of primary HIV isolates, but they appear to be ineffective against the autologous virus in the infected subject. Upon close examination, these broadly neutralizing antibodies manifest a high degree of somatic mutations that were accumulated over time and are responsible for their affinity maturation and broadly neutralizing capacity. The goal of current efforts is to develop the conformationally correct HIV envelope epitopes that, when used as immunogens, would direct the immune response of an uninfected individual to the production of broadly neutralizing antibodies over a reasonable time frame by sequential immunizations. It remains to be seen whether this approach will be feasible.

PREVENTION OF HIV ACQUISITION

Education, counseling, and behavior modification are the cornerstones of any HIV prevention strategy. A major problem in the United States and elsewhere is that many infections are passed on by those who do not know that they are infected. Of the ~1.1 million persons in the United States who are HIV-infected, it is estimated that ~15% do not know their HIV status and approximately 23% of all new infections are transmitted by those people who are not aware that they are infected. In this regard, the CDC has recommended that HIV testing become part of routine medical care and that all individuals between the ages of 13 and 64 years be tested at least one time. These individuals should be informed of the testing and be tested without the need for written informed consent. Each individual can "opt out" of testing, but testing should otherwise be routinely administered. Individuals who are practicing high-risk behavior should be tested more often. In addition to identifying individuals who might benefit from cART, information gathered from such an approach should serve as the basis for behavior-modification programs, both for infected individuals who may be unaware of their HIV status and who could infect others and for uninfected individuals practicing high-risk behavior. The practice of "safer sex" is the most effective way for sexually active uninfected individuals to avoid contracting HIV infection and for infected individuals to avoid spreading infection. Abstinence from sexual relations is the only absolute way to prevent sexual transmission of HIV infection. However, for most individuals this is not feasible, and there are a number of relatively safe practices that can markedly decrease the chances of transmission of HIV infection. Partners engaged in monogamous sexual relationships who wish to be assured of safety should both be tested for HIV antibody. If both are negative, it must be understood that any divergence from monogamy puts both partners at risk; open discussion of the importance of honesty in such relationships should be encouraged. When the HIV status of either partner is not known, or when one partner is positive, there are a number of options. Use of condoms can markedly decrease the chance of HIV transmission. It should be remembered that condoms are not 100% effective in preventing transmission of HIV infection, and there is a ~10% failure rate of condoms used for contraceptive purposes. Most condom failures result from breakage or improper usage, such as not wearing the condom for the entire period of intercourse. Latex condoms are preferable, since virus has been shown to leak through natural skin condoms. Petroleum-based gels should never be used for lubrication of the condom, since they increase the likelihood of condom rupture. Some men who have sex with men practice exclusively fellatio as a "minimal-risk" activity compared with anal intercourse. It should be emphasized that receptive fellatio is not guaranteed safe sex, and although the incidence of transmission via fellatio is considerably less than that of rectal or vaginal intercourse, there has been documentation of transmission of HIV where receptive fellatio was the only sexual act performed (see "Transmission," above). Topical microbicides composed of gels containing antiretroviral drugs have been shown to be only modestly and variably efficacious in preventing acquisition of HIV infection in women engaging in vaginal intercourse. The considerable degree of variability in efficacy relates to the generally poor adherence of participants to the use of the intervention. Pre-exposure prophylaxis (PrEP) using oral antiretroviral drugs such as Truvada (tenofovir + emtricitabine) as a single daily pill in uninfected men who have sex with men and transgender women is highly efficacious in preventing acquisition of HIV infection. The degree of efficacy can be greater than 95% if subjects adhere strictly to the regimen. CDC estimates that approximately 1.2 million people in the United States are at "substantial risk" for HIV infection and should be counseled about PrEP. As of 2016, however, fewer than half of primary physicians and nurses have heard of PrEP.

Adult male circumcision, which has been shown to result in a 50–65% reduction in HIV acquisition in the circumcised subject, is

currently being pursued, particularly in developing nations, as a component of HIV prevention. The most effective way to prevent transmission of HIV infection among IDUs is to stop the use of injectable drugs. Unfortunately, that is extremely difficult to accomplish unless the individual enters a treatment program. For those who will not or cannot participate in a drug treatment program and who will continue to inject drugs, the avoidance of sharing of needles and other paraphernalia ("works") is the next best way to avoid transmission of infection. However, the cultural and social factors that contribute to the sharing of paraphernalia are complex and difficult to overcome. Under these circumstances, paraphernalia should be cleaned after each usage with a virucidal solution, such as undiluted sodium hypochlorite (household bleach). Needle exchange programs have been highly successful in decreasing HIV transmission among injection drug users without increasing the use of injection drugs. Oral PrEP also is effective in preventing acquisition of HIV infections among IDUs. It is important for IDUs to be tested for HIV infection and counseled to avoid transmission to their sexual partners. Prevention of transmission through blood or blood products and prevention of mother-to-child transmission are discussed in "Transmission," above.

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Section 15 Infections Due to RNA Viruses

198 Viral Gastroenteritis

Umesh D. Parashar, Roger I. Glass

Acute infectious gastroenteritis is a common illness that affects persons of all ages worldwide. It is a leading cause of death among children in developing countries, accounting for an estimated 0.6 million deaths each year, and is responsible for up to 10–12% of all hospitalizations among children in industrialized countries, including the United States. Elderly persons, especially those with debilitating health conditions, also are at risk of severe complications and death from acute gastroenteritis. Among healthy young adults, acute gastroenteritis is rarely fatal but incurs substantial medical and social costs, including those of time lost from work.

Several enteric viruses have been recognized as important etiologic agents of acute infectious gastroenteritis **(Table 198-1, Fig. 198-1)**. Although most viral gastroenteritis is caused by RNA viruses, the DNA viruses that are occasionally involved (e.g., adenovirus types 40 and 41) are included in this chapter. Illness caused by these viruses is characterized by the acute onset of vomiting and/or diarrhea, which may be accompanied by fever, nausea, abdominal cramps, anorexia, and malaise. As shown in **Table 198-2**, several features can help distinguish gastroenteritis caused by viruses from that caused by bacterial agents. However, the distinction based on clinical and epidemiologic parameters alone is often difficult, and laboratory tests are required to confirm the diagnosis.

HUMAN CALICIVIRUSES

Etiologic Agent The Norwalk virus is the prototype strain of a group of small (27–40 nm), nonenveloped, round, icosahedral viruses with relatively amorphous surface features on visualization by electron microscopy. Molecular cloning and characterization have demonstrated that the viruses have a single, positive-strand RNA genome ~7.5 kb in length and possess a single virion-associated protein—similar to that of typical caliciviruses—with a molecular mass of 60 kDa. On the basis of these molecular characteristics, these viruses are presently classified into two genera belonging to the family Caliciviridae: the *noroviruses* and the *sapoviruses* (previously called Norwalk-like viruses and Sapporo-like viruses, respectively). Human noroviruses can be classified into three genogroups: GI, GII, and GIV, which include 9, 22, and 1 genotype, respectively.

Epidemiology Infections with the Norwalk and related human caliciviruses are common worldwide, and most adults have antibodies to these viruses. Antibody is acquired at an earlier age in developing countries—a pattern consistent with the presumed fecal–oral mode of transmission. Infections occur year-round, although, in temperate climates, a distinct increase has been noted in cold-weather months. Noroviruses may be the most common infectious agents of mild gastroenteritis in the community and affect all age groups, whereas sapoviruses primarily cause gastroenteritis in children. Noroviruses also cause traveler's diarrhea, and outbreaks have occurred among military personnel deployed to various parts of the world. The limited data available indicate that norovirus may be the second most common viral agent (after rotavirus) among young children and the most common agent among older children and adults. In the United States, with the decline in severe rotavirus disease following implementation of a rotavirus vaccination program, norovirus has become the leading cause of medically attended gastroenteritis in young children. Noroviruses are also recognized as the major cause of epidemics of gastroenteritis worldwide. In the United States, ~50% of all reported outbreaks of gastroenteritis are caused by noroviruses.

Virus is transmitted predominantly by the fecal–oral route but is also present in vomitus. Because an inoculum with very few viruses can be infectious, transmission can occur by aerosolization, by contact with contaminated fomites, and by person-to-person contact. Viral shedding and infectivity are greatest during the acute illness, but challenge studies with Norwalk virus in volunteers indicate that viral antigen may be shed by asymptomatically infected persons and also by symptomatic persons before the onset of symptoms and for several weeks after the resolution of illness. Viral shedding can be prolonged in immunocompromised individuals.

Pathogenesis The exact sites and cellular receptors for attachment of viral particles have not been determined. Data suggest that carbohydrates that are similar to human histo-blood group antigens and are present on the gastroduodenal epithelium of individuals with the secretor phenotype may serve as ligands for the attachment of Norwalk virus. Additional studies must more fully elucidate norovirus–carbohydrate interactions, including potential strain-specific variations. After

TABLE 198-1 Viral Causes of Gastroenteritis Among Humans

VIRUS	FAMILY	GENOME	PRIMARY AGE GROUP AT RISK	CLINICAL SEVERITY	DETECTION ASSAYS
Group A rotavirus	Reoviridae	Double-strand segmented RNA	Children <5 years	+ + +	EM, EIA (commercial), PAGE, RT-PCR
Norovirus	Caliciviridae	Positive-sense single-strand RNA	All ages	+ +	EM, RT-PCR
Sapovirus	Caliciviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, RT-PCR
Astrovirus	Astroviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, EIA, RT-PCR
Adenovirus (mainly types 40 and 41)	Adenoviridae	Double-strand DNA	Children <5 years	+/+ +	EM, EIA (commercial), PCR

Abbreviations: EIA, enzyme immunoassay; EM, electron microscopy; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction; RT-PCR, reverse-transcription PCR.

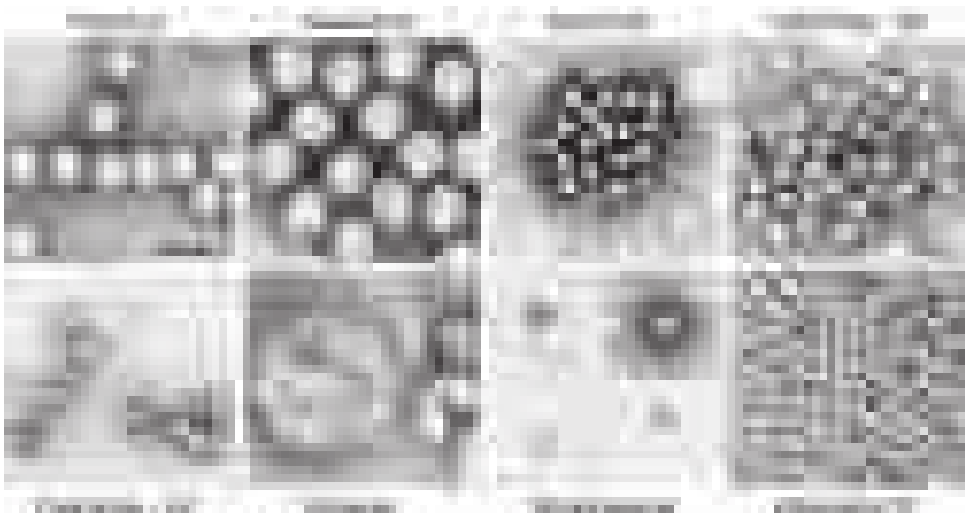

FIGURE 198-1 Viral agents of gastroenteritis. NV, norovirus; SV, sapovirus.

TABLE 198-2 Characteristics of Gastroenteritis Caused by Viral and Bacterial Agents

FEATURE	VIRAL GASTROENTERITIS	BACTERIAL GASTROENTERITIS
Setting	Incidence similar in developing and developed countries	More common in settings with poor hygiene and sanitation
Infectious dose	Low (10–100 viral particles) for most agents	High (>10^5 bacteria) for *Escherichia coli, Salmonella, Vibrio;* medium (10^2–10^5 bacteria) for *Campylobacter jejuni;* low (10–100 bacteria) for *Shigella*
Seasonality	In temperate climates, winter seasonality for most agents; year-round occurrence in tropical areas	More common in summer or rainy months, particularly in developing countries with a high disease burden
Incubation period	1–3 days for most agents; can be shorter for norovirus	1–7 days for common agents (e.g., *Campylobacter, E. coli, Shigella, Salmonella);* a few hours for bacteria producing preformed toxins (e.g., *Staphylococcus aureus*, *Bacillus cereus*)
Reservoir	Primarily humans	Depending on bacterial species, human (e.g., *Shigella, Salmonella*), animal (e.g., *Campylobacter*, *Salmonella, E. coli*), and water (e.g., *Vibrio*) reservoirs exist
Fever	Common with rotavirus and norovirus; uncommon with other agents	Common with agents causing inflammatory diarrhea (e.g., *Salmonella*, *Shigella*)
Vomiting	Prominent and can be the only presenting feature, especially in children	Common with bacteria producing preformed toxins; less prominent in diarrhea due to other agents
Diarrhea	Common; non-bloody in almost all cases	Prominent and occasionally bloody with agents causing inflammatory diarrhea
Duration	1–3 days for norovirus and sapovirus; 2–8 days for other viruses	1–2 days for bacteria producing preformed toxins; 2–8 days for most other bacteria
Diagnosis	This is often a diagnosis of exclusion in clinical practice. Commercial enzyme immunoassays are available for detection of rotavirus and adenovirus, but identification of other agents is limited to research and public health laboratories.	Fecal examination for leukocytes and blood is helpful in differential diagnosis. Culture of stool specimens, sometimes on special media, can identify several pathogens. Molecular techniques are useful epidemiologic tools but are not routinely used in most laboratories.
Treatment	Supportive therapy to maintain adequate hydration and nutrition should be given. Antibiotics and antimotility agents are contraindicated.	Supportive hydration therapy is adequate for most patients. Antibiotics are recommended for patients with dysentery caused by *Shigella* or diarrhea caused by *Vibrio cholerae* and for some patients with *Clostridium difficile* colitis.

the infection of volunteers, reversible lesions are noted in the upper jejunum, with broadening and blunting of the villi, shortening of the microvilli, vacuolization of the lining epithelium, crypt hyperplasia, and infiltration of the lamina propria by polymorphonuclear neutrophils and lymphocytes. The lesions persist for at least 4 days after the resolution of symptoms and are associated with malabsorption of carbohydrates and fats and a decreased level of brush-border enzymes. Adenylate cyclase activity is not altered. No histopathologic changes are seen in the stomach or colon, but gastric motor function is delayed, and this alteration is believed to contribute to the nausea and vomiting that are typical of this illness.

Clinical Manifestations Gastroenteritis caused by Norwalk and related human caliciviruses has a sudden onset following an average incubation period of 24 h (range, 12–72 h). The illness generally lasts 12–60 h and is characterized by one or more of the following symptoms: nausea, vomiting, abdominal cramps, and diarrhea. Vomiting is more prevalent among children, whereas a greater proportion of adults develop diarrhea. Constitutional symptoms are common, including headache, fever, chills, and myalgias. The stools are characteristically loose and watery, without blood, mucus, or leukocytes. White cell counts are generally normal; rarely, leukocytosis with relative lymphopenia may be observed. Death is a rare outcome and usually results from severe dehydration in vulnerable persons (e.g., elderly patients with debilitating health conditions).

Immunity Approximately 50% of persons challenged with Norwalk virus become ill and acquire short-term immunity against the infecting strain. Immunity to Norwalk virus appears to correlate inversely with level of antibody; i.e., persons with higher levels of preexisting antibody to Norwalk virus are more susceptible to illness. This observation suggests that some individuals have a genetic predisposition to illness. Specific ABO, Lewis, and secretor blood group phenotypes influence susceptibility to norovirus infection.

Diagnosis Cloning and sequencing of the genomes of Norwalk and several other human caliciviruses have allowed the development of assays based on polymerase chain reaction (PCR) for detection of virus in stool and vomitus. Virus-like particles (VLPs) produced by expression of capsid proteins in a recombinant baculovirus vector have been used to develop enzyme immunoassays (EIAs) for detection of virus in stool or a serologic response to a specific viral antigen. These newer diagnostic techniques are considerably more sensitive than previous detection methods, such as electron microscopy, immune electron microscopy, and EIAs based on reagents derived from humans. However, no currently available single assay can detect all human caliciviruses because of their great genetic and antigenic diversity. In addition, the assays are still cumbersome and are available primarily in research laboratories, although they are increasingly being adopted by public health laboratories for routine screening of fecal specimens from patients affected by outbreaks of gastroenteritis. Commercial EIA kits have limited sensitivity and usefulness in clinical practice and are of greatest utility in outbreaks, in which many specimens are tested and only a few need be positive to identify norovirus as the cause.

TREATMENT

Infections with Norwalk and Related Human Caliciviruses

The disease is self-limited, and oral rehydration therapy is generally adequate. If severe dehydration develops, IV fluid therapy is indicated. No specific antiviral therapy is available.

Prevention Epidemic prevention relies on situation-specific measures, such as control of contamination of food and water, exclusion of ill food handlers, and reduction of person-to-person spread through good personal hygiene and disinfection of contaminated fomites. The role of immunoprophylaxis is not clear, given the lack of long-term immunity from natural disease, but efforts to develop norovirus vaccines are ongoing. Vaccines based on VLPs are being tested in human volunteers. In a proof-of-concept trial, the efficacy of a monovalent GI.1 VLP vaccine was 47% among volunteers who received the vaccine intranasally and were then challenged with a homologous strain. In a second trial, norovirus disease severity was reduced in volunteers who received a bivalent G1.1/GII.4 VLP vaccine intramuscularly (with the GII.4 component including a consensus sequence from three different GII.4 strains) and were subsequently challenged with a GII.4 norovirus strain. While these initial data are encouraging, key issues to be further studied include the duration of protection and the level of heterotypic protection against antigenically distinct strains, particularly given the continuing and rapid natural evolution leading to the emergence of novel norovirus strains.

ROTAVIRUS

Etiologic Agent Rotaviruses are members of the family Reoviridae. The viral genome consists of 11 segments of double-strand RNA that is enclosed in a triple-layered, nonenveloped, icosahedral capsid 75 nm in diameter. Viral protein 6 (VP6), the major structural protein, is the target of commercial immunoassays and determines the group specificity of rotaviruses. There are seven major groups of rotavirus (A through G); human illness is caused primarily by group A and, to a much lesser extent, by groups B and C. Two outer-capsid proteins, VP7 (G-protein) and VP4 (P-protein), determine serotype specificity, induce neutralizing antibodies, and form the basis for binary classification of rotaviruses (G and P types). The segmented genome of rotavirus allows genetic reassortment (i.e., exchange of genome segments between viruses) during co-infection—a property that plays a role in viral evolution and that has been utilized in the development of reassortant animal/human rotavirus–based vaccines.

Epidemiology Worldwide, nearly all children are infected with rotavirus by 3–5 years of age. Neonatal infections are common but are often asymptomatic or mild, presumably because of protection by maternal antibody or breast milk. Compared with rotavirus disease in industrialized countries, disease in developing countries occurs at a younger age, is less seasonal, and is more frequently caused by uncommon rotavirus strains. Moreover, because of suboptimal access to hydration therapy, rotavirus is a leading cause of diarrheal death among children in the developing world, with the highest mortality rates among children in sub-Saharan Africa and southern Asia **(Fig. 198-2)**.

First infections after 3 months of age are likely to be symptomatic, and the incidence of disease peaks among children 4–23 months of age. Reinfections are common, but the severity of disease decreases with each repeat infection. Therefore, severe rotavirus infections are less common among older children and adults than among younger individuals. Nevertheless, rotavirus can cause illness in parents and caretakers of children with rotavirus diarrhea, immunocompromised persons, travelers, and elderly individuals and should be considered in the differential diagnosis of gastroenteritis among adults.

In tropical settings, rotavirus disease occurs year-round, with less pronounced seasonal peaks than in temperate settings, where rotavirus disease occurs predominantly during the cooler fall and winter months. Before the introduction of rotavirus vaccine in the United States, the rotavirus season each year began in the Southwest during the autumn and early winter (October through December) and migrated across the continent, peaking in the Northeast during late winter and spring (March through May). The reasons for this characteristic pattern are not clear but may be correlated with state-specific differences in birth rates, which could influence the rate of accumulation of susceptible infants after each rotavirus season. After the implementation of routine vaccination of U.S. infants against rotavirus in 2006, the characteristic prevaccine geotemporal pattern of U.S. rotavirus was dramatically altered, and these changes were accompanied by substantial declines in rotavirus detections by a national network of sentinel laboratories **(Fig. 198-3)**. During the seven seasons since vaccine introduction (spanning 2008–2014), the number of rotavirus detections has declined by 58–90% from the prevaccine baseline, and the annual proportion of

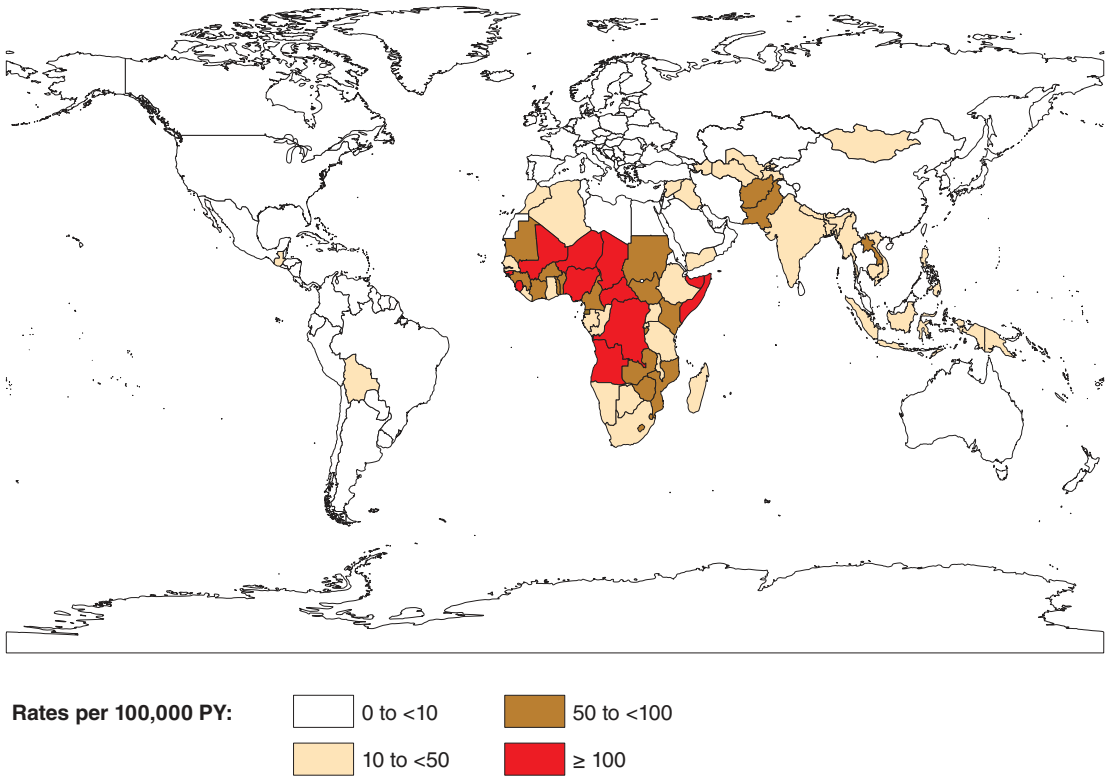

FIGURE 198-2 Rotavirus mortality rates by country, per 100,000 children <5 years of age. *(Reproduced with permission from JE Tate et al: Clin Infect Dis 62 (Suppl 2):S96, 2016.)*

rotavirus tests positive in postvaccine seasons has ranged from 4% to 11%, in contrast to a prevaccine baseline median of 26%. In addition, a pattern of biennial increases in rotavirus activity has emerged during postvaccine seasons.

During episodes of rotavirus-associated diarrhea, virus is shed in large quantities in stool (10^7–10^{12}/g). Viral shedding detectable by EIA usually subsides within 1 week but may persist for >30 days in immunocompromised individuals; it may be detected for longer periods by sensitive molecular assays, such as PCR. The virus is transmitted predominantly through the fecal–oral route. Spread through respiratory secretions, person-to-person contact, or contaminated environmental surfaces has been postulated to explain the rapid acquisition of antibody in the first 3 years of life, regardless of sanitary conditions.

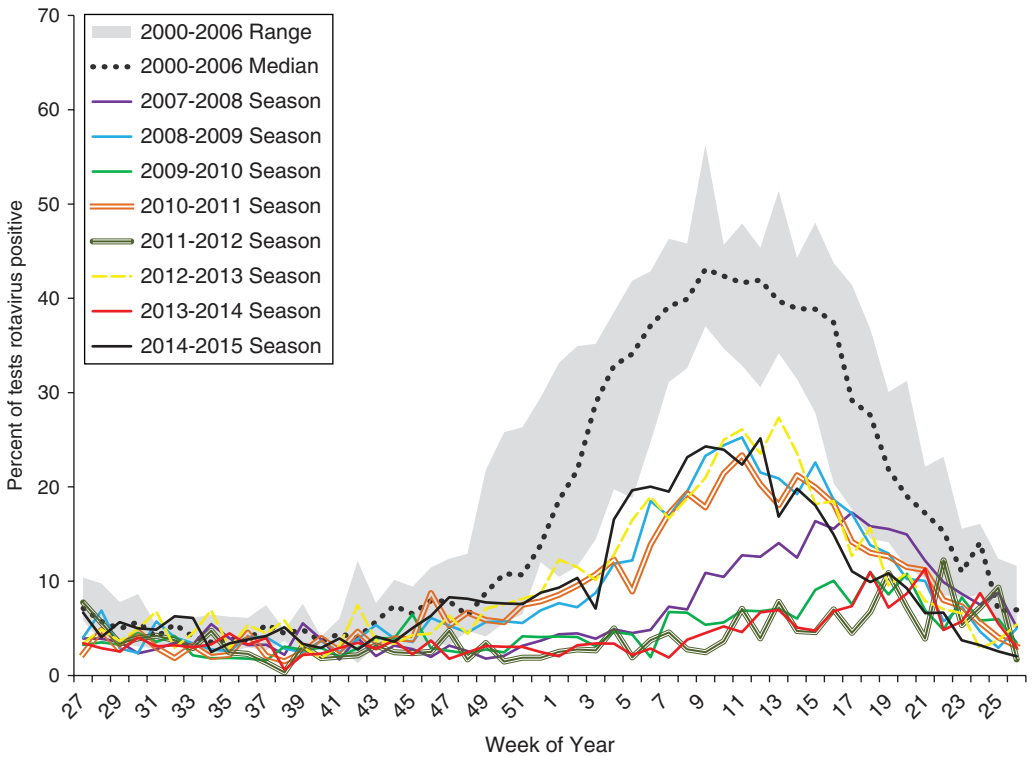

FIGURE 198-3 Percentage of rotavirus tests with positive results, by week of year, July–June, 2000–2015. The maximal or minimal percentage of rotavirus-positive tests for 2000–2006 may have occurred during any of the six baseline seasons. Data are from the National Respiratory and Enteric Virus Surveillance System. *(Adapted from Centers for Disease Control and Prevention, 2015.)*

At least 10 different G serotypes of group A rotavirus have been identified in humans, but only 5 types (G1 through G4 and G9) are common. While human rotavirus strains that possess a high degree of genetic homology with animal strains have been identified, animal-to-human transmission appears to be uncommon.

Group B rotaviruses have been associated with several large epidemics of severe gastroenteritis among adults in China since 1982 and have also been identified in India. Group C rotaviruses have been associated with a small proportion of pediatric gastroenteritis cases in several countries worldwide.

Pathogenesis Rotaviruses infect and ultimately destroy mature enterocytes in the villous epithelium of the proximal small intestine. The loss of absorptive villous epithelium, coupled with the proliferation of secretory crypt cells, results in secretory diarrhea. Brush-border enzymes characteristic of differentiated cells are reduced, and this change leads to the accumulation of unmetabolized disaccharides and consequent osmotic diarrhea. Studies in mice indicate that a nonstructural rotavirus protein, NSP4, functions as an enterotoxin and contributes to secretory diarrhea by altering epithelial cell function and permeability. In addition, rotavirus may evoke fluid secretion through activation of the enteric nervous system in the intestinal wall. Data indicate that rotavirus antigenemia and viremia are common among children with acute rotavirus infection, although the antigen and RNA levels in serum are substantially lower than those in stool.

Clinical Manifestations The clinical spectrum of rotavirus infection ranges from subclinical infection to severe gastroenteritis leading to life-threatening dehydration. After an incubation period of 1–3 days, the illness has an abrupt onset, with vomiting frequently preceding the onset of diarrhea. Up to one-third of patients may have a temperature of >39°C. The stools are characteristically loose and watery and only infrequently contain red or white cells. Gastrointestinal symptoms generally resolve in 3–7 days.

Respiratory and neurologic features in children with rotavirus infection have been reported, but causal associations have not been proven. Moreover, rotavirus infection has been associated with a variety of other clinical conditions (e.g., sudden infant death syndrome, necrotizing enterocolitis, intussusception, Kawasaki disease, and type 1 diabetes), but no causal relationship has been confirmed with any of these syndromes.

Rotavirus does not appear to be a major opportunistic pathogen in children with HIV infection. In severely immunodeficient children, rotavirus can cause protracted diarrhea with prolonged viral excretion and, in rare instances, can disseminate systemically. Persons who are immunosuppressed for bone marrow transplantation also are at risk for severe or even fatal rotavirus disease.

Immunity Protection against rotavirus disease is correlated with the presence of virus-specific secretory IgA antibodies in the intestine and, to some extent, the serum. Because virus-specific IgA production at the intestinal surface is short-lived, complete protection against disease is only temporary. However, each infection and subsequent reinfection confers progressively greater immunity; thus severe disease is most common among young children with first or second infections. Immunologic memory is believed to be important in the attenuation of disease severity upon reinfection.

Diagnosis Illness caused by rotavirus is difficult to distinguish clinically from that caused by other enteric viruses. Because large quantities of virus are shed in feces, the diagnosis can usually be confirmed by a wide variety of commercially available EIAs or by techniques for detecting viral RNA, such as gel electrophoresis, probe hybridization, or PCR.

TREATMENT

Rotavirus Infections

Rotavirus gastroenteritis can lead to severe dehydration. Thus appropriate treatment should be instituted early. Standard oral rehydration therapy is successful for most children who can take fluids by mouth, but IV fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting. The therapeutic roles of probiotics, bismuth subsalicylate, enkephalinase inhibitors, and nitazoxanide have been evaluated in clinical studies but are not clearly defined. Antibiotics and antimotility agents should be avoided. In immunocompromised children with chronic symptomatic rotavirus disease, orally administered immunoglobulins or colostrum may result in the resolution of symptoms, but the best choices regarding agents and their doses have not been well studied, and treatment decisions are often empirical.

Prevention Efforts to develop rotavirus vaccines were pursued because it was apparent—given the similar rates in less developed and industrialized nations—that improvements in hygiene and sanitation were unlikely to reduce disease incidence. The first rotavirus vaccine licensed in the United States in 1998 was withdrawn from the market within 1 year because it was linked with a low incidence of intussusception, a form of bowel obstruction.

In 2006, promising safety and efficacy results for two new rotavirus vaccines were reported from large clinical trials conducted in North America, Europe, and Latin America. Both vaccines are now recommended for routine immunization of all U.S. infants, and their use has rapidly led to a >70–80% decline in rotavirus hospitalizations and emergency department visits at hospitals across the United States. Somewhat unexpectedly, rotavirus vaccination of young infants has also resulted in the added benefit of declines in rotavirus disease among children who miss vaccination and even among older children and adults who are not eligible for vaccination in some settings. The reason is likely to be a reduction in community transmission of rotavirus because of vaccination—i.e., herd protection. In April 2009, the World Health Organization recommended the use of rotavirus vaccines in all countries worldwide. As of December 2016, a total of 82 countries, including 38 low-income countries in Africa and Asia, have incorporated rotavirus vaccine into their national childhood immunization programs. In Mexico and Brazil, a decline in deaths from childhood diarrhea following introduction of rotavirus vaccines has been documented. Postmarketing surveillance has identified a low risk of intussusception in some countries; however, the benefits of vaccination exceed the risks, and no changes in vaccine administration policy have been implemented.

The different epidemiology of rotavirus disease and the greater prevalence of co-infection with other enteric pathogens, of comorbidities, and of malnutrition in developing countries may adversely affect the performance of oral rotavirus vaccines, as is the case with oral vaccines against poliomyelitis, cholera, and typhoid in these regions. Therefore, evaluation of the efficacy of rotavirus vaccines in resource-poor settings of Africa and Asia was specifically recommended, and these trials have now been completed. As anticipated, the efficacy of rotavirus vaccines was moderate (50–65%) in these settings when compared with that in industrialized countries. Despite modest efficacy, routine use of rotavirus vaccines in low-income African countries with a heavy disease burden has yielded substantial public health benefits.

Several manufacturers in emerging markets, including India, China, Vietnam, Indonesia, and Brazil, are developing candidate rotavirus vaccines. In 2014, India licensed an indigenously manufactured rotavirus vaccine that showed 56% efficacy against severe rotavirus gastroenteritis during the first year of life. The vaccine has been recommended for inclusion in the Universal Immunization Program of India, and its use was initially implemented in four Indian states in 2015.

OTHER VIRAL AGENTS OF GASTROENTERITIS

Enteric *adenoviruses* of serotypes 40 and 41 belonging to subgroup F are 70- to 80-nm viruses with double-strand DNA that cause ~2–12% of all diarrhea episodes in young children. Unlike adenoviruses that cause respiratory illness, enteric adenoviruses are difficult to cultivate in cell lines, but they can be detected with commercially available EIAs. Adenovirus types 31 and 42–49 have been linked to diarrhea in HIV-infected and other immunocompromised persons.

Astroviruses are 28- to 30-nm viruses with a characteristic icosahedral structure and a positive-sense, single-strand RNA. At least seven serotypes have been identified, of which serotype 1 is most common. Astroviruses are primarily pediatric pathogens, causing ~2–10% of cases of mild to moderate gastroenteritis in children. The availability of simple immunoassays to detect virus in fecal specimens and of molecular methods to confirm and characterize strains will permit more comprehensive assessment of the etiologic role of these agents.

Toroviruses are 100- to 140-nm, enveloped, positive-strand RNA viruses that are recognized as causes of gastroenteritis in horses (Berne virus) and cattle (Breda virus). Their role as a cause of diarrhea in humans is still unclear, but studies from Canada have demonstrated associations between torovirus excretion and both nosocomial gastroenteritis and necrotizing enterocolitis in neonates. These associations require further evaluation.

Picobirnaviruses are small, bisegmented, double-strand RNA viruses that cause gastroenteritis in a variety of animals. Their role as primary causes of gastroenteritis in humans remains unclear, but several studies have found an association between picobirnaviruses and gastroenteritis in HIV-infected adults.

Several other viruses (e.g., enteroviruses, reoviruses, pestiviruses, and parvovirus B) have been identified in the feces of patients with diarrhea, but their etiologic role in gastroenteritis has not been proven. Diarrhea has also been noted as a manifestation of infection with recently recognized viruses that primarily cause severe respiratory illness: the severe acute respiratory syndrome–associated coronavirus (SARS-CoV), influenza A/H5N1 virus, and the current pandemic strain of influenza A/H1N1 virus.

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199 Enterovirus, Parechovirus, and Reovirus Infections

Jeffrey I. Cohen

ENTEROVIRUSES

CLASSIFICATION AND CHARACTERIZATION

Enteroviruses, members of the family Picornaviridae, are so designated because of their ability to multiply in the gastrointestinal tract. Despite their name, these viruses are not a prominent cause of gastroenteritis. Enteroviruses encompass more than 115 human serotypes: 3 serotypes of poliovirus, 21 serotypes of coxsackievirus A, 6 serotypes of coxsackievirus B, 28 serotypes of echovirus, enteroviruses 68–71, and multiple new enteroviruses (beginning with enterovirus 73) that have been identified by molecular techniques. Human enteroviruses have been reclassified into four species designated A–D. Echoviruses 22 and 23 have been reclassified as parechoviruses 1 and 2 on the basis of low nucleotide homology and differences in viral proteins. Enterovirus and parechovirus surveillance conducted in the United States by the Centers for Disease Control and Prevention (CDC) in 2009–2013 showed that the most common enteroviruses and parechoviruses were coxsackievirus A6 and human parechovirus 3, followed in frequency by echoviruses 11 and 18, coxsackieviruses A9 and B4, and echoviruses 6 and 30. Together, these eight viruses accounted for 58% of all isolates.

Human enteroviruses contain a single-stranded RNA genome surrounded by an icosahedral capsid comprising four viral proteins. These viruses have no lipid envelope and are stable in acidic environments, including the stomach. They are susceptible to chlorine-containing cleansers but resistant to inactivation by standard disinfectants (e.g., alcohol, detergents) and can persist for days at room temperature.

PATHOGENESIS AND IMMUNITY

Much of what is known about the pathogenesis of enteroviruses has been derived from studies of poliovirus infection. After ingestion, poliovirus is thought to infect epithelial cells in the mucosa of the gastrointestinal tract and then to spread to and replicate in the submucosal lymphoid tissue of the tonsils and Peyer's patches. The virus next spreads to the regional lymph nodes, a viremic phase ensues, and the virus replicates in organs of the reticuloendothelial system. In some cases, a second episode of viremia occurs and the virus replicates further in various tissues, sometimes causing symptomatic disease.

It is uncertain whether poliovirus reaches the central nervous system (CNS) during viremia or whether it also spreads via peripheral nerves. Since viremia precedes the onset of neurologic disease in humans, it has been assumed that the virus enters the CNS via the bloodstream. The poliovirus receptor is a member of the immunoglobulin superfamily. Poliovirus infection is limited to primates, largely because their cells express the viral receptor. Studies demonstrating the poliovirus receptor in the end-plate region of muscle at the neuromuscular junction suggest that, if the virus enters the muscle during viremia, it could travel across the neuromuscular junction up the axon to the anterior horn cells. Studies of monkeys and of transgenic mice expressing the poliovirus receptor show that, after IM injection, poliovirus does not reach the spinal cord if the sciatic nerve is cut. Taken together, these findings suggest that poliovirus can spread directly from muscle to the CNS by neural pathways.

Poliovirus can usually be cultured from the blood 3–5 days after infection, before the development of neutralizing antibodies. While viral replication at secondary sites begins to slow 1 week after infection, it continues in the gastrointestinal tract. Poliovirus is shed from the oropharynx for up to 3 weeks after infection and from the gastrointestinal tract for as long as 12 weeks; hypogammaglobulinemic patients can shed poliovirus for >20 years. During replication in the gastrointestinal tract, attenuated oral poliovirus can mutate, reverting to a more neurovirulent phenotype within a few days; however, additional mutations are probably required for full neurovirulence. One patient with hypogammaglobulinemia who had been infected 12 years earlier and was receiving IV immune globulin suddenly developed quadriplegia and respiratory muscle paralysis and died; analysis showed that the virus had reverted to a more wild-type sequence.

Humoral and secretory immunity in the gastrointestinal tract is important for the control of enterovirus infections. Enteroviruses induce specific IgM, which usually persists for <6 months, and specific IgG, which persists for life. Capsid protein VP1 is the predominant target of neutralizing antibody, which generally confers lifelong protection against subsequent disease caused by the same serotype but does not prevent infection or virus shedding. Enteroviruses also induce cellular immunity whose significance is uncertain. Patients with impaired cellular immunity are not known to develop unusually severe disease when infected with enteroviruses. In contrast, the severe infections in patients with agammaglobulinemia emphasize the importance of humoral immunity in controlling enterovirus infections. Disseminated enterovirus infections have occurred in hematopoietic cell transplant recipients. IgA antibodies are instrumental in reducing poliovirus replication in and shedding from the gastrointestinal tract. Breast milk contains IgA specific for enteroviruses and can protect humans from infection.

EPIDEMIOLOGY

Enteroviruses have a worldwide distribution. More than 50% of nonpoliovirus enterovirus infections and more than 90% of poliovirus infections are subclinical. When symptoms do

develop, they are usually nonspecific and occur in conjunction with fever; only a minority of infections are associated with specific clinical syndromes. The incubation period for most enterovirus infections ranges from 2 to 14 days but usually is <1 week.

Enterovirus infection is more common in socioeconomically disadvantaged areas, especially in those where conditions are crowded and in tropical areas where hygiene is poor. Infection is most common among infants and young children; serious illness develops most often during the first few days of life and in older children and adults. In developing countries, where children are infected at an early age, poliovirus infection has less often been associated with paralysis; in countries with better hygiene, older children and adults are more likely to be seronegative, become infected, and develop paralysis. Passively acquired maternal antibody reduces the risk of symptomatic infection in neonates. Young children are the most frequent shedders of enteroviruses and are usually the index cases in family outbreaks. In temperate climates, enterovirus infections occur most often in the summer and fall; no seasonal pattern is apparent in the tropics.

Most enteroviruses are transmitted primarily by the fecal-oral or oral-oral route. Patients are most infectious shortly before and after the onset of symptomatic disease, when virus is present in the stool and throat. The ingestion of virus-contaminated food or water also can cause disease. Certain enteroviruses (such as enterovirus 70, which causes acute hemorrhagic conjunctivitis) can be transmitted by direct inoculation from the fingers to the eye. Airborne transmission is important for some viruses that cause respiratory tract disease, such as coxsackievirus A21. Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. The transmission of enteroviruses through blood transfusions or insect bites has not been documented. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries.

CLINICAL FEATURES

Poliovirus Infection Most infections with poliovirus are asymptomatic. After an incubation period of 3–6 days, ~5% of patients present with a minor illness (abortive poliomyelitis) manifested by fever, malaise, sore throat, anorexia, myalgias, and headache. This condition usually resolves in 3 days. About 1% of patients present with aseptic meningitis (nonparalytic poliomyelitis). Examination of cerebrospinal fluid (CSF) reveals lymphocytic pleocytosis, a normal glucose level, and a normal or slightly elevated protein level; CSF polymorphonuclear leukocytes may be present early. In some patients, especially children, malaise and fever precede the onset of aseptic meningitis.

PARALYTIC POLIOMYELITIS The least common presentation is that of paralytic disease. After one or several days, signs of aseptic meningitis are followed by severe back, neck, and muscle pain and by the rapid or gradual development of motor weakness. In some cases the disease appears to be biphasic, with aseptic meningitis followed first by apparent recovery but then (1–2 days later) by the return of fever and the development of paralysis; this form is more common among children than among adults. Weakness is generally asymmetric, is proximal more than distal, and may involve the legs (most commonly); the arms; or the abdominal, thoracic, or bulbar muscles. Paralysis develops during the febrile phase of the illness and usually does not progress after defervescence. Urinary retention also may occur. Examination reveals weakness, fasciculations, decreased muscle tone, and reduced or absent reflexes in affected areas. Transient hyperreflexia sometimes precedes the loss of reflexes. Patients frequently report sensory symptoms, but objective sensory testing usually yields normal results. Bulbar paralysis may lead to dysphagia, difficulty in handling secretions, or dysphonia. Respiratory insufficiency due to aspiration, involvement of the respiratory center in the medulla, or paralysis of the phrenic or intercostal nerves may develop, and severe medullary involvement may lead to circulatory collapse. Most patients with paralysis recover some function weeks to months after infection. About two-thirds of patients have residual neurologic sequelae.

Paralytic disease is more common among older individuals, pregnant women, and persons exercising strenuously or undergoing trauma at the time of CNS symptoms. Tonsillectomy predisposes to bulbar poliomyelitis, and IM injections increase the risk of paralysis in the involved limb(s).

VACCINE-ASSOCIATED POLIOMYELITIS The risk of developing poliomyelitis after oral vaccination is estimated at 1 case per 2.5 million doses. The risk is ~2000 times higher among immunodeficient persons, especially persons with hypo- or agammaglobulinemia. Before 1997, an average of eight cases of vaccine-associated poliomyelitis occurred—in both vaccinees and their contacts—in the United States each year. With the change in recommendations first to a sequential regimen of inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV) in 1997 and then to an all-IPV regimen in 2000, the number of cases of vaccine-associated polio declined. From 1997 to 1999, six such cases were reported in the United States; no cases have been reported since 1999.

POSTPOLIO SYNDROME The *postpolio syndrome* presents as a new onset of weakness, fatigue, fasciculations, and pain with additional atrophy of the muscle group involved during the initial paralytic disease 20–40 years earlier. The syndrome is more common among women and with increasing time after acute disease. The onset is usually insidious, and weakness occasionally extends to muscles that were not involved during the initial illness. The prognosis is generally good; progression to further weakness is usually slow, with plateau periods of 1–10 years. The postpolio syndrome is thought to be due to progressive dysfunction and loss of motor neurons that compensated for the neurons lost during the original infection and not to persistent or reactivated poliovirus infection.

Other Enteroviruses An estimated 5–10 million cases of symptomatic disease due to enteroviruses other than poliovirus occur in the United States each year. Among neonates, enteroviruses are the most common cause of aseptic meningitis and nonspecific febrile illnesses. Certain clinical syndromes are more likely to be caused by certain serotypes (Table 199-1).

NONSPECIFIC FEBRILE ILLNESS (SUMMER GRIPPE) The most common clinical manifestation of enterovirus infection is a nonspecific febrile illness. After an incubation period of 3–6 days, patients present with an acute onset of fever, malaise, and headache. Occasional cases are associated with upper respiratory symptoms, and some cases include nausea and vomiting. Symptoms often last for 3–4 days, and most cases resolve in a week. While infections with other respiratory viruses occur more

TABLE 199-1 Manifestations Commonly Associated with Enterovirus Serotypes

MANIFESTATION	SEROTYPE(S) OF INDICATED VIRUS	
	COXSACKIEVIRUS	ECHOVIRUS (E) AND ENTEROVIRUS (Ent)
Acute hemorrhagic conjunctivitis	A24	E70
Aseptic meningitis	A2, 4, 7, 9, 10; B1–5	E4, 6, 7, 9, 11, 13, 16, 18, 19, 30, 33; Ent70, 71
Encephalitis	A9; B1–5	E3, 4, 6, 7, 9, 11, 18, 25, 30; Ent71
Exanthem	A4, 5, 6, 9, 10, 16; B1, 3–5	E4–7, 9, 11, 16–19, 25, 30; Ent71
Generalized disease of the newborn	B1–5	E4–7, 9, 11, 14, 16, 18, 19
Hand-foot-and-mouth disease	A5–7, 9, 10, 16; B1, 2, 5	Ent71
Herpangina	A1–10, 16, 22; B1–5	E6, 9, 11, 16, 17, 25, 30; Ent71
Myocarditis, pericarditis	A4, 9, 16; B1–5	E6, 9, 11, 22
Paralysis	A4, 7, 9; B1–5	E2–4, 6, 7, 9, 11, 18, 30; Ent70, 71
Pleurodynia	A1, 2, 4, 6, 9, 10, 16; B1–6	E1–3, 6, 7, 9, 11, 12, 14, 16, 19, 24, 25, 30
Pneumonia	A9, 16; B1–5	E6, 7, 9, 11, 12, 19, 20, 30; EntD68, 71

often from late fall to early spring, febrile illness due to enteroviruses frequently occurs in the summer and early fall.

GENERALIZED DISEASE OF THE NEWBORN Most serious enterovirus infections in infants develop during the first week of life, although severe disease can occur up to 3 months of age. Neonates often present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, and CSF pleocytosis. The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia. It may be difficult to distinguish neonatal enterovirus infection from bacterial sepsis, although a history of a recent virus-like illness in the mother provides a clue.

ASEPTIC MENINGITIS AND ENCEPHALITIS In children and young adults, enteroviruses are the cause of up to 90% of cases of aseptic meningitis in which an etiologic agent can be identified. Patients with aseptic meningitis typically present with an acute onset of fever, chills, headache, photophobia, and pain on eye movement. Nausea and vomiting also are common. Examination reveals meningismus without localizing neurologic signs; drowsiness or irritability also may be apparent. In some cases, a febrile illness may be reported that remits but returns several days later in conjunction with signs of meningitis. Other systemic manifestations may provide clues to an enteroviral cause, including diarrhea, myalgias, rash, pleurodynia, myocarditis, and herpangina. Examination of the CSF invariably reveals pleocytosis; the CSF cell count shows a shift from neutrophil to lymphocyte predominance within 1 day of presentation, and the total cell count does not exceed 1000/μL. The CSF glucose level is usually normal (in contrast to the low CSF glucose level in mumps), with a normal or slightly elevated protein concentration. Partially treated bacterial meningitis may be particularly difficult to exclude in some instances. Enteroviral meningitis is more common in summer and fall in temperate climates, while viral meningitis of other etiologies is more common in winter and spring. Symptoms ordinarily resolve within a week, although CSF abnormalities can persist for several weeks. Enteroviral meningitis is often more severe in adults than in children. Neurologic sequelae are rare, and most patients have an excellent prognosis.

Enteroviral encephalitis is much less common than enteroviral aseptic meningitis. Occasional highly inflammatory cases of enteroviral meningitis may be complicated by a mild form of encephalitis that is recognized on the basis of progressive lethargy, disorientation, and sometimes seizures. Less commonly, severe primary encephalitis may develop. An estimated 10–35% of cases of viral encephalitis are due to enteroviruses. Immunocompetent patients generally have a good prognosis.

Patients with hypogammaglobulinemia, agammaglobulinemia, or severe combined immunodeficiency may develop chronic meningitis or encephalitis; about half of these patients have a dermatomyositis-like syndrome, with peripheral edema, rash, and myositis. They may also have chronic hepatitis. Patients may develop neurologic disease while receiving immunoglobulin replacement therapy. Echoviruses (especially echovirus 11) are the most common pathogens in this situation.

Paralytic disease due to enteroviruses other than poliovirus occurs sporadically and is usually less severe than poliomyelitis. Most cases are due to enterovirus 70 or 71 or to coxsackievirus A7 or A9. Guillain-Barré syndrome is also associated with enterovirus infection. While earlier studies suggested a link between enteroviruses and chronic fatigue syndrome, most recent studies have not demonstrated such an association.

PLEURODYNIA (BORNHOLM DISEASE) Patients with pleurodynia present with an acute onset of fever and spasms of pleuritic chest or upper abdominal pain. Chest pain is more common in adults, and abdominal pain is more common in children. Paroxysms of severe, knifelike pain usually last 15–30 min and are associated with diaphoresis and tachypnea. Fever peaks within an hour after the onset of paroxysms and subsides when pain resolves. The involved muscles are tender to palpation, and a pleural rub may be detected. The white blood cell count and chest x-ray results are usually normal. Most cases are due to coxsackievirus B and occur during epidemics. Symptoms resolve in a few days, and recurrences are rare. Treatment includes the administration of nonsteroidal anti-inflammatory agents or the application of heat to the affected muscles.

MYOCARDITIS AND PERICARDITIS Enteroviruses are estimated to cause up to one-third of cases of acute myocarditis. Coxsackievirus B and its RNA have been detected in pericardial fluid and myocardial tissue in some cases of acute myocarditis and pericarditis. Most cases of enteroviral myocarditis or pericarditis occur in newborns, adolescents, or young adults. More than two-thirds of patients are male. Patients often present with an upper respiratory tract infection that is followed by fever, chest pain, dyspnea, arrhythmias, and occasionally heart failure. A pericardial friction rub is documented in half of cases, and the electrocardiogram shows ST-segment elevations or ST- and T-wave abnormalities. Serum levels of myocardial enzymes are often elevated. Neonates commonly have severe disease, while most older children and adults recover completely. Up to 10% of cases progress to chronic dilated cardiomyopathy. Chronic constrictive pericarditis also may be a sequela.

EXANTHEMS Enterovirus infection is the leading cause of exanthems in children in the summer and fall. While exanthems are associated with many enteroviruses, certain types have been linked to specific syndromes. Echoviruses 9 and 16 have frequently been associated with exanthem and fever. Rashes may be discrete or confluent, beginning on the face and spreading to the trunk and extremities. Echovirus 9 is the most common cause of a rubelliform (discrete) rash. Unlike the rash of rubella, the enteroviral rash occurs in the summer and is not associated with lymphadenopathy. Roseola-like rashes develop after defervescence, with macules and papules on the face and trunk. The Boston exanthem, caused by echovirus 16, is a roseola-like rash. A variety of other rashes have been associated with enteroviruses, including erythema multiforme **(see Fig. A1-24)** and vesicular, urticarial, petechial, bullous, or purpuric lesions. Enanthems also occur, including lesions that resemble the Koplik's spots seen with measles **(see Fig. A1-2)**.

HAND-FOOT-AND-MOUTH DISEASE (FIG. 199-1) After an incubation period of 4–6 days, patients with hand-foot-and-mouth disease present with fever, anorexia, and malaise; these manifestations are followed by the development of sore throat and vesicles **(see Fig. A1-22)** on the buccal mucosa and often on the tongue and then by the appearance of tender vesicular lesions on the dorsum of the hands, sometimes with involvement of the palms. The vesicles may form bullae and quickly ulcerate. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars, and one-third have a rash on the feet (including the soles) or on the buttocks. Generalized rashes also have been reported. The disease is highly infectious, with attack rates of close to 100% among young children. The lesions usually resolve in 1 week. Most cases are due to coxsackievirus A16 or enterovirus 71.

An epidemic of enterovirus 71 infection in Taiwan in 1998 resulted in thousands of cases of hand-foot-and-mouth disease or herpangina (see below). Severe complications included CNS disease, myocarditis, and pulmonary hemorrhage. About 90% of those who died were children ≤5 years old, and death was associated with pulmonary edema or pulmonary hemorrhage. CNS disease included aseptic meningitis, flaccid paralysis (similar to that seen in poliomyelitis), and rhombencephalitis with myoclonus and tremor or ataxia. The mean age of patients with CNS complications was 2.5 years, and MRI in cases with encephalitis usually showed brain-stem lesions. Follow-up of children at 6 months showed persistent dysphagia, cranial nerve palsies, hypoventilation, limb weakness, and atrophy; at 3 years, persistent neurologic sequelae were documented, with delayed development and impaired cognitive function.

Yearly epidemics of enterovirus 71 infection have occurred in China since 2008, with hundreds of thousands of cases and hundreds of deaths each year. Infections have been associated with fever, rash, brain-stem encephalitis with myoclonic jerks, and limb trembling; some cases have progressed to seizures and coma. Lung findings include pulmonary

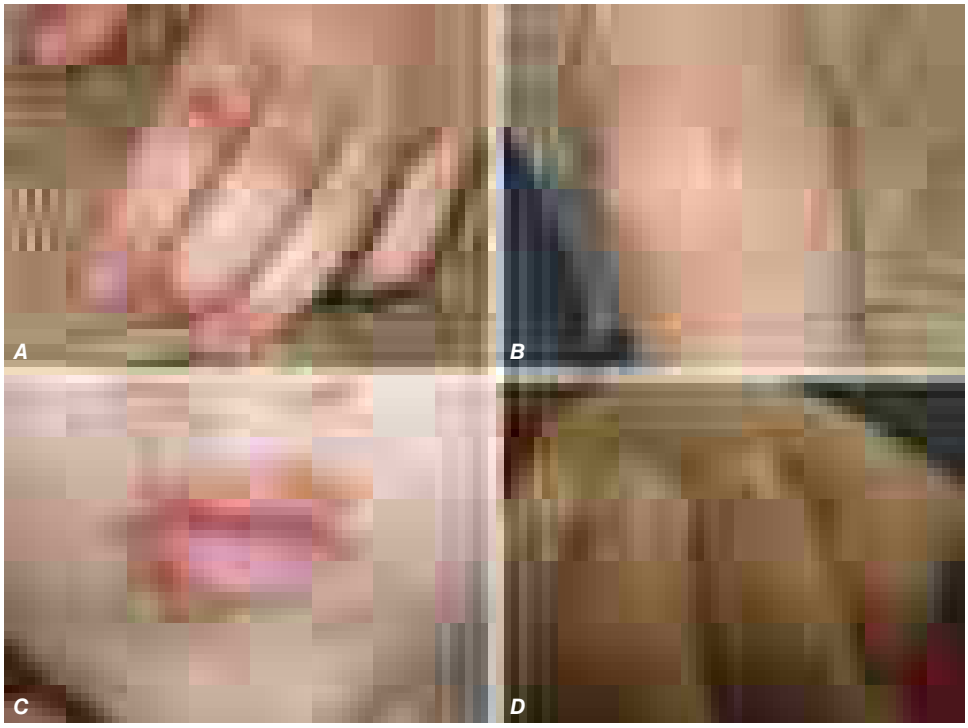

FIGURE 199-1 Vesicular eruptions of the hand (*A*), knee (*B*), and mouth (*C*) of a 6-year-old boy with coxsackievirus A6 infection. Several of his fingernails were shed 2 months later (*D*). *(Images reprinted courtesy of Centers for Disease Control and Prevention/Emerging Infectious Diseases.)*

edema and hemorrhage. While the level of creatine kinase MB is sometimes elevated, myocardial necrosis generally is not found.

Cyclic epidemics occur every 2–3 years in other Asian countries. However, the virus circulates at lower rates in the United States, Europe, and Africa. In the United States, hand-foot-and-mouth disease is most commonly associated with coxsackievirus A16. Between November 2011 and February 2012, outbreaks of hand-foot-and-mouth disease due to coxsackievirus A6 occurred in several U.S. states, and 19% of the affected persons were hospitalized.

HERPANGINA Herpangina is usually caused by coxsackievirus A and presents as acute-onset fever, sore throat, odynophagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate. The lesions can persist for weeks; are present on the soft palate, anterior pillars of the tonsils, and uvula; and are concentrated in the posterior portion of the mouth. In contrast to herpes stomatitis, enteroviral herpangina is not associated with gingivitis. Acute lymphonodular pharyngitis associated with coxsackievirus A10 presents as white or yellow nodules surrounded by erythema in the posterior oropharynx. The lesions do not ulcerate.

ACUTE HEMORRHAGIC CONJUNCTIVITIS Patients with acute hemorrhagic conjunctivitis present with an acute onset of severe eye pain, blurred vision, photophobia, and watery discharge from the eye. Examination reveals edema, chemosis, and subconjunctival hemorrhage and often shows punctate keratitis and conjunctival follicles as well **(Fig. 199-2)**. Preauricular adenopathy is often found. Epidemics and nosocomial spread have been associated with enterovirus 70 and coxsackievirus A24. Recent outbreaks have been due to coxsackievirus A24 in China and India (2010), Japan (2011), and Thailand (2014). Systemic symptoms, including headache and fever, develop in 20% of cases, and recovery is usually complete in 10 days. The sudden onset and short duration of the illness help to distinguish acute hemorrhagic conjunctivitis from other ocular infections, such as those due to adenovirus and *Chlamydia trachomatis*. Paralysis has been associated with some cases of acute hemorrhagic conjunctivitis due to enterovirus 70 during epidemics.

OTHER MANIFESTATIONS Enteroviruses are an infrequent cause of childhood pneumonia and the common cold. From mid-August 2014 to January 2015, enterovirus D68 infection was confirmed in more than 1000 persons with mild to severe respiratory illnesses in 49 U.S. states. Nearly all reported cases were in children, many of whom had asthma. Enterovirus D68 has been detected in upper respiratory tract samples and very rarely in stool and serum from patients with acute flaccid myelitis. While epidemiologic evidence in 2014 suggested that enterovirus D68 may be associated with paralysis, the link was not definitively established, and more recent cases of acute flaccid myelitis in children generally have not been associated with enterovirus D68. Coxsackievirus B has been isolated at autopsy from the pancreas of a few children presenting with type 1 diabetes mellitus; however, most attempts to isolate the virus have been unsuccessful. Other diseases that have been associated with enterovirus infection include parotitis, bronchitis, bronchiolitis, croup, infectious lymphocytosis, polymyositis, acute arthritis, and acute nephritis.

DIAGNOSIS

Isolation of enterovirus in cell culture is the traditional diagnostic procedure. While cultures of stool, nasopharyngeal, or throat samples from patients with enterovirus diseases are often positive, isolation of the virus from these sites does not prove that it is directly associated with disease because these sites are frequently colonized for weeks in patients with subclinical infections. Isolation of virus from the throat is more likely to be associated with disease than is isolation from the stool since virus is shed for shorter periods from the throat. Cultures of CSF, serum, fluid from body cavities, or tissues are positive less frequently, but a positive result is indicative of disease caused by enterovirus. In some cases, the virus is isolated only from the blood or only from the CSF; therefore, it is important to culture multiple sites. Cultures are more likely to be positive earlier than later in the course of infection. Most human enteroviruses can be detected within a week after inoculation of cell cultures. Cultures may be negative because of the presence of neutralizing antibody, lack of susceptibility of the cells used, or inappropriate handling of the specimen. Coxsackievirus A may require inoculation into special cell-culture lines or into suckling mice.

Identification of the enterovirus serotype is useful primarily for epidemiologic studies and, with a few exceptions, has little clinical utility.

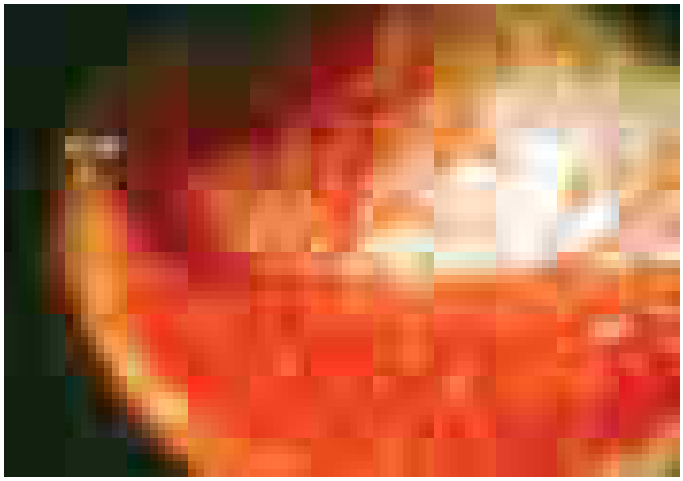

FIGURE 199-2 Acute hemorrhagic conjunctivitis due to enterovirus 70. *(Image reprinted courtesy of Jerri Ann Jenista, MD.)*

It is important to identify serious infections with enterovirus during epidemics and to distinguish the vaccine strain of poliovirus from the other enteroviruses in the throat or in the feces. Stool and throat samples for culture as well as acute- and convalescent-phase serum specimens should be obtained from all patients with suspected poliomyelitis. In the absence of a positive CSF culture, a positive culture of stool obtained within the first 2 weeks after the onset of symptoms is most often used to confirm the diagnosis of poliomyelitis. If poliovirus infection is suspected, two or more fecal and throat swab samples should be obtained at least 1 day apart and cultured for enterovirus as soon as possible. If poliovirus is isolated, it should be sent to the CDC for identification as either wild-type or vaccine virus.

Reverse-transcription polymerase chain reaction (PCR) has been used to amplify viral nucleic acid from CSF, serum, urine, stool, conjunctiva, throat swabs, and tissues. A pan-enterovirus PCR assay can detect all human enteroviruses. With the proper controls, PCR of the CSF is highly sensitive (70–100%) and specific (>80%) and is more rapid than culture. PCR of the CSF is less likely to be positive when patients present ≥3 days after the onset of meningitis or with enterovirus 71 infection; in these cases, PCR of throat or rectal swabs—although less specific than PCR of CSF—should be considered.

PCR of serum is also highly sensitive and specific in the diagnosis of disseminated disease. PCR may be particularly helpful for the diagnosis and follow-up of enterovirus disease in immunodeficient patients receiving immunoglobulin therapy, whose viral cultures may be negative. Antigen detection is less sensitive than PCR.

Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstration of seroconversion may be useful in rare cases for confirmation of culture results, but serologic testing is usually limited to epidemiologic studies. Serum should be collected and frozen soon after the onset of disease and again ~4 weeks later. Measurement of neutralizing titers is the most accurate method for antibody determination; measurement of complement-fixation titers is usually less sensitive. Titers of virus-specific IgM are elevated in both acute and chronic infection.

TREATMENT

Enterovirus Infections

Most enterovirus infections are mild and resolve spontaneously; however, intensive supportive care may be needed for cardiac, hepatic, or CNS disease. IV, intrathecal, or intraventricular immunoglobulin has been used with apparent success in some cases for the treatment of chronic enterovirus meningoencephalitis and dermatomyositis in patients with hypogammaglobulinemia or agammaglobulinemia. The disease may stabilize or resolve during therapy; however, some patients decline inexorably despite therapy. IV immunoglobulin often prevents severe enterovirus disease in these patients. IV administration of immunoglobulin with high titers of antibody to the infecting virus has been used in some cases of life-threatening infection in neonates, who may not have maternally acquired antibody. In one trial involving neonates with enterovirus infections, immunoglobulin containing very high titers of antibody to the infecting virus reduced rates of viremia; however, the study was too small to show a substantial clinical benefit. The level of enteroviral antibodies varies with the immunoglobulin preparation. A phase 2 trial of pleconaril for neonatal enterovirus sepsis showed that the time to serum PCR negativity was reduced and the survival rate increased in newborns who had confirmed enterovirus infections and were treated with the drug, although in this small study the differences did not reach significance; as of this writing, the drug is not available on a compassionate-use basis. Pocapavir and vapendavir are also being tested for enterovirus infections. Glucocorticoids are contraindicated.

Good hand-washing practices and the use of gowns and gloves are important in limiting nosocomial transmission of enteroviruses during epidemics. Enteric precautions are indicated for 7 days after the onset of enterovirus infections. Inactivated enterovirus 71 vaccines have been shown to be efficacious in large clinical trials; they are not yet licensed.

PREVENTION AND ERADICATION OF POLIOVIRUS

(See also Chap. 118) After a peak of 57,879 cases of poliomyelitis in the United States in 1952, the introduction of IPV in 1955 and of OPV in 1961 ultimately eradicated disease due to wild-type poliovirus in the Western Hemisphere. Such disease has not been documented in the United States since 1979, when cases occurred among religious groups who had declined immunization. In the Western Hemisphere, paralysis due to wild-type poliovirus was last documented in 1991.

In 1988, when ~350,000 cases of polio occurred in 125 countries, the World Health Organization adopted a resolution to eradicate poliomyelitis by the year 2000. From 1988 to 2001, the number of cases worldwide decreased by >99%, with only 496 confirmed cases reported in 2001. Wild-type poliovirus type 2 has not been detected in the world since 1999 and wild-type poliovirus type 3 has not been circulating since 2012. The Americas were certified free of indigenous wild-type poliovirus transmission in 1994, the Western Pacific Region in 2000, the European Region in 2002, and Southeast Asia in 2014. After the nadir of 496 cases in 2001, 21 countries that had previously been free of polio reported cases imported from 6 polio-endemic countries in 2002–2005. By 2006, polio transmission had been reduced in most of these 21 countries. In 2016, there were 37 cases of wild-type polio; all of these cases were from Nigeria, Pakistan, and Afghanistan, the only countries where polio remains endemic **(Table 199-2)**. In 2017, wild-type poliovirus was detected in many sewage samples in Pakistan. As of early 2018, 22 cases of wild-type polio occurring in 2017 had been reported in Afghanistan and Pakistan. Polio is a source of concern for unimmunized or partially immunized travelers. While importation of poliovirus accounted for nearly 50% of cases in 2013 and also occurred in 2014, it has not been reported recently. Clearly, global eradication of polio is necessary to eliminate the risk of importation of wild-type virus. Outbreaks are thought to have been facilitated by suboptimal rates of vaccination, isolated pockets of unvaccinated children, poor sanitation and crowding, improper vaccine-storage conditions, and a reduced level of response to one of the serotypes in the vaccine. While the global eradication campaign has markedly reduced the number of cases of endemic polio, doubts have been raised as to whether eradication is a realistic goal, given the large number of asymptomatic infections and the political instability in developing countries.

Use of OPV, especially in areas with low vaccination rates, has been associated with vaccine-derived polio due to mutations that result in restoration of viral fitness and neurovirulence during prolonged replication in individuals or person-to-person transmission. Vaccine-derived polio was recognized in Egypt in 1983–1993, and hundreds of cases have been reported in many countries, including 385 cases in Nigeria in 2005–2012. Epidemics have been rapidly terminated after intensive vaccination with OPV. In 2005, a case of vaccine-derived polio occurred in an unvaccinated U.S. woman returning from a visit to Central and South America. In the same year, an unvaccinated immunocompromised infant in Minnesota was found to be shedding vaccine-derived poliovirus; further investigation identified 4 of 22 infants in the same community who were shedding the virus. All 5 infants were asymptomatic. These outbreaks emphasize the need for maintaining high levels of vaccine coverage and continued surveillance for circulating virus. From 2010 to 2014, 60–70 cases of vaccine-derived polio were reported annually. In 2016, only 5 cases were reported

TABLE 199-2 Laboratory-Confirmed Cases of Poliomyelitis in 2016

COUNTRY	ENDEMIC CASES	VACCINE-DERIVED CASES
Pakistan	20	1
Afghanistan	13	—
Nigeria	4	1
Laos	—	3
Total	37	5

(in Nigeria, Pakistan, and Laos). As of early 2018, 92 cases of vaccine-derived polio occurring in 2017 had been reported in Syria and the Democratic Republic of the Congo. Of the 721 cases of vaccine-derived polio reported from January 2006 to May 2016, 94% were due to type 2 virus. Cessation of vaccination with type 2 OPV should reduce the number of these cases further.

IPV is used in most industrialized countries and OPV in most developing countries, including those in which polio still is or recently was endemic. While IM injections of other vaccines (live or attenuated) can be given concurrently with OPV, unnecessary IM injections should be avoided during the first month after OPV vaccination because they increase the risk of vaccine-associated paralysis. Since 1988, an enhanced-potency inactivated poliovirus vaccine has been available in the United States.

After several doses of OPV alone, the seropositivity rate for individual poliovirus serotypes may still be suboptimal for children in developing countries; one or more supplemental doses of IPV can increase the rate of seropositivity for these serotypes. Against a given serotype, monovalent OPV containing only that serotype is more immunogenic than trivalent vaccine because of a lack of interference from other serotypes. Given the eradication of wild-type poliovirus type 2 and the establishment of OPV type 2 as the primary cause of vaccine-derived polio, bivalent OPV (types 1 and 3), which had been shown to be superior to trivalent OPV in inducing antibodies to types 1 and 3, replaced trivalent OPV vaccine in April 2016. Addition of at least one dose of trivalent IPV after immunization with bivalent OPV will reduce the risk of vaccine-derived polio associated with type 2 virus and enhance immunity to poliovirus types 1 and 3. Accordingly, in 2016, ~90% of countries included trivalent IPV in their immunization schedules. As the frequency of wild-type polio declines and reports of polio associated with circulating vaccine-derived viruses increase, the World Health Organization is investigating whether IPV can be produced from OPV strains that require less biocontainment, ultimately replacing OPV.

OPV and IPV induce antibodies that persist for at least 5 years. Both vaccines induce IgG and IgA antibodies. Compared with recipients of IPV, recipients of OPV shed less virus and less frequently develop reinfection with wild-type virus after exposure to poliovirus. Although IPV is safe and efficacious, OPV offers the advantages of ease of administration, lower cost, and induction of intestinal immunity resulting in a reduction in the risk of community transmission of wild-type virus. Because of progress toward global eradication of polio and the continued occurrence of cases of vaccine-associated polio, an all-IPV regimen was recommended in 2000 for childhood poliovirus vaccination in the United States, with vaccine administration at 2, 4, and 6–18 months and 4–6 years of age. The risk of vaccine-associated polio should be discussed before OPV is administered. Recommendations for vaccination of adults are listed in **Table 199-3**.

There are concerns about discontinuing vaccination in the event that endemic spread of poliovirus is eliminated. Among the reasons for these concerns are that poliovirus is shed from some immunocompromised persons for >25 years, that vaccine-derived poliovirus can circulate and cause disease, and that wild-type poliovirus is present in research laboratories and vaccine manufacturing facilities. Antivirals and monoclonal antibodies are in development to reduce or terminate shedding of poliovirus by long-term virus excretors. Pocapavir was recently shown to reduce shedding of OPV type 1 in a clinical trial, but rapid development of resistance with virus transmission, despite reduced shedding, indicates that combination therapy with antivirals and/or monoclonal antibodies will be needed.

TABLE 199-3 Recommendations for Poliovirus Vaccination of Adults

1. Most adults in the United States have little risk for exposure to polioviruses, and most are immune as a result of vaccination during childhood. Vaccination is recommended for those at greater risk for exposure to polioviruses than the general population:
   a. travelers to areas or countries where polio is epidemic or endemic or where wild-type virus is known to have been circulating in the past year;
   b. members of communities or specific population groups with disease caused by wild-type polioviruses;
   c. laboratory workers who handle specimens that might contain polioviruses; and
   d. health care workers who have close contact with patients who might be excreting wild-type polioviruses.
2. Adults who are unvaccinated or whose vaccination status is unknown and who are at increased risk should receive three doses of IPV. Two doses of IPV should be administered at intervals of 4–8 weeks; a third dose should be administered 6–12 months after the second.
3. Adults who have had a primary series of polio vaccine and who are at increased risk should receive another dose of IPV. Currently, data do not indicate a need for more than a single lifetime booster dose with IPV for adults. However, adults who will be in a polio-infected or polio-exporting country for >4 weeks and whose booster dose of polio vaccine was administered >1 year earlier should receive an additional booster dose of vaccine before departing for that country.

Abbreviation: IPV, inactivated poliovirus vaccine.

Source: Modified from Centers for Disease Control and Prevention: MMWR Recomm Rep 46(RR-3):1, 1997; and Wallace et al: MMWR Morb Mortal Wkly Rep 63(27):591, 2014.

PARECHOVIRUSES

Human parechoviruses (HPeVs), like enteroviruses, are members of the family Picornaviridae. The 16 serotypes of HPeV commonly cause infections in early childhood. Infections with HPeV type 1 (HPeV-1) occur throughout the year, while other parechovirus infections occur more commonly in summer and fall. Infections with HPeVs present similarly to those due to enteroviruses and may cause generalized disease of the newborn, aseptic meningitis, encephalitis, seizures, transient paralysis, exanthems, respiratory tract disease, rash, hepatitis, and gastroenteritis. While HPeV-1 is the most common serotype and generally causes mild disease, deaths of infants in the United States have been associated with HPeV-1, HPeV-3, and HPeV-6. HPeVs can be isolated from the same sites as enteroviruses, including the nasopharynx, stool, and respiratory tract secretions. PCR using pan-enterovirus primers does not detect HPeVs, and while PCR assays are performed by the CDC and research laboratories, many commercial laboratories do not perform the test. Pleconaril is not active against parechoviruses.

REOVIRUSES

Reoviruses are double-stranded RNA viruses encompassing three serotypes. Serologic studies indicate that most humans are infected with reoviruses during childhood. Most infections either are asymptomatic or cause mild upper respiratory tract symptoms. Reovirus is considered a rare cause of mild gastroenteritis or meningitis in infants and children. Speculation regarding an association of reovirus type 3 with idiopathic neonatal hepatitis and extrahepatic biliary atresia is based on an elevated prevalence of antibody to reovirus in some affected patients and the detection of viral RNA by PCR in hepatobiliary tissues in some studies. New orthoreoviruses have been associated with human disease—e.g., Melaka and Kampar viruses with fever and acute respiratory disease in Malaysia and Nelson Bay virus with acute respiratory disease in a traveler from Bali.

FURTHER READING

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200 Measles (Rubeola)

Kaitlin Rainwater-Lovett, William J. Moss

DEFINITION

Measles is a highly contagious viral disease that is characterized by a prodromal illness of fever, cough, coryza, and conjunctivitis followed by the appearance of a generalized maculopapular rash. Before the widespread use of measles vaccines, it was estimated that measles caused >2 million deaths worldwide each year.

GLOBAL CONSIDERATIONS

Remarkable progress has been made in reducing global measles incidence and mortality rates through measles vaccination. In the Americas, intensive vaccination and surveillance efforts—based in part on the successful Pan American Health Organization strategy of periodic nationwide measles vaccination campaigns (supplementary immunization activities, or SIAs)—and high levels of routine measles vaccine coverage interrupted endemic transmission of measles virus. The World Health Organization's (WHO's) Region of the Americas was declared to have eliminated measles in September 2016—the first region in the world to do so. In the United States, high-level coverage with two doses of measles vaccine eliminated endemic measles virus transmission in 2000. More recently, progress has been made in reducing measles incidence and mortality rates in sub-Saharan Africa and Asia as a consequence of increasing routine measles vaccine coverage and provision of a second dose of measles vaccine through mass measles vaccination campaigns and childhood immunization programs.

In 2003, the World Health Assembly endorsed a resolution urging member countries to reduce the number of deaths attributed to measles by 50% (compared with 1999 estimates) by the end of 2005. This target was met. Global measles mortality continued to decline and, by 2015, there were an estimated 134,200 deaths due to measles (uncertainty bounds: 74,400 and 353,600 deaths). These achievements attest to the enormous public-health significance of measles vaccination. However, recent large outbreaks of measles in Europe and Africa illustrate the challenges faced in sustaining measles control: in these outbreaks, measles was imported into countries that had eliminated indigenous transmission of measles virus.

The Measles and Rubella Initiative, a partnership led by the American Red Cross, the United Nations Foundation, UNICEF, the U.S. Centers for Disease Control and Prevention (CDC), and the WHO, is playing an important role in reducing global measles incidence and mortality rates. Since its inception in 2001, the Initiative has provided governments and communities in more than 80 countries with technical and financial support for routine immunization activities, mass vaccination campaigns, and disease surveillance systems. Through its 2012–2020 Global Measles and Rubella Strategic Plan, the Initiative aimed to reduce measles deaths by 95% (compared with year 2000 estimates) by 2015 and to eliminate measles from at least five of the six WHO regions by 2020. The mortality reduction goal was not met, but an increasing number of countries have introduced a second dose of measles-containing vaccine into their routine immunization schedule. All six WHO regions have adopted goals for measles elimination by 2020 or earlier, and global measles eradication is likely to become a public health goal in the near future.

ETIOLOGY

Measles virus is a spherical, nonsegmented, single-stranded, negative-sense RNA virus and a member of the *Morbillivirus* genus in the family Paramyxoviridae. Measles was originally a zoonotic infection, arising from animal-to-human transmission of an ancestral morbillivirus ~10,000 years ago, when human populations had attained sufficient size to sustain virus transmission. Although RNA viruses typically have high mutation rates, measles virus is considered to be an antigenically monotypic virus; i.e., the surface proteins responsible for inducing protective immunity have retained their antigenic structure across time and distance. The public health significance of this stability is that measles vaccines developed decades ago from a single strain of measles virus remain protective worldwide. Measles virus is killed by ultraviolet light and heat, and attenuated measles vaccine viruses retain these characteristics, necessitating a cold chain for vaccine transport and storage.

EPIDEMIOLOGY

Measles virus is one of the most highly contagious directly transmitted pathogens. Outbreaks can occur in populations in which <10% of persons are susceptible. Chains of transmission are common among household contacts, school-age children, and health care workers. There are no latent or persistent measles virus infections that result in prolonged contagiousness, nor are there animal reservoirs for the virus. Thus, measles virus can be maintained in human populations only by an unbroken chain of acute infections, which requires a continuous supply of susceptible individuals. Newborns become susceptible to measles virus infection when passively acquired maternal antibody is lost; when not vaccinated, these infants account for the bulk of new susceptible individuals.

Endemic measles has a typical temporal pattern characterized by yearly seasonal epidemics superimposed on longer epidemic cycles of 2–5 years or more. In temperate climates, annual measles outbreaks typically occur in the late winter and early spring. These annual outbreaks are probably attributable to social networks facilitating transmission (e.g., congregation of children at school) and environmental factors favoring the viability and transmission of measles virus. Measles cases continue to occur during interepidemic periods in large populations, but at low incidence. The longer epidemic cycles occurring every several years result from the accumulation of susceptible persons over successive birth cohorts and the subsequent decline in the number of susceptibles following an outbreak.

Secondary attack rates among susceptible household and institutional contacts generally exceed 90%. The average age at which measles occurs depends on rates of contact with infected persons, protective maternal antibody decline, and vaccine coverage. In densely populated urban settings with low-level vaccination coverage, measles is a disease of infants and young children. The cumulative incidence can reach 50% by 1 year of age, with a significant proportion of children acquiring measles before 9 months—the age of routine vaccination in many countries, in line with the schedule recommended by the WHO's Expanded Programme on Immunization. As measles vaccine coverage increases or population density decreases, the age distribution shifts toward older children. In such situations, measles cases predominate in school-age children. Infants and young children, although susceptible if not protected by vaccination, are not exposed to measles virus at a rate sufficient to cause a heavy disease burden in this age group. As vaccination coverage increases further, the age distribution of cases may be shifted into adolescence and adulthood; this distribution is seen in measles outbreaks in the United States and necessitates targeted measles vaccination programs for these older age groups. Many countries have a bimodal distribution, with measles cases predominantly in young infants and adults.

Persons with measles are infectious for several days before and after the onset of rash, when levels of measles virus in blood and body fluids are highest and when cough, coryza, and sneezing, which facilitate virus spread, are most severe. The contagiousness of measles before the onset of recognizable disease hinders the effectiveness of quarantine measures. Viral shedding by children with impaired cell-mediated immunity can be prolonged.

Medical settings are well-recognized sites of measles virus transmission. Children may present to health care facilities during the prodrome, when the diagnosis is not obvious although the child is infectious and is likely to infect susceptible contacts. Health care workers can acquire measles from infected children and transmit measles virus to others. Nosocomial transmission can be reduced by maintenance of a high index of clinical suspicion, use of appropriate isolation precautions when measles is suspected, administration of measles vaccine to susceptible children and health care workers, and documentation of health care workers' immunity to measles (i.e., proof of receipt of two doses of measles vaccine or detection of antibodies to measles virus).

As efforts at measles control are increasingly successful, public perceptions of the risk of measles as a disease diminish and are replaced by concerns about possible adverse events associated with measles vaccine. As a consequence, numerous measles outbreaks have occurred because of opposition to vaccination on religious or philosophical grounds or unfounded fears of serious adverse events (see "Active Immunization," below).

PATHOGENESIS

Measles virus is transmitted primarily by respiratory droplets over short distances and, less commonly, by small-particle aerosols that remain suspended in the air for long periods. Airborne transmission appears to be important in certain settings, including schools, physicians' offices, hospitals, and enclosed public places. The virus can be transmitted by direct contact with infected secretions but does not survive for long on fomites.

The incubation period for measles is ~10 days to fever onset and 14 days to rash onset. This period may be shorter in infants and longer (up to 3 weeks) in adults. Infection is initiated when measles virus is deposited in the respiratory tract, oropharynx, or conjunctivae **(Fig. 200-1*A*)**.

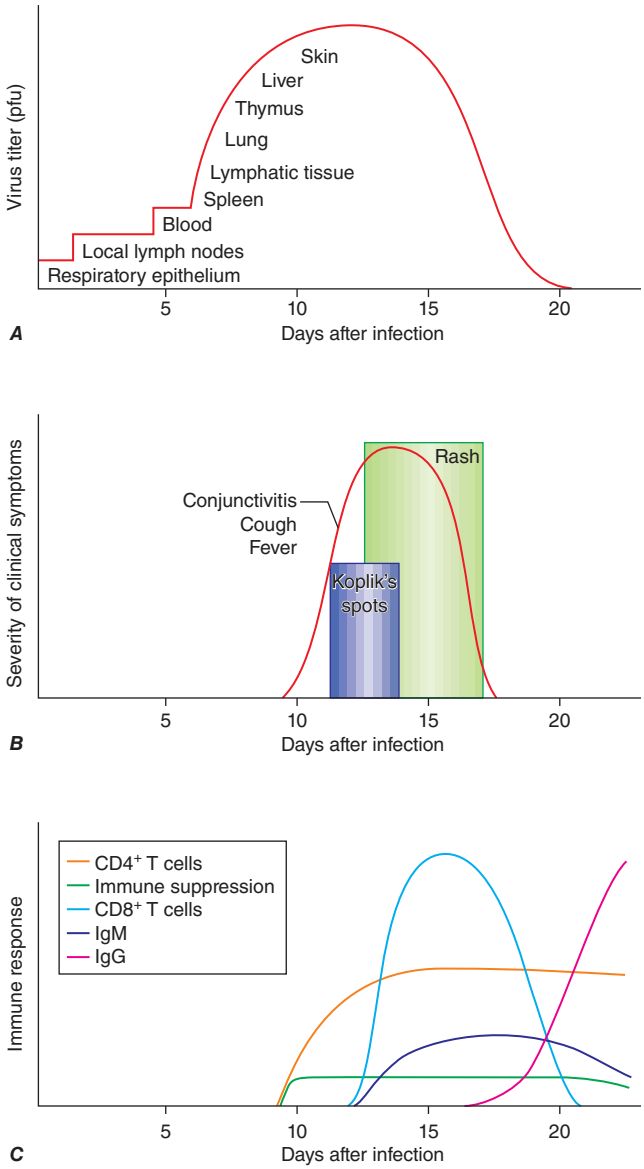

FIGURE 200-1 Measles virus infection: pathogenesis, clinical features, and immune responses. ***A.*** Spread of measles virus, from initial infection of the respiratory tract through dissemination to the skin. ***B.*** Appearance of clinical signs and symptoms, including Koplik's spots and rash. ***C.*** Antibody and T cell responses to measles virus. The signs and symptoms of measles arise coincident with the host immune response. *(Source: Modified from WJ Moss, DE Griffin: Nat Rev Microbiol 4:900, 2006.)*

During the first 2–4 days after infection, measles virus proliferates locally in the respiratory mucosa, primarily in dendritic cells and lymphocytes, and spreads to draining lymph nodes. Virus then enters the bloodstream in infected leukocytes, producing the primary viremia that disseminates infection throughout the reticuloendothelial system. Further replication results in secondary viremia that begins 5–7 days after infection and disseminates measles virus throughout the body. Replication of measles virus in the target organs, together with the host's immune response, is responsible for the signs and symptoms of measles that occur 8–12 days after infection and mark the end of the incubation period **(Fig. 200-1*B*)**.

IMMUNE RESPONSES

Host immune responses to measles virus are essential for viral clearance, clinical recovery, and the establishment of long-term immunity **(Fig. 200-1*C*)**. Early nonspecific (innate) immune responses during the prodromal phase include activation of natural killer cells and increased production of antiviral proteins. The adaptive immune responses consist of measles virus–specific antibody and cellular responses. The protective efficacy of antibodies to measles virus is illustrated by the immunity conferred to infants from passively acquired maternal antibodies and the protection of exposed, susceptible individuals after administration of anti–measles virus immunoglobulin. The first measles virus–specific antibodies produced after infection are of the IgM subtype, with a subsequent switch to predominantly IgG1 and IgG4 isotypes. The IgM antibody response is typically absent following reexposure or revaccination and serves as a marker of primary infection.

The importance of cellular immunity to measles virus is demonstrated by the ability of children with agammaglobulinemia (congenital inability to produce antibodies) to recover fully from measles and the contrasting picture for children with severe defects in T lymphocyte function, who often develop severe or fatal disease **(Chap. 344)**. The initial predominant T_H1 response (characterized by interferon γ) is essential for viral clearance, and the later T_H2 response (characterized by interleukin 4) promotes the development of measles virus–specific antibodies that are critical for protection against reinfection.

The duration of protective immunity following wild-type measles virus infection is generally thought to be lifelong. Immunologic memory to measles virus includes both continued production of measles virus–specific antibodies and circulation of measles virus–specific $CD4^+$ and $CD8^+$ T lymphocytes.

However, the intense immune responses induced by measles virus infection are paradoxically associated with depressed responses to unrelated (non–measles virus) antigens, which persist for several weeks to months beyond resolution of the acute illness. This state of immune suppression enhances susceptibility to secondary infections with bacteria and viruses that cause pneumonia and diarrhea and is responsible for a substantial proportion of measles-related morbidity and deaths. Delayed-type hypersensitivity responses to recall antigens, such as tuberculin, are suppressed, and cellular and humoral responses to new antigens are impaired. Reactivation of tuberculosis and remission of autoimmune diseases after measles have been described and are attributed to this period of immune suppression.

APPROACH TO THE PATIENT

Measles

Clinicians should consider measles in persons presenting with fever and generalized erythematous rash, particularly when measles virus is known to be circulating or the patient has a history of travel to endemic areas. Appropriate precautions must be taken to prevent nosocomial transmission. The diagnosis requires laboratory confirmation except during large outbreaks in which an epidemiologic link to a confirmed case can be established. Care is largely supportive and consists of the administration of vitamin A and antibiotics (see "Treatment," below). Complications of measles, including secondary bacterial infections and encephalitis, may occur after acute illness and require careful monitoring, particularly in immunocompromised persons.

CLINICAL MANIFESTATIONS

In most persons, the signs and symptoms of measles are highly characteristic (Fig. 200-1*B*). Fever and malaise beginning ~10 days after exposure are followed by cough, coryza, and conjunctivitis. These signs and symptoms increase in severity over 4 days. Koplik's spots **(see Fig. A1-2)** develop on the buccal mucosa ~2 days before the rash appears. The characteristic rash of measles **(see Fig. A1-3)** begins 2 weeks after infection, when the clinical manifestations are most severe, and signal the host's immune response to the replicating virus. Headache, abdominal pain, vomiting, diarrhea, and myalgia may be present.

Koplik's spots are pathognomonic of measles and consist of bluish white dots ~1 mm in diameter surrounded by erythema. The lesions appear first on the buccal mucosa opposite the lower molars but rapidly increase in number and may involve the entire buccal mucosa. They fade with the onset of rash.

The rash of measles begins as erythematous macules behind the ears and on the neck and hairline. The rash progresses to involve the face, trunk, and arms, with involvement of the legs and feet by the end of the second day. Areas of confluent rash appear on the trunk and extremities, and petechiae may be present. The rash fades slowly in the same order of progression as it appeared, usually beginning on the third or fourth day after onset. Resolution of the rash may be followed by desquamation, particularly in undernourished children.

Because the characteristic rash of measles is a consequence of the cellular immune response, it may not develop in persons with impaired cellular immunity (e.g., those with AIDS; **Chap. 197**). These persons have a high case–fatality rate and frequently develop giant-cell pneumonitis caused by measles virus. T lymphocyte defects due to causes other than HIV-1 infection (e.g., cancer chemotherapy) also are associated with increased severity of measles.

A severe atypical measles syndrome was observed in recipients of a formalin-inactivated measles vaccine (used in the United States from 1963 to 1967 and in Canada until 1970) who were subsequently exposed to wild-type measles virus. The atypical rash began on the palms and soles and spread centripetally to the proximal extremities and trunk, sparing the face. The rash was initially erythematous and maculopapular but frequently progressed to vesicular, petechial, or purpuric lesions.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of measles includes other causes of fever, rash, and conjunctivitis, including rubella, Kawasaki disease, infectious mononucleosis, roseola, scarlet fever, Rocky Mountain spotted fever, enterovirus or adenovirus infection, and drug sensitivity. Rubella is a milder illness without cough and with distinctive lymphadenopathy. The rash of roseola (exanthem subitum) **(see Fig. A1-5)** appears after fever has subsided. The atypical lymphocytosis in infectious mononucleosis contrasts with the leukopenia commonly observed in children with measles.

DIAGNOSIS

Measles is readily diagnosed on clinical grounds by clinicians familiar with the disease, particularly during outbreaks. Koplik's spots are especially helpful because they appear early and are pathognomonic. Clinical diagnosis is more difficult (1) during the prodromal illness; (2) when the rash is attenuated by passively acquired antibodies or prior immunization; (3) when the rash is absent or delayed in immunocompromised children or severely undernourished children with impaired cellular immunity; and (4) in regions where the incidence of measles is low and other pathogens are responsible for the majority of illnesses with fever and rash. The CDC case definition for measles requires (1) a generalized maculopapular rash of at least 3 days' duration; (2) fever of at least 38.3°C (101°F); and (3) cough, coryza, or conjunctivitis.

Serology is the most common method of laboratory diagnosis. The detection of measles virus–specific IgM in a single specimen of serum or oral fluid is considered diagnostic of acute infection, as is a fourfold or greater increase in measles virus–specific IgG antibody levels between acute- and convalescent-phase serum specimens. Primary infection in the immunocompetent host results in antibodies that are detectable within 1–3 days of rash onset and reach peak levels in 2–4 weeks. Measles virus–specific IgM antibodies may not be detectable until 4–5 days or more after rash onset and usually fall to undetectable levels within 4–8 weeks of rash onset.

Several methods for measurement of antibodies to measles virus are available. Neutralization tests are sensitive and specific, and the results are highly correlated with protective immunity; however, these tests require propagation of measles virus in cell culture and thus are expensive and laborious. Commercially available enzyme immunoassays are most frequently used. Measles can also be diagnosed by isolation of the virus in cell culture from respiratory secretions, nasopharyngeal or conjunctival swabs, blood, or urine. Direct detection of giant cells in respiratory secretions, urine, or tissue obtained by biopsy provides another method of diagnosis.

For detection of measles virus RNA by reverse-transcription polymerase chain reaction amplification of RNA extracted from clinical specimens, primers targeted to highly conserved regions of measles virus genes are used. Extremely sensitive and specific, this assay may also permit identification and characterization of measles virus genotypes for molecular epidemiologic studies and can distinguish wild-type from vaccine virus strains.

TREATMENT

Measles

There is no specific antiviral therapy for measles. Treatment consists of general supportive measures, such as hydration and administration of antipyretic agents. Because secondary bacterial infections are a major cause of morbidity and death attributable to measles, effective case management involves prompt antibiotic treatment for patients who have clinical evidence of bacterial infection, including pneumonia and otitis media. *Streptococcus pneumoniae* and *Haemophilus influenzae* type b are common causes of bacterial pneumonia following measles; vaccines against these pathogens probably lower the incidence of secondary bacterial infections following measles.

Vitamin A is effective for the treatment of measles and can markedly reduce rates of morbidity and mortality. The WHO recommends administration of once-daily doses of 200,000 IU of vitamin A for 2 consecutive days to all children with measles who are ≥12 months of age. Lower doses are recommended for younger children: 100,000 IU per day for children 6–12 months of age and 50,000 IU per day for children <6 months old. A third dose is recommended 2–4 weeks later for children with evidence of vitamin A deficiency. While such deficiency is not a widely recognized problem in the United States, many American children with measles do, in fact, have low serum levels of vitamin A, and these children experience increased measles-associated morbidity. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that the administration of two consecutive daily doses of vitamin A be considered for children who are hospitalized with measles and its complications as well as for children with measles who are immunodeficient; who have ophthalmologic evidence of vitamin A deficiency, impaired intestinal absorption, or moderate to severe malnutrition; or who have recently immigrated from areas with high measles mortality rates. Parenteral and oral formulations of vitamin A are available.

Anecdotal reports have described the recovery of previously healthy pregnant and immunocompromised patients with measles pneumonia and of immunocompromised patients with measles encephalitis after treatment with aerosolized and IV ribavirin. However, the clinical benefits of ribavirin in measles have not been conclusively demonstrated in clinical trials.

COMPLICATIONS

Most complications of measles involve the respiratory tract and include the effects of measles virus replication itself and secondary bacterial infections. Acute laryngotracheobronchitis (croup) can occur during measles and may result in airway obstruction, particularly in young

children. Giant-cell pneumonitis due to replication of measles virus in the lungs can develop in immunocompromised children, including those with HIV-1 infection. Many children with measles develop diarrhea, which contributes to undernutrition.

Most complications of measles result from secondary bacterial infections of the respiratory tract that are attributable to a state of immune suppression lasting for several weeks to months after acute measles. Otitis media and bronchopneumonia are most common and may be caused by *S. pneumoniae*, *H. influenzae* type b, or staphylococci. Recurrence of fever or failure of fever to subside with the rash suggests secondary bacterial infection.

Rare but serious complications of measles involve the central nervous system (CNS). Post-measles encephalomyelitis complicates ~1 in 1000 cases, affecting mainly older children and adults. Encephalomyelitis occurs within 2 weeks of rash onset and is characterized by fever, seizures, and a variety of neurologic abnormalities. The finding of periventricular demyelination, the induction of immune responses to myelin basic protein, and the absence of measles virus in the brain suggest that post-measles encephalomyelitis is an autoimmune disorder triggered by measles virus infection. Other CNS complications that occur months to years after acute infection are measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). In contrast to post-measles encephalomyelitis, MIBE and SSPE are caused by persistent measles virus infection. MIBE is a rare but fatal complication that affects individuals with defective cellular immunity and typically occurs months after infection. SSPE is a slowly progressive disease characterized by seizures and progressive deterioration of cognitive and motor functions, with death occurring 5–15 years after measles virus infection. SSPE most often develops in persons infected with measles virus at <2 years of age.

PROGNOSIS

Most persons with measles recover and develop long-term protective immunity to reinfection. Measles case–fatality proportions vary with the average age of infection, the nutritional and immunologic status of the population, measles vaccine coverage, and access to health care. Among previously vaccinated persons who do become infected, disease is less severe and mortality rates are significantly lower. In developed countries, <1 in 1000 children with measles dies. In endemic areas of sub-Saharan Africa, the measles case–fatality proportion may be 5–10% or even higher. Measles is a major cause of childhood deaths in refugee camps and in internally displaced populations, where case–fatality proportions have been as high as 20–30%.

PREVENTION

Passive Immunization Human immunoglobulin given shortly after exposure can attenuate the clinical course of measles. In immunocompetent persons, administration of immunoglobulin within 72 h of exposure usually prevents measles virus infection and almost always prevents clinical measles. Administered up to 6 days after exposure, immunoglobulin will still prevent or modify the disease. Prophylaxis with immunoglobulin is recommended for susceptible household and nosocomial contacts who are at risk of developing severe measles, particularly children <1 year of age, immunocompromised persons (including HIV-infected persons previously immunized with live attenuated measles vaccine), and pregnant women. Except for premature infants, children <6 months of age usually will be partially or completely protected by passively acquired maternal antibody. Infants born to women with vaccine-induced measles immunity become susceptible to measles at a younger age than infants born to women with acquired immunity from natural infection. If measles is diagnosed in a household member, all unimmunized children in the household should receive immunoglobulin. The recommended dose is 0.25 mL/kg given intramuscularly. Immunocompromised persons should receive 0.5 mL/kg. The maximal total dose is 15 mL. IV immunoglobulin contains antibodies to measles virus; the usual dose of 100–400 mg/kg generally provides adequate prophylaxis for measles exposures occurring as long as 3 weeks or more after IV immunoglobulin administration.

Active Immunization The first live attenuated measles vaccine was developed by passage of the Edmonston strain in chick embryo fibroblasts to produce the Edmonston B virus, which was licensed in 1963 in the United States. Further passage of Edmonston B virus produced the more attenuated Schwarz vaccine that currently serves as the standard in much of the world. The Moraten ("more attenuated Enders") strain, which was licensed in 1968 and is used in the United States, is genetically closely related to the Schwarz strain.

Lyophilized measles vaccines are relatively stable, but reconstituted vaccine rapidly loses potency. Live attenuated measles vaccines are inactivated by light and heat and lose about half their potency at 20°C and almost all their potency at 37°C within 1 h after reconstitution. Therefore, a cold chain must be maintained before and after reconstitution. Antibodies first appear 12–15 days after vaccination, and titers peak at 1–3 months. Measles vaccines are often combined with other live attenuated virus vaccines, such as those for mumps and rubella (MMR) and for mumps, rubella, and varicella (MMR-V).

The recommended age of first vaccination varies from 6 to 15 months and represents a balance between the optimal age for seroconversion and the probability of acquiring measles before that age. The proportions of children who develop protective levels of antibody after measles vaccination approximate 85% at 9 months of age and 95% at 12 months. Common childhood illnesses concomitant with vaccination may reduce the level of immune response, but such illness is not a valid reason to withhold vaccination. Measles vaccines have been well tolerated and immunogenic in HIV-1-infected children and adults, although antibody levels may wane. Because of the potential severity of wild-type measles virus infection in HIV-1-infected children, routine measles vaccination is recommended except for those who are severely immunocompromised. Measles vaccination is contraindicated in individuals with other severe deficiencies of cellular immunity because of the possibility of disease due to progressive pulmonary or CNS infection with the vaccine virus.

The duration of vaccine-induced immunity is at least several decades, if not longer. Rates of secondary vaccine failure 10–15 years after immunization have been estimated at ~5%, but are probably lower when vaccination takes place after 12 months of age. Decreasing antibody concentrations do not necessarily imply a complete loss of protective immunity: a secondary immune response usually develops after reexposure to measles virus, with a rapid rise in antibody titers in the absence of overt clinical disease.

Standard doses of currently licensed measles vaccines are safe for immunocompetent children and adults. Fever to 39.4°C (103°F) occurs in ~5% of seronegative vaccine recipients, and 2% of vaccine recipients develop a transient rash. Mild transient thrombocytopenia has been reported, with an incidence of ~1 case per 40,000 doses of MMR vaccine.

Since the publication of a report in 1998 hypothesizing that MMR vaccine may cause a syndrome of autism and intestinal inflammation, much public attention has focused on this purported association. The events that followed publication of this report led to diminished vaccine coverage in the United Kingdom and provide important lessons in the misinterpretation of epidemiologic evidence and the communication of scientific results to the public. The publication that incited the concern was a case series describing 12 children with a regressive developmental disorder and chronic enterocolitis; 9 of these children had autism. In 8 of the 12 cases, the parents associated onset of the developmental delay with MMR vaccination. This simple temporal association was misinterpreted and misrepresented as a possible causal relationship, first by the lead author of the study and then by elements of the media and the public. Subsequently, many comprehensive reviews and additional epidemiologic studies refuted evidence of a causal relationship between MMR vaccination and autism.

PROSPECTS FOR MEASLES ERADICATION

Progress in global measles control has renewed discussion of measles eradication. In contrast to poliovirus eradication, the eradication of measles virus will not entail challenges posed by prolonged shedding of potentially virulent vaccine viruses and environmental viral

reservoirs. However, in comparison with smallpox eradication, higher levels of population immunity will be necessary to interrupt measles virus transmission, more highly skilled health care workers will be required to administer measles vaccines, and containment through case detection and ring vaccination will be more difficult for measles virus because of infectivity before rash onset. New tools, such as microneedle patches to deliver measles vaccine, will facilitate mass vaccination campaigns. Despite enormous progress, measles remains a leading vaccine-preventable cause of childhood mortality worldwide and continues to cause outbreaks in communities with low vaccination coverage rates in industrialized nations.

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201 Rubella (German Measles)

Laura A. Zimmerman, Susan E. Reef

Rubella was historically viewed as a variant of measles or scarlet fever. Not until 1962 was a separate viral agent for rubella isolated. After an epidemic of rubella in Australia in the early 1940s, the ophthalmologist Norman Gregg noticed the occurrence of congenital cataracts among infants whose mothers had reported rubella during early pregnancy, and congenital rubella syndrome (CRS; see "Clinical Manifestations," below) was first described.

ETIOLOGY

Rubella virus is a member of the Togaviridae family and the only member of the genus *Rubivirus*. This single-strand RNA enveloped virus measures 40–80 nm in diameter. Its core protein is surrounded by a single-layer lipoprotein envelope with spike-like projections containing two glycoproteins, E1 and E2. There is only one antigenic type of rubella virus, and humans are its only known reservoir.

PATHOGENESIS AND PATHOLOGY

Although the pathogenesis of postnatal (acquired) rubella has been well documented, data on pathology are limited because of the mildness of the disease. Rubella virus is spread from person to person via respiratory droplets. Primary implantation and replication in the nasopharynx are followed by spread to the lymph nodes. Subsequent viremia occurs, which in pregnant women often results in infection of the placenta. Placental virus replication may lead to infection of fetal organs. The pathology of CRS in the infected fetus is well defined, with almost all organs found to be infected; however, the pathogenesis of CRS is only poorly delineated. In tissue, infections with rubella virus have diverse effects, ranging from no obvious impact to cell destruction. The hallmark of fetal infection is chronicity, with persistence throughout fetal development in utero and for up to 1 year after birth.

Individuals with acquired rubella may shed virus from 7 days before rash onset to ~5–7 days thereafter. Both clinical and subclinical infections are considered contagious. Infants with CRS may shed large quantities of virus from bodily secretions, particularly from the throat and in the urine, up to 1 year of age. Outbreaks of rubella, including some in nosocomial settings, have originated with index cases of CRS. Thus only individuals immune to rubella virus should have contact with infants who have CRS or who are congenitally infected with rubella virus but are not showing signs of CRS.

EPIDEMIOLOGY

The largest recent rubella epidemic in the United States took place in 1964–1965, when an estimated 12.5 million cases occurred, resulting in ~20,000 cases of CRS. Since the introduction of the routine rubella vaccination program in the United States in 1969, the number of rubella cases reported each year has dropped by >99%; the rate of vaccination coverage with rubella-containing vaccine (RCV) has been >90% among children 19–35 months old since 1995 and >95% for kindergarten and first-grade entrants since 1980. In the United States, a goal for the elimination of rubella and CRS was set in 1989. Interruption of endemic transmission of rubella virus was achieved by 2001. In 2004, a panel of experts agreed unanimously that rubella was no longer an endemic disease in the United States. The criteria used to document lack of endemic transmission included low disease incidence, high nationwide rubella antibody seroprevalence, outbreaks that were few and contained (i.e., small numbers of cases), and lack of endemic virus transmission (as assessed by genetic sequencing). Although interruption of endemic transmission has been sustained since 2001, rubella virus importations continue to occur and cases continue to develop among susceptible persons. During 2004–2015, 60% of rubella cases occurred in persons 20–49 years old—an age group that includes women of childbearing age. Cases of CRS in infants whose mothers have acquired rubella abroad (including three cases in 2012, one case in 2016, and one case thus far in 2017) continue to be identified and reported in the United States. Therefore, health care providers should remain vigilant, considering the possibility of rubella virus infection in adults (especially those emigrating or returning from countries without rubella control programs) and recognizing the potential for CRS among their infants.

The Global Vaccine Action Plan 2011–2020 calls for the elimination of rubella in five of the six World Health Organization (WHO) regions by 2020. Although rubella and CRS are no longer endemic in the WHO Region of the Americas, they remain important public health problems globally. The number of rubella cases reported worldwide in 2000 was ~700,000; this figure declined to 22,427 in 2015. However, numbers of rubella cases may be underestimated because cases are often mild and may not be reported and, in some countries, are identified through measles surveillance systems that are not specific for rubella. Despite an increase in the number of countries with rubella vaccination programs, more than half of the world's children remained unvaccinated against rubella in 2015. In 2010, it was estimated that 105,000 cases of CRS occurred globally.

CLINICAL FEATURES

Acquired Rubella Acquired rubella commonly presents with a generalized maculopapular rash that usually lasts for up to 3 days (Fig. 201-1), although as many as 50% of cases may be subclinical or without rash. When it occurs, the rash is usually mild and may be difficult to detect in persons with darker skin. In children, rash is usually the first sign of illness. However, in older children and adults, a 1- to 5-day prodrome often precedes the rash and may include low-grade fever, malaise, and upper respiratory symptoms. The incubation period is 14 days (range, 12–23 days).

Lymphadenopathy, particularly occipital and postauricular, may be noted during the second week after exposure. Although acquired rubella is usually thought of as a benign disease, arthralgia and arthritis are common in infected adults, particularly women. Thrombocytopenia and encephalitis are less common complications.

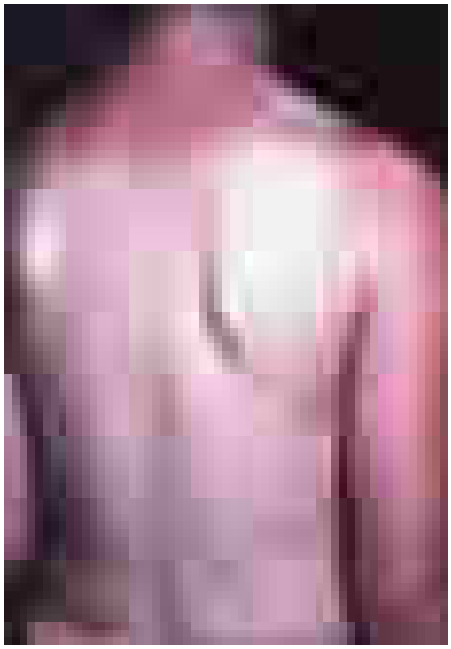

FIGURE 201-1 Mild maculopapular rash of rubella in a child.

Congenital Rubella Syndrome The most serious consequence of rubella virus infection can develop when a woman becomes infected during pregnancy, particularly during the first trimester. The resulting complications may include miscarriage, fetal death, premature delivery, or live birth with congenital defects. Infants infected with rubella virus in utero may have myriad physical defects (Table 201-1), which most commonly relate to the eyes, ears, and heart. This constellation of severe birth defects is known as *CRS*. In addition to permanent manifestations, there are a host of transient physical manifestations, including thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis, "blueberry muffin syndrome"). Some infants may be born with congenital rubella virus infection but have no apparent signs or symptoms of CRS and are referred to as "infants with congenital rubella virus infection only."

DIAGNOSIS

Acquired Rubella Clinical diagnosis of acquired rubella is difficult because of the mimicry of many illnesses with rashes, the varied clinical presentations, and the high rates of subclinical and mild disease. Illnesses that may be similar to rubella in presentation include scarlet fever, roseola, toxoplasmosis, fifth disease, measles, Zika, and illnesses with suboccipital and postauricular lymphadenopathy. Thus, laboratory documentation of rubella virus infection is considered the only reliable way to confirm acute disease.

Laboratory assessment of rubella virus infection is conducted by serologic and virologic methods. For acquired rubella, serologic diagnosis is most common and depends on the demonstration of IgM antibodies in an acute-phase serum specimen or a fourfold rise in IgG antibody titer between acute- and convalescent-phase specimens. The enzyme-linked immunosorbent assay IgM capture technique is considered most accurate for serologic diagnosis, but the indirect IgM assay also is acceptable. After rubella virus infection, IgM antibody may be detectable for up to 6 weeks. In case of a negative result for IgM in specimens taken earlier than day 5 after rash onset, serologic testing should be repeated. Although uncommon, reinfection with rubella virus is possible, and IgM antibodies may be present. To detect a rise in IgG antibody titer indicative of acute disease, the acute-phase serum specimen should be collected within 7–10 days after onset of illness and the convalescent-phase specimen ~14–21 days after the first specimen.

IgG avidity testing is used in conjunction with IgG testing. Low-avidity antibodies indicate recent infection. Mature (high-avidity) IgG antibodies most likely indicate an infection occurring at least 2 months previously. This test helps distinguish primary infection from reinfection. Avidity testing may be particularly useful in diagnosing rubella in pregnant women and assessing the risk of CRS.

Rubella virus can be isolated from the blood and nasopharynx during the prodromal period and for as long as 2 weeks after rash onset. However, as the secretion of virus in individuals with acquired rubella is maximal just before or up to 4 days after rash onset, this is the optimal time frame for collecting specimens for viral cultures. Rubella can also be diagnosed by viral RNA detection in a reverse-transcriptase polymerase chain reaction (RT-PCR) assay.

Congenital Rubella Syndrome The classic triad of CRS—clinical manifestations of cataracts, hearing impairment, and heart defects—is seen in ~10% of infants with CRS. Infants may present with different combinations of defects depending on when infection occurs during gestation. Hearing impairment is the most common single defect of CRS. However, as with acquired rubella, laboratory diagnosis of congenital infection is highly recommended, particularly because most features of the clinical presentation are nonspecific and may be associated with other intrauterine infections. Early diagnosis of CRS facilitates appropriate medical intervention for specific disabilities and prompts implementation of infection control measures.

Diagnostic tests used to confirm CRS include serologic assays and virus detection. In an infant with congenital infection, serum IgM antibodies are normally present for up to 6 months but may be detectable for up to 1 year after birth. In some instances, IgM may not be detectable until 1 month of age; thus infants who have symptoms consistent with CRS but who test negative shortly after birth should be retested at 1 month. A rubella serum IgG titer persisting beyond the time expected after passive transfer of maternal IgG antibody (i.e., a rubella titer that does not decline at the expected rate of a twofold dilution per month) is another serologic criterion used to confirm CRS.

In congenital infection, rubella virus is isolated most commonly from throat swabs and less commonly from urine and cerebrospinal fluid. Infants with congenital rubella may excrete virus for up to 1 year, but specimens for virus isolation are most likely to be positive if obtained within the first 6 months after birth. Rubella virus in infants with CRS can also be detected by RT-PCR.

Rubella Diagnosis in Pregnant Women In the United States, screening for rubella IgG antibodies is recommended as part of routine prenatal care. Pregnant women with a positive IgG antibody serologic test are considered immune. Susceptible pregnant women should be vaccinated postpartum.

A susceptible pregnant woman exposed to rubella virus should be tested for IgM antibodies and/or a fourfold rise in IgG antibody titer between acute- and convalescent-phase serum specimens to determine whether she was infected during pregnancy. Pregnant women with evidence of acute infection must be clinically monitored, and gestational age at the time of maternal infection must be determined to assess the possibility of risk to the fetus. Among women infected with rubella virus during the first 11 weeks of gestation, up to 90% deliver an infant with CRS; with maternal infection during the first 20 weeks of pregnancy, the CRS rate is 20%. Because of the potential for false-positive results, rubella IgM antibody testing is not recommended for pregnant women with no history of illness or contact with a rubella-like illness.

TABLE 201-1 Common Transient and Permanent Manifestations in Infants with Congenital Rubella Syndrome

TRANSIENT MANIFESTATIONS	PERMANENT MANIFESTATIONS
Hepatosplenomegaly	Hearing impairment/deafness
Interstitial pneumonitis	Congenital heart defects (patent ductus arteriosus, pulmonary arterial stenosis)
Thrombocytopenia with purpura/petechiae (e.g., dermal erythropoiesis or "blueberry muffin syndrome")	Eye defects (cataracts, cloudy cornea, microphthalmos, pigmentary retinopathy, congenital glaucoma)
Hemolytic anemia	Microcephaly
Bony radiolucencies	Central nervous system sequelae (mental and motor delay, autism)
Intrauterine growth retardation	
Adenopathy	
Meningoencephalitis	

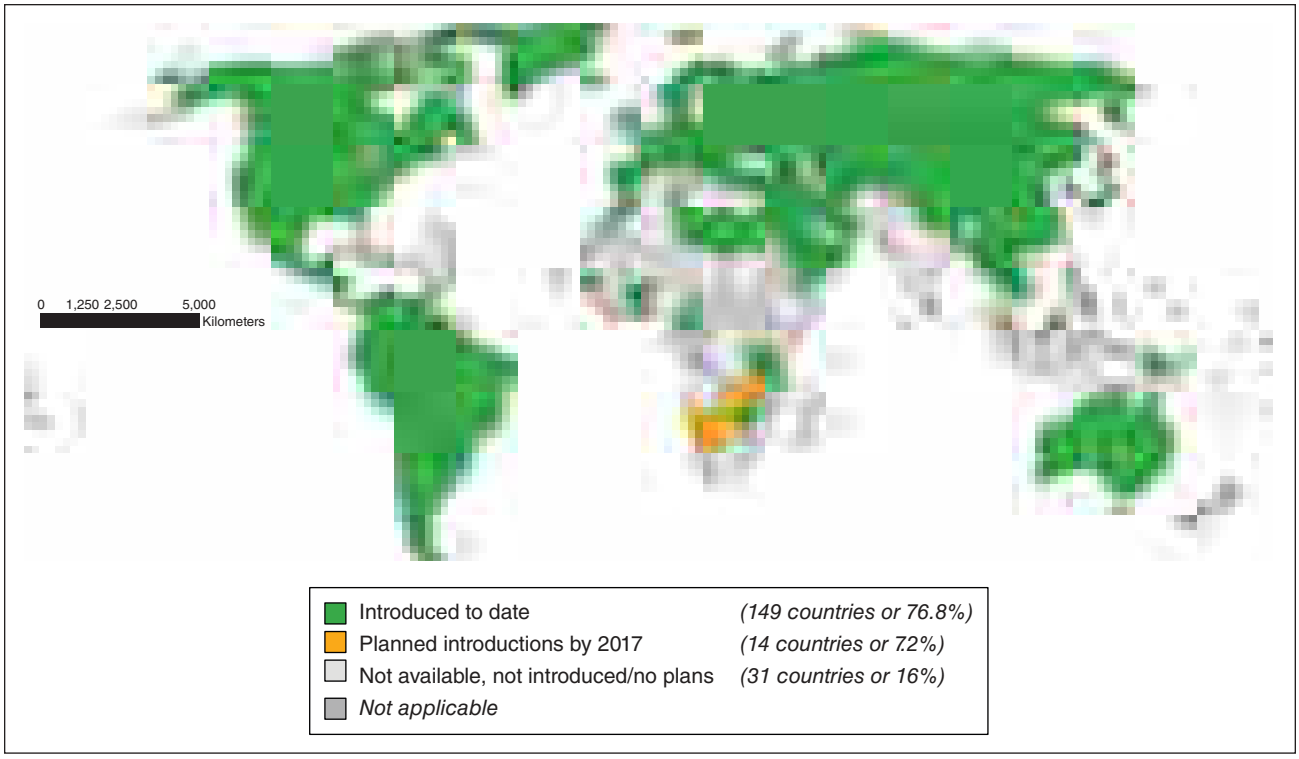

FIGURE 201-2 Countries using rubella vaccine in national childhood immunization schedules, 2017. *(From the World Health Organization.)*

TREATMENT

Rubella

No specific therapy is available for rubella virus infection. Symptom-based treatment for various manifestations, such as fever and arthralgia, is appropriate. Immunoglobulin does not prevent rubella virus infection after exposure and therefore is not recommended as routine postexposure prophylaxis. Although immunoglobulin may modify or suppress symptoms, it can create an unwarranted sense of security: infants with congenital rubella have been born to women who received immunoglobulin shortly after exposure. Administration of immunoglobulin should be considered only if a pregnant woman who has been exposed to a person with rubella will not consider termination of the pregnancy under any circumstances. In such cases, IM administration of 20 mL of immunoglobulin within 72 h of rubella exposure may reduce—but does not eliminate—the risk of rubella.

PREVENTION

After the isolation of rubella virus in the early 1960s and the occurrence of a devastating pandemic in 1964–1965, a vaccine for rubella was developed and licensed in 1969. The majority of RCVs used worldwide are combined measles and rubella (MR) or measles, mumps, and rubella (MMR) formulations. A tetravalent measles, mumps, rubella, and varicella (MMRV) vaccine is available but is not widely used.

The public health burden of rubella virus infection is measured primarily through the occurrence of CRS cases among women who were infected during pregnancy. The 1964–1965 rubella epidemic in the United States resulted in >30,000 infections during pregnancy. CRS occurred in ~20,000 infants born alive, including >11,000 infants who were deaf, >3500 infants who were blind, and almost 2000 infants who were mentally retarded. The medical cost of this epidemic exceeded $1.5 billion. In 1983, the lifetime cost per child with CRS was estimated at $200,000.

In some countries, there are few data to document the epidemiology of CRS, but clusters of CRS cases have been reported in developing countries. Before the introduction of routine immunization against rubella in the United States, the incidence of CRS was 0.1–0.2 case per 1000 live births during endemic periods and 1–4 cases per 1000 live births during epidemic periods. Where rubella virus is circulating and women of childbearing age are susceptible, CRS cases will continue to occur.

The most effective method of preventing acquired rubella and CRS is through vaccination with an RCV. One dose induces seroconversion in ≥95% of persons ≥1 year of age. Immunity is considered long-term and is probably lifelong. The most commonly used vaccine globally is the RA27/3 virus strain. The recommendation for routine rubella vaccination schedules in the United States is a first dose of MMR vaccine at 12–15 months of age and a second dose at 4–6 years. Target groups for rubella vaccine include children ≥1 year of age, adolescents and adults without documented evidence of immunity, individuals in congregate settings (e.g., college students, military personnel, child care and health care workers), and susceptible women before and after pregnancy.

Because of the theoretical risk of transmission of live attenuated rubella vaccine virus to the developing fetus, women known to be pregnant should not receive RCV. In addition, pregnancy should be avoided for 28 days after receipt of RCV. In follow-up studies of ~3000 unknowingly pregnant women who received rubella vaccine, no infant was born with CRS. Receipt of RCV during pregnancy is not ordinarily a reason to consider termination of the pregnancy.

In 2017, 149 (77%) of the 194 member countries of the WHO recommend inclusion of RCV in the routine childhood vaccination schedule; by the end of 2017, 14 more countries will follow suit **(Fig. 201-2)**. Goals for control or elimination of rubella and CRS have been established in the WHO American, European, South-East Asia, and Western Pacific regions. The Eastern Mediterranean and African regions have not yet set such goals.

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202 Mumps

Steven A. Rubin

DEFINITION

Mumps is an illness characterized by acute-onset unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland(s) that lasts at least 2 days and has no other apparent cause.

ETIOLOGIC AGENT

Mumps is caused by a paramyxovirus with a negative-strand, nonsegmented RNA genome of 15,384 bases encoding at least 8 proteins: the nucleo- (N), phospho- (P), V, matrix (M), fusion (F), small hydrophobic (SH), hemagglutinin–neuraminidase (HN), and large (L) proteins. The N, P, and L proteins together provide the polymerase activity responsible for genome transcription and replication. The viral genome is surrounded by a host cell–derived lipid bilayer envelope containing the M, F, SH, and HN proteins. The M protein is involved in viral assembly, whereas the HN and F proteins are responsible for cell attachment and entry and are the major targets of virus-neutralizing antibody. The V and SH proteins are accessory proteins, acting as antagonists of the host antiviral response; the former interferes with the interferon response and the latter with the tumor necrosis factor α (TNF-α)–mediated apoptotic signaling pathway. Because of the hypervariability of the SH gene, its nucleotide sequence is used to genotype the virus for molecular epidemiologic purposes. Thus far, 12 mumps virus genotypes have been assigned by SH gene sequence and are designated A–N (with the exclusion of E and M, which have been merged with genotypes C and K, respectively).

Nucleotide sequencing of clinical isolates shows that virus genotypes D and G circulate predominantly in the Western Hemisphere; genotypes F, C, and I in the Asia–Pacific region; and genotypes B, H, J, and K in the Southern Hemisphere **(Fig. 202-1)**. Although numerous mumps virus genotypes have been identified and some vary antigenically from others, only one serotype exists, and there is no evidence to suggest that certain circulating virus strains are more virulent or contagious than others.

EPIDEMIOLOGY

Mumps is endemic worldwide, with epidemics every 3–5 years in unvaccinated populations. These epidemics typically occur in locations where children and young adults congregate, such as schools, military barracks, and other institutions. In countries without national mumps vaccination programs, the estimated annual global incidence is 100–1000 cases per 100,000 population. After the introduction of mumps vaccine in the United States in 1967, the number of reported cases declined dramatically. Within a few years of the 1977 recommendation by the Advisory Committee on Immunization Practices (ACIP) for use of mumps-containing vaccine (measles–mumps–rubella; MMR) in the national immunization schedule, the number of reported cases declined by >97%. In the years following implementation of a two-dose schedule in 1989 and the passage of school immunization laws in 1991, fewer than 400 cases were being reported annually—a 99.8% reduction from prevaccine-era levels. Mumps incidence remained at historic lows in the United States until 2006, when 6584 cases were reported—the largest outbreak since 1987. At the time of the 2006 outbreak, the disease was resurging globally, even in populations with high-level vaccination coverage. Since this time, the mean number of mumps cases reported annually has increased by more than threefold over numbers in the prior decade (1996–2005). Vaccine coverage among kindergartners has remained relatively stable over the past 20 years at 94–95% (according to data compiled from the *Morbidity and Mortality Weekly Report*). This picture suggests that the resurgence in cases is not due to a failure to vaccinate—a notion supported by outbreak investigations showing that nearly all patients had a history of mumps vaccination.

Although historically a disease of childhood, with the largest proportion of cases occurring in children 5–9 years of age, mumps now most frequently occurs in older age groups, primarily college students. This shift in age distribution and the occurrence of mumps in vaccinated populations suggest waning of vaccine immunity. Thus the introduction of a third dose of MMR vaccine into the national immunization schedule to boost antibody titers has been investigated. However, in a study of 656 subjects, this additional dose only transiently raised levels of neutralizing antibody to mumps virus: levels returned to baseline within a year. While this temporary increase in antibody titers could reduce mumps attack rates during outbreaks, the value of the third dose for routine use in vaccinated populations was determined to be low. Therefore, this option is not being pursued.

PATHOGENESIS

Humans are the only natural hosts for mumps virus, although a virus with >90% sequence identity to mumps virus has recently been identified in bats. The incubation period of mumps is ~19 days (range, 7–23 days). The virus is transmitted by the respiratory route via droplets, saliva, and fomites. Mumps virus is typically shed from 1 week before to 1 week after symptom onset, although this window appears to be narrower in vaccinated individuals. Persons are most contagious 1–2 days before onset of clinical symptoms. Inference from related respiratory diseases and animal studies indicates that primary replication likely occurs in the nasal mucosa or upper respiratory mucosal epithelium. Mononuclear cells and cells within regional lymph nodes can become infected; such infection facilitates the development of viremia, posing a risk for a wide array of acute inflammatory reactions, most commonly parotitis and orchitis. Other common sites of virus dissemination include the kidneys (reflected in the frequency of viruria) and the central nervous system (CNS). Less common sites include the pancreas, heart, ovaries, mammary glands, perilymphatic fluid within the cochlea, and (during pregnancy) the fetus.

Little is known about the pathology of mumps since the disease is rarely fatal. Affected salivary glands contain perivascular and interstitial mononuclear-cell infiltrates and exhibit hemorrhage with prominent edema. Necrosis of acinar and epithelial duct cells is evident in

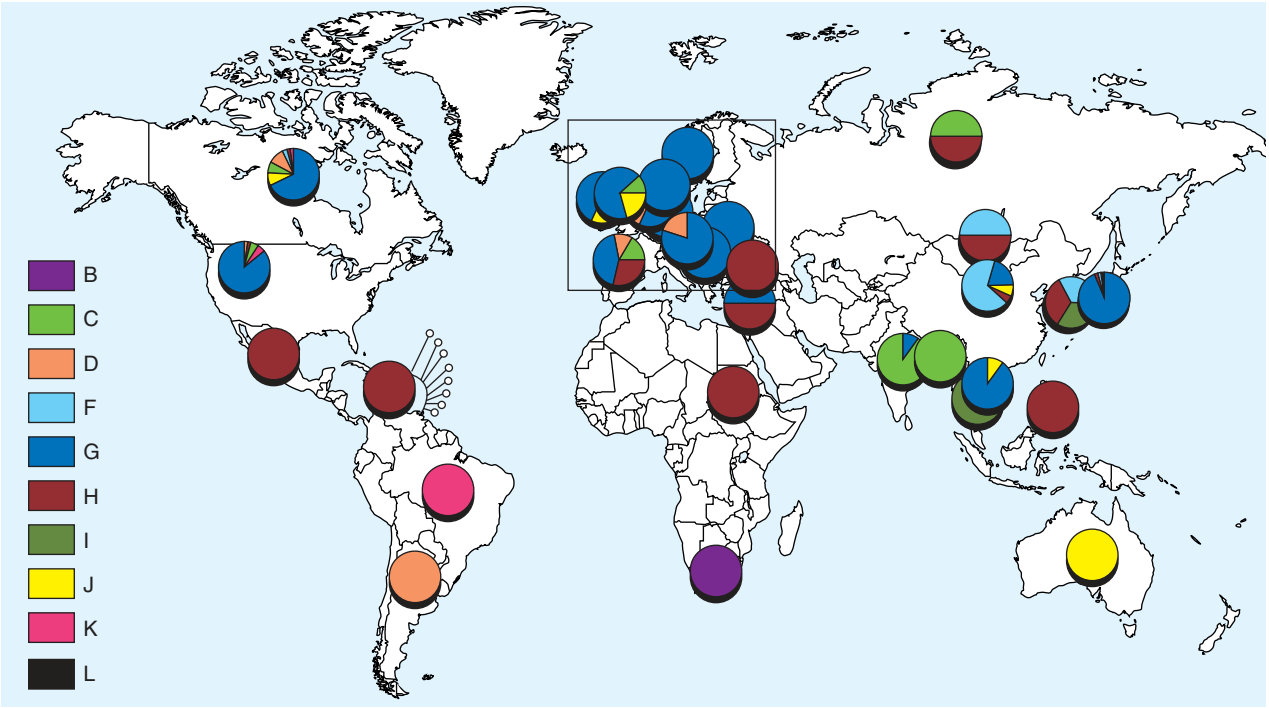


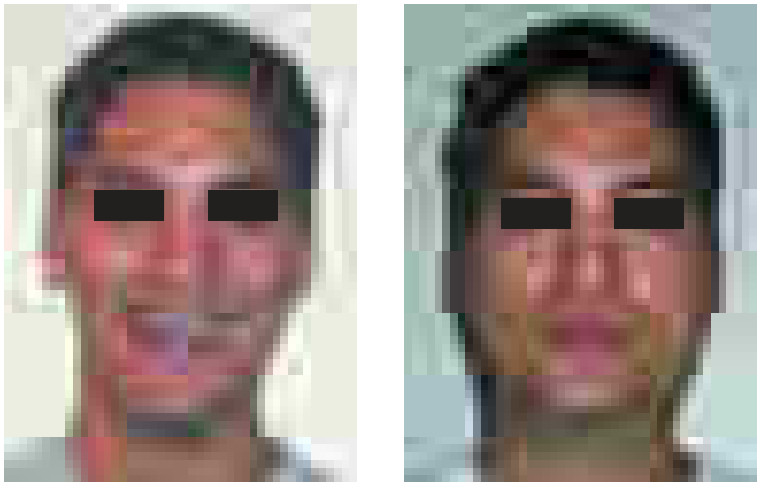
FIGURE 202-1 Distribution of reported mumps genotypes, 2005–2016. Pie-slice size represents the frequency of the reported genotype. *(Figure courtesy of WHO, with permission. This figure has been updated by the author to include data on mumps virus genotypes reported since 2012.)*

the salivary glands and in the germinal epithelium of the seminiferous tubules of the testes. The virus probably enters cerebrospinal fluid (CSF) through the choroid plexus or via transiting mononuclear cells during plasma viremia. Although relevant data are limited, in most cases mumps encephalitis appears to be secondary to respiratory spread and is probably a parainfectious or postinfectious process (as suggested by perivenous demyelination and perivascular mononuclear-cell inflammation) rather than a result of direct virus damage to brain tissue. However, although rare, primary mumps encephalitis does occur, as shown by mumps virus isolation from brain tissue. Infection of the perilymphatic fluid likely develops via retrograde penetration by the virus from the cervical lymph nodes following viremia, but infection could also occur via the CSF in cases of mumps CNS infection, given that the perilymph communicates with the CSF. Virus in the perilymph can result in infection of the cochlea and damage to the organ of Corti and the tectorial membrane, leading to transient or permanent deafness. Evidence of placental and intrauterine spread has been found in both early and late gestation. Mumps during the first trimester of pregnancy increases the risk of miscarriage, but there is no evidence that mumps during pregnancy increases the risk of premature delivery or birth defects.

CLINICAL MANIFESTATIONS

Up to half of mumps virus infections are asymptomatic or lead to nonspecific respiratory symptoms. Inapparent infections are more common among adults than among children. The prodrome of mumps consists of low-grade fever, malaise, myalgia, headache, and anorexia. Mumps parotitis or swelling of other salivary glands usually occurs within 24 h of prodromal symptoms but sometimes as long as 1 week thereafter. Parotitis is generally bilateral, although the two sides may not be involved synchronously. Unilateral involvement occurs in about one-third of cases. Swelling of the parotid is accompanied by tenderness and obliteration of the space between the earlobe and the angle of the mandible (Figs. 202-2 and 202-3). The patient frequently reports an earache and finds it difficult to eat, swallow, or talk. The orifice of the parotid duct is commonly red and swollen. The submaxillary and sublingual glands are involved less often than the parotid gland and are almost never involved alone. Glandular swelling increases for a few days and then gradually subsides, disappearing within 1 week. Recurrent sialadenitis is a rare sequela of mumps parotitis. In ~6% of mumps cases, obstruction of lymphatic drainage secondary to bilateral salivary-gland swelling may lead to presternal pitting edema, associated often with submandibular adenitis and rarely with the more life-threatening supraglottic edema.

Epididymo-orchitis is the next most common manifestation of mumps, developing in 15–30% of cases in postpubertal males, with bilateral involvement in 10–30% of those cases. Orchitis, accompanied by fever, typically occurs during the first week of parotitis but can develop up to 6 weeks after parotitis or in its absence. The testis is painful and tender and can be enlarged to several times its normal size; this condition usually resolves within 1 week. Testicular atrophy develops in one-half of affected men. Sterility after mumps is rare, although subfertility is estimated to occur in 13% of cases of unilateral orchitis



A *B*

FIGURE 202-2 The same person before mumps acquisition (*A*) and on day 3 of acute bilateral parotitis (*B*). *(Courtesy of patient C.M. From JD Shanley: The resurgence of mumps in young adults and adolescents. Cleve Clin J Med 74:42, 2007. Reprinted with permission. Copyright © 2007 Cleveland Clinic Foundation. All rights reserved.)*

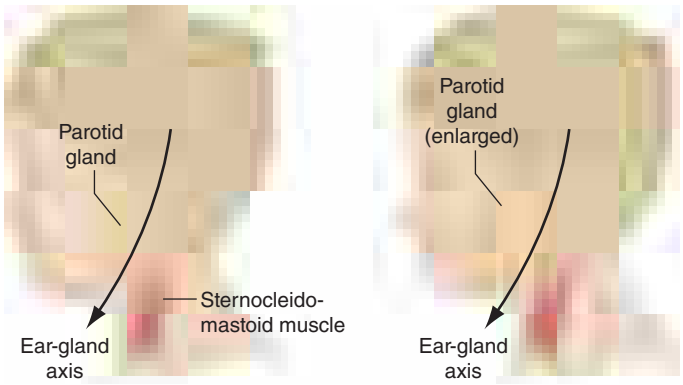


FIGURE 202-3 Schematic drawings of a normal parotid gland *(left)* and a parotid gland infected with mumps virus *(right)*. An enlarged cervical lymph node is usually posterior to the imaginary line. *(Reprinted with permission from A Gershon et al: Mumps, in Krugman's Infectious Diseases of Children, 11th ed. Philadelphia, Elsevier, 2004, p 392.)*

and in 30–87% of cases of bilateral orchitis. Oophoritis occurs in ~5% of women with mumps and may be associated with lower abdominal pain and vomiting, but has only rarely been associated with sterility or premature menopause. Mumps infection in postpubertal women may also present with mastitis.

Documented CSF pleocytosis indicates that the virus invades the CNS in ~50% of cases; however, symptomatic CNS disease, typically in the form of aseptic meningitis, occurs in <10% of cases, with a male predominance. Symptoms of aseptic meningitis include stiff neck, headache, and drowsiness and typically appear ~5 days after parotitis but can occur in the absence of parotid involvement. Mumps meningitis is a self-limited manifestation without significant risk of death or long-term sequelae. In ~0.1% of infections, mumps virus may cause encephalitis, which presents as high fever with marked changes in the level of consciousness, seizures, and focal neurologic symptoms. Electroencephalographic abnormalities may be seen. Permanent sequelae are sometimes identified in survivors, and adult infections more commonly have poor outcomes than do pediatric infections. The mortality rate associated with mumps encephalitis is ~1.5%. Other CNS problems occasionally associated with mumps include cerebellar ataxia, facial palsy, transverse myelitis, hydrocephalus, Guillain-Barré syndrome, flaccid paralysis, and behavioral changes. Mumps deafness, which may or may not be related to CNS infection, occurs in 1 in 1000 to 1 in 100,000 mumps cases.

Mumps pancreatitis, which may present as abdominal pain, occurs in ~4% of infections but is difficult to diagnose because an elevated serum amylase level can be associated with either parotitis or pancreatitis. An etiologic association of mumps virus and juvenile diabetes mellitus remains controversial. Myocarditis and endocardial fibroelastosis are rare and self-limited but may represent severe complications of mumps infection; however, mumps-associated electrocardiographic abnormalities have been reported in up to 15% of cases. Other unusual complications include thyroiditis, nephritis, arthritis, hepatic disease, keratouveitis, and thrombocytopenic purpura. Abnormal renal function is common, but severe, life-threatening nephritis is rare.

DIFFERENTIAL DIAGNOSIS

During a mumps outbreak, the diagnosis is made easily in patients with parotitis and a history of recent exposure; however, when disease incidence is low, other causes of parotitis should be considered and laboratory testing is required for case confirmation. In two recent studies, 13–15% of patients with suspected mumps parotitis who tested negative for mumps virus by polymerase chain reaction (PCR) tested positive for influenza A virus. Other viruses known to cause parotitis include HIV, coxsackievirus, parainfluenza virus type 3, Epstein-Barr virus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, and human herpesvirus 6. Gram-positive bacteria, atypical mycobacteria, and *Bartonella* species can cause parotitis. Parotitis can also develop in the setting of sarcoidosis, Sjögren's syndrome, Mikulicz's syndrome, Parinaud's syndrome, uremia, diabetes mellitus, laundry starch ingestion, malnutrition, cirrhosis, and some drug treatments. Unilateral parotitis can be caused by ductal obstruction, cysts, and tumors. In the absence of parotitis or other salivary gland enlargement, symptoms of other visceral-organ and/or CNS involvement may predominate, and a laboratory diagnosis is required. Other entities should be considered when manifestations consistent with mumps appear in organs other than the parotid. For example, testicular torsion may produce a painful scrotal mass resembling that seen in mumps orchitis, and a number of viruses (e.g., enteroviruses) can cause aseptic meningitis that is clinically indistinguishable from that due to mumps virus.

LABORATORY DIAGNOSIS

Laboratory diagnosis is primarily based on detection of viral RNA by reverse-transcriptase PCR (RT-PCR) or on serology. Detection of viral antigens (e.g., via mumps virus–specific immunofluorescent staining of cultured clinical specimens) is comparatively inefficient and is no longer commonly performed.

For RT-PCR-based testing, viral RNA can be extracted directly from clinical samples. Buccal swabs appear to be the best specimens for virus detection, particularly when obtained within 2 days of clinical onset; however, mumps virus can also be detected readily in throat swabs and saliva and, in cases of meningitis, in CSF. Despite the apparent high frequency of viremia during mumps, mumps virus has rarely been detected in blood. The ability to detect viral RNA in clinical samples rapidly diminishes beyond the first week after symptom onset, and in several studies rates of virus detection were substantially lower in recipients of two doses of mumps-containing vaccine than in unvaccinated persons or recipients of one dose of vaccine. The rate of false-negative RT-PCR findings can be quite high, approaching 70% in some studies. Nonetheless, RT-PCR-based testing is more sensitive than other methods and is the preferred means of case confirmation. While serologic testing is commonly performed (typically via enzyme-linked immunosorbent assay [ELISA]), its diagnostic value is complicated by the fact that most people are vaccinated and may not mount a detectable IgM response upon reinfection since IgM is not a major component of the anamnestic response. Thus, a negative IgM result does not necessarily rule out mumps. In addition, regardless of vaccination status, IgM may not be detectable if serum is assayed too early (prior to day 3 of symptom onset) or too late (beyond 6 weeks after symptom onset) in the course of disease. Reliance on a rise in IgG titer in paired acute- and convalescent-phase sera also is problematic: IgG titers in convalescent-phase sera may be only nominally greater than those in acute-phase sera. Traditional and labor-intensive serologic tests such as complement fixation, hemagglutination inhibition, and virus neutralization are now performed only rarely. The main downside to replacement of these functional serologic assays with the more rapid ELISA method is the latter's detection of all virus-specific antibodies, including those that are non-neutralizing and may not be protective. Thus, an individual who is seropositive by ELISA may lack protective levels of antibody. While there is a strong association between the presence of neutralizing antibody to mumps virus and protection from disease, an antibody titer predictive of serologic protection is lacking; in this respect, mumps differs from other respiratory infections, such as measles and influenza.

TREATMENT

Mumps

Mumps is generally a benign, self-resolving illness. Therapy for parotitis and other clinical manifestations is symptom based and supportive. The administration of analgesics and the application of warm or cold compresses to the parotid area may be helpful. Testicular pain may be minimized by the local application of cold compresses and gentle support for the scrotum. Anesthetic blocks also may be used. Neither the administration of glucocorticoids nor incision of the tunica albuginea is of proven value in severe orchitis. Anecdotal information on a small number of patients with orchitis

suggests that SC administration of interferon α2b may help preserve the organ and fertility. Lumbar puncture is occasionally performed to relieve headache associated with meningitis. Mumps immune globulin has not been consistently effective in preventing mumps and is not recommended for treatment or postexposure prophylaxis.

PREVENTION

Vaccination is the only practical control measure. Nearly all developed countries use mumps-containing vaccines, but in many countries mumps is not a notifiable disease and vaccination is voluntary. However, where used, mumps vaccination has had a tremendous impact, with reductions in incidence and morbidity typically exceeding 90%. Despite the tremendous success of mumps vaccination programs, large mumps outbreaks continue to occur globally, even in settings of high-level two-dose vaccine coverage.

In the United States, the benefit–cost ratios for mumps vaccination alone are >13 for direct costs (e.g., medical expenses) and >24 for societal costs (including productivity losses for patients and caregivers). Several mumps virus vaccines are used throughout the world; in the United States, only the live attenuated Jeryl Lynn strain is used. Current recommendations are that mumps vaccine be administered as part of the combined trivalent MMR vaccine (M-M-R®$_{II}$) or the quadrivalent measles–mumps–rubella–varicella vaccine (ProQuad®). Monovalent vaccine is no longer produced for the U.S. market but is available in other countries.

Before administering mumps-containing vaccine, physicians should consult the latest recommendations from the ACIP. Current recommendations for children specify two doses of mumps-containing vaccine: the first dose given on or after the first birthday and the second dose administered no earlier than 28 days after the first. In the United States, children often receive the second dose between the ages of 4 and 6 years.

In 2009, the ACIP revised its recommendations for evidence of mumps immunity in health care personnel to include (1) documented administration of two doses of a preparation containing live mumps vaccine, (2) laboratory evidence of immunity or laboratory confirmation of disease, or (3) birth date before 1957. For unvaccinated health care personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of mumps, health care facilities should consider two doses of MMR vaccine separated by the appropriate interval; during a mumps outbreak, vaccination of these individuals is recommended.

Mumps vaccine contains live attenuated virus. It is not recommended for pregnant women, for individuals who have had a life-threatening allergic reaction to components of the vaccine, for persons with evidence of severe immunosuppression, or for persons receiving chemotherapy or long-term immunosuppressive therapy. (For details, see the ACIP guidelines on the CDC's website: *www.cdc.gov/vaccines/hcp/acip-recs/*.) Occasionally, febrile reactions and parotitis have been reported soon after mumps vaccination. Allergic reactions after vaccination (e.g., rash and pruritus) are uncommon and are usually mild and self-limited. More serious complications, such as aseptic meningitis, have been causally associated with certain vaccine strains but not with the Jeryl Lynn strain.

Immunity to mumps is associated with the development of neutralizing antibody, although a specific correlate of protection has not been established. Seroconversion occurs in ~95% of recipients of the Jeryl Lynn strain; however, the vaccine efficacy rate is ~78% for one dose and 88% for two doses. In several studies, seropositivity rates and vaccine efficacy have declined with time since vaccination. Administration of an additional dose of vaccine results in a transient increase in antibody levels, but the restorative effect of this increase on vaccine efficacy remains to be demonstrated. The effectiveness of vaccine use during mumps outbreaks was studied in school-based outbreaks in Guam, New York, and Illinois. In all, the intervention was linked with reduced attack rates, but either statistical significance could not be established because of the small number of cases recorded or it was impossible to evaluate effectiveness because the intervention was initiated after the outbreak started to decline. The role of the cellular arm of the immune response is unclear, but there is evidence that it may help limit the spread of mumps virus and the development of complications.

Acknowledgment

The authors thank and acknowledge Drs. Anne Gershon and Kathryn M. Carbone, authors of this chapter in earlier editions.

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203 Rabies and Other Rhabdovirus Infections

Alan C. Jackson

RABIES

Rabies is a rapidly progressive, acute infectious disease of the central nervous system (CNS) in humans and animals that is caused by infection with rabies virus. The infection is normally transmitted from animal vectors. Rabies has encephalitic and paralytic forms that progress to death.

ETIOLOGIC AGENT

Rabies virus is a member of the family Rhabdoviridae. Two genera in this family, *Lyssavirus* and *Vesiculovirus*, contain species that cause human disease. Rabies virus is a lyssavirus that infects a broad range of animals and causes serious neurologic disease when transmitted to humans. This single-strand RNA virus has a nonsegmented, negative-sense (antisense) genome that consists of 11,932 nucleotides and encodes 5 proteins: nucleocapsid protein, phosphoprotein, matrix protein, glycoprotein, and a large polymerase protein. Rabies virus variants, which can be characterized by distinctive nucleotide sequences, are associated with specific animal reservoirs. Six other non–rabies virus species in the *Lyssavirus* genus have been reported to cause a clinical picture similar to rabies. Vesicular stomatitis virus, a vesiculovirus, causes vesiculation and ulceration in cattle, horses, and other animals and causes a self-limited, mild, systemic illness in humans (see "Other Rhabdoviruses," below).

EPIDEMIOLOGY

Rabies is a zoonotic infection that occurs in a variety of mammals throughout the world except in Antarctica and on some islands. Rabies virus is usually transmitted to humans by the bite of an infected animal. Worldwide, endemic canine rabies is estimated to cause 59,000 human deaths annually. Most of these deaths occur in Asia and Africa, with rural populations and children most frequently affected. Thus, in many resource-poor and resource-limited countries, canine rabies continues to be a threat to humans. However, in Latin America, rabies control efforts in dogs have been quite successful in recent years. Endemic canine rabies has been eliminated from the United States and most other resource-rich countries. Rabies is endemic

FIGURE 203-1 Distribution of global rabies vectors. *(Courtesy of the Centers for Disease Control and Prevention.)*

in wildlife species, and a variety of animal reservoirs have been identified in different countries of the world **(Fig. 203-1)**. Surveillance data from 2015 identified 5508 confirmed animal cases of rabies in the United States and Puerto Rico. Only 7.6% of these cases were in domestic animals, including 244 cases in cats, 67 in dogs, and 85 in cattle. In North American wildlife reservoirs, including bats, raccoons, skunks, and foxes, the infection is endemic, with involvement of one or more rabies virus variants in each reservoir species **(Fig. 203-2)**. "Spillover" of rabies to other wildlife species and to domestic animals occurs. Bat rabies virus variants are present in every state except Hawaii and are responsible for most indigenously acquired human rabies cases in the United States. Raccoon rabies is endemic along the entire eastern coast of the United States. Skunk rabies is present in the midwestern states, with another focus in California. Rabies in foxes occurs in Texas, New Mexico, Arizona, and Alaska.

In Canada and Europe, epizootics of rabies in red foxes have been well controlled with the use of baits containing rabies vaccine. A similar approach, along with additional measures, is used in Canada to control incursions of raccoon rabies.

FIGURE 203-2 Distribution of the major rabies virus variants among wild terrestrial reservoirs in the United States and Puerto Rico, 2009–2015. Black diagonal lines represent gray fox rabies variants. Solid borders represent 5-year rabies virus variant aggregates for 2011 through 2015; dashed borders represent the previous 5-year aggregates for 2010 through 2014. *(From MG Birhane et al: J Am Vet Med Assoc 250:1117, 2017.)*

Rabies virus variants isolated from humans or other mammalian species can be identified by reverse-transcription polymerase chain reaction (RT-PCR) amplification and sequencing or by characterization with monoclonal antibodies. These techniques are helpful in human cases with no known history of exposure. Worldwide, most human rabies is transmitted from dogs in countries with endemic canine rabies and dog-to-dog transmission, and human cases can be imported by travelers returning from these regions. In North America, human disease is usually associated with transmission from bats; there may be no known history of bat bite or other bat exposure in these cases. Most human cases are due to a bat rabies virus variant associated with silver-haired and tricolored bats. These are small bats whose bite may not be recognized, and the virus has adapted for replication at skin temperature and in cell types that are present in the skin.

Transmission from nonbite exposures is relatively uncommon. Aerosols generated in the laboratory or in caves containing millions of Brazilian free-tail bats have rarely caused human rabies. Transmission has resulted from corneal transplantation and also from solid-organ transplantation and a vascular conduit (for a liver transplant) from undiagnosed donors with rabies in Texas, Florida, Germany, Kuwait, and China. Human-to-human transmission is extremely rare, although hypothetical concern about transmission to health care workers has prompted the implementation of barrier techniques to prevent exposures from patients with rabies.

PATHOGENESIS

The incubation period of rabies (defined as the interval between exposure and the onset of clinical disease) is usually 20–90 days, but in rare cases is either as short as a few days or >1 year. During most of the incubation period, rabies virus is thought to be present at or close to the site of inoculation **(Fig. 203-3)**. In muscles, the virus is known to bind to nicotinic acetylcholine receptors on postsynaptic membranes at neuromuscular junctions, but the exact details of viral entry into the skin and SC tissues have not yet been clarified. Rabies virus spreads centripetally along peripheral nerves toward the spinal cord or brainstem via retrograde fast axonal transport (rate, up to ~250 mm/d), with delays at intervals of ~12 h at each synapse. Once the virus enters the CNS, it rapidly disseminates to other regions of the CNS via fast axonal transport along neuroanatomic connections. Neurons are prominently infected in rabies; infection of astrocytes is unusual. After CNS infection becomes established, there is centrifugal spread along sensory and autonomic nerves to other tissues, including the salivary glands, heart, adrenal glands, and skin. Rabies virus replicates in acinar cells of the salivary glands and is secreted in the saliva of rabid animals that serve as vectors

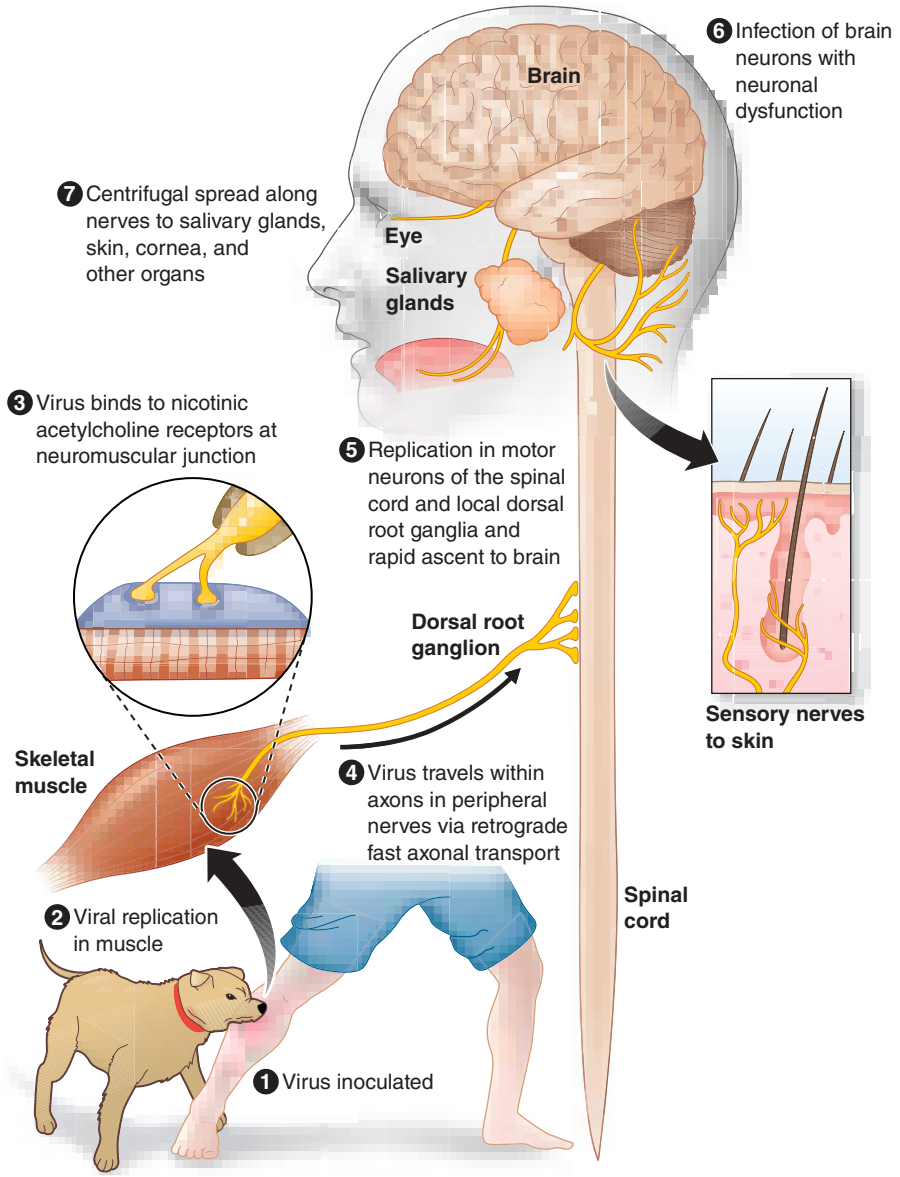

FIGURE 203-3 Schematic representation of events in rabies pathogenesis following peripheral inoculation of rabies virus by an animal bite. *(Adapted from AC Jackson: Human disease, in Rabies: Scientific basis of the disease and its management, 3rd ed. AC Jackson [ed], Oxford, UK, Elsevier Academic Press, 2013, pp 269–298; adapted with permission.)*

of the disease. There is no well-documented evidence for hematogenous spread of rabies virus.

Pathologic studies show mild inflammatory changes in the CNS in rabies, with mononuclear inflammatory infiltration in the leptomeninges, perivascular regions, and parenchyma, including microglial nodules called *Babes nodules*. Degenerative neuronal changes usually are not prominent, and there is little evidence of neuronal death; neuronophagia is observed occasionally. The pathologic changes are surprisingly mild in light of the clinical severity and fatal outcome of the disease. The most characteristic pathologic finding in rabies is the *Negri body* **(Fig. 203-4)**. Negri bodies are eosinophilic cytoplasmic inclusions in brain neurons that are composed of rabies virus proteins and viral RNA. These inclusions occur in a minority of infected neurons, are commonly observed in Purkinje cells of the cerebellum and in pyramidal neurons of the hippocampus, and are less frequently seen in cortical and brainstem neurons. Negri bodies are not observed in all cases of rabies. The lack of prominent degenerative neuronal changes has led to the concept that neuronal dysfunction—rather than neuronal death—is responsible for clinical disease in rabies. The basis for behavioral changes, including the aggressive behavior of rabid animals, is not well understood but may be related to infection of serotonergic neurons in the brainstem.

CLINICAL MANIFESTATIONS

In rabies, the emphasis must be on postexposure prophylaxis (PEP) initiated after a recognized exposure and before any symptoms or signs develop. Rabies should usually be suspected on the basis of the clinical presentation. The disease generally presents as atypical encephalitis with relative preservation of consciousness. Rabies may be difficult to recognize late in the clinical course when progression to coma has occurred. A minority of patients present with acute flaccid paralysis. There are prodromal, acute neurologic, and comatose phases that usually progress to death despite aggressive therapy **(Table 203-1)**.

Prodromal Features The clinical features of rabies begin with nonspecific prodromal manifestations, including fever, malaise, headache, nausea, and vomiting. Anxiety or agitation may also occur. The earliest specific neurologic symptoms of rabies include paresthesias, pain, or pruritus near the site of the exposure, one or more of which occur in 50–80% of patients and strongly suggest rabies. The wound has usually healed by this point, and these symptoms probably reflect infection with associated inflammatory changes in local dorsal root or cranial sensory ganglia.

Encephalitic Rabies Two acute neurologic forms of rabies are seen in humans: the encephalitic (furious) form in 80% and the paralytic form in 20%. Some of the manifestations of encephalitic rabies, including fever, confusion, hallucinations, combativeness, and seizures, may be seen in other viral encephalitides as well. Autonomic dysfunction is common and may result in hypersalivation, gooseflesh, cardiac arrhythmia, and priapism. In encephalitic rabies, episodes of hyperexcitability are typically followed by periods of complete lucidity that become shorter as the disease progresses. Rabies encephalitis is distinguished by early brainstem involvement, which results in the classic features of *hydrophobia* (involuntary, painful contraction of the diaphragm and accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquids) **(Fig. 203-5)** and *aerophobia* (the same features caused by stimulation from a draft of air). These symptoms are probably due to dysfunction of infected brainstem neurons that normally inhibit inspiratory neurons near the nucleus ambiguus, resulting in exaggerated defense reflexes that protect the respiratory tract. The combination of hypersalivation and pharyngeal dysfunction is also responsible for the classic appearance of "foaming at the mouth". Brainstem dysfunction progresses rapidly, and coma—followed within days by death—is the rule unless the course is prolonged by supportive measures. With such measures, late complications can include cardiac and/or respiratory failure, disturbances of water balance (syndrome of inappropriate antidiuretic hormone secretion or diabetes insipidus), noncardiogenic pulmonary edema, and gastrointestinal hemorrhage. Cardiac arrhythmias may be due to dysfunction affecting vital centers in the brainstem or to myocarditis. Multiple-organ failure is common in patients treated aggressively in critical care units.

Paralytic Rabies About 20% of patients have paralytic rabies in which muscle weakness predominates and cardinal features of encephalitic rabies (hyperexcitability, hydrophobia, and aerophobia) are lacking. There is early and prominent flaccid muscle weakness,

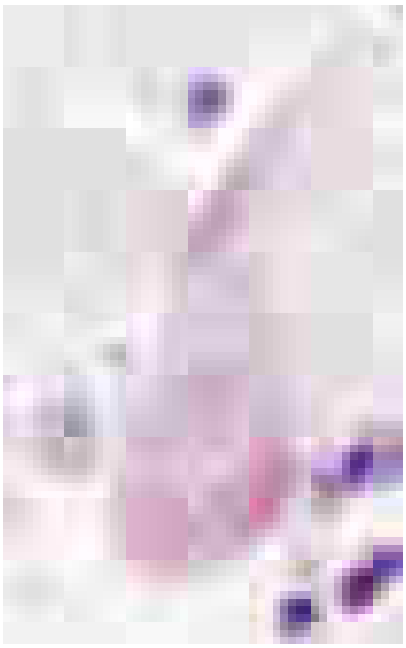

FIGURE 203-4 Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. *(From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)*

FIGURE 203-5 Hydrophobic spasm of inspiratory muscles associated with terror in a patient with encephalitic (furious) rabies who is attempting to swallow water. *(Copyright DA Warrell, Oxford, UK; with permission.)*

often beginning in the bitten extremity and spreading to produce quadriparesis and facial weakness. Sphincter involvement is common, sensory involvement is usually mild, and these cases are commonly misdiagnosed as Guillain-Barré syndrome. Patients with paralytic rabies generally survive a few days longer than those with encephalitic rabies, but multiple-organ failure nevertheless ensues.

LABORATORY INVESTIGATIONS

Most routine laboratory tests in rabies yield normal results or show nonspecific abnormalities. Complete blood counts are usually normal. Examination of cerebrospinal fluid (CSF) often reveals mild mononuclear-cell pleocytosis with a mildly elevated protein level. Severe pleocytosis (>1000 white cells/μL) is unusual and should prompt a search for an alternative diagnosis. Imaging is usually performed to exclude other diagnostic possibilities. CT head scans are usually normal in rabies. MRI brain scans may show signal abnormalities in the brainstem or other gray-matter areas, but these findings are variable and nonspecific. Electroencephalograms typically show only nonspecific abnormalities. Of course, important tests in suspected cases of rabies include those that may identify an alternative, potentially treatable diagnosis (see "Differential Diagnosis," below).

TABLE 203-1 Clinical Stages of Rabies

STAGE	TYPICAL DURATION	SYMPTOMS AND SIGNS
Incubation period	20–90 days	None
Prodrome	2–10 days	Fever, malaise, anorexia, nausea, vomiting; paresthesias, pain, or pruritus at the wound site
Acute Neurologic Disease		
Encephalitic (80%)	2–7 days	Anxiety, agitation, hyperactivity, bizarre behavior, hallucinations, autonomic dysfunction, hydrophobia
Paralytic (20%)	2–10 days	Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis
Coma, death[a]	0–14 days	

[a]Recovery is rare.

Source: MAW Hattwick: Rabies virus, in *Principles and Practice of Infectious Diseases,* GL Mandell et al (eds). New York, Wiley, 1979, pp 1217–1228. Adapted with permission from Elsevier.

DIAGNOSIS

In North America, a diagnosis of rabies often is not considered until relatively late in the clinical course, even with a typical clinical presentation. This diagnosis should be considered in patients presenting with acute atypical encephalitis or acute flaccid paralysis, including those in whom Guillain-Barré syndrome is suspected. The absence of an animal-bite history is common in North America. The lack of hydrophobia is not unusual in rabies. Once rabies is suspected, rabies-specific laboratory tests should be performed to confirm the diagnosis. Diagnostically useful specimens include serum, CSF, fresh saliva, skin biopsy samples from the neck, and brain tissue (rarely obtained before death). Because skin biopsy relies on the demonstration of rabies virus antigen in cutaneous nerves at the base of hair follicles, samples are usually taken from hairy skin at the nape of the neck. Corneal impression smears are of low diagnostic yield and are generally not performed. Negative antemortem rabies-specific laboratory tests never exclude a diagnosis of rabies, and tests may need to be repeated after an interval for diagnostic confirmation.

Rabies Virus–Specific Antibodies In a previously unimmunized patient, serum neutralizing antibodies to rabies virus are diagnostic. However, because rabies virus infects immunologically privileged neuronal tissues, serum antibodies may not develop until late in the disease. Antibodies may be detected within a few days after the onset of symptoms, but some patients die without detectable antibodies. The presence of rabies virus–specific neutralizing antibodies in the CSF suggests rabies encephalitis, regardless of immunization status. A diagnosis of rabies is questionable in patients who recover from their illness without developing serum neutralizing antibodies to rabies virus.

RT-PCR Amplification Detection of rabies virus RNA by RT-PCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, skin biopsy specimens, CSF, and brain tissues. In addition, RT-PCR with genetic sequencing can distinguish among rabies virus variants, permitting identification of the probable source of an infection.

Direct Fluorescent Antibody Testing Direct fluorescent antibody (DFA) testing with rabies virus antibodies conjugated to fluorescent dyes is highly sensitive and specific for the detection of rabies virus antigen in tissues; the test can be performed quickly and applied to skin biopsy and brain tissue samples. In skin biopsy samples, rabies virus antigen may be detected in cutaneous nerves at the base of hair follicles.

DIFFERENTIAL DIAGNOSIS

The diagnosis of rabies may be difficult without a history of animal exposure, and no exposure to an animal (e.g., a bat) may be recalled. The presentation of rabies is usually quite different from that of acute viral encephalitis due to most other causes, including herpes simplex encephalitis and arboviral (e.g., West Nile) encephalitis. Early neurologic symptoms may occur at the site of the bite, and there may be early features of brainstem involvement with preservation of consciousness. Anti–*N*-methyl-D-aspartate receptor (anti-NMDA) encephalitis occurs in young patients (especially females) and is characterized by behavioral changes, autonomic instability, hypoventilation, and seizures. Many other antibodies are associated with autoimmune encephalitis. Postinfectious (immune-mediated) encephalomyelitis may follow influenza, measles, mumps, and other infections; it may also occur as a sequela of immunization with rabies vaccines derived from neural tissues, which are used only in resource-limited and resource-poor countries. Rabies may present with unusual neuropsychiatric symptoms and may be misdiagnosed as a psychiatric disorder. Rabies hysteria (now classified as a somatic symptom disorder) may occur as a psychological response to the fear of rabies and is often characterized by a shorter incubation period than rabies, aggressive behavior, inability to communicate, and a long course with recovery.

As previously mentioned, paralytic rabies may mimic Guillain-Barré syndrome. In these cases, fever, bladder dysfunction, a normal sensory examination, and CSF pleocytosis favor a diagnosis of rabies. Conversely, Guillain-Barré syndrome may occur as a complication of rabies vaccination with a neural tissue–derived product (e.g., suckling mouse brain vaccine) and may be mistaken for paralytic rabies (i.e., vaccine failure).

TREATMENT

Rabies

There is no established treatment for rabies. Aggressive management with supportive care in critical care units has resulted in the survival of more than 15 patients with rabies. There have been many recent treatment failures (~40) with the combination of antiviral drugs, ketamine, and therapeutic (induced) coma—measures that were used in a healthy survivor in whom neutralizing antibodies to rabies virus were detected at presentation. Expert opinion is recommended before a course of experimental therapy is embarked upon. A palliative approach may be appropriate for many patients.

PROGNOSIS

Rabies is an almost uniformly fatal disease but is nearly always preventable after recognized exposures with appropriate postexposure therapy during the early incubation period (see below). All but one of more than 15 documented survivors of rabies received one or more doses of rabies vaccine before disease onset. The single survivor who had not received vaccine had neutralizing antibodies to rabies virus in serum and CSF at clinical presentation. Most patients with rabies die within several days of the onset of illness, despite aggressive care in a critical care unit.

PREVENTION

Postexposure Prophylaxis Since there is no effective therapy for rabies, it is extremely important to prevent the disease after an animal exposure. Figure 203-6 shows the steps involved in making decisions about PEP. On the basis of the exposure history and local epidemiologic information, the physician must decide whether initiation

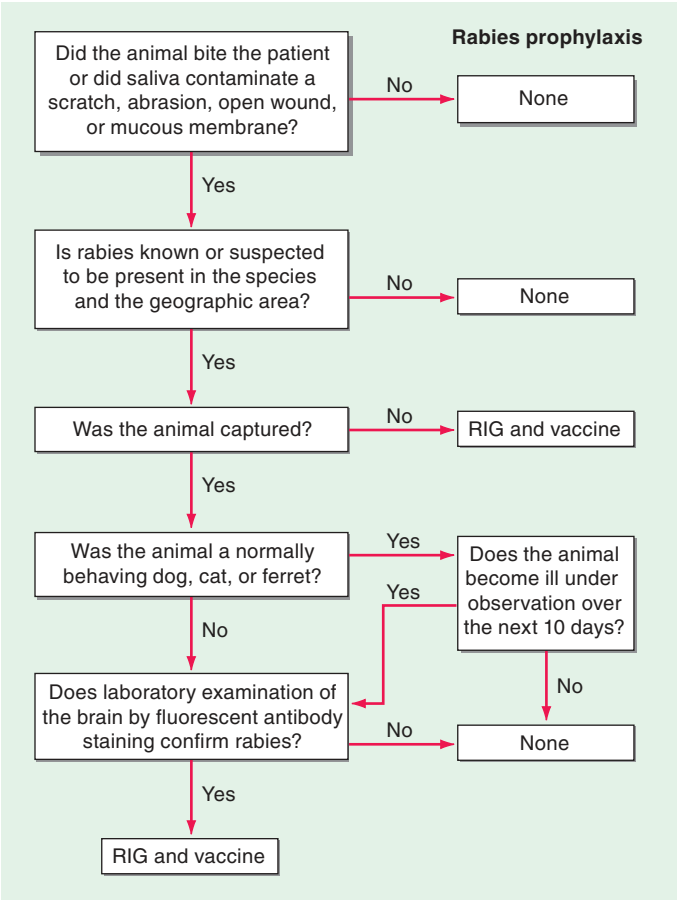

FIGURE 203-6 Algorithm for rabies postexposure prophylaxis. RIG, rabies immune globulin. (*From L Corey, in Harrison's Principles of Internal Medicine, 15th ed. E Braunwald et al [eds]: New York, McGraw-Hill, 2001; adapted with permission.*)

of PEP is warranted. Healthy dogs, cats, or ferrets may be confined and observed for 10 days. PEP is not necessary if the animal remains healthy. If the animal develops signs of rabies during the observation period, it should be euthanized immediately; the head should be transported to the laboratory under refrigeration, rabies virus should be sought by DFA testing, and viral isolation should be attempted by cell culture and/or mouse inoculation. Any animal other than a dog, cat, or ferret should be euthanized immediately and the head submitted for laboratory examination. In high-risk exposures and in areas where canine rabies is endemic, rabies prophylaxis should be initiated without waiting for laboratory results. If the laboratory results prove to be negative, it may safely be concluded that the animal's saliva did not contain rabies virus, and immunization should be discontinued. If an animal escapes after an exposure, it must be considered rabid, and PEP must be initiated unless information from public health officials indicates otherwise (i.e., there is no endemic rabies in the area). Although controversial, the use of PEP may be warranted when a person (e.g., a small child or a sleeping adult) has been present in the same space as a bat and an unrecognized bite cannot be reliably excluded.

PEP includes local wound care and both active and passive immunization. It is important that current recommendations are followed very closely because minor deviations can lead to failure of prophylactic measures. Local wound care is essential and may greatly decrease the risk of rabies virus infection. Wound care should not be delayed, even if the initiation of immunization is postponed pending the results of the 10-day observation period. All bite wounds and scratches should be washed thoroughly with soap and water. Devitalized tissues should be debrided, tetanus prophylaxis given, and antibiotic treatment initiated whenever indicated.

All previously unvaccinated persons (but not those who have previously been immunized) should be passively immunized with rabies

immune globulin (RIG). If RIG is not immediately available, it should be administered no later than 7 days after the first vaccine dose. After day 7, endogenous antibodies are being produced, and passive immunization may actually be counterproductive. If anatomically feasible, the entire dose of RIG (20 IU/kg) should be infiltrated at the site of the bite, and any RIG remaining after infiltration of the bite site should be administered IM at a distant site. With multiple or large wounds, the RIG preparation may need to be diluted in order to obtain a sufficient volume for adequate infiltration of all wound sites. If the exposure involves a mucous membrane, the entire dose should be administered IM. Rabies vaccine and RIG should never be administered at the same site or with the same syringe. Commercially available RIG in the United States is purified from the serum of hyperimmunized human donors. These human RIG preparations are much better tolerated than are the equine-derived preparations still in use in some countries (see below). Serious adverse effects of human RIG are uncommon. Local pain and low-grade fever may occur.

Two purified inactivated rabies vaccines are available for rabies PEP in the United States. They are highly immunogenic and remarkably safe compared with earlier vaccines. Four 1-mL doses of rabies vaccine should be given IM in the deltoid area. (The anterolateral aspect of the thigh also is acceptable in children.) Gluteal injections, which may not always reach muscle, should not be given and have been associated with rare vaccine failures. Ideally, the first dose should be given as soon as possible after exposure; failing that, it should be given without further delay. The three additional doses should be given on days 3, 7, and 14; a fifth dose on day 28 is no longer recommended. Pregnancy is not a contraindication for immunization. Glucocorticoids and other immunosuppressive medications may interfere with the development of active immunity and should not be administered during PEP unless they are essential. Routine measurement of serum neutralizing antibody titers is not required, but titers should be measured 2–4 weeks after immunization in immunocompromised persons. Local reactions (pain, erythema, edema, and pruritus) and mild systemic reactions (fever, myalgias, headache, and nausea) are common; anti-inflammatory and antipyretic medications may be used, but immunization should not be discontinued. Systemic allergic reactions are uncommon, but anaphylaxis does occur rarely and can be treated with epinephrine and antihistamines. The risk of rabies development should be carefully considered before the decision is made to discontinue vaccination because of an adverse reaction.

Most of the burden of rabies PEP is borne by persons with the fewest resources. In addition to the rabies vaccines discussed above, vaccines grown in either primary cell lines (hamster or dog kidney) or continuous cell lines (Vero cells) are satisfactory and are available in many countries outside the United States. Less expensive vaccines derived from neural tissues are still used in a diminishing number of developing countries; however, these vaccines are associated with serious neuroparalytic complications, including postinfectious encephalomyelitis and Guillain-Barré syndrome. The use of these vaccines should be discontinued as soon as possible, and progress has been made in this regard. Worldwide, more than 10 million individuals receive postexposure rabies vaccine each year.

If human RIG is unavailable, purified equine RIG can be used in the same manner at a dose of 40 IU/kg. The incidence of anaphylactic reactions and serum sickness has been low with recent equine RIG products.

Preexposure Rabies Vaccination Preexposure rabies prophylaxis should be considered for people with an occupational or recreational risk of rabies exposures and also for certain travelers to rabies-endemic areas. The primary schedule consists of three doses of rabies vaccine given on days 0, 7, and 21 or 28. Serum neutralizing antibody tests help determine the need for subsequent booster doses. When a previously immunized individual is exposed to rabies, two booster doses of vaccine should be administered on days 0 and 3. Wound care remains essential. As stated above, RIG should not be administered to previously vaccinated persons.

OTHER RHABDOVIRUSES

OTHER LYSSAVIRUSES

A growing number of lyssaviruses other than rabies virus have been discovered to infect bat populations in Europe, Africa, Asia, and Australia. Six of these viruses have produced a very small number of cases of a human disease indistinguishable from rabies: European bat lyssaviruses 1 and 2, Australian bat lyssavirus, Irkut virus, and Duvenhage virus. Mokola virus, a lyssavirus that has been isolated from shrews with an unknown reservoir species in Africa, may also produce human disease indistinguishable from rabies.

VESICULAR STOMATITIS VIRUS

Vesicular stomatitis is a viral disease of cattle, horses, pigs, and some wild mammals. Vesicular stomatitis virus is a member of the genus *Vesiculovirus* in the family Rhabdoviridae. Outbreaks of vesicular stomatitis in horses and cattle occur sporadically in the southwestern United States. The animal infection is associated with severe vesiculation and ulceration of oral tissues, teats, and feet and may be clinically indistinguishable from the more dangerous foot-and-mouth disease. Epidemics are usually seasonal, typically beginning in the late spring, and are probably due to arthropod vectors. Direct animal-to-animal spread can also occur, although the virus cannot penetrate intact skin. Transmission to humans usually results from direct contact with infected animals (particularly cattle) and occasionally follows laboratory exposure. In human disease, early conjunctivitis is followed by an acute influenza-like illness with fever, chills, nausea, vomiting, headache, retrobulbar pain, myalgias, substernal pain, malaise, pharyngitis, and lymphadenitis. Small vesicular lesions may be present on the buccal mucosa or on the fingers. Encephalitis is very rare. The illness usually lasts 3–6 days, with complete recovery. Subclinical infections are common. A serologic diagnosis can be made on the basis of a rise in titer of complement-fixing or neutralizing antibodies. Therapy is symptom-based.

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204 Arthropod-Borne and Rodent-Borne Virus Infections

Jens H. Kuhn, Rémi N. Charrel

This chapter summarizes the major features of selected arthropod-borne and rodent-borne viruses. Numerous viruses of this category are transmitted in nature among animals without ever infecting humans. Other viruses incidentally infect humans, but only a proportion of these viruses induce human disease. In addition, certain viral agents are regularly introduced into human populations or spread among humans by certain arthropods (specifically, insects and ticks) or by chronically

infected rodents. These zoonotic viruses are taxonomically diverse and therefore differ fundamentally from one another in terms of virion morphology, replication strategies, genomic organization, and genome sequence. While a virus's classification in a taxon is enlightening with regard to natural maintenance strategies, sensitivity to antiviral agents, and particular aspects of pathogenesis, the classification does not necessarily predict which clinical signs and symptoms (if any) the virus will cause in humans. Zoonotic viruses are evolving, and "new" zoonotic viruses are regularly discovered. The epizootiology and epidemiology of zoonotic viruses continue to change because of environmental alterations affecting vectors, reservoirs, wildlife, livestock, and humans. Zoonotic viruses are most numerous in the tropics but are also found in temperate and even frigid climates. The distribution and seasonal activity of a zoonotic virus may vary, and the rate at which they change is likely to depend largely on ecologic conditions (e.g., rainfall and temperature), which can affect the density of virus vectors and reservoirs and the development of infection.

Arthropod-borne viruses (arboviruses) infect their vectors after ingestion of a blood meal from a viremic, usually nonhuman vertebrate; some arthropods may also become infected by saliva-activated transmission. The arthropod vectors then develop chronic, systemic infection as the viruses penetrate the gut and spread throughout the body to the salivary glands; such virus dissemination, referred to as *extrinsic incubation*, typically lasts 1–3 weeks in mosquitoes. At this point, if the salivary glands become involved, the arthropod vector is competent to continue the chain of transmission by infecting a vertebrate during a subsequent blood meal. An alternative mechanism for virus maintenance in its arthropod vector is *transovarial transmission*. The arthropod generally is unharmed by the infection, and the natural vertebrate partner usually has only transient viremia with no overt disease.

Rodent-borne viruses are maintained in nature by transmission between rodents, which become chronically infected. Usually a high degree of rodent–virus specificity is observed, and overt disease in the reservoir host is rare.

ETIOLOGY

Arthropod-borne and rodent-borne zoonotic viruses belong to the proposed orders "*Articulavirales*" (family *Orthomyxoviridae*), the order *Bunyavirales* (families *Arenaviridae, Hantaviridae, Nairoviridae, Peribunyaviridae, Phenuiviridae*), and the order *Mononegavirales* (family *Rhabdoviridae*) and to the unassigned families *Flaviviridae, Reoviridae,* and *Togaviridae* **(Table 204-1)**.

"ARTICULAVIRALES": ORTHOMYXOVIRIDAE

The family *Orthomyxoviridae* includes two genera of medically relevant arthropod-borne viruses: *Quaranjavirus* and *Thogotovirus*. Quaranjaviruses are transmitted among birds by ixodid ticks, whereas hogotoviruses have a predilection for mammalian host reservoirs and can be transmitted by both ixodid ticks and mosquitoes.

BUNYAVIRALES: ARENAVIRIDAE

The members of the family *Arenaviridae* that infect humans are all assigned to the genus *Mammarenavirus*. The members of this genus are divided into two main phylogenetic branches: Old World viruses (the Lassa–lymphocytic choriomeningitis serocomplex) and New World viruses (the Tacaribe serocomplex). Mammarenaviruses form spherical, oval, or pleomorphic enveloped and spiked virions (~50–300 nm in diameter) that bud from the infected cell's plasma membrane. The particles contain two genomic single-stranded RNAs (S, ~3.5 kb; and L, ~7.5 kb) encoding structural proteins in an ambisense orientation. Most mammarenaviruses persist in nature by chronically infecting rodents. The human Old World mammarenaviruses are maintained by murid rodents that often are persistently viremic and commonly transmit viruses vertically and horizontally. One Old World mammarenavirus that has been associated with human infections is maintained by shrews. Human New World mammarenaviruses are found in cricetid rodents; horizontal transmission is typical, vertical infection may occur, and persistent viremia may be observed. Strikingly, each mammarenavirus is predominantly adapted to one particular type of rodent. Humans usually become infected through inhalation of or direct contact with infected rodent excreta or secreta (e.g., aerosols of rodents in harvesting machines; aerosolized dried rodent urine or feces in barns or houses; direct contact with rodents in traps). Person-to-person transmission of mammarenaviruses is uncommon.

BUNYAVIRALES: HANTAVIRIDAE, NAIROVIRIDAE, PERIBUNYAVIRIDAE, AND PHENUIVIRIDAE

The members of all these families that infect humans form spherical-to-pleomorphic enveloped virions containing three genomic single-stranded RNAs (S, ~1–2 kb; M, 3.6–5.3 kb; and L, 6.4–12.3 kb) of negative (hantaviruses, nairoviruses, peribunyaviruses) or ambisense (phenuiviruses) polarity. These bunyaviruses mature into particles ~80–120 nm in diameter in the Golgi complex of infected cells and exit these cells by exocytosis.

Hantaviruses that infect humans are classified in the genus *Orthohantavirus* and are maintained in nature by rodents that chronically shed virions. Old World orthohantaviruses are harbored by murid and cricetid rodents, and New World orthohantaviruses are maintained by cricetid rodents. As with mammarenaviruses, individual orthohantaviruses usually are specifically adapted to a particular type of rodent. However, orthohantaviruses do not cause chronic viremia in their rodent hosts and are transmitted only horizontally from rodent to rodent. Similar to mammarenaviruses, hantaviruses infect humans primarily through inhalation of or direct contact with rodent excreta or secreta, and person-to-person transmission is not a common event (with the notable exception of Andes virus). Although there is overlap, the human Old World orthohantaviruses usually are the etiologic agents of hemorrhagic fever with renal syndrome (HFRS), whereas the New World orthohantaviruses usually cause hantavirus (cardio)pulmonary syndrome.

Nairoviruses that infect humans are classified in the genus *Orthonairovirus*. These orthonairoviruses are maintained by ixodid ticks, which vertically (transovarially and transstadially) transmit these viruses to progeny tick generations and horizontally spread them through viremic vertebrate hosts. Humans are usually infected via a tick bite or during handling of infected vertebrates.

Peribunyaviruses of one genus (*Orthobunyavirus*) infect humans. Orthobunyaviruses are largely mosquito-borne and rarely midge-borne and have viremic vertebrate intermediate hosts. Many orthobunyaviruses are also transovarially transmitted in their mosquito hosts. Numerous orthobunyaviruses have been associated with human infection and disease. They have been considered to be members of ~19 serogroups based on antigenic cross-reactions, but this grouping is currently undergoing revision with the accumulation of new genomic data and phylogenetic analyses. Humans are infected by viruses in at least nine serogroups.

Phenuiviruses are transmitted vertically (transovarially) in their arthropod hosts and horizontally through viremic vertebrate hosts. Human phenuiviruses are found in two genera: "*Banyangvirus*" and *Phlebovirus*. "Banyangviruses" and viruses of the phlebovirus Uukuniemi group are transmitted by ticks, whereas those of the phlebovirus sandfly fever group are transmitted by sandflies. Phleboviruses are assigned to at least 10 serocomplexes; human pathogens are found in at least four of these serocomplexes.

MONONEGAVIRALES: RHABDOVIRIDAE

Rhabdoviruses have linear, typically nonsegmented, single-stranded RNA genomes of negative polarity (~11–15 kb) and form bullet-shaped to pleomorphic enveloped particles (100–430 nm long and 45–100 nm wide). Only the genus *Vesiculovirus* includes confirmed human arthropod-borne viruses, all of which are transmitted by insects (biting midges, mosquitoes, and sandflies). **The general properties of rhabdoviruses are discussed in more detail in Chap. 203.**

FLAVIVIRIDAE

The family *Flaviviridae* currently includes only one genus (*Flavivirus*) that comprises arthropod-borne human viruses. Flaviviruses sensu

TABLE 204-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans

VIRUS GROUP	VIRUS (ABBREVIATION)	PRINCIPAL RESERVOIR HOST(S)	VECTOR(S)	SYNDROME[a]
Alphaviruses (Barmah Forest serocomplex)	Barmah Forest virus (BFV)	Horses, marsupials	Biting midges (*Culicoides marksi*), mosquitoes (*Aedes camptorhynchus, A. normanensis, A. notoscriptus, A. vigilax, Culex annulirostris*)	A/R
Alphaviruses (Semliki Forest serocomplex)	Chikungunya virus (CHIKV)	Bats, nonhuman primates	Mosquitoes (*Aedes, Culex* spp.)	A/R[b]
	Mayaro virus (MAYV)	Nonhuman primates, possums, rodents	Mosquitoes (predominantly *Haemagogus* spp.)	A/R
	O'nyong-nyong virus (ONNV)	Unknown	Mosquitoes (in particular *Anopheles gambiae*, *A. funestus*, *Mansonia* spp.)	A/R
	Una virus (UNAV)	Birds, horses, rodents	Mosquitoes (*Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Ochlerotatus, Psorophora* spp.)	F/M
	Ross River virus (RRV)	Macropods, rodents	Mosquitoes (*Aedes normanensis*, *A. vigilax*, *Culex annulirostris*)	A/R
	Semliki Forest virus (SFV)	Birds, rodents	Mosquitoes (*Aedes*, *Culex* spp.)	A/R
Alphaviruses (eastern equine encephalitis serocomplex)	Eastern equine encephalitis virus (EEEV)	Freshwater swamp birds	Mosquitoes (*Aedes*, *Coquillettidia*, *Culex* spp.; *Culiseta melanura*, *Mansonia perturbans*, *Psorophora* spp.)	E
Alphaviruses (Venezuelan equine encephalitis serocomplex)	Everglades virus (EVEV)	Hispid cotton rats (*Sigmodon hispidus*)	Mosquitoes (*Culex cedecei*)	F/M, E
	Mucambo virus (MUCV)	Nonhuman primates, rodents	Mosquitoes (*Culex*, *Ochlerotatus* spp.)	F/M, E
	Tonate virus (TONV)	Suriname crested oropendolas (*Psarocolius decumanus*)	Mosquitoes (*Culex portesi*)	F/M, E
	Venezuelan equine encephalitis virus (VEEV)	Horses, rodents	Mosquitoes (*Aedes*, *Culex* spp.; *Psorophora confinnis*)	F/M, E
Alphaviruses (western equine encephalitis serocomplex)	Sindbis virus (SINV)	Birds	Mosquitoes (*Culex*, *Culiseta* spp.)	A/R
	Western equine encephalitis virus (WEEV)	Lagomorphs, passerine birds	Mosquitoes (*Culex tarsalis*)	E
"Banyangviruses" (Bhanja serocomplex)	Bhanja virus[c] (BHAV)	Cattle, four-toed hedgehog (*Atelerix albiventris*), goats, sheep, striped ground squirrels (*Xerus erythropus*)	Ixodid ticks (*Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Rhipicephalus* spp.)	E, F/M
	Heartland virus	Cattle, deer, elk, goats, sheep?	Ixodid ticks (*Amblyomma americanum*)	F/M
	Severe fever with thrombocytopenia syndrome virus (SFTSV)[d]	Cattle, chicken, dogs, goats, rodents, sheep?	Ixodid ticks (*Haemaphysalis longicornis*, *Rhipicephalus microplus*)	F/M, VHF
Bunyaviruses (family and genus undetermined)	Bangui virus (BGIV)	Unknown	Unknown	F/M
Coltiviruses	Colorado tick fever virus (CTFV)	Bushy-tailed woodrats (*Neotoma cinerea*), Columbian ground squirrels (*Spermophilus columbianus*), deer mice (*Peromyscus maniculatus*), golden-mantled ground squirrels (*Spermophilus lateralis*), least chipmunks (*Tamias minimus*), North American porcupines (*Erethizon dorsata*), yellow pine chipmunks (*Tamias amoenus*)	Ixodid ticks (predominantly *Dermacentor andersoni*)	E, F/M
	Eyach virus (EYAV)	Lagomorphs, rodents	Ixodid ticks (*Ixodes ricinus*, *I. ventalloi*)	E, F/M
	Salmon River virus (SRV)	Unknown	Ixodid ticks (*Ixodes* spp.)	E, F/M
Flaviviruses (mosquito-borne)	Dengue viruses 1–4 (DENV 1–4)	Nonhuman primates	Mosquitoes (predominantly *Aedes aegypti*, *A. albopictus*)	F/M, VHF
	Japanese encephalitis virus (JEV)	Ardeid wading birds (in particular herons), horses, pigs	Mosquitoes (*Culex* spp., in particular *C. tritaeniorhynchus*)	E
	Kokobera virus (KOKV)	Macropods, horses	Mosquitoes (*Culex* spp.)	A/R
	Murray Valley encephalitis virus (MVEV)	Birds	Mosquitoes (predominantly *Culex annulirostris*)	E
	Rocio virus (ROCV)	Rufous-collared sparrows (*Zonotrichia capensis*)	Mosquitoes (*Aedes*, *Culex*, *Psorophora* spp.)	E
	St. Louis encephalitis virus (SLEV)	Columbiform and passeriform birds (finches, sparrows)	Mosquitoes (predominantly *Culex* spp., in particular *C. nigripalpus*, *C. pipiens*, *C. quinquefasciatus*, *C. tarsalis*)	E
	Usutu virus (USUV)	Passerine birds	Mosquitoes (*Culex* spp., in particular *C. pipiens*)	(E)

(*Continued*)

TABLE 204-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans (Continued)

VIRUS GROUP	VIRUS (ABBREVIATION)	PRINCIPAL RESERVOIR HOST(S)	VECTOR(S)	SYNDROME[a]
Flaviviruses (mosquito-borne)	West Nile virus (WNV)[e]	Passerine birds (blackbirds, crows, finches, sparrows), small mammals, horses	Mosquitoes (*Culex* spp., in particular *C. pipiens*, *C. quinquefasciatus*, *C. restuans*, *C. tarsalis*)	E
	Yellow fever virus (YFV)	Nonhuman primates (*Alouatta*, *Ateles*, *Cebus*, *Cercopithecus*, *Colobus* spp.)	Mosquitoes (*Aedes* spp., in particular *A. aegypti*)	VHF
	Zika virus (ZIKV)	Nonhuman primates (*Macaca*, *Pongo* spp.)	Mosquitoes (*Aedes* spp.)	A/R, F/M
Flaviviruses (tick-borne)	Kyasanur Forest disease virus (KFDV)[f]	Indomalayan vandeleurias (*Vandeleuria oleracea*), roof rats (*Rattus rattus*)	Ixodid ticks (predominantly *Haemaphysalis spinigera*), sand tampans (*Ornithodoros savignyi*)	VHF
	Omsk hemorrhagic fever virus (OHFV)	Migratory birds, rodents	Ixodid ticks (predominantly *Dermacentor* spp.)	VHF
	Powassan virus (POWV)	Red squirrels (*Tamiasciurus hudsonicus*), white-footed deer mice (*Peromyscus leucopus*), woodchucks (*Marmota monax*), other small mammals	Ixodid ticks (in particular *Ixodes cookei*, other *Ixodes* spp., *Dermacentor* spp.)	E
	Tick-borne encephalitis virus (TBEV)	Passerine birds, deer, eulipotyphla, goats, grouse, small mammals, rodents, sheep	Ixodid ticks (*Ixodes gibbosus*, *I. persulcatus*, *I. ricinus*; sporadically *Dermacentor*, *Haemaphysalis*, *Hyalomma* spp.)	E, F/M, (VHF)
Mammarenaviruses (Old World)	Lassa virus (LASV)	Natal mastomys (*Mastomys natalensis*)	None	F/M, VHF
	Lujo virus (LUJV)	Unknown	None	VHF
	Lymphocytic choriomeningitis virus (LCMV)	House mice (*Mus musculus*)	None	E, F/M, (VHF)
Mammarenaviruses (New World)	Chapare virus (CHAPV)	Unknown	None	VHF
	Guanarito virus (GTOV)	Short-tailed zygodonts (*Zygodontomys brevicauda*)	None	VHF
	Junín virus (JUNV)	Drylands lauchas (*Calomys musculinus*)	None	VHF
	Machupo virus (MACV)	Big lauchas (*Calomys callosus*)	None	VHF
	Sabiá virus (SABV)	Unknown	None	VHF
	Whitewater Arroyo virus (WWAV)[g]	White-throated woodrats (*Neotoma albigula*)	None	(E)
Orbiviruses	Kemerovo virus (KEMV)	Birds, rodents	Ixodid ticks (*Ixodes persulcatus*)	E, F/M
	Lebombo virus (LEBV)	Unknown	Mosquitoes (*Aedes*, *Mansonia* spp.)	F/M
	Orungo virus (ORUV)	Camels, cattle, goats, nonhuman primates, sheep	Mosquitoes (*Aedes*, *Anopheles*, *Culex* spp.)	E, F/M
	Tribeč virus (TRBV)[h]	Bank voles (*Myodes glareolus*), birds, common pine voles (*Microtus subterraneus*), goats, hares	Ixodid ticks (*Ixodes persulcatus*, *I. ricinus*)	F/M
Orthobunyaviruses (Anopheles A serogroup)	Tacaiuma virus (TCMV)	Nonhuman primates	Mosquitoes (*Anopheles*, *Haemagogus* spp.)	F/M
Orthobunyaviruses (Bunyamwera serogroup)	Batai virus (BATV)[i]	Birds, camels, cattle, goats, rodents, sheep	Mosquitoes (*Aedes abnormalis*, *A. curtipes*, *Anopheles barbirostris*, *Culex gelidus*, other spp.)	F/M
	Bunyamwera virus (BUNV)	Birds, cows, goats, horses, sheep	Mosquitoes (*Aedes* spp.)	F/M
	Cache Valley virus (CVV)	Cattle, deer, foxes, horses, nonhuman primates, raccoons	Mosquitoes (*Aedes*, *Anopheles*, *Culiseta* spp.)	F/M
	Fort Sherman virus (FSV)	Unknown	Mosquitoes?	F/M
	Germiston virus (GERV)	Rodents	Mosquitoes (*Culex* spp.)	F/M
	Guaroa virus (GROV)	Unknown	Mosquitoes (*Anopheles* spp.)	F/M
	Ilesha virus (ILEV)	Unknown	Mosquitoes (*Anopheles gambiae*)	F/M, (VHF)
	Maguari virus (MAGV)	Birds, cattle, horses, sheep, water buffalo	Mosquitoes (*Aedes*, *Anopheles*, *Culex*, *Psorophora*, *Wyeomyia* spp.)	F/M
	Ngari virus (NRIV)	Unknown	Mosquitoes (*Aedes*, *Anopheles* spp.)	F/M, VHF
	Shokwe virus (SHOV)	Rodents	Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.)	F/M
	Xingu virus (XINV)	Unknown	Unknown	F/M
Orthobunyaviruses (Bwamba serogroup)	Bwamba virus (BWAV)	Unknown	Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.)	F/M
	Pongola virus (PGAV)	Cattle, donkeys, goats, sheep	Mosquitoes (*Aedes*, *Anopheles*, *Mansonia* spp.)	F/M
Orthobunyaviruses (California serogroup)	California encephalitis virus (CEV)	Lagomorphs, rodents	Mosquitoes (*Aedes*, *Culex*, *Culiseta*, *Psorophora* spp.)	E, F/M
	Inkoo virus (INKV)	Cattle, foxes, hares, moose, rodents	Mosquitoes (*Aedes* spp.)	E, F/M

(*Continued*)

TABLE 204-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans (Continued)

VIRUS GROUP	VIRUS (ABBREVIATION)	PRINCIPAL RESERVOIR HOST(S)	VECTOR(S)	SYNDROME[a]
	Jamestown Canyon virus (JCV)	Bison, deer, elk, moose	Mosquitoes (*Aedes*, *Culiseta*, *Ochlerotatus* spp.)	E, F/M
	La Crosse virus (LACV)	Chipmunks, squirrels	Mosquitoes (*Ochlerotatus triseriatus*)	E, F/M
	Lumbo virus (LUMV)	Unknown	Mosquitoes (*Aedes pembaensis*)	E, F/M
	Snowshoe hare virus (SSHV)	Snowshoe hares, squirrels, other small mammals	Mosquitoes (*Aedes*, *Culiseta*, *Ochlerotatus* spp.)	E, F/M
	Ťahyňa virus (TAHV)	Cattle, dogs, eulipotyphla, foxes, hares, horses, pigs, rodents	Mosquitoes (*Aedes*, *Culex*, *Culiseta* spp.)	E, F/M
Orthobunyaviruses (group C serogroup)	Apeú virus (APEUV)	Bare-tailed woolly opossums (*Caluromys philander*) and other opossums; rodents; tufted capuchins (*Cebus apella*)	Mosquitoes (*Aedes*, *Culex* spp.)	F/M
	Caraparú virus (CARV)	Rodents, tufted capuchins (*C. apella*)	Mosquitoes (*Culex* spp.)	F/M
	Itaquí virus (ITQV)	Capuchins (*Cebus* spp.), opossums, rodents	Mosquitoes (*Culex* spp.)	F/M
	Madrid virus (MADV)	Capuchins (*Cebus* spp.), opossums, rodents	Mosquitoes (*Culex* spp.)	F/M
	Marituba virus (MTBV)	Capuchins (*Cebus* spp.), opossums, rodents	Mosquitoes (*Culex* spp.)	F/M
	Murutucú virus (MURV)	Capuchins (*Cebus* spp.), opossums, pale-throated sloths (*Bradypus tridactylus*), rodents	Mosquitoes (*Coquillettidia*, *Culex* spp.)	F/M
	Nepuyo virus (NEPV)	Bats (*Artibeus* spp.), rodents	Mosquitoes (*Culex* spp.)	F/M
	Oriboca virus (ORIV)	Capuchins (*Cebus* spp.), opossums, rodents	Mosquitoes (*Aedes*, *Culex*, *Mansonia*, *Psorophora* spp.)	F/M
	Ossa virus (OSSAV)	Rodents	Mosquitoes (*Culex* spp.)	F/M
	Restan virus (RESV)	Unknown	Mosquitoes (*Culex* spp.)	F/M
	Zungarococha virus (ZUNV)	Unknown	Unknown	F/M
Orthobunyaviruses (Guamá serogroup)	Catú virus (CATUV)	Bats, capuchins (*Cebus* spp.), opossums, rodents	Mosquitoes (*Culex* spp.)	F/M
	Guamá virus (GMAV)	Bats, capuchins (*Cebus* spp.), howlers (*Alouatta* spp.), marsupials, rodents	Mosquitoes (*Aedes*, *Culex*, *Limatus*, *Mansonia*, *Psorophora*, *Trichoprosopon* spp.)	F/M
Orthobunyaviruses (Mapputta serogroup)	Gan Gan virus (GGV)	Unknown	Mosquitoes (*Aedes*, *Culex* spp.)	A/R
	Trubanaman virus (TRUV)	Unknown	Mosquitoes (*Anopheles*, *Culex* spp.)	(A/R)
Orthobunyaviruses (Nyando serogroup)	Nyando virus (NDV)	Unknown	Mosquitoes (*Aedes*, *Anopheles* spp.), sandflies (*Lutzomyia* spp.)	F/M
Orthobunyaviruses (Simbu serogroup)	Iquitos virus (IQTV)	Unknown	Unknown	F/M
	Oropouche virus (OROV)	Marmosets (*Callithrix* spp.), pale-throated sloths (*B. tridactylus*)	Biting midges (*Culicoides paraensis*), mosquitoes (*Coquillettidia venezuelensis*, *Culex quinquefasciatus*, *Mansonia* spp., *Ochlerotatus serratus*)	F/M
Orthobunyaviruses (Wyeomyia serogroup)	Wyeomyia virus (WYOV)	Unknown	Mosquitoes (*Wyeomyia* spp.)	F/M
Orthobunyaviruses (serogroup undetermined)	Tataguine virus (TATV)	Unknown	Mosquitoes (*Anopheles* spp.)	F/M
Orthohantaviruses (Old World)	Amur/Soochong virus (ASV)	Korean field mice (*Apodemus peninsulae*)	None	VHF
	Dobrava-Belgrade virus (DOBV)	Caucasus field mice (*Apodemus ponticus*), striped field mice (*Apodemus agrarius*), yellow-necked field mice (*Apodemus flavicollis*)	None	VHF
	Gōu virus (GOUV)	Brown rats (*Rattus norvegicus*), roof rats (*R. rattus*), Oriental house rats (*Rattus tanezumi*)	None	VHF
	Hantaan virus (HTNV)	Striped field mice (*A. agrarius*)	None	VHF
	Kurkino virus (KURV)	Striped field mice (*A. agrarius*)	None	VHF
	Muju virus (MUJV)	Korean red-backed voles (*Myodes regulus*)	None	VHF
	Puumala virus (PUUV)	Bank voles (*Myodes glareolus*)	None	(P), VHF
	Saaremaa virus (SAAV)	Striped field mice (*A. agrarius*)	None	VHF
	Seoul virus (SEOV)	Brown rats (*R. norvegicus*), roof rats (*R. rattus*)	None	VHF
	Sochi virus	Caucasus field mice (*A. ponticus*)	None	VHF
	Tula virus (TULV)	Common voles (*Microtus arvalis*), East European voles (*Microtus levis*), field voles (*Microtus agrestis*)	None	(P), VHF

(*Continued*)

TABLE 204-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans (Continued)

VIRUS GROUP	VIRUS (ABBREVIATION)	PRINCIPAL RESERVOIR HOST(S)	VECTOR(S)	SYNDROME[a]
Orthohantaviruses (New World)	Anajatuba virus (ANJV)	Fornes' colilargos (*Oligoryzomys fornesi*)	None	P
	Andes virus (ANDV)	Long-tailed colilargos (*Oligoryzomys longicaudatus*)	None	P
	Araraquara virus (ARAV)	Hairy-tailed akodonts (*Necromys lasiurus*)	None	P
	Araucária virus (ARAUV)	Black-footed colilargos (*Oligoryzomys nigripes*)	None	P
	Bayou virus (BAYV)	Marsh rice rats (*Oryzomys palustris*)	None	P
	Bermejo virus (BMJV)	Chacoan colilargos (*Oligoryzomys chacoensis*)	None	P
	Black Creek Canal virus (BCCV)	Hispid cotton rats (*S. hispidus*)	None	P
	Blue River virus (BRV)	White-footed deer mice (*P. leucopus*)	None	P
	Castelo dos Sonhos virus (CASV)	Brazilian colilargos (*Oligoryzomys eliurus*)	None	P
	Choclo virus (CHOV)	Fulvous colilargos (*Oligoryzomys fulvescens*)	None	F/M
	El Moro Canyon virus (ELMCV)	Sumichrast's harvest mice (*Reithrodontomys sumichrasti*), western harvest mice (*Reithrodontomys megalotis*)	None	P
	Juquitiba virus (JUQV)	Black-footed colilargos (*O. nigripes*)	None	P
	Laguna Negra virus (LANV)	Little lauchas (*Calomys laucha*)	None	P
	Lechiguanas virus (LECV)	Flavescent colilargos (*Oligoryzomys flavescens*)	None	P
	Maciel virus (MCLV)	Dark-furred akodonts (*Necromys obscurus*)	None	P
	Maripa virus (MARV)	Unknown	None	P
	Monongahela virus (MGLV)	North American deer mice (*P. maniculatus*)	None	P
	Muleshoe virus (MULV)	Hispid cotton rats (*S. hispidus*)	None	P
	New York virus (NYV)	White-footed deer mice (*P. leucopus*)	None	P
	Orán virus (ORNV)	Long-tailed colilargos (*O. longicaudatus*)	None	P
	Paranoá virus	Unknown	None	P
	Pergamino virus (PRGV)	Azara's akodonts (*Akodon azarae*)	None	P
	Río Mamoré virus (RIOMV)	Common bristly mice (*Neacomys spinosus*)	None	P
	Sin nombre virus (SNV)	North American deer mice (*P. maniculatus*)	None	P
	Tunari virus (TUNV)	Unknown	None	P
Orthonairoviruses (Crimean-Congo hemorrhagic fever virus group)	Crimean-Congo hemorrhagic fever virus (CCHFV)	Cattle, dogs, goats, hares, hedgehogs, mice, ostriches, sheep	Predominantly ixodid ticks (*Hyalomma* spp.)	VHF
Orthonairoviruses (Dugbe virus group)	Dugbe virus (DUGV)	Northern giant pouched rats (*Cricetomys gambianus*), Zébu cattle (*Bos primigenius*)	Biting midges (*Culicoides* spp.), ixodid ticks (*Amblyomma, Hyalomma, Rhipicephalus* spp.)	F/M
	Nairobi sheep disease virus[j] (NSDV)	Sheep	Ixodid ticks (*Haemaphysalis*, *Rhipicephalus* spp.), mosquitoes (*Culex* spp.)	F/M
Orthonairoviruses (Sakhalin virus group)	Avalon virus (AVAV)	European herring gulls (*Larus argentatus*)	Ixodid ticks (*Ixodes uriae*)	(Polyradiculoneuritis?)
Orthonairoviruses (Thiafora virus group)	Erve virus (ERVEV)	Greater white-toothed shrews (*Crocidura russula*)	?	(Thunderclap headache?)
Phleboviruses (Candiru serocomplex)	Alenquer virus (ALEV)	Unknown	Unknown	F/M
	Candiru virus (CDUV)	Unknown	Unknown	F/M
	Escharate virus (ESCV)	Unknown	Unknown	F/M
	Maldonado virus (MLOV)	Unkown	Unknown	F/M
	Morumbi virus (MRBV)	Unknown	Unknown	F/M
	Serra Norte virus (SRNV)	Unknown	Unknown	F/M
Phleboviruses (Punta Toro serocomplex)	Coclé virus (CCLV)	Unknown	Sandlfies	F/M
	Punta Toro virus (PTV)	Unknown	Sandflies (*Lutzomyia* spp.)	F/M
Phleboviruses (sandfly fever serocomplex)	Chagres virus (CHGV)	Unknown	Sandflies (*Lutzomyia* spp.)	F/M
	Chios virus	Unknown	Unknown	E
	Granada virus (GRV)	Unknown	Sandflies	F/M
	Rift Valley fever virus (RVFV)	Cattle, sheep	Mosquitoes (*Aedes*, *Anopheles*, *Coquillettidia*, *Culex*, *Eretmapodites*, *Mansonia* spp.)	E, F/M, VHF
	Sandfly fever Cyprus virus (SFCV)	Unknown	Unknown	F/M

(*Continued*)

TABLE 204-1 Zoonotic Arthropod- and Rodent-Borne Viruses That Infect Humans (Continued)

VIRUS GROUP	VIRUS (ABBREVIATION)	PRINCIPAL RESERVOIR HOST(S)	VECTOR(S)	SYNDROME[a]
	Sandfly fever Ethiopia virus (SFEV)	Unknown	Sandflies	F/M
	Sandfly fever Naples virus (SFNV)	Unknown	Sandflies (*Phlebotomus papatasi*, *P. perfiliewi*, *P. perniciosus*)	F/M
	Sandfly fever Sicilian virus (SFSV)	Eulipotyphla, least weasles (*Mustela nivalis*), rodents	Sandflies (particularly *Phlebotomus papatasi*)	F/M
	Sandfly fever Turkey virus (SFTV)	Unknown	Sandflies (*Phlebotomus* spp.)	F/M
	Toscana virus (TOSV)	Unknown	Sandflies (*Phlebotomus papatasi*, *P. perfiliewi*)	E, F/M
Phleboviruses (Salehabad serocomplex)	Adria virus (ADRV)	Unknown	Sandlfies	E
Phleboviruses (Uukuniemi serocomplex)	Uukuniemi virus (UUKV)	Birds, cattle, rodents	Ixodid ticks (*Ixodes* spp.)	F/M
Quaranjaviruses	Quaranfil virus (QRFV)	Birds	Ixodid ticks (*Argas arboreus*)	F/M
Seadornaviruses	Banna virus (BAV)	Cattle, pigs	Mosquitoes (*Aedes*, *Anopheles*, *Culiseta* spp.)	E
Thogotoviruses	Bourbon virus (BRBV)	Unknown	Ticks?	F/M
	Dhori virus (DHOV)[k]	Bats, camels, horses	Mosquitoes (*Aedes*, *Anopheles*, *Culex* spp.), ixodid ticks (*Dermacentor*, *Hyalomma*, *Ornithodoros* spp.)	E, F/M
	Thogoto virus (THOV)	Camels, cattle	Ixodid ticks (*Amblyomma*, *Hyalomma*, *Rhipicephalus* spp.)	E, F/M
Vesiculoviruses	Chandipura virus (CHPV)	Hedgehogs	Mosquitoes (*Aedes aegypti*), sandflies (*Phlebotomus*, *Sergentomyia* spp.)	E, F/M
	Isfahan virus (ISFV)	Great gerbils (*Rhombomys opimus*)	Sandflies (*Phlebotomus papatasi*)	F/M
	Piry virus (PIRYV)	Gray four-eyed opossums (*Philander opossum*)	Mosquitoes (*Aedes*, *Culex*, *Toxorhynchites* spp.)	F/M
	Vesicular stomatitis Indiana virus (VSIV)	Cattle, horses, pigs	Sandflies (*Lutzomyia* spp.)	F/M
	Vesicular stomatitis New Jersey virus (VSNJV)	Cattle, horses, pigs	Biting midges (*Culicoides* spp.), chloropid flies, mosquitoes (*Culex*, *Mansonia* spp.), muscoid flies (*Musca* spp.), simuliid flies	F/M

[a]Abbreviations refer to the syndrome most commonly associated with the virus: A/R, arthritis/rash; E, encephalitis; F/M, fever/myalgia; P, pulmonary; VHF, viral hemorrhagic fever. Abbreviations are placed in parentheses when cases are either extremely rare or controversial. [b]In the older literature, chikungunya virus often is also listed as a causative agent of VHF. However, later studies revealed that, in most cases, people with "chikungunya hemorrhagic fever" were co-infected with one or more dengue viruses, an observation suggesting that the VHF was actually severe dengue. [c]Also known as Palma virus. [d]Alternatives used in the literature are Huaiyangshan virus (HYSV) and Henan fever virus (HNFV). [e]Also includes Kunjin virus. [f]Includes the recently described Alkhurma/Alkhumra and Nanjianyin variants of Kyasanur Forest disease virus. [g]Whitewater Arroyo virus is often listed as a causative agent of VHF in the literature, but convincing data associating this virus with VHF have not been published. [h]Also known as Brezová virus, Cvilín virus, Kharagysh virus, Koliba virus, or Lipovník virus. [i]Also known as Čalovo virus or Chittoor virus. [j]Also known as Ganjam virus. [k]Also known as Astra virus and Batken virus.

stricto have single-stranded positive-sense RNA genomes (~11 kb) and form spherical enveloped particles 40–60 nm in diameter. The flaviviruses discussed here belong to two phylogenetically and antigenically distinct groups that are transmitted among vertebrates by mosquitoes and ixodid ticks, respectively. Vectors are usually infected when they feed on viremic hosts; as in the case of most other viruses discussed here, humans are accidental hosts who usually are infected by arthropod bites. Arthropods maintain flavivirus infections horizontally, although transovarial transmission has been documented. Under certain circumstances, flaviviruses can also be transmitted by aerosols or via contaminated food products; in particular, raw milk can transmit tick-borne encephalitis virus.

REOVIRIDAE

The family *Reoviridae* contains viruses with linear, multisegmented, double-stranded RNA genomes (~16–29 kb in total). These viruses produce particles that have icosahedral symmetry and are 60–80 nm in diameter. In contrast to all other virions discussed here, reovirions are not enveloped and thus are insensitive to detergent inactivation. Human arthropod-borne viruses are found among the genera *Coltivirus* (subfamily *Spinareovirinae*), *Orbivirus*, and *Seadornavirus* (subfamily *Sedoreovirinae*). Arthropod-borne coltiviruses possess 12 genome segments. Coltiviruses are transmitted by numerous tick types transstadially but not transovarially. Overall maintenance of the transmission cycle, therefore, involves viremic mammalian hosts infected by tick bites. Arthropod-borne orbiviruses have 10 genome segments and are transmitted by mosquitoes or ixodid ticks, whereas relevant seadornaviruses have 12 genome segments and are transmitted exclusively by mosquitoes.

TOGAVIRIDAE

The members of the family *Togaviridae* have linear, single- and positive-stranded RNA genomes (~9.7–11.8 kb) and form enveloped icosahedral virions (~60–70 nm in diameter) that bud from the plasma membrane of the infected cell. The togaviruses discussed here are all members of the genus *Alphavirus* and are transmitted among vertebrates by mosquitoes.

EPIDEMIOLOGY

The distributions of arthropod-borne and rodent-borne viruses are restricted by the areas inhabited by their reservoir hosts and/or vectors. Consequently, a patient's geographic origin or travel history can provide important clues in the differential diagnosis. **Table 204-2** lists the approximate geographic distribution of most arthropod-borne and rodent-borne infections. Many of these diseases can be acquired in either rural or urban settings; these diseases include yellow fever,

TABLE 204-2 Geographic Distribution (United Nations Geoscheme) of Zoonotic Arthropod-Borne or Rodent-Borne Viral Diseases

	TYPE OF DISEASE[a]						
AREA	**ARENAVIRAL**	**BUNYAVIRAL**	**FLAVIVIRAL**	**ORTHOMYXOVIRAL**	**REOVIRAL**	**RHABDOVIRAL**	**TOGAVIRAL**
Africa	Lassa fever; Lujo virus infection	Bangui, Batai, Bhanja, Bunyamwera, and Bwamba virus infections; Crimean-Congo hemorrhagic fever; Dugbe, Germiston, Ilesha virus infections; Nairobi sheep disease virus infection; Ngari, Nyando, and Pongola virus infections; Rift Valley fever, sandfly fever/Pappataci fever/phlebotomus fever; Shokwe, Tataguine virus infections	Dengue/severe dengue; (Usutu virus infection); West Nile virus infection; yellow fever; Zika virus disease	Dhori, Quaranfil, and Thogoto virus infections	Lebombo, Orungo, and Tribeč virus infections	—	Chikungunya virus disease; o'nyong-nyong fever; Semliki Forest and Sindbis virus infections
Central Asia	—	Bhanja virus infection; Crimean-Congo hemorrhagic fever	Tick-borne viral encephalitis	Dhori virus infections	—	Isfahan virus infections	—
Eastern Asia	—	Crimean-Congo hemorrhagic fever; hemorrhagic fever with renal syndrome; sandfly fever/Pappataci fever/phlebotomus fever; severe fever with thrombocytopenia syndrome	Dengue/severe dengue; Japanese encephalitis; Kyasanur Forest disease; tick-borne viral encephalitis	—	Banna virus infections	—	—
Southern Asia	—	Batai and Bhanja virus infections; Crimean-Congo hemorrhagic fever; hemorrhagic fever with renal syndrome; Nairobi sheep disease virus infection; sandfly fever/Pappataci fever/phlebotomus fever	Dengue/severe dengue; Japanese encephalitis; Kyasanur Forest disease; West Nile virus infection; Zika virus disease	Dhori, Quaranfil, and Thogoto virus infections	—	Chandipura and Isfahan virus infections	Chikungunya virus disease
South-Eastern Asia	—	Batai virus infection; hemorrhagic fever with renal syndrome	Dengue/severe dengue; Japanese encephalitis; West Nile virus infection; Zika virus disease	—	—	—	Chikungunya virus disease
Western Asia	—	Batai and Bhanja virus infections; Crimean-Congo hemorrhagic fever; hemorrhagic fever with renal syndrome; sandfly fever/Pappataci fever/phlebotomus fever	Dengue/severe dengue; Kyasanur Forest disease; tick-borne viral encephalitis; West Nile virus infection	Dhori and Quaranfil virus infections	—	—	Chikungunya virus disease
Latin/Central America and the Caribbean	"Brazilian hemorrhagic fever"; Chapare virus infection; Junín/Argentinian hemorrhagic fever; lymphocytic choriomeningitis/meningoencephalitis; Machupo/Bolivian hemorrhagic fever; "Venezuelan hemorrhagic fever"	Alenquer, Apeú, Bunyamwera, Cache Valley, Candiru, Caraparú, Catú, Chagres, Coclé, Escharate, Fort Sherman, Guamá, and Guaroa virus infections; hantavirus (cardio)pulmonary syndrome; Itaquí, Juquitiba, Madrid, Maguari, Maldonado, Marituba, Mayaro, Morumbi, Murutucú, Nepuyo, and Oriboca virus infections; Oropouche virus disease; Ossa, Punta Toro, Restan, Serra Norte, Tacaiuma, Trinidad, Wyeomyia, Xingu, and Zungarococha virus infections	Dengue/severe dengue; Rocio virus disease; yellow fever; Zika virus disease	—	—	Piry virus disease; vesicular stomatitis virus disease/Indiana fever	Chikungunya virus disease; Mayaro virus infection; Mucambo, Tonate, and Una virus infections; Venezuelan equine fever
Northern America	Lymphocytic choriomeningitis/meningoencephalitis; (Whitewater Arroyo virus infection)	(Avalon and) Cache Valley virus infections; California (meningo)encephalitis; hantavirus (cardio)pulmonary syndrome; Heartland virus and Nepuyo virus infections	Dengue/severe dengue; Powassan virus disease; St. Louis encephalitis; West Nile virus infection; Zika virus disease	Bourbon virus infection	Colorado tick fever; Salmon River virus infection	Vesicular stomatitis virus disease/Indiana fever	Eastern equine encephalitis; Everglades virus infection; western equine encephalitis

(*Continued*)

TABLE 204-2 Geographic Distribution (United Nations Geoscheme) of Zoonotic Arthropod-Borne or Rodent-Borne Viral Diseases (Continued)

AREA	TYPE OF DISEASE[a]						
	ARENAVIRAL	BUNYAVIRAL	FLAVIVIRAL	ORTHOMYXOVIRAL	REOVIRAL	RHABDOVIRAL	TOGAVIRAL
Europe	Lymphocytic choriomeningitis/ meningoencephalitis	(Adria, Avalon, and) Bhanja virus infections; California (meningo)encephalitis; Crimean-Congo hemorrhagic fever; (Erve virus infection); hemorrhagic fever with renal syndrome; Inkoo virus infection; sandfly fever/ Pappataci fever/phlebotomus fever; Uukuniemi virus infection	Dengue/severe dengue; tick-borne viral encephalitis; Omsk hemorrhagic fever; (Usutu virus infection); West Nile virus infection	Dhori and Thogoto virus infections	Eyach, Kemerovo, and Tribeč virus infections	—	Chikungunya virus disease; Sindbis virus infection
Oceania	—	Gan Gan (and Trubanaman virus) infections	Australian encephalitis; dengue/severe dengue; Japanese encephalitis; Kokobera virus infection; Murray Valley encephalitis; West Nile virus infection; Zika virus disease	—	—	—	Barmah Forest virus infection; Ross River disease; Sindbis virus infection

[a]Quotation marks indicate common usage in the absence of International Classification of Disease version 10 (ICD-10) recognition. Diseases not acknowledged by the ICD-10 are designated as "virus infection(s)." Disease names are placed in parentheses when cases are either extremely rare or controversial.

dengue (previously called dengue fever), severe dengue (previously called dengue hemorrhagic fever and dengue shock syndrome), chikungunya virus disease, HFRS caused by Seoul virus, sandfly fever caused by sandfly fever Naples and Sicilian viruses, and Oropouche virus disease.

DIAGNOSIS

In patients with suspected viral infection, a recognized history of mosquito bite(s) has little diagnostic significance, but a history of tick bite(s) is more diagnostically useful. Exposure to rodents is sometimes reported by persons infected with mammarenaviruses or orthohantaviruses. Laboratory diagnosis is required in all cases, although epidemics occasionally provide enough clinical and epidemiologic clues for a presumptive etiologic diagnosis. For most arthropod-borne and rodent-borne viruses, acute-phase serum samples (collected within 3 or 4 days of onset) have yielded isolates. Paired serum samples have been used to demonstrate rising antibody titers. Intensive efforts to develop rapid tests for viral hemorrhagic fevers (VHFs) have resulted in reliable antigen-detection enzyme-linked immunosorbent assays (ELISAs), IgM-capture ELISAs, and multiplex polymerase chain reaction (PCR) assays. These tests can provide a diagnosis based on a single serum sample within a few hours and are particularly useful in patients with severe disease. More sensitive reverse-transcription PCR (RT-PCR) assays may yield diagnoses based on samples without detectable antigen and may also provide useful genetic information about the etiologic agent.

Orthohantavirus infections differ from other viral infections discussed here in that severe acute disease is immunopathologic; patients present with serum IgM that serves as the basis for a sensitive and specific test. At diagnosis, patients with encephalitides generally are no longer viremic or antigenemic and usually do not have virions in cerebrospinal fluid (CSF). In this situation, the value of serologic methods for IgM determination and RT-PCR is high. IgM-capture ELISA is increasingly used for the simultaneous testing of serum and CSF. IgG ELISA or classic serology is useful in the evaluation of past exposure to viruses, many of which circulate in areas with minimal medical infrastructures and sometimes cause only mild or subclinical infections.

SYNDROMES

The spectrum of possible human responses to infection with arthropod- or rodent-borne viruses is wide, and knowledge of the outcome of most of these infections is limited. People infected with these viruses may not develop signs of illness. If viral disease is recognized, it can usually be grouped into one of five broad categories: arthritis and rash, encephalitis, fever and myalgia, pulmonary disease, or VHF (Table 204-3). These categories often overlap. For example, infections with West Nile and Venezuelan equine encephalitis viruses are discussed here as encephalitides, but during epidemics many patients present with much milder febrile syndromes. Similarly, Rift Valley fever virus is best known as a cause of VHF, but the attack rates for febrile disease are far higher, and encephalitis and blindness occasionally occur as well. Lymphocytic choriomeningitis virus is classified here as a cause of fever and myalgia because this syndrome is the most common disease manifestation. Even when central nervous system (CNS) disease evolves during infection with this virus, neural manifestations are usually mild and are preceded by fever and myalgia. However, this virus may also cause fetal microcephaly. Infection with any dengue virus (1, 2, 3, or 4) is considered as a cause of fever and myalgia because this syndrome is by far the most common manifestation worldwide. However, severe dengue is a VHF with a complicated pathogenesis that is of tremendous importance in pediatric practice in certain areas of the world. Unfortunately, most of the known arthropod- or rodent-borne viral diseases have not been studied in detail with modern medical approaches; thus available data may be incomplete or biased. The reader must be aware that data on geographic distribution are often fuzzy: the literature frequently is not clear as to whether the data pertain to the distribution of a particular virus or to the areas where human disease has been observed. In addition, the designations for viruses and viral diseases have changed multiple times over decades. Here, virus and taxon names are in line with the latest reports of the International Committee on Taxonomy of Viruses, and disease names are in accordance with the World Health Organization's International Classification of Disease version 10 (ICD-10) and more recent updates.

ARTHRITIS AND RASH

Arthritides are common accompaniments of several viral diseases, such as hepatitis B, parvovirus B19 infection, and rubella, and occasionally accompany infection due to adenoviruses, enteroviruses, herpesviruses, or mumps virus. Two orthobunyaviruses—Gan Gan virus and Trubanaman virus—and the flavivirus Kokobera virus have been associated with single cases of polyarthritic disease. Arthropod-borne alphaviruses are also common causes of arthritides—usually acute febrile diseases accompanied by the development of a maculopapular

TABLE 204-3 Clinical Syndromes Caused by Zoonotic Arthropod-Borne or Rodent-Borne Viruses

SYNDROME	VIRUS[a]
Arthritis and rash (A/R)	*Flaviviridae:* Kokobera and Zika viruses
	Peribunyaviridae: Gan Gan (and Trubanaman) viruses
	Togaviridae: Barmah Forest, chikungunya, Mayaro, o'nyong-nyong, Ross River, Semliki Forest, and Sindbis viruses
Encephalitis (E)	*Arenaviridae:* lymphocytic choriomeningitis (and Whitewater Arroyo) viruses
	Flaviviridae: Japanese encephalitis, Murray Valley encephalitis, Powassan, Rocio, St. Louis encephalitis, tick-borne encephalitis, (Usutu), and West Nile viruses
	Orthomyxoviridae: Dhori and Thogoto viruses
	Peribunyaviridae: California encephalitis, Inkoo, Jamestown Canyon, La Crosse, Lumbo, snowshoe hare, and Ťahyňa viruses
	Phenuiviridae: Adria, Bhanja, Chios, Rift Valley fever, and Toscana viruses
	Reoviridae: Banna, Colorado tick fever, Eyach, Kemerovo, Orungo, and Salmon River viruses
	Rhabdoviridae: Chandipura virus
	Togaviridae: eastern equine encephalitis, Everglades, Mucambo, Tonate, Venezuelan equine encephalitis, and western equine encephalitis viruses
Fever and myalgia (F/M)	*Arenaviridae:* Lassa and lymphocytic choriomeningitis viruses
	Bunyavirales (unclassified): Bangui virus
	Flaviviridae: dengue 1–4, tick-borne encephalitis, and Zika viruses
	Hantaviridae: Choclo virus
	Nairoviridae: Dugbe and Nairobi sheep disease viruses
	Orthomyxoviridae: Bourbon, Dhori, and Thogoto viruses
	Peribunyaviridae: Apeú, Batai, Bunyamwera, Bwamba, Cache Valley, California encephalitis, Caraparú, Catú, Fort Sherman, Germiston, Guamá, Guaroa, Ilesha, Inkoo, Iquitos, Itaquí, Jamestown Canyon, La Crosse, Lumbo, Madrid, Maguari, Marituba, Nepuyo, Ngari, Nyando, Oriboca, Oropouche, Ossa, Pongola, Restan, Shokwe, snowshoe hare, Tacaiuma, Ťahyňa, Tataguine, Wyeomyia, Xingu, and Zungarococha viruses
	Phenuiviridae: Alenquer, Bhanja, Candiru, Chagres, Escharate, Heartland, Maldonado, Morumbi, Punta Toro, Rift Valley fever, sandfly fever Cyprus, sandfly fever Ethiopia, sandfly fever Naples, sandfly fever Sicilian, sandfly fever Turkey, Serra Norte, severe fever with thrombocytopenia syndrome, Toscana, and Uukuniemi viruses
	Reoviridae: Colorado tick fever, Eyach, Kemerovo, Lebombo, Orungo, Salmon River, and Tribeč viruses
	Rhabdoviridae: Chandipura, Isfahan, Piry, vesicular stomatitis Indiana, and vesicular stomatitis New Jersey viruses
	Togaviridae: Everglades, Mucambo, Tonate, Una, and Venezuelan equine encephalitis viruses
Pulmonary disease (P)	*Hantaviridae:* Anajatuba, Andes, Araucária, bayou, Bermejo, Black Creek Canal, Blue River, Castelo dos Sonhos, El Moro Canyon, Juquitiba, Laguna Negra, Lechiguanas, Maciel, Monongahela, Muleshoe, New York, Orán, Paranoá, Pergamino, (Puumala), Río Mamoré, sin nombre, (Tula), and Tunari viruses
Viral hemorrhagic fever (VHF)	*Arenaviridae:* Chapare, Guanarito, Junín, Lassa, Lujo, (lymphocytic choriomeningitis), Machupo, and Sabiá viruses
	Hantaviridae: Amur/Soochong, Dobrava-Belgrade, Gōu, Hantaan, Kurkino, Muju, Puumala, Saaremaa, Seoul, Sochi, and Tula viruses
	Nairoviridae: Crimean-Congo hemorrhagic fever virus
	Peribunyaviridae: (Ilesha and) Ngari viruses
	Phenuiviridae: Rift Valley fever and severe fever with thrombocytopenia syndrome viruses
	Flaviviridae: dengue 1–4, Kyasanur Forest disease, Omsk hemorrhagic fever, (tick-borne encephalitis), and yellow fever viruses

[a]Virus names are placed in parentheses when human infections are either extremely rare or controversial.

rash. Rheumatic involvement includes arthralgia alone, periarticular swelling, and (less commonly) joint effusions. Most alphavirus infections are less severe and have fewer articular manifestations in children than in adults. In temperate climates, these ailments are summer diseases. No specific therapies or licensed vaccines exist. The most important alphavirus arthritides are Barmah Forest virus infection, chikungunya virus disease, Ross River disease, and Sindbis virus infection. A large (>2 million cases), albeit isolated, epidemic was caused by o'nyong nyong virus in 1959–1961 (o'nyong nyong fever). Mayaro, Semliki Forest, and Una viruses caused isolated cases or limited and infrequent epidemics (30 to several hundred cases per year). Signs and symptoms of infections with these viruses often are similar to those observed with chikungunya virus disease.

Chikungunya Virus Disease Disease caused by chikungunya virus is endemic in rural areas of Africa. Intermittent epidemics take place in towns and cities of both Africa and Asia. Yellow fever mosquitoes (*Aedes aegypti*) are the usual vectors for the disease in urban areas. In 2004, a massive epidemic began in the Indian Ocean region (in particular on the islands of Réunion and Mauritius) and was most likely spread by travelers. The Asian tiger mosquito (*Aedes albopictus*) was identified as the major vector of chikungunya virus during that epidemic. From 2013 and 2014, several thousand chikungunya virus infections were reported (and several tens to hundreds of thousands of cases were suspected) from Caribbean islands. The virus was imported to Italy, France, and the United States by travelers from the Caribbean. Chikungunya virus poses a threat to the continental United States as suitable vector mosquitoes are present in southern states. The disease is most common among adults, in whom the clinical presentation may be dramatic. The abrupt onset of chikungunya virus disease follows an incubation period of 2–10 days. Fever (often severe) with a saddleback pattern and severe arthralgia are accompanied by chills and constitutional symptoms and signs, such as abdominal pain, anorexia, conjunctival injection, headache, nausea, and photophobia. Migratory polyarthritis mainly affects the small joints of the ankles, feet, hands, and wrists, but the larger joints are not necessarily spared. Rash may appear at the outset or several days into the illness; its development often coincides with defervescence, which occurs around day 2 or 3 of the disease. The rash is most intense on the trunk and limbs and may desquamate. Young children develop less prominent signs and are therefore less frequently hospitalized. Children also often develop a bullous rather than a maculopapular/petechial rash. Maternal–fetal transmission has been reported and, in some cases, has led to fetal death. Recovery may require weeks, and some elderly patients may continue to experience joint pain, recurrent effusions, or stiffness for several years. This persistence of signs and symptoms may be especially common in human leukocyte antigen B27 subtype (HLA-B27)–positive patients. In addition to arthritis, petechiae are occasionally seen, and epistaxis is not uncommon, but chikungunya virus should not be considered a VHF agent. A few patients develop leukopenia. Elevated concentrations of aspartate aminotransferase (AST) and C-reactive protein have been described, as have mildly decreased platelet counts. Treatment of chikungunya virus disease relies on nonsteroidal anti-inflammatory drugs and sometimes chloroquine for refractory arthritis.

Ross River Disease and Barmah Forest Virus Infection Ross River virus and Barmah Forest virus cause diseases that are indistinguishable on clinical grounds alone (hence the previously common disease designation *epidemic polyarthritis* for both infections). Ross River virus has caused epidemics in Australia, Papua New Guinea, and the South Pacific since the beginning of the twentieth century. In 1979–1980, the virus swept through the Pacific Islands, causing more than 500,000 infections. In 1991–2011, Ross River virus caused a total of 92,559 infections or disease in rural and suburban areas. Ross River virus is predominantly transmitted by *Aedes normanensis*, *Aedes vigilax*, and *Culex annulirostris* mosquitoes. Wallabies and rodents are probably the main vertebrate hosts. Barmah Forest virus infections have been on the rise in recent years. For instance, in 1991–2011, 21,815 cases were recorded in Australia. Barmah Forest virus is transmitted by both *Aedes* and *Culex* mosquitoes and has been isolated from biting midges. The vertebrate hosts remain to be determined, but serologic studies implicate horses and possums.

Of the human Barmah Forest and Ross River virus infections surveyed, 55–75% were asymptomatic; however, these viral diseases can be debilitating. The incubation period is 7–9 days; the onset of illness is sudden, and disease is usually ushered in by disabling symmetrical joint pain. A non-itchy, diffuse, maculopapular rash (more common in Barmah Forest virus infection) generally develops coincidentally or follows shortly, but in some patients rash can precede joint pain by several days. Constitutional symptoms such as low-grade fever, asthenia, headache, myalgia, and nausea are not prominent or are absent in many patients. Most patients are incapacitated for considerable periods (≥6 months) by joint involvement, which interferes with grasping, sleeping, and walking. Ankle, interphalangeal, knee, metacarpophalangeal, and wrist joints are most often involved, although elbows, shoulders, and toes may also be affected. Periarticular swelling and tenosynovitis are common, and one-third of patients have true arthritis (more common in Ross River disease). Myalgia and nuchal stiffness may accompany joint pains. Only half of all patients with arthritis can resume normal activities within 4 weeks, and 10% still must limit their activity after 3 months. Occasional patients are symptomatic for 1–3 years but without progressive arthropathy.

In the diagnosis of either infection, clinical laboratory values are normal or variable. Tests for rheumatoid factor and antinuclear antibodies are negative, and the erythrocyte sedimentation rate is acutely elevated. Joint fluid contains 1000–60,000 mononuclear cells/μL, and viral antigen can usually be detected in macrophages. IgM antibodies are valuable in the diagnosis of this infection, although such antibodies occasionally persist for years. Isolation of the virus from blood after mosquito inoculation or growth of the virus in cell culture is possible early in the illness. Because of the great economic impact of annual epidemics in Australia, an inactivated Ross River virus vaccine is under advanced development; phase 3 trials were completed in 2015. Nonsteroidal anti-inflammatory drugs, such as naproxen or acetylsalicylic acid, are effective for treatment.

Sindbis Virus Infection Sindbis virus is transmitted among birds by infected mosquitoes. Infections with Northern European or Southern African variants are particularly likely in rural environments. After an incubation period of <1 week, Sindbis virus infection begins with rash and arthralgia. Constitutional clinical signs are not marked, and fever is modest or lacking altogether. The rash, which lasts ~1 week, begins on the trunk, spreads to the extremities, and evolves from macules to papules that often vesiculate. The arthritis is multiarticular, migratory, and incapacitating, with resolution of the acute phase in a few days. The ankles, elbows, knees, phalangeal joints, wrists, and—to a much lesser extent—proximal and axial joints are involved. Persistence of joint pain and occasionally of arthritis is a major problem and may continue for months or even years despite lack of deformities.

Zika Virus Disease Zika virus is an emerging pathogen that is transmitted among nonhuman primates and humans by *Aedes* mosquitoes. The virus was discovered 1947 in a sentinel rhesus monkey (*Macaca mulatta*) and *Aedes africanus* mosquitoes in the Zika Forest in what was then the British Protectorate of Uganda. Human Zika virus infection was first documented during a yellow fever outbreak in 1954 in Nigeria. Later, Zika virus infections were recognized in South-Eastern and Southern Asia. Prior to 2007, only 14 clinically identified cases of Zika virus disease had been reported. In recent years, the number of Zika virus infections reported has increased steadily and rapidly, with large, but generally mild, disease outbreaks on Yap Island, Micronesia (2007), and in Cambodia (2010), the Philippines (2012), and French Polynesia (2013–2014). Invasion of the New World was first reported in 2014 on Easter Island in Chile and in 2015 in Brazil. At the end of May 2017, Zika virus infections had been recorded on the five continents in 85 countries, including Mexico and the United States. An estimated 440,000 to 1.3 million cases had occurred in Brazil by the end of 2015.

Phylogenetic analysis of all available African Zika virus isolates revealed two geographically overlapping clades (Western and Eastern Africa). A descendant Asian lineage, represented by viruses collected from mosquitoes trapped in homes in Malaysia, was first reported in 1969. All Zika virus isolates causing human cases outside of Africa trace back to this Asian lineage.

Human infections are usually asymptomatic or benign and self-resolving and are most likely misdiagnosed as dengue or influenza. Zika virus disease is typically characterized by low-grade fever, headache, and malaise. An itchy maculopapular rash, nonpurulent conjunctivitis, myalgia, and arthralgia usually accompany or follow those manifestations. Vomiting, hematospermia, and hearing impairments are relatively common clinical signs. In severe cases, Zika virus infection is associated with serious complications such as Guillain-Barré syndrome or fetal microcephaly after congenital transmission. Other neurologic complications of Zika virus infection are encephalitis, meningoencephalitis, transverse myelitis, peripheral neuropathies, retinopathies, and neurologic birth defects. Although most human Zika virus infections are acquired after bites by infected female mosquitoes, transmission may also occur perinatally or via heterosexual or homosexual contact with an infected person, breastfeeding, or transfusion of blood products. Specifically, viral persistence in the testes, which can last up to at least 160 days, is worrisome, as sexual virus transmission be may be possible throughout that period. Unfortunately, antiviral treatments (curative or preventive) and licensed vaccines against Zika virus are not yet available.

ENCEPHALITIS

The major encephalitis viruses are found in the families *Flaviviridae, Peribunyaviridae, Rhabdoviridae,* and *Togaviridae*. However, individual agents of other families, including Dhori virus and Thogoto virus *(Orthomyxoviridae)* and Banna virus *(Reoviridae)*, have been known to cause isolated cases of encephalitis as well. Arboviral encephalitides are seasonal diseases, commonly occurring in the warmer months. Their incidence varies markedly with time and place, depending on ecologic factors. The causative viruses differ substantially in terms of case–infection ratio (i.e., the ratio of clinical to subclinical infections), lethality, and residual disease. Humans are not important amplifiers of these viruses.

All the viral encephalitides discussed in this section have a similar pathogenesis. An infected arthropod ingests blood from a human and thereby initiates infection. The initial viremia is thought to originate from the lymphoid system. Viremia leads to multifocal entry into the CNS, presumably through infection of olfactory neuroepithelium, with passage through the cribriform plate; "Trojan horse" entry with infected macrophages; or infection of brain capillaries. During the viremic phase, there may be little or no recognizable disease except in tick-borne flavivirus encephalitides, which may manifest with clearly delineated phases of fever and systemic illness.

CNS lesions arise partly from direct neuronal infection and subsequent damage and partly from edema, inflammation, and other indirect effects. The usual pathologic features of arboviral encephalitides are focal necroses of neurons, inflammatory glial nodules, and perivascular lymphoid cuffing. Involved areas display the "luxury perfusion" phenomenon, with normal or increased total blood flow and low oxygen extraction. The typical patient presents with a prodrome of nonspecific constitutional signs and symptoms, including fever,

abdominal pain, sore throat, and respiratory signs. Headache, meningeal signs, photophobia, and vomiting follow quickly. The severity of human infection varies from an absence of signs/symptoms to febrile headache, aseptic meningitis, and full-blown encephalitis. The proportions and severity of these manifestations vary with the infecting virus. Involvement of deeper brain structures in less severe cases may be signaled by lethargy, somnolence, and intellectual deficit (as disclosed by the mental status examination). More severely affected patients are obviously disoriented and may become comatose. Tremors, loss of abdominal reflexes, cranial nerve palsies, hemiparesis, monoparesis, difficulty swallowing, limb-girdle syndrome, and frontal lobe signs are all common. Spinal and motor neuron diseases are documented after West Nile and Japanese encephalitis virus infections. Seizures and focal signs may be evident early or may appear during the course of the disease. Some patients present with an abrupt onset of fever, convulsions, and other signs of CNS involvement. The acute encephalitis usually lasts from a few days to as long as 2–3 weeks. The infections may be fatal, or recovery may be slow, with weeks or months required for the return of maximal recoupable function, or incomplete, with persisting long-term deficits. Difficulty concentrating, fatigability, tremors, and personality changes are common during recovery.

The diagnosis of arboviral encephalitides depends on the careful evaluation of a febrile patient with CNS disease and the performance of laboratory studies to determine etiology. Clinicians should (1) consider empirical acyclovir treatment for herpesvirus meningoencephalitis and antibiotic treatment for bacterial meningitis until test results are received; (2) exclude intoxination and metabolic or oncologic causes, including paraneoplastic syndromes, hyperammonemia, liver failure, and anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis; and (3) rule out a brain abscess or a stroke. Leptospirosis, neurosyphilis, Lyme disease, cat-scratch disease, and more recently described viral encephalitides (e.g., Nipah virus infection), among others, should be considered if epidemiologically relevant. CSF examination usually shows a modest increase in leukocyte counts—in the tens or hundreds or perhaps a few thousand. Early in the process, a significant proportion of these leukocytes may be polymorphonuclear, but mononuclear cells are usually predominant later. CSF glucose concentrations are generally normal. There are exceptions to this pattern of findings: in eastern equine encephalitis, for example, polymorphonuclear leukocytes may predominate during the first 72 h of disease, and hypoglycorrhachia may be detected. In lymphocytic choriomeningitis/meningoencephalitis, lymphocyte counts may be in the thousands, and glucose concentrations may be diminished. A humoral immune response is usually detectable at or near the onset of disease. Both serum (acute- or convalescent-phase) and CSF should be examined for IgM antibodies, and viruses should be detected by plaque-reduction neutralization assay and/or (RT)-PCR. Virus generally cannot be isolated from blood or CSF, although Japanese encephalitis virus has been recovered from CSF of patients with severe disease. RT-PCR analysis of CSF may yield positive results. Viral antigen is present in brain tissue, although its distribution may be focal. Electroencephalography usually shows diffuse abnormalities and is not directly helpful.

Experience with medical imaging is still evolving. Both CT and MRI scans may be normal except for evidence of preexisting conditions or occasional diffuse edema. Imaging is generally nonspecific, as most patients do not present with pathognomonic lesions, but it can be used to rule out other suspected causes of disease. It is important to remember that imaging may yield negative results if done early in the disease course but may later detect lesions. For example, eastern equine encephalitis (focal abnormalities) and severe Japanese encephalitis (hemorrhagic bilateral thalamic lesions) have caused lesions detectable by medical imaging.

Comatose patients may require management of intracranial pressure elevations, inappropriate secretion of antidiuretic hormone, respiratory failure, or seizures. Specific therapies for these viral encephalitides are not available. The only practical preventive measures are vector management and personal protection against the arthropod transmitting the virus. For Japanese encephalitis or tick-borne viral encephalitis, vaccination should be considered in certain circumstances (see relevant sections below).

Flaviviruses The most important flavivirus encephalitides are Japanese encephalitis, St. Louis encephalitis, tick-borne encephalitis, and West Nile virus infection. Australian encephalitis (Murray Valley encephalitis) and Rocio virus infection resemble Japanese encephalitis but are documented only occasionally in Australia and Brazil, respectively. Powassan virus has caused ~77 cases of often-severe disease (lethality, ~10%), frequently occurring among children in eastern Canada and the United States. Usutu virus has caused only individual cases of human infection, but such infections may be underdiagnosed.

JAPANESE ENCEPHALITIS Japanese encephalitis is the most important viral encephalitis in Asia. Each year ~68,000 cases and ~13,600–20,400 deaths are reported. Japanese encephalitis virus is found throughout Asia, including in Far Eastern Russia, Japan, China, India, Pakistan, and South-Eastern Asia, and causes occasional epidemics on western Pacific islands. The virus has been detected in the Torres Strait islands, and five human encephalitis cases have been identified on the nearby Australian mainland. The virus is particularly common in areas where irrigated rice fields attract the natural avian vertebrate hosts and provide abundant breeding sites for *Culex tritaeniorhynchus* mosquitoes, which transmit the virus to humans. Additional amplification by pigs, which suffer abortion, and horses, which develop encephalitis, may be significant as well. Vaccination of these additional amplifying hosts may reduce the transmission of the virus.

Clinical signs of Japanese encephalitis emerge after an incubation period of 5–15 days and range from an unspecific febrile presentation (nausea, vomiting, diarrhea, cough) to aseptic meningitis, meningoencephalitis, acute flaccid paralysis, and severe encephalitis. Common findings are cerebellar signs, cranial nerve palsies, and cognitive and speech impairments. A Parkinsonian presentation and seizures are typical in severe cases. Effective vaccines are available. Vaccination is indicated for summer travelers to rural Asia, where the risk of acquiring Japanese encephalitis is considered to be about 1 per 5000 to 1 per 20,000 travelers per week if travel duration exceeds 3 weeks. Usually two intramuscular doses of the vaccine are given 28 days apart, with the second dose administered at least 1 week prior to travel.

ST. LOUIS ENCEPHALITIS St. Louis encephalitis virus is transmitted between mosquitoes and birds. This virus causes a low-level endemic infection among rural residents of the western and central United States, where *Culex tarsalis* mosquitoes serve as vectors (see "Western Equine Encephalitis," below). The more urbanized mosquitoes (*Culex pipiens* and *Culex quinquefasciatus*) have been responsible for epidemics resulting in hundreds or even thousands of cases in cities of the central and eastern United States. Most cases occur in June through October. The urban mosquitoes breed in accumulations of stagnant water and sewage with high organic content and readily feed on humans in and around houses at dusk. The elimination of open sewers and trash-filled drainage systems is expensive and may not be possible. However, screening of houses and implementation of personal protective measures may be effective approaches to the prevention of infection. The rural mosquito vector is most active at dusk and outdoors; its bites can be avoided by modification of activities and use of repellents.

Disease severity increases with age. St. Louis encephalitis virus infections that result in aseptic meningitis or mild encephalitis are concentrated among children and young adults, whereas severe and fatal cases primarily affect the elderly. Infection rates are similar in all age groups; thus, the greater susceptibility of older persons to disease is a biologic consequence of aging. St. Louis encephalitis has an abrupt onset after an incubation period of 4–21 days, sometimes following a prodrome, and begins with fever, lethargy, confusion, and headache. In addition, nuchal rigidity, hypotonia, hyperreflexia, myoclonus, and tremors are common. Severe cases can include cranial nerve palsies, hemiparesis, and seizures. Patients often report dysuria and may have viral antigen in urine as well as pyuria. The overall lethality is generally ~7% but may reach 20% among patients >60 years of age. Recovery is slow. Emotional lability, difficulties with concentration and memory, asthenia, and tremors are commonly prolonged in older convalescent patients. The CSF of patients with St. Louis encephalitis usually contains tens to hundreds of leukocytes, with a lymphocytic

predominance and a left shift. The CSF glucose concentration is normal in these patients.

TICK-BORNE VIRAL ENCEPHALITIS Tick-borne encephalitis viruses are currently subdivided into four groups: the western/European subtype (previously called central European encephalitis virus), the (Ural-)Siberian subtype (previously called Russian spring–summer encephalitis virus), the Far Eastern subtype, and the louping ill subtype (previously called louping ill virus or, in Japan, Negishi virus). Small mammals and grouse, deer, and sheep are the vertebrate amplifiers for these viruses, which are transmitted by ticks. The risk of infection varies by geographic area and can be highly localized within a given area. Human infections usually follow either outdoor activities resulting in tick bites or consumption of raw (unpasteurized) milk from infected goats or, less commonly, from other infected animals (cows, sheep). Milk seems to represent the main transmission route for louping ill–subtype viruses, which cause disease only very rarely. The western/European-subtype viruses are transmitted mainly by *Ixodes ricinus* ticks from Scandinavia to the Ural Mountains. (Ural-)Siberian viruses are transmitted predominantly by *Ixodes persulcatus* ticks from Europe across the Ural Mountains to the Pacific Ocean. Louping ill–subtype viruses seem to be confined primarily to Great Britain. Several thousand infections with tick-borne encephalitis virus are recorded each year among people of all ages. Human tick-borne viral encephalitis occurs between April and October, with a peak in June and July.

Western/European viruses classically caused bimodal disease. After an incubation period of 7–14 days, the illness begins with a *fever–myalgia phase* (arthralgia, fever, headaches, myalgia, nausea) that lasts for 2–4 days and is thought to correlate with viremia. A subsequent remission for several days is followed by the recurrence of fever and the onset of meningeal signs. The *CNS phase* (7–10 days before onset of improvement) varies from mild aseptic meningitis, which is more common among younger patients, to severe (meningo)encephalitis with coma, seizures, tremors, and motor signs. Spinal and medullary involvement can lead to typical limb-girdle paralysis and respiratory paralysis. Most patients with western/European virus infections recover (lethality, 1%), and only a minority of patients have significant deficits. However, the lethality from (Ural-)Siberian virus infections reaches 7–8%.

Infections with Far Eastern viruses generally run a more abrupt course. The encephalitic syndrome caused by these viruses sometimes begins without a remission from the fever–myalgia phase and has more severe manifestations than the western/European syndrome. Lethality is high (20–40%), and major sequelae—most notably, lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck—are common, developing in approximately one-half of patients. Thrombocytopenia sometimes develops during the initial febrile illness, resembling the early hemorrhagic phase of some other tick-borne flavivirus infections, such as Kyasanur Forest disease. In the early stage of the illness, virus may be isolated from the blood. In the CNS phase, IgM antibodies are detectable in serum and/or CSF.

Diagnosis of tick-borne viral encephalitis primarily relies on serology and detection of viral genomes by RT-PCR. There is no specific therapy for infection. However, effective alum-adjuvanted, formalin-inactivated virus vaccines are produced in Austria, Germany, and Russia in chicken embryo cells (FSME-Immun® and Encepur®). Two doses of the Austrian vaccine separated by an interval of 1–3 months appear to be effective in the field, and antibody responses are similar when vaccine is given on days 0 and 14. Because rare cases of postvaccination Guillain-Barré syndrome have been reported, vaccination should be reserved for persons likely to experience rural exposure in an endemic area during the season of transmission. Cross-neutralization for the western/European and Far Eastern variants has been established, but there are no published field studies on cross-protection among formalin-inactivated vaccines.

Because 0.2–4% of ticks in endemic areas may be infected, the use of immunoglobulin prophylaxis of tick-borne viral encephalitis has been raised. Prompt administration of high-titered specific antibody preparations should probably be undertaken, although no controlled data are available to prove the efficacy of this measure. Immunoglobulins should be considered because of the risk of antibody-mediated enhancement of infection or antigen–antibody complex deposition in tissues.

WEST NILE VIRUS INFECTION West Nile virus is now the primary cause of arboviral encephalitis in the United States. From 1999 to 2015, 20,265 cases of neuroinvasive disease (e.g., meningitis, encephalitis, acute flaccid paralysis), with 1783 deaths, and 23,672 cases of non-neuroinvasive infection, with 128 deaths, were reported. West Nile virus was initially described as being transmitted among wild birds by *Culex* mosquitoes in Africa, Asia, and Southern Europe. In addition, the virus has been implicated in severe and fatal hepatic necrosis in Africa. West Nile virus was introduced into New York City in 1999 and subsequently spread to other areas of the northeastern United States, causing die-offs among crows, exotic zoo birds, and other birds. The virus has continued to spread and is now found in almost all U.S. states as well as in Canada, Mexico, South America, and the Caribbean islands. *C. pipiens* mosquitoes remain the major vectors in the northeastern United States, but mosquitoes of several other *Culex* species and *A. albopictus* mosquitoes are also involved. Jays compete with crows and other corvids as amplifiers and lethal targets in other areas of the country.

West Nile virus is a common cause of febrile disease without CNS involvement (incubation period, 3–14 days), but it occasionally causes aseptic meningitis and severe encephalitis, particularly among the elderly. The fever–myalgia syndrome caused by West Nile virus differs from that caused by other viruses in terms of the frequent—rather than occasional—appearance of a maculopapular rash concentrated on the trunk (especially in children) and the development of lymphadenopathy. Back pain, fatigue, headache, myalgia, retroorbital pain, sore throat, nausea and vomiting, and arthralgia (but not arthritis) are common accompaniments that may persist for several weeks. Encephalitis, sequelae, and death are all more common among elderly, diabetic, and hypertensive patients and among patients with previous CNS insults. In addition to the more severe motor and cognitive sequelae, milder findings may include tremor, slight abnormalities in motor skills, and loss of executive functions. Intense clinical interest and the availability of laboratory diagnostic methods have made it possible to define a number of unusual clinical features. Such features include chorioretinitis, flaccid paralysis with histologic lesions resembling poliomyelitis, and initial presentation with fever and focal neurologic deficits in the absence of diffuse encephalitis. Immunosuppressed patients may have fulminant courses or develop persistent CNS infection. Virus transmission through both transplantation and blood transfusion has necessitated screening of blood and organ donors by nucleic acid–based tests. Occasionally, pregnant women infect their fetuses with West Nile virus.

Peribunyaviruses • **CALIFORNIA (MENINGO)ENCEPHALITIS** The isolation of California encephalitis virus established California serogroup orthobunyaviruses as causes of encephalitides. However, California encephalitis virus has been implicated in only a very few cases of encephalitis, whereas its close relative, La Crosse virus, is the major cause of encephalitis in this serogroup (~80–100 cases per year in the United States). California (meningo)encephalitis due to La Crosse virus infection is most commonly reported from the upper midwestern United States but is also found in other areas of the central and eastern parts of the country, such as West Virginia, Tennessee, North Carolina, and Georgia. The serogroup includes 13 other viruses, some of which (e.g., Inkoo, Jamestown Canyon, Lumbo, snowshoe hare, and Ťahyňa viruses) also cause human disease. Transovarial transmission is a strong component of transmission of the California serogroup viruses in *Aedes* and *Ochlerotatus* mosquitoes. The vector of La Crosse virus is the *Ochlerotatus triseriatus* mosquito. In addition to transovarial transmission, acquisition through feeding on viremic chipmunks and other mammals and venereal transmission can result in infection of this mosquito. *O. triseriatus* breeds in sites such as tree holes and abandoned tires and bites during daylight hours. The habits of this mosquito correlate with the risk factors for human cases: recreation in forested areas, residence at a forest's edge, and the presence of water-containing abandoned tires around the home. Intensive environmental modification based on these

findings has reduced the incidence of disease in a highly endemic area in the midwestern United States.

Most humans are infected from July through September. *A. albopictus* mosquitoes efficiently transmit La Crosse virus to mice and also transmit the agent transovarially in the laboratory. This aggressive anthropophilic mosquito has the capacity to urbanize, and its possible impact on transmission of virus to humans is of concern. The prevalence of antibody to La Crosse virus in humans is ≥20% in endemic areas, a figure indicating that infection is common but often asymptomatic. CNS disease has been recognized primarily in children <15 years of age.

The illness from La Crosse virus varies from aseptic meningitis accompanied by confusion to severe and occasionally fatal encephalitis (lethality, <0.5%). The incubation period is ~3–7 days. Although there may be prodromal symptoms/signs, the onset of CNS disease is sudden, with fever, headache, and lethargy often joined by nausea and vomiting, convulsions (in one-half of patients), and coma (in one-third of patients). Focal seizures, hemiparesis, tremor, aphasia, chorea, Babinski signs, and other evidence of significant neurologic dysfunction are common, but residual disease is not. Approximately 10% of patients have recurrent seizures in the succeeding months. Other serious sequelae of La Crosse virus infection are rare, although a decrease in scholastic standing among children has been reported, and mild personality change has occasionally been suggested.

The blood leukocyte count is commonly elevated in patients with La Crosse virus infection, sometimes reaching 20,000/μL, and is usually accompanied by a left shift. CSF leukocyte counts are typically 30–500/μL, usually with a mononuclear cell predominance (although 25–90% of cells are polymorphonuclear in some patients). The blood protein concentration is normal or slightly increased, and the glucose concentration is normal. Specific virologic diagnosis based on IgM-capture assays of serum and CSF is efficient. The only human anatomic site from which virus has been isolated is the brain.

Treatment is supportive over a 1- to 2-week acute phase during which status epilepticus, cerebral edema, and inappropriate secretion of antidiuretic hormone are important concerns. A phase 2B clinical trial of IV ribavirin in children with La Crosse virus infection was discontinued during dose escalation because of adverse effects.

Jamestown Canyon virus has been implicated in several cases of encephalitis in adults, usually with a significant respiratory illness at onset. Human infection with this virus has been documented in New York, Wisconsin, Ohio, Michigan, Ontario, and other areas of North America where the vector mosquito (*Aedes stimulans*) feeds on its main host, the white-tailed deer (*Odocoileus virginianus*). Tahyňa virus can be found in central Europe, Russia, China, and Africa. The virus is a prominent cause of febrile disease but can also cause pharyngitis, pulmonary syndromes, aseptic meningitis, or meningoencephalitis.

Rhabdoviruses • **CHANDIPURA VIRUS INFECTION** Chandipura virus is an emerging and increasingly important human virus in India, where it is transmitted among hedgehogs by mosquitoes and sandflies. In humans, the disease begins as an influenza-like illness, with fever, headache, abdominal pain, nausea, and vomiting. These manifestations are followed by neurologic impairment and infection-related or autoimmune-mediated encephalitis. Chandipura virus infection is characterized by high lethality in children. Several hundred cases of infection are recorded in India every year. Infections with other arthropod-borne rhabdoviruses (Isfahan, Piry, vesicular stomatitis Indiana, vesicular stomatitis New Jersey viruses) may imitate the early febrile stage of Chandipura virus infection.

Togaviruses • **EASTERN EQUINE ENCEPHALITIS** This disease is encountered primarily in swampy foci along the eastern coast of the United States, with a few inland foci as far removed as Michigan. Infected humans present for medical care from June through October. During this period, the bird–*Culiseta* mosquito cycle spills over into other vectors such as *Aedes sollicitans* or *Aedes vexans* mosquitoes, which are more likely to feed on mammals. There is concern over the potential role of introduced *A. albopictus* mosquitoes, which have been found to be infected with eastern equine encephalitis virus and are an effective experimental vector in the laboratory. Horses are a common target for the virus. Contact with unvaccinated horses may be associated with human disease, but horses probably do not play a significant role in amplification of the virus.

Eastern equine encephalitis is one of the most destructive of the arboviral diseases, with a sudden onset after an incubation period of ~5–10 days, rapid progression, 50–75% lethality, and frequent sequelae in survivors. This severity is reflected in the extensive necrotic lesions and polymorphonuclear infiltrates found at postmortem examination of the brain. Acute polymorphonuclear CSF pleocytosis, often occurring during the first 1–3 days of disease, is another indication of severity. In addition, leukocytosis with a left shift is a common feature. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available or applicable.

VENEZUELAN EQUINE FEVER Venezuelan equine encephalitis viruses are separated into epizootic viruses (subtypes IA/B and IC) and enzootic viruses (subtypes ID, IE, and IF). Closely related enzootic viruses are Everglades virus, Mucambo virus, and Tonate virus. Enzootic viruses are found primarily in humid tropical-forest habitats and are maintained between culicoid mosquitoes and rodents. These viruses cause acute febrile human disease but are not pathogenic for horses and do not cause epizootics. Everglades virus has caused encephalitis in humans in Florida in the United States. Extrapolation from the rate of genetic change suggests that Everglades virus may have been introduced into Florida <200 years ago. Everglades virus is most closely related to the ID-subtype viruses that appear to have given evolutionary rise to the epizootic variants active in South America.

Epizootic viruses have an unknown natural cycle but periodically cause extensive epizootics/epidemics in equids and humans in the Americas. These epizootics/epidemics are the result of high-level viremia in horses and mules, which transmit the infection to several types of mosquitoes. Infected mosquitoes in turn infect humans and perpetuate virus transmission. Humans also have high-level viremia, but their role in virus transmission is unclear. Relatively restricted epizootics of Venezuelan equine fever occurred repeatedly in South America at intervals of ≤10 years from the 1930s until 1969, when a massive epizootic, including tens of thousands of equine and human infections, spread throughout Central America and Mexico, reaching southern Texas in 1971. Genetic sequencing suggested that the virus from that outbreak originated from residual "unactivated" IA/B-subtype virus in veterinary vaccines. The outbreak was terminated in Texas with a live attenuated vaccine (TC-83) originally developed for human use by the U.S. Army; the epizootic virus was then used for further production of inactivated veterinary vaccines. No further major epizootic disease outbreaks occurred until 1995 and 1996, when large epizootics of Venezuelan equine fever occurred in Colombia/Venezuela and Mexico, respectively. Of the more than 85,000 clinical cases, 4% (with a higher proportion among children than adults) included neurologic symptoms/signs, and 300 cases ended in death. The viruses involved in these epizootics as well as previously epizootic IC viruses are close phylogenetic relatives of known enzootic ID viruses. This finding suggests that active evolution and selection of epizootic viruses are underway in South America.

During epizootics, extensive human infection is typical, with clinical disease occurring in 10–60% of infected individuals. Most infections result in notable acute febrile disease, whereas relatively few infections (5–15%) result in neurologic disease. A low rate of CNS invasion is supported by the absence of encephalitis among the many infections resulting from exposure to aerosols in the laboratory setting or from vaccination accidents.

The prevention of epizootic Venezuelan equine fever depends on vaccination of horses with the attenuated TC-83 vaccine or with an inactivated vaccine prepared from that variant. Enzootic viruses are genetically and antigenically different from epizootic viruses, and protection against the former with vaccines prepared from the latter is relatively ineffective. Humans can be protected by immunization with similar vaccines prepared from Everglades virus, Mucambo virus, and Venezuelan equine encephalitis virus, but the use of the vaccines is

restricted to laboratory personnel because of reactogenicity, possible fetal pathogenicity, and limited availability.

WESTERN EQUINE ENCEPHALITIS The primary maintenance cycle of western equine encephalitis virus in the United States is between *C. tarsalis* mosquitoes and birds, principally sparrows and finches. Equids and humans become infected, and both suffer encephalitis without amplifying the virus in nature. St. Louis encephalitis virus is transmitted in a similar cycle in the same regions harboring western equine encephalitis virus; disease caused by the former occurs about a month earlier than that caused by the latter (July through October). Large epidemics of western equine encephalitis occurred in the western and central United States and Canada during the 1930s through 1950s, but in recent years the disease has been uncommon. From 1964 through 2010, only 640 cases were reported in the United States. This decline in incidence may reflect in part the integrated approach to mosquito management that has been employed in irrigation projects and in part the increasing use of agricultural pesticides. The decreased incidence of western equine encephalitis almost certainly reflects the increased tendency for humans to be indoors behind closed windows at dusk—the peak biting period by the major vector.

After an incubation period of ~5–10 days, western equine encephalitis virus causes a typical diffuse viral encephalitis, with an increased attack rate and increased morbidity among the young, particularly children <2 years old. In addition, lethality is high among the young and the very elderly (3–7% overall). One-third of individuals who have convulsions during the acute illness have subsequent seizure activity. Infants <1 year old—particularly those in the first months of life—are at serious risk of motor and intellectual damage. Twice as many males as females develop clinical encephalitis after 5–9 years of age. This difference in incidence may be related to greater outdoor exposure of boys to the vector but may also be due in part to biologic differences. A formalin-inactivated vaccine has been used to protect laboratory workers but is not generally available.

FEVER AND MYALGIA

The fever and myalgia syndrome is most commonly associated with zoonotic virus infection. Many of the numerous viruses listed in Table 204-1 probably cause at least a few cases of this syndrome, but only some of these viruses have prominent associations with the syndrome and are of biomedical importance. The fever and myalgia syndrome typically begins with the abrupt onset of fever, chills, intense myalgia, and malaise. Patients may also report joint or muscle pains, but true arthritis is not found. Anorexia is characteristic and may be accompanied by nausea or even vomiting. Headache is common and may be severe, with photophobia and retroorbital pain. Physical findings are minimal and are usually confined to conjunctival injection with pain on palpation of muscles or the epigastrium. The duration of symptoms/signs is quite variable (generally 2–5 days), with a biphasic course in some instances. The spectrum of disease varies from subclinical to temporarily incapacitating. Less constant findings include a nonpruritic maculopapular rash. Epistaxis may occur but does not necessarily indicate a bleeding diathesis. A minority of patients may develop aseptic meningitis. This diagnosis is difficult to make in remote areas, given patients' photophobia and myalgia as well as the lack of opportunity to examine the CSF. Although pharyngitis or radiographic evidence of pulmonary infiltrates is found in some patients, the agents causing this syndrome are not primary respiratory pathogens.

The differential diagnosis includes anicteric leptospirosis, rickettsial diseases, and the early stages of other syndromes discussed in this chapter. The fever and myalgia syndrome is often described as "influenza-like," but the usual absence of cough and coryza makes influenza an unlikely confounder except at the earliest stages. Treatment is supportive, but acetylsalicylic acid is avoided because of the potential for exacerbated bleeding or Reye's syndrome. Complete recovery is the general outcome for people with this syndrome, although prolonged asthenia and nonspecific symptoms have been described in some patients, particularly after infection with lymphocytic choriomeningitis virus or dengue viruses 1–4.

Efforts for preventing viral infection are best based on vector control, which, however, may be expensive or impossible. For mosquito control, destruction of breeding sites is generally the most economically and environmentally sound approach. Emerging containment technologies include the release of genetically modified mosquitoes and the spread of *Wolbachia* bacteria to limit mosquito multiplication rates. Depending on the vector and its habits, other possible approaches include the use of screens or other barriers (e.g., permethrin-impregnated bed nets) to prevent the vector from entering dwellings, judicious application of arthropod repellents such as *N,N,*-diethyltoluamide (DEET) to the skin, use of long-sleeved and ideally permethrin-impregnated clothing, and avoidance of the vectors' habitats and times of peak activity.

Bunyaviruses Numerous bunyaviruses cause fever and myalgia. Many of these viruses cause individual infections and usually do not result in epidemics. These viruses include arenaviruses, such as lymphocytic choriomeningitis virus; hantaviruses, such as the orthohantavirus Choclo virus; nairoviruses, such as the orthonairoviruses Dugbe virus and Nairobi sheep disease virus; peribunyaviruses, such as the viruses of the orthobunyavirus Anopheles A serogroup (e.g., Tacaiuma virus), the Bunyamwera serogroup (Bunyamwera, Batai, Cache Valley, Fort Sherman, Germiston, Guaroa, Ilesha, Ngari, Shokwe, and Xingu viruses), the Bwamba serogroup (Bwamba virus, Pongola virus), the Guamá serogroup (Catú virus, Guamá virus), the Nyando serogroup (Nyando virus), the Wyeomyia serogroup (Wyeomyia virus), and the ungrouped orthobunyavirus Tataguine virus; and phenuiviruses, such as the "banyangvirus" Bhanja complex (Bhanja virus, Heartland virus) and the phlebovirus Candiru complex (Alenquer, Candiru, Escharate, Maldonado, Morumbi, and Serra Norte viruses).

ARENAVIRUSES Lymphocytic choriomeningitis/meningoencephalitis is the only human mammarenavirus infection resulting predominantly in fever and myalgia. Lymphocytic choriomeningitis virus is transmitted to humans from the common house mouse (*Mus musculus*) by aerosols of excreta or secreta. The virus is maintained in the mouse mainly by vertical transmission from infected dams. The vertically infected mouse remains viremic and sheds virus for life, with high concentrations of virus in all tissues. Infected colonies of pet hamsters also can serve as a link to humans. Infections among scientists and animal caretakers can occur because the virus is widely used in immunology laboratories as a model of T cell function and can silently infect cell cultures and passaged tumor lines. In addition, patients may have a history of residence in rodent-infested housing or other exposure to rodents. An antibody prevalence of ~5–10% has been reported among adults from Argentina, Germany, and the United States.

Lymphocytic choriomeningitis/meningoencephalitis differs from the general syndrome of fever and myalgia in that the onset is gradual. Conditions occasionally associated with the disease are orchitis, transient alopecia, arthritis, pharyngitis, cough, and maculopapular rash. An estimated one-fourth of patients (or fewer) experience a febrile phase of 3–6 days. After a brief remission, many develop renewed fever accompanied by severe headache, nausea and vomiting, and meningeal signs lasting for ~1 week (the CNS phase). These patients virtually always recover fully, as do the rare patients with clear-cut signs of encephalitis. Recovery may be delayed by transient hydrocephalus. During the initial febrile phase, leukopenia and thrombocytopenia are common, and virus can usually be isolated from blood. During the CNS phase, the virus may be found in the CSF, and antibodies are present in the blood. The pathogenesis of lymphocytic choriomeningitis/meningoencephalitis is thought to resemble manifestations following direct intracranial inoculation of the virus into adult mice. The onset of the immune response leads to T cell–mediated immunopathologic meningitis. During the meningeal phase, CSF mononuclear-cell counts range from the hundreds to the low thousands per microliter, and hypoglycorrhachia is found in one-third of patients.

IgM-capture ELISA, immunochemistry, and RT-PCR are used in the diagnosis of lymphocytic choriomeningitis/meningoencephalitis. IgM-capture ELISA of serum and CSF usually yields positive results; RT-PCR assays have been developed for probing CSF. Because patients

who have fulminant infections transmitted by recent organ transplantation do not mount an immune response, immunohistochemistry or RT-PCR is required for diagnosis. Infection should be suspected in acutely ill febrile patients with marked leukopenia and thrombocytopenia. In patients with aseptic meningitis, any of the following suggests lymphocytic choriomeningitis/meningoencephalitis: a well-marked febrile prodrome, adult age, occurrence in the autumn, low CSF glucose levels, or CSF mononuclear-cell counts of >1000/μL. In pregnant women, infection may lead to fetal invasion with consequent congenital hydrocephalus, microcephaly, and/or chorioretinitis. Because the maternal infection may be mild, causing only a short febrile illness, antibodies to the virus should be sought in both the mother and the fetus under suspicious circumstances, particularly in TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV)–negative neonatal hydrocephalus.

ORTHOBUNYAVIRUS GROUP C SEROGROUP Apeú, Caraparú, Itaquí, Madrid, Marituba, Murutucú, Nepuyo, Oriboca, Ossa, Restan, and Zungarococha viruses are among the most common causes of arboviral infection in humans entering South American jungles. These viruses cause acute febrile disease and are transmitted by mosquitoes in neotropical forests.

ORTHOBUNYAVIRUS SIMBU SEROGROUP Oropouche virus is transmitted in Central and South America by biting midges (*Culicoides paraensis*), which often breed to high density in cacao husks and other vegetable detritus found in towns and cities. Explosive epidemics involving thousands of patients have been reported from several towns in Brazil and Peru. Rash and aseptic meningitis have been detected in a number of patients. Iquitos virus, a recently discovered reassortant and close relative of Oropouche virus, causes disease that is easily mistaken for Oropouche virus disease; its overall epidemiologic significance remains to be determined.

PHLEBOVIRUS SANDFLY FEVER GROUP The phlebovirus sandfly fever group consists of numerous viruses that may cause human infection. Sandfly fever Cyprus virus, sandfly fever Ethiopia virus, sandfly fever Sicilian virus, and sandfly fever Turkey virus (and the encephalitis-causing Chios virus) are very closely related genetically and antigenically; they likely belong to the same species, in which they may constitute variants of the same virus. In contrast, sandfly fever Naples virus (SFNV) is genetically and antigenically distantly related to these viruses. SFNV has not been detected in sandflies, humans, or nonhuman vertebrates since the 1980s and therefore may be extinct. SFNV is the prototypic member of the species *Sandfly fever Naples phlebovirus* that includes other human viruses such as Granada and Toscana viruses. Toscana virus is thus far the only phlebovirus transmitted by sandflies that is known to cause diseases affecting the central and the peripheral nervous systems, such as encephalitis, meningitis, myositis, or polymyeloradiculopathy. *Phlebotomus* sandflies transmit the virus, probably by biting small mammals and humans. Female sandflies may be infected by the oral route as they take a blood meal and may transmit the virus to offspring when they lay their eggs after a second blood meal. This prominent transovarial transmission confounds virus control.

Sandfly fever is found in the circum-Mediterranean area, extending to the east through the Balkans into parts of China as well as into Western Asia. Sandflies are found in both rural and urban settings and are known for their short flight ranges and their small sizes; the latter enables them to penetrate standard mosquito screens and netting. Epidemics have been described in the wake of natural disasters and wars. After World War II, extensive spraying in parts of Europe to control malaria greatly reduced sandfly populations and SFNV transmission; the incidence of sandfly fever continues to be low.

A common pattern of disease in endemic areas consists of high attack rates among travelers and military personnel and little or no disease in the local population, who are protected after childhood infection. Toscana virus infection is common during the summer among rural residents and vacationers, particularly in Italy, Spain, and Portugal; a number of cases have been identified in travelers returning to Germany and Scandinavia. The disease may manifest as an uncomplicated febrile illness but is often associated with aseptic meningitis, with virus isolated from the CSF.

Coclé virus and Punta Toro virus are phleboviruses that are not part of the sandfly fever serocomplex but that, like the members of this complex, are transmitted by sandflies. These two viruses cause a sandfly fever–like disease in Latin American and Caribbean tropical forests, respectively, where the vectors rest on tree buttresses. Epidemics have not been reported, but antibody prevalence among inhabitants of villages in endemic areas indicates a cumulative lifetime exposure rate of >50% in the case of Punta Toro virus.

Flaviviruses The most clinically important flaviviruses that cause the fever and myalgia syndrome are dengue viruses 1–4. In fact, dengue is probably the most important arthropod-borne viral disease worldwide, with ~390 million infections occurring per year, of which ~96 million cause signs of disease. Year-round transmission of dengue viruses 1–4 occurs between latitudes 25°N and 25°S, but seasonal forays of the viruses into the United States and Europe have been documented. All four viruses have *A. aegypti* mosquitoes as their principal vectors. Through increasing spread of mosquitoes throughout the tropics and subtropics and international travel of infected humans, large areas of the world have become vulnerable to the introduction of dengue viruses. Thus, dengue and severe dengue (see "Viral Hemorrhagic Fevers," below) are becoming increasingly common. For instance, conditions favorable to dengue virus 1–4 transmission via *A. aegypti* mosquitoes exist in Hawaii and the southern United States. The range of a lesser dengue virus vector (*A. albopictus*) now extends from Asia to the United States, the Indian Ocean, parts of Europe, and Hawaii. *A. aegypti* mosquitoes typically breed near human habitation, using relatively fresh water from sources such as water jars, vases, discarded containers, coconut husks, and old tires. These mosquitoes usually inhabit dwellings and bite during the day. Bursts of dengue cases are to be expected in the southern United States, particularly along the Mexican border, where containers of water may be infested with *A. aegypti* mosquitoes. Closed habitations with air-conditioning may inhibit transmission of many arboviruses, including dengue viruses 1–4.

Dengue begins after an incubation period averaging 4–7 days, when the typical patient experiences the sudden onset of fever, frontal headache, retroorbital pain, and back pain along with severe myalgias. These symptoms gave rise to the colloquial designation of dengue as "break-bone fever." Often a transient macular rash appears on the first day, as do adenopathy, palatal vesicles, and scleral injection. The illness may last a week, with additional symptoms and clinical signs usually including anorexia, nausea or vomiting, and marked cutaneous hypersensitivity. Near the time of defervescence on days 3–5, a maculopapular rash begins on the trunk and spreads to the extremities and the face. Epistaxis and scattered petechiae are often noted in uncomplicated dengue, and preexisting gastrointestinal lesions may bleed during the acute illness.

Laboratory findings of dengue include leukopenia, thrombocytopenia, and, in many cases, elevations of serum aminotransferase concentrations. The diagnosis is made by IgM ELISA or paired serology during recovery or by antigen-detection ELISA or RT-PCR during the acute phase. Virus is readily isolated from blood in the acute phase if mosquito inoculation or mosquito cell culture is used.

Orthomyxoviruses Bourbon virus was recently identified as the cause of a severe and sometimes fatal febrile disease of humans in the midwestern and southern United States.

Reoviruses Several orbiviruses (Lebombo, Kemerovo, Orungo, and Tribeč viruses) and coltiviruses (Colorado tick fever, Eyach, and Salmon River viruses) can cause fever and myalgia in humans. With the exception of Lebombo and Orungo viruses, all of these viruses are transmitted by ticks. The most important reoviral arthropod-borne disease is Colorado tick fever. Several hundred patients with this disease are reported annually in the United States. The infection is acquired between March and November through the bite of an infected ixodid tick, the Rocky Mountain wood tick (*Dermacentor andersoni*), in

mountainous western regions at altitudes of 1200–3000 m. Small mammals serve as amplifying hosts. The most common presentation is fever and myalgia; meningoencephalitis is not uncommon, and hemorrhagic disease, pericarditis, myocarditis, orchitis, and pulmonary presentations have also been reported. Rash develops in a minority of patients. Leukopenia and thrombocytopenia are also noted. The disease usually lasts 7–10 days and is often biphasic. The most important differential diagnostic considerations since the beginning of the twentieth century have been Rocky Mountain spotted fever (although Colorado tick fever is much more common in Colorado) and tularemia. Colorado tick fever virus replicates for several weeks in erythropoietic cells and can be found in erythrocytes. This feature, detected in erythroid smears stained by immunofluorescence, can be diagnostically helpful and is important during screening of blood donors.

PULMONARY DISEASE

Hantavirus (cardio)pulmonary syndrome, or H(C)PS, was first described in 1993, but retrospective identification of cases by immunohistochemistry (1978) and serology (1959) support the idea that H(C)PS is a recently discovered rather than a truly new disease. The causative agents are orthohantaviruses of a distinct phylogenetic lineage that is associated with the cricetid rodent subfamily *Sigmodontinae*. Sin nombre virus, which chronically infects North American deer mice (*Peromyscus maniculatus*), is the most important agent of H(C)PS in the United States. Several other related viruses (Anajatuba, Andes, Araraquara, Araucária, bayou, Bermejo, Black Creek Canal, Blue River, Castelo dos Sonhos, El Moro Canyon, Juquitiba, Laguna Negra, Lechiguanas, Maciel, Monongahela, Muleshoe, New York, Orán, Paranoá, Pergamino, Río Mamoré, and Tunari viruses) cause the disease in North and South America. Andes virus is unusual in that it has been implicated in human-to-human transmission. H(C)PS particularly affects rural residents living in dwellings permeable to rodent entry or working in occupations that pose a risk of rodent exposure. Each type of rodent has its own particular habits; in the case of deer mice, these behaviors include living in and around human habitation.

H(C)PS begins with a prodrome of ~3–4 days (range, 1–11 days) comprising fever, malaise, myalgia, and—in many cases—gastrointestinal disturbances such as abdominal pain, nausea, and vomiting. Dizziness is common, and vertigo is occasional. Severe prodromal symptoms/signs may bring some patients to medical attention, but most cases are recognized as the pulmonary phase begins. Typical signs are slightly lowered blood pressure, tachycardia, tachypnea, mild hypoxemia, thrombocytopenia, and early radiographic signs of pulmonary edema. Physical findings in the chest are often surprisingly scant. The conjunctival and cutaneous signs of vascular involvement seen in hantavirus VHFs (see below) are uncommon. During the next few hours, decompensation may progress rapidly to severe hypoxemia and respiratory failure.

The H(C)PS differential diagnosis includes abdominal surgical conditions and pyelonephritis as well as rickettsial disease, sepsis, meningococcemia, plague, tularemia, influenza, and relapsing fever. A specific diagnosis is best made by IgM antibody testing of acute-phase serum, which has yielded positive results even in the prodrome. Tests using a sin nombre virus antigen detect antibodies to the related H(C)PS-causing hantaviruses. Occasionally, heterotypic viruses will react only in the IgG ELISA, but such a finding is highly suspicious given the very low seroprevalence of these viruses in normal populations. RT-PCR is usually positive when used to test blood clots obtained in the first 7–9 days of illness and when used to test tissues. This assay is useful in identifying the infecting virus in areas outside the home range of deer mice and in atypical cases.

During the prodrome, the differential diagnosis of H(C)PS is difficult, but by the time of presentation or within 24 h thereafter, a number of diagnostically helpful clinical features become apparent. Cough usually is not present at the outset. Interstitial edema is evident on a chest x-ray. Later, bilateral alveolar edema with a central distribution develops in the setting of a normal-sized heart; occasionally, the edema is initially unilateral. Pleural effusions are often seen. Thrombocytopenia, circulating atypical lymphocytes, and a left shift (often with leukocytosis) are almost always evident; thrombocytopenia is a particularly important early clue. Hemoconcentration, hypoalbuminemia, and proteinuria should also be sought for diagnosis. Although thrombocytopenia virtually always develops and prolongation of the partial thromboplastin time is the rule, clinical evidence for coagulopathy or laboratory indications of disseminated intravascular coagulation (DIC) are found in only a minority of severely ill patients. Patients with severe illness also have acidosis and elevated serum lactate concentrations. Mildly increased values in renal function tests are common, but patients with severe H(C)PS often have markedly elevated serum creatinine concentrations. Some New World hantaviruses other than sin nombre virus (e.g., Andes virus) have been associated with more kidney involvement, but few such cases have been studied.

Management of H(C)PS during the first few hours after presentation is critical. The goal is to prevent severe hypoxemia by oxygen therapy, with intubation and intensive respiratory management if needed. During this period, hypotension and shock with increasing hematocrit invite aggressive fluid administration, but this intervention should be undertaken with great caution. Because of low cardiac output with myocardial depression and increased pulmonary vascular permeability, shock should be managed expectantly with vasopressors and modest infusion of fluid guided by pulmonary capillary wedge pressure. Mild cases can be managed by frequent monitoring and oxygen administration without intubation. Many patients require intubation to manage hypoxemia and developing shock. Extracorporeal membrane oxygenation is instituted in severe cases, ideally before the onset of shock. The procedure is indicated in patients who have a cardiac index of 2.3 $L/min/m^2$ or an arterial oxygen tension/fractional inspired oxygen (PaO_2/FIO_2) ratio of <50 and who are unresponsive to conventional support. Lethality remains at ~30–40% even with good management, but most patients surviving the first 48 h of hospitalization are extubated and discharged within a few days with no apparent long-term residua. The antiviral drug ribavirin inhibits hantaviruses in vitro but did not have a marked effect on patients treated in an open-label study.

VIRAL HEMORRHAGIC FEVER

VHF is a constellation of findings based on vascular instability and decreased vascular integrity. An assault, direct or indirect, on the microvasculature leads to increased permeability and (particularly when platelet function is decreased) to actual disruption and local hemorrhage (a positive tourniquet sign). Blood pressure is decreased, and in severe cases shock supervenes. Cutaneous flushing and conjunctival suffusion are examples of common, observable abnormalities in the control of local circulation. Hemorrhage occurs infrequently. In most patients, hemorrhage is an indication of widespread vascular damage rather than a life-threatening loss of blood volume. In some VHFs, specific organs may be particularly impaired. For instance, the kidneys are primary targets in HFRS, and the liver is a primary target in yellow fever and filovirus diseases. However, in all of these diseases, generalized circulatory disturbance is critically important. The pathogenesis of VHF is poorly understood and varies among the viruses regularly implicated in the syndrome. In some viral infections, direct damage to the vascular system or even to parenchymal cells of target organs is an important factor; in other viral infections, soluble mediators are thought to play a major role in the development of hemorrhage or fluid redistribution.

The acute phase in most cases of VHF is associated with ongoing virus replication and viremia. VHFs begin with fever and myalgia, usually of abrupt onset. (Mammarenavirus infections are the exceptions as they often develop gradually.) Within a few days, the patient presents for medical attention because of increasing prostration that is often accompanied by abdominal or chest pain, anorexia, dizziness, severe headache, hyperesthesia, photophobia, and nausea or vomiting and other gastrointestinal disturbances. Initial examination often reveals only an acutely ill patient with conjunctival suffusion, tenderness to palpation of muscles or abdomen, and borderline hypotension or postural hypotension, perhaps with tachycardia. Petechiae (often best visualized in the axillae), flushing of the head and thorax, periorbital

edema, and proteinuria are common. AST concentrations are usually elevated at presentation or within a day or two thereafter. Hemoconcentration from vascular leakage, which is usually evident, is most marked in HFRS and in severe dengue. The seriously ill patient progresses to more severe clinical signs and develops shock and other findings typical of the causative virus. Shock, multifocal bleeding, and CNS involvement (encephalopathy, coma, seizures) are all poor prognostic signs.

One of the major diagnostic clues to VHF is travel to an endemic area within the incubation period for a given syndrome. Except in infections with Seoul, dengue, and yellow fever viruses, which have urban hosts/vectors, travel to a rural setting is especially suggestive of a diagnosis of VHF. In addition, several diseases considered in the differential diagnosis—falciparum malaria, shigellosis, typhoid fever, leptospirosis, relapsing fever, and rickettsial diseases—are treatable and potentially lethal.

Early recognition of VHF is important because of the need for virus-specific therapy and supportive measures. Such measures include prompt, atraumatic hospitalization; judicious fluid therapy that takes into account the patient's increased capillary permeability; administration of cardiotonic drugs; use of vasopressors to maintain blood pressure at levels that will support renal perfusion; treatment of the relatively common secondary bacterial (and the more rare fungal) infections; replacement of clotting factors and platelets as indicated; and the usual precautionary measures used in the treatment of patients with hemorrhagic diatheses. DIC should be treated only if clear laboratory evidence of its existence is found and if laboratory monitoring of therapy is feasible; there is no proven benefit of such therapy. The available evidence suggests that VHF patients have decreased cardiac output and will respond poorly to fluid loading as it is often practiced in the treatment of shock associated with bacterial sepsis. Specific therapy is available for several of the VHFs. Strict barrier nursing and other precautions against infection of medical staff and visitors are indicated when VHFs are encountered except when the illness is due to dengue viruses, hantaviruses, Rift Valley fever virus, or yellow fever virus.

Novel VHF-causing agents are still being discovered. Besides the viruses listed below, the latest additions are the "banyangvirus" severe fever with thrombocytopenia syndrome virus, which is continuing to cause VHF cases in China, Korea, and Japan, and possibly the tibrovirus Bas-Congo virus, which has been associated with three cases of VHF in the Democratic Republic of the Congo. However, Koch's postulates have not yet been fulfilled to prove cause and effect in the case of Bas-Congo virus.

Bunyaviruses The most important VHF-causing bunyaviruses are arenaviruses (Junín, Lassa, and Machupo viruses), hantaviruses, nairoviruses (Crimean-Congo hemorrhagic fever virus), and phenuiviruses (Rift Valley fever and severe fever with thrombocytopenia syndrome viruses). Other bunyaviruses—e.g., the Garissa variant of Ngari virus and Ilesha virus (both orthobunyaviruses) or Chapare, Guanarito, Lujo, and Sabiá viruses (all mammarenaviruses)—have caused sporadic VHF outbreaks.

JUNÍN/ARGENTINIAN AND MACHUPO/BOLIVIAN HEMORRHAGIC FEVERS These severe diseases (with lethality reaching 15–30%) are caused by Junín virus and Machupo virus, respectively. Their clinical presentations are similar, but their epidemiology differs because of the distribution and behavior of the viruses' rodent reservoirs. Junín/Argentinian hemorrhagic fever has thus far been recorded only in rural areas of Argentina, whereas Machupo/Bolivian hemorrhagic fever seems to be confined to rural Bolivia. Infection with the causative agents almost always results in disease, and all ages and both sexes are affected. Person-to-person or nosocomial transmission is rare but has occurred. The transmission of Junín/Argentinian hemorrhagic fever from convalescing men to their wives suggests the need for counseling of patients with mammarenavirus hemorrhagic fever concerning the avoidance of intimate contacts for several weeks after recovery. In contrast to the pattern in Lassa fever (see below), thrombocytopenia—often marked—is the rule, hemorrhage is common, and CNS dysfunction (e.g., marked confusion, tremors of the upper extremities and tongue, and cerebellar signs) is much more common in disease caused by Junín virus and Machupo virus. Some cases follow a predominantly neurologic course, with a poor prognosis.

The clinical laboratory is helpful in diagnosis since thrombocytopenia, leukopenia, and proteinuria are typical findings. Junín/Argentinian hemorrhagic fever is readily treated with convalescent-phase plasma given within the first 8 days of illness. In the absence of passive antibody therapy, IV ribavirin in the dose recommended for Lassa fever is likely to be effective in all the South American VHFs caused by mammarenaviruses. A safe, effective, live attenuated vaccine exists for Junín/Argentinian hemorrhagic fever. After vaccination of more than 250,000 high-risk persons in the endemic area, the incidence of this VHF decreased markedly. In experimental animals, this vaccine is cross-protective against Machupo/Bolivian hemorrhagic fever.

LASSA FEVER Lassa virus is known to cause endemic and epidemic disease in Nigeria, Sierra Leone, Guinea, and Liberia, although it is probably more widely distributed in Western Africa. In countries where Lassa virus is endemic, Lassa fever can be a prominent cause of febrile disease. For example, in one hospital in Sierra Leone, laboratory-confirmed Lassa fever is consistently responsible for one-fifth of admissions to the medical wards. In Western Africa alone, probably tens of thousands of Lassa virus infections occur annually. Lassa virus can be transmitted by close person-to-person contact. The virus is often present in urine during convalescence and is suspected to be present in seminal fluid early in recovery. Nosocomial spread has occurred but is uncommon if proper sterile parenteral techniques are used. All ages and both sexes are affected; the incidence of disease is highest in the dry season, but transmission takes place year-round.

Among the VHF agents, only mammarenaviruses are typically associated with a gradual onset of illness, which begins after an incubation period of 5–16 days. Hemorrhage is seen in only ~15–30% of Lassa fever patients; a maculopapular rash is often noted in light-skinned patients. Effusions are common, and male-dominant pericarditis may develop late in infection. Maternal lethality is higher than the usual 15–30% and is especially increased during the last trimester. Fetal lethality reaches 90%. Excavation of the uterus may increase survival rates of pregnant women, but data on Lassa fever and pregnancy are still sparse. These figures suggest that interruption of the pregnancy of Lassa virus–infected women should be considered. White blood cell counts are normal or slightly elevated, and platelet counts are normal or somewhat low. Deafness coincides with clinical improvement in ~20% of patients and is permanent and bilateral in some patients. Reinfection may occur but has not been associated with severe disease.

High-level viremia or a high serum AST concentration statistically predicts a fatal outcome. Thus, patients with an AST concentration of >150 IU/mL should be treated with IV ribavirin. This antiviral nucleoside analogue appears to be partially effective in reducing lethality from that documented among retrospective controls. However, possible side effects, such as reversible anemia (which usually does not require transfusion), dependent hemolytic anemia, and bone marrow suppression, need to be kept in mind. Ribavirin should be given by slow IV infusion in a dose of 32 mg/kg; this dose should be followed by 16 mg/kg every 6 h for 4 days and then by 8 mg/kg every 8 h for 6 days. Inactivated Lassa virus vaccines failed in preclinical studies, but several promising vaccine platforms are currently under experimental evaluation.

HEMORRHAGIC FEVER WITH RENAL SYNDROME HFRS is the most important VHF today, with more than 100,000 cases of severe disease in Asia annually and milder infections numbering in the thousands in Europe. The disease is widely distributed in Eurasia. The major causative viruses are Puumala virus (Europe), Dobrava-Belgrade virus (the Balkans), and Hantaan virus (Eastern Asia). Amur/Soochong, Gōu, Kurkino, Muju, Saaremaa, Sochi, and Tula viruses also cause HFRS but much less frequently and in more geographically confined areas determined by the distribution of reservoir hosts. Seoul virus is exceptional in that it is associated with brown rats (*Rattus norvegicus*); therefore, the virus has a worldwide distribution because of the migration of these

rodents on ships. Despite the wide distribution of Seoul virus, only mild or moderate HFRS occurs in Asia, and human disease has been difficult to identify in many areas of the world. Most cases of HFRS occur in rural residents or vacationers; the exception is Seoul virus infection, which may be acquired in an urban or rural setting or from contaminated laboratory-rat colonies. Classic Hantaan virus infection in Korea and in rural China is most common in the spring and fall and is related to rodent density and agricultural practices. Human infection is acquired primarily through aerosols of rodent urine, although virus is also present in rodent saliva and feces. Patients with HFRS are not infectious.

Severe cases of HFRS evolve in four identifiable stages. The *febrile stage* lasts 3 or 4 days and is identified by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back is characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate DIC is present. Other laboratory findings of HFRS include proteinuria and active urinary sediment. The *hypotensive stage* lasts from a few hours to 48 h and begins with falling blood pressure and sometimes shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Kinin activation is marked. The rising hematocrit reflects increasing vascular leakage. Leukocytosis with a left shift develops, and thrombocytopenia continues. Atypical lymphocytes—which in fact are activated CD8+ and, to a lesser extent, CD4+ T cells—circulate. Proteinuria is marked, and the urine's specific gravity falls to 1.010. Renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria. During the *oliguric stage*, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. Oliguria persists for 3–10 days before the return of renal function marks the onset of the *polyuric stage* (diuresis and hyposthenuria), which carries the danger of dehydration and electrolyte abnormalities.

Mild cases of HFRS may be much less stereotypical. The presentation may include only fever, gastrointestinal abnormalities, and transient oliguria followed by hyposthenuria. Infections with Puumala virus, the most common cause of HFRS in Europe (*nephropathia epidemica*), result in a much-attenuated picture but the same general presentation. Bleeding manifestations are found in only 10% of patients, hypotension rather than shock is usually documented, and oliguria is present in only about half of patients. The dominant features may be fever, abdominal pain, proteinuria, mild oliguria, and sometimes blurred vision or glaucoma followed by polyuria and hyposthenuria in recovery. Lethality is <1%.

HFRS should be suspected in patients with rural exposure in an endemic area. Prompt recognition of the disease permits rapid hospitalization and expectant management of shock and renal failure. Useful clinical laboratory parameters include leukocytosis, which may be leukemoid and is associated with a left shift; thrombocytopenia; and proteinuria. HFRS is readily diagnosed by an IgM-capture ELISA that is positive at admission or within 24–48 h thereafter. The isolation of hantaviruses is difficult, but RT-PCR of a blood clot collected early in the clinical course or of tissues obtained postmortem should give positive results. Such testing is usually undertaken if definitive identification of the infecting virus is required.

Mainstays of therapy are management of shock, reliance on vasopressors, modest crystalloid infusion, IV human serum albumin administration, treatment of renal failure with prompt dialysis to prevent overhydration that may result in pulmonary edema, and control of hypertension that increases the possibility of intracranial hemorrhage. Use of IV ribavirin has reduced lethality and morbidity in severe cases, provided treatment is begun within the first 4 days of illness. Lethality may be as high as 15%, but with proper therapy lethality should be <5%. Sequelae have not been definitively established.

CRIMEAN-CONGO HEMORRHAGIC FEVER (CCHF) This severe VHF has a wide geographic distribution, potentially emerging wherever virus-bearing ticks occur. Because of the propensity of CCHF virus–transmitting ticks to feed on domestic livestock and certain wild mammals, veterinary serosurveys are the most effective mechanism for the monitoring of virus circulation in a particular region. Human infections are acquired via tick bites or during the crushing of infected ticks. Domestic animals do not become ill but do develop viremia. Thus, risk of acquiring CCHF occurs during sheep shearing, slaughter, and contact with infected hides or carcasses from recently slaughtered, infected animals. Nosocomial epidemics are common and are usually related to extensive blood exposure or needlesticks.

Although generally similar to other VHFs, CCHF causes extensive liver damage, resulting in jaundice in some patients. Clinical laboratory values indicate DIC and elevations in concentrations of AST, creatine phosphokinase, and bilirubin. Patients who do not survive generally have more distinct changes than survivors in the concentrations of these markers, even in the early days of illness, and also develop leukocytosis rather than leukopenia. In addition, thrombocytopenia is more marked and develops earlier in patients who do not survive than in survivors. The benefit of IV ribavirin for treatment remains hotly debated and unproven. Clinical experience and retrospective comparison of patients with ominous clinical laboratory values support a contention that ribavirin may be efficacious, but a randomized clinical trial was not supportive of a benefit in lowering lethality rates. No human or veterinary vaccines are recommended.

RIFT VALLEY FEVER The natural range of Rift Valley fever virus was previously confined to sub-Saharan Africa, with circulation of the virus markedly enhanced by substantial rainfall. The El Niño Southern Oscillation phenomenon of 1997 facilitated subsequent spread of Rift Valley fever to the Arabian Peninsula, with epidemic disease in 2000. The virus has also been found in Madagascar and introduced into Egypt, where it caused major epidemics in 1977–1979, 1993, and thereafter. Rift Valley fever virus is maintained in nature by transovarial transmission in floodwater *Aedes* mosquitoes and presumably also has a vertebrate amplifier. Increased transmission during particularly heavy rains leads to epizootics characterized by high-level viremia in cattle, goats, or sheep. Numerous types of mosquitoes then feed on these animals and become infected, thereby increasing the possibility of human infections. Remote sensing via satellite can detect the ecologic changes associated with high rainfall that predict the likelihood of Rift Valley fever virus transmission. High-resolution satellites can also detect the special depressions in floodwaters from which the mosquitoes emerge. In addition, the virus can be transmitted by contact with blood or aerosols from domestic animals. Transmission risk is therefore high during birthing, and both abortuses and placentas need to be handled with caution. Slaughtered animals are not infectious because anaerobic glycolysis in postmortem tissues results in an acidic environment that rapidly inactivates bunyaviruses. Neither person-to-person nor nosocomial transmission of Rift Valley fever has been documented.

Rift Valley fever virus is unusual in that it causes several clinical syndromes. Most infections are manifested as the fever–myalgia syndrome. A small proportion of infections result in VHF with especially prominent liver involvement or encephalitis. Renal failure and DIC are also common features. Perhaps 10% of otherwise mild infections lead to retinal vasculitis, and some patients have permanently impaired vision. Funduscopic examination reveals edema, hemorrhages, and infarction of the retina as well as optic nerve degeneration. In a small proportion of patients (<1 in 200), retinal vasculitis is followed by viral encephalitis.

No proven therapy exists for Rift Valley fever. Both retinal disease and encephalitis occur after the acute febrile syndrome has resolved and serum neutralizing antibody has developed—events suggesting that only supportive care need be given. Epidemic disease is best prevented by vaccination of livestock. The ability of this virus to propagate after introduction into Egypt suggests that other potentially receptive areas, including the United States, should develop response plans. Rift Valley fever, like Venezuelan equine fever, is likely to be controlled only

with adequate stocks of an effective live attenuated vaccine, but such global stocks are unavailable. A formalin-inactivated vaccine confers immunity in humans, but quantities are limited, and three injections are required. This vaccine is recommended for potentially exposed laboratory workers and for veterinarians working in sub-Saharan Africa. A new live attenuated vaccine, MP-12, is being tested in humans (phase 2 trials have been completed). The vaccine is safe and licensed for use in sheep and cattle. In addition, several vaccines are being developed specifically for use in animals.

SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME This recently described tick-borne disease is caused by severe fever with thrombocytopenia syndrome virus. Numerous human infections have been reported during the past few years from China, and several cases have also been detected in Japan and South Korea. The clinical presentation ranges from mild nonspecific fever to severe VHF with a high (>12%) lethality.

Flaviviruses The most important flaviviruses that cause VHF are the mosquito-borne dengue viruses 1–4 and yellow fever virus. These viruses are widely distributed and cause tens to hundreds of thousands of infections each year. Kyasanur Forest disease virus and Omsk hemorrhagic fever virus are geographically very restricted but important tick-borne flaviviruses that cause VHF, sometimes with subsequent viral encephalitis. Tick-borne encephalitis virus has caused VHF in a few patients. There is currently no therapy for these VHFs, but an inactivated vaccine has been used in India to prevent Kyasanur Forest disease.

SEVERE DENGUE Several weeks after convalescence from infection with dengue virus 1, 2, 3, or 4, the transient protection conferred by that infection against reinfection with a heterotypic dengue virus usually wanes. Heterotypic reinfection may result in classic dengue or, less commonly, in severe dengue. In the past 20 years, *A. aegypti* mosquitoes have progressively reinvaded Latin America and other areas, and frequent travel by infected individuals has introduced multiple variants of dengue viruses 1–4 from many geographic areas. Thus, the pattern of hyperendemic transmission of multiple dengue virus serotypes established in the Americas and the Caribbean has led to the emergence of severe dengue as a major problem. Among the millions of dengue virus 1–4 infections, ~500,000 cases of severe dengue occur annually, with a lethality of ~2.5%. The induction of vascular permeability and shock depends on multiple factors, such as the presence or absence of enhancing and nonneutralizing antibodies, age (susceptibility to severe dengue drops considerably after 12 years of age), sex (females are more often affected than males), race (whites are more often affected than blacks), nutritional status (malnutrition is protective), and sequence of infections (e.g., dengue virus 1 infection followed by dengue virus 2 infection seems to be more dangerous than dengue virus 4 infection followed by dengue virus 2 infection). In addition, considerable heterogeneity exists among each dengue virus population. For instance, South-Eastern Asian dengue virus 2 variants have more potential to cause severe dengue than do other variants.

Severe dengue is identified by the detection of bleeding tendencies (tourniquet test, petechiae) or overt bleeding in the absence of underlying causes, such as preexisting gastrointestinal lesions. Shock may result from increased vascular permeability. In milder cases of severe dengue, restlessness, lethargy, thrombocytopenia (<100,000/μL), and hemoconcentration are detected 2–5 days after the onset of typical dengue, usually at the time of defervescence. The maculopapular rash that often develops in dengue may also appear in severe dengue. In more severe cases, frank shock is apparent, with low pulse pressure, cyanosis, hepatomegaly, pleural effusions, and ascites; in some patients, severe ecchymoses and gastrointestinal bleeding develop. The period of shock lasts only 1 or 2 days.

A virologic diagnosis of severe dengue can be made by the usual means. However, multiple flavivirus infections result in broad immune responses to several members of the genus, and this situation may result in a lack of virus specificity of the IgM and IgG immune responses. A secondary antibody response can be sought with tests against several flavivirus antigens to demonstrate the characteristic wide spectrum of reactivity.

Most patients with shock respond promptly to close monitoring, oxygen administration, and infusion of crystalloid or—in severe cases—colloid. Lethality varies greatly with case ascertainment and quality of treatment. However, most patients with severe dengue respond well to supportive therapy, and the overall lethality at an experienced center in the tropics is probably as low as 1%.

The key to control of both dengue and severe dengue is the control of *A. aegypti* mosquitoes, which also reduces the risk of urban yellow fever and chikungunya virus circulation. Control efforts have been handicapped by the presence of nondegradable tires and long-lived plastic containers in trash repositories (perfect mosquito breeding grounds when filled with water during rainfall) and by insecticide resistance. Urban poverty and an inability of the public health community to mobilize the populace to respond to the need to eliminate mosquito breeding sites are also factors in lack of mosquito control. A tetravalent live attenuated dengue vaccine based on the attenuated yellow fever virus 17D platform is under advanced development (phase 1 to phase 3 trials for various platforms in Latin America, Asia, and Australia). At least two live attenuated candidate vaccines based on modified recombinant dengue viruses have been evaluated in phase 1 clinical studies, but the results have not been promising.

YELLOW FEVER Yellow fever virus had caused major epidemics in Africa and Europe before its transmission by *A. aegypti* mosquitoes was discovered in 1900. Urban yellow fever became established in the New World as a result of colonization with *A. aegypti*—originally an African mosquito. Subsequently, different types of mosquitoes and nonhuman primates were found to maintain yellow fever virus in Africa and also in Central and South American jungles. Transmission to humans is incidental, occurring via bites from mosquitoes that have fed on viremic monkeys. After the identification of *A. aegypti* mosquitoes as vectors of yellow fever, containment strategies were aimed at increased mosquito control. Today, urban yellow fever transmission occurs only in some African cities, but the threat exists in the great cities of South America, where reinfestation by *A. aegypti* mosquitoes has taken place, and dengue virus 1–4 transmission by the same mosquito is common. Despite the existence of a highly effective and safe vaccine, several hundred jungle yellow fever cases occur annually in South America, and 84,000–170,000 severe jungle and urban cases, including 29,000–60,000 deaths, occurred in 2013 in Africa.

Yellow fever is a typical VHF accompanied by prominent hepatic necrosis. A period of viremia, typically lasting 3 or 4 days, is followed by a period of "intoxication." During the latter phase in severe cases, characteristic jaundice, hemorrhages, black vomit, anuria, and terminal delirium occur, perhaps related in part to extensive hepatic involvement. Blood leukocyte counts may be normal or reduced and are often high in terminal stages. Albuminuria is usually noted and may be marked. As renal function fails in terminal or severe cases, the concentration of blood urea nitrogen rises proportionately. Abnormalities detected in liver function tests range from modest elevations of AST concentrations in mild cases to severe derangement.

Urban yellow fever can be prevented by the control of *A. aegypti* mosquitoes. The continuing sylvatic cycles require vaccination of all visitors to areas of potential transmission with live attenuated variant 17D vaccine virus, which cannot be transmitted by mosquitoes. With few exceptions, reactions to the vaccine are minimal; immunity is provided within 10 days and lasts for at least 25–35 years. An egg allergy mandates caution in vaccine administration. Although there are no documented harmful effects of the vaccine on fetuses, pregnant women should be immunized only if they are definitely at risk of exposure to yellow fever virus. Because vaccination has been associated with several cases of encephalitis in children <6 months of age, it is contraindicated in this age group, nor is it recommended for infants 6–8 months of age unless the risk of exposure is very high. Rare, serious, multisystemic adverse reactions (occasionally fatal) have been reported, particularly affecting the elderly, and risk-to-benefit should be weighed prior to vaccine administration to individuals ≥60 years

of age. Nevertheless, the number of deaths of unvaccinated travelers with yellow fever exceeds the number of deaths from vaccination, and a liberal vaccination policy for travelers to involved areas should be pursued. Timely information on changes in yellow fever distribution and yellow fever vaccine requirements can be obtained from the U.S. Centers for Disease Control and Prevention (*http://www.cdc.gov/vaccines/vpd-vac/yf/default.htm*).

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205 Ebolavirus and Marburgvirus Infections

Jens H. Kuhn

Several viruses of the family *Filoviridae* cause severe and frequently fatal infections in humans. Introduction of filoviruses into human populations is an extremely rare event that most likely occurs by direct or indirect contact with healthy filovirus hosts or by contact with infected, sick, or deceased mammals. Filoviruses are highly infectious but not especially contagious. Human-to-human transmission takes place through direct person-to-person (usually skin-to-skin) contact or exposure to infected bodily fluids and tissues; no evidence of such transmission by aerosol or respiratory droplets in natural outbreak settings is available. Infections progress rapidly from influenza-like to gastrointestinal manifestations and coagulopathy, typically culminating in multiple-organ dysfunction syndrome and shock. The occurrence of primary subclinical infections is controversial, but a small percentage of survivors may be subclinically and persistently infected. Treatment of filovirus infections is entirely supportive in nature because no specific efficacious antiviral agents or vaccines are yet licensed.

Filoviruses are categorized as World Health Organization (WHO) Risk Group 4 Pathogens. Consequently, all work with material suspected of containing replicating filoviruses should be conducted only in maximal containment (biosafety level 4) laboratories, or the viruses should be properly inactivated prior to further analysis in biosafety level 2 laboratories. Experienced personnel handling these viruses must wear appropriate personal protective equipment (see "Control and Prevention," below) and follow rigorous standard operating procedures. The proper national authorities and WHO reference laboratories should be contacted immediately when filovirus infections are suspected.

ETIOLOGY

The family *Filoviridae* includes three genera: *Cuevavirus*, *Ebolavirus*, and *Marburgvirus* **(Table 205-1 and Fig. 205-1)**. The available data suggest that the only known cuevavirus, Lloviu virus, does not infect humans, and that one ebolavirus, Reston virus, may infect but not cause disease in humans. The remaining four ebolaviruses—Bundibugyo virus, Ebola virus, Sudan virus, and Taï Forest virus—cause Ebola virus disease (EVD; International Classification of Disease, Tenth Revision [ICD-10], code A98.4). The two marburgviruses, Marburg virus and Ravn virus, are the etiologic agents of Marburg virus disease (MVD; ICD-10 code A98.3).

Filoviruses have linear, nonsegmented, single-stranded, negative-sense RNA genomes that are ~19 kb in length. These genomes contain six or seven genes that encode the following seven structural proteins: nucleoprotein (NP), polymerase cofactor (VP35), matrix protein (VP40), glycoprotein ($GP_{1,2}$), transcriptional cofactor/viral protein 30 (VP30), nucleocapsid-associated protein (VP24), and RNA-dependent RNA polymerase (L). Cuevaviruses and ebolaviruses, but not marburgviruses, also encode three nonstructural proteins of unknown function (sGP, ssGP, and Δ-peptide). Filovirions are unique among human virus particles in that they are predominantly pleomorphic filaments but also assume torus- or 6-like shapes (width, ~80 nm; average length, ≥790 nm). These enveloped virions contain helical ribonucleocapsids and are covered with $GP_{1,2}$ spikes **(Fig. 205-2)**.

EPIDEMIOLOGY

As of October 1, 2017, a total of 31,602 human filovirus infections and 13,350 filovirus deaths had been recorded **(Fig. 205-3)**. Of those, 28,652 cases and 11,325 deaths occurred in a single outbreak, the 2013–2016 EVD outbreak in Western Africa. The total numbers emphasize both the high degree of lethality (number of deaths per number of sick people; 41.7%) and the overall low mortality (impact on the healthy population) of filovirus infections. Until 2013, natural filovirus infections were not considered a global threat. However, the large 2013–2016 EVD outbreak challenged this assessment. Filoviruses pathogenic for humans appear to be exclusively endemic to equatorial (Western, Middle, and Eastern) Africa **(Fig. 205-4)**, although this distribution may change if natural or artificial environmental alterations lead to filovirus host migration and increased contacts between nonhuman hosts and humans.

The majority of recorded EVD and MVD outbreaks, including the 2013–2016 EVD outbreak, can be traced back to single index cases who transmitted the infection to others. These chains of contacts suggest that only around 50 natural host-to-human spillover events have

TABLE 205-1 Current Filovirus Taxonomy

Order *Mononegavirales*
Family *Filoviridae*
Genus *Marburgvirus*
Species *Marburg marburgvirus*
Virus 1: Marburg virus (MARV)
Virus 2: Ravn virus (RAVV)
Genus *Ebolavirus*
Species *Bundibugyo ebolavirus*
Virus: Bundibugyo virus (BDBV)
Species *Reston ebolavirus*
Virus: Reston virus (RESTV)
Species *Sudan ebolavirus*
Virus: Sudan virus (SUDV)
Species *Tai Forest ebolavirus*
Virus: Taï Forest virus (TAFV)
Species *Zaire ebolavirus*
Virus: Ebola virus (EBOV)
Genus *Cuevavirus*
Species *Lloviu cuevavirus*
Virus: Lloviu virus (LLOV)

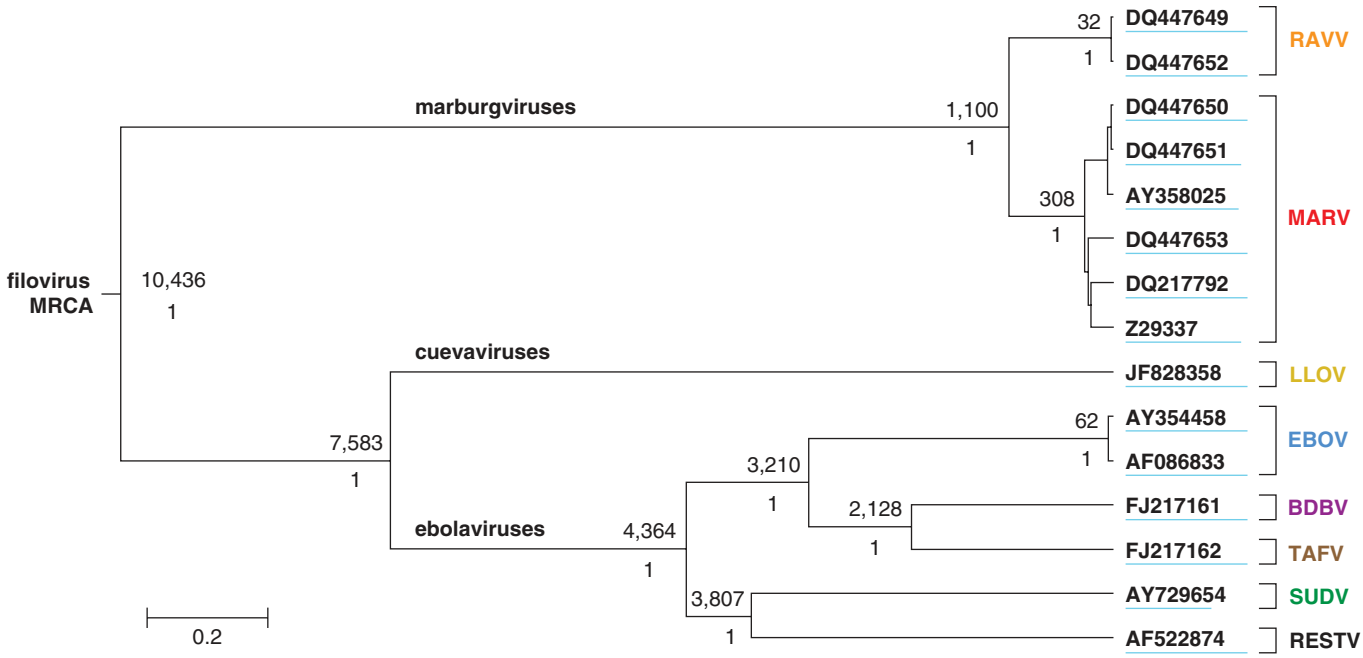

FIGURE 205-1 Filovirus phylogeny/evolution. Bayesian coalescent analysis of representative variants of all known filovirus clades (represented by underlined GenBank accession numbers). The maximal clade credibility tree is shown with the most recent common ancestor (MRCA) at each node. Posterior probability values are shown beneath MRCA estimates in years. Scale is in substitutions/site based on an analysis performed by Dr. Serena Carroll, US Centers for Disease Control and Prevention. BDBV, Bundibugyo virus; EBOV, Ebola virus; LLOV, Lloviu virus; MARV, Marburg virus; RAVV, Ravn virus; RESTV, Reston virus; SUDV, Sudan virus; TAFV, Taï Forest virus.

occurred since the discovery of filoviruses in 1967. Outbreak frequency, case numbers, and overall lethality probably depend on the particular etiologic agent, the geographic location and socioeconomic conditions of the affected country, and local customs. In particular, the accessibility of health-care centers and the availability of personal protective equipment and reusable medical equipment, such as syringes and needles, have affected overall case numbers in the past. Outbreaks have been contained when local burial practices, such as ritual washing, have been either prevented or altered by the use of gloves. The incidence of EVD and MVD may have increased over the past two decades (Figs. 205-3 and 205-4), but debate continues about whether the observed change is due to increased filovirus activity, more frequent contact between filovirus hosts and humans, or continuous improvement in surveillance capabilities.

FIGURE 205-2 Ebola virus particle: The first transmission electron micrograph of an Ebola virion in a culture of grivet (*Chlorocebus aethiops*) Vero cells inoculated with a blood sample from a patient from the 1976 Zaire outbreak of Ebola virus disease. Shown is the typical and unique filamentous and pleomorphic structure of filovirions. *(PHIL ID#1833, taken by Dr. Fredrick A. Murphy, US Centers for Disease Control and Prevention.)*

EVD and MVD outbreaks are associated with distinct meteorological and geographic conditions and are probably associated with distinct hosts or reservoirs. The four ebolaviruses that cause disease in humans appear to be endemic in humid rainforests. EVD outbreaks have often been associated with hunting or contact with bushmeat (i.e., meat from apes, other nonhuman primates, duikers, or bush pigs) in forests. Ecologic studies indicate that Ebola virus may play a role in extensive and frequently fatal epizootics among wild ape populations. However, replicating isolates of ebolaviruses from wild nonhuman primates thus far have not been obtained. The marburgviruses, Marburg virus and Ravn virus, on the other hand, seem to infect hosts inhabiting arid woodlands. MVD outbreaks have almost always been epidemiologically linked to visits to or work in natural or artificial caves or mines. A pteropodid (fruit) bat, the cave-dwelling Egyptian rousette (*Rousettus aegyptiacus*), serves as a natural and subclinically infected reservoir for both Marburg virus and Ravn virus. Although bats are suspected to be the hosts for ebolaviruses as well, definitive proof is lacking. In fact, thus far, only Ebola virus and Reston virus have been loosely connected to frugivorous and insectivorous bats by means of antibody or genome fragment detection, whereas the hosts of Bundibugyo virus, Sudan virus, and Taï Forest virus are enigmatic.

PATHOGENESIS

Human infections typically occur through direct exposure of skin lesions or mucosal surfaces to contaminated bodily fluids or material or by parenteral inoculation (e.g., via accidental needlesticks or reuse of needles in poorly equipped hospitals). Numerous studies, both in vitro and in vivo (in several animal models of human disease), have shed light on key pathogenetic events that evolve subsequent to filovirion exposure. The $GP_{1,2}$ spikes on the surface of filovirions determine their cell and tissue tropism by engaging yet-unidentified cell-surface molecules and the intracellular receptor Niemann-Pick C1.

One of the pathogenetic hallmarks of filovirus infection is a pronounced modulation of the immune system. The first targets of filovirions are local macrophages, monocytes, and dendritic cells. Several structural proteins of filovirions (i.e., VP35, VP40, and/or VP24) then

FIGURE 205-3 Characteristics of outbreaks of human filovirus disease. Seven of eight known filoviruses have caused infections in humans. Outbreaks are listed by virus in chronological order in the left column. Laboratory infections are *shaded gray and italicized*. *Arrows* indicate international case exportation. The total number of cases and lethal cases are summarized in the middle column. The lethality or case–fatality rate (*colored dots*) for each outbreak is plotted on a 0–100% scale along with 99% confidence intervals (*gray horizontal bars*). The overall case–fatality rate for disease caused by a particular virus is delineated by *vertical bold-colored lines*, with *vertical bold-colored dashed lines* indicating the corresponding 99% confidence intervals. The overall case–fatality rates for all ebolavirus infections, all marburgvirus infections, and all filovirus infections are shown by (overlapping) *vertical gray bars*. BDBV, Bundibugyo virus; COD, Democratic Republic of the Congo (formerly Zaire); COG, Republic of the Congo; EBOV, Ebola virus; MARV, Marburg virus; RAVV, Ravn virus; RESTV, Reston virus; SUDV, Sudan virus; TAFV, Taï Forest virus; UK, United Kingdom; USSR, Union of Soviet Socialist Republics (today Russia).

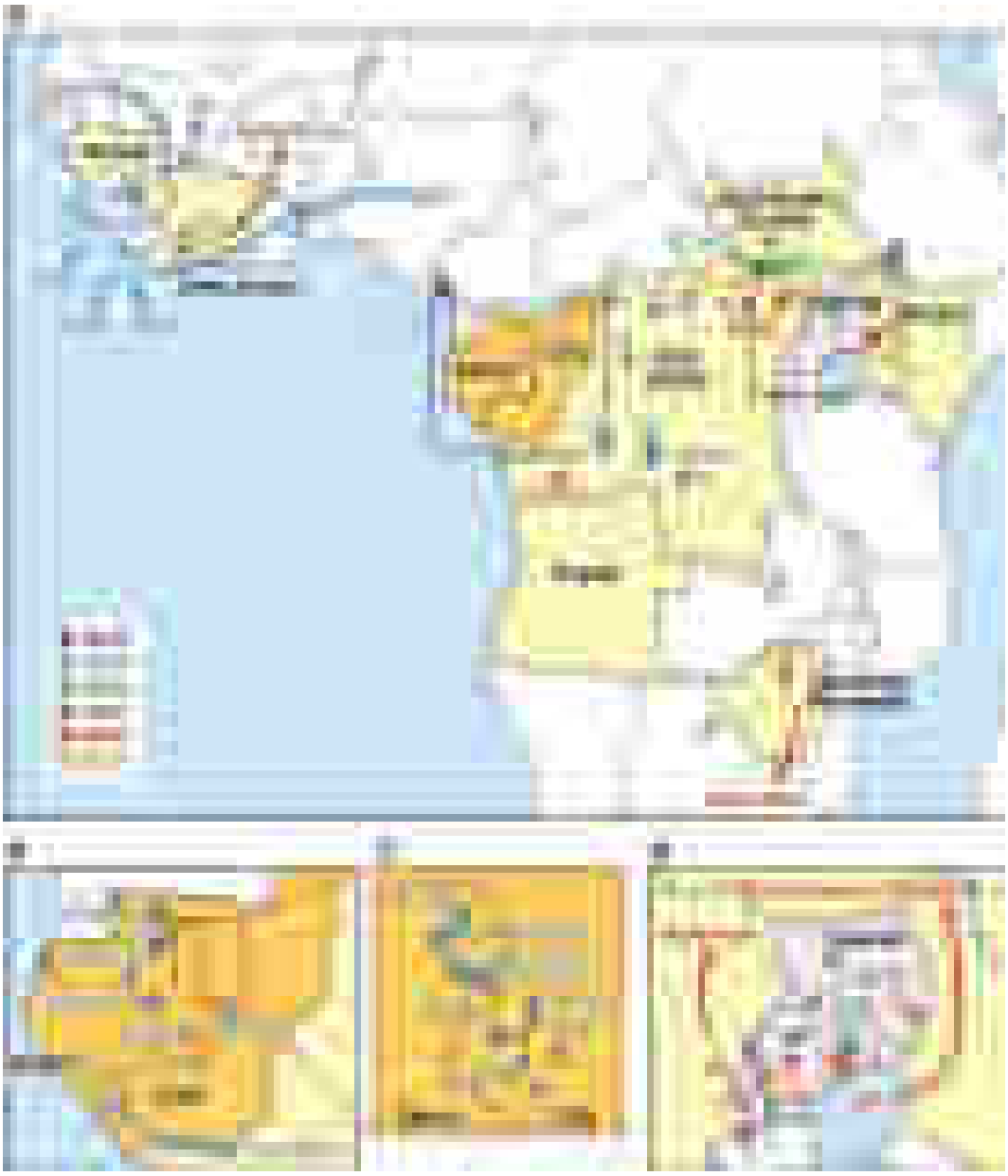

FIGURE 205-4 Geographic distribution of human filovirus disease outbreaks and years of occurrence. *Arrows* indicate international case exportation. BDBV, Bundibugyo virus; COD, Democratic Republic of the Congo (formerly Zaire); COG, Republic of the Congo; EBOV, Ebola virus; MARV, Marburg virus; RAVV, Ravn virus; SUDV, Sudan virus; TAFV, Taï Forest virus.

suppress intrinsic and innate immune responses by, for instance, inhibiting the interferon pathways and enabling a productive filovirus infection. The result is the secretion of copious numbers of progeny virions, as evidenced by high titers in the bloodstream (>10^6 plaque-forming units [pfu]/mL of serum in humans) and the lymphatics, and dissemination to most tissues. Filovirions then infect additional phagocytic cells, including other macrophages (alveolar, peritoneal, and pleural macrophages; Kupffer cells in the liver; and microglia). Other targets, such as adrenal cortical cells, fibroblasts, hepatocytes, endothelial cells, and a variety of epithelial cells, are also infected. Infection leads to the secretion of soluble signaling molecules (varying with the cell type) that most likely are crucial factors in immune response modulation and development of multiorgan dysfunction syndrome. For instance, infected macrophages react by secreting proinflammatory cytokines, a response that leads to further recruitment of macrophages to the site of infection. In contrast, infected dendritic cells are not activated to secrete cytokines, and expression of major histocompatibility class II antigens is partially suppressed. Immunosuppression occurs in part by massive lymphoid depletion in lymph nodes, spleen, and thymus in the absence of reactive inflammatory cellular responses. Results from animal studies suggest that depletion is a direct consequence of considerable bystander apoptosis of lymphocytes; this explanation would also account for the severe lymphopenia that develops in patients. The consequence of these events is not only florid filovirus dissemination but also a proclivity of the patient for secondary bacterial and fungal infections.

Other pathogenetic hallmarks of filovirus infections are a severe disturbance of the clotting system and the impairment of vascular integrity. Disseminated intravascular coagulation is the cause of the severe imbalance in the clotting system of filovirus-infected patients. Thrombocytopenia, increased concentrations of tissue factor, consumption of clotting factors, increased concentrations of fibrin degradation products (D-dimers), and declining concentrations of protein C are typical features of infection. Consequently, the occlusion of small vessels by widely distributed microthrombi leads to extensive necroses/hypoxic infarcts in target tissues (particularly the gonads, kidneys, liver, and spleen) in the absence of marked inflammatory responses. In addition, petechiae, ecchymoses, extensive visceral effusions, and other hemorrhagic signs are observed in internal organs, mucous membranes, and skin. Actual severe blood loss, however, is a rare event (although it

frequently occurs during or after childbirth). Aberrance in cytokines or other factors such as nitric oxide and direct infection and activation of endothelial cells most likely are responsible for upregulated permeability of blood-vessel endothelia. This upregulation leads to fluid redistribution (*third spacing*); interstitial and myocardial edema and hypovolemic shock are common developments. Clinical improvement is possible and is usually characterized by falling viral titers during the development of a virus-specific immune response.

CLINICAL MANIFESTATIONS

MVD and EVD cannot be differentiated by mere observation of clinical manifestations and for all practical purposes may be considered the same disease. The incidence of clinical signs does not differ significantly among infections caused by disparate filoviruses **(Table 205-2)**, although, apart from the patients in the 2013–2016 EVD outbreak, the numbers of thoroughly observed patients are very low. The incubation period ranges from 3 to 25 days, after which infected people develop a biphasic syndrome with a 1- to 2-day relative remission separating the two phases. The first phase (disease onset until around day 5–7) resembles influenza and is characterized by sudden onset of fever and chills, severe headaches, cough, myalgia, pharyngitis, arthralgia of the larger joints, development of a maculopapular rash, and other signs/symptoms (Table 205-2). The second phase (~5–7 days after disease onset and thereafter) involves the gastrointestinal tract (abdominal pain with vomiting and/or diarrhea), respiratory tract (chest pain, cough), vascular system (postural hypotension, edema), and central nervous system (confusion, coma, headache). Hemorrhagic manifestations such as subconjunctival injection, epistaxis, hematemesis, hematuria, and melena are typical (Table 205-2). Relapses are extremely rare, but, when they do occur, their course resembles that of the primary disease.

Typical laboratory findings are leukopenia (with cell counts as low as 1000/μL) with a left shift prior to leukocytosis, thrombocytopenia (with counts as low as 50,000/μL), increased concentrations of liver and pancreatic enzymes (aspartate aminotransferase > alanine

TABLE 205-2 Distribution of Clinical Signs/Symptoms of Filovirus-Infected Patients in Three Representative Outbreaks

	FREQUENCY (%) AMONG SURVIVORS			FREQUENCY (%) AMONG FATAL CASES		
SIGN/SYMPTOM	BDBV (2007–2009)	EBOV (1995)[a]	MARV (1998–2000)	BDBV (2007–2009)	EBOV (1995)[a]	MARV (1998–2000)
Abdominal pain	88	68	59	93	62	57
Abortion	NR	5	NR	NR	2	NR
Anorexia	83	47	77	80	43	72
Anuria	NR	0	NR	NR	7	NR
Arthralgia or myalgia	83	79	55	86	50	55
Asthenia	NR	95	NR	NR	85	NR
Bleeding from puncture sites	NR	5	0	NR	8	7
Bleeding from the gums	NR	0	23	NR	15	36
Bleeding from any site	NR	NR	59	NR	NR	71
Bloody stools	NR	5	NR	NR	7	NR
Chest pain	NR	5	18	NR	10	4
Conjunctival injection	NR	47	14	NR	42	42
Convulsions	NR	0	NR	NR	2	NR
Cough	NR	26	9	NR	7	5
Diarrhea	92	84	59	87	86	56
Difficulty breathing	26	NR	36	57	NR	58
Dysesthesia	NR	5	NR	NR	0	NR
Epistaxis	NR	0	18	NR	2	34
Fever	100	95	100	100	93	92
Headaches	84	74	73	93	52	79
Hearing loss	NR	11	NR	NR	5	NR
Hematemesis	NR	0	68	NR	13	76
Hematoma	NR	0	0	NR	2	3
Hematuria	NR	16	NR	NR	7	NR
Hemoptysis	NR	11	9	NR	0	4
Hepatomegaly (without jaundice)	NR	5	NR	NR	2	NR
Hiccups	17	5	18	40	17	44
Lumbar pain	NR	26	5	NR	12	8
Maculopapular rash	35	16	NR	33	14	NR
Malaise or fatigue	96	NR	86	100	NR	83
Melena	NR	16	41	NR	8	58
Nausea and vomiting	92	68	77	87	73	76
Petechiae	NR	0	9	NR	8	7
Sore throat, odynophagia, or dysphagia	43	58	43	60	56	43
Splenomegaly	NR	5	NR	NR	2	NR
Tachypnea	NR	0	NR	NR	31	NR
Tinnitus	NR	11	NR	NR	1	NR

[a]In contrast to the 1995 outbreak (317 cases), the 2013–2016 EVD outbreak (28,652 cases) would yield much more statistically robust numbers. However, to date, only very few reports have been published on patient cohorts larger than a few hundred cases. Metastudies comparing these reports are largely absent or focus on very few symptoms or signs.

Abbreviations: BDBV, Bundibugyo virus; EBOV, Ebola virus; MARV, Marburg virus; NR, not reported.

aminotransferase, γ-glutamyltransferase, serum amylase), hypokalemia, hypoproteinemia, increased creatinine and urea concentrations with proteinuria, and prolonged prothrombin and partial thromboplastin times.

Patients usually succumb to disease 4–14 days after infection. Patients who survive often report prolonged and sometimes incapacitating arthralgia, asthenia, iridocyclitis, hearing loss, myalgia, orchitis, parotitis, psychosis, recurrent hepatitis, transverse myelitis, or uveitis, but clinical research is still ongoing to ascertain that these are true sequelae. Temporary hair loss and desquamation of skin areas previously affected by a typical maculopapular rash are visible consequences of the disease. Rarely, filoviruses can persist in the brain, eyes, liver, or testicles of survivors and may cause recurrent disease after convalescence and/or sexual transmission.

DIAGNOSIS

Filovirus infections cannot be diagnosed on the basis of clinical presentation alone. Numerous diseases typical for equatorial Africa need to be considered in the differential diagnosis of a febrile patient. Almost all of these diseases occur at a much higher incidence than filovirus infections and are therefore the more likely candidates during differential diagnostic deliberations. The most important of the infectious diseases that closely mimic EVD and MVD are falciparum malaria and typhoid fever; also important are enterohemorrhagic *Escherichia coli* enteritis, gram-negative septicemia (including shigellosis), meningococcal septicemia, rickettsial infections, fulminant viral hepatitis, leptospirosis, measles, and all other viral hemorrhagic fevers (in particular, Lassa and yellow fevers). Other ailments, such as venomous snakebites, warfarin intoxication, and the many transient or inherited platelet and vascular disorders, also must be considered. Visits to caves or mines and direct contact with bats, nonhuman primates, or bushmeat should raise suspicion of filovirus infection, as should admission to or treatment in rural hospitals or direct contact with severely ill local residents.

If EVD or MVD is suspected on the basis of epidemiologic history, exposure history, and/or clinical manifestations, infectious disease specialists and the proper public health authorities, including the WHO, should be notified immediately. Laboratory diagnosis of EVD and MVD is relatively straightforward but ideally requires maximal containment (biosafety level 4), which usually is not available in filovirus-endemic countries. Alternatively, laboratory diagnosis is performed using inactivated samples in lower-containment settings by on-site personnel trained in the use of diagnostic assays adapted for field use. Consequently, diagnostic samples should be collected with great caution and with use of proper personal protective equipment and strict barrier nursing techniques. With adherence to established biosafety precautionary measures, samples should be sent in suitable transport media to national or international WHO reference laboratories. Acute-phase blood/serum is the preferred diagnostic specimen because it usually contains high titers of filovirions and filovirion-specific antibodies.

The current methods of choice for the diagnosis of filovirus infection are reverse-transcription polymerase chain reaction (typical detection limit, 1000–5000 pfu per milliliter of serum, depending on the assay) and antigen capture enzyme-linked immunosorbent assay (ELISA) for the detection of filovirus genomes and filovirion proteins, respectively. Direct IgM and IgG–capture or IgM-capture ELISA is used for the detection of filovirion-targeting antibodies from patients in later stages of disease—i.e., those who have been able to mount a detectable immune response, including survivors. All these assays can be conducted on samples treated with guanidinium isothiocyanate (for polymerase chain reaction) or cobalt-60 irradiation (for ELISA) or subjected to other effective measures that render filoviruses noninfectious. Virus isolation in cell culture and plaque assays for quantification or diagnostic confirmation are relatively easy but must be performed in maximal-containment laboratories. If available, electron microscopic examination of properly inactivated samples or cultures can further support the diagnosis because filovirions have unique filamentous shapes (Fig. 205-2). Formalin-fixed skin biopsies and possibly skin swabs can be useful for safe postmortem diagnoses.

TREATMENT

Filovirus Infections

Any treatment of patients with suspected or confirmed filovirus infection must be administered under increased safety precautions by experienced specialists using appropriate personal protective equipment (see "Control and Prevention," below). Treatment of EVD and MVD is entirely supportive because no accepted/approved, efficacious, specific antiviral agents or vaccines are yet licensed. Exceptions are hyperimmune equine immunoglobulin, which has been approved in Russia for emergency treatment of laboratory infections, and the anti–Ebola virus monoclonal antibody cocktail ZMapp, which is on its way to becoming available under U.S. Emergency Use Authorization. However, convincing efficacy data are still missing for both medical countermeasures. Given the high lethality of filoviruses, special protocols may be established by ad hoc expert groups to outline treatment of exposed individuals with one of several regimens that have shown promise in experimental nonhuman primate models. Current options include post-exposure vaccination with filovirus $GP_{1,2}$-expressing recombinant replicating vesicular stomatitis Indiana virus or administration of filovirus-specific antibodies or antibody cocktails (convalescent sera have not yet been proven effective), synthetic adenosine analogs (galidesivir/BCX4430, GS-5734) that act as non-obligate RNA chain terminators, or favipiravir. Regardless of the availability of these experimental agents, measures to stabilize patients include those generally recommended for severe septicemia/sepsis/shock **(Chap. 297)** and should be applied with an emphasis on fluid and electrolyte replacement. Countermeasures should address hypotension and hypoperfusion, vascular leakage in the systemic and pulmonary circulatory system, disseminated intravascular coagulation and overt hemorrhaging, acute kidney failure, and electrolyte (especially potassium) imbalances. Pain management and administration of antipyretics, antiemetics, and antidiarrheal agents should be considered. Aggressive supportive measures, including mechanical ventilatory support and renal replacement therapy, may shore up patients with severe EVD until their immune systems respond and virus is cleared.

COMPLICATIONS

Secondary infections should be kept in mind and appropriately treated as early as possible. Pregnancy and labor cause severe and frequently fatal complications in filovirus infections due to clotting factor consumption, fetal loss, and/or severe blood loss during birth.

PROGNOSIS

The prognosis of filovirus infections is generally poor, although outcome probably depends somewhat on which particular virus causes the infection (Fig. 205-3). Convalescence may take months, with skin peeling, alopecia, prostration, weight loss, orchitis, amnesia, confusion, and anxiety as typical sequelae. Rarely, filoviruses persist in apparently healthy survivors and are either reactivated by unknown means at a later point or transmitted sexually. Abstinence from sexual activity for at least 12 months after disappearance of clinical signs is recommended for survivors unless testing proves semen to be free of filoviruses. The use of condoms is generally recommended for all sexual activities.

CONTROL AND PREVENTION

Currently, licensed filovirus vaccines are not available. Prevention of filovirus infection in nature is difficult because the ecology of the viruses is not completely understood. At present, to prevent marburgvirus infection, avoidance of direct or indirect contact with Egyptian rousettes is the most useful advice to people entering or living in areas where these animals can be found. Prevention seems to be more difficult in the case of ebolaviruses, for which definite reservoirs have not yet been pinpointed. EVD outbreaks have been associated not so much with bats as with hunting or consumption of nonhuman primates. The mechanism of introduction of ebolaviruses into nonhuman primate populations is unclear. Therefore, the best advice to locals and travelers is to avoid contact with bushmeat, nonhuman primates, and bats.

Relatively simple barrier nursing techniques, vigilant use of proper personal protective equipment, and quarantine measures (including contact tracing) usually suffice to terminate or at least contain filovirus disease outbreaks. Isolation of filovirus-infected people and their contacts and avoidance of direct person-to-person contact without proper personal protective equipment usually suffice to prevent further spread as the pathogens are not transmitted through droplets or aerosols under natural conditions. Typical protective gear sufficient to prevent filovirus infections consists of disposable gloves, gowns, and shoe covers and a face shield and/or goggles. If available, N-95 or N-100 respirators may be used to further limit infection risk. Positive air pressure respirators should be considered for high-risk medical procedures such as intubation or suctioning. Medical equipment used in the care of a filovirus-infected patient, such as gloves or syringes, should never be reused. Because filovirions are enveloped, disinfection with detergents, such as 1% sodium deoxycholate, diethyl ether, or phenolic compounds, is relatively straightforward. Bleach solutions of 1:100 or 1:10 are recommended for surface disinfection and application to excreta or corpses, respectively. Whenever possible, potentially contaminated materials should be autoclaved, irradiated, or destroyed.

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Section 16 Fungal Infections

206 Diagnosis and Treatment of Fungal Infections

John E. Edwards, Jr.

TERMINOLOGY AND MICROBIOLOGY

Traditionally, fungal infections have been classified into specific categories based on both anatomic location and epidemiology. The most common general anatomic categories are mucocutaneous and deep organ infection; the most common general epidemiologic categories are endemic and opportunistic infection. Although *mucocutaneous infections* can cause serious morbidity, they are rarely fatal. *Deep organ infections* also cause severe illness in many cases and, in contrast to mucocutaneous infections, are often fatal. The *endemic mycoses* (e.g., coccidioidomycosis) are caused by fungal organisms that are not part of the normal human microbiota, but rather are acquired from environmental sources. In contrast, *opportunistic mycoses* are caused by organisms (e.g., *Candida* and *Aspergillus*) that commonly are components of the normal human microbiota and whose ubiquity in nature renders them easily acquired by the immunocompromised host (Table 206-1). Opportunistic fungi cause serious infections when the immunologic response of the host becomes ineffective, allowing the organisms to transition from harmless commensals to invasive pathogens. Frequently, the diminished effectiveness of the immune system is a result of advanced modern therapies that coincidentally either cause an imbalance in the host's microbiota or directly interfere with immunologic responses. Endemic mycoses usually cause more severe illness in immunocompromised patients than in immunocompetent individuals.

TABLE 206-1 Endemic and Opportunistic Mycoses

ENDEMIC MYCOSES[a]	OPPORTUNISTIC MYCOSES
Coccidioidomycosis	Candidiasis
Histoplasmosis	Aspergillosis
Blastomycosis	Cryptococcosis
Phaeohyphomycosis	Mucormycosis (zygomycosis)
Penicilliosis	Scedosporiosis
Sporotrichosis	Trichosporonosis
Paracoccidioidomycosis	Fusariosis
Adiaspiromycosis	Pneumocystosis

[a]The endemic mycoses can also occur as opportunistic infections.

Patients acquire deep organ infection with endemic fungi almost exclusively by inhalation. Cutaneous infections result either from hematogenous dissemination or, more often, from direct contact with soil—the natural reservoir for the vast majority of endemic mycoses. The dermatophytic fungi may be acquired by human-to-human transmission, but the majority of infections result from environmental contact. In contrast, the opportunistic fungus *Candida* invades the host from normal sites of colonization, usually the mucous membranes of the gastrointestinal tract. In general, innate immunity is the primary defense mechanism against fungi. Although antibodies are formed during many fungal infections (and even during commensalism), they generally do not constitute the primary mode of host defense. Nevertheless, in selected infections, as discussed below, measurement of antibody titers may be a useful diagnostic test.

Three other terms frequently used in clinical discussions of fungal infections are *yeast*, *mold*, and *dimorphic fungus*. *Yeasts* are seen as rounded single cells or as budding organisms. *Molds* grow as filamentous forms called *hyphae* both at room temperature and in invaded tissue. *Aspergillus*, *Rhizopus* (the genus that causes mucormycosis, also known as zygomycosis), and fungi commonly infecting the skin to cause ringworm and related cutaneous conditions are classified as molds. Variations occur within this classification of yeasts and molds. For instance, when *Candida* infects tissue, both yeasts and filamentous forms may be present (except with *Candida glabrata*, which forms only yeasts in tissue); in contrast, *Cryptococcus* exists only in yeast form. *Dimorphic* is the term used to describe fungi that grow as yeasts or large spherical structures in tissue but as filamentous forms at room temperature in the environment. Classified in this group are the organisms causing candidiasis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis, histoplasmosis, and sporotrichosis as well as *Emonsia* and *Ustilago*.

The incidence of nearly all fungal infections has risen substantially. Opportunistic infections have increased in frequency as a consequence of intentional immunosuppression in organ and stem cell transplantation and other disorders, the administration of cytotoxic chemotherapy for cancers, the liberal use of antibacterial agents, and, more recently, the increasing use of monoclonal antibodies.

Within a global context, the incidence of endemic mycoses has increased in geographic locations where there has been substantial population growth. When advances in medical care (e.g., more aggressive treatment of cancer or organ transplantation) are introduced into a given area, the opportunistic mycoses increase in incidence.

DIAGNOSIS

The definitive diagnosis of any fungal infection requires histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response. The identification of an inflammatory response has been especially important with regard to *Aspergillus* infection. *Aspergillus* is ubiquitous and can float in the air onto biopsy material. Therefore, in rare but important instances, this fungus is an ex vivo contaminant during processing of a specimen for microscopy, with a consequent incorrect diagnosis. The stains most commonly used to identify fungi are periodic acid–Schiff and Gomori methenamine silver. *Candida*, unlike other fungi, is visible on gram-stained tissue smears. Hematoxylin and eosin stain is not sufficient to identify *Candida* in tissue specimens. When positive, an india ink preparation of cerebrospinal fluid (CSF) is diagnostic for cryptococcosis. Most laboratories now use calcofluor white staining coupled with fluorescent microscopy to identify fungi in fluid specimens. Matrix-assisted laser desorption ionization–time of flight mass spectometry (MALDI-TOF MS) will likely be used extensively for detection and speciation in the future. Point-of-care, lateral-flow testing techniques are being developed for many fungal infections.

Extensive investigations of the diagnosis of deep organ fungal infections have yielded a variety of tests with different degrees of specificity and sensitivity. The most reliable tests are the detection of antibody to *Coccidioides immitis* in serum and CSF; of *Histoplasma capsulatum* antigen in urine, serum, and CSF; and of cryptococcal polysaccharide antigen in serum and CSF. Commercially available antibody detection systems can now be used for blastomycosis, histoplasmosis, cryptococcosis, aspergillosis, and β-glucan detection. These tests have a general sensitivity and specificity of 90%; however, because of variability among laboratories, testing on multiple occasions is advisable. The test for galactomannan has been used extensively in Europe and is now approved in the United States for diagnosis of aspergillosis. Sources of concern regarding galactomannan are the incidence of false-negative results and the need for multiple serial tests to reduce this incidence. This test is most useful when applied to bronchoalveolar lavage fluid. The β-glucan test for *Candida* is also under evaluation but, like the galactomannan test, requires additional validation; this test has a negative predictive value of ~90%. Both of these tests are being used with increasing frequency, especially for guiding the timing of initiation and the duration of therapy and for following principles of antimicrobial stewardship. One of the most useful applications of these non-culture-based tests has been the detection of *Histoplasma* antigens in serum and urine. T2 magnetic resonance is also being extensively evaluated for *Candida* and other organisms. It has been approved by the U.S. Food and Drug Administration (FDA) for detection of *Candida* in serum. Numerous polymerase chain reaction assays to detect antigens are in the developmental stages, as are nucleic acid hybridization techniques; currently, these tests are not widely available.

Of the fungal organisms, *Candida* is by far the most frequently recovered from blood. Although *Candida* species can be detected with any of the automated blood culture systems widely used at present, the lysis–centrifugation technique increases the sensitivity of blood cultures for *Candida* and for less common organisms (e.g., *H. capsulatum*). Lysis–centrifugation should be used when disseminated fungal infection is suspected.

Except in the cases of coccidioidomycosis, cryptococcosis, and histoplasmosis, there are no fully validated and widely used tests for serodiagnosis of disseminated fungal infection. Skin tests for the endemic mycoses are no longer available.

TREATMENT

Fungal Infections

This discussion is intended as a brief overview of general strategies for the use of antifungal agents in the treatment of fungal infections. Regimens, schedules, and choices are detailed in the chapters on specific mycoses that follow in this section. The doses cited here are standard doses for adults with invasive infection.

Since fungal organisms are eukaryotic cells that contain most of the same organelles (with many of the same physiologic functions) as human cells, the identification of drugs that selectively kill or inhibit fungi, but are not toxic to human cells, has been highly problematic. Far fewer antifungal than antibacterial agents have been introduced into clinical medicine.

AMPHOTERICIN B

The introduction of amphotericin B (AmB) in the late 1950s revolutionized the treatment of fungal infections in deep organs. Before AmB became available, cryptococcal meningitis and other disseminated fungal infections were nearly always fatal. For nearly a decade after AmB was introduced, it was the only effective agent for the treatment of life-threatening fungal infections. AmB remains the broadest-spectrum antifungal agent but carries several disadvantages, including significant nephrotoxicity, lack of an oral preparation, and unpleasant side effects (fever, chills, and nausea) during treatment. To circumvent nephrotoxicity and infusion side effects, lipid formulations of AmB were developed and have virtually replaced the original colloidal deoxycholate formulation in clinical use (although the older formulation is still available). The lipid formulations include liposomal AmB (L-AmB; 3–5 mg/kg per day) and AmB lipid complex (ABLC; 5 mg/kg per day). A third preparation, AmB colloidal dispersion (ABCD; 3–4 mg/kg per day), is rarely used because of the high incidence of side effects associated with infusion.

The lipid formulations of AmB have the disadvantage of being considerably more expensive than the deoxycholate formulation. Experience is still accumulating on the comparative efficacy, toxicity, and advantages of the different formulations for specific clinical fungal infections, including central nervous system (CNS) infection. Whether there is a clinically significant difference in these drugs with respect to CNS penetration or nephrotoxicity remains controversial. Despite these issues and despite the expense, the lipid formulations are now much more commonly used than AmB deoxycholate in developed countries. In developing countries, AmB deoxycholate is still preferred because of the expense of the lipid formulations.

AZOLES

This class of antifungal drugs offers important advantages over AmB: the azoles cause little or no nephrotoxicity and are available in oral formulations. Early azoles included ketoconazole and miconazole, which have been replaced by newer agents for the treatment of deep organ fungal infections. The azoles' mechanism of action is inhibition of ergosterol synthesis in the fungal cell wall. Unlike AmB, these drugs are considered fungistatic, not fungicidal.

Fluconazole Since its introduction, fluconazole has played an extremely important role in the treatment of a wide variety of serious fungal infections. Its major advantages are the availability of both oral and IV formulations, a long half-life, satisfactory penetration of most body fluids (including ocular fluid and CSF), and minimal toxicity (especially relative to that of AmB). Its disadvantages include (usually reversible) hepatotoxicity and—at high doses—alopecia, muscle weakness, and dry mouth with a metallic taste. Fluconazole is not effective for the treatment of aspergillosis, mucormycosis, or *Scedosporium apiospermum* infections. It is less effective than the newer azoles against *C. glabrata* and *Candida krusei.*

Fluconazole has become the agent of choice for the treatment of coccidioidal meningitis, although relapses have followed therapy with this drug. In addition, fluconazole is useful as both consolidation and maintenance therapy for cryptococcal meningitis. This agent has been shown to be as efficacious as AmB in the treatment of candidemia. The effectiveness of fluconazole and the echinocandins (see below) in candidemia and the drugs' relatively minimal toxicity, in conjunction with the inadequacy of diagnostic tests for widespread hematogenously disseminated candidiasis, have led to a change in the paradigm for candidemia management. The standard

of care is now to treat all candidemic patients with an antifungal agent and to change all their intravascular lines, if feasible, rather than merely removing a singular suspect intravascular line and then observing the patient. The usual fluconazole regimen for treatment of candidemia is a loading dose of 12 mg/kg on day 1 and then 6 mg/kg per day until 2 weeks after the last positive blood culture.

Fluconazole is considered effective as fungal prophylaxis in bone marrow transplant recipients and high-risk liver transplant patients. Its general use for prophylaxis in patients with leukemia, in AIDS patients with low CD4+ T cell counts, and in patients on surgical intensive care units remains controversial. Many centers are now using posaconazole for prophylaxis in neutropenic patients (see below). Because of concern about the possibility of infection due to resistant *Candida* species and of infection with *Aspergillus* species in neutropenic patients, many clinicians are initiating therapy with an echinocandin, which is replaced by fluconazole once a susceptible *Candida* species is recovered and concern about *Aspergillus* is diminished. In a recent report, even low doses of fluconazole used for the treatment of vulvovaginal candidiasis were associated with an increased incidence of miscarriage in pregnant patients.

Voriconazole Voriconazole, which is available in both oral and IV formulations, has a broader spectrum than fluconazole against *Candida* species (including *C. glabrata* and *C. krusei*) and is active against *Aspergillus*, *Scedosporium*, *Fusarium*, and *Coccidioides*. It is generally considered the first-line drug of choice for treatment of aspergillosis. Case reports have shown voriconazole to be effective in individual patients with coccidioidomycosis, blastomycosis, and histoplasmosis; however, because the data are limited, this agent is not generally recommended for primary treatment of the endemic mycoses. Among the disadvantages of voriconazole (compared with fluconazole) are its more numerous interactions with many of the drugs used in patients predisposed to fungal infections. Hepatotoxicity, skin rashes (including photosensitivity), and visual disturbances are relatively common. Skin cancer surveillance is now recommended for patients taking voriconazole. In addition, voriconazole is considerably more expensive than fluconazole. Moreover, it is advisable to monitor voriconazole levels in certain patients since (1) this drug is completely metabolized in the liver by CYP2C9, CYP3A4, and CYP2C19; and (2) human genetic variability in CYP2C19 activity exists. Dosages should be reduced accordingly in patients with liver failure. Dose adjustments for renal insufficiency are not necessary; however, because the IV formulation is prepared in cyclodextrin, it should not be given to patients with severe renal insufficiency.

Itraconazole Itraconazole is available in IV and oral (capsule and suspension) formulations. Varying blood levels among patients taking oral itraconazole reflect a disadvantage compared with the other azoles. Itraconazole is the drug of choice for mild to moderate histoplasmosis and blastomycosis and has often been used for chronic mucocutaneous candidiasis. It has been approved by the FDA for use in febrile neutropenic patients; however, most centers use other azoles in neutropenic patients for both prophylaxis and treatment. Itraconazole has also proved useful for the treatment of chronic coccidioidomycosis, sporotrichosis, and *S. apiospermum* infection. The mucocutaneous and cutaneous fungal infections that have been treated successfully with itraconazole include oropharyngeal candidiasis (especially in AIDS patients), tinea versicolor, tinea capitis, and onychomycosis. Disadvantages of itraconazole include its poor penetration into CSF, the use of cyclodextrin in both the oral suspension and the IV formulation, the variable absorption of the drug in capsule form, and the need for monitoring of blood levels in patients taking capsules for disseminated mycoses. Reported cases of severe congestive heart failure in patients taking itraconazole have been a source of concern. Like the other azoles, itraconazole can cause hepatic toxicity.

Posaconazole Posaconazole is approved by the FDA for prophylaxis of aspergillosis and candidiasis in patients at high risk for developing these infections because of severe immunocompromise. It has also been approved for the treatment of oropharyngeal candidiasis and has been evaluated as therapy for zygomycosis, fusariosis, aspergillosis, cryptococcosis, and various other forms of candidal infection except candidemia. The relevant studies of posaconazole in zygomycosis, fusariosis, and aspergillosis have examined salvage therapy. A study of >90 patients whose zygomycosis was refractory to other therapy yielded encouraging results. No trials of posaconazole for the treatment of candidemia have yet been reported. Case reports have described the drug's efficacy in coccidioidomycosis and histoplasmosis. Controlled trials have shown its effectiveness as a prophylactic agent in patients with acute leukemia and in bone marrow transplant recipients. In addition, posaconazole has been found to be effective against fluconazole-resistant *Candida* species. The results of a large-scale study of the use of posaconazole as salvage therapy for aspergillosis indicated that it is an alternative to other agents for salvage therapy; however, that study predated the use of voriconazole and the echinocandins.

Isavuconazole Isavuconazole is the newest of the azoles to be approved by the FDA. It is approved for invasive aspergillosis and invasive mucormycosis. Because of the paucity of drugs effective in mucormycosis and the high mortality rate from this infection, isavuconazole was approved on the basis of an open-label, noncomparative trial in 37 patients. Future experience will more definitively determine its place in the antifungal armamentarium.

ECHINOCANDINS

The echinocandins, including the FDA-approved drugs caspofungin, anidulafungin, and micafungin, have added considerably to the stock of available antifungal drugs. All three of these agents inhibit β-1,3-glucan synthase, which is necessary for cell wall synthesis in fungi and is not a component of human cells. None of these agents is currently available in an oral formulation. The echinocandins are considered fungicidal for *Candida* and fungistatic for *Aspergillus*. Their greatest use to date is against candidal infections. They offer two advantages: broad-spectrum activity against all *Candida* species and relatively low toxicity. The minimal inhibitory concentrations (MICs) of all the echinocandins are highest against *Candida parapsilosis*; it is not clear whether these higher MIC values represent less clinical effectiveness against this species. The echinocandins are among the safest antifungal agents.

In controlled trials, *caspofungin* has been at least as efficacious as AmB for the treatment of candidemia and invasive candidiasis and as efficacious as fluconazole for the treatment of candidal esophagitis. In addition, caspofungin has been efficacious as salvage therapy for aspergillosis. *Anidulafungin* has been approved by the FDA as therapy for candidemia in nonneutropenic patients and for *Candida* esophagitis, intraabdominal infection, and peritonitis. In controlled trials, anidulafungin has been shown to be noninferior and possibly superior to fluconazole against candidemia and invasive candidiasis. It is as efficacious as fluconazole against candidal esophagitis. When anidulafungin is used with cyclosporine, tacrolimus, or voriconazole, no dosage adjustment is required for either drug in the combination. *Micafungin* has been approved for the treatment of esophageal candidiasis and candidemia and for prophylaxis in patients receiving stem cell transplants. In a head-to-head trial, micafungin was noninferior to caspofungin for the treatment of candidemia. Studies thus far have shown that coadministration of micafungin and cyclosporine does not require dose adjustments for either drug. When micafungin is given with sirolimus, the area under the plasma drug concentration–time curve rises for sirolimus, usually necessitating a reduction in its dose. In open-label trials, favorable results have been obtained with micafungin for the treatment of deep-seated *Aspergillus* and *Candida* infections.

FLUCYTOSINE (5-FLUOROCYTOSINE)

The use of flucytosine has diminished as newer antifungal drugs have been developed. This agent is now used most commonly in combination with AmB (deoxycholate or lipid formulations) for

the initial treatment of cryptococcal meningitis. Flucytosine has a unique mechanism of action based on intrafungal conversion to 5-fluorouracil, which is toxic to the fungal cell. Development of resistance to the compound has limited its use as a single agent. Flucytosine is nearly always used in combination with AmB. Its good penetration into the CSF makes it attractive for use with AmB for treatment of cryptococcal meningitis. Flucytosine has also been recommended for the treatment of candidal meningitis in combination with AmB; comparative trials with AmB alone have not been done. Significant and frequent bone marrow depression is seen with flucytosine when this drug is used with AmB.

GRISEOFULVIN AND TERBINAFINE

Historically, griseofulvin has been useful primarily for ringworm infection. This agent is usually given for relatively long periods. Terbinafine has been used primarily for onychomycosis but also for ringworm. In comparative studies, terbinafine has been as effective as itraconazole and more effective than griseofulvin for both conditions.

TOPICAL ANTIFUNGAL AGENTS

A detailed discussion of the agents used for the treatment of cutaneous fungal infections and onychomycosis is beyond the scope of this chapter; the reader is referred to **Chap. 214** and the dermatology literature. Many classes of compounds have been used to treat the common fungal infections of the skin. Among the azoles used are clotrimazole, econazole, miconazole, oxiconazole, sulconazole, ketoconazole, tioconazole, butoconazole, and terconazole. In general, topical treatment of vaginal candidiasis has been successful. Since little difference is thought to exist in the efficacy of the various vaginal preparations, the choice of agent is made by the physician and/or the patient on the basis of preference and availability. Fluconazole given orally at 150 mg has the advantage of not requiring repeated intravaginal application. Nystatin is a polyene that has been used for both oropharyngeal thrush and vaginal candidiasis. Useful agents in other classes include ciclopirox olamine, haloprogin, terbinafine, naftifine, tolnaftate, and undecylenic acid.

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207 Histoplasmosis

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ETIOLOGY

Histoplasma capsulatum, a thermal dimorphic fungus, is the etiologic agent of histoplasmosis. In most endemic areas, *H. capsulatum* var. *capsulatum* is the causative agent. In Central and South America, histoplasmosis is common and is caused by genetically different clades of *H. capsulatum* var. *capsulatum*. In Africa, *H. capsulatum* var. *duboisii* is also found. Yeasts of var. *duboisii* are larger than those of var. *capsulatum*.

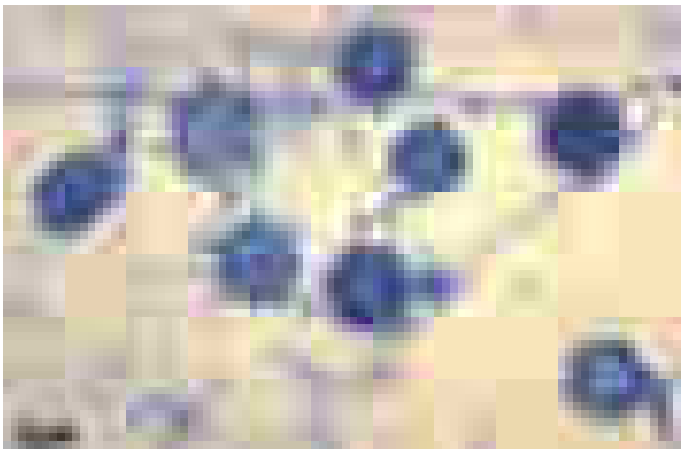

FIGURE 207-1 Spiked spherical conidia of *H. capsulatum* (lacto-phenol cotton blue stain).

Mycelia—the naturally infectious form of *Histoplasma*—have a characteristic appearance, with microconidial and macroconidial forms **(Fig. 207-1)**. Microconidia are oval and are small enough (2–4 μm) to reach the terminal bronchioles and alveoli. Shortly after infecting the host, mycelia transform into the yeasts that are found inside macrophages and other phagocytes. The yeast forms are characteristically small (2–5 μm), with occasional narrow budding **(Fig. 207-2)**. In the laboratory, mycelia are best grown at room temperature, whereas yeasts are grown at 37°C on enriched media.

EPIDEMIOLOGY

Histoplasmosis is the most prevalent endemic mycosis in North America. Although this fungal disease has been reported throughout the world, its endemicity is particularly notable in the Ohio and Mississippi river valleys of North America and in certain parts of Central and South America, Africa, and Asia. In Europe, histoplasmosis is diagnosed fairly often, mostly in emigrants from or travelers to endemic areas on other continents. The geographic distribution of histoplasmosis is related to the humid and acidic nature of the soil in the endemic areas. Soil enriched with bird or bat droppings promotes the growth and sporulation of *Histoplasma.* Disruption of soil containing the organism leads to aerosolization of the microconidia and exposure of humans nearby. Activities associated with high-level exposure include spelunking, excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. Most cases seen outside of highly endemic areas represent imported disease—e.g., cases reported in Europe after travel to the Americas, Africa, or Asia. The epidemiology of histoplasmosis is changing with the continued expansion of at-risk populations and the acceleration of intercontinental and international travel that brings this infection to areas of the world that are not known to be endemic. The population at risk for histoplasmosis continues to grow as a result of increasing numbers of patients receiving immunosuppressive therapies for autoimmune disorders, cancers, and organ transplants.

PATHOGENESIS AND PATHOLOGY

Infection follows inhalation of microconidia (Fig. 207-1). Once they reach the alveolar spaces, microconidia are rapidly recognized and engulfed by alveolar macrophages. At this point, the microconidia transform into budding yeasts (Fig. 207-2), a process that is integral to the pathogenesis of histoplasmosis and is dependent on the availability of calcium and iron inside the phagocytes. The yeasts are capable of multiplying inside resting macrophages. Neutrophils and then lymphocytes are attracted to the site of infection. Before the development of cellular immunity, yeasts use the phagosomes as a vehicle for translocation to local draining lymph nodes, whence they spread hematogenously throughout the reticuloendothelial system. Adequate

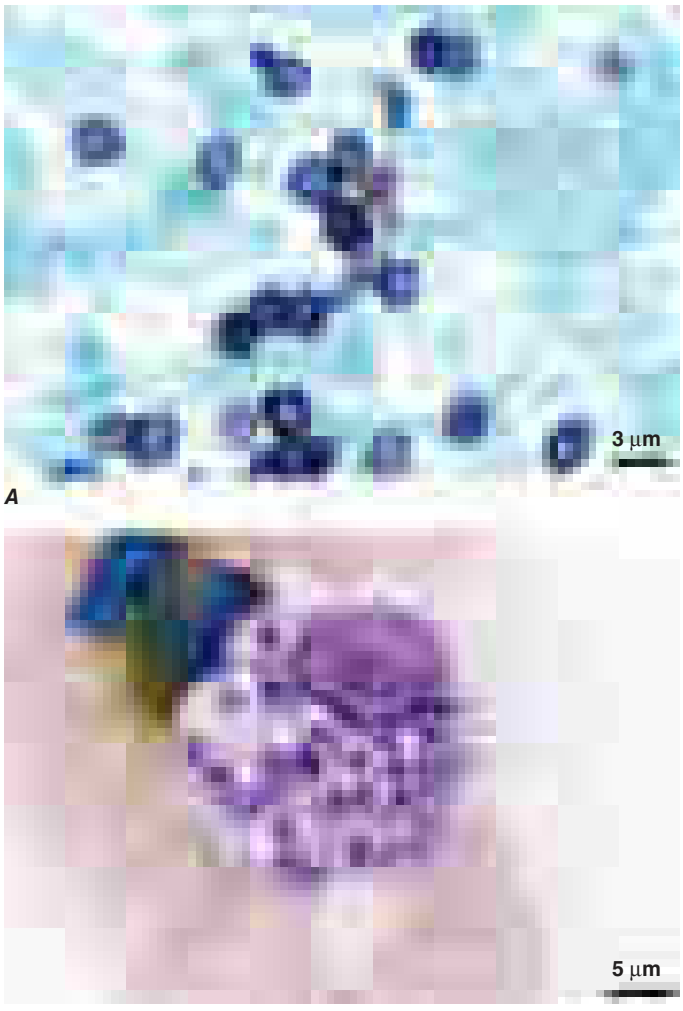

FIGURE 207-2 ***A.*** Small (2–5 μm) narrow budding yeasts of *H. capsulatum* from bronchoalveolar lavage fluid (Grocott's methenamine silver stain). ***B.*** Intracellular yeasts of *H. capsulatum* within an alveolar macrophage from a patient with AIDS and disseminated histoplasmosis (Giemsa stain).

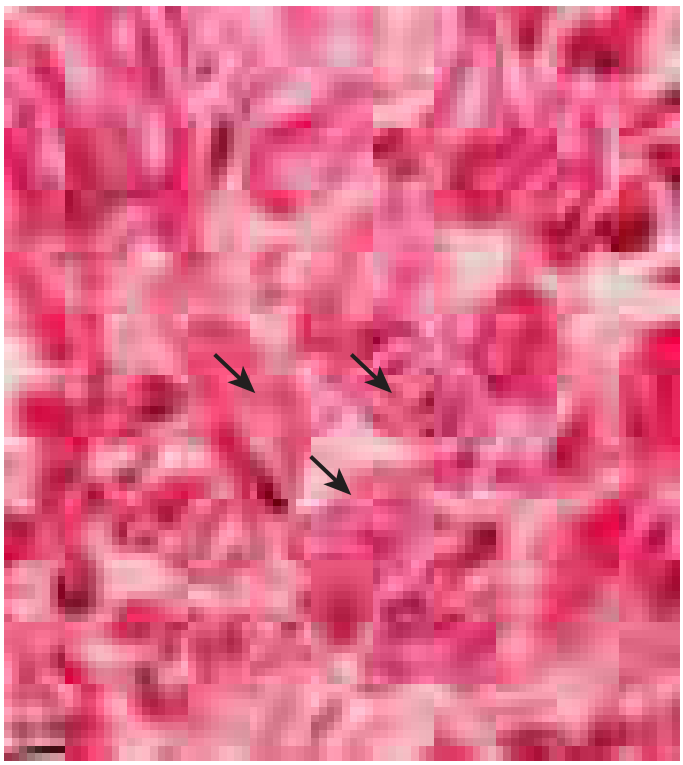

FIGURE 207-3 **Intracellular yeasts** (*arrows*) of *H. capsulatum* in a liver biopsy specimen (hematoxylin and eosin stain).

cellular immunity develops ~2 weeks after infection. T cells produce interferon γ to assist the macrophages in killing the organism and controlling the progression of disease. Interleukin 12 and tumor necrosis factor α (TNF-α) play an essential role in cellular immunity to *H. capsulatum*. In the immunocompetent host, macrophages, lymphocytes, and epithelial cells eventually organize and form granulomas that contain the organisms. These granulomas typically fibrose and calcify; calcified lung nodules, mediastinal lymph nodes, and hepatosplenic calcifications are frequently found in healthy individuals from endemic areas. In immunocompetent hosts, infection with *H. capsulatum* confers some immunity to reinfection. In patients with impaired cellular immunity, the infection is not properly contained and can disseminate throughout the reticuloendothelial system. Progressive disseminated histoplasmosis (PDH) can involve multiple organs, most commonly the lungs, bone marrow, spleen, liver (Fig. 207-3), adrenal glands, and mucocutaneous membranes. Unlike latent tuberculosis, latent histoplasmosis rarely reactivates.

Structural lung disease (e.g., emphysema) impairs the clearance of pulmonary histoplasmosis, and chronic pulmonary disease can result. This chronic process is characterized by progressive inflammation, tissue necrosis, and fibrosis mimicking cavitary tuberculosis.

CLINICAL MANIFESTATIONS

The clinical spectrum of histoplasmosis ranges from asymptomatic infection to life-threatening illness. The attack rate and the extent and severity of the disease depend on the intensity of exposure, the immune status of the exposed individual, and the underlying lung architecture of the host.

In immunocompetent individuals with low-level exposure, most *Histoplasma* infections are either asymptomatic or mild and self-limited. Of adults residing in endemic areas, 50–80% have skin-test and/or radiographic evidence of previous infection without clinical manifestations. Asymptomatic lung nodules representing controlled histoplasmosis are frequently found on chest CT scans obtained during screening for lung cancer in smokers from endemic areas. When symptoms of acute histoplasmosis develop, they usually appear 1–4 weeks after exposure. Heavy exposure leads to a flulike illness with fever, chills, sweats, headache, myalgia, anorexia, cough, dyspnea, and chest pain. Chest radiographs usually show signs of pneumonitis with prominent hilar or mediastinal adenopathy. Pulmonary infiltrates may be focal with light exposure or diffuse with heavy exposure. Rheumatologic symptoms of arthralgia or arthritis, often associated with erythema nodosum, occur in 5–10% of patients with acute histoplasmosis. Pericarditis may also develop. These manifestations represent inflammatory responses to the acute pulmonary infection rather than extrapulmonary spread. Affected hilar or mediastinal lymph nodes may undergo necrosis and coalesce to form large mediastinal masses that can cause compression of great vessels, proximal airways, and the esophagus. These necrotic lymph nodes may also rupture and create fistulas between mediastinal structures (e.g., bronchoesophageal fistulas).

PDH is typically seen in immunocompromised individuals, who account for ~70% of cases. Common risk factors include AIDS (CD4+ T cell count, <200/μL), extremes of age, the administration of immunosuppressive medications to prevent or treat rejection following transplantation (e.g., prednisone, mycophenolate, calcineurin inhibitors), and the use of methotrexate, anti-TNF-α agents, and other biological response modifiers for autoimmune disorders.

The clinical spectrum of PDH ranges from an acute, rapidly fatal course—with diffuse interstitial or reticulonodular lung infiltrates causing respiratory failure, shock, coagulopathy, and multiorgan failure—to a more subacute course with a focal organ distribution. Common manifestations include fever, weight loss, hepatosplenomegaly, and thrombocytopenia. Other findings may include meningitis

or focal brain lesions, ulcerations of the oral mucosa, gastrointestinal ulcerations and bleeding, and adrenal insufficiency. Prompt recognition of this devastating illness is of paramount importance in patients with more severe manifestations or with underlying immunosuppression, especially that due to AIDS **(Chap. 197)**.

Chronic cavitary histoplasmosis is seen in smokers who have structural lung disease (e.g., bullous emphysema). This chronic illness is characterized by productive cough, dyspnea, low-grade fever, night sweats, and weight loss. Chest radiographs usually show upper-lobe infiltrates, cavitation, and pleural thickening—findings resembling those of tuberculosis. Without treatment, the course is slowly progressive.

Fibrosing mediastinitis is an uncommon and serious complication of histoplasmosis. In certain patients, acute infection is followed for unknown reasons by progressive fibrosis around the hilar and mediastinal lymph nodes. Involvement may be unilateral or bilateral; bilateral involvement carries a worse prognosis. Major manifestations include superior vena cava syndrome, obstruction of pulmonary vessels, and airway obstruction. Patients may experience recurrent pneumonia, hemoptysis, or respiratory failure. Fibrosing mediastinitis is fatal in up to one-third of cases.

In healed histoplasmosis, calcified mediastinal nodes or lung parenchymal nodules may erode through the walls of the airways and cause hemoptysis and expectoration of calcified material. This condition is called *broncholithiasis*.

The clinical features and management of histoplasmosis caused by the genetically different clades in Central and South America are similar to those of the disease in North America. African histoplasmosis caused by var. *duboisii* is clinically distinct and is characterized by frequent skin and bone involvement.

DIAGNOSIS

Recommendations for the diagnosis and treatment of histoplasmosis are summarized in **Table 207-1**. Once suspected, the diagnosis of histoplasmosis is usually straightforward as many diagnostic tools are now available. This is not the case in resource-limited endemic regions of Central America, South America, and Africa, where the diagnosis is often delayed, with consequently poor outcomes.

Fungal culture remains the gold standard diagnostic test for histoplasmosis. However, culture results may not be known for up to 1 month, and cultures are often negative in less severe cases. Cultures are positive in ~75% of cases of PDH and chronic pulmonary histoplasmosis. Cultures of bronchoalveolar lavage (BAL) fluid are positive in about half of patients with acute pulmonary histoplasmosis causing diffuse infiltrates with hypoxemia. In PDH, the culture yield is highest for BAL fluid, bone marrow aspirate, and blood. Cultures of sputum or bronchial washings are usually positive in chronic pulmonary histoplasmosis. Cultures are typically negative, however, in other forms of histoplasmosis.

Fungal stains of cytopathology or biopsy materials showing structures resembling *Histoplasma* yeasts are helpful in the diagnosis of PDH, yielding positive results in about half of cases. Yeasts can be seen in BAL fluid (Fig. 207-2) from patients with diffuse pulmonary infiltrates, in bone marrow biopsy samples, and in biopsy specimens of other involved organs (e.g., the adrenal glands). Occasionally, yeasts are seen within circulating phagocytes on blood smears from patients with severe PDH. However, staining artifacts and other fungal elements sometimes stain positively and may be misidentified as *Histoplasma* yeasts.

The detection of *Histoplasma* antigen in body fluids is extremely useful in the diagnosis of PDH and acute diffuse pulmonary histoplasmosis. The sensitivity of this technique is >95% in patients with PDH and >80% in patients with acute pulmonary histoplasmosis if both urine and serum are tested. Antigen levels correlate with severity of illness in PDH and can be used to follow disease progression, as levels predictably decrease with effective therapy. Increased antigen levels also predict relapse. Antigen can be detected in cerebrospinal fluid from patients with meningitis and in BAL fluid from those with pneumonia. Cross-reactivity occurs with African histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infection.

Serologic tests, including immunodiffusion and complement fixation, are useful for the diagnosis of histoplasmosis in immunocompetent patients. At least 1 month is required for the production of antibodies after the onset of infection; thus the utility of serology for early diagnosis of acute histoplasmosis is limited. The antibody titer may rise by fourfold in patients with acute histoplasmosis. Serologic tests are especially useful for the diagnosis of chronic pulmonary histoplasmosis. Limitations of serology, however, include insensitivity early in the course of infection and in immunosuppressed patients and the persistence of detectable antibody for several years after infection. Positive results from past infection may lead to a misdiagnosis of active histoplasmosis in a patient with another disease process.

TREATMENT

Histoplasmosis

Treatment is indicated for all patients with PDH or chronic pulmonary histoplasmosis as well as for symptomatic patients with acute pulmonary histoplasmosis causing diffuse infiltrates, especially with hypoxemia. In most cases of pulmonary histoplasmosis, treatment is not recommended because the immune system of the host is intact and the degree of exposure is not heavy; the infection is

TABLE 207-1 Recommendations for the Diagnosis and Treatment of Histoplasmosis

TYPE OF HISTOPLASMOSIS	DIAGNOSTIC TESTS	TREATMENT RECOMMENDATIONS	COMMENTS
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	*Histoplasma* antigen (BAL fluid, serum, urine) Cytopathology on and fungal culture of BAL fluid	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Patients with mild cases usually recover without therapy, but itraconazole should be considered if the patient's condition has not improved after 1 month.
Chronic/cavitary pulmonary	*Histoplasma* serology (immunodiffusion and complement fixation) Fungal culture of sputum or BAL fluid	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	*Histoplasma* antigen (serum, urine) Fungal culture of blood or bone marrow aspirate Cytopathology on biopsy of affected organ	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	*Histoplasma* antigen and serology of CSF Fungal culture of CSF	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until CSF or CT abnormalities clear.

Abbreviations: AmB, amphotericin B; BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid.

asymptomatic or symptoms are mild, subacute, and not progressive; and the illness resolves without therapy.

The preferred treatments for histoplasmosis (Table 207-1) include the lipid formulations of amphotericin B in more severe cases and itraconazole in others. Liposomal amphotericin B is more effective and better tolerated than the deoxycholate formulation for treatment of PDH in patients with AIDS. The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation for patients at low risk for nephrotoxicity. Voriconazole, posaconazole, and isavuconazole are alternatives for patients who cannot take itraconazole.

In severe cases requiring hospitalization, a lipid formulation of amphotericin B is used first, followed by itraconazole. In patients with meningitis, a lipid formulation of amphotericin B should be given for 4–6 weeks before switching to itraconazole. In immunosuppressed patients, the degree of immunosuppression should be reduced if possible, although immune reconstitution inflammatory syndrome (IRIS) may ensue. Antiretroviral treatment improves the outcome of PDH in patients with AIDS and is recommended; however, whether antiretroviral treatment should be delayed to avoid IRIS is unknown.

Blood levels of itraconazole should be monitored to ensure adequate drug exposure, with target concentrations of the parent drug and its hydroxy metabolites measuring 1–5 μg/mL. Drug interactions should be carefully assessed: itraconazole not only is cleared by cytochrome P450 metabolism but also inhibits cytochrome P450. This profile causes interactions with many other medications.

The duration of treatment for acute pulmonary histoplasmosis is 6–12 weeks, while that for PDH and chronic pulmonary histoplasmosis is ≥1 year. Antigen levels in urine and serum should be monitored during and for at least 1 year after therapy for PDH. Stable or rising antigen levels suggest treatment failure or relapse.

Lifelong itraconazole maintenance therapy is recommended for patients with persistently suppressed immunity but not for those with immune recovery—e.g., patients with AIDS who respond well to antiretroviral therapy, with CD4+ T cell counts of at least 150/μL (preferably >250/μL); who complete at least 1 year of itraconazole therapy; and who exhibit neither clinical evidence of active histoplasmosis nor an antigenuria level of >2 ng/mL. Similarly, maintenance therapy is not necessary in patients receiving immunosuppressive treatment if the degree of immunosuppression can be reduced along with effective control of the infection.

Fibrosing mediastinitis, which represents a chronic fibrotic reaction to past mediastinal histoplasmosis rather than an active infection, does not respond to antifungal therapy. While treatment is often prescribed for patients with pulmonary histoplasmosis who have not recovered within 1 month and for those with persistent mediastinal lymphadenopathy, the effectiveness of antifungal therapy in these situations is unknown.

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208 Coccidioidomycosis

Neil M. Ampel

DEFINITION AND ETIOLOGY

Coccidioidomycosis, commonly known as Valley fever (see "Epidemiology," below), is caused by dimorphic soil-dwelling fungi of the genus *Coccidioides*. Genetic analysis has demonstrated the existence of two species, *C. immitis* and *C. posadasii*. These species are indistinguishable with regard to the clinical disease they cause and their appearance on routine laboratory media. Thus, the organisms will be referred to simply as *Coccidioides* for the remainder of this chapter.

EPIDEMIOLOGY

Coccidioidomycosis is confined to the Western Hemisphere between the latitudes of 40°N and 40°S. In the United States, areas of high endemicity include the southern portion of the San Joaquin Valley of California (hence the sobriquet "Valley fever") and the south-central region of Arizona. However, infection may be acquired in other areas of the southwestern United States, including the southern coastal counties in California, southern Nevada, southwestern Utah, southern New Mexico, and western Texas (including the Rio Grande Valley). The recent acquisition of cases well outside the recognized areas, including in eastern Washington state and in northeastern Utah, suggests that the endemic region may be expanding. Outside the United States, coccidioidomycosis is endemic to northern Mexico as well as to localized regions of Central America. In South America, there are endemic foci in Colombia, Venezuela, northeastern Brazil, Paraguay, Bolivia, and north-central Argentina.

The risk of infection is increased by direct exposure to soil harboring *Coccidioides*. Because of difficulty in isolating *Coccidioides* from the soil, the precise characteristics of potentially infectious soil are not known. In the United States, several outbreaks of coccidioidomycosis have been associated with soil from archaeologic excavations of Amerindian sites both within and outside of the recognized endemic region. These cases often involved alluvial soils in regions of relative aridity with moderate temperature ranges. When found, *Coccidioides* is isolated 2–20 cm below the surface; it is not found in soil at greater depths, nor is it usually isolated from cultivated soil.

In endemic areas, many cases of *Coccidioides* infection occur without obvious soil or dust exposure. Climatic factors appear to increase the infection rate in these regions. In particular, periods of aridity following rainy seasons have been associated with marked increases in the number of symptomatic cases. Overall, the incidence within the United States increased substantially over the past decade, with nearly 43 cases per 100,000 residents of the endemic region in 2011. Most of that increase occurred in south-central Arizona, where most of that state's population resides, and in the southern San Joaquin Valley of California, a less populated region. The factors causing this increase have not been fully elucidated; however, an influx of older individuals without prior coccidioidal infection appears to be involved. Other variables, such as climate change, construction activity, and increased awareness and reporting, may also be contributors. Health care providers should consider coccidioidomycosis when evaluating persons with pneumonia who live in or have traveled to endemic areas.

PATHOGENESIS, PATHOLOGY, AND IMMUNE RESPONSE

On agar media and in the soil, *Coccidioides* organisms exist as filamentous molds. Within this mycelial structure, individual filaments (*hyphae*) elongate and branch, some growing upward. Alternating cells within the hyphae degenerate, leaving barrel-shaped viable elements called *arthroconidia*. Measuring ~2 μm by 5 μm, arthroconidia may become airborne for extended periods. Their small size allows them to evade initial mechanical mucosal defenses and reach deep into the bronchial tree, where infection is initiated in the nonimmune host.

Once in a susceptible host, the arthroconidia enlarge, become rounded, and develop internal septations. The resulting structures, called *spherules* **(Fig. 208-1)**, may attain sizes of 200 μm and are unique to *Coccidioides*. The septations encompass uninuclear elements called *endospores*. Spherules may rupture and release packets of endospores that can themselves develop into spherules, thus propagating infection locally. If returned to artificial media or the soil, the fungus reverts to its mycelial stage.

Clinical observations and data from studies of animals strongly support the critical role of a robust cellular immune response in the host's control of coccidioidomycosis. Necrotizing granulomas containing spherules are typically identified in patients with resolved

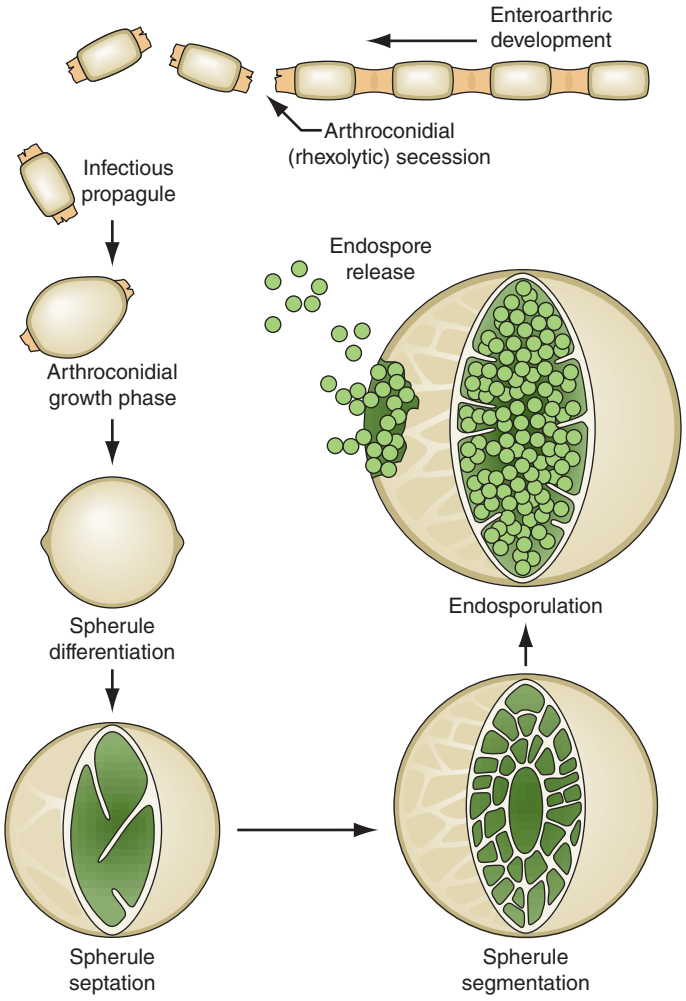

FIGURE 208-1 Life cycle of *Coccidioides.* *(From TN Kirkland, J Fierer: Emerg Infect Dis 2:192, 1996.)*

pulmonary infection. In disseminated disease, granulomas are generally poorly formed or do not develop at all, and a polymorphonuclear leukocyte response occurs frequently. In patients who are asymptomatic or in whom the initial pulmonary infection resolves, delayed-type hypersensitivity to coccidioidal antigens has been routinely documented.

CLINICAL AND LABORATORY MANIFESTATIONS

Among infected individuals, 60% are completely asymptomatic, and the remaining 40% have symptoms that are related principally to pulmonary infection, including fever, cough, and pleuritic chest pain. The risk of symptomatic illness increases with age. Coccidioidomycosis is commonly misdiagnosed as community-acquired bacterial pneumonia.

There are several cutaneous manifestations of primary pulmonary coccidioidomycosis. Toxic erythema consisting of a maculopapular rash has been noted in some cases. Erythema nodosum **(see Fig. A1-39)**—typically over the lower extremities—or erythema multiforme **(see Fig. A1-24)**—usually in a necklace distribution—may occur; these manifestations are seen especially often in women. Arthralgias and arthritis may develop. The diagnosis of primary pulmonary coccidioidomycosis is particularly suggested by a history of night sweats or profound fatigue as well as by peripheral-blood eosinophilia and hilar or mediastinal lymphadenopathy on chest radiography. While pleuritic chest pain is common, pleural effusions occur in fewer than 10% of cases. Such effusions are invariably associated with a pulmonary infiltrate on the same side. The cellular content of these effusions is mononuclear in nature; *Coccidioides* is rarely isolated on culture of effusions.

In most patients, primary pulmonary coccidioidomycosis usually resolves without sequelae in weeks. However, several pneumonic complications may arise. Pulmonary nodules are residua of primary pneumonia. Generally single, frequently located in the upper lobes, and ≤4 cm in diameter, nodules are often discovered on a routine chest radiograph in an asymptomatic patient. Calcification is uncommon. Coccidioidal pulmonary nodules can be difficult to distinguish radiographically from pulmonary malignancies. Like malignancies, coccidioidal nodules often enhance on positron emission tomography. However, unlike malignancies, routine CT often demonstrates multiple nodules in coccidioidomycosis. Biopsy is often required to distinguish between these two conditions.

Pulmonary cavities occur when a nodule extrudes its contents into the bronchus, resulting in a thin-walled shell. These cavities can be associated with persistent cough, hemoptysis, and pleuritic chest pain. Rarely, a cavity may rupture into the pleural space, causing pyopneumothorax. In such cases, patients present with acute dyspnea, and the chest radiograph reveals a collapsed lung with a pleural air-fluid level. Chronic or persistent pulmonary coccidioidomycosis manifests with prolonged fever, cough, and weight loss and is radiographically associated with pulmonary scarring, fibrosis, and cavities. It occurs most commonly in patients who already have chronic lung disease due to other etiologies.

In some cases, primary pneumonia presents as a diffuse reticulonodular pulmonary process (detected by plain chest radiography) in association with dyspnea and fever. Primary diffuse coccidioidal pneumonia may occur in settings of intense environmental exposure or profoundly suppressed cellular immunity (e.g., in patients with AIDS), with unrestrained fungal growth that is frequently associated with fungemia.

Clinical dissemination outside the thoracic cavity occurs in fewer than 1% of infected individuals. Dissemination is more likely to occur in male patients, particularly those of African-American or Filipino ancestry, and in persons with depressed cellular immunity, including patients with HIV infection and peripheral-blood CD4+ T cell counts of <250/μL; those receiving chronic glucocorticoid therapy; those with allogeneic solid-organ transplants; and those being treated with tumor necrosis factor α antagonists. Women who acquire infection during the second or third trimester of pregnancy or postpartum also are at risk for disseminated disease. Common sites for dissemination include the skin, bones, joints, soft tissues, and meninges. Dissemination may follow symptomatic or asymptomatic pulmonary infection and may involve only one site or multiple anatomic foci. When it occurs, clinical dissemination is usually evident within the first 6 months after primary pulmonary infection.

Coccidioidal meningitis, if untreated, is uniformly fatal. Patients usually present with a persistent headache, which is sometimes accompanied by lethargy and confusion. Nuchal rigidity, if present, is not severe. Examination of cerebrospinal fluid (CSF) demonstrates lymphocytic pleocytosis with profound hypoglycorrhachia and elevated protein levels. CSF eosinophilia is occasionally documented. With or without appropriate therapy, patients may develop hydrocephalus, either communicating or non-communicating, which presents clinically as a marked decline in mental status, often with gait disturbances.

DIAGNOSIS

As mentioned above, coccidioidomycosis is often misdiagnosed as community-acquired bacterial pneumonia. Clues that suggest a diagnosis of coccidioidomycosis include peripheral-blood eosinophilia, hilar or mediastinal adenopathy on radiographic imaging, marked fatigue, and failure to improve with antibiotic therapy.

Serology plays an important role in establishing a diagnosis of coccidioidomycosis. Several techniques are available, including the traditional tube-precipitin (TP) and complement-fixation (CF) assays, immunodiffusion TP and CF (IDTP and IDCF), and enzyme immunoassay (EIA) to detect IgM and IgG antibodies. TP and IgM antibodies are found in serum soon after infection and persist for weeks. They are not useful for gauging disease progression and are not found in the CSF. The CF and IgG antibodies occur later in the course of the disease and persist longer than TP and IgM antibodies. Rising CF titers are associated with clinical progression, and the presence of CF antibody in CSF is indicative of coccidioidal meningitis. Antibodies disappear over time in persons whose clinical illness resolves.

Because of its commercial availability, the coccidioidal EIA is frequently used as a screening tool for coccidioidal serology. There has been concern that the IgM EIA is occasionally falsely positive, particularly in asymptomatic individuals. In addition, while the sensitivity and specificity of the IgG EIA appear to be higher than those of the CF and IDCF assays, the optical density obtained in the EIA does not correlate with the serologic titer of either of the latter tests.

Coccidioides grows within 3–7 days at 37°C on a variety of artificial media, including blood agar. Therefore, it is always useful to obtain samples of sputum or other respiratory fluids and tissues for culture in suspected cases of coccidioidomycosis. The clinical laboratory should be alerted to the possibility of this diagnosis, since *Coccidioides* poses a significant laboratory hazard if it is inadvertently inhaled. The organism can also be identified directly. While treatment of samples with potassium hydroxide is rarely fruitful in establishing the diagnosis, examination of sputum or other respiratory fluids after Papanicolaou, Gomori methenamine silver, or calcofluor white staining reveals spherules in a significant proportion of patients with pulmonary coccidioidomycosis. For fixed tissues (e.g., those obtained from biopsy specimens), spherules with surrounding inflammation can be demonstrated with hematoxylin-eosin or Gomori methenamine silver staining.

A commercially available test for coccidioidal antigenuria and antigenemia has been developed and appears to be particularly useful in immunosuppressed patients with severe or disseminated disease. False-positive results may occur in cases of histoplasmosis or blastomycosis. Some laboratories offer genomic detection by polymerase chain reaction; this assay has not been shown to be more sensitive than culture.

TREATMENT

Coccidioidomycosis

Currently, two main classes of antifungal agents are useful for the treatment of coccidioidomycosis **(Table 208-1)**. While once prescribed routinely, amphotericin B in all its formulations is now reserved for only the most severe cases of dissemination and for intrathecal or intraventricular administration to patients with coccidioidal meningitis in whom triazole antifungal therapy has failed. The original formulation of amphotericin B, which is dispersed with deoxycholate, is usually administered intravenously in doses of 0.7–1.0 mg/kg either daily or three times per week. The newer lipid-based formulations are associated with less renal toxicity but have not been demonstrated to lead to better improvement than the deoxycholate formulation in coccidioidomycosis. The lipid dispersions are administered intravenously at doses of 3–5 mg/kg daily or three times per week.

TABLE 208-1 Clinical Presentations of Coccidioidomycosis, Their Frequency, and Recommended Initial Therapy for the Immunocompetent Host

CLINICAL PRESENTATION	FREQUENCY, %	RECOMMENDED THERAPY
Asymptomatic infection	60	None
Primary pneumonia (focal)	40	In most cases, none[a]
Diffuse pneumonia	<1	Amphotericin B followed by prolonged oral triazole therapy
Pulmonary sequelae	5	
Nodule		None
Cavity		In most cases, none[b]
Chronic pneumonia		Prolonged triazole therapy
Disseminated disease	≤1	
Skin, bone, joint, soft tissue disease		Prolonged triazole therapy[c]
Meningitis		Lifelong triazole therapy[d]

[a]Treatment is indicated for hosts with depressed cellular immunity as well as for those with prolonged symptoms and signs of increased severity, including night sweats for >3 weeks, weight loss of >10%, a complement-fixation titer of >1:16, and extensive pulmonary involvement on chest radiography. [b]Treatment (usually with the oral triazoles fluconazole and itraconazole) is recommended for persistent symptoms. [c]In severe cases, some clinicians would use amphotericin B as initial therapy. [d]Intraventricular or intrathecal amphotericin B is recommended in cases of triazole failure. Hydrocephalus may occur, requiring a CSF shunt.

Note: See text for dosages and durations.

Triazole antifungals are the principal drugs now used to treat most cases of coccidioidomycosis. Clinical trials have demonstrated the usefulness of both fluconazole and itraconazole. Evidence indicates that itraconazole is efficacious against bone and joint disease. Because of its demonstrated penetration into CSF, fluconazole is the azole of choice for the treatment of coccidioidal meningitis, but itraconazole also is effective. For both drugs, a minimal oral adult dosage of 400 mg/d should be used. The maximal dose of itraconazole is 200 mg three times daily, but higher doses of fluconazole may be given. The newer triazole antifungals, posaconazole and especially voriconazole, appear to be useful against clinical disease, including meningitis, in which prior fluconazole therapy has failed. High-dose triazole therapy may be teratogenic during the first trimester of pregnancy; thus, amphotericin B should be considered as therapy for coccidioidomycosis in pregnant women during this period. Isavuconazole has been used in limited circumstances in coccidioidomycosis.

Most patients with focal primary pulmonary coccidioidomycosis do not require antifungal therapy. Patients for whom antifungal therapy should be considered include those with underlying cellular immunodeficiencies and those with prolonged symptoms and signs of extensive disease. Specific criteria include symptoms persisting for ≥2 months, night sweats occurring for >3 weeks, weight loss of >10%, a serum CF antibody titer of >1:16, and extensive pulmonary involvement apparent on chest radiography. When antifungal therapy is used, either fluconazole or itraconazole at 400 mg daily for 6 months is considered appropriate.

Diffuse pulmonary coccidioidomycosis represents a special situation. Because most patients with this form of disease are profoundly hypoxemic and critically ill, many clinicians favor beginning therapy with an amphotericin B formulation and switching to an oral triazole antifungal once clinical improvement occurs.

The nodules that may follow primary pulmonary coccidioidomycosis do not require treatment. As noted above, these nodules are not easily distinguished from pulmonary malignancies by means of radiographic imaging. Close clinical follow-up and biopsy may be required to distinguish between these two entities. Most pulmonary cavities do not require therapy. Antifungal treatment should be considered in patients with persistent cough, pleuritic chest pain, and hemoptysis. Occasionally, pulmonary coccidioidal cavities become secondarily infected. This development is usually manifested by an air-fluid level within the cavity. Bacterial flora or *Aspergillus* species are commonly involved, and therapy directed at these organisms should be considered. Surgery is rarely required in cases of persistent hemoptysis or pyopneumothorax. In addition, cavities >4 cm in diameter are unlikely to resolve spontaneously, and their surgical extirpation should be considered. For chronic pulmonary coccidioidomycosis, prolonged antifungal therapy—lasting for at least 1 year—is usually required, with monitoring of symptoms, radiographic changes, sputum cultures, and serologic titers.

Most cases of disseminated coccidioidomycosis require prolonged antifungal therapy. Duration of treatment is based on clinical improvement in conjunction with a significant decline in serum CF antibody titer. Such therapy routinely is continued for at least several years. Relapse occurs in 15–30% of individuals once therapy is discontinued.

Coccidioidal meningitis poses a special challenge. While most patients with this form of disease respond to treatment with oral triazoles, 80% experience relapse when therapy is stopped. Thus, lifelong therapy is recommended. In cases of triazole failure, intrathecal or intraventricular amphotericin B may be used. Installation requires considerable expertise and should be undertaken only by an experienced health care provider. Shunting of CSF in addition

to appropriate antifungal therapy is required in cases of meningitis complicated by hydrocephalus. It is prudent to obtain expert consultation in all cases of coccidioidal meningitis.

PREVENTION

There are no proven methods to reduce the risk of acquiring coccidioidomycosis among residents of an endemic region, but avoidance of direct contact with uncultivated soil or with visible dust containing soil is a reasonable measure. For individuals with suppressed cellular immunity, the risk of developing symptomatic coccidioidomycosis is greater than that in the general population. Among those about to undergo allogeneic solid-organ transplantation, antifungal therapy is appropriate when there is evidence of active or recent coccidioidomycosis. Some transplant centers in the endemic region are providing universal antifungal prophylaxis for 6 months to 1 year after solid organ transplantation. Several cases of donor-transmitted coccidioidomycosis have occurred during transplantation. If possible, donors from an endemic region should be screened for coccidioidomycosis before transplantation. Data on the use of antifungal agents for prophylaxis in other situations are limited. The administration of prophylactic antifungals is not recommended for HIV-1-infected patients who live in an endemic region. Most experts would administer a triazole antifungal to patients with a history of active coccidioidomycosis or a positive coccidioidal serology in whom therapy with tumor necrosis factor α antagonists is being initiated.

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209 Blastomycosis

S. Travis King, Rathel L. Nolan, III

Blastomycosis is a systemic pyogranulomatous infection, involving primarily the lungs, that follows inhalation of the conidia of *Blastomyces dermatitidis*. Pulmonary blastomycosis varies from an asymptomatic infection to acute or chronic pneumonia. Hematogenous dissemination to skin, bones, and the genitourinary system is common; however, almost any organ can be involved.

ETIOLOGIC AGENT

B. dermatitidis is the asexual state of *Ajellomyces dermatitidis*. Two serotypes have been identified on the basis of the presence or absence of the A antigen. Distinct genotypic groups have been differentiated by rDNA polymerase chain reaction restriction fragment length polymorphisms and microsatellite markers. *B. dermatitidis* exhibits thermal dimorphism, growing as the mycelial phase at room temperature and as the yeast phase at 37°C. Primary isolation in the laboratory is most dependable for the mycelial phase incubated at 30°C. Definitive identification usually requires conversion to the yeast phase at 37°C or—now more commonly—the use of nucleic acid amplification techniques that detect mycelial-phase growth. Under the microscope, the yeast cells are usually 8–15 μm in diameter, have thick refractile cell walls, are multinucleate, and exhibit a single, large, broad-based bud **(Fig. 209-1)**.

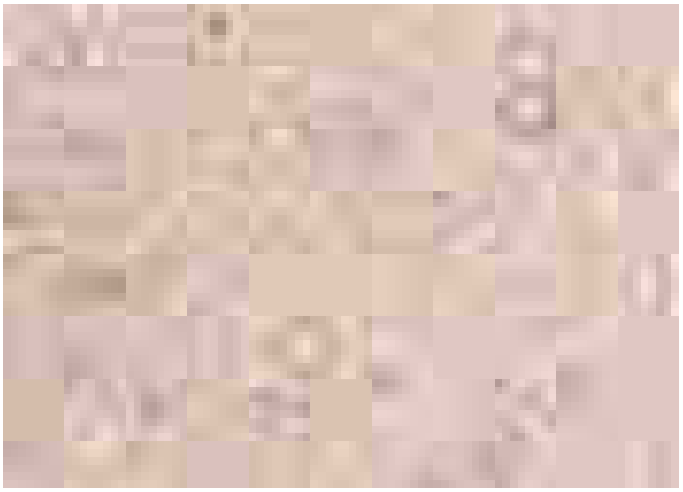

FIGURE 209-1 *Blastomyces dermatitidis* broad-based budding yeast in the aspirate of a chest wall abscess. Note the presence of multiple nuclei, the thickened cell wall, and the broad-based bud.

EPIDEMIOLOGY

Most cases of blastomycosis have been reported in North America. Endemic areas include the southeastern and south-central states bordering the Mississippi and Ohio river basins, the midwestern states, and the Canadian provinces bordering the Great Lakes. A small endemic area exists in New York and Canada along the St. Lawrence River. Acute blastomycosis is typically found only in North America, and the clinical presentation of blastomycosis in nonendemic areas is as a chronic disease.

Outside North America, blastomycosis occurs sporadically in Nigeria, Zimbabwe, Tunisia, Saudi Arabia, Israel, Lebanon, and India. The disease has been reported most frequently in Africa.

Early studies indicated that middle-aged men with outdoor occupations were at greatest risk. Reported outbreaks, however, do not suggest a predilection according to sex, age, race, occupation, or season. The specific niche in nature in which the organism resides remains uncertain; *B. dermatitidis* probably grows as microfoci in the warm, moist soil of wooded areas rich in organic debris. Inhalation of conidia following exposure to soil, whether related to work or recreation, appears to be the common factor associated with infection. Outbreaks of human disease may be preceded by the occurrence of disease in simultaneously exposed dogs. Zoonotic transmission is rare but has been reported in association with dog bites, pet kinkajou bites, cat scratches, and animal necropsies.

PATHOGENESIS

Alveolar macrophages and polymorphonuclear leukocytes are critical for phagocytosis and killing of the inhaled conidia of *B. dermatitidis*. The interaction of these mediators of the innate immune response with local host factors, such as lung surfactant, plays a significant role in inhibiting conversion to the pathogenic yeast form. This inhibition prevents the establishment of symptomatic disease and may account for the high frequency of asymptomatic infections in outbreaks. Once conversion to the thick-walled yeast form has occurred, phagocytosis and killing are much more difficult, and the development of clinically apparent infection is much more likely. Ultimately, the T lymphocyte response—specifically, a T_H1 response—is the primary factor in limiting infection and dissemination. Moreover, yeast-phase conversion results in the expression of yeast phase–specific proteins such as the 120-kDa glycoprotein adhesin BAD-1 and the *Blastomyces* yeast phase–specific protein 1 (BYS1). BAD-1 has been well characterized as a virulence factor and is the major epitope for humoral and

cellular immunity. The role of BYS1, putatively identified as a signal peptide, has not been determined.

APPROACH TO THE PATIENT

Blastomycosis

Blastomycosis most commonly presents as acute or chronic pneumonia that has been refractory to therapy with antibacterial drugs. Whether acute or chronic, blastomycosis may mimic many other disease processes. For example, acute pulmonary blastomycosis may present with signs and symptoms indistinguishable from those of bacterial pneumonia or influenza, and chronic pulmonary blastomycosis may mimic malignancy or tuberculosis. Skin lesions are often misdiagnosed as basal cell or squamous cell carcinoma, pyoderma gangrenosum, or keratoacanthoma. Laryngeal lesions are frequently mistaken for squamous cell carcinoma. Thus, the clinician must maintain a high index of suspicion and ensure that secretions or biopsy materials from patients who live in or have visited regions endemic for blastomycosis are subjected to careful histologic evaluation. This diligence is especially important in caring for individuals with pneumonia who fail to respond to treatment with antibacterial agents.

CLINICAL MANIFESTATIONS

Acute pulmonary infection is often diagnosed in association with point-source outbreaks. Typical symptoms include the abrupt onset of fever, chills, pleuritic chest pain, arthralgias, and myalgias. Cough is initially nonproductive but frequently becomes purulent as disease progresses. Chest radiographs usually reveal alveolar infiltrates with consolidation. Pleural effusions and hilar adenopathy are uncommon. Most patients diagnosed with pulmonary blastomycosis have chronic indolent pneumonia with signs and symptoms of fever, weight loss, productive cough, and hemoptysis. The most common radiologic findings are alveolar infiltrates with or without cavitation, mass lesions that mimic bronchogenic carcinoma, and fibronodular infiltrates. Hematogenous dissemination to the skin, bones, and genitourinary tract occurs most often in association with chronic pulmonary disease. Although blastomycosis is not considered an opportunistic infection, immunosuppression has been recognized as a risk factor for more serious pulmonary involvement, including respiratory failure (adult respiratory distress syndrome) associated with miliary disease or diffuse pulmonary infiltrates. In the late stages of AIDS, mortality rates of ≥50% have been documented. Most deaths occur within the first few days of therapy. Solid-organ transplant recipients with endemic fungal infections, including both histoplasmosis and blastomycosis, frequently have more severe pulmonary disease as well as dissemination. Blastomycosis has been associated with a mortality rate of 36% in these patients.

In Africa, pulmonary cases typically include bony involvement (frequently of the vertebrae), with subcutaneous abscesses of the chest wall or legs. All of the manifestations seen in African patients fall within the spectrum of blastomycosis observed in North America. The increased prevalence of chronic and disseminated bone disease in these patients may reflect a delay in diagnosis in regions where spinal disease is often treated empirically as tuberculosis.

Skin disease is the most common extrapulmonary manifestation of blastomycosis. Two types of skin lesions occur: verrucous (more common) and ulcerative. Osteomyelitis occurs in as many as one-fourth of *B. dermatitidis* infections. The vertebrae, pelvis, sacrum, skull, ribs, and long bones are most frequently involved. Patients with *B. dermatitidis* osteomyelitis often present with contiguous soft-tissue abscesses or chronic draining sinuses. In men, blastomycosis may involve the prostate and epididymis. Central nervous system (CNS) disease occurs in fewer than 5% of immunocompetent patients with blastomycosis. A recent multicenter review identified 22 patients with CNS disease, of whom 12 (54%) met at least one criterion for immunosuppression; although most cases of CNS blastomycosis are associated with infection at other sites, 22.7% of the reviewed cases had only CNS involvement. CNS disease, usually presenting as a brain abscess, has been reported in ~40% of cases in patients with AIDS. Less common forms of CNS disease are cranial or spinal epidural abscess and meningitis.

DIAGNOSIS

Definitive diagnosis of blastomycosis requires growth of the organism from sputum, bronchial washings, pus, or biopsy material. Specimens should be inoculated onto a fungal medium such as Sabouraud dextrose agar, with or without chloramphenicol. *B. dermatitidis* is generally visible in 5–10 days but may require incubation for up to 30 days if only a few organisms are present in the specimen. A presumptive diagnosis may be based on demonstration of the characteristic broad-based budding yeast by microscopic examination of wet preps of sputum in pneumonia or of skin-lesion scrapings.

An assay that detects *Blastomyces* antigen in urine and serum is commercially available and is reasonably sensitive and specific (MiraVista Diagnostics, Indianapolis, IN). Antigen detection appears to be more sensitive in urine than in serum. This antigen test may be useful for monitoring of patients during therapy or for early detection of relapse. Recently, a *Blastomyces* antibody enzyme immunoassay targeting the BAD-1 protein was developed (MiraVista Diagnostics). In combination with antigen testing, the sensitivity was >95% in blastomycosis patients, with 94% specificity in histoplasmosis patients. Chemiluminescent DNA probes (AccuProbe; GenProbe Inc., San Diego, CA) are commonly used to confirm identification of *B. dermatitidis* once growth has been detected in culture. Repetitive sequence–based PCR is available (DiversiLab System; bioMérieux, Durham, NC). Molecular identification techniques are currently used only to supplement traditional diagnostic methods.

TREATMENT

Blastomycosis

The Infectious Diseases Society of America has published guidelines for the treatment of blastomycosis. Selection of an appropriate therapeutic regimen must be based on the clinical form and severity of the disease, the immune status of the patient, and the toxicity of the antifungal agent **(Table 209-1)**. Although spontaneous cures of acute pulmonary infection are well documented, there are no criteria by which to distinguish patients whose disease will progress or resolve without treatment. Thus all patients with blastomycosis should be treated.

Itraconazole is the agent of choice for immunocompetent patients with mild to moderate pulmonary or non-CNS extrapulmonary disease. Therapy is continued for 6–12 months. Amphotericin B (AmB) is preferred for initial treatment of patients who are severely immunocompromised, who have life-threatening disease or CNS disease, or whose disease progresses during treatment with itraconazole. Although not rigorously studied, lipid formulations of AmB provide an alternative for patients who cannot tolerate AmB deoxycholate. Most patients with non-CNS disease whose clinical condition improves after an initial course of AmB (usually 2 weeks in duration) can be switched to itraconazole to complete 6–12 months of therapy. Fluconazole, because of its excellent penetration of the CNS, is useful in the treatment of patients with brain abscess or meningitis after an initial course of AmB.

Voriconazole has been used successfully to treat refractory blastomycosis, blastomycosis in immunosuppressed patients, and—given its good penetration of cerebrospinal fluid—CNS disease. Posaconazole has also been used for refractory pulmonary disease. The echinocandins have variable activity against *B. dermatitidis* and therefore are not used in the treatment of blastomycosis.

Posaconazole's role in the management of blastomycosis is unclear. Case reports have detailed success in the management of osseous blastomycosis; however, until recently, only a pharmacokinetically unfavorable suspension has been available, and the lack of a preferable formulation has likely limited the drug's utility.

TABLE 209-1 Treatment of Blastomycosis[a]

DISEASE	PRIMARY THERAPY	ALTERNATIVE THERAPY
Immunocompetent Patient/Life-Threatening Disease		
Pulmonary	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)
Disseminated		
CNS	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: at least 2 g)	Fluconazole, 800 mg/d (if patient is intolerant to full course of AmB)
Non-CNS	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)
Immunocompetent Patient/Non-Life-Threatening Disease		
Pulmonary or disseminated (non-CNS)	Itraconazole, 200–400 mg/d, *or* Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.5–0.7 mg/kg qd (in patients intolerant to itraconazole or whose disease progresses despite therapy)	Fluconazole, 400–800 mg/d, *or* Ketoconazole, 400–800 mg/d
Immunocompromised Patient[b]		
All infections	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (non-CNS disease, once clinically improved)

[a]Therapy is generally given for 6–12 months. For bone and joint disease, a 12-month course is usually necessary. [b]Suppressive therapy with itraconazole may be considered for patients whose immunocompromised state continues. Fluconazole (800 mg/d) may be useful for patients who have CNS disease or cannot tolerate itraconazole.

Abbreviations: AmB, amphotericin B; CNS, central nervous system.

Approval of delayed-release tablets and intravenous formulations may enhance the role of posazonazole in salvage therapy.

In a recent study including only three patients, isavuconazole, the most recent addition to the azole antifungal class, showed variable clinical efficacy (i.e., a 33% success rate) in the management of pulmonary and non-CNS disseminated blastomycosis. Its role in the management of blastomycosis is uncertain at this time, but its consideration may be warranted for salvage therapy in milder pulmonary disease.

PROGNOSIS

Cure rates are 90–95% among compliant immunocompetent patients given itraconazole for mild to moderate pulmonary and extrapulmonary disease without CNS involvement. Bone and joint disease usually requires 12 months of therapy. The fewer than 5% of infections that relapse after an initial course of itraconazole usually respond well to a second treatment course.

GLOBAL CONSIDERATIONS

Blastomyces remains a prominent cause of dimorphic fungal infections worldwide. In the United States, changes in mandatory reporting requirements have probably blurred estimates of the current incidence of blastomycosis. Diagnostic delays continue to contribute to increased use of health care resources and administration of unnecessary antibacterial courses and probably contribute to global resistance as well.

ACKNOWLEDGMENT

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210 Cryptococcosis

Arturo Casadevall

DEFINITION AND ETIOLOGY

Cryptococcus, a genus of yeast-like fungi, is the etiologic agent of cryptococcosis. Until recently, cryptococcal strains were separated into two species, *Cryptococcus neoformans* and *Cryptococcus gattii*, both of which can cause cryptococcosis in humans. The two varieties of *C. neoformans*—*grubii* and *neoformans*—correlate with serotypes A and D, respectively. *C. gattii*, although not divided into varieties, also is antigenically diverse, encompassing serotypes B and C. However, genome sequencing studies have now revealed tremendous diversity among isolates previously assigned to each species, suggesting that some may be reclassified as new species. Most clinical microbiology laboratories do not routinely distinguish between *C. neoformans* and *C. gattii* or among varieties, but rather identify and report all isolates simply as *C. neoformans*.

EPIDEMIOLOGY

Cryptococcosis was first described in the 1890s but remained relatively rare until the mid-twentieth century, when advances in diagnosis and increases in the number of immunosuppressed individuals markedly raised its reported prevalence. Although serologic evidence of cryptococcal *infection* is common among immunocompetent individuals, cryptococcal *disease* (cryptococcosis) is relatively rare in the absence of impaired immunity. Individuals at high risk for disease due to *C. neoformans* include patients with hematologic malignancies, recipients of solid organ transplants who require ongoing immunosuppressive therapy, persons whose medical conditions necessitate glucocorticoid therapy, and patients with advanced HIV infection and CD4+ T lymphocyte counts of <200/μL. In contrast, *C. gattii*–related disease is not associated with specific immune deficits and often occurs in immunocompetent individuals.

Cryptococcal infection is acquired from the environment. *C. neoformans* and *C. gattii* inhabit different ecologic niches. *C. neoformans* is frequently found in soils contaminated with avian excreta and can easily be recovered from shaded and humid soils contaminated with pigeon droppings. In contrast, *C. gattii* is not found in bird feces. Instead, it inhabits a variety of arboreal species, including several types of eucalyptus tree. *C. neoformans* strains are found throughout the world; however, var. *grubii* (serotype A) strains are far more common than var. *neoformans* (serotype D) strains among both clinical and environmental isolates. The geographic distribution of *C. gattii* was thought to be largely limited to tropical regions until an outbreak of cryptococcosis caused by a new serotype B strain began in Vancouver in 1999. This outbreak has extended into the United States, and *C. gattii* infections are being encountered increasingly in several states in the Pacific Northwest.

The global burden of cryptococcosis was recently estimated at ~1 million cases, with >600,000 deaths annually. Thus cryptococci are important human pathogens. Since the onset of the HIV pandemic in the early 1980s, the overwhelming majority of cryptococcosis cases

have occurred in patients with AIDS (Chap. 197). To comprehend the impact of HIV infection on the epidemiology of cryptococcosis, it is instructive to note that in the early 1990s there were >1000 cases of cryptococcal meningitis each year in New York City—a figure far exceeding that for all cases of bacterial meningitis. With the advent of effective antiretroviral therapy, the incidence of AIDS-related cryptococcosis has been sharply reduced among treated individuals. Therefore, most cases of cryptococcosis now occur in resource-limited regions of the world. The disease remains distressingly common in regions where antiretroviral therapy is not readily available (e.g., parts of Africa and Asia); in these regions, up to one-third of patients with AIDS have cryptococcosis. Among HIV-infected persons, those with a decreased percentage of memory B cells expressing IgM may be at greater risk for cryptococcosis.

PATHOGENESIS

Cryptococcal infection is acquired by inhalation of aerosolized infectious particles. The exact nature of these particles is not known; the two leading candidate forms are small desiccated yeast cells and basidiospores. Little is known about the pathogenesis of initial infection. Serologic studies have shown that cryptococcal infection is acquired in childhood, but it is not known whether the initial infection is symptomatic. Given that cryptococcal infection is common while disease is rare, the consensus is that pulmonary defense mechanisms in immunologically intact individuals are highly effective at containing this fungus. It is not clear whether initial infection leads to a state of immunity or whether most individuals are subject throughout life to frequent and recurrent infections that resolve without clinical disease. However, evidence indicates that some human cryptococcal infections lead to a state of latency in which viable organisms are harbored for prolonged periods, possibly in granulomas. Thus the inhalation of cryptococcal cells and/or spores can be followed by either clearance or establishment of the latent state. The consequences of prolonged harboring of cryptococcal cells in the lung are not known, but evidence from animal studies indicates that the organisms' prolonged presence could alter the immunologic milieu in the lung and predispose to allergic airway disease.

Cryptococcosis usually presents clinically as chronic meningoencephalitis. The mechanisms by which the fungus undergoes extrapulmonary dissemination and enters the central nervous system (CNS) remain poorly understood. The mechanism by which cryptococcal cells cross the blood–brain barrier is a subject of intensive study. Current evidence suggests that both direct fungal-cell migration across the endothelium and fungal-cell carriage inside macrophages as "Trojan horse" invaders can occur. *Cryptococcus* species have well-defined virulence factors that include the expression of the polysaccharide capsule, the ability to make melanin, and the elaboration of enzymes (e.g., phospholipase and urease) that enhance the survival of fungal cells in tissue. Among these virulence factors, the capsule and melanin production have been most extensively studied. The cryptococcal capsule is antiphagocytic, and the capsular polysaccharide has been associated with numerous deleterious effects on host immune function. Cryptococcal infections can elicit little or no tissue inflammatory response. The immune dysfunction seen in cryptococcosis has been attributed to the release of copious amounts of capsular polysaccharide into tissues, where it probably interferes with local immune responses (Fig. 210-1). In clinical practice, the capsular polysaccharide is the antigen that is measured as a diagnostic marker of cryptococcal infection.

APPROACH TO THE PATIENT

Cryptococcosis

Cryptococcosis should be included in the differential diagnosis when any patient presents with findings suggestive of chronic meningitis. Concern about cryptococcosis is heightened by a history of headache and neurologic symptoms in a patient with an underlying immunosuppressive disorder or state that is associated with an increased incidence of cryptococcosis, such as advanced HIV infection or solid organ transplantation.

FIGURE 210-1 Cryptococcal antigen in human brain tissue, as revealed by immunohistochemical staining. Brown areas show polysaccharide deposits in the midbrain of a patient who died of cryptococcal meningitis. *(Reprinted with permission from SC Lee et al: Am J Pathol 148; 1267, 1996.)*

CLINICAL MANIFESTATIONS

The clinical manifestations of cryptococcosis reflect the site of fungal infection. The spectrum of disease caused by *Cryptococcus* species consists predominantly of meningoencephalitis and pneumonia, but skin and soft tissue infections also occur; in fact, cryptococcosis can affect any tissue or organ. CNS involvement usually presents as signs and symptoms of chronic meningitis, such as headache, fever, lethargy, sensory deficits, memory deficits, cranial nerve paresis, vision deficits, and meningismus. Cryptococcal meningitis differs from bacterial meningitis in that many *Cryptococcus*-infected patients present with symptoms of several weeks' duration. In addition, classic characteristics of meningeal irritation, such as meningismus, may be absent in cryptococcal meningitis. Indolent cases can present as subacute dementia. Meningeal cryptococcosis can lead to sudden catastrophic vision loss.

Pulmonary cryptococcosis usually presents as cough, increased sputum production, and chest pain. Patients infected with *C. gattii* can present with granulomatous pulmonary masses known as *cryptococcomas*. Fever develops in a minority of cases. Like CNS disease, pulmonary cryptococcosis can follow an indolent course, and the majority of cases probably do not come to clinical attention. In fact, many cases are discovered incidentally during the workup of an abnormal chest radiograph obtained for other diagnostic purposes. Pulmonary cryptococcosis can be associated with antecedent diseases such as malignancy, diabetes, and tuberculosis.

Skin lesions are common in patients with disseminated cryptococcosis and can be highly variable, including papules, plaques, purpura, vesicles, tumor-like lesions, and rashes. The spectrum of cryptococcosis in HIV-infected patients is so varied and has changed so much since the advent of antiretroviral therapy that a distinction between HIV-related and HIV-unrelated cryptococcosis is no longer pertinent. In patients with AIDS and solid organ transplant recipients, the lesions of cutaneous cryptococcosis often resemble those of molluscum contagiosum (Fig. 210-2; Chap. 191).

DIAGNOSIS

A diagnosis of cryptococcosis requires the demonstration of yeast cells in normally sterile tissues. Visualization of the capsule of fungal cells in cerebrospinal fluid (CSF) mixed with India ink is a useful rapid diagnostic technique. Cryptococcal cells in India ink have a distinctive appearance because their capsules exclude ink particles. However, the CSF India ink examination may yield negative results in patients with a low fungal burden. This examination should be performed by a trained individual, since leukocytes and fat globules can sometimes be mistaken for fungal cells. Cultures of CSF and blood that are positive for cryptococcal cells are diagnostic for cryptococcosis. In cryptococcal meningitis, CSF examination usually reveals evidence of

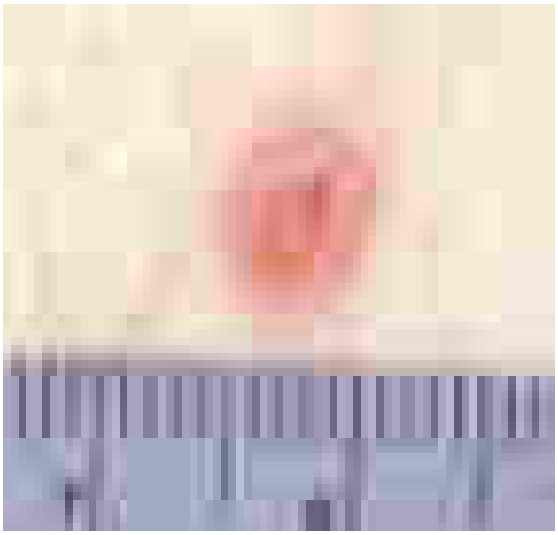

FIGURE 210-2 Disseminated fungal infection. A liver transplant recipient developed six cutaneous lesions similar to the one shown. Biopsy and serum antigen testing demonstrated *Cryptococcus*. Important features of the lesion include a benign-appearing fleshy papule with central umbilication resembling molluscum contagiosum. *(Photo courtesy of Dr. Lindsey Baden; with permission.)*

chronic meningitis with mononuclear cell pleocytosis and increased protein levels. A particularly useful test is cryptococcal antigen (CRAg) detection in CSF and blood. The assay is based on serologic detection of cryptococcal polysaccharide and is both sensitive and specific. A positive CRAg test provides strong presumptive evidence for cryptococcosis; however, because the result is often negative in pulmonary cryptococcosis, the test is less useful in the diagnosis of pulmonary disease and is of only limited usefulness in monitoring the response to therapy.

In areas of Africa where there is a high prevalence of HIV infection, routine screening of blood for CRAg in HIV-infected patients with low CD4+ T lymphocyte counts may identify individuals at high risk of cryptococcal disease who are candidates for antifungal therapy. CRAg screening has shown that a significant proportion of HIV-infected patients hospitalized with pneumonia in Thailand harbor cryptococcal infection. Inexpensive point-of-care CRAg tests are under development and could be of great diagnostic benefit in resource-limited regions.

TREATMENT

Cryptococcosis

Both the site of infection and the immune status of the host must be considered in the selection of therapy for cryptococcosis. The disease has two general patterns of manifestation: (1) pulmonary cryptococcosis, with no evidence of extrapulmonary dissemination; and (2) extrapulmonary (systemic) cryptococcosis, with or without meningoencephalitis. Pulmonary cryptococcosis in an immunocompetent host sometimes resolves without therapy. However, given the propensity of *Cryptococcus* species to disseminate from the lung, the inability to gauge the host's immune status precisely, and the availability of low-toxicity therapy in the form of fluconazole, the current recommendation is for pulmonary cryptococcosis in an immunocompetent individual to be treated with fluconazole (200–400 mg/d for 3–6 months). Extrapulmonary cryptococcosis without CNS involvement in an immunocompetent host can be treated with the same regimen, although amphotericin B (AmB; 0.5–1 mg/kg daily for 4–6 weeks) may be required for more severe cases. In general, extrapulmonary cryptococcosis without CNS involvement requires less intensive therapy, with the caveat that morbidity and death in cryptococcosis are associated with meningeal involvement. Thus the decision to categorize cryptococcosis as "extrapulmonary without CNS involvement" should be made only after careful evaluation of the CSF reveals no evidence of cryptococcal infection. For CNS involvement in a host without AIDS or obvious immune impairment, most authorities recommend initial therapy with AmB (0.5–1 mg/kg daily) during an induction phase, which is followed by prolonged therapy with fluconazole (400 mg/d) during a consolidation phase. For cryptococcal meningoencephalitis without a concomitant immunosuppressive condition, the recommended regimen is AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 6–10 weeks. Alternatively, patients can be treated with AmB (0.5–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks and then with fluconazole (400 mg/d) for at least 10 weeks. Patients with immunosuppression are treated with the same initial regimens except that consolidation therapy with fluconazole is given for a prolonged period to prevent relapse.

Cryptococcosis in patients with HIV infection always requires aggressive therapy and is considered incurable unless immune function improves. Consequently, therapy for cryptococcosis in the setting of AIDS has two phases: induction therapy (intended to reduce the fungal burden and alleviate symptoms) and lifelong maintenance therapy (to prevent a symptomatic clinical relapse). Pulmonary and extrapulmonary cryptococcosis without evidence of CNS involvement can be treated with fluconazole (200–400 mg/d). In patients who have more extensive disease, flucytosine (100 mg/kg per day) may be added to the fluconazole regimen for 10 weeks, with lifelong fluconazole maintenance therapy thereafter. For HIV-infected patients with evidence of CNS involvement, most authorities recommend induction therapy with AmB. An acceptable regimen is AmB (0.7–1 mg/kg) plus flucytosine (100 mg/kg) daily for 2 weeks followed by fluconazole (400 mg/d) for at least 10 weeks and then by lifelong maintenance therapy with fluconazole (200 mg/d). Fluconazole (400–800 mg/d) plus flucytosine (100 mg/kg per day) for 6–10 weeks followed by fluconazole (200 mg/d) as maintenance therapy is an alternative. Newer triazoles like voriconazole and posaconazole are highly active against cryptococcal strains and appear to be clinically effective, but clinical experience with these agents in the treatment of cryptococcosis is limited. Lipid formulations of AmB can be substituted for AmB deoxycholate in patients with renal impairment. Neither caspofungin nor micafungin is effective against *Cryptococcus* species; consequently, neither drug has a role in the treatment of cryptococcosis. Cryptococcal meningoencephalitis is often associated with increased intracranial pressure, which is believed to be responsible for damage to the brain and cranial nerves. Appropriate management of CNS cryptococcosis requires careful attention to the management of intracranial pressure, including the reduction of pressure by repeated therapeutic lumbar puncture and the placement of shunts. Studies suggest that the addition of a short course of interferon γ to antifungal therapy in patients with HIV infection increases clearance of cryptococci from the CSF.

In HIV-infected patients with previously treated cryptococcosis who are receiving fluconazole maintenance therapy, it may be possible to discontinue antifungal drug treatment if antiretroviral therapy results in immunologic improvement.

PROGNOSIS AND COMPLICATIONS

Even with antifungal therapy, cryptococcosis is associated with high rates of morbidity and death. For the majority of patients with cryptococcosis, the most important prognostic factors are the extent and the duration of the underlying immunologic deficits that predisposed them to develop the disease. Therefore, cryptococcosis is often curable with antifungal therapy in individuals with no apparent immunologic dysfunction, but, in patients with severe immunosuppression (e.g., those with AIDS), the best that can be hoped for is that antifungal therapy will induce remission, which can then be maintained with lifelong suppressive therapy. Before the advent of antiretroviral therapy, the median overall survival period for AIDS patients with cryptococcosis was <1 year. Cryptococcosis in patients with underlying neoplastic disease has a particularly poor prognosis. For CNS cryptococcosis, poor prognostic markers are a CSF assay positive for yeast cells on

initial India ink examination (evidence of a heavy fungal burden), high CSF pressure, low CSF glucose levels, low CSF pleocytosis (<2/μL), recovery of yeast cells from extraneural sites, absence of antibody to capsular polysaccharide, a CSF or serum cryptococcal antigen level of ≥1:32, and concomitant glucocorticoid therapy or hematologic malignancy. A response to treatment does not guarantee cure since relapse of cryptococcosis is common even among patients with relatively intact immune systems. Complications of CNS cryptococcosis include cranial nerve deficits, vision loss, and cognitive impairment.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

The frequent chronicity of cryptococcal infections and their common occurrence in settings of changing immunity can result in new clinical syndromes, such as the immune reconstitution inflammatory syndrome (IRIS). IRIS occurs when immunity rebounds in the setting of treated cryptococcosis (or an undiagnosed asymptomatic infection) and the immune response to cryptococcal antigens in tissue triggers an inflammatory response that can be difficult to distinguish from a relapsing infection. IRIS can occur when patients with AIDS and treated cryptococcosis are given antiretroviral therapy that results in improved immunity. Apart from the difficulties in distinguishing IRIS from cryptococcal relapse, the management of this syndrome is complex because it is caused by the desirable outcome of improving immunity, which is important in controlling cryptococcal infection and preventing relapses. The approach to the patient with IRIS must attempt to balance resurgent immunity against immune-mediated damage. Currently, management of IRIS is individualized and can involve the use of glucocorticoids to reduce inflammation.

PREVENTION

No vaccine is available for cryptococcosis. In patients at high risk (e.g., those with advanced HIV infection and CD4+ T lymphocyte counts of <200/μL), primary prophylaxis with fluconazole (200 mg/d) is effective in reducing the prevalence of disease. Since antiretroviral therapy raises the CD4+ T lymphocyte count, it constitutes an immunologic form of prophylaxis.

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211 Candidiasis

John E. Edwards, Jr.

The genus *Candida* encompasses >150 species, only a few of which cause disease in humans. With rare exceptions (although the exceptions are increasing in number), the human pathogens are *C. albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. lusitaniae*, *C. dubliniensis*, *C. glabrata*, and *C. auris*. Ubiquitous in nature, they inhabit the gastrointestinal tract (including the mouth and oropharynx), the female genital tract, and the skin. Although cases of candidiasis have been described since antiquity in debilitated patients, the advent of *Candida* species as common human pathogens dates to the introduction of modern therapeutic approaches that suppress normal host-defense mechanisms. Of these relatively recent advances, the most important is the use of antibacterial agents that alter the normal human microbiota and allow nonbacterial species to become more prevalent in the commensal flora. With the introduction of antifungal agents, the causes of *Candida* infections shifted from an almost complete dominance of *C. albicans* to the common involvement of *C. glabrata* and the other species listed above. The non-*albicans* species now account for approximately half of all cases of candidemia and hematogenously disseminated candidiasis. Recognition of this change is clinically important, since the various species differ in susceptibility to the newer antifungal agents.

Candida is a small, thin-walled, ovoid yeast that measures 4–6 μm in diameter and reproduces by budding. Organisms of this genus occur in three forms in tissue: blastospores, pseudohyphae, and hyphae. *Candida* grows readily on simple medium; lysis centrifugation enhances its recovery from blood. Species are identified by biochemical testing (currently with automated devices) or on special agar (e.g., CHROMagar).

EPIDEMIOLOGY

Candida are present in humans as commensals, in animals, in foods, and on inanimate objects. In developed countries, where contemporary medical therapeutics are commonly used, *Candida* species are now among the most common nosocomial pathogens. In the United States, these species are the fourth most common isolates from the blood of hospitalized patients. In a recent point-prevalence study, *Candida* species were the most common organisms infecting the bloodstream of hospitalized patients. In regions where advanced medical care is rarely available, mucocutaneous *Candida* infections, such as thrush, are more common than deep-organ infections, which rarely occur. However, the incidence of deep-organ candidiasis increases steadily as advances in health care—such as therapy with broad-spectrum antibiotics, more aggressive treatment of cancer, and the use of immunosuppression for sustaining organ transplants—are implemented. In aggregate, the global incidence of infections due to *Candida* species has risen steadily over the past few decades. Of great recent concern has been the global emergence of *C. auris*; certain strains of this organism are resistant to all classes of antifungal agents, and mortality rates from infection have been very high.

PATHOGENESIS

In the most serious form of *Candida* infection, the organisms disseminate hematogenously and form microabscesses and small macroabscesses in major organs. Although the exact mechanism is not known, *Candida* probably enters the bloodstream from mucosal surfaces after growing to large numbers as a consequence of bacterial suppression by antibacterial drugs; alternatively, in some instances, the organism may enter from the skin. A change from the blastospore stage to the pseudohyphal and hyphal stages is generally considered integral to *Candida*'s penetration into tissue. However, *C. glabrata* can cause extensive infection even though it does not transform into pseudohyphae or hyphae. Adherence to both epithelial and endothelial cells is thought to be the first step in invasion and infection; several adhesins have been identified as well as a mucosal toxin, candidalysin. Biofilm formation also is considered important in pathogenesis. Numerous reviews of cases of hematogenously disseminated candidiasis have identified the predisposing factors or conditions associated with disseminated disease **(Table 211-1)**. Women who receive antibacterial agents may develop vaginal candidiasis.

Innate immunity is the most important defense mechanism against hematogenously disseminated candidiasis, and the neutrophil is the most important component of this defense. Macrophages also play an important defensive role. STAT1, Dectin-1, CARD9, and T_H1 and T_H17 lymphocytes contribute significantly to innate defense (see "Clinical Manifestations," below). Although many immunocompetent individuals have antibodies to *Candida*, the role of these antibodies in defense against the organism is not clear. Multiple genetic polymorphisms that predispose to disseminated candidiasis will most likely be identified in future studies.

TABLE 211-1 Well-Recognized Factors and Conditions Predisposing to Hematogenously Disseminated Candidiasis

Antibacterial agents	Abdominal and thoracic surgery
Indwelling intravenous catheters	Cytotoxic chemotherapy
Hyperalimentation fluids	Immunosuppressive agents for organ transplantation
Indwelling urinary catheters	Respirators
Parenteral glucocorticoids	Neutropenia
Severe burns	Low birth weight (neonates)
HIV-associated low CD4+ T-cell counts	Diabetes

CLINICAL MANIFESTATIONS

Mucocutaneous Candidiasis *Thrush* is characterized by white, adherent, painless, discrete or confluent patches in the mouth, on the tongue, or in the esophagus, occasionally with fissuring at the corners of the mouth. This form of disease caused by *Candida* can also occur at points of contact with dentures. Organisms are identifiable in gram-stained scrapings from lesions. The occurrence of thrush in a young, otherwise healthy-appearing person should prompt an investigation for underlying HIV infection. More commonly, thrush is seen as a nonspecific manifestation of severe debilitating illness. Vulvovaginal candidiasis is accompanied by pruritus, pain, and vaginal discharge, which is usually thin but may contain whitish "curds" in severe cases. A subset of patients with recurrent vulvovaginitis have a deficiency in the surface expression of Dectin-1, a major recognition factor for β-glucan on *Candida*. This deficiency leads to suboptimal functioning of the CARD9 pathway, which ultimately increases the propensity for recurrent vaginal infections.

Other *Candida* skin infections include *paronychia*, a painful swelling at the nail–skin interface; *onychomycosis*, a fungal nail infection rarely caused by this genus; *intertrigo*, an erythematous irritation with redness and pustules in the skin folds; *balanitis*, an erythematous-pustular infection of the glans penis; *erosio interdigitalis blastomycetica*, an infection between the digits of the hands or toes; *folliculitis*, with pustules developing most frequently in the area of the beard; *perianal candidiasis*, a pruritic, erythematous, pustular infection surrounding the anus; and *diaper rash*, a common erythematous, pustular perineal infection in infants. *Generalized disseminated cutaneous candidiasis*, another form of infection that occurs primarily in infants, is characterized by widespread eruptions over the trunk, thorax, and extremities. The diagnostic macronodular lesions of hematogenously disseminated candidiasis (Fig. 211-1) indicate a high probability of dissemination to multiple organs as well as the skin. While the lesions are seen predominantly in immunocompromised patients treated with cytotoxic drugs, they may also develop in patients without neutropenia.

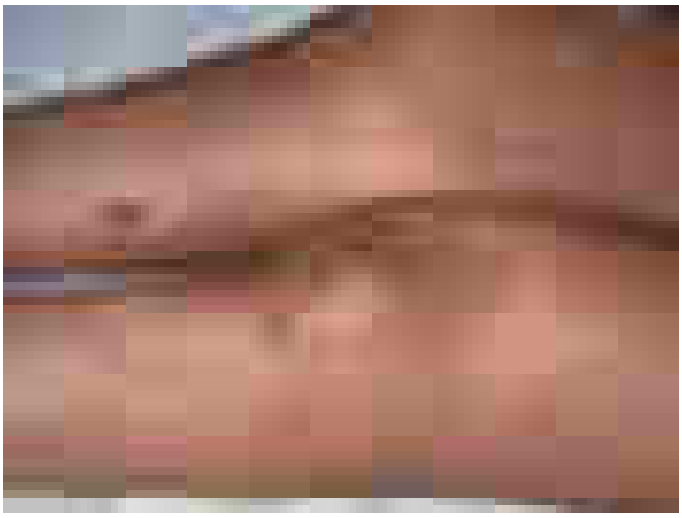

FIGURE 211-1 Macronodular skin lesions associated with hematogenously disseminated candidiasis. *Candida* organisms are usually but not always visible on histopathologic examination. The fungi grow when a portion of the biopsied specimen is cultured. Therefore, for optimal identification, both histopathology and culture should be performed. *(Image courtesy of Dr. Noah Craft and the Victor Newcomer collection at UCLA, archived by Logical Images, Inc.; with permission.)*

Chronic mucocutaneous candidiasis is a heterogeneous infection of the hair, nails, skin, and mucous membranes that persists despite intermittent therapy. The onset of disease usually comes in infancy or within the first two decades of life, but in rare cases comes in later life. The condition may be mild and limited to a specific area of the skin or nails, or it may take a severely disfiguring form (*Candida* granuloma) characterized by exophytic outgrowths on the skin. Chronic mucocutaneous candidiasis is usually associated with specific immunologic dysfunction; most frequently reported is a failure of T lymphocytes to proliferate or to excrete cytokines in response to stimulation by *Candida* antigens in vitro. A subset of the affected patients have mutations in the STAT1 gene resulting in an insufficiency of interferon γ, interleukin 17, and interleukin 22.

Approximately half of patients with chronic mucocutaneous candidiasis have associated endocrine abnormalities that together are designated the *a*utoimmune *p*oly*e*ndocrinopathy–*c*andidiasis–*e*ctodermal *d*ystrophy (APECED) syndrome. This syndrome is due to mutations in the autoimmune regulator (*AIRE*) gene and is most prevalent among Finns, Iranian Jews, Sardinians, northern Italians, and Swedes. Conditions that usually follow the onset of the disease include hypoparathyroidism, adrenal insufficiency, autoimmune thyroiditis, Graves' disease, chronic active hepatitis, alopecia, juvenile-onset pernicious anemia, malabsorption, and primary hypogonadism. In addition, dental enamel dysplasia, vitiligo, pitted nail dystrophy, and calcification of the tympanic membranes may occur. Patients with chronic mucocutaneous candidiasis rarely develop hematogenously disseminated candidiasis, probably because their neutrophil function remains intact.

Deeply Invasive Candidiasis Deeply invasive *Candida* infections may or may not be due to hematogenous seeding. Deep esophageal infection may result from penetration by organisms from superficial esophageal erosions; joint or deep-wound infection from contiguous spread of organisms from the skin; kidney infection from catheter-initiated spread of organisms through the urinary tract; infection of intraabdominal organs and the peritoneum from perforation of the gastrointestinal tract; and gallbladder infection from retrograde migration of organisms from the gastrointestinal tract into the biliary drainage system.

However, far more commonly, deeply invasive candidiasis results from hematogenous seeding of various organs as a complication of candidemia. Once the organism gains access to the intravascular compartment (either from the gastrointestinal tract or, less often, from the skin through the site of an indwelling intravascular catheter), it may spread hematogenously to a variety of deep organs. The brain, chorioretina (Fig. 211-2), heart, and kidneys are most commonly infected and the liver and spleen less commonly so (most often in neutropenic patients). In fact, nearly any organ can become involved, including the endocrine glands, pancreas, heart valves (native or prosthetic), skeletal muscle, joints (native or prosthetic), bones, and meninges. *Candida* organisms can also spread hematogenously to the skin and cause classic macronodular lesions (Fig. 211-1). Frequently, painful muscular involvement is evident beneath the area of affected skin. Chorioretinal involvement and skin involvement are highly significant, since both findings are associated with a very high probability of abscess formation in multiple deep organs as a result of generalized hematogenous seeding. Ocular involvement (Fig. 211-2) may require specific treatment (e.g., partial vitrectomy or intraocular injection of antifungal agents) to prevent permanent blindness. An ocular examination is indicated for all patients with candidemia, whether or not they have ocular manifestations.

DIAGNOSIS

The diagnosis of *Candida* infection is established by visualization of pseudohyphae or hyphae on wet mount (saline and 10% KOH), tissue Gram's stain, periodic acid–Schiff stain, or methenamine silver stain in the presence of inflammation. Absence of organisms on hematoxylin-eosin staining does not reliably exclude *Candida* infection. The most challenging

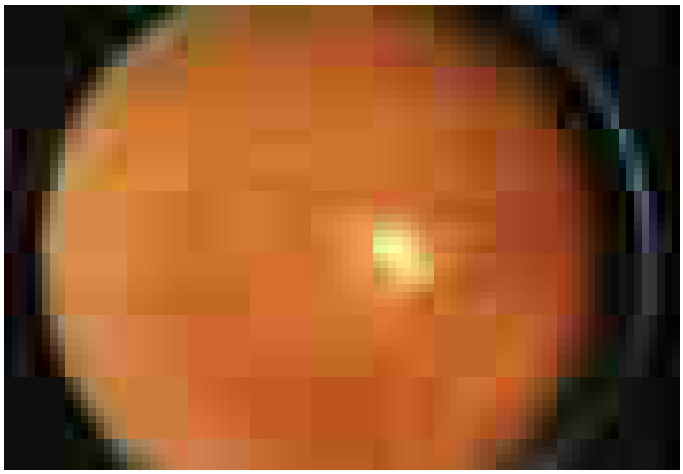

FIGURE 211-2 Hematogenous *Candida* endophthalmitis. A classic off-white lesion projecting from the chorioretina into the vitreous causes the surrounding haze. The lesion is composed primarily of inflammatory cells rather than organisms. Lesions of this type may progress to cause extensive vitreal inflammation and eventual loss of the eye. Partial vitrectomy, combined with IV and possibly intravitreal antifungal therapy, may be helpful in controlling the lesions. *(Image courtesy of Dr. Gary Holland; with permission.)*

aspect of diagnosis is determining which patients with *Candida* isolates have hematogenously disseminated candidiasis. For instance, recovery of *Candida* from sputum, urine, or peritoneal catheters may indicate mere colonization rather than deep-seated infection, and *Candida* isolation from the blood of patients with indwelling intravascular catheters may reflect inconsequential seeding of the blood from or growth of the organisms on the catheter. Despite extensive research into both antigen and antibody detection systems, there is currently no widely available and validated diagnostic test to distinguish patients with inconsequential seeding of the blood from those whose positive blood cultures represent hematogenous dissemination to multiple organs. Many studies are under way to establish the utility of the β-glucan test; at present, its greatest utility is its negative predictive value (~90%). Meanwhile, the presence of ocular or macronodular skin lesions is highly suggestive of widespread infection of multiple deep organs. Despite extensive tests for hematogenous dissemination, such as polymerase chain reaction and T2 technology, no test is fully validated or widely available at present. Matrix-assisted laser desorption–ionization–time-of-flight mass spectometry (MALDI-TOF MS) will likely be used extensively for detection and speciation in the future.

TREATMENT

Candida Infections

MUCOCUTANEOUS *CANDIDA* INFECTION

The treatment of mucocutaneous candidiasis is summarized in **Table 211-2**.

TABLE 211-2 Treatment of Mucocutaneous Candidal Infections

DISEASE	PREFERRED TREATMENT	ALTERNATIVES
Cutaneous	Topical azole	Topical nystatin
Vulvovaginal	Oral fluconazole (150 mg) or azole cream or suppository	Nystatin suppository
Oral (thrush)	Clotrimazole troches	Nystatin, fluconazole
Esophageal	Fluconazole tablets (100–200 mg/d) or itraconazole solution (200 mg/d)	Caspofungin, micafungin, or amphotericin B

CANDIDEMIA AND SUSPECTED HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

All patients with candidemia are treated with a systemic antifungal agent. A certain percentage of patients, including many of those who have candidemia associated with an indwelling intravascular catheter, probably have "benign" candidemia rather than deep-organ seeding. However, because there is no reliable way to distinguish benign candidemia from deep-organ infection, and because antifungal drugs less toxic than amphotericin B are available, antifungal treatment for candidemia—with or without clinical evidence of deep-organ involvement—has become the standard of practice. In addition, if an indwelling intravascular catheter is present, it is best to remove or replace the device whenever feasible.

The drugs used for the treatment of candidemia and suspected disseminated candidiasis are listed in **Table 211-3**. Various lipid formulations of amphotericin B, three echinocandins, and the azoles fluconazole and voriconazole are used; no agent within a given class has been clearly identified as superior to the others. Most institutions choose an agent from each class on the basis of their own specific microbial epidemiology, strategies to minimize toxicities, and cost considerations. There is a trend to treat with an echinocandin until sensitivities or speciation is determined. In stable patients, many centers then switch to fluconazole if a sensitive strain is identified and there is no evidence of hematogenous disemination. For hemodynamically unstable or neutropenic patients, initial treatment with broader-spectrum agents is desirable; these drugs include polyenes, echinocandins, or later-generation azoles such as voriconazole. Once the clinical response has been assessed and the pathogen specifically identified, the regimen can be altered accordingly. At present, the vast majority of *C. albicans* isolates are sensitive to fluconazole. Isolates of *C. glabrata* and *C. krusei* are less sensitive to fluconazole and more sensitive to polyenes and echinocandins. *C. parapsilosis* is less sensitive to echinocandins in vitro; however, this lesser sensitivity is considered insignificant. Posaconazole has been approved for prophylaxis, including that against *Candida*, in neutropenic patients. Itraconazole is rarely used for *Candida*, and isavuconazole has not been approved for this indication to date.

Some generalizations exist regarding the management of specific *Candida* infections. Recovery of *Candida* from sputum is almost never indicative of underlying pulmonary candidiasis and does not by itself warrant antifungal treatment. Similarly, *Candida* in the urine of a patient with an indwelling bladder catheter may represent colonization only rather than bladder or kidney infection; however, the threshold for systemic treatment is lower in severely ill patients in this category since it is impossible to distinguish colonization from lower or upper urinary tract infection. If the isolate is *C. albicans*, most clinicians use oral fluconazole rather than a bladder washout with amphotericin B, which was more commonly used in the past. Caspofungin has been used with success; although echinocandins are poorly excreted into the urine, they may be an option, especially for non-*albicans* isolates. The doses and duration are the same as for disseminated candidiasis. The significance of the recovery of *Candida* from abdominal drains in postoperative patients is unclear, but again the threshold for treatment is generally low because most of the affected patients have been subjected to factors predisposing to disseminated candidiasis. In addition, there has been a considerable increase in the recognition and diagnosis of intraabdominal candidiasis.

Removal of the infected valve and long-term antifungal administration constitute appropriate treatment for *Candida* endocarditis. Although definitive studies are not available, patients usually are treated for weeks with a systemic antifungal agent (Table 211-3) and then given chronic suppressive therapy for months or years (sometimes indefinitely) with an oral azole (usually fluconazole at 400–800 mg/d).

Hematogenous *Candida* endophthalmitis is a special problem requiring ophthalmologic consultation. When lesions are expanding or are threatening the macula, an IV polyene combined with flucytosine (25 mg/kg four times daily) has been the regimen of choice, although comparative studies with other regimens have not yet been reported. As more data on the azoles (e.g., voriconazole) and the echinocandins become available, new strategies involving these agents are developing. Of paramount importance is the decision to

TABLE 211-3 Agents for the Treatment of Disseminated Candidiasis

AGENT	ROUTE OF ADMINISTRATION	DOSE[a]	COMMENT
Amphotericin B deoxycholate	IV only	0.5–1.0 mg/kg daily	Being replaced by lipid formulations
Amphotericin B lipid formulations			Not approved as primary therapy by the U.S. Food and Drug Administration, but used commonly because less toxic than amphotericin B deoxycholate
Liposomal (AmBiSome, Abelcet)	IV only	3.0–5.0 mg/kg daily	
Lipid complex (ABLC)	IV only	3.0–5.0 mg/kg daily	
Colloidal dispersion (ABCD)	IV only	3.0–5.0 mg/kg daily	Associated with frequent infusion reactions
Azoles[b]			
Posaconazole	IV and oral	300 mg/d (IV) 200 mg tid (oral)	Approved for prophylaxis
Fluconazole	IV and oral	400 mg/d	Most commonly used
Voriconazole	IV and oral	400 mg/d	Multiple drug interactions Approved for candidemia in nonneutropenic patients
Echinocandins			Broad spectrum against *Candida* species; approved for disseminated candidiasis
Caspofungin	IV only	50 mg/d	
Anidulafungin	IV only	100 mg/d	
Micafungin	IV only	100 mg/d	

[a]For loading doses and adjustments in renal failure, see Pappas PG et al: Clinical practice guidelines for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62:e1, 2016. The recommended duration of therapy is 2 weeks beyond the last positive blood culture and the resolution of signs and symptoms of infection. [b]Although ketoconazole is approved for the treatment of disseminated candidiasis, it has been replaced by the newer agents listed in this table. Posaconazole has been approved for prophylaxis in neutropenic patients and for oropharyngeal candidiasis.

perform a partial vitrectomy. This procedure debulks the infection and can preserve sight, which may otherwise be lost due to vitreal scarring. All patients with candidemia should undergo ophthalmologic examination because of the relatively high frequency of this ocular complication. Not only can this examination detect a developing eye lesion early in its course; in addition, identification of a lesion signifies a probability of ~90% of deep-organ abscesses and may prompt prolongation of therapy for candidemia beyond the recommended 2 weeks after the last positive blood culture. Although the basis for the consensus is a very small data set, the recommended treatment for *Candida* meningitis is a polyene (Table 211-3) plus flucytosine (25 mg/kg four times daily). Successful treatment of *Candida*-infected prosthetic material (e.g., an artificial joint) nearly always requires removal of the infected material followed by long-term administration of an antifungal agent selected on the basis of the isolate's sensitivity and the logistics of administration.

PROPHYLAXIS

The use of antifungal agents to prevent *Candida* infections has been controversial, but some general principles have emerged. Most centers administer prophylactic fluconazole (400 mg/d) to recipients of allogeneic stem cell transplants. High-risk liver transplant recipients also are given fluconazole prophylaxis in most centers. The use of prophylaxis for neutropenic patients has varied considerably from center to center; many centers that elect to give prophylaxis to this population use either fluconazole (200–400 mg/d) or a lipid formulation of amphotericin B (AmBiSome, 1–2 mg/d). Caspofungin (50 mg/d) also has been recommended. Some centers have used itraconazole suspension (200 mg/d). Posaconazole (200 mg three times daily) has been approved by the U.S. Food and Drug Administration for prophylaxis in neutropenic patients; it is gaining in popularity and may replace fluconazole.

Prophylaxis is sometimes given to surgical patients at very high risk. The widespread use of prophylaxis for nearly all patients in general surgical or medical intensive care units is not—and should not be—a common practice for three reasons: (1) the incidence of disseminated candidiasis is relatively low, (2) the cost–benefit ratio is suboptimal, and (3) increased resistance with widespread prophylaxis is a valid concern.

Prophylaxis for oropharyngeal or esophageal candidiasis in HIV-infected patients is not recommended unless there are frequent recurrences.

FURTHER READING

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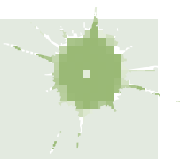
212 Aspergillosis

David W. Denning



Aspergillosis is the collective term used to describe all disease entities caused by any one of ~50 pathogenic and allergenic species of *Aspergillus*. Only those species that grow at 37°C can cause invasive infection, although some species without this ability can cause allergic syndromes. Each common pathogenic species is actually a complex of many species (many of them cryptic), but is referred to as a single species here for simplicity. *A. fumigatus* is responsible for most cases of invasive aspergillosis, almost all cases of chronic aspergillosis, and most allergic syndromes. *A. flavus* is more prevalent in some hospitals and causes a higher proportion of cases of sinus infections, cutaneous infections, and keratitis than *A. fumigatus*. *A. niger* can cause invasive infection but more commonly colonizes the respiratory tract and causes external otitis. *A. terreus* causes only invasive disease, usually with a poor prognosis. *A. nidulans* occasionally causes invasive infection, primarily in patients with chronic granulomatous disease.

EPIDEMIOLOGY AND ECOLOGY

Aspergillus has a worldwide distribution, most commonly growing in decomposing plant materials (i.e., compost) and in bedding. This hyaline (nonpigmented), septate, branching mold produces vast numbers of conidia (spores) on stalks above the surface of mycelial growth. Aspergilli are found in indoor and outdoor air, on surfaces, and in

TABLE 212-1 Disease Frequency and Diagnostic Sensitivity for Different Manifestations of Aspergillosis

PARAMETER	TYPE OF DISEASE		
	INVASIVE	CHRONIC	ALLERGIC
Incidence/100,000[a]	3.5	10.4	?[b]
Prevalence/100,000[a]	—	32.8	286[c]
Global burden[a]	~250,000	~3,000,000	~10,000,000
Mortality rate without treatment	~100%	~50%	<1%
Respiratory Diagnostic Sensitivity[d]			
Culture	✓	✓	✓
Microscopy[e]	✓	✓	?
Antigen	✓✓✓	✓✓	✓✓✓
Real-time PCR	✓✓✓	✓✓✓	✓✓✓
Blood Diagnostic Sensitivity[d]			
Culture	×	×	×
Antigen	✓✓	✓	×
β-D-glucan	✓✓	✓	?
Real-time PCR	✓✓	×	×
IgG antibody	✓	✓✓✓✓	✓✓
IgE antibody	×	✓✓	✓✓✓✓

[a]*http://www.gaffi.org/roadmap/*. [b]Allergic fungal disease can develop at any age, usually in adulthood; the annual frequency with which it occurs is not known. [c]Allergic bronchopulmonary aspergillosis and severe asthma with fungal sensitization. [d]Key for sensitivity: 1 check = limited (as the text indicates, 10–30% for culture); 2 checks = higher; 3 checks = >80%; and 4 checks = ~95%. [e]High-volume fungal culture increases sensitivity to the same level as PCR.

Abbreviation: PCR, polymerase chain reaction.

water from surface reservoirs. Daily exposures vary from a few to many millions of conidia; high numbers of conidia are encountered in hay barns and other very dusty environments. The required size of the infecting inoculum is uncertain; however, only intense exposures (e.g., during construction work, handling of moldy bark or hay, or composting) are sufficient to cause disease—acute community-acquired pulmonary aspergillosis—in healthy immunocompetent individuals. Allergic syndromes may be exacerbated by continuous antigenic exposure arising from sinus or airway colonization or from nail infection. High-efficiency particulate air (HEPA) filtration is often protective against infection; thus HEPA filters should be installed and monitored for efficiency in operating rooms and in areas of the hospital that house high-risk patients.

The incubation period of invasive aspergillosis after exposure is highly variable, extending in documented cases from 2 to 90 days. Thus community acquisition of an infecting strain frequently manifests as invasive infection during hospitalization, although nosocomial acquisition is also common. Outbreaks usually are directly related to a contaminated air source in the hospital.

Global aspergillosis incidence and prevalence have been estimated (Table 212-1). The frequency of different manifestations of aspergillosis varies considerably with geographic location; most notably, chronic granulomatous sinusitis is rare outside the Middle East and India. Fungal (mycotic) keratitis is particularly common in Nepal, Myanmar, Bhutan, and India but occurs globally. Chronic pulmonary aspergillosis follows pulmonary tuberculosis in ~6–10% of treated cases and also mimics pulmonary tuberculosis as smear-negative or "clinically diagnosed" tuberculosis.

RISK FACTORS AND PATHOGENESIS

The primary risk factors for invasive aspergillosis are profound neutropenia and glucocorticoid use; risk increases with longer duration of these conditions. Higher doses of glucocorticoids increase the risk of both acquisition of invasive aspergillosis and death from the infection. Neutrophil and/or phagocyte dysfunction also is an important risk factor, as evidenced by aspergillosis in chronic granulomatous disease, advanced HIV infection, and relapsed leukemia. An increasing incidence of invasive aspergillosis in medical intensive-care units suggests that, in patients who are not immunocompromised, temporary abrogation of protective responses as a result of glucocorticoid use or a general anti-inflammatory state is a significant risk factor. Many patients have some evidence of prior pulmonary disease—typically, a history of pneumonia or chronic obstructive pulmonary disease. Many new immunomodulating agents, such as infliximab and ibrutinib, increase the risk of invasive aspergillosis, as do severe liver disease and high levels of stored iron in bone marrow. Influenza infection and extracorporeal membrane oxygenation therapy have recently been recognized as risk factors.

Patients with chronic pulmonary aspergillosis have a wide spectrum of underlying pulmonary disease, including tuberculosis, prior pneumothorax, or chronic obstructive pulmonary disease. These patients are immunocompetent except for some cytokine-regulation defects, most of which are consistent with an inability to mount an inflammatory immune (T_H1-like) response or to control it adequately. Glucocorticoids accelerate disease progression.

Allergic bronchopulmonary aspergillosis (ABPA) complicates asthma and cystic fibrosis. Many genetic associations indicate a strong basis for the development of a T_H2-like and "allergic" response to *A. fumigatus*. Remarkably, high-dose glucocorticoid treatment for exacerbations of ABPA almost never leads to invasive aspergillosis. Most patients with *Aspergillus* bronchitis have bronchiectasis, including those with cystic fibrosis.

Different genetic traits are associated with invasive, chronic, and allergic aspergillosis; the majority of people probably are not at risk for aspergillosis. Multiple gene variants appear to be necessary for susceptibility to each form of aspergillosis.

CLINICAL FEATURES AND APPROACH TO THE PATIENT

(Table 212-2)

Invasive Pulmonary Aspergillosis Both the frequency of invasive disease and the pace of its progression increase with greater degrees of immunocompromise. Invasive aspergillosis is arbitrarily classified as acute and subacute, with courses of ≤1 month and 1–3 months, respectively. More than 80% of cases of invasive aspergillosis involve the lungs. The most common clinical features are no symptoms at all, fever, cough (sometimes productive), nondescript chest discomfort, trivial hemoptysis, and shortness of breath. Although the fever often responds to glucocorticoids, the disease progresses. The keys to early diagnosis in at-risk patients are a high index of suspicion, screening for circulating antigen (in leukemia), and urgent CT of the thorax. Invasive aspergillosis is one of the most common diagnostic errors revealed at autopsy.

Invasive Sinusitis The sinuses are involved in 5–10% of cases of invasive aspergillosis, especially affecting patients with leukemia and recipients of hematopoietic stem cell transplants. In addition to fever, the most common features are nasal or facial discomfort, blocked nose, and nasal discharge (sometimes bloody). Endoscopic examination of the nose reveals pale, dusky or necrotic-looking tissue in any location. CT or MRI of the sinuses is essential but does not distinguish invasive *Aspergillus* sinusitis from preexisting allergic or bacterial sinusitis early in the disease process.

Tracheobronchitis Occasionally, only the airways are infected by *Aspergillus*. The resulting manifestations seen on bronchoscopy range from acute or chronic bronchitis to ulcerative or pseudomembranous tracheobronchitis. These entities are particularly common among lung transplant recipients and patients on artificial ventilation. Obstruction with mucous plugs may occur and is called obstructing bronchial aspergillosis in immunocompromised patients and mucous impaction in other patients, such as those with ABPA.

***Aspergillus* Bronchitis** Recurrent chest infections that only partially improve with antibiotic treatment and are associated with significant breathlessness or coughing up of thick sputum plugs are typical features of *Aspergillus* bronchitis. Patients are not significantly immunocompromised and usually have bronchiectasis or cystic fibrosis.

TABLE 212-2 Major Manifestations of Aspergillosis

ORGAN	TYPE OF DISEASE			
	INVASIVE (ACUTE AND SUBACUTE)	CHRONIC	SAPROPHYTIC	ALLERGIC
Lung	Angioinvasive (in neutropenia), non-angioinvasive, granulomatous	Chronic cavitary, *Aspergillus* nodule, chronic fibrosing	Aspergilloma (single), airway colonization	Allergic bronchopulmonary, severe asthma with fungal sensitization, extrinsic allergic alveolitis
Sinus	Acute invasive	Chronic invasive, chronic granulomatous	Maxillary fungal ball	Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis
Brain	Abscess, hemorrhagic infarction, meningitis	Granulomatous, meningitis	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None	None	None
Eye	Keratitis, endophthalmitis	None	None	None described

Occasional patients present with respiratory failure because of airway obstruction with mucus. Concurrent bacterial bronchitis is common. The diagnosis rests on recurrent detection of *Aspergillus* in the airway by microscopy, culture, or polymerase chain reaction (PCR). *Aspergillus* IgG is usually detectable.

Disseminated Aspergillosis In the most severely immunocompromised patients, *Aspergillus* disseminates from the lungs to multiple organs—most often to the brain but also to the skin, thyroid, bone, kidney, liver, gastrointestinal tract, eye (endophthalmitis), and heart valve. Aside from cutaneous lesions, the most common features are gradual clinical deterioration over 1–3 days, with low-grade fever and features of mild sepsis, and nonspecific abnormalities in laboratory tests. In most cases, at least one localization becomes apparent before death. Blood cultures are almost always negative.

Cerebral Aspergillosis Hematogenous dissemination to the brain is a devastating complication of invasive aspergillosis. Single or multiple lesions may develop. In acute disease, hemorrhagic infarction is most typical, and cerebral abscess is common. Rarer manifestations include meningitis, mycotic aneurysm, and cerebral granuloma (mimicking a brain tumor). Local spread from cranial sinuses also occurs. Postoperative infection develops rarely and is exacerbated by glucocorticoids, which are often given after neurosurgery. The presentation can be either acute or subacute, with mood changes, focal signs, seizures, and decline in mental status. MRI is the most useful immediate investigation; unenhanced CT of the brain is usually nonspecific, and contrast is often contraindicated because of poor renal function.

Endocarditis Most cases of *Aspergillus* endocarditis are prosthetic-valve infections resulting from contamination during surgery. Native-valve disease is reported, especially as a feature of disseminated infection and in persons using illicit IV drugs. Culture-negative endocarditis with large vegetations is the most common presentation; embolectomy occasionally reveals the diagnosis.

Cutaneous Aspergillosis Dissemination of *Aspergillus* occasionally results in cutaneous features, usually an erythematous or purplish nontender area that progresses to a necrotic eschar. Direct invasion of the skin occurs in neutropenic patients at the site of IV catheter insertion and in burn patients. Surgical, burn, and trauma wounds may become infected with *Aspergillus* (especially *A. flavus*).

Chronic Pulmonary Aspergillosis The hallmark of chronic cavitary pulmonary aspergillosis (CPA; also called semi-invasive aspergillosis, chronic necrotizing aspergillosis, or complex aspergilloma) **(Fig. 212-1)** is one or more pulmonary cavities expanding over a period of months or years in association with pulmonary symptoms and systemic manifestations such as fatigue and weight loss. Often mistaken initially for tuberculosis, more than 90% of CPA cases occur in patients with prior pulmonary disease (e.g., tuberculosis, atypical mycobacterial infection, sarcoidosis, rheumatoid lung disease, pneumothorax, bullae) or lung surgery. The onset is insidious, and systemic features may be more prominent than pulmonary symptoms. Cavities may have a fluid level or a well-formed fungal ball, but pericavitary infiltrates and multiple cavities—with or without pleural thickening—are typical. An irregular internal cavity surface and thickened cavity walls are indicative of disease activity. CPA is usually caused by *A. fumigatus*, but *A. niger* has been implicated, particularly in diabetic patients, and is linked to oxalosis with renal dysfunction. IgG antibodies to *Aspergillus* are detectable in ~95% of patients with CPA. Some patients have concurrent infections—even without a fungal ball—with atypical mycobacteria and/or other bacterial pathogens. The most significant complication is life-threatening hemoptysis, which may be the presenting manifestation.

A recently recognized form of chronic pulmonary aspergillosis is the *Aspergillus* nodule, which may resemble early lung carcinoma and may cavitate. Nodules may be single or multiple and 5–50 mm in diameter. Larger mass lesions are rarely seen. Nodules are usually avid on positron emission tomography. IgG antibodies to *Aspergillus* are detectable in ~65% of patients with an *Aspergillus* nodule. If untreated, chronic cavitary pulmonary aspergillosis typically progresses (sometimes relatively rapidly) to unilateral or upper-lobe fibrosis. This end-stage entity is termed *chronic fibrosing pulmonary aspergillosis*.

Aspergilloma Aspergilloma (fungal ball) is a late manifestation of CPA, but some patients are asymptomatic. The inside of a pulmonary cavity allows growth that peels off, forming the layers of the fungal ball.

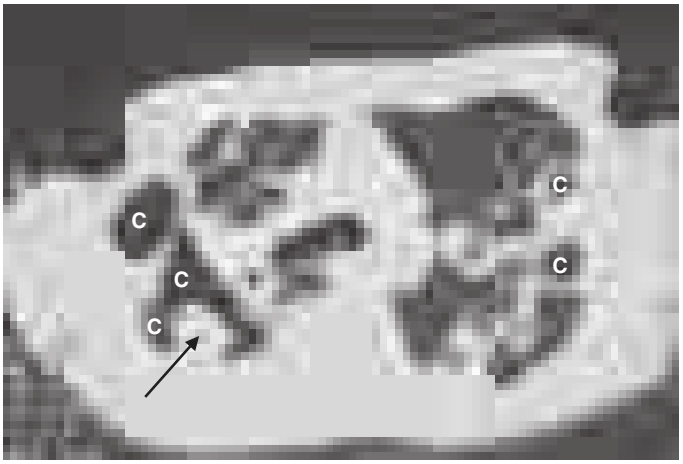


FIGURE 212-1 CT scan image of the chest in a patient with long-standing bilateral chronic cavitary pulmonary aspergillosis. This patient had a history of several bilateral pneumothoraces and had required bilateral pleurodesis in 1990. CT then demonstrated multiple bullae, and sputum cultures grew *A. fumigatus*. The patient had initially weakly and later strongly positive serum IgG *Aspergillus* antibody tests. This scan (2003) shows a mixture of thick- and thin-walled cavities in both lungs (each marked with C), with a probable fungal ball (*black arrow*) protruding into the large cavity on the patient's right side (*R*). There is also considerable pleural thickening bilaterally.

Signs and symptoms associated with single (simple) aspergillomas are minor, including cough (sometimes productive), hemoptysis, wheezing, and mild fatigue. More significant signs and symptoms are associated with chronic cavitary pulmonary aspergillosis and should be treated as such. About 10% of fungal balls resolve spontaneously (by being coughed up), but the cavity may still be infected.

Chronic *Aspergillus* Sinusitis Three entities are subsumed under this broad designation: fungal ball of the sinus, chronic invasive sinusitis, and chronic granulomatous sinusitis. Fungal ball of the sinus is limited to the maxillary sinus (except in rare cases involving the sphenoid sinus) and consists of a chronic saprophytic entity in which the sinus cavity is filled with a fungal ball. Maxillary disease is associated with prior upper-jaw root canal work and chronic (bacterial) sinusitis. About 90% of CT scans show focal hyperattenuation related to concretions; on MRI scans, the T2-weighted signal is decreased, whereas it is increased in bacterial sinusitis. Removal of the fungal ball is curative. No tissue invasion is demonstrable histologically or radiologically.

In contrast, chronic invasive sinusitis is a slowly destructive process that most commonly affects the ethmoid and sphenoid sinuses. Patients are usually but not always immunocompromised to some degree (e.g., as a result of diabetes or HIV infection). Imaging of the cranial sinuses shows opacification of one or more sinuses, local bone destruction, and invasion of local structures. The differential diagnosis is wide, including other infections. Apart from a history of chronic nasal discharge and blockage, loss of the sense of smell, and persistent headache, the usual presenting features are related to local involvement of critical structures. The orbital apex syndrome (blindness and proptosis) is characteristic. Facial swelling, cavernous sinus thrombosis, carotid artery occlusion, pituitary fossa, and brain and skull-base invasion are complications.

Chronic granulomatous sinusitis due to *Aspergillus* is most commonly seen in the Middle East and India and is often caused by *A. flavus*. It typically presents late, with facial swelling and unilateral proptosis. The prominent granulomatous reaction histologically distinguishes this disease from chronic invasive sinusitis, in which tissue necrosis with a low-grade mixed-cell infiltrate is typical. IgG antibodies to *A. flavus* are usually detectable.

Allergic Bronchopulmonary Aspergillosis In almost all cases, ABPA represents a hypersensitivity reaction to *A. fumigatus*; rare cases are due to other aspergilli and other fungi. ABPA occurs in ~2.5% of patients with asthma who are referred to secondary care and in up to 15% of teenagers with cystic fibrosis. Episodes of bronchial obstruction with mucous plugs leading to coughing fits, "pneumonia," consolidation, and breathlessness are typical. Many patients report coughing up thick sputum casts. Eosinophilia commonly develops before systemic glucocorticoids are given. The cardinal diagnostic test is detection of *Aspergillus*-specific IgE (or a positive skin-prick test in response to *A. fumigatus* extract) together with an elevated serum level of total IgE (usually >1000 IU/mL). The presence of hyperattenuated mucus in airways is highly specific. Bronchiectasis is characteristic, and some patients develop chronic cavitary pulmonary aspergillosis.

Severe Asthma with Fungal Sensitization (SAFS) Many adults with severe asthma do not fulfill the criteria for ABPA and yet are allergic to fungi. Although *A. fumigatus* is a common allergen, numerous other fungi (e.g., *Cladosporium* and *Alternaria* species) are implicated by skin-prick testing and/or specific IgE testing. Serum total IgE concentrations are <1000 IU/mL, and bronchial-wall thickening is common. ABPA and SAFS are referred to as *fungal asthma*.

Allergic Fungal Rhinosinusitis Like the lungs, the sinuses manifest allergic responses to *Aspergillus* and other fungi. The affected patients present with chronic (i.e., perennial) sinusitis that is relatively unresponsive to antibiotics. Many of these patients have nasal polyps, and all have congested nasal mucosae and sinuses full of mucoid material. The histologic hallmarks of allergic fungal sinusitis are local eosinophilia and Charcot-Leyden crystals. Removal of abnormal mucus and polyps, with local and occasionally systemic administration of glucocorticoids, usually leads to resolution. Persistent or recurrent signs and symptoms may require more extensive surgery (ethmoidectomy) and possibly antifungal therapy. Recurrence is common, often after another bacterial or viral infection.

Superficial Aspergillosis *Aspergillus* can cause keratitis and otitis externa. The former may be difficult to diagnose early enough to save the patient's sight. Treatment requires local surgical debridement as well as intensive topical antifungal therapy with natamycin (5%). Otitis externa usually resolves with debridement and local application of antifungal agents.

DIAGNOSIS

Several techniques are required to establish the diagnosis of any form of aspergillosis with confidence (Table 212-1).

Acute Invasive Aspergillosis Patients with acute invasive aspergillosis have a relatively heavy load of fungus in the affected organ; thus culture, molecular diagnosis, antigen detection, and histopathology usually confirm the diagnosis. However, the pace of progression leaves only a narrow window for making the diagnosis without losing the patient, and some invasive procedures are not possible because of coagulopathy, respiratory compromise, and other factors. Currently, ~40% of cases of invasive aspergillosis are missed clinically and are diagnosed only at autopsy. Histologic examination of affected tissue reveals either infarction, with invasion of blood vessels by many fungal hyphae, or acute necrosis, with limited inflammation and fewer hyphae. *Aspergillus* hyphae are hyaline, narrow, and septate, with branching at 45°; no yeast forms are present in infected tissue. Hyphae can be seen in cytology or microscopy preparations, which therefore provide a rapid means of presumptive diagnosis.

A positive culture supports the diagnosis, given that multiple other (rarer) fungi can mimic *Aspergillus* species histologically, but only 10–30% of patients with invasive aspergillosis have a positive culture. Bacterial agar is less sensitive than fungal media for culture; thus, if physicians do not request fungal culture, the diagnosis may be missed. A positive culture may represent noninvasive forms of aspergillosis or airway colonization. Both antigen detection and real-time PCR are faster and much more sensitive than culture of respiratory samples and blood.

The *Aspergillus* antigen test relies on detection of galactomannan release from *Aspergillus* organisms during growth. Positive serum antigen results usually precede clinical or radiologic features by several days. The sensitivity of antigen detection is reduced by antifungal prophylaxis and empirical therapy.

Definitive confirmation of a diagnosis of invasive aspergillosis requires (1) a positive culture of a sample taken directly from an ordinarily sterile site (e.g., a brain abscess) or (2) positive results of both histologic testing and culture of a sample taken from an affected organ (e.g., sinuses or skin). Most diagnoses of invasive aspergillosis are inferred from fewer data, including the presence of the *halo sign* on a high-resolution thoracic CT scan, in which a localized ground-glass appearance representing hemorrhagic infarction surrounds a nodule or consolidation. Halo signs are present for ~7 days early in the course of infection in neutropenic patients and are a good prognostic feature, reflecting an early diagnosis. Other characteristic radiologic features of invasive pulmonary aspergillosis include nodules and pleural-based infarction or cavitation, but nonspecific consolidation is common.

Chronic Aspergillosis For chronic aspergillosis, *Aspergillus* antibody testing combined with characteristic imaging is sufficient for the diagnosis. Biopsy of *Aspergillus* nodules reveals hyphae surrounded by cells of chronic inflammation and sometimes granulomas. Antibody titers fall slowly with successful therapy. Cultures are infrequently positive but are important in checking for azole resistance. Real-time PCR of sputum is often strongly positive. Some patients with chronic pulmonary aspergillosis also have elevated titers of total serum IgE and *Aspergillus*-specific IgE.

ABPA, SAFS, and Allergic *Aspergillus* Sinusitis ABPA and SAFS are diagnosed serologically with elevated specific and total

serum IgE levels or with skin-prick tests. Allergic *Aspergillus* sinusitis is usually diagnosed histologically, although measurement of IgE antibodies in blood also may be useful.

TREATMENT

Aspergillosis

Antifungal drugs active against *Aspergillus* include voriconazole, itraconazole, posaconazole, isavuconazole, caspofungin, micafungin, and amphotericin B (AmB). Possible interactions with other drugs must be considered before azoles are prescribed. In addition, plasma azole concentrations vary substantially from one patient to another, and many authorities recommend monitoring levels to ensure that drug concentrations are adequate but not excessive, especially with itraconazole and voriconazole. Initial IV administration is preferred for acute invasive aspergillosis and oral administration for all other diseases that require antifungal therapy. Current recommendations are shown in **Table 212-3**.

Voriconazole and isavuconazole are the preferred agents for invasive aspergillosis; caspofungin, posaconazole, micafungin, and lipid-associated AmB are second-line agents. AmB is not active against *A. terreus* or *A. nidulans*; multi-azole resistance in *A. fumigatus* is present in <5% of isolates but is increasing; and *A. niger* is resistant to itraconazole and isavuconazole. An infectious disease consultation is advised for patients with invasive disease, given the complexity of management. Immune reconstitution can complicate recovery. The duration of therapy for invasive aspergillosis varies from ~3 months to several years, depending on the patient's immune status and response to therapy. Relapse occurs if the response is suboptimal and immune reconstitution is not complete.

Itraconazole is currently the preferred oral agent for chronic and allergic forms of aspergillosis. Voriconazole or posaconazole can be substituted when failure, emergence of resistance, or adverse events occur. An itraconazole dose of 200 mg twice daily is recommended, with monitoring of drug concentrations in the blood. Acute exacerbations of ABPA respond well to a short course of glucocorticoids. Because chronic cavitary pulmonary aspergillosis responds slowly, therapy for >6 months is necessary, and disease control may require years of treatment, whereas the duration of treatment for other forms of chronic and allergic aspergillosis requires case-by-case evaluation. Glucocorticoids should be used in chronic cavitary pulmonary aspergillosis only if covered by adequate antifungal therapy. Antifungal response in *Aspergillus* bronchitis is gratifying, but relapse after 4 months of therapy is common.

Resistance in *A. fumigatus* to one or more azoles, although uncommon, is increasingly found globally. Resistance may be derived from azole fungicide use for crops. In addition, resistance arising from multiple mechanisms may develop during long-term treatment, and a positive culture during antifungal therapy is an indication for susceptibility testing.

Surgical treatment is important in several forms of aspergillosis, including fungal ball of the sinus and single aspergillomas, in which surgery is curative; invasive aspergillosis involving bone, heart valve, sinuses, and proximal areas of the lung; brain abscess; keratitis; and endophthalmitis. In allergic fungal sinusitis, removal of abnormal mucus and polyps, with local and occasionally systemic glucocorticoid treatment, usually leads to resolution. Persistent or recurrent signs and symptoms may require more extensive surgery (ethmoidectomy) and possibly antifungal therapy. Surgery is problematic in chronic cavitary pulmonary aspergillosis, usually resulting in serious complications. Bronchial artery embolization is preferred for problematic hemoptysis.

PROPHYLAXIS

In situations in which moderate or high risk is predicted (e.g., after induction therapy for acute myeloid leukemia), the need for antifungal prophylaxis for superficial and systemic candidiasis and for invasive aspergillosis is generally accepted. Fluconazole is commonly used in these situations but has no activity against *Aspergillus* species. Itraconazole capsules are ineffective, and itraconazole solution offers only modest efficacy. Posaconazole tablets are more effective in reducing infection rates and the need for empirical antifungal therapy. Some data support the use of IV micafungin. No prophylactic regimen is completely successful.

OUTCOME

Invasive aspergillosis is curable if immune reconstitution occurs, whereas allergic and chronic forms are not. The mortality rate for invasive aspergillosis is 30–70% if the infection is treated but is 100% if the diagnosis is missed. Infection with a voriconazole-resistant strain

TABLE 212-3 Treatment of Aspergillosis[a]

INDICATION	PRIMARY TREATMENT	PRECAUTIONS	SECONDARY TREATMENT	COMMENTS
Invasive disease[b]	Voriconazole, isavuconazole	Drug interactions (especially with rifampin and carbamazepine)[c]	AmB, caspofungin, posaconazole, micafungin	As primary therapy, voriconazole and isavuconazole have a 20% higher response rate than AmB. Therapeutic drug monitoring is recommended for voriconazole.
Prophylaxis	Posaconazole tablet, itraconazole solution	Diarrhea and vomiting with itraconazole, vincristine interaction	Micafungin, aerosolized AmB	Some centers monitor plasma levels of itraconazole and posaconazole.
Single aspergilloma	Surgery	Multicavity disease: poor outcome of surgery, medical therapy preferable	Itraconazole, voriconazole, intracavity AmB	Single large cavities with an aspergilloma are best resected.
Chronic pulmonary disease[b]	Itraconazole, voriconazole	Poor absorption of itraconazole capsules with proton pump inhibitors or H_2 blockers	Posaconazole, IV AmB, IV micafungin	Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic.
ABPA/SAFS ("fungal asthma")	Itraconazole	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole, posaconazole	Long-term therapy is helpful in most cases. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis.

[a]For information on duration of therapy and drug resistance in certain *Aspergillus* species, see text. [b]An infectious disease consultation is appropriate for these patients. [c]Online drug-interaction resource: *www.aspergillus.org.uk/content/antifungal-drug-interactions*.

Note: After loading doses, the oral dose is usually 200 mg bid for voriconazole and itraconazole, 300 mg qd for posaconazole tablets, and 200 mg qd for isavuconazole. The IV dose of voriconazole for adults is 6 mg/kg twice at 12-h intervals (loading doses) followed by 4 mg/kg q12h; a larger dose is required for children and teenagers; a lower dose may be safer for persons >70 years of age. Plasma monitoring is helpful in optimizing the dosage. The IV dose of isavuconazole is 200 mg tid for 2 days (loading dose) followed by 200 mg qd. Caspofungin is given as a single loading dose of 70 mg and then at 50 mg/d; some authorities use 70 mg/d for patients weighing >80 kg, and lower doses are required with hepatic dysfunction. Micafungin is given as 50 mg/d for prophylaxis and as at least 150 mg/d for treatment; this drug has not yet been approved by the U.S. Food and Drug Administration (FDA) for this indication. AmB deoxycholate is given at a daily dose of 1 mg/kg if tolerated. Several strategies are available for minimizing renal dysfunction. Lipid-associated AmB is given at 3 mg/kg (AmBisome) or 5 mg/kg (Abelcet). Different regimens are available for aerosolized AmB, but none is FDA approved. Other considerations that may alter dose selection or route include age; concomitant medications; renal, hepatic, or intestinal dysfunction; and drug tolerability.

Abbreviations: AmB, amphotericin B; ABPA, allergic bronchopulmonary aspergillosis; SAFS, severe asthma with fungal sensitization.

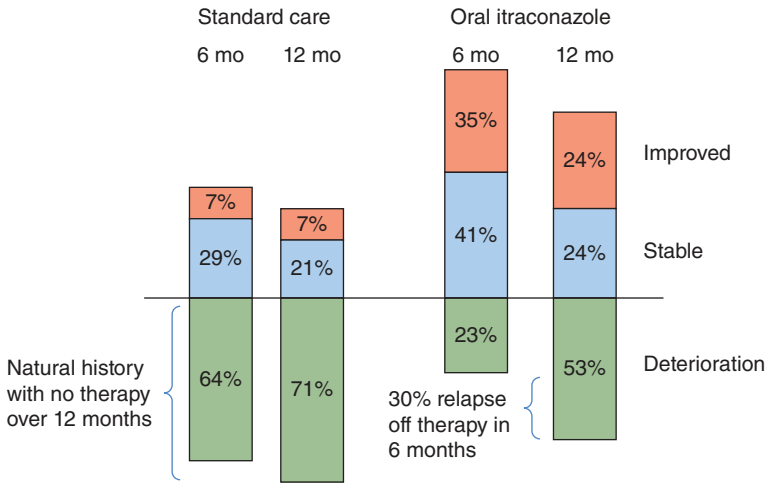


FIGURE 212-2 Comparison of the impact of itraconazole therapy (400 mg/d) and that of standard care on chronic cavitary pulmonary aspergillosis at 6 and 12 months. *(After R Agarwal et al: Itraconazole in chronic cavitary pulmonary aspergillosis: A randomised controlled trial and systematic review of literature. Mycoses 56:559, 2013.)*

carries a mortality rate of 90%. Cerebral aspergillosis, *Aspergillus* endocarditis, and bilateral extensive invasive pulmonary aspergillosis have very poor outcomes, as does invasive infection in persons with late-stage AIDS or relapsed uncontrolled leukemia.

The mortality rate for chronic cavitary pulmonary aspergillosis is ~40% over 5 years if the patient is actively treated with antifungal agents. After 12 months with no antifungal therapy, 70% of patients have deteriorated and 30% are stable **(Fig. 212-2)**. Therapy fails in ~30% of recipients of antifungal therapy and still more often if azole resistance is present.

Both ABPA and SAFS patients respond to antifungal therapy; ~60% respond to itraconazole and ~80% to voriconazole and posaconazole (if tolerated). Inhaled amphotericin B is effective in and tolerated by ~15% of patients. If the severity of asthma declines, the inhaled glucocorticoid dose can be reduced and oral glucocorticoids can be stopped. Relapse after discontinuation is common but not universal.

FURTHER READING

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213 Mucormycosis

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Mucormycosis represents a group of life-threatening infections caused by fungi of the order Mucorales of the subphylum Mucoromycotina (formerly known as the class Zygomycetes). Mucormycosis is highly invasive and relentlessly progressive, resulting in higher rates of morbidity and mortality than many other infections. Although mortality rates from mucormycosis have declined in recent years as a result of early initiation of more effective antifungal therapies, they remain high overall.

ETIOLOGY

Fungi of the order Mucorales belong to seven families **(Table 213-1)**, all of which can cause mucormycosis. Among the Mucorales, *Rhizopus oryzae* and *R. delemar* (a related, more recently recognized species)—both in the family Mucoraceae—are by far the most common causes of mucormycosis in the Western Hemisphere. Less frequently isolated species of the Mucoraceae that cause a similar spectrum of infections include *Rhizopus microsporus*, *Rhizomucor pusillus*, *Lichtheimia corymbifera* (formerly *Absidia corymbifera*), *Apophysomyces elegans*, and *Mucor* species. Increasing numbers of cases of mucormycosis due to infection with *Cunninghamella* species (family Cunninghamellaceae) have also been reported, particularly in highly immunocompromised patients. Only rare case reports have demonstrated the ability of fungi in the remaining families of the Mucorales to cause mucormycosis, although other Mucorales can be the major cause of disease in certain geographic areas (e.g., *A. elegans* in India and *Mucor irregularis* in China).

PATHOGENESIS

The Mucorales are ubiquitous environmental fungi to which humans are constantly exposed. These fungi cause infection primarily in patients with diabetes, defects in phagocytic function (e.g., neutropenia or glucocorticoid treatment), and/or elevated levels of free iron, which supports fungal growth in serum and tissues. In the past, iron-overloaded patients with end-stage renal failure who were treated with deferoxamine had a high risk of developing rapidly fatal disseminated mucormycosis; deferoxamine is an iron chelator for the human host, but it serves as a fungal siderophore, directly delivering iron to the Mucorales. Furthermore, patients with diabetic ketoacidosis (DKA) are at high risk of developing rhinocerebral mucormycosis. The acidosis causes dissociation of iron from sequestering proteins, resulting in enhanced fungal survival and virulence. The ketoacid β-hydroxybutyrate increases

TABLE 213-1 Taxonomy of Fungi Causing Mucormycosis (Subphylum Mucoromycotina, Order Mucorales)

FAMILY	GENUS (SPECIES LISTED FOR SOME)
Mucoraceae	*Rhizopus oryzae* *Rhizopus delemar* *Rhizopus microsporus* *Rhizomucor* *Mucor* *Actinomucor*
Lichtheimiaceae	*Lichtheimia* (formerly *Mycocladus*, formerly *Absidia*)
Cunninghamellaceae	*Cunninghamella*
Thamnidiaceae	*Cokeromyces*
Mortierellaceae	*Mortierella*
Saksenaceae	*Saksenaea* *Apophysomyces*
Syncephalastraceae	*Syncephalastrum*

expression of host and fungal receptors that result in fungal adherence and penetration into tissues.

Nevertheless, the majority of diabetic patients who present with mucormycosis are not acidotic, and, even absent acidosis, hyperglycemia directly contributes to the risk of mucormycosis by at least four likely mechanisms: (1) hyperglycation of iron-sequestering proteins, disrupting normal iron sequestration; (2) upregulation of a mammalian cell receptor (GRP78) that binds to Mucorales, enabling tissue penetration (due to both a direct effect of hyperglycemia and increasing levels of free iron, which independently enhances GRP78 expression); (3) induction of poorly characterized defects in phagocytic function; and (4) enhanced expression of CotH, a Mucorales-specific protein that mediates host cell invasion by binding to GRP78 (due to hyperglycemia and the resulting free iron).

EPIDEMIOLOGY

Mucormycosis typically occurs in patients with diabetes mellitus, solid organ or hematopoietic stem cell transplantation (HSCT), prolonged neutropenia, or malignancy. The majority of diabetic patients are not acidotic on presentation with mucormycosis. Furthermore, patients often have no previously recognized history of diabetes mellitus when they present with mucormycosis. In these instances, presentation for mucormycosis may result in the first clinical recognition of hyperglycemia, which often has been unmasked by recent glucocorticoid use. Thus a high index of suspicion of mucormycosis must be maintained, even in the absence of a known history of diabetes, if hyperglycemia is present. In patients undergoing HSCT, mucormycosis develops at least as commonly during nonneutropenic as during neutropenic periods, probably because of glucocorticoid treatment of graft-versus-host disease. Mucormycosis can occur as isolated cutaneous or subcutaneous infection in immunologically normal individuals after traumatic implantation of soil or vegetation (e.g., due to natural disasters, motor vehicle accidents, or—in soldiers—severe injuries during combat operations) or in nosocomial settings via direct access through IV catheters, SC injections, or maceration of the skin by a moist dressing.

Patients receiving antifungal prophylaxis with either itraconazole or voriconazole may be at increased risk of mucormycosis. These patients typically present with disseminated mucormycosis, the most lethal form of disease. Breakthrough mucormycosis also has been described in patients receiving posaconazole or echinocandin prophylaxis.

CLINICAL MANIFESTATIONS

Mucormycosis can be divided into at least six clinical syndromes: rhino-orbital-cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. Patients with specific defects in host defense tend to develop specific syndromes. For example, patients with diabetes mellitus and/or DKA typically develop the rhino-orbital-cerebral form and much more rarely develop pulmonary or disseminated disease. In contrast, pulmonary mucormycosis occurs most commonly in leukemic patients who are receiving chemotherapy and in patients undergoing HSCT.

Rhino-Orbital-Cerebral Disease Rhino-orbital-cerebral mucormycosis continues to be the most common form of the disease. Most cases occur in patients with diabetes, although such cases are increasingly being described in the transplantation setting, often along with glucocorticoid-induced diabetes mellitus. The initial symptoms of rhino-orbital-cerebral mucormycosis are nonspecific and include eye or facial pain and facial numbness followed by the onset of conjunctival suffusion and blurry vision. Fever may be absent in up to half of cases. White blood cell counts are typically elevated as long as the patient has functioning bone marrow. If untreated, infection usually spreads from the ethmoid sinus to the orbit, resulting in compromise of extraocular muscle function and proptosis, typically with chemosis. From the orbit, spread often takes place via hematogenous or contiguous dissemination to the frontal lobe of the brain and/or via venous drainage to the cavernous sinus. Onset of signs and symptoms in the contralateral eye, with resulting bilateral proptosis, chemosis, vision loss, and ophthalmoplegia, is ominous, suggesting the development of cavernous sinus thrombosis.

Upon visual inspection, infected tissue may appear to be normal during the earliest stages of fungal spread, then progressing through an erythematous phase, with or without edema, before the onset of a violaceous appearance and finally the development of a black necrotic eschar. Infection can sometimes extend from the sinuses into the mouth and produce painful necrotic ulcerations of the hard palate, but this is a late finding that suggests extensive, well-established infection.

One common misperception about mucormycosis is that it is always rapidly progressive. In fact, the rate of progression is extremely variable and is possibly dependent on the immune status of the patient and the causative Mucorales species, some of which are more virulent and/or have faster growth rates than others. Patients may go from initial symptoms to death in days; alternatively, it can take months or even a year or more for lethal progression to occur.

Pulmonary Disease Pulmonary mucormycosis is the second most common manifestation. Symptoms include dyspnea, cough, and chest pain; fever is often but not invariably present. Angioinvasion results in necrosis, cavitation, and/or hemoptysis. Lobar consolidation, isolated masses, nodular disease, cavities, or wedge-shaped infarcts may be seen on chest radiography. High-resolution chest CT is the best method for determining the extent of pulmonary mucormycosis and may demonstrate evidence of infection before it is seen on chest x-ray. In the setting of cancer, where mucormycosis may be difficult to differentiate from aspergillosis, the presence of ≥10 pulmonary nodules, pleural effusion, or concomitant sinusitis makes mucormycosis more likely. It is critical to distinguish mucormycosis from aspergillosis as rapidly as possible because treatments for these infections differ. Indeed, voriconazole—the first-line treatment for aspergillosis—exacerbates mucormycosis in mouse and fly models of infection.

Cutaneous Disease Cutaneous mucormycosis may result from external implantation of the fungus or from hematogenous dissemination. External implantation–related infection has been described in the setting of soil exposure from trauma (e.g., in a motor vehicle accident, a natural disaster, or combat-related injuries), penetrating injury with plant material (e.g., a thorn), injections of medications (e.g., insulin), catheter insertion, contamination of surgical dressings, and use of tape to secure endotracheal tubes. Cutaneous disease can be highly invasive, penetrating into muscle, fascia, and even bone. Necrotizing fasciitis caused by mucormycosis carries a mortality rate approaching 80%. Necrotic cutaneous lesions in the setting of hematogenous dissemination also are associated with an extremely high mortality rate. However, with prompt, aggressive surgical debridement, isolated cutaneous mucormycosis has a favorable prognosis and a low mortality rate.

Gastrointestinal Disease In the past, gastrointestinal mucormycosis occurred primarily in premature neonates in association with disseminated disease and necrotizing enterocolitis. However, there has been a marked increase in case reports describing adults with neutropenia, glucocorticoid use, or other immunocompromising conditions. In addition, gastrointestinal disease has been reported as a nosocomial process following administration of medications mixed with contaminated wooden applicator sticks. Nonspecific abdominal pain and distention associated with nausea and vomiting are the most common symptoms. Gastrointestinal bleeding is common, and fungating masses may be seen in the stomach at endoscopy. The disease may progress to visceral perforation, with extremely high mortality rates.

Disseminated and Miscellaneous Forms of Disease Hematogenously disseminated mucormycosis may originate from any primary site of infection. The most common site of dissemination is the brain, but metastatic lesions may also be found in any other organ. Mortality rates for widely disseminated mucormycosis exceed 90%; however, these high rates are likely to be due in part to the underlying predisposing condition leading to the infection. Miscellaneous forms of mucormycosis may affect any body site, including bones, mediastinum, trachea, kidneys, and peritoneum (in association with dialysis); even isolated infection of teeth has been reported.

FIGURE 213-1 Histopathology sections of *Rhizopus delemar* in infected brain. ***A.*** Broad, ribbon-like, nonseptate hyphae in the parenchyma (*arrows*) and a thrombosed blood vessel with extensive intravascular hyphae (*arrowhead*) (hematoxylin and eosin). ***B.*** Extensive, broad, ribbon-like hyphae invading the parenchyma (Gomori methenamine silver).

DIAGNOSIS

A high index of suspicion is required for diagnosis of mucormycosis. Unfortunately, autopsy series have shown that up to half of cases are diagnosed only post-mortem. Because the Mucorales are environmental isolates, definitive diagnosis requires a positive culture from a sterile site (e.g., a needle aspirate, a tissue biopsy specimen, or pleural fluid) or histopathologic evidence of invasive mucormycosis. A probable diagnosis of mucormycosis can be established by culture from a nonsterile site (e.g., sputum or bronchoalveolar lavage) or the detection of Mucorales on the surface of histopathology samples (without visualization of evidence of invasion) when a patient has appropriate risk factors as well as clinical and radiographic evidence of disease. In such cases, given the urgency of administering therapy early, the patient should be treated while confirmation of the diagnosis is awaited.

Biopsy with histopathologic examination remains the most sensitive and specific modality for definitive diagnosis **(Fig. 213-1)**. Biopsy reveals characteristic wide (≥6- to 30-μm), thick-walled, ribbon-like, aseptate hyphal elements that branch at right angles. Other fungi, including *Aspergillus, Fusarium*, and *Scedosporium* species, have septa, are thinner, and branch at acute angles. Because artificial septa may result from folding of tissue during processing (which may also alter the appearance of the angle of branching), the width and the ribbon-like form of the fungus are the most reliable features distinguishing mucormycosis. The Mucorales are visualized most effectively with periodic acid–Schiff or hematoxylin and eosin; in contrast to many other fungi, methenamine silver may not result in optimal staining. While histopathology can identify the Mucorales, species can be identified only by culture. Polymerase chain reaction (PCR) is being investigated as a diagnostic tool for mucormycosis but is not yet approved by the U.S. Food and Drug Administration (FDA) for this purpose and is not generally available.

Unfortunately, cultures are positive in fewer than half of cases of mucormycosis. Nevertheless, the Mucorales are not fastidious organisms and tend to grow quickly (i.e., within 48–96 h) on culture media. The likely explanation for the low sensitivity of culture is that the Mucorales form long filamentous structures that are killed by tissue homogenization—the standard method for preparing tissue cultures in the clinical microbiology laboratory. Thus the laboratory should be advised when a diagnosis of mucormycosis is suspected, and the tissue should be cut into sections and placed in the center of culture dishes rather than homogenized. Because there is also substantial variability among isolates in optimal growth temperature, growth at both room temperature and 37°C is advisable.

Imaging techniques often yield subtle findings that underestimate the extent of disease. For example, the most common finding on CT or MRI of the head or sinuses of a patient with rhino-orbital mucormycosis is sinusitis that is indistinguishable from bacterial sinusitis. It is also common to detect no abnormalities in sinus bones despite clinical evidence of progressive disease. MRI is more sensitive (~80%) for detecting orbital and CNS disease than is CT. High-risk patients should always undergo endoscopy and/or surgical exploration, with biopsy of the areas of suspected infection. If mucormycosis is suspected, initial empirical therapy with a polyene antifungal agent should be initiated while the diagnosis is being confirmed.

DIFFERENTIAL DIAGNOSIS

Other mold infections, including aspergillosis, scedosporiosis, fusariosis, and infections caused by the dematiaceous fungi (brown-pigmented soil organisms), can cause clinical syndromes identical to mucormycosis. Histopathologic examination usually allows distinction of the Mucorales from these other organisms, and a positive culture permits definitive species identification. As stated above, it is important to distinguish the Mucorales from these other fungi, as the preferred antifungal treatments differ (i.e., polyenes for the Mucorales vs expanded-spectrum triazoles for most septate molds). The entomophthoromycoses caused by *Basidiobolus* and *Conidiobolus* also can cause identical clinical syndromes. These fungi cannot be readily distinguished from the Mucorales by histopathology but can be reliably distinguished by culture. Fortunately, entomophthoromycoses are uncommon in developed countries and can be treated with polyenes; in this setting, it is not urgent to distinguish them from mucormycosis.

In a patient with sinusitis and proptosis, orbital cellulitis and cavernous sinus thrombosis caused by bacterial pathogens (most commonly *Staphylococcus aureus*, but also streptococcal and gram-negative species) must be excluded. *Klebsiella rhinoscleromatis* is a rare cause of an indolent facial rhinoscleroma syndrome that may appear similar to mucormycosis. Finally, the Tolosa-Hunt syndrome causes painful ophthalmoplegia, ptosis, headache, and cavernous sinus inflammation; biopsies and clinical follow-up may be needed to distinguish the Tolosa-Hunt syndrome from mucormycosis by the lack of progression of the former entity.

TREATMENT

Mucormycosis

GENERAL PRINCIPLES

Optimizing the chances for successful treatment of mucormycosis requires three steps: (1) early initiation of therapy; (2) rapid reversal of underlying predisposing risk factors, if possible; and (3) surgical debridement, when possible. Maintaining a high index of suspicion for patients at risk for mucormycosis is critical. Multiple studies have found that earlier initiation of polyene-based therapy improves survival of patients with mucormycosis. Because the disease can present subtly at first and because confirmation of the diagnosis can take days, therapy often must be started empirically before the diagnosis is established. When there is a reasonable suspicion of mucormycosis, clinicians should not hesitate to initiate therapy with a lipid polyene as soon as possible, since the toxicity of lipid polyenes (unlike that of amphotericin B [AmB] deoxycholate) is rarely substantial after one or two doses.

It is also crucial to rapidly reverse (or prevent) underlying defects in host defense during treatment (e.g., by stopping or reducing the dosage of immunosuppressive medications or by rapidly restoring euglycemia and normal acid–base status). Indeed, a recent study confirmed that resolution of acidosis in mice with DKA via the administration of sodium bicarbonate (in lieu of insulin) improved survival. Administration of glucocorticoids predisposes animals to death from mucormycosis in experimental models. Similarly, iron administration to patients with active mucormycosis should be avoided, as iron exacerbates infection in experimental models. Blood transfusion typically results in some liberation of free iron due to hemolysis, so a conservative approach to red blood cell transfusions is advisable.

Blood vessel thrombosis and resulting tissue necrosis during mucormycosis can result in poor penetration of antifungal agents to the site of infection. Therefore, debridement of all necrotic tissues is critical for eradication of disease. Surgery has been found (by logistic regression and in multiple case series) to be an independent variable for favorable outcome in patients with mucormycosis. Limited data from a retrospective study support the use of intraoperative frozen sections to delineate the margins of infected tissues, with sparing of tissues lacking evidence of infection. A multidisciplinary team, including an internist, an infectious disease specialist, and surgical specialists whose expertise is relevant to the sites of infection, is typically required for the management of mucormycosis.

ANTIFUNGAL THERAPY

Primary therapy for mucormycosis should be based on a polyene antifungal agent **(Table 213-2)**, except perhaps in mild localized infection (e.g., isolated suprafascial cutaneous infection) that has been eradicated surgically in an immunocompetent patient. Lipid formulations of AmB are significantly less nephrotoxic than AmB deoxycholate, can be administered at higher doses, and are probably more effective for this purpose. Liposomal amphotericin B (LAmB) is preferred to amphotericin B lipid complex (ABLC) for management of central nervous system (CNS) infection on the basis of retrospective survival data and superior brain penetration; there is no clear efficacy advantage of either agent for non-CNS infections, although LAmB may be less nephrotoxic than ABLC.

Starting dosages of 1 mg/kg per day for AmB deoxycholate and 5 mg/kg per day for LAmB and ABLC are commonly given to adults and children to treat mucormycosis. Dose escalation of LAmB to 7.5 or 10 mg/kg per day for CNS mucormycosis may be considered in light of the limited penetration of polyenes into the brain. Because of auto-induction of metabolism, which results in paradoxically lower drug levels, there is no advantage to escalating the LAmB dose above 10 mg/kg per day, and doses of 5 mg/kg per day are probably adequate for non-CNS infections. ABLC dose escalation above 5 mg/kg per day is not advisable given the lack of relevant data and the drug's potential toxicity.

In multiple studies, various combinations of lipid polyenes (both ABLC and LAmB) plus echinocandins (e.g., caspofungin, micafungin, and anidulafungin) improved survival rates among mice with disseminated mucormycosis (including CNS disease). Furthermore, combination lipid polyene–echinocandin therapy was associated with significantly better outcomes than polyene monotherapy in a retrospective clinical study involving patients with rhino-orbital-cerebral

TABLE 213-2 Antifungal Options for the Treatment of Mucormycosis[a]

DRUG	RECOMMENDED DOSAGE	ADVANTAGES AND SUPPORTING STUDIES	DISADVANTAGES
First-Line Antifungal Therapy			
AmB deoxycholate	1.0–1.5 mg/kg once per day	· >5 decades of clinical experience · Inexpensive · FDA-approved for treatment of mucormycosis	· Highly toxic · Poor CNS penetration
LAmB	5–10 mg/kg once per day	· Less nephrotoxic than AmB deoxycholate · Better CNS penetration than AmB deoxycholate or ABLC · Better outcomes than with AmB deoxycholate in murine models and a retrospective clinical review	· Expensive
ABLC	5 mg/kg once per day	· Less nephrotoxic than AmB deoxycholate · Murine and retrospective clinical data suggest benefit of combination therapy with echinocandins	· Expensive · Possibly less efficacious than LAmB for CNS infection
Second-Line/Salvage Option			
Isavuconazole	200 mg of isavuconazole (372 mg of isavuconazonium sulfate), load q8h × 6 followed by once-daily dosing	· Efficacy similar to that of LAmB in mouse models · FDA-approved for treatment of mucormycosis · May be a rational empirical option when septate mold vs. mucormycosis is not yet established	· Much less clinical experience; concern about a more slowly cidal agent than lipid polyenes · Clinical study supporting approval was small and historically controlled.
Posaconazole	200 mg four times per day	· In vitro activity against the Mucorales, with lower MICs than isavuconazole · Retrospective data for salvage therapy in mucormycosis	· Substantially lower blood levels than isavuconazole · No data on initial therapy for mucormycosis, and no evidence for combination therapy with posaconazole · Experience limited, potential use for salvage therapy
Combination Therapy[b]			
Echinocandin plus lipid polyene	Standard echinocandin doses	· Favorable toxicity profile · Synergistic in murine disseminated mucormycosis · Retrospective clinical data suggest superior outcomes for rhino-orbital-cerebral mucormycosis.	· Limited clinical data on combination therapy
Lipid polyene plus azole (posaconazole or isavuconazole)	Standard doses	· Favorable toxicity profile	· Limited efficacy data, with no available evidence of superiority vs. monotherapy
Triple therapy (lipid polyene plus echinocandin plus azole)	Standard doses	· Maximal aggressiveness	· Limited efficacy data, with no available evidence for superiority vs. monotherapy or dual therapy

[a]Primary therapy should generally include a polyene. Non-polyene-based regimens may be appropriate for patients who refuse polyene therapy or for relatively immunocompetent patients with mild disease (e.g., isolated suprafascial cutaneous infection) that can be surgically eradicated. [b]Prospective randomized trials are necessary to confirm the suggested benefit (from animal and small retrospective human studies) of combination therapy for mucormycosis. Dose escalation of any echinocandin is not recommended because of a paradoxical loss of benefit of combination therapy at echinocandin doses of ≥3 mg/kg per day.

Abbreviations: ABLC, AmB lipid complex; AmB, amphotericin B; CNS, central nervous system; FDA, U.S. Food and Drug Administration; LAmB, liposomal AmB; MIC, minimal inhibitory concentration.

Source: Modified from B Spellberg et al: Clin Infect Dis 48:1743, 2009.

mucormycosis (including CNS disease). The effect of echinocandins appears to be to down-modulate the virulence of the fungus and reduce tissue necrosis and destruction from fungal invasion. On the basis of such data, some experts prefer combination lipid polyene–echinocandin therapy as a first-line option. However, definitive clinical trials are needed to establish whether the combination is superior in efficacy to monotherapy for mucormycosis. When used, echinocandins should be administered at standard, FDA-approved doses, since dose escalation has resulted in paradoxical loss of efficacy in preclinical models.

In contrast to deferoxamine, the iron chelator deferasirox is fungicidal against clinical isolates of the Mucorales. In mice with DKA and disseminated mucormycosis, combination deferasirox–LAmB therapy resulted in synergistic improvement of survival rates and reduced the fungal burden in the brain. Unfortunately, a randomized, double-blind, phase 2 safety clinical trial of adjunctive therapy with deferasirox (plus LAmB) documented excess mortality among patients treated with deferasirox. Of note, the study population included primarily patients with active malignancy, and few patients in the study had diabetes mellitus as their only risk factor. Deferasirox is therefore contraindicated as therapy in patients with active malignancy, but its role in patients who have diabetes mellitus without malignancy (the setting in which its preclinical efficacy was optimal) remains uncertain.

Posaconazole and isavuconazole are the only FDA-approved azoles with in vitro activity against the Mucorales. However, posaconazole has been found to be inferior in efficacy to AmB for the treatment of murine mucormycosis and was not superior to placebo. Moreover, posaconazole–polyene combination therapy was not superior to polyene monotherapy for mucormycosis in mice, and no comparative data are available for combination therapy in humans. Thus no data support the use of combination posaconazole–polyene regimens. Although the minimal inhibitory concentrations (MICs) of isavuconazole against the Mucorales are four- to eightfold higher than those of posaconazole, blood levels may be higher with standard isavuconazole dosing than with posaconazole. Therefore, neither azole is clearly preferable to the other as a therapeutic option. Isavuconazole is approved for the treatment of mucormycosis on the basis of a small, historically controlled study. Given this limited dataset, many experts continue to think that lipid polyenes are first-line options and that isavuconazole, like posaconazole, is best reserved for oral step-down therapy in patients whose condition has substantially improved on polyene-based therapy or for salvage therapy in patients who are intolerant of polyene-based regimens or whose infection is refractory to these regimens. As for posaconazole, no data support the use of combination isavuconazole–polyene regimens in lieu of polyene monotherapy or polyene–echinocandin combination regimens. Some experts use triple therapy with a polyene, echinocandin, and either posaconazole or isavuconazole for patients who have extensive disease or whose disease has progressed on prior therapy. Empirical, dual lipid polyene–azole therapy is a rational choice in a patient with likely invasive mold infections when septate molds and mucormycosis are both in the differential diagnosis and the etiologic agent has not yet been confirmed.

The roles of recombinant cytokines and neutrophil transfusions in the primary treatment of mucormycosis are not clear, although it is intuitive that earlier recovery of neutrophil counts should improve survival rates. Limited data from uncontrolled studies support the use of hyperbaric oxygen in centers with the appropriate technical expertise and facilities; its efficacy remains undefined. As mentioned previously, one study in mice with DKA found that administration of sodium bicarbonate improved survival from mucormycosis; however, because insulin was not administered to the mice, it is unclear whether the therapeutic effect is clinically relevant.

In general, antifungal therapy for mucormycosis should be continued until resolution of clinical signs and symptoms of infection and resolution of underlying immunosuppression. However, after several weeks of daily therapy in a patient who is clinically improving, it is reasonable to consider switching to thrice-weekly lipid polyene doses—with ultimate weaning down to twice-weekly doses—for maintenance therapy. For patients with mucormycosis who are receiving immunosuppressive medications, secondary antifungal prophylaxis is typically continued for as long as the immunosuppressive regimen is administered.

One common vexing problem encountered in long-term management is the role of radiographic follow-up. Analysis of data from the phase 2 DEFEAT Mucor study indicated that early radiographic progression (within the first 2 weeks) did not predict long-term survival. Caution should be used in reacting to short-term, serial radiographic results, and greater emphasis should be placed on clinical response, particularly within the first 2–4 weeks after initiation of therapy.

PROGNOSIS

Over the past two decades, the prognosis of mucormycosis has substantially improved with aggressive antifungal therapy. Even CNS infection is often successfully treated. The key driver of outcome may now be control of the patient's predisposing condition. In the past, experts often recommended delaying chemotherapy in infected patients with cancer in order to try to eradicate the fungus. However, cure of mucormycosis is not likely to be effected until underlying malignancy is controlled. Thus, a balanced approach is required. It may be far more harmful to long-term success to withhold chemotherapy than to try to treat the patient with antifungal agents during chemotherapy; some consideration can be given to moderating the aggressiveness of the chemotherapy and the resulting duration and depth of neutropenia.

FURTHER READING

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214 Superficial Mycoses and Less Common Systemic Mycoses

Carol A. Kauffman

ENDEMIC MYCOSES (DIMORPHIC FUNGI)

Dimorphic fungi exist in discrete environmental niches as molds that produce conidia, which are their infectious form. In tissues and at temperatures of >35°C, the mold converts to the yeast form. **Other endemic mycoses—histoplasmosis, coccidioidomycosis, and blastomycosis—are discussed in Chaps. 207, 208, and 209, respectively.**

Etiologic Agent, Epidemiology, and Pathogenesis

Sporothrix schenckii is a thermally dimorphic fungus that is found worldwide in sphagnum moss, decaying vegetation, and soil. Sporotrichosis most commonly affects persons who participate in outdoor activities such as landscaping, gardening, and tree farming. Infected animals can transmit *S. schenckii* to humans. A large ongoing outbreak of sporotrichosis in Rio de Janeiro has been traced to cats, which are highly susceptible to this infection. Sporotrichosis is primarily a localized infection of skin and subcutaneous tissues that follows traumatic inoculation of conidia. Osteoarticular sporotrichosis is uncommon, occurring most often in middle-aged men who abuse alcohol, and pulmonary sporotrichosis occurs almost exclusively in persons with chronic obstructive pulmonary disease who have inhaled the organism from the environment. Dissemination occurs rarely, almost always affecting markedly immunocompromised patients, especially those with AIDS.

Clinical Manifestations and Differential Diagnosis Days or weeks after inoculation, a papule develops at the site and then usually ulcerates but is not very painful. Similar lesions develop sequentially along the lymphatic channels proximal to the original lesion **(Fig. 214-1)**. Some patients develop a fixed cutaneous lesion that can be verrucous or ulcerative and that remains localized without lymphatic extension. The differential diagnosis of lymphocutaneous sporotrichosis includes nocardiosis, tularemia, nontuberculous mycobacterial infection (especially that due to *Mycobacterium marinum*), and leishmaniasis. Osteoarticular sporotrichosis can present as chronic synovitis or septic arthritis. Pulmonary sporotrichosis must be differentiated from tuberculosis and from other fungal pneumonias. Numerous ulcerated skin lesions, with or without spread to visceral organs (including the central nervous system [CNS]), are characteristic of disseminated sporotrichosis.

Diagnosis *S. schenckii* usually grows readily as a mold on Sabouraud's agar when material from a cutaneous lesion is incubated at room temperature. Histopathologic examination of biopsy material shows a mixed granulomatous and pyogenic reaction, and tiny oval or cigar-shaped yeasts sometimes can be seen with special stains. In cases in which the organism has not grown, polymerase chain reaction (PCR) of tissue samples can sometimes be helpful.

Treatment and Prognosis Guidelines for the management of the various forms of sporotrichosis have been published by the Infectious Diseases Society of America **(Table 214-1)**. Itraconazole is the drug of choice for lymphocutaneous sporotrichosis. Fluconazole is less effective, voriconazole is not effective, and posaconazole has been used successfully in a few instances. Saturated solution of potassium iodide (SSKI) continues to be used for lymphocutaneous infection because it costs much less than itraconazole. However, SSKI is poorly tolerated because of adverse reactions, including metallic taste, salivary gland swelling, rash, and fever. High-dose terbinafine may be effective for lymphocutaneous infection. Treatment for lymphocutaneous sporotrichosis is continued for 2–4 weeks after all lesions have resolved, usually for a total of 3–6 months. The success rate for treatment of lymphocutaneous sporotrichosis is 90–100%.

Pulmonary and osteoarticular forms of sporotrichosis are treated with itraconazole for at least 1 year. Severe pulmonary infection and disseminated sporotrichosis, including that involving the CNS, should be treated initially with amphotericin B (AmB), with a switch to itraconazole after improvement has been noted. Lifelong suppressive therapy with itraconazole often is required for AIDS patients. These forms of sporotrichosis respond poorly to antifungal therapy.

TABLE 214-1 Suggested Treatment for Endemic Mycoses

DISEASE	FIRST-LINE THERAPY	ALTERNATIVES/COMMENTS
Sporotrichosis		
Cutaneous, lymphocutaneous	Itraconazole, 200 mg/d until 2–4 weeks after lesions resolve	SSKI, increasing doses[a] Terbinafine, 500 mg bid
Pulmonary, osteoarticular	Itraconazole, 200 mg bid for 12 months	Lipid AmB[b] for severe pulmonary disease until stable; then itraconazole
Disseminated, central nervous system	Lipid AmB[b] for 4–6 weeks	Itraconazole, 200 mg bid after AmB for 12 months AIDS patients: itraconazole maintenance, 200 mg/d until CD4+ T cell count is >200/μL for ≥12 months
Paracoccidioidomycosis		
Chronic (adult form)	Itraconazole, 100–200 mg/d for 6–12 months	Voriconazole, 200 mg bid for 6–12 months Posaconazole, 300 mg/d for 6–12 months TMP-SMX, 160/800 mg bid for 12–36 months
Acute (juvenile form)	AmB[c] or lipid AmB[b] until improvement	Itraconazole, 200 mg bid after AmB for 12 months Voriconazole or posaconazole at doses noted above may be used
Talaromycosis (Penicilliosis)		
Mild or moderate	Itraconazole, 200 mg bid for 12 weeks	Voriconazole, 200 mg bid
Severe	Lipid AmB[b] or AmB[c] until improvement	Itraconazole, 200 mg bid after AmB for 12 weeks
Maintenance therapy (AIDS)	200 mg/d until CD4+ T cell count is >100/μL for ≥6 months	

[a]The starting dosage is 5–10 drops tid in water or juice. The dosage is increased weekly by 10 drops per dose, as tolerated, up to 40–50 drops tid. [b]The dosage of lipid AmB is 3–5 mg/kg daily; the higher dosage should be used when the central nervous system is involved. [c]The dosage of AmB deoxycholate is 0.6–1.0 mg/kg daily.

Abbreviations: AmB, amphotericin B; SSKI, saturated solution of potassium iodide; TMP-SMX, trimethoprim-sulfamethoxazole.

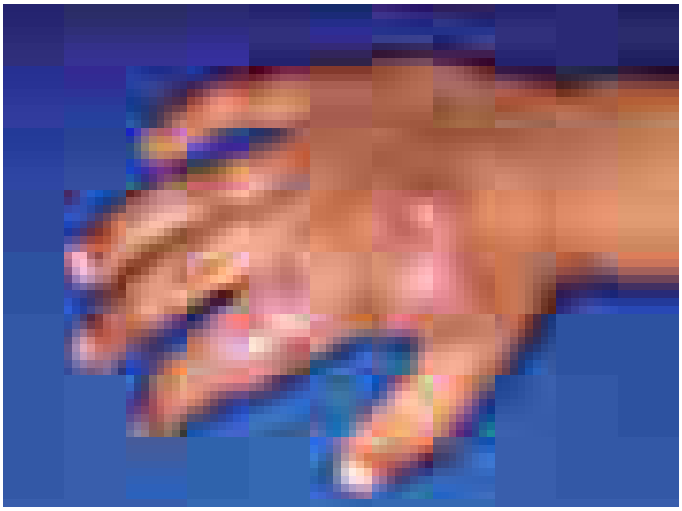

FIGURE 214-1 Several nodular lesions that developed after a young boy pricked his index finger with a thorn. A culture yielded *S. schenckii*. *(Courtesy of Dr. Angela Restrepo.)*

PARACOCCIDIOIDOMYCOSIS

Etiologic Agent, Epidemiology, and Pathogenesis

Paracoccidioides brasiliensis is a thermally dimorphic fungus that is found in humid areas of Central and South America and is highly endemic in Brazil. A striking male-to-female ratio varies from 14:1 to as high as 70:1 in various reports. Most patients are middle-aged or elderly men from rural areas. Paracoccidioidomycosis develops after the inhalation of aerosolized conidia encountered in the environment. For most patients, disease rarely develops at the time of

the initial infection but appears years later, presumably after reactivation of a latent infection.

Clinical Manifestations Two major syndromes are associated with paracoccidioidomycosis: the acute or juvenile form and the chronic or adult form. The acute form is uncommon, occurs mostly in persons <30 years old, and manifests as disseminated infection of the reticuloendothelial system. Immunocompromised individuals also manifest this type of rapidly progressive disease. The chronic form of paracoccidioidomycosis accounts for ~90% of cases and predominantly affects older men. The primary manifestation is progressive pulmonary disease, primarily in the lower lobes, with fibrosis. Ulcerative and nodular mucocutaneous lesions in the nares and mouth—another common manifestation of chronic paracoccidioidomycosis—must be differentiated from leishmaniasis **(Chap. 221)** and squamous cell carcinoma **(Chap. 72)**.

Diagnosis The diagnosis is established by growth of the mold form of *P. brasiliensis* in culture at room temperature. A presumptive diagnosis can be made by detection of the distinctive thick-walled yeast, which has multiple narrow-necked buds attached circumferentially, in purulent material or tissue biopsies.

Treatment and Prognosis Itraconazole is the treatment of choice for paracoccidioidomycosis (Table 214-1). Ketoconazole is also effective but more toxic; voriconazole and posaconazole also appear to be effective. Sulfonamides have been used for years and are the least costly agents; however, the response is slower and the relapse rate higher. Seriously ill patients should be treated with AmB initially. Patients with paracoccidioidomycosis have an excellent response to therapy, but pulmonary fibrosis can be progressive in those with chronic disease.

TALAROMYCOSIS (PENICILLIOSIS)

Etiologic Agent, Epidemiology, and Pathogenesis *Talaromyces marneffei (formerly Penicillium marneffei)* is a thermally dimorphic fungus that is endemic in the soil in certain areas of Vietnam, Thailand, and other southeastern Asian countries. The epidemiology of talaromycosis is linked to bamboo rats that are infected with the fungus but rarely manifest disease. The disease occurs most often among persons living in rural areas in which the rats are found, but there is no evidence for transmission of the infection directly from rats to humans. Infection is rare in immunocompetent hosts, and most cases are reported in persons who have advanced AIDS. Infection results from the inhalation of conidia from the environment. The organism converts to the yeast phase in the lungs and then spreads hematogenously to the reticuloendothelial system.

Clinical Manifestations The clinical manifestations of talaromycosis mimic those of disseminated histoplasmosis and include fever, fatigue, weight loss, dyspnea, diarrhea (in some cases), lymphadenopathy, hepatosplenomegaly, and skin lesions, which appear as papules that often umbilicate and resemble molluscum contagiosum **(Chap. 191)**.

Diagnosis Talaromycosis is diagnosed by culture of *T. marneffei* from blood or from biopsy samples of skin, bone marrow, or lymph node. The organism usually grows within 1 week as a mold producing a distinctive red pigment that diffuses into the agar. Histopathologic examination of tissues and smears of blood or material from skin lesions shows oval or elliptical yeast-like organisms with central septation and can quickly establish a presumptive diagnosis.

Treatment and Prognosis For mild or moderate infection, itraconazole is the drug of choice; voriconazole can also be used. Severe infection should be treated with AmB until improvement occurs; then therapy can be changed to itraconazole (Table 214-1). For patients with AIDS, suppressive therapy with itraconazole is recommended until the CD4+ T cell count has been >100 cells/μL for at least 6 months. Disseminated talaromycosis is usually fatal if not treated. With treatment, the mortality rate is ~10%.

PHAEOHYPHOMYCOSES

Dematiaceous or brown-black fungi, the common soil organisms that cause phaeohyphomycoses, contain melanin, which causes the hyphae and conidia to be darkly pigmented. The term *phaeohyphomycosis* is used to describe any infection with a pigmented mold. This definition encompasses two specific syndromes—eumycetoma and chromoblastomycosis—as well as all other types of infections caused by these organisms. It is important to note that eumycetomas can be caused by hyaline molds as well as by brown-black molds and that only about half of all mycetomas are due to fungi. Actinomycetes cause the remainder **(Chap. 169)**. Most dematiaceous fungi cause localized subcutaneous infections after direct inoculation, but disseminated infections and serious focal visceral infections do occur, especially in immunocompromised patients.

Etiologic Agents A large number of pigmented molds can cause human infection. Most are found in the soil or on plants, and some cause economically important plant diseases. Disseminated infection and focal visceral infections are caused by a variety of dematiaceous fungi; *Alternaria*, *Exophiala*, *Curvularia*, and *Wangiella* species are among the more common molds reported to cause human infection. In 2012, *Exserohilum* species caused a large outbreak of severe, sometimes fatal CNS and osteoarticular infections after the injection of methylprednisolone contaminated with this fungus. The most common cause of eumycetoma is *Madurella* species. *Fonsecaea* and *Cladophialophora* species are responsible for most cases of chromoblastomycosis.

Epidemiology and Pathogenesis Infections with dematiaceous molds are acquired by traumatic inoculation into the eye or through the skin, by inhalation, or by injection of contaminated medication. Melanin is a virulence factor for all the pigmented molds. Several organisms, specifically *Cladophialophora bantiana* and *Rhinocladiella mackenziei*, are neurotropic and likely to cause CNS infection. When a patient is immunocompromised or when a pigmented mold is injected directly into a deep structure, these organisms become opportunists, invading blood vessels and mimicking better-known opportunistic infections, such as aspergillosis. Eumycetoma and chromoblastomycosis are acquired by inoculation through the skin; these two syndromes are seen almost entirely in tropical and subtropical areas and occur mostly in rural laborers who are frequently exposed to the organisms.

Clinical Manifestations Dematiaceous molds are the most common cause of allergic fungal sinusitis and a less common cause of invasive fungal sinusitis. Keratitis occurs with traumatic corneal inoculation. Even in many immunocompromised patients, inoculation through the skin generally produces only localized cyst-like, nodular lesions at the entry site. However, other immunocompromised patients develop pneumonia, brain abscess, or disseminated infection. In the outbreak mentioned above, epidural injection of *Exserohilum*-contaminated glucocorticoids led to meningitis, basilar stroke, epidural abscess and phlegmon, vertebral osteomyelitis, and arachnoiditis.

Eumycetoma is a chronic subcutaneous and cutaneous infection that usually occurs on the lower extremities and that is characterized by swelling, the development of sinus tracts, and the appearance of grains that are actually colonies of fungi discharged from the sinus tract. As the infection progresses, adjacent fascia and bony structures become involved. The disease is indolent and disfiguring, progressing slowly over years. Complications include fractures of infected bone and bacterial superinfection.

Chromoblastomycosis is an indolent subcutaneous infection characterized by nodular, verrucous, or plaque-like painless lesions that occur predominantly on the lower extremities and grow slowly over months to years. There is hardly ever extension to adjacent structures, as is seen with eumycetoma. Long-term consequences include bacterial superinfection, chronic lymphedema, and (rarely) the development of squamous cell carcinoma.

Diagnosis The specific diagnosis of infection with a pigmented mold is established by growth of the organism in culture, which is essential to differentiate infection with a hyaline mold (e.g., *Aspergillus*

TABLE 214-2 Suggested Treatment for Phaeohyphomycoses and Opportunistic Infections

DISEASE	FIRST-LINE THERAPY	ALTERNATIVES/ COMMENTS
Phaeohyphomycoses	Voriconazole, 200 mg bid Itraconazole, 200 mg bid Posaconazole, 300 mg/d	Lipid AmB may be effective against some mold species.
Fusariosis	Voriconazole, 200–300 mg bid Lipid AmB, 5 mg/kg per day Posaconazole, 300 mg/d	Lipid AmB plus voriconazole or posaconazole is used by some physicians for initial therapy.
Scedosporiosis	Voriconazole, 200–300 mg bid Posaconazole, 300 mg/d	Not susceptible to AmB *Scedosporium prolificans* is resistant to almost all antifungal drugs.
Trichosporonosis	Voriconazole, 200–300 mg bid	Posaconazole, 300 mg/d

Abbreviation: AmB, amphotericin B.

or *Fusarium*) from that due to a pigmented mold. A tentative clinical diagnosis of mycetoma can be made when a patient presents with a lesion characterized by swelling, sinus tracts, and grains. Histopathologic examination and culture are necessary to confirm that the etiologic agent is a mold and not an actinomycete. In chromoblastomycosis, the diagnosis rests on the histologic demonstration of sclerotic bodies (dark brown, thick-walled, septate fungal forms that resemble large yeasts) in the tissues; culture establishes which pigmented mold is causing the infection. PCR assays are increasingly used in the diagnosis of infection due to dematiaceous molds but are available only through fungal reference laboratories.

Treatment and Prognosis The choice of antifungal agent to treat disseminated and focal visceral infections with brown-black molds is based on the location and extent of the infection, in vitro test results, and clinical experience with the specific infecting organism. AmB is not effective against many of these organisms but has been used successfully against some species **(Table 214-2)**. Itraconazole, voriconazole, or posaconazole can be used in the treatment of localized infections. Voriconazole is preferred when infections involve the CNS because this drug reaches adequate concentrations at that site. Voriconazole or posaconazole could be used for disseminated infection; these agents are available as both IV and well-absorbed oral formulations. Disseminated and focal visceral infections, especially those involving the CNS, are associated with high mortality rates.

Treatment of eumycetoma and chromoblastomycosis involves both surgical extirpation of the lesion and use of antifungal agents. Surgical removal of the lesions is most effective if performed before extensive spread has occurred. In chromoblastomycosis, cryosurgery and laser therapy have been used with variable success. The antifungal agents of choice are itraconazole, voriconazole, and posaconazole. The most experience has accrued with itraconazole; less experience has been gained with the newer azoles, which are active in vitro and have been reported to be effective in a few patients. Flucytosine and terbinafine also have been used to treat chromoblastomycosis. Chromoblastomycosis and eumycetoma are chronic indolent infections that are difficult to cure but are not life-threatening.

OPPORTUNISTIC FUNGAL INFECTIONS

Two genera of hyaline (nonpigmented) molds, *Fusarium* and *Scedosporium*, and one yeast-like genus, *Trichosporon*, have become prominent pathogens among immunocompromised patients. Infections caused by *Fusarium* and *Scedosporium* species overlap with invasive aspergillosis in their clinical manifestations; when seen in tissues, these organisms appear similar to *Aspergillus*. In the immunocompetent host, these fungi cause localized infections of skin, skin structures, and subcutaneous tissues, but their role as causes of infection in immunocompromised patients will be emphasized in this section.

FUSARIOSIS

Etiologic Agent, Epidemiology, and Pathogenesis *Fusarium* species, which are found worldwide in soil and on plants, have emerged as major opportunists in markedly immunocompromised patients. Most human infections follow inhalation of conidia, but ingestion and direct inoculation also can lead to disease. An outbreak of severe *Fusarium* keratitis among soft contact lens wearers was traced back to a particular brand of contact lens solution and individual contact lens cases that had been contaminated. Disseminated infection is reported most often in patients who have a hematologic malignancy, are neutropenic, have received a hematopoietic cell or solid organ transplant, or have a severe burn.

Clinical Manifestations In immunocompetent persons, *Fusarium* species cause localized infections of various organs. These organisms commonly cause fungal keratitis, which can extend into the anterior chamber of the eye; cause loss of vision; and require corneal transplantation. Onychomycosis due to *Fusarium* species, while basically an annoyance in immunocompetent patients, is a source of subsequent hematogenous dissemination and should be aggressively sought and treated in neutropenic patients. In profoundly immunocompromised patients, fusariosis is angioinvasive, and clinical manifestations mimic those of aspergillosis. Pulmonary infection is characterized by multiple nodular lesions. Sinus infection is likely to lead to invasion of adjacent structures. Disseminated fusariosis occurs primarily in neutropenic patients with hematologic malignancies and in allogeneic hematopoietic cell transplant recipients, especially those with graft-versus-host disease. Disseminated fusariosis differs from disseminated aspergillosis in that skin lesions are extremely common with fusariosis; the lesions are nodular or necrotic, are usually painful, and appear over time in different locations **(Fig. 214-2)**.

Diagnosis The diagnostic approach usually includes both documentation of the growth of *Fusarium* species from involved tissue and demonstration of invasion by histopathologic techniques that show septate hyphae in tissues. The organism is difficult to differentiate from *Aspergillus* species in tissues; thus, identification with culture is imperative. An extremely helpful diagnostic clue is growth in blood cultures, which are positive in as many as 50% of patients with disseminated fusariosis.

Treatment and Prognosis *Fusarium* species are resistant to many antifungal agents. A lipid formulation of AmB, voriconazole, or posaconazole is recommended. Many physicians use both a lipid formulation of AmB and either voriconazole or posaconazole because susceptibility information is not available when therapy must be initiated.

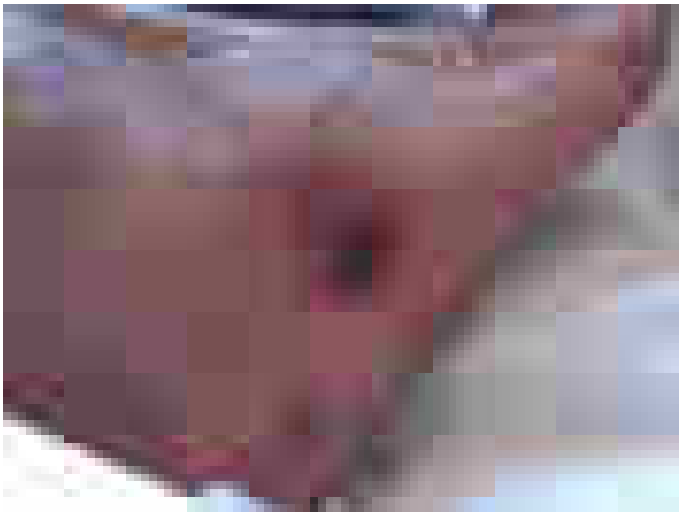

FIGURE 214-2 Painful necrotic foot lesion that developed over a week in a woman who had acute leukemia and who had been neutropenic for 2 months. *Fusarium* species were grown from a punch biopsy. *(Courtesy of Dr. Nessrine Ktaich.)*

Serum drug levels should be monitored with either azole to ensure that absorption is adequate and with voriconazole to avoid toxicity. Mortality rates for disseminated fusariosis have been as high as 85%. With the improved antifungal therapy now available, mortality rates have fallen to ~50%. However, if neutropenia persists, the mortality rate approaches 100%.

SCEDOSPORIOSIS

Etiologic Agent The genus *Scedosporium* includes several pathogens. The major causes of human infections are the *Scedosporium apiospermum* complex (composed of several species) and *Scedosporium prolificans*, which has been renamed *Lomentospora prolificans*.

Epidemiology and Pathogenesis Organisms of the *S. apiospermum* complex are found worldwide in temperate climates in tidal flats, swamps, ponds, manure, and soil. These organisms cause pneumonia, disseminated infection, and brain abscess and are common pathogens in near-drowning victims. *L. prolificans* is also found in soil but is more geographically restricted. Infection occurs predominantly through inhalation of conidia, but direct inoculation through the skin or into the eye also can occur.

Clinical Manifestations Among immunocompetent persons, *Scedosporium* species are a prominent cause of eumycetoma. Keratitis as a result of accidental corneal inoculation is a sight-threatening infection. In patients who have hematologic malignancies (especially acute leukemia with neutropenia), recipients of solid organ or hematopoietic stem cell transplants, and patients receiving glucocorticoids, *Scedosporium* species are angioinvasive, causing pneumonia and widespread dissemination. Pulmonary infection mimics aspergillosis; nodules, cavities, and lobar infiltrates are common. Disseminated infection involves the skin, heart, brain, and many other organs. Skin lesions are not as common or as painful as those of fusariosis.

Diagnosis Diagnosis depends on the growth of *Scedosporium* species from involved tissue and the demonstration of invasion by histopathologic techniques that show septate hyphae in tissues. Culture evidence is essential because *Scedosporium* species are difficult to differentiate from *Aspergillus* in tissues, and demonstration of tissue invasion is essential because these ubiquitous environmental molds can be mere contaminants or colonizers. *L. prolificans* can grow in blood cultures, but *S. apiospermum* usually does not.

Treatment and Prognosis *Scedosporium* species are resistant to AmB, echinocandins, and some azoles. Voriconazole is the agent of choice for *S. apiospermum*, and posaconazole also can be used for this infection. *L. prolificans* is resistant in vitro to almost every available antifungal agent; the addition of agents such as terbinafine to a voriconazole regimen has been attempted because in vitro data suggest possible synergy against some strains of *L. prolificans*. Mortality rates for invasive *S. apiospermum* infection are ~50%, but those for invasive *L. prolificans* infection remain as high as 85–100%.

TRICHOSPORONOSIS

Etiologic Agent The genus *Trichosporon* contains many species, some of which cause localized infection of hair and nails. The major pathogen responsible for invasive infection is *Trichosporon asahii. Trichosporon* species grow as yeast-like colonies in vitro; in vivo, however, hyphae, pseudohyphae, and arthroconidia, in addition to yeast forms, can be seen.

Epidemiology and Pathogenesis These yeasts are commonly found in soil, sewage, and water and in rare instances can colonize human skin and the human gastrointestinal tract. Most infections follow inhalation or entry via central venous catheters. Systemic infection occurs almost exclusively in immunocompromised hosts, including those who have hematologic malignancies, are neutropenic, have received a solid organ transplant, or are receiving glucocorticoids.

Clinical Manifestations Disseminated trichosporonosis resembles invasive candidiasis, and fungemia is often the initial manifestation of infection. Pneumonia, skin lesions, and sepsis are common. The skin lesions begin as papules or nodules surrounded by erythema and progress to central necrosis. A chronic form of infection mimics hepatosplenic candidiasis (chronic disseminated candidiasis).

Diagnosis The diagnosis of systemic *Trichosporon* infection is established by growth of the organism from involved tissues or from blood. Histopathologic examination of a skin lesion showing a mixture of yeast forms, arthroconidia, and hyphae can lead to an early presumptive diagnosis of trichosporonosis. The serum cryptococcal antigen latex agglutination test may be positive in patients with disseminated trichosporonosis because *T. asahii* and *Cryptococcus neoformans* share polysaccharide antigens.

Treatment and Prognosis Rates of response to AmB have been disappointing, and many *Trichosporon* isolates are resistant in vitro. Voriconazole is the antifungal agent of choice. The mortality rates for disseminated *Trichosporon* infection have been as high as 70% but are decreasing with the use of voriconazole; however, patients who remain neutropenic are likely to succumb to this infection.

SUPERFICIAL CUTANEOUS INFECTIONS

Fungal infections of the skin and skin structures are caused by molds and yeasts that do not invade deeper tissues but rather cause disease merely by inhabiting the superficial layers of skin, hair follicles, and nails. These agents are the most common fungal infections of humans but only rarely cause serious infections.

YEAST INFECTIONS

Etiologic Agents, Epidemiology, and Pathogenesis The lipophilic yeast *Malassezia* is dimorphic in that it colonizes the skin in the yeast phase but transforms to the mold phase when it causes disease. *Malassezia* species are part of the indigenous human flora found in the stratum corneum of the back, chest, scalp, and face—areas rich in sebaceous glands. The organisms do not invade below the stratum corneum and generally elicit little if any inflammatory response.

Clinical Manifestations *Malassezia* species cause tinea versicolor (also called *pityriasis versicolor*), folliculitis, and seborrheic dermatitis. Tinea versicolor presents as flat round scaly patches of hypo- or hyperpigmented skin on the neck, chest, or upper arms. The lesions are usually asymptomatic but can be pruritic. They can be mistaken for vitiligo, but the latter is not scaly. Folliculitis occurs on the back and chest and mimics bacterial folliculitis. Seborrheic dermatitis manifests as erythematous pruritic scaly lesions in the eyebrows, moustache, nasolabial folds, and scalp (*dandruff*). Seborrheic dermatitis can be severe in patients with advanced AIDS. Fungemia and disseminated infection occur rarely with *Malassezia* species—almost always in premature neonates receiving parenteral lipid preparations through a central venous catheter.

Diagnosis *Malassezia* infections are diagnosed clinically in most cases. If scrapings are collected on a microscope slide on which a drop of potassium hydroxide has been placed, a mixture of budding yeasts and short septate hyphae is seen. In order to culture *M. furfur* from those patients in whom disseminated infection is suspected, sterile olive oil must be added to the medium.

Treatment and Prognosis Topical creams and lotions, including selenium sulfide shampoo, ketoconazole shampoo or cream, and terbinafine cream, are effective in treating *Malassezia* infections and are usually given for 2 weeks. Other more expensive antifungal creams are rarely needed. Mild topical steroid creams are sometimes used to treat seborrheic dermatitis. For extensive disease, oral itraconazole or fluconazole (200 mg daily) can be used for 5–7 days. The rare cases of fungemia caused by *Malassezia* species are treated with AmB or fluconazole, prompt removal of the catheter, and discontinuance of parenteral lipid infusions. *Malassezia* skin infections are benign and

self-limited, although recurrences are the rule. The outcome of systemic infection depends on the host's underlying conditions, but most infected infants do well.

DERMATOPHYTE (MOLD) INFECTIONS

Etiologic Agents The molds that cause skin infections in humans include the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. These organisms, which are not components of the normal skin flora, can live within the keratinized structures of the skin—hence the term *dermatophytes*.

Epidemiology and Pathogenesis Dermatophytes occur worldwide, and infections with these organisms are extremely common. Some organisms cause disease only in humans and can be transmitted by person-to-person contact and by fomites, such as hairbrushes or wet floors, that have been contaminated by infected individuals. Several species cause infections in cats and dogs and can readily be transmitted from these animals to humans. Finally, some dermatophytes are spread from contact with soil. The characteristic ring shape of cutaneous lesions is the result of the organisms' outward growth in a centrifugal pattern in the stratum corneum. Fungal invasion of the nail usually occurs through the lateral or superficial nail plates and then spreads throughout the nail; when hair shafts are invaded, the organisms can be found either within the shaft or surrounding it. Symptoms are caused by the inflammatory reaction elicited by fungal antigens and not by tissue invasion. Dermatophyte infections occur more commonly in males than in females, and progesterone has been shown to inhibit dermatophyte growth.

Clinical Manifestations Dermatophyte infection of the skin is often called *ringworm*. This term is confusing because worms are not involved. *Tinea*, the Latin word for *worm*, describes the serpentine nature of the skin lesions and is a less confusing designation that is used in conjunction with the name of the body part affected—e.g., tinea capitis (head), tinea pedis (feet), tinea corporis (body), tinea cruris (crotch), and tinea unguium (nails, although infection at this site is more often termed *onychomycosis*).

Tinea capitis occurs most commonly in children 3–7 years old. Children with tinea capitis usually present with well-demarcated scaly patches in which hair shafts are broken off right above the skin; alopecia can result. Tinea corporis is manifested by well-demarcated, annular, pruritic, scaly lesions that undergo central clearing. Usually one or several small lesions are present. However, in some patients, tinea corporis can involve much of the trunk. The rash should be differentiated from contact dermatitis, eczema, and psoriasis. Tinea cruris is seen almost exclusively in men. The perineal rash is erythematous and pustular, has a discrete scaly border, is without satellite lesions, and is usually pruritic. The rash must be differentiated from intertriginous candidiasis, erythrasma, and psoriasis.

Tinea pedis also is more common among men than among women. It usually starts in the web spaces of the toes; peeling, maceration, and pruritus are followed by development of a scaly pruritic rash along the lateral and plantar surfaces of the feet. Hyperkeratosis of the soles of the feet often ensues. Tinea pedis has been implicated in lower-extremity cellulitis, as streptococci and staphylococci can gain entrance to the tissues through fissures between the toes. Onychomycosis affects toenails more often than fingernails and is most common among persons who have tinea pedis. The nail becomes thickened and discolored and may crumble; onycholysis almost always occurs. Onychomycosis is more common in older adults and in persons with vascular disease, diabetes mellitus, and trauma to the nails. Fungal infection must be differentiated from psoriasis, which can mimic onychomycosis but usually has associated skin lesions.

Diagnosis Many dermatophyte infections are diagnosed by their clinical appearance. If the diagnosis is in doubt, scrapings should be taken from the edge of a lesion with a scalpel blade, transferred to a slide to which a drop of potassium hydroxide is added, and examined under a microscope for the presence of hyphae. Cultures are indicated if an outbreak is suspected or the patient does not respond to therapy.

TABLE 214-3 Suggested Oral Treatment for Extensive Tinea Infections and Onychomycosis

ANTIFUNGAL AGENT	SUGGESTED DOSAGE	COMMENTS
Extensive Tinea Infection		
Terbinafine	250 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period
Itraconazole[a]	200 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period except for drug interactions
Onychomycosis		
Terbinafine	250 mg/d for 3 months	Slightly superior to itraconazole; monitor for hepatotoxicity
Itraconazole[a]	200 mg/d for 3 months *or* 200 mg bid for 1 week each month for 3 months	Drug interactions frequent; monitor for hepatotoxicity; rarely causes hypokalemia, hypertension, edema; use with caution in patients with congestive heart failure

[a]Itraconazole capsules require food and gastric acid for absorption, whereas itraconazole solution is taken on an empty stomach.

Treatment and Prognosis Dermatophyte infections usually respond to topical therapy. Lotions or sprays are easier than creams to apply to large or hairy areas. Particularly for tinea cruris, the affected area should be kept as dry as possible. When patients have extensive skin lesions, oral itraconazole or terbinafine can hasten resolution (Table 214-3). Terbinafine interacts with fewer drugs than itraconazole and is generally the first-line agent.

Onychomycosis does not respond to topical therapy although ciclopirox nail lacquer applied daily for a year is occasionally beneficial. Itraconazole and terbinafine both accumulate in the nail plate and can be used to treat onychomycosis (Table 214-3). The major decision to be made with regard to therapy is whether the extent of nail involvement justifies the use of systemic antifungal agents that have adverse effects, may interact with other drugs, and are costly. Treating for cosmetic reasons alone is discouraged. Relapses of tinea cruris and tinea pedis are common and should be treated early with topical creams to avoid development of more extensive disease. Relapses of onychomycosis follow treatment in 25–30% of cases.

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215 *Pneumocystis* Infections

Alison Morris, Henry Masur

DEFINITION AND DESCRIPTION

Pneumocystis is an opportunistic pathogen that is an important cause of pneumonia in immunocompromised hosts, particularly those with HIV infection **(Chap. 197)**, organ transplants, or hematologic malignancies and those receiving high-dose glucocorticoids or certain immunosuppressive monoclonal antibodies. *Pneumocystis* was discovered in rodents in 1906 and was initially believed to be a protozoan. Because *Pneumocystis* cannot be cultured, our understanding of its biology has been limited, but molecular techniques have demonstrated that the organism is actually a fungus. Formerly known as *Pneumocystis carinii*, the species infecting humans has been renamed *Pneumocystis jirovecii*.

EPIDEMIOLOGY

P. jirovecii pneumonia (PCP) came to medical attention when cases were reported in malnourished orphans in Europe during World War II. The disease was later recognized in other immunosuppressed populations but was rare in the era before HIV/AIDS and before intensive immunosuppressive therapy for organ transplantation and autoimmune disorders. In 1981, PCP was first reported in men who had sex with men and in IV drug users who had no obvious cause of immunosuppression. These cases were subsequently recognized as the first cases of what came to be known as the acquired immunodeficiency syndrome (AIDS) **(Chap. 197)**.

The incidence of PCP increased dramatically as the AIDS epidemic grew: without chemoprophylaxis or antiretroviral therapy (ART), 80–90% of patients with HIV/AIDS in North America and Western Europe ultimately develop one or more episodes of PCP. While its incidence declined with the introduction of anti-*Pneumocystis* prophylaxis and combination ART, PCP has continued to be a leading cause of AIDS-associated morbidity in the United States and Western Europe, particularly in individuals who do not know they are infected with HIV until they are profoundly immunosuppressed and in HIV-infected patients with CD4+ T lymphocyte counts of <200/μL who are not receiving ART or PCP prophylaxis.

PCP also develops in HIV-uninfected patients who are immunocompromised secondary to hematologic or malignant neoplasms, stem cell or solid organ transplantation, and treatment with immunosuppressive medications. The incidence of PCP depends on the degree and duration of immunosuppression. PCP is increasingly reported among individuals receiving tumor necrosis factor α inhibitors and antilymphocyte monoclonal antibodies for rheumatologic or other diseases. While clinical PCP in immunocompetent hosts has not been clearly documented, studies have shown that *Pneumocystis* organisms can colonize the airways of children and adults who are not overtly immunocompromised. The relevance of these organisms to acute or chronic syndromes, such as chronic obstructive pulmonary disease (COPD), in immunocompetent patients is being investigated.

In some developing countries, the incidence of PCP among HIV-infected individuals has been found to be lower than that in industrialized countries. This lower incidence may be due to competing mortality from infectious diseases such as tuberculosis and bacterial pneumonia, which typically occur before patients become immunosuppressed enough to develop PCP. Geographic variations in *Pneumocystis* exposure and underdiagnosis attributable to lack of diagnostic resources also may explain the apparent lower frequency of PCP in some countries.

PATHOGENESIS AND PATHOLOGY

Life Cycle and Transmission The life cycle of *Pneumocystis* involves both sexual and asexual reproduction, and the organism exists as a trophic form, a cyst, and a precyst at various points. Serologic and molecular studies have demonstrated that most humans are exposed to *Pneumocystis* early in life. It was historically thought that *Pneumocystis* developed from reactivation of latent infection, but de novo infections from environmental sources and person-to-person transmission occur as well. Outbreaks of PCP suggest that nosocomial transmission can take place, and studies with rodents show that immunocompetent animals can serve as reservoirs for transmission of *P. carinii* (the infecting species in rodents) to immunocompetent and immunosuppressed animals. However, *Pneumocystis* organisms are species-specific. Thus, humans are infected only by other humans who transmit *P. jirovecii*; humans cannot be infected with species of *Pneumocystis* that infect other animals, such as *P. carinii* (rats), *P. murina* (mice), or *P. oryctolagi* (rabbits). The utility of respiratory isolation in preventing transmission from patients with PCP to other immunosuppressed individuals has been debated; no clear evidence exists, although it seems prudent to isolate patients with active PCP from other immunosuppressed patients.

Role of Immunity Defects in cellular and/or humoral immunity predispose to development of PCP. Such defects may be congenital, or they may be acquired as a result of HIV infection or of treatment with immunosuppressive drugs such as glucocorticoids, fludarabine, temozolomide, temsirolimus, cyclophosphamide, rituximab, or alemtuzumab. CD4+ T cells are critical in host defense against *Pneumocystis*. Among HIV-infected patients, the incidence is inversely related to the CD4+ T cell count: at least 80% of cases occur at counts of <200/μL, and most of these cases develop at counts of <100/μL. HIV load is another factor that predisposes patients to PCP. CD4+ T cell counts are less specific and thus less useful in predicting the risk of PCP in patients who are immunosuppressed for reasons other than HIV infection.

Lung Pathology *Pneumocystis* has a unique tropism for the lung. It is presumably inhaled into the alveolar space. Clinically apparent pneumonia occurs only if an individual is immunocompromised. *Pneumocystis* proliferates in the lung, provoking a mononuclear cell response. The alveoli become filled with proteinaceous material, and alveolar damage results in increased alveolar-capillary injury and surfactant abnormalities. Stained lung sections typically show foamy, vacuolated alveolar exudates composed largely of viable and nonviable organisms **(Fig. 215-1*A*)**. Interstitial edema and fibrosis may develop, and organisms can be seen in the alveolar space with silver or other stains. Moreover, the organisms can be seen when tissue is subjected to colorimetric or immunofluorescent staining **(Fig. 215-1*B–1D*)**.

CLINICAL FEATURES

Clinical Presentation PCP presents as acute or subacute pneumonia that may initially be characterized by a vague sense of dyspnea alone but that subsequently manifests as fever and nonproductive cough with progressive shortness of breath, ultimately resulting in respiratory failure and death. Extrapulmonary manifestations of PCP are rare but can include involvement of almost any organ, most notably lymph nodes, spleen, and liver.

Physical Examination The physical examination findings in PCP are nonspecific. Patients have decreased oxygen saturation—at rest or with exertion—that, without treatment, progresses to severe hypoxemia. Patients may initially have a normal chest examination and no adventitious sounds, but later develop diffuse rales and signs of consolidation.

Laboratory Findings The results of routine laboratory tests are nonspecific in PCP. Serum levels of lactate dehydrogenase (LDH) are often elevated as a result of pulmonary damage; however, a normal LDH level does not rule out PCP, nor is an elevated LDH value specific for PCP. The peripheral white blood cell count may be elevated in relation to the patient's baseline values, but the increase is usually modest. Hepatic and renal function are typically normal.

Radiographic Findings Although the initial chest radiograph may be normal when patients have mild symptoms, the classic radiographic appearance of symptomatic PCP consists of diffuse bilateral

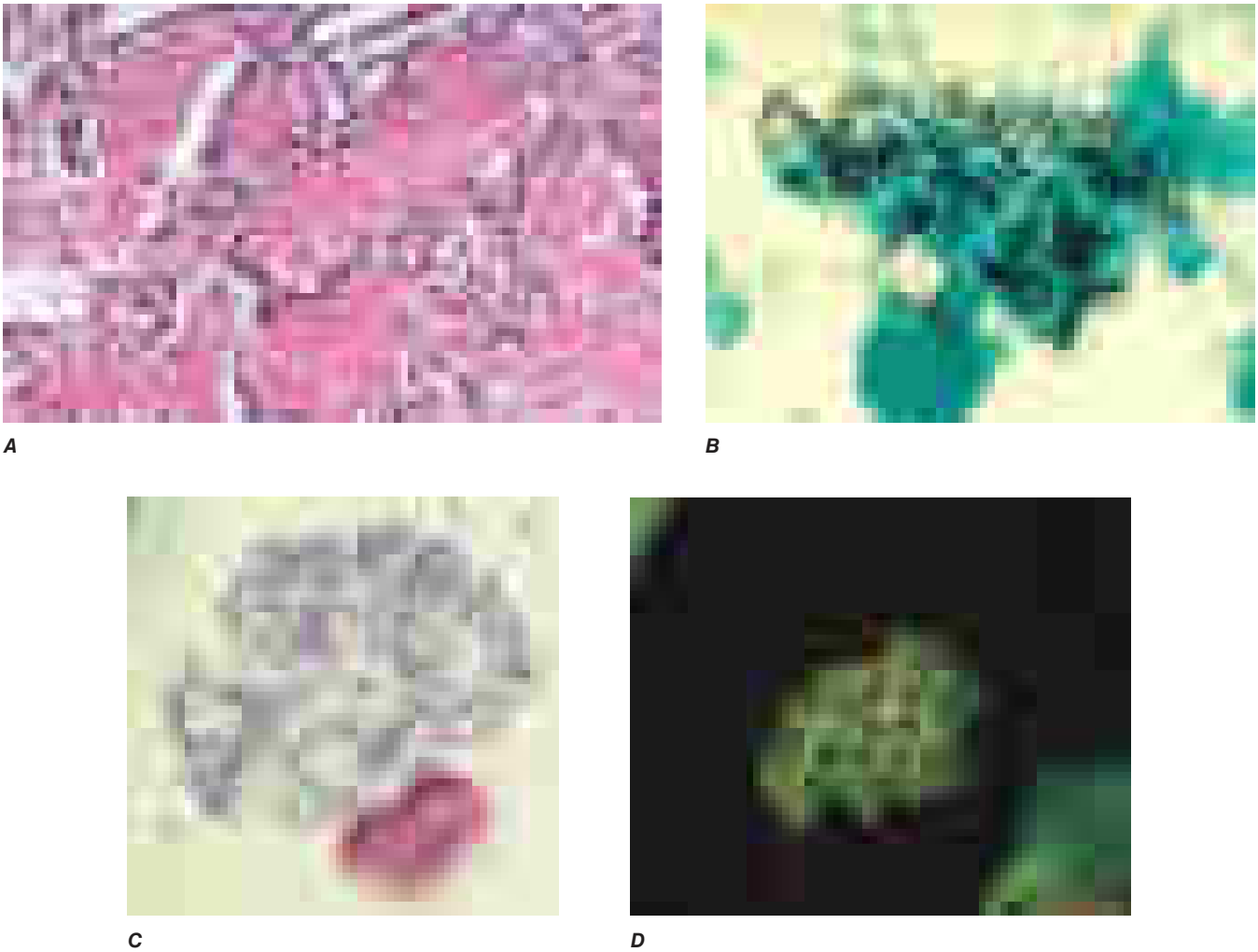

FIGURE 215-1 Direct microscopy of *Pneumocystis* pneumonia. ***A.*** Transbronchial lung biopsy stained with hematoxylin and eosin shows eosinophilic alveolar filling. ***B.*** Methenamine silver–stained bronchoalveolar lavage (BAL) fluid. ***C.*** Giemsa-stained BAL fluid. ***D.*** Immunofluorescent stain of BAL fluid.

interstitial infiltrates that are perihilar and symmetric (Fig. 215-2*A*)—yet another finding that is not specific for PCP. The interstitial infiltrates can progress to alveolar filling (Fig. 215-2*B*). High-resolution chest CT shows diffuse ground-glass opacities in virtually all patients with PCP (Fig. 215-2*C*). A normal chest CT essentially rules out the diagnosis of PCP. Cysts and pneumothoraces are common chest radiographic findings, especially in patients with HIV infection (Fig. 215-2*D*). A wide variety of atypical radiographic findings have been described, including asymmetric patterns, upper-lobe infiltrates, mediastinal adenopathy, nodules, cavities, and effusions.

DIAGNOSIS

The optimal sample for diagnostic examination depends on how ill the patient is and what resources are available. Before the 1990s, diagnoses of PCP were usually established by open lung biopsy; later, transbronchial lung biopsy was employed. Hematoxylin and eosin staining of pulmonary tissue demonstrates a foamy alveolar infiltrate and a mononuclear interstitial infiltrate (Fig. 215-1*A*). This appearance is pathognomonic for PCP even though the organisms cannot be specifically identified with this stain. The diagnosis is typically established in lung tissue or pulmonary secretions by highly specific staining of the cyst—e.g., with methenamine silver (Fig. 215-1*B*), toluidine blue O, or Giemsa (Fig. 215-1*C*)—or by staining with a specific immunofluorescent antibody (Fig. 215-1*D*).

The demonstration of organisms in bronchoalveolar lavage (BAL) fluid is almost 100% sensitive and specific for PCP in patients with HIV infection and is almost as sensitive in patients with immunosuppression due to other processes. The organisms are identified with the specific stains indicated above for lung biopsy. While expectorated sputum or throat swabs have very low sensitivity, an induced sputum sample obtained and interpreted by an experienced provider can be highly sensitive and specific. The reported sensitivity of induced sputum for PCP is widely variable (55–90%), however, and is dependent on both the characteristics of the patient and the experience of the center conducting the test.

Many laboratories now offer polymerase chain reaction (PCR) testing of respiratory specimens for *Pneumocystis* in preference to direct microscopy of appropriately stained respiratory secretions. However, these PCR tests are so sensitive that it is difficult to distinguish patients with colonization (i.e., those whose acute lung disease is due to some other process but who have low levels of *Pneumocystis* DNA in the lungs) from those with acute pneumonia due to *Pneumocystis*. Such PCR tests on appropriate samples may be more useful for ruling out a diagnosis of PCP if they are negative than for definitively attributing the disease to *Pneumocystis*.

There has been considerable interest in serologic tests such as assays for (1→3)-β-D-glucan, levels of which are frequently elevated in patients with PCP. However, no serologic assays developed to date offer both substantial sensitivity and specificity.

COURSE AND PROGNOSIS

Untreated, PCP is invariably fatal. Patients with HIV infection often have an indolent course that presents as mild exercise intolerance or chest tightness without fever or cough and a normal or nearly normal posterior–anterior chest radiograph, with progression over days, weeks, or even a few months to fever, cough, diffuse alveolar

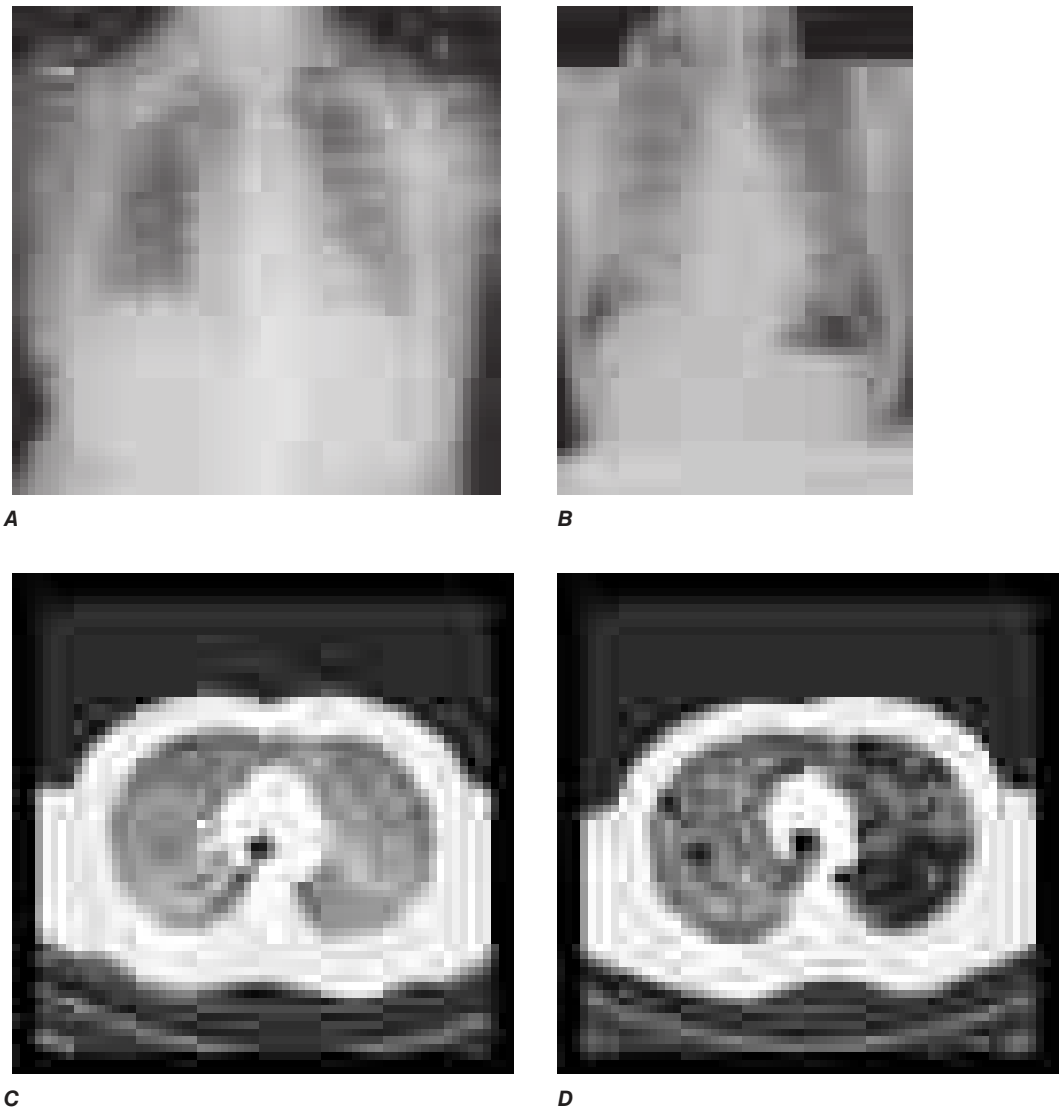

FIGURE 215-2 Radiographs in *Pneumocystis* pneumonia. *A.* Posterior–anterior chest radiograph showing symmetric interstitial infiltrates. ***B.*** Posterior–anterior chest radiograph showing symmetric alveolar infiltrates (courtesy of Alison Morris). ***C.*** CT image demonstrating symmetric interstitial infiltrates and ground-glass opacities. ***D.*** CT image showing symmetric interstitial infiltrates, ground-glass opacities, and pneumatoceles.

infiltrates, and profound hypoxemia. Some patients with HIV infection and most patients with other types of immunosuppression have more acute disease that progresses over a few days to respiratory failure. Rare patients also develop distributive shock. A few unusual patients present with extrapulmonary manifestations in the skin or soft tissue, retina, brain, liver, kidney, or spleen. Extrapulmonary disease is nonspecific in presentation and can be diagnosed only by histology.

Factors that influence mortality risk include the patient's age and degree of immunosuppression as well as comorbidities, the presence of preexisting lung disease, a low serum albumin level, the need for mechanical ventilation, and the development of a pneumothorax. With advances in supportive critical care, the prognosis for patients with PCP who require intubation and respiratory support has improved and now depends to a large extent on comorbidities and the prognosis of the underlying disease. Since patients typically do not respond to therapy for 4–8 days, supportive care for a minimum of 10 days is a reasonable consideration if such support is compatible with the patient's wishes and the prognosis of comorbidities. Patients whose condition continues to deteriorate after 3 or 4 days or has not improved after 7–10 days should be reevaluated to determine whether other infectious processes are present (either having been missed on initial evaluation or having developed during treatment), whether initial anti-*Pneumocystis* treatment has failed, or whether noninfectious processes (e.g., congestive heart failure, pulmonary emboli, pulmonary hypertension, drug toxicity, or a neoplastic process) are causing pulmonary dysfunction.

TREATMENT

P. jirovecii Pneumonia

The treatment of choice for PCP is trimethoprim-sulfamethoxazole (TMP-SMX), given either IV or PO for 14 days to non-HIV-infected patients with mild disease and for 21 days to all other patients **(Table 215-1)**. TMP-SMX, which interferes with the organism's folate metabolism, is at least as effective as alternative agents and is better tolerated. TMP-SMX can cause leukopenia, hepatitis, rash, and fever as well as anaphylactic and anaphylactoid reactions, and patients with HIV infection have an unusually high incidence of hypersensitivity to TMP-SMX. Monitoring of serum drug levels is useful if renal function or toxicities are issues. Maintenance of a 2-h post-dose serum sulfamethoxazole level of 100–150 μg/mL has been associated with a successful outcome. Resistance to TMP-SMX cannot be measured by organism growth inhibition in the laboratory because *Pneumocystis* cannot be cultured. However, mutations in the target gene for sulfamethoxazole that confer in vitro sulfa resistance to other organisms have been found in *Pneumocystis*. The clinical relevance of these mutations for the response to therapy is unknown. Sulfadiazine plus pyrimethamine, an oral regimen more often used for treatment of toxoplasmosis, also is highly effective. Dapsone plus pyrimethamine or dapsone plus trimethoprim also can be used.

TABLE 215-1 Treatment of Pneumocystosis[a]

DRUG(S)	DOSE, ROUTE	ADVERSE EFFECTS
First-Choice Agent		
TMP-SMX	TMP (5 mg/kg) plus SMX (25 mg/kg) q6–8h PO or IV (i.e., 2 double-strength tablets tid or qid)	Fever, rash, cytopenias, hepatitis, hyperkalemia
Alternative Agents		
Atovaquone	750 mg bid PO	Rash, fever, hepatitis
Clindamycin ***plus*** Primaquine	300–450 mg q6h PO or 600 mg q6–8h IV 15–30 mg qd PO	Hemolysis (G6PD deficiency), methemoglobinemia, neutropenia, rash
Pentamidine	3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias (torsades des pointes), pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Adjunctive Agent		
Prednisone or methylprednisolone	40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV	Peptic ulcer disease, hyperglycemia, mood alteration, hypertension

[a]Treatment can be administered for 14 days to non-HIV-infected patients with mild disease and for 21 days to all other patients.

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

Intravenous pentamidine or the combination of clindamycin plus primaquine is an option for patients who cannot tolerate TMP-SMX and for patients in whose treatment TMP-SMX appears to be failing. Pentamidine must be given IV over at least 60 min to avoid potentially lethal hypotension. Adverse effects can be severe and irreversible and include renal dysfunction, dysglycemia (life-threatening hypoglycemia that can occur days or weeks after initial infusion and be followed by hyperglycemia), neutropenia, and torsades des pointes. Clindamycin plus primaquine is effective, but primaquine can be given only by the oral route—a disadvantage for patients who cannot ingest or absorb oral drugs. Oral atovaquone is also a reasonable option for patients with mild disease who have no impediments to absorbing an oral drug that requires a high-fat meal for optimal absorption.

A major advance in therapy for PCP was the recognition that glucocorticoids could improve survival rates among HIV-infected patients with moderate to severe disease (room air PO_2, <70 mmHg; or alveolar–arterial oxygen gradient, ≥35 mmHg). Glucocorticoids appear to reduce the pulmonary inflammation that occurs after specific therapy is started and organisms begin to die, eliciting inflammation. Therapy with glucocorticoids should be the standard of care for patients with HIV infection and probably is also effective for patients with other immunodeficiencies. This treatment should be started for moderate or severe disease when therapy for PCP is initiated, even if the diagnosis has not yet been confirmed. If HIV-infected or HIV-uninfected patients are receiving high-dose glucocorticoids when they develop PCP, there are theoretical advantages to either increasing the steroid dose (to reduce the inflammatory response to the dying organisms) or decreasing the steroid dose (to improve immune function), but there is no convincing evidence on which to base any specific strategy.

No definitive trials have defined the best therapeutic algorithm for patients in whom TMP-SMX treatment for PCP is failing. If no other treatable infectious or noninfectious processes are detected and pulmonary dysfunction appears to be due to PCP alone, many authorities would switch from TMP-SMX to either IV pentamidine or IV clindamycin plus oral primaquine. Some authorities would add the second drug or drug combination to TMP-SMX rather than switching regimens. If patients are not already receiving them, glucocorticoids should be added to the regimen; the dosage and regimen, which are usually chosen empirically, depend on what glucocorticoid regimen (if any) the patient was receiving when PCP therapy was begun.

For patients with HIV infection who present with PCP before the initiation of ART, ART should be started within the first 2 weeks of therapy for PCP in most situations. Immune reconstitution inflammatory syndrome (IRIS) can occur, however, and the decision to initiate ART thus requires considerable expertise in optimal timing relative to PCP recovery as well as in the other factors that are relevant when ART is initiated in any patient.

PREVENTION

The most effective method for preventing PCP is to eliminate the cause of immunosuppression by withdrawing immunosuppressive therapy or treating the underlying cause (e.g., HIV infection). Patients who are susceptible to PCP benefit from chemoprophylaxis during the period of susceptibility. For patients with HIV infection, CD4+ T cell counts are a reliable marker of susceptibility, and counts below 200/μL are an indication to start prophylaxis **(Table 215-2)**.

For patients who are immunosuppressed as a result of factors other than HIV infection, there is no laboratory parameter, including the CD4+ T cell count, that predicts susceptibility to PCP with adequate positive and negative accuracy. The period of susceptibility is usually estimated on the basis of experience with the underlying disease and immunosuppressive regimen. Premature cessation of prophylaxis has been associated with clusters of cases in certain patient populations, such as solid-organ transplant recipients. Patients receiving a prolonged course of high-dose glucocorticoids appear to be particularly susceptible to PCP. The glucocorticoid exposure threshold that warrants chemoprophylaxis is controversial, but such preventive therapy should be strongly considered for any patient who is receiving more than the equivalent of 20 mg of prednisone daily for 30 days or who is receiving glucocorticoids in conjunction with other immunosuppressive agents. Clinical experience also suggests that chemoprophylaxis is useful for patients receiving certain immunosuppressive agents (e.g., tumor necrosis factor inhibitors, antithymocyte globulin, rituximab, and alemtuzumab). The duration of such chemoprophylaxis is empirically determined by clinical and laboratory indicators of immunologic vulnerability.

TABLE 215-2 Prophylaxis of Pneumocystosis

DRUG(S)	DOSE, ROUTE	COMMENTS
First-Choice Agent		
TMP-SMX	1 tablet (double- or single-strength) qd PO	Incidence of hypersensitivity is high. Rechallenge for non-life-threatening hypersensitivity; consider dose-escalation protocol.
Alternative Agents		
Dapsone	50 mg bid or 100 mg qd PO	Hemolysis is associated with G6PD deficiency.
Dapsone ***plus*** Pyrimethamine ***plus*** Leucovorin	50 mg qd PO 50 mg weekly PO 25 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Dapsone ***plus*** Pyrimethamine ***plus*** Leucovorin	200 mg weekly PO 75 mg weekly PO 25 mg weekly PO	Leucovorin ameliorates cytopenias due to pyrimethamine.
Pentamidine	300 mg monthly via Respirgard II nebulizer	Aerosol may cause bronchospasm. Pentamidine is probably less effective than TMP-SMX or dapsone regimens.
Atovaquone	1500 mg qd PO	Requires fatty meal for optimal absorption

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim-sulfamethoxazole.

TMP-SMX is the most effective prophylactic drug; few patients experience a PCP breakthrough when they are reliably taking a recommended TMP-SMX chemoprophylactic regimen. Several TMP-SMX regimens have been used successfully. One double-strength tablet daily is the regimen with which there is the most experience, but either one single-strength tablet daily or one double-strength tablet two or three times weekly also has been recommended for various populations of patients.

For patients who cannot tolerate TMP-SMX (usually because of hypersensitivity or bone marrow suppression), alternative drugs include daily dapsone, weekly dapsone-pyrimethamine, atovaquone, and monthly aerosol pentamidine. Patients who develop hypersensitivity to TMP-SMX can sometimes tolerate the drug if a gradual dose-escalation protocol is used. Dapsone cross-reacts with sulfonamides in a substantial fraction of patients and therefore is rarely useful in patients with a history of life-threatening reactions to TMP-SMX. Aerosolized pentamidine is highly effective, but it is not as effective as TMP-SMX and may not provide protection in areas of the lung that are not well ventilated. Atovaquone is also effective and well tolerated; however, this drug is available only as an oral preparation, and gastrointestinal absorption is unpredictable in patients with abnormal gastrointestinal motility or function.

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Section 17 Protozoal and Helminthic Infections: General Considerations

216 Introduction to Parasitic Infections

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The word *parasite* comes originally from the Greek *parasitos* (*para*, alongside of; and *sitos*, food), meaning someone who eats at another's table or lives at another's expense. Although the same is true of many bacteria and viruses, the designation *parasite* is reserved, by convention, for helminths and protozoa. These organisms are larger and more complex than bacteria, with a eukaryotic cell structure similar to that of human host cells. Historically, this similarity has made it difficult to find effective antiparasitic agents that do not cause unacceptable toxicity to human cells. Fortunately, intensive research and modern techniques have now provided suitable agents for safe and effective treatment of most parasitic infections. **See Chap. S14 for details on diagnostic procedures and Chap. 217 for details on treatment.**

Internal parasites of human beings are divided into two types: helminths (worms) and protozoa. *Helminths* are multicellular organisms that can be seen with the naked eye **(Chap. 225)**. There are two phyla: Platyhelminthes (flat worms) and Nemathelminthes (roundworms). Both phyla include some genera that mature in the gastrointestinal tract and others that migrate through the tissue after ingestion or skin penetration. **Tables S14-1 and S14-2** present the helminthic genera, their definitive and intermediate hosts, geographic distributions, and the parasitic stages in the human body.

The key to understanding which helminths use humans as definitive hosts is to remember that helminth ova develop into larvae, and larval stages develop into adults. Humans serve as the definitive host when they ingest helminth larvae, which develop into adults in the intestine and usually cause mild disease, often without any symptoms. (The exception is ingestion of the late-stage larvae of the somatic or tissue flukes, as shown in **Table S14-2**.) In contrast, if humans ingest helminth ova and serve as the intermediate host, the ova develop into larvae, which penetrate the intestine, migrate through the tissue, and invade organs where they mature into adults. Intermediate hosts with parasitic invasion of organs may experience severe disease.

Protozoa are microscopic single-celled organisms. Among the many differences between helminths and protozoans, the most important is the ability of protozoa (like bacteria) to multiply within the human body and cause overwhelming infections. A major mechanism promoting unrestrained growth is evasion of the host immune response either by antigenic variation (*Trypanosoma brucei*) or by survival inside host cells (e.g., *Plasmodium*, *Babesia*, *Cryptosporidium*, *Leishmania*, and *Toxoplasma*). In contrast, almost all helminths require stages in other hosts to complete their life cycles and multiply. As a result, except for *Strongyloides* and *Capillaria*, which can complete their life cycle in humans, increases in the burden of infection with helminths require repeated exogenous reinfections. Thus permanent residents of endemic countries, who are exposed repeatedly, may have heavy severe infections, while most travelers with one or two exposures are unlikely to experience the full spectrum of chronic helminthic infections.

In contrast to helminthic infections, naïve patients with their first protozoal infection usually are the most severely affected because partial immunity often limits the number of parasites during recurrent infections. Protozoan replication to large numbers in the host also promotes the development of drug-resistant forms, especially in malaria **(Chap. 217)**. Because protozoa belong to many different phyla, it is easier to understand the pathogenesis and management of protozoal infections when they are classified by the site of infection (intestinal protozoans, free-living amebae, and blood and tissue protozoans) **(Table S14-3)**. Immunocompromised hosts are at risk of disseminated infection with a number of protozoa, including *Leishmania*, *Toxoplasma*, *Cryptosporidium*, *and Trypanosoma cruzi*, which are AIDS-defining illnesses. In contrast, *Strongyloides* is the only helminth to disseminate.

HELMINTHIC INFECTIONS

The Platyhelminthes (flatworms) are categorized as tapeworms (cestodes) and flukes (trematodes). Tapeworms are composed of a head or scolex bearing the holdfast organs and segments, which become gravid as they mature. Some tapeworms can reach lengths of many yards; the longest tapeworms develop in the intestine, where they rarely cause serious disease. In contrast, flukes are small leaf-shaped organisms whose size is not a measure of disease severity.

FLATWORMS

Cestodes Tapeworms cause either intestinal or somatic infection, depending on the species. *Intestinal* infections occur when the human

host ingests larvae in the tissue of the intermediate host, whereas *somatic* infections occur when humans accidentally ingest ova excreted from the wild or domesticated definitive animal host.

INTESTINAL TAPEWORMS As shown in **Table S14-1**, humans acquire most intestinal tapeworms by eating the insufficiently cooked flesh of the intermediate host. Thus *Taenia saginata* is commonly called the beef tapeworm, *Taenia solium* the pork tapeworm, and *Diphyllobothrium latum* the fish tapeworm. *Hymenolepis nana* is capable of completing its life cycle in the human intestine and is acquired by ingestion of infected grain beetles or of ova from infected humans or mice. None of these parasites causes significant damage, and infection is usually asymptomatic. There are two occasional exceptions. When people ingest *T. solium* ova from their own intestine or from another infected individual, it can cause somatic infection. *D. latum* avidly absorbs vitamin B_{12} in the intestine and can cause pernicious anemia in 1–2% of infected Scandinavians with a genetic predisposition.

SOMATIC TAPEWORMS There are three major causes of somatic tapeworm infections. Two species of *Echinococcus* cause echinococcosis. *E. granulosus* is acquired by accidental ingestion of ova from dogs infected when fed the infected tissues of sheep or other animals by sheepherders or hunters. *E. multilocularis* is transmitted primarily in sub-Arctic areas when humans ingest ova from foxes, dogs, or cats that have been infected through consumption of the tissues of infected rodents. Both species cause hydatid cysts when the eggs hatch into larvae, penetrate the intestine, and migrate into the liver or lung. Ingested *T. solium* ova cause somatic disease (cysticercosis) when the larvae penetrate the intestine, migrate into tissue, and form cysts (*cysterci*), usually in the muscles or central nervous system (CNS).

Trematodes Flukes also cause both intestinal and somatic infections **(Chap. 229 and Table S14-1)**. Most fluke infections are localized to Asia, Africa, Southeast Asia, or the Pacific islands. Infection with intestinal flukes is usually asymptomatic, although heavy infections sometimes cause abdominal discomfort and mucous diarrhea. Liver flukes and lung flukes cause somatic infections when humans ingest a larval form from an intermediate host. Adults develop in the intestine, migrate into adjacent tissues, and cause disease. The major liver flukes (*Clonorchis sinensis*, *Opisthorchis* spp., and *Fasciola hepatica*) are causes of recurrent bacterial cholangitis (due to obstruction) or portal hypertension and cirrhosis. Only *F. hepatica* can be acquired worldwide; it is especially common in sheep-raising areas, where the animals ingest water plants (e.g., watercress). The lung flukes (*Paragonimus* spp.) occur globally except in North America and Europe; most lesions occur as pulmonary cysts, although occasional lesions develop in the CNS or the abdominal cavity.

The blood flukes cause schistosomiasis, one of the most common and serious parasitic infections **(Chap. 229 and Table S14-1)**. The major species are *Schistosoma mansoni*, S. *haematobium*, and *S. japonicum*. All are transmitted to humans when free-swimming larvae exit an infected snail in freshwater and penetrate the skin. Swimmer's itch sometimes follows skin penetration but is usually of short duration. The larvae then wander in the skin until they find a blood vessel and migrate to the target organ. *S. mansoni* and *S. japonicum* migrate to the mesentery vessels and eventually make their way to the liver, while *S. haematobium* targets the veins around the ureter and bladder. Extensive egg deposition by *S. mansoni* and *S. japonicum* and the immune reactions to the ova cause granuloma formation and, with many repeated exposures, portal vein obstruction and cirrhosis. The same process in the ureters and bladders during infection with *S. haematobium* eventually interferes with urine flow and leads to repeated urinary tract infections and kidney damage.

ROUNDWORMS

Nematodes Roundworms are nonsegmented bisexual organisms. The species that infect humans include intestinal and tissue groups. Humans may also acquire certain nonhuman mammalian roundworms that either can be limited to the skin or can migrate to tissues and cause serious disease (the larva migrans syndromes).

INTESTINAL ROUNDWORMS The major intestinal roundworms are *Ascaris lumbricoides*, *Necator americanus* (New World hookworms), *Ancylostoma duodenale* (Old World hookworms), *Trichuris trichiura* (whipworms), *Enterobius vermicularis* (pinworms), and *Strongyloides stercoralis*. Taken together, infections caused by intestinal roundworms are the most common infections in the world. *Ascaris*, hookworms, and *Trichuris* each infect about 1 billion individuals, and at least 30–100 million have strongyloidiasis. These infections are most common in resource-poor developing countries, especially where people defecate outside and/or human feces is used as fertilizer ("night soil"). Infection is transmitted either by ingestion of ova (*A. lumbricoides*, *T. trichiura*, and *E. vermicularis*) or by active penetration of the skin by larvae (hookworms and *S. stercoralis* **(Table S14-2)**.

Intestinal roundworms cause serious health problems in residents of endemic regions with poor sanitation, but travelers are at low risk of developing significant disease from most of these parasites. Intestinal blockage and malnutrition from heavy *Ascaris* infections and anemia from heavy hookworm infections are now restricted to areas of heavy endemicity. Except in the case of *Strongyloides* and *Capillaria*, which can reproduce in the body, multiple exposures over time are necessary for the development of severe disease. S*trongyloides* infection persists over decades and can disseminate when the immune system is compromised. Although *Capillaria* remains localized to the intestine, infections can become so heavy that protein-losing enteropathy and malnutrition cause serious disease.

The life cycles of *Ascaris* and the hookworms involve migration through the heart and lungs before development into adults in the intestine. In particular, *Ascaris* occasionally causes eosinophilic pneumonia (Loeffler's syndrome) during heavy infections. Pinworms are the most common causes of intestinal roundworm infection persisting in the United States and other developed countries. The anal and perineal itching caused by pinworm migration out of the anus and subsequent egg deposition is well known to families throughout the world.

TISSUE ROUNDWORMS The major diseases caused by tissue roundworms are filariasis, angiostrongyliasis, gnathostomiasis, and trichinellosis. By far the most important globally is filariasis; the thread-like filarial worms infect more than 150 million individuals, and almost 1 billion are at risk in sub-Saharan Africa and other poor tropical countries. Four filarial species cause three distinct diseases: lymphatic filariasis (*Wuchereria bancrofti* and *Brugia malayi*), river blindness (*Onchocercus volvulus*), and loiasis (*Loa loa*, the African eye worm). Humans, the major reservoir, acquire these infections from bites of infected arthropods **(Table S14-2)**. The larvae develop into adults, which remain static in tissue: the lymphatics for lymphatic filariasis and subcutaneous tissue for *O. volvulus* and *L. loa*. After adults mate, next-stage larvae are produced, and their migration causes additional damage.

Repeated bouts of migrating larvae and blocking of the lymphatics by adults are necessary to establish the syndrome of lymphatic filariasis; thus it is unusual for the short-term traveler (<3 months' residence in an endemic region) to develop significant disease. In river blindness, the larvae produced by adult *O. volvulus* migrate through the skin and eye, causing skin damage and eventual blindness. Loiasis is a milder disease restricted to central and western Africa. Although both the adults and the larvae of *L. loa* migrate through the skin and eye, many infected individuals are asymptomatic, and the infection is often diagnosed only when an adult worm migrates across the subconjunctival tissue and is visible to the patient and the physician. Red lumps in the skin from heavy cutaneous migration are called *Calabar swellings*.

The other four major roundworm tissue infections are acquired by ingestion of larvae in undercooked food. The sources for trichinellosis are swine and other large mammals; for gnathostomiasis, freshwater fish and chicken; for ancylostomiasis, snails, fish, prawns, and crabs; and for Guinea worm, infected water fleas. Guinea worm infection (dracunculiasis, caused by *Dracunculus medinensis*) has been almost eradicated. *Trichinella spiralis* larvae penetrate the intestine and migrate widely, with a preference for skeletal tissue; the release of eosinophils and IgE causes muscle soreness and may cause palpebral swelling and other manifestations of generalized allergic reactions. *Angiostrongylus cantonensis* is the most common parasitic cause of eosinophilic meningitis. Ingested larvae penetrate the intestine and migrate to the brain and meninges, where they quickly die and attract massive numbers

of eosinophils. Although complications can occur, most individuals recover spontaneously. *Gnathostoma spinigerum* larvae also penetrate the intestine and migrate, showing a preference for the skin, eyes, and meninges. Mechanical damage from the migration and inflammation produced by the resultant immune reaction can cause boil-like lesions on the skin, painful eye damage, and eosinophilic meningitis. Although eosinophilic meningitis caused by *G. spinigerum* is less common than that caused by *A. cantonensis*, it is often more severe and can result in paralysis or brain hemorrhage.

PROTOZOAL INFECTIONS

INTESTINAL PROTOZOA

Entamoeba histolytica is the one intestinal protozoan that causes invasive disease. This disease consists of dysentery or bloody diarrhea that must be differentiated from that due to bacteria such as *Salmonella*, *Campylobacter*, and *Shigella.* Although amebiasis usually has a slower onset with lower fever than these bacterial infections, *E. histolytica* can disseminate from the bloodstream to cause distant abscesses, particularly of the liver. The diagnosis cannot be made by identification of the characteristic cyst or trophozoites **(Chap. 218)** as they are identical to those of the noninvasive *E. dispar*, which is more common globally.

Cryptosporidium and *Giardia* are the most common water-borne protozoal infections. *Cryptosporidium* can cause major outbreaks because it is highly infectious and resistant to high levels of chlorine **(Chap. 224)**. Without immune reconstitution, immunosuppressed patients, particularly those with AIDS, can develop severe, even fatal watery diarrhea. Infections caused by the remaining intestinal protozoans—*Giardia*, *Isospora*, *Cyclospora*, and microsporidia **(Chap. 224)**—have a much more indolent course, with intermittent diarrhea. Microsporidia, unique intracellular protozoa that form infectious spores, may cause limited gastrointestinal infection in immunocompetent hosts, but patients with AIDS can develop chronic diarrhea and wasting or disseminated infection to the biliary or respiratory tract.

FREE-LIVING AMEBAS

The free-living amebas *Acanthamoeba* and *Naegleria* are found worldwide in freshwater and brackish water **(Chap. 218 and Table S14-3)**. Organisms of these two genera cause very different syndromes. In immunocompromised individuals, *Acanthamoeba* usually causes invasive infection, with brain masses and skin lesions. However, all humans are susceptible to *Acanthamoeba* keratitis after trauma to the eye and exposure to contaminated water. In contrast, naeglerial meningitis, acquired in warm lakes or hot springs, causes sudden pyogenic and usually fatal meningitis. *Balamuthia*, reported only from the Americas, causes indolent meningoencephalitis, with both cerebrospinal fluid pleocytosis and a space-occupying lesion, in immunocompetent patients. Despite the availability of miltefosine, which is active in vitro against *Naegleria*, infection of the CNS is almost universally fatal.

BLOOD AND TISSUE PROTOZOANS

Plasmodium* and *Babesia Malaria, caused by six species of *Plasmodium,* carries higher mortality rates than any other parasitic infection **(Chap. 219)**. All species are transmitted in tropical and subtropical areas by female *Anopheles* mosquitoes. *Plasmodium falciparum* is most common in sub-Saharan Africa, where it causes more than 80% of malaria infections and 90% of malarial deaths. Infection with *P. falciparum* may be particularly severe because the organism can invade any erythrocyte, reaches very high parasite loads, damages organs by adhering to vascular epithelium, and is the most likely *Plasmodium* species to be resistant to antimalarial drugs. *Plasmodium vivax,* the dominant cause of malaria outside sub-Saharan Africa, reaches lower levels of parasitemia and exhibits less drug resistance because it invades only reticulocytes with Duffy antigen. Many Africans, especially in the western part of the continent, lack the Duffy blood group; consequently, *Plasmodium ovale*, another cause of milder malaria, can compete successfully with *P. vivax*. Both *P. vivax* and *P. ovale* produce persistent liver forms, which must be treated with primaquine **(Chap. 217)**. Because malaria can cause a variety of symptoms ranging from acute fever to coma, this diagnosis must be considered in any traveler or immigrant from a malarial area. *Babesia* also infects erythrocytes and may cause a nonspecific febrile illness or, in asplenic patients, severe infection. This parasite is carried by ixodid ticks and is geographically limited to the northeastern and midwestern United States, with only sporadic cases in Europe and other temperate areas.

Trypanosomes The three species of trypanosomes all have flagellated bloodstream forms, but they cause very different diseases. *T. cruzi*, the cause of Chagas disease, is transmitted in South and Central America in the feces of blood-sucking reduviid bugs **(Chap. 222)**. After initial parasitemia, patients are often asymptomatic for years while the parasite multiplies intracellularly in muscle and ganglion cells. Although only a minority of patients go on to develop organ damage (megaesophagus and cardiomyopathy), all infected patients can spread the disease through transfusions, mother-to-child transmission, and organ transplants.

African trypanosomiasis is limited to sub-Saharan Africa, where it is transmitted by the bite of a tsetse fly. A history of a tsetse bite and the presence of a painful chancre are strong diagnostic clues **(Chap. 222)**. Although the parasites causing this disease in western Africa (*Trypanosoma brucei gambiense*) and eastern Africa (*T. brucei rhodesiense*) look identical, they are genetically and clinically distinct. *T. b. gambiense* causes low-level parasitemia with cyclical fevers over months or years before CNS invasion, while *T. b. rhodesiense* causes high-level parasitemia, invades the CNS early on, and can lead to death within weeks of onset.

Leishmania Leishmaniasis is caused by more than 20 species of obligate intracellular protozoa transmitted by sandflies, which are present in almost 100 countries in tropical and temperate zones **(Chap. 221)**. A wide spectrum of clinical symptoms result, ranging from self-healing, painless skin ulcers to mucocutaneous disease with destruction of the nose and palate to disseminated visceral leishmaniasis with hepatic and splenic involvement. The resulting disease depends on the infecting strain and the host immune response. Visceral leishmaniasis can present as an acute febrile illness, with the later development of hepatosplenomegaly, and is an AIDS-defining illness in HIV-infected patients. More than 90% of cases of visceral leishmaniasis occur in India, Bangladesh, Ethiopia, Sudan, and Brazil.

Toxoplasma *Toxoplasma gondii* is an obligate intracellular parasite that is found worldwide. Infection follows ingestion of oocysts in food or water contaminated by cat feces, ingestion of tissue cysts in undercooked meat, or transplacental transmission. After gastrointestinal invasion, tachyzoites can invade any nucleated cell and cause lifelong infection in most patients **(Chap. 223)**. Clinical manifestations depend on the host's age and immune status at the time of infection. Congenital toxoplasmosis results from primary maternal infection; outcomes are most severe early in pregnancy and include visual, hearing, and cognitive impairments. Babies infected later in pregnancy may appear normal but can develop chorioretinitis decades later. Primary infection in immunocompetent hosts may be asymptomatic, may present as an infectious mononucleosis–like syndrome, or may manifest as chorioretinitis during outbreaks. During immunosuppression by AIDS or organ transplantation, reactivation of latent cerebral infection can be fatal unless diagnosed and treated early.

APPROACH TO THE PATIENT

Parasitic Infection

A thorough history and physical examination are the keys to diagnosis of any disease and particularly of parasitic infections. Because many of the more serious parasitic infections are uncommon in the United States, a travel history, particularly to developing nations, is a critical component. The longer the stay in an area endemic for significant parasitic infections, the greater the risk, even for healthy travelers. In addition, other factors increase the chance of acquiring these infections. Notably, immunocompromise greatly increases the likelihood of developing some of the more serious parasitic infections.

Even healthy travelers with adventure itineraries, extensive travel to rural areas, or involvement in war zones or refugee camps are at increased risk. Immigrants from developing countries may seek care for symptoms or signs associated with parasitic infections.

Information on the patient's immunization history and adherence to appropriate malarial chemoprophylaxis is critical. Although no vaccines against parasitic infections are commercially available, the likelihood of many viral and bacterial infections is much lower if the patient has been properly immunized. For example, typhoid fever is much less likely to be the cause of prolonged fever in an immunized individual. Similarly, hepatitis A or B is unlikely to be the cause of jaundice and fever in fully immunized patients. In this era of increasing drug resistance, even adherence to appropriate malarial chemoprophylaxis does not guarantee that fever is not malarial. Nevertheless, most travelers who acquire malaria have taken inadequate or no prophylaxis. Although these considerations do not prove that the symptoms are caused by parasites, they narrow the differential diagnosis.

There are many other important aspects of the history, including when symptoms began. Was the individual still in the endemic area at the time, or did the symptoms commence after return to the United States? If they started during travel, was any treatment received? If the patient was well upon return from travel, the timing of symptom onset is a critical point. For example, if the chief manifestation is fever that began >10–14 days after departure from the endemic region, many tropical diseases can be ruled out, including dengue fever, chikungunya fever, and Zika virus infection. On the other hand, fever beginning several months or later after return makes malaria a likely diagnosis. Travelers' diarrhea, the most common complaint of travelers, is usually caused by bacteria or viruses and resolves in a short time with or without treatment. Travelers' diarrhea that persists for weeks is much more likely to be parasitic in origin.

Most patients who consult physicians after international travel either have troublesome symptoms or have been referred for symptoms or signs whose source was unclear to a referring caregiver. After a careful travel history including the individual's symptoms and the exact geographic zones visited, a thorough physical examination must be conducted. The symptoms, signs, and physical findings should help to establish possible diagnoses. **Table 216-1** breaks down the symptoms of major parasitic infections by organ system and geographic distribution, with comments on clinical and epidemiologic associations.

TABLE 216-1 Parasitic Infections, by Organ System and Signs/Symptoms[a]

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Skin			
Serpentine rash	Hookworm	Worldwide	Can cause anemia in heavy infections
	Strongyloides	Moist tropics and subtropics	Disseminated infection in immunocompromise
	Toxocara (animal roundworm)	Tropical and temperate zones	Cutaneous or visceral larva migrans
Itchy skin rash	*Onchocerca*	Mexico, Central/South America, Africa	Larvae detectable in skin snips and nodules
Painless ulcers	*Leishmania*	Tropics and subtropics	Amastigotes detectable in biopsies; may cause destructive mucocutaneous infection; AIDS-defining infection
Skin nodules	*Onchocerca*	Mexico, South America, Africa	Large nodules of adult worms
	Loa loa (African eye worm)	Western and central Africa	Migratory nodules
	Gnathostoma	Southeast Asia and China	Migratory nodules with eosinophilia
Painful nodules, especially involving feet	*Dracunculus* (Guinea worm)	Africa	Nearly eradicated
Central Nervous System			
Somnolence, seizures, coma	*Plasmodium falciparum*	Subtropics and tropics	Cerebral malaria, especially in children
	Trypanosoma brucei rhodesiense	Sub-Saharan eastern Africa	Painful chancre from tsetse fly bite; death in weeks to months
Space-occupying lesions, seizures	*Acanthamoeba*	Worldwide	Immunocompromised individuals
	Balamuthia	Americas	Indolent meningoencephalitis with brain mass
	Toxoplasma	Worldwide	Reactivation disease in immunocompromise; ring-enhancing lesions; AIDS-defining infection
	Taenia solium	Mexico, Central/South America, Africa	Cysticercosis; variable sized or calcified larval cysts on CT
	Schistosoma japonicum	Far East	Aberrant eggs can form brain or spinal cord masses.
	Schistosoma mansoni	Africa, Central/South America	Aberrant eggs can form brain or spinal cord masses.
Pyogenic meningitis	*Naegleria*	Worldwide	Motile trophozoites in fresh cerebrospinal fluid; rapid death
Eosinophilic meningitis	*Angiostrongylus* (rat lung worm)	Southeast Asia, Pacific, Caribbean	Most common cause globally; spontaneous resolution
	Gnathostoma	Southeast Asia and China	Migratory nodules
Eyes			
Painful corneal ulcers	*Acanthamoeba*	Worldwide	Freshwater and brackish water; corneal trauma; long-wear contact lenses
Corneal opacification	*Onchocerca*	Mexico, Central/South America, Africa	Immune response to microfilaria in cornea
Congenital or adult visual loss	*Toxoplasma*	Worldwide	Primary infection in pregnancy and subsequent primary or reactivation infection
Retinal mass	*Toxocara*	Worldwide	Ocular larva migrans
Visible roundworm in eye	*Onchocerca*	Mexico, Central/South America, Africa	Worms may cross eye during migration.
	L. loa	Western and central Africa	Worms may cross eye during migration.
Pain, possible vision loss	*Gnathostoma*	Southeast Asia and China	Migratory skin nodules, eosinophilia

(*Continued*)

TABLE 216-1 Parasitic Infections, by Organ System and Signs/Symptoms[a] (Continued)

ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S)	PARASITE(S)	GEOGRAPHIC DISTRIBUTION	COMMENTS
Lungs			
Pulmonary nodule/ abscess	*Paragonimus*	Far East , Africa, Americas	Ectopic migration to abdomen or central nervous system
Cough, transient infiltrates, eosinophilia	Migrating helminths	Worldwide	Loeffler's syndrome from migrating *Ascaris*, hookworm, *Strongyloides*
Heart			
Pulmonary edema	*P. falciparum* (complication)	Tropics and subtropics	End-organ damage from severe malaria
Cardiomegaly, arrhythmias	*Trypanosoma cruzi*	Mexico, Central/South America	Late amastigote infection of myocardium; AIDS-defining infection
Gastrointestinal Tract			
Hepatosplenomegaly	Malaria (multiple episodes)	Tropics and subtropics	Splenomegaly with anemia and recurrent fever are hallmarks of malaria.
	S. mansoni	Africa, Central/South America	Portal obstruction with cirrhosis and late varices
	Leishmania donovani complex	Tropics and subtropics	Visceral leishmaniasis; AIDS-defining infection
Hepatomegaly	*Entamoeba histolytica*	Tropics	Acute with fever, right-upper-quadrant pain; or chronic with enlarged liver; hypoechoic abscess(es) on ultrasound or CT
	Echinococcus	Sheep-raising areas	Characteristic cysts of liver > lung
	Fasciola	Sheep-raising areas	Eosinophilia
Cholangitis	*Clonorchis*	China, Southeast Asia	Recurrent cholangitis and late cholangiocarcinoma
	Microsporidia	Worldwide	AIDS
	Cryptosporidium	Worldwide	AIDS-defining infection
Bloody diarrhea	*E. histolytica*	Tropics	Less fever than in diarrhea of bacterial etiology
	S. mansoni	Africa, Central/South America	Only in heavy, acute infection with fever and eosinophilia
	S. japonicum	Far East	Only in heavy, acute infection
Watery diarrhea	*Cryptosporidium*	Worldwide	Severe in immunocompromised patients
	Giardia	Worldwide	Foul-smelling stool with steatorrhea
	Isospora belli	Worldwide	Fever, abdominal pain, chronic diarrhea
	Microsporidia	Worldwide	Chronic diarrhea with AIDS
	Capillaria	Southeast Asia, Egypt	Malabsorption, wasting
Passage of large roundworm (>6 cm)	*Ascaris*	Worldwide	Patients may confuse the roundworm with an earthworm.
Small roundworms visible around anus	Pinworm	Worldwide	Anal itching; eggs rarely detected by ova and parasite (O&P) exam
	Trichuris	Worldwide	Rectal prolapse with heavy infection in children
Passage of tapeworm segments	*T. solium* or *Taenia saginata*	Worldwide	Usual reason for seeking medical care
	Diphyllobothrium latum	Worldwide	Pernicious anemia in genetically predisposed Scandinavians
Genitourinary System			
Itchy discharge	*Trichomonas vaginalis*	Worldwide	Common sexually transmitted disease of both sexes
Hematuria	*Schistosoma haematobium*	Africa	Hematuria with negative cultures, urinary tract infections, and late bladder cancer
Muscular System			
Myalgias, myositis	*Trichinella*	Worldwide	Palpebral swelling; high-level eosinophilia
Bloodstream			
Fever without localizing symptoms	*Plasmodium*	Tropics and subtropics	Consider in any patient from a malarious area.
	Babesia	New England, United States	Geographically limited; worse with splenectomy
	T. brucei rhodesiense, *T. brucei gambiense*	Sub-Saharan Africa	Limited to tsetse fly range; painful chancre; adenopathy and cyclical fevers; early (*rhodesiense*) or late (*gambiense*) central nervous system involvement
	Filariae	Asia, India	Periodic fever with eosinophilia, adenolymphangitis, chronic lymphangitis
	L. donovani complex	Tropics and subtropics	Hepatosplenomegaly, fever, wasting; AIDS-defining infection

[a]See also text and **Tables S14-1, S14-2, and S14-3** for vectors and routes of transmission.

FURTHER READING

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217 Agents Used to Treat Parasitic Infections

Thomas A. Moore

Parasitic infections continue to afflict more than half of the world's population and impose a substantial health burden, particularly in underdeveloped nations, where they are most prevalent. The reach of some parasitic diseases, including malaria, has expanded over the past few decades as a result of factors such as deforestation, population shifts, global warming, and other climatic events. Although there have been significant advances in vaccine development and vector control, chemotherapy remains the single most effective means of controlling parasitic infections. Efforts to combat the spread of some diseases are hindered by the development and spread of drug resistance, the limited introduction of new antiparasitic agents, the proliferation of counterfeit medications, and, most recently, profiteering, which has dramatically increased the cost of once-affordable agents. However, there are good reasons to be optimistic. Ambitious global initiatives aimed at controlling or eliminating threats such as AIDS, tuberculosis, and malaria have demonstrated successes. The ongoing efforts of multinational partnerships to address the substantial burden imposed by neglected tropical diseases have generated mechanisms to develop and deploy effective antiparasitic agents. In addition, the development of vaccines against several tropical diseases, including malaria, continues.

This chapter deals exclusively with the agents used to treat infections due to parasites. Specific treatment recommendations for the parasitic diseases of humans are listed in subsequent chapters. Many of the agents discussed herein are approved by the U.S. Food and Drug Administration (FDA), but are considered investigational for the treatment of certain infections. Drugs marked in the text with an asterisk (*) are available through the Centers for Disease Control and Prevention (CDC) Drug Service (telephone: 404-639-3670; email: drugservice@cdc.gov; *www.cdc.gov/ncpdcid/dsr/*). Drugs marked with a dagger (†) are available only through their manufacturers; contact information for these manufacturers may be available from the CDC.

Table 217-1 presents a brief overview of each agent (including some drugs that are covered in other chapters), along with major toxicities, spectrum of activity, and safety for use during pregnancy and lactation.

Albendazole Like all benzimidazoles, albendazole acts by selectively binding to free β-tubulin in nematodes, inhibiting the polymerization of tubulin and the microtubule-dependent uptake of glucose. Irreversible damage occurs in gastrointestinal (GI) cells of the nematodes, resulting in starvation, death, and expulsion by the host. This fundamental disruption of cellular metabolism offers treatment for a wide range of parasitic diseases.

Albendazole is poorly absorbed from the GI tract, a feature that is advantageous for the treatment of intestinal helminths but not for that of tissue helminth infections (e.g., hydatid disease and neurocysticercosis), which requires that a sufficient amount of active drug reach the site of infection. Administration with a high-fat meal (~40 g) increases the drug's absorption by up to fivefold. The metabolite albendazole sulfoxide is responsible for the drug's therapeutic effect outside the gut lumen. Albendazole sulfoxide crosses the blood–brain barrier, reaching a level significantly higher than that achieved in plasma. The high concentrations of albendazole sulfoxide attained in cerebrospinal fluid (CSF) may explain the efficacy of albendazole in the treatment of neurocysticercosis.

Albendazole is extensively metabolized in the liver, but there are few data regarding the drug's use in patients with hepatic disease. Single-dose albendazole therapy in humans is largely without side effects (overall frequency, ≤1%). More prolonged courses (e.g., as administered for cystic and alveolar echinococcal disease) have been associated with liver function abnormalities and bone marrow toxicity. Thus, when prolonged use is anticipated, the drug should be administered in treatment cycles of 28 days interrupted by 14-day intervals off therapy. Prolonged therapy with full-dose albendazole (800 mg/d) should be approached cautiously in patients also receiving drugs with known effects on the cytochrome P450 system.

Amodiaquine Amodiaquine has been widely used in the treatment of malaria for >60 years. Like chloroquine (the other major 4-aminoquinoline), amodiaquine is now of limited use because of the spread of resistance. Amodiaquine interferes with hemozoin formation through complexation with heme. It is rapidly absorbed and acts as a prodrug after oral administration; the principal plasma metabolite, monodesethylamodiaquine, is the predominant antimalarial agent. Amodiaquine and its metabolites are all excreted in urine, but there are no recommendations concerning dosage adjustment in patients with impaired renal function. Agranulocytosis and hepatotoxicity can develop with repeated use; therefore, this drug should not be used for prophylaxis. Despite widespread resistance, amodiaquine is effective in some areas when combined with other antimalarial drugs (e.g., artesunate, sulfadoxine-pyrimethamine), particularly in children. Although on the World Health Organization's *List of Essential Medicines*, amodiaquine is not yet available in the United States.

Amphotericin B **See** Table 217-1 and **Chap. 206.**

Antimonials* Despite associated adverse reactions and the need for prolonged parenteral treatment, the pentavalent antimonial compounds (designated Sb^v) have remained the first-line therapy for all forms of leishmaniasis throughout the world, primarily because they are affordable and effective and have survived the test of time. Pentavalent antimonials are active only after bioreduction to the trivalent Sb(III) form, which inhibits trypanothione reductase, a critical enzyme involved in the oxidative stress management of *Leishmania* species. The fact that *Leishmania* species use trypanothione rather than glutathione (which is used by mammalian cells) may explain the parasite-specific activity of antimonials. The drugs are taken up by the reticuloendothelial system, and their activity against *Leishmania* species may be enhanced by this localization. Sodium stibogluconate is the only pentavalent antimonial available in the United States; meglumine antimoniate is used principally in francophone countries.

Resistance is a major problem in some areas. Although low-level unresponsiveness to Sb^v was identified in India in the 1970s, incremental increases in both the recommended daily dosage (to 20 mg/kg) and the duration of treatment (to 28 days) satisfactorily compensated for the growing resistance until around 1990. There has since been steady erosion in the capacity of Sb^v to induce long-term cure in patients with kala-azar who live in eastern India. Co-infection with HIV impairs the treatment response.

Sodium stibogluconate is available in aqueous solution and is administered parenterally. Antimony appears to have two elimination phases. When the drug is administered IV, the mean half-life of the first phase is <2 h; the mean half-life of the terminal elimination phase is nearly 36 h. This slower phase may be due to conversion of pentavalent antimony to a trivalent form that is the likely cause of the side effects often seen with prolonged therapy.

Artemisinin Derivatives* Artesunate, artemether, artemotil, and the parent compound artemisinin are sesquiterpene lactones derived from the wormwood plant *Artemisia annua*. These agents are at least tenfold more potent in vivo than other antimalarial drugs and presently show no cross-resistance with known antimalarial drugs; thus, they have become first-line agents for the treatment of severe falciparum malaria. The artemisinin compounds are rapidly effective against the asexual blood forms of *Plasmodium* species but are not active against intrahepatic forms. With the exception of artesunate, artemisinin and its derivatives are highly lipid soluble and readily cross both host and parasite cell membranes. One factor that explains the drugs' highly selective toxicity against malaria is that parasitized erythrocytes concentrate artemisinin and its derivatives to concentrations 100-fold higher than those in uninfected erythrocytes. The antimalarial effect of these agents results primarily from the active

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
4-Aminoquinolines					
Amodiaquine	Malaria[b]	Agranulocytosis, hepatotoxicity	No information	Not assigned	Yes[c]
Chloroquine	Malaria[b]	*Occasional:* pruritus, nausea, vomiting, headache, hair depigmentation, exfoliative dermatitis, reversible corneal opacity *Rare:* irreversible retinal injury, nail discoloration, blood dyscrasias	Antacids and kaolin: reduced absorption of chloroquine Ampicillin: bioavailability reduced by chloroquine Cimetidine: increased serum levels of chloroquine Cyclosporine: serum levels increased by chloroquine	Not assigned[d]	Yes[c]
Piperaquine	Malaria[b]	*Occasional:* GI disturbances	None reported	Not assigned	Yes
8-Aminoquinolines					
Primaquine	Malaria[b]	*Frequent:* hemolysis in patients with G6PD deficiency *Occasional:* methemoglobinemia, GI disturbances *Rare:* CNS symptoms	Quinacrine: potentiated toxicity of primaquine	Contraindicated	Yes
Tafenoquine	Malaria[b]	*Frequent:* hemolysis in patients with G6PD deficiency, mild GI upset *Occasional:* methemoglobinemia, headaches	No information	Not assigned	Yes
Aminoalcohols					
Halofantrine	Malaria[b]	*Frequent:* abdominal pain, diarrhea *Occasional:* ECG disturbances (dose-related prolongation of QTc and PR interval), nausea, pruritus; contraindicated in persons who have cardiac disease or who have taken mefloquine in the preceding 3 weeks	Concomitant use of agents that prolong QTc interval contraindicated	C	No information
Lumefantrine	Malaria[b]	*Occasional:* nausea, vomiting, diarrhea, abdominal pain, anorexia, headache, dizziness	Plasma levels increased by darunavir and nevirapine, decreased by etravirine	Not assigned	No information
Aminoglycosides					
Paromomycin	Amebiasis,[b] infection with *Dientamoeba fragilis*, giardiasis, cryptosporidiosis, leishmaniasis	*Frequent:* GI disturbances (oral dosing only) *Occasional:* nephrotoxicity, ototoxicity, vestibular toxicity (parenteral dosing only)	No major interactions	Oral: B Parenteral: not assigned[d]	No information
Amphotericin B Amphotericin B deoxycholate Amphotec (InterMune) Amphotericin B lipid complex, ABLC (Abelcet) Amphotericin B, liposomal (AmBisome)	Leishmaniasis,[e] amebic meningoencephalitis	*Frequent:* fever, chills, hypokalemia, hypomagnesemia, nephrotoxicity *Occasional:* vomiting, dyspnea, hypotension	Antineoplastic agents: renal toxicity, bronchospasm, hypotension Glucocorticoids, ACTH, digitalis: hypokalemia Zidovudine: increased myelo- and nephrotoxicity	B	No information
Antimonials Pentavalent antimony[f] Meglumine antimoniate	Leishmaniasis	*Frequent:* arthralgias/myalgias, pancreatitis, ECG changes (QT prolongation, T wave flattening or inversion)	No major interactions Antiarrhythmics and tricyclic antidepressants: increased risk of cardiotoxicity	Not assigned Not assigned	Yes No information
Artemisinin and derivatives Arteether Artemether Artesunate[f] Dihydroartemisinin	Malaria[g]	*Occasional:* neurotoxicity (ataxia, convulsions), nausea, vomiting, anorexia, contact dermatitis	No information Artemether levels decreased by darunavir, etravirine, and nevirapine Mefloquine: levels decreased and clearance accelerated by artesunate Mefloquine: increased absorption	Not assigned C C Not assigned	Yes[c] Yes[c] Yes[c] Yes[c]

(*Continued*)

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections (Continued)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Atovaquone	Malaria,[b] babesiosis	*Frequent:* nausea, vomiting *Occasional:* abdominal pain, headache	Plasma levels decreased by rifampin, tetracycline, atazanavir, efavirenz, lopinavir/ritonavir; bioavailability decreased by metoclopramide	C	No information
Azoles Fluconazole Itraconazole Ketoconazole	Leishmaniasis	*Serious:* hepatotoxicity *Rare:* exfoliative skin disorders, anaphylaxis	Warfarin, oral hypoglycemics, phenytoin, cyclosporine, theophylline, digoxin, dofetilide, quinidine, carbamazepine, rifabutin, busulfan, docetaxel, vinca alkaloids, pimozide, alprazolam, diazepam, midazolam, triazolam, verapamil, atorvastatin, cerivastatin, lovastatin, simvastatin, tacrolimus, sirolimus, indinavir, ritonavir, saquinavir, alfentanil, buspirone, methylprednisolone, trimetrexate: plasma levels increased by azoles Carbamazepine, phenobarbital, phenytoin, isoniazid, rifabutin, rifampin, antacids, H_2-receptor antagonists, proton pump inhibitors, nevirapine: decreased plasma levels of azoles Clarithromycin, erythromycin, indinavir, ritonavir: increased plasma levels of azoles	C	Yes
Benzimidazoles					
Albendazole	Ascariasis, capillariasis, clonorchiasis, cutaneous larva migrans, cysticercosis,[b] echinococcosis,[b] enterobiasis, eosinophilic enterocolitis, gnathostomiasis, hookworm, lymphatic filariasis, microsporidiosis, strongyloidiasis, trichinellosis, trichostrongyliasis, trichuriasis, visceral larva migrans	*Occasional:* nausea, vomiting, abdominal pain, headache, reversible alopecia, elevated aminotransferases *Rare:* leukopenia, rash	Dexamethasone, praziquantel: plasma level of albendazole sulfoxide increased by ~50%	C	Yes[c]
Mebendazole	Ascariasis,[b] capillariasis, eosinophilic enterocolitis, enterobiasis,[b] hookworm,[b] trichinellosis, trichostrongyliasis, trichuriasis,[b] visceral larva migrans	*Occasional:* diarrhea, abdominal pain, elevated aminotransferases *Rare:* agranulocytosis, thrombocytopenia, alopecia	Cimetidine: inhibited mebendazole metabolism	C	No information
Thiabendazole	Strongyloidiasis,[b] cutaneous larva migrans,[b] visceral larva migrans[b]	*Frequent:* anorexia, nausea, vomiting, diarrhea, headache, dizziness, asparagus-like urine odor *Occasional:* drowsiness, giddiness, crystalluria, elevated aminotransferases, psychosis *Rare:* hepatitis, seizures, angioneurotic edema, Stevens-Johnson syndrome, tinnitus	Theophylline: serum levels increased by thiabendazole	C	No information
Triclabendazole	Fascioliasis, paragonimiasis	*Occasional:* abdominal cramps, diarrhea, biliary colic, transient headache	No information	Not assigned	Yes
Benznidazole	Chagas disease	*Frequent:* rash, pruritus, nausea, leukopenia, paresthesias	No major interactions	Not assigned	No information

(*Continued*)

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections (Continued)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Clindamycin	Babesiosis, malaria, toxoplasmosis	*Occasional:* pseudomembranous colitis, abdominal pain, diarrhea, nausea/vomiting *Rare:* pruritus, skin rashes	No major interactions	B	Yes[c]
Diloxanide furoate	Amebiasis	*Frequent:* flatulence *Occasional:* nausea, vomiting, diarrhea *Rare:* pruritus	None reported	Contraindicated	No information
Eflornithine[h] (difluoromethylornithine, DFMO)	Trypanosomiasis	*Frequent:* pancytopenia *Occasional:* diarrhea, seizures *Rare:* transient hearing loss	No major interactions	Contraindicated	No information
Emetine and dehydroemetine[f]	Amebiasis, fascioliasis	*Severe:* cardiotoxicity *Frequent:* pain at injection site *Occasional:* dizziness, headache, GI symptoms	None reported	X	No information
Folate antagonists					
Dihydrofolate reductase inhibitors					
Pyrimethamine	Malaria,[b] isosporiasis, toxoplasmosis[b]	*Occasional:* folate deficiency *Rare:* rash, seizures, severe skin reactions (toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome)	Sulfonamides, proguanil, zidovudine: increased risk of bone marrow suppression when used concomitantly	C	Yes
Proguanil and chlorproguanil	Malaria	*Occasional:* urticaria *Rare:* hematuria, GI disturbances	Atazanavir, efavirenz, lopinavir/ritonavir: plasma levels of proquanil decreased	C	Yes
Trimethoprim	Cyclosporiasis, isosporiasis	Hyperkalemia, GI upset, mild stomatitis	Methotrexate: reduced clearance Warfarin: effect prolonged Phenytoin: hepatic metabolism increased	C	Yes
Dihydropteroate synthetase inhibitors: sulfonamides Sulfadiazine Sulfamethoxazole Sulfadoxine	Malaria,[b] toxoplasmosis[b]	*Frequent:* GI disturbances, allergic skin reactions, crystalluria *Rare:* severe skin reactions (toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome), agranulocytosis, aplastic anemia, hypersensitivity of the respiratory tract, hepatitis, interstitial nephritis, hypoglycemia, aseptic meningitis	Thiazide diuretics: increased risk of thrombocytopenia in elderly patients Warfarin: effect prolonged by sulfonamides Methotrexate: levels increased by sulfonamides Phenytoin: metabolism impaired by sulfonamides Sulfonylureas: effect prolonged by sulfonamides	B	Yes
Dihydropteroate synthetase inhibitors: sulfones					
Dapsone	Leishmaniasis, malaria, toxoplasmosis	*Frequent:* rash, anorexia *Occasional:* hemolysis, methemoglobinemia, neuropathy, allergic dermatitis, anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis *Rare:* agranulocytosis	Rifampin: lowered plasma levels of dapsone	C	Yes
Fumagillin	Microsporidiosis	*Rare:* neutropenia, thrombocytopenia	None reported	No information	No information
Furazolidone	Giardiasis	*Frequent:* nausea/vomiting, brown urine *Occasional:* rectal itching, headache *Rare:* hemolytic anemia, disulfiram-like reactions, MAO inhibitor interactions	Risk of hypertensive crisis when administered for >5 days with MAO inhibitors	C	No information
Iodoquinol	Amebiasis,[b] balantidiasis, *D. fragilis* infection	*Occasional:* headache, rash, pruritus, thyrotoxicosis, nausea, vomiting, abdominal pain, diarrhea *Rare:* optic neuritis, peripheral neuropathy, seizures, encephalopathy	No major interactions	C	No information

(*Continued*)

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections (Continued)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Ivermectin	Ascariasis, cutaneous larva migrans, gnathostomiasis, loiasis, lymphatic filariasis, onchocerciasis,[b] scabies, strongyloidiasis,[b] trichuriasis	*Occasional:* fever, pruritus, headache, myalgias *Rare:* hypotension	No major interactions	C	Yes[c]
Macrolides					
Azithromycin	Babesiosis	*Occasional:* nausea, vomiting, diarrhea, abdominal pain *Rare:* angioedema, cholestatic jaundice	Cyclosporine and digoxin: levels increased by azithromycin Nelfinavir: increased levels of azithromycin	B	Yes
Spiramycin[h]	Toxoplasmosis	*Occasional:* GI disturbances, transient skin eruptions *Rare:* thrombocytopenia, QT prolongation in an infant, cholestatic hepatitis	No major interactions	Not assigned[d]	Yes[c]
Mefloquine	Malaria[b]	*Frequent:* lightheadedness, nausea, headache *Occasional:* confusion; nightmares; insomnia; visual disturbance; transient and clinically silent ECG abnormalities, including sinus bradycardia, sinus arrhythmia, first-degree AV block, prolongation of QTc interval, and abnormal T waves *Rare:* psychosis, convulsions, hypotension	Administration of halofantrine <3 weeks after mefloquine use may produce fatal QTc prolongation. Mefloquine may lower plasma levels of anticonvulsants. Levels are decreased and clearance is accelerated by artesunate. Mefloquine decreases plasma levels of ritonavir and possibly other protease inhibitors.	C	Yes
Melarsoprol[f]	Trypanosomiasis	*Frequent:* myocardial injury, encephalopathy, peripheral neuropathy, hypertension *Occasional:* G6PD-induced hemolysis, erythema nodosum leprosum *Rare:* hypotension	No major interactions	Not assigned	No information
Metrifonate	Schistosomiasis	*Frequent:* abdominal pain, nausea, vomiting, diarrhea, headache, vertigo, bronchospasm *Rare:* cholinergic symptoms	No major interactions	B	No
Miltefosine	Leishmaniasis,[b] primary amebic meningoencephalitis	*Frequent:* mild and transient (1–2 days) GI disturbances within first 2 weeks of therapy (resolve after treatment completion); motion sickness *Occasional:* reversible elevations of creatinine and aminotransferases	No major interactions	Not assigned	No information
Niclosamide	Intestinal cestode infections[b]	*Occasional:* nausea, vomiting, dizziness, pruritus	No major interactions	B	No information
Nifurtimox[f]	Chagas disease	*Frequent:* nausea, vomiting, abdominal pain, insomnia, paresthesias, weakness, tremors *Rare:* seizures (all reversible and dose-related)	No major interactions	Not assigned	No information
Nitazoxanide	Cryptosporidiosis,[b] giardiasis[b]	*Occasional:* abdominal pain, diarrhea *Rare:* vomiting, headache	Increases plasma levels of highly protein-bound drugs (e.g., phenytoin, warfarin)	B	No information
Nitroimidazoles					
Metronidazole	Amebiasis,[b] balantidiasis, dracunculiasis, giardiasis, trichomoniasis,[b] *D. fragilis* infection	*Frequent:* nausea, headache, anorexia, metallic aftertaste *Occasional:* vomiting, insomnia, vertigo, paresthesias, disulfiram-like effects *Rare:* seizures, peripheral neuropathy	Warfarin: effect enhanced by metronidazole Disulfiram: psychotic reaction Phenobarbital, phenytoin: accelerate elimination of metronidazole Lithium: serum levels elevated by metronidazole Cimetidine: prolonged half-life of metronidazole Oral solutions of antiretrovirals containing alcohol: disulfiram effect due to alcohol	B	Yes

(*Continued*)

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections (Continued)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Tinidazole	Amebiasis,[b] giardiasis, trichomoniasis	*Occasional:* nausea, vomiting, metallic taste	See metronidazole	C	Yes
Oxamniquine	Schistosomiasis	*Occasional:* dizziness, drowsiness, headache, orange urine, elevated aminotransferases *Rare:* seizures	No major interactions	C	No information
Pentamidine isethionate	Leishmaniasis, trypanosomiasis	*Frequent:* hypotension, hypoglycemia, pancreatitis, sterile abscesses at IM injection sites, GI disturbances, reversible renal failure *Occasional:* hepatotoxicity, cardiotoxicity, delirium *Rare:* anaphylaxis	No major interactions	C	No information
Piperazine and derivatives					
Piperazine	Ascariasis, enterobiasis	*Occasional:* nausea, vomiting, diarrhea, abdominal pain, headache *Rare:* neurotoxicity, seizures	None reported	C	No information
Diethylcarbamazine[f]	Lymphatic filariasis, loiasis, tropical pulmonary eosinophilia	*Frequent:* dose-related nausea, vomiting *Rare:* fever, chills, arthralgias, headaches	None reported	Not assigned[d]	No information
Praziquantel	Clonorchiasis,[b] cysticercosis, diphyllobothriasis, hymenolepiasis, taeniasis, opisthorchiasis, intestinal trematodes, paragonimiasis, schistosomiasis[b]	*Frequent:* abdominal pain, diarrhea, dizziness, headache, malaise *Occasional:* fever, nausea *Rare:* pruritus, singultus	No major interactions	B	Yes
Pyrantel pamoate	Ascariasis, eosinophilic enterocolitis, enterobiasis,[b] hookworm, trichostrongyliasis	*Occasional:* GI disturbances, headache, dizziness, elevated aminotransferases	No major interactions	C	No information
Pyronaridine	Malaria	*Occasional:* headache, nausea	None reported to date	B	Yes
Quinacrine[h]	Giardiasis[b]	*Frequent:* headache, nausea, vomiting, bitter taste *Occasional:* yellow-orange discoloration of skin, sclerae, urine; begins after 1 week of treatment and lasts up to 4 months after drug discontinuation *Rare:* psychosis, exfoliative dermatitis, retinopathy, G6PD-induced hemolysis, exacerbation of psoriasis, disulfiram-like effects	Primaquine: toxicity potentiated by quinacrine	C	No information
Quinine and quinidine	Malaria, babesiosis	*Frequent:* cinchonism (tinnitus, high-tone deafness, headache, dysphoria, nausea, vomiting, abdominal pain, visual disturbances, postural hypotension), hyperinsulinemia resulting in life-threatening hypoglycemia *Occasional:* deafness, hemolytic anemia, arrhythmias, hypotension due to rapid IV infusion	Carbonic anhydrase inhibitors, thiazide diuretics: reduced renal elimination of quinidine Amiodarone, cimetidine: increased quinidine levels Nifedipine: decreased quinidine levels; quinidine slows metabolism of nifedipine Phenobarbital, phenytoin, rifampin: accelerated hepatic elimination of quinidine Verapamil: reduced hepatic clearance of quinidine Diltiazem: decreased clearance of quinidine	X	Yes[c]

(*Continued*)

TABLE 217-1 Overview of Agents Used for the Treatment of Parasitic Infections (Continued)

DRUGS BY CLASS	PARASITIC INFECTION(S)	ADVERSE EFFECTS	MAJOR DRUG–DRUG INTERACTIONS	PREGNANCY CLASS[a]	BREAST MILK
Quinolones					
Ciprofloxacin	Cyclosporiasis, isosporiasis	*Occasional:* nausea, diarrhea, vomiting, abdominal pain/discomfort, headache, restlessness, rash *Rare:* myalgias/arthralgias, tendon rupture, CNS symptoms (nervousness, agitation, insomnia, anxiety, nightmares or paranoia); convulsions	Probenecid: increased serum levels of ciprofloxacin Theophylline, warfarin: serum levels increased by ciprofloxacin	C	Yes
Suramin[f]	Trypanosomiasis	*Frequent:* immediate: fever, urticaria, nausea, vomiting, hypotension; delayed (up to 24 h): exfoliative dermatitis, stomatitis, paresthesias, photophobia, renal dysfunction *Occasional:* nephrotoxicity, adrenal toxicity, optic atrophy, anaphylaxis	No major interactions	Not assigned	No information
Tetracyclines	Balantidiasis, *D. fragilis* infection, malaria; lymphatic filariasis (doxycycline)	*Frequent:* GI disturbances *Occasional:* photosensitivity dermatitis *Rare:* exfoliative dermatitis, esophagitis, hepatotoxicity	Warfarin: effect prolonged by tetracyclines	D	Yes

[a]Based on U.S. Food and Drug Administration (FDA) pregnancy categories of A–D, X. [b]Approved by the FDA for this indication. [c]Not believed to be harmful. [d]Use in pregnancy is recommended by international organizations outside the United States. [e]Only AmBisome has been approved by the FDA for this indication. [f]Available through the CDC. [g]Only artemether (in combination with lumefantrine) and artesunate have been approved by the FDA for this indication. [h]Available through the manufacturer.

Abbreviations: ACTH, adrenocorticotropic hormone; AV, atrioventricular; CNS, central nervous system; ECG, electrocardiogram; G6PD, glucose 6-phosphate dehydrogenase; GI, gastrointestinal; MAO, monoamine oxidase.

metabolite dihydroartemisinin; in the presence of heme or molecular iron, the endoperoxide moiety of dihydroartemisinin decomposes, generating free radicals and other metabolites that damage parasite proteins. The compounds are available for oral, rectal, IV, or IM administration, depending on the derivative. In the United States, IV artesunate is available for the treatment of severe, quinidine-unresponsive malaria through the CDC malaria hotline (770-488-7788 or 855-856-4713 [toll-free], M–F, 0800–1630 EST; 770-488-7100 after hours). Artemisinin and its derivatives are cleared rapidly from the circulation. Their short half-lives limit their value for prophylaxis and monotherapy. Side effects appear to be minor, although sinus bradycardia and transient first-degree heart block have been reported. Although seen in animal models, embryotoxicity and neurotoxicity have not been identified in humans despite active investigation. These agents should be used only in combination with another, longer-acting agent (e.g., artesunate-mefloquine, dihydroartemisinin-piperaquine). A combined formulation of artemether and lumefantrine is available for the treatment of acute uncomplicated falciparum malaria acquired in areas where *Plasmodium falciparum* is resistant to chloroquine and antifolates.

Atovaquone Atovaquone is a hydroxynaphthoquinone that exerts broad-spectrum antiprotozoal activity via selective inhibition of parasite mitochondrial electron transport. This agent exhibits potent activity against toxoplasmosis and babesiosis when used with pyrimethamine and azithromycin, respectively. Atovaquone possesses a novel mode of action against *Plasmodium* species, inhibiting the electron transport system at the level of the cytochrome bc1 complex. The drug is active against both the erythrocytic and the exoerythrocytic stages of *Plasmodium* species; however, because it does not eradicate hypnozoites from the liver, patients with *Plasmodium vivax* or *Plasmodium ovale* infections must be given radical prophylaxis.

Malarone® is a fixed-dose combination of atovaquone and proguanil used for malaria prophylaxis as well as for the treatment of acute, uncomplicated *P. falciparum* malaria. Malarone has been shown to be effective in regions with multidrug-resistant *P. falciparum*. Resistance to atovaquone develops rapidly via mutations in the parasite's mitochondrial cytochrome b complex. However, the mutations result in sterility of female parasites; thus, atovaquone-resistant parasites cannot be transmitted to another person. This situation may explain why clinical resistance has yet to be reported.

The bioavailability of atovaquone varies considerably. Absorption after a single oral dose is slow, increases two- to threefold with a fatty meal, and is dose-limited above 750 mg. The elimination half-life is increased in patients with moderate hepatic impairment. Because of the potential for drug accumulation, the use of atovaquone is generally contraindicated in persons with a creatinine clearance rate <30 mL/min. No dosage adjustments are needed in patients with mild to moderate renal impairment.

Azithromycin See Table 217-1 and Chap. 139.

Azoles See Table 217-1 and Chap. 206.

Benznidazole* This oral nitroimidazole derivative is used to treat Chagas disease, with cure rates of 80–90% recorded in acute infections. Benznidazole is believed to exert its trypanocidal effects by generating oxygen radicals to which the parasites are more sensitive than mammalian cells because of a relative deficiency in antioxidant enzymes. Benznidazole also appears to alter the balance between pro- and anti-inflammatory mediators by downregulating the synthesis of nitrite, interleukin (IL) 6, and IL-10 in macrophages. Benznidazole is highly lipophilic and readily absorbed. The drug is extensively metabolized; only 5% of the dose is excreted unchanged in the urine. Benznidazole is well tolerated; adverse effects are rare and usually manifest as GI upset or pruritic rash.

Chloroquine This 4-aminoquinoline has marked, rapid schizonticidal and gametocidal activity against blood forms of *P. ovale* and *Plasmodium malariae* and against susceptible strains of *P. vivax* and *P. falciparum*. It is not active against intrahepatic forms (*P. vivax* and *P. ovale*). Parasitized erythrocytes accumulate chloroquine in significantly greater concentrations than do normal erythrocytes. Chloroquine, a weak base, concentrates in the food vacuoles of intraerythrocytic parasites because of a relative pH gradient between the extracellular space and the acidic food vacuole. Once it enters the acidic food vacuole, chloroquine is rapidly converted to a membrane-impermeable protonated form and is trapped. Continued accumulation of chloroquine in the parasite's acidic food vacuoles results in drug levels that are 600-fold higher at this site than in plasma. The high accumulation of chloroquine results in an increase in pH within the food vacuole to a level above that required for the acid proteases' optimal activity, inhibiting parasite heme polymerase; as a result, the parasite is effectively killed with

its own metabolic waste. Compared with susceptible strains, chloroquine-resistant plasmodia transport chloroquine out of intraparasitic compartments more rapidly and maintain lower chloroquine concentrations in their acid vesicles. Hydroxychloroquine, a congener of chloroquine, is equivalent to chloroquine in its antimalarial efficacy but is preferred to chloroquine for the treatment of autoimmune disorders because it produces less ocular toxicity when used in high doses.

Chloroquine is well absorbed. However, because it exhibits extensive tissue binding, a loading dose is required to yield effective plasma concentrations. A therapeutic drug level in plasma is reached 2–3 h after oral administration (the preferred route). Chloroquine can be administered IV, but excessively rapid parenteral administration can result in seizures and death from cardiovascular collapse. The mean half-life of chloroquine is 4 days, but the rate of excretion decreases as plasma levels decline, making once-weekly administration possible for prophylaxis in areas with sensitive strains. About one-half of the parent drug is excreted in urine, but the dose should not be reduced for persons with acute malaria and renal insufficiency.

Ciprofloxacin See Table 217-1 and Chap. 139.

Clindamycin See Table 217-1 and Chap. 139.

Dapsone See Table 217-1 and Chap. 176.

Dehydroemetine Emetine is an alkaloid derived from ipecac; dehydroemetine is synthetically derived from emetine and is considered less toxic. Both agents are active against *Entamoeba histolytica* and appear to work by blocking peptide elongation and thus inhibiting protein synthesis. Emetine is rapidly absorbed after parenteral administration, rapidly distributed throughout the body, and slowly excreted in the urine in unchanged form. Both agents are contraindicated in patients with renal disease.

Diethylcarbamazine* A derivative of the antihelminthic agent piperazine with a long history of successful use, diethylcarbamazine (DEC) remains the treatment of choice for lymphatic filariasis and loiasis and has also been used for visceral larva migrans. Although piperazine itself has no antifilarial activity, the piperazine ring of DEC is essential for the drug's activity. DEC's mechanism of action remains to be fully defined. Proposed mechanisms include immobilization due to inhibition of parasite cholinergic muscle receptors, disruption of microtubule formation, and alteration of helminthic surface membranes resulting in enhanced killing by the host's immune system. DEC enhances adherence properties of eosinophils. The development of resistance under drug pressure (i.e., a progressive decrease in efficacy when the drug is used widely in human populations) has not been observed, although DEC has variable effects when administered to persons with filariasis. Monthly administration provides effective prophylaxis against both bancroftian filariasis and loiasis.

DEC is well absorbed after oral administration, with peak plasma concentrations reached within 1–2 h. No parenteral form is available. The drug is eliminated largely by renal excretion, with <5% found in feces. If more than one dose is to be administered to an individual with renal dysfunction, the dose should be reduced commensurate with the reduction in creatinine clearance rate. Alkalinization of the urine prevents renal excretion and increases the half-life of DEC. Use in patients with onchocerciasis can precipitate a Mazzotti reaction, with pruritus, fever, and arthralgias. Like other piperazines, DEC is active against *Ascaris* species. Patients co-infected with this nematode may expel live worms after treatment.

Diloxanide Furoate Diloxanide furoate, a substituted acetanilide, is a luminally active agent used to eradicate the cysts of *E. histolytica*. After ingestion, diloxanide furoate is hydrolyzed by enzymes in the lumen or mucosa of the intestine, releasing furoic acid and the ester diloxanide; the latter acts directly as an amebicide.

Diloxanide furoate is given alone to asymptomatic cyst passers. For patients with active amebic infections, diloxanide is generally administered in combination with a 5-nitroimidazole such as metronidazole or tinidazole. Diloxanide furoate is rapidly absorbed after oral administration. When coadministered with a 5-nitroimidazole, diloxanide levels peak within 1 h and disappear within 6 h. About 90% of an oral dose is excreted in the urine within 48 h, chiefly as the glucuronide metabolite. Diloxanide furoate is contraindicated in pregnant and breast-feeding women and in children <2 years of age.

Eflornithine* Eflornithine (difluoromethylornithine, or DFMO) is a fluorinated analogue of the amino acid ornithine. Although originally designed as an antineoplastic agent, eflornithine has proven effective against some trypanosomatids.

Eflornithine has specific activity against all stages of infection with *Trypanosoma brucei gambiense*; however, it is inactive against *Trypanosoma brucei rhodesiense*. The drug acts as an irreversible suicide inhibitor of ornithine decarboxylase, the first enzyme in the biosynthesis of the polyamines putrescine and spermidine. Polyamines are essential for the synthesis of trypanothione, an enzyme required for the maintenance of intracellular thiols in the correct redox state and for the removal of reactive oxygen metabolites. However, polyamines are also essential for cell division in eukaryotes, and ornithine decarboxylase is similar in trypanosomes and mammals. The selective antiparasitic activity of eflornithine is partly explained by the structure of the trypanosomal enzyme, which lacks a 36-amino-acid C-terminal sequence found on mammalian ornithine decarboxylase. This difference results in a lower turnover of ornithine decarboxylase and a more rapid decrease of polyamines in trypanosomes than in the mammalian host. The diminished effectiveness of eflornithine against *T. b. rhodesiense* appears to be due to the parasite's ability to replace the inhibited enzyme more rapidly than *T. b. gambiense*.

Eflornithine is less toxic but more costly than conventional therapy. It can be administered IV or PO. The dose should be reduced in renal failure. Eflornithine readily crosses the blood–brain barrier; CSF levels are highest in persons with the most severe central nervous system (CNS) involvement.

Fumagillin† Originally discovered as an anti-angiogenic compound derived from the fungus *Aspergillus fumigatus*, fumagillin is a water-insoluble antibiotic that is active against microsporidia and is used topically to treat ocular infections due to *Encephalitozoon* species. When given systemically, fumagillin was effective but caused thrombocytopenia in all recipients in the second week of treatment; this side effect was readily reversed when administration of the drug was stopped. Fumagillin acts by binding to methionine aminopeptidase 2, thus inhibiting microsporidial replication by irreversibly blocking the active site.

Furazolidone This nitrofuran derivative is an effective alternative agent for the treatment of giardiasis and also exhibits activity against *Isospora belli*. Because it is the only agent active against *Giardia* that is available in liquid form, it is most often used to treat young children. Furazolidone undergoes reductive activation in *Giardia lamblia* trophozoites—an event that, unlike the reductive activation of metronidazole, involves an NADH oxidase. The killing effect correlates with the toxicity of reduced products, which damage important cellular components, including DNA. Although furazolidone had been thought to be largely unabsorbed when administered orally, the occurrence of systemic adverse reactions indicates that this is not the case. More than 65% of the drug dose can be recovered from the urine as colored metabolites. Omeprazole reduces the oral bioavailability of furazolidone.

Furazolidone is a monoamine oxidase (MAO) inhibitor; thus, caution should be used in its concomitant administration with other drugs (especially indirectly acting sympathomimetic amines) and in the consumption of food and drink containing tyramine during treatment. However, hypertensive crises have not been reported in patients receiving furazolidone, and it has been suggested that—because furazolidone inhibits MAOs gradually over several days—the risks are small if treatment is limited to a 5-day course. Because hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and glutathione instability, furazolidone treatment is contraindicated in mothers who are breast-feeding and in neonates.

Halofantrine This 9-phenanthrenemethanol is one of three classes of arylaminoalcohols first identified as potential antimalarial agents by the World War II Malaria Chemotherapy Program. Its activity is believed to be similar to that of chloroquine, although it is an oral alternative for the treatment of malaria due to chloroquine-resistant *P. falciparum*.

Halofantrine is thought to share one or more mechanisms with the 4-aminoquinolines, forming a complex with ferriprotoporphyrin IX and interfering with the degradation of hemoglobin. It has been shown to bind to plasmepsin, a hemoglobin-degrading enzyme unique to plasmodia.

Halofantrine exhibits erratic bioavailability, but its absorption is significantly enhanced when it is taken with a fatty meal. The elimination half-life of halofantrine is 1–2 days; it is excreted mainly in feces. Halofantrine is metabolized into *N*-debutyl-halofantrine by the cytochrome P450 enzyme CYP3A4. Grapefruit juice should be avoided during treatment because it increases both halofantrine's bioavailability and halofantrine-induced QT interval prolongation by inhibiting CYP3A4 at the enterocyte level.

Iodoquinol Iodoquinol (diiodohydroxyquin), a hydroxyquinoline, is an effective luminal agent for the treatment of amebiasis, balantidiasis, and infection with *Dientamoeba fragilis*. Its mechanism of action is unknown. It is poorly absorbed. Because the drug contains 64% organically bound iodine, it should be used with caution in patients with thyroid disease. Iodine dermatitis occurs occasionally during iodoquinol treatment. Protein-bound serum iodine levels may be increased during treatment and can interfere with certain tests of thyroid function. These effects may persist for as long as 6 months after discontinuation of therapy. Iodoquinol is contraindicated in patients with liver disease. Most serious are the reactions related to prolonged high-dose therapy (optic neuritis, peripheral neuropathy), which should not occur if the recommended dosage regimens are followed.

Ivermectin Ivermectin (22,23-dihydroavermectin) is a derivative of the macrocyclic lactone avermectin produced by the soil-dwelling actinomycete *Streptomyces avermitilis*. Ivermectin is active at low doses against a wide range of helminths and ectoparasites. It is the drug of choice for the treatment of onchocerciasis, strongyloidiasis, cutaneous larva migrans, and scabies. Ivermectin is highly active against microfilariae of the lymphatic filariases but has no macrofilaricidal activity. When ivermectin is used in combination with other agents such as DEC or albendazole for treatment of lymphatic filariasis, synergistic activity is seen. Although active against the intestinal helminths *Ascaris lumbricoides* and *Enterobius vermicularis*, ivermectin is only variably effective in trichuriasis and is ineffective against hookworms. Widespread use of ivermectin for treatment of intestinal nematode infections in sheep and goats has led to the emergence of drug resistance in veterinary practice; this development may portend problems in human medical use.

Data suggest that ivermectin acts by opening the neuromuscular membrane-associated, glutamate-dependent chloride channels. The influx of chloride ions results in hyperpolarization and muscle paralysis—particularly of the nematode pharynx, with consequent blockage of the oral ingestion of nutrients. As these chloride channels are present only in invertebrates, paralysis is seen only in the parasite.

Ivermectin is available for administration to humans only as an oral formulation. The drug is highly protein bound; it is almost completely excreted in feces. Both food and beer increase the bioavailability of ivermectin significantly. Ivermectin is distributed widely throughout the body; animal studies indicate that it accumulates at the highest concentration in adipose tissue and liver, with little accumulation in the brain. Few data exist to guide therapy in hosts with conditions that may influence drug pharmacokinetics.

Ivermectin is generally administered as a single dose of 150–200 µg/kg. In the absence of parasitic infection, the adverse effects of ivermectin in therapeutic doses are minimal. Adverse effects in patients with filarial infections include fever, myalgia, malaise, lightheadedness, and (occasionally) postural hypotension. The severity of such side effects is related to the intensity of parasite infection, with more symptoms in individuals with a heavy parasite burden. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. The adverse effects are generally self-limiting and only occasionally require symptom-based treatment with antipyretics or antihistamines. More severe complications of ivermectin therapy for onchocerciasis include encephalopathy in patients heavily infected with *Loa loa*.

Lumefantrine Lumefantrine (benflumetol), a fluorene arylaminoalcohol derivative synthesized in the 1970s by the Chinese Academy of Military Medical Sciences (Beijing), has marked blood schizonticidal activity against a wide range of plasmodia. This agent conforms structurally and in mode of action to other arylaminoalcohols (quinine, mefloquine, and halofantrine). Lumefantrine exerts its antimalarial effect as a consequence of its interaction with heme, a degradation product of hemoglobin metabolism. Although its antimalarial activity is slower than that of the artemisinin-based drugs, the recrudescence rate with the recommended lumefantrine regimen is lower. The pharmacokinetic properties of lumefantrine are reminiscent of those of halofantrine, with variable oral bioavailability, considerable augmentation of oral bioavailability by concomitant fat intake, and a terminal elimination half-life of ~4–5 days in patients with malaria.

Artemether and lumefantrine have synergistic activity, and the combined formulation of artemether and lumefantrine is effective for the treatment of falciparum malaria in areas where *P. falciparum* is resistant to chloroquine and antifolates.

Mebendazole This benzimidazole is a broad-spectrum antiparasitic agent widely used to treat intestinal helminthiases. Its mechanism of action is similar to that of albendazole; however, it is a more potent inhibitor of parasite malic dehydrogenase and exhibits a more specific and selective effect against intestinal nematodes than the other benzimidazoles.

Mebendazole is available only in oral form but is poorly absorbed from the GI tract; only 5–10% of a standard dose is measurable in plasma. The proportion absorbed from the GI tract is extensively metabolized in the liver. Metabolites appear in the urine and bile; impaired liver or biliary function results in higher plasma mebendazole levels in treated patients. No dose reduction is warranted in patients with renal function impairment. Because mebendazole is poorly absorbed, its incidence of side effects is low. Transient abdominal pain and diarrhea sometimes occur, usually in persons with massive parasite burdens.

Mefloquine Mefloquine is effective prophylaxis of chloroquine-resistant malaria; high doses can be used for treatment. Despite the development of drug-resistant strains of *P. falciparum* in parts of Africa and Southeast Asia, mefloquine remains an effective drug throughout most of the world. Cross-resistance of mefloquine with halofantrine and with quinine has been documented in limited areas. Like quinine and chloroquine, this quinoline is active only against the asexual erythrocytic stages of malarial parasites. Unlike quinine, however, mefloquine has a relatively poor affinity for DNA and, as a result, does not inhibit the synthesis of parasitic nucleic acids and proteins. Although both mefloquine and chloroquine inhibit hemozoin formation and heme degradation, mefloquine differs in that it forms a complex with heme that may be toxic to the parasite.

Mefloquine HCl is poorly water soluble and intensely irritating when given parenterally; thus it is available only in tablet form. Its absorption is adversely affected by vomiting and diarrhea but is significantly enhanced when the drug is administered with or after food. About 98% of the drug binds to protein. Mefloquine is excreted mainly in the bile and feces; therefore, no dose adjustment is needed in persons with renal insufficiency. The drug and its main metabolite are not appreciably removed by hemodialysis. No special chemoprophylactic dosage adjustments are indicated for the achievement of plasma concentrations in dialysis patients that are similar to those in healthy persons. Pharmacokinetic differences have been detected among various ethnic populations; however, these distinctions are of minor importance compared with host immune status and parasite sensitivity. In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma levels.

Mefloquine should be used with caution by individuals participating in activities requiring alertness and fine-motor coordination because dizziness, vertigo, or tinnitus can develop and persist. If the drug is to be administered for a prolonged period, periodic evaluations are recommended, including liver function tests and ophthalmic examinations. Sleep abnormalities (insomnia, abnormal dreams) have occasionally been reported. Psychosis and seizures occur rarely; mefloquine should not be prescribed to patients with neuropsychiatric conditions. The development of acute anxiety, depression, restlessness, or confusion may be considered prodromal to a more serious event, and the drug should be discontinued.

Concomitant use of quinine, quinidine, or drugs producing β-adrenergic blockade may cause significant electrocardiographic abnormalities or cardiac arrest. Halofantrine must not be given simultaneously with or <3 weeks after mefloquine because a potentially fatal prolongation of the QTc interval on electrocardiography may occur. No data exist on mefloquine use after halofantrine use. Administration of mefloquine with quinine or chloroquine may increase the risk of convulsions. Mefloquine may lower plasma levels of anticonvulsants. Caution should be exercised with regard to concomitant antiretroviral therapy, since mefloquine has been shown to exert variable effects on ritonavir pharmacokinetics that are not explained by hepatic CYP3A4 activity or ritonavir protein binding. Vaccinations with attenuated live bacteria should be completed at least 3 days before the first dose of mefloquine.

Women of childbearing age who are traveling to areas where malaria is endemic should be warned against becoming pregnant and encouraged to practice contraception during malaria prophylaxis with mefloquine and for up to 3 months thereafter. However, in the case of unplanned pregnancy, use of mefloquine is not considered an indication for pregnancy termination. Analysis of prospectively monitored cases demonstrates a prevalence of birth defects and fetal loss comparable to background rates.

Melarsoprol* Melarsoprol has been used since 1949 for the treatment of human African trypanosomiasis. This trivalent arsenical compound is indicated for the treatment of African trypanosomiasis with neurologic involvement and for the treatment of early disease that is resistant to suramin or pentamidine. Melarsoprol, like other drugs containing heavy metals, interacts with thiol groups of several different proteins; however, its antiparasitic effects appear to be more specific. Trypanothione reductase is a key enzyme involved in the oxidative stress management of both *Trypanosoma* and *Leishmania* species, helping to maintain an intracellular reducing environment by reduction of disulfide trypanothione to its dithiol derivative dihydrotrypanothione. Melarsoprol sequesters dihydrotrypanothione, depriving the parasite of its main sulfhydryl antioxidant, and inhibits trypanothione reductase, depriving the parasite of the essential enzyme system that is responsible for keeping trypanothione reduced. These effects are synergistic. The selectivity of arsenical action against trypanosomes is due at least in part to the greater melarsoprol affinity of reduced trypanothione than of other monothiols (e.g., cysteine) on which the mammalian host depends for maintenance of high thiol levels. Melarsoprol enters the parasite via an adenosine transporter; drug-resistant strains lack this transport system.

Melarsoprol is always administered IV. A small but therapeutically significant amount of the drug enters the CSF. The compound is excreted rapidly, with ~80% of the arsenic found in feces.

Melarsoprol is highly toxic. The most serious adverse reaction is reactive encephalopathy, which affects 6% of treated individuals and usually develops within 4 days of the start of therapy, with an average case–fatality rate of 50%. Glucocorticoids are administered with melarsoprol to prevent this development. Because melarsoprol is intensely irritating, care must be taken to avoid infiltration of the drug.

Metrifonate Metrifonate has selective activity against *Schistosoma haematobium*. This organophosphorous compound is a prodrug that is converted nonenzymatically to dichlorvos (2,2-dichlorovinyl dimethylphosphate, DDVP), a highly active chemical that irreversibly inhibits the acetylcholinesterase enzyme. Schistosomal cholinesterase is more susceptible to dichlorvos than is the corresponding human enzyme. The exact mechanism of action of metrifonate is uncertain, but the drug is believed to inhibit tegumental acetylcholine receptors that mediate glucose transport.

Metrifonate is administered in a series of three doses at 2-week intervals. After a single oral dose, metrifonate produces a 95% decrease in plasma cholinesterase activity within 6 h, with a fairly rapid return to normal. However, 2.5 months are required for erythrocyte cholinesterase levels to return to normal. Treated persons should not be exposed to neuromuscular blocking agents or organophosphate insecticides for at least 48 h after treatment.

Metronidazole and Other Nitroimidazoles See Table 217-1 and Chap. 139.

Miltefosine In the early 1990s, miltefosine (hexadecylphosphocholine), originally developed as an antineoplastic agent, was discovered to have significant antiproliferative activity against *Leishmania* species, *Trypanosoma cruzi*, and *Trypanosoma brucei* parasites in vitro and in experimental animal models. Miltefosine is the first oral drug that has proved to be highly effective and comparable to amphotericin B against visceral leishmaniasis in India, where antimonial-resistant cases are prevalent. Miltefosine is also effective in previously untreated visceral infections. Cure rates in cutaneous leishmaniasis are comparable to those obtained with antimony. Miltefosine is also effective against the free-living ameba *Naegleria fowleri*.

The activity of miltefosine is attributed to interaction with cell signal transduction pathways and inhibition of phospholipid and sterol biosynthesis. Resistance to miltefosine has not been observed clinically. The drug is readily absorbed from the GI tract, is widely distributed, and accumulates in several tissues. The efficacy of a 28-day treatment course in Indian visceral leishmaniasis is equivalent to that of amphotericin B therapy; however, it appears that a shortened course of 21 days may be equally efficacious.

General recommendations for the use of miltefosine are limited by the exclusion of specific groups from the published clinical trials: persons <12 or >65 years of age, persons with the most advanced disease, breast-feeding women, HIV-infected patients, and individuals with significant renal or hepatic insufficiency.

Niclosamide† Niclosamide is active against a wide variety of adult tapeworms but not against tissue cestodes. The drug uncouples oxidative phosphorylation in parasite mitochondria, thereby blocking the uptake of glucose by the intestinal tapeworm and resulting in the parasite's death. Niclosamide rapidly causes spastic paralysis of intestinal cestodes in vitro. Its use is limited by its side effects, the necessarily long duration of therapy, the recommended use of purgatives, and—most important—limited availability (i.e., on a named-patient basis from the manufacturer).

Niclosamide is poorly absorbed. Tablets are given on an empty stomach in the morning after a liquid meal the night before, and this dose is followed by another 1 h later. For treatment of hymenolepiasis, the drug is administered for 7 days. A second course is often prescribed. The scolex and proximal segments of the tapeworms are killed on contact with niclosamide and may be digested in the gut. However, disintegration of the adult tapeworm results in the release of viable ova, which theoretically can result in autoinfection. Although fears of the development of cysticercosis in patients with *Taenia solium* infections have proved unfounded, it is still recommended that a brisk purgative be given 2 h after the first dose.

Nifurtimox* This nitrofuran compound is an inexpensive and effective oral agent for the treatment of acute Chagas disease. Trypanosomes lack catalase and have very low levels of peroxidase; as a result, they are very vulnerable to by-products of oxygen reduction. When nifurtimox is reduced in the trypanosome, a nitro anion radical is formed and undergoes autooxidation, resulting in the generation of the superoxide anion O_2^-, hydrogen peroxide (H_2O_2), hydroperoxyl radical (HO_2), and other highly reactive and cytotoxic molecules. Despite the

abundance of catalases, peroxidases, and superoxide dismutases that neutralize these destructive radicals in mammalian cells, nifurtimox has a poor therapeutic index. Prolonged use is required, but the course may have to be interrupted because of drug toxicity, which develops in 40–70% of recipients. Nifurtimox is well absorbed and undergoes rapid and extensive biotransformation; <0.5% of the original drug is excreted in urine.

Nitazoxanide Nitazoxanide is a 5-nitrothiazole compound used for the treatment of cryptosporidiosis and giardiasis; it is active against other intestinal protozoa as well. The drug is approved for use in children 1–11 years of age.

The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme–dependent electron transfer reaction that is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from *G. lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of *Cryptosporidium parvum* appears to be similar to that of *G. lamblia*. Interference with the PFOR enzyme–dependent electron transfer reaction may not be the only pathway by which nitazoxanide exerts antiprotozoal activity.

After oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. It is recommended that nitazoxanide be taken with food; however, no studies have been conducted to determine whether the pharmacokinetics of tizoxanide and tizoxanide glucuronide differ in fasted versus fed subjects. Tizoxanide is excreted in urine, bile, and feces, and tizoxanide glucuronide is excreted in urine and bile. The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function have not been studied. Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering this agent concurrently with other highly plasma protein–bound drugs that have narrow therapeutic indices, as competition for binding sites may occur.

Oxamniquine This tetrahydroquinoline derivative is an effective alternative agent for the treatment of *Schistosoma mansoni*, although susceptibility to this drug exhibits regional variation. Oxamniquine exhibits anticholinergic properties, but its primary mode of action seems to rely on ATP-dependent enzymatic drug activation generating an intermediate that alkylates essential macromolecules, including DNA. In treated adult schistosomes, oxamniquine produces marked tegumental alterations that are similar to those seen with praziquantel but that develop less rapidly, becoming evident 4–8 days after treatment.

Oxamniquine is administered orally as a single dose and is well absorbed. Food retards absorption and reduces bioavailability. About 70% of an administered dose is excreted in urine as a mixture of pharmacologically inactive metabolites. Patients should be warned that their urine might have an intense orange–red color. Side effects are uncommon and usually mild, although hallucinations and seizures have been reported.

Paromomycin (Aminosidine) First isolated in 1956, this aminoglycoside is an effective oral agent for the treatment of infections due to intestinal protozoa. Parenteral paromomycin appears to be effective against visceral leishmaniasis in India.

Paromomycin inhibits protozoan protein synthesis by binding to the 30S ribosomal RNA in the aminoacyl-tRNA site, causing misreading of mRNA codons. Paromomycin is less active against *G. lamblia* than standard agents; however, like other aminoglycosides, paromomycin is poorly absorbed from the intestinal lumen, and the high levels of drug in the gut compensate for this relatively weak activity. If absorbed or administered systemically, paromomycin can cause ototoxicity and nephrotoxicity. However, systemic absorption is very limited, and toxicity should not be a concern in persons with normal kidneys. Topical formulations are not generally available.

Pentamidine Isethionate This diamidine is an effective alternative agent for some forms of leishmaniasis and trypanosomiasis. It is available for parenteral and aerosolized administration. Although its mechanism of action remains undefined, it is known to exert a wide range of effects, including interaction with trypanosomal kinetoplast DNA; interference with polyamine synthesis by a decrease in the activity of ornithine decarboxylase; and inhibition of RNA polymerase, topoisomerase, ribosomal function, and the synthesis of nucleic acids and proteins.

Pentamidine isethionate is well absorbed, highly tissue bound, and excreted slowly over several weeks, with an elimination half-life of 12 days. No steady-state plasma concentration is attained in persons given daily injections; the result is extensive accumulation of pentamidine in tissues, primarily the liver, kidney, adrenal gland, and spleen. Pentamidine does not penetrate well into the CNS. Pulmonary concentrations of pentamidine are increased when the drug is delivered in aerosolized form, but not when it is delivered systemically.

Rapid (<1-h) infusion of intravenous pentamidine often results in hypotension. Because electrolyte disturbances and mild to moderate nephrotoxicity occur commonly, pentamidine should be used with caution with other nephrotoxic agents. Pancreatitis and QT prolongation may also occur; cumulative damage to pancreatic islet cells may result in drug-induced diabetes mellitus. Similarly, hypoglycemia can develop, although much less commonly when pentamidine is given by the inhaled route.

Piperaquine This bisquinoline was synthesized in the 1960s and used widely for malaria control in China. The development of artemisinin-based combination therapy led to its evaluation as a partner drug, and it is now combined with dihydroartemisinin. Piperaquine is highly lipophilic and has a prolonged half-life (~20 days), thus providing a period of post-treatment prophylaxis. The drug's mechanisms of action and resistance have not been well studied but are presumed to be similar to those of the other 4-aminoquinolines.

Piperazine The antihelminthic activity of piperazine is confined to ascariasis and enterobiasis. Piperazine acts as an agonist at extrasynaptic γ-aminobutyric acid (GABA) receptors, causing an influx of chloride ions in the nematode somatic musculature. Although the initial result is hyperpolarization of the muscle fibers, the ultimate effect is flaccid paralysis, leading to the expulsion of live worms. Patients should be warned, as this occurrence can be unsettling.

Praziquantel This heterocyclic pyrazinoisoquinoline derivative is highly active against a broad spectrum of trematodes and cestodes. It is the mainstay of treatment for schistosomiasis and is a critical part of community-based control programs.

All of the effects of praziquantel can be attributed either directly or indirectly to an alteration of intracellular calcium concentrations. Although the exact mechanism of action remains unclear, the major mechanism is disruption of the parasite tegument, causing tetanic contractures with loss of adherence to host tissues and, ultimately, disintegration or expulsion. Praziquantel induces changes in the antigenicity of the parasite by causing the exposure of concealed antigens. Praziquantel also produces alterations in schistosomal glucose metabolism, including decreases in glucose uptake, lactate release, glycogen content, and ATP levels.

Praziquantel exerts its parasitic effects directly and does not need to be metabolized to be effective. It is well absorbed but undergoes extensive first-pass hepatic clearance. Levels of the drug are increased when it is taken with food, particularly carbohydrates, or with cimetidine. Serum levels are reduced by glucocorticoids, chloroquine, carbamazepine, and phenytoin. Praziquantel is completely metabolized in humans, with 80% of the dose recovered as metabolites in urine within 4 days. It is not known to what extent praziquantel crosses the placenta, but retrospective studies suggest that it is safe in pregnancy.

Patients with schistosomiasis who have heavy parasite burdens may develop abdominal discomfort, nausea, headache, dizziness, and drowsiness. Symptoms begin 30 min after ingestion, may require spasmolytics for relief, and usually disappear spontaneously after a few hours.

Primaquine Phosphate Primaquine, an 8-aminoquinoline, has a broad spectrum of activity against all stages of plasmodial development in humans but has been used most effectively for eradication of the hepatic stage of these parasites. Despite its toxicity, it remains the drug of choice for radical cure of *P. vivax* infections. Primaquine must be metabolized by the host to be effective. It is, in fact, rapidly metabolized; only a small fraction of the dose of the parent drug is excreted unchanged. Although the parasiticidal activity of the three oxidative metabolites remains unclear, they are believed to affect both pyrimidine synthesis and the mitochondrial electron transport chain. The metabolites appear to have significantly less antimalarial activity than primaquine; however, their hemolytic activity is greater than that of the parent drug.

Primaquine causes marked hypotension after parenteral administration and therefore is given only by the oral route. It is rapidly and almost completely absorbed from the GI tract.

Patients should be tested for G6PD deficiency before they receive primaquine. The drug may induce the oxidation of hemoglobin into methemoglobin, regardless of the G6PD status of the patient. Primaquine is otherwise well tolerated.

Proguanil (Chloroguanide) Proguanil inhibits plasmodial dihydrofolate reductase and is used with atovaquone for oral treatment of uncomplicated malaria or with chloroquine for malaria prophylaxis in parts of Africa without widespread chloroquine-resistant *P. falciparum*.

Proguanil exerts its effect primarily by means of the metabolite cycloguanil, whose inhibition of dihydrofolate reductase in the parasite disrupts deoxythymidylate synthesis, thus interfering with a key pathway involved in the biosynthesis of pyrimidines required for nucleic acid replication. There are no clinical data indicating that folate supplementation diminishes drug efficacy; women of childbearing age for whom atovaquone/proguanil is prescribed should continue taking folate supplements to prevent neural tube birth defects.

Proguanil is extensively absorbed regardless of food intake. The drug is 75% protein bound. The main routes of elimination are hepatic biotransformation and renal excretion; 40–60% of the proguanil dose is excreted by the kidneys. Drug levels are increased and elimination is impaired in patients with hepatic insufficiency.

Pyrantel Pamoate Pyrantel is a tetrahydropyrimidine formulated as pamoate. This safe, well-tolerated, inexpensive drug is used to treat a variety of intestinal nematode infections but is ineffective in trichuriasis. Pyrantel pamoate is usually effective in a single dose. Its target is the nicotinic acetylcholine receptor on the surface of nematode somatic muscle. Pyrantel depolarizes the neuromuscular junction of the nematode, resulting in its irreversible paralysis and allowing the natural expulsion of the worm.

Pyrantel pamoate is poorly absorbed from the intestine; >85% of the dose is passed unaltered in feces. The absorbed portion is metabolized and excreted in urine. Piperazine is antagonistic to pyrantel pamoate and should not be used concomitantly.

Pyrantel pamoate has minimal toxicity at the oral doses used to treat intestinal helminthic infection. It is not recommended for pregnant women or for children <12 months old.

Pyrimethamine When combined with short-acting sulfonamides, this diaminopyrimidine is effective in malaria, toxoplasmosis, and isosporiasis. Unlike mammalian cells, the parasites that cause these infections cannot use preformed pyrimidines obtained through salvage pathways but rather rely completely on de novo pyrimidine synthesis, for which folate derivatives are essential cofactors. The efficacy of pyrimethamine is increasingly limited by the development of resistant strains of *P. falciparum* and *P. vivax*. Single amino acid substitutions to parasite dihydrofolate reductase confer resistance to pyrimethamine by decreasing the enzyme's binding affinity for the drug.

Pyrimethamine is well absorbed; the drug is 87% bound to human plasma proteins. In healthy volunteers, drug concentrations remain at therapeutic levels for up to 2 weeks; drug levels are lower in patients with malaria.

At the usual dosage, pyrimethamine alone causes little toxicity except for occasional skin rashes and, more rarely, blood dyscrasias. Bone marrow suppression sometimes occurs at the higher doses used for toxoplasmosis; at these doses, the drug should be administered with folinic acid.

Pyronaridine This potent antimalarial is a benzonaphthyridine derivative first synthesized by Chinese researchers in 1970. Like chloroquine, pyronaridine targets hematin formation, inhibiting the production of β-hematin by forming complexes with it, with consequent enhancement of hematin-induced hemolysis. However, this drug is more potent than chloroquine: for complete lysis, pyronaridine is required at only 1/100th of the concentration needed with chloroquine. It also inhibits glutathione-dependent heme degradation. Despite its similar mode of action, pyronaridine remains effective against chloroquine-resistant strains. When combined with artesunate, it is effective for the treatment of acute, uncomplicated infection caused by *P. falciparum* or *P. vivax* in areas of low transmission with evidence of artemisinin resistance.

Pyronaridine is readily absorbed, widely distributed throughout the body, metabolized by the liver, and excreted in urine and stool. Its use is contraindicated in patients with severe liver or kidney impairment. Pyronaridine inhibits both CYP2D6 and P-glycoprotein in vitro, and these effects may have clinical relevance for patients taking medications for cardiac disease (e.g., metoprolol and digoxin).

Quinacrine* Quinacrine is the only drug approved by the FDA for the treatment of giardiasis. Although its production was discontinued in 1992, quinacrine can be obtained from alternative sources through the CDC Drug Service. The antiprotozoal mechanism of quinacrine has not been fully elucidated. The drug inhibits NADH oxidase—the same enzyme that activates furazolidone. The differing relative quinacrine uptake rate between human cells and *G. lamblia* may explain the selective toxicity of the drug. Resistance correlates with decreased drug uptake.

Quinacrine is rapidly absorbed from the intestinal tract and is widely distributed in body tissues. Alcohol is best avoided because of a disulfiram-like effect.

Quinine and Quinidine When combined with another agent, the cinchona alkaloid quinine is effective for the oral treatment of both uncomplicated, chloroquine-resistant malaria and babesiosis. Quinine acts rapidly against the asexual blood stages of all forms of the human malaria parasites. For severe malaria, only quinidine (the dextroisomer of quinine) is available in the United States. Quinine concentrates in the acidic food vacuoles of *Plasmodium* species. The drug inhibits the nonenzymatic polymerization of the highly reactive, toxic heme molecule into the nontoxic polymer pigment hemozoin.

Quinine is readily absorbed when given orally. In patients with malaria, the elimination half-life of quinine increases according to the severity of the infection. However, toxicity is avoided by an increase in the concentration of plasma glycoproteins. The cinchona alkaloids are extensively metabolized, particularly by CYP3A4; only 20% of the dose is excreted unchanged in urine. The drug's metabolites are also excreted in urine and may be responsible for toxicity in patients with renal failure. Renal excretion of quinine is decreased when cimetidine is taken and increased when the urine is acidic. The drug readily crosses the placenta.

Quinidine is both more potent as an antimalarial and more toxic than quinine. Its use requires cardiac monitoring. Dose reduction is necessary in persons with severe renal impairment.

Spiramycin† This macrolide is used to treat acute toxoplasmosis in pregnancy and congenital toxoplasmosis. While the mechanism of action is similar to that of other macrolides, the efficacy of spiramycin in toxoplasmosis appears to stem from its rapid and extensive intracellular penetration, which results in macrophage drug concentrations 10–20 times greater than serum concentrations.

Spiramycin is rapidly and widely distributed throughout the body and reaches concentrations in the placenta up to five times those in

serum. This agent is excreted mainly in bile. Indeed, in humans, the urinary excretion of active compounds represents only 20% of the administered dose.

Serious reactions to spiramycin are rare. Of the available macrolides, spiramycin appears to have the lowest risk of drug interactions. Complications of treatment are rare but, in neonates, can include life-threatening ventricular arrhythmias that disappear with drug discontinuation.

Sulfonamides See Table 217-1 and Chap. 139.

Suramin* This derivative of urea is the drug of choice for the early stage of African trypanosomiasis. The drug is polyanionic and acts by forming stable complexes with proteins, thus inhibiting multiple enzymes essential to parasite energy metabolism. Suramin appears to inhibit all trypanosome glycolytic enzymes more effectively than it inhibits the corresponding host enzymes.

Suramin is parenterally administered. It binds to plasma proteins and persists at low levels for several weeks after infusion. Its metabolism is negligible. This drug does not penetrate the CNS.

Tafenoquine Tafenoquine is an 8-aminoquinoline with causal prophylactic activity. Its prolonged half-life (2–3 weeks) allows longer dosing intervals when the drug is used for prophylaxis. Tafenoquine has been well tolerated in clinical trials. When tafenoquine is taken with food, its absorption is increased by 50% and the most commonly reported adverse event—mild GI upset—is diminished. Like primaquine, tafenoquine is a potent oxidizing agent, causing hemolysis in patients with G6PD deficiency as well as methemoglobinemia.

Tetracyclines See Table 217-1 and Chap. 139.

Thiabendazole Discovered in 1961, thiabendazole remains one of the most potent of the numerous benzimidazole derivatives. However, its use has declined significantly because of a higher frequency of adverse effects than is seen with other, equally effective agents.

Thiabendazole is active against most intestinal nematodes that infect humans. Although the exact mechanism of its antihelminthic activity has not been fully elucidated, it is likely to be similar to that of other benzimidazole drugs: namely, inhibition of polymerization of parasite β-tubulin. The drug also inhibits the helminth-specific enzyme fumarate reductase. In animals, thiabendazole has anti-inflammatory, antipyretic, and analgesic effects, which may explain its usefulness in dracunculiasis and trichinellosis. Thiabendazole also suppresses egg and/or larval production by some nematodes and may inhibit the subsequent development of eggs or larvae passed in feces. Despite the emergence and global spread of thiabendazole-resistant trichostrongyliasis among sheep, there have been no reports of drug resistance in humans.

Thiabendazole is available in tablet form and as an oral suspension. The drug is rapidly absorbed from the GI tract but can also be absorbed through the skin. Thiabendazole should be taken after meals. This agent is extensively metabolized in the liver before ultimately being excreted; most of the dose is excreted within the first 24 h. The usual dose of thiabendazole is determined by the patient's weight, but some treatment regimens are parasite specific. No particular adjustments are recommended in patients with renal or hepatic failure; only cautious use is advised.

Coadministration of thiabendazole to patients taking theophylline can result in an increase in theophylline levels by >50%. Therefore, serum levels of theophylline should be monitored closely in this situation.

Tinidazole This nitroimidazole is effective for the treatment of amebiasis, giardiasis, and trichomoniasis. Like metronidazole, tinidazole must undergo reductive activation by the parasite's metabolic system before it can act on protozoal targets. Tinidazole inhibits the synthesis of new DNA in the parasite and causes degradation of existing DNA. The reduced free-radical derivatives alkylate DNA, with consequent cytotoxic damage to the parasite. This damage appears to be produced by short-lived reduction intermediates, resulting in helix destabilization and strain breakage of DNA. The mechanism of action and side effects of tinidazole are similar to those of metronidazole, but adverse events appear to be less frequent and severe with tinidazole. In addition, the significantly longer half-life of tinidazole (>12 h) offers potential cure with a single dose.

Triclabendazole While most benzimidazoles have broad-spectrum antihelminthic activity, they exhibit minimal or no activity against *Fasciola hepatica*. In contrast, the antihelminthic activity of triclabendazole is highly specific for *Fasciola* and *Paragonimus* species, with little activity against nematodes, cestodes, and other trematodes. Triclabendazole is effective against all stages of *Fasciola* species. The active sulfoxide metabolite of triclabendazole binds to fluke tubulin by assuming a unique nonplanar configuration and disrupts microtubule-based processes. Resistance to triclabendazole in veterinary use has been reported in Australia and Europe; however, no resistance has been documented in humans.

Triclabendazole is rapidly absorbed after oral ingestion; administration with food enhances its absorption and shortens the elimination half-life of the active metabolite. Both the sulfoxide and the sulfone metabolites are highly protein bound (>99%). Treatment with triclabendazole is typically given in one or two doses. No clinical data are available regarding dose adjustment in renal or hepatic insufficiency; however, given the short course of therapy and extensive hepatic metabolism of triclabendazole, dose adjustment is unlikely to be necessary. No information exists on drug interactions.

Trimethoprim-Sulfamethoxazole See Table 217-1 and Chap. 139.

FURTHER READING

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Section 18 Protozoal Infections

218 Amebiasis and Infection with Free-Living Amebae

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AMEBIASIS

DEFINITION

Amebiasis is an infection caused by *Entamoeba histolytica*, an intestinal protozoan. Its spectrum of clinical syndromes ranges from asymptomatic colonization (90% of cases) to invasive amebiasis, which accounts for 10% of affected individuals. Invasive amebiasis frequently presents as intestinal colitis (dysentery or diarrhea) or as extraintestinal amebiasis, in which abscesses of the liver are more commonly found than involvement of the lungs or brain.

LIFE CYCLE AND TRANSMISSION

E. histolytica is acquired by ingestion of viable cysts from fecally contaminated water, food, or hands (Fig. 218-1). Food-borne exposure is most prevalent and is particularly likely when food handlers are shedding cysts or food is being grown with feces-contaminated

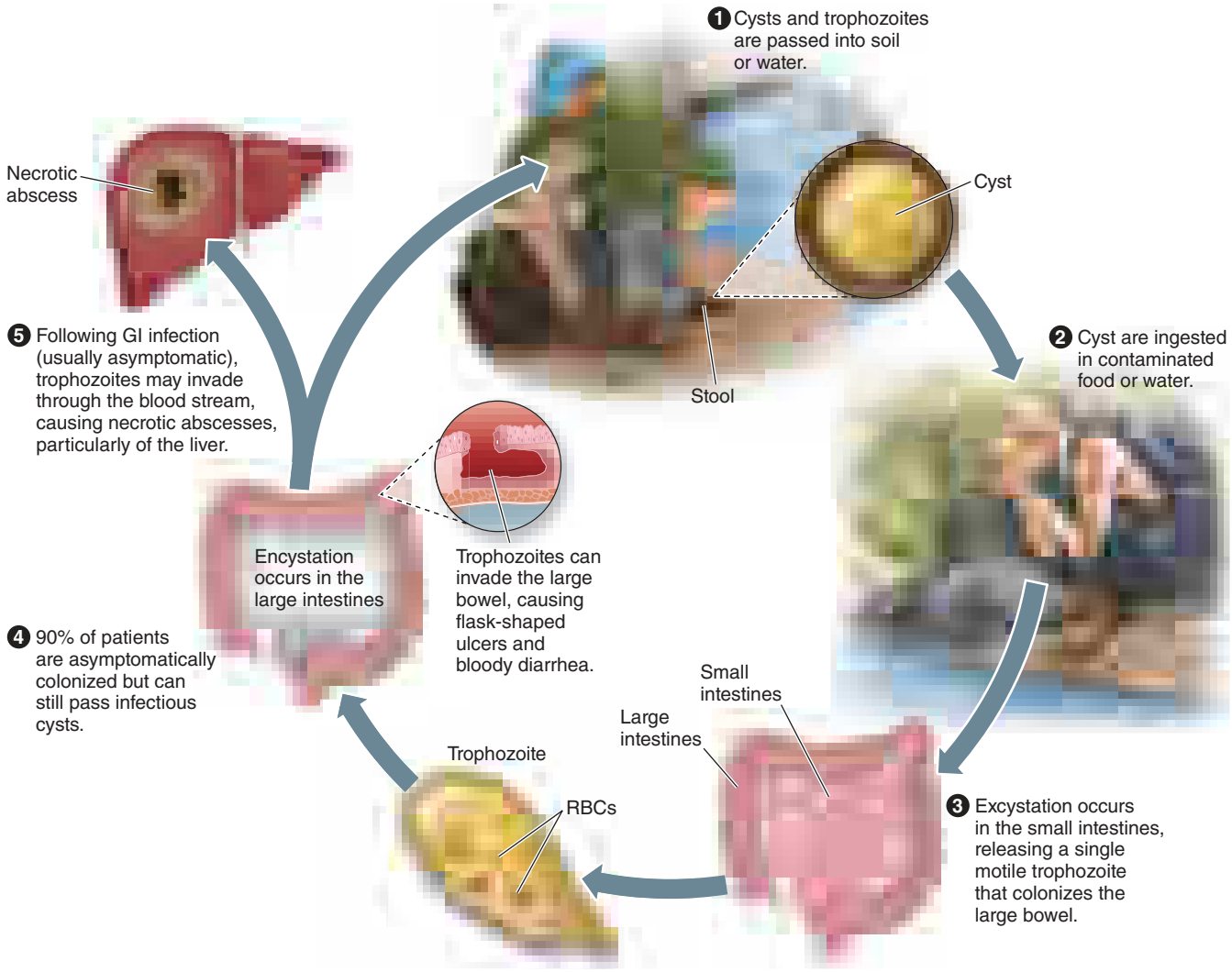


FIGURE 218-1 Life cycle of *Entamoeba histolytica*. GI, gastrointestinal; RBCs, red blood cells.

soil, fertilizer, or water. Besides the drinking of contaminated water, less common means of transmission include oral and anal sexual practices and—in rare instances—direct rectal inoculation through colonic irrigation devices. Motile trophozoites are released from cysts in the small intestine and, in most patients, remain as harmless commensals in the large bowel. After encystation, infectious cysts are shed in the stool and can survive for several weeks in a moist environment. In some patients, the trophozoites invade either the bowel mucosa, causing symptomatic colitis, or the bloodstream, causing distant abscesses of the liver, lungs, or brain. The trophozoites may not encyst in patients with active dysentery, and motile hematophagous trophozoites are frequently present in fresh stools. Trophozoites are rapidly killed by exposure to air or stomach acid, however, and therefore cannot transmit infection.

EPIDEMIOLOGY

E. histolytica infection typically affects tropical underdeveloped regions with poor sanitation systems and hygiene, occurring particularly often in children <5 years of age. This infection is widespread on the Indian subcontinent and in Africa, parts of East Asia (Thailand), and Central and South America (Mexico and Colombia). According to the Global Burden of Disease 2015 study, amebiasis accounts for 67,900 all-age deaths, including 15,500 children <5 years old.

In contrast, the main groups at risk for amebiasis in developed countries are returned travelers, recent immigrants, men who have sex with men (MSM), military personnel, and inmates of institutions. Data for 1997–2011 from the GeoSentinel Surveillance Network, which encompasses information from tropical medicine clinics on six continents, showed that, among long-term travelers (trip duration, >6 months), diarrhea due to *E. histolytica* was among the most common diagnoses. In fact, amebiasis may be considered an emerging infectious disease in developed countries such as Japan, where the number of reported cases among HIV-positive patients, and particularly among MSM, has increased.

Worldwide, *E. histolytica* is the second most common cause of death related to parasitic infection (after malaria). Invasive colitis and liver abscesses are tenfold more common among men than among women; this difference has been attributed to a disparity in complement-mediated killing and effects of testosterone on the secretion of interferon γ. The wide spectrum of clinical disease caused by *Entamoeba* is due in part to the differences between the two major infecting species, *E. histolytica* and *E. dispar*. *E. histolytica* has unique surface antigens, is genetically distinct, and possesses virulence properties that distinguish it from the morphologically identical *E. dispar*.

Most asymptomatic carriers, including MSM and patients with AIDS, harbor *E. dispar* and have self-limited infections. In this respect, *E. dispar* is dissimilar to other enteric pathogens such as *Cryptosporidium* and *Cystoisospora belli*, which can cause self-limited illnesses in immunocompetent hosts but devastating diarrhea in patients with AIDS. These observations indicate that *E. dispar* is incapable of causing invasive disease. Through genomic sequencing, new species of *Entamoeba* have been identified: *E. moshkowskii* and *E. bangladeshi*. These new species are microscopically indistinguishable from *E. histolytica*. Although *E. moshkovskii* causes diarrhea, weight loss, and colitis in mice, a prospective evaluation of children from the Mirpur community of Dhaka, Bangladesh, found that most children who had diarrheal diseases associated with *E. moshkovskii* were simultaneously infected

with at least one other enteric pathogen. In 2012, *E. bangladeshi nov.* sp., *Bangladesh* was first reported in this same Bangladeshi community, having been isolated from the stools of both asymptomatic children and those with diarrhea. Additional clinical and epidemiologic studies are needed to discern the true role of *E. bangladeshi* in the human host.

PATHOGENESIS AND PATHOLOGY

Both trophozoites and cysts are found in the intestinal lumen, but only trophozoites of *E. histolytica* invade tissue. The trophozoite is 20–60 μm in diameter and contains vacuoles and a nucleus with a characteristic central nucleolus. Trophozoites attach to colonic mucus and epithelial cells by Gal/GalNAc adherence lectin and release glycosidases and proteases that cause degradation of mucous polymers. Extracellular cysteine proteinases degrade collagen, elastin, IgA, IgG, and the anaphylatoxins C3a and C5a. After disruption of the mucous layer, trophozoites damage the mucosa by contact-dependent and contact-independent cytotoxicity. The contact-dependent cytotoxicity is attributable to induction of apoptotic cell death; trogocytosis-mediated cell death (ingestion of fragments of living cells); and lysis of inflammatory cells (neutrophils, monocytes, and lymphocytes), colonic cells, and hepatic cells through release of phospholipase A and pore-forming peptides. Contact-independent cytotoxicity follows production of inflammatory mediators, such as prostaglandin E2, by trophozoites, ultimately leading to increased ion permeability of intercellular tight junctions.

E. histolytica trophozoites are constantly exposed to reactive oxygen and nitrogen species arising from their own metabolism and from the host during tissue invasion. The ability to resist reactive oxygen species or reactive nitrogen species such as nitric oxide or *S*-nitrosothiols (e.g., *S*-nitrosoglutathione [GSNO] and *S*-nitrosocysteine [CySNO]) is also a virulence factor. Overexpression of hydrogen peroxide–regulatory motif-binding protein appears to increase *E. histolytica* cytotoxicity. Since *E. histolytica* lacks glutathione and glutathione reductase, it relies on its thioredoxin–thioredoxin reductase system to prevent, regulate, and repair the damage caused by oxidative stress. This antioxidant system is versatile: it has the ability to reduce reactive nitrogen species and use an alternative electron donor, such as nicotinamide adenine dinucleotide. Metronidazole, the current standard of therapy for amebiasis, seems to exert its antiparasitic effect through inhibition of this antioxidant system. Auranofin, a reprofiled drug approved by the U.S. Food and Drug Administration for rheumatoid arthritis, inhibits thioredoxin reductase and displays in vitro and in vivo efficacy against *E. histolytica* and *Giardia intestinalis*. Auranofin is currently undergoing clinical trials against *E. histolytica* and *Giardia* infections in Bangladesh.

Phagocytosis is a virulence factor that leads to defective proliferation of *E. histolytica* if inhibited. Trophozoites use membrane-associated carbohydrate-binding proteins to phagocytose intestinal bacteria, especially gram-negative Enterobacteriaceae, for their nutrients. Interactions with commensal bacteria, such as *Escherichia coli*, can attenuate the virulence of *E. histolytica* by decreasing the expression of Gal/GalNAc lectin. In contrast, ingestion of enteropathogenic bacteria, such as enteropathogenic *E. coli* and *Shigella dysenteriae*, increases expression of the Gal/GalNAc lectin and enhances *E. histolytica* cysteine protease activity.

E. histolytica is capable of altering the commensal gut microbiota. In a cohort in northern India, adult patients who had had amebic dysentery for 5–7 days had significant decreases in intestinal *Bacteroides*, the *Clostridium coccoides* subgroup, the *Clostridium leptum* subgroup, *Lactobacillus*, *Campylobacter*, and *Eubacterium* but displayed increases in *Bifidobacterium*. During the first 2 years of life, the gut immune system and the microbiota mature rapidly. In one study, ~80% of children from the Bangladeshi community of Dhaka were found to be infected with *E. histolytica* by 2 years of age. Fecal anti–Gal/GalNAc lectin IgA was associated with protection from reinfection, while a high parasite burden in the first year of life and expansion of *Prevotella copri* levels were associated with diarrhea.

Antimicrobial peptides, such as cathelicidins, are an important component of innate immunity and are induced by *E. histolytica* upon intestinal invasion in a mouse model. In this model, cecal cathelicidin-related antimicrobial peptide mRNA increased by >4-fold at 3 days and >100-fold at 7 days. However, *E. histolytica* remained resistant to cathelicidin-mediated killing, probably because the antimicrobial peptide was digested by amebic cysteine proteinases.

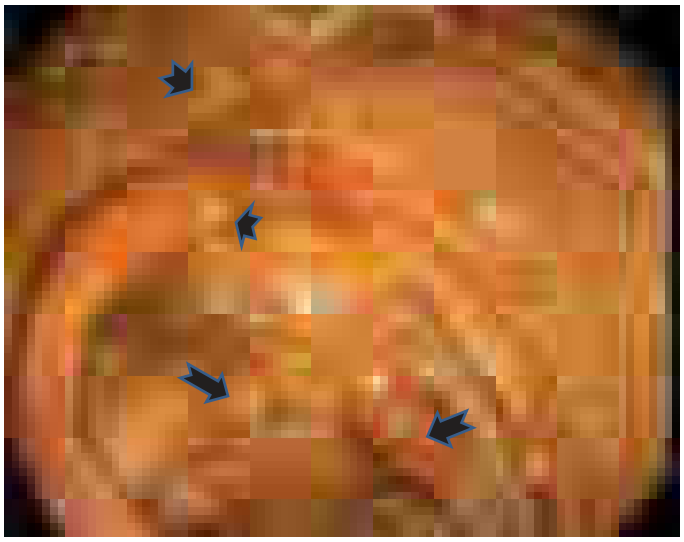
IgA plays a critical role in acquired immunity to *E. histolytica*. A study in Bangladeshi schoolchildren revealed that an intestinal IgA response to Gal/GalNAc reduced the risk of new *E. histolytica* infection by 64%. Serum IgG antibody is not protective; titers correlate with the duration of illness rather than with the severity of disease. Indeed, Bangladeshi children with a serum IgG response were more likely than those without such a response to develop new *E. histolytica* infection. In infants from this same Bangladeshi community, passive immunity conferred by maternal parasite-specific IgA via breastfeeding resulted in a 39% reduced risk of infection and a 64% reduced risk of diarrheal disease from *E. histolytica* during the first year of life. However, this protection appeared to be species-specific, with little or no protection conferred from infections with other species such as *E. dispar* or *E. bangladeshi*.

Genetic susceptibility to amebiasis in humans is associated with a polymorphism in the receptor for the adipocytokine leptin (LEPR). Children in a Bangladeshi cohort carrying arginine at LEPR position 223 (R223) were nearly twice as susceptible to *E. histolytica* as those carrying glutamine at this position (Q223). This mutant allele is overrepresented in many geographic areas with a high prevalence of amebiasis, such as Bangladesh and India. LEPRs are expressed on intestinal epithelial cells, where they prevent apoptosis, promote tissue repair, and may decrease neutrophil infiltration.

The earliest intestinal lesions are micro-ulcerations of the mucosa of the cecum, sigmoid colon, or rectum that release erythrocytes, inflammatory cells, and epithelial cells. Colonoscopy reveals small ulcers with heaped-up margins and normal intervening mucosa **(Fig. 218-2*A*)**. Submucosal extension of ulcerations under viable-appearing surface mucosa causes the classic "flask-shaped" ulcer containing trophozoites at the margins of dead and viable tissues. Although neutrophilic infiltrates may accompany early lesions in animals, human intestinal infection is marked by a paucity of inflammatory cells, probably in part because of the killing of neutrophils by trophozoites **(Fig. 218-2*B*)**. Treated ulcers characteristically heal with little or no scarring. Occasionally, however, full-thickness necrosis and perforation occur.

Rarely, intestinal infection results in the formation of a mass lesion, or *ameboma*, in the bowel lumen. The overlying mucosa is usually thin and ulcerated, while other layers of the wall are thickened, edematous, and hemorrhagic; this condition results in exuberant formation of granulation tissue with little fibrous-tissue response.

Amebic liver abscesses are age- and gender-dependent. Men 30–60 years of age are most commonly infected at a rate 10–12 times higher than women in the same age group. Studies in animal models have demonstrated that testosterone may increase susceptibility to amebic liver abscess by modulating the secretion of interferon γ by natural killer T cells, which are activated through *E. histolytica* lipopeptidophosphoglycan present on the surface of ameba trophozoites. Liver abscesses are always preceded by intestinal colonization, which may be asymptomatic. Blood vessels may be compromised early by wall lysis and thrombus formation. Trophozoites invade veins to reach the liver through the portal venous system. *E. histolytica* is resistant to complement-mediated lysis—a property critical to survival in the bloodstream. Inoculation of amebae into the portal system of hamsters results in an acute cellular infiltrate consisting predominantly of neutrophils. Later, the neutrophils are lysed by contact with amebae, and the release of neutrophil toxins may contribute to necrosis of hepatocytes. The liver parenchyma is replaced by necrotic material that is surrounded by a thin rim of congested liver tissue. Although the necrotic contents of a liver abscess are classically described as "anchovy paste," the fluid is variable in color; it is composed of bacteriologically sterile granular debris with few or no cells. Amebae, if seen, tend to be found near the capsule of the abscess.



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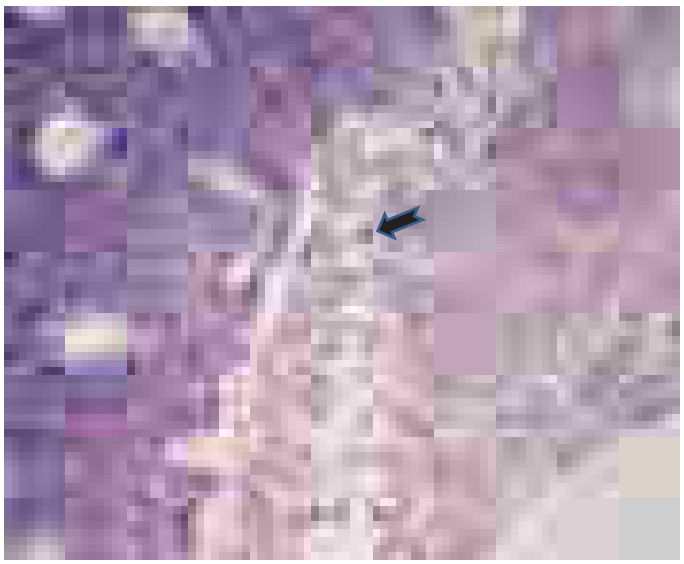

B

FIGURE 218-2 Endoscopic and histopathologic features of intestinal amebiasis. ***A.*** Appearance of ulcers on colonoscopy (*arrows*). ***B.*** Inflammatory infiltrate and *Entamoeba histolytica* trophozoites (*arrows*) in invasive amebic colitis (hematoxylin and eosin). (*Courtesy of the Department of Pathology and Gastroenterology, San Diego VA Medical Center.*)

CLINICAL SYNDROMES

Intestinal Amebiasis The most common type of amebic infection is asymptomatic cyst passage. Even in highly endemic areas, most patients harbor *E. dispar*.

Symptomatic amebic colitis develops 2–6 weeks after the ingestion of infectious cysts. A gradual onset of lower abdominal pain and mild diarrhea is followed by malaise, weight loss, and diffuse lower abdominal or back pain. Cecal involvement may mimic acute appendicitis. Patients with full-blown dysentery may pass 10–12 stools per day. The stools contain little fecal material and consist mainly of blood and mucus. In contrast to those with bacterial diarrhea, fewer than 40% of patients with amebic dysentery are febrile. Virtually all patients have heme-positive stools.

More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. Patients may develop toxic megacolon, in which there is severe bowel dilation with intramural air. Patients receiving glucocorticoids are at risk for severe amebiasis. The association between severe amebiasis complications and glucocorticoid therapy emphasizes the importance of excluding amebiasis when inflammatory bowel disease is suspected. An occasional patient presents with only an asymptomatic or tender abdominal mass caused by an ameboma, which is easily confused with cancer on barium studies. A positive serologic test or biopsy can prevent unnecessary surgery in this setting.

Environmental enteropathy ("impoverished gut"; blunted small-intestinal villi with lamina propria inflammation) is observed in tropical developing areas with endemic enteric infections, such as amebiasis. It is associated with functional gastrointestinal impairment causing malnutrition and stunted growth in children within the first 2 years of life. Bangladeshi children with symptomatic *E. histolytica* infections were 2.9 times more likely to be malnourished and 4.7 times more likely to be short for their age than were children without symptomatic infections. These factors affect their cognitive development and may be linked to loss of productivity in adulthood.

Amebic Liver Abscess Extraintestinal infection by *E. histolytica* most often involves the liver. Of travelers who develop an amebic liver abscess after leaving an endemic area, 95% do so within 5 months. Young patients with an amebic liver abscess are more likely than older patients to present in the acute phase with prominent symptoms of <10 days' duration. Most patients are febrile and have right-upper-quadrant pain, which may be dull or pleuritic in nature and may radiate to the shoulder. Point tenderness over the liver and right-sided pleural effusion are common. Jaundice is rare. Although the initial site of infection is the colon, fewer than one-third of patients with an amebic abscess have active diarrhea. Older patients from endemic areas are more likely to have a subacute course lasting 6 months, with weight loss and hepatomegaly. About one-third of patients with chronic presentations are febrile. Thus, the clinical diagnosis of an amebic liver abscess may be difficult to establish because the symptoms and signs are often nonspecific. Since 10–15% of patients present only with fever, amebic liver abscess must be considered in the differential diagnosis of fever of unknown origin (Chap. 17).

Complications of Amebic Liver Abscess Pleuropulmonary involvement, which is reported in 20–30% of patients, is the most frequent complication of amebic liver abscess. Manifestations include sterile effusions, contiguous spread from the liver, and rupture into the pleural space. Sterile effusions and contiguous spread usually resolve with medical therapy, but frank rupture into the pleural space requires drainage. A hepatobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebae. This dramatic complication carries a good prognosis. Abscesses that rupture into the peritoneum may present as an indolent leak or an acute abdomen and require both percutaneous catheter drainage and medical therapy. Rupture into the pericardium, usually from abscesses of the left lobe of the liver, carries the gravest prognosis; it can occur during medical therapy and requires surgical drainage.

Involvement of Other Extraintestinal Sites The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, may develop secondary to extension from either the intestine or the liver. Both of these conditions respond well to medical therapy. Cerebral involvement has been reported in fewer than 0.1% of patients in large clinical series. Symptoms and prognosis depend on the size and location of the lesion.

DIAGNOSTIC TESTS

Laboratory Diagnosis Stool examinations, serologic tests, and noninvasive imaging of the liver are the most important procedures in the diagnosis of amebiasis. Fecal findings suggestive of amebic colitis include a positive test for heme, a paucity of neutrophils, and amebic cysts or trophozoites. The definitive diagnosis of amebic colitis is made by the demonstration of hematophagous trophozoites of *E. histolytica*. Because trophozoites are killed rapidly by water, drying, or barium,

it is important to examine at least three fresh stool specimens. Examination of a combination of wet mounts, iodine-stained concentrates, and trichrome-stained preparations of fresh stool and concentrates for cysts or trophozoites confirms the diagnosis in 75–95% of cases. Cultures of amebae are more sensitive but are not routinely available. If stool examinations are negative, sigmoidoscopy with biopsy of the edge of ulcers may increase the yield, but this procedure is dangerous during fulminant colitis because of the risk of perforation. Trophozoites in a biopsy specimen from a colonic mass confirm the diagnosis of ameboma, but trophozoites are rare in liver aspirates because they are found in the abscess capsule and not in the readily aspirated necrotic center. Accurate diagnosis requires experience, since the trophozoites may be confused with neutrophils and the cysts must be differentiated morphologically from those of *Entamoeba hartmanni*, *Entamoeba coli*, and *Endolimax nana*, which do not cause clinical disease and do not warrant therapy. Unfortunately, the cysts of *E. histolytica* cannot be distinguished microscopically from those of *E. dispar*, *E. moshkovskii*, or *E. bangladeshi*. Therefore, the microscopic diagnosis of *E. histolytica* can be made only by the detection of *Entamoeba* trophozoites that have ingested erythrocytes. More sensitive and specific tests in stool include enzyme immunoassay detection of the Gal/GalNAc lectin of *E. histolytica* and new multiplex polymerase chain reaction (PCR) stool panels that include *E. histolytica*.

Serology is an important addition to the methods used for parasitologic diagnosis of invasive amebiasis. Enzyme-linked immunosorbent assays and agar gel diffusion assays are positive in >90% of cases with colitis, ameboma, or liver abscess. Positive results in conjunction with the appropriate clinical syndrome suggest active disease because serologic findings usually revert to negative within 6–12 months. Even in highly endemic areas such as South Africa, fewer than 10% of asymptomatic individuals have a positive amebic serology. The interpretation of the indirect hemagglutination test is difficult because titers may remain positive for as long as 10 years.

Up to 10% of patients with acute amebic liver abscess may have negative serologic findings; in suspected cases with an initially negative result, testing should be repeated in a week. In contrast to carriers of *E. dispar*, most asymptomatic carriers of *E. histolytica* develop antibodies. Thus, serologic tests are helpful in assessing the risk of invasive amebiasis in asymptomatic, cyst-passing individuals in nonendemic areas. Serologic tests also should be performed in patients with ulcerative colitis before the institution of glucocorticoid therapy to prevent the development of severe colitis or toxic megacolon owing to unsuspected amebiasis. Recently, a loop-mediated isothermal amplification (LAMP) assay was shown to be a potential alternative for direct detection of *E. histolytica* DNA in pus samples from amebic liver abscesses. LAMP is a relatively simple, rapid, and low-cost method of DNA amplification that could be a better alternative for diagnosis in developing countries. Routine hematology and chemistry tests usually are not very helpful in the diagnosis of invasive amebiasis. About three-fourths of patients with an amebic liver abscess have leukocytosis (>10,000 cells/μL); this condition is particularly likely if symptoms are acute or complications have developed. Invasive amebiasis does not elicit eosinophilia. Anemia, if present, is usually multifactorial. Even with large liver abscesses, liver enzyme levels are normal or minimally elevated. The alkaline phosphatase level is most often elevated and may remain so for months. Aminotransferase elevations suggest acute disease or a complication.

Radiographic Studies Radiographic barium studies are potentially dangerous in acute amebic colitis. Amebomas are usually identified first by a barium enema, but biopsy is necessary for differentiation from carcinoma.

Radiographic techniques such as ultrasonography, CT, and MRI are all useful for detection of the round or oval hypoechoic cyst. More than 80% of patients who have had symptoms for >10 days have a single abscess of the right lobe of the liver **(Fig. 218-3)**. Approximately 50% of patients who have had symptoms for <10 days have multiple abscesses. Findings associated with complications include large abscesses (>10 cm) in the superior part of the right lobe, which may rupture into the pleural space; multiple lesions, which must be differentiated from pyogenic abscesses; and lesions of the left lobe, which may rupture into the pericardium. Because abscesses resolve slowly and may increase in size despite a clinical response to therapy, frequent follow-up ultrasonography may prove confusing. Complete resolution of a liver abscess within 6 months can be anticipated in two-thirds of patients, but 10% may have persistent abnormalities for a year.

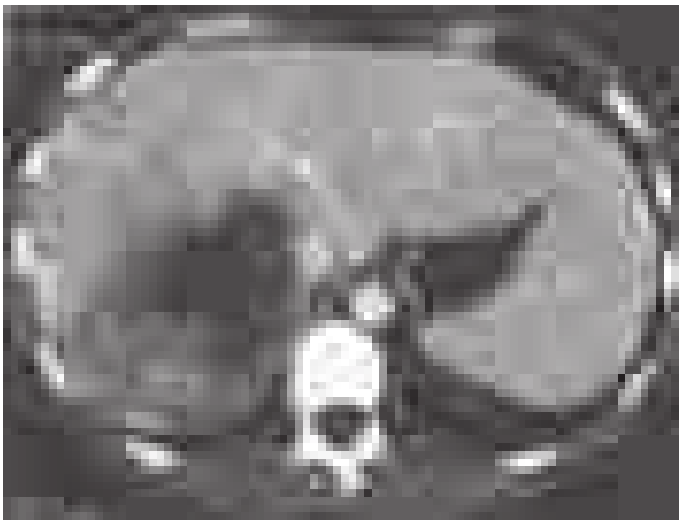

FIGURE 218-3 Abdominal CT scan of a large amebic abscess of the right lobe of the liver. *(Courtesy of the Department of Radiology, UCSD Medical Center, San Diego; with permission.)*

Differential Diagnosis The differential diagnosis of intestinal amebiasis includes bacterial diarrheas **(Chap. 128)** caused by *Campylobacter* **(Chap. 162)**; enteroinvasive *Escherichia coli* **(Chap. 156)**; and species of *Shigella* **(Chap. 161)**, *Salmonella* **(Chap. 160)**, and *Vibrio* **(Chap. 163)**. Because the typical patient with amebic colitis has less prominent fever than in these other conditions as well as heme-positive stools with few neutrophils, correct diagnosis requires bacterial cultures, microscopic examination of stools, and amebic serologic testing. As has been mentioned, amebiasis must be ruled out in any patient thought to have inflammatory bowel disease.

Because of the variety of presenting signs and symptoms, amebic liver abscess can easily be confused with pulmonary or gallbladder disease or with any febrile illness with few localizing signs, such as malaria **(Chap. 219)** or typhoid fever **(Chap. 160)**. The diagnosis should be considered in members of high-risk groups who have recently traveled outside the United States **(Chap. 119)** and in inmates of institutions. Once radiographic studies have identified an abscess in the liver, the most important differential diagnosis is between amebic and pyogenic abscess. Patients with pyogenic abscess typically are older and have a history of underlying bowel disease or recent surgery. Amebic serology is helpful, but aspiration of the abscess, with Gram's staining and culture of the material, may be required for differentiation of the two diseases.

TREATMENT

Amebiasis

INTESTINAL DISEASE **(TABLE 218-1)**

The drugs used to treat amebiasis can be classified according to their primary site of action. Luminal amebicides are poorly absorbed and reach high concentrations in the bowel, but their activity is limited to cysts and trophozoites close to the mucosa. Only two luminal drugs are available in the United States: iodoquinol and paromomycin. Indications for the use of luminal agents include eradication of cysts in patients with colitis or a liver abscess and treatment of asymptomatic carriers. The majority of asymptomatic individuals who pass cysts are colonized with *E. dispar*, which does not warrant

TABLE 218-1 Drug Therapy for Amebiasis

INDICATION	THERAPY
Asymptomatic carriage	Luminal agent: iodoquinol (650-mg tablets), 650 mg tid for 20 days; *or* paromomycin (250-mg tablets), 500 mg tid for 10 days
Acute colitis	Metronidazole (250- or 500-mg tablets), 750 mg PO or IV tid for 5–10 days; *or* tinidazole, 2 g/d PO for 3 days ***plus*** Luminal agent as above
Amebic liver abscess	Metronidazole, 750 mg PO or IV for 5–10 days; *or* tinidazole, 2 g PO once; *or* ornidazole,[a] 2 g PO once ***plus*** Luminal agent as above

[a]Not available in the United States.

specific therapy. However, it is prudent to treat asymptomatic individuals who pass cysts unless *E. dispar* colonization can be definitively demonstrated by specific antigen-detection tests.

Tissue amebicides reach high concentrations in the blood and tissue after oral or parenteral administration. The development of nitroimidazole compounds, especially metronidazole, was a major advance in the treatment of invasive amebiasis. Patients with amebic colitis should be treated with IV or oral metronidazole. Side effects include nausea, vomiting, abdominal discomfort, and a disulfiram-like reaction. Another, longer-acting imidazole compound, tinidazole, is likewise effective and is available in the United States. All patients should also receive a full course of therapy with a luminal agent, since metronidazole does not eradicate cysts. Resistance to metronidazole has been selected in the laboratory but has not been found in clinical isolates. Relapses are not uncommon and probably represent reinfection or failure to eradicate amebae from the bowel because of an inadequate dosage or duration of therapy.

AMEBIC LIVER ABSCESS

Metronidazole is the drug of choice for amebic liver abscess. Longer-acting nitroimidazoles (tinidazole and ornidazole) have been effective as single-dose therapy in developing countries. With early diagnosis and therapy, mortality rates from uncomplicated amebic liver abscess are <1%. There is no evidence that combined therapy with two drugs is more effective than the single-drug regimen. Studies of South Africans with liver abscesses demonstrated that 72% of patients without intestinal symptoms had bowel infection with *E. histolytica*; thus, all treatment regimens should include a luminal agent to eradicate cysts and prevent further transmission. Amebic liver abscess recurs rarely.

More than 90% of patients respond dramatically to metronidazole therapy with decreases in both pain and fever within 72 h. Indications for aspiration of liver abscesses are (1) the need to rule out a pyogenic abscess, particularly in patients with multiple lesions; (2) the lack of a clinical response in 3–5 days; (3) the threat of imminent rupture; and (4) the need to prevent rupture of left-lobe abscesses into the pericardium. There is no evidence that aspiration, even of large abscesses (up to 10 cm), accelerates healing. Percutaneous drainage may be successful even if the liver abscess has already ruptured. Surgery should be reserved for instances of bowel perforation and rupture into the pericardium.

PREVENTION

Amebic infection is spread by ingestion of food or water contaminated with cysts. Since an asymptomatic carrier may excrete up to 15 million cysts per day, prevention of infection requires adequate sanitation and eradication of cyst carriage. In high-risk areas, infection can be minimized by the avoidance of unpeeled fruits and vegetables and the use of bottled water. Because cysts are resistant to readily attainable levels of chlorine, disinfection by iodination (tetraglycine hydroperiodide) is recommended. There is no effective prophylaxis.

INFECTION WITH FREE-LIVING AMEBAE

EPIDEMIOLOGY

There are multiple genera of free-living amebae, but the major human pathogens are *Acanthamoeba*, *Naegleria*, and *Balamuthia*. All of these parasites can cause serious central nervous system (CNS) infections, which are almost always fatal. *Acanthamoeba* and *Naegleria* are distributed throughout the world and have been isolated from a wide variety of fresh and brackish water, including water from taps, lakes, hot springs, swimming pools, heating and air-conditioning units, and hospital water networks, and even from the nasal passages of healthy children. Encystation may protect these protozoa from desiccation and food deprivation. The persistence of *Legionella pneumophila* in water supplies is attributable in part to chronic infection of free-living amebae, particularly *Acanthamoeba*. Recent in vitro studies have suggested that a number of pathogens that can resist phagosome-mediated killing may be able to survive within water systems in free-living amebae. These include *Pseudomonas aeruginosa*, mycobacteria (both slow-growing species—e.g., those in the *Mycobacterium avium* complex, *M. kansasii*, and *M. gordonae*—and rapid-growing species—e.g., *M. chelonae and M. abscessus*), and viruses such as adenoviruses and echoviruses.

In contrast, the environmental niche of free-living amebae of the genus *Balamuthia* appears to be soil. A soil sample from a flowerpot was linked to a fatal infection in a child. Cases have been reported from all continents except Africa, but the majority of cases are from warm, dry areas of the southwestern United States and Latin America.

With better recognition of these pathogens, additional risk factors have been identified. Since 2010, five cases of *Naegleria fowleri* infection have been reported in northern U.S. states and have been associated with exposure to piped water, which represents a new ecologic niche. Since 2009, three clusters of *Balamuthia mandrillaris* infections have been associated with organ transplantation. *Acanthamoeba* species have caused large outbreaks of microbial keratitis associated with contact lens wear.

NAEGLERIA INFECTIONS

Primary amebic meningoencephalitis (PAM) is a fulminant CNS infection caused by the free-living ameba *N. fowleri*, which thrives in warm freshwater of lakes and rivers. In the United States, 138 cases of PAM were reported from 1962 through 2015. Although the number of infections reported annually has remained stable (0–8), recent changes in the epidemiology of PAM are a cause of concern. In 2010–2015, 24 cases of PAM were reported and confirmed by the Centers for Disease Control and Prevention (CDC). In 2010, a PAM case was reported for the first time from the northern state of Minnesota; this case was followed by additional cases from Minnesota, Indiana, and Kansas in 2011 and 2012. With climate change, other areas may be at risk because of higher temperatures. The remaining cases were reported mostly from southern states. Sixty-three percent of cases affected female patients, and the median age of patients was 11 years (range, 4–56 years). The majority of patients (19, or 79%) were exposed to recreational freshwater from lakes, reservoirs, rivers, streams, or ditches. The remaining five cases (21%) were due to tap-water exposure through nasal irrigation with a neti pot, playing on a backyard waterslide, and swimming in a poorly maintained pool.

PAM follows the aspiration of water contaminated with trophozoites or cysts or the inhalation of contaminated dust leading to invasion of the olfactory neuroepithelium. Infection is most common in otherwise healthy children or young adults, who often report recent swimming in lakes or heated swimming pools. In rare instances, cases occur when contaminated water is used for nasal irrigation. After an incubation period of 2–15 days, severe headache, high fever, nausea, vomiting, and meningismus develop. Photophobia and palsies of the third, fourth, and sixth cranial nerves are common. Rapid progression to seizures and coma may follow. The prognosis is uniformly poor: most patients die within a week.

The diagnosis of *Naegleria* infection should be considered in any patient who has purulent meningitis without evidence of bacteria on

Gram's staining, antigen detection assay, and culture. Other laboratory findings resemble those for fulminant bacterial meningitis, with elevated intracranial pressure, high white blood cell counts (up to 20,000/μL), and elevated protein concentrations and low glucose levels in cerebrospinal fluid (CSF). Diagnosis depends on the detection of motile trophozoites in wet mounts of fresh spinal fluid. Antibodies to *Naegleria* species have been detected in healthy adults; thus serologic testing is not useful in the diagnosis of acute infection. Diagnostic PCR and histochemical staining of biopsies are available through the CDC.

A number of antimicrobial agents have in vitro activity against *N. fowleri*, but the prognosis remains poor. The few survivors have been treated with amphotericin B and rifampin. The new antiparasitic agent miltefosine—an alkylphosphocholine compound used to treat visceral leishmaniasis—is active in vitro against *Naegleria*, *Acanthamoeba*, and *Balamuthia* and is available from the CDC. Of three patients who received miltefosine for *Naegleria* infection, one recovered completely, one survived with significant neurologic deficits, and one died. Since 2013, when miltefosine became available through the CDC, this drug has been administered to both of two surviving U.S. patients with PAM and to three (33%) of nine patients who died of PAM (CDC, unpublished data). Early diagnosis, prompt combination therapy including miltefosine, and aggressive management of neurologic complications are important factors in better outcomes. A clinician whose patient may have PAM should contact the CDC Emergency Operations Center at (770) 488-7100 for assistance in diagnosis by PCR and treatment recommendations (which should include miltefosine).

ACANTHAMOEBA INFECTIONS

Granulomatous Amebic Encephalitis Infection with *Acanthamoeba* species follows a more indolent course than *Naegleria* infection and typically occurs in chronically ill or debilitated patients. Risk factors include lymphoproliferative disorders, chemotherapy, glucocorticoid therapy, lupus erythematosus, and AIDS. Infection usually reaches the CNS hematogenously from a primary focus in the sinuses, skin, or lungs. In the CNS, the onset is insidious, and the syndrome often mimics a space-occupying lesion. Altered mental status, headache, and stiff neck may be accompanied by focal findings such as cranial nerve palsies, ataxia, and hemiparesis. Cutaneous ulcers or hard nodules containing amebae are frequently detected in AIDS patients with disseminated *Acanthamoeba* infection.

Examination of the CSF for trophozoites may be diagnostically helpful, but lumbar puncture may be contraindicated because of increased intracerebral pressure. CT frequently reveals cortical and subcortical lesions of decreased density consistent with embolic infarcts. In other patients, multiple enhancing lesions with edema may mimic the CT appearance of toxoplasmosis **(Chap. 223)**. Demonstration of the trophozoites and cysts of *Acanthamoeba* on wet mounts or in biopsy specimens establishes the diagnosis. Culture on non-nutrient agar plates seeded with *Escherichia coli* also may be helpful. Fluorescein-labeled antiserum is available from the CDC for the detection of protozoa in biopsy specimens. Granulomatous amebic encephalitis in patients with AIDS may have an accelerated course (with survival for only 3–40 days) because of the difficulty these individuals have in forming granulomas. Various antimicrobial agents have been used to treat *Acanthamoeba* infection, but miltefosine from the CDC should be included in combination therapy.

Keratitis The incidence of keratitis caused by *Acanthamoeba* has increased in the past 20 years, in part as a result of improved diagnosis. Earlier infections were associated with trauma to the eye and exposure to contaminated water. At present, most infections are linked to extended-wear contact lenses, and rare cases are associated with laser-assisted in situ keratomileusis (LASIK). Risk factors include the use of homemade saline, the wearing of lenses while swimming, and inadequate disinfection. Since contact lenses presumably cause microscopic trauma, early corneal findings may be nonspecific. The first symptoms usually include tearing and the painful sensation of a foreign body. Once infection is established, progression is rapid. The characteristic clinical sign is an annular, paracentral corneal ring representing a corneal abscess. Deeper corneal invasion and loss of vision may follow.

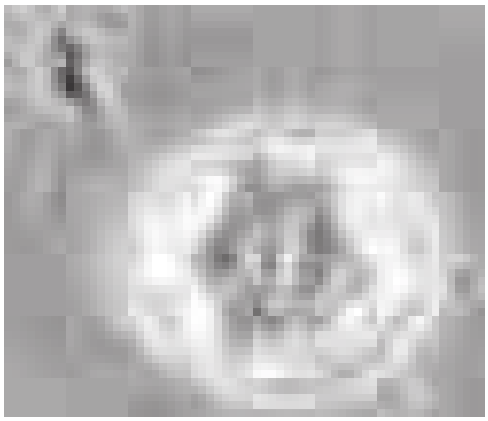

FIGURE 218-4 Double-walled cyst of *Acanthamoeba castellani*, as seen by phase-contrast microscopy. *(From DJ Krogstad et al, in A Balows et al [eds]: Manual of Clinical Microbiology, 5th ed. Washington, DC, American Society for Microbiology, 1991.)*

The differential diagnosis includes bacterial, mycobacterial, and herpetic infection. The irregular polygonal cysts of *Acanthamoeba* **(Fig. 218-4)** may be identified in corneal scrapings or biopsy material, and trophozoites can be grown on special media. Cysts are resistant to available drugs, and the results of medical therapy have been disappointing. Some reports have suggested partial responses to propamidine isethionate eyedrops. Severe infections usually require keratoplasty.

BALAMUTHIA INFECTIONS

Balamuthia mandrillaris is a free-living ameba that was first identified in 1986 as the cause of a fatal infection in a mandrill baboon at the Wild Animal Park in San Diego, California. The parasite has been isolated from soil and dust and is probably widespread in the environment. It is an important etiologic agent of granulomatous amebic encephalitis, cutaneous lesions, and sinus infections in humans. The potential risk factors for granulomatous amebic encephalitis identified by the California Encephalitis Project include young age, immunocompromising conditions, and Hispanic ethnicity. The infection likely starts with percutaneous or mucous membrane exposure and then spreads hematogenously to the brain and other organs—a pattern that explains the risk for transmission through organ transplantation. In 2009–2010, two clusters of organ transplant–transmitted *B. mandrillaris* infections were detected by recognition of severe unexpected illness in multiple recipients from the same donor after an incubation period of 17–24 days.

Frequently, *Balamuthia* affects immunocompetent individuals, in whom the course is typically subacute, with focal neurologic signs, fever, seizures, and headaches leading to death within 1 week to several months after onset. Skin lesions may occur on the face, trunk, or extremities. In addition to dust inhalation, inoculation of trophozoites or cysts from stagnant water may occur through open wounds or mucous membranes. Diagnosis relies on examination of CSF, which reveals mononuclear or neutrophilic pleocytosis, elevated protein levels, and normal to low glucose concentrations. Amebae are rarely isolated from CSF. Multiple hypodense lesions are usually detected with imaging studies **(Fig. 218-5)**. Fluorescent antibody and PCR assays are available from the CDC.

The fewer than five surviving patients in the United States have been treated with a variety of drugs, including pentamidine, flucytosine, sulfadiazine, and macrolides. The CDC recommends that miltefosine now be included, as for treatment of other free-living amebae. The differential diagnosis includes tuberculomas **(Chap. 173)** and neurocysticercosis **(Chap. 230)**.

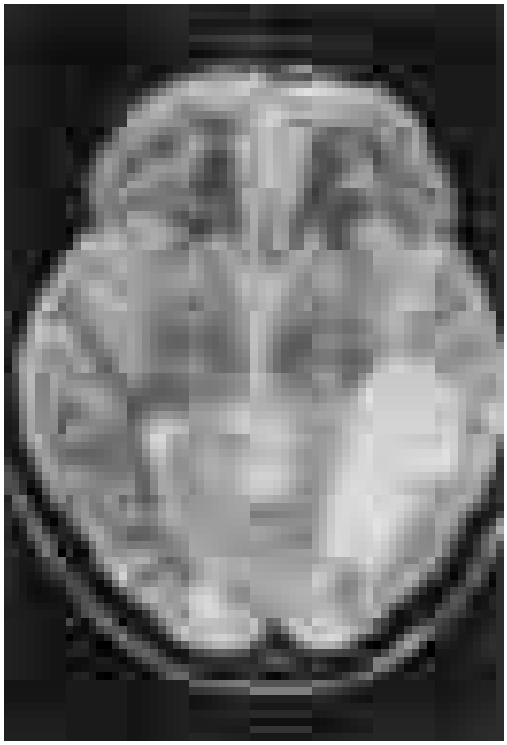

FIGURE 218-5 Brain MRI of amebic meningoencephalitis due to *Balamuthia mandrillaris*. A large lesion in the parieto-occipital lobe and other smaller lesions are seen. *(Courtesy of the Department of Radiology, UCSD Medical Center, San Diego.)*

FURTHER READING

Amebiasis

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Free-Living Amebae

Capewell LG et al: Diagnosis, clinical course, and treatment of primary amoebic meningoencephalitis in the United States, 1937–2013. J Ped Infect Dis Soc 4:e68, 2015.

Farnon EC et al: Transmission of *Balamuthia mandrillaris* by organ transplantation. Clin Infect Dis 63:878, 2016.

219 Malaria

Nicholas J. White, Elizabeth A. Ashley

Humanity has but three great enemies: Fever, famine, and war; of these by far the greatest, by far the most terrible, is fever.

—William Osler, 1896

Malaria is a protozoan disease transmitted by the bite of infected female *Anopheles* mosquitoes. The most important of the parasitic diseases of humans, malaria is transmitted in 91 countries containing 3 billion people and causes ~1200 deaths each day. Mortality rates have decreased dramatically over the past 15 years as a result of highly effective control programs in several countries. Malaria was eliminated from the United States, Canada, Europe, and Russia >50 years ago, but its prevalence rose in many parts of the tropics between 1970 and 2000. In response to this rise, there has been substantial investment aimed at increasing access to accurate diagnosis, effective treatments, and insecticide-treated bed nets. This investment has resulted in a decline in the global burden of malaria, although in the past few years progress has stalled. An increasing number of countries are now targeting malaria elimination. This ambitious goal is threatened by increasing resistance to antimalarial drugs and insecticides.

Malaria remains today, as it has been for centuries, a heavy burden on tropical communities, a threat to nonendemic countries, and a danger to travelers.

ETIOLOGY AND PATHOGENESIS

Six species of the genus *Plasmodium* cause nearly all malarial infections in humans. These are *P. falciparum*, *P. vivax*, two morphologically identical sympatric species of *P. ovale* (*curtisi* and *wallikeri*), *P. malariae*, and—in Southeast Asia—the monkey malaria parasite *P. knowlesi* **(Table 219-1)**. While almost all deaths are caused by falciparum malaria, *P. knowlesi* and occasionally *P. vivax* can also cause severe illness. Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from its salivary glands during a blood meal **(Fig. 219-1)**. These microscopic motile forms of the malaria parasite are carried rapidly via the bloodstream to the liver, where they invade hepatic parenchymal cells and begin a period of asexual reproduction. By this amplification process (known as *intrahepatic* or *preerythrocytic schizogony*), a single sporozoite may produce from 10,000 to >30,000 daughter merozoites. The swollen infected liver cells eventually burst, discharging motile *merozoites* into the bloodstream. These merozoites then invade red blood cells (RBCs) to become *trophozoites* and multiply six- to twentyfold every 48 h (*P. knowlesi*, 24 h; *P. malariae*, 72 h). When the parasites reach densities of ~50/μL of blood (~100 million parasites in the blood of an adult), the symptomatic stage of the infection begins. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain inert for a period ranging from 2 weeks to ≥1 year. These dormant forms, or *hypnozoites*, are the cause of the relapses that characterize infection with these species.

Attachment of merozoites to erythrocytes is mediated via a complex interaction with several specific erythrocyte surface receptors. *P. falciparum* merozoites bind to erythrocyte binding antigen 175 and glycophorin A. The other glycophorins also contribute. The merozoite reticulocyte-binding protein homologue 5 (PfRh5) plays a critical role binding to red cell basigin (CD147, EMMPRIN). *P. vivax* binds to receptors on young red cells. The Duffy blood-group antigen Fy^a or Fy^b plays an important role in invasion. Most West Africans and people with origins in that region carry the Duffy-negative FyFy phenotype and are generally resistant to *P. vivax* malaria. *P. knowlesi* also invades Duffy-positive human RBCs preferentially. During the first few hours of intraerythrocytic development, the small "ring forms" of the different malaria species appear similar under light microscopy. As the trophozoites enlarge, species-specific characteristics become evident, malaria pigment (hemozoin) becomes visible, and the parasite assumes an irregular or ameboid shape. By the end of the intraerythrocytic life cycle, the parasite has consumed two-thirds of the RBC's hemoglobin and has grown to occupy most of the cell. It is now called a *schizont*. Multiple nuclear divisions have taken place (*schizogony* or *merogony*). The infected RBC then ruptures to release 6–30 daughter merozoites, each potentially capable of invading a new RBC and repeating the cycle. The disease in human beings is caused by the direct effects of the asexual parasite—RBC invasion and destruction—and by the host's reaction. Some of the blood-stage parasites develop into morphologically distinct, longer-lived sexual forms (*gametocytes*) that can transmit malaria. In falciparum malaria, a delay of several asexual cycles precedes this switch to gametocytogenesis. Female gametocytes typically outnumber males by 4:1.

After being ingested in the blood meal of a biting female anopheline mosquito, the male and female gametocytes fuse to form a zygote

TABLE 219-1 Characteristics of *Plasmodium* Species Infecting Humans

CHARACTERISTIC	FINDING FOR INDICATED SPECIES				
	P. FALCIPARUM	*P. VIVAX*	*P. OVALE*[a]	*P. MALARIAE*	*P. KNOWLESI*
Duration of intrahepatic phase (days)	5.5	8	9	15	5.5
Number of merozoites released per infected hepatocyte	30,000	10,000	15,000	15,000	20,000
Duration of erythrocytic cycle (hours)	48	48	50	72	24
Red cell preference	Younger cells (but can invade cells of all ages)	Reticulocytes and cells up to 2 weeks old	Reticulocytes	Older cells	Younger cells
Morphology	Usually only ring forms; banana-shaped gametocytes	Irregularly shaped large rings and trophozoites; enlarged erythrocytes; Schüffner's dots	Infected erythrocytes, enlarged and oval with tufted ends; Schüffner's dots	Band or rectangular forms of trophozoites common	Resembles *P. falciparum* (early trophozoites) or *P. malariae* (later trophozoites, including band forms)
Pigment color	Black	Yellow-brown	Dark brown	Brown-black	Dark brown
Ability to cause relapses	No	Yes	Yes	No	No

[a]Genomic studies have revealed *P. ovale* to be two sympatric species: *P. ovale curtisi* and *P. ovale wallikeri*.

in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feed, thus completing the life cycle.

EPIDEMIOLOGY

Malaria occurs throughout most of the tropical regions of the world (Fig. 219-2). *P. falciparum* predominates in Africa, New Guinea, and Hispaniola (i.e., the Dominican Republic and Haiti); *P. vivax* is more common in Central and South America. The prevalence of these two species is approximately equal on the Indian subcontinent and in eastern Asia and Oceania. *P. malariae* is found in most endemic areas, especially throughout sub-Saharan Africa, but is much less common. *P. ovale* is relatively unusual outside of Africa and, where it is found, comprises <1% of isolates. *P. knowlesi* causes human infections commonly on the island of Borneo and, to a lesser extent, elsewhere in Southeast Asia, where the main hosts, long-tailed and pig-tailed macaques, are found.

The epidemiology of malaria is complex and may vary considerably even within relatively small geographic areas. Endemicity traditionally has been defined in terms of rates of microscopy-detected parasitemia or palpable spleens in children 2–9 years of age and has been classified as hypoendemic (<10%), mesoendemic (11–50%), hyperendemic (51–75%), and holoendemic (>75%). In holo- and hyperendemic areas (e.g., certain regions of tropical Africa or coastal New Guinea) where there is intense *P. falciparum* transmission, people may sustain as much as one infectious mosquito bite per day and are infected repeatedly throughout their lives. In such settings, malaria morbidity and mortality are substantial during early childhood. Immunity against disease is hard won in these areas following repeated symptomatic infections in childhood, but, if the child survives, infections become increasingly likely to be asymptomatic. These asymptomatic older children and adults are a major source of malaria transmission. As control measures progress and urbanization expands, environmental conditions become less conducive to malaria transmission, and all age groups may lose protective immunity and become susceptible to illness. Constant, frequent, year-round infection is termed *stable transmission*. In areas where transmission is low, erratic, or focal, full protective immunity is not acquired, and symptomatic disease may occur at all ages. This situation usually exists in hypoendemic areas and is termed *unstable transmission*. Even in stable-transmission areas, there is often an increased incidence of symptomatic malaria during the rainy season coinciding with increased mosquito breeding and transmission. Malaria can behave like an epidemic disease in some areas, particularly those with unstable malaria, such as northern India (the Punjab region), the Horn of Africa, Rwanda, Burundi, southern Africa, and Madagascar. Epidemics may occur when changes in environmental, economic, or social conditions (e.g., heavy rains following drought or migration—usually of refugees or workers—from a non-malarious region to an area of high transmission) are compounded by failure to invest in national programs or by a breakdown in malaria control and prevention services caused by war or civil disorder. Epidemics often result in high mortality rates among all age groups.

The principal determinants of the epidemiology of malaria are the number (density), the human-biting habits, and the longevity of the anopheline mosquito vectors. More than 100 of the >400 anopheline species can transmit

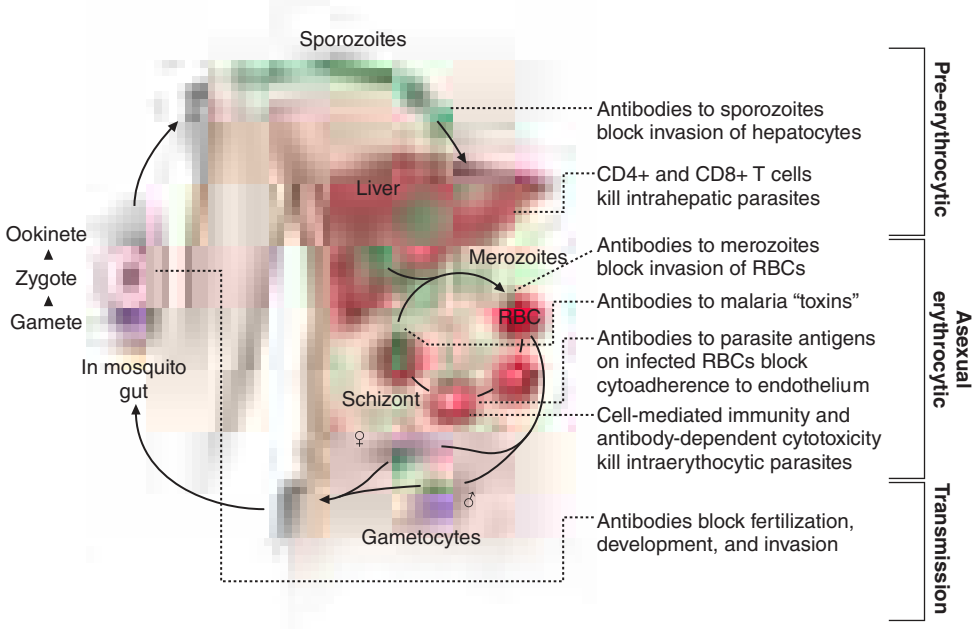


FIGURE 219-1 The malaria transmission cycle from mosquito to human and targets of immunity. RBC, red blood cell.

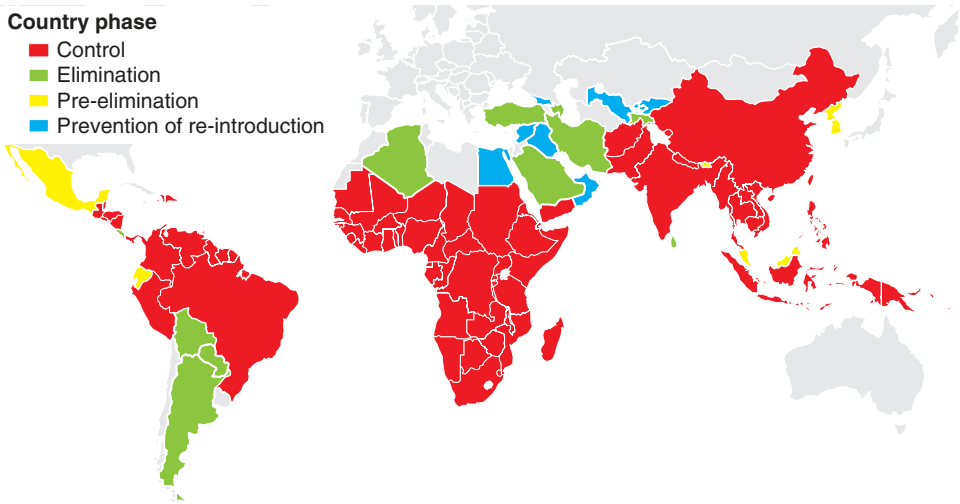


FIGURE 219-2 Malaria-endemic countries showing progress towards elimination. (*Source: worldmalariareport.org/.*)

malaria, but the ~40 species that do so commonly vary considerably in their efficiency as malaria vectors. More specifically, the transmission of malaria is directly proportional to the density of the vector, the square of the number of human bites per day per mosquito, and the tenth power of the probability of the mosquito's surviving for 1 day. Mosquito longevity is particularly important as a determinant of malaria transmissibility because the portion of the parasite's life cycle that takes place within the mosquito—from gametocyte ingestion to subsequent inoculation (*sporogony*)—lasts 8–30 days, depending on ambient temperature. In order to transmit malaria, the mosquito must therefore survive for >7 days. Sporogony is not completed at cooler temperatures—i.e., <16°C (<60.8°F) for *P. vivax* and <21°C (<69.8°F) for *P. falciparum*; thus transmission does not occur below these temperatures or at high altitudes, although malaria outbreaks and transmission have occurred in the highlands (>1500 m) of eastern Africa, which were previously free of vectors. The most effective mosquito vectors of malaria are those, such as the *Anopheles gambiae* species complex in Africa, that are long-lived, occur in high densities in tropical climates, breed readily, and bite humans in preference to other animals. The entomologic inoculation rate (i.e., the number of sporozoite-positive mosquito bites per person per year) is the most common measure of malaria transmission and varies from <1 in some parts of Latin America and Southeast Asia to >300 in parts of tropical Africa.

PATHOPHYSIOLOGY

ERYTHROCYTE CHANGES

After invading an erythrocyte, the growing malarial parasite progressively consumes and degrades intracellular proteins, principally hemoglobin. The potentially toxic heme is detoxified by lipid-mediated crystallization to biologically inert hemozoin (malaria pigment). The parasite also alters the RBC membrane by changing its transport properties, exposing cryptic surface antigens, and inserting new parasite-derived proteins. The RBC becomes more irregular in shape, more antigenic, and less deformable.

In *P. falciparum* infections, membrane protuberances appear on the erythrocyte's surface 12–15 h after the cell's invasion. These "knobs" extrude a high-molecular-weight, antigenically variant, strain-specific erythrocyte membrane adhesive protein (PfEMP1) that mediates attachment to receptors on venular and capillary endothelium (*cytoadherence*). Several vascular receptors have been identified; intercellular adhesion molecule 1 and endothelial protein C receptor are important in the brain, chondroitin sulfate B predominates in the placenta, and CD36 binds parasitized RBCs in most other organs. Erythrocytes containing more mature parasites stick inside and eventually block capillaries and venules. These infected RBCs may also adhere to uninfected RBCs (to form rosettes) and to other parasitized erythrocytes (agglutination). The processes of cytoadherence, rosetting, and agglutination are central to the pathogenesis of falciparum malaria. They result in the sequestration of infected RBCs in vital organs (particularly the brain), where they interfere with microcirculatory flow and metabolism. Sequestered parasites continue to develop out of reach of the principal host defense mechanism: splenic processing and filtration. As a consequence, only the younger ring forms of the asexual parasites are seen circulating in the peripheral blood in falciparum malaria, and the level of peripheral parasitemia underestimates the true number of parasites within the body. Severe malaria is also associated with reduced deformability of uninfected erythrocytes, which compromises their passage through the partially obstructed capillaries and venules and shortens their survival.

In the other human malarias, significant sequestration does not occur, and all stages of the parasite's development are evident on peripheral-blood smears. *P. vivax* and *P. ovale* show a marked predilection for young RBCs and *P. malariae* for old cells; these species produce a level of parasitemia that seldom exceeds 2%. In contrast, *P. falciparum* can invade erythrocytes of all ages and may be associated with very high parasite densities. Dangerously high parasite densities may also occur in *P. knowlesi* infections, with rapid increases as a result of the shorter (24-h) asexual life cycle.

HOST RESPONSE

Initially, the host responds to malaria infection by activating nonspecific defense mechanisms. Splenic immunologic and filtrative clearance functions are augmented, and the removal of both parasitized and uninfected erythrocytes is accelerated. The spleen also removes damaged ring-form parasites (a process known as "pitting") and returns the once-infected erythrocytes to the circulation, where their survival is shortened. The parasitized cells escaping splenic removal are destroyed when the schizont ruptures. The material released induces monocyte/macrophage activation and the release of proinflammatory cytokines, which cause fever and other pathologic effects. Temperatures of ≥40°C (≥104°F) damage mature parasites; in untreated infections, the effect of such temperatures is to further synchronize the parasitic cycle, with eventual production of the regular fever spikes and rigors that originally characterized the different malarias. These regular fever patterns (*quotidian*, daily; *tertian*, every 2 days; *quartan*, every 3 days) are seldom seen today as patients receive prompt and effective antimalarial treatment.

The geographic distributions of the thalassemias, sickle cell disease, hemoglobins C and E, hereditary ovalocytosis, and glucose-6-phosphate dehydrogenase (G6PD) deficiency closely resemble that of falciparum malaria before the introduction of control measures. This similarity suggests that these genetic disorders confer protection against death from falciparum malaria. For example, HbA/S heterozygotes (sickle cell trait) have a sixfold reduction in the risk of dying from severe falciparum malaria and are correspondingly protected from bacterial infections that complicate malaria. Hemoglobin S–containing RBCs impair parasite growth at low oxygen tensions, and *P. falciparum*–infected RBCs containing hemoglobin S or C exhibit reduced cytoadherence because of reduced surface presentation of the adhesin PfEMP1. Parasite multiplication in HbA/E heterozygotes is reduced at high parasite densities. In Melanesia, children with α-thalassemia have more frequent malaria (both vivax and falciparum) in the early years of life, and this pattern of infection appears to protect them against severe disease. In Melanesian ovalocytosis, rigid erythrocytes resist merozoite invasion, and the intraerythrocytic milieu is hostile.

Nonspecific host defense mechanisms stop the infection's expansion, and the subsequent strain-specific immune response then controls the infection. Eventually, exposure to sufficient strains confers

protection from high-level parasitemia and disease but not from infection. As a result of this state of infection without illness (*premunition*), asymptomatic parasitemia is very common among adults and older children living in regions with stable and intense transmission (i.e., holo- or hyperendemic areas) and also in parts of low-transmission areas. Parasitemia in asymptomatic infections fluctuates in density but often averages ~5000/mL—just below the level of microscopy detection but sufficient to generate transmissible densities of gametocytes. Immunity is mainly specific for both the species and the strain of infecting malarial parasite. Both humoral immunity and cellular immunity are necessary for protection, but the mechanisms of each are incompletely understood (Fig. 219-1). Immune individuals have a polyclonal increase in serum levels of IgM, IgG, and IgA, although much of this antibody is unrelated to protection. Antibodies to a variety of parasite antigens presumably act in concert to limit in vivo replication of the parasite. In the case of falciparum malaria, the most important of these antigens is the surface adhesin—the variant protein family PfEMP1. Passively transferred IgG from immune adults has been shown to reduce levels of parasitemia in children. Passive transfer of maternal antibody contributes to the partial protection of infants from severe malaria in the first months of life. This complex immunity to disease declines when a person lives outside an endemic area for several months or longer.

Several factors retard the development of cellular immunity to malaria. These factors include the absence of major histocompatibility antigens on the surface of infected RBCs, which precludes direct T cell recognition; malaria antigen–specific immune unresponsiveness; and the enormous strain diversity of malarial parasites, along with the ability of the parasites to express variant immunodominant antigens on the erythrocyte surface that change during the course of infection. Parasites may persist in the blood for months or years (or, in the case of *P. malariae*, for decades) if treatment is not given. The complexity of the immune response in malaria, the sophistication of the parasites' evasion mechanisms, and the lack of a good in vitro correlate with clinical immunity have all slowed progress toward an effective vaccine.

CLINICAL FEATURES

Malaria is a common cause of fever in tropical countries. Clinical diagnosis is notoriously unreliable. The first symptoms of malaria are nonspecific; the lack of a sense of well-being, headache, fatigue, abdominal discomfort, and muscle aches followed by fever are all similar to the symptoms of a minor viral illness. In some instances, a prominence of headache, chest pain, abdominal pain, cough, arthralgia, myalgia, or diarrhea may suggest another diagnosis. Although headache may be severe in malaria, the neck stiffness and photophobia seen in meningitis do not occur. While myalgia may be prominent, it is not usually as severe as in dengue fever, and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common. The classic malarial paroxysms, in which fever spikes, chills, and rigors occur at regular intervals, are relatively unusual and suggest infection (often relapse) with *P. vivax* or *P. ovale*. The fever is usually irregular at first (that of falciparum malaria may never become regular). The temperature of nonimmune individuals and children often rises above 40°C (104°F), with accompanying tachycardia and sometimes delirium. Although childhood febrile convulsions may occur with any of the malarias, generalized seizures are associated specifically with falciparum malaria and may herald the development of encephalopathy (cerebral malaria). Many clinical abnormalities have been described in acute malaria, but most patients with uncomplicated infections have few abnormal physical findings other than fever, malaise, mild anemia, and (in some cases) a palpable spleen. Anemia is common among young children living in areas with stable transmission (e.g., much of West Africa), particularly where resistance has compromised the efficacy of antimalarial drugs. Frequent vivax relapse is an important cause of anemia in young children in some areas (e.g., on the island of New Guinea). In nonimmune individuals with acute malaria, the spleen takes several days to become palpable, but splenic enlargement is found in a high proportion of otherwise healthy individuals in malaria-endemic areas and reflects repeated infections. Slight enlargement of the liver is also common, particularly among young children. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated malaria and usually resolves over 1–3 weeks. Malaria is not associated with a rash. Petechial hemorrhages in the skin or mucous membranes—features of viral hemorrhagic fevers and leptospirosis—develop only very rarely in severe falciparum malaria.

SEVERE FALCIPARUM MALARIA

Appropriately and promptly treated, uncomplicated falciparum malaria (i.e., that in which the patient can sit or stand unaided and can swallow medicines and food) carries a mortality rate of <0.1%. However, once vital-organ dysfunction occurs or the total proportion of erythrocytes infected increases to >2% (a level corresponding to $>10^{12}$ parasites in an adult), mortality risk rises steeply, depending on the immunity of the host. The major manifestations of severe falciparum malaria are shown in **Table 219-2**, and features indicating a poor prognosis are listed in **Table 219-3**.

Cerebral Malaria Coma is a characteristic and ominous feature of falciparum malaria and, even with treatment, has been associated with death rates of ~20% among adults and 15% among children. Any obtundation, delirium, or abnormal behavior in falciparum malaria

TABLE 219-2 Manifestations of Severe Falciparum Malaria

SIGNS	MANIFESTATIONS
Major	
Unarousable coma/cerebral malaria	Failure to localize or respond appropriately to noxious stimuli; coma persisting for >30 min after generalized convulsion
Acidemia/acidosis	Arterial pH of <7.25, base deficit >8 meq/L, or plasma bicarbonate level of <15 mmol/L; venous lactate level of >5 mmol/L; manifests as labored deep breathing, often termed "respiratory distress"
Severe normochromic, normocytic anemia	Hematocrit of <15% or hemoglobin level of <50 g/L (<5 g/dL) with parasitemia level of <10,000/μL
Renal failure	Serum or plasma creatinine level of >265 μmol/L (>3 mg/dL); urine output (24 h) of <400 mL for adults or <12 mL/kg for children; no improvement with rehydration
Pulmonary edema/adult respiratory distress syndrome	Noncardiogenic pulmonary edema, often aggravated by overhydration
Hypoglycemia	Plasma glucose level of <2.2 mmol/L (<40 mg/dL)
Hypotension/shock	Systolic blood pressure of <50 mmHg in children 1–5 years or <80 mmHg in adults; core/skin temperature difference of >10°C; capillary refill >2 s
Bleeding/disseminated intravascular coagulation	Significant bleeding and hemorrhage from the gums, nose, and gastrointestinal tract and/or evidence of disseminated intravascular coagulation
Convulsions	More than two generalized seizures in 24 h; signs of continued seizure activity, sometimes subtle (e.g., tonic-clonic eye movements without limb or face movement)
Other	
Hemoglobinuria[a]	Macroscopic black, brown, or red urine; not associated with effects of oxidant drugs and red blood cell enzyme defects (such as G6PD deficiency)
Extreme weakness	Prostration; inability to sit unaided[b]
Hyperparasitemia	Parasitemia level of >5% in nonimmune patients (>10% in any patient)
Jaundice	Serum bilirubin level of >50 mmol/L (>3 mg/dL) if combined with a parasite density of 100,000/μL or other evidence of vital-organ dysfunction

[a]Hemoglobinuria may also occur in uncomplicated malaria and in patients with G6PD deficiency who take primaquine. [b]In children who are normally able to sit.

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

TABLE 219-3 Features Indicating a Poor Prognosis in Severe Falciparum Malaria

Clinical
Marked agitation
Hyperventilation (respiratory distress)
Low core temperature (<36.5°C; <97.7°F)
Bleeding
Deep coma
Repeated convulsions
Anuria
Shock
Laboratory
Biochemistry
Hypoglycemia (<2.2 mmol/L)
Hyperlactatemia (>5 mmol/L)
Acidemia (arterial pH <7.25, base deficit >8 meq/L, or serum HCO_3 <15 mmol/L)
Elevated serum creatinine (>265 μmol/L)
Elevated total bilirubin (>50 μmol/L)
Elevated liver enzymes (AST/ALT 3 times upper limit of normal)
Elevated muscle enzymes (CPK ↑, myoglobin ↑)
Elevated urate (>600 μmol/L)
Hematology
Leukocytosis (>12,000/μL)
Severe anemia (PCV <15%)
Coagulopathy
Decreased platelet count (<50,000/μL)
Prolonged prothrombin time (>3 s)
Prolonged partial thromboplastin time
Decreased fibrinogen (<200 mg/dL)
Parasitology
Hyperparasitemia
Increased mortality at >100,000/μL
High mortality at >500,000/μL
>20% of parasites identified as pigment-containing trophozoites and schizonts
>5% of neutrophils contain visible malaria pigment

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; PCV, packed cell volume.

should be taken very seriously. The onset of coma may be gradual or sudden following a convulsion.

Cerebral malaria manifests as diffuse symmetric encephalopathy; focal neurologic signs are unusual. Although some passive resistance to head flexion may be detected, signs of meningeal irritation are absent. The eyes may be divergent, and bruxism and a pout reflex are common, but other primitive reflexes are usually absent. The corneal reflexes are preserved, except in deep coma. Muscle tone may be either increased or decreased. The tendon reflexes are variable, and the plantar reflexes may be flexor or extensor; the abdominal and cremasteric reflexes are absent. Flexor or extensor posturing may be seen. On routine funduscopy, ~15% of patients have retinal hemorrhages; with pupillary dilation and indirect ophthalmoscopy, this figure increases to 30–40%. Other funduscopic abnormalities **(Fig. 219-3)** include discrete spots of retinal opacification (30–60%), papilledema (8% among children, rare among adults), cotton wool spots (<5%), and decolorization of a retinal vessel or segment of vessel (occasional cases). Convulsions, which are usually generalized and often repeated, occur in ~10% of adults and up to 50% of children with cerebral malaria. More covert seizure activity is common, particularly among children, and may manifest as repetitive tonic–clonic eye movements or even hypersalivation. Whereas adults rarely (<3% of cases) suffer neurologic sequelae, ~10% of children surviving cerebral malaria—especially those with hypoglycemia, severe anemia, repeated seizures, and deep coma—have residual neurologic deficits when they regain consciousness; hemiplegia, cerebral palsy, cortical blindness, deafness, and impaired cognition may all occur.

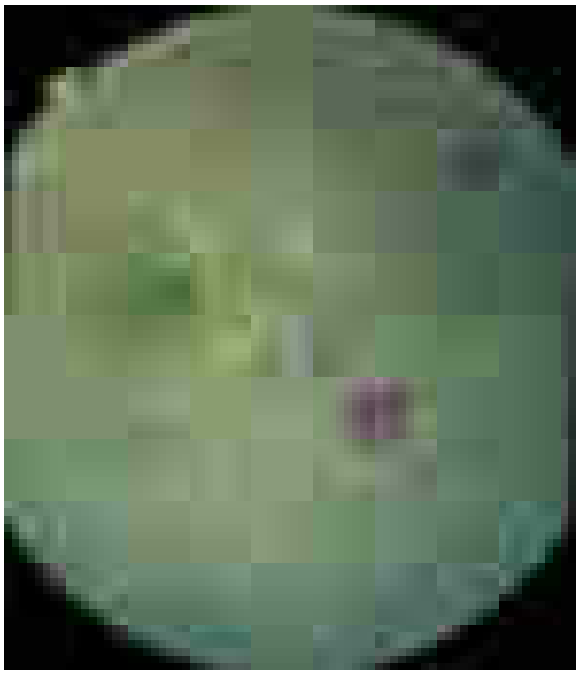


FIGURE 219-3 The eye in cerebral malaria: perimacular whitening and pale-centered retinal hemorrhages. *(Courtesy of N. Beare, T. Taylor, S. Harding, S. Lewallen, and M. Molyneux; with permission.)*

The majority of these deficits improve markedly or resolve completely within 6 months. However, the prevalence of some other deficits increases over time; ~10% of children surviving cerebral malaria have a persistent language deficit. There may also be deficits in learning, planning and executive functions, attention, memory, and nonverbal functioning. The incidence of epilepsy is increased and life expectancy decreased among these children.

Hypoglycemia Hypoglycemia, an important and common complication of severe malaria, is associated with a poor prognosis and is particularly problematic in children and pregnant women. Hypoglycemia in malaria results from a failure of hepatic gluconeogenesis and an increase in the consumption of glucose by both the host and, to a much lesser extent, the malaria parasites. This abnormality may be compounded by quinine, a powerful stimulant of pancreatic insulin secretion, which is still widely used for the treatment of both severe and uncomplicated falciparum malaria. Hyperinsulinemic hypoglycemia is especially troublesome in pregnant women receiving quinine treatment. In severe disease, the clinical diagnosis of hypoglycemia is difficult: the usual physical signs (sweating, gooseflesh, tachycardia) are absent, and the neurologic impairment caused by hypoglycemia cannot be distinguished from that caused by malaria.

Acidosis Acidosis is an important cause of death from severe malaria and results from accumulation of organic acids. Hyperlactatemia commonly coexists with hypoglycemia. In adults, coexisting renal impairment often compounds acidosis. In children, ketoacidosis also may contribute. Hydroxyphenyllactic acid, α-hydroxybutyric acid, and β-hydroxybutyric acid concentrations are elevated. Acidotic breathing, sometimes called "respiratory distress," is a sign of poor prognosis. It is followed often by circulatory failure refractory to volume expansion or inotropic drug treatment and ultimately by respiratory arrest. Plasma concentrations of bicarbonate or lactate are the best biochemical prognosticators in severe malaria. Hypovolemia is not a major contributor to acidosis. Lactic acidosis is caused by the combination of anaerobic glycolysis in tissues where sequestered parasites interfere with microcirculatory flow, lactate production by the parasites, and a failure of hepatic and renal lactate clearance.

Noncardiogenic Pulmonary Edema Adults with severe falciparum malaria may develop noncardiogenic pulmonary edema even after several days of antimalarial therapy. The pathogenesis of

this variant of the adult respiratory distress syndrome is unclear. The mortality rate is >80%. Pulmonary edema can be precipitated by overly vigorous administration of IV fluid. Noncardiogenic pulmonary edema can also develop in otherwise uncomplicated vivax malaria, where recovery is usual.

Renal Impairment Acute kidney injury is common in severe falciparum malaria. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration and agglutination interfering with renal microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days **(Chap. 304)**. Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure. Oliguric renal failure is rare among children.

Hematologic Abnormalities Anemia results from accelerated RBC removal by the spleen, obligatory RBC destruction at parasite schizogony, and ineffective erythropoiesis. In severe malaria, the deformability of both infected and uninfected RBCs is reduced. The degree of reduced deformability correlates with prognosis and with the development of anemia. Splenic clearance of all RBCs is increased. In nonimmune individuals and in areas with unstable transmission, anemia can develop rapidly and transfusion is often required. Acute hemolytic anemia with massive hemoglobinuria ("blackwater fever") may occur. Hemoglobinuria may contribute to renal injury. Some patients with blackwater fever have G6PD deficiency, but in the majority of cases it is unclear why massive hemolysis has occurred. Sudden hemolysis may follow many days after artesunate treatment of hyperparasitemia, usually as a result of relatively synchronous loss of once-parasitized "pitted" RBCs. As a consequence of repeated malarial infections, children in high-transmission areas may develop severe anemia resulting from both shortened survival of uninfected RBCs and marked dyserythropoiesis. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection.

Slight coagulation abnormalities are common in falciparum malaria, and mild thrombocytopenia is usual (a normal platelet count should raise questions about the diagnosis of malaria). Fewer than 5% of patients with severe malaria have significant bleeding with evidence of disseminated intravascular coagulation. Hematemesis from stress ulceration or acute gastric erosions also may occur rarely.

Liver Dysfunction Mild hemolytic jaundice is common in malaria. Severe jaundice is associated with *P. falciparum* infections; is more common among adults than among children; and results from hemolysis, hepatocyte injury, and cholestasis. When accompanied by other vital-organ dysfunction (often renal impairment), liver dysfunction carries a poor prognosis. Hepatic dysfunction contributes to hypoglycemia, lactic acidosis, and impaired drug metabolism. Occasional patients with falciparum malaria may develop deep jaundice (with hemolytic, hepatic, and cholestatic components) without evidence of other vital-organ dysfunction, in which case the prognosis is good.

Other Complications HIV/AIDS and malnutrition predispose to more severe malaria in nonimmune individuals. Malaria anemia is worsened by concurrent infections with intestinal helminths, hookworm in particular. Septicemia may complicate severe malaria, particularly in children. Differentiating severe malaria from sepsis with incidental parasitemia in childhood is very difficult. In endemic areas, *Salmonella* spp. bacteremia has been associated specifically with *P. falciparum* infections. Chest infections and catheter-induced urinary tract infections are common among patients who are unconscious for >3 days. Aspiration pneumonia may follow generalized convulsions. The frequencies of complications of severe falciparum malaria are summarized in **Table 219-4**.

TABLE 219-4 Relative Incidence of Severe Complications of Falciparum Malaria

COMPLICATION	NONPREGNANT ADULTS	PREGNANT WOMEN	CHILDREN
Anemia	+	++	+++
Convulsions	+	+	+++
Hypoglycemia	+	+++	+++
Jaundice	+++	+++	+
Renal failure	+++	+++	–
Pulmonary edema	++	+++	+

Note: –, rare; +, infrequent; ++, frequent; +++, very frequent.

MALARIA IN PREGNANCY

Malaria in early pregnancy causes fetal loss. In areas of high malaria transmission, falciparum malaria in primi- and secundigravid women is associated with low birth weight (average reduction, ~170 g) and consequently increased infant mortality rates. In general, infected mothers in areas of stable transmission remain asymptomatic despite intense accumulation of parasitized erythrocytes in the placental microcirculation. Maternal HIV infection predisposes pregnant women to more frequent and higher-density malaria infections, predisposes their newborns to congenital malarial infection, and exacerbates the reduction in birth weight associated with malaria.

In areas with unstable transmission of malaria, pregnant women are prone to severe infections and are particularly likely to develop high parasitemias with anemia, hypoglycemia, and acute pulmonary edema. Fetal distress, premature labor, and stillbirth or low birth weight are common results. Fetal death is usual in severe malaria. Congenital malaria occurs in fewer than 5% of newborns whose mothers are infected; its frequency and the level of parasitemia are related directly to the timing of maternal infection and the parasite density in maternal blood and in the placenta. *P. vivax* malaria in pregnancy is also associated with a reduction in birth weight (average, 110 g) but, in contrast to observations in falciparum malaria, this effect is more pronounced in multigravid than in primigravid women. About 300,000 women die in childbirth yearly, with most deaths occurring in low-income countries; maternal death from hemorrhage at childbirth is correlated with malaria-induced anemia.

MALARIA IN CHILDREN

Most of the estimated 445,000 deaths from falciparum malaria each year are in young African children. Convulsions, coma, hypoglycemia, metabolic acidosis, and severe anemia are relatively common among children with severe malaria, whereas deep jaundice, oliguric acute kidney injury, and acute pulmonary edema are unusual. Severely anemic children may present with labored deep breathing, which in the past has been attributed incorrectly to "anemic congestive cardiac failure" but in fact is usually caused by metabolic acidosis, sometimes compounded by hypovolemia. In general, children tolerate antimalarial drugs well and respond rapidly to treatment.

TRANSFUSION MALARIA

Malaria can be transmitted by blood transfusion, needlestick injury, or organ transplantation. The incubation period in these settings is often short because there is no preerythrocytic stage of development. The clinical features and management of these cases are the same as for naturally acquired infections. Radical chemotherapy with primaquine is unnecessary for transfusion-transmitted *P. vivax* and *P. ovale* infections.

CHRONIC COMPLICATIONS OF MALARIA

HYPERREACTIVE MALARIAL SPLENOMEGALY

Chronic or repeated malarial infections produce hypergammaglobulinemia; normochromic, normocytic anemia; and, in certain situations, splenomegaly. Some residents of malaria-endemic areas in tropical countries exhibit an abnormal immunologic response to repeated infections that is characterized by massive splenomegaly, hepatomegaly, marked elevations in serum IgM and malarial antibody titers, hepatic

sinusoidal lymphocytosis, and (in Africa) peripheral B cell lymphocytosis. This syndrome has been associated with the production of cytotoxic IgM antibodies to CD8+ T lymphocytes, antibodies to CD5+ T lymphocytes, and an increase in the ratio of CD4+ to CD8+ T cells. These events may lead to uninhibited B cell production of IgM and the formation of cryoglobulins (IgM aggregates and immune complexes). This immunologic process stimulates lymphoid hyperplasia and clearance activity and eventually produces splenomegaly. Patients with hyperreactive malarial splenomegaly present with an abdominal mass or a dragging sensation in the abdomen and occasional sharp abdominal pains suggesting perisplenitis. There is usually anemia and some degree of pancytopenia (hypersplenism). In some cases, malaria parasites cannot be found in peripheral-blood smears by microscopy. Vulnerability to respiratory and skin infections is increased; many patients die of overwhelming sepsis. Persons with hyperreactive malarial splenomegaly living in endemic areas should receive antimalarial chemoprophylaxis; the results are usually good. In nonendemic areas, antimalarial treatment is advised. Some cases have been mistaken for hematologic malignancy. However, in other cases refractory to therapy, clonal lymphoproliferation may develop and can evolve into a malignant lymphoproliferative disorder.

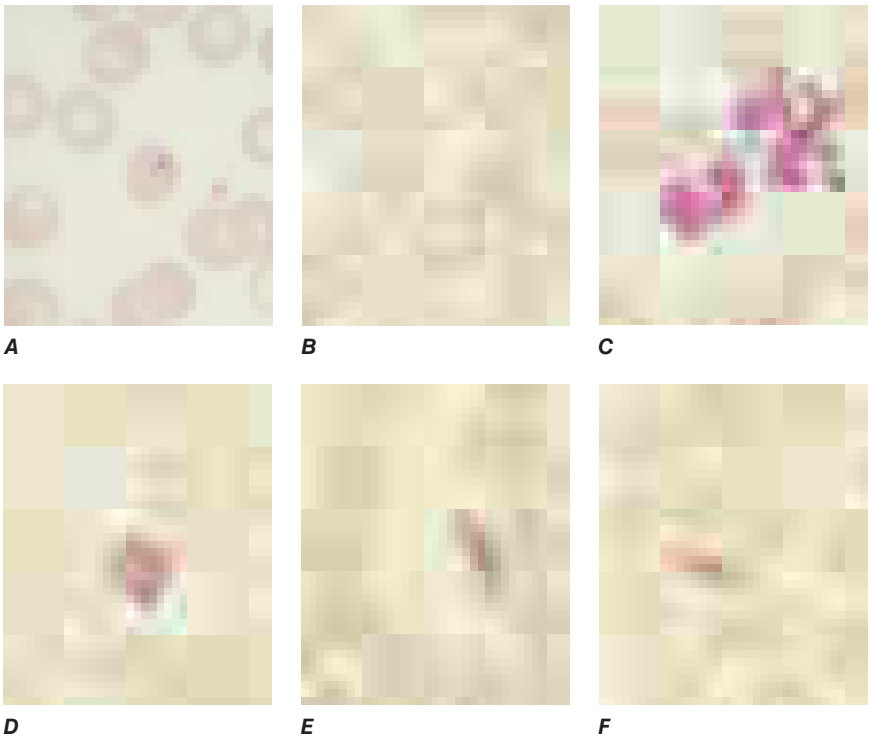


FIGURE 219-4 Thin blood films of *Plasmodium falciparum*. *A.* Young trophozoite. ***B.*** Old trophozoite. ***C.*** Trophozoites in erythrocytes and pigment in polymorphonuclear cells. ***D.*** Mature schizont. ***E.*** Female gametocyte. ***F.*** Male gametocyte. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*

QUARTAN MALARIAL NEPHROPATHY

Chronic or repeated infections with *P. malariae* (and possibly with other malarial species) may cause soluble immune complex injury to the renal glomeruli, resulting in the nephrotic syndrome. Other unidentified factors must contribute to this process since only a very small proportion of infected patients develop renal disease. The histologic appearance is that of focal or segmental glomerulonephritis with splitting of the capillary basement membrane. Subendothelial dense deposits are seen on electron microscopy, and immunofluorescence reveals deposits of complement and immunoglobulins; in samples of renal tissue from children, *P. malariae* antigens are often visible. A coarse-granular pattern of basement membrane immunofluorescent deposits (predominantly IgG3) with selective proteinuria carries a better prognosis than a fine-granular, predominantly IgG2 pattern with nonselective proteinuria. Quartan nephropathy is rarely reported nowadays. It usually responds poorly to treatment with either antimalarial agents or glucocorticoids and cytotoxic drugs.

BURKITT'S LYMPHOMA AND EPSTEIN-BARR VIRUS INFECTION

It is possible that malaria-related immune dysregulation provokes infection with lymphoma viruses. Burkitt's lymphoma is strongly associated with Epstein-Barr virus. The prevalence of this childhood tumor is high in high-malaria-transmission areas of Africa.

DIAGNOSIS OF MALARIA

When a patient in or from a malarious area presents with fever, thick and thin blood smears should be prepared and *examined immediately* to confirm the diagnosis and identify the species of infecting parasite (Figs. 219-4 through 219-9). In general, if the blood smear is negative when examined by an experienced microscopist, the patient does not have malaria. If reliable microscopy is not available, a rapid test should be performed.

DEMONSTRATION OF THE PARASITE

The diagnosis of malaria rests on the demonstration of asexual forms of the parasite in stained peripheral-blood smears. Of the Romanowsky

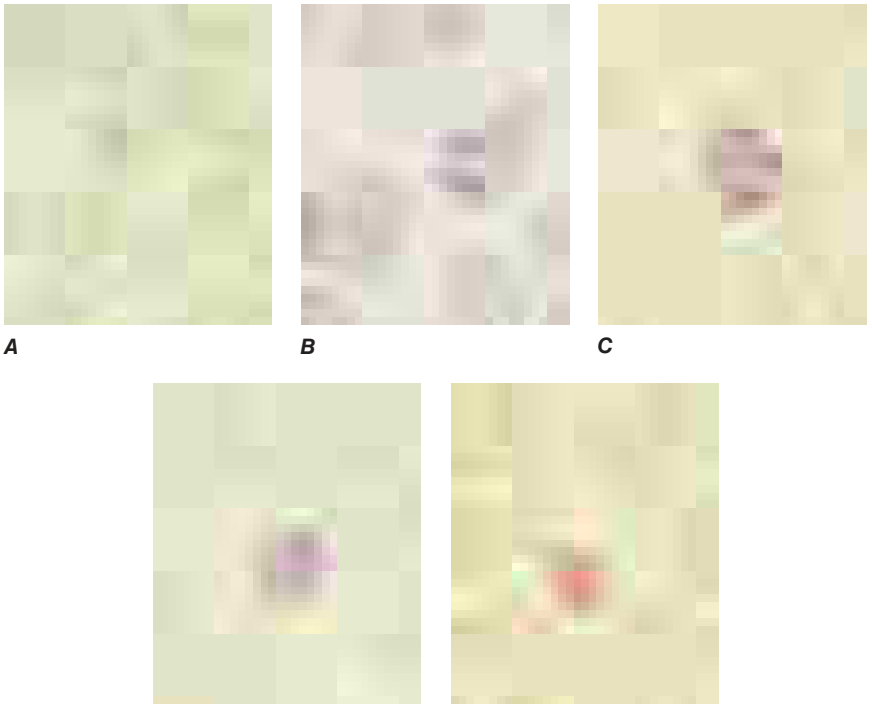


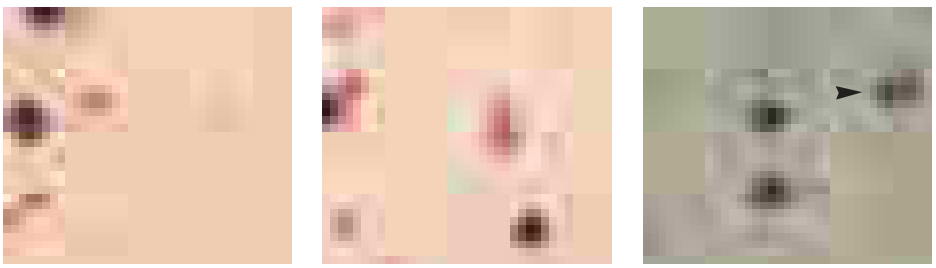
FIGURE 219-5 Thin blood films of *Plasmodium vivax*. *A.* Young trophozoite. ***B.*** Old trophozoite. ***C.*** Mature schizont. ***D.*** Female gametocyte. ***E.*** Male gametocyte. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*

A B

FIGURE 219-6 Thick blood films of *Plasmodium falciparum*. *A.* Trophozoites. ***B.*** Gametocytes. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*

A B C

FIGURE 219-7 Thick blood films of *Plasmodium vivax*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*



A B C

FIGURE 219-8 Thick blood films of *Plasmodium ovale*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*

A B C

FIGURE 219-9 Thick blood films of *Plasmodium malariae*. *A.* Trophozoites. ***B.*** Schizonts. ***C.*** Gametocytes. *(Reproduced from Bench Aids for the Diagnosis of Malaria Infections, 2nd ed, with the permission of the World Health Organization.)*

stains, Giemsa at pH 7.2 is preferred; Field's, Wright's, or Leishman's stain can also be used. Staining of parasites with the fluorescent dye acridine orange allows more rapid diagnosis of malaria (but not speciation of the infection) in patients with low-level parasitemia.

Both thin (Figs. 219-4 and 219-5) and thick (Figs. 219-6, 219-7, 219-8, and 219-9) blood smears should be examined. The thin blood smear should be air-dried, fixed in anhydrous methanol, and stained; the RBCs in the tail of the film should then be examined under oil immersion (×1000 magnification). The density of parasitemia is expressed as the number of parasitized erythrocytes per 1000 RBCs. The thick blood film should be of uneven thickness. The smear should be dried thoroughly and stained without fixing. As many layers of erythrocytes overlie one another and are lysed during the staining procedure, the thick film has the advantage of concentrating the parasites (by 40- to 100-fold compared with a thin blood film) and thus increasing diagnostic sensitivity. Both parasites and white blood cells (WBCs) are counted, and the number of parasites per unit volume is calculated from the total leukocyte count. Alternatively, a WBC count of 8000/μL is assumed. This figure is converted to the number of parasitized erythrocytes per microliter. A minimum of 200 WBCs should be counted under oil immersion. Interpretation of blood smears, particularly thick films, requires some experience because artifacts are common. Before a thick smear is judged to be negative, 100–200 fields should be examined. In high-transmission areas, the presence of up to 10,000 parasites/μL of blood may be tolerated without symptoms or signs in partially immune individuals. Thus, in these areas, the detection of low-density malaria parasitemia is sensitive but has low specificity in identifying malaria as the cause of illness. Because the prevalence of asymptomatic parasitemia is often high, low-density parasitemia is a common incidental finding in other conditions causing fever.

Rapid, simple, sensitive, and specific antibody-based diagnostic stick or card tests that detect *P. falciparum*–specific, histidine-rich protein 2 (PfHRP2), lactate dehydrogenase, or aldolase antigens in finger-prick blood samples are now being used widely in control programs **(Table 219-5)**. Some of these rapid diagnostic tests carry a second antibody (either pan-malaria or *P. vivax*–specific) and so distinguish falciparum malaria from the less dangerous malarias. PfHRP2-based tests may remain positive for several weeks after acute infection. This prolonged positivity is a disadvantage in high-transmission areas where infections are frequent, but it is of value in the diagnosis of severe malaria in patients who have taken antimalarial drugs and cleared peripheral parasitemia but who still have a strongly positive PfHRP2 test. A disadvantage of rapid tests is that they do not quantify parasitemia. Widespread use of PfHRP2 rapid tests has put strong selection pressure on *P. falciparum* populations in some areas, leading to an increased prevalence of mutant parasites that are not detected by the current generation of PfHRP2-based tests.

The relationship between parasite density and prognosis is complex; in general, patients with $>10^5$ parasites/μL are at increased risk of dying, but nonimmune patients may die with much lower counts, and partially immune persons may tolerate parasitemia levels many times higher with only minor symptoms. In severe malaria, a poor prognosis is indicated by a predominance of more mature *P. falciparum* parasites (i.e., >20% of parasites with visible pigment) in the peripheral-blood film or by the presence of phagocytosed malarial pigment in

TABLE 219-5 Standard Methods for the Diagnosis of Malaria[a]

METHOD	PROCEDURE	ADVANTAGES	DISADVANTAGES
Thick blood film[b]	Blood should be uneven in thickness but thin enough that the hands of a watch can be read through part of the spot. Stain dried, unfixed blood spot with Giemsa, Field's, or another Romanowsky stain. Count number of asexual parasites per 200 WBCs (or per 500 at low densities). Count gametocytes separately.[c]	Sensitive (0.001% parasitemia); species specific; inexpensive	Requires experience (artifacts may be misinterpreted as low-level parasitemia); underestimates true count
Thin blood film[d]	Stain fixed smear with Giemsa, Field's, or another Romanowsky stain. Count number of RBCs containing asexual parasites per 1000 RBCs. In severe malaria, assess stage of parasite development and count neutrophils containing malaria pigment.[e] Count gametocytes separately.[c]	Rapid; species specific; inexpensive; in severe malaria, provides prognostic information[e]	Insensitive (<0.05% parasitemia); uneven distribution of *P. vivax*, as enlarged infected red cells concentrate at leading edge
PfHRP2 dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibody capture of parasitic antigens reads out as a colored band.	Robust and relatively inexpensive; rapid; sensitivity similar to or slightly lower than that of thick films (~0.001% parasitemia)	Detects only *Plasmodium falciparum*; remains positive for weeks after infection[f]; does not quantitate *P. falciparum* parasitemia; evasion of detection by certain strains due to polymorphisms in HRP2 gene
Plasmodium LDH dipstick or card test	A drop of blood is placed on the stick or card, which is then immersed in washing solutions. Monoclonal antibody capture of parasitic antigens reads out as two colored bands. One band is genus specific (all malarias), and the other is specific for *P. falciparum.*	Rapid; sensitivity similar to or slightly lower than that of thick films for *P. falciparum* (~0.001% parasitemia)	May miss low-level parasitemia with *P. vivax*, *P. ovale*, and *P. malariae* and may not speciate these organisms; does not quantitate *P. falciparum* parasitemia; lower sensitivity for detection of *P. knowlesi*, which may be misidentified as *P. falciparum*
Microtube concentration methods with acridine orange staining	Blood is collected in a specialized tube containing acridine orange, anticoagulant, and a float. After centrifugation, which concentrates the parasitized cells around the float, fluorescence microscopy is performed.	Sensitivity similar or superior to that of thick films (~0.001% parasitemia); ideal for processing large numbers of samples rapidly	Does not speciate or quantitate; requires fluorescence microscopy

[a]Malaria cannot be diagnosed clinically with accuracy, but treatment should be started on clinical grounds if laboratory confirmation is likely to be delayed. In areas of the world where malaria is endemic and transmission rates are high, low-level asymptomatic parasitemia is common in otherwise healthy people. Thus malaria may not be the cause of a fever, although in this context the presence of >10,000 parasites/μL (~0.2% parasitemia) does indicate that malaria is the cause. Antibody and polymerase chain reaction (PCR) tests have no role in the diagnosis of malaria except that PCR is increasingly used for genotyping and speciation in mixed infections and for detection of low-level parasitemia in asymptomatic residents of endemic areas. [b]Asexual parasites/200 WBCs × 40 = parasite count/μL (assumes a WBC count of 8000/μL). See Figs. 219-6 through 219-9. [c]*P. falciparum* gametocytemia may persist for days or weeks after clearance of asexual parasites. Gametocytemia without asexual parasitemia does not indicate active infection. [d]Parasitized RBCs (%) × hematocrit × 1256 = parasite count/μL. See Figs. 219-4 and 219-5. [e]The presence of >100,000 parasites/μL (~2% parasitemia) is associated with an increased risk of severe malaria, but some patients have severe malaria with lower counts. At any level of parasitemia, the finding that >50% of parasites are tiny rings (cytoplasm thickness less than half of nucleus width) carries a relatively good prognosis. The presence of visible pigment in >20% of parasites or of phagocytosed pigment in >5% of polymorphonuclear leukocytes (indicating massive recent schizogony) carries a worse prognosis. [f]Persistence of PfHRP2 is a disadvantage in high-transmission settings, where many asymptomatic people have positive tests, but can be used to diagnostic advantage in low-transmission settings when a sick patient has previously received unknown treatment (which, in endemic areas, often consists of antimalarial drugs). In this situation, a positive PfHRP2 test indicates that the illness is falciparum malaria, even if the blood smear is negative.

Abbreviations: LDH, lactate dehydrogenase; PfHRP2, *P. falciparum* histidine-rich protein 2; RBCs, red blood cells; WBCs, white blood cells.

>5% of neutrophils (an indicator of recent schizogony). In *P. falciparum* infections, gametocytemia peaks 1 week after the peak of asexual parasite densities. Because the mature gametocytes of *P. falciparum* (unlike those of other plasmodia) are not affected by most antimalarial drugs, their persistence does not constitute evidence of drug resistance or a need to re-treat if a full course of appropriate antimalarial drugs has already been given. Phagocytosed malarial pigment seen inside peripheral-blood monocytes may provide a clue to recent infection if malaria parasites are not detectable. After parasite clearance, this intraphagocytic malarial pigment is often evident for several days in peripheral-blood films or for longer in bone marrow aspirates or smears of fluid expressed after intradermal puncture.

Molecular diagnosis by polymerase chain reaction (PCR) amplification of parasite nucleic acid is more sensitive than microscopy or rapid diagnostic tests for detecting malaria parasites and defining malarial species. While currently impractical in the standard clinical setting, PCR is used in reference centers in endemic areas. In epidemiologic surveys, ultrasensitive PCR detection may prove very useful in identifying asymptomatic infections as control and eradication programs drive parasite prevalences down to very low levels. Serologic diagnosis with either indirect fluorescent antibody or enzyme-linked immunosorbent assays is useful for screening of prospective blood donors and may prove useful as a measure of transmission intensity in future epidemiologic studies. It has no place in the diagnosis of acute illness.

LABORATORY FINDINGS IN ACUTE MALARIA

Normochromic, normocytic anemia is usual. The leukocyte count is generally normal, although it may be raised in very severe infections. There is slight monocytosis, lymphopenia, and eosinopenia, with reactive lymphocytosis and eosinophilia in the weeks after acute infection. The platelet count is usually reduced to ~10^5/μL. The erythrocyte sedimentation rate, plasma viscosity, and levels of C-reactive protein and other acute-phase proteins are elevated. Severe infections may be accompanied by prolonged prothrombin and partial thromboplastin times and by more severe thrombocytopenia. Antithrombin III levels are reduced even in mild infection. In uncomplicated malaria, plasma concentrations of electrolytes, blood urea nitrogen (BUN), and creatinine are usually normal. Findings in severe malaria may include metabolic acidosis, with low plasma concentrations of glucose, sodium, bicarbonate, phosphate, and albumin, together with elevations in lactate, BUN, creatinine, urate, muscle and liver enzymes, and conjugated and unconjugated bilirubin. Hypergammaglobulinemia is usual in immune and semi-immune subjects living in malaria-endemic areas. Urinalysis generally gives normal results. In adults and children with cerebral malaria, the mean cerebrospinal fluid (CSF) opening pressure at lumbar puncture is ~160 mm H_2O; usually the CSF content is normal or there is a slight elevation of total protein level (<1.0 g/L [<100 mg/dL]) and cell count (<20/μL).

TREATMENT

Malaria

Patients with severe malaria and those unable to take oral drugs should receive parenteral antimalarial therapy immediately **(Table 219-6)**. Antimalarial drug susceptibility testing can be performed but is rarely available, has poor predictive value in an individual case, and yields results too slowly to influence the choice of treatment. If there is any doubt about the resistance status of the infecting organism, it should be considered resistant.

The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated falciparum malaria in malaria-endemic areas. ACT is also the recommended first-line treatment for *P. knowlesi* infections and is highly effective against the other malarias as well. The choice of an ACT partner drug depends on the likely sensitivity of the infecting parasites. Artemisinin-based combinations are sometimes unavailable in temperate countries, where treatment recommendations are limited to the registered available drugs. Despite increasing evidence of chloroquine resistance in *P. vivax* (from parts of Indonesia, Oceania, eastern and southern Asia, and Central and South America), chloroquine remains an effective treatment for *P. vivax* malaria in many areas and for *P. ovale* and *P. malariae* infections everywhere.

Artemisinin resistance in *P. falciparum* has emerged in Southeast Asia over the past decade and has been followed by piperaquine and mefloquine resistance. ACTs are starting to fail in Cambodia, Vietnam, and the border regions of Thailand. Significant artemisinin resistance is now prevalent throughout the Greater Mekong subregion but has not been reported from other malaria-endemic regions. Falsified or substandard antimalarial drugs are sold in many Asian and African countries and may be the cause of a failure to respond to therapy. Characteristics of antimalarial drugs are shown in **Table 219-7**.

SEVERE MALARIA

In large randomized controlled clinical trials, parenteral artesunate, a water-soluble artemisinin derivative, has reduced mortality rates in severe falciparum malaria among Asian adults and children by 35% and among African children by 22.5% compared with quinine treatment. Artesunate therefore is now the drug of choice for all patients with severe malaria everywhere. Artesunate is given by IV injection but is also absorbed rapidly following IM injection. Artemether and the closely related drug artemotil (arteether) are oil-based formulations given by IM injection; they are erratically absorbed and do not confer the same survival benefit as artesunate. A rectal formulation of artesunate has been developed as a community-based pre-referral treatment for patients in the rural tropics who cannot take oral medications. Pre-referral administration of rectal artesunate has been shown to decrease mortality rates among severely ill children without access to immediate parenteral treatment. Although the artemisinin compounds are safer than quinine and considerably safer than quinidine, only one formulation is available in the United States. IV artesunate has been approved by the U.S. Food and Drug Administration for emergency use in severe malaria and can be obtained through the Centers for Disease Control and Prevention (CDC) Drug Service (see end of chapter for contact information). The antiarrhythmic quinidine gluconate was used to treat severe malaria in the United States previously but is now in short supply; artesunate is much more effective and safer. Parenteral quinidine is potentially dangerous and must be closely monitored if dysrhythmias and hypotension are to be avoided. If total plasma levels exceed 8 μg/mL, if the QT_c interval exceeds 0.6 s, or if the QRS complex widens by more than 25% over baseline, then infusion rates should be slowed or infusion stopped temporarily. If arrhythmia or saline-unresponsive hypotension develops, treatment with this drug should be discontinued. Quinine is safer than quinidine; cardiovascular monitoring is not required except when the recipient has cardiac disease. Although parenteral quinine is steadily being replaced by parenteral artesunate in endemic areas, it still has a role in the very few cases of artemisinin-resistant severe falciparum malaria from Southeast Asia, where both artesunate and quinine are given together in full doses.

Severe falciparum malaria constitutes a medical emergency requiring intensive nursing care and careful management. Frequent evaluation of the patient's condition is essential. Adjunctive treatments such as high-dose glucocorticoids, urea, heparin, dextran, desferrioxamine, antibody to tumor necrosis factor α, high-dose phenobarbital (20 mg/kg), mannitol, or large-volume fluid or albumin boluses have proved either ineffective or harmful in clinical trials and should not be used. In acute renal failure or severe metabolic acidosis, hemofiltration or hemodialysis should be started as early as possible.

In severe malaria, parenteral antimalarial treatment should be started immediately. Artesunate, given by either IV or IM injection, is the treatment of choice; it is simple to administer, very safe, and rapidly effective. It does not require dose adjustments in liver dysfunction or renal failure. It should be used in pregnant women with severe malaria. If artesunate is unavailable and artemether, quinine, or quinidine is used, an initial loading dose must be given so that therapeutic concentrations are reached as soon as possible. Both quinine and quinidine will cause dangerous hypotension if

TABLE 219-6 Regimens for the Treatment of Malaria[a]

TYPE OF DISEASE OR TREATMENT	REGIMEN(S)
Uncomplicated Malaria	
Known chloroquine-sensitive strains of *Plasmodium vivax*, *P. malariae*, *P. ovale*, *P. falciparum*[b]	Chloroquine (10 mg of base/kg stat followed by 5 mg/kg at 12, 24, and 36 h or by 10 mg/kg at 24 h and 5 mg/kg at 48 h) ***or*** Amodiaquine (10–12 mg of base/kg qd for 3 days)
Radical treatment for *P. vivax or P. ovale* infection	In addition to chloroquine or amodiaquine as detailed above or ACT as detailed below, primaquine (0.5 mg of base/kg qd in Southeast Asia and Oceania and 0.25 mg/kg elsewhere) should be given for 14 days to prevent relapse. In mild G6PD deficiency, 0.75 mg of base/kg should be given once weekly for 8 weeks. Primaquine should not be given in severe G6PD deficiency.
P. falciparum malaria[c]	Artesunate[d] (4 mg/kg qd for 3 days) *plus* sulfadoxine (25 mg/kg)/pyrimethamine (1.25 mg/kg) as a single dose ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* amodiaquine (10 mg of base/kg qd for 3 days)[e] ***or*** Artemether-lumefantrine[d] (1.5/9 mg/kg bid for 3 days with food) ***or*** Artesunate[d] (4 mg/kg qd for 3 days) *plus* mefloquine (24–25 mg of base/kg—either 8 mg/kg qd for 3 days or 15 mg/kg on day 2 and then 10 mg/kg on day 3)[e] ***or*** DHA-piperaquine[d] (target dose: 4/24 mg/kg qd for 3 days in children weighing <25 kg and 4/18 mg/kg qd for 3 days in persons weighing ≥25 kg)
Second-line treatment/treatment of imported malaria	Artesunate[d] (2 mg/kg qd for 7 days) *or* quinine (10 mg of salt/kg tid for 7 days) *plus 1 of the following 3:* 1. Tetracycline[f] (4 mg/kg qid for 7 days) 2. Doxycycline[f] (3 mg/kg qd for 7 days) 3. Clindamycin (10 mg/kg bid for 7 days) ***or*** Atovaquone-proguanil (20/8 mg/kg qd for 3 days with food)
Severe Falciparum Malaria[g,h]	
	Artesunate[d] (2.4 mg/kg stat IV followed by 2.4 mg/kg at 12 and 24 h and then daily if necessary; for children weighing <20 kg, give 3 mg/kg per dose)[h] ***or, if unavailable,*** Artemether[d] (3.2 mg/kg stat IM followed by 1.6 mg/kg qd) ***or, if unavailable,*** Quinine dihydrochloride (20 mg of salt/kg[i] infused over 4 h, followed by 10 mg of salt/kg infused over 2–8 h q8h[j]) ***or, if none of the above are available,*** Quinidine (10 mg of base/kg[i] infused over 1–2 h, followed by 1.2 mg of base/kg per hour[j] with electrocardiographic monitoring)

[a]In endemic areas where malaria transmission is low, except in pregnant women and infants, a single dose of primaquine (0.25 mg of base/kg) should be added as a gametocytocide to all falciparum malaria treatments to prevent transmission. This addition is considered safe, even in G6PD deficiency. [b]Very few areas now have chloroquine-sensitive *P. falciparum* malaria. [c]In areas where the partner drug to artesunate is known to be effective. [d]Artemisinin derivatives are not readily available in some temperate countries. [e]Fixed-dose co-formulated combinations are available. The World Health Organization now recommends artemisinin combination regimens as first-line therapy for falciparum malaria in all tropical countries and advocates use of fixed-dose combinations. [f]Tetracycline and doxycycline should not be given to pregnant women after 15 weeks of gestation or to children <8 years of age. [g]Oral treatment should be substituted as soon as the patient recovers sufficiently to take fluids by mouth. [h]Artesunate is the drug of choice when available. The data from large studies in Southeast Asia showed a 35% lower mortality rate than with quinine, and very large studies in Africa showed a 22.5% reduction in mortality rate compared with quinine. The doses of artesunate in children weighing <20 kg should be 3 mg/kg. [i]A loading dose should not be given if therapeutic doses of quinine or quinidine have definitely been administered in the previous 24 h. Some authorities recommend a lower dose of quinidine. [j]Infusions can be given in 0.9% saline and 5–10% dextrose in water. Infusion rates for quinine and quinidine should be carefully controlled.

Abbreviations: ACT, artemisinin combination therapy; DHA, dihydroartemisinin; G6PD, glucose-6-phosphate dehydrogenase.

injected rapidly; when given IV, they must be administered carefully by rate-controlled infusion only. If this approach is not possible, quinine may be given by deep IM injections into the anterior thigh. The optimal therapeutic ranges for quinine and quinidine in severe malaria are not known with certainty, but total plasma concentrations of 8–15 mg/L for quinine and 3.5–8.0 mg/L for quinidine are effective and do not cause serious toxicity. The systemic clearance and apparent volume of distribution of these alkaloids are markedly reduced and plasma protein binding is increased in severe malaria, so that the blood concentrations attained with a given dose are higher. If the patient remains seriously ill or in acute renal failure for >2 days, maintenance doses of quinine or quinidine should be reduced by 30–50% to prevent toxic accumulation of the drug. The initial doses should never be reduced. If safe and feasible, exchange transfusion may be considered for patients with severe malaria, although the precise indications for this procedure have not been agreed upon and there is no clear evidence that this measure is beneficial, particularly with artesunate treatment. Convulsions should be treated promptly with IV (or rectal) benzodiazepines. The role of prophylactic anticonvulsants in children is uncertain. If respiratory support is not available, a full loading dose of phenobarbital (20 mg/kg) to prevent convulsions should *not* be given as it may cause respiratory arrest.

When the patient is unconscious, the blood glucose level should be measured every 4–6 h. All patients should receive a continuous infusion of dextrose, and blood concentrations ideally should be maintained above 4 mmol/L. Hypoglycemia (<2.2 mmol/L or 40 mg/dL) should be treated immediately with bolus glucose. The parasite count and hematocrit should be measured every 6–12 h. Anemia develops rapidly; if the hematocrit falls to <20%, whole blood (preferably fresh) or packed cells should be transfused slowly, with careful attention to circulatory status. In areas with higher malaria transmission, where blood for transfusion is in short supply, a threshold of 15% is widely used. Renal function should be checked at least daily. Children presenting with severe anemia and acidotic breathing require immediate blood transfusion. Accurate assessment

TABLE 219-7 Properties of Antimalarial Drugs

DRUG(S)	PHARMACOKINETIC PROPERTIES	ANTIMALARIAL ACTIVITY	MINOR TOXICITY	MAJOR TOXICITY
Quinine, quinidine	Good oral and IM absorption (quinine); *Cl* and V_d reduced, but plasma protein binding (principally to α1 acid glycoprotein) increased (90%) in malaria; quinine $t_{1/2}$: 16 h in malaria, 11 h in healthy persons; quinidine $t_{1/2}$: 13 h in malaria, 8 h in healthy persons	Acts mainly on trophozoite blood stage; kills gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* (but not *P. falciparum*); no action on liver stages	*Common:* cinchonism (tinnitus, high-tone hearing loss, nausea, vomiting, dysphoria, postural hypotension); ECG QT interval prolongation (quinine usually by <10% but quinidine by up to 25%). *Rare:* diarrhea, visual disturbance, rashes. *Note:* very bitter taste	*Common:* hypoglycemia. *Rare:* hypotension, blindness, deafness, cardiac arrhythmias, thrombocytopenia, hemolysis, hemolytic-uremic syndrome, vasculitis, cholestatic hepatitis, neuromuscular paralysis. *Note:* quinidine more cardiotoxic
Chloroquine	Good oral absorption, very rapid IM and SC absorption; complex pharmacokinetics; enormous *Cl* and V_d (unaffected by malaria); blood concentration profile determined by distribution processes in malaria; $t_{1/2}$: 1–2 months	As for quinine, but acts slightly earlier in asexual cycle	*Common:* nausea, dysphoria, pruritus in dark-skinned patients, postural hypotension, ECG QT prolongation. *Rare:* accommodation difficulties, keratopathy, rash. *Note:* bitter taste but usually well tolerated	*Acute:* hypotensive shock (parenteral), cardiac arrhythmias, neuropsychiatric reactions. *Chronic:* retinopathy (cumulative dose, >100 g), skeletal and cardiac myopathy
Piperaquine	Adequate oral absorption, may be enhanced by fats; similar pharmacokinetics to chloroquine; $t_{1/2}$: 21–28 days	As for chloroquine; retains activity against multidrug-resistant *P. falciparum*, but resistance has emerged in Southeast Asia	Occasional epigastric pain, diarrhea, ECG QT_c prolongation	None identified
Amodiaquine	Good oral absorption; largely converted to active metabolite desethylamodiaquine; $t_{1/2}$: 4–5 days	As for chloroquine, but more active against chloroquine-resistant *P. falciparum*	Nausea (tastes better than chloroquine), dysphoria, headache, ECG QTc prolongation	Agranulocytosis; hepatitis, mainly with prophylactic use; should not be used with efavirenz
Primaquine	Complete oral absorption; active metabolite produced via CYP2D6; $t_{1/2}$: 5–7 h	Radical cure; eradicates hepatic forms of *P. vivax* and *P. ovale;* kills all stages of *P. falciparum* gametocyte development; kills developing liver stages of all species	Nausea, vomiting, diarrhea, abdominal pain, hemolysis, methemoglobinemia	Serious hemolytic anemia, severe G6PD deficiency; hemoglobinuria
Mefloquine	Adequate oral absorption; no parenteral preparation; $t_{1/2}$: 14–20 days (shorter in malaria)	As for quinine	Nausea, giddiness, dysphoria, fuzzy thinking, sleeplessness, nightmares, sense of dissociation	Neuropsychiatric reactions, convulsions, encephalopathy
Lumefantrine	Highly variable absorption related to fat intake; $t_{1/2}$: 3–4 days	As for quinine	None identified	None identified
Artemisinin and derivatives (artemether, artesunate)	Good oral absorption; good absorption of IM artesunate but slow and variable absorption of IM artemether; artesunate and artemether biotransformed to active metabolite dihydroartemisinin; all drugs eliminated very rapidly; $t_{1/2}$: <1 h	Broader stage specificity and more rapid than other drugs; no action on liver stages; kills all but fully mature gametocytes of *P. falciparum*	Reduction in reticulocyte count (but not anemia); neutropenia at high doses; in some cases, delayed anemia after treatment of severe malaria with hyperparasitemia	Anaphylaxis, urticaria, fever
Pyrimethamine	Good oral absorption, variable IM absorption; $t_{1/2}$: 4 days	For blood stages, acts mainly on mature forms; causal prophylactic	Well tolerated	Megaloblastic anemia, pancytopenia, pulmonary infiltration
Proguanil[a] (chloroguanide)	Good oral absorption; biotransformed to active metabolite cycloguanil; $t_{1/2}$: 16 h; biotransformation reduced by oral contraceptive use and in pregnancy	Causal prophylactic; not used alone for treatment	Well tolerated; mouth ulcers and rare alopecia	Megaloblastic anemia in renal failure
Atovaquone[a]	Highly variable absorption related to fat intake; $t_{1/2}$: 30–70 h	Acts mainly on trophozoite blood stage	None identified	None identified
Tetracycline, doxycycline[b]	Excellent absorption; $t_{1/2}$: 8 h for tetracycline, 18 h for doxycycline	Weak antimalarial activity; should not be used alone for treatment	Gastrointestinal intolerance, deposition in growing bones and teeth, photosensitivity, moniliasis, benign intracranial hypertension	Renal failure in patients with impaired renal function (tetracycline)
Pyronaridine	Rapid variable absorption, large V_d; $t_{1/2}$: 12–14 days	Acts mainly on trophozoite blood stage; kills gametocytes of *P. vivax*, *P. ovale*, and *P. malariae* (but not *P. falciparum*); no action on liver stages	Gastrointestinal intolerance, anemia, transient elevation of aminotransferases, hypoglycemia, headache	None identified
Arterolane	$t_{1/2}$: 3 h	Broad stage specificity; no action on liver stages; kills all but fully mature gametocytes of *P. falciparum*	Gastrointestinal intolerance, transient elevation of aminotransferases	None identified

[a]Atovaquone and proguanil are prescribed as a fixed-dose combination. This and proguanil alone should not be given if the estimated glomerular filtration rate is <30 mL/min. [b]Tetracycline and doxycycline should not be given to pregnant women after 15 weeks of gestation or to children <8 years of age.

Abbreviations: Cl, systemic clearance; ECG, electrocardiogram; G6PD, glucose-6-phosphate dehydrogenase; V_d, total apparent volume of distribution.

is vital. Management of fluid balance is difficult in severe malaria, particularly in adults, because of the thin dividing line between overhydration (leading to pulmonary edema) and underhydration (contributing to renal impairment). Fluid balance management is *different* from that in sepsis: fluid boluses are potentially dangerous in severe malaria. Nasogastric feeding should be delayed in non-intubated patients (for 60 h in adults and 36 h in children) to reduce the risk of aspiration pneumonia. As soon as the patient can take fluids, oral therapy should be substituted for parenteral treatment and a full 3-day course of ACT given. Mefloquine should be avoided as follow-on treatment for severe malaria because of the increased risk of post-malaria neurologic syndrome.

In areas of high transmission of both *P. falciparum* and *P. vivax* (the island of New Guinea), severe and potentially life-threatening anemia is common among children, and both species contribute. Elsewhere, severe vivax malaria may occur but is uncommon. Many patients have had comorbidities contributing to vital-organ dysfunction.

P. knowlesi can cause severe disease associated with high parasite densities. Acute kidney injury, respiratory distress, and shock have all been described, but cerebral malaria does not occur. Treatment for severe vivax and knowlesi malaria should follow the recommendations given for falciparum malaria.

UNCOMPLICATED MALARIA

P. falciparum and *P. knowlesi* infections should be treated with an artemisinin-based combination because of their propensity for high parasite densities and severe disease. Infections with sensitive strains of *P. vivax*, *P. malariae*, and *P. ovale* should be treated with an artemisinin-based combination or oral chloroquine (total dose, 25 mg of base/kg). The ACT regimens now recommended are safe and effective in adults, children, and pregnant women. The rapidly eliminated artemisinin component is usually an artemisinin derivative (artesunate, artemether, or dihydroartemisinin) given for 3 days, and the partner drug is usually a more slowly eliminated antimalarial to which *P. falciparum* in the area is sensitive. Five ACT regimens are currently recommended by the WHO: artemether-lumefantrine, artesunate-mefloquine, dihydroartemisinin-piperaquine, artesunate-sulfadoxine-pyrimethamine, and artesunate-amodiaquine. There is increasing evidence for both the efficacy and the safety of artesunate-pyronaridine. In areas of low malaria transmission, a single dose of primaquine (0.25 mg/kg) should be added to ACT as a *P. falciparum* gametocytocide to reduce the transmissibility of the infection. This low dose of primaquine is safe even in G6PD deficiency. Pregnant women should not be given primaquine. Atovaquone-proguanil is highly effective everywhere, although it is seldom used in endemic areas because of its high cost and the propensity for rapid emergence of resistance. Recovery is slower after atovaquone-proguanil treatment than after ACT. Of great concern is the emergence of artemisinin-resistant *P. falciparum* in the Greater Mekong subregion of Southeast Asia. Infections with these parasites are cleared slowly from the blood, with clearance times typically exceeding 3 days, and cure rates with ACT have fallen to unacceptably low levels in some areas. Extended treatment courses and triple antimalarial combinations are under evaluation.

The 3-day ACT regimens are all well tolerated, although mefloquine is associated with increased rates of vomiting and dizziness. As second-line treatments for recrudescence following first-line therapy, a different ACT regimen may be given; another alternative is a 7-day course of either artesunate or quinine plus tetracycline, doxycycline, or clindamycin. Tetracycline and doxycycline cannot be given to pregnant women after 15 weeks of gestation or to children <8 years of age. Oral quinine is extremely bitter and regularly produces cinchonism comprising tinnitus, high-tone deafness, nausea, vomiting, and dysphoria. Clinical responses are slower than those following ACT. Adherence is poor with the required 7-day regimens of quinine.

Patients should be monitored for vomiting for 1 h after the administration of any oral antimalarial drug. If there is vomiting, the dose should be repeated. Symptom-based treatment, with tepid sponging and acetaminophen (paracetamol) administration, lowers fever and thereby reduces the patient's propensity to vomit these drugs. Minor central nervous system reactions (nausea, dizziness, sleep disturbances) are common. The incidence of serious adverse neuropsychiatric reactions to mefloquine treatment is ~1 in 1000 in Asia but may be as high as 1 in 200 among Africans and Caucasians. All the antimalarial quinolines (chloroquine, mefloquine, and quinine) exacerbate the orthostatic hypotension associated with malaria, and all are tolerated better by children than by adults. Pregnant women, young children, patients unable to tolerate oral therapy, and nonimmune individuals (e.g., travelers) with suspected malaria should be evaluated carefully and hospitalization considered. If there is any doubt as to the identity of the infecting malarial species, treatment for falciparum malaria should be given. A negative blood smear read by an experienced microscopist makes malaria very unlikely but does not rule it out completely; thick blood films should be checked again 1 and 2 days later to exclude the diagnosis. Nonimmune patients receiving treatment for malaria should have daily parasite counts performed until the thick films are negative. If the level of parasitemia does not fall below 25% of the admission value in 72 h or if parasitemia has not cleared by 7 days (and adherence is assured), drug resistance is likely and the regimen should be changed.

To eradicate persistent liver stages and prevent relapse (radical treatment), primaquine (0.5 mg of base/kg in East Asia and Oceania and 0.25 mg/kg elsewhere) should be given once daily for 14 days to patients with *P. vivax* or *P. ovale* infection after laboratory tests for G6PD deficiency have proved negative. If the patient has a mild variant of G6PD deficiency, primaquine can be given in a dose of 0.75 mg of base/kg (maximum, 45 mg) once weekly for 8 weeks. Pregnant women with vivax or ovale malaria should not be given primaquine but should receive suppressive prophylaxis with chloroquine (5 mg of base/kg per week) until delivery, after which radical treatment can be given.

MANAGEMENT OF COMPLICATIONS

Acute Renal Failure If plasma levels of BUN or creatinine rise despite adequate rehydration, fluid administration should be restricted to prevent volume overload. As in other forms of hypercatabolic acute renal failure, renal replacement therapy is best performed early **(Chap. 304)**. Hemofiltration and hemodialysis are more effective than peritoneal dialysis and are associated with lower mortality risk. Some patients with renal impairment pass small volumes of urine sufficient to allow control of fluid balance; these cases can be managed conservatively if other indications for dialysis do not arise. Renal function usually improves within days, but full recovery may take weeks.

Acute Pulmonary Edema (Acute Respiratory Distress Syndrome) This syndrome is caused by increased pulmonary capillary permeability. Patients should be positioned with the head of the bed at a 45° elevation and should be given oxygen and IV diuretics. Positive-pressure ventilation should be started early if the immediate measures fail **(Chap. 298)**. Rarely, patients may require extracorporeal membrane oxygenation.

Hypoglycemia An initial slow injection of 20% dextrose (2 mL/kg over 10 min) should be followed by an infusion of 10% dextrose (0.10 g/kg per hour). The blood glucose level should be checked regularly thereafter as recurrent hypoglycemia is common, particularly among patients receiving quinine or quinidine. In severely ill patients, hypoglycemia commonly occurs together with metabolic (lactic) acidosis and carries a poor prognosis.

Sepsis Hypoglycemia or gram-negative septicemia should be suspected when the condition of any patient suddenly deteriorates for no obvious reason during antimalarial treatment. In malaria-endemic areas where a high proportion of children are parasitemic, it is usually impossible to distinguish severe malaria from bacterial sepsis with confidence. These children should be treated with both antimalarials and broad-spectrum antibiotics from the outset. Because infections

with nontyphoidal *Salmonella* species are particularly common, empirical antibiotics should be selected to cover these organisms. Antibiotics should be considered for severely ill patients of any age who are not responding to antimalarial treatment.

Other Complications Patients who develop spontaneous bleeding should be given fresh blood and IV vitamin K. Convulsions should be treated with IV or rectal benzodiazepines and, if necessary, respiratory support. Aspiration pneumonia should be suspected in any unconscious patient with convulsions, particularly with persistent hyperventilation; IV antimicrobial agents and oxygen should be administered, and pulmonary toilet should be undertaken.

GLOBAL CONSIDERATIONS

In recent years, considerable progress has been made in malaria prevention and control. Distribution of insecticide-treated bed nets (ITNs) has been shown to reduce all-cause mortality in African children by 20%. New drugs have been discovered and are being developed, and one vaccine candidate (the RTS,S/AS01 vaccine) has been licensed for use. Highly effective drugs, long-lasting ITNs, and insecticides for anopheline vector control are being purchased for endemic countries by international donors. The WHO now calls for all countries to work toward a goal of malaria elimination, and many countries have set ambitious timelines to achieve this goal. Success will require strong leadership, increased national commitment, and international support. The numerous challenges that lie ahead include the widespread distribution of *Anopheles* breeding sites, the enormous number of infected persons, the emergence and spread of resistance in *P. falciparum* to common artemisinin-based combinations in Southeast Asia, increasing insecticide resistance and behavioral changes (to avoid ITN contact) in anopheline mosquito vectors, and inadequacies in human and material resources, infrastructure, and control programs. Eliminating vivax malaria is further hindered by the lack of a simple, safe radical curative regimen.

MALARIA PREVENTION

Malaria may be contained by judicious use of insecticides to kill the mosquito vector, rapid diagnosis, patient management, and—where effective and feasible—administration of intermittent preventive treatments, seasonal malaria chemoprevention, or chemoprophylaxis to high-risk groups such as pregnant women and young children. Focal elimination of *P. falciparum* can be accelerated by mass treatment with slowly eliminated antimalarials such as dihydroartemisinin-piperaquine. Despite the enormous investment in efforts to develop a malaria vaccine, no safe, highly effective, long-lasting vaccine is likely to be available for general use in the near future **(Chap. 118)**. The licensed recombinant protein sporozoite-targeted adjuvanted vaccine RTS,S was only moderately efficacious in protecting African children from malaria in field trials, and protection of the very youngest recipients waned to 16% only 4 years after vaccination. The vaccine will be deployed in Ghana, Kenya, and Malawi as part of a large-scale pilot project before a decision on its more general use is taken. An irradiated live sporozoite vaccine is in late-stage development, and research is ongoing to develop a vaccine to protect against placental malaria (targeting VAR2CSA). While there is great promise for one or several malaria vaccines on the more distant horizon, prevention and control measures will continue to rely on antivector and drug-use strategies for the foreseeable future.

PERSONAL PROTECTION AGAINST MALARIA

Simple measures to reduce the frequency of bites by infected mosquitoes in malarious areas are very important. These measures include the avoidance of exposure to mosquitoes at their peak feeding times (usually dusk to dawn) and the use of insect repellents containing 10–35% DEET (or, if DEET is unacceptable, 7% picaridin), suitable clothing, and ITNs or other insecticide-impregnated materials. Widespread use of bed nets treated with residual pyrethroids reduces the incidence of malaria in areas where vectors bite indoors at night.

CHEMOPROPHYLAXIS

(Table 219-8; *wwwnc.cdc.gov/travel/yellowbook/2018/chapter-3-infectious-diseases-related-to-travel/malaria*) Recommendations for malaria prophylaxis depend on knowledge of local patterns of drug sensitivity in *Plasmodium* species and the likelihood of acquiring malarial infection. When there is uncertainty, drugs effective against resistant *P. falciparum* should be used (atovaquone-proguanil [Malarone], doxycycline, or mefloquine). Chemoprophylaxis is never entirely reliable, and malaria should always be considered in the differential diagnosis of fever in patients who have traveled to endemic areas, even if they are taking prophylactic antimalarial drugs.

Pregnant women planning to visit malarious areas should be warned about the potential risks and advised to avoid all nonessential travel. All pregnant women who live in endemic areas should be encouraged to attend regular antenatal clinics. Mefloquine is the only drug advised for pregnant women traveling to areas with drug-resistant malaria; this drug is generally considered safe in the second and third trimesters of pregnancy; the data on first-trimester exposure, although limited, are reassuring. Chloroquine and proguanil are regarded as safe, but there are now very few regions where these drugs can be recommended for protection. Doxycycline may be given until 15 weeks of pregnancy, at which point it should be discontinued. The safety of other prophylactic antimalarial agents in pregnancy has not been established. Antimalarial prophylaxis has been shown to reduce mortality rates among children between the ages of 3 months and 4 years in malaria-endemic areas; however, it is not a logistically or economically feasible option in many countries. The alternative—to give intermittent preventive treatment (IPT) to pregnant women, and in some areas to infants as well, or seasonal malaria chemoprevention (SMC) to young children—is being implemented. Other strategies are being evaluated, such as intermittent screening and treatment.

IPT in pregnancy (IPTp) involves giving treatment doses of sulfadoxine-pyrimethamine at each antenatal visit (maximum, once monthly) in the second and third trimesters of pregnancy. Women with HIV infection who are taking trimethoprim-sulfamethoxazole as prophylaxis should not be given concomitant sulfadoxine-pyrimethamine. IPT in infancy (IPTi) involves giving treatment doses of sulfadoxine-pyrimethamine along with the immunizations included in the WHO's Expanded Program on Immunization at 2, 3, and 9 months of life. Seasonal malaria chemoprevention involves giving monthly doses of amodiaquine and sulfadoxine-pyrimethamine to children 3 months to 5 years of age during the 3- to 4-month rainy season across the Sahel region of Africa. Children born to nonimmune mothers in malaria-endemic areas (usually expatriates moving to these areas) should receive prophylaxis from birth.

Travelers should start taking antimalarial drugs 2 days to 2 weeks before departure so that any untoward reactions can be detected before travel and so that therapeutic antimalarial blood concentrations will be present if and when any infections develop (Table 219-8). Antimalarial prophylaxis should continue for 4 weeks after the traveler has left the endemic area, except if atovaquone-proguanil or primaquine has been taken; these drugs have significant activities against the liver stage of the infection (causal prophylaxis) and can be discontinued 1 week after departure from the endemic area. If suspected malaria develops while a traveler is abroad, obtaining a reliable diagnosis and antimalarial treatment locally is a top priority. Presumptive self-treatment for malaria with atovaquone-proguanil (for 3 consecutive days) or one of the artemisinin-based combinations can be considered under special circumstances; medical advice on self-treatment should be sought before departure for malaria-endemic areas and as soon as possible after illness begins. Every effort should be made to confirm the diagnosis.

Atovaquone-proguanil (Malarone; 3.75/1.5 mg/kg or 250/100 mg, daily adult dose) is a fixed-combination, once-daily prophylactic agent that is very well tolerated by adults and children. This combination is effective against all types of malaria, including multidrug-resistant falciparum malaria. Atovaquone-proguanil is best taken with food or a milky drink to optimize absorption. It is not recommended if the estimated glomerular filtration rate is <30 mL/min. There are insufficient data on the safety of this regimen in pregnancy.

TABLE 219-8 Drugs Used in the Prophylaxis of Malaria

DRUG	USAGE	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Atovaquone-proguanil (Malarone)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *Plasmodium falciparum*	1 adult tablet PO[a]	5–8 kg: ½ pediatric tablet[b] daily ≥8–10 kg: ¾ pediatric tablet daily ≥10–20 kg: 1 pediatric tablet daily ≥20–30 kg: 2 pediatric tablets daily ≥30–40 kg: 3 pediatric tablets daily ≥40 kg: 1 adult tablet daily	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Atovaquone-proguanil is contraindicated in persons with severe renal impairment (creatinine clearance rate, <30 mL/min). In the absence of data, it is not recommended for children weighing <5 kg, pregnant women, or women breast-feeding infants weighing <5 kg. Atovaquone-proguanil should be taken with food or a milky drink.
Chloroquine phosphate (Aralen and generic)	Prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	300 mg of base (500 mg of salt) PO once weekly	5 mg of base/kg (8.3 mg of salt/kg) PO once weekly, up to maximum adult dose of 300 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Chloroquine phosphate may exacerbate psoriasis.
Doxycycline (many brand names and generic)	Prophylaxis in areas with chloroquine- or mefloquine-resistant *P. falciparum*[c]	100 mg PO qd (except in pregnant women; see Comments)	≥8 years of age: 2 mg/kg, up to adult dose	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 4 weeks after leaving such areas. Doxycycline is contraindicated in children aged <8 years and in pregnant women after 15 weeks of gestation.
Hydroxychloroquine sulfate (Plaquenil)	An alternative to chloroquine for primary prophylaxis only in areas with chloroquine-sensitive *P. falciparum*[c] or areas with *P. vivax* only	310 mg of base (400 mg of salt) PO once weekly	5 mg of base/kg (6.5 mg of salt/kg) PO once weekly, up to maximum adult dose of 310 mg of base	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Hydroxychloroquine may exacerbate psoriasis.
Mefloquine (Lariam and generic)	Prophylaxis in areas with chloroquine-resistant *P. falciparum*[c]	228 mg of base (250 mg of salt) PO once weekly	≤9 kg: 4.6 mg of base/kg (5 mg of salt/kg) PO once weekly 10–19 kg: ¼ tablet[d] once weekly 20–30 kg: ½ tablet once weekly 31–45 kg: ¾ tablet once weekly ≥46 kg: 1 tablet once weekly	Begin 1–2 weeks before travel to malarious areas. Take weekly on the same day of the week while in the malarious areas and for 4 weeks after leaving such areas. Mefloquine is contraindicated in persons allergic to this drug or related compounds (e.g., quinine and quinidine) and in persons with active or recent depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Use with caution in persons with psychiatric disturbances or a history of depression. Mefloquine is not recommended for persons with cardiac conduction abnormalities.
Primaquine	For prevention of malaria in areas with mainly *P. vivax*	30 mg of base (52.6 mg of salt) PO qd	0.5 mg of base/kg (0.8 mg of salt/kg) PO qd, up to adult dose; should be taken with food	Begin 1–2 days before travel to malarious areas. Take daily at the same time each day while in the malarious areas and for 7 days after leaving such areas. Primaquine is contraindicated in persons with G6PD deficiency. It is also contraindicated during pregnancy.
Primaquine	Used for presumptive anti-relapse therapy (terminal prophylaxis) to decrease risk of relapses of *P. vivax* and *P. ovale*	30 mg of base (52.6 mg of salt) PO qd for 14 days after departure from the malarious area	0.5 mg of base/kg (0.8 mg of salt/kg), up to adult dose, PO qd for 14 days after departure from the malarious area	This therapy is indicated for persons who have had prolonged exposure to *P. vivax* and/or *P. ovale*. It is contraindicated in persons with G6PD deficiency as well as during pregnancy.

[a]An adult tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride. [b]A pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. [c]Very few areas now have chloroquine-sensitive malaria. [d]One tablet contains 228 mg of base (250 mg of salt).

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

Source: CDC: *www.cdc.gov/malaria/travelers/drugs.html.*

Mefloquine (250 mg of salt weekly, adult dose) has been widely used for malarial prophylaxis because it is usually effective against multidrug-resistant falciparum malaria and is reasonably well tolerated. Mefloquine has been associated with rare episodes of psychosis and seizures at prophylactic doses; these reactions are more frequent at the higher doses used for treatment. More common side effects with prophylactic doses of mefloquine include mild nausea, dizziness, fuzzy thinking, disturbed sleep patterns, vivid dreams, dysphoria, and malaise. Mefloquine is contraindicated for use by travelers with known hypersensitivity and by persons with active or recent depression, anxiety disorder, psychosis, schizophrenia, another major psychiatric disorder, or seizures; it is not recommended for persons with cardiac conduction abnormalities although the evidence that it is cardiotoxic is very weak. Confidence is increasing with regard to the safety of mefloquine prophylaxis during pregnancy; in studies in Africa, mefloquine prophylaxis was found to be effective and safe during pregnancy. Daily administration of doxycycline (100 mg daily, adult dose) is an effective alternative to atovaquone-proguanil or mefloquine. Doxycycline is generally well tolerated but may cause vulvovaginal thrush, diarrhea, and photosensitivity and is not recommended for prophylaxis in children <8 years old or pregnant women after 15 weeks of gestation.

Chloroquine can no longer be relied upon to prevent *P. falciparum* infections in most areas but is still used to prevent and treat malaria due to the other human *Plasmodium* species and for *P. falciparum* malaria in Central American countries west and north of the Panama Canal and in Caribbean countries. Chloroquine-resistant *P. vivax* has been reported from parts of eastern Asia, Oceania, and Central and South America. High-level resistance in *P. vivax* is prevalent in Oceania and Indonesia. Chloroquine is generally well tolerated, although some patients cannot take it because of malaise, headache, visual symptoms (due to reversible keratopathy), gastrointestinal intolerance, alopecia, or pruritus. Chloroquine is considered safe in pregnancy. With chronic administration for >5 years, a characteristic dose-related retinopathy may develop, but this condition is rare at the doses used for antimalarial prophylaxis.

Idiosyncratic or allergic reactions are also rare. Skeletal and/or cardiac myopathy is a potential problem with protracted prophylactic use, although it is more likely to occur at the high doses used in the treatment of rheumatoid arthritis. Neuropsychiatric reactions and skin rashes are unusual. Amodiaquine should not be used for weekly prophylaxis because continuous weekly use is associated with a high risk of agranulocytosis (~1 person in 2000) and hepatotoxicity (~1 person in 16,000).

Primaquine (0.5 mg of base/kg or a daily adult dose of 30 mg taken with food), an 8-aminoquinoline compound, has proved safe and effective in the prevention of drug-resistant falciparum and vivax malaria in adults. Primaquine can be considered for persons who are intolerant to other recommended drugs. Abdominal pain can be prevented by taking primaquine with food. Primaquine should not be given to G6PD-deficient persons, in whom it can cause serious hemolysis; G6PD deficiency must therefore be excluded before primaquine is prescribed. Primaquine should not be given to pregnant women or infants <6 months old.

In the past, the dihydrofolate reductase inhibitors pyrimethamine and proguanil (chloroguanide) were administered widely, but the rapid selection of resistance in both *P. falciparum* and *P. vivax* has limited their use. Whereas antimalarial quinolines such as chloroquine (a 4-aminoquinoline) act only on the erythrocyte stage of parasitic development, the dihydrofolate reductase inhibitors (as well as atovaquone and primaquine) also inhibit preerythrocytic growth in the liver (causal prophylaxis) and development in the mosquito (sporontocidal activity). Proguanil is safe and well tolerated, although mouth ulceration occurs in ~8% of persons using this drug; it is considered safe for antimalarial prophylaxis in pregnancy. Prophylactic use of the combination of pyrimethamine and sulfadoxine is not recommended for weekly administration because of an unacceptable incidence of severe toxicity, principally exfoliative dermatitis and other skin rashes, agranulocytosis, hepatitis, and pulmonary eosinophilia (incidence, 1 in 7000; fatal reactions, 1 in 18,000).

Because of the increasing spread and intensity of antimalarial drug resistance **(Fig. 219-10)**, the CDC recommends that travelers and their providers consider their destination, type of travel, and current medications and health risks when choosing antimalarial chemoprophylaxis. There is an increasingly appreciated problem of falsified and substandard antimalarial drugs (and other medicines) on the shelves of pharmacies in Southeast Asia and sub-Saharan Africa; hence, travelers should purchase their preventive drugs from a reputable source before going to a malarious country. Consultation for the evaluation of prophylaxis failures or treatment of malaria can be obtained from state and local health departments and the CDC Malaria Hotline (855-856-4713) or the CDC Emergency Operations Center (770-488-7100).

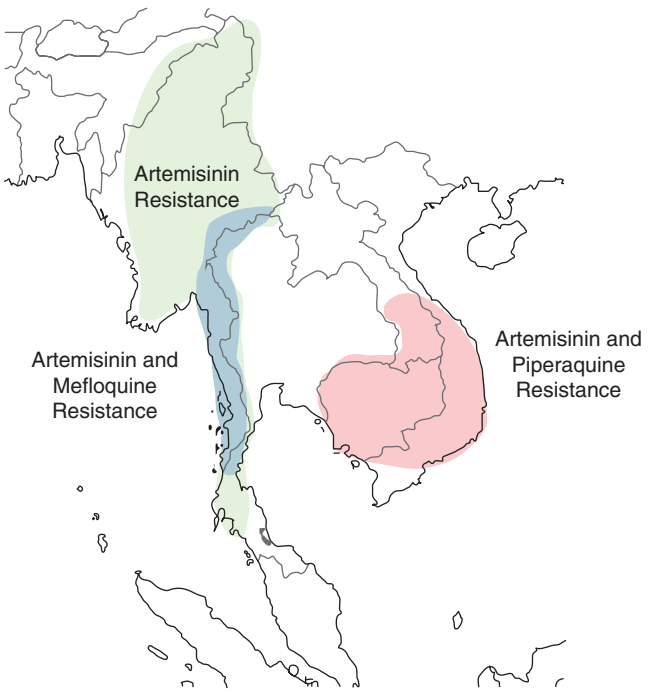


FIGURE 219-10 Current geographic extent of artemisinin resistance and artemisinin-based combination therapy partner drug resistance in *Plasmodium falciparum* in the Greater Mekong subregion.

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FURTHER READING

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220 Babesiosis

Edouard Vannier, Peter J. Krause

Babesiosis is a worldwide **(Fig. 220-1)** emerging tick-borne infectious disease caused by protozoan parasites of the genus *Babesia* that invade and eventually lyse red blood cells (RBCs). More than 100 *Babesia* species infect a broad array of wild and domestic animals, but only a few of these species have been identified as etiologic agents of human babesiosis. Most cases are due to *Babesia microti* and occur in the United States. The infection typically is mild or asymptomatic in young and otherwise healthy individuals but can be severe and sometimes fatal in the elderly and the immunocompromised.

ETIOLOGY AND EPIDEMIOLOGY

United States • Geographic distribution In the United States, human babesiosis caused by *B. microti* is endemic in the Northeast and upper Midwest; seven states in these two regions (Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin) account for more than 90% of reported cases. Whole-genome analysis shows that isolates in the continental United States began to diverge from those in Asia between 1400 and 14,000 years ago and are polyphyletic. Isolates in New England appear to have separated from those in the Midwest some 600 years ago; those on Nantucket Island form a separate subgroup. Other *Babesia* species causing sporadic disease in the United States include *B. duncani* and *B. duncani*–type organisms along the Pacific Coast and *B. divergens*–like organisms in Arkansas, Kentucky, Missouri, and Washington State.

Incidence National surveillance for human babesiosis was begun in the United States in January 2011. More than 1600 cases were reported in 2016—up from ~100 cases in 1996 and ~500 cases in 2006. The steady increase in the number of reported cases is due to the geographic expansion of *Babesia*-infected ticks and reservoir hosts as well as to a greater awareness of the disease among health care workers and improved reporting to state health departments and the Centers for

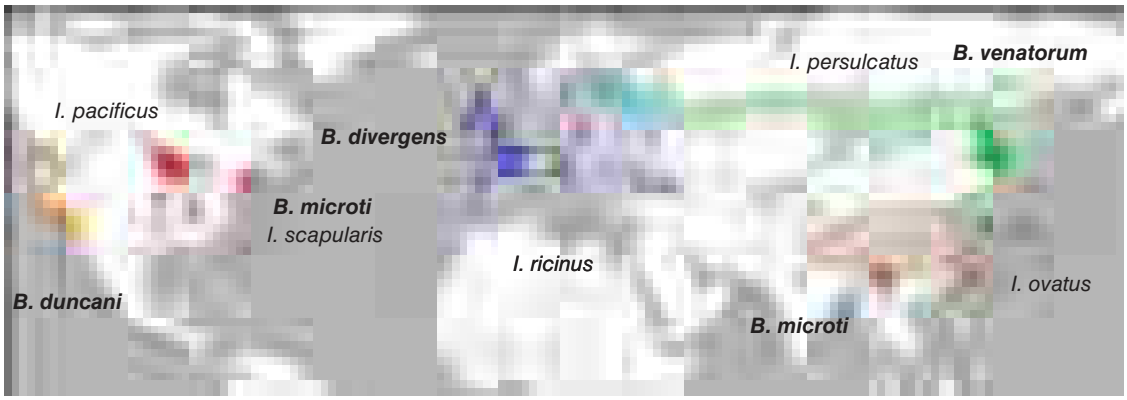

FIGURE 220-1 Worldwide distribution of human babesiosis. The geographic distribution of human babesiosis and its tick vectors is shown. Dark colors indicate areas where human babesiosis is endemic or sporadic (defined by ≥5 cases), whereas light colors indicate areas where tick vectors are present but human babesiosis is rare (<5 cases), undocumented, or absent. Circles depict single cases except in two locations (Montenegro and eastern Poland), where ≥5 cases occurred but all patients were diagnosed at the same hospital. Colors distinguish the etiologic agents: red for *B. microti*, orange for *B. duncani*, blue for *B. divergens*, green for *B. venatorum*, brown for *B. bovis*, black for KO-1, and yellow for *Babesia* species XXB. White circles depict cases caused by uncharacterized *Babesia* species. Asymptomatic infections are omitted. *(Adapted from E Vannier, PJ Krause: N Engl J Med 366:2397, 2012.)*

Disease Control and Prevention (CDC). Babesiosis is reported from areas that have long been endemic for Lyme disease but rarely from areas to which *Borrelia burgdorferi* has recently spread. The delay in geographic expansion of *B. microti* is best explained by its poor ecologic fitness compared with that of *B. burgdorferi* and supports the hypothesis that *B. burgdorferi* promotes maintenance of *B. microti* in the enzootic cycle. Even in highly *Babesia*-endemic areas, the incidence of babesiosis is uneven, sometimes reaching one-third the incidence of Lyme disease. The incidence of babesiosis is underestimated because symptoms are nonspecific and because young healthy individuals typically experience mild or asymptomatic infection and may not seek medical attention.

MODES OF TRANSMISSION In the United States, *B. microti* is transmitted to humans primarily by the nymphal stage of the deer tick (*Ixodes scapularis*), the same tick that transmits the causative agents of Lyme disease **(Chap. 181)** and human granulocytotropic anaplasmosis **(Chap. 182)**. Transmission generally occurs from May through October, with at least three-fourths of cases presenting from June through August. The vectors for transmission of *B. duncani*/*B. duncani*–type and *B. divergens*–like organisms are thought to be *Ixodes pacificus* and *Ixodes dentatus*, respectively.

Babesiosis occasionally is acquired through transfusion of blood products, mostly packed RBCs. More than 200 cases of transfusion-transmitted babesiosis due to *B. microti* have been reported but only three cases due to *B. duncani*. One-fifth of patients whose cases were caused by *B. microti* died, whereas all three patients infected with *B. duncani* survived. Like that of tick-transmitted babesiosis, the incidence of transfusion-transmitted babesiosis has steadily increased over the past 15 years. Transfusion-transmitted cases occur year-round but are most common from June through November. More than 85% of transfusion-transmitted cases occur in endemic areas. Transfusion-transmitted babesiosis occurs in nonendemic areas when unrecognized *Babesia*-contaminated blood products are imported from endemic areas; when asymptomatically infected residents of endemic areas donate blood in nonendemic areas; or when residents of nonendemic areas travel to endemic areas, become infected, and donate blood after they return home.

B. microti can be transmitted through solid organ transplantation. Congenital *B. microti* transmission has been described but is rare. Other cases of neonatal babesiosis are acquired through transfusion or tick bite.

Global Considerations In Europe, the primary causative agent of human babesiosis is *B. divergens*, but *B. venatorum* and *B. microti* occasionally are reported. *Ixodes ricinus* is the tick vector for all three of these *Babesia* species. *B. microti* infection is indigenous to Europe but often is diagnosed in individuals who have recently returned from areas of the United States where babesiosis is endemic. Travel-associated babesiosis may become more frequent if, as anticipated, *Babesia* species continue to emerge worldwide. In Asia, cases due to *B. microti* were first documented in Japan and Taiwan. The case in Japan was acquired through blood transfusion, but *B. microti* organisms were found in *Ixodes ovatus* ticks in the region. Cases of *B. microti* infection have been identified in southwestern China along the border with Myanmar, where malaria is endemic. Two of the patients were co-infected with *Plasmodium* species. A recent case series established that *B. venatorum* is endemic in the northeastern province of Heilongjiang and that *Ixodes persulcatus* is the likely vector. *I. persulcatus* also can transmit *B. microti*. One case of *B. microti* infection has been reported in Australia and another in Canada, along the border with the upper midwestern United States. Sporadic cases due to uncharacterized *Babesia* species have been reported in mainland China, Egypt, India, Mexico, Montenegro, and South Africa.

CLINICAL MANIFESTATIONS

Asymptomatic *B. microti* Infection Studies in highly endemic areas consistently indicate that 1–2% of individuals who donate blood are seropositive for *B. microti* without ever having been diagnosed with babesiosis. A carefully designed epidemiologic study revealed that 20% of adults and 40% of children do not experience symptoms following *B. microti* infection. If left untreated, asymptomatic infection may persist for >2 years. There is no evidence of long-term complications following asymptomatic infection; however, people who are asymptomatically infected may transmit the infection when they donate blood.

Mild to Moderate *B. microti* Illness Symptoms typically develop 1–4 weeks after tick bite and 1–9 weeks (but as long as 6 months) after transfusion of contaminated blood products. Patients experience a gradual onset of fatigue, malaise, and weakness. Fever can reach 40.9°C (105.6°F) and often is accompanied by chills, sweats, headache, myalgia, and anorexia. Less frequent symptoms include arthralgia, nausea, vomiting, and dry cough. Sore throat, photophobia, abdominal pain, weight loss, shortness of breath, neck stiffness, and emotional lability have been reported. On physical examination, fever is the salient feature. Splenomegaly and hepatomegaly occasionally are noted, but lymphadenopathy is absent. Ecchymoses, petechiae, jaundice, slight pharyngeal erythema, and retinopathy with splinter hemorrhages and retinal infarcts rarely are observed. An erythema migrans rash **(Fig. A1-8)** signifies concurrent Lyme disease **(Chap. 181)**. Symptoms typically last 1–2 weeks, but fatigue may persist for several months. Patients who are co-infected with *B. burgdorferi* and *B. microti* experience a greater number of symptoms for a longer duration than patients with Lyme disease alone.

Severe *B. microti* Illness Severe babesiosis requires hospital admission. The median length of hospital stay was 4 days (range, 1–39 days) among babesiosis patients reported to the CDC in 2011–2014. Severe babesiosis typically occurs in patients with one or more of the following characteristics: age >50 years, neonatal prematurity, asplenia/hyposplenism, HIV/AIDS, malignancy, and immunosuppressive therapy. More than one-third of hospitalized patients develop one or more complications, including acute respiratory distress syndrome, disseminated intravascular coagulation, congestive heart failure, renal failure, and hemophagocytic lymphohistiocytosis. Patients who develop these complications tend to have severe anemia (hemoglobin, ≤10 g/dL). Splenic infarcts and splenic rupture can occur, despite low-level parasitemia. In the absence of hemoperitoneum, splenic rupture should be managed without surgery, as removal of the spleen leaves these patients at risk for relapse of *Babesia* infection and for severe disease caused by other microorganisms. Production of autoantibodies can result in autoimmune hemolytic anemia, even after parasitemia has resolved. Babesiosis-associated immune thrombocytopenia has been reported. Death is not uncommon among hospitalized patients (3–9%), particularly those who are immunocompromised or who acquire the infection through blood transfusion (~20%). Laboratory prognostic factors for severe outcome, as defined by hospitalization for >14 days, intensive care unit stay of >2 days, or death, include an alkaline phosphatase level >125 U/L and a parasitemia level >4%.

Other *Babesia* Infections *B. duncani* and *B. duncani*–type infections range in severity from asymptomatic to fatal. Although few cases have been documented, clinical manifestations have been similar to those reported for *B. microti* infections. All four patients infected with *B. divergens*–like organisms in the United States required hospitalization; two died. Most cases of *B. divergens* infection in Europe have occurred in people lacking a spleen. The incubation period is 1–3 weeks. Symptoms develop suddenly and consist of fever (>41°C [105.8°F]), shaking chills, drenching sweats, headache, myalgia, and lumbar and abdominal pain. Hemoglobinuria and jaundice are common, and mild hepatomegaly may occur. If the infection is not treated rapidly, patients may experience pulmonary edema and renal failure. All four patients infected with *B. venatorum* in Europe had been splenectomized; their illness ranged from mild to severe, and none died. Forty-eight cases of *B. venatorum* infection were reported in northeastern China in immunocompetent residents. Symptoms were similar to those of *B. microti* infection, although fever and chills were less common. Seven of the 48 patients were hospitalized, but all recovered despite receiving nonstandard antibiotic regimens, including clindamycin without quinine.

PATHOGENESIS

Anemia is a key feature of the pathogenesis of babesiosis. Hemolytic anemia caused by rupture of infected RBCs generates cell debris that may accumulate in the kidney and cause renal failure. Anemia also results from the clearance of intact RBCs as they pass through the splenic red pulp and encounter resident macrophages. *Babesia* antigens expressed on the RBC membrane promote opsonization and facilitate uptake by splenic macrophages. In addition, RBCs are poorly deformable as a result of oxidation generated by the parasite and the host immune response and are filtered out as they attempt to squeeze across the venous vasculature. Bone marrow suppression due to cytokine production may also contribute to anemia.

An appropriate immune response is necessary for the control and clearance of *Babesia*. Studies in laboratory mice have established that $CD4^+$ T cells are critical for resistance to and resolution of *B. microti* infection. $CD4^+$ T cells are a major source of interferon γ (IFN-γ), and lack of this cytokine causes resistant mice to become highly susceptible to *B. microti*. IFN-γ is central to host resistance in *B. duncani* infection, but natural killer cells are its main source. Several lines of evidence suggest that an excessive immune response contributes to pathogenesis. Blockade of tumor necrosis factor receptor p55 (TNFRp55) accelerates resolution of *B. microti* parasitemia. *B. duncani* infection is more severe than *B. microti* infection in rodents and is characterized by pulmonary inflammation. Tumor necrosis factor α is expressed around alveolar septa, whereas IFN-γ is detected around pulmonary vessels. Blockade of either cytokine promotes the survival of mice infected with *B. duncani*.

DIAGNOSIS

A diagnosis of babesiosis should be considered for any patient who lives or travels in a *Babesia*-endemic area and presents with a febrile illness in late spring, summer, or early autumn or within 6 months after a blood transfusion. Co-infection with *Babesia* should be considered when symptoms are more severe than expected or persist in patients who are diagnosed with and treated for Lyme disease and/or human granulocytotropic anaplasmosis.

Screening laboratory tests can help support the diagnosis of babesiosis. A complete blood count often shows anemia and thrombocytopenia. White blood cell counts can be elevated, reduced, or unchanged, but neutropenia occurs in approximately three-quarters of infants and one-third of adults. A low haptoglobin level or an elevated lactate dehydrogenase level is consistent with hemolytic anemia. Liver function tests often reveal elevated levels of alkaline phosphatase, aspartate and alanine aminotransferases, and bilirubin. Urinalysis may show hemoglobinuria, excess urobilinogen, and proteinuria. Elevated levels of blood urea nitrogen and serum creatinine indicate renal compromise.

A specific diagnosis usually is established by microscopic examination of Giemsa-stained thin blood smears **(Fig. 220-2)**. *Babesia* trophozoites appear round or ameboid. The ring form is most common and lacks the central brownish deposit (hemozoin) typical of *Plasmodium falciparum* trophozoites **(see Fig. A6-1*C*)**. Other distinguishing features are the absence of schizonts and gametocytes and the occasional presence of tetrads ("Maltese cross"). Tetrads are characteristic of *B. microti*, *B. duncani*, *B. venatorum*, and *B. divergens*–like organisms in human erythrocytes but rarely are observed. Because parasitemia may be as low as 0.01%, particularly at the onset of symptoms, identification of the parasite may require multiple blood smears over several days. Parasitemia generally ranges from 0.1 to 5% but has reached as high as 85% in an immunocompromised patient. If parasites cannot be identified by microscopy and the disease is still suspected, amplification

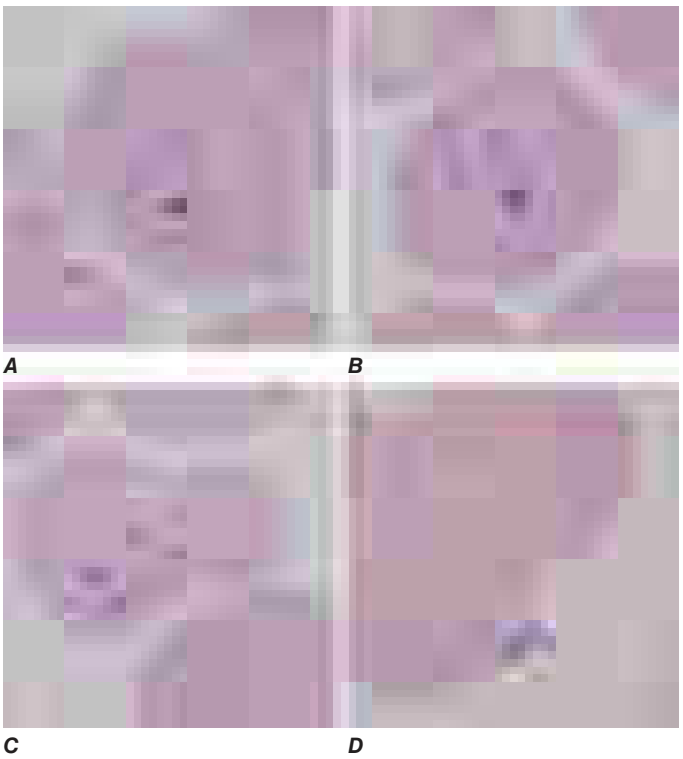

FIGURE 220-2 Giemsa-stained thin blood films showing *Babesia microti* parasites. *B. microti* are obligate parasites of erythrocytes. Trophozoites may appear as ring forms (***A***) or as ameboid forms (***B***). Merozoites can be arranged in tetrads that are pathognomonic (***C***). Extracellular parasites can be noted, particularly when parasitemia is high (***D***). *(Adapted from E Vannier, PJ Krause: N Engl J Med 366:2397, 2012.)*

of the *Babesia* 18S rRNA gene by polymerase chain reaction (PCR) or real-time PCR is recommended. Real-time PCR assays detect as few as 0.1–10 parasites/μL of blood, thereby increasing analytical sensitivity by 10- to 1000-fold over that of blood smear examination.

Serology can suggest or confirm the diagnosis of babesiosis. An indirect immunofluorescent antibody test for *B. microti* is most commonly used. IgM titers of ≥1:64 and IgG titers of ≥1:1024 suggest active or recent infection. Titers typically decline over 6–12 months but may persist for >1 year. Antibodies to *B. microti* do not cross-react with *B. duncani* or *B. divergens* antigen. In *B. divergens* infection, serology is of limited use because symptoms often appear before antibodies can be detected. Sera from patients infected with *B. divergens*–like organisms or *B. venatorum* are reactive against *B. divergens* antigen. In the past decade, automated antibody assays that are standardized and suitable for screening the blood supply have been developed, including both an enzyme-linked immunosorbent assay that uses four *Babesia* peptides as antigen and an IgG arrayed fluorescence immunoassay that uses whole-cell sonicate as antigen.

TREATMENT

Babesiosis

ASYMPTOMATIC *B. MICROTI* INFECTION

Asymptomatic *B. microti* infection is seldom diagnosed, and no evidence suggests that treatment is beneficial. Because of the increasing incidence and high mortality rate of transfusion-transmitted babesiosis, it is likely that screening of blood donations will be instituted. The combined use of assays to detect *B. microti* antibody and *B. microti* DNA can reliably identify blood donations that contain *B. microti* organisms, thereby effectively preventing transfusion-transmitted babesiosis once a screening algorithm approved by the U.S. Food and Drug Administration is implemented.

MILD TO MODERATE *B. MICROTI* ILLNESS

The first successful therapy for babesiosis consisted of clindamycin combined with quinine, but the combination of atovaquone plus azithromycin was subsequently shown in a prospective trial to be as effective in resolving symptoms and clearing parasitemia in adults with nonlife-threatening babesiosis. In that study, adverse effects were reported in 15% of patients who received atovaquone plus azithromycin but in 72% of those who received clindamycin plus quinine. The adverse reactions were so severe that treatment had to be stopped or the dosage reduced in one-third of participants taking clindamycin plus quinine, but in only 2% of those taking atovaquone plus azithromycin. Thus, atovaquone plus azithromycin, given orally for 7–10 days, is the recommended antibiotic regimen for mild to moderate babesiosis **(Table 220-1)**. Symptoms usually begin to resolve within 48 h of therapy initiation, but complete resolution of symptoms may take weeks or months. An atypical or poor response to therapy should raise suspicion of concurrent tick-borne disease or drug resistance.

SEVERE *B. MICROTI* ILLNESS

Azithromycin given intravenously plus atovaquone given orally for 7–10 days is recommended for treatment of severe babesiosis. Clindamycin given intravenously plus quinine given orally is an alternative regimen. Standard antimicrobial therapy sometimes is insufficient to resolve symptoms and clear parasitemia, especially in patients with marked immunosuppression—e.g., those who have received or are receiving rituximab or prednisone for B cell lymphomas or autoimmune disorders, who receive other immunosuppressive regimens for organ or bone marrow transplantation or malignancy, or who have HIV infection with low CD4+ T cell counts (AIDS). In such patients, antimicrobial therapy should be administered for at least 6 weeks, including 2 weeks after parasites are no longer observed on blood smear. In most instances, PCR should not be used to monitor the response to therapy because *B. microti* can persist in the blood at very low levels for weeks or months after symptoms have resolved and parasites are no longer detected on blood smears. A combination of high-dose azithromycin (600–1000 mg/d) plus atovaquone has been successfully used in immunocompromised patients. Failure to respond to atovaquone plus azithromycin has been documented in a few highly immunocompromised patients and has been attributed to accumulation of mutations in the *Babesia* genome, particularly in genes for which the encoded proteins are targets of atovaquone or azithromycin. Given that *B. microti* organisms circulate in a zoonotic cycle and that humans are dead-end hosts, use of atovaquone or azithromycin for the treatment of babesiosis does not increase the risk of overall antibiotic resistance. Patients who are unresponsive to atovaquone plus azithromycin or who do not tolerate clindamycin plus quinine can be successfully treated with alternative regimens (Table 220-1, footnote d).

Partial or complete RBC exchange transfusion is recommended in patients with high-grade parasitemia (≥10%); severe anemia (hemoglobin, <10 g/dL); or pulmonary, hepatic, or renal compromise. A desirable target of RBC exchange transfusion is a reduction in parasitemia by >90%. Parasitemia and hematocrit should be monitored daily until symptoms improve.

TABLE 220-1 Treatment of Human Babesiosis

ADULTS	CHILDREN
***B. microti* Infection (Mild to Moderate Illness[a,b])**	
Atovaquone (750 mg q12h PO) ***plus*** Azithromycin (500 mg/d PO on day 1, 250 mg/d PO thereafter)	Atovaquone (20 mg/kg q12h PO; maximum, 750 mg/dose) ***plus*** Azithromycin (10 mg/kg qd PO on day 1 [maximum, 500 mg/dose], 5 mg/kg qd PO thereafter [maximum, 250 mg/dose])
***B. microti* Infection (Severe Illness[c,d])**	
Azithromycin (500 mg q24h IV) ***plus*** Atovaquone (750 mg q12h PO) ***OR*** Clindamycin (300–600 mg q6h IV or 600 mg q8h PO) ***plus*** Quinine (650 mg q6–8h PO) ***plus*** Consider exchange transfusion	Azithromycin (10 mg/kg up to adult dose q24h IV) ***plus*** Atovaquone (20 mg/kg per dose up to adult dose q12h PO) ***OR*** Clindamycin (7–10 mg/kg q6–8h IV or 7–10 mg/kg q6–8h PO; maximum, 600 mg/dose) ***plus*** Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose) ***plus*** Consider exchange transfusion
***B. divergens* Infection**	
Immediate complete exchange transfusion ***plus*** Clindamycin (600 mg q6–8h IV) ***plus*** Quinine (650 mg q8h PO)	Immediate complete exchange transfusion ***plus*** Clindamycin (7–10 mg/kg q6–8h IV; maximum, 600 mg/dose) ***plus*** Quinine (8 mg/kg q8h PO; maximum, 650 mg/dose)

[a]Treatment duration, 7–10 days. [b]A high dose of azithromycin (600–1000 mg) combined with atovaquone has been recommended for immunocompromised hosts. [c]Treatment typically is given for 7–10 days, but its duration may vary. In severely immunocompromised patients, therapy should be continued for at least 6 weeks, including 2 weeks after parasites are no longer detected on blood smear. [d]Several alternative regimens have been used in a limited number of cases of *B. microti* infection, and their efficacy is uncertain. These regimens include atovaquone plus clindamycin (with or without azithromycin), azithromycin plus quinine, and atovaquone-proguanil added to atovaquone plus azithromycin and/or clindamycin plus quinine.

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B. duncani and *B. duncani*–type infections have been treated with IV clindamycin (600 mg three or four times daily or 1200 mg twice daily) plus oral quinine (600–650 mg three times daily) for 7–10 days. A regimen used for *B. divergens*–like infections consists of IV clindamycin (600 mg three or four times daily, 900 mg three times daily, or 1200 mg twice daily) plus oral quinine (650 mg three times daily). In Europe, *B. divergens* infection is considered a medical emergency. The recommended treatment is immediate, complete blood exchange transfusion combined with administration of IV clindamycin plus oral quinine. Some cases have been cured with exchange transfusion and clindamycin monotherapy. Anemia may persist for >1 month and require blood transfusion. The first line of therapy for *B. venatorum* infection in Europe has been the combination of clindamycin plus quinine. In an immunocompromised patient intolerant to quinine, cure was achieved by administration of atovaquone plus azithromycin. A pediatric case of *B. venatorum* in northwestern China was successfully treated by a standard course of atovaquone plus azithromycin.

PREVENTION

No vaccine is available for human use. There is no role for antibiotic prophylaxis. Individuals who reside in endemic areas, especially those at risk for severe babesiosis, should wear clothing that covers the lower and upper parts of the body, apply tick repellents (such as DEET) to the skin and permethrin to clothing, and limit outdoor activities where ticks may abound from May through October. The skin should be thoroughly examined after outdoor activities, and ticks should be removed with tweezers. Individuals with a history of babesiosis or asymptomatic *Babesia* infection confirmed by laboratory testing are indefinitely deferred from donating blood.

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221 Leishmaniasis

Shyam Sundar

Encompassing a complex group of disorders, leishmaniasis is caused by unicellular eukaryotic obligatory intracellular protozoa of the genus *Leishmania* and primarily affects the host's reticuloendothelial system. *Leishmania* species produce widely varying clinical syndromes ranging from self-healing cutaneous ulcers to fatal visceral disease. These syndromes fall into three broad categories: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucosal leishmaniasis (ML).

ETIOLOGY AND LIFE CYCLE

Leishmaniasis is caused by ~20 species of the genus *Leishmania* in the order Kinetoplastida and the family Trypanosomatidae **(Table 221-1)**. Several clinically important species are of the subspecies *Viannia*. The organisms are transmitted by phlebotomine sandflies of the genus *Phlebotomus* in the "Old World" (Asia, Africa, and Europe) and the genus *Lutzomyia* in the "New World" (the Americas). Transmission may be anthroponotic (i.e., the vector transmits the infection from infected humans to healthy humans) or zoonotic (i.e., the vector transmits the infection from an animal reservoir to humans). Human-to-human transmission via shared infected needles has been documented in IV drug users in the Mediterranean region. In utero transmission to the fetus occurs rarely.

Leishmania organisms occur in two forms: extracellular, flagellate promastigotes (length, 10–20 μm) in the sandfly vector and intracellular, nonflagellate amastigotes (length, 2–4 μm; **Fig. 221-1**) in vertebrate hosts, including humans. Promastigotes are introduced through the proboscis of the female sandfly into the skin of the vertebrate host. Neutrophils predominate among the host cells that first encounter and take up promastigotes at the site of parasite delivery. The infected neutrophils may undergo apoptosis and release viable parasites that are taken up by macrophages, or the apoptotic cells may themselves be taken up by macrophages and dendritic cells. The parasites multiply as amastigotes inside macrophages, causing cell rupture with subsequent invasion of other macrophages. While feeding on infected hosts, sandflies pick up amastigotes, which transform into the flagellate form in the flies' posterior midgut and multiply by binary fission; the promastigotes then migrate to the anterior midgut and can infect a new host when flies take another blood meal.

EPIDEMIOLOGY

Leishmaniasis occurs in 98 countries—most of them developing—in tropical and temperate regions **(Fig. 221-2)**. More than 1.5 million cases occur annually, of which 0.7–1.2 million are CL (and its variations) and 200,000–400,000 are VL. More than 350 million people are at risk, with an overall prevalence of 12 million. The distribution of *Leishmania* is limited by the distribution of sandfly vectors. Human leishmaniasis is on the increase worldwide except on the Indian subcontinent, where a VL elimination program has been implemented and VL incidence is markedly declining.

VISCERAL LEISHMANIASIS

VL (also known as *kala-azar*, a Hindi term meaning "black fever") is caused by the *Leishmania donovani* complex, which includes *L. donovani* and *Leishmania infantum* (the latter designated *Leishmania chagasi* in the New World); these species are responsible for anthroponotic and zoonotic transmission, respectively. India and neighboring Bangladesh, Sudan and neighboring South Sudan, Ethiopia, and Brazil are the four largest foci of VL and account for 90% of the world's VL burden. Zoonotic VL is reported from all countries in the Middle East, Pakistan, and other countries from western Asia to China. Endemic foci also exist in the independent states of the former Soviet Union, mainly Georgia and Azerbaijan. In the Horn of Africa, Sudan, South Sudan, Ethiopia, Kenya, Uganda, and Somalia report VL. In Sudan and South Sudan, large outbreaks are thought to be anthroponotic, although zoonotic transmission also occurs. VL is rare in West and sub-Saharan Africa.

Mediterranean VL, long an established endemic disease due to *L. infantum*, has a large canine reservoir and was seen primarily in infants before the advent of HIV infection. In Mediterranean Europe, 70% of adult VL cases are associated with HIV co-infection. The combination is deadly because of the combined impact of the two infections on the immune system. IV drug users are at particular risk. Other forms of immunosuppression (e.g., that associated with organ transplantation) also predispose to VL. In the Americas, disease caused by *L. infantum* is endemic from Mexico to Argentina, but 90% of cases in the New World are reported from northeastern Brazil. After the introduction of highly active antiretroviral therapy, the incidence of HIV–VL co-infection declined significantly in Europe; however, ~30 and 5% of VL patients are co-infected with HIV in Ethiopia and India, respectively.

Immunopathogenesis The majority of individuals infected by *L. donovani* or *L. infantum* mount a successful immune response and control the infection, never developing symptomatic disease.

TABLE 221-1 Geographic Distribution and Characteristic Epidemiology of Leishmaniases

ORGANISM, ENDEMIC REGION	CLINICAL SYNDROME	SPECIES	VECTOR	RESERVOIR	TRANSMISSION	SETTING
***Leishmania donovani* Complex**						
South Asia	VL, PKDL	*L. donovani*	*Phlebotomus argentipes*	Humans	Anthroponotic	Rural, domestic
Sudan, South Sudan, Somalia, Ethiopia, Kenya, Uganda	VL, PKDL	*L. donovani*	*P. orientalis, P. martini*	Humans, rodents in Sudan, canines	Anthroponotic, occasionally zoonotic	Majority peridomestic, occasionally sylvatic
Mediterranean basin, Middle East, Central Asia, China	VL, CL	*L. infantum*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Middle East, Saudi Arabia, Yemen	VL	*L. donovani*	*P. perniciosus, P. ariasi*	Dogs, foxes, jackals	Zoonotic	Domestic, peridomestic
Central and South America	VL, CL	*L. infantum*[a]	*Lutzomyia longipalpis*	Foxes, dogs, opossums	Zoonotic	Domestic, peridomestic, periurban
Azerbaijan, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan	VL	*L. infantum*	*P. turanicus*	Humans, dogs, foxes	Anthroponotic, zoonotic	Domestic
L. tropica						
Western India to Turkey, parts of North and East Africa	CL, leishmaniasis recidivans	*L. tropica*	*P. sergenti*	Humans	Anthroponotic	Urban domestic, peridomestic
L. major						
Western and Central Asia, North and sub-Saharan Africa	CL	*L. major*	*P. papatasi, P. duboscqi*	Nile rats, rodents	Zoonotic	Sylvatic, peridomestic
Kazakhstan, Turkmenistan, Uzbekistan	CL	*L. major*	*P. papatasi, P. duboscqi*	Gerbils	Zoonotic	Rural
L. aethiopica						
Ethiopia, Uganda, Kenya	CL, DCL	*L. aethiopica*	*P. longipes, P. pedifer*	Hyraxes	Zoonotic	Sylvatic, peridomestic
Subspecies *Viannia*						
Peru, Ecuador	CL, ML	*L. (V.) peruviana*	*Lutzomyia verrucarum, L. peruensis*	Wild rodents	Zoonotic	Andean Valleys
Guyana, Surinam, French Guyana, Ecuador, Brazil, Colombia, Bolivia	CL, ML	*L. (V.) guyanensis*	*L. umbratilis*	Sloths, arboreal anteaters, opossums	Zoonotic	Tropical forest
Central America, Ecuador, Colombia	CL, ML	*L. (V.) panamensis*	*L. trapidoi*	Sloths	Zoonotic	Tropical forest and deforested areas
South and Central America	CL, ML	*L. (V.) braziliensis*	*Lutzomyia* spp., *L. umbratilis, Psychodopygus wellcomei*	Forest rodents, peridomestic animals	Zoonotic	Tropical forest and deforested areas
***L. mexicana* Complex**						
Central America and northern parts of South America	CL, ML, DCL	*L. amazonensis*	*L. flaviscutellata*	Forest rodents	Zoonotic	Tropical forest and deforested areas
	CL, ML, DCL	*L. mexicana*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	Tropical forest and deforested areas
	CL, DCL	*L. pifanoi*	*L. olmeca*	Variety of forest rodents and marsupials	Zoonotic	Tropical forest and deforested areas

[a]*L. infantum* is designated *L. chagasi* in the New World.

Abbreviations: CL, cutaneous leishmaniasis; DCL, diffuse cutaneous leishmaniasis; ML, mucosal leishmaniasis; PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

Forty-eight hours after intradermal injection of killed promastigotes, these individuals exhibit delayed-type hypersensitivity (DTH) to leishmanial antigens in the leishmanin skin test (also called the Montenegro skin test). Results in mouse models indicate that the development of acquired resistance to leishmanial infection is controlled by the production of interleukin (IL) 12 by antigen-presenting cells and the subsequent secretion of interferon (IFN) γ, tumor necrosis factor (TNF) α, and other proinflammatory cytokines by the T helper 1 (T_H1) subset of T lymphocytes. The immune response in patients developing active VL is complex; in addition to increased production of multiple proinflammatory cytokines and chemokines, patients with active disease have markedly elevated levels of IL-10 in serum as well as enhanced IL-10 mRNA expression in lesional tissues. A direct role for IL-10 in the pathology of VL in humans is supported by studies demonstrating that IL-10 blockade can enhance IFN-γ responses in whole blood from VL patients. The main disease-promoting activity of IL-10 in VL may be to condition host macrophages for enhanced survival and growth of the parasite. IL-10 can render macrophages unresponsive to activation signals and inhibit killing of amastigotes by downregulating the production of TNF-α and nitric oxide. Multiple antigen-presentation functions of dendritic cells and macrophages are also suppressed by IL-10. Patients with such suppression do not have positive leishmanin skin tests, nor do their peripheral-blood mononuclear cells respond to leishmanial antigens in vitro. Organs of the reticuloendothelial system are predominantly affected, with remarkable enlargement of the spleen, liver, and lymph nodes in some regions. The tonsils and intestinal submucosa

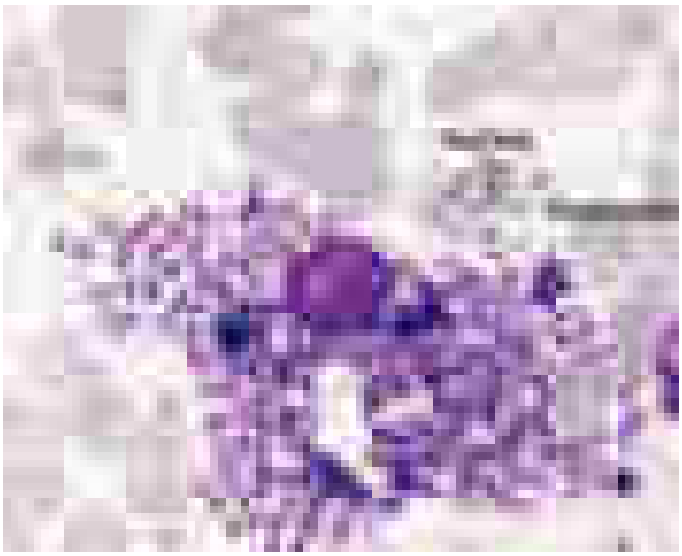

FIGURE 221-1 A macrophage with numerous intracellular amastigotes (2–4 μm) in a Giemsa-stained splenic smear from a patient with visceral leishmaniasis. Each amastigote contains a nucleus and a characteristic kinetoplast consisting of multiple copies of mitochondrial DNA. A few extracellular parasites are also visible.

are also heavily infiltrated with parasites. Bone marrow dysfunction results in pancytopenia.

Clinical Features On the Indian subcontinent and in the Horn of Africa, persons of all ages are affected by VL. In endemic areas of the Americas and the Mediterranean basin, immunocompetent infants and small children as well as immunodeficient adults are affected especially often. The most common presentation of VL is an abrupt onset of moderate- to high-grade fever associated with rigor and chills. Fever may continue for several weeks with decreasing intensity, and the patient may become afebrile for a short period before experiencing another bout of fever. The spleen may be palpable by the second week of illness and, depending on the duration of illness, may become hugely enlarged **(Fig. 221-3)**. Hepatomegaly (usually moderate in degree) soon follows. Lymphadenopathy is common in most endemic regions of the world except the Indian subcontinent, where it is rare. Patients lose weight and feel weak, and the skin gradually develops dark discoloration due to hyperpigmentation that is most easily seen in brown-skinned individuals. In advanced illness, hypoalbuminemia

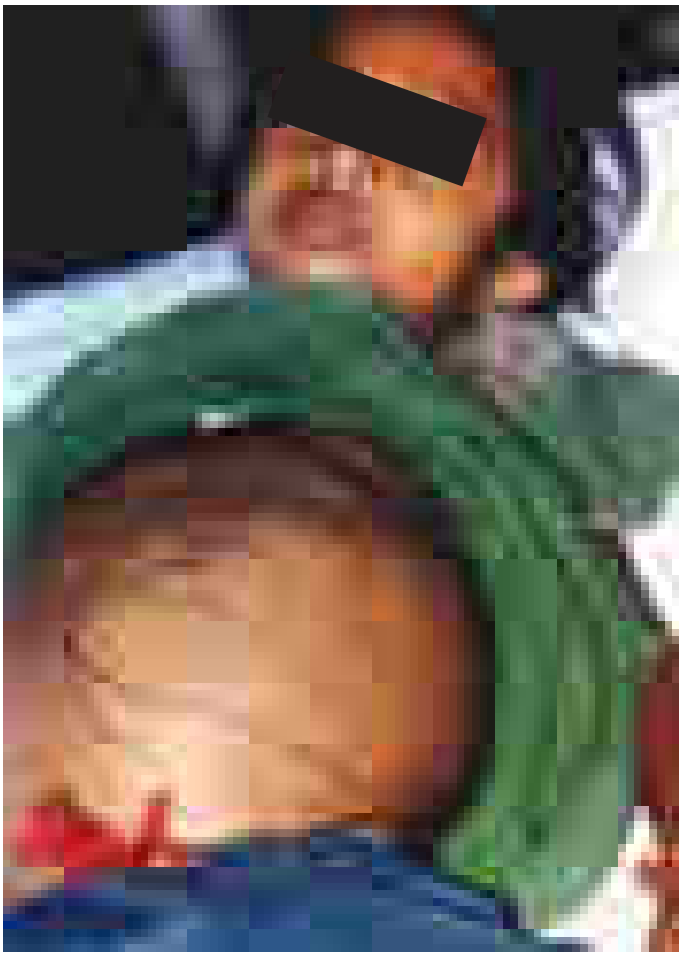

FIGURE 221-3 A patient with visceral leishmaniasis has a hugely enlarged spleen visible through the surface of the abdomen. Splenomegaly is the most important feature of visceral leishmaniasis.

may manifest as pedal edema and ascites. Anemia appears early and may become severe enough to cause congestive heart failure. Epistaxis, retinal hemorrhages, and gastrointestinal bleeding are associated with thrombocytopenia. Secondary infections such as measles, pneumonia, tuberculosis, bacillary or amebic dysentery, and gastroenteritis are common. Herpes zoster, chickenpox, boils in the skin, and scabies may

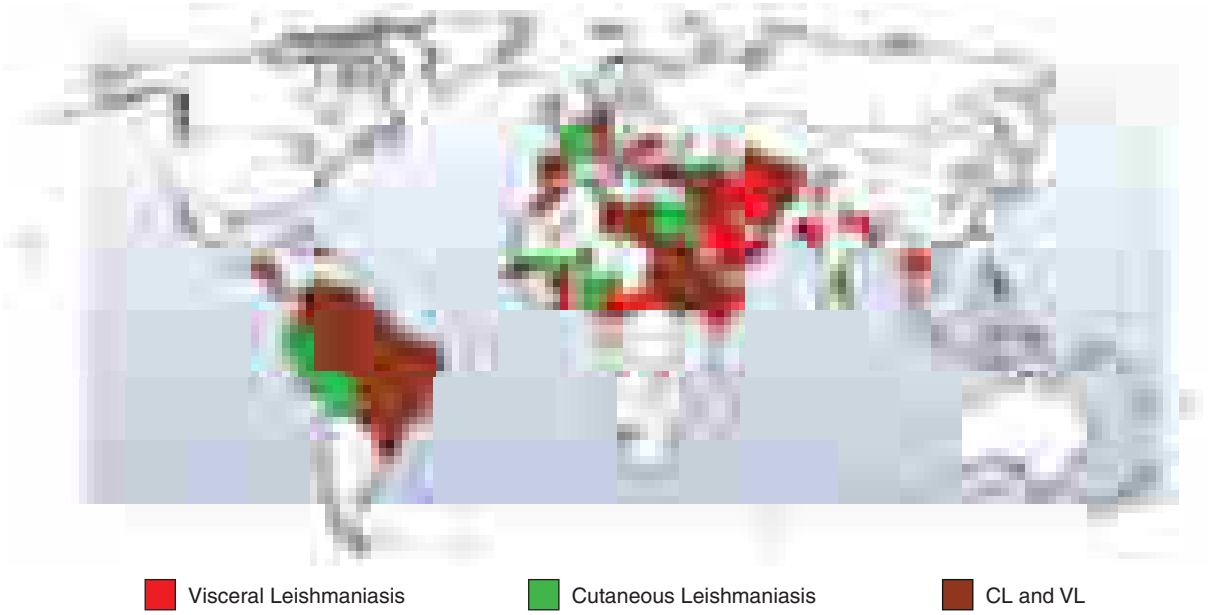

FIGURE 221-2 Worldwide distribution of human leishmaniasis. CL, cutaneous leishmaniasis; VL, visceral leishmaniasis.

also occur. Untreated, the disease is fatal in most patients, including 100% of those with HIV co-infection.

Leukopenia and anemia occur early and are followed by thrombocytopenia. There is a marked polyclonal increase in serum immunoglobulins. Serum levels of hepatic aminotransferases are raised in a significant proportion of patients, and serum bilirubin levels are elevated occasionally. Renal dysfunction is uncommon.

Laboratory Diagnosis Demonstration of amastigotes in smears of tissue aspirates is the gold standard for the diagnosis of VL (Fig. 221-1). The sensitivity of splenic smears is >95%, whereas smears of bone marrow (60–85%) and lymph node aspirates (50%) are less sensitive. Culture of tissue aspirates increases sensitivity. Splenic aspiration is invasive and may be dangerous in untrained hands. Several serologic techniques are currently used to detect antibodies to *Leishmania*. An enzyme-linked immunosorbent assay (ELISA) and the indirect immunofluorescent antibody test (IFAT) are used in sophisticated laboratories.

In the field, however, a rapid immunochromatographic test based on the detection of antibodies to a recombinant antigen (rK39) consisting of 39 amino acids conserved in the kinesin region of *L. infantum* is used worldwide. The test requires only a drop of fingerprick blood or serum, and the result can be read within 15 min. Except in East Africa (where both its sensitivity and its specificity are lower), the sensitivity of the rK39 rapid diagnostic test (RDT) in immunocompetent individuals is ~98% and its specificity is ~90%. In Sudan, an RDT based on a new synthetic polyprotein, rK28, was more sensitive (96.8%) and specific (96.2%) than rK39-based RDTs. Since these antibody detection tests remain positive for years after cure, they cannot be used for measurement of cure or detection of relapse. Qualitative detection of leishmanial nucleic acid by polymerase chain reaction (PCR) or by loop-mediated isothermal amplification (LAMP) and quantitative detection by real-time PCR are highly sensitive; however, because the capacity to perform these tests is confined to specialized laboratories, they have yet to be used for routine diagnosis of VL in endemic areas. PCR can distinguish among the major species of *Leishmania* infecting humans.

Differential Diagnosis VL is easily mistaken for malaria. Other febrile illnesses that may mimic VL include typhoid fever, tuberculosis, brucellosis, schistosomiasis, and histoplasmosis. Splenomegaly due to portal hypertension, chronic myeloid leukemia, tropical splenomegaly syndrome, and (in Africa) schistosomiasis may also be confused with VL. Fever with neutropenia or pancytopenia in patients from an endemic region strongly suggests a diagnosis of VL; hypergammaglobulinemia in patients with long-standing illness strengthens the diagnosis. In nonendemic countries, a careful travel history is essential when any patient presents with fever.

TREATMENT

Visceral Leishmaniasis

GENERAL CONSIDERATIONS

Severe anemia should be corrected by blood transfusion, and other comorbid conditions should be managed promptly. Treatment of VL is complex because the optimal drug, dosage, and duration vary with the endemic region. Despite completing recommended treatment, some patients experience relapse (most often within 6 months), and prolonged follow-up is recommended. A pentavalent antimonial is the drug of choice in most endemic regions of the world, but there is widespread resistance to antimony in the Indian state of Bihar, where either amphotericin B (AmB)—deoxycholate or liposomal—or miltefosine is preferred. Dose requirements for AmB are lower in India than in the Americas, Africa, or the Mediterranean region. In Mediterranean countries, where cost is seldom an issue, liposomal AmB (LAmB) is the drug of choice. In immunocompetent patients, relapses are uncommon with AmB in its deoxycholate and lipid formulations. Antileishmanial therapy has recently evolved as new drugs and delivery systems have become available and resistance to antimonial compounds has emerged.

Except for AmB (deoxycholate and lipid formulations), antileishmanial drugs are available in the United States only from the Centers for Disease Control and Prevention.

PENTAVALENT ANTIMONIAL COMPOUNDS

Two pentavalent antimonial (Sb^V) preparations are available: sodium stibogluconate (100 mg of Sb^V/mL) and meglumine antimoniate (85 mg of Sb^V/mL). The daily dose is 20 mg/kg by IV infusion or IM injection, and therapy continues for 28–30 days. Cure rates exceed 90% in Africa, the Americas, and most of the Old World but are <50% in Bihar, India, as a result of resistance. Adverse reactions to Sb^V treatment are common and include arthralgia, myalgia, and elevated serum levels of aminotransferases. Electrocardiographic changes are common. Concave ST-segment elevation is not significant, but prolongation of QT_c to >0.5 s may herald ventricular arrhythmia and sudden death. Chemical pancreatitis is common but usually does not require discontinuation of treatment; severe clinical pancreatitis occurs in immunosuppressed patients.

AMPHOTERICIN B

AmB is currently used as a first-line drug in Bihar, India. In other parts of the world, it is used when initial antimonial treatment fails. Conventional AmB deoxycholate is administered in doses of 0.75–1.0 mg/kg on alternate days for a total of 15 infusions. Fever with chills is an almost universal adverse reaction to AmB infusions. Nausea and vomiting are also common, as is thrombophlebitis in the infused veins. Acute toxicities can be minimized by administration of antihistamines like chlorpheniramine and antipyretic agents like acetaminophen before each infusion. AmB can cause renal dysfunction and hypokalemia and, in rare instances, elicits hypersensitivity reactions, bone marrow suppression, and myocarditis, all of which can be fatal.

Several lipid formulations of AmB, developed to replace the deoxycholate formulation, are preferentially taken up by reticuloendothelial tissues. Because very little free drug is available to cause toxicity, a large amount of drug can be delivered over a short period. LAmB has been used extensively to treat VL in all parts of the world. With a terminal half-life of ~150 h, LAmB can be detected in the liver and spleen of animals for several weeks after a single dose. This is the only drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of VL; the regimen is 3 mg/kg daily on days 1–5, 14, and 21 (total dose, 21 mg/kg). However, the total-dose requirement for different regions of the world varies widely. In Asia, it is 10–15 mg/kg; in Africa, ~18 mg/kg; and in Mediterranean/American regions, ≥20 mg/kg. The daily dose is flexible (1–10 mg/kg). In a study in India, a single dose of 10 mg/kg cured infection in 96% of patients. This single-dose regimen is the preferred treatment in India, Bangladesh, and Nepal. Adverse effects of LAmB are usually mild and include infusion reactions, backache, and occasional reversible nephrotoxicity.

PAROMOMYCIN

Paromomycin (aminosidine) is an aminocyclitol-aminoglycoside antibiotic with antileishmanial activity. Its mechanism of action against *Leishmania* has yet to be established. Paromomycin is approved in India for the treatment of VL at an IM dose of 11 mg of base/kg daily for 21 days; this regimen produces a cure rate of 94.6%. However, the optimal dose has not been established in other endemic regions. Paromomycin is a relatively safe drug, but some patients develop hepatotoxicity, reversible ototoxicity, and (in rare instances) nephrotoxicity and tetany. Paromomycin, in combination with Sb^V, is used in sub-Saharan Africa.

MILTEFOSINE

Miltefosine, an alkylphosphocholine, is the first oral compound approved for the treatment of leishmaniasis. This drug has a long half-life (150–200 h); its mechanism of action is not clearly understood. The recommended therapeutic regimens for patients on the Indian subcontinent are a daily dose of 50 mg for 28 days for

patients weighing <25 kg, a twice-daily dose of 50 mg for 28 days for patients weighing ≥25 kg, and 2.5 mg/kg for 28 days for children 2–11 years of age. These regimens have resulted in a cure rate of 94% in India. However, recent studies from the Indian subcontinent indicate a decline in the cure rate. Doses in other regions remain to be established. Because of its long half-life, miltefosine is prone to induce resistance in *Leishmania*. Its adverse effects include mild to moderate vomiting and diarrhea in 40 and 20% of patients, respectively; these reactions usually clear spontaneously after a few days. Rare cases of severe allergic dermatitis, hepatotoxicity, and nephrotoxicity have been reported. Because miltefosine is expensive and is associated with significant adverse events, it is best administered as directly observed therapy to ensure completion of treatment and to minimize the risk of resistance induction. Because miltefosine is teratogenic in rats, its use is contraindicated during pregnancy and (unless contraceptive measures are strictly adhered to for at least 3 months after treatment) in women of childbearing age.

MULTIDRUG THERAPY

Multidrug therapy for leishmaniasis is likely to be preferred in the future. Its potential advantages in VL include (1) better compliance and lower costs associated with shorter treatment courses and decreased hospitalization, (2) less toxicity due to lower drug doses and/or shorter duration of treatment, and (3) a reduced likelihood that resistance to either agent will develop. In a study from India, one dose of LAmB (5 mg/kg) followed by miltefosine for 7 days, paromomycin for 10 days, or both miltefosine and paromomycin simultaneously for 10 days (in their usual daily doses) produced a cure rate of >97% (all three combinations). In Africa, a combination of Sb^v and paromomycin given for 17 days was as effective and safe as Sb^v given for 30 days.

Prognosis of Treated Vl Patients Recovery from VL is quick. Within a week after the start of treatment, defervescence, regression of splenomegaly, weight gain, and recovery of hematologic parameters are evident. With effective treatment, no parasites are recovered from tissue aspirates at the post-treatment evaluation. Continued clinical improvement over 6–12 months is suggestive of cure. A small percentage of patients (with the exact figure depending on the regimen used) relapse but respond well to treatment with AmB deoxycholate or lipid formulations.

Vl in the Immunocompromised Host HIV/VL co-infection has been reported from 35 countries. Where both infections are endemic, VL behaves as an opportunistic infection in HIV-1-infected patients. HIV infection can increase the risk of VL development by several-fold in endemic areas. Co-infected patients usually show the classic signs of VL, but they may present with atypical features due to loss of immunity and involvement of unusual anatomic locations—e.g., infiltration of the skin, oral mucosa, gastrointestinal tract, lungs, and other organs. Serodiagnostic tests may be negative in up to 50% of patients. Parasites can be recovered from unusual sites such as bronchoalveolar lavage fluid and buffy coat. LAmB is the drug of choice for HIV/VL co-infection—both for primary treatment and for treatment of relapses. A total dose of 40 mg/kg, administered as 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38, is considered optimal and is approved by the FDA, but most patients experience a relapse within 1 year. Pentavalent antimonials and AmB deoxycholate can also be used where LAmB is not accessible. Reconstitution of patients' immunity by antiretroviral therapy has led to a dramatic decline in the incidence of co-infection in the Mediterranean basin. In contrast, HIV/VL co-infection is on the rise in African and Asian countries. Ethiopia is worst affected: up to 30% of VL patients are also infected with HIV. Because restoration of the CD4+ T cell count to >200/μL does decrease the frequency of relapse, antiretroviral therapy (in addition to antileishmanial therapy) is a cornerstone of the management of HIV/VL co-infection. Secondary prophylaxis with pentamidine or lipid AmB has been shown to delay relapses, but no regimen has been established as optimal.

TABLE 221-2 Clinical, Epidemiologic, and Therapeutic Features of Post–Kala-Azar Dermal Leishmaniasis: East Africa and the Indian Subcontinent

FEATURE	EAST AFRICA	INDIAN SUBCONTINENT
Most affected country	Sudan and South Sudan	Bangladesh
Incidence among patients with VL	~50%	~2–17%
Interval between VL and PKDL	During VL to 6 months	6 months to 3 years
Age distribution	Mainly children	Any age
History of prior VL	Yes	Not necessarily
Rashes of PKDL in presence of active VL	Yes	No
Treatment with sodium stibogluconate	2–3 months	2–4 months
Natural course	Spontaneous cure in majority of patients	Spontaneous cure in minority of patients

Abbreviations: PKDL, post–kala-azar dermal leishmaniasis; VL, visceral leishmaniasis.

Post–Kala-Azar Dermal Leishmaniasis On the Indian subcontinent and in Sudan and other East African countries, 2–50% of patients develop skin lesions concurrent with or after the cure of VL. Most common are hypopigmented macules, papules, and/or nodules or diffuse infiltration of the skin and sometimes of the oral mucosa. The African and Indian diseases differ in several respects; important features of post–kala-azar dermal leishmaniasis (PKDL) in these two regions are listed in Table 221-2, and disease in an Indian patient is depicted in Fig. 221-4.

In PKDL, parasites are scanty in hypopigmented macules but may be seen and cultured more easily from nodular lesions. Cellular infiltrates are heavier in nodules than in macules. Lymphocytes are the

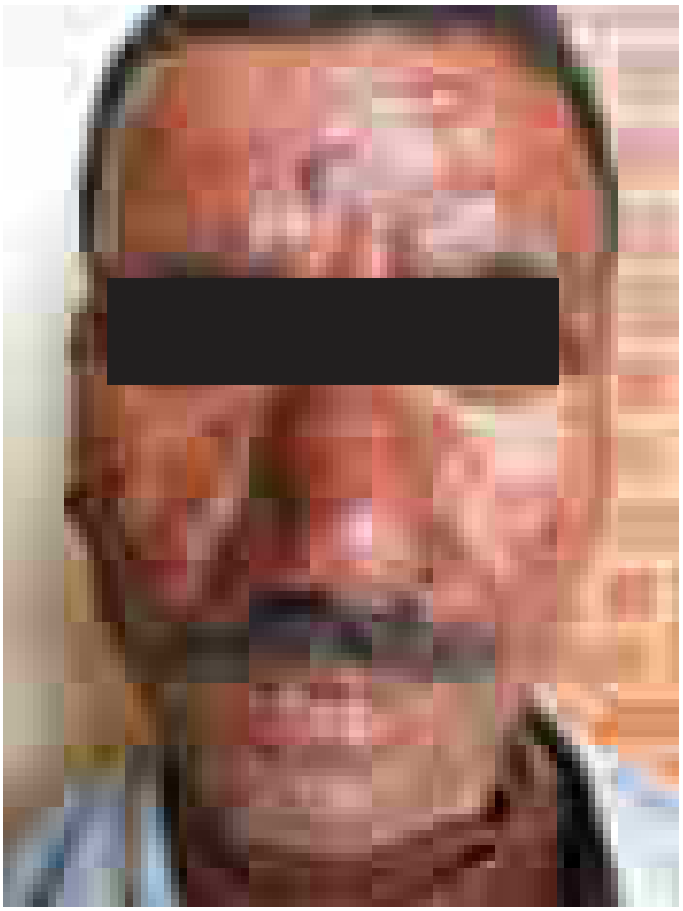

FIGURE 221-4 Post–kala-azar dermal leishmaniasis in an Indian patient. Note nodules of varying size involving the entire face. The face is erythematous, and the surface of some of the large nodules is discolored.

dominant cells; next most common are histiocytes and plasma cells. In about half of cases, epithelioid cells—scattered individually or forming compact granulomas—are seen. The diagnosis is based on history and clinical findings, but rK39 and other serologic tests are positive in most cases. Indian PKDL was treated with prolonged courses (up to 120 days) of pentavalent antimonials. This prolonged course frequently led to noncompliance. The alternative—several courses of AmB spread over several months—is expensive and unacceptable for most patients. Oral miltefosine for 12 weeks, in the usual daily doses, cures most patients with Indian PKDL. The efficacy of LAmB is being tested on the Indian subcontinent. In East Africa, a majority of patients experience spontaneous healing. In those with persistent lesions, the response to 60 days of treatment with a pentavalent antimonial is good.

CUTANEOUS LEISHMANIASIS

CL can be broadly divided into Old World and New World forms. Old World CL caused by *Leishmania tropica* is anthroponotic and is confined to urban or suburban areas throughout its range. Zoonotic CL is most commonly due to *Leishmania major*, which naturally parasitizes several species of desert rodents that act as reservoirs over wide areas of the Middle East, Africa, and central Asia. Local outbreaks of human disease are common. Major outbreaks currently affect Afghanistan, Syria, Iraq, Lebanon, and Turkey in association with refugees and population movement. CL is increasingly seen in tourists and military personnel on mission in CL-endemic regions of countries and as a co-infection in HIV-infected patients. *Leishmania aethiopica* is restricted to the highlands of Ethiopia, Kenya, and Uganda, where it is a natural parasite of hyraxes. New World CL is mainly zoonotic and is most often caused by *Leishmania mexicana, Leishmania (Viannia) panamensis*, and *Leishmania amazonensis*. A wide range of forest animals act as reservoirs, and human infections with these species are predominantly rural. As a result of extensive urbanization and deforestation, *Leishmania (Viannia) braziliensis* has adapted to peridomestic and urban animals, and CL due to this organism is increasingly becoming an urban disease. In the United States, a few cases of CL have been acquired indigenously in Texas.

Immunopathogenesis As in VL, the proinflammatory (T_H1) response in CL may result in either asymptomatic or subclinical infection. However, in some individuals, the immune response causes ulcerative skin lesions, the majority of which heal spontaneously, leaving a scar. Healing is usually followed by immunity to reinfection with that species of parasite.

Clinical Features A few days or weeks after the bite of a sandfly, a papule develops and grows into a nodule that ulcerates over weeks or months. The base of the ulcer, which is usually painless, consists of necrotic tissue and crusted serum, but secondary bacterial infection sometimes occurs. The margins of the ulcer are raised and indurated. Lesions may be single or multiple and vary in size from 0.5 to >3 cm **(Fig. 221-5)**. Lymphatic spread and lymph gland involvement may be palpable and may precede the appearance of the skin lesion. There may be satellite lesions, especially in *L. major* and *L. tropica* infections. The lesions usually heal spontaneously after 2–15 months. Lesions due to *L. major* and *L. mexicana* tend to heal rapidly, whereas those due to *L. tropica* and parasites of subspecies *Viannia* heal more slowly. In CL caused by *L. tropica*, new lesions—usually scaly, erythematous papules and nodules—develop in the center or periphery of a healed sore, a condition known as *leishmaniasis recidivans*. Lesions of *L. mexicana* and *Leishmania (Viannia) peruviana* closely resemble those seen in the Old World; however, lesions on the pinna of the ear are common, chronic, and destructive in the former infections. *L. mexicana* is responsible for chiclero's ulcer, the so-called self-healing sore of Mexico. CL lesions on exposed body parts (e.g., the face and hands), permanent scar formation, and social stigmatization may cause anxiety and depression and may affect the quality of life of CL patients.

Differential Diagnosis A typical history (an insect bite followed by the events leading to ulceration) in a resident of or a traveler to an endemic focus strongly suggests CL. Cutaneous tuberculosis, fungal infections, leprosy, sarcoidosis, and malignant ulcers are sometimes mistaken for CL.

FIGURE 221-5 Cutaneous leishmaniasis in a Bolivian child. There are multiple ulcers resulting from several sandfly bites. The edges of the ulcers are raised. *(Courtesy of P. Desjeux, Retired Medical Officer, World Health Organization, Geneva, Switzerland.)*

Laboratory Diagnosis Demonstration of amastigotes in material obtained from a lesion remains the diagnostic gold standard. Microscopic examination of slit skin smears, aspirates, or biopsies of the lesion is used for detection of parasites. Culture of smear or biopsy material may yield *Leishmania*. PCR is more sensitive than microscopy and culture and allows identification of *Leishmania* to the species level. This information is important in decisions about therapy because responses to treatment can vary with the species. Isoenzyme profiling is used to determine species for research purposes.

TREATMENT

Cutaneous Leishmaniasis

Although lesions heal spontaneously in the majority of cases, their spread or persistence indicates that treatment may be needed. One or a few small lesions due to "self-healing species" can be treated with topical agents. Systemic treatment is required for lesions over the face, hands, or joints; multiple lesions; large ulcers; lymphatic spread; New World CL with the potential for development of ML; and CL in HIV-co-infected patients.

A pentavalent antimonial is the first-line drug for all forms of CL and is used in a dose of 20 mg/kg for 20 days. The exceptions to this rule are CL caused by *Leishmania (Viannia) guyanensis*, for which pentamidine isethionate is the drug of choice (two injections of 4 mg of salt/kg separated by a 48-h interval), and CL due to *L. aethiopica*, which responds to paromomycin (16 mg/kg daily) but not to antimonials. Relapses usually respond to a second course of treatment. In Peru, topical imiquimod (5–7.5%) plus parenteral antimonials have been shown to cure CL more rapidly than antimonials alone. Azoles and triazoles have been used with mixed responses in both Old and New World CL, but have not been adequately assessed for this indication in clinical trials. In *L. major* infection, oral fluconazole (200 mg/d for 6 weeks) resulted in a higher rate of cure than placebo (79% vs 34%) and also cured infection faster. Adverse effects include gastrointestinal symptoms and hepatotoxicity. Ketoconazole (600 mg/d for 28 days) is 76–90% effective in CL due to *L. (V.) panamensis* and *L. mexicana* in Panama and Guatemala. Miltefosine has been used in CL in doses of 2.5 mg/kg for 28 days. This agent is effective against *L. major* infections. In Colombia, where CL is due to *L. (V.) panamensis*, miltefosine was also effective, with a cure rate of 91%. For *L. (V.) braziliensis* infections, however, the results with miltefosine are less consistent. In Brazil, miltefosine cured 71% of patients with *L. (V.) guyanensis* infection. Other drugs, such as dapsone, allopurinol,

rifampin, azithromycin, and pentoxifylline, have been used either alone or in combinations, but most of the relevant studies have had design limitations that preclude meaningful conclusions.

Small lesions (≤3 cm in diameter) may conveniently be treated weekly until cure with an intralesional injection of a pentavalent antimonial at a dose adequate to blanch the lesion (0.2–2.0 mL). An ointment containing 15% paromomycin sulfate, either alone or with 0.5% gentamicin or 12% methylbenzonium chloride, cured 70–82% of lesions due to *L. major* in 20 days and may be suitable for lesions caused by other species. Heat therapy with an FDA-approved radiofrequency generator and cryotherapy with liquid nitrogen have also been used successfully.

Diffuse Cutaneous Leishmaniasis (DCL) DCL is a rare form of leishmaniasis caused by *L. amazonensis* and *L. mexicana* in South and Central America and by *L. aethiopica* in Ethiopia and Kenya. DCL is characterized by the lack of a cell-mediated immune response to the parasite, the uncontrolled multiplication of which thus continues unabated. The DTH response does not develop, and lymphocytes do not respond to leishmanial antigens in vitro. DCL patients have a polarized immune response with high levels of immunosuppressive cytokines, including IL-10, transforming growth factor (TGF) β, and IL-4, and low concentrations of IFN-γ. Profound immunosuppression leads to widespread cutaneous disease. Lesions may initially be confined to the face or a limb but spread over months or years to other areas of the skin. They may be symmetrically or asymmetrically distributed and include papules, nodules, plaques, and areas of diffuse infiltration. These lesions do not ulcerate. The overlying skin is usually erythematous in pale-skinned patients. The lesions are teeming with parasites, which are therefore easy to recover. DCL does not heal spontaneously and is difficult to treat. If relapse and drug resistance are to be prevented, treatment should be continued for some time after lesions have healed and parasites can no longer be isolated. In the New World, repeated 20-day courses of pentavalent antimonials are given, with an intervening drug-free period of 10 days. Miltefosine has been used for several months with a good initial response. Combinations should be tried. In Ethiopia, a combination of paromomycin (14 mg/kg per day) and sodium stibogluconate (10 mg/kg per day) is effective.

MUCOSAL LEISHMANIASIS

The subgenus *Viannia* is widespread from the Amazon basin to Paraguay and Costa Rica and is responsible for deep sores and for ML (Table 221-1). In *L. (V.) braziliensis* infections, cutaneous lesions may be simultaneously accompanied by mucosal spread of the disease or followed by spread years later. ML is typically caused by *L. (V.) braziliensis* and rarely by *L. amazonensis*, *L. (V.) guyanensis*, and *L. (V.) panamensis*. Young men with chronic lesions of CL are at particular risk. Overall, ~3% of infected persons develop ML. Not every patient with ML has a history of prior CL. ML is almost entirely confined to the Americas. In rare cases, ML may also be caused by Old World species like *L. major, L. infantum* (*L. chagasi*), or *L. donovani*.

Immunopathogenesis and Clinical Features The immune response is polarized toward a T_H1 response, with marked increases of IFN-γ and TNF-α and varying levels of T_H2 cytokines (IL-10 and TGF-β). Patients have a stronger DTH response with ML than with CL, and their peripheral-blood mononuclear cells respond strongly to leishmanial antigens. The parasite spreads via the lymphatics or the bloodstream to mucosal tissues of the upper respiratory tract. Intense inflammation leads to destruction, and severe disability ensues. Lesions in or around the nose or mouth (espundia; Fig. 221-6) are the typical presentation of ML. Patients usually provide a history of self-healed CL preceding ML by 1–5 years. Typically, ML presents as nasal stuffiness and bleeding followed by destruction of nasal cartilage, perforation of the nasal septum, and collapse of the nasal bridge. Subsequent involvement of the pharynx and larynx leads to difficulty in swallowing and phonation. The lips, cheeks, and soft palate may also be affected. Secondary bacterial infection is common, and aspiration pneumonia may be fatal. Despite the high degree of T_H1 immunity and the strong DTH response, ML does not heal spontaneously.

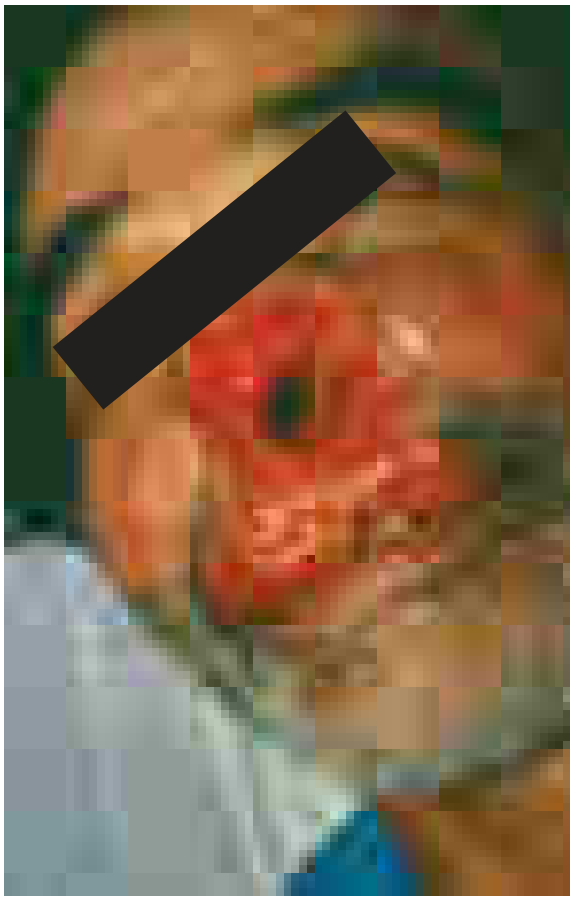

FIGURE 221-6 Mucosal leishmaniasis in a Brazilian patient. There is extensive inflammation around the nose and mouth, destruction of the nasal mucosa, ulceration of the upper lip and nose, and destruction of the nasal septum. *(Courtesy of R. Dietz, Universidade Federal do Espírito Santo, Vitória, Brazil.)*

Laboratory Diagnosis Tissue biopsy is essential for identification of parasites, but the rate of detection is poor unless PCR techniques are used. The strongly positive DTH response fails to distinguish between past and present infection.

TREATMENT

Mucosal Leishmaniasis

The regimen of choice is a pentavalent antimonial agent administered at a dose of 20 mg of Sb^V/kg for 30 days. Patients with ML require long-term follow-up with repeated oropharyngeal and nasal examination. With failure of therapy or relapse, patients may receive another course of an antimonial but then become unresponsive, presumably because of resistance in the parasite. In this situation, AmB should be used. An AmB deoxycholate dose totaling 25–45 mg/kg is appropriate. There are no controlled trials of LAmB, but administration of 2–3 mg/kg for 20 days is considered adequate. Miltefosine (2.5 mg/kg for 28 days) cured 71% of ML patients in Bolivia. The more extensive the disease, the worse the prognosis; thus prompt, effective treatment and regular follow-up are essential.

PREVENTION OF LEISHMANIASIS

No vaccine is available for any form of leishmaniasis. Inoculation with live *L. major* ("leishmanization") is practiced in Iran; 80% of recipients were protected, according to one report. Anthroponotic leishmaniasis is controlled by case finding, treatment, and vector control with insecticide-impregnated bed nets and curtains and residual insecticide spraying. Control of zoonotic leishmaniasis is more difficult. Use of

insecticide-impregnated collars for dogs, treatment of infected domestic dogs, and culling of street dogs are measures that have been used with uncertain efficacy to prevent transmission of *L. infantum*. In Brazil, a canine vaccine has been found to promote a decrease in the human and canine incidence of zoonotic VL. Two vaccines, Leishmune® and Leish-Tec®, are licensed in Brazil; Leishmune provides significant protection to vaccinated dogs. CaniLeish® is the first licensed canine vaccine developed in Europe. Personal prophylaxis with bed nets and repellants may reduce the risk of CL infections in the New World.

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222 Chagas Disease and African Trypanosomiasis

François Chappuis, Yves Jackson

Myriads of protozoan parasites of the genus *Trypanosoma* infect plants and animals worldwide. Among these, three are of clinical significance for humans: *T. cruzi* causes Chagas disease, and *T. brucei gambiense* and *T. brucei rhodesiense* cause human African trypanosomiasis (HAT), which is also known as "sleeping sickness." Despite obvious differences in their geographic distribution, parasitic life cycle, clinical presentation, treatment, and outcome, these vector-borne diseases are archetypal examples of neglected tropical diseases. More broadly, these infectious diseases affect neglected populations of the lowest socioeconomic class who have limited access to care and who live either in remote rural areas of low- or middle-income tropical/subtropical countries or in urban areas of both endemic and nonendemic countries. The drugs to treat these conditions are several decades old, their availability is fragile, and their efficacy and/or safety is suboptimal.

Other trypanosome species (e.g., *T. congolense* and *T. evansi*) predominantly cause nonhuman zoonoses and only occasionally cause illness in humans.

CHAGAS DISEASE (AMERICAN TRYPANOSOMIASIS)

DEFINITION

First described in 1909 by Carlos Chagas, Chagas disease (American trypanosomiasis) is a zoonosis caused by the flagellated protozoan *T. cruzi*. After a frequently asymptomatic acute phase, 30–40% of patients develop life-threatening chronic cardiomyopathy and/or digestive-tract dysfunction over the course of decades. Acute reactivation may occur in immunocompromised patients. Chagas disease imposes an important human and social burden in Latin America and has recently spread outside its natural boundaries to become a global public health problem. A vast majority of affected individuals are unaware of being infected and do not have access to appropriate clinical management and counseling.

TRANSMISSION

Vectorial Transmission *T. cruzi* infection is primarily a zoonosis transmitted to a range of wild and domestic mammals by blood-sucking triatomine bugs. Sylvatic, peridomiciliary, and intradomiciliary vectorial cycles sometimes overlap. Over a large geographic area in the Americas (from northern Argentina to the southern United States), most human infections are intradomiciliary, arising from a triatomine bite during nighttime sleep. Feces released by triatomines during a blood meal contain the infective metacyclic form of *T. cruzi* that enters the human body through cutaneous breaks, mucosae, or conjunctivae. Despite recent laboratory research showing the potential for transmission by bedbugs, there is no evidence that bedbugs actually transmit *T. cruzi* to humans.

Nonvectorial Transmission Other modes of transmission can cause infection in both endemic and nonendemic regions. *T. cruzi* can be transmitted congenitally from mother to newborn, by transfusion of blood products, by tissue or organ transplantation, or by ingestion of contaminated food or drink. Congenital infection occurs in 1–10% of newborns of infected mothers. The risk of infection from contaminated blood products is low (1.7% overall, 13% for platelet recipients, and close to 0 for recipients of red blood cells and plasma). Transmission by infected organ and tissue transplants mostly affects heart, liver, and kidney recipients. Oral transmission is increasingly reported after ingestion of contaminated food (berries) or drinks (fruit or sugar cane juice) and occasionally causes outbreaks.

EPIDEMIOLOGY

An estimated 5.7 million people are infected by *T. cruzi*, including >1 million individuals with chronic cardiomyopathy. However, the true global burden of Chagas disease is in fact uncertain. The highest numbers of infected individuals reside in Argentina, Brazil, and Mexico; the prevalence is highest in Bolivia (6.1%), Argentina (3.6%), and Paraguay (2.1%). In highly endemic regions of these countries, the prevalence may exceed 40%. Formerly restricted to poor rural populations, the distribution of cases—and, to some extent, *T. cruzi* transmission—has progressively extended to cities in the context of rapid urbanization and rural migration. A recent history of migration from a rural area is the main risk factor in urban settings.

Overall, the prevalence and incidence of Chagas disease have sharply declined in recent decades because of improved housing and socioeconomic conditions as well as public health interventions, including regional vector-control initiatives, implementation of systematic screening of blood products, and improved detection of congenital transmission. Several countries have been declared free of domiciliary transmission as a result of sustained residual insecticide-spraying campaigns. This progress is threatened by adaptation of the vector to the periurban environment, its resurgence in areas where spraying has been discontinued, the development of resistance to pyrethroid insecticides, and the persistence of peridomiciliary transmission. A growing number of localized outbreaks are being reported in previously stable areas, with the Amazon basin particularly at risk.

Chagas disease distribution has recently expanded to nonendemic countries in the context of increased global travel, with cases reported more frequently in North America, Western Europe, Australia, and Japan. The United States harbors up to 300,000 cases, mostly among immigrants from Central America. In addition, sporadic vector-borne infections occur in the southern states. Western Europe has 68,000–123,000 cases, and Japan and Australia report a few thousand cases. Despite the implementation of blood bank screening and of some dedicated medical programs, only a small proportion of cases have been identified and properly managed to date. A low level of awareness among health care professionals and difficulties experienced by some groups in accessing care appear to be major drivers. At-risk migrant communities are frequently subject to factors that render them socially, legally, or economically vulnerable. Moreover, the cultural perception of Chagas as a disease embedded in poverty can create a social stigma that complicates its management at the community level. In contrast to immigrants, international tourists visiting endemic countries are at very low risk of being infected, whether by reduviid bug bites or by other routes, and reports of Chagas disease in travelers are rare.

PATHOLOGY

Several *T. cruzi* strains have been identified. These strains have partially overlapping transmission cycles and geographic distributions, but no definitive evidence supports an association of certain strains with specific clinical manifestations or with variation in disease severity. The rarity of digestive tract involvement north of the Amazon basin suggests that specific parasitic and host genetic factors may influence the disease course. The pathogenesis of Chagas disease results from the complex interactions between the pathogen and the host immune response. Many questions about the relative importance of these interactions, including the role of autoimmune mechanisms, remain unanswered. After local penetration of trypomastigotes, parasites rapidly enter the bloodstream and disseminate through the body, infecting a wide range of nucleated cells in which they differentiate into amastigotes (Fig. 222-1). The innate immune response triggered by parasite mucins and DNA leads to a predominantly T-helper 1 response. The production of various proinflammatory cytokines and the activation of $CD8^+$ T lymphocytes reduce parasitemia to a subpatent level within 4–8 weeks, a point marking the end of the acute phase.

Immune evasion mechanisms allow persistent low-intensity proliferation of amastigotes and their release into the bloodstream, with subsequent infection of potentially all types of nucleated cells—notably cardiac, skeletal, and smooth-muscle cells. Mechanisms that have been postulated to determine the pathogenic evolution toward cardiomyopathy include the parasites' persistence and the host's inability to downregulate the initial immune response, resulting in cell-mediated damage and an imbalance of T-helper 1 and 2 responses with excessive production of proinflammatory cytokines. Secondary mechanisms, such as microcirculation abnormalities and dysautonomia, may also influence the progression of tissue damage.

In the myocardium, chronic inflammation results in cellular destruction and the development of fibrosis leading to a segmental loss of contractility and dilatation of the chambers, with the associated risk of left-ventricle apical aneurism. Focal hypoperfusion and tissue damage are sources of ventricular arrhythmias, while scarring lesions mostly affect the conduction system. Autonomic cell destruction leads to vagal and sympathetic denervation whose exact clinical significance remains to be clarified.

T. cruzi appears to have a direct toxic effect on digestive-tract intramural autonomic ganglion cells. Over time, the loss of neural cells affects muscular tone, leading to motility disorders and ultimately to organ dilatation (megaviscera syndrome). The esophagus and colon are primarily affected, but lesions may occur along the whole digestive tract. Inadequate relaxation of the lower esophageal sphincter causes symptoms of achalasia, whereas damage to the colon ultimately mimics Hirschsprung disease, with severe constipation and the risk of volvulus and toxic dilatation.

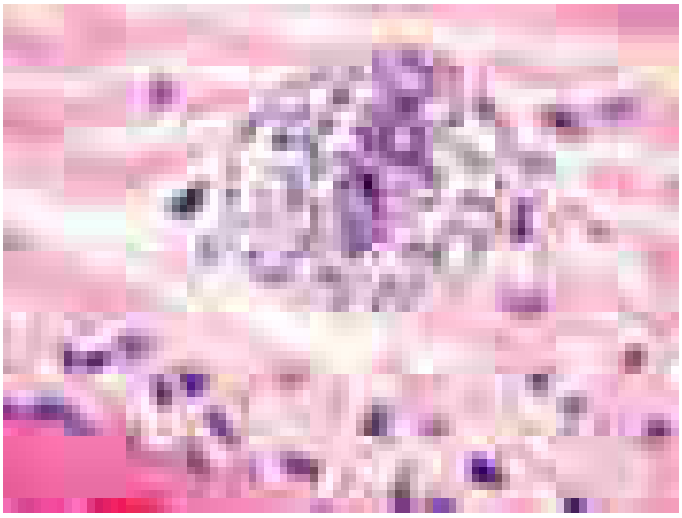

FIGURE 222-1 A cluster of *Trypanosoma cruzi* amastigotes with an inflammatory infiltrate in the placenta of a congenitally infected newborn infant.

Factors reducing the cellular immune response, such as HIV infection, posttransplantation immunosuppressive therapies, or hematologic malignancies, may increase intracellular replication of amastigotes, with increased parasitemia (reactivation). Lesions develop predominantly in the central nervous system (CNS), the heart, and the skin. Among HIV patients, the risk of reactivation is ~20% in the absence of antiretroviral therapies and occurs when the $CD4^+$ T cell count falls <100/μL. Clinically manifest *T. cruzi* reactivation is an AIDS-defining opportunistic infection.

CLINICAL MANIFESTATIONS

The clinical manifestations of *T. cruzi* infection vary greatly among individuals. The infection course is divided into two phases that are associated with different clinical features, duration, and prognosis (Table 222-1). The acute phase remains undetected and undiagnosed in most individuals. While 5–10% of these early infections spontaneously resolve without treatment, *T. cruzi* persists for life in the vast majority of individuals (the chronic phase); 60–70% of these individuals never develop apparent tissue damage (the indeterminate form), but the remaining 30–40% progress toward detectable organ damage of variable severity over decades (the determinate form). These chronic complications include cardiac (20–30%), digestive (5–20%), or mixed (5–10%) disorders. There is no predictor of evolution toward clinical manifestations during the chronic phase. In patients with cardiomyopathy, bundle branch blocks are usually the first signs and may cause no symptoms for years until more severe conduction-system disease, arrhythmias, and left ventricular dysfunction occur. Advanced cardiac damage entails a worse prognosis than other cardiomyopathies—notably, ischemic heart disease.

APPROACH TO THE PATIENT

Chagas Disease (American Trypanosomiasis)

More than 90% of infections go undiagnosed, and cases are frequently identified at a late stage once chronic complications develop. The vast majority of *T. cruzi*–infected individuals are asymptomatic (i.e., in the indeterminate form of the chronic phase). An awareness of potential Chagas disease is important for general practitioners as well as for physicians from various specialties, including gastroenterologists, cardiologists, neurologists, obstetricians, pediatricians, and infectious disease specialists. Outside endemic areas, screening for Chagas disease should be proposed when any Latin American individual has evocative symptoms and signs, including abnormalities on electrocardiography (ECG) or increased risk of (1) *T. cruzi* infection (Chagas disease in the mother or other family members; origins in a highly endemic country or area; history of unscreened blood transfusion in Latin America); (2) transmission to others (e.g., via pregnancy or blood or organ donation); or (3) reactivation (current or pending immunosuppression). Screening of the relatives of an index case will probably identify additional cases.

DIAGNOSIS AND STAGING

Diagnostic Confirmation Diagnostic strategies depend on the clinical phase (Table 222-2). Detection of circulating parasites by microscopy of the blood with concentration (e.g., by the Strout method, microhematocrit) or by nucleic acid–based assay (polymerase chain reaction [PCR]) is the best diagnostic approach when the parasitemia level is high—i.e., during the acute phases, including reactivation. Once parasitemia becomes undetectable by microscopy (a point marking the end of the acute phase), diagnosis relies on immunologic tests that detect anti–*T. cruzi* IgG. The most common techniques include a conventional or recombinant enzyme-linked immunosorbent assay (ELISA) and immunofluorescence assays. Two positive serologic tests using different techniques and targeting different antigens confirm the diagnosis of Chagas disease during the chronic phase. In the presence of discordant serologic results, a third serologic test is warranted. Some of the immunochromatographic rapid diagnostic tests on the market have sufficient

TABLE 222-1 Characteristics of the Stages of *Trypanosoma cruzi* Infection

PHASE OR SETTING	CONTEXT	ONSET OF FIRST SYMPTOMS	CLINICAL MANIFESTATIONS	DURATION	PROGNOSIS
Acute (congenital)	~5% risk of maternal transmission to newborn	At birth or weeks after delivery	>90% asymptomatic; rare lymphadenopathy, hepatosplenomegaly, jaundice, respiratory distress, growth retardation	2–8 weeks	Favorable when infant is born alive; unknown rate of in utero or neonatal death
Acute	Vector-borne transmission; oral transmission (ingestion of contaminated food/drinks); blood product transfusion; tissue/organ transplantation	1–2 weeks after vectorial transmission; may be sooner (days) after oral transmission or later (months) after transfusion/transplantation	>90% asymptomatic or mild febrile illness; local swelling at inoculation site (eyelid [Romaña sign] or skin [chagoma]); polyadenopathy; splenomegaly; myocarditis, hepatitis, and encephalitis more frequent with oral transmission	4–8 weeks	Mortality: 0.1–5% with oral transmission or myocarditis/encephalitis
Chronic (indeterminate form)	Balanced immune response after acute phase subsides	No symptoms	Normal clinical examination and ECG result	Lifelong or until determinate phase	No attributable mortality
Chronic (determinate form)	Predominant inflammatory response (in cardiomyopathy only)	Years to decades after initial infection	Dyspnea, chest pain, palpitation, syncope, sudden death, stroke, dysphagia, regurgitation, constipation, fecaloma, volvulus, peripheral neuropathy	Chronic	5-year mortality: 2–63%, depending on extent of cardiac damage; most important causes of death: cardiac failure and sudden death, followed by stroke
Acute (reactivation)	Severe immunosuppression	Variable	Myocarditis, erythema nodosum, panniculitis, *Toxoplasma*-like focal brain lesion, meningoencephalitis	Variable	Mortality depends on rapidity of diagnosis and treatment and on underlying conditions

Abbreviation: ECG, electrocardiography.

sensitivity and specificity to be used as first-line screening tests where laboratory facilities are not easily accessible. If the rapid diagnostic test result is positive, at least one conventional serologic assay is necessary to confirm infection.

Diagnosis of congenital infection relies on examination of cord and/or peripheral blood by microscopy or PCR during the first days or weeks of life. A test conducted after 4 weeks of age is most accurate: PCR earlier in life may be falsely positive, likely because of the passage of *T. cruzi* DNA fragments from the mother to the child. If results are negative, serologic tests should be performed at 9 months of age, once maternal antibodies have been cleared. During the chronic phase, the limited sensitivity (50–80%) of PCR restricts its usefulness for primary diagnosis; however, PCR can document therapeutic failure if it yields positive results after the completion of treatment. In the United States, the Centers for Disease Control and Prevention (CDC) provides reference laboratory testing (see contact information in the treatment section).

Disease Staging Once *T. cruzi* infection is confirmed, clinicians should assess the presence of complications and concomitant factors that may influence the course of the disease. The initial evaluation includes a thorough cardiac, neurologic, and digestive history and a clinical examination. Twelve-lead ECG with a 30-s strip is a good screening test for Chagas-associated cardiomyopathy. The most frequently found abnormalities are right bundle branch block, left anterior fascicular block, ventricular premature beats, repolarization disorders, Q waves, and low QRS voltage **Fig. 222-2**). An abnormal ECG result or the presence of suggestive cardiac symptoms warrants further investigation. Echocardiography and the 24-h Holter test are the preferred methods for assessment of chamber dilatation, apical aneurysm, ventricular dysfunction, and arrhythmias. Depending on the findings, the workup can be supplemented by MRI or electrophysiologic studies. Gastroenterologic investigations are performed in patients with suggestive symptoms, such as dysphagia and severe constipation. Barium esophagraphy and enema are first-line diagnostic procedures, which can be supplemented by esophageal manometry. Megacolon is diagnosed when the sigmoid or descending colon diameter is ≥6.5 cm.

Comorbidities, including other cardiovascular risk factors, immunosuppressive conditions, and other chronic infections (e.g., with *Strongyloides stercoralis* or HIV) should be investigated.

TREATMENT

Chagas Disease (American Trypanosomiasis)

ETIOLOGIC TREATMENT

Only two drugs, benznidazole and nifurtimox **(Table 222-3)**, have shown efficacy against *T. cruzi* infection when administered for ≥30 days. While these drugs have been used since the early 1970s, many questions remain about their mode of action and efficacy at the different stages of infection. The treatment goal depends on the clinical stage; the overall objectives are to cure patients who have recent infection or reactivation, to reduce morbidity, and to prevent transmission at later stages. Treatment is most effective during the acute (including congenital) phase and the early chronic phase (i.e.,

TABLE 222-2 Diagnostic Procedures of Choice for Clinical Stages of *T. cruzi* Infection

STAGE	TECHNIQUE OF CHOICE	SAMPLE	DIAGNOSTIC CRITERIA
Acute	Microscopy after concentration, PCR	Peripheral blood, cerebrospinal or other body fluids	Positivity in one test
Acute (early congenital during first 9 months of life)	Microscopy after concentration, PCR	Cord or peripheral blood	Positivity in one test
Chronic (indeterminate and determinate forms)	Serology	Peripheral blood	Positivity in two tests with different techniques and antigens
Reactivation	Microscopy after concentration, PCR	Peripheral blood, cerebrospinal or other body fluids	Positivity with evidence of increasing parasitemia on serial samples or extremely high parasite load

Abbreviation: PCR, polymerase chain reaction.

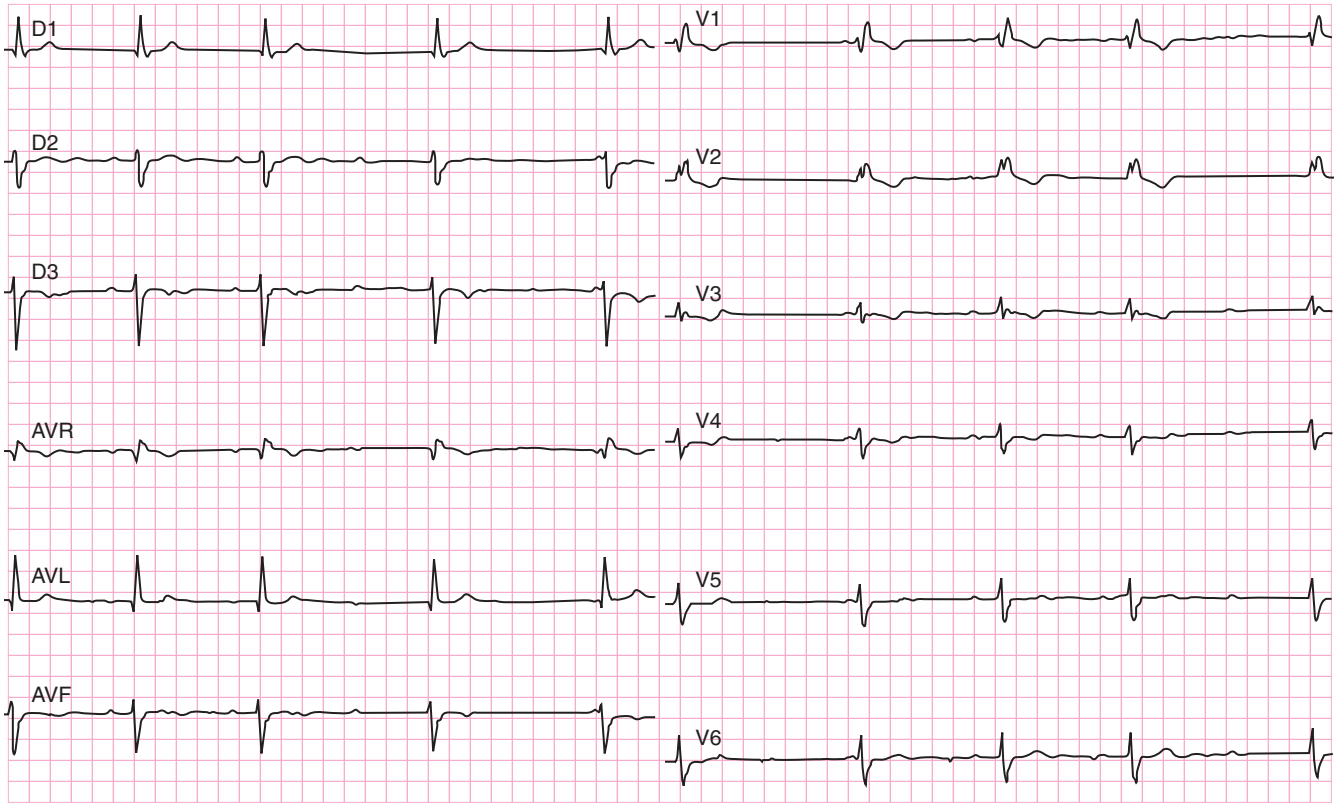

FIGURE 222-2 Electrocardiogram of a 43-year-old patient shows bradycardia with alternating second- and third-degree atrioventricular (type 1), left anterior fascicular, and right bundle branch blocks.

in patients <18 years of age), with a 60–100% cure rate. The efficacy of treatment during the indeterminate form of the chronic phase in patients >18 years old is not known; however, treatment may protect against the development of cardiac damage later in life and sharply reduces the risk of vertical transmission when given before conception. In adults with chronic cardiomyopathy, benznidazole has no impact on disease progression and mortality risk. Neither benznidazole nor nifurtimox is effective against digestive complications. Treatment is contraindicated during pregnancy and in advanced renal or hepatic failure. Preferred regimens and drug tolerance vary with age. Adverse events are more frequent among adults, who are therefore at increased risk of premature treatment discontinuation (Table 222-3). As benznidazole seems better tolerated than nifurtimox in adults, it is the recommended first-line drug in this age range. Close (e.g., weekly) clinical and biological monitoring is necessary during treatment. While treatment is usually prescribed for 60 days, the optimal duration remains a matter of debate, with a growing interest in shorter courses.

Treatment should be undertaken for all children, women of child-bearing age, patients in the acute phase, and patients with reactivation. Given the uncertainties about the impact of treatment, the decision to treat patients >18 years old who have the indeterminate form of the chronic phase should be made on an individual basis after discussing the pros and cons with the patient. A negative pregnancy test is mandatory before initiating treatment as the recommended drugs have not been proven to be safe in pregnancy. The efficacy of second-line treatment (e.g., nifurtimox after failure with benznidazole) has not been evaluated to date.

The limited efficacy of current regimens and the understanding that living parasites are a driver of immunopathologic processes have fueled interest in novel therapeutic approaches. These include the addition of immunomodulatory interventions to antiparasitic treatment and the use of combinations of antiparasitic drugs. Drugs can be obtained through the CDC (Parasitic Diseases Public Inquiries line [404-718-4745] or parasites@cdc.gov), the CDC Drug Service (404-639-3670), or the CDC Emergency Operations Center (770-488-7100). In 2017, benznidazole was approved by the U.S. Food and Drug Administration for treatment of children 2–12 years of age.

NONETIOLOGIC TREATMENT

The management of Chagas cardiomyopathy generally follows the management guidelines for heart failure, conduction disturbances,

TABLE 222-3 Chagas Treatment Regimens and Adverse Reactions to Benznidazole and Nifurtimox

DRUG	REGIMEN	DURATION	ADVERSE EVENTS IN ADULTS (FREQUENCY)	PREMATURE DISCONTINUATION (RATE)
Benznidazole	Age <12 years: 5–7.5 mg/kg per day in 2 doses Age >12 years: 5 mg/kg per day in 2 doses	30–60 days	Allergic dermatitis (29–50%), anorexia and weight loss (5–40%), paresthesia (0–30%), peripheral neuropathy (0–30%), nausea and vomiting (0–5%), leukopenia and thrombocytopenia (<1%)	7–20%
Nifurtimox	Age <10 years: 15–20 mg/kg per day in 3 or 4 doses Age 11–16 years: 12.5–15 mg/kg per day in 3 or 4 doses Age >16 years: 15 mg/kg per day in 3 or 4 doses	60–90 days	Anorexia and weight loss (50–81%), nausea and vomiting (15–50%), abdominal discomfort (12–40%), headaches (13–70%), dizziness and vertigo (12–33%), anxiety and depression (10–49%), insomnia (10–54%), myalgia (13–30%), peripheral neuropathy (2–5%), memory loss (6–14%), leukopenia (<1%)	6–44%

Source: C Bern: N Engl J Med 373:456, 2015.

or ventricular arrhythmia of other etiologies. Given the high risk of sudden death, early initiation of treatment with amiodarone or implantation of a cardioverter defibrillator should be considered in the presence of pathologic electrophysiologic abnormalities. Anticoagulation is recommended for primary and secondary prevention of cardioembolic events in the presence of an intramural thrombus or apical aneurysm. Strict control of other cardiovascular risk factors is warranted. Chagas cardiomyopathy is a prominent indication for heart transplantation in Latin America; some evidence indicates that the results are better than in cardiomyopathy of other etiologies. Posttransplantation immunosuppression requires close monitoring, given the high risk of reactivation.

Treatment of digestive dysmotility includes dietary counseling and meals rich in fiber and hydration, with smaller portions eaten more frequently. Drugs releasing the lower esophageal sphincter (e.g., nifedipine or isosorbide dinitrate before meals), pneumatic balloon dilatation, or laparoscopic myotomy improves upper gastrointestinal symptoms in the early stage. Use of botulinum toxin is effective but requires repeated injections. Laxatives and enemas alleviate chronic constipation in most patients. Surgery is indicated in patients with distressing symptoms that are refractory to medical treatment.

CLINICAL FOLLOW-UP

Defining the optimal cure after treatment remains very challenging and is a crucial topic of research. While the search for biomarkers (including through proteomics) to identify early indicators of treatment response holds some promise, serologic follow-up remains the cornerstone of posttreatment monitoring in the acute phase. In the chronic phase, there is no assay of proven value for documentation of response. The time needed for negative seroconversion after treatment indeed depends on the duration of infection. The interval is short (usually months) when infection is treated during the acute (including congenital) phase. In contrast, decades are required in adults infected during childhood. A positive result in a posttreatment PCR indicates treatment failure, but a negative result cannot be interpreted because of the low sensitivity of PCR during the chronic phase. The status of patients with negative PCR results but persistent positive serology is therefore uncertain, but these patients should be considered potentially infective as long as serologic tests continue to yield positive results. All patients, treated or not, should be regularly monitored. The basic yearly assessment includes history-taking for detection of new symptoms, clinical examination, and 12-lead ECG.

PREVENTION

In the absence of a vaccine, preventive measures—primary (prevention of *T. cruzi* transmission), secondary (avoidance of complications), and tertiary (reduction of morbidity and mortality)—are necessary. Screening of blood donations is being progressively implemented in endemic areas and in countries to which high-risk groups are immigrating, and screening should be extended to organ donation. When sustained over prolonged periods, vector control is an effective and cost-effective strategy to curb intradomiciliary transmission. Insecticide-impregnated bed nets (as used for malaria) provide individual protection against reduviid bug bites. Screening of child-bearing-age and pregnant Latin American migrant women has been highly cost-effective in Spain, although the cost per case detected varies with the prevalence of infection in the targeted population. Early identification of cases through passive and active screening of the population at risk, along with provision of treatment, may reduce the risk of complications and secondary transmission, particularly congenital transmission. Finally, identification and treatment of cardiac complications and prevention of cardioembolic events at an early stage positively influence the disease course.

GLOBAL CONSIDERATIONS

With its geographic expansion, Chagas disease has become a global health issue, predominantly affecting vulnerable people on four continents. Yet, as with other neglected tropical diseases, progress against Chagas is limited by a lack of research and development and a lack of financial and political commitment. For example, the production and registration of existing drugs, and access to them, are still problematic in many countries, including the United States. Research on and development of new drugs are compounded by the lack of financial incentives. The future of Chagas disease is likely to be influenced by global phenomena. Climatic changes, population aging, increasing prevalences of noncommunicable comorbidities (e.g., diabetes, hypertension) in low- and middle-income countries, and increasing use of immunosuppressive drugs are likely to impact the epidemiology, clinical course, and burden of Chagas disease. To tackle these challenges, clinical, public health, and policy interventions need to be scaled up and improved in areas of high or hidden prevalence (e.g., in the Chaco Region of Argentina, Bolivia, and Paraguay and in Mexico, Western Europe, and the United States, respectively).

HUMAN AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS)

DEFINITION

HAT is a life-threatening illness caused by infection with extracellular protozoan parasites that are transmitted by tsetse flies in sub-Saharan Africa. *T. b. gambiense* and *T. b. rhodesiense* are the two pathogenic subspecies affecting humans; their epidemiologic and clinical features largely differ.

EPIDEMIOLOGY

The geographic range of HAT is restricted to sub-Saharan Africa in line with the distribution of its vector, the tsetse fly (*Glossina* species; **Fig. 222-3**). HAT due to *T. b. gambiense* is endemic in 24 countries of western and central Africa. Between 1999 and 2015, the number of reported cases fell by 90% (from 27,862 to 2733) as a result of successful control measures based on systematic screening of populations at risk, diagnostic confirmation, and treatment of infected individuals. During the same period, the number of reported cases of HAT due to *T. b. rhodesiense* fell by 89% (from 619 to 71) in the 13 disease-endemic countries of eastern and southeastern Africa. However, the ratio of reported to unreported cases remains uncertain for disease caused by both species. In 2015, most cases of *T. b. gambiense* HAT were reported by the Democratic Republic of the Congo (DRC; 86%), whereas Malawi and Uganda reported most of the cases caused by *T. b. rhodesiense* (42 and 39%, respectively). The geographic distributions of *T. b. gambiense* and *T. b. rhodesiense* do not overlap, but the two species are present in distinct regions of Uganda and the DRC. A roadmap for HAT elimination as a public health problem is being mapped out by the World Health Organization; the objective is to decrease the frequency of new cases to <1 per 10,000 people in endemic areas by 2020.

Humans are the predominant or exclusive reservoir of *T. b. gambiense*. Rare cases of vertical (in utero) or transfusional transmission have been reported, but almost all patients are infected by the bite of tsetse flies during their daily activities along or near rivers, where the flies live and reproduce. In contrast, *T. b. rhodesiense* causes zoonosis in a variety of wild and domesticated animals (e.g., antelopes and cattle, respectively), which act as reservoirs. Humans are infected by *T. b. rhodesiense* via tsetse bites in woodland savannah. Honey gatherers, game park rangers, poachers, and firewood collectors are particularly at risk. Imported cases of HAT are occasionally diagnosed among African immigrants and other travelers. While long-term travelers (>30 days) are at increased risk of *T. b. gambiense* HAT, most imported cases of *T. b. rhodesiense* HAT are seen in short-term travelers, typically following visits to game parks.

PATHOLOGY AND PATHOGENESIS

T. b. rhodesiense and *T. b. gambiense*, unlike other trypanosome species, can infect humans because they resist lytic factors in human serum—namely, apolipoprotein L-1. The serum resistance–associated protein is responsible for resistance in *T. b. rhodesiense*, whereas other

FIGURE 222-3 Areas at risk for human African trypanosomiasis, 2010–2014. *(Courtesy of Jose Ramon Franco, MD.)*

mechanisms, notably involving the *T. b. gambiense*–specific glycoprotein (TgsGP) gene, are used by *T. b. gambiense*.

Trypanosomes are transmitted to humans by the tsetse bite, proliferate, and induce a local inflammatory reaction that is sometimes clinically apparent as a chancre. Trypanosomes then disseminate into the hematolymphatic system, with lymph nodes becoming enlarged after infiltration by mononuclear cells and lymphocytes. The degree of enlargement of the liver and spleen is usually mild to moderate, with infiltration by mononuclear cells as a prominent feature. Trypanosomes multiply in the blood, but their presence and density vary. This variation is mainly due to a cyclic immune-evasion process, whereby the parasite population can be decimated by the host's immune response until the reemergence of offspring parasites that express a different variant surface glycoprotein to which the immune system is temporarily blind. Each trypanosome genome encodes a repertoire of ~1000 variant surface glycoproteins between which the parasites can switch genetically. Trypanosomes also multiply in extravascular tissues during the first stage of illness. The skin, skeletal muscles, serous membranes (peritoneum, pleurae, and pericardium), and heart can be involved, with interstitial infiltration of mononuclear cells and vasculitis evident on microscopic examination. Myocarditis and pericarditis with myocardial degeneration and interstitial hemorrhage are common features of *T. b. rhodesiense* infection.

The CNS is invaded weeks to months (*T. b. rhodesiense*) or months to years (*T. b. gambiense*) after initial infection. This invasion corresponds to the second stage of HAT, which is defined by the presence of trypanosomes or mononuclear cells in the cerebrospinal fluid (CSF). The white matter is predominantly affected, with perivascular proliferation of astrocytes, microglial cells, and Mott's (morular) cells that contain IgM in intracellular vacuoles. The location of white-matter lesions in the brain correlates with the main neurologic clinical features. The cerebral cortex and neurons are spared until the terminal stages of illness. Because reversible inflammatory lesions predominate over the irreversible destruction of tissue, neuropsychiatric symptoms and signs resolve partially or completely during or after treatment of second-stage HAT.

APPROACH TO THE PATIENT

Human African Trypanosomiasis

HAT is usually lethal in the absence of treatment, and treatment is simpler and safer during the first stage of illness. Therefore, early diagnosis is crucial; physicians should include HAT in the differential diagnosis of several clinical syndromes when a patient has traveled or lived in at-risk sub-Saharan African countries, and obtaining a thorough recent and remote travel history from the patient is a prerequisite for diagnosis. In particular, HAT due to *T. b. gambiense* should be suspected in patients with persistent and intermittent fever or headaches, progressive neuropsychiatric disorders, and biological signs of systemic inflammation, even if the last exposure occurred several years previously. HAT due to *T. b. rhodesiense* should be suspected in patients with an acute febrile illness and a recent exposure to tsetse flies in an eastern African country, especially if diagnostic tests for malaria are negative.

CLINICAL MANIFESTATIONS

The clinical presentations of *T. b. gambiense* and *T. b. rhodesiense* HAT usually differ. *T. b. gambiense* HAT is a slowly evolving illness with a long incubation period (months to years) and a prolonged disease course. In contrast, *T. b. rhodesiense* HAT is an acute febrile illness with a short (<3-week) incubation period and a shorter (weeks to months) disease course. There are exceptions to this classical pattern. Acute forms of *T. b. gambiense* HAT have been reported, especially among travelers, and chronic forms of *T. b. rhodesiense* HAT occur in the southern range of its geographic distribution (e.g., Zambia and Malawi). Trypanotolerance—i.e., the long-term persistence of parasites without clinical features of disease—is increasingly being reported for *T. b. gambiense*. Concomitant HIV co-infection does not seem to predispose individuals to an increased risk of HAT, and the virus's impact on the clinical presentation of HAT is not known.

T. b. gambiense The occurrence of trypanosomal chancre is reported in a sizeable proportion of travelers, but very rarely in patients

living in endemic areas, where the nonpurulent, painful, and itchy nodule can easily be confused with the bite of another arthropod. The chancre spontaneously disappears in 1–3 weeks.

SYSTEMIC FEATURES After an asymptomatic incubation period that usually lasts for weeks or months but occasionally lasts for years, patients may present with irregular and remittent fever, sometimes accompanied by fatigue, malaise, and myalgia. Fever is more frequent among travelers than among natives, but the absence of fever in no way rules out the disease. Circinate or serpiginous rashes, commonly called *trypanids*, can occur on the trunk and on proximal parts of the extremities. Trypanids are almost impossible to detect on dark skin and have been reported only in Caucasians. Pruritus is a common but nonspecific symptom that affects up to half of patients during the second stage. Painless edema of the face and extremities occasionally occurs during the first phase.

Enlarged lymph nodes—a classical sign of HAT—are detected in 38–85% patients at both disease stages. Cervical palpation is essential in patients with suspected HAT. The lateroposterior cervical group (Winterbottom sign) and the supraclavicular group are most commonly affected. Lymph nodes are movable, soft initially, harder later, and painless. A variable proportion of patients present with mild to moderate hepatomegaly and splenomegaly. Signs of myocarditis and pericarditis are occasionally detected by ECG and echocardiography but are usually clinically silent. Symptoms of HAT may mimic hypothyroidism or adrenal insufficiency, but thyroid and adrenal function tests yield normal results. Loss of libido, impotence, and amenorrhea, with decreased levels of testosterone and estradiol, are common in second-stage patients and are most likely caused by dysfunction of the hypothalamic–pituitary axis.

NEUROPSYCHIATRIC FEATURES Most patients with second-stage illness have no or only mild specific neuropsychiatric symptoms and signs, which, when they develop, tend to do so late in the disease course. In contrast, some nonspecific features, such as headaches and mood and behavioral changes, are present in both disease stages but become more permanent and severe during the second stage. As mentioned earlier, HAT is commonly called "sleeping sickness" because of various sleep disturbances (daytime somnolence, nocturnal insomnia) that are more pronounced later in the second stage. Dysregulation of the daily sleep/wake cycle and fragmentation of sleeping patterns are characteristic. Depending on the area of the brain affected, various neurologic syndromes can also develop, including disorders that are pyramidal-related (e.g., motor weakness, rare instances of hemiplegia), extrapyramidal-related (e.g., rigidity, paratonia), and cerebellar-related (e.g., ataxia, abnormal gait). Fine tremor, resting myoclonus, and abnormal (athetoid or choreic) movements have also been reported. Mental disorder is a key feature of HAT and can easily be misdiagnosed as primary psychiatric illness. Common presentations are antisocial or aggressive behavior, mood disorders (e.g., irritability, indifference), apathy or hyperactivity, and depression or psychosis (e.g., delirium, hallucinations). In the final stage of illness, decreased consciousness, dementia, and sometimes epilepsy are present, leading to coma, bed sores, aspiration pneumonia, or other bacterial infections and ultimately to death.

T. b. rhodesiense The clinical presentation of *T. b. rhodesiense* HAT can be similar to that of *T. b. gambiense* HAT in areas (e.g., Zambia, Malawi) that characteristically harbor specific parasite genotypes and host factors. The typical acute form with an incubation period of <3 weeks occurs in the northern range of the disease's distribution (e.g., Tanzania, Uganda) and in travelers. The initial trypanosomal chancre is clinically similar to that seen in *T. b. gambiense* HAT but is more common, especially among travelers.

SYSTEMIC FEATURES Fever can be high and occurs in both first- and second-stage patients, often in association with headaches and with diffuse myalgia and arthralgia. Pruritus and edema of the face and legs can be present. Lymphadenopathies have been reported in variable proportions in both disease stages and predominately affect the submandibular, axillary, and inguinal regions. Mild to moderate hepatomegaly and splenomegaly are documented in a minority of patients. Myocarditis and pericarditis appear to influence clinical course and outcome, even though clinical features of cardiac failure or arrhythmia have not been prominent findings in large case series. In contrast, conduction abnormalities, with various degrees of atrioventricular block, have been reported in travelers. Sepsis-like features, with disseminated intravascular coagulation and multiple-organ failure, can occur in the terminal stage.

NEUROPSYCHIATRIC FEATURES Neuropsychiatric symptoms and signs in *T. b. rhodesiense* HAT are reported with varying frequency but overall are similar to those described above for *T. b. gambiense* HAT. The notable exception in *T. b. rhodesiense* disease is a more rapid evolution toward coma and death.

DIAGNOSIS

The clinical and biological features of *T. b. gambiense* and *T. b. rhodesiense* HAT—anemia, thrombocytopenia, elevated levels of C-reactive protein and IgM—are not sufficiently specific and current drug regimens are not sufficiently simple and safe to allow the initiation of treatment solely on the basis of suspicion. Diagnostic confirmation is therefore mandatory in all patients.

T. b. gambiense The diagnosis of *T. b. gambiense* HAT is based on a three-step approach: screening, diagnostic confirmation, and staging.

SCREENING Immunologic (serologic) methods constitute the preferred screening tool. The card agglutination test for trypanosomiasis (CATT) has been used in most endemic areas for several decades. The test reagent contains stained, freeze-dried trypanosomes of selected variable-antigen types. If specific antibodies are present in the patient's blood or serum, agglutination can be seen with the naked eye. The sensitivity of the CATT on undiluted blood or serum is 69–100% (>90% in most studies), with some regional variation; its specificity is 84–99%. The CATT and associated equipment (e.g., a rotator) are manufactured and distributed by the Institute of Tropical Medicine in Antwerp, Belgium, but are not widely available outside endemic areas. In recent years, lateral flow tests have been developed and commercialized, first based on whole parasites and later on recombinant antigens. Their diagnostic performance appears similar to that of the CATT. Other serologic test formats (ELISA, immunofluorescence, indirect hemagglutination) are available in some reference laboratories in both endemic and nonendemic countries.

DIAGNOSTIC CONFIRMATION The microscopic observation of trypanosomes in the lymph, blood, or CSF confirms the diagnosis. Direct observation of motile trypanosomes on a wet preparation of lymph obtained by cervical lymph-node puncture is simple and cheap but has limited sensitivity (50–65% in most studies). Trypanosomes can be found in the blood but often occur at low densities. Therefore, stained thin and thick blood smears have very low sensitivity. Sensitivity is improved (to 40–60% in most studies) with the microhematocrit centrifugation technique, which is based on microscopic examination of the buffy coat after centrifugation of four to six microhematocrit tubes. The most sensitive method (~90%) is the miniature anion-exchange centrifugation technique, which is based on the visualization of trypanosomes in eluate after the passage of a large volume (500 µL) of blood through an anion-exchange column and subsequent centrifugation.

STAGING As long as treatment of first- and second-stage HAT differs, staging remains an obligatory diagnostic step and is based on the examination of CSF obtained by lumbar puncture. Second-stage HAT is defined by the presence in CSF of a raised leukocyte count (>5/µL) and/or of trypanosomes. The latter can be detected in the cell-counting chamber or, preferably, after centrifugation of the CSF.

Several molecular methods based on PCR or loop-mediated isothermal amplification have been developed, mostly based on the detection of multiple-copy DNA targets of the Trypanozoon group (to which *T. brucei* belongs) or the single-copy TgsGP gene of *T. b. gambiense.* None of these methods have been fully validated for diagnostic purposes, and a positive result of their application to blood should be interpreted as suspected rather than confirmed HAT. Molecular methods applied

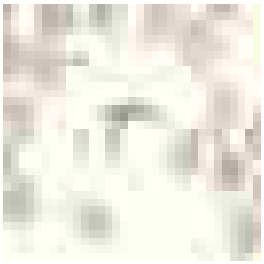

FIGURE 222-4 ***Trypanosoma brucei rhodesiense*** **in blood** (thin smear, Giemsa stain). *(Credit to the DPDx team, U.S. Centers for Disease Control and Prevention, Atlanta.)*

to CSF (to detect biomarkers) have not proven more accurate than classical methods for staging and have yielded false-positive results in a substantial proportion of cases.

T. b. rhodesiense The diagnosis of *T. b. rhodesiense* HAT is usually simpler because parasites are more numerous in body fluids. They can occasionally be visualized in a chancre aspirate. In light of the lack of available serologic tests and the high sensitivity of parasite detection methods in blood, wet mounts, and thin/thick smears **(Fig. 222-4)**, the microhematocrit or other concentration techniques are used for both screening and confirmation. For staging, the definition and methods used are the same as for *T. b. gambiense* HAT.

TREATMENT

Human African Trypanosomiasis

The management of HAT is based on general supportive therapy (e.g., rehydration, pain management), treatment of concomitant infections (e.g., malaria, pneumonia), and antiparasitic treatment. The modalities of antitrypanosomal treatment depend on the *Trypanosoma* species, the stage of illness, and the presence of contraindications **(Table 222-4)**.

T. B. GAMBIENSE

Pentamidine isethionate is highly effective (>95%) against first-stage *T. b. gambiense* HAT. It is generally well tolerated and can therefore be administered in peripheral health care centers in endemic countries **(Fig. 222-5)**. Hypotension after injection is common but generally mild. Hypoglycemia or hyperglycemia occasionally occurs, but permanent diabetes is very rare. Pain at the injection site is common after intramuscular (IM) injections, but local sterile or bacterial abscesses are rare if basic aseptic precautions are taken. Severe adverse events, such as acute pancreatitis and anaphylaxis, occur extremely rarely.

Nifurtimox–eflornithine combination therapy is also extremely effective (>95% cure rate) and is safer than 14 days of eflornithine monotherapy for treatment of second-stage *T. b. gambiense* HAT.

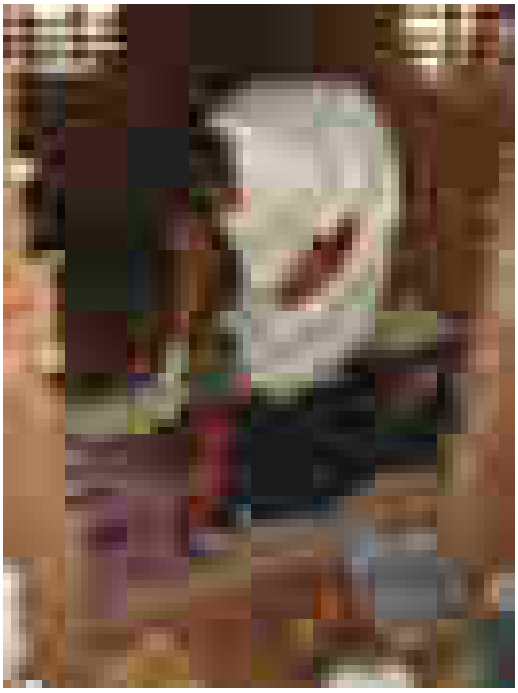

FIGURE 222-5 **Intramuscular injection of pentamidine** by a nurse in a village health center, Province Orientale, Democratic Republic of the Congo.

Common adverse reactions include gastrointestinal disturbances (nausea, vomiting, abdominal pain), headaches, anorexia, and reversible bone-marrow toxicity (anemia, leukopenia). Convulsions and psychosis are reported in fewer than 5% of patients.

T. B. RHODESIENSE

Suramin has been used for >90 years and remains the first-line treatment for first-stage *T. b. rhodesiense* HAT. Common adverse events are pyrexia and nephrotoxicity, which is usually mild and reversible but necessitates surveillance of albuminuria and renal function before each dose.

As eflornithine is ineffective against *T. b. rhodesiense*, melarsoprol, an arsenic-based derivative, remains the only existing treatment for second-stage *T. b. rhodesiense* HAT. Reactive encephalopathy is a life-threatening adverse event that occurs in 5–18% of patients, with an associated mortality rate of 10–70%. The efficacy of concomitant high-dose prednisolone to prevent reactive encephalopathy in patients with *T. b. rhodesiense* HAT is not known. Other severe but less frequent adverse reactions to melarsoprol include exfoliative dermatitis, bloody diarrhea, peripheral neuropathy, renal dysfunction, and liver toxicity. Phlebitis is common, as is soft tissue necrosis if the drug is accidentally given paravenously.

TABLE 222-4 Treatment of Human African Trypanosomiasis (HAT)

DISEASE AND STAGE	FIRST-LINE TREATMENT		ALTERNATIVE TREATMENT
	DRUG(S) AND ROUTE	DOSE AND DURATION	
***T. b. gambiense* HAT**[a]			
First stage	Pentamidine isethionate IM or IV[a]	4 mg/kg per day for 7 days	Suramin IV[b]
Second stage	Eflornithine IV + nifurtimox PO	Eflornithine: 200 mg/kg bid for 7 days Nifurtimox: 5 mg/kg tid for 10 days	Eflornithine IV: 100 mg/kg qid for 14 days[c]
***T. b. rhodesiense* HAT**			
First stage	Suramin IV	4–5 mg/kg on day 1 followed by 5 weekly injections of 20 mg/kg (e.g., days 3, 10, 17, 24, 31)[d]	Pentamidine isethionate IM or IV[e]
Second stage	Melarsoprol IV	2.2 mg/kg per day for 10 days	—

[a]For IV administration, slow infusion (60–120 min) should be used. [b]Use only if there is a strict contraindication to pentamidine and after exclusion of concomitant onchocerciasis (in which there is a risk of severe immunologic reaction to suramin). The dose and duration are the same as for first-stage *T. b. rhodesiense* HAT. [c]Use if there is a contraindication to nifurtimox, such as allergy, severe epilepsy, or psychosis. [d]The maximal dose is 1 g per injection; drug should be diluted in distilled water. [e]Use at the same dose and for the same duration as for first-stage *T. b. gambiense* HAT.

Source: Control and surveillance of human African trypanosomiasis: Report of a WHO Expert Committee. WHO Technical Report Series 984, 2013.

PROGNOSIS

More than 95% of patients with first-stage and second-stage *T. b. gambiense* HAT are definitively cured with pentamidine and nifurtimox–eflornithine combination therapy, respectively. The overall case–fatality rate is <1% except in very advanced cases. As relapses can occur long after completion of treatment, follow-up visits are advised every 6 months for at least 2 years. The relapse rate is very low (<2%) with current first-line therapies; thus blood and CSF examinations during follow-up visits are no longer standard but can be restricted to symptomatic patients. Patients with second-stage *T. b. rhodesiense* HAT are at a 5–10% risk of dying during or after melarsoprol treatment, but relapses are very rare.

GLOBAL CONSIDERATIONS

The elimination of sleeping sickness as a public health problem is in sight, thanks to increased control activities run by national control programs and nongovernmental medical organizations, improved funding, and the end of several civil wars (e.g., in Angola) in the last 15 years. Funding for research, development, and implementation of improved diagnostic methods (e.g., rapid diagnostic tests) and therapeutic tools (e.g., oral drugs) remains crucial to sustain recent achievements.

FURTHER READING

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223 *Toxoplasma* Infections

Kami Kim

DEFINITION

Toxoplasmosis is caused by infection with the obligate intracellular parasite *Toxoplasma gondii*. Acute infection acquired after birth may be asymptomatic but is thought to result in the lifelong chronic persistence of cysts in the host's tissues. In both acute and chronic toxoplasmosis, the parasite is responsible for clinically evident disease, including lymphadenopathy, encephalitis, myocarditis, and pneumonitis. *Congenital* toxoplasmosis is an infection of newborns that results from the transplacental passage of parasites from an infected mother to the fetus. These infants may be asymptomatic at birth, but many later manifest a wide range of signs and symptoms, including chorioretinitis, strabismus, epilepsy, and psychomotor retardation. In immunocompetent individuals, toxoplasmosis can also present as acute disease (typically chorioretinitis) associated with food- or waterborne sources.

ETIOLOGY

T. gondii is an intracellular coccidian that infects both birds and mammals. There are two distinct stages in the life cycle that are transmissible to humans **(Fig. 223-1)**. Tissue cysts that contain bradyzoites are transmitted in undercooked meat. After an intermediate host (e.g., a human, mouse, sheep, pig, or bird) ingests the cyst, it is rapidly digested by the acidic-pH gastric secretions. Sporulated oocysts that contain sporozoites are products of the sexual cycle in feline intestines and are acquired by ingestion of food or water contaminated with infected cat feces. Bradyzoites or sporozoites are released, enter the intestinal epithelium, and transform into rapidly dividing tachyzoites. The tachyzoites can infect and replicate in all mammalian cells except red blood cells. The parasite actively penetrates the cell and forms a parasitophorous vacuole. Parasite replication continues within the vacuole. After the parasites reach a critical mass, intracellular signaling within the host and the parasite, including calcium fluxes, results in parasite egress from the vacuole. The host cell is destroyed, and the released tachyzoites infect adjoining cells. Parasites can disseminate throughout the body as free tachyzoites or within phagocytic cells in the bloodstream or via lymphatics. Tachyzoites actively invade host cells and can cross epithelial barriers.

The tachyzoite replication cycle within an infected organ causes cytopathology and clinical symptoms. Most tachyzoites are eliminated by the host's humoral and cell-mediated immune responses. Tissue cysts containing bradyzoites develop 7–10 days after systemic tachyzoite infection. These tissue cysts occur in various host organs but persist principally within the central nervous system (CNS) and muscle. The development of this chronic stage completes the asexual portion of the life cycle. Active infection in the immunocompromised host is most likely to be due to the spontaneous release of encysted parasites that undergo rapid transformation into tachyzoites within the CNS and are not contained by the immune system.

The *sexual* stage in the life cycle takes place in the cat (the definitive host) and is defined by the formation of oocysts within the feline host. This enteroepithelial cycle begins with the ingestion of the bradyzoite tissue cysts and, after several intermediate stages, culminates in the production of gametes. Gamete fusion produces a zygote, which envelops itself in a rigid wall and is secreted in the feces as an unsporulated oocyst. After 2–3 days of exposure to air at ambient temperature, the noninfectious oocyst sporulates to produce eight sporozoite progeny. The sporulated oocyst can be ingested by an intermediate host, such as a person emptying a cat's litter box or a pig rummaging in a barnyard. It is in the intermediate host that *T. gondii* completes its life cycle.

Sporulated oocysts are environmentally hardy and very infectious; they are thought to be sources of waterborne outbreaks such as those reported in Victoria (British Columbia, Canada) and in South America. Strains found in South America are more virulent than those from the Northern Hemisphere and are more likely to be associated with symptomatic disease—usually ocular—in immunocompetent individuals; thus ocular toxoplasmosis should be considered in a person from South America with ocular symptoms and retinal abnormalities. Severe disease, including sepsis, fever of unknown origin, and pneumonia, have been reported and should be considered in a patient with a history of travel to South America.

EPIDEMIOLOGY

T. gondii infects a wide range of mammals and birds. Its seroprevalence depends on the locale and the age of the population. Generally, hot arid climatic conditions are associated with a low prevalence of infection. In the United States and most European countries, seroprevalence increases with age and exposure. In the United States, 13.2% of individuals >6 years old had serologic evidence of exposure in a 2009–2010 survey, with foreign-born Americans having a higher rate of seroprevalence. In most other regions of the world, the seroprevalence is higher. Perhaps because of increased awareness of foodborne infections, the prevalence of seropositivity has decreased worldwide over the past two decades.

TRANSMISSION

Oral Transmission Most cases of human *Toxoplasma* infection are thought to be acquired by the oral route. Transmission can be attributable to ingestion of sporulated oocysts from contaminated soil, food, or water. During acute feline infection, a cat may excrete as many as 100 million oocysts per day. These sporozoite-containing oocysts are highly infectious and may remain viable for many years in soil or water. Humans infected during an oocyst-transmitted infection develop stage-specific antibodies to the oocyst/sporozoite.

Children and adults also acquire infection from tissue cysts containing bradyzoites. Undercooking or insufficient freezing of meat is an important source of infection in the developed world. More recent epidemiologic studies have associated acute infections with ingestion of untreated water or shellfish (oysters, mussels, and clams).

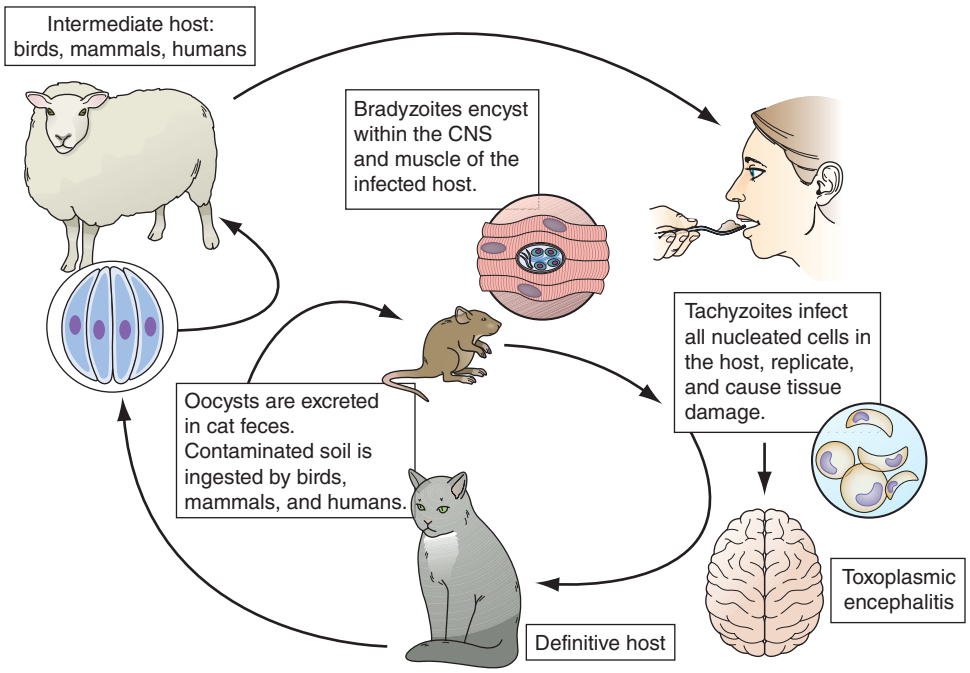

FIGURE 223-1 Life cycle of *Toxoplasma gondii*. The cat is the definitive host in which the sexual phase of the cycle is completed. Oocysts shed in cat feces can infect a wide range of animals, including birds, rodents, grazing domestic animals, and humans. The bradyzoites found in the muscle of food animals may infect humans who eat insufficiently cooked meat products, particularly lamb and pork. Although human disease can take many forms, congenital infection and encephalitis from reactivation of latent infection in the brains of immunosuppressed persons are the most important manifestations. CNS, central nervous system. (*Courtesy of Dominique Buzoni-Gatel, Institut Pasteur, Paris; with permission.*)

Transmission via Blood or Organs In addition to being transmitted orally, *T. gondii* can be transmitted directly from a seropositive donor to a seronegative recipient in a transplanted heart, heart–lung, kidney, liver, or pancreas. Viable parasites can be cultured from refrigerated anticoagulated blood, which may be a source of infection in individuals receiving blood transfusions. *T. gondii* reactivation has been reported in bone marrow, hematopoietic stem cell, and liver transplant recipients as well as in individuals with AIDS. Although antibody titers generally are not useful in monitoring *T. gondii* infection, individuals with higher antibody titers may be at relatively high risk for reactivation after hematopoietic stem cell transplantation; thus routine polymerase chain reaction (PCR) screening of blood from these patients may be in order. Screening of *Toxoplasma* serologies (donor and recipient) before transplantation may identify patients potentially at risk for reactivated toxoplasmosis. Finally, laboratory personnel can be infected after contact with contaminated needles or glassware or with infected tissue.

Transplacental Transmission On average, about one-third of all women who acquire infection with *T. gondii* during pregnancy transmit the parasite to the fetus; the remainder give birth to normal, uninfected babies. Of the various factors that influence fetal outcome, gestational age at the time of infection is the most critical (see below). Recrudescent maternal infection is rarely the source of congenital disease, although rare cases of transmission by immunocompromised women (e.g., those infected with HIV or those receiving high-dose glucocorticoids) have been reported. Thus women who are seropositive before pregnancy usually are protected against acute infection and do not give birth to congenitally infected neonates.

There is essentially no risk of congenital infection if the mother becomes infected ≥6 months before conception. If infection is acquired <6 months before conception, the likelihood of transplacental infection increases as the interval between infection and conception decreases. Women with documented acute toxoplasmosis should be counseled to use appropriate measures to prevent pregnancy for 6 months after infection. In pregnancy, if the mother becomes infected during the first trimester, the incidence of transplacental infection is lowest (~15%), but the disease in the neonate is most severe. If maternal infection occurs during the third trimester, the incidence of transplacental infection is greatest (65%), but the infant is usually asymptomatic at birth. Infected infants who are normal at birth may have a higher incidence of learning disabilities and chronic neurologic sequelae than uninfected children. Only a small proportion (20%) of women infected with *T. gondii* develop clinical signs of infection. Often the diagnosis is first appreciated when routine postconception serologic tests show evidence of specific antibody.

PATHOGENESIS

Upon the host's ingestion of either tissue cysts containing bradyzoites or oocysts containing sporozoites, the parasites are released from the cysts by the digestive process. Bradyzoites are resistant to the effect of pepsin and invade the host's gastrointestinal tract. Within enterocytes (or other gut-associated cells), the parasites undergo morphologic transformation, giving rise to invasive tachyzoites. From the gastrointestinal tract, parasites disseminate to a variety of organs, particularly lymphatic tissue, skeletal muscle, myocardium, retina, placenta, and the CNS. At these sites, the parasite infects host cells, replicates, and invades the adjoining cells. In this fashion, the hallmarks of the infection develop: cell death and focal necrosis surrounded by an acute inflammatory response.

In the immunocompetent host, both the humoral and the cellular immune responses control infection; parasite virulence and tissue tropism may be strain specific. Tachyzoites are sequestered by a variety of immune mechanisms, including induction of parasiticidal antibody, activation of macrophages with radical intermediates, production of interferon γ (IFN-γ), and stimulation of CD8+ cytotoxic T lymphocytes. These antigen-specific lymphocytes are capable of killing both extracellular parasites and target cells infected with parasites. As tachyzoites are cleared from the acutely infected host, tissue cysts containing bradyzoites begin to appear, usually within the CNS, the skeletal muscle, and the retina. Studies indicate that *Toxoplasma* secretes signaling molecules into infected host cells and that these molecules modulate host gene expression, host metabolism, and host immune response. While it was initially thought that cysts with bradyzoites are not eliminated by the immune system, recent studies in the murine model indicate that both CD8+ T cells and alternatively activated macrophages are able to kill cysts in vivo; some cysts persist, however, and the ability to eliminate cysts may depend on the genetic background of the infected host.

In the immunocompromised or fetal host, the immune factors necessary to control the spread of tachyzoite infection are lacking. This altered immune state allows the persistence of tachyzoites and gives rise to progressive focal destruction in affected organs (i.e., necrotizing encephalitis, pneumonia, and myocarditis).

It is thought that all infected individuals have persistent infection with cysts containing bradyzoites, but this lifelong infection usually remains subclinical. Although bradyzoites are in a slow metabolic phase, cysts do degenerate and rupture within the CNS. This degenerative process, with the development of new bradyzoite-containing cysts, is the most probable source of recrudescent infection in immunocompromised individuals and the most likely stimulus for the persistence of antibody titers in the immunocompetent host. Although the concept is controversial, the persistence of toxoplasmosis has been hypothesized to be a contributing factor to a variety of neuropsychiatric

conditions, including schizophrenia and bipolar disease. In rodents, chronic infection clearly has significant effects on behavior, increasing predation.

PATHOLOGY

Cell death and focal necrosis due to replicating tachyzoites induce an intense mononuclear inflammatory response in any tissue or cell type infected. Tachyzoites rarely can be visualized by routine histopathologic staining of these inflammatory lesions. However, immunofluorescent staining with parasitic antigen–specific antibodies can reveal the organism. In contrast to this inflammatory process caused by tachyzoites, bradyzoite-containing cysts cause inflammation only at the early stages of development. Once the cysts reach maturity, the inflammatory process can no longer be detected, and the cysts remain immunologically quiescent within the brain matrix until they rupture.

Lymph Nodes During acute infection, lymph node biopsy demonstrates characteristic findings, including follicular hyperplasia and irregular clusters of tissue macrophages with eosinophilic cytoplasm. Granulomas rarely are evident in these specimens. Although tachyzoites are not usually visible, they can be sought either by subinoculation of infected tissue into mice, with resultant disease, or by PCR. PCR amplification of DNA fragments of *Toxoplasma* genes is effective and sensitive in establishing lymph node infection by tachyzoites.

Eyes In the eye, infiltrates of monocytes, lymphocytes, and plasma cells may produce uni- or multifocal lesions. Granulomatous lesions and chorioretinitis can be observed in the posterior chamber after acute necrotizing retinitis. Other ocular complications include iridocyclitis, cataracts, and glaucoma.

Central Nervous System During CNS involvement, both focal and diffuse meningoencephalitis can be documented, with evidence of necrosis and microglial nodules. Necrotizing encephalitis in patients without AIDS is characterized by small diffuse lesions with perivascular cuffing in contiguous areas. In the AIDS population, polymorphonuclear leukocytes may be present in addition to monocytes, lymphocytes, and plasma cells. Cysts containing bradyzoites frequently are found contiguous with the necrotic tissue border. As a consequence of combined antiretroviral therapy (cART) for AIDS, the incidence of toxoplasmosis has decreased in the developed world. Its incidence in under-resourced settings is not known but is likely to be high.

Lungs and Heart Among patients with AIDS who die of toxoplasmosis, 40–70% have involvement of the lungs and heart. Interstitial pneumonitis can develop in neonates and immunocompromised patients. Thickened and edematous alveolar septa infiltrated with mononuclear and plasma cells are apparent. This inflammation may extend to the endothelial walls. Tachyzoites and bradyzoite-containing cysts have been observed within the alveolar membrane. Superimposed bronchopneumonia can be caused by other microbial agents. Cysts and aggregates of parasites in cardiac muscle tissue are evident in patients with AIDS who die of toxoplasmosis. Focal necrosis surrounded by inflammatory cells is associated with hyaline necrosis and disrupted myocardial cells. Pericarditis is associated with toxoplasmosis in some patients.

Gastrointestinal Tract Rare cases of human gastrointestinal tract infection with *T. gondii* have presented as ulcerations in the mucosa. Acute infection in certain strains of inbred mice (C57BL/6) results in lethal ileitis within 7–9 days. This inflammatory bowel disease has been recognized in several other mammalian species, including pigs and nonhuman primates.

Other Sites Pathologic changes during disseminated infection are similar to those described for the lymph nodes, eyes, and CNS. In patients with AIDS, the skeletal muscle, pancreas, stomach, and kidneys can be involved, with necrosis, invasion by inflammatory cells, and (rarely) tachyzoites detectable by routine staining. Large necrotic lesions may cause direct tissue destruction. In addition, secondary effects from acute infection of these various organs, including pancreatitis, myositis, and glomerulonephritis, have been reported.

HOST IMMUNE RESPONSE

Acute *Toxoplasma* infection evokes a cascade of protective immune responses in the immunocompetent host. *Toxoplasma* enters the host at the gut mucosal level and evokes a mucosal immune response that includes the production of antigen-specific secretory IgA. Titers of serum IgA antibody directed at the tachyzoite surface antigen p30/SAG1 are a useful marker for congenital and acute toxoplasmosis.

Within the host, *T. gondii* rapidly induces detectable levels of both IgM and IgG serum antibodies. Monoclonal gammopathy of the IgG class can occur in congenitally infected infants. IgM levels may be increased in newborns with congenital infection. The polyclonal IgG antibodies evoked by infection are parasiticidal in vitro in the presence of serum complement and are the basis for the Sabin–Feldman dye test. However, cell-mediated immunity is the major protective response evoked by the parasite during infection. Macrophages are activated after phagocytosis of antibody-opsonized parasites. This activation can lead to death of the parasite by either an oxygen-dependent or an oxygen-independent process. If the parasite is not phagocytosed and enters the macrophage by active penetration, it continues to replicate, and this replication may represent the mechanism for transport and dissemination to distant organs. *Toxoplasma* stimulates a robust interleukin (IL) 12 response by human dendritic cells. The CD4+ and CD8+ T cell responses are antigen-specific and further stimulate the production of a variety of important lymphokines that expand the T cell and natural killer cell repertoire. *T. gondii* is a potent inducer of a T_H1 phenotype, with IL-12 and IFN-γ playing an essential role in the control of the parasites' growth in the host. Regulation of the inflammatory response is at least partially under the control of a T_H2 response that includes the production of IL-4 and IL-10 in seropositive individuals. Human T cell clones of both the CD4+ and the CD8+ phenotypes are cytolytic against parasite-infected macrophages. These T cell clones produce cytokines that are "microbistatic." IL-18, IL-7, and IL-15 upregulate the production of IFN-γ and may be important during acute and chronic infection. The effect of IFN-γ may be paradoxical, with stimulation of a host downregulatory response as well.

Although *T. gondii* infection is thought to be recrudescent in patients with AIDS or other immunocompromised states, antibody titers are not useful in establishing reactivation or in following the activity of infection. An absence of positive serologic results suggests an alternative diagnosis, although AIDS patients may have borderline positive or low serologic values. T cells from AIDS patients with reactivation of toxoplasmosis fail to secrete both IFN-γ and IL-2. This alteration in the production of these critical immune cytokines contributes to the persistence of infection. *Toxoplasma* infection frequently develops late in the course of AIDS (CD4+ T cell count, <100/μL), when the loss of T cell–dependent protective mechanisms, particularly CD8+ T cells, becomes most pronounced.

CLINICAL MANIFESTATIONS

In persons whose immune systems are intact, acute toxoplasmosis is usually asymptomatic and self-limited. This condition can go unrecognized in 80–90% of adults and children with acquired infection. The asymptomatic nature of this infection makes diagnosis difficult in mothers infected during pregnancy. In contrast, the wide range of clinical manifestations in congenitally infected children includes severe neurologic complications such as hydrocephalus, microcephaly, mental retardation, and chorioretinitis. If prenatal infection is severe, multiorgan failure and subsequent intrauterine fetal death can occur. In children and adults, chronic infection can persist throughout life, with little consequence to the immunocompetent host.

Toxoplasmosis in Immunocompetent Patients The most common manifestation of acute toxoplasmosis is cervical lymphadenopathy. The nodes may be single or multiple, are usually nontender, are discrete, and vary in firmness. Lymphadenopathy also may be found in suboccipital, supraclavicular, inguinal, and mediastinal areas.

Generalized lymphadenopathy occurs in 20–30% of symptomatic patients. Between 20 and 40% of patients with lymphadenopathy also have headache, malaise, fatigue, and fever (usually with a temperature of <40°C [<104°F]). A smaller proportion of symptomatic individuals have myalgia, sore throat, abdominal pain, maculopapular rash, meningoencephalitis, and confusion. Rare complications associated with infection in the normal immune host include pneumonia, myocarditis, encephalopathy, pericarditis, and polymyositis. Signs and symptoms associated with acute infection usually resolve within several weeks, although the lymphadenopathy may persist for some months. In one epidemic, toxoplasmosis was diagnosed correctly in only 3 of the 25 patients who consulted physicians. If toxoplasmosis is considered in the differential diagnosis, routine laboratory and serologic screening should precede node biopsy.

In North America and Europe, there are three predominant genotypes of *T. gondii*, but strains are more genetically diverse in South America. Genotypes of *T. gondii* prevalent in South America are more virulent than those typically seen in North America or Europe. These genotypes may be associated with acute or recurrent ocular disease in immunocompetent individuals and have also been associated with pneumonitis and a fulminant sepsis picture in immunologically normal individuals. Thus a detailed history is critical for establishing a diagnosis.

The results of routine laboratory studies are usually unremarkable except for minimal lymphocytosis, an elevated erythrocyte sedimentation rate, and a nominal increase in serum aminotransferase levels. Evaluation of cerebrospinal fluid (CSF) in cases with evidence of encephalopathy or meningoencephalitis shows an elevation of intracranial pressure, mononuclear pleocytosis (10–50 cells/mL), a slight increase in protein concentration, and (occasionally) an increase in the gamma globulin level. PCR amplification of the *Toxoplasma* DNA target sequence in CSF is specific for active toxoplasmosis, but not sensitive. The CSF of chronically infected individuals is normal.

Infection of Immunocompromised Patients Patients with AIDS and those receiving immunosuppressive therapy for lymphoproliferative disorders are at greatest risk for developing acute toxoplasmosis. Toxoplasmosis has also been reported after treatment with antibodies to tumor necrosis factor. The infection may be due either to reactivation of latent infection or to acquisition of parasites from exogenous sources such as blood or transplanted organs. In individuals with AIDS, >95% of cases of *Toxoplasma* encephalitis (TE) are believed to be due to recrudescent infection. In most of these cases, encephalitis develops when the CD4+ T cell count falls below 100/μL. In immunocompromised hosts, the disease may be rapidly fatal if untreated. Thus, accurate diagnosis and initiation of appropriate therapy are necessary to prevent fulminant infection.

Toxoplasmosis is a principal opportunistic infection of the CNS in persons with AIDS. Although geographic origin may be related to frequency of infection, it has no correlation with the severity of disease in immunocompromised hosts. Individuals with AIDS who are seropositive for *T. gondii* are at high risk for encephalitis. Before the advent of current cART, about one-third of the 15–40% of adult AIDS patients in the United States who were latently infected with *T. gondii* developed TE. TE may still be a presenting infection in individuals who are unaware of their positive HIV status.

The signs and symptoms of acute toxoplasmosis in immunocompromised patients principally involve the CNS **(Fig. 223-2)**. More than 50% of patients with clinical manifestations have intracerebral involvement. Clinical findings at presentation range from nonfocal to focal dysfunction. CNS findings include encephalopathy, meningoencephalitis, and mass lesions. Patients may present with altered mental status (75%), fever (10–72%), seizures (33%), headaches (56%), and focal neurologic findings (60%), including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss, and aphasia. Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurologic disease as infection progresses. This altered condition is due not only to the necrotizing encephalitis caused by direct invasion by the parasite but also to secondary effects, including vasculitis, edema, and hemorrhage. The onset of infection can range from an insidious process over several weeks to an acute presentation with fulminant focal deficits, including hemiparesis, hemiplegia, visual-field defects, localized headache, and focal seizures.

Although lesions can occur anywhere in the CNS, the areas most often involved appear to be the brainstem, basal ganglia, pituitary gland, and corticomedullary junction. Brainstem involvement gives rise to a variety of neurologic dysfunctions, including cranial nerve palsy, dysmetria, and ataxia. With basal ganglion infection, patients may develop hydrocephalus, choreiform movements, and choreoathetosis. *Toxoplasma* usually causes encephalitis, and meningeal involvement is uncommon. CSF findings may be unremarkable or may include a modest increase in cell count and in protein—but not glucose—concentration.

Cerebral toxoplasmosis must be differentiated from other opportunistic infections or tumors in the CNS of AIDS patients. The differential diagnosis includes herpes simplex encephalitis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma. Involvement of the pituitary gland can give rise to panhypopituitarism and hyponatremia from inappropriate secretion of vasopressin (antidiuretic hormone). HIV-associated neurocognitive disorder (HAND) may present as cognitive impairment, attention loss, and altered memory. Brain biopsy in patients who have been treated for TE but who continue to exhibit neurologic dysfunction often fails to identify organisms.

Autopsies of *Toxoplasma*-infected patients have demonstrated the involvement of multiple organs, including the lungs, gastrointestinal tract, pancreas, skin, eyes, heart, and liver. *Toxoplasma* pneumonia can be confused with *Pneumocystis* pneumonia (PcP). Respiratory involvement usually presents as dyspnea, fever, and a nonproductive cough and may rapidly progress to acute respiratory failure with hemoptysis, metabolic acidosis, hypotension, and (occasionally) disseminated intravascular coagulation. Histopathologic studies demonstrate necrosis and a mixed cellular infiltrate. The presence of organisms is a helpful diagnostic indicator, but organisms can also be found in healthy tissue. Infection of the heart is usually asymptomatic but can be associated with cardiac tamponade or biventricular failure. Infections of the gastrointestinal tract and the liver have been documented.

Congenital Toxoplasmosis Between 400 and 4000 infants born each year in the United States are affected by congenital toxoplasmosis. Acute infection in mothers acquiring *T. gondii* during pregnancy is usually asymptomatic; most such women are diagnosed via prenatal serologic screening. Infection of the placenta leads to hematogenous infection of the fetus. As gestation proceeds, the proportion of fetuses that become infected increases, but the clinical severity of the infection declines. Although infected children may initially be asymptomatic,

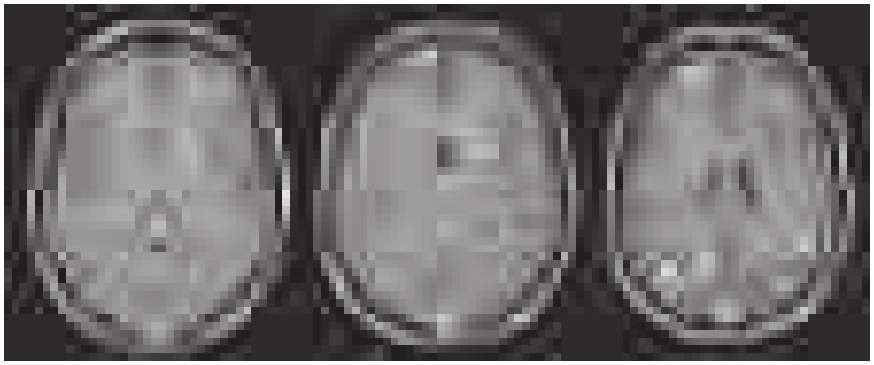

FIGURE 223-2 Toxoplasmic encephalitis in a 36-year-old patient with AIDS. The multiple lesions are demonstrated by MRI scanning (T1-weighted with gadolinium enhancement). (*Courtesy of Clifford Eskey, Dartmouth Hitchcock Medical Center, Hanover, NH; with permission.*)

the persistence of *T. gondii* can result in reactivation and clinical disease—most frequently chorioretinitis—decades later. Factors associated with relatively severe disabilities include delays in diagnosis and in initiation of therapy, neonatal hypoxia and hypoglycemia, profound visual impairment (see "Ocular Infection," below), uncorrected hydrocephalus, and increased intracranial pressure. If treated appropriately, upwards of 70% of children have normal developmental, neurologic, and ophthalmologic findings at follow-up evaluations. Treatment for 1 year with pyrimethamine, a sulfonamide, and folinic acid is tolerated with minimal toxicity (see "Treatment," below).

Ocular Infection Infection with *T. gondii* is estimated to cause 35% of all cases of chorioretinitis in the United States and Europe. It was formerly thought that the majority of cases of ocular disease were due to congenital infection. New ocular toxoplasmosis in immunocompetent individuals occurs more commonly than was previously appreciated and has been associated with outbreaks in Victoria (British Columbia) and in South America. A variety of ocular manifestations are documented, including blurred vision, scotoma, photophobia, and eye pain. Macular involvement occurs, with loss of central vision, and nystagmus is secondary to poor fixation. Involvement of the extraocular muscles may lead to disorders of convergence and to strabismus. Ophthalmologic examination should be undertaken in newborns with suspected congenital infection. As the inflammation resolves, vision improves, but episodic flare-ups of chorioretinitis, which progressively destroy retinal tissue and lead to glaucoma, are common. The ophthalmologic examination reveals yellow-white, cotton-like patches with indistinct margins of hyperemia. As the lesions age, white plaques with distinct borders and black spots within the retinal pigment become more apparent. Lesions usually are located near the posterior pole of the retina; they may be single but are more commonly multiple. Congenital lesions may be unilateral or bilateral and show evidence of massive chorioretinal degeneration with extensive fibrosis. Surrounding these areas of involvement are a normal retina and vasculature. In patients with AIDS, retinal lesions are often large, with diffuse retinal necrosis, and include both free tachyzoites and cysts containing bradyzoites. Toxoplasmic chorioretinitis may be a prodrome to the development of encephalitis.

TABLE 223-1 Differential Laboratory Diagnosis of Toxoplasmosis

CLINICAL SETTING	ALTERNATIVE DIAGNOSIS	DISTINGUISHING CHARACTERISTICS
Mononucleosis syndrome	Epstein-Barr virus infection	Serology/PCR
	Cytomegalovirus infection	Serology/PCR or culture
	HIV infection	Serology/viral load
	Bartonella infection (cat-scratch disease)	Biopsy (PCR or culture)/ serology
	Lymphoma	Biopsy
Congenital infection	Cytomegalovirus infection	Viral culture/PCR
	Herpes simplex virus infection	Viral culture/PCR
	Rubella virus infection	Serology
	Syphilis	Serology
	Listeriosis	Bacterial culture
Chorioretinitis in immunocompetent individual	Tuberculosis	Bacterial culture/PCR
	Syphilis	Serology
	Histoplasmosis	Serology/culture/ antigen
Chorioretinitis in AIDS patient	Cytomegalovirus infection	Viral culture/PCR
	Syphilis	Serology
	Herpes simplex virus infection	Viral culture/PCR
	Varicella-zoster virus infection	Viral culture/PCR
	Fungal infection	Culture
CNS lesions in AIDS patient	Lymphoma or metastatic tumor	Tissue biopsy
	Brain abscess	Biopsy/culture
	Progressive multifocal leukoencephalopathy	PCR for JC virus
	Fungal infection	Biopsy/culture
	Mycobacterial infection	Biopsy/culture/PCR

Abbreviations: CNS, central nervous system; PCR, polymerase chain reaction.

Source: Adapted from JD Schwartzman: Toxoplasmosis, in *Principles and Practice of Clinical Parasitology*. Hoboken, Wiley, 2001.

DIAGNOSIS

Tissues and Body Fluids The differential diagnosis of acute toxoplasmosis can be made by appropriate culture, serologic testing, and PCR (Table 223-1). Although performed only at specialized laboratories, the isolation of *T. gondii* from blood or other body fluids can be accomplished after subinoculation of the sample into the peritoneal cavity of mice. If no parasites are found in the mouse's peritoneal fluid 6–10 days after inoculation, its anti-*Toxoplasma* serum titer can be evaluated 4–6 weeks after inoculation. Isolation of *T. gondii* from the patient's body fluids reflects acute infection, whereas isolation from biopsied tissue is an indication only of the presence of tissue cysts and should not be misinterpreted as evidence of acute toxoplasmosis. Persistent parasitemia in patients with latent, asymptomatic infection is rare. Histologic examination of lymph nodes may suggest the characteristic changes described above. Demonstration of tachyzoites in lymph nodes establishes the diagnosis of acute toxoplasmosis. Like subinoculation into mice, histologic demonstration of cysts containing bradyzoites confirms prior infection with *T. gondii* but is nondiagnostic for acute infection.

Serology Because some diagnostic tests are available only at specialty laboratories and are technically challenging, serologic testing has become the routine method of diagnosis. Diagnosis of acute infection with *T. gondii* can be established by detection of the simultaneous presence of IgG and IgM antibodies to *Toxoplasma* in serum. The presence of circulating IgA favors the diagnosis of an acute infection. The Sabin–Feldman dye test, the indirect fluorescent antibody test, and the enzyme-linked immunosorbent assay (ELISA) all satisfactorily measure circulating IgG antibody to *Toxoplasma*. Positive IgG titers (>1:10) can be detected as early as 2–3 weeks after infection. These titers usually peak at 6–8 weeks and decline slowly to a new baseline level that persists for life. Antibody avidity increases with time and can be useful in difficult cases during pregnancy for establishing when infection may have occurred. The serum IgM titer should be measured in concert with the IgG titer to better establish the time of infection; either the double-sandwich IgM-ELISA or the IgM-immunosorbent assay (IgM-ISAGA) should be used. Both assays are specific and sensitive, with fewer false-positive results than other commercial tests. The double-sandwich IgA-ELISA is more sensitive than the IgM-ISAGA for detecting congenital infection in the fetus and newborn. Although a negative IgM result with a positive IgG titer indicates distant infection, IgM can persist for >1 year and should not necessarily be considered a reflection of acute disease. If acute toxoplasmosis is suspected, a more extensive panel of serologic tests can be performed. In the United States, testing is available at the *Toxoplasma* Serology Laboratory at Palo Alto Medical Foundation (*http://www.pamf.org/serology/clinicianguide.html*).

Molecular Diagnostics Molecular approaches can directly detect *T. gondii* in biologic samples independent of the serologic response. Results obtained with PCR have suggested high sensitivity, specificity, and clinical utility in the diagnosis of TE, and PCR technology may be becoming more readily available in resource-poor settings. Real-time PCR is a promising technique that can provide quantitative results. Isolates can be genotyped and polymorphic sequences can be obtained, with consequent identification of the precise strain. Molecular epidemiologic studies with polymorphic markers have been useful in correlating clinical signs and symptoms of disease with different *T. gondii* genotypes.

The Immunocompetent Adult or Child For the patient who presents with lymphadenopathy only, a positive IgM titer is an indication of acute infection—and an indication for therapy, if clinically warranted (see "Treatment," below). The serum IgM titer should be determined again in 3 weeks. An elevation in the IgG titer without an increase in the IgM titer suggests that infection is present but is not acute. If there is a borderline increase in either IgG or IgM, the titers should be reassessed in 3–4 weeks.

The Immunocompromised Host A presumptive clinical diagnosis of TE in patients with AIDS is based on clinical presentation, history of exposure (as evidenced by positive serology), and radiologic evaluation. To detect latent infection with *T. gondii*, HIV-infected persons should be tested for IgG antibody to *Toxoplasma* soon after HIV infection is diagnosed. When these criteria are used, the predictive value is as high as 80%. More than 97% of patients with AIDS and toxoplasmosis have IgG antibody to *T. gondii* in serum. IgM serum antibody usually is not detectable. Although IgG titers do not correlate with active infection, serologic evidence of infection virtually always precedes the development of TE. It is therefore important to determine the *Toxoplasma* antibody status of all patients infected with HIV. Antibody titers may range from negative to 1:1024 in patients with AIDS and TE. Fewer than 3% of patients have no demonstrable antibody to *Toxoplasma* at diagnosis of TE.

Patients with TE have focal or multifocal abnormalities demonstrable by CT or MRI. Neuroradiologic evaluation should include double-dose contrast CT of the head. By this test, single and frequently multiple contrast-enhancing lesions (<2 cm) may be identified. MRI usually demonstrates multiple lesions located in both hemispheres, with the basal ganglia and corticomedullary junction most commonly involved; MRI provides a more sensitive evaluation of the efficacy of therapy than does CT (Fig. 223-2). These findings are not pathognomonic of *Toxoplasma* infection, because 40% of CNS lymphomas are multifocal and 50% are ring-enhancing. For both MRI and CT scans, the rate of false-negative results is ~10%. The finding of a single lesion on an MRI scan increases the likelihood of primary CNS lymphoma (in which solitary lesions are four times more likely than in TE) and strengthens the argument for the performance of a brain biopsy. A therapeutic trial of anti-*Toxoplasma* medications is frequently used to assess the diagnosis. Treatment of presumptive TE with pyrimethamine plus sulfadiazine or clindamycin results in quantifiable clinical improvement in >50% of patients by day 3. Leucovorin is administered to prevent bone marrow toxicity. By day 7, >90% of treated patients show evidence of improvement. In contrast, if patients fail to respond or have lymphoma, clinical signs and symptoms worsen by day 7. Patients in this category require brain biopsy with or without a change in therapy. This procedure can now be performed by a stereotactic CT-guided method that reduces the potential for complications. Brain biopsy for *T. gondii* identifies organisms in 50–75% of cases. PCR amplification of CSF may also confirm toxoplasmosis or suggest alternative diagnoses (Table 223-1), such as progressive multifocal leukoencephalopathy (JC virus positive) or primary CNS lymphoma (Epstein-Barr virus positive).

CT and MRI with contrast are currently the standard diagnostic imaging tests for TE. As in other conditions, the radiologic response may lag behind the clinical response. Resolution of lesions may take from 3 weeks to 6 months. Some patients show clinical improvement despite worsening radiographic findings.

Congenital Infection The issue of concern when a pregnant woman has evidence of recent *T. gondii* infection is whether the fetus is infected. PCR analysis of the amniotic fluid for the B1 gene of *T. gondii* has replaced fetal blood sampling. Serologic diagnosis is based on the persistence of IgG antibody or a positive IgM titer after the first week of life (a time frame that excludes placental leak). The IgG determination should be repeated every 2 months. An increase in IgM beyond the first week of life is indicative of acute infection. Up to 25% of infected newborns may be seronegative and have normal routine physical examinations. Thus assessment of the eye and the brain, with ophthalmologic testing, CSF evaluation, and radiologic studies, is important in establishing the diagnosis.

Ocular Toxoplasmosis The serum antibody titer may not correlate with the presence of active lesions in the fundus, particularly in cases of congenital toxoplasmosis. In general, a positive IgG titer (measured in undiluted serum if necessary) in conjunction with typical lesions establishes the diagnosis. If lesions are atypical and the serum antibody titer is in the low-positive range, the diagnosis is presumptive. The parasitic antigen–specific polyclonal IgG assay as well as parasite-specific PCR may facilitate the diagnosis. Accordingly, the clinical diagnosis of ocular toxoplasmosis can be supported in 60–90% of cases by laboratory tests, depending on the time of anterior chamber puncture and the panel of antibody analyses used. In the remaining cases, the possibility of a falsely negative laboratory diagnosis or of an incorrect clinical diagnosis cannot be clarified further.

TREATMENT

Toxoplasmosis

CONGENITAL INFECTION

Congenitally infected neonates are treated with daily oral pyrimethamine (1 mg/kg) and sulfadiazine (100 mg/kg) along with folinic acid for 1 year. Depending on the signs and symptoms, prednisone (1 mg/kg per day) may be used for congenital infection. Some U.S. states and some countries routinely screen pregnant women (France, Austria) and/or newborns (Denmark, Massachusetts). Management and treatment regimens vary with the country and the treatment center. Most experts use spiramycin to treat pregnant women who have acute toxoplasmosis early in pregnancy and use pyrimethamine/sulfadiazine/folinic acid to treat women who seroconvert after 18 weeks of pregnancy or in cases of documented fetal infection. This treatment is somewhat controversial: clinical studies, which have included few untreated women, have not proven the efficacy of such therapy in preventing congenital toxoplasmosis. However, studies do suggest that treatment during pregnancy decreases the severity of infection. Many women who are infected in the first trimester elect termination of pregnancy. Those who do not terminate pregnancy are offered prenatal antibiotic therapy to reduce the frequency and severity of *Toxoplasma* infection in the infant. The optimal duration of treatment for a child with asymptomatic congenital toxoplasmosis is not clear, although most clinicians in the United States would treat the child for 1 year in light of cohort investigations conducted by the National Collaborative Chicago-Based Congenital Toxoplasmosis Study.

INFECTION IN IMMUNOCOMPETENT PATIENTS

Immunologically competent adults and older children who have only lymphadenopathy do not require specific therapy unless they have persistent, severe symptoms. Patients with ocular toxoplasmosis are usually treated for 1 month with pyrimethamine plus either sulfadiazine or clindamycin and sometimes with prednisone. Treatment should be supervised by an ophthalmologist familiar with *Toxoplasma* disease. Ocular disease can be self-limited without treatment, but therapy is typically considered for lesions that are severe or close to the fovea or optic disc. Prolonged treatment may prevent recurrences of ocular toxoplasmosis, but whether treatment improves long-term visual outcomes is unclear.

INFECTION IN IMMUNOCOMPROMISED PATIENTS

Primary Prophylaxis Patients with AIDS should be treated for acute toxoplasmosis; in immunocompromised patients, toxoplasmosis is rapidly fatal if untreated. Despite their toxicity, the drugs used to treat TE were required for survival prior to cART. The incidence of TE has declined as the survival of patients with HIV infection has increased through the use of cART.

In Africa, many patients are diagnosed with HIV infection only after developing opportunistic infections. Hence, the optimal management of these opportunistic infections is important if the benefits of subsequent cART are to be realized. The incidence of TE in under-resourced settings is unknown because

serologic testing and imaging are not available. AIDS patients who are seropositive for *T. gondii* and who have a CD4+ T lymphocyte count of <100/μL should receive prophylaxis against TE.

Of the currently available agents, trimethoprim-sulfamethoxazole (TMP-SMX) appears to be an effective alternative for treatment of TE in resource-poor settings where the preferred combination of pyrimethamine plus sulfadiazine is not available. The daily dose of TMP-SMX (one double-strength tablet) recommended for prophylaxis of PcP is effective against TE. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which likewise is effective against PcP. Atovaquone with or without pyrimethamine also can be considered. Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, clarithromycin, or aerosolized pentamidine is probably insufficient. AIDS patients who are seronegative for *Toxoplasma* and are not receiving prophylaxis for PcP should be retested for IgG antibody to *Toxoplasma* if their CD4+ T cell count drops to <100/μL. If seroconversion has taken place, then the patient should be given prophylaxis as described above.

Discontinuing Primary Prophylaxis Current studies indicate that prophylaxis against TE can be discontinued in patients who have responded to cART and whose CD4+ T lymphocyte count has been >200/μL for 3 months. Although patients with CD4+ T lymphocyte counts of <100/μL are at greatest risk for developing TE, the risk that this condition will develop when the count has increased to 100–200/μL has not been established. Thus, prophylaxis should be discontinued when the count has increased to >200/μL. Discontinuation of therapy reduces the pill burden; the potential for drug toxicity, drug interaction, or selection of drug-resistant pathogens; and cost. Prophylaxis should be recommenced if the CD4+ T lymphocyte count again decreases to <100–200/μL.

Individuals who have completed initial therapy for TE should receive treatment indefinitely unless immune reconstitution, with a CD4+ T cell count of >200/μL, occurs as a consequence of cART. Combination therapy with pyrimethamine plus sulfadiazine plus leucovorin is effective for this purpose. An alternative to sulfadiazine in this regimen is clindamycin.

Discontinuing Secondary Prophylaxis (Long-Term Maintenance Therapy) Patients receiving secondary prophylaxis for TE are at low risk for recurrence when they have completed initial therapy for TE, remain asymptomatic, and have evidence of restored immune function. Individuals with HIV infection should have a CD4+ T lymphocyte count of >200/μL for at least 6 months after cART. This recommendation is consistent with more extensive data indicating the safety of discontinuing secondary prophylaxis for other opportunistic infections during advanced HIV disease. A repeat MRI brain scan is recommended. Secondary prophylaxis should be reintroduced if the CD4+ T lymphocyte count decreases to <200/μL.

PREVENTION

All HIV-infected persons should be counseled regarding sources of *Toxoplasma* infection. The chances of primary infection with *Toxoplasma* can be reduced by not eating undercooked meat and by avoiding oocyst-contaminated material (i.e., a cat's litter box). Specifically, lamb, beef, and pork should be cooked to an internal temperature of 165–170°F (74–77°C); from a more practical perspective, meat cooked until it is no longer pink inside usually satisfies this requirement. Hands should be washed thoroughly after work in the garden, and all fruits and vegetables should be washed. Ingestion of raw shellfish is a risk factor for toxoplasmosis, given that the filter-feeding mechanism of clams and mussels concentrates oocysts.

If the patient owns a cat, the litter box should be cleaned or changed daily, preferably by an HIV-negative, nonpregnant person; alternatively, patients should wash their hands thoroughly after changing the litter box. Litter boxes should be changed daily if possible, as freshly excreted oocysts will not have sporulated and will not be infectious. Patients should be encouraged to keep their cats inside and not to adopt or handle stray cats. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis. Blood intended for transfusion into *Toxoplasma*-seronegative immunocompromised individuals should be screened for antibody to *T. gondii*. Although such serologic screening is not routinely performed, seronegative women should be screened for evidence of infection several times during pregnancy if they are exposed to environmental conditions that put them at risk for infection with *T. gondii*. HIV-positive individuals should adhere closely to these preventive measures.

Acknowledgment

The author would like to acknowledge Dr. Lloyd Kasper for his numerous contributions to our understanding of the pathogenesis of toxoplasmosis and his essential role in preparation of this chapter for prior editions.

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224 Protozoal Intestinal Infections and Trichomoniasis

Peter F. Weller

PROTOZOAL INFECTIONS

GIARDIASIS

Giardia intestinalis (also known as *G. lamblia* or *G. duodenalis*) is a cosmopolitan protozoal parasite that inhabits the small intestines of humans and other mammals. Giardiasis is one of the most common parasitic diseases in both developed and developing countries worldwide, causing both endemic and epidemic intestinal disease and diarrhea.

Life Cycle and Epidemiology (Fig. 224-1) Infection follows the ingestion of environmentally hardy cysts, which excyst in the small intestine, releasing flagellated trophozoites (Fig. 224-2) that multiply by binary fission. *Giardia* remains a pathogen of the proximal small bowel and does not disseminate hematogenously. Trophozoites remain free in the lumen or attach to the mucosal epithelium by means of a ventral sucking disk. As a trophozoite encounters altered conditions, it forms a morphologically distinct cyst, which is the stage of the parasite usually found in the feces. Trophozoites may be present and even predominate in loose or watery stools, but it is the resistant cyst that survives outside the body and is responsible for transmission. Cysts do not tolerate heating or desiccation, but they do remain viable for months in cold fresh water. The number of cysts excreted varies widely but can approach 10^7 per gram of stool.

Ingestion of as few as 10 cysts is sufficient to cause infection in humans. Because cysts are infectious when excreted, person-to-person transmission occurs where fecal hygiene is poor. Giardiasis is especially prevalent in day-care centers; person-to-person spread also takes place in other institutional settings with poor fecal hygiene and during anal–oral contact. If food is contaminated with *Giardia* cysts after cooking or preparation, food-borne transmission can occur. Waterborne transmission accounts for episodic infections (e.g., in campers and travelers)

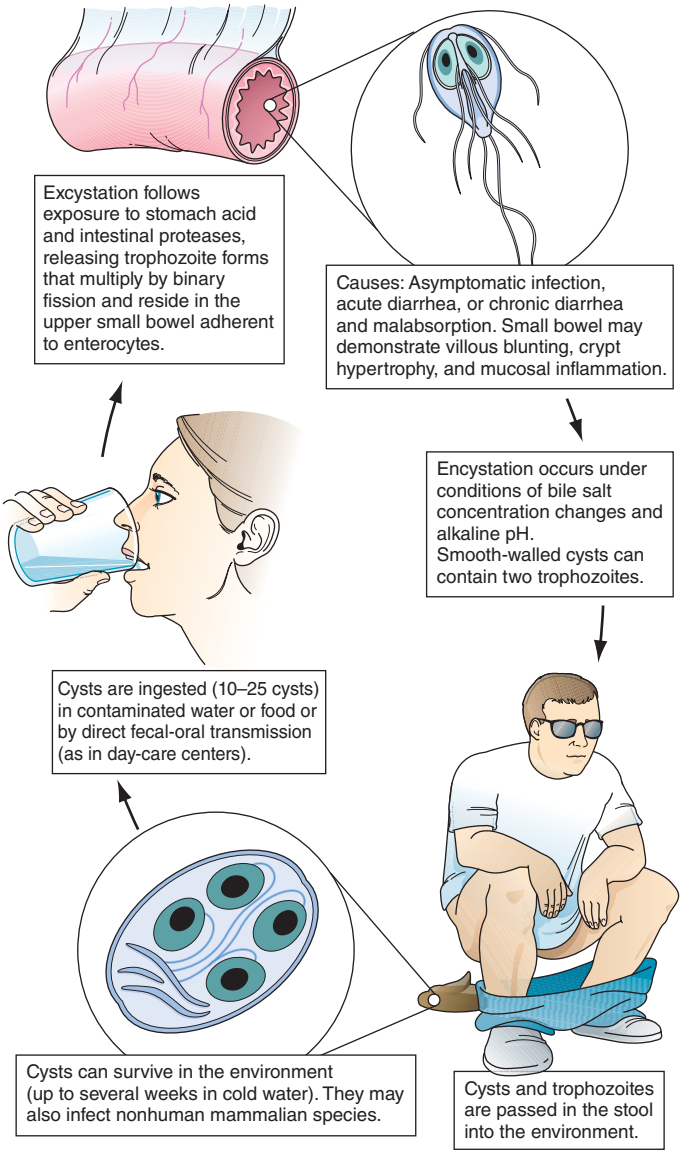

FIGURE 224-1 Life cycle of *Giardia*. *(Reprinted with permission from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 987. © 2006, with permission from Elsevier Science.)*

and for major epidemics in metropolitan areas. Surface water, ranging from mountain streams to large municipal reservoirs, can become contaminated with fecally derived *Giardia* cysts. The efficacy of water as a means of transmission is enhanced by the small infectious inoculum of *Giardia*, the prolonged survival of cysts in cold water, and the resistance of cysts to killing by routine chlorination methods that are adequate for controlling bacteria. Viable cysts can be eradicated from water by either boiling or filtration.

FIGURE 224-2 Flagellated, binucleate *Giardia* trophozoites.

In the United States, *Giardia* (like *Cryptosporidium*; see below) is a common cause of waterborne epidemics of gastroenteritis. *Giardia* is common in developing countries, and infections may be acquired by travelers.

There are several recognized genotypes or assemblages of *G. intestinalis*. Human infections are due to assemblages A and B, whereas other assemblages are more common in other animals, including cats and dogs. Like beavers from reservoirs implicated in epidemics, dogs and cats have been found to be infected with assemblages A and B; this finding suggests both that these animals may have been infected from human sources and that they might be sources of further human infections.

Giardiasis, like cryptosporidiosis, creates a significant economic burden because of the costs incurred in the installation of water filtration systems required to prevent waterborne epidemics, in the management of epidemics that involve large communities, and in the evaluation and treatment of endemic infections.

Pathophysiology The reasons that some, but not all, infected patients develop clinical manifestations and the mechanisms by which *Giardia* causes alterations in small-bowel function are largely unknown. Although trophozoites adhere to the epithelium, they are not invasive but may elicit apoptosis of enterocytes, epithelial barrier dysfunction, and epithelial cell malabsorption and secretion. Consequent lactose intolerance and, in a minority of infected adults and children, significant malabsorption are clinical signs of the loss of brush-border enzyme activities. In most infections, the morphology of the bowel is unaltered; however, in chronically infected, symptomatic patients, the histopathologic findings (including flattened villi) and the clinical manifestations at times resemble those of tropical sprue and gluten-sensitive enteropathy. The pathogenesis of diarrhea in giardiasis is not known.

The natural history of *Giardia* infection varies markedly. Infections may be aborted, transient, recurrent, or chronic. *G. intestinalis* parasites vary genotypically, and such variations might contribute to different courses of infection. Parasite as well as host factors may be important in determining the course of infection and disease. Both cellular and humoral responses develop in human infections, but their precise roles in disease pathogenesis and/or control of infection are unknown. Because patients with hypogammaglobulinemia suffer from prolonged, severe infections that are poorly responsive to treatment, humoral immune responses appear to be important. The greater susceptibilities of the young than of the old and of newly exposed persons than of chronically exposed populations suggest that at least partial protective immunity may develop.

Clinical Manifestations Disease manifestations of giardiasis range from asymptomatic carriage to fulminant diarrhea and malabsorption. Most infected persons are asymptomatic, but in epidemics the proportion of symptomatic cases may be higher. Symptoms may develop suddenly or gradually. In persons with acute giardiasis, symptoms develop after an incubation period that lasts at least 5–6 days and usually 1–3 weeks. Prominent early symptoms include diarrhea, abdominal pain, bloating, belching, flatus, nausea, and vomiting. Although diarrhea is common, upper intestinal manifestations such as nausea, vomiting, bloating, and abdominal pain may predominate. The duration of acute giardiasis is usually >1 week, although diarrhea often subsides. Individuals with chronic giardiasis may present with or without having experienced an antecedent acute symptomatic episode. Diarrhea is not necessarily prominent, but increased flatus, loose stools, sulfurous belching, and (in some instances) weight loss occur. Symptoms may be continual or episodic and may persist for years. Some persons who have relatively mild symptoms for long periods recognize the extent of their discomfort only in retrospect. Fever, the presence of blood and/or mucus in the stools, and other signs and symptoms of colitis are uncommon and suggest a different diagnosis or a concomitant illness. Symptoms tend to be intermittent yet recurring

and gradually debilitating, in contrast with the acute disabling symptoms associated with many enteric bacterial infections. Because of the less severe illness early on and the propensity for chronic infections, patients may seek medical advice late in the course of the illness; however, disease can be severe, resulting in malabsorption, weight loss, growth retardation, and dehydration. A number of extraintestinal manifestations have been described, such as urticaria, anterior uveitis, and arthritis; whether these are caused by giardiasis or concomitant processes is unclear.

Giardiasis can be severe in patients with hypogammaglobulinemia and can complicate other preexisting intestinal diseases, such as that occurring in cystic fibrosis. In patients with AIDS, *Giardia* can cause enteric illness that is refractory to treatment.

Diagnosis (Table 224-1) Giardiasis is diagnosed by detection of parasite antigens in the feces, by identification of cysts in the feces or of trophozoites in the feces or small intestines, or by nucleic acid amplification tests (NAATs). Cysts are oval, measure 8–12 μm × 7–10 μm, and characteristically contain four nuclei. Trophozoites are pear-shaped, dorsally convex, flattened parasites with two nuclei and four pairs of flagella (Fig. 224-2). The diagnosis is sometimes difficult to establish. Direct examination of fresh or properly preserved stools as well as concentration methods should be used. Because cyst excretion is variable and may be undetectable at times, repeated examination of stool, sampling of duodenal fluid, and biopsy of the small intestine may be required to detect the parasite. Tests for parasitic antigens in stool are at least as sensitive and specific as good microscopic examinations and are easier to perform. Newer NAATs are highly sensitive but are not always available for clinical use at present.

TREATMENT

Giardiasis

Cure rates with metronidazole (250 mg thrice daily for 5 days) are usually >90%. Tinidazole (2 g once by mouth) may be more effective than metronidazole. Nitazoxanide (500 mg twice daily for 3 days) is an alternative agent for treatment of giardiasis. Paromomycin, an oral aminoglycoside that is not well absorbed, can be given to symptomatic pregnant patients, although information is limited on how effectively this agent eradicates infection.

Almost all patients respond to therapy and are cured, although some with chronic giardiasis experience delayed resolution of symptoms after eradication of *Giardia*. For many of the latter patients, residual symptoms probably reflect delayed regeneration of intestinal brush-border enzymes. Continued infection should be documented by stool examinations before treatment is repeated. Patients who remain infected after repeated treatments should be evaluated for reinfection through family members, close personal contacts, and environmental sources as well as for hypogammaglobulinemia. In cases refractory to multiple treatment courses, prolonged therapy with metronidazole (750 mg thrice daily for 21 days) or therapy with varied combinations of multiple agents has been successful.

Prevention Giardiasis can be prevented by consumption of uncontaminated food and water and by personal hygiene during the provision of care for infected children. Boiling or filtering potentially contaminated water prevents infection.

CRYPTOSPORIDIOSIS

The coccidian parasite *Cryptosporidium* causes diarrheal disease that is self-limited in immunocompetent human hosts but can be severe in persons with AIDS or other forms of immunodeficiency. Two species of *Cryptosporidium*, *C. hominis* and *C. parvum*, cause most human infections.

Life Cycle and Epidemiology *Cryptosporidium* species are widely distributed in the world. Cryptosporidiosis is acquired by the consumption of oocysts (50% infectious dose: ~132 *C. parvum* oocysts in nonimmune individuals), which excyst to liberate sporozoites that in turn enter and infect intestinal epithelial cells. The parasite's further development involves both asexual and sexual cycles, which produce forms capable of infecting other epithelial cells and of generating oocysts that are passed in the feces. *Cryptosporidium* species infect a number of animals, and *C. parvum* can spread from infected animals to humans. Since oocysts are immediately infectious when passed in feces, person-to-person transmission takes place in day-care centers and among household contacts and medical providers. Waterborne transmission (especially that of *C. hominis*) accounts for infections in travelers and for common-source epidemics. Oocysts are quite hardy and resist killing by routine chlorination. Both drinking water and recreational water (e.g., pools, waterslides) have been increasingly recognized as sources of infection.

Pathophysiology Although intestinal epithelial cells harbor cryptosporidia in an intracellular vacuole, the means by which secretory diarrhea is elicited remain uncertain. No characteristic pathologic changes are found by biopsy. The distribution of infection can be spotty within the principal site of infection, the small bowel. Cryptosporidia are found in the pharynx, stomach, and large bowel of some patients and at times in the respiratory tract. Especially in patients with AIDS, involvement of the biliary tract can cause papillary stenosis, sclerosing cholangitis, or cholecystitis.

Clinical Manifestations Asymptomatic infections can occur in both immunocompetent and immunocompromised hosts. In immunocompetent persons, symptoms develop after an incubation period of ~1 week and consist principally of watery nonbloody diarrhea, sometimes in conjunction with abdominal pain, nausea, anorexia, fever, and/or weight loss. In these hosts, the illness usually subsides after 1–2 weeks. In contrast, in immunocompromised hosts (especially those with AIDS and CD4+ T cell counts <100/μL), diarrhea can be chronic, persistent, and remarkably profuse, causing clinically significant fluid and electrolyte depletion. Stool volumes may range from 1 to 25 L/d. Weight loss, wasting, and abdominal pain may be severe. Biliary tract involvement can manifest as mid-epigastric or right-upper-quadrant pain.

Diagnosis (Table 224-1) Evaluation starts with fecal examination for small oocysts, which are smaller (4–5 μm in diameter) than the fecal stages of most other parasites. Because conventional stool examination for ova and parasites (O+P) does not detect *Cryptosporidium*, specific testing must be requested. Detection is enhanced by evaluation of stools (obtained on multiple days) by several techniques, including modified acid-fast and direct immunofluorescent stains and enzyme immunoassays. Newer NAATs are being employed. Cryptosporidia can also be identified by light and electron microscopy at the apical surfaces of intestinal epithelium from biopsy specimens of the small bowel and, less frequently, the large bowel.

TABLE 224-1 Diagnosis of Intestinal Protozoal Infections

PARASITE	STOOL O+P[a]	FECAL ACID-FAST STAIN	FECAL ANTIGEN IMMUNOASSAYS	FECAL NAATS[b]	OTHER
Giardia	+		+	+	
Cryptosporidium	–	+	+	+	
Isospora	–	+		+	
Cyclospora	–	+		+	
Microsporidia	–			+	Special fecal stains, tissue biopsies

[a]O+P, ova and parasites. [b]Nucleic acid amplification tests.

TREATMENT

Cryptosporidiosis

Nitazoxanide, approved by the U.S. Food and Drug Administration (FDA) for the treatment of cryptosporidiosis, is available in tablet form for adults (500 mg twice daily for 3 days) and as an elixir for children. This agent has not been effective for the treatment of HIV-infected patients, in whom improved immune status due to antiretroviral therapy can lead to amelioration of cryptosporidiosis. Otherwise, treatment includes supportive care with replacement of fluids and electrolytes and administration of antidiarrheal agents. Biliary tract obstruction may require papillotomy or T-tube placement. Prevention requires minimizing exposure to infectious oocysts in human or animal feces. Use of submicron water filters may minimize acquisition of infection from drinking water.

CYSTOISOSPORIASIS

The coccidian parasite *Cystoisospora belli* causes human intestinal disease. Infection is acquired by the consumption of oocysts, after which the parasite invades intestinal epithelial cells and undergoes both sexual and asexual cycles of development. Oocysts excreted in stool are not immediately infectious but must undergo further maturation.

Although *C. belli* infects many animals, little is known about the epidemiology or prevalence of this parasite in humans. It is most common in tropical and subtropical countries. Acute infections can begin abruptly with fever, abdominal pain, and watery nonbloody diarrhea and can last for weeks or months. In patients who have AIDS or are immunocompromised for other reasons, infections often are not self-limited but rather resemble cryptosporidiosis, with chronic, profuse watery diarrhea. Eosinophilia, which is not found in other enteric protozoan infections, may be detectable. The diagnosis (Table 224-1) is usually made by detection of the large (~25 µm) oocysts in stool by modified acid-fast staining. Oocyst excretion may be low-level and intermittent; if repeated stool examinations are unrevealing, sampling of duodenal contents by aspiration or small-bowel biopsy (often with electron microscopic examination) may be necessary. NAATs are promising newer diagnostic tools.

TREATMENT

Cystoisosporiasis

Trimethoprim-sulfamethoxazole (TMP-SMX, 160/800 mg two times daily for 10 days; and, for HIV-infected patients, then continuing three times daily for 3 weeks) is effective. For patients intolerant of sulfonamides, pyrimethamine (50–75 mg/d) can be used. Relapses can occur in persons with AIDS and necessitate maintenance therapy with TMP-SMX (160/800 mg three times per week).

CYCLOSPORIASIS

Cyclospora cayetanensis, a cause of diarrheal illness, is globally distributed: illness due to *C. cayetanensis* has been reported in the United States, Asia, Africa, Latin America, and Europe. The epidemiology of this parasite has not yet been fully defined, but waterborne transmission and food-borne transmission (e.g., by basil, sweet peas, and imported raspberries) have been recognized. The full spectrum of illness attributable to *Cyclospora* has not been delineated. Some infected patients may be without symptoms, but many have diarrhea, flulike symptoms, and flatulence and belching. The illness can be self-limited, can wax and wane, or, in many cases, can involve prolonged diarrhea, anorexia, and upper gastrointestinal symptoms, with sustained fatigue and weight loss in some instances. Diarrheal illness may persist for >1 month. *Cyclospora* can cause enteric illness in patients infected with HIV.

The parasite is detectable in epithelial cells of small-bowel biopsy samples and elicits secretory diarrhea by unknown means. The absence of fecal blood and leukocytes indicates that disease due to *Cyclospora* is not caused by destruction of the small-bowel mucosa. The diagnosis (Table 224-1) can be made by detection of spherical 8- to 10-µm oocysts in the stool, although routine stool O+P examinations are not sufficient. Specific fecal examinations must be requested to detect the oocysts, which are variably acid-fast and are fluorescent when viewed with ultraviolet light microscopy. Newer NAATs are proving to be sensitive. Cyclosporiasis should be considered in the differential diagnosis of prolonged diarrhea, with or without a history of travel by the patient to other countries.

TREATMENT

Cyclosporiasis

Cyclosporiasis is treated with TMP-SMX (160/800 mg twice daily for 7–10 days). HIV-infected patients may experience relapses after such treatment and thus may require longer-term suppressive maintenance therapy.

MICROSPORIDIOSIS

Microsporidia are obligate intracellular spore-forming protozoa that infect many animals and cause disease in humans, especially as opportunistic pathogens in AIDS. Microsporidia are members of a distinct phylum, Microspora, which contains dozens of genera and hundreds of species. The various microsporidia are differentiated by their developmental life cycles, ultrastructural features, and molecular taxonomy based on ribosomal RNA. The complex life cycles of the organisms result in the production of infectious spores **(Fig. 224-3)**. Currently, eight genera of microsporidia—*Encephalitozoon*, *Pleistophora*, *Nosema*, *Vittaforma*, *Trachipleistophora*, *Anncalia*, *Microsporidium*, and *Enterocytozoon*—are recognized as causes of human disease. Although some microsporidia are probably prevalent causes of self-limited or asymptomatic infections in immunocompetent patients, little is known about how microsporidiosis is acquired.

Microsporidiosis is most common among patients with AIDS, less common among patients with other types of immunocompromise, and rare among immunocompetent hosts. In patients with AIDS, intestinal infections with *Enterocytozoon bieneusi* and *Encephalitozoon* (formerly *Septata*) *intestinalis* are recognized to contribute to chronic diarrhea and wasting; these infections have been found in 10–40% of patients with chronic diarrhea. Both organisms have been found in the biliary tracts of patients with cholecystitis. *E. intestinalis* may also disseminate to cause fever, diarrhea, sinusitis, cholangitis, and bronchiolitis. In patients with AIDS, *Encephalitozoon hellem* has caused superficial keratoconjunctivitis as well as sinusitis, respiratory tract disease, and disseminated infection. Myositis due to *Pleistophora* has been documented. *Nosema*, *Vittaforma*, and *Microsporidium* have caused stromal keratitis associated with trauma in immunocompetent patients.

Microsporidia are small gram-positive organisms with mature spores measuring 0.5–2 µm × 1–4 µm. Diagnosis of microsporidial infections in tissue often requires electron microscopy, although intracellular spores can be visualized by light microscopy with hematoxylin and eosin, Giemsa, or tissue Gram's stain. For the diagnosis of intestinal microsporidiosis, modified trichrome or chromotrope 2R–based staining and Uvitex 2B or calcofluor fluorescent staining reveal spores in smears of feces or duodenal aspirates. Definitive therapies for microsporidial infections remain to be established. For superficial keratoconjunctivitis due to *E. hellem*, topical therapy with fumagillin suspension has shown promise **(Chap. 217)**. For enteric infections with *E. bieneusi* and *E. intestinalis* in HIV-infected patients, therapy with albendazole may be efficacious **(Chap. 217)**.

OTHER INTESTINAL PROTOZOA

Balantidiasis *Balantidium coli* is a large ciliated protozoal parasite that can produce a spectrum of large-intestinal disease analogous to amebiasis. The parasite is widely distributed in the world. Since it infects pigs, cases in humans are more common where pigs are raised. Infective cysts can be transmitted from person to person and through water, but many cases are due to the ingestion of cysts derived from porcine feces in association with

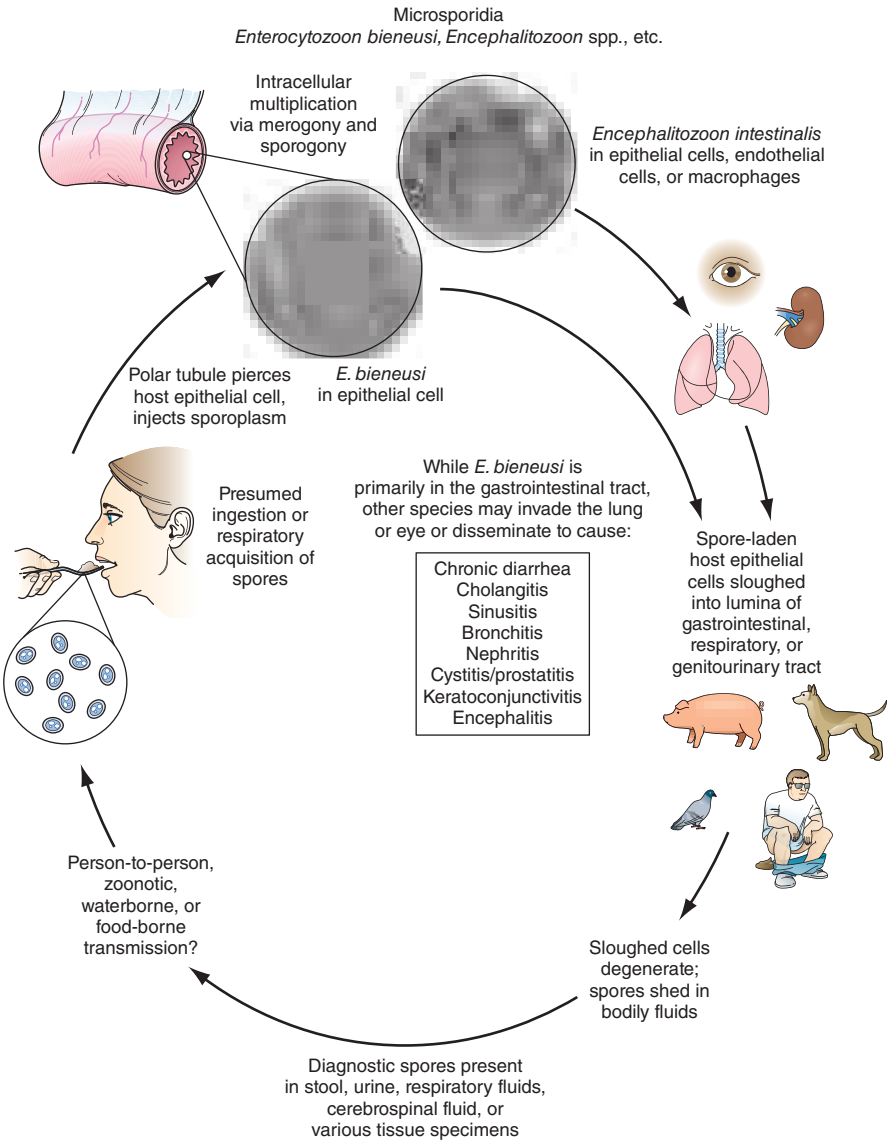

FIGURE 224-3 Life cycle of microsporidia. *(Reprinted with permission from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1128. © 2006, with permission from Elsevier Science.)*

slaughtering, with use of pig feces for fertilizer, or with contamination of water supplies by pig feces.

Ingested cysts liberate trophozoites, which reside and replicate in the large bowel. Many patients remain asymptomatic, but some have persisting intermittent diarrhea, and a few develop more fulminant dysentery. In symptomatic individuals, the pathology in the bowel—both gross and microscopic—is similar to that seen in amebiasis, with varying degrees of mucosal invasion, focal necrosis, and ulceration. Balantidiasis, unlike amebiasis, only rarely spreads hematogenously to other organs. The diagnosis is made by detection of the trophozoite stage in stool or sampled colonic tissue. Tetracycline (500 mg four times daily for 10 days) is an effective therapeutic agent.

Blastocystosis *Blastocystis hominis* remains an organism of uncertain pathogenicity. Some patients who pass *B. hominis* in their stools are asymptomatic, whereas others have diarrhea and associated intestinal symptoms. Diligent evaluation reveals other potential bacterial, viral, or protozoal causes of diarrhea in some but not all patients with symptoms. Because the pathogenicity of *B. hominis* is uncertain and because therapy for *Blastocystis* infection is neither specific nor uniformly effective, patients with prominent intestinal symptoms should be fully evaluated for other infectious causes of diarrhea. If diarrheal symptoms associated with *Blastocystis* are prominent, either metronidazole (750 mg thrice daily for 10 days) or TMP-SMX (160 mg/800 mg twice daily for 7 days) can be used.

Dientamoebiasis *Dientamoeba fragilis* is unique among intestinal protozoa in that it has a trophozoite stage but not a cyst stage. How trophozoites survive to transmit infection is not known. When symptoms develop in patients with *D. fragilis* infection, they are generally mild and include intermittent diarrhea, abdominal pain, and anorexia. The diagnosis is made by the detection of trophozoites in stool; the lability of these forms accounts for the greater yield when fecal samples are preserved immediately after collection. Since fecal excretion rates vary, examination of several samples obtained on alternate days increases the rate of detection. Iodoquinol (650 mg three times daily for 20 days) or paromomycin (25–35 mg/kg per day in three doses for 7 days) is appropriate for treatment.

TRICHOMONIASIS

Various species of trichomonads can be found in the mouth (in association with periodontitis) and occasionally in the gastrointestinal tract. *Trichomonas vaginalis*—one of the most prevalent protozoal parasites in the United States—is a pathogen of the genitourinary tract and a major cause of symptomatic vaginitis (Chap. 131).

Life Cycle and Epidemiology *T. vaginalis* is a pear-shaped, actively motile organism that measures about 10 × 7 μm, replicates by binary fission, and inhabits the lower genital tract of females and the urethra and prostate of males. In the United States, it accounts for ~3 million infections per year in women. While the organism can survive for a few hours in moist environments and could be acquired by direct contact, person-to-person venereal transmission accounts for virtually all cases of trichomoniasis. Its prevalence is greatest among persons with multiple sexual partners and among those with other sexually transmitted diseases (Chap. 131).

Clinical Manifestations Many men infected with *T. vaginalis* are asymptomatic, although some develop urethritis and a few have epididymitis or prostatitis. In contrast, infection in women, which has an incubation period of 5–28 days, is usually symptomatic and manifests with malodorous vaginal discharge (often yellow), vulvar erythema and itching, dysuria or urinary frequency (in 30–50% of patients), and dyspareunia. These manifestations, however, do not clearly distinguish trichomoniasis from other types of infectious vaginitis.

Diagnosis Detection of motile trichomonads by microscopic examination of wet mounts of vaginal or prostatic secretions has been the conventional means of diagnosis. Although this approach provides an immediate diagnosis, its sensitivity for the detection of *T. vaginalis* is only ~50–60% in routine evaluations of vaginal secretions. Direct immunofluorescent antibody staining is more sensitive (70–90%) than wet-mount examinations. *T. vaginalis* can be recovered from the urethra of both males and females and is detectable in males after prostatic massage. NAATs are FDA approved and are highly sensitive and specific for urine and for endocervical and vaginal swabs from women.

TREATMENT

Trichomoniasis

Metronidazole (either a single 2-g dose or 500-mg doses twice daily for 7 days) or tinidazole (a single 2-g dose) is effective. All sexual partners must be treated concurrently to prevent reinfection,

especially from asymptomatic males. In males with persistent symptomatic urethritis after therapy for nongonococcal urethritis, metronidazole therapy should be considered for possible trichomoniasis. Alternatives to metronidazole for treatment during pregnancy are not readily available. Reinfection often accounts for apparent treatment failures, but strains of *T. vaginalis* exhibiting high-level resistance to metronidazole have been encountered. Treatment of these resistant infections with higher oral doses, parenteral doses, or concurrent oral and vaginal doses of metronidazole or with tinidazole has been successful.

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Section 19 Helminthic Infections

225 Introduction to Helminthic Infections

Peter F. Weller

The word *helminth* is derived from the Greek *helmins* ("parasitic worm"). Helminthic worms are highly prevalent and, depending on the species, may exist as free-living organisms or as parasites of plant or animal hosts. The parasitic helminths have co-evolved with specific mammalian and other host species. Accordingly, most helminthic infections are restricted to nonhuman hosts, and only rarely do these zoonotic helminths accidentally cause human infections.

Helminthic parasites of humans belong to two phyla: Nemathelminthes, which includes nematodes (roundworms), and Platyhelminthes, which includes cestodes (tapeworms) and trematodes (flukes). Helminthic parasites of humans reside within the human body and hence are the cause of true infections. In contrast, parasites of other genera that reside only on mucocutaneous surfaces of humans (e.g., the parasites causing myiasis and scabies) are considered to represent infestations rather than infections.

Helminthic parasites differ substantially from protozoan parasites in several respects. First, protozoan parasites are unicellular organisms, whereas helminthic parasites are multicellular worms that possess differentiated organ systems. Second, helminthic parasites have complex life cycles that require sequential stages of development outside the human host. Thus, most helminths do not complete their replication within the human host; rather, they develop to a certain stage within the mammalian host and, as part of their obligatory life cycle, must mature further outside that host. During the "extra-human" stages of their life cycle, helminths exist either as free-living organisms or as parasites within another host species and thereafter mature into new developmental stages capable of infecting humans. Thus, with only two exceptions (*Strongyloides stercoralis* and *Capillaria philippinensis*, which are capable of internal human reinfections), increases in the number of adult helminths (i.e., the "worm burden") within the human host require repeated exogenous reinfections. In the case of protozoan parasites, a brief, even singular exposure (e.g., a single mosquito bite transmitting malaria) may lead rapidly to intense parasite loads and overwhelming infections; in contrast, for all but the two helminths noted above, increases in worm burden require multiple and usually ongoing exposures to infectious forms, such as ingestion of eggs of intestinal helminths or waterborne exposures to infectious cercariae of *Schistosoma mansoni*. This requirement is germane both to the consideration of helminthic infections in individuals and to ongoing global efforts to interrupt and/or minimize the acquisition of helminthic infections by humans.

Third, helminthic infections have a predilection toward stimulation of host immune responses that elicit eosinophilia within human tissues and blood. The many protozoan infections characteristically do not elicit eosinophilia in infected humans, with only three exceptions (two intestinal protozoan parasites, *Cystoisospora belli* and *Dientamoeba fragilis*, and tissue-borne *Sarcocystis* species). The magnitude of helminth-elicited eosinophilia tends to correlate with the extent of tissue invasion by larvae or adult helminths. For example, in several helminthic infections, including acute schistosomiasis (Katayama syndrome), paragonimiasis, and hookworm and *Ascaris* infections, eosinophilia is most pronounced during the early phases of infection, when migrations of infecting larvae and progression of subsequent developmental stages through the tissues are greatest. In established infections, local eosinophilia is often present around helminths in tissues, but blood eosinophilia may be intermittent, mild, or absent. In helminthic infections in which parasites are well contained within tissues (e.g., echinococcal cysts) or confined within the lumen of the intestinal tract (e.g., adult *Ascaris* or tapeworms), eosinophilia is usually absent.

NEMATODES

Nematodes are nonsegmented roundworms. Species of nematodes are remarkably diverse and abundant in nature. Among the many thousands of nematode species, few are parasites of humans. Most nematodes are free-living, and these species have variably evolved to survive in diverse ecologic niches, including saltwater, freshwater, or soil. The well-studied organism *Caenorhabditis elegans* is a free-living nematode. Nematodes can be either beneficial or deleterious parasites of plants. Parasitic nematodes have co-evolved with specific mammalian hosts and have no capacity to live their full life cycles in other hosts. Uncommonly, humans are exposed to infectious stages of nonhuman nematode parasites, and the resultant zoonotic nematode infections can elicit inflammatory and immune responses as larval forms migrate and die in the unsuitable human host. Examples include pulmonary coin lesions due to mosquito-transmitted infections with the dog heartworm *Dirofilaria immitis*; eosinophilic meningoencephalitis due to ingested eggs of the raccoon ascarid *Baylisascaris procyonis*; and eosinophilic meningitis due to ingestion of larvae of the rat lungworm *Angiostrongylus cantonensis*.

Nematode parasites of humans include worms that reside in the intestinal tract or localize in extraintestinal vascular or tissue sites. Roundworms are bisexual, with separate male and female forms (except for *S. stercoralis*, whose adult females are hermaphroditic in the human intestinal tract). Depending on the species, fertilized females release either larvae or eggs containing larvae. Nematodes have five developmental stages: an adult stage and four sequential larval stages. These parasites characteristically are surrounded by a durable outer cuticular layer. Nematodes have a nervous system; a muscular system, including muscle cells under the cuticle; and a developed intestinal tract, including an oral cavity and an elongated gut that ends in an anal pore.

Adults may range in size from minute to >1 meter in length (with *Dracunculus medinensis*, for example, at the long end of this spectrum).

Humans acquire infections with nematode parasites by various routes, depending on the parasitic species. Ingestion of eggs passed in human feces is a major global health problem with many of the intestinal helminths (e.g., *Ascaris lumbricoides).* In other species, infecting larvae penetrate skin exposed to fecally contaminated soil (e.g., *S. stercoralis*, hookworms) or traverse the skin after the bite of infected insect vectors (e.g., filariae). Some nematode infections are acquired by consumption of specific animal-derived foods (e.g., trichinellosis from raw or undercooked pork or wild carnivorous mammals). As noted above, only two nematodes, *S. stercoralis* and *C. philippinensis*, can internally reinfect humans; thus, for all other nematodes, any increases in worm burden must be due to continued exogenous reinfections.

CESTODES

Tapeworms are the cestode parasites of humans. Adult tapeworms are elongated, segmented, hermaphroditic flatworms that reside in the intestinal lumen or, in their larval forms, may live in extraintestinal tissues. Tapeworms include a head (*scolex*) and a number of attached segments (*proglottids*). The worms attach to the intestinal tract via their scolices, which may possess suckers, hooks, or grooves. The scolex is the site of formation of new proglottids. Tapeworms do not have a functional gut tract; rather, each tapeworm segment passively and actively obtains nutrients through its specialized surface tegument. Mature proglottids possess both male and female sex organs, but insemination usually occurs between adjacent proglottids. Fertilized proglottids release eggs that are passed in the feces. When ingested by an intermediate host, an egg releases an oncosphere that penetrates the gut and develops further in tissues as a cysticercus. Humans acquire infection by ingesting animal tissues that contain cysticerci, and the resultant tapeworms develop and reside in the proximal small bowel (e.g., *Taenia solium*, *T. saginata*). Alternatively, if humans ingest eggs of these cestodes that have been passed in human or animal feces, oncospheres develop and can cause space-occupying extraintestinal cystic lesions in tissues; examples include cysticercosis due to *T. solium* and hydatid disease due to species of *Echinococcus*.

TREMATODES

Trematodes of medical importance include blood flukes, intestinal flukes, and tissue flukes. Adult flukes are often leaf-shaped flatworms. Oral and/or ventral suckers help adult flukes maintain their positions in situ. Flukes have an oral cavity but no distal anal pore. Nutrients are obtained both through their integument and by ingestion into the blind intestinal tract. Flukes are hermaphroditic except for blood flukes (schistosomes), which are bisexual. Eggs are passed in human feces (*Fasciola*, *Fasciolopsis*, *Clonorchis*, *Schistosoma japonicum*, *S. mansoni*), urine (*Schistosoma haematobium*), or sputum and feces (*Paragonimus*). Expelled eggs release miracidia—usually in water—that infect specific snail species. Within snails, parasites multiply and cercariae are released. Depending on the species, cercariae can penetrate the skin (schistosomes) or can develop into metacercariae that can be ingested with plants (e.g., watercress for *Fasciola*) or with fish (*Clonorchis*) or crabs (*Paragonimus*).

CONCLUSION

Many of the so-called neglected tropical diseases are due to helminthic infections. The health impacts of many helminthic infections are varied and are based on the frequent need for repeated exposures to increase the worm burdens in infected humans. In global regions where exposures to specific helminths occur even in childhood (e.g., fecally derived intestinal nematodes, mosquito-transmitted filariae, or waterborne snail-transmitted schistosomes), the morbidities in infected individuals can include nutritional, developmental, cognitive, and functional impairments. Ongoing global mass-treatment programs are currently aimed at diminishing the local prevalences of specific helminths and their consequent impacts on the health of local populations.

226 Trichinellosis and Other Tissue Nematode Infections

Peter F. Weller

Nematodes are elongated, symmetric roundworms. Parasitic nematodes of medical significance may be broadly classified as either predominantly intestinal or tissue nematodes. The intestinal nematodes are covered in **Chap. 227**. This chapter covers the tissue nematodes that cause trichinellosis, visceral and ocular larva migrans, cutaneous larva migrans, cerebral angiostrongyliasis, and gnathostomiasis. All of these zoonotic infections result from incidental exposure to infectious nematodes. The clinical symptoms of these infections are due largely to invasive larval stages that (except in the case of *Trichinella*) do not reach maturity in humans.

TRICHINELLOSIS

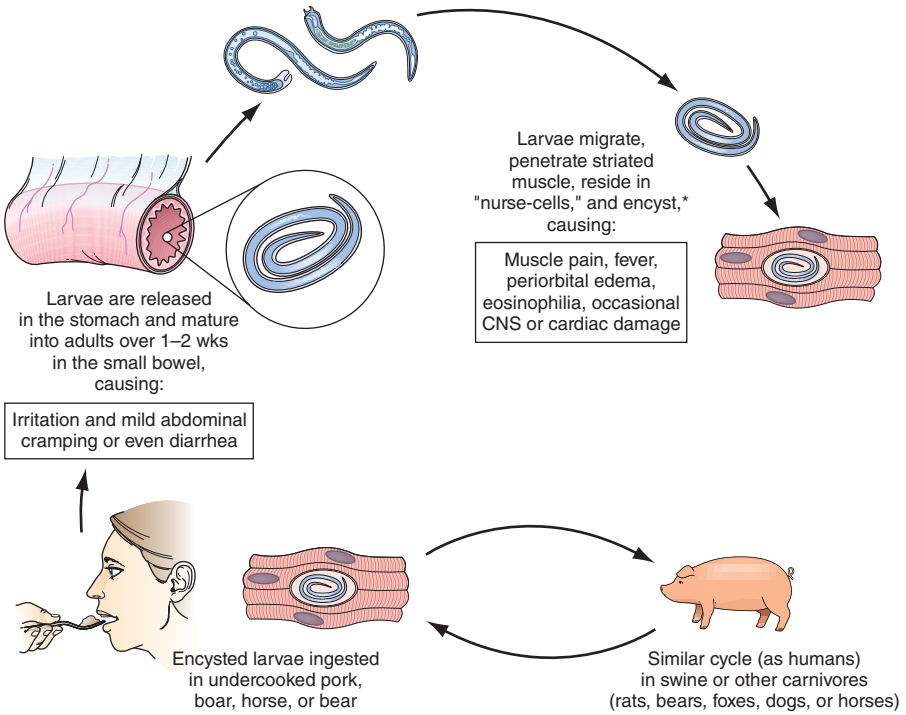
Trichinellosis develops after the ingestion of meat containing cysts of *Trichinella* (e.g., pork or other meat from a carnivore). Although most infections are mild and asymptomatic, heavy infections can cause severe enteritis, periorbital edema, myositis, and (infrequently) death.

Life Cycle and Epidemiology Eight species of *Trichinella* are recognized as causes of infection in humans. Two species are distributed worldwide: *T. spiralis*, which is found in a great variety of carnivorous and omnivorous animals, and *T. pseudospiralis*, which is found in mammals and birds. *T. nativa* is present in Arctic regions and infects bears; *T. nelsoni* is found in equatorial eastern Africa, where it is common among felid predators and scavengers such as hyenas and bush pigs; and *T. britovi* is found in Europe, western Africa, and western Asia among carnivores but not among domestic swine. *T. murrelli* is present in North American game animals.

After human consumption of trichinous meat, encysted larvae are liberated by digestive acid and proteases **(Fig. 226-1)**. The larvae invade the small-bowel mucosa and mature into adult worms. After ~1 week, female worms release newborn larvae that migrate via the circulation to striated muscle. The larvae of all species except *T. pseudospiralis*, *T. papuae*, and *T. zimbabwensis* then encyst by inducing a radical transformation in the muscle cell architecture. Although host immune responses may help to expel intestinal adult worms, they have few deleterious effects on muscle-dwelling larvae.

Human trichinellosis is often caused by the ingestion of infected pork products and thus can occur in almost any location where the meat of domestic or wild swine is eaten. Human trichinellosis may also be acquired from the meat of other animals, including dogs (in parts of Asia and Africa), horses (in Italy and France), and bears and walruses (in northern regions). Although cattle (being herbivores) are not natural hosts of *Trichinella*, beef has been implicated in outbreaks when contaminated or adulterated with trichinous pork. Laws that prohibit the feeding of uncooked garbage to pigs have greatly reduced the transmission of trichinellosis in the United States. About 12 cases of trichinellosis are reported annually in this country, but most mild cases probably remain undiagnosed. Recent U.S. and Canadian outbreaks have been attributable to consumption of wild game (especially bear meat) and, less frequently, of pork.

Pathogenesis and Clinical Features Clinical symptoms of trichinellosis arise from the successive phases of parasite enteric invasion, larval migration, and muscle encystment (Fig. 226-1). Most light infections (those with <10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve >50 larvae per gram of muscle) can be life-threatening. Invasion of the gut by large numbers of parasites occasionally provokes diarrhea during the first week after infection. Abdominal pain, constipation, nausea, or vomiting also may be prominent.



T. papuae, T. zimbabwensis, and *T. pseudospiralis* do not encyst.

FIGURE 226-1 Life cycle of *Trichinella* *spiralis* (cosmopolitan); *nelsoni* (equatorial Africa); *britovi* (Europe, western Africa, western Asia); *nativa* (Arctic); *murrelli* (North America); *papuae* (Papua New Guinea); *zimbabwensis* (Tanzania); and *pseudospiralis* (cosmopolitan). CNS, central nervous system. *(Reprinted from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1218. © 2006, with permission from Elsevier Science.)*

Symptoms due to larval migration and muscle invasion begin to appear in the second week after infection. The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophilia. Periorbital and facial edema is common, as are hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea, or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure—and, less commonly, encephalitis or pneumonitis—may develop and accounts for most deaths of patients with trichinellosis.

Upon onset of larval encystment in muscle 2–3 weeks after infection, symptoms of myositis with myalgias, muscle edema, and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the extraocular muscles; the biceps; and the muscles of the jaw, neck, lower back, and diaphragm. Peaking ~3 weeks after infection, symptoms subside only gradually during a prolonged convalescence. Uncommon infections with *T. pseudospiralis*, whose larvae do not encapsulate in muscles, elicit prolonged polymyositis-like illness.

Laboratory Findings and Diagnosis Blood eosinophilia develops in >90% of patients with symptomatic trichinellosis and may peak at a level of >50% 2–4 weeks after infection. Serum levels of muscle enzymes, including creatine phosphokinase, are elevated in most symptomatic patients. Patients should be questioned thoroughly about their consumption of pork or wild animal meat and about illness in other individuals who ate the same meat. A presumptive clinical diagnosis can be based on fevers, eosinophilia, periorbital edema, and myalgias after a suspect meal. A rise in the titer of parasite-specific antibody, which usually does not occur until after the third week of infection, confirms the diagnosis. Alternatively, a definitive diagnosis requires surgical biopsy of at least 1 g of involved muscle; the yields are highest near tendon insertions. The fresh muscle tissue should be compressed between glass slides and examined microscopically (Fig. 226-2) because larvae may be missed by examination of routine histopathologic sections alone.

TREATMENT

Trichinellosis

Most lightly infected patients recover uneventfully with bed rest, antipyretics, and analgesics. Glucocorticoids like prednisone (Table 226-1) are beneficial for severe myositis and myocarditis. Mebendazole and albendazole are active against enteric stages of the parasite, but their efficacy against encysted larvae has not been conclusively demonstrated.

Prevention Larvae are usually killed by cooking pork until it is no longer pink or by freezing it at –15°C for 3 weeks. However, Arctic

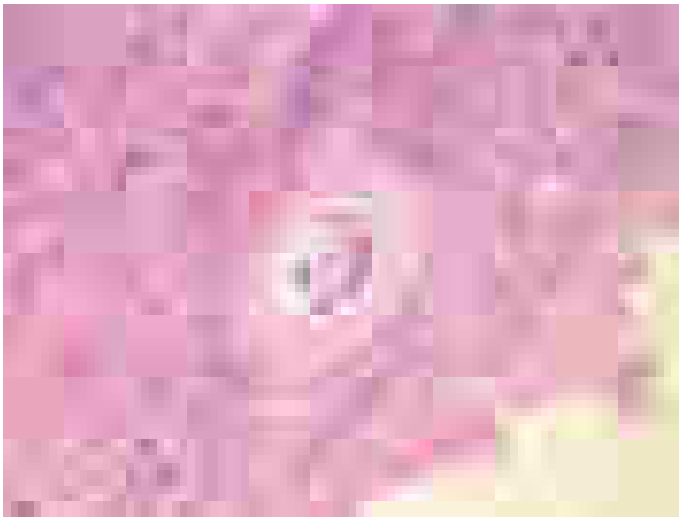


FIGURE 226-2 *Trichinella* larva encysted in a characteristic hyalinized capsule in striated muscle tissue. *(Photo/Wadsworth Center, New York State Department of Health. Reprinted from MMWR 53:606, 2004; public domain.)*

TABLE 226-1 Therapy for Tissue Nematode Infections

INFECTION	SEVERITY	TREATMENT
Trichinellosis	Mild	Supportive
	Moderate	Albendazole (400 mg bid × 8–14 days) *or*
		Mebendazole (200–400 mg tid × 3 days, then 400 mg tid × 8–14 days)
	Severe	Add glucocorticoids (e.g., prednisone, 1 mg/kg qd × 5 days)
Visceral larva migrans	Mild to moderate	Supportive
	Severe	Glucocorticoids (as above)
	Ocular	Not fully defined; albendazole (800 mg bid for adults, 400 mg bid for children) with glucocorticoids × 5–20 days has been effective
Cutaneous larva migrans		Ivermectin (single dose, 200 µg/kg) *or*
		Albendazole (200 mg bid × 3 days)
Angiostrongyliasis	Mild to moderate	Supportive
	Severe	Glucocorticoids (as above)
Gnathostomiasis		Ivermectin (200 µg/kg per day × 2 days) *or*
		Albendazole (400 mg bid × 21 days)

T. nativa larvae in walrus or bear meat are relatively resistant and may remain viable despite freezing.

VISCERAL AND OCULAR LARVA MIGRANS

Visceral larva migrans is a syndrome caused by nematodes that are normally parasitic for nonhuman host species. In humans, these nematode larvae do not develop into adult worms but instead migrate through host tissues and elicit eosinophilic inflammation. The most common form of visceral larva migrans is toxocariasis due to larvae of the canine ascarid *Toxocara canis*; the syndrome is due less commonly to the feline ascarid *T. cati* and even less commonly to the pig ascarid *Ascaris suum*. Rare cases with eosinophilic meningoencephalitis have been caused by the raccoon ascarid *Baylisascaris procyonis*.

Life Cycle and Epidemiology The canine roundworm *T. canis* is distributed among dogs worldwide. Ingestion of infective eggs by dogs is followed by liberation of *Toxocara* larvae, which penetrate the gut wall and migrate intravascularly into canine tissues, where most remain in a developmentally arrested state. During pregnancy, some larvae resume migration in bitches and infect puppies prenatally (through transplacental transmission) or after birth (through suckling). Thus, in lactating bitches and puppies, larvae return to the intestinal tract and develop into adult worms, which produce eggs that are released in the feces. Eggs must undergo embryonation over several weeks to become infectious. Humans acquire toxocariasis mainly by eating soil contaminated by puppy feces that contains infective *T. canis* eggs. Visceral larva migrans is most common among children who habitually eat dirt.

Pathogenesis and Clinical Features Clinical disease most commonly afflicts preschool children. After humans ingest *Toxocara* eggs, the larvae hatch and penetrate the intestinal mucosa, from which they are carried by the circulation to a wide variety of organs and tissues. The larvae invade the liver, lungs, central nervous system (CNS), and other sites, provoking intense local eosinophilic granulomatous responses. The degree of clinical illness depends on larval number and tissue distribution, reinfection, and host immune responses. Most light infections are asymptomatic and may be evidenced only by blood eosinophilia. Characteristic symptoms of visceral larva migrans include fever, malaise, anorexia and weight loss, cough, wheezing, and rashes. Hepatosplenomegaly is common. These features may be accompanied by extraordinary peripheral eosinophilia at levels that may approach 90%. Uncommonly, seizures or behavioral disorders develop. Rare deaths are due to severe neurologic, pneumonic, or myocardial involvement.

The ocular form of the larva migrans syndrome occurs when *Toxocara* larvae invade the eye. An eosinophilic granulomatous mass, most commonly in the posterior pole of the retina, develops around the entrapped larva. The retinal lesion can mimic retinoblastoma in appearance, and mistaken diagnosis of the latter condition can lead to unnecessary enucleation. The spectrum of eye involvement also includes endophthalmitis, uveitis, and chorioretinitis. Unilateral visual disturbances, strabismus, and eye pain are the most common presenting symptoms. In contrast to visceral larva migrans, ocular toxocariasis usually develops in older children or young adults with no history of pica; these patients seldom have eosinophilia or visceral manifestations.

Diagnosis In addition to eosinophilia, leukocytosis and hypergammaglobulinemia may be evident. Transient pulmonary infiltrates are apparent on chest x-rays of about one-half of patients with symptoms of pneumonitis. The clinical diagnosis can be confirmed by an enzyme-linked immunosorbent assay for toxocaral antibodies. Stool examination for parasite eggs is worthless in toxocariasis, since the larvae do not develop into egg-producing adults in humans.

TREATMENT

Visceral and Ocular Larva Migrans

The vast majority of *Toxocara* infections are self-limited and resolve without specific therapy. In patients with severe myocardial, CNS, or pulmonary involvement, glucocorticoids may be employed to reduce inflammatory complications. Available anthelmintic drugs, including mebendazole and albendazole, have not been shown conclusively to alter the course of larva migrans. Control measures include prohibiting dog excreta in public parks and playgrounds, deworming dogs, and preventing pica in children. Treatment of ocular disease is not fully defined, but the administration of albendazole in conjunction with glucocorticoids has been effective (Table 226-1).

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans ("creeping eruption") is a serpiginous skin eruption caused by burrowing larvae of animal hookworms, usually the dog and cat hookworm *Ancylostoma braziliense*. The larvae hatch from eggs passed in dog and cat feces and mature in the soil. Humans become infected after skin contact with soil in areas frequented by dogs and cats, such as areas underneath house porches. Cutaneous larva migrans is prevalent among children and travelers in regions with warm humid climates, including the southeastern United States.

After larvae penetrate the skin, erythematous lesions form along the tortuous tracks of their migration through the dermal-epidermal junction; the larvae advance several centimeters in a day. The intensely pruritic lesions may occur anywhere on the body and can be numerous if the patient has lain on the ground. Vesicles and bullae may form later. The animal hookworm larvae do not mature in humans and, without treatment, will die after an interval ranging from weeks to a couple of months, with resolution of skin lesions. The diagnosis is made on clinical grounds. Skin biopsies only rarely detect diagnostic larvae. Symptoms can be alleviated by ivermectin or albendazole (Table 226-1).

ANGIOSTRONGYLIASIS

Angiostrongylus cantonensis, the rat lungworm, is the most common cause of human eosinophilic meningitis **(Fig. 226-3)**.

Life Cycle and Epidemiology This infection occurs principally in Southeast Asia and the Pacific Basin but has spread to other areas of the world, including the Caribbean islands, countries in Central and South America, and the southern United States. *A. cantonensis* larvae produced by adult worms in the rat lung migrate to the gastrointestinal tract and are expelled with the feces.

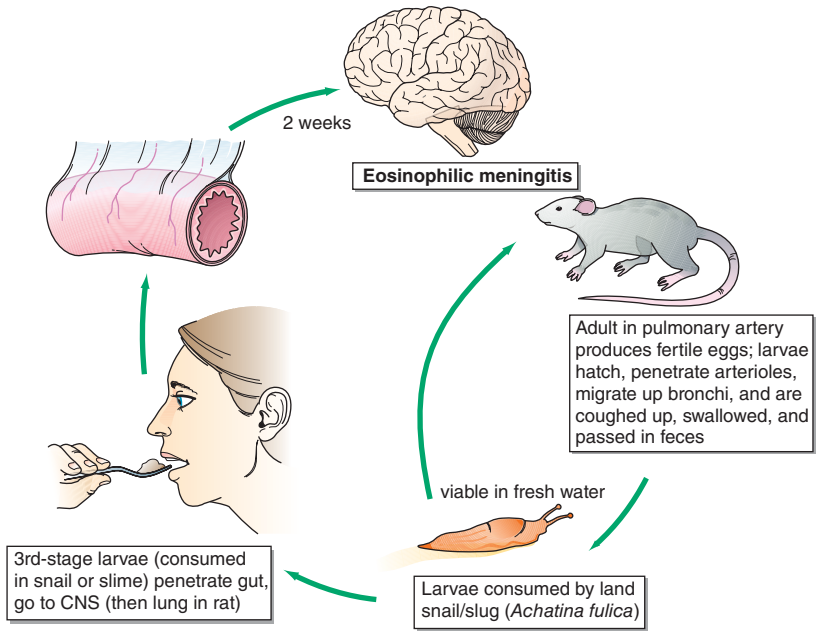


FIGURE 226-3 Life cycle of *Angiostrongylus cantonensis* (rat lung worm) found in Southeast Asia and the Pacific Basin as well as on Caribbean islands, in countries of Central and South America, and in the southern United States. CNS, central nervous system. *(Reprinted from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1225. © 2006, with permission from Elsevier Science.)*

They develop into infective larvae in land snails and slugs. Humans acquire the infection by ingesting raw infected mollusks; vegetables contaminated by mollusk slime; or crabs, freshwater shrimp, and certain marine fish that have themselves eaten infected mollusks. The larvae then migrate to the brain.

Pathogenesis and Clinical Features The parasites eventually die in the CNS, but not before initiating pathologic consequences that, in heavy infections, can result in permanent neurologic sequelae or death. Migrating larvae cause marked local eosinophilic inflammation and hemorrhage, with subsequent necrosis and granuloma formation around dying worms. Clinical symptoms develop 2–35 days after the ingestion of larvae. Patients usually present with an insidious or abrupt excruciating frontal, occipital, or bitemporal headache. Neck stiffness, nausea and vomiting, and paresthesias are also common. Fever, cranial and extraocular nerve palsies, seizures, paralysis, and lethargy are uncommon.

Laboratory Findings Examination of cerebrospinal fluid (CSF) is mandatory in suspected cases and usually reveals an elevated opening pressure, a white blood cell count of 150–2000/μL, and an eosinophilic pleocytosis of >20%. The protein concentration is usually elevated and the glucose level normal. The larvae of *A. cantonensis* are only rarely seen in CSF. Peripheral-blood eosinophilia may be mild. The diagnosis is generally based on the clinical presentation of eosinophilic meningitis together with a compatible epidemiologic history.

TREATMENT

Angiostrongyliasis

Specific chemotherapy is not of benefit in angiostrongyliasis; larvicidal agents may exacerbate inflammatory brain lesions. Management consists of supportive measures, including the administration of analgesics, sedatives, and—in severe cases—glucocorticoids (Table 226-1). Repeated lumbar punctures with removal of CSF can relieve symptoms. In most patients, cerebral angiostrongyliasis has a self-limited course, and recovery is complete. The infection may be prevented by adequately cooking snails, crabs, and prawns and inspecting vegetables for mollusk infestation. Other parasitic or fungal causes of eosinophilic meningitis in endemic areas may include gnathostomiasis (see below), paragonimiasis **(Chap. 229)**, schistosomiasis **(Chap. 229)**, neurocysticercosis **(Chap. 230)**, and coccidioidomycosis **(Chap. 208)**.

GNATHOSTOMIASIS

Infection of human tissues with larvae of *Gnathostoma spinigerum* can cause eosinophilic meningoencephalitis, migratory cutaneous swellings, or invasive masses of the eye and visceral organs.

Life Cycle and Epidemiology Human gnathostomiasis occurs in many countries and is notably endemic in Southeast Asia and parts of China and Japan. In nature, the mature adult worms parasitize the gastrointestinal tract of dogs and cats. First-stage larvae hatch from eggs passed into water and are ingested by *Cyclops* species (water fleas). Infective third-stage larvae develop in the flesh of many animal species (including fish, frogs, eels, snakes, chickens, and ducks) that have eaten either infected *Cyclops* or another infected second intermediate host. Humans typically acquire the infection by eating raw or undercooked fish or poultry. Raw fish dishes, such as *som fak* in Thailand and *sashimi* in Japan, account for many cases of human gnathostomiasis. Some cases in Thailand result from the local practice of applying frog or snake flesh as a poultice.

Pathogenesis and Clinical Features Clinical symptoms are due to the aberrant migration of a single larva into cutaneous, visceral, neural, or ocular tissues. After invasion, larval migration may cause local inflammation, with pain, cough, or hematuria accompanied by fever and eosinophilia. Painful, itchy, migratory swellings may develop in the skin, particularly in the distal extremities or periorbital area. Cutaneous swellings usually last ~1 week, but often recur intermittently over many years. Larval invasion of the eye can provoke a sight-threatening inflammatory response. Invasion of the CNS results in eosinophilic meningitis with myeloencephalitis, a serious complication due to ascending larval migration along a large nerve tract. Patients characteristically present with agonizing radicular pain and paresthesias in the trunk or a limb, which are followed shortly by paraplegia. Cerebral involvement, with focal hemorrhages and tissue destruction, is often fatal.

Diagnosis and Treatment Cutaneous migratory swellings with marked peripheral eosinophilia, supported by an appropriate geographic and dietary history, generally constitute an adequate basis for a clinical diagnosis of gnathostomiasis. However, patients may

present with ocular or cerebrospinal involvement without antecedent cutaneous swellings. In the latter case, eosinophilic pleocytosis is demonstrable (usually along with hemorrhagic or xanthochromic CSF), but worms are almost never recovered from CSF. Surgical removal of the parasite from subcutaneous or ocular tissue, though rarely feasible, is both diagnostic and therapeutic. Albendazole or ivermectin may be helpful (Table 226-1). At present, cerebrospinal involvement is managed with supportive measures and generally with a course of glucocorticoids. Gnathostomiasis can be prevented by adequate cooking of fish and poultry in endemic areas.

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227 Intestinal Nematode Infections

Peter F. Weller, Thomas B. Nutman

More than a billion persons worldwide are infected with one or more species of intestinal nematodes. Table 227-1 summarizes biologic and clinical features of infections due to the major intestinal parasitic nematodes. These parasites are most common in regions with poor fecal sanitation, particularly in resource-poor countries in the tropics and subtropics, but they have also been seen with increasing frequency among immigrants and refugees to resource-rich countries. Although nematode infections are not usually fatal, they contribute to malnutrition and diminished work capacity. It is interesting that these helminth infections may protect some individuals from allergic disease. Humans may on occasion be infected with nematode parasites that ordinarily infect animals; these zoonotic infections produce diseases such as trichostrongyliasis, anisakiasis, capillariasis, and abdominal angiostrongyliasis.

Intestinal nematodes are roundworms; they range in length from 1 mm to many centimeters when mature (Table 227-1). Their life cycles are complex and highly varied; some species, including *Strongyloides stercoralis* and *Enterobius vermicularis*, can be transmitted directly from person to person, while others, such as *Ascaris lumbricoides*, *Necator americanus*, and *Ancylostoma duodenale*, require a soil phase for development. Because most helminth parasites do not self-replicate, the acquisition of a heavy burden of adult worms requires repeated exposure to the parasite in its infectious stage, whether larva or egg. Hence, clinical disease, as opposed to asymptomatic (or subclinical) infection, generally develops only with prolonged exposure in an endemic area and is typically related to infection intensity. In persons with marginal nutrition, intestinal helminth infections may impair growth and development. Eosinophilia and elevated serum IgE levels are features of many helminth infections and, when unexplained, should always prompt a search for intestinal helminths. Significant protective immunity to intestinal nematodes appears not to develop in humans, although the host immune response to these infections has not been elucidated in detail.

ASCARIASIS

A. lumbricoides is the largest intestinal nematode parasite of humans, reaching up to 40 cm in length. Most infected individuals have low worm burdens and are asymptomatic. Clinical disease arises from larval migration in the lungs or effects of the adult worms in the intestines.

Life Cycle Adult worms live in the lumen of the small intestine. Mature female *Ascaris* worms are extraordinarily fecund, each producing up to 240,000 eggs a day that pass with the feces. Ascarid eggs, which are remarkably resistant to environmental stresses, become infective after several weeks of maturation in the soil and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine invade the mucosa, migrate through the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return—through swallowing—to the small intestine, where they develop into adult worms. Between 2 and 3 months elapse between initial infection and egg production. Adult worms live for 1–2 years.

Epidemiology *Ascaris* is widely distributed in tropical and subtropical regions as well as in other humid areas in more temperate regions of the world. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human feces as fertilizer. With their propensity for hand-to-mouth fecal carriage, younger children are most often affected. Infection outside endemic areas, though uncommon, can occur when eggs on transported vegetables are ingested.

Clinical Features During the lung phase of larval migration, ~9–12 days after egg ingestion, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever can occur. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Löffler's syndrome), with rounded infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks. Where there is seasonal transmission of the parasite, seasonal pneumonitis with eosinophilia may develop in previously infected and sensitized hosts.

In established infections, adult worms in the small intestine usually cause no symptoms. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction, sometimes complicated by perforation, intussusception, or volvulus. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses. Migration of an adult worm up the esophagus can provoke coughing and oral expulsion of the worm. In highly endemic areas, intestinal and biliary ascariasis can rival acute appendicitis and gallstones as causes of surgical acute abdomen.

Laboratory Findings Most cases of ascariasis can be diagnosed by microscopic detection of characteristic *Ascaris* eggs (65 by 45 μm) in fecal samples, although increasingly polymerase chain reaction (PCR) of DNA extracted from stool is being used in research and some clinical settings. Occasionally, patients present after passing an adult worm—identifiable by its large size and smooth cream-colored surface—in the stool or, much less commonly, through the mouth or nose. During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection. Adult worms may be visualized, occasionally serendipitously, on contrast studies of the gastrointestinal tract. A plain abdominal film may reveal masses of worms in gas-filled loops of bowel in patients with intestinal obstruction. Pancreaticobiliary worms can be detected by ultrasound and endoscopic retrograde cholangiopancreatography; the latter method also has been used to extract biliary *Ascaris* worms.

TABLE 227-1 Major Human Intestinal Parasitic Nematodes

FEATURE	PARASITIC NEMATODE				
	ASCARIS LUMBRICOIDES (ROUNDWORM)	*NECATOR AMERICANUS, ANCYLOSTOMA DUODENALE* (HOOKWORM)	*STRONGYLOIDES STERCORALIS*	*TRICHURIS TRICHIURA* (WHIPWORM)	*ENTEROBIUS VERMICULARIS* (PINWORM)
Global prevalence in humans (millions)	807	576	100	604	209
Endemic areas	Worldwide	Hot, humid regions	Hot, humid regions	Worldwide	Worldwide
Infective stage	Egg	Filariform larva	Filariform larva	Egg	Egg
Route of infection	Oral	Percutaneous	Percutaneous or autoinfective	Oral	Oral
Gastrointestinal location of worms	Jejunal lumen	Jejunal mucosa	Small-bowel mucosa	Cecum, colonic mucosa	Cecum, appendix
Adult worm size	15–40 cm	7–12 mm	2 mm	30–50 mm	8–13 mm (female)
Pulmonary passage of larvae	Yes	Yes	Yes	No	No
Incubation period[a] (days)	60–75	40–100	17–28	70–90	35–45
Longevity	1 year	*N. americanus*: 2–5 years *A. duodenale:* 6–8 years	Decades (owing to autoinfection)	5 years	2 months
Fecundity (eggs/day/worm)	240,000	*N. americanus:* 4000–10,000 *A. duodenale:* 10,000–25,000	5000–10,000	3000–7000	2000
Principal symptoms	Rarely, biliary obstruction or, in heavy infections, gastrointestinal obstruction	Iron-deficiency anemia in heavy infection	Gastrointestinal symptoms; malabsorption or sepsis in hyperinfection	Gastrointestinal symptoms or anemia in heavy infection	Perianal pruritus
Diagnostic stage	Eggs in stool	Eggs in fresh stool, larvae in old stool	Larvae in stool or duodenal aspirate; sputum in hyperinfection	Eggs in stool	Eggs from perianal skin on cellulose acetate tape
Treatment	Mebendazole Albendazole Ivermectin	Mebendazole Albendazole	Ivermectin Albendazole	Mebendazole Albendazole Ivermectin	Mebendazole Albendazole

[a]Time from infection to egg production by mature female worm.

TREATMENT

Ascariasis

Ascariasis should always be treated to prevent potentially serious complications. Albendazole (400 mg once), mebendazole (100 g twice daily for 3 days or 500 mg once), or ivermectin (150–200 µg/kg once) is effective. These medications are contraindicated in pregnancy, however. Mild diarrhea and abdominal pain are uncommon side effects of these agents. Partial intestinal obstruction should be managed with nasogastric suction, IV fluid administration, and instillation of piperazine through the nasogastric tube, but complete obstruction and its severe complications require immediate surgical intervention.

HOOKWORM

Two species (*A. duodenale* and *N. americanus*) are responsible for most human hookworm infections, although *A. ceylanicum* is being recognized as a major hookworm pathogen in parts of Asia. Most infected individuals are asymptomatic. Hookworm disease develops from a combination of factors—a heavy worm burden, a prolonged duration of infection, and an inadequate iron intake—and results in iron-deficiency anemia and, on occasion, hypoproteinemia.

Life Cycle Adult hookworms, which are ~1 cm long, use buccal teeth (*Ancylostoma*) or cutting plates (*Necator*) to attach to the small-bowel mucosa and suck blood (0.2 mL/d per *Ancylostoma* adult) and interstitial fluid. The adult hookworms produce thousands of eggs daily. The eggs are deposited with feces in soil, where rhabditiform larvae hatch and develop over a 1-week period into infectious filariform larvae. Infective larvae penetrate the skin and reach the lungs by way of the bloodstream. There they invade alveoli and ascend the airways before being swallowed and reaching the small intestine. The prepatent period from skin invasion to appearance of eggs in the feces is ~6–8 weeks, but it may be longer with *A. duodenale*. Larvae of *A. duodenale*, if swallowed, can survive and develop directly in the intestinal mucosa. Adult hookworms may survive over a decade but usually live ~6–8 years for *A. duodenale* and 2–5 years for *N. americanus*.

Epidemiology *A. duodenale* is prevalent in southern Europe, North Africa, and northern Asia, and *N. americanus* is the predominant species in the Western Hemisphere and equatorial Africa. *A. ceylanicum* is most prevalent in Southeast Asia. The species can overlap geographically, particularly in Southeast Asia. Age prevalence studies have shown a constant increase in hookworm prevalence over time; older children have the greatest intensity of hookworm infection; however, in rural areas where fields are fertilized with human feces, older working adults also may be heavily infected.

Clinical Features Most hookworm infections are clinically asymptomatic. Infective larvae may provoke pruritic maculopapular dermatitis ("ground itch") at the site of skin penetration as well as serpiginous tracks of subcutaneous migration (similar to those of cutaneous larva migrans; Chap. 226) in previously sensitized hosts. Larvae migrating through the lungs occasionally cause mild transient pneumonitis, but this condition develops less frequently in hookworm infection than in ascariasis. In the early intestinal phase, infected persons may develop epigastric pain (often with postprandial accentuation), inflammatory diarrhea, or other abdominal symptoms accompanied by eosinophilia. The major consequence of chronic hookworm infection is iron deficiency. Symptoms are minimal if iron intake is adequate, but marginally nourished individuals develop symptoms of progressive iron-deficiency anemia and hypoproteinemia, including weakness and shortness of breath.

Laboratory Findings The diagnosis is established by the finding of characteristic 40- by 60-μm oval hookworm eggs in the feces. Stool-concentration procedures may be required to detect light infections. Eggs of the three species are indistinguishable by light microscopy, whereas PCR has provided a significant improvement in species-specific diagnosis. In a stool sample that is not fresh, the eggs may have hatched to release rhabditiform larvae, which need to be differentiated from those of *S. stercoralis*. Hypochromic microcytic anemia, occasionally with eosinophilia or hypoalbuminemia, is characteristic of hookworm disease.

TREATMENT

Hookworm Infection

Hookworm infection can be treated with several safe and highly effective anthelmintic drugs, including albendazole (400 mg once) and mebendazole (500 mg once). Mild iron-deficiency anemia can often be treated with oral iron alone. Severe hookworm disease with protein loss and malabsorption necessitates nutritional support and oral iron replacement along with deworming. There is significant concern that the benzimidazoles (mebendazole and albendazole) are becoming much less effective against human hookworms.

Ancylostoma caninum* and *Ancylostoma braziliense *A. caninum*, the canine hookworm, has been identified as a cause of human eosinophilic enteritis, especially in northeastern Australia. In this zoonotic infection, adult hookworms attach to the small intestine (where they may be visualized by endoscopy) and elicit abdominal pain and intense local eosinophilia. Treatment with mebendazole (100 mg twice daily for 3 days) or albendazole (400 mg once) or endoscopic removal is effective. Both of these animal hookworm species can cause cutaneous larva migrans ("creeping eruption"; Chap. 226).

STRONGYLOIDIASIS

S. stercoralis is distinguished by its ability—unique among helminths (except for *Capillaria*; see below)—to replicate in the human host. This capacity permits ongoing cycles of autoinfection as infective larvae are internally produced. Infection with *S. stercoralis* can thus persist for decades without further exposure of the host to exogenous infective larvae. In immunocompromised hosts, large numbers of invasive *Strongyloides* larvae can disseminate widely and can be fatal.

Life Cycle In addition to a parasitic cycle of development, *Strongyloides* can undergo a free-living cycle of development in the soil (Fig. 227-1). This adaptability facilitates the parasite's survival in the absence of mammalian hosts. Rhabditiform larvae passed in feces can transform into infectious filariform larvae either directly or after a free-living phase of development. Humans acquire *S. stercoralis* when filariform larvae in fecally contaminated soil penetrate the skin or mucous membranes. The larvae then travel through the bloodstream to the lungs, where they break into the alveolar spaces, ascend the bronchial tree, are swallowed, and thereby reach the small intestine. There the larvae mature into adult worms that penetrate the mucosa of the proximal small bowel. The minute (2-mm-long) parasitic adult female worms reproduce by parthenogenesis; adult males do not exist. Eggs hatch in the intestinal mucosa, releasing rhabditiform larvae that migrate to the lumen and pass with the feces into soil. Alternatively, rhabditiform larvae in the bowel can develop directly into filariform larvae that penetrate the colonic wall or perianal skin and enter the circulation to repeat the migration that establishes ongoing internal reinfection. This autoinfection cycle allows strongyloidiasis to persist for decades.

Epidemiology *S. stercoralis* is spottily distributed in tropical areas and other hot, humid regions and is particularly common in Southeast Asia, sub-Saharan Africa, and Brazil. In the United States, the parasite is endemic in parts of the Southeast and is found in immigrants, refugees, travelers, and military personnel who have lived in endemic areas.

Clinical Features In uncomplicated strongyloidiasis, many patients are asymptomatic or have mild cutaneous and/or abdominal symptoms. Recurrent urticaria, often involving the buttocks and wrists, is the most common cutaneous manifestation. Migrating larvae can elicit a pathognomonic serpiginous eruption, *larva currens* ("running larva"). This pruritic, raised, erythematous lesion advances as rapidly as 10 cm/h along the course of larval migration. Adult parasites burrow into the duodenojejunal mucosa and can cause abdominal (usually midepigastric) pain, which resembles peptic ulcer pain except that it is aggravated by food ingestion. Nausea, diarrhea, gastrointestinal bleeding, mild chronic colitis, and weight loss can occur. Small-bowel obstruction may develop with early, heavy infection. Pulmonary symptoms are rare in uncomplicated strongyloidiasis. Eosinophilia is common, with levels fluctuating over time.

The ongoing autoinfection cycle of *S. stercoralis* is normally constrained by unknown factors of the host's immune system. Abrogation of host immunity, especially with glucocorticoid therapy and much less commonly with other immunosuppressive medications, leads to hyperinfection, with the generation of large numbers of filariform larvae. Colitis, enteritis, or malabsorption may develop. In disseminated

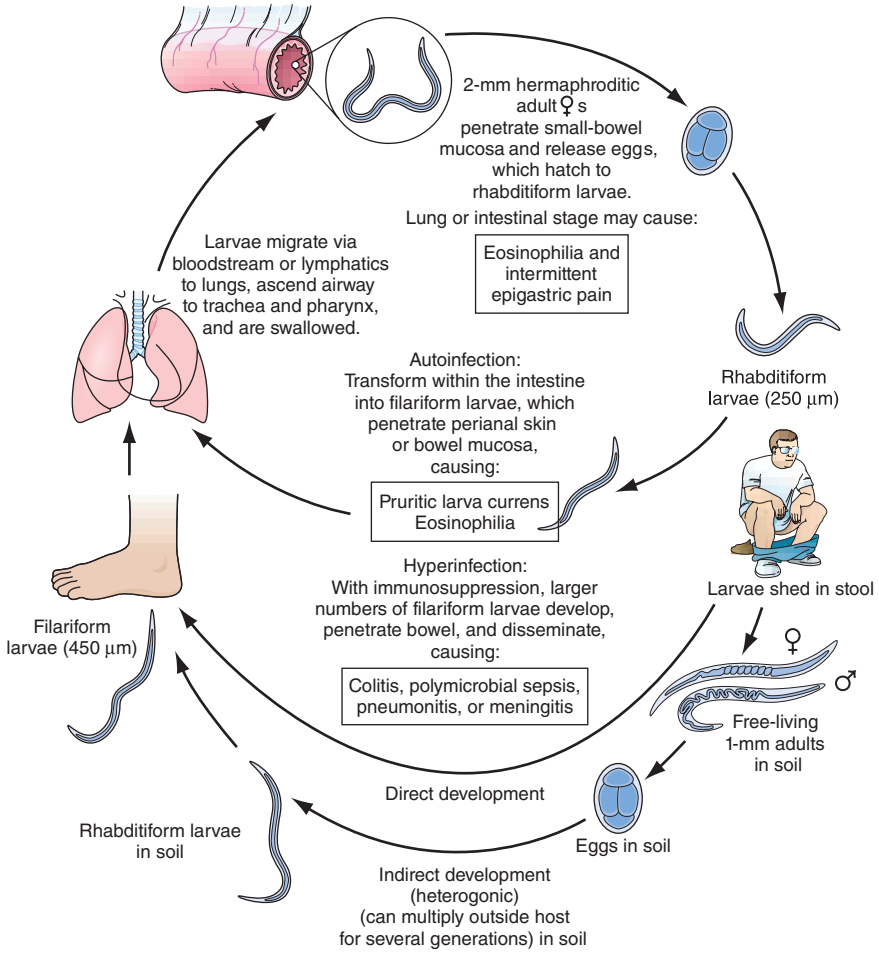

FIGURE 227-1 Life cycle of *Strongyloides stercoralis*. *(Adapted from Guerrant RL et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1276. © 2006, with permission from Elsevier Science.)*

strongyloidiasis, larvae may invade not only gastrointestinal tissues and the lungs but also the central nervous system, peritoneum, liver, and kidneys. Moreover, bacteremia may develop because of the passage of enteric flora through disrupted mucosal barriers. Gram-negative sepsis, pneumonia, or meningitis may complicate or dominate the clinical course. Eosinophilia is often absent in severely infected patients. Disseminated strongyloidiasis, particularly in patients with unsuspected infection who are given glucocorticoids, can be fatal. Strongyloidiasis is a frequent complication of infection with human T cell lymphotropic virus type 1 (HTLV-1), but disseminated strongyloidiasis is not common among patients infected with HIV-1.

Diagnosis In uncomplicated strongyloidiasis, the finding of rhabditiform larvae in feces is diagnostic. Rhabditiform larvae are ~250 µm long, with a short buccal cavity that distinguishes them from hookworm larvae. In uncomplicated infections, few larvae are passed and single stool examinations detect only about one-third of cases. Serial examinations and the use of the agar plate detection method improve the sensitivity of stool diagnosis. Again, PCR has begun to be used more widely and provides increased diagnostic specificity. In uncomplicated strongyloidiasis (but not in hyperinfection), microscopy-based stool examinations may be repeatedly negative. *Strongyloides* larvae may also be found by sampling of the duodenojejunal contents by aspiration or biopsy. An enzyme-linked immunosorbent assay for serum antibodies to antigens of *Strongyloides* is a sensitive method for diagnosing uncomplicated infections. Such serologic testing should be performed for patients whose geographic histories indicate potential exposure, especially those who exhibit eosinophilia and/or are candidates for glucocorticoid treatment of other conditions. In disseminated strongyloidiasis, filariform larvae should be sought in stool as well as in samples obtained from sites of potential larval migration, including sputum, bronchoalveolar lavage fluid, or surgical drainage fluid.

TREATMENT

Strongyloidiasis

Even in the asymptomatic state, strongyloidiasis must be treated because of the potential for subsequent dissemination and fatal hyperinfection. Ivermectin (200 µg/kg daily for 2 days) is consistently more effective than albendazole (400 mg daily for 3 days). For disseminated strongyloidiasis, treatment with ivermectin should be extended for at least 5–7 days or until the parasites have been eradicated. In immunocompromised hosts, the course of ivermectin should be repeated 2 weeks after initial treatment.

TRICHURIASIS

Most infections with *Trichuris trichiura* are asymptomatic, but heavy infections may cause gastrointestinal symptoms. Like the other soil-transmitted helminths, whipworm is distributed globally in the tropics and subtropics and is most common among poor children from resource-poor regions of the world.

Life Cycle Adult *Trichuris* worms reside in the colon and cecum, the anterior portions threaded into the superficial mucosa. Thousands of eggs laid daily by adult female worms pass with the feces and mature in the soil. After ingestion, infective eggs hatch in the duodenum, releasing larvae that mature before migrating to the large bowel. The entire cycle takes ~3 months, and adult worms may live for several years.

Clinical Features Tissue reactions to *Trichuris* are mild. Most infected individuals have no symptoms or eosinophilia. Heavy infections may result in anemia, abdominal pain, anorexia, and bloody or mucoid diarrhea resembling inflammatory bowel disease. Rectal prolapse can result from massive infections in children, who often suffer from malnourishment and other diarrheal illnesses. Moderately heavy *Trichuris* burdens also contribute to growth retardation.

Diagnosis and Treatment The characteristic 50- by 20-µm lemon-shaped *Trichuris* eggs are readily detected on stool examination. Adult worms, which are 3–5 cm long, are occasionally seen on proctoscopy. Mebendazole (500 mg once) or albendazole (400 mg daily for 3 doses) is safe and moderately effective for treatment, with cure rates of 70–90%. Ivermectin (200 µg/kg daily for 3 doses) is also safe but is not quite as efficacious as the benzimidazoles.

ENTEROBIASIS (PINWORM)

E. vermicularis is more common in temperate countries than in the tropics. In the United States, ~40 million persons are infected with pinworms, with a disproportionate number of cases among children.

Life Cycle and Epidemiology *Enterobius* adult worms are ~1 cm long and dwell in the cecum. Gravid female worms migrate nocturnally into the perianal region and release up to 2000 immature eggs each. The eggs become infective within hours and are transmitted by hand-to-mouth passage. From ingested eggs, larvae hatch and mature into adults. This life cycle takes ~1 month, and adult worms survive for ~2 months. Self-infection results from perianal scratching and transport of infective eggs on the hands or under the nails to the mouth. Because of the ease of person-to-person spread, pinworm infections are common among family members.

Clinical Features Most pinworm infections are asymptomatic. Perianal pruritus is the cardinal symptom. The itching, which is often worse at night as a result of the nocturnal migration of the female worms, may lead to excoriation and bacterial superinfection. Heavy infections have been alleged to cause abdominal pain and weight loss. On rare occasions, pinworms invade the female genital tract, causing vulvovaginitis and pelvic or peritoneal granulomas. Eosinophilia is uncommon.

Diagnosis Since pinworm eggs are not released in feces, the diagnosis cannot be made by conventional fecal ova and parasite tests. Instead, eggs are detected by the application of clear cellulose acetate tape to the perianal region in the morning. After the tape is transferred to a slide, microscopic examination will detect pinworm eggs, which are oval, measure 55 by 25 µm, and are flattened along one side.

TREATMENT

Enterobiasis

Infected children and adults should be treated with mebendazole (100 mg once) or albendazole (400 mg once), with the same treatment repeated after 2 weeks. Treatment of household members is advocated to eliminate asymptomatic reservoirs of potential reinfection.

TRICHOSTRONGYLIASIS

Trichostrongylus species, which are normally parasites of herbivorous animals, occasionally infect humans, particularly in Asia and Africa. Humans acquire the infection by accidentally ingesting *Trichostrongylus* larvae on contaminated leafy vegetables. The larvae do not migrate in humans but mature directly into adult worms in the small bowel. These worms ingest far less blood than hookworms; most infected persons are asymptomatic, but heavy infections may give rise to mild anemia and eosinophilia. In stool examinations, *Trichostrongylus* eggs resemble hookworm eggs but are larger (85 by 115 µm). Treatment consists of mebendazole or albendazole **(Chap. 217)**.

ANISAKIASIS

Anisakiasis is a gastrointestinal infection caused by the accidental ingestion in uncooked saltwater fish of nematode larvae belonging to the family Anisakidae. The incidence of anisakiasis in the United States has increased as a result of the growing popularity of raw fish dishes. Most cases occur in Japan, the Netherlands, and Chile, where raw fish—sashimi, pickled green herring, and ceviche, respectively—are national culinary staples. Anisakid nematodes parasitize large sea mammals such as whales, dolphins, and seals. As part of a complex parasitic life cycle involving marine food

chains, infectious larvae migrate to the musculature of a variety of fish. Both *Anisakis simplex* and *Pseudoterranova decipiens* have been implicated in human anisakiasis, but an identical gastric syndrome may be caused by the red larvae of eustrongylid parasites of fish-eating birds.

When humans consume infected raw fish, live larvae may be coughed up within 48 h. Alternatively, larvae may immediately penetrate the mucosa of the stomach. Within hours, violent upper abdominal pain accompanied by nausea and occasionally vomiting ensues, mimicking an acute abdomen. The diagnosis can be established by direct visualization on upper endoscopy, outlining of the worm by contrast radiographic studies, or histopathologic examination of extracted tissue. Extraction of the burrowing larvae during endoscopy is curative. In addition, larvae may pass to the small bowel, where they penetrate the mucosa and provoke a vigorous eosinophilic granulomatous response. Symptoms may appear 1–2 weeks after the infective meal, with intermittent abdominal pain, diarrhea, nausea, and fever resembling the manifestations of Crohn's disease. Ingestion of *Anisakis*-derived proteins through consumption of fish meat containing *Anisakis* parasites can elicit allergic gastrointestinal and even anaphylactic responses.

The diagnosis may be suggested by barium studies and confirmed by curative surgical resection of a granuloma in which the worm is embedded. Anisakid eggs are not found in the stool, since the larvae do not mature in humans. Serologic tests have been developed but are not widely available.

Anisakid larvae in saltwater fish are killed by cooking to 60°C, freezing at 20°C for 3 days, or commercial blast freezing, but usually not by salting, marinating, or cold smoking. No medical treatment is available; surgical or endoscopic removal should be undertaken.

CAPILLARIASIS

Intestinal capillariasis is caused by ingestion of raw fish infected with *Capillaria philippinensis*. Subsequent autoinfection can lead to a severe wasting syndrome. The disease occurs in the Philippines and Thailand and, on occasion, elsewhere in Asia. The natural cycle of *C. philippinensis* involves fish from fresh and brackish water. When humans eat infected raw fish, the larvae mature in the intestine into adult worms, which produce invasive larvae that cause intestinal inflammation and villus loss. Capillariasis has an insidious onset with nonspecific abdominal pain and watery diarrhea. If untreated, progressive autoinfection can lead to protein-losing enteropathy, severe malabsorption, and ultimately death from cachexia, cardiac failure, or superinfection. The diagnosis is established by identification of the characteristic peanut-shaped (20- by 40-µm) eggs on stool examination. Severely ill patients require hospitalization and supportive therapy in addition to prolonged anthelmintic treatment with albendazole (200 mg twice daily for 10 days; **Chap. 217**).

ABDOMINAL ANGIOSTRONGYLIASIS

Abdominal angiostrongyliasis is found in Latin America and Africa. The zoonotic parasite *Angiostrongylus costaricensis* causes eosinophilic ileocolitis after the ingestion of contaminated vegetation. *A. costaricensis* normally parasitizes the cotton rat and other rodents, with slugs and snails serving as intermediate hosts. Humans become infected by accidentally ingesting infective larvae in mollusk slime deposited on fruits and vegetables; children are at highest risk. The larvae penetrate the gut wall and migrate to the mesenteric artery, where they develop into adult worms. Eggs deposited in the gut wall provoke an intense eosinophilic granulomatous reaction, and adult worms may cause mesenteric arteritis, thrombosis, or frank bowel infarction. Symptoms may mimic those of appendicitis, including abdominal pain and tenderness, fever, vomiting, and a palpable mass in the right iliac fossa. Leukocytosis and eosinophilia are prominent. CT with contrast medium typically shows inflamed bowel, often with concomitant obstruction, but a definitive diagnosis is usually made surgically with partial bowel resection. Pathologic study reveals a thickened bowel wall with eosinophilic granulomas surrounding the *Angiostrongylus* eggs. In nonsurgical cases, the diagnosis rests solely on clinical grounds because larvae and eggs cannot be detected in the stool. Medical therapy for abdominal angiostrongyliasis is of uncertain efficacy. Careful observation and surgical resection for severe symptoms are the mainstays of treatment.

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228 Filarial and Related Infections

Thomas B. Nutman, Peter F. Weller

Filarial worms are nematodes that dwell in the subcutaneous tissues and the lymphatics. Eight filarial species infect humans **(Table 228-1)**; of these, four—*Wuchereria bancrofti*, *Brugia malayi*, *Onchocerca volvulus*, and *Loa loa*—are responsible for most serious filarial infections. Filarial parasites, which infect an estimated 170 million persons worldwide, are transmitted by specific species of mosquitoes or other arthropods and have a complex life cycle, including infective larval stages carried by insects and adult worms that reside in either lymphatic or subcutaneous tissues of humans. The offspring of adults are microfilariae, which, depending on their species, are 200–250 µm long and 5–7 µm wide, may or may not be enveloped in a loose sheath, and either circulate in the blood or migrate through the skin (Table 228-1). To complete the life cycle, microfilariae are ingested by the arthropod vector and develop over 1–2 weeks into new infective larvae. Adult worms live for many years, whereas microfilariae survive for 3–36 months. The bacterial endosymbiont *Wolbachia* has been found intracellularly in all stages of *Brugia*, *Wuchereria*, *Mansonella*, and *Onchocerca* species and has become a target for antifilarial chemotherapy.

Usually, infection is established only with repeated, prolonged exposures to infective larvae. Since the clinical manifestations of filarial diseases develop relatively slowly, these infections should be considered to induce chronic infections with possible long-term debilitating effects. In terms of the nature, severity, and timing of clinical manifestations, patients with filarial infections who are native to endemic areas and have lifelong exposure may differ significantly from those who are travelers or who have recently moved to these areas. Characteristically, filarial disease is more acute and intense in newly exposed individuals than in natives of endemic areas.

LYMPHATIC FILARIASIS

Lymphatic filariasis is caused by *W. bancrofti*, *B. malayi*, or *Brugia timori*. The threadlike adult parasites reside in afferent lymphatics or lymph nodes, where they may remain viable for more than two decades.

EPIDEMIOLOGY

W. bancrofti, the most widely distributed filarial parasite of humans, affects an estimated 110 million people and is found throughout the tropics and subtropics, including Asia and the Pacific Islands, Africa, areas of South America, and the Caribbean basin. Humans are the only definitive host for the parasite. Generally, the subperiodic form is found only in the Pacific Islands; elsewhere, *W. bancrofti* is nocturnally periodic. Nocturnally periodic forms of

TABLE 228-1 Characteristics of the Filariae

ORGANISM	PERIODICITY	DISTRIBUTION	VECTOR	LOCATION OF ADULT	MICROFILARIAL LOCATION	SHEATH
Wuchereria bancrofti	Nocturnal	Cosmopolitan areas worldwide, including South America, Africa, southern Asia, Papua New Guinea, China, Indonesia	*Culex*, *Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
	Subperiodic	Eastern Pacific	*Aedes* (mosquitoes)	Lymphatic tissue	Blood	+
Brugia malayi	Nocturnal	Southeast Asia, Indonesia, India	*Mansonia*, *Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
	Subperiodic	Indonesia, Southeast Asia	*Coquillettidia*, *Mansonia* (mosquitoes)	Lymphatic tissue	Blood	+
Brugia timori	Nocturnal	Indonesia	*Anopheles* (mosquitoes)	Lymphatic tissue	Blood	+
Loa loa	Diurnal	West and Central Africa	*Chrysops* (deerflies)	Subcutaneous tissue	Blood	+
Onchocerca volvulus	None	South and Central America, Africa	*Simulium* (blackflies)	Subcutaneous tissue	Skin, eye	–
Mansonella ozzardi	None	South and Central America	*Culicoides* (midges)	Undetermined site	Blood	–
	None	Caribbean	*Simulium* (blackflies)	Undetermined site	Blood	–
Mansonella perstans	None	South and Central America, Africa	*Culicoides* (midges)	Body cavities, mesentery, perirenal tissue	Blood	–
Mansonella streptocerca	None	West and Central Africa	*Culicoides* (midges)	Subcutaneous tissue	Skin	–

microfilariae are scarce in peripheral blood by day and increase at night, whereas subperiodic forms are present in peripheral blood at all times and reach maximal levels in the afternoon. Natural vectors for *W. bancrofti* are *Culex* mosquitoes in urban settings and *Anopheles* or *Aedes* mosquitoes in rural areas.

Brugian filariasis due to *B. malayi* occurs primarily in eastern India, Indonesia, Malaysia, and the Philippines. *B. malayi* also has two forms distinguished by the periodicity of microfilaremia. The more common nocturnal form is transmitted in areas of coastal rice fields, while the subperiodic form is found in forests. *B. malayi* naturally infects cats as well as humans. The distribution of *B. timori* is limited to the islands of southeastern Indonesia.

PATHOLOGY

The principal pathologic changes result from inflammatory damage to the lymphatics, which is typically caused by adult worms and not by microfilariae. Adult worms live in afferent lymphatics or sinuses of lymph nodes and cause lymphatic dilation and thickening of the vessel walls. The infiltration of plasma cells, eosinophils, and macrophages in and around the infected vessels, along with endothelial and connective tissue proliferation, leads to tortuosity of the lymphatics and damaged or incompetent lymph valves. Lymphedema and chronic stasis changes with hard or brawny edema develop in the overlying skin. These consequences of filarial infection are due both to the direct effects of the worms and to the host's inflammatory response to the parasite. Inflammatory responses are believed to cause the granulomatous and proliferative processes that precede total lymphatic obstruction. It is thought that the lymphatic vessel remains patent as long as the worm remains viable and that the death of the worm leads to enhanced granulomatous reactions and fibrosis. Lymphatic obstruction results, and, despite collateralization, lymphatic function is compromised.

CLINICAL FEATURES

The most common presentations of the lymphatic filariases are asymptomatic (or subclinical) microfilaremia, hydrocele **(Fig. 228-1)**, acute adenolymphangitis (ADL), and chronic lymphatic disease. In areas where *W. bancrofti* or *B. malayi* is endemic, the overwhelming majority of infected individuals have few overt clinical manifestations of filarial infection despite the presence of circulating microfilariae in the peripheral blood. Although they may be clinically asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease that includes microscopic hematuria and/or proteinuria, dilated (and tortuous) lymphatics (visualized by imaging), and—in men with *W. bancrofti* infection—scrotal lymphangiectasia (detectable by ultrasound). Despite these findings, the majority of individuals appear to remain clinically asymptomatic for years; in relatively few does the infection progress to either acute or chronic disease.

ADL is characterized by high fever, lymphatic inflammation (lymphangitis and lymphadenitis), and transient local edema. The lymphangitis is retrograde, extending peripherally from the lymph node draining the area where the adult parasites reside. Regional lymph nodes are often enlarged, and the entire lymphatic channel can become indurated and inflamed. Concomitant local thrombophlebitis can occur as well. In brugian filariasis, a single local abscess may form along the involved lymphatic tract and subsequently rupture to the surface. The lymphadenitis and lymphangitis can involve both the upper and lower extremities in both bancroftian and brugian filariasis, but involvement of the genital lymphatics occurs almost exclusively with *W. bancrofti* infection. This genital involvement can be manifested by funiculitis, epididymitis, and scrotal pain and tenderness. In endemic areas, another type of acute disease—dermatolymphangioadenitis (DLA)—is recognized as a syndrome that includes high fever, chills, myalgias, and

FIGURE 228-1 Hydrocele associated with *Wuchereria bancrofti* infection.

FIGURE 228-2 Elephantiasis of the lower extremity associated with *Wuchereria bancrofti* infection.

headache. Edematous inflammatory plaques clearly demarcated from normal skin are seen. Vesicles, ulcers, and hyperpigmentation also may be noted. There is often a history of trauma, burns, irradiation, insect bites, punctiform lesions, or chemical injury. Entry lesions, especially in the interdigital area, are common. DLA is often diagnosed as cellulitis.

If lymphatic damage progresses, transient lymphedema can develop into lymphatic obstruction and the permanent changes associated with elephantiasis **(Fig. 228-2)**. Brawny edema follows early pitting edema, the subcutaneous tissues thicken, and hyperkeratosis occurs. Fissuring of the skin develops, as do hyperplastic changes. Superinfection of these poorly vascularized tissues becomes a problem. In bancroftian filariasis, in which genital involvement is common, hydroceles may develop (Fig. 228-1); in advanced stages, this condition may evolve into scrotal lymphedema and scrotal elephantiasis. Furthermore, if there is obstruction of the retroperitoneal lymphatics, increased renal lymphatic pressure leads to rupture of the renal lymphatics and the development of chyluria, which is usually intermittent and most prominent in the morning.

The clinical manifestations of filarial infections in travelers or transmigrants who have recently entered an endemic region are distinctive. Given a sufficient number of bites by infected vectors, usually over a 3- to 6-month period, recently exposed patients can develop acute lymphatic or scrotal inflammation with or without urticaria and localized angioedema. Lymphadenitis of epitrochlear, axillary, femoral, or inguinal lymph nodes is often followed by evolving retrograde lymphangitis. Acute attacks are short-lived and are not usually accompanied by fever. With prolonged exposure to infected mosquitoes, these attacks, if untreated, become more severe and lead to permanent lymphatic inflammation and obstruction.

DIAGNOSIS

A definitive diagnosis can be made only by detection of the parasites and hence can be difficult. Adult worms localized in lymphatic vessels or nodes are largely inaccessible. Microfilariae can be found in blood, in hydrocele fluid, or (occasionally) in other body fluids. Such fluids can be examined microscopically, either directly or—for greater sensitivity—after concentration of the parasites by the passage of fluid through a polycarbonate cylindrical-pore filter (pore size, 3 μm) or by the centrifugation of fluid fixed in 2% formalin (Knott's concentration technique). The timing of blood collection is critical and should be based on the periodicity of the microfilariae in the endemic region involved. Many infected individuals do not have microfilaremia, and definitive diagnosis in such cases can be difficult. Assays for circulating antigens of *W. bancrofti* permit the diagnosis of microfilaremic and cryptic (amicrofilaremic) infection. Two tests are commercially available: an enzyme-linked immunosorbent assay and a rapid-format immunochromatographic card test. Both assays have sensitivities of 93–100% and specificities approaching 100%. There are currently no tests for circulating antigens in brugian filariasis.

Polymerase chain reaction (PCR)–based assays for DNA of *W. bancrofti* and *B. malayi* in blood have been developed. A number of studies indicate that the sensitivity of this diagnostic method is equivalent to or greater than that of parasitologic methods.

In cases of suspected lymphatic filariasis, examination of the scrotum, the lymph nodes, or (in female patients) the breast by means of high-frequency ultrasound in conjunction with Doppler techniques may result in the identification of motile adult worms within dilated lymphatics. Worms may be visualized in the lymphatics of the spermatic cord in up to 80% of men infected with *W. bancrofti*. Live adult worms have a distinctive pattern of movement within the lymphatic vessels (termed the *filarial dance sign*). Radionuclide lymphoscintigraphic imaging of the limbs reliably demonstrates widespread lymphatic abnormalities in both subclinical microfilaremic persons and those with clinical manifestations of lymphatic pathology. Although of potential utility in the delineation of anatomic changes associated with infection, lymphoscintigraphy is unlikely to assume primacy in the diagnostic evaluation of individuals with suspected infection; it is principally a research tool, although it has been used more widely for assessment of lymphedema of any cause. Eosinophilia and elevated serum concentrations of IgE and antifilarial antibody support the diagnosis of lymphatic filariasis. There is, however, extensive cross-reactivity between filarial antigens and antigens of other helminths. Of note, *W. bancrofti*– and *B. malayi*–specific antigens have been identified and are now available for use in rapid diagnostic tests with specificities of >98%. However, seropositivity cannot be equated with active infection: residents of endemic areas can become sensitized to filarial antigens through exposure to infective mosquitoes without having patent filarial infections.

The ADL associated with lymphatic filariasis must be distinguished from thrombophlebitis, infection, and trauma. Retrograde evolution is a characteristic feature that helps distinguish filarial lymphangitis from ascending bacterial lymphangitis. Chronic filarial lymphedema must also be distinguished from the lymphedema of malignancy, postoperative scarring, trauma, chronic edematous states, and congenital lymphatic system abnormalities.

TREATMENT

Lymphatic Filariasis

With newer definitions of clinical syndromes in lymphatic filariasis and new tools to assess clinical status (e.g., ultrasound, lymphoscintigraphy, circulating filarial antigen assays, PCR), approaches to treatment based on infection status can be considered.

Orally administered diethylcarbamazine (DEC; 6 mg/kg daily for 12 days), which has both macro- and microfilaricidal properties, remains the drug of choice for the treatment of active lymphatic filariasis (defined by microfilaremia, antigen positivity, or adult worms on ultrasound), although albendazole (400 mg twice daily by mouth for 21 days) also has demonstrated macrofilaricidal efficacy. A 4- to 6-week course of oral doxycycline (targeting the intracellular *Wolbachia*) also has significant macrofilaricidal activity, as does DEC/albendazole used daily for 7 days. The addition of DEC to a 3-week course of doxycycline is efficacious in lymphatic filariasis.

Regimens that combine single doses of albendazole (400 mg) with either DEC (6 mg/kg) or ivermectin (200 μg/kg) all have a sustained microfilaricidal effect and are the mainstay of programs

for the eradication of lymphatic filariasis in Africa (albendazole/ivermectin) and elsewhere (albendazole/DEC) (see "Prevention and Control," below). Recently, a regimen using single doses of the three major antifilarial drugs (albendazole/DEC/ivermectin) has been shown to sustain microfilarial clearance out to at least 2 years.

As has already been mentioned, a growing body of evidence indicates that, although they may be asymptomatic, virtually all persons with *W. bancrofti* or *B. malayi* microfilaremia have some degree of subclinical disease (hematuria, proteinuria, abnormalities on lymphoscintigraphy). Thus, early treatment of asymptomatic persons who have microfilaremia is recommended to prevent further lymphatic damage. For ADL, supportive treatment (including the administration of antipyretics and analgesics) is recommended, as is antibiotic therapy if secondary bacterial infection is likely. Similarly, because lymphatic disease is associated with the presence of adult worms, treatment with DEC is recommended for microfilaria-negative carriers of adult worms.

In persons with chronic manifestations of lymphatic filariasis, treatment regimens that emphasize hygiene, prevention of secondary bacterial infections, and physiotherapy have gained wide acceptance for morbidity control. These regimens are similar to those recommended for lymphedema of most nonfilarial causes and are known by a variety of names, including *complex decongestive physiotherapy* and *complex lymphedema therapy*. Hydroceles (Fig. 228-1) can be managed surgically. With chronic manifestations of lymphatic filariasis, drug treatment should be reserved for individuals who have evidence of active infection; however, a 6-week course of doxycycline has been shown to provide improvement in filarial lymphedema irrespective of disease activity.

Side effects of DEC treatment include fever, chills, arthralgias, headaches, nausea, and vomiting. Both the development and the severity of these reactions are directly related to the number of microfilariae circulating in the bloodstream. The adverse reactions may represent either an acute hypersensitivity reaction to the antigens being released by dead and dying parasites or an inflammatory reaction induced by the intracellular *Wolbachia* endosymbionts freed from their intracellular niche.

Ivermectin has a side effect profile similar to that of DEC when used in lymphatic filariasis. In patients infected with *L. loa* who have high levels of microfilaremia, DEC—like ivermectin (see "Loiasis," below)—can elicit severe encephalopathic complications. When used in single-dose regimens for the treatment of lymphatic filariasis, albendazole is associated with relatively few side effects.

PREVENTION AND CONTROL

To protect themselves against filarial infection, individuals must avoid contact with infected mosquitoes by using personal protective measures, including bed nets, particularly those impregnated with insecticides such as permethrin. Mass drug administration (MDA) is the current approach to elimination of lymphatic filariasis as a public health problem. The underlying tenet of this approach is that mass annual distribution of antifilarial chemotherapy—albendazole with either DEC (for all areas except those where onchocerciasis is coendemic; see section on onchocerciasis treatment, below) or ivermectin or with both ivermectin and DEC (triple-drug therapy) will profoundly suppress microfilaremia. If the suppression is sustained, then transmission can be interrupted.

Created by the World Health Organization in 1997, the Global Programme to Eliminate Lymphatic Filariasis is based on mass administration of single annual doses of DEC plus albendazole in non-African regions and of albendazole plus ivermectin in Africa. Available information from late 2013 indicated that more than 792 million persons in 53 countries had thus far participated. Not only has lymphatic filariasis been eliminated in some defined areas, but collateral benefits—avoidance of disability and treatment of intestinal helminths and other conditions (e.g., scabies and louse infestation)—also have been noted. The strategy of the global program is being refined, and attempts are being made to integrate this effort with other mass-treatment strategies (e.g., deworming programs, malaria control, and trachoma control) in an integrated control strategy.

TROPICAL PULMONARY EOSINOPHILIA

Tropical pulmonary eosinophilia (TPE) is a distinct syndrome that develops in some individuals infected with the lymphatic-dwelling filarial species. The majority of cases have been reported from India, Pakistan, Sri Lanka, Brazil, Guyana, and Southeast Asia; the decreasing incidence of TPE in last decade probably reflects global MDA efforts.

CLINICAL FEATURES

The main features include a history of residence in filaria-endemic regions, paroxysmal cough and wheezing (usually nocturnal and probably related to the nocturnal periodicity of microfilariae), weight loss, low-grade fever, lymphadenopathy, and pronounced blood eosinophilia (>3000 eosinophils/μL). Chest x-rays or CT scans may be normal, but generally show increased bronchovascular markings. Diffuse miliary lesions or mottled opacities may be present in the middle and lower lung fields. Tests of pulmonary function show restrictive abnormalities in most cases and obstructive defects in half. Characteristically, total serum IgE levels (4–40 KIU/mL) and antifilarial antibody levels are markedly elevated.

PATHOLOGY

In TPE, microfilariae and parasite antigens are rapidly cleared from the bloodstream by the lungs. The clinical symptoms result from allergic and inflammatory reactions elicited by the cleared parasites. In some patients, trapping of microfilariae in other reticuloendothelial organs can cause hepatomegaly, splenomegaly, or lymphadenopathy. A prominent, eosinophil-enriched, intra-alveolar infiltrate is common, and with it comes the release of cytotoxic proinflammatory eosinophil granule proteins that may mediate some of the pathology seen in TPE. In the absence of successful treatment, interstitial fibrosis can lead to progressive pulmonary damage.

DIFFERENTIAL DIAGNOSIS

TPE must be distinguished from asthma, Löffler syndrome, allergic bronchopulmonary aspergillosis, allergic granulomatosis with polyangiitis (EGPA or Churg-Strauss syndrome), other systemic vasculitides (most notably, periarteritis nodosa), chronic eosinophilic pneumonia, and the hypereosinophilic syndromes (HESs).

TREATMENT

Tropical Pulmonary Eosinophilia

DEC is used at a daily dosage of 4–6 mg/kg for 14 days. Symptoms usually resolve within 3–7 days after the initiation of therapy. Relapse, which occurs in ~12–25% of cases (sometimes after an interval of several years), requires re-treatment.

ONCHOCERCIASIS

EPIDEMIOLOGY

Onchocerciasis ("river blindness") is caused by the filarial nematode *O. volvulus*, which infects an estimated 37 million individuals in 31 countries worldwide. The majority of individuals infected with *O. volvulus* live in the equatorial region of Africa extending from the Atlantic coast to the Red Sea. In the Americas, the only remaining countries with isolated foci are Venezuela and Brazil. The infection is also found in Yemen.

ETIOLOGY

Infection in humans begins with the deposition of infective larvae on the skin by the bite of an infected blackfly. The larvae develop into adults, which are typically found in subcutaneous nodules. About 7 months to 3 years after infection, the gravid female releases microfilariae that migrate out of the nodule and throughout the tissues, concentrating in the dermis. Infection is transmitted to other persons

when a female fly ingests microfilariae from the host's skin and these microfilariae then develop into infective larvae. Adult *O. volvulus* females and males are ~40–60 cm and ~3–6 cm in length, respectively. The life span of adults can be as long as 18 years, with an average of ~9 years. Because the blackfly vector breeds along free-flowing rivers and streams (particularly in rapids) and generally restricts its flight to an area within several kilometers of these breeding sites, both biting and disease transmission are most intense in these locations.

PATHOLOGY

Onchocerciasis primarily affects the skin, eyes, and lymph nodes. In contrast to the pathology in lymphatic filariasis, the damage in onchocerciasis is elicited by microfilariae and not by adult parasites. In the skin, there are mild but chronic inflammatory changes that can result in loss of elastic fibers, atrophy, and fibrosis. The subcutaneous nodules (*onchocercomata*) consist primarily of fibrous tissues surrounding the adult worm, often with a peripheral ring of inflammatory cells surrounded by an endothelial layer (characterized as lymphatic in origin). In the eye, neovascularization and corneal scarring lead to corneal opacities and blindness. Inflammation in the anterior and posterior chambers frequently results in anterior uveitis, chorioretinitis, and optic atrophy. Although punctate opacities are due to an inflammatory reaction surrounding dead or dying microfilariae, the pathogenesis of most manifestations of onchocerciasis is still unclear.

CLINICAL FEATURES

Skin Pruritus and rash are the most common manifestations of onchocerciasis. The pruritus can be incapacitating; the rash is typically a papular eruption **(Fig. 228-3)** that is generalized rather than localized to a particular region of the body. Long-term infection results in exaggerated and premature wrinkling of the skin, loss of elastic fibers, and epidermal atrophy that can lead to loose, redundant skin and hypo- or hyperpigmentation. Localized eczematoid dermatitis can cause hyperkeratosis, scaling, and pigmentary changes. In an immunologically hyperreactive form of onchodermatitis (commonly termed *sowdah* or *localized onchodermatitis*), the affected skin darkens as a consequence of the profound inflammation that occurs as microfilariae in the skin are cleared.

Onchocercomata These subcutaneous nodules, which can be palpable and/or visible, contain the adult worm. They are most common over the coccyx and sacrum, the trochanter of the femur, the lateral anterior crest, and other bony prominences. Nodules vary in size and characteristically are firm and not tender. It has been estimated that, for every palpable nodule, there are four deeper nonpalpable ones.

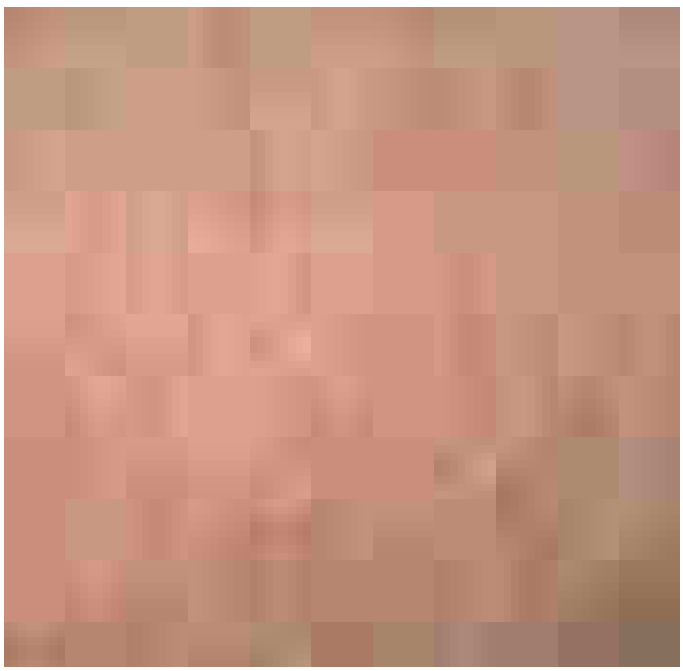

FIGURE 228-3 **Papular eruption** as a consequence of onchocerciasis.

Ocular Tissue Visual impairment is the most serious complication of onchocerciasis and usually affects only those persons with moderate or heavy infections. Lesions may develop in all parts of the eye. The most common early finding is conjunctivitis with photophobia. Punctate keratitis—acute inflammatory reactions surrounding dying microfilariae and manifested as "snowflake" opacities—is common among younger patients and resolves without apparent complications. Sclerosing keratitis occurs in 1–5% of infected persons and is the leading cause of onchocercal blindness. Anterior uveitis and iridocyclitis develop in ~5% of infected persons. Characteristic chorioretinal lesions develop as a result of atrophy and hyperpigmentation of the retinal pigment epithelium. Constriction of the visual fields and overt optic atrophy may occur.

Lymph Nodes Mild to moderate lymphadenopathy is common, particularly in the inguinal and femoral areas, where the enlarged nodes may hang down in response to gravity ("hanging groin"), sometimes predisposing to inguinal and femoral hernias.

Other Manifestations Some heavily infected individuals develop cachexia with loss of adipose tissue and muscle mass. A form of dwarfism, Nakalanga dwarfism, has been attributed to pituitary involvement in this infection. An association between onchocerciasis and epilepsy (including an epidemic form termed nodding syndrome) has gained attention recently. Among adults who become blind, there is a three- to fourfold increase in mortality rate.

DIAGNOSIS

Definitive diagnosis depends on the detection of an adult worm in an excised nodule or, more commonly, of microfilariae in a skin snip. Skin snips are obtained with a corneal-scleral punch or by lifting of the skin with the tip of a needle and excision of a small (1- to 3-mm) piece with a sterile scalpel blade. Both methods collect a blood-free skin biopsy sample extending to just below the epidermis. The biopsy tissue can be incubated in tissue culture medium or in saline on a glass slide or flat-bottomed microtiter plate. After incubation for 2–4 h (or occasionally overnight in light infections), microfilariae emergent from the skin can be seen by low-power microscopy or can be detected by PCR.

Eosinophilia and elevated serum IgE levels are common but, because these features are seen in many parasitic infections, are not diagnostic in themselves. Immunoassays to detect antibodies to *Onchocerca*-specific antigens are being used both in specialized laboratories and at the point of contact in rapid-diagnostic formats.

TREATMENT

Onchocerciasis

The main goals of therapy are to prevent the development of irreversible lesions and to alleviate symptoms. Chemotherapy is the mainstay of management. Ivermectin, a semisynthetic macrocyclic lactone active against microfilariae, is the first-line agent for the treatment of onchocerciasis. It is given orally in a single dose of 150 µg/kg, either yearly or semiannually. More frequent ivermectin administration (every 3 months) has been suggested to ameliorate pruritus and skin disease.

After treatment, most individuals have few or no reactions. Pruritus, cutaneous edema, and/or maculopapular rash occurs in ~1–10% of treated individuals. In areas of Africa coendemic for *O. volvulus* and *L. loa*, however, ivermectin is contraindicated (as it is for pregnant or breast-feeding women) because of severe post-treatment encephalopathy, especially in patients who are heavily microfilaremic for *L. loa* (>30,000 microfilariae/mL). Although ivermectin treatment results in a marked drop in microfilarial density, its effect can be short-lived (<3 months in some cases). Thus, it is occasionally necessary to give ivermectin more frequently for persistent symptoms.

A 6-week course of doxycycline is macrofilaristatic, rendering female adult worms sterile for long periods.

PREVENTION

Vector control has been beneficial in highly endemic areas in which breeding sites are vulnerable to insecticide spraying, but most areas endemic for onchocerciasis are not suited to this type of control. Community-based administration of ivermectin every 6–12 months is being used to interrupt transmission in endemic areas. This measure, in conjunction with vector control, has already helped eliminate the infection in most of Latin America and has reduced the prevalence of disease in many endemic foci in Africa. No drug has proved useful for prophylaxis of *O. volvulus* infection.

LOIASIS

ETIOLOGY AND EPIDEMIOLOGY

Loiasis is caused by *L. loa* (the African eye worm), which is present in the rainforests of West and Central Africa. Adult parasites (females, 50–70 mm long and 0.5 mm wide; males, 25–35 mm long and 0.25 mm wide) live in subcutaneous tissues. Microfilariae circulate in the blood with a diurnal periodicity that peaks between 10:00 A.M. and 2:00 P.M.

CLINICAL FEATURES

Manifestations of loiasis in natives of endemic areas may differ from those in temporary residents or visitors. Among the indigenous population, loiasis is often an asymptomatic infection with microfilaremia. Infection may be recognized only after subconjunctival migration of an adult worm **(Fig. 228-4)** or may be manifested by episodic *Calabar swellings*—evanescent localized areas of angioedema and erythema developing on the extremities and less frequently at other sites. Nephropathy, encephalopathy, and cardiomyopathy can occur but are rare. In patients who are not residents of endemic areas, allergic symptoms predominate, episodes of Calabar swelling tend to be more frequent, microfilaremia is less common, and eosinophilia and increased levels of antifilarial antibodies are characteristic.

PATHOLOGY

The pathogenesis of the manifestations of loiasis is poorly understood. Calabar swellings are thought to result from a hypersensitivity reaction to adult worm antigens.

DIAGNOSIS

Definitive diagnosis of loiasis requires the detection of microfilariae in the peripheral blood or the isolation of the adult worm from the eye (Fig. 228-4) or from a subcutaneous biopsy specimen collected from a site of swelling developing after treatment. PCR-based assays for the detection of *L. loa* DNA in blood are available in specialized laboratories and are highly sensitive and specific, as are some newer recombinant antigen–based serologic techniques. In practice, the diagnosis must often be based on a characteristic history and clinical presentation, blood eosinophilia, and elevated levels of antifilarial antibodies, particularly in travelers to an endemic region, who are often amicrofilaremic.

FIGURE 228-4 Adult *Loa loa* worm being surgically removed after its subconjunctival migration.

TREATMENT

Loiasis

DEC (8–10 mg/kg per day administered orally for 21 days) is effective against both the adult and the microfilarial forms of *L. loa*, but multiple courses are frequently necessary before loiasis resolves completely. In cases of heavy microfilaremia, allergic or other inflammatory reactions can take place during treatment, including central nervous system involvement with coma and encephalitis. Heavy infections can be treated initially with apheresis to remove the microfilariae and with glucocorticoids (40–60 mg of prednisone per day) followed by doses of DEC (0.5 mg/kg per day). If antifilarial treatment has no adverse effects, the prednisone dose can be rapidly tapered and the dose of DEC gradually increased to 8–10 mg/kg per day.

Albendazole or ivermectin is effective in reducing microfilarial loads, although neither is approved for this purpose by the U.S. Food and Drug Administration. Moreover, ivermectin is contraindicated in patients with >30,000 microfilariae/mL because this drug has been associated with severe adverse events (including encephalopathy and death) in heavily infected patients with loiasis in West and Central Africa. DEC (300 mg weekly) is an effective prophylactic regimen for loiasis.

STREPTOCERCIASIS

Mansonella streptocerca, found mainly in the tropical forest belt of Africa from Ghana to the Democratic Republic of the Congo, is transmitted by biting midges. The major clinical manifestations involve the skin and include pruritus, papular rashes, and pigmentation changes. Many infected individuals have inguinal adenopathy, although most are asymptomatic. The diagnosis is made by detection of the characteristic microfilariae in skin snips. Ivermectin at a single dose of 150 µg/kg leads to sustained suppression of microfilariae in the skin and is probably the treatment of choice for streptocerciasis.

MANSONELLA PERSTANS INFECTION

M. perstans, distributed across the center of Africa and in northeastern South America, is transmitted by midges. Adult worms reside in serous cavities—pericardial, pleural, and peritoneal—as well as in the mesentery and the perirenal and retroperitoneal tissues. Microfilariae circulate in the blood without periodicity. The clinical and pathologic features of the infection are poorly defined. Most patients appear to be asymptomatic, but manifestations may include transient angioedema and pruritus of the arms, face, or other parts of the body (analogous to the Calabar swellings of loiasis); fever; headache; arthralgias; and right-upper-quadrant pain. Occasionally, pericarditis and hepatitis occur. The diagnosis is based on the demonstration of microfilariae in blood or serosal effusions. Perstans filariasis is often associated with peripheral-blood eosinophilia and antifilarial antibody elevations.

With the identification of a *Wolbachia* endosymbiont in *M. perstans*, doxycycline (200 mg twice a day) for 6 weeks has been established as the first effective treatment for this infection.

MANSONELLA OZZARDI INFECTION

The distribution of *M. ozzardi* is restricted to Central and South America and certain Caribbean islands. Adult worms are rarely recovered from humans. Microfilariae circulate in the blood without periodicity. Although this organism has often been

considered nonpathogenic, headache, articular pain, fever, pulmonary symptoms, adenopathy, hepatomegaly, pruritus, and eosinophilia have been ascribed to *M. ozzardi* infection. The diagnosis is made by detection of microfilariae in peripheral blood. Ivermectin is effective in treating this infection.

ZOONOTIC FILARIAL INFECTIONS

Dirofilariae that affect primarily dogs, cats, and raccoons occasionally infect humans incidentally, as do *Brugia* and *Onchocerca* parasites that affect small mammals. Because humans are an abnormal host, the parasites never develop fully. Pulmonary dirofilarial infection caused by the canine heartworm *Dirofilaria immitis* generally presents in humans as a solitary pulmonary nodule. Chest pain, hemoptysis, and cough are uncommon. Infections with *D. repens* (from dogs) or *D. tenuis* (from raccoons) can cause local subcutaneous nodules in humans. Zoonotic *Brugia* infection can produce isolated lymph node enlargement, whereas zoonotic *Onchocerca* species (particularly *O. lupi*) can cause subconjunctival masses. Eosinophilia levels and antifilarial antibody titers are not commonly elevated. Excisional biopsy is both diagnostic and curative. These infections usually do not respond to antifilarial chemotherapy.

DRACUNCULIASIS (GUINEA WORM INFECTION)

ETIOLOGY AND EPIDEMIOLOGY

The incidence of dracunculiasis, caused by *Dracunculus medinensis*, has declined dramatically because of global eradication efforts. In 2017, only 30 cases worldwide were identified. The infection appears to be endemic only in Chad and Ethiopia.

Humans acquire *D. medinensis* when they ingest water containing infective larvae derived from *Cyclops*, a crustacean that is the intermediate host. Larvae penetrate the stomach or intestinal wall, mate, and mature. The adult male probably dies; the female worm develops over a year and migrates to subcutaneous tissues, usually in the lower extremity. As the thin female worm, ranging in length from 30 cm to 1 m, approaches the skin, a blister forms that, over days, breaks down and forms an ulcer. When the blister opens, large numbers of motile, rhabditiform larvae can be released into stagnant water; ingestion by *Cyclops* completes the life cycle.

CLINICAL FEATURES

Few or no clinical manifestations of dracunculiasis are evident until just before the blister forms, when there is an onset of fever and generalized allergic symptoms, including periorbital edema, wheezing, and urticaria. The emergence of the worm is associated with local pain and swelling. When the blister ruptures (usually as a result of immersion in water) and the adult worm releases larva-rich fluid, symptoms are relieved. The shallow ulcer surrounding the emerging adult worm heals over weeks to months. Such ulcers, however, can become secondarily infected, the result being cellulitis, local inflammation, abscess formation, or (uncommonly) tetanus. Occasionally, the adult worm does not emerge but becomes encapsulated and calcified.

DIAGNOSIS

The diagnosis is based on the findings developing with the emergence of the adult worm, as described above.

TREATMENT

Dracunculiasis

Gradual extraction of the worm by winding of a few centimeters on a stick each day remains the common and effective practice. Worms may be excised surgically. No drug is effective in treating dracunculiasis.

PREVENTION

Prevention, which remains the only real control measure, depends on the provision of safe drinking water.

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229 Schistosomiasis and Other Trematode Infections

Birgitte Jyding Vennervald

Trematodes, or flatworms, are a group of helminths that belong to the phylum Platyhelminthes. The adult flatworms share some common characteristics, such as macroscopic size (from one to several centimeters); dorsoventrally flattened, bilaterally symmetric bodies; and two suckers—oral and ventral. Except for schistosomes, which have separate sexes, all human parasitic trematodes are hermaphroditic. Their life cycles involve a mammalian/human definitive host, in which sexual reproduction by adult worms takes place, and an intermediate host (snails), in which asexual multiplication occurs. Some species of trematodes have more than one intermediate host.

Humans are infected either by direct penetration of intact skin (schistosomiasis) or by ingestion of raw freshwater fish, crustaceans, or aquatic plants with metacercariae—the infective larval stage.

Significant trematode infections of humans may be divided according to the location of the adult worms: blood, liver (biliary tree), intestines, or lungs **(Table 229-1)**. Adult worms do not multiply within the mammalian host but can live for up to 30 years. Infections are often chronic.

Although it is relatively rare to encounter patients with trematode infections in the United States, many millions of people are infected worldwide. Both schistosomiasis and food-borne trematode infections are poverty-related chronic diseases with high morbidity and a significant public health impact. Various factors may increase the spread of the infections globally. Increasing temperatures may render new areas suitable for the intermediate host snails, and an increase in travel and migration may increase the number of patients with trematode infections—for example, in the United States.

APPROACH TO THE PATIENT

Trematode Infection

In the evaluation of a patient in whom trematode infection is suspected, certain questions are highly relevant and can assist in establishing a diagnosis: Where have you been? If you have traveled, when did you return? What activities have you been involved in (trekking, swimming, whitewater rafting)? What have you been eating (local dishes while traveling; raw, poorly cooked, or pickled freshwater fish or crustaceans)? Definitive diagnosis is based on detection of parasite eggs in stool, urine, sputum, and sometimes tissue samples or on serologic tests. The presence of eosinophilia and a history of travel to endemic areas should raise suspicion

TABLE 229–1 Major Human Trematode Infections

TREMATODE	TRANSMISSION ROUTE	GEOGRAPHIC DISTRIBUTION
Blood Flukes		
Intestinal schistosomiasis		
Schistosoma mansoni	Skin penetration by cercariae released from snails (*Biomphalaria* spp.)	Africa, Brazil, Venezuela, Surinam, the Caribbean (low risk)
Shistosoma japonicum	Skin penetration by cercariae released from snails (*Oncomelania* spp.)	China, Indonesia, Philippines
Schistosoma guineensis and *Schistosoma intercalatum*	Skin penetration by cercariae released from snails (*Bulinus* spp.)	Rain forest areas of Central Africa
Schistosoma mekongi	Skin penetration by cercariae released from snails (*Neotricula aperta*)	Several districts of Cambodia and Lao People's Democratic Republic (PDR)
Urogenital schistosomiasis		
Schistosoma haematobium	Skin penetration by cercariae released from snails (*Bulinus* spp.)	Africa, Middle East, Corsica (France)
Liver Flukes		
Clonorchis sinensis	Ingestion of metacercariae in freshwater fish	Asia, including Republic of Korea, China, Taiwan, Vietnam
Opisthorchis viverrini	Ingestion of metacercariae in freshwater fish	Northeast Thailand, Lao PDR, Cambodia, Vietnam
Opisthorchis felineus	Ingestion of metacercariae in freshwater fish	Former Soviet Union, Kazakhstan, Ukraine, Turkey
Fasciola hepatica	Ingestion of metacercariae on aquatic plants or in water	Worldwide
Fasciola gigantica	Ingestion of metacercariae on aquatic plants or in water	Africa, Asia
Intestinal Flukes		
Fasciolopsis buski	Ingestion of metacercariae on aquatic plants	Bangladesh, China, India, Indonesia, Lao PDR, Malaysia, Taiwan, Thailand, Vietnam
Echinostoma spp.	Ingestion of freshwater fish, frogs, mussels, snails	China, India, Indonesia, Japan, Malaysia, Russia, Republic of Korea, Philippines, Thailand
Heterophyes heterophyes, several other species	Ingestion of metacercariae in freshwater or brackish-water fish	Egypt, Greece, Islamic Republic of Iran, Italy, Japan, Republic of Korea, Sudan, Tunisia, Turkey
Lung Flukes		
Paragonimus westermani	Ingestion of metacercariae in crayfish or crabs	Tropical and subtropical areas of eastern and southern Asia and sub-Saharan Africa
Paragonimus kellicotti	Ingestion of metacercariae in crayfish or crabs	North America

of trematode infection. The U.S. Centers for Disease Control and Prevention (CDC) can provide guidance with respect to diagnosis and treatment.

SCHISTOSOMIASIS

Human schistosomiasis is caused by five species of the parasitic genus *Schistosoma*: *S. mansoni*, *S. japonicum*, *S. mekongi*, and *S. intercalatum* cause intestinal disease, and *S. haematobium* causes urogenital disease (Table 229-1). The infection may cause considerable intestinal, hepatic, and genitourinary morbidity. Avian schistosomes may penetrate human skin, but they die in subcutaneous tissue, producing only cutaneous manifestations.

ETIOLOGY

Schistosoma infection is contracted through contact with freshwater bodies harboring infected intermediate-host snails. Cercariae, the infective larval stage released from the snail, penetrate intact human skin within a few minutes after attaching to the skin. After penetration, the cercariae transform to schistosomula, which then enter a small vein or lymphatic vessel, circulate in the bloodstream through the lung capillaries, and are pumped via the heart to all parts of the body to reach the portal vein. There, the worms mature into adult males or females, pair, and migrate to their final location in the mesenteric or pelvic venous plexus.

The interval from cercarial penetration to sexual maturation and egg production, termed the *prepatent period*, lasts 5–7 weeks (up to 12 weeks for *S. haematobium*). The female worm then begins to produce eggs, which are excreted via feces or, for *S. haematobium*, urine. Approximately 50% of eggs are retained in tissue, where they are responsible for organ-specific morbidity (see "Pathogenesis," below). When excreted eggs reach water, they hatch and release a free-swimming larval stage (*miracidium*), which, after penetrating a host snail, undergoes several rounds of asexual multiplication. After ~4–6 weeks, infective cercariae are shed from the infected snails into the water. One snail, infected by one miracidium, can shed thousands of cercariae per day for several months; thus the transmission potential of schistosomes is enormous.

The schistosome egg **(Fig. 229-1)** is the only stage of the parasites' life cycle that can be detected in humans, either in excreta or in tissue biopsies. The eggs are large and can easily be distinguished morphologically from other helminth eggs. *S. haematobium* eggs are ~140 mm long, with a terminal spine; *S. mansoni* eggs are ~150 mm long, with a lateral spine; and *S. japonicum* eggs are smaller, rounder, and ~90 mm long, with a small lateral spine or knob.

Adult schistosomes are ~1–2 cm long. The male worm is flat, and the body forms a groove or gynecophoric canal in which the mature adult female is held like a sausage in a hotdog roll. Females are longer, thinner, and rounded. The females produce hundreds (African species) to thousands (Asian species) of eggs per day. Each ovum contains a ciliated miracidium larva, which secretes proteolytic enzymes that help the eggs to migrate into the lumen of the bladder (*S. haematobium*) or the intestine (other species). The lifespan of an adult schistosome averages 3–5 years but can be as long as 30 years. Schistosome worms feed on red blood cells; the debris is regurgitated in the host's blood, where it can be detected as circulating antigens (see "Diagnosis," below).

Adult schistosomes persist in the bloodstream for years and have evolved strategies of evading attack using immune effector mechanisms. This immune evasion is a result of several processes, such as

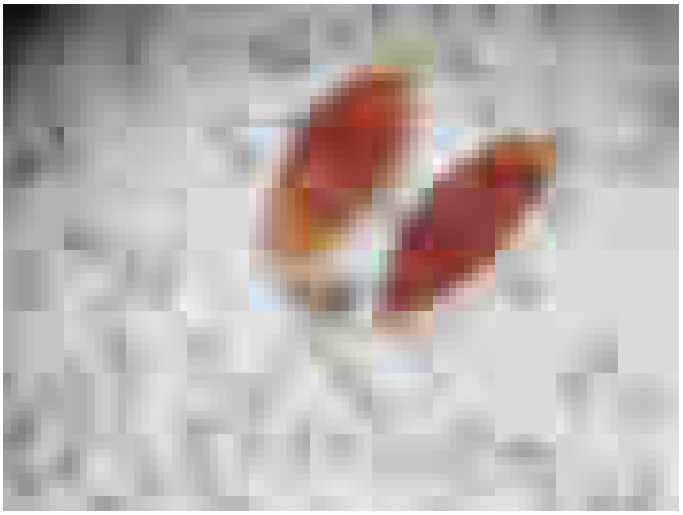

FIGURE 229-1 ***Schistosoma haematobium* eggs.**

binding of host proteins to the schistosome surface, which renders the parasite invisible to the host immune system.

The genome of schistosomes is relatively large (~270 Mb). Whole-genome sequences are available for *S. mansoni*, *S. japonicum*, and *S. haematobium*.

EPIDEMIOLOGY

Because of the complex life cycle of schistosomes, with snails as an intermediate host and humans as the final host, transmission is dependent on freshwater habitats that are suitable for the snails, are areas of human activity, and have climatic conditions favoring the survival of the snails and the development of the parasites inside the snail host. These requirements are reflected in the global distribution of schistosomiasis as well as in its microgeographic distribution within an endemic area. For *S. mansoni*, *S. haematobium*, and *S. intercalatum*, humans are the most important definitive host. *S. japonicum* and *S. mekongi* are zoonotic parasites, with a wide range of definitive hosts such as pigs, water buffaloes, and various rodents.

It is estimated that 230 million people are infected globally, with ~800 million people living in areas where there is a risk of infection **(Fig. 229-2)**. More than 70% of infected people live in sub-Saharan Africa. Schistosomiasis is the most important of the neglected tropical diseases and is second only to malaria in public health impact. It is a poverty-related disease, and infection is prevalent in areas where adequate water supplies and sanitary facilities are lacking. In these areas, people come into contact with infested water through a variety of activities, including bathing, washing clothes, and collecting water for drinking or cooking. In some areas, adults have a high occupational risk of exposure; fishermen, canal cleaners, and workers in rice fields fall into this category. Among children, playing in water and swimming pose a risk. Large-scale irrigation and hydroelectric power operations can create suitable habitats for host snails and thus increase the risk of schistosomiasis transmission.

In general, children living in endemic areas initially acquire infection at ~3–4 years of age—i.e., when they are old enough to walk and come into contact with infested water. However, infection does occur in much younger children. As children grow older, the prevalence and intensity of infection increase, peaking around puberty. A characteristic feature of schistosomiasis infection in human populations is a convex age–prevalence curve, with low prevalence in very young children, higher prevalence in older children with a peak at 10–15 years of age, and declining prevalence in adults. The same pattern is observed between age and intensity of infection and is attributable to various factors. Generally, children have more frequent, prolonged, and extensive water contact than adults through activities like playing and swimming. Furthermore, several studies have indicated that acquired immunity to schistosomiasis develops slowly over several years, so that adults are reinfected to a much lesser extent than children. These factors, combined with progressive spontaneous death of adult worms from infections acquired during childhood, lead to lower levels of infection in the adult population.

PATHOGENESIS

Cercarial invasion may be associated with dermatitis arising from dermal and subdermal inflammatory reactions in response to dying cercariae that trigger innate immune responses. However, most manifestations of schistosomiasis—in the acute, established, and chronic phases of infection—are due to immunologic reactions to eggs retained in host tissues.

Around the time when oviposition commences, acute schistosomiasis (Katayama fever) may occur (see "Clinical Features," below). Antigen excess from eggs results in the formation of soluble immune complexes, which may be deposited in several tissues and initiate a serum sickness–like illness. All evidence suggests that schistosome eggs, and not adult worms, induce the organ-specific morbidity caused by schistosome infections. Approximately half of the eggs are not excreted via feces or urine but are trapped in intestinal or hepatic tissue (*S. mansoni*, *S. japonicum*, and *S. mekongi*) or in the bladder and urogenital system (*S. haematobium*). The eggs induce a granulomatous host immune response composed primarily of lymphocytes, eosinophils, and alternatively activated macrophages. The lymphocytes produce various T_H2 cytokines such as interleukins 4, 5, and 13. Later, in the chronic phase of infection, regulatory cytokines are responsible for immunomodulation or downregulation of host responses to schistosome eggs and play an important role in reducing the size of granulomas.

When *S. mansoni* or *S. japonicum* eggs are swept into the small portal branches of the liver via the portal vein, they lodge in the presinusoidal periportal tissues. The formation of granulomas around the eggs can cause significant enlargement of the spleen and liver. High-intensity infections in children are often accompanied by hepatosplenomegaly

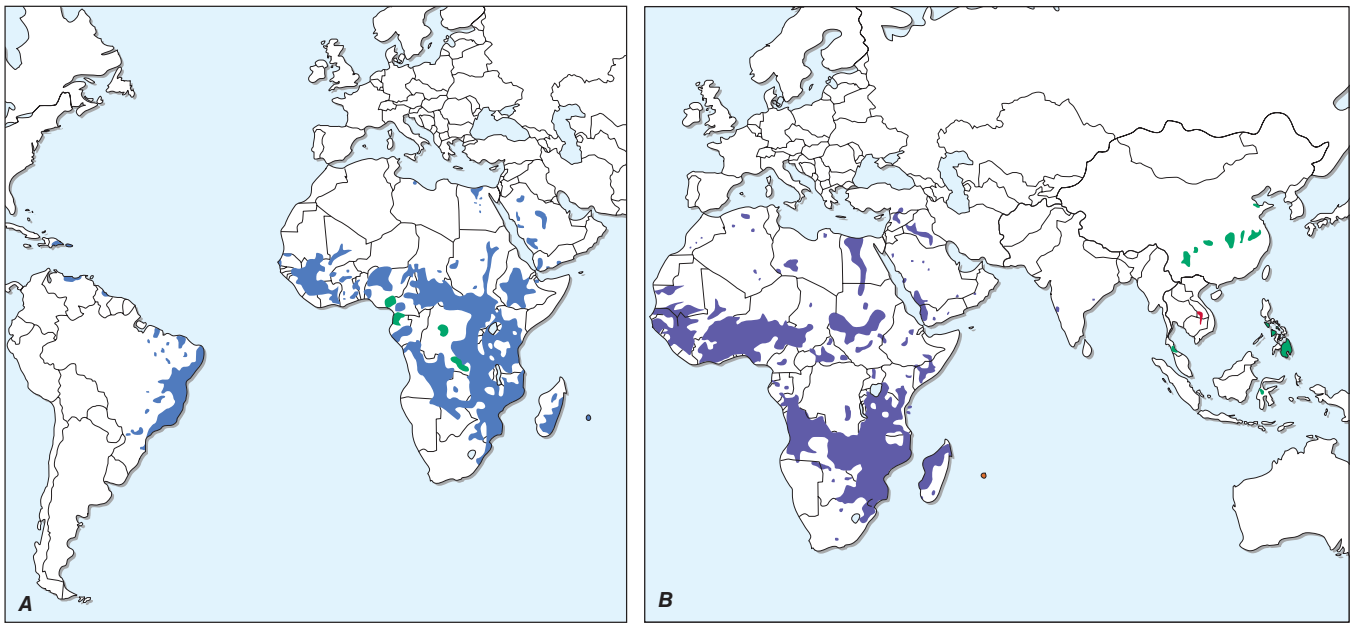

FIGURE 229-2 Global distribution of human schistosomiasis. ***A.*** *Schistosoma mansoni* infection (*dark blue*) is endemic in Africa, the Middle East, South America, and a few Caribbean countries. *S. intercalatum* infection (*green*) is endemic in sporadic foci in West and Central Africa. ***B.*** *Schistosoma haematobium* infection (*purple*) is endemic in Africa and the Middle East. The major endemic countries for *S. japonicum* infection (*green*) are China, the Philippines, and Indonesia. *Schistosoma mekongi* infection (*red*) is endemic in sporadic foci in Southeast Asia. *(Reprinted with permission from CH King, AAF Mahmoud: Schistosomiasis and Other Trematode Infections, in DL Kasper et al [eds], Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015, pp 1423–1429.)*

that generally decreases over time, partly because the number of eggs being deposited in the tissue gradually declines after the early teenage years as partial immunity to new infections develops and partly because of immunologic downregulation of the granulomatous response. However, in some infected individuals, egg-induced granulomatous responses lead to severe periportal fibrosis (*Symmers clay pipestem fibrosis*), with deposition of collagen around the portal vein, occlusion of the smaller portal branches, and severe, often irreversible, pathology. Occlusion of the portal branches may result in marked portal hypertension.

The signs and symptoms of *S. haematobium* infection relate to the worms' predilection for the veins of the urogenital plexus and result from deposition of eggs in the bladder, ureters, and genital organs. During established active infection, clusters of living eggs in the urogenital tissues can be found surrounded by intense inflammatory reactions and intense tissue eosinophilia. Movement of egg clusters into the lumen of the bladder is often followed by sloughing off of the epithelial surface, ulceration, and bleeding. Intense egg-induced tissue inflammation can result in bladder wall thickening and development of masses and pseudopolyps. Inflammation and granuloma formation around the ureteral ostia can lead to hydronephrosis.

Generally, late chronic-stage infections are characterized by accumulation of dead calcified eggs in tissue. Characteristic cervical lesions are found in *S. haematobium* infections, including active-stage lesions with intense tissue inflammation around live eggs and chronic-stage sandy patches with clusters of calcified eggs.

CLINICAL FEATURES

In general, disease manifestations of schistosomiasis occur in three stages—acute, active, and chronic—according to the duration and intensity of infection.

Cercarial Dermatitis ("Swimmer's Itch") Cercarial penetration of the skin may result in a maculopapular rash called cercarial dermatitis or "swimmer's itch." Cercarial dermatitis can develop in people who have not previously been exposed to schistosomiasis (e.g., travelers), whereas it is rare among people living in endemic areas. A particularly severe form of cercarial dermatitis is commonly seen after exposure to cercariae from avian schistosomes. These cercariae cannot complete their development in humans and die in the skin, causing an inflammatory allergic reaction. This form of cercarial dermatitis can occur in people who have been in contact with water from lakes (e.g., in Europe or the United States) where various species of water birds, such as ducks, geese, and swans, are found. The rash may last for 1–2 weeks. This condition normally requires no treatment, but systemic antihistamines or topical antihistamines or glucocorticoids can be used to reduce symptoms.

Acute Schistosomiasis (Katayama Fever) Symptomatic acute schistosomiasis, also known as Katayama fever or Katayama syndrome, is usually seen in travelers who have contracted the infection for the first time. The onset occurs between 2 weeks and 3 months after exposure to the parasite. The symptoms may appear suddenly and include fever, myalgia, general malaise and fatigue, headache, nonproductive cough, and intestinal symptoms such as abdominal tenderness or pain. Various combinations of these symptoms are often accompanied by eosinophilia and transient pulmonary infiltrates. Many patients recover spontaneously from acute schistosomiasis after 2–10 weeks, but the illness follows a more severe clinical course in some individuals, with weight loss, dyspnea, diarrhea, and hepatomegaly. Severe cerebral or spinal cord manifestations may occur, and even light infections may cause severe illness. The syndrome can, in rare cases, be fatal.

Differential diagnosis includes many other febrile infectious diseases with acute onset, including malaria, salmonellosis, and acute hepatitis. Fever and eosinophilia occur in trichinosis, tropical eosinophilia, invasive ankylostomiasis, strongyloidiasis, visceral larva migrans, and infections with *Opisthorchis* and *Clonorchis* species. Katayama fever is rare in people chronically exposed to infection in areas endemic for *S. mansoni* or *S. haematobium*.

Intestinal Schistosomiasis (*S. mansoni*, *S. japonicum*, *S. mekongi*) In intestinal schistosomiasis, adult worms are located in the mesenteric veins, and disease manifestations are associated with parasite eggs passing through or becoming trapped in intestinal tissue. This event induces mucosal granulomatous inflammation with microulcerations, superficial bleeding, and sometimes pseudopolyposis. The symptoms tend to be more pronounced with a high intensity of infection and include intermittent abdominal pain, loss of appetite, and sometimes bloody diarrhea. The clinical manifestations of *S. intercalatum* and *S. mekongi* infection are generally milder.

Hepatosplenic Schistosomiasis Hepatosplenic schistosomiasis is caused by schistosome eggs trapped in liver tissue and occurs in *S. mansoni* and *S. japonicum* infections. There are two distinct clinical entities: early inflammatory hepatosplenomegaly and late hepatosplenic disease with periportal fibrosis.

Early inflammatory hepatosplenic schistosomiasis is the main entity seen in children and adolescents. The liver is enlarged, especially the left lobe, and is smooth and firm. The spleen is enlarged, often extending below the umbilicus, and is firm or hard. Generally, ultrasonography shows no hepatic fibrosis. This form of hepatosplenic schistosomiasis may be found in up to 80% of infected children. Its severity is closely associated with the intensity of infection and may also be associated with concomitant chronic exposure to malaria.

Late hepatosplenic schistosomiasis with periportal or Symmers fibrosis may develop in young and middle-aged adults with long-standing, high-level exposure to infection. Patients with periportal fibrosis may excrete very few or no eggs in feces. During the early stage, the liver is enlarged, especially the left lobe; it is smooth and firm or hard. The spleen is enlarged, often massively, and is firm or hard. The patient may report a left hypochondrial mass with discomfort and anorexia. Ultrasonography reveals typical periportal fibrosis and dilation of the portal vein. Other complications include delayed growth and puberty, especially in *S. japonicum* infections, and severe anemia. Severe hepatosplenic schistosomiasis may lead to portal hypertension, but hepatic function usually remains normal, even in cases with marked periportal fibrosis and portal hypertension.

Ascites, attributable both to portal hypertension and to hypoalbuminemia, may be seen, especially in *S. japonicum* infection. Patients with severe hepatosplenic disease and portal hypertension may develop esophageal varices detectable by endoscopy or ultrasound. These patients may experience repeated bouts of hematemesis, melena, or both. Hematemesis is the most severe complication of hepatosplenic schistosomiasis, and death may result from massive loss of blood.

Urogenital Schistosomiasis (*S. haematobium*) The signs and symptoms of *S. haematobium* infection relate to the worms' predilection for the veins of the urogenital tract. Two stages of infection are recognized. An active stage occurring mainly in children, adolescents, and younger adults is characterized by egg excretion in the urine, with proteinuria and macroscopic or microscopic hematuria and deposition of eggs in the urinary tract. A chronic stage in older individuals is characterized by sparse or no urinary egg excretion despite urogenital tract pathology.

A characteristic sign in the active stage is painless, terminal hematuria. Dysuria and suprapubic discomfort or pain are associated with active urogenital schistosomiasis and may persist throughout the course of active infection. Eggs deposited in the bladder mucosa may give rise to an intense inflammatory response of the bladder wall, which may cause ureteric obstruction and lead to hydroureter and hydronephrosis. These early inflammatory lesions, including obstructive uropathy, can be visualized by ultrasonography.

As the infection progresses, the inflammatory component decreases and fibrosis becomes more prominent. The symptoms at this stage are nocturia, urine retention, dribbling, and incontinence. Cystoscopy reveals "sandy patches" composed of large numbers of calcified eggs surrounded by fibrous tissue and an atrophic mucosal surface. The ureters are less commonly involved, but ureteral fibrosis can cause irreversible obstructive uropathy that can progress to uremia.

Egg deposition may cause granulomas and lesions in the genital organs, most commonly in the cervix and vagina in women and the seminal vessels in men. The results may include dyspareunia, abnormal vaginal discharge, contact bleeding, and lower back pain in women and perineal pain, painful ejaculation, and hematospermia in men. Genital symptoms like bloody discharge and genital itch are associated with *S. haematobium* infection in school-aged girls living in schistosomiasis-endemic areas. Symptoms such as hematospermia and perineal discomfort have been described in travelers, and eggs have been demonstrated in seminal fluid. An association between female genital schistosomiasis and HIV infection has been demonstrated, but the impact of genital schistosomiasis on HIV transmission needs further elucidation.

S. haematobium has been classified by the International Agency for Research on Cancer (IARC) as definitely carcinogenic to humans (i.e., a group 1 carcinogen). Chronic *S. haematobium* infection is associated with squamous cell carcinoma of the urinary bladder.

Other Manifestations Worms and eggs can sometimes be located in ectopic sites, causing site-specific manifestations and symptoms. Neuroschistosomiasis is one of the most severe clinical forms of schistosomiasis and is caused by the inflammatory response around eggs in the cerebral or spinal venous plexus. *S. mansoni* and *S. haematobium* worms can end up in the spinal venous plexus, where they may cause transverse myelitis—an acute complication sometimes seen in travelers returning home with schistosomiasis. *S. japonicum* is mainly associated with granulomatous lesions in the brain, causing epileptic seizures, encephalopathy with headache, visual impairment, motor deficit, and ataxia. Pulmonary schistosomiasis is caused by portacaval shunting of eggs into the lung capillaries, where they induce granulomas in the perialveolar area. The consequences may be fibrosis, pulmonary hypertension, and cor pulmonale.

DIAGNOSIS

Anamnestic information on recent travels to endemic areas and exposure to freshwater bodies through recreational or other activities is important in the diagnosis of schistosomiasis in travelers. Information about exact geographic locations can facilitate identification of the relevant species of *Schistosoma*. Eosinophilia is a common finding and is often associated with helminthic infections such as schistosomiasis.

Detection of schistosome eggs in stool or urine is indicative of active infection and is the standard diagnostic method. The diagnosis is often based on the detection of eggs in a fixed small amount of excreta—e.g., 50 mg of stool or filtration of 10 mL of urine. This method is widely used among populations in endemic areas and allows quantitation of the level of infection (eggs per gram of feces or per 10 mL of urine). However, levels of egg excretion in people from nonendemic areas may be very low, in which case a larger sample and concentration methods (e.g., formol-ether concentration) may be needed.

Eggs can also be detected in rectal biopsies (both *S. mansoni* and *S. haematobium*) and occasionally in Pap smears and semen samples (*S. haematobium*). Polymerase chain reaction (PCR)–based detection of parasite DNA in stool or urine is more sensitive than parasitologic methods and is increasingly used. *Schistosoma* DNA can be detected in cerebrospinal fluid samples for diagnosis of neuroschistosomiasis.

Serology, with detection of specific antibodies to schistosomes, is useful in travelers but less so in people from endemic areas where transmission is ongoing. The serologic assays employed at the CDC are a Falcon assay screening test/enzyme-linked immunosorbent assay (FAST-ELISA) using *S. mansoni* adult microsomal antigen and a confirmatory species-specific immunoblot assay performed in light of the patient's travel history.

Schistosome proteoglycans—circulating anodic and cathodic antigens (CAAs and CCAs)—regurgitated into the bloodstream by the feeding worms can be detected in serum and urine by ELISA or monoclonal antibody–based lateral flow assays. The presence of CAA or CCA is an indication of active infection, and levels of these antigens correlate well with the intensity of infection. However, detection of CAAs and CCAs is not currently suitable for diagnosis in travelers, who are likely to have low levels of infection and very few worms. A commercially available point-of-care assay (Rapid Medical Diagnostics, Pretoria, South Africa) that detects CCA in urine is now widely used for screening of infected communities in relation to mass drug administration programs.

TREATMENT

Schistosomiasis

The drug of choice for treatment of schistosomiasis is praziquantel. It is administered orally, is available as 600-mg tablets, and is effective against all schistosome species infecting humans. The drug is safe and well tolerated. Standard regimens are shown in **Table 229-2**. In patients who are not cured by initial treatment, the same dose can be repeated at weekly intervals for 2 weeks. Since praziquantel does not affect the young migrating stages of the schistosomes, it may be necessary to repeat the dose 6–12 weeks later, especially if eosinophilia or symptoms persist despite treatment.

As a general principle, all patients with acute schistosomiasis should be treated with praziquantel. Glucocorticoids can be added in Katayama fever to suppress the hypersensitivity reaction. However, treatment for acute schistosomiasis or Katayama fever must be adjusted appropriately for each case, and in the most severe cases management in an acute-care setting is necessary.

Praziquantel is effective in cerebral *S. japonicum* infections, resulting in rapid dissipation of cerebral edema and resolution of cerebral masses. However, glucocorticoids and anticonvulsants are sometimes needed in neuroschistosomiasis.

The effect of antischistosomal treatment on disease manifestations depends on the stage and severity of the lesions. Early hepatosplenomegaly, mild or moderate fibrosis, and urinary bladder lesions seen during active infection resolve after chemotherapy. However, for late-stage manifestations (e.g., severe fibrosis with portal hypertension), praziquantel treatment is only one component of management, since the main complications are due to obstructive pathology. Management of portal hypertension and prevention of bleeding from esophageal varices should follow clinical guidelines for treatment of these conditions.

TABLE 229–2 Treatment of Schistosomiasis and Food-Borne Trematode Infections

INFECTION	DRUG OF CHOICE	ADULT DOSE[a]
Schistosoma mansoni, *S. haematobium*, *S. intercalatum*, *S. guineensis*	Praziquantel[b]	40 mg/kg PO in 2 divided doses for 1 day
S. japonicum, *S. mekongi*	Praziquantel	60 mg/kg PO in 3 divided doses for 1 day
Clonorchis sinensis, *Opisthorchis viverrini*, *Opisthorchis felineus*	Praziquantel	25 mg/kg PO tid for 2 consecutive days
Fasciola hepatica, *Fasciola gigantica*	Triclabendazole[c]	10 mg/kg PO as a single dose[d]
Fasciolopsis buski	Praziquantel	75 mg/kg PO in 3 divided doses for 1 day
Echinostoma spp., *Heterophyes heterophyes*, several other species	Praziquantel	25 mg/kg PO tid
Paragonimus westermani, *Paragonimus kellicotti*	Praziquantel	25 mg/kg PO tid for 2 consecutive days
	Triclabendazole[c]	10 mg/kg PO once (or twice, 12–24 h apart)

[a]The pediatric dose is the same as the adult dose in all instances. [b]The safety of praziquantel in children <4 years old has not been established, although many children in this age group have been treated with praziquantel during mass drug-administration programs. [c]Triclabendazole is not approved by the U.S. Food and Drug Administration and is not yet commercially available in the United States. It is available through the Centers for Disease Control and Prevention Drug Service (404-639-3670; *drugservice@cdc.gov*). [d]A second dose (10 mg/kg) can be administered 12–24 h after the first dose in severe fascioliasis.

PREVENTION AND CONTROL

Schistosomiasis is contracted through direct contact with infested freshwater. Travelers should be made aware of the risk of infection if they come into contact with freshwater sources in schistosomiasis-endemic areas. For people living in rural areas where schistosomiasis is endemic, it may be very difficult, if not impossible, to avoid water contact—for example, during occupational activities such as fishing and working in rice fields. Schistosomiasis is a poverty-related disease, and access to safe water and good sanitary facilities may rarely be available. Because *S. japonicum* is a zoonotic parasite, preventive measures should target not only the human population but also animals such as water buffalo, which act as reservoirs for infection.

Praziquantel treatment of infected people, often during mass drug-administration programs, is a cornerstone of the management and control of schistosomiasis. Regular treatment will reduce the level of schistosomiasis morbidity in affected populations. However, treatment should be combined with other relevant strategies, such as control of the intermediate host snails, improved water-quality and sanitation facilities, and health education. Schistosomiasis control measures should be integrated into local health programs.

There have been intensive efforts to develop vaccines, but none is yet available. One vaccine candidate, *S. haematobium* 28GST, has been tested in a clinical phase 3 trial in populations living in an endemic area.

FOOD-BORNE TREMATODE INFECTIONS

Food-borne trematode infections are a group of zoonotic diseases caused by hepatic, intestinal, and pulmonary parasitic flukes. These infections are contracted by ingestion of infective parasites in undercooked aquatic food or water plants. In 2005, an estimated 56.2 million people were infected with food-borne trematodes and 7.9 million had severe sequelae of these infections.

LIVER FLUKES

The most important liver flukes causing human infections are the related species *Opisthorchis viverrini* and *Opisthorchis felineus*, which cause opisthorchiasis; *Clonorchis sinensis*, which causes clonorchiasis; and *Fasciola hepatica* and *Fasciola gigantica*, which cause fascioliasis (Table 229-1).

Opisthorchiasis and Clonorchiasis *O. viverrini* is found mainly in northeastern Thailand, Laos, and Cambodia; *O. felineus* mainly in Europe and Asia, including the former Soviet Union; and *C. sinensis* in Asia, including Korea, China, Taiwan, Vietnam, Japan, and Asian regions of Russia. Parasite eggs excreted from infected humans or animals are ingested by a host snail (the first intermediate host), where they undergo several developmental stages. Cercariae are then released from the snail and penetrate freshwater fish (the second intermediate host), encysting as metacercariae in the muscles or under the scales. Humans become infected by eating raw or undercooked fish from endemic countries. After ingestion, the metacercariae excyst in gastric juices and migrate via the duodenum, the ampulla of Vater, and the extrahepatic biliary system to the intrahepatic bile ducts.

The clinical manifestations of infection with *Opisthorchis* species and *C. sinensis* are similar. Pathologic changes are typically seen in the bile ducts, liver, and gallbladder **(Table 229-3)**. Tissue damage and intense inflammation is caused by mechanical and chemical irritation and immune responses to worms or worm products, and chronic inflammation may result in the development of cholangiocarcinoma. Both *O. viverrini* and *C. sinensis* are classified by the IARC as definitely carcinogenic (class 1). Acute and light infections are mostly asymptomatic, but hepatitis-like signs and symptoms, with high fever and chills, have been reported, especially in *O. felineus* infections. In general, only heavily infected people have symptoms and severe complications (Table 229-3).

The diagnosis of these infections is based on microscopic identification of parasite eggs in stool specimens. The eggs of *Opisthorchis* are indistinguishable from those of *Clonorchis*.

Fascioliasis Fascioliasis occurs in many areas of the world and usually is caused by *Fasciola hepatica*, a common liver fluke of sheep and cattle. *F. hepatica* is found in more than 50 countries on all continents except Antarctica; *F. gigantica* is less widespread. The areas with the highest known rates of human *Fasciola* infection are in the Andean highlands of Bolivia and Peru. In other areas where fascioliasis is found, human cases are sporadic.

Unlike the other liver flukes, *Fasciola* species have no second intermediate host, as their infectious metacercariae adhere directly to aquatic plants. Humans usually acquire infection by ingesting aquatic plants, such as watercress, that contain viable metacercariae or by drinking water with free metacercariae.

After metacercariae have excysted in the duodenum, *Fasciola* species migrate through the intestinal wall into the body cavity, penetrate the liver capsule, and move through the liver into the bile ducts. This migration route is different from that of other liver flukes and gives

TABLE 229–3 Clinical Features of Food-Borne Trematode Infections

INFECTION	SYMPTOMS OR SIGNS		COMPLICATIONS
	EARLY OR ACUTE STAGE	ESTABLISHED OR CHRONIC STAGE	
Liver Flukes			
Clonorchis sinensis, *Opisthorchis viverrini*, *Opisthorchis felineus*	Often asymptomatic; sometimes hepatitis-like symptoms and high fever (especially with *O. felineus*)	Biliary colic, cholestatic jaundice, recurrent cholangitis and cholelithiasis; hepatomegaly, gallbladder enlargement, periductal fibrosis. Light infections are often asymptomatic and remain so for years.	Pancreatitis, cholangiocarcinoma[a]
Fasciola hepatica, *Fasciola gigantica*	Acute onset (1–4 weeks after infection) with high fever, weight loss, sometimes urticaria and liver tenderness	Biliary colic, cholestatic jaundice, recurrent cholangitis and cholelithiasis; thickening, enlargement, and fibrosis of biliary ducts; sometimes repeated relapses of acute symptoms	Pancreatitis. In rare cases: ectopic infections in the central nervous system, orbital area, gastrointestinal tract, lungs, and other organs. Rarely, fascioliasis can be fatal.
Intestinal Flukes			
Fasciolopsis buski, *Echinostoma* spp., *Heterophyes heterophyes*, several other species	Often asymptomatic; sometimes nonspecific gastrointestinal symptoms	Heavy infection may lead to ulceration of intestinal mucosa and malabsorption. Mild infections are often asymptomatic.	Malnutrition, anemia; rarely, ectopic infection in the central nervous system
Lung Flukes			
Paragonimus westermani, *Paragonimus kellicotti*	Often asymptomatic; sometimes insidious onset with anorexia and weight loss	Bronchitis-, asthma-, and tuberculosis-like symptoms and signs such as chronic cough, dyspnea, bloody ("rusty") sputum	Pulmonary cyst formation; ectopic infection in the central nervous system, eyes, skin, heart, abdominal and reproductive organs

[a]Carcinogenesis has not yet been established for *O. felineus*.

rise to symptoms during the acute migratory phase; the parasites may cause tissue destruction, focal bleeding, and inflammation. Some migrating flukes may deviate from their usual route to cause ectopic infections. In the established latent stage of infection, the parasites may cause bile duct inflammation, resulting in thickening and expansion of the ducts, fibrosis, and ultimately biliary obstruction (Table 229-3). Although some infected people are asymptomatic in the latent phase, others may experience repeated relapses of acute manifestations.

The most widely used diagnostic approach is direct detection of *Fasciola* eggs by microscopic examination of stool or of duodenal or biliary aspirates. Eggs generally cannot be detected until 3–4 months after exposure, whereas antibodies to the parasite may become detectable 2–4 weeks after exposure. More than one stool specimen may be needed for diagnosis, especially in light infections.

INTESTINAL FLUKES

More than 70 species of intestinal flukes can cause human infection. These parasites are found in different geographic areas, with a relatively high prevalence in Southeast Asia. Humans are infected by ingestion of infective metacercariae attached to aquatic plants (*Fasciolopsis buski*) or encysted in freshwater fish. Flukes mature in the human intestines, and eggs are passed with feces. Mechanical irritation of the intestinal wall and inflammation may lead to nonspecific gastrointestinal symptoms such as diarrhea, constipation, and abdominal pain. Most individuals infected with intestinal flukes are asymptomatic, but heavy infections can be severe, with intestinal mucosal ulcerations and malabsorption (Table 229-3). The diagnosis is established by detection of eggs in stool samples. However, eggs from various intestinal trematodes are often morphologically similar, and it is very difficult to distinguish among species. A cautionary note: *Fasciola* eggs can be difficult to distinguish on the basis of morphologic criteria from the eggs of the intestinal fluke *F. buski*. The distinction has implications for therapy: infection with *F. buski* is treated with praziquantel, which is not effective against fascioliasis (Table 229-2).

LUNG FLUKES

Paragonimiasis is a parasitic lung infection caused by lung flukes of the genus *Paragonimus*. It is a food-borne parasitic zoonosis, with most cases reported from Asia and attributable to consumption of raw or undercooked freshwater crustaceans. *Paragonimus westermani* and related species (e.g., *Paragonimus africanus*) are endemic in West Africa, Central and South America, and Asia. The United States has one indigenous species of lung fluke, *Paragonimus kellicotti.*

Paragonimus species require two intermediate hosts: first, a freshwater snail; and second, a freshwater crustacean, such as a freshwater crab. Humans are infected by consuming raw or undercooked infected crustaceans containing *Paragonimus* metacercariae. *Paragonimus* infects other carnivores such as cats, dogs, foxes, rodents, and pigs in addition to humans. After ingestion, metacercariae quickly penetrate the duodenum and traverse the peritoneal cavity, diaphragm, and parietal pleura to mature into hermaphroditic worm pairs in the pleural spaces or lungs within 6–10 weeks. Adults cross-fertilize in cystic cavities in the pleural spaces or lungs within another 4–16 weeks and release unembryonated eggs into bronchioles. The eggs are then coughed up in bloody ("rusty") sputum and either discharged in sputum or swallowed and later excreted in feces. Unembryonated eggs are passed from the mammalian host into freshwater ecosystems, where they infect intermediate host snails.

The symptoms and signs of paragonimiasis are fever, cough, hemoptysis, and peripheral eosinophilia. Some patients with paragonimiasis and low parasite burdens may remain relatively asymptomatic for prolonged periods or may have recurrent attacks of cough, sputum production, fever, and night sweats that mimic tuberculosis. Infective metacercariae may migrate to extrapulmonary sites such as the brain (cerebral paragonimiasis).

Pulmonary paragonimiasis is diagnosed by detection of parasite ova in sputum and/or feces. Serology can be helpful in egg-negative cases and in cerebral paragonimiasis. Anamnestic information about the consumption of raw or undercooked freshwater crabs by immigrants, expatriates, and returning travelers—and, in the United States, the consumption of raw or undercooked crayfish from freshwater river systems where *P. kellicotti* is endemic—is important in patients presenting with fever, cough, hemoptysis, pleural effusions, and peripheral eosinophilia.

TREATMENT

Food-Borne Trematode Infections

Praziquantel and triclabendazole are the two drugs of choice; Table 229-2 summarizes the dosages recommended for the various trematode infections. All confirmed cases of human paragonimiasis should be treated with praziquantel (Table 229-2) to avoid the complications of extrapulmonary disease. Surgical management may be needed for pulmonary or cerebral lesions.

CONTROL AND PREVENTION

Drugs are currently the main method of controlling the morbidity associated with food-borne trematode infections, but integrated programs (including improved sanitation; food inspections; and information, education, and communication campaigns) are important for sustainable disease control. Collaboration with other sectors (e.g., agricultural, environmental, and educational) is necessary to tackle highly complex situations in which human behavior, biological factors, and agricultural practices all play a role.

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230 Cestode Infections

A. Clinton White, Jr., Peter F. Weller

Cestodes, or tapeworms, are segmented worms. The adults reside in the gastrointestinal tract, but the larvae can be found in almost any organ. Human tapeworm infections can be divided into two major clinical groups. In one group, humans are the definitive hosts, with the adult tapeworms living in the gastrointestinal tract (*Taenia saginata*, *Diphyllobothrium*, and *Dipylidium caninum*). In the other, humans are

intermediate hosts, with larval-stage parasites present in the tissues; diseases in this category include echinococcosis, sparganosis, and coenurosis. Humans may be the definitive and/or intermediate hosts for *Taenia solium*; both stages of *Hymenolepis nana* are found simultaneously in the human intestines.

The ribbon-shaped tapeworm attaches to the intestinal mucosa by means of sucking cups or hooks located on the scolex. Behind the scolex is a short, narrow neck from which proglottids (segments) form. As each proglottid matures, it is displaced further back from the neck by the formation of new, less mature segments. The progressively elongating chain of attached proglottids, called the *strobila*, constitutes the bulk of the tapeworm. The length varies among species. In some, the tapeworm may consist of more than 1000 proglottids and may be several meters long. The mature proglottids are hermaphroditic and produce eggs, which are subsequently released. Because eggs of the different *Taenia* species are morphologically identical, differences in the morphology of the scolex or proglottids provide the basis for diagnostic identification to the species level.

Most human tapeworms require at least one intermediate host for complete larval development. After ingestion of the eggs or proglottids by an intermediate host, the larval oncospheres are activated, escape the egg, and penetrate the intestinal mucosa. The oncosphere migrates to tissues and develops into an encysted form known as a *cysticercus* (single scolex), a *coenurus* (multiple scolices), or a *hydatid* (cyst with daughter cysts, each containing several protoscolices). The definitive host's ingestion of tissues containing a cyst enables a scolex to develop into a tapeworm.

TAENIASIS SAGINATA AND TAENIASIS ASIATICA

The beef tapeworm *T. saginata* occurs in all countries where raw or undercooked beef is eaten. It is most prevalent in sub-Saharan African and Middle Eastern countries. *Taenia asiatica* is closely related to *T. saginata* and is found in Asia, with pigs as intermediate hosts. The clinical manifestations and morphology of these two species are very similar and are therefore discussed together.

Etiology and Pathogenesis Humans are the only definitive host for the adult stage of *T. saginata* and *T. asiatica*. The tapeworms, which can reach 8 m in length with 1000–2000 proglottids, inhabit the upper jejunum. The scolex of *T. saginata* has four prominent suckers, whereas *T. asiatica* has an unarmed rostellum. Each gravid segment has 15–30 uterine branches (in contrast to 8–12 for *T. solium*). The eggs are indistinguishable from those of *T. solium*; they measure 30–40 µm, contain the oncosphere, and have a thick brown striated shell. Eggs deposited on vegetation can live for months or years until they are ingested by cattle or other herbivores (*T. saginata*) or pigs (*T. asiatica*). The embryo released after ingestion invades the intestinal wall and is carried to striated muscle or viscera, where it transforms into the cysticercus. When ingested in raw or undercooked meat, the cysticercus evaginates and forms a tapeworm in the human intestines. Over ~2 months, the adult worm matures and begins to produce eggs.

Clinical Manifestations Patients become aware of the infection most commonly by noting passage of proglottids in their feces. The proglottids of *T. saginata* are motile, and patients may experience perianal discomfort when proglottids are discharged. Mild abdominal pain or discomfort, nausea, change in appetite, weakness, and weight loss can occur.

Diagnosis The diagnosis is made by the detection of eggs or proglottids in the stool. Eggs may also be present in the perianal area; thus, if proglottids or eggs are not found in the stool, the perianal region should be examined with use of a cellophane-tape swab (as in pinworm infection; Chap. 227). Distinguishing *T. saginata* or *T. asiatica* from *T. solium* requires examination of mature proglottids. All three species can be distinguished by examining the scolex. Available serologic tests are not helpful diagnostically. Eosinophilia and elevated levels of serum IgE are usually absent.

TREATMENT

Taeniasis Saginata and Taeniasis Asiatica

A single dose of praziquantel (10 mg/kg) is highly effective.

Prevention The major method of preventing infection is the adequate cooking of beef or pork viscera; exposure to temperatures as low as 56°C for 5 min will destroy cysticerci. Refrigeration or salting for long periods or freezing at –10°C for 9 days also kills cysticerci in beef. General preventive measures include inspection of beef and proper disposal of human feces.

TAENIASIS SOLIUM AND CYSTICERCOSIS

The pork tapeworm *T. solium* can cause two distinct forms of infection in humans: adult tapeworms in the intestine or larval forms in the tissues (cysticercosis). Humans are the only definitive hosts for *T. solium*; pigs are the usual intermediate hosts, although other animals may harbor the larval forms.

T. solium is found worldwide in areas where pigs are raised and have access to human feces. However, it is most prevalent in Latin America, sub-Saharan Africa, China, India, and Southeast Asia. Cysticercosis occurs in industrialized nations largely as a result of the immigration of infected persons from endemic areas.

Etiology and Pathogenesis The adult tapeworm generally resides in the upper jejunum. The scolex attaches by both sucking disks and two rows of hooklets. The adult worm usually lives for a few years. The mature tapeworm, usually ~3 m in length, may have as many as 1000 proglottids, each of which produces up to 50,000 eggs. Proglottids are released and excreted into the feces, and the eggs in these proglottids are infective for both humans and animals. After ingestion of eggs by the pig intermediate host, the larvae are activated, escape the egg, penetrate the intestinal wall, and are carried to many tissues; they are most frequently identified in striated muscle of the neck, tongue, and trunk. Within 60–90 days, the encysted larval stage develops. These cysticerci can survive for months to years. By ingesting undercooked pork containing cysticerci, humans acquire infections that lead to intestinal tapeworms. Infections that cause human cysticercosis follow the ingestion of *T. solium* eggs. The eggs are sticky and may be found under the fingernails of tapeworm carriers. Transmission is usually associated with close contact with a tapeworm carrier. Autoinfection may occur if an individual with an egg-producing tapeworm ingests eggs derived from his or her own feces.

Clinical Manifestations Intestinal infections with *T. solium* may be asymptomatic. Fecal passage of proglottids may be noted by patients. Other symptoms are infrequent.

In cysticercosis, the clinical manifestations are variable. Cysticerci can be found anywhere in the body but are most commonly detected in the brain, cerebrospinal fluid (CSF), skeletal muscle, subcutaneous tissue, or eye. The clinical presentation of cysticercosis depends on the number and location of cysticerci as well as on the extent of associated inflammatory responses or scarring. Neurologic manifestations are the most common **(Fig. 230-1)**. Seizures are associated with inflammation surrounding cysticerci in the brain parenchyma. These seizures may be generalized, focal, or Jacksonian. Hydrocephalus results from CSF flow obstruction by cysticerci and accompanying inflammation or by CSF outflow obstruction from arachnoiditis. Symptoms of increased intracranial pressure, including headache, nausea, vomiting, changes in vision, dizziness, ataxia, or confusion, are often evident. Patients with hydrocephalus may develop papilledema or display altered mental status. When cysticerci develop at the base of the brain or in the subarachnoid space, they may cause chronic meningitis or arachnoiditis, communicating hydrocephalus, hemorrhages, or strokes.

Diagnosis The diagnosis of intestinal *T. solium* infection is made by the detection of eggs or proglottids, as described for *T. saginata*. More sensitive methods, including antigen-capture enzyme-linked immunosorbent assay (ELISA), polymerase chain reaction (PCR), and

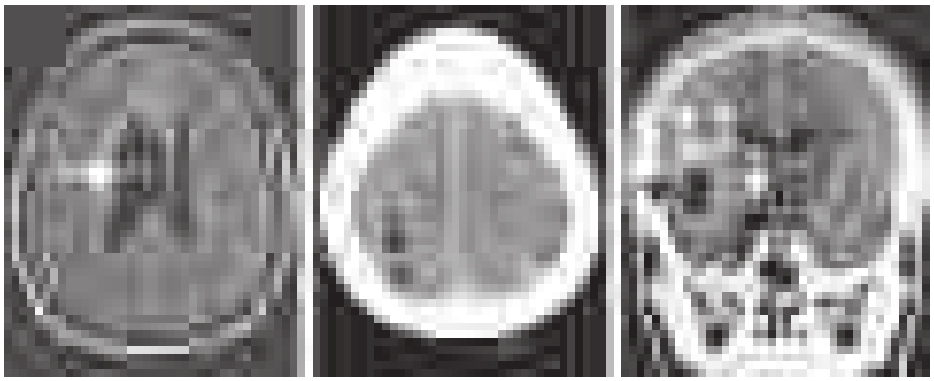

FIGURE 230-1 Neurocysticercosis is caused by *Taenia solium*. Neurologic infection can be classified on the basis of the location and viability of the parasites. When the parasites are in the ventricles, they often cause obstructive hydrocephalus. ***Left:*** Magnetic resonance imaging showing a cysticercus in the lateral ventricle, with resultant hydrocephalus. The *arrow* points to the scolex within the cystic parasite. ***Center:*** CT showing a parenchymal cysticercus, with enhancement of the cyst wall and an internal scolex (*arrow*). ***Right:*** Multiple cysticerci, including calcified lesions from prior infection (*arrowheads*), viable cysticerci in the basilar cisterns (*white arrow*), and a large degenerating cysticercus in the Sylvian fissure (*black arrow*). *(Modified with permission from JC Bandres et al: Clin Infect Dis 15:799, 1992. © The University of Chicago Press.)*

serology for tapeworm stage-specific antigens, are currently available only as research techniques. In cysticercosis, diagnosis can be difficult. A panel of international experts recently proposed revised diagnostic criteria **(Table 230-1)**. Diagnostic certainty is possible only with definite demonstration of the parasite (absolute criteria). This task can be accomplished by histologic observation of the parasite in excised tissue, by funduscopic visualization of the parasite in the subretinal space of the eye, or by neuroimaging studies with definite evidence of a cystic lesion containing a characteristic scolex (Fig. 230-1). With improving resolution of neuroimaging studies, the scolex can now be identified in a large proportion of cases. In other instances, a clinical diagnosis is based on a combination of clinical presentation, radiographic studies, and exposure history (including serodiagnosis).

Neuroimaging findings constitute the primary major diagnostic criteria (Fig. 230-1). Major findings include cystic lesions with or without enhancement (e.g., ring enhancement), one or more nodular calcifications (which may also have associated enhancement), focal enhancing lesions, or multilobulated cystic lesions in the subarachnoid space. Cysticerci in the brain parenchyma are usually 5–20 mm in diameter and rounded. Cystic lesions in the subarachnoid space or fissures may enlarge up to 6 cm in diameter and may be lobulated. For cysticerci within the subarachnoid space or ventricles, the walls may be very thin and the cyst fluid is often isodense with CSF. Thus, obstructive hydrocephalus or enhancement of the basilar meninges may be the only finding on CT in extraparenchymal neurocysticercosis. However, since these findings are less specific, they are considered only minor criteria. Cysticerci in the ventricles or subarachnoid space are more readily identified by MRI, especially with three-dimensional views (e.g., fast imaging employing steady-state acquisition [FIESTA] or three-dimensional constructive interference in steady state [3D CISS]). CT is more sensitive than MRI in identifying calcified lesions, whereas MRI is better for identifying cystic lesions, scolices, and enhancement. Spontaneous resolution, resolution after therapy with albendazole, or mobile cystic lesions within the ventricles are findings that can confirm the diagnosis of neurocysticercosis.

Prior exposure significantly modifies the interpretation of neuroimaging studies. Detection of specific antibodies to or antigens of *T. solium* are major exposure criteria. Antibody tests using unfractionated antigens (e.g., ELISAs using crude parasite antigen) have high rates of false-positive and false-negative results and should be avoided. An immunoblot assay using lentil lectin–purified glycoproteins is >99% specific and highly sensitive. However, patients with single intracranial lesions or with calcifications may be seronegative. With this assay, serum samples provide greater diagnostic sensitivity than CSF. All of the diagnostic antigens have been cloned, and assays using recombinant antigens are being developed. Antigen detection assays using monoclonal antibodies to detect parasite antigen in the blood or CSF may also facilitate diagnosis and patient follow-up. These assays are currently available commercially in Europe but not in the United States.

Other major clinical/exposure criteria for neurocysticercosis include the presence of cysticerci outside the central nervous system (CNS) (e.g., typical cigar-shaped calcifications in muscle) or exposure to a tapeworm carrier or a household member infected with *T. solium*. Minor clinical/exposure criteria include residence in an endemic area or clinical symptoms suggestive of neurocysticercosis (e.g., seizures or obstructive hydrocephalus).

Studies have demonstrated that clinical criteria may aid in diagnosis in selected cases. In patients from endemic areas who had single enhancing lesions presenting with seizures, a normal physical examination, and no evidence of systemic disease (e.g., no fever, adenopathy, or chest radiographic abnormalities), the constellation of rounded CT lesions 5–20 mm in diameter with no midline shift was almost always caused by neurocysticercosis.

A definite or probable diagnosis is made in accordance with the criteria and combinations of criteria listed in the footnote of Table 230-1. Patients may have CSF pleocytosis with a predominance of

TABLE 230-1 Revised Diagnostic Criteria for Neurocysticercosis[a]

1. Absolute criteria	
	a. Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
	b. Visualization of subretinal cysticercus
	c. Conclusive demonstration of a scolex within a cystic lesion on neuroimaging studies
2. Neuroimaging criteria	
	a. Major neuroimaging criteria
	Cystic lesions without a discernible scolex, typical small enhancing lesions, multilobulated cystic lesions in the subarachnoid space, typical parenchymal brain calcifications
	b. Confirmative neuroimaging criteria
	Resolution of cystic lesions spontaneously or after cysticidal drug therapy
	Migration of ventricular cysts documented on sequential neuroimaging studies
	c. Minor neuroimaging criteria
	Obstructive hydrocephalus or abnormal enhancement of basal leptomeninges
3. Clinical/exposure criteria	
	a. Major clinical/exposure criteria
	Detection of specific anticysticercal antibodies (e.g., by enzyme-linked immunoelectrotransfer blot [EITB]) or cysticercal antigens by well-standardized immunodiagnostic tests
	Cysticercosis outside the central nervous system
	Evidence of a household contact with *T. solium* infection
	b. Minor clinical/exposure criteria
	Clinical manifestations suggestive of neurocysticercosis
	Individuals coming from or living in an area where cysticercosis is endemic

[a]Diagnosis is confirmed by one absolute criterion, by two major criteria or one major and one confirmatory neuroimaging criteria plus any clinical/exposure criterion, or by one major neuroimaging criterion plus two clinical/exposure criteria (including at least one major clinical/exposure criterion), together with the exclusion of other pathologies producing similar neuroimaging findings. A probable diagnosis is supported by one major neuroimaging criterion plus any two clinical/exposure criteria or by one minor neuroimaging criterion plus at least one major clinical/exposure criterion.

Source: Modified from OH Del Brutto et al: J Neurol Sci 372:202, 2017.

lymphocytes, neutrophils, or eosinophils. The protein level in CSF may be elevated; the glucose concentration is usually normal but may be depressed.

TREATMENT

Taeniasis Solium and Cysticercosis

Intestinal *T. solium* infection is treated with a single dose of praziquantel (10 mg/kg). However, praziquantel occasionally evokes an inflammatory response in the CNS if concomitant cryptic cysticercosis is present. Niclosamide (2 g) is also effective but is not widely available.

The initial management of neurocysticercosis should focus on symptom-based treatment of seizures or hydrocephalus. Seizures can usually be controlled with antiepileptic treatment. If parenchymal lesions resolve without development of calcifications and patients remain free of seizures, antiepileptic therapy can usually be discontinued after 1–2 years. Placebo-controlled trials are clarifying the clinical advantage of antiparasitic drugs for parenchymal neurocysticercosis. Trends toward faster resolution of neuroradiologic abnormalities have been observed in most studies. The clinical benefits are less dramatic and consist mainly of shortening the period during which recurrent seizures occur and decreasing the number of patients who have many recurrent seizures. For the treatment of patients with brain parenchymal cysticerci, most authorities favor antiparasitic drugs, including albendazole (15 mg/kg per day for 8–28 days) or praziquantel (50–100 mg/kg daily in three divided doses for 15–30 days). A combination of albendazole and praziquantel (50 mg/kg per day) is more effective in patients with more than two cystic lesions. A longer course or combination therapy is often needed in patients with multiple subarachnoid cysticerci. Both agents may exacerbate the inflammatory response around the dying parasite, thereby exacerbating seizures or hydrocephalus as well. Thus, patients receiving these drugs should be carefully monitored. High-dose glucocorticoids should be used during treatment. Because glucocorticoids induce first-pass metabolism of praziquantel and may decrease its antiparasitic effect, cimetidine should be coadministered to inhibit praziquantel metabolism.

For patients with hydrocephalus, the emergent reduction of intracranial pressure is the mainstay of therapy. In the case of obstructive hydrocephalus, the preferred approach is removal of the cysticercus via endoscopic surgery. However, this intervention is not always possible. An alternative approach is initially to perform a diverting procedure, such as ventriculoperitoneal shunting. Historically, shunts have usually failed, but failure rates have been lowered by administration of antiparasitic drugs and glucocorticoids. Open craniotomy to remove cysticerci is now required only infrequently but is effective for fourth-ventricular cysticerci. For patients with subarachnoid cysts or giant cysticerci, anti-inflammatory medications such as glucocorticoids are needed to reduce arachnoiditis and accompanying vasculitis. Most authorities recommend prolonged courses of antiparasitic drugs as well as shunting when hydrocephalus is present. Methotrexate should be used as a steroid-sparing agent in patients requiring prolonged therapy. In patients with diffuse cerebral edema and elevated intracranial pressure due to multiple inflamed lesions, glucocorticoids are the mainstay of therapy, and antiparasitic drugs should be avoided. For ocular and spinal medullary lesions, drug-induced inflammation may cause irreversible damage. Ocular disease should be managed surgically. Recent data suggest that either medical or surgical therapy can be used for spinal disease.

Prevention Measures for the prevention of intestinal *T. solium* infection consist of the application to pork of precautions similar to those described above for beef with regard to *T. saginata* infection. The prevention of cysticercosis involves minimizing the opportunities for ingestion of fecally derived eggs by means of good personal hygiene, effective fecal disposal, and treatment and prevention of human intestinal infections. Mass chemotherapy has been administered to human and porcine populations in efforts at disease eradication. Finally, vaccines to prevent porcine cysticercosis have shown promise in studies and are under development.

ECHINOCOCCOSIS

Echinococcosis is an infection caused in humans by the larval stage of *Echinococcus granulosus* sensu lato, *E. multilocularis*, or *E. vogeli*. *E. granulosus* sensu lato parasites produce cystic hydatid disease, with unilocular cystic lesions. These infections are prevalent in most areas where livestock is raised in association with dogs. Molecular evidence has demonstrated that *E. granulosus* strains belong to a range of genotypes and more than one species. Currently, human cystic hydatid disease is caused by organisms formerly termed *E. granulosus* that are now classified as *E. granulosus* sensu stricto (genotypes 1–3), *E. canadensis* (genotypes 6–8 and 10), and *E. ortleppi* (genotype 5). Other species—*E. equinus* (genotype 4) and *E. felidis* (lion strain)—have not been identified in human infections. *E. granulosus* sensu lato parasites are found on all continents, with areas of high prevalence in China, central Asia, the Middle East, the Mediterranean region, eastern Africa, and parts of South America. *E. multilocularis*, which causes multilocular alveolar lesions that are locally invasive, is found in Alpine, sub-Arctic, or Arctic regions, including central and northern Europe; western China and central Asia; and isolated areas in North America. *E. vogeli* causes polycystic hydatid disease and is found only in Central and South America.

Like other cestodes, echinococcal species have both intermediate and definitive hosts. The definitive hosts are canines that pass eggs in their feces. After the ingestion of eggs, cysts develop in the intermediate hosts—sheep, cattle, humans, goats, camels, and horses for the *E. granulosus* complex and mice and other rodents for *E. multilocularis*. When a dog (*E. granulosus*) or fox (*E. multilocularis*) ingests infected meat containing cysts, the life cycle is completed.

Etiology The small (5-mm-long) adult *E. granulosus* sensu lato worms live for 5–20 months in the jejunum of dogs. They have three proglottids: one immature, one mature, and one gravid. The gravid segment splits to release eggs that are morphologically similar to *Taenia* eggs and are extremely hardy. After humans ingest the eggs, embryos escape from the eggs, penetrate the intestinal mucosa, enter the portal circulation, and are carried to various organs, most commonly the liver and lungs. Larvae of *E. granulosus* sensu lato develop into fluid-filled unilocular hydatid cysts that consist of an external membrane and an inner germinal layer. Daughter cysts develop from the inner aspect of the germinal layer, as do germinating cystic structures called *brood capsules*. New larvae, called *protoscolices*, develop in large numbers within the brood capsule. The cysts expand slowly over a period of years.

The life cycle of *E. multilocularis* is similar except that wild canines, such as foxes, serve as the definitive hosts, and small rodents serve as the intermediate hosts. The larval form of *E. multilocularis*, however, is quite different in that it remains in the proliferative phase, the parasite is always multilocular, and vesicles without brood capsules or protoscolices progressively invade the host tissue by peripheral extension of processes from the germinal layer.

Clinical Manifestations Slowly enlarging echinococcal cysts generally remain asymptomatic until their expanding size or their space-occupying effect in an involved organ elicits symptoms. The liver and the lungs are the most common sites of these cysts. The liver is involved in about two-thirds of *E. granulosus* infections and in nearly all *E. multilocularis* infections. Because a period of years elapses before cysts enlarge sufficiently to cause symptoms, they may be discovered incidentally on a routine x-ray or ultrasound study.

Patients with hepatic echinococcosis who are symptomatic most often present with abdominal pain or a palpable mass in the right upper quadrant. Compression of a bile duct or leakage of cyst fluid into the biliary tree may mimic recurrent cholelithiasis, and biliary obstruction can result in jaundice. Rupture of or episodic leakage from

a hydatid cyst may produce fever, pruritus, urticaria, eosinophilia, or anaphylaxis. Pulmonary hydatid cysts may rupture into the bronchial tree or pleural cavity and produce cough, salty phlegm, dyspnea, chest pain, or hemoptysis. Rupture of hydatid cysts, which can occur spontaneously or at surgery, may lead to multifocal dissemination of protoscolices, which can form additional cysts. Other presentations are due to the involvement of bone (invasion of the medullary cavity with slow bone erosion producing pathologic fractures), the CNS (space-occupying lesions), the heart (conduction defects, pericarditis), and the pelvis (pelvic mass).

The larval forms of *E. multilocularis* characteristically present as a slowly growing hepatic tumor, with progressive destruction of the liver and extension into vital structures. Patients commonly report upper-quadrant and epigastric pain. Liver enlargement and obstructive jaundice may be apparent. The lesions may infiltrate adjoining organs (e.g., diaphragm, kidneys, or lungs) or may metastasize to the spleen, lungs, or brain.

Diagnosis Radiographic and related imaging studies are important in detecting and evaluating echinococcal cysts. Plain x-rays will define pulmonary cysts of *E. granulosus* sensu lato—usually as rounded masses of uniform density—but may miss cysts in other organs unless there is cyst wall calcification (as occurs in the liver). MRI, CT, and ultrasound reveal well-defined cysts with thick or thin walls. Imaging methods may reveal a fluid layer of different density, termed *hydatid sand*, that contains protoscolices. However, the most pathognomonic finding, if demonstrable, is that of daughter cysts within the larger cyst. This finding, like eggshell or mural calcification on CT, is indicative of *E. granulosus* infection and helps to distinguish the cyst from carcinomas, bacterial or amebic liver abscesses, or hemangiomas. In contrast, ultrasound or CT of alveolar hydatid cysts reveals indistinct solid masses with central necrosis and plaquelike calcifications.

A specific diagnosis of cystic hydatid disease can be made by the examination of aspirated fluids for protoscolices or hooklets, but diagnostic aspiration is not usually recommended because of the potential risk of fluid leakage resulting in either dissemination of infection or anaphylactic reactions. Serodiagnostic assays can be useful, although a negative test does not exclude the diagnosis of echinococcosis. Cysts in the liver elicit positive antibody responses in ~90% of cases, whereas up to 50% of individuals with cysts in the lungs are seronegative. Detection of antibody to specific echinococcal antigens by immunoblotting has the highest degree of specificity.

TREATMENT

Echinococcosis

Therapy for cystic echinococcosis is based on considerations of the size, location, and manifestations of cysts and the overall health of the patient. Surgery has traditionally been the principal definitive method of treatment. Currently, ultrasound staging is recommended for cystic echinococcosis **(Fig. 230-2)**. Small CL, CE1, and CE3 lesions may respond to chemotherapy with albendazole. For CE1 lesions and uncomplicated CE3 lesions, PAIR (*p*ercutaneous *a*spiration, *i*nfusion of scolicidal agents, and *r*easpiration) is now recommended instead of surgery. PAIR is contraindicated for superficially located cysts (because of the risk of rupture), for cysts with multiple thick internal septal divisions (honeycombing pattern), and for cysts communicating with the biliary tree. For prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during PAIR, the administration of albendazole (15 mg/kg daily in two divided doses) should be initiated at least 2 days before the procedure and continued for at least 4 weeks afterward. Ultrasound- or CT-guided aspiration allows confirmation of the diagnosis by demonstration of protoscolices in the aspirate. After aspiration, contrast material should be injected to detect occult communications with the biliary tract. Alternatively, the fluid should be checked for bile staining visually and by dipstick. If no bile is found and no communication is visualized, the contrast material is reaspirated, with subsequent infusion of scolicidal agents (usually 95% ethanol; alternatively, hypertonic saline). This approach, when implemented by a skilled practitioner, yields rates of cure and relapse equivalent to those following surgery, with less perioperative morbidity and shorter hospitalization. In experienced hands, some CE2 lesions can be treated by modified catheter drainage. Daughter cysts within the primary cyst may need to be punctured separately.

Surgery remains the treatment of choice for complicated cystic echinococcosis (e.g., cysts communicating with the biliary tract), for most thoracic and intracranial cysts, and for areas where PAIR is not possible. For liver cysts, the preferred surgical approach is total cystectomy, in which the entire cyst and the surrounding fibrous tissue are removed. The risks posed by leakage of fluid during surgery or PAIR include anaphylaxis and dissemination of infectious protoscolices. The latter complication has been minimized by careful attention to the prevention of spillage of the cyst and by soaking

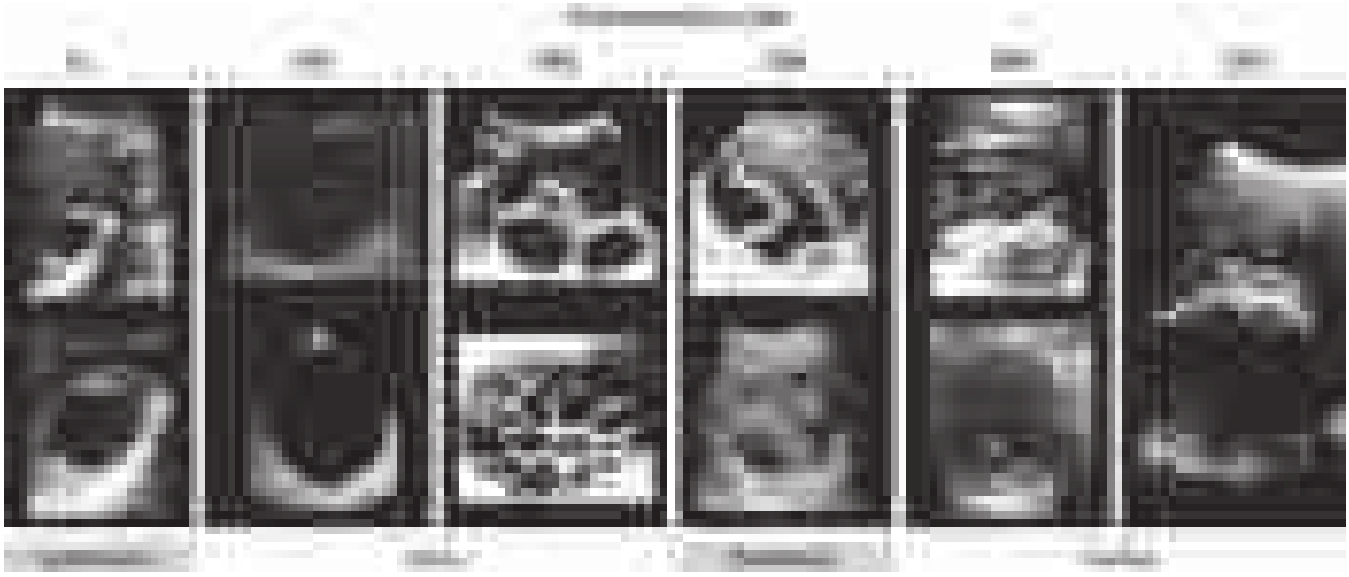

FIGURE 230-2 Management of cystic hydatid disease caused by *Echinococcus granulosus* should be based on viability of the parasite, which can be estimated from radiographic appearance. The ultrasound appearance includes lesions classified as active, transitional, and inactive. *Active* cysts include types CL (with a cystic lesion and no visible cyst wall), CE1 (with a visible cyst wall and internal echoes [*snowflake sign*]), and CE2 (with a visible cyst wall and internal septation). *Transitional* cysts (CE3) may have detached laminar membranes or may be partially collapsed. *Inactive cysts* include types CE4 (a nonhomogeneous mass) and CE5 (a cyst with a thick calcified wall). *(Adapted from RL Guerrant et al [eds]: Tropical Infectious Diseases: Principles, Pathogens and Practice, 2nd ed, p 1312. © 2005, with permission from Elsevier Science.)*

of the drapes with hypertonic saline. Infusion of scolicidal agents is no longer recommended because of problems with hypernatremia, intoxication, or sclerosing cholangitis. Albendazole, which is active against *Echinococcus*, should be administered adjunctively, beginning several days before resection of the liver and continuing for several weeks for *E. granulosus*. Praziquantel (50 mg/kg daily for 2 weeks) may hasten the death of the protoscolices. Medical therapy with albendazole alone for 12 weeks to 6 months results in cure in ~30% of cases and in improvement in another 50%. In many instances of treatment failure, *E. granulosus* infections are subsequently treated successfully with PAIR or additional courses of medical therapy. Response to treatment is best assessed by serial imaging studies, with attention to cyst size and consistency. Some cysts may not demonstrate complete radiologic resolution even though no viable protoscolices are present. Some of these cysts with partial radiologic resolution (e.g., CE4 or CE5) can be managed with observation only.

Surgical resection remains the treatment of choice for *E. multilocularis* infection. Complete removal of the parasite continues to offer the best chance for cure. Ongoing therapy with albendazole for at least 2 years after presumptively curative surgery is recommended. Positron emission tomography can be used to follow disease activity. Most cases are diagnosed at a stage at which complete resection is not possible; in these cases, albendazole treatment should be continued indefinitely, with careful monitoring. In some cases, liver transplantation has been used because of the size of the necessary liver resection. However, continuous immunosuppression favors the proliferation of *E. multilocularis* larvae and reinfection of the transplant. Thus, indefinite treatment with albendazole is required.

Prevention In endemic areas, echinococcosis can be prevented by administering praziquantel to infected dogs, by denying dogs access to viscera from infected animals, or by vaccinating sheep. Limiting the number of stray dogs is helpful in reducing the prevalence of infection among humans. In Europe, *E. multilocularis* infection has been associated with gardening; gloves should be used when working with soil.

HYMENOLEPIASIS NANA

Infection with *H. nana*, the dwarf tapeworm, is the most common of all the cestode infections. *H. nana* is endemic in both temperate and tropical regions of the world. Infection is spread by fecal/oral contamination.

Etiology and Pathogenesis *H. nana* is the only cestode of humans that does not require an intermediate host. Both the larval and adult phases of the life cycle take place in the human. The adult—the smallest tapeworm parasitizing humans—is ~2 cm long and dwells in the proximal ileum. Proglottids, which are small and rarely seen in the stool, release spherical eggs 30–44 µm in diameter, each of which contains an oncosphere with six hooklets. The eggs are immediately infective and are unable to survive for >10 days in the external environment. When the egg is ingested by a new host, the oncosphere is freed and penetrates the intestinal villi, becoming a cysticercoid larva. Larvae migrate back into the intestinal lumen, attach to the mucosa, and mature into adult worms over 10–12 days. Eggs may also hatch before passing into the stool, causing internal autoinfection with increasing numbers of intestinal worms. Although the life span of adult *H. nana* worms is only ~4–10 weeks, the autoinfection cycle perpetuates the infection.

Clinical Manifestations *H. nana* infection, even with many intestinal worms, is usually asymptomatic. Heavy infection may be associated with diarrhea, abdominal pain, and weight loss.

Diagnosis Infection is diagnosed by the finding of eggs in the stool.

TREATMENT

Hymenolepiasis Nana

Praziquantel (25 mg/kg once) is the treatment of choice, because it acts against both the adult worms and the cysticercoids in the intestinal villi. Nitazoxanide (500 mg bid for 3 days) may be used as an alternative.

Prevention Good personal hygiene and improved sanitation can eradicate the disease. Epidemics have been controlled by mass chemotherapy coupled with improved hygiene.

HYMENOLEPIASIS DIMINUTA

Hymenolepis diminuta, a cestode of rodents, occasionally infects small children, who ingest the larvae in uncooked cereal foods contaminated by fleas and other insects in which larvae develop. Infection is usually asymptomatic and is diagnosed by the detection of eggs in the stool. Treatment with praziquantel results in cure in most cases.

DIPHYLLOBOTHRIASIS

Diphyllobothrium latum and other diphyllobothriid parasites (including *Adenocephlus pacificus* and *Diplogonoporus* species) are found in the lakes, rivers, and deltas of the Northern Hemisphere, central Africa, and South America.

Etiology and Pathogenesis The adult worm—the longest tapeworm (up to 25 m)—attaches to the ileal and occasionally to the jejunal mucosa by its suckers, which are located on its elongated scolex. The adult worm has 3000–4000 proglottids, which release ~1 million eggs daily into the feces. If an egg reaches water, it hatches and releases a free-swimming embryo that can be eaten by small freshwater crustaceans (*Cyclops* or *Diaptomus* species). After an infected crustacean containing a developed procercoid is swallowed by a fish, the larva migrates into the fish's flesh and grows into a sparganum, or plerocercoid larva. Humans acquire the infection by ingesting infected raw or smoked fish. Within 3–5 weeks, the tapeworm matures into an adult in the human intestine.

Clinical Manifestations Most *D. latum* infections are asymptomatic, although manifestations may include transient abdominal discomfort, diarrhea, vomiting, weakness, and weight loss. Occasionally, infection can cause acute abdominal pain and intestinal obstruction; in rare cases, cholangitis or cholecystitis may be produced by migrating proglottids.

Because the tapeworm absorbs large quantities of vitamin B_{12} and interferes with ileal B_{12} absorption, vitamin B_{12} deficiency can develop, but this effect has been noted only in Scandinavia, where up to 2% of infected patients, especially the elderly, have megaloblastic anemia resembling pernicious anemia and may exhibit neurologic sequelae of B_{12} deficiency.

Diagnosis The diagnosis is made readily by the detection of the characteristic eggs in the stool. The eggs possess a single shell with an operculum at one end and a knob at the other. Mild to moderate eosinophilia may be detected.

TREATMENT

Diphyllobothriasis

Praziquantel (5–10 mg/kg once) is highly effective. Parenteral vitamin B_{12} should be given if B_{12} deficiency is manifest.

Prevention Infection can be prevented by heating fish to 54°C for 5 min or by freezing it at –18°C for 24 h. Placing fish in brine with a high salt concentration for long periods kills the eggs.

DIPYLIDIASIS

Dipylidium caninum, a common tapeworm of dogs and cats, may accidentally infect humans. Dogs, cats, and occasionally humans become

infected by ingesting fleas harboring cysticercoids. Children are more likely to become infected than adults. Most infections are asymptomatic, but passage of segments in the stool or vague abdominal symptoms may occur. The diagnosis is made by the detection of proglottids or ova in the stool. As in *D. latum* infection, therapy consists of praziquantel. Prevention requires anthelmintic treatment and flea control for pet dogs or cats.

SPARGANOSIS

Humans can be infected by the sparganum, or plerocercoid larva, of a diphyllobothriid tapeworm of the genus *Spirometra*. Infection can be acquired by the consumption of water containing infected *Cyclops*; by the ingestion of infected snakes, birds, or mammals; or by the application of infected flesh as poultices. The worm migrates slowly in tissues, and infection commonly presents as a subcutaneous swelling. Periorbital tissues can be involved, and ocular sparganosis may destroy the eye. Surgical excision is used to treat localized sparganosis.

COENUROSIS

This rare infection of humans by the larval stage (coenurus) of the dog tapeworm *Taenia multiceps* or *T. serialis* results in a space-occupying cystic lesion. As in cysticercosis, involvement of the CNS and subcutaneous tissue is most common. Both definitive diagnosis and treatment require surgical excision of the lesion. Chemotherapeutic agents generally are not effective.

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Section 1 Introduction to Cardiovascular Disorders

231 Approach to the Patient with Possible Cardiovascular Disease

Joseph Loscalzo

THE MAGNITUDE OF THE PROBLEM

Cardiovascular diseases comprise the most prevalent serious disorders in industrialized nations and are a rapidly growing problem in developing nations (Chap. 233). Age-adjusted death rates for coronary heart disease have declined by two-thirds in the last four decades in the United States, reflecting the identification and reduction of risk factors as well as improved treatments and interventions for the management of coronary artery disease, arrhythmias, and heart failure. Nonetheless, cardiovascular diseases remain the most common causes of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population. The growing prevalence of obesity (Chap. 395), type 2 diabetes mellitus (Chap. 396), and metabolic syndrome (Chap. 401), which are important risk factors for atherosclerosis, now threatens to reverse the progress that has been made in the age-adjusted reduction in the mortality rate of coronary heart disease.

For many years, cardiovascular disease was considered to be more common in men than in women. In fact, the percentage of all deaths secondary to cardiovascular disease is higher among women (43%) than among men (37%) (Chap. 391). In addition, although the absolute number of deaths secondary to cardiovascular disease has declined over the past decades in men, this number has actually risen in women. Inflammation, obesity, type 2 diabetes mellitus, and the metabolic syndrome appear to play more prominent roles in the development of coronary atherosclerosis in women than in men. Coronary artery disease (CAD) is more frequently associated with dysfunction of the coronary microcirculation in women than in men. Exercise electrocardiography has a lower diagnostic accuracy in the prediction of epicardial obstruction in women than in men.

NATURAL HISTORY

Cardiovascular disorders often present acutely, as in a previously asymptomatic person who develops an acute myocardial infarction (Chap. 269), or a previously asymptomatic patient with hypertrophic cardiomyopathy (Chap. 254) or with a prolonged QT interval (Chap. 247) whose first clinical manifestation is syncope or even sudden death. However, the alert physician may recognize the patient at risk for these complications long before they occur and often can take measures to prevent their occurrence. For example, a patient with acute myocardial infarction will often have had risk factors for atherosclerosis for many years. Had these risk factors been recognized, their elimination or reduction might have delayed or even prevented the infarction. Similarly, a patient with hypertrophic cardiomyopathy may have had a heart murmur for years and a family history of this disorder. These findings could have led to an echocardiographic examination, recognition of the condition, and appropriate therapy long before the occurrence of a serious acute manifestation.

Patients with valvular heart disease or idiopathic dilated cardiomyopathy, by contrast, may have a prolonged course of gradually increasing dyspnea and other manifestations of chronic heart failure that is punctuated by episodes of acute deterioration only late in the course of the disease. Understanding the natural history of various cardiac disorders is essential for applying appropriate diagnostic and therapeutic measures to each stage of the condition, as well as for providing the patient and family with the likely prognosis.

CARDIAC SYMPTOMS

The symptoms caused by heart disease result most commonly from myocardial ischemia, disturbance of the contraction and/or relaxation of the myocardium, obstruction to blood flow, or an abnormal cardiac rhythm or rate. Ischemia, which is caused by an imbalance between the heart's oxygen supply and demand, is manifest most frequently as chest discomfort (Chap. 11), whereas reduction of the pumping ability of the heart commonly leads to fatigue and elevated intravascular pressure upstream of the failing ventricle. The latter results in abnormal fluid accumulation, with peripheral edema (Chap. 37) or pulmonary congestion and dyspnea (Chap. 33). Obstruction to blood flow, as occurs in valvular stenosis, can cause symptoms resembling those of myocardial failure (Chap. 252). Cardiac arrhythmias often develop suddenly, and the resulting symptoms and signs—palpitations (Chap. 39), dyspnea, hypotension, and syncope (Chap. 18)—generally occur abruptly and may disappear as rapidly as they develop.

Although dyspnea, chest discomfort, edema, and syncope are cardinal manifestations of cardiac disease, they occur in other conditions as well. Thus, dyspnea is observed in disorders as diverse as pulmonary disease, marked obesity, and anxiety (Chap. 33). Similarly, chest discomfort may result from a variety of noncardiac and cardiac causes other than myocardial ischemia (Chap. 11). Edema, an important finding in untreated or inadequately treated heart failure, also may occur with primary renal disease and in hepatic cirrhosis (Chap. 37). Syncope occurs not only with serious cardiac arrhythmias but in a number of neurologic conditions as well (Chap. 18). Whether heart disease is responsible for these symptoms frequently can be determined by carrying out a careful clinical examination (Chap. 234), supplemented by noninvasive testing using electrocardiography at rest and during exercise (Chap. 235), echocardiography, roentgenography, and other forms of myocardial imaging (Chap. 236).

Myocardial or coronary function that may be adequate at rest may be insufficient during exertion. Thus, dyspnea and/or chest discomfort that appear during activity are characteristic of patients with heart disease, whereas the opposite pattern, that is, the appearance of these symptoms at rest and their remission during exertion, is rarely observed in such patients. It is important, therefore, to question the patient carefully about the relation of symptoms to exertion.

Many patients with cardiovascular disease may be asymptomatic both at rest and during exertion but may present with an abnormal physical finding such as a heart murmur, elevated arterial pressure, or an abnormality of the electrocardiogram (ECG) or imaging test. It is important to assess the global risk of CAD in asymptomatic individuals, using a combination of clinical assessment and measurement of cholesterol and its fractions, as well as other biomarkers, such as C-reactive protein, in some patients. Since the first clinical manifestation of CAD may be catastrophic—sudden cardiac death, acute myocardial infarction, or stroke in previous asymptomatic persons—it is mandatory to identify those at high risk of such events and institute further testing and preventive measures.

DIAGNOSIS

As outlined by the New York Heart Association (NYHA), the elements of a complete cardiac diagnosis include the systematic consideration of the following:

1. *The underlying etiology*. Is the disease congenital, hypertensive, ischemic, or inflammatory in origin?
2. *The anatomic abnormalities*. Which chambers are involved? Are they hypertrophied, dilated, or both? Which valves are affected? Are they

TABLE 231-1 New York Heart Association Functional Classification

Class I	**Class III**
No limitation of physical activity	Marked limitation of physical activity
No symptoms with ordinary exertion	Less than ordinary activity causes symptoms
Class II	Asymptomatic at rest
Slight limitation of physical activity	**Class IV**
Ordinary activity causes symptoms	Inability to carry out any physical activity without discomfort
	Symptoms at rest

Source: Data from The Criteria Committee of the New York Heart Association.

regurgitant and/or stenotic? Is there pericardial involvement? Has there been a myocardial infarction?

3. *The physiologic disturbances*. Is an arrhythmia present? Is there evidence of congestive heart failure or myocardial ischemia?
4. *Functional disability*. How strenuous is the physical activity required to elicit symptoms? The classification provided by the NYHA has been found to be useful in describing functional disability **(Table 231-1)**.

One example may serve to illustrate the importance of establishing a complete diagnosis. In a patient who presents with exertional chest discomfort, the identification of myocardial ischemia as the etiology is of great clinical importance. However, the simple recognition of ischemia is insufficient to formulate a therapeutic strategy or prognosis until the underlying anatomic abnormalities responsible for the myocardial ischemia, for example, coronary atherosclerosis or aortic stenosis, are identified and a judgment is made about whether other physiologic disturbances that cause an imbalance between myocardial oxygen supply and demand, such as severe anemia, thyrotoxicosis, or supraventricular tachycardia, play contributory roles. Finally, the severity of the disability should govern the extent and tempo of the workup and strongly influence the therapeutic strategy that is selected.

The establishment of a correct and complete cardiac diagnosis usually commences with the history and physical examination **(Chap. 234)**. Indeed, the clinical examination remains the basis for the diagnosis of a wide variety of disorders. The clinical examination may then be supplemented by five types of laboratory tests: (1) ECG **(Chap. 235)**, (2) noninvasive imaging examinations (chest roentgenogram, echocardiogram, radionuclide imaging, computed tomographic imaging, positron emission tomography, and magnetic resonance imaging) **(Chap. 236)**, (3) blood tests to assess risk (e.g., lipid determinations, C-reactive protein) or cardiac function (e.g., brain natriuretic peptide [BNP] **[Chap. 252]**), (4) occasionally specialized invasive examinations (i.e., cardiac catheterization and coronary arteriography **[Chap. 237]**), and (5) genetic tests to identify monogenic cardiac diseases (e.g., hypertrophic cardiomyopathy **[Chap. 254]**, Marfan's syndrome **[Chap. 406]**, and abnormalities of cardiac ion channels that lead to prolongation of the QT interval and an increase in the risk of sudden death **[Chap. 241]**). These tests are becoming more widely available.

FAMILY HISTORY

In eliciting the history of a patient with known or suspected cardiovascular disease, particular attention should be directed to the family history. Familial clustering is common in many forms of heart disease. Mendelian transmission of single-gene defects may occur, as in hypertrophic cardiomyopathy **(Chap. 254)**, Marfan's syndrome **(Chap. 406)**, and sudden death associated with a prolonged QT syndrome **(Chap. 247)**. Premature coronary disease and essential hypertension, type 2 diabetes mellitus, and hyperlipidemia (the most important risk factors for CAD) are usually polygenic disorders. Although familial transmission may be less obvious than in the monogenic disorders, it is helpful in assessing risk and prognosis in polygenic disorders, as well. Familial clustering of cardiovascular diseases not only may occur on a genetic basis but also may be related to familial dietary or behavior patterns, such as excessive ingestion of salt or calories and cigarette smoking.

ASSESSMENT OF FUNCTIONAL IMPAIRMENT

When an attempt is made to determine the severity of functional impairment in a patient with heart disease, it is helpful to ascertain the level of activity and the rate at which it is performed before symptoms develop. Thus, it is not sufficient to state that the patient complains of dyspnea. The breathlessness that occurs after running up two long flights of stairs denotes far less functional impairment than do similar symptoms that occur after taking a few steps on level ground. In addition, the degree of customary physical activity at work and during recreation should be considered. The development of two-flight dyspnea in a well-conditioned marathon runner may be far more significant than the development of one-flight dyspnea in a previously sedentary person. The history should include a detailed consideration of the patient's therapeutic regimen. For example, the persistence or development of edema, breathlessness, and other manifestations of heart failure in a patient who is receiving optimal doses of diuretics and other therapies for heart failure **(Chap. 252)** is far graver than are similar manifestations in the absence of treatment. Similarly, the presence of angina pectoris despite treatment with optimal doses of multiple antianginal drugs **(Chap. 267)** is more serious than it is in a patient on no therapy. In an effort to determine the progression of symptoms, and thus the severity of the underlying illness, it may be useful to ascertain what, if any, specific tasks the patient could have carried out 6 months or 1 year earlier that he or she cannot carry out at present.

ELECTROCARDIOGRAM

(See also Chap. 235) Although an ECG usually should be recorded in patients with known or suspected heart disease, with the exception of the identification of arrhythmias, conduction abnormalities, ventricular hypertrophy, and acute myocardial infarction, it generally does not establish a specific diagnosis. The range of normal electrocardiographic findings is wide, and the tracing can be affected significantly by many noncardiac factors, such as age, body habitus, and serum electrolyte concentrations. In general, electrocardiographic changes should be interpreted in the context of other abnormal cardiovascular findings.

ASSESSMENT OF THE PATIENT WITH A HEART MURMUR

(Fig. 231-1) The cause of a heart murmur can often be readily elucidated from a systematic evaluation of its major attributes: timing, duration, intensity, quality, frequency, configuration, location, and radiation when considered in the light of the history, general

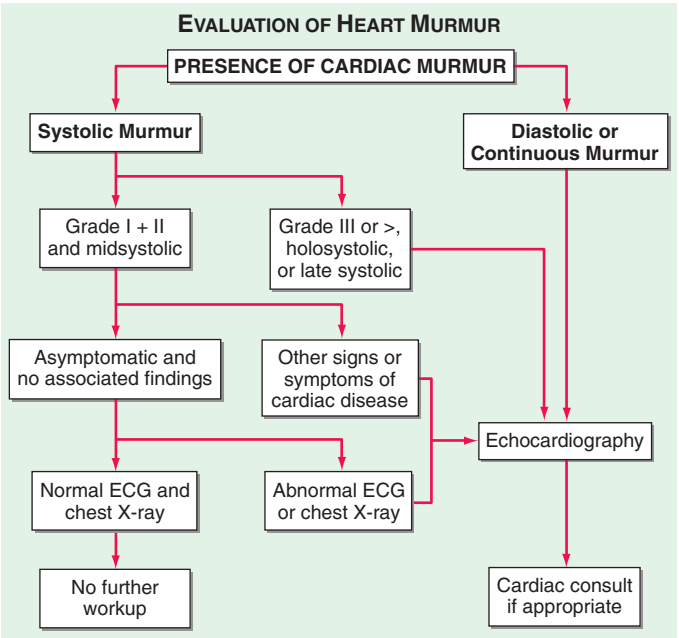

FIGURE 231-1 Approach to the evaluation of a heart murmur. ECG, electrocardiogram. *(Reproduced with permission from Primary Cardiology, 2nd ed, E Braunwald, L Goldman [eds]. Philadelphia, Saunders, 2003.)*

physical examination, and other features of the cardiac examination, as described in **Chap. 234**.

The majority of heart murmurs are midsystolic and soft (grades I–II/VI). When such a murmur occurs in an asymptomatic child or young adult *without* other evidence of heart disease on clinical examination, it is usually benign and echocardiography generally is not required. By contrast, two-dimensional and Doppler echocardiography **(Chap. 236)** are indicated in patients with loud systolic murmurs (grades ≥III/VI), especially those that are holosystolic or late systolic, and in most patients with diastolic or continuous murmurs.

PITFALLS IN CARDIOVASCULAR MEDICINE

Increasing subspecialization in internal medicine and the perfection of advanced diagnostic techniques in cardiology can lead to several undesirable consequences. Examples include the following:

1. Failure by the *noncardiologist* to recognize important cardiac manifestations of systemic illnesses. For example, the presence of mitral stenosis, patent foramen ovale, and/or transient atrial arrhythmia should be considered in a patient with stroke, or the presence of pulmonary hypertension and cor pulmonale should be considered in a patient with scleroderma or Raynaud's syndrome. A cardiovascular examination should be carried out to identify and estimate the severity of the cardiovascular involvement that accompanies many noncardiac disorders.
2. Failure by the *cardiologist* to recognize underlying systemic disorders in patients with heart disease. For example, hyperthyroidism should be considered in an elderly patient with atrial fibrillation and unexplained heart failure, and Lyme disease should be considered in a patient with unexplained fluctuating atrioventricular block. A cardiovascular abnormality may provide the clue critical to the recognition of some systemic disorders. For example, an unexplained pericardial effusion may provide an early clue to the diagnosis of tuberculosis or a neoplasm.
3. Overreliance on and overutilization of laboratory tests, particularly invasive techniques, for the evaluation of the cardiovascular system. Cardiac catheterization and coronary arteriography **(Chap. 237)** provide precise diagnostic information that may be crucial in developing a therapeutic plan in patients with known or suspected CAD. Although a great deal of attention has been directed to these examinations, it is important to recognize that they serve to *supplement*, not *supplant*, a careful examination carried out with clinical and noninvasive techniques. A coronary arteriogram should not be performed in lieu of a careful history in patients with chest pain suspected of having ischemic heart disease. Although coronary arteriography may establish whether the coronary arteries are obstructed and to what extent, the results of the procedure by themselves often do not provide a definitive answer to the question of whether a patient's complaint of chest discomfort is attributable to coronary atherosclerosis and whether or not revascularization is indicated.

Despite the value of invasive tests in certain circumstances, they entail some small risk to the patient, involve discomfort and substantial cost, and place a strain on medical facilities. Therefore, they should be carried out only if the results can be expected to modify the patient's management.

DISEASE PREVENTION AND MANAGEMENT

The prevention of heart disease, especially of CAD, is one of the most important tasks of primary health care givers as well as cardiologists. Prevention begins with risk assessment, followed by attention to lifestyle, such as achieving optimal weight, physical activity, and smoking cessation, and then aggressive treatment of all abnormal risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus **(Chap. 396)**.

After a complete diagnosis has been established in patients with known heart disease, a number of management options are usually available. Several examples may be used to demonstrate some of the principles of cardiovascular therapeutics:

1. In the absence of evidence of heart disease, the patient should be clearly informed of this assessment and *not* be asked to return at intervals for repeated examinations. If there is no evidence of disease, such continued attention may lead to the patient's developing inappropriate concern about the possibility of heart disease.
2. If there is no evidence of cardiovascular disease but the patient has one or more risk factors for the development of ischemic heart disease **(Chap. 267)**, a plan for their reduction should be developed and the patient should be retested at intervals to assess compliance and efficacy in risk reduction.
3. Asymptomatic or mildly symptomatic patients with valvular heart disease that is anatomically severe should be evaluated periodically, every 6 to 12 months, by clinical and noninvasive examinations. Early signs of deterioration of ventricular function may signify the need for surgical treatment before the development of disabling symptoms, irreversible myocardial damage, and excessive risk of surgical treatment **(Chap. 256)**.
4. In patients with CAD **(Chap. 267)**, available practice guidelines should be considered in the decision on the form of treatment (medical, percutaneous coronary intervention, or surgical revascularization). Mechanical revascularization may be employed too frequently in the United States and too infrequently in Eastern Europe and developing nations. The mere presence of angina pectoris and/or the demonstration of critical coronary arterial narrowing at angiography should not reflexively evoke a decision to treat the patient by revascularization. Instead, these interventions should be limited to patients with CAD whose angina has not responded adequately to medical treatment or in whom revascularization has been shown to improve the natural history (e.g., acute coronary syndrome or multivessel CAD with left ventricular dysfunction).

232 Basic Biology of the Cardiovascular System

Joseph Loscalzo, Peter Libby, Calum A. MacRae

DEVELOPMENTAL BIOLOGY OF THE CARDIOVASCULAR SYSTEM

The heart forms early during embryogenesis **(Fig. 232-1)**, circulating blood, nutrients, and oxygen to the other developing organs while continuing to grow and undergo complex morphogenetic changes. Early cardiac progenitors arise within crescent-shaped fields of lateral splanchnic mesoderm under the influence of multiple signals and migrate to the midline to form the linear heart tube: a single layer of endocardium and a single layer of cardiomyocyte precursors.

The linear heart tube undergoes asymmetric looping, that coordinates with chamber specification and multilayer growth of different regions of the heart tube to produce the presumptive atria and ventricles. Cells continue to migrate into the heart at both ends from later, or second, heart fields in pharyngeal mesoderm as looping and growth occur. These cells exhibit distinctive gene expression (e.g., Islet-1) and distinctive physiology (e.g., calcium handling), contributing to discrete areas of the adult heart, including the right atrium and the right ventricle. Different embryologic origins of cells within the right and left ventricles help explain why some forms of congenital and adult heart diseases affect regions of the heart to varying degrees.

After looping and chamber formation, a series of morphogenetic events divide the left and right sides of the heart, separate the atria from the ventricles, and form the aorta and pulmonary artery from the truncus arteriosus. Cardiac valves form between the atria and the ventricles and between the ventricles and the outflow vessels. Early in development, the single layer of myocardial cells secretes an extracellular matrix rich in hyaluronic acid, or "cardiac jelly," which accumulates within the endocardial cushions, precursors of the cardiac valves. Signals from overlying myocardial cells trigger migration, invasion, and phenotypic changes in underlying endocardial cells, which undergo

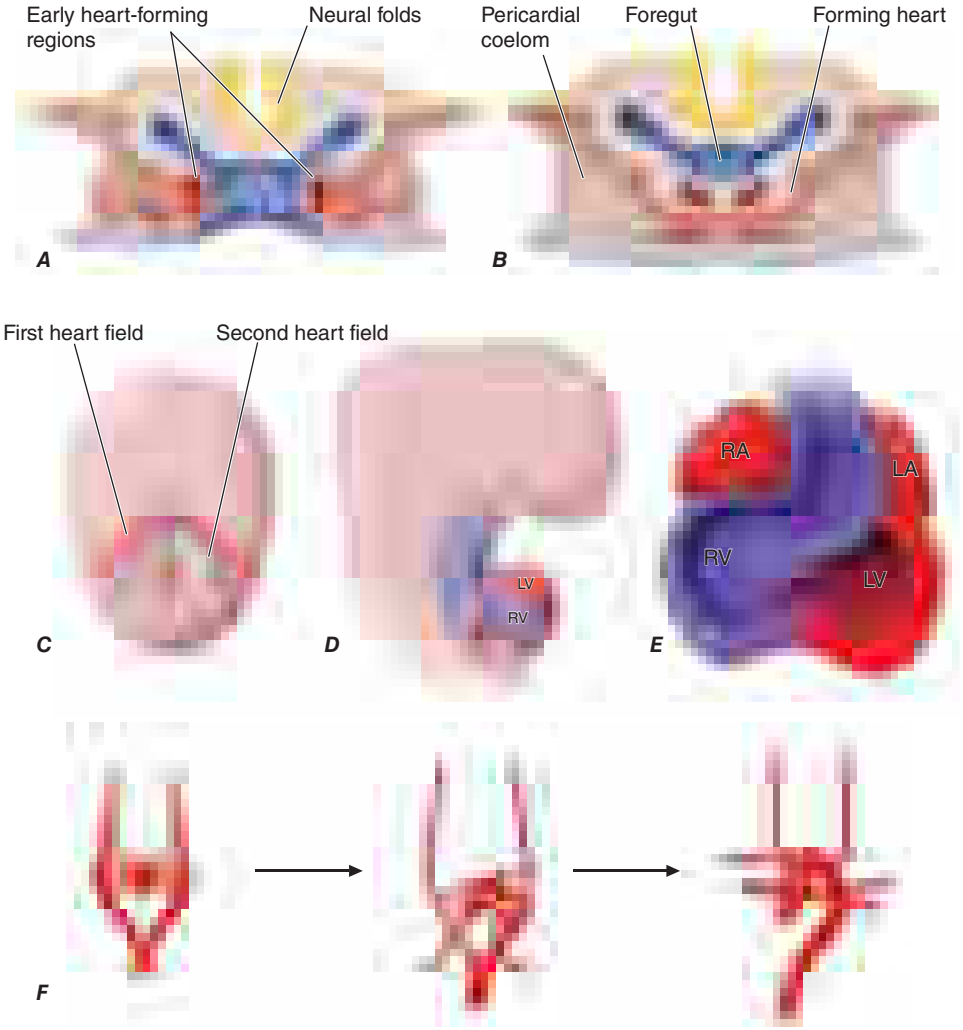

FIGURE 232-1 ***A.*** Schematic depiction of a transverse section through an early embryo depicts the bilateral regions where early heart tubes form. ***B.*** The bilateral heart tubes subsequently migrate to the midline and fuse to form the linear heart tube. ***C.*** At the early cardiac crescent stage of embryonic development, cardiac precursors include a primary heart field fated to form the linear heart tube and a second heart field fated to add myocardium to the inflow and outflow poles of the heart. ***D.*** Second heart field cells populate the pharyngeal region before subsequently migrating to the maturing heart. ***E.*** Large portions of the right ventricle and outflow tract and some cells within the atria derive from the second heart field. ***F.*** The aortic arch arteries form as symmetric sets of vessels that then remodel under the influence of the neural crest to form the asymmetric mature vasculature. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

an epithelial-mesenchymal transformation to invade and populate the endocardial cushion matrix with cells. Mesenchymal cells then proliferate and form the mature valve leaflets.

The great vessels form as a series of bilaterally symmetric aortic arch arteries that remodel asymmetrically to define the mature central vasculature. Migrating neural crest cells from the dorsal neural tube orchestrate this process and are necessary for aortic arch remodeling and the septation of the truncus arteriosus. The smooth-muscle cells within the tunica media of the aortic arch, the ductus arteriosus, and the carotid arteries all derive from neural crest. By contrast, smooth-muscle within the descending aorta arises from lateral plate mesoderm, and smooth muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A and folic acid, and congenital heart disease involving abnormal remodeling of the aortic arch arteries can associate with maternal deficiencies of these vitamins. The shared embryologic origins of different cardiovascular cell types lead to syndromic associations between various congenital heart diseases and a range of extracardiac abnormalities.

Coronary artery formation requires the addition of yet another cell population to the embryonic heart. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm and to the liver. Proepicardial cells contribute smooth-muscle to the coronary arteries and are required for proper coronary patterning. Other cell types within the heart, (e.g., fibroblasts) also can arise from the proepicardium.

The cardiac conduction system, which generates and propagates electrical impulses, differentiates from cardiomyocyte precursors. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into heterogeneous cell types that compose the AV node. So-called decremental conduction through the AV node delays the electrical impulses between atria and ventricles, whereas the distal conduction system rapidly delivers the impulse throughout the ventricles. Each compartment within the conduction system expresses distinct gap junction proteins and ion channels that characterize the discrete cell fates and electrical properties. Developmental defects in the conduction system can lead to clinical electrophysiologic disorders, such as congenital heart block or preexcitation (Wolff-Parkinson-White syndrome) **(Chap. 241)**.

ORIGIN OF VASCULAR CELLS

As noted above, smooth-muscle cells in various types of artery derive from different sources. Some upper-body arterial smooth-muscle cells derive from the neural crest, whereas lower-body arteries generally recruit smooth-muscle cells from neighboring mesodermal structures during development. Bone marrow–derived endothelial progenitors may aid repair of damaged or aging arteries. In addition, multipotent vascular stem cells resident in vessel walls may give rise to the smooth-muscle cells that accumulate in injured or atheromatous arteries **(Chaps. 92 and 473)**.

THE BLOOD VESSEL

VASCULAR ULTRASTRUCTURE

Blood vessels participate in physiologic function and play roles in disease biology in virtually every organ system. The smallest blood vessels—capillaries—consist of a monolayer of endothelial cells on a basement membrane, adjacent to a discontinuous layer of smooth-muscle-like cells known as *pericytes* **(Fig. 232-2*A*)**. Arteries typically have a trilaminar structure **(Fig. 232-2*B–E*)**. The *intima* consists of a monolayer of endothelial cells continuous with those of the capillaries. The middle layer, or *tunica media*, consists of smooth-muscle cells, in veins, the media can contain just a few layers of smooth-muscle cells (Fig. 232-2***B***). The outer layer, the *adventitia*, consists of looser extracellular matrix with fibroblasts, mast cells, and nerve terminals. Larger arteries have their own vasculature, the *vasa vasorum*, which nourishes the tunica media.

Arteriolar muscle tone regulates blood pressure and flow through arterial beds (Fig. 232-2***C***). Medium-size muscular arteries also contain prominent smooth muscle layers (Fig. 232-2***D***) that participate in atherosclerosis. Larger elastic arteries have a highly structured tunica media with concentric bands of smooth-muscle cells, interspersed with

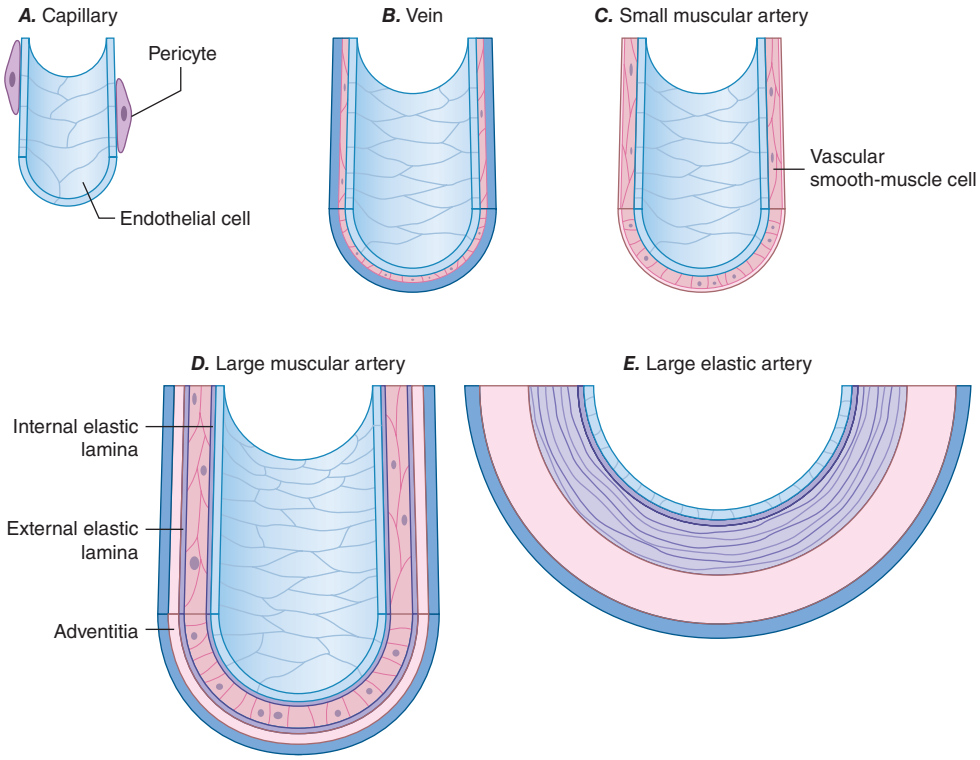

FIGURE 232-2 Schematics of the structures of various types of blood vessels. ***A.*** Capillaries consist of an endothelial tube in contact with a discontinuous population of pericytes. ***B.*** Veins typically have thin medias and thicker adventitias. ***C.*** A small muscular artery features a prominent tunica media. ***D.*** Larger muscular arteries have a prominent media with smooth-muscle cells embedded in a complex extracellular matrix. ***E.*** Larger elastic arteries have cylindrical layers of elastic tissue alternating with concentric rings of smooth-muscle cells.

strata of elastin-rich extracellular matrix (Fig. 232-2*E*). Larger arteries form an internal elastic lamina between intima and media while an external elastic lamina partitions media from surrounding adventitia.

VASCULAR CELL BIOLOGY

Endothelial Cell The endothelium forms the interface between tissues and the blood compartment, regulating the passage of molecules and cells. The ability of endothelial cells to serve as a selectively permeable barrier fails in vascular diseases, including atherosclerosis, hypertension, and renal disease, as well as in pulmonary edema, sepsis and other situations of "capillary leak."

The endothelium also participates in the local regulation of vascular tone and blood flow. Endogenous substances produced by endothelial cells such as prostacyclin, endothelium-derived hyperpolarizing factor, nitric oxide (NO), and hydrogen peroxide (H_2O_2) provide tonic vasodilatory stimuli under physiologic conditions in vivo (Table 232-1). Impaired production or excess catabolism of NO impairs endothelium-dependent vasodilator function contributing to pathologic vasoconstriction. Measurement of flow-mediated dilatation can assess endothelial vasodilator function in humans (Fig. 232-3). Endothelial cells also produce potent vasoconstrictor substances such as endothelin. Excessive production of reactive oxygen species, such as superoxide anion (O_2^-), by endothelial or smooth-muscle cells under pathologic conditions (e.g., excessive exposure to angiotensin II), can promote local oxidative stress and inactivate NO.

Normal endothelium exhibits limited interaction with circulating leukocytes, but when activated by bacterial products such as endotoxin or by proinflammatory cytokines released during infection or injury, endothelial cells express an array of adhesion molecules that selectively bind various classes of leukocytes in different pathologic conditions. The adhesion molecules and chemokines generated during acute bacterial infection tend to recruit granulocytes, while in chronic inflammatory diseases such as tuberculosis or atherosclerosis, the adhesion molecules expressed favor monocyte recruitment. Endothelial cells participate in the pathophysiology of many immune-mediated diseases. Complement-mediated lysis of endothelial cells is an example of immunologically mediated tissue injury. The presentation of foreign histocompatibility complex antigens by endothelial cells in solid-organ allografts can promote allograft arteriopathy, while immune-mediated endothelial injury also plays a role in thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome.

The endothelium also regulates the balance between thrombosis and hemostasis through a highly tuned set of regulatory pathways. When activated by inflammatory cytokines, bacterial endotoxin, or angiotensin II, for example, endothelial cells can produce substantial quantities of the major inhibitor of fibrinolysis, plasminogen activator inhibitor 1 (PAI-1). Thus, in pathologic circumstances, the endothelial cell may promote local thrombus accumulation rather than combat it. Inflammatory stimuli also induce the expression of the potent procoagulant tissue factor, a contributor to disseminated intravascular coagulation in sepsis.

Endothelial cells regulate the growth of subjacent smooth-muscle cells. For example, heparan sulfate glycosaminoglycans elaborated by endothelial cells can inhibit smooth-muscle proliferation, and in the setting of injury endothelial cells produce growth factors and chemoattractants, such as platelet-derived growth factor, which cause the migration and proliferation of vascular smooth-muscle cells. Dysregulation of these growth-stimulatory molecules may promote smooth-muscle accumulation in atherosclerotic lesions.

Vascular Smooth-Muscle Cell Contraction and relaxation of vascular smooth-muscle cells in muscular arteries determines blood pressure, regional flow and the afterload experienced by the left ventricle (see below). Venous tone regulates the capacitance of the venous tree and so influences ventricular preload. Smooth-muscle cells in the adult vessel seldom replicate in the absence of arterial injury or inflammatory activation, but proliferation and migration of arterial smooth-muscle cells contributes to arterial stenoses in atherosclerosis, arteriolar remodeling in hypertension, and the hyperplastic response of arteries injured by percutaneous intervention. In the pulmonary circulation, smooth-muscle migration and proliferation underlie the vascular disease that occurs in sustained high-flow states such as left-to-right shunts in congenital heart disease.

Smooth-muscle cells secrete the bulk of vascular extracellular matrix. Excessive production of collagen and glycosaminoglycans contributes to the remodeling, altered biomechanics and physiology of arteries affected by hypertension or atherosclerosis. In larger elastic arteries, such as the aorta, the ability to store the kinetic energy of

TABLE 232-1 Endothelial Functions in Health and Disease

HOMEOSTATIC PROPERTIES	DYSFUNCTIONAL PROPERTIES
Optimize balance between vasodilation and vasoconstriction	Impaired dilation, vasoconstriction
Antithrombotic, profibrinolytic	Prothrombotic, antifibrinolytic
Anti-inflammatory	Proinflammatory
Antiproliferative	Proproliferative
Antioxidant	Prooxidant
Permselectivity	Impaired barrier function

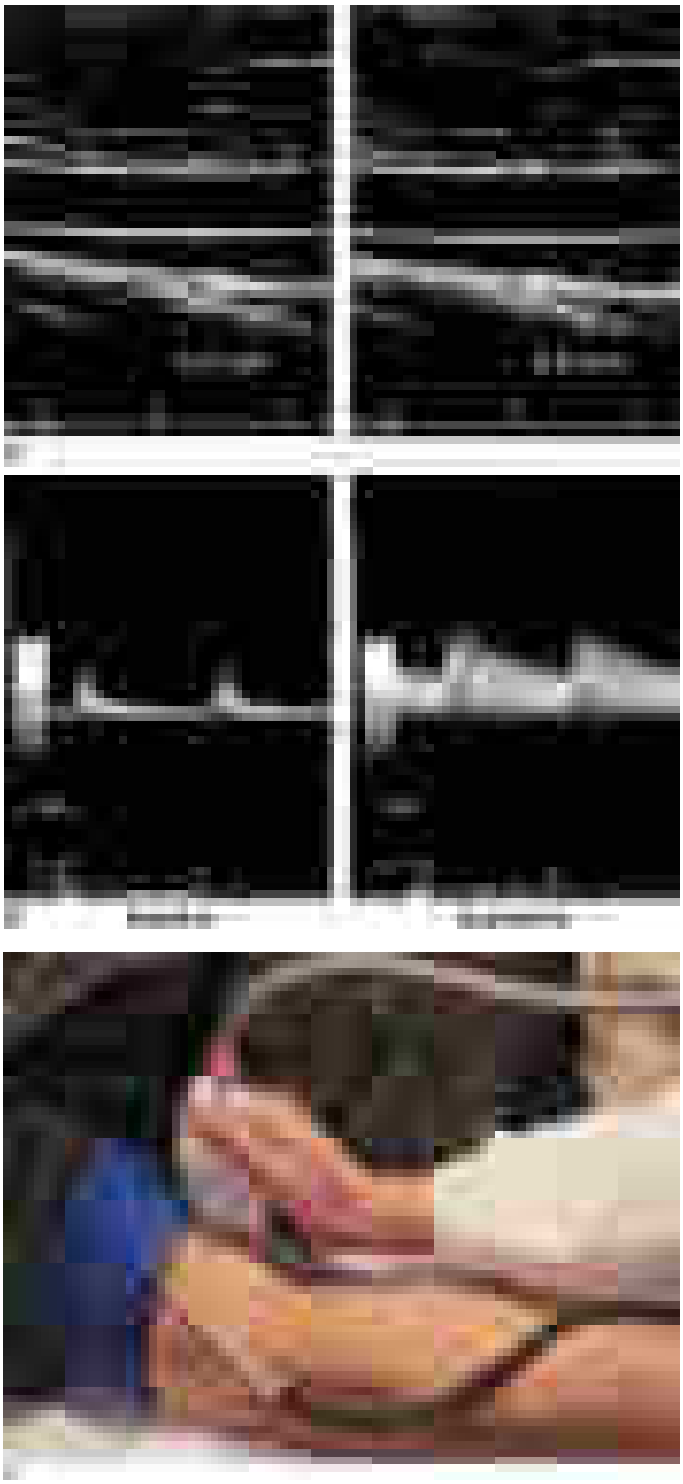

FIGURE 232-3 Assessment of endothelial function in vivo using blood pressure cuff occlusion and release. Upon deflation of the cuff, an ultrasound probe monitors changes in diameter (***A***) and blood flow (***B***) of the brachial artery (***C***). *(Reproduced with permission of J. Vita, MD.)*

systole promotes tissue perfusion during diastole. Arterial stiffness associated with aging or disease, evident in a widening pulse pressure, increases left ventricular afterload and portends a poor outcome.

Like endothelial cells, vascular smooth-muscle cells do not merely respond to vasomotor or inflammatory stimuli elaborated by other cell types, but can themselves serve as a source of such stimuli. For example, when exposed to proinflammatory stimuli, smooth-muscle cells elaborate cytokines and other mediators which drive thrombosis and fibrinolysis as well as proliferation.

Vascular Smooth-Muscle Cell Contraction Vascular smooth-muscle cells contract as cytoplasmic calcium concentration rises due to transmembrane influx and triggered release from intracellular calcium stores **(Fig. 232-4)**. In vascular smooth-muscle cells, voltage-dependent L-type calcium channels open with membrane depolarization. Local changes in intracellular calcium concentration, termed *calcium sparks*, can trigger release from intracellular stores which results in more contraction and higher vessel tone (see below). Opposing currents balance the effects of individual ionic fluxes, promoting homeostasis which is tightly regulated by neural and metabolic influences.

Biochemical agonists also increase intracellular [Ca^{2+}] by various mechanisms including receptor-dependent phospholipase C activation with hydrolysis of phosphatidylinositol 4,5-bisphosphate to generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). These membrane lipid derivatives in turn activate protein kinase C and increase intracellular [Ca^{2+}]. In addition, IP_3 binds specific sarcoplasmic reticulum (SR) receptors to increase calcium efflux from this storage pool into the cytoplasm.

Vascular smooth-muscle cell contraction depends on myosin light chain phosphorylation, which in the steady state reflects the balance between the actions of the relevant kinases and phosphatases. Calcium activates myosin light chain kinase via calmodulin, augmenting myosin ATPase activity enhancing contraction. Myosin light chain phosphatase conversely reduces myosin ATPase activity and contractile force. Other kinase/phosphorylase combinations result in a complex regulatory network that refines vascular tone and links it to physiologic requirements.

Control of Vascular Smooth-Muscle Cell Tone The autonomic nervous system and endothelial cells modulate vascular smooth-muscle cells through similar convergent pathways. Autonomic neurons enter vessel media and modulate vascular smooth-muscle cell tone in response to baroreceptors and chemoreceptors within the aortic arch or carotid bodies and to thermoreceptors in the skin. Rapidly acting reflex arcs modulated by central inputs respond to multiple sensory inputs as well as emotional stimuli through three neuronal classes: *sympathetic*, whose principal neurotransmitters are epinephrine and norepinephrine; *parasympathetic*, whose principal neurotransmitter is acetylcholine; and *nonadrenergic/noncholinergic*, which include two subgroups—nitrergic, whose principal neurotransmitter is NO, and peptidergic, whose principal neurotransmitters are substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, as well as a non-peptide, adenosine triphosphate (ATP).

Each of these neurotransmitters acts through specific receptors on the vascular smooth-muscle cell to modulate intracellular Ca^{2+} and consequently, contractile tone. Norepinephrine activates α adrenergic receptors, and epinephrine activates both α and β receptors; in most blood vessels, norepinephrine activates postjunctional α_1 receptors in large arteries and α_2 receptors in small arteries and arterioles, leading to vasoconstriction. Most blood vessels express β_2-adrenergic receptors on their vascular smooth-muscle cells and respond to β agonists by cyclic AMP–dependent relaxation. Acetylcholine released from parasympathetic neurons binds to muscarinic receptors on vascular smooth-muscle cells causing vasorelaxation. Nitrergic neurons release NO, which relaxes vascular smooth-muscle cell via the cyclic GMP–dependent and –independent mechanisms outlined, and other peptidergic inputs that regulate vascular tone. **For the detailed molecular physiology of the autonomic nervous system, see Chap. 432.**

The release of endothelial effectors of vascular smooth-muscle cell tone (Figs. 232-2 and 232-3) integrates mechanical (shear stress, cyclic strain, etc.) and biochemical stimuli (purinergic agonists, muscarinic agonists, peptidergic agonists). In addition to these local paracrine modulators, a complex system of circulating modulators ranging from norepinephrine to the natriuretic peptides also modulate vascular smooth-muscle cell tone.

VASCULAR REGENERATION

Growth of new blood vessels can occur in response to conditions such as chronic hypoxemia and tissue ischemia. Growth factors, including vascular endothelial growth factor (VEGF) and forms of fibroblast

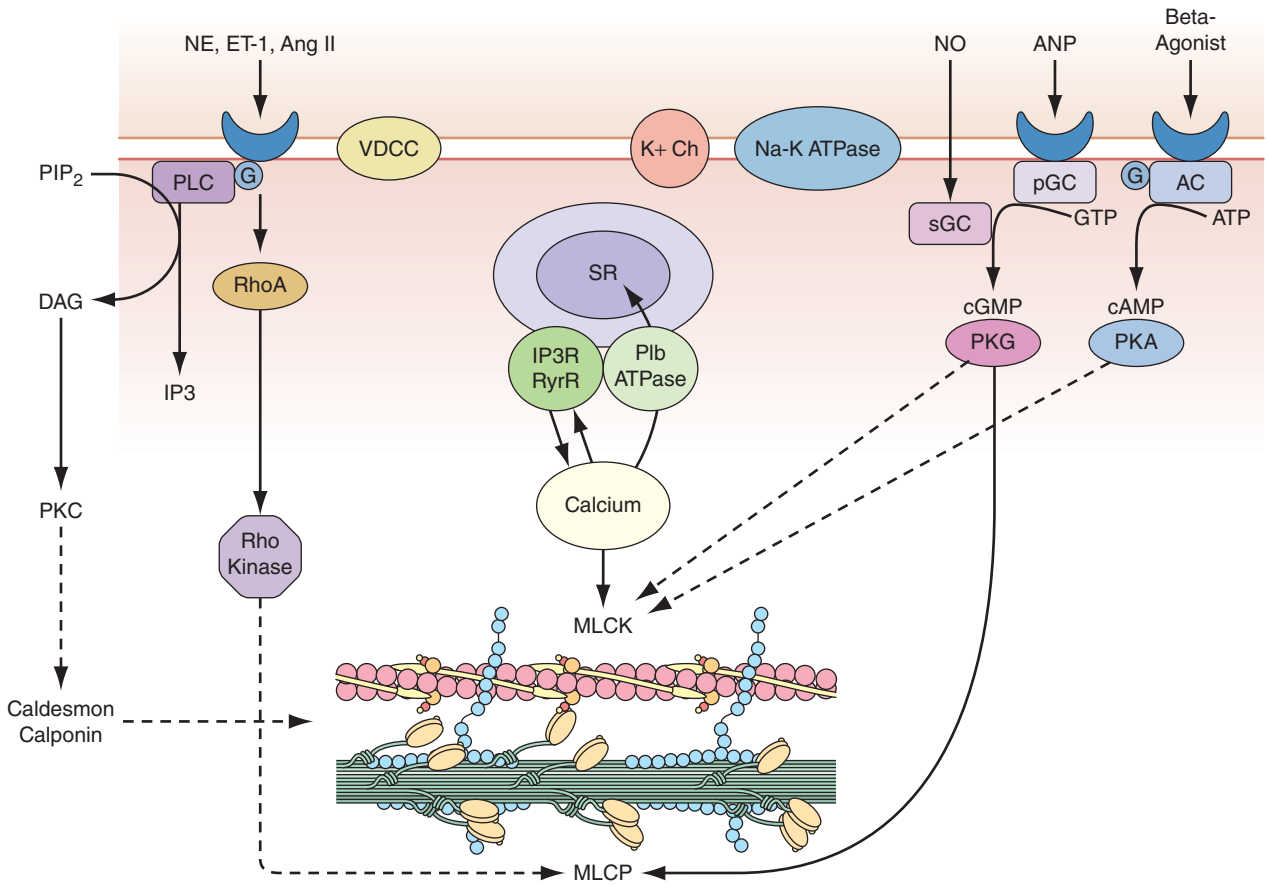

FIGURE 232-4 Regulation of vascular smooth-muscle cell calcium concentration and actomyosin ATPase-dependent contraction. AC, adenylyl cyclase; Ang II, angiotensin II; ANP, atrial natriuretic peptide; DAG, diacylglycerol; ET-1, endothelin-1; G, G protein; IP_3, inositol 1,4,5-trisphosphate; MLCK, myosin light chain kinase; MLCP, myosin light chain phosphatase; NE, norepinephrine; NO, nitric oxide; pGC, particular guanylyl cyclase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PKG, protein kinase G; PLC, phospholipase C; sGC, soluble guanylyl cyclase; SR, sarcoplasmic reticulum; VDCC, voltage-dependent calcium channel. *(Modified from B Berk, in Vascular Medicine, 3rd ed. Philadelphia, Saunders, Elsevier, 2006, p. 23; with permission.)*

growth factor (FGF), activate a signaling cascade that stimulates endothelial proliferation and tube formation, defined as *angiogenesis*. Guidance molecules, including members of the semaphorin family of secreted peptides, direct blood vessel patterning by attracting or repelling nascent endothelial tubes. The development of collateral vascular networks in the ischemic myocardium, an example of angiogenesis, can result from selective activation of local or circulating endothelial progenitor cells. True arteriogenesis, or the development of a new blood vessel that includes all three cell layers, normally does not occur in adult mammals, but recent scientific advances might help obviate such limitations **(Chaps. 92 and 473)**.

CELLULAR BASIS OF CARDIAC CONTRACTION

CARDIAC ULTRASTRUCTURE

Most of the ventricular mass is composed of cardiomyocytes, normally 60–140 µm in length and 17–25 µm in diameter **(Fig. 232-5*A*)**. Each cell contains multiple myofibrils that run the length of the cell and are composed of series of repeating sarcomeres. The cytoplasm between the myofibrils contains other cell constituents, including a single centrally located nucleus, mitochondria, and the intracellular membrane system, the SR.

The *sarcomere*, the structural and functional unit of contraction, lies between adjacent Z lines, which are dark repeating bands apparent on transmission electron microscopy. The distance between Z lines varies with the degree of contraction or stretch of the muscle and ranges between 1.6 and 2.2 µm. At the center of the sarcomere is a dark band of constant length (1.5 µm), the A band, which is flanked by two lighter bands, the I bands, which are of variable length. The sarcomere of heart muscle, like that of skeletal muscle, consists of interdigitating thick and thin myofilaments. Thicker filaments, composed principally of the protein myosin, traverse the A band; they are about 10 nm (100 Å) in diameter, with tapered ends. Thinner filaments, composed primarily of actin, course from the Z lines through the I band into the A band; they are ~5 nm (50 Å) in diameter and 1.0 µm in length. Thus, thick and thin filaments overlap only within the (dark) A band, whereas the (light) I band contains only thin filaments. On electron-microscopic examination, bridges extend between the thick and thin filaments within the A band; these are myosin heads (see below) bound to actin filaments.

THE CONTRACTILE PROCESS

The sliding filament model for muscle contraction rests on the central observation that both the thick and the thin filaments are constant in length during both contraction and relaxation. With activation, the actin filaments are propelled farther into the A band. In the process, the A band remains constant in length, whereas the I band shortens and the Z lines move toward one another.

The *myosin* molecule is a complex, asymmetric protein with a molecular mass of about 500,000 Da; it has a rod-like portion that is about 150 nm (1500 Å) in length with a globular portion (head) at its end. The globular portions of myosin form the bridges to actin and are the site of ATPase activity. In thick myofilaments, composed of ~300 longitudinally stacked myosin molecules, the rod-like segments of myosin assume an orderly, polarized manner, with outwardly projecting globular heads interacting with actin to generate force and shorten **(Fig. 232-5*B*)**.

Actin has a molecular mass of about 47,000 Da. Thin filaments consist of a double helix of two chains of actin molecules wound about each other on a larger molecule, tropomyosin. A group of regulatory proteins—troponins C, I, and T—localize at regular intervals on this filament **(Fig. 232-6)**. In contrast to myosin, actin lacks intrinsic enzymatic

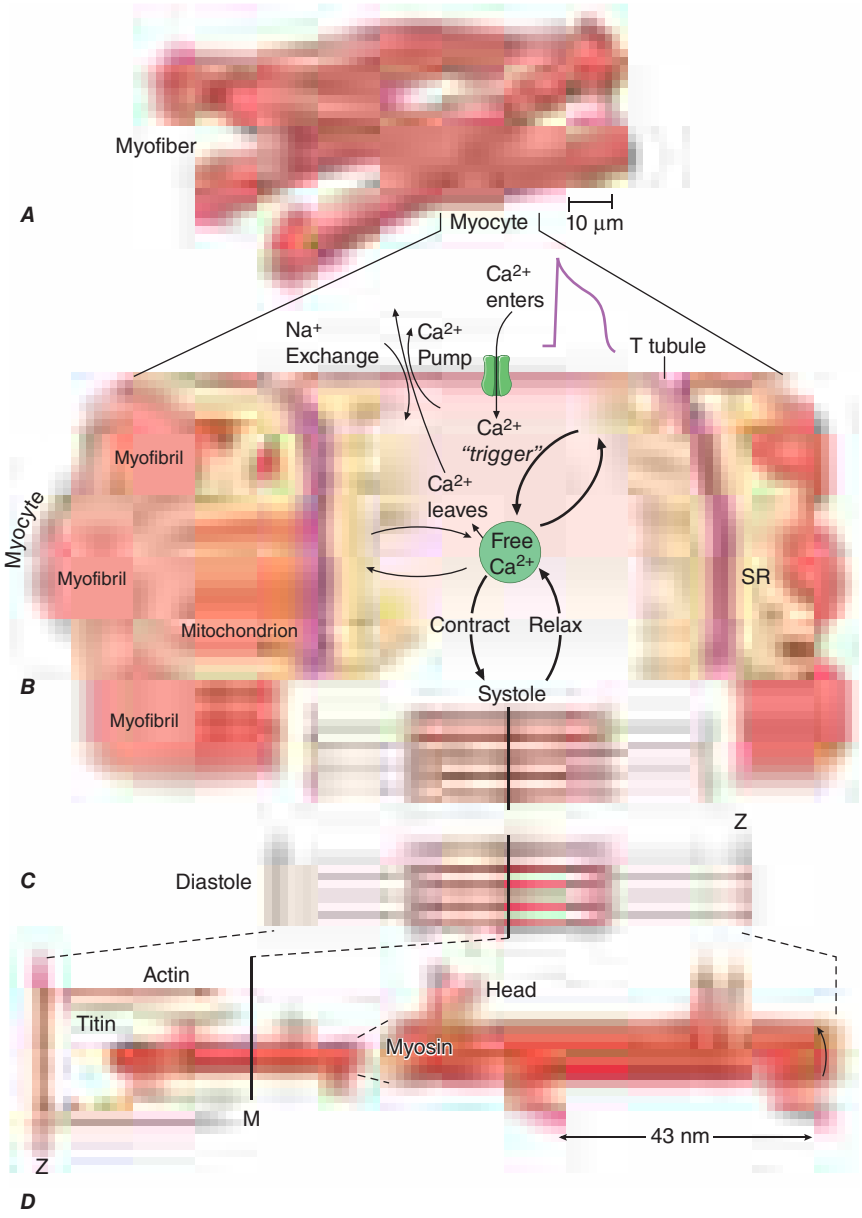

FIGURE 232-5 ***A*** shows the branching myocytes making up the cardiac myofibers. ***B*** illustrates the critical role played by the changing [Ca^{2+}] in the myocardial cytosol. Ca^{2+} ions are schematically shown as entering through the calcium channel that opens in response to the wave of depolarization that travels along the sarcolemma. These Ca^{2+} ions "trigger" the release of more calcium from the sarcoplasmic reticulum (SR) and thereby initiate a contraction-relaxation cycle. Eventually the small quantity of Ca^{2+} that has entered the cell leaves predominantly through an Na^+/Ca^{2+} exchanger, with a lesser role for the sarcolemmal Ca^{2+} pump. The varying actin-myosin overlap is shown for (***B***) systole, when [Ca^{2+}] is maximal, and (***C***) diastole, when [Ca^{2+}] is minimal. ***D.*** The myosin heads, attached to the thick filaments, interact with the thin actin filaments. *(From LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)*

activity, but combines reversibly with myosin in the presence of ATP and Ca^{2+}. Calcium activates the myosin ATPase, which breaks down ATP to supply the energy for contraction (Fig. 232-6). The activity of myosin ATPase determines the rate of actomyosin cross-bridge formation and breakdown, and ultimately determines contraction velocity. In relaxed muscle, tropomyosin inhibits this interaction. *Titin* (Fig. 232-5D) an enormous, flexible, myofibrillar protein, connects myosin to the Z line; its stretching contributes to the elasticity of the heart. Dystrophin, a long cytoskeletal protein that binds to the dystroglycan complex at adherens junctions on the cell membrane, tethers the sarcomere to the cell membrane at regions tightly coupled to adjacent contracting myocytes. Mutations in multiple sarcomeric and cytoskeletal proteins cause different forms of inherited disease involving the heart and skeletal muscle.

During activation of the cardiac myocyte, Ca^{2+} binds the heterotrimer troponin C, resulting in conformational changes in the regulatory protein tropomyosin and exposing actin cross-bridge interaction sites (Fig. 232-6). Repetitive interaction between myosin heads and actin filaments is termed *cross-bridge cycling*, and results in sliding of the actin along the myosin filaments, with muscle shortening and/or the development of tension. The splitting of ATP then dissociates the myosin cross-bridge from actin. In the presence of ATP (Fig. 232-6), actin and myosin filaments bind and dissociate cyclically if sufficient Ca^{2+} is present; these linkages cease when [Ca^{2+}] falls below a critical level, and the troponin-tropomyosin complex once more inhibits actin-myosin interactions **(Fig. 232-7)**.

Intracytoplasmic [Ca^{2+}] is a principal determinant of the inotropic state of the heart. Most agents that stimulate myocardial contractility (positive inotropic stimuli), including digitalis glycosides and β-adrenergic agonists, increase cytoplasmic [Ca^{2+}], triggering cross-bridge cycling. Increased adrenergic neuronal activity stimulates myocardial contractility through norepinephrine release, activation of β adrenergic receptors and, via G_s-stimulated guanine nucleotide-binding proteins, activation of the adenylyl cyclase, which leads to the formation of

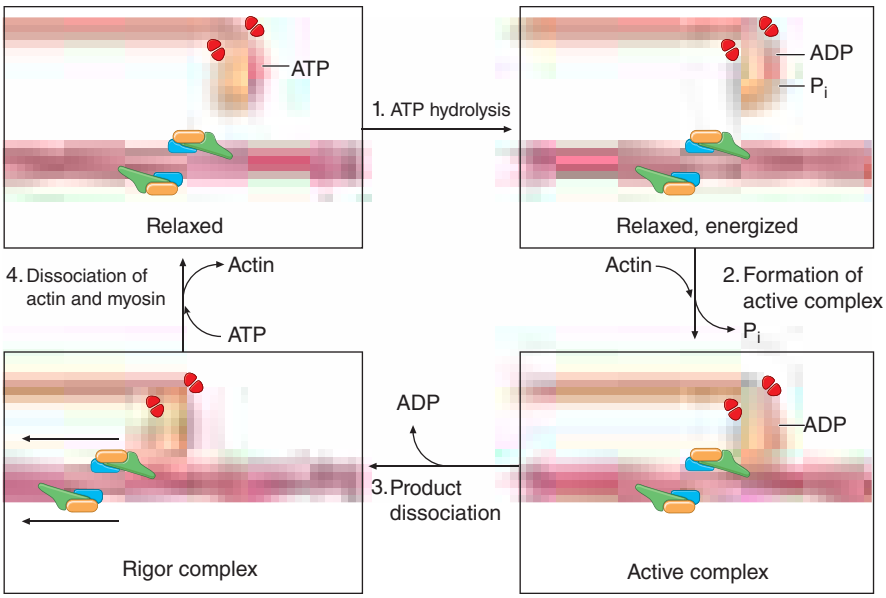

FIGURE 232-6 Four steps in cardiac muscle contraction and relaxation. In relaxed muscle (*upper left*), ATP bound to the myosin cross-bridge dissociates the thick and thin filaments. ***Step 1:*** Hydrolysis of myosin-bound ATP by the ATPase site on the myosin head transfers the chemical energy of the nucleotide to the activated cross-bridge (*upper right*). When cytosolic Ca^{2+} concentration is low, as in relaxed muscle, the reaction cannot proceed because tropomyosin and the troponin complex on the thin filament do not allow the active sites on actin to interact with the cross-bridges. Therefore, even though the cross-bridges are energized, they cannot interact with actin. ***Step 2:*** When Ca^{2+} binding to troponin C has exposed active sites on the thin filament, actin interacts with the myosin cross-bridges to form an active complex (*lower right*) in which the energy derived from ATP is retained in the actin-bound cross-bridge, whose orientation has not yet shifted. ***Step 3:*** The muscle contracts when ADP dissociates from the cross-bridge. This step leads to the formation of the low-energy rigor complex (*lower left*) in which the chemical energy derived from ATP hydrolysis has been expended to perform mechanical work (the "rowing" motion of the cross-bridge). ***Step 4:*** The muscle returns to its resting state, and the cycle ends when a new molecule of ATP binds to the rigor complex and dissociates the cross-bridge from the thin filament. This cycle continues until calcium is dissociated from troponin C in the thin filament, which causes the contractile proteins to return to the resting state with the cross-bridge in the energized state. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase. *(From AM Katz: Heart failure: Cardiac function and dysfunction, in Atlas of Heart Diseases, 3rd ed, WS Colucci [ed]. Philadelphia, Current Medicine, 2002. Reprinted with permission.)*

the intracellular second messenger cyclic AMP from ATP (Fig. 232-7). Cyclic AMP in turn activates protein kinase A (PKA), which phosphorylates sarcolemmal Ca^{2+} channels, thereby enhancing the influx of Ca^{2+} into the myocyte.

The SR **(Fig. 232-8)**, a complex network of anastomosing intracellular channels, invests the myofibrils. The transverse tubules, or T system, closely related to the SR, both structurally and functionally, arise from invaginations of the sarcolemma that extend into the myocardial fiber along the Z lines, i.e., the ends of the sarcomeres.

CARDIAC ACTIVATION

In the inactive state, the cardiac cell is electrically polarized; i.e., the interior has a negative charge relative to the outside of the cell, with a transmembrane potential of –80 to –100 mV **(Chap. 238)**. The sarcolemma, which in the resting state is largely impermeable to Na^+, and a Na^+- and K^+- pump energized by ATP extrudes Na^+ from the cell, and maintains the resting potential. In the resting state, intracellular $[K^+]$ is relatively high and $[Na^+]$ is far lower; conversely, extracellular $[Na^+]$ is high and $[K^+]$ is low. At the same time, in the resting state, extracellular $[Ca^{2+}]$ greatly exceeds free intracellular $[Ca^{2+}]$.

The action potential has four phases **(see Fig. 238-1*B*)**. During the action potential plateau (phase 2), there is a slow inward current through sarcolemmal L-type Ca^{2+} channels (Fig. 232-8). Depolarizing current spreads across the cell membrane, penetrating deeply into the cell via the T tubular system. The absolute quantity of Ca^{2+} traversing sarcolemma and T tubules is modest and insufficient to fully activate contraction. However, this Ca^{2+} current, through *Ca^{2+}-induced Ca^{2+} release*, triggers substantial Ca^{2+} release from the SR, inducing contraction.

Ca^{2+} is released from the SR through a Ca^{2+} release channel, a cardiac isoform of the ryanodine receptor (RyR2). Several regulatory proteins, including *calstabin 2*, inhibit RyR2 and thus SR Ca^{2+} release. Inherited disorders or exogenous factors affecting the efficiency or stability of SR Ca^{2+} handling can impair contraction, leading to heart failure, or to ventricular arrhythmias.

The Ca^{2+} released from the SR diffuses to interact with myofibrillar troponin C (Fig. 232-7), repressing this protein's inhibition of contraction, and so activating myofilaments to shorten. During repolarization, the activity of the SR Ca^{2+} ATPase ($SERCA_{2A}$) leads to Ca^{2+} uptake against a concentration gradient into the SR where complexes with another specialized protein, *calsequestrin*. The uptake of Ca^{2+} is ATP (energy)-dependent and lowers cytoplasmic $[Ca^{2+}]$ to a level where actomyosin interaction is inhibited and myocardial relaxation occurs. There is also a sarcolemmal exchange of Ca^{2+} for Na^+ (Fig. 232-8), reducing the cytoplasmic $[Ca^{2+}]$. Additional control of calcium compartmentalizaion results from cyclic AMP–dependent PKA phosphorylation of the SR protein *phospholamban*, permitting $SERCA_{2A\ activation}$, increasing SR Ca^{2+} uptake, and so accelerating the relaxation rates, loading the SR with Ca^{2+} for subsequent release, and stimulating contraction.

Thus, the combination of the cell membrane, transverse tubules, and SR, with their ability to transmit the action potential and release and then reaccumulate Ca^{2+}, controls the cyclic contraction and relaxation of heart muscle. Genetic or pharmacologic alterations of any component, whatever its etiology, can disturb any of the functions of this finely tuned system.

CONTROL OF CARDIAC PERFORMANCE AND OUTPUT

The extent of shortening of heart muscle and, therefore, ventricular stroke volume in the intact heart, depends on three major influences: (1) the length of the muscle at the onset of contraction, i.e., the preload; (2) the tension that the muscle must develop during contraction, i.e., the afterload; and (3) muscle contractility, i.e., the extent and velocity of shortening at any given preload and afterload. **Table 232-2** lists the major determinants of preload, afterload, and contractility.

THE ROLE OF MUSCLE LENGTH (PRELOAD)

Preload determines sarcomere length at the onset of contraction. Contractile force is optimal at specific sarcomere lengths (~2.2 μm) where myofilament Ca^{2+} sensitivity is maximal, and where myofilament interactions and activation of contraction are most efficient. The relationship

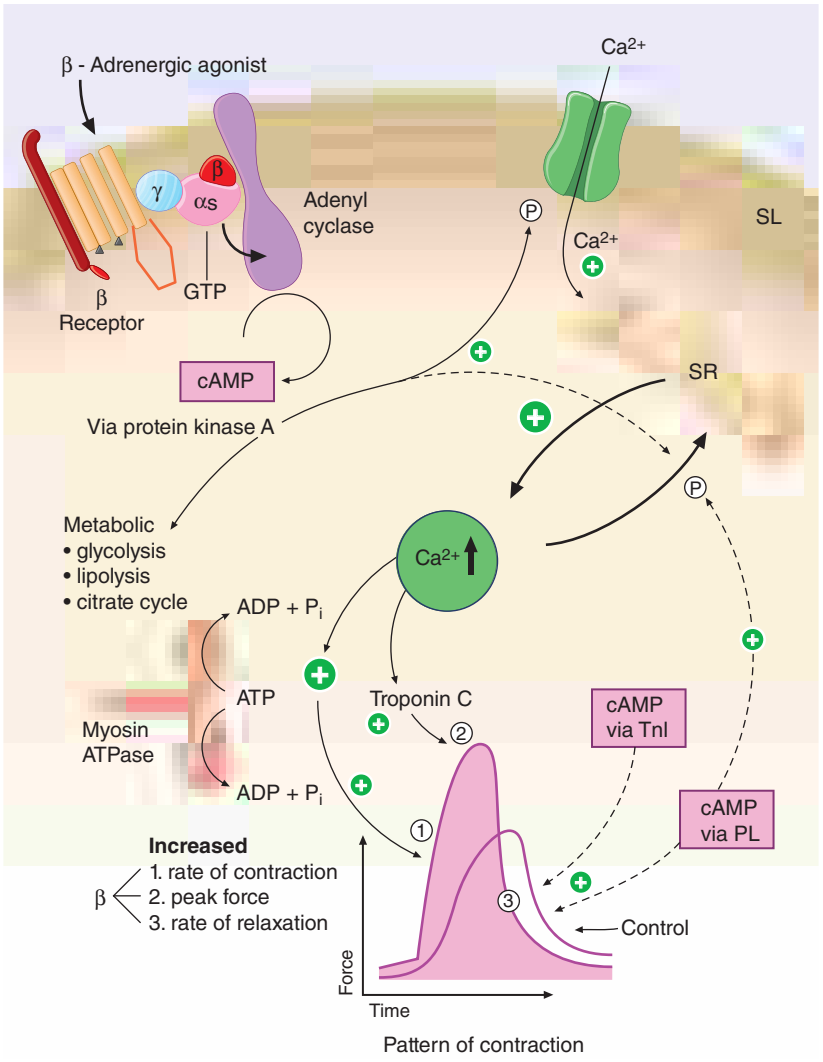

FIGURE 232-7 Signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects of β-adrenergic stimulation. When the β-adrenergic agonist interacts with the β receptor, a series of G protein–mediated changes leads to activation of adenylyl cyclase and the formation of cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism (*left*) and phosphorylate the Ca^{2+} channel protein (*right*). The result is an enhanced opening probability of the Ca^{2+} channel, thereby increasing the inward movement of Ca^{2+} ions through the sarcolemma (SL) of the T tubule. These Ca^{2+} ions release more calcium from the sarcoplasmic reticulum (SR) to increase cytosolic Ca^{2+} and activate troponin C. Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (Pi). Enhanced myosin ATPase activity explains the increased rate of contraction, with increased activation of troponin C explaining increased peak force development. An increased rate of relaxation results from the ability of cAMP to activate as well the protein phospholamban, situated on the membrane of the SR, that controls the rate of uptake of calcium into the SR. The latter effect explains enhanced relaxation (lusitropic effect). P, phosphorylation; PL, phospholamban; TnI, troponin I. *(Modified from LH Opie: Heart Physiology: From Cell to Circulation, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2004. Reprinted with permission. Copyright LH Opie, 2004.)*

between initial muscle fiber length and the developed force is the basis of Starling's law of the heart, which states that within limits, the ventricular contraction force depends on the end-diastolic length of the cardiac muscle; which in vivo relates closely to the ventricular end-diastolic volume.

CARDIAC PERFORMANCE

Ventricular end-diastolic or "filling" pressure can serve as a surrogate for end-diastolic volume. In isolated heart and heart-lung preparations, stroke volume varies directly with the end-diastolic fiber length (preload) and inversely with the arterial resistance (afterload), and as the heart fails—i.e., as its contractility declines—it delivers a progressively smaller stroke volume from a normal or even elevated end-diastolic volume. The relation between ventricular end-diastolic pressure and the stroke work of the ventricle (the ventricular function curve) provides a working definition of cardiac contractility in the intact organism. An increase in contractility is accompanied by a shift of the ventricular function curve upward and to the left (greater stroke work at any level of ventricular end-diastolic pressure, or lower end-diastolic volume at any level of stroke work), whereas a shift downward and to the right characterizes depression of contractility (Fig. 232-9).

VENTRICULAR AFTERLOAD

In the intact heart, as ex vivo, the extent and velocity of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility relate inversely to the afterload, i.e., the instantaneous load opposing shortening. In the intact heart, the afterload may be defined as the tension developed in the ventricular wall during ejection. Afterload is determined by the aortic pressure as well as by the volume and thickness of the ventricular cavity. Laplace's law specifies that the tension of the myocardial fiber is the product of the intra-cavitary ventricular pressure and ventricular radius divided by wall thickness. Therefore, at any given aortic pressure, the afterload on a dilated left ventricle exceeds that on a normal-sized ventricle. Conversely, at the same aortic pressure and ventricular diastolic volume, the afterload on a hypertrophied ventricle is lower than that on a normal chamber. Aortic pressure in turn depends on the peripheral vascular resistance, the biomechanics of the arterial tree, and the volume of blood it contains at the onset of ejection.

Ventricular afterload finely regulates cardiovascular performance (Fig. 232-10). As noted, elevations in both preload and contractility increase myocardial fiber shortening, whereas increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular

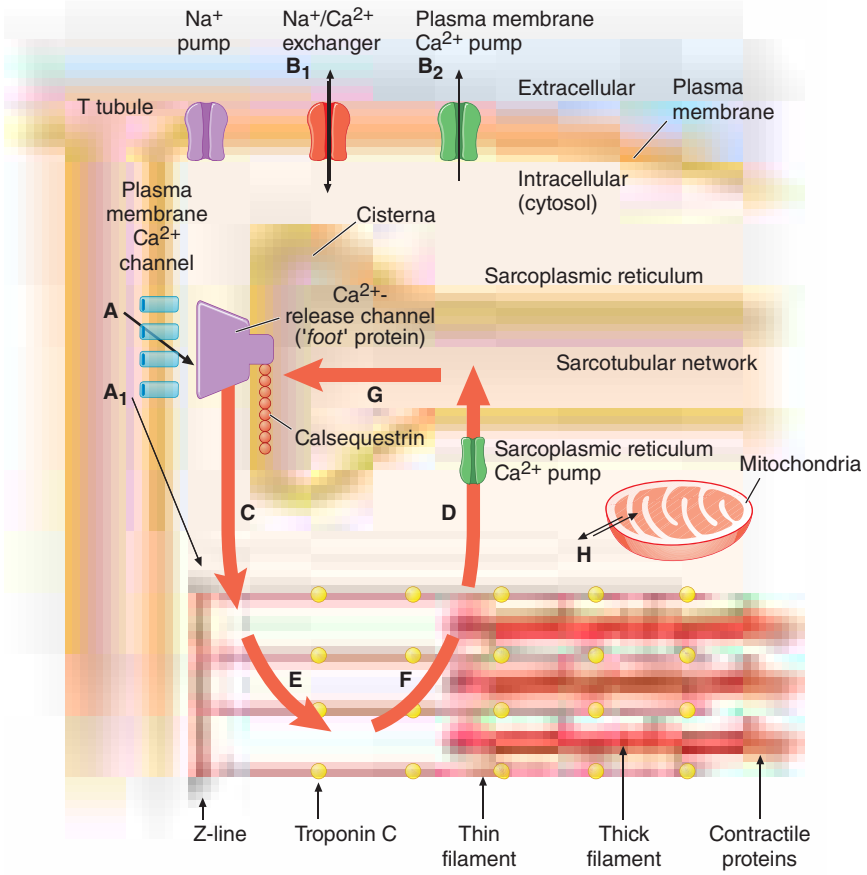

FIGURE 232-8 The Ca^{2+} fluxes and key structures involved in cardiac excitation-contraction coupling. The *arrows* denote the direction of Ca^{2+} fluxes. The *thickness* of each arrow indicates the magnitude of the calcium flux. Two Ca^{2+} cycles regulate excitation-contraction coupling and relaxation. The larger cycle is entirely intracellular and involves Ca^{2+} fluxes into and out of the sarcoplasmic reticulum, as well as Ca^{2+} binding to and release from troponin C. The smaller extracellular Ca^{2+} cycle occurs when this cation moves into and out of the cell. The action potential opens plasma membrane Ca^{2+} channels to allow passive entry of Ca^{2+} into the cell from the extracellular fluid (*arrow A*). Only a small portion of the Ca^{2+} that enters the cell directly activates the contractile proteins (*arrow* A_1). The extracellular cycle is completed when Ca^{2+} is actively transported back out to the extracellular fluid by way of two plasma membrane fluxes mediated by the sodium-calcium exchanger (*arrow* B_1) and the plasma membrane calcium pump (*arrow* B_2). In the intracellular Ca^{2+} cycle, passive Ca^{2+} release occurs through channels in the cisternae (*arrow C*) and initiates contraction; active Ca^{2+} uptake by the Ca^{2+} pump of the sarcotubular network (*arrow D*) relaxes the heart. Diffusion of Ca^{2+} within the sarcoplasmic reticulum (*arrow G*) returns this activator cation to the cisternae, where it is stored in a complex with calsequestrin and other calcium-binding proteins. Ca^{2+} released from the sarcoplasmic reticulum initiates systole when it binds to troponin *C* (*arrow E*). Lowering of cytosolic [Ca^{2+}] by the sarcoplasmic reticulum (SR) causes this ion to dissociate from troponin (*arrow F*) and relaxes the heart. Ca^{2+} also may move between mitochondria and cytoplasm (H). *(Adapted from AM Katz: Physiology of the Heart, 4th ed. Philadelphia, Lippincott, Williams & Wilkins, 2005, with permission.)*

size determine stroke volume. An increase in arterial pressure induced by vasoconstriction, for example, augments afterload, which opposes myocardial fiber shortening, reducing stroke volume.

When myocardial contractility is impaired and the ventricle dilates, afterload rises (Laplace's law) and limits cardiac output. Increased afterload also may result from neural and humoral stimuli that occur in response to a fall in cardiac output. This increased afterload may reduce cardiac output further, thereby increasing ventricular volume and initiating a vicious circle, especially in patients with ischemic heart disease and limited myocardial O_2 supply. Treatment with vasodilators has the opposite effect; when afterload falls, cardiac output rises **(Chap. 252)**.

Under normal circumstances, the various influences acting on cardiac performance interact in a complex fashion to maintain cardiac output at a level responsive to the requirements of tissue metabolic demands (Fig. 232-10). Interference with a single mechanism may not influence the cardiac output due to homeostatic adjustments. For example, a moderate reduction of blood volume or the loss of the atrial contribution to ventricular contraction can be tolerated without a reduction in resting cardiac output. Under these circumstances, other factors, such as adrenergic neuronal impulses to the heart, heart rate, and venous tone, will serve as compensatory mechanisms and sustain cardiac output in a normal individual. Ultimately, understanding the complex interactions between these different variables requires rigorous models to predict relevant outcomes, and led to the early application of systems engineering principles in medicine.

EXERCISE

The integrated response to exercise illustrates the interactions among the three determinants of stroke volume: preload, afterload, and contractility (Fig. 232-9). Hyperventilation, the pumping action of the exercising muscles, and venoconstriction during exercise all augment venous return and hence ventricular filling and preload (Table 232-2). Simultaneously, the increase in the adrenergic neuronal stimulation of the myocardium, the increased concentration of circulating catecholamines, and the tachycardia that occur during exercise combine to augment the myocardial contractility (Fig. 232-9, curves 1 and 2), together elevating stroke volume and stroke work, without a change in or even a reduction of end-diastolic pressure and volume (Fig. 232-9, points A and B). Vasodilation occurs in the exercising muscles, thus limiting the increase in afterload that otherwise would occur as cardiac output rises to levels as high as five times greater than basal levels during maximal exercise. This vasodilation ultimately allows the achievement of elevated cardiac outputs during exercise at arterial pressures only moderately higher than the resting state.

ASSESSMENT OF CARDIAC FUNCTION

Several techniques can define impaired cardiac function in clinical practice. Cardiac output and stroke volume may decline in the presence of heart failure, but these variables are often within normal limits, especially at rest. A more sensitive index of cardiac function is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = 67 ± 8%), which is frequently depressed in systolic heart failure even when stroke volume is normal. Alternatively, abnormally elevated ventricular end-diastolic volume (normal value = 75 ± 20 mL/m^2) or end-systolic volume (normal value = 25 ± 7 mL/m^2) signifies left ventricular systolic impairment.

Noninvasive techniques, particularly echocardiography, radionuclide scintigraphy and cardiac magnetic resonance imaging (MRI) **(Chap. 236)** have great value in the clinical assessment of myocardial function. They provide measurements of end-diastolic and end-systolic volumes, ejection fraction, and systolic shortening rate, and they allow assessment of ventricular filling (see below) as well as regional contraction and relaxation. The latter measurements have particular importance in ischemic heart disease, as myocardial infarction causes regional myocardial damage.

Strong dependence on ventricular loading conditions influence the of measurements of cardiac output, ejection fraction, and ventricular volumes as indices of cardiac function. Thus, a depressed ejection fraction and lowered cardiac output may occur in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

The end-systolic left ventricular pressure-volume relationship has particular value as an index of ventricular performance as it does

TABLE 232-2 Determinants of Stroke Volume

I. Ventricular Preload

A. Blood volume
B. Distribution of blood volume
   1. Body position
   2. Intrathoracic pressure
   3. Intrapericardial pressure
   4. Venous tone
   5. Pumping action of skeletal muscles
C. Atrial contraction

II. Ventricular Afterload

A. Systemic vascular resistance
B. Elasticity of arterial tree
C. Arterial blood volume
D. Ventricular wall tension
   1. Ventricular radius
   2. Ventricular wall thickness

III. Myocardial Contractility[a]

A. Intramyocardial [Ca^{2+}] ↑↓
B. Cardiac adrenergic nerve activity ↑↓[b]
C. Circulating catecholamines ↑↓[b]
D. Cardiac rate ↑↓[b]
E. Exogenous inotropic agents ↑
F. Myocardial ischemia ↓
G. Myocardial cell death (necrosis, apoptosis, autophagy) ↓
H. Alterations of sarcomeric and cytoskeletal proteins ↓
   1. Genetic
   2. Hemodynamic overload
I. Myocardial fibrosis ↓
J. Chronic overexpression of neurohormones ↓
K. Ventricular remodeling ↓
L. Chronic and/or excessive myocardial hypertrophy ↓

[a]Arrows indicate directional effects of determinants of contractility. [b]Contractility rises initially but later becomes depressed.

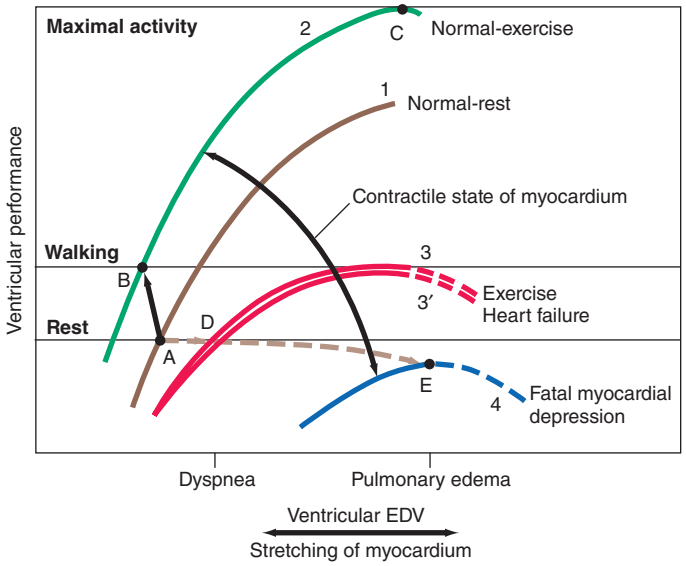

FIGURE 232-9 The interrelations among influences on ventricular end-diastolic volume (EDV) through stretching of the myocardium and the contractile state of the myocardium. Levels of ventricular EDV associated with filling pressures that result in dyspnea and pulmonary edema are shown on the abscissa. Levels of ventricular performance required when the subject is at rest, while walking, and during maximal activity are designated on the ordinate. The *broken lines* are the descending limbs of the ventricular-performance curves, which are rarely seen during life but show the level of ventricular performance if end-diastolic volume could be elevated to very high levels. For further explanation, see text. *(Modified from WS Colucci and E Braunwald: Pathophysiology of heart failure, in Braunwald's Heart Disease, 7th ed, DP Zipes et al [eds]. Philadelphia: Elsevier, 2005, pp 509–538.)*

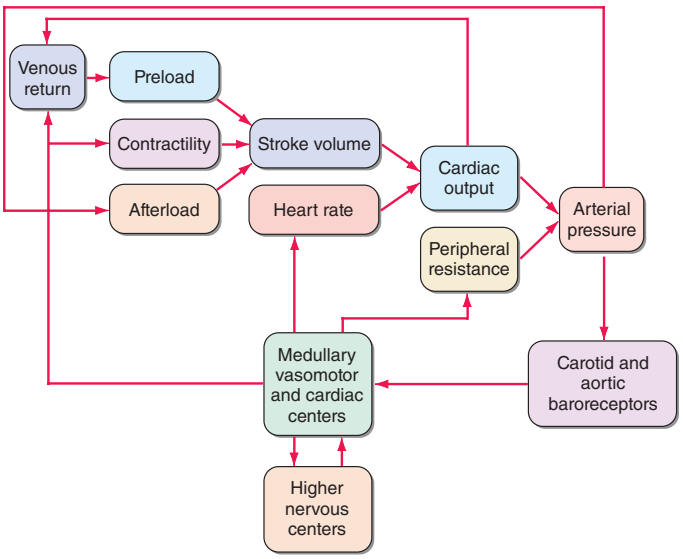

FIGURE 232-10 Interactions in the intact circulation of preload, contractility, and afterload in producing stroke volume. Stroke volume combined with heart rate determines cardiac output, which, when combined with peripheral vascular resistance, determines arterial pressure for tissue perfusion. The characteristics of the arterial system also contribute to afterload, an increase that reduces stroke volume. The interaction of these components with carotid and aortic arch baroreceptors provides a feedback mechanism to higher medullary and vasomotor cardiac centers and to higher levels in the central nervous system to effect a modulating influence on heart rate, peripheral vascular resistance, venous return, and contractility. *(From MR Starling: Physiology of myocardial contraction, in Atlas of Heart Failure: Cardiac Function and Dysfunction, 3rd ed, WS Colucci and E Braunwald [eds]. Philadelphia: Current Medicine, 2002, pp 19–35.)*

not depend on preload and afterload **(Fig. 232-11)**. At any level of myocardial contractility, left ventricular end-systolic volume varies inversely with end-systolic pressure; as contractility declines, end-systolic volume (at any level of end-systolic pressure) rises. Measurement of end-systolic left ventricular pressure-volume loops adds rigor to research studies of left ventricular function, but has not replaced the more readily assessed indices, such as ventricular volumes and ejection fraction, in clinical practice.

DIASTOLIC FUNCTION

Ventricular filling is influenced by the extent and speed of myocardial relaxation, a function of the rate of uptake of Ca^{2+} by the SR; the latter may be enhanced by adrenergic activation and reduced by ischemia, which reduces the ATP available for pumping Ca^{2+} into the SR (see above). The passive stiffness of the ventricular wall also may impede filling. Ventricular stiffness increases with hypertrophy and conditions that infiltrate the ventricle, such as amyloid, or can result from an extrinsic constraint (e.g., pericardial compression) **(Fig. 232-12)**.

Ventricular filling can be assessed by measuring flow velocity across the mitral valve using Doppler ultrasound. Normally, inflow velocity is more rapid in early diastole than during atrial systole; with mild to moderately impaired relaxation, the rate of early diastolic filling declines, as presystolic filling rates rise. With further stiffening, flow is "pseudo-normalized," as early ventricular filling becomes more rapid with rising left atrial pressure upstream of the left ventricle.

CARDIAC METABOLISM

The heart requires a continuous supply of energy (ATP) not only to drive mechanical contraction, but also to maintain ionic and biochemical homeostasis. The development of tension, the frequency of contraction, and myocardial contractility levels are the principal determinants of the heart's energy needs, rendering its O_2 requirements ~15% of that of the entire organism.

Most ATP production depends on oxidation of the substrates glucose and free fatty acids (FFAs). FFAs used by the myocardium derive from circulating FFAs, principally from lipolysis in adipose tissue, whereas the myocyte's glucose derives from plasma as well as from

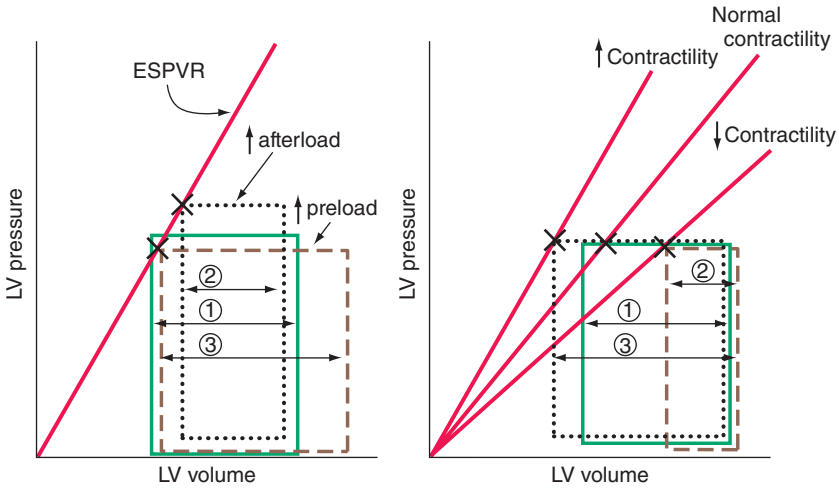

FIGURE 232-11 The responses of the left ventricle to increased afterload, increased preload, and increased and reduced contractility are shown in the pressure-volume plane. ***Left.*** Effects of increases in preload and afterload on the pressure-volume loop. Because there has been no change in contractility, the end-systolic pressure-volume relationship (ESPVR) is unchanged. With an increase in afterload, stroke volume falls (1 → 2); with an increase in preload, stroke volume rises (1 → 3). ***Right.*** With increased myocardial contractility and constant left ventricular end-diastolic volume, the ESPVR moves to the left of the normal line (lower end-systolic volume at any end-systolic pressure) and stroke volume rises (1 → 3). With reduced myocardial contractility, the ESPVR moves to the right; end-systolic volume is increased, and stroke volume falls (1 → 2).

the cell's breakdown of its glycogen stores (glycogenolysis). These two principal sources of acetyl coenzyme A in cardiac muscle vary reciprocally. Glucose is broken down in the cytoplasm into a three-carbon product, pyruvate, which passes into mitochondria, where it is metabolized to the two-carbon fragment, acetyl-CoA, and undergoes oxidation. FFAs are converted to acyl-CoA in the cytoplasm and acetyl-CoA in the mitochondria. Acetyl-CoA enters the citric acid (Krebs) cycle to produce ATP by oxidative phosphorylation; ATP then enters the cytoplasm from the mitochondrial compartment. Intracellular adenosine diphosphate (ADP), resulting from ATP breakdown, enhances ATP production.

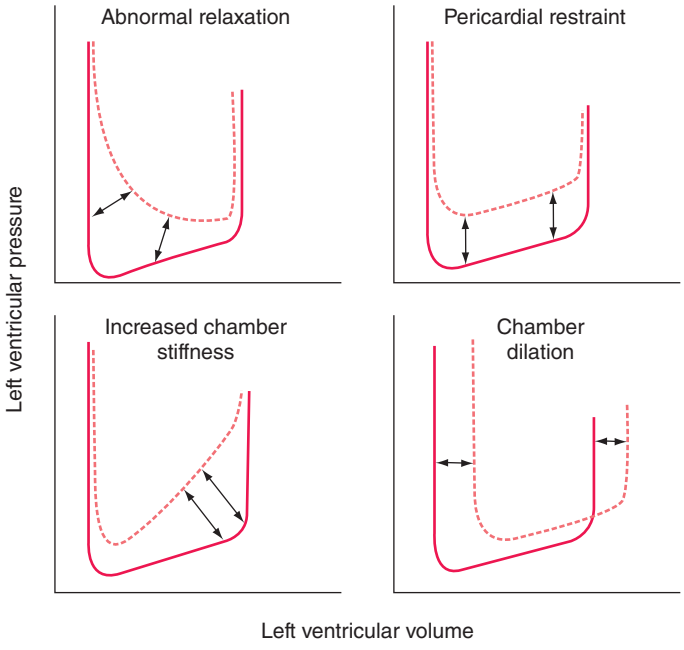

FIGURE 232-12 Mechanisms that cause diastolic dysfunction reflected in the pressure-volume relation. The bottom half of the pressure-volume loop is depicted. *Solid lines* represent normal subjects; *broken lines* represent patients with diastolic dysfunction. *(From JD Carroll et al: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. Circulation 74:815, 1986; with permission.)*

In the fasted, resting state, circulating FFA concentrations and their myocardial uptake are high, and they furnish most of the heart's acetyl-CoA (~70%). In the fed state, with elevations of blood glucose and insulin, glucose oxidation increases and FFA oxidation subsides. Increased cardiac work, inotropic agents, hypoxia, and mild ischemia all enhance myocardial glucose uptake, glucose production resulting from glycogenolysis, and glucose metabolism to pyruvate (glycolysis). By contrast, β-adrenergic stimulation, possibly due to stress, raises the circulating levels and metabolism of FFAs in favor of glucose. Severe ischemia inhibits the cytoplasmic pyruvate dehydrogenase, and despite both glycogen and glucose breakdown, glucose undergoes incomplete metabolism to lactic acid (anaerobic glycolysis), which does not enter the citric acid cycle. Anaerobic glycolysis produces much less ATP than does aerobic glucose metabolism. High concentrations of circulating FFAs, which can occur when adrenergic stimulation is superimposed on severe ischemia, reduce oxidative phosphorylation and cause ATP wastage; the myocardial content of ATP declines impairing contraction. In addition, FFA breakdown products may exert toxic or arrhythmogenic effects on cardiac cell membranes.

Myocardial energy is stored as creatine phosphate (CP), which is in equilibrium with ATP, the immediate energy source. In states of reduced energy availability, the CP stores decline first. Cardiac hypertrophy, fibrosis, tachycardia, increased wall tension due to ventricular dilation, and increased intracytoplasmic [Ca^{2+}] all contribute to increased myocardial energy needs. When coupled with reduced coronary flow reserve, as occurs with obstruction of coronary arteries or abnormalities of the coronary microcirculation, an imbalance in myocardial ATP production relative to demand may occur, and the resulting ischemia can worsen or cause heart failure.

REGENERATING CARDIAC TISSUE

Until very recently, adult mammalian myocardial cells were viewed as fully differentiated and without regenerative potential. Evidence currently supports the existence of limited regenerative potential of the mature heart. Considerable current effort is being devoted to evaluating the utility of various putative stem cell populations and regenerative approaches to enhance cardiac repair after injury. The success of such approaches would offer the exciting possibility of reconstructing an infarcted or failing ventricle **(Chap. 473)**.

ACKNOWLEDGMENT

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233 Epidemiology of Cardiovascular Disease

Thomas A. Gaziano, J. Michael Gaziano

Cardiovascular disease (CVD) is now the most common cause of death worldwide. Before 1900, infectious diseases and malnutrition were the most common causes, and CVD was responsible for <10% of all deaths. In 2015, CVD accounted for ~17.9 million deaths worldwide (32%), including nearly 34% of deaths in high-income countries and about 32% in low- and middle-income countries.

THE EPIDEMIOLOGIC TRANSITION

The global rise in CVD is the result of an unprecedented transformation in the causes of morbidity and mortality during the twentieth century. Known as the epidemiologic transition, this shift is driven by industrialization, urbanization, and associated lifestyle changes and is taking place in every part of the world among all races, ethnic groups, and cultures. The transition is divided into four basic stages: pestilence and famine, receding pandemics, degenerative and man-made diseases, and delayed degenerative diseases. A fifth stage, characterized by an epidemic of inactivity and obesity, is emerging in some countries **(Table 233-1)**.

The *age of pestilence and famine* is marked by malnutrition, infectious diseases, and high infant and child mortality that are offset by high fertility. Tuberculosis, dysentery, cholera, and influenza are often fatal, resulting in a mean life expectancy of about 30 years. CVD, which accounts for <10% of deaths, takes the form of rheumatic heart disease and cardiomyopathies due to infection and malnutrition. Approximately 10% of the world's population remains in the age of pestilence and famine.

Per capita income and life expectancy increase during the *age of receding pandemics* as the emergence of public health systems, cleaner water supplies, and improved nutrition combine to drive down deaths from infectious disease and malnutrition. Infant and childhood mortality also decline, but deaths due to CVD increase to between 10 and 35% of all deaths. Rheumatic valvular disease, hypertension, coronary heart disease (CHD), and stroke are the predominant forms of CVD. Almost 40% of the world's population is currently in this stage.

The *age of degenerative and man-made diseases* is distinguished by mortality from noncommunicable diseases—primarily CVD—surpassing mortality from malnutrition and infectious diseases. Caloric intake, particularly from animal fat, increases. CHD and stroke are prevalent, and between 35 and 65% of all deaths can be traced to CVD. Typically, the rate of CHD deaths exceeds that of stroke by a ratio of 2:1 to 3:1. During this period, average life expectancy surpasses the age of 50. Roughly 35% of the world's population falls into this category.

In the *age of delayed degenerative diseases*, CVD and cancer remain the major causes of morbidity and mortality, with CVD accounting for 40% of all deaths. However, age-adjusted CVD mortality declines, aided by preventive strategies (for example, smoking cessation programs and effective blood pressure control), acute hospital management, and technologic advances, such as the availability of bypass surgery. CHD, stroke, and congestive heart failure are the primary forms of CVD. About 15% of the world's population is now in the age of delayed degenerative diseases or is exiting this age and moving into the fifth stage of the epidemiologic transition.

In the industrialized world, physical activity continues to decline while total caloric intake increases. The resulting epidemic of overweight and obesity may signal the start of the *age of inactivity and obesity*. Rates of type 2 diabetes mellitus, hypertension, and lipid abnormalities are on the rise, trends that are particularly evident in children. If these risk factor trends continue, age-adjusted CVD mortality rates could increase in the coming years.

PATTERNS IN THE EPIDEMIOLOGIC TRANSITION

Unique regional features have modified aspects of the transition in various parts of the world. High-income countries experienced declines in CVD death rates by as much as 50–60% over the last 60 years, whereas CVD death rates increased by 15% over the past 20 years in the low- and middle-income range. However, given the large amount of available data, the United States serves as a useful reference point for comparisons. The age of pestilence and famine occurred before 1900, with a largely agrarian economy and population. Infectious diseases accounted for more deaths than any other cause. By the 1930s, the country proceeded through the age of receding pandemics. The establishment of public health infrastructures resulted in dramatic declines in infectious disease mortality rates. Lifestyle changes due to rapid urbanization resulted in a simultaneous increase in CVD mortality rates, reaching ~390 per 100,000. Between 1930 and 1965, the country entered the age of degenerative and man-made diseases. Infectious disease mortality rates fell to fewer than 50 per 100,000 per year, whereas CVD mortality rates reached peak levels with increasing urbanization and lifestyle changes in diet, physical activity, and tobacco consumption. The age of delayed degenerative diseases took place between 1965 and 2000. New therapeutic approaches, preventive measures, and exposure to public health campaigns promoting lifestyle modifications

TABLE 233-1 Five Stages of the Epidemiologic Transition

STAGE	DESCRIPTION	DEATHS RELATED TO CVD, %	PREDOMINANT CVD TYPE
Pestilence and famine	Predominance of malnutrition and infectious diseases as causes of death; high rates of infant and child mortality; low mean life expectancy	<10	Rheumatic heart disease, cardiomyopathies caused by infection and malnutrition
Receding pandemics	Improvements in nutrition and public health lead to decrease in rates of deaths related to malnutrition and infection; precipitous decline in infant and child mortality rates	10–35	Rheumatic valvular disease, hypertension, CHD, and stroke (predominantly hemorrhagic)
Degenerative and man-made diseases	Increased fat and caloric intake and decrease in physical activity lead to emergence of hypertension and atherosclerosis; with increase in life expectancy, mortality from chronic, noncommunicable diseases exceeds mortality from malnutrition and infectious disease	35–65	CHD and stroke (ischemic and hemorrhagic)
Delayed degenerative diseases	CVD and cancer are the major causes of morbidity and mortality; better treatment and prevention efforts help avoid deaths among those with disease and delay primary events; age-adjusted CVD morality declines; CVD affecting older and older individuals	40–50	CHD, stroke, and congestive heart failure
Inactivity and obesity	Overweight and obesity increase at alarming rate; diabetes and hypertension increase; decline in smoking rates levels off; a minority of the population meets physical activity recommendations	38	CHD, stroke, and congestive heart failure, peripheral vascular disease

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease.

Source: Data from AR Omran: The epidemiologic transition: A theory of the epidemiology of population change. Milbank Mem Fund Q 49:509, 1971; and SJ Olshansky, AB Ault: The fourth stage of the epidemiologic transition: The age of delayed degenerative diseases. Milbank Q 64:355, 1986.

led to substantial declines in age-adjusted mortality rates and a steadily rising age at which a first CVD event occurs.

Currently, the United States is entering what appears to be a fifth phase. The decline in the age-adjusted CVD death rate of 3% per year through the 1970s and 1980s has tapered off in the 1990s to 2%. However, CVD death rates have declined by 3–5% per year during the first decade of the new millennium. Competing trends appear to be at play. On the one hand, an increase in the prevalence of diabetes and obesity, a slowing in the rate of decline in smoking, and a leveling off in the rate of detection and treatment for hypertension are in the negative column. On the other hand, cholesterol levels continue to decline in the face of increased statin use.

Many high-income countries (HICs)—which together account for 15% of the population—have proceeded through four stages of the epidemiologic transition in roughly the same pattern as the United States. CHD is the dominant form of CVD in these countries, with rates that tend to be two- to fivefold higher than stroke rates. However, variations exist. Whereas North America, Australia, and central northwestern European HICs experienced significant increases than rapid declines in CVD rates, southern and central European countries experienced a more gradual rise and fall in rates. More specifically, central European countries (i.e., Austria, Belgium, and Germany) declined at slower rates compared to their northern counterparts (i.e., Finland, Sweden, Denmark, and Norway). Countries such as Portugal, Spain, and Japan never reached the high mortality rates that the United States and other countries did, with CHD mortality rates at 200 per 100,000, or less. The countries of Western Europe also exhibit a clear north/south gradient in absolute rates of CVD, with rates highest in northern countries (i.e., Finland, Ireland, and Scotland) and lowest in Mediterranean countries (i.e., France, Spain, and Italy). Japan is unique among the HICs, most likely due to the unique dietary patterns of its population. Although stroke rates increased dramatically, CHD rates did not rise as sharply in Japan. However, Japanese dietary habits are undergoing substantial changes, reflected in an increase in cholesterol levels.

Patterns in low- and middle-income countries (LMICs; gross national income per capita <$12,736) depend, in part, on cultural differences, secular trends, and responses at the country level, with regard to both public health and treatment infrastructure. Although communicable diseases continue to be a major cause of death, CVD has emerged as a significant health concern in LMICs. With 85% of the world's population, LMICs are driving the rates of change in the global burden of CVD **(Fig. 233-1)**. In most LMICs, an urban/rural gradient has emerged for CHD, stroke, and hypertension, with higher rates in urban centers.

However, although CVD rates are rapidly rising, vast differences exist among the regions and countries, and even within the countries themselves **(Fig. 233-2)**. The East Asia and Pacific regions appear to be straddling the second and third phases of the epidemiologic transition. CVD is a major cause of death in China, but like Japan, stroke causes more deaths than CHD in a ratio of about three to one. Vietnam and Cambodia, on the other hand, are just emerging from the pestilence and famine transition. The Middle East and North Africa regions also appear to be entering the third phase of the epidemiologic transition, with increasing life expectancy and CVD death rates just below those of HICs. In general, Latin America appears to be in the third phase of the transition, although there is vast regional heterogeneity with some areas in the second phase of the transition and some in the fourth. The Eastern Europe and Central Asia regions, however, are firmly in the peak of the third phase, with the highest death rates due to CVD (~66%) in the world. Importantly, deaths due to CHD are not limited to the elderly in this region and have a significant effect on working-age populations. South Asia—and more specifically, India, which accounts for the greatest proportion of the region's population—is experiencing an alarming increase in heart disease. The transition appears to be in the Western style, with CHD as the dominant form of CVD. However, rheumatic heart disease continues to be a major cause of morbidity and mortality. As in South Asia, rheumatic heart disease is also an important cause of CVD morbidity and mortality in sub-Saharan Africa, which largely remains in the first phase of the epidemiologic transition.

Many factors contribute to this heterogeneity among LMICs. First, the regions are in various stages of the epidemiologic transition. Second, vast differences in lifestyle and behavioral risk factors exist. Third, racial and ethnic differences may lead to altered susceptibilities to various forms of CVD. In addition, it should be noted that for most countries in these regions, accurate country-wide data on cause-specific mortality are not complete.

GLOBAL TRENDS IN CARDIOVASCULAR DISEASE

CVD accounts for 32% of deaths worldwide, a number that is expected to increase. In 2015, CHD accounted for 16.7% of all deaths globally and the largest portion (10%) of global years of life lost (YLLs) and disability-adjusted life-years (DALYs) (7%). The third largest cause of death was stroke (11.9% of all deaths), which was also the third largest contributor to global YLLs and DALYs. Together, CHD and stroke accounted for nearly a quarter of all deaths worldwide. The burden of stroke is of growing concern among LMICs. The impact of stroke on DALYs and mortality rates is more than three times greater in LMICs as compared to HICs.

With nearly 81% of the world's population, LMICs largely drive global CVD rates and trends. More than 14 million (14.2) CVD deaths occurred in LMICs in 2015, compared to 3.7 million in HICs. Globally, there is evidence of significant delays in age of occurrence and/or improvements in case fatality rates; between 1990 and 2015, the number of CVD deaths increased by 42%, but age-adjusted death rates decreased by 27.3% in the same period. Age-standardized death rates, however, have declined faster in high-income countries than in middle-income and lower-income regions **(Fig. 233-3)**. Population growth has been greater in low- and middle-income countries compared to high-income countries. As a result of slower rates of population growth in high-income countries, overall CVD deaths remained steady. However, in the lower and middle-income countries, the population aging and

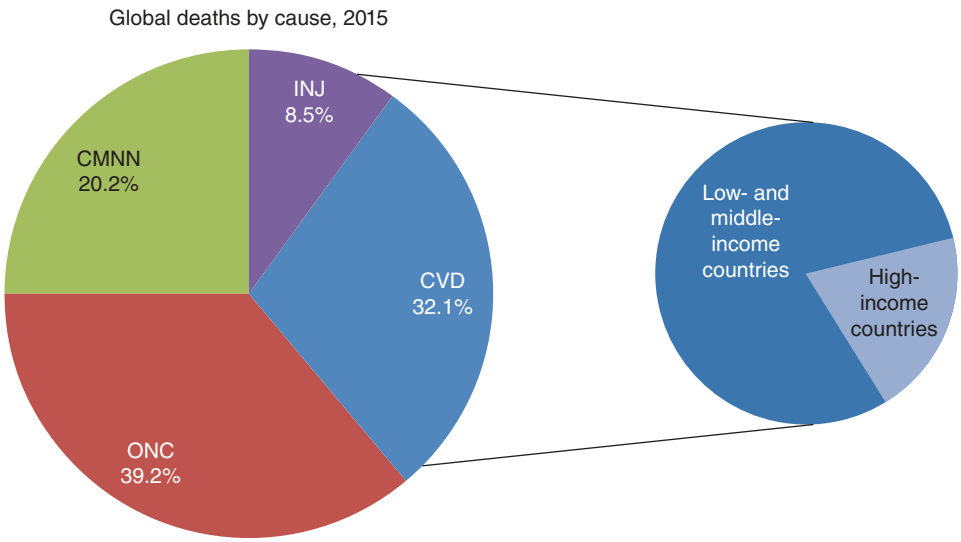

FIGURE 233-1 Global deaths by cause, 2015. CMNN, communicable, maternal, neonatal, and nutritional disorders; CVD, cardiovascular diseases; INJ, injuries; ONC, other noncommunicable diseases. *(Based on data from Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 [GBD 2015] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2016.)*

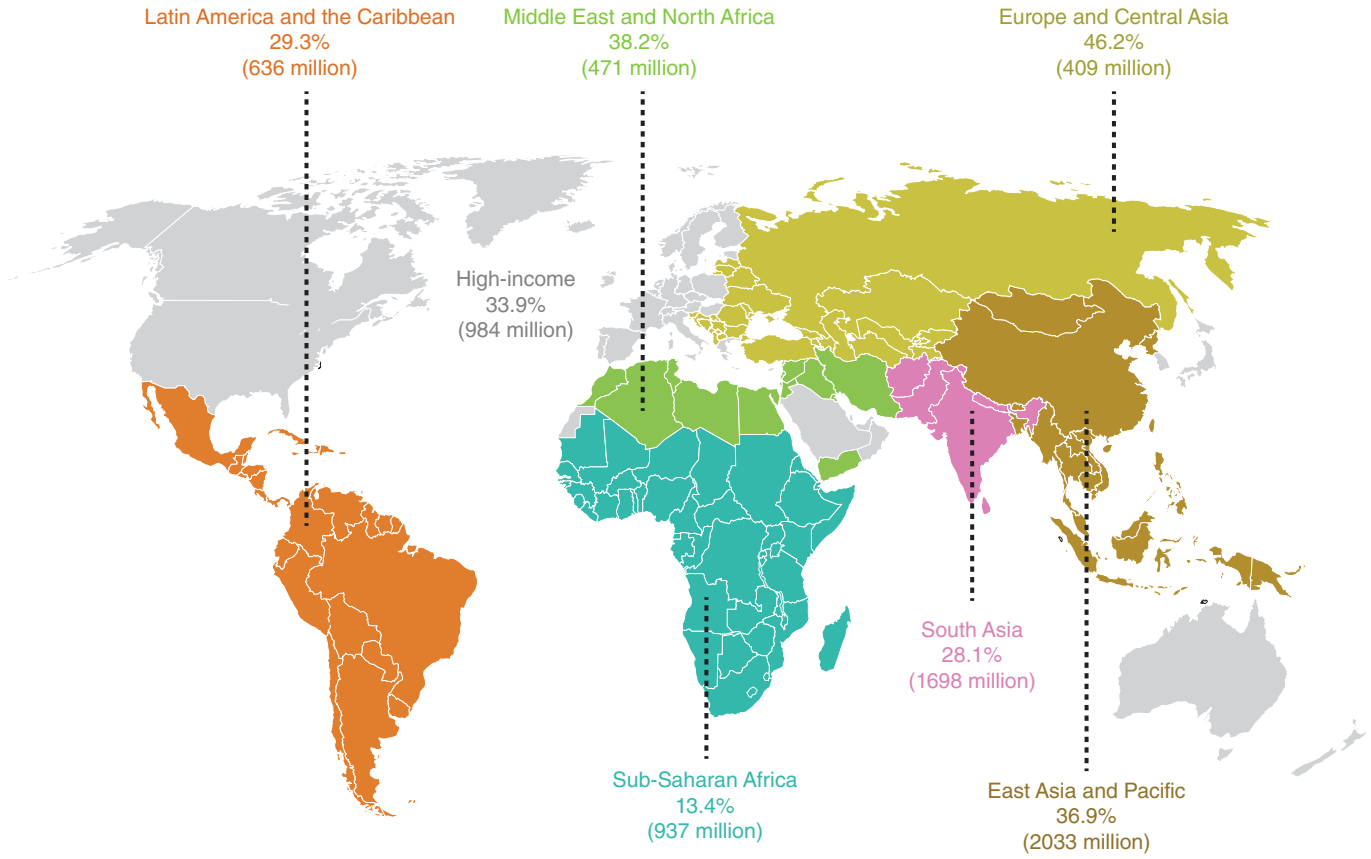

FIGURE 233-2 Cardiovascular disease deaths as a percentage of total deaths and total population in seven economic regions of the world defined by the World Bank. *(Based on data from Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 [GBD 2015] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2016.)*

growth outstripped gains in age-adjusted mortality reductions such that overall CVD deaths continued to climb over the last 25 years (Fig. 233-4).

Although HIC population growth will be fueled by emigration from LMICs, the populations of HICs will shrink as a proportion of the world's population. The modest decline in CVD death rates that began in the HICs in the latter third of the twentieth century will continue, but the rate of decline appears to be slowing. However, these countries are expected to see an increase in the prevalence of CVD, as well as the absolute number of deaths as the population ages.

Significant portions of the population living in LMICs have entered the third phase of the epidemiologic transition, and some are entering the fourth stage. Changing demographics play a significant role in future predictions for CVD throughout the world. For example, the population growth rate in Eastern Europe and Central Asia was 0.7% in 2014, whereas it was 1.4% in South Asia.

CVD rates will also have an economic impact. Even assuming no increase in CVD risk factors, most countries, but especially India and South Africa, will see a large number of people between 35 and 64 die of CVD over the next 30 years, as well as an increasing level of morbidity among middle-aged people related to heart disease and stroke. In China, it is estimated that there will be 9 million deaths from CVD in 2030—up from 2.4 million in 2002—with half occurring in individuals between 35 and 64 years old.

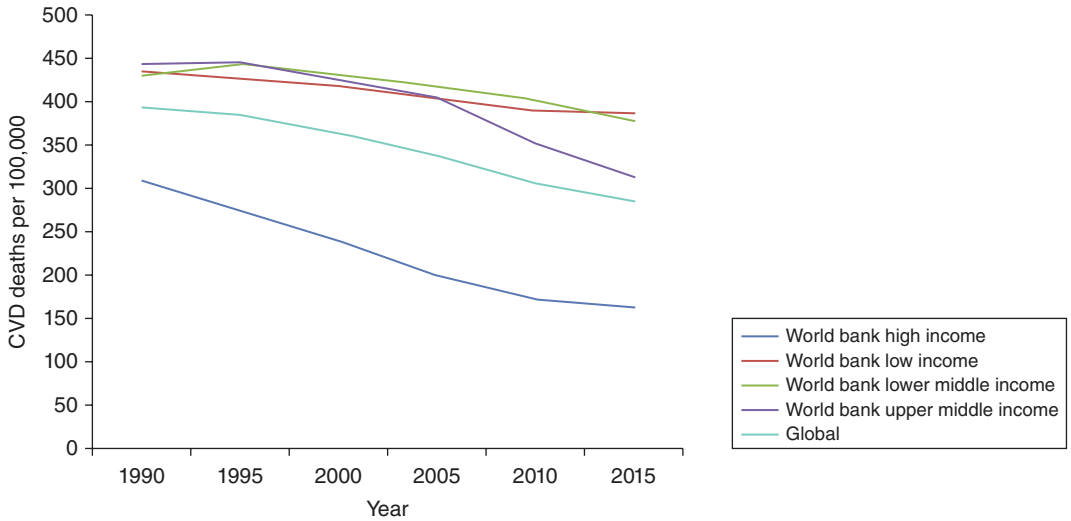

FIGURE 233-3 Age-standardized cardiovascular diseases (CVD) death rate per 100,000 from 1990 to 2015, by World Bank income. *(Based on data from Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 [GBD 2015] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2016.)*

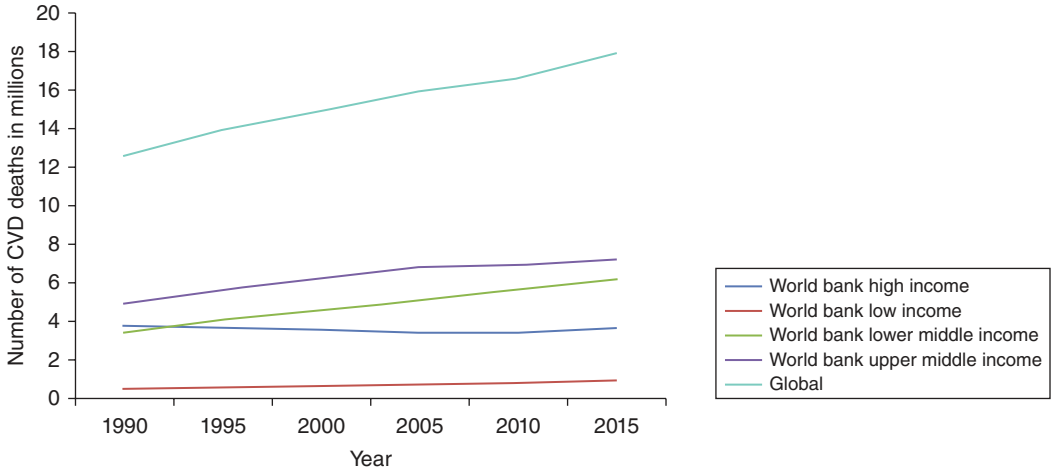

FIGURE 233-4 Number of cardiovascular diseases (CVD) deaths from 1990 to 2015, by World Bank income. *(Based on data from Global Burden of Disease Study 2015. Global Burden of Disease Study 2015 [GBD 2015] Results. Seattle, United States: Institute for Health Metrics and Evaluation [IHME], 2016.)*

RISK FACTORS

The global variation in CVD rates is related to temporal and regional variations in known risk behaviors and factors. Ecological analyses of major CVD risk factors and mortality demonstrate high correlations between expected and observed mortality rates for the three main risk factors—smoking, serum cholesterol, and hypertension—and suggest that many of the regional variations are based on differences in conventional risk factors.

Behavioral Risk Factors • **TOBACCO** Over 1.3 billion people use tobacco worldwide, a number that is projected to increase to 1.6 billion by 2030. Tobacco use currently causes about 6.4 million deaths annually (11.5% of all deaths), ~2.4 million of which are CVD-related. If current smoking patterns continue, the global burden of disease attributable to tobacco will reach 10 million deaths by 2030. Although tobacco use has been greatest in HICs historically, consumption has shifted dramatically to LMICs in recent decades. Some of the highest tobacco use now occurs in the East Asia and Pacific region. A unique feature of LMICs is easy access to smoking during the early stages of the epidemiologic transition due to the availability of relatively inexpensive tobacco products. In South Asia, the prominence of other locally produced forms of tobacco besides manufactured cigarettes makes control of consumption more challenging. Secondhand smoke is another well-established cause of CHD, responsible for 886,000 deaths of nonsmokers in 2015. Although smoking bans have both immediate and long-term benefits, implementation varies greatly between countries.

DIET Total caloric intake per capita increases as countries develop. With regard to CVD, a key element of dietary change is an increase in intake of saturated animal fats and hydrogenated vegetable fats, which contain atherogenic *trans* fatty acids, along with a decrease in intake of plant-based foods and an increase in simple carbohydrates. Fat contributes <20% of calories in rural China and India, <30% in Japan, and well above 30% in the United States. Caloric contributions from fat appear to be falling in the HICs. In the United States, between 1971 and 2010, the percentage of calories derived from saturated fat decreased from 13 to 11%.

PHYSICAL INACTIVITY The increased mechanization that accompanies the economic transition leads to a shift from physically demanding, agriculture-based work to largely sedentary industry- and office-based work. In the United States, approximately one-quarter of the population does not participate in any leisure-time physical activity, and only 51.6% of adults report engaging in physical activity three or more times a week. Physical inactivity is similarly high in other regions of the world and is increasing in countries that are rapidly urbanizing as part of their economic transition. In urban China, for example, the proportion of adults who participate in moderate- or high-level activity has decreased significantly, whereas proportion of those who participate in low-level activity has increased.

METABOLIC RISK FACTORS

Examination of trends in metabolic risk factors provides insight into changes in the CVD burden globally. Here we describe four metabolic risk factors—lipid levels, hypertension, obesity, and diabetes mellitus—using data from the Global Burden of Disease, Injuries, and Risk Factors Study (GBD 2015). The GBD project identified and compiled mortality and morbidity data from 187 countries from 1990 to 2015.

Lipid Levels Worldwide, high cholesterol levels are estimated to play a role in 56% of ischemic heart disease events and 18% of strokes, amounting to 4.3 million deaths annually. Although mean population plasma cholesterol levels tend to rise as countries move through the epidemiologic transition, mean serum total cholesterol levels have decreased globally between 1980 and 2008 by 0.08 mmol/L per decade in men and 0.07 mmol/L per decade in women. In 2008, age-standardized mean total cholesterol was 4.64 mmol/L (179.4 mg/dL) in men and 4.76 mmol/L (184.2 mg/dL) in women. Large declines occurred in Australasia, North America, and Western Europe (0.19–0.21 mmol/L). Countries in the East Asia and Pacific region experienced increases of >0.08 mmol/L in both men and women. Social and individual changes that accompany urbanization clearly play a role because plasma cholesterol levels tend to be higher among urban residents than among rural residents. This shift is largely driven by greater consumption of dietary fats—primarily from animal products and processed vegetable oils—and decreased physical activity. In HICs, in general, mean population cholesterol levels are falling, whereas wide variation is seen in the LMICs.

Hypertension Elevated blood pressure is an early indicator of the epidemiologic transition. Worldwide, ~62% of strokes and 49% of CHD are attributable to suboptimal (>115 mmHg systolic) blood pressure, which is believed to account for >7 million deaths annually. Remarkably, nearly half of this burden occurs among those with systolic blood pressure <140 mmHg, even as this level is used at the arbitrary threshold for defining hypertension in many national guidelines. Between 1980 and 2008, the age-standardized prevalence of uncontrolled prevalence has decreased even as the number of people with uncontrolled hypertension has increased. This trend results largely from population growth and aging. Rising mean population blood pressure also occurs as populations industrialize and move from rural to urban settings. For example, the prevalence of hypertension in urban India is 25%, but varies between 10 and 15% in rural communities. One major concern in LMICs is the high rate of undetected, and therefore untreated, hypertension. This may explain, at least in part, the higher stroke rates in these countries in relation to CHD rates during the early stages of the transition. The high rates of hypertension throughout Asia, especially

undiagnosed hypertension, likely contribute to the high prevalence of hemorrhagic stroke in the region. Globally, however, mean systolic blood pressure has decreased among both genders (0.8 mmHg per decade among men; 1.0 mmHg per decade among women).

Obesity Although clearly associated with increased risk of CHD, much of the risk posed by obesity may be mediated by other CVD risk factors, including hypertension, diabetes mellitus, and lipid profile imbalances. According to the latest GBD data, nearly 1.46 billion adults were overweight (body mass index [BMI] ≥25 kg/m^2) in 2008, and ~508 million were obese (BMI ≥30 kg/m^2). Obesity is increasing throughout the world, particularly in developing countries, where the trajectories are steeper than those experienced by the developed countries. In many of the LMICs, obesity appears to coexist with undernutrition and malnutrition. Adolescents are at particular risk. Currently, 1 in 10 children are estimated to be overweight, a number that is increasing worldwide. Women are also more affected than men, with the number of overweight women generally exceeding underweight women based on data from 36 LMICs.

Diabetes Mellitus As a consequence of, or in addition to, increasing BMI and decreasing levels of physical activity, worldwide rates of diabetes—predominantly type 2 diabetes—are on the rise. According to the most recent data from the GBD project, mean fasting plasma glucose levels have increased globally between 1980 and 2008. An estimated 346 million people worldwide have diabetes. The International Diabetes Foundation predicts that this number will reach 522 million by 2030, a yearly rate of growth that is higher than that of the world's adult population. Nearly 50% of people with diabetes are undiagnosed, and 80% live in LMICs. The highest regional prevalence for diabetes occurs in the Middle East and North Africa, where an estimated 12.5% of the adult population has diabetes. Future growth will also largely occur in this region, along with other LMICs in South Asia and sub-Saharan Africa. There appear to be clear genetic susceptibilities to diabetes mellitus of various racial and ethnic groups. For example, migration studies suggest that South Asians and Indians tend to be at higher risk than those of European extraction.

SUMMARY

Although CVD rates are declining in the HICs, they are increasing in virtually every other region of the world. The consequences of this preventable epidemic will be substantial on many levels, including individual mortality and morbidity, family suffering, and staggering economic costs.

Three complementary strategies can be used to lessen the impact. First, the overall burden of CVD risk factors can be lowered through population-wide public health measures, such as national campaigns against cigarette smoking, unhealthy diets, and physical inactivity. Second, it is important to identify higher risk subgroups of the population who stand to benefit the most from specific, low-cost prevention interventions, including screening for and treatment of hypertension and elevated cholesterol. Simple, low-cost interventions, such as the "polypill," a regimen of aspirin, a statin, and an antihypertensive agent, also need to be explored. Third, resources should be allocated to acute as well as secondary prevention interventions. For countries with limited resources, a critical first step in developing a comprehensive plan is better assessment of cause-specific mortality and morbidity, as well as the prevalence of the major preventable risk factors.

In the meantime, the HICs must continue to bear the burden of research and development aimed at prevention and treatment, being mindful of the economic limitations of many countries. The concept of the epidemiologic transition provides insight into how to alter the course of the CVD epidemic. The efficient transfer of low-cost preventive and therapeutic strategies could alter the natural course of this epidemic and thereby reduce the excess global burden of preventable CVD.

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Section 2 Diagnosis of Cardiovascular Disorders

234 Physical Examination of the Cardiovascular System

Patrick T. O'Gara, Joseph Loscalzo

The approach to a patient with known or suspected cardiovascular disease begins with the time-honored traditions of a directed history and a targeted physical examination. The scope of these activities depends on the clinical context at the time of presentation, ranging from an elective ambulatory follow-up visit to a more urgent emergency department encounter. There has been a gradual decline in physical examination skills over the last two decades at every level, from student to faculty specialist, a development of great concern to both clinicians and medical educators. Classic cardiac findings are recognized by only a minority of internal medicine and family practice residents. Despite popular perceptions, clinical performance does not improve predictably as a function of experience; instead, the acquisition of new examination skills may become more difficult for a busy individual practitioner. Less time is now devoted to mentored cardiovascular examinations during the training of students and residents. One widely recognized outcome of these trends is the progressive overutilization of noninvasive imaging studies to establish the presence and severity of cardiovascular disease even when the examination findings imply a low pretest probability of significant pathology. Proponents of the use of hand-held ultrasound devices to identify and characterize structural cardiac disease have called for its incorporation into educational curricula. Techniques to improve bedside examination skills include repetition, patient-centered teaching conferences, visual display feedback of auscultatory events using Doppler echocardiographic imaging and simulation-based training.

The evidence base that links the findings from the history and physical examination to the presence, severity, and prognosis of cardiovascular disease has been established most rigorously for coronary artery disease, heart failure, and valvular heart disease. For example, observations regarding heart rate, blood pressure, signs of pulmonary congestion, and the presence of mitral regurgitation (MR) contribute importantly to bedside risk assessment in patients with acute coronary syndromes. Observations from the physical examination in this setting can inform clinical decision-making before the results of cardiac biomarker testing are known. The prognosis of patients with systolic heart failure can be predicted on the basis of the jugular venous pressure (JVP) and the presence or absence of a third heart sound (S_3). Accurate characterization of cardiac murmurs provides important insight into the natural history of many valvular and congenital heart lesions. Finally, the important role played by the physical examination in enhancing the clinician-patient relationship cannot be overstated.

THE GENERAL PHYSICAL EXAMINATION

Any examination begins with an assessment of the general appearance of the patient, with notation of age, posture, demeanor, and overall

health status. Is the patient in pain or resting quietly, dyspneic or diaphoretic? Does the patient choose to avoid certain body positions to reduce or eliminate pain, as might be the case with suspected acute pericarditis? Are there clues indicating that dyspnea may have a pulmonary cause, such as a barrel chest deformity with an increased anterior-posterior diameter, tachypnea, and pursed-lip breathing? Skin pallor, cyanosis, and jaundice can be appreciated readily and provide additional clues. A chronically ill-appearing emaciated patient may suggest the presence of long-standing heart failure or another systemic disorder, such as a malignancy. Various genetic syndromes, often with cardiovascular involvement, can also be recognized easily, such as trisomy 21, Marfan syndrome, and Holt-Oram syndrome. Height and weight should be measured routinely, and both body mass index and body surface area should be calculated. Knowledge of the waist circumference and the waist-to-hip ratio can be used to predict long-term cardiovascular risk. Mental status, level of alertness, and mood should be assessed continuously during the interview and examination.

Skin Central cyanosis occurs with significant right-to-left shunting at the level of the heart or lungs, allowing deoxygenated blood to reach the systemic circulation. Peripheral cyanosis or acrocyanosis, in contrast, is usually related to reduced extremity blood flow due to small vessel constriction, as seen in patients with severe heart failure, shock, or peripheral vascular disease; it can be aggravated by the use of β-adrenergic blockers with unopposed α-mediated vasoconstriction. Differential cyanosis refers to isolated cyanosis affecting the lower but not the upper extremities in a patient with a large patent ductus arteriosus (PDA) and secondary pulmonary hypertension with right-to-left to shunting at the great vessel level. Hereditary telangiectasias on the lips, tongue, and mucous membranes, as part of the Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia), resemble spider nevi and can be a source of right-to-left shunting when also present in the lung. Malar telangiectasias also are seen in patients with advanced mitral stenosis (MS) or scleroderma. An unusually tan or bronze discoloration of the skin may suggest hemochromatosis as the cause of the associated systolic heart failure. Jaundice, which may be visible first in the sclerae, has a broad differential diagnosis but, in the appropriate setting, can be consistent with advanced right heart failure and congestive hepatomegaly or anticoagulants or antiplatelet agents such as aspirin and P2Y12 receptor antagonists. Various hereditary lipid disorders sometimes are associated with subcutaneous xanthomas, particularly along the tendon sheaths or over the extensor surfaces of the extremities. Severe hypertriglyceridemia can be associated with eruptive xanthomatosis and lipemia retinalis. Palmar crease xanthomas are specific for type III hyperlipoproteinemia. Pseudoxanthoma elasticum, a disease associated with premature atherosclerosis, is manifested by a leathery, cobblestoned appearance of the skin in the axilla and neck creases and by angioid streaks on funduscopic examination. Extensive lentiginoses have been described in a variety of development delay—cardiovascular syndromes, including Carney's syndrome, which includes multiple atrial myxomas. Cutaneous manifestations of sarcoidosis such as lupus pernio and erythema nodosum may suggest this disease as a cause of an associated dilated cardiomyopathy, especially with heart block, intraventricular conduction delay, or ventricular tachycardia.

Head and Neck Dentition and oral hygiene should be assessed in every patient both as a source of potential infection and as an index of general health. A high-arched palate is a feature of Marfan syndrome and other connective tissue disease syndromes. Bifid uvula has been described in patients with Loeys-Dietz syndrome, and orange tonsils are characteristic of Tangier disease. The ocular manifestations of hyperthyroidism have been well described. Many patients with congenital heart disease have associated hypertelorism, low-set ears, or micrognathia. Blue sclerae are a feature of osteogenesis imperfecta. An arcus senilis pattern lacks specificity as an index of coronary heart disease risk. The funduscopic examination is an often underused method by which to assess the microvasculature, especially among patients with established atherosclerosis, hypertension, or diabetes mellitus. A mydriatic agent may be necessary for optimal visualization. A funduscopic examination should be performed routinely in the assessment of patients with suspected endocarditis and those with a history of acute visual change. Branch retinal artery occlusion or visualization of a Hollenhorst plaque can narrow the differential diagnosis rapidly in the appropriate setting. Relapsing polychondritis may manifest as an inflamed pinna or, in its later stages, as a saddle-nose deformity because of destruction of nasal cartilage; granulomatosis with polyangiitis (Wegener's) can also lead to a saddle-nose deformity.

Chest Midline sternotomy, left posterolateral thoracotomy, or infraclavicular scars at the site of pacemaker/defibrillator generator implantation should not be overlooked and may provide the first clue regarding an underlying cardiovascular disorder in patients unable to provide a relevant history. A prominent venous collateral pattern may suggest subclavian or vena caval obstruction. If the head and neck appear dusky and slightly cyanotic and the venous pressure is grossly elevated without visible pulsations, a diagnosis of superior vena cava syndrome should be entertained. Thoracic cage abnormalities have been well described among patients with connective tissue disease syndromes. They include pectus carinatum ("pigeon chest") and pectus excavatum ("funnel chest"). Obstructive lung disease is suggested by a barrel chest deformity, especially with tachypnea, pursed-lip breathing, and use of accessory muscles. The characteristically severe kyphosis and compensatory lumbar, pelvic, and knee flexion of ankylosing spondylitis should prompt careful auscultation for a murmur of aortic regurgitation (AR). Straight back syndrome refers to the loss of the normal kyphosis of the thoracic spine and has been described in patients with mitral valve prolapse (MVP) and its variants. In some patients with cyanotic congenital heart disease, the chest wall appears to be asymmetric, with anterior displacement of the left hemithorax. The respiratory rate and pattern should be noted during spontaneous breathing, with additional attention to depth, audible wheezing, and stridor. Lung examination can reveal adventitious sounds indicative of pulmonary edema, pneumonia, or pleuritis.

Abdomen In some patients with advanced obstructive lung disease, the point of maximal cardiac impulse may be in the epigastrium. The liver is frequently enlarged and tender in patients with chronic heart failure. Systolic pulsations over the liver signify severe tricuspid regurgitation (TR). Splenomegaly may be a feature of infective endocarditis, particularly when symptoms have persisted for weeks or months. Ascites is a nonspecific finding but may be present with advanced chronic right heart failure, constrictive pericarditis, hepatic cirrhosis, or an intraperitoneal malignancy. The finding of an elevated JVP implies a cardiovascular etiology. In nonobese patients, the aorta typically is palpated between the epigastrium and the umbilicus. The sensitivity of palpation for the detection of an abdominal aortic aneurysm (pulsatile and expansile mass) decreases as a function of body size. Because palpation alone is not sufficiently accurate to establish this diagnosis, a screening ultrasound examination is advised when appropriate. The presence of an arterial bruit over the abdomen suggests high-grade atherosclerotic disease, although precise localization is difficult.

Extremities The temperature and color of the extremities, the presence of clubbing, arachnodactyly, and pertinent nail findings can be surmised quickly during the examination. Clubbing implies the presence of central right-to-left shunting, although it has also been described in patients with endocarditis. Its appearance can range from cyanosis and softening of the root of the nail bed, to the classic loss of the normal angle between the base of the nail and the skin, to the skeletal and periosteal bony changes of hypertrophic osteoarthropathy, which is seen rarely in patients with advanced lung or liver disease. Patients with the Holt-Oram syndrome have an unopposable, "fingerized" thumb, whereas patients with Marfan syndrome may have arachnodactyly and a positive "wrist" (overlapping of the thumb and fifth finger around the wrist) or "thumb" (protrusion of the thumb beyond the ulnar aspect of the hand when the fingers are clenched over the thumb in a fist) sign. The Janeway lesions of endocarditis

are nontender, slightly raised hemorrhages on the palms and soles, whereas Osler's nodes are tender, raised nodules on the pads of the fingers or toes. Splinter hemorrhages are classically identified as linear petechiae in the midposition of the nail bed and should be distinguished from the more common traumatic petechiae, which are seen closer to the distal edge.

Lower extremity or presacral edema in the setting of an elevated JVP defines volume overload and may be a feature of chronic heart failure or constrictive pericarditis. Lower extremity edema in the absence of jugular venous hypertension may be due to profound hypoalbuminemia as seen in nephrotic syndrome or liver failure. Other causes include lymphatic or venous obstruction or, more commonly, venous insufficiency, as would be further suggested by the appearance of varicosities, venous ulcers (typically medial in location), and brownish cutaneous discoloration from hemosiderin deposition (eburnation). Pitting edema can also be seen in patients who use dihydropyridine calcium channel blockers. A Homan's sign (posterior calf pain on active dorsiflexion of the foot against resistance) is neither specific nor sensitive for deep venous thrombosis. Muscular atrophy or the absence of hair along an extremity is consistent with severe arterial insufficiency or a primary neuromuscular disorder.

CARDIOVASCULAR EXAMINATION

Jugular Venous Pressure and Waveform The JVP is the single most important bedside measurement from which to estimate the volume status. The internal jugular vein is preferred because the external jugular vein is valved and not directly in line with the superior vena cava and right atrium. Nevertheless, the external jugular vein has been used to discriminate between high and low central venous pressure (CVP) when tested among medical students, residents, and attending physicians. Precise estimation of the central venous or right atrial pressure from bedside assessment of the jugular venous waveform has proved difficult. Venous pressure traditionally has been measured as the vertical distance between the top of the jugular venous pulsation and the sternal inflection point (angle of Louis). A distance >4.5 cm at 30° elevation is considered abnormal. However, the actual distance between the mid-right atrium and the angle of Louis varies considerably as a function of both body size and the patient angle at which the assessment is made (30°, 45°, or 60°). The use of the sternal angle as a reference point leads to systematic underestimation of CVP, and this method should be used less for semiquantification than to distinguish a normal from an abnormally elevated CVP. The use of the clavicle may provide an easier reference for standardization. Venous pulsations above this level in the sitting position are clearly abnormal, as the distance between the clavicle and the right atrium is at least 10 cm. The patient should always be placed in the sitting position, with the legs dangling below the bedside, when an elevated pressure is suspected in the semisupine position. It should also be noted that bedside estimates of CVP are made in centimeters of water, but must be converted to millimeters of mercury to provide correlation with accepted hemodynamic norms (1.36 cmH_2O = 1.0 mmHg).

The venous waveform sometimes can be difficult to distinguish from the carotid pulse, especially during casual inspection. Nevertheless, the venous waveform has several characteristic features, and its individual components can be appreciated in most patients **(Fig. 234-1)**. The arterial pulsation is not easily obliterated with palpation; the venous waveform in patients with sinus rhythm is usually biphasic, while the carotid pulse is monophasic; and the jugular venous pulsation should change with changes in posture or inspiration (unless the venous pressure is quite elevated).

The venous waveform is divided into several distinct peaks. The *a* wave reflects right atrial presystolic contraction and occurs just after the electrocardiographic P wave, preceding the first heart sound (S_1). A prominent *a* wave is seen in patients with reduced right ventricular compliance; a cannon *a* wave occurs with atrioventricular (AV) dissociation and right atrial contraction against a closed tricuspid valve. In a patient with a wide complex tachycardia, the appreciation of cannon *a* waves in the jugular venous waveform identifies the rhythm as ventricular in origin. The *a* wave is not present with atrial fibrillation. The *x* descent defines the fall in right atrial pressure after inscription of the *a* wave. The *c* wave, which occurs as the closed tricuspid valve is pushed into the right atrium during early ventricular systole, interrupts this *x* descent and is followed by a further descent. The *v* wave represents atrial filling (atrial diastole) and occurs during ventricular systole. The height of the *v* wave is determined by right atrial compliance as well as the volume of blood returning to the right atrium

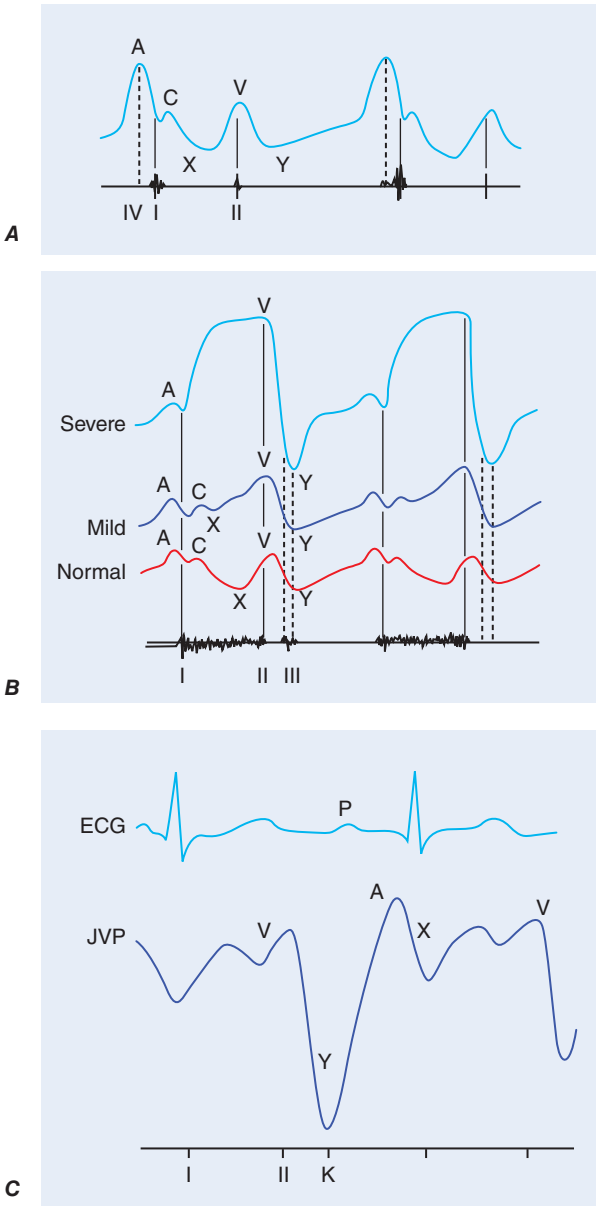


FIGURE 234-1 ***A.*** Jugular venous pulse wave tracing (*top*) with heart sounds (*bottom*). The A wave represents right atrial presystolic contraction and occurs just after the electrocardiographic P wave and just before the first heart sound (I). In this example, the A wave is accentuated and larger than normal due to decreased right ventricular compliance, as also suggested by the right-sided S_4 (IV). The C wave may reflect the carotid pulsation in the neck and/or an early systolic increase in right atrial pressure as the right ventricle pushes the closed tricuspid valve into the right atrium. The *x* descent follows the A wave just as atrial pressure continues to fall. The V wave represents atrial filling during ventricular systole and peaks at the second heart sound (II). The *y* descent corresponds to the fall in right atrial pressure after tricuspid valve opening. ***B.*** Jugular venous wave forms in mild (*middle*) and severe (*top*) tricuspid regurgitation, compared with normal, with phonocardiographic representation of the corresponding heart sounds below. With increasing degrees of tricuspid regurgitation, the waveform becomes "ventricularized." ***C.*** Electrocardiogram (ECG) (*top*), jugular venous waveform (JVP) (*middle*), and heart sounds (*bottom*) in pericardial constriction. Note the prominent and rapid *y* descent, corresponding in timing to the pericardial knock (K). *(From J Abrams: Synopsis of Cardiac Physical Diagnosis, 2nd ed. Boston, Butterworth Heinemann, 2001, pp 25–35.)*

either antegrade from the cavae or retrograde through an incompetent tricuspid valve. In patients with TR, the *v* wave is accentuated and the subsequent fall in pressure (*y* descent) is rapid. With progressive degrees of TR, the *v* wave merges with the *c* wave, and the right atrial and jugular vein waveforms become "ventricularized." The *y* descent, which follows the peak of the *v* wave, can become prolonged or blunted with obstruction to right ventricular inflow, as may occur with tricuspid stenosis or pericardial tamponade. Normally, the venous pressure should fall by at least 3 mmHg with inspiration. Kussmaul's sign is defined by either a rise or a lack of fall of the JVP with inspiration and is classically associated with constrictive pericarditis, although it has been reported in patients with restrictive cardiomyopathy, massive pulmonary embolism, right ventricular infarction, and advanced left ventricular (LV) systolic heart failure. It is also a common, isolated finding in patients after cardiac surgery without other hemodynamic abnormalities.

Venous hypertension sometimes can be elicited by passive leg elevation or performance of the abdominojugular reflux maneuver. When these signs are positive, a volume-overloaded state with limited compliance of an overly distended or constricted venous system is present. Abdominojugular reflux is produced with firm and consistent pressure over the upper portion of the abdomen, preferably over the right upper quadrant, for >15 s. A positive response is defined by a sustained rise of >3 cm in the JVP during the application of firm abdominal pressure. The response should be assessed after 10 s of continuous pressure to allow for respiratory artifacts and tensing of the abdominal muscles to subside. Patients must be coached to refrain from breath holding or a Valsalva-like maneuver during the procedure. Performance of the abdominojugular reflux maneuver is useful in predicting a pulmonary artery wedge pressure >15 mmHg in patients with heart failure.

Although the JVP estimates right ventricular filling pressure, it has a predictable relationship with the pulmonary artery wedge pressure. In a large study of patients with advanced heart failure, the presence of a right atrial pressure >10 mmHg (as predicted on bedside examination) had a positive value of 88% for the prediction of a pulmonary artery wedge pressure of >22 mmHg. In addition, an elevated JVP has prognostic significance in patients with both symptomatic heart failure and asymptomatic LV systolic dysfunction. The presence of an elevated JVP is associated with a higher risk of subsequent hospitalization for heart failure, death from heart failure, or both.

Assessment of Blood Pressure Measurement of blood pressure usually is delegated to a medical assistant but should be repeated by the examining clinician. Accurate measurement depends on body position, arm size, time of measurement, place of measurement, device, device size, technique, and examiner. In general, physician-recorded blood pressures are higher than both nurse-recorded pressures and self-recorded pressures at home. Blood pressure is best measured in the seated position with the arm at the level of the heart and the feet on the floor with the back supported, using an appropriately sized cuff, after 5–10 min of relaxation. When it is measured in the supine position, the arm should be raised to bring it to the level of the mid-right atrium. The length and width of the blood pressure cuff bladder should be 80 and 40% of the arm's circumference, respectively. A common source of error in practice is to use an inappropriately small cuff, resulting in marked overestimation of true blood pressure, or an inappropriately large cuff, resulting in underestimation of true blood pressure. The cuff should be inflated to 30 mmHg above the expected systolic pressure and the pressure released at a rate of 2–3 mmHg/s. Systolic and diastolic pressures are defined by the first and fifth Korotkoff sounds, respectively. Very low (even 0 mmHg) diastolic blood pressures may be recorded in patients with chronic, severe AR or a large arteriovenous fistula because of enhanced diastolic "run-off." In these instances, both the phase IV and phase V Korotkoff sounds should be recorded. Blood pressure is best assessed at the brachial artery level, though it can be measured at the radial, popliteal, or pedal pulse level. In general, systolic pressure increases and diastolic pressure decreases when measured in more distal arteries. Blood pressure should be measured in both arms, and the difference should be <10 mmHg. A blood pressure differential that exceeds this threshold may be associated with atherosclerotic or inflammatory subclavian artery disease, supravalvular aortic stenosis, aortic coarctation, or aortic dissection. Systolic leg pressures are usually as much as 20 mmHg higher than systolic arm pressures. Greater leg–arm pressure differences are seen in patients with chronic severe AR as well as patients with extensive and calcified lower extremity peripheral arterial disease. The ankle-brachial index (systolic pressure in the dorsalis pedis and/or posterior tibial artery divided by the higher of the two brachial artery pressures) is a powerful predictor of long-term cardiovascular mortality.

The blood pressure measured in an office or hospital setting may not accurately reflect the pressure in other venues. "White coat hypertension" is defined by at least three separate clinic-based measurements >140/90 mmHg and at least two non-clinic-based measurements <140/90 mmHg in the absence of any evidence of target organ damage. Individuals with white coat hypertension may not benefit from drug therapy, although they may be more likely to develop sustained hypertension over time. Masked hypertension should be suspected when normal or even low blood pressures are recorded in patients with advanced atherosclerotic disease, especially when evidence of target organ damage is present or bruits are audible. Higher systolic blood pressures measured with a 24-h ambulatory blood pressure device are associated with a higher risk of cardiovascular disease and all-cause death independent of blood pressures measured in the outpatient setting.

Orthostatic hypotension is defined by a fall in systolic pressure >20 mmHg or in diastolic pressure >10 mmHg in response to assumption of the upright posture from a supine position within 3 min. There may also be a lack of a compensatory tachycardia, an abnormal response that suggests autonomic insufficiency, as may be seen in patients with diabetes or Parkinson's disease. Orthostatic hypotension is a common cause of postural lightheadedness/syncope and should be assessed routinely in patients for whom this diagnosis might pertain. It can be exacerbated by advanced age, dehydration, certain medications, food, deconditioning, and ambient temperature/humidity.

Arterial Pulse The carotid artery pulse occurs just after the ascending aortic pulse. The aortic pulse is best appreciated in the epigastrium, just above the level of the umbilicus. Peripheral arterial pulses that should be assessed routinely include the subclavian, brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial. In patients in whom the diagnosis of either temporal arteritis or polymyalgia rheumatica is suspected, the temporal arteries also should be examined. Although one of the two pedal pulses may not be palpable in up to 10% of normal subjects, the pair should be symmetric. The integrity of the arcuate system of the hand is assessed by Allen's test, which is performed routinely before instrumentation of the radial artery. The pulses should be examined for their symmetry, volume, timing, contour, amplitude, and duration. If necessary, simultaneous auscultation of the heart can help identify a delay in the arrival of an arterial pulse. Simultaneous palpation of the radial and femoral pulses may reveal a femoral delay in a patient with hypertension and suspected aortic coarctation. The carotid upstrokes should never be examined simultaneously or before listening for a bruit. Light pressure should always be used to avoid precipitation of carotid hypersensitivity syndrome and syncope in a susceptible elderly individual. The arterial pulse usually becomes more rapid and spiking as a function of its distance from the heart, a phenomenon that reflects the muscular status of the more peripheral arteries and the summation of the incident and reflected waves. In general, the character and contour of the arterial pulse depend on the stroke volume, ejection velocity, vascular compliance, and systemic vascular resistance. The pulse examination can be misleading in patients with reduced cardiac output and in those with stiffened arteries from aging, chronic hypertension, or peripheral arterial disease.

The character of the pulse is best appreciated at the carotid level **(Fig. 234-2)**. A weak and delayed pulse (*pulsus parvus et tardus*) defines severe aortic stenosis (AS). Some patients with AS may also have a slow, notched, or interrupted upstroke (anacrotic pulse) with a thrill

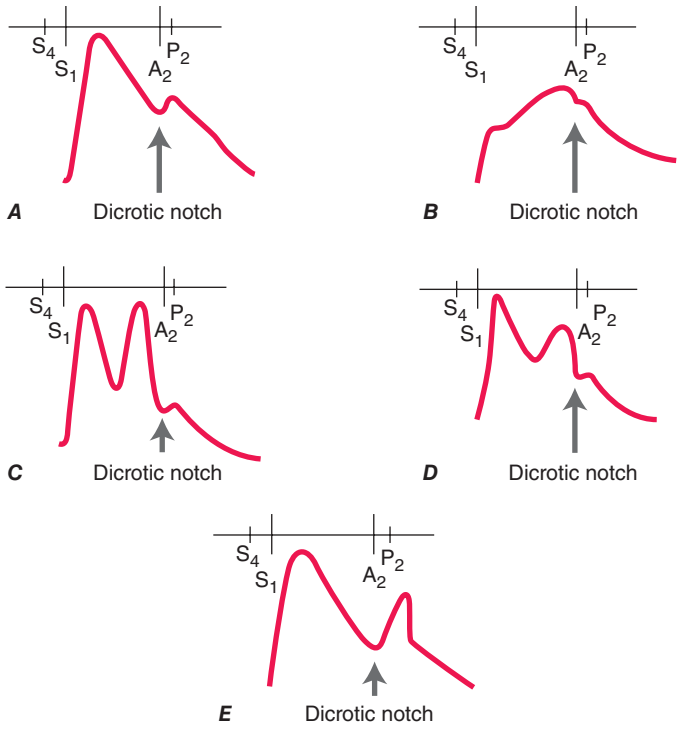


FIGURE 234-2 Schematic diagrams of the configurational changes in carotid pulse and their differential diagnoses. Heart sounds are also illustrated. ***A.*** Normal. S_4, fourth heart sound; S_1, first heart sound; A_2, aortic component of second heart sound; P_2, pulmonic component of second heart sound. ***B.*** Aortic stenosis. Anacrotic pulse with slow upstroke to a reduced peak. ***C.*** Bisferiens pulse with two peaks in systole. This pulse is rarely appreciated in patients with severe aortic regurgitation. ***D.*** Bisferiens pulse in hypertrophic obstructive cardiomyopathy. There is a rapid upstroke to the first peak (percussion wave) and a slower rise to the second peak (tidal wave). ***E.*** Dicrotic pulse with peaks in systole and diastole. This waveform may be seen in patients with sepsis or during intraaortic balloon counterpulsation with inflation just after the dicrotic notch. *(From K Chatterjee, W Parmley [eds]: Cardiology: An Illustrated Text/Reference. Philadelphia, Gower Medical Publishers, 1991.)*

or shudder. With chronic severe AR, by contrast, the carotid upstroke has a sharp rise and rapid fall-off (Corrigan's or water-hammer pulse). Some patients with advanced AR may have a bifid or bisferiens pulse, in which two systolic peaks can be appreciated. A bifid pulse is also described in patients with hypertrophic obstructive cardiomyopathy (HOCM), with inscription of percussion and tidal waves. A bifid pulse is easily appreciated in patients on intraaortic balloon counterpulsation (IABP), in whom the second pulse is diastolic in timing.

Pulsus paradoxus refers to a fall in systolic pressure >10 mmHg with inspiration that is seen in patients with pericardial tamponade but also is described in those with massive pulmonary embolism, hemorrhagic shock, severe obstructive lung disease, and tension pneumothorax. Pulsus paradoxus is measured by noting the difference between the systolic pressure at which the Korotkoff sounds are first heard (during expiration) and the systolic pressure at which the Korotkoff sounds are heard with each heartbeat, independent of the respiratory phase. Between these two pressures, the Korotkoff sounds are heard only intermittently and during expiration. The cuff pressure must be decreased slowly to appreciate the finding. It can be difficult to measure pulsus paradoxus in patients with tachycardia, atrial fibrillation, or tachypnea. A pulsus paradoxus may be palpable at the brachial artery or femoral artery level when the pressure difference exceeds 15 mmHg. This inspiratory fall in systolic pressure is an exaggerated consequence of interventricular dependence.

Pulsus alternans, in contrast, is defined by beat-to-beat variability of pulse amplitude. It is present only when every other phase I Korotkoff sound is audible as the cuff pressure is lowered slowly, typically in a patient with a regular heart rhythm and independent of the respiratory cycle. Pulsus alternans is seen in patients with severe LV systolic dysfunction and is thought to be due to cyclic changes in intracellular calcium and action potential duration. When pulsus alternans is associated with electrocardiographic T-wave alternans, the risk for an arrhythmic event appears to be increased.

Ascending aortic aneurysms can rarely be appreciated as a pulsatile mass in the right parasternal area. Appreciation of a prominent abdominal aortic pulse should prompt noninvasive imaging with ultrasound or computed tomography for better characterization. Femoral and/or popliteal artery aneurysms should be sought in patients with abdominal aortic aneurysm disease.

The level of a claudication-producing arterial obstruction can often be identified on physical examination **(Fig. 234-3)**. For example, in a patient with calf claudication, a decrease in pulse amplitude between the common femoral and popliteal arteries will localize the obstruction to the level of the superficial femoral artery, although inflow obstruction above the level of the common femoral artery may coexist. Auscultation for carotid, subclavian, abdominal aortic, and femoral artery bruits should be routine. However, the correlation between the presence of a bruit and the degree of vascular obstruction is poor. A cervical bruit is a weak indicator of the degree of carotid artery stenosis; the absence of a bruit does not exclude the presence of significant luminal obstruction. If a bruit extends into diastole or if a thrill is present, the obstruction is usually severe. Another cause of an arterial bruit is an arteriovenous fistula with enhanced flow.

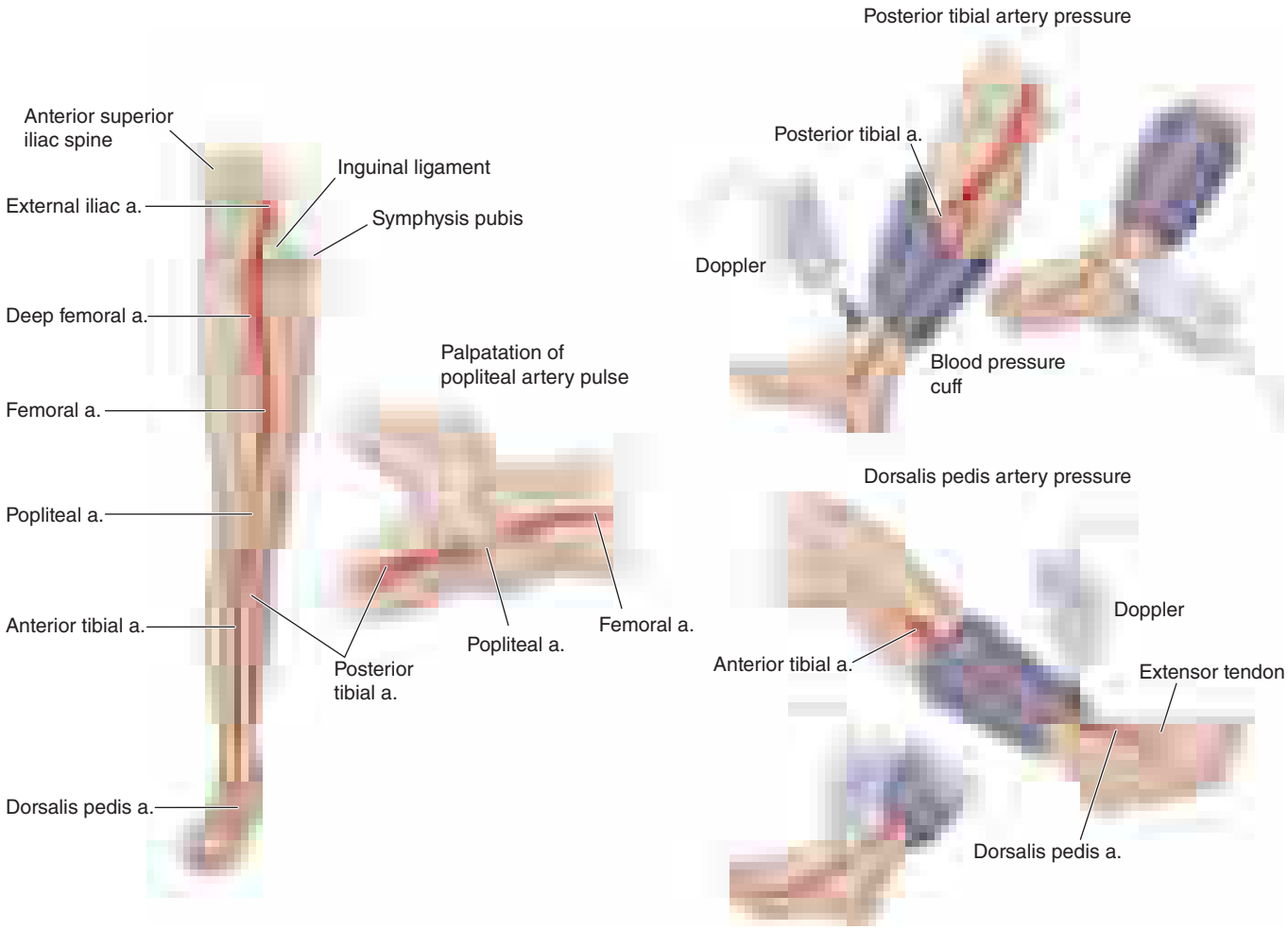
The likelihood of significant lower extremity peripheral arterial disease increases with typical symptoms of claudication, cool skin, abnormalities on pulse examination, or the presence of a vascular bruit. Abnormal pulse oximetry (a >2% difference between finger and toe oxygen saturation) can be used to detect lower extremity peripheral arterial disease and is comparable in its performance characteristics to the ankle-brachial index.

Inspection and Palpation of the Heart The LV apex beat may be visible in the midclavicular line at the fifth intercostal space in thin-chested adults. Visible pulsations anywhere other than this expected location are abnormal. The left anterior chest wall may heave in patients with an enlarged or hyperdynamic left or right ventricle. As noted previously, a visible right upper parasternal pulsation may be suggestive of ascending aortic aneurysm disease. In thin, tall patients and patients with advanced obstructive lung disease and flattened diaphragms, the cardiac impulse may be visible in the epigastrium and should be distinguished from a pulsatile liver edge.

Palpation of the heart begins with the patient in the supine position at 30° and can be enhanced by placing the patient in the left lateral decubitus position. The normal LV impulse is <2 cm in diameter and moves quickly away from the fingers; it is better appreciated at end expiration, with the heart closer to the anterior chest wall. Characteristics such as size, amplitude, and rate of force development should be noted.

Enlargement of the LV cavity is manifested by a leftward and downward displacement of an enlarged apex beat. A sustained apex beat is a sign of pressure overload, such as that which may be present in patients with AS or chronic hypertension. A palpable presystolic impulse corresponds to the fourth heart sound (S_4) and is indicative of reduced LV compliance and the forceful contribution of atrial contraction to ventricular filling. A palpable third sound (S_3), which is indicative of a rapid early filling wave in patients with heart failure, may be present even when the gallop itself is not audible. A large LV aneurysm may sometimes be palpable as an ectopic impulse, discrete from the apex beat. HOCM may very rarely cause a triple cadence beat at the apex with contributions from a palpable S_4 and the two components of the bisferiens systolic pulse.

Right ventricular pressure or volume overload may create a sternal lift. Signs of either TR (*cv* waves in the jugular venous pulse) and/or pulmonary arterial hypertension (a loud single or palpable P_2) would be confirmatory. The right ventricle can enlarge to the extent that left-sided events cannot be appreciated. A zone of retraction between the right and LV impulses sometimes can be appreciated in patients with right ventricle pressure or volume overload when they are placed in the left lateral decubitus position. Systolic and diastolic thrills signify



A **Major arteries of the lower limb** ***B*** **Measurement of ankle systolic pressure**

FIGURE 234-3 ***A.*** Anatomy of the major arteries of the leg. ***B.*** Measurement of the ankle systolic pressure. *(From NA Khan et al: JAMA 295:536, 2006.)*

turbulent and high-velocity blood flow. Their locations help identify the origin of heart murmurs.

CARDIAC AUSCULTATION

Heart Sounds Ventricular systole is defined by the interval between the first (S_1) and second (S_2) heart sounds **(Fig. 234-4)**. The first heart sound (S_1) includes mitral and tricuspid valve closure. Normal splitting can be appreciated in young patients and those with right bundle branch block, in whom tricuspid valve closure is relatively delayed. The intensity of S_1 is determined by the distance over which the anterior leaflet of the mitral valve must travel to return to its annular plane, leaflet mobility, LV contractility, and the PR interval. S_1 is classically loud in the early phases of rheumatic MS and in patients with hyperkinetic circulatory states or short PR intervals. S_1 becomes softer in the later stages of MS when the leaflets are rigid and calcified, after exposure to β-adrenergic receptor blockers, with long PR intervals, and with LV contractile dysfunction. The intensity of heart sounds, however, can be reduced by any process that increases the distance between the stethoscope and the responsible cardiac event, including mechanical ventilation, obstructive lung disease, obesity, pneumothorax, and a pericardial effusion.

Aortic and pulmonic valve closure constitutes the second heart sound (S_2). With normal or physiologic splitting, the A_2–P_2 interval increases with inspiration and narrows during expiration. This physiologic interval will widen with right bundle branch block because of the further delay in pulmonic valve closure and in patients with severe MR because of the premature closure of the aortic valve. An unusually narrowly split or even a singular S_2 is a feature of pulmonary arterial hypertension. Fixed splitting of S_2, in which the A_2–P_2 interval is wide and does not change during the respiratory cycle, occurs in patients with a secundum atrial septal defect (ASD). Reversed or paradoxical splitting refers to a pathologic delay in aortic valve closure, such as that which occurs in patients with left bundle branch block, right ventricular pacing, severe AS, HOCM, and acute myocardial ischemia. With reversed or paradoxical splitting, the individual components of S_2 are audible at end expiration, and their interval narrows with inspiration, the opposite of what would be expected under normal physiologic conditions. P_2 is considered loud when its intensity exceeds that of A_2 at the base, when it can be palpated in the area of the proximal main pulmonary artery (second left interspace), or when both components of S_2 can be appreciated at the lower left sternal border or apex. The intensity of A_2 and P_2 decreases with aortic and pulmonic stenosis (PS), respectively. In these conditions, a single S_2 may result.

Systolic Sounds An ejection sound is a high-pitched early systolic sound that corresponds in timing to the upstroke of the carotid pulse. It usually is associated with congenital bicuspid aortic or pulmonic valve disease; however, ejection sounds are also sometimes audible in patients with isolated aortic or pulmonary root dilation and normal semilunar valves. The ejection sound that accompanies bicuspid aortic valve disease becomes softer and then inaudible as the valve calcifies and becomes more rigid. The ejection sound that accompanies PS moves closer to the first heart sound as the severity of the stenosis increases. In addition, the pulmonic ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. Ejection sounds are often heard more easily at the lower left sternal border than they are at the base. Nonejection sounds (clicks), which occur after the onset of the carotid upstroke, are related to MVP and may be single or multiple. The nonejection click may introduce a murmur. This

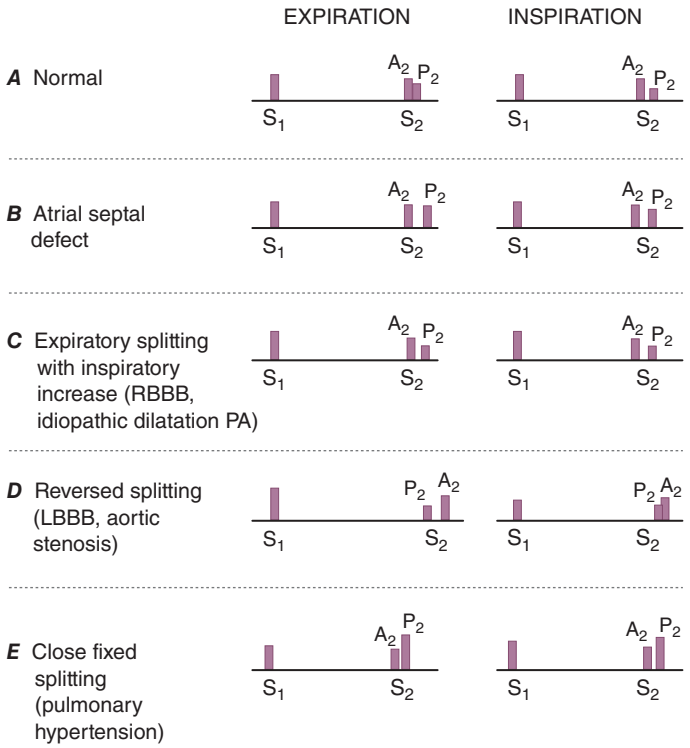


FIGURE 234-4 Heart sounds. ***A.*** Normal. S_1, first heart sound; S_2, second heart sound; A_2, aortic component of the second heart sound; P_2, pulmonic component of the second heart sound. ***B.*** Atrial septal defect with fixed splitting of S_2. ***C.*** Physiologic but wide splitting of S_2 with right bundle branch block (RBBB). PA, pulmonary artery. ***D.*** Reversed or paradoxical splitting of S_2 with left bundle branch block (LBBB). ***E.*** Narrow splitting of S_2 with pulmonary hypertension. *(From NO Fowler: Diagnosis of Heart Disease. New York, Springer-Verlag, 1991, p 31.)*

click-murmur complex will move away from the first heart sound with maneuvers that increase ventricular preload, such as squatting. On standing, the click and murmur move closer to S_1.

Diastolic Sounds The high-pitched opening snap (OS) of MS occurs after a very short interval after the second heart sound. The A_2–OS interval is inversely proportional to the height of the left atrial–left ventricular diastolic pressure gradient. The intensity of both S_1 and the OS of MS decreases with progressive calcification and rigidity of the anterior mitral leaflets. The pericardial knock (PK) is also high-pitched and occurs slightly later than the OS, corresponding in timing to the abrupt cessation of ventricular expansion after tricuspid valve opening and to an exaggerated *y* descent seen in the jugular venous waveform in patients with constrictive pericarditis. A tumor plop is a lower-pitched sound that rarely can be heard in patients with atrial myxoma. It may be appreciated only in certain positions and arises from the diastolic prolapse of the tumor across the mitral valve.

The third heart sound (S_3) occurs during the rapid filling phase of ventricular diastole. It can be a normal finding in children, adolescents, and young adults; however, in older patients, it signifies heart failure. A left-sided S_3 is a low-pitched sound best heard over the LV apex. A right-sided S_3 is usually better heard over the lower left sternal border and becomes louder with inspiration. A left-sided S_3 in patients with chronic heart failure is predictive of cardiovascular morbidity and mortality. Interestingly, an S_3 is equally prevalent among heart failure patients with and without LV systolic dysfunction.

The fourth heart sound (S_4) occurs during the atrial filling phase of ventricular diastole and indicates LV presystolic expansion. An S_4 is more common among patients who derive significant benefit from the atrial contribution to ventricular filling, such as those with chronic LV hypertrophy or active myocardial ischemia. An S_4 is not present with atrial fibrillation.

Cardiac Murmurs Heart murmurs result from audible vibrations that are caused by increased turbulence and are defined by their timing within the cardiac cycle. Not all murmurs are indicative of structural heart disease, and the accurate identification of a benign or functional systolic murmur often can obviate the need for additional testing in healthy subjects. The duration, frequency, configuration, and intensity of a heart murmur are dictated by the magnitude, variability, and duration of the responsible pressure difference between two cardiac chambers, the two ventricles, or the ventricles and their respective great arteries. The intensity of a heart murmur is graded on a scale of 1 to 6; a thrill is present with murmurs of grade 4 or greater intensity. Other attributes of the murmur that aid in its accurate identification include its location, radiation, and response to bedside maneuvers. Although clinicians can detect and correctly identify heart murmurs with only fair reliability, a careful and complete bedside examination usually can identify individuals with valvular heart disease for whom transthoracic echocardiography and clinical follow-up are indicated and exclude subjects for whom no further evaluation is necessary.

Systolic murmurs can be early, mid, late, or holosystolic in timing (Fig. 234-5). Acute severe MR results in a decrescendo early systolic murmur, the characteristics of which are related to the progressive attenuation of the LV to left atrial pressure gradient during systole because of the steep and rapid rise in left atrial pressure in this context. Severe MR associated with posterior leaflet prolapse or flail radiates anteriorly and to the base, where it can be confused with the murmur of AS. MR that is due to anterior leaflet involvement radiates posteriorly and to the axilla. With acute TR in patients with normal pulmonary artery pressures, an early systolic murmur that may increase in intensity with inspiration may be heard at the left lower sternal border, with regurgitant *cv* waves visible in the jugular venous pulse.

A midsystolic murmur begins after S_1 and ends before S_2; it is typically crescendo-decrescendo in configuration. AS is the most common cause of a midsystolic murmur in an adult. It is often difficult to estimate the severity of the valve lesion on the basis of the physical

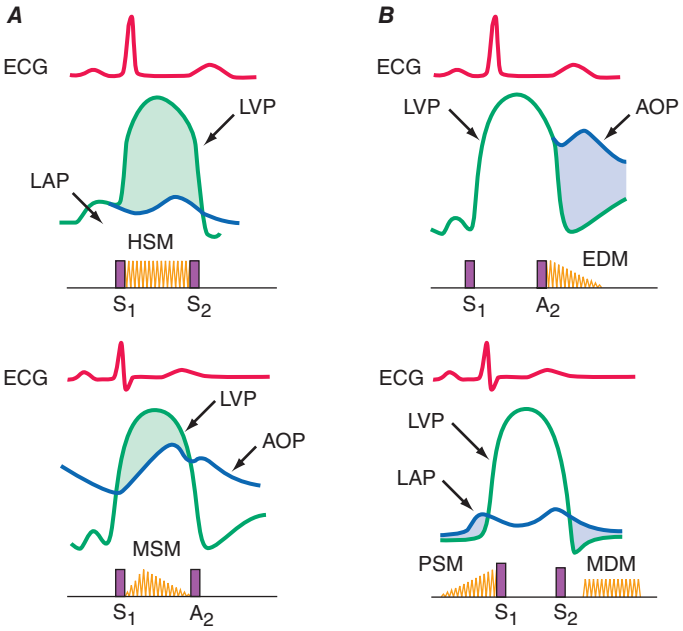


FIGURE 234-5 ***A. Top.*** Graphic representation of the systolic pressure difference (*green shaded area*) between left ventricle and left atrium with phonocardiographic recording of a holosystolic murmur (HSM) indicative of mitral regurgitation. ECG, electrocardiogram; LAP, left atrial pressure; LVP, left ventricular pressure; S_1, first heart sound; S_2, second heart sound. ***Bottom.*** Graphic representation of the systolic pressure gradient (*green shaded area*) between left ventricle and aorta in patient with aortic stenosis. A midsystolic murmur (MSM) with a crescendo-decrescendo configuration is recorded. AOP, aortic pressure. ***B. Top.*** Graphic representation of the diastolic pressure difference between the aorta and left ventricle (*blue shaded area*) in a patient with aortic regurgitation, resulting in a decrescendo, early diastolic murmur (EDM) beginning with A_2. ***Bottom.*** Graphic representation of the diastolic left atrial–left ventricular gradient (*blue areas*) in a patient with mitral stenosis with a mid-diastolic murmur (MDM) and late presystolic murmurs (PSM).

examination findings, especially in older hypertensive patients with stiffened carotid arteries or patients with low cardiac output in whom the intensity of the systolic heart murmur is misleadingly soft. Examination findings consistent with severe AS would include *parvus et tardus* carotid upstrokes, a late-peaking grade 3 or greater midsystolic murmur, a soft A_2, a sustained LV apical impulse, and an S_4. It is sometimes difficult to distinguish aortic sclerosis from more advanced degrees of valve stenosis. The former is defined by focal thickening and calcification of the aortic valve leaflets that is not severe enough to result in obstruction. These valve changes are associated with a Doppler jet velocity across the aortic valve of 2.5 m/s or less. Patients with aortic sclerosis can have grade 2 or 3 midsystolic murmurs identical in their acoustic characteristics to the murmurs heard in patients with more advanced degrees of AS. Other causes of a midsystolic heart murmur include pulmonic valve stenosis (with or without an ejection sound), HOCM, increased pulmonary blood flow in patients with a large ASD and left-to-right shunting, and several states associated with accelerated blood flow in the absence of structural heart disease, such as fever, thyrotoxicosis, pregnancy, anemia, and normal childhood/adolescence.

The murmur of HOCM has features of both obstruction to LV outflow and MR, as would be expected from knowledge of the pathophysiology of this condition. The systolic murmur of HOCM usually can be distinguished from other causes on the basis of its response to bedside maneuvers, including Valsalva, passive leg raising, and standing/squatting. In general, maneuvers that decrease LV preload (or increase LV contractility) will cause the murmur to intensify, whereas maneuvers that increase LV preload or afterload will cause a decrease in the intensity of the murmur. Accordingly, the systolic murmur of HOCM becomes louder during the strain phase of the Valsalva maneuver and after standing quickly from a squatting position. The murmur becomes softer with passive leg raising and when squatting. The murmur of AS is typically loudest in the second right interspace with radiation into the carotids, whereas the murmur of HOCM is best heard between the lower left sternal border and the apex. The murmur of PS is best heard in the second left interspace. The midsystolic murmur associated with enhanced pulmonic blood flow in the setting of a large ASD is usually loudest at the mid-left sternal border.

A late systolic murmur, heard best at the apex, indicates MVP. As previously noted, the murmur may or may not be introduced by a nonejection click. Differential radiation of the murmur, as previously described, may help identify the specific leaflet involved by the myxomatous process. The click-murmur complex behaves in a manner directionally similar to that demonstrated by the murmur of HOCM during the Valsalva and stand/squat maneuvers **(Fig. 234-6)**. The murmur of MVP can be identified by the accompanying nonejection click.

Holosystolic murmurs are plateau in configuration and reflect a continuous and wide pressure gradient between the left ventricle and left atrium with chronic MR, the left ventricle and right ventricle with a ventricular septal defect (VSD), and the right ventricle and right atrium with TR. In contrast to acute MR, in chronic MR the left atrium is enlarged and its compliance is normal or increased to the extent that there is little if any further increase in left atrial pressure from any increase in regurgitant volume. The murmur of MR is best heard over the cardiac apex. The intensity of the murmur increases with maneuvers that increase LV afterload, such as sustained hand grip. The murmur of a VSD (without significant pulmonary hypertension) is holosystolic and loudest at the mid-left sternal border, where a thrill is usually present. The murmur of TR is loudest at the lower left sternal border, increases in intensity with inspiration (Carvallo's sign), and is accompanied by visible *cv* waves in the jugular venous wave form and, on occasion, by pulsatile hepatomegaly.

Diastolic Murmurs In contrast to some systolic murmurs, diastolic heart murmurs always signify structural heart disease (Fig. 234-5). The murmur associated with acute, severe AR is relatively soft and of short duration because of the rapid rise in LV diastolic pressure and the progressive diminution of the aortic-LV diastolic pressure gradient. In contrast, the murmur of chronic severe AR is classically heard as a decrescendo, blowing diastolic murmur along the left sternal border in patients with primary valve pathology and sometimes along the right sternal border in patients with primary aortic root pathology. With chronic AR, the pulse pressure is wide and the arterial pulses are bounding in character. These signs of significant diastolic run-off are absent in the acute phase. The murmur of pulmonic regurgitation is also heard along the left sternal border. It is most commonly due to pulmonary hypertension and enlargement of the annulus of the pulmonic valve. S_2 is single and loud and may be palpable. There is a right ventricular/parasternal lift that is indicative of chronic right ventricular pressure overload. A less impressive murmur of PR is present after repair of tetralogy of Fallot or pulmonic valve atresia. In this postoperative setting, the murmur is softer and lower-pitched, and the severity of the accompanying pulmonic regurgitation can be underestimated significantly.

MS is the classic cause of a mid- to late diastolic murmur, which is best heard over the apex in the left lateral decubitus position, is low-pitched or rumbling, and is introduced by an OS in the early stages of the rheumatic disease process. Presystolic accentuation refers to an increase in the intensity of the murmur just before the first heart sound and occurs in patients with sinus rhythm. It is absent in patients with atrial fibrillation. The auscultatory findings in patients with rheumatic tricuspid stenosis typically are obscured by left-sided events, although they are similar in nature to those described in patients with MS. "Functional" mitral or tricuspid stenosis refers to the generation of

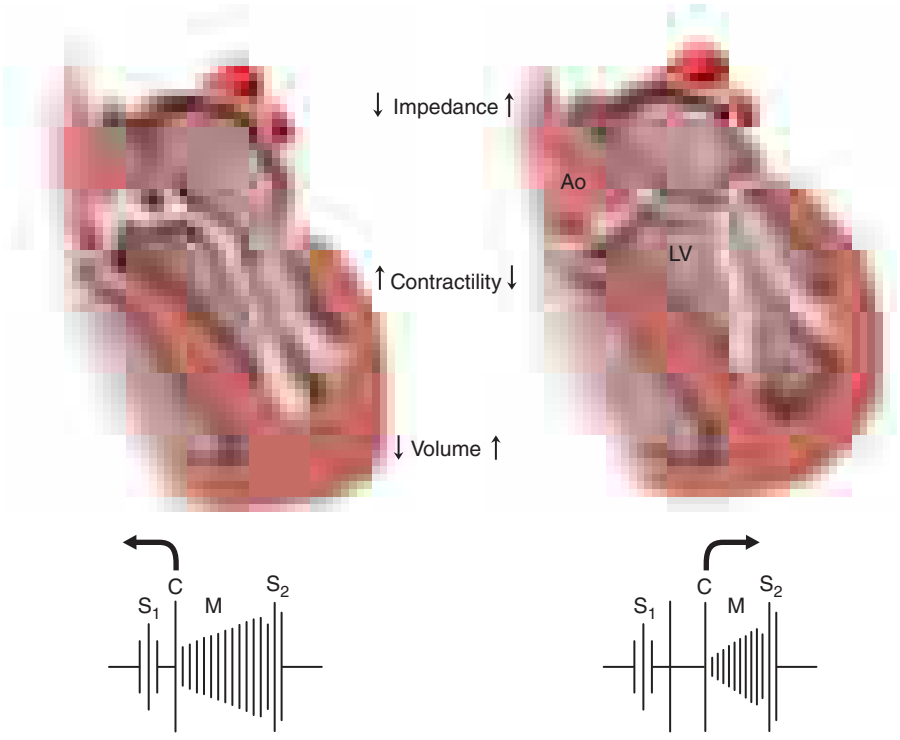


FIGURE 234-6 Behavior of the click (C) and murmur (M) of mitral valve prolapse with changes in loading (volume, impedance) and contractility. S_1, first heart sound; S_2, second heart sound. With standing (left side of figure), volume and impedance decrease, as a result of which the click and murmur move closer to S_1. With squatting (right), the click and murmur move away from S_1 due to the increases in left ventricular volume and impedance (afterload). Ao, aorta; LV, left ventricle. *(Adapted from RA O'Rourke, MH Crawford: Curr Prob Cardiol 1:9, 1976.)*

mid-diastolic murmurs that are created by increased and accelerated transvalvular diastolic flow, even in the absence of valvular obstruction, in the setting of severe MR, severe TR, or a large ASD with left-to-right shunting. The Austin Flint murmur of chronic severe AR is a low-pitched mid- to late apical diastolic murmur that sometimes can be confused with MS. The Austin Flint murmur typically decreases in intensity after exposure to vasodilators, whereas the murmur of MS may be accompanied by an OS and also may increase in intensity after vasodilators because of the associated increase in cardiac output. Unusual causes of a mid-diastolic murmur include atrial myxoma, complete heart block, and acute rheumatic mitral valvulitis.

Continuous Murmur A continuous murmur is predicated on a pressure gradient that persists between two cardiac chambers or blood vessels across systole and diastole. The murmurs typically begin in systole, envelop the second heart sound (S_2), and continue through some portion of diastole. They can often be difficult to distinguish from individual systolic and diastolic murmurs in patients with mixed valvular heart disease. The classic example of a continuous murmur is that associated with a PDA, which usually is heard in the second or third interspace at a slight distance from the sternal border. Other causes of a continuous murmur include a ruptured sinus of Valsalva aneurysm with creation of an aortic–right atrial or right ventricular fistula, a coronary or great vessel arteriovenous fistula, and an arteriovenous fistula constructed to provide dialysis access. There are two types of benign continuous murmurs. The cervical venous hum is heard in children or adolescents in the supraclavicular fossa. It can be obliterated with firm pressure applied to the diaphragm of the stethoscope, especially when the subject turns his or her head toward the examiner. The mammary soufflé of pregnancy relates to enhanced arterial blood flow through engorged breasts. The diastolic component of the murmur can be obliterated with firm pressure over the stethoscope.

Dynamic Auscultation Diagnostic accuracy can be enhanced by the performance of simple bedside maneuvers to identify heart murmurs and characterize their significance **(Table 234-1)**. Except for the pulmonic ejection sound, right-sided events increase in intensity with inspiration and decrease with expiration; left-sided events behave oppositely (100% sensitivity, 88% specificity). As previously noted, the intensity of the murmurs associated with MR, VSD, and AR will increase in response to maneuvers that increase LV afterload, such as hand grip and vasopressors. The intensity of these murmurs will decrease after exposure to vasodilating agents. Squatting is associated with an abrupt increase in LV preload and afterload, whereas rapid standing results in a sudden decrease in preload. In patients with MVP, the click and murmur move away from the first heart sound with squatting because of the delay in onset of leaflet prolapse at higher ventricular volumes. With rapid standing, however, the click and murmur move closer to the first heart sound as prolapse occurs earlier in systole at a smaller chamber dimension. The murmur of HOCM behaves similarly, becoming softer and shorter with squatting (95% sensitivity, 85% specificity) and longer and louder on rapid standing (95% sensitivity, 84% specificity). A change in the intensity of a systolic murmur in the first beat after a premature beat or in the beat after a long cycle length in patients with atrial fibrillation suggests valvular AS rather than MR, particularly in an older patient in whom the murmur of the AS may be well transmitted to the apex (Gallavardin effect). Of note, however, the systolic murmur of HOCM also increases in intensity in the beat after a premature beat. This increase in intensity of any LV outflow murmur in the beat after a premature beat relates to the combined effects of enhanced LV filling (from the longer diastolic period) and postextrasystolic potentiation of LV contractile function. In either instance, forward flow will accelerate, causing an increase in the gradient across the LV outflow tract (dynamic or fixed) and a louder systolic murmur. In contrast, the intensity of the murmur of MR does not change in a postpremature beat, because there is relatively little change in the nearly constant LV to left atrial pressure gradient or further alteration in mitral valve flow. Bedside exercise can sometimes be performed to increase cardiac output and, secondarily, the intensity of both systolic and diastolic heart murmurs. Most left-sided heart murmurs decrease in intensity and duration during the strain phase of the Valsalva maneuver. The murmurs associated with MVP and HOCM are the two notable exceptions. The Valsalva maneuver also can be used to assess the integrity of the heart and vasculature in the setting of advanced heart failure.

TABLE 234-1 Effects of Physiologic and Pharmacologic Interventions on the Intensity of Heart Murmurs and Sounds

Respiration
Right-sided murmurs and sounds generally increase with inspiration, except for the PES. Left-sided murmurs and sounds are usually louder during expiration.
Valsalva Maneuver
Most murmurs decrease in length and intensity. Two exceptions are the systolic murmur of HOCM, which usually becomes much louder, and that of MVP, which becomes longer and often louder. After release of the Valsalva maneuver, right-sided murmurs tend to return to control intensity earlier than do left-sided murmurs.
After VPB or AF
Murmurs originating at normal or stenotic semilunar valves increase in the cardiac cycle after a VPB or in the cycle after a long cycle length in AF. By contrast, systolic murmurs due to AV valve regurgitation do not change, diminish (papillary muscle dysfunction), or become shorter (MVP).
Positional Changes
With *standing*, most murmurs diminish, with two exceptions being the murmur of HOCM, which becomes louder, and that of MVP, which lengthens and often is intensified. With *squatting*, most murmurs become louder, but those of HOCM and MVP usually soften and may disappear. Passive leg raising usually produces the same results.
Exercise
Murmurs due to blood flow across normal or obstructed valves (e.g., PS, MS) become louder with both isotonic and submaximal isometric (hand grip) exercise. Murmurs of MR, VSD, and AR also increase with hand grip exercise. However, the murmur of HOCM often decreases with nearly maximum hand grip exercise. Left-sided S_4 and S_3 sounds are often accentuated by exercise, particularly when due to ischemic heart disease.

Abbreviations: AF, atrial fibrillation; AR, aortic regurgitation; HOCM, hypertrophic obstructive cardiomyopathy; MR, mitral regurgitation; MS, mitral stenosis; MVP, mitral valve prolapse; PES, pulmonic ejection sound; PR, pulmonic regurgitation; PS, pulmonic stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis; VPB, ventricular premature beat; VSD, ventricular septal defect.

Prosthetic Heart Valves The first clue that prosthetic valve dysfunction may contribute to recurrent symptoms is frequently a change in the quality of the heart sounds or the appearance of a new murmur. The heart sounds with a bioprosthetic valve resemble those generated by native valves. A mitral bioprosthesis usually is associated with a grade 2 or 3 midsystolic murmur along the left sternal border (created by turbulence across the valve struts as they project into the LV outflow tract) as well as by a soft mid-diastolic murmur that occurs with normal LV filling. This diastolic murmur often can be heard only in the left lateral decubitus position and after exercise. A high-pitched or holosystolic apical murmur is indicative of pathologic MR due to a paravalvular leak and/or intra-annular bioprosthetic regurgitation from leaflet degeneration, for which additional imaging is indicated. Clinical deterioration can occur rapidly after the first expression of mitral bioprosthetic valve failure. A tissue valve in the aortic position is always associated with a grade 2 to 3 midsystolic murmur at the base or just below the suprasternal notch. A diastolic murmur of AR is abnormal in any circumstance. Mechanical valve dysfunction may first be suggested by a decrease in the intensity of either the opening or the closing sound. A high-pitched apical systolic murmur in patients with a mechanical mitral prosthesis and a diastolic decrescendo murmur in patients with a mechanical aortic prosthesis indicate paravalvular regurgitation. Patients with prosthetic valve thrombosis may present clinically with signs of shock, muffled heart sounds, and soft murmurs.

Pericardial Disease A pericardial friction rub is nearly 100% specific for the diagnosis of acute pericarditis, although the sensitivity of this finding is not nearly as high, because the rub may come and go over the course of an acute illness or be very difficult to elicit. The rub is heard as a leathery or scratchy three-component or two-component sound, although it may be monophasic. Classically, the three components are ventricular systole, rapid early diastolic filling, and late presystolic filling after atrial contraction in patients in sinus rhythm.

It is necessary to listen to the heart in several positions. Additional clues may be present from the history and 12-lead electrocardiogram. The rub typically disappears as the volume of any pericardial effusion increases. Pericardial tamponade can be diagnosed with a sensitivity of 98%, a specificity of 83%, and a positive likelihood ratio of 5.9 (95% confidence interval 2.4–14) by a pulsus paradoxus that exceeds 12 mmHg in a patient with a large pericardial effusion.

The findings on physical examination are integrated with the symptoms previously elicited with a careful history to construct an appropriate differential diagnosis and proceed with indicated imaging and laboratory assessment. The physical examination is an irreplaceable component of the diagnostic algorithm and in selected patients can inform prognosis. Educational efforts to improve clinician competence eventually may result in cost saving, particularly if the indications for imaging can be influenced by the examination findings.

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235 Electrocardiography

Ary L. Goldberger

An *electrocardiogram* (ECG or EKG) is a graphic representation of electrical activity generated by the heart. The signals, detected by means of metal electrodes attached to the extremities and chest wall, are amplified and recorded by the *electrocardiograph*. ECG leads (derivations) are configured to display the instantaneous *differences* in potential between specific pairs of electrodes. The utility of the ECG derives from its immediate availability as a noninvasive, inexpensive, and highly versatile test. In addition to its use in detecting arrhythmias and myocardial ischemia, it may reveal findings related to life-threatening metabolic disturbances or to increased susceptibility to sudden cardiac arrest **(see also Chaps. 299 and 401)**.

ELECTROPHYSIOLOGIC BACKGROUND

Depolarization of the heart is the initiating event for cardiac contraction. The electric currents that spread through the heart are produced by three components: cardiac pacemaker cells, specialized conduction tissue, and the heart muscle itself. The ECG records only the depolarization (stimulation) and repolarization (recovery) potentials generated by the "working" atrial and ventricular myocardium **(see also Chaps. 239 and 241)**.

The stimulus initiating the normal heartbeat originates in the *sinoatrial* (SA) *node* **(Fig. 235-1)**, which possesses spontaneous automaticity. Spread of the depolarization wave through the right and left atria induces contraction of these chambers. Next, the impulse stimulates specialized conduction tissues in the atrioventricular (AV) nodal and His-bundle areas; together, these two regions constitute the AV junction. The bundle of His fans bifurcates into two main branches, the right and left bundles, which rapidly transmit depolarization wavefronts in a synchronous way to the right and left ventricular myocardium by way of Purkinje fibers. The main left bundle bifurcates into left anterior and left posterior fascicle subdivisions. The depolarization wavefronts then spread through the ventricular wall, from endocardium to epicardium, triggering coordinated ventricular contraction. Since the cardiac depolarization and repolarization waves have directions and magnitudes, they can be represented by vectors.

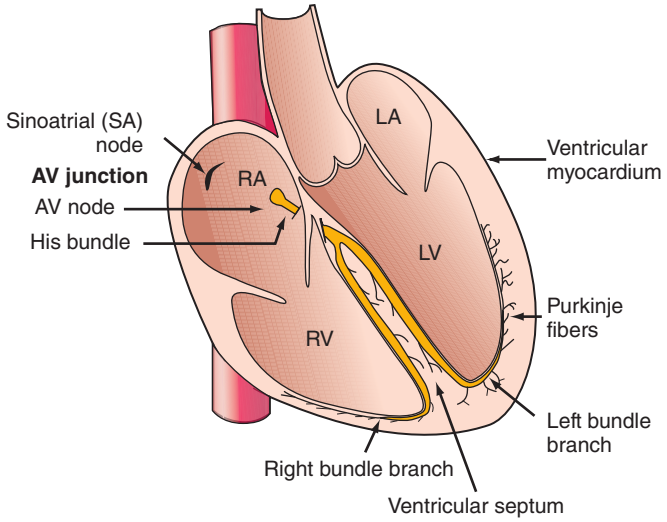

FIGURE 235-1 Schematic of the cardiac conduction system.

ECG WAVEFORMS AND INTERVALS

The ECG waveforms are labeled alphabetically, beginning with the P wave, which represents atrial depolarization **(Fig. 235-2)**. The QRS complex represents ventricular depolarization, and the ST-T-U complex (ST segment, T wave, and U wave) represents ventricular repolarization. The J point is the junction between the end of the QRS complex and the beginning of the ST segment. Atrial repolarization waveforms (ST-T_a) are usually of too low in amplitude to be detected, it may become apparent in acute pericarditis, atrial infarction, and AV heart block.

The QRS-T waveforms of the surface ECG correspond in a general way with the different phases of simultaneously obtained ventricular *action potentials*, the intracellular recordings from single myocardial fibers **(Chap. 239)**. The rapid upstroke (phase 0) of the action potential corresponds to the onset of QRS. The plateau (phase 2) corresponds to the isoelectric ST segment, and active repolarization (phase 3) corresponds to the inscription of the T wave. Factors that decrease the slope of phase 0 by impairing the influx of Na^+ (e.g., hyperkalemia and drugs such as flecainide) tend to increase QRS duration. Conditions that prolong phase 2 or 3 (amiodarone, hypocalcemia) increase the QT interval. In contrast, factors (e.g., hypercalcemia, digoxin) associated with shortening of ventricular repolarization duration shorten the QT.

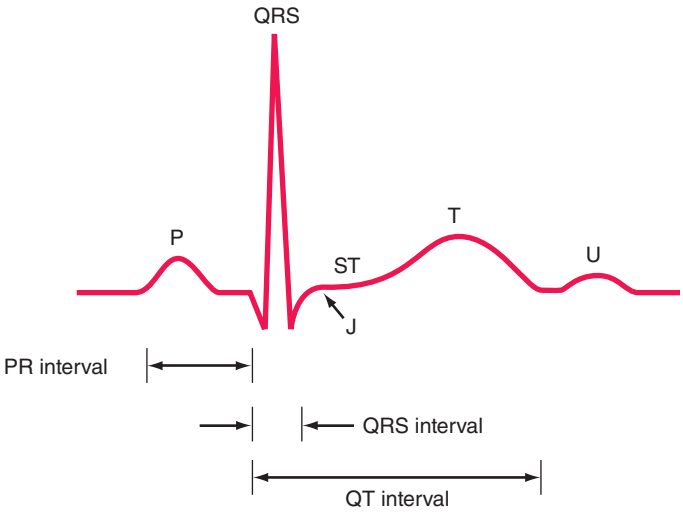

FIGURE 235-2 Basic ECG waveforms and intervals. Not shown is the RR interval, the time between consecutive QRS complexes.

The ECG is usually recorded on graph paper divided into 1-mm^2 gridlike boxes. When the recording speed of 25 mm/s, the smallest (1 mm) horizontal divisions correspond to 0.04 (40 ms), with heavier lines at intervals of 0.20 s (200 ms). Vertically, the ECG graph measures the amplitude of a specific wave or deflection (1 mV = 10 mm with standard calibration; the voltage criteria for hypertrophy mentioned below are given in millimeters). There are four major sets of ECG intervals: RR, PR, QRS, and QT/QTc (Fig. 235-2). The instantaneous heart rate (beats per minute) can be computed from the interbeat (RR) interval by dividing the number of large (0.20 s) time units between consecutive R waves into 300 or the number of small (0.04 s) units into 1500. The PR interval measures the time (normally 120–200 ms) between atrial and ventricular depolarization, which includes the physiologic delay imposed by stimulation of cells in the AV junction area. The QRS interval (normally 100–110 ms or less) reflects the duration of ventricular depolarization. The QT interval subtends both ventricular depolarization and (primarily) repolarization times and varies inversely with the heart rate. A rate-related ("corrected") QT interval, QT_c, can be calculated as $QT/\sqrt{RR}$ and is normally ≤0.44 s. Some references give the QT_c upper normal limits as 0.45 s in men and 0.46 s in women. A number of other rate-correction formulas have been proposed, without consensus.

ECG LEADS

The 12 conventional ECG leads are divided into two groups: six limb (extremity) leads and six chest (precordial) leads. The limb leads record potentials transmitted onto the *frontal plane* **(Fig. 235-3*A*)**; the chest leads record potentials transmitted onto the *horizontal plane* **(Fig. 235-3*B*)**.

The orientation and polarity of the frontal plane leads are represented on a hexaxial diagram **(Fig. 235-4)**. The six chest leads are obtained by exploring electrodes as shown in **Fig. 235-5**.

Each lead is analogous to a different video camera angle "looking" at the same events—atrial and ventricular depolarization and repolarization—from different spatial orientations. The 12-lead ECG can be supplemented with additional leads in special circumstances. For example, right precordial leads V_3R to V_6R are useful in detecting evidence of acute right ventricular ischemia. Bedside monitors and ambulatory ECG (Holter and event) recordings usually employ only one or two modified leads. The ECG leads are configured such that a positive (upright) deflection is recorded in a lead if a wave of depolarization spreads toward the positive pole of that lead, and a negative deflection is recorded if the wave spreads toward the negative pole. If the *mean* orientation of the depolarization vector is at right angles to a particular lead axis, a biphasic (equally positive and negative) deflection will be recorded.

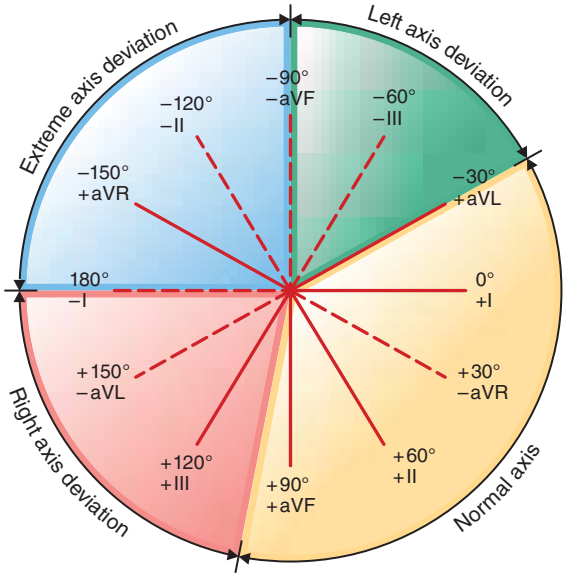

FIGURE 235-4 The frontal plane (limb or extremity) leads are represented on a hexaxial diagram. Each ECG lead has a specific spatial orientation and polarity. The positive pole of each lead axis (*solid line*) and the negative pole (*hatched line*) are designated by their angular position relative to the positive pole of lead I (0°). The mean electrical axis of the QRS complex is measured with respect to this display.

GENESIS OF THE NORMAL ECG

P WAVE

The normal atrial depolarization vector is oriented downward and toward the subject's left, reflecting the spread of depolarization from the sinus node to the right and then the left atrial myocardium. Since this vector points toward the positive pole of lead II and toward the negative pole of lead aVR, the normal P wave will be positive in lead II and negative in aVR. By contrast, activation of the atria from an ectopic pacemaker in the lower part of either atrium or in the AV junction region may produce retrograde P waves (negative in II, positive in aVR). The normal P wave in lead V_1 may be biphasic with a positive component reflecting right atrial depolarization, followed by a small (<1 mm^2) negative component reflecting left atrial depolarization.

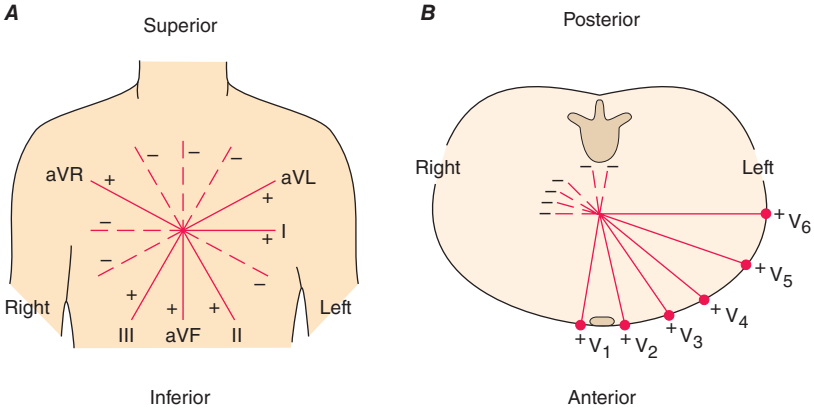

FIGURE 235-3 The six frontal plane (*A*) and six horizontal plane (*B*) leads provide a three-dimensional representation of cardiac electrical activity.

QRS COMPLEX

Normal ventricular depolarization proceeds as a rapid, continuous spread of activation wave fronts. This complex process can be divided into two major sequential phases, and each phase can be represented by a mean vector **(Fig. 235-6)**. The first phase is depolarization of the interventricular septum from the left to the right and anteriorly (vector 1). The second results from the simultaneous depolarization of the right and left ventricles; it normally is dominated by the more massive left ventricle, so that vector 2 points leftward and posteriorly. Therefore, a right precordial lead (V_1) will record this biphasic depolarization process with a small positive deflection (septal r wave) followed by a larger negative deflection (S wave). A left precordial lead, for example, V_6, will record the same sequence with a small negative deflection (septal q wave) followed by a relatively tall positive deflection (R wave). Intermediate leads show a relative increase in R-wave amplitude (normal R-wave progression) and a decrease in S-wave amplitude progressing across the chest from right to left. The lead where the R and S waves are of about equal amplitude is referred to as the *transition zone* (usually V_3 or V_4) **(Fig. 235-7)**.

The QRS pattern in the extremity leads may vary considerably from one normal subject to another depending on the *electrical axis* of the QRS, which describes the mean orientation of the QRS vector with reference to the six frontal plane leads. Normally, the QRS axis ranges from −30° to +100° (Fig. 235-4). An axis more negative than −30° is referred to as *left axis deviation*, and an axis more positive than +90 to +100° is referred to as *right axis deviation*. Left axis deviation may occur as a normal variant but

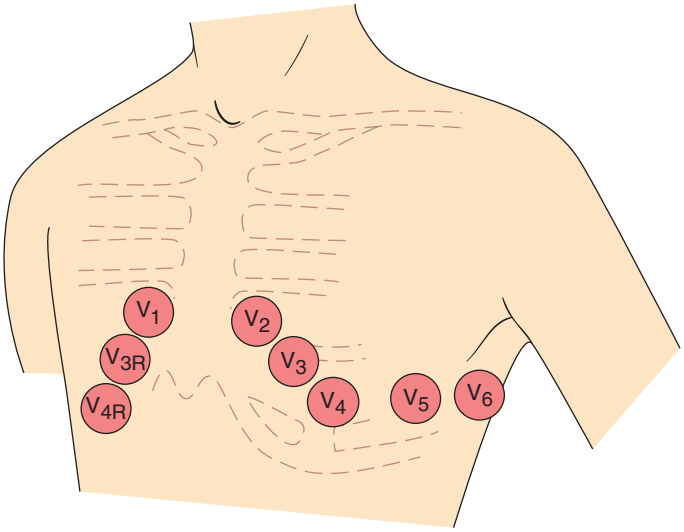

FIGURE 235-5 The horizontal plane (chest or precordial) leads are obtained with electrodes in the locations shown. Additional posterior leads are sometimes placed on the same horizontal plane as V_4 to facilitate detection of acute posterolateral infarction (V_7, midaxillary line; V_8, posterior axillary line; and V_9, posterior scapular line). Right chest leads (V_3R–V_6R) may enhance detection of right ventricular involvement in the context of inferior infarction.

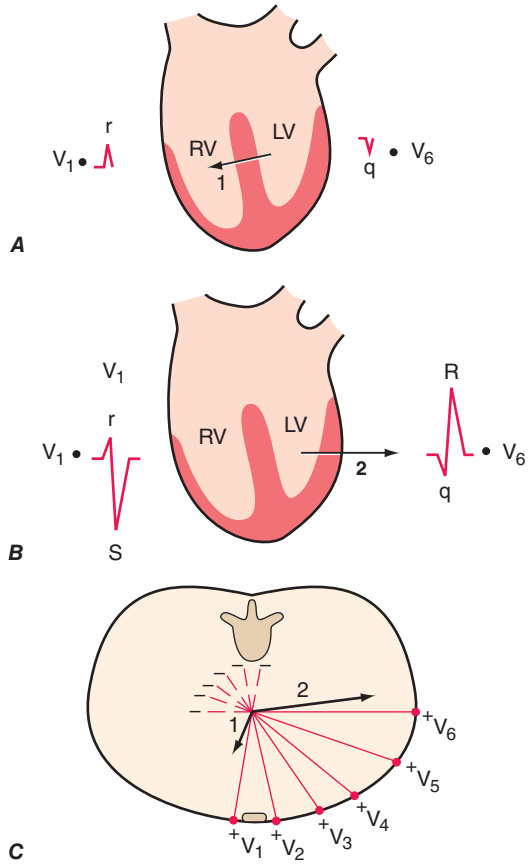

FIGURE 235-6 Ventricular depolarization can be divided into two major phases, each represented by a vector. *A.* The first phase (*arrow 1*) denotes depolarization of the ventricular septum, beginning on the left side and spreading to the right. This process is represented by a small "septal" r wave in lead V_1 and a small septal q wave in lead V_6. ***B.*** Simultaneous depolarization of the left and right ventricles (LV and RV) constitutes the second phase. Vector 2 is oriented to the left and posteriorly, reflecting the electrical predominance of the LV. ***C.*** Vectors (*arrows*) representing these two phases are shown in reference to the horizontal plane leads. *(After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 9h ed. Philadelphia, Elsevier/Saunders, 2017.)*

is more commonly associated with left ventricular hypertrophy, a block in the anterior fascicle of the left bundle system (left anterior fascicular block or hemiblock), or inferior myocardial infarction. Right axis deviation also may occur as a normal variant (particularly in children and young adults), as a spurious finding due to reversal of the left and right arm electrodes, or in conditions such as right ventricular overload (acute or chronic), lateral infarction, dextrocardia, left pneumothorax, and left posterior fascicular block.

T WAVE AND U WAVE

Normally, the mean T-wave vector is oriented roughly concordant with the mean QRS vector (within about 45° in the frontal plane). Since depolarization and repolarization are electrically opposite processes, this normal QRS–T-wave vector concordance indicates that repolarization normally must proceed in the reverse direction from depolarization (i.e., from ventricular epicardium to endocardium). The normal U wave is a small, rounded deflection (≤1 mm) that follows the T wave and usually has the same polarity as the T wave. An abnormal increase in U-wave amplitude is most commonly due to drugs (e.g., dofetilide, amiodarone, sotalol, quinidine) or to hypokalemia. Very prominent U waves are a marker of increased susceptibility to *torsades de pointes* **(Chap. 241)**.

MAJOR ECG ABNORMALITIES

CARDIAC ENLARGEMENT AND HYPERTROPHY

Right atrial overload (acute or chronic) may lead to an increase in P-wave amplitude (≥2.5 mm) **(Fig. 235-8)**, previously referred to as "P-pulmonale." Left atrial overload typically produces a biphasic P wave in V_1 with a broad negative component or a broad (≥120 ms), often notched P wave in one or more limb leads (Fig. 235-8). This pattern, previously referred to as "P-mitrale," may also occur with left atrial conduction delays in the absence of actual atrial enlargement, leading to the more general designation of *left atrial abnormality*.

Right ventricular hypertrophy due to a sustained, severe pressure load (e.g., due to tight pulmonic valve stenosis or certain pulmonary artery hypertension syndromes) is characterized by a relatively tall R wave in lead V_1 (R ≥ S wave), usually with right axis deviation **(Fig. 235-9)**; alternatively, there may be a qR pattern in V_1 or V_3R. ST depression and T-wave inversion in the right-to-midprecordial leads are also often present. This pattern, formerly called right ventricular "strain," is attributed to repolarization abnormalities in acutely or chronically overloaded muscle. Prominent S waves may occur in the left lateral precordial leads. Right ventricular hypertrophy due to ostium secundum–type atrial septal defects, with the accompanying right ventricular volume overload, is commonly associated with an incomplete or complete right bundle branch block pattern with a rightward QRS axis.

Acute cor pulmonale due to pulmonary embolism **(Chap. 273)**, for example, may be associated with a normal ECG or a variety of abnormalities. Sinus tachycardia is the most common arrhythmia, although other tachyarrhythmias, such as atrial fibrillation or flutter, may occur. The QRS axis may shift to the right, sometimes in concert with the so-called $S_1Q_3T_3$ pattern (prominence of the S wave in lead I and the Q wave in lead III, with T-wave inversion in lead III). Acute right ventricular dilation also may be associated with slow R-wave progression and ST-T abnormalities in V_1 to V_4 simulating acute anterior infarction. A right ventricular conduction disturbance may appear.

Chronic cor pulmonale due to obstructive lung disease **(Chap. 252)** usually does not produce the classic ECG patterns of right ventricular hypertrophy noted above. Instead of tall right precordial R waves, chronic lung disease more typically is associated with small R waves in right-to-midprecordial leads (slow R-wave progression) due in part to downward displacement of the diaphragm and the heart. Low-voltage complexes are commonly present, owing to hyperaeration.

Multiple voltage criteria for *left ventricular hypertrophy* (Fig. 235-9) have been proposed on the basis of the presence of tall left precordial R waves and deep right precordial S waves (e.g., SV_1 + [RV_5 or RV_6] >35 mm). Repolarization abnormalities (ST depression with T-wave inversions, formerly called the left ventricular "strain" pattern) also

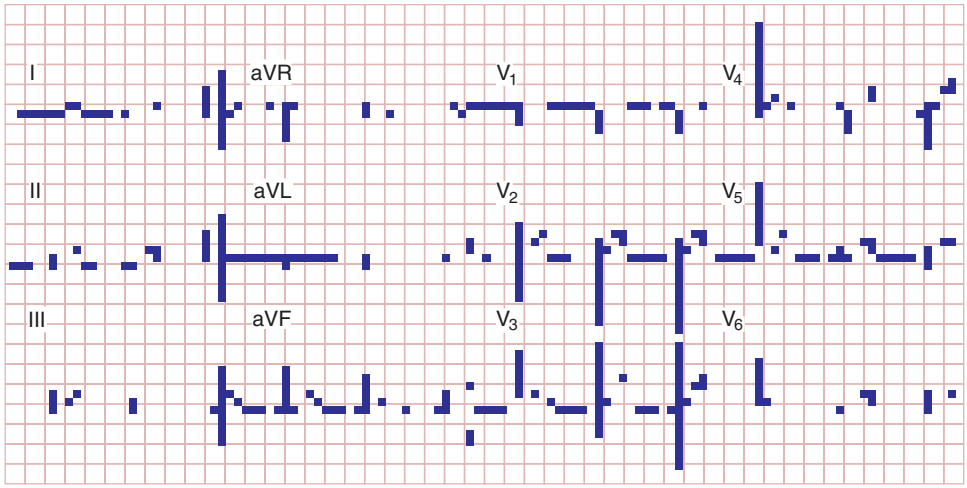

FIGURE 235-7 Normal electrocardiogram from a healthy subject. Sinus rhythm is present with a heart rate of 75 beats per minute. PR interval is 0.16 s; QRS interval (duration) is 0.08 s; QT interval is 0.36 s; QT_c is 0.40 s; the mean QRS axis is about +70°. The precordial leads show normal R-wave progression with the transition zone (R wave = S wave) in lead V_3.

may appear in leads with prominent R waves. However, prominent precordial voltages may occur as a normal variant, especially in athletic or young individuals. Left ventricular hypertrophy may increase limb lead voltage with or without increased precordial voltage (e.g., RaVL + SV_3 >20 mm in women and >28 mm in men). The presence of left atrial abnormality increases the likelihood of underlying left ventricular hypertrophy in cases with borderline voltage criteria. Left ventricular hypertrophy often progresses to incomplete or complete left bundle branch block. The sensitivity of conventional voltage criteria for left ventricular hypertrophy is decreased in obese persons and smokers. ECG evidence for left ventricular hypertrophy is a major noninvasive marker of increased risk of cardiovascular morbidity and mortality rates, including sudden cardiac death. However, because of false-positive and false-negative diagnoses, the ECG is of limited utility in diagnosing atrial or ventricular enlargement. More definitive information is provided by echocardiography (Chap. 236).

BUNDLE BRANCH BLOCKS AND RELATED PATTERNS

Intrinsic impairment of conduction in either the right or the left bundle system (intraventricular conduction disturbances) leads to prolongation of the QRS interval. With complete bundle branch blocks, the widest QRS interval is ≥120 ms in duration; with incomplete blocks, the QRS interval is between about 110 and 120 ms. The QRS vector usually is oriented in the direction of the myocardial region where depolarization is delayed (Fig. 235-10). Thus, with right bundle branch block, the terminal QRS vector is oriented to the right and anteriorly (rSR′ in V_1 and qRS in V_6, typically). Left bundle branch block alters both early and later phases of ventricular depolarization. The major QRS vector is directed to the left and posteriorly. In addition, the normal early left-to-right pattern of septal activation is disrupted such that

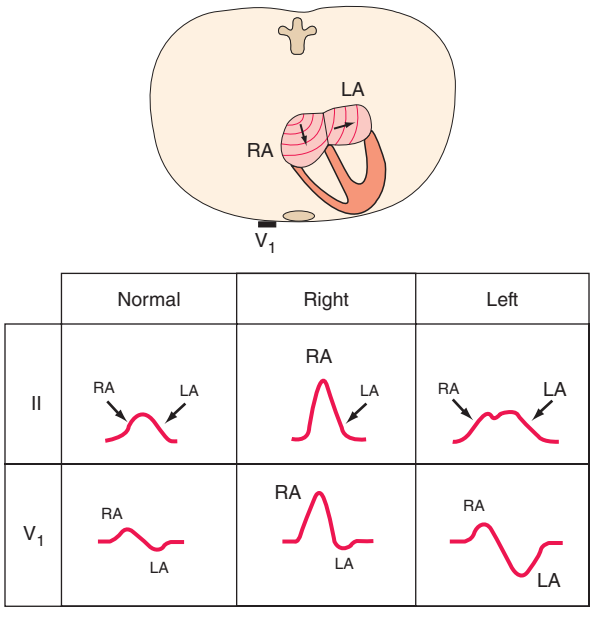

FIGURE 235-8 Right atrial (RA) overload may cause tall, peaked P waves in the limb or precordial leads. Left atrial (LA) abnormality may cause broad, often notched P waves in the limb leads and a biphasic P wave in lead V_1 with a prominent negative component representing delayed depolarization of the LA. *(After MK Park, WG Guntheroth: How to Read Pediatric ECGs, 4th ed. St. Louis, Mosby/Elsevier, 2006.)*

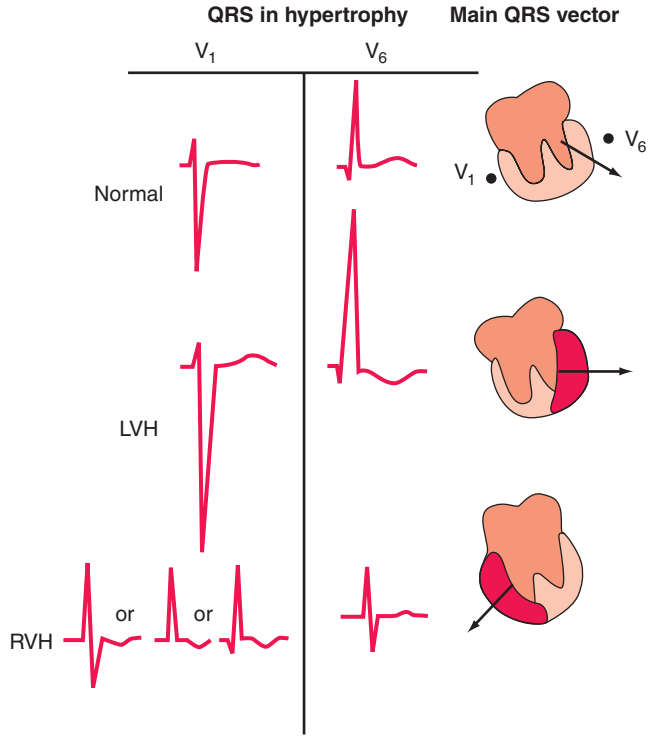

FIGURE 235-9 Left ventricular hypertrophy (LVH) increases the amplitude of electrical forces directed to the left and posteriorly. In addition, repolarization abnormalities may cause ST-segment depression and T-wave inversion in leads with a prominent R wave. Right ventricular hypertrophy (RVH) may shift the QRS vector to the right; this effect usually is associated with an R, RS, or qR complex in lead V_1. T-wave inversions may be present in right precordial leads.

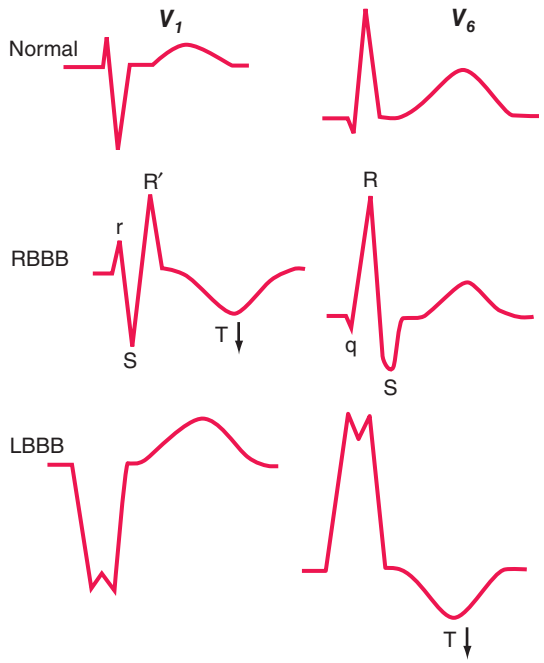

FIGURE 235-10 Comparison of typical QRS-T patterns in right bundle branch block (RBBB) and left bundle branch block (LBBB) with the normal pattern in leads V_1 and V_6. Note the secondary T-wave inversions (*arrows*) in leads with an rSR′ complex with RBBB and in leads with a wide R wave with LBBB.

septal depolarization proceeds from right to left as well. As a result, left bundle branch block generates wide, predominantly negative (QS) complexes in lead V_1 and entirely positive (R) complexes in V_6. A pattern identical to that of left bundle branch block, preceded by a sharp spike, is seen in most cases of electronic right ventricular pacing due to the relative delay in left ventricular activation.

Bundle branch block may occur in a variety of conditions. In subjects without structural heart disease, right bundle branch block is seen more commonly than left bundle branch block. Right bundle branch block also occurs with heart disease, both congenital (e.g., atrial septal defect) and acquired (e.g., valvular, ischemic). Left bundle branch block is often a marker of one of four underlying conditions associated with increased risk of cardiovascular morbidity and mortality rates: coronary heart disease (frequently with impaired left ventricular function), hypertensive heart disease, aortic valve disease, and cardiomyopathy. Bundle branch blocks may be chronic or intermittent. A bundle branch block may be rate-related; for example, it often occurs when the heart rate exceeds some critical value.

Bundle branch blocks and depolarization abnormalities secondary to artificial pacemakers not only affect ventricular depolarization (QRS) but also are characteristically associated with *secondary repolarization* (ST-T) abnormalities. With bundle branch blocks, the T wave is typically opposite in polarity to the last deflection of the QRS (Fig. 235-10). This discordance of the QRS–T-wave vectors is caused by the altered sequence of repolarization that occurs secondary to altered depolarization. In contrast, *primary repolarization* abnormalities are independent of QRS changes and are related instead to actual alterations in the electrical properties of the myocardial fibers themselves (e.g., in the resting membrane potential or action potential duration), not just to changes in the sequence of repolarization. Ischemia, electrolyte imbalance, and drugs such as digitalis all cause such primary ST–T-wave changes. Primary and secondary T-wave changes may coexist. For example, T-wave inversions in the right precordial leads with left bundle branch block or in the left precordial leads with right bundle branch block may be important markers of underlying ischemia or other abnormalities. A distinctive abnormality simulating right bundle branch block with ST-segment elevations in the right chest leads is seen with the Brugada pattern **(Chap. 250)**.

Partial blocks (fascicular or "hemiblocks") in the left bundle system (left anterior or posterior fascicular blocks) generally do not prolong the QRS duration substantially but instead are associated with shifts in the frontal plane QRS axis (leftward or rightward, respectively). Left anterior fascicular block (QRS axis more negative than –45°) is probably the most common cause of marked left axis deviation in adults. In contrast, left posterior fascicular block (QRS axis more rightward than +110–120°) is extremely rare as an isolated finding and requires exclusion of other factors causing right axis deviation mentioned earlier. Intraventricular conduction delays also can be caused by extrinsic (toxic) factors that slow ventricular conduction, particularly hyperkalemia or drugs (e.g., class 1 antiarrhythmic agents, tricyclic antidepressants, phenothiazines). Prolongation of QRS duration does not necessarily indicate a conduction delay but may be due to *preexcitation* of the ventricles via a bypass tract, as in Wolff-Parkinson-White (WPW) patterns **(Chap. 244)** and related variants.

MYOCARDIAL ISCHEMIA AND INFARCTION

(See also Chap 269) The ECG is central to the diagnosis of acute and chronic ischemic heart disease. Ischemia exerts complex time-dependent effects on the electrical properties of myocardial cells. Severe, acute ischemia lowers the resting membrane potential and shortens the duration of the action potential. Such changes cause a voltage gradient between normal and ischemic zones. As a consequence, current flows between those regions. These currents of injury are represented on the surface ECG by deviation of the ST segment **(Fig. 235-11)**. When the acute ischemia is *transmural*, the ST vector usually is shifted in the direction of the outer (epicardial) layers, producing ST elevations and sometimes, in the earliest stages of ischemia, tall, positive so-called hyperacute T waves over the ischemic zone. With ischemia confined primarily to the *subendocardium*, the ST vector typically shifts toward the subendocardium and ventricular cavity, so that overlying (e.g., anterior precordial) leads show ST-segment depression (with ST elevation in lead aVR). Multiple factors affect the amplitude of acute ischemic ST deviations. Profound ST elevation or depression in multiple leads usually indicates very severe ischemia. From a clinical viewpoint, the division of acute myocardial infarction into ST-segment elevation and non-ST elevation types is useful since the consistent efficacy of emergency (minutes to hours) reperfusion therapy is limited to the former group; the evolving indications for acute reperfusion therapy in non-ST elevation MI are a focus of intensive investigation **(see Chap. 268)**. Takostubo syndrome may exactly simulate the patterns of STEMI or non-STEMI **(Chap. 266)**.

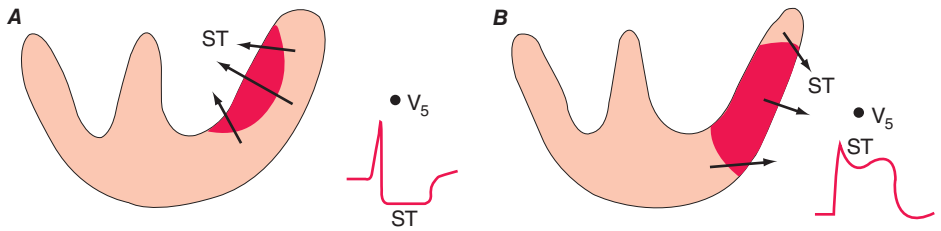

FIGURE 235-11 Acute ischemia causes a current of injury. With predominant subendocardial ischemia (***A***), the resultant ST vector will be directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore will record ST depression. With ischemia involving the outer ventricular layer (***B***) (transmural or epicardial injury), the ST vector will be directed outward. Overlying leads will record ST elevation.

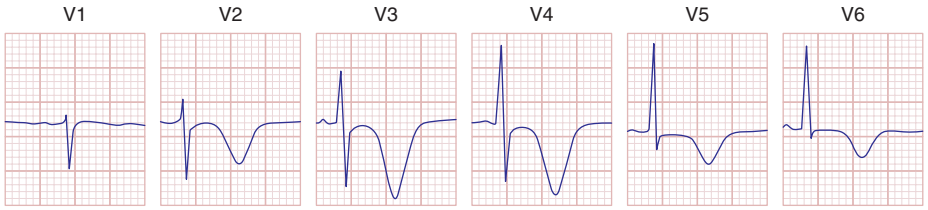

FIGURE 235-12 Severe anterior wall ischemia (with or without infarction) may cause prominent T-wave inversions in the precordial leads and in leads I and aVL. This pattern (sometimes referred to as Wellens T waves) is usually associated with a high-grade stenosis of the left anterior descending coronary artery.

The ECG leads are usually more helpful in localizing regions of ST elevation than non-ST elevation ischemia. For example, acute transmural anterior (including apical and lateral) wall ischemia is reflected by ST elevations or increased T-wave positivity in one or more of the precordial leads (V_1–V_6) and leads I and aVL. Inferior wall ischemia produces changes in leads II, III, and aVF. "Posterior" wall ischemia (usually associated with lateral or inferior involvement) may be indirectly recognized by *reciprocal* ST depressions in leads V_1 to V_3 (thus constituting an ST elevation "equivalent" acute coronary syndrome). Right ventricular ischemia usually produces ST elevations in right-sided chest leads (Fig. 235-5). When ischemic ST elevations occur as the earliest sign of acute infarction, they typically are followed within a period ranging from hours to days by evolving T-wave inversions and often by Q waves occurring in the same lead distribution. Reversible transmural ischemia, for example, due to coronary vasospasm (Prinzmetal's angina) may cause transient ST-segment elevations without development of Q waves. Depending on the severity and duration of ischemia, the ST elevations may resolve completely in minutes or be followed by T-wave inversions that persist for hours or even days. Patients with ischemic chest pain who present with deep T-wave inversions in multiple precordial leads (e.g., V_1–V_4, I, and aVL) with or without cardiac enzyme elevations typically have severe obstruction in the left anterior descending coronary artery **(Fig. 235-12)**.

With infarction, depolarization (QRS) changes often accompany repolarization (ST-T) abnormalities. Necrosis of sufficient myocardial tissue may lead to decreased R-wave amplitude or abnormal Q waves (even in the absence of transmural ischemia) in the anterior or inferior leads **(Fig. 235-13)**. Abnormal Q waves were once considered markers of transmural myocardial infarction, whereas subendocardial infarcts were thought not to produce Q waves. However, careful ECG-pathology correlative studies have indicated that transmural infarcts may occur without Q waves and that subendocardial (nontransmural) infarcts sometimes may be associated with Q waves. Therefore, evolving or chronic infarcts are more appropriately classified as "Q-wave" or "non-Q-wave" **(Chap. A7)**. Loss of depolarization forces due to posterior or lateral infarction may cause reciprocal increases in R-wave amplitude in leads V_1 and V_2 without diagnostic Q waves in any of the conventional leads. (Additional leads V7-V9 may show acute changes.) In the weeks and months after infarction, these ECG changes may persist or begin to resolve. Complete normalization of the ECG after Q-wave infarction is uncommon but may occur, particularly with smaller infarcts. In contrast, ST-segment elevations that persist for several weeks or more after a Q-wave infarct usually correlate with a severe underlying wall motion disorder, although not necessarily a frank ventricular aneurysm.

The ECG has important limitations in both sensitivity and specificity in the diagnosis of ischemic heart disease. Although a single normal ECG does not exclude ischemia or even acute infarction, a normal ECG *throughout* the course of an acute infarct is distinctly uncommon. Prolonged chest pain without diagnostic ECG changes therefore should always prompt a careful search for other noncoronary causes of chest pain **(Chap. 11)**. Furthermore, the diagnostic changes of acute or evolving ischemia are often masked by the presence of left bundle branch block, electronic ventricular pacemaker patterns, and Wolff-Parkinson-White preexcitation. However, clinicians continue to overdiagnose ischemia or infarction based on the presence of ST-segment elevations or depressions; T-wave inversions; tall, positive T waves; or Q waves *not* related to ischemic heart disease (pseudoinfarct patterns).

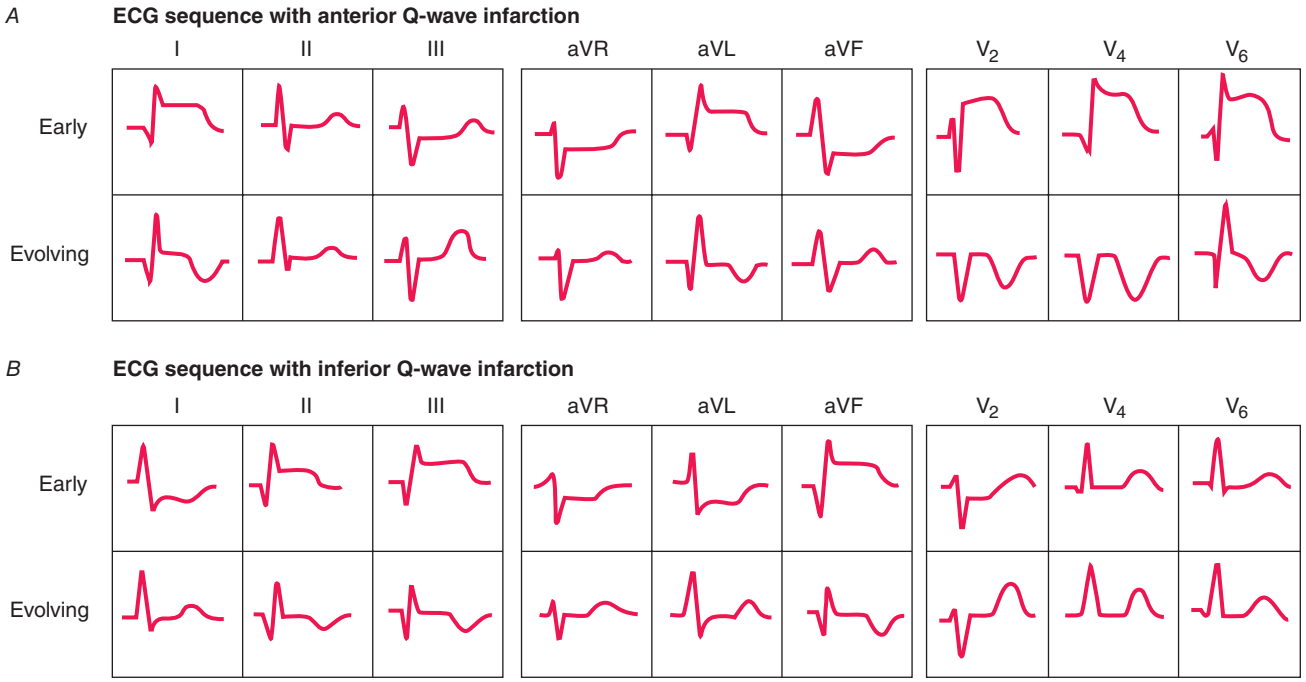

FIGURE 235-13 Sequence of depolarization and repolarization changes with (***A***) acute anterior and (***B***) acute inferior wall Q-wave infarctions. With anterior infarcts, ST elevation in leads I and aVL and the precordial leads may be accompanied by reciprocal ST depressions in leads II, III, and aVF. Conversely, acute inferior (or posterolateral) infarcts may be associated with reciprocal ST depressions in leads V_1 to V_3. *(After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)*

TABLE 235-1 Differential Diagnosis of ST-Segment Elevations

Ischemia/myocardial infarction
Noninfarction, transmural ischemia (Prinzmetal's angina, and probably Takotsubo syndrome, which may also exactly simulate classical acute infarction)
Acute myocardial infarction
Postmyocardial infarction (ventricular aneurysm pattern)
Acute pericarditis
Normal variants (including benign "early repolarization" patterns)
Left ventricular hypertrophy/left bundle branch block[a]
Other (rarer)
Acute pulmonary embolism[a]
Brugada patterns (right bundle branch block–like pattern with ST elevations in right precordial leads)[a]
Class 1C antiarrhythmic drugs[a]
DC cardioversion
Hypercalcemia[a]
Hyperkalemia[a]
Hypothermia (J [Osborn] waves)
Nonischemic myocardial injury
Myocarditis
Tumor invading left ventricle
Trauma to ventricles

[a]Usually localized to V_1–V_2 or V_3.

Source: Modified from AL Goldberger et al: *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 9th ed. Philadelphia, Elsevier/Saunders, 2017.

For example, ST-segment elevations simulating ischemia may occur with acute pericarditis or myocarditis, as a normal variant (including the typical "early repolarization" pattern), or in a variety of other conditions **(Table 235-1)**. Similarly, tall T waves do not invariably represent hyperacute ischemic changes but may also be caused by normal variants, hyperkalemia, cerebrovascular injury, among other causes.

ST-segment elevations and tall, positive T waves are common findings in leads V_1 and V_2 in left bundle branch block or left ventricular hypertrophy in the absence of ischemia. The differential diagnosis of Q waves includes physiologic or positional variants, ventricular hypertrophy, acute or chronic noncoronary myocardial injury, hypertrophic cardiomyopathy, and ventricular conduction disorders. Digoxin, ventricular hypertrophy, hypokalemia, and a variety of other factors may cause ST-segment depression mimicking subendocardial ischemia. Prominent T-wave inversion may occur with ventricular hypertrophy, cardiomyopathies, myocarditis, and cerebrovascular injury (particularly intracranial bleeds), among others causes.

METABOLIC FACTORS AND DRUG EFFECTS

A variety of metabolic abnormalities and pharmacologic agents alter the ECG and, in particular, causing changes in repolarization (ST-T-U) and sometimes QRS prolongation. Certain life-threatening electrolyte disturbances may be diagnosed initially and monitored from the ECG. *Hyperkalemia* produces a sequence of changes **(Fig. 235-14)**, usually beginning with narrowing and peaking (tenting) of the T waves. Further elevation of extracellular K^+ leads to AV conduction disturbances, diminution in P-wave amplitude, and widening of the QRS interval. Severe hyperkalemia eventually causes cardiac arrest with a slow sinusoidal type of mechanism ("sine-wave" pattern) followed by asystole. *Hypokalemia* **(Fig. 235-15)** prolongs ventricular repolarization, often with prominent U waves. Prolongation of the QT interval is also seen with drugs that increase the duration of the ventricular action potential: class 1A antiarrhythmic agents and related drugs (e.g., quinidine, disopyramide, procainamide, tricyclic antidepressants, phenothiazines) and class III agents (e.g., amiodarone [Fig. 235-15], dofetilide, sotalol, ibutilide). Systemic *hypothermia* (Fig. 235-15) also prolongs repolarization, usually with a distinctive convex elevation of the J point (Osborn wave). Marked QT prolongation, sometimes with deep, wide T-wave inversions, may occur with intracranial bleeds, particularly subarachnoid hemorrhage ("CVA T-wave" pattern) (Fig. 235-15). *Hypocalcemia* typically prolongs the QT interval (ST portion), whereas *hypercalcemia* shortens it **(Fig. 235-16)**. Digitalis glycosides also shorten the QT interval, often with a characteristic "scooping" of the ST–T-wave complex (*digitalis effect*).

NON-SPECIFIC ST-T CHANGES AND LOW QRS VOLTAGE

Many other factors are associated with ECG changes, particularly alterations in ventricular repolarization. T-wave flattening, minimal T-wave inversions, or slight ST-segment depression ("nonspecific ST–T-wave changes") may occur with a variety of electrolyte and acid-base disturbances, infectious or inflammatory processes, central nervous system disorders, endocrine abnormalities, many drugs, ischemia, hypoxia, and virtually any type of cardiopulmonary abnormality, in addition to physiologic changes (e.g., with posture or with meals). Low QRS voltage is arbitrarily defined as peak-to-trough QRS amplitudes of ≤5 mm in the six limb leads and/or ≤10 mm in the chest leads. Multiple factors may be responsible. Among the most serious include pericardial **(Fig. 235-17)** or pleural effusions, chronic obstructive pulmonary disease, infiltrative cardiomyopathies, and anasarca.

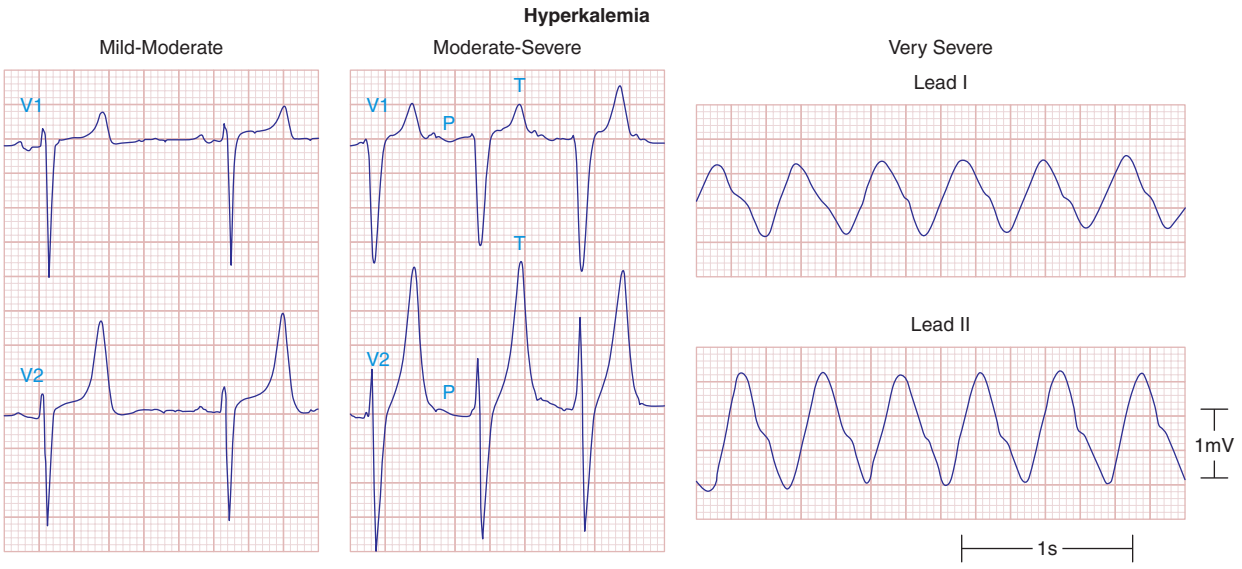

FIGURE 235-14 The earliest ECG change with hyperkalemia is usually peaking ("tenting") of the T waves. With further increases in the serum potassium concentration, the QRS complexes widen, the P waves decrease in amplitude and may disappear, and finally a sine-wave pattern leads to asystole unless emergency therapy is given. *(After AL Goldberger et al: Goldberger's Clinical Electrocardiography: A Simplified Approach, 9th ed. Philadelphia, Elsevier/Saunders, 2017.)*

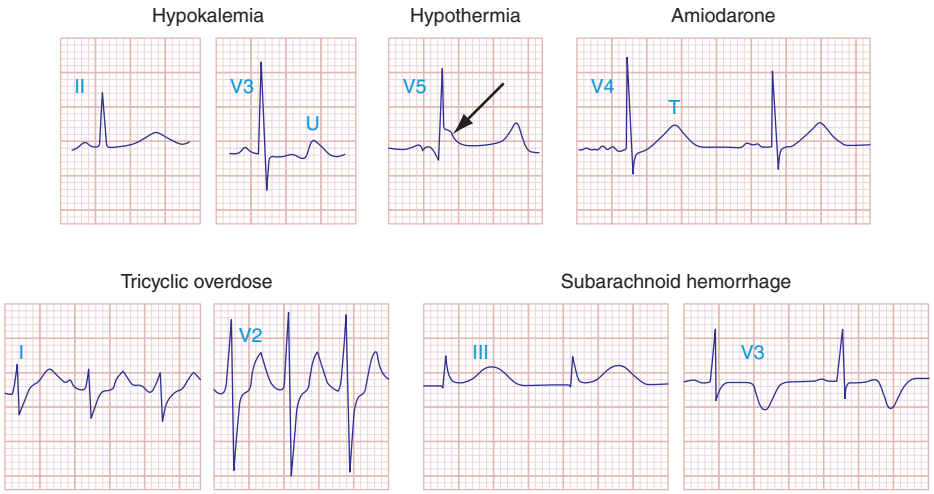

FIGURE 235-15 A variety of metabolic derangements, drug effects, and other factors may prolong ventricular repolarization with QT prolongation or prominent U waves. Prominent repolarization prolongation, particularly if due to hypokalemia, inherited "channelopathies," or certain pharmacologic agents, indicates increased susceptibility to *torsades des pointes* ventricular tachycardia **(Chap. 249)**. Marked systemic hypothermia is associated with a distinctive convex "hump" at the J point (Osborn wave, *arrow*) due to altered ventricular action potential characteristics. Note QRS and QT prolongation along with sinus tachycardia in the case of tricyclic antidepressant overdose.

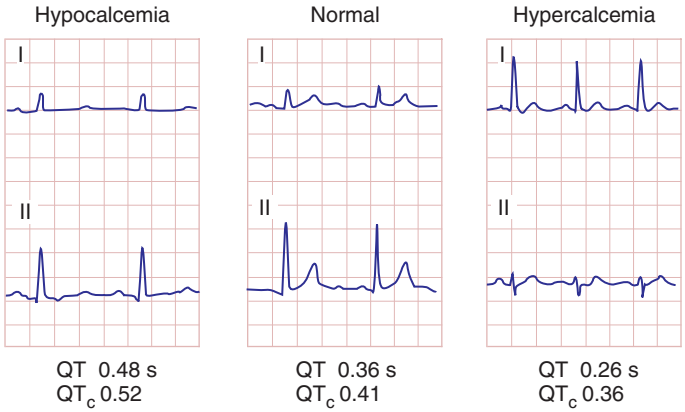

FIGURE 235-16 Prolongation of the Q-T interval (ST-segment portion) is typical of hypocalcemia. Hypercalcemia may cause abbreviation of the ST segment and shortening of the QT interval.

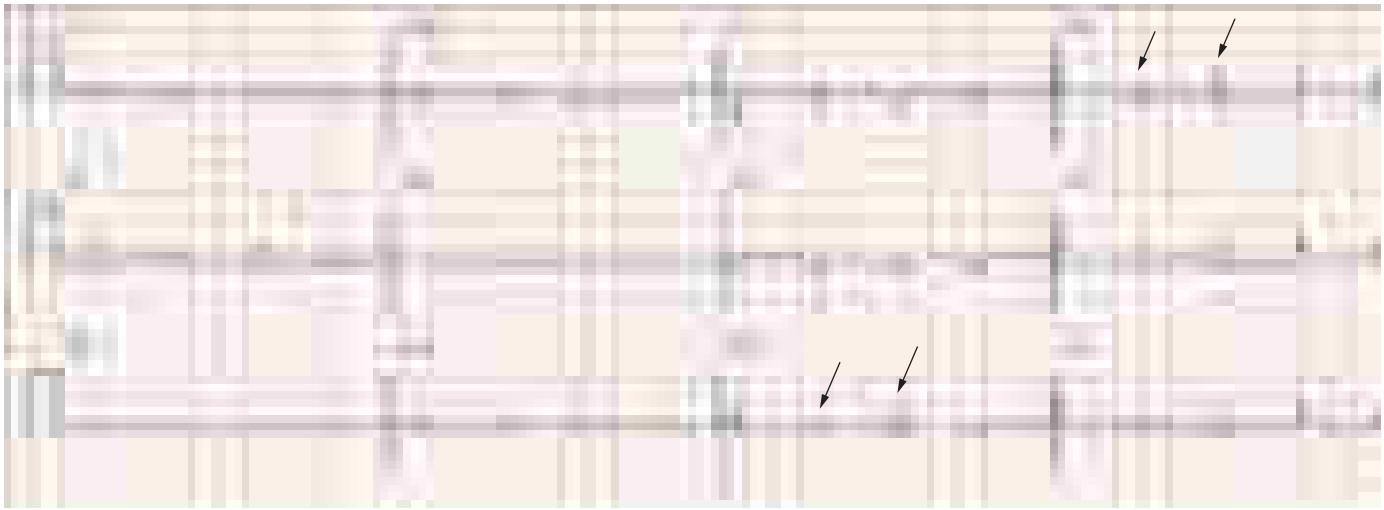

FIGURE 235-17 Classic triad of findings for pericardial effusion with cardiac tamponade: (1) sinus tachycardia; (2) low QRS voltages; and (3) electrical alternans (best seen in leads V_3 and V_4 in this case; *arrows*). This triad is highly specific for pericardial effusion, usually with tamponade physiology, but of limited sensitivity. *(Adapted from LA Nathanson et al: ECG Wave-Maven. http://ecg.bidmc.harvard.edu.)*

ELECTRICAL ALTERNANS

Electrical alternans—a beat-to-beat alternation in one or more components of the ECG signal—is a common type of nonlinear cardiovascular response to a variety of hemodynamic and electrophysiologic perturbations. Total electrical alternans (P-QRS-T) with sinus tachycardia is a relatively specific sign of pericardial effusion, usually with cardiac tamponade (Fig. 235-17). In contrast, pure repolarization (ST-T or U wave) alternans is a sign of electrical instability and may precede ventricular tachyarrhythmias.

CLINICAL INTEPRERATION OF THE ECG

Accurate analysis of ECGs requires thoroughness and care. The patient's age, gender, and clinical status should always be taken into account. Many mistakes in ECG interpretation are errors of omission. Therefore, a systematic approach is essential. The following 14 points should be analyzed carefully in every ECG: (1) standardization (calibration) and technical features (including lead placement and artifacts), (2) rhythm, (3) heart rate, (4) PR interval/AV conduction, (5) QRS interval, (6) QT/QT_c intervals, (7) mean QRS electrical axis, (8) P waves, (9) QRS voltages, (10) precordial R-wave progression, (11) abnormal Q waves, (12) ST segments, (13) T waves, and (14) U waves. Comparison with any previous ECGs is invaluable.

COMPUTERIZED ELECTROCARDIOGRAPHY

Computerized systems are widely used for immediate retrieval of thousands of ECG records. Computer analysis of ECGs still has major limitations and, therefore, should not be accepted without careful clinician review.

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236 Noninvasive Cardiac Imaging: Echocardiography, Nuclear Cardiology, and Magnetic Resonance/Computed Tomography Imaging

Marcelo F. Di Carli, Raymond Y. Kwong, Scott D. Solomon

The ability to image the heart and blood vessels noninvasively has been one of the greatest advances in cardiovascular medicine since the development of the electrocardiogram (ECG). Cardiac imaging complements history taking and physical examination, blood and laboratory testing, and exercise testing in the diagnosis and management of most diseases of the cardiovascular system. Modern cardiovascular imaging consists of echocardiography (cardiac ultrasound), nuclear scintigraphy including positron emission tomography (PET) imaging, magnetic resonance imaging (MRI), and computed tomography (CT). These studies, often used in conjunction with exercise testing, can be used independently or in concert depending on the specific diagnostic needs. In this chapter, we review the principles of each of these modalities and the utility and relative benefits of each for the most common cardiovascular diseases.

PRINCIPLES OF MULTIMODALITY CARDIAC IMAGING

ECHOCARDIOGRAPHY

Echocardiography uses high-frequency sound waves (ultrasound) to penetrate the body, reflect from relevant structures, and generate an image. The basic physical principles of echocardiography are identical to other types of ultrasound imaging, although the hardware and software are optimized for evaluation of cardiac structure and function. Early echocardiography machines displayed "M-mode" echocardiograms in which a single ultrasound beam was displayed over time on a moving sheet of paper **(Fig. 236-1, *left panel*)**. Modern echocardiographic machinery uses phased array transducers that contain up to 512 elements and emit ultrasound in sequence. The reflected ultrasound is then sensed by the receiving elements. A "scan converter" uses information about the timing and magnitude of the reflected ultrasound to generate an image **(Fig. 236-1, *right panel*)**. This sequence happens repeatedly in "real time" to generate moving images with frame rates that are typically greater than 30 frames per second, but can exceed 100 frames per second. The gray scale of the image features indicates the intensity of the reflected ultrasound; fluid or blood appears black, and highly reflective structures, such as calcifications on cardiac valves or the pericardium, appear white. Tissues such as myocardium appear more gray, and tissues such as muscle display a unique speckle pattern. Although M-mode echocardiography has largely been supplanted by two-dimensional (2D) echocardiography, it is still used because of its high temporal resolution and accuracy for making linear measurements.

The spatial resolution of ultrasound is dependent on the wavelength: the smaller the wavelength and the higher the frequency of the ultrasound beam, the greater are the spatial resolution and ability to discern small structures. Increasing the frequency of ultrasound will increase resolution but at the expense of reduced penetration. Higher frequencies can be used in pediatric imaging or transesophageal echocardiography where the transducer can be much closer to the structures being interrogated, and this is a rationale for using transesophageal echocardiography to obtain higher quality images.

Three-dimensional ultrasound transducers use a waffle-like matrix array transducer and receive a pyramidal data sector. Three-dimensional echocardiography is being increasingly used for

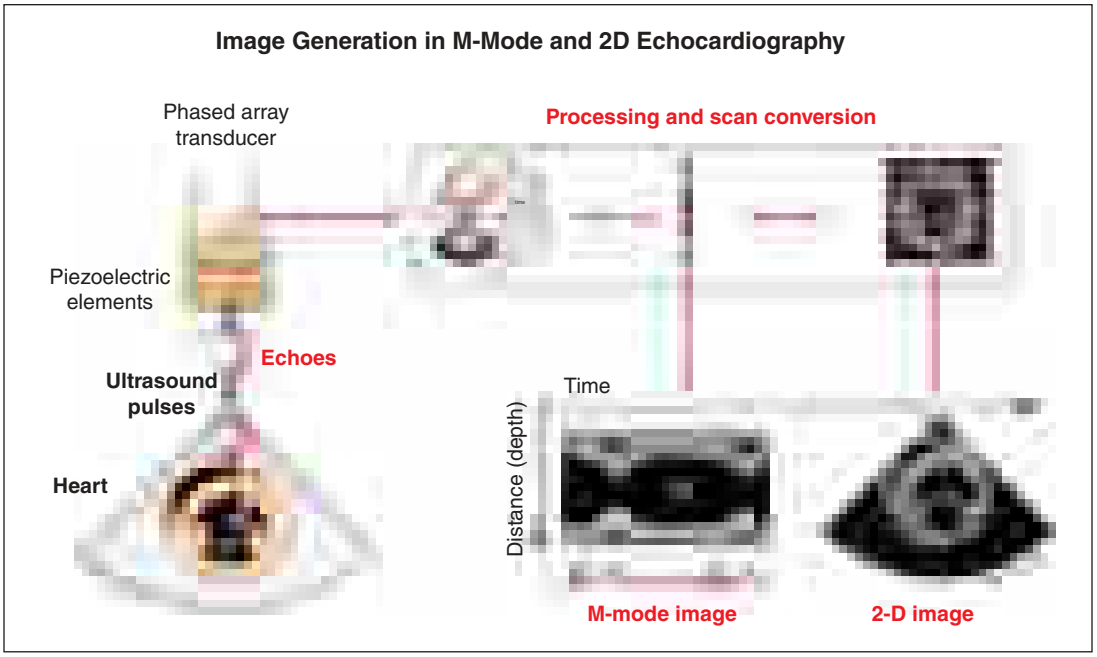

FIGURE 236-1 Principle of image generation in two-dimensional (2D) echocardiography. An electronically steerable phased-array transducer emits ultrasound from piezoelectric elements, and returning echoes are used to generate a 2D image (*right*) using a scan converter. Early echocardiography machines used a single ultrasound beam to generate an "M-mode" echocardiogram (see text), although modern equipment generates M-mode echocardiograms digitally from the 2D data. LV, left ventricle.

assessment of congenital heart disease and valves, although current image quality lags behind 2D ultrasound **(Fig. 236-2)**.

In addition to the generation of 2D images that provide information about cardiac structure and function, echocardiography can be used to interrogate blood flow within the heart and blood vessels by using the Doppler principle to ascertain the velocity of blood flow. When ultrasound emitted from a transducer reflects off red blood cells that are moving toward the transducer, the reflected ultrasound will return at a slightly higher frequency than emitted; the opposite is true when flow moves away from the transducer. That frequency difference, termed the Doppler shift, is directly related to the velocity of the flow of the red blood cells. The velocity of blood flow between two chambers will be directly related to the pressure gradient between those chambers. A modified form of the Bernoulli equation,

$$p = 4v^2$$

where p = the pressure gradient and v = the velocity of blood flow in meters per second, can be used to calculate this pressure gradient in the majority of clinical circumstances. This principle can be used to determine the pressure gradient between chambers and across valves and has become central to the quantitative assessment of valvular heart disease.

There are three types of Doppler ultrasound that are typically used in standard echocardiographic examinations: spectral Doppler, which consists of both pulsed wave Doppler and continuous wave Doppler, and color flow Doppler. Both types of spectral Doppler will display a waveform representing the velocity of blood flow, with time on the horizontal axis and velocity on the vertical axis. Pulsed wave Doppler is used to interrogate relatively low velocity flow and has the ability to determine blood flow velocity at a particular location within the heart. Continuous wave Doppler is used to assess high-velocity flow, but can only identify the highest velocity in a particular direction and cannot interrogate the velocity at a specific depth location. Both of these techniques can only accurately assess velocities that are in the direction of the ultrasound scan lines, and velocities that are at an angle to the direction of the ultrasound beam will be underestimated. Color flow Doppler is a form of pulsed wave Doppler in which the velocity of blood flow is color encoded according to a scale and superimposed on a 2D grayscale image in real time, giving the appearance of real-time flow within the heart. The Doppler principle can also be used to assess the velocity of myocardial motion, which is a sensitive way to assess myocardial function **(Fig. 236-3)**. A standard full transthoracic echocardiographic examination consists of a series of 2D views made up of different imaging planes from various scanning locations and spectral and color flow Doppler assessment.

Transesophageal echocardiography is a form of echocardiography in which the transducer is located on the tip of an endoscope that can be inserted into the esophagus. This procedure allows closer, less obstructed views of cardiac structures, without having to penetrate through chest wall, muscle, and ribs. Because less penetration is needed, a higher frequency probe can be used, and image quality and spatial resolution are generally higher than with standard transthoracic imaging, particularly for structures that are more posterior. Transesophageal echocardiography has become the test of choice for assessment of small lesions in the heart such as valvular vegetations, especially in the setting of a prosthetic valve disease, and intracardiac thrombi, including assessment of the left atrial appendage, which is difficult to visualize with standard transthoracic imaging, and for assessment of congenital abnormalities. Transesophageal echocardiography requires both topical and systemic anesthesia, generally conscious sedation, and carries

FIGURE 236-2 Three-dimensional (3D) probe and 3D image.

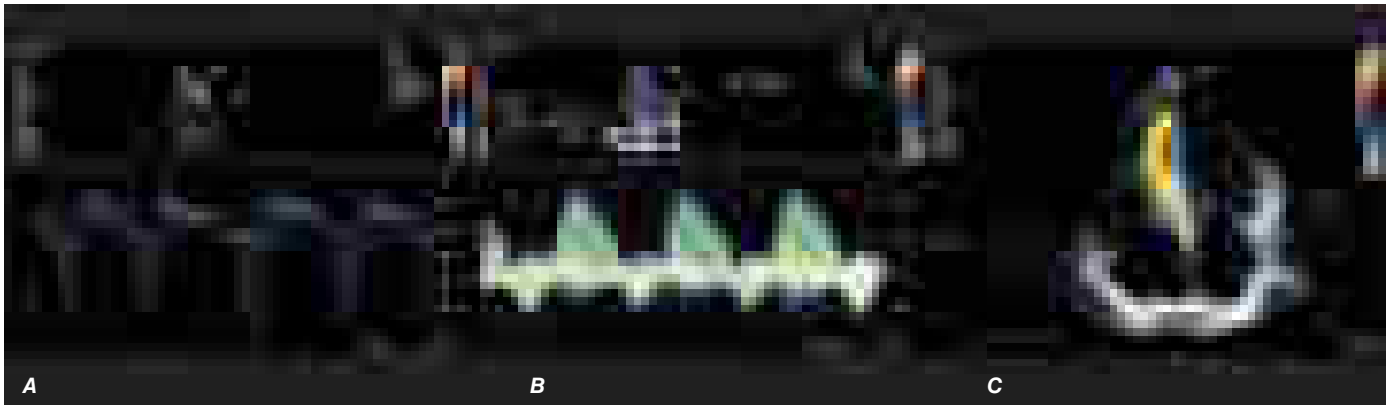

FIGURE 236-3 Three types of Doppler ultrasound. ***A*** and ***B.*** Pulsed and continuous wave Doppler waveforms with time on horizontal axis and velocity of blood flow on vertical axis. ***C.*** Color flow Doppler, where velocities are encoded by colors according to scale on right side of screen and superimposed on a two-dimensional grayscale image.

additional risks such as potential damage to the esophagus, including the rare possibility of perforation, aspiration, and anesthesia-related complications. Patients generally need to give consent for transesophageal echocardiography and be monitored during and subsequent to the procedure. Transesophageal echocardiography can be carried out in intubated patients and is routinely used for intraoperative monitoring during cardiac surgery.

Stress echocardiography is routinely used to assess cardiac function during exercise and can be used to identify myocardial ischemia or to assess valvular function under exercise conditions. Stress echocardiography is typically performed in conjunction with treadmill or bicycle exercise testing, but can also be performed using pharmacologic stress most typically with an intravenous infusion of dobutamine (see section on stress imaging below).

Whereas typical echocardiographic equipment is large, bulky, and expensive, small hand-held ultrasound equipment developed over the last decade now offers diagnostic quality imaging in a package small enough to be carried on rounds **(Fig. 236-4)**. These relatively inexpensive point-of-care devices currently lack full diagnostic capabilities but represent an excellent screening tool if used by an experienced operator. As these units become even smaller and less expensive, they are being increasingly used not just by cardiologists, but also by emergency medicine physicians, intensivists, anesthesiologists, and internists.

RADIONUCLIDE IMAGING

Radionuclide imaging techniques are commonly used for the evaluation of patients with known or suspected coronary artery disease (CAD), including for initial diagnosis and risk stratification as well as the assessment of myocardial viability. These techniques use small amounts of radiopharmaceuticals **(Table 236-1)**, which are injected intravenously and trapped in the heart and/or vascular cells. Radioactivity within the heart and vasculature decays by emitting gamma rays. The interaction between these gamma rays and the detectors in specialized scanners (single-photon emission computed tomography [SPECT] and PET) creates a scintillation event or light output, which can be captured by digital recording equipment to form an image of the heart and vasculature. Like CT and MRI, radionuclide images also generate tomographic (three-dimensional) views of the heart and vasculature.

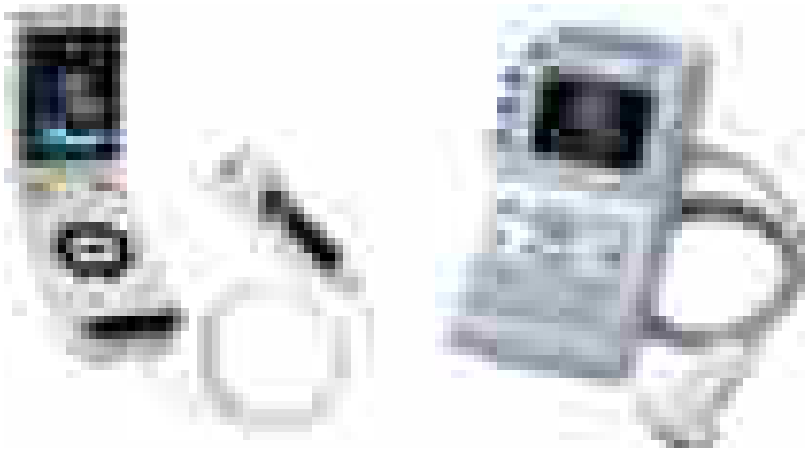

FIGURE 236-4 Two examples of hand-held ultrasound equipment: V-Scan (General Electric, *left*) and Sonosite (*right*).

Radiopharmaceuticals Used in Clinical Imaging

Table 236-1 summarizes the most commonly used radiopharmaceuticals in clinical SPECT and PET imaging.

Protocols for Stress Myocardial Perfusion Imaging Both exercise and pharmacologic stress can be used for myocardial perfusion imaging. Exercise stress is generally preferred because it is physiologic and provides additional clinically important information (i.e., clinical and hemodynamic responses, ST-segment changes, exercise duration, and functional status). However, submaximal effort will lower the sensitivity of the test and should be avoided, especially if the test is requested for initial diagnosis of CAD. In patients who are unable to exercise or who exercise submaximally, pharmacologic stress offers an adequate alternative to exercise stress testing. Pharmacologic stress can be accomplished either with coronary vasodilators, such as adenosine, dipyridamole, or regadenoson, or β_1-receptor agonists, such as dobutamine. For patients unable to exercise, vasodilators are the most commonly used stressors in combination with myocardial perfusion imaging. Dobutamine is a potent β_1-receptor agonist that increases myocardial oxygen demand by augmenting contractility, heart rate, and blood pressure similar to exercise. It is generally used as an alternative to vasodilator stress in patients with chronic pulmonary disease, in whom vasodilators may be contraindicated. Dobutamine is also commonly used as a pharmacologic alternative to stress testing in stress echocardiography.

Myocardial Perfusion and Viability Imaging Protocols Imaging protocols are tailored to the individual patient based on the clinical question, patient's risk, ability to exercise, body mass index, and other factors.

For SPECT imaging, technetium-99m (^{99m}Tc)-labeled tracers are the most commonly used imaging agents because they are associated with the best image quality and the lowest radiation dose to the patient **(Fig. 236-5)**. Selection of the protocol (stress-only, single-day, or 2-day) depends on the patient and clinical question. After intravenous injection, myocardial uptake of ^{99m}Tc-labeled tracers is rapid (1–2 min). After uptake, these tracers become trapped intracellularly in mitochondria and show minimal change over time. This is why ^{99m}Tc tracers can be helpful in patients with chest pain of unclear etiology

TABLE 236-1 Radiopharmaceuticals for Clinical Nuclear Cardiology

RADIOPHARMACEUTICAL	IMAGING TECHNIQUE	PHYSICAL HALF-LIFE	APPLICATION
Technetium-99m sestamibi	SPECT	6 h	Myocardial perfusion imaging
Technetium-99m tetrofosmin	SPECT	6 h	Myocardial perfusion imaging
Thalium-201	SPECT	72 h	Myocardial perfusion imaging
Iodine-123 metaiodobenzylguanidine (MIBG)	SPECT	13 h	Cardiac sympathetic innervation
Rubidium-82	PET	76 s	Myocardial perfusion imaging
^{13}N-ammonia	PET	10 min	Myocardial perfusion imaging
^{18}*F-fluorodeoxyglucose*	PET	110 min	Myocardial viability and inflammation imaging

Abbreviations: PET, positron emission tomography; SPECT, single-photon emission computed tomography.

occurring at rest, because patients can be injected while having chest pain and imaged some time later after symptoms subside. Indeed, a normal myocardial perfusion study following a rest injection in a patient with active chest pain effectively excludes myocardial ischemia as the cause of chest pain (high negative predictive value). While used commonly in the past for perfusion imaging, thallium-201 protocols are now rarely used because they are associated with a higher radiation dose to the patient.

PET myocardial perfusion imaging is an alternative to SPECT and is associated with improved diagnostic accuracy and lower radiation dose to patients (Table 236-1). The ultra-short half-life of some PET radiopharmaceuticals in clinical use (e.g., rubidium-82) is the primary reason why imaging is generally combined with pharmacologic stress, as opposed to exercise. However, exercise is possible for relatively longer lived radiotracers (e.g., ^{13}N-ammonia). PET imaging protocols are typically faster than SPECT, but more expensive. In comparison to SPECT, PET has improved spatial and contrast resolution and provides absolute measures of myocardial perfusion (in mL/min per gram of tissue), thereby providing the patients' regional and global coronary flow reserve. The latter helps improve diagnostic accuracy and risk stratification, especially in obese patients, women, and higher risk individuals (e.g., diabetes mellitus) **(Fig. 236-6)**. Contemporary PET and SPECT scanners are combined with a CT scanner (so-called *hybrid PET/CT* and *SPECT/CT*). CT is used primarily to guide patient positioning in the field of view and for correcting inhomogeneities in radiotracer distribution due to attenuation by soft tissues (so-called *attenuation correction*). However, it can also be used to obtain diagnostic data including coronary artery calcium (CAC) score and/or CT coronary angiography (discussed below).

For the evaluation of myocardial viability in patients with ischemic cardiomyopathy, myocardial perfusion imaging (with SPECT or PET) is usually combined with metabolic imaging (i.e., fluorodeoxyglucose [FDG] PET). In hospital settings lacking access to PET scanning, thallium-201 SPECT imaging is an excellent alternative.

CARDIAC COMPUTED TOMOGRAPHY

CT acquires images by passing a thin x-ray beam through the body at many angles to generate cross-sectional images. The x-ray transmission measurements are collected by a detector array and digitized into pixels that form an image. The grayscale information in individual pixels is determined by the attenuation of the x-ray beam along its path by tissues of different densities, referenced to the value for water

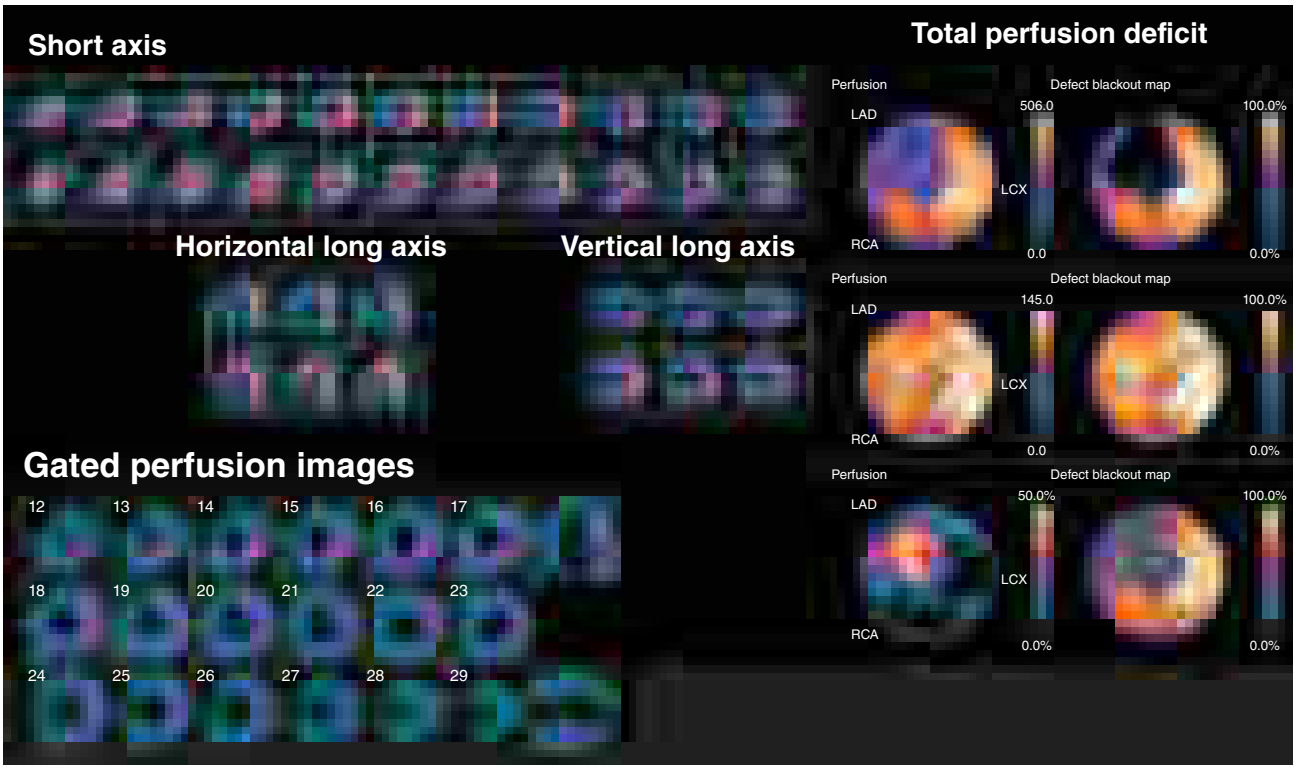

FIGURE 236-5 Tomographic stress (top of each pair) and rest myocardial perfusion images with technetium-99m sestamibi single-photon emission computed tomography imaging demonstrating a large perfusion defect throughout the anterior and anteroseptal walls. The *right panel* demonstrates the quantitative extent of the perfusion abnormality at stress (*top bull's-eye*), at rest (*middle bull's-eye*), and the extent of defect reversibility (*lower bull's-eye*). The *lower left panel* demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction.

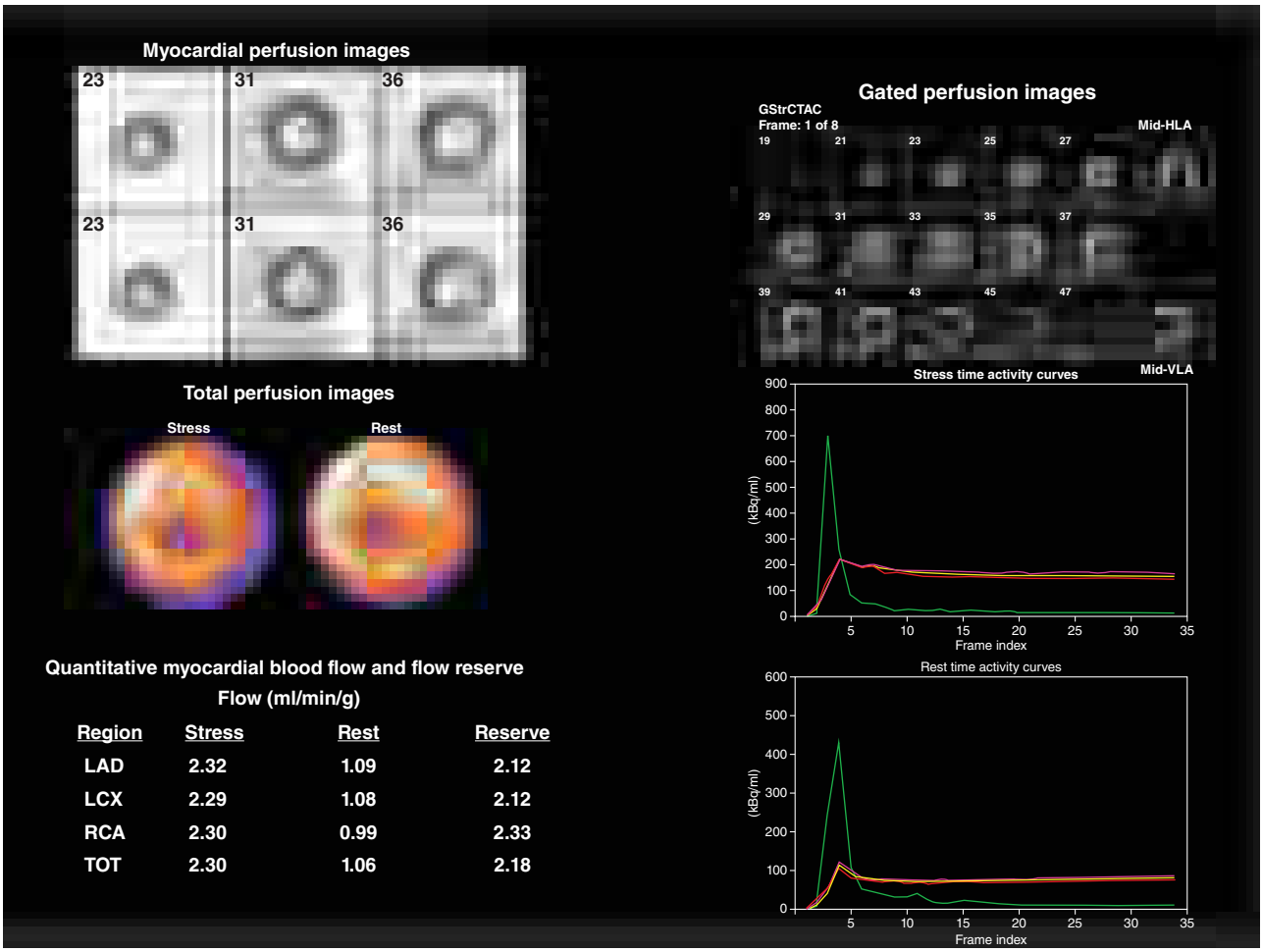

FIGURE 236-6 Multidimensional cardiac imaging protocol with positron emission tomography. The *left upper panel* demonstrates stress and rest short-axis images of the left and right ventricles demonstrating normal regional myocardial perfusion. The *middle panel* demonstrates the quantitative bull's-eye display to evaluate the extent and severity of perfusion defects. The *lower right panel* illustrates the time-activity curves for quantification of myocardial blood flow. The *right upper panel* demonstrates electrocardiogram-gated myocardial perfusion images from which one can determine the presence of regional wall motion abnormalities and calculate left ventricular volumes and ejection fraction. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TOT, total left ventricle.

in units known as Hounsfield units. In the resulting CT images, bone appears bright white, air is black, and blood and muscle show varying shades of gray. However, due to the limited contrast between cardiac chambers and vascular structures, iodinated contrast agents are necessary for most cardiovascular indications. Cardiac CT produces tomographic images of the heart and surrounding structures. With modern CT scanners, a three-dimensional dataset of the heart can be acquired in 5–15 s with submillimeter spatial resolution.

CT Calcium Scoring CT calcium scoring is the simplest application of cardiac CT and does not require administration of iodinated contrast. The presence of coronary artery calcification has been associated with increased burden of atherosclerosis and cardiovascular mortality. Coronary calcium is then quantified (e.g., Agatston score) and categorized as minimal (0–10), mild (10–100), moderate (100–400), or severe (>400) (Fig. 236-7). CAC scores are then normalized by age and gender and reported as percentile scores. Population-based studies in asymptomatic cohorts have reported high cardiac prognostic value of CT calcium score. With appropriate techniques, the radiation dose associated with CAC scanning is very low (~1–2 mSv).

CT Coronary Angiography Coronary CT angiography (CTA) is emerging as a viable alternative to

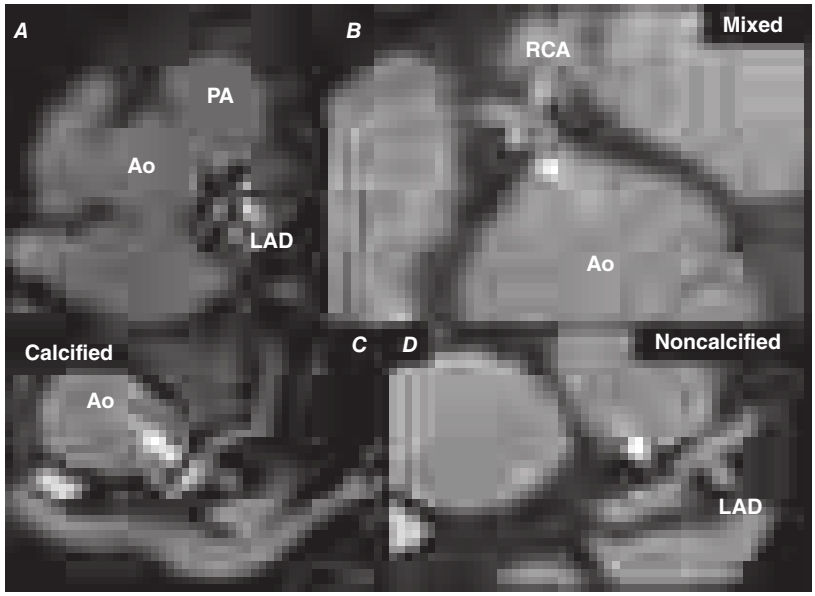

FIGURE 236-7 Examples of non-contrast- and contrast-enhanced coronary imaging with computed tomography (CT). ***A.*** Calcified coronary plaques in the distal left main and proximal left anterior descending coronary artery (LAD) in a noncontrast cardiac CT scan. Calcium deposits are dense and present as bright white structures on CT, even without contrast enhancement. ***B, C,*** and ***D.*** Different types of atherosclerotic plaques on contrast-enhanced CT scans. Importantly, noncalcified plaques are evident only on contrast-enhanced CT scans. AO, aorta; PA, pulmonary artery; RCA, right coronary artery.

invasive coronary angiography in selected patients. Imaging of the coronary arteries by CT is challenging because of their small luminal size and because of cardiac and respiratory motion. Respiratory motion can be reduced by breath-holding, and cardiac motion is best reduced by slowing the patient's heart rate, ideally to under 60 beats/min, using intravenous or oral beta blockade or other rate-lowering drugs. When performing a coronary CTA, image quality is further enhanced using sublingual nitroglycerin to enlarge the coronary lumen just prior to contrast injection. Imaging the whole-heart volume is synchronized to the administration of weight-based and appropriately timed intravenous iodinated contrast. Image acquisition is linked to the timing of the cardiac cycle through ECG triggering. The resulting images are then postprocessed using a three-dimensional workstation, which facilitates interpretation of the coronary anatomy and estimation of the severity of atherosclerosis (Fig. 236-7).

CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) imaging is based on imaging of protons in hydrogen, which is an advantage, given the abundance of water in the human body. When the body is placed inside a MRI scanner, protons in different tissues, such as in simple fluid or complex macromolecules such as fat or protein, interact with the magnetic field at their unique frequencies. A set of orthogonal gradient coils in the scanner is designed to locate protons spatially so that radiofrequency (RF) pulses of energy can be delivered to select imaging planes of interests. Once the RF pulses stop, the energy absorbed will be released, collected by the phased-array receiver coils placed on the patient's body surface, digitally recorded in a data matrix known as the K-space, then reconstructed into a magnetic resonance image. The large arrays of software methods of delivering RF pulses are known as pulse sequences which aim at extraction of different types of cardiac structural or physiologic information. In CMR, T1-weighted pulse sequences are most common and they assess cardiac structure and function, blood flow, and myocardial perfusion. T2-weighted and $T2^*$-weighted pulse sequences, on the other hand, evaluate myocardial edema and myocardial iron infiltration, respectively. Vector ECG-gating and repetitive patient breath-holding are used by convention to suppress cardiac and respiratory motions, respectively. However, with technical advent, rapid data collection algorithm and diaphragmatic position gating have eliminated the need for ECG-gating and breath-holding in challenging situations. A list of common pulse sequence used in CMR is shown in Table 236-2.

TABLE 236-2 Clinical Cardiac Magnetic Resonance Pulse Sequences and Their Application

PULSE SEQUENCE	KEY IMAGING INTERESTS
Cardiac Morphology	
Still frame imaging (black or bright blood)	Cardiac structures
Cardiac Function	
Cine imaging	Left ventricular volume and function
Cine myocardial tagging	Left ventricular deformation (strain)
Blood Flow Imaging	
Velocity-encoded phase contrast	Cardiac and great vessel flow
Stress Testing	
Myocardial perfusion imaging	Regional myocardial blood flow
Cine imaging	Regional wall motion
Myocardial Tissue Characterization	
Late gadolinium enhancement	Myocardial infarction and infiltrative disease
T2-weighted imaging	Myocardial edema
Iron content imaging	Myocardial iron infiltration
Magnetic Resonance Angiography	
Aorta, peripheral and coronary arteries	Luminal stenosis and vessel wall remodeling

ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

Echocardiography, CMR, and cardiac CT are all capable of assessing cardiac structure and function, although echocardiography is generally considered the primary imaging method for these assessments. Radionuclide imaging can also be used to assess left ventricular regional and global systolic function. Echocardiography is most often used to assess the size of all four chambers and thickness of ventricular walls, which are affected by both cardiac and systemic diseases.

The structure of the left ventricle is generally assessed by determining its volume and mass. Left ventricular volumes can be easily estimated from 2D echocardiography by using methods incorporating geometric assumptions. The accuracy of these echocardiographic methods is reduced when foreshortening of the imaging plane leads to underestimation of volumes. Moreover, these methods require accurate delineation of the endocardial border. In this regard, high-resolution tomographic techniques such as CMR or cardiac CT are more accurate for volumetric assessment. Three-dimensional (3D) echocardiography does not require any geometric assumptions about the left ventricle for quantification of volumes and ejection fraction. However, 3D echocardiographic imaging requires substantial expertise and currently is not widely used in practice.

Left ventricular dilatation is common to a number of cardiac diseases. For example, regional dysfunction secondary to myocardial infarction can ultimately lead to progressive ventricular dilatation or remodeling. Although dilatation often begins in the region affected by the infarction, subsequent compensatory dilatation can occur in remote myocardial regions as well. The presence of regional wall motion abnormalities associated with ventricular thinning (reflecting scar) in a coronary distribution is strongly suggestive of an ischemic etiology. Direct assessment of infarcted myocardium is possible with both CMR (evident as areas of late gadolinium enhancement [LGE]) and radionuclide imaging (as assessed by regional perfusion or metabolic defects at rest). CMR can be particularly useful in determining etiology of cardiomegaly and ventricular dysfunction, with LGE in coronary distributions being nearly pathognomonic for infarction **(Video 236-1)**.

More global ventricular dilatation is seen in cardiomyopathy and dilatation due to valvular heart disease. Idiopathic, nonischemic cardiomyopathies will typically result in global ventricular dilatation and dysfunction, with thinning of the walls. Patients with substantial ventricular dyssynchrony due to conduction abnormalities will have a typical pattern of contraction (e.g., delay of contraction of the lateral wall with left bundle branch block). As discussed later in this chapter, regurgitant lesions of either the mitral or aortic valves can lead to substantial ventricular dilatation, and assessment of ventricular size is integral in the evaluation and timing of surgical correction. Because changes in ventricular size are used clinically to determine which patients should undergo valve surgery, accurate assessment of changes in ventricular size is essential. Although serial echocardiography can provide these data, serial assessment by CMR may be more accurate when appreciation of subtle changes over time is important.

Left ventricular wall thickness and mass are also important measures of cardiac and systemic disease. The left ventricle will hypertrophy under any condition in which its afterload is increased, including conditions that obstruct outflow, such as aortic stenosis, hypertrophic cardiomyopathy, and subaortic membranes; in postcardiac aortic obstruction seen in coarctation; or in systemic conditions characterized by increased afterload, such as hypertension. The pattern of ventricular hypertrophy can change depending on the etiology. Aortic stenosis and hypertension are typically characterized by concentric hypertrophy, in which the ventricular walls thicken "concentrically" and cavity size is usually small. In volume overload conditions such as mitral or aortic regurgitation, there may be minimal increase in ventricular wall thickness, but substantial ventricular dilatation leads to marked increases in left ventricular mass.

Ventricular wall thickness can be measured and ventricular mass can be calculated by either echocardiography or CMR. Although radionuclide imaging and cardiac CT can also provide measures of

left ventricular mass, they are not generally used for this purpose. Although measurement of wall thickness with echocardiography is relatively straightforward and accurate, determining left ventricular mass by echocardiography requires using one of several formulas that takes into account both wall thickness and ventricular cavity dimensions. Assessment of left ventricular mass by CMR has the advantage of not requiring geometric assumptions and is thus more accurate than echocardiography.

ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC FUNCTION

Assessment of ejection fraction, or the percentage of blood ejected with each beat, has been the primary method to assess systolic function and is generally calculated by subtracting end-systolic volume from end-diastolic volume and dividing by end-diastolic volume. All cardiac imaging modalities can provide direct measurements of left ventricular ejection fraction (LVEF). As discussed above, tomographic techniques (e.g., CMR, CT, and radionuclide imaging) are generally more accurate and reproducible than echocardiography because there are no geometric assumptions. A LVEF of 55% or greater is generally considered normal, and an LVEF of 50–55% is considered in the low-normal range.

Newer methods to assess systolic function, such as myocardial strain or deformation imaging using speckle-tracking methods on echocardiography, or myocardial tagging, and more recently, feature tracking on CMR, can provide a more sensitive approach to detection of systolic dysfunction. Additional assessments based on these novel methods include assessment of myocardial twist and torsion. Although these techniques are not used routinely, they may be especially useful in certain conditions such as valvular heart disease and early detection of cardiotoxicity following chemotherapy and/or radiation therapy. In addition to estimation or calculation of ejection fraction, stroke volume can be assessed by any of the imaging methods, by subtracting the end-systolic volume from the end-diastolic volume, or by quantifying forward flows using echocardiographic Doppler methods or phase-contrast CMR imaging. They offer measures of systolic function other than LVEF.

ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography remains the primary method for clinical assessment of diastolic function. Recent advances in Doppler tissue imaging allow for accurate assessment of the velocity of myocardial wall motion by assessing the excursion of the mitral annulus in diastole. Mitral annular relaxation velocity, or E′, is inversely related to the time constant of relaxation, tau, and has been shown to have prognostic significance. Dividing the standard mitral inflow maximal velocity, E, by the mitral annular relaxation velocity yields E/E′, which has been shown to correlate with left ventricular filling pressures. The utility of standard E and A wave ratios for assessment of diastolic function has been questioned. Mitral deceleration time can be a useful measure if very short (<150 ms), suggesting restrictive physiology and severe diastolic dysfunction. Several grading methods for diastolic function have been proposed that take into account a number of diastolic parameters, including Doppler tissue-based relaxation velocities, pulmonary venous Doppler, and left atrial size **(Fig. 236-8)**. Diastolic function worsens with aging, and most diastolic parameters need to be adjusted for age.

ASSESSMENT OF RIGHT VENTRICULAR FUNCTION

Right ventricular size and function have been shown to be prognostically important in a variety of conditions, and can be assessed by echocardiography, CMR, CT, or radionuclide imaging methods. CMR is considered the most accurate noninvasive technique to evaluate the structure and ejection fraction of the right ventricle **(Video 236-2)**. Assessment of the right ventricle by echocardiography has generally been qualitative, owing in part to the unusual geometry of the right ventricle. However, several quantitative methods are available for assessment of right ventricular function, including fractional area change (FAC = [diastolic area – systolic area]/diastolic area), which has been shown to correlate with outcomes in heart failure and after myocardial infarction. Excursion of the tricuspid annulus (tricuspid annular plane systolic excursion, TAPSE) is another method to assess right ventricular function, although it is mostly used in research settings.

Abnormalities of right ventricular size and function are generally secondary to either diseases that affect the right ventricle intrinsically or disease in which the right ventricle responds to abnormalities elsewhere in the heart or pulmonary vasculature. Intrinsic diseases that affect the RV include congenital abnormalities, including hypoplastic right ventricle and arrhythmogenic right ventricular dysplasia, and acquired conditions, such as right ventricular infarction and infiltrative diseases. Right ventricular dilatation can occur due to both chronic and acute processes. Long-standing pulmonary hypertension or pulmonary outflow tract obstruction leads to right ventricular hypertrophy and ultimately dilatation. An acute process that can cause profound right ventricular dilatation and dysfunction is acute pulmonary embolism. In the setting of acute occlusion of a pulmonary artery or branch, an acute rise in pulmonary vascular resistance causes a previously normal right ventricle to dilate and fail due to the increased afterload. In acute pulmonary embolism, right ventricular dilatation and dysfunction are signs of substantial hemodynamic compromise and are associated with a marked increased risk of death. In addition to right ventricular dilatation, acute pulmonary embolism is often associated with a specific pattern of regional right ventricular dysfunction, commonly referred to as the McConnell sign, characterized by preservation of right ventricular wall motion in the basal and apical regions and dyskinesis in the region of the mid right ventricular free wall. This abnormality is highly specific for acute pulmonary embolism and is likely secondary to acute increases in right ventricular load.

Any disease that causes increased pulmonary vascular resistance can lead to right ventricular dilatation and dysfunction. For example, long-standing chronic obstructive pulmonary disease increases pulmonary vascular resistance and results in cor pulmonale. Acute pneumonia can cause findings that are similar to acute pulmonary embolism. In patients with right ventricular dilatation without obvious pulmonary disease, intracardiac shunts should be considered. The increased flow through the pulmonary vasculature as a result of an atrial septal or ventricular septal defect can, over time, result in elevation in pulmonary vascular resistance with subsequent dilatation and hypertrophy of the right ventricle. Right ventricular dilatation and dysfunction also have prognostic significance in left-sided heart disease and have been shown to be important predictors of outcome in patients with heart failure or acute myocardial infarction.

In addition to assessment of left and right ventricular structure and function, assessment of the other cardiac chambers also provides important clues to intracardiac and systemic diseases. Enlargement of the left atrium is common in patients with hypertension and is also suggestive of increased left ventricular filling pressures; indeed, left atrial size is often termed the "hemoglobin A_{1c}" of diastolic function, because left atrial enlargement reflects long-standing increase in left-sided filling pressures. Right atrial dilatation and dilatation of the inferior vena cava are common in conditions in which central venous pressure is elevated.

PATIENT SAFETY CONSIDERATIONS

RADIATION EXPOSURE

Both cardiac CT and radionuclide imaging expose patients to ionizing radiation. Several recent publications have raised concern regarding the potential harmful effects of ionizing radiation associated with cardiac imaging. The *effective dose* is a measure used to estimate the biologic effects of radiation and is expressed in millisieverts (mSv). However, measuring the radiation effective dose associated with diagnostic imaging is complex and imprecise and often results in varying estimates, even among experts. The effective dose from a typical myocardial perfusion SPECT scan ranges between ~4 and 11 mSv, depending on the protocol and type of scanner used. The effective dose from a typical myocardial perfusion PET scan is lower, ~2.5–4 mSv. Radiation exposure associated

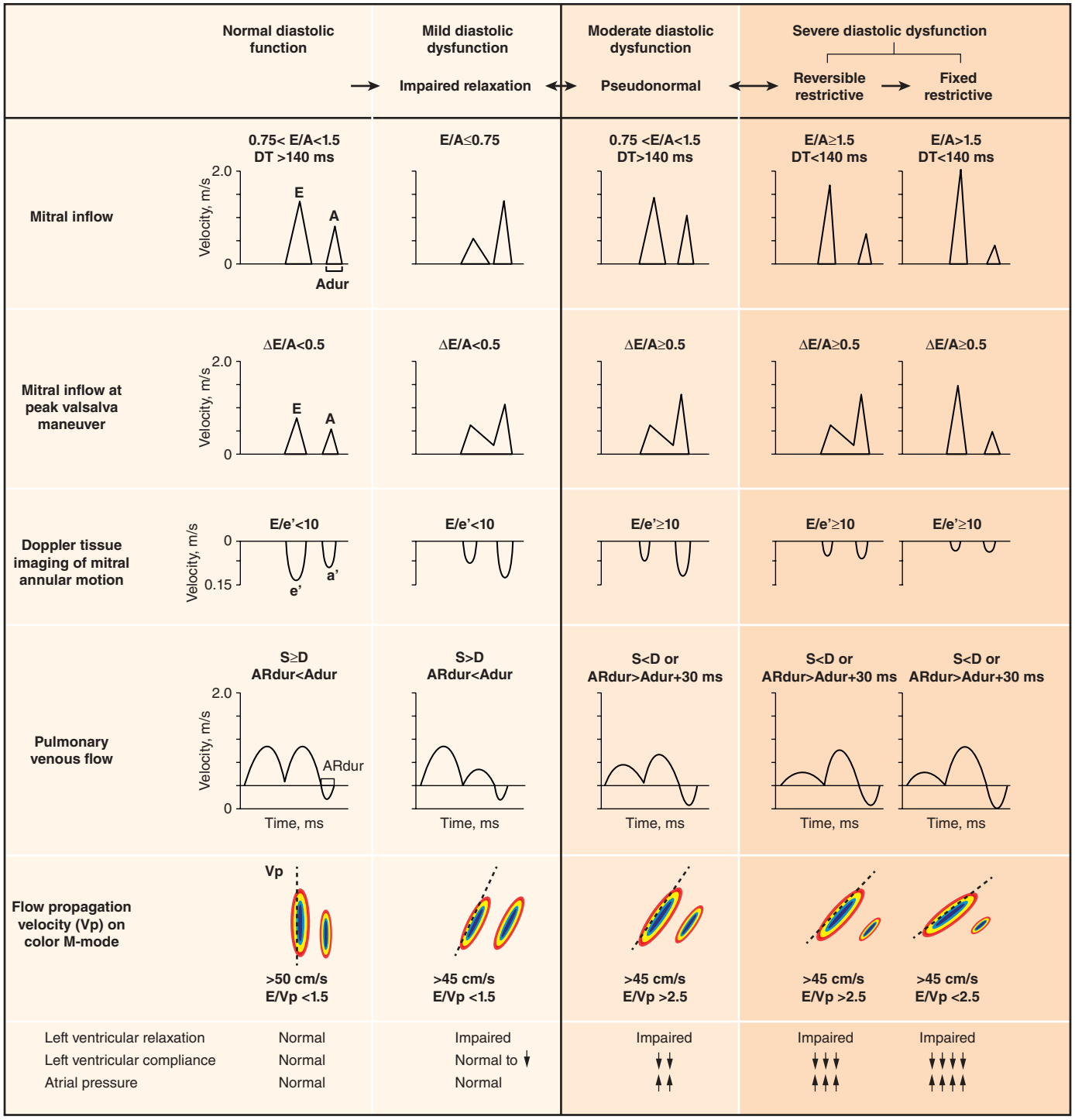

FIGURE 236-8 Stages of diastolic function based on various parameters, including mitral inflow (with and without Valsalva maneuver), Doppler tissue imaging, pulmonary venous flow, and flow propagation. *(Adapted with permission from MM Redfield et al: JAMA 289:194, 2003.)*

with cardiac CT is variable and, as with radionuclide imaging, also depends on the imaging protocol and scanner used. Although historic radiation doses with cardiac CT have been quite high, the introduction of newer technologies (e.g., x-ray tube modulation, prospective ECG gating) has resulted in a significant dose reduction. The current average radiation dose for a coronary CTA ranges from 5 to 15 mSv and, in selected cases, can be as low as 1 mSv. Imaging laboratories follow the ALARA (as low as reasonably achievable) principle when balancing the clinical need and imaging approach. By comparison, the average dose for invasive coronary angiography is ~7 mSv, whereas exposure to radiation from natural sources in the United States amounts to ~3 mSv annually.

The risk of a fatal malignancy from medical imaging–related radiation is difficult to estimate precisely but is likely small and difficult to discern from the background risk of natural malignancies. The small but potential radiation risks from imaging mandate an assessment of the risk-versus-benefit ratio in the individual patient. In this context, one must not fail to take into account the risks of missing important diagnostic information by not performing a test (which could potentially influence near-term management and outcomes) for a theoretical concern of a small long-term risk of malignancy. Before ordering any test, especially one associated with ionizing radiation, we must ensure the appropriateness of the study and that the potential benefits outweigh the risks. The likelihood that the study being considered will

affect clinical management of the patient should be addressed before testing is performed. It is also important that "routine" follow-up scans in asymptomatic individuals be avoided.

CONTRAST AGENTS

Contrast agents are commonly used in cardiac CT, CMR, and echocardiography. Although their use significantly enhances the diagnostic information of each of these tests, there are also potential risks from the administration of contrast agents that should be considered.

The risk of adverse reactions from iodinated contrast agents used in cardiac CT is well established. The precise pathogenesis of contrast reactions following intravascular administration of iodinated contrast media is not known. The overall incidence of contrast reactions is 0.4–3% with nonionic formulations and higher for ionic formulations. Most contrast adverse reactions are mild and self-limiting. The risk of contrast-induced nephropathy (CIN) in patients with relatively normal renal function (estimated glomerular filtration rate [eGFR] >60 mL/min) is low. In most patients, CIN is self-limited, and renal function usually returns to baseline within 7–10 days, without progressing to chronic renal failure. However, this risk increases in patients with GFR <60 mL/min, especially older diabetic subjects. In such patients, appropriate screening and pre- and postscan hydration are necessary.

The use of gadolinium-based contrast agents (GBCAs) enhances the versatility of CMR imaging. There are many commercially available GBCAs in the United States, but their use in cardiac imaging is off-label. Mild reactions from GBCAs occur in ~1% of patients, but severe or anaphylactic reactions are very rare. All GBCAs are chelated to make the compounds nontoxic and facilitate renal excretion. This chelation was less stable in some brands of GBCAs with a linear molecular structure. As a result the unchelated free form of gadolinium leads to a rare but serious condition known as nephrogenic systemic fibrosis (NSF), which is an interstitial inflammatory reaction manifested as fibrosis of tissues or internal organs and even death. Risk factors to developing NSF include high-dose use in presence of severe renal dysfunction (eGFR <30 mL/min per 1.73 m^2), need for hemodialysis, an eGFR <15 mL/min per 1.73 m^2, acute renal deterioration, and concurrent proinflammatory/systemic illnesses. With widespread routine pretest screening and weight-based dosing, a near-zero incidence of NSF has been reported in the past decade. Most CMR centers use the newer, more stable macrocyclic GBCAs which further lower the risk of NSF.

Contrast agents can also be used in echocardiography. Injected agitated saline is used routinely to assess cardiac shunts, because these "bubbles" are too large to traverse the pulmonary circulation. After saline injection, the presence of bubbles in the left side of the heart is indicative of shunt, although the location can sometimes be difficult to determine. The current U.S. Food and Drug Administration (FDA) approved use of echocardiographic contrast agents is for opacification of left-sided chambers and to improve delineation of left ventricular endocardial border in patients with suboptimal echocardiograms. These agents are either albumin- or lipid-based microspheres filled with inert gases, typically perfluorocarbons. They are considered extremely safe, although they have, in extremely rare instances, been associated with allergic reactions and neurologic events.

SAFETY CONSIDERATIONS OF CMR IN PATIENTS WITH PACEMAKERS AND DEFIBRILLATORS

A presence of a pacemaker or defibrillator is a contraindication to MRI scanning, with patient risks include generation of electrical current from the metallic hardware (especially if wire loops exist), device movement induced by the magnetic field, inappropriate pacing and sensing, and heating because of the "antenna's effect." By contrast, experienced centers had reported success in performing CMR in highly selected patients and in a carefully monitored clinical setting. In past years, several models of permanent pacemakers and automatic implantable cardioverter defibrillator (AICD) have been designed and approved for clinical use to allow CMR imaging under strict imaging conditions and they have achieved FDA approval.

PATIENT-CENTERED APPLICATIONS OF CARDIAC IMAGING

CORONARY ARTERY DISEASE

The basis for the diagnostic application of imaging tests in patients with known or suspected CAD should be viewed considering the pretest probability of disease as well as the specific characteristics of imaging tests (i.e., sensitivity and specificity). In symptomatic patients, the prevalence or pretest probability of CAD differs based on the type of symptom (typical angina, atypical angina, noncardiac chest pain), as well as on age, gender, and coronary risk factors. In an individual patient, the results of the initial test inform the posttest likelihood of CAD. In patients undergoing sequential testing (e.g., ECG treadmill testing followed by stress imaging), the posttest probability of disease after the first test becomes the pretest likelihood of disease for the second test. Regardless of the sequence, the expectation is that a test will provide sufficient information to confirm or exclude the diagnosis of CAD and that such information will allow accurate risk stratification to be able to guide management decisions.

Table 236-3 summarizes the relative diagnostic accuracies of cardiac imaging modalities for the diagnosis of CAD.

It is important to highlight that most studies included in meta-analyses of the diagnostic accuracy of cardiac imaging modalities for the diagnosis of CAD were retrospective, small, single-center studies, comprising predominantly male patients with a high prevalence of CAD (>50–60%). Multicenter studies assessing the performance of individual modalities or comparing different modalities have consistently resulted in more modest diagnostic accuracies, tracking more closely with how these tests perform in practice.

Stress Echocardiography The hallmark of myocardial ischemia during stress echocardiography is the development of new regional wall motion abnormalities and reduced systolic wall thickening (Video 236-3). Stress echocardiography can be performed in conjunction with exercise or dobutamine stress. Stress echocardiography is best at identifying inducible wall motion abnormalities in previously normally contracting segments. In a patient with wall motion abnormalities at rest, the specificity of stress echocardiography is reduced, and worsening regional function of a previously abnormal segment

TABLE 236-3 Comparative Diagnostic Accuracy of Cardiac Imaging Approaches to Coronary Artery Disease

IMAGING MODALITY	PUBLISHED DATA	SENSITIVITY	SPECIFICITY
Exercise echocardiography	15 studies (n = 1849 patients)	84%	82%
Dobutamine echocardiography	28 studies (n = 2246 patients)	80%	84%
SPECT MPI	113 studies (n = 11,212 patients)	88%	76%
Myocardial perfusion PET	9 studies (n = 650 patients)	93%	81%
CMR perfusion	37 studies (n = 2841 patients)	91%	81%
CMR wall motion	14 studies (n = 754 patients)	83%	86%
Coronary CTA	18 studies (n = 1286 patients)	99%	89%

Note: In these studies, the diagnosis of coronary artery disease was based on the presence of a >50% or >70% stenosis on invasive coronary angiography.

Abbreviations: CMR, cardiac magnetic resonance; CTA, computed tomography angiography; MPI, myocardial perfusion imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

might reflect worsening contractile function in the setting of increased wall stress rather than new evidence of inducible ischemia.

The advantages of stress echocardiography over other stress imaging techniques include its relatively good diagnostic accuracy, widespread availability, no use of ionizing radiation, and relatively low cost. Limitations of stress echocardiography include (1) the technical challenges associated with image acquisition at peak exercise because of exertional hyperpnoea and cardiac excursion, (2) the fact that rapid recovery of wall motion abnormalities can be seen with mild ischemia (especially with one-vessel disease, which limits sensitivity), (3) difficulty detecting residual ischemia within an infarcted territory because of resting wall motion abnormality, (4) high operator dependence for acquisition of echocardiographic data and analysis of images, and (5) the fact that good-quality complete images viewing all myocardial segments occurs in only 85% of patients. Newer techniques including second harmonic imaging and the use of intravenous contrast agents improve image quality, but their effect on diagnostic accuracy has not been well documented.

As with nuclear perfusion imaging, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. A negative stress echocardiogram is associated with an excellent prognosis, allowing identification of patients at low risk. Conversely, the risk of adverse events increases with the extent and severity of wall motion abnormalities on stress echocardiography.

Stress Radionuclide Imaging SPECT myocardial perfusion imaging is the most common form of stress imaging tests for CAD evaluation. The presence of a reversible myocardial perfusion defect is indicative of ischemia **(Fig. 236-9, *left panel*)**, whereas a fixed perfusion defect generally reflects prior myocardial infarction **(Fig. 236-9, *right panel*)**. As discussed above, PET has advantages compared to SPECT, but it is not widely available and is more expensive and, thus, considered an emerging technology in clinical practice.

Nuclear perfusion imaging is another robust approach to diagnose obstructive CAD, quantify the magnitude of inducible myocardial ischemia, assess the extent of tissue viability, and guide therapeutic management (i.e., selection of patients for revascularization). One of the most valuable clinical applications of radionuclide perfusion imaging is for risk stratification. It is well established that patients with a normal SPECT or PET study exhibit a low rate of major adverse cardiac events of <1% annually. Importantly, the risks of death and myocardial infarction increase linearly with increasing magnitude of perfusion abnormalities, reflecting the extent and severity of CAD.

Despite the widespread use and clinical acceptance of radionuclide imaging in CAD evaluation, a recognized limitation of this approach is that it often uncovers only coronary territories supplied by the most severe stenoses. Consequently, it is relatively insensitive to accurately delineate the extent of obstructive angiographic CAD, especially in the setting of multivessel disease. The use of quantitative myocardial blood flow and coronary flow reserve with PET can help mitigate this limitation. In patients with so-called "balanced" ischemia or diffuse CAD, measurements of coronary flow reserve uncover areas of myocardium at risk that would generally be missed by performing only relative assessments of myocardial perfusion **(Fig. 236-10)**. Conversely, a normal coronary flow reserve is associated with a very high negative predictive value for excluding high-risk angiographic CAD. These measurements of coronary flow reserve also contribute to risk stratification across the spectrum of ischemic changes, including patients with visually normal myocardial perfusion.

HYBRID CT AND NUCLEAR PERFUSION IMAGING Because many of the newer generation nuclear medicine scanners integrate CT and a gamma camera in the same acquisition gantry, it is now possible to acquire and quantify myocardial scar and ischemia and CAC scoring from a single dual-modality study (SPECT/CT or PET/CT) **(Fig. 236-11)**. The rationale for this integrated approach is predicated on the fact that the perfusion imaging approach is designed to uncover only obstructive atherosclerosis. Conversely, CAC scoring provides a quantitative measure of the anatomic extent of atherosclerosis. This provides an opportunity to improve the conventional models for risk assessment using nuclear imaging alone, especially in patients without known CAD.

Cardiac CT Voluminous plaques are more prone to calcification, and stenotic lesions frequently contain large amounts of calcium. Indeed, there is evidence that high CAC scores are generally predictive of a higher likelihood of obstructive CAD, and the available data support the concept of a threshold phenomenon governing this relationship (i.e., Agatston score >400). However, given the fact that CAC scores are not specific markers of obstructive CAD, one should be cautious in using this information as the basis for referral of patients to coronary angiography, especially in symptomatic patients with low-risk stress tests. Conversely, CAC scores <400, especially in symptomatic patients with intermediate-high likelihood of CAD, as in those with typical angina, may be less effective in excluding CAD, especially in young symptomatic men and women who may have primarily noncalcified atherosclerosis **(Fig. 236-12)**.

As discussed above, the improved temporal and spatial resolution of modern multidetector CT scanners offer a unique noninvasive approach to delineate the extent and severity of coronary atherosclerosis with coronary CTA. The extremely high sensitivity of this approach offers a very effective means for excluding the presence of CAD (high negative predictive value) (Table 236-3). In the setting of high coronary calcium scores (e.g., >400), however, specificity is reduced because the blooming artifact of calcium does not allow one to evaluate the vessel lumen accurately. Given the high negative predictive value of CTA, a normal scan result effectively excludes obstructive CAD and abolishes the need for further investigation. As discussed below, this may be quite useful in patients with low-intermediate clinical risk presenting to the emergency room for chest pain. However, the limited capability of this technique to determine which coronary plaques are flow limiting can make abnormal scan results more difficult to interpret, especially in terms of the possible need of revascularization. There are emerging data suggesting that by adding a stress myocardial perfusion CT evaluation (similar to stress perfusion CMR) **(Fig. 236-13, *top panel*)**

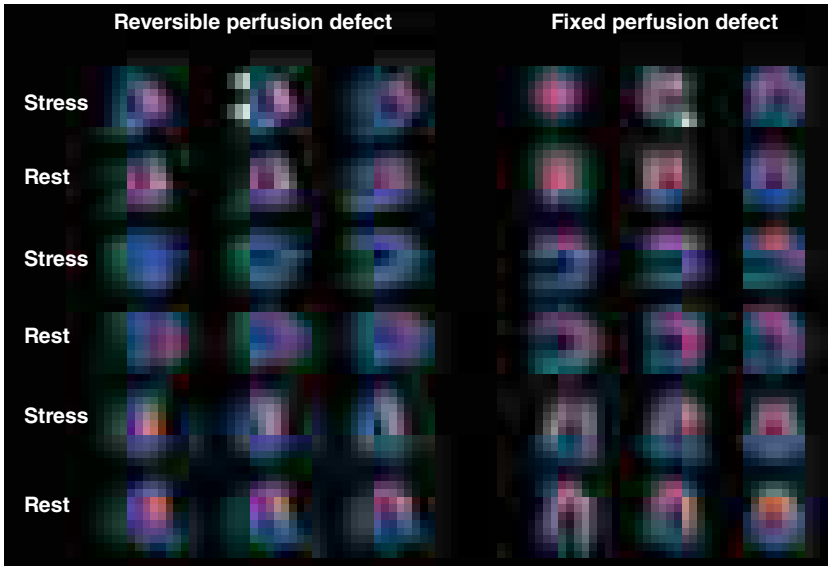

FIGURE 236-9 Selected technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography images of two different patients demonstrating a reversible perfusion defect involving the anterior and septal left ventricular wall, reflecting ischemia in the left anterior descending coronary territory (*arrows in left panel*), and a fixed perfusion defect involving the inferior and inferolateral walls consistent with myocardial scar in the right coronary territory (*arrow in right panel*).

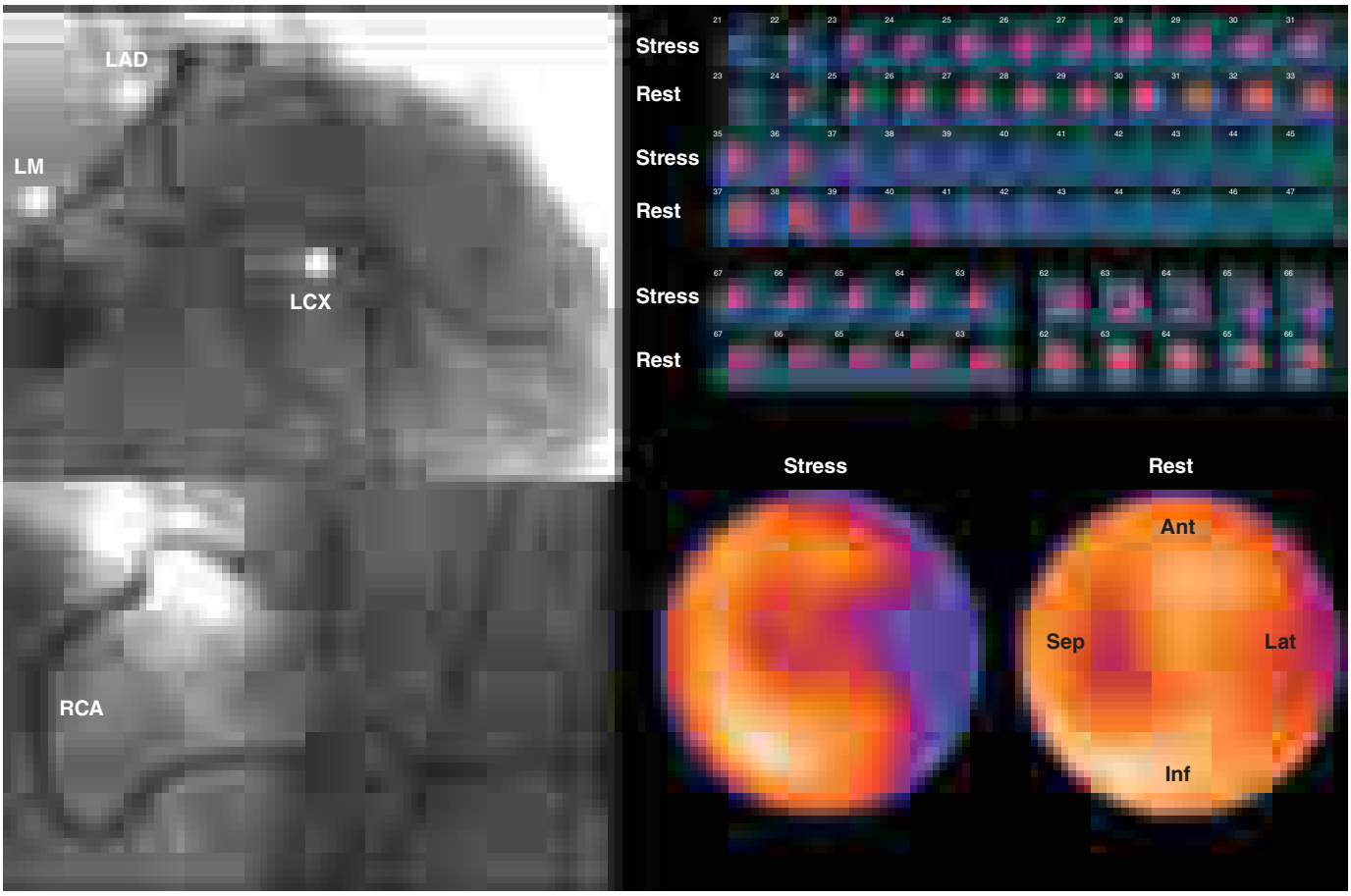

FIGURE 236-10 Coronary angiographic (*left panel*) and rubidium-82 myocardial perfusion positron emission tomography images (*right panel*) in an 85-year-old female with diabetes presenting with chest pain. The coronary angiogram demonstrates significant stenoses of the left main and circumflex coronary arteries. However, the perfusion images demonstrate only a reversible lateral wall defect. Quantification of stress and rest myocardial blood flow demonstrated a significant, global reduction on coronary flow reserve (estimated at 1.2, normal value >2.0), reflecting extensive myocardium risk that was underestimated by the semiquantitative estimates of myocardial perfusion. LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery.

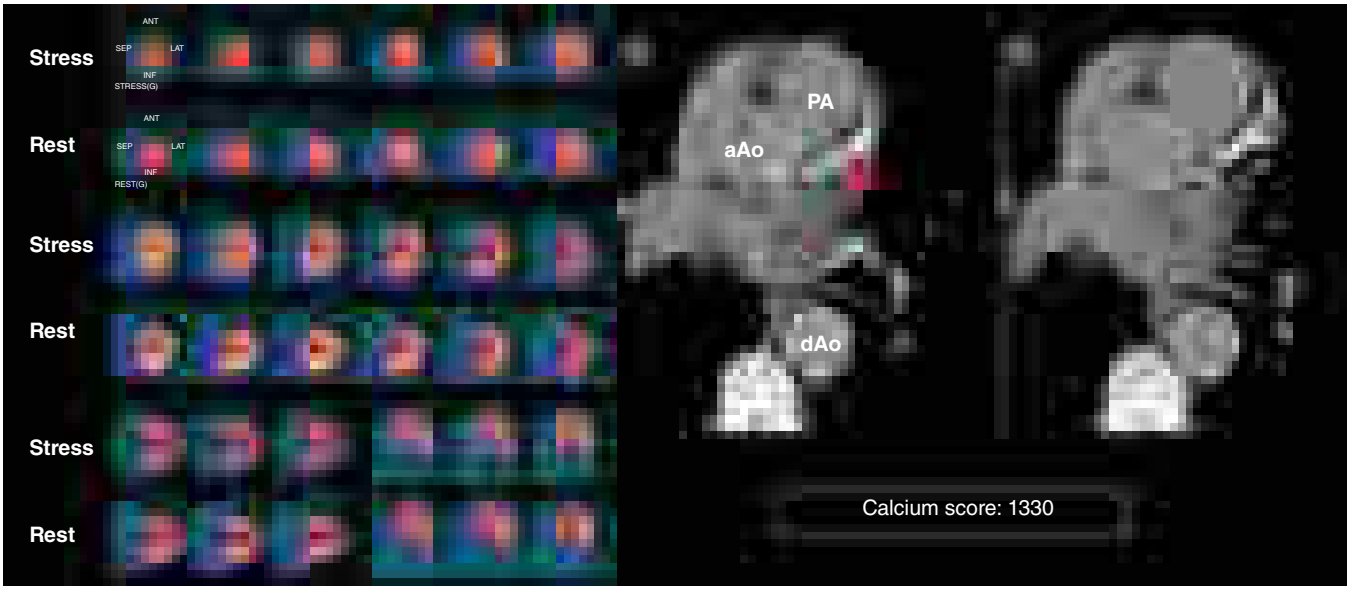

FIGURE 236-11 Stress and rest rubidium-82 myocardial perfusion positron emission tomography (PET) images (*left*) and noncontrast gated computed tomography (CT) images (*right*) delineating the extent and severity of coronary artery calcifications obtained with integrated PET/CT imaging. The images demonstrate extensive atherosclerosis (Agatston coronary calcium score = 1330) without flow-limiting disease based on the normal perfusion study. aAo, ascending aorta; dAo, descending aorta; PA, pulmonary artery.

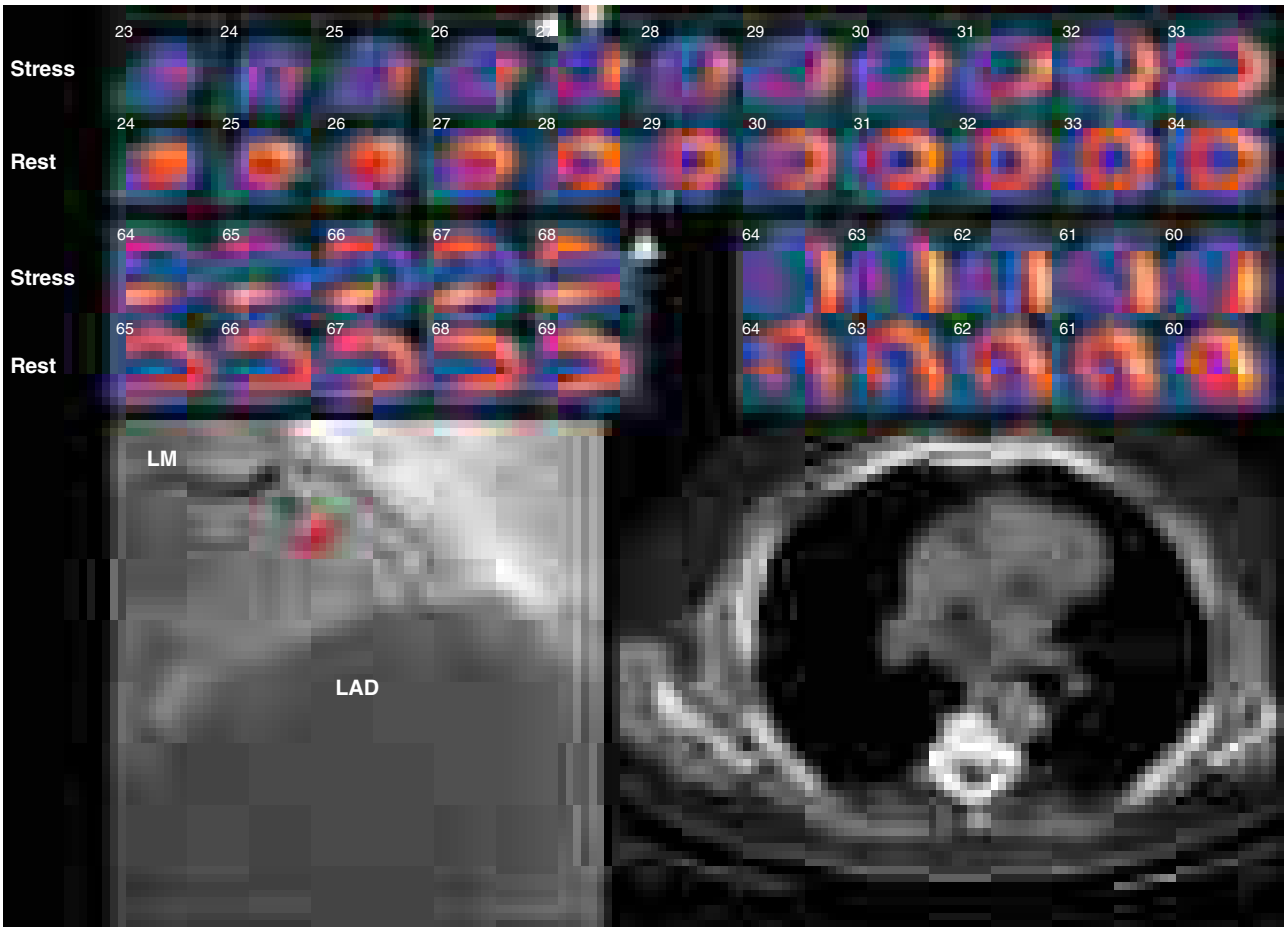

FIGURE 236-12 Stress and rest rubidium-82 myocardial perfusion positron emission tomography images (*top*), noncontrast gated computed tomography images (*lower right*), and selected coronary angiographic images obtained on a 59-year-old male patient with atypical angina. Despite the absence of significant coronary calcifications (Agatston calcium score = 0), the perfusion images demonstrated a dense and reversible perfusion defect involving the anterior and anteroseptal walls (*arrows*), reflecting significant obstructive disease in the left anterior descending coronary artery (LAD), confirmed on angiography. LM, left main artery.

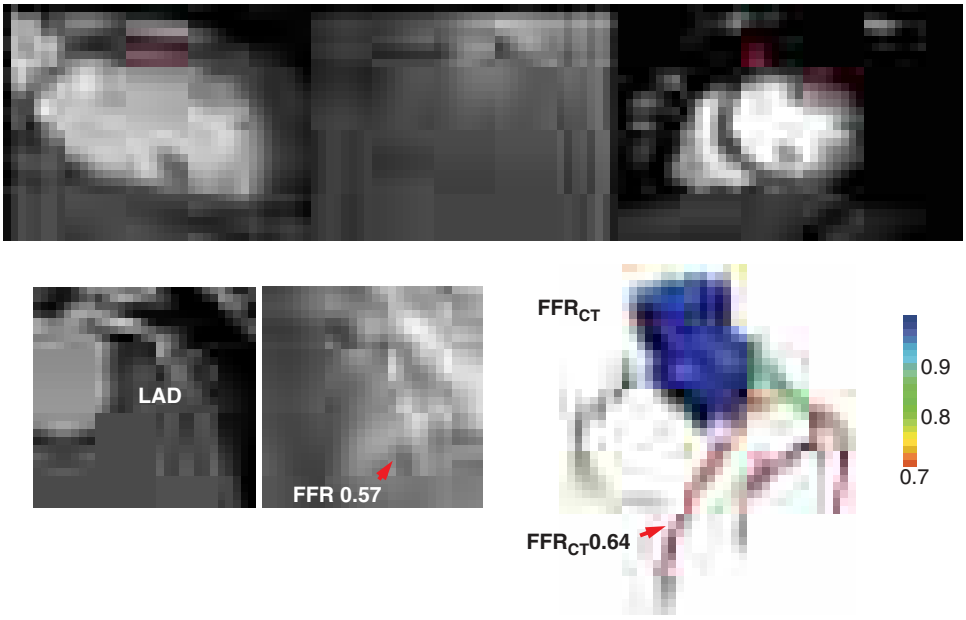

FIGURE 236-13 Examples of novel approaches to the assessment of flow-limiting coronary artery disease (CAD) with cardiac computed tomography (CT). In the *top panel*, representative views of a coronary CT angiogram (CTA; *left*), coronary angiogram (*middle*), and stress myocardial perfusion CT (*right*) images in a patient with CAD and prior stenting of the left anterior descending coronary artery (LAD) are presented. On the CTA, the stent (*arrows*) is totally occluded as evidenced by the loss of contrast enhancement distal to the stent. The coronary angiogram demonstrates a concordant total occlusion of the LAD. On the perfusion CT images, there is a black rim (*arrows*) involving the anterior and anterolateral walls, indicating the lack of contrast opacification during stress consistent with myocardial ischemia. *(Images courtesy of CORE 320 investigators.)* The *lower panel* illustrates an example of fractional flow reserve (FFR) estimates with coronary CTA (*left*) compared to the reference standard of invasive FFR. The FFR reflects the pressure differential between a coronary segment distal to a stenosis and the aorta. In normal coronary arteries, there is no gradient, and FFR is 1. An FFR <0.80 is consistent with a hemodynamically significant stenosis. *(Images courtesy of Dr. James Min, Cornell University, New York.)*

or an estimated fractional flow reserve (so-called FFR_{CT}) **(Fig. 236-13, *lower panel*)**, one can define the hemodynamic significance of anatomic stenosis. However, these are not in routine clinical use and remain emerging technologies.

As with invasive coronary angiography, assessments of the extent of CAD by CTA can also provide useful prognostic information. A low 1-year cardiac event rate has been reported for patients without coronary atherosclerosis on CTA. For patients with obstructive CAD, the risk of adverse cardiac events increases proportionally with the extent of angiographically obstructive CAD. There is new evidence that even the presence of non-obstructive atherosclerosis increases the risk of adverse cardiac events.

Although CTA can be helpful in assessing patency of bypass grafts, the assessment of stents is somewhat more challenging because the limited spatial resolution of CT and stent diameter (<3 mm being associated with the highest number of partial lumen visualization and nondiagnostic scans) both contribute to limited clinical results.

CMR Imaging CMR evaluates for ischemia from CAD by assessing regional myocardial perfusion or regional wall motion at rest and during stress, the latter analogous to dobutamine echocardiography. Stress CMR studies use pharmacologic vasodilator agents or dobutamine. Myocardial perfusion is evaluated by injecting a GBCA bolus followed by imaging data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Relative perfusion deficits are recognized as regions of low signal intensity (black) within the myocardium **(Video 236-4)**. Several minutes after GBCA injection, LGE imaging allows detection of bright areas of myocardial scar (white), which permits comparison of regions of hypoperfusion and infarction to quantify myocardial ischemia **(Fig. 236-14)**.

With better delineation of the endocardial borders, dobutamine CMR has better diagnostic accuracy than dobutamine echocardiography for detection of CAD, especially in patients with poor acoustic window (Table 236-3). High-dose dobutamine carries the risk of serious ventricular arrhythmias (~1%), but most cases can be prevented with proper monitoring of vital signs and regional cine function. The advantages of stress perfusion CMR over SPECT include its higher spatial resolution which allows detection of subendocardial ischemia or infarction that may be missed by SPECT. As with other imaging modalities, stress CMR studies can provide robust prognostic value. A normal CMR study in patients with chest pain at intermediate pretest risk is associated with a <1% annual rate of death or myocardial infarction.

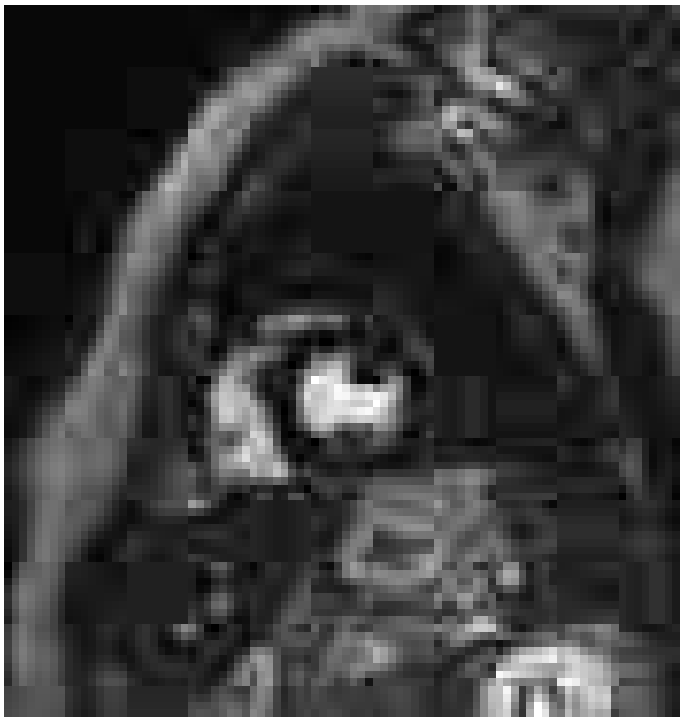

FIGURE 236-14 The image shows the late gadolinium enhancement image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

Selecting a Testing Strategy in Patients without Known CAD As discussed above, there are many options for the evaluation of a patient with suspected CAD presenting with chest pain symptoms. The critical questions to be answered by a testing strategy include the following: (1) Does the chest pain reflect obstructive CAD? (2) What are the short- and long-term risks? (3) Does the patient need to be considered for revascularization?

For symptomatic patients without a prior history of CAD and a normal or nearly normal resting ECG who are able to exercise, the American College of Cardiology/American Heart Association guidelines recommend standard exercise treadmill testing (ETT) as the initial testing strategy. The guidelines further suggest that patients who are categorized as low risk by ETT (e.g., those achieving >10 metabolic equivalents [METS] without chest pain or ECG changes) be treated initially with medical therapy, and those with high-risk ETT findings (i.e., typical angina with >2 mm ST-segment depression in multiple leads, ST elevation during exercise, drop in blood pressure, or sustained ventricular arrhtyhmias) be referred for coronary angiography.

The use of exercise testing in women presents difficulties that are not seen in men, reflecting the differences in the lower prevalence of obstructive CAD in women and the different accuracy of exercise testing in men and women. Compared with men, the lower pretest probability of disease in women means that more test results are false positive. In some of these patients, a positive ETT may reflect true myocardial ischemia caused my microvascular coronary artery dysfunction (so-called *microvascular disease*). In addition, the inability of many women to exercise to maximum aerobic capacity, the greater prevalence of mitral valve prolapse and microvascular disease, and possibly other reasons may contribute to the differences with men as well. The difficulties of using exercise testing for diagnosing obstructive CAD in women have led to speculation that stress imaging may be preferred over standard stress testing. However, recent data from the WOMEN study suggests that in symptomatic, low-risk women who can exercise, standard ETT is a very effective initial diagnostic strategy as compared to stress radionuclide imaging. Indeed, the 2-year outcomes were similar in both diagnostic strategies, and the ETT-first approach resulted in 48% lower costs compared to exercise radionuclide imaging.

Patients with intermediate-high risk after ETT (e.g., low exercise capacity, chest pain, and/or ST-segment depression without high-risk features) will often require additional testing, either stress imaging or coronary CTA, to more accurately characterize clinical risk. Most common stress imaging strategies in intermediate-risk patients include stress echocardiography and radionuclide imaging. In such patients, stress imaging with either SPECT or echocardiography has been shown to accurately reclassify patients who are initially classified as intermediate risk by ETT as low or high risk **(Fig. 236-15)**. Following this staged strategy of applying the low-cost ETT first and reserving more expensive imaging to refine risk stratification to patients initially classified as intermediate risk by ETT is more cost-effective than applying stress or anatomic imaging as the initial test routinely.

An imaging strategy is the recommended first step for patients who are unable to exercise to an adequate workload and/or those with abnormal resting ECGs (e.g., left ventricular hypertrophy with strain, left bundle branch block). Importantly, the most recent documents regarding appropriate use of imaging also considered that an imaging strategy may be an appropriate first step in patients with intermediate-high likelihood of CAD (e.g., diabetics, renal impairment) due to increased overall sensitivity for diagnosis of CAD and improved risk stratification. In considering an imaging strategy, the evidence supporting the role of ischemia assessment versus anatomy must be considered. From the discussion above, a normal coronary CTA is helpful because it effectively excludes the presence of obstructive CAD and the need

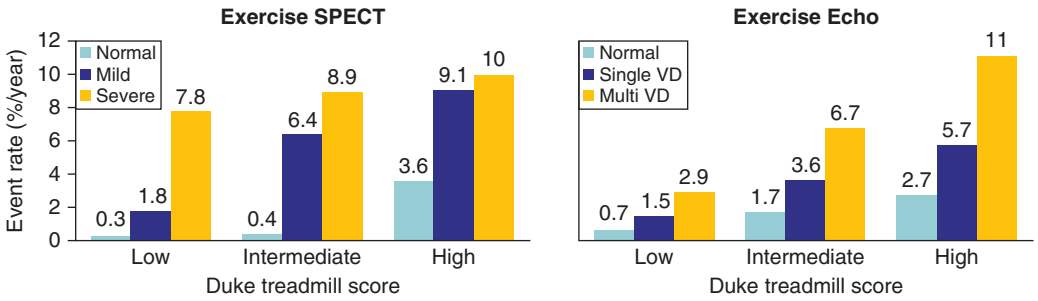

FIGURE 236-15 Incremental risk stratification of stress imaging over Duke treadmill score in patients with suspected coronary artery disease. Stress imaging is most valuable in the intermediate-risk group. SPECT, single-photon emission computed tomography; VD, vessel disease. *(Part A reproduced with permission from R Hachamovitch et al: Circulation 93:905, 1996. Part B data from TH Marwick et al: Circulation 103:2566, 2001.)*

for further testing, defines a low clinical risk, and makes management decisions regarding referral to coronary angiography straightforward. Because of its limited accuracy to define stenosis severity and predict ischemia, however, abnormal CTA results are more problematic to interpret and to use as the basis for defining the potential need of invasive coronary angiography and revascularization. In such patients, a follow-up stress test is usually required to determine the possible need of revascularization **(Fig. 236-16)**.

The justification of stress imaging in testing strategies has hinged on the identification of which patients may benefit from a revascularization strategy by means of noninvasive estimates of jeopardized myocardium rather than angiography-derived anatomic stenoses. Indeed, there is evidence that only the presence of moderate-severe ischemia identifies patients with apparent improved survival with revascularization. Patients with mild or no ischemia are better candidates for optimal medical therapy. The advantages of this approach include avoidance of excess catheterizations with their associated cost and risk and the potential for intervening unnecessarily. The acceptable diagnostic accuracy of stress imaging approaches, along with their robust risk stratification, and the ability of ischemia information to identify patients who would benefit from revascularization suggest a potential role as a first imaging strategy in patients with intermediate-high likelihood of CAD. While the available data suggest similar diagnostic accuracy for SPECT and echocardiography but higher for PET and CMR, the choice of strategy depends on availability and local expertise.

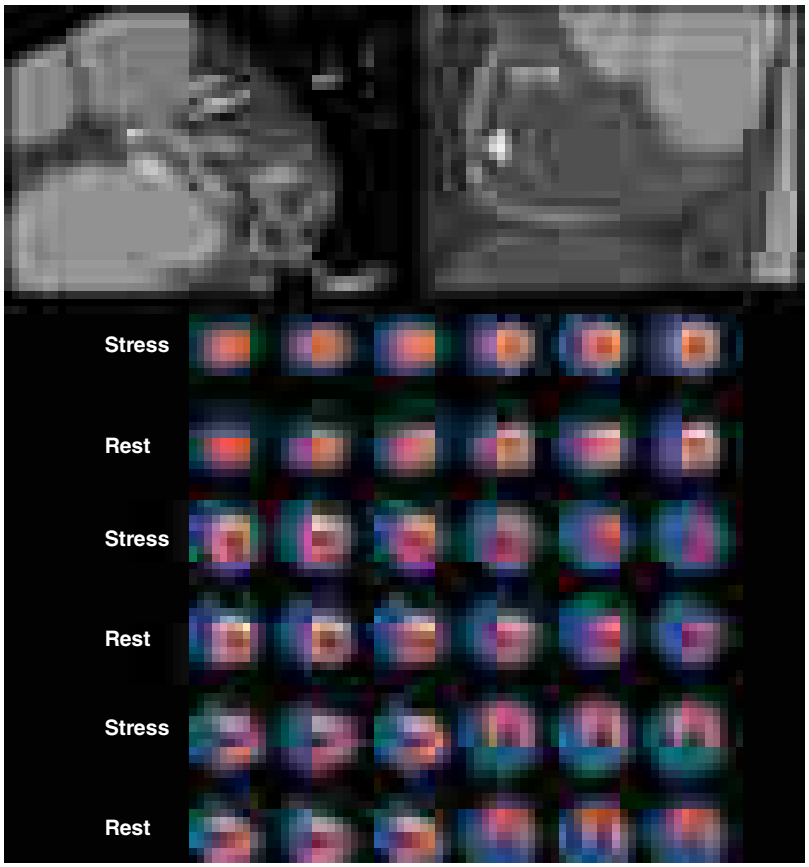

FIGURE 236-16 Selected views from coronary computed tomography angiographic (CTA) images (*top panel*) and stress and rest rubidium-82 myocardial perfusion positron emission tomography images (*lower panel*) obtained on a 64-year-old male patient with atypical angina. The CTA images demonstrate dense focal calcifications in the left main (LM) and left anterior descending (LAD) coronary arteries and a significant noncalcified plaque in the mid right coronary artery (RCA; *arrow*). The myocardial perfusion images demonstrated no evidence of flow-limiting stenosis. LCx, left circumflex artery; OM, obtuse marginal branch.

Selecting a Testing Strategy in Patients with Known CAD Use and selection of testing strategies in symptomatic patients with established CAD (i.e., prior angiography, prior myocardial infarction, prior revascularization) differ from those in patients without prior CAD. Although standard ETT may help distinguish cardiac from non-cardiac chest pain, exercise ECG has several limitations following myocardial infarction and revascularization (especially coronary artery bypass grafting). These patients frequently have rest ECG abnormalities. In addition, there is a clinical need to document both the magnitude and localization of ischemia to be able to direct therapy, especially the potential need for targeted revascularization. Consequently, imaging tests are preferred for evaluating patients with known CAD.

There are also important differences in the effectiveness of imaging tests in these patients. As discussed above, coronary CTA is limited in patients with prior revascularization. While CTA provides excellent visualization of the bypass grafts, the native circulation tends to get heavily calcified and is generally not a good target for imaging with CTA. Likewise, blooming artifacts from metallic stents also limit the application of coronary CTA in patients with prior percutaneous coronary intervention. If an anatomic strategy is indicated, direct referral to invasive angiography is preferred.

Stress imaging approaches are especially useful and preferred in symptomatic patients with established CAD. As in patients without prior CAD, normal imaging studies in symptomatic patients with established CAD also identify a low-risk cohort. In those with abnormal stress imaging studies, the degree of abnormality relates to posttest risk. In addition, stress imaging approaches can localize and quantify the magnitude of ischemia, thereby assisting in planning targeted revascularization procedures. As in patients without prior CAD, the choice of stress imaging strategy depends on availability and local expertise.

Testing Strategy Considerations in Patients Presenting with Chest Pain to the Emergency Department Although acute chest pain is a frequent reason for patient visits to the emergency department (ED), only a small minority of those presentations

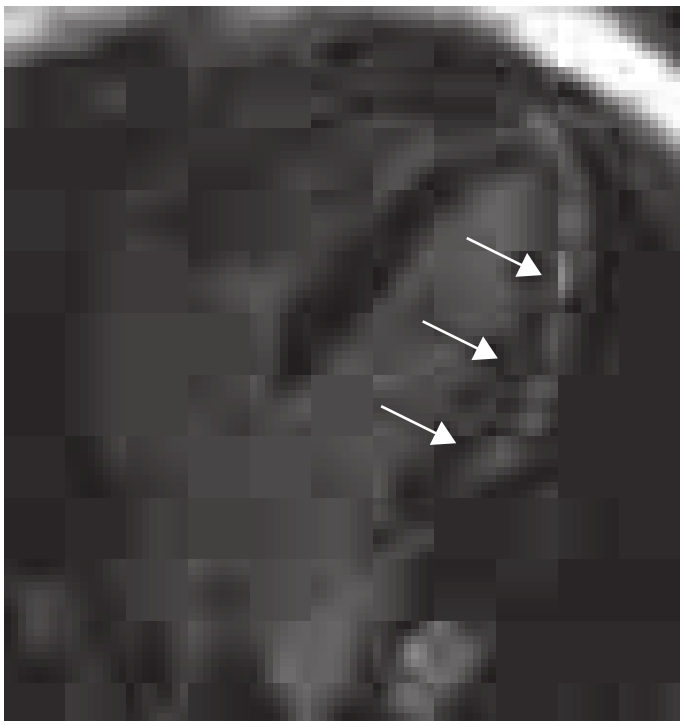

FIGURE 236-17 A four-chamber long-axis late gadolinium enhancement (LGE) image of a patient with acute myocarditis. Note that the LGE primarily involved the epicardial aspect of the myocardium (*arrows*), sparing the endocardium, which is a feature that distinguishes myocarditis from myocardial infarction, which affects the endocardium. Also note the multiple foci of LGE in this case affecting the lateral wall of the left ventricle. Viral myocarditis often presents with this pattern.

represent an acute coronary syndrome (ACS). Strategies used in the evaluation of these patients include novel cardiac biomarkers (e.g., serum troponins), conventional stress testing (ETT), and noninvasive cardiac imaging. It is generally accepted that the primary goal of this evaluation is exclusion of ACS and other serious conditions rather than detection of CAD.

The routine evaluation of acute chest pain in most centers in the United States includes admission to a chest pain unit to rule out ACS with the use of serial ECGs and cardiac biomarkers. In selected patients, stress testing with or without imaging may be used for further risk stratification. Stress echocardiography and radionuclide imaging are among the most frequently used imaging approaches in these patients. Multiparametric CMR imaging has also been used successfully in patients with acute chest pain **(Video 236-5)**. Due to its ability to probe multiple aspects of myocardial physiology, cardiac anatomy, and tissue characterization with LGE imaging, CMR is useful in diagnosing conditions that mimic ACS (e.g., acute myocarditis, takotsubo cardiomyopathy, pericarditis) **(Fig. 236-17)**.

As discussed above, coronary CTA is a rapid and accurate imaging technique to exclude the presence of CAD and is well suited for the evaluation of patients with acute chest pain **(Fig. 236-18)**. Four randomized clinical trials have demonstrated the feasibility, safety, and accuracy of coronary CTA in the ED as compared to usual care (which typically includes stress imaging). Patients in these trials had a very low clinical risk. Overall, there were no deaths and very few myocardial infarctions without differences between the groups. Likewise, there were no differences in postdischarge ED visits or rehospitalizations. These studies showed decreased length of stay with coronary CTA, and most but not all reported cost savings. An observation from a recent meta-analysis was that, compared to usual care, more patients assigned to coronary CTA underwent cardiac catheterization (6.3% vs 8.4%, respectively) and revascularization (2.6% vs 4.6%, respectively). The relative increased frequency in the referral to cardiac catheterization and revascularization after coronary CTA compared to stress imaging testing strategies has also been observed in patients with stable chest pain syndromes.

Taken together, the available data clearly suggest that not all patients presenting with acute chest pain require specialized imaging testing. Patients with very low clinical risk and negative biomarkers (especially high-sensitivity troponin assays) can be safely triaged. The use of imaging tests in patients with low-intermediate risk should be carefully considered, especially given the trade-offs discussed above.

VALVULAR HEART DISEASE

Abnormalities of any of the four valvular structures in the heart can lead to significant cardiac dysfunction, heart failure, or even death. Echocardiography, CMR, and cardiac CT can be used for the evaluation of valvular heart disease, although echocardiography has generally been considered the first imaging test for the assessment of valvular heart disease. In addition, echocardiography is the most cost-effective screening method for valvular heart disease. In some cases, CMR can complement echocardiography when echocardiographic acoustic window is inadequate, quantifying blood flow data more precisely, or providing complimentary assessment of adjacent vascular structures relevant to the valvular condition.

Echocardiography can be used to assess both regurgitant and stenotic lesions of any of the cardiac valves. Typical indications for echocardiography to assess valvular heart disease include cardiac murmurs identified on physical examination, symptoms of breathlessness that may represent valvular heart disease, syncope or presyncope, and preoperative exams in patients undergoing bypass surgery. A standard echocardiographic examination should include qualitative and quantitative assessment of all valves regardless of indication and should serve as an adequate screening test for significant valvular disease.

Assessment of Aortic Stenosis Aortic stenosis, one of the most common forms of valvular heart disease, most often occurs because of gradual progression of valvular calcification in both normal and congenitally abnormal valves. Assessment of aortic stenosis is most commonly performed with echocardiography, although techniques for

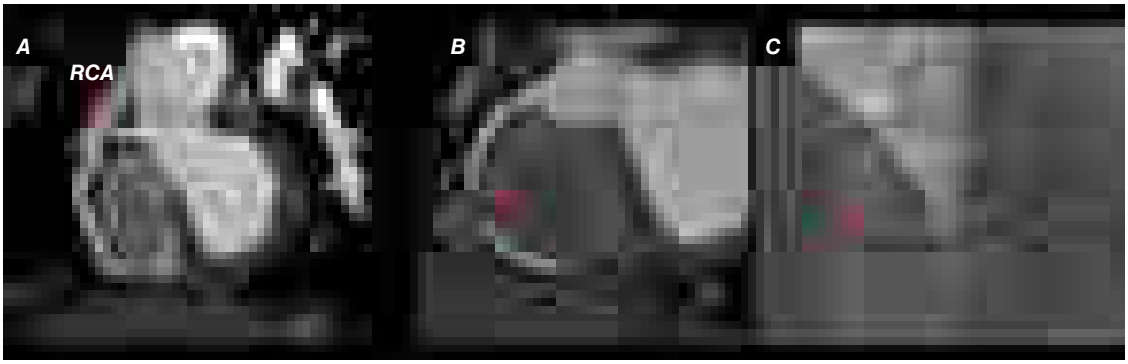

FIGURE 236-18 Representative coronary computed tomography angiographic (CTA) images of two patients presenting to the emergency department with chest pain and negative biomarkers. The patient in ***A*** had angiographically normal coronary arteries; the panel shows a representative view of the right coronary artery (RCA). ***B*** and ***C*** show a corresponding significant stenosis in the mid portion of the RCA on both the CTA (***B***) and invasive angiographic view (***C***). *(Images used with permission from Dr. Quynh Truong, Massachusetts General Hospital, Boston, MA.)*

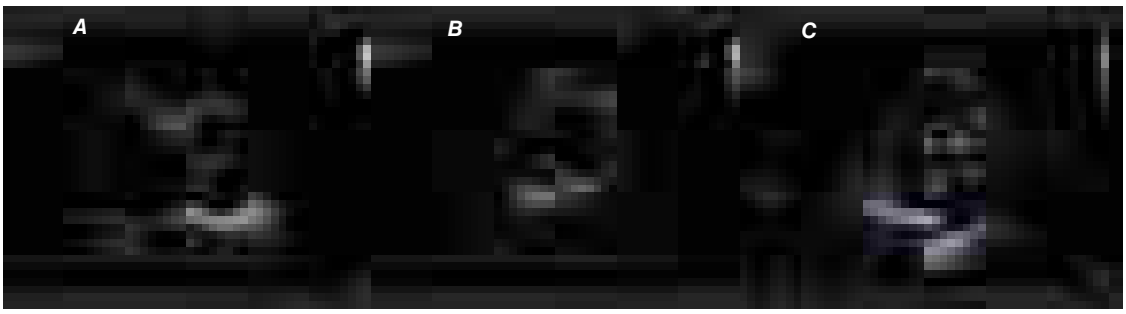

FIGURE 236-19 Normal aortic valve in the parasternal long-axis view (***A***) and short-axis view (***B***), and bicuspid aortic valve showing typical 10 o'clock to 4 o'clock leaflet orientation (***C***).

quantitative assessment of aortic stenosis with CMR have been developed and increasingly used over the past decade. Echocardiographic assessment generally begins with visual inspection of the valve. This allows for assessment of valvular morphology, whether it is tricuspid, bicuspid, or some variant; degree of leaflet calcification; and leaflet excursion.

The normal aortic valve consists of three leaflets or cusps: the right coronary, the left coronary, and the noncoronary cusps. Abnormalities of cusp development are some of the most common congenital heart anomalies, the most common of which is bicuspid aortic valve, with two opening leaflets rather than three **(Fig. 236-19)**. The aortic valve can be visualized on echocardiography, although sometimes it can be difficult to distinguish true bicuspid aortic valve from variants, including the presence of a vestigial commissure (raphe). Bicuspid aortic valve, one of the most common congenital anomalies, predisposes to both aortic stenosis and aortic insufficiency.

The degree of aortic stenosis is assessed by estimating both the pressure gradient across the valve and the valve area. Patients with moderate aortic stenosis or higher generally have peak instantaneous velocities of 3.0 m/s and higher, and often higher than 4.0 m/s, corresponding to pressure gradients of 36 and 64 mmHg, respectively. Because pressure gradients across the aortic valve can be underestimated in patients with severe left ventricular dysfunction, estimation of valve area by the continuity principle is the most accurate technique for assessing the severity of the stenosis. However, evaluation of the patient with so-called low-flow or low-gradient aortic stenosis can be challenging and can sometimes require provocative testing such as dobutamine echocardiography. In these cases, it is important to distinguish whether the valve is indeed capable of opening further or simply behaving like a stenotic valve because of the low-pressure gradient.

Aortic valve areas <1.0 cm^2 are generally considered severe, and valve areas <0.6 cm^2 are considered critical. Because patients with good left ventricular function can often tolerate severe aortic stenosis for a considerable period of time, valve areas or gradients alone should not be used to determine whether an individual patient should undergo aortic valve surgery, as this remains a clinical decision.

Some patients with apparent aortic stenosis have subvalvular or even supravalvular obstruction. Hypertrophic cardiomyopathy represents the classic form of subvalvular aortic stenosis, but this is usually easily distinguished from aortic stenosis on echocardiography as the valve leaflets can be seen opening during systole. Subaortic membranes can behave very similarly to leaflet aortic stenosis, and the membranes themselves can be very thin and difficult to visualize, although the presence of a murmur, a gradient across the valve with aortic leaflets that appear to open normally, is highly suggestive of a membrane. Supravalvular aortic stenosis, although exceedingly rare, also occurs.

The emergence of transcatheter aortic valve intervention as a therapeutic option for patients with severe aortic stenosis who are not optimal candidates for surgical replacement has resulted in a very important clinical role for multimodality imaging. Imaging plays a critical role in preprocedural planning, intraprocedural implantation optimization, and follow-up of these patients. CT plays an important role in defining the eligibility of the proposed access site (CTA of the aorta and iliac arteries) and in defining the anatomic relationships between the aortic valve and aortic root, left ventricle, and coronary ostia. Cardiac CT and transesophageal echocardiography are also used to define the device size. Transesophageal echocardiography is used during the device implantation to ensure the best prosthesis–patient match, to assess prosthesis position and function after deployment, and to identify immediate complications (e.g., aortic insufficiency, paravalvular leak resulting from patient–prosthesis mismatch). Echocardiography is the imaging modality of choice for long-term surveillance.

Assessment of Aortic Regurgitation Assessment of aortic regurgitation requires qualitative assessment of the aortic valve structure. Aortic regurgitation is common with congenital abnormalities of the aortic valve, the most common of which is bicuspid aortic valve. Aortic regurgitation often coexists with aortic stenosis, and it is not uncommon for patients to have both severe aortic stenosis and regurgitation. Congenital abnormalities of the aortic leaflets, such as bicuspid aortic valve, are common causes of aortic insufficiency. Dilatation of the aortic root, as occurs in patients with hypertension and other disorders in which aortic dilatation can occur, can also lead to aortic regurgitation even when the valve leaflets are intrinsically normal due to malcoaptation of the leaflets. Aortic root dilatation is common in patients with aortic regurgitation, both as a cause or coexisting lesion, and the aortic root and ascending aorta should be measured and followed in these patients **(Fig. 236-20)**.

Because aortic regurgitation can result in dilatation of the left ventricle over time with ultimate reduction in ventricular function, caring for the patient with aortic regurgitation requires serial assessment of ventricular size and function. Patients whose ventricles dilate beyond an end-systolic diameter of 5.5 cm or whose LVEF declines below normal are at significantly higher risk of death or heart failure, and these measures are often used to decide the need for valve surgery. Quantitation of regurgitation itself can be performed using a number of methods. Semiquantitative visual assessment of aortic regurgitant jet width and depth by color flow Doppler remains the most used. The jet diameter as a ratio of the left ventricular outflow tract diameter proximal to the valve represents one of the most reliable indices of severity and correlates well with angiographic assessment. Similarly, the vena

FIGURE 236-20 Aortic regurgitation visualized by color flow Doppler in the parasternal long-axis view (***A***) and the parasternal short-axis view (***B***).

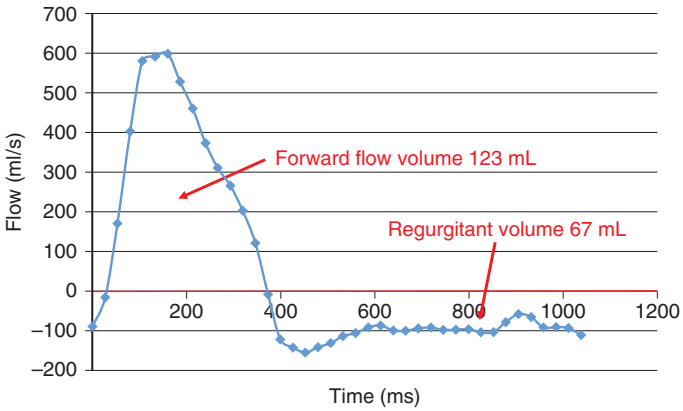

FIGURE 236-21 The resultant flow curve generated from phase contrast imaging demonstrates a forward flow of 123 mL and a regurgitant volume of 67 mL, yielding a regurgitant fraction of 54% indicating severe aortic regurgitation.

contracta, which represents the smallest diameter of the regurgitant flow at the level of the valve, can be used to assess the severity of aortic regurgitation. Other Doppler-based methods include assessing the pressure half-time, or rate of decline of the pressure gradient between the aorta and left ventricle, a measure of acuity of aortic regurgitation, and assessing aortic flow reversal in the descending aorta. The regurgitant volume can be calculated by comparing the flow across the aortic and pulmonic valves, assuming the pulmonic valve is competent.

CMR offers several advantages over echocardiography in the assessment of aortic regurgitation. CMR is more accurate than echocardiography for assessing small changes in cardiac size or function longitudinally in patients with aortic insufficiency. In addition, CMR can accurately quantify aortic regurgitant volume secondary to aortic insufficiency better than echocardiography. CMR can also capture aortic size in 3D that may be helpful in determining the etiology of the aortic regurgitation or in monitoring progression of the condition **(Fig. 236-21 and Video 236-6)**.

Assessment of Mitral Regurgitation The normal mitral valve consists of an anterior and posterior leaflet in a saddle shape configuration **(Fig. 236-22)**. The leaflets are attached to the papillary muscles via chordae tendineae that insert on the ventricular side of the leaflets. Mitral regurgitation can occur due to abnormalities of the leaflets, the chordal structures, or the ventricle, or any combination of these **(Fig. 236-23)**.

Mitral valve prolapse, in which one leaflet moves behind the plane of the other leaflet, can be due to myxomatous degeneration of the valves and leaflet redundancy, disruption of chordal structures secondary to degenerative disease, or papillary muscle rupture or dysfunction following myocardial infarction. Regurgitant jets can be visualized using color flow Doppler. The velocity of regurgitant jets is driven by the pressure gradient between the two chambers. This velocity tends to be quite high for left-sided regurgitant lesions, including mitral regurgitation and aortic regurgitation, resulting in turbulent jets on color flow Doppler (Fig. 236-23). Visual estimation of color flow Doppler is generally sufficient for qualitative assessment of regurgitant severity but can dramatically under- or overestimate regurgitation severity, particularly when regurgitant jets are quite eccentric. For this reason, quantitative assessment is generally recommended, especially when making clinical decisions about surgical intervention. The proximal isovelocity surface area (PISA) method is generally used for quantitative assessment of severity of mitral regurgitation. This method relies on estimation of the velocity of flow acceleration at a specific distance proximal to the valve with the assumption that the flow accelerates in concentric hemispheres.

As with aortic insufficiency, assessment of ventricular structure and function is also integral in the evaluation of mitral regurgitation. Although some patients have mitral regurgitation due to intrinsic abnormalities of the valve itself, in others, the valve can be relatively normal but the mitral regurgitation can be secondary to dilatation and remodeling of the left ventricle. So-called functional mitral regurgitation is generally secondary to apical displacement of the papillary muscles in a dilated ventricle, resulting in the leaflets of the mitral valve being pulled toward the apex of the heart, resulting in poor coaptation during systole and resultant relatively central mitral regurgitation. This type of mitral regurgitation can generally be distinguished from intrinsic mitral valve disease, and the surgical or procedural treatment of these conditions can be different. Knowledge of the etiology of mitral regurgitation can be important for a surgeon planning mitral valve surgery. Moreover, new procedural approaches to mitral valve disease may be different depending on the etiology.

Ventricular dilatation is an important predictor of outcome in patients with mitral regurgitation of any cause. It is important to realize that in a patient with significant mitral regurgitation, a large portion of the blood being ejected from the left ventricle with every beat is regurgitant, thus artificially increasing the ejection fraction. Thus, an ejection fraction of 55% in a patient with severe mitral regurgitation may actually represent substantial reduction in myocardial systolic function.

CMR can be helpful in evaluating mitral regurgitation in a subset of patients when echocardiographic assessment is inadequate. CMR can directly quantify regurgitant volume of the mitral regurgitant jet or indirectly quantify regurgitant volume by measuring the difference of left ventricular stroke volume and aortic forward flow.

Assessment of Mitral Stenosis Rheumatic mitral disease remains the most common cause of mitral stenosis, although mitral stenosis can also result from severe calcification of the mitral leaflets. Rheumatic mitral stenosis has a distinct appearance characterized by tethering at the leaflet tips and relative pliability of the leaflets themselves, resulting in a hockey stick–type deformation particularly of the anterior leaflet **(Fig. 236-24)**. Narrowing of the mitral orifice impedes flow from the left atrium to the left ventricle, resulting in increased pressures in the left atrium, which are then transmitted backward into the pulmonary vasculature and the right side of the heart. When mitral stenosis is suspected, echocardiography can be useful for determining etiology (specifically whether it is rheumatic or not), estimating the valve areas and gradients across the valve, assessing the left atrium, and assessing right ventricular size and function. Assessment of left atrial size and right ventricular size and function is particularly useful in helping determine the severity of the mitral stenosis.

MYOCARDIAL INFARCTION AND HEART FAILURE

Role of Imaging after Myocardial Infarction Imaging can be useful in the immediate and long-term follow-up of patients with myocardial infarction. As discussed earlier in the chapter, LGE imaging by CMR is the best technique for imaging for presence or the extent of infarcted myocardium. In a recent multicenter study, LGE imaging identified infarct location accurately and detected acute and chronic infarcts at a sensitivity of 99 and 94%, respectively. In addition, regions of microvascular obstruction (no-reflow) can be seen as dense hypoenhanced areas within the core of a bright region of infarction **(Fig. 236-25)**. Both the presence of LGE and microvascular obstruction are markers of increased clinical risk.

While echocardiography is often used to assess myocardial function immediately after myocardial infarction, myocardial stunning is common in the early post–myocardial infarction period, especially in patients who undergo reperfusion therapy. In these patients, either partial or complete recovery of ventricular function is common within several days, so that early estimation of ejection fraction may be misleading. In patients with uncomplicated myocardial infarction, imaging can generally be deferred for several days so that a more accurate assessment of cardiac function, including regional wall motion, can be assessed **(Fig. 236-26)**.

Echocardiography is the best method for assessment of patients with suspected mechanical complications after myocardial infarction. These include mitral regurgitation secondary to either papillary muscle dysfunction or rupture of papillary muscle head, ventricular septal defect, or even cardiac rupture. A new severe systolic murmur should raise suspicions for either severe mitral regurgitation or ventricular

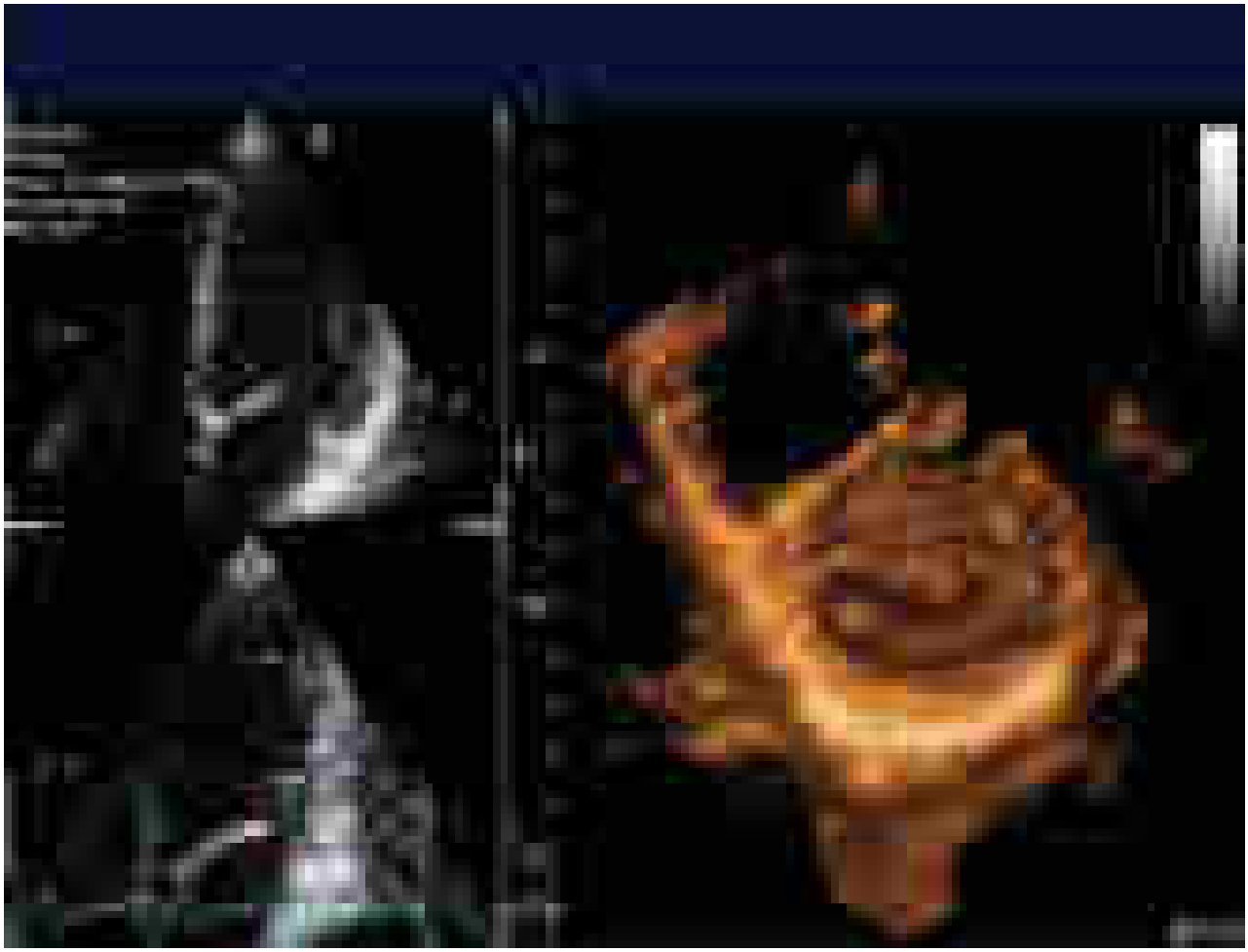

FIGURE 236-22 **Normal mitral valve** in two-dimensional views (*left*) and with three-dimensional imaging (*right*).

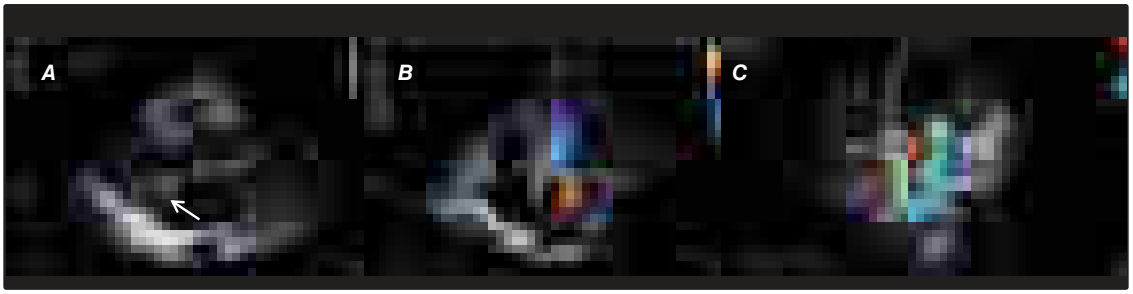

FIGURE 236-23 ***A.*** Mitral valve prolapse with posterior leaflet visualized prolapsing behind the plane of the anterior leaflet (*arrow*). ***B.*** Color flow Doppler showing mitral regurgitation in a patient with mitral valve prolapse. ***C.*** Severe functional mitral regurgitation in a patient with a dilated left ventricle.

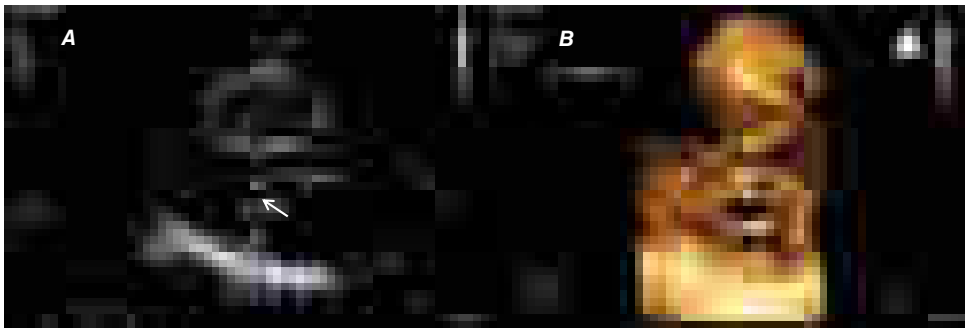

FIGURE 236-24 ***A.*** Rheumatic mitral stenosis showing pliable leaflets tethered at the tips (*arrow*). Note the characteristically enlarged left atrium. ***B.*** Mitral stenosis visualized from a three-dimensional echocardiogram.

FIGURE 236-25 Example of a patient who presented with inferior ST segment elevation myocardial infarction after several days of intermittent chest pain. The MRI confirmed an inferior MI by the location of LGE (*red arrows*). In addition, there is a central area of microvascular obstruction (dark region surrounded by the bright LGE, *white arrow*). RV: right ventricle, LV: left ventricle.

septal defect. While cardiac rupture is often catastrophic, contained ruptures, also known as pseudoaneurysms, can occur, and early diagnosis and surgical treatment are the best way to maximize survival. The presence of thrombus within the pericardial space following myocardial infarction should immediately raise suspicion of myocardial rupture and represents a surgical emergency.

Some patients demonstrate progressive left ventricular dilatation and dysfunction, known as cardiac remodeling, after myocardial infarction. Assessment of cardiac function and regional wall motion is useful in the follow-up period, generally between 1 and 6 months following infarction. The persistence of left ventricular systolic dysfunction following infarction is used to determine the type of therapy (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are typically used in patients with systolic dysfunction following myocardial infarction).

In patients with acute or subacute myocardial infarction, investigation of residual ischemia and/or viability is occasionally an important clinical question, especially among those with recurrent symptoms after myocardial infarction **(Fig. 236-27)**. All cardiac imaging techniques

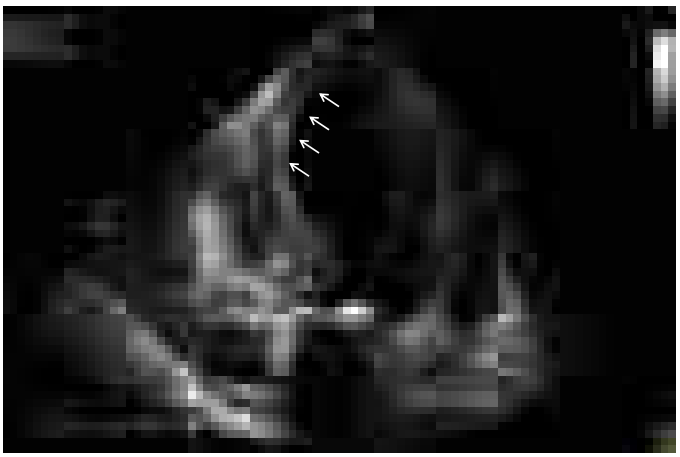

FIGURE 236-26 Acute left anterior descending artery distribution myocardial infarction at end systole showing akinetic region (*arrows*).

can provide information regarding myocardial viability and ischemia. The available data suggest that radionuclide imaging, especially PET, is highly sensitive, with higher negative predictive value than dobutamine echocardiography. In contrast, dobutamine echocardiography tends to be associated with higher specificity and positive predictive accuracy than the radionuclide imaging methods. The experience with CMR suggests that it offers similar predictive accuracies as those seen with dobutamine echocardiography.

Role of Imaging in New-Onset Heart Failure Echocardiography is usually a first-line test in patients presenting with new-onset heart failure. As discussed above, this test provides a direct assessment of ventricular function and can help distinguish patients with reduced from those with preserved ejection fraction. In addition, it provides additional structural information including an assessment of valves, myocardium, and pericardium.

Although coronary angiography is commonly performed in patients with reduced ejection fraction, the determination of heart failure etiology in an individual patient may be difficult even if angiographically obstructive CAD is present. Indeed, patients with heart failure and no angiographic CAD may have typical angina or regional wall motion abnormalities on noninvasive imaging, whereas patients with angiographically obstructive CAD may have no symptoms of angina or history of myocardial infarction. Thus, the appropriate classification for any given patient is not always clear, and it often requires the complementary information of coronary angiography and noninvasive imaging. Stress radionuclide imaging and echocardiography can be helpful in delineating the extent and severity of inducible myocardial ischemia and viability. Multiparametric CMR can be quite helpful in the differential diagnosis of heart failure etiologies. Apart from quantifying left and right ventricular volumes and function, CMR can provide information about myocardial ischemia and scar. The pattern of LGE helps differentiate infarction (typically starting in the subendocardium and involving a coronary territory) from other forms of infiltrative or inflammatory cardiomyopathies (typically involving the mid- or subepicardial layers without following a coronary distribution) **(Fig. 236-28)**. In addition, it can assess the presence of myocardial edema (e.g., myocarditis) and quantify myocardial iron deposition that can potentially lead to cardiac toxicity. Infiltrative cardiomyopathy such as amyloidosis typically has a restrictive cardiomyopathy pattern (bilateral atrial enlargement and biventricular increased wall thickness). CMR of patients with cardiac amyloidosis often also demonstrates a characteristic pattern of diffuse endocardial infiltration of the left ventricle and the atria (Fig. 236-28). Hypertrophic cardiomyopathy has variable degree of increased ventricular thickness, and often is seen to have outflow obstruction and intense LGE in regions with marked hypertrophy **(Fig. 236-29)**. CMR also can quantify myocardial iron content in patients at risk of iron-overload cardiomyopathy **(Video 236-7)**.

PET metabolic imaging has a complementary role in the evaluation of inflammatory cardiomyopathies, especially sarcoidosis where the presence of focal and/or diffuse glucose uptake can help identify areas of active inflammation. In addition, for patients undergoing immunosuppressive therapy, PET is frequently used to monitor therapeutic response **(Fig. 236-30)**. In patients with ischemic cardiomyopathy, radionuclide imaging in general and PET in particular are frequently used to quantify the presence and extent of myocardial ischemia and viability to assist with clinical decision making related to myocardial revascularization (Fig. 236-26).

ASSESSING CARDIAC FUNCTION IN PATIENTS UNDERGOING CANCER TREATMENT

Therapies used to treat cancer can adversely affect the cardiovascular system. As the efficacy of cancer treatment and survival improve, many patients are presenting with late adverse consequences from chemotherapy and/or radiation therapy on cardiovascular function. Thus, the morbidity and mortality from late cardiovascular complications threaten to offset the early gains in cancer survival, especially among children and young adults. Early recognition and treatment of cardiomyocyte injury are critical for successful application of preventative

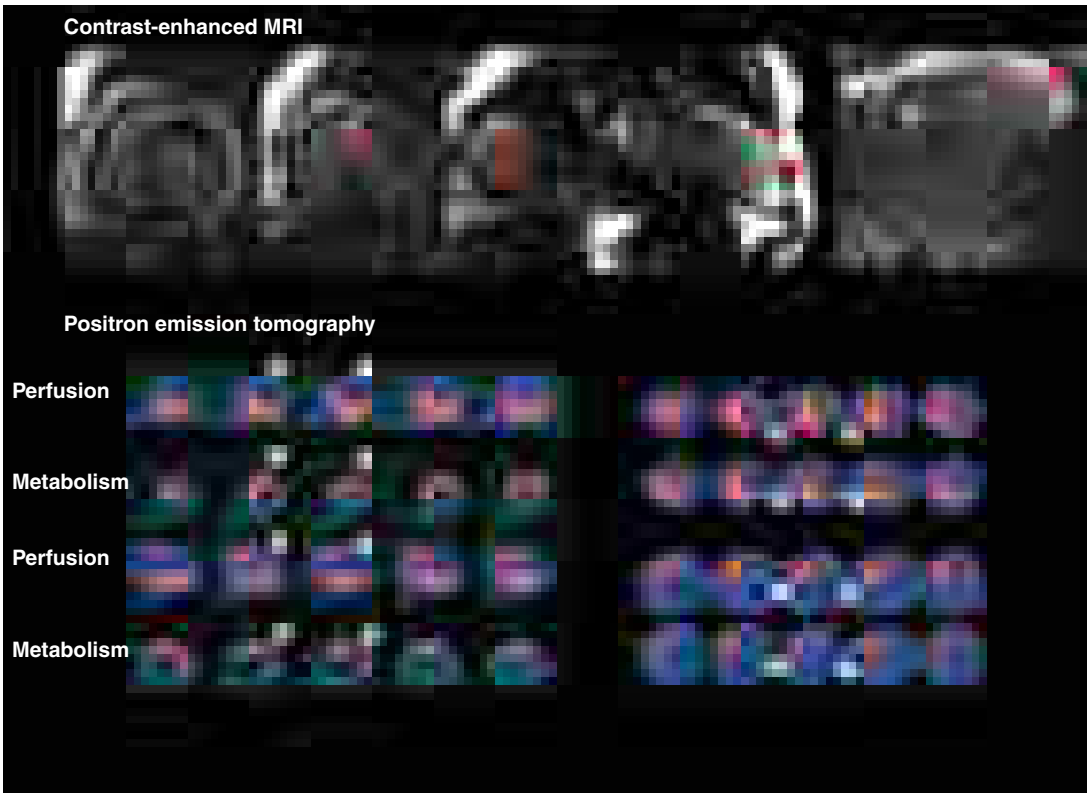

FIGURE 236-27 Examples of myocardial viability patterns obtained with cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) in three different patients with coronary artery disease. The *top panel* demonstrates extensive late gadolinium enhancement (bright white areas) involving the anterior, anteroseptal, and apical left ventricular walls (*arrows*), consistent with myocardial scar and nonviable myocardium. The *lower left panel* demonstrates rubidium-82 myocardial perfusion and ^{18}F-fluorodeoxyglucose (FDG) images showing a large and severe perfusion defect in the anterior, anterolateral, and apical walls, indicating preserved glucose metabolism (so-called *perfusion-metabolic mismatch*) consistent with viable myocardium. The *right lower panel* shows similar PET images demonstrating concordant reduction in perfusion and metabolism (so-called *perfusion-metabolic match*) in the lateral wall, consistent with nonviable myocardium.

therapies, but difficult because the adverse effects on cardiac function are a relatively late manifestation after exposure to anticancer therapy.

The accepted standard for clinical diagnosis of cardiotoxicity is defined as a >5% reduction in LVEF to <55% with symptoms of heart failure, or a >10% drop in LVEF to <55% in patients who are asymptomatic. Thus, noninvasive imaging plays a major role in diagnosing and monitoring for cardiac toxicity in patients undergoing cancer treatment. Radionuclide angiography has been the technique of choice for quite some time. However, echocardiography now plays a major role in this application.

Recently, more novel imaging approaches have been advocated, including deformation imaging with echocardiography and fibrosis imaging with CMR. These techniques have shown promising results in experimental animal models and in humans. In addition, there are also proof-of-concept studies in animal models using molecular imaging approaches targeting the mechanisms of cardiac toxicity (e.g., apoptosis and oxidant stress), which can presumably provide the earliest signs of the off-target effects of these therapies. However, these techniques are currently considered experimental.

PERICARDIAL DISEASE

The fibroelastic pericardial sac surrounding the heart consists of a visceral, or epicardial, layer and a parietal layer, with a generally small amount of pericardial fluid in between layers. The pericardium is generally quite pliable and moves easily with the heart during contraction and relaxation. Abnormalities of the pericardium can affect cardiac function primarily by impairing the heart's ability to fill. Inflammation of the pericardium can lead to an accumulation of fluid between the two layers, or *pericardial effusion*, which can be visualized by echocardiography, CMR, or CT. Other reasons for accumulation of pericardial fluid include infection, malignancy, and bleeding into the pericardium. The latter can be the result of catastrophic processes such as trauma, cardiac rupture, perforation in the setting of a cardiac procedure, cardiac surgery, or dissection of the aorta with extension in the pericardium.

Echocardiography remains the initial test of choice for assessing pericardial disease, especially effusions **(Fig. 236-31)**. Moreover, echocardiography can be useful in evaluating for pericardial constrictive physiology, in which a thick noncompliant pericardium impairs cardiac filling. The location, size, and physiologic consequences of accumulated pericardial effusion can generally easily be determined by echocardiography. Pericardial tamponade occurs when enough pericardial fluid accumulates so that the intrapericardial pressure exceeds filling pressures of the heart, generally the right ventricle. The balance between intrapericardial pressure and ventricular pressure is more important than the extent of fluid accumulation. Conditions in which pericardial effusions accumulate over a long period of time, as can be the case in the setting of malignant effusions, can lead to large pericardial fluid accumulations without the classic hemodynamic findings associated with pericardial tamponade. In contrast, rapid accumulations of pericardial fluid, such as those that occur due to cardiac rupture or perforation, can lead to tamponade physiology without very large effusions. In patients with suspected pericardial effusion or tamponade, echocardiography can usually be performed rapidly, at the bedside, and even by operators with limited skill. The distance from the parietal to the visceral pericardial layer can be measured, and when this exceeds ~1 cm, an effusion is considered significant. Echocardiographic features suggestive of tamponade include diastolic collapse of the right ventricular free wall, suggestive of pericardial pressures that exceed right ventricular filling pressures, and Doppler evidence of respiratory flow variation, which is the Doppler equivalent of pulsus paradoxus. Despite the benefits of echocardiography in suspected pericardial tamponade, the diagnosis of tamponade remains a clinical diagnosis, and other important features, such as patient's blood pressure in the presence of pulsus paradoxus, needs to be taken into account when considering therapeutic options.

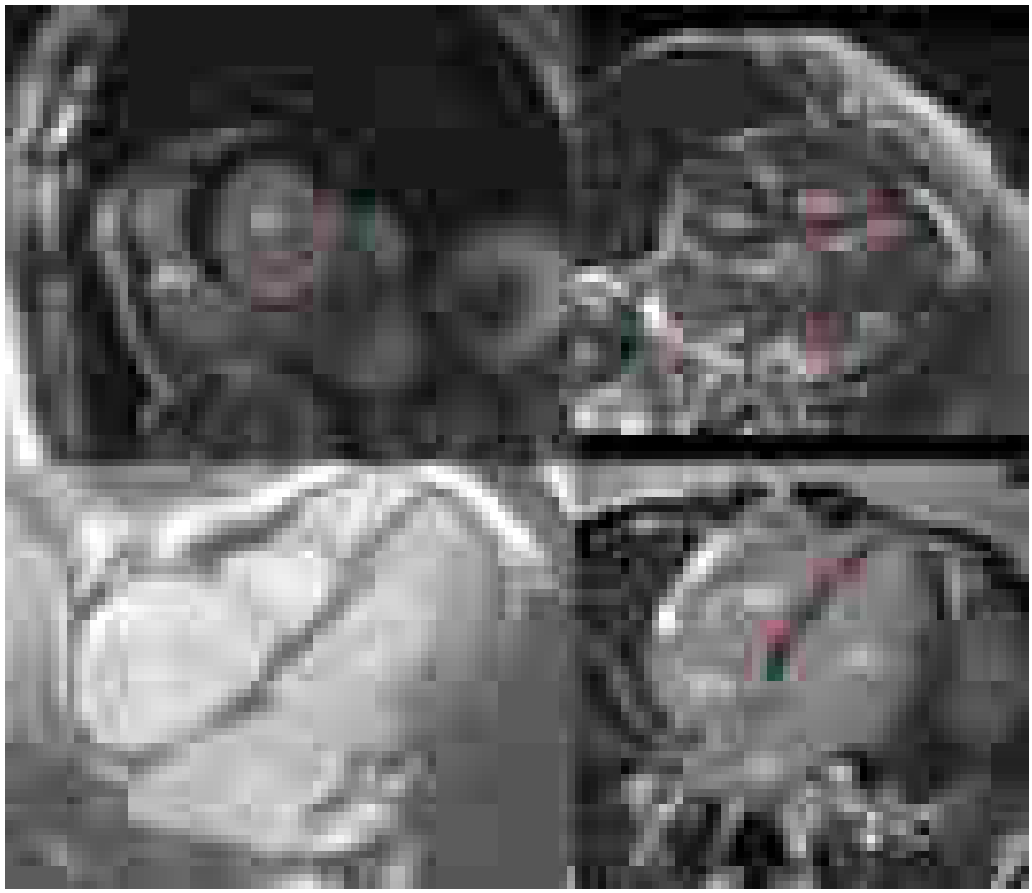

FIGURE 236-28 Differentiation of various cardiomyopathies by CMR. The left upper panel shows the short-axis late gadolinium enhancement (LGE) imaging of a patient who suffered an acute myocardial infarction. Note LGE of the endocardial myocardium in the inferior wall extending from the septum to the lateral wall associated with myocardial thinning (*arrows*). The right upper panel shows the long-axis LGE imaging of a patient who has cardiac amyloidosis. Note the diffuse LGE throughout left ventricular myocardium, the left atrium, and the interatrial septum (*arrows*). In addition, the blood pool is characteristically dark in signal indicating sequestration of gadolinium contrast out of the blood pool after injection due to a high burden of amyloidosis in other organs. The left lower panel shows a cine diastolic long-axis image of a patient with a non-ischemic dilated cardiomyopathy. Note that there is extensive sponge-like non-compacted myocardium of the LV as well as dilatation of all four cardiac chambers. This patient has a non-ischemic dilated cardiomyopathy secondary to LV non-compaction. The right lower panel shows a 22-year-old female patient with a recent episode of acute chest pain and troponins elevation. Note the multiple mid-wall foci of LGE which suggests acute myocarditis (*arrows*). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

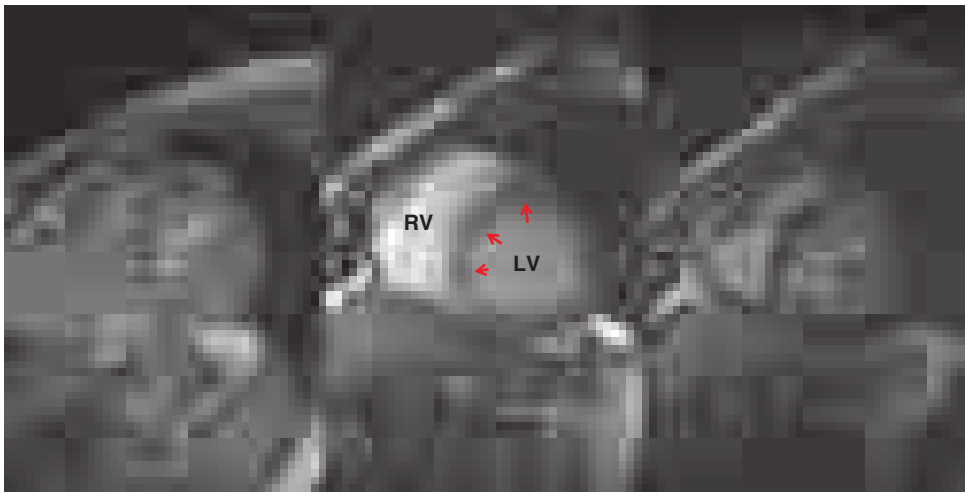

FIGURE 236-29 This figure demonstrates three pulse sequence techniques by cardiac magnetic resonance that are often used to assess patients with hypertrophic cardiomyopathy, all displayed in the mid short-axis scan plane. The *center panel* demonstrates that the left ventricle (LV) was markedly thickened in its wall thickness especially in the LV septum (*red arrows*). This finding was matched by marked regions of late gadolinium enhancement (LGE), which was consistent with fibrosis in these segments (*right panel, white arrows*). The *left panel* was cine myocardial tagging in the same slice plane. Myocardial tagging is used to assess the normal intramyocardial strain by assessing distortion of the myocardial grids during systole. In this case, despite normal-appearing systolic radial wall thickening, the myocardial strain as assessed by the distortion of grids was markedly reduced (*left panel, white arrows*). This finding is consistent with substantial myofibril disarray in the anterior and anteroseptal segments in this patient. RV, right ventricle.

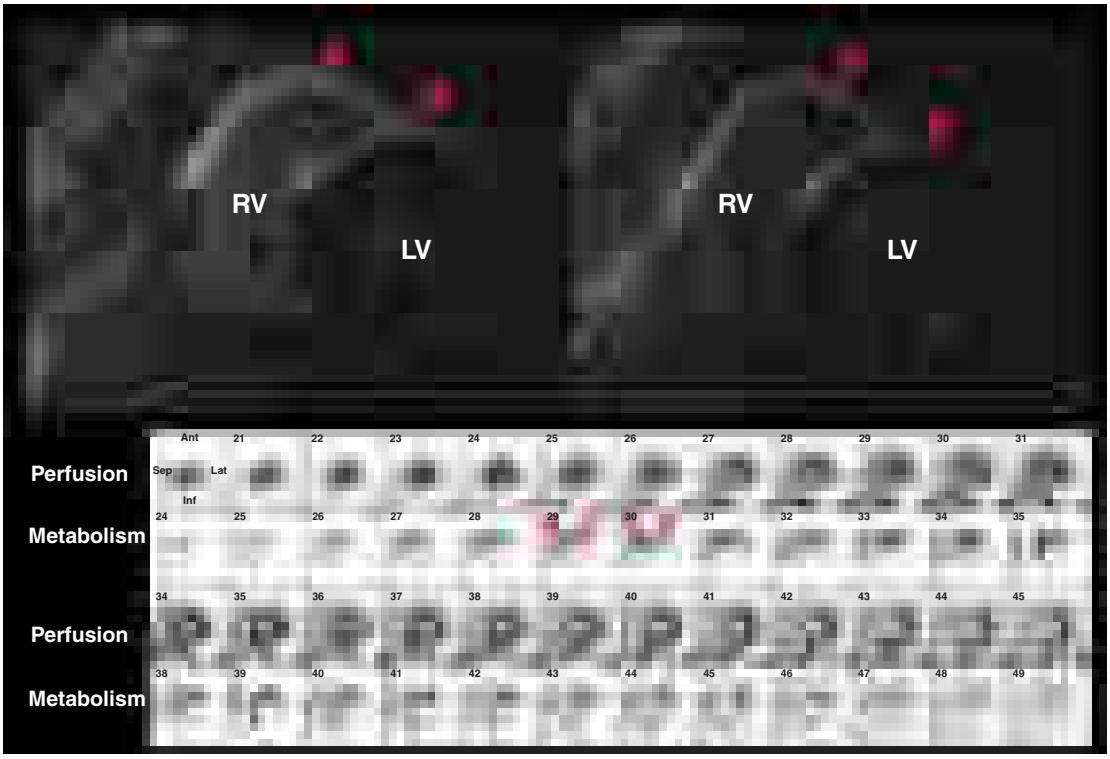

FIGURE 236-30 Representative cardiac magnetic resonance (CMR; *top panel*) and positron emission tomography (PET; *lower panel*) images from a 45-year-old male presenting with complete heart block. The CMR images demonstrate extensive late gadolinium enhancement in the subepicardial left ventricular (LV) anterior and anteroseptal walls and also in the right ventricular (RV) free wall (*arrows*). The PET images demonstrate extensive fluorodeoxyglucose uptake in the same areas, most consistent with active inflammation due to sarcoidosis.

Chronic inflammation of the pericardium leads to thickening and calcification of the parietal pericardium, resulting in pericardial constriction in which diastolic filling can be severely impaired. In these cases, filling of the ventricles comes to an abrupt halt when the volume of ventricular filling is impaired by the constricting pericardium. Assessment of pericardial thickness in these patients is important, but it is just as important to note that approximately one in five patients with severe pericardial constriction have no significant pericardial thickening by imaging or at surgery. Thus, a lack of thickened pericardium does not rule out pericardial constriction, and patients' signs and symptomatology and physiologic evidence of constriction should be assessed independently. Pericardial constriction typically demonstrates marked respiratory changes in diastolic flow on Doppler echocardiography, in contrast to restrictive cardiomyopathy, but substantial overlap exists. CT and CMR offer tomographic, whole-heart assessment of pericardial thickening and other anatomy abnormalities in pericardial constriction (enlarged atria, vena cavas, pleural and pericardial effusions) **(Fig. 236-32 and Video 236-8)**. CMR offers the

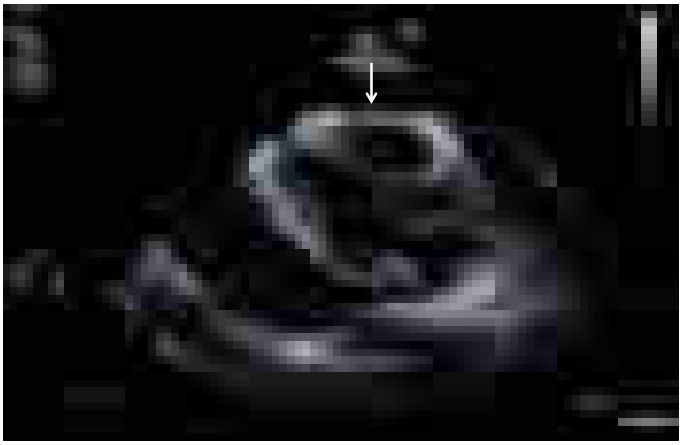

FIGURE 236-31 Pericardial effusion with tamponade physiology. The right ventricle (*arrow*) is small and collapsing in end diastole due to increased pericardial pressure.

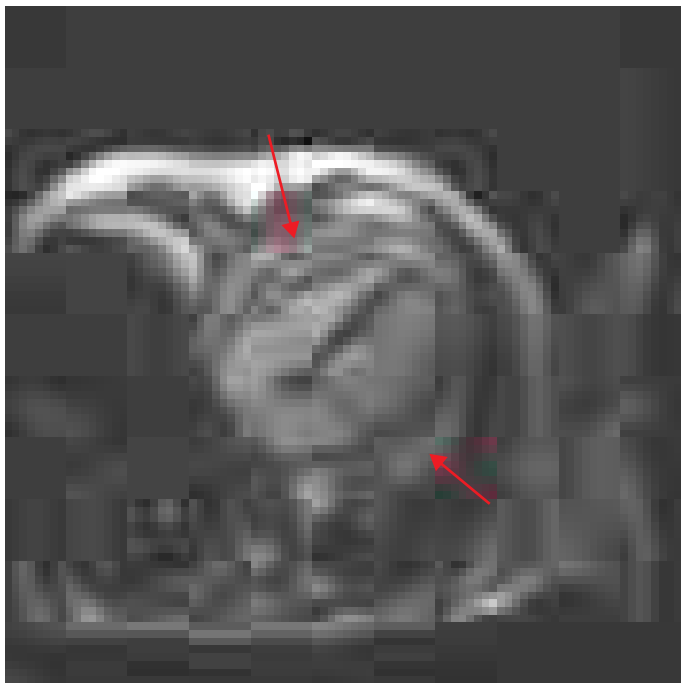

FIGURE 236-32 A female patient developed pericardial constriction and right heart failure, secondary to radiation therapy for breast cancer. Note the multiple pericardial adhesions (*red arrows*).

additional information of pericardial fibrosis and inflammation by LGE imaging and evidence of constrictive physiology (e.g., regional relaxation concordance due to myocardial adhesions, abnormal septal bounce with Valsalva maneuver).

CARDIAC THROMBUS AND MASS

Echocardiography is usually the modality that first detects a cardiac mass with differential diagnoses including thrombus, tumor, or vegetation. Given their unrestricted tomographic views and multiplanar three-dimensional imaging, CMR and CT can complement echocardiography by further characterizing the physical features of the cardiac mass. Compared to CT, CMR has the advantage of higher tissue contrast differentiation, more robust cine imaging, and the use of multifaceted techniques within the same imaging session to determine the physiologic characteristics of the mass. Gadolinium contrast enhancement patterns of increased capillary perfusion can detect vascularity within a mass which differentiates a tumor from a thrombus. Structures that are known to mimic a cardiac mass include (1) anatomic variants, such as the Eustachian valve, Chiari network, crista sagittalis or terminalis, and the right ventricular moderator band, and (2) "pseudotumors," such as interatrial septal aneurysm, coronary or aortic aneurysm, lipomatous hypertrophy of interatrial septum, hiatal hernia, or a catheter/pacemaker lead. Coexisting abnormalities that raise the likelihood of a cardiac thrombus **(Fig. 236-33)** include regional wall motion abnormality from an infarction or ventricular aneurysm, atrial fibrillation leading to slow flow in the left atrial appendage, or presence of venous catheters or recent endovascular injury. CMR has the advantage of being able to assess regional wall motion and infarction or ventricular aneurysm in matching scan planes, adjacent to the cardiac thrombus, using cine and LGE imaging, respectively. For ventricular thrombus, gadolinium-enhanced LGE imaging can detect thrombus at a higher sensitivity than echocardiography by depicting high-contrast difference between the dark thrombus and its adjacent structures and by imaging in three dimensions. In addition, mural thrombus does not enhance on first-pass perfusion and often has a characteristic "etched" appearance (black border surrounding a bright center) on LGE imaging, thus providing higher diagnostic specificity than anatomic information alone **(Fig. 236-34)**. Comparing the signal intensities of a mass before and after contrast injection may confirm the lack of tissue vascularity (i.e., thrombus) by the lack of signal enhancement after contrast administration. Like intracardiac thrombus, regions of microvascular obstruction also appear dark, but microvascular obstruction is confined within the myocardium and surrounded by infarction and thus can be differentiated from intracardiac thrombus. Cardiac CT imaging is ideally suited for small thrombus in the left atrial appendage especially in cases where transesophageal echocardiography is suboptimal or not feasible.

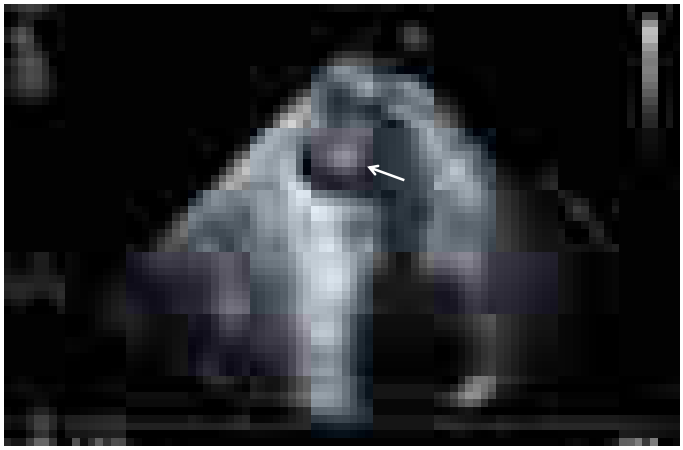

FIGURE 236-33 Cardiac thrombus (*arrow*) in an apical aneurysmal region following acute myocardial infarction.

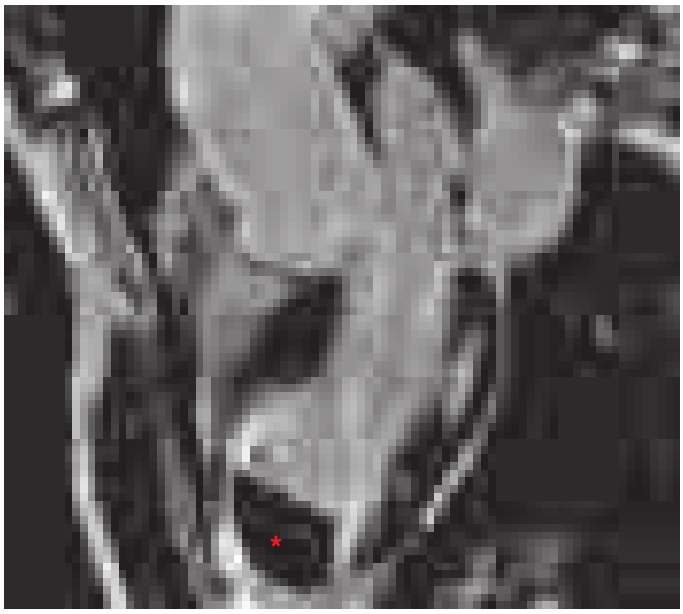

FIGURE 236-34 Late gadolinium enhancement image of a massive anterior infarction complicated by a dyskinetic left ventricular LV aneurysm and intracavitary thrombus (*red asterisk*).

The majority of cardiac malignancy is metastatic which is about twentyfold more common than primary cardiac malignancies. Metastasis to the heart can be the result of direct invasion (e.g., lung and breast), lymphatic spread (e.g., lymphomas and melanomas), or hematogenous spread (e.g., renal cell carcinoma). Primary benign cardiac tumors are seen mostly in children and young adults and include atrial myxoma, rhabdomyoma, fibroma, and endocardial fibroelastoma **(Fig. 236-35)**. Atrial myxomas are often seen as a round or multilobar mass in the left atrium (75%), right atrium (20%), or ventricles or mixed chambers (5%). They typically have inhomogeneous brightness in the center on cine steady-state free precession imaging due to their gelatinous contents and may have a pedunculated attachment to the fossa ovalis. Primary malignant cardiac tumors are rare and may include angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma.

ROLE OF IMAGING IN INFECTIOUS AND INFLAMMATORY DISEASE

Patients with suspected endocarditis often undergo echocardiography for the purpose of identifying vegetations or intramyocardial abscesses. Vegetations are generally highly mobile structures that most typically are attached to valves or present in areas of the heart with turbulent flow. The absence of a vegetation on echocardiography does not rule out endocarditis, because small vegetations below the resolution of the imaging techniques can be present. Echocardiography remains the best technique for assessment of vegetations because its high temporal resolution allows visualization of the typical oscillating motion, although large vegetations can be visualized with other techniques **(Fig. 236-36)**. The size and location of a vegetation do not necessarily provide any specific information about the type of infection. Abscesses, particularly around the aortic and mitral annuli, are particularly concerning in patients with endocarditis and should be suspected in patients with prolongation of cardiac intervals in the setting of endocarditis. Visualization of both vegetations and possible abscesses is best done with transesophageal echocardiography, particularly in patients with prosthetic valves. Indeed, transesophageal echocardiography is the first test of choice in a patient with a mechanical mitral or aortic valve and suspected endocarditis (Fig. 236-36). Vegetations should be measured because their size has prognostic importance and can be used to decide whether a patient should be taken to surgery.

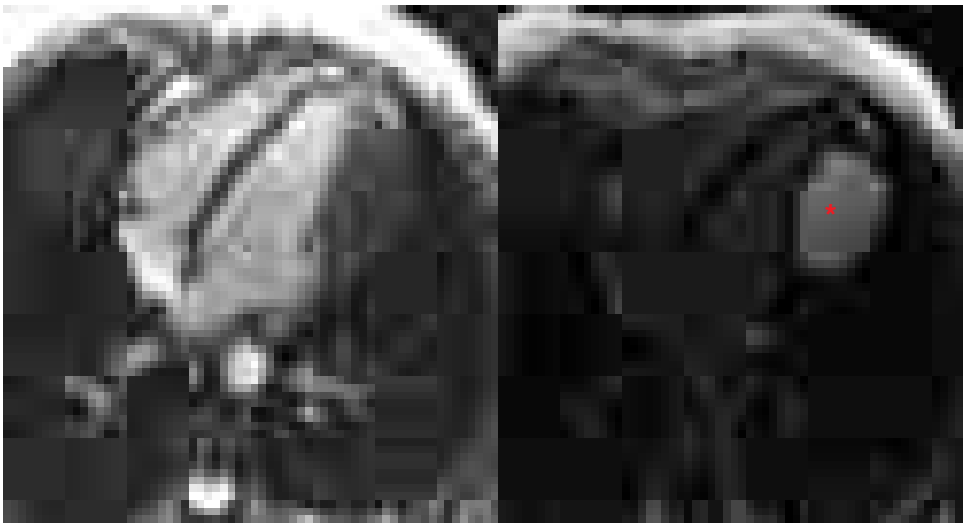

FIGURE 236-35 A case of a cardiac fibroma. A patient presented with shortness of breath and was found to have a large myocardial mass on echocardiography. Cine cardiac magnetic resonance imaging confirmed the large myocardial mass involving the anterolateral wall. Shortly after gadolinium contrast was injected, the myocardial mass demonstrated intense accumulation of contrast on LGE imaging (*right panel, asterisk*). This is a case of cardiac fibroma. The patient also has gingival hyperplasia and bifid thoracic ribs, a part of the rare Gorlin's syndrome.

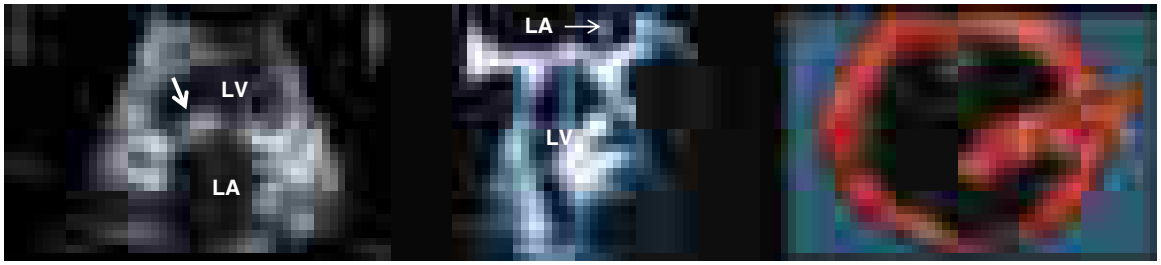

FIGURE 236-36 Vegetation on native mitral valve (*left panel, arrow*). Left atrium (LA) and left ventricle (LV) are indicated. *Middle panel* shows a vegetation on a mechanical prosthesis (St. Jude) indicated by an *arrow*; *right panel* shows vegetation on prosthesis after excision.

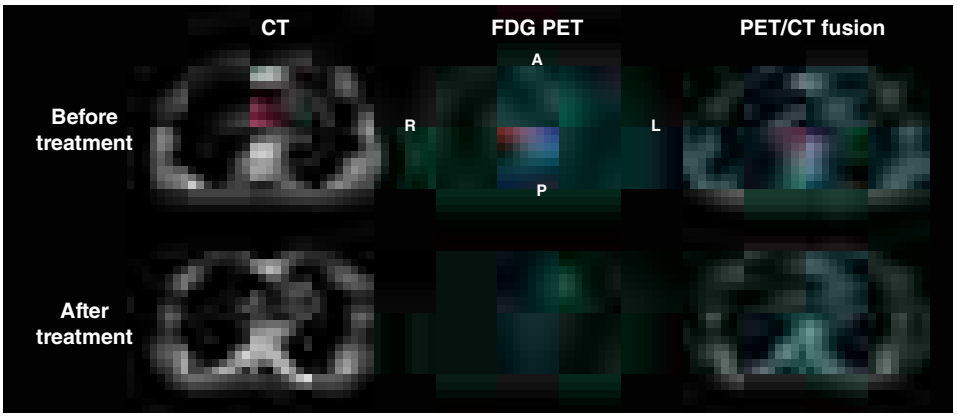

FIGURE 236-37 Representative cross-sectional computed tomography (CT; *left*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle*), and fused CT and PET (*right*) images before and after antibiotic treatment in a patient with fever and suspected infection of the stent placed in the descending portion of the aortic arch (*arrow*) for treatment of aortic coarctation. The FDG images before treatment demonstrate intense glucose uptake within the stent, consistent with inflammation/infection. The *lower panel* demonstrates significant attenuation of the FDG signal after treatment. *(Images used with permission from Dr. Sharmila Dorbala, Brigham and Women's Hospital.)*

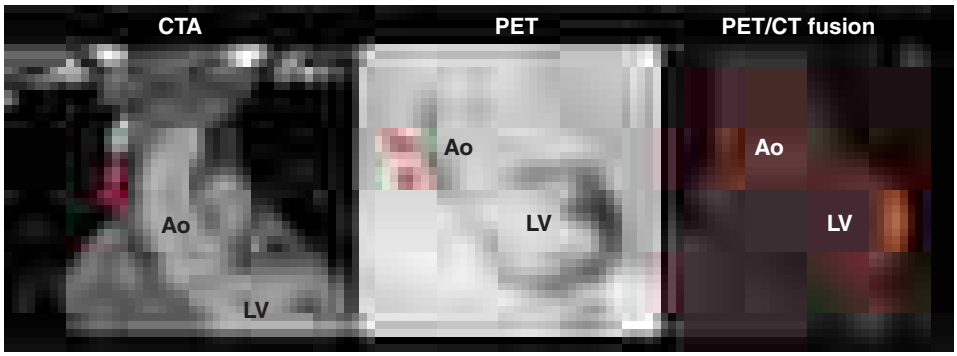

FIGURE 236-38 Representative coronal computed tomography (CT) angiographic (CTA; *left panel*), fluorodeoxyglucose (FDG) positron emission tomography (PET; *middle panel*), and fused CT and PET (*right panel*) images in a patient with suspected aortitis. The CTA images demonstrate thickening of the ascending aorta (Ao), which correlates with intense, focal FDG uptake consistent with active inflammation. LV, left ventricle.

PET metabolic imaging is emerging as a potentially useful imaging technique to identify the source of infection in patients with prosthetic valves, vascular grafts, and implantable pacemakers/defibrillators, especially in patients in whom echocardiography and/or blood cultures are negative. There is an emerging literature documenting the potential value of macrophage-targeted metabolic imaging with ^{18}F-FDG and PET **(Fig. 236-37)**. Likewise, FDG PET is also useful to identify vascular inflammation and monitor the response to immunosuppressive therapy **(Fig. 236-38)**.

EVALUATION OF COMMON CONGENITAL ABNORMALITIES IN THE ADULT

While a discussion of complex congenital heart disease is beyond the scope of this chapter, several common congenital abnormalities are present in adults, and cardiac imaging is essential to diagnosing and managing these conditions. Abnormalities of the interatrial septum probably represent the most common adult congenital cardiac abnormalities. Patent foramen ovale (PFO) can be identified in almost 25% of patients. In patients with PFO, a one-way flap in the region of the fossa ovalis is normally kept close by the left atrial pressure, which is generally higher than right atrial pressure for much of the cardiac cycle. However, right-to-left flow through a PFO can occur any time the right atrial pressure exceeds the left atrial pressure, including with maneuvers or conditions in which intrathoracic pressure is increased. The presence of a PFO can increase the likelihood of the paradoxical embolus, and thus the presence of a PFO should be determined in patients with stroke or systemic embolus of unknown etiology. Because the one-way flap of the PFO will be closed during much of the cardiac cycle, color flow Doppler will usually not reveal a PFO. Instead, agitated saline (bubble study) is the best way to assess for PFO or atrial septal defect. Saline is agitated and injected peripherally and then enters the right atrium. If no shunt is present, only the right side of the heart will be pacified because the air bubbles will be too small to traverse the lungs. Because PFO is a one-way flap, maneuvers should be used to temporarily increase right atrial pressure. Either a Valsalva maneuver or sniff maneuver can be effective.

Atrial septal defects occur most commonly in the region of the fossa ovalis, referred to as secundum-type defects **(Fig. 236-39)**. Additional atrial septal defects include defects of the sinus venosus and atrium primum. Color flow Doppler echocardiography is usually sufficient for diagnosis of a secundum-type atrial septal defect, but agitated saline is generally needed for the diagnosis of other types of atrial septal defects.

Ventricular septal defects can generally be visualized by color flow Doppler as turbulent high-velocity jets from the left to the right ventricle. In cases where the jet origin is unclear, continuous wave Doppler can estimate the velocities. These would be expected to be extremely high to reflect the pressure gradient between the left and right ventricles. Defects can occur in both the muscular and membranous portions of the ventricular septum.

In patients with either atrial or ventricular septal defects, estimation of the severity of the left-to-right shunt is essential and can be an important determinant in management decisions. Shunts are generally assessed by echocardiography by assessing the relationship between pulmonary flow and aortic flow, the Qp/Qs ratio. Shunts and cardiac anatomy of most congenital heart diseases can also be accurately evaluated by CMR **(Fig. 236-40)**.

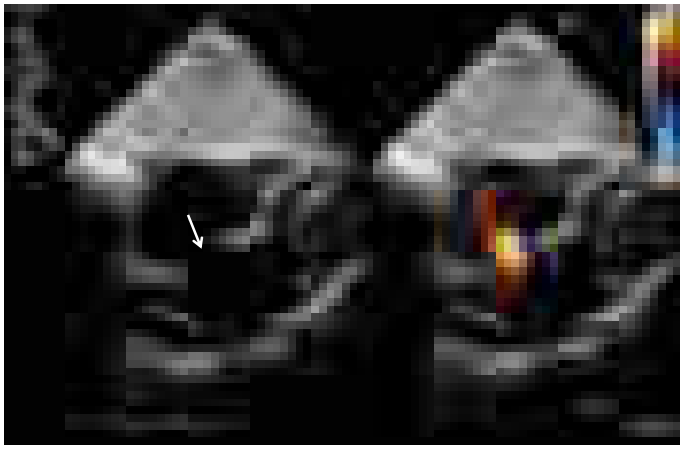

FIGURE 236-39 Large secundum-type atrial septal defect (*arrow*) noted in the subcostal view with color flow Doppler showing flow through the defect (*right*).

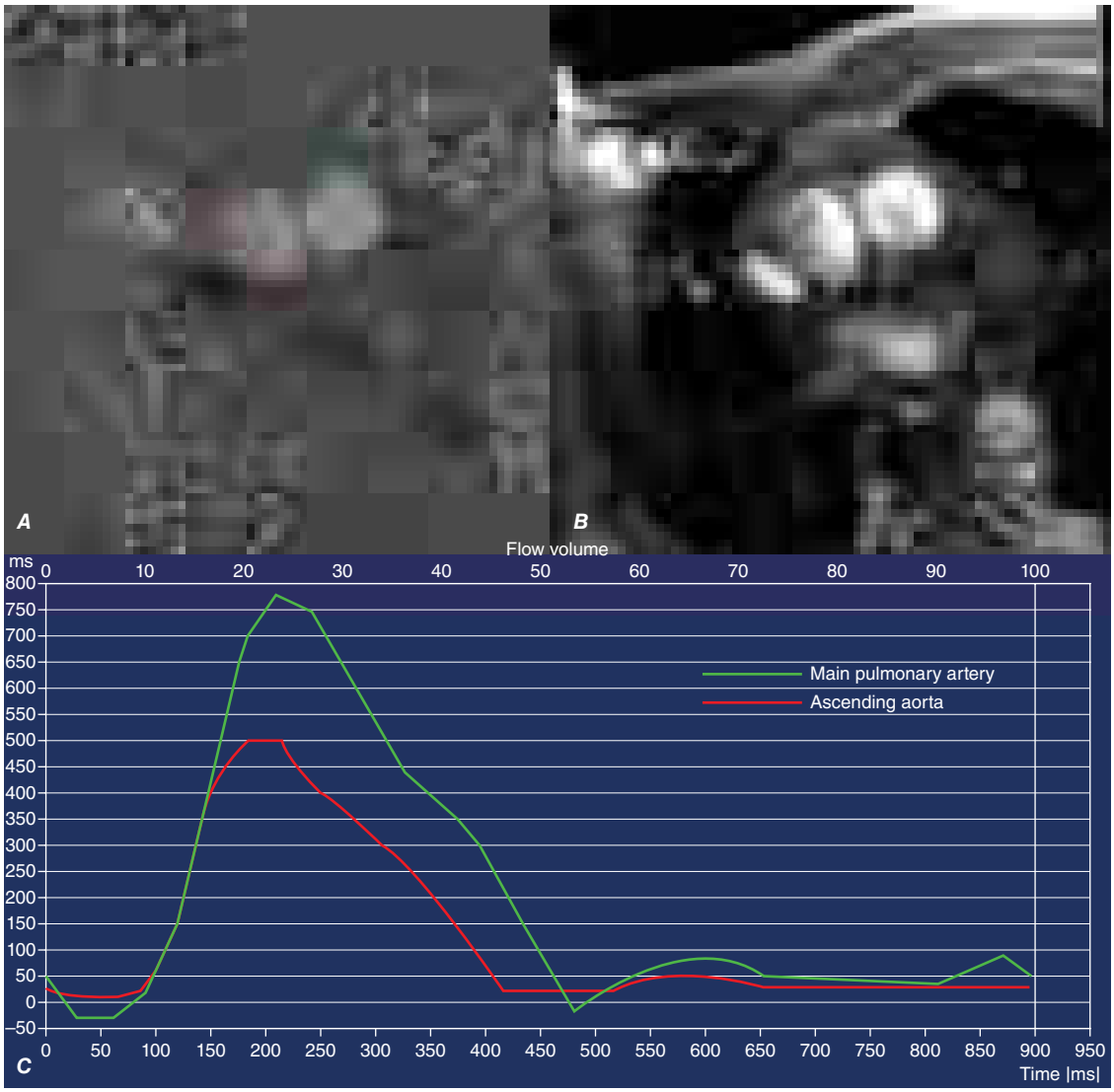

FIGURE 236-40 ***A*** and ***B*** are phase contrast images that display blood flow (phase images on ***A***) and anatomy (structural images on ***B***) of the aorta (*red*) and pulmonary artery (*green*). ***C*** demonstrates the flow curves of the aorta (*red*) and the pulmonary artery (*green*). Note that the total flow (area under the curve) was substantially higher in the pulmonary artery than the aorta, indicative of a marked elevated pulmonary-to-systemic shunt ratio, as a result of the partial anomalous pulmonary venous return that drained into the superior vena cava.

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VIDEO 236-1 Cine steady-state free precession (SSFP) imaging (*left*) in short axis in a patient who had a large anterior myocardial infarction. Only one cut of a stack of short axis is shown. This method allows quantification of left ventricular (LV) and right ventricular (RV) volumes in diastole and systole and calculation of the LV ejection fraction, stroke volumes, and cardiac output (a product of LV stroke volume and heart rate). Note that in this case there is anterior and anteroseptal akinesia (lack of systolic wall thickening, as shown by the left cine movie, *red arrows*) matching by a near-transmural myocardial infarction as seen by the matching late gadolinium enhancement (LGE) image (*right picture*, *white arrows*).

VIDEO 236-2 This is cine cardiac magnetic resonance (CMR) imaging of a patient in the long-axis four-chamber view. Note that the basal aspect of the right ventricular (RV) free wall is thickened, aneurysmal, and akinetic (*red arrows*). The global RV systolic function is mildly reduced, and the RV is dilated. CMR can image the RV using tomographic views and can quantify the RV volumes and ejection fraction volumetrically. This is a patient who presented with syncopal spells and inducible ventricular tachycardia on subsequent workup. He was diagnosed to have arrhythmogenic right ventricular dysplasia.

VIDEO 236-3 Exercise echocardiogram showing rest images on left and poststress images on right, with parasternal long-axis, upper panel, and apical four-chamber, lower panel, end-systolic frames. Following exercise, the distal septal/apical region becomes akinetic. A = upper left (UL); B = upper right (UR); C = lower left (LL); D = lower right (LR).

VIDEO 236-4 The VIDEO shows cardiac magnetic resonance (CMR) myocardial perfusion imaging during vasodilating stress, in three parallel-short-axis views. A bolus of gadolinium contrast was injected intravenously while rapid imaging acquisition occurred. The contrast enhances the right ventricle first, then travels through the pulmonary circulation, enters the left ventricle (LV), and then perfuses the LV myocardium. Myocardial perfusion defects with this technique show as black subendocardial rims, reflecting lack of contrast accumulation due to ischemia and/or scar. In this case, the anterior wall has a severe perfusion defect (*red arrow*). Figure 236-14 shows the late gadolinium enhancement (LGE) image of a mid short-axis view. There is no evidence of infarction in the anterior wall, which would be seen as bright white areas, indicating that the stress perfusion defect primarily represents myocardial ischemia. This patient had a significant stenosis of the left anterior descending coronary artery.

VIDEO 236-5 A 60-year-old female presented with intermittent chest pain of 3 days in duration but was pain-free at the time of assessment in the emergency room. Admission electrocardiogram (ECG) demonstrated T-wave inversion in the anterior precordial lead, but cardiac enzymes were normal. A resting cardiac magnetic resonance (CMR) study reviewed a large area of anteroseptal hypokinesia (*left picture*, region of hypokinesia shown by the *red arrows*), matching with a large resting perfusion defect (*middle picture*, perfusion defect shown by the *blue arrows*). Late gadolinium enhancement (LGE) imaging (*right picture*), however, did not show any enhancement to indicate any infarction in the anteroseptal wall, suggesting that the hypocontractile and hypoperfused anteroseptal wall was viable. Urgent coronary angiography demonstrated an acute thrombus in the mid left anterior descending coronary artery, which required coronary stenting. This case represents an example of acute coronary syndrome with hibernating but viable myocardium in the anteroseptal wall. The anteroseptal wall recovered contractile function when reassessed 6 months later.

VIDEO 236-6 A patient with severe aortic regurgitation quantified by cardiac magnetic resonance (CMR). Notice the dark flow jet during diastolic across the aortic valve. For quantitation of the aortic regurgitation severity, a cross-sectional cut was made just below the aortic valve, perpendicular to the aortic regurgitation jet, using phase contrast flow imaging. Apart from aortic regurgitation fraction and volume, CMR also can volumetrically quantify ventricular sizes and dimensions of the aorta, which are useful in monitoring patients with aortic valve diseases.

VIDEO 236-7 These are T2* images of the heart (*left panel*) and the liver (*right panel*) of a patient who has hemochromatosis. Note that iron and the liver are markedly darkened in these movies, indicating high load of iron in the heart muscle and liver. The rate of signal reduction (decay) in the myocardium and liver can be calculated as T2* value expressed in milliseconds. In this case, the T2* was at 10 ms. T2* <20 ms in patients with cardiomyopathy has been shown to indicate iron toxicity as the etiology of the cardiomyopathy, and it carries prognostic valve for such patients at risk of cardiac iron toxicity.

VIDEO 236-8 This video shows the heart in long and short axis. Note the large atria, thickened pericardium, and extensive pericardial adhesions. Given the extensive pericardial adhesions, there is little shearing motion of the ventricles against the parietal pericardium.

237 Diagnostic Cardiac Catheterization and Coronary Angiography

Jane A. Leopold, David P. Faxon

Diagnostic cardiac catheterization and coronary angiography are considered the gold standard in the assessment of the anatomy and physiology of the heart and its associated vasculature. In 1929, Forssmann demonstrated the feasibility of cardiac catheterization in humans when he passed a urological catheter from a vein in his arm to his right atrium and documented the catheter's position in the heart by x-ray. In the 1940s, Cournand and Richards applied this technique to patients with cardiovascular disease to evaluate cardiac function. These three physicians were awarded the Nobel Prize in 1956. In 1958, Sones inadvertently performed the first selective coronary angiography when a catheter in the left ventricle slipped back across the aortic valve, engaged the right coronary artery, and power-injected 40 mL of contrast down the vessel. The resulting angiogram provided superb anatomic detail of the artery, and the patient suffered no adverse effects. Sones went on to develop selective coronary catheters, which were modified further by Judkins, who developed preformed catheters and allowed coronary artery angiography to gain widespread use as a diagnostic tool. In the United States, cardiac catheterization is the second most common operative procedure, with more than 1.5 million procedures performed annually.

CARDIAC CATHETERIZATION

INDICATIONS, RISKS, AND PREPROCEDURE MANAGEMENT

Cardiac catheterization and coronary angiography are indicated to evaluate the extent and severity of cardiac disease in symptomatic patients and to determine if medical, surgical, or catheter-based interventions are warranted (Table 237-1). They are also used to exclude severe disease in symptomatic patients with equivocal findings on noninvasive studies and in patients with chest-pain syndromes of unclear etiology for whom a definitive diagnosis is necessary for management. Cardiac catheterization is not mandatory prior to cardiac surgery in some younger patients who have congenital or valvular heart disease that is well defined by noninvasive imaging, and who do not have symptoms or risk factors that suggest concomitant coronary artery disease.

The risks associated with elective cardiac catheterization are relatively low, with a reported risk of <0.1% for myocardial infarction,

TABLE 237-1 Indications for Cardiac Catheterization and Coronary Angiography

CORONARY ARTERY DISEASE
Asymptomatic or Symptomatic
High risk for adverse outcome based on noninvasive testing
Sudden cardiac death
Sustained (>30 s) monomorphic ventricular tachycardia
Nonsustained (<30 s) polymorphic ventricular tachycardia
Symptomatic
Canadian Cardiology Society Class II, III, or IV stable angina on medical therapy
Acute coronary syndrome (unstable angina and non-ST-segment elevation myocardial infarction)
Chest-pain syndrome of unclear etiology and equivocal findings on noninvasive tests
ST-Segment Elevation Acute Myocardial Infarction
Reperfusion with primary percutaneous coronary intervention
Persistent or recurrent ischemia
Pulmonary edema and/or reduced ejection fraction
Cardiogenic shock or hemodynamic instability
Risk stratification or positive stress test after acute myocardial infarction
Mechanical complications—mitral regurgitation, ventricular septal defect
Valvular Heart Disease
Suspected severe valve disease in symptomatic patients—dyspnea, angina, heart failure, syncope
Infective endocarditis with need for cardiac surgery
Asymptomatic patients with aortic regurgitation and cardiac enlargement or ↓ ejection fraction
Prior to cardiac surgery in patients with suspected coronary artery disease
Congestive Heart Failure
New onset with angina or suspected undiagnosed coronary artery disease
New-onset cardiomyopathy of uncertain cause or suspected to be due to coronary artery disease
Congenital Heart Disease
Prior to surgical correction, when symptoms or noninvasive testing suggests coronary disease
Suspicion for congenital coronary anomalies
Pericardial Disease
Symptomatic patients with suspected cardiac tamponade or constrictive pericarditis
Cardiac Transplantation
Preoperative and postsurgical evaluation
Other Conditions
Hypertrophic cardiomyopathy with angina
Diseases of the aorta when knowledge of coronary artery involvement is necessary for management

0.01% for stroke, and 0.1% for death. These risks increase substantially if the catheterization is performed emergently, during acute myocardial infarction or in hemodynamically unstable patients. Additional risks of the procedure include tachy- or bradyarrhythmias that require countershock or pharmacologic therapy, acute renal failure leading to transient or permanent dialysis, vascular complications that necessitate surgical repair or percutaneous intervention, and significant access-site bleeding. Of these risks, vascular access-site bleeding is the most common complication, occurring in 1.5–2.0% of patients, with major bleeding events associated with a worse short- and long-term outcome.

In patients who understand and accept the risks associated with cardiac catheterization, there are no absolute contraindications when the procedure is performed in anticipation of a life-saving intervention. Relative contraindications do, however, exist; these include decompensated congestive heart failure; acute renal failure; severe chronic renal insufficiency, unless dialysis is planned; bacteremia; acute stroke; active gastrointestinal bleeding; excessive anticoagulation or recent lytic administration, severe, uncorrected electrolyte abnormalities; a history of an anaphylactic/anaphylactoid reaction to iodinated contrast agents; and a history of allergy/anaphylaxis/bronchospasm to aspirin in patients for whom progression to a percutaneous coronary intervention is likely and aspirin desensitization has not been performed.

Contrast allergy and contrast-induced acute kidney injury merit further consideration, because these adverse events may occur in otherwise healthy individuals and prophylactic measures exist to reduce risk. Allergic reactions to contrast agents occur in <5% of cases, with severe anaphylactoid (clinically indistinguishable from anaphylaxis, but not mediated by an IgE mechanism) reactions occurring in 0.1–0.2% of patients. Mild reactions manifest as nausea, vomiting, and urticaria, while severe anaphylactoid reactions lead to hypotensive shock, pulmonary edema, and cardiorespiratory arrest. Patients with a history of significant contrast allergy should be premedicated for at least 24 hours prior to planned coronary angiography with corticosteroids and antihistamines (H_1- and H_2-blockers) and studies performed with nonionic, low-osmolar contrast agents that have a lower reported rate of allergic reactions.

Contrast-induced acute kidney injury, defined as an increase in creatinine >0.5 mg/dL or 25% above baseline that occurs 48–72 h after contrast administration, occurs in ~2–7% of patients with rates of 20–30% reported in high-risk patients, including those with diabetes mellitus, congestive heart failure, chronic kidney disease, anemia, and older age. Dialysis is required in 0.3–0.7% of patients and is associated with a fivefold increase in in-hospital mortality. For all patients, adequate intravascular volume expansion with intravenous 0.9% saline (1.0–1.5 mL/kg per hour) for 3–12 h before and continued 6–24 h after the procedure limits the risk of contrast-induced acute kidney injury. Pretreatment with *N*-acetylcysteine (Mucomyst) has not reduced the risk of contrast-induced acute kidney injury consistently and, therefore, is no longer recommended routinely. Diabetic patients treated with metformin should stop the drug 24 hours prior to the procedure and not restart until 48 hours after contrast administration to limit the associated risk of lactic acidosis. Other strategies to decrease risk include the administration of sodium bicarbonate (3 mL/kg per hour) 1 hour before and 6 hours after the procedure; use of low- or iso-osmolar contrast agents; and limiting the volume of contrast to <50 mL per procedure.

Cardiac catheterization is performed after the patient has fasted for 6 h and has received intravenous conscious sedation to remain awake but sedated during the procedure. All patients with suspected coronary artery disease are pretreated with 325 mg aspirin. In patients in whom the procedure is likely to progress to a percutaneous coronary intervention, an additional antiplatelet agent should be started: clopidogrel (600-mg loading dose and 75 mg daily) or prasugrel (60-mg loading dose and 10 mg daily), or ticagrelor (180-mg loading and 90 mg twice daily). Prasugrel should not be selected for individuals with prior stroke or transient ischemic attack. Warfarin is held starting 2–3 days prior to the catheterization to allow the international normalized ratio (INR) to fall to <1.7 and limit access-site bleeding complications. The novel oral anticoagulants should be stopped 24–48 h prior to the test. Cardiac catheterization is a sterile procedure, so antibiotic prophylaxis is not required.

TECHNIQUE

Cardiac catheterization and coronary angiography provide a detailed hemodynamic and anatomic assessment of the heart and coronary arteries. The selection of procedures is dependent on the patient's symptoms and clinical condition, with some direction provided by noninvasive studies.

Vascular Access Cardiac catheterization procedures are performed using a percutaneous technique to enter the femoral or radial artery and femoral, brachial, or internal jugular vein as the access sites for left and right heart catheterization, respectively. A flexible sheath is inserted into the vessel over a guidewire, allowing diagnostic catheters to be introduced into the vessel and advanced toward the heart using fluoroscopic guidance. The radial artery (or rarely the brachial artery) access site is advantageous in patients with peripheral arterial disease that involves the abdominal aorta, iliac, or femoral vessels; severe iliac artery tortuosity; morbid obesity; or preference for early postprocedure ambulation. Use of radial-artery access is also gaining popularity due to a lower rate of access-site bleeding complications. A normal modified Allen's test or Barbeau test confirming dual blood supply to the hand from the radial and ulnar arteries is recommended prior to access at this site. The internal jugular or antecubital veins serve as the preferred access sites to the right heart when the patient has an inferior vena cava filter in place or requires prolonged hemodynamic monitoring.

Right Heart Catheterization This procedure measures pressures in the right heart and pulmonary artery. Right heart catheterization is no longer a routine part of diagnostic cardiac catheterization, but it is reasonable in patients with unexplained dyspnea, pulmonary hypertension, valvular heart disease, pericardial disease, right and/or left ventricular dysfunction, congenital heart disease, and suspected intracardiac shunts. Right heart catheterization most commonly uses a balloon-tipped flotation catheter that is advanced sequentially to the right atrium, right ventricle, pulmonary artery, and pulmonary wedge position (as a surrogate for left atrial pressure) using fluoroscopic guidance; in each cardiac chamber, pressure is measured and blood samples are obtained for oxygen saturation analysis to screen for intracardiac shunts and calculate a cardiac output.

Left Heart Catheterization This procedure measures pressures in the left heart as a determinant of left ventricular performance. With the aid of fluoroscopy, a catheter is guided to the ascending aorta and across the aortic valve into the left ventricle to provide a direct measure of left ventricular pressure. In patients with a tilting-disc prosthetic aortic valve, crossing the valve with a catheter is contraindicated, and the left heart may be accessed via a transseptal technique from the right atrium using a needle-tipped catheter to puncture the atrial septum at the fossa ovalis. Once the catheter crosses from the right to the left atrium, it can be advanced across the mitral valve to the left ventricle. This technique is also used for mitral valvuloplasty. Heparin is given for prolonged procedures to limit the risk of stroke from embolism of clots that may form on the catheter. For patients with heparin-induced thrombocytopenia, the direct thrombin inhibitors bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg per hour for the duration of the procedure) or argatroban (350 μg/kg bolus, 15 μg/kg per min for the duration of the procedure) may be used.

HEMODYNAMICS

A comprehensive hemodynamic assessment involves obtaining pressure measurements in the right and left heart and peripheral arterial system and determining the cardiac output **(Table 237-2)**. The shape and magnitude of the pressure waveforms provide important

TABLE 237-2 Normal Values for Hemodynamic Measurements

Pressures (mmHg)	
Right atrium	
Mean	0–5
a wave	1–7
v wave	1–7
Right ventricle	
Peak systolic/end diastolic	17–32/1–7
Pulmonary artery	
Peak systolic/end diastolic	17–32/1–7
Mean	9–19
Pulmonary capillary wedge (mean)	4–12
Left atrium	
Mean	4–12
a wave	4–15
v wave	4–15
Left ventricle	
Peak systolic/end diastolic	90–130/5–12
Aorta	
Peak systolic/end diastolic	90–130/60–85
Mean	70–100
(Resistances [dyn-s]/cm^5)	
Systemic vascular resistance	900–1400
Pulmonary vascular resistance	40–120
Oxygen Consumption Index ([L-min]/m^2)	**115–140**
Arteriovenous oxygen difference (vol %)	3.5–4.8
Cardiac index ([L-min]/m^2)	2.8–4.2

diagnostic information; an example of normal pressure tracings is shown in Fig. 237-1. In the absence of valvular heart disease, the atria and ventricles are "one chamber" during diastole when the tricuspid and mitral valves are open while in systole, when the pulmonary and aortic valves are open, the ventricles and their respective outflow tracts are considered "one chamber." These concepts form the basis by which hemodynamic measurements are used to assess valvular stenosis. When aortic stenosis is present, there is a systolic pressure gradient between the left ventricle and the aorta; when mitral stenosis is present, there is a diastolic pressure gradient between the pulmonary capillary wedge (left atrial) pressure and the left ventricle (Fig. 237-2). Hemodynamic measurements also discriminate between aortic stenosis and hypertrophic obstructive cardiomyopathy where the asymmetrically hypertrophied septum creates a dynamic intraventricular pressure gradient during ventricular systole. The magnitude of this obstruction is measured using an end-hole catheter positioned at the left ventricular apex that is pulled back while recording pressure; once the catheter has passed the septal obstruction and is positioned in the apex of the left ventricle, a gradient can be measured between the left ventricular apex and the aorta. Hypertrophic obstructive cardiomyopathy is confirmed by the Brockenbrough-Braunwald sign: following a premature ventricular contraction, there is an increase in the left ventricular–aorta pressure gradient with a simultaneous decrease in the aortic pulse pressure. The finding of a decrease in pulse pressure is absent in aortic stenosis.

Regurgitant valvular lesions increase volume (and pressure) in the "receiving" cardiac chamber. In severe mitral and tricuspid regurgitation, the increase in blood flow to the atria takes place during ventricular systole, leading to an increase in the *v* wave (often two times greater than the mean pressure). Severe aortic regurgitation leads to a decrease in aortic diastolic pressure with a concomitant rise in left ventricular end-diastolic pressure, resulting in equalization of pressures between the two chambers at end-diastole.

Hemodynamic measurements are also used to differentiate between cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy (Table 237-3). In cardiac tamponade, right atrial pressure is increased with a decreased or absent "y" descent, indicative of impaired right atrial emptying in diastole, and there is diastolic equalization of pressures in all cardiac chambers. In constrictive pericarditis, right atrial pressure is elevated with a prominent "y" descent, indicating rapid filling of the right ventricle during early diastole. A diastolic dip and plateau or "square root sign," in the ventricular waveforms due to an abrupt halt in ventricular filling during diastole; right ventricular and pulmonary artery pressures are elevated; and discordant pressure changes in the right and left ventricles with inspiration (right ventricular systolic pressure increases while left ventricular systolic pressure decreases) are observed. The latter hemodynamic phenomenon is the most specific for constriction. Restrictive cardiomyopathy may be distinguished from constrictive pericarditis by a marked increase in right ventricular and pulmonary artery systolic pressures (usually >60 mmHg), a separation of the left and right ventricular diastolic pressures by >5 mmHg (at baseline or with acute volume loading), and concordant changes in left and right ventricular diastolic filling pressures with inspiration (both increase).

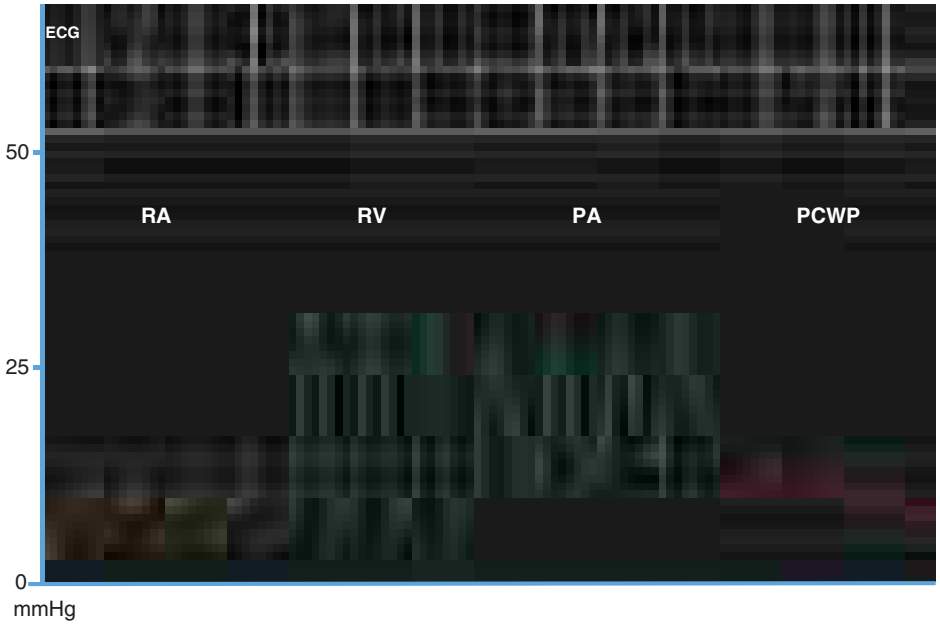

FIGURE 237-1 Normal hemodynamic waveforms recorded during right heart catheterization. Atrial pressure tracings have a characteristic "*a*" wave that reflects atrial contraction and a "*v*" wave that reflects pressure changes in the atrium during ventricular systole. Ventricular pressure tracings have a low-pressure diastolic filling period and a sharp rise in pressure that occurs during ventricular systole. d, diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrium; RV, right ventricle; s, systole.

Cardiac Output Cardiac output is measured by the Fick method or the thermodilution technique. Typically, the Fick method and thermodilution technique are both performed during cardiac catheterization, although the Fick method is considered more reliable in the presence of tricuspid regurgitation and in low-output states. The Fick method uses oxygen as the indicator substance and is based on the principle that the amount of a substance taken up or released by an organ (oxygen consumption) is equal to the product of its blood flow (cardiac output) and the difference in the concentration of the substance in

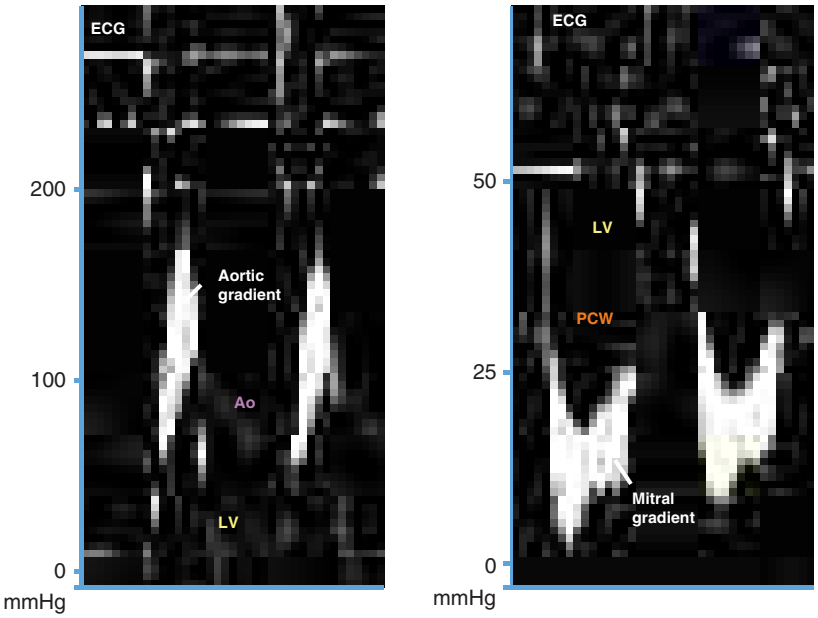

FIGURE 237-2 Severe aortic and mitral stenosis. Simultaneous recording of left ventricular (LV) and aortic (Ao) pressure tracings demonstrates a 62-mmHg mean systolic gradient (*shaded area*) that corresponds to an aortic valve area of 0.6 cm^2 (*left*). Simultaneous recording of LV and pulmonary capillary wedge (PCW) pressure tracings reveals a 14-mmHg mean diastolic gradient (*shaded area*) that is consistent with critical mitral stenosis (mitral valve area = 0.5 cm^2). d, diastole; e, end diastole; s, systole.

the arterial and venous circulation (arterial-venous oxygen difference). Thus, the formula for calculating the Fick cardiac output is:

Cardiac output (L/min) = (oxygen consumption [mL/min])/(arterial-venous oxygen difference [mL/L])

Oxygen consumption is estimated as 125 mL oxygen/minute × body surface area, and the arterial-venous oxygen difference is determined by first calculating the oxygen carrying capacity of blood (hemoglobin [g/100 mL] × 1.36 [mL oxygen/g hemoglobin] × 10) and multiplying this product by the fractional oxygen saturation. The thermodilution method measures a substance that is injected into and adequately mixes with blood. In contemporary practice, thermodilution cardiac outputs are measured using temperature as the indicator. Measurements are made with a thermistor-tipped catheter that detects temperature deviations in the pulmonary artery after the injection of 10 mL of room-temperature normal saline into the right atrium.

Vascular Resistance Resistance across the systemic and pulmonary circulations is calculated by extrapolating from Ohm's law of electrical resistance and is equal to the mean pressure gradient divided by the mean flow (cardiac output). Therefore, systemic vascular resistance is ([mean aortic pressure − mean right atrial pressure]/cardiac output) multiplied by 80 to convert the resistance from Wood units to dyn-s-cm^{-5}. Similarly, the pulmonary vascular resistance is ([mean pulmonary artery − mean pulmonary capillary wedge pressure]/cardiac output) × 80. Pulmonary vascular resistance is lowered by oxygen, nitroprusside, calcium channel blockers, prostacyclin infusions, and inhaled nitric oxide; these therapies may be administered during catheterization to determine if increased pulmonary vascular resistance is fixed or reversible.

Valve Area Hemodynamic data may also be used to calculate the valve area using the Gorlin formula that equates the area to the flow across the valve divided by the pressure gradient between the cardiac chambers surrounding the valve. The formula for the assessment of valve area is: Area = (cardiac output [cm^3/min]/[systolic ejection period or diastolic filling period][heart rate])/44.3 C × square root of the pressure gradient, where C = 1 for aortic valve and 0.85 for the mitral valve. A valve area of <1.0 cm^2 and a mean gradient >40 mmHg indicate severe aortic stenosis, while a valve area of <1.5 cm^2 and a mean gradient >5–10 mmHg are consistent with moderate-to-severe mitral stenosis; in symptomatic patients with a mitral valve area >1.5 cm^2, a mean gradient >15 mmHg, pulmonary artery pressure >60 mmHg, or a pulmonary artery wedge pressure >25 mmHg after exercise is also considered significant and may warrant intervention. The modified Hakki formula has also been used to estimate aortic valve area. This formula calculates the valve area as the cardiac output (L/min) divided by the square root of the pressure gradient. Aortic valve area calculations based on the Gorlin formula are flow-dependent and, therefore, for patients with low cardiac outputs, it is imperative to determine if a decreased valve area actually reflects a fixed stenosis or is overestimated by a low cardiac output and stroke volume that is insufficient to open the valve leaflets fully. In these instances, cautious hemodynamic manipulation using dobutamine to increase the cardiac output and recalculation of the aortic valve area may be necessary.

TABLE 237-3 Hemodynamic Findings in Tamponade, Constrictive Pericarditis, and Restrictive Cardiomyopathy

	CARDIAC TAMPONADE	CONSTRICTIVE PERICARDITIS	EFFUSIVE-CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY
Pericardial pressure	↑	↑	↑	Normal
Right atrium pressure	↑	↑	↑ (Fails to decrease by 50% or to <10 mmHg after pericardiocentesis)	↑
Right atrium pressure waveform	Prominent "x" descent Diminished or absent "y" descent	Prominent "x" descent Prominent "y" descent	Prominent "x" descent "y" descent less prominent than expected	Prominent "y" descent
Right ventricle systolic pressure	<50 mmHg	<50 mmHg	<50 mmHg	>60 mmHg
Right ventricle end-diastolic pressure	Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	>1/3 right ventricular systolic pressure Equals left ventricular end-diastolic pressure within 5 mmHg	<1/3 right ventricular systolic pressure Less than left ventricular end-diastolic pressure by ≥5 mmHg
Right ventricle pressure waveform		Dip and plateau or "square root" sign	Dip and plateau or "square root" sign	Dip and plateau or "square root" sign
Right ventricle–left ventricle systolic pressure relationship with inspiration	Discordant	Discordant	Discordant	Concordant

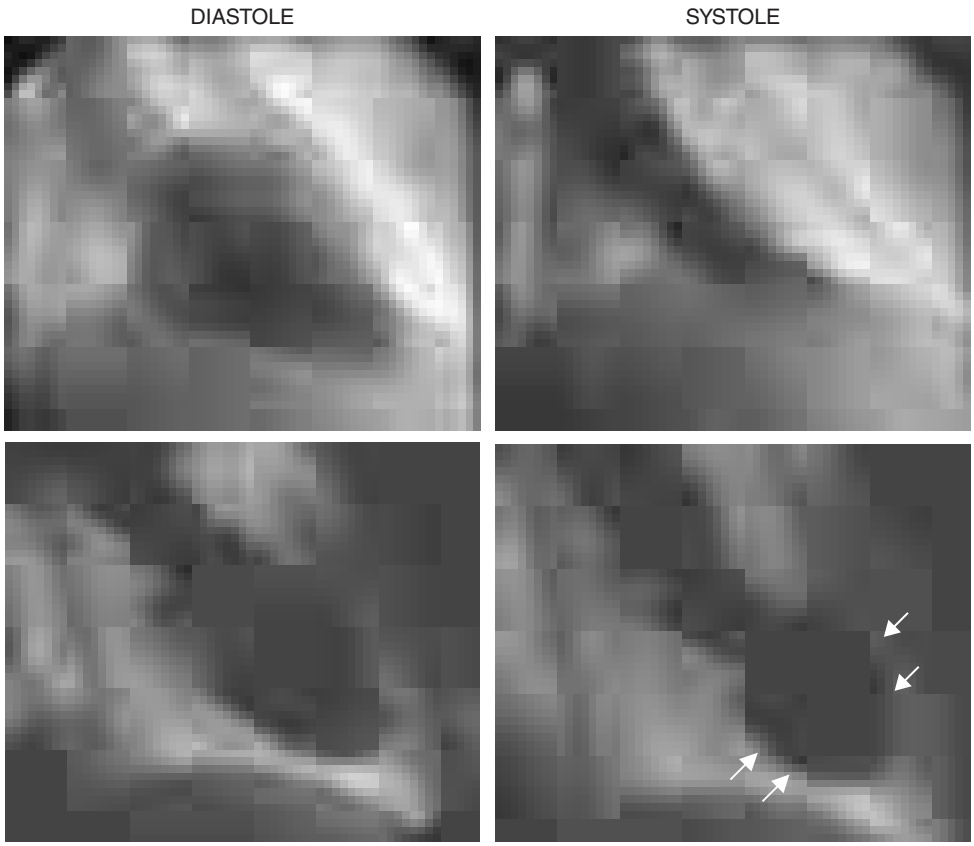

FIGURE 237-3 Left ventriculogram at end diastole (*left*) and end systole (*right*). In patients with normal left ventricular function, the ventriculogram reveals symmetric contraction of all walls (*top*). Patients with coronary artery disease may have wall motion abnormalities on ventriculography as seen in this 60-year-old male following a large anterior myocardial infarction. In systole, the anterior, apical, and inferior walls are akinetic (*white arrows*) (*bottom*).

Intracardiac Shunts In patients with congenital heart disease, detection, localization, and quantification of the intracardiac shunt should be evaluated. A shunt should be suspected when there is unexplained arterial desaturation or increased oxygen saturation of venous blood. A "step up" or increase in oxygen content indicates the presence of a left-to-right shunt while a "step down" indicates a right-to-left shunt. The shunt is localized by detecting a difference in oxygen saturation levels of 5–7% between adjacent cardiac chambers. The severity of the shunt is determined by the ratio of pulmonary blood flow (Q_p) to the systemic blood flow (Q_s), or Q_p/Q_s = ([systemic arterial oxygen content – mixed venous oxygen content]/pulmonary vein oxygen content – pulmonary artery oxygen content). For an atrial septal defect, a shunt ratio of 1.5 is considered significant and factored with other clinical variables to determine the need for intervention. When a congenital ventricular septal defect is present, a shunt ratio of ≥2.0 with evidence of left ventricular volume overload is a strong indication for surgical correction.

VENTRICULOGRAPHY AND AORTOGRAPHY

Ventriculography to assess left ventricular function may be performed during cardiac catheterization. A pigtail catheter is advanced retrograde across the aortic valve into the left ventricle and 30–45 mL of contrast is power-injected to visualize the left ventricular chamber during the cardiac cycle. The ventriculogram is usually performed in the right anterior oblique projection to examine wall motion and mitral valve function. Normal wall motion is observed as symmetric contraction of all segments; hypokinetic segments have decreased contraction, akinetic segments do not contract, and dyskinetic segments appear to bulge paradoxically during systole (Fig. 237-3). Ventriculography may also reveal a left ventricular aneurysm, pseudoaneurysm, or diverticulum and can be used to assess mitral valve prolapse and the severity of mitral regurgitation. The degree of mitral regurgitation is estimated by comparing the density of contrast opacification of the left atrium with that of the left ventricle. Minimal contrast reflux into the left atrium is considered 1+ mitral regurgitation, while contrast density in the left atrium that is greater than that in the left ventricle with reflux of contrast into the pulmonary veins within three beats defines 4+ mitral regurgitation. Ventriculography performed in the left anterior oblique projection can be used to identify a ventricular septal defect. Calculation of the ventricular volumes in systole and diastole allows calculation of stroke volume and cardiac output.

Aortography in the cardiac catheterization laboratory visualizes abnormalities of the ascending aorta, including aneurysmal dilation and involvement of the great vessels, as well as dissection with compression of the true lumen by an intimal flap that separates the true and false lumina. Aortography can also be used to identify patent saphenous vein grafts that elude selective cannulation, identify shunts that involve the aorta such as a patent ductus arteriosus, and provide a qualitative assessment of aortic regurgitation using a 1+–4+ scale similar to that used for mitral regurgitation.

CINEFLUOROSCOPY OF PROSTHETIC MECHANICAL VALVES

Prosthetic valve leaflet dysfunction may occur as a result of thrombus or obstruction of leaflet excursion by pannus (Fig. 237-4). The incidence of prosthetic valve thrombosis in left-sided valves is 0.1–6.0% per patient-year with differences in rates attributable to valve type, position, anticoagulation status, and left ventricular function. Prosthetic valve dysfunction should be suspected in patients with subtherapeutic anticoagulation with a low mean International Normalized Ratio (INR), a prothrombotic state, recent onset heart failure, cardiogenic shock, cardiac arrest, thromboembolic event or, in asymptomatic patients, an increasing gradient across the valve. Cinefluoroscopy visualizes the motion of mechanical valve leaflets, and is noninvasive, available in most centers, and can be performed rapidly with minimal radiation exposure. Prosthetic mechanical valves should be imaged *en face* and at a 90° angle over several cardiac cycles to document opening and closing of the valve leaflets as well as motion of the base ring. Each type of prosthetic valve has leaflet opening and closing angles that are reported by the manufacturer and can be used to determine if movement or closure of the valve leaflets is restricted suggestive of mechanical obstruction.

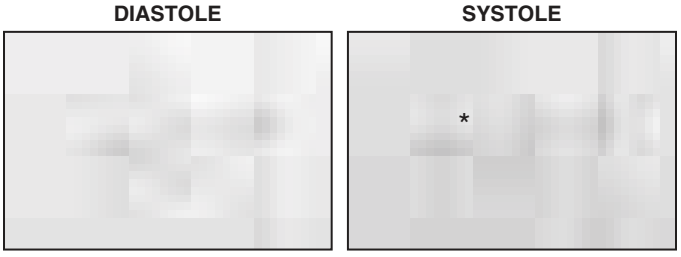

FIGURE 237-4 Cinefluoroscopic detection of mechanical valve leaflet dysfunction. Images of a bileaflet mechanical valve in the aortic position taken during diastole (*left*) and systole (*right*) show that one leaflet opens normally during systole while the other leaflet (below asterisk) remains immobile and fixed consistent with valve leaflet thrombosis.

CORONARY ANGIOGRAPHY

Selective coronary angiography is almost always performed during cardiac catheterization and is used to define the coronary anatomy and determine the extent of epicardial coronary artery and coronary artery bypass graft disease. Specially shaped coronary catheters are used to engage the left and right coronary ostia. Hand injection of radiopaque contrast agents creates a coronary "luminogram" that is recorded as radiographic images (cine angiography). Because the coronary arteries are three-dimensional objects that are in motion with the cardiac cycle, angiograms of the vessels using several different orthogonal projections are taken to best visualize the vessels without overlap or foreshortening.

The normal coronary anatomy is highly variable between individuals, but, in general, there are two coronary ostia and three major coronary vessels—the left anterior descending, the left circumflex, and the right coronary arteries with the left anterior descending and left circumflex arteries arising from the left main coronary artery (Fig. 237-5). When the right coronary artery is the origin of the atrioventricular nodal branch, the posterior descending artery, and the posterior lateral vessels, the circulation is defined as right dominant; this is found in ~85% of individuals. When these branches arise from the left circumflex artery as occurs in ~5% of individuals, the circulation is defined as left dominant. The remaining ~10% of patients have a codominant circulation with the posterior descending vessel arising from both the right coronary and the posterior lateral vessels from left coronary circulation. In some patients, a ramus intermedius branch arises directly from the left main coronary artery; this finding is a normal variant. Coronary artery anomalies occur in 1–2% of patients, with separate ostia for the left anterior descending and left circumflex arteries being the most common (0.41%).

Coronary angiography visualizes coronary artery stenoses as luminal narrowings on the cine angiogram. The degree of narrowing is referred to as the percent stenosis and is determined visually by comparing the most severely diseased segment with a proximal or distal "normal segment"; a stenosis >50% is considered significant (Fig. 237-6). Online quantitative coronary angiography can provide a more accurate assessment of the percent stenosis and lessen the tendency to overestimate lesion severity visually. The presence of a myocardial bridge, which most commonly involves the left anterior descending artery, may be mistaken for a significant stenosis; this occurs when a portion of the vessel dips below the epicardial surface into the myocardium and is subject to compressive forces during ventricular systole. The key to differentiating a myocardial bridge from a fixed stenosis is that the "stenosed" part of the vessel returns to normal during diastole. Coronary calcification is also seen during angiography prior to the injection of contrast agents. Collateral blood vessels may be seen traversing from one vessel to the distal vasculature of a severely stenosed or totally occluded vessel. Thrombolysis in myocardial infarction (TIMI) flow grade, a measure of the relative duration of time that it takes for contrast to opacify the coronary artery fully, may provide an additional clue to the degree of lesion severity, and the presence of TIMI grade 1 (minimal filling) or 2 (delayed filling) suggests that a severe coronary artery stenosis is present.

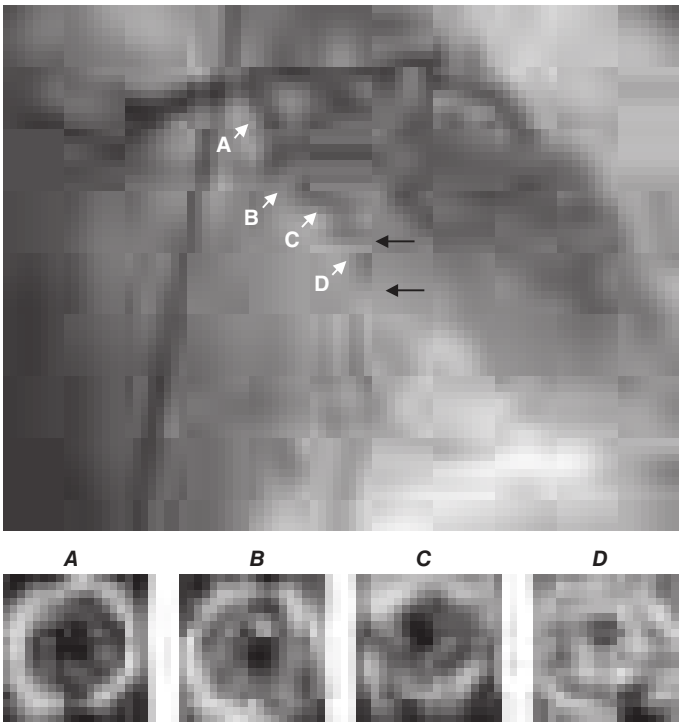

FIGURE 237-6 Coronary stenoses on cine angiogram and intravascular ultrasound. Significant stenoses in the coronary artery are seen as narrowings (*black arrows*) of the vessel. Intravascular ultrasound shows a normal segment of artery (***A***), areas with eccentric plaque (***B, C***), and near total obliteration of the lumen at the site of the significant stenosis (***D***). Note that the intravascular ultrasound catheter is present in the images as a black circle.

INTRAVASCULAR ULTRASOUND, OPTICAL COHERENCE TOMOGRAPHY, AND FRACTIONAL FLOW RESERVE

During coronary angiography, intermediate stenoses (40–70%), indeterminate findings, or anatomic findings that are incongruous with the patient's symptoms may require further interrogation. In these cases, intravascular ultrasound (IVUS) provides a more accurate anatomic assessment of the coronary artery and the degree of coronary atherosclerosis (Fig. 237-6). IVUS is performed using a small flexible catheter

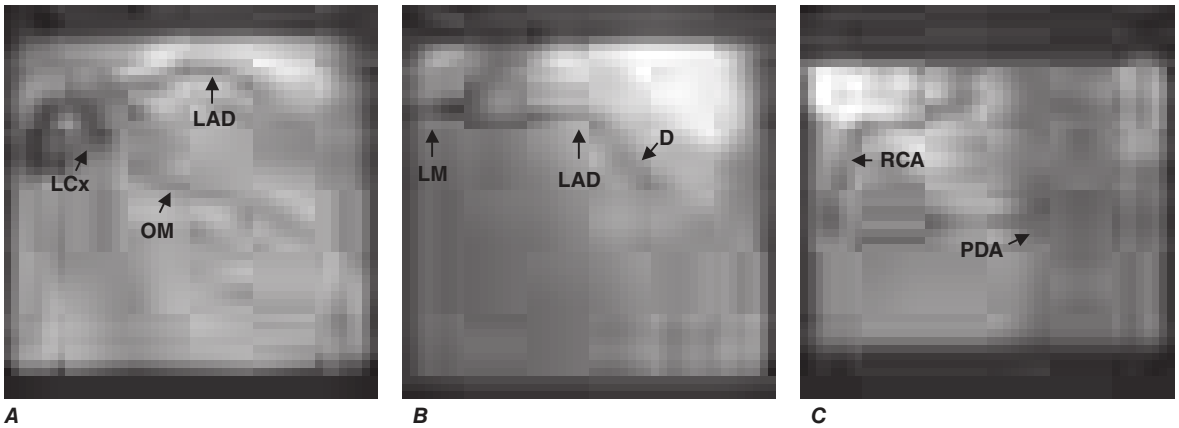

FIGURE 237-5 Normal coronary artery anatomy. ***A.*** Coronary angiogram showing the left circumflex (LCx) artery and its obtuse marginal (OM) branches. The left anterior descending (LAD) artery is also seen but may be foreshortened in this view. ***B.*** The LAD and its diagonal (D) branches are best seen in cranial views. In this angiogram, the left main (LM) coronary artery is also seen. ***C.*** The right coronary artery (RCA) gives off the posterior descending artery (PDA), so this is a right dominant circulation.

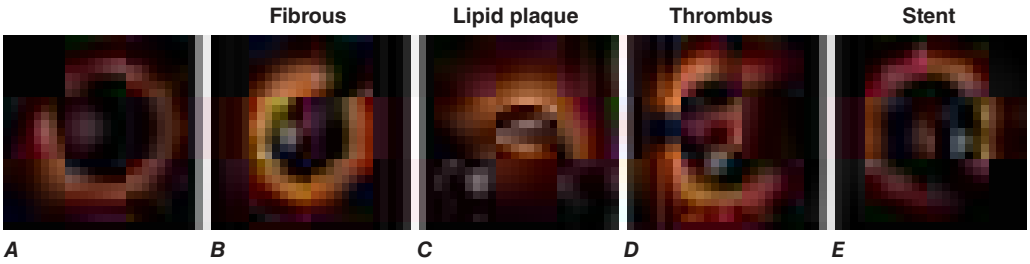

FIGURE 237-7 Optical coherence tomography imaging. ***A.*** The optical coherence tomography (OCT) catheter (*) in the lumen of a coronary artery with limited neointima formation. The intima is seen with high definition, but unlike intravascular ultrasound imaging, the vessel media and adventitia are not well visualized. ***B.*** A fibrous plaque (*arrow*) is characterized by a bright signal. ***C.*** A large, eccentric, lipid-rich plaque obscures part of the vessel lumen. Because lipid in the plaque absorbs light, the lipid-rich plaque appears as a dark area with irregular borders (*arrow*). The plaque is covered by a thin fibrous cap (*arrowhead*) typical of a vulnerable plaque. ***D.*** A thrombus (*arrow*) adherent to a ruptured plaque that is protruding into the vessel lumen. ***E.*** A coronary stent is that is well opposed to the vessel wall. The stent struts appear as short bright lines with dropout behind the struts (*arrow*).

with a 40-mHz transducer at its tip that is advanced into the coronary artery over a guidewire. Data from IVUS studies may be used to image atherosclerotic plaque precisely, determine luminal cross-sectional area, and measure vessel size; it is also used during or following percutaneous coronary intervention to assess the stenosis and determine the adequacy of stent placement. Optical coherence tomography (OCT) is a catheter-based imaging technique that uses near-infrared light to generate images with better spatial resolution than IVUS (12–18 microns vs 150–200 microns); however, the depth of field is smaller. The advantage of OCT imaging over IVUS lies in its ability to image characteristics of the atherosclerotic plaque (lipid, fibrous cap) with high definition and to assess coronary stent placement, apposition, and patency **(Fig. 237-7)**.

Measurement of the fractional flow reserve provides a functional assessment of the stenosis and is more accurate in predicting long-term clinical outcome than imaging techniques. The fractional flow reserve is the ratio of the pressure in the coronary artery distal to the stenosis divided by the pressure in the artery proximal to the stenosis at maximal vasodilation. Fractional flow reserve is measured using a coronary pressure–sensor guidewire at rest and at maximal hyperemia following the injection of adenosine **(Fig. 237-8)**. A fractional flow reserve of <0.80 indicates a hemodynamically significant stenosis that would benefit from intervention. Using both pressure and velocity, an index of myocardial resistance can also be calculated. Studies have shown this to be an important predictor of outcome as well.

POSTPROCEDURE CARE

Once the procedure is completed, vascular access sheaths are removed. If the femoral approach is used, direct manual compression or vascular closure devices that immediately close the arteriotomy site with a staple/clip, collagen plug, or sutures are used to achieve hemostasis. These devices decrease the length of supine bed rest (from 6 hours to 2–4 hours) and improve patient satisfaction, but have not been shown definitively to be superior to manual compression with respect to access-site complications. With radial-artery access, bed rest is needed for only 2 h. When cardiac catheterization is performed as an elective outpatient procedure, the patient completes postprocedure bed rest in a monitored setting and is discharged home with instructions to liberalize fluids because contrast agents promote an osmotic diuresis, to avoid strenuous activity, and to observe the vascular access site for signs of complications. Overnight hospitalization may be required for high-risk patients with significant comorbidities, patients with complications occurring during the catheterization, or patients who have undergone a percutaneous coronary intervention. Hypotension early after the procedure may be due to inadequate fluid replacement or retroperitoneal bleeding from the access site. Patients who received >2 Gy of radiation

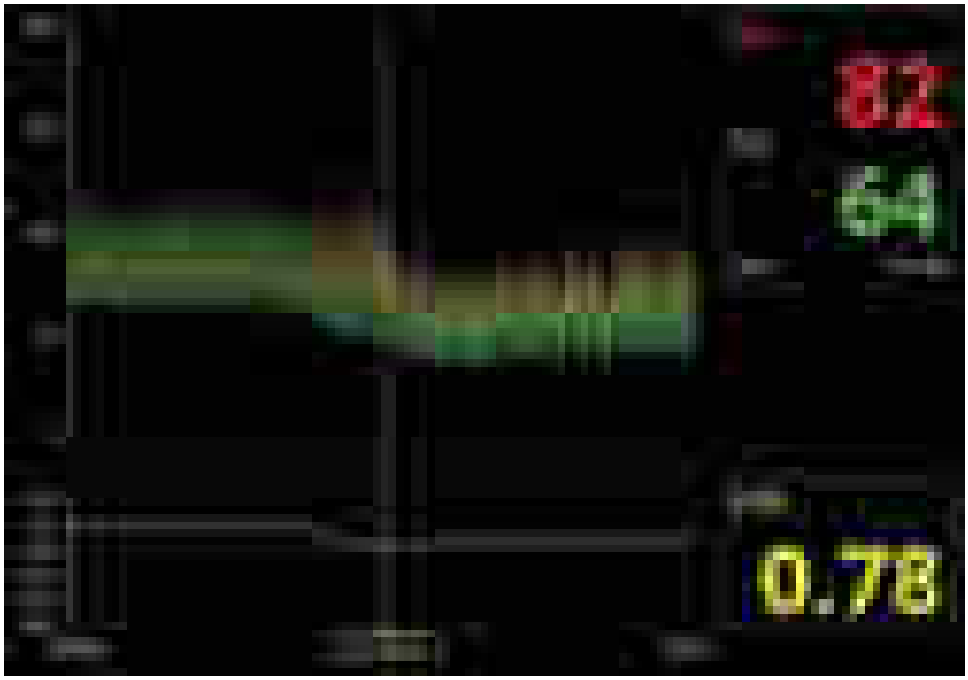

FIGURE 237-8. Fractional flow reserve. The fractional flow reserve is measured using a coronary pressure-sensor guidewire that measures the ratio of the pressure in the coronary artery distal to the stenosis (Pd, *green*) divided by the pressure in the artery proximal to the stenosis (Pa, *red*) at maximal hyperemia following the injection of adenosine. A fractional flow reserve of <0.80 indicates that revascularization would be beneficial.

during the procedure should be examined for signs of erythema. For patients who received higher doses (>5 Gy), clinical follow-up within 1 month to assess for skin injury is recommended.

FURTHER READING

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Section 3 Disorders of Rhythm

238 Principles of Electrophysiology

David D. Spragg, Gordon F. Tomaselli

HISTORY AND INTRODUCTION

The field of cardiac electrophysiology was ushered in with the development of the electrocardiogram (ECG) by Einthoven at the turn of the twentieth century. Subsequent recording of cellular membrane currents demonstrated that the body surface ECG is the timed sum of the cellular action potentials in the atria and ventricles. In the late 1960s, the development of intracavitary recording, in particular, His bundle electrograms, marked the beginning of contemporary clinical electrophysiology. Adoption of radiofrequency (RF) technology to ablate cardiac tissue in the early 1990s heralded the birth of interventional cardiac electrophysiology.

The clinical problem of sudden death caused by ventricular arrhythmias, most commonly in the setting of coronary artery obstruction, was recognized as early as the late nineteenth century. The problem was vexing and led to the development of pharmacologic and nonpharmacologic therapies, including transthoracic defibrillators, cardiac massage, and, most recently, implantable intravascular and subcutaneous defibrillators. Over time the limitations of antiarrhythmic drug therapy have been highlighted repeatedly in clinical trials, and now ablation and devices are first-line therapy for a number of cardiac arrhythmias.

In the last two decades, the genetic basis of a number of heritable arrhythmias has been elucidated, revealing important insights into the mechanisms not only of these rare arrhythmias but also of similar rhythm disturbances observed in more common forms of heart disease.

DESCRIPTIVE PHYSIOLOGY

The normal cardiac impulse is generated by pacemaker cells in the sinoatrial (SA) node situated at the junction of the right atrium and the superior vena cava **(see Fig. 235-1)**. This impulse is transmitted slowly through nodal tissue to the anatomically complex atria, where it is conducted more rapidly to the atrioventricular node (AVN), inscribing the P wave of the ECG **(see Fig. 235-2)**. There is a perceptible delay in conduction through the anatomically and functionally heterogeneous AV. The time needed for activation of the atria and the AVN delay is represented as the PR interval of the ECG. The AVN is the only electrical connection between the atria and the ventricles in the normal heart. The electrical impulse emerges from the AVN and is transmitted to the His-Purkinje system, specifically the common bundle of His, then the left and right bundle branches, and then to the Purkinje network, facilitating activation of ventricular muscle. In normal circumstances, the ventricles are activated rapidly in a well-defined fashion that is determined by the course of the Purkinje network, and this inscribes the QRS complex **(see Fig. 235-2)**. Recovery of electrical excitability occurs more slowly and is governed by the time of activation and duration of regional action potentials. The relative brevity of epicardial action potentials in the ventricle results in repolarization that occurs first on the epicardial surface and then proceeds to the endocardium, which inscribes a T wave normally of the same polarity as the QRS complex. The duration of ventricular activation and recovery is determined by the action potential duration and is represented on the body surface ECG by the QT interval **(see Fig. 235-2)**.

Cardiac myocytes exhibit a characteristically long action potential (200–400 ms) compared with neurons and skeletal muscle cells (1–5 ms). The action potential profile is sculpted by the orchestrated activity of multiple distinctive time- and voltage-dependent ionic currents **(Fig. 238-1*A*)**. The currents are carried by transmembrane proteins that passively conduct ions down their electrochemical gradients through selective pores (ion channels), actively transport ions against their electrochemical gradient (pumps, transporters), or electrogenically exchange ionic species (exchangers).

Action potentials in the heart are regionally distinct. The regional variability in cardiac action potentials is a result of differences in the number and types of ion channel proteins expressed by different cell types in the heart. Further, unique sets of ionic currents are active in pacemaking and muscle cells, and the relative contributions of these currents may vary in the same cell type in different regions of the heart (Fig. 238-1*A*).

Ion channels are complex, multisubunit transmembrane glycoproteins that open and close in response to a number of biologic stimuli, including a change in membrane voltage, ligand binding (directly to the channel or to a G protein–coupled receptor), and mechanical deformation **(Fig. 238-2)**. Other ion motive exchangers and transporters contribute importantly to cellular excitability in the heart. Ion pumps establish and maintain the ionic gradients across the cell membrane that serve as the driving force for current flow through ion channels. Transporters or exchangers that do not move ions in an electrically neutral manner (e.g., the sodium-calcium exchanger transports three Na^+ for one Ca^{2+}) are termed *electrogenic* and contribute directly to the action potential profile.

The most abundant superfamily of ion channels expressed in the heart is voltage gated. Several structural themes are common to all voltage-dependent ion channels. First, the architecture is modular, consisting either of four homologous subunits (e.g., K channels) or of four internally homologous domains (e.g., Na and Ca channels). Second, the proteins fold around a central pore lined by amino acids that exhibit exquisite conservation within a given channel family of like selectivity (e.g., all Na channels have very similar P segments). Third, the general strategy for activation gating (opening and closing in response to changes in membrane voltage) is highly conserved: the fourth transmembrane segment (S4), studded with positively charged residues, lies within the membrane field and moves in response to depolarization, opening the channel. Fourth, most ion channel complexes include not only the pore-forming proteins (α subunits) but also auxiliary subunits (e.g., β subunits) that modify channel function (Fig. 238-2).

Na and Ca channels are the primary carriers of depolarizing current in both the atria and the ventricles; inactivation of these currents and activation of repolarizing K currents hyperpolarize the heart cells, reestablishing the negative resting membrane potential **(Fig. 238-1*B*)**. The *plateau phase* is a time when little current is flowing, and relatively minor changes in depolarizing or repolarizing currents can have

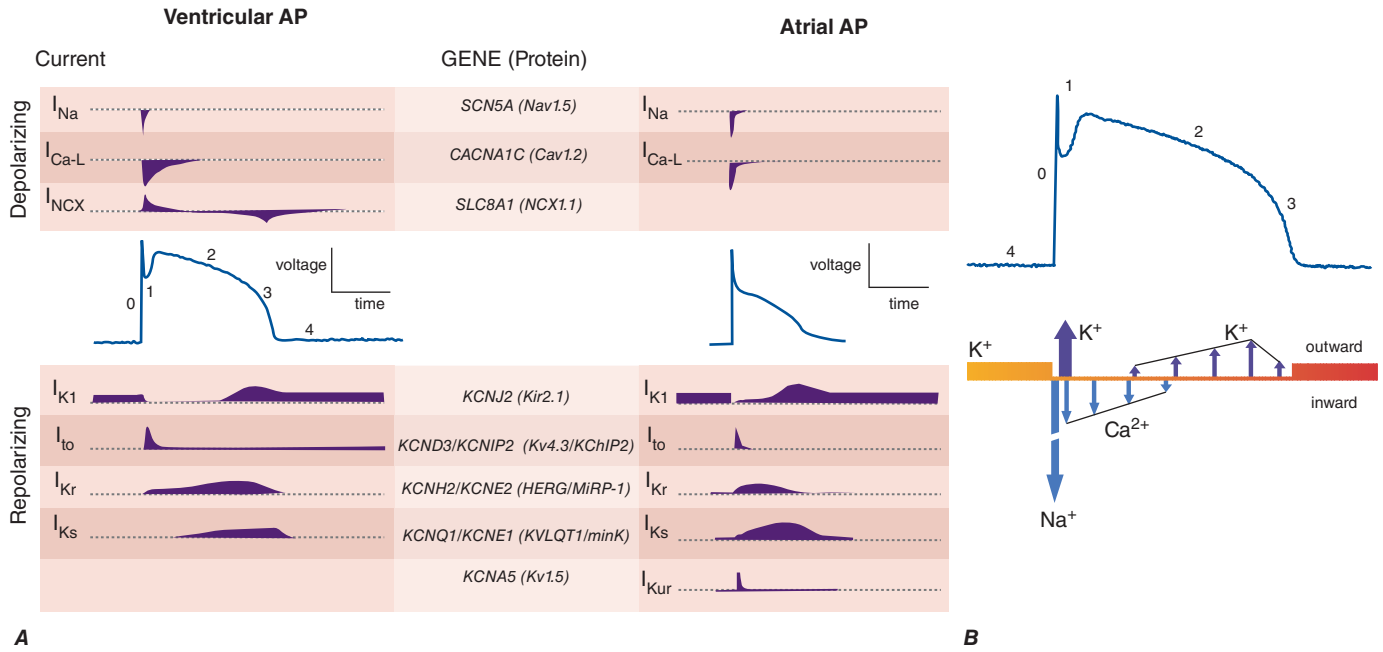

FIGURE 238-1 ***A.*** Cellular atrial and ventricular action potentials. Phases 0–4 are the rapid upstroke, early repolarization, plateau, late repolarization, and diastole, respectively. The ionic currents and their respective genes are shown above and below the action potentials. The major currents that underlie the action potentials vary in atrial and ventricular myocytes. ***B.*** A ventricular action potential with a schematic of the ionic currents flowing during the phases of the action potential. Potassium current (I_{K1}) is the principal current during phase 4 and determines the resting membrane potential of the myocyte. Sodium current generates the upstroke of the action potential (phase 0); activation of I_{to} with inactivation of the Na current inscribes early repolarization (phase 1). The plateau (phase 2) is generated by a balance of repolarizing potassium currents and depolarizing calcium current. Inactivation of the calcium current with persistent activation of potassium currents (predominantly I_{Kr} and I_{Ks}) causes phase 3 repolarization.

profound effects on the shape and duration of the action profile. Mutations in subunits of these channel proteins produce arrhythmogenic alterations in the action potentials that cause long and short QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, familial atrial fibrillation, and some forms of conduction system disease.

MECHANISMS OF CARDIAC ARRHYTHMIAS

Cardiac arrhythmias result from abnormalities of electrical impulse generation, conduction, or both. Bradyarrhythmias typically arise from disturbances in impulse formation at the level of the SA node or from disturbances in impulse propagation at any level, including exit block from the sinus node, conduction block in the AVN, and impaired conduction in the His-Purkinje system. Tachyarrhythmias can be classified according to mechanism, including enhanced automaticity (spontaneous depolarization of atrial, junctional, or ventricular pacemakers), triggered arrhythmias (initiated by afterdepolarizations occurring during or immediately after cardiac repolarization, during phase 3 or 4 of the action potential), or reentry (circus propagation of a depolarizing wavefront). A variety of mapping and pacing maneuvers typically performed during invasive electrophysiologic testing can often determine the underlying mechanism of a tachyarrhythmia **(Table 238-1)**.

Alterations in Impulse Initiation: Automaticity Spontaneous (phase 4) diastolic depolarization underlies the property of automaticity characteristic of pacemaking cells in the SA and atrioventricular (AV) nodes, His-Purkinje system, coronary sinus, and pulmonary veins. Phase 4 depolarization results from the concerted action of a number of ionic currents, including K^+ currents, Ca^{2+} currents, electrogenic Na, K-ATPase, the Na-Ca exchanger, and the so-called funny, or pacemaker, current (I_f); however, the relative importance of these currents remains controversial.

The rate of phase 4 depolarization and, therefore, the firing rates of pacemaker cells are dynamically regulated. Prominent among the factors that modulate phase 4 is autonomic nervous system tone. The negative chronotropic effect of activation of the parasympathetic nervous system is a result of the release of acetylcholine that binds to muscarinic receptors, releasing G protein βγ subunits that activate a potassium current (I_{KACh}) in nodal and atrial cells. The resulting increase in K^+ conductance opposes membrane depolarization, slowing the rate of rise of phase 4 of the action potential. Conversely, augmentation of sympathetic nervous system tone increases myocardial catecholamine concentrations, which activate both α- and β-adrenergic receptors. The effect of β_1-adrenergic stimulation predominates in pacemaking cells, augmenting both L-type Ca current (I_{Ca-L}) and I_f, thus increasing the slope of phase 4. Enhanced sympathetic nervous system activity can dramatically increase the rate of firing of SA nodal cells, producing sinus tachycardia with rates >200 beats/min. By contrast, the increased rate of firing of Purkinje cells is more limited, rarely producing ventricular tachyarrhythmias >120 beats/min.

Normal automaticity may be affected by a number of other factors associated with heart disease. Hypokalemia and ischemia may reduce the activity of Na, K-ATPase, thereby reducing the background repolarizing current and enhancing phase 4 diastolic depolarization. The end result would be an increase in the spontaneous firing rate of pacemaking cells. Modest increases in extracellular potassium may render the maximum diastolic potential more positive, thereby also increasing the firing rate of pacemaking cells. A more significant increase in $[K^+]_o$, however, renders the heart inexcitable by depolarizing the membrane potential.

Normal or enhanced automaticity of subsidiary latent pacemakers produces escape rhythms in the setting of failure of more dominant pacemakers. Suppression of a pacemaker cell by a faster rhythm leads to an increased intracellular Na^+ load ($[Na^+]_i$), and extrusion of Na^+ from the cell by Na, K-ATPase produces an increased background repolarizing current that slows phase 4 diastolic depolarization. At slower rates, $[Na^+]_i$ is decreased, as is the activity of the Na, K-ATPase, resulting in progressively more rapid diastolic depolarization and warm-up of the tachycardia rate. Overdrive suppression and warm-up are characteristic of, but may not be observed in, all automatic tachycardias. Abnormal conduction into tissue with enhanced automaticity (*entrance block*) may blunt or eliminate the phenomena of overdrive suppression and warm-up of automatic tissue.

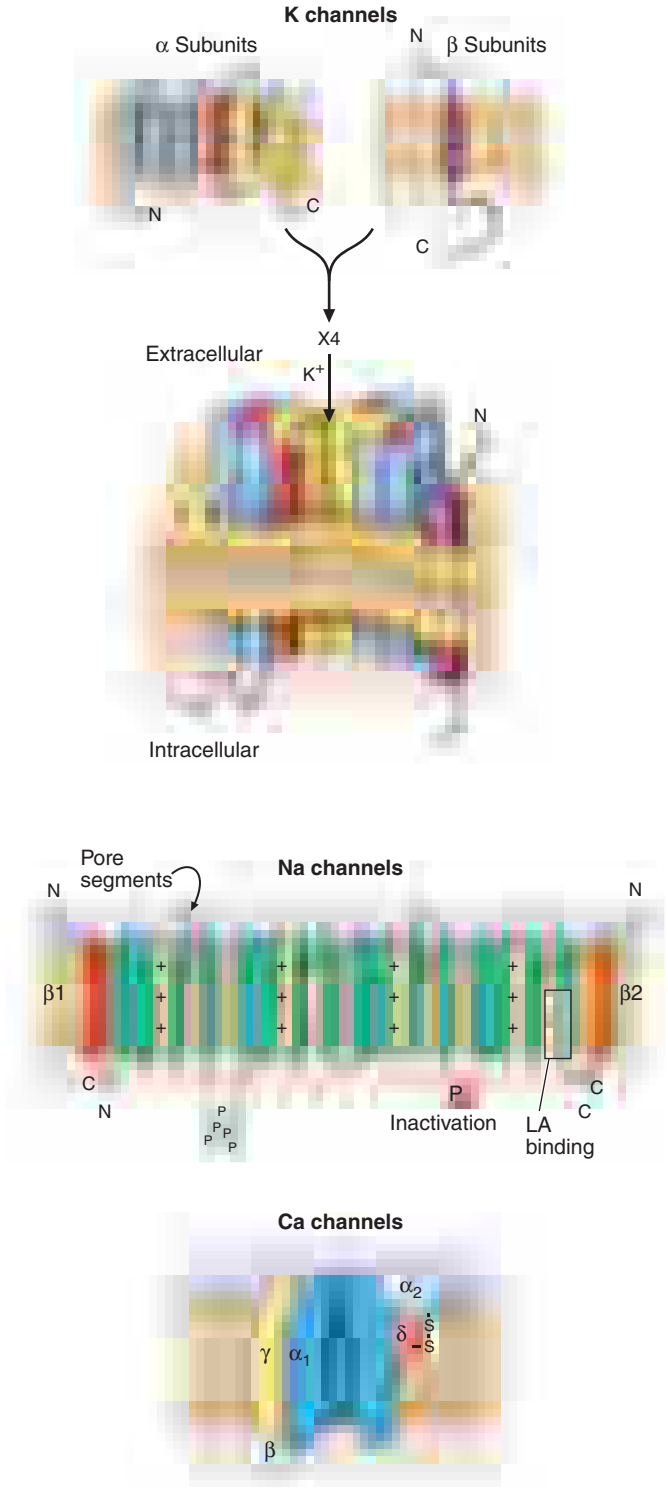

FIGURE 238-2 Topology and subunit composition of the voltage-dependent ion channels. Potassium channels are formed by the tetramerization of α or pore-forming subunits and one or more β subunits; only single β subunits are shown for clarity. Sodium and calcium channels are composed of α subunits with four homologous domains and one or more ancillary subunits. In all channel types, the loop of protein between the fifth and sixth membrane-spanning repeat in each subunit or domain forms the ion-selective pore. In the case of the sodium channel, the channel is a target for phosphorylation, the linker between the third and fourth homologous domain is critical to inactivation, and the sixth membrane-spanning repeat in the fourth domain is important in local anesthetic antiarrhythmic drug binding. The Ca channel is a multisubunit protein complex with the α_1 subunit containing the pore and major drug binding domain.

Abnormal automaticity may produce atrial tachycardia, accelerated idioventricular rhythms, and ventricular tachycardia, particularly associated with ischemia and reperfusion. It has also been suggested that injury currents at the borders of ischemic myocardium may depolarize adjacent nonischemic tissue, predisposing to automatic ventricular tachycardia.

Afterdepolarizations and Triggered Automaticity Triggered automaticity or activity refers to impulse initiation that is dependent on afterdepolarizations **(Fig. 238-3)**. Afterdepolarizations are membrane voltage oscillations that occur during (early afterdepolarizations, EADs) or after (delayed afterdepolarizations, DADs) an action potential.

The cellular feature common to the induction of DADs is the presence of an increased Ca^{2+} load in the cytosol and sarcoplasmic reticulum. Digitalis glycoside toxicity, catecholamines, and ischemia all can enhance Ca^{2+} loading sufficiently to produce DADs. Accumulation of lysophospholipids in ischemic myocardium with consequent Na^+ and Ca^{2+} overload has been suggested as a mechanism for DADs and triggered automaticity. Cells from damaged areas or cells that survive a myocardial infarction may display spontaneous release of calcium from the sarcoplasmic reticulum, and this may generate "waves" of intracellular calcium elevation and arrhythmias.

EADs occur during the action potential and interrupt the orderly repolarization of the myocyte. Traditionally, EADs have been thought to arise from action potential prolongation and reactivation of depolarizing currents, but more recent experimental evidence suggests a previously unappreciated interrelationship between intracellular calcium loading and EADs. Cytosolic calcium may increase when action potentials are prolonged. This, in turn, appears to enhance L-type Ca current, further prolonging action potential duration as well as providing the inward current driving EADs. Intracellular calcium loading by action potential prolongation may also enhance the likelihood of DADs. The interrelationship among intracellular [Ca^{2+}], EADs, and DADs may be one explanation for the susceptibility of hearts that are calcium loaded (e.g., in ischemia or congestive heart failure [CHF]) to develop arrhythmias, particularly on exposure to action potential–prolonging drugs.

EAD-triggered arrhythmias exhibit rate dependence. In general, the amplitude of an EAD is augmented at slow rates when action potentials are longer. Indeed, a fundamental condition that underlies the development of EADs is action potential and QT prolongation. Hypokalemia, hypomagnesemia, bradycardia, and, most commonly, drugs can predispose to the generation of EADs, invariably in the context of prolonging the action potential. Antiarrhythmics with class IA and III action (see below) produce action potential and QT prolongation intended to be therapeutic but frequently causing arrhythmias. Noncardiac drugs such as phenothiazines, nonsedating antihistamines, and some antibiotics can also prolong the action potential duration and predispose to EAD-mediated triggered arrhythmias. Decreased $[K^+]_o$ paradoxically may decrease membrane potassium currents (particularly the delayed rectifier current, I_{Kr}) in the ventricular myocyte, explaining why hypokalemia causes action potential prolongation and EADs. In fact, potassium infusions in patients with the congenital long QT syndrome (LQTS) and in those with drug-induced acquired QT prolongation shorten the QT interval.

EAD-mediated triggered activity probably underlies initiation of the characteristic polymorphic ventricular tachycardia, torsades des pointes, seen in patients with congenital and acquired forms of LQTS. Structural heart disease, such as cardiac hypertrophy and heart failure, may also delay ventricular repolarization (so-called electrical remodeling) and predispose to arrhythmias related to abnormalities of repolarization. The abnormalities of repolarization in hypertrophy and heart failure are often magnified by concomitant drug therapy or electrolyte disturbances.

Abnormal Impulse Conduction: Reentry The most common arrhythmia mechanism is reentry resulting from abnormal electrical impulse conduction and is defined as the circulation of an activation wave around an inexcitable obstacle. The requirements for reentry are two electrophysiologically dissimilar pathways for impulse propagation around an inexcitable region **(Fig. 238-4)**. Reentry can occur around a fixed anatomic structure (e.g., myocardial scar), with a stable pattern of cardiac depolarization moving in series over the anterograde

TABLE 238-1 Arrhythmia Mechanisms

ELECTROPHYSIOLOGIC PROPERTY	MOLECULAR COMPONENTS	MECHANISM	PROTOTYPIC ARRHYTHMIAS
Cellular			
Impulse Initiation			
Automaticity	I_f, $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, I_K, I_{K1}	Suppression/acceleration of phase 4	Sinus bradycardia, sinus tachycardia
Triggered automaticity	Calcium overload, I_{TI}	DADs	Digitalis toxicity, reperfusion VT
	$I_{Ca\text{-}L}$, I_K, I_{Na}	EADs	Torsades des pointes, congenital and acquired
Excitation	I_{Na}	Suppression of phase 0	Ischemic VF
	$I_{K\text{-}ATP}$	AP shortening, inexcitability	
	$I_{Ca\text{-}L}$	Suppression	AV block
Repolarization	I_{Na}, $I_{Ca\text{-}L}$, I_K, I_{K1}, Ca^{2+} homeostasis	AP prolongation, EADs, DADs	Polymorphic VT (HF, LVH)
	$I_{Ca\text{-}L}$, K channels, Ca^{2+} homeostasis	AP shortening	Atrial fibrillation
Multicellular			
Cellular Coupling	Connexins (Cx43), I_{Na}, $I_{K\text{-}ATP}$	Decreased coupling	Ischemic VT/VF
Tissue Structure	Extracellular matrix, collagen	Excitable gap and functional reentry	Monomorphic VT, atrial fibrillation

Abbreviations: AP, action potential; AV, atrioventricular; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; HF, heart failure; LVH, left ventricular hypertrophy; VF, ventricular fibrillation; VT, ventricular tachyarrhythmia.

and retrograde limbs of the circuit. This form of reentry, referred to as *anatomic reentry* or *excitable gap reentry* (see below), is initiated when a depolarizing wavefront encounters an area of unidirectional conduction block in the retrograde limb of the circuit. Conduction across the anterograde limb occurs with a delay that, if of sufficient duration, allows for recovery of conduction in the retrograde limb with reentry of the depolarization wave into the retrograde limb of the circuit. Sustained reentry requires that the functional dimension of depolarized tissue or the tachycardia wavelength (λ = conduction velocity × refractory period) fits within the total anatomic length of the circuit, referred to as the path length. When the path length of the circuit exceeds the λ of the tachycardia, the region between the head of the activation wave and the refractory tail is referred to as the excitable gap. Anatomically determined, excitable gap reentry can explain several clinically important tachycardias, such as AV reentry, atrial flutter, bundle branch reentry ventricular tachycardia, and ventricular tachycardia in scarred myocardium.

Reentrant arrhythmias may exist in the heart in the absence of an excitable gap and with a tachycardia wavelength nearly the same size as the path length. In this case, the wavefront propagates through partially refractory tissue without a fixed anatomic obstacle and no fully excitable gap; this is referred to as *leading circle reentry*, a form of functional reentry (reentry that depends on functional properties of the tissue). Unlike excitable gap reentry, there is no fixed anatomic circuit in leading circle reentry, and it may, therefore, not be possible to disrupt the tachycardia with pacing or destruction of a part of the circuit. Furthermore, the circuit in leading circle reentry tends to be less stable than that in excitable gap reentrant arrhythmias, with large variations in cycle length and a predilection to termination. There is strong evidence to suggest that less organized arrhythmias, such as atrial and ventricular fibrillation, are associated with more complex activation of the heart and are due to functional reentry.

Catheter-based and pharmacologic therapies for reentrant arrhythmias are designed to disrupt the anatomic circuit or alter the relationship between the wavelength and path length of the arrhythmia circuit, eliminating pathologic conduction. For example, antiarrhythmic drugs that prolong the action potential (Class III) are effective if they sufficiently prolong the λ such that it can no longer fit within the anatomic circuit. Catheter ablation is often undertaken with the goal of identifying and destroying a critical limb of the reentrant circuit (i.e., ablation of the cavotricuspid isthmus in the treatment of typical, right atrial flutter). Due to the less defined pathways of myocardial activation seen in functional reentry, ablation of these rhythms tends to target initiating triggers (e.g., pulmonary vein potentials in catheter ablation of atrial fibrillation) rather than the anatomic circuit.

Structural heart disease is associated with changes in conduction and refractoriness that increase the risk of reentrant arrhythmias. Chronically ischemic myocardium exhibits a downregulation of the gap junction channel protein (connexin 43) that carries intercellular ionic current. The border zones of infarcted and failing ventricular myocardium exhibit not only functional alterations of ionic currents but also remodeling of tissue and altered distribution of gap junctions. The changes in gap junction channel expression and distribution, in

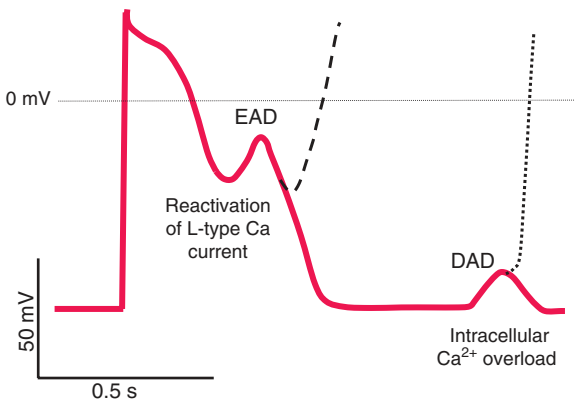

FIGURE 238-3 Schematic action potentials with early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs). Afterdepolarizations are spontaneous depolarizations in cardiac myocytes. EADs occur before the end of the action potential (phases 2 and 3), interrupting repolarization. DADs occur during phase 4 of the action potential after completion of repolarization. The cellular mechanisms of EADs and DADs differ (see text).

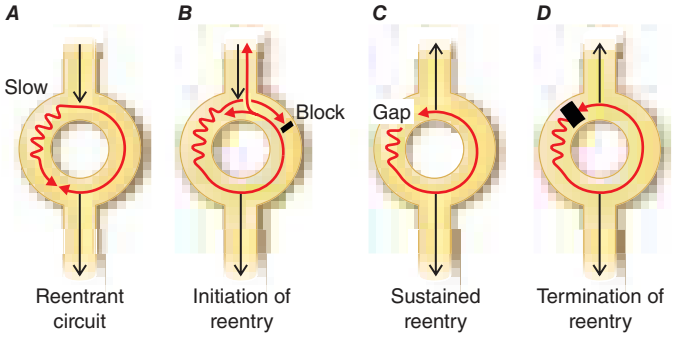

FIGURE 238-4 Schematic diagram of reentry. *A.* The circuit contains two limbs, one with slow conduction. ***B.*** A premature impulse blocks in the fast pathway and conducts over the slow pathway, allowing the fast pathway to recover so that the activation wave can reenter the fast pathway from the retrograde direction. ***C.*** During sustained reentry utilizing such a circuit, a gap (excitable gap) exists between the activating head of the wave and the recovering tail. ***D.*** One mechanism of termination of reentry occurs when the conduction and recovery characteristics of the circuit change and the activating head of the wave collides with the tail, extinguishing the tachycardia.

combination with macroscopic tissue alterations, support a role for slowed conduction in reentrant arrhythmias that complicate chronic coronary artery disease (CAD). Aged human atrial myocardium exhibits altered conduction, manifest as highly fractionated atrial electrograms, producing an ideal substrate for the reentry that may underlie the very common development of atrial fibrillation in the elderly.

APPROACH TO THE PATIENT

Cardiac Arrhythmias

The evaluation of patients with suspected cardiac arrhythmias is highly individualized; however, two key features—the history and ECG—are pivotal in directing the diagnostic workup and therapy. Patients with cardiac arrhythmias exhibit a wide spectrum of clinical presentations that range from asymptomatic ECG abnormalities to survival from cardiac arrest. In general, the more severe the presenting symptoms are, the more aggressive the evaluation and treatment are. Loss of consciousness that is believed to be of cardiac origin typically mandates an exhaustive search for the etiology and often requires invasive, device-based therapy. The presence of structural heart disease and prior myocardial infarction dictates a change in the approach to the management of syncope or ventricular arrhythmias. The presence of a family history of serious ventricular arrhythmias or premature sudden death will influence the evaluation of presumed heritable arrhythmias.

The physical examination is focused on determining whether there is cardiopulmonary disease that is associated with specific cardiac arrhythmias. The absence of significant cardiopulmonary disease often, but not always, suggests benignity of the rhythm disturbance. In contrast, palpitations, syncope, or near syncope in the setting of significant heart or lung disease have more ominous implications. In addition, the physical examination may reveal the presence of a persistent arrhythmia such as atrial fibrillation.

The judicious use of noninvasive diagnostic tests is an important element in the evaluation of patients with arrhythmias, and there is no test more important than the ECG, particularly if recorded at the time of symptoms. Uncommon but diagnostically important signatures of electrophysiologic disturbances may be unearthed on the resting ECG, such as delta waves in Wolff-Parkinson-White (WPW) syndrome, prolongation or shortening of the QT interval, right precordial ST-segment abnormalities in Brugada syndrome, and epsilon waves in arrhythmogenic right ventricular dysplasia. Variants of body surface ECG recording can provide important information about arrhythmia substrates and triggers. Holter monitoring and event recording, either continuous or intermittent, record the body surface ECG over longer periods, enhancing the possibility of observing the cardiac rhythm during symptoms. Holter monitoring is particularly useful in assessing daily symptoms thought to be attributable to arrhythmia or for quantifying a particular arrhythmia phenomenon (e.g., premature ventricular complex burden). Ambulatory event monitors are indicated when symptoms thought to be due to arrhythmia occur less frequently (i.e., several episodes per month), and, because the monitors are typically patient-activated, they are optimal for correlating symptoms with rhythm disturbances. Implantable long-term monitors permit prolonged telemetric monitoring both for diagnosis and to assess the efficacy of therapy. Implantable monitors are typically used for the evaluation of malignant symptoms that occur quite infrequently and that cannot be provoked at diagnostic electrophysiology study and increasingly assessing the presence or burden of atrial fibrillation in patients with complications of this arrhythmia, such as stroke.

Exercise electrocardiography is important in determining the presence of myocardial demand ischemia; more recently, analysis of the morphology of the QT interval with exercise has been used to assess the risk of serious ventricular arrhythmias. The exercise ECG may be particularly useful in patients with symptoms that occur during activity. Cardiac imaging plays an important role in the detection and characterization of myocardial structural abnormalities that may render the heart more susceptible to arrhythmia. Ventricular tachyarrhythmias, for instance, occur more frequently in patients with ventricular systolic dysfunction and chamber dilation, in hypertrophic cardiomyopathy, and in the setting of infiltrative diseases such as sarcoidosis. Supraventricular arrhythmias may be associated with particular congenital conditions, including AV reentry in the setting of Ebstein's anomaly. Echocardiography is a frequently employed imaging technique to screen for disorders of cardiac structure and function. Increasingly, magnetic resonance imaging of the myocardium is being used to screen for scar burden, fibrofatty infiltration of the myocardium as seen in arrhythmogenic right ventricular cardiomyopathy, and other structural changes that affect arrhythmia susceptibility.

Head-up tilt (HUT) testing is useful in the evaluation of patients with syncope in whom there is a suspicion that exaggerated vagal tone or vasodepression may play a causal role. The physiologic response to HUT is incompletely understood; however, redistribution of blood volume and increased ventricular contractility occur consistently. Exaggerated activation of a central reflex in response to HUT produces a stereotypic response of an initial increase in heart rate, then a drop in blood pressure followed by a reduction in heart rate characteristic of neurally mediated hypotension. Other responses to HUT may be observed in patients with orthostatic hypotension and autonomic insufficiency. HUT is used most often in patients with recurrent syncope, although it may be useful in patients with single syncopal episodes with associated injury, particularly in the absence of structural heart disease. In patients with structural heart disease, HUT may be indicated in those with syncope, in whom other causes (e.g., asystole, ventricular tachyarrhythmias) have been excluded. HUT has been suggested as a useful tool in the diagnosis of and therapy for recurrent idiopathic vertigo, chronic fatigue syndrome, recurrent transient ischemic attacks, and repeated falls of unknown etiology in the elderly. Importantly, HUT is relatively contraindicated in the presence of severe CAD with proximal coronary stenoses, known severe cerebrovascular disease, severe mitral stenosis, and obstruction to left ventricular outflow (e.g., aortic stenosis).

Electrophysiologic testing is central to the understanding and treatment of many cardiac arrhythmias. Indeed, most frequently, electrophysiologic testing is interventional, providing both diagnosis and therapy. The indications for electrophysiologic testing fall into several categories: to define the mechanism of an arrhythmia; to deliver catheter-based ablative treatment; and to determine the etiology of symptoms that may be caused by an arrhythmia (e.g., syncope, palpitations). The components of the electrophysiologic test are baseline measurements of conduction under resting and stressed (rate or pharmacologic) conditions and maneuvers, both pacing and pharmacologic, to induce arrhythmias. A number of sophisticated electrical mapping and catheter-guidance techniques have been developed to facilitate catheter-based therapeutics in the electrophysiology laboratory.

TREATMENT

Cardiac Arrhythmias

ANTIARRHYTHMIC DRUG THERAPY

The interaction of antiarrhythmic drugs with cardiac tissues and the resulting electrophysiologic changes are complex. An incomplete understanding of the effects of these drugs has produced serious missteps that have had adverse effects on patient outcomes and the development of newer pharmacologic agents. Currently, antiarrhythmic drugs have been relegated to an ancillary role in the treatment of most cardiac arrhythmias.

There are several explanations for the complexity of antiarrhythmic drug action: the structural similarity of target ion channels;

TABLE 238-2 Antiarrhythmic Drug Actions

DRUG	CLASS ACTIONS I	II	III	IV	MISCELLANEOUS ACTION
Quinidine	++		++		α-Adrenergic blockade
Procainamide	++		++		Ganglionic blockade
Flecainide	+++		+		
Propafenone	++	+			
Ranolazine	++		++		Late Na^+ current blockade
Eleclazine	++				Late Na^+ current blockade
Sotalol		++	+++		
Dofetilide			+++		
Amiodarone	++	++	+++	+	α-Adrenergic blockade
Dronedarone	++	+	+++	++	HCN4 blockade
Ibutilide			+++		Na^+ channel activator

regional differences in the levels of expression of channels and transporters, which change with disease; time and voltage dependence of drug action; and the effect of these drugs on targets other than ion channels. Because of the limitations of any scheme to classify antiarrhythmic agents, a shorthand that is useful in describing the major mechanisms of action is of some utility. Such a classification scheme was proposed in 1970 by Vaughan-Williams and later modified by Singh and Harrison. The classes of antiarrhythmic action are class I, local anesthetic effect due to blockade of Na^+ current; class II, interference with the action of catecholamines at the β-adrenergic receptor; class III, delay of repolarization due to inhibition of K^+ current or activation of depolarizing current; and class IV, interference with calcium conductance **(Table 238-2)**. Class I antiarrhythmics have been further subdivided based on the kinetics and potency of Na^+ channel binding; class Ia agents (quinidine, procainamide) are those with moderate potency and intermediate kinetics; class Ib agents (lidocaine, mexiletine) are those with low potency and rapid kinetics; and class Ic drugs (flecainide, propafenone) are those with high potency and the slowest kinetics. The limitations of the Vaughan-Williams classification scheme include multiple actions of most drugs, overwhelming consideration of antagonism as a mechanism of action, and the fact that several agents have none of the four classes of action in the scheme.

CATHETER ABLATION

The use of catheter ablation is based on the principle that there is a critical anatomic region of impulse generation or propagation that is required for the initiation and maintenance of cardiac arrhythmias. Destruction of such a critical region results in the elimination of the arrhythmia. The use of RF energy in clinical medicine is nearly a century old. The first catheter ablation using a DC energy source was performed in the early 1980s by Scheinman and colleagues. By the early 1990s, RF had been adapted for use in catheter-based ablation in the heart **(Fig. 238-5)**.

The RF band (300–30,000 kHz) is used to generate energy for several biomedical applications, including coagulation and cauterization of tissues. Energy of this frequency will not stimulate skeletal muscle or the heart and heats tissue by a resistive mechanism, with the intensity of heating and tissue destruction being proportional to the delivered power. Alternative, less frequently used energy sources for catheter ablation of cardiac arrhythmias include microwaves (915 MHz or 2450 MHz), lasers, ultrasound, and freezing (cryoablation). Of these alternative ablation techniques, cryoablation is being used clinically with the most frequency, especially ablation in the region of the AVN. At temperatures just below 32°C, membrane ion transport is disrupted, producing depolarization of cells, decreased action potential amplitude and duration, and slowed conduction velocity (resulting in local conduction block)—all of which are reversible if the tissue is rewarmed in a timely fashion. Tissue

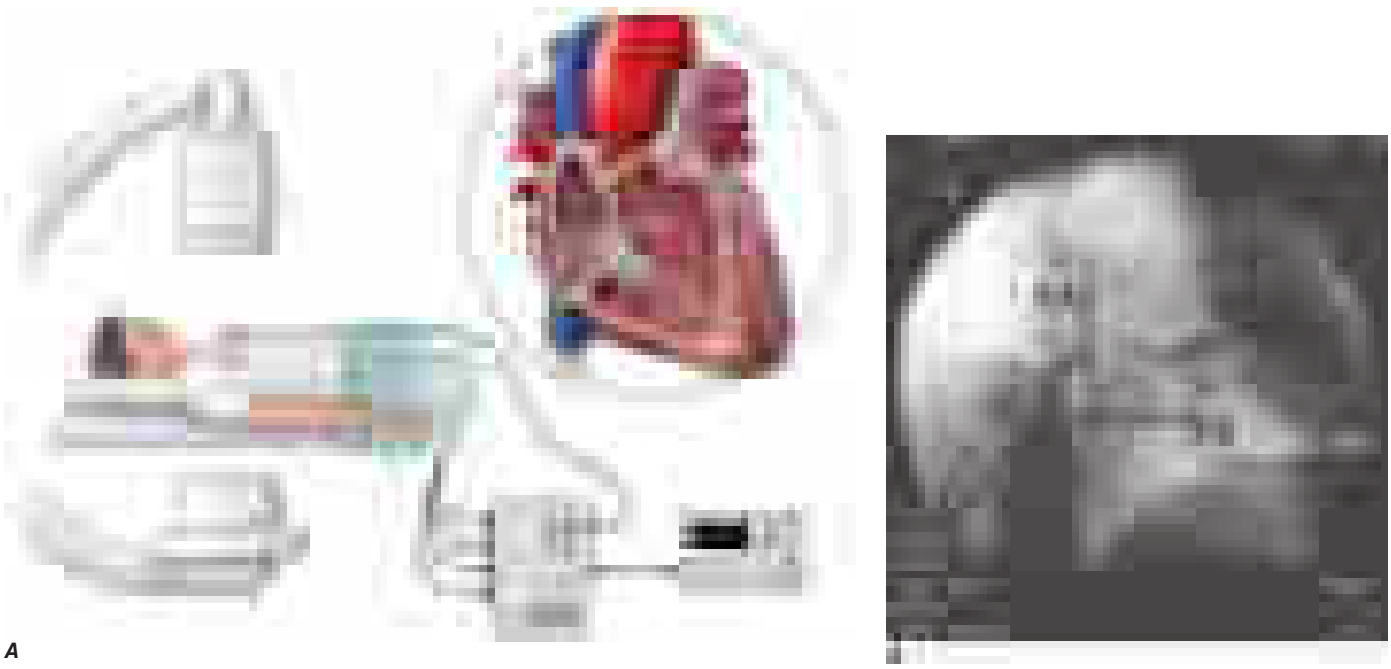

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FIGURE 238-5 Catheter ablation of cardiac arrhythmias. *A.* A schematic of the catheter system and generator in a patient undergoing radiofrequency catheter ablation (RFCA); the circuit involves the catheter in the heart and a dispersive patch placed on the body surface (usually the back). The inset shows a diagram of the heart with a catheter located at the AV valve ring for ablation of an accessory pathway. ***B.*** A right anterior oblique fluoroscopic image of the catheter position for ablation of a left-sided accessory pathway. A catheter is placed in the atrial side of the mitral valve ring (abl) via a transseptal puncture. Other catheters are placed in the coronary sinus (CS), in the right atrium (RA), and in the right ventricular (RV) apex to record local electrical activation. ***C.*** Body surface electrocardiogram recordings (I, II, V_1) and endocardial electrograms (HRA, high right atrium; HISp, proximal His bundle electrogram; CS 7, 8, recordings from poles 7 and 8 of a decapolar catheter placed in the coronary sinus) during RFCA of a left-sided accessory pathway in a patient with Wolff-Parkinson-White syndrome. The QRS narrows at the fourth complex; the *arrow* shows the His bundle electrogram, which becomes apparent with elimination of ventricular preexcitation over the accessory pathway.

FIGURE 238-5 (*Continued*)

cooling can be used for mapping and ablation. Cryomapping can be used to confirm the location of a desired ablation target, such as an accessory pathway in WPW syndrome, or can be used to determine the safety of ablation around the AVN by monitoring AV conduction during cooling. Another advantage of cryoablation is that once the catheter tip cools below freezing, it adheres to the tissue, increasing catheter stability independent of the rhythm or pacing.

DEVICE THERAPY

Bradyarrhythmias due either to primary sinus node dysfunction or to AV conduction defects are readily treated through implantation of a permanent pacemaker. Clinical indications for pacemaker implantation often depend on the presence either of symptomatic bradycardia or of an unreliable endogenous escape rhythm and are more fully reviewed in **Chaps. 239 and 240**.

Ventricular tachyarrhythmias, particularly those occurring in the context of progressive structural heart diseases such as ischemic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, may recur despite therapy with antiarrhythmic drugs or catheter ablation. In appropriate candidates, implantation of an internal cardioverter-defibrillator (ICD) may reduce mortality rates from sudden cardiac death. In a subset of patients with CHF and ventricular mechanical dyssynchrony, ICD, or pacemaker platforms can be used to provide cardiac resynchronization therapy, typically through implantation of a left ventricular pacing lead. In patients with dyssynchronous CHF, such therapy has been shown to improve both morbidity and mortality rates. The use of a completely subcutaneous ICD may be most appropriate in patients at risk for arrhythmic sudden death without a need for pacing.

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239 The Bradyarrhythmias: Disorders of the Sinoatrial Node

David D. Spragg, Gordon F. Tomaselli

Electrical activation of the heart normally originates in the sinoatrial (SA) node, the predominant pacemaker. Other subsidiary pacemakers in the atrioventricular (AV) node, specialized conducting system, and muscle may initiate electrical activation if the SA node is dysfunctional or suppressed. Typically, subsidiary pacemakers discharge at a slower rate and, in the absence of an appropriate increase in stroke volume, may result in tissue hypoperfusion.

Spontaneous activation and contraction of the heart are a consequence of the specialized pacemaking tissue in these anatomic locales. As described in **Chap. 238**, action potentials in the heart are regionally heterogeneous. The action potentials in cells isolated from nodal tissue are distinct from those recorded from atrial and ventricular myocytes **(Fig. 239-1)**. The complement of ionic currents present in nodal cells results in a less negative resting membrane potential compared with atrial or ventricular myocytes. Electrical diastole in nodal cells is characterized by slow diastolic depolarization (phase 4), which generates an action potential as the membrane voltage reaches threshold. The action potential upstrokes (phase 0) are slow compared with atrial or ventricular myocytes, being mediated by calcium rather than sodium current. Cells with properties of SA and AV nodal tissue are electrically connected to the remainder of the myocardium by cells with an electrophysiologic phenotype between that of nodal cells and that of atrial or ventricular myocytes. Cells in the SA node exhibit the most rapid phase 4 depolarization and thus are the dominant pacemakers in a normal heart.

Bradycardia results from a failure of either impulse initiation or impulse conduction. Failure of impulse initiation may be caused by depressed automaticity resulting from a slowing or failure of phase 4 diastolic depolarization **(Fig. 239-2)**, which may result from disease or exposure to drugs. Prominently, the autonomic nervous system modulates the rate of phase 4 diastolic depolarization and thus the firing rate of both primary (SA node) and subsidiary pacemakers. Failure of conduction of an impulse from nodal tissue to atrial or ventricular myocardium may produce bradycardia as a result of exit block. Conditions that alter the activation and connectivity of cells (e.g., fibrosis) in the heart may result in failure of impulse conduction.

SA node dysfunction and AV conduction block are the most common causes of pathologic bradycardia. SA node dysfunction may be difficult to distinguish from physiologic sinus bradycardia, particularly

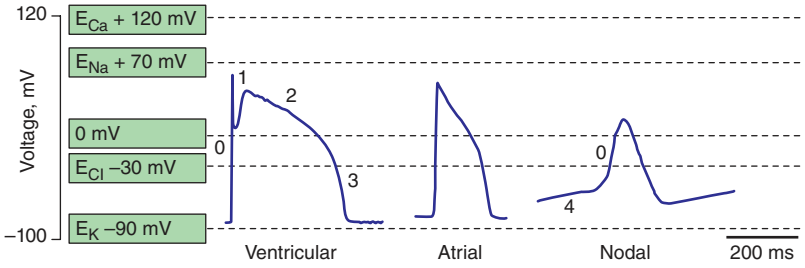

FIGURE 239-1 Action potential profiles recorded in cells isolated from sinoatrial or atrioventricular nodal tissue compared with those of cells from atrial or ventricular myocardium. Nodal cell action potentials exhibit more depolarized resting membrane potentials, slower phase 0 upstrokes, and phase 4 diastolic depolarization.

in the young. SA node dysfunction increases in frequency between the fifth and sixth decades of life and should be considered in patients with fatigue, exercise intolerance, or syncope and sinus bradycardia.

Permanent pacemaking is the only reliable therapy for symptomatic bradycardia in the absence of extrinsic and reversible etiologies such as increased vagal tone, hypoxia, hypothermia, and drugs **(Table 239-1)**. Approximately 50% of the 160,000 permanent pacemakers implanted in the United States and 20–30% of those in Europe were implanted for SA node disease.

STRUCTURE AND PHYSIOLOGY OF THE SA NODE

The SA node is composed of a cluster of small fusiform cells in the sulcus terminalis on the epicardial surface of the heart at the right atrial–superior vena caval junction, where they envelop the SA nodal artery. The SA node is structurally heterogeneous, but the central prototypic nodal cells have fewer distinct myofibrils than does the surrounding atrial myocardium, no intercalated disks visible on light microscopy, a poorly developed sarcoplasmic reticulum, and no T-tubules. Cells in the peripheral regions of the SA node are transitional in both structure and function. The SA nodal artery arises from the right coronary artery in 55–60% and the left circumflex artery in 40–45% of persons. The SA node is richly innervated by sympathetic and parasympathetic nerves and ganglia.

Irregular and slow propagation of impulses from the SA node can be explained by the electrophysiology of nodal cells and the structure of the SA node itself. The action potentials of SA nodal cells are characterized by a relatively depolarized membrane potential (Fig. 239-1) of –40 to –60 mV, slow phase 0 upstroke, and relatively rapid phase 4 diastolic depolarization compared with the action potentials recorded in cardiac muscle cells. The relative absence of inward rectifier potassium current (I_{K1}) accounts for the depolarized membrane potential; the slow upstroke of phase 0 results from the absence of available fast sodium current (I_{Na}) and is mediated by L-type calcium current ($I_{Ca\text{-}L}$); and phase 4 depolarization is a result of the aggregate activity of a number of ionic currents. Prominently, both L- and T-type ($I_{Ca\text{-}T}$) calcium currents, the pacemaker current (so-called funny current, or I_f) formed by hyperpolarization-activated cyclic nucleotide-gated channels, and the electrogenic sodium-calcium exchanger provide depolarizing current that is antagonized by delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACh}) potassium currents. $I_{Ca\text{-}L}$, $I_{Ca\text{-}T}$, and I_f are modulated by β-adrenergic stimulation and I_{KACh} by vagal stimulation, explaining the exquisite sensitivity of diastolic depolarization to autonomic nervous system activity. The slow conduction within the SA node is explained by the absence of I_{Na} and poor electrical coupling of cells in the node, resulting from sizable amounts of interstitial tissue and a low abundance of gap junctions. The poor coupling allows for graded electrophysiologic properties within the node, with the peripheral transitional cells being silenced by electrotonic coupling to atrial myocardium.

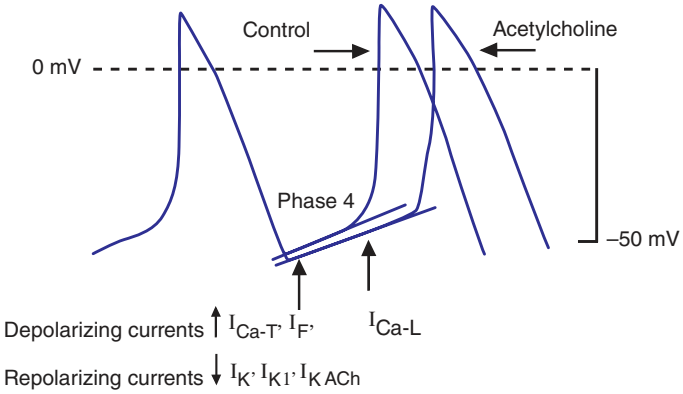

FIGURE 239-2 Schematics of nodal action potentials and the currents that contribute to phase 4 depolarization. Relative increases in depolarizing L- ($I_{Ca\text{-}L}$) and T- ($I_{Ca\text{-}T}$) type calcium and pacemaker currents (I_f) along with a reduction in repolarizing inward rectifier (I_{K1}) and delayed rectifier (I_K) potassium currents result in depolarization. Activation of ACh-gated (I_{KACh}) potassium current and beta blockade slow the rate of phase 4 and decrease the pacing rate. *(Modified from J Jalife et al: Basic Cardiac Electrophysiology for the Clinician, Blackwell Publishing, 1999.)*

ETIOLOGY OF SA NODAL DISEASE

SA nodal dysfunction has been classified as intrinsic or extrinsic. The distinction is important because extrinsic dysfunction is often reversible and generally should be corrected before pacemaker therapy is considered (Table 239-1). The most common causes of extrinsic SA node dysfunction are drugs and autonomic nervous system influences that suppress automaticity and/or compromise conduction. Other extrinsic causes include hypothyroidism, sleep apnea, and conditions likely to occur in critically ill patients such as hypothermia, hypoxia, increased

TABLE 239-1 Etiologies of SA Node Dysfunction

EXTRINSIC	INTRINSIC
Autonomic	Sick-sinus syndrome (SSS)
Carotid sinus hypersensitivity	Coronary artery disease (chronic and acute MI)
Vasovagal (cardioinhibitory) stimulation	Inflammatory
Drugs	Pericarditis
Beta blockers	Myocarditis (including viral)
Calcium channel blockers	Rheumatic heart disease
Digoxin	Collagen vascular diseases
Ivabradine	Lyme disease
Antiarrhythmics (class I and III)	Senile amyloidosis
Adenosine	Congenital heart disease
Clonidine (other sympatholytics)	TGA/Mustard and Fontan repairs
Lithium carbonate	Iatrogenic
Cimetidine	Radiation therapy
Amitriptyline	Postsurgical
Phenothiazines	Chest trauma
Narcotics (methadone)	Familial
Pentamidine	SSS2, AD, OMIM #163800 (15q24-25)
Hypothyroidism	SSS1, AR OMIM #608567 (3p21)
Sleep apnea	SSS3, AD, OMIM #614090 (14q11.2)
Hypoxia	SA node disease with myopia, OMIM #182190
Endotracheal suctioning (vagal maneuvers)	Kearns-Sayre syndrome, OMIM #530000
Hypothermia	Myotonic dystrophy
Increased intracranial pressure	Type 1, OMIM #160900 (19q13.2-13.3)
	Type 2, OMIM #602668 (3q13.3-q24)
	Friedreich's ataxia, OMIM #229300 (9q13, 9p23-p11)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database); TGA, transposition of the great arteries.

intracranial pressure (Cushing's response), and endotracheal suctioning via activation of the vagus nerve.

Intrinsic sinus node dysfunction is degenerative and often is characterized pathologically by fibrous replacement of the SA node or its connections to the atrium. Acute and chronic coronary artery disease (CAD) may be associated with SA node dysfunction, although in the setting of acute myocardial infarction (MI; typically inferior), the abnormalities are transient. Inflammatory processes may alter SA node function, ultimately producing replacement fibrosis. Pericarditis, myocarditis, and rheumatic heart disease have been associated with SA nodal disease with sinus bradycardia, sinus arrest, and exit block. Carditis associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and mixed connective tissue disorders (MCTDs) may also affect SA node structure and function. Senile amyloidosis is an infiltrative disorder in patients typically in the ninth decade of life; deposition of amyloid protein in the atrial myocardium can impair SA node function. Some SA node disease is iatrogenic and results from direct injury to the SA node during cardiothoracic surgery.

Rare heritable forms of sinus node disease have been described, and several have been characterized genetically. Autosomal dominant sinus node dysfunction in conjunction with supraventricular tachycardia (i.e., tachycardia-bradycardia variant of sick-sinus syndrome [SSS2]) has been linked to mutations in the pacemaker current (I_f) subunit gene *HCN4* on chromosome 15. An autosomal recessive form of SSS1 with the prominent feature of atrial inexcitability and absence of P waves on the electrocardiogram (ECG) is caused by mutations in the cardiac sodium channel gene, *SCN5A*, on chromosome 3. Variants in myosin heavy chain 6 (*MYH6*) increase the susceptibility to SSS (SSS3). SA node dysfunction associated with myopia has been described but not genetically characterized. There are several neuromuscular diseases, including Kearns-Sayre syndrome (ophthalmoplegia, pigmentary degeneration of the retina, and cardiomyopathy) and myotonic dystrophy that have a predilection for the conducting system and SA node.

SSS in both the young and the elderly is associated with an increase in fibrous tissue in the SA node. The onset of SSS may be hastened by coexisting disease, such as CAD, diabetes mellitus, hypertension, and valvular diseases and cardiomyopathies.

CLINICAL FEATURES OF SA NODE DISEASE

SA node dysfunction may be completely asymptomatic and manifest as an ECG anomaly such as sinus bradycardia; sinus arrest and exit block; or alternating supraventricular tachycardia, usually atrial fibrillation, and bradycardia. Symptoms associated with SA node dysfunction, in particular tachycardia-bradycardia syndrome, may be related to both slow and fast heart rates. For example, tachycardia may be associated with palpitations, angina pectoris, and heart failure, and bradycardia may be associated with hypotension, syncope, presyncope, fatigue, and weakness. In the setting of SSS, overdrive suppression of the SA node may result in prolonged pauses and syncope upon termination of the tachycardia. In many cases, symptoms associated with SA node dysfunction result from concomitant cardiovascular disease. A significant minority of patients with SSS develop signs and symptoms of heart failure that may be related to slow or fast heart rates.

One-third to one-half of patients with SA node dysfunction develop supraventricular tachycardia, usually atrial fibrillation or atrial flutter. The incidence of persistent atrial fibrillation in patients with SA node dysfunction increases with advanced age, hypertension, diabetes mellitus, left ventricular dilation, valvular heart disease, and ventricular pacing. Remarkably, some symptomatic patients may experience an improvement in symptoms with the development of atrial fibrillation, presumably from an increase in their average heart rate. Patients with the tachycardia-bradycardia variant of SSS, similar to patients with atrial fibrillation, are at risk for thromboembolism, and *those at greatest risk*, including patients aged ≥65 years and patients with a prior history of stroke, valvular heart disease, left ventricular dysfunction, or atrial enlargement, should be treated with anticoagulants. Up to one-quarter of patients with SA node disease will have concurrent AV conduction disease, although only a minority will require specific therapy for high-grade AV block.

The natural history of SA node dysfunction is one of varying intensity of symptoms even in patients who present with syncope. Symptoms related to SA node dysfunction may be significant, but overall longevity usually is not compromised in the absence of other significant comorbid conditions. These features of the natural history need to be taken into account in considering therapy for these patients.

ELECTROCARDIOGRAPHY OF SA NODE DISEASE

The electrocardiographic manifestations of SA node dysfunction include sinus bradycardia, sinus pauses, sinus arrest, sinus exit block, tachycardia (in SSS), and chronotropic incompetence. It is often difficult to distinguish pathologic from physiologic sinus bradycardia. By definition, sinus bradycardia is a rhythm driven by the SA node with a rate of <60 beats/min; sinus bradycardia is very common and typically benign. Resting heart rates <60 beats/min are very common in young healthy individuals and physically conditioned subjects. A sinus rate of <40 beats/min in the awake state in the absence of physical conditioning generally is considered abnormal. Sinus pauses and sinus arrest result from failure of the SA node to discharge, producing a pause without P waves visible on the ECG **(Fig. 239-3)**. Sinus pauses of up to 3 s are common in awake athletes, and pauses of this duration or longer may be observed in asymptomatic elderly subjects. Intermittent failure of conduction from the SA node produces sinus exit block. The severity of sinus exit block may vary in a manner similar to that of AV block **(Chap. 240)**. Prolongation of conduction from the sinus node will not be apparent on the ECG; second-degree SA block will produce intermittent conduction from the SA node and a regularly irregular atrial rhythm.

Type I second-degree SA block results from progressive prolongation of SA node conduction with intermittent failure of the impulses originating in the sinus node to conduct to the surrounding atrial tissue. Second-degree SA block appears on the ECG as an intermittent absence of P waves **(Fig. 239-4)**. In type II second-degree SA block, there is no change in SA node conduction before the pause. Complete or third-degree SA block results in no P waves on the ECG. Tachycardia-bradycardia syndrome is manifest as alternating sinus bradycardia and atrial tachyarrhythmias. Although atrial tachycardia, atrial flutter, and atrial fibrillation may be observed, the latter is the most common tachycardia. Chronotropic incompetence is the inability to increase the heart rate in response to exercise or other stress appropriately and is defined in greater detail below.

DIAGNOSTIC TESTING

SA node dysfunction is most commonly a clinical or electrocardiographic diagnosis. Sinus bradycardia or pauses on the resting ECG are rarely sufficient to diagnose SA node disease, and longer-term

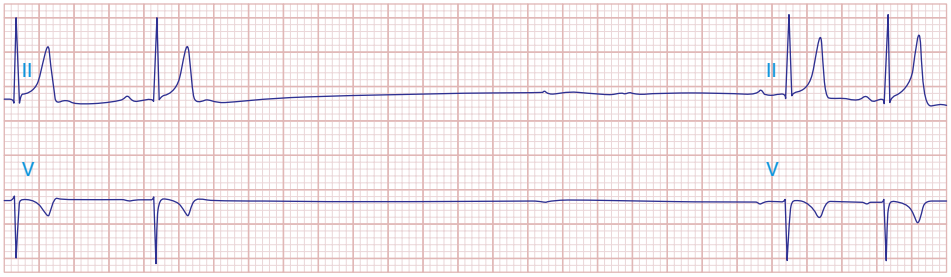

FIGURE 239-3 Sinus slowing and pauses on the electrocardiogram (ECG). The ECG is recorded during sleep in a young patient without heart disease. The heart rate before the pause is slow, and the PR interval is prolonged, consistent with an increase in vagal tone. The P waves have a morphology consistent with sinus rhythm. The recording is from a two-lead telemetry system in which the tracing labeled II mimics frontal lead II and V represents Modified Central Lead 1, which mimics lead V_1 of the standard 12-lead ECG.

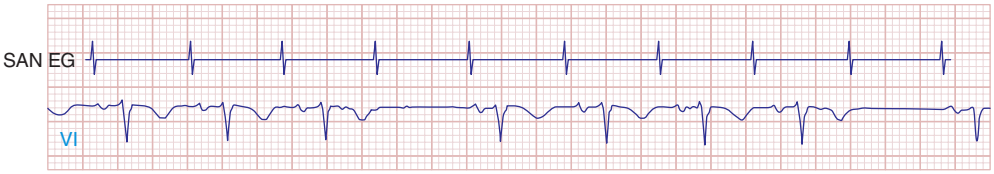

FIGURE 239-4 Mobitz type I SA nodal exit block. A theoretical SA node electrogram (SAN EG) is shown. Note that there is grouped beating producing a regularly irregular heart rhythm. The SA node EG rate is constant with progressive delay in exit from the node and activation of the atria, inscribing the P wave. This produces subtly decreasing P-P intervals before the pause, and the pause is less than twice the cycle length of the last sinus interval.

recording and symptom correlation generally are required. Symptoms in the absence of sinus bradyarrhythmias may be sufficient to exclude a diagnosis of SA node dysfunction.

Electrocardiographic recording plays a central role in the diagnosis and management of SA node dysfunction. Despite the limitations of the resting ECG, longer-term recording employing Holter or event monitors may permit correlation of symptoms with the cardiac rhythm. Many contemporary event monitors may be automatically triggered to record the ECG when certain programmed heart rate criteria are met. Implantable ECG monitors permit long-term recording (12–18 months) in particularly challenging patients.

Failure to increase the heart rate with exercise is referred to as *chronotropic incompetence*. This is alternatively defined as failure to reach 85% of predicted maximal heart rate at peak exercise or failure to achieve a heart rate >100 beats/min with exercise or a maximal heart rate with exercise less than two standard deviations below that of an age-matched control population. Exercise testing may be useful in discriminating chronotropic incompetence from resting bradycardia and may aid in the identification of the mechanism of exercise intolerance.

Autonomic nervous system testing is useful in diagnosing carotid sinus hypersensitivity; pauses >3 s are consistent with the diagnosis but may be present in asymptomatic elderly subjects. Determining the intrinsic heart rate (IHR) may distinguish SA node dysfunction from slow heart rates that result from high vagal tone. The normal IHR after administration of 0.2 mg/kg propranolol and 0.04 mg/kg atropine is 117.2 – (0.53 × age) in beats/min; a low IHR is indicative of SA disease.

Electrophysiologic testing may play a role in the assessment of patients with presumed SA node dysfunction and in the evaluation of syncope, particularly in the setting of structural heart disease. In this circumstance, electrophysiologic testing is used to rule out more malignant etiologies of syncope, such as ventricular tachyarrhythmias and AV conduction block. There are several ways to assess SA node function invasively. They include the sinus node recovery time (SNRT), defined as the longest pause after cessation of overdrive pacing of the right atrium near the SA node (normal: <1500 ms or, corrected for sinus cycle length, <550 ms), and the sinoatrial conduction time (SACT), defined as one-half the difference between the intrinsic sinus cycle length and a noncompensatory pause after a premature atrial stimulus (normal <125 ms). The combination of an abnormal SNRT, an abnormal SACT, and a low IHR is a sensitive and specific indicator of intrinsic SA node disease.

TREATMENT

Sinoatrial Node Dysfunction

Since SA node dysfunction is not associated with increased mortality rates, the aim of therapy is alleviation of symptoms. Exclusion of extrinsic causes of SA node dysfunction and correlation of the cardiac rhythm with symptoms is an essential part of patient management. Pacemaker implantation is the primary therapeutic intervention in patients with symptomatic SA node dysfunction. Pharmacologic considerations are important in the evaluation and management of patients with SA nodal disease. A number of drugs modulate SA node function and are extrinsic causes of dysfunction (Table 239-1). Beta blockers and calcium channel blockers increase SNRT in patients with SA node dysfunction, and antiarrhythmic drugs with class I and III action may promote SA node exit block. In general, such agents should be discontinued before decisions regarding the need for permanent pacing in patients with SA node disease are made. Chronic pharmacologic therapy for sinus bradyarrhythmias is limited. Some pharmacologic agents may improve SA node function; digitalis, for example, has been shown to shorten SNRT in patients with SA node dysfunction. Isoproterenol or atropine administered IV may increase the sinus rate acutely. Theophylline has been used both acutely and chronically to increase heart rate but has liabilities when used in patients with tachycardia-bradycardia syndrome, increasing the frequency of supraventricular tachyarrhythmias, and in patients with structural heart disease, increasing the risk of potentially serious ventricular arrhythmias. Currently, there is only a single randomized study of therapy for SA node dysfunction. In patients with resting heart rates <50 and >30 beats/min on a Holter monitor, patients who received dual-chamber pacemakers experienced significantly fewer syncopal episodes and had symptomatic improvement compared with patients randomized to theophylline or no treatment.

In certain circumstances, sinus bradycardia requires no specific treatment or only temporary rate support. Sinus bradycardia is common in patients with acute inferior or posterior MI and can be exacerbated by vagal activation induced by pain or the use of drugs such as morphine. Ischemia of the SA nodal artery probably occurs in acute coronary syndromes more typically with involvement with the right coronary artery, and even with infarction, the effect on SA node function most often is transient.

Sinus bradycardia is a prominent feature of carotid sinus hypersensitivity and neurally mediated hypotension associated with vasovagal syncope that responds to pacemaker therapy. Carotid hypersensitivity with recurrent syncope or presyncope associated with a predominant cardioinhibitory component responds to pacemaker implantation. Several randomized trials have investigated the efficacy of permanent pacing in patients with drug-refractory vasovagal syncope, with mixed results. Although initial trials suggested that patients undergoing pacemaker implantation have fewer recurrences and a longer time to recurrence of symptoms, at least one follow-up study did not confirm these results.

PERMANENT PACEMAKERS

Nomenclature and Complications The main therapeutic intervention in SA node dysfunction is permanent pacing. Since the first implementation of permanent pacing in the 1950s, many advances in technology have resulted in miniaturization, increased longevity of pulse generators, improvement in leads, and increased functionality. To better understand pacemaker therapy for bradycardias, it is important to be familiar with the fundamentals of pacemaking. Pacemaker modes and function are named using a five-letter code. The first letter indicates the chamber(s) that is paced (O, none; A, atrium; V, ventricle; D, dual; S, single), the second is the chamber(s) in which sensing occurs (O, none; A, atrium; V, ventricle; D, dual; S, single), the third is the response to a sensed event (O, none; I, inhibition; T, triggered; D, inhibition + triggered), the fourth refers to the programmability or rate response (R, rate responsive), and the fifth refers to the existence of antitachycardia functions if present (O, none; P, antitachycardia pacing; S, shock; D, pace + shock). Almost all modern pacemakers are multiprogrammable and have the capability for rate responsiveness using one of several rate sensors: activity or motion, minute ventilation, or QT interval. The

most commonly programmed modes of implanted single- and dual-chamber pacemakers are VVIR and DDDR, respectively, although multiple modes can be programmed in modern pacemakers.

Although pacemakers are highly reliable, they are subject to a number of complications related to implantation and electronic function. In adults, permanent pacemakers are most commonly implanted with access to the heart by way of the subclavian–superior vena cava venous system. Rare, but possible, acute complications of transvenous pacemaker implantation include infection, hematoma, pneumothorax, cardiac perforation, diaphragmatic/phrenic nerve stimulation, and lead dislodgment. Limitations of chronic pacemaker therapy include infection, erosion, lead failure, and abnormalities resulting from inappropriate programming or interaction with the patient's native electrical cardiac function. Rotation of the pacemaker pulse generator in its subcutaneous pocket, either intentionally or inadvertently, often referred to as "twiddler's syndrome," can wrap the leads around the generator and produce dislodgment with failure to sense or pace the heart. The small size and light weight of contemporary pacemakers make this a rare complication. Transvenous leads are considered the "Achilles heel" of permanent pacing systems. Enhancements in battery technology and component design have produced a pacing system small enough to be implanted in the heart without the need for a transvenous lead. These "leadless" pacemakers are appropriate for patients with indications for single chamber ventricular (right ventricle) pacing (see Chap. 240).

Complications stemming from chronic cardiac pacing also result from disturbances in AV synchrony and/or left ventricular mechanical synchrony. Pacing modes that interrupt or fail to restore AV synchrony may lead to a constellation of signs and symptoms, collectively referred to as pacemaker syndrome, that include neck pulsation, fatigue, palpitations, cough, confusion, exertional dyspnea, dizziness, syncope, elevation in jugular venous pressure, canon A waves, and stigmata of congestive heart failure, including edema, rales, and a third heart sound. Right ventricular apical pacing can induce dyssynchronous activation of the left ventricle, leading to compromised left ventricular systolic function, mitral valve regurgitation, and the previously mentioned stigmata of congestive heart failure. Maintenance of AV synchrony can minimize the sequelae of pacemaker syndrome. Selection of pacing modes that minimize unnecessary ventricular pacing or implantation of a device capable of right and left ventricular pacing (biventricular pacing) can help minimize the deleterious consequences of pacing-induced mechanical dyssynchrony at the ventricular level.

Pacemaker Therapy in SA Node Dysfunction Pacing in SA nodal disease is indicated to alleviate symptoms of bradycardia. Consensus guidelines published by the American Heart Association (AHA)/American College of Cardiology/Heart Rhythm Society (ACC/HRS) outline the indications for the use of pacemakers and categorize them by class based on levels of evidence. Class I conditions are those for which there is evidence or consensus of opinion that therapy is useful and effective. In class II conditions, there is conflicting evidence or a divergence of opinion about the efficacy of a procedure or treatment; in class IIa conditions, the weight of evidence or opinion favors treatment; and in class IIb conditions, efficacy is less well established by the evidence or opinion of experts. In class III conditions, the evidence or weight of opinion indicates that the therapy is not efficacious or useful and may be harmful.

Class I indications for pacing in SA node dysfunction include documented symptomatic bradycardia, sinus node dysfunction–associated long-term drug therapy for which there is no alternative, and symptomatic chronotropic incompetence. Class IIa indications include those outlined previously in which sinus node dysfunction is suspected but not documented and for syncope of unexplained origin in the presence of major abnormalities of SA node dysfunction. Mildly symptomatic individuals with heart rates consistently <40 beats/min constitute a class IIb indication for pacing. Pacing is not indicated in patients with SA node dysfunction who do not have symptoms and in those in whom bradycardia is associated with the use of nonessential drugs (Table 239-2).

TABLE 239-2 Summary of Guidelines for Pacemaker Implantation in SA Node Dysfunction

Class I
1. SA node dysfunction with symptomatic bradycardia or sinus pause
2. Symptomatic SA node dysfunction as a result of essential long-term drug therapy with no acceptable alternatives
3. Symptomatic chronotropic incompetence
4. Atrial fibrillation with bradycardia and pauses >5 s
Class IIa
1. SA node dysfunction with heart rates <40 beats/min without a clear and consistent relationship between bradycardia and symptoms
2. SA node dysfunction with heart rates <40 beats/min on an essential long-term drug therapy with no acceptable alternatives, without a clear and consistent relationship between bradycardia and symptoms
3. Syncope of unknown origin when major abnormalities of SA node dysfunction are discovered or provoked by electrophysiologic testing
Class IIb
1. Mildly symptomatic patients with waking chronic heart rates <40 beats/min
Class III
1. SA node dysfunction in asymptomatic patients, even those with heart rates <40 beats/min
2. SA node dysfunction in which symptoms suggestive of bradycardia are not associated with a slow heart rate
3. SA node dysfunction with symptomatic bradycardia due to nonessential drug therapy

Source: Data from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008 and CM Tracy et al: J Am Coll Cardiol 61:e6, 2013.

There is some controversy about the mode of pacing that should be employed in SA node disease. A number of randomized, single-blind trials of pacing mode have been performed. There are no trials that demonstrate an improvement in mortality rate with AV synchronous pacing compared with single-chamber pacing in SA node disease. In some of these studies, the incidence of atrial fibrillation and thromboembolic events was reduced with AV synchronous pacing. In trials of patients with dual-chamber pacemakers designed to compare single-chamber with dual-chamber pacing by crossover design, the need for AV synchronous pacing due to pacemaker syndrome was common. Pacing modes that preserve AV synchrony appear to be associated with a reduction in the incidence of atrial fibrillation and improved quality of life. Because of the low but finite incidence of AV conduction disease, patients with SA node dysfunction usually undergo dual-chamber pacemaker implantation.

Pacemaker Therapy in Carotid Sinus Hypersensitivity and Vasovagal Syncope Carotid sinus hypersensitivity, if accompanied by a significant cardioinhibitory component, responds well to pacing. In this circumstance, pacing is required only intermittently and single-chamber ventricular pacing is often sufficient. The mechanism of vasovagal syncope is incompletely understood but appears to involve activation of cardiac mechanoreceptors with consequent activation of neural centers that mediate vagal activation and withdrawal of sympathetic nervous system tone. Several randomized clinical trials have been performed in patients with drug-refractory vasovagal syncope, with some studies suggesting reduction in the frequency and the time to recurrent syncope in patients who were paced compared with those who were not. A recent follow-up study to one of those initial trials, however, found less convincing results, casting some doubt on the utility of pacing for vagally mediated syncope.

FURTHER READING

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240 The Bradyarrhythmias: Disorders of the Atrioventricular Node

David D. Spragg, Gordon F. Tomaselli

Impulses generated in the sinoatrial (SA) node or in ectopic atrial loci are conducted to the ventricles through the electrically and anatomically complex atrioventricular (AV) node. As described in **Chap. 239**, the electrophysiologic properties of nodal tissue are distinct from atrial and ventricular myocardium. Cells located in the AV node sit at a relatively higher resting membrane potential than surrounding atrial and ventricular myocytes, exhibit spontaneous depolarization during phase 4 of the action potential, and have slower phase 0 depolarization (mediated by calcium influx in nodal tissue) than that seen in ventricular tissue (mediated by sodium influx).

Bradycardia may occur when conduction across the AV node is compromised, resulting in slow ventricular rates, with the possibility of attendant symptoms, including fatigue, syncope, and (if subsidiary pacemaker activity is insufficient) even death. It is important to recognize that in the setting of disturbed AV conduction, SA activation and atrial systole may occur at normal or even accelerated rates, while ventricular activation is either slowed or nonexistent. Transient AV conduction block is common in the young and is most likely the result of high vagal tone found in up to 10% of young adults. Acquired and persistent failure of AV conduction is decidedly rare in healthy adult populations, with an estimated incidence of 200 per million population per year. In the setting of myocardial ischemia, aging and fibrosis, or cardiac infiltrative diseases, however, persistent AV block is much more common.

As with symptomatic bradycardia arising from SA node dysfunction, permanent pacing is the only reliable therapy for symptoms arising from AV conduction block. Approximately 50% of the 160,000 permanent pacemakers implanted in the United States and 70–80% of those in Europe are implanted for disorders of AV conduction.

STRUCTURE AND PHYSIOLOGY OF THE AV NODE

The AV conduction axis is structurally complex, involving the atria and ventricles as well as the AV node. Unlike the SA node, the AV node is a subendocardial structure originating in the transitional zone, which is composed of aggregates of cells in the posterior-inferior right atrium. Superior, medial, and posterior transitional atrionodal bundles converge on the compact AV node. The compact AV node (~1 × 3 × 5 mm) is situated at the apex of the triangle of Koch, which is defined by the coronary sinus ostium posteriorly, the septal tricuspid valve annulus anteriorly, and the tendon of Todaro superiorly. The compact AV node continues as the penetrating AV bundle where it immediately traverses the central fibrous body and is in close proximity to the aortic, mitral, and tricuspid valve annuli; thus, it is subject to injury in the setting of valvular heart disease or its surgical treatment. The penetrating AV bundle continues through the annulus fibrosis and emerges along the ventricular septum adjacent to the membranous septum as the bundle of His. The right bundle branch (RBB) emerges from the distal AV bundle in a band that traverses the right ventricle (moderator band). In contrast, the left bundle branch (LBB) is a broad subendocardial sheet of tissue on the septal left ventricle. The Purkinje fiber network emerges from the RBB and LBB and extensively ramifies on the endocardial surfaces of the right and left ventricles, respectively.

The blood supply to the penetrating AV bundle is from the AV nodal artery and first septal perforator of the left anterior descending coronary artery. The bundle branches also have a dual blood supply from the septal perforators of the left anterior descending coronary artery and branches of the posterior descending coronary artery. The AV node is highly innervated with postganglionic sympathetic and parasympathetic nerves. The bundle of His and distal conducting system are minimally influenced by autonomic tone.

The cells that constitute the AV node complex are heterogeneous with a range of action potential profiles. In the transitional zones, the cells have an electrical phenotype between those of atrial myocytes and cells of the compact node **(see Fig. 239-1)**. Atrionodal transitional connections may exhibit *decremental conduction*, defined as slowing of conduction with increasingly rapid rates of stimulation. Fast and slow AV nodal pathways have been described, but it is controversial whether these two types of pathway are anatomically distinct or represent functional heterogeneities in different regions of the AV nodal complex. Myocytes that constitute the compact node are depolarized (resting membrane potential ~–60 mV) and exhibit action potentials with low amplitudes, slow upstrokes of phase 0 (<10 V/s), and phase 4 diastolic depolarization; high-input resistance; and relative insensitivity to external [K^+]. The action potential phenotype is explained by the complement of ionic currents expressed. AV nodal cells lack a robust inward rectifier potassium current (I_{K1}) and fast sodium current (I_{Na}); L-type calcium current ($I_{Ca\text{-}L}$) is responsible for phase 0; and phase 4 depolarization reflects the composite activity of the depolarizing currents—funny current (I_f), $I_{Ca\text{-}L}$, T-type calcium current ($I_{Ca\text{-}T}$), and sodium calcium exchanger current (I_{NCX})—and the repolarizing currents—delayed rectifier (I_{Kr}) and acetylcholine-gated (I_{KACh}) potassium currents. Electrical coupling between cells in the AV node is tenuous due to the relatively sparse expression of gap junction channels (predominantly connexin-40) and increased extracellular volume.

The His bundle and the bundle branches are insulated from ventricular myocardium. The most rapid conduction in the heart is observed in these tissues. The action potentials exhibit very rapid upstrokes (phase 0), prolonged plateaus (phase 2), and modest automaticity (phase 4 depolarization). Gap junctions, composed largely of connexin-40, are abundant, but bundles are poorly connected transversely to ventricular myocardium.

ETIOLOGY OF AV CONDUCTION DISEASE

Conduction block from the atrium to the ventricle can occur for a variety of reasons in a number of clinical situations, and AV conduction block may be classified in a number of ways. The etiologies may be functional or structural, in part analogous to extrinsic and intrinsic causes of SA nodal dysfunction. The block may be classified by its severity from first to third degree or complete AV block or by the location of block within the AV conduction system. **Table 240-1** summarizes the etiologies of AV conduction block. Those that are functional (autonomic, metabolic/endocrine, and drug-related) tend to be reversible. Most other

TABLE 240-1 Etiologies of Atrioventricular Block

Autonomic	
Carotid sinus hypersensitivity	Vasovagal
Metabolic/Endocrine	
Hyperkalemia	Hypothyroidism
Hypermagnesemia	Adrenal insufficiency
Drug-Related	
Beta blockers	Adenosine
Calcium channel blockers	Antiarrhythmics (class I and III)
Digitalis	Lithium
Infectious	
Endocarditis	Tuberculosis
Lyme disease	Diphtheria
Chagas' disease	Toxoplasmosis
Syphilis	
Heritable/Congenital	
Congenital heart disease	Facioscapulohumeral MD, OMIM #158900 (4q35)
Maternal SLE	Emery-Dreifuss MD, OMIM #310300 (Xq28)
Kearns-Sayre syndrome, OMIM #530000	Progressive familial heart block, type IA OMIM #113900 (3p21)
Myotonic dystrophy	Progressive familial heart block, type IB, OMIM #604559 (19q13.32)
Type 1, OMIM #160900 (19q13.2-13.3)	Progressive familial heart block, type II, OMIM %140400 (1q32)
Type 2, OMIM #602668 (3q13.3-q24)	
Inflammatory	
SLE	MCTD
Rheumatoid arthritis	Scleroderma
Infiltrative	
Amyloidosis	Hemochromatosis
Sarcoidosis	
Neoplastic/Traumatic	
Lymphoma	Radiation
Mesothelioma	Catheter ablation
Melanoma	
Degenerative	
Lev's disease	Lenègre's disease
Coronary Artery Disease	
Acute MI	

Abbreviations: MCTD, mixed connective tissue disease; MI, myocardial infarction; OMIM, Online Mendelian Inheritance in Man (database; designations: #, phenotypic description, molecular basis known; %, phenotypic description); SLE, systemic lupus erythematosus.

etiologies produce structural changes, typically fibrosis, in segments of the AV conduction axis that are generally permanent. Heightened vagal tone during sleep or in well-conditioned individuals can be associated with all grades of AV block. Carotid sinus hypersensitivity, vasovagal syncope, and cough and micturition syncope may be associated with SA node slowing and AV conduction block. Transient metabolic and endocrinologic disturbances as well as a number of pharmacologic agents also may produce reversible AV conduction block.

Several infectious diseases have a predilection for the conducting system. Lyme disease may involve the heart in up to 50% of cases; 10% of patients with Lyme carditis develop AV conduction block, which is generally reversible but may require temporary pacing support. Chagas' disease, which is common in Latin America, and syphilis may produce more persistent AV conduction disturbances. Some autoimmune and infiltrative diseases may produce AV conduction block, including systemic lupus erythematosus (SLE), rheumatoid arthritis, mixed connective tissue disease, scleroderma, amyloidosis (primary and secondary), sarcoidosis, and hemochromatosis; rare malignancies also may impair AV conduction.

Idiopathic progressive fibrosis of the conduction system is one of the more common and degenerative causes of AV conduction block. Aging is associated with degenerative changes in the summit of the ventricular septum, central fibrous body, and aortic and mitral annuli and has been described as "sclerosis of the left cardiac skeleton." The process typically begins in the fourth decade of life and may be accelerated by atherosclerosis, hypertension, and diabetes mellitus. Accelerated forms of progressive familial heart block have been identified in families with mutations in the cardiac sodium channel gene (*SCN5A*) and other loci that have been mapped to chromosomes 1 and 19.

AV conduction block has been associated with heritable neuromuscular diseases, including the nucleotide repeat disease myotonic dystrophy, the mitochondrial myopathy Kearns-Sayre syndrome **(Chap. 441)**, and several of the monogenic muscular dystrophies. Congenital AV block may be observed in complex congenital cardiac anomalies **(Chap. 264)**, such as transposition of the great arteries, ostium primum atrial septal defects (ASDs), ventricular septal defects (VSDs), endocardial cushion defects, and some single-ventricle defects. Congenital AV block in the setting of a structurally normal heart has been seen in children born to mothers with SLE. Iatrogenic AV block may occur during mitral or aortic valve surgery, rarely in the setting of thoracic radiation, and as a consequence of catheter ablation. AV block is a decidedly rare complication of the surgical repair of VSDs or ASDs but may complicate repairs of transposition of the great arteries.

Coronary artery disease may produce transient or persistent AV block. In the setting of coronary spasm, ischemia, particularly in the right coronary artery distribution, may produce transient AV block. In acute myocardial infarction (MI), AV block transiently develops in 10–25% of patients; most commonly, this is first- or second-degree AV block, but complete heart block (CHB) may also occur. Second-degree and higher-grade AV block tends to occur more often in inferior than in anterior acute MI; however, the level of block in inferior MI tends to be in the AV node with more stable, narrow escape rhythms. In contrast, acute anterior MI is associated with block in the distal AV nodal complex, His bundle, or bundle branches and results in wide complex, unstable escape rhythms and a worse prognosis with high mortality rates.

ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY OF AV CONDUCTION BLOCK

AV conduction block typically is diagnosed electrocardiographically, which characterizes the severity of the conduction disturbance and allows one to draw inferences about the location of the block. AV conduction block manifests as slow conduction in its mildest forms and failure to conduct, either intermittent or persistently, in more severe varieties. First-degree AV block (PR interval >200 ms) is a slowing of conduction through the AV junction **(Fig. 240-1)**. The site of delay is typically in the AV node but may be in the atria, bundle of His, or His-Purkinje system. A wide QRS is suggestive of delay in the distal conduction system, whereas a narrow QRS suggests delay in the AV node proper or, less commonly, in the bundle of His. In second-degree AV block there is an intermittent failure of electrical impulse conduction from atrium to ventricle. Second-degree AV block is subclassified as Mobitz type I (Wenckebach) or Mobitz type II. The periodic failure of conduction in Mobitz type I block is characterized by a progressively lengthening PR interval, shortening of the RR interval, and a pause that is less than two times the immediately preceding RR interval on the electrocardiogram (ECG). The ECG complex after the pause exhibits a shorter PR interval than that immediately preceding the pause **(Fig. 240-2)**. This ECG pattern most often arises because of decremental conduction of electrical impulses in the AV node.

It is important to distinguish type I from type II second-degree AV nodal block because the latter has more serious prognostic implications. Type II second-degree AV block is characterized by intermittent failure of conduction of the P wave without changes in the preceding PR or RR intervals. When AV block is 2:1, it may be difficult to distinguish type I from type II block. Type II second-degree AV block typically occurs in the distal or infra-His conduction system, is often associated with intraventricular conduction delays (e.g., bundle branch

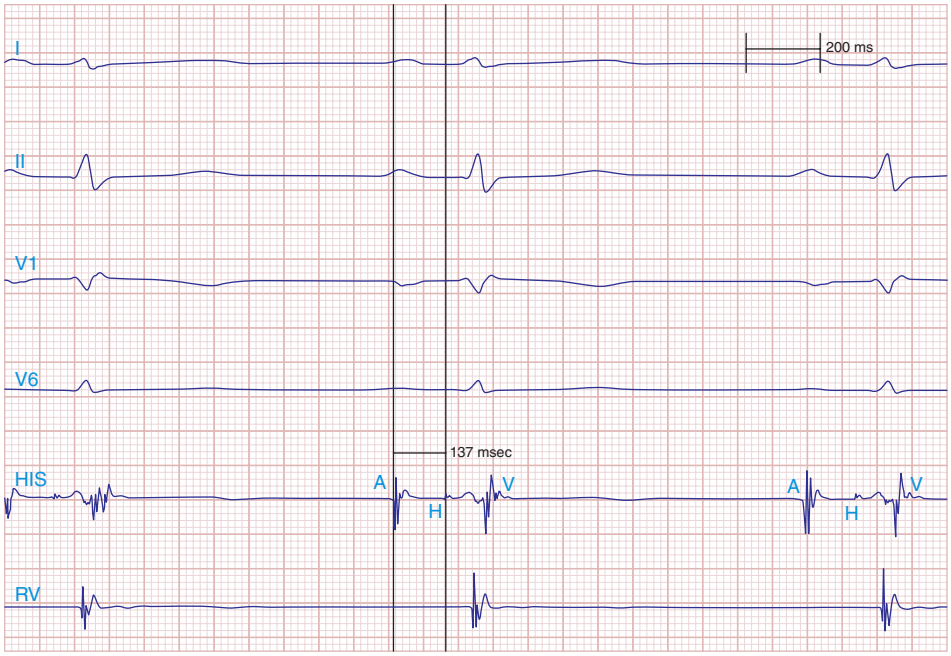

FIGURE 240-1 First-degree AV block with slowing of conduction in the AV node as indicated by the prolonged atrial-to-His bundle electrogram (AH) interval, in this case 157 ms. The His bundle-to-earliest ventricular activation on the surface ECG (HV) interval is normal. The normal HV interval suggests normal conduction below the AV node to the ventricle. I and V_1 are surface ECG leads, and HIS is the recording of the endocavitary electrogram at the His bundle position. A, H, and V are labels for the atrial, His bundle, and right ventricular electrograms, respectively.

block), and is more likely to proceed to higher grades of AV block than is type I second-degree AV block. Second-degree AV block (particularly type II) may be associated with a series of nonconducted P waves, referred to as *paroxysmal AV block* **(Fig. 240-3)**, and implies significant conduction system disease and is an indication for permanent pacing. Complete failure of conduction from atrium to ventricle is referred to as complete or third-degree AV block. AV block that is intermediate between second degree and third degree is referred to as high-grade AV block and, as with CHB, implies advanced AV conduction system disease. In both cases, the block is most often distal to the AV node, and the duration of the QRS complex can be helpful in determining the level of the block. In the absence of a preexisting bundle branch block, a wide QRS escape rhythm **(Fig. 240-4*B*)** implies a block in the distal His or bundle branches; in contrast, a narrow QRS rhythm implies a block in the AV node or proximal His and an escape rhythm originating in the AV junction **(Fig. 240-4*A*)**. Narrow QRS escape rhythms are typically faster and more stable than wide QRS escape rhythms and originate more proximally in the AV conduction system.

DIAGNOSTIC TESTING

Diagnostic testing in the evaluation of AV block is aimed at determining the level of conduction block, particularly in asymptomatic patients, since the prognosis and therapy depend on whether the block is in or below the AV node. Vagal maneuvers, carotid sinus massage, exercise, and administration of drugs such as atropine and isoproterenol may be diagnostically informative. Owing to the differences in the innervation of the AV node and infranodal conduction system, vagal stimulation and carotid sinus massage slow conduction in the AV node but have less of an effect on infranodal tissue and may even improve conduction due to a reduced rate of activation of distal tissues. Conversely, atropine, isoproterenol, and exercise improve conduction through the AV node and impair infranodal conduction. In patients with congenital CHB and a narrow QRS complex, exercise typically increases heart rate; by contrast, those with acquired CHB, particularly with wide QRS, do not respond to exercise with an increase in heart rate.

Additional diagnostic evaluation, including electrophysiologic testing, may be indicated in patients with syncope and suspected high-grade AV block. This is particularly relevant if noninvasive testing does not reveal the cause of syncope or if the patient has structural heart disease with ventricular tachyarrhythmias as a cause of symptoms. Electrophysiologic testing provides more precise information regarding the location of AV conduction block and permits studies of AV conduction under conditions of pharmacologic stress and exercise. Recording of the His bundle electrogram by a catheter positioned at the superior margin of the tricuspid valve annulus provides information about conduction at all levels of the AV conduction axis. A properly recorded His bundle electrogram reveals local atrial activity, the His electrogram, and local ventricular activation; when it is monitored simultaneously with recorded body surface electrocardiographic traces, intraatrial, AV nodal, and infranodal conduction times can be assessed (Fig. 240-1). The time from the most rapid deflection of the atrial electrogram in the His bundle recording to the His electrogram (*AH interval*) represents conduction through the AV node and is normally <130 ms. The time from the His electrogram to the earliest onset of the QRS on the surface

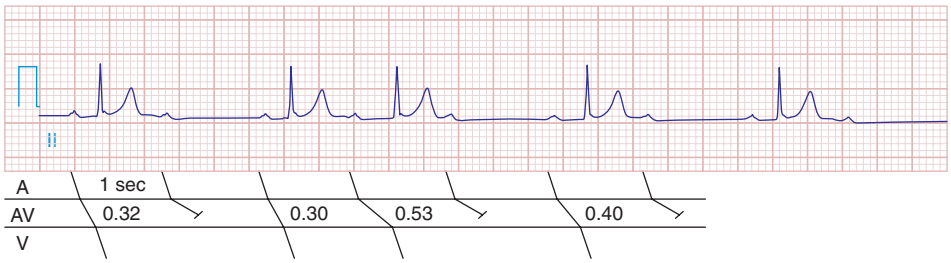

FIGURE 240-2 Mobitz type I second-degree AV block. The PR interval prolongs before the pause, as shown in the ladder diagram. The ECG pattern results from slowing of conduction in the AV node.

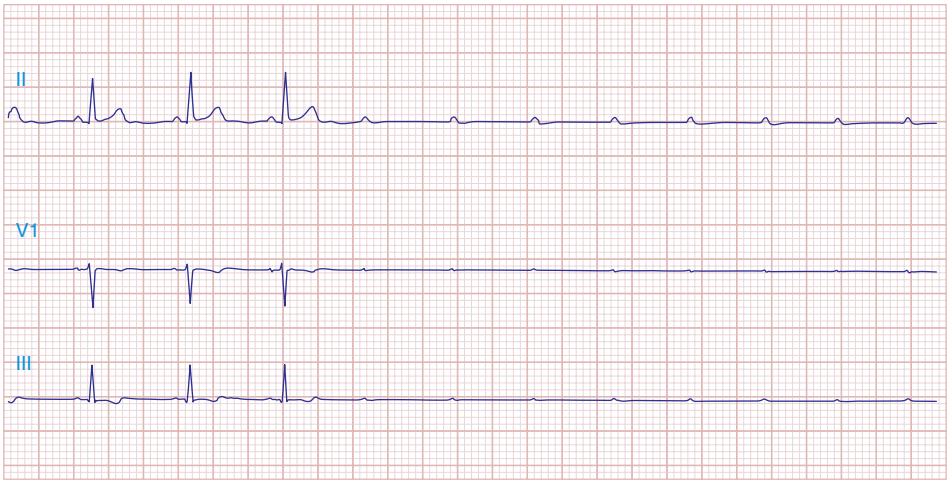

FIGURE 240-3 Paroxysmal AV block. Multiple nonconducted P waves after a period of sinus bradycardia with a normal PR interval. This implies significant conduction system disease, requiring permanent pacemaker implantation.

ECG (*HV interval*) represents the conduction time through the His-Purkinje system and is normally ≤55 ms.

Rate stress produced by pacing can unveil abnormal AV conduction. Mobitz I second-degree AV block at short atrial paced cycle lengths is a normal response. However, when it occurs at atrial cycle lengths >500 ms (<120 beats/min) in the absence of high vagal tone, it is abnormal. Typically, type I second-degree AV block is associated with prolongation of the AH interval, representing conduction slowing and block in the AV node. AH prolongation occasionally is due to the effect of drugs (beta blockers, calcium channel blockers, digitalis) or increased vagal tone. Atropine can be used to reverse high vagal tone; however, if AH prolongation and AV block at long pacing cycle lengths persist, intrinsic AV node disease is likely. Type II second-degree block is typically infranodal, often in the His-Purkinje system. Block below the node with prolongation of the HV interval or a His bundle electrogram with no ventricular activation **(Fig. 240-5)** is abnormal unless it is elicited at fast pacing rates or short coupling intervals with extra stimulation. It is often difficult to determine the type of second-degree AV block when 2:1 conduction is present; however, the finding of a His bundle electrogram after every atrial electrogram indicates that block is occurring in the distal conduction system.

Intracardiac recording at electrophysiologic study that reveals prolongation of conduction through the His-Purkinje system (i.e., long HV interval) is associated with an increased risk of progression to higher grades of block and is generally an indication for pacing. In the setting of bundle branch block, the HV interval may reveal the condition of the unblocked bundle and the prognosis for developing more advanced AV conduction block. Prolongation of the HV interval in patients with asymptomatic bundle branch block is associated with an increased risk of developing higher-grade AV block. The risk increases with greater prolongation of the HV interval such that in patients with an HV interval >100 ms, the annual incidence of complete AV block approaches 10%, indicating a need for pacing. In patients with acquired CHB, even if intermittent, there is little role for electrophysiologic testing, and pacemaker implantation is almost always indicated.

TREATMENT

Management of AV Conduction Block

Temporary or permanent artificial pacing is the most reliable treatment for patients with symptomatic AV conduction system disease. However, exclusion of reversible causes of AV block and the need for temporary heart rate support based on the hemodynamic condition of the patient are essential considerations in each patient. Correction of electrolyte derangements and ischemia, inhibition of excessive vagal tone, and withholding of drugs with AV nodal blocking properties may increase the heart rate. Adjunctive pharmacologic treatment with atropine or isoproterenol may be useful if the block is in the AV node. Since most pharmacologic treatment may take some time to initiate and become effective, temporary pacing may be necessary. The most expeditious technique is the use of transcutaneous pacing, where pacing patches are placed anteriorly over the cardiac apex (cathode) and posteriorly between the spine and the scapula or above the right nipple (anode). Acutely, transcutaneous pacing is highly effective, but its duration is limited by patient discomfort and longer-term failure to capture the ventricle owing to changes in lead impedance. If a patient requires more than a few minutes of pacemaker support, transvenous temporary pacing should be

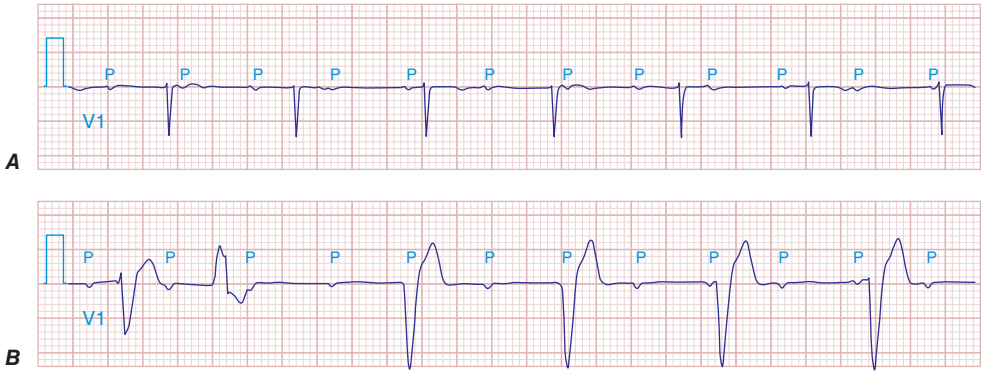

FIGURE 240-4 High-grade AV block. ***A.*** Multiple nonconducted P waves with a regular narrow complex QRS escape rhythm probably emanating from the AV junction. ***B.*** A wide complex QRS escape and a single premature ventricular contraction. In both cases, there is no consistent temporal relationship between the P waves and QRS complexes.

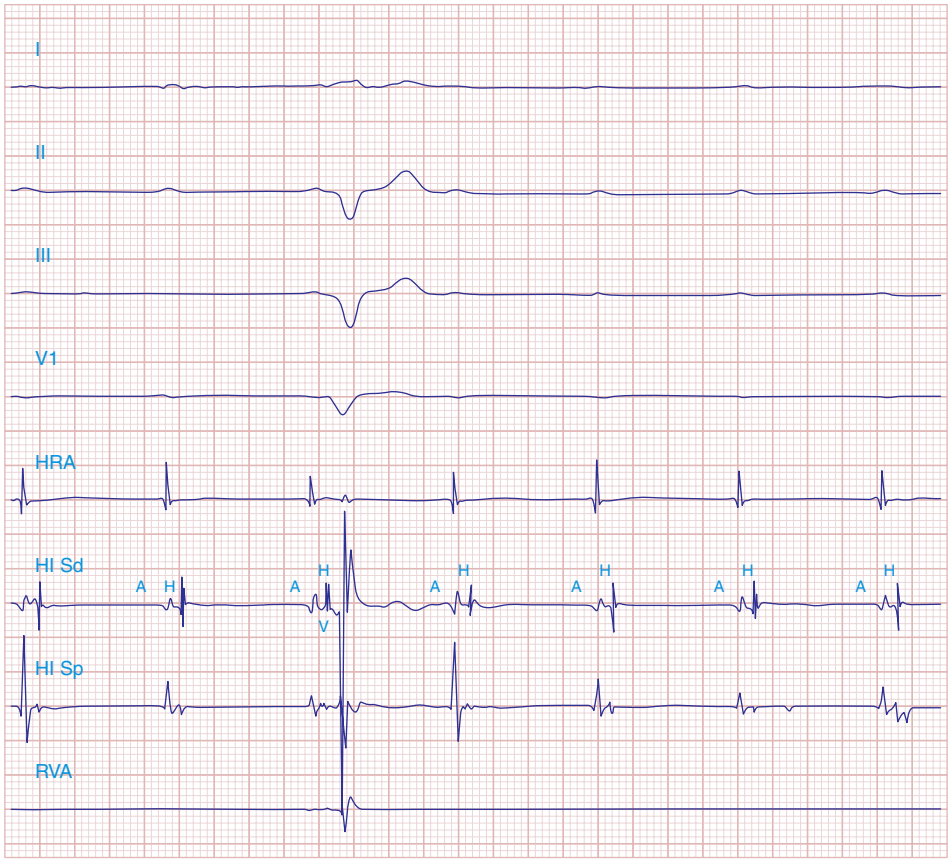

FIGURE 240-5 High-grade AV block below the His. The AH interval is normal and is not changing before the block. Atrial and His bundle electrograms are recorded consistent with block below the distal AV junction. I, II, III, and V_1 are surface ECG leads. HISp, HISd, and RVA are the proximal HIS, distal HIS, and right ventricular apical electrical recordings, respectively. A, H, and V represent the atrial, His, and ventricular electrograms on the His bundle recording, respectively. *(Used with permission from Dr. Joseph Marine.)*

instituted. Temporary pacing leads can be placed from the jugular or subclavian venous system and advanced to the right ventricle, permitting stable temporary pacing for many days, if necessary. In most circumstances, in the absence of prompt resolution, conduction block distal to the AV node requires permanent pacemaking.

PACEMAKERS IN AV CONDUCTION DISEASE

There are no randomized trials that evaluate the efficacy of pacing in patients with AV block, as there are no reliable therapeutic alternatives for AV block and untreated high-grade AV block is potentially lethal. The consensus guidelines for pacing in acquired AV conduction block in adults provide a general outline for situations in which pacing is indicated **(Table 240-2)**. Pacemaker implantation should be performed in any patient with symptomatic bradycardia and irreversible second- or third-degree AV block, regardless of the cause or level of block in the conducting system. Symptoms may include those directly related to bradycardia and low cardiac output or to worsening heart failure, angina, or intolerance to an essential medication. Pacing in patients with asymptomatic AV block should be individualized; situations in which pacing should be considered are patients with acquired CHB, particularly in the setting of cardiac enlargement; left ventricular dysfunction; and waking heart rates ≤40 beats/min. Patients who have asymptomatic second-degree AV block of either type should be considered for pacing if the block is demonstrated to be intra- or infra-His or is associated with a wide QRS complex. Pacing may be indicated in asymptomatic patients in special circumstances, in patients with profound first-degree AV block and left ventricular dysfunction in whom a shorter AV interval produces hemodynamic improvement, and in the setting of milder forms of AV conduction delay (first-degree AV block, intraventricular conduction delay) in patients with neuromuscular diseases that have a predilection for the conduction system, such as myotonic dystrophy and other muscular dystrophies, and Kearns-Sayre syndrome.

PACEMAKER THERAPY IN MYOCARDIAL INFARCTION

AV block in acute MI is often transient, particularly in inferior infarction. The circumstances in which pacing is indicated in acute MI are persistent second- or third-degree AV block, particularly if symptomatic, and transient second- or third-degree AV block associated with bundle branch block **(Table 240-3)**. Pacing is generally not indicated in the setting of transient AV block in the absence of intraventricular conduction delays or in the presence of fascicular block or first-degree AV block that develops in the setting of preexisting bundle branch block. Fascicular blocks that develop in acute MI in the absence of other forms of AV block also do not require pacing (Table 240-3 and **Table 240-4**).

PACEMAKER THERAPY IN BIFASCICULAR AND TRIFASCICULAR BLOCK

Distal forms of AV conduction block may require pacemaker implantation in certain clinical settings. Patients with bifascicular or trifascicular block and symptoms, particularly syncope that is not attributable to other causes, should undergo pacemaker implantation. Pacemaking is indicated in asymptomatic patients with bifascicular or trifascicular block who experience intermittent third-degree, type II second-degree AV block or alternating bundle branch block. In patients with fascicular block who are undergoing electrophysiologic study, a markedly prolonged HV interval or block below the His at long cycle lengths also may constitute an indication for permanent pacing. Patients with fascicular block and the neuromuscular diseases previously described should also undergo pacemaker implantation (Table 240-4).

TABLE 240-2 Guideline Summary for Pacemaker Implantation in Acquired AV Block

Class I

1. Third-degree or high-grade AV block at any anatomic level associated with:
   a. Symptomatic bradycardia
   b. Essential drug therapy that produces symptomatic bradycardia
   c. Periods of asystole >3 s or any escape rate <40 beats/min while awake, or an escape rhythm originating below the AV node
   d. Postoperative AV block not expected to resolve
   e. Catheter ablation of the AV junction
   f. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy, regardless of the presence of symptoms
2. Second-degree AV block with symptomatic bradycardia
3. Type II second-degree AV block with a wide QRS complex with or without symptoms
4. Exercise-induced second- or third-degree AV block in the absence of ischemia
5. Atrial fibrillation with bradycardia and pauses >5 s

Class IIa

1. Asymptomatic third-degree AV block regardless of level
2. Asymptomatic type II second-degree AV block with a narrow QRS complex
3. Asymptomatic type II second-degree AV block with block within or below the His at electrophysiologic study
4. First- or second-degree AV block with symptoms similar to pacemaker syndrome

Class IIb

1. AV block in the setting of drug use/toxicity, when the block is expected to recur even with drug discontinuation
2. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of AV block regardless of the presence of symptoms

Class III

1. Asymptomatic first-degree AV block
2. Asymptomatic type I second-degree AV block at the AV node level
3. AV block that is expected to resolve or is unlikely to recur (Lyme disease, drug toxicity)

Source: Data from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

TABLE 240-3 Guideline Summary for Pacemaker Implantation in AV Conduction Block in Acute Myocardial Infarction (AMI)

Class I

1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree block within or below the His after AMI
2. Transient advanced (second- or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary
3. Persistent and symptomatic second- or third-degree AV block

Class IIb

1. Persistent second- or third-degree AV block at the AV node level

Class III

1. Transient AV block in the absence of intraventricular conduction defects
2. Transient AV block in the presence of isolated left anterior fascicular block
3. Acquired left anterior fascicular block in the absence of AV block
4. Persistent first-degree AV block in the presence of bundle branch block that is old or age-indeterminate

Source: Data from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

TABLE 240-4 Indications for Pacemaker Implantation in Chronic Bifascicular and Trifascicular Block

Class I

1. Intermittent third-degree AV block
2. Type II second-degree AV block
3. Alternating bundle branch block

Class IIa

1. Syncope not demonstrated to be due to AV block when other likely causes (e.g., ventricular tachycardia) have been excluded
2. Incidental finding at electrophysiologic study of a markedly prolonged HV interval (>100 ms) in asymptomatic patients
3. Incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic

Class IIb

1. Neuromuscular diseases such as myotonic dystrophy, Kearns-Sayre syndrome, Erb dystrophy, and peroneal muscular atrophy with any degree of fascicular block regardless of the presence of symptoms, because there may be unpredictable progression of AV conduction disease

Class III

1. Fascicular block without AV block or symptoms
2. Fascicular block with first-degree AV block without symptoms

Source: Data from AE Epstein et al: J Am Coll Cardiol 51:e1, 2008.

SELECTION OF PACING MODE

In general, a pacing mode that maintains AV synchrony reduces complications of pacing such as pacemaker syndrome and pacemaker-mediated tachycardia. This is particularly true in younger patients; the importance of dual-chamber pacing in the elderly, however, is not well established. The availability of leadless miniaturized pacing systems may be appropriate in patients with indications for single chamber ventricular pacing, such as patients with atrial fibrillation and AV conduction block. Several studies have failed to demonstrate a difference in mortality rate in older patients with AV block treated with a single-(VVI) compared with a dual-(DDD) chamber pacing mode. In some of the studies that randomized pacing mode, the risk of chronic atrial fibrillation and stroke risk decreased with physiologic pacing. In patients with sinus rhythm and AV block, the very modest increase in risk with dual-chamber pacemaker implantation appears to be justified to avoid the possible complications of single-chamber pacing.

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241 Approach to Supraventricular Tachyarrhythmias

Gregory F. Michaud, William G. Stevenson

Supraventricular tachyarrhythmias originate from or are dependent on conduction through the atrium or atrioventricular (AV) node to the ventricles. Most produce narrow QRS-complex tachycardia (QRS duration <120 ms) characteristic of ventricular activation over the Purkinje system. Conduction block in the left or right bundle branch or activation of the ventricles from an accessory pathway produces a wide QRS complex during supraventricular tachycardia that must be distinguished from ventricular tachycardia **(Chap. 249)**. Mechanisms of supraventricular tachyarrhythmia can be divided into physiologic sinus tachycardia and pathologic tachycardia **(Table 241-1)**. Pathologic tachycardia can be further sub-classified in terms of mechanism as reentrant arrhythmias dependendent on AV nodal conduction (e.g., AV reentry), large reentry circuits within the atrial tissue alone (e.g., atrial flutter) or focal atrial tachycardias that can be due to automaticity or small reentry circuits (**see Figs. 243-3 and 245-1**). The prognosis and treatment vary considerably depending on the mechanism and underlying heart disease.

Supraventricular tachycardia can be of brief duration, termed *nonsustained*, or can be sustained such that an intervention, such as cardioversion or drug administration, is required for termination. Episodes that occur with sudden onset and termination are referred to as paroxysmal. *Paroxysmal supraventricular tachycardia* (PSVT) refers to a family of tachycardias including AV node reentry, AV reentry using an accessory pathway, and atrial tachycardia.

CLINICAL PRESENTATION

Symptoms of supraventricular arrhythmia vary depending on the rate, duration, associated heart disease, and comorbidities and include palpitations, chest pain, dyspnea, diminished exertional capacity, and occasionally syncope. Rarely, a supraventricular arrhythmia precipitates cardiac arrest in patients with the Wolff-Parkinson-White syndrome or severe heart disease, such as hypertrophic cardiomyopathy.

Initial Evaluation Diagnosis requires obtaining an electrocardiogram (ECG) at the time of symptoms. When the arrhythmia is ongoing, the ECG usually establishes or suggests the diagnosis **(Figs.** 241-1 to **241-3** and **Table 241-2)**. Treatment is determined by the type of arrhythmia and its hemodynamic effect. For transient arrhythmias, ambulatory ECG recording is warranted. Exercise testing is useful for assessing exercise-related symptoms. Occasionally an invasive electrophysiology study is warranted to provoke the arrhythmia with pacing, confirm the mechanism, and usually, perform catheter ablation.

Paroxysmal supraventricular tachycardia is most commonly encountered in patients who do not have structural heart disease. Other supraventricular arrhythmias, particularly atrial fibrillation, are associated with a variety of heart diseases. At initial evaluation history and examination should assess possible underlying heart disease. Any abnormal findings may warrant further cardiac evaluation.

The most common supraventricular tachycardia is sinus tachycardia in response to physiologic stress, such as exercise, but it can also be a manifestation acute illness. The first step in diagnosis of supraventricular tachycardia is to consider the possibility of sinus tachycardia. **(Chap. 242)**. Therapy is then determined by the clinical findings. If the arrhythmia is ongoing and is not due to sinus tachycardia, initial assessment determines whether immediate therapy is needed to terminate the arrhythmia or slow the rate. Arrhythmias causing hypotension, impaired consciousness, angina, or heart failure warrant immediate therapy, guided by the type of arrhythmia.

TABLE 241-1 Supraventricular Tachycardia

I. Physiologic sinus tachycardia

Defining feature: normal sinus mechanism precipitated by exertion, stress, concurrent illness (Table 242-1)

II. Pathologic supraventricular tachycardia

A. Tachycardias originating from the atrium

Defining feature: tachycardia may continue despite beats that fail to conduct to the ventricles, indicating that the AV node is not participating in the tachycardia circuit

1. ***Inappropriate sinus tachycardia***

Defining feature: tachycardia from the normal sinus node area that occurs without an identifiable precipitating factor as a result of dysfunctional autonomic regulation

2. ***Focal atrial tachycardia (AT)***

Defining feature: Regular atrial tachycardia with defined p wave; may be sustained, nonsustained, paroxysmal, or incessant. Frequent sites of origin occur along the valve annuli of left or right atrium, pulmonary veins, coronary sinus musculature, superior vena cava

3. ***Atrial flutter***—macroreentrant atrial tachycardia

Defining feature: organized reentry creates organized atrial activity, commonly seen as sawtooth flutter waves at rates typically faster than 200 beats/min

a. Common atrial flutter

i. Right atrial reentry parallel to the tricuspid annulus and dependent on conduction through the isthmus between the inferior vena cava and tricuspid annulus

1. Counterclockwise (as viewed from the ventricular aspect)

2. Clockwise

b. Atypical atrial flutter

i. Usually due to reentry in left or right atrium associated with scars usually from prior surgery or catheter ablation for atrial fibrillation, but may be idiopathic

4. ***Atrial fibrillation***

Defining feature: chaotic rapid atrial electrical activity with variable ventricular rate; the most common sustained cardiac arrhythmia in older adults

5. ***Multifocal atrial tachycardia***

Defining feature: multiple discrete p waves often seen in patients with pulmonary disease during acute exacerbations of pulmonary insufficiency

B. AV nodal reentry tachycardia (AVNRT)

Defining feature: paroxsymal regular tachycardia with P waves visible at the end of the QRS complex or not visible at all; the most common paroxysmal sustained tachycardia in healthy young adults; more common in women

C. Tachycardias associated with accessory atrioventricular pathways

1. ***Orthodromic AV reentry tachycardia (AVRT)***

Defining feature: paroxysmal sustained tachycardia similar to AV nodal reentry; during sinus rhythm, evidence of ventricular preexcitation may be present (Wolff-Parkinson-White syndrome) or absent (concealed accessory pathway)

2. ***Preexcited tachycardia***

Defining feature: wide QRS tachycardia with QRS morphology similar to VT

a. Antidromic AV reentry—regular paroxysmal tachycardia

b. Atrial fibrillation with preexcitation—irregular wide complex, or intermittently wide complex tachycardia, some with dangerously rapid rates faster than 250/min

c. Atrial tachycardia or flutter with preexcitation

Abbreviations: AV, atrioventricular; VT, ventricular tachycardia.

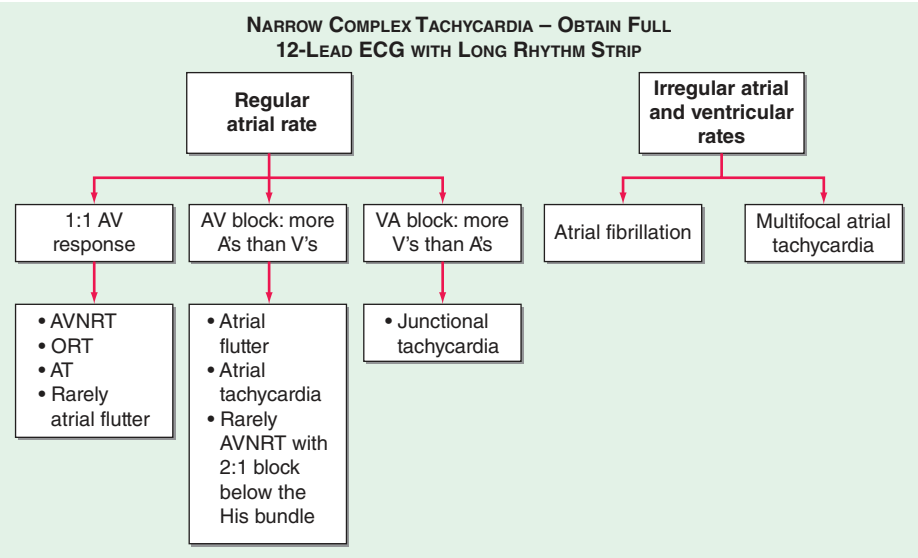

FIGURE 241-1 Diagnostic possibilities based on the appearance of the 12-lead ECG recorded during an episode of SVT. AVNRT, AV nodal reentry tachycardia; ORT, orthodromic AV reentry tachycardia; AT, focal atrial tachycardia.

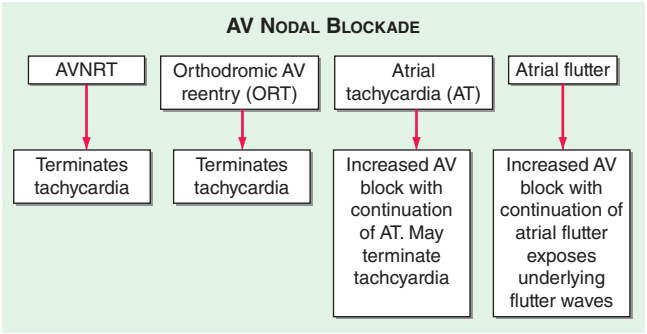

FIGURE 241-2 Diagnostic effect of increasing AV node blockade with vagal maneuvers, adenosine, verapamil or beta blockers.

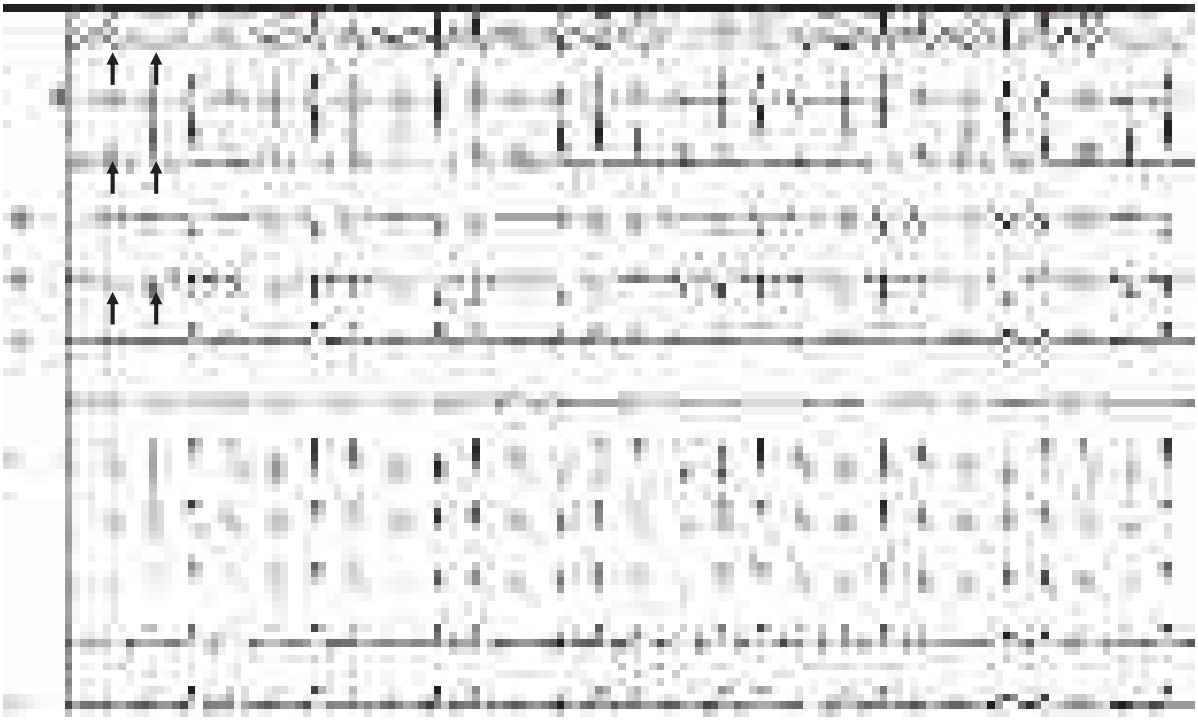

FIGURE 241-3 12-lead ECG of ORT due to an accessory pathway between the left ventricle and left atrium. The ECG is from an otherwise healthy young woman who had recurrent episodes of tachycardia, sometimes terminating with vagal maneuvers and always terminated by administration of adenosine. Termination with AV node blocking agents make atrial flutter and atrial tachycardia unlikely and are consistent with mechanisms dependent on AV nodal conduction, such as ORT or AVNRT. The 12-lead ECG shows a narrow complex tachycardia with a regular atrial rate and 1:1 atrioventricular response. Using the algorithm shown in Fig. 241-2, the most likely mechanisms are AVNRT or ORT. The P wave can be seen in the ST segment (arrows) and appears to be positive in lead III and negative in leads I and aVL, which suggests a left free wall origin. Ablation of the left free wall accessory pathway eliminated further episodes of SVT. **(See Chap. 244 for further discussion of ORT and accessory pathways).**

TABLE 241-2 Usual Relation of P-wave to QRS in Paroxysmal Supraventricular Tachycardias (see also Fig. 241-3)

Regular tachycardia with 1:1 AV conduction:

- AVNRT either has no discernible p-waves because they are synchronous with the QRS, or p-waves that are negative in II, III, aVF immediately following the QRS (referred to as short R-P tachycardia). Atypical forms may have a longer R-P interval.
- ORT has p-waves following the QRS, although they may be difficult to define when simultaneous with the T-wave. (See example in Fig. 241-3.)
- AT typically has p-waves preceding the QRS (R-P) interval > P-R interval. P wave morphology depends on the focus location and is different compared to sinus rhythm unless the focus is near the sinus node.

Note: Further analysis of SVT with a regular ventricular rate may allow discrimination among the three most common forms: atrioventricular nodal reentry tachycardia (AVNRT), orthodromic reentrant tachycardia (ORT), or atrial tachycardia (AT).

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242 Physiologic and Nonphysiologic Sinus Tachycardia

Gregory F. Michaud, William G. Stevenson

Physiologic Sinus Tachycardia The sinus node is comprised of a group of cells dispersed within the superior aspect of the thick ridge of muscle known as the crista terminalis where the posterior smooth atrial wall derived from the sinus venosus meets the trabeculated anterior portion of the right atrium (Fig. 242-1). Sinus p waves are characterized by a frontal plane axis directed inferiorly and leftward, with positive p waves in leads II, III, and aVF; a negative p wave in aVR; and an initially positive biphasic p wave in V1. Normal sinus rhythm has a range of rates between 60–100 beats/min. Sinus tachycardia (>100 beats/min) typically occurs in response to sympathetic stimulation and vagal withdrawal, whereby the rate of spontaneous depolarization of the sinus node increases and the focus of earliest activation within the node typically shifts more leftward and closer to the superior septal aspect of the crista terminalis, thus producing taller p waves in the inferior limb leads when compared to normal sinus rhythm. Sinus bradycardia is defined as rates less than 60 beats/min; however, bradycadia can be normal during sleep and in fit individuals.

TABLE 242-1 Common Causes of Physiologic Sinus Tachycardia

1. Exercise
2. Acute illness with fever, infection, pain
3. Hypovolemia, anemia
4. Hyperthyroidism
5. Pulmonary insufficiency
6. Drugs that have sympathomimetic, vagolytic, or vasodilator properties, e.g., albuterol, theophylline, tricyclic antidepressants, nifedipine, hydralazine
7. Pheochromocytoma

Sinus tachycardia is considered physiologic when it is an appropriate response to exercise, stress, or illness. Sinus tachycardia can be difficult to distinguish from focal atrial tachycardia (see below) that originates near the sinus node. A causative factor (such as exertion) and a gradual increase and decrease in rate favor sinus tachycardia, whereas abrupt onset and offset favor atrial tachycardia. The distinction can be difficult and occasionally requires extended ECG monitoring or even invasive electrophysiology study. Treatment for physiologic sinus tachycardia is aimed at the underlying condition (Table 242-1), but frequently no therapy is necessary.

Nonphysiologic Sinus Tachycardia *Inappropriate sinus tachycardia* is an uncommon condition in which the sinus rate increases spontaneously at rest or out of proportion to physiologic stress or exertion and is within a spectrum of ill-defined conditions associated with autonomic dysregulation. Affected individuals are often women in the third or fourth decade of life. Fatigue, dizziness, and even syncope may accompany palpitations, which can be disabling. Additional symptoms

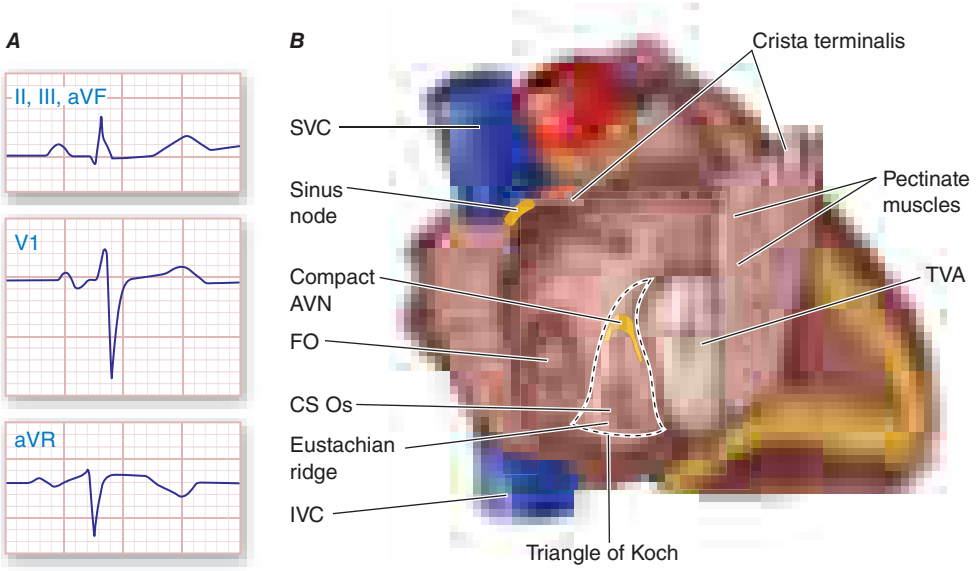

FIGURE 242-1 Right atrial anatomy pertinent to normal sinus rhythm and supraventricular tachycardia. *A.* Typical P-wave morphology during normal sinus rhythm based on standard 12-lead electrocardiogram. There is a positive P wave in leads II, III, and aVF; biphasic, initially positive P wave in V_1; and negative P wave in aVR. ***B.*** Right atrial anatomy seen from a right lateral perspective with the lateral wall opened to view the septum. AVN, atrioventricular node; CS Os, coronary sinus ostium; FO, fossa ovalis; IVC, inferior vena cava; SVC, superior vena cava; TVA, tricuspid valve annulus.

of chest pain, headaches, and gastrointestinal upset are common. It must be distinguished from appropriate sinus tachycardia and from focal atrial tachycardia. The distinction between physiologic sinus tachycardia due to an anxiety disorder and inappropriate sinus tachycardia can be difficult. Therapy is often ineffective or poorly tolerated. Careful titration of beta blockers and/or calcium channel blockers may reduce symptoms. Clonidine and serotonin reuptake inhibitors have also been used. Ivabradine, a drug that blocks the I_f current that causes sinus node depolarization, is now approved in the United States for use in heart failure, but it has also been effective in the treatment of inappropriate sinus tachycardia. Catheter ablation of the sinus node has been performed, but long-term control of symptoms is usually poor, and it often leaves young individuals with a permanent pacemaker.

Postural orthostatic tachycardia syndrome (POTS) is characterized by symptomatic sinus tachycardia that occurs with postural change from a supine position to standing. The sinus rate increases by 30 beats/min or to >120 beats/min within 10 min of standing and in the absence of hypotension. Symptoms are often similar to those in patients with inappropriate sinus tachycardia. POTS is sometimes due to autonomic dysfunction following a viral illness and may resolve spontaneously over 3–12 months. Volume expansion with salt supplementation, oral fludrocortisone, compression stockings, and the α-agonist midodrine, often in combination, can be helpful. Exercise training has also been purported to improve symptoms.

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243 Focal Atrial Tachycardia

Gregory F. Michaud, William G. Stevenson

Focal atrial tachycardia (AT) can be due to abnormal automaticity, triggered automaticity, or a small reentry circuit confined to the atrium or atrial tissue extending into a pulmonary vein, the coronary sinus, or vena cava. It can be sustained, nonsustained, paroxysmal, or incessant. Focal AT accounts for ~10% of PSVTs in patients referred for catheter ablation. Nonsustained AT is commonly observed on 24-h ambulatory ECG recordings, and the prevalence increases with age. In fact, frequent atrial ectopy and nonsustained AT is often a precursor to more significant arrhythmias such as atrial fibrillation and flutter. Though unsustained, frequent atrial ectopy or short bursts of AT may be symptomatic and require therapy similar to that required for focal AT.

AT can occur in the absence of structural heart disease or may be associated with any condition that causes atrial fibrosis, including prior catheter ablation. Areas of fibrosis can be a nidus for abnormal automaticity from damaged cells or microreentry within zones of slow conduction within and on the border of fibrotic areas. Sympathetic stimulation is a promoting factor and the emergence of AT can be a sign of underlying illness. AT with AV block may occur in digitalis toxicity. Symptoms from AT are highly variable but similar to other supraventricular tachycardias (SVTs). Incessant AT can cause tachycardia-induced cardiomyopathy.

AT typically presents with 1:1 AV conduction or with AV block that can be Wenckebach type conduction or fixed (e.g., 2:1 or 3:1). Because it is not dependent on AV nodal conduction, AT will not terminate with AV block, and the atrial rate will not be affected, which distinguishes AT from most AV nodal–dependent SVTs, such as AV nodal reentry and AV reentry using an accessory pathway (see below). An accelerated warm-up phase after initiation or cool-down phase prior to termination also favors AT rather than AV nodal–dependent SVT, as this is a common observation with triggered automaticity. P waves are often discrete, with an intervening isoelectric segment, in contrast to atrial flutter and macroreentrant AT (see below) because atrial activation from a focal source occurs though a small portion of the tachycardia cycle. When 1:1 conduction to the ventricles is present, the arrhythmia can resemble sinus tachycardia typically with a P-R interval shorter than the R-P interval **(Fig. 243-1),** *particularly when sympathetic tone produces rapid AV nodal conduction*. It can be distinguished from sinus tachycardia by the P-wave morphology, which usually differs from sinus p waves depending on the location of the focus. Focal AT tends to originate in areas of complex atrial anatomy, such as the crista terminalis, valve annuli, atrial septum, and atrial muscle extending along cardiac thoracic veins (superior vena cava, coronary sinus, and pulmonary veins) **(Fig. 243-2)**, and the location can often be estimated by the P-wave morphology. AT from the atrial septum will frequently have a narrower P-wave duration than sinus rhythm. AT from the left atrium will usually have a monophasic, positive P wave in lead V_1 and negative P waves in I and aVL indicating movement away from the left atrial free wall. AT that originates from superior atrial locations, such as the superior vena cava or superior pulmonary veins, will be positive in the inferior limb leads II, III, and aVF, whereas AT from a more inferior location, such as the ostium of the coronary sinus, will inscribe negative P waves in these same leads. When the focus is in the superior aspect of the crista terminalis, close to the sinus node, however, the p wave will resemble that of sinus tachycardia. Abrupt onset and offset then favor AT rather than sinus tachycardia. Depending on the atrial rate, the P wave may fall on top of the T wave or, during 2:1 conduction, may fall coincident with the QRS. Maneuvers that increase AV block, such as carotid sinus massage, Valsalva maneuver, or administration of AV nodal–blocking agents, such as adenosine, are useful to create AV block that will expose the p wave **(Fig. 243-3)**.

Acute management of sudden-onset, sustained AT is the same as for other forms of PSVT **(Chaps. 241 and 244)**, but the response to pharmacologic therapy is variable, likely depending on the mechanism. For AT due to reentry, administration of adenosine or vagal maneuvers may transiently increase AV block without terminating tachycardia. Some ATs terminate with a sufficient dose of adenosine, consistent with triggered activity as the mechanism. Cardioversion can be effective in some, but fails in others because of immediate recurrence, suggesting automaticity as the mechanism in these cases. Beta blockers and calcium channel blockers may slow the ventricular rate by increasing AV block, which can improve tolerance of the arrhythmias, but large doses are sometimes required. Potential precipitating factors and intercurrent illness should be sought and corrected. Underlying heart disease should be considered and excluded.

For patients with recurrent episodes, beta blockers, calcium channel blockers such as diltiazem or verapamil, and antiarrhythmic drugs such as flecainide, propafenone, disopyramide, sotalol, and amiodarone can be effective, but potential toxicities and adverse effects often warrant avoidance for long term use **(Tables 243-1, 243-2, and 243-3)**. Catheter ablation targeting the AT focus is effective in more than 80% of patients and is recommended for recurrent symptomatic AT when drugs fail or are not desired or for incessant AT causing tachycardia-induced cardiomyopathy.

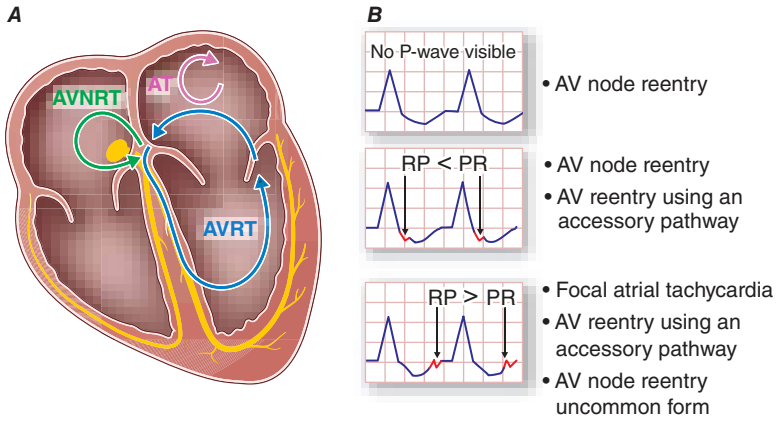

FIGURE 243-1 Common mechanisms underlying paroxysmal supraventricular tachycardia along with typical R-P relationships. ***A.*** Schematic showing a four-chamber view of the heart with atrioventricular node in *green* and an accessory pathway between the left atrium and left ventricle in *blue*. Atrial tachycardia (AT; *red circuit*) is confined completely to atrial tissue. Atrioventricular nodal reentry tachycardia (AVNRT; *blue circuit*) uses atrioventricular (AV) nodal and perinodal atrial tissue. Atrioventricular reentry tachycardia (AVRT; *black circuit*) uses atrial and ventricular tissue, accessory pathway, AV node, and specialized conduction fibers (His-Purkinje) as part of the reentry circuit. ***B.*** Typical relation of the P wave to QRS, commonly described as the R-P to P-R relationships for the different tachycardia mechanisms.

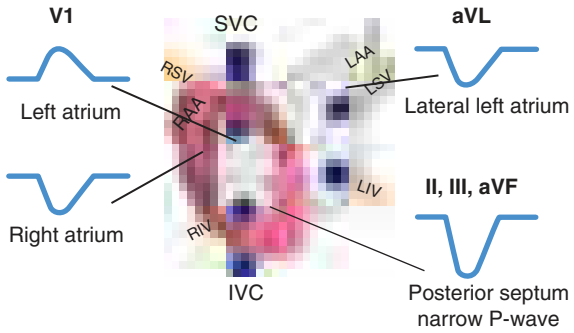

FIGURE 243-2 Location of focal atrial tachycardia focus estimated by P-wave morphology. LAA, left atrial appendage; LIV, left inferior pulmonary vein; LSV, left superior pulmonary vein; RAA, right atrial appendage; RIV, right inferior pulmonary vein; RSV, right superior pulmonary vein; SVC, superior vena cava.

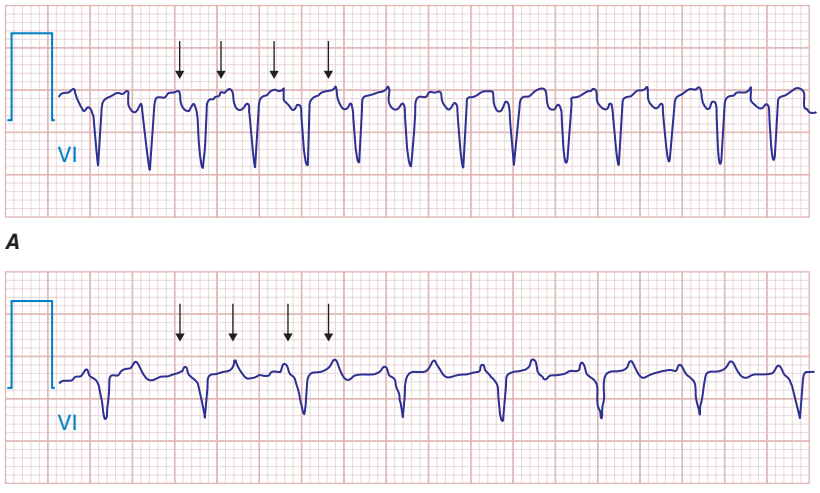

FIGURE 243-3 Atrial tachycardia (AT) with 1:1 and 2:1 atrioventricular (AV) conduction. *Arrows* indicate P waves. ***A.*** AT with 1:1 AV relationship and R-P > P-R. ***B.*** Same AT with 2:1 AV relationship after AV nodal–blocking agent administered. *(Adapted from F Marchlinski: The tachyarrhythmias in DL Longo et al [eds]: Harrison's Principles of Internal Medicine, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.)*

TABLE 243-1 Commonly Used Antiarrhythmic Agents—Intravenous Dose Range/Primary Indication

DRUG	LOADING	MAINTENANCE	PRIMARY INDICATION	CLASS[a]
Adenosine	6–18 mg (rapid bolus)	N/A	Terminate reentrant SVT involving AV node	—
Amiodarone	15 mg/min for 10 min, 1 mg/min for 6 h	0.5–1 mg/min	AF, AFL, SVT, VT/VF	III
Digoxin	0.25 mg q2h until 1 mg total	0.125–0.25 mg/d	AF/AFL rate control	—
Diltiazem	0.25 mg/kg over 3–5 min (max 20 mg)	5–15 mg/h	SVT, AF/AFL rate control	IV
Esmolol	500 μg/kg over 1 min	50 μg/kg per min	AF/AFL rate control	II
Ibutilide	1 mg over 10 min if over 60 kg	N/A	Terminate AF/AFL	III
Lidocaine	1–3 mg/kg at 20–50 mg/min	1–4 mg/min	VT	IB
Metoprolol	5 mg over 3–5 min × 3 doses	1.25–5 mg q6h	SVT, AF rate control; exercise-induced VT; long QT	II
Procainamide	15 mg/kg over 60 min	1–4 mg/min	Convert/prevent AF/VT	IA
Quinidine	6–10 mg/kg at 0.3–0.5 mg/kg per min	N/A	Convert/prevent AF/VT	IA
Verapamil	5–10 mg over 3–5 min	2.5–10 mg/h	SVT, AF rate control	IV

[a]Classification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class IA agents also prolong action potential duration; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel–blocking agents.

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; AV, atrioventricular; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 243-2 Commonly Used Antiarrhythmic Agents: Chronic Oral Dosing/Primary Indications

DRUG	DOSING ORAL, mg, MAINTENANCE	HALF-LIFE, h	PRIMARY ROUTE(S) OF METABOLISM/ELIMINATION	MOST COMMON INDICATION	CLASS[a]
Acebutolol	200–400 q12h	6–7	Renal/hepatic	AF rate control/SVT Long QT/RVOT VT	II
Amiodarone	100–400 qd	40–55 d	Hepatic	AF/VT prevention	III[b]
Atenolol	25–100 per d	6–9	Renal	AF rate control/SVT Long QT/RVOT VT	II
Digoxin	0.125–0.25 qd	38–48	Renal	AF rate control	—
Diltiazem	30–60 q6h	3–4.5	Hepatic	AF rate control/SVT	IV
Disopyramide	100–300 q6–8h	4–10	Renal 50%/hepatic	AF/SVT prevention	Ia
Dofetilide	0.125–0.5 q12h	10	Renal	AF prevention	III
Dronedarone	400 q12h	13–19	Hepatic	AF prevention	IIIb
Flecainide	50–200 q12h	7–22	Hepatic 75%/renal	AF/SVT/VT prevention	Ic
Metoprolol	25–100 q6h	3–8	Hepatic	AF rate control/SVT Long QT/RVOT VT	II
Mexiletine	150–300 q8–12h	10–14	Hepatic	VT prevention	Ib
Nadolol	40–240 per d	10–24	Renal	Same as metoprolol	II
Propafenone	150–300 q8h	2–8	Hepatic	AF/SVT/VT prevention	Ic
Quinidine	300–600 q6h	6–8	Hepatic 75%/renal	AF/SVT/VT prevention	Ia
Sotalol	80–160 q12h	12	Renal	AF/VT prevention	III
Verapamil	80–120 q6–8h	4.5–12	Hepatic/renal	AF rate control/RVOT VT Idiopathic LV VT	IV

[a]Classification of antiarrhythmic drugs: class I—agents that primarily block inward sodium current; class II—antisympathetic agents; class III—agents that primarily prolong action potential duration; class IV—calcium channel-blocking agents. [b]Amiodarone and dronedarone both are grouped in class III, but both also have class I, II, and IV properties.

Abbreviations: AF, atrial fibrillation; LV, left ventricular; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

TABLE 243-3 Common and Proarrhythmic Toxicities of Antiarrhythmic Agents

DRUG	POTENTIAL PROARRHYTHMIC TOXICITIES	COMMON TOXICITIES
Amiodarone	Sinus bradycardia, AV block, increase in defibrillation threshold. Rare: long QT and torsades des pointes, incessant slow VT in heart disease	Tremor, peripheral neuropathy, pulmonary fibrosis or inflammation, hypo- and hyperthyroidism, hepatitis, photosensitivity
Adenosine	Transient profound pauses, atrial fibrillation	Cough, flushing, chest pain, anxiety
Digoxin	AV block, fascicular tachycardia, accelerated junctional rhythm, atrial tachycardia with AV block	Anorexia, nausea, vomiting, visual changes
Disopyramide	Long QT and torsades des pointes, 1:1 ventricular response to atrial flutter	Anticholinergic effects, acute urinary retention (males), negative inotropy
Dofetilide	Long QT and torsades des pointes	Nausea
Dronedarone	Bradyarrhythmias and AV block, long QT and torsades des pointes (rare)	Gastrointestinal intolerance, exacerbation of heart failure
Flecainide	1:1 Ventricular response to atrial flutter; increased risk of ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Dizziness, nausea, headache, decreased myocardial contractility
Ibutilide	Long QT and torsades des pointes	Nausea
Lidocaine	Slow VT in some patients with structural heart disease	Dizziness, confusion, delirium, seizures, coma
Mexiletine	Slow VT in patients with structural heart disease	Ataxia, tremor, gait disturbances, rash, nausea
Procainamide	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Lupus erythematosus–like syndrome (more common in slow acetylators), anorexia, nausea, neutropenia
Propafenone	1:1 Ventricular response to atrial flutter; increased risk ventricular tachycardias in patients with structural heart disease; sinus bradycardia	Taste disturbance, dyspepsia, nausea, vomiting
Quinidine	Long QT and torsades des pointes, accelerated ventricular rate in AF or flutter	Diarrhea, nausea, vomiting, cinchonism, thrombocytopenia
Sotalol	Long QT and torsades des pointes	Hypotension, bronchospasm from β-blocking effect

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; VT, ventricular tachycardia.

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244 Paroxysmal Supraventricular Tachycardias

Gregory F. Michaud, William G. Stevenson

Atrioventricular Nodal Reentry Tachycardia AV nodal reentry tachycardia (AVNRT) is the most common form of paroxysmal supraventricular tachycardia (PSVT), representing ~60% of cases referred for catheter ablation. It most commonly manifests in the second to fourth decades of life, often in women. It is often well tolerated, but rapid tachycardia, particularly in the elderly, may cause angina, pulmonary edema, hypotension, or syncope. It is not usually associated with structural heart disease.

The mechanism is reentry involving the AV node and the perinodal atrium, made possible by the existence of multiple pathways for conduction from the atrium into the AV node that are capable of conduction in two directions **(Fig. 244-1)**. Most forms of AVNRT utilize a slowly conducting AV nodal pathway (right inferior extension) that extends from the compact AV node near the His bundle, inferiorly along the tricuspid valve annulus to the floor of the coronary sinus. The reentry wavefront propagates up this slowly conducting pathway to the compact AV node and then exits from the fast pathway at the top of the AV node. The path back to the slow pathway probably involves the left atrial septum which has connections to the coronary sinus musculature. More unusual forms of AVNRT utilize a left inferior extension that connects to the compact AV node through the roof of the coronary sinus, or in extremely rare cases, directly from the mitral valve annulus avoiding the coronary sinus musculature altogether. In typical forms, the conduction time from the compact AV node region to the atrium is similar to that from the compact node to the His bundle and ventricles, such that atrial activation occurs at about the same time as ventricular activation. The P wave is therefore inscribed during, slightly before, or slightly after the QRS and can be difficult to discern. Often the P wave is seen at the end of the QRS complex as a pseudo-r' in lead V_1 and pseudo-S waves in leads II, III, and aVF **(Fig. 244-1*A*)**. More unusual forms of AVNRT have P waves falling later, anywhere between QRS complexes, in which case an inverted P wave is seen in the inferior limb leads as seen in **Fig. 244-2** where the inverted P wave is seen in the T wave. The rate can vary with sympathetic tone. Simultaneous atrial and ventricular contraction results in atrial contraction against a closed tricuspid valve producing cannon a wave visible in the jugular venous pulse often perceived as a fluttering sensation in the neck. Elevated venous pressures may also lead to release of natriuretic peptides that cause post-tachycardia diuresis. In contrast to ATs, maneuvers or medications that produce AV nodal block terminate the arrhythmia.

Acute treatment is the same as for other forms of PSVT (discussed below). Whether ongoing therapy is warranted depends on the severity of symptoms and frequency of episodes. Reassurance and instruction as to how to perform the Valsalva maneuver to terminate episodes are sufficient for many patients. Administration of an oral beta blocker, verapamil, or diltiazem at the onset of an episode has been used to facilitate termination. Chronic therapy with these medications or flecainide is an option if prophylactic therapy is needed. Catheter ablation of the slow AV nodal pathway is recommended for patients with recurrent or severe episodes or when drug therapy is ineffective, not tolerated, or not desired by the patient. Catheter ablation is curative in >95% of patients. The major risk is atrioventricular (AV) block requiring permanent pacemaker implantation, which occurs in <1% of patients.

Junctional Tachycardia Junctional ectopic tachycardia (JET) is due to automaticity within the AV node. It is rare in adults and more frequently encountered as an incessant tachycardia in children, often in the perioperative period of surgery for congenital heart disease. It presents as a narrow QRS tachycardia, often with ventriculoatrial (VA) block, such that AV dissociation is present. JET can occur as a manifestation of increased adrenergic tone and may be seen after administration of isoproterenol, particularly after catheter ablation in the perinodal region. It may also occur for a short period of time after ablation for AVNRT.

Accelerated junctional rhythm is a junctional automatic rhythm between 50 and 100 beats/min. Initiation may occur with gradual acceleration in rate, suggesting an automatic focus, or after a premature ventricular contraction, suggesting a focus of triggered automaticity. VA conduction is usually present, with P-wave morphology and timing such that it resembles AVNRT at a slow rate. It can be related to increased sympathetic tone and may produce palpitations. It usually does not require specific therapy.

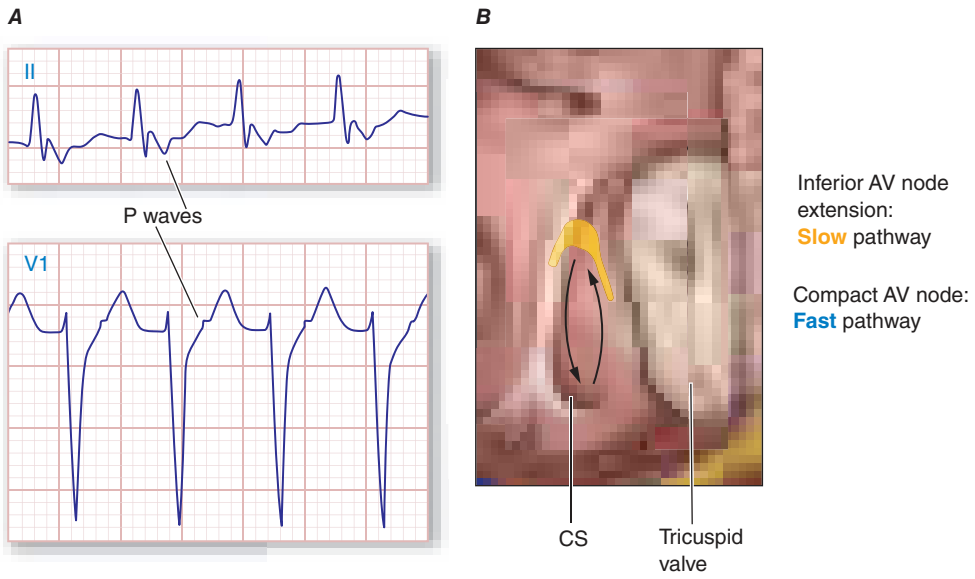


FIGURE 244-1 Atrioventricular (AV) node reentry. *A.* Leads II and V_1 are shown. P waves are visible at the end of the QRS complex and are negative in lead II, and may give the impression of S waves in the inferior limb leads II, III, and aVF and an R' in lead V_1. ***B.*** Stylized version of the AV nodal reentry circuit within the triangle of Koch **(see Fig. 242-1)** that involves AV node and its extensions along with perinodal atrial tissue.

ACCESSORY PATHWAYS AND THE WOLFF-PARKINSON-WHITE SYNDROME

Accessory pathways (APs) occur in 1 in 1500–2000 people and are associated with a variety of arrhythmias including narrow-complex PSVT, wide-complex tachycardias, and, rarely, sudden death. Most patients have structurally normal hearts, but APs are associated with Ebstein's anomaly of the tricuspid valve and forms of hypertrophic cardiomyopathy including *PRKAG2* mutations, Danon's disease, and Fabry's disease.

APs are abnormal connections that allow conduction between the atrium and ventricles across the AV ring

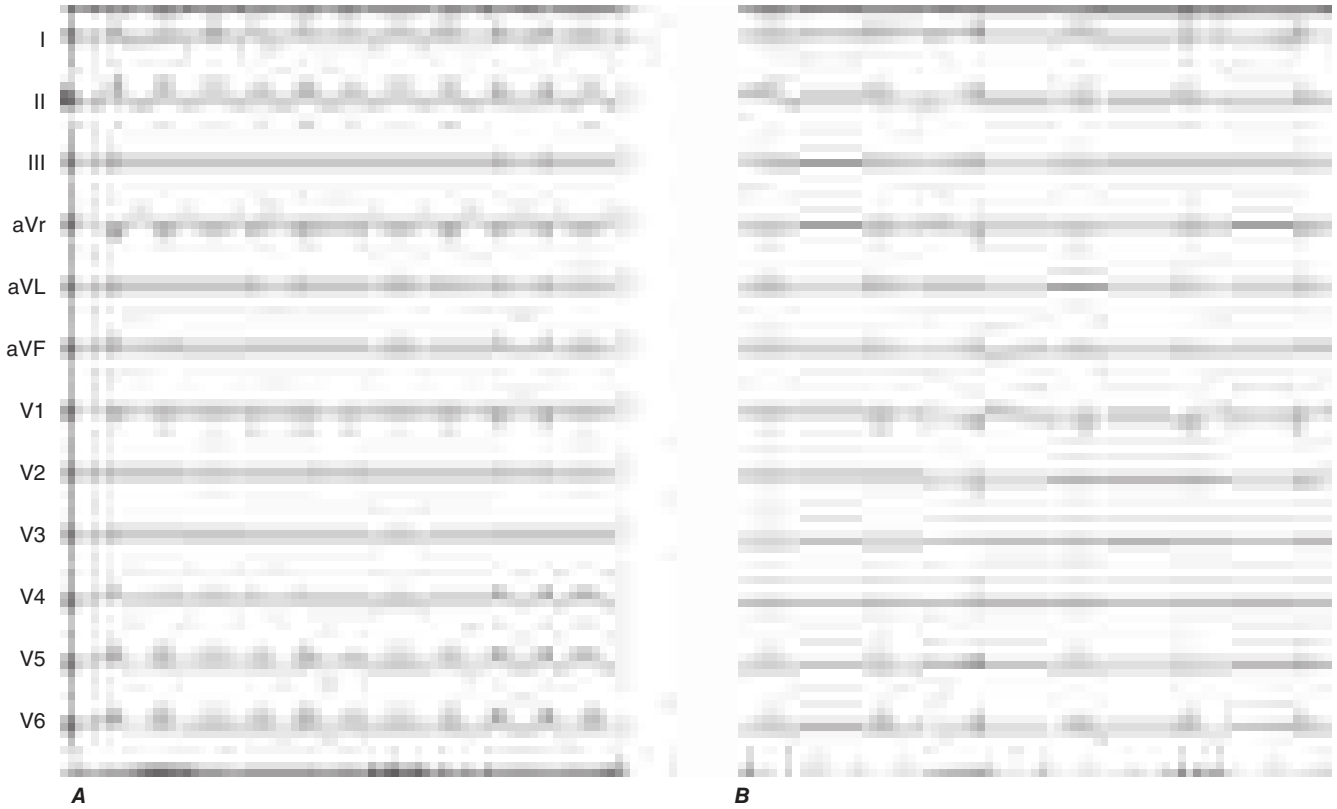


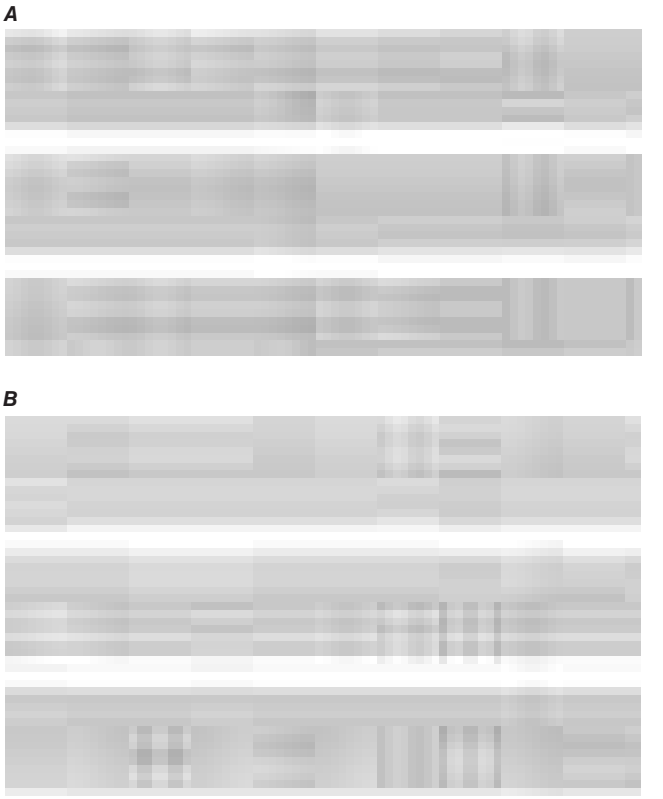
FIGURE 244-2 Comparison of 12-lead ECG tracings showing SVT (Panel A) and normal sinus rhythm (Panel B). The P wave is observed at the end of the T wave and morphology can be inferred from comparing to sinus rhythm. P waves are inverted in the inferior limb leads (II, III, and aVF), positive in V1, I, and aVL consistent with conduction retrogradely through the AV junction. In typical forms of AVNRT, the P wave is not visible or is seen at the end of the QRS complex.

(Fig. 244-3). They are present from birth and are due to failure of complete partitioning of atrium and ventricle by the fibrous AV rings. They occur across either an AV valve annulus or the septum, most frequently between the left atrium and free wall of the left ventricle, followed by posteroseptal, right free wall, and anteroseptal locations. If the impulse from the sinus node conducts through the AP to the ventricle (antegrade) before the impulse conducts through the AV node and His bundle, then the ventricles are preexcited during sinus rhythm, and the ECG shows a short P-R interval (<0.12 s), slurred initial portion of the QRS (delta wave), and prolonged QRS duration produced by slow conduction through direct activation of ventricular myocardium over the AP (Fig. 244-3*A*). The morphology of the QRS and delta wave is determined by the AP location (Fig. 244-4) and the degree of fusion between the excitation wavefronts from conduction over the AV node and conduction over the AP. Right-sided pathways preexcite the right ventricle, producing a left bundle branch block–like configuration in lead V_1, and often create marked preexcitation because of relatively close proximity of the AP to the sinus node (Fig. 244-4). Left-sided pathways preexcite the left ventricle and may produce a right bundle branch–like configuration in lead V_1 and a negative delta wave in aVL, indicating initial depolarization of the lateral portion of the left ventricle that can mimic q waves of lateral wall infarction (Fig. 244-4). Because of the relatively large distance between the sinus node and left free wall APs, preexcitation may be minimal or absent on 12-lead ECG. Preexcitation due to an AP at the diaphragmatic surface of the heart, typically in the paraseptal region, produces delta waves that are negative in leads III and aVF, mimicking the q waves of inferior wall infarction (Fig. 244-4). Preexcitation can be intermittent and disappear during exercise as conduction over the AV node accelerates and may take over ventricular activation completely.

Wolff-Parkinson-White (WPW) syndrome is defined as a preexcited QRS during sinus rhythm and episodes of PSVT. There are a number of variations of APs, which may not cause preexcitation and/or arrhythmias. Concealed APs allow only retrograde conduction, from ventricle to atrium, so no preexcitation is present during sinus rhythm, but SVT can occur. Other unusual forms of APs occur. Fasciculoventricular connections between the His bundle and ventricular septum produce preexcitation but do not cause arrhythmia, probably because the circuit is too short to promote reentry. Atriofascicular pathways, also known as Mahaim fibers, probably represent a duplicate AV node and His-Purkinje system that connect the right atrium to fascicles of the right bundle branch and produce a wide complex tachycardia having a left bundle branch block configuration.

AV Reentry Tachycardia The most common tachycardia caused by an AP is the PSVT designated *orthodromic AV reentry*. The circulating reentry wavefront propagates from the atrium anterogradely over the AV node and His-Purkinje system to the ventricles and then reenters the atria via retrograde conduction over the AP (Fig. 244-3*B*). The QRS is narrow or may have typical right or left bundle branch block, but without preexcitation during tachycardia. Because excitation through the AV node and AP are necessary, AV or VA block results in tachycardia termination. During sinus rhythm, preexcitation is seen if the pathway also allows anterograde conduction (Fig. 244-3*A*). Most commonly, during tachycardia the R-P interval is shorter than the P-R interval and can resemble AVNRT (see Fig. 242-1). Unlike typical AVNRT, P waves always follow the QRS and are never simultaneous with a narrow QRS complex because the ventricles must be activated before the reentry wavefront reaches the AP and conducts back to the atrium. The morphology of the P wave is determined by the pathway location, but can be difficult to assess because it is usually inscribed during the ST segment. The P wave in posteroseptal APs is negative in leads II, III, and aVF, similar to that of AV nodal reentry, but P-wave morphology differs from AV nodal reentry for pathways in other locations (Fig. 244-4). Figure 241-3 is an example of a pathway that has clear negative P waves in leads I and aVL that was due to an AP inserting in the lateral left atrium.

Occasionally, an AP conducts extremely slowly in the retrograde direction, resulting in tachycardia with a long R-P interval, similar to most ATs. These pathways are usually located in the septal region and have negative P waves in leads II, III, and aVF. Slow AP conduction facilitates reentry, often leading to nearly incessant tachycardia, known



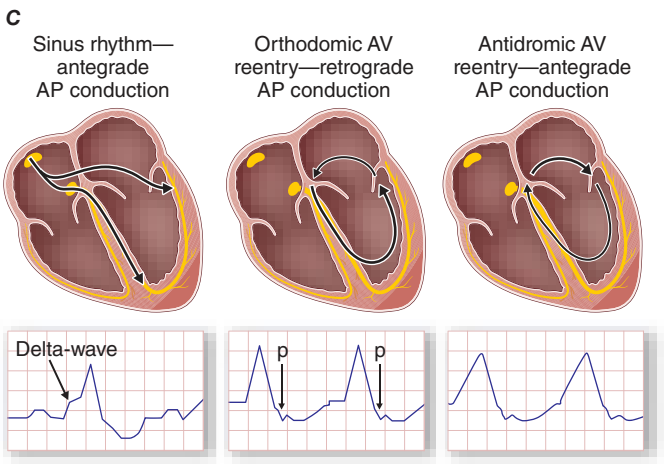


FIGURE 244-3 Wolff-Parkinson-White (WPW) syndrome. ***A.*** A 12-lead electrocardiogram in sinus rhythm (SR) of a patient with WPW demonstrating short P-R interval, delta waves, and widened QRS complex. This patient had an anteroseptal location of the AP. ***B.*** Orthodromic AV reentry in a patient with WPW syndrome using a posteroseptal AP. Note the P waves in the ST segment (*arrows*) seen in lead III and normal appearance of QRS complex. ***C.*** Three most common rhythms associated with WPW syndrome: sinus rhythm demonstrating antegrade conduction over the AP and AV node; orthodromic AVRT using retrograde conduction over the AP and antegrade conduction over the AV node; and antidromic AVRT using retrograde conduction over the AV node and antegrade conduction over the AP AP, accessory pathway; AV, atrioventricular; AVRT, atrioventricular reentry tachycardia; WPW, Wolff-Parkinson-White.

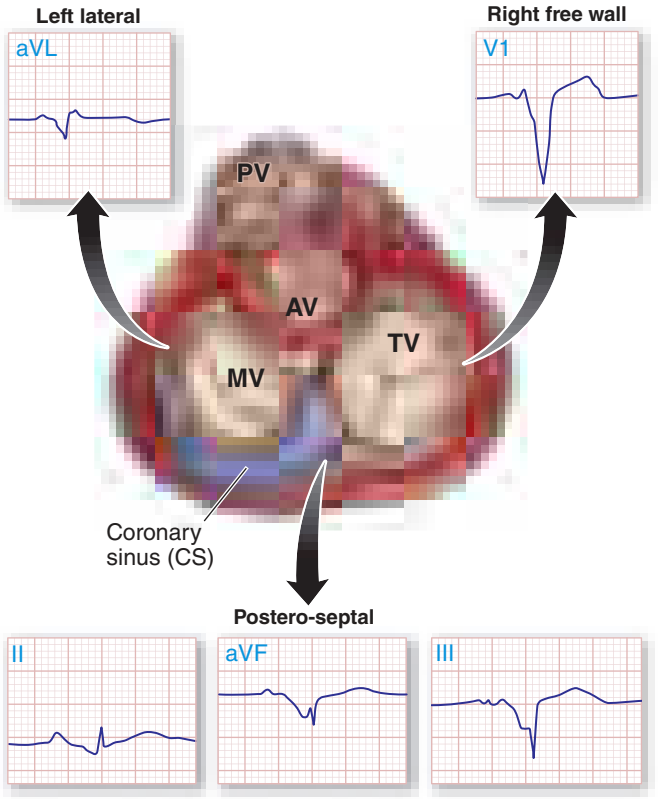


FIGURE 244-4 Potential locations for accessory pathways in patients with Wolff-Parkinson-White Syndrome and typical QRS appearance of delta waves that can mimic underlying structural heart disease such as myocardial infraction of bundle branch block. AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

as *permanent junctional reciprocating tachycardia* (PJRT). Tachycardia-induced cardiomyopathy can occur. Without an invasive electrophysiology study, it may be difficult to distinguish this form of orthodromic AV reentry from atypical AV nodal reentry or AT.

Preexcited Tachycardias Preexcited tachycardia occurs when the ventricles are activated by antegrade conduction over the AP (Fig. 244-3*C*). The most common mechanism is *antidromic AV reentry* in which activation propagates from atrium to ventricle via the AP and then conducts retrogradely to the atria via the His-Purkinje system and the AV node (or rarely a second AP). The wide QRS complex is produced entirely via ventricular excitation over the AP because there is no contribution of ventricular activation over more rapidly conducting specialized His-Purkinje fibers. This tachycardia is often indistinguishable from monomorphic ventricular tachycardia. The presence of preexcitation in sinus rhythm suggests the diagnosis.

Preexcited tachycardia also occurs if an AP allows antegrade conduction to the ventricles during AT, atrial flutter, atrial fibrillation (AF) (Fig. 244-5), or AV nodal reentry, otherwise known as bystander AP conduction. AF and atrial flutter are potentially life threatening if the AP allows very rapid repetitive conduction. Approximately 25% of APs causing preexcitation allow minimum R-to-R intervals of <250 ms during AF and are associated with a higher risk of inducing ventricular fibrillation and sudden death. Preexcited AF presents as a wide-complex, very irregular rhythm. During AF, the ventricular rate is determined by the conduction properties of the AP and AV node. The QRS complex can appear quite bizarre and change on a beat-to-beat basis due to the variability in the degree of fusion from activation over the AV node and AP, or all beats may be due to conduction over the AP (Fig. 244-5). Ventricular activation from the Purkinje system may depolarize the ventricular end of the AP and prevent atrial wavefront conduction over the AP. Slowing AV nodal conduction without slowing AP conduction can thereby facilitate AP conduction and dangerously accelerate the ventricular rate. Administration of AV nodal–blocking agents including oral or intravenous verapamil, diltiazem, beta blockers, intravenous adenosine, and intravenous amiodarone are contraindicated during preexcited AF. Rapid preexcited tachycardia should be treated with electrical cardioversion or intravenous procainamide or ibutilide, which may terminate the arrhythmia or slow the ventricular rate.

Management of Patients with APs Acute management of orthodromic AV reentry is discussed below for PSVT. Patients with WPW syndrome may have wide-complex tachycardia due to antidromic AV reentry, orthodromic AV with bundle branch block, or a

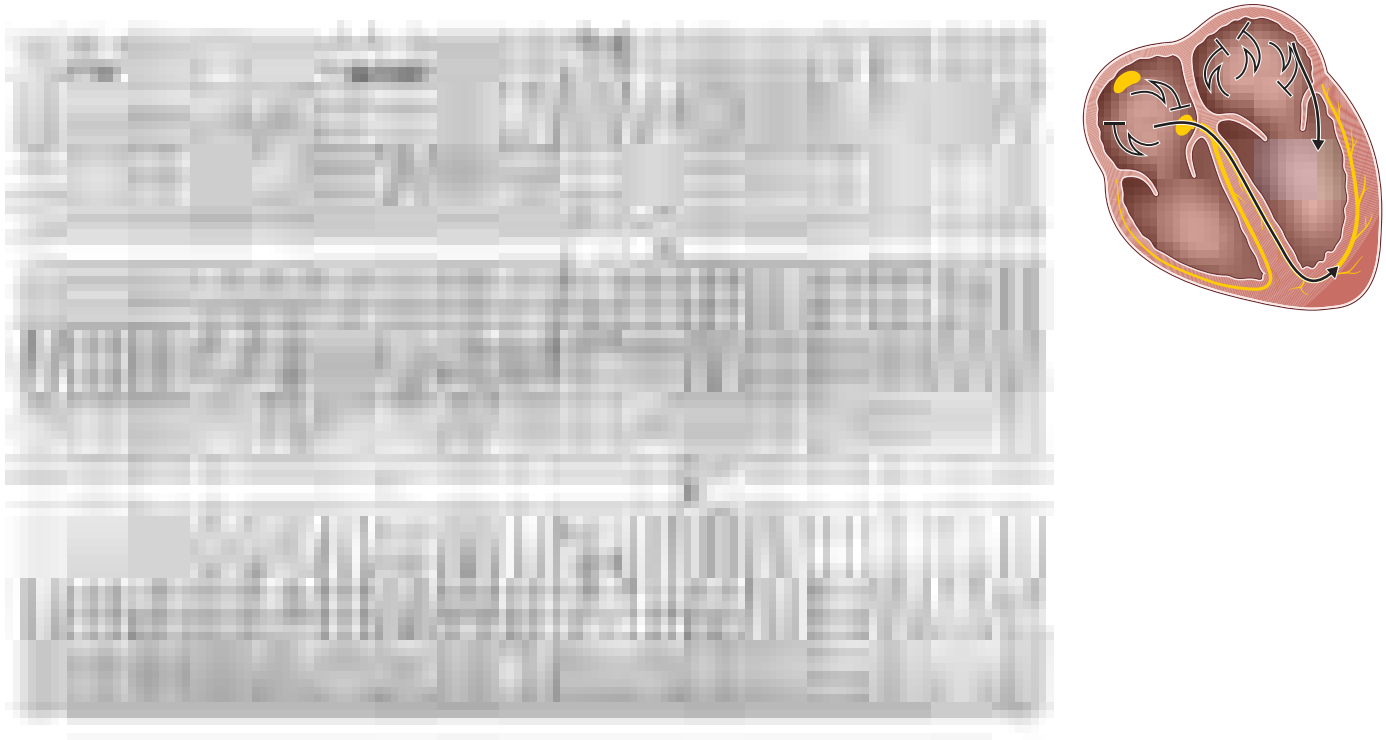


FIGURE 244-5 Preexcited atrial fibrillation (AF) due to conduction over a left free wall accessory pathway (AP). The electrocardiogram shows rapid irregular QRS complexes that represent fusion between conduction over the atrioventricular node and left free wall AP. Shortest R-R intervals between preexcited QRS complexes of <250 ms, as in this case, indicate a risk of sudden death with this arrhythmia.

preexcited tachycardia, and treatment depends on the underlying rhythm.

Initial patient evaluation should include assessment for aggravating factors, including intercurrent illness and factors that increase sympathetic tone. Examination should focus on excluding underlying heart disease. An echocardiogram is reasonable to exclude Ebstein's anomaly and forms of hypertrophic cardiomyopathy that can be associated with APs.

Patients with preexcitation who have symptoms of arrhythmia are at risk for developing AF and sudden death if they have an AP that allows rapid antegrade conduction. The risk of cardiac arrest is in the range of 2 per 1000 patients in adults but is likely greater in children. An invasive electrophysiology study is recommended to assess whether the pathway can support dangerously rapid heart rates if AF were to occur, and is usually combined with potentially curative catheter ablation. Catheter ablation is warranted for recurrent arrhythmias when drugs are ineffective, not tolerated, or not desired by the patient (Fig. 244-5). Efficacy is in the range of 95% depending on the location of the AP. Serious complications occur in fewer than 3% of patients, but can include AV block, cardiac tamponade, thromboemboli, coronary artery injury, and vascular access complications. Procedure mortality is <1 in 1000 patients. Alternatively attempts to gain reassurance that the AP is not high risk with ambulatory monitoring or exercise testing; abrupt loss of conduction (preexcitation) at physiologic heart rates is consistent with a low risk pathway, but is not completely reliable. Gradual loss of AP conduction with increased sympathetic tone does not reliably indicate low risk since this can occur as AV nodal conduction time shortens.

For patients with concealed APs or known low-risk APs causing orthodromic AV reentry, chronic therapy is guided by symptoms and frequency of events. Vagal maneuvers may terminate episodes, as may a dose of beta blocker, verapamil, or diltiazem taken at the onset of an episode. Chronic therapy with these agents or flecainide can reduce the frequency of episodes in some patients.

Adults who have preexcitation but no arrhythmia symptoms have a risk of sudden death estimated to be 1 per 1000 patient-years. Electrophysiology study is usually advised for people in occupations for which an arrhythmia occurrence would place them or others at risk, such as police, military, and pilots, or for individuals who desire evaluation for risk. Routine follow-up without therapy is reasonable in others. Children are at greater risk of sudden death, ~2 per 1000 patient-years.

TREATMENT

Paroxysmal Supraventricular Tachycardia

Acute management of narrow QRS PSVT is guided by the clinical presentation. Continuous ECG monitoring should be implemented and a 12-lead ECG should always be obtained when possible, since this may be useful in determining the mechanism. In the presence of hypotension with unconsciousness or respiratory distress, QRS-synchronous direct current cardioversion is warranted, but this is rarely needed, because intravenous adenosine works promptly in most situations (see below). For stable individuals, initial therapy takes advantage of the fact that most PSVTs are dependent on AV nodal conduction (AV nodal reentry or orthodromic AV reentry) and therefore likely to respond to sympatholytic and vagotonic maneuvers and drugs **(Fig. 244-6)**. As these are administered, the ECG should be continuously recorded, because the response can establish the diagnosis. AV block with only transient slowing of tachycardia may expose ongoing P waves, indicating AT or atrial flutter as the mechanism.

Carotid sinus massage is reasonable provided the risk of carotid vascular disease is low, as indicated by absence of carotid bruits and no prior history of stroke. A Valsalva maneuver should be attempted in cooperative individuals, and if effective, the patient can be taught to perform this maneuver as needed. If vagal maneuvers fail or cannot be performed, intravenous adenosine will terminate the vast majority of PSVT episodes by transiently blocking conduction in the AV node. Adenosine may produce transient chest pain, dyspnea, and anxiety. It is contraindicated in patients with prior cardiac transplantation due to potential hypersensitivity. It can theoretically

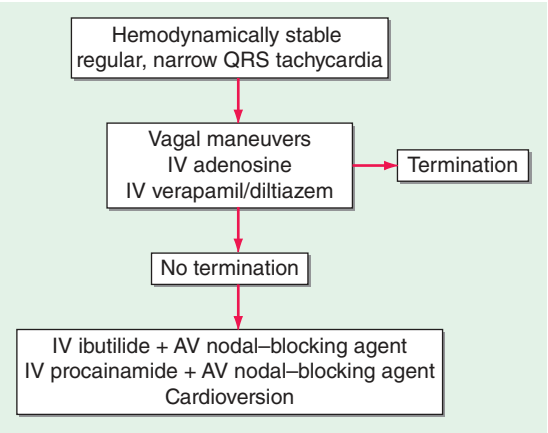


FIGURE 244-6 Treatment algorithm for patients presenting with hemodynamically stable paroxysmal supraventricular tachycardia. AV, atrioventricular.

aggravate bronchospasm. Adenosine precipitates AF, which is usually brief, in up to 15% of patients, so it should be used cautiously in patients with WPW syndrome in whom AF may produce hemodynamic instability. Intravenous beta blockers and calcium channel blockers (verapamil or diltiazem) are also effective but may cause hypotension before and after arrhythmia termination and have a longer duration of action. These agents can also be given orally and can be taken by the patient on an as-needed basis to slow ventricular rate and facilitate termination by Valsalva maneuver.

The differential diagnosis of wide-complex tachycardia includes ventricular tachycardia **(Chap. 247)**, PSVT with bundle branch block aberrancy, and preexcited tachycardia (see above). In general, these should be managed as ventricular tachycardia until proven otherwise. If the tachycardia is regular and the patient is stable, a trial of intravenous adenosine is reasonable. Very irregular wide-complex tachycardia is most likely preexcited AF or flutter (see above) and should be managed with cardioversion, intravenous procainamide, or ibutilide. If the diagnosis of PSVT with aberrancy is unequivocal, as may be the case in patients with prior episodes, treatment for PSVT with vagal maneuvers and adenosine is reasonable. In all cases, continuous ECG monitoring should be implemented, and emergency cardioversion and defibrillation should be available.

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245 Common Atrial Flutter, Macroreentrant, and Multifocal Atrial Tachycardias

Gregory F. Michaud, William G. Stevenson

Macroreentrant atrial tachycardia is due to a large reentry circuit, often associated with areas of scar in the atria. *Common or typical right atrial flutter* is due to a circuit that revolves around the tricuspid valve annulus, bounded anteriorly by the annulus and posteriorly by functional conduction block in the crista terminalis. The wavefront passes between the inferior vena cava and the tricuspid valve annulus, known as the sub-Eustachian or cavotricuspid isthmus, where it is susceptible to interruption by catheter ablation. Thus, common atrial flutter is also known as *cavotricuspid isthmus-dependent atrial flutter*. This circuit most commonly revolves in a counterclockwise direction (as viewed looking toward the tricuspid annulus from the ventricular apex), which produces the characteristic negative sawtooth flutter waves in leads II, III, and aVF and positive P waves in lead V_1 **(Fig. 245-1)**. When the direction is reversed, clockwise rotation produces the opposite P-wave vector in those leads. The atrial rate is typically 240–300 beats/min but may be slower in the presence of atrial disease or antiarrhythmic drugs. It often conducts to the ventricles with 2:1 AV block, creating a regular tachycardia at 150 beats/min, with P waves that may be difficult to discern. Maneuvers that increase AV nodal block will typically expose flutter waves, allowing diagnosis.

Common right atrial flutter usually occurs in association with atrial fibrillation and often with atrial scar from senescence or prior cardiac surgery. Some patients with atrial fibrillation treated with an antiarrhythmic drug, particularly flecainide, propafenone, or amiodarone, will present with atrial flutter rather than fibrillation, since these agents slow atrial conduction velocity and can promote reentry.

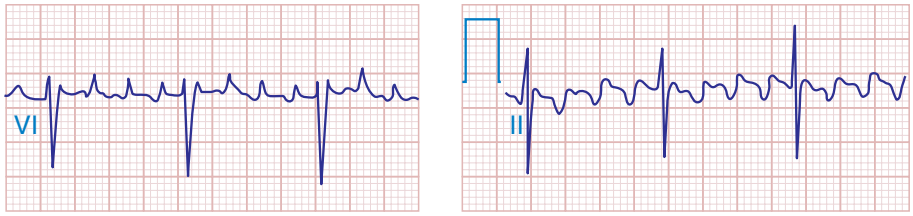
Macroreentrant ATs that are not dependent on conduction through the cavotricuspid isthmus are referred to as *atypical atrial flutters*. They can occur in either atrium and are almost universally associated with areas of atrial scar. Left atrial flutter and perimitral left atrial flutter are commonly seen after extensive left atrial ablation for atrial fibrillation or atrial surgery. The clinical presentation is similar to common atrial flutter, but with different P-wave morphologies **(Fig 245-2)**. They can be difficult to distinguish from focal AT, and in most cases, the mechanism can only be confirmed by an electrophysiology study.

TREATMENT

Atrial Flutter

Initial management of atrial flutter is similar to that for atrial fibrillation, discussed in more detail below. Electrical cardioversion is warranted for hemodynamic instability or severe symptoms. Otherwise, rate control can be achieved with administration of AV nodal–blocking agents, but this is often more difficult than for atrial fibrillation. The risk of thromboembolic events is felt to be similar to that associated with atrial fibrillation. Anticoagulation is warranted prior to conversion for episodes more than 48 h in duration and chronically for patients at increased risk of thromboembolic stroke based on the CHA_2DS_2-VASc scoring system **(Table 245-1)**.

For a first episode of atrial flutter, conversion to sinus rhythm with no antiarrhythmic drug therapy is reasonable. For recurrent episodes, antiarrhythmic drug therapy with sotalol, dofetilide, disopyramide, and amiodarone may be considered, but >70% of patients experience recurrences. For recurrent episodes of common atrial flutter, catheter ablation of the cavotricuspid isthmus abolishes the arrhythmia in >90% of patients with a low risk of complications that are largely related to vascular access, and rarely heart



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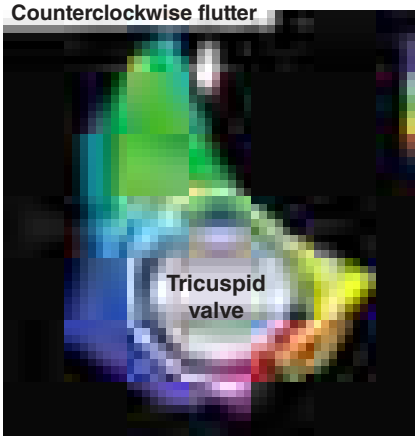

B

FIGURE 245-1 ***A.*** Common right atrial flutter, also known as cavotricuspid isthmus flutter, showing positive P waves in lead V_1 and negative "sawtooth" pattern in lead II typical of counterclockwise rotation relative to the tricuspid valve annulus. *(Adapted from F Marchlinski: The tachyarrhythmias in DL Longo et al [eds]: Harrison's Principles of Internal Medicine, 18th ed. New York, McGraw-Hill, 2012, pp 1878–1900.)* ***B.*** A right atrial map of common counterclockwise flutter is shown. Colors indicate activation time, progressing from red to yellow to green, blue, and purple. The reentry path parallels the tricuspid annulus.

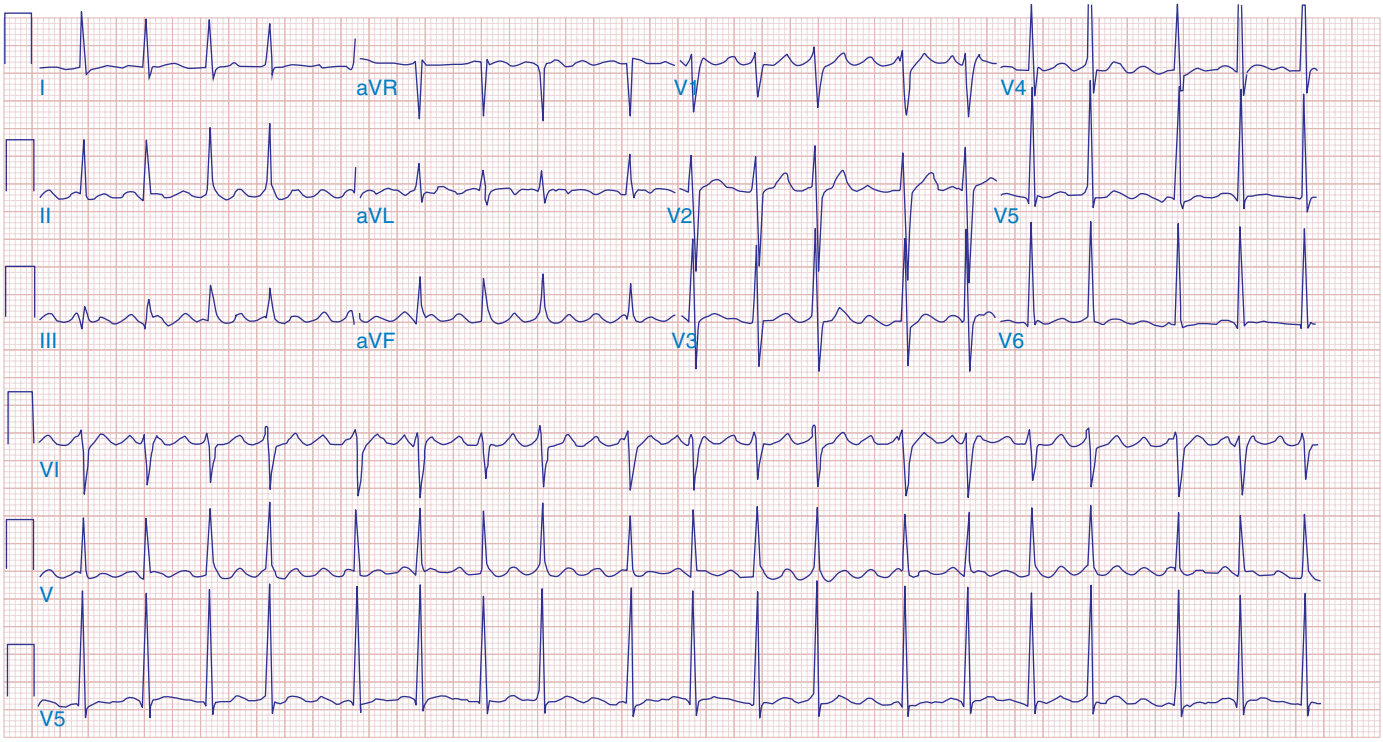

FIGURE 245-2 **Atrial flutter in a 52-year-old man that occurred one year after extensive left atrial ablation for persistent atrial fibrillation.** In contrast to common flutter the P waves in V1 and inferior limb leads (II, III, and aVF) have the same polarity (positive in this case). Also, lead aVL shows a predominant negative P wave consistent with a left atrial focus, however P-wave morphology used to diagnose arrhythmia mechanism and location is unreliable in the setting of advanced atrial fibrosis, such as after extensive catheter ablation.

TABLE 245-1 CHA_2DS_2-VASc Risk Assessment and Oral Anticoagulants

RISK FACTORS	POINTS		CHA_2DS_2-VASc SCORE	ESTIMATED ANNUAL STROKE RATE[a]
C—congestive heart failure	1		0	0
H—hypertension	1		1	1.3%
A—age ≥75 y	2		2	2.2%
D—diabetes mellitus	1		3	3.2%
S—stroke or TIA, embolus	2		4	4.0%
V—vascular disease	1		5	6.7%
A—age 65–75 y	1		6–9	>9%
Sex—female	1			
ANTICOAGULANTS	**MECHANISM**	**EXCRETION**	**DOSING CONSIDERATIONS**	**RISK/BENEFIT**
Warfarin	Vitamin K antagonist	Liver	Adjusted to INR 2–3 Days to therapeutic effect Multiple drug/food interactions (e.g., amiodarone)	Major hemorrhage: 1% per year Intracranial hemorrhage: 0.1–0.6% per year Risk of bleeding increases with INR >3.5 Inexpensive
Dabigatran[b]	Thrombin inhibitor	Kidney CCr >30 mL/min CCr 15–30 mL/min	 150 mg bid 75 mg bid P-glycoprotein substrate (inducers—rifampin, reduce concentration) (inhibitors—amiodarone, verapamil, dronedarone, quinidine) Proton pump inhibitors may reduce absorption	 Onset of action within hours No reversal agent for bleeding
Rivaroxaban	Xa inhibitor	Kidney CCr ≥50 mL/min CCr 15–50 mL/min	P-glycoprotein substrate 20 mg daily 15 mg daily	No reversal agent for bleeding
Apixaban	Xa inhibitor	Kidney and liver Any 2 of: Cr >1.5 mg/dL, age >80 yrs, or wt <60 kg	P-glycoprotein substrate 5 mg bid 2.5 mg bid	No reversal agent for bleeding

[a]Modified from GY Lip et al: Lancet 379:648, 2012. [b]U.S. Food and Drug Administration recommended dosing; other regimens are available outside the United States.

Abbreviations: CCr, creatinine clearance; Cr, creatinine; INR, international normalized ratio; TIA, transient ischemic attack; wt, weight.

block. Approximately 50% of patients presenting with atrial flutter develop atrial fibrillation within 5 years after diagnosis, which is an important consideration in patients with a high risk profile for thromboembolism.

MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal AT (MAT) is characterized by a rhythm with at least three distinct P-wave morphologies with rates typically between 100 and 150 beats/min. Unlike atrial fibrillation, there are clear isoelectric intervals between P waves **(Fig. 245-3)** and the atrial rate is slower. The mechanism is likely triggered automaticity from multiple atrial foci. It is usually encountered in patients with chronic pulmonary disease and acute illness.

Therapy for MAT is directed at treating the underlying disease and correcting any metabolic abnormalities. Electrical cardioversion is ineffective. The calcium channel blockers verapamil or diltiazem may slow the atrial and ventricular rate. Patients with severe pulmonary disease often do not tolerate beta blocker therapy. MAT may respond to amiodarone, but long-term therapy with this agent is usually avoided due to its toxicities, particularly pulmonary fibrosis.

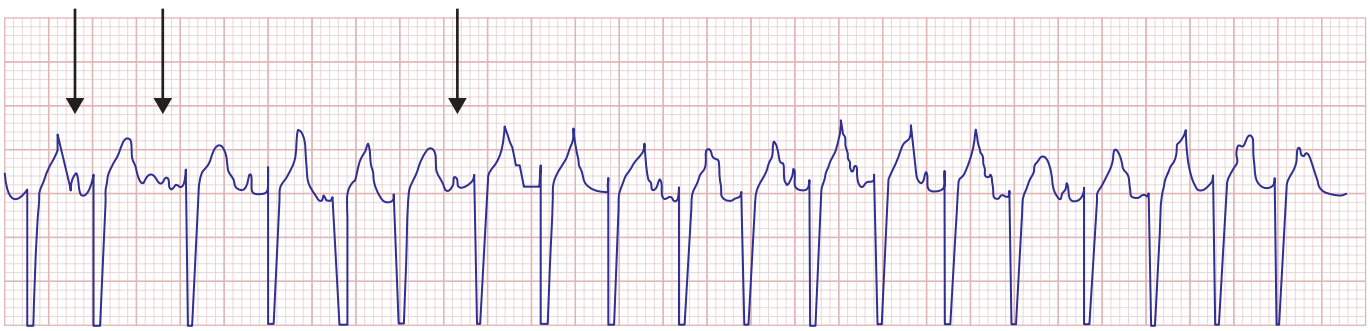

FIGURE 245-3 Multifocal atrial tachycardia. Rhythm strip obtained from a patient with severe pulmonary disease during an acute illness. *Arrows* note three distinct P-wave morphologies.

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246 Atrial Fibrillation

Gregory F. Michaud, William G. Stevenson

Atrial fibrillation (AF) is characterized by disorganized, rapid, and irregular atrial activation with loss of atrial contraction and with an irregular ventricular rate that is determined by AV nodal conduction (Fig. 246-1). In an untreated patient, the ventricular rate also tends to be rapid and variable, between 120 and 160 beats/min, but in some patients, it may exceed 200 beats/min. Patients with high vagal tone or AV nodal conduction disease may have slow ventricular rates.

AF is the most common sustained arrhythmia and is a major public health problem. Prevalence increases with age, and >95% of AF patients are >60 years of age. The prevalence by age 80 is ~10%. The lifetime risk of developing AF for men 40 years old is ~25%. AF is slightly more common in men than women and more common in whites than blacks. Risk factors for developing AF in addition to age and underlying cardiac disease include hypertension, diabetes mellitus, cardiac disease, obesity, and sleep apnea. AF is associated with a 1.5- to 1.9-fold increased risk of mortality after controlling for underlying heart disease. AF is also associated with a risk of developing heart failure and vice-versa—patients with heart failure have an increased risk of developing AF. AF increases the risk of stroke by fivefold and is estimated to be the cause of 25% of strokes. It also increases the risk of dementia and silent strokes detected by MRI. Since AF is a marker for other predictors of mortality and morbidity, such as the severity of heart disease, it is difficult to determine the extent to which AF itself contributes to associated increased mortality and morbidity.

AF is occasionally associated with an acute precipitating factor such as hyperthyroidism, acute alcohol intoxication, or an acute illness such as myocardial infarction or pulmonary embolism. AF occurs in up to 30% of patients recovering from cardiac surgery, associated with inflammatory pericarditis.

The clinical pattern of AF suggests the underlying pathophysiology (Fig. 246-1). Paroxysmal AF is defined by episodes that start spontaneously and stop within 7 days of onset. Paroxysmal AF is often initiated by small reentrant or rapidly firing foci in sleeves of atrial muscle that extend into the pulmonary veins (PV). Catheter ablation that isolates these foci usually abolishes paroxysmal AF, although some patients also have initiating foci in other locations. These non-PV triggers tend to occur in older patients and those with more severe underlying cardiac disease. Persistent AF has a longer duration, exceeding 7 days, and, in many cases, will continue indefinitely unless cardioversion is performed. Cardioversion can be followed by prolonged periods of sinus rhythm. As for paroxysmal AF, episodes are often initiated by rapidly firing foci within PVs, but non-PV sites, including myocardial sleeves around the superior vena cava (SVC) or coronary sinus are encountered more often than when AF is paroxysmal. In addition, persistence of the AF is likely facilitated by structural and electrophysiologic atrial abnormalities, particularly fibrosis that uncouples atrial fibers, promoting reentry and focal automaticity. In patients with long-standing persistent AF (>1 year), significant fibrosis is usually present and it is difficult to restore and maintain sinus rhythm. Some patients progress over years from paroxysmal to persistent AF. Although fibrosis that develops with aging and atrial hypertrophy in response to hypertension and other cardiac disease appears to be an important promoting factor, electrophysiologic remodeling that affects conduction and refractoriness occur as well in response to chronic tachycardia. Thus, AF tends to promote AF.

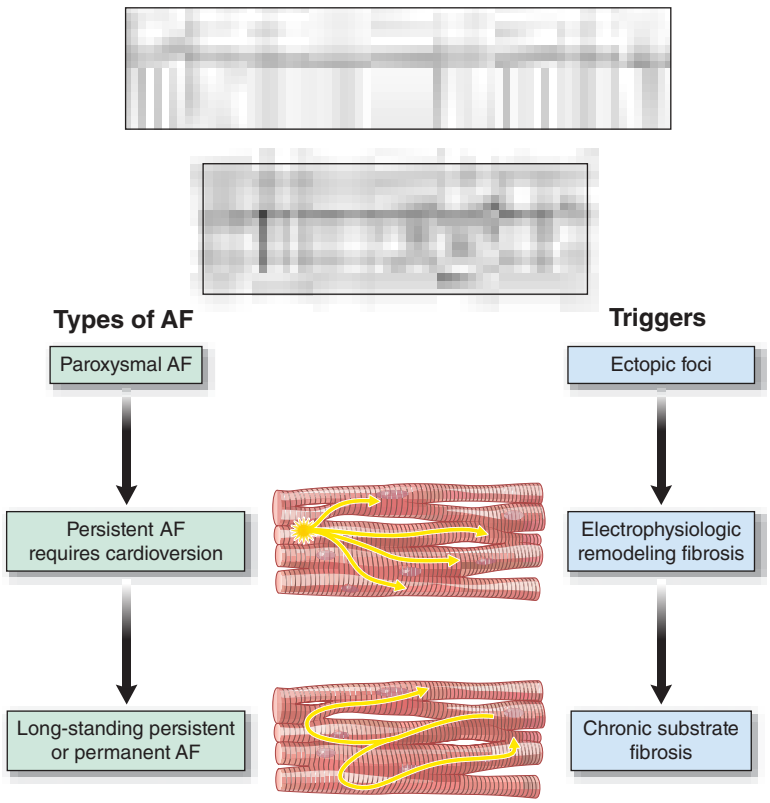

FIGURE 246-1 A rhythm strip of atrial fibrillation (AF) showing absence of distinct P-waves and an irregularly irregular ventricular response. Diagram depicts atrial fibrillation types. Paroxysmal AF is initiated by premature beats, as shown in the rhythm strip (*arrow*) after two sinus beats. Triggering foci are often an important cause of this arrhythmia. Persistent AF is associated with atrial structural and electrophysiologic remodeling, as well as with triggering foci in many patients. Long-standing persistent AF is associated with greater structural remodeling with atrial fibrosis and electrophysiologic remodeling.

Clinical consequences of AF are related to rapid ventricular rates, loss of atrial contribution to ventricular filling, and predisposition to thrombus formation in the left atrial appendage with potential embolization. Presentations vary with the ventricular rate and underlying heart disease and comorbidities. Rapid rates may cause hemodynamic collapse or heart failure exacerbation particularly in patients with impaired cardiac function, hypertrophic cardiomyopathy, and heart failure with preserved systolic function. Exercise intolerance and easy fatigability are common despite the absence of palpitations in many patients. Occasionally, dizziness or syncope occurs due to pauses when AF terminates to sinus rhythm (Fig. 246-2). Depressed ventricular function with cardiomyopathy may develop in response to chronic tachycardia (rates persistently faster than 100–110 bpm) and is probably more common in patients who do not sense palpitations, since they may not seek medical care until heart failure symptoms develop. Tachycardia-related cardiomyopathy is usually reversible with control of ventricular rate.

Treatment for AF is primarily guided by patients' symptoms, the hemodynamic effect of AF, the duration of AF, the risk of stroke and the underlying heart disease. *New-onset AF* that produces severe hypotension, pulmonary edema, or angina should be electrically cardioverted starting with a QRS synchronous shock of 200 J, ideally after sedation or anesthesia is achieved. Greater shock energy and different electrode placements may be tried if the shock fails to terminate AF. Administration of intravenous ibutilide lowers the energy requirement for atrial defibrillation and may be useful if AF terminates and reinitiates, but should not be used in patients

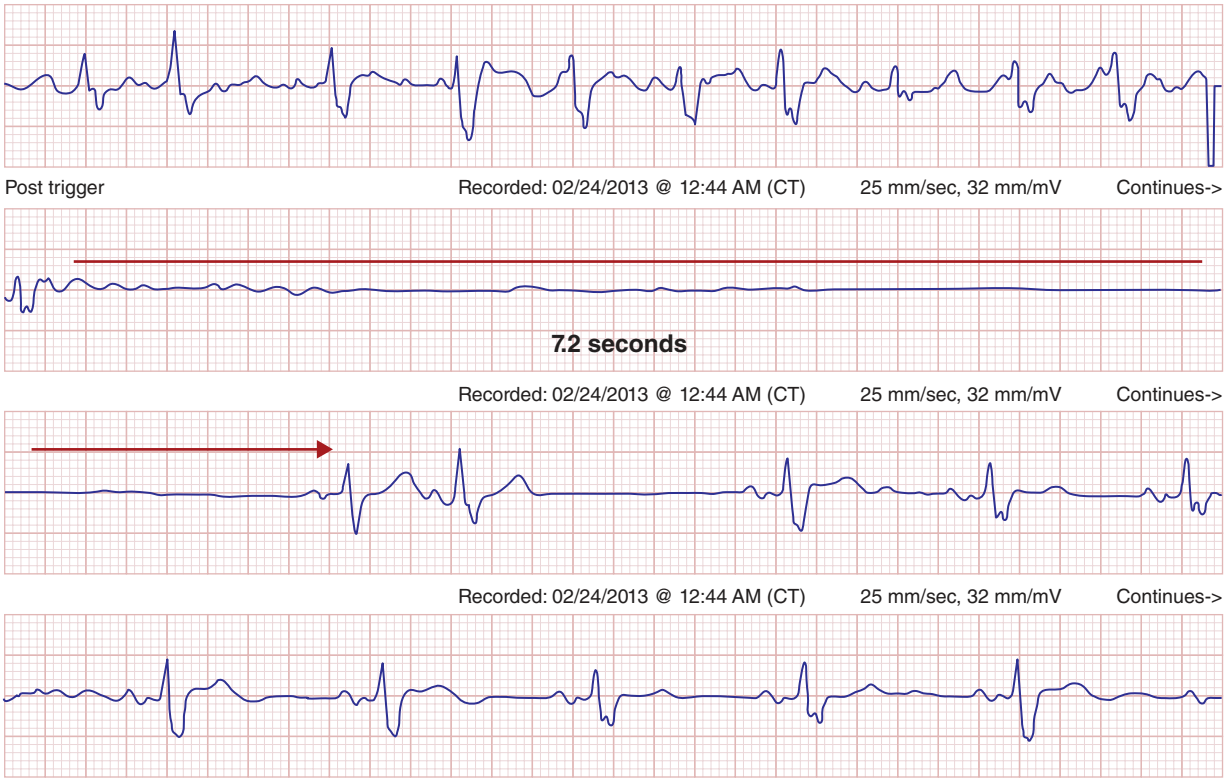

FIGURE 246-2 A continuous rhythm strip is shown from a patient with tachy-brady syndrome. Atrial fibrillation is present at the top and abruptly terminates in the second tracing, with atrial and ventricular standstill for 7.2 s until resumption of sinus rhythm. The patient experienced syncope.

with a prolonged QT interval or severe LV dysfunction because of a significant risk of torsades de Pointes. If the patient is stable, immediate management involves rate control to alleviate or prevent symptoms, and consideration of whether anticoagulation is warranted to reduce stroke risk. Consideration is then given to whether therapy is warranted to restore and maintain sinus rhythm, or whether the patient will be allowed to continue in AF, and managed with rate control and measures for stroke prevention. It is critical to consider the risk of stroke when attempting to restore sinus rhythm. If the duration of AF is unclear or is known to be >48 h, anticoagulation must be commenced before cardioversion. Anticoagulation strategies for new-onset AF are debated. In the absence of contraindications, it is usually appropriate to initiate systemic anticoagulation with heparin immediately or with an oral anticoagulant that has rapid onset of action, while evaluation and other therapies are implemented.

CARDIOVERSION AND ANTICOAGULATION

The major source of thromboembolism and stroke in AF is formation of thrombus in the left atrial appendage where flow is relatively stagnant, although thrombus occasionally forms in other locations as well. Following conversion from prolonged AF to sinus rhythm, atrial mechanical function can be delayed for weeks, such that thrombi can form even during sinus rhythm. When AF has been present for >48 h and in patients at high risk for thromboembolism, such as those with mitral stenosis or hypertrophic cardiomyopathy, conversion to sinus rhythm is associated with an increased risk of thromboembolism. Thromboembolism can occur soon, or several days after restoration of sinus rhythm if appropriate anticoagulation measures are not taken.

Cardioversion *within 48 h of the onset of AF* is common practice in patients who have not been anticoagulated, provided that they are not at high risk for stroke due to a prior history of embolic events, rheumatic mitral stenosis, or hypertrophic cardiomyopathy with marked left atrial enlargement. These low-risk patients with occasional episodes of AF can be instructed to notify their physician when AF occurs to arrange for cardioversion to be done within 48 h.

If the duration of AF exceeds 48 h or is unknown, there is greater concern for thromboembolism after cardioversion, even in patients considered low risk (CHA_2DS_2-VASc of 0 or 1 [see below]) for stroke. There are two approaches to mitigate the risk related to cardioversion. One option is to anticoagulate continuously for 3 weeks before and a minimum of 4 weeks after cardioversion. A second approach is to start anticoagulation and perform a transesophageal echocardiogram to determine if thrombus is present in the left atrial appendage. If thrombus is absent, cardioversion can be performed and anticoagulation continued for a minimum of 4 weeks to allow time for recovery of atrial mechanical function. In either case, cardioversion of AF is associated with a substantial risk of recurrence, which may not be symptomatic. Longer-term maintenance of anticoagulation is considered based on the patient's individual risk for stroke, commonly assessed from the CHA_2DS_2-VASc score.

RATE CONTROL

Acute rate control can be achieved with beta blockers and/or the calcium channel blockers verapamil and diltiazem administered either intravenously or orally, as warranted by the urgency of the clinical situation. Digoxin may be added, particularly in heart failure patients, if negative inotropic and other adverse effects of beta blockers and calcium channel blockers limit their use. Digoxin lacks negative inotropic effects, but is less effective in slowing the ventricular rate in AF, particularly when sympathetic tone is high. It is synergistic with the other AV nodal–blocking agents. Its use has been associated with increased mortality in some studies. Typically, the goal of acute rate control is to reduce the ventricular rate to less than 100/min, but the goal must be guided by the clinical situation and the adverse effects of rate control medications.

CHRONIC RATE CONTROL

For patients who remain in AF chronically, the goal of rate control is to alleviate and prevent deterioration of ventricular function from excessive rates. β-Adrenergic blockers and calcium channel blockers are often used in combination. Digoxin is added selectively when these are not sufficient. Exertion-related symptoms are often an indication of inadequate rate control. Rate should be assessed with exertion and medications adjusted accordingly. The initial goal is a resting heart rate of <80 beats/min that increases to <100 beats/min with light exertion, such as walking. If it is difficult to slow the ventricular rate to that degree, allowing a resting rate of up to 110 beats/min is acceptable

provided it does not cause symptoms and ventricular functioniss normal, but periodic assessment of ventricular function is warranted because some patients develop tachycardia-induced cardiomyopathy.

If adequate rate control in AF is difficult to achieve, further consideration should be given to restoring sinus rhythm (see below). Catheter ablation of the AV junction to create heart block and implantation of a permanent pacemaker reliably achieves rate control without the need for AV nodal blocking agents, but mandates lifelong permanent pacing. Right ventricular apical pacing induces dyssynchronous ventricular activation that can depress ventricular function in some patients. Biventricular pacing or direct pacing of the His bundle may be used to minimize the degree of ventricular dyssynchrony.

STROKE PREVENTION IN ATRIAL FIBRILLATION

The majority of patients warrant chronic anticoagulation, but selection of therapy should be individualized based on patient profile and risks and benefits of individual agents. Anticoagulation is warranted for patients with mitral stenosis, hypertrophic cardiomyopathy, and those with a prior history of stroke. Patients without mitral stenosis are often referred to as having nonvalvular AF. The CHA_2DS_2-VASc score **(Table 246-1)** can be used to estimate stroke risk in these patients. Anticoagulation is recommended for a score of ≥2 and may be considered for a score of 1. The approach to patients with paroxysmal AF is the same as for persistent AF. It is recognized that many patients who appear to have infrequent AF episodes based on office visits often have asymptomatic episodes that put them at risk. Absence of AF during periodic monitoring is not sufficient to indicate low risk. The role of continuous monitoring with implanted recorders or pacemakers is not yet clear as a guide for anticoagulation in patients with a borderline risk profile.

The major options for anticoagulation are the antithrombin inhibitor dabigitran, factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, the vitamin K antagonist warfarin. Antiplatelet agents alone are generally not sufficient. In non-valvular AF, warfarin reduces the annual risk of stroke by 64% compared to placebo and by 37% compared to antiplatelet therapy. Patients with AF with an increased risk of stroke also have an increased risk of venous thromboembolism, which appears to be lower with oral anticoagulation. The direct acting anticoagulants, dabigatran, rivaroxaban, apixaban, and edoxaban were noninferior to warfarin in individual trials, and analysis of pooled data suggests superiority to warfarin by small absolute margins of 0.4–0.7% in reduction of mortality, stroke, major bleeding, and intracranial hemorrhage. Warfarin is the agent required for patients with rheumatic mitral stenosis or mechanical heart valves. The newer, direct acting anticoagulants have not been tested in rheumatic heart disease and a direct thrombin inhibitor did not prevent thromboemboli in patients with mechanical heart valves. Warfarin is an inconvenient agent that requires several days to achieve a therapeutic effect (prothrombin time [PT]/international normalized ratio [INR] >2), requires monitoring of PT/INR to adjust dose, and has many drug and food interactions, that can hinder patient compliance. The direct acting agents are easier to use and achieve reliable anticoagulation promptly without requiring dosage adjustment based on blood tests. Dabigatran, rivaroxaban, and apixaban have renal excretion, cannot be used with severe renal insufficiency (CrCl <15 mL/min), and require dose adjustment for

TABLE 246-1 CHA_2DS_2-VASc Risk Assessment and Oral Anticoagulants

RISK FACTORS	POINTS		CHA_2DS_2-VASc SCORE	ESTIMATED ANNUAL STROKE RATE[a]
C—congestive heart failure	1		0	0
H—hypertension	1		1	1.3%
A—age ≥75 y	2		2	2.2%
D—diabetes mellitus	1		3	3.2%
S—stroke or TIA, embolus	2		4	4.0%
V—vascular disease	1		5	6.7%
A—age 65–75 y	1		6–9	>9%
Sex—female	1			
ANTICOAGULANTS	**MECHANISM**	**EXCRETION**	**DOSING CONSIDERATIONS**	**RISK/BENEFIT**
Warfarin	Vitamin K antagonist	Liver	Adjusted to INR 2–3 Days to therapeutic effect Multiple drug/food interactions (e.g., amiodarone)	Major hemorrhage: 1% per year Intracranial hemorrhage: 0.1–0.6% per year Risk of bleeding increases with INR >3.5 Inexpensive
Dabigatran[b]	Thrombin inhibitor	Kidney CCr >30 mL/min CCr 15–30 mL/min	 150 mg bid 75 mg bid P-glycoprotein substrate (inducers—rifampin, reduce concentration) (inhibitors—amiodarone, verapamil, dronedarone, quinidine), Proton pump inhibitors may reduce absorption	 Onset of action within hours Reversal agent available
Rivaroxaban	Xa inhibitor	Kidney CCr ≥50 mL/min CCr 15–50 mL/min	P-glycoprotein substrate 20 mg daily 15 mg daily	Reversal agent for bleeding in development
Apixaban	Xa inhibitor	Kidney and liver Any 2 of Cr>1.5 mg/dl, age > 80 yrs or wt < 60 kg.	P-glycoprotein substrate 5 mg bid 2.5 mg bid	Reversal agent for bleeding in development
Edoxaban	Xa inhibitor	Kidney and Liver CCr> 60 <95 mL/min CCr 15–60 mL/min	P-glycoprotein substrate 60 mg 30 mg	

[a]Modified from GY Lip et al: Lancet 379:648, 2012. [b]U.S. Food and Drug Administration recommended dosing; other regimens are available outside the United States.

Abbreviations: CCr, creatinine clearance; Cr, creatinine; INR, international normalized ratio; TIA, transient ischemic attack.

modest renal impairment, which is of particular concern in the elderly, who are at increased bleeding risk. Excretion can also be influenced by P-glycoprotein inducers and inhibitors. Warfarin anticoagulation can be reversed by administration of fresh frozen plasma and vitamin K. A reversal agent (idarucizumab) is available for dabigatran and reversal agents for the Xa inhibitors are being evaluated (andexanet alfa and ciraparantag). For now, bleeding that occurs during Xa inhibitor use must be managed with supportive care, with the expectation that clotting will improve over 12 h as the anticoagulant is excreted, although reversal agents are anticipated.

The antiplatelet agents aspirin and clopidogrel are inferior to warfarin for stroke prevention in AF and do not have less risk of bleeding. Clopidogrel combined with aspirin is better than aspirin alone for stroke prevention, but is inferior to warfarin and has a greater bleeding risk than aspirin alone.

Bleeding is the major risk of anticoagulation. Major bleeding requiring transfusion or intracranial bleeding occurs in ~1% of patients per year with warfarin. Direct acting anticoagulants appear to have a lower risk of intracranial bleeding relative to warfarin without sacrificing protective effects against thromboembolism. Risk factors for bleeding include age >65–75 years, heart failure, renal insufficiency, prior bleeding, and excessive alcohol or nonsteroidal anti-inflammatory drug use. In patients who require dual antiplatelet therapy (e.g., aspirin and clopidogril) after coronary or peripheral arterial stenting, there is a substantially increased bleeding risk when standard oral anticoagulation with warfarin or a direct acting anticoagulant is added. The optimal combination of agents for patients with AF who also require antiplatelet therapy is unclear.

Chronic anticoagulation is contraindicated in some patients due to bleeding risks. Because most atrial thrombi likely originate in the left atrial appendage, surgical removal of the appendage, combined with atrial maze surgery, may be considered for patients undergoing surgery, although removal of the appendage has not been unequivocally shown to reduce the risk of thromboembolism. Percutaneously deployed devices that occlude or ligate the left atrial appendage are also available, appear to be non-inferior to warfarin in reducing stroke risk and are considered in patients who have a high risk of thromboembolism, but serious bleeding risk from chronic oral anticoagulation.

RHYTHM CONTROL

AF is associated with obesity, hypertension, excessive alcohol use and sleep apnea. Aggressive treatment of these risk factors can substantially reduce AF episodes in some patients and is warranted in all patients.

The decision to administer antiarrhythmic drugs or perform catheter ablation to attempt maintenance of sinus rhythm (commonly referred to as the "rhythm control strategy") is mainly guided by patient symptoms and preferences regarding the benefits and risks of therapies. In general, patients who maintain sinus rhythm have better survival than those who continue to have AF. This may be because continued AF is a marker of disease severity. In randomized trials, administration of antiarrhythmic medications to maintain sinus rhythm did not improve survival or symptoms compared to a rate control strategy, and the drug therapy group had more hospitalizations. Disappointing efficacy and toxicities of available antiarrhythmic drugs and patient selection bias may be factors that influenced the results of these trials. The impact of catheter ablation on mortality is not known but the subject of ongoing randomized, controlled trials. A rhythm control strategy is usually selected for patients with symptomatic paroxysmal AF, recurrent episodes of symptomatic persistent AF, AF with difficult rate control, and AF that has resulted in depressed ventricular function or that aggravates heart failure. A rhythm control strategy is more likely to be favored in younger patients than in sedentary or elderly patients in whom rate control is more easily achieved. Even if sinus rhythm is apparently maintained, anticoagulation is recommended according to the CHA_2DS_2-VASc stroke risk profile because asymptomatic episodes of AF are common. Following a first episode of persistent AF, a strategy using AV nodal–blocking agents, cardioversion, and anticoagulation is reasonable, in addition to addressing possible aggravating factors. If recurrences are infrequent, periodic cardioversion is reasonable.

Pharmacologic Therapy for Maintaining Sinus Rhythm

The goal of pharmacologic therapy is to maintain sinus rhythm or reduce episodes of AF. Risks and side effects of antiarrhythmic drugs are a major consideration in selecting therapy. Drug therapy can be instituted once sinus rhythm has been established or in anticipation of cardioversion. β-Adrenergic blockers and calcium channel blockers help control ventricular rate, improve symptoms, and possess a low-risk profile, but have low efficacy for preventing AF episodes. Class I sodium channel–blocking agents (e.g., flecainide, propafenone, disopyramide) are options for subjects without significant structural heart disease, but negative inotropic and proarrhythmic effects warrant avoidance in patients with coronary artery disease or heart failure. The class III agents sotalol and dofetilide can be administered to patients with coronary artery disease or structural heart disease but have ~3% risk of inducing excessive QT prolongation and torsades des pointes. Dofetilide should be initiated only in a hospital with ECG monitoring, and many physicians take this approach with sotalol as well. Dronedarone increases mortality in patients with heart failure. All of these agents have modest efficacy in patients with paroxysmal AF, of whom ~30–50% will benefit. Amiodarone is more effective, maintaining sinus rhythm in approximately two-thirds of patients. It can be administered to patients with heart failure and coronary artery disease. Over 40% of patients experience amiodarone-related toxicities during long-term therapy.

CATHETER AND SURGICAL ABLATION FOR ATRIAL FIBRILLATION

Successful catheter ablation avoids antiarrhythmic drug toxicities but procedural risks and efficacy depend on operator experience. For patients with previously untreated but recurrent paroxysmal AF, catheter ablation has mildly better efficacy compared to antiarrhythmic drug therapy and is clearly superior to antiarrhythmic drugs for patients who have recurrent AF despite drug treatment. Long-term control of AF is more difficult to achieve in patients with persistent AF, likely because of more extensive atrial abnormality and associated greater co-morbidities in these patients.

Catheter ablation involves cardiac catheterization, trans(atrial) septal puncture, and radiofrequency ablation or cryoablation to electrically isolate the left atrial regions around the PV, abolishing the ability of triggering foci in these regions to initiate AF, and also likely impacting the substrate for reentry in the left atrium. Extensive areas of ablation are required, and gaps in healed ablation areas or emergence of new trigger sites outside the PV necessitate a repeat procedure in 20–50% of patients.

In patients with paroxysmal AF, sinus rhythm is maintained for >1 year after one ablation procedure in ~60% of patients; and is achieved in 70–80% of patients after multiple procedures. Many patients become more responsive to antiarrhythmic drugs after a PV isolation procedure. Ablation is less effective in patients with persistent AF, and particularly long-standing persistent AF, particularly when associated with more extensive cardiac disease and co-morbidities. More extensive ablation is often required, targeting areas that likely support reentry in regions outside but adjacent to the pulmonary venous antra. There is no proven strategy for selecting ablation targets outside the PV antral regions and a variety of approaches have been pursued. Ablation of areas of rapid activity during AF or creation of ablation lines to block conduction across regions of the atria did not improve outcomes in some studies. Other ablation targets include foci that fire in response to isoproterenol, areas of atrial fibrosis, and regions with activation consistent with reentrant rotors during AF. More than one ablation procedure is often required to maintain sinus rhythm in patients with persistent and long-standing persistent AF.

Catheter ablation has a 2–7% risk of major procedure-related complications, including stroke (0.5–1%), cardiac tamponade (1%), phrenic nerve paralysis, bleeding from femoral access sites, and fluid overload with heart failure, that can emerge 1–3 days after the procedure. It is important to recognize the potential for delayed presentation of some complications. Ablation within the PV can lead to PV stenosis, presenting weeks to months after the procedure with dyspnea or hemoptysis. The esophagus abuts the posterior wall of the left atrium where it is

subject to injury, and esophageal ulcers can form immediately after the procedure and may rarely lead to a fistula between the left atrium and esophagus (estimated incidence of < 0.1%) that presents as endocarditis and stroke 10 days to 3 weeks after the procedure. Early diagnosis of atrioesophageal fistula is important because delayed diagnosis leads to death. Diagnosis is made by chest CT scan with water soluble oral and IV contrast. Endoscopy should be avoided in patients with a suspected fistula because of the risk of air/esophageal fluid embolus. Definitive repair of the atrioesophageal fistula by emergent cardiothoracic surgery is required.

Surgical ablation of AF is most frequently performed concomitant with cardiac valve or coronary artery surgery and less commonly as a stand-alone procedure. However, for patients with persistent AF, surgical or hybrid procedures appear to have higher single-procedure efficacy than catheter ablation. Risks include sinus node injury requiring pacemaker implantation. Surgical removal of the left atrial appendage may reduce stroke risk, although thrombus can form in the remnant of the appendage or if the appendage is not completely ligated.

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247 Approach to Ventricular Arrhythmias

Roy M. John, William G. Stevenson

TYPES OF VENTRICULAR ARRHYTHMIAS

Ventricular arrhythmias originate from a focus of myocardial or Purkinje cells capable of automaticity, or triggered automaticity, or from reentry through areas of scar or a diseased Purkinje system. They are characterized by their electrocardiographic appearance and duration. Conduction away from the ventricular focus through the ventricular myocardium is slower than activation of the ventricles over the Purkinje system. Hence, the QRS complex during ventricular arrhythmias will be wide, typically >0.12 s.

Premature ventricular beats (also referred to as a premature ventricular *contraction or PVC*) are single ventricular beats that fall earlier than the next anticipated supraventricular beat **(Fig. 247-1)**. PVCs that originate from the same focus will have the same QRS morphology and are referred to as unifocal **(Fig. 247-1*A*)**. PVCs that originate from different ventricular sites have different QRS morphologies and are referred to as multifocal **(Fig. 247-1*B*)**. Two consecutive ventricular beats are ventricular couplets.

Ventricular tachycardia (*VT*) is three or more consecutive beats at a rate faster than 100 beats/min. Three or more consecutive beats at slower rates are designated an idioventricular rhythm **(Fig. 247-1*C*)**. VT that terminates spontaneously within 30 s is designated *non-sustained* **(Fig. 247-2)** whereas sustained VT persists >30 s or is terminated by an active intervention, such as administration of an intravenous medication, external cardioversion, or pacing or a shock from an implanted cardioverter defibrillator.

Monomorphic VT has the same QRS complex from beat to beat, indicating that the activation sequence is the same from beat to beat, and that each beat likely originates from the same source **(Fig. 247-3*A*)**. The initial site of ventricular activation largely determines the sequence of ventricular activation. Therefore, the QRS morphology of PVCs and monomorphic VT provides an indication of the site of origin within the ventricles **(Fig. 247-4)**. The likely origin often suggests whether an arrhythmia is idiopathic or associated with structural disease. Arrhythmias that originate from the right ventricle or septum result in late activation of much of the left ventricle, thereby producing a prominent S-wave in V1 referred to as a left bundle branch block–like configuration. Arrhythmias that originate from the free wall of the left ventricle have a prominent positive deflection in V1, thereby producing a right bundle branch block–like morphology in V1. The frontal plane axis of the QRS is also useful. An axis that is directed inferiorly, as indicated by dominant R waves in lead II, III, and AVF, suggests initial activation of the cranial portion of the ventricle, whereas a frontal plane axis that is directed superiorly (dominant S waves in II, III, and AVF) suggests initial activation at the inferior wall.

Very rapid monomorphic VT has a sinusoidal appearance, also called *ventricular flutter*, because it is not possible to distinguish the QRS complex from the T wave **(Fig. 247-3*B*)**. Relatively slow *sinusoidal* VTs have a wide QRS indicative of slowed ventricular conduction **(Fig. 247-3*C*)**. Hyperkalemia, toxicity from excessive effects of drugs that block sodium channels (e.g., flecainide, propafenone, or tricyclic antidepressants) and severe global myocardial ischemia are causes.

Polymorphic VT has a continually changing QRS morphology indicating a changing ventricular activation sequence. Polymorphic VT that occurs in the context of congenital or acquired prolongation of the QT interval often has a waxing and waning QRS amplitude creating a "twisting about the points" appearance referred to as Torsade de Pointes **(Fig. 247-3*D*)**.

Ventricular fibrillation (VF) has continuous irregular activation with no discrete QRS complexes **(Fig. 247-3*E*)**. Monomorphic or polymorphic VT may transition to VF in susceptible patients.

The term *idiopathic ventricular arrhythmias* generally refers to PVCs or VT that occurs in patients without structural heart disease and which is not associated with a genetic syndrome or risk of sudden death.

CLINICAL MANIFESTATIONS

Common symptoms of ventricular arrhythmias include palpitations, dizziness, exercise intolerance, episodes of lightheadedness, syncope or sudden cardiac arrest leading to sudden death. Ventricular arrhythmias can also be asymptomatic and encountered unexpectedly as an irregular pulse or heart sounds on examination, or seen on a routine ECG, exercise test or cardiac ECG monitoring.

Syncope is a concerning symptom, that can be due to an episode of VT that produces severe hypotension, which often indicates that there is a risk for cardiac arrest and sudden death with arrhythmia recurrence. Although benign processes, such as reflex mediated neurocardiogenic (vasovagal) syncope and orthostatic hypotension, are the most common causes, it is important to consider the possibility of heart disease or a genetic syndrome causing VT. When these are

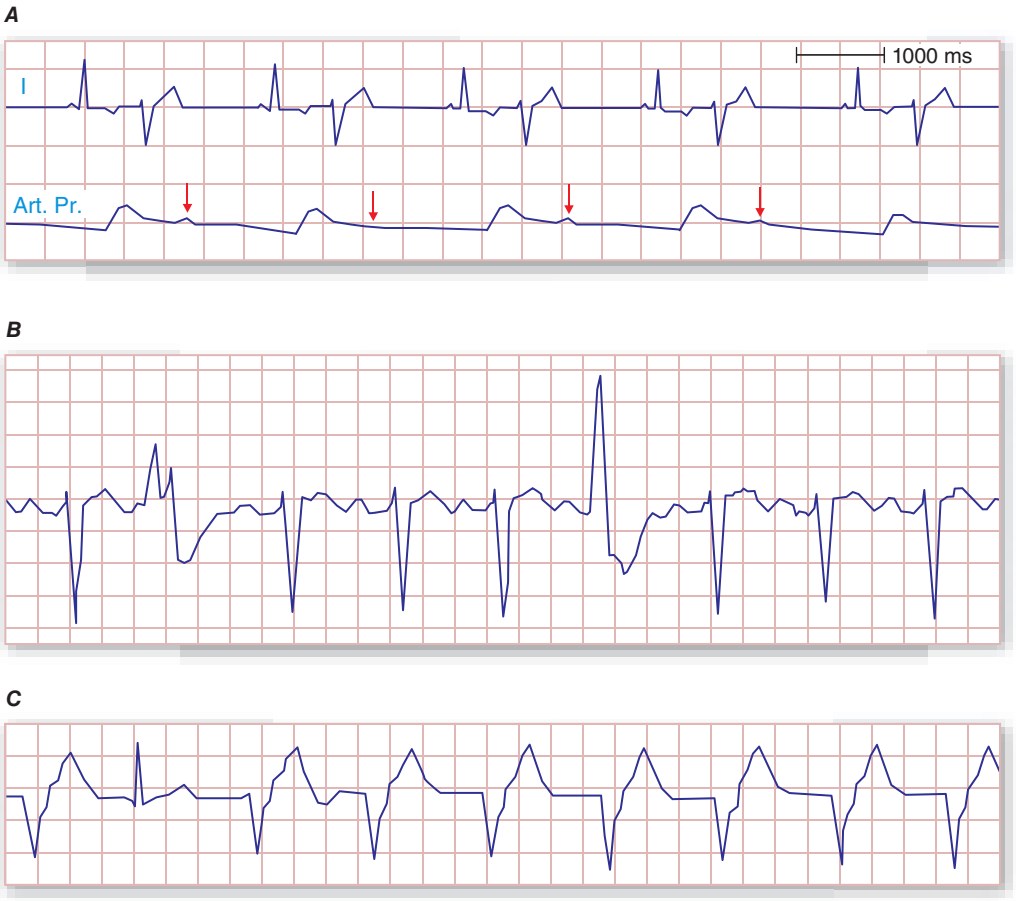

FIGURE 247-1 ***A.*** Unifocal premature ventricular contractions (PVCs) at bigeminal frequency. Trace shows ECG lead 1 and arterial pressure (Art. Pr.). Sinus rhythm beats are followed by normal arterial waveform. The arterial pressure following premature beats is attenuated (arrows) and imperceptible to palpation. The pulse in this patient is registered at half the heart rate. ***B.*** Multifocal PVCs. The two PVCs shown have different morphologies. ***C.*** Example of accelerated idio-ventricular rhythm (see text for details).

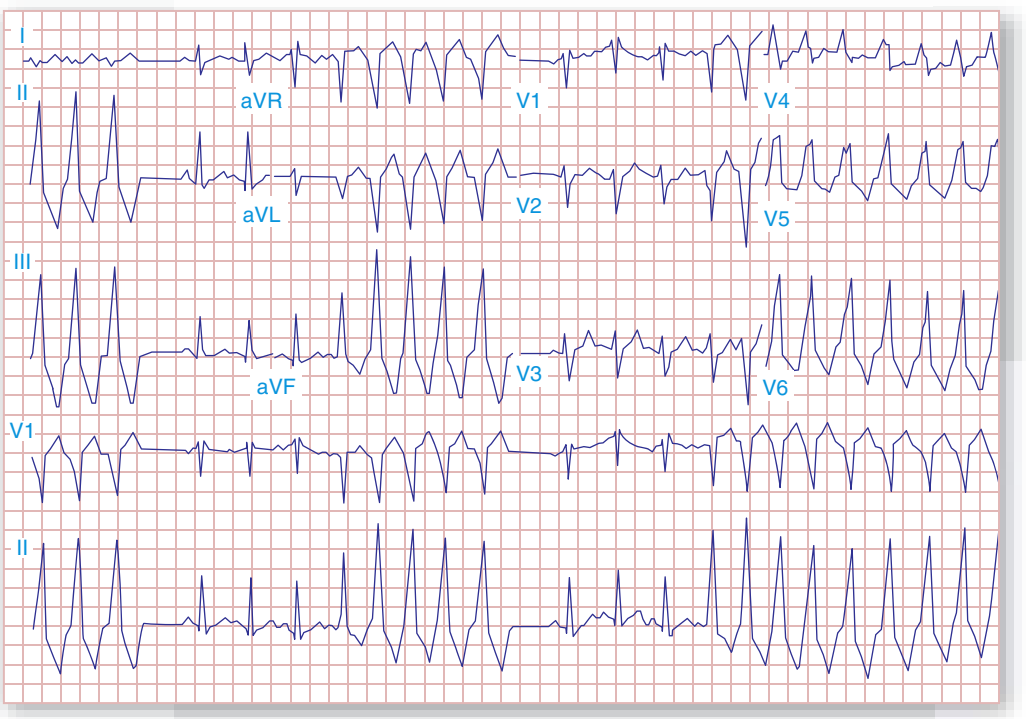

FIGURE 247-2 **Repetitive monomorphic non-sustained ventricular tachycardia (VT) of right ventricular outflow tract origin.** The VT has a left bundle branch block pattern with inferior axis with tall QRS complexes in the inferior leads.

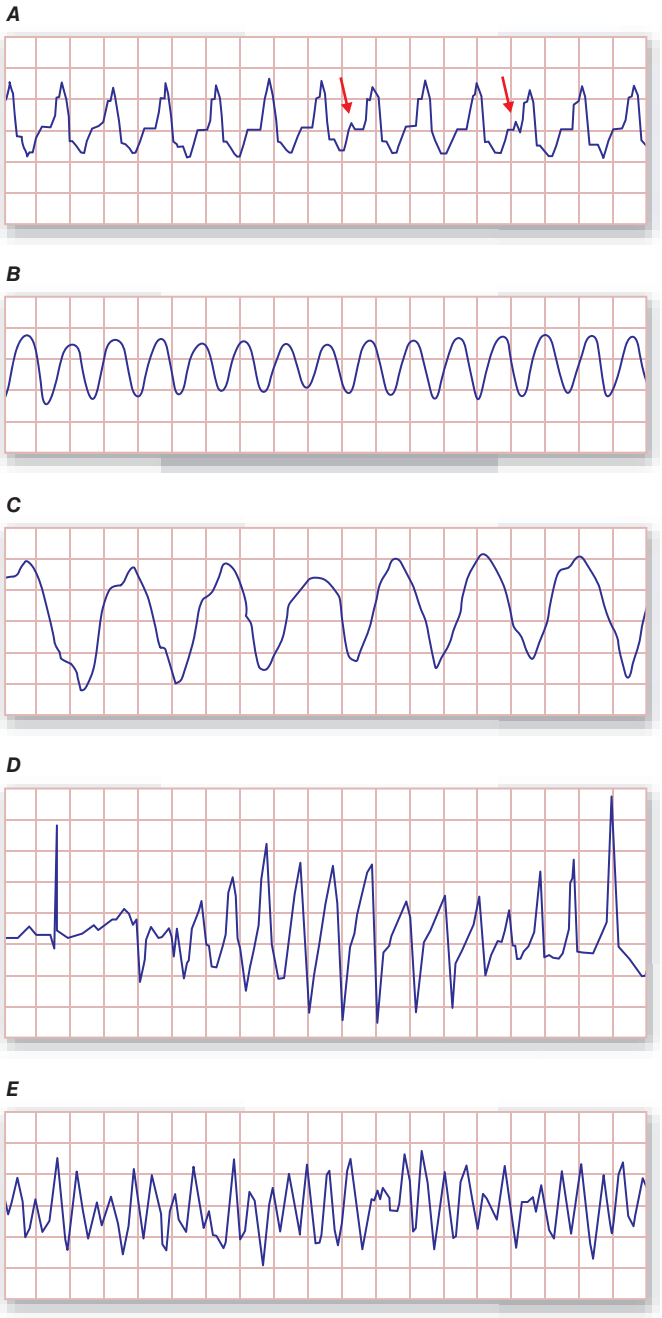

FIGURE 247-3 ***A.*** Monomorphic ventricular tachycardia (VT) with dissociated P waves (short arrows). ***B.*** Ventricular flutter. ***C.*** Sinusoidal VT due to electrolyte disturbance or drug effects. ***D.*** Polymorphic VT resulting from prolongation of QT interval (torsade de Pointes VT). ***E.*** Ventricular fibrillation (see text for details).

suspected, hospitalization for further evaluation and monitoring is often appropriate.

Sustained VT may present as a wide QRS complex tachycardia that must be distinguished from supraventricular tachycardia with aberrancy **(see Chap. 241)** causing symptoms that range from mild to severe impairment with hypotension with syncope and imminent cardiac arrest. Sustained VT may degenerate to VF, particularly if it is rapid and polymorphic. Many patients who are at risk for VT have known heart disease and many have an implantable cardioverter defibrillator (ICD). In patients with an ICD, VT episodes may cause transient lightheadedness, palpitations or syncope that may be followed by a shock from the ICD (see below).

EVALUATION OF PATIENTS WITH DOCUMENTED OR SUSPECTED VENTRICULAR ARRHYTHMIAS

There are several important considerations that guide evaluation of patients with documented or suspected cardiac arrhythmias. First, establish whether a ventricular arrhythmia is the cause of the symptoms or clinical presentation. Second, determine whether the arrhythmia is associated with a cardiac disease and establish the prognostic significance of that disease, and in particular whether it is associated with a risk of sudden cardiac death. Finally, define the likelihood of arrhythmia recurrence and the symptoms and risk imposed by the recurrence. The risk of cardiac arrest and sudden cardiac death are largely determined by the cause of the arrhythmia and the associated underlying heart disease.

The diagnosis of ventricular arrhythmias is established by recording of the arrhythmia on an ECG, by an implanted rhythm management device such as a pacemaker or ICD, or in some cases, initiation of the arrhythmia during an electrophysiologic study **(Table 247-1)**. A 12 lead ECG of the arrhythmia should be obtained when possible and often provides clues to the potential site of origin and possible presence of underlying heart disease (see above). For patients with sustained wide complex tachycardia initial management is guided by the patient's hemodynamic stability. The approach to sustained wide complex tachycardia is discussed in **Chap. 249**. The management of VT that causes cardiac arrest is discussed in **Chap. 299**. Once hemodynamic stability is restored further management is guided by the possibility of a recurrence and the risk imposed by a recurrence.

Evaluation of the Patient with Arrhythmia Symptoms

When symptoms are intermittent, initial evaluation aims to establish symptom severity, provocative factors and presence of underlying heart disease. Syncope or near syncope raises concern that an arrhythmia is causing episodes of hypotension and that there may be a risk of cardiac arrest if that persists. Symptoms that occur with exertion suggest arrhythmias that are provoked by sympathetic stimulation, but can also be related to exertional ischemia in patients with coronary artery disease, although non-arrhythmia causes must also be considered. A past history of any cardiac disease is important. A review of all medications is relevant. Medications that prolong the QT interval predispose to polymorphic VT **(see Chap. 250)**. Adrenergic stimulants can provoke premature ventricular contractions.

Family history should determine the presence of premature coronary artery disease, cardiomyopathy, or cardiac arrhythmias, particularly a history of sudden death. Family history may also suggest that a possibility of a genetic cause of an arrhythmia warrants careful consideration. Details of premature deaths are relevant. Sudden death victims are often said to have died of a "massive heart attack" despite absence of definite confirmation of thrombotic myocardial infarction and when other causes such as arrhythmia may have been possible.

The physical examination focuses on evidence of structural heart disease with assessment of pulse, jugular venous pressure lung fields and cardiac auscultation. Stigmata of neuromuscular disease or dysmorphic features may suggest a genetic arrhythmia syndrome.

A 12-lead ECG should be obtained even if the patient is not having symptoms at the time of evaluation. Occasionally premature ventricular beats will be detected. Patients with benign idiopathic arrhythmias usually have a completely normal ECG during sinus rhythm. Any ECG abnormality warrants further evaluation. Particularly relevant findings include Q-waves that indicate prior myocardial infarction, which may have been silent, and ventricular hypertrophy, which may indicate hypertrophic cardiomyopathy or other ventricular disease. An ECG finding is the major diagnostic manifestation of several genetic arrhythmia syndromes in patients without structural heart disease, including the long QT syndrome, Brugada syndrome, and short QT syndrome **(see Chap. 250)**.

If there is suspicion for structural heart disease, cardiac imaging is warranted to assess ventricular function and structure. Transthoracic echocardiography is most frequently employed for initial evaluation. Depressed ventricular function increases concern for a risk of sudden death and warrants further evaluation to establish the cause, which may be cardiomyopathy, coronary artery disease, or valvular heart disease. Ventricular thickening may indicate hypertrophic cardiomyopathy or infiltrative diseases such as amyloidosis. Cardiac MRI with gadolinium contrast imaging provides similar assessment, but also can

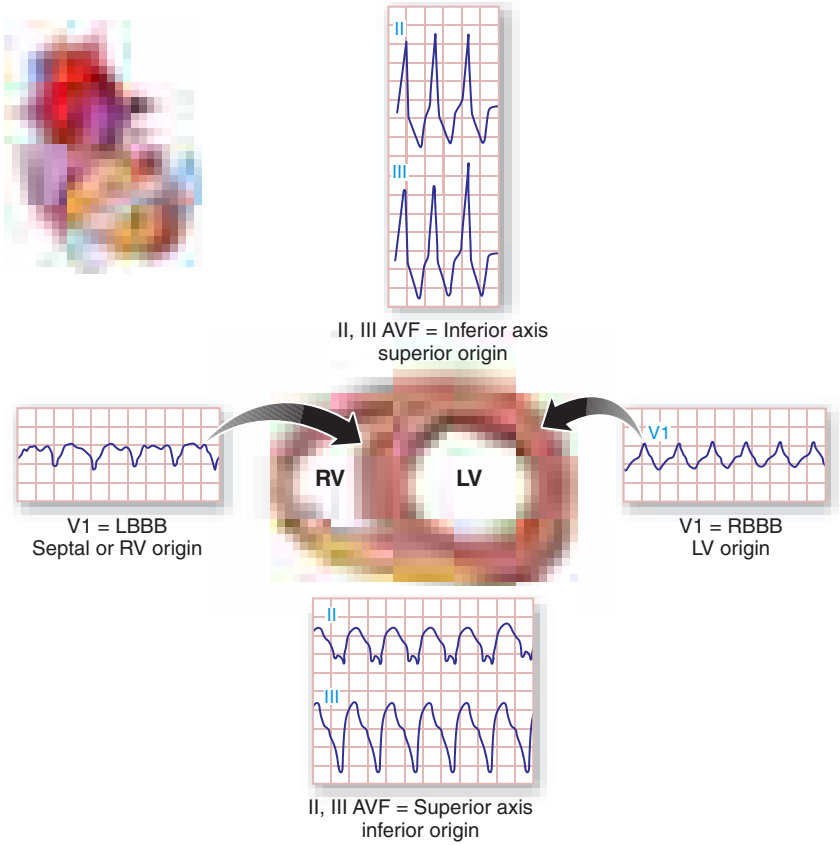

FIGURE 247-4 Site of ventricular tachycardia (VT) origin based on QRS morphology (see text for details).

detect areas of ventricular scar, evident as regions of delayed hyperenhancement, which are usually present in patients who have sustained monomorphic VT (Fig. 247-5). The nature and location of abnormalities is helpful in assessing the type of heart disease. Evaluation to exclude atherosclerotic coronary artery disease should be performed in patients at risk, guided by age and other risk factors.

TREATMENT OPTIONS FOR VENTRICULAR ARRHYTHMIAS

Treatment of ventricular arrhythmias is guided by the severity and frequency of symptoms. For some, reassurance and removal of aggravating factors (e.g., caffeine) is all that is needed. For arrhythmias associated with a sudden death risk, ICD implantation is usually indicated and will provide a "safety-net" to terminate life-threatening VT or VF, preventing sudden death, but without preventing the arrhythmia. When suppression of the arrhythmia is required, antiarrhythmic drug therapy or catheter ablation are major considerations.

Antiarrhythmic Drugs Use of antiarrhythmic drugs is based on consideration of the risks and potential benefit for the individual patient. Efficacy and side effects for the individual patient is not predictable and is assessed by individual therapeutic trial. Adverse effects are mostly non-cardiac and minor, but can sometimes be severe enough to limit their use. Cardiac side effects, however, include the potential for "pro-arrhythmia" whereby a drug can increase the frequency of arrhythmia or cause a new arrhythmia. Aggravation of bradyarrhythmias is also a common concern. Although anti-arrhythmic drugs are classified based on their actions on receptors or ion channels, most have multiple effects, affecting more than one channel.

Beta-adrenergic Blockers Many ventricular arrhythmias are sensitive to sympathetic stimulation, and beta-adrenergic stimulation also diminishes the electrophysiologic effects of many membrane active anti-arrhythmic drugs. The safety of beta-blocking agents makes them the first choice of therapy for most ventricular arrhythmias. They are particularly useful for exercise-induced arrhythmias and idiopathic arrhythmias, but have limited efficacy for most arrhythmias associated with heart disease. Bradyarrhythmias and negative inotrophic effects are the major cardiac adverse effects.

Calcium Channel Blockers The non-dihydropyridine calcium channel blockers diltiazem and verapamil can be effective for some idiopathic VTs. The risk of pro-arrhythmia is low, but they have negative inotropic and vasodilatory effects that can aggravate hypotension.

Sodium Channel Blocking Agents Drugs whose major effect is mediated through sodium channel blockade include mexiletine, quinidine, disopyramide, flecainide, and propafenone, which are available for chronic oral therapy. Blockade of the fast inward sodium current has been referred to as a Class I antiarrhythmic drug effect. Antiarrhythmic actions are the result of depressing of cardiac conduction and membrane excitability. Conduction slowing can be manifest as a prolongation of QRS duration. Lidocaine, quinidine, and procainamide are available as intravenous formulations. Quinidine, disopyramide, and procainamide also have potassium channel blocking effects that prolong the QT interval (Class III antiarrhythmic drug action) that contributes to its antiarrhythmic effect. These agents have potential pro-arrhythmic effects and, with the possible exception of quinidine, also have negative inotropic effects that may contribute to increased mortality observed when some were administered chronically to

TABLE 247-1 Diagnostic Tests for Ventricular Arrhythmias

12-Lead ECG

Event recorder

Non-looping, patient activated recorder

- Records only when the patient puts the device in contact with the chest wall and activates it
- Useful for episodes that are infrequent but last for more than several minutes

Looping event recorders

- Continuously recording, storing only segments triggered by the patient or with a heart rate outside set parameters
- Useful for intermittent, infrequent symptomatic and asymptomatic arrhythmias

Continuous ambulatory recording

Holter monitor—typically used for 24–48 h

- Records all arrhythmias during the recording period
- Useful for very frequent arrhythmias (daily) or when quantitation of an arrhythmia is needed (e.g., quantitation of premature ventricular contraction [PVCs] potentially contributing to depressed ventricular function)

Implanted loop recorders

- Allow continuous recording for >1 year
- Useful for capturing rare events such as rare syncopal episodes

Exercise Testing

- Useful for evaluation of exercise induced symptoms; arrhythmias usually emerge during the early recovery phase after exercise
- QT interval response to exercise may be abnormal in long QT syndrome

Electrophysiologic study

- Invasive test that attempts to initiate ventricular arrhythmias in a controlled setting
- Useful for assessing arrhythmia risk when there is concern for a risk of sudden death, but a sufficient diagnosis to guide therapy has not been achieved
- Useful for distinguishing between wide complex tachycardia due to ventricular tachycardia (VT) versus supraventricular tachycardia with aberrancy

FIGURE 247-5 Imaging studies of the left ventricle (LV) used to assist ablation for VT. Left panel is an MRI image of a longitudinal section demonstrating thinning of the anterior wall and late gadolinium enhancement in a sub-endocardial scar (*white arrows*). The middle panel shows a 2-D image of the LV in long axis corresponding to the sector through the mid LV (*arrow in figure on right panel*) obtained by an intra-cardiac echo probe positioned in the RV. An electro-anatomic 3-D map of the LV in the left anterior oblique projection is displayed in the right panel. The purple areas depict areas of normal voltage (>1.5 mV). Blue, green, and yellow represent progressively lower voltages with the red areas indicating scar (<0.5 mV). Channel of viable myocardium with slow conduction within the scar are identified with the light blue dots. Areas of ablation delivered to regions involved in re-entrant VT are indicated by maroon dots.

patients with prior myocardial infarction. Long-term therapy is generally avoided in patients with structural heart disease, but may be used to reduce symptomatic arrhythmias in patients with ICDs.

Potassium Channel Blocking Agents Sotalol and dofetilide block the delayed rectifier potassium channel IKr, thereby prolonging action potential duration (QT interval) and the cardiac refractory period, known as the Class III antiarrhythmic drug effect. Sotalol also has non-selective beta-adrenergic blocking activity. It has been shown to have a modest effect on reducing ICD shocks due to ventricular and atrial arrhythmias. Proarrhythmia due to the polymorphic VT *torsade de pointes* that is associated with QT prolongation occurs in 3–5% of patients. Both sotalol and dofetilide are excreted via the kidneys, necessitating dose adjustment or avoidance in renal insufficiency. These drugs must be avoided in patients with other risk factors for torsade de pointes, including QT prolongation, hypokalemia and significant bradycardia.

Amiodarone and Dronedarone Amiodarone blocks multiple cardiac ionic currents and has sympatholytic activity. It is the most effective antiarrhythmic drug for suppressing ventricular arrhythmias. It is administered intravenously for life-threatening arrhythmias. During chronic oral therapy, electrophysiologic effects develop over several days. It is more effective than sotalol in reducing ICD shocks and is the preferred drug for ventricular arrhythmias in patients with heart disease who are not candidates for an ICD. Bradyarrhythmias are the major cardiac adverse effect. Ventricular pro-arrhythmia can occur, but *torsade de pointes* VT is rare. Non-cardiac toxicities are a major problem and contribute to drug discontinuation in approximately a third of patients during long-term therapy. Hyper or hypothyroidism are related to the iodine content of the drug. Pneumonitis or pulmonary fibrosis occurs in ~1% of patients. Photosensitivity is common, and neuropathy and ocular toxicity can occur. Systematic monitoring is recommended during chronic therapy including assessment for thyroid, liver, and pulmonary toxicity. Intravenous administration of amiodarone via a peripheral vein for >24 h can cause severe peripheral thrombophlebitis. Dronaedarone has structural similarities to amiodarone but without the iodine moiety. Efficacy for ventricular arrhythmias is poor and it increases mortality in patients with heart failure.

Implantable Cardioverter Defibrillators (ICD) ICDs detect sustained VT, largely based on heart rate, and then terminate the arrhythmia. VF is terminated by a shock applied between a lead in the RV and the ICD pulse generator. Monomorphic VT can often be terminated by a burst of rapid pacing faster than the VT, known as anti-tachycardia pacing (ATP) **(Fig. 247-6*A*)**. If ATP fails or is not a programmed treatment, as is often the case for rapid VT or VF, a shock is delivered **(Fig. 247-6*B*)**. Shocks are painful if the patient is conscious. ICDs are highly effective for termination of VT and VF and also provide bradycardia pacing. The most common ICD complication is the delivery of unnecessary therapy (either ATP or shocks) in response to a rapid supraventricular tachycardia or electrical noise as a result of an ICD lead fracture. ICDs record and store electrograms from arrhythmia episodes which can be retrieved by interrogation of the ICD, which can be performed remotely and communicated via internet. This assessment is critical after an ICD shock to determine the arrhythmia diagnosis and exclude an unnecessary therapy. Device infection occurs in ~1% of patients.

ICDs decrease mortality in patients at risk for sudden death due to structural heart diseases. In all cases ICDs are recommended only if there is also expectation for survival of at least a year with acceptable functional capacity. The exception is in cases of patients with end-stage heart disease who are awaiting cardiac transplantation outside the hospital, or who have left bundle branch block QRS prolongation such that they are likely to have improvement in ventricular function with cardiac resynchronization therapy from a biventricular ICD **(Fig. 247-6*C*)**.

Despite prompt termination of VT or VF by an ICD, the occurrence of these arrhythmias predicts subsequent increased mortality and risk of heart failure. Occurrence of VT or VF should therefore prompt assessment for potential causes including worsening heart failure, electrolyte abnormalities, and ischemia. Repeated shocks, even if appropriate, often induce posttraumatic stress disorder. Antiarrhythmic drug therapy, most commonly amiodarone, or catheter ablation is often required for suppression of recurrent arrhythmias. Antiarrhythmic drug therapy can alter the VT rate and the energy required for defibrillation, thereby necessitating programming changes in the ICD's algorithms for detection and therapy.

The commonly used ICD system consists of endocardial leads to the right heart chambers with a pulse generator implanted in the pre-pectoral area (Fig. 247-6*C*). This transvenous form of ICD has the disadvantage of vascular occlusion, endocarditis in the event of infection, and difficulty with removal. A totally subcutaneous ICD system is now available. While it has the advantage of avoiding endovascular complications, the present iteration lacks the ability to pace the heart for tachycardia termination or for long-term pacing. A wearable ICD system with electrodes incorporated into a vest and an external battery pack is also available for short-term use in patients pending decision regarding a permanent implanted system.

Catheter Ablation for VT Catheter ablation is usually performed by applying radiofrequency (RF) current to cause thermal injury by resistive heating of cardiac tissue responsible for the arrhythmia. An electrode catheter is used to map local electrical activity to identify the ventricular myocardium that is causing the arrhythmia, referred to as the arrhythmia substrate. The size and location of the arrhythmia substrate determines the ease and likely effectiveness of the procedure, as well as the potential complications. When the arrhythmia originates from the endocardium, as is most commonly the case, it can be reached from an endovascular approach via a femoral vein or artery. Less commonly

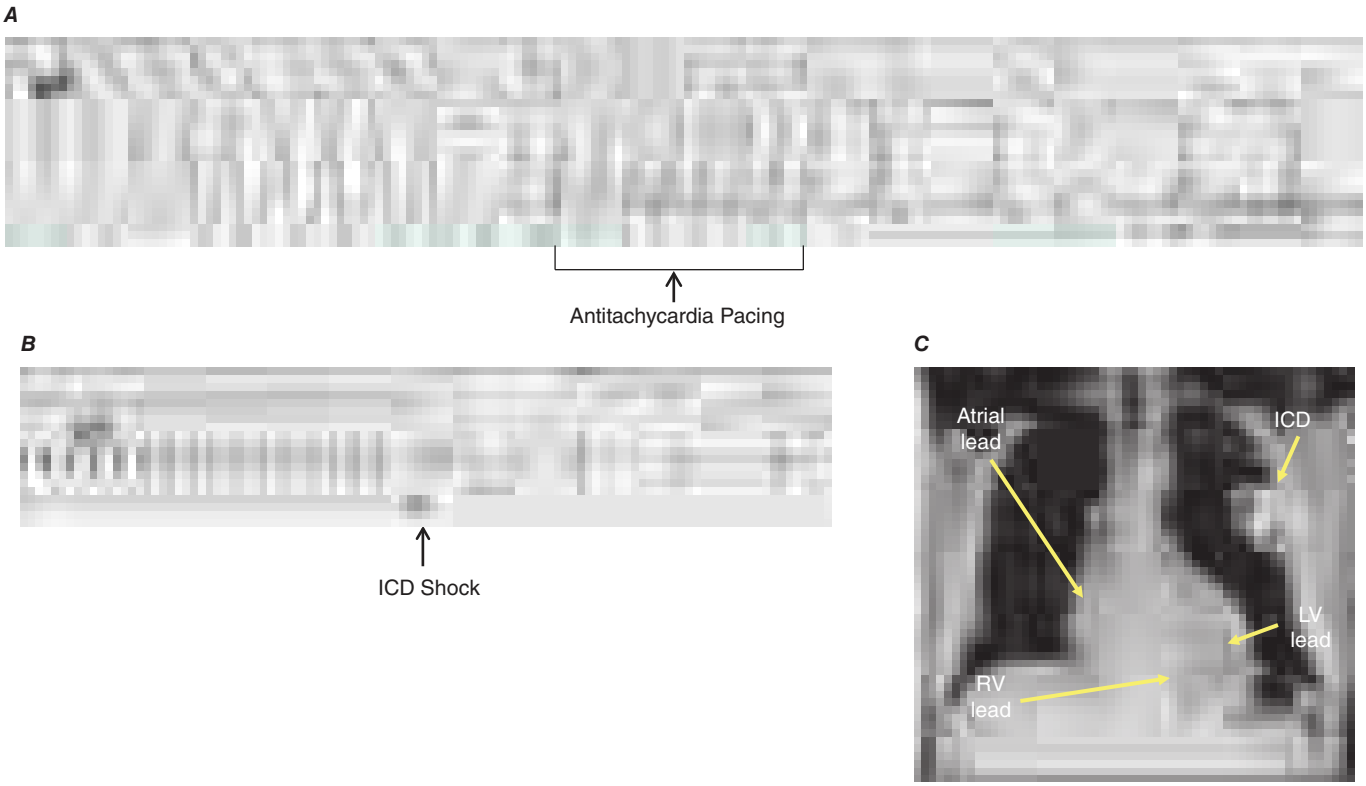

FIGURE 247-6 Implantable cardioverter defibrillator (ICD) and therapies for ventricular arrhythmias. ***A.*** A monomorphic ventricular tachycardia (VT) is terminated by a burst of pacing impulses at a rate faster than VT (anti-tachycardia pacing). ***B.*** A rapid VT is converted with a high voltage shock (*arrow*). The chest x-ray in Panel ***C*** shows the components of an ICD capable of biventricular pacing. ICD generator in the subcutaneous tissue of the left upper chest, pacing leads in the right atrium and the LV branch of the coronary sinus (LV lead) and a pacing/defibrillating lead in the right ventricle (RV lead) are shown.

arrhythmias originate from the subepicardium, and percutaneous pericardial puncture, similar to pericardiocentesis, is required to insert a catheter into the pericardial space for mapping and ablation. In patients with scar-related VT due to prior infarction or cardiomyopathy, ablation targets abnormal regions in the scar. Because these scars often contain multiple reentry circuits over relatively large regions, extensive areas of ablation are required and these areas are often identified as regions of low voltage displayed on anatomic reconstructions of the ventricle (Fig. 247-5).

Catheter ablation is often performed in patients with recurrent ventricular arrhythmias associated with poor cardiac function, and the procedure-related mortality in this situation is 0.5–3%. Outcomes are better for patients with prior infarction and VT than for patients with nonischemic cardiomyopathies in which the scar locations are more variable and often intramural or sub-epicardial. Ablation can be lifesaving for patients with very frequent or incessant VT.

Idiopathic VTs and PVCs that occur in the absence of structural heart disease usually originate from a small focus, for which catheter ablation has a higher success rate for preventing recurrent arrhythmia **(see Chaps. 248 and 249)**.

ARRHYTHMIA SURGERY

When antiarrhythmic drug therapy and catheter ablation fails, or is not an option, surgical cryoablation, often combined with aneurysmectomy, can be effective therapy for recurrent VT due to prior myocardial infarction and has also been used successfully in a few patients with nonischemic heart disease. Few centers now maintain the expertise for this therapy.

FURTHER READING

PEDERSEN CT et al: EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. Europace 16:1257, 2014.

PRIORI SG et al: 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 36:2793, 2015.

248 Premature Ventricular Beats, Non-Sustained Ventricular Tachycardia, and Idioventricular Rhythm

Roy M. John, William G. Stevenson

PREMATURE VENTRICULAR CONTRACTIONS AND NON-SUSTAINED VT

Premature ventricular contractions **(see Fig. 247-1*A*)** can be due to automaticity or reentry **(see Chap. A9)**. They are often sensitive to sympathetic stimulation and can be a sign of increased sympathetic tone, myocardial ischemia, hypoxia, electrolyte abnormalities, particularly hypokalemia, or underlying heart disease. During myocardial ischemia or in association with other heart disease, PVCs can be a harbinger of sustained VT or VF.

The ECG characteristics of the arrhythmia are often suggestive of whether structural heart disease is present. PVCs with smooth uninterrupted contours and sharp QRS deflections suggest an ectopic focus in relatively normal myocardium whereas broad notching and slurred QRS deflections suggest a diseased myocardial substrate. The QRS morphology also suggests the likely site of origin within the ventricle **(see Fig. 247-4)**. PVCs that have a dominant S-wave in V1, referred to as left bundle branch block–like configuration originate from the right ventricle or interventricular septum. Those with a dominant R-wave in

V1 originate from the left ventricle. A superior frontal plane axis (negative in II, III, AVF) indicates initial depolarization of the inferior wall (diaphraghmatic aspect of the heart), while an inferior frontal plane axis (positive in II, III, AVF) indicates an origin in the cranial aspect of the heart. The location of arrhythmia origin often suggests the nature of underlying heart disease. Most ventricular arrhythmias that are not associated with structural heart disease have a left bundle branch block–like configuration. PVCs with RBBB configuration are more likely to be associated with structural heart disease. Multiple morphologies of PVCs (multifocal PVCs) are also more likely to indicate structural heart disease **(see Fig. 247-1*B*)**. In patients with heart disease, a greater frequency and complexity (couplets and non-sustained VT) of these arrhythmias are associated with more severe disease.

PVCs AND NON-SUSTAINED VT DURING ACUTE ILLNESS

These arrhythmias are often encountered in patients who are being evaluated in the emergency room, or who have been hospitalized and are on a cardiac monitor. When encountered during acute illness or as a new finding, evaluation should focus on detection and correction of potential aggravating factors and causes, specifically myocardial ischemia, ventricular dysfunction and electrolyte abnormalities, most commonly hypokalemia. Underlying heart disease should be defined.

PVCs AND NON-SUSTAINED VT IN PATIENTS WITHOUT HEART DISEASE

The most frequent site of origin for idiopathic ventricular arrhythmias is the right ventricular outflow tract, giving rise to PVCs or VT that have a left bundle branch block–like configuration, with an inferiorly directed frontal plane axis as discussed below **(see Fig. 247-2)**. However, QRS morphology alone is not reliable as an indicator of disease or subsequent risk. Non-sustained VT is usually monomorphic with rates <200 beats/min and typically lasting <8 beats **(see Fig. 247-2)**. Non-sustained VT that is very rapid, polymorphic, or with a first beat that occurs prior to the peak of the T-wave ("short-coupled") is uncommon and should prompt careful evaluation for underlying disease or genetic syndromes associated with sudden death.

A family history of sudden death should prompt evaluation for genetic syndromes associated with sudden death, including cardiomyopathy, long QT syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC) (see below). Any abnormality on the 12-lead ECG warrants further evaluation **(Fig. 248-1)**. Repolarization abnormalities are seen in a number of genetically determined syndromes associated with sudden death, including the long QT syndrome, Brugada syndrome, ARVC, and hypertrophic cardiomyopathy (Fig. 248-1). An echocardiogram is often necessary to assess ventricular function, wall motion abnormalities, and valvular heart disease. Contrast enhanced cardiac magnetic resonance imaging is also useful for this purpose and for the detection of ventricular scarring that is the substrate for sustained VT **(see Fig. 247-5)**. Exercise stress testing should be performed in patients with effort-related symptoms and for those at risk for coronary artery disease.

TREATMENT OF IDIOPATHIC ARRHYTHMIAS

For PVC and non-sustained VT in the absence of structural heart disease, or a genetic sudden death syndrome, no specific therapy is needed unless the patient has significant symptoms or evidence that frequent PVCs are depressing ventricular function (see below). Reassurance that the arrhythmia is benign is often sufficient to allow the patient to cope with the symptoms, which will often wax and wane in frequency over years. Avoiding stimulants, such as caffeine and alcohol, is helpful in some patients. If symptoms require treatment, beta-adrenergic blockers and non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are sometimes helpful. If these fail more membrane active antiarrhythmic drugs or catheter ablation are options. Antiarrhythmic agents flecainide, propafenone, mexiletine, and amiodarone can be effective but the potential for side effects, warrants careful consideration. Catheter ablation is effective at suppressing this arrhythmia in about 80% of patients. Failure of ablation is usually due to inability to provoke the arrhythmia for mapping in the electrophysiology laboratory, or an origin that is not accessible, such as deep within the myocardium.

PVCs AND NON-SUSTAINED VT ASSOCIATED WITH ACUTE CORONARY SYNDROMES

During and soon after acute myocardial infarction (MI), PVCs and non-sustained VT are common and can be an early manifestation of ischemia and a harbinger of subsequent VF. Treatment with beta-adrenergic blockers and correction of hypokalemia and hypomagnesemia reduce the risk of VF. Routine administration of antiarrhythmic drugs such as lidocaine does not reduce mortality and is not indicated for suppression of PVCs or asymptomatic non-sustained VT, but may be implemented transiently if an episode of sustained VT or VF occurs, with the goal of reducing the likelihood of a subsequent episode.

Following recovery from acute MI, frequent PVCs (typically >10 PVCs/h), repetitive PVCs with couplets, and non-sustained VT are markers for depressed ventricular function and increased mortality, but routine antiarrhythmic drug therapy to suppress these arrhythmias does not improve mortality and treatment with the sodium channel blocker flecainide increases mortality. Amiodarone therapy reduces sudden death, but does not improve total mortality. Therefore, amiodarone is an option for treatment of symptomatic arrhythmias in this population when the potential benefit outweighs its potential toxicities. Beta-adrenergic blockers reduce sudden death, but have limited effect on spontaneous arrhythmias.

For survivors of an acute MI, an implantable cardioverter defibrillator (ICD) reduces mortality in certain high-risk groups: patients who have survived >40 days after the acute MI and have a left ventricular ejection fraction of ≤0.30, or who have an ejection fraction <0.35 and have symptomatic heart failure (functional Class II or III); and patients >5 days after MI who have a reduced left ventricular ejection fraction, nonsustained VT, and inducible sustained VT or VF on electrophysiological testing. ICDs do not reduce mortality when routinely implanted soon after MI, and

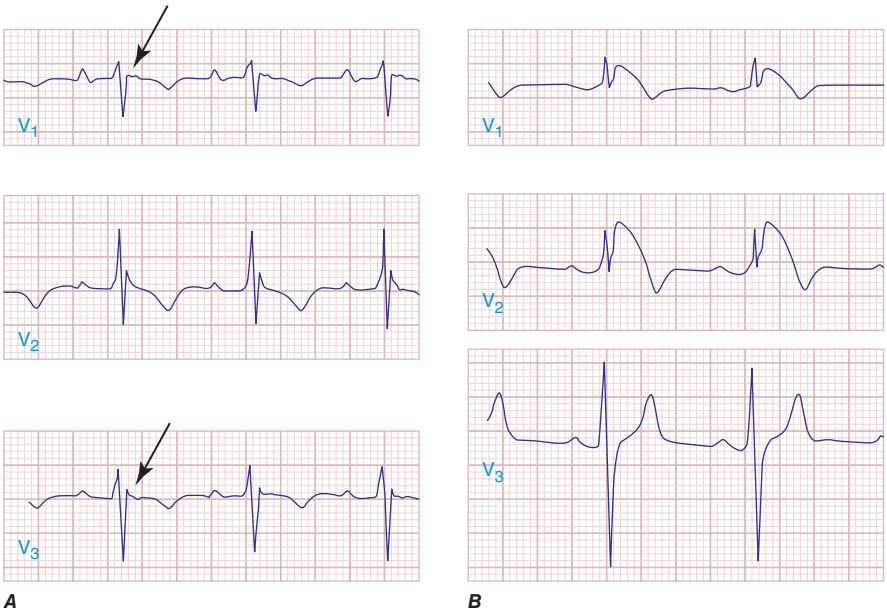

FIGURE 248-1 Precordial chest leads V1–V3 showing typical abnormalities of arrhythmogenic right ventricular cardiomyopathy (ARVC) (*A*) and Brugada syndrome (*B*). In ARVC, there is T inversion and delayed ventricular activation manifest as Epsilon waves (*arrows*). Panel B shows ST elevation in V1 and V2 typical of the Brugada syndrome.

have not been demonstrated to improve mortality when implanted soon after coronary artery revascularization.

PVCs AND NON-SUSTAINED VT ASSOCIATED WITH DEPRESSED VENTRICULAR FUNCTION AND HEART FAILURE

Premature ventricular beats and non-sustained VT are common in patients with depressed ventricular function and heart failure, and are markers for disease severity and increased mortality, but antiarrhythmic drug therapy to suppress these arrhythmias has not been shown to improve survival. The use of anti-arrhythmic drugs whose major action is blockade of the cardiac sodium channel (flecainide, propafenone, mexiletine, quinidine, and disopyramide) is avoided in patients with structural heart disease because of a risk of pro-arrhythmia, negative inotropic effects and increased mortality. Therapy with the potassium channel blocker dofetilide, does not reduce mortality. Amiodarone suppresses ventricular ectopy and reduces sudden death but does not improve overall survival. ICDs are the major therapy to protect against sudden death in patients at high risk and are recommended for those with LV ejection fraction <0.35 and NYHA class II and III heart failure, in whom they reduce mortality from 36 to 29%, over 5 years.

PVC AND NON-SUSTAINED VT ASSOCIATED WITH OTHER CARDIAC DISEASES

Ventricular ectopy is associated with increased mortality in patients with *hypertrophic cardiomyopathy* **(Chap. 254)** or with *congenital heart disease* associated with right or left ventricular dysfunction. In these patients, management is similar to that for patients with ventricular dysfunction. Pharmacologic suppression of the arrhythmia has not been shown to improve mortality. ICDs are indicated for patients considered at high risk for sudden cardiac death.

PVC-INDUCED VENTRICULAR DYSFUNCTION

Very frequent ventricular ectopy and repetitive non-sustained VT **(see Fig. 247-2)** can depress ventricular function, possibly through an effect similar to chronic tachycardia or by inducing ventricular dysynchrony. Depression of ventricular function rarely occurs unless PVCs account for >15 to 20% of total beats over a 24-h period. Often the PVCs are idiopathic and unifocal, most commonly originating from the left ventricular papillary muscles or outflow tract regions where they can be targeted for ablation. The distinction between PVC- induced ventricular dysfunction as compared to a primary cardiomyopathic process causing ventricular dysfunction and arrhythmia is difficult and in some cases can be made only retrospectively by observing an improvement in ventricular function after the arrhythmia is suppressed with an antiarrhythmic drug, such as amiodarone, or by catheter ablation.

IDIOVENTRICULAR RHYTHMS

Three or more ventricular beats at a rate slower than 100 beats/min are termed an idioventricular rhythm **(see Fig. 247-1*C*)**. Automaticity is the likely mechanism. Idioventricular rhythms are common during acute MI and may emerge during sinus bradycardia. Often, they are not symptomatic, but hemodynamic compromise may occur with the loss of ventricular synchrony in susceptible patients. Atropine may be administered to increase the sinus rates if this is a concern. This rhythm is also common in patients with cardiomyopathies or sleep apnea. It can also be idiopathic, often emerging when the sinus rate slows during sleep. Therapy should target any underlying cause and correction of bradycardia. Specific antiarrhythmic therapy for asymptomatic idioventricular rhythm is not necessary.

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249 Sustained Ventricular Tachycardia

Roy M. John, William G. Stevenson

Sustained monomorphic ventricular tachycardia (VT) presents as a wide QRS tachycardia that has the same QRS configuration from beat to beat indicating an identical sequence of ventricular depolarization for each beat **(see Fig. 247-3A)**. VT originates from a stable focus or reentry circuit. In structural heart disease, the substrate is often an area of patchy replacement fibrosis due to infarction, inflammation or prior cardiac surgery that creates anatomical or functional reentry pathways **(see Fig. 247-5)**. Less commonly, VT is related to reentry or automaticity in a diseased Purkinje system. Idiopathic VT occurs in the absence of structural heart disease and is due to a focal region of automaticity or reentry involving a portion of the Purkinje system.

The clinical presentation varies depending on the rate of the arrhythmia, underlying cardiac function, and autonomic adaptation in response to the arrhythmia. While rapid VT, >200 beats/min, usually causes hypotension that may present as syncope, patients with normal cardiac function might tolerate rapid VT, and those with severe left venricular (LV) dysfunction may experience symptoms of hypotension, even if VT is slower than 150 beats/min. Monomorphic VT that is rapid or associated with structural heart disease may deteriorate to ventricular fibrillation (VF), which may be the initial cardiac rhythm recorded at the time of resuscitation of a cardiac arrest.

DIAGNOSIS

Sustained monomorphic VT has to be distinguished from other causes of uniform wide QRS tachycardia. These include supraventricular tachycardia with left or right bundle branch block aberrant conduction, supraventricular tachycardias conducted to the ventricles over an accessory pathway **(Chap. 241)**, and rapid cardiac pacing in a patient with a pacemaker or defibrillator. In the presence of known heart disease VT is the most likely diagnosis of a wide QRS tachycardia. Hemodynamic stability during the arrhythmia does not exclude VT. A number of ECG criteria have been evaluated to distinguish supraventricular tachycardia with aberrancy from VT. The presence of AV dissociation is usually a reliable marker for VT **(Fig. 249-1)**, but P-waves can be difficult to define. A P-wave following each QRS does not exclude VT because 1:1 conduction from ventricle to atrium can occur. A monophasic R wave or Rs complex in AVR or concordance from V1 to V6 of

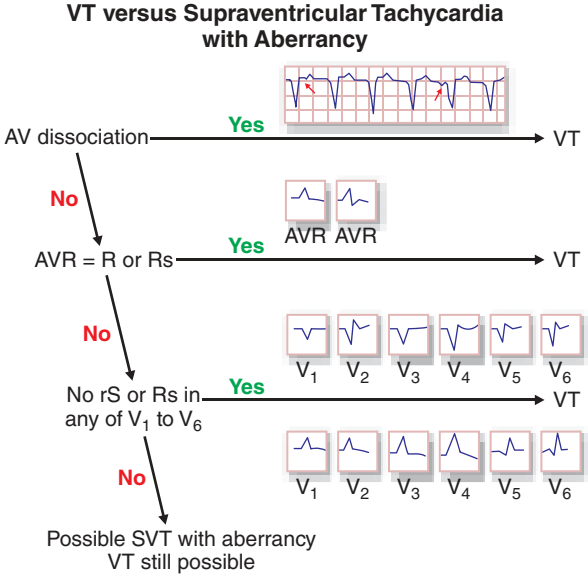

FIGURE 249-1 Algorithm for differentiation of ventricular tachycardia from supraventricular tachycardia with aberration.

monophasic R or S waves are also relatively specific for VT (Fig. 249-1). A number of other QRS morphology criteria have also been described, but all have limitations, and are not very reliable in patients with severe heart disease. In patients with known bundle branch block, the same QRS morphology during tachycardia as during sinus rhythm suggests supraventricular tachycardia rather than VT, but is not absolutely reliable. An electrophysiological study is sometimes required for definitive diagnosis. Occasionally, noise and movement artifacts on telemetry recordings can simulate VT; prompt recognition can avoid unnecessary tests and interventions.

When LV function is depressed or there is evidence of structural myocardial disease, scar-related reentry is the most likely cause of sustained monomorphic VT. Scars are suggested by pathologic Q-waves on the ECG, segmental left or right ventricular wall motion abnormalities on echocardiogram or nuclear imaging, and areas of delayed gadolinium enhancement during MR imaging **(see Fig. 247-5)**.

TREATMENT AND PROGNOSIS

Initial management follows Advanced Cardiac Life Support (ACLS) guidelines **(Chap. 299)**. If hypotension, impaired consciousness, or pulmonary edema are present, QRS synchronous electrical cardioversion should be performed, ideally after sedation if the patient is conscious. For stable tachycardia a trial of adenosine is reasonable, as this may clarify a supraventricular tachycardia with aberrancy **(Chap. 241)**. Intravenous amiodarone is the drug of choice if heart disease is present. Following restoration of sinus rhythm, hospitalization and evaluation to define underlying heart disease is required. Assessment of cardiac biomarkers for evidence of myocardial infarction (MI) is appropriate, but acute MI is rarely a cause of sustained monomorphic VT, and elevations in troponin or CK-MB are more likely to indicate myocardial damage that is secondary to hypotension and ischemia from the VT. Subsequent management is determined by the underlying heart disease and frequency of VT. If VT recurs frequently or is incessant, administration of antiarrhythmic medications, or catheter ablation may be required to restore stability. More commonly sustained monomorphic VT occurs as an isolated episode, but with a risk of recurrence. Implantable cardioverter defibrillators (ICDs) are usually warranted for sustained VT associated with structural heart disease.

SUSTAINED MONOMORPHIC VT IN SPECIFIC DISEASES

Coronary Artery Disease Patients who present with sustained monomorphic VT associated with coronary artery disease typically have a history of prior large MI and present years after the acute infarct with a remodeled ventricle and markedly depressed left ventricular function. Even when there is biomarker evidence of acute MI, a preexisting scar from previous MI should be suspected as the cause of the VT. Infarct scars provide a durable substrate for sustained VT and up to 70% of patients have a recurrence of the arrhythmia within 2 years. Scar-related reentry is not dependent on recurrent acute myocardial ischemia, so coronary revascularization cannot be anticipated to prevent recurrent VT, even when it may be appropriate for treatment of angina or other indications. Depressed ventricular function, which is a risk factor for sudden death, is usually present. Implantation of an ICD is indicated for most patients provided that there is a reasonable expectation of survival with acceptable functional status for the next year after recovery from the VT episode. Compared with antiarrhythmic drug therapy ICDs reduce annual mortality from 12.3 to 8.8% and lower arrhythmic deaths by 50% in patients with hemodynamically significant sustained VT or a history of cardiac arrest. Chronic amiodarone therapy may be considered for patients who are not candidates for, or who decline ICD placement.

Following ICD implantation, patients remain at risk for heart failure, recurrent ischemic events, and recurrent VT, with a 5-year mortality that exceeds 30%. Attention to therapies that benefit patients with depressed ventricular function, including beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, and statins is important. Patients with frequent symptomatic recurrences of VT require antiarrhythmic drug therapy or catheter ablation.

TABLE 249-1 Ventricular Arrhythmias Associated with Different Forms of Heart Disease

1. Idiopathic ventricular tachycardia (VT) without structural heart disease
   - A. Outflow tract origin
     - a. Right ventricular (RV) outflow tract: left bundle branch block pattern with inferior axis (tall QRS in inferior leads) and late transition in the precordial leads
     - b. Left ventricular (LV) outflow tract: prominent "r" in V1
   - B. Left posterior fascicular VT
     - Right bundle branch block pattern with left axis deviation (most common)
2. Ischemic cardiomyopathy
   - Monomorphic VT is common with prior large myocardial infarction
   - Polymorphic VT and ventricular fibrillation (VF) should prompt ischemia evaluation
3. Nonischemic cardiomyopathy
   - Polymorphic VT and VF more common but fibrotic scars can cause monomorphic VT especially with sarcoidosis, Chagas disease, Lamin A/C genetic cardiomyopathy
4. Arrhythmogenic Right Ventricular Cardiomyopathy
   - Monomorphic VT usually of right ventricular origin (left bundle branch morphology)
   - Polymorphic VT and VF can occur independently or through degeneration of monomorphic VT
5. Repaired Tetralogy of Fallot
   - Monomorphic VT of right ventricular origin (usually left bundle branch morphology)
6. Hypertrophic Cardiomyopathy
   - Polymorphic VT or ventricular fibrillation
   - Less commonly, monomorphic VT associated with myocardial scars
7. Genetic Arrhythmia Syndromes:
   - A. Long QT syndrome
     - *Torsade de Pointes* VT
   - B. Brugada syndrome
     - Ventricular fibrillation
   - C. Catecholaminergic polymorphic VT
     - Polymorphic VT or bidirectional VT
   - D. Short QT syndrome
     - Ventricular fibrillation
   - E. Early repolarization syndrome
8. Polymorphic VT or VF

Nonischemic Dilated Cardiomyopathy Sustained monomorphic VT associated with nonischemic cardiomyopathy is usually due to scar-related reentry. The etiology of scar is often unclear, but progressive replacement fibrosis is the likely cause. On cardiac MR imaging, scars are detectable as areas of delayed gadolinium enhancement and are more often intramural or sub-epicardial in location as compared with patients with prior MI. Scars that cause VT are often located adjacent to a valve annulus and can occur in either ventricle. Any cardiomyopathic process can cause scars and VT, but cardiac sarcoidosis, Chagas disease, and cardiomyopathy due to Lamin A/C mutations are particularly associated with monomorphic VT **(Table 249-1)**. An ICD is usually indicated with additional drugs or catheter ablation for control of recurrent VT.

MONOMORPHIC VT IN ARRHYTHMOGENIC RIGHT VENTRICULAR (RV) CARDIOMYOPATHY (ARVC)

ARVC **(Chap. 254)** is a rare genetic disorder most commonly due to mutations in genes encoding for cardiac desmosomal proteins. Approximately 50% have a familial transmission with autosomal dominant inheritance. A less common, autosomal recessive form is associated with cardio-cutaneous syndromes that include Naxos disease and Carvajal syndrome. Patients typically present between the second and fifth decade with palpitations, syncope or cardiac arrest owing to sustained monomorphic VT, although polymorphic VT can also occur. Fibrosis and fibro-fatty replacement most commonly involves the right

ventricular myocardium, and provide the substrate for reentrant VT that usually has a left bundle branch block–like configuration, consistent with the right ventricular origin and can resemble idiopathic VT. The sinus rhythm ECG suggests the disease in >85% of patients, most often showing T-wave inversions in V1-V3 **(see Fig. 248-1)**. Delayed activation of the right ventricle may cause a widened QRS (>110 ms) in the right precordial leads and a prolonged S-wave upstroke in those leads, and occasionally a deflection at the end of the QRS known as an "Epsilon" wave **(see Fig. 248-1)**. Cardiac imaging may show right ventricular enlargement or areas of abnormal motion, or reveal areas of scar on contrast enhanced MRI.

Left ventricular involvement can occur and occasionally precede manifest right ventricular disease. Heart failure is rare except in late stages, and survival to advanced age can be anticipated provided that VT can be controlled. An ICD is recommended. When VT is exercise-induced, it may respond to beta-adrenergic blockers and limiting exercise. Sotalol and amiodarone have been used to reduce recurrences. Catheter ablation prevents or reduces VT episodes in 70% of patients, but epicardial mapping and ablation is often required.

Tetralogy of Fallot Ventricular tachycardia occurs in 3–14% of patients late after repair of tetralogy of Fallot, and contributes to a 2% per decade risk of sudden death. Monomorphic VT is due to reentry around areas of surgically created scar in the RV (Table 249-1). Factors associated with VT risk include age >5 years at the time of repair, high-grade ventricular ectopy, inducible VT on an electrophysiologic study, abnormal RV hemodynamics, and sinus rhythm QRS duration >180 ms. An ICD is usually warranted for patients who have a spontaneous episode of VT, but criteria for a prophylactic ICD in other patients have not been established. Catheter ablation or anti-arrhythmic drug therapy is used to control recurrent episodes.

BUNDLE BRANCH REENTRY VT

Reentry through the Purkinje system occurs in ~5% of patients with monomorphic VT in the presence of structural heart disease. The reentry circuit typically revolves retrograde via the left bundle and anterograde down the right bundle, thereby producing VT that has a left bundle branch block configuration. Catheter ablation of the right bundle branch abolishes this VT. Bundle branch reentry is usually associated with severe underlying heart disease. Other scar-related VTs are often present and often require additional therapy or ICD implantation.

IDIOPATHIC MONOMORPHIC VT

Idiopathic VT in patients without structural heart disease usually presents with palpitations, lightheadedness, and occasionally syncope, often provoked by sympathetic stimulation during exercise or emotional upset. The QRS morphology of the arrhythmia suggests the diagnosis (see below). The sinus rhythm ECG is normal. Cardiac imaging shows normal ventricular function and no evidence of ventricular scar. Occasionally a patient with structural heart disease is found to have concomitant idiopathic VT, unrelated to the structural disease. Sudden death is rare.

Outflow *Tract* VTs originate from a focus, usually with features consistent with triggered automaticity. The arrhythmia may present with sustained VT, non-sustained VT or PVCs often provoked by exercise or emotional upset. Repeated bursts of non-sustained VT, which may occur incessantly, are known as repetitive monomorphic VT and can cause tachycardia—induced cardiomyopathy with depressed ventricular function that recovers after suppression of the arrhythmia. Most originate in the right ventricular outflow tract, which gives rise to VT that has a left bundle branch block configuration in V1 and an axis that is directed inferiorly, with tall R-waves in II, III, and AVF **(see Fig. 247-2)**. Idiopathic VT can also arise in the left ventricular outflow tract or in sleeves of myocardium that extend along the aortic root. LV origin is suspected when leads V1 or V2 have prominent R-waves (Table 249-1). Although this typical outflow tract QRS morphology favors idiopathic VT, some cardiomyopathies, notably ARVC, can cause PVCs or VT from this region. Excluding these diseases is an initial focus of evaluation.

***Left ventricular* intrafascicular VT** presents with sustained VT that has a right bundle branch block–like configuration. It is often exercise induced and occurs more often in men than women. The mechanism is reentry in or near the septal ramifications of the left ventricular Purkinje system.

MANAGEMENT OF IDIOPATHIC VT

Treatment is required for symptoms or when frequent or incessant arrhythmias depress ventricular function. Beta-adrenergic blockers are first-line therapy. Non-dihydropyridine calcium channel blockers (diltiazem and verapamil) are sometimes effective. Catheter ablation is warranted for severe symptoms or when beta-blockers or calcium channel blockers are not effective or not desired. Efficacy and risks of catheter ablation vary with the specific site of origin of the VT, being most favorable for arrhythmias originating in the right ventricular outflow tract. Failure of ablation is often due to inability to initiate the arrhythmia for mapping in the electrophysiology laboratory.

Left ventricular interfascicular VT can be terminated by intravenous administration of verapamil, although chronic therapy with oral verapamil is not always effective. Catheter ablation is recommended if beta-adrenergic blockers or calcium channel blockers are ineffective or not desired.

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250 Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

Roy M. John, William G. Stevenson

POLYMORPHIC VENTRICULAR TACHYCARDIA (VT)

Sustained polymorphic VT can be seen with any form of structural heart disease. However, unlike sustained monomorphic VT, polymorphic VT does not always indicate a structural abnormality or focus of automaticity. Reentry with continually changing reentrant paths, spiral wave reentry and multiple automatic foci are potential mechanisms **(Chap. A9)**. Sustained polymorphic VT usually degenerates into ventricular fibrillation (VF). Polymorphic VT is typically seen in association with acute myocardial infarction or ischemia (MI), ventricular hypertrophy, and a number of genetic mutations that affect cardiac ion channels **(see Table 249-1)**.

Polymorphic VT Associated with Acute Myocardial Infarction/Ischemia Acute MI or ischemia is a common cause of polymorphic VT and should be the initial consideration in management. Approximately 10% of patients with acute MI develop VT that degenerates to VF, likely related to reentry through the infarct border zone. The risk is greatest in the first hour of acute MI. Following defibrillation as per the Advanced Cardiac Life Support (ACLS) guidelines, management is as for acute MI **(Chap. 269)**. Beta-adrenergic blockers, correction of electrolyte abnormalities, and prompt myocardial reperfusion are required. Repeated episodes of polymorphic VT suggest ongoing MI and warrant assessment of adequacy of myocardial reperfusion. Polymorphic VT and VF that occur within the first 48 h of acute MI are associated with greater in-hospital mortality, but those that survive past hospital discharge are not at increased risk for arrhythmic

sudden death. Long-term therapy for post-infarct ventricular arrhythmia is determined by residual left ventricular (LV) function with an implantable cardioverter defibrillator (ICD) being indicated for persistent severe left ventricular (LV) dysfunction (LV ejection fraction <0.35).

Repolarization Abnormalities and Genetic Arrhythmia Syndromes

ACQUIRED LONG QT Abnormal prolongation of the QT interval is associated with the polymorphic VT *torsades des pointes* (Fig. 250-1). The VT often has a characteristic initiation sequence of a premature ventricular beat that induces a pause, followed by a sinus beat that has a longer QT interval and interruption of the T-wave by the premature ventricular contraction (PVC) that is the first beat of the polymorphic VT. This characteristic initiation is termed "pause-dependent" (Fig. 250-1). Causes of QT prolongation include electrolyte abnormalities, bradycardia, and a number of medications that block repolarizing potassium currents, notably the antiarrhythmic drugs sotalol, dofetilide, and ibutilide, but also a number of other medications used for non-cardiac diseases, including erythromycin, pentamidine, haloperidol, phenothiazines, and methadone (Table 250-1). Individual susceptibility may be related to genetic polymorphisms or mutations that influence repolarization.

Patients typically present with near-syncope, syncope, or cardiac arrest. Sustained episodes degenerate to VF requiring defibrillation. PVCs and non-sustained VT often precede episodes of sustained VT. Intravenous administration of 1–2 g of magnesium sulphate, usually suppresses recurrent episodes. If magnesium alone is ineffective, increasing heart rate with isoproterenol infusion or pacing, to a rate of 100–120 depolarizations/min as required to suppress PVCs, usually suppresses VT recurrences. These maneuvers allow time for correction of associated electrolyte disturbance (hypokalemia and hypocalcemia) and bradycardia and removal of any causative drugs (Table 250-1). Drug interactions that elevate levels of the offending agent are often a precipitating factor. Patients who experience a polymorphic VT induced by QT prolongation should be considered to have a susceptibility to the arrhythmia, and should avoid all future exposure to medications known to prolong the QT interval.

CONGENITAL LONG QT SYNDROME The congenital long QT syndrome (LQTS) is caused by mutations in genes coding for cardiac ion channels responsible for ventricular repolarization. The corrected QT (QTc) is typically prolonged to >440 ms in men and 460 ms in women. Symptoms are due to *torsades des pointes* VT (Fig. 250-1). Several forms of congenital LQTS have been identified, but three groups of mutations that lead to LQT-1, LQT-2 or LQT-3 syndromes account for 90% of cases. The most frequently encountered mutations, LQTS 1 and 2, are due to abnormalities of potassium channels, but mutations affecting the sodium channel (LQTS-3) and calcium channels have also been described (Table 250-1).

Typical presentation is with syncope or cardiac arrest, usually during childhood. In LQTS-1, episodes tend to occur during exertion, particularly swimming. In LQTS-2, sudden auditory stimuli or emotional upset predispose to events. In LQTS-3, sudden death tends to occur during sleep. Asymptomatic patients may be discovered in the course of family screening or on a routine ECG. Genotyping can be helpful for family screening and to provide reassurance regarding the diagnosis. Correlations of genotype with risk and response to therapy are beginning to emerge. In most patients with LQT-1 or LQT-2, adequate doses of beta-blocker therapy (the non-selective agents nadolol or propranolol are favored) are sufficient protection from arrhythmia episodes. Markers of increased risk include QTc interval exceeding 0.5 s, female gender, and a history of syncope or cardiac arrest. Recurrent syncope despite beta-blocker therapy or a high-risk profile merits consideration of an ICD. Avoidance of QT prolonging drugs is critical for all patients with the LQTS including those who are genotype positive, but have normal QT intervals.

SHORT QT SYNDROME Short QT syndrome is very rare compared to the LQTS. The QTc is shorter than 0.36, and usually less than 0.3 s. The genetic abnormality causes a gain of function of the potassium channel (I_{Kr}) or reduced inward depolarizing currents. The abnormality is associated with atrial fibrillation, polymorphic VT, and sudden death.

BRUGADA SYNDROME Brugada syndrome is a rare syndrome characterized by >0.2 mV of ST segment elevation with a coved ST segment

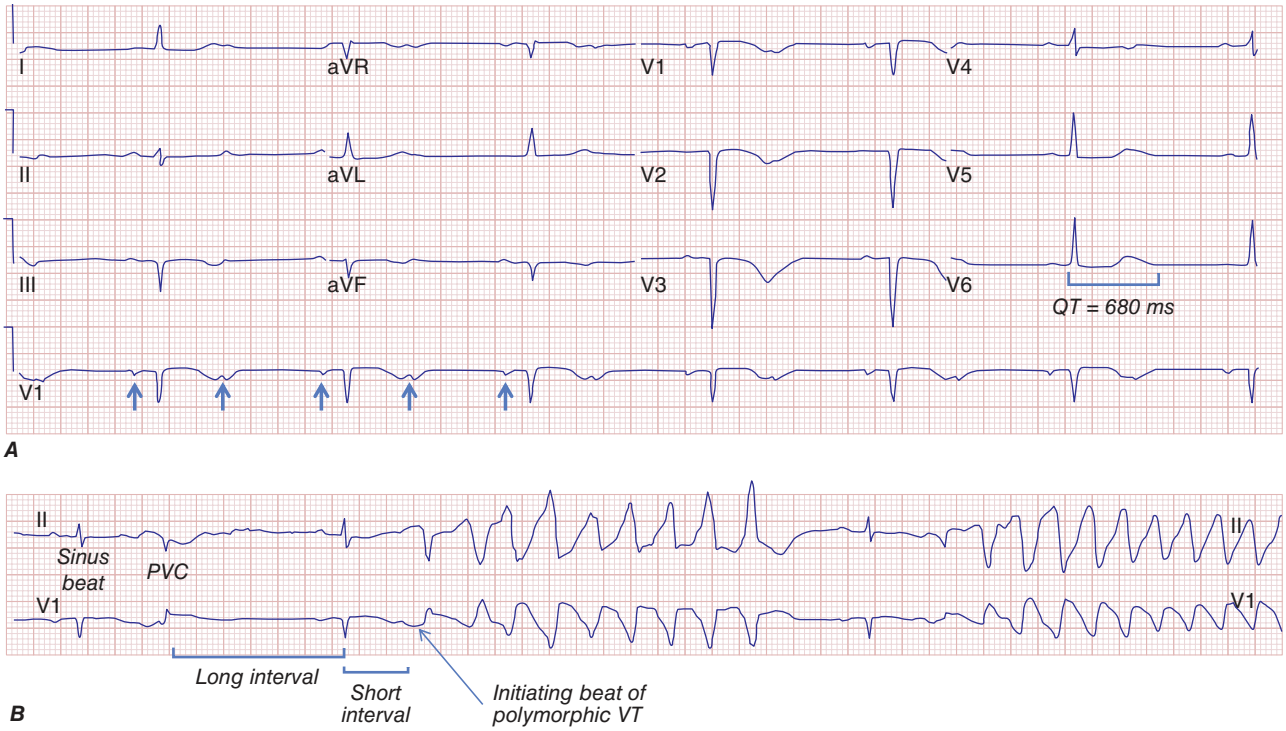

FIGURE 250-1 ***Torsades des pointes*** **VT in patient with bradycardia and marked QT prolongation.** ***A.*** 12-lead ECG showing 2:1 AV block (*P waves marked by blue arrows*) with heart rate of 40 bpm and QT interval of 680 ms and corrected QT of 550 ms. ***B.*** The bottom panel shows a telemetry rhythm strip with periods of self-limiting *torsades des pointes* polymorphic VT. Following a normally conducted sinus beat, a premature ventricular contraction (PVC) causes a compensatory pause leading to a long RR interval. A PVC after the next sinus beat initiates VT. This is the classic "pause dependent" mode of initiation of *torsades des pointes* VT with long–short intervals. VT, ventricular tachycardia.

TABLE 250-1 Causes of QT Prolongation and *Torsade de Pointes* Ventricular Tachycardia (VT)

1. Congenital long QT syndromes (see text for details)
   - Long QT syndrome type 1: Reduced repolarizing current I_{Ks} due to mutation in *KCNQ1* gene
   - Long QT syndrome type 2: Reduced repolarizing current I_{Kr} due to mutation in *KCNH2* gene
   - Long QT syndrome type 3: Delayed inactivation of the I_{Na} due to mutations in *SCN5A* gene
   - Others: Several other types of Long QT syndromes have been described; long QT types 1, 2, and 3 account for 80–90% of cases
2. Acquired Prolongation of QT Interval
   - Electrolyte abnormalities:
     - Hypokalemia
     - Hypomagnesemia
     - Hypocalcemia
   - Drugs:
   - *Antiarrhythmic drugs*
     - Class IA: Quinidine, disopyramide, procainamide
     - Class III: Sotalol, amiodarone (QT prolongation common but torsade VT is rare), ibutilide, dofetilide, almokalant
   - *Antibiotics*
     - Macrolides: Erythromycin, clarithromycin, azithromycin
     - Fluroquinolones: Levofloxacin, moxifloxacin, gatifloxacin,
     - Trimethoprim-sulfamethoxazole
     - Clindamycin
     - Pentamidine
     - Chloroquine
     - Antifungals: Ketoconazole, itraconazole
     - Antivirals: Amantadine
   - *Antipsychotics*
     - Haloperidol, phenothiazines, thioridazine, trifluoperazine, sertindole, zimeldine, ziprasidone
     - Tricyclic and tetracyclic antidepressants
   - *Antihistamines (histamine 1-receptor antagonists)*
     - Terfenadine, astemizole, diphenhydramine, hydroxyzine
   - *Cholinergic antagonists:* Cisapride, organophosphates
   - *Citrate* (massive blood transfusions)
   - *Cocaine*
   - *Methadone*
   - *Fluoxetine* (in conjunction with other drugs that prolong QT)
   - *Cardiac conditions*
     - Myocardial ischemia and infarction
     - Myocarditis
     - Marked bradycardia
     - Stress cardiomyopathy
   - *Endocrine disorders*
     - Hypothyroidism
     - Hyperparathyroidism
     - Pheochromocytoma
     - Hyperaldosteronism
   - *Intracranial disorders*
     - Subarachnoid hemorrhage
     - Thalamic hematoma
     - Cerebrovascular accident
     - Encephalitis
     - Head injury
   - *Nutritional disorders*
     - Anorexia nervosa
     - Starvation
     - Liquid protein diets
     - Gastroplasty and ileojejunal bypass
     - Celiac disease

and negative T-wave in more than one anterior precordial lead (V1–V3) (see Fig. 248-1) and episodes of syncope or cardiac arrest due to polymorphic VT in the absence of structural heart disease. Cardiac arrest may occur during sleep or be provoked by febrile illness. Males are more commonly affected than females. Mutations involving cardiac sodium channels are identified in ~25% of cases. Distinction from patients with similar ST elevation owing to left ventricular hypertrophy, pericarditis, myocardial ischemia or MI hyperkalemia, hypothermia, right bundle branch block and arrhythmogenic right ventricular cardiomyopathy (ARVC) is often difficult. Furthermore, the characteristic ST-segment elevation can wax and wane over time and may become pronounced during acute illness and fever. Administration of the sodium channel blocking drug flecainide, ajmaline, or procainamide can augment or unmask ST elevation in affected individuals. An ICD is indicated for individuals who have had unexplained syncope or been resuscitated from cardiac arrest. Quinidine and catheter ablation of abnormal regions in the epicardial right ventricular (RV) has been used successfully to suppress frequent episodes of VT.

EARLY REPOLARIZATION SYNDROME Patients resuscitated from VF who have no structural heart disease or other identified abnormality have a higher prevalence of J-point elevation with notching in the terminal QRS. A family history of sudden death is present in some patients, suggesting a potential genetic basis. J-point elevation is also seen in some patients with the Brugada syndrome and is associated with a higher risk of arrhythmias. An ICD is recommended for those who have had prior cardiac arrest. It should be noted that J-point elevation is commonly seen as a normal variant in patients without arrhythmias and in the absence of specific symptoms, the clinical relevance is not known.

CATECHOLAMINERGIC POLYMORPHIC VT This rare familial syndrome is due to mutations in the cardiac ryanodine receptor and less commonly, the sarcoplasmic calcium binding protein, calsequestin 2. These mutations result in abnormal sarcoplasmic calcium handling and polymorphic ventricular arrhythmias that resemble those seen with digitalis toxicity. The VT is polymorphic or has a characteristic alternating QRS morphology termed bidirectional VT. Patients usually present during childhood with exercise or emotion induced palpitations, syncope, or cardiac arrest. Beta-adrenergic blockers (e.g., nadolol and propranolol) and an implantable defibrillator are usually recommended. Verapamil or flecainide or surgical left cardiac sympathetic denervation reduces or prevents recurrent VT in some patients.

HYPERTROPHIC CARDIOMYOPATHY (HCM) HCM is the most common genetic cardiovascular disorder occurring in 1 in 500 individuals and is a prominent cause of sudden death before the age of 35 years (Chap. 254). Sudden death can be due to polymorphic VT/VF. Rarely sustained monomorphic VT occurs related to areas of ventricular scar. Risk factors for sudden death in this disease include young age, non-sustained VT, failure of blood pressure to increase during exercise, recent (within 6 months) syncope, ventricular wall thickness >3 cm, and possibly the severity of LV outflow obstruction. An ICD is generally indicated for high-risk subjects, but the specific risk profile warranting an ICD continues to be debated. Surgical myectomy, performed to relieve outflow obstruction has been associated with a sudden death rate of <1% per year. The reported annual rate of sustained VT or sudden death after transcoronary ethanol septal ablation done to relieve outflow obstruction has been reported to range between 1 and 5%.

GENETIC DILATED CARDIOMYOPATHIES Genetic dilated cardiomyopathies account for 30–40% of cases of nonischemic dilated cardiomyopathies. Some are associated with muscular dystrophy. Autosomal dominant, recessive, X-linked, and mitochondrial inheritance patterns are recognized. Mutations in genes coding for structural proteins of the nuclear lamina (Lamin A/C) and the SCN5A gene are particularly associated with conduction system disease and ventricular arrhythmias. They can experience polymorphic VT and cardiac arrest or develop areas of scar causing sustained monomorphic VT. ICDs are recommended for those who have had a sustained VT or are at high risk due to significantly depressed ventricular function (LV ejection

fraction ≤0.35 and associated with heart failure) or a malignant family history of sudden death.

VENTRICULAR FIBRILLATION

VF is characterized by disordered electrical ventricular activation without identifiable QRS complexes **(see Fig. 247-3E)**. Spiral wave reentry and multiple circulating reentry wavefronts are possible mechanisms. Sustained polymorphic or monomorphic VT that degenerates to VF is a common cause of out of hospital cardiac arrest. Treatment follows ACLS guidelines with defibrillation to restore sinus rhythm. If resuscitation is successful, further evaluation is performed to identify and treat underlying heart disease and potential causes of the arrhythmia, including the possibility that monomorphic or polymorphic VT could have initiated VF. If a transient reversible cause such as acute MI is not identified, therapy to reduce the risk of sudden death with an ICD is often warranted. Chronic amiodarone therapy may be considered for individuals who are not ICD candidates.

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251 Electrical Storm and Incessant VT

Roy M. John, William G. Stevenson

ELECTRICAL STORM

Electrical storm or ventricular tachycardia (VT) storm refers to the occurrence of three or more episodes of VT or ventricular fibrillation (VF) within 24 h. This severity of electrical instability is associated with a high mortality and requires prompt therapeutic intervention. Electrical storms occur in 4% of patients with a primary prevention implantable cardioverter defibrillator (ICD) but in as many as 20% of patients with a history of known VT or resuscitated sudden death.

MANAGEMENT OF THE PATIENT WITH ELECTRICAL STORM

Patients should be adequately sedated to allay anxiety. Recurrent VT/VF is treated using standard advanced cardiac life support guidelines and include the use of medications such as beta blockers, amiodarone, lidocaine with correction of any metabolic abnormalities. Recordings from ECG monitoring or an implanted ICD are important to assess whether VT is monomorphic or polymorphic that suggest possible precipitating or aggravating factors. Ischemia should be considered especially if polymorphic VT or VF is identified as the primary arrhythmia. If QT prolongation causing *torsades des pointes* is possible intravenous magnesium should be administered and bradycardia treated. If the QT interval is not prolonged and Brugada syndrome is possible, administration of quinidine and/or isoproterenol may abolish recurrent polymorphic VT/VF episodes. If the above measures fail, general anesthesia should be considered for suppression of recurrent hemodynamically unstable ventricular arrhythmia. Left stellate ganglion block and upper thoracic epidural anesthesia may reduce cardiac sympathetic outflow and have been used to restore stability in some patients. Catheter ablation of PVCs that are observed to repeatedly initiate the arrhythmia can be effective. Rarely, mechanical ventricular support or transplantation may have to be considered.

Once the acute episode is controlled, strategies to prevent recurrent VT or VF should be considered (see below).

INCESSANT VT

VT is designated incessant when VT continues to recur shortly after electrical, pharmacologic, or spontaneous conversion to sinus rhythm **(Fig. 251-1)**. Typically, VT is monomorphic. Rarely, a slow incessant monomorphic VT will fail detection by the ICD because it falls outside of the programmed detection parameters. If the arrhythmia is hemodynamically stable acutely, patients can present with symptoms of gradual cardiac decompensation. VT may become incessant due to the pro-arrhythmic effect of an antiarrhythmic drugs such as amiodarone or a sodium channel blocker such as flecainide. Hemodynamic support may be required until the precipitating factors can be corrected. Urgent catheter ablation is often warranted.

MANAGEMENT OF PATIENTS PRESENTING WITH ICD SHOCKS

A substantial number of patients who receive an ICD can be expected to have an arrhythmia that is terminated by the ICD, either by a shock or antitachycardia pacing. Although this is an expected event, it can be a sign of impending instability, deterioration of cardiac function, emergence of a new arrhythmia or ICD malfunction, and therefore requires evaluation. Interrogation of the ICD is crucial after a patient reports a shock or symptoms of arrhythmia to confirm that the therapy was indeed delivered for a ventricular arrhythmia and not for lead malfunction or an atrial arrhythmia. After a single shock or two successive shocks occurring within a few seconds, and in the absence of other symptoms to suggest arrhythmia or ischemia, patients have the option of waiting until the next working day or using remote monitoring to transmit device interrogation data to their physician. However, occurrence of multiple ICD shocks constitutes a medical emergency and warrants immediate medical attention, usually by summoning emergency medical responders.

Spontaneous arrhythmias, particularly those that are converted with a shock, are associated with a subsequent increased risk of death and hospitalization in patients with depressed ventricular function. The occurrence of an arrhythmia, therefore, warrants a re-evaluation for possible decline in cardiac function, emergence of ischemia or inter-current illness.

If the ICD therapy is appropriate for VT or VF, consideration is given to whether therapy is warranted to reduce further episodes with either antiarrhythmic drug therapy or catheter ablation. Patients who have a rare episode of VT that is appropriately terminated and who have no other evidence of instability may not need any additional therapy, particularly if the VT is terminated by antitachycardia pacing rather than a shock **(see Fig. 247-6)**. Shocks reduce quality of life and can lead to posttraumatic stress disorder. In many patients the possibility of a shock can be reduced with appropriate ICD programming. Studies have shown that antitachycardia pacing effectively terminates >70% of VT episodes, even when VT is very rapid. Most ICDs can be

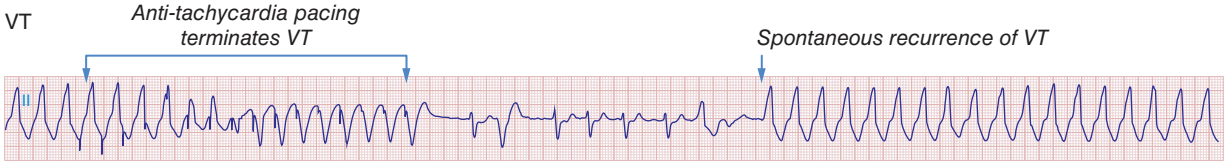

FIGURE 251-1 Example of incessant monomorphic VT. In the initial portion of this ECG tracing, monomorphic VT is present. A train of antitachycardia pacing (*area bracketed by arrows*) that is initiated at the 4th VT complex results in ventricular capture with fusion by the 8th beat and termination of VT at cessation of pacing. The patient has underlying atrial fibrillation. Multifocal PVCs are present. VT similar in morphology to the initial VT restarts spontaneously toward the latter part of the trace (*arrow*). VT, ventricular tachycardia.

programmed to attempt overdrive pace-termination during capacitor charge. If the arrhythmia then terminates, the shock is aborted. Appropriate programming of antitachycardia pacing is therefore critical for reducing shocks. For patients implanted with ICDs as primary prevention, programming of VF detection zones >220 beats/min significantly reduce unnecessary and inappropriate shocks. Long detection times will also help avoid unnecessary therapies for VT episodes liable to terminate spontaneously.

Recurrent symptomatic episodes of VT or VF warrant specific therapy with antiarrhythmic drugs or ablation as discussed for the specific arrhythmia in Chaps. 247–250. Beta blockers sotalol and amiodarone are the most common pharmacological options. Amiodarone combined with beta blockers is more effective than sotalol or beta blockers alone. It is important to recognize that although VT/VF episodes may represent a deterioration of clinical status in these patients, interventions to control the arrhythmia itself may have adverse effects on outcome. Most antiarrhythmic drugs have the potential to induce bradycardia to the point of requiring pacing from the ICD that in itself, may have deleterious effects on ventricular function. Catheter ablation is an important option for patients with monomorphic VT.

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Section 4 Disorders of the Heart

252 Heart Failure: Pathophysiology and Diagnosis

Douglas L. Mann, Murali Chakinala

HEART FAILURE

DEFINITION

Despite repeated attempts to develop a mechanistic definition that encompasses the heterogeneity and complexity of heart failure (HF), no single conceptual paradigm has withstood the test of time. The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to the cardinal clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales. Because many patients present without signs or symptoms of volume overload, the term "heart failure" is preferred over the older term "congestive heart failure."

EPIDEMIOLOGY

HF is a burgeoning problem worldwide, with >20 million people affected. The overall prevalence of HF in the adult population in developed countries is 2%. HF prevalence follows an exponential pattern, rising with age, and affects 6–10% of people aged >65. Although the relative incidence of HF is lower in women than in men, women constitute at least one-half the cases of HF because of their longer life expectancy. In North America and Europe, the lifetime risk of developing HF is approximately one in five for a 40-year-old. The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders, such as myocardial infarction (MI), valvular heart disease, and arrhythmias, are allowing patients to survive longer. The prevalence of HF in emerging nations is uncertain because of the lack of population-based studies in those countries. HF was once thought to arise primarily in the setting of a depressed left ventricular (LV) ejection fraction (EF); however, epidemiologic studies have shown that approximately one-half of patients who develop HF have a normal or preserved EF (EF ≥50%). Accordingly, the historical terms "systolic" and "diastolic" HF have been abandoned, and HF patients are now broadly categorized into HF with a reduced EF (HFrEF; formerly *systolic failure*) or HF with a preserved EF (HRpEF; formerly *diastolic failure*). Patients with a LV EF between 40 and 50% have been considered as having a borderline or mid-range EF. At the time of this writing, the epidemiology of these patients is unclear.

ETIOLOGY

As shown in Table 252-1, any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF. Although the etiology of HF in patients with a preserved EF differs from that of patients with depressed EF, there is considerable overlap between the etiologies of these two conditions. In industrialized countries, coronary artery disease (CAD) has become the predominant cause in men and women and is responsible for 60–75% of cases of HF. Hypertension contributes to the development of HF in 75% of patients, including most patients with CAD. Both CAD and hypertension interact to augment the risk of HF, as does diabetes mellitus.

In 20–30% of the cases of HF with a depressed EF, the exact etiologic basis is not known. These patients are referred to as having nonischemic, dilated, or idiopathic cardiomyopathy if the cause is unknown (Chap. 254). Prior viral infection or toxin exposure (e.g., alcoholic or chemotherapeutic) also may lead to a dilated cardiomyopathy. Moreover, it is becoming increasingly clear that a large number of cases of dilated cardiomyopathy are secondary to specific genetic defects, most notably those in the cytoskeleton. Most forms of familial dilated cardiomyopathy are inherited in an autosomal dominant fashion. Mutations of genes that encode cytoskeletal proteins (desmin, cardiac myosin, vinculin) and nuclear membrane proteins (laminin) have been

TABLE 252-1 Etiologies of Heart Failure

Depressed Ejection Fraction (<40%)	
Coronary artery disease	Nonischemic dilated cardiomyopathy
Myocardial infarction[a]	Familial/genetic disorders
Myocardial ischemia[a]	Infiltrative disorders[a]
Chronic pressure overload	Toxic/drug-induced damage
Hypertension[a]	Metabolic disorder[a]
Obstructive valvular disease[a]	Viral
Chronic volume overload	Chagas' disease
Regurgitant valvular disease	Disorders of rate and rhythm
Intracardiac (left-to-right) shunting	Chronic bradyarrhythmias
Extracardiac shunting	Chronic tachyarrhythmias
Chronic lung disease	
Cor pulmonale	
Pulmonary vascular disorders	
Preserved Ejection Fraction (>40–50%)	
Pathologic hypertrophy	Restrictive cardiomyopathy
Primary (hypertrophic cardiomyopathies)	Infiltrative disorders (amyloidosis, sarcoidosis)
Secondary (hypertension)	Storage diseases (hemochromatosis)
Aging	
Endomyocardial disorders	Fibrosis
High-Output States	
Metabolic disorders	Excessive blood flow requirements
Thyrotoxicosis	Systemic arteriovenous shunting
Nutritional disorders (beriberi)	Chronic anemia

[a]Indicates conditions that can also lead to heart failure with a preserved ejection fraction.

identified thus far. Dilated cardiomyopathy also is associated with Duchenne's, Becker's, and limb-girdle muscular dystrophies. Conditions that lead to a high cardiac output (e.g., arteriovenous fistula, anemia) are seldom responsible for the development of HF in a normal heart; however, in the presence of underlying structural heart disease, these conditions can lead to overt HF.

GLOBAL CONSIDERATIONS

Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause of HF in the African and African-American populations. Chagas' disease is still a major cause of HF in South America. Not surprisingly, anemia is a frequent concomitant factor in HF in many developing nations. As developing nations undergo socioeconomic development, the epidemiology of HF is becoming similar to that of Western Europe and North America, with CAD emerging as the single most common cause of HF. Although the contribution of diabetes mellitus to HF is not well understood, diabetes accelerates atherosclerosis and often is associated with hypertension.

PROGNOSIS

Despite recent advances in the management of HF, the development of symptomatic HF still carries a poor prognosis. Community-based studies indicate that 30–40% of patients die within 1 year of diagnosis and 60–70% die within 5 years, mainly from worsening HF or as a sudden event (probably because of a ventricular arrhythmia). Although it is difficult to predict prognosis in an individual, patients with symptoms at rest (New York Heart Association [NYHA] class IV) have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5–10%. Thus, functional status is an important predictor of patient outcome **(Table 252-2)**.

PATHOGENESIS

Figure 252-1 provides a conceptual framework for considering the development and progression of HFrEF. HF is a progressive disorder that is initiated after an *index event* either damages the heart muscle, with a resultant loss of functioning cardiac myocytes, or, alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally. This index event may have an abrupt onset, as in the case of an MI; it may have a gradual or insidious onset, as in the case of hemodynamic pressure or volume overloading; or it may be hereditary, as in the case of many of the genetic cardiomyopathies. Regardless of the nature of the inciting event, the feature that is common to each of these index events is that they all in some manner produce a decline in the pumping capacity of the heart. In most instances, patients remain asymptomatic or minimally symptomatic after the initial decline in pumping capacity of the heart or develop symptoms only after the dysfunction has been present for some time.

TABLE 252-2 New York Heart Association Classification

FUNCTIONAL CAPACITY	OBJECTIVE ASSESSMENT
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: Adapted from New York Heart Association, Inc., *Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis*, 6th ed. Boston, Little Brown, 1964, p. 114.

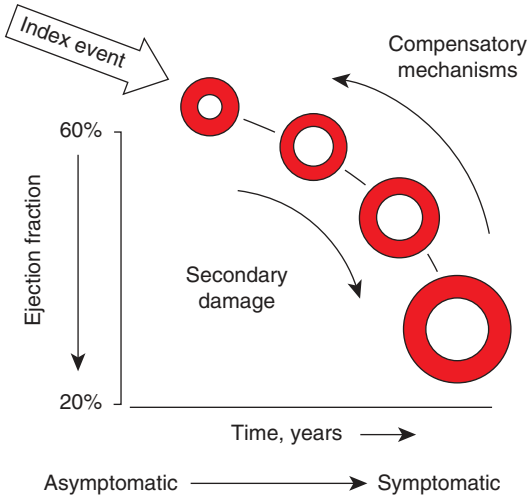

FIGURE 252-1 Pathogenesis of heart failure with a depressed ejection fraction. Heart failure begins after an index event produces an initial decline in the heart's pumping capacity. After this initial decline in pumping capacity, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin-aldosterone system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range with the result that the patient remains asymptomatic. However, sustained activation of these systems leads to secondary end-organ damage within the ventricle, with worsening left ventricular remodeling and subsequent cardiac decompensation. *(From D Mann: Circulation 100:999, 1999.)*

Although the precise reasons why patients with LV dysfunction may remain asymptomatic is not certain, one potential explanation is that a number of compensatory mechanisms become activated in the presence of cardiac injury and/or LV dysfunction allowing patients to sustain and modulate LV function for a period of months to years. The compensatory mechanisms that have been described thus far include (1) activation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic nervous system, which are responsible, respectively, for maintaining cardiac output through increased retention of salt and water **(Fig. 252-2)** and (2) increased myocardial contractility. In addition, a family of countervailing vasodilatory molecules are activated, including the atrial and brain natriuretic peptides (ANP and BNP), bradykinin, prostaglandins (PGE_2 and PGI_2), and nitric oxide (NO), that offset the excessive peripheral vascular vasoconstriction. Many of these vasodilatory peptides, including bradykinin and natriuretic peptides, are degraded by a neprilysin, which is a membrane-bound peptidase. These compensatory mechanisms are able to modulate LV function within a physiologic/homeostatic range so that the functional capacity of the patient is preserved or is minimally depressed. Thus, patients may remain asymptomatic or minimally symptomatic for a period of years; however, at some point patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality rates. Although the exact mechanisms that are responsible for this transition are not known, as will be discussed below, the transition to symptomatic HF is accompanied by increasing activation of neurohormonal, adrenergic, and cytokine systems that lead to a series of adaptive changes within the myocardium collectively referred to as *LV remodeling*.

In contrast to our understanding of the pathogenesis of HF with a depressed EF, our understanding of the mechanisms that contribute to the development of HF with a preserved EF is still evolving. That is, although diastolic dysfunction (see below) was thought to be the only mechanism responsible for the development of HF with a preserved EF, community-based studies suggest that additional extracardiac mechanisms may be important, such as increased vascular stiffness and impaired renal function.

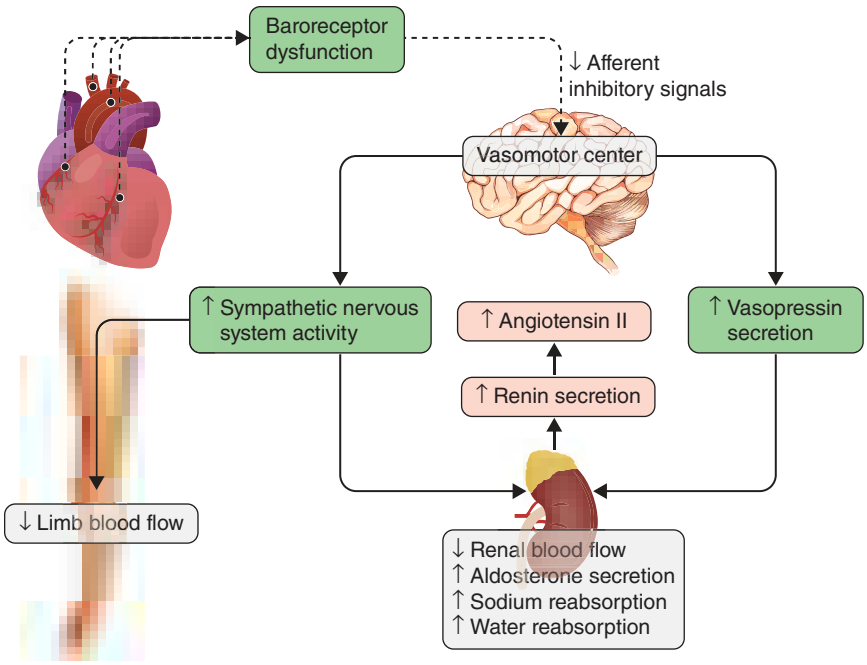

FIGURE 252-2 Activation of neurohormonal systems in heart failure. The decreased cardiac output in heart failure (HF) patients results in an "unloading" of high-pressure baroreceptors (*circles*) in the left ventricle, carotid sinus, and aortic arch. This unloading of the peripheral baroreceptors leads to a loss of inhibitory parasympathetic tone to the central nervous system (CNS), with a resultant generalized increase in efferent sympathetic tone, and nonosmotic release of arginine vasopressin (AVP) from the pituitary. AVP (or antidiuretic hormone [ADH]) is a powerful vasoconstrictor that increases the permeability of the renal collecting ducts, leading to the reabsorption of free water. These afferent signals to the CNS also activate efferent sympathetic nervous system pathways that innervate the heart, kidney, peripheral vasculature, and skeletal muscles.

Sympathetic stimulation of the kidney leads to the release of renin, with a resultant increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system promotes salt and water retention and leads to vasoconstriction of the peripheral vasculature, myocyte hypertrophy, myocyte cell death, and myocardial fibrosis. Although these neurohormonal mechanisms facilitate short-term adaptation by maintaining blood pressure, these same neurohormonal mechanisms result in end-organ changes in the heart and the circulation, as well as to the excessive salt and water retention in advanced HF. *(Modified from A Nohria et al: Atlas of Heart Failure: Cardiac Function and Dysfunction, 4th ed, WS Colucci [ed]. Philadelphia, Current Medicine Group, 2002, p. 104 and J Hartupee, DL Mann: Nat Rev Cardiol 14:30, 2017.)*

BASIC MECHANISMS OF HF

HF with a Reduced Ejection Fraction LV remodeling develops in response to a series of complex events that occur at the cellular and molecular levels **(Table 252-3)**. These changes include (1) myocyte hypertrophy; (2) alterations in the contractile properties of the myocyte; (3) progressive loss of myocytes through necrosis, apoptosis, and autophagic cell death; (4) β-adrenergic desensitization; (5) abnormal myocardial energetics and metabolism; and (6) reorganization of the extracellular matrix with dissolution of the organized structural collagen weave surrounding myocytes and subsequent replacement by an interstitial collagen matrix that does not provide structural support to the myocytes. The biologic stimuli for these profound changes include mechanical stretch of the myocyte, circulating neurohormones (e.g., norepinephrine, angiotensin II), inflammatory cytokines (e.g., tumor necrosis factor [TNF]), other peptides and growth factors (e.g., endothelin), and reactive oxygen species (e.g., superoxide). The sustained overexpression of these biologically active molecules contributes to the progression of HF by virtue of the deleterious effects they exert on the heart and the circulation. Indeed, this insight forms the clinical rationale for using pharmacologic agents that antagonize these systems (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor-neprilysin inhibitors [ARNIs] and beta blockers) in treating patients with HF **(Chap. 253)**.

To understand how the changes that occur in the failing cardiac myocyte contribute to depressed LV systolic function in HF, it is instructive first to review the biology of the cardiac muscle cell **(Chap. 232)**. Sustained neurohormonal activation and mechanical overload result in transcriptional and posttranscriptional changes in the genes and proteins that regulate excitation-contraction coupling and cross-bridge interaction **(see Figs. 232-6 and 232-7)**. The changes that regulate excitation-contraction include decreased function of sarcoplasmic reticulum (SR) Ca^{2+} adenosine triphosphatase (SERCA2A), resulting in decreased calcium uptake into the SR, and hyperphosphorylation of the ryanodine receptor, leading to calcium leakage from the SR. The changes that occur in the cross-bridges include decreased expression of α-myosin heavy chain and increased expression of β-myosin heavy chain, myocytolysis, and disruption of the cytoskeletal links between the sarcomeres and the extracellular matrix. Collectively, these changes impair the ability of the myocyte to contract and therefore contribute to the depressed LV systolic function observed in patients with HF.

Myocardial relaxation is an adenosine triphosphate (ATP)-dependent process that is regulated by uptake of cytoplasmic calcium into the SR by SERCA2A and extrusion of calcium by sarcolemmal pumps **(see Fig. 232-7)**. Accordingly, reductions in ATP concentration, as occurs in ischemia, may interfere with these processes and lead to slowed myocardial relaxation. Alternatively, if LV filling is delayed because LV compliance is reduced (e.g., from hypertrophy or fibrosis), LV filling pressures will similarly remain elevated at end diastole **(see Fig. 232-11)**. An increase in heart rate disproportionately shortens the time for diastolic filling, which may lead to elevated LV filling pressures, particularly in noncompliant ventricles. Elevated LV end-diastolic filling pressures result in increases in pulmonary capillary pressures, which can contribute to the dyspnea experienced by patients with diastolic dysfunction. In addition to impaired myocardial relaxation, increased

TABLE 252-3 Overview of Left Ventricular Remodeling

Alterations in Myocyte Biology
Excitation-contraction coupling
Myosin heavy chain (fetal) gene expression
β-Adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins
Myocardial Changes
Myocyte loss
Necrosis
Apoptosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Myocardial fibrosis
Alterations in Left Ventricular Chamber Geometry
Left ventricular (LV) dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

Source: Adapted from D. Mann: Pathophysiology of heart failure, in *Braunwald's Heart Disease,* 8th ed, PL Libby et al (eds). Philadelphia, Elsevier, 2008, p. 550.

myocardial stiffness secondary to cardiac hypertrophy and increased myocardial collagen content may contribute to diastolic failure. Importantly, diastolic dysfunction can occur alone or in combination with systolic dysfunction in patients with HF.

Left Ventricular Remodeling *Ventricular remodeling* refers to the changes in LV mass, volume, and shape and the composition of the heart that occur after cardiac injury and/or abnormal hemodynamic loading conditions. LV remodeling contributes to the progression of HF by virtue of the mechanical burdens that are engendered by the changes in the geometry of the remodeled LV. In addition to the increase in LV end-diastolic volume, LV wall thinning occurs as the left ventricle begins to dilate. The increase in wall thinning, along with the increase in afterload created by LV dilation, leads to a functional *afterload mismatch* that may contribute further to a decrease in stroke volume. Moreover, the high end-diastolic wall stress might be expected to lead to (1) hypoperfusion of the subendocardium, with resultant worsening of LV function; (2) increased oxidative stress, with the resultant activation of families of genes that are sensitive to free radical generation (e.g., TNF and interleukin 1β); and (3) sustained expression of stretch activation of hypertrophic signaling pathways. Increasing LV dilation also results in tethering of the papillary muscles with resulting incompetence of the mitral valve apparatus and functional mitral regurgitation, which in turn leads to further hemodynamic overloading of the ventricle. Taken together, the mechanical burdens that are engendered by LV remodeling contribute to the progression of HF. Recent studies have shown that LV remodeling can be reversed following medical and device therapy and that reverse LV remodeling is associated with improved clinical outcomes in patients with HFrEF. Indeed, one of the goals of therapy for HF is to prevent and/or reverse LV remodeling.

CLINICAL MANIFESTATIONS

Symptoms The cardinal symptoms of HF are fatigue and shortness of breath. Although fatigue traditionally has been ascribed to the low cardiac output in HF, it is likely that skeletal-muscle abnormalities and other noncardiac comorbidities (e.g., anemia) also contribute to this symptom. In the early stages of HF, dyspnea is observed only during exertion; however, as the disease progresses, dyspnea occurs with less strenuous activity, and it ultimately may occur even at rest. The origin of dyspnea in HF is probably multifactorial **(Chap. 33)**. The most important mechanism is pulmonary congestion with accumulation of interstitial or intra-alveolar fluid, which activates juxtacapillary J receptors, which in turn stimulate the rapid, shallow breathing characteristic of cardiac dyspnea. Other factors that contribute to dyspnea on exertion include reductions in pulmonary compliance, increased airway resistance, respiratory muscle and/or diaphragm fatigue, and anemia. Dyspnea may become less frequent with the onset of right ventricular (RV) failure and tricuspid regurgitation.

ORTHOPNEA Orthopnea, which is defined as dyspnea occurring in the recumbent position, is usually a later manifestation of HF than is exertional dyspnea. It results from redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbency, with a resultant increase in pulmonary capillary pressure. Nocturnal cough is a common manifestation of this process and a frequently overlooked symptom of HF. Orthopnea generally is relieved by sitting upright or sleeping with additional pillows. Although orthopnea is a relatively specific symptom of HF, it may occur in patients with abdominal obesity or ascites and patients with pulmonary disease whose lung mechanics favor an upright posture.

PAROXYSMAL NOCTURNAL DYSPNEA (PND) This term refers to acute episodes of severe shortness of breath and coughing that generally occur at night and awaken the patient from sleep, usually 1–3 h after the patient retires. PND may manifest as coughing or wheezing, possibly because of increased pressure in the bronchial arteries leading to airway compression, along with interstitial pulmonary edema that leads to increased airway resistance. Whereas orthopnea may be relieved by sitting upright at the side of the bed with the legs in a dependent position, patients with PND often have persistent coughing and wheezing even after they have assumed the upright position. *Cardiac asthma* is closely related to PND, is characterized by wheezing secondary to bronchospasm, and must be differentiated from primary asthma and pulmonary causes of wheezing.

CHEYNE-STOKES RESPIRATION Also referred to as periodic respiration or cyclic respiration, Cheyne-Stokes respiration is present in 40% of patients with advanced HF and usually is associated with low cardiac output. Cheyne-Stokes respiration is caused by an increased sensitivity of the respiratory center to arterial Pco_2 and a lengthy circulatory time. There is an apneic phase, during which arterial Po_2 falls and arterial Pco_2 rises. These changes in the arterial blood gas content stimulate the respiratory center, resulting in hyperventilation and hypocapnia, followed by recurrence of apnea.

ACUTE PULMONARY EDEMA See Chap. 298.

Other Symptoms Patients with HF also may present with gastrointestinal symptoms. Anorexia, nausea, and early satiety associated with abdominal pain and fullness are common complaints and may be related to edema of the bowel wall and/or a congested liver. Congestion of the liver and stretching of its capsule may lead to right upper-quadrant pain. Cerebral symptoms such as confusion, disorientation, and sleep and mood disturbances may be observed in patients with severe HF, particularly elderly patients with cerebral arteriosclerosis and reduced cerebral perfusion. Nocturia is common in HF and may contribute to insomnia.

PHYSICAL EXAMINATION

A careful physical examination is always warranted in the evaluation of patients with HF, in order to determine the cause of HF, as well as to assess the severity of the syndrome.

General Appearance and Vital Signs In mild or moderately severe HF, the patient appears to be in no distress at rest except for feeling uncomfortable when lying flat for more than a few minutes. In more severe HF, the patient must sit upright, may have labored breathing, and may not be able to finish a sentence because of shortness of breath. Systolic blood pressure may be normal or high in early HF, but it generally is reduced in advanced HF because of severe LV dysfunction. The pulse pressure may be diminished, reflecting a reduction in stroke volume. Sinus tachycardia is a nonspecific sign caused by increased adrenergic activity. Peripheral vasoconstriction leading to cool peripheral extremities and cyanosis of the lips and nail beds is also caused by excessive adrenergic activity.

Jugular Veins (See also Chap. 234) Examination of the jugular veins provides an estimation of right atrial pressure. The jugular venous pressure is best appreciated with the patient lying recumbent, with the head tilted at 45°. The jugular venous pressure should be quantified in centimeters of water (normal ≤8 cm) by estimating the height of the venous column of blood above the sternal angle in centimeters and then adding 5 cm. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated with sustained (~15 s) pressure on the abdomen (positive abdominojugular reflux). Giant *v* waves indicate the presence of tricuspid regurgitation.

Pulmonary Examination Pulmonary crackles (rales or crepitations) result from the transudation of fluid from the intravascular space into the alveoli. In patients with pulmonary edema, rales may be heard widely over both lung fields and may be accompanied by expiratory wheezing (cardiac asthma). When present in patients without concomitant lung disease, rales are specific for HF. Importantly, rales are frequently absent in patients with chronic HF, even when LV filling pressures are elevated, because of increased lymphatic drainage of alveolar fluid. Pleural effusions result from the elevation of pleural capillary pressure and the resulting transudation of fluid into the pleural cavities. Since the pleural veins drain into both the systemic and the pulmonary veins, pleural effusions occur most commonly with biventricular failure. Although pleural effusions are often bilateral in HF, when they are unilateral, they occur more frequently in the right pleural space.

Cardiac Examination Examination of the heart, although essential, frequently does not provide useful information about the severity of HF. If cardiomegaly is present, the point of maximal impulse (PMI) usually is displaced below the fifth intercostal space and/or lateral to the midclavicular line, and the impulse is palpable over two interspaces. Severe LV hypertrophy leads to a sustained PMI. In some patients, a third heart sound (S_3) is audible and palpable at the apex. Patients with enlarged or hypertrophied right ventricles may have a sustained and prolonged left parasternal impulse extending throughout systole. An S_3 (or *protodiastolic gallop*) is most commonly present in patients with volume overload who have tachycardia and tachypnea, and it often signifies severe hemodynamic compromise. A fourth heart sound (S_4) is not a specific indicator of HF but is usually present in patients with diastolic dysfunction. The murmurs of mitral and tricuspid regurgitation are frequently present in patients with advanced HF.

Abdomen and Extremities Hepatomegaly is an important sign in patients with HF. When it is present, the enlarged liver is frequently tender and may pulsate during systole if tricuspid regurgitation is present. Ascites, a late sign, occurs as a consequence of increased pressure in the hepatic veins and the veins draining the peritoneum. Jaundice, also a late finding in HF, results from impairment of hepatic function secondary to hepatic congestion and hepatocellular hypoxemia and is associated with elevations of both direct and indirect bilirubin.

Peripheral edema is a cardinal manifestation of HF, but it is nonspecific and usually is absent in patients who have been treated adequately with diuretics. Peripheral edema is usually symmetric and dependent in HF and occurs predominantly in the ankles and the pretibial region in ambulatory patients. In bedridden patients, edema may be found in the sacral area (*presacral edema*) and the scrotum. Long-standing edema may be associated with indurated and pigmented skin.

Cardiac Cachexia With severe chronic HF, there may be marked weight loss and cachexia. Although the mechanism of cachexia is not entirely understood, it is probably multifactorial. When present, cachexia augurs a poor overall prognosis.

DIAGNOSIS

The diagnosis of HF is relatively straightforward when the patient presents with classic signs and symptoms of HF; however, the signs and symptoms of HF are neither specific nor sensitive. Accordingly, the key to making the diagnosis is to have a high index of suspicion, particularly for high-risk patients. When these patients present with signs or symptoms of HF, additional laboratory testing should be performed.

Routine Laboratory Testing Patients with new-onset HF and those with chronic HF and acute decompensation should have a complete blood count, a panel of electrolytes, blood urea nitrogen, serum creatinine, hepatic enzymes, and a urinalysis. Selected patients should have assessment for diabetes mellitus (fasting serum glucose or oral glucose tolerance test), dyslipidemia (fasting lipid panel), and thyroid abnormalities (thyroid-stimulating hormone level).

Electrocardiogram (ECG) A routine 12-lead ECG is recommended. The major importance of the ECG is to assess cardiac rhythm and determine the presence of LV hypertrophy or a prior MI (presence or absence of Q-waves) as well as to determine QRS width to ascertain whether the patient may benefit from resynchronization therapy (see below). A normal ECG virtually excludes LV systolic dysfunction.

Chest X-Ray A chest x-ray provides useful information about cardiac size and shape, as well as the state of the pulmonary vasculature, and may identify noncardiac causes of the patient's symptoms. Although patients with acute HF have evidence of pulmonary hypertension, interstitial edema, and/or pulmonary edema, the majority of patients with chronic HF do not. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid.

Assessment of LV Function Noninvasive cardiac imaging (Chap. 236) is essential for the diagnosis, evaluation, and management of HF. The most useful test is the two-dimensional (2-D) echocardiogram/Doppler, which can provide a semiquantitative assessment of LV size and function as well as the presence or absence of valvular and/or regional wall motion abnormalities (indicative of a prior MI). The presence of left atrial dilation and LV hypertrophy, together with abnormalities of LV diastolic filling provided by pulse-wave and tissue Doppler, is useful for the assessment of HF with a preserved EF. The 2-D echocardiogram/Doppler is also invaluable in assessing RV size and pulmonary pressures, which are critical in the evaluation and management of cor pulmonale (see below). Magnetic resonance imaging (MRI) also provides a comprehensive analysis of cardiac anatomy and function and is now the gold standard for assessing LV mass and volumes. MRI also is emerging as a useful and accurate imaging modality for evaluating patients with HF, both in terms of assessing LV structure and for determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, hemochromatosis).

The most useful index of LV function is the EF (stroke volume divided by end-diastolic volume). Because the EF is easy to measure by noninvasive testing and easy to conceptualize, it has gained wide acceptance among clinicians. Unfortunately, the EF has a number of limitations as a true measure of contractility, since it is influenced by alterations in afterload and/or preload. Nonetheless, with the exceptions indicated above, when the EF is normal (≥50%), systolic function is usually adequate, and when the EF is significantly depressed (<30–40%), contractility is usually depressed. Myocardial strain rate imaging using speckle tracking has been shown to add incremental value to standard measurements of LV EF and to have prognostic value.

Biomarkers Circulating levels of natriuretic peptides are useful and important adjunctive tools in the diagnosis of patients with HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP), which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF; they also are elevated in HF patients with a preserved EF, albeit to a lesser degree. In ambulatory patients with dyspnea, the measurement of BNP or NT-proBNP is useful to support clinical decision-making regarding the diagnosis of HF, especially in the setting of clinical uncertainty. Moreover, the measurement of BNP or NT-proBNP is useful for establishing prognosis or disease severity in chronic HF and can be useful to achieve optimal dosing of medical therapy in select clinically euvolemic patients. However, it is important to recognize that natriuretic peptide levels increase with age and renal impairment, are more elevated in women, and can be elevated in right HF from any cause. BNP levels may increase in patients taking ARNIs. Levels can be falsely low in obese patients. Other biomarkers, such as soluble ST-2 and galectin-3, are newer biomarkers that can be used for determining the prognosis of HF patients.

Exercise Testing Treadmill or bicycle exercise testing is not routinely advocated for patients with HF, but either is useful for assessing the need for cardiac transplantation in patients with advanced HF (Chap. 255). A peak oxygen uptake (vo_2) <14 mL/kg per min is associated with a relatively poor prognosis. Patients with a vo_2 <14 mL/kg per min have been shown, in general, to have better survival when transplanted than when treated medically.

DIFFERENTIAL DIAGNOSIS

HF resembles but should be distinguished from (1) conditions in which there is circulatory congestion secondary to abnormal salt and water retention but in which there is no disturbance of cardiac structure or function (e.g., renal failure), and (2) noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome). In most patients who present with classic signs and symptoms of HF, the diagnosis is relatively straightforward. However, even experienced clinicians have difficulty differentiating the dyspnea that arises from cardiac and pulmonary causes (Chap. 33). In this regard, noninvasive cardiac imaging, biomarkers, pulmonary function testing, and chest x-ray may be useful. A very low BNP or NT-proBNP may be helpful in excluding a cardiac cause of dyspnea in this setting. Ankle edema may arise secondary to varicose veins, obesity, renal disease, or gravitational effects. When HF develops in patients with a preserved EF, it may be difficult to

determine the relative contribution of HF to the dyspnea that occurs in chronic lung disease and/or obesity.

COR PULMONALE

DEFINITION

Cor pulmonale, also referred to as *pulmonary heart disease*, is broadly defined by altered RV structure and/or function in the context of chronic lung disease and is triggered by the presence of pulmonary hypertension. Although RV dysfunction is an important sequela of HFpEF and HFrEF, this is not considered as cor pulmonale.

ETIOLOGY AND EPIDEMIOLOGY

Chronic cor pulmonale develops in response to chronic pulmonary hypertension resulting from parenchymal lung disorders, primary pulmonary vascular diseases, or conditions leading to alveolar hypoxia (Table 252-4). The true prevalence of cor pulmonale is difficult to ascertain. First, not all patients with chronic lung disease will develop cor pulmonale, which may be subclinical in compensated individuals. Second, the ability to detect pulmonary hypertension and cor pulmonale by routine physical examination and laboratory testing is relatively insensitive. However, advances in 2-D echo/Doppler imaging and biomarkers (BNP) can make it easier to identify.

Once susceptible patients develop cor pulmonale, their prognosis worsens, regardless of the underlying etiology. Although chronic obstructive pulmonary disease (COPD) and chronic bronchitis are responsible for ~50% of the cases of cor pulmonale in North America (Chap. 286), any disease that affects the pulmonary vasculature (Chap. 277) or parenchyma can lead to cor pulmonale (Table 252-4). Primary pulmonary vascular disorders, such as pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, are relatively rare causes of cor pulmonale, but cor pulmonale is extremely common with these conditions, given the magnitude of elevated pulmonary artery pressures and pulmonary vascular resistance.

TABLE 252-4 Etiology of Chronic Cor Pulmonale

Diseases of the Lung Parenchyma
Chronic obstructive pulmonary disease
Emphysema
Chronic bronchitis
Interstitial lung diseases
Idiopathic interstitial pneumonias (e.g., IPF, UIP)
Secondary interstitial diseases
Sarcoidosis
Combined pulmonary fibrosis and emphysema
Bronchiectasis
Cystic fibrosis
Pulmonary Langerhans cell histiocytosis
Lymphangioleiomyomatosis
Developmental lung disorders
Disorders of Chronic (Alveolar) Hypoxia
Alveolar hypoventilation syndromes
Obesity hypoventilation syndrome
Central hypoventilation syndrome
Neuromuscular respiratory failure
Chest wall disorders
Kyphoscoliosis
Chronic exposure to high altitude
Diseases of the Pulmonary Vasculature
Pulmonary arterial hypertension (PAH)
Idiopathic PAH
Heritable PAH
Drug and toxin-induced
Associated PAH
Venoocclusive disease
Chronic thromboembolic pulmonary hypertension
Pulmonary tumor thrombotic microangiopathy
Mediastinal disorders affecting central pulmonary vasculature

Abbreviations: IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonitis.

PATHOPHYSIOLOGY AND BASIC MECHANISMS

Although many conditions can lead to cor pulmonale, the common pathophysiologic mechanism is pulmonary hypertension and increased RV afterload sufficient to alter RV structure (i.e., dilation with or without hypertrophy) and function. Normally, mean pulmonary artery pressure is only ~15 mmHg and does not increase significantly even with increasing multiples of cardiac output, because of pulmonary vasodilation and blood vessel recruitment in the pulmonary circulatory bed. But, in the setting of parenchymal lung diseases, primary pulmonary vascular disorders, or chronic (alveolar) hypoxia, the circulatory bed undergoes vascular remodeling, vasoconstriction, and destruction. As a result, pulmonary artery pressures and RV afterload increases, setting the stage for cor pulmonale (Table 252-4). The systemic consequences of cor pulmonale relate to alterations in cardiac output as well as salt and water homeostasis. Anatomically, the RV is a thin-walled, compliant chamber better suited to handle volume overload than pressure overload. Thus, the sustained pressure overload eventually leads to RV dysfunction and failure.

The response of the RV to pulmonary hypertension depends on the acuteness and severity of the pressure overload. Acute cor pulmonale occurs after a sudden and severe stimulus (e.g., massive pulmonary embolus), with RV dilatation and failure but no RV hypertrophy (Chap. 273). Chronic cor pulmonale, however, evolves slowly and in conjunction with modest, compensatory RV hypertrophy that lowers wall tension and preserves RV function. Over time, RV dilation ensues leading to an increase in RV wall tension and overt dysfunction. Acute decompensation of compensated chronic cor pulmonale is a common clinical occurrence. Triggers include worsening hypoxia from any cause (e.g., pneumonia), acidemia (e.g., exacerbation of COPD), acute pulmonary embolus, atrial tachyarrhythmia, hypervolemia, and mechanical ventilation that compresses blood vessels associated with alveoli and further increasing RV afterload.

CLINICAL MANIFESTATIONS

Symptoms The symptoms in chronic cor pulmonale generally are related to the underlying pulmonary disorder. Dyspnea, the most common symptom, is usually the result of the increased work of breathing secondary to changes in elastic recoil of the lung (fibrosing lung diseases), altered respiratory mechanics (e.g., over-inflation with COPD), or inefficient ventilation (e.g., primary pulmonary vascular disease). Dyspnea can also be due to cardiovascular limitations with decreased oxygen delivery due to reduced cardiac output. Lower-extremity edema and even increased abdominal girth due to ascites formation occurs secondary to neurohormonal activation, elevated RV filling and right atrial pressures, or increased levels of carbon dioxide and hypoxemia, which can lead to peripheral vasodilation and edema formation.

Signs Auscultation of the heart reveals the findings of pulmonary hypertension (Chap. 33), while auscultation of the lungs can highlight the underlying parenchymal lung disorder. In chronic cor pulmonale, the murmur of tricuspid regurgitation, an S_3 gallop and a RV heave palpable along the left sternal border can be appreciated. But the most blatant findings are reflective of high right-sided filling pressures and hypervolemia such as elevated jugular venous pressures with prominent *v* waves indicative of tricuspid regurgitation, hepatomegaly, pulsatile liver, ascites, and especially lower-extremity edema. Cyanosis is a late finding in cor pulmonale and is secondary to a low cardiac output (i.e., cardiogenic shock), systemic vasoconstriction, and hypoxemia.

DIAGNOSIS

It is important to evaluate the patient for LV systolic and diastolic dysfunction as a cause of right-sided HF. The ECG in severe pulmonary hypertension shows P pulmonale, right axis deviation, and RV hypertrophy. Radiographic examination of the chest may show enlargement

of the main central pulmonary arteries and hilar vessels. Spirometry and lung volumes can identify obstructive and/or restrictive defects indicative of parenchymal lung diseases and reduced diffusing capacity; arterial blood gases typically reveal hypoxemia with or without hypercapnia. A high-resolution computed tomography (CT) scan of the chest can identify interstitial lung disease and the extent of emphysema. Chest CT angiogram is useful in diagnosing acute pulmonary emboli; however, the ventilation-perfusion scan remains best suited for diagnosing *chronic thromboembolic disease* **(Chap. 273)**.

Two-dimensional echocardiography is used to measure RV wall thickness and chamber dimensions. The interventricular septum may move paradoxically during systole in the presence of RV pressure overload, highlighting a deleterious interaction between the RV and the LV. Doppler echocardiography can be used to assess pulmonary artery pressures. The location of the RV behind the sternum and its crescent shape can challenge assessment of RV function by echocardiography, especially when parenchymal lung disease is present. Calculated measures of RV function (e.g., tricuspid annular plane systolic excursion [TAPSE], systolic velocity of the RV free wall, strain of the RV free wall, or the Tei Index) supplement more subjective assessments. MRI is also useful for assessing RV structure and function, particularly in patients who are difficult to image with 2-D echocardiography because of severe lung disease. Cardiac catheterization confirms the diagnosis of pulmonary hypertension and can exclude elevated left-sided pressures (measured as the pulmonary capillary wedge pressure or the LV end-diastolic pressure) as a cause for right-sided HF. BNP and N-terminal BNP levels are elevated in patients with cor pulmonale secondary to RV myocardial stretch.

FURTHER READING

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253 Heart Failure: Management

Mandeep R. Mehra

Distinctive phenotypes of presentation with diverse management targets exemplify the extensive syndrome of heart failure. These range from chronic heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), acute decompensated heart failure (ADHF), and advanced heart failure. Early management evolved from symptom control to disease-modifying therapy in HFrEF with the advent of renin-angiotensin-aldosterone system (RAAS)–directed therapy, beta receptor antagonists, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardio-defibrillators. However, similar advances have been elusive in the syndromes of HFpEF and ADHF, which have remained devoid of convincing therapeutic advances to alter their natural history. In advanced heart failure, a stage of disease typically encountered in HFrEF, the patient remains markedly symptomatic with demonstrated refractoriness or inability to tolerate full-dose neurohormonal antagonism, often requires escalating doses of diuretics, and exhibits persistent hyponatremia and renal insufficiency with frequent episodes of heart failure decompensation requiring recurrent hospitalizations. Such individuals are at the highest risk of sudden or progressive pump failure–related deaths **(Chap. 255)**. In contrast, early-stage asymptomatic left ventricular dysfunction is amenable to preventive care, and its natural history is modifiable by neurohormonal antagonism (not further discussed).

HEART FAILURE WITH PRESERVED EJECTION FRACTION

GENERAL PRINCIPLES

Therapeutic targets in HFpEF include control of congestion, stabilization of heart rate and blood pressure, and efforts at improving exercise tolerance. Addressing surrogate targets, such as regression of ventricular hypertrophy in hypertensive heart disease, and use of lusitropic agents, such as calcium channel blockers and beta receptor antagonists, have been disappointing. Experience has demonstrated that lowering blood pressure alleviates symptoms more effectively than targeted therapy with specific agents.

CLINICAL TRIALS IN HFpEF

The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the angiotensin receptor blocker (ARB), candesartan. Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in meaningful endpoints in such patients treated with irbesartan. An earlier analysis of a subset of the Digitalis Investigation Group (DIG) trial found no role for digoxin in the treatment of HFpEF. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, the subgroup of elderly patients with prior hospitalization and HFpEF did not appear to benefit in terms of all-cause or cardiovascular mortality. Much smaller mechanistic studies in the elderly with the angiotensin-converting enzyme inhibitor (ACEI) enalapril showed no effect on peak exercise oxygen consumption, 6-min walk distance, aortic distensibility, left ventricular mass, or peripheral neurohormone expression.

NOVEL TARGETS

A small trial demonstrated that the phosphodiesterase-5 inhibitor *sildenafil* improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase II trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (left ventricular ejection fraction [LVEF] >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, quality of life (QOL), or other clinical and surrogate parameters. Conceptually targeting myocardial fibrosis in HFpEF, the large-scale Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) trial has been completed. This trial demonstrated no improvement in the primary composite endpoint, but did show a secondary signal of benefit on HF hospitalizations, counterbalanced, however, by an increase in adverse effects, particularly hyperkalemia. However, pessimism has been generated by the negative outcome of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study wherein *spironolactone* improved echocardiographic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or QOL measures. On the premise that nitrates, which are nitric oxide donors, might improve preload, coronary perfusion, endothelial function and improved exercise tolerance, the Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) study was conducted. Isosorbide mononitrate did not improve QOL or submaximal exercise capacity, and decreased overall activity levels in treated patients. A unique molecule that hybridizes an *ARB with an endopeptidase inhibitor*, LCZ696, increases the generation of myocardial cyclic guanosine 3′,5′-monophosphate, enhances myocardial relaxation, and reduces ventricular hypertrophy. This dual blocker has been shown to reduce circulating natriuretic peptides and reduce left atrial size to a significantly greater extent than valsartan alone in patients with HFpEF. This molecule is currently being tested in a pivotal clinical trial (PARAGON-HF).

CLINICAL PEARLS

Even as efforts to control hypertension in HFpEF are critical, evaluation for and correction of underlying ischemia may be beneficial. Appropriate identification and treatment of sleep-disordered breathing should be strongly considered. Excessive decrease in preload with vasodilators may lead to underfilling the ventricle and subsequent hypotension and syncope. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency and that such aberrations could be corrected with use of rate responsive pacemakers, but this remains an inadequately investigated contention (Fig. 253-1).

ACUTE DECOMPENSATED HEART FAILURE

GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5% in-hospital) and long-term cardiovascular mortality (20% at 1 year). Importantly, long-term aggregate outcomes remain poor, with a combined incidence of cardiovascular deaths, heart failure hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients has remained difficult and principally revolves around volume control and decrease of vascular impedance while maintaining attention to end-organ perfusion (coronary and renal).

The first principle of management of these patients is to identify and tackle known precipitants of decompensation. Identification and management of medication nonadherence and use of prescribed medicines such as nonsteroidal anti-inflammatory drugs, cold and flu preparations with cardiac stimulants, and herbal preparations, including licorice, ginseng, and herbal forms of ephedrine (now banned in most places), are required. Active infection and overt or covert pulmonary thromboembolism should be sought, identified, and treated when clinical clues suggest such direction. When possible, arrhythmias should be corrected by controlling heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting ongoing ischemia with coronary revascularization or by correcting offenders such as ongoing bleeding in demand-related ischemia. A parallel step in management involves stabilization of hemodynamics in those with instability. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. Analysis of in-hospital registries has identified several parameters associated with worse outcomes: a blood urea nitrogen level >43 mg/dL (to convert to mmol/L, multiply by 0.357), systolic blood pressure <115 mmHg, a serum creatinine level >2.75 mg/dL (to convert to μmol/L, multiply by 88.4), and an elevated troponin I level. A useful clinical schema to identify treatment targets for the various phenotypic presentations and management goals in ADHF is depicted in Fig. 253-2.

VOLUME MANAGEMENT

Intravenous Diuretic Agents Intravenous diuretic agents rapidly and effectively relieve symptoms of congestion and are essential when oral drug absorption is impaired. When high doses of diuretic agents are required or when the effect is suboptimal, a continuous infusion may be needed to reduce toxicity and maintain stable serum drug levels. Randomized clinical trials of high- versus low-dose or bolus versus continuous infusion diuresis have not provided clear justification for the best diuretic strategy in ADHF, and as such, the use

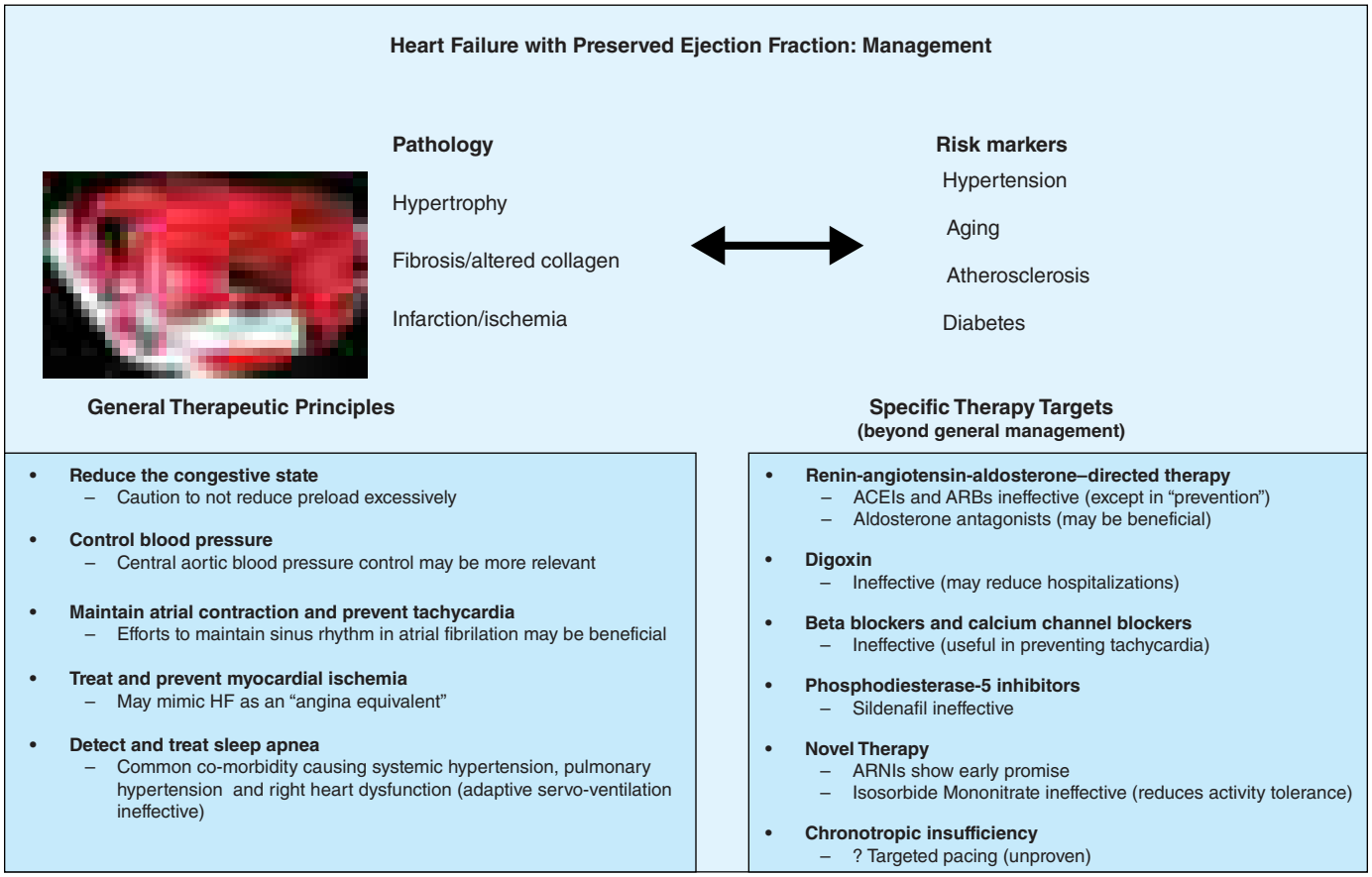

FIGURE 253-1 Pathophysiologic correlations, general therapeutic principles, and results of specific "directed" therapy in heart failure (HF) with preserved ejection fraction. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

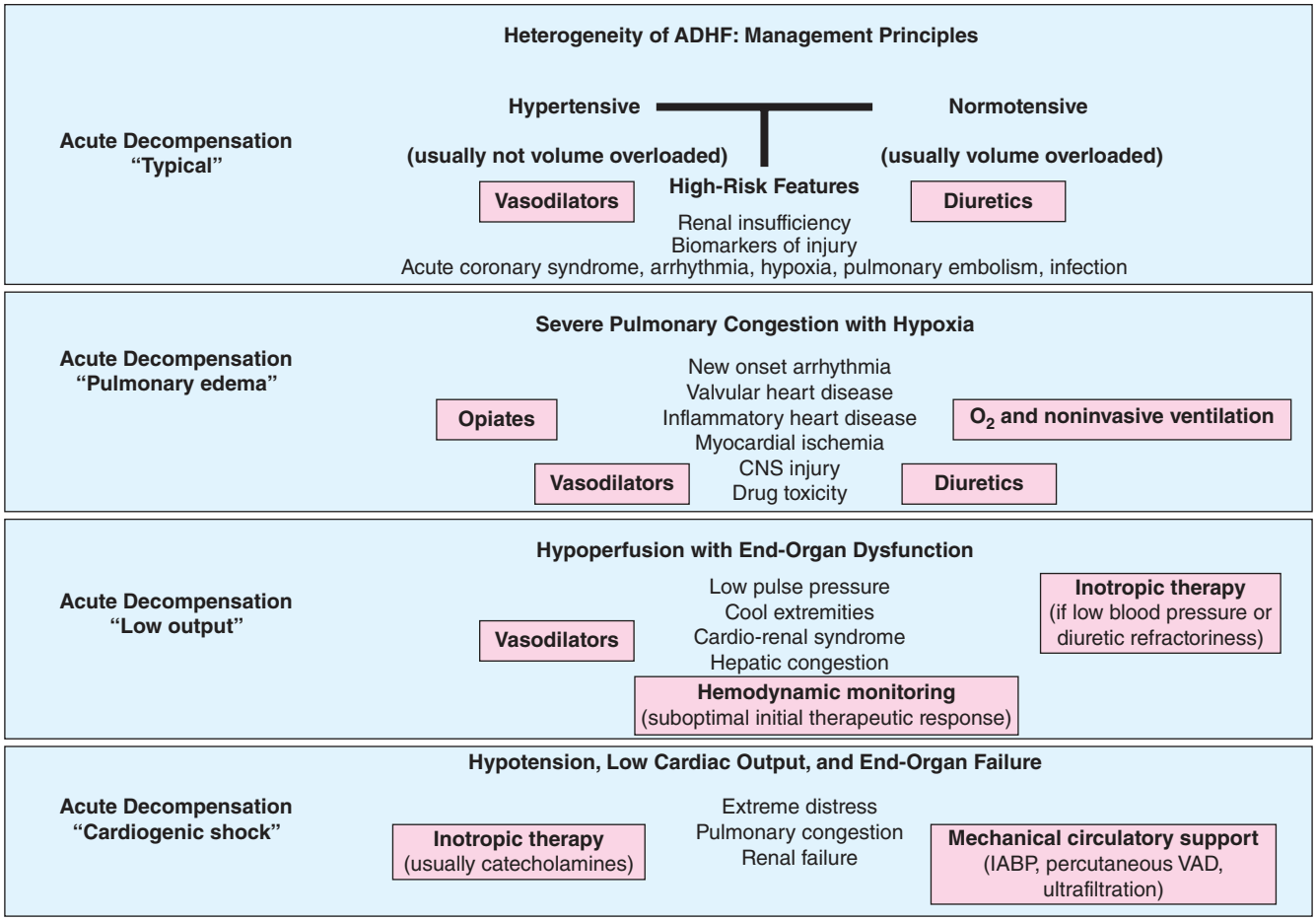

FIGURE 253-2 The distinctive phenotypes of acute decompensated heart failure (ADHF), their presentations, and suggested therapeutic routes. (Unique causes of ADHF, such as isolated right heart failure and pericardial disease, and rare causes, such as aortic and coronary dissection or ruptured valve structures or sinuses of Valsalva, are not delineated and are covered elsewhere.) IABP, intraaortic balloon pump; VAD, ventricular assist device.

of diuretic regimens remains an art rather than science. Addition of a thiazide diuretic agent such as metolazone in combination provides a synergistic effect and is often required in patients receiving long-term therapy with loop diuretic agents. Change in weight is often used as a surrogate for adequate diuresis, but this objective measure of volume status may be surprisingly difficult to interpret, and weight loss during hospitalization does not necessarily correlate closely with outcomes. It is generally advisable to continue diuresis until euvolemia has been achieved. Physical examination findings, specifically the jugular venous pressure coupled with biomarker trends, are useful in timing discharge planning.

The Cardiorenal Syndrome The cardiorenal syndrome is being recognized increasingly as a complication of ADHF. Multiple definitions have been proposed for the cardiorenal syndrome, but at its simplest, it can be thought to reflect the interplay between abnormalities of heart and kidney function, with deteriorating function of one organ while therapy is administered to preserve the other. Approximately 30% of patients hospitalized with ADHF exhibit abnormal renal function at baseline, and this is associated with longer hospitalizations and increased mortality. However, mechanistic studies have been largely unable to find correlation between deterioration in renal function, cardiac output, left-sided filling pressures, and reduced renal perfusion; most patients with cardiorenal syndrome demonstrate a preserved cardiac output. It is hypothesized that in patients with established heart failure, this syndrome represents a complex interplay of neurohormonal factors, potentially exacerbated by "backward failure" resulting from increased intraabdominal pressure and impairment in return of renal venous blood flow. Continued use of diuretic therapy may be associated with a reduction in glomerular filtration rate and a worsening of the cardiorenal syndrome when right-sided filling pressures remain elevated. In patients in the late stages of disease characterized by profound low cardiac output state, inotropic therapy or mechanical circulatory support has been shown to preserve or improve renal function in selected individuals in the short term until more definitive therapy such as assisted circulation or cardiac transplantation is implemented.

Ultrafiltration Ultrafiltration (UF) is an invasive fluid removal technique that may supplement the need for diuretic therapy. Proposed benefits of UF include controlled rates of fluid removal, neutral effects on serum electrolytes, and decreased neurohormonal activity. This technique has also been referred to as aquapheresis in recognition of its electrolyte depletion–sparing effects. In a pivotal study evaluating UF versus conventional therapy, fluid removal was improved and subsequent heart failure hospitalizations and urgent clinic visits were reduced with UF; however, no improvement in renal function and no subjective differences in dyspnea scores or adverse outcomes were noted. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, 188 patients with ADHF and worsening renal failure were randomized to stepped pharmacologic care or UF. The primary endpoint was a change in serum creatinine and change in weight (reflecting fluid removal) at 96 h. Although similar weight loss occurred in both groups (~5.5 kg), there was worsening in creatinine in the UF group. Deaths and hospitalizations for heart failure were no different between groups, but there were more adverse events in the UF group, mainly due to kidney failure, bleeding complications, and intravenous catheter-related complications. This investigation argues against using UF as a primary strategy in patients with ADHF who are nonetheless responsive to diuretics. Whether UF is useful in states of diuretic unresponsiveness remains an open question, and this strategy continues to be employed judiciously in such situations.

VASCULAR THERAPY

Vasodilators including *intravenous nitrates*, *nitroprusside*, and *nesiritide* (a recombinant brain-type natriuretic peptide) have been advocated for upstream therapy in an effort to stabilize ADHF. The latter agent was introduced in a fixed dose for therapy after a comparison with intravenous nitrates suggested more rapid and greater reduction in pulmonary capillary wedge pressure. Enthusiasm for nesiritide waned due to concerns within the pivotal trials for development of renal insufficiency and an increase in mortality. To address these concerns, a large-scale morbidity and mortality trial, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) study was completed in 2011 and randomly enrolled 7141 patients with ADHF to nesiritide or placebo for 24–168 h in addition to standard care. Nesiritide was not associated with an increase or a decrease in the rates of death and rehospitalization and had a clinically insignificant benefit on dyspnea. Renal function did not worsen, but increased rates of hypotension were noted. Although this trial established the safety for this drug, the routine use cannot be advocated due to lack of significant efficacy. *Recombinant human relaxin-2*, or serelaxin, is a peptide upregulated in pregnancy and examined in ADHF patients with a normal or elevated blood pressure. In the Relaxin in Acute Heart Failure (RELAX-AHF) trial, serelaxin or placebo was added to a regimen of standard therapy in 1161 patients hospitalized with ADHF, evidence of congestion, and systolic pressure >125 mmHg. Serelaxin improved dyspnea, reduced signs and symptoms of congestion, and was associated with less early worsening of HF. Exploratory endpoints of hard outcomes at 6 months suggested positive signals in favor of mortality reduction. A subsequent larger study failed to demonstrate a benefit. Recently, the natriuretic peptide urodilatin was tested in a large trial (TRUE-AHF) in ADHF patients and while evidence for decongestion was forthcoming along with a reduction in net endogenous expression of natriuretic peptides, there was no improvement in clinical outcomes at 6 months. Urodilatin was associated with a higher rate of hypotension and worsening serum creatinine.

INOTROPIC THERAPY

Impairment of myocardial contractility often accompanies ADHF, and pharmacologic agents that increase intracellular concentration of cyclic adenosine monophosphate via direct or indirect pathways, such as sympathomimetic amines (dobutamine) and phosphodiesterase-3 inhibitors (milrinone), respectively, serve as positive inotropic agents. Their activity leads to an increase in cytoplasmic calcium. Inotropic therapy in those with a low-output state augments cardiac output, improves perfusion, and relieves congestion acutely. Although milrinone and dobutamine have similar hemodynamic profiles, milrinone is slower acting and is renally excreted and thus requires dose adjustments in the setting of kidney dysfunction. Since milrinone acts downstream from the β_1-adrenergic receptor, it may provide an advantage in patients receiving beta blockers when admitted to the hospital. Studies are in universal agreement that long-term inotropic therapy increases mortality. However, the short-term use of inotropic agents in ADHF is also associated with increased arrhythmia, hypotension, and no beneficial effects on hard outcomes. Inotropic agents are currently indicated as bridge therapy (to either left ventricular assist device support or to transplant) or as selectively applied palliation in end-stage heart failure.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. *Levosimendan* is a calcium sensitizer that provides inotropic activity, but also possesses phosphodiesterase-3 inhibition properties that are vasodilators in action. This makes the drug unsuitable in states of low output in the setting of hypotension. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional non-inotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Another drug that functions as a selective myosin activator, *omecamtiv mecarbil*, prolongs the ejection period and increases fractional shortening. Distinctively, the force of contraction is not increased, and as such, this agent does not increase myocardial oxygen demand. As a follow-up to early encouraging data, the COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) study evaluated 448 patients with chronic heart failure and left ventricular systolic dysfunction, for 20 weeks of treatment, and observed improvements with this agent on cardiac function, left ventricular remodeling indices and natriuretic peptide expression. Other inotropic agents that increase myocardial calcium sensitivity through mechanisms that reduce cTnI phosphorylation or inhibit protein kinase A are being developed. (**Table 253-1** depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.)

NEUROHORMONAL ANTAGONISTS

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. The Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial of selective adenosine antagonism and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial of an oral selective vasopressin-2 antagonist in ADHF were both negative with respect to hard outcomes.

In patients who fail to respond adequately to medical therapy, mechanical assist devices may be required. This is covered in more detail in Chap. 255.

HEART FAILURE WITH REDUCED EJECTION FRACTION

The last 50 years have witnessed great strides in the management of HFrEF. The treatment of symptomatic heart failure that evolved from a renocentric (diuretics) and hemodynamic therapy model (digoxin, inotropic therapy) ushered in the era of disease-modifying therapy with neurohormonal antagonism. In this regard, RAAS blockers and beta blockers form the cornerstone of pharmacotherapy and lead to attenuation of decline and improvement in cardiac structure and function with consequent reduction in symptoms, improvement in QOL, decreased burden of hospitalizations, and a decline in mortality from both pump failure and arrhythmic deaths **(Fig. 253-3)**.

NEUROHORMONAL ANTAGONISM

Meta-analyses suggest a 23% reduction in mortality and a 35% reduction in the combination endpoint of mortality and hospitalizations for heart failure in patients treated with ACEIs. Patients treated with beta blockers provide a further 35% reduction in mortality on top of the benefit provided by ACEIs alone. Increased experience with both agents in a broad range of patients with HFrEF has demonstrated the safety of ACEIs in treating patients with mild renal insufficiency and the tolerability of beta blockers in patients with moderately controlled diabetes, asthma, and obstructive lung disease. The benefits of ACEIs and beta blockers extend to advanced symptoms of disease (NYHA class IIIb–IV). However, a substantial number of patients with advanced heart failure may not be able to achieve optimal doses of neurohormonal inhibitors and require cautious reduction in dose exposure to maintain clinical stability. Such individuals with lower exposure to ACEIs and beta blockers represent a high-risk cohort with poor prognosis.

Class Effect and Sequence of Administration ACEIs exert their beneficial effects in HFrEF as a class; however, the beneficial effects of beta blockers are thought to be limited to specific drugs. Beta blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit. On the basis of investigations, beta blocker use in HFrEF

TABLE 253-1 Intravenous Therapy in Acute Decompensated Heart Failure

DRUG CLASS	GENERIC DRUG	USUAL DOSING	SPECIAL CAUTION	COMMENTS
Inotropic therapy				Use in hypotension, end-organ hypoperfusion, or shock states
	Dobutamine	2–20 μg/kg per min	Increased myocardial oxygen demand, arrhythmia	Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
	Milrinone	0.375–0.75 μg/kg per min	Hypotension, arrhythmia	Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
	Levosimendan	0.1 μg/kg per min, range, 0.05–0.2 μg/kg per min	Hypotension, arrhythmia	Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
	Omecamtiv Mecarbil	N/A	*In trials	Increases contractility without increasing myocardial oxygen demand; in confirmatory trials
Vasodilators				Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
	Nitroglycerine	10–20 μg/min, increase up to 200 μg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
	Nesiritide	Bolus 2 μg/kg and infusion at 0.01 μg/kg per min	Hypotension	Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
	Nitroprusside	0.3 μg/kg per min titrated to 5 μg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 h)	Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
	Serelaxin	N/A (tested at 30 μg/kg per d)	Baseline blood pressure should be >125 mmHg	Not widely commercially available; ineffective in confirmatory trials
	Ularitide	15 ng/kg/min (48 h)	Baseline blood pressure >116 mmHg	Excess hypotension and increase serum creatinine
Diuretics				First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1 × home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
	Furosemide	20–240 mg daily	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion (not trial supported)
	Torsemide	10–100 mg daily	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)
	Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
	Adjuvant diuretics for augmentation	n/a	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis; metolazone given in 2.5- to 10-mg doses; causes severe electrolyte imbalance; spironolactone is useful in presence of severe hypokalemia and normal renal function

should ideally be restricted to carvedilol, bisoprolol, and metoprolol succinate—agents tested and proven to improve survival in clinical trials. Whether beta blockers or ACEIs should be started first was answered by the Cardiac Insufficiency Bisoprolol Study (CIBIS) III, in which outcomes did not vary when either agent was initiated first. Thus, it matters little which agent is initiated first; what does matter is that optimally titrated doses of both ACEIs and beta blockers be established in a timely manner.

Dose and Outcome A trial has indicated that higher tolerated doses of ACEIs achieve greater reduction in hospitalizations without materially improving survival. Beta blockers demonstrate a dose-dependent improvement in cardiac function and reductions in mortality and hospitalizations. Clinical experience suggests that, in the absence of symptoms to suggest hypotension (fatigue and dizziness), pharmacotherapy may be up-titrated every 2 weeks in stable ambulatory patients as tolerated.

MINERALOCORTICOID ANTAGONISTS

Aldosterone antagonism is associated with a reduction in mortality in all stages of symptomatic NYHA class II to IV HFrEF. Elevated aldosterone levels in HFrEF promote sodium retention, electrolyte imbalance, and endothelial dysfunction and may directly contribute to myocardial fibrosis. The selective agent eplerenone (tested in NYHA class II and post–myocardial infarction heart failure) and the nonselective antagonist spironolactone (tested in NYHA class III and IV heart failure) reduce mortality and hospitalizations, with significant reductions in sudden cardiac death (SCD). Hyperkalemia and worsening renal function are concerns, especially in patients with underlying chronic kidney disease, and renal function and serum potassium levels must be closely monitored.

RAAS THERAPY AND NEUROHORMONAL "ESCAPE"

Neurohormonal "escape" has been witnessed in patients with HFrEF by the finding that circulating levels of angiotensin II return to pretreatment levels with long-term ACEI therapy. ARBs blunt this phenomenon by binding competitively to the AT_1 receptor. Meta-analysis of 24 randomized trials demonstrated the superiority of ARBs to placebo in patients with intolerable adverse effects with ACEIs and their non-inferiority in all-cause mortality or hospitalizations when compared with ACEIs. The Valsartan Heart Failure Trial (Val-HeFT) suggested that addition of valsartan in patients already receiving treatment with ACEIs and beta blockers was associated with a trend toward worse outcomes. Similarly, adding valsartan to captopril in patients with heart failure after myocardial infarction who were receiving background beta blocker therapy was associated with an increase in adverse events without any added benefit compared with monotherapy for either group. Thus, the initial clinical strategy should be to use a two-drug combination first (ACEI and beta blocker; if beta blocker intolerant, then ACEI and ARB; if ACEI intolerant, then ARB and beta blocker). In symptomatic patients (NYHA class II–IV), an aldosterone antagonist should be strongly considered, but four-drug therapy should be avoided.

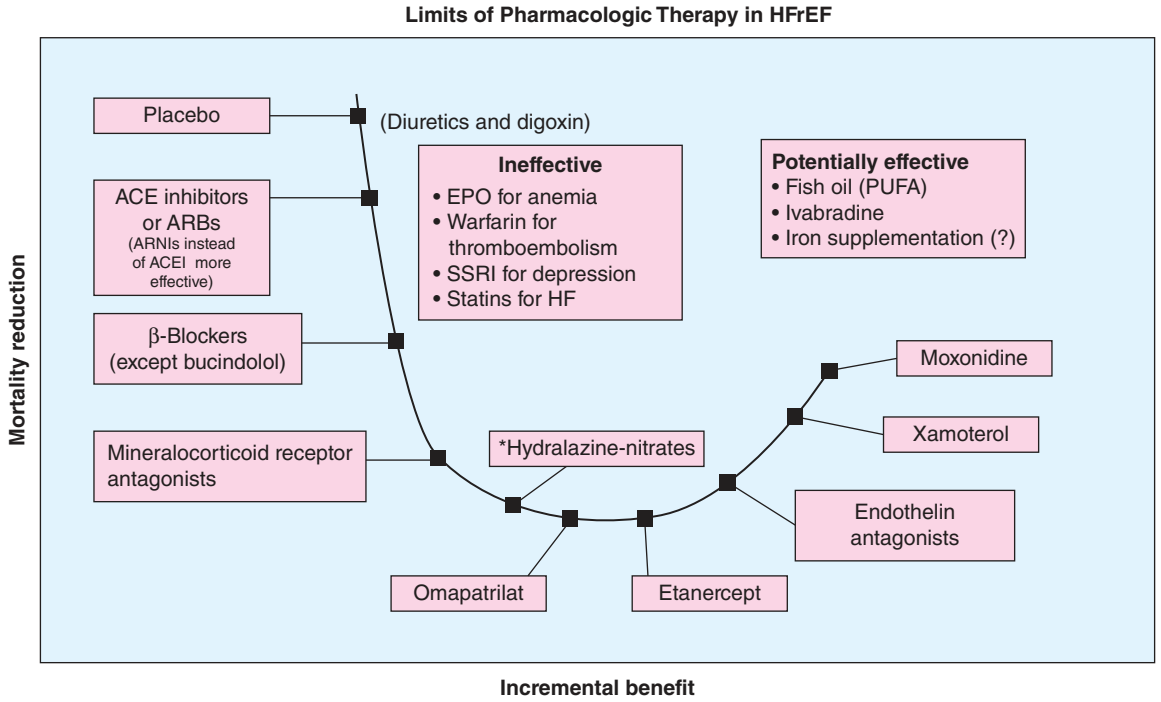

FIGURE 253-3 Progressive decline in mortality with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNIs), beta blockers, mineralocorticoid receptor antagonists, and balanced vasodilators (*selected populations such as African Americans); further stack-on neurohormonal therapy is ineffective or results in worse outcome; management of comorbidity is of unclear efficacy. EPO, erythropoietin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; PUFA, polyunsaturated fatty acid; SSRI, selective serotonin reuptake inhibitor.

A recent trial called the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) tested a direct renin inhibitor, aliskiren, in addition to other heart failure medications, within a week after discharge from a hospitalization for decompensated HFrEF. No significant difference in cardiovascular death or hospitalization at 6 or 12 months was noted. Aliskiren was associated with a reduction in circulating natriuretic peptides, but any disease-modifying effect was overcome by excessive adverse events including hyperkalemia, hypotension, and renal dysfunction. These studies point to the limits achieved with RAAS modulation in this clinical syndrome.

ARTERIOVENOUS VASODILATION

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into nitric oxide, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival, but not to the magnitude evidenced by ACEIs or ARBs. However, in individuals with HFrEF unable to tolerate RAAS-based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-Heft), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy. The study demonstrated benefit in survival and hospitalization recidivism in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule.

NOVEL NEUROHORMONAL ANTAGONISM

Despite an abundance of animal and clinical data demonstrating deleterious effects of activated neurohormonal pathways beyond the RAAS and sympathetic nervous system, targeting such pathways with incremental blockade has been largely unsuccessful. As an example, the endothelin antagonist bosentan is associated with worsening heart failure in HFrEF despite demonstrating benefits in right-sided heart failure due to pulmonary arterial hypertension. Similarly, the centrally acting sympatholytic agent moxonidine worsens outcomes in left heart failure. The combined drug omapatrilat hybridizes an ACEI with a neutral endopeptidase inhibitor, and this agent was tested in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial. This drug did not favorably influence the primary outcome measure of the combined risk of death or hospitalization for heart failure requiring intravenous treatment. The risk of angioedema was notably higher with omapatrilat than ACEIs alone.

More recently, the introduction of LCZ696, an ARB (valsartan) with an endopeptidase inhibitor (sacubitril), has shown a survival benefit in a large trial versus ARB alone. The drug, referred to as an angiotensin receptor–neprilysin inhibitor (ARNI) (and denoted Entrezto), was tested in the PARADIGM-HF trial as an alternate to optimally dosed ACEI and demonstrated an incremental improvement in survival when compared to ACEI alone. Most guidelines now advocate switching ACEI to this drug as a standard in patients with mild-moderate systolic heart failure when they remain symptomatic despite fully tolerated doses of conventional therapy.

Table 253-2 lists the common neurohormonal and vasodilator regimens for HFrEF.

HEART RATE MODIFICATION

Ivabradine, an inhibitor of the I_f current in the sinoatrial node, slows the heart rate without a negative inotropic effect. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with class II or III HFrEF, a heart rate >70 beats/min, and history of hospitalization for heart failure during the previous year. Ivabradine reduced hospitalizations and the combined endpoint of cardiovascular-related death and heart failure hospitalization. The study population was not necessarily representative of North American patients with HFrEF since, with a few exceptions, most did not receive internal cardioverter-defibrillation or cardiac resynchronization therapy and 40% did not receive a mineralocorticoid receptor antagonist. Although 90% received beta blockers, only a quarter were on full doses. Whether this agent would have been effective in patients receiving robust, guideline-recommended therapy for heart failure remains unclear. In the 2012 European Society of Cardiology guidelines for the treatment of heart failure, clinically, Ivabradine should be considered in patients who remain symptomatic after guideline-based ACEIs, beta blockers,

TABLE 253-2 Pharmacologic Therapy and Target Doses in Heart Failure with Reduced Ejection Fraction

DRUG CLASS	GENERIC DRUG	MEAN DAILY DOSE IN CLINICAL TRIALS (mg)	INITIATION (mg)	TARGET DOSE (mg)
Angiotensin-Converting Enzyme Inhibitors				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
Angiotensin Receptor Blockers				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
Aldosterone Antagonists				
	Eplerenone	42.6	25 qd	50 qd
	Spironolactone	26	12.5–25 qd	25–50 qd
Beta Blockers				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
Arteriovenous Vasodilators				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/ isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid
Angiotensin Receptor Neprilysin Inhibitor				
	Sacubitril-valsartan	375	100 bid	200 bid

and mineralocorticoid receptor antagonists and with residual heart rate >70 beats/min. Another group in whom potential benefit may be expected includes those unable to tolerate beta blockers.

DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympatho-inhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The DIG trial demonstrated a reduction in heart failure hospitalizations in the treatment group (patients with heart failure and sinus rhythm) but no reduction in mortality or improvement in QOL. Importantly, treatment with digoxin resulted in a higher mortality rate and hospitalizations in women than men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Loop diuretic agents are often required because of their increased potency, and frequent dose adjustments may be necessary because of variable oral absorption and fluctuations in renal function. Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival. Thus, diuretic agents should ideally be used in tailored dosing schedules to avoid excessive exposure. Indeed, diuretics are essential at the outset to achieve volume control before neurohormonal therapy is likely to be well tolerated or titrated.

CALCIUM CHANNEL ANTAGONISTS

Amlodipine and felodipine, second-generation calcium channel–blocking agents, safely and effectively reduce blood pressure in HFrEF but do not affect morbidity, mortality, or QOL. The first-generation agents, including verapamil and diltiazem, may exert negative inotropic effects and destabilize previously asymptomatic patients. Their use should be discouraged.

INFLAMMATION

Targeting inflammatory cytokines such as tumor necrosis factor α (TNF-α) by using anticytokine agents such as infliximab and etanercept has been unsuccessful and associated with worsening heart failure. Use of intravenous immunoglobulin therapy in nonischemic etiology of heart failure has not been shown to result in beneficial outcomes. Nonspecific immunomodulation has been tested in the Advanced Chronic Heart Failure Clinical Assessment of Immune Modulation Therapy (ACCLAIM-HF) trial where ex-vivo exposure of a blood sample from systolic heart failure patients to controlled oxidative stress was hypothesized to initiate apoptosis of leukocytes soon after intramuscular gluteal injection of the treated sample. The physiologic response to apoptotic cells results in a reduction in inflammatory cytokine production and upregulation of anti-inflammatory cytokines. This promising hypothesis was not proven, although certain subgroups (those with no history of previous myocardial infarction and those with mild heart failure) showed signals in favor of immunomodulation.

STATINS

Potent lipid-altering and pleiotropic effects of statins reduce major cardiovascular events and improve survival in non–heart failure populations. Once heart failure is well established, this therapy may not be as beneficial and theoretically could even be detrimental by depleting ubiquinone in the electron transport chain. Two trials, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiac (GISSI-HF), have tested low-dose rosuvastatin in patients with HFrEF and demonstrated no improvement in aggregate clinical outcomes. If statins are required to treat progressive coronary artery disease in the background setting of heart failure, then they should be employed. However, no rationale appears to exist for routine statin therapy in nonischemic heart failure.

ANTICOAGULATION AND ANTIPLATELET THERAPY

HFrEF is accompanied by a hypercoagulable state and therefore a high risk of thromboembolic events, including stroke, pulmonary embolism, and peripheral arterial embolism. Although long-term oral anticoagulation is established in certain groups, including patients with atrial

fibrillation, the data are insufficient to support the use of warfarin in patients in normal sinus rhythm without a history of thromboembolic events or echocardiographic evidence of left ventricular thrombus. In the large Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, full-dose aspirin or international normalized ratio–controlled warfarin was tested with follow-up for 6 years. Among patients with reduced LVEF in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. Aspirin blunts ACEI-mediated prostaglandin synthesis, but the clinical importance of this finding remains unclear. Current guidelines support the use of aspirin in patients with ischemic cardiomyopathy.

FISH OIL

Treatment with long-chain omega-3 polyunsaturated fatty acids (ω-3 PUFAs) has been shown to be associated with modestly improved clinical outcomes in patients with HFrEF. This observation from the GISSI-HF trial was extended to measurements of ω-3 PUFAs in plasma phospholipids at baseline and after 3 months. Three-month treatment with ω-3 PUFAs enriched circulating eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Low EPA levels are inversely related to total mortality in patients with HFrEF.

MICRONUTRIENTS

A growing body of evidence suggests an association between heart failure and micronutrient status. Reversible heart failure has been described as a consequence of severe thiamine and selenium deficiency. Thiamine deficiency has received attention in heart failure due to the fact that malnutrition and diuretics are prime risk factors for thiamine loss. Small exploratory randomized studies have suggested a benefit of supplementation of thiamine in HFrEF with evidence of improved cardiac function. This finding is restricted to chronic heart failure states and does not appear to be beneficial in the ADHF phenotype. Due to the exploratory nature of the evidence, no recommendations for routine supplementation or testing for thiamine deficiency can be made.

ENHANCED EXTERNAL COUNTERPULSATION (EECP)

Peripheral lower extremity therapy using graded external pneumatic compression at high pressure is administered in 1-h sessions for 35 treatments (7 weeks) and has been proposed to reduce angina symptoms and extend time to exercise-induced ischemia in patients with coronary artery disease. The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) study assessed the benefits of enhanced external counterpulsation in the treatment of patients with mild-to-moderate heart failure. This randomized trial improved exercise tolerance, QOL, and NYHA functional classification but without an accompanying increase in peak oxygen consumption. A placebo effect due to the nature of the intervention simply cannot be excluded.

EXERCISE

The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study investigated short-term (3-month) and long-term (12-month) effects of a supervised exercise training program in patients with moderate HFrEF. Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction. Maximal changes in 6-min walk distance were evident at 3 months with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months. Therefore, exercise training is recommended as an adjunctive treatment in patients with heart failure.

MANAGEMENT OF SELECTED COMORBIDITY

Sleep-disordered breathing is common in HF and particularly in HFrEF. A range of presentations exemplified by obstructive sleep apnea, central sleep apnea, and its extreme form of Cheyne-Stokes breathing are noted. Frequent periods of hypoxia and repeated micro- and macro-arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function. A high index of suspicion is required, especially in patients with difficult-to-control hypertension or with predominant symptoms of fatigue despite reverse remodeling in response to optimal medical therapy. Worsening of right heart function with improvement of left ventricular function noted on medical therapy should immediately trigger a search for underlying sleep-disordered breathing or pulmonary complications such as occult embolism or pulmonary hypertension. Treatment with nocturnal positive airway pressure improves oxygenation, LVEF, and 6-min walk distance. However, no conclusive data exist to support this therapy as a disease-modifying approach with reduction in mortality. A recent trial, using adaptive servo-ventilation in patients who had HFrEF and predominantly central sleep apnea increased all cause and cardiovascular mortality.

Anemia is common in heart failure patients, reduces functional status and QOL, and is associated with increased proclivity for hospital admissions and mortality. Anemia in heart failure is more common in the elderly, in those with advanced stages of HFrEF, in the presence of renal insufficiency, and in women and African Americans. The mechanisms include iron deficiency, dysregulation of iron metabolism, and occult gastrointestinal bleeding. Intravenous iron using either iron sucrose or carboxymaltose (Ferric Carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure [FAIR-HF] trial) has been shown to correct anemia and improve functional capacity. Another trial, CONFIRM-HF, enrolled similar patients with iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation <20%) and demonstrated that use of ferric carboxymaltose in a simplified high dose schedule resulted in improvement in functional capacity, symptoms, and QOL. Oral iron supplementation does not appear to be effective in treating iron deficiency in heart failure. Erythropoiesis-regulating agents such as erythropoietin analogues have been studied with disappointing results. The Reduction of Events by Darbepoetin Alfa in Heart Failure (RED-HF) trial demonstrated that treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure.

Depression is common in HFrEF, with a reported prevalence of one in five patients, and is associated with a poor QOL, limited functional status, and increased risk of morbidity and mortality in this population. However, the largest randomized study of depression in HFrEF, the Sertraline Against Depression and Heart Disease in Chronic Heart Failure (SADHART-CHF) trial, showed that although sertraline was safe, it did not provide greater reduction in depression or improve cardiovascular status among patients with heart failure and depression compared with nurse-driven multidisciplinary management.

Atrial arrhythmias, especially atrial fibrillation, are common and serve as a harbinger of worse prognosis in patients with heart failure. When rate control is inadequate or symptoms persist, pursuing a rhythm control strategy is reasonable. Rhythm control may be achieved via pharmacotherapy or by percutaneous or surgical techniques, and referral to practitioners or centers experienced in these modalities is recommended. Antiarrhythmic drug therapy should be restricted to amiodarone and dofetilide, both of which have been shown to be safe and effective but do not alter the natural history of the underlying disease. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) studied the effects of the novel antiarrhythmic agent dronedarone and found an increased mortality due to worsening heart failure. Catheter ablation and pulmonary vein isolation appear to be safe and effective in this high-risk cohort and compare favorably with the more established practice of atrioventricular node ablation and biventricular pacing.

Diabetes mellitus is a frequent co-morbidity in heart failure. Prior studies using thiazolidinediones (activators of peroxisome proliferator-activated receptors) have been associated with worsening heart failure. Glucagon-like peptide 1 (GLP-1) agonists such as liraglutide have also been tested and do not lead to greater post-hospitalization clinical stability or worsening in heart failure. Recently, the drug empagloflozin was tested in the EMPA-REG study and demonstrated a decrease in

cardiovascular mortality as well as hospitalizations for heart failure. This drug, a sodium–glucose cotransporter 2 (SGLT2), induces an osmotic diuresis as well as ketosis. This drug class may represent a viable therapeutic avenue in diabetics with heart failure.

NEUROMODULATION USING DEVICE THERAPY

Autonomic dysfunction is common in heart failure and attempts at using devices to modulate the sympathetic and parasympathetic systems have been undertaken. Broadly, devices that achieve vagal nerve stimulation, baroreflex activation, renal sympathetic denervation, spinal cord stimulation, or left cardiac sympathetic denervation have been employed. While small preclinical and clinical studies have demonstrated benefits, large-sized randomized trials, when conducted, have failed. The INOVATE-HF study tested vagal nerve stimulation versus optimal medical therapy among individuals with stable HF. Vagus nerve stimulation did not reduce the rate of death or hospitalization for HF. However, functional capacity and QOL were favorably affected by vagus nerve stimulation.

CARDIAC RESYNCHRONIZATION THERAPY

Nonsynchronous contraction between the walls of the left ventricle (intraventricular) or between the ventricular chambers (interventricular) impairs systolic function, decreases mechanical efficiency of contraction, and adversely affects ventricular filling. Mechanical dyssynchrony results in an increase in wall stress and worsens functional mitral regurgitation. The single most important association of extent of dyssynchrony is a widened QRS interval on the surface electrocardiogram, particularly in the presence of a left bundle branch block pattern. With placement of a pacing lead via the coronary sinus to the lateral wall of the ventricle, cardiac resynchronization therapy (CRT) enables a more synchronous ventricular contraction by aligning the timing of activation of the opposing walls. Early studies showed improved exercise capacity, reduction in symptoms, and evidence of reverse remodeling. The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was the first study to demonstrate a reduction in all-cause mortality with CRT placement in patients with HFrEF on optimal therapy with continued moderate-to-severe residual symptoms of NYHA class III or IV heart failure. More recent clinical trials have demonstrated disease-modifying properties of CRT in even minimally symptomatic patients with HFrEF, including the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), both of which sought to use CRT in combination with an implantable defibrillator. Most benefit in mildly symptomatic HFrEF patients accrues from applying this therapy in those with a QRS width of >149 ms and a left bundle branch block pattern. Attempts to further optimize risk stratification and expand indications for CRT using modalities other than electrocardiography have proven disappointing. In particular, echocardiographically derived measures of dyssynchrony vary tremendously, and narrow QRS dyssynchrony has not proven to be a good target for treatment. Uncertainty surrounds the benefits of CRT in those with ADHF, a predominant right bundle branch block pattern, atrial fibrillation, and evidence of scar in the lateral wall, which is the precise location where the CRT lead is positioned.

SUDDEN CARDIAC DEATH PREVENTION IN HEART FAILURE

SCD due to ventricular arrhythmias is the mode of death in approximately half of patients with heart failure and is particularly proportionally prevalent in HFrEF patients with early stages of the disease. Patients who survive an episode of SCD are considered to be at very high risk and qualify for placement of an implantable cardioverter-defibrillator (ICD). Although primary prevention is challenging, the degree of residual left ventricular dysfunction despite optimal medical therapy (≤35%) to allow for adequate remodeling and the underlying etiology (post–myocardial infarction or ischemic cardiomyopathy) are the two single most important risk markers for stratification of need and benefit. Currently, patients with NYHA class II or III symptoms of heart failure and an LVEF <35%, irrespective of etiology of heart failure, are appropriate candidates for ICD prophylactic therapy. In patients with a myocardial infarction and optimal medical therapy with residual LVEF ≤30% (even when asymptomatic), placement of an ICD is appropriate. A recent Danish trial suggested that prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. In this trial, benefits were noted in those aged <60 years. In patients with a terminal illness and a predicted life span of <6 months or in those with NYHA class IV symptoms who are refractory to medications and who are not candidates for transplant, the risks of multiple ICD shocks must be carefully weighed against the survival benefits. If a patient meets the QRS criteria for CRT, combined CRT with ICD is often employed (Table 253-3).

TABLE 253-3 Principles of ICD Implantation for Primary Prevention of Sudden Death

PRINCIPLE	COMMENT
Arrhythmia–sudden death mismatch	Sudden death in heart failure patients is generally due to progressive LVD, not a focal arrhythmia substrate (except in patients with post-MI HF)
Diminishing returns with advanced disease	Intervention at early stages of HF most successful since sudden death diminishes as cause of death with advanced HF
Timing of benefits	LVEF should be evaluated on optimal medical therapy or after revascularization before ICD therapy is employed; no benefit to ICD implant within 40 days of an MI (unless for secondary prevention)
Estimation of benefits and prognosis	Patients and clinicians often overestimate benefits of ICDs; an ICD discharge is not equivalent to an episode of sudden death (some ventricular arrhythmias terminate spontaneously); appropriate ICD discharges are associated with a worse near-term prognosis

Abbreviations: HF, heart failure; ICD, implantable cardioverter-defibrillator; LVD, left ventricular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

SURGICAL THERAPY IN HEART FAILURE

Coronary artery bypass grafting (CABG) is considered in patients with ischemic cardiomyopathy with multivessel coronary artery disease. The recognition that hibernating myocardium, defined as myocardial tissue with abnormal function but maintained cellular function, could recover after revascularization led to the notion that revascularization with CABG would be useful in those with living myocardium. Revascularization is most robustly supported in individuals with ongoing angina and left ventricular failure. Revascularizing those with left ventricular failure in the absence of angina remains controversial. The Surgical Treatment for Ischemic Heart Failure (STICH) trial in patients with an ejection fraction of ≤35% and coronary artery disease amenable to CABG demonstrated no significant initial benefit compared to medical therapy. However, patients assigned to CABG had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes over 10 years than among those who received medical therapy alone. An ancillary study of this trial also determined that the detection of hibernation pre-revascularization did not materially influence the efficacy of this approach, nor did it help to define a population unlikely to benefit if hibernation was not detected.

Surgical ventricular restoration (SVR), a technique characterized by infarct exclusion to remodel the left ventricle by reshaping it surgically in patients with ischemic cardiomyopathy and dominant anterior left ventricular dysfunction, has been proposed. However, in a 1000-patient trial in patients with HFrEF who underwent CABG alone or CABG plus SVR, the addition of SVR to CABG had no disease-modifying effect. However, left ventricular aneurysm surgery is still advocated in those with refractory heart failure, ventricular

arrhythmias, or thromboembolism arising from an akinetic aneurysmal segment of the ventricle. Other remodeling procedures, such as use of an external mesh-like net attached around the heart to limit further enlargement, have not been shown to provide hard clinical benefits, although favorable cardiac remodeling was noted.

Mitral regurgitation (MR) occurs with varying degrees in patients with HFrEF and dilated ventricles. Annular dilatation and leaflet noncoaptation in the setting of anatomically normal papillary muscles, chordal structures, and valve leaflets characterize functional MR. In patients who are not candidates for surgical coronary revascularization, mitral valve repair remains controversial. Ischemic MR (or infarct-related MR) is typically associated with leaflet tethering and displacement related to abnormal left ventricular wall motion and geometry. No evidence to support the use of surgical or percutaneous valve correction for functional MR exists as disease-modifying therapy even though MR can be corrected.

CELLULAR AND GENE-BASED THERAPY

The cardiomyocyte possesses regenerative capacity and such renewal is accelerated under conditions of stress and injury, such as an ischemic event or heart failure. Investigations that use either bone marrow–derived precursor cells or autologous cardiac-derived cells have gained traction but have not generally improved clinical outcomes in a convincing manner. More promising, however, are cardiac-derived stem cells. Two preliminary pilot trials delivering cells via an intracoronary approach have been reported. In one, autologous c-kit–positive cells isolated from the atria obtained from patients undergoing CABG were cultured and reinfused. In another, cardiosphere-derived cells grown from endomyocardial biopsy specimens were used. These small trials demonstrated improvements in left ventricular function but require far more work to usher in a clinical therapeutic success. The appropriate route of administration, the quantity of cells to achieve a minimal therapeutic threshold, the constitution of these cells (single source or mixed), the mechanism by which benefit accrues, and short- and long-term safety remain to be elucidated.

Targeting molecular aberrations using gene transfer therapy, mostly with an adenoviral vector, has been tested in HFrEF. A cellular target includes calcium cycling proteins such as inhibitors of phospholamban such as SERCA2a which is deficient in patients with HFrEF. Primarily responsible for reincorporating calcium into the sarcoplasmic reticulum during diastole, this target was tested in the CUPID (Efficacy and Safety Study of Genetically Targeted Enzyme Replacement Therapy for Advanced Heart Failure) trial. This study used coronary arterial infusion of adeno-associated virus type 1 carrying the gene for SERCA2a and initially demonstrated that natriuretic peptides were decreased, reverse remodeling was noted, and symptomatic improvements were forthcoming. However, a confirmatory trial failed to meet its primary efficacy endpoint.

More advanced therapies for late-stage heart failure such as left ventricular assist devices and cardiac transplantation are covered in detail in Chap. 255.

DISEASE MANAGEMENT AND SUPPORTIVE CARE

Despite stellar outcomes with medical therapy, admission rates following heart failure hospitalization remain high, with nearly half of all patients readmitted to hospital within 6 months of discharge. Recurrent heart failure and related cardiovascular conditions account for only half of readmissions in patients with heart failure, whereas other comorbidity-related conditions account for the rest. The key to achieving enhanced outcomes must begin with the attention to transitional care at the index hospitalization with facilitated discharge through comprehensive discharge planning, patient and caregiver education, appropriate use of visiting nurses, and planned follow-up. Early postdischarge follow-up, whether by telephone or clinic-based, may be critical to ensuring stability because most heart failure–related readmissions tend to occur within the first 2 weeks after discharge. Although routinely advocated, intensive surveillance of weight and vital signs with use of telemonitoring has not decreased hospitalizations. Intrathoracic impedance measurements have been advocated for the identification of early rise in filling pressure and worsened hemodynamics so that preemptive management may be employed. However, this has not been successful and may worsen outcomes in the short term. Implantable pressure monitoring systems do tend to provide signals for early decompensation, and in patients with moderately advanced symptoms, such systems have been shown to provide information that can allow implementation of therapy to avoid hospitalizations by as much as 39% (in the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients [CHAMPION] trial). Once heart failure becomes advanced, regularly scheduled review of the disease course and options with the patient and family is recommended including discussions surrounding end-of-life preferences when patients are comfortable in an outpatient setting. As the disease state advances further, integrating care with social workers, pharmacists, and community-based nursing may be critical in improving patient satisfaction with the therapy, enhancing QOL, and avoiding heart failure hospitalizations. Equally important is attention to seasonal influenza vaccinations and periodic pneumococcal vaccines that may obviate non–heart failure hospitalizations in these ill patients. When nearing end of life, facilitating a shift in priorities to outpatient and hospice palliation is key, as are discussions around advanced therapeutics and continued use of ICD prophylaxis, which may worsen QOL and prolong death.

GLOBAL CONSIDERATIONS

Substantial differences exist in the practice of heart failure therapeutics and outcomes by geographic location. The penetrance of CRT and ICD is higher in the United States than in Europe. Conversely, therapy unavailable in the United States, such as levosimendan, is designated as useful in Europe. Variation in the benefits of beta blockers based on world region remains an area of controversy. In oral pharmacologic therapy trials of HFrEF, patients from southwest Europe have a lower incidence of ischemic cardiomyopathy and those in North America tend to have more diabetes and prior coronary revascularization. There is also regional variation in medication use even after accounting for indication. In trials of heart failure, disparate effects are noted across populations. As a recent example, in TOPCAT, the drug spironolactone was effective when used in the US population while patients recruited from Russia and contiguous territories showed no difference. Whether this represents population differences or trial conduct disparity remains to be investigated. ADHF, patients in Eastern Europe tend to be younger, with higher ejection fractions and lower natriuretic peptide levels. Patients from South America tend to have the lowest rates of comorbidities, revascularization, and device use. In contrast, patients from North America have the highest comorbidity burden with high revascularization and device use rates. Given geographic differences in baseline characteristics and clinical outcomes, the generalizability of therapeutic outcomes in patients in the United States and Western Europe may require verification.

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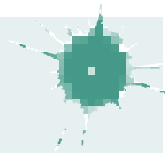

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DEFINITION AND CLASSIFICATION

Cardiomyopathy is disease of the heart muscle. It is estimated that cardiomyopathy accounts for 5–10% of the heart failure in the 5–6 million patients carrying that diagnosis in the United States. This term is intended to exclude cardiac dysfunction that results from other structural heart disease, such as coronary artery disease, primary valve disease, or severe hypertension; however, in general usage, the phrase *ischemic cardiomyopathy* is sometimes applied to describe diffuse dysfunction attributed to multivessel coronary artery disease, and *nonischemic cardiomyopathy* to describe cardiomyopathy from other causes. As of 2013, cardiomyopathies are defined as "disorders characterized by morphologically and functionally abnormal myocardium in the absence of any other disease that is sufficient, by itself, to cause the observed phenotype." *It was further specified that many cardiomyopathies will be attributable to genetic disease.*[1]

The traditional classification of cardiomyopathies into a triad of dilated, restrictive, and hypertrophic was based initially on autopsy specimens and later on echocardiographic findings. Dilated and hypertrophic cardiomyopathies can be distinguished on the basis of left ventricular wall thickness and cavity dimension; however, restrictive cardiomyopathy can have variably increased wall thickness and chamber dimensions that range from reduced to slightly increased, with prominent atrial enlargement. Restrictive cardiomyopathy is now defined more on the basis of abnormal diastolic function, which is also present but initially less prominent in dilated and hypertrophic cardiomyopathy. Restrictive cardiomyopathy can overlap in presentation, gross morphology, and etiology with both hypertrophic and dilated cardiomyopathies **(Table 254-1)**.

Expanding information renders this classification triad based on phenotype increasingly inadequate to define disease or therapy. Identification of more genetic determinants of cardiomyopathy has suggested a four-way classification scheme of etiology as primary (affecting primarily the heart) and secondary to other systemic disease. The primary causes are then divided into genetic, mixed genetic and acquired, and acquired. In practice however, genetic information is rarely available at initial presentation, the phenotypic expression of a given mutation varies widely, and genetic predisposition also influences acquired cardiomyopathies. Although the proposed genetic classification does not yet guide many current clinical strategies, it will become increasingly relevant as classification of disease moves beyond individual organ pathology to more integrated systems approaches.

GENERAL PRESENTATION

For all cardiomyopathies, the early symptoms often relate to exertional intolerance with breathlessness or fatigue, usually from inadequate cardiac reserve during exercise. These symptoms may initially be unnoticed or attributed to other causes, commonly lung disease or "getting older." As fluid retention leads to elevation of resting filling pressures, shortness of breath may occur during routine daily activity such as dressing and may manifest as dyspnea or cough when lying down at night. Although often considered the hallmark of congestion, peripheral edema may be absent despite severe fluid retention, particularly in younger patients in whom ascites and abdominal discomfort may dominate. The nonspecific term *congestive heart failure* describes only the resulting syndrome of fluid retention, which is common to all three types of cardiomyopathy and also to cardiac structural diseases associated with elevated filling pressures. All three types of cardiomyopathy can be associated with atrioventricular (AV) valve regurgitation, typical and atypical chest pain, atrial and ventricular tachyarrhythmias, and embolic events (Table 254-1). Initial evaluation begins with a detailed clinical history and examination, looking for clues to cardiac, extracardiac, and familial disease **(Table 254-2)**.

GENETIC CAUSES OF CARDIOMYOPATHY

Estimates for the prevalence of genetic etiology of cardiomyopathy continue to rise, with increasing availability of genetic testing and attention to the family history. Well-recognized in hypertrophic cardiomyopathy, heritability is also present in at least 30% of dilated cardiomyopathy (DCM) without other clear etiology. Careful family history should elicit not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to "a massive heart attack," who have had atrial fibrillation or pacemaker implantation by middle age, or who have muscular dystrophy.

Most familial cardiomyopathies are inherited in an autosomal dominant pattern, with occasional autosomal recessive and X-linked inheritance **(Table 254-3)**. Missense mutations with amino acid substitutions are the most common in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Mutations introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein the lack of which causes cardiomyopathy (haploinsufficiency). Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies.

Many different genes have been implicated in human cardiomyopathy (locus heterogeneity), and many mutations within those genes have been associated with disease (allelic heterogeneity). Although most identified mutations are "private" to individual families, several specific mutations are found repeatedly, either due to a founder effect or recurrent mutations at a common residue.

Genetic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never manifest. Related individuals who carry the *same* mutation may differ in the severity and rate of progression of cardiac dysfunction and associated rhythm disorders, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. Clinical disease expression is generally more severe in the 3–5% of individuals who harbor two or more mutations linked to cardiomyopathy. However, the clinical course of a patient usually cannot be predicted based on which mutation is present; thus, current therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing occasionally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry's disease and Gaucher disease.

GENES AND PATHWAYS IN CARDIOMYOPATHY

Mutations in sarcomeric genes, encoding the thick and thin myofilament proteins, are the best characterized. While the majority are associated with hypertrophic cardiomyopathy, an increasing number of sarcomeric mutations have now been implicated in DCM, and some

[1]From E Arbustini et al: J Am Coll Cardiol 62:2046, 2013.

TABLE 254-1 Presentation with Symptomatic Cardiomyopathy

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Normal or decreased	Normal or increased	Markedly increased
Atrial size	Increased, may also be primarily affected	Increased; may be massive	Increased; related to elevated filling pressures
Valvular regurgitation	Related to annular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance; may have chest pain
Congestive symptoms[a]	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion at rest may develop late
Arrhythmias	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular uncommon except in sarcoidosis, conduction block in sarcoidosis and amyloidosis. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

[a]Left-sided symptoms of pulmonary congestion: dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea. Right-sided symptoms of systemic venous congestion: hepatic and abdominal distention, discomfort on bending, peripheral edema.

TABLE 254-2 Initial Evaluation of Cardiomyopathy

Clinical Evaluation
Thorough history and physical examination to identify cardiac and noncardiac disorders[a]
Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death
History of alcohol, illicit drugs, chemotherapy or radiation therapy[a]
Assessment of ability to perform routine and desired activities[a]
Assessment of volume status, orthostatic blood pressure, body mass index[a]
Laboratory Evaluation
Electrocardiogram[a]
Chest radiograph[a]
Two-dimensional and Doppler echocardiogram[a]
Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis
Chemistry:
Serum sodium,[a] potassium,[a] calcium,[a] magnesium[a]
Fasting glucose (glycohemoglobin in diabetes mellitus)
Creatinine,[a] blood urea nitrogen[a]
Albumin,[a] total protein,[a] liver function tests[a]
Lipid profile
Thyroid-stimulating hormone[a]
Serum iron, transferrin saturation
Urinalysis
Creatine kinase isoforms
Cardiac troponin levels
Hematology:
Hemoglobin/hematocrit[a]
White blood cell count with differential,[a] including eosinophils
Erythrocyte sedimentation rate
Initial Evaluation When Specific Diagnoses Are Suspected
DNA sequencing for genetic disease, panel selection based on phenotype
Titers for infection in the setting of clinical suspicion:
Acute viral (coxsackie, echovirus, influenza)
Human immunodeficiency virus
Chagas' (*Trypanosoma cruzi*), Lyme (*Borrelia burgdorferi*), toxoplasmosis
Catheterization with coronary angiography in patients with angina who are candidates for intervention[a]
Serologies for active rheumatologic disease
Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications
Screening for sleep-disordered breathing

[a]Level I recommendations from ACC/AHA Practice Guidelines for Chronic Heart Failure in the Adult.

in left ventricular noncompaction. The most commonly recognized genetic causes of DCM are truncating mutations of the giant protein titin, encoded by *TTN*, which maintains sarcomere structure and acts as a key signaling molecule.

As cytoskeletal proteins play crucial roles in the structure, connection, and stability of the myocyte, multiple defects in these proteins can lead to cardiomyopathy, usually with a dilated phenotype **(Fig. 254-1)**. For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines, and the intercalated disks between muscle cells. Desmin mutations impair the transmission of force and signaling for both cardiac and skeletal muscle and may cause combined cardiac and skeletal myopathy.

Defects in the sarcolemmal membrane proteins are associated with DCM. The best known is dystrophin, encoded by the X chromosome gene *DMD*, abnormalities of which cause Duchenne's and Becker's muscle dystrophy. (Interestingly, abnormal dystrophin can be acquired when the coxsackie virus cleaves dystrophin during viral myocarditis.) This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive functional defect in both cardiac and skeletal muscle reflects vulnerability to mechanical stress. Dystrophin is associated at the membrane with a complex of other proteins, such as metavinculin, abnormalities of which also cause DCM. Defects in the sarcolemmal channel proteins (*channelopathies*) are generally associated with primary arrhythmias, but mutations in *SCN5A*, distinct from those that cause the Brugada or long QT syndromes, have been implicated in DCM with conduction disease.

Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C) or X-linked (emerin) patterns. These defects are associated with a high prevalence of atrial arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomyopathy.

Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connections to desmin filaments within the cell. Mutations in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhythmogenic right ventricular cardiomyopathy), this condition can affect both ventricles and has also been termed "arrhythmogenic cardiomyopathy."

As many signaling pathways are conserved over multiple systems, we anticipate discovering extracardiac manifestations of abnormal proteins initially considered restricted to the heart. In contrast, the monogenic disorders of metabolism that affect the heart are already clearly recognized to affect multiple organ systems. Currently, it is most important to diagnose defective enzymes for which specific enzyme

TABLE 254-3 Selected Genetic Defects Associated with Cardiomyopathy

	GENE PRODUCT	INHERITANCE	CARDIAC PHENOTYPE	ISOLATED CARDIAC PHENOTYPE[a]	EXTRACARDIAC MANIFESTATIONS
Sarcomere	*MYH7* (β myosin heavy chain)	AD	HCM, DCM, LVNC	Yes	Skeletal myopathy
	MYBPC3 (myosin binding protein C)	AD	HCM	Yes	
	TNNT2 (cardiac troponin T)	AD	HCM, DCM, LVNC	Yes	
	TNNI3 (cardiac troponin I)	AD, AR	HCM, DCM, RCM	Yes	
	TTN (Titin)	AD	DCM	Yes	
	TPM1 (α-tropomyosin)	AD	HCM, DCM	Yes	
	TNNC1 (cardiac troponin C)	AD	DCM	Yes	
	MYL2 (myosin regulatory light chain)	AD	HCM	Yes	Skeletal myopathy
	MYL3 (myosin essential light chain)	AD	HCM	Yes	
Z-disk and Cytoskeleton	*DES* (Desmin)	AD	DCM, RCM	Yes	Skeletal myopathy
	ANKRD1 (CARP)	AD	HCM, (DCM)	Yes	
	CSRP3 (MLP)	AD	DCM, (HCM)	Yes	
	ACTN2 (α-actinin-2)	AD	DCM	Yes	
	CRYAB (αB-crystallin)	AD	DCM	Yes	
	FLNC (Filamin C)	AD	DCM	Yes	Skeletal myopathy
Nuclear Membrane	*LMNA* (Lamin A/C)	AD, AR	CDDC	Yes	Skeletal myopathy
	EMD (Emerin)	X-linked	CDDC	No	Skeletal myopathy, contractures
Excitation-Contraction Coupling	*PLN* (Phospholamban)	AD	DCM	Yes	
	SCN5A (NAV 1.5)	AD	CDDC	Yes	Note other mutations associated with Brugada syndrome
	RYR2 (cardiac ryanodine receptor)	AD	ARVC	Yes	
	CASQ2 (calsequestrin 2)	AR	ARVC	Yes	
Cellular Metabolism	*PRKAG2* (γ-subunit of AMP kinase)	AD	HCM+	Yes	
	LAMP2 (lysosomal associated membrane protein)	X-linked	HCM+	No[a]	Danon's disease: skeletal myopathy, cognitive impairment
	TAZ (Tafazzin)	X-linked	DCM, LVNC	No	Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia
	FXN (Frataxin)	AR	HCM	No	Friedreich's ataxia: ataxia, diabetes mellitus type 2
	TMEM43 (transmembrane protein 43)	AD	ARVC	Yes	
	GLA (α-galactosidase-A)	X-linked	HCM+	Yes	Fabry's disease: renal failure, angiokeratomas and painful neuropathy
Mitochondria	Mitochondrial DNA	Maternal transmission	DCM, HCM	No	MELAS, MERRF, Kearns-Sayre syndrome, ocular myopathy
Sarcolemmal Membrane	*DMD* (Dystrophin)	X-linked	DCM	No[a]	Duchenne's and Becker's muscular dystrophy
	DMPK (dystrophica myotonica protein kinase)	AD	DCM	No	Myotonic dystrophy type 1
	SGCD (δ-sarcoglycan)	AD	DCM	Yes	
Desmosome	*DSP* (Desmoplakin) *JUP* (Plakoglobin)	AD, AR	ARVC	Yes	Carvajal syndrome (AR), Naxos syndrome (AR), "woolly hair" and hyperkeratosis of palms and soles
	DSG2 (Desmoglein 2) *DSC2* (Desmocollin 2) *PKP2* (Plakophilin 2)	AD	ARVC	Yes	
Other Examples	*RBM20* (RNA binding motif 20)	AD	DCM	Yes	
	PSEN1 (Presenilin-1,2)	AD	DCM	Yes	Dementia
	BAG3 (BCL2-associated athanogene 3)	AD	DCM	Yes	
	ALPK3 (Alpha-kinase 3)	AR	HCM	Yes	

[a]Indicates that the usual clinical presentation is of isolated cardiomyopathy, however occasionally present extra cardiac manifestations are also provided. [a]Indicates that isolated cardiac phenotype can occur in women with the X-linked defects.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; HCMc, HCM with conduction disease; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy.

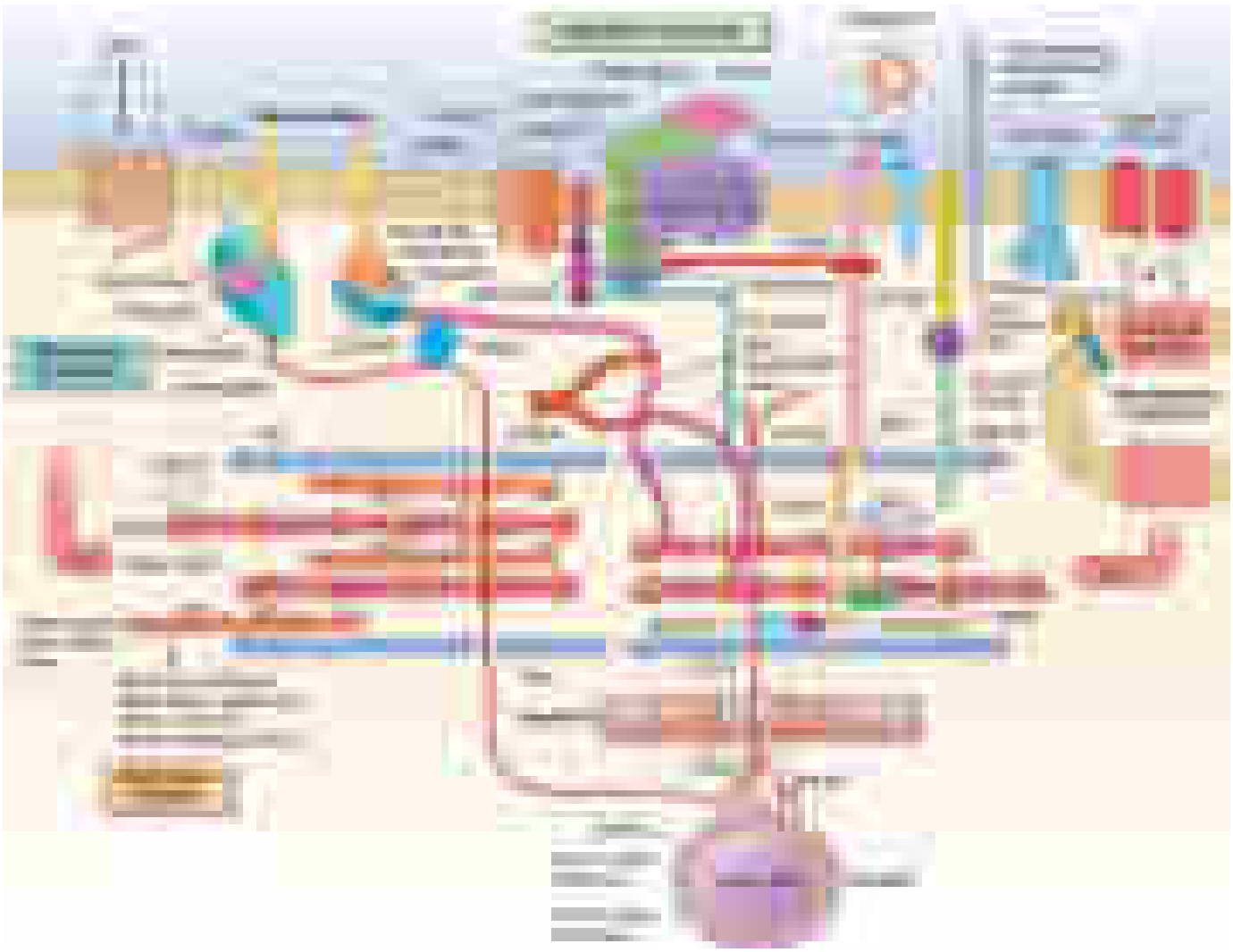

FIGURE 254-1 Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin, tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. *(Figure adapted from Jeffrey A. Towbin, MD, University of Tennessee Health Science Center, with permission.)*

replacement therapy can now ameliorate the course of disease, such as with alpha-galactosidase A deficiency (Fabry's disease). Abnormalities of mitochondrial DNA (maternally transmitted) impair energy production with multiple clinical manifestations, including impaired cognitive function and skeletal myopathy. The phenotypic expression is highly variable depending on the distribution of the maternal mitochondria during embryonic development. Heritable systemic diseases, such as familial amyloidosis and hemochromatosis, can affect the heart without mutation of genes expressed in the heart.

For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion. Screening includes an echocardiogram and electrocardiogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific mutation. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

DILATED CARDIOMYOPATHY

An enlarged left ventricle with reduced systolic function as measured by left ventricular ejection fraction characterizes DCM **(Figs. 254-2, 254-3, and 254-4)**. *Systolic failure* is more prominent than diastolic dysfunction. Although the syndrome of DCM has many disparate etiologies **(Table 254-4)**, many converge to common pathways of secondary response and disease progression. When myocardial injury is acquired, some myocytes may die initially, whereas others survive only to have later programmed cell death (apoptosis), and remaining myocytes hypertrophy in response to increased wall stress. Local and circulating factors stimulate deleterious secondary responses that contribute to progression of disease. Dynamic remodeling of the interstitial scaffolding affects diastolic function and the amount of ventricular dilation. Mitral regurgitation commonly develops as the valvular apparatus is distorted and is usually substantial by the time heart failure is severe. Many cases that present "acutely" have progressed silently through these stages over months to years. Dilation and decreased function of the right ventricle may result directly from the initial injury, but more often develops later in response to elevated afterload presented by secondary pulmonary hypertension and in relation to mechanical interactions with the failing left ventricle.

Regardless of the nature and degree of direct cell injury, the resulting functional impairment often reflects contribution from secondary responses that may be modifiable or reversible. Almost half of all patients with new-onset cardiomyopathy demonstrate substantial spontaneous recovery. Even with long-standing disease, some patients have dramatic improvement to near-normal ejection fractions during pharmacologic therapy, particularly notable with the β-adrenergic antagonists coupled with renin-angiotensin system inhibition. For patients in whom left bundle branch block precedes clinical heart failure by many years, cardiac resynchronization pacing may be particularly likely to improve ejection fraction and decrease ventricular size. Interest in the potential for recovery of cardiomyopathy has been further stimulated by occasional "recovery" of left ventricular function

FIGURE 254-2 Dilated cardiomyopathy. This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs >800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

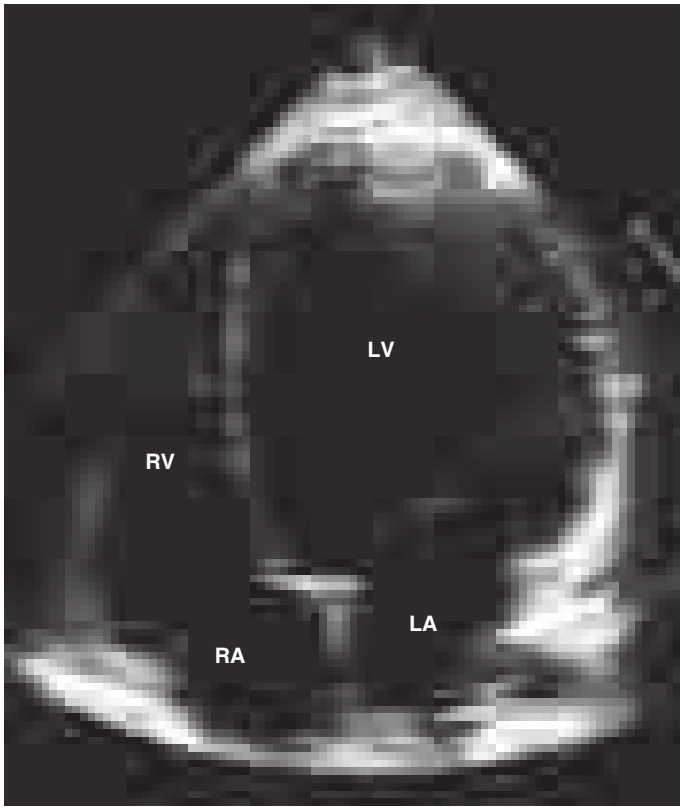

FIGURE 254-3 Dilated cardiomyopathy. This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. *(Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)*

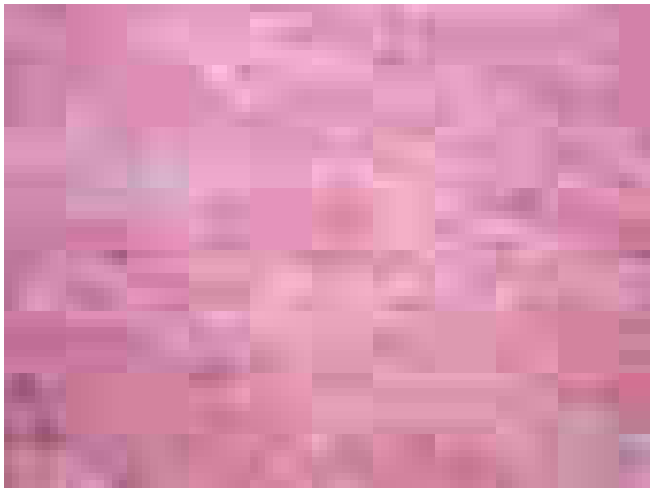

FIGURE 254-4 Dilated cardiomyopathy. Microscopic specimen of a dilated cardiomyopathy showing the nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin–stained section, 100× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

after prolonged mechanical circulatory support. The current evaluation and therapy for DCM is generally dictated by the stage of heart failure **(Chap. 252)**, with specific aspects discussed for relevant etiologies below.

MYOCARDITIS

Myocarditis (inflammation of the heart) can result from multiple causes but is most commonly attributed to infective agents that can injure the myocardium through direct invasion, production of cardiotoxic substances, or chronic inflammation with or without persistent infection. Myocarditis cannot be assumed from a presentation of decreased systolic function in the setting of an acute infection, as any severe infection causing systemic cytokine release can depress cardiac function transiently. Infectious myocarditis has been reported with almost all types of infective agents but is most commonly associated with viruses and the protozoan *Trypanosoma cruzi*.

INFECTIVE MYOCARDITIS

The pathogenesis of viral myocarditis has been extensively studied in murine models. After viruses gain entry through the respiratory or gastrointestinal tract, they can infect organs possessing specific receptors, such as the coxsackie-adenovirus receptor on the heart. Viral infection and replication can cause myocardial injury and lysis. For example, the enteroviral protease 2A facilitates viral replication and infection through degradation of the myocyte protein dystrophin, which is crucial for myocyte stability. Activation of viral receptor proteins can also activate host tyrosine kinases, which modify the cytoskeleton to facilitate further viral entry.

The first host response to infection is the nonspecific innate immune response, heavily dependent on Toll-like receptors that recognize common antigenic patterns. Cytokine release is rapid, followed by triggered activation and expansion of specific T- and B-cell populations. This initial response appears to be crucial, as early immunosuppression in animal models can increase viral replication and worsen cardiac injury. However, successful recovery from viral infection depends not only on the efficacy of the immune response to limit viral infection, but also on timely downregulation to prevent ongoing autoimmune injury to the host.

The secondary acquired immune response is specifically addressed against the viral proteins and can include both T-cell infiltration and antibodies to viral proteins. If unchecked, the acquired immune response can perpetuate secondary cardiac damage. Ongoing cytokine release activates matrix metalloproteinases that can disrupt the collagen and elastin scaffolding of the heart, potentiating ventricular dilation. Stimulation of pro-fibrotic factors leads to pathologic interstitial fibrosis.

TABLE 254-4 Major Causes of Dilated Cardiomyopathy (with Common Examples)

Inflammatory Myocarditis
Infective
Viral (coxsackie,[a] adenovirus,[a] HIV, hepatitis C)
Parasitic (*T. cruzi*—Chagas' disease, trypanosomiasis, toxoplasmosis)
Bacterial (diphtheria)
Spirochetal (*Borrelia burgdorferi*—Lyme disease)
Rickettsial (Q fever)
Fungal (with systemic infection)
Noninfective
Granulomatous inflammatory disease
Sarcoidosis
Giant cell myocarditis
Eosinophilic myocarditis
Polymyositis, dermatomyositis
Collagen vascular disease
Checkpoint inhibitor chemotherapy
Transplant rejection
Toxic
Alcohol
Catecholamines: amphetamines, cocaine
Chemotherapeutic agents (anthracyclines, trastuzumab)
Interferon
Other therapeutic agents (hydroxychloroquine, chloroquine)
Drugs of misuse (emetine, anabolic steroids)
Heavy metals: lead, mercury
Occupational exposure: hydrocarbons, arsenicals
Metabolic[a]
Nutritional deficiencies: thiamine, selenium, carnitine
Electrolyte deficiencies: calcium, phosphate, magnesium
Endocrinopathy
Thyroid disease
Pheochromocytoma
Diabetes
Obesity
Hemochromatosis
Inherited Metabolic Pathway Defects[a]
Familial[a] (See Table 254-3)
Skeletal and cardiac myopathy
Dystrophin-related dystrophy (Duchenne's, Becker's)
Mitochondrial myopathies (e.g., Kearns-Sayre syndrome)
Arrhythmogenic ventricular cardiomyopathy
Hemochromatosis
Associated with other systemic diseases
Susceptibility to immune-mediated myocarditis
Overlap with Nondilated Cardiomyopathy
"Minimally dilated cardiomyopathy"
Hemochromatosis[a]
Amyloidosis[a]
Hypertrophic cardiomyopathy[a] ("burned-out")
"Idiopathic"[a]
Miscellaneous (Shared Elements of Above Etiologies)
Peripartum cardiomyopathy
Left ventricular noncompaction[a]
Tachycardia-related cardiomyopathy
Supraventricular arrhythmias with uncontrolled rate
Very frequent nonsustained ventricular tachycardia or high premature ventricular complex burden

[a]Some specific cases can be linked now to specific genetic mutation in a familial cardiomyopathy; others with similar phenotypes that appear to be acquired or idiopathic may represent genetic factors not yet identified.

Some of the antibodies triggered through co-stimulation or molecular mimicry also recognize targets within the host myocyte, such as the β-adrenergic receptor, troponin, and Na^+/K^+ ATPase, but it remains unclear whether these antibodies contribute actively to cardiac dysfunction in humans or merely serve as markers of cardiac injury.

It is not known how long the viruses persist in the human heart, whether late persistence of the viral genome continues to be deleterious, or how often a dormant virus can again become pathogenic. Genomes of common viruses have frequently been detected in patients with clinical diagnoses of myocarditis or DCM, but there is little information on how often these are present in patients without cardiac disease (see below). Further information is needed to understand the relative timing and contribution of infection, immune responses, and secondary adaptations in the progression of heart failure after viral myocarditis **(Fig. 254-5)**.

Clinical Presentation of Viral Myocarditis *Acute viral myocarditis* often presents with symptoms and signs of heart failure. Some patients present with chest pain suggestive of pericarditis or acute myocardial infarction. Occasionally, the presentation is dominated by atrial or ventricular tachyarrhythmias, or by pulmonary or systemic emboli from intracardiac thrombi. Electrocardiographic or echocardiographic abnormalities may also be detected incidentally during evaluation for other diagnoses. The typical patient with presumed viral myocarditis is a young to middle-aged adult who develops progressive dyspnea and weakness within a few days to weeks after a viral syndrome that was accompanied by fever and myalgias.

A small number of patients present with fulminant myocarditis, with rapid progression within hours from a severe febrile respiratory syndrome to cardiogenic shock that may involve multiple organ systems, leading to renal failure, hepatic failure, and coagulopathy. These patients are typically young adults who have recently been dismissed from urgent care settings with antibiotics for bronchitis or oseltamivir for viral syndromes, only to return within a few days in rapidly progressive cardiogenic shock. Prompt triage is vital to provide aggressive support with high-dose intravenous catecholamine therapy and sometimes with temporary mechanical circulatory support. Recognition of patients with this fulminant presentation is potentially life-saving as more than half can survive, with marked improvement demonstrable within the first few weeks. The ejection fraction function of these patients often recovers to near-normal, although residual diastolic dysfunction may limit vigorous exercise for some survivors.

Chronic viral myocarditis is often invoked, but rarely proven, as a diagnosis when no other cause of DCM can be identified. However, many cases assumed to result from "silent" myocarditis will later be recognized as due to genetic causes or consumption of excess alcohol or illicit stimulant drugs. The proportion of chronic, DCM due to viral infection remains a subject of controversy.

Laboratory Evaluation for Myocarditis The initial evaluation for suspected myocarditis includes an ECG, an echocardiogram, and serum levels of troponin and creatine phosphokinase fractions. Magnetic resonance imaging is increasingly used for the diagnosis of myocarditis, which is supported but not proven by evidence of increased tissue edema and gadolinium enhancement **(Fig. 254-6)**, particularly in the mid-wall (as distinct from usual coronary artery territories).

Endomyocardial biopsy is not often indicated for the initial evaluation of suspected viral myocarditis unless ventricular tachyarrhythmias suggest possible etiologies of sarcoidosis or giant cell myocarditis. The indications, yield, and benefit of endomyocardial biopsy for evaluation of myocarditis or new-onset cardiomyopathy are not well-established. When biopsy is performed, the Dallas Criteria for myocarditis include lymphocytic infiltrate with evidence of myocyte necrosis **(Fig. 254-7)** and are negative in 80–90% of patients with clinical myocarditis. Negative Dallas Criteria can reflect sampling error or early resolution of lymphocytic infiltrates, but also the insensitivity of the test when inflammation results from cytokines and antibody-mediated injury. Routine histologic examination of endomyocardial biopsy rarely reveals a specific infective etiology, such as toxoplasmosis or *Cytomegalovirus*.

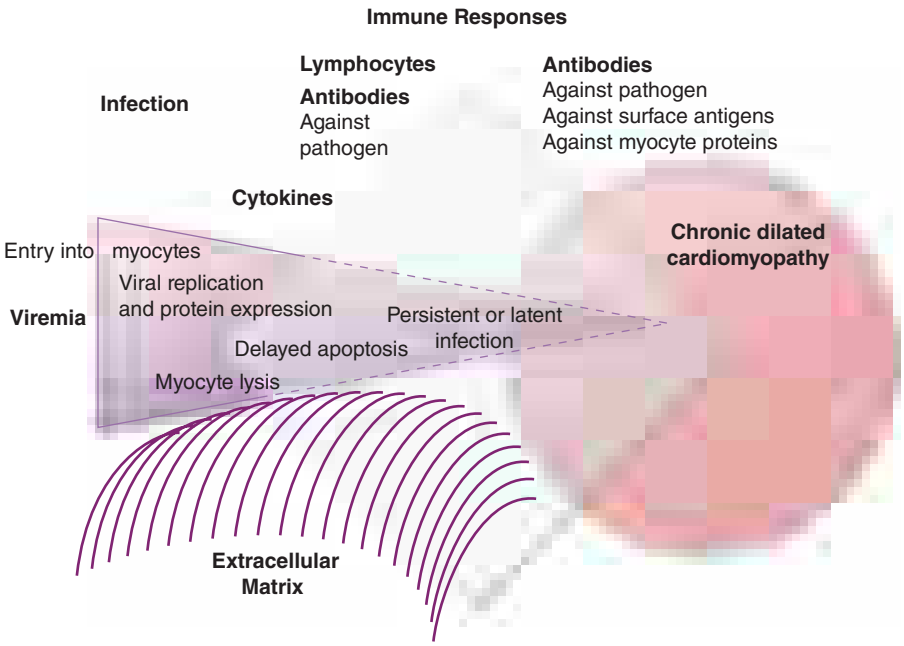

FIGURE 254-5 Schematic diagram demonstrating the possible progression from infection through direct, secondary, and autoimmune responses to dilated cardiomyopathy. Most of the supporting evidence for this sequence is derived from animal models. It is not known to what degree persistent infection and/or ongoing immune responses contribute to ongoing myocardial injury in the chronic phase.

Immunohistochemistry of myocardial biopsy samples is commonly used to identify active lymphocyte subtypes and may also detect upregulation of HLA antigens and the presence of complement components attributed to inflammation, but the specificity and significance of these findings are uncertain.

An increase in circulating viral titers between acute and convalescent blood samples supports a diagnosis of acute viral myocarditis with potential spontaneous improvement. There is no established role for measuring circulating anti-heart antibodies, which may be the result, rather than a cause, of myocardial injury and have been found also in patients with coronary artery disease and genetic cardiomyopathy.

Patients with recent or ongoing viral syndromes have been classified into three levels of myocarditis diagnosis. (1) *Possible subclinical acute myocarditis* is diagnosed when a typical viral syndrome occurs without cardiac symptoms, but with elevated biomarkers of cardiac injury, ECG suggestive of acute injury, reduced left ventricular ejection fraction or regional wall motion abnormality. (2) *Probable acute myocarditis* is diagnosed when the above criteria are met and accompanied by cardiac symptoms, such as shortness of breath or chest pain, which can result from pericarditis or myocarditis. When clinical findings of pericarditis are accompanied by elevated troponin or CK-MB or abnormal cardiac wall motion, the terms perimyocarditis or myopericarditis are sometimes used. (3) *Definite myocarditis* is diagnosed when there is histologic or immunohistologic evidence of inflammation on endomyocardial biopsy (see below) and does not require any other laboratory or clinical criteria. These have not been revised to include findings from MRI.

SPECIFIC VIRUSES IMPLICATED IN MYOCARDITIS

In humans, viruses are often suspected but rarely proven to be the direct cause of clinical myocarditis. First implicated was the picornavirus family of RNA viruses, principally the enteroviruses, coxsackie virus, echovirus, and poliovirus. Influenza, another RNA virus, is implicated with varying frequency every winter and spring as epitopes change. Of the DNA viruses, adenovirus, vaccinia (smallpox vaccine), and the herpesviruses (varicella zoster, cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6 [HHV6]) are well-recognized to cause myocarditis but also occur commonly in the healthy population. Polymerase chain reaction (PCR) detects viral genomes in the majority of patients with DCM, but also in normal "control" hearts. Most often detected are parvovirus B19 and HHV6, which may affect the cardiovascular system, in part, through infection of vascular endothelial cells. However, their contribution to chronic cardiomyopathy is uncertain, as serologic evidence of exposure is present in many children and most adults.

Human immunodeficiency virus (HIV) was associated with an incidence of DCM of 1–2%; however, with the advent of highly active antiretroviral therapy (HAART), HIV has been associated with a significantly lower incidence of cardiac disease. Cardiomyopathy in HIV may result from cardiac involvement with other associated viruses,

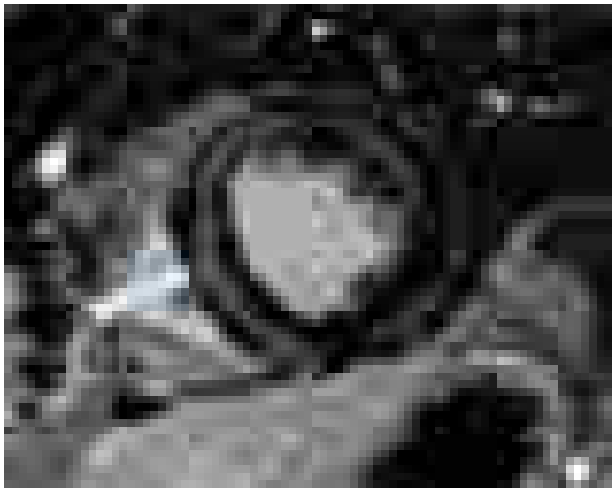

FIGURE 254-6 Magnetic resonance image of myocarditis showing the typical midwall location (*arrow*) for late gadolinium enhancement from cardiac inflammation and scarring. *(Image courtesy of Ron Blankstein, MD, and Marcelo Di Carli, MD, Division of Nuclear Medicine, Brigham and Women's Hospital, Boston.)*

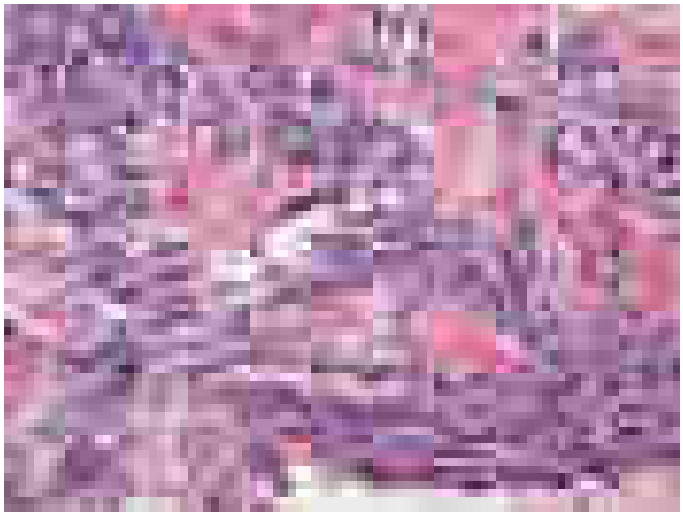

FIGURE 254-7 Acute myocarditis. Microscopic image of an endomyocardial biopsy showing massive infiltration with mononuclear cells and occasional eosinophils associated with clear myocyte damage. The myocyte nuclei are enlarged and reactive. Such extensive involvement of the myocardium would lead to extensive replacement fibrosis even if the inflammatory response could be suppressed. Hematoxylin and eosin–stained section, 200× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

such as cytomegalovirus and hepatitis C, as well as by HIV directly. Antiviral drugs to treat chronic HIV can cause cardiomyopathy, both directly and through drug hypersensitivity. The clinical picture may be complicated by pericardial effusions and pulmonary hypertension. There is a high frequency of lymphocytic myocarditis found at autopsy, and viral particles have been demonstrated in the myocardium in some cases, consistent with direct causation.

Hepatitis C has been repeatedly implicated in cardiomyopathy, particularly in Germany and Asia. Cardiac dysfunction may improve after interferon therapy. As this cytokine itself often depresses cardiac function transiently, careful coordination of administration and ongoing clinical evaluation are critical. *The effect of new treatments for hepatitis C on cardiac function has not yet been well-studied*. Involvement of the heart with hepatitis B is uncommon, but can be seen when associated with systemic vasculitis (polyarteritis nodosa).

Additional viruses implicated specifically in myocarditis include *mumps, respiratory syncytial virus*, the *arboviruses (dengue fever and yellow fever),* and *arenaviruses (Lassa fever)*. However, for any serious infection, the systemic inflammatory response can cause nonspecific depression of cardiac function, which is generally reversible if the patient survives.

THERAPY

There is currently no specific therapy recommended during any stage of viral myocarditis. During acute infection, therapy with anti-inflammatory or immunosuppressive medications is avoided, as their use has been shown to increase viral replication and myocardial injury in animal models. Therapy with specific antiviral agents (such as oseltamivir) has not been studied in relation to cardiac involvement. There is ongoing investigation into the impact of antiviral therapy to treat chronic viral persistence identified from endomyocardial biopsy. Large trials of immunosuppressive therapy for Dallas Criteria–positive myocarditis have been negative. There are some initial encouraging results and ongoing investigations with immunosuppressive therapy for immune-mediated myocarditis defined by immunohistologic criteria on biopsy or circulating anti-heart antibodies in the absence of myocardial viral genomes. However, neither antiviral nor anti-inflammatory therapies are currently recommended. Until we have a better understanding of the phases of viral myocarditis and the effects of targeted therapies, treatment will continue to be guided by general recommendations for DCM.

Parasitic Myocarditis *Chagas' disease* is the third most common parasitic infection in the world and the most common infective cause of cardiomyopathy. The protozoan *T. cruzi* is transmitted by the bite of the reduviid bug, endemic in the rural areas of South and Central America. Transmission can also occur through blood transfusion, organ donation, from mother to fetus, and occasionally orally. While programs to eradicate the insect vector have decreased the prevalence from about 16 million to <10 million in South America, cases are increasingly recognized in Western developed countries (see Global Perspectives below).

Multiple pathogenic mechanisms are implicated. The parasite itself can cause myocyte lysis and primary neuronal damage. Specific immune responses may recognize the parasites or related antigens and lead to chronic immune activation in the absence of detectable parasites. Molecular techniques have revealed persistent parasite DNA fragments in infected individuals. Further evidence for persistent infection is the eruption of parasitic skin lesions during immunosuppression after cardiac transplantation. As with viral myocarditis, the relative roles of persistent infection and of secondary autoimmune injury have not been resolved (Fig. 254-5). An additional factor in the progression of Chagas' disease is the autonomic dysfunction and microvascular damage that may contribute to cardiac and gastrointestinal disease.

The acute phase of Chagas' disease with parasitemia is usually unrecognized, but in fewer than 5% of cases, it presents clinically within a few weeks of infection, with nonspecific symptoms or occasionally with acute myocarditis and meningoencephalitis. In the absence of antiparasitic therapy, the silent stage progresses slowly for >10–30 years in almost half of patients to manifest chronically in the cardiac and gastrointestinal systems. Features typical of Chagas' disease are conduction system abnormalities, particularly sinus node and AV node dysfunction and right bundle branch block. Atrial fibrillation and ventricular tachyarrhythmias also occur. Small ventricular aneurysms are common, particularly at the ventricular apex. These dilated ventricles are particularly thrombogenic, giving rise to pulmonary and systemic emboli. Xenodiagnosis, detection of the parasite itself, is rarely performed. The serologic tests for specific IgG antibodies against the trypanosome lack sufficient specificity and sensitivity, requiring two separate positive tests required to make a diagnosis.

Treatment of the advanced stages focuses on clinical manifestations of the disease and includes heart failure medications, pacemaker-defibrillators, and anticoagulation. The most common antiparasitic therapies are benznidazole and nifurtimox which have been effective in children with chronic *T. cruzi* infection. Both drugs are associated with multiple severe reactions, including dermatitis, gastrointestinal distress, and neuropathy. Moreover, in a large trial of adults with established Chagas' cardiomyopathy, benznidazole did not prevent disease progression, leaving the role of antiparasitic therapy unclear. Survival is <30% at 5 years after the onset of overt clinical heart failure. Patients without major extracardiac disease have occasionally undergone transplantation, after which they require surveillance testing and recurrent antiparasitic therapy to suppress reactivation of infection.

African trypanosomiasis infection results from the tsetse fly bite and can occur in travelers exposed during trips to Africa. The West African form is caused by *Trypanosoma brucei gambiense* and progresses silently over years. The East African form caused by *T. brucei rhodesiense* can progress rapidly through perivascular infiltration to myocarditis and heart failure, with frequent arrhythmias. The diagnosis is made by identification of trypanosomes in blood, lymph nodes, or other affected sites. Antiparasitic therapy has limited efficacy and is determined by the specific type and the stage of infection (hemolymphatic or neurologic).

Toxoplasmosis is contracted through undercooked infected beef or pork, transmission from feline feces, organ transplantation, transfusion, or maternal-fetal transmission. Immunocompromised hosts are most likely to experience reactivation of latent infection from cysts, found in up to 40% of autopsies of patients dying from HIV infection. Toxoplasmosis may present with encephalitis or chorioretinitis and, in the heart, can cause myocarditis, pericardial effusion, constrictive pericarditis, and heart failure. The diagnosis in an immunocompetent patient is made when the IgM is positive and the IgG becomes positive later. Active toxoplasmosis may be suspected in an immunocompromised patient with myocarditis and a positive IgG titer for toxoplasmosis, particularly when avidity testing identifies high specificity of the antibody. Fortuitous sampling occasionally reveals the cysts in the myocardium. Combination therapy can include pyrimethamine and sulfadiazine or clindamycin.

Trichinellosis is caused by *Trichinella spiralis* larva ingested with undercooked meat. Larvae migrating into skeletal muscles cause myalgias, weakness, and fever. Periorbital and facial edema and conjunctival and retinal hemorrhage may also be seen. Although the larva may occasionally invade the myocardium, clinical heart failure is rare and, when observed, attributed to the eosinophilic inflammatory response. The diagnosis is made from the specific serum antibody and is further supported by the presence of eosinophilia. Treatment includes antihelminthic drugs (albendazole, mebendazole) and glucocorticoids if inflammation is severe.

Cardiac involvement with *Echinococcus* is rare, but cysts can form and rupture in the myocardium and pericardium.

Bacterial Infections Most bacterial infections can involve the heart occasionally through direct invasion and abscess formation, but do so rarely. More commonly, systemic inflammatory responses depress contractility in severe infection and sepsis. *Diphtheria* specifically affects the heart in almost one-half of cases, and cardiac involvement is the most common cause of death in patients with this infection. The prevalence of vaccines has shifted the incidence of diphtheria from children worldwide to countries without routine immunization and to older populations who have lost their immunity. The bacillus releases

a toxin that impairs protein synthesis and may particularly affect the conduction system. The specific antitoxin should be administered as soon as possible, with higher priority than antibiotic therapy. Other systemic bacterial infections that can involve the heart include *brucellosis, chlamydophila, legionella, meningococcus, mycoplasma, psittacosis*, and *salmonellosis,* for which specific treatment is directed at the systemic infection.

Clostridial infections cause myocardial damage from the released toxin. Gas bubbles can be detected in the myocardium, and occasionally abscesses can form in the myocardium and pericardium. *Streptococcal infection* with β-hemolytic streptococci is most commonly associated with acute rheumatic fever and is characterized by inflammation and fibrosis of cardiac valves and systemic connective tissue, but it can also lead to a myocarditis with focal or diffuse infiltrates of mononuclear cells.

Tuberculosis can involve the myocardium directly as well as through tuberculous pericarditis, but rarely does so when the disease is treated with antibiotics. *Whipple's disease* is caused by *Tropheryma whipplei.* The usual manifestations are in the gastrointestinal tract, but pericarditis, coronary arteritis, valvular lesions, and occasionally clinical heart failure may also occur. Multidrug antituberculous regimens are effective, but the disease tends to relapse even with appropriate treatment.

Other Infections **Spirochetal myocarditis** has been diagnosed from myocardial biopsies containing *Borrelia burgdorferi* that causes *Lyme disease.* Lyme carditis most often presents with arthritis and conduction system disease that resolves within 1–2 weeks of antibiotic treatment, only rarely implicated in chronic heart failure. **Fungal myocarditis** can occur due to hematogenous or direct spread of infection from other sites, as has been described for aspergillosis, actinomycosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, and mucormycosis. However, cardiac involvement is rarely the dominant clinical feature of these infections. The **rickettsial infections,** *Q fever, Rocky Mountain spotted fever, and scrub typhus* are frequently accompanied by ECG changes, but most clinical manifestations relate to systemic vascular involvement.

NONINFECTIVE MYOCARDITIS

Myocardial inflammation can occur without apparent preceding infection. The paradigm of noninfective inflammatory myocarditis is cardiac transplant rejection, from which we have learned that myocardial depression can develop and reverse quickly, that noncellular mediators such as antibodies and cytokines play a major role in addition to lymphocytes, and that myocardial antigens are exposed by prior physical injury and viral infection.

The most commonly diagnosed noninfective inflammation is granulomatous myocarditis, including both sarcoidosis and giant cell myocarditis. Sarcoidosis, as discussed in **Chap. 360**, is a multisystem disease most commonly affecting the lungs. Although classically presenting with higher prevalence in young African-American men, the epidemiology appears to be changing, with increasing recognition of sarcoidosis in Caucasian patients in nonurban areas. Patients with pulmonary sarcoid are at high risk for cardiac involvement, but cardiac sarcoidosis also occurs without clinical lung disease. Regional clustering of the disease supports the suspicion that the granulomatous reaction is triggered by an infectious or environmental allergen not yet identified.

The sites and density of cardiac granulomata, the time course, and the degree of extracardiac involvement are remarkably variable. Patients may present with rapid-onset heart failure and ventricular tachyarrhythmias, conduction block, chest pain syndromes, or minor cardiac findings in the setting of ocular involvement, an infiltrative skin rash, or a nonspecific febrile illness. They may also present less acutely after months to years of fluctuating cardiac symptoms. When ventricular tachycardia or conduction block dominates the initial presentation of heart failure without coronary artery disease, suspicion should be high for these granulomatous myocarditides.

Depending on the time course, the ventricles may appear restrictive or dilated. There is often right ventricular predominance of both dilation and ventricular arrhythmias, sometimes initially attributed to arrhythmogenic right ventricular cardiomyopathy. Small ventricular aneurysms are common. Computed tomography of the chest often reveals pulmonary lymphadenopathy even in the absence of clinical lung disease. Metabolic imaging (positron emission tomography [PET]) of the whole chest can highlight active sarcoid lesions that are avid for glucose. Magnetic resonance imaging (MRI) of the heart can identify areas likely to be inflammatory. To rule out chronic infections, such as tuberculosis or histoplasmosis as the cause of adenopathy, the diagnosis usually requires pathologic confirmation. Biopsy of enlarged mediastinal nodes may provide the highest yield. The scattered granulomata of sarcoidosis can easily be missed on cardiac biopsy **(Fig. 254-8)**.

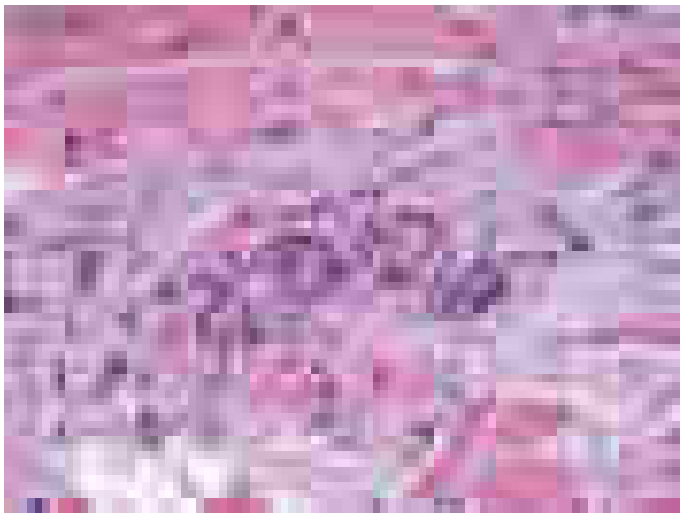

FIGURE 254-8 Sarcoidosis. Microscopic image of an endomyocardial biopsy showing a noncaseating granuloma and associated interstitial fibrosis typical of sarcoidosis. No microorganisms were present on special stains, and no foreign material was identified. Hematoxylin and eosin–stained section, 200× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

Immunosuppressive treatment for sarcoidosis is initiated with high-dose glucocorticoids, which are often more effective for arrhythmias than for the heart failure. Patients with sarcoid lesions that persist or recur during tapering of corticosteroids are considered candidates for other immunosuppressive therapies, frequently with agents also used for cardiac transplantation. Pacemakers and implantable defibrillators are generally indicated to prevent life-threatening heart block or ventricular tachycardia, respectively. Because the inflammation often resolves into extensive fibrosis that impairs cardiac function and provides pathways for reentrant arrhythmias, the prognosis for improvement is best when the granulomata are not extensive and the ejection fraction is not severely reduced.

Giant cell myocarditis is less common than sarcoidosis, but accounts for 10–20% of biopsy-positive cases of myocarditis. Giant cell myocarditis typically presents with rapidly progressive heart failure and tachyarrhythmias. Diffuse granulomatous lesions are surrounded by extensive inflammatory infiltrate unlikely to be missed on endomyocardial biopsy, often with eosinophilic infiltration. Associated conditions are thymomas, thyroiditis, pernicious anemia, other autoimmune diseases, and occasionally recent infections. Glucocorticoid therapy is less effective than for sarcoidosis and is sometimes combined with other immunosuppressive agents. The course is often of rapid deterioration requiring urgent mechanical support or transplantation. Although the severity of presentation and myocardial histology are more fulminant than with sarcoidosis, the occasional finding of giant cell myocarditis after sarcoidosis suggests that they may in some cases represent different stages of the same disease spectrum.

Eosinophilic myocarditis can be an important manifestation of the hypereosinophilic syndrome, which in Western countries is often considered idiopathic, although in Mediterranean and African countries, is

associated with antecedent infection. It may also be seen with systemic eosinophilic syndromes such as Churg-Strauss syndrome or malignancies. *Hypersensitivity myocarditis* is often an unexpected diagnosis, made when the biopsy reveals infiltration with lymphocytes and mononuclear cells with a high proportion of eosinophils. Most commonly, the reaction is attributed to antibiotics, particularly those taken chronically, but thiazides, anticonvulsants, indomethacin, and methyldopa have also been implicated. Occasional associations with the smallpox vaccine have been reported. Although the circulating eosinophil count may be slightly elevated in hypersensitivity myocarditis, it does not reach the high levels of the hypereosinophilic syndrome. High-dose glucocorticoids and discontinuation of the trigger agent can be curative for hypersensitivity myocarditis. A severe lymphocytic myocarditis has been seen with combination of immune checkpoint inhibitors (see toxic cardiomyopathy below).

Myocarditis is often associated with systemic inflammatory diseases, such as *polymyositis* and *dermatomyositis*, which affect skeletal and cardiac muscle. Although noninfective inflammatory myocarditis is sometimes included in the differential diagnosis of cardiac findings in patients with connective tissue disease such as systemic lupus erythematosus, pericarditis, vasculitis, pulmonary hypertension, and accelerated coronary artery disease are more common cardiac manifestations of connective tissue disease.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) develops during the last trimester or within the first 6 months after pregnancy, affecting between 1:2000 and 1:4000 deliveries in the United Sates. Risk factors are increased maternal age, increased parity, twin pregnancy, malnutrition, use of tocolytic therapy for premature labor, and preeclampsia or toxemia of pregnancy. Several of these risk factors contribute to anti-angiogenic signaling through secreted vascular endothelial growth factor (VEGF) inhibitors, such as soluble FLT1 (sFLT1). Recent animal and human studies have confirmed the role of decreased angiogenic reserve in the pathogenesis of PPCM, which may be rescued by correcting the angiogenic imbalance. Another recently proposed mechanism invokes an abnormal prolactin cleavage fragment, which is induced by oxidative stress and also affects angiogenesis; this observation has led to preliminary investigation of bromocriptine as possible therapy.

However, other processes also contribute to PPCM. Heart failure early after delivery was previously common in Nigeria, when the custom for new mothers included salt ingestion while reclining on a warm bed, which likely impaired mobilization of the excess circulating volume after delivery. In the Western world, lymphocytic myocarditis has sometimes been found on myocardial biopsy. This inflammation has been hypothesized to reflect increased susceptibility to viral myocarditis or an autoimmune myocarditis due to cross-reactivity of anti-uterine antibodies against cardiac muscle.

As the increased circulatory demand of pregnancy can aggravate other cardiac disease that was clinically unrecognized, it is crucial to the diagnosis of PPCM that there be no evidence for a preexisting cardiac disorder. By contrast, heart failure presenting earlier in pregnancy has been termed pregnancy-associated cardiomyopathy (PACM). Both PPCM and PACM have been found in some families with other presentations of DCM. As in familial and sporadic DCM, truncating mutations in *TTN* are present in 15% of patients with PPCM and are associated with systolic dysfunction that persists. Pregnancy may, thus, represent an environmental trigger for accelerated phenotypic expression of genetic and other cardiomyopathies.

TOXIC CARDIOMYOPATHY

Cardiotoxicity has been reported with multiple environmental and pharmacologic agents. Often these associations are seen only with very high levels of exposure or acute overdoses, in which acute electrocardiographic and hemodynamic abnormalities may reflect both direct drug effect and systemic toxicity.

Alcohol is the most common toxin implicated in chronic DCM. Excess consumption may contribute to more than 10% of cases of heart failure, including exacerbation of cases with other primary etiologies such as valvular disease or previous infarction. Toxicity is attributed both to alcohol and to its primary metabolite, acetaldehyde. Polymorphisms of the genes encoding alcohol dehydrogenase and the angiotensin-converting enzyme may influence the likelihood of alcoholic cardiomyopathy in an individual with excess consumption. Superimposed vitamin deficiencies and toxic alcohol additives are rarely implicated currently. The alcohol consumption necessary to produce cardiomyopathy in an otherwise normal heart has been estimated to be five to six drinks (about 4 ounces of pure ethanol) daily for 5–10 years, but frequent binge drinking may also be sufficient. Many patients with alcoholic cardiomyopathy are fully functional in their daily lives without apparent stigmata of alcoholism. The cardiac impairment in severe alcoholic cardiomyopathy is the sum of both permanent damage and a substantial component that is reversible after cessation of alcohol consumption. Atrial fibrillation occurs commonly both early in the disease ("holiday heart") and in advanced stages. Medical therapy includes neurohormonal antagonists and diuretics as needed for fluid management. Withdrawal should be supervised to avoid exacerbations of heart failure or arrhythmias, and ongoing support arranged. Even with severe disease, marked improvement can occur within 3–6 months of abstinence. Implantable defibrillators are generally deferred until an adequate period of abstinence, after which they may not be necessary if the ejection fraction has improved. With continued consumption, the prognosis is grim.

Cocaine, amphetamines, and related catecholaminergic stimulants can produce chronic cardiomyopathy as well as acute ischemia and tachyarrhythmias. Pathology reveals microinfarcts consistent with small vessel ischemia, similar to those seen with pheochromocytoma.

Chemotherapy agents are the most common drugs implicated in toxic cardiomyopathy. Judicious use of these drugs requires balancing the risks of the malignancy and the risks of cardiotoxicity, as many cancers have a chronic course with better prognosis than heart failure.

Anthracyclines (e.g., doxorubicin) cause characteristic histologic changes of vacuolar degeneration and myofibrillar loss. Generation of reactive oxygen species involving heme compounds is currently the favored explanation for myocyte injury and fibrosis. Risk for cardiotoxicity increases with higher doses, preexisting cardiac disease, extremes of age, concomitant chemotherapy, or chest irradiation and in women. Although cardiomyopathy has frequently been considered to occur late after exposure, a recent study shows that systolic dysfunction is usually evident within 1 year after anthracycline exposure among adult patients who develop cardiomyopathy. Doxorubicin cardiotoxicity generally results in minimal ventricular dilation, perhaps due to accompanying fibrosis. Thus, the stroke volume may be severely reduced with an ejection fraction of 30–40%, in contrast to the hemodynamic compensation possible in a dilated ventricle typical of other heart failure with reduced ejection fraction. Therapy includes angiotensin-converting enzyme inhibitors and β-adrenergic blocking agents, with careful suppression of "inappropriate" sinus tachycardia, and attention to postural hypotension that can occur in these patients. Once thought to have an inexorable downward course, many patients with doxorubicin cardiotoxicity improve with careful management to near-normal clinical function, particularly if additional insults such as hypertension or supraventricular tachycardias can be avoided. The course differs for patients receiving these drugs before puberty, in whom inadequate growth of the heart may lead to inexorable heart failure by the time the patient reaches the early twenties.

Trastuzumab (Herceptin) is a monoclonal antibody that interferes with human epidermal growth receptor 2 (HER2) crucial for some tumor growth and for cardiac adaptation. The incidence of cardiotoxicity is lower than for anthracyclines but enhanced by coadministration with them. Although considered to be more often reversible, trastuzumab cardiotoxicity does not always resolve, and some patients progress to clinical heart failure and death. As with anthracycline cardiotoxicity, therapy is as usual for heart failure, but it is not clear whether the spontaneous rate of improvement is enhanced by neurohormonal antagonists. The cardiotoxic effects of other recently introduced anti-HER2 therapies (e.g., pertuzumab) are similar to that caused by trastuzumab.

Cardiotoxicity with *cyclophosphamide and ifosfamide* generally occurs acutely and with very high doses. 5-Fluorouracil, cisplatin, and some other alkylating agents can cause recurrent coronary spasm that occasionally leads to depressed contractility. Acute administration of *interferon-α* can cause hypotension and arrhythmias. Clinical heart failure occurring during repeated chronic administration usually resolves after discontinuation.

Many small-molecule *tyrosine kinase inhibitors* that affect VEGF are under use for different malignancies. Although these agents are "targeted" at specific tumor receptors or pathways, the biologic conservation of signaling pathways can cause these inhibitors to have "off-target" effects that include the cardiovascular system and as a group are associated with a ~2.7-fold increased risk of heart failure. Recognition of cardiotoxicity during therapy with these agents is complicated because they occasionally cause peripheral fluid accumulation (ankle edema, periorbital swelling, pleural effusions) due to local factors rather than elevated central venous pressures. Therapeutic approaches include withdrawal of the tyrosine kinase inhibitor (when possible) and substitution with a congener (when available), as well as conventional treatment for heart failure.

Proteasome inhibitors used to treat multiple myeloma are associated with an increased risk of heart failure. The more potent agent, carfilzomib, appears more cardiotoxic than bortezomib.

Immune *checkpoint inhibitors*, such as ipilimumab and nivolumab, are associated with multisystem autoimmune inflammatory toxicities (e.g., thyroiditis, hypophysitis, pancreatitis, and pneumonitis) and rarely myocarditis. However, combination therapy with two checkpoint inhibitors can cause fulminant myocarditis with associated systolic dysfunction, AV block, and ventricular tachycardia within weeks after initial chemotherapy. This presentation has been accompanied by acute skeletal myocarditis and rapid progression to death.

Other therapeutic drugs that can cause cardiotoxicity during chronic use include hydroxychloroquine, chloroquine, emetine, and antiretroviral therapies.

Toxic exposures can cause arrhythmias or respiratory injury acutely during accidents. Chronic exposures implicated in cardiotoxicity include hydrocarbons, fluorocarbons, arsenicals, lead, and mercury.

METABOLIC CAUSES OF CARDIOMYOPATHY

Endocrine disorders affect multiple organ systems, including the heart. *Hyperthyroidism and hypothyroidism* do not often cause clinical heart failure in an otherwise normal heart, but commonly exacerbate heart failure. Clinical signs of thyroid disease may be masked, so tests of thyroid function are part of the routine evaluation of cardiomyopathy. Hyperthyroidism should always be considered with new-onset atrial fibrillation or ventricular tachycardia or atrial fibrillation in which the rapid ventricular response is difficult to control. The most common current reason for thyroid abnormalities in the cardiac population is the treatment of tachyarrhythmias with amiodarone, a drug with substantial iodine content. Hypothyroidism should be treated with very slow escalation of thyroid supplements to avoid exacerbating tachyarrhythmias and heart failure. Hyperthyroidism and heart failure create a dangerous combination that merits very close supervision, often hospitalization, during titration of antithyroid medications, during which decompensation of heart failure may occur precipitously and fatally.

Pheochromocytoma is rare, but should be considered when a patient has heart failure and very labile blood pressure and heart rate, sometimes with episodic palpitations **(Chap. 380)**. Patients with pheochromocytoma often have postural hypotension. In addition to α-adrenergic receptor antagonists, definitive therapy requires surgical extirpation. Very high renin states, such as those caused by renal artery stenosis, can lead to modest depression in ejection fraction with little or no ventricular dilation and markedly labile symptoms with flash pulmonary edema, related to sudden shifts in vascular tone and intravascular volume.

Controversies remain regarding whether *diabetes* and *obesity* are sufficient to cause cardiomyopathy. Most heart failure in diabetes results from epicardial coronary disease, with further increase in coronary artery risk due to accompanying hypertension and renal dysfunction. Cardiomyopathy may result in part from insulin resistance and increased advanced-glycosylation end products, which impair both systolic and diastolic function. However, much of the dysfunction can be attributed to scattered focal ischemia resulting from distal coronary artery tapering and limited microvascular perfusion even without proximal focal stenoses. Diabetes is a typical factor in heart failure with "preserved" ejection fraction, along with hypertension, advanced age, and female gender.

The existence of a cardiomyopathy due to *obesity* is generally accepted. In addition to cardiac involvement from associated diabetes, hypertension, and vascular inflammation of the metabolic syndrome, obesity alone is associated with impaired excretion of excess volume load, which, over time, can lead to increased wall stress and secondary adaptive neurohumoral responses. Fluid retention may be aggravated by large fluid intake and the rapid clearance of natriuretic peptides by adipose tissue. In the absence of another obvious cause of cardiomyopathy in an obese patient with systolic dysfunction without marked ventricular dilation, effective weight reduction is often associated with major improvement in ejection fraction and clinical function. Improvement in cardiac function has been described after successful bariatric surgery, although all major surgical therapy poses increased risk for patients with heart failure. Postoperative malabsorption and nutritional deficiencies, such as calcium and phosphate deficiencies, may be particularly deleterious for patients with cardiomyopathy.

Nutritional deficiencies can occasionally cause DCM but are not commonly implicated in developed Western countries. *Beri-beri heart disease* due to thiamine deficiency can result from poor nutrition in undernourished populations and in patients deriving most of their calories from alcohol, and has been reported in teenagers subsisting only on highly processed foods. This disease is initially a vasodilated state with very high output heart failure that can later progress to a low output state; thiamine repletion can lead to prompt recovery of cardiovascular function. Abnormalities in *carnitine* metabolism can cause dilated or restrictive cardiomyopathies, usually in children. Deficiency of trace elements such as *selenium* can cause cardiomyopathy (Keshan's disease).

Calcium is essential for excitation-contraction coupling. Chronic deficiencies of calcium, such as can occur with hypoparathyroidism (particularly postsurgical) or intestinal dysfunction (from diarrheal syndromes and following extensive resection), can cause severe chronic heart failure that responds over days or weeks to vigorous calcium repletion. *Phosphate* is a component of high-energy compounds needed for efficient energy transfer and multiple signaling pathways. *Hypophosphatemia* can develop during starvation and early refeeding following a prolonged fast, and occasionally during hyperalimentation. *Magnesium* is a cofactor for thiamine-dependent reactions and for the sodium-potassium adenosine triphosphatase (ATPase), but hypomagnesemia rarely becomes sufficiently profound to cause clinical cardiomyopathy.

Hemochromatosis is variably classified as a metabolic or storage disease **(Chap. 407)**. It is included among the causes of restrictive cardiomyopathy, but the clinical presentation is often that of a DCM. The autosomal recessive form is related to the *HFE* gene. With up to 10% of the population heterozygous for one mutation, the clinical prevalence might be as high as 1 in 500. The lower observed rates highlight the limited penetrance of the disease, suggesting the role of additional genetic and environmental factors such as alcoholism affecting clinical expression. Hemochromatosis can also be acquired from iron overload due to hemolytic anemia and transfusions. Excess iron is deposited in the perinuclear compartment of cardiomyocytes, with resulting disruption of intracellular architecture and mitochondrial function. Diagnosis is easily made from measurement of serum iron and transferrin saturation, with a threshold of >60% for men and >45–50% for women. MRI can help to quantitate iron stores in the liver and heart, and endomyocardial biopsy tissue can be stained for iron **(Fig. 254-9)**, which is particularly important if the patient has another cause for cardiomyopathy. If diagnosed early, hemochromatosis can often be managed by repeated phlebotomy to remove iron. For more severe iron overload, iron chelation therapy with desferrioxamine (deferoxamine)

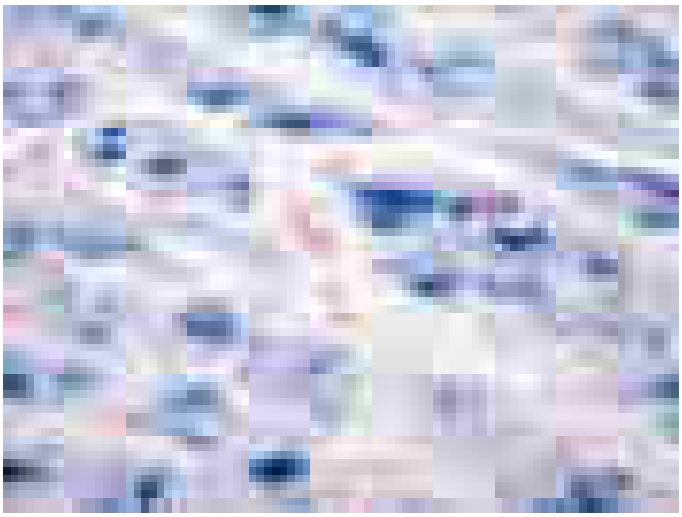

FIGURE 254-9 Hemochromatosis. Microscopic image of an endomyocardial biopsy showing extensive iron deposition within the cardiac myocytes with the Prussian blue stain (400× original magnification). *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

or deferasirox can help to improve cardiac function if myocyte loss and replacement fibrosis are not too severe.

Inborn disorders of metabolism occasionally present with DCM, although they are most often associated with restrictive cardiomyopathy (Table 254-4).

FAMILIAL DCM

The genetic basis for cardiomyopathy is discussed in the section "Genetic Etiologies of Cardiomyopathy." The recognized frequency of familial involvement in DCM has increased to over 30%. Mutations in *TTN*, encoding the giant sarcomeric protein titin, are the most common cause of DCM, accounting for up to 25% of familial disease. On average, men with *TTN* mutations develop cardiomyopathy a decade before women, without distinctive clinical features. Mutations in thick and thin filament genes account for ~8% of DCM and may manifest in early childhood.

The most recognizable familial cardiomyopathy syndromes with extracardiac manifestations are the *muscular dystrophies.* Both Duchenne's and the milder Becker's dystrophies result from abnormalities in the X-linked dystrophin gene of the sarcolemmal membrane. Skeletal myopathy is present in multiple other genetic cardiomyopathies (Table 254-3), some of which are associated with creatine kinase elevations.

Patients and families with a history of arrhythmias and/or conduction system disease which precede or supersede cardiomyopathy may have abnormalities of the nuclear membrane lamin proteins. While all dilated cardiomyopathies carry a risk of sudden death, a family history of cardiomyopathy with sudden death raises suspicion for a particularly arrhythmogenic mutation; affected family members may be considered for implantable defibrillators even before meeting the reduced ejection fraction threshold for primary prevention of sudden death.

A prominent family history of sudden death or ventricular tachycardia before clinical cardiomyopathy suggests genetic defects in the desmosomal proteins **(Fig. 254-10)**. Originally described as affecting the right ventricle (arrhythmogenic right ventricular cardiomyopathy [ARVC]), this disorder (arrhythmogenic cardiomyopathy) can affect either or both ventricles. Patients often present first with ventricular tachycardia. Genetic defects in proteins of the desmosomal complex disrupt myocyte junctions and adhesions, leading to replacement of myocardium by deposits of fat. Thin ventricular walls may be recognized on echocardiography but are better visualized on MRI. Because desmosomes are also important for elasticity of hair and skin, some of the defective desmosomal proteins are associated with striking "woolly hair" and thickened skin on the palms and soles. Implantable defibrillators are usually indicated to prevent sudden death. There is variable progression to right, left, or biventricular failure.

Left ventricular noncompaction is a condition of unknown prevalence that is increasingly revealed with the refinement of imaging techniques. The diagnostic criteria include the presence of multiple trabeculations in the left ventricle distal to the papillary muscles, creating a "spongy" appearance of the apex, but are increasingly recognized as non-specific findings in other cardiac diseases. Noncompaction has been associated with multiple genetic variants in the sarcomeric and other genes, such as *TAZ* (encoding tafazzin). The diagnosis may be made incidentally or in patients previously diagnosed with cardiomyopathy, in whom the criteria for noncompaction may appear and resolve with changing left ventricular size and function. The three cardinal clinical features of ventricular arrhythmias, embolic events, and heart failure are largely restricted to patients with concomitant systolic dysfunction. Treatment generally includes anticoagulation and early consideration for an implantable defibrillator, in addition to neurohormonal antagonists as indicated by stage of disease.

Some families inherit a susceptibility to viral-induced myocarditis. This propensity may relate to abnormalities in cell surface receptors, such as the coxsackie-adenovirus receptor, that bind viral proteins. Some may have partial homology with viral proteins such that an autoimmune response is triggered against the myocardium.

Prognosis and therapy of familial DCM are dictated primarily by the stage of clinical disease and the risk for sudden death. In some cases, the familial etiology facilitates prognostic decisions, particularly regarding the likelihood of recovery after a new diagnosis, which is unlikely for familial disease. The rate of progression of disease is to some extent heritable, although marked variation can be seen. However, there have been cases of remarkable clinical remission after acute presentation, likely after a reversible additional insult, such as prolonged tachycardia or infective myocarditis.

TAKOTSUBO CARDIOMYOPATHY

The apical ballooning syndrome, or stress-induced cardiomyopathy, occurs typically in older women after sudden intense emotional or physical stress. The ventricle shows global ventricular dilation with basal contraction, forming the shape of the narrow-necked jar (*takotsubo*) used in Japan to trap octopuses. Originally described in Japan, it is increasingly recognized elsewhere during emergency cardiac catheterization and intensive care unit admissions for noncardiac conditions. Presentations include pulmonary edema, hypotension, and chest pain with ECG changes mimicking an acute infarction. The left ventricular dysfunction extends beyond a specific coronary artery distribution and generally resolves within days to weeks. Animal models

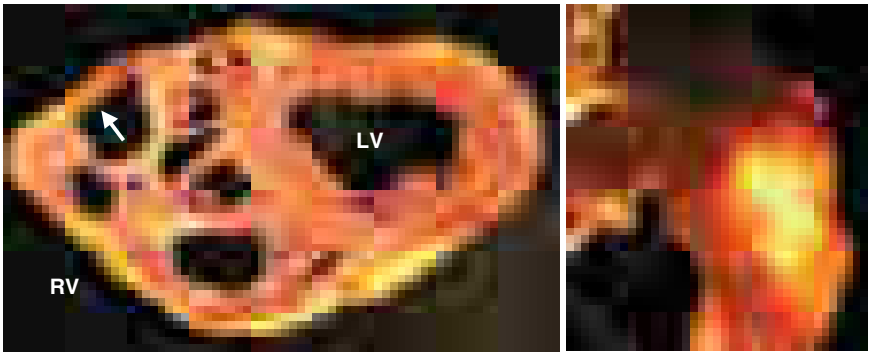

FIGURE 254-10 Arrhythmogenic right ventricular cardiomyopathy. *A.* Cross-sectional slice of a pathology specimen removed at transplantation, showing severe dilation and thinning of the right ventricle (RV) with extensive fatty replacement of right ventricular myocardium. ***B.*** The remarkably thin right ventricular free wall is revealed by transillumination. LV, left ventricle. *(Images courtesy of Gayle Winters, MD, and Richard Mitchell, MD, PhD, Division of Pathology, Brigham and Women's Hospital, Boston.)*

and ventricular biopsies suggest that this acute cardiomyopathy may result from intense sympathetic activation with heterogeneity of myocardial autonomic innervation, diffuse microvascular spasm, and/or direct catecholamine toxicity. Coronary angiography may be required to rule out acute coronary occlusion. No therapies have been proven beneficial, but reasonable strategies include nitrates for pulmonary edema, intraaortic balloon pump if needed for low output, combined alpha and beta blockers rather than selective beta blockade if hemodynamically stable, and magnesium for arrhythmias related to QT prolongation. Anticoagulation is generally withheld due to the occasional occurrence of ventricular rupture. While the prognosis is generally good, recurrences have been described in up to 10% of patients.

IDIOPATHIC DCM

Idiopathic DCM is a diagnosis of exclusion, when all other known factors have been excluded. Approximately two-thirds of dilated cardiomyopathies are still labeled as idiopathic; however, a substantial proportion of these may reflect unrecognized genetic disease. Continued reconsideration of etiology during chronic heart failure management often reveals specific causes later in a patient's course.

OVERLAPPING TYPES OF CARDIOMYOPATHY

The limitations of our phenotypic classification are revealed through the multiple overlaps between the etiologies and presentations of the three types. Cardiomyopathy with reduced systolic function but without severe dilation can represent early DCM, "minimally dilated cardiomyopathy," or restrictive diseases without marked increases in ventricular wall thickness. For example, sarcoidosis and hemochromatosis can present as dilated or restrictive disease. Early stages of amyloidosis are often mistaken for hypertrophic cardiomyopathy. Progression of hypertrophic cardiomyopathy into a "burned-out" phase occurs occasionally, with decreased contractility and modest ventricular dilation. Overlaps are particularly common with the inherited metabolic disorders, which can present as any of the three major phenotypes (Fig. 254-4).

DISORDERS OF METABOLIC PATHWAYS

Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumulation within cells (see Tables 254-3, and 254-4). Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing "pseudohypertrophy," usually with an abnormally short PR interval. The pseudo-hypertrophic phenotype is most common, but restrictive and DCM may occur. Most of these diseases are diagnosed during childhood.

Fabry's disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by one of more than 160 mutations in *GLA*. This disorder of glycosphingolipid metabolism is an X-linked disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues but usually also involves the skin, peripheral nerve, and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures **(Fig. 254-11)**. Diagnosis can be made through assessment of enzyme activity and/or *GLA* sequencing and is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well-established for this therapy, which requires frequent infusions of the enzyme at a cost of >$100,000 a year. Enzyme replacement can also improve the course of Gaucher's disease, in which cerebroside-rich cells accumulate in multiple organs due to a deficiency of beta-glucosidase. Cerebroside-rich cells infiltrate the heart, which can also lead to a hemorrhagic pericardial effusion and valvular disease.

Glycogen storage diseases lead to accumulation of lysosomal storage products and intracellular glycogen accumulation, particularly with *glycogen storage disease type III,* due to a defective debranching enzyme. There are >10 types of *mucopolysaccharidoses,* in which autosomal recessive or X-linked deficiencies of lysosomal enzymes lead to the accumulation of glycosaminoglycans in the skeleton, nervous system, and occasionally the heart. With characteristic facies, short stature, and frequent cognitive impairment, most individuals are diagnosed early in childhood and die before adulthood.

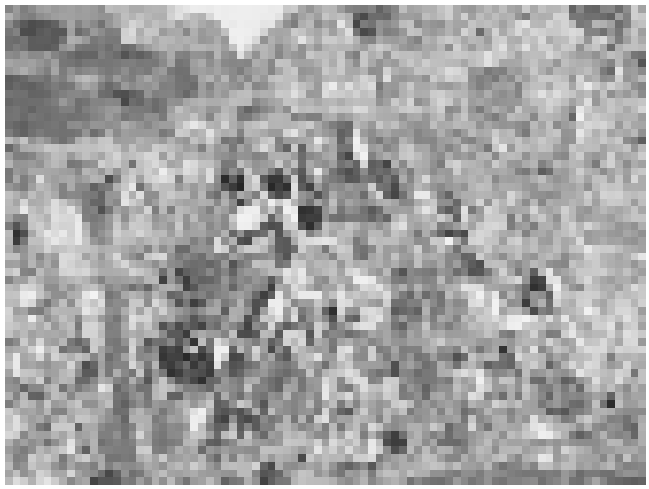

FIGURE 254-11 Fabry's disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

Carnitine is an essential cofactor in long-chain fatty acid metabolism. Multiple defects have been described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive or DCM, often presenting in children. Fatty acid oxidation requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replacement of fatty acid intermediates and carnitine.

Two monogenic metabolic cardiomyopathies cause markedly increased ventricular wall thickness without an increase of muscle subunits or an increase in contractility. Mutations in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (*PRKAG2*) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation. Several defects have been reported in an X-linked lysosome-associated membrane protein (*LAMP2*). This defect can be maternally transmitted or sporadic and has occasionally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, mental retardation, and hepatic dysfunction referred to as *Danon's disease.* Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is dominated by abnormal diastolic function, often with mildly decreased contractility and ejection fraction (usually >30–50%). Both atria are enlarged, sometimes massively. Modest left ventricular dilation can be present, usually with an end-diastolic dimension <6 cm. End-diastolic pressures are elevated in both ventricles, with preservation of cardiac output until late in the disease. Subtle exercise intolerance is usually the first symptom but is often not recognized until after clinical presentation with congestive symptoms. The restrictive diseases often present with relatively more right-sided symptoms, such as edema, abdominal discomfort, and ascites, although filling pressures are elevated in both ventricles. The cardiac impulse is less displaced than in DCM and less dynamic than in hypertrophic cardiomyopathy. A fourth heart sound is more common than a third heart sound in sinus rhythm, but atrial fibrillation is common. Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul's sign).

TABLE 254-5 Causes of Restrictive Cardiomyopathies
Infiltrative (Between Myocytes)
Amyloidosis
Primary (light chain amyloid)
Familial (abnormal transthyretin)[a]
Senile (normal transthyretin or atrial peptides)
Inherited metabolic defects[a]
Storage (Within Myocytes)
Hemochromatosis (iron)[a]
Inherited metabolic defects[a]
Fabry's disease
Glycogen storage disease (II, III)
Fibrotic
Radiation
Scleroderma
Endomyocardial
Possibly related fibrotic diseases
Tropical endomyocardial fibrosis
Hypereosinophilic syndrome (Löffler's endocarditis)
Carcinoid syndrome
Radiation
Drugs: e.g., serotonin, ergotamine
Overlap with Other Cardiomyopathies
Hypertrophic cardiomyopathy/"pseudohypertrophic"[a]
"Minimally dilated" cardiomyopathy
Early-stage dilated cardiomyopathy
Partial recovery from dilated cardiomyopathy
Sarcoidosis
Idiopathic[a]

[a]Can be familial.

FIGURE 254-12 Restrictive cardiomyopathy—amyloidosis. Gross specimen of a heart with amyloidosis. The heart is firm and rubbery with a waxy cut surface. The atria are markedly dilated, and the left atrial endocardium, normally smooth, has yellow-brown amyloid deposits that give texture to the surface. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury (Table 254-5). The differential diagnosis should include constrictive pericardial disease, which may also be dominated by right-sided heart failure.

INFILTRATIVE DISEASE

Amyloidosis is the major cause of restrictive cardiomyopathy (Figs. 254-12, 254-13, and 254-14). Several proteins can self-assemble to form the beta-sheets of amyloid proteins, which deposit with different consequences depending on the type of protein. The systemic amyloidoses are discussed in Chap. 108. In addition to cardiac infiltration, neurologic involvement occurs commonly with primary amyloidosis (immunoglobulin light chains) and with familial amyloidosis (genetic abnormalities of transthyretin). There are >100 identified mutations in transthyretin on chromosome 13, among which the V122I transthyretin mutation has been identified in ~4% of African Americans in whom it is associated with a 50% increased risk of heart failure. However, penetrance of the V122I mutation is incomplete with most mutation carriers free of heart failure at 70 years of age.

Organ dysfunction in amyloidosis was once attributed solely to physical disruption from the infiltrating amyloid fibrils, but newer information suggests additional direct toxicity from the immunoglobulin light chain and abnormal transthyretin protein aggregates themselves. In senile amyloidosis, there is abnormal accumulation of normal transthyretin or natriuretic peptide folding, detected in 10% of people aged >80 years and half of those aged >90 years but often without apparent clinical disease. Men show a greater burden of amyloid deposition and twentyfold greater likelihood of clinical disease with senile amyloidosis. The aging of the population will soon render senile amyloidosis the most common of the amyloidoses.

Cardiac amyloid is classically suspected from thickened ventricular walls with an ECG that shows low voltage. However, low voltage is not always present and is less common in familial or senile amyloidosis

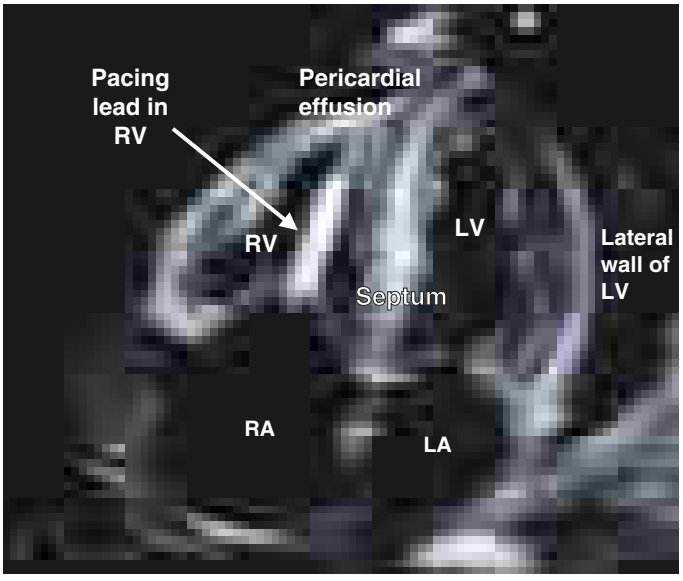

FIGURE 254-13 Restrictive cardiomyopathy—amyloidosis. Echocardiogram showing thickened walls of both ventricles without major chamber dilation. The atria are markedly dilated, consistent with chronically elevated ventricular filling pressures. In this example, there is a characteristic hyperrefractile "glittering" of the myocardium typical of amyloid infiltration, which is a non-specific finding with contemporary echocardiography. The mitral and tricuspid valves are thickened. A pacing lead is visible in the right ventricle (RV), and a pericardial effusion is evident. Note that the echocardiographic and pathologic images are vertically opposite, such that the left ventricle (LV) is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. LA, left atrium; RA, right atrium. *(Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)*

FIGURE 254-14 Amyloidosis—microscopic images of amyloid involving the myocardium. The left panel (hematoxylin and eosin stain) shows glassy, grey-pink amorphous material infiltrating between cardiomyocytes, which stain a darker pink. The right panel shows a sulfated blue stain that highlights the amyloid green and stains the cardiac myocytes yellow. (The Congo red stain can also be used to highlight amyloid; under polarized light, amyloid will have an apple-green birefringence when stained with Congo red.) Images at 100× original magnification. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

than in primary AL amyloidosis. A characteristic refractile brightness in the septum on echocardiography is suggestive of the diagnosis, but neither sensitive nor specific. Both atria are dilated, often dramatically, and diastolic dysfunction may be more obvious than in left ventricular hypertrophy from other causes. Amyloid infiltration can also be detected with gadolinium enhancement in MRI. Technetium pyrophosphate imaging is sensitive and specific for *TTR* amyloidosis as opposed to AL amyloidosis. The diagnosis of primary or familial amyloidosis can sometimes be made from biopsies of an abdominal fat pad or the rectum, but cardiac amyloidosis is most reliably identified from a biopsy of the heart, in which amyloid fibrils infiltrate the myocardium diffusely, particularly around the conduction system and coronary vessels (Fig. 254-14). Diagnosis of the type of amyloid protein requires immunohistochemistry of biopsied tissue rather than serum or urine electrophoresis, which can lead to incorrect classification.

Therapy for all types of amyloid is predominantly for symptoms of fluid retention, which often requires high doses of loop diuretics. Digoxin bound to the amyloid fibrils can reach toxic levels, and should therefore be used only in very low doses, if at all. There is no evidence regarding use of neurohormonal antagonists in amyloid heart disease, where the possible theoretical benefit has to be balanced against the possibility of aggravating postural hypotension and diminishing the crucial heart rate reserve. The risk of intracardiac thrombi may warrant chronic anticoagulation.

The prognosis is worst for primary amyloid, with a median survival of 6–12 months after presentation, but that has improved substantially with the use of the proteasome inhibitor bortezomib. If present, multiple myeloma is treated with chemotherapy, the extent of which is often limited by the potential of worsening cardiac dysfunction. Immunoglobulin-associated amyloid has occasionally been treated with sequential heart transplantation and delayed bone marrow transplant, with frequent recurrence of amyloid in the transplanted heart. Abnormal transthyretin-associated cardiac amyloid has a somewhat better prognosis and can be treated in selected patients with heart and liver transplantation. Senile cardiac amyloid has the slowest progression and best overall prognosis. Novel therapies including RNA interference and small molecules are being studied in *TTR* amyloidosis.

FIBROTIC RESTRICTIVE CARDIOMYOPATHY

Progressive fibrosis can cause restrictive myocardial disease without ventricular dilation. Thoracic radiation, common for breast and lung cancer or mediastinal lymphoma, can produce early or late restrictive cardiomyopathy. Patients with *radiation cardiomyopathy* may present with a possible diagnosis of constrictive pericarditis, as the two conditions often coexist. Careful hemodynamic evaluation and, often, endomyocardial biopsy should be performed if considering pericardial stripping surgery, which is unlikely to be successful in the presence of underlying restrictive cardiomyopathy. *Scleroderma* causes small vessel spasm and ischemia that can lead to a small, stiff heart with reduced ejection fraction without dilation. The pulmonary hypertension associated with scleroderma may lead to more clinical right heart failure because of concomitant fibrotic disease of the right ventricle.

ENDOMYOCARDIAL DISEASE

The physiologic picture of elevated filling pressures with atrial enlargement and preserved ventricular contractility with normal or reduced ventricular volumes can result from extensive fibrosis of the endocardium, without transmural myocardial disease. For patients who have not lived in the equatorial regions, this picture is rare, and when seen is often associated with a history of chronic hypereosinophilic syndrome (*Löffler's endocarditis*), which is more common in men than women. In this disease, persistent hypereosinophilia of >1500 eos/μL for at least 6 months can cause an acute phase of eosinophilic injury in the endocardium (see earlier discussion of eosinophilic myocarditis), with systemic illness and injury to other organs. There is usually no obvious cause, but the hypereosinophilia can occasionally be explained by allergic, parasitic, or malignant disease. It is postulated to be followed by a period in which cardiac inflammation is replaced by evidence of fibrosis with superimposed thrombosis. In severe disease, the dense fibrotic layer can obliterate the ventricular apices and extend to thicken and tether the AV valve leaflets. The clinical disease may present with heart failure, embolic events, and atrial arrhythmias. While plausible, the sequence of transition from eosinophilic myocarditis or Löffler's endocarditis to endomyocardial fibrosis has not been clearly demonstrated.

In tropical countries, up to one-quarter of heart failure may be due to *endomyocardial fibrosis,* affecting either or both ventricles. This condition shares with the previous condition the partial obliteration of the ventricular apex with fibrosis extending into the valvular inflow tract and leaflets; however, it is not clear that the etiologies are the same for all cases. Pericardial effusions frequently accompany endomyocardial fibrosis but are not common in Löffler's endocarditis. For endomyocardial fibrosis, there is no gender difference, but a higher prevalence in African-American populations. While tropical endomyocardial fibrosis could represent the end-stage of previous hypereosinophilic disease triggered by endemic parasites, neither prior parasitic infection nor hypereosinophilia is usually documented. Geographic nutritional deficiencies have also been proposed as an etiology.

Medical treatment focuses on glucocorticoids and chemotherapy to suppress hypereosinophilia when present. Fluid retention may become increasingly resistant to diuretic therapy. Anticoagulation is recommended. Atrial fibrillation is associated with worse symptoms and prognosis, but may be difficult to suppress. Surgical resection of the apices and replacement of the fibrotic valves can improve symptoms, but surgical morbidity and mortality and later recurrence rates are high.

The serotonin secreted by *carcinoid* tumors can produce fibrous plaques in the endocardium and right-sided cardiac valves, occasionally affecting left-sided valves, as well. Valvular lesions may be stenotic or regurgitant. Systemic symptoms include flushing and diarrhea. Liver disease from hepatic metastases may play a role by limiting hepatic function and thereby allowing more serotonin to reach the venous circulation.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases **(Figs. 254-15 and 254-16)**. It has previously been termed *hypertrophic obstructive cardiomyopathy* (HOCM), *asymmetric*

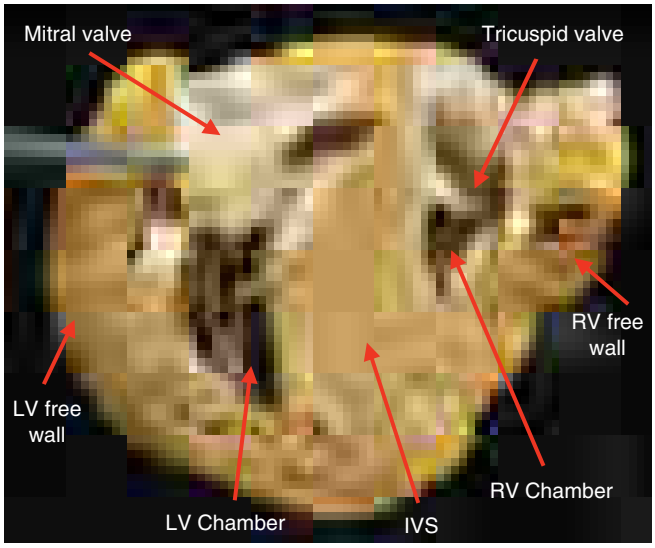

FIGURE 254-15 Hypertrophic cardiomyopathy. Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

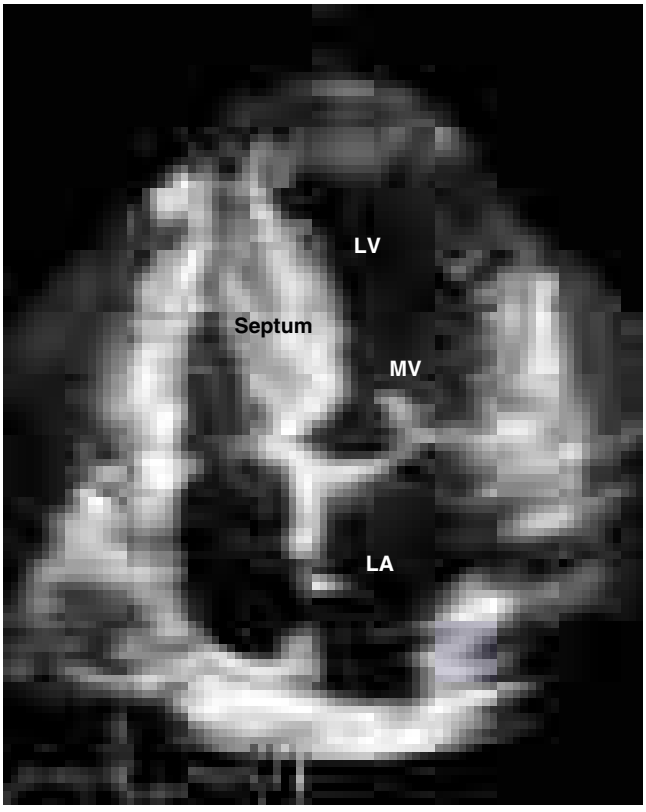

FIGURE 254-16 Hypertrophic cardiomyopathy. This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. *(Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)*

septal hypertrophy (ASH), and *idiopathic hypertrophic subaortic stenosis* (IHSS). However, the accepted terminology is now hypertrophic cardiomyopathy with or without obstruction. Prevalence in North America, Africa, and Asia is about 1:500. It is the leading cause of sudden death in the young and is an important cause of heart failure. Although pediatric presentation is associated with increased early morbidity and mortality, the prognosis for patients diagnosed as adults is generally favorable.

The clustering of hypertrophic cardiomyopathy within families has been appreciated since recognition of the disease ~55 years ago. Echocardiographic screening of families revealed an autosomal dominant pattern of inheritance. Initial genetic studies using linkage analysis in large families identified disease-causing mutations in sarcomeric genes. A sarcomere mutation is present in ~60% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different sarcomere genes with >1400 mutations have been implicated, although ~80% of patients have a mutation in either *MYH7* or *MYBPC3* (Table 254-3).

Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present at birth and usually develops later in life. Accordingly, screening of family members should begin in adolescence and extend through adulthood. In *MYBPC3* mutation carriers, the average age of disease development is 40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the *same* mutation may have a different extent and pattern of hypertrophy (e.g., asymmetric versus concentric), occurrence of outflow tract obstruction, and associated clinical outcomes (e.g., sudden death, atrial fibrillation).

At the level of the sarcomere, hypertrophic cardiomyopathy mutations lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere mutations lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes **(Fig. 254-17)**, which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily detected with MRI. These areas of "scar" may represent substrate for the development of ventricular arrhythmias. Increased

FIGURE 254-17 Hypertrophic cardiomyopathy. Microscopic image of hypertrophic cardiomyopathy showing the characteristic disarrayed myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size and interstitial fibrosis is present. *(Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)*

thickness and decreased luminal area of the intramural vessels in hypertrophied myocardium contribute to microvascular ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation.

Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (Fig. 254-15). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic cardiomyopathy) is less often familial and has a different genetic substrate, with sarcomere mutations present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteriorly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. In order to maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the severity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish ventricular volume and transiently worsen obstruction, such as standing from a squatting position or the Valsalva maneuver.

DIAGNOSIS

The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or symptoms of exertional dyspnea, angina, or syncope. Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (Fig. 254-16) is central to diagnosis due to the insensitivity of examination and ECG and the need to exclude other causes for hypertrophy. The identification of a disease-causing mutation in a proband can focus family evaluations on mutation carriers, but this strategy requires a high degree of certainty that the mutation is truly pathogenic and not a benign DNA variant. Biopsy is not needed to diagnose hypertrophic cardiomyopathy but can be used to exclude infiltrative and metabolic diseases. Rigorous athletic training (athlete's heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic cardiomyopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete's heart regresses with cessation of training, and is accompanied by supernormal exercise capacity (VO_{2max} >50 mL/kg per min), mild ventricular dilation, and normal diastolic function.

TREATMENT

Hypertrophic Cardiomyopathy

Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 254-18). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. β-Adrenergic blocking agents and L-type calcium channel blockers

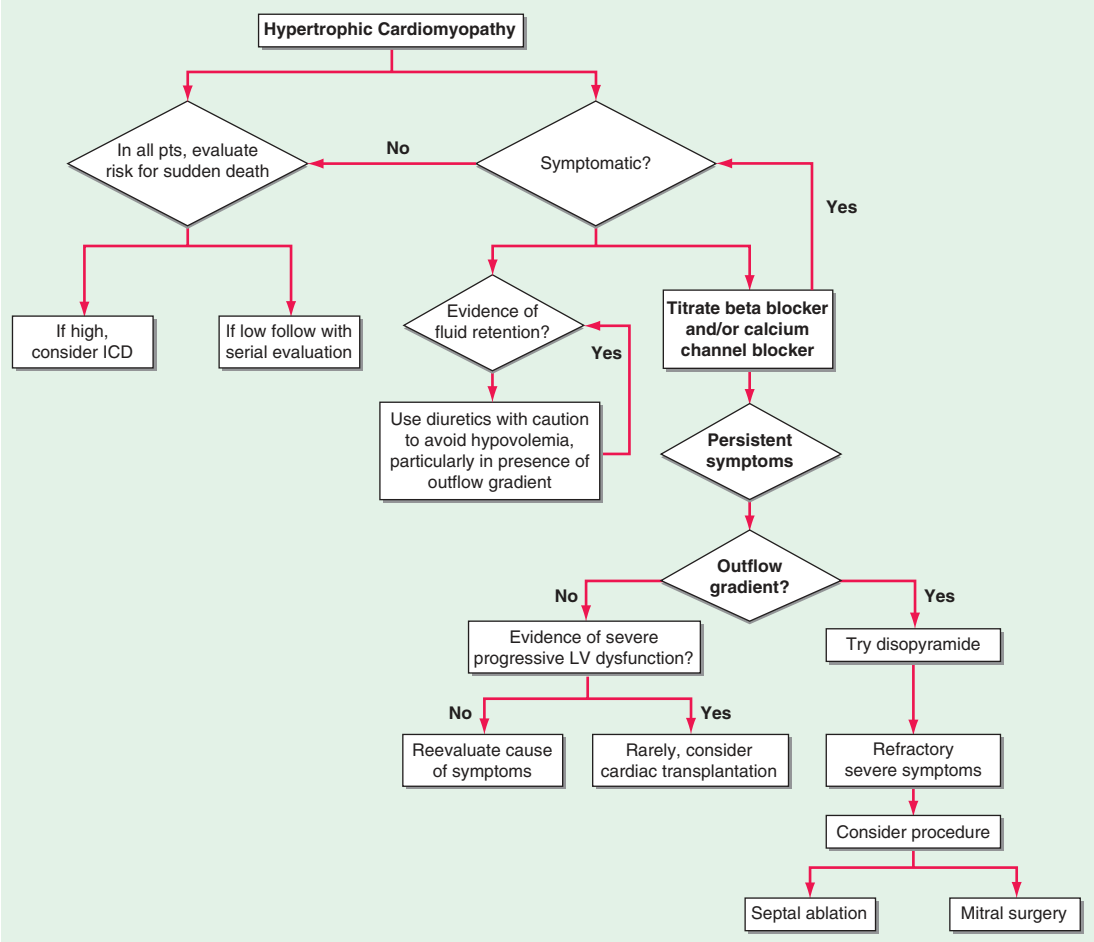

FIGURE 254-18 Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

(e.g., verapamil) are first-line agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can sometimes be controlled with the addition of disopyramide, an antiarrhythmic agent with potent negative inotropic properties.

Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in ~5% of patients, for whom surgical myectomy or alcohol septal ablation may be effective. Developed over 50 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and symptoms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar periprocedural outcomes and gradient reduction as surgical myomectomy. Until long-term outcomes are demonstrated for this procedure, it is relegated primarily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised.

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sport are prohibited. Factors that increase the risk of sudden death from a baseline of 0.5% per year are presented in **Table 254-6**. As sudden death has not been reduced by medical or procedural interventions, an implantable cardioverter-defibrillator is advised for patients with two or more risk factors and is advised on a selected basis for patient with one risk factor. Nevertheless, the positive predictive value of most risk factors is low, and many patients receiving a defibrillator never receive an appropriate therapy. Long-term use of a defibrillator may be associated with serious device-related complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing.

TABLE 254-6 Risk Factors for Sudden Death in Hypertrophic Cardiomyopathy

MAJOR RISK FACTOR		SCREENING TECHNIQUE
History of cardiac arrest or spontaneous sustained ventricular tachycardia[a]		History
Syncope	Nonvagal, often with or after exertion	History
Family history of sudden cardiac death		Family history
Spontaneous nonsustained ventricular tachycardia[b]	>3 beats at rate >120	Exercise or 24- to 48-h ambulatory recording
LV thickness >30 mm	Present in <10% of patients	Echocardiography
Abnormal blood pressure response to exercise[b]	Systolic blood pressure fall or failure to increase at peak exercise	Maximal upright exercise testing

[a]Implantable cardioverter-defibrillator advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors. [b] Prognostic value most applicable to patients <40 years old.

Abbreviation: LV, left ventricle.

Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. β-Adrenergic blocking agents and L-type calcium channel blockers slow AV nodal conduction and improve symptoms; cardiac glycosides should be avoided, as they may increase contractility and worsen obstruction. Symptoms exacerbated by atrial fibrillation may persist despite adequate rate control due to loss of AV synchrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended.

PROGNOSIS

The general prognosis for hypertrophic cardiomyopathy is better than in early studies of referral populations. For patients diagnosed as adults, survival is comparable to an age-matched population without cardiomyopathy. The sudden death risk is <1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction with or without dilated remodeling ("burned out" or end-stage hypertrophic cardiomyopathy). These patients suffer from low cardiac output and have a high risk of death from progressive heart failure and sudden death unless they undergo cardiac transplantation.

GLOBAL PERSPECTIVES

Comparison of myocardial diseases across eras and countries is complicated by differences in techniques for diagnosis, such as endomyocardial biopsy, testing for viral genomes, and specific antibodies. Deaths attributed to cardiomyopathy/myocarditis in the Global Burden of Disease study have increased by 51% between 1990 and 2013 while the age-adjusted mortality rates have declined by 12.6% and the disability-adjusted life years lost have declined by almost 4%. For comparison, the current mortality rates are comparable to those of rheumatic heart disease, which has declined overall by 26.5 and by 55% after adjustment for age. Deaths from Chagas' cardiomyopathy worldwide have declined from 12.7 thousand to 10.6 thousand, with a reduction of 51.7% in the age-adjusted rates per 100,000 population to 0.2, attributable in major part to improved health conditions in rural areas of South and Central America. By contrast, there has been an increase in the prevalence of Chagas' disease to an estimated 300,000 in the United States, detected largely through blood donation. It is no longer limited to patients from known endemic areas as de novo infection is increasingly recognized in warmer regions of the country.

Health care for other diseases affects myocarditis and cardiomyopathy. Developed nations will see a higher prevalence of cardiomyopathy due to chemotherapy. However, vaccination has reduced deaths from diphtheria myocarditis to <50 per 100 million population, currently most common in Russia. World regions providing highly active antiviral therapy for HIV have decreased not only transmission but also the rate of associated cardiomyopathy by several-fold. Increasing availability of clinical genetic testing is expected to shift the apparent epidemiology of cardiomyopathy away from acquired causes toward causative and facilitating genetic factors. For instance, heart failure with preserved ejection fraction attributed to hypertension and diabetes is increasingly recognized to represent amyloidosis from mutant transthyretin, with distinct recognized mutations in Portugal, Japan, and the African-Caribbean population.

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255 Cardiac Transplantation and Prolonged Assisted Circulation

Mandeep R. Mehra

Advanced heart failure, a distinct syndrome, is characterized by refractoriness to conventional therapy and represents a vexing clinical dilemma that is associated with an increased symptom burden, frequent hospitalization, a poor quality of life and high risk of death. Such individuals do not tolerate neurohormonal antagonists at recommended doses, exhibit cardiorenal syndrome, maintain markedly poor cardiac reserve on cardiopulmonary stress testing, and typically display a low cardiac output state with elevated pulmonary pressures. In general, therapeutic targets shift away from disease modifying neurohormonal therapy to surgical options that attend directly to the myocardial stress and strain relationship. Most often, prolonged circulatory assistance using mechanical pumps or cardiac transplantation is required to reliably improve quality of life and long-term survival.

CARDIAC TRANSPLANTATION

A decade after Norman Shumway had accomplished the technique of a successful heart transplant in canines, Christiaan Barnard successfully performed the first human to human transplant on December 3, 1967. Now, 5 decades later, this surgery has become entrenched in the standard armamentarium for treating patients with advanced heart failure who are otherwise healthy enough to receive such a life altering treatment. Globally, >150,000 patients have undergone cardiac transplantation with a 1 year survival >80% and median survival of nearly 11 years. These gains have been ushered in due to advances in immunosuppression and identification and management of allograft rejection, as well as a comprehensive appreciation for late complications including accelerated coronary artery disease, malignancy, and renal failure.

CANDIDATES FOR CARDIAC TRANSPLANTATION

The demand for cardiac transplantation outstrips the availability of organ donors. Hence, attention to the optimal utility, equitable allocation, and patient autonomy must dominate the decisions to identify and list candidates for transplantation. Simultaneously, attempts at expanding the donor pool have surfaced. However, vigilance to evaluating candidates most likely to have a successful outcome from transplantation takes pre-eminence. In 2006, the International Society for Heart and Lung Transplantation identified a set of criteria to guide listing of patients. These criteria were updated in 2016 and include additional attention to the growing epidemiology of candidates suffering from congenital heart disease, restrictive and infiltrative cardiomyopathy (such as amyloidosis), and chronic infections in recipients (such as Chagas' disease, tuberculosis and hepatitides). Selected general principles for listing candidates for cardiac transplantation are enumerated in Table 255-1.

TABLE 255-1 Principles for Listing Candidates for Cardiac Transplantation

PRINCIPLE	COMMENT
Advanced Disease Severity	Refractory heart failure with a VO_2 of <14 mL/kg/min (<12, if on beta blockers) or percent predicted VO_2 <50%; combination of intolerance to disease modifying therapy, cardiorenal syndrome, use of inotropic therapy to maintain stability or need for a left ventricular assist system.
Co-Morbidity	Age is not an absolute contraindication, but frailty should be considered a relative contraindication; a BMI > 35 kg/m^2 should require weight loss; cancer should be dealt with on an individual basis (e.g., low-grade prostate cancer may not be a contraindication); poorly controlled diabetes mellitus or end-organ damage may be a contraindication; eGFR <30 mL/min/1.73 m^2 is a relative contraindication; severe cerebrovascular disease or peripheral vascular disease (which will limit rehabilitation or function) is also a relative contraindication.
Donor-Recipient Matching	Sensitized individuals with circulating antibodies should have a prospective or virtual cross match; pulmonary vascular resistance with a transpulmonary gradient >15, PVR >3 Wood Units and absolute PA systolic pressure >50 mmHg provided the systolic BP is >85 mmHg is a relative contraindication unless reactive.
Psychosocial Issues	Tobacco use in any form limits posttransplant survival and should be stopped for at least 6-months; substance abuse, including marijuana, should be a contraindication if the individual cannot demonstrate control and cessation; patients with severe cognitive-behavioral disabilities or dementia (inability to ever understand and cooperate with medical care) have the potential for self-harm and should not receive a transplant.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PA, pulmonary artery; PVR, pulmonary vascular resistance; VO_2, peak oxygen consumption.

PRINCIPLES OF DONOR RECOVERY AND ALLOCATION

Although listing criteria for candidates are typically adjudicated at a center level, organ allocation is handled by national regulatory processes in most countries. The allocation of donor hearts is based on (a) the urgency of the clinical situation, (b) the time spent on the waiting list, and (c) the distance from the recipient center. Thus, candidates who are hospitalized and require temporary mechanical cardiac support devices or daily invasive hemodynamic evaluation and intravenous inotropic therapy to maintain stability are given the highest urgency status, while those able to ambulate and live at home receive a lower urgency status. The geographical regional reach for allocation is based not only on territorial considerations but also on the time that a donor heart would be in transit and therefore in out of body "cold ischemia time," which is typically limited to 4 h. The final key feature that is included in the allocation offer relates to the ABO blood group. Donor organs are offered based on these initial characteristics and then a more detailed donor assessment ensues, resulting in acceptance or decline for any given donor heart. It is important to note that the time constraints imposed on the retrieval process make it difficult to invoke HLA matching of the donor and recipient. In cases where there is a high likelihood of sensitization in the recipient (preformed circulating antibodies against donor antigens), a prospective or virtual cross match is entertained prior to acceptance. Other clinical criteria that are employed in the decision on accepting an offered donor include the donor-recipient size match, the age of the donor (typically restricted to under 55 years) and presence or absence of concomitant pathology such as coronary artery disease, left ventricular hypertrophy or severe injury to the allograft manifest by excess leak of injury markers (troponins) or poor contractile performance. In many cases, the prospective cardiac allograft can be reconditioned by use of hormonal therapy (including thyroid hormone supplementation) and used for transplantation even

if the initial evaluation suggests poor function. In efforts to enhance the donor pool, systems that allow ex-vivo normothermic perfusion to evaluate and reanimate organs with a prolonged out of body time are being developed. The classic heart donor is derived from a donor with brain death; however, donors with circulatory death are being increasingly evaluated as candidates for cardiac reanimation using a variety of techniques including ex-vivo reanimation and subsequent transplantation.

SURGERY FOR CARDIAC TRANSPLANTATION

The most common contemporary operation is referred to as a "bicaval" orthotopic cardiac transplant that mimics the natural anatomic position. In this operation, the donor and recipient superior and inferior vena cava are connected as are the aortic and pulmonary great vessels. The left atrium of the recipient retains its roof including the draining pulmonary veins and the donor left atrium is then sutured to the retained atrial tissue. This technique maintains function of the donor right atrium, important for governing early postoperative right heart output, and may prevent atrial arrhythmias. The recipient is left with a surgical denervation and the allograft is not responsive to any direct sympathetic or parasympathetic stimuli. Therefore, early in the adaptive postoperative phase, high-dose catecholamines are required to maintain adequate function. Due to denervation, bradycardia in a cardiac allograft cannot be treated with atropine and the drug of choice is isoproterenol. Once the cardiac allograft adapts to its host circulation, the function is usually adequate at rest and with exercise to provide normal physical activity.

CARDIAC ALLOGRAFT REJECTION AND IMMUNOSUPPRESSION

The ability to perform endomyocardial biopsies, evaluate rejection pathologically and the introduction of the immunosuppression agent cyclosporine heralded cardiac transplantation as a viable clinical therapy. Triple drug immunosuppression, which includes a calcineurin inhibitor (cyclosporine or tacrolimus), corticosteroids and antiproliferative immunosuppression (azathioprine, mycophenolate mofetil, sirolimus or everolimus) is now the standard cocktail used. The combination that is most commonly used and achieves the best standard outcomes includes the combination of tacrolimus, mycophenolate mofetil, and prednisone. In those at high risk for rejection (multiparous women, sensitized individuals) or in situations where use of calcineurin inhibitors is delayed (renal dysfunction), induction therapy using monoclonal (basiliximab) or polyclonal antibodies (antithymocyte globulin) to provide augmented immunosuppression is used. The typical management strategy includes gradual weaning of steroids over time as surveillance endomyocardial biopsies are performed and clinical as well as sub-clinical pathological quiescence is established. Table 255-2 describes the immunosuppression drugs in common use.

Acute cellular rejection (ACR) and antibody-mediated rejection (AMR) are two separate forms of cardiac allograft rejection that are recognized and can sometimes coexist. ACR occurs early after transplantation and then declines in incidence after 6 months. This occurs due to a T cell–mediated assault on the donor allograft tissue and histologically is characterized by lymphocytic infiltrates. In mild cases these infiltrates are localized to the peri-venular regions, and in severe cases progresses diffusely into the cardiac interstitium. In late stages of severe ACR, most often associated with hemodynamic compromise, multi-clonal cells such as macrophages, neutrophils, and eosinophils are observed with intramyocardial hemorrhage, myocyte injury and myocyte necrosis. Subclinical ACR is typically treated with high doses of corticosteroid pulses although some centers choose to simply observe mild forms of infiltration since it is known that these recover longitudinally. If hemodynamic compromise occurs, rescue polyclonal antibodies are used in tandem with corticosteroids. Conversely, AMR is immunologically described as a non-cellular antibody-driven phenomenon associated with a pattern of immunopathologic findings of immunoglobulin deposition and complement fixation on immunofluorescence, along with histopathologic findings of endothelial swelling and interstitial edema and cardiac allograft arteriolar vasculitis. AMR is characterized by the emergence of circulating donor-specific antibodies that are thought to fix, complement, and bind to the allograft. Commonly, AMR leads to acute allograft dysfunction and increases the risk for cardiac allograft vasculopathy, and results in worsened cardiac allograft survival compared with ACR. In this form of rejection, therapy is directed towards suppression and removal of circulating antibodies using plasmapheresis and drugs such as rituximab (chimeric monoclonal antibody directed against the CD20 antigen) or in refractory cases, bortezomib (a proteasome inhibitor) or eculizumab (a terminal complement inhibitor). The treatment with immunosuppression requires prophylaxis for opportunistic infections and ongoing surveillance and expertise in recognizing the more common clinical presentations of infections caused by cytomegalovirus (CMV), aspergillus, and other opportunistic agents such as nocardia and toxoplasmosis.

TABLE 255-2 Immunoprophylaxis Drugs in Cardiac Transplantation

DRUG CLASS	GENERIC DRUG	CELLULAR TARGET	MAJOR SIDE EFFECTS
Calcineurin Inhibitors	Cyclosporine	Binds to cyclophilin which then inhibits calcineurin	Hypertension, dyslipidemia, gum hypertrophy, hypertrichosis
	Tacrolimus	Binds to immunophilin FK506 binding protein which inhibits calcineurin	Hypertension, dyslipidemia, alopecia, diabetes mellitus
Anti-Thymocyte Globulin (ATG)	Rabbit ATG	T-cell depletion in blood and peripheral lymphoid tissues through complement-dependent lysis and T-cell activation and apoptosis	Cytokine release syndrome, leukopenia, thrombocytopenia, serum sickness
	Horse ATG	Same as above	Same as above
Interleukin-2 receptor antagonists	Basiliximab	Inhibition of CD-25 of IL-2 receptor	Well tolerated; rare hypersensitivity; increased infection risk
Anti-metabolites	Azathioprine	Imidazolyl derivative and prodrug of 6-mercaptopurine (cell cycle inhibitor)	Bone marrow suppression, pancreatitis, hepatitis
	Mycophenolate Mofetil	Inhibits inosine monophosphate dehydrogenase, which controls guanine monophosphate in the de novo pathway of purine synthesis (inhibits T and B cell proliferation)	Leukopenia, gastrointestinal toxicity
Proliferation-Signal Inhibitors	Sirolimus	Binds with FKBP12 and complex inhibits the mechanistic Target of Rapamycin (mTOR)	Delayed wound healing, non-specific pneumonia, pericardial effusion, hyperlipidemia (hypertriglyceridemia)
	Everolimus	Binds to FKBP12, which inhibits mTORC1 (and not mTORC2)	Dyslipidemia, stomatitis, pericardial effusions and pancytopenia

LATE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

The long-term consequences of exposure to chronic immunosuppression result in a variety of non-immunological cardio-metabolic effects such as hypertension and hyperlipidemia as well as systemic disorders of bone loss and renal dysfunction. One aggressive complication that limits late survival of cardiac allografts includes the development of an accelerated form of coronary artery disease, referred to as cardiac allograft vasculopathy (CAV). This is characterized by a proliferative thickening of the vascular intima of the vasculature that is initiated as a diffuse endothelialitis in the setting of the confluence of the consequences of brain death, ischemia reperfusion injury during the transplant process and early immunological insults. Chronically, the metabolic consequences of hypertension, hyperlipidemia, and disordered glucose regulation result in a further worsening of vascular lesions that are diffuse and noted throughout the coronary tree. Early diagnosis and preventative therapy are critical since it is commonly silent in genesis. Statins, antihypertensive agents, and anti-CMV agents all have demonstrated benefits in reducing CAV. Anti-proliferative immunosuppressive therapy such as mycophenolate mofetil and sirolimus or everolimus prevent vascular intimal thickening compared with azathioprine-based regimens. However, retransplantation is the only definitive form of therapy for advanced allograft CAV **(Fig. 255-1)**.

Another consternation in cardiac transplantation is the development of malignancy with a greater frequency than in the normal population, suggesting that immunosuppression plays a sentinel role in its generation. Posttransplant lymphoproliferative disorders, typically driven by Epstein-Barr virus, occur most frequently and require a reduction in immunosuppression, administration of antiviral agents, and traditional chemo- and radiotherapy. Specific antilymphocyte (targeted against CD20) therapy has also shown promise. Solid cancers most often manifest as skin malignancies (both basal cell and squamous cell carcinomas), and use of sun-screens is advised. Future research is required to define strategies for immune modulation, immune suppression, and malignancy prevention, however the impact of decreasing immunosuppression in the treatment of these cancers is unclear.

PROLONGED ASSISTED CIRCULATION

The quest for a prolonged implantable mechanical circulatory support device has led to the development of continuous flow left ventricular assist systems (LVAS). Initially designed for short-term support as a bridge to recovery or to cardiac transplantation, the most frequent use today entails permanent support for lifetime therapy ("destination therapy"). The decision to implant LVAS dichotomously as either a bridge to transplantation or for destination therapy is not always clear and in several instances, these devices are used as a "bridge to decision" (in those with potentially reversible underlying relative contraindications such as renal insufficiency or pulmonary hypertension, who may become future candidates for transplantation).

LEFT VENTRICULAR ASSIST SYSTEMS AND CLINICAL TRIALS

A pivotal trial, REMATCH, published in 2001, was the first study to reliably demonstrate that survival of transplant ineligible refractory, predominantly inotropic therapy supported heart failure is improved by implantation of a LVAS. This study used an early generation pulsatile flow device and demonstrated a 48% reduction in risk of death. However, the LVAS used was of limited durability and median meaningful "out of hospital" survival was prolonged by only 5 months. Furthermore, complications of strokes, multisystem organ failure, and infections reduced enthusiasm for widespread adoption. Over time, continuous flow systems that were small turbo-pumps with minimal moving parts and no valves were introduced, leading to a more generalized world-wide adoption. A landmark trial compared the older bulky pulsatile LVAS to the newer generation axial continuous flow LVAS, the HeartMate II, and demonstrated a marked improvement in short- and long-term survival, along with an improvement in functional capacity and meaningful quality of life enhancement. A centrifugal continuous flow LVAS, the HeartWare HVAD, is also in common use. A newer centrifugal device, with a fully magnetically levitated system, the HeartMate 3 LVAS is now available. Unlike the HeartMate II LVAS, which requires an abdominal pump pocket, this smaller device is fully implanted in the pericardial space in

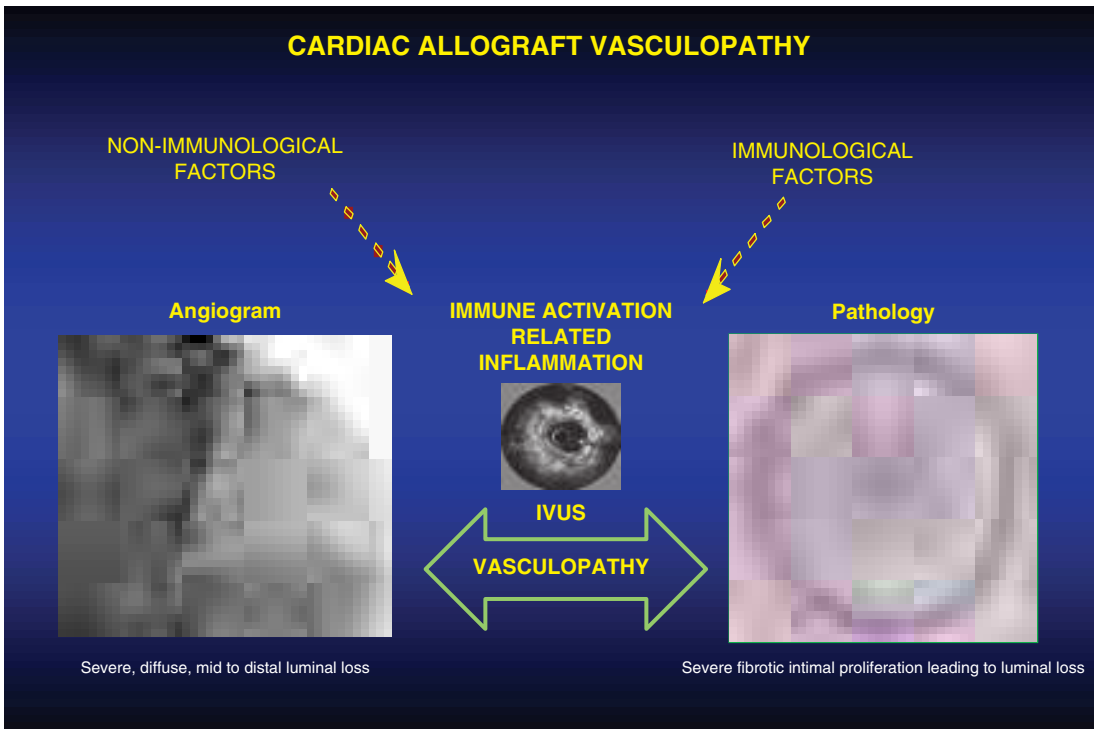

FIGURE 255-1 Cardiac allograft vasculopathy is initiated and propagated by the combined influence of immunological and non-immunological insults on the allograft vasculature. An inflammatory milieu determines the development of diffuse, aggressive luminal blockages that in early forms exhibit intimal thickening and fibrosis. IVUS, Intravascular Ultrasound (can be used to diagnose early forms of intimal thickening).

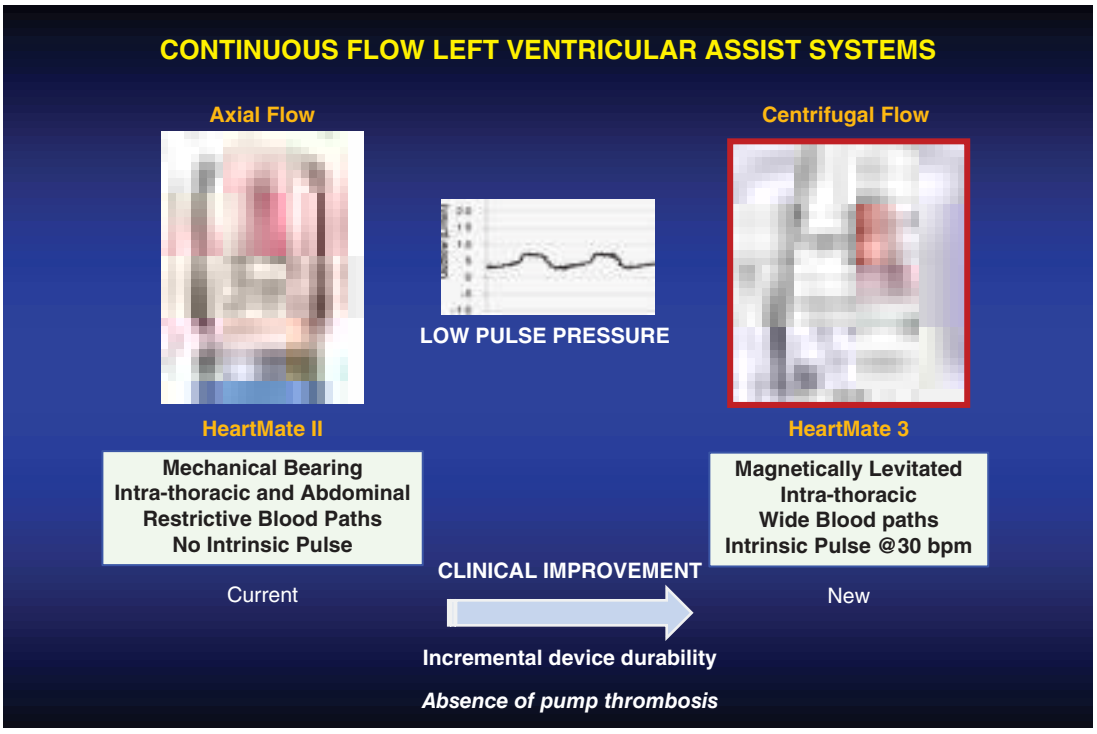

FIGURE 255-2 Continuous flow left ventricular assist systems (LVAS), their types and mechanisms. The mechanical bearing axial flow HeartMate II pump is prone to thrombosis, while the frictionless magnetically levitated centrifugal flow HeartMate 3 does not induce hemolysis or pump thrombosis.

the thoracic cavity (Fig. 255-2). Real world experience from registry analyses has pointed to a >70% 2-year survival with currently available LVAS, nearly approaching the outcomes achieved with transplantation, however long-term durability beyond 5–10 years remains a question. The patients for whom LVAS should ideally be employed include those with severe persistent systolic heart failure symptoms who have failed to respond to optimal medical management. Commonly, these patients have marked functional limitation indicated by a peak oxygen consumption of <12 mL/kg/min; or the patient is bound to continuous intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening congestion. Currently, the role of LVAS in "less sick" patients (those with moderate symptoms) is not advocated since sufficient equipoise does not exist due to the adverse risk benefit ratio from device-related complications.

MANAGEMENT OF LVAS AND THEIR COMPLICATIONS

Continuous flow LVAS rely on pressure gradients between the left ventricular cavity and the aorta. As such, forward flow is critically dependent on management of systemic blood pressure. Due to the non-pulsatile nature of the blood flow, blood pressure is measured by using a Doppler ultrasound (mean or opening blood pressure, which is less than the systolic blood pressure) since a peripheral pulse is usually not detectable. The ideal mean arterial blood pressure should be kept to <90 mmHg and antihypertensive drug therapy prescribed using RAAS drugs or other vasodilators. A common complication encountered in patients is that of an anemia, often due to iron deficiency. The blood flow path through current devices results in increased shear stress which is manifested in the form of low grade hemolysis and the development of an acquired von Willebrand disease due to loss of high molecular weight multimers. This hematological aberration has been associated with a risk of gastrointestinal bleeding, particularly resulting from arteriovenous malformations in the intestines.

The unsupported right ventricle often demonstrates failure and results in congestion requiring diuretic therapy. While unloading of the left ventricle decreases right-sided afterload, increased device flow results in a greater right heart preload and effects of the LVAS on the septum reduce right ventricular contractile efficiency, leading to development of right ventricular dilatation and maladaptation between the right ventricle and pulmonary circuit. Cardiac arrhythmias are common in patients supported with LVAS and often require antiarrhythmic therapy for quiescence since such events can trigger low flow through the device.

Hemocompatibility-related adverse outcomes include neurological events (ischemic and hemorrhagic strokes), device-related thrombosis leading to pump malfunction, and non-surgical bleeding complications (Fig. 255-3). Antiplatelet therapy using aspirin in doses of 81–325 mg daily along with warfarin targeted to an INR of 2–3 are required for current LVAS to avoid the morbidity of hemocompatibility-related adverse events. On one hand, this therapy is protective for thrombotic complications while on another it predisposes the patient to bleeding complications. Strokes occur with a frequency ranging from 8% with the HeartMate II LVAS to as much as 29% with the HeartWare HVAD device, by 2 years of treatment. Optimal control of blood pressure is associated with improved rates of strokes; however, this complication is a critical reason for lack of adoption of device therapy to the less sick population. Another cause of morbidity is pump thrombosis requiring reoperation for device malfunction. This complication is noted in 6–12% of LVAS implants, occurs early (in the first 6 months), and is more common with the HeartMate II device than with other LVAS. The subclinical phase of LVAS thrombosis is characterized by increasing hemolysis and elevation in the device power. Progressively, inability to "unload" the left ventricle is manifest leading to decompensated heart failure and possibly hemodynamic compromise. Lactate dehydrogenase (LDH) is an excellent (although non-specific) biomarker of hemolysis and hence impending or established pump thrombosis. Patients who have suspected left ventricular assist device (LVAD) thrombosis and do not undergo LVAD exchange or cardiac transplantation have a 6-month mortality rate of 48%, inferring that medical therapy for VAD thrombosis may be inadequate (or cause harm in the case of thrombolytic use). Reoperation (pump exchange) carries a modest 6.5% perioperative mortality risk and a 65% 2-year survival following exchange.

Infection is common, most often involving the driveline (the conduit connecting the device to the external controller and batteries) and occurs in 1 in 5 patients following LVAS implant. Such an infection is treated with local internal exploration and requires long-term suppressive antibiotics unless the patient undergoes cardiac transplantation or the device is exchanged. Infection and its inflammatory sequelae

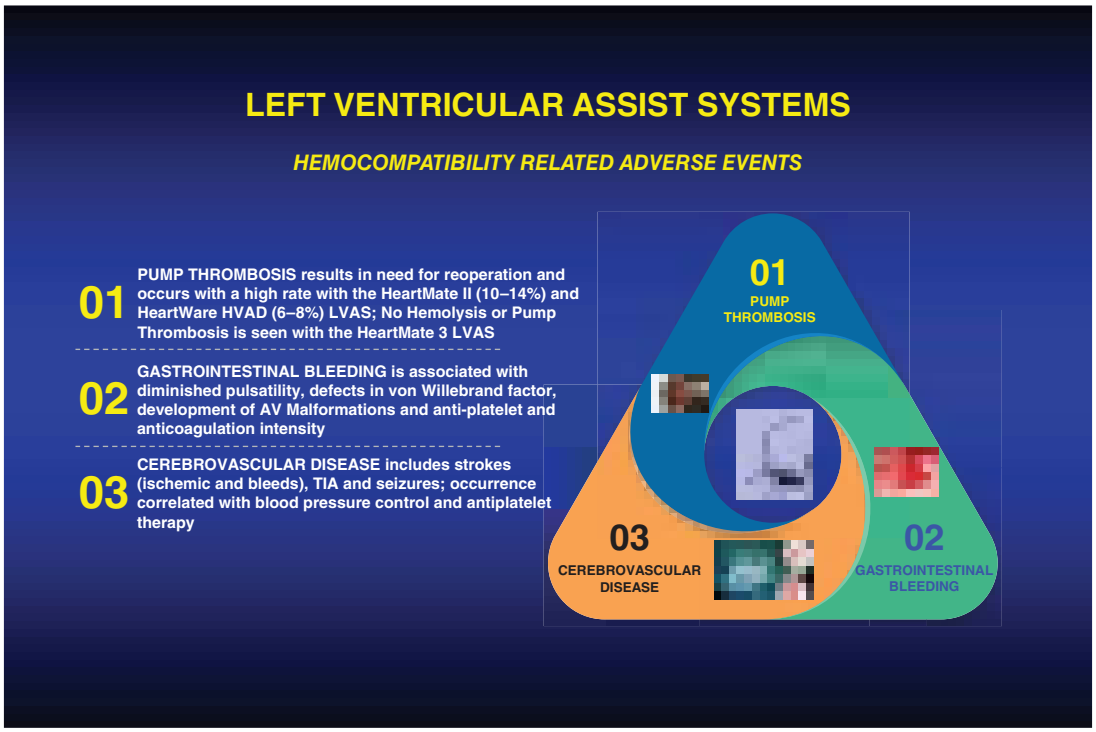

FIGURE 255-3 Hemocompatibility-related adverse events with LVAS are often interrelated and typically result in cerebrovascular, gastrointestinal, or pump malfunction events.

predispose to thrombosis and heighten the risk of neurological complications, leading to a worsening milieu in hemocompatibility.

NOVEL DEVICES

The HeartMate 3 is a centrifugal, continuous flow pump that is placed in the thorax and is engineered to be a more hemocompatible LVAS. This device is constructed with a fully magnetically levitated motor, offers wider blood flow paths, and even exhibits a fixed intrinsic pulse (by the motor ramping its speed up and down at 2 s intervals). This pump has been tested in the large MOMENTUM 3 trial, the early 6 month results for which suggest that this LVAS incrementally improves outcome compared with the HeartMate II device. Importantly, this pump does not exhibit hemolysis or shear high molecular weight multimers of von Willebrand antigen as with other devices and is not associated with pump thrombosis. Long-term experience with this LVAS will be important in discerning whether these early short-term findings result in a reduction in hemocompatibility-related adverse events, improved quality of life, and survival.

TOTAL ARTIFICIAL HEART

Not all patients are candidates for a LVAS, particularly those with severe right-sided heart failure or conditions that do not allow placement of an LVAS (restrictive cardiomyopathy, massive anterior myocardial infarction, complex congenital heart disease). In such patients, either a biventricular assist device approach or a total artificial heart pump can be considered. The SynCardia total artificial heart is a pulsatile, implantable pump that consists of two polyurethane ventricles with pneumatically driven diaphragms, and four tilting disc valves. This requires excision of the native ventricles and thus cannot be employed as a myocardial recovery strategy. There are specific clinical issues that are unique to the total artificial heart management. This device operates on a steep physiological curve and has little adaptability to tolerate either systemic blood pressure changes or large shifts in blood volume. As the ventricles are excised, most patients exhibit a sharp decline in renal function due to the loss of natriuretic peptide expression by the myocardium. Severe hemolysis is common due to the presence of four mechanical valves and aberrant erythropoiesis is noted leading to a severe refractory anemia. Newer artificial hearts using biocompatible surfaces are under development, as well as those that use continuous flow technology.

GLOBAL CONSIDERATIONS

While LVAS are available worldwide, their use and indications vary from country to country. In the United States, payers require discrete discrimination of indication into either a bridge to transplant or destination therapy, whereas in most European countries this artificial segregation is not used. Cost effectiveness studies suggest improvement with newer devices, yet some countries only allow use of this technology as a bridge to transplantation (UK), awaiting more definitive long-term studies for lifetime use. Now, the use in moderately symptomatic ambulatory patients with chronic systolic heart failure is equally discouraged throughout the world, awaiting the availability of a more hemocompatible LVAS.

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256 Aortic Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

GLOBAL BURDEN OF VALVULAR HEART DISEASE

Primary valvular heart disease ranks well below coronary heart disease, stroke, hypertension, obesity, and diabetes as a major threat to the public health. Nevertheless, it can cause significant morbidity and lead to premature death. Rheumatic fever (Chap. 352) is the dominant cause of valvular heart disease in developing and low-income countries. Its prevalence has been estimated to range from as low as 1 per 100,000 school-age children in Costa Rica to as high as 150 per 100,000 in China (Fig. 256-1). Rheumatic heart disease accounts for 12–65% of hospital admissions related to cardiovascular disease and 2–10% of hospital discharges in some developing countries. Prevalence and mortality rates vary among communities even within the same country as a function of overcrowding and the availability of medical resources and population-wide programs for detection and treatment of group A streptococcal pharyngitis. In economically deprived areas, tropical and subtropical climates (particularly on the Indian subcontinent and in Southeast Asia), Central America, and the Middle East, rheumatic valvular disease progresses more rapidly than in more-developed nations and frequently causes serious symptoms in patients aged <20 years. This accelerated natural history may be due to repeated infections with more virulent strains of rheumatogenic streptococci. Approximately 15–20 million people live with rheumatic heart disease worldwide, an estimated prevalence characterized by 300,000 new cases and 233,000 case fatalities per year, with the highest mortality rates reported from Southeast Asia (~7.6 per 100,000). In the United States, rheumatic heart disease accounted for 20,000 hospital admissions in 2010 and 3281 deaths in 2014.

Although there have been recent reports of isolated outbreaks of streptococcal infection in North America, valve disease in high-income countries is dominated by degenerative or inflammatory processes that lead to valve thickening, calcification, and dysfunction. The prevalence of valvular heart disease increases significantly with age for both men and women. Important left-sided valve disease may affect as many as 12–13% of adults aged >75 years (Fig. 256-2). Severe aortic stenosis (AS) is estimated to affect 3.5% of the population aged >75 years. In the United States, there were 85,000 hospital discharges with valvular heart disease in 2010, and the vast majority of these were related to surgical procedures for heart valve disease (mostly involving the aortic and mitral valves).

The incidence of infective endocarditis (Chap. 123) has increased with the aging of the population, the more widespread prevalence of vascular grafts and intracardiac devices, the emergence of more virulent multidrug-resistant microorganisms, and the growing epidemic of diabetes. The more restricted use of antibiotic prophylaxis since 2007 has thus far not been convincingly associated with an increase in incidence rates for infective endocarditis cases attributable to oropharyngeal pathogens. Infective endocarditis has become a relatively more frequent cause of acute valvular regurgitation. Rates of valve surgery during the acute phase of infective endocarditis increased significantly in U.S. hospitals over the decade from 2000 to 2010.

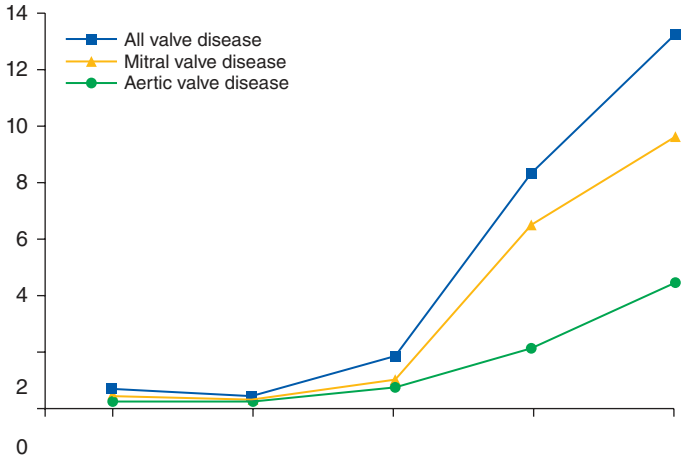


FIGURE 256-2 The burden of moderate or severe mitral and aortic valve disease in the United States. Prevalence estimates are derived from three population-based studies comprising a total of 11,911 individuals: The Coronary Artery Risk Development in Young Adults (CARDIA), the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS). *(From VT Nkomo et al: Lancet 368:1005, 2006.)*

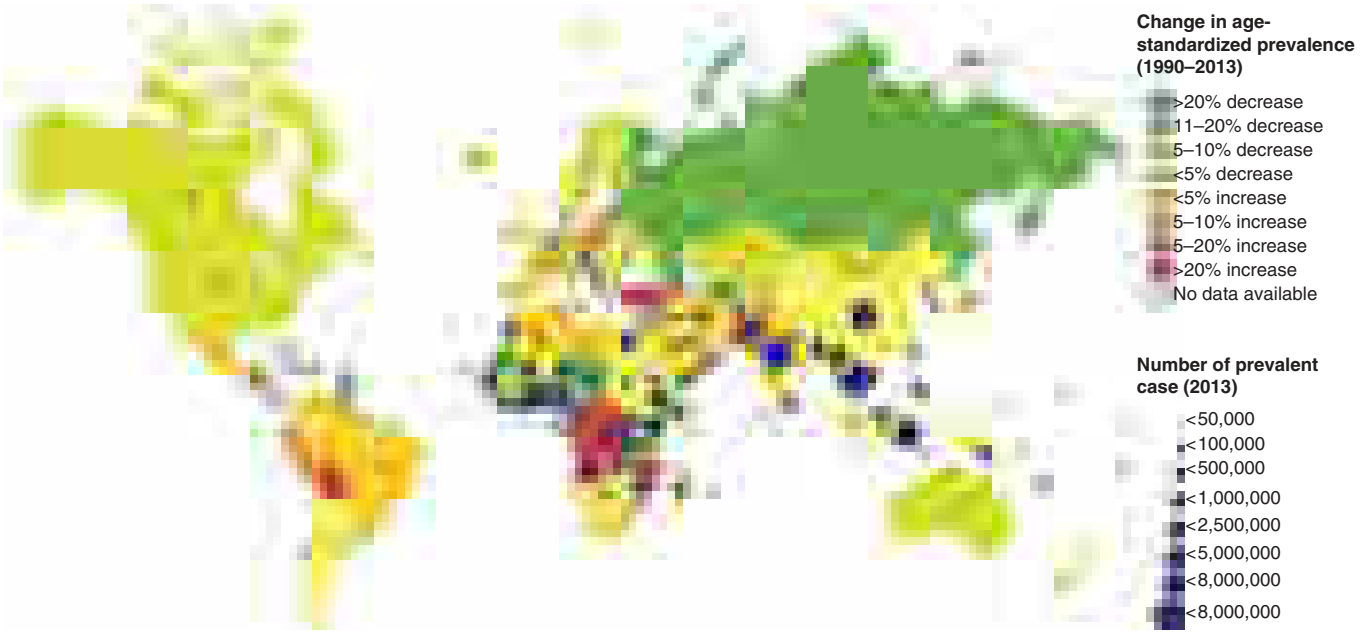


FIGURE 256-1 The global burden of rheumatic heart disease. This world map provides a snapshot of both the change in prevalence of rheumatic heart disease cases between 1990 and 2013 (upper right legend) and the estimated number of rheumatic heart disease cases per country (lower right legend). Regions in which the disease is highly prevalent include sub-Saharan Africa, India, China, and Southeast Asia. *(From JR Carapetis et al: Nat Rev Dis Primers 2:15084, 2016.)*

Bicuspid aortic valve (BAV) disease affects as many as 0.5–1.4% of the general population, with an associated incidence of aortopathy involving root or ascending aortic aneurysm disease or coarctation. An increasing number of childhood survivors of congenital heart disease present later in life with valvular dysfunction. The global burden of valvular heart disease is expected to progress.

As is true for many other chronic health conditions, disparities in access to and quality of care for patients with valvular heart disease have been well documented, especially for those patients with rheumatic heart disease in low- and middle-income countries. Management decisions and outcome differences based on age, gender, race, and geography require educational efforts across all levels of providers and prioritization of resources.

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 38 and 234**; of electrocardiography (ECG) in **Chap. 235**; of echocardiography and other noninvasive imaging techniques in **Chap. 236**; and of cardiac catheterization and angiography in **Chap. 237**.

AORTIC STENOSIS

Aortic stenosis (AS) occurs in about one-fourth of all patients with chronic valvular heart disease; ~80% of adult patients with symptomatic, valvular AS are male.

ETIOLOGY AND PATHOGENESIS

(Table 256-1) AS in adults is due to degenerative calcification of the aortic cusps and occurs most commonly on a substrate of congenital disease (BAV), chronic (trileaflet) deterioration, or previous rheumatic inflammation. A pathologic study of specimens removed at the time of aortic valve replacement for AS in adults showed that 53% were bicuspid and 4% unicuspid. The process of aortic valve deterioration and calcification is not a passive one, but rather one that shares many features with vascular atherosclerosis, including endothelial dysfunction, lipid accumulation, inflammatory cell activation, cytokine release, and upregulation of several signaling pathways **(Fig. 256-3)**. Eventually, a fibrocalcific response is established wherein collagen is deposited and valvular myofibroblasts differentiate phenotypically into osteoblasts and actively produce bone matrix proteins that allow for the deposition of calcium hydroxyapatite crystals. Genetic polymorphisms involving the vitamin D receptor, the estrogen receptor in postmenopausal women, interleukin 10, and apolipoprotein E4 have been linked to the development of calcific AS, and a strong familial clustering of cases has been reported from western France. Several traditional atherosclerotic risk factors have also been associated with the development and progression of calcific AS, including low-density lipoprotein (LDL) cholesterol, lipoprotein a (Lp[a]), diabetes mellitus, smoking, chronic kidney disease, and the metabolic syndrome. The presence of aortic valve sclerosis (focal thickening and calcification of the leaflets not severe enough to cause obstruction) is associated with an excess risk of cardiovascular death and myocardial infarction (MI) among persons aged >65. Approximately 30% of persons aged >65 years exhibit some degree of aortic valve sclerosis. Rate and extent of progression to valve obstruction (stenosis) vary among individual patients.

Rheumatic disease of the aortic leaflets produces commissural fusion, sometimes resulting in a bicuspid-appearing valve. This condition, in turn, makes the leaflets more susceptible to trauma and ultimately leads to fibrosis, calcification, and further narrowing. By the time obstruction to left ventricular (LV) outflow causes serious clinical disability, the valve is usually a rigid calcified mass, and careful examination may make it difficult or even impossible to determine the etiology of the underlying process. Rheumatic AS is almost always associated with involvement of the mitral valve and with aortic regurgitation (AR). Mediastinal radiation can also result in late scarring, fibrosis, and calcification of the leaflets with AS.

TABLE 256-1 Major Causes of Aortic Stenosis

VALVE LESION	ETIOLOGIES
Aortic stenosis	Congenital (bicuspid, unicuspid)
	Degenerative calcific
	Rheumatic fever
	Radiation

BICUSPID AORTIC VALVE DISEASE

A bicuspid aortic valve (BAV) is the most common congenital heart valve defect and occurs in 0.5–1.4% of the population with a 2–4:1 male-to-female predominance. The inheritance pattern appears to be autosomal dominant with incomplete penetrance, although some have questioned an X-linked component as suggested by the prevalence of BAV disease among patients with Turner's syndrome. The prevalence of BAV disease among first-degree relatives of an affected individual is ~10%. A single gene defect to explain the majority of cases has not been identified, although a mutation in the *NOTCH1* gene has been described in some families. Abnormalities in endothelial nitric oxide synthase and NKX2.5 have been implicated as well. Medial degeneration with ascending aortic aneurysm formation occurs commonly among patients with BAV disease; aortic coarctation is less frequently encountered. Patients with BAV disease have larger aortas than patients with comparable tricuspid aortic valve disease. The aortopathy develops independently of the hemodynamic severity of the valve lesion, but directional shear forces dictated by the anatomic configuration of the valve may influence its expression. For example, enlargement of the ascending aorta along its greater curvature is most often associated with right-left cusp fusion, the most common bicuspid variant. Patients with BAV disease are at risk for aneurysm formation and/or dissection. A BAV can be a component of more complex congenital heart disease with or without other left heart obstructing lesions, as seen in Shone's complex.

OTHER FORMS OF OBSTRUCTION TO LEFT VENTRICULAR OUTFLOW

In addition to valvular AS, three other lesions may be responsible for obstruction to LV outflow: *hypertrophic obstructive cardiomyopathy* **(Chap. 254)**, *discrete fibromuscular/membranous subaortic stenosis*, and *supravalvular AS* **(Chap. 264)**. The causes of LV outflow obstruction can be differentiated on the basis of the cardiac examination and Doppler echocardiographic findings.

PATHOPHYSIOLOGY

The obstruction to LV outflow produces a systolic pressure gradient between the LV and aorta. When severe obstruction is suddenly produced experimentally, the LV responds by dilation and reduction of stroke volume. However, in some patients, the obstruction may be present at birth and/or increase gradually over the course of many years, and LV contractile performance is maintained by the presence of concentric LV hypertrophy. Initially, this serves as an adaptive mechanism because it reduces toward normal the systolic stress developed by the myocardium, as predicted by the Laplace relation ($S = Pr/h$, where S = systolic wall stress, P = pressure, r = radius, and h = wall thickness). A large transaortic valve pressure gradient may exist for many years without a reduction in cardiac output (CO) or the development of LV dilation. Ultimately, however, excessive hypertrophy becomes maladaptive, LV systolic function declines because of afterload mismatch, abnormalities of diastolic function progress, and irreversible myocardial fibrosis develops.

A mean systolic pressure gradient >40 mmHg with a normal CO or an effective aortic orifice area of ~<1 cm^2 (or ~<0.6 cm^2/m^2 body surface area in a normal-sized adult)—i.e., less than approximately one-third of the normal orifice area—is generally considered to represent severe obstruction to LV outflow. The elevated LV end-diastolic pressure observed in many patients with severe AS and preserved ejection fraction (EF) signifies the presence of diminished compliance of the hypertrophied LV. Although the CO at rest is within normal limits in most patients with severe AS, it usually fails to rise normally during exercise. Loss of an appropriately timed, vigorous atrial contraction,

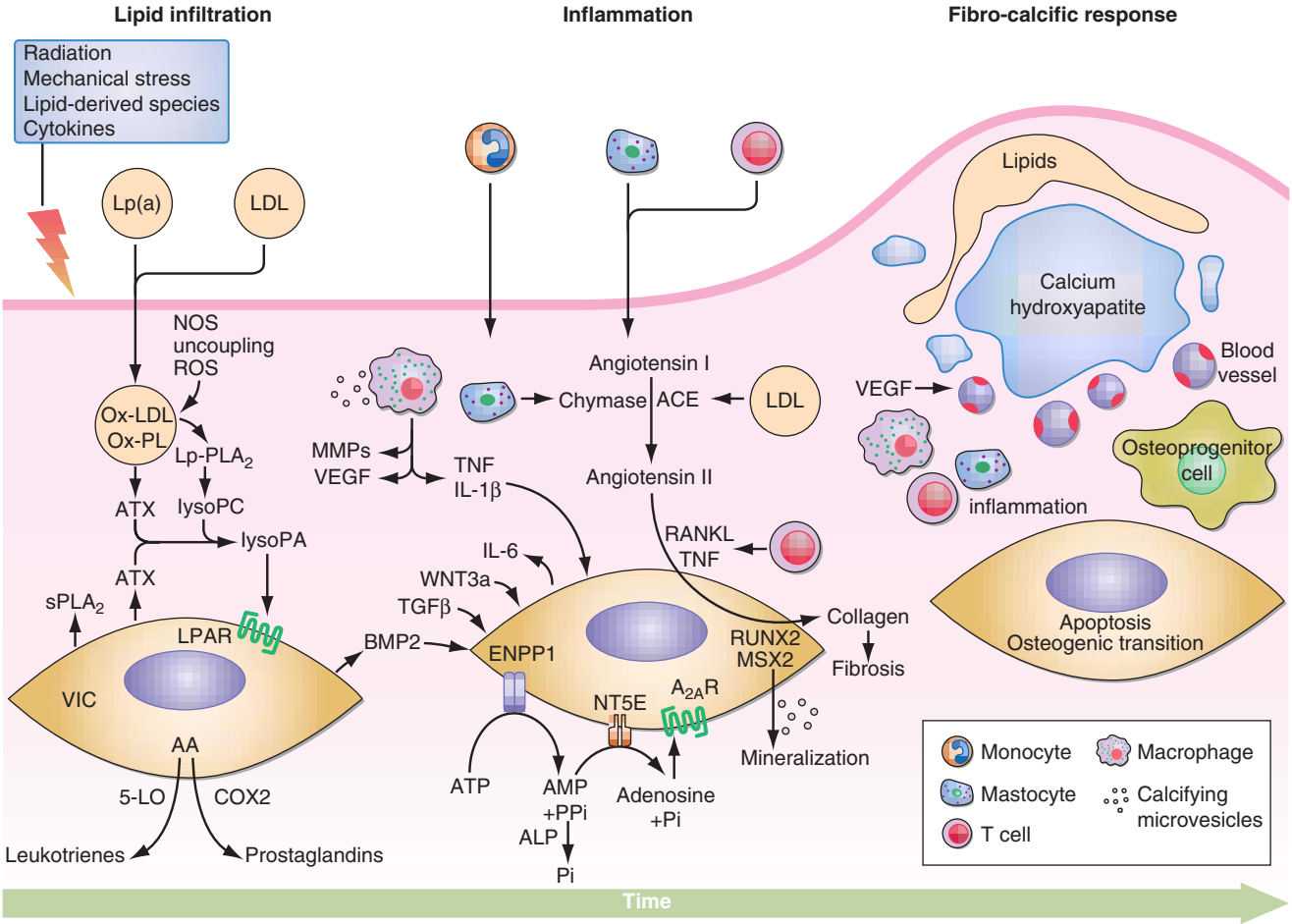


FIGURE 256-3 Pathogenesis of calcific aortic stenosis. Lipid and inflammatory cell infiltration occurs across damaged endothelium. A cascade of events follows that leads eventually to formation of disorganized collagen (fibrosis) and calcium hydroxyapatite (bone) deposition. Valvular interstitial cells (VIC) are critical participants in this active process. AA, arachidonic acid; ACE, angiotensin-converting enzyme; ALP, alkaline phosphatase; ApoB, apolipoprotein B; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ATX, autotaxin; A2AR, adenosine A2A receptor; BMP, bone morphogenetic protein; COX2, cyclo-oxygenase2; ENPP, ectonucleotide pyrophosphatase/phosphodiesterase; IL, interleukin; 5-LO, 5-lipoxygenase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LPAR, lysophosphatidic acid receptor; Lp-PLA2, lipoprotein-associated phospholipase A2; lysoPA, lysophosphatidic acid; lysoPC, lysophosphatidylcholine; MMP, matrix metalloproteinase; NOS, nitric oxide synthase; Ox-PL, oxidized phospholipid; Ox-LDL, oxidized LDL; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; RUNX2, runt-related transcription factor 2; sPLA2, secreted PLA2; TGFβ, transforming growth factor-β; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIC, valvular interstitial cell. *(From B Lindman et al: Nat Rev Dis Primers 2:16006, 2016.)*

as occurs in atrial fibrillation (AF) or atrioventricular dissociation, may cause rapid progression of symptoms. Late in the course, contractile function deteriorates because of afterload excess, the CO and LV–aortic pressure gradient decline, and the mean left atrial (LA), pulmonary artery (PA), and right ventricular (RV) pressures rise. LV performance can be further compromised by superimposed epicardial coronary artery disease (CAD). Stroke volume (and thus CO) can also be reduced in patients with significant hypertrophy and a small LV cavity despite a normal EF. Low-flow, low-gradient AS (with either reduced or normal LV systolic function) is both a diagnostic and therapeutic challenge.

The hypertrophied LV causes an increase in myocardial oxygen requirements. In addition, even in the absence of obstructive CAD, coronary blood flow is impaired to the extent that ischemia can be precipitated under conditions of excess demand. Capillary density is reduced relative to wall thickness, compressive forces are increased, and the elevated LV end-diastolic pressure reduces the coronary driving pressure. The subendocardium is especially vulnerable to ischemia by this mechanism.

SYMPTOMS

AS is rarely of clinical importance until the valve orifice has narrowed to ~1 cm^2. Even severe AS may exist for many years without producing any symptoms because of the ability of the hypertrophied LV to generate the elevated intraventricular pressures required to maintain a normal stroke volume. Once symptoms occur, valve replacement is indicated.

Most patients with pure or predominant AS have gradually increasing obstruction over years but do not become symptomatic until the sixth to eighth decades. Adult patients with BAV disease, however, develop significant valve dysfunction and symptoms one to two decades sooner. Exertional dyspnea, angina pectoris, and syncope are the three cardinal symptoms. Often, there is a history of insidious progression of fatigue and dyspnea associated with gradual curtailment of activities and reduced effort tolerance. *Dyspnea* results primarily from elevation of the pulmonary capillary pressure caused by elevations of LV diastolic pressures secondary to impaired relaxation and reduced LV compliance. *Angina pectoris* usually develops somewhat later and reflects an imbalance between the augmented myocardial oxygen requirements and reduced oxygen availability. CAD may or may not be present, although its coexistence is common among AS patients age >65. *Exertional syncope* may result from a decline in arterial pressure caused by vasodilation in the exercising muscles and inadequate vasoconstriction in nonexercising muscles in the face of a fixed CO, or from a sudden fall in CO produced by an arrhythmia.

Because the CO at rest is usually well maintained until late in the course, marked fatigability, weakness, peripheral cyanosis, cachexia, and other clinical manifestations of a low CO are usually not prominent until this stage is reached. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema, i.e., symptoms of LV failure, also occur only in the advanced stages of the disease. Severe pulmonary hypertension leading to RV failure and systemic venous hypertension,

hepatomegaly, AF, and tricuspid regurgitation (TR) are usually late findings in patients with isolated severe AS.

When AS and mitral stenosis (MS) coexist, the reduction in flow (CO) induced by MS lowers the pressure gradient across the aortic valve and, thereby, masks many of the clinical findings produced by AS. The transaortic pressure gradient can be increased in patients with concomitant AR due to higher aortic valve flow rates.

PHYSICAL FINDINGS

The rhythm is generally regular until late in the course; at other times, AF should suggest the possibility of associated mitral valve disease. Hypertension occurs commonly among older adults with AS. In the late stages, however, when stroke volume declines, the systolic pressure may fall and the pulse pressure narrow. The carotid arterial pulse rises slowly to a delayed peak (*pulsus parvus et tardus*). A thrill or anacrotic "shudder" may be palpable over the carotid arteries, more commonly the left. In the elderly, the stiffening of the arterial wall may mask this important physical sign. In many patients, the *a* wave in the jugular venous pulse is accentuated. This results from the diminished distensibility of the RV cavity caused by the bulging, hypertrophied interventricular septum.

The LV impulse is sometimes displaced laterally in the later stages of the disease. A double apical impulse (with a palpable S_4) may be recognized, particularly with the patient in the left lateral recumbent position. A systolic thrill may be present at the base of the heart to the right of the sternum when leaning forward or in the suprasternal notch.

Auscultation An early systolic ejection sound is frequently audible in children, adolescents, and young adults with congenital BAV disease. This sound usually disappears when the valve becomes calcified and rigid. As AS increases in severity, LV systole may become prolonged so that the aortic valve closure sound no longer precedes the pulmonic valve closure sound, and the two components may become synchronous, or aortic valve closure may even follow pulmonic valve closure, causing paradoxical splitting of S_2 **(Chap. 234)**. The sound of aortic valve closure can be heard most frequently in patients with AS who have pliable valves, and calcification diminishes the intensity of this sound. Frequently, an S_4 is audible at the apex and reflects the presence of LV hypertrophy and an elevated LV end-diastolic pressure; an S_3 generally occurs late in the course, when the LV dilates and its systolic function becomes severely compromised.

The murmur of AS is characteristically an ejection (mid) systolic murmur that commences shortly after the S_1, increases in intensity to reach a peak toward the middle of ejection, and ends just before aortic valve closure. It is characteristically low-pitched, rough and rasping in character, and loudest at the base of the heart, most commonly in the second right intercostal space. It is transmitted upward along the carotid arteries. Occasionally it is transmitted downward and to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR) (Gallavardin effect). In almost all patients with severe obstruction and preserved CO, the murmur is at least grade III/VI. In patients with mild degrees of obstruction or in those with severe stenosis with heart failure and low CO in whom the stroke volume and, therefore, the transvalvular flow rate are reduced, the murmur may be relatively soft and brief.

LABORATORY EXAMINATION

ECG In most patients with severe AS, there is LV hypertrophy. In advanced cases, ST-segment depression and T-wave inversion (LV "strain") in standard leads I and aVL and in the left precordial leads are evident. However, there is no close correlation between the ECG and the hemodynamic severity of obstruction, and the absence of ECG signs of LV hypertrophy does not exclude severe obstruction. Systemic hypertension can coexist and also contribute to the development of hypertrophy.

Echocardiogram The key findings on TTE are thickening, calcification, and reduced systolic opening of the valve leaflets and LV hypertrophy. Eccentric closure of the aortic valve cusps is characteristic of congenitally bicuspid valves. TEE imaging can display the obstructed orifice extremely well, but it is not routinely required for accurate characterization of AS. The valve gradient and aortic valve area can be estimated by Doppler measurement of the transaortic velocity. Severe AS is defined by a valve area <1 cm^2, whereas moderate AS is defined by a valve area of 1–1.5 cm^2 and mild AS by a valve area of 1.5–2 cm^2. Aortic valve sclerosis, conversely, is accompanied by a jet velocity of <2.5 m/s (peak gradient <25 mmHg). LV dilation and reduced systolic shortening reflect impairment of LV function. There is increasing experience with the use of longitudinal strain and strain rate to characterize earlier changes in LV systolic function, well before a decline in EF can be appreciated. Doppler indices of impaired diastolic function are frequently seen.

Echocardiography is useful for identifying coexisting valvular abnormalities, differentiating valvular AS from other forms of LV outflow obstruction, and measuring the aortic root and proximal ascending aortic dimensions. These aortic measurements are particularly important for patients with BAV disease. Dobutamine stress echocardiography is useful for the evaluation of patients with AS and severe LV systolic dysfunction (low-flow, low-gradient, severe AS with reduced EF), in whom the severity of the AS can often be difficult to judge. Patients with severe AS (i.e., valve area <1 cm^2) with a relatively low mean gradient (<40 mmHg) despite a normal EF (low-flow, low-gradient, severe AS with normal EF) are often hypertensive, and efforts to control their systemic blood pressure should be optimized before Doppler echocardiography is repeated. The use of dobutamine stress echocardiography in this setting is under investigation. When there is continued uncertainty regarding the severity of AS in patients with reduced CO, quantitative analysis of the amount of aortic valve calcium with chest computed tomography (CT) may be helpful. There is increasing use of chest CT to assess aortic valve morphology and function. It has become the imaging method of choice to plan for transcatheter aortic valve replacement (TAVR).

Chest X-Ray The chest x-ray may show no or little overall cardiac enlargement for many years. Hypertrophy without dilation may produce some rounding of the cardiac apex in the frontal projection and slight backward displacement in the lateral view. A dilated proximal ascending aorta may be seen along the upper right heart border in the frontal view. Aortic valve calcification may be discernible in the lateral view, but it is usually readily apparent on fluoroscopic examination or by echocardiography; the absence of valvular calcification on fluoroscopy in an adult suggests that severe valvular AS is *not* present. In later stages of the disease, as the LV dilates, there is increasing roentgenographic evidence of LV enlargement, pulmonary congestion, and enlargement of the LA, PA, and right-sided heart chambers.

Catheterization Right- and left-sided heart catheterization for invasive assessment of AS is performed infrequently but can be useful when there is a discrepancy between the clinical and noninvasive findings. Concern has been raised that attempts to cross the aortic valve for measurement of LV pressures are associated with a risk of cerebral embolization. Catheterization is also useful in three distinct categories of patients: (1) *patients with multivalvular disease*, in whom the role played by each valvular deformity should be defined to aid in the planning of operative treatment; (2) *young, asymptomatic patients with noncalcific congenital AS*, to define the severity of obstruction to LV outflow, because operation or percutaneous aortic balloon valvuloplasty (PABV) may be indicated in these patients if severe AS is present, even in the absence of symptoms; and (3) *patients in whom it is suspected that the obstruction to LV outflow may not be at the level of the aortic valve* but rather at the sub- or supravalvular level.

Coronary angiography is indicated to screen for CAD in appropriate patients with severe AS who are being considered for surgical or transcatheter valve replacement. The incidence of significant CAD for which bypass grafting is indicated at the time of surgical aortic valve replacement (SAVR) exceeds 50% among adult patients.

TABLE 256-2 Mortality Rates after Aortic Valve Surgery[a]

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
AVR (isolated)	21,921	2.2
AVR + CAB	13,000	4.0
AVR + MVR	1349	8.0

[a]Data are for the first three quarters of calendar year 2015 during which 1033 sites reported a total of 210,421 procedures. Data (accessed March 9, 2017) are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2015Harvest4_ExecutiveSummary.pdf*.

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass; MVR, mitral valve replacement.

NATURAL HISTORY

Death in patients with severe AS occurs most commonly in the seventh and eighth decades. Based on data obtained at postmortem examination in patients before surgical treatment became widely available, the average time to death after the onset of various symptoms was as follows: angina pectoris, 3 years; syncope, 3 years; dyspnea, 2 years; congestive heart failure, 1.5–2 years. Moreover, in >80% of patients who died with AS, symptoms had existed for <4 years. Among adults dying with valvular AS, sudden death, which presumably resulted from an arrhythmia, occurred in 10–20%; however, most sudden deaths occurred in patients who had previously been symptomatic. Sudden death as the first manifestation of severe AS is very uncommon (~1% per year) in asymptomatic adult patients. Calcific AS is a progressive disease, with an annual reduction in valve area averaging 0.1 cm^2 and annual increases in the peak jet velocity and mean valve gradient averaging 0.3 m/s and 7 mmHg, respectively **(Table 256-2)**.

TREATMENT

Aortic Stenosis (Fig. 256-4)

MEDICAL TREATMENT

In patients with severe AS (valve area <1 cm^2), strenuous physical activity and competitive sports should be avoided, even in the asymptomatic stage. Care must be taken to avoid dehydration and

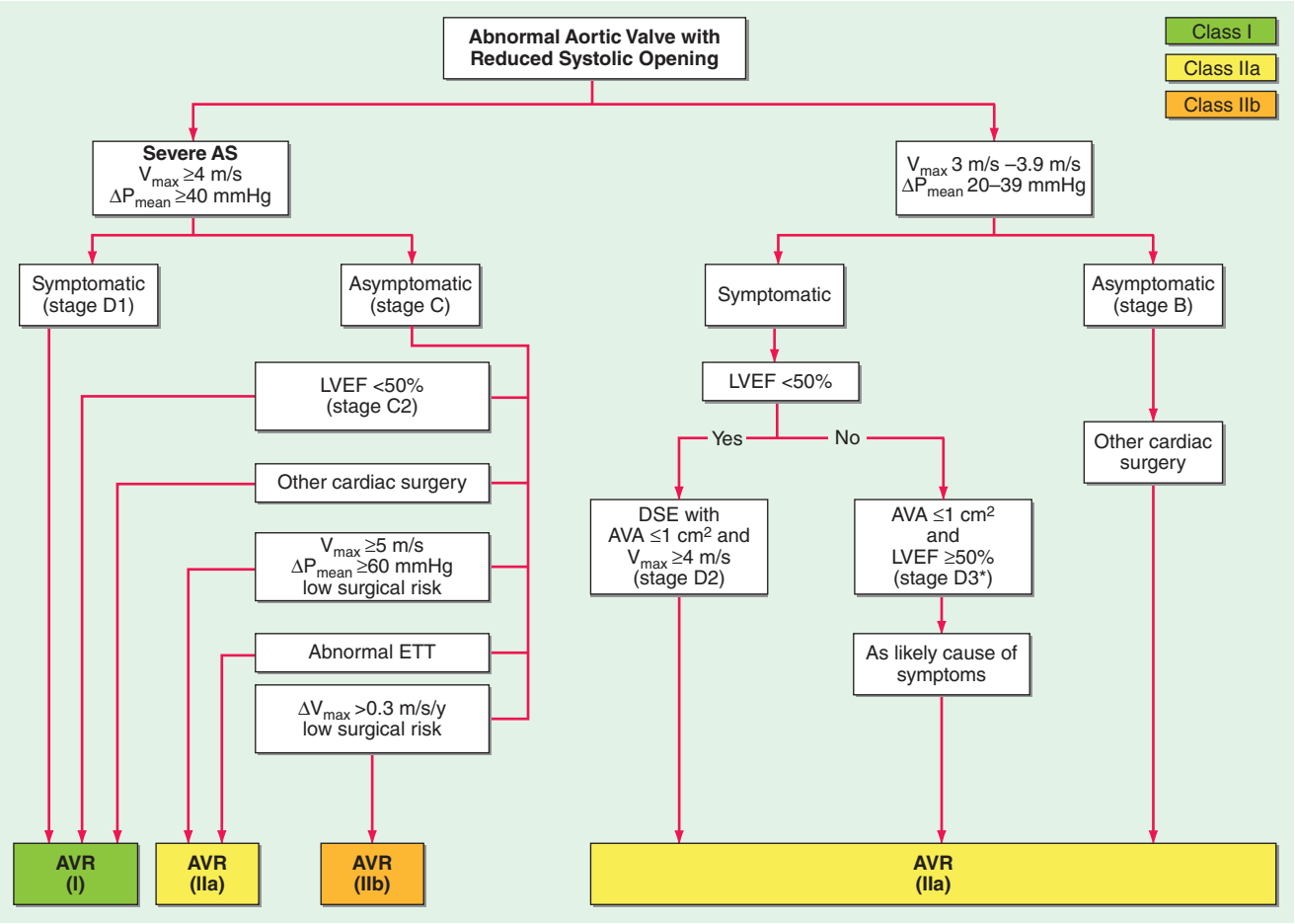


FIGURE 256-4 Management strategy for patients with aortic stenosis. Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. The class designations refer to the American Heart Association/American College of Cardiology methodology for treatment recommendations. Class I recommendations should be performed or are indicated; Class IIa recommendations are considered reasonable to perform; Class IIb recommendations may be considered. The stages refer to the stages of progression of the disease. At disease stage A, risk factors are present for the development of valve dysfunction; stage B refers to progressive, mild-moderate, asymptomatic valve disease; stage C disease is severe in nature but clinically asymptomatic; stage C1 characterizes asymptomatic patients with severe valve disease but compensated ventricular function; stage C2 refers to asymptomatic, severe disease with ventricular decompensation; stage D refers to severe, symptomatic valve disease. With aortic stenosis, stage D1 refers to symptomatic patients with severe aortic stenosis and a high valve gradient (>40 mmHg mean gradient); stage D2 comprises patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and low left ventricular ejection fraction; and stage D3 characterizes patients with symptomatic, severe, low-flow, low-gradient aortic stenosis and preserved left ventricular ejection fraction (paradoxical, low-flow, low-gradient severe aortic stenosis). AS, aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement; DSE, dobutamine stress echocardiography; ETT, exercise treadmill test; LVEF, left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; V_{max}, maximum velocity. *(Adapted from RA Nishimura et al: J Am Coll Cardiol 70:252, 2017.)*

hypovolemia to protect against a significant reduction in CO. Medications used for the treatment of hypertension or CAD, including beta blockers and angiotensin-converting enzyme (ACE) inhibitors, are generally safe for asymptomatic patients with preserved LV systolic function. Nitroglycerin is helpful in relieving angina pectoris in patients with CAD. Retrospective studies suggested that patients with degenerative calcific AS who receive HMG-CoA reductase inhibitors ("statins") exhibit slower progression of leaflet calcification and aortic valve area reduction than those who do not. However, randomized prospective studies with either high-dose atorvastatin or combination simvastatin/ezetimibe have failed to show a measurable effect on valve-related outcomes. The use of statin medications should be driven by considerations regarding primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) events. ACE inhibitors have not been studied prospectively for AS-related outcomes. The need for endocarditis prophylaxis is restricted to AS patients with a prior history of endocarditis.

SURGICAL TREATMENT

Asymptomatic patients with calcific AS and severe obstruction should be followed carefully for the development of symptoms and by serial echocardiograms for evidence of deteriorating LV function. Operation is indicated in patients with severe AS (valve area <1 cm^2 or 0.6 cm^2/m^2 body surface area) who are symptomatic, those who exhibit LV systolic dysfunction (EF <50%), and those with BAV disease and an aneurysmal root or ascending aorta (maximal dimension >5.5 cm). Operation for aneurysm disease is recommended at smaller aortic diameters (4.5–5.0 cm) for patients with a family history of an aortic catastrophe and for patients who exhibit rapid aneurysm growth (>0.5 cm/year). Patients with asymptomatic moderate or severe AS who are referred for coronary artery bypass grafting surgery should also have AVR. In patients without heart failure, the operative risk of SAVR (including patients with AS or AR) is ~2% (Table 256-2) but increases as a function of age and the need for concomitant aortic surgery or coronary revascularization with bypass grafting. The indications for SAVR in the asymptomatic patient have been the subject of intense debate, as surgical outcomes in selected patients have continued to improve. Relative indications for which surgery can be considered include an abnormal response to treadmill exercise; rapid progression of AS, especially when urgent access to medical care might be compromised; very severe AS, defined by an aortic valve jet velocity >5 m/s or mean gradient >60 mmHg and low operative risk; and excessive LV hypertrophy in the absence of systemic hypertension. Exercise testing can be safely performed in asymptomatic patients, as many as one-third of whom will show signs of functional impairment. A randomized controlled trial (RCT) of SAVR versus active surveillance in patients with asymptomatic severe AS is in the planning stages.

Operation should be carried out promptly (1–3 months) after symptom onset. In patients with low-flow, low-gradient severe AS with reduced LVEF, the perioperative mortality risk is high (15–20%), and evidence of myocardial disease may persist even when the operation is technically successful. Long-term postoperative survival correlates with preoperative LV function. Nonetheless, in view of the even worse prognosis of such patients when they are treated medically, there is usually little choice but to advise valve replacement, especially in patients in whom contractile reserve can be demonstrated by dobutamine stress echocardiography (defined by a ≥20% increase in stroke volume after dobutamine challenge). Patients in this high surgical risk group may benefit from TAVR, (see below), but data from RCTs in this population are lacking. The treatment of patients with low-flow, low-gradient severe AS with normal LVEF is also difficult. Outcomes appear to be better with surgery compared with conservative medical care for symptomatic patients with this type of "paradoxical" low-flow AS, but more research is needed to guide therapeutic decision making. In patients in whom severe AS and CAD coexist, relief of the AS and revascularization may sometimes result in striking clinical and hemodynamic improvement (Table 256-2).

Because many patients with calcific AS are elderly, particular attention must be directed to the adequacy of hepatic, renal, and pulmonary function before AVR is recommended. Age alone is not a contraindication to SAVR for AS. The perioperative mortality rate depends to a substantial extent on the patient's preoperative clinical and hemodynamic state. Assessment of frailty is a critical component of preprocedural evaluation. Treatment decisions for AS patients who are not at low operative risk should be made by a multidisciplinary heart team with representation from general cardiology, interventional cardiology, imaging, cardiac surgery, and other allied specialties as needed, including geriatrics. The 10-year survival rate of older adult patients with AVR is ~60%. Recommendations regarding the type of valve prosthesis (tissue or mechanical) must weigh the trade-offs between durability and thromboembolism/bleeding and are heavily influenced by patient age and preferences. Bioprostheses are favored for patients age >65 years. Shared decision making with younger patients must be individualized. Approximately 30% of bioprosthetic valves evidence primary valve failure in 10 years, requiring re-replacement, and an approximately equal percentage of patients with mechanical prostheses develop hemorrhagic complications as a consequence of treatment with vitamin K antagonists. Homograft AVR is usually reserved for patients with aortic valve endocarditis.

The Ross procedure involves replacement of the diseased aortic valve with the autologous pulmonic valve and implantation of a homograft in the native pulmonic position. Its use has declined considerably in the United States because of the technical complexity of the procedure and the incidence of late postoperative aortic root dilation and autograft failure with AR. There is also a low incidence of pulmonary homograft stenosis.

PERCUTANEOUS AORTIC BALLOON VALVULOPLASTY (PABV)

This procedure is preferable to operation in many children and young adults with congenital, noncalcific AS **(Chap. 264)**. It is not commonly used as definitive therapy in adults with severe calcific AS because of a very high restenosis rate (80% within 1 year) and the risk of procedural complications, but on occasion, it has been used successfully as a "bridge to operation" in patients with severe LV dysfunction and shock who are too ill to tolerate surgery. It is performed routinely as part of the TAVR procedure (see below).

TRANSCATHETER AORTIC VALVE REPLACEMENT

TAVR for treatment of AS has been performed with increasing frequency in prohibitive-, high-, and intermediate surgical-risk adult patients worldwide using one of two available systems, a balloon-expandable valve and a self-expanding valve, both of which incorporate a pericardial prosthesis **(Fig. 256-5)**. Newer valve platforms are under investigation. Nearly 25,000 U.S. patients underwent TAVR in 2015 across more than 415 centers. TAVR is most frequently performed via the transfemoral route, although trans-LV apical, subclavian, carotid, and ascending aortic routes have been used. Aortic balloon valvuloplasty under rapid RV pacing is performed as a first step to create an orifice of sufficient size for the prosthesis. Procedural success rates exceed 90%. Among elderly patients with severe AS who are considered inoperable (i.e., prohibitive surgical risk), 1- and 2-year survival rates are significantly higher with TAVR compared with medical therapy (including PABV) **(Fig. 256-6)**. One- and 2-year survival rates are essentially equal for high-surgical-risk patients treated with TAVR or SAVR **(Fig. 256-7)**. Last, the 2-year rate of death or disabling stroke is lower in intermediate surgical risk patients who undergo transfemoral TAVR compared with SAVR **(Fig. 256-8)**. TAVR is associated with an early hazard for stroke and a higher incidence of postprocedural, paravalvular AR, a risk factor for mortality over the next 2 years. The rate of postprocedural heart block requiring permanent pacemaker (~10%) is significantly more common after TAVR. Valve performance characteristics are excellent

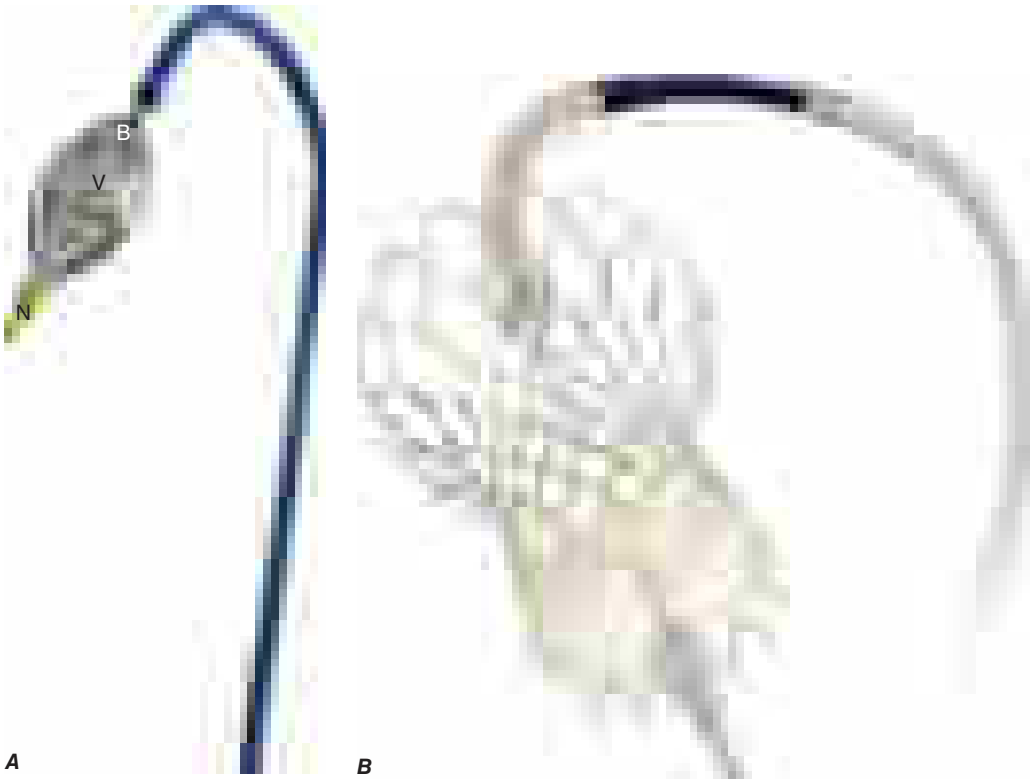
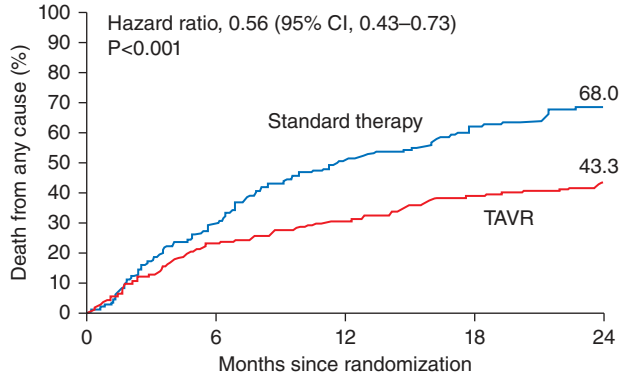


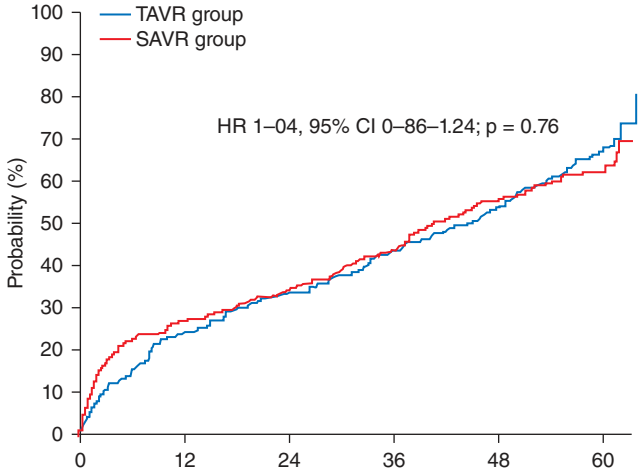
FIGURE 256-5 Balloon-expandable (***A***) and self-expanding (***B***) valves for transcatheter aortic valve replacement (TAVR). B, inflated balloon; N, nose cone; V, valve. *(Part A, courtesy of Edwards Lifesciences, Irvine, CA; with permission. NovaFlex+ is a trademark of Edwards Lifesciences Corporation. Part B, © Medtronic, Inc. 2015. Medtronic CoreValve Transcatheter Aortic Valve. CoreValve is a registered trademark of Medtronic, Inc.)*

over 5 years; longer-term durability assessment is ongoing, but results at 5 years are acceptable. Overall outcomes with this transformative technology have been very favorable and have allowed the extension of AVR to groups of patients previously considered at high or prohibitive risk for conventional surgery. Nevertheless, some patients are not candidates for this procedure because their comorbidity profile and frailty would make its undertaking inappropriate. The heart team is specifically charged with making challenging decisions of this nature. The use of these devices for the treatment of patients with structural deterioration of bioprosthetic aortic valves ("valve-in-valve"), as an alternative to reoperative valve replacement, has been approved. Presently, patients with BAV are not candidates for TAVR.



No. at Risk					
TAVR	179	138	124	110	83
Standard therapy	179	121	85	62	42

FIGURE 256-6 Twenty-four-month outcomes following transcatheter aortic valve replacement (TAVR) for inoperable patients in the PARTNER I trial (cohort B). CI, confidence interval. *(Adapted from RR Makkar et al: N Engl J Med 366:1696, 2012; with permission.)*



No. at Risk						
TAVR group	348	262	228	191	154	61
SAVR group	351	236	210	174	131	62

FIGURE 256-7 Five-year mortality rates following transcatheter (TAVR) or surgical aortic valve replacement (SAVR) for high-surgical-risk patients (cohort A) in the PARTNER I trial. Mortality rates in this AS patient cohort are similar for TAVR and SAVR. CI, confidence interval. *(Adapted from MJ Mack et al: Lancet 2015; 385:2477–2484.)*

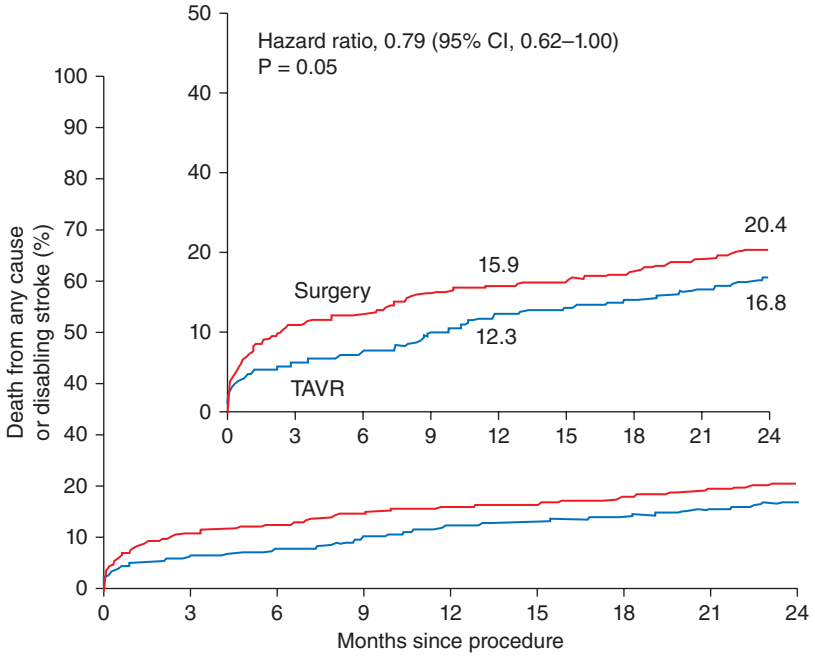


FIGURE 256-8 Rates of death from any cause or disabling stroke for intermediate surgical risk as patients undergoing surgical aortic valve replacement (SAVR) or transfemoral transcatheter aortic valve replacement (TAVR). In this intention-to-treat analysis, transfemoral TAVR proved superior to SAVR. *(Adapted from MB Leon et al: N Engl J Med 374:1609, 2016.)*

FURTHER READING

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NISHIMURA RA et al: 2014 AHA/ACC Guideline for management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 63:e57, 2014.

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257 Aortic Regurgitation

Patrick T. O'Gara, Joseph Loscalzo

ETIOLOGY

(Table 257-1) Aortic regurgitation (AR) may be caused by primary valve disease, aortic root disease or their combination.

Primary Valve Disease Rheumatic disease results in thickening, deformity, and shortening of the individual aortic valve cusps, changes that prevent their proper opening during systole and closure during diastole. A rheumatic origin is much less common in patients with isolated AR who do not have associated rheumatic mitral valve disease. Patients with congenital bicuspid aortic valve (BAV) disease may develop predominant AR, and ~20% of these patients will require aortic valve surgery between 10 and 40 years of age. Congenital fenestrations of the aortic valve occasionally produce mild AR. Membranous subaortic stenosis results in a high velocity systolic jet that often leads to thickening and scarring of the aortic valve leaflets and secondary AR. Prolapse of an aortic cusp, resulting in progressive chronic AR, occurs in ~15% of patients with ventricular septal defect **(Chap. 264)**, but may also occur as an isolated phenomenon or as a consequence of myxomatous degeneration sometimes associated with mitral and/or tricuspid valve involvement.

AR may result from infective endocarditis (IE), which can develop on a valve previously affected by rheumatic disease, a congenitally deformed valve, or on a normal aortic valve, and may lead to perforation or erosion of one or more leaflets. The aortic valve leaflets may become scarred and retracted during the course of syphilis or ankylosing spondylitis and contribute further to the AR that derives primarily from the associated root disease. Although traumatic rupture or avulsion of an aortic cusp is an uncommon cause of acute AR, it represents the most frequent serious lesion in patients surviving nonpenetrating cardiac injuries. The coexistence of hemodynamically significant AS with AR usually excludes all the rarer forms of AR because it occurs

TABLE 257-1 Major Causes of Aortic Valve Disease

VALVE LESION	ETIOLOGIES
Aortic regurgitation	**Valvular**
	Congenital (bicuspid)
	Endocarditis
	Rheumatic fever
	Myxomatous (prolapse)
	Traumatic
	Syphilis
	Ankylosing spondylitis
	Root disease
	Aortic dissection
	Cystic medial degeneration
	Marfan syndrome
	Bicuspid aortic valve
	Nonsyndromic familial aneurysm
	Aortitis
	Hypertension

almost exclusively in patients with rheumatic or congenital AR. In patients with AR due to primary valvular disease, dilation of the aortic annulus may occur secondarily and lead to worsening regurgitation.

Primary Aortic Root Disease AR also may be due entirely to marked aortic annular dilation, i.e., aortic root disease, without primary involvement of the valve leaflets; widening of the aortic annulus and lack of diastolic coaptation of the aortic leaflets are responsible for the AR **(Chap. 274)**. Medial degeneration of the ascending aorta, which may or may not be associated with other manifestations of Marfan syndrome; idiopathic dilation of the aorta; annuloaortic ectasia; osteogenesis imperfecta; and severe, chronic hypertension may all widen the aortic annulus and lead to progressive AR. Occasionally AR is caused by retrograde dissection of the aorta involving the aortic annulus. Syphilis and ankylosing spondylitis, both of which may also affect the aortic leaflets, may be associated with cellular infiltration and scarring of the media of the thoracic aorta, leading to aortic dilation, aneurysm formation, and severe regurgitation. In syphilis of the aorta **(Chap. 177)**, now a very rare condition, the involvement of the intima may narrow the coronary ostia, which in turn may be responsible for myocardial ischemia. Takayasu's aortitis and giant cell aortitis can also result in aneurysm formation and secondary AR.

PATHOPHYSIOLOGY

The total stroke volume ejected by the left ventricle (LV) (i.e., the sum of the effective forward stroke volume and the volume of blood that regurgitates back into the LV) is increased in patients with AR. In patients with severe AR, the volume of regurgitant flow may equal the effective forward stroke volume. In contrast to MR, in which a portion of the LV stroke volume is delivered into the low-pressure left atrium (LA), in AR the entire LV stroke volume is ejected into a high-pressure zone, the aorta. An increase in the LV end-diastolic volume (increased preload) constitutes the major hemodynamic compensation for AR. The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril. Therefore, severe AR may occur with a normal effective forward stroke volume and a normal LV ejection fraction (LVEF, total [forward plus regurgitant] stroke volume/end-diastolic volume), together with an elevated LV end-diastolic pressure and volume. However, through the operation of Laplace's law, LV dilation increases the LV systolic tension required to develop any given level of systolic pressure. Chronic AR is, thus, a state in which LV preload and afterload are both increased. Ultimately, these adaptive measures fail. As LV function deteriorates, the end-diastolic volume rises further and the forward stroke volume and EF decline. Deterioration of LV function often precedes the development of symptoms. Considerable thickening of the LV wall also occurs with chronic AR, and at autopsy, the hearts of these patients may be among the largest encountered, sometimes weighing >1000 g.

The reverse pressure gradient from aorta to LV, which drives the AR flow, falls progressively during diastole, accounting for the decrescendo nature of the diastolic murmur. Equilibration between aortic and LV pressures may occur toward the end of diastole in patients with chronic severe AR, particularly when the heart rate is slow. In patients with acute severe AR, the LV is unprepared for the regurgitant volume load. LV compliance is normal or reduced, and LV diastolic pressures rise rapidly, occasionally to levels >40 mmHg. The LV pressure may exceed the LA pressure toward the end of diastole, and this reversed pressure gradient closes the mitral valve prematurely.

In patients with chronic severe AR, the effective forward cardiac output (CO) usually is normal or only slightly reduced at rest, but often it fails to rise normally during exercise. An early sign of LV dysfunction is a reduction in the EF. In advanced stages, there may be considerable elevation of the LA, pulmonary artery (PA) wedge, PA, and right ventricular (RV) pressures and lowering of the forward CO at rest.

Myocardial ischemia may occur in patients with AR because myocardial oxygen requirements are elevated by LV dilation, hypertrophy, and elevated LV systolic tension, and coronary blood flow may be compromised. A large fraction of coronary blood flow occurs during diastole, when arterial pressure is low, thereby reducing coronary perfusion or driving pressure. This combination of increased oxygen demand and reduced supply may cause myocardial ischemia, particularly of the subendocardium, even in the absence of epicardial coronary artery disease (CAD).

HISTORY

Approximately three-fourths of patients with pure or predominant valvular AR are men; women predominate among patients with primary valvular AR who have associated rheumatic mitral valve disease. A history compatible with IE may sometimes be elicited from patients with rheumatic or congenital involvement of the aortic valve, and the infection often precipitates or seriously aggravates preexisting symptoms.

In patients with *acute severe AR*, as may occur in IE, aortic dissection, or trauma, the LV cannot dilate sufficiently to maintain stroke volume, and LV diastolic pressure rises rapidly with associated marked elevations of LA and PA wedge pressures. Pulmonary edema and/or cardiogenic shock may develop rapidly.

Chronic severe AR may have a long latent period, and patients may remain relatively asymptomatic for as long as 10–15 years. Uncomfortable awareness of the heartbeat, especially on lying down, may be an early complaint. Sinus tachycardia, during exertion or with emotion, or premature ventricular contractions may produce particularly uncomfortable palpitations as well as head pounding. These complaints may persist for many years before the development of exertional dyspnea, usually the first symptom of diminished cardiac reserve. The dyspnea is followed by orthopnea, paroxysmal nocturnal dyspnea, and excessive diaphoresis. Anginal chest pain even in the absence of CAD may occur in patients with severe AR, even in younger patients. Anginal pain may develop at rest as well as during exertion. Nocturnal angina may be a particularly troublesome symptom, and it may be accompanied by marked diaphoresis. The anginal episodes can be prolonged and often do not respond satisfactorily to sublingual nitroglycerin. Systemic fluid accumulation, including congestive hepatomegaly and ankle edema, may develop late in the course of the disease.

PHYSICAL FINDINGS

In chronic severe AR, the jarring of the entire body and the bobbing motion of the head with each systole can be appreciated, and the abrupt distention and collapse of the larger arteries are easily visible. The examination should be directed toward the detection of conditions predisposing to AR, such as bicuspid valve, IE, Marfan syndrome, or ankylosing spondylitis.

Arterial Pulse A rapidly rising "water-hammer" pulse, which collapses suddenly as arterial pressure falls rapidly during late systole and diastole (Corrigan's pulse), and capillary pulsations, an alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse), are characteristic of chronic severe AR. A booming "pistol-shot" sound can be heard over the femoral arteries (Traube's sign), and a to-and-fro murmur (Duroziez's sign) is audible if the femoral artery is lightly compressed with a stethoscope.

The arterial pulse pressure is widened as a result of both systolic hypertension and a lowering of the diastolic pressure. The measurement of arterial diastolic pressure with a sphygmomanometer may be complicated by the fact that systolic sounds are frequently heard with the cuff completely deflated. However, the level of cuff pressure at the time of muffling of the Korotkoff sounds (phase IV) generally corresponds fairly closely to the true intraarterial diastolic pressure. As the disease progresses and the LV end-diastolic pressure rises, the arterial diastolic pressure may actually rise as well, because the aortic diastolic pressure cannot fall below the LV end-diastolic pressure. For the same reason, acute severe AR may also be accompanied by only a slight widening of the pulse pressure. Such patients are invariably tachycardic as the heart rate increases in an attempt to preserve the CO.

Palpation In patients with chronic severe AR, the LV impulse is heaving and displaced laterally and inferiorly. The systolic expansion and diastolic retraction of the apex are prominent. A diastolic thrill may be palpable along the left sternal border in thin-chested individuals,

and a prominent systolic thrill may be palpable in the suprasternal notch and transmitted upward along the carotid arteries. This systolic thrill and the accompanying murmur do not necessarily signify the coexistence of aortic stenosis (AS). In some patients with AR or with combined AS and AR, the carotid arterial pulse may be bisferiens, i.e., with two systolic waves separated by a trough **(see Fig. 234-2*D*)**.

Auscultation In patients with severe AR, the aortic valve closure sound (A_2) is usually absent. A systolic ejection sound is audible in patients with BAV disease, and occasionally an S_4 also may be heard. The murmur of chronic AR is typically a high-pitched, blowing, decrescendo diastolic murmur, heard best in the third intercostal space along the left sternal border **(see Fig. 234-5*B*)**. In patients with mild AR, this murmur is brief, but as the severity increases, it generally becomes louder and longer, indeed holodiastolic. When the murmur is soft, it can be heard best with the diaphragm of the stethoscope and with the patient sitting up, leaning forward, and with the breath held in forced expiration. In patients in whom the AR is caused by primary valvular disease, the diastolic murmur is usually louder along the left than the right sternal border. However, when the murmur is louder along the right sternal border, it suggests that the AR is caused by aneurysmal dilation of the aortic root. "Cooing" or musical diastolic murmurs suggest eversion of an aortic cusp vibrating in the regurgitant stream.

A mid-systolic ejection murmur is frequently audible in isolated AR. It is generally heard best at the base of the heart and is transmitted along the carotid arteries. This murmur may be quite loud without signifying aortic obstruction. A third murmur sometimes heard in patients with severe AR is the *Austin Flint murmur*, a soft, low-pitched, rumbling mid-to-late diastolic murmur. It is probably produced by the diastolic displacement of the anterior leaflet of the mitral valve by the AR stream and is not associated with hemodynamically significant mitral obstruction. The auscultatory features of AR are intensified by strenuous and sustained handgrip, which augments systemic vascular resistance.

In acute severe AR, the elevation of LV end-diastolic pressure may lead to early closure of the mitral valve, a soft S_1, a pulse pressure that is not particularly wide, and a soft, short, early diastolic murmur of AR.

LABORATORY EXAMINATION

ECG In patients with chronic severe AR, the ECG signs of LV hypertrophy are common **(Chap. 235)**. In addition, these patients frequently exhibit ST-segment depression and T-wave inversion in leads I, aVL, V_5, and V_6 ("LV strain"). Left-axis deviation and/or QRS prolongation denote diffuse myocardial disease, generally associated with patchy fibrosis, and usually signify a poor prognosis.

Echocardiogram LV size is increased in chronic AR and systolic function is normal or even supernormal until myocardial contractility declines, as signaled by a decrease in ejection fraction (EF) or increase in the end-systolic dimension. A rapid, high-frequency diastolic fluttering of the anterior mitral leaflet produced by the impact of the regurgitant jet is a characteristic finding. The echocardiogram is also useful in determining the cause of AR, by detecting dilation of the aortic annulus and root, aortic dissection **(see Fig. 236-5**, or primary leaflet pathology). With severe AR, the central jet width assessed by color flow Doppler imaging exceeds 65% of the LV outflow tract, the regurgitant volume is ≥60 mL/beat, the regurgitant fraction is ≥50%, and there is diastolic flow reversal in the proximal descending thoracic aorta. The continuous-wave Doppler profile of the AR jet shows a rapid deceleration time in patients with acute severe AR, due to the rapid increase in LV diastolic pressure. Surveillance transthoracic echocardiography (TTE) forms the cornerstone of longitudinal follow-up and allows for the early detection of changes in LV size and/or function. For patients in whom TTE is limited by poor acoustical windows or inadequate characterization of LV function or the severity of the regurgitation, cardiac magnetic resonance (CMR) imaging can be performed. This modality also allows for accurate assessment of aortic size and contour. Transesophageal echocardiography (TEE) can also provide detailed anatomic assessment of the valve, root, and portions of the aorta. There is increasing experience with the use of 3D echocardiography to measure LV volumes.

Chest X-Ray In chronic severe AR, the apex is displaced downward and to the left in the frontal projection. In the left anterior oblique and lateral projections, the LV is displaced posteriorly and encroaches on the spine. When AR is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view. Echocardiography, cardiac MRI, and chest CT angiography are more sensitive than the chest x-ray for the detection of root and ascending aortic enlargement.

Cardiac Catheterization and Angiography When needed, right and left heart catheterization with contrast aortography can provide confirmation of the magnitude of regurgitation and the status of LV function. Coronary angiography is performed routinely in appropriate patients prior to surgery.

TREATMENT

Aortic Regurgitation

ACUTE AORTIC REGURGITATION **(FIG. 257-1)**

Patients with acute severe AR may respond to intravenous diuretics and vasodilators (such as sodium nitroprusside), but stabilization is usually short-lived and operation is indicated urgently. Intraaortic balloon counterpulsation is contraindicated. Beta blockers are also best avoided so as not to reduce the CO further or slow the heart rate, thus allowing more time for diastolic filling of the LV. Surgery is the treatment of choice and is usually necessary within 24 h of diagnosis.

CHRONIC AORTIC REGURGITATION

Early symptoms of dyspnea and effort intolerance respond to treatment with diuretics; vasodilators (Angiotensin converting enzyme [ACE] inhibitors, dihydropyridine calcium channel blockers, or hydralazine) may be useful as well. Surgery can then be performed in a more controlled setting. The use of vasodilators to extend the compensated phase of chronic severe AR before the onset of symptoms or the development of LV dysfunction is more controversial and less well established. Systolic blood pressure should be controlled (goal <140 mmHg) in patients with chronic AR, and vasodilators are an excellent first choice as antihypertensive agents. It is often difficult to achieve adequate control because of the increased stroke volume that accompanies severe AR. Cardiac arrhythmias and systemic infections are poorly tolerated in patients with severe AR and must be treated promptly and vigorously. Although nitroglycerin and long-acting nitrates are not as helpful in relieving anginal pain as they are in patients with ischemic heart disease, they are worth a trial. Patients with syphilitic aortitis should receive a full course of penicillin therapy **(Chap. 177)**. Beta blockers and the angiotensin receptor blocker (ARB) losartan may be useful to retard the rate of aortic root enlargement in young patients with Marfan syndrome and aortic root dilation. A randomized controlled trial showed no difference in efficacy between atenolol and losartan for this indication. Whether beta blockers or ARBs is useful in retarding the rate of growth of aortic aneurysms in other patient subsets (e.g., BAV disease with aortopathy, Takaysu's disease) have not been demonstrated. Beta blockers in patients with valvular AR were previously considered relatively contraindicated due to concerns that the resulting slowing of the heart rate would allow more time for diastolic regurgitation. Observational reports, however, have suggested that beta blockers may provide functional benefit in some patients with chronic AR. Beta blockers can sometimes provide incremental blood pressure lowering in patients with chronic AR and hypertension. They can also lessen the sense of forceful heart action that many patients find uncomfortable. Patients with severe AR, particularly those with an associated aortopathy, should avoid isometric exercises.

SURGICAL TREATMENT

In deciding on the advisability and proper timing of surgical treatment, two points should be kept in mind: (1) patients with chronic severe AR usually do not become symptomatic until *after* the

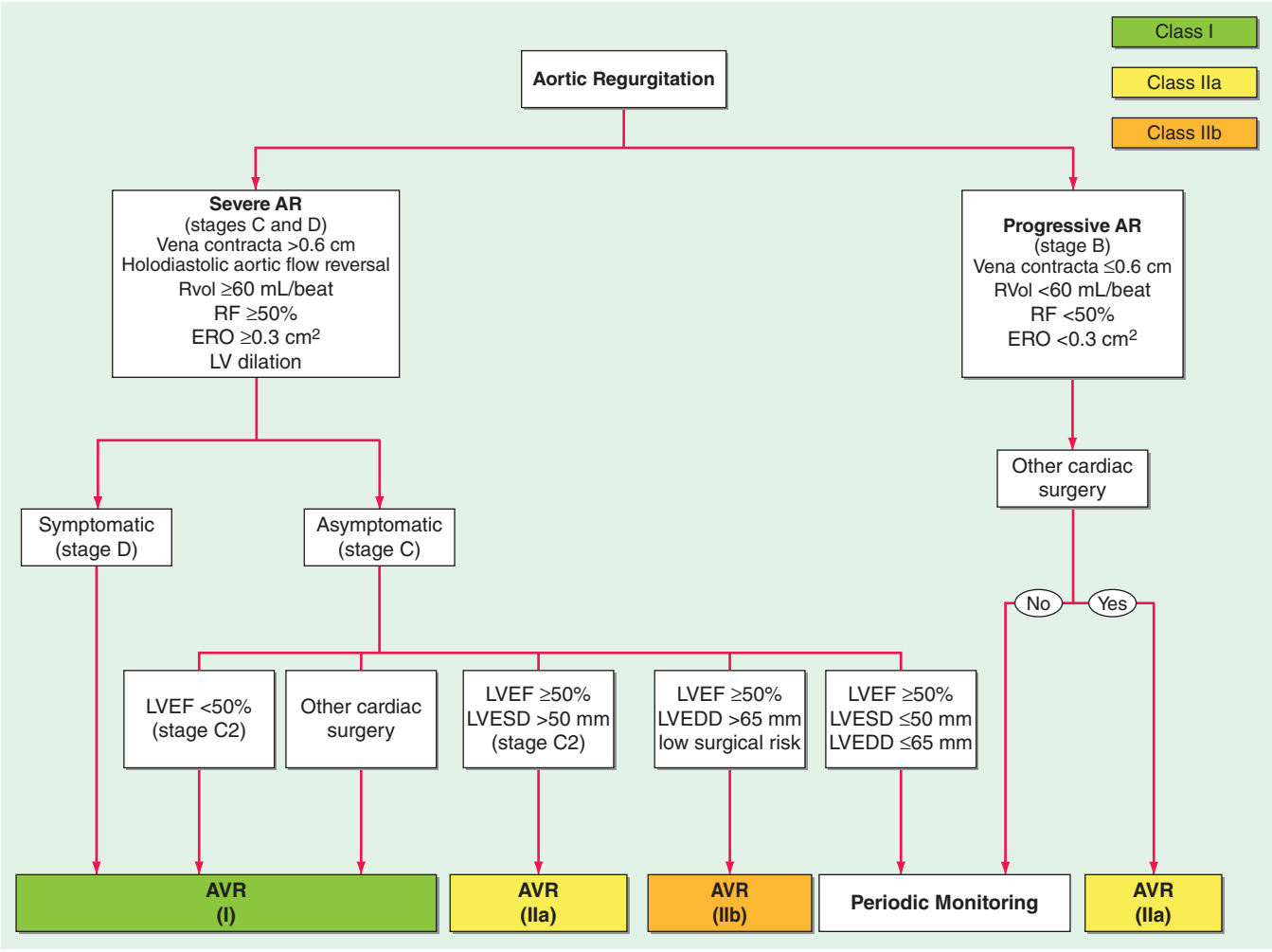

FIGURE 257-1 Management of patients with aortic regurgitation. See legend for Fig. 256-4 for explanation of treatment recommendations (Class I, IIa, and IIb) and disease stages (B, C1, C2, and D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. Patients who do not meet criteria for intervention should be monitored periodically with clinical and echocardiographic follow-up. AR, aortic regurgitation; AVR, aortic valve replacement (valve repair may be appropriate in selected patients); ERO, effective regurgitant orifice; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RF, regurgitant fraction; RVol, regurgitant volume. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57-185, 2014, with permission.)*

development of myocardial dysfunction; and (2) when delayed too long (defined as >1 year from onset of symptoms or LV dysfunction), surgical treatment often does not restore normal LV size and function. Therefore, in patients with chronic severe AR, careful clinical follow-up and noninvasive testing with echocardiography at ~6- to 12-month intervals are necessary if operation is to be undertaken at the optimal time, i.e., *after* the onset of LV dysfunction but *prior to* the development of severe symptoms. Exercise testing may be helpful to assess effort tolerance more objectively. Operation can be deferred as long as the patient both remains asymptomatic and retains normal LV function without severe or progressive chamber dilation.

Aortic valve replacement (AVR) is indicated for the treatment of severe AR in symptomatic patients irrespective of LV function. In general, the operation should be carried out in asymptomatic patients with severe AR and progressive LV dysfunction defined by an LVEF <50%, an LV end-systolic dimension >50 mm, or an LV diastolic dimension >65 mm. Smaller dimensions may be appropriate thresholds in individuals of smaller stature or when there is evidence of progressively decreasing LV function or increasing LV size on serial studies. Patients with severe AR without indications for operation should be followed by clinical and echocardiographic examination every 6–12 months.

Surgical options for management of aortic valve and root disease have expanded considerably over the past decade. AVR with a suitable mechanical or tissue prosthesis is generally necessary in patients with rheumatic AR and in many patients with other forms of regurgitation. Rarely, when a leaflet has been perforated during IE or torn from its attachments to the aortic annulus by thoracic trauma, primary surgical repair may be possible. When AR is due to aneurysmal dilation of the root or proximal ascending aorta rather than to primary valve involvement, it may be possible to reduce or eliminate the regurgitation by narrowing the annulus or by excising a portion of the aortic root without replacing the valve. Elective, valve-sparing aortic root reconstruction generally involves reimplantation of the valve in a contoured graft with reattachment of the coronary artery buttons into the side of the graft and is best undertaken in specialized surgical centers (Fig. 257-2). Resuspension of the native aortic valve leaflets is possible in ~50% of patients with acute AR in the setting of type A aortic dissection. In other conditions, however, regurgitation can be effectively eliminated only by replacing the aortic valve, the dilated or aneurysmal ascending aorta responsible for the regurgitation, and implanting a composite valve-graft conduit. This formidable procedure entails a higher risk than isolated AVR.

As in patients with other valvular abnormalities, both the operative risk and the late mortality rate are largely dependent on the stage of the disease and myocardial function at the time of operation. The overall operative mortality rate for isolated AVR

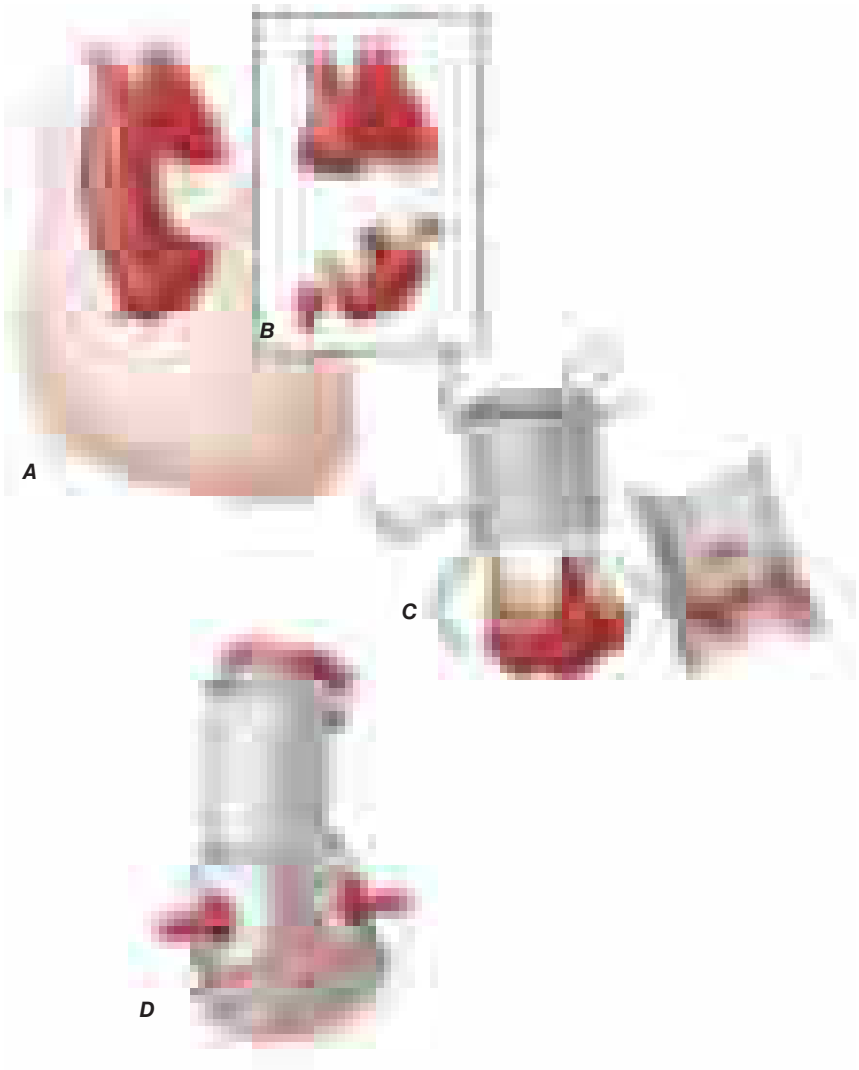

FIGURE 257-2 Valve-sparing aortic root reconstruction (David procedure). Aortic root and proximal ascending aorta (***A***) are resected (***B***) with sinuses of Valsalva and mobilized coronary artery buttons remaining. Subannular sutures (***C***) are placed, commissural posts are drawn up inside the valve and the annular sutures are passed through the proximal end of the graft. The annular sutures are tied (***D***), the valve is re-implanted inside the graft, aortic continuity is re-established with another graft of appropriate size and the coronary buttons are attached to the side of the graft. *(From P Steltzer et al [eds]: Valvular Heart Disease: A Companion to Braunwald's Heart Disease, 3rd ed, Fig 12-27, p. 200.)*

(performed for either or both AS or AR) is ~2% (Table 257-2). However, patients with AR, marked cardiac enlargement, and prolonged LV dysfunction experience an operative mortality rate of ~10% and a late mortality rate of ~5% per year due to LV failure despite a technically satisfactory operation. Nonetheless, because of the very poor prognosis with medical management, even patients with advanced LV systolic dysfunction should be considered for operation.

Patients with acute severe AR require prompt (24–48 h) surgical treatment, which may be lifesaving.

TABLE 257-2 Mortality Rates After Aortic Valve Surgery[a]

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
AVR (isolated)	14,795	2.3
AVR + CAB	9158	4.2
AVR + MVR	876	8.8

Abbreviations: AVR, aortic valve replacement; CAB, coronary artery bypass; MVR, mitral valve replacement.

[a]Data are for the first two quarters of calendar year 2013, during which 1004 sites reported a total of 135,666 procedures. Data are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2013_3rdHarvestExecutiveSummary.pdf*.

FURTHER READING

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Malaisrie SC, McCarthy PM: Surgical approach to disease of the aortic valve and the aortic root, in *Valvular Heart Disease: A Companion to Braunwald's Heart Disease*, 4th ed. CM Otto, RO Bonow (eds). Philadelphia, Elsevier Saunders, 2014, pp 199–218.

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258 Mitral Stenosis

Patrick T. O'Gara, Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 38 and 234; of electrocardiography (ECG) in Chap. 235; of echocardiography and other noninvasive imaging techniques in Chap. 236; and of cardiac catheterization and angiography in Chap. 237.

ETIOLOGY AND PATHOLOGY

Rheumatic fever is the leading cause of mitral stenosis (MS) **(Table 258-1; see also Chap. 352)**. Other less common etiologies of obstruction to left ventricular inflow include congenital mitral valve stenosis, cor triatriatum, mitral annular calcification with extension onto the leaflets, systemic lupus erythematosus, rheumatoid arthritis, left atrial myxoma, and infective endocarditis with large vegetations. Pure or predominant MS occurs in ~40% of all patients with rheumatic heart disease and a history of rheumatic fever **(Chap. 352)**. In other patients with rheumatic heart disease, lesser degrees of MS may accompany mitral regurgitation (MR) and aortic valve disease. With reductions in the incidence of acute rheumatic fever, particularly in temperate climates and developed countries, the incidence of MS has declined considerably over the past several decades. However, it remains a major problem in developing nations, especially in tropical and semitropical climates.

In rheumatic MS, chronic inflammation leads to diffuse thickening of the valve leaflets with formation of fibrous tissue often with calcific deposits. The mitral commissures fuse, the chordae tendineae fuse and shorten, the valvular cusps become rigid, and the pathologic process eventually leads to narrowing at the apex of the funnel-shaped ("fish-mouth") valve. Although the initial insult to the mitral valve is rheumatic, later changes may be exacerbated by a nonspecific process resulting from trauma to the valve due to altered flow patterns. Calcification of the stenotic mitral valve immobilizes the leaflets and narrows the orifice further. Thrombus formation and arterial embolization may arise from the calcific valve itself, but in patients with atrial fibrillation (AF), thrombi arise more frequently from the dilated left atrium (LA), particularly from within the LA appendage.

PATHOPHYSIOLOGY

In normal adults, the area of the mitral valve orifice is 4–6 cm^2. In the presence of significant obstruction, i.e., when the orifice area is reduced to <~2 cm^2, blood can flow from the LA to the left ventricle (LV) only if propelled by an abnormally elevated left atrioventricular pressure gradient, the hemodynamic hallmark of MS. When the mitral valve opening is reduced to <1.5 cm^2, referred to as "severe" MS, an LA pressure of ~25 mmHg is required to maintain a normal cardiac output (CO). The elevated pulmonary venous and pulmonary arterial (PA) wedge pressures reduce pulmonary compliance, contributing to exertional dyspnea. The first bouts of dyspnea are usually precipitated by clinical events that increase the rate of blood flow across the mitral orifice, resulting in further elevation of the LA pressure (see below).

To assess the severity of obstruction hemodynamically, both the transvalvular pressure gradient and the flow rate must be measured **(Chap. 237)**. The latter depends not only on the CO but on the heart rate, as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore, at any given level of CO, tachycardia, including that associated with rapid AF, augments the transvalvular pressure gradient and elevates further the LA pressure. Similar considerations apply to the pathophysiology of tricuspid stenosis (TS).

The LV diastolic pressure and ejection fraction (EF) are normal in isolated MS. In MS and sinus rhythm, the elevated LA and PA wedge pressures exhibit a prominent atrial contraction pattern (*a* wave) and a gradual pressure decline after the *v* wave and mitral valve opening (*y* descent). In severe MS and whenever pulmonary vascular resistance is significantly increased, the PA pressure (PAP) is elevated at rest and rises further during exercise, often causing secondary elevations of right ventricular (RV) end-diastolic pressure and volume.

TABLE 258-1 Major Causes of Mitral Stenosis

Etiologies
Rheumatic fever
Congenital (parachute valve, cor triatriatum)
Severe mitral annular calcification with leaflet involvement
SLE, RA
Myxoma
IE with large vegetations

Abbreviations: IE, infective endocarditis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Cardiac Output In patients with severe MS (mitral valve orifice 1–1.5 cm^2), the CO is normal or almost so at rest, but rises subnormally during exertion. In patients with very severe MS (valve area <1 cm^2), particularly those in whom pulmonary vascular resistance is markedly elevated, the CO is subnormal at rest and may fail to rise or may even decline during activity.

Pulmonary Hypertension The clinical and hemodynamic features of MS are influenced importantly by the level of the PAP. Pulmonary hypertension results from: (1) passive backward transmission of the elevated LA pressure; (2) pulmonary arteriolar constriction (the so-called "second stenosis"), which presumably is triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension); (3) interstitial edema in the walls of the small pulmonary vessels; and (4) at end stage, organic obliterative changes in the pulmonary vascular bed. Severe pulmonary hypertension results in RV enlargement, secondary tricuspid regurgitation (TR), and pulmonic regurgitation (PR), as well as right-sided heart failure.

SYMPTOMS

In temperate climates, the latent period between the initial attack of rheumatic carditis (in the increasingly rare circumstances in which a history of one can be elicited) and the development of symptoms due to MS is generally about two decades; most patients begin to experience disability in the fourth decade of life. Studies carried out before the development of surgical mitral valvotomy revealed that once a patient with MS became seriously symptomatic, the disease progressed inexorably to death within 2–5 years.

In patients whose mitral orifices are large enough to accommodate a normal blood flow with only mild elevations of LA pressure, marked elevations of this pressure leading to dyspnea and cough may be precipitated by sudden changes in the heart rate, volume status, or CO, as, for example, with severe exertion, excitement, fever, severe anemia, paroxysmal AF and other tachycardias, sexual intercourse, pregnancy, and thyrotoxicosis. As MS progresses, lesser degrees of stress precipitate dyspnea, the patient becomes limited in daily activities, and orthopnea and paroxysmal nocturnal dyspnea develop. The development of persistent AF often marks a turning point in the patient's course and is generally associated with acceleration of the rate at which symptoms progress. *Hemoptysis* **(Chap. 35)** results from rupture of pulmonary-bronchial venous connections secondary to pulmonary venous hypertension. It occurs most frequently in patients who have elevated LA pressures without markedly elevated pulmonary vascular resistances and is rarely fatal. *Recurrent pulmonary emboli* **(Chap. 273)**, sometimes with infarction, are an important cause of morbidity and mortality late in the course of MS. *Pulmonary infections*, i.e., bronchitis, bronchopneumonia, and lobar pneumonia, commonly complicate untreated MS, especially during the winter months.

Pulmonary Changes In addition to the aforementioned changes in the pulmonary vascular bed, fibrous thickening of the walls of the alveoli and pulmonary capillaries occurs commonly in MS. The vital capacity, total lung capacity, maximal breathing capacity, and oxygen uptake per unit of ventilation are reduced **(Chap. 279)**. Pulmonary compliance falls further as pulmonary capillary pressure rises during exercise.

Thrombi and Emboli *Thrombi* may form in the left atria, particularly within the enlarged atrial appendages of patients with MS. Systemic embolization, the incidence of which is 10–20%, occurs more frequently in patients with AF, in patients >65 years of age, and in those with a reduced CO. However, systemic embolization may be the presenting feature in otherwise asymptomatic patients with only mild MS.

PHYSICAL FINDINGS

(See also Chaps. 38 and 234)

Inspection and Palpation In patients with severe MS, there may be a malar flush with pinched and blue facies. In patients with sinus rhythm and severe pulmonary hypertension or associated TS, the jugular venous pulse reveals prominent *a* waves due to vigorous right atrial systole. The systemic arterial pressure is usually normal or slightly low. A parasternal lift signifies an enlarged RV. A diastolic thrill may rarely be present at the cardiac apex, with the patient in the left lateral recumbent position.

Auscultation The first heart sound (S_1) is usually accentuated in the early stages of the disease and slightly delayed. The pulmonic component of the second heart sound (P_2) also is often accentuated with elevated PAPs, and the two components of the second heart sound (S_2) are closely split. The opening snap (OS) of the mitral valve is most readily audible in expiration at, or just medial to, the cardiac apex. This sound generally follows the sound of aortic valve closure (A_2) by 0.05–0.12 s. The time interval between A_2 and OS varies inversely with the severity of the MS. The OS is followed by a low-pitched, rumbling, diastolic murmur, heard best at the apex with the patient in the left lateral recumbent position (see Fig. 234-5); it is accentuated by mild exercise (e.g., a few rapid sit-ups) carried out just before auscultation. In general, the duration of this murmur correlates with the severity of the stenosis in patients with preserved CO. In patients with sinus rhythm, the murmur often reappears or becomes louder during atrial systole (presystolic accentuation). Soft, grade I or II/VI systolic murmurs may be heard at or medial to the apex and may signify mixed mitral valve disease with regurgitation. Hepatomegaly, ankle edema, ascites, and pleural effusion, particularly in the right pleural cavity, may occur in patients with MS and RV failure.

Associated Lesions With severe pulmonary hypertension, a pansystolic murmur produced by functional TR may be audible along the left sternal border. This murmur is usually louder during inspiration and diminishes during forced expiration (Carvallo's sign). When the CO is markedly reduced in MS, the typical auscultatory findings, including the diastolic rumbling murmur, may not be detectable (silent MS), but they may reappear as compensation is restored. The *Graham Steell murmur* of PR, a high-pitched, diastolic, decrescendo blowing murmur along the left sternal border, results from dilation of the pulmonary valve ring and occurs in patients with mitral valve disease and severe pulmonary hypertension. This murmur may be indistinguishable from the more common murmur produced by aortic regurgitation (AR), although it may increase in intensity with inspiration and is accompanied by a loud and often palpable P_2.

LABORATORY EXAMINATION

ECG In MS and sinus rhythm, the P wave usually suggests LA enlargement (see Fig. 235-8). It may become tall and peaked in lead II and upright in lead V_1 when severe pulmonary hypertension or TS complicates MS and right atrial (RA) enlargement occurs. The QRS complex is usually normal. However, with severe pulmonary hypertension, right axis deviation and RV hypertrophy are often present.

Echocardiogram (See also Chap. 236) Transthoracic echocardiography (TTE) with color flow and spectral Doppler imaging provides critical information, including measurements of mitral inflow velocity during early (E wave) and late (A wave in patients in sinus rhythm) diastolic filling, estimates of the transvalvular peak and mean gradients and mitral orifice area, the presence and severity of any associated MR, the extent of leaflet calcification and restriction, the degree of distortion of the subvalvular apparatus, and the anatomic suitability for percutaneous mitral balloon valvotomy (PMBV; see below). In addition, TTE provides an assessment of LV and RV function, chamber sizes, an estimation of the PA systolic pressure based on the tricuspid regurgitant jet velocity, and an indication of the presence and severity of any associated valvular lesions, such as aortic stenosis (AS) and/or regurgitation. Transesophageal echocardiography (TEE) provides superior images and should be used when TTE is inadequate for guiding management decisions. TEE is especially indicated to exclude the presence of LA thrombus prior to PMBV. The performance of TTE with exercise to evaluate the mean mitral diastolic gradient and PAPs can be very helpful in the evaluation of patients with MS when there is a discrepancy between the clinical findings and the resting hemodynamics.

Chest X-Ray The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main PAs, dilation of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged LA. Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields that result from distention of interlobular septae and lymphatics with edema when the resting mean LA pressure exceeds ~20 mmHg.

DIFFERENTIAL DIAGNOSIS

Like MS, significant MR may also be associated with a prominent diastolic murmur at the apex due to increased antegrade transmitral flow, but in patients with isolated MR, this diastolic murmur commences slightly later than in patients with MS, and there is often clear-cut evidence of LV enlargement. An OS and increased P_2 are absent, and S_1 is soft or absent. An apical pansystolic murmur of at least grade III/VI intensity as well as an S_3 suggests significant MR. Similarly, the apical mid-diastolic murmur associated with severe AR (*Austin Flint murmur*) may be mistaken for MS, but can be differentiated from it because it is not intensified in presystole and becomes softer with administration of amyl nitrite or other arterial vasodilators. TS, which occurs rarely in the absence of MS, may mask many of the clinical features of MS or be clinically silent; when present, the diastolic murmur of TS increases with inspiration and the *y* descent in the jugular venous pulse is delayed.

Atrial septal defect (Chap. 264) may be mistaken for MS; in both conditions, there is often clinical, ECG, and chest x-ray evidence of RV enlargement and accentuation of pulmonary vascularity. However, the absence of LA enlargement and of Kerley B lines and the demonstration of fixed splitting of S_2 with a grade II or III mid-systolic murmur at the mid to upper left sternal border all favor atrial septal defect over MS. Atrial septal defects with large left-to-right shunts may result in functional TS because of the enhanced diastolic flow.

Left atrial myxoma (Chap. 266) may obstruct LA emptying, causing dyspnea, a diastolic murmur, and hemodynamic changes resembling those of MS. However, patients with an LA myxoma often have features suggestive of a systemic disease, such as weight loss, fever, anemia, systemic emboli, and elevated serum IgG and interleukin 6 (IL-6) concentrations. The auscultatory findings may change markedly with body position. The diagnosis can be established by the demonstration of a characteristic echo-producing mass in the LA with TTE.

CARDIAC CATHETERIZATION

Left and right heart catheterization can be useful when there is a discrepancy between the clinical and noninvasive findings, including those from TEE and exercise echocardiographic testing when appropriate. Catheterization is helpful in assessing associated lesions, such as AS and AR. Catheterization and coronary angiography are not usually necessary to aid in decision-making about surgery in patients <65 years of age with typical findings of severe mitral obstruction on physical examination and TTE. In men >40 years of age, women >45 years of age, and younger patients with coronary risk factors, especially those with positive noninvasive stress tests for myocardial ischemia, coronary angiography is advisable preoperatively to identify patients with critical coronary obstructions that should be bypassed at the time of operation. Computed tomographic coronary angiography (CTCA) is often used to screen preoperatively for the presence of coronary artery disease (CAD) in appropriate patients with valvular heart disease and low pretest likelihood of CAD. Catheterization and left ventriculography may be useful in patients who have undergone PMBV or previous mitral valve surgery for MS, and who have redeveloped limiting symptoms, especially if questions regarding the severity of the valve lesion(s) remain after noninvasive study.

TREATMENT

Mitral Stenosis (Fig. 258-1)

Penicillin prophylaxis of group A β-hemolytic streptococcal infections (Chap. 352) for secondary prevention of rheumatic fever is important for at-risk patients with rheumatic MS. Recommendations for infective endocarditis prophylaxis are similar to those for other valve lesions and are restricted to patients at high risk for complications from infection, including patients with a history of endocarditis. In symptomatic patients, some improvement usually occurs with restriction of sodium intake and small doses of oral diuretics. Beta blockers, nondihydropyridine calcium channel blockers (e.g., verapamil or diltiazem), and digitalis glycosides are useful in slowing the ventricular rate of patients with AF. Warfarin therapy targeted to an international normalized ratio (INR) of 2–3 should be administered indefinitely to patients with MS who have AF or a history of thromboembolism. The routine use of warfarin in patients in sinus rhythm with LA enlargement (maximal dimension >5.5 cm) with or without spontaneous echo contrast is more controversial. As of this writing, direct oral anticoagulants (e.g., apixaban, rivaroxaban) are not approved for use in patients with rheumatic MS.

If AF is of relatively recent onset in a patient whose MS is not severe enough to warrant PMBV or surgical intervention, reversion to sinus rhythm pharmacologically or by means of electrical countershock is indicated. Usually, cardioversion should be undertaken after the patient has had at least 3 consecutive weeks of anticoagulant treatment to a therapeutic INR. If cardioversion is indicated more urgently, then intravenous heparin should be provided and TEE performed to exclude the presence of LA thrombus before the procedure. Conversion to sinus rhythm is rarely successful or sustained in patients with severe MS, particularly those in whom the LA is especially enlarged or in whom AF has been present for more than 1 year.

MITRAL VALVOTOMY

Unless there is a contraindication, mitral valvotomy is indicated in symptomatic (New York Heart Association [NYHA] Functional Class II–IV) patients with isolated severe MS, whose effective orifice (valve area) is < ~1 cm^2/m^2 body surface area, or <1.5 cm^2 in normal-sized adults. Mitral valvotomy can be carried out either percutaneously or surgically. In PMBV (Figs. 258-2 and 258-3), a catheter is directed into the LA after transseptal puncture, and a single balloon is directed across the valve and inflated in the valvular orifice. Ideal patients have relatively pliable leaflets with little or no commissural calcium. In addition, the subvalvular structures should not be significantly scarred or thickened, and there should be no LA thrombus. The short- and long-term results of this procedure in appropriate patients are similar to those of surgical valvotomy, but with less morbidity and a lower periprocedural mortality rate. Event-free survival in younger (<45 years) patients with pliable valves is excellent, with rates as high as 80–90% over 3–7 years. Therefore, PMBV has become the procedure of choice for such patients when it can be performed by a skilled operator in a high-volume center.

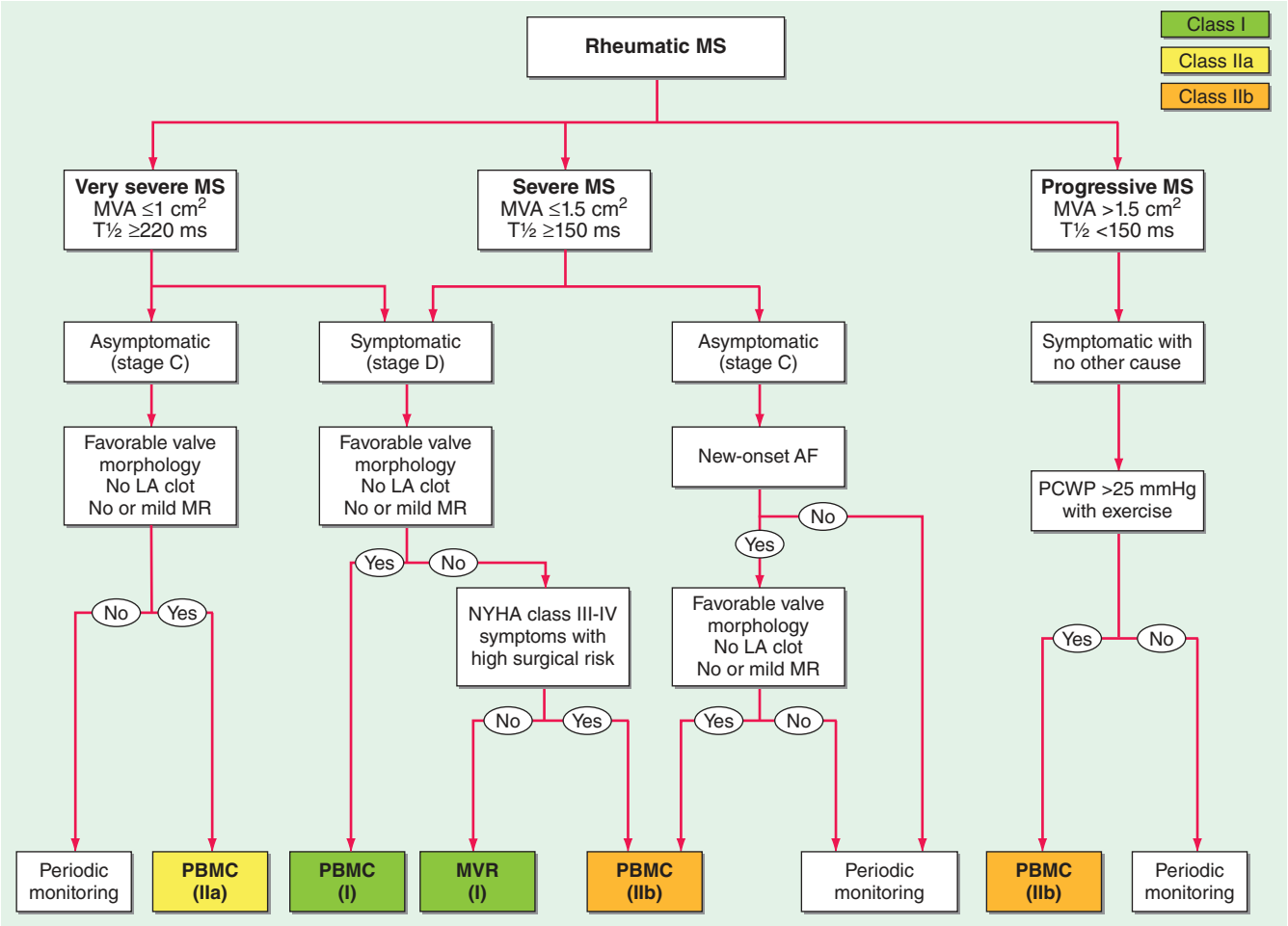

FIGURE 258-1 Management of rheumatic mitral stenosis. See legend for Fig. 256-4 for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T ½, pressure half-time. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57-185, 2014, with permission.)*

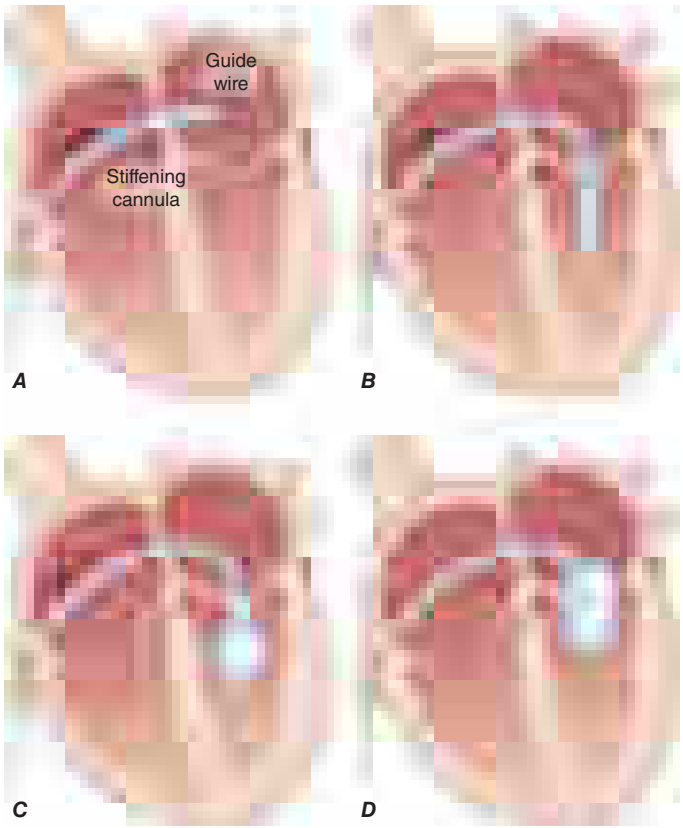

FIGURE 258-2 Inoue balloon technique for percutaneous mitral balloon valvotomy. *A.* After transseptal puncture, the deflated balloon catheter is advanced across the interatrial septum, then across the mitral valve and into the left ventricle. ***B–D.*** The balloon is inflated stepwise within the mitral orifice.

TTE is helpful in identifying patients for the percutaneous procedure; TEE is performed routinely to exclude LA thrombus and to assess the degree of MR at the time of the scheduled procedure. An "echo score" has been developed to help guide decision-making. The score accounts for the degree of leaflet thickening, calcification, and mobility, and for the extent of subvalvular thickening. A lower score predicts a higher likelihood of successful PMBV.

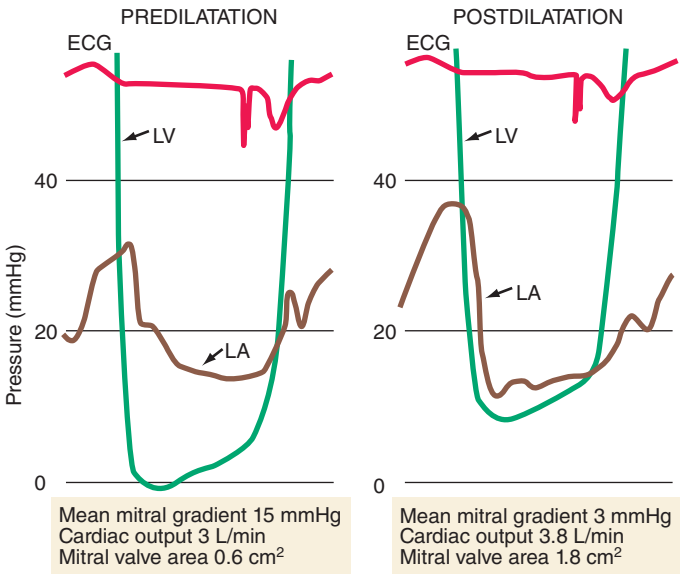

FIGURE 258-3 Simultaneous left atrial (LA) and left ventricular (LV) pressure before and after percutaneous mitral balloon valvotomy (PMBV) in a patient with severe mitral stenosis. ECG, electrocardiogram. *(Courtesy of Raymond G. McKay, MD; with permission.)*

TABLE 258-2 Mortality Rates after Mitral Valve Surgery[a]

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR (isolated)	3448	4.6
MVR + CAB	1321	10.0
MVRp	4284	1.2
MVRp + CAB	2051	4.8

[a]Data are for the first two quarters of calendar year 2015, during which 1013 sites reported a total of 141,225 procedures. Data are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2015Harvest3_ExecutiveSummary.pdf.*

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

In patients in whom PMBV is not possible or unsuccessful, or in many patients with restenosis after previous surgery, an "open" surgical valvotomy using cardiopulmonary bypass is necessary. In addition to opening the valve commissures, it is important to loosen any subvalvular fusion of papillary muscles and chordae tendineae; to remove large deposits of calcium, thereby improving valvular function; and to remove atrial thrombi. The perioperative mortality rate is ~2%.

Successful valvotomy is defined by a 50% reduction in the mean mitral valve gradient and a doubling of the mitral valve area. Successful valvotomy, whether balloon or surgical, usually results in striking symptomatic and hemodynamic improvement and prolongs survival. However, there is no evidence that the procedure improves the prognosis of patients with slight or no functional impairment. Therefore, unless recurrent systemic embolization or severe pulmonary hypertension has occurred (PA systolic pressures >50 mmHg at rest or >60 mmHg with exercise), valvotomy is *not* recommended for patients who are entirely asymptomatic and/or who have mild or moderate stenosis (mitral valve area >1.5 cm^2). When there is little symptomatic improvement after valvotomy, it is likely that the procedure was ineffective, that it induced MR, or that associated valvular or myocardial disease was present. About half of all patients undergoing surgical mitral valvotomy require reoperation by 10 years. In the pregnant patient with MS, valvotomy should be carried out if pulmonary congestion occurs despite intensive medical treatment. PMBV is the preferred strategy in this setting and is performed with TEE and no or minimal x-ray exposure.

Mitral valve replacement (MVR) is necessary in patients with MS and significant associated MR, those in whom the valve has been severely distorted by previous transcatheter or operative manipulation, or those in whom the surgeon does not find it possible to improve valve function significantly with valvotomy. MVR is now routinely performed with preservation of the chordal attachments to optimize LV functional recovery. Perioperative mortality rates with MVR vary with age, LV function, the presence of CAD, and associated comorbidities. They average 5% overall but are lower in young patients and may be twice as high in patients >65 years of age with significant comorbidities (Table 258-2). Because there are also long-term complications of valve replacement, patients in whom preoperative evaluation suggests the possibility that MVR may be required should be operated on only if they have severe MS—i.e., an orifice area ≤1.5 cm^2—and are in NYHA Class III, i.e., symptomatic with ordinary activity despite optimal medical therapy. The overall 10-year survival of surgical survivors is ~70%. Long-term prognosis is worse in patients >65 years of age and those with marked disability and marked depression of the CO preoperatively. Pulmonary hypertension and RV dysfunction are additional risk factors for poor outcome.

FURTHER READING

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NISHIMURA RA et al: Mitral valve disease–Current management and future challenges. Lancet 387:1324, 2016.

259 Mitral Regurgitation

Patrick T. O'Gara, Joseph Loscalzo

The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in Chaps. 38 and 234; of electrocardiography (ECG) in Chap. 235; of echocardiography and other noninvasive imaging techniques in Chap. 236; and of cardiac catheterization and angiography in Chap. 237.

ETIOLOGY

Mitral regurgitation (MR) may result from an abnormality or disease process that affects any one or more of the five functional components of the mitral valve apparatus (leaflets, annulus, chordae tendineae, papillary muscles, and subjacent myocardium) (Table 259-1). Acute MR can occur in the setting of acute myocardial infarction (MI) with papillary muscle rupture (Chap. 269), following blunt chest wall trauma, or during the course of infective endocarditis (IE) owing to leaflet perforation or destruction. With acute MI, the posteromedial papillary muscle is involved much more frequently than the anterolateral papillary muscle because of its singular blood supply. Transient, acute MR can occur during periods of active ischemia and bouts of angina pectoris. Rupture of chordae tendineae can result in "acute-on-chronic MR" in patients with myxomatous degeneration of the valve apparatus.

Chronic MR can result from several disease processes (Table 259-1). Distinction should be drawn between primary MR, in which the leaflets and/or chordae tendineae are primarily responsible for abnormal valve function, and secondary (functional) MR, in which the leaflets and chordae tendineae are usually normal but the regurgitation is caused by left ventricular (LV) remodeling with annular enlargement, papillary muscle displacement, leaflet tethering, or their combination. Patient assessment, treatment approach, and long-term prognosis differ significantly between primary and secondary MR. Mitral valve prolapse (MVP) is discussed more extensively in Chap. 260. The rheumatic process produces rigidity, deformity, and retraction of the valve cusps and commissural fusion, as well as shortening, contraction, and fusion of the chordae tendineae. MR can persist after resolution of the acute phase of infection and inflammation. MR may occur as a congenital anomaly (Chap. 264), most commonly as a defect of the endocardial cushions (atrioventricular cushion defects). A cleft anterior mitral valve leaflet accompanies ostium primum atrial septal defect. Radiation can result in leaflet thickening, retraction, and calcification, often in association with annular and chordal involvement. Chronic MR is frequently secondary to ischemia and may occur as a consequence of ventricular remodeling, papillary muscle displacement, and leaflet tethering, or with fibrosis of a papillary muscle, in patients with healed MI(s) and ischemic cardiomyopathy. Similar mechanisms of annular dilation and ventricular remodeling contribute to the MR that occurs among patients with nonischemic forms of dilated cardiomyopathy once the LV end-diastolic dimension reaches 6 cm. The MR associated with hypertrophic obstructive cardiomyopathy (HOCM) is usually dynamic in nature and dependent on systolic anterior motion of the anterior mitral valve leaflet into a narrowed LV outflow tract. Patients with long-standing, chronic atrial fibrillation (AF) develop atrial remodeling and annular dilatation that can result in MR. Annular calcification can result in MR when it encroaches on the leaflets or results in decreased sphincteric function and is especially prevalent among patients with advanced renal disease and is commonly observed in women >65 years of age with hypertension and diabetes. Irrespective of cause, chronic severe MR is often progressive, because enlargement of the left atrial (LA) places tension on the posterior mitral leaflet, pulling it away from the mitral orifice and thereby aggravating the valvular dysfunction. Similarly, LV dilation increases the regurgitation, which, in turn, enlarges the LA and LV further, resulting in a vicious circle; hence the aphorism, "MR begets MR."

TABLE 259-1 Major Causes of Mitral Regurgitation

Etiologies
Acute
IE
Papillary muscle rupture (post-MI)
Chordal rupture/leaflet flail (MVP, IE)
Blunt trauma
Chronic
Primary (affecting leaflets, chordae)
Myxomatous (MVP, Barlow's, forme fruste)
Rheumatic fever
IE (healed)
Congenital (cleft, AV canal)
Radiation
Secondary (leaflets, chordae are "innocent bystanders")
Ischemic cardiomyopathy
Dilated cardiomyopathy
HOCM (with SAM)
Chronic AF with LA enlargement and annular dilatation
Mitral annular calcification[a]

[a]Mitral annular calcification may include elements of both primary and secondary MR as the disease process may encroach on the leaflets, impair the normal sphincteric function of the annulus, or both.

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; IE, infective endocarditis; HOCM, hypertrophic obstructive cardiomyopathy; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MVP, mitral valve prolapse; SAM, systolic anterior motion.

PATHOPHYSIOLOGY

The resistance to LV emptying (LV afterload) is reduced in patients with MR. As a consequence, the LV is decompressed into the LA during ejection, and with the reduction in LV size during systole, there is a rapid decline in LV tension. The initial compensation to MR is more complete LV emptying. However, LV volume increases progressively with time as the severity of the regurgitation increases and as LV contractile function deteriorates. This increase in LV volume is often accompanied by a reduced forward cardiac output (CO). LV compliance is often increased, and thus, LV diastolic pressure does not increase until late in the course. The regurgitant volume varies directly with the LV systolic pressure and the size of the regurgitant orifice; the latter, in turn, is influenced by the extent of LV and mitral annular dilation. Because ejection fraction (EF) rises in severe MR in the presence of normal LV function, even a modest reduction in this parameter (<60%) reflects significant contractile dysfunction.

During early diastole, as the distended LA empties, there is a particularly rapid *y* descent in the absence of accompanying MS. A brief, early diastolic LA-LV pressure gradient (often generating a rapid filling sound [S_3] and mid-diastolic murmur masquerading as MS) may occur in patients with pure, severe MR as a result of the very rapid flow of blood across a normal-sized mitral orifice.

Measurements of LV ejection fraction (LVEF), CO, pulmonary arterial (PA) systolic pressure, regurgitant volume, regurgitant fraction (RF), and the effective regurgitant orifice area can be obtained during a careful Doppler echocardiographic examination. These measurements can also be obtained accurately with cardiac magnetic resonance (CMR) imaging, although this technology is not widely available. Left and right heart catheterization with contrast ventriculography is used less frequently. Chronic, severe MR is defined by a regurgitant volume ≥60 mL/beat, RF ≥50%, and effective regurgitant orifice area ≥0.40 cm^2. In patients with secondary MR, in whom the severity of MR can be underappreciated, lesser degrees of regurgitation carry relatively greater prognostic weight.

LA Compliance In acute severe MR, the regurgitant volume is delivered into a normal-sized LA having normal or reduced compliance. As a result, LA pressures rise markedly for any increase in LA volume.

The *v* wave in the LA pressure pulse is usually prominent, LA and pulmonary venous pressures are markedly elevated, and pulmonary edema is common. Because of the rapid rise in LA pressures during ventricular systole, the murmur of acute MR is early in timing and decrescendo in configuration ending well before S_2, as a reflection of the progressive diminution in the LV-LA pressure gradient. LV systolic function in acute MR may be normal, hyperdynamic, or reduced, depending on the clinical context.

Patients with chronic severe MR, on the other hand, develop marked LA enlargement and *increased* LA compliance with little if any increase in LA and pulmonary venous pressures for any increase in LA volume. The LA *v* wave is relatively less prominent. The murmur of chronic MR is classically holosystolic in timing and plateau in configuration, as a reflection of the near-constant LV-LA pressure gradient. These patients usually complain of severe fatigue and exhaustion secondary to a low forward CO, whereas symptoms resulting from pulmonary congestion are less prominent initially; AF is almost invariably present once the LA dilates significantly.

SYMPTOMS

Patients with chronic mild-to-moderate, isolated MR are usually asymptomatic. This form of LV volume overload is well tolerated. Fatigue, exertional dyspnea, and orthopnea are the most prominent complaints in patients with chronic severe MR. Palpitations are common and may signify the onset of AF. Right-sided heart failure, with painful hepatic congestion, ankle edema, distended neck veins, ascites, and secondary tricuspid regurgitation (TR), occurs in patients with MR who have associated pulmonary vascular disease and pulmonary hypertension. Acute pulmonary edema is common in patients with acute severe MR.

PHYSICAL FINDINGS

In patients with chronic severe MR, the arterial pressure is usually normal, although the carotid arterial pulse may show a sharp, low-volume upstroke owing to the reduced forward CO. A systolic thrill is often palpable at the cardiac apex, the LV is hyperdynamic with a brisk systolic impulse and a palpable rapid-filling wave (S_3), and the apex beat is often displaced laterally.

In patients with acute severe MR, the arterial pressure may be reduced with a narrow pulse pressure, the jugular venous pressure and waveforms may be normal or increased and exaggerated, the apical impulse is not displaced, and signs of pulmonary congestion are prominent.

Auscultation S_1 is generally absent, soft, or buried in the holosystolic murmur of chronic, severe MR. In patients with severe MR, the aortic valve may close prematurely, resulting in wide but physiologic splitting of S_2. A low-pitched S_3 occurring 0.12–0.17 s after the aortic valve closure sound, i.e., at the completion of the rapid-filling phase of the LV, is believed to be caused by the sudden tensing of the papillary muscles, chordae tendineae, and valve leaflets. It may be followed by a short, rumbling, mid-diastolic murmur, even in the absence of structural MS. In patients with ischemic or dilated cardiomyopathy, however, a third sound (S_3) may also signify ventricular dysfunction. A fourth heart sound is often audible in patients with *acute* severe MR who are in sinus rhythm. A presystolic murmur is not ordinarily heard with isolated MR.

A systolic murmur of at least grade III/VI intensity is the most characteristic auscultatory finding in chronic severe MR. It is usually holosystolic **(see Fig. 234-5*A*)**, but as previously noted, it is decrescendo and ceases in mid-to-late systole in patients with acute severe MR. The systolic murmur of chronic MR is usually most prominent at the apex and radiates to the axilla. However, in patients with ruptured chordae tendineae or primary involvement of the posterior mitral leaflet with prolapse or flail, the regurgitant jet is eccentric, directed anteriorly, and strikes the LA wall adjacent to the aortic root. In this situation, the systolic murmur is transmitted to the base of the heart and, therefore, may be confused with the murmur of AS. In patients with ruptured chordae tendineae, the systolic murmur may have a cooing or "seagull" quality, whereas a flail leaflet may produce a murmur with a musical quality. The systolic murmur of chronic MR not due to MVP is intensified by isometric exercise (handgrip) but is reduced during the strain phase of the Valsalva maneuver because of the associated decrease in LV preload.

LABORATORY EXAMINATION

ECG In patients with sinus rhythm, there is evidence of LA enlargement, but right atrial (RA) enlargement also may be present when pulmonary hypertension is significant and affects RV function and size. Chronic severe MR is frequently associated with AF. In many patients, there is no clear-cut ECG evidence of enlargement of either ventricle. In others, the signs of eccentric LV hypertrophy are present.

Echocardiogram Transthoracic echocardiography (TTE) is indicated to assess the mechanism of the MR and its hemodynamic severity. LV function can be assessed from LV end-diastolic and end-systolic volumes and EF. Observations can be made regarding leaflet structure and function, chordal integrity, LA and LV size, annular calcification, and regional and global LV systolic function. Doppler imaging should demonstrate the width or area of the color flow MR jet within the LA, the duration and intensity of the continuous wave Doppler signal, the pulmonary venous flow contour, the early peak mitral inflow velocity, and quantitative measures of regurgitant volume, RF, and effective regurgitant orifice area. In addition, the PA pressures (PAPs) can be estimated from the TR jet velocity. TTE is also indicated to follow the course of patients with chronic MR and to provide rapid assessment for any clinical change. Transesophageal echocardiography (TEE) provides greater anatomic detail than TTE **(see Fig. 236-5)**. Exercise testing with TTE can be useful to assess exercise capacity as well as any dynamic change in MR severity, PA systolic pressures, and biventricular function, for patients in whom there is a discrepancy between clinical findings and the results of other noninvasive testing.

Chest X-Ray The LA and LV are the dominant chambers in chronic MR. Late in the course of the disease, the LA may be massively enlarged and forms the right border of the cardiac silhouette. Pulmonary venous congestion, interstitial edema, and Kerley B lines are sometimes noted. Marked calcification of the mitral leaflets occurs commonly in patients with long-standing, combined rheumatic MR and MS. Calcification of the mitral annulus may be visualized, particularly on the lateral view of the chest. Patients with acute severe MR may have asymmetric pulmonary edema if the regurgitant jet is directed predominantly to the orifice of an upper lobe pulmonary vein.

TREATMENT

Mitral Regurgitation

MEDICAL TREATMENT **(FIG. 259-1)**

The management of chronic severe MR depends to some degree on its cause. Anticoagulation with either warfarin or a direct oral agent (e.g., apixaban, rivaroxaban) should be provided if AF intervenes, as guided by the CHA2DS2-VASc risk score. The direct oral anticoagulants should not be used if rheumatic mitral stenosis is also present; they are also not approved for use in patients with mechanical prosthetic heart valves. Cardioversion should be considered depending on the clinical context, AF chronicity, LA size. In contrast to the acute setting, there are no large, long-term prospective studies to substantiate the use of vasodilators for the treatment of chronic, isolated severe MR with preserved LV systolic function *in the absence of systemic hypertension.* The severity of MR in the setting of an ischemic or dilated cardiomyopathy may diminish with aggressive guideline-directed treatment of heart failure including the use of diuretics, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, digitalis, and biventricular pacing (cardiac resynchronization therapy [CRT]) when otherwise indicated. Antibiotic prophylaxis for prevention of IE is indicated for MR patients with a prior history of IE. Asymptomatic patients with severe MR in sinus rhythm with normal LV size and systolic function should avoid isometric forms of exercise.

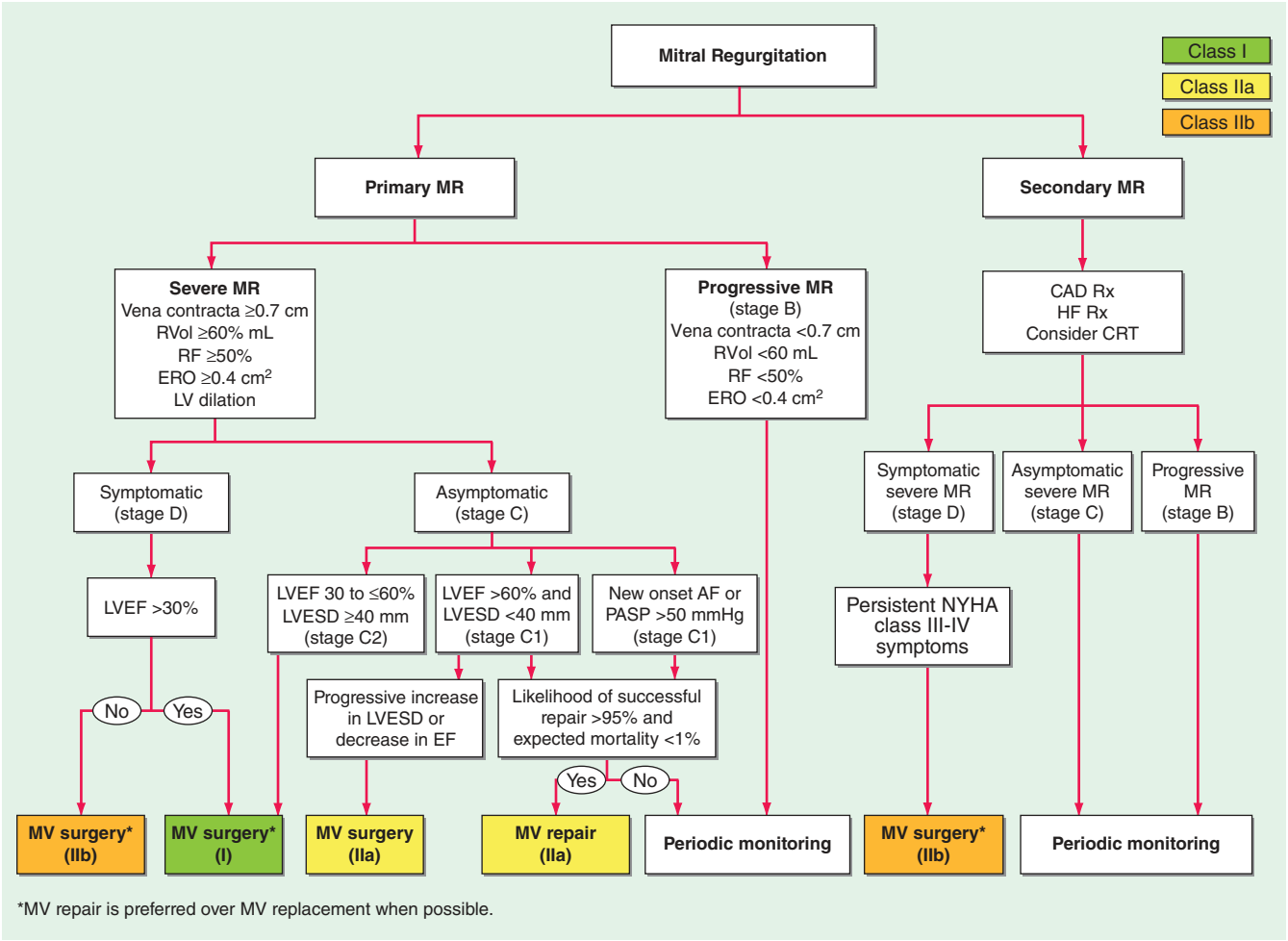

FIGURE 259-1 Management of mitral regurgitation. See legend for **Fig. 256-4** for explanation of treatment recommendations (class I, IIa, IIb) and disease stages (B, C1, C2, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. AF, atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy. *(Adapted from RA Nishimura et al: 2017 Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol. Available at www.onlinejacc.org/lookup/doi/10.1016/j.jacc.2017.03.011.)*

Patients with acute severe MR require urgent stabilization and preparation for surgery. Diuretics, intravenous vasodilators (particularly sodium nitroprusside), and even mechanical support may be needed for patients with post-MI papillary muscle rupture or other forms of acute severe MR.

SURGICAL TREATMENT

In the selection of patients with chronic, severe, primary MR for surgical treatment, the often slowly progressive nature of the condition must be balanced against the immediate and long-term risks associated with operation. These risks are significantly lower for primary valve repair than for valve replacement **(Table 259-2)**. Repair usually consists of valve reconstruction using a variety of valvuloplasty techniques and insertion of an annuloplasty ring. Repair spares the patient the long-term adverse consequences of valve replacement, including thromboembolic and hemorrhagic complications in the case of mechanical prostheses and late valve failure necessitating repeat valve replacement in the case of bioprostheses. In addition, by preserving the integrity of the papillary muscles, subvalvular apparatus, and chordae tendineae, mitral repair and valvuloplasty maintain LV function to a relatively greater degree than does valve replacement.

Surgery for chronic severe primary MR is indicated once symptoms occur, especially if valve repair is feasible (Fig. 259-1). Surgery should also be recommended for asymptomatic patients with LV dysfunction characterized by an EF <60% or an LV end-systolic dimension (LV ESD) >40 mm. Other indications for early consideration of mitral valve repair in asymptomatic patients include (1) recent-onset AF (duration <3 months); (2) pulmonary hypertension (defined as a systolic PA pressure ≥50 mmHg at rest or ≥60 mmHg with exercise); and (3) a progressive decrease in LV EF or increase in LV ESD on serial imaging. These aggressive recommendations for surgery are predicated on the adverse long-term consequences of

TABLE 259-2 Mortality Rates after Mitral Valve Surgery[a]

OPERATION	NUMBER	UNADJUSTED OPERATIVE MORTALITY (%)
MVR (isolated)	3448	4.6
MVR + CAB	1321	10.0
MVRp	4284	1.2
MVRp + CAB	2051	4.8

[a]Data are for the first two quarters of calendar year 2015, during which 1013 sites reported a total of 141,225 procedures. Data are available from the Society of Thoracic Surgeons at *http://www.sts.org/sites/default/files/documents/2015Harvest3_ExecutiveSummary.pdf*.

Abbreviations: CAB, coronary artery bypass; MVR, mitral valve replacement; MVRp, mitral valve repair.

waiting for LV function to decline further as well as the outstanding results achievable with mitral valve repair by reference surgeons at high-volume centers. Indeed, repair of myxomatous MR (e.g., prolapse, flail) in patients <75 years with normal LV systolic function and no coronary artery disease (CAD) can now be performed by experienced surgeons with <1% perioperative mortality risk. The risk of stroke, however, is also ~1%. Repair is feasible in up to 95% of patients with myxomatous disease operated on by a high-volume surgeon in a referral center of excellence. Repair techniques include chordal transfer, creation of neochords, limited leaflet resection, and insertion of an annuloplasty band. Long-term durability is excellent; the incidence of reoperative surgery for failed primary repair is ~1% per year for the first 10 years after surgery. For patients with AF, left or biatrial maze surgery, or radiofrequency isolation of the pulmonary veins is often performed to reduce the risk of recurrent postoperative AF.

The surgical management of patients with secondary MR is more complicated. Surgery for patients with ischemic MR most often involves simultaneous coronary artery revascularization. Current surgical practice includes annuloplasty repair with an undersized, rigid ring or chord-sparing valve replacement for patients with moderate or greater degrees of MR. Valve repair for ischemic MR is associated with lower perioperative mortality rates than valve replacement but significantly higher rates of recurrent MR over time. In patients with ischemic MR and significantly impaired LV systolic function (EF <30%), the risk of surgery is higher, recovery of LV performance is incomplete, and long-term survival is reduced. Referral for surgery must be individualized and made only after aggressive attempts to improve symptoms with guideline-directed medical therapy and CRT, when indicated. The routine performance of valve repair in patients with significant secondary MR due to a dilated cardiomyopathy has not been shown to improve long-term survival compared with optimal medical therapy. Patients with acute severe MR can often be stabilized temporarily with appropriate medical therapy, but surgical correction will be necessary emergently in the case of papillary muscle rupture and within days to weeks in most other settings.

When surgical treatment is contemplated, left and right heart catheterization and left ventriculography *may* be helpful in confirming the presence of severe MR in patients in whom there is a discrepancy between the clinical and TTE findings that cannot be resolved with TEE or CMR. Coronary angiography identifies patients who require concomitant coronary revascularization.

TRANSCATHETER MITRAL VALVE REPAIR AND REPLACEMENT

A transcatheter approach to the treatment of either primary or functional MR may be feasible in selected patients with appropriate anatomy. The proper role of currently available techniques remains under active investigation. One approach involves the deployment of a clip delivered via transseptal puncture that grasps the leading edges of the mitral leaflets in their mid-portion (anterior scallop to posterior scallop or A2-P2; **Fig. 259-2**). The length and width of the gap between these leading edges dictate patient eligibility. The device is commercially available. In the United States only for the treatment of prohibitive- or high-surgical risk, symptomatic patients with severe, primary (myxomatous) MR. The edge-to-edge clip technique is undergoing study in the United States for treatment of patients with symptomatic heart failure, reduced LVEF, and severe, secondary MR despite guideline-directed medical therapy. Other approaches include the deployment of a device within the coronary sinus that can be adjusted to reduce mitral annular circumference and the effective orifice area of the valve much like a surgically implanted ring. Variations in the anatomic relationship of the coronary sinus to the mitral annulus and circumflex coronary artery have limited the applicability of this technique. Attempts to reduce the septal-lateral dimension of a dilated annulus using adjustable cords placed across the LV in a subvalvular location have also been investigated. Construction of neochords to the mitral leaflets under TEE guidance using a system delivered via the cardiac apex is also under study. Investigational experience to date with transcatheter mitral valve replacement systems is in early clinical stages, although the field is evolving rapidly.

FIGURE 259-2 Clip used to grasp the free edges of the anterior and posterior leaflets in their midsections during transcatheter repair of selected patients with mitral regurgitation. *(Courtesy of Abbott Vascular. © 2014 Abbott Laboratories. All rights reserved.)*

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260 Mitral Valve Prolapse

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The role of the physical examination in the evaluation of patients with valvular heart disease is also considered in **Chaps. 38 and 234**; of electrocardiography (ECG) in **Chap. 235**; of echocardiography and other noninvasive imaging techniques in **Chap. 236**; and of cardiac catheterization and angiography in **Chap. 237**.

MITRAL VALVE PROLAPSE

Mitral valve prolapse (MVP), also variously termed the *systolic click-murmur syndrome, Barlow's syndrome* **(Fig. 260-1)**, *floppy-valve syndrome, and billowing mitral leaflet syndrome*, is a relatively common but highly

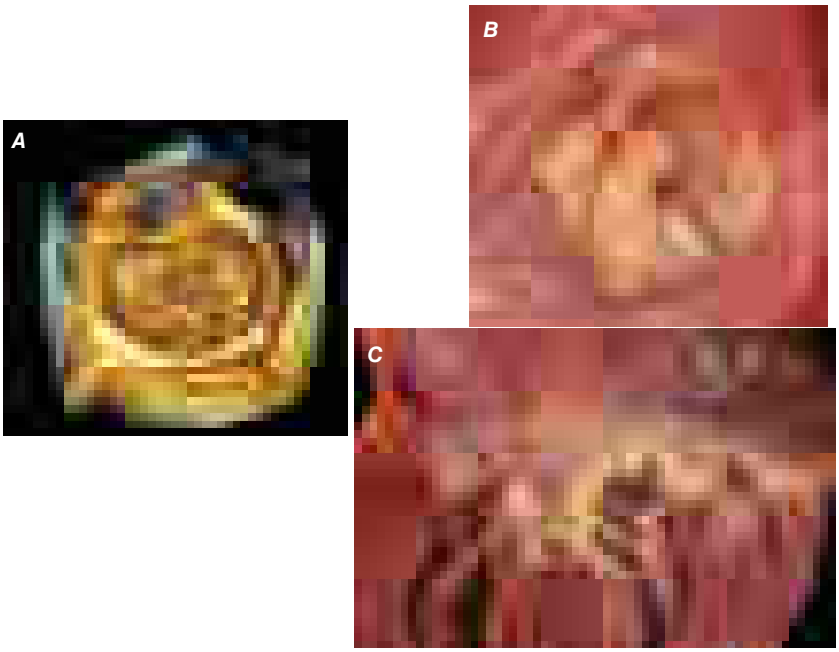

FIGURE 260-1 Congenital or developmental mitral valve prolapse. Myxomatous thickening and prolapse of the mitral valve can occur in isolation in 2–3% of the general population, or may be associated with heritable collagen-vascular disorders and aortic root dilatation, such as in Marfan syndrome. Myxomatous degeneration of the valve predisposes to severe regurgitation and chordal rupture, and is a frequent indication for mitral valve repair or replacement. Prolapse can affect only one or both leaflets, to varying degrees. ***A.*** Three-dimensional transesophageal echocardiogram showing a myxomatous mitral valve from the left atrial *en face* aspect. There is billowing and prolapse of the entire middle scallop of the posterior leaflet. *(Figure courtesy of Douglas C. Shook, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital).* ***B.*** The posterior leaflet of the mitral valve demonstrates marked prolapse and hooding in all segments and severe redundancy in this photograph taken from the vantage point of the left atrium. ***C.*** Opening the left heart reveals prominent mitral leaflet hooding (*arrows*). The chordae are focally thickened, but are not fused as would be the case in rheumatic valve disease. *(Used with permission from JC Wu, RF Padera: Clinicopathologic correlates, in Atlas of Echocardiography, 2nd ed, SD Solomon [ed], E Braunwald [series ed]. Philadelphia, Current Medicine Group LLC, 2008. p 363.)*

variable clinical syndrome resulting from diverse pathologic mechanisms of the mitral valve apparatus. Among these are excessive or redundant mitral leaflet tissue, which is commonly associated with myxomatous degeneration and greatly increased concentrations of certain glycosaminoglycans. MVP is the most common abnormality leading to primary mitral regurgitation (MR) **(see Chap. 259)**.

In most patients with MVP, the cause is unknown, but in some, it appears to be genetically determined. A reduction in the production of type III collagen has been incriminated, and electron microscopy has revealed fragmentation of collagen fibrils.

MVP is a frequent finding in patients with heritable disorders of connective tissue, including Marfan syndrome **(Chap. 406)**, osteogenesis imperfecta, and Ehlers-Danlos syndrome. MVP may be associated with thoracic skeletal deformities similar to but not as severe as those in Marfan syndrome, such as a high-arched palate and alterations of the chest and thoracic spine, including the so-called straight back syndrome. Other associated features can include a history of inguinal hernias, joint dislocations, meniscal tears, and easy bruisability.

In most patients with MVP, myxomatous degeneration is confined to the mitral valve, although the tricuspid and aortic valves may also be affected. The posterior mitral leaflet is usually more affected than the anterior, and the mitral valve annulus is often dilated. In many patients, elongated, redundant, or ruptured chordae tendineae cause or contribute to the regurgitation.

MVP also may occur rarely as a sequel to acute rheumatic fever, in ischemic heart disease, and in various cardiomyopathies, as well as in 20% of patients with ostium secundum atrial septal defect.

MVP may lead to excessive stress on the papillary muscles, which, in turn, leads to dysfunction and ischemia of the papillary muscles and the subjacent ventricular myocardium. Rupture of chordae tendineae and progressive annular dilation and calcification contribute to valvular regurgitation, which then places more stress on the diseased mitral valve apparatus, thereby creating a vicious circle. ECG changes (see below) and ventricular arrhythmias described in some patients with MVP appear to result from regional ventricular dysfunction related to the increased stress placed on the papillary muscles.

CLINICAL FEATURES

MVP is more common in women and occurs most frequently between the ages of 15 and 30 years; the clinical course is most often benign. MVP may also be observed in older (>50 years) patients, often men, in whom MR is often more severe and requires surgical treatment. There is an increased familial incidence for some patients, suggesting an autosomal dominant form of inheritance with incomplete penetrance. MVP varies in its clinical expression, ranging from only a systolic click and murmur with mild prolapse of the posterior leaflet to severe MR due to chordal rupture and leaflet flail. The degree of myxomatous change of the leaflets can also vary widely. In many patients, the condition progresses over years or decades; in others, it worsens rapidly as a result of chordal rupture or endocarditis.

Most patients are asymptomatic and remain so for their entire lives. However, in North America, MVP is now the most common cause of isolated severe MR requiring surgical treatment. Arrhythmias, most commonly ventricular premature contractions and paroxysmal supraventricular and ventricular tachycardia, as well as atrial fibrillation (AF), have been reported and may cause palpitations, lightheadedness, and syncope. Sudden death is a very rare complication and occurs most often in patients with severe MR and depressed left ventricle (LV) systolic function, although it can occur in individuals with normal LV size and function. There may be an excess risk of sudden death among patients with a flail leaflet. Many patients have chest pain that is difficult to evaluate; it is often substernal, prolonged, and not related to exertion, but may rarely resemble angina pectoris. Transient cerebral ischemic attacks secondary to emboli from the mitral valve due to endothelial disruption have been reported. Infective endocarditis may occur in patients with MR and/or leaflet thickening.

Auscultation A frequent finding is the mid- or late- (nonejection) systolic click, which occurs 0.14 s or more after S_1 and is thought to be generated by the sudden tensing of slack, elongated chordae tendineae or by the prolapsing mitral leaflet when it reaches its maximal excursion. Systolic clicks may be multiple and may be followed by a high-pitched, mid-late systolic crescendo–decrescendo murmur, which occasionally is "whooping" or "honking" and is heard best at the apex. Radiation of the murmur will depend on the involved leaflet. With posterior leaflet prolapse, the jet of MR is directed anteriorly and the murmur will radiate to the base of the heart. With anterior leaflet involvement, the jet of MR is directed posteriorly and the murmur will radiate to the axilla and back. The click and murmur occur earlier with standing, during the strain phase of the Valsalva maneuver, and with any intervention that decreases LV volume (preload), exaggerating the propensity of mitral leaflet prolapse. Conversely, squatting and isometric exercises, which increase LV volume, diminish MVP; the click-murmur complex is delayed, moves away from S_1, and may even disappear. Some patients have a mid-systolic click without a murmur; others have a murmur without a click. Still others have both sounds at different times.

LABORATORY EXAMINATION

The ECG most commonly is normal but may show biphasic or inverted T-waves in leads II, III, and aVF, and occasionally supraventricular or ventricular premature beats. Transthoracic echocardiography (TTE) is particularly effective in identifying the abnormal position and prolapse of the mitral valve leaflets. A useful echocardiographic definition of

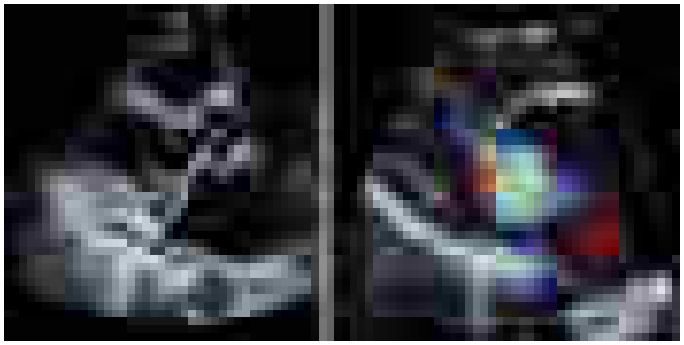

FIGURE 260-2. Barlow's valve with classic mitral valve prolapse, as seen on transthoracic echocardiogram in parasternal long-axis windows. Left: parasternal long-axis window, showing both myxomatous leaflets billowing into the left atrium in late systole. Right: same window with color Doppler showing significant mitral regurgitation (*yellow jet*) in systole. *(Courtesy of Justina Wu, MD, PhD.)*

MVP is systolic displacement (in the parasternal long axis view) of the belly of the mitral valve leaflets by at least 2 mm into the left atrium (LA) superior to the plane of the mitral annulus. There can be prolapse of one or both leaflets **(Fig. 260-2)**. Color flow and continuous wave Doppler imaging is helpful to evaluate the associated MR and provide semiquantitative estimates of severity. The jet lesion of MR due to MVP is most often eccentric, and assessment of the effective regurgitant orifice area and regurgitant volume can be difficult. Both three-dimensional echocardiography and cardiac magnetic resonance can provide more precise determinations of LV volumes. Transesophageal echocardiography (TEE) is indicated when more accurate anatomic information is required and is performed routinely for intraoperative guidance during valve repair. Exercise testing can be performed when there is uncertainty regarding functional capacity. It is often combined with rest and immediate poststress TTE to assess LV and right ventricular (RV) function, and the dynamic nature of MR and pulmonary artery pressures. Invasive left ventriculography done at the time of right and left heart catheterization is rarely necessary but can also show prolapse of the posterior and sometimes of both mitral valve leaflets.

TREATMENT

Mitral Valve Prolapse

Infective endocarditis prophylaxis is indicated for patients with a prior history of endocarditis. Beta blockers sometimes relieve chest pain and control palpitations. Decisions regarding anticoagulation for stroke prevention in AF should be based on the CHA2DS2-VASc score and an assessment of bleeding risk. If the patient is symptomatic from severe MR, mitral valve repair is indicated **(see Fig. 259-1)**. Other indications for surgery for MVP with severe primary MR include signs of established or progressive LV systolic dysfunction, pulmonary artery hypertension, or recent onset AF. Mitral valve repair is preferred over replacement in patients with MVP or flail mitral leaflet **(see Table 258-2)**; technical success is dependent not only on the anatomic findings, but also on the skill and experience of the surgeon. Repair of isolated posterior leaflet prolapse is usually straightforward, but increasingly more complex pathologies (e.g., anterior leaflet prolapse, bileaflet prolapse, Barlow's deformity) require advanced skills. Careful pre- and intraoperative TEE imaging is an important component of patient evaluation and surgical planning. Transcatheter edge-to-edge repair using a clip to grasp the anterior and posterior leaflets together can be considered for treatment of symptomatic patients at high surgical risk with severe primary MR due to MVP **(see Fig. 259-2)**. Most often, the MR will be reduced in severity but not eliminated. Nevertheless, symptom status and indices of LV size and function can be improved with this approach, which is now offered at >200 specialized sites in the United States. Reported hospital mortality rates following the procedure are ~2%. Other transcatheter repair and replacement devices are not yet approved for clinical use in the United States **(see Chap. 259)**.

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261 Tricuspid Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

TRICUSPID STENOSIS

Tricuspid stenosis (TS), which is much less prevalent than mitral stenosis (MS) in North America and Western Europe, is generally rheumatic in origin, and is more common in women than men **(Table 261-1)**. It does not occur as an isolated lesion and is usually associated with MS. Hemodynamically significant TS occurs in 5–10% of patients with severe MS; rheumatic TS is commonly associated with some degree of tricuspid regurgitation (TR). Nonrheumatic causes of TS are rare.

PATHOPHYSIOLOGY

A diastolic pressure gradient between the right atrium (RA) and right ventricle (RV) defines TS. It is augmented when the transvalvular blood flow increases during inspiration and declines during expiration. A mean diastolic pressure gradient of 4 mmHg is usually sufficient to elevate the mean RA pressure to levels that result in systemic venous congestion. Unless sodium intake has been restricted and diuretics administered, this venous congestion is associated with hepatomegaly, ascites, and edema, sometimes severe. In patients with sinus rhythm, the RA *a* wave may be extremely tall and may even approach the level of the RV systolic pressure. The *y* descent is prolonged. The cardiac output (CO) at rest is usually depressed, and it fails to rise during exercise. The low CO is responsible for the normal or only slightly elevated left atrial (LA), pulmonary artery (PA), and RV systolic pressures despite

TABLE 261-1 Causes of Tricuspid Valve Diseases

VALVE LESION	ETIOLOGIES
Tricuspid stenosis	Rheumatic
	Congenital
Tricuspid regurgitation	Primary (organic)
	Rheumatic
	Endocarditis
	Myxomatous (TVP)
	Carcinoid
	Radiation
	Congenital (Ebstein's)
	Trauma
	Papillary muscle injury (post-MI)
	Secondary (functional)
	RV and tricuspid annular dilatation due to multiple causes of RV enlargement (e.g., long-standing pulmonary HTN, remodeling post-RV MI, left-sided valve disease, cardiomyopathy, AF)
	Chronic RV apical pacing

Abbreviations: AF, atrial fibrillation; HTN, hypertension; MI, myocardial infarction; RV, right ventricular; TVP, tricuspid valve prolapse.

the presence of MS. Thus, the presence of TS can mask the hemodynamic and clinical features of any associated MS.

SYMPTOMS

Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion and fatigue. Characteristically, patients with severe TS complain of relatively little dyspnea for the degree of hepatomegaly, ascites, and edema that they have. However, fatigue secondary to a low CO and discomfort due to refractory edema, ascites, and marked hepatomegaly are common in patients with advanced TS and/or TR. In some patients, TS may be suspected for the first time when symptoms of right-sided failure persist after an adequate mitral valvotomy.

PHYSICAL FINDINGS

Because TS usually occurs in the presence of other obvious valvular disease, the diagnosis may be missed unless it is considered. Severe TS is associated with marked hepatic congestion, often resulting in cirrhosis, jaundice, serious malnutrition, anasarca, and ascites. Congestive hepatomegaly and, in cases of severe tricuspid valve disease, splenomegaly are present. The jugular veins are distended, and in patients with sinus rhythm, there may be giant *a* waves. The *v* waves are less conspicuous, and because tricuspid obstruction impedes RA emptying during diastole, there is a slow *y* descent. In patients with sinus rhythm, there may be prominent presystolic pulsations of the enlarged liver as well.

On auscultation, an opening snap (OS) of the tricuspid valve may rarely be heard ~0.06 s after pulmonic valve closure. The diastolic murmur of TS has many of the qualities of the diastolic murmur of MS, and because TS almost always occurs in the presence of MS, it may be missed. However, the tricuspid murmur is generally heard best along the left lower sternal border and over the xiphoid process, and is most prominent during presystole in patients with sinus rhythm. The murmur of TS is augmented during inspiration, and it is reduced during expiration and particularly during the strain phase of the Valsalva maneuver, when tricuspid transvalvular flow is reduced.

LABORATORY EXAMINATION

The electrocardiogram (ECG) features of RA enlargement **(see Fig. 235-8)** include tall, peaked P waves in lead II, as well as prominent, upright P waves in lead V_1. The *absence* of ECG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease. The chest x-ray in patients with combined TS and MS shows particular prominence of the RA and superior vena cava without much enlargement of the PA and with less evidence of pulmonary vascular congestion than occurs in patients with isolated MS; engorgement of the azygos vein can often be appreciated. On transthoracic echocardiographic (TTE) examination, the tricuspid valve is usually thickened and domes in diastole; the transvalvular gradient can be estimated by continuous wave Doppler echocardiography. Severe TS is characterized by a valve area ≤1 cm^2 or pressure half-time of ≥190 ms. The RA and inferior vena cava (IVC) are enlarged. TTE provides additional information regarding the severity of any associated TR, mitral valve structure and function, left ventricle (LV) and RV size and function, and PA pressure. Cardiac catheterization is not routinely necessary for assessment of TS.

TREATMENT

Tricuspid Stenosis

Patients with TS generally exhibit marked systemic venous congestion; salt restriction, bed rest, and diuretic therapy are required during the preoperative period. Such a preparatory period may diminish hepatic congestion and thereby improve hepatic function sufficiently so that the risks of operation, particularly bleeding, are diminished. Surgical relief of the TS should be carried out, preferably at the time of surgical mitral valvotomy or mitral valve replacement (MVR) for mitral valve disease, in patients with moderate or severe TS who have mean diastolic pressure gradients exceeding ~4 mmHg and tricuspid orifice areas <1.5–2 cm^2. TS is almost always accompanied by significant TR. Operative repair may permit substantial improvement of tricuspid valve function. If repair cannot be accomplished, the tricuspid valve may have to be replaced. Meta-analysis has shown no difference in overall survival between mechanical and tissue valve replacement. Mechanical valves in the tricuspid position are more prone to thromboembolic complications than in other positions. Percutaneous tricuspid balloon valvotomy for isolated severe TS without significant TR is very rarely performed.

TRICUSPID REGURGITATION

More than 80% of TR cases encountered in clinical practice are secondary (functional) in nature and related to tricuspid annular dilatation and leaflet tethering in the setting of RV remodeling caused by pressure or volume overload (or both), myocardial infarction (MI) or trauma (Table 261-1). Secondary TR is commonly seen in the late stages of heart failure due to rheumatic or congenital heart disease with severe PA hypertension (PA systolic pressure >55 mmHg), as well as in other types of left-sided valvular (e.g., mitral regurgitation) or myocardial diseases (e.g., ischemic and idiopathic dilated cardiomyopathies). It is reversible in part if PA hypertension can be relieved. Secondary TR can also develop from chronic RV apical pacing and dyssynchronous contraction; in some patients, the RV leads may also perforate or entrap the TV leaflets. TR can often emerge in the setting of new onset atrial fibrillation (AF), particularly in elderly patients. Rheumatic fever may produce primary TR, often associated with TS. Tricuspid valve prolapse, carcinoid heart disease, endomyocardial fibrosis, radiation, infective endocarditis, and leaflet trauma can also produce primary TR. Less commonly, primary TR results from congenitally deformed tricuspid valves, and can occur with defects of the atrioventricular canal, as well as with Ebstein's malformation of the tricuspid valve **(Chap. 264)**.

PATHOPHYSIOLOGY

The incompetent tricuspid valve allows blood to flow backward from the RV into the RA, the volume of which is dependent on the driving pressure (i.e., RV systolic pressure) and the size of the regurgitant orifice. The severity and physical signs of TR can vary as a function of PA systolic pressure (in the absence of RV outflow tract stenosis), the dimension of the tricuspid valve annulus, the respiratory cycle-dependent changes in RV preload, and RA compliance. RV filling is increased during inspiration. Forward CO is reduced and does not augment with exercise. Significant degrees of TR will lead to RA enlargement and elevation of the RA and jugular venous pressures with prominent *c-v* waves in the pulse tracings. Progressively severe TR can lead to "ventricularization" of the RA wave form **(see Fig. 234-1*B*)**. Severe TR is also characterized by RV dilation (RV volume overload) and eventual systolic dysfunction, the progression of which can be accelerated by a concomitant pressure load from PA hypertension or by myocardial fibrosis from previous injury.

SYMPTOMS

Mild or moderate degrees of TR are usually well tolerated in the absence of other hemodynamic disturbances. Because TR most often coexists with left-sided valve lesions, LV dysfunction, and/or PA hypertension, symptoms related to these lesions may dominate the clinical picture. Fatigue and exertional dyspnea owing to reduced forward CO are early symptoms of isolated, severe TR. As the disease progresses and RV function declines, patients may report cervical pulsations, abdominal fullness/bloating, diminished appetite, and muscle wasting, although with progressive weight gain and painful swelling of the lower extremities.

PHYSICAL FINDINGS

The neck veins in patients with severe TR are distended with prominent *c-v* waves and rapid *y* descents (in the absence of TS). TR is more often diagnosed by examination of the neck veins than by auscultation of the heart sounds. Other findings may include marked hepatomegaly with systolic pulsations, ascites, pleural effusions, edema, and a positive hepatojugular reflux sign. A prominent RV pulsation along the

left parasternal region and a blowing holosystolic murmur along the lower left sternal margin, which may be intensified during inspiration (Carvallo's sign) and reduced during expiration or the strain phase of the Valsalva maneuver, are characteristic findings. The murmur of TR may sometimes be confused with that of mitral regurgitation (MR) unless attention is paid to its variation during the respiratory cycle and the extent of RV enlargement is appreciated. AF is usually present in the chronic phase of the disease.

LABORATORY EXAMINATION

The ECG may show changes characteristic of the lesion responsible for the TR, e.g., an inferior Q-wave MI suggestive of a prior RV MI, RVH, or a bizarre right bundle branch block-type pattern with preexcitation in patients with Ebstein's anomaly. ECG signs of RA enlargement may be present in patients with sinus rhythm; AF is frequently noted. The chest x-ray may show RA and RV enlargement, depending on the chronicity and severity of TR. TTE is usually definitive with demonstration of RA dilation and RV volume overload and prolapsing, flail, scarred, or displaced/tethered tricuspid leaflets with annular dilatation; the diagnosis and assessment of TR can be made by color flow Doppler imaging **(see Fig. 236-8)**. Severe TR is accompanied by hepatic vein systolic flow reversal. Continuous wave Doppler of the TR velocity profile is useful in estimating PA systolic pressure, except when the TR is very severe and the jet velocity is blunted by rapidly increasing RA pressure. Accurate assessment of TR severity, PA pressures, and RV size and systolic function with TTE can be quite challenging in many patients. Real-time three-dimensional echocardiography and cardiac magnetic resonance (CMR) imaging provide alternative imaging modalities, although they are not widely available. In patients with severe TR, the CO is usually markedly reduced, and the RA pressure pulse may not exhibit an *x* descent during early systole but rather show a prominent *c-v* wave with a rapid *y* descent. The mean RA and RV end-diastolic pressures are often elevated. Exercise testing can be used to assess functional capacity in patients with asymptomatic severe TR. The prognostic significance of exercise-induced changes in TR severity and RV function has not been well studied.

TREATMENT

Tricuspid Regurgitation (Fig. 261-1)

Diuretics can be useful for patients with severe TR and signs of right heart failure. An aldosterone antagonist may be particularly helpful because many patients have secondary hyperaldosteronism from marked hepatic congestion. Therapies to reduce elevated PA pressures and/or pulmonary vascular resistance, including those targeted at left-sided heart disease, can also be considered for patients with PA hypertension and severe secondary TR. Tricuspid valve surgery is recommended for patients with severe TR who are undergoing left-sided valve surgery and is also undertaken frequently for treatment of even moderate TR in patients undergoing left-sided valve surgery who have tricuspid annular dilation (>40 mm), a history of right heart failure, or PA hypertension. Operation most often comprises repair rather than replacement in these settings and has become routine in most major surgical centers. Surgery may also infrequently be required for treatment of severe, primary TR with right heart failure not responsive to standard medical therapy or because of progressively declining RV systolic function. Reported perioperative mortality rates for isolated tricuspid valve surgery (repair and replacement) are high (~8–9%) and likely are influenced by the hazards encountered during reoperation on patients who have undergone previous left-sided valve surgery and have reduced RV function. Indwelling pacemaker or defibrillator leads can also pose technical challenges. Investigation of transcatheter tricuspid valve repair and replacement systems is in its earliest clinical stages.

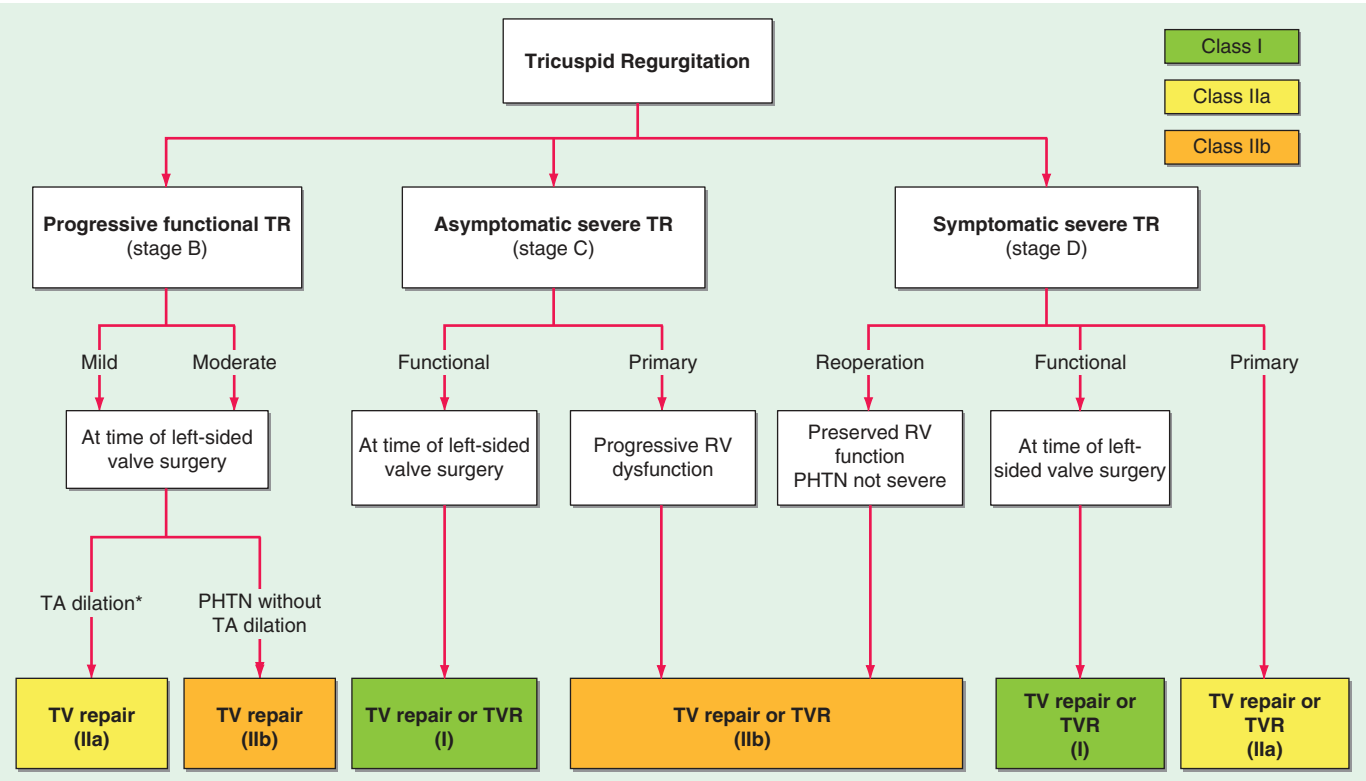

FIGURE 261-1 Management of tricuspid regurgitation. See legend for **Fig. 256-4** for explanation of treatment recommendations (Class I, IIa, IIb) and disease stages (B, C, D). Preoperative coronary angiography should be performed routinely as determined by age, symptoms, and coronary risk factors. Cardiac catheterization and angiography may also be helpful when there is a discrepancy between clinical and noninvasive findings. PHTN, pulmonary hypertension; RV, right ventricular; TA, tricuspid annular; TTE, transthoracic echocardiogram; TR, tricuspid regurgitation; TV, tricuspid valve; TVR, tricuspid valve replacement. TA dilation is defined by >40 mm on TTE (>21 mm/m^2) or >70 mm on direct intraoperative measurement. *(Adapted from RA Nishimura et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol 63:e57-185, 2014, with permission.)*

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262 Pulmonic Valve Disease

Patrick T. O'Gara, Joseph Loscalzo

PULMONIC STENOSIS

Pulmonic valve stenosis (PS) is essentially a congenital disorder **(Table 262-1)**. With isolated PS, the valve is typically domed. Dysplastic pulmonic valves are seen as part of the Noonan syndrome **(Chap. 275)**, which maps to chromosome 12. Mutations in the *PTPN1* gene are associated with about half of all cases of Noonan syndrome. Much less common etiologies include carcinoid and obstructing tumors or bulky vegetations. The pulmonic valve is only very rarely affected by the rheumatic process.

PATHOPHYSIOLOGY

PS is defined hemodynamically by a systolic pressure gradient between the right ventricle (RV) and main pulmonary artery (PA). RV hypertrophy (RVH) develops as a consequence of sustained obstruction to RV outflow, and systolic ejection is prolonged. Compared with the ability of the LV to compensate for the pressure overload imposed by aortic stenosis (AS), RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures, because the RV adapts less well to this type of hemodynamic burden. With normal systolic function and cardiac output (CO), severe PS is defined by a peak systolic gradient across the pulmonic valve of >50 mmHg; moderate PS correlates with a peak gradient of 30–50 mmHg. PS rarely progresses in patients with peak gradients <30 mmHg, but may worsen in those with moderate disease due to valve thickening and calcification with age. The RA *a* wave elevates in relation to the higher pressures needed to fill a noncompliant, hypertrophied RV. A prominent RA *v* wave signifies functional tricuspid regurgitation (TR) from RV and annular dilation. The CO is maintained until late in the course of the disease.

TABLE 262-1 Causes of Pulmonic Valve Disease

VALVE LESION	ETIOLOGIES
Pulmonic stenosis	Congenital
	Carcinoid
	Tumor
	Endocarditis
Pulmonic regurgitation	Primary valve disease
	Congenital
	Postvalvotomy
	Endocarditis
	Carcinoid
	Annular enlargement
	Pulmonary hypertension
	Idiopathic dilation
	Marfan syndrome

SYMPTOMS

Patients with mild or even moderate PS are usually asymptomatic and first come to medical attention because of a heart murmur (or early systolic click) that leads to echocardiography. With severe PS, patients may report exertional dyspnea or early-onset fatigue. Anginal chest pain from RV oxygen supply-demand mismatch and syncope may occur with very severe forms of obstruction, particularly in the presence of a destabilizing trigger such as atrial fibrillation, fever, infection, anemia, or pregnancy.

PHYSICAL FINDINGS

The murmur of mild or moderate PS is mid-systolic in timing, crescendo–decrescendo in configuration, heard best in the left second interspace, and usually introduced by an ejection sound (click) in younger adults whose valves are still pliable. The ejection sound is the only right-sided acoustic event that decreases in intensity with inspiration. This phenomenon reflects premature opening of the pulmonic valve by the elevated RV end-diastolic (postatrial *a* wave) pressure. The systolic murmur increases in intensity during inspiration. With progressively severe PS, the ejection sound moves closer to the first heart sound and eventually becomes inaudible. A right-sided fourth heart sound may emerge. The systolic murmur peaks later and may persist through the aortic component of the second heart sound (A_2). Pulmonic valve closure is delayed, and the pulmonic component of the second heart sound (P_2) is reduced or absent. A prominent *a* wave, indicative of the higher atrial pressure necessary to fill the noncompliant RV, may be seen in the jugular venous pulse. A parasternal or RV lift can be felt with significant pressure overload. Signs of right heart failure, such as hepatomegaly, ascites, and edema, are uncommon but may appear very late in the disease.

LABORATORY EXAMINATION

The electrocardiogram (ECG) will show right axis deviation, RVH, and RA enlargement in adult patients with severe PS. Chest x-ray findings include poststenotic dilation of the main PA in the frontal plane projection and filling of the retrosternal airspace due to RV enlargement on the lateral film. In some patients with RVH, the cardiac apex appears to be lifted off the left hemidiaphragm. The RA may also be enlarged. Transthoracic echocardiography (TTE) allows definitive diagnosis and characterization in most cases, with depiction of the valve and assessment of the gradient, RV function, PA pressures (which should be low), and any associated cardiac lesions. Transesophageal echocardiography (TEE) may be useful in some patients for improved delineation of the RV outflow tract (RVOT) and assessment of infundibular hypertrophy. Cardiac catheterization is not usually necessary for diagnostic purposes, but if performed, pressures should be obtained from just below and above the pulmonic valve with attention to the possibility that a dynamic component to the gradient may exist. The correlation between Doppler assessment of peak instantaneous gradient and catheterization-measured peak-to-peak gradient is weak. The latter may correlate better with the Doppler mean gradient.

TREATMENT

Pulmonic Stenosis

Diuretics can be used to treat symptoms and signs of right heart failure. Provided there is less than moderate pulmonic regurgitation (PR), percutaneous pulmonic balloon valvotomy is recommended for symptomatic patients with a domed valve and a peak gradient >50 mmHg (or mean gradient >30 mmHg) and for asymptomatic patients with a peak gradient >60 mmHg (or mean gradient >40 mmHg). Surgery may be required when the valve is dysplastic (as seen in patients with Noonan's syndrome and other disorders). A multidisciplinary heart team is best positioned to make treatment decisions of this nature.

PULMONIC REGURGITATION

PR may develop as a consequence of primary valve pathology, annular enlargement, or their combination; after surgical treatment of RVOT obstruction in children with such disorders as tetralogy of Fallot; or

after percutaneous pulmonic balloon valvotomy (Table 262-1). Carcinoid usually causes mixed pulmonic valve disease with PR and PS. Long-standing severe PA hypertension from any cause can result in dilation of the pulmonic valve ring and PR.

PATHOPHYSIOLOGY

Severe PR results in RV chamber enlargement and eccentric hypertrophy. As is the case for aortic regurgitation (AR), PR is a state of increased preload and afterload. The reverse pressure gradient from the PA to the RV, which drives the PR, progressively decreases throughout diastole and accounts for the decrescendo nature of the diastolic murmur. As RV diastolic pressure increases, the murmur becomes shorter in duration. The forward CO is preserved during the early stages of the disease, but may not increase normally with exercise and declines over time. A reduction in RV ejection fraction may be an early indicator of hemodynamic compromise. In advanced stages, there is significant enlargement of the RV and RA with marked elevation of the jugular venous pressure.

SYMPTOMS

Mild or moderate degrees of PR do not, by themselves, result in symptoms. Other problems, such as PA hypertension, may dominant the clinical picture. With progressively severe PR and RV dysfunction, fatigue, exertional dyspnea, abdominal fullness/bloating, and lower extremity swelling may be reported.

PHYSICAL FINDINGS

The physical examination hallmark of PR is a high-pitched, decrescendo diastolic murmur (Graham Steell murmur) heard along the left sternal border that can be difficult to distinguish from the more frequently appreciated murmur of AR. The Graham Steell murmur may become louder with inspiration and is usually associated with a loud and sometimes palpable P_2 and an RV lift, as would be expected in patients with significant PA hypertension of any cause. Survivors of childhood surgery for tetralogy of Fallot or PS/pulmonary atresia may have an RV-PA conduit that is freely regurgitant because it does not contain a valve. PA pressures in these individuals are not elevated and the diastolic murmur can be misleadingly low pitched and of short duration despite significant degrees of PR and RV volume overload.

LABORATORY EXAMINATION

Depending on both the etiology and severity of PR, the ECG may show findings of RVH and RA enlargement. On chest x-ray, the RV and RA may be enlarged. Pulmonic valve morphology and function can be assessed with transthoracic Doppler echocardiography. PA pressures can be estimated from the tricuspid valve systolic jet velocity. Cardiac magnetic resonance (CMR) provides greater anatomic detail, particularly in patients with repaired congenital heart disease, and more precise assessment of RV volumes. Cardiac catheterization is not routinely necessary but would be performed as part of a planned transcatheter procedure.

TREATMENT

Pulmonic Regurgitation

In patients with functional PR due to PA hypertension and annular dilation, efforts to reduce PA vascular resistance and pressure should be optimized. Such efforts may include pharmacologic/vasodilator and/or surgical/interventional strategies, depending on the cause of the PA hypertension (e.g., idiopathic PA hypertension, left-sided heart valve disease). Diuretics can be used to treat the manifestations of right heart failure. Surgical valve replacement for primary, severe, pulmonic valve disease, such as carcinoid or endocarditis, is rarely undertaken. Transcatheter pulmonic valve replacement has been successfully performed in many patients with severe PR after childhood repair of tetralogy of Fallot or pulmonic valve stenosis or atresia. This procedure was introduced clinically prior to transcatheter aortic valve replacement.

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263 Multiple and Mixed Valvular Heart Disease

Patrick T. O'Gara, Joseph Loscalzo

Many acquired and congenital cardiac lesions may result in stenosis and/or regurgitation of one or more heart valves. For example, rheumatic heart disease can involve the mitral (mitral stenosis [MS], mitral regurgitation [MR], or MS and MR), aortic (aortic stenosis [AS], aortic regurgitation [AR], or AS and AR), and tricuspid (tricuspid stenosis [TS], tricuspid regurgitation [TR], or TS and TR) valve, alone or in combination. The common association of functional TR with significant mitral valve disease is discussed in **Chap. 261**. Severe mitral annular calcification can result in regurgitation (due to decreased annular shortening during systole) and mild or moderate stenosis (caused by extension of the calcification onto the leaflets resulting in restricted valve opening). Patients with severe AS and LV remodeling may develop functional MR that may not improve after isolated aortic valve replacement (AVR). Chordal rupture has been described infrequently in patients with severe AS. Aortic valve infective endocarditis (IE) may secondarily involve the mitral apparatus either by abscess formation and contiguous spread via the intervalvular fibrosa or by "drop metastases" from the aortic leaflets onto the anterior leaflet of the mitral valve. Mediastinal radiation may result in aortic, mitral, and even tricuspid valve disease, most often with mixed stenosis and regurgitation. Carcinoid heart disease may cause mixed lesions of either or both the tricuspid and pulmonic valves. Ergotamines, and the previously used combination of fenfluramine and phentermine, can rarely result in mixed lesions of the aortic and/or mitral valve. Patients with Marfan syndrome may have both AR from aortic root dilation and MR due to mitral valve prolapse (MVP). Myxomatous degeneration causing prolapse of multiple valves (mitral, aortic, tricuspid) can also occur in the absence of an identifiable connective tissue disorder. Bicuspid aortic or pulmonic valve disease can result in mixed stenosis and regurgitation. The former is also associated with aortic aneurysm disease and a predisposition to aortic dissection.

PATHOPHYSIOLOGY

In patients with multivalvular heart disease, the pathophysiologic derangements associated with the more proximal valve disease can mask the full expression of the attributes of the more distal valve lesion. For example, in patients with rheumatic mitral and aortic valve disease, the reduction in cardiac output (CO) imposed by the mitral valve disease will decrease the magnitude of the hemodynamic derangements related to the severity of the aortic valve lesion (stenotic, regurgitant, or both). Alternatively, the development of atrial fibrillation (AF) during the course of MS can lead to sudden worsening in a patient whose aortic valve disease was not previously felt to be significant. The development of reactive pulmonary vascular disease, sometimes referred to as a "secondary obstructive lesion in series," can impose an additional challenge in these settings. As CO falls with progressive tricuspid valve disease, the severity of any associated mitral or aortic disease can be underestimated.

One of the most common examples of multivalve disease is that of functional TR in the setting of significant mitral valve disease.

Functional TR occurs as a consequence of right ventricular and annular dilation; pulmonary artery (PA) hypertension is often present. The tricuspid leaflets are morphologically normal. Progressive degrees of TR lead to right ventricular volume overload and continued chamber and annular dilation. The TR is usually central in origin; reflux into the right atrium (RA) is expressed as large, systolic *c-v* waves in the RA pressure pulse. The height of the *c-v* wave is dependent on RA compliance and the volume of regurgitant flow. The RA waveform may become "ventricularized" in advanced stages of chronic, severe TR with PA hypertension. CO falls and the severity of the associated mitral valve disease may become more difficult to appreciate. Findings related to advanced right heart failure (e.g., ascites, edema) predominate. Primary rheumatic tricuspid valve disease may occur with rheumatic mitral disease and cause hemodynamic changes reflective of TR, TS, or their combination. With TS, the *y* descent in the RA pressure pulse is prolonged.

Another example of rheumatic, multivalve disease involves the combination of mitral and aortic valve pathology, frequently characterized by MS and AR. In isolated MS, left ventricular (LV) preload and diastolic pressure are reduced as a function of the severity of inflow obstruction. With concomitant AR, however, LV filling is enhanced and diastolic pressure may rise depending on the compliance characteristics of the chamber. Because the CO falls with progressive degrees of MS, transaortic valve flows will decline, masking the potential severity of the aortic valve lesion (AR, AS, or its combination). As noted above, onset of AF in such patients can be especially deleterious. The loss of atrial systole with AF may result in a critical reduction in CO, a rise in LA and LV diastolic pressures, and a further deleterious increase in heart rate.

Secondary (functional) MR may complicate the course of some patients with severe AS. The mitral valve leaflets and chordae tendineae are usually normal. Incompetence is related to changes in LV geometry (remodeling) and abnormal systolic tethering of the leaflets in the context of markedly elevated LV systolic pressures. Relief of the excess afterload with surgical or transcatheter AVR often, but not always, results in reduction or elimination of the MR. Persistence of significant MR following AVR is associated with impaired functional outcomes and reduced survival. Identification of patients who would benefit from concomitant treatment of their functional MR at time of AVR is quite challenging. Most surgeons advocate for repair of moderate-to-severe or severe functional MR at time of surgical AVR. Significant primary MR is routinely managed with repair or replacement at the time of AVR.

In patients with mixed AS and AR, assessment of valve stenosis can be influenced by the magnitude of the regurgitant valve flow. Because transvalvular systolic flow velocities are augmented in patients with AR and preserved LV systolic function, the LV-aortic Doppler-derived pressure gradient and the intensity of the systolic murmur will be elevated to values higher than expected for the true systolic valve orifice size as delineated by planimetry. Uncorrected, the Gorlin formula, which relies on forward CO (systolic transvalvular flow) and the mean pressure gradient for calculation of valve area, is not accurate in the setting of mixed aortic valve disease. Similar considerations apply to patients with mixed mitral valve disease. The peak mitral valve Doppler E wave velocity (v_0) is increased in the setting of severe MR because of enhanced early diastolic flow and may not accurately reflect the contribution to left atrial (LA) hypertension from any associated MS. When either AR or MR is the dominant lesion in patients with mixed aortic or mitral valve disease, respectively, the LV is dilated. When AS or MS predominates, LV chamber size will be normal or small. It can sometimes be difficult to ascertain whether stenosis or regurgitation is the dominant lesion in patients with mixed valve disease, although an integrated clinical and noninvasive assessment can usually provide clarification for purposes of patient management and follow-up.

Patients with significant AS, a nondilated LV chamber, and concentric hypertrophy will poorly tolerate the abrupt development of aortic regurgitation, as may occur, for example, with IE or after surgical or transcatheter AVR (TAVR) complicated by paravalvular leakage. The noncompliant LV is not prepared to accommodate the sudden volume load, and as a result, LV diastolic pressure rises rapidly and severe heart failure develops. Indeed, paravalvular regurgitation is a significant risk factor for short- to intermediate-term death following transcatheter AVR. Conditions in which the LV may not be able to dilate in response to chronic AR (or MR) include radiation heart disease and, in some patients, the cardiomyopathy associated with obesity and diabetes. Noncompliant ventricles of small chamber size predispose to earlier onset diastolic dysfunction and heart failure in response to any further perturbation in valve function.

SYMPTOMS

Compared with patients with isolated, single-lesion valve disease, patients with multiple or mixed valve disease may develop symptoms at a relatively earlier stage in the natural history of their disease. Symptoms such as exertional dyspnea and fatigue are usually related to elevated filling pressures, reduced CO, or their combination. Palpitations may signify AF and identify mitral valve disease as an important component of the clinical presentation, even when not previously suspected. Chest pain compatible with angina could reflect left or right ventricular oxygen supply/demand mismatch on a substrate of hypertrophy and pressure/volume overload with or without superimposed coronary artery disease. Symptoms related to right heart failure (abdominal fullness/bloating, edema) are late manifestations of advanced disease.

PHYSICAL FINDINGS

Mixed disease of a single valve is most often manifested by systolic and diastolic murmurs, each with the attributes expected for the valve in question. Thus, patients with AS and AR will have characteristic mid-systolic, crescendo-decrescendo and blowing, decrescendo diastolic murmurs at the base of the heart in the second right interspace and along the left sternal edge, respectively. Many patients with significant AR have mid-systolic outflow murmurs even in the absence of valve sclerosis/stenosis, and other findings of AS must be sought. The separate murmurs of AS and AR can occasionally be difficult to distinguish from the continuous murmurs associated with either a patent ductus arteriosus (PDA) or ruptured sinus of Valsalva aneurysm. With mixed aortic valve disease, the systolic murmur should end before, and not envelope or extend through, the second heart sound (S_2). The murmur associated with a PDA is heard best to the left of the upper sternum. The continuous murmur heard with a ruptured sinus of Valsalva aneurysm is often first appreciated after an episode of acute chest pain. An early ejection click, which usually defines bicuspid aortic valve disease in young adults, is often not present in patients with congenital, mixed AS and AR. As noted above, both the intensity and duration of these separate murmurs can be influenced by a reduction in CO and transvalvular flow due to coexistent mitral valve disease. In patients with isolated MS and MR, expected findings would include a blowing, holosystolic murmur and a mid-diastolic rumble (with or without an opening snap) best heard at the cardiac apex. An irregularly irregular heart rhythm in such patients would likely signify AF. Findings with TS and TR would mimic those of left-sided MS and MR, save for the expected changes in the murmurs with respiration. The murmurs of pulmonic stenosis and regurgitation behave in a fashion directionally similar to AS and AR; dynamic changes during respiration should be noted. Specific attributes of these cardiac murmurs are reviewed in Chaps. 38 and 261.

LABORATORY EXAMINATION

The electrocardiogram (ECG) may show evidence of ventricular hypertrophy and/or atrial enlargement. ECG signs indicative of right-sided cardiac abnormalities in patients with left-sided valve lesions should prompt additional assessment for PA hypertension and/or right-sided valve disease. The presence of AF in patients with aortic valve disease may be a clue to the presence of previously unsuspected mitral valve disease in the appropriate context. The chest x-ray can be reviewed for evidence of cardiac chamber enlargement, valve and/or annular calcification, and any abnormalities in the appearance of the pulmonary vasculature. The latter could include enlargement of the main and proximal pulmonary arteries with PA hypertension and pulmonary

venous redistribution/engorgement or Kerley B lines with increasing degrees of LA hypertension. An enlarged azygos vein in the frontal projection indicates RA hypertension. Roentgenographic findings not expected based on a single or mixed valve lesion may reflect other valve disease.

Transthoracic echocardiography (TTE) is the most commonly used imaging modality for the diagnosis and characterization of multiple and/or mixed valvular heart disease and may often demonstrate findings not clinically suspected. Transesophageal echocardiography (TEE) may sometimes be required for more accurate assessment of valve anatomy (specifically, the mitral valve) and when IE is considered responsible for the clinical presentation. TTE findings of particular interest include those related to valve morphology and function, calcification, chamber size, ventricular wall thickness, estimated PA systolic pressure, and the dimensions of the great vessels, including the root and ascending aorta, PA, and inferior vena cava. Exercise testing (with or without echocardiography) can be useful when the degree of functional limitation reported by the patient is not adequately explained by the findings on TTE performed at rest. An integrated assessment of the clinical and TTE findings is needed to help determine the dominant valve lesion(s) and establish an appropriate plan for treatment and follow-up. Natural history is usually influenced to a relatively greater degree by the dominant lesion.

Cardiac magnetic resonance (CMR) can be used to provide additional anatomic and physiologic information when echocardiography proves suboptimal, but is less well suited to the evaluation of valve morphology. Cardiac computed tomography (CT) has been used to assess intracardiac structures in patients with complicated IE. It is invaluable in planning for transcatheter valve replacement. Coronary CT angiography provides a noninvasive alternative for the assessment of coronary artery anatomy prior to surgery or transcatheter intervention.

Invasive hemodynamic evaluation with right and left heart catheterization may be required to characterize more completely the individual contributions of each lesion in patients with either multiple or mixed valvular heart disease. It is strongly recommended when there is a discrepancy between the clinical and non-invasive findings in a symptomatic patient. Measurement of PA pressures and calculation of pulmonary vascular resistance (PVR) can help inform clinical decision-making in certain patient subsets, such as those with advanced mitral and tricuspid valve disease. It is important to identify any potential contribution to the clinical picture from pulmonary vascular disease. Attention to the accurate assessment of CO is essential. Coronary angiography (if indicated) can be performed as part of the procedure. Contrast ventriculography and great vessel angiography are performed infrequently.

TREATMENT

Multiple and Mixed Valve Disease

Management of patients with multiple or mixed valve disease can be challenging. As noted above, it is helpful to determine the dominant valve lesion and proceed according to the treatment and follow-up recommendations for it **(Chaps. 256–262)**, being mindful of deviations from the expected course due to the contributions of more than one valve lesion. For example, AF that emerges in the course of moderate mitral valve disease may precipitate heart failure in patients with concomitant, severe aortic valve disease that was previously asymptomatic.

Medical therapies are limited and include diuretics when indicated for relief of congestion and anticoagulation to prevent stroke and thromboembolism in patients with AF. Blood pressure–lowering medications may be needed to treat systemic hypertension, which may aggravate left-sided regurgitant valve lesions, but should be initiated and titrated carefully. Pulmonary vasodilators to lower PVR are not generally effective in this context.

There is a paucity of evidence to inform practice guidelines for surgical and/or transcatheter valve intervention in patients with multiple or mixed valve disease. When there is a clear, dominant lesion, as for example in a patient with severe AS and mild AR, indications for intervention are straightforward and follow those recommended for patients with AS **(Chap. 256)**. In other patients, however, there is less clarity, and decisions regarding intervention should be based on several considerations, including those related to lesion severity, ventricular remodeling, functional capacity, and PA pressures. In this regard, it is important to realize that patients with multiple and/or mixed valve disease may develop limiting symptoms or signs of physiologic impairment even with moderate valve lesions.

Concomitant aortic and mitral valve replacement surgery is associated with a significantly higher perioperative mortality risk than replacement of either valve alone, and operation should be carefully considered. Double valve replacement surgery is usually performed for treatment of severe (unrepairable) valve disease at both locations and for the combination of severe disease at one location with moderate disease at the other, so as to avoid the hazards of reoperation in the intermediate to late term for progressive disease of the unoperated valve. In addition, the presence of a prosthesis in the aortic position significantly restricts surgical exposure of the native mitral valve. The need for double valve replacement may also impact the decision regarding the type of prosthesis (i.e., mechanical vs tissue).

Tricuspid valve repair for moderate or severe secondary (functional) TR at the time of left-sided valve surgery is now commonplace, particularly if there is dilation of the tricuspid annulus (>40 mm). The addition of tricuspid valve repair, consisting usually of insertion of an annuloplasty ring, adds little time or complexity to the procedure and is well tolerated. Reoperation for repair (or replacement) of progressive TR years after initial surgery for left-sided valve disease, on the other hand, is associated with a relatively high perioperative mortality risk. Repair of moderate or severe functional MR at time of AVR for AS can usually be undertaken with acceptable risk for perioperative death or major complication.

The presence of moderate or severe MR in patients with rheumatic MS is a contraindication to percutaneous mitral balloon valvotomy (PMBV). Likewise, the presence of significant AR in patients with AS disqualifies them from percutaneous aortic balloon valvotomy (PABV). TAVR is generally not undertaken for patients with severe, mixed AS and AR. Transcatheter management of both severe AS (with TAVR) and functional MR (with deployment of an edge-to-edge clip) has been reported. Further advances in transcatheter treatments for multiple and mixed valve disease are anticipated.

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264 Congenital Heart Disease in the Adult

Anne Marie Valente, Michael J. Landzberg

PREVALENCE

The number of adults with congenital heart disease (CHD) living in the United States is estimated to be at least 1.4 million, with just over one in five having a complex form of CHD. The majority of adults with CHD were diagnosed in childhood, although a substantial percentage may have CHD first recognized as adults. Lifelong follow-up

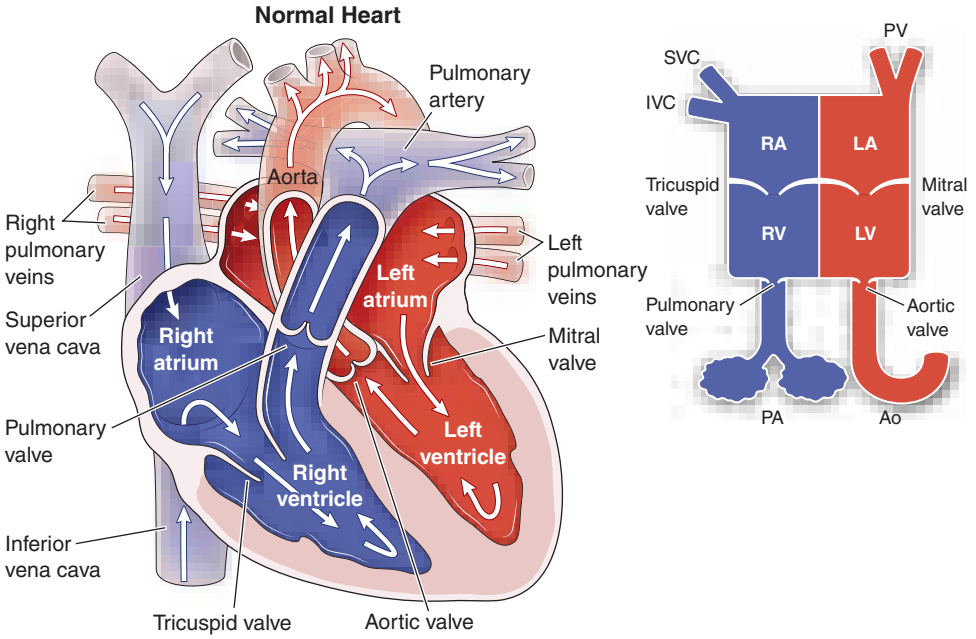


FIGURE 264-1 Normal heart. Understanding of congenital cardiac anatomy and physiology is facilitated by use of box diagrams, displaying passage of blood flow between blood vessels and cardiac chambers. Labeling (e.g., structure names, arrows to denote direction of flow, coloring to represent oxygen saturation, connections or obstructions, chamber or vascular pressures, oxygen saturations) can aid in representation. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

in coordination with, or directly by, clinicians with expertise in adult congenital heart disease (ACHD) is recommended. In this chapter, we will review the current field of ACHD, with an introduction to CHD nomenclature and cardiac development. This is followed by a summary of the more common CHD lesions that may be diagnosed in adulthood. Lastly, some of the common repaired CHD lesions that are encountered in adults are discussed. Throughout the chapter, to aid in the understanding of congenital cardiac anatomy and physiology, we include figures displaying the passage of blood flow between blood vessels and cardiac chambers in various disorders (Fig. 264-1).

THE CHANGING LANDSCAPE OF ADULT CHD

A Relatively New Subspecialty in Cardiovascular Disease

Over the past decade, the field of caring for adults with CHD (ACHD) has blossomed, and several nationwide initiatives have been initiated in an attempt to standardize care. The American College of Cardiology and American Heart Association developed guidelines for the care of adults with CHD, first published in 2008. These guidelines emphasize the need for collaboration among primary care practitioners, cardiologists, and ACHD subspecialty cardiologists. The body of medical knowledge and competencies attendant with ACHD combined with skill acquisition in coordination of complex care over a patient's medical lifetime led in 2015 to both ACHD board certification examinations by the American Board of Medical Subspecialties, as well as the establishment of requirements for 2-year subspecialty fellowship training in ACHD care, by the Accreditation Council for Graduate Medical Education. In temporal association, the Adult Congenital Heart Association (ACHA) developed a process for ACHD care program accreditation based upon standardization of infrastructural components felt requisite to achieve quality outcomes for ACHD.

SPECIAL CONSIDERATIONS FOR THE ACHD PATIENT

Adults with CHD may not recognize subtle changes in their exercise capacity, some of which are associated with worse survival; by the time symptoms are recognized, irreversible physiological changes may have occurred. ACHD patients are, therefore, advised to undergo regular evaluations for surveillance of anatomic, hemodynamic, and electrophysiologic sequelae that may be present. In addition, specific situations may arise in which it is prudent to review care in consultation with an ACHD specialist, several of which are outlined below.

Non-Cardiac Surgery Nearly all adults with CHD can be classified with stage A (harboring risk) or greater degrees of heart failure. As such, adults with CHD may demonstrate limited hemodynamic reserve to altered myocardial perfusion or loading conditions, and may have subclinical organ dysfunction that is not recognized by standard laboratory assessment. Comprehensive, multi-specialty assessment and care strategy review are recommended in advance of invasive or operative procedures for adults with CHD. Table 264-1 lists the multi-organ considerations that should be taken into account in adults with CHD during perioperative resuscitation and convalescence. Anesthetic management requires particular knowledge of anatomy, physiologic consequence of underlying defects, myocardial and vascular performance, presence and nature of previous palliative procedures and

TABLE 264-1 Multi-Organ Considerations in ACHD Patients

Neurologic	Increased incidence of occult or clinically evident strokes
	Decreased level of executive functioning skills
	Anxiety, post-traumatic stress disorder, depression
	Psychosocial disorders
Lungs	Restrictive lung disease
	Pulmonary vascular disease
Renal	Decreased perfusion
Hepatic	Liver fibrosis
Peripheral Vasculature	Increased chronic venous insufficiency
Lymphatic	Impaired reabsorption
Orthopedic	Scoliosis
	Kyphosis
Hematologic	Anemia
	Coagulopathies

residual shunts, alteration of venous or arterial pathways within the circulation, and status of non-cardiovascular organ physiology.

Pregnancy Women with CHD should receive counseling regarding both maternal and fetal risks prior to conceiving a pregnancy and should be cared for in institutions with experience in treating CHD during pregnancy. Preconception evaluation includes detailed medical history, with a focus on the women's functional capacity, which is closely linked to maternal and fetal outcomes. Table 264-2 lists the World Health Organization Classification of risk during pregnancy in women with heart disease; women at risk should be strongly counseled about the significant risks of morbidity and mortality during pregnancy and the postpartum period. Normal physiological hemodynamic changes of pregnancy are significant, occur over a relatively condensed period of time, and may be compounded in adults with CHD. Women with certain forms of CHD, particularly those complicated by elevated pulmonary artery (PA) pressures, decreased ventricular function, or symptomatic left-sided obstructive lesions, may not tolerate these dramatic changes.

Pre-pregnancy medications should be reviewed to ensure their safety in pregnancy. Alternatives to angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and endothelin-receptor blockers should be considered, as these agents are teratogenic and contraindicated during pregnancy, and should be discontinued. Traditionally, the FDA utilized a classification system of five categories (A, B, C, D, X) to indicate the teratogenic potential of a drug; in December of 2014, the FDA promulgated the Pregnancy and Lactation Labeling Rule, requiring removal of these categories from all human prescription drugs and biological products, and replacement with three comprehensive subsections that provide details about the use of the drug in pregnancy and lactation in women and men of reproductive potential. These pregnancy subsections include potential risks to the developing fetus, known dosing alterations in pregnancy, effects of timing and duration of exposure during pregnancy, adverse maternal reactions, effects of the drug on labor and delivery, and information on pregnancy exposure registry for the drug, if such exists. Women requiring anticoagulation must be advised of the challenges of managing anticoagulation during pregnancy and individualized strategies should be developed. A fetal echocardiogram between 18 and 22 weeks of gestation is advised for parents with CHD. Additionally, both men and women with CHD should be counseled regarding the risk of CHD in their offspring.

TABLE 264-2 Modified WHO Classification of Heart Disease in Pregnancy

WHO I
• Uncomplicated, small or mild pulmonary stenosis, patent ductus arteriosus, mitral valve prolapse
• Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, partially anomalous pulmonary venous drainage).
• Isolated atrial or ventricular ectopic beats
WHO II (if otherwise well and uncomplicated)
• Unoperated atrial or ventricular septal defect
• Repaired tetralogy of Fallot
• Most arrhythmias
WHO II-III (depending on individual)
• Mild left ventricular impairment
• Hypertrophic cardiomyopathy
• Native or tissue valvular heart disease not considered WHO I or IV
• Marfan syndrome without aortic dissection
• Aorta < 45 mm in bicuspid aortic valve
• Repaired coarctation
WHO III
• Mechanical valve
• Systemic right ventricle
• Fontan circulation
• Cyanotic heart disease (unrepaired)
• Other complex congenital heart disease
• Aortic dilation 40–45 mm in Marfan syndrome
• Aortic dilation 45–50 mm in bicuspid aortic valve
WHO IV (pregnancy contraindicated)
• Pulmonary arterial hypertension
• Severe systemic ventricular dysfunction (LVEF <30%, NYHA class > II)
• Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
• Severe mitral stenosis, severe symptomatic aortic stenosis
• Marfan syndrome with aorta dilated >45 mm
• Aortic dilation >50 mm in bicuspid aortic valve
• Native severe aortic coarctation

CONGENITAL TERMINOLOGY, DEVELOPMENT, AND GENETICS

Congenital Nomenclature One of the challenges in caring for adults with CHD is the inconsistent terminology used to describe the congenital heart lesions. Several classification systems have been proposed, from the initial descriptions by Maude Abbott, Maurice Lev, and Jesse Edwards, to the extensive characterizations by Stella and Richard Van Praagh and Robert Anderson. In this chapter, we follow a segmental approach. The heart is composed of several segments that are analyzed separately before formulating a comprehensive diagnosis. The principal segments are the atria, the ventricles, and the great arteries, which are joined together by the atrioventricular canal and the conus (infundibulum). In the normal heart, the right ventricle (RV) is right-sided and organized inflow-to-outflow from right to left, while the left ventricle (LV) is left-sided and organized inflow-to-outflow from left to right. It is important to determine the segmental alignments: that is, what drains into what. For example, in the normal heart the right atrium (RA) is aligned with the RV and the LV with the aorta. Finally, the segmental connections, the way in which adjacent segments are physically linked to each other, are described. For example, in the normal heart the PA is connected to the RV by a complete muscular conus (infundibulum), while the aorta is connected to the LV by aortic-mitral fibrous continuity (without a complete conus). Alignment and connection are different concepts and both are important, especially in complex defects.

Cardiac Development The heart starts to form in the third week of gestation, and is nearly fully formed by 8 weeks' gestation. Mesodermal precardiac cells migrate to form the cardiac crescents (primary heart fields) in anterior lateral plate mesoderm, which are then brought together to form a primary linear heart tube by ventral closure of the embryo. Cells of the second heart field continue to proliferate outside the heart and are added to the heart tube over the course of embryogenesis, contributing to the atria, the RV, and outflow tract. Additionally, cardiac neural crest cells migrate into the developing heart in the 5th–6th weeks and are essential for septation of the outflow, formation of the semilunar valves, and patterning of the aortic arches. Once formed, the heart tube grows and elongates by addition of cells from the second heart field. The ends of the heart tube are relatively fixed by the pericardial sac so that as it elongates it must loop (bend), and in the vast majority of hearts the loop falls to the right (D-loop). Further elongation pushes the mid-portion of the tube (future ventricles) inferior or caudal to the inflow, resulting in the normal relationship between the atria and ventricles. Further growth pushes the outflow medially and is associated with outflow rotation, both processes essential for normal alignment of the outflow. Finally the proximal part of the outflow is incorporated in the RV, shortening the outflow in association with further rotation. While this remodeling is occurring, the outflow is undergoing septation under the influence of cardiac neural crest cells. Septation proceeds from distal to proximal, culminating in formation and muscularization of the infundibular, or muscular, outflow septum, which inserts onto the superior endocardial cushion at the rightward rim of the outflow foramen, walling the aorta into the LV via the outflow foramen and the PA directly into the RV.

Genetic Considerations CHD is the most commonly occurring birth defect; etiological contributors are increasingly recognized, although often speculated to be multifactorial. Children born with Trisomy 21

have a 50% chance of having CHD, most commonly defects in the atrioventicular canal. Conotruncal defects are associated with a number of chromosomal abnormalities, most notably a deletion at chromosome 22q11 (DiGeorge syndrome). Echocardiographic clues to this association in patients with a conotruncal defect include an associated right aortic arch or aberrant subclavian artery. Many adults currently living with conotruncal defects may not have undergone testing for DiGeorge syndrome. This condition is important to recognize as a variety of psychiatric disorders and disabilities in cognitive function may be present and go untreated. Patients with Noonan syndrome commonly have a dysplastic pulmonary valve and have facial and lymphatic abnormalities. Several defects in specific genes have been associated with Noonan syndrome, most notably PTPN11. Adults with Williams syndrome (7q11.23 deletion) commonly have supravalvar aortic stenosis and diffuse arteriopathy, with a "cocktail-like" personality and hypercalcemia. There is a growing importance of genome-wide analyses in subjects with CHD.

SPECIFIC CHD LESIONS

Dilated Right Heart There are many congenital etiologies for right heart dilation **(Table 264-3)**. These include congenital valvular anomalies (such as Ebstein anomaly or pulmonary regurgitation), intrinsic RV myocardial anomalies (arrhythromogenic RV dysplasia, Uhl's anomaly), or shunt lesions occurring proximal to the tricuspid valve. Cardiac imaging is critical in determining the etiology of right heart dilation, and knowledge of the anatomy and physiology of various shunt lesions is essential.

Atrial Septal Defect One of the most common etiologies of right heart dilation is presence of an atrial septal defect (ASD, **Fig. 264-2*A***). Intracardiac holes allow blood transmission between chambers or spaces based upon relative resistance, propulsion, and flow patterns. Patients with large ASDs often present in childhood; however, many ASDs are not discovered until adult life. The physiology of an ASD is predominantly that of a "left-to-right" shunt (flow of pulmonary venous, or oxygenated, blood toward systemic venous, or deoxygenated, chambers or vessels). The degree of left-to-right shunting determines the amount of right heart volume loading and is dictated by the size of the defect as well as the diastolic properties of the heart. As patients age, several factors, such as diabetes mellitus, systemic hypertension, and atherosclerosis, may contribute to decreased compliance of the left-sided cardiac chambers and contribute to increased left-to-right shunting and symptomatology. The classic physical examination finding is a wide, fixed splitting of the second heart sound, which is due to prolonged RV ejection and increased PA capacitance, which, in turn, delay pulmonary valve closure. The surface electrocardiogram (ECG) commonly displays an incomplete right bundle branch block. Symptoms, when they occur, most commonly include exercise intolerance, arrhythmia, and dyspnea with exertion. It is not uncommon for adults to have incidentally noted asymptomatic ASD during evaluation of other comorbid issues. Right heart dilation, without additional etiology for such, in the setting of unrepaired ASD is considered a risk for progression toward symptomatic right heart failure, atrial arrhythmias, and potential development of pulmonary arterial hypertension (if such is not already present). Therefore, a patient with an ASD and right heart dilation, particularly with symptoms attributable to such, should be offered ASD closure. Pulmonary vascular disease leading to pulmonary hypertension develops in up to 10% of patients with unrepaired ASD, and Eisenmenger syndrome (ES) is a rare complication (see below). Management of patients with concomitant ASD and pulmonary hypertension should be coordinated with both ACHD and pulmonary hypertension experts.

Figure 264-2*B* illustrates the locations of various ASDs. The most common type of an ASD is a secundum ASD, which is a defect, or true deficiency in the atrial septum, in the region of the fossa ovalis. This should be differentiated from a patent foramen ovale (PFO), which is persistence of patency of the flap valve of the fossa ovalis (not associated with right-sided cardiac dilation) and persists in up to 25% of adults. Secundum ASDs can often be closed with occluder devices placed percutaneously. However, certain anatomic determinants make percutaneous closure less favorable, including large defects, inadequate tissue rims surrounding the defect, and concomitance of anomalous draining pulmonary veins. A primum ASD is a deficiency of the AV canal portion of the atrial septum; primum ASD is always associated with abnormal development of the AV valves, most commonly resulting in a cleft in the mitral valve. A coronary sinus defect is rare and involves an opening between the coronary sinus and the left atrium. A sinus venosus defect is not a defect in the atrial septum, but, rather, a defect between either the right superior vena caval-atrial junction and the right upper pulmonary vein(s) or, less commonly, the inferior vena caval-atrial junction and the right lower pulmonary veins. Surgical closure is required for primum ASDs, sinus venosus defects, and coronary sinus septal defects.

Partial Anomalous Pulmonary Venous Return Partial anomalous pulmonary venous return (PAPVR) is occasionally discovered in adults with right heart dilation, or incidentally on cross-sectional imaging **(Fig. 264-3)**. There are several possible anomalous connections, with the most common being a left upper pulmonary vein to an ascending vertical vein into the innominate vein or the right upper pulmonary vein draining to the superior vena cava. In the latter case, careful attention should be paid to ensure that there is not an associated sinus venosus defect. Concomitant pulmonary hypertension can occur, but is uncommon. Symptomatology may be absent, and decision to repair isolated PAPVR should take into account variance in anatomy, lung ventilation and perfusion, hemodynamic response to shunt, symptoms, and surgical experience.

Ebstein Anomaly Ebstein anomaly **(Fig. 264-4)** is the result of embryologic failure of delamination, or "peeling away," of the tricuspid valve leaflets from the ventricular myocardium, resulting in adherence of the valve leaflets to the underlying myocardium. This results in a wide variety of abnormalities, including apical and posterior displacement of the dilated tricuspid valve annulus, dilation of the "atrialized" portion of the RV, and fenestrations, redundancy, and tethering typically of the anterior leaflet of the tricuspid valve. The malformed tricuspid valve is usually regurgitant, but may occasionally be stenotic. The clinical presentation of Ebstein anomaly in the adult depends on several factors, including the extent of tricuspid valve leaflet distortion, degree of tricuspid regurgitation (TR), right atrial pressure, and presence of an atrial level shunt. The physical examination of a patient with Ebstein anomaly may vary depending on the severity of disease. In more severe cases, the first heart sound may be split and the second component of the first heart sound may have a distinctive snapping quality (known as the sail sign, due to the redundancy of the anterior tricuspid valve leaflet). Patients with significant TR may have prominent "v" waves of the jugular venous pulsations; however, this finding is often absent due to abnormal right atrial compliance. The ECG is often abnormal, with right atrial and ventricular enlargement. Up to 20% of patients have evidence

TABLE 264-3 Congenital Etiologies of Right Heart Dilation

Congenital tricuspid valve disease
Tricuspid valve dysplasia with regurgitation
Ebstein anomaly
Congenital pulmonary valve regurgitation
Pulmonary arterial hypertension
Myocardial abnormalities
Arrhythmogenic RV cardiomyopathy
Uhl's anomaly
Shunt lesions
Partial anomalous pulmonary venous return
Primum ASD
Secundum ASD
Sinus venosus defect
Coronary sinus septal defect
Gerbode defect (LV-RA shunt)
Coronary artery fistula to the RA, CS
Postoperative residual shunts

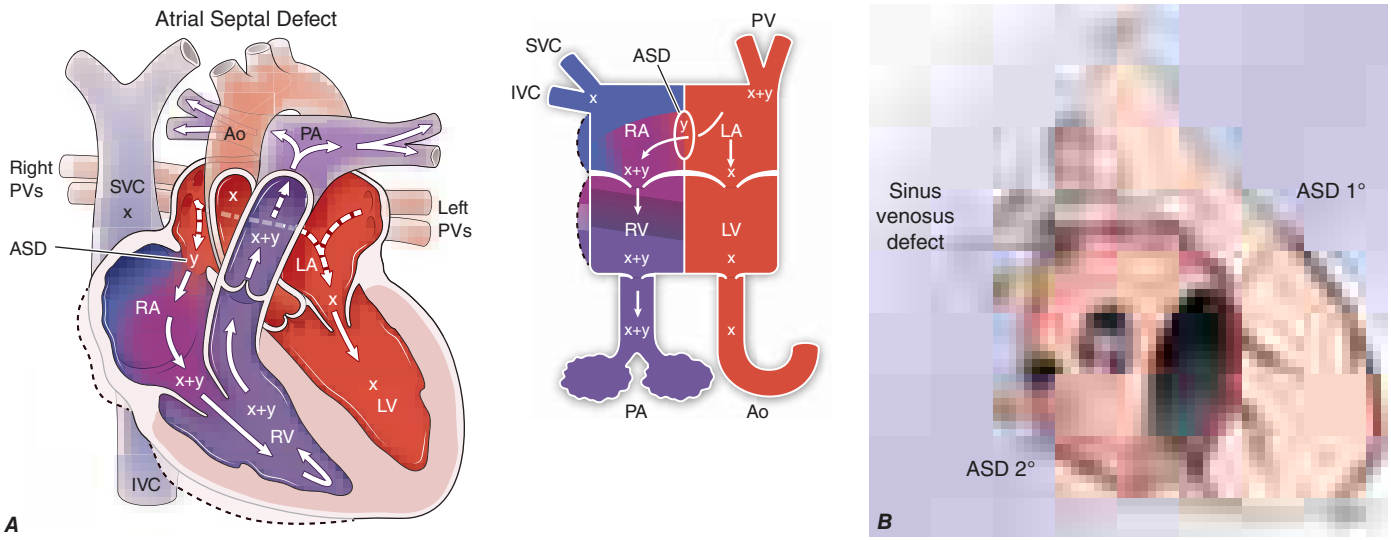


FIGURE 264-2 ***A.*** **Atrial septal defect.** In the presence of an atrial septal defect, the difference in compliance between the (RA+ RV) as compared to the (LA+LV), combined with the size of the defect itself, allows for a "shunt" of flow ("y") of "red" (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood ("x") is increased by the oxygenated shunted blood ("y") to increase volume of blood ("x + y") in the RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood is sufficient, RA and RV can dilate (*hashed lines*), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; ASD, atrial septal defect; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava. ***B.*** Diagrammatic representation of the location of various atrial septal defects. ASD 1, primum atrial septal defect; ASD 2, secundum atrial septal defect. *(Part B used with permission from Emily Flynn McIntosh, illustrator.)*

of ventricular pre-excitation (Wolff-Parkinson White pattern). Surgical treatment includes a tricuspid valve repair or replacement, closure of any atrial level defects, and arrhythmia ablative procedures.

Shunt Lesions Causing Left Heart Dilation Intracardiac shunts or intravascular passages that occur below the level of the tricuspid valve result in left heart dilation. The two major types of congenital shunts that result in left heart dilation are a ventricular septal defect (VSD, Fig. 264-5*A*) and patent ductus arteriosus (PDA, Fig. 264-6).

Ventricular Septal Defects VSD are the most common congenital anomaly recognized at birth, however, they account for only about 10% of CHD in the adult, due to the high rate of spontaneous closure of small VSDs during the early years of life. Large VSDs usually cause symptoms of heart failure and poor somatic growth, and are most often closed before adulthood. Several classification systems for VSDs exist. Figure 264-5*B* illustrates various locations of VSDs; the most common location is in the membranous septum (also referred to as perimembranous, or outlet defects). Muscular defects that persist into adult life are often pressure and flow restricted, resulting in no significant hemodynamic consequence. Atrioventricular canal defects, also referred to as inlet defects, are located in the crux of the heart and are associated with abnormalities of the atrioventricular valve leaflets. Subpulmonary defects, also known as conal septal defects, are commonly associated

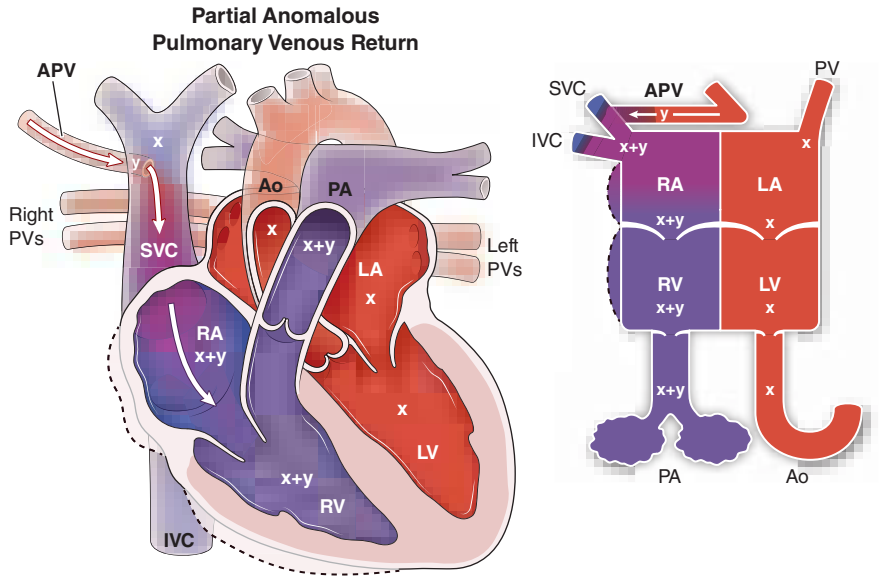


FIGURE 264-3 **Partial anomalous pulmonary venous return.** In the presence of an anomalously draining pulmonary vein (typically to a systemic vein such as the left innominate vein, SVC, or rarely IVC), an obligate "shunt" of flow ("y") of "red" (oxygenated) blood from the affected pulmonary vein to the right heart (deoxygenated) ensues. Systemic venous return of pure deoxygenated blood ("x") is increased by the oxygenated shunted blood ("y") to increase volume of blood ("x + y") in the SVC, RA, RV, and total blood flow to the lungs. If the volume or the sequelae of the shunted blood is sufficient, RA and RV can dilate (*hashed lines*), or shortness of breath can ensue. Ao, aorta; APV, anomalous pulmonary vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

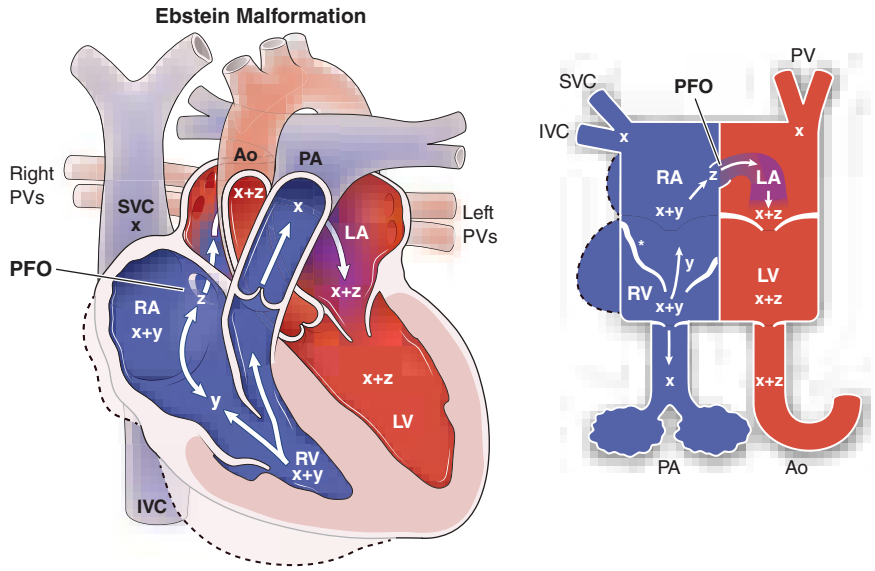


FIGURE 264-4 Ebstein malformation. In the presence of Ebstein anomaly, the tricuspid valve leaflets can be redundant, fenestrated and sail-like (typically seen in the anterior leaflet *), or adherent to the underlying myocardium with apical displacement of the non-adherent components (typically the septal and posterior leaflets). Location and degree of leaflet coaptation are variable and account for varying degrees of tricuspid regurgitation, shift of the functional tricuspid valve anterior from the anatomic annulus into the right ventricle, "atrialization" of the right ventricle, and most commonly angulation of the tricuspid valve into the RV outflow tract. RA and RV dilation (*hashed lines*) can occur due to the effects of combined volume from systemic venous return ("x") and tricuspid regurgitant flow ("y"). PFO is frequent; worsening compliance and elevation of pressure in the RA as compared to the LA can lead to increasing "right-to-left" (deoxygenated to oxygenated) shunt and cyanosis. RV myocardial function may be abnormal. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PFO, patent foramen ovale; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; *, anterior tricuspid valve leaflet.

with prolapse of the right coronary cusp and aortic insufficiency. The outcome for adults with small VSDs without evidence of ventricular dilation or pulmonary hypertension is generally excellent.

Patent Ductus Arteriosus A PDA courses between the aortic isthmus and the origin of one of the branch pulmonary arteries. Small PDAs are often silent to auscultation, and do not cause hemodynamic changes. The classic murmur is heard best just below the left clavicle and typically extends from systole past the second heart sound into diastole, reflecting flow turbulence and gradient between the aorta and the pulmonary arteries (resulting in left-to-right shunting). Large PDAs will lead to left heart dilation and may lead to chronically elevated pulmonary vascular resistance, including the potential for ES.

MODERATE AND COMPLEX CHD

Tetralogy of Fallot Tetralogy of Fallot (TOF) is the most common form of cyanotic CHD, occurring in 0.5 per 1000 live births. It involves what may be a singular deviation of the anterior conal septum, resulting in right ventricular outflow tract (RVOT) obstruction, a VSD, right

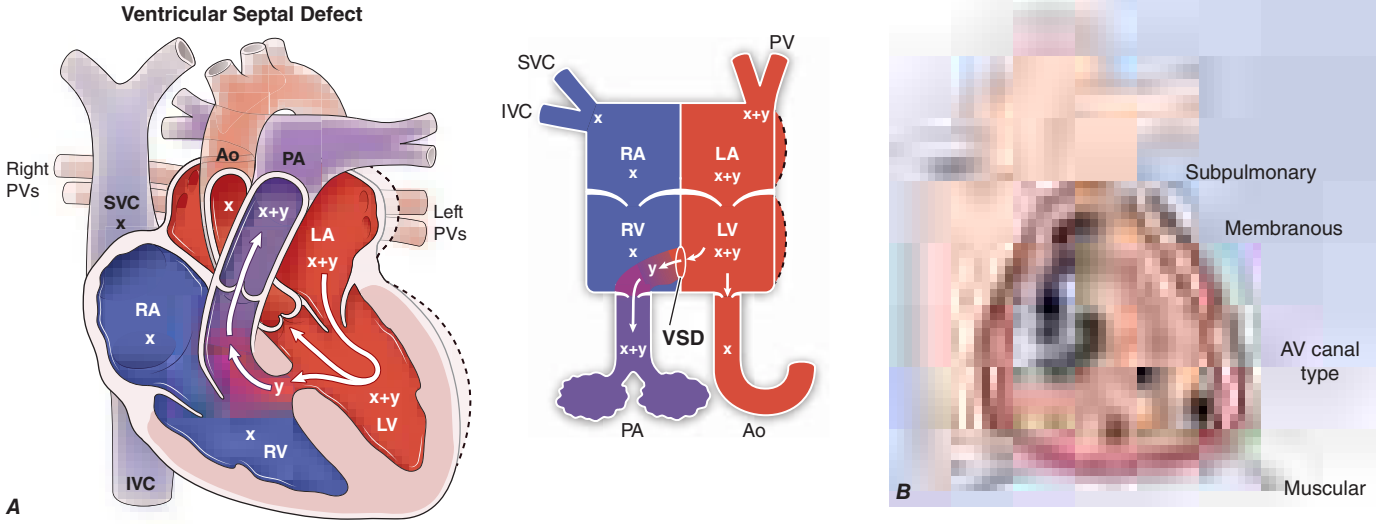


FIGURE 264-5 *A.* Ventricular septal defect. In the presence of a ventricular septal defect, the difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the RV and LV, combined with the size of the defect itself, allow for a "shunt" of flow ("y") of "red" (oxygenated) blood from the left side of the heart to the right side (deoxygenated). Systemic venous return of pure deoxygenated blood ("x") is increased by the oxygenated shunted blood ("y") to increase volume of blood ("x + y") through the outflow of the RV into the lungs, and in the left atrium and left ventricle. If the volume or the sequelae of the shunted blood is sufficient, LA and LV can dilate (*hashed lines*), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava; VSD, ventricular septal defect. ***B.*** Diagrammatic representation of the location of various ventricular septal defects. AV, atrioventricular. *(Part B used with permission from Emily Flynn McIntosh, illustrator.)*

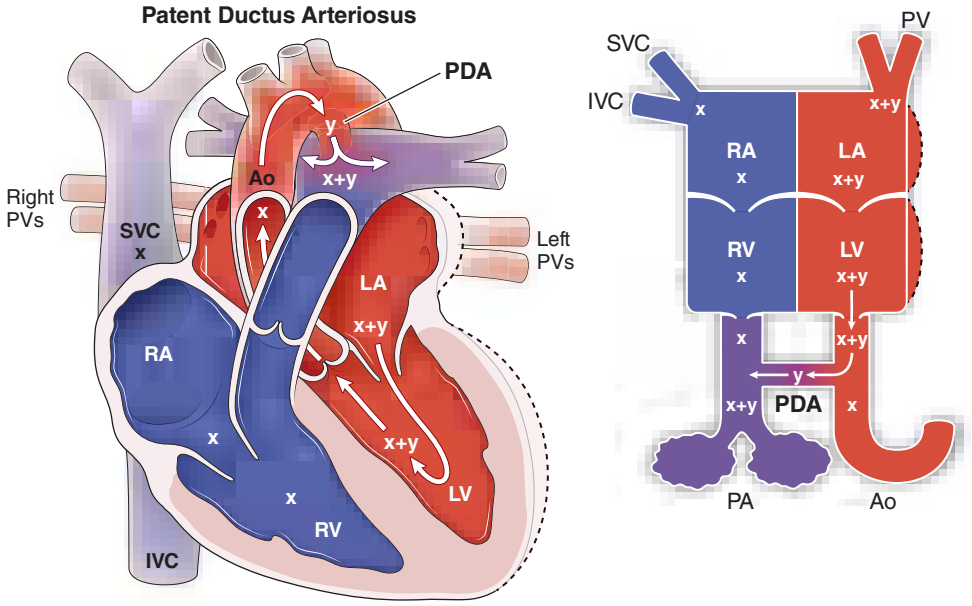


FIGURE 264-6 Patent ductus arteriosus. In the presence of a patent ductus arteriosus, the difference in pressure and resistance in both systole and diastole between the pulmonary arteries and the aorta, combined with the size of the ductus itself, allow for a "shunt" of flow ("y") of "red" (oxygenated) blood from the aorta to the pulmonary arteries (deoxygenated). Systemic venous return of pure deoxygenated blood ("x") is increased by the oxygenated shunted blood ("y") to increase volume of blood ("x + y") in the lungs, the left atrium, the left ventricle, and out the aortic valve. If the volume or the sequelae of the shunted blood is sufficient, LA and LV can dilate (*hashed lines*), and arrhythmias or shortness of breath (and occasionally pulmonary hypertension) can ensue. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PDA, patent ductus arteriosus; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

ventricular hypertrophy and an overriding aorta **(Fig. 264-7*A, B*)**. There is a large spectrum of severity of disease in TOF, from patients who have only mild pulmonary stenosis to those with complete pulmonary atresia (TOF/PA). Current surgical strategies involve primary repair in infancy **(Fig. 264-7*C*)**; however, many adults may have first undergone palliative procedures (Blalock-Taussig, Potts, Waterston shunts) prior to a complete repair. The goal of surgical repair is to alleviate the pulmonary stenosis and close the VSD. Up to 7% of patients with TOF have an anomalous coronary artery, most commonly, an anomalous left anterior descending coronary artery from the right coronary cusp. Patients with an anomalous coronary as well as those with TOF/PA may require a RV-to-PA conduit.

Adults with repaired TOF often have hemodynamic sequelae that may require re-intervention in adulthood **(Table 264-4)**. Pulmonary regurgitation is common following TOF repair and is usually associated with RV dilation. Accurate quantification of RV size, function, and mass is particularly important in adults after repair of TOF, as RV dilation, dysfunction, and hypertrophy are associated with adverse outcomes in these patients. Patients may also have residual RVOT obstruction, which may occur beneath the pulmonary valve, at the valve level, above the valve, or in the branch pulmonary arteries. Cardiac magnetic resonance imaging is routinely used in the surveillance of these patients. Left ventricular dysfunction is present in at least 20% of adults with repaired TOF, particularly those who were repaired later in life, had prior palliative shunts, or have concomitant RV dysfunction.

As patients age with repaired TOF, both atrial and ventricular arrhythmias occur with increasing frequency. A QRS duration on a resting ECG of 180 ms or more has been associated with increased risk of ventricular tachycardia and sudden death in this patient population. In one prospective follow-up study of 144 adults with repaired TOF, there was a 72% survival at 40 years, but only a 25% cumulative event free survival. These events include need for re-intervention (most commonly pulmonary valve replacement, PVR), symptomatic arrhythmias, and heart failure.

The most common re-intervention in a repaired TOF patient is a PVR. However, optimal timing of PVR in these patients remains unclear. Although PVR has been shown to decrease right ventricular volumes and subjectively improve symptoms, it has not been proven to result in an improved ejection fraction or less adverse outcomes, such as ventricular arrhythmias or death. Traditionally, PVR has been accomplished with a surgical procedure; however, percutaneous implantation of pulmonary valves is becoming increasingly utilized in clinical practice.

Patients with repaired TOF may also undergo interventions including closure of residual VSDs, dilation and/or stenting of the RVOT or branch pulmonary arteries, and tricuspid valve repair. Patients with clinically significant arrhythmias may benefit from catheter ablation.

Transposition of the Great Arteries Transposition of the great arteries (TGA) is defined by the great arteries arising from the opposite side of the ventricular septum than normal; as such, the aorta arises from the RV and the PA from the LV. The more common form of TGA, known as D-loop TGA, involves atrioventricular concordance and ventricular-arterial discordance, resulting in a physiology that allows two circuits to be in parallel rather than in series **(Fig. 264-8*A*)** and intense cyanosis shortly after birth. This physiology is not compatible with long-term survival without surgical intervention. Patients with TGA may be born with additional congenital defects (most commonly a VSD).

The surgical repairs for D-loop TGA have evolved over time. In the late 1950s through the 1970s, the atrial switch procedure (Mustard, Senning procedures) was performed **(Fig. 264-8*B*)**. These atrial switch procedures relieved the cyanosis but left the patient with a systemic RV. Despite moderate-term survival over decades, there are multiple long-term sequelae that may present following the atrial switch procedure. The most worrisome complication is that of systemic right ventricular dysfunction. The prevalence of right ventricular dysfunction in this population is not well defined due to difficulties in quantifying systemic RV function. Limited study has failed to reveal medical therapies effective for systemic right ventricular dysfunction.

A subset of patients with D-loop TGA, VSD, and PS may have undergone a Rastelli procedure. This intervention involves placing a RV-to-PA conduit and routing the LV to the aorta through the VSD, which results in relief of cyanosis and the benefit of a systemic LV.

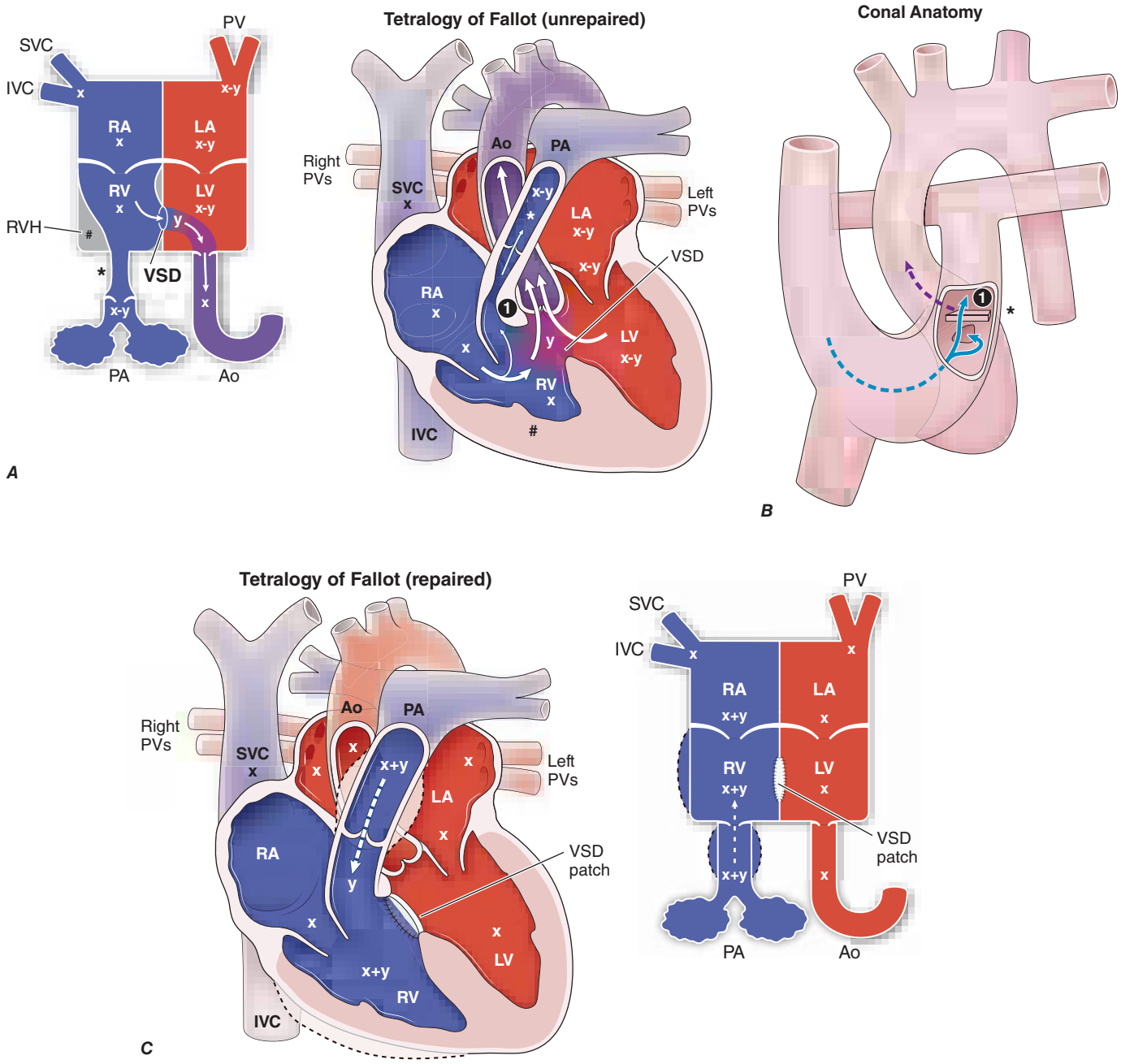


FIGURE 264-7 ***A.*** Tetralogy of Fallot involves anterior and superior malalignment of a bar of tissue (conal septum) (see * in Fig. 264-7B, which presents a cut-away view through the anterior surface of the RV, into the RV outflow), partially obstructing the right ventricular outflow (under the pulmonary valve, i.e., "subpulmonary stenosis"-labeled as 1), and leaving a gap in the interventricular septum (VSD). The pulmonary valve annulus is typically hypoplastic. Outflow obstruction prevents regression of right ventricular hypertrophy #, which was present in utero. The difference in pressure and outflow resistance in systole (and the difference in compliance in diastole) between the obstructed RV and the LV allow for a "shunt" of flow ("y") of "blue" (deoxygenated) blood from the right side of the heart to the left side (oxygenated). Systemic venous return of pure deoxygenated blood ("x") is decreased by the shunted blood ("y") leading to a total decrease in the volume of blood ("x – y") passing beyond into the lungs. The deoxygenated shunted blood ("y") mixes with fully oxygenated blood in the LV, contributing to systemic arterial cyanosis. ***C.*** Tetralogy of Fallot—repaired. After modern repair of tetralogy of Fallot, VSD has been patched closed, and outflow tract obstruction has been surgically removed, frequently at the expense of a patch enlarging the pulmonary valve annulus at the expense of sacrificing the integrity of the pulmonary valve (causing pulmonary regurgitation). Volume of pulmonary regurgitant volume ("y") is added to systemic venous return ("x"), contributing to RV chamber enlargement (*hashed lines*), and may be associated with tricuspid annular dilation and valve regurgitation resulting in RA enlargement. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; RVH, right ventricular hypertrophy; SVC, superior vena cava; VSD, ventricular septal defect.

In the 1980s, the arterial switch procedure (ASO, Fig. 264-8*C*) became the surgical procedure of choice for D-loop TGA. This procedure involves transecting the great arteries above the sinuses, and placing the pulmonary arteries anteriorly to come into alignment with the RV, resulting in draping of the branch pulmonary arteries over the ascending aorta. A coronary artery translocation is performed. The arterial switch operation has resulted in substantial long-term survival.

The potential long-term sequelae of the various surgical procedures for D-loop TGA are listed in Table 264-5.

The less common form of TGA, known as L-loop TGA (physiologically corrected TGA, Fig. 264-9), may not require surgical intervention, but is presented here in relation to other forms of TGA. L-loop TGA involves both atrioventricular discordance (RA allowing passage of deoxygenated systemic venous return to the LV, and conversely, the left atrium conducting oxygenated pulmonary venous blood to the RV) as well as ventriculo-arterial discordance (connections of LV to PA, RV to aorta). This results in normal arterial oxygen saturation, yet an RV associated with the aorta. Patients with L-loop TGA commonly

TABLE 264-4 Potential Sequelae of Repaired Tetralogy of Fallot
Right atrial dilation
Right ventricular dilation
Right ventricular dysfunction
Right ventricular outflow tract obstruction
Pulmonary regurgitation
Branch pulmonary artery stenosis
Tricuspid regurgitation
Residual ventricular septal defect
Left ventricular dysfunction
Aortic root dilation
Atrial arrhythmias
Ventricular arrhythmias
Sudden cardiac death

have associated congenital anomalies, including dextrocardia, ASDs, a dysplastic tricuspid valve, and pulmonary stenosis. Conduction disturbances are common, and complete heart block occurs in up to 30% of patients. Those patients without associated defects may not present until later in life, most commonly with heart failure, tricuspid regurgitation, or newly recognized conduction disease.

Coarctation of the Aorta Adults with coarctation of the aorta (Fig. 264-10) typically have a shelf-like obstruction at the level of the descending aorta that passes just posterior to the junction of the main and left PA; obstruction less commonly involves the transverse aortic arch. On physical examination, the lower extremity blood pressure and pulses are lower than (and delayed in timing, in contrast to) the upper extremity values, unless significant aortic collaterals have developed. A continuous murmur over the scapula may be present, due to the collateral blood flow. Significant coarctation increases afterload to all proximal structures in the path of oxygenated blood, from LV and coronary arteries, to ascending and transverse aorta, to cerebral and arm vessels and proximal descending aorta. Bicuspid aortic valve (typically with right-left commissural fusion) is a common association. In women with short stature, webbed neck, lymphedema, and primary amenorrhea, a concomitant diagnosis of Turner syndrome should be considered the presence of which indicates greater degree of, and risks from, sequelae from seemingly similar anatomy and physiology. Patients who have undergone surgical repair in general have a good prognosis; however, they remain at risk for systemic hypertension, premature atherosclerosis, LV failure, as well as aortic aneurysm, dissection, and recurrent coarctation.

Single Ventricle Physiology The term, "single ventricle heart disease," is imprecise, but useful in some settings, as it refers to congenital heart conditions in which one ventricle or its valves preclude surgical creation of a biventricular circulation. Common congenital diagnoses in this category include tricuspid atresia, double inlet LV, and hypoplastic left heart syndrome. Most patients with single ventricle physiology undergo a series of surgeries culminating in a Fontan procedure (Fig. 264-11*A, B*). Since its initial use for tricuspid valve atresia in 1971, multiple modifications of this procedure have occurred,

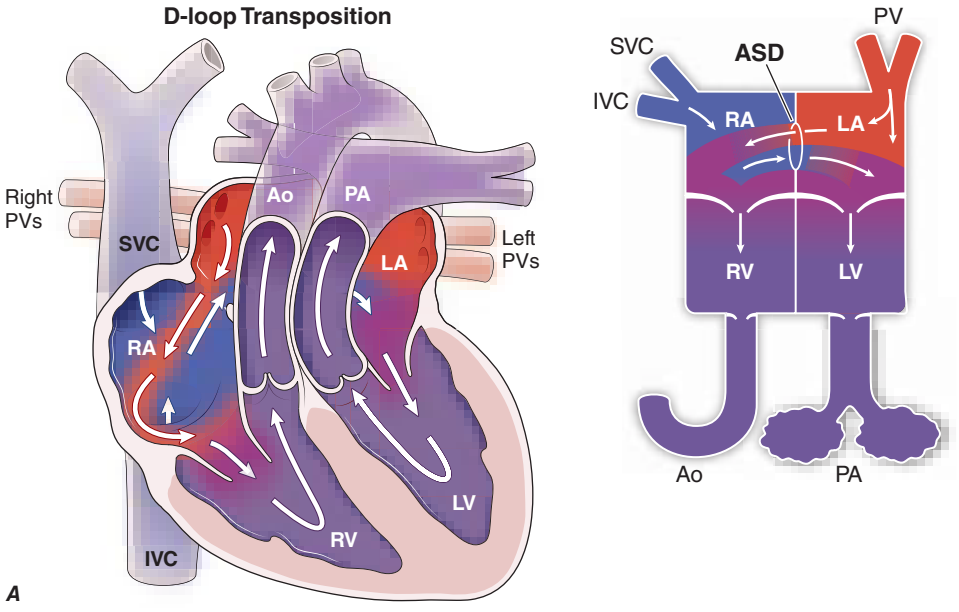


FIGURE 264-8 ***A.*** Transposition of the great arteries. When the great arteries are transposed, the aorta arises from the RV, and the pulmonary artery arises from the LV, leaving deoxygenated blood circulating from systemic veins to systemic arteries in separated fashion from oxygenated blood, which circulates from pulmonary veins to pulmonary arteries. Without interchamber or intravascular communications, this circulation is incompatible with life. Presence of an atrial septal defect (ASD), depicted here, ventricular septal defect (VSD), or patent ductus arteriosus (PDA), allow for some interchamber or intravascular mixing, and, at best, partial relief of cyanosis and sustenance of life, at the expense of increased pulmonary blood flow. ***B.*** Atrial switch. Atrial level switch procedures ("Mustard" and "Senning") were the first standardized surgeries to alter the natural course of complex congenital heart disease, utilizing intracardiac re-routing via a "baffle" to re-direct blood flow. The atrial switch simulates inverted trousers, with each "pants-leg" * attaching to either the SVC or the IVC, transporting deoxygenated blood through the interior of the trousers to the "waist of the trousers" and directing blood through the mitral valve to the LV and out the PA. Surgical removal of the atrial septum allows pulmonary venous return to traverse from posterior left atrium through the space between the pants legs of the baffle, through the tricuspid valve to the RV (serving as the "systemic ventricle," i.e., that pumps to the systemic arterial circulation) and out the aorta. Non-infrequent sequelae include sinus node dysfunction, atrial arrhythmias, systolic dysfunction of the RV, tricuspid regurgitation (from RV to LA), leaks in the baffle material allowing shunting of blood, and obstruction of the systemic or pulmonary venous baffles. ***C.*** Arterial switch. The arterial switch operation allowed both anatomic and physiologic correction for D-loop transposition of the great arteries. Successful surgical switching of the PA and the Ao above the level of the native roots (*hashed lines*) necessitated ability to transfer coronary artery origins contained within a button of tissue * back to the neo-aorta (now supported by the LV). Deoxygenated blood flow from SVC and IVC pass from RA to RV to PA, and oxygenated blood passes from PV to LA to LV to Ao. Uncommon sequelae include obstruction at any of the surgical sites (supravalvar PA or Ao stenosis, coronary orifice obstruction), or more distal obstructions due to tension placed on the PA, Ao or coronary arteries. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

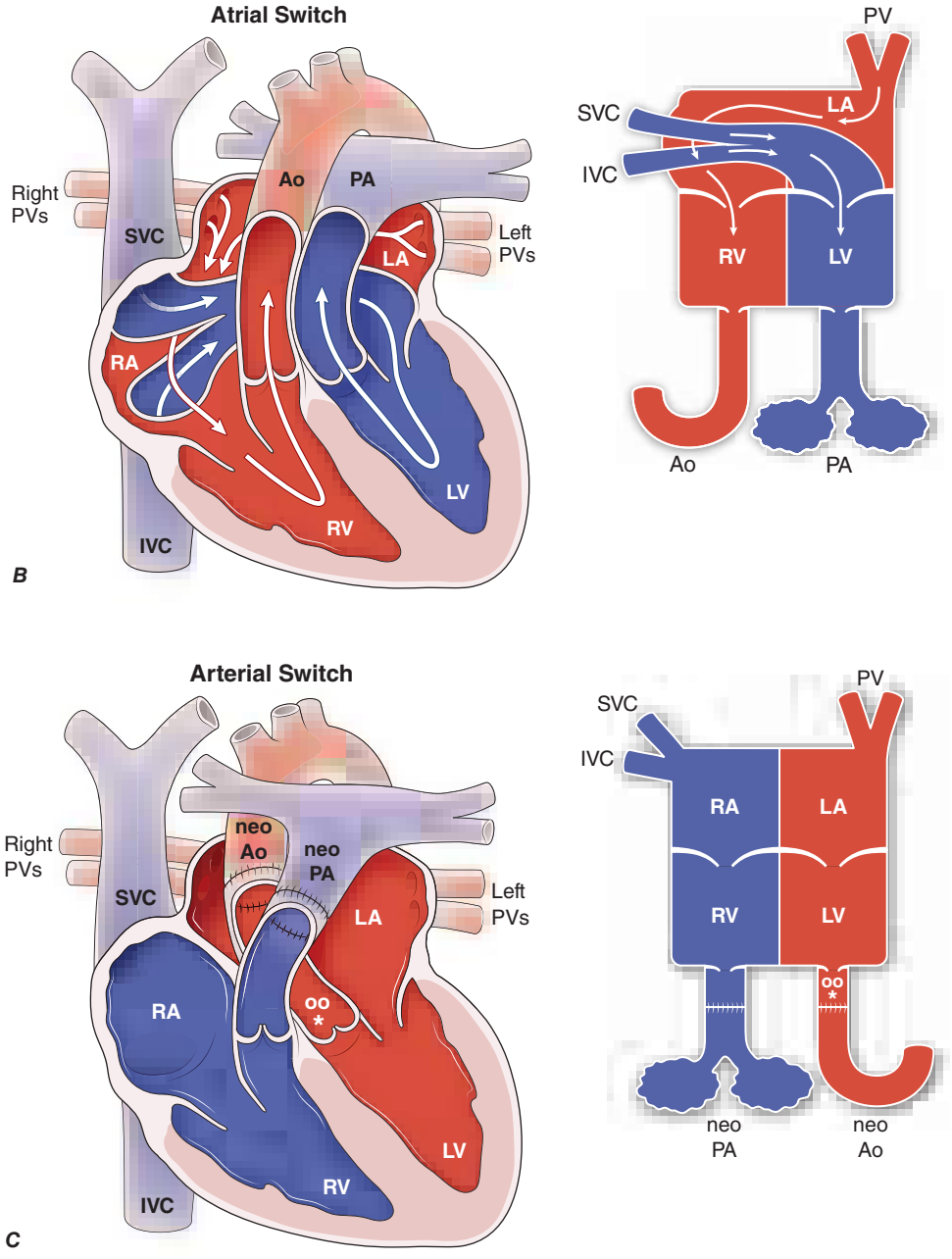


FIGURE 264-8 (Continued)

with common features of near complete separation of the pulmonary and systemic circulations. The Fontan procedure utilizes the single ventricle to pump pulmonary venous (oxygenated) blood through the aorta to the body, and allows for "passive" flow of systemic venous return of deoxygenated blood through surgically created connections to the lungs. Patients who have undergone a Fontan procedure are at risk for multiple comorbidities in adulthood, including atrial arrhythmias, heart failure, renal and hepatic dysfunction, and both venous and arterial thrombosis and embolism.

TABLE 264-5 Long-Term Sequelae of D-loop TGA Surgery

ATRIAL SWITCH	ARTERIAL SWITCH	RASTELLI PROCEDURE
Systemic venous baffle	Arterial anastomosis stenosis	Subaortic stenosis
Pulmonary venous baffle	Branch PA stenosis	RV-PA conduit obstruction
RV (systemic) dysfunction	Neo-aortic root dilation	Pulmonary regurgitation
Tricuspid regurgitation	Neo-aortic regurgitation	Ventricular dysfunction
Baffle leaks	Coronary artery stenosis	
LVOT obstruction (PS)	LV dysfunction	

Abbreviations: LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; RV, right ventricle.

UNREPAIRED CYANOTIC CHD

Eisenmenger Syndrome ES is felt to be the consequence of a long-standing high volume or pressurized left-to-right shunt in which excessive blood flow to the pulmonary vasculature leads to severely increased pulmonary vascular resistance that eventually results in reversal of the shunt, creating bidirectional or right-to-left flow. ES is a multiple-organ condition and may occur with any CHD with an initial left-to-right shunt. The natural history of ES is variable, and although there is significant morbidity, in general, adults with ES appear to survive longer than those with other forms of pulmonary

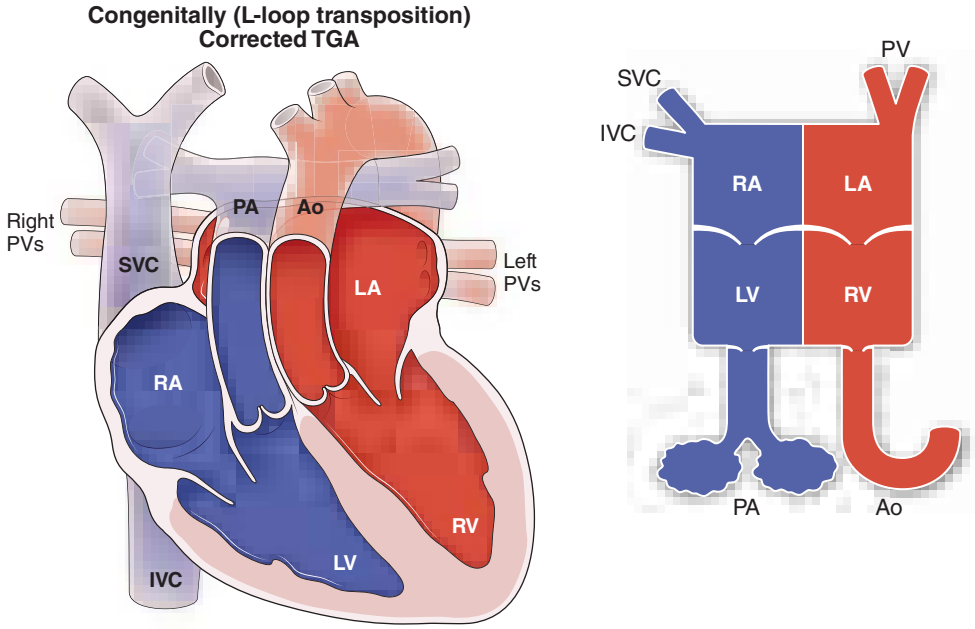


FIGURE 264-9 Congenitally corrected transposition of the great arteries. Physiologically corrected transposition of the great arteries (also known as congenitally corrected transposition of the great arteries) is characterized by atrioventricular discordance and ventriculoarterial discordance. Systemic venous blood passes from the right atrium (RA) through the mitral valve into the morphologic left ventricle (LV) to the pulmonary artery (PA). Oxygenated blood then returns to the lungs to the left atrium (LA) through the tricuspid valve into the morphologic right ventricle (RV) and then out the aorta (Ao). IVC, inferior vena cava; PV, pulmonary veins; SVC, superior vena cava.

arterial hypertension. Medical care recommendations have included sustaining adequate hydration, avoiding and treating anemia including iron supplementation when appropriate, and anticoagulation (although this remains controversial due to predisposition to bleeding and occurrence of clinical hemoptysis, which has frequently been associated with pulmonary vascular thrombosis). Elevation of hematocrit above that considered appropriate for the degree of cyanosis can be managed in symptomatic patients by hydration alone, or on occasion by performing phlebotomy with isovolumic replenishment. Routine phlebotomy in the asymptomatic adult with ES is contraindicated. Appropriate optimization of iron stores has been demonstrated to improve quality of life and functional performance in iron deficient adults with ES. Contraception for women with ES who are of childbearing age is strongly recommended, avoiding use of estrogen, which may be thrombogenic. Pregnancy is contraindicated in these women due to the high risk of maternal mortality.

Recent evidence suggests that the use of selective pulmonary vasodilators, such as bosentan or sildenafil, may be efficacious in ES. Select patients may be candidates for combined heart–lung transplantation or preferably lung transplantation with concomitant repair of the intracardiac defect, if feasible.

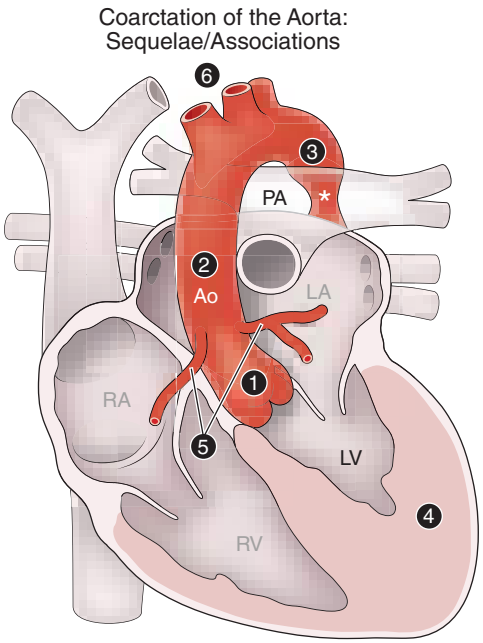
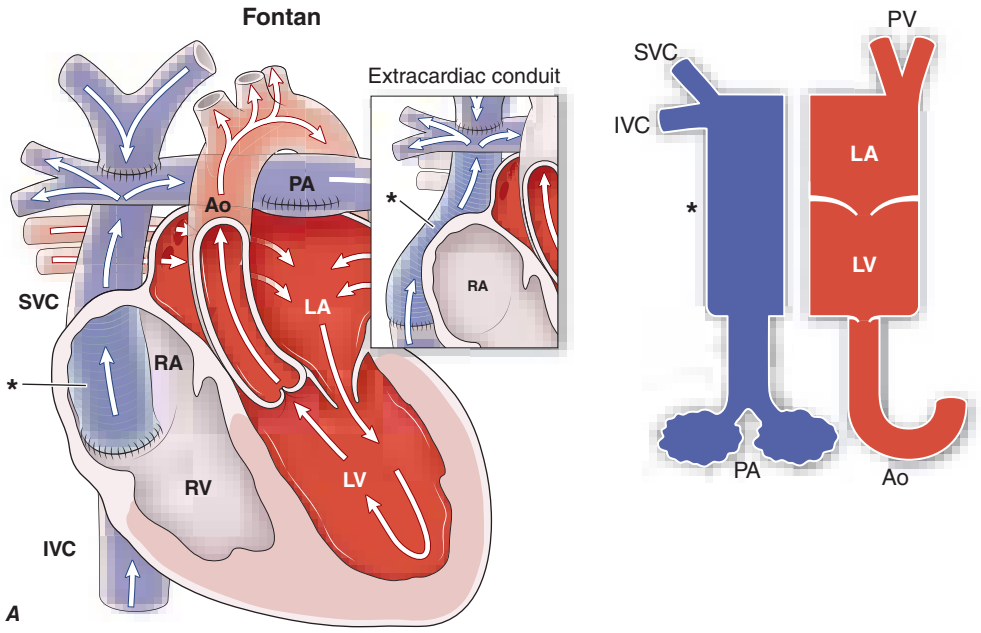


FIGURE 264-10 Aortic coarctation (*). Bicuspid aortic valve (1) is most common concomitant lesion. Sequelae from aortic coarctation (unrepaired or repaired) include systemic arterial hypertension, ascending (2) or descending (3) aortic enlargement or aneurysm formation, left ventricular hypertrophy (4), LV diastolic and systolic heart failure, accelerated coronary (5) or cerebral (6) atherosclerosis, cerebral aneurysm formation, and recurrence of coarctation after repair. Ao, aorta; LV, left ventricle; PA, pulmonary arteries.

Global Considerations As survival patterns improve for all medically complex patients, the internist and general practitioner are faced with particular challenges and dilemmas; foremost is accrual of sufficient knowledge and competency so as to be able both to engage in patient care provision as well as to seek greater expertise, guidance, and support, when such is appropriate. Across the globe, lifelong care for adults with CHD typifies this growing demand. Care for adults with CHD within medical care centers that contain an ACHD specialty care program has been associated with improved overall survival. However, current analyses suggest that the majority of adults with CHD seek and receive their medical care outside of such ACHD specialty care centers and within the hands of the general practitioner, internist and cardiologist. Under a surface of adaptability and determination, adults with CHD present a wide spectrum of cognitive and functional performance, multiple organ system comorbidities, abnormalities of systemic and pulmonary vasculature, and a near universal presence of heart failure of one stage or another, all over a lifetime. It appears incumbent on the ACHD specialist and ACHD specialty care centers to serve as a hub for partnering practitioners, encouraging engagement to the level of highest competencies, and providing education, oversight, and support, so as to achieve optimal outcomes.



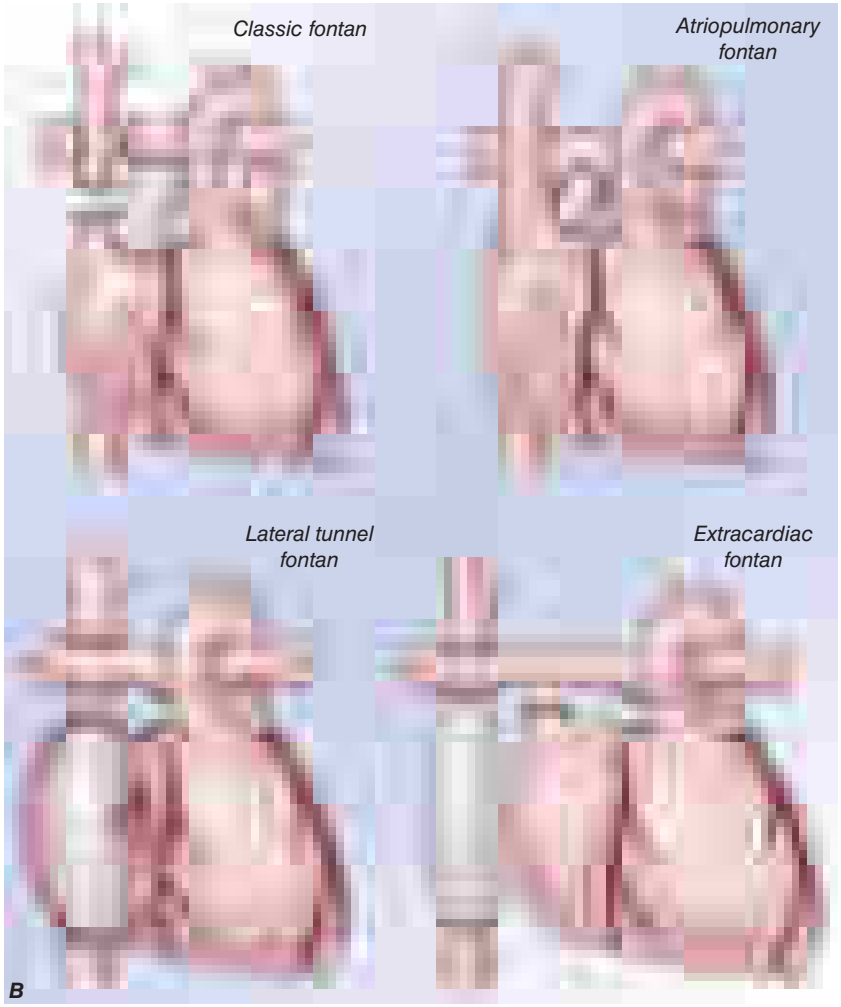


FIGURE 264-11 ***A.*** Fontan surgery creates a unique circulation in which deoxygenated blood is directed to the PAs from the SVC and IVC in a fashion that bypasses any pumping chamber. The SVC and IVC are connected * via either an internal "tunnel" or an extracardiac conduit that guides flow to the PA. Pulmonary venous (oxygenated) return courses from PV to LA to LV to aorta. In contrast to physiology in normal adults (where pressure is generated by an RV to propel blood flow from a lower pressure RA to a higher pressure LA), in Fontan circulation, by definition, due to the absence of a pumping chamber to the PA, RA pressure is greater than LA pressure, permitting flow through the lungs. Ao, aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; PV, pulmonary veins; SVC, superior vena cava, * Fontan baffle. ***B.*** Diagrammatic representation of the location of various types of Fontan operations. *(Part B used with permission from Emily Flynn McIntosh, illustrator.)*

FURTHER READING

Gilboa SM et al: Congenital Heart Defects in the United States: Estimating the magnitude of the affected population in 2010. Circulation 134:101, 2016.

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265 Pericardial Disease

Eugene Braunwald

NORMAL FUNCTIONS OF THE PERICARDIUM

The normal pericardium is a double-layered sac; the visceral pericardium is a serous membrane that is separated from the fibrous parietal pericardium by a small quantity (15–50 mL) of fluid, an ultrafiltrate of plasma. The normal pericardium, by exerting a restraining force, prevents sudden dilation of the cardiac chambers, especially the right atrium and ventricle, during exercise and with hypervolemia. It also restricts the anatomic position of the heart, and probably retards the spread of infections from the lungs and pleural cavities to the heart. Nevertheless, *total* absence of the pericardium, either congenital or after surgery, does not produce obvious clinical disease. In *partial* left pericardial defects, the main pulmonary artery and left atrium may bulge through the defect; very rarely, herniation and subsequent strangulation of the left atrium may cause sudden death.

ACUTE PERICARDITIS

Acute pericarditis, by far the most common pathologic process involving the pericardium **(Table 265-1)**, has four principal diagnostic features:

1. *Chest pain* is usually present in acute infectious pericarditis and in many of the forms presumed to be related to hypersensitivity, autoimmunity, or of unknown cause (idiopathic). The pain of acute pericarditis is often severe, retrosternal and/or left precordial, and referred to the neck, arms, or left shoulder. Frequently the pain is pleuritic, consequent to accompanying pleural inflammation (i.e., sharp and aggravated by inspiration and coughing), but sometimes it is steady, radiates to the trapezius ridge, or into either arm, and resembles that of myocardial ischemia; therefore, confusion with acute myocardial infarction (AMI) is common. Characteristically, pericardial pain may be intensified by lying supine, and relieved by sitting up and leaning forward **(Chap. 11)**. Pain is often absent in slowly developing tuberculous, postirradiation, neoplastic, and uremic pericarditis.

   The differentiation of AMI from acute pericarditis may be challenging when, with the latter, serum biomarkers of myocardial damage such as troponin and creatine kinase-MB rise, presumably because of concomitant involvement of the epicardium in the inflammatory process (an epi-myocarditis) with resulting myocyte necrosis. However, these elevations, if they occur, are quite modest compared to those in AMI, given the extensive electrocardiographic ST-segment elevation in pericarditis. This dissociation is useful in differentiating between these conditions.
2. A *pericardial friction rub* is audible at some point in the illness in about 85% of patients with acute pericarditis, it may have up to three components per cardiac cycle, is rasping, scratching, or grating **(Chap. 234)**. It is heard most frequently at end expiration with the patient upright and leaning forward.
3. The *electrocardiogram* (ECG) in acute pericarditis without massive effusion usually displays changes secondary to acute subepicardial inflammation **(Fig. 265-1*A*)**. It typically evolves through four stages. In stage 1, there is widespread elevation of the ST segments, often with upward concavity, involving two or three standard limb leads

TABLE 265-1 Classification of Pericarditis

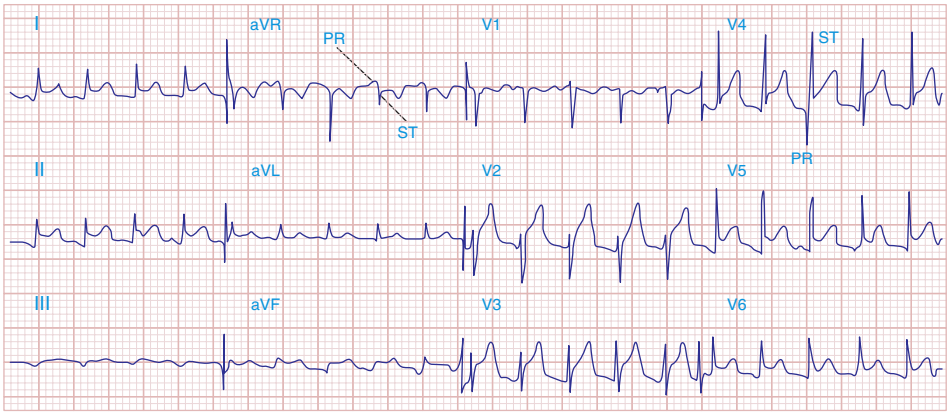
Clinical Classification

- I. Acute pericarditis (<6 weeks)
  - A. Fibrinous
  - B. Effusive (serous or sanguineous)
- II. Subacute pericarditis (6 weeks to 6 months)
  - A. Effusive-constrictive
  - B. Constrictive
- III. Chronic pericarditis (>6 months)
  - A. Constrictive
  - B. Adhesive (nonconstrictive)

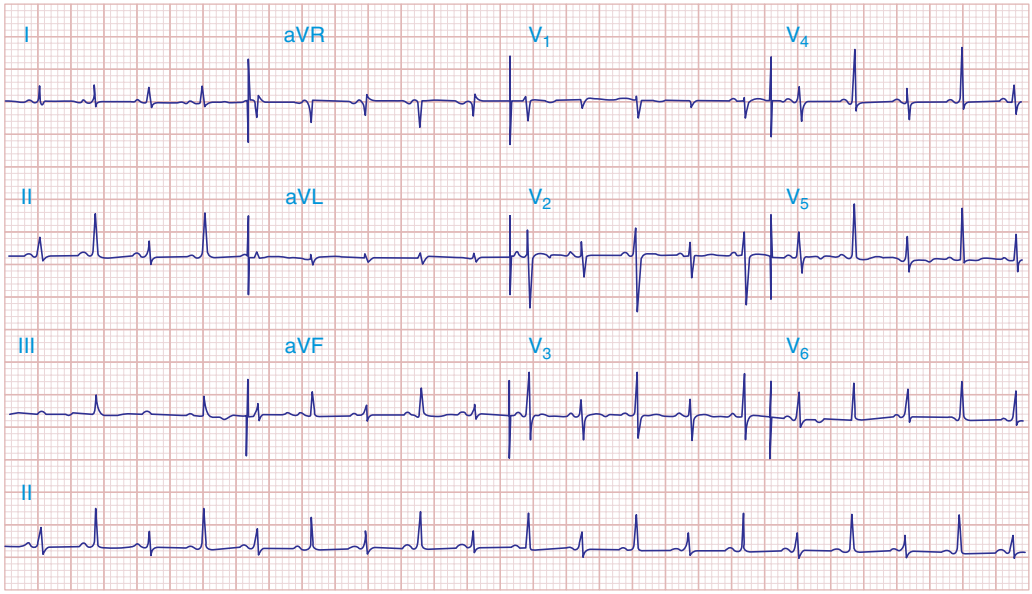
Etiologic Classification

- I. Infectious pericarditis
  - A. Viral (coxsackievirus A and B, echovirus, herpesviruses, mumps, adenovirus, hepatitis, HIV)
  - B. Pyogenic (pneumococcus, *Streptococcus, Staphylococcus, Neisseria, Legionella, Chlamydia*)
  - C. Tuberculous
  - D. Fungal (histoplasmosis, coccidioidomycosis, *Candida*, blastomycosis)
  - E. Other infections (syphilitic, protozoal, parasitic)
- II. Noninfectious pericarditis
  - A. Acute idiopathic
  - B. Renal failure
  - C. Neoplasia
    1. Primary tumors (benign or malignant, mesothelioma)
    2. Tumors metastatic to pericardium (lung and breast cancer, lymphoma, leukemia)
  - D. Trauma (penetrating chest wall, nonpenetrating)
  - E. Aortic dissection (with leakage into pericardial sac)
  - F. Acute myocardial infarction
  - G. Postirradiation
  - H. Familial Mediterranean fever
  - I. Familial pericarditis
    1. Mulibrey nanism[a]
  - J. Metabolic (myxedema, cholesterol)
- III. Pericarditis presumably related to hypersensitivity or autoimmunity
  - A. Rheumatic fever
  - B. Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, scleroderma, acute rheumatic fever, granulomatosis with polyangiitis [Wegener's])
  - C. Drug-induced (e.g., procainamide, hydralazine, phenytoin, isoniazid, minoxidil, anticoagulants, methysergide)
  - D. Postcardiac injury
    1. Postpericardiotomy
    2. Posttraumatic
    3. Postmyocardial infarction (Dressler's syndrome)

[a]An autosomal recessive syndrome characterized by growth failure, muscle hypotonia, hepatomegaly, ocular changes, enlarged cerebral ventricles, mental retardation, ventricular hypertrophy, and chronic constrictive pericarditis.



A



B

FIGURE 265-1 ***A.*** Acute pericarditis. There are diffuse ST-segment elevations in leads I, II, aVF, and V_2–V_6. There is PR-segment depression due to a concomitant atrial injury current. ***B.*** Electrical alternans. This tracing was obtained from a patient with a large pericardial effusion with cardiac tamponade.

and V_2–V_6, with reciprocal depressions only in aVR and sometimes V_1. Also, there is depression of the PR segment below the TP segment, reflecting atrial involvement. Usually there are no significant changes in QRS complexes, unless a large pericardial effusion develops (see below). After several days, the ST segments return to normal (stage 2), and only then, or even later, do the T waves become inverted (stage 3). Weeks or months after the onset of acute pericarditis, the ECG returns to normal (stage 4). In contrast, in AMI, ST elevations are upwardly convex, and reciprocal depression is usually more prominent; these changes may return to normal within a day or two. Q waves may develop, with loss of R-wave amplitude, and T-wave inversions; these changes are usually seen within hours *before* the ST segments have become isoelectric **(Chaps. 268 and 269)**.

4. *Pericardial effusion* is usually associated with pain and/or the ECG changes mentioned above, and if the effusion is large with electrical alternans **(Fig. 265-1*B*)**. Pericardial effusion is especially important clinically when it develops within a relatively short time because it may lead to cardiac tamponade (see below). Differentiation from cardiac enlargement on physical examination may be difficult, but heart sounds may be fainter with large pericardial effusion. The friction rub and the apex impulse may disappear. The base of the left lung may be compressed by pericardial fluid, producing *Ewart's sign*, a patch of dullness and increased fremitus beneath the angle of the left scapula. The chest roentgenogram may show enlargement of the cardiac silhouette, with a "water bottle" configuration, but may be normal in patients with small effusions.

Diagnosis *Echocardiography* **(Chap. 236)** is the most widely used imaging technique. It is sensitive, specific, simple, noninvasive, may be performed at the bedside, and allows localization and estimation of the quantity of pericardial fluid. The presence of pericardial fluid is recorded by two-dimensional transthoracic echocardiography as a relatively echo-free space between the posterior pericardium and left ventricular epicardium and/or as a space between the anterior right ventricle and the parietal pericardium just beneath the anterior chest wall **(Fig. 265-2)**.

The diagnosis of pericardial fluid or thickening may be confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). These techniques may be superior to echocardiography in detecting loculated pericardial effusions, pericardial thickening, and the identification of pericardial masses. MRI is also helpful in detecting pericardial inflammation **(Fig. 265-3)**.

TREATMENT

Acute Pericarditis

There is no specific therapy for acute idiopathic pericarditis, but bed rest and anti-inflammatory treatment with aspirin (2–4 g/d), with nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (600–800 mg tid) or indomethacin (25–50 mg tid), and should be administered along with gastric protection (e.g., omeprazole 20 mg/d). In responsive patients, these doses should be continued for 1–2 weeks and then tapered over several weeks. In addition,

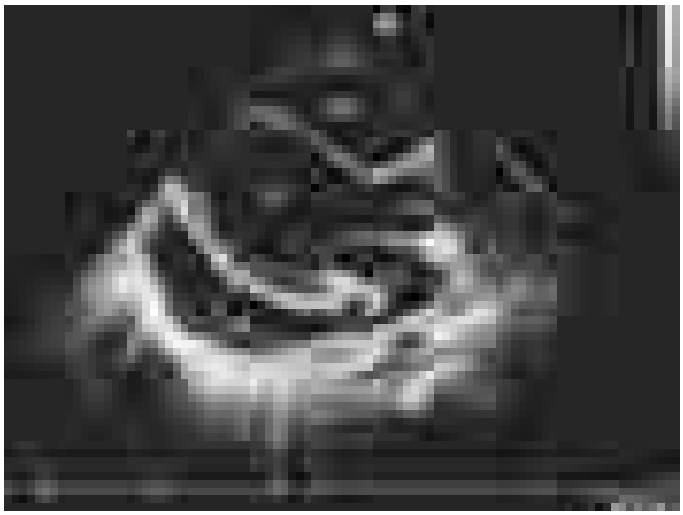


FIGURE 265-2 Two-dimensional echocardiogram in lateral view in a patient with a large pericardial effusion. Ao, aorta; LV, left ventricle; pe, pericardial effusion; RV, right ventricle. *(From M Imazio: Curr Opin Cardiol 27:308, 2012.)*

colchicine (0.5 mg qd [<70 kg] or 0.5 mg bid [>70 kg]), should be administered for 3 months. Colchicine enhances the response to NSAIDs and also aids in reducing the risk of recurrent pericarditis. This drug is concentrated in and interferes with the migration of neutrophils, may cause diarrhea and other gastrointestinal side effects, and is contraindicated in patients with hepatic or renal dysfunction. Glucocorticoids (e.g., prednisone 1 mg/kg per day) usually suppress the clinical manifestations of acute pericarditis in patients who have failed therapy with or do not tolerate NSAIDs and colchicine. However, since they increase the risk of subsequent recurrence, full-dose corticosteroids should be given for only 2–4 days and then tapered. Anticoagulants should be avoided because their use could cause bleeding into the pericardial cavity and tamponade.

In patients with multiple, frequent, and disabling recurrences that continue for more than 2 years, and are not prevented by continuing colchicine and other NSAIDs and are not controlled by glucocorticoids, azathioprine, or anakinra (an IL-1β receptor antagonist) have been reported to be of benefit. Rarely, pericardial stripping may be necessary but this procedure may not always terminate the recurrences.

The majority of patients with acute pericarditis can be managed as outpatients with careful follow-up. However, when specific causes (tuberculosis, neoplastic disease, bacterial infection) are suspected, or if any of the predictors of poor prognosis (fever >38°C, subacute onset, or large pericardial effusion) are present, hospitalization is advisable.

CARDIAC TAMPONADE

The accumulation of fluid in the pericardial space in a quantity sufficient to cause serious obstruction of the inflow of blood into the ventricles results in cardiac tamponade. This complication may be fatal if it is not recognized and treated promptly. The most common causes of tamponade are idiopathic pericarditis and pericarditis secondary to neoplastic disease, tuberculosis, or bleeding into the pericardial space after leakage from an aortic dissection, cardiac operation, trauma, and treatment with anticoagulants.

The three principal features of tamponade (*Beck's triad*) are hypotension, soft or absent heart sounds, and jugular venous distention with a prominent *x* (early systolic) descent but an absent *y* (early diastolic) descent. The limitations to ventricular filling are responsible for reductions of cardiac output and arterial pressure. The quantity of fluid necessary to produce cardiac tamponade may be as small as 200 mL when the fluid develops rapidly to as much as >2000 mL in slowly developing effusions when the pericardium has had the opportunity to stretch and adapt to an increasing volume.

A high index of suspicion for cardiac tamponade is required because in many instances no obvious cause for pericardial disease is apparent, and this diagnosis should be considered in any patient with otherwise unexplained sudden enlargement of the cardiac silhouette, hypotension, and elevation of jugular venous pressure. There also may be reductions in amplitude of the QRS complexes, and *electrical alternans* of the P, QRS, or T waves should raise the suspicion of cardiac tamponade (Fig. 265-1).

Table 265-2 lists the features that distinguish acute cardiac tamponade from constrictive pericarditis.

Paradoxical Pulse This important clue to the presence of cardiac tamponade consists of a greater than normal (10 mmHg) inspiratory decline in systolic arterial pressure. When severe it may be detected by palpating weakness or even disappearance of the arterial pulse during inspiration, but usually sphygmomanometric measurement of systolic pressure during slow respiration is required.

Because both ventricles share a tight incompressible covering, i.e., the pericardial sac, the inspiratory enlargement of the right ventricle causes leftward bulging of the interventricular septum, compresses and reduces left ventricular volume; stroke volume, and arterial systolic pressure. Paradoxical pulse also occurs in approximately one-third of patients with constrictive pericarditis (see below), and in some cases of hypovolemic shock, acute and chronic obstructive airway disease, and pulmonary embolism. Right ventricular infarction **(Chap. 269)** may resemble cardiac tamponade with hypotension, elevated jugular venous pressure, an absent *y* descent in the jugular venous pulse, and, occasionally, a paradoxical pulse (Table 265-2).

Diagnosis Because immediate treatment of cardiac tamponade may be lifesaving, prompt establishment of the diagnosis, usually by echocardiography, should be undertaken. When pericardial effusion causes tamponade, Doppler ultrasound shows that tricuspid and pulmonic valve flow velocities increase markedly during inspiration,

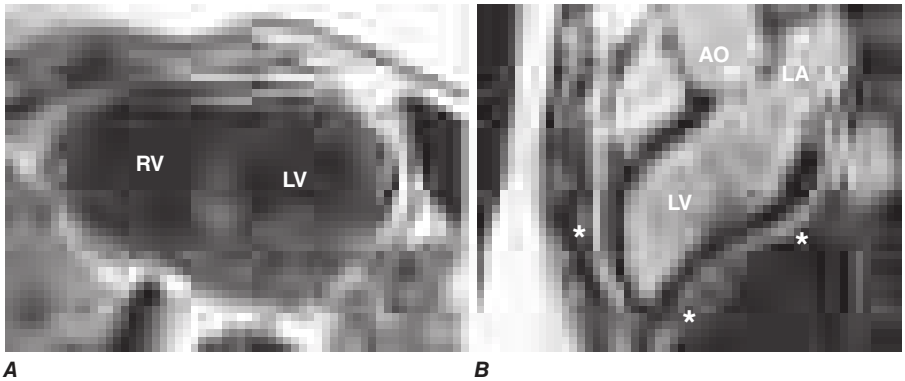


FIGURE 265-3 Pericardial inflammation by cardiac magnetic resonance imaging. *A.* Short axis view. The pericardium is thickened and enhanced on T2 magnetic images. Note thickened white line denoted by arrow. ***B.*** Long axis view. Late gadolinium enhancement of thickened, inflamed pericardium. AO, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle. *(From RY Kwong: Cardiovascular magnetic resonance imaging, in Braunwald's Heart Disease, 10th ed, Mann DL et al [eds]. Philadelphia: Elsevier, 2015, pp 320–40.)*

TABLE 265-2 Features That Distinguish Cardiac Tamponade from Constrictive Pericarditis and Similar Clinical Disorders

CHARACTERISTIC	TAMPONADE	CONSTRICTIVE PERICARDITIS	RESTRICTIVE CARDIOMYOPATHY	RVMI	EFFUSIVE CONSTRICTIVE PERICARDITIS
Clinical					
Pulsus paradoxus	+++	+	+	+	+++
Jugular veins					
Prominent *y* descent	–	++	+	+	–
Prominent *x* descent	+++	++	+++	+	+++
Kussmaul's sign	–	+++	+	+++	++
Third heart sound	–	–	+	+	+
Pericardial knock	–	++	–	–	–
Electrocardiogram					
Low ECG voltage	++	++	+	–	+
Electrical alternans	++	–	–	–	+
Echocardiogram					
Thickened pericardium	–	+++	–	–	++
Pericardial calcification	–	++	–	–	–
Pericardial effusion	+++	–	–	–	++
RV size	Usually small	Usually normal	Usually normal	Enlarged	Usually normal
Exaggerated respiratory variation in flow velocity	+++	+++	–	+++	+
CT/MRI					
Thickened pericardium	–	+++	–		++
Equalization of diastolic pressures	+++	+++	–	++	++

Abbreviations: +++, always present; ++, usually present; +, rare; –, absent; DC, diastolic collapse; ECG, electrocardiogram; RV, right ventricle; RVMI, right ventricular myocardial infarction.

Source: Adapted from GM Brockington et al: Cardiol Clin 8:645, 1990, with permission.

whereas pulmonic vein, mitral, and aortic flow velocities diminish (as in constrictive pericarditis, see below) **(Fig. 265-4)**. In tamponade, there is late diastolic inward motion (collapse) of the right ventricular free wall and the right atrium. Transesophageal echocardiography, CT, or cardiac MRI may be necessary to diagnose a loculated effusion responsible for cardiac tamponade.

TREATMENT

Cardiac Tamponade

Patients with acute pericarditis should be observed frequently for the development of an effusion. If a large effusion is present, pericardiocentesis should be carried out or the patient watched closely for signs of tamponade with serial echocardiography and monitoring of arterial and venous pressures.

PERICARDIOCENTESIS

If manifestations of tamponade appear, pericardiocentesis using an apical, parasternal, or, most commonly, subxiphoid approach must be carried out at once because if left untreated, tamponade may be rapidly fatal. Whenever possible, this procedure should be carried out under echocardiographic guidance. Intravenous saline may be administered as the patient is being readied for the procedure, but the pericardiocentesis must not be delayed. If possible, intrapericardial pressure should be measured before fluid is withdrawn, and the pericardial cavity should be drained as completely as possible. A small, multiholed catheter may be advanced over the needle inserted into the pericardial cavity and left in place to allow draining of the pericardial space if fluid reaccumulates. Surgical drainage through a limited (subxiphoid) thoracotomy may be required in recurrent tamponade to remove loculated effusions, and/or when it is necessary to obtain tissue for diagnosis.

Pericardial fluid obtained from an effusion may have the physical characteristics of an exudate. In developed nations, bloody fluid is most commonly due to neoplasm, renal failure, or after cardiac injury. In developing nations, tuberculosis, often associated with HIV infection, may also cause exudative and/or bloody effusion.

The pericardial fluid should be analyzed for red and white blood cells and cytology for neoplastic cells. Cultures should be obtained. The presence of DNA of *Mycobacterium tuberculosis* determined by the polymerase chain reaction strongly supports the diagnosis of tuberculous pericarditis **(Chap. 173)**.

VIRAL OR IDIOPATHIC ACUTE PERICARDITIS

In many instances, acute pericarditis occurs in association with or following illnesses of known or presumed viral origin and probably is caused by the same agent. There may be an antecedent infection

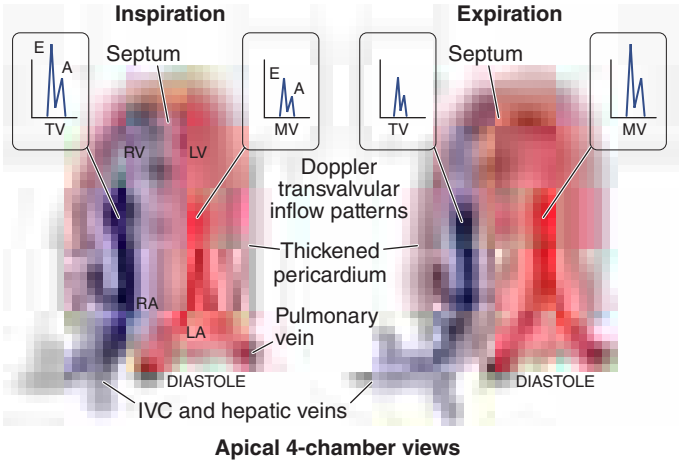


FIGURE 265-4 Constrictive pericarditis. Doppler schema of respirophasic changes in mitral and tricuspid inflow. Reciprocal patterns of ventricular filling are assessed on pulsed Doppler examination of mitral valve (MV) and tricuspid valve (TV) inflow. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. *(Courtesy of Bernard E. Bulwer, MD; with permission.)*

of the respiratory tract, but viral isolation and serologic studies are usually negative. In some cases coxsackievirus A or B or the virus of influenza, echovirus, mumps, herpes simplex, chickenpox, adenovirus, or cytomegalovirus has been isolated from pericardial fluid and/or appropriate elevations in viral antibody titers have been observed. Frequently, a viral cause cannot be established, and the term *idiopathic acute pericarditis* is appropriate.

Viral or idiopathic acute pericarditis occurs at all ages but is most common in young adult males, and is often associated with pleural effusion and pneumonitis. The almost simultaneous development of fever and precordial pain, often 10–12 days after a presumed viral illness, constitutes an important feature in the differentiation of acute pericarditis from AMI, in which chest pain precedes fever. The constitutional symptoms are usually mild to moderate, and a pericardial friction rub is often audible. The disease ordinarily runs its course in a few days to 4 weeks. Elevations of C-reactive protein and of the white blood cell count are common. The ST-segment alterations in the ECG usually disappear after 1 or more weeks, but the abnormal T waves may persist for several years and be a source of confusion in persons without a clear history of pericarditis. Accumulation of some pericardial fluid is common, and both tamponade and constrictive pericarditis are possible, but infrequent, complications.

The most frequent complication is recurrent (relapsing) pericarditis, which occurs in about one-fourth of patients with acute idiopathic pericarditis. In a smaller number, there are multiple recurrences.

Postcardiac Injury Syndrome Acute pericarditis may appear in a variety of circumstances that have one common feature—previous injury to the myocardium with blood in the pericardial cavity. The syndrome may develop after a cardiac operation (postpericardiotomy syndrome), after blunt or penetrating cardiac trauma **(Chap. S8)**, or after perforation of the heart with a catheter; rarely, it follows AMI.

The clinical picture mimics acute viral or idiopathic pericarditis. The principal symptom is the pain of acute pericarditis, which usually develops 1–4 weeks after the cardiac injury. Recurrences are common and may occur up to 2 years or more following the injury. Fever, pleuritis, and pneumonitis are accompanying features, and the illness usually subsides in 1 or 2 weeks. The pericarditis may be of the fibrinous variety, or it may be a pericardial effusion, which is often serosanguineous and rarely causes tamponade. ECG changes typical of acute pericarditis may also occur. This syndrome is probably the result of a hypersensitivity reaction to antigen(s) that originate from injured myocardial tissue and/or pericardium.

Often no treatment is necessary aside from aspirin and analgesics. When the illness is severe or followed by a series of disabling recurrences, therapy with another NSAID, colchicine, or a glucocorticoid, such as described for treatment of acute pericarditis, is usually effective.

DIFFERENTIAL DIAGNOSIS

Because there is no specific test for *acute idiopathic pericarditis*, the diagnosis is one of exclusion. Consequently, all other disorders that may be associated with acute fibrinous pericarditis must be considered. A common diagnostic error is mistaking acute viral or idiopathic pericarditis for AMI and vice versa.

Pericarditis secondary to postcardiac injury is differentiated from acute idiopathic pericarditis chiefly by timing. If it occurs within a few days or weeks of a chest blow, a cardiac perforation, a cardiac operation, or an AMI, the two are probably related.

It is important to distinguish *pericarditis due to collagen vascular disease* from acute idiopathic pericarditis. Most important in the differential diagnosis is the pericarditis due to systemic lupus erythematosus (SLE; **Chap. 349**) or drug-induced (procainamide or hydralazine) lupus. When pericarditis occurs in the absence of any obvious underlying disorder, the diagnosis of SLE may be suggested by a rise in the titer of antinuclear antibodies. Acute pericarditis is an occasional complication of *rheumatoid arthritis*, *scleroderma*, and *polyarteritis nodosa*, and other evidence of these diseases is usually obvious.

Pyogenic (purulent) pericarditis is usually secondary to cardiothoracic operations, by extension of infection from the lungs or pleural cavities, from rupture of the esophagus into the pericardial sac, or from rupture of a valvular ring abscess in a patient with infective endocarditis. It may also complicate the viral, bacterial, mycobacterial, and fungal infections that occur with HIV infection. It is generally accompanied by fever, chills, septicemia, and evidence of infection elsewhere and generally has a poor prognosis. The diagnosis is made by examination of the pericardial fluid. It requires immediate drainage as well as vigorous antibiotic treatment.

Pericarditis of renal failure (*uremic pericarditis)* occurs in up to one-third of patients with severe renal dysfunction, and is also seen in patients undergoing chronic dialysis who have normal levels of blood urea (*dialysis-associated pericarditis*). These two forms of pericarditis may be fibrinous and are generally associated with serosanguineous effusions. A pericardial friction rub is common, but pain is usually absent or mild. Treatment with an NSAID and intensification of dialysis are usually adequate. Occasionally, tamponade occurs and pericardiocentesis is required. When the pericarditis of renal failure is recurrent or persistent, a pericardial window should be created or pericardiectomy may be necessary.

Pericarditis due to *neoplastic diseases* results from extension or invasion of metastatic tumors (most commonly carcinoma of the lung and breast, malignant melanoma, lymphoma, and leukemia) to the pericardium. The pain of pericarditis, tamponade, and atrial arrhythmias are complications that occur occasionally. Diagnosis is made by pericardial fluid cytology or pericardial biopsy. *Mediastinal irradiation* for neoplasm may cause acute pericarditis and/or chronic constrictive pericarditis. Unusual causes of acute pericarditis include syphilis, fungal infection (histoplasmosis, blastomycosis, aspergillosis, and candidiasis), and parasitic infestation (amebiasis, toxoplasmosis, echinococcosis, and trichinosis) (Table 265-1).

CHRONIC PERICARDIAL EFFUSIONS

Chronic pericardial effusions are sometimes encountered in patients without an antecedent history of acute pericarditis. They may cause few symptoms *per se*, and their presence may be detected by finding an enlarged cardiac silhouette on a chest roentgenogram. *Tuberculosis* and myxedema may be causal. Neoplasms, SLE, rheumatoid arthritis, mycotic infections, radiation therapy to the chest, and chylopericardium may also cause chronic pericardial effusion and should be considered and specifically sought in such patients. Aspiration and analysis of the pericardial fluid are often helpful in diagnosis. Pericardial fluid should be analyzed as described under pericardiocentesis. Grossly sanguineous pericardial fluid results most commonly from a neoplasm, tuberculosis, renal failure, or slow leakage from an aortic dissection. Pericardiocentesis may resolve large effusions, but pericardiectomy may be required in patients with recurrence. Intrapericardial instillation of sclerosing agents may be used to prevent reaccumulation of fluid.

CHRONIC CONSTRICTIVE PERICARDITIS

This disorder results when the healing of an acute fibrinous or serofibrinous pericarditis or the resorption of a chronic pericardial effusion is followed by obliteration of the pericardial cavity with the formation of granulation tissue. The latter gradually contracts and forms a firm scar encasing the heart, which may become calcified. In developing nations, a high percentage of cases are of tuberculous origin, but this is now an uncommon cause in North America or Western Europe. Chronic constrictive pericarditis may follow acute or relapsing viral or idiopathic pericarditis, trauma with organized blood clot, or cardiac surgery of any type, or results from mediastinal irradiation, purulent infection, histoplasmosis, neoplastic disease (especially breast cancer, lung cancer, and lymphoma), rheumatoid arthritis, SLE, or chronic renal failure treated by chronic dialysis. In many patients, the cause of the pericardial disease is undetermined, and in these patients an asymptomatic or forgotten bout of viral pericarditis, idiopathic or acute, may have been the inciting event.

The basic physiologic abnormality in patients with chronic constrictive pericarditis is the inability of the ventricles to fill because of the limitations imposed by the rigid, thickened pericardium. Ventricular filling is unimpeded during early diastole but is reduced abruptly when the elastic limit of the pericardium is reached, whereas in cardiac tamponade, ventricular filling is impeded throughout diastole. In both

conditions, ventricular end-diastolic and stroke volumes are reduced and the end-diastolic pressures in both ventricles and the mean pressures in the atria, pulmonary veins, and systemic veins are all elevated to similar levels (i.e., within 5 mmHg of one another). Despite these hemodynamic changes, systolic function may be normal or only slightly impaired at rest. However, in advanced cases, the fibrotic process may extend into the myocardium and cause myocardial scarring and atrophy, and venous congestion may then be due to the combined effects of the pericardial and myocardial lesions.

In constrictive pericarditis, the right and left atrial pressure pulses display an M-shaped contour, with prominent *x* and *y* descents. The *y* descent, which is absent or diminished in cardiac tamponade, is the most prominent deflection in constrictive pericarditis; it reflects rapid early filling of the ventricles. The *y* descent is interrupted by a rapid rise in atrial pressure during early diastole, when ventricular filling is impeded by the constricting pericardium. These characteristic changes are transmitted to the jugular veins, where they may be recognized by inspection. In constrictive pericarditis, the ventricular pressure pulses in both ventricles exhibit characteristic "square root" signs during diastole. These hemodynamic changes, although characteristic, are not pathognomonic of constrictive pericarditis and may also be observed in restrictive cardiomyopathies **(Chap. 254, Table 254-2)**.

CLINICAL AND LABORATORY FINDINGS

Weakness, fatigue, weight gain, increased abdominal girth, abdominal discomfort, and edema are common. The patient often appears chronically ill, and in advanced cases, anasarca, skeletal muscle wasting, and cachexia may be present. Exertional dyspnea is common, and orthopnea may occur, although it is usually not severe. The cervical veins are distended and may remain so even after intensive diuretic treatment, and venous pressure may fail to decline during inspiration (*Kussmaul's sign*). The latter is common in chronic pericarditis but may also occur in tricuspid stenosis, right ventricular infarction, and restrictive cardiomyopathy.

The pulse pressure is normal or reduced. A paradoxical pulse can be detected in about one-third of cases. Congestive hepatomegaly is pronounced and may impair hepatic function and cause jaundice; ascites is common and is usually more prominent than dependent edema. Pleural effusions and splenomegaly may also be present. The apical pulse is reduced and may retract in systole (*Broadbent's sign*). The heart sounds may be distant; an early third heart sound (i.e., a pericardial knock) occurring at the cardiac apex with the abrupt cessation of ventricular filling is often conspicuous.

The ECG frequently displays low voltage of the QRS complexes and diffuse flattening or inversion of the T waves. Atrial fibrillation is present in about one-third of patients. The *chest roentgenogram* shows a normal or slightly enlarged heart. Pericardial calcification is most common in tuberculous pericarditis. Pericardial calcification may, however, occur in the absence of constriction, and constriction may occur without calcification.

Inasmuch as the common physical signs of cardiac disease (murmurs, cardiac enlargement) may be inconspicuous or absent in chronic constrictive pericarditis, hepatic enlargement, and dysfunction associated with jaundice and intractable ascites may lead to a mistaken diagnosis of hepatic cirrhosis. This error can be avoided if the neck veins are inspected and found to be distended.

The transthoracic *echocardiogram* often shows pericardial thickening, dilation of the inferior vena cava and hepatic veins, and a sharp halt to rapid left ventricular filling in early diastole, with normal ventricular systolic function and flattening of the left ventricular posterior wall. There is a distinctive pattern of transvalvular flow velocity on Doppler echocardiography (Fig. 265-4). During inspiration, there is an exaggerated reduction in blood flow velocity in the pulmonary veins and across the mitral valve and a leftward shift of the ventricular septum; the opposite occurs during expiration. Diastolic flow velocity in the inferior vena cava into the right atrium and across the tricuspid valve increases in an exaggerated manner during inspiration and declines during expiration. However, echocardiography cannot definitively establish or exclude the diagnosis of constrictive pericarditis; CT and MRI are more accurate, the latter is useful in evaluating myocardial involvement.

DIFFERENTIAL DIAGNOSIS

Like chronic constrictive pericarditis, cor pulmonale **(Chap. 252)** may be associated with marked systemic venous hypertension, little pulmonary congestion, a heart that is not enlarged, and a paradoxical pulse. However, in cor pulmonale, advanced parenchymal pulmonary disease is usually apparent and venous pressure *falls* during inspiration (i.e., Kussmaul's sign is negative). *Tricuspid stenosis* **(Chap. 261)** may also simulate chronic constrictive pericarditis with congestive hepatomegaly, splenomegaly, ascites, and venous distention. However, the characteristic murmur and that of accompanying mitral stenosis are usually present.

Because it can be corrected surgically, it is important to distinguish chronic constrictive pericarditis from restrictive cardiomyopathy **(Chap. 254)**, which has a similar physiologic abnormality (i.e., restriction of ventricular filling). The differentiating features are summarized in Table 265-2. When a patient has progressive, disabling, and unresponsive congestive heart failure and displays any of the features of constrictive heart disease, Doppler echocardiography to record respiratory effects on transvalvular flow (Fig. 265-4) and an MRI or CT scan should be obtained to detect or exclude constrictive pericarditis, because the latter is usually correctable.

TREATMENT

Constrictive Pericarditis

Pericardial resection is the only definitive treatment of constrictive pericarditis and should be as complete as possible. Dietary sodium restriction and diuretics are useful during preoperative preparation. Coronary arteriography should be carried out preoperatively in patients aged >50 years to exclude unsuspected accompanying coronary artery disease. The benefits derived from cardiac decortication are usually progressive over a period of months. The risk of this operation depends on the extent of penetration of the myocardium by the fibrotic and calcific process, the severity of myocardial atrophy, the extent of secondary impairment of hepatic and/or renal function, and the patient's general condition. Operative mortality is in the range of 5–10% even in experienced centers; the patients with the most severe disease, especially secondary to radiation therapy, are at highest risk. Therefore, surgical treatment should, if possible, be carried out as early as possible.

Subacute Effusive-Constrictive Pericarditis This form of pericardial disease is characterized by the combination of a tense effusion in the pericardial space and constriction of the heart by thickened pericardium. As such, it shares a number of features with both chronic pericardial effusion producing cardiac compression and with pericardial constriction. It may be caused by tuberculosis (see below), multiple attacks of acute idiopathic pericarditis, radiation, traumatic pericarditis, renal failure, scleroderma, and neoplasms. The heart is generally enlarged, and a paradoxical pulse is usually present. After pericardiocentesis, the physiologic findings may change from those of cardiac tamponade to those of pericardial constriction. Furthermore, the intrapericardial pressure and the central venous pressure may decline, but not to normal. The diagnosis can be established by pericardiocentesis followed by pericardial biopsy. Wide excision of both the visceral and parietal pericardium is usually effective therapy.

Tuberculous Pericardial Disease This chronic infection is a common cause of chronic pericardial effusion, especially in the developing world where active tuberculosis and HIV are endemic. Tuberculous pericarditis may present as pericardial effusion, chronic constrictive pericarditis, or subacute effusive constrictive pericarditis (see above). The clinical picture is that of a chronic, systemic illness in a patient with pericardial effusion. It is important to consider this diagnosis in a patient with known tuberculosis, with HIV, and with fever, chest pain, weight loss, and enlargement of the cardiac silhouette

of undetermined origin. If the etiology of chronic pericardial effusion remains obscure despite detailed analysis including culture of the pericardial fluid, a pericardial biopsy, preferably by a limited thoracotomy, should be performed. If definitive evidence is still lacking but the specimen shows granulomas with caseation, antituberculous chemotherapy **(Chap. 173)** is indicated.

If the biopsy specimen shows a thickened pericardium after 2–4 weeks of antituberculous therapy, pericardiectomy should be carried out to prevent the development of constriction. Tubercular cardiac constriction should be treated surgically while the patient is receiving antituberculous chemotherapy.

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266 Atrial Myxoma and Other Cardiac Tumors

Eric H. Awtry

Cardiac tumors can be broadly classified into those that arise primarily in the heart and those that reflect metastatic disease from a distant primary source. Primary cardiac tumors can be further divided into those that are pathologically benign and those that are malignant. Overall, primary cardiac tumors are relatively uncommon, whereas secondary involvement of the heart or pericardium occurs in as many as 20% of patients with end-stage metastatic cancer. While patients with cardiac tumors may present with a variety of symptoms, many patients are asymptomatic at the time of diagnosis as the tumor may be identified incidentally on imaging studies performed for other reasons. Such findings need to be differentiated from other cardiac masses such as vegetation, thrombus, or myocardial hypertrophy. Echocardiography is usually the initial method of evaluation of cardiac tumors; however, a variety of imaging modalities are now available and a multimodality approach is often necessary for accurate diagnosis and clarification of treatment options **(Table 266-1)**.

TABLE 266-1 Imaging Modalities and Their Utility in the Evaluation of Cardiac Tumors

MODALITY	UTILITY IN CARDIAC TUMOR EVALUATION
Transthoracic echocardiography (TTE) (including 2-D, 3-D, and contrast)	Assessment of tumor location and size, and its impact on adjacent structures (e.g., valves, pericardium).
Transesophageal echocardiography (TEE)	Improved tumor characterization and spatial resolution compared with TTE. May aid in determining surgical approach.
Cardiac MRI with gadolinium contrast	Improved tissue characterization, definition of tumor size and identification of local invasion when compared with TTE or TEE. May differentiate tumor from thrombus.
Gated cardiac CT	Provides anatomic assessment and tissue characterization of the tumor. Useful when patients cannot tolerate MRI or when MRI is not feasible (e.g., patients with implantable cardiac devices). Allows for better assessment of calcified lesions and evaluation of extra-cardiac tumor involvement.
Nuclear Imaging (including ^{18}F-fluorodeoxyglucose positron emission tomography [FDG-PET])	Definition of extra-cardiac disease. May be useful in diagnosis of certain cardiac tumors (e.g., neuroendocrine tumors) but assessment of smaller tumors may be limited by surrounding myocardial FDG uptake.

PRIMARY TUMORS

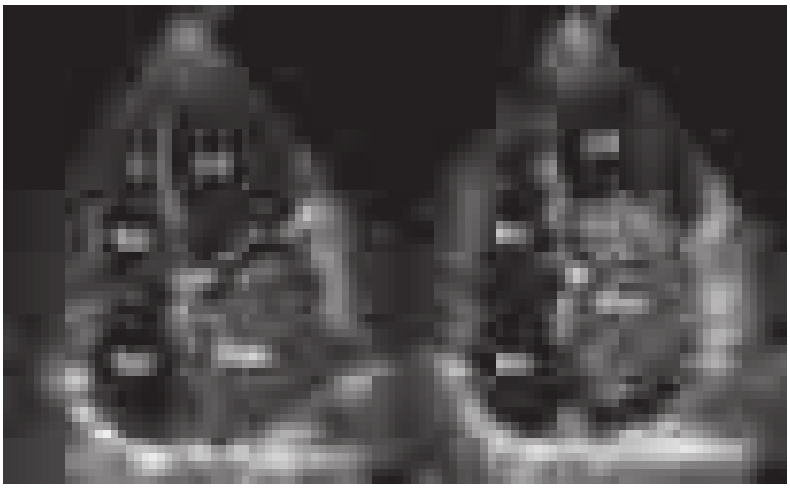
Primary tumors of the heart are rare. Approximately three-quarters are histologically benign, and the majority of these tumors are myxomas. Malignant tumors, almost all of which are sarcomas, account for 25% of primary cardiac tumors. All cardiac tumors, regardless of pathologic type, have the potential to cause life-threatening complications. Many tumors are now surgically curable; thus, early diagnosis is imperative.

Clinical Presentation Cardiac tumors may present with a wide array of cardiac and noncardiac manifestations. These manifestations, which depend in large part on the location and size of the tumor as well as its impact on surrounding cardiac structures, are often nonspecific features of more common forms of heart disease, such as chest pain, syncope, congestive heart failure (CHF), murmurs, arrhythmias, conduction disturbances, and pericardial effusion with or without tamponade. Additionally, embolic phenomena and constitutional symptoms may occur.

Myxoma Myxomas are the most common type of primary cardiac tumor in adults, accounting for one-third to one-half of all cases at postmortem examination, and approximately three-quarters of the tumors treated surgically. They occur at all ages, most commonly in the third through sixth decades, with a female predilection. Approximately 90% of myxomas are sporadic; the remainder are familial with autosomal dominant transmission. The familial variety often occurs as part of a syndrome complex (Carney complex) that includes (1) myxomas (cardiac, skin, and/or breast), (2) lentigines and/or pigmented nevi, and (3) endocrine overactivity (primary nodular adrenal cortical disease with or without Cushing's syndrome, testicular tumors, and/or pituitary adenomas with gigantism or acromegaly). Certain constellations of findings have been referred to as the *NAME* syndrome (*n*evi, *a*trial myxoma, *m*yxoid neurofibroma, and *e*phelides) or the *LAMB* syndrome (*l*entigines, *a*trial *m*yxoma, and *b*lue nevi), although these syndromes probably represent subsets of the Carney complex. The genetic basis of this complex has not been elucidated completely; however, inactivating mutations in the tumor-suppressor gene *PRKAR1A*, which encodes the protein kinase A type I-α regulatory subunit, have been identified in ~70% of patients with Carney complex.

Pathologically, myxomas are gelatinous structures that consist of myxoma cells embedded in a stroma rich in glycosaminoglycans. Most sporadic tumors are solitary, arise from the interatrial septum in the vicinity of the fossa ovalis (particularly in the left atrium), and are often pedunculated on a fibrovascular stalk. In contrast, familial or syndromic tumors tend to occur in younger individuals, are often multiple, may be ventricular in location, and are more likely to recur after initial resection.

Myxomas commonly present with obstructive signs and symptoms. The most common clinical presentation mimics that of mitral valve disease: either stenosis owing to tumor prolapse into the mitral orifice or regurgitation resulting from tumor-induced valvular trauma or distortion. Ventricular myxomas may cause outflow tract obstruction similar to that caused by subaortic or subpulmonic stenosis. The symptoms and signs of myxoma may be sudden in onset or positional in nature,



A B

FIGURE 266-1 Transthoracic echocardiogram demonstrating a large atrial myxoma. The myxoma (Myx) fills the entire left atrium in systole (***A***) and prolapses across the mitral valve and into the left ventricle (LV) during diastole (***B***). RA, right atrium; RV, right ventricle. *(Courtesy of Dr. Michael Tsang; with permission.)*

owing to the effects of gravity on tumor position. A characteristic low-pitched sound, a "tumor plop," may be appreciated on auscultation during early or mid-diastole and is thought to result from the impact of the tumor against the mitral valve or ventricular wall. Myxomas also may present with peripheral or pulmonary embolic phenomenon (resulting from embolization of tumor fragments or tumor-associated thrombus) or with constitutional signs and symptoms, including fever, weight loss, cachexia, malaise, arthralgias, rash, digital clubbing, and Raynaud's phenomenon. Laboratory abnormalities, such as hypergammaglobulinemia, anemia, polycythemia, leukocytosis, elevated erythrocyte sedimentation rate, elevated C-reactive protein level, thrombocytopenia, and thrombocytosis are often present. These features account for the frequent misdiagnosis of patients with myxomas as having endocarditis, collagen vascular disease, or a paraneoplastic syndrome.

Two-dimensional and three-dimensional transthoracic and/or transesophageal echocardiography are useful in the diagnosis of cardiac myxoma and allow for assessment of tumor size and determination of the site of tumor attachment, both of which are important considerations in the planning of surgical excision **(Fig. 266-1)**. Computed tomography (CT) and magnetic resonance imaging (MRI) may provide important information regarding size, shape, composition, and surface characteristics of the tumor **(Fig. 266-2)**.

Although cardiac catheterization and angiography were previously performed routinely before tumor resection, they no longer are considered mandatory when adequate noninvasive information is available and other cardiac disorders (e.g., coronary artery disease) are not considered likely. Additionally, catheterization of the chamber from which the tumor arises carries the risk of tumor embolization. Because myxomas may be familial, echocardiographic screening of first-degree relatives is appropriate, particularly if the patient is young and has multiple tumors or features of a myxoma syndrome.

TREATMENT

Myxoma

Surgical excision using cardiopulmonary bypass is indicated regardless of tumor size, and is generally curative. Myxomas recur in 12–22% of familial cases but in only 1–2% of sporadic cases. Tumor recurrence most likely results from multifocal lesions in the former setting and incomplete tumor resection in the latter.

Other Benign Tumors Cardiac *lipomas*, although relatively common, are usually incidental findings at postmortem examination; however, they may grow as large as 15 cm, may present as an abnormality of the cardiac silhouette on chest x-ray, and should be resected if they produce symptoms owing to mechanical interference with cardiac function, arrhythmias, or conduction disturbances. *Papillary fibroelastomas* are friable tumors with frond-like projections that are usually solitary and are the most common tumors of the cardiac valves. Remnants of cytomegalovirus have been recovered from these tumors, raising the possibility that they arise as a result of chronic viral endocarditis. Although usually clinically silent, they can cause valve dysfunction and may embolize distally, resulting in transient ischemic attacks, stroke, or myocardial infarction. In general, these tumors should be resected even when asymptomatic, although a more conservative approach may be considered for small, right-sided lesions. *Rhabdomyomas* and *fibromas* are the most common cardiac tumors in infants and children and usually occur in the ventricles, where they may produce mechanical obstruction to blood flow, thereby mimicking valvular stenosis, CHF, restrictive or hypertrophic cardiomyopathy, or pericardial constriction. Rhabdomyomas are probably hamartomatous growths, are multiple in 90% of cases, and are strongly associated with tuberous sclerosis

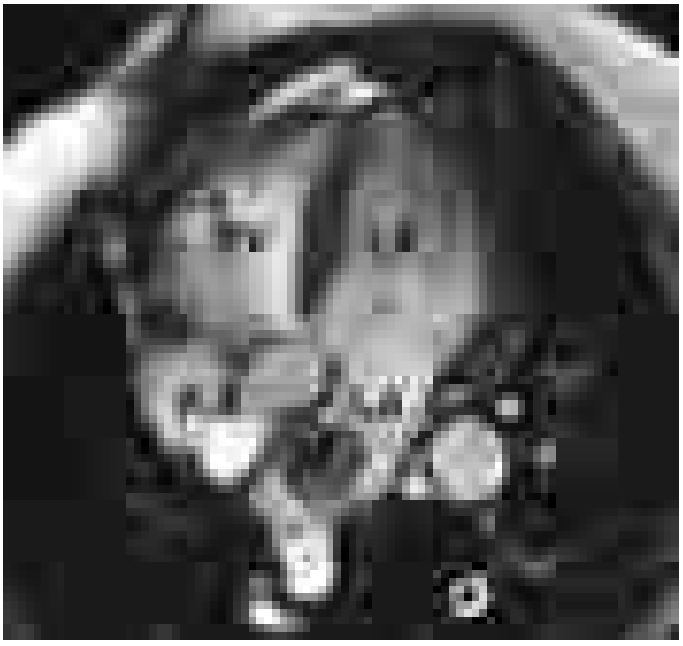


FIGURE 266-2 Cardiac magnetic resonance imaging demonstrating a rounded mass (M) within the left atrium (LA). Pathologic evaluation at the time of surgery revealed it to be an atrial myxoma. LV, left ventricle; RA, right atrium; RV, right ventricle.

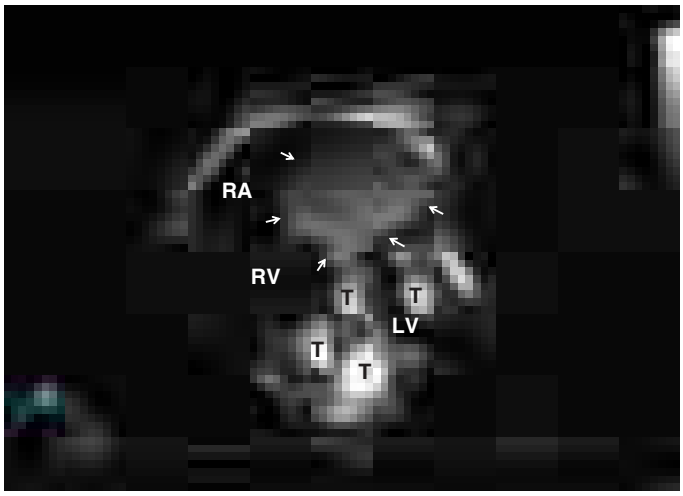


FIGURE 266-3 Transthoracic echocardiogram revealing multiple tumors (T) consistent with rhabdomyomas in a 1-day-old infant. The largest tumor (*arrows*) was located in the left AV groove and measured 2 cm × 2 cm. LV; left ventricle; RA, right atrium; RV, right ventricle.

(Fig. 266-3). These tumors have a tendency to regress completely or partially; only tumors that cause obstruction require surgical resection. Fibromas are usually single, universally ventricular in location, often calcified, tend to grow and cause arrhythmias and obstructive symptoms, and should be completely resected when possible. *Paragangliomas* are rare chromaffin cell tumors that represent extra-adrenal pheochromocytomas. Most are located in the roof of the left atrium and can be identified on cardiac CT or MRI, or with nuclear scanning using 131-I-metaiodobenzylguanidine. They are highly vascular and may be hormonally active, resulting in uncontrolled hypertension. Extensive surgical resection is usually required. *Hemangiomas* and *mesotheliomas* are generally small tumors, most often intramyocardial in location, and may cause atrioventricular (AV) conduction disturbances and even sudden death as a result of their propensity to develop in the region of the AV node. Other benign tumors arising from the heart include *teratoma*, *chemodectoma*, *neurilemoma*, *granular cell myoblastoma*, and *paraganglioma*.

Sarcoma Almost all malignant primary cardiac tumors are sarcomas; isolated cardiac lymphomas have been rarely described, but usually occur in the context of more systemic disease. Sarcomas may be of several histologic types; angiosarcomas are the most common type in adults while rhabdomyosarcomas are the most common type in children. In general, sarcomas are characterized by rapid progression that culminates in the patient's death within weeks to months from the time of presentation as a result of hemodynamic compromise, local invasion, or distant metastases. Almost one-third are metastatic at the time of initial diagnosis, usually involving the lungs. Sarcomas commonly involve the right side of the heart, are rapidly growing, frequently invade the pericardial space, and may obstruct the cardiac chambers or venae cavae. Sarcomas also may occur on the left side of the heart and may be mistaken for myxomas.

TREATMENT

Sarcoma

The optimal therapy for cardiac sarcoma is complete resection often with neoadjuvant and postoperative chemotherapy; however, at the time of presentation, many of these tumors have spread too extensively to allow for surgical excision. Although there are scattered reports of palliation with radiotherapy and/or chemotherapy, the response of cardiac sarcomas to these therapies is generally poor. The one exception appears to be cardiac lymphosarcomas, which may respond to a combination of chemo- and radiotherapy.

TUMORS METASTATIC TO THE HEART

Tumors metastatic to the heart are much more common than primary tumors, and their incidence is likely to increase as the life expectancy of patients with various forms of malignant neoplasms is extended by more effective therapy and improved imaging modalities allow earlier identification of metastatic disease. Although cardiac metastases may occur with any tumor type, the relative incidence is especially high in malignant melanoma and, to a somewhat lesser extent, leukemia and lymphoma (Fig. 266-4). In absolute terms, the most common primary sites from which cardiac metastases originate are carcinoma of the breast and lung, reflecting the high incidence of those cancers. Cardiac metastases almost always occur in the setting of widespread primary disease, and most often there is either primary or metastatic disease elsewhere in the thoracic cavity. Nevertheless, cardiac metastasis occasionally may be the initial presentation of an extrathoracic tumor.

Cardiac metastases may occur via hematogenous or lymphangitic spread or by direct tumor invasion. They generally manifest as small, firm nodules; diffuse infiltration also may occur, especially with sarcomas or hematologic neoplasms. The pericardium is most often involved, followed by myocardial involvement of any chamber and, rarely, by involvement of the endocardium or cardiac valves.

Cardiac metastases are clinically apparent only ~10% of the time, are usually not the cause of the patient's presentation, and rarely are the cause of death. The vast majority occur in the setting of a previously recognized malignant neoplasm. As with primary cardiac tumors, the clinical presentation reflects more the location and size of the tumor than its histologic type. When symptomatic, cardiac metastases may result in a variety of clinical features, including dyspnea, acute pericarditis, cardiac tamponade, ectopic tachyarrhythmias, heart block, and CHF. Importantly, many of these signs and symptoms may also result from myocarditis, pericarditis, or cardiomyopathy induced by radiotherapy or chemotherapy, and a high index of suspicion for cardiac involvement should be maintained for patients with malignant disease who develop these symptoms.

Electrocardiographic (ECG) findings are nonspecific but may reveal features consistent with pericarditis or may demonstrate low QRS voltage and electrical alternans in the setting of a large pericardial effusion. On chest x-ray, the cardiac silhouette is most often normal but may be enlarged or exhibit a bizarre contour. Echocardiography is useful for identifying and assessing the significance of pericardial effusions and visualizing larger metastases, although CT and radionuclide imaging may define the tumor burden more clearly. Cardiac MRI offers superb image quality and plays a central role in the diagnostic evaluation of cardiac metastases and cardiac tumors in general. Pericardiocentesis may allow for a specific cytologic diagnosis in patients with malignant

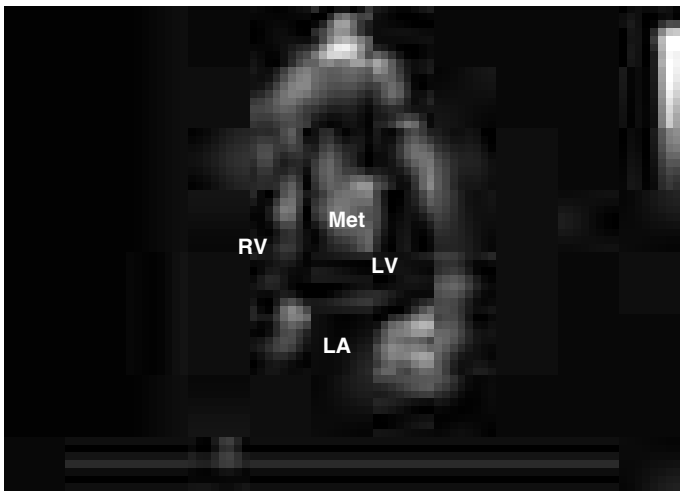


FIGURE 266-4 Large metastatic lesion (Met) in the left ventricle (LV) of a patient with diffusely metastatic bladder cancer. The mass arose from the interventricular septum and prolapsed into the aortic outflow tract during systole.

pericardial effusions. Angiography is rarely necessary but may help to delineate discrete myocardial lesions.

TREATMENT

Tumors Metastatic to the Heart

Most patients with cardiac metastases have advanced malignant disease; thus, therapy is generally palliative and consists of controlling symptoms and treatment of the primary tumor. Symptomatic malignant pericardial effusions should be drained by pericardiocentesis. Prolonged drainage (3–5 days) and concomitant instillation of a sclerosing agent (e.g., tetracycline or bleomycin) may delay or prevent reaccumulation of the effusion, and creation of a pericardial window allows drainage of the effusion to the adjacent pleural or peritoneal space. Given the overall poor prognosis of these patients, discussions regarding goals of care and involvement of palliative care services are often appropriate.

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Section 5 Coronary and Peripheral Vascular Disease

267 Ischemic Heart Disease

Elliott M. Antman, Joseph Loscalzo

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery. **Chapter 291e** (from the 19th edition of *Harrison's*) deals with the development and treatment of atherosclerosis. This chapter focuses on the chronic manifestations and treatment of IHD. The subsequent chapters address the acute phases of IHD.

EPIDEMIOLOGY AND GLOBAL TRENDS

IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. IHD is the most common, serious, chronic, life-threatening illness in the United States, where 15.5 million persons have IHD, and 3.4 million people aged ≥40 years have angina pectoris. Although there is regional variation, about 4% of the population has sustained a myocardial infarction. Genetic factors, a high-fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, IHD is growing among low-income groups, but primary prevention has delayed the disease to later in life across socioeconomic groups. Despite these sobering statistics, it is worth noting that epidemiologic data show a decline in the rate of deaths due to IHD, about half of which is attributable to treatments and half to prevention by risk factor modification.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. These trends are occurring in the general context of population growth and as a result of the increase in the average age of the world's population. With urbanization in countries with emerging economies and a growing middle class, elements of the energy-rich Western diet are being adopted. As a result, the prevalence of risk factors for IHD and the prevalence of IHD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to noncommunicable diseases. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East. In light of the projection of large increases in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020.

PATHOPHYSIOLOGY

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. In normal conditions, for any given level of a demand for oxygen, the myocardium will control the supply of oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction. The major determinants of myocardial oxygen demand (MVO_2) are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries: (1) large epicardial arteries (Resistance 1 = R_1), (2) prearteriolar vessels (R_2), and (3) arteriolar and intramyocardial capillary vessels (R_3). In the absence of significant flow-limiting atherosclerotic obstructions, R_1 is trivial; the major determinant of coronary resistance is found in R_2 and R_3 **(Fig. 267-1)**. The normal coronary circulation is dominated and controlled by the heart's requirements for oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate a great capacity for dilation (R_2 and R_3 decrease). For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow also can be limited by spasm (see Prinzmetal's angina in **Chap. 268**), arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities such as the origin of the left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased and particularly when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy (LVH) due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia **(Chap. 256)**. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

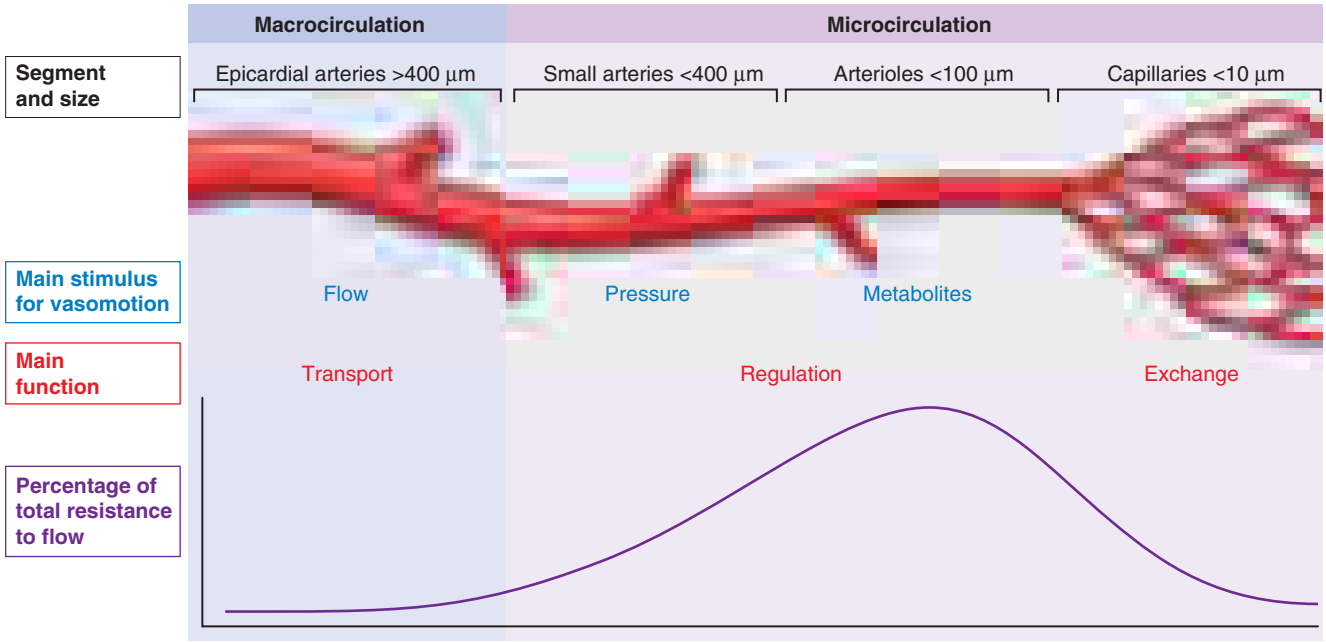


FIGURE 267-1 Macrocirculation and microcirculation across segments and sizes of the arteries. The location and size of the arteries supplying blood to the heart is shown at the top. Vasomotion of the arterial segments occurs in response to the stimuli shown. The main function of each of the arterial segments is shown next, followed by a depiction of the relative resistance to antegrade flow. *(Modified from B De Bruyne et al: J Am Coll Cardiol 67:1170, 2016.)*

Not infrequently, two or more causes of ischemia coexist in a patient, such as an increase in oxygen demand due to LVH secondary to hypertension and a reduction in oxygen supply secondary to coronary atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. When it causes angina, this condition is referred to as *microvascular angina*.

CORONARY ATHEROSCLEROSIS

Epicardial coronary arteries are the major site of atherosclerotic disease. The major risk factors for atherosclerosis (high levels of plasma low-density lipoprotein [LDL], low plasma high-density lipoprotein [HDL], cigarette smoking, hypertension, and diabetes mellitus vary in their relative impact on disturbing the normal functions of the vascular endothelium. These functions include local control of vascular tone, maintenance of an antithrombotic surface, and control of inflammatory cell adhesion and diapedesis. The loss of these defenses leads to inappropriate constriction, luminal thrombus formation, and abnormal interactions between blood cells, especially monocytes and platelets, and the activated vascular endothelium. Functional changes in the vascular milieu ultimately result in the subintimal collections of fat, smooth muscle cells, fibroblasts, and intercellular matrix that define the atherosclerotic plaque. Rather than viewing atherosclerosis strictly as a vascular problem, it is useful to consider it in the context of alterations in the nature of the circulating blood (hyperglycemia; increased concentrations of LDL cholesterol, tissue factor, fibrinogen, von Willebrand factor, coagulation factor VII, and platelet microparticles). The combination of a "vulnerable vessel" in a patient with "vulnerable blood" promotes a state of hypercoagulability and hypofibrinolysis. This is especially true in patients with diabetes mellitus.

Atherosclerosis develops at irregular rates in different segments of the epicardial coronary tree and leads eventually to segmental reductions in cross-sectional area, i.e., plaque formation. There is also a predilection for atherosclerotic plaques to develop at sites of increased turbulence in coronary flow, such as at branch points in the epicardial arteries. When a stenosis reduces the diameter of an epicardial artery by 50%, there is a limitation of the ability to increase flow to meet increased myocardial demand. When the diameter is reduced by ~80%, blood flow at rest may be reduced, and further minor decreases in the stenotic orifice area can reduce coronary flow dramatically to cause myocardial ischemia at rest or with minimal stress.

Segmental atherosclerotic narrowing of epicardial coronary arteries is caused most commonly by the formation of a plaque, which is subject to rupture or erosion of the cap separating the plaque from the bloodstream. Upon exposure of the plaque contents to blood, two important and interrelated processes are set in motion: (1) platelets are activated and aggregate, and (2) the coagulation cascade is activated, leading to deposition of fibrin strands. A thrombus composed of platelet aggregates and fibrin strands traps red blood cells and can reduce coronary blood flow, leading to the clinical manifestations of myocardial ischemia.

The location of the obstruction influences the quantity of myocardium rendered ischemic and determines the severity of the clinical manifestations. Thus, critical obstructions in vessels, such as the left main coronary artery and the proximal left anterior descending coronary artery, are particularly hazardous. Chronic severe coronary narrowing and myocardial ischemia frequently are accompanied by the development of collateral vessels, especially when the narrowing develops gradually. When well developed, such vessels can by themselves provide sufficient blood flow to sustain the viability of the myocardium at rest but not during conditions of increased demand.

With progressive worsening of a stenosis in a proximal epicardial artery, the distal resistance vessels (when they function normally) dilate to reduce vascular resistance and maintain coronary blood flow. A pressure gradient develops across the proximal stenosis, and poststenotic pressure falls. When the resistance vessels are maximally dilated, myocardial blood flow becomes dependent on the pressure in the coronary artery distal to the obstruction. In these circumstances, ischemia, manifest clinically by angina or electrocardiographically by ST-segment deviation, can be precipitated by increases in myocardial oxygen demand caused by physical activity, emotional stress, and/or tachycardia. Changes in the caliber of the stenosed coronary artery resulting from physiologic vasomotion, loss of endothelial control of dilation (as occurs in atherosclerosis), pathologic spasm (Prinzmetal's angina), or small platelet-rich plugs also can upset the critical balance between oxygen supply and demand and thereby precipitate myocardial ischemia.

EFFECTS OF ISCHEMIA

During episodes of inadequate perfusion caused by coronary atherosclerosis, myocardial tissue oxygen tension falls and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium (Fig. 267-2). Coronary atherosclerosis is a

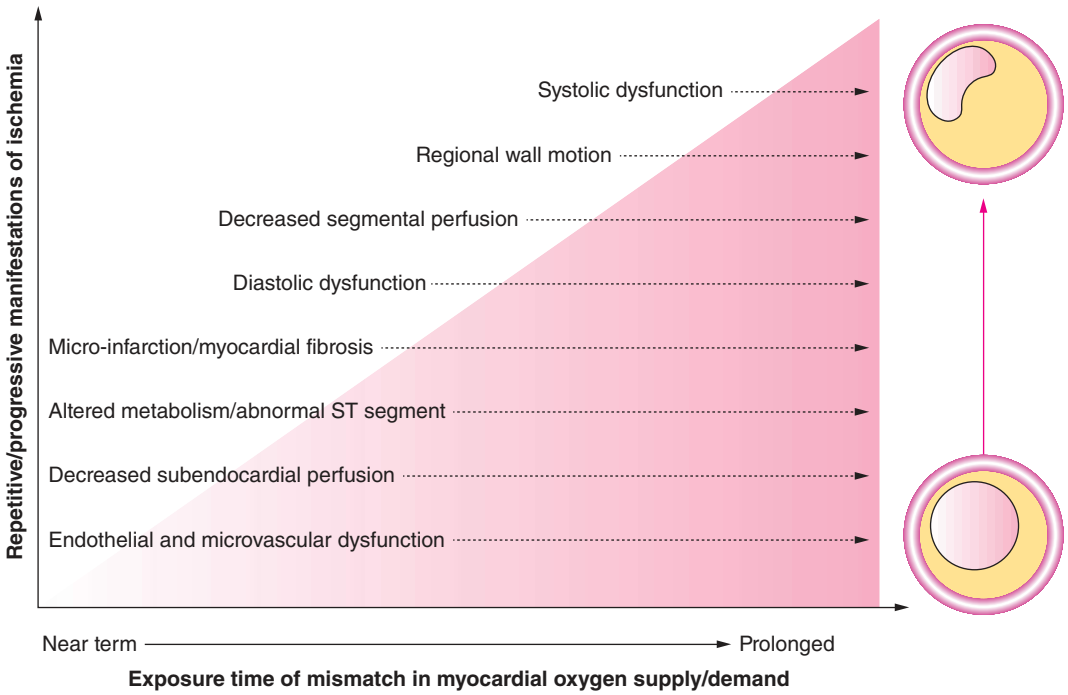


FIGURE 267-2 Cascade of mechanisms and manifestations of ischemia. *(Modified from LJ Shaw et al: J Am Coll Cardiol 54:1561, 2009. Original figure illustration by Rob Flewell.)*

focal process that usually causes nonuniform ischemia. During ischemia, regional disturbances of ventricular contractility cause segmental hypokinesia, akinesia, or, in severe cases, bulging (dyskinesia), which can reduce myocardial pump function.

The abrupt development of severe ischemia, as occurs with total or subtotal coronary occlusion, is associated with almost instantaneous failure of normal muscle relaxation and then contraction. The relatively poor perfusion of the subendocardium causes more intense ischemia of this portion of the wall (compared with the subepicardial region). Ischemia of large portions of the ventricle causes transient left ventricular (LV) failure, and if the papillary muscle apparatus is involved, mitral regurgitation can occur. When ischemia is transient, it may be associated with angina pectoris; when it is prolonged, it can lead to myocardial necrosis and scarring with or without the clinical picture of acute myocardial infarction **(Chap. 269)**.

A wide range of abnormalities in cell metabolism, function, and structure underlie these mechanical disturbances during ischemia. The normal myocardium metabolizes fatty acids and glucose to carbon dioxide and water. With severe oxygen deprivation, fatty acids cannot be oxidized, and glucose is converted to lactate; intracellular pH is reduced, as are the myocardial stores of high-energy phosphates, i.e., ATP and creatine phosphate. Impaired cell membrane function leads to the leakage of potassium and the uptake of sodium by myocytes as well as an increase in cytosolic calcium. The severity and duration of the imbalance between myocardial oxygen supply and demand determine whether the damage is reversible (≤20 min for total occlusion in the absence of collaterals) or permanent, with subsequent myocardial necrosis (>20 min).

Ischemia also causes characteristic changes in the electrocardiogram (ECG) such as repolarization abnormalities, as evidenced by inversion of T waves and, when more severe, displacement of ST segments **(Chap. 235)**. Transient T-wave inversion probably reflects nontransmural, intramyocardial ischemia; transient ST-segment depression often reflects patchy subendocardial ischemia; and ST-segment elevation is thought to be caused by more severe transmural ischemia. Another important consequence of myocardial ischemia is electrical instability, which may lead to isolated ventricular premature beats or even ventricular tachycardia or ventricular fibrillation **(Chaps. 249 and 250)**. Most patients who die suddenly from IHD do so as a result of ischemia-induced ventricular tachyarrhythmias **(Chap. 299)**.

ASYMPTOMATIC VERSUS SYMPTOMATIC IHD

Although the prevalence is decreasing, postmortem studies of accident victims and military casualties in Western countries show that coronary atherosclerosis can begin before age 20 and is present even among adults who were asymptomatic during life. Exercise stress tests in asymptomatic persons may show evidence of silent myocardial ischemia, i.e., exercise-induced ECG changes not accompanied by angina pectoris; coronary angiographic studies of such persons may reveal coronary artery plaques and previously unrecognized obstructions **(Chap. 237)**. Coronary artery calcifications (CAC) may be seen on CT images of the heart, can be quantified in a CAC score, and may be used as adjunctive information to support a diagnosis of IHD. However, they should not be used as the primary screening modality or as the isolated basis on which to formulate therapeutic decisions. (See further discussion below.) Postmortem examination of patients with such obstructions without a history of clinical manifestations of myocardial ischemia often shows macroscopic scars secondary to myocardial infarction in regions supplied by diseased coronary arteries, with or without collateral circulation. According to population studies, ~25% of patients who survive acute myocardial infarction may not come to medical attention, and these patients have the same adverse prognosis as do those who present with the classic clinical picture of acute myocardial infarction **(Chap. 269)**. Sudden death may be unheralded and is a common presenting manifestation of IHD **(Chap. 299)**.

Patients with IHD also can present with cardiomegaly and heart failure secondary to ischemic damage of the LV myocardium that may have caused no symptoms before the development of heart failure; this condition is referred to as *ischemic cardiomyopathy*. In contrast to the asymptomatic phase of IHD, the symptomatic phase is characterized by chest discomfort due to either angina pectoris or acute myocardial infarction **(Chap. 269)**. Having entered the symptomatic phase, the patient may exhibit a stable or progressive course, revert to the asymptomatic stage, or die suddenly.

STABLE ANGINA PECTORIS

This episodic clinical syndrome is due to transient myocardial ischemia. Various diseases that cause myocardial ischemia and the numerous forms of discomfort with which it may be confused are discussed in **Chap. 11**. Males constitute ~70% of all patients with angina pectoris and an even greater proportion of those aged <50 years. It is, however,

important to note that angina pectoris in women is often atypical in presentation (see below).

HISTORY

The typical patient with angina is a man >50 years or a woman >60 years of age who complains of episodes of chest discomfort, usually described as heaviness, pressure, squeezing, smothering, or choking and only rarely as frank pain. When the patient is asked to localize the sensation, he or she typically places a hand over the sternum, sometimes with a clenched fist, to indicate a squeezing, central, substernal discomfort (Levine's sign). Angina is usually crescendo-decrescendo in nature, typically lasts 2–5 min, and can radiate to either shoulder and to both arms (especially the ulnar surfaces of the forearm and hand). It also can arise in or radiate to the back, interscapular region, root of the neck, jaw, teeth, and epigastrium. Angina is rarely localized below the umbilicus or above the mandible. A useful finding in assessing a patient with chest discomfort is the fact that myocardial ischemic discomfort does not radiate to the trapezius muscles; that radiation pattern is more typical of pericarditis.

Although episodes of angina typically are caused by exertion (e.g., exercise, hurrying, or sexual activity) or emotion (e.g., stress, anger, fright, or frustration) and are relieved by rest, they also may occur at rest **(Chap. 268)** and while the patient is recumbent (angina decubitus). The patient may be awakened at night by typical chest discomfort and dyspnea. Nocturnal angina may be due to episodic tachycardia, diminished oxygenation as the respiratory pattern changes during sleep, or expansion of the intrathoracic blood volume that occurs with recumbency; the latter causes an increase in cardiac size (end-diastolic volume), wall tension, and myocardial oxygen demand that can lead to ischemia and transient LV failure.

The threshold for the development of angina pectoris may vary by time of day and emotional state. Many patients report a fixed threshold for angina, which occurs predictably at a certain level of activity, such as climbing two flights of stairs at a normal pace. In these patients, coronary stenosis and myocardial oxygen supply are fixed, and ischemia is precipitated by an increase in myocardial oxygen demand; they are said to have stable exertional angina. In other patients, the threshold for angina may vary considerably within any particular day and from day to day. In such patients, variations in myocardial oxygen supply, most likely due to changes in coronary vasomotor tone, may play an important role in defining the pattern of angina. A patient may report symptoms upon minor exertion in the morning (a short walk or shaving) yet by midday be capable of much greater effort without symptoms. Angina may also be precipitated by unfamiliar tasks, a heavy meal, exposure to cold, or a combination of these factors.

Exertional angina typically is relieved in 1–5 min by slowing or ceasing activities and even more rapidly by rest and sublingual nitroglycerin (see below). Indeed, the diagnosis of angina should be suspect if it does not respond to the combination of these measures. The severity of angina can be conveniently summarized by the Canadian Cardiac Society functional classification **(Table 267-1)**. Its impact on the patient's functional capacity can be described by using the New York Heart Association functional classification (Table 267-1).

Sharp, fleeting chest pain or a prolonged, dull ache localized to the left submammary area is rarely due to myocardial ischemia. However, especially in women and diabetic patients, angina pectoris may be atypical in location and not strictly related to provoking factors. In addition, this symptom may exacerbate and remit over days, weeks, or months. Its occurrence can be seasonal, occurring more frequently in the winter in temperate climates. Anginal "equivalents" are symptoms of myocardial ischemia other than angina. They include dyspnea, nausea, fatigue, and faintness and are more common in the elderly and in diabetic patients.

Systematic questioning of a patient with suspected IHD is important to uncover the features of an unstable syndrome associated with increased risk, such as angina occurring with less exertion than in the past, occurring at rest, or awakening the patient from sleep. Since coronary atherosclerosis often is accompanied by similar lesions in other arteries, a patient with angina should be questioned and examined for peripheral arterial disease (intermittent claudication **[Chap. 275]**), stroke, or transient ischemic attacks **(Chap. 419)**. It is also important to uncover a family history of premature IHD (<55 years in first-degree male relatives and <65 in female relatives) and the presence of diabetes mellitus, hyperlipidemia, hypertension, cigarette smoking, and other risk factors for coronary atherosclerosis.

TABLE 267-1 Cardiovascular Disease Classification Chart

CLASS	NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION	CANADIAN CARDIOVASCULAR SOCIETY FUNCTIONAL CLASSIFICATION
I	Patients have cardiac disease but *without* the resulting *limitations* of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity, such as walking and climbing stairs, *does not cause angina*. Angina present with strenuous or rapid or prolonged exertion at work or recreation.
II	Patients have cardiac disease resulting in *slight limitation* of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	*Slight limitation* of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, or when under emotional stress or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions.
III	Patients have cardiac disease resulting in *marked limitation* of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	*Marked limitation* of ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions.
IV	Patients have cardiac disease resulting in *inability* to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	*Inability* to carry on any physical activity without discomfort—anginal syndrome *may* be present at rest.

Source: Modified from L Goldman et al: Circulation 64:1227, 1981.

The history of typical angina pectoris establishes the diagnosis of IHD until proven otherwise. The coexistence of advanced age, male sex, the postmenopausal state, and risk factors for atherosclerosis increase the likelihood of hemodynamically significant coronary disease. A particularly challenging problem is the evaluation and management of patients with persistent ischemic-type chest discomfort but no flow-limiting obstructions in their epicardial coronary arteries. This situation arises more often in women than in men. Potential etiologies include microvascular coronary disease (detectable on coronary reactivity testing in response to vasoactive agents such as intracoronary adenosine, acetylcholine, and nitroglycerin) and abnormal cardiac nociception. Treatment of microvascular coronary disease should focus on efforts to improve endothelial function, including nitrates, beta blockers, calcium antagonists, statins, and angiotensin-converting enzyme (ACE) inhibitors. Abnormal cardiac nociception is more difficult to manage and may be ameliorated in some cases by imipramine.

PHYSICAL EXAMINATION

The physical examination is often normal in patients with stable angina when they are asymptomatic. However, because of the increased likelihood of IHD in patients with diabetes and/or peripheral arterial disease, clinicians should search for evidence of atherosclerotic disease at other sites, such as an abdominal aortic aneurysm, carotid arterial bruits, and diminished arterial pulses in the lower extremities. The physical examination also should include a search for evidence of risk factors for atherosclerosis such as xanthelasmas and xanthomas.

Evidence for peripheral arterial disease should be sought by evaluating the pulse contour at multiple locations and comparing the blood pressure between the arms and between the arms and the legs (ankle-brachial index). Examination of the fundi may reveal an increased light reflex and arteriovenous nicking as evidence of hypertension. There also may be signs of anemia, thyroid disease, and nicotine stains on the fingertips from cigarette smoking.

Palpation may reveal cardiac enlargement and abnormal contraction of the cardiac impulse (LV dyskinesia). Auscultation can uncover arterial bruits, a third and/or fourth heart sound, and, if acute ischemia or previous infarction has impaired papillary muscle function, an apical systolic murmur due to mitral regurgitation. These auscultatory signs are best appreciated with the patient in the left lateral decubitus position. Aortic stenosis, aortic regurgitation **(Chap. 256)**, pulmonary hypertension **(Chap. 277)**, and hypertrophic cardiomyopathy **(Chap. 254)** must be excluded, since these disorders may cause angina in the absence of coronary atherosclerosis. Examination during an anginal attack is useful, since ischemia can cause transient LV failure with the appearance of a third and/or fourth heart sound, a dyskinetic cardiac apex, mitral regurgitation, and even pulmonary edema. Tenderness of the chest wall, localization of the discomfort with a single fingertip on the chest, or reproduction of the pain with palpation of the chest makes it unlikely that the pain is caused by myocardial ischemia. A protuberant abdomen may indicate that the patient has the metabolic syndrome and is at increased risk for atherosclerosis.

LABORATORY EXAMINATION

Although the diagnosis of IHD can be made with a high degree of confidence from the history and physical examination, a number of simple laboratory tests can be helpful. The urine should be examined for evidence of diabetes mellitus and renal disease (including microalbuminuria) since these conditions accelerate atherosclerosis. Similarly, examination of the blood should include measurements of lipids (cholesterol—total, LDL, HDL—and triglycerides), glucose (hemoglobin A_{1C}), creatinine, hematocrit, and, if indicated based on the physical examination, thyroid function. A chest x-ray is important as it may show the consequences of IHD, i.e., cardiac enlargement, ventricular aneurysm, or signs of heart failure. These signs can support the diagnosis of IHD and are important in assessing the degree of cardiac damage. Evidence exists that an elevated level of high-sensitivity C-reactive protein (CRP) (specifically, between 0 and 3 mg/dL) is an independent risk factor for IHD and may be useful in therapeutic decision-making about the initiation of hypolipidemic treatment. The major benefit of high-sensitivity CRP is in reclassifying the risk of IHD in patients in the "intermediate" risk category on the basis of traditional risk factors.

ELECTROCARDIOGRAM

A 12-lead ECG recorded at rest may be normal in patients with typical angina pectoris, but there may also be signs of an old myocardial infarction **(Chap. 235)**. Although repolarization abnormalities, i.e., ST-segment and T-wave changes, as well as LVH and disturbances of cardiac rhythm or intraventricular conduction are suggestive of IHD, they are nonspecific, since they also can occur in pericardial, myocardial, and valvular heart disease or, in the case of the former, transiently with anxiety, changes in posture, drugs, or esophageal disease. The presence of LVH is a significant indication of increased risk of adverse outcomes from IHD. Of note, even though LVH and cardiac rhythm disturbances are nonspecific indicators of the development of IHD, they may be contributing factors to episodes of angina in patients in whom IHD has developed as a consequence of conventional risk factors. Dynamic ST-segment and T-wave changes that accompany episodes of angina pectoris and disappear thereafter are more specific.

STRESS TESTING

Electrocardiographic The most widely used test for both the diagnosis of IHD and the estimation of risk and prognosis involves recording of the 12-lead ECG before, during, and after exercise, usually on a treadmill **(Fig. 267-3)**. The test consists of a standardized incremental increase in external workload **(Table 267-2)** while symptoms, the ECG, and arm blood pressure are monitored. Exercise duration is usually symptom-limited, and the test is discontinued upon evidence of chest discomfort, severe shortness of breath, dizziness, severe fatigue, ST-segment depression >0.2 mV (2 mm), a fall in systolic blood pressure >10 mmHg, or the development of a ventricular tachyarrhythmia. This test is used to discover any limitation in exercise performance, detect typical ECG signs of myocardial ischemia, and establish their relationship to chest discomfort. The ischemic ST-segment response generally is defined as flat or downsloping depression of the ST segment >0.1 mV below baseline (i.e., the PR segment) and lasting longer than 0.08 s (Fig. 267-2). Upsloping or junctional ST-segment changes are not considered characteristic of ischemia and do not constitute a positive test. Although T-wave abnormalities, conduction disturbances, and ventricular arrhythmias that develop during exercise should be noted, they are also not diagnostic. Negative exercise tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered nondiagnostic.

In interpreting ECG stress tests, the probability that coronary artery disease (CAD) exists in the patient or population under study (i.e., pretest probability) should be considered. Overall, false-positive or false-negative results occur in one-third of cases. However, a positive result on exercise indicates that the likelihood of CAD is 98% in males who are >50 years with a history of typical angina pectoris and who develop chest discomfort during the test. The likelihood decreases if the patient has atypical or no chest pain by history and/or during the test.

The incidence of false-positive tests is significantly increased in patients with low probabilities of IHD, such as asymptomatic men age <40 or premenopausal women with no risk factors for premature atherosclerosis. It is also increased in patients taking cardioactive drugs, such as digitalis and antiarrhythmic agents, and in those with intraventricular conduction disturbances, resting ST-segment and T-wave abnormalities, ventricular hypertrophy, or abnormal serum potassium levels. Obstructive disease limited to the circumflex coronary artery may result in a false-negative stress test since the lateral portion of the heart that this vessel supplies is not well represented on the surface 12-lead ECG. Since the overall sensitivity of exercise stress electrocardiography is only ~75%, a negative result does not exclude CAD, although it makes the likelihood of three-vessel or left main CAD extremely unlikely.

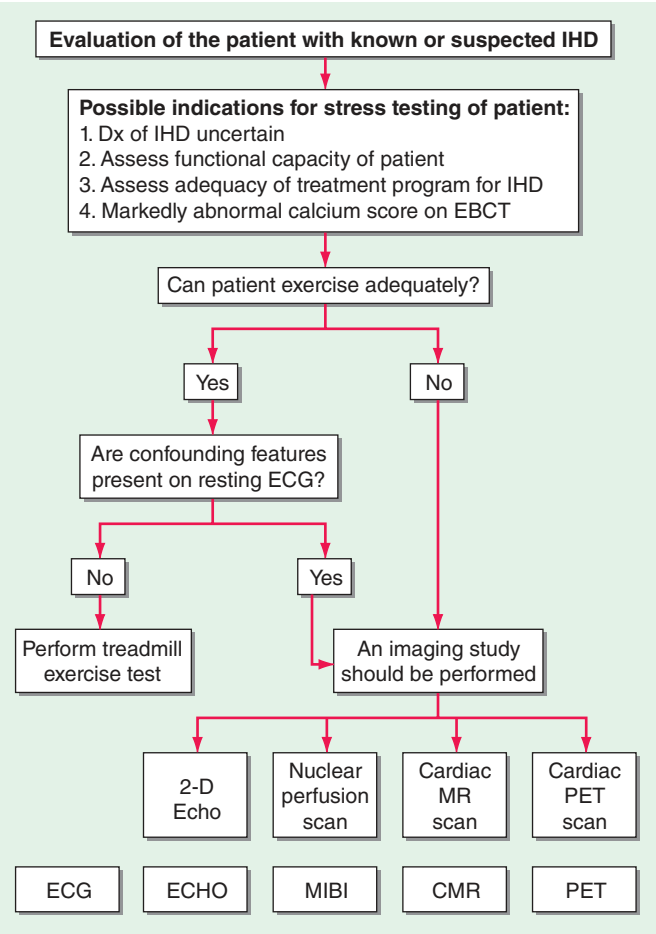
A medical professional should be present throughout the exercise test. It is important to measure total duration of exercise, the times to the onset of ischemic ST-segment change and chest discomfort, the external work performed (generally expressed as the stage of exercise), and the internal cardiac work performed, i.e., by the heart rate–blood pressure product. The depth of the ST-segment depression and the time needed for recovery of these ECG changes are also important. Because the risks of exercise testing are small but real—estimated at one fatality and two nonfatal complications per 10,000 tests—equipment for resuscitation should be available. Modified (heart rate–limited rather than symptom-limited) exercise tests can be performed safely in patients as early as 6 days after uncomplicated myocardial infarction (Table 267-2). Contraindications to exercise stress testing include rest angina within 48 h, unstable rhythm, severe aortic stenosis, acute myocarditis, uncontrolled heart failure, severe pulmonary hypertension, and active infective endocarditis.

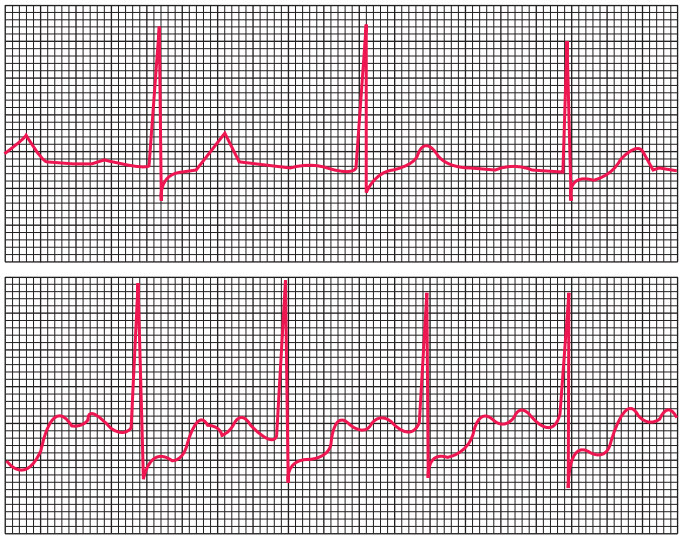
The normal response to graded exercise includes progressive increases in heart rate and blood pressure. Failure of the blood pressure to increase or an actual decrease with signs of ischemia during the test is an important adverse prognostic sign, since it may reflect ischemia-induced global LV dysfunction. The development of angina and/or severe (>0.2 mV) ST-segment depression at a low workload, i.e., before completion of stage II of the Bruce protocol, and/or ST-segment depression that persists >5 min after the termination of exercise increases the specificity of the test and suggests severe IHD and a high risk of future adverse events.

Cardiac Imaging **(See also Chap. 236)** When the resting ECG is abnormal (e.g., preexcitation syndrome, >1 mm of resting ST-segment depression, left bundle branch block, paced ventricular rhythm), information gained from an exercise test can be enhanced by stress myocardial radionuclide perfusion imaging after the intravenous administration of thallium-201 or 99m-technetium sestamibi

during exercise (or with pharmacologic) stress. Contemporary data also suggest positron emission tomography (PET) imaging (with exercise or pharmacologic stress) using N-13 ammonia or rubidium-82 nuclide as another technique for assessing perfusion. Images obtained immediately after cessation of exercise to detect regional ischemia are compared with those obtained at rest to confirm reversible ischemia and regions of persistently absent uptake that signify infarction.

A sizable fraction of patients who need noninvasive stress testing to identify myocardial ischemia and increased risk of coronary events cannot exercise because of peripheral vascular or musculoskeletal disease, exertional dyspnea, or deconditioning. In these circumstances, an intravenous pharmacologic challenge is used in place of exercise. For example, dipyridamole or adenosine can be given to create a coronary "steal" by temporarily increasing flow in nondiseased segments of the coronary vasculature at the expense of diseased segments. Alternatively, a graded incremental infusion of dobutamine may be administered to increase MVO_2. A variety of imaging options are available to accompany these pharmacologic stressors (Fig. 267-3). The development of a transient perfusion defect with a tracer such as thallium-201 or 99m-technetium sestamibi is used to detect myocardial ischemia.





A

FIGURE 267-3 Evaluation of the patient with known or suspected ischemic heart disease. On the left of the figure is an algorithm for identifying patients who should be referred for stress testing and the decision pathway for determining whether a standard treadmill exercise with electrocardiogram (ECG) monitoring alone is adequate. A specialized imaging study is necessary if the patient cannot exercise adequately (pharmacologic challenge is given) or if there are confounding features on the resting ECG (symptom-limited treadmill exercise may be used to stress the coronary circulation). Panels B–E on the next page are examples of the data obtained with ECG monitoring and specialized imaging procedures. CMR, cardiac magnetic resonance; EBCT, electron beam computed tomography; ECHO, echocardiography; IHD, ischemic heart disease; MIBI, methoxyisobutyl isonitrite; MR, magnetic resonance; PET, positron emission tomography. ***A.*** Lead V_4 at rest (*top panel*) and after 4.5 min of exercise (*bottom panel*). There is 3 mm (0.3 mV) of horizontal ST-segment depression, indicating a positive test for ischemia. *(Modified from BR Chaitman, in E Braunwald et al [eds]: Heart Disease, 8th ed, Philadelphia, Saunders, 2008.)* ***B.*** A 45-year-old avid jogger who began experiencing classic substernal chest pressure underwent an exercise echo study. With exercise the patient's heart rate increased from 52 to 153 beats/min. The left ventricular chamber dilated with exercise, and the septal and apical portions became akinetic to dyskinetic (*red arrow*). These findings are strongly suggestive of a significant flow-limiting stenosis in the proximal left anterior descending artery, which was confirmed at coronary angiography. *(Modified from SD Solomon, in E. Braunwald et al [eds]: Primary Cardiology, 2nd ed, Philadelphia, Saunders, 2003.)* ***C.*** Stress and rest myocardial perfusion single-photon emission computed tomography images obtained with 99m-technetium sestamibi in a patient with chest pain and dyspnea on exertion. The images demonstrate a medium-size and severe stress perfusion defect involving the inferolateral and basal inferior walls, showing nearly complete reversibility, consistent with moderate ischemia in the right coronary artery territory (*red arrows*). *(Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)* ***D.*** A patient with a prior myocardial infarction presented with recurrent chest discomfort. On cardiac magnetic resonance (CMR) cine imaging, a large area of anterior akinesia was noted (marked by the *arrows* in the top left and right images, systolic frame only). This area of akinesia was matched by a larger extent of late gadolinium-DTPA enhancements consistent with a large transmural myocardial infarction (marked by *arrows* in the middle left and right images). Resting (*bottom left*) and adenosine vasodilating stress (*bottom right*) first-pass perfusion images revealed reversible perfusion abnormality that extended to the inferior septum. This patient was found to have an occluded proximal left anterior descending coronary artery with extensive collateral formation. This case illustrates the utility of different modalities in a CMR examination in characterizing ischemic and infarcted myocardium. DTPA, diethylenetriamine penta-acetic acid. *(Images provided by Dr. Raymond Kwong, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA.)* ***E.*** Stress and rest myocardial perfusion PET images obtained with rubidium-82 in a patient with chest pain on exertion. The images demonstrate a large and severe stress perfusion defect involving the mid and apical anterior, anterolateral, and anteroseptal walls and the left ventricular apex, showing complete reversibility, consistent with extensive and severe ischemia in the mid-left anterior descending coronary artery territory (*red arrows*). *(Images provided by Dr. Marcello Di Carli, Nuclear Medicine Division, Brigham and Women's Hospital, Boston, MA.)*

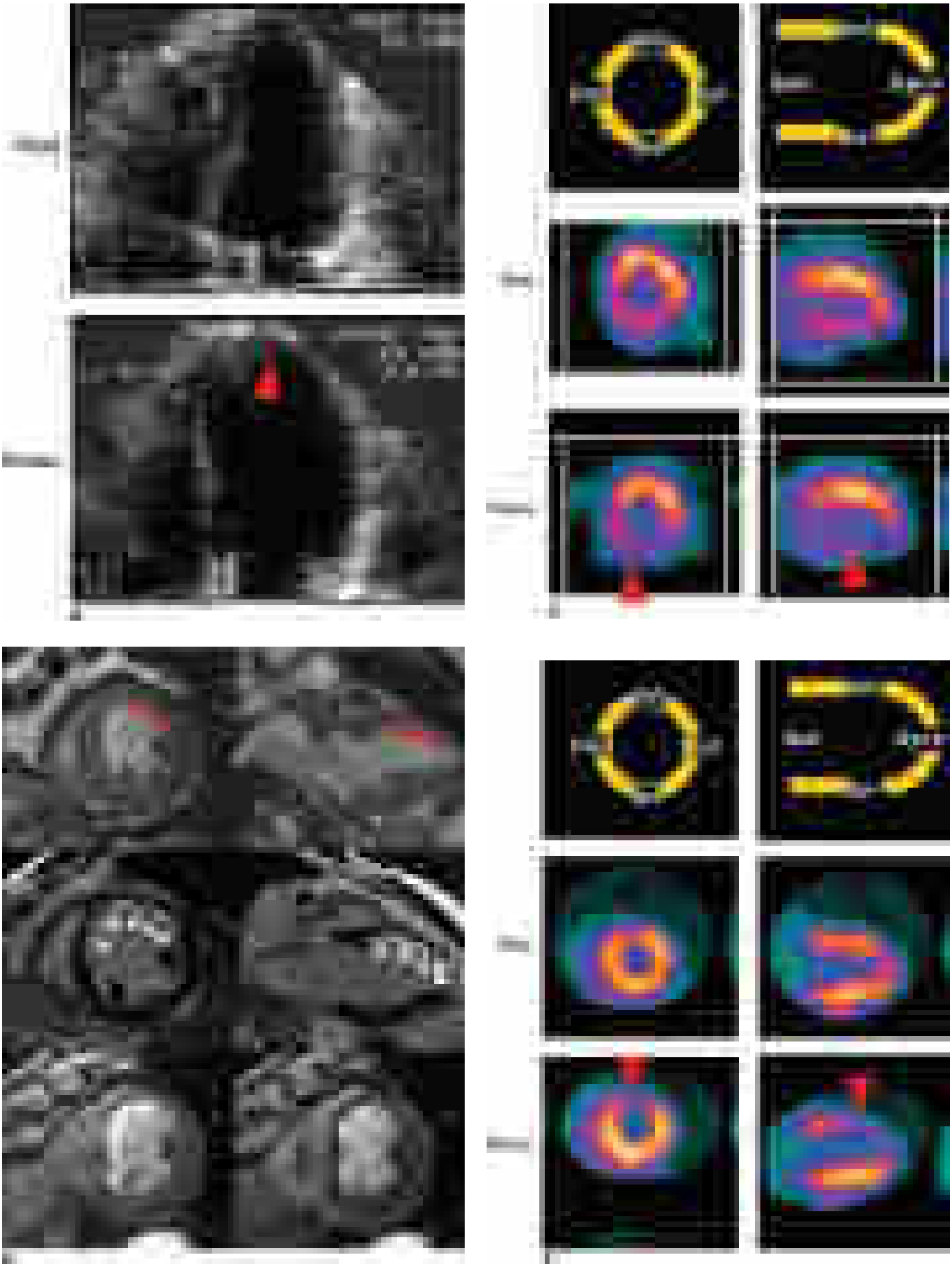


FIGURE 267-3 (*Continued*)

TABLE 267-2 Relation of Metabolic Equivalent Tasks (METs) to Stages in Various Testing Protocols

FUNCTIONAL CLASS	CLINICAL STATUS				O_2 COST mL/kg/min	METs	TREADMILL PROTOCOLS			
							BRUCE Modified 3 min Stages		BRUCE 3 min Stages	
							MPH	%GR	MPH	%GR
							6.0	22	6.0	22
	HEALTHY; DEPENDENT ON AGE, ACTIVITY						5.5	20	5.2	20
							5.0	18	5.0	18
					56.0	16				
NORMAL					52.5	15				
AND					49.0	14				
I					45.5	13	4.2	16	4.2	16
					42.0	12				
					38.5	11	3.4	14	3.4	14
		SEDENTARY HEALTHY			35.0	10				
					31.5	9				
					28.0	8				
			LIMITED		24.5	7	2.5	12	2.5	12
II				SYMPTOMATIC	21.0	6				
					17.5	5	1.7	10	1.7	10
III					14.0	4				
					10.5	3	1.7	5		
					7.0	2	1.7	0		
IV					3.5	1				

Note: The standard Bruce treadmill protocol (right hand column) begins at 1.7 MPH and 10% gradient (GR) and progresses every 3 min to a higher speed and elevation. The corresponding oxygen consumption and clinical status of the patient are shown in the center and left hand columns.

Abbreviations: GR, grade; MPH, miles per hour.

Source: Modified from GF Fletcher et al: Circulation 104:1694, 2001.

Echocardiography is used to assess LV function in patients with chronic stable angina and patients with a history of a prior myocardial infarction, pathologic Q waves, or clinical evidence of heart failure. Two-dimensional echocardiography can assess both global and regional wall motion abnormalities of the left ventricle that are transient when due to ischemia. Stress (exercise or dobutamine) echocardiography may cause the emergence of regions of akinesis or dyskinesis that are not present at rest. Stress echocardiography, like stress myocardial perfusion imaging, is more sensitive than exercise electrocardiography in the diagnosis of IHD. Cardiac magnetic resonance (CMR) stress testing is also evolving as an alternative to radionuclide, PET, or echocardiographic stress imaging. CMR stress testing performed with dobutamine infusion can be used to assess wall motion abnormalities accompanying ischemia, as well as myocardial perfusion. CMR can be used to provide more complete ventricular evaluation using multislice magnetic resonance imaging (MRI) studies.

Atherosclerotic plaques become progressively calcified over time, and coronary calcification in general increases with age. For this reason, methods for detecting coronary calcium have been developed as a measure of the presence of coronary atherosclerosis. These methods involve computed tomography (CT) applications that achieve rapid acquisition of images (electron beam [EBCT] and multidetector [MDCT] detection). Coronary calcium detected by these imaging techniques most commonly is quantified by using the Agatston score, which is based on the area and density of calcification. Although the diagnostic accuracy of this imaging method is high (sensitivity, 90–94%; specificity, 95–97%; negative predictive value, 93–99%), its prognostic utility has not been defined. Thus, its role in CT, EBCT, and MDCT scans for the detection and management of patients with IHD has not been clarified.

CORONARY ARTERIOGRAPHY

(See also Chap. 237) This diagnostic method outlines the lumina of the coronary arteries and can be used to detect or exclude serious coronary obstruction. However, coronary arteriography provides no information about the arterial wall, and severe atherosclerosis that does not encroach on the lumen may go undetected. Of note, atherosclerotic plaques characteristically are scattered throughout the coronary tree, tend to occur more frequently at branch points, and grow progressively in the intima and media of an epicardial coronary artery at first without encroaching on the lumen, causing an outward bulging of the artery—a process referred to as remodeling. Later in the course of the disease, further growth causes luminal narrowing.

Indications Coronary arteriography is indicated in (1) patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are being considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); (2) patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD; (3) patients with known or possible angina pectoris who have survived cardiac arrest; (4) patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction; and (5) patients judged to be at high risk of sustaining coronary events based on signs of severe ischemia on noninvasive testing, regardless of the presence or severity of symptoms (see below).

Examples of other indications for coronary arteriography include the following:

1. Patients with chest discomfort suggestive of angina pectoris but a negative or nondiagnostic stress test who require a definitive diagnosis for guiding medical management, alleviating psychological stress, career or family planning, or insurance purposes.
2. Patients who have been admitted repeatedly to the hospital for a suspected acute coronary syndrome **(Chaps. 268 and 269)**, but in whom this diagnosis has not been established and in whom the presence or absence of CAD should be determined.
3. Patients with careers that involve the safety of others (e.g., pilots, firefighters, police) who have questionable symptoms or suspicious or positive noninvasive tests and in whom there are reasonable doubts about the state of the coronary arteries.
4. Patients with aortic stenosis or hypertrophic cardiomyopathy and angina in whom the chest pain could be due to IHD.

5. Male patients >45 years and females >55 years who are to undergo a cardiac operation such as valve replacement or repair and who may or may not have clinical evidence of myocardial ischemia.
6. Patients after myocardial infarction, especially those who are at high risk after myocardial infarction because of the recurrence of angina or the presence of heart failure, frequent ventricular premature contractions, or signs of ischemia on the stress test.
7. Patients with angina pectoris, regardless of severity, in whom noninvasive testing indicates a high risk of coronary events (poor exercise performance or severe ischemia).
8. Patients in whom coronary spasm or another nonatherosclerotic cause of myocardial ischemia (e.g., coronary artery anomaly, Kawasaki disease) is suspected.

Noninvasive alternatives to diagnostic coronary arteriography include CT angiography and CMR angiography **(Chap. 236)**. Although these new imaging techniques can provide information about obstructive lesions in the epicardial coronary arteries, their exact role in clinical practice has not been rigorously defined. Important aspects of their use that should be noted include the substantially higher radiation exposure with CT angiography compared to conventional diagnostic arteriography and the limitations on CMR imposed by cardiac movement during the cardiac cycle, especially at high heart rates.

PROGNOSIS

The principal prognostic indicators in patients known to have IHD are age, the functional state of the left ventricle, the location(s) and severity of coronary artery narrowing, and the severity or activity of myocardial ischemia. Angina pectoris of recent onset, unstable angina **(Chap. 268)**, early postmyocardial infarction angina, angina that is unresponsive or poorly responsive to medical therapy, and angina accompanied by symptoms of congestive heart failure all indicate an increased risk for adverse coronary events. The same is true for the physical signs of heart failure, episodes of pulmonary edema, transient third heart sounds, and mitral regurgitation and for echocardiographic or radioisotopic (or roentgenographic) evidence of cardiac enlargement and reduced (<0.40) ejection fraction.

Most important, any of the following signs during noninvasive testing indicates a high risk for coronary events: inability to exercise for 6 min, i.e., stage II (Bruce protocol) of the exercise test; a strongly positive exercise test showing onset of myocardial ischemia at low workloads (≥0.1 mV ST-segment depression before completion of stage II, ≥0.2 mV ST-segment depression at any stage, ST-segment depression for >5 min after the cessation of exercise, a decline in systolic pressure >10 mmHg during exercise, or the development of ventricular tachyarrhythmias during exercise); the development of large or multiple perfusion defects or increased lung uptake during stress radioisotope perfusion imaging; and a decrease in LV ejection fraction during exercise on radionuclide ventriculography or during stress echocardiography. Conversely, patients who can complete stage III of the Bruce exercise protocol and have a normal stress perfusion scan or negative stress echocardiographic evaluation are at very low risk for future coronary events. The finding of frequent episodes of ST-segment deviation on ambulatory ECG monitoring (even in the absence of symptoms) is also an adverse prognostic finding.

On cardiac catheterization, elevations of LV end-diastolic pressure and ventricular volume and reduced ejection fraction are the most important signs of LV dysfunction and are associated with a poor prognosis. Patients with chest discomfort but normal LV function and normal coronary arteries have an excellent prognosis. Obstructive lesions of the left main (>50% luminal diameter) or left anterior descending coronary artery proximal to the origin of the first septal artery are associated with a greater risk than are lesions of the right or left circumflex coronary artery because of the greater quantity of myocardium at risk. Atherosclerotic plaques in epicardial arteries with fissuring or filling defects indicate increased risk. These lesions go through phases of inflammatory cellular activity, degeneration, endothelial dysfunction, abnormal vasomotion, platelet aggregation, and fissuring or hemorrhage. These factors can temporarily worsen the stenosis and cause thrombosis and/or abnormal reactivity of the vessel wall, thus exacerbating the manifestations of ischemia. The recent onset of symptoms, the development of severe ischemia during stress testing (see above), and unstable angina pectoris **(Chap. 268)** all reflect episodes of rapid progression in coronary lesions.

With any degree of obstructive CAD, mortality is greatly increased when LV function is impaired; conversely, at any level of LV function, the prognosis is influenced importantly by the quantity of myocardium perfused by critically obstructed vessels. Therefore, it is essential to collect all the evidence substantiating past myocardial damage (evidence of myocardial infarction on ECG, echocardiography, radioisotope imaging, or left ventriculography), residual LV function (ejection fraction and wall motion), and risk of future damage from coronary events (extent of coronary disease and severity of ischemia defined by noninvasive stress testing). The larger the quantity of established myocardial necrosis is, the less the heart is able to withstand additional damage and the poorer the prognosis is. Risk estimation must include age, presenting symptoms, all risk factors, signs of arterial disease, existing cardiac damage, and signs of impending damage (i.e., ischemia).

The greater the number and severity of risk factors for coronary atherosclerosis (advanced age [>75 years], hypertension, dyslipidemia, diabetes, morbid obesity, accompanying peripheral and/or cerebrovascular disease, previous myocardial infarction), the worse the prognosis of an angina patient. Evidence exists that elevated levels of CRP in the plasma, extensive coronary calcification on electron beam CT (see above), and increased carotid intimal thickening on ultrasound examination also indicate an increased risk of coronary events.

TREATMENT

Stable Angina Pectoris

Once the diagnosis of IHD has been made, each patient must be evaluated individually with respect to his or her level of understanding, expectations and goals, control of symptoms, and prevention of adverse clinical outcomes such as myocardial infarction and premature death. The degree of disability and the physical and emotional stress that precipitates angina must be recorded carefully to set treatment goals. The management plan should include the following components: (1) explanation of the problem and reassurance about the ability to formulate a treatment plan, (2) identification and treatment of aggravating conditions, (3) recommendations for adaptation of activity as needed, (4) treatment of risk factors that will decrease the occurrence of adverse coronary outcomes, (5) drug therapy for angina, and (6) consideration of revascularization.

EXPLANATION AND REASSURANCE

Patients with IHD need to understand their condition and realize that a long and productive life is possible even though they have angina pectoris or have experienced and recovered from an acute myocardial infarction. Offering results of clinical trials showing improved outcomes can be of great value in encouraging patients to resume or maintain activity and return to work. A planned program of rehabilitation can encourage patients to lose weight, improve exercise tolerance, and control risk factors with more confidence.

IDENTIFICATION AND TREATMENT OF AGGRAVATING CONDITIONS

A number of conditions may increase oxygen demand or decrease oxygen supply to the myocardium and may precipitate or exacerbate angina in patients with IHD. LVH, aortic valve disease, and hypertrophic cardiomyopathy may cause or contribute to angina and should be excluded or treated. Obesity, hypertension, and hyperthyroidism should be treated aggressively to reduce the frequency and severity of anginal episodes. Decreased myocardial oxygen supply may be due to reduced oxygenation of the arterial blood (e.g., in pulmonary disease or, when carboxyhemoglobin is present, due to cigarette or cigar smoking) or decreased oxygen-carrying

capacity (e.g., in anemia). Correction of these abnormalities, if present, may reduce or even eliminate angina pectoris.

ADAPTATION OF ACTIVITY

Myocardial ischemia is caused by a discrepancy between the demand of the heart muscle for oxygen and the ability of the coronary circulation to meet that demand. Most patients can be helped to understand this concept and utilize it in the rational programming of activity. Many tasks that ordinarily evoke angina may be accomplished without symptoms simply by reducing the speed at which they are performed. Patients must appreciate the diurnal variation in their tolerance of certain activities and should reduce their energy requirements in the morning, immediately after meals, and in cold or inclement weather. On occasion, it may be necessary to recommend a change in employment or residence to avoid physical stress.

Physical conditioning usually improves the exercise tolerance of patients with angina and has substantial psychological benefits. A regular program of isotonic exercise that is within the limits of the individual patient's threshold for the development of angina pectoris and that does not exceed 80% of the heart rate associated with ischemia on exercise testing should be strongly encouraged. Based on the results of an exercise test, the number of metabolic equivalent tasks (METs) performed at the onset of ischemia can be estimated (Table 267-2) and a practical exercise prescription can be formulated to permit daily activities that will fall below the ischemic threshold **(Table 267-3)**.

TREATMENT OF RISK FACTORS

A *family history* of premature IHD is an important indicator of increased risk and should trigger a search for treatable risk factors such as hyperlipidemia, hypertension, and diabetes mellitus. *Obesity* impairs the treatment of other risk factors and increases the risk of adverse coronary events. In addition, obesity often is accompanied by three other risk factors: diabetes mellitus, hypertension, and hyperlipidemia. The treatment of obesity and these accompanying risk factors is an important component of any management plan. A diet low in saturated and *trans*-unsaturated fatty acids and a reduced caloric intake to achieve optimal body weight are a cornerstone in the management of chronic IHD. It is especially important to emphasize weight loss and regular exercise in patients with the metabolic syndrome or overt diabetes mellitus.

Cigarette smoking accelerates coronary atherosclerosis in both sexes and at all ages and increases the risk of thrombosis, plaque instability, myocardial infarction, and death. In addition, by increasing myocardial oxygen needs and reducing oxygen supply, it aggravates angina. Smoking cessation studies have demonstrated important benefits with a significant decline in the occurrence of these adverse outcomes. Noncombustible tobacco in the form of electronic cigarettes (nicotine delivery systems) may also increase the frequency of anginal episodes. The physician's message must be clear and strong and supported by programs that achieve and monitor abstinence of tobacco product use **(Chap. 448)**.

Hypertension **(Chap. 271)** is associated with an increased risk of adverse clinical events from coronary atherosclerosis as well as stroke. In addition, the LVH that results from sustained hypertension aggravates ischemia. There is evidence that long-term effective treatment of hypertension can decrease the occurrence of adverse coronary events **(Chap. 271)**.

Diabetes mellitus **(Chap. 396)** accelerates coronary and peripheral atherosclerosis and is frequently associated with dyslipidemias and increases in the risk of angina, myocardial infarction, and sudden coronary death. Aggressive control of the dyslipidemia (target LDL cholesterol <70 mg/dL) and hypertension (target blood pressure 120/80 mmHg) that are frequently found in diabetic patients is highly effective and therefore essential, as described below.

DYSLIPIDEMIA

The treatment of dyslipidemia is central in aiming for long-term relief from angina, reduced need for revascularization, and reduction in myocardial infarction and death. The control of lipids can be achieved by the combination of a diet low in saturated and *trans*-unsaturated fatty acids, exercise, and weight loss. Nearly always, HMG-CoA reductase inhibitors (statins) are required and can lower LDL cholesterol (25–50%), raise HDL cholesterol (5–9%), and lower

TABLE 267-3 Energy Requirements for Some Common Activities

LESS THAN 3 METs	3–5 METs	5–7 METs	7–9 METs	MORE THAN 9 METs
Self-Care				
Washing/shaving	Cleaning windows	Easy digging in garden	Heavy shoveling	Carrying loads up stairs (objects more than 90 lb)
Dressing	Raking	Level hand lawn mowing	Carrying objects (60–90 lb)	Climbing stairs (quickly)
Light housekeeping	Power lawn mowing	Carrying objects (30–60 lb)		Shoveling heavy snow
Desk work	Bed making/stripping			
Driving auto	Carrying objects (15–30 lb)			
Occupational				
Sitting (clerical/assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Heavy labor
Desk work	Light welding/carpentry	Shoveling dirt		
Standing (store clerk)		Sawing wood		
Recreational				
Golf (cart)	Dancing (social)	Tennis (singles)	Canoeing	Squash
Knitting	Golf (walking)	Snow skiing (downhill)	Mountain climbing	Ski touring
	Sailing	Light backpacking		Vigorous basketball
	Tennis (doubles)	Basketball		
		Stream fishing		
Physical Conditioning				
Walking (2 mph)	Level walking (3–4 mph)	Level walking (4.5–5.0 mph)	Level jogging (5 mph)	Running more than 6 mph
Stationary bike	Level biking (6–8 mph)	Bicycling (9–10 mph)	Swimming (crawl stroke)	Bicycling (more than 13 mph)
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Rope jumping
			Heavy calisthenics	Walking uphill (5 mph)
			Bicycling (12 mph)	

Abbreviation: METs, metabolic equivalent tasks.

Source: Modified from WL Haskell: Rehabilitation of the coronary patient, in NK Wenger, HK Hellerstein (eds): *Design and Implementation of Cardiac Conditioning Program*. New York, Churchill Livingstone, 1978.

triglycerides (5–30%). A powerful treatment effect of statins on atherosclerosis, IHD, and outcomes is seen regardless of the pretreatment LDL cholesterol level. Fibrates or niacin can be used to raise HDL cholesterol and lower triglycerides **(Chap. 400)**. Controlled trials with lipid-regulating regimens have shown equal proportional benefit for men, women, the elderly, diabetic patients, and smokers. Injectable monoclonal antibodies against PCSK9 are now available and are capable of producing dramatic lowering of LDL cholesterol beyond that achieved with a statin alone.

Compliance with the health-promoting behaviors listed above is generally very poor, and a conscientious physician must not underestimate the major effort required to meet this challenge. Many patients who are discharged from the hospital with proven coronary disease do not receive adequate treatment for dyslipidemia. In light of the proof that treating dyslipidemia brings major benefits, physicians need to establish treatment pathways, monitor compliance, and follow up regularly.

RISK REDUCTION IN WOMEN WITH IHD

The incidence of clinical IHD in premenopausal women is very low; however, after menopause, the atherogenic risk factors increase (e.g., increased LDL, reduced HDL) and the rate of clinical coronary events accelerates to the levels observed in men. Women have not given up cigarette smoking as effectively as have men. Diabetes mellitus, which is more common in women, greatly increases the occurrence of clinical IHD and amplifies the deleterious effects of hypertension, hyperlipidemia, and smoking. Cardiac catheterization and coronary revascularization are underused in women and are performed at a later and more severe stage of the disease than in men. When cholesterol lowering, beta blockers after myocardial infarction, and CABG are applied in the appropriate patient groups, women benefit to the same degree as men.

DRUG THERAPY

The commonly used drugs for the treatment of angina pectoris are summarized in **Tables 267-4 through 267-6**. Pharmacotherapy for IHD is designed to reduce the frequency of anginal episodes, myocardial infarction, and coronary death. Trial data emphasize how important medical management is when added to the health-promoting behaviors discussed above. To achieve maximum benefit from medical therapy for IHD, it is frequently necessary to combine agents from different classes and titrate the doses as guided by the individual profile of risk factors, symptoms, hemodynamic responses, and side effects.

TABLE 267-4 Nitrate Therapy in Patients with Ischemic Heart Disease

PREPARATION OF AGENT	DOSE	SCHEDULE
Nitroglycerin[a]		
Ointment	0.5–2 in.	Two or three times daily
Transdermal patch	0.2–0.8 mg/h	Every 24 h; remove at bedtime for 12–14 h
Sublingual tablet	0.3–0.6 mg	As needed, up to three doses 5 min apart
Spray	One or two sprays	As needed, up to three doses 5 min apart
Isosorbide dinitrate[a]		
Oral	10–40 mg	Two or three times daily
Oral sustained release	80–120 mg	Once or twice daily (eccentric schedules)
Isosorbide 5-mononitrate		
Oral	20 mg	Twice daily (given 7–8 h apart)
Oral sustained release	30–240 mg	Once daily

[a]A 10- to 12-h nitrate-free interval is recommended.

Source: Modified from DA Morrow, WE Boden: Stable ischemic heart disease. In RO Bonow et al (eds): *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 9th ed. Philadelphia, Saunders, 2012, p. 1224.

TABLE 267-5 Properties of Beta Blockers in Clinical Use for Ischemic Heart Disease

DRUGS	SELECTIVITY	PARTIAL AGONIST ACTIVITY	USUAL DOSE FOR ANGINA
Acebutolol	β_1	Yes	200–600 mg twice daily
Atenolol	β_1	No	50–200 mg/d
Betaxolol	β_1	No	10–20 mg/d
Bisoprolol	β_1	No	10 mg/d
Esmolol (intravenous)[a]	β_1	No	50–300 μg/kg/min
Labetalol[b]	None	Yes	200–600 mg twice daily
Metoprolol	β_1	No	50–200 mg twice daily
Nadolol	None	No	40–80 mg/d
Nebivolol	β_1 (at low doses)	No	5–40 mg/d
Pindolol	None	Yes	2.5–7.5 mg 3 times daily
Propranolol	None	No	80–120 mg twice daily
Timolol	None	No	10 mg twice daily

[a]Esmolol is an ultra-short-acting beta blocker that is administered as a continuous intravenous infusion. Its rapid offset of action makes esmolol an attractive agent to use in patients with relative contraindications to beta blockade. [b]Labetolol is a combined alpha and beta blocker.

Note: This list of beta blockers that may be used to treat patients with angina pectoris is arranged alphabetically. The agents for which there is the greatest clinical experience include atenolol, metoprolol, and propranolol. It is preferable to use a sustained-release formulation that may be taken once daily to improve the patient's compliance with the regimen.

Source: Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

NITRATES

The organic nitrates are a valuable class of drugs in the management of angina pectoris (Table 267-4). Their major mechanisms of action include systemic venodilation with concomitant reduction in LV

TABLE 267-6 Calcium Channel Blockers in Clinical Use for Ischemic Heart Disease

DRUGS	USUAL DOSE	DURATION OF ACTION	SIDE EFFECTS
Dihydropyridines			
Amlodipine	5–10 mg qd	Long	Headache, edema
Felodipine	5–10 mg qd	Long	Headache, edema
Isradipine	2.5–10 mg bid	Medium	Headache, fatigue
Nicardipine	20–40 mg tid	Short	Headache, dizziness, flushing, edema
Nifedipine	Immediate release:[a] 30–90 mg daily orally Slow release: 30–180 mg orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
Nisoldipine	20–40 mg qd	Short	Similar to nifedipine
Nondihydropyridines			
Diltiazem	Immediate release: 30–80 mg 4 times daily Slow release: 120–320 mg qd	Short Long	Hypotension, dizziness, flushing, bradycardia, edema
Verapamil	Immediate release: 80–160 mg tid Slow release: 120–480 mg qd	Short Long	Hypotension, myocardial depression, heart failure, edema, bradycardia

[a]May be associated with increased risk of mortality if administered during acute myocardial infarction.

Note: This list of calcium channel blockers that may be used to treat patients with angina pectoris is divided into two broad classes, dihydropyridines and nondihydropyridines, and arranged alphabetically within each class. Among the dihydropyridines, the greatest clinical experience has been obtained with amlodipine and nifedipine. After the initial period of dose titration with a short-acting formulation, it is preferable to switch to a sustained-release formulation that may be taken once daily to improve patient compliance with the regimen.

Source: Data from RJ Gibbons et al: J Am Coll Cardiol 41:159, 2003.

end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.

The absorption of these agents is rapid and complete through mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also ~5 min before activities that are likely to induce an episode. The value of this prophylactic use of the drug cannot be overemphasized.

Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with Prinzmetal's variant angina **(Chap. 268)**. A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

Long-Acting Nitrates None of the long-acting nitrates is as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route (Table 267-4). They provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of nitrate tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

β-Adrenergic Blockers These drugs represent an important component of the pharmacologic treatment of angina pectoris (Table 267-5). They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing (Table 267-5). The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents.

Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, LV failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative β_1-receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers Calcium channel blockers (Table 267-6) are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Because of differences in the dose-response relationship on cardiac electrical activity between the dihydropyridine and nondihydropyridine calcium channel blockers, verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate LV failure, particularly when used in patients with LV dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Variant (Prinzmetal's) angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates **(Chap. 268)**.

Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta blocker therapy.

Choice Between Beta Blockers and Calcium Channel Blockers for Initial Therapy Since beta blockers have been shown to improve life expectancy after acute myocardial infarction **(Chaps. 268 and 269)** and calcium channel blockers have not, the former may also be preferable in patients with angina and a damaged left ventricle. However, calcium channel blockers are indicated in patients with the following: (1) inadequate responsiveness to the combination of beta blockers and nitrates; many of these patients do well with a combination of a beta blocker and a dihydropyridine calcium channel blocker; (2) adverse reactions to beta blockers such as depression, sexual disturbances, and fatigue; (3) angina and a history of asthma or chronic obstructive pulmonary disease; (4) sick-sinus syndrome or significant atrioventricular conduction disturbances; (5) Prinzmetal's angina; or (6) symptomatic peripheral arterial disease.

A comparison of the common side effects, contraindications, and potential drug interactions of many of the frequently presented antianginal agents is shown in **Table 267-7**.

Antiplatelet Drugs Aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 81–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of gastrointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg loading and 75 mg/d) is an oral agent that blocks P2Y12 ADP receptor–mediated platelet aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome **(Chap. 268)** and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery **(Chap. 270)**. Alternative antiplatelet agents that block the P2Y12 platelet receptor such as prasugrel and ticagrelor have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome, but are associated with an increased risk

TABLE 267-7 Antianginal Agents

AGENT	COMMON SIDE EFFECTS	CONTRAINDICATIONS	POTENTIAL DRUG INTERACTIONS
Agents That Have a Physiological Effect			
Short-acting and long-acting nitrates	Headache, flushing, hypotension, syncope and postural hypotension, reflex tachycardia, methemoglobinemia	Hypertrophic obstructive cardiomyopathy	Phosphodiesterase type 5 inhibitors (sildenafil and similar agents), beta-adrenergic blockers, calcium-channel blockers
Beta blockers	Fatigue, depression, bradycardia, heart block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, masked signs of hypoglycemia	Low heart rate or heart conduction disorder, cardiogenic shock, asthma, severe peripheral vascular disease, decompensated heart failure, vasospastic angina; use with caution in patients with COPD (cardio-selective beta blockers may be used if patient receives adequate treatment with long-acting beta agonists)	Heart-rate-lowering calcium-channel blockers, sinus-node or AV conduction depressors
Calcium-channel blockers			
Heart-rate-lowering agents	Bradycardia, heart conduction defect, low ejection fraction, constipation, gingival hyperplasia	Cardiogenic shock, severe aortic stenosis, obstructive cardiomyopathy	CYP3A4 substrates (digoxin, simvastatin, cyclosporine)
Dihydropyridine	Headache, ankle swelling fatigue, flushing, reflex tachycardia	Low heart rate or heart rhythm disorder, sick sinus syndrome, congestive heart failure, low blood pressure	Agents with cardiodepressant effects (beta-blockers, flecainide), CYP3A4 substrates
Agents That Affect Myocardial Metabolism			
Ranolazine	Dizziness, constipation, nausea, QT-interval prolongation	Liver cirrhosis	CYP3A4 substrates (digoxin, simvastatin, cyclosporine), drugs that prolong the corrected QT interval

Abbreviations: COPD, chronic obstructive pulmonary disease; CYP3A4, cytochrome P-450 3A4.

Source: Data from SE Husted: Lancet 386:691, 2015 and EM Ohman: N Engl J Med 374:1167, 2016.

of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

OTHER THERAPIES

The ACE inhibitors are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors are most evident in IHD patients at increased risk, especially if diabetes mellitus or left ventricle dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors to IHD patients who have normal LV function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective.

Despite treatment with nitrates, beta blockers, or calcium channel blockers, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy (see Table 267-7). Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include limitation of the Na overload of ischemic myocytes and prevention of Ca^{2+} overload via the Na^+–Ca^{2+} exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QT_c prolongation and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and large quantities of grapefruit juice) are being used.

Nonsteroidal anti-inflammatory drug (NSAID) use in patients with IHD may be associated with a small but finite increased risk of myocardial infarction and mortality. For this reason, they generally should be avoided in IHD patients. If they are required for symptom relief, it is advisable to coadminister aspirin and strive to use an NSAID associated with the lowest risk of cardiovascular events, in the lowest dose required, and for the shortest period of time.

Another class of agents opens ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. The major drug in this class is nicorandil, which typically is administered orally in a dose of 20 mg twice daily for prevention of angina. (Nicorandil is not available for use in the United States but is used in several other countries.)

Ivabradine (2.5–7.5 mg orally twice daily) is a specific sinus node inhibiting agent that may be helpful for preventing cardiovascular events in patients with IHD who have a resting heart rate ≥70 beats/min (alone or in combination with a beta blocker) *and* LV systolic dysfunction. It does not appear to offer any benefit in patients with IHD but who do *not* have clinical heart failure.

Angina and Heart Failure Transient LV failure with angina can be controlled by the use of nitrates. For patients with established congestive heart failure, the increased LV wall tension raises myocardial oxygen demand. Treatment of congestive heart failure with an ACE inhibitor, a diuretic, and digoxin **(Chap. 252)** reduces heart size, wall tension, and myocardial oxygen demand, which helps control angina and ischemia. If the symptoms and signs of heart failure are controlled, an effort should be made to use beta blockers not only for angina but because trials in heart failure have shown significant improvement in survival. A trial of the intravenous ultra-short-acting beta blocker esmolol may be useful to establish the safety of beta blockade in selected patients. Nocturnal angina often can be relieved by the treatment of heart failure.

The combination of congestive heart failure and angina in patients with IHD usually indicates a poor prognosis and warrants serious consideration of cardiac catheterization and coronary revascularization.

CORONARY REVASCULARIZATION

Clinical trials have confirmed that with the initial diagnosis of stable IHD, it is first appropriate to initiate a medical regimen as described above. Revascularization should be considered in the presence of unstable phases of the disease, intractable symptoms, severe ischemia

or high-risk coronary anatomy, diabetes, and impaired LV function. *Revascularization should be employed in conjunction with but not replace the continuing need to modify risk factors and assess medical therapy.* An algorithm for integrating medical therapy and revascularization options in patients with IHD is shown in Fig. 267-4.

PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 270) PCI involving balloon dilatation usually accompanied by coronary stenting is widely used to achieve revascularization of the myocardium in patients with symptomatic IHD and suitable stenoses of epicardial coronary arteries. Whereas patients with stenosis of the left main coronary artery and those with three-vessel IHD (especially with diabetes and/or impaired LV function) who require revascularization are best treated with CABG, PCI is widely employed in patients with symptoms and evidence of ischemia due to stenoses of one or two vessels and even in selected patients with three-vessel disease (and, perhaps, in some patients with left main disease) and may offer many advantages over surgery.

Indications and Patient Selection The most common clinical indication for PCI is symptom-limiting angina pectoris, despite medical therapy, accompanied by evidence of ischemia during a stress test.

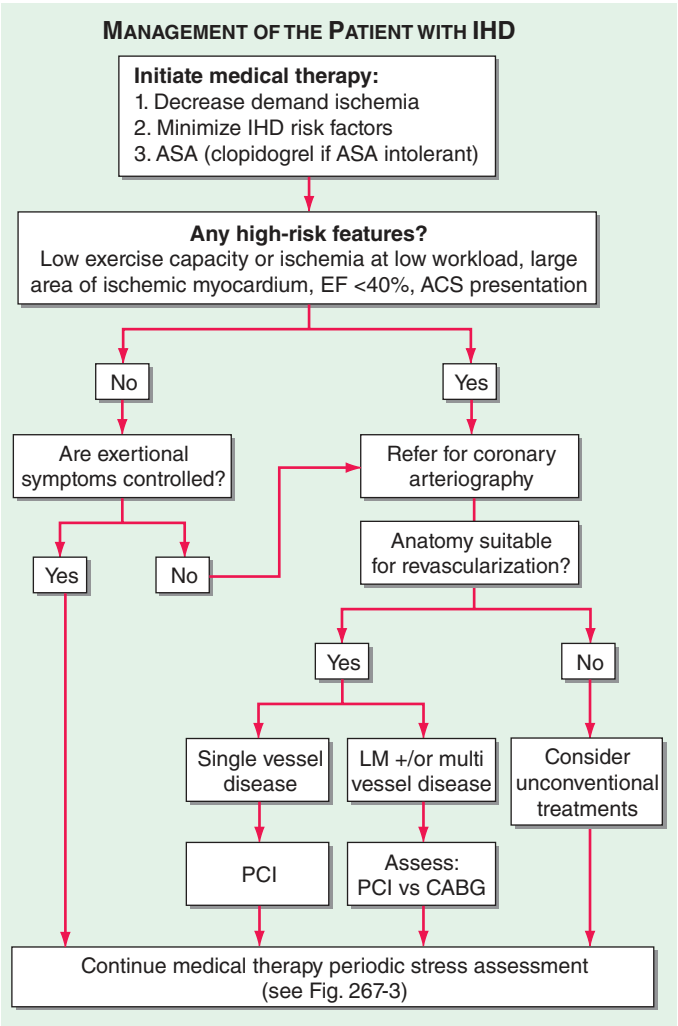


FIGURE 267-4 Algorithm for management of a patient with ischemic heart disease. All patients should receive the core elements of medical therapy as shown at the top of the algorithm. If high-risk features are present, as established by the clinical history, exercise test data, and imaging studies, the patient should be referred for coronary arteriography. Based on the number and location of the diseased vessels and their suitability for revascularization, the patient is treated with a percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery or should be considered for unconventional treatments. See text for further discussion. ACS, acute coronary syndrome; ASA, aspirin; EF, ejection fraction; IHD, ischemic heart disease; LM, left main.

PCI is more effective than medical therapy for the relief of angina. PCI improves outcomes in patients with unstable angina or when used early in the course of myocardial infarction with and without cardiogenic shock. However, in patients with stable exertional angina, clinical trials have confirmed that PCI does not reduce the occurrence of death or myocardial infarction compared to optimum medical therapy. PCI can be used to treat stenoses in native coronary arteries as well as in bypass grafts in patients who have recurrent angina after CABG.

Risks When coronary stenoses are discrete and symmetric, two and even three vessels can be treated in sequence. However, case selection is essential to avoid a prohibitive risk of complications, which are usually due to dissection or thrombosis with vessel occlusion, uncontrolled ischemia, and ventricular failure (Chap. 270). Oral aspirin, a $P2Y_{12}$ antagonist, and an antithrombin agent are given to reduce coronary thrombus formation. Left main coronary artery stenosis generally is regarded as a lesion that should be treated with CABG. In selected cases such as patients with prohibitive surgical risks, PCI of an unprotected left main can be considered, but such a procedure should be performed only by a highly skilled operator; importantly, there are regional differences in the use of this approach internationally.

Efficacy Primary success, i.e., adequate dilation (an increase in luminal diameter >20% to a residual diameter obstruction <50%) with relief of angina, is achieved in >95% of cases. Recurrent stenosis of the dilated vessels occurs in ~20% of cases within 6 months of PCI with bare metal stents, and angina will recur within 6 months in 10% of cases. Restenosis is more common in patients with diabetes mellitus, arteries with small caliber, incomplete dilation of the stenosis, long stents, occluded vessels, obstructed vein grafts, dilation of the left anterior descending coronary artery, and stenoses containing thrombi. In diseased vein grafts, procedural success has been improved by the use of capture devices or filters that prevent embolization, ischemia, and infarction.

It is usual clinical practice to administer aspirin indefinitely and a $P2Y_{12}$ antagonist for 1–3 months after the implantation of a bare metal stent. Although aspirin in combination with a thienopyridine may help prevent coronary thrombosis during and shortly after PCI with stenting, there is no evidence that these medications reduce the incidence of restenosis.

The use of drug-eluting stents that locally deliver antiproliferative drugs can reduce restenosis to much less than 10%. Advances in PCI, especially the availability of drug-eluting stents, have vastly extended the use of this revascularization option in patients with IHD. Of note, however, the delayed endothelial healing in the region of a drug-eluting stent also extends the period during which the patient is at risk for subacute stent thrombosis. Aspirin administered indefinitely and a P2Y12 antagonist daily (dual antiplatelet therapy [DAPT]) for at least 1 year after implantation of a drug-eluting stent. Evidence exists of a benefit of continuing DAPT for up to 30 months, albeit at the cost of a higher risk of bleeding. When a situation arises in which temporary discontinuation of antiplatelet therapy is necessary, the clinical circumstances should be reviewed with the operator who performed the PCI and a coordinated plan should be established for minimizing the risk of late stent thrombus; central to this plan is the discontinuation of antiplatelet therapy for the shortest acceptable period. The risk of stent thrombosis is dependent on stent size and length, complexity of the lesions, age, diabetes, and technique. However, compliance with DAPT and individual responsiveness to platelet inhibition are very important factors as well.

Successful PCI produces effective relief of angina in >95% of cases. The majority of patients with symptomatic IHD who require revascularization can be treated initially by PCI. Successful PCI is less invasive and expensive than CABG and permits savings in the *initial* cost of care. Successful PCI avoids the risk of stroke associated with CABG surgery, allows earlier return to work, and allows the resumption of an active life. However, the early health-related and economic benefit of PCI is reduced over time because of the greater need for follow-up and the increased need for repeat procedures. When directly compared in patients with diabetes or three-vessel or left main CAD, CABG was

superior to PCI in preventing major adverse cardiac or cerebrovascular events over a 12-month follow-up.

CORONARY ARTERY BYPASS GRAFTING

Anastomosis of one or both of the internal mammary arteries or a radial artery to the coronary artery distal to the obstructive lesion is the preferred procedure. For additional obstructions that cannot be bypassed by an artery, a section of a vein (usually the saphenous) is used to form a venous bypass conduit between the aorta and the coronary artery distal to the obstructive lesion.

Although some indications for CABG are controversial, certain areas of agreement exist:

1. The operation is relatively safe, with mortality rates <1% in patients without serious comorbid disease and normal LV function and when the procedure is performed by an experienced surgical team.
2. Intraoperative and postoperative mortality rates increase with the severity of ventricular dysfunction, comorbidities, age >80 years, and lack of surgical experience. The effectiveness and risk of CABG vary widely depending on case selection and the skill and experience of the surgical team.
3. Occlusion of *venous* grafts is observed in 10–20% of patients during the first postoperative year and in ~2% per year during 5- to 7-year follow-up and 4% per year thereafter. Long-term patency rates are considerably higher for internal mammary and radial artery implantations than for saphenous vein grafts. In patients with left anterior descending coronary artery obstruction, survival is better when coronary bypass involves the internal mammary artery rather than a saphenous vein. Graft patency and outcomes are improved by meticulous treatment of risk factors, particularly dyslipidemia.
4. Angina is abolished or greatly reduced in ~90% of patients after complete revascularization. Although this usually is associated with graft patency and restoration of blood flow, the pain may also have been alleviated as a result of infarction of the ischemic segment or a placebo effect. Within 3 years, angina recurs in about one-fourth of patients but is rarely severe.
5. Survival may be improved by operation in patients with stenosis of the left main coronary artery as well as in patients with three- or two-vessel disease with significant obstruction of the proximal left anterior descending coronary artery. The survival benefit is greater in patients with abnormal LV function (ejection fraction <50%). Survival *may* also be improved in the following patients: (a) patients with obstructive CAD who have survived sudden cardiac death or sustained ventricular tachycardia; (b) patients who have undergone previous CABG and have multiple saphenous vein graft stenoses, especially of a graft supplying the left anterior descending coronary artery; and (c) patients with recurrent stenosis after PCI and high-risk criteria on noninvasive testing.
6. Minimally invasive CABG through a small thoracotomy and/or off-pump surgery can reduce morbidity and shorten convalescence in suitable patients but does not appear to reduce significantly the risk of neurocognitive dysfunction postoperatively.
7. Among patients with type 2 diabetes mellitus and multivessel coronary disease, CABG surgery plus optimal medical therapy is superior to optimal medical therapy alone in preventing major cardiovascular events, a benefit mediated largely by a significant reduction in nonfatal myocardial infarction. The benefits of CABG are especially evident in diabetic patients treated with an insulin-sensitizing strategy as opposed to an insulin-providing strategy. CABG has also been shown to be superior to PCI (including the use of drug-eluting stents) in preventing death, myocardial infarction, and repeat revascularization in patients with diabetes mellitus and multivessel IHD.

Indications for CABG usually are based on the severity of symptoms, coronary anatomy, and ventricular function. The ideal candidate is male, <80 years of age, has no other complicating disease, and has troublesome or disabling angina that is not adequately controlled by medical therapy or does not tolerate medical therapy. Great symptomatic benefit can be anticipated if a patient wishes to lead a more active life and has severe stenoses of two or three epicardial coronary arteries with objective evidence of myocardial ischemia as a cause of the chest discomfort. Congestive heart failure and/or LV dysfunction, advanced age (>80 years), reoperation, urgent need for surgery, and the presence of diabetes mellitus are all associated with a higher perioperative mortality rate.

LV dysfunction can be due to noncontractile or hypocontractile segments that are viable but are chronically ischemic (hibernating myocardium). As a consequence of chronic reduction in myocardial blood flow, these segments downregulate their contractile function. They can be detected by using radionuclide scans of myocardial perfusion and metabolism, PET, cardiac MRI, or delayed scanning with thallium-201 or by improvement of regional functional impairment provoked by low-dose dobutamine. In such patients, revascularization improves myocardial blood flow, can return function, and can improve survival.

The Choice Between PCI and CABG All the clinical characteristics of each individual patient must be used to decide on the method of revascularization (e.g., LV function, diabetes, lesion complexity). A number of randomized clinical trials have compared PCI and CABG in patients with multivessel CAD who were suitable technically for both procedures. The redevelopment of angina requiring repeat coronary angiography and repeat revascularization is higher with PCI. This is a result of restenosis in the stented segment (a problem largely solved with drug-eluting stents) and the development of new stenoses in unstented portions of the coronary vasculature. It has been argued that PCI with stenting focuses on culprit lesions, whereas a bypass graft to the target vessel also provides a conduit around future culprit lesions proximal to the anastomosis of the graft to the native vessel **(Fig. 267-5)**. By contrast, stroke rates are lower with PCI.

Based on available evidence, it is now recommended that patients with an unacceptable level of angina despite optimal medical management be considered for coronary revascularization. Patients with single- or two-vessel disease with normal LV function and anatomically suitable lesions ordinarily are advised to undergo PCI **(Chap. 270)**. Patients with three-vessel disease (or two-vessel disease that includes the proximal left descending coronary artery) and impaired global LV function (LV ejection fraction <50%) or diabetes mellitus and those with left main CAD or other lesions unsuitable for catheter-based procedures should be considered for CABG as the initial method of revascularization. In light of the complexity of the decision-making, it is desirable to have a multidisciplinary team, including a cardiologist and a cardiac surgeon in conjunction with the patient's primary care physician, provide input along with ascertaining the patient's preferences before committing to a particular revascularization option.

UNCONVENTIONAL TREATMENTS FOR IHD

On occasion clinicians will encounter a patient who has persistent disabling angina despite maximally tolerated medical therapy and for whom revascularization is not an option (e.g., small diffusely diseased vessels not amenable to stent implantation or acceptable targets for bypass grafting). In such situations, unconventional treatments should be considered.

Enhanced external counterpulsation utilizes pneumatic cuffs on the lower extremities to provide diastolic augmentation and systolic unloading of blood pressure to decrease cardiac work and oxygen consumption while enhancing coronary blood flow. Clinical trials have shown that regular application improves angina, exercise capacity, and regional myocardial perfusion. Experimental approaches, such as stem cell therapies and cardiac repair with small non-coding RNA molecules (miRNA), are also under active study.

ASYMPTOMATIC (SILENT) ISCHEMIA

Obstructive CAD, acute myocardial infarction, and transient myocardial ischemia are frequently asymptomatic. During continuous ambulatory ECG monitoring, the majority of ambulatory patients with typical chronic stable angina are found to have objective evidence of myocardial ischemia (ST-segment depression) during episodes of chest discomfort while they are active outside the hospital. In addition, many of these patients also have more frequent episodes of

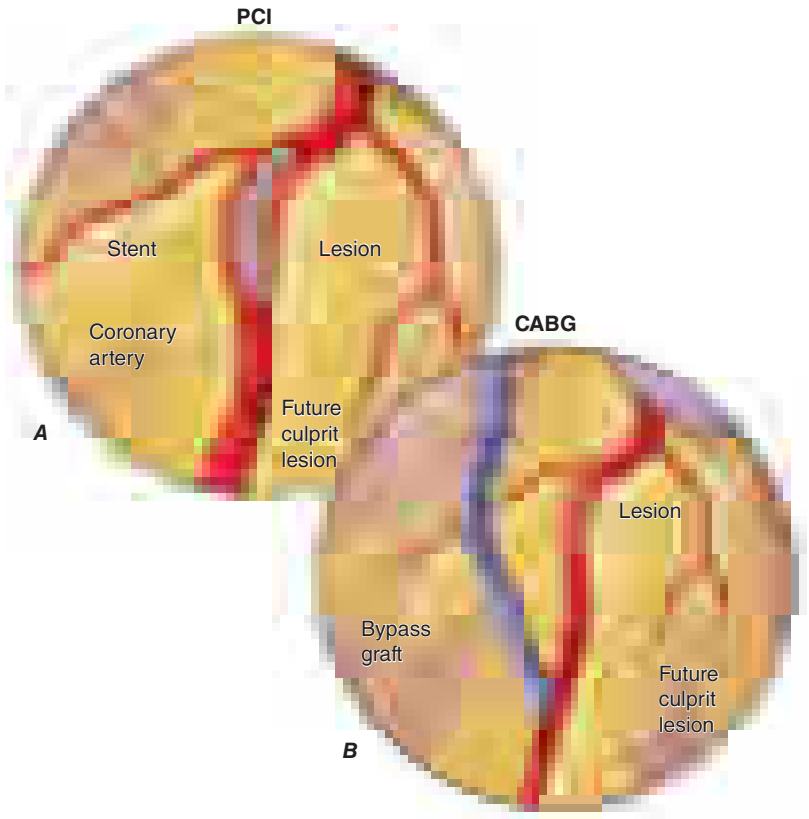


FIGURE 267-5 Difference in the approach to the lesion with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). PCI is targeted at the "culprit" lesion or lesions, whereas CABG is directed at the epicardial vessel, including the culprit lesion or lesions and future culprits, proximal to the insertion of the vein graft, a difference that may account for the superiority of CABG, at least in the intermediate term, in patients with multivessel disease. *(Reproduced from BJ Gersh, RL Frye: N Engl J Med 352:2235, 2005.)*

asymptomatic ischemia. Frequent episodes of ischemia (symptomatic and asymptomatic) during daily life appear to be associated with an increased likelihood of adverse coronary events (death and myocardial infarction). In addition, patients with asymptomatic ischemia after a myocardial infarction are at greater risk for a second coronary event. The widespread use of exercise ECG during routine examinations has also identified some of these previously unrecognized patients with asymptomatic CAD. Longitudinal studies have demonstrated an increased incidence of coronary events in asymptomatic patients with positive exercise tests.

TREATMENT

Asymptomatic Ischemia

The management of patients with asymptomatic ischemia must be individualized. When coronary disease has been confirmed, the aggressive treatment of hypertension and dyslipidemia is essential and will decrease the risk of infarction and death. In addition, the physician should consider the following: (1) the degree of positivity of the stress test, particularly the stage of exercise at which ECG signs of ischemia appear; the magnitude and number of the ischemic zones of myocardium on imaging; and the change in LV ejection fraction that occurs on radionuclide ventriculography or echocardiography during ischemia and/or during exercise; (2) the ECG leads showing a positive response, with changes in the anterior precordial leads indicating a less favorable prognosis than changes in the inferior leads; and (3) the patient's age, occupation, and general medical condition.

Most would agree that an asymptomatic 45-year-old commercial airline pilot with significant (0.4-mV) ST-segment depression in leads V_1 to V_4 during mild exercise should undergo coronary arteriography, whereas an asymptomatic, sedentary 85-year-old retiree with 0.1-mV ST-segment depression in leads II and III during maximal activity need not. However, there is no consensus about the most appropriate approach in the large majority of patients for whom the situation is less extreme. Asymptomatic patients with silent ischemia, three-vessel CAD, and impaired LV function may be considered appropriate candidates for CABG.

The treatment of risk factors, particularly lipid lowering and blood pressure control as described above, and the use of aspirin, statins, and beta blockers after infarction have been shown to reduce events and improve outcomes in asymptomatic as well as symptomatic patients with ischemia and proven CAD. Although the incidence of asymptomatic ischemia can be reduced by treatment with beta blockers, calcium channel blockers, and long-acting nitrates, it is not clear whether this is necessary or desirable in patients who have not had a myocardial infarction.

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268 Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

Robert P. Giugliano, Christopher P. Cannon, Eugene Braunwald

Patients with acute coronary syndrome (ACS) commonly are classified into two groups to facilitate evaluation and management, namely patients with acute myocardial infarction with ST-segment elevation (STEMI) on their presenting electrocardiogram (ECG) **(Chap. 269)** and those with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The latter include patients with non-ST-segment elevation myocardial infarction (NSTEMI), who, by definition, have evidence of myocyte necrosis, and those with unstable angina (UA), who do not **(Fig. 268-1)**.

The relative incidence of NSTEMI is rising due to the increasing burden of diabetes and chronic kidney disease in an aging population, while STEMI is declining due to greater use of aspirin, statins, and less smoking. Among patients with NSTE-ACS, the proportion with NSTEMI is rising while that with UA is falling because of the wider use of troponin assays with higher sensitivity to detect myocyte necrosis, thereby reclassifying UA as NSTEMI.

PATHOPHYSIOLOGY

NSTE-ACS is caused by an imbalance between myocardial oxygen supply and demand resulting from one or more of the following four processes that lead to thrombus formation : (1) disruption of an unstable coronary plaque due to plaque rupture, erosion, or a calcified protruding nodule that leads to intracoronary thrombus formation **(Fig. 268-2)** and an inflammatory response; (2) coronary arterial vasoconstriction; (3) gradual intraluminal narrowing; and (4) increased myocardial oxygen demand produced by conditions such as fever, tachycardia, and thyrotoxicosis in the presence of fixed epicardial coronary obstruction. While plaque rupture remains the most common etiology of coronary thrombosis, erosion of an intracoronary plaque is increasing in frequency, perhaps related to the above mentioned shifts in the underlying risk factors for ACS.

Among patients with NSTE-ACS studied at angiography, ~10% have stenosis of the left main coronary artery, 35% have three-vessel CAD, 20% have two-vessel disease, 20% have single-vessel disease, and 15% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation and/or spasm of the epicardial vessels. The so-called "vulnerable plaques" responsible for ischemia may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on coronary angiography. Vulnerable plaques are composed of a lipid-rich core with a thin fibrous cap. Patients with NSTE-ACS frequently have multiple such plaques that are at risk of disruption.

CLINICAL PRESENTATION

Diagnosis The diagnosis of NSTE-ACS is based largely on the clinical presentation **(Fig. 268-3)**.

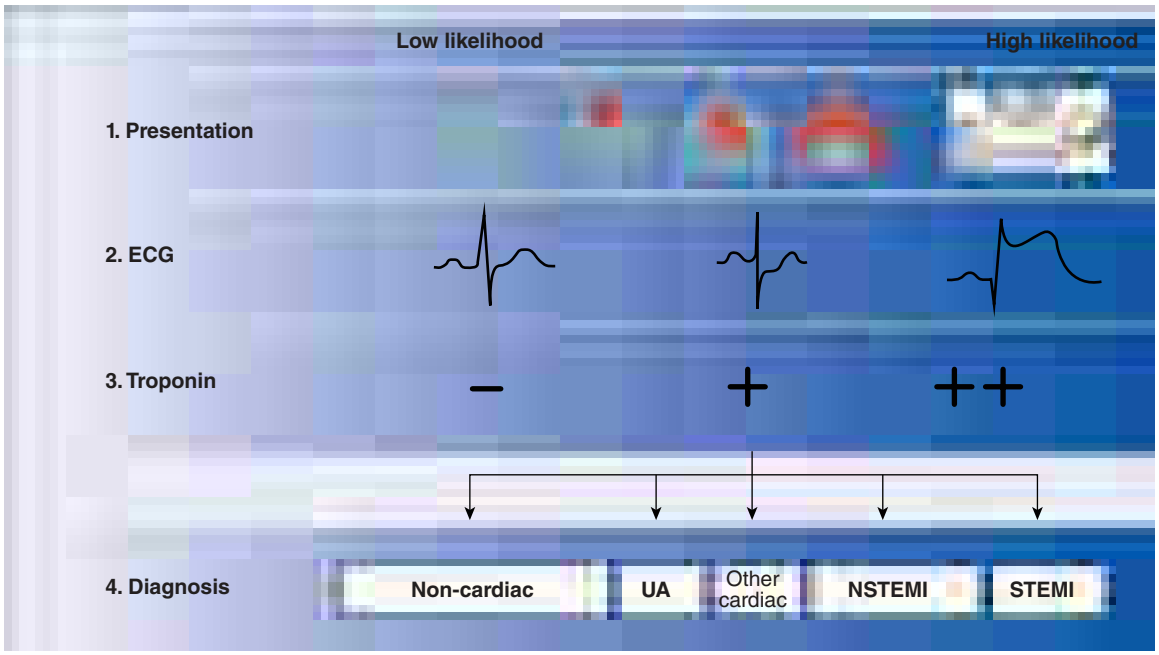

FIGURE 268-1 Assessment of patients with suspected acute coronary syndromes. The initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation (i.e., symptoms, vital signs), 12-lead electrocardiogram and cardiac troponin. The proportion of the final diagnoses derived from the integration of these parameters is visualized by the size of the respective boxes. (*From Roffi M et al: 2015 European Society of Cardiology Guidelines for the management of acute coronary syndromes. Eur Heart J 37:267, 2016.*)

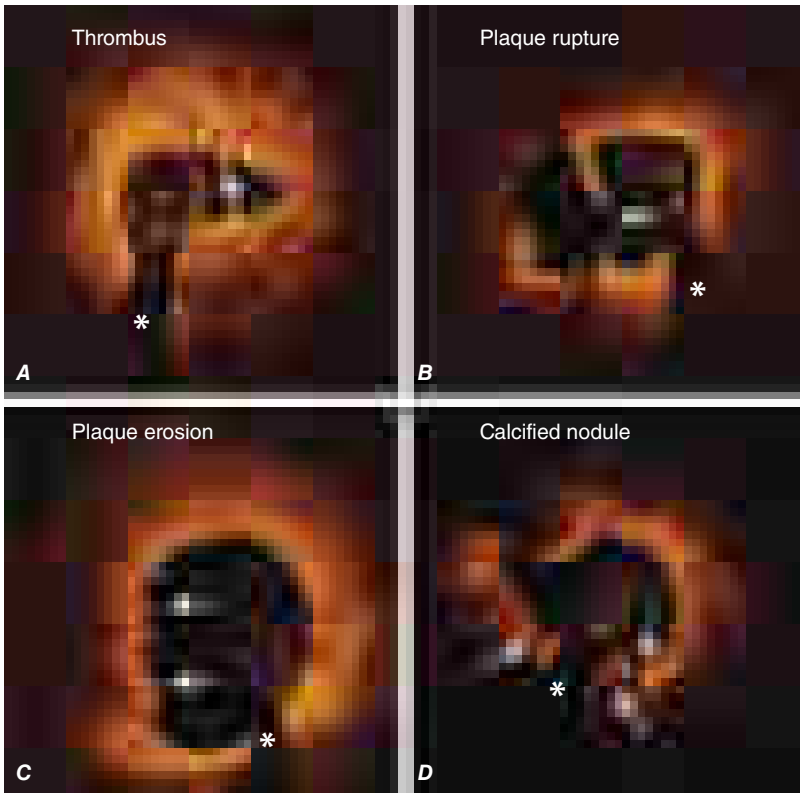

FIGURE 268-2 Intracoronary thrombosis and the three most common plaque morphologies resulting in acute coronary syndrome as visualized by optical coherence tomography. *A.* Thrombus (*arrow*) is identified as a protruding mass attached to the arterial wall. ***B.*** Plaque rupture is identified as lipid plaque with fibrous cap discontinuity (*arrow*) and cavity formation inside the plaque. ***C.*** Plaque erosion is confirmed by the presence of attached thrombus (*arrows*) overlying an intact and visualized plaque. ***D.*** Calcified nodule appears on optical coherence tomography as a site with fibrous cap disruption (*dotted arrow*) and underlying plaque characterized by protruding calcification, superficial calcium, and significant calcium adjacent to the lesion (*arrows*). The asterisks denote guidewire shadow artifact. *(Modified from H Jia et al: J Am Coll Cardiol 62:1748, 2013 and I Jang, D Ong: Optical coherence tomography and other emerging diagnostic procedures for vulnerable plaque, in D Morrow (ed): Myocardial Infarction: A Companion to Braunwald's Heart Disease. Philadelphia, Elsevier Health Sciences, 2017.)*

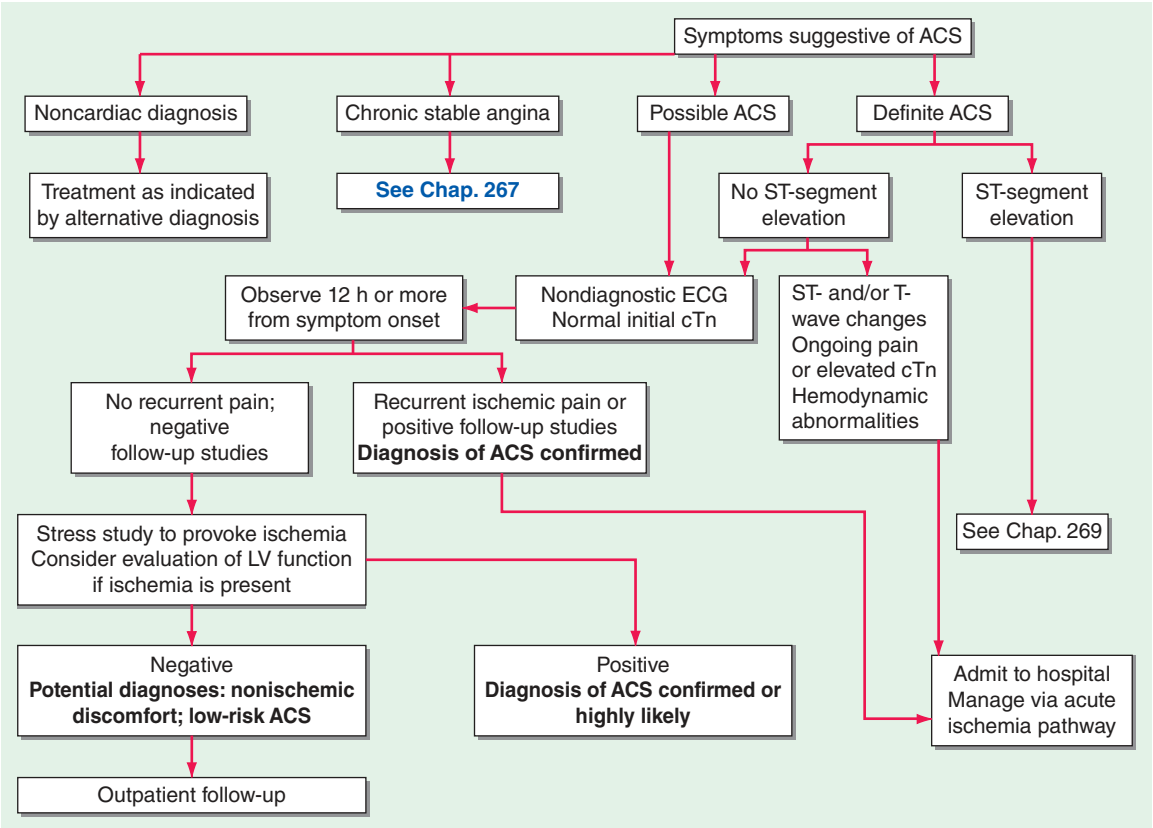

FIGURE 268-3 Algorithm for evaluation and management of patients with suspected acute coronary syndrome (ACS). Follow-up studies refer to ST deviation and elevation of troponin levels. cTn, cardiac troponin; ECG, electrocardiogram; LV, left ventricular. *(Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.)*

History and Physical Examination Typically, chest discomfort is severe and has at least one of three features: (1) occurrence at rest (or with minimal exertion), lasting >10 min; (2) of relatively recent onset (i.e., within the prior 2 weeks); and/or (3) a crescendo pattern, i.e., distinctly more severe, prolonged, or frequent than previous episodes. The diagnosis of NSTEMI is established if a patient with any of these features (without electrocardiographic ST segment elevations) develops evidence of myocardial necrosis, as reflected in abnormally elevated levels of biomarkers (see below). The chest discomfort is typically located in the substernal region and radiates to the left arm, left shoulder, and/or superiorly to the neck and jaw. Anginal equivalents such as dyspnea, epigastric discomfort, nausea, or weakness may occur instead of chest discomfort. They appear to be more frequent in women, the elderly, and patients with diabetes mellitus. The physical examination resembles that in patients with stable angina **(Chap. 267)** and may be unremarkable. However, if the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; and, sometimes, hypotension.

Electrocardiogram New ST-segment depression occurs in about one-third of patients with NSTE-ACS. It may be transient but may persist for several days following NSTEMI. T-wave changes are more common but are less specific signs of ischemia, unless they are new and deep T-wave inversions (≥0.3 mV).

Cardiac Biomarkers Patients with NSTEMI have elevated biomarkers of necrosis, such as cardiac troponin (cTn) I or T, which are specific, sensitive, and the preferred markers of myocardial necrosis. The MB isoform of creatine kinase (CK-MB) is a less sensitive alternative. Elevated levels of any of these markers distinguish patients with NSTEMI from those with UA. There is a characteristic temporal rise and fall peaking 12–24 h post onset of symptoms of the plasma concentration of these markers and a direct relationship between the degree of elevation and mortality. However, in patients *without* a clear clinical history of myocardial ischemia, minor cTn elevations have been reported and can be caused by heart failure, myocarditis, or pulmonary embolism, or with high-sensitivity assays (hs cTn) may be observed in ostensibly normal subjects. Thus, in patients with an *unclear* history, small elevations of cTn, especially if they are persistent, may not be diagnostic of an ACS. In such cases, both cardiac and non-cardiac causes of an elevated cTn should be considered **(Table 268-1)**.

TABLE 268-1 Causes of Elevated Cardiac Troponin Reflecting Direct Myocardial Damage Other Than Spontaneous Myocardial Infarction (Type 1)

CARDIAC	NON-CARDIAC OR SYSTEMIC
Tachyarrhythmias	Pulmonary embolism/pulmonary hypertension
Congestive heart failure	Trauma (e.g., electrical shock, burns, blunt chest wall)
Hypertensive emergencies	Hypo or hyperthyroidism
Infection/inflammation (e.g., myocarditis, pericarditis)	Toxicity (e.g., anthracyclines, snake venom)
Stress cardiomyopathy (Tako-Tsubo cardiomyopathy)	Renal failure
Structural heart disease (e.g., aortic stenosis)	Sepsis, shock
Aortic dissection	Stroke or other acute neurologic event
Coronary spasm	Extreme endurance efforts (e.g., ultra-marathon)
Cardiac procedures (endomyocardial biopsy, ablation, CABG, PCI)	Rhabdomyolysis
Infiltrative diseases (e.g., amyloidosis, hemochromatosis, malignancy)	

Source: Data from LK Newby et al: J Am Coll Cardiol 60:2427, 2012 and M Roffi: Eur Heart J 37:267, 2016.

DIAGNOSTIC EVALUATION

In addition to the clinical examination, three major noninvasive tools are used in the evaluation of NSTEMI-ACS: the ECG, cardiac biomarkers, and stress testing. In equivocal cases, coronary computed tomographic angiography (CCTA) may be useful to improve the accuracy and speed of the diagnostic evaluation. The goals are to: (1) recognize or exclude myocardial infarction (MI) using cardiac biomarkers, preferably cTn; (2) detect rest ischemia (using serial or continuous ECGs); and (3) detect significant coronary obstruction at rest with CCTA and/or myocardial ischemia using stress testing **(Chap. 236)**.

Patients with a low likelihood of ischemia are usually managed in an emergency department or a dedicated "chest pain unit" following a critical pathway. Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort and continuous monitoring of ECGs and cardiac markers, typically obtained at baseline and at 4–6 h and 12 h after presentation. If new elevations in cardiac markers or ST-T-wave changes on the ECG are noted, the patient should be admitted to the hospital. Patients who remain pain-free with negative markers may proceed to stress testing to determine the presence of ischemia or CCTA to detect coronary luminal obstruction (Fig. 268-3).

The hs cTn assays permit a more rapid (3-h and even 1-h) rule-out MI determination and have been adopted by the 2015 European Guidelines for the management of NSTE-ACS.

RISK STRATIFICATION

Patients with documented NSTE-ACS exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and a recurrent ACS rate of 5–15% during the first year. Assessment of risk can be accomplished by clinical risk scoring systems such as that developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors (age ≥ 65 years, 3 or more of the traditional risk factors for coronary heart disease, known history of coronary artery disease or coronary stenosis of at least 50%, daily aspirin use in the prior week, more than one anginal episode in the past 24 h, ST segment deviation of at least 0.5 mm, and an elevated cardiac specific biomarker above the upper limit of normal). Additional risk factors include diabetes mellitus, left ventricular dysfunction, renal dysfunction, and elevated levels of B-type natriuretic peptides. Multibiomarker strategies are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a given patient's presentation and to stratify the patient's risk further. Patients with ACS without elevated levels of cTn (infrequently encountered with the new sensitive troponin assays) are considered to have UA and have a more favorable prognosis than those with cTn elevations (NSTEMI).

Early risk assessment is useful in identifying patients who would derive the greatest benefit from an early invasive strategy (see below). For example, in the TACTICS-TIMI 18 Trial, an early invasive strategy conferred a 40% reduction in recurrent cardiac events in patients with an elevated cTn level, whereas no benefit was observed in those without detectable troponin.

TREATMENT

Non-ST-Segment Elevation Acute Coronary Syndrome (Non-ST-Segment Elevation Myocardial Infarction and Unstable Angina)

MEDICAL TREATMENT

Patients should be placed at bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias, preferably on a specialized cardiac unit. Ambulation is permitted if the patient shows no recurrence of ischemia (symptoms or ECG changes) and does not develop an elevation of a biomarker of necrosis for 12–24 h.

Medical therapy consists of an acute phase focused on the clinical symptoms and stabilization of the culprit lesion(s) and a longer-term phase that involves therapies directed at the prevention of disease progression and future plaque rupture/erosion.

ANTI-ISCHEMIC TREATMENT (TABLE 268-2)

To provide relief and prevention of recurrence of ischemic discomfort, initial treatment should include bed rest, nitrates, beta adrenergic blockers, and inhaled oxygen in patients with arterial O_2 saturation (<90%) and/or in those with heart failure and rales.

Nitrates These should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic discomfort. If symptoms persists after three doses given 5 min apart, intravenous nitroglycerin (5–10 µg/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 µg/min every 3–5 min until symptoms are relieved, systolic arterial pressure falls to <90 mmHg, or the dose reaches 200 µg/min. Topical or oral nitrates (Chap. 267) can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been symptom-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the recent use of a phosphodiesterase type 5 (PDE-5) inhibitor, sildenafil or vardenafil (within 24 h), or tadalafil (within 48 h).

Beta-Adrenergic Blockers and Other Agents Beta blockers are the other mainstay of anti-ischemic treatment. They may be started by the intravenous route in patients with severe ischemia, but should be avoided in the presence of acute or severe heart failure, low cardiac output, hypotension, or contraindications to beta-blocker therapy (e.g., high-degree atrioventricular block, active bronchospasm). Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended. Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter, has been shown to reduce periprocedural MI and recurrences of ACS. In patients who do not have an adequate response to maximally tolerated statin (i.e., <50% decrease in LDL-C from untreated baseline or LDL-C on treatment >70 mg/dL), addition of ezetimibe 10 mg daily to reduce further the LDL-C has been shown to reduce future cardiovascular events.

ANTITHROMBOTIC THERAPY (FIG. 268-4 AND TABLE 268-3)

Antithrombotic therapy consisting of antiplatelet and anticoagulant drugs represent the second major cornerstone of treatment.

Antiplatelet Drugs (See Chap. 114) Initial treatment should begin with the cyclooxygenase inhibitor aspirin with a dose of at least 162 mg of a rapidly acting preparation (oral non-enteric coated or intravenous). Lower doses (75–100 mg/d) are recommended thereafter, since they maintain efficacy while causing less bleeding. Contraindications are severe active bleeding or aspirin allergy.

In the absence of a high risk for bleeding, patients with NSTE-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, also should receive a platelet $P2Y_{12}$ receptor blocker to inhibit platelet activation. There are now four oral and one intravenous $P2Y_{12}$ inhibitors to choose from (although the first in class, ticlopidine, is rarely used due to poor tolerability); advantages for each of the others are noted below.

The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet $P2Y_{12}$ receptor. The loading dose of clopidogrel is 600 or 300 mg while the maintenance dose is 75 mg daily. When clopidogrel is added to aspirin, so-called dual antiplatelet therapy (DAPT), has been shown to confer a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone, but to be associated with a moderate (absolute 1%) increase in major bleeding.

TABLE 268-2 Drugs Commonly Used in Intensive Medical Management of Patients with Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

DRUG CATEGORY	CLINICAL CONDITION	WHEN TO AVOID[a]	DOSAGE
Nitrates	Patients with ACS who have chest discomfort or an anginal equivalent	Hypotension Right ventricular infarction Severe aortic stenosis Patient receiving a PDE-5 inhibitor	Initially administer via sublingual or buccal route, and, if symptoms persist, intravenously. Topical or oral nitrates are acceptable alternatives for patients without ongoing or refractory symptoms 5–10 µg/min by continuous infusion titrated up to 75–100 µg/min until relief of symptoms or limiting side effects (headache or hypotension with a systolic blood pressure <90 mmHg or >30% below starting mean arterial pressure levels if significant hypertension is present)
Beta blockers[b]	All patients with ACS	PR interval (ECG) >0.24 s 2° or 3° atrioventricular block Heart rate <50 beats/min Systolic pressure <90 mmHg Shock Left ventricular failure Severe reactive airway disease	Metoprolol 25–50 mg by mouth every 6 h If needed, and no heart failure, 5-mg increments by slow (over 1–2 min) IV administration
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and beta blockers, or in patients unable to tolerate adequate doses of one or both of these agents, or in patients with variant angina	Pulmonary edema Evidence of left ventricular dysfunction (for diltiazem or verapamil)	Dependent on specific agent
Morphine sulfate	Patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 min as needed to relieve symptoms and maintain patient comfort

[a]Allergy or prior intolerance is a contraindication for all categories of drugs listed in this chart. [b]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

Initial Treatment

DAPT and Anticoagulant therapy:
1. Aspirin (COR I, LOE A).
2. P2Y 12 inhibitor: clopidogrel or ticagrelor (COR I, LOE B).
3. Anticoagulant:
   Enoxaparin (COR I, LOE A) or UFH (COR I, LOE B) or fondaparinux (COR I, LOE B) or bivalirudin (for early invasive strategy, COR I, LOE B).
4. Can consider GP IIb/IIIa receptor inhibitors in high-risk patients stratified to early invasive strategy (eptifibatide or tirofiban; COR IIb, LOE B).

During Hospitalization

Medically treated patients:
1. Aspirin (COR I, LOE A).
2. P2Y 12 inhibitor: either ticagrelor or clopidogrel (COR I, LOE B).
3. Anticoagulant:
   Enoxaparin (COR I, LOE A) or UFH (COR I, LOE B) or fondaparinux (COR I, LOE B).

PCI treated patients:
1. Aspirin (COR I. LOE A).
2. P2Y 12: inhibitor: clopidogrel or ticagrelor or prasugrel (COR I, LOE B).
3. Anticoagulant:
   Enoxaparin (COR I, LOE A) or UFH (COR I, LOE B) or fondaparinux* (COR I, LOE B) or bivalirudin (COR I, LOE B).
4. Can consider GP IIb/IIIa receptor inhibitors in high-risk patients not adequately per-treated with clopidogrel (COR I, LOE A) or in high-risk patients adequately pre-treated with clopidogrel (COR IIa, LOE B).

Long-term

Medically treated patients:
1. Aspirin indefinitely (COR I, LOE A).
2. P2Y 12 inhibitor: clopidogrel or ticagrelor for up to 12 months (COR I, LOE B)

PCI treated patients:
1. Aspirin indefinitely (COR I, LOE A).
2. P2Y 12 inhibitor: clopidogrel or ticagrelor or prasugrel for at least 12 months (COR I, LOE B).

(*Supplemental UFH or bivalirudin is required during PCI to prevent procedure-related thrombosis in patients treated with fondaparinux.)

FIGURE 268-4 Antiplatelet and anticoagulation treatment summary for NSTE-ACS according to the 2014 American Heart Association/American College of Cardiology Practice Guideline. COR, classes of recommendation; DAPT, dual antiplatelet therapy; GP IIb/IIIa, glycoprotein IIb/IIIa; LOE, levels of evidence; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. *(From A Eisen, RP Giugliano: Cardiol Rev 24;170, 2016.)*

TABLE 268-3 Clinical Use of Antithrombotic Therapy

Oral Antiplatelet Therapy	
Aspirin	Initial dose of 325 mg nonenteric formulation followed by 75–100 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 300–600 mg followed by 75 mg/d
Prasugrel	Pre-PCI: Loading dose 60 mg followed by 10 mg/d
Ticagrelor	Loading dose of 180 mg followed by 90 mg twice daily
Intravenous Antiplatelet Therapy	
Abciximab	0.25 mg/kg bolus followed by infusion of 0.125 μg/kg per min (maximum 10 μg/min) for 12–24 h
Eptifibatide	180 μg/kg bolus followed 10 min later by second bolus of 180 μg with infusion of 2.0 μg/kg per min for 72–96 h following first bolus
Tirofiban	25 μg/kg per min followed by infusion of 0.15 μg/kg per min for 48–96 h
Cangrelor	30 μg/kg bolus followed immediately by a 4 μg/kg per min infusion
Anticoagulants[a]	
Unfractionated heparin (UFH)	[b]Bolus 70–100 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h (initial maximum 1000 U/h) titrated to ACT 250–300 s
Enoxaparin	1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine clearance <30 mL/min
Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial IV bolus of 0.75 mg/kg and an infusion of 1.75 mg/kg per h

[a]Other low-molecular-weight heparins have been studied other than enoxaparin; however there are less data to support their use. [b]If no glycoprotein IIb/IIIa inhibitor planned.

Abbreviations: ACT, activated clotting time for HemoTec; IV, intravenous; SC, subcutaneous.

Source: Modified from J Anderson et al: J Am Coll Cardiol 61:e179, 2013.

Two newer $P2Y_{12}$ inhibitors (prasugrel, ticagrelor) have been found to be superior to clopidogrel in preventing recurrent cardiac ischemic events in randomized double-blind studies although both increase bleeding. Prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of platelet inhibition than clopidogrel. It has been approved for ACS patients following angiography when PCI is planned. It should be administered at a loading dose of 60 mg followed by 10 mg/d. Compared to clopidogrel, prasugrel was shown to significantly reduce by 19% the combined risk of cardiovascular death, MI, or stroke, and reduced stent thrombosis by 50%. Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding. It has not been found to be effective in patients treated by a conservative strategy prior to coronary angiography (see below).

Ticagrelor is a novel, potent, *reversible* platelet $P2Y_{12}$ inhibitor that was shown to reduce the risk of cardiovascular death, total mortality or MI compared to clopidogrel across a broad spectrum patients with ACS. After a loading dose of 180 mg, 90 mg bid is administered as maintenance. Unlike prasugrel, ticagrelor demonstrated benefit whether patients were managed conservatively or with an early invasive strategy. Some patients may develop dyspnea early after administration of ticagrelor, although the symptoms are most often transient and infrequently serious, and are not associated with clinical exacerbations of chronic obstructive pulmonary disease or congestive heart failure.

DAPT should continue for at least 1 year in patients with NSTE-ACS, especially those with a drug-eluting stent, to prevent stent thrombosis. Up to one-third of patients have an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a genetic variant of the cytochrome P450 system involving the 2C19 gene that leads to reduced conversion of clopidogrel into its active metabolite. Thus, alternate $P2Y_{12}$ blockers should be considered in patients with NSTE-ACS who develop a coronary event while receiving clopidogrel and aspirin, who are hyporesponsive to clopidogrel, or are at high risk for ischemic complications. Clinicians should select

the antiplatelet regimen that provides the best balance of efficacy and safety based on the individual patient characteristics and clinical scenario.

More recently, an intravenous, direct and rapidly acting, $P2Y_{12}$ inhibitor, cangrelor, was evaluated in three large outcome studies in >25,000 patients undergoing PCI across a broad spectrum of clinical presentations (stable angina, UA, NSTEMI, STEMI). Among the 14,282 patients who underwent PCI following a NSTE-ACS, cangrelor reduced the risk of the primary composite outcome of death, MI, ischemia-driven revascularization, and stent thrombosis at 48 h by 18% relative to control. There was an excess of 3 per 1000 major bleeding events with cangrelor. This drug is approved as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a GP IIb/III inhibitor.

In the 1990s and early 2000s several trials had shown the benefit of intravenous glycoprotein IIb/IIIa inhibitors in patients with NSTE-ACS, with the majority of studies performed without concomitant $P2Y_{12}$ inhibition. The benefits, however, were modest (i.e., an ~1% absolute reduction in death or MI at 30 day) and counterbalanced by a 1% absolute increase in the rate of major bleeding. Two recent studies failed to show a benefit of routine early initiation of a drug in this class compared with their use only in patients who undergo PCI. The addition of these agents to aspirin and a $P2Y_{12}$ inhibitor (i.e., triple antiplatelet therapy) should be reserved for unstable patients undergoing PCI. These include patients with recurrent rest pain, elevated cTn, and ECG changes, as well as those who have a coronary thrombus evident on angiography.

Anticoagulants (See Chap. 114) Four options are available for anticoagulant therapy to be added to antiplatelet agents: (1) unfractionated heparin (UFH), long the mainstay of therapy; (2) the low-molecular-weight heparin (LMWH), enoxaparin, which has been shown to be superior to UFH in reducing recurrent cardiac events, especially in patients managed by a conservative strategy. However, it is accompanied by a slight increase in bleeding compared to UFH; (3) bivalirudin, a direct thrombin inhibitor that is similar in efficacy to either UFH or LMWH but causes less bleeding and is used just prior to and/or during PCI; and (4) the indirect factor Xa inhibitor, fondaparinux, which is equivalent in efficacy to enoxaparin but has a lower risk of major bleeding. While UFH and enoxaparin have been widely studied in patients managed either with an early conservative or invasive strategy, the role of bivalirudin in conservatively managed patients is less clear, while fondaparinux requires supplemental UFH or bivalirudin during PCI to prevent procedure-related thrombosis.

Excessive bleeding is the most important adverse effect of all antithrombotic agents, including both antiplatelet agents and anticoagulants. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for body weight, creatinine clearance, and a previous history of excessive bleeding, as a means of reducing the risk of bleeding. Patients who have experienced a stroke are at higher risk of intracranial bleeding with potent antiplatelet agents and combinations of antithrombotic drugs.

INVASIVE VERSUS CONSERVATIVE STRATEGY

In an invasive strategy, following initiation of anti-ischemic and antithrombotic agents, coronary arteriography is carried out within ~48 h of presentation, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy. Multiple clinical trials have demonstrated the benefit of this strategy in high-risk patients (i.e., patients with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers) **(Table 268-4)**. In patients at low risk, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy. The latter consists of anti-ischemic and antithrombotic therapy followed by a "selective invasive approach," in which the patient is closely observed and coronary arteriography is carried out if rest pain or ST-segment changes recur, a biomarker of necrosis becomes positive, or there is evidence of severe ischemia on a stress test.

TABLE 268-4 Factors Associated with Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients with NSTE-ACS

Immediate invasive (within 2 h)	Refractory angina Signs or symptoms of heart failure or new or worsening mitral regurgitation Hemodynamic instability Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Sustained ventricular tachycardia or ventricular fibrillation
Early invasive (within 24 h)	None of the above, but GRACE[a] risk score >140 Temporal change in troponin New or presumably new ST segment depression
Delayed invasive (within 25–72 h)	None of the above but diabetes mellitus Renal insufficiency (eGFR <60 mL/min per 1.73 m^2) Reduced left ventricular systolic function (ejection fraction <0.40) Early postinfarction angina Percutaneous coronary intervention within 6 months prior Prior coronary artery bypass graft surgery GRACE[a] risk score 109–140 or TIMI[b] risk score ≥2
Ischemia-guided strategy	Low-risk score (e.g., TIMI[b] [0 or 1], GRACE[a] [<109]) Low-risk, troponin-negative female patients Patient or clinician preference in the absence of high-risk features

[a]See CB Granger (Arch Intern Med 163:2345, 2003). [b]See EM Antman (JAMA 284:835, 2000).

Abbreviations: eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; TIMI, Thrombolysis in Myocardial Infarction.

Source: Modified from EA Amsterdam et al: J Am Coll Cardiol 64:e139, 2014.

LONG-TERM MANAGEMENT

The time of hospital discharge is a "teachable moment" for the patient with NSTE-ACS, when the physician can review and optimize the medical regimen. Risk-factor modification is key, and the caregiver should discuss with the patient the importance of smoking cessation, achieving optimal weight, daily exercise, blood-pressure control, following an appropriate diet, control of hyperglycemia (in diabetic patients), and lipid management as recommended for patients with chronic stable angina **(Chap. 267)**.

There is evidence of benefit with long-term therapy with five classes of drugs that are directed at different components of the atherothrombotic process. Beta blockers, lipid lowering therapy (statins at high dose, e.g., atorvastatin 80 mg/d, with ezetimibe if needed to achieve an LDL-C below 70 mg/dL), and ACE inhibitors or angiotensin receptor blockers are recommended. The recommended antiplatelet regimen consists of the combination of low-dose (75–100 mg/d) aspirin and a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) for 1 year, with aspirin continued thereafter. In selected patients at high ischemic risk (e.g., those with prior MI, diabetes mellitus, vein graft stent, congestive heart failure) who are also at low risk of bleeding, continuation of DAPT out to 3 years has been shown to be beneficial. These measures, taken together, reduce the incidence of recurrent ACS.

Registries have shown that women and racial minorities, as well as patients with NSTE-ACS at high risk, including the elderly and patients with diabetes or chronic kidney disease, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life. Special attention should be directed to these groups.

PRINZMETAL'S VARIANT ANGINA

In 1959, Prinzmetal et al. described a syndrome of severe ischemic pain that usually occurs at rest and is associated with transient ST-segment elevation. Prinzmetal's variant angina (PVA) is caused by focal spasm of an epicardial coronary artery with resultant transmural ischemia and abnormalities in left ventricular function that may lead to acute MI, ventricular tachycardia or fibrillation, and sudden cardiac death. The cause of the spasm is not well defined, but it may be related to hypercontractility of

vascular smooth muscle due to adrenergic vasoconstrictors, leukotrienes, or serotonin. For reasons that are not clear, the prevalence of PVA has decreased substantially during the past few decades, although it remains more frequent in Japan than in North America or Western Europe.

Clinical and Angiographic Manifestations Patients with PVA are generally younger and, with the exception of cigarette smoking, have fewer coronary risk factors than do patients with NSTE-ACS. Cardiac examination is usually unremarkable in the absence of ischemia. However, a minority of patients have a generalized vasospastic disorder associated with migraine and/or Raynaud's phenomenon. The clinical diagnosis of PVA is made by the detection of transient ST-segment *elevation* with rest pain, although many patients may also exhibit episodes of silent ischemia.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of PVA. Atherosclerotic plaques in at least one proximal coronary artery occur in about half of patients. Hyperventilation or intracoronary acetylcholine has been used to provoke focal coronary stenosis on angiography or to provoke rest angina with ST-segment elevation to establish the diagnosis.

TREATMENT

Prinzmetal's Variant Angina

Nitrates and calcium channel blockers are the main therapeutic agents. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. Statin therapy has been shown to reduce the risk of major adverse events, although the precise mechanism is not established. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, flow-limiting, proximal fixed obstructive lesions. Patients who have had ischemia-associated ventricular fibrillation despite maximal medical therapy should receive an implantable cardioverter-defibrillator.

Prognosis Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation. Survival at 5 years is excellent (~90–95%), but as many as 20% of patients experience an MI. Patients with no or mild fixed coronary obstruction experience a low rate of cardiac death or MI compared to patients with associated severe obstructive lesions, although about half of the patients without obstructive CAD still experience frequent angina at rest. Patients with PVA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, there is a tendency for symptoms and cardiac events to diminish over time.

GLOBAL CONSIDERATIONS

Ischemic heart disease (IHD), and its most dangerous manifestation, ACS, remains the most frequent cause of death and disability worldwide. In the mid-twentieth century these conditions were most common in high income countries. The elucidation of risk factors leading to IHD and the development of therapies to reduce the deleterious consequences of ACS were responsible for dramatic reductions in these events, and in cardiovascular and all cause mortality. Although these achievements were most prominent in North America, Western Europe, and Japan, they have not affected all population groups equally. In Europe, there remains a northeast to southwest gradient, with higher prevalence in northern Russia and the Baltic nations, and considerably lower prevalence in France, Italy, and Spain.

Simultaneous with these important advances in the high income countries, the low and middle income countries have moved in the opposite direction. The improvements in agriculture, nutrition, sanitation, prevention and treatment of infections, management of maternal-early childhood disorders, as well as urbanization, and a reduction of physical labor have, in combination, led to marked increases in coronary risk factors—hypertension, cigarette smoking, obesity, diabetes mellitus, and elevations of circulating low density lipoprotein cholesterol. These, in turn, have been responsible for marked increases in ACS events and in premature mortality. The region in which these changes have been most prominent are central Asia, India, and Pakistan, as well as in the more developed regions of sub-Saharan Africa.

However, while there are many similarities, there are major differences between the rise of IHD which occurred in the high income countries in mid-twentieth century, and that which is now taking place in low and middle income countries. When the former occurred, the coronary risk factors had not yet been clearly defined and treatments of ACS were primitive by current standards. It was the successful application of prevention of IHD and therapy of ACS in high income countries that was responsible for the above-mentioned striking improvements in life expectancy. The current challenge is to apply what was learned in high-income countries to the vast populations in the low and middle income countries that are now at high risk. This will require large educational efforts directed at both the populations and their caregivers. An additional challenge will be to provide the trained specialized personnel, facilities, drugs, and devices to deal with these threats. The successful implementation of measures to reduce threats in the developing world is now principally a socio-politico-economic issue. One mitigating factor is that many of the important drugs to prevent and treat these disorders, such as statins, angiotensin converting enzyme inhibitors, diuretics, beta blockers, and calcium antagonists are off patent and are now inexpensive.

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269 ST-Segment Elevation Myocardial Infarction

Elliott M. Antman, Joseph Loscalzo

Acute myocardial infarction (AMI) is a most common diagnosis in hospitalized patients in industrialized countries. In the United States, ~660,000 patients experience a new AMI, and 305,000 experience a recurrent AMI each year. About half of AMI-related deaths occur before the stricken individual reaches the hospital. Of note, the in-hospital

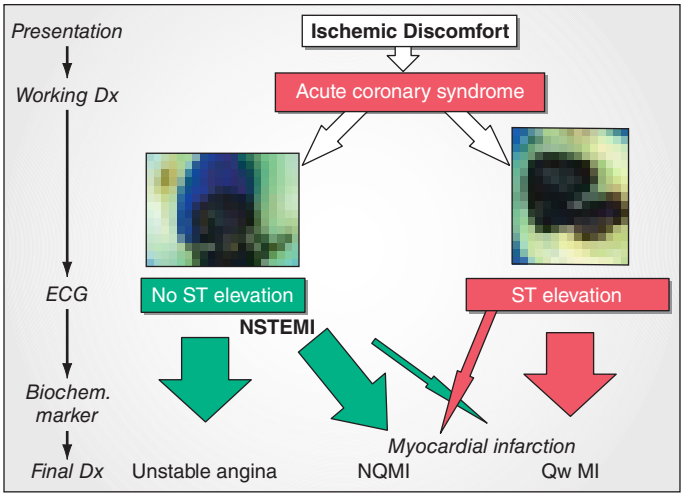

FIGURE 269-1 Acute coronary syndromes. Following disruption of a vulnerable plaque, patients experience ischemic discomfort resulting from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (*right*) or subtotally occlusive thrombus (*left*). Patients with ischemic discomfort may present with or without ST-segment elevation. Of patients with ST-segment elevation, the majority (*wide red arrow*) ultimately develop a Q wave on the ECG (Qw MI), while a minority (*thin red arrow*) do not develop Q wave and, in older literature, were said to have sustained a non-Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina or a non-ST-segment elevation MI (NSTEMI) (*wide green arrows*), a distinction that is ultimately made based on the presence or absence of a serum cardiac biomarker such as CK-MB or a cardiac troponin detected in the blood. The majority of patients presenting with NSTEMI do not develop a Q wave on the ECG; a minority develop a Qw MI (*thin green arrow*). Dx, diagnosis; ECG, electrocardiogram; MI, myocardial infarction. *(Adapted from CW Hamm et al: Lancet 358:1533, 2001, and MJ Davies: Heart 83:361, 2000; with permission from the BMJ Publishing Group.)*

mortality rate after admission for AMI has declined from 10 to about 5% over the past decade. The 1-year mortality rate after AMI is about 15%. Mortality is approximately fourfold higher in elderly patients (aged >75) as compared with younger patients.

When patients with prolonged ischemic discomfort at rest are first seen, the working clinical diagnosis is that they are suffering from an acute coronary syndrome **(Fig. 269-1)**. The 12-lead electrocardiogram (ECG) is a pivotal diagnostic and triage tool because it is at the center of the decision pathway for management; it permits distinction of those patients presenting with ST-segment elevation from those presenting without ST-segment elevation. Serum cardiac biomarkers are obtained to distinguish unstable angina (UA) from non-ST-segment elevation myocardial infarction (NSTEMI) and to assess the magnitude of an ST-segment elevation myocardial infarction (STEMI). Epidemiologic studies indicate there is a shift in the pattern of AMI over the last 15 years with more patients with NSTEMI than STEMI. This chapter focuses on the evaluation and management of patients with STEMI, while **Chap. 268** discusses UA/NSTEMI.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE

STEMI usually occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis. Slowly developing, high-grade coronary artery stenoses do not typically precipitate STEMI because of the development of a rich collateral network over time. Instead, STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury. This injury is produced or facilitated by factors such as cigarette smoking, hypertension, and lipid accumulation. In most cases, STEMI occurs when the surface of an atherosclerotic plaque becomes disrupted (exposing its contents to the blood) and conditions (local or systemic) favor thrombogenesis. A mural thrombus forms at the site of plaque disruption, and the involved coronary artery becomes occluded. Histologic studies indicate that the coronary plaques prone to disruption are those with a rich lipid core and a thin fibrous cap **(Chap. 291e** from the 19th edition of *Harrison's***)**. After an initial platelet monolayer forms at the site of the disrupted plaque, various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation. After agonist stimulation of platelets, thromboxane A_2 (a potent local vasoconstrictor) is released, further platelet activation occurs, and potential resistance to fibrinolysis develops.

In addition to the generation of thromboxane A_2, activation of platelets by agonists promotes a conformational change in the glycoprotein IIb/IIIa receptor **(Chap. 111)**. Once converted to its functional state, this receptor develops a high affinity for soluble adhesive proteins (i.e., integrins) such as fibrinogen. Since fibrinogen is a multivalent molecule, it can bind to two different platelets simultaneously, resulting in platelet cross-linking and aggregation.

The coagulation cascade is activated on exposure of tissue factor in damaged endothelial cells at the site of the disrupted plaque. Factors VII and X are activated, ultimately leading to the conversion of prothrombin to thrombin, which then converts fibrinogen to fibrin **(Chap. 112)**. Fluid-phase and clot-bound thrombin participate in an autoamplification reaction leading to further activation of the coagulation cascade. The culprit coronary artery eventually becomes occluded by a thrombus containing platelet aggregates and fibrin strands **(Fig. 269-2)**.

In rare cases, STEMI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a

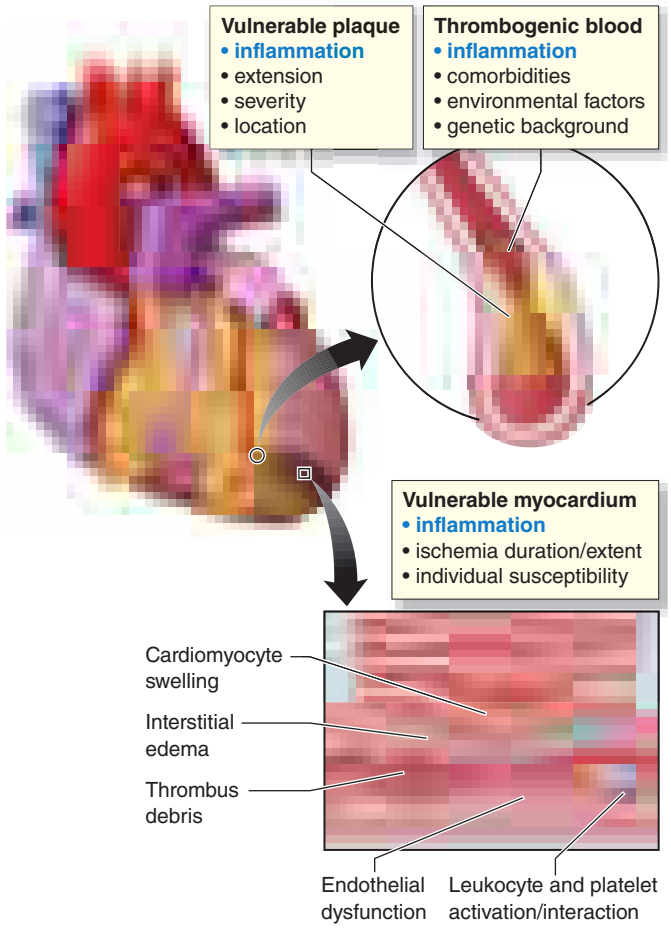

FIGURE 269-2 Critical determinants of myocardial infarction injury. The overlapping of vulnerable plaque and thrombogenic blood are critical determinants for myocardial infarction occurrence and extension. In addition, myocardial vulnerability, which is largely due to coronary microvascular dysfunction, contributes to extension and severity of ischemic injury. In the most severe form (known as no-reflow), structural and functional impairment sustain vascular obstruction. Endothelial dysfunction triggers leukocyte and platelet activation/interaction, whereas thrombotic debris may worsen the obstruction. Furthermore, cardiomyocyte swelling, interstitial edema, and tissue inflammation promote extravascular compression. *(Reproduced from F Montecucco et al: Eur Heart J 37:1268, 2016. Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015.)*

wide variety of systemic—particularly inflammatory—diseases. The amount of myocardial damage caused by coronary occlusion depends on (1) the territory supplied by the affected vessel, (2) whether or not the vessel becomes totally occluded, (3) the duration of coronary occlusion, (4) the quantity of blood supplied by collateral vessels to the affected tissue, (5) the demand for oxygen of the myocardium whose blood supply has been suddenly limited, (6) endogenous factors that can produce early spontaneous lysis of the occlusive thrombus, and (7) the adequacy of myocardial perfusion in the infarct zone when flow is restored in the occluded epicardial coronary artery.

Patients at increased risk for developing STEMI include those with multiple coronary risk factors and those with UA **(Chap. 268)**. Less common underlying medical conditions predisposing patients to STEMI include hypercoagulability, collagen vascular disease, cocaine abuse, and intracardiac thrombi or masses that can produce coronary emboli.

There have been major advances in the management of STEMI with recognition that the "chain of survival" involves a highly integrated system starting with prehospital care and extending to early hospital management so as to provide expeditious implementation of a reperfusion strategy.

CLINICAL PRESENTATION

In up to one-half of cases, a precipitating factor appears to be present before STEMI, such as vigorous physical exercise, emotional stress, or a medical or surgical illness. Although STEMI may commence at any time of the day or night, circadian variations have been reported such that clusters are seen in the morning within a few hours of awakening.

Pain is the most common presenting complaint in patients with STEMI. The pain is deep and visceral; adjectives commonly used to describe it are *heavy*, *squeezing*, and *crushing*; although, occasionally, it is described as stabbing or burning **(Chap. 11)**. It is similar in character to the discomfort of angina pectoris **(Chap. 267)** but commonly occurs at rest, is usually more severe, and lasts longer. Typically, the pain involves the central portion of the chest and/or the epigastrium, and, on occasion, it radiates to the arms. Less common sites of radiation include the abdomen, back, lower jaw, and neck. The frequent location of the pain beneath the xiphoid and epigastrium and the patients' denial that they may be suffering a heart attack are chiefly responsible for the common mistaken impression of indigestion. The pain of STEMI may radiate as high as the occipital area but not below the umbilicus. It is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and a sense of impending doom. The pain may commence when the patient is at rest, but when it begins during a period of exertion, it does not usually subside with cessation of activity, in contrast to angina pectoris.

The pain of STEMI can simulate pain from acute pericarditis **(Chap. 265)**, pulmonary embolism **(Chap. 273)**, acute aortic dissection **(Chap. 274)**, costochondritis, and gastrointestinal disorders. These conditions should therefore be considered in the differential diagnosis. Radiation of discomfort to the trapezius is not seen in patients with STEMI and may be a useful distinguishing feature that suggests pericarditis is the correct diagnosis. However, *pain is not uniformly present in patients with STEMI*. The proportion of painless STEMIs is greater in patients with diabetes mellitus, and it increases with age. In the elderly, STEMI may present as sudden-onset breathlessness, which may progress to pulmonary edema. Other less common presentations, with or without pain, include sudden loss of consciousness, a confusional state, a sensation of profound weakness, the appearance of an arrhythmia, evidence of peripheral embolism, or merely an unexplained drop in arterial pressure.

PHYSICAL FINDINGS

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. The combination of substernal chest pain persisting for >30 min and diaphoresis strongly suggests STEMI. Although many patients have a normal pulse rate and blood pressure within the first hour of STEMI, about one-fourth of patients with anterior infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia and/or hypertension), and up to one-half with inferior infarction show evidence of parasympathetic hyperactivity (bradycardia and/or hypotension).

The precordium is usually quiet, and the apical impulse may be difficult to palpate. In patients with anterior wall infarction, an abnormal systolic pulsation caused by dyskinetic bulging of infarcted myocardium may develop in the periapical area within the first days of the illness and then may resolve. Other physical signs of ventricular dysfunction include fourth and third heart sounds, decreased intensity of the first heart sound, and paradoxical splitting of the second heart sound **(Chap. 234)**. A transient midsystolic or late systolic apical systolic murmur due to dysfunction of the mitral valve apparatus may be present. A pericardial friction rub may be heard in patients with transmural STEMI at some time in the course of the illness, if they are examined frequently. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. Temperature elevations up to 38°C may be observed during the first week after STEMI. The arterial pressure is variable; in most patients with transmural infarction, systolic pressure declines by ~10–15 mmHg from the preinfarction state.

LABORATORY FINDINGS

STEMI progresses through the following temporal stages: (1) acute (first few hours–7 days), (2) healing (7–28 days), and (3) healed (≥29 days). When evaluating the results of diagnostic tests for STEMI, the temporal phase of the infarction must be considered. The laboratory tests of value in confirming the diagnosis may be divided into four groups: (1) ECG, (2) serum cardiac biomarkers, (3) cardiac imaging, and (4) nonspecific indices of tissue necrosis and inflammation.

ELECTROCARDIOGRAM

The electrocardiographic manifestations of STEMI are described in **Chap. 235**. During the initial stage, total occlusion of an epicardial coronary artery produces ST-segment elevation. Most patients initially presenting with ST-segment elevation ultimately evolve Q waves on the ECG. However, Q waves in the leads overlying the infarct zone may vary in magnitude and even appear only transiently, depending on the reperfusion status of the ischemic myocardium and restoration of transmembrane potentials over time. A small proportion of patients initially presenting with ST-segment elevation will not develop Q waves when the obstructing thrombus is not totally occlusive, obstruction is transient, or if a rich collateral network is present. Among patients presenting with ischemic discomfort but *without* ST-segment elevation, if a serum cardiac biomarker of necrosis (see below) is detected, the diagnosis of NSTEMI is ultimately made (Fig. 269-1). A minority of patients who present initially without ST-segment elevation may develop a Q-wave MI. Previously, it was believed that transmural myocardial infarction (MI) is present if the ECG demonstrates Q waves or loss of R waves, and nontransmural MI may be present if the ECG shows only transient ST-segment and T-wave changes. However, electrocardiographic-pathologic correlations are far from perfect and terms such as *Q-wave MI*, *non-Q-wave MI*, *transmural MI*, and *nontransmural MI* have been replaced by STEMI and NSTEMI (Fig. 269-1). Contemporary studies using magnetic resonance imaging (MRI) suggest that the development of a Q wave on the ECG is more dependent on the volume of infarcted tissue rather than the transmurality of infarction.

SERUM CARDIAC BIOMARKERS

Certain proteins, referred to as serum cardiac biomarkers, are released from necrotic heart muscle after STEMI. The rate of liberation of specific proteins differs depending on their intracellular location, their molecular weight, and the local blood and lymphatic flow. Cardiac biomarkers become detectable in the peripheral blood once the capacity of the cardiac lymphatics to clear the interstitium of the infarct zone is exceeded and spillover into the venous circulation occurs. The temporal pattern of protein release is of diagnostic importance. The criteria for AMI require a rise and/or fall in cardiac biomarker values with at

least one value above the 99th percentile of the upper reference limit for normal individuals.

Cardiac-specific troponin T (cTnT) and *cardiac-specific troponin I* (cTnI) have amino-acid sequences different from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. cTnT and cTnI may increase after STEMI to levels many times higher than the upper reference limit (the highest value seen in 99% of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI **(Fig. 269-3)**. With improvements in the assays for the cardiac-specific troponins, it is now possible to detect concentrations <1 ng/L in patients without ischemic-type chest discomfort. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and its MB isoenzyme (CK-MB) measurements, and they are, therefore, of particular value in distinguishing UA from NSTEMI. In practical terms, the high-sensitivity troponin assays are of less immediate value in patients with STEMI. Contemporary urgent reperfusion strategies necessitate making a decision (based largely on a combination of clinical and ECG findings) before the results of blood tests have returned from the laboratory. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK rises within 4–8 h and generally returns to normal by 48–72 h (Fig. 269-3). An important drawback of total CK measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore, is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CK-MB mass to CK activity ≥2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK-MB elevation.

Many hospitals are using cTnT or cTnI rather than CK-MB as the routine serum cardiac marker for diagnosis of STEMI, although any of these analytes remains clinically acceptable. It is *not* cost-effective to measure both a cardiac-specific troponin and CK-MB at all time points in every patient.

While it has long been recognized that the total quantity of protein released correlates with the size of the infarct, the peak protein concentration correlates only weakly with infarct size. Recanalization of a coronary artery occlusion (either spontaneously or by mechanical or pharmacologic means) in the early hours of STEMI causes earlier peaking of biomarker measurements (Fig. 269-3) because of a rapid washout from the interstitium of the infarct zone, quickly overwhelming lymphatic clearance of the proteins.

The *nonspecific reaction* to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days; the white blood cell count often reaches levels of 12,000–15,000/μL. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for 1 or 2 weeks.

CARDIAC IMAGING

Abnormalities of wall motion on *two-dimensional echocardiography* **(Chap. 236)** are almost universally present. Although acute STEMI cannot be distinguished from an old myocardial scar or from acute severe ischemia by echocardiography, the ease and safety of the procedure make its use appealing as a screening tool in the Emergency Department setting. When the ECG is not diagnostic of STEMI, early detection of the presence or absence of wall motion abnormalities by echocardiography can aid in management decisions, such as whether the patient should receive reperfusion therapy (e.g., fibrinolysis or a percutaneous coronary intervention [PCI]). Echocardiographic estimation of left ventricular (LV) function is useful prognostically; detection of reduced function serves as an indication for therapy with an inhibitor of the renin-angiotensin-aldosterone system. Echocardiography

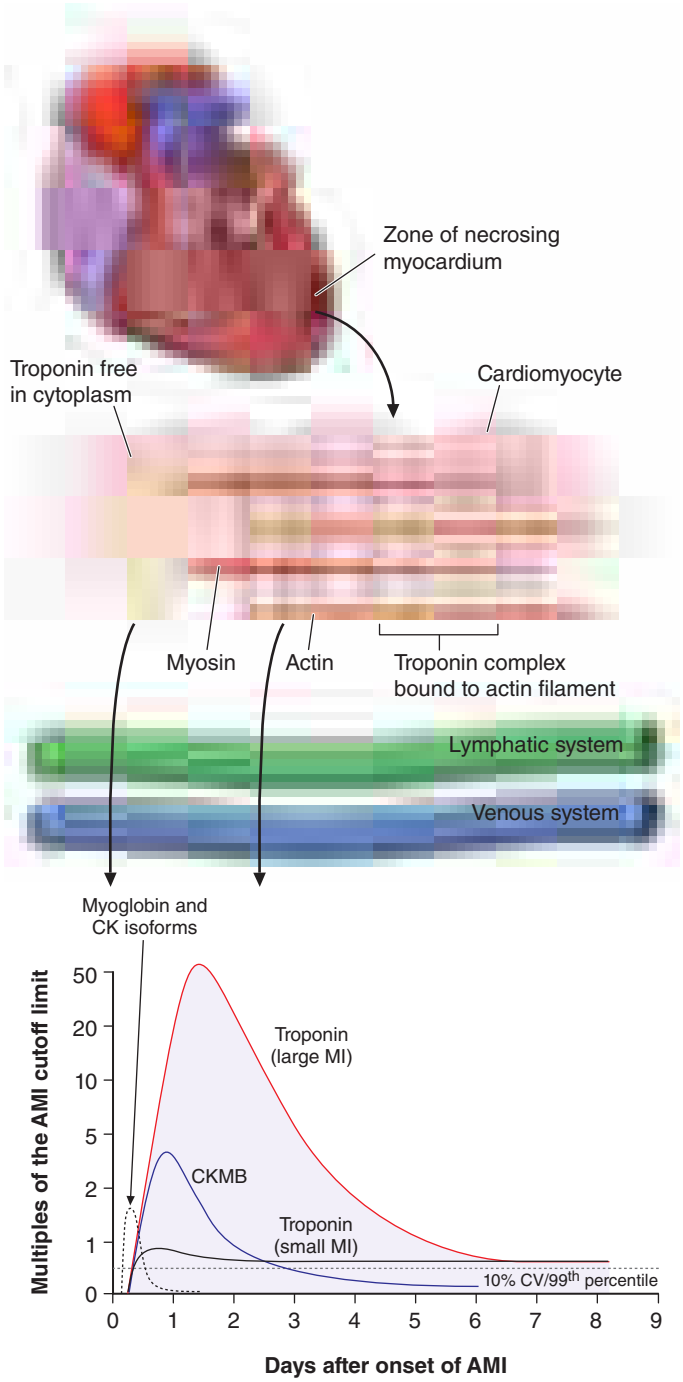

FIGURE 269-3 The zone of necrosing myocardium is shown at the top of the figure, followed in the middle portion of the figure by a diagram of a cardiomyocyte that is in the process of releasing biomarkers. The biomarkers that are released into the interstitium are first cleared by lymphatics followed subsequently by spillover into the venous system. After disruption of the sarcolemmal membrane of the cardiomyocyte, the cytoplasmic pool of biomarkers is released first (*left-most arrow in bottom portion of figure*). Markers such as myoglobin and CK isoforms are rapidly released, and blood levels rise quickly above the cutoff limit; this is then followed by a more protracted release of biomarkers from the disintegrating myofilaments that may continue for several days. Cardiac troponin levels rise to about 20–50 times the upper reference limit (the 99th percentile of values in a reference control group) in patients who have a "classic" acute myocardial infarction (MI) and sustain sufficient myocardial necrosis to result in abnormally elevated levels of the MB fraction of creatine kinase (CK-MB). Clinicians can now diagnose episodes of microinfarction by sensitive assays that detect cardiac troponin elevations above the upper reference limit, even though CK-MB levels may still be in the normal reference range (not shown). CV, coefficient of variation. *(Modified from EM Antman: Decision making with cardiac troponin tests. N Engl J Med 346:2079, 2002 and AS Jaffe, L Babiun, FS Apple: Biomarkers in acute cardiac disease: The present and the future. J Am Coll Cardiol 48:1, 2006.)*

may also identify the presence of right ventricular (RV) infarction, ventricular aneurysm, pericardial effusion, and LV thrombus. In addition, Doppler echocardiography is useful in the detection and quantitation of a ventricular septal defect and mitral regurgitation, two serious complications of STEMI.

Several *radionuclide imaging techniques* **(Chap. 236)** are available for evaluating patients with suspected STEMI. However, these imaging modalities are used less often than echocardiography because they are more cumbersome and lack sensitivity and specificity in many clinical circumstances. Myocardial perfusion imaging with [^{201}Tl] or [^{99m}Tc]-sestamibi, which are distributed in proportion to myocardial blood flow and concentrated by viable myocardium **(Chap. 267)**, reveals a defect ("cold spot") in most patients during the first few hours after development of a transmural infarct. Although perfusion scanning is extremely sensitive, it cannot distinguish acute infarcts from chronic scars and, thus, is not specific for the diagnosis of *acute* MI. Radionuclide ventriculography, carried out with [^{99m}Tc]-labeled red blood cells, frequently demonstrates wall motion disorders and reduction in the ventricular ejection fraction in patients with STEMI. While of value in assessing the hemodynamic consequences of infarction and in aiding in the diagnosis of RV infarction when the RV ejection fraction is depressed, this technique is nonspecific, as many cardiac abnormalities other than MI alter the radionuclide ventriculogram.

MI can be detected accurately with high-resolution cardiac MRI **(Chap. 236)** using a technique referred to as late enhancement. A standard imaging agent (gadolinium) is administered and images are obtained after a 10-min delay. Since little gadolinium enters normal myocardium, where there are tightly packed myocytes, but does percolate into the expanded intercellular region of the infarct zone, there is a bright signal in areas of infarction that appears in stark contrast to the dark areas of normal myocardium.

An Expert Consensus Task Force for the Universal Definition of Myocardial Infarction has provided a comprehensive set of criteria for the definition of MI that integrates the clinical and laboratory findings discussed earlier **(Table 269-1)** as well as a classification of MI into five types that reflect the clinical circumstances in which it may occur **(Table 269-2)**.

TABLE 269-1 Definition of Myocardial Infarction

Criteria for Acute Myocardial Infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment T-wave (ST-T) changes or new left bundle branch block (LBBB)
  - Development of pathologic Q waves in the electrocardiogram (ECG)
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes of new LBBB, but death occurred before cardiac biomarkers were obtained or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI)–related MI is arbitrarily defined by elevation of cTn values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG)–related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for Prior Myocardial Infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathologic Q waves with or without symptoms in the absence of nonischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause.
- Pathologic findings of a prior MI.

Source: Data from K Thygesen: Eur Heart J 33:2551, 2012.

INITIAL MANAGEMENT

PREHOSPITAL CARE

The prognosis in STEMI is largely related to the occurrence of two general classes of complications: (1) electrical complications (arrhythmias) and (2) mechanical complications ("pump failure"). Most out-of-hospital deaths from STEMI are due to the sudden development of ventricular fibrillation. The vast majority of deaths due to ventricular fibrillation occur within the first 24 h of the onset of symptoms, and of these, over half occur in the first hour. Therefore, the major elements of prehospital care of patients with suspected STEMI include (1) recognition of symptoms by the patient and prompt seeking of medical attention; (2) rapid deployment of an emergency medical team capable of performing resuscitative maneuvers, including defibrillation; (3) expeditious transportation of the patient to a hospital facility that is continuously staffed by physicians and nurses skilled in managing arrhythmias and providing advanced cardiac life support; and (4) expeditious implementation of reperfusion therapy. The greatest delay usually occurs not during transportation to the hospital but, rather, between the onset of pain and the patient's decision to call for help. This delay can best be reduced by health care professionals educating the public concerning the significance of chest discomfort and the importance of seeking early medical attention. Regular office visits with patients having a history of, or who are at risk for ischemic heart disease are important "teachable moments" for clinicians to review the symptoms of STEMI and the appropriate action plan.

Increasingly, monitoring and treatment are carried out by trained personnel in the ambulance, further shortening the time between the onset of the infarction and appropriate treatment. General guidelines for initiation of fibrinolysis in the prehospital setting include the ability to transmit 12-lead ECGs to confirm the diagnosis, the presence of paramedics in the ambulance, training of paramedics in the interpretation of ECGs and management of STEMI, and online medical command and control that can authorize the initiation of treatment in the field.

MANAGEMENT IN THE EMERGENCY DEPARTMENT

In the Emergency Department, the goals for the management of patients with suspected STEMI include control of cardiac discomfort, rapid identification of patients who are candidates for urgent reperfusion therapy, triage of lower-risk patients to the appropriate location in the hospital, and avoidance of inappropriate discharge of patients with STEMI. Many aspects of the treatment of STEMI are initiated in the Emergency Department and then continued during the in-hospital phase of management **(Fig. 269-4)**. The overarching goal is to minimize the time from first medical contact to initiation of reperfusion therapy. This may involve transfer from a non-PCI hospital to one that is PCI capable, with a goal of initiating PCI within 120 min of first medical contact (Fig. 269-4).

Aspirin is essential in the management of patients with suspected STEMI and is effective across the entire spectrum of acute coronary syndromes (Fig. 269-1). Rapid inhibition of cyclooxygenase-1 in platelets followed by a reduction of thromboxane A_2 levels is achieved by buccal absorption of a chewed 160–325-mg tablet in the Emergency Department.

TABLE 269-2 Classification of Myocardial Infarction

Type I: Spontaneous Myocardial Infarction
Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion nonobstructive or no CAD.
Type 2: Myocardial Infarction Secondary to an Ischemic Imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy.
Type 3: Myocardial Infarction Resulting in Death When Biomarker Values Are Unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiogram (ECG) changes or new left bundle branch block (LBBB), but death occurring before blood samples could be obtained or before cardiac biomarker could rise, or in rare cases, cardiac biomarkers were not collected.
Type 4a: Myocardial Infarction Related to Percutaneous Coronary Intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cardiac troponin (cTn) values >5 × 99th percentile upper reference limit (URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
Type 4b: Myocardial Infarction Related to Stent Thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
Type 5: Myocardial Infarction Related to Coronary Artery Bypass Grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 × 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathologic Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Source: K Thygesen: Eur Heart J 33:2551, 2012.

This measure should be followed by daily oral administration of aspirin in a dose of 75–162 mg.

In patients whose arterial O_2 saturation is normal, supplemental O_2 is of limited if any clinical benefit and therefore is not cost-effective. However, when hypoxemia is present, O_2 should be administered by nasal prongs or face mask (2–4 L/min) for the first 6–12 h after infarction; the patient should then be reassessed to determine if there is a continued need for such treatment.

CONTROL OF DISCOMFORT

Sublingual *nitroglycerin* can be given safely to most patients with STEMI. Up to three doses of 0.4 mg should be administered at about 5-min intervals. In addition to diminishing or abolishing chest discomfort, nitroglycerin may be capable of both decreasing myocardial oxygen demand (by lowering preload) and increasing myocardial oxygen supply (by dilating infarct-related coronary vessels or collateral vessels). In patients whose initially favorable response to sublingual nitroglycerin is followed by the return of chest discomfort, particularly if accompanied by other evidence of ongoing ischemia such as further ST-segment or T-wave shifts, the use of intravenous nitroglycerin should be considered. Therapy with nitrates should be avoided in patients who present with low systolic arterial pressure (<90 mmHg) or in whom there is clinical suspicion of RV infarction (inferior infarction on ECG, elevated jugular venous pressure, clear lungs, and hypotension). Nitrates should not be administered to patients who have taken a phosphodiesterase-5 inhibitor for erectile dysfunction within the preceding 24 h, because it may potentiate the hypotensive effects of nitrates. An idiosyncratic reaction to nitrates, consisting of sudden marked hypotension, sometimes occurs but can usually be reversed promptly by the rapid administration of intravenous atropine.

Morphine is a very effective analgesic for the pain associated with STEMI. However, it may reduce sympathetically mediated arteriolar and venous constriction, and the resulting venous pooling may reduce cardiac output and arterial pressure. These hemodynamic disturbances usually respond promptly to elevation of the legs, but in some patients, volume expansion with intravenous saline is required. The patient may experience diaphoresis and nausea, but these events usually pass and are replaced by a feeling of well-being associated with the relief of pain. Morphine also has a vagotonic effect and may cause bradycardia or advanced degrees of heart block, particularly in patients with inferior infarction. These side effects usually respond to atropine (0.5 mg intravenously). Morphine is routinely administered by repetitive (every 5 min) intravenous injection of small doses (2–4 mg), rather than by the subcutaneous administration of a larger quantity, because absorption may be unpredictable by the latter route.

Intravenous *beta blockers* are also useful in the control of the pain of STEMI. These drugs control pain effectively in some patients, presumably by diminishing myocardial O_2 demand and hence ischemia. More important, there is evidence that intravenous beta blockers reduce the risks of reinfarction and ventricular fibrillation (see "Beta-Adrenoceptor Blockers" below). A commonly employed regimen is metoprolol, 5 mg every 2–5 min for a total of three doses, provided the patient has a heart rate >60 beats/min, systolic pressure >100 mmHg, a PR interval <0.24 s, and rales that are no higher than 10 cm up from the diaphragm. Fifteen minutes after the last intravenous dose, an oral regimen is initiated of 50 mg every 6 h for 48 h, followed by 100 mg every 12 h.

Patient selection is important when considering beta blockers for STEMI. Oral beta blocker therapy should be initiated in the first 24 h for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk for cardiogenic shock, or (4) other relative contraindications to beta blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease).

Unlike beta blockers, calcium antagonists are of little value in the acute setting, and there is evidence that short-acting dihydropyridines may be associated with an increased mortality risk.

MANAGEMENT STRATEGIES

The primary tool for screening patients and making triage decisions is the initial 12-lead ECG. When ST-segment elevation of at least 2 mm in two contiguous precordial leads and 1 mm in two adjacent limb leads is present, a patient should be considered a candidate for *reperfusion therapy* (Figs. 269-1 and 269-4). The process of selecting patients for fibrinolysis versus primary PCI (angioplasty or stenting; **Chap. 270**) is discussed below. In the absence of ST-segment elevation, fibrinolysis is not helpful, and evidence exists suggesting that it may be harmful.

LIMITATION OF INFARCT SIZE

The quantity of myocardium that becomes necrotic as a consequence of a coronary artery occlusion is determined by factors other than just the site of occlusion. While the central zone of the infarct contains necrotic tissue that is irretrievably lost, the fate of the surrounding ischemic myocardium (ischemic penumbra) may be improved by timely restoration of coronary perfusion, reduction of myocardial O_2 demands, prevention of the accumulation of noxious metabolites, and blunting of the impact of mediators of reperfusion injury (e.g., calcium overload and oxygen-derived free radicals). Up to one-third of patients with STEMI may achieve *spontaneous* reperfusion of the infarct-related coronary artery within 24 h and experience improved healing of infarcted tissue. Reperfusion, either pharmacologically (by fibrinolysis) or by PCI, accelerates the opening of infarct-related arteries in those patients in whom spontaneous fibrinolysis ultimately would have occurred and

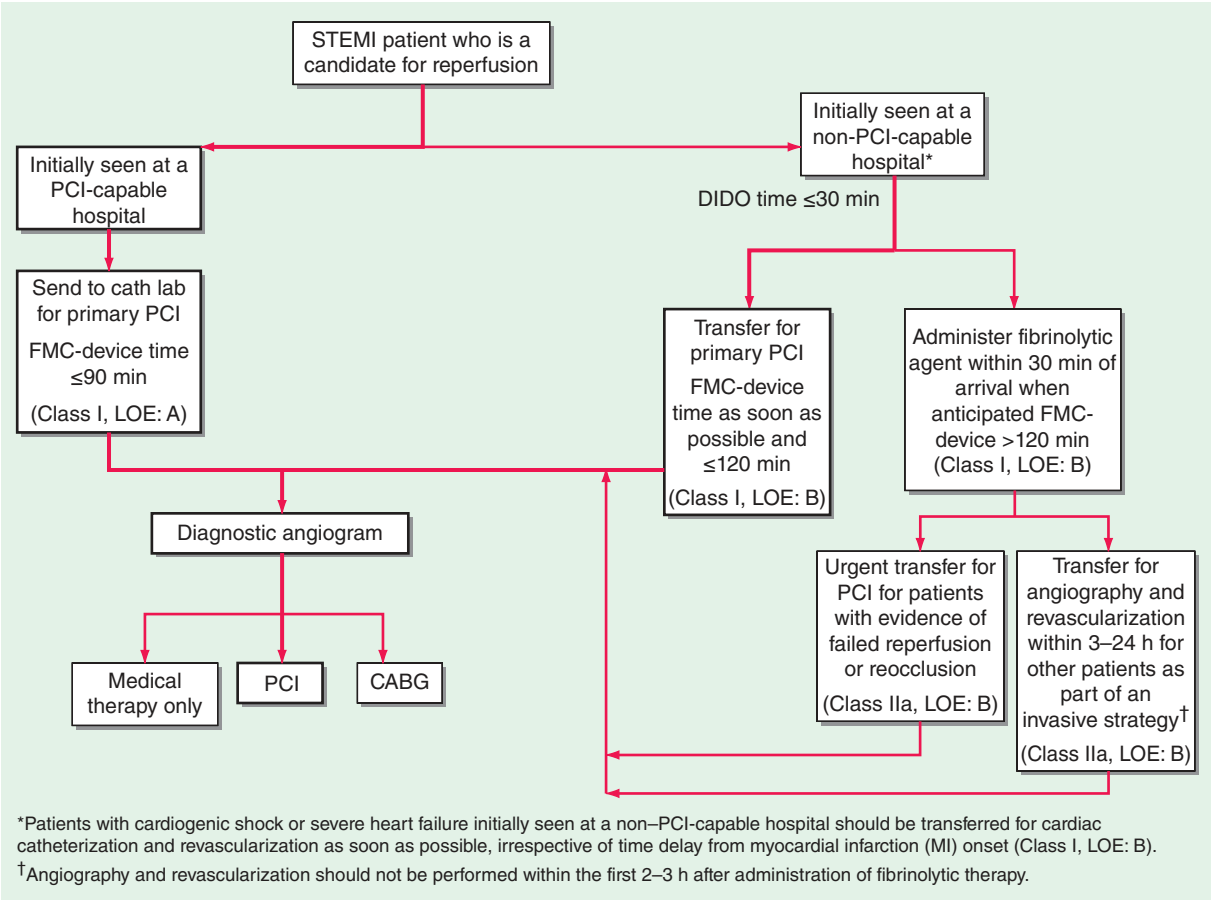

FIGURE 269-4 Reperfusion therapy for patients with ST-segment elevation myocardial infarction (STEMI). The *bold arrows* and *boxes* are the preferred strategies. Performance of percutaneous coronary intervention (PCI) is dictated by an anatomically appropriate culprit stenosis. CABG, coronary artery bypass graft; DIDO, door-in–door-out; FMC, first medical contact; LOE, level of evidence; STEMI, ST-elevation myocardial infarction. *(Adapted with permission from P O'Gara et al: Circulation 127:e362, 2013.)*

also greatly increases the number of patients in whom restoration of flow in the infarct-related artery is accomplished. Timely restoration of flow in the epicardial infarct–related artery combined with improved perfusion of the downstream zone of infarcted myocardium results in a limitation of infarct size. Protection of the ischemic myocardium by the maintenance of an optimal balance between myocardial O_2 supply and demand through pain control, treatment of congestive heart failure (CHF), and minimization of tachycardia and hypertension extends the "window" of time for the salvage of myocardium by reperfusion strategies.

Glucocorticoids and nonsteroidal anti-inflammatory agents, with the exception of aspirin, should be avoided in patients with STEMI. They can impair infarct healing and increase the risk of myocardial rupture, and their use may result in a larger infarct scar. In addition, they can increase coronary vascular resistance, thereby potentially reducing flow to ischemic myocardium.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

(See also Chap. 270) PCI, usually angioplasty and/or stenting without preceding fibrinolysis, referred to as *primary PCI*, is effective in restoring perfusion in STEMI when carried out on an emergency basis in the first few hours of MI. It has the advantage of being applicable to patients who have contraindications to fibrinolytic therapy (see below) but otherwise are considered appropriate candidates for reperfusion. It appears to be more effective than fibrinolysis in opening occluded coronary arteries and, *when performed by experienced operators in dedicated medical centers*, is associated with better short-term and long-term clinical outcomes. Compared with fibrinolysis, primary PCI is generally preferred when the diagnosis is in doubt, cardiogenic shock is present, bleeding risk is increased, or symptoms have been present for at least 2–3 h when the clot is more mature and less easily lysed by fibrinolytic drugs. However, PCI is expensive in terms of personnel and facilities, and its applicability is limited by its availability, around the clock, in only a minority of hospitals (Fig. 269-4).

FIBRINOLYSIS

If no contraindications are present (see below), fibrinolytic therapy should ideally be initiated within 30 min of presentation (i.e., door-to-needle time ≤30 min). The principal goal of fibrinolysis is prompt restoration of full coronary arterial patency. The fibrinolytic agents tissue plasminogen activator (tPA), streptokinase, tenecteplase (TNK), and reteplase (rPA) have been approved by the U.S. Food and Drug Administration for intravenous use in patients with STEMI. These drugs all act by promoting the conversion of plasminogen to plasmin, which subsequently lyses fibrin thrombi. Although considerable emphasis was first placed on a distinction between more fibrin-specific agents, such as tPA, and non-fibrin-specific agents, such as streptokinase, it is now recognized that these differences are only relative, as some degree of systemic fibrinolysis occurs with the former agents. TNK and rPA are referred to as *bolus fibrinolytics* since their administration does not require a prolonged intravenous infusion.

When assessed angiographically, flow in the culprit coronary artery is described by a simple qualitative scale called the *Thrombolysis in Myocardial Infarction (TIMI) grading system*: grade 0 indicates complete occlusion of the infarct-related artery; grade 1 indicates some penetration of the contrast material beyond the point of obstruction, but without perfusion of the distal coronary bed; grade 2 indicates perfusion of the entire infarct vessel into the distal bed, but with flow that is delayed compared with that of a normal artery; and grade 3 indicates full perfusion of the infarct vessel with normal flow. The latter is the goal of reperfusion therapy, because full perfusion of the infarct-related

coronary artery yields far better results in terms of limiting infarct size, maintenance of LV function, and reduction of both short- and long-term mortality rates. Additional methods of angiographic assessment of the efficacy of fibrinolysis include counting the number of frames on the cine film required for dye to flow from the origin of the infarct-related artery to a landmark in the distal vascular bed (*TIMI frame count*) and determining the rate of entry and exit of contrast dye from the microvasculature in the myocardial infarct zone (*TIMI myocardial perfusion grade*). These methods have an even tighter correlation with outcomes after STEMI than the more commonly employed TIMI flow grade.

tPA and the other relatively fibrin-specific plasminogen activators, rPA and TNK, are more effective than streptokinase at restoring full perfusion—i.e., TIMI grade 3 coronary flow—and have a small edge in improving survival as well. The current recommended regimen of tPA consists of a 15-mg bolus followed by 50 mg intravenously over the first 30 min, followed by 35 mg over the next 60 min. Streptokinase is administered as 1.5 million units (MU) intravenously over 1 h. rPA is administered in a double-bolus regimen consisting of a 10-MU bolus given over 2–3 min, followed by a second 10-MU bolus 30 min later. TNK is given as a single weight-based intravenous bolus of 0.53 mg/kg over 10 s. In addition to the fibrinolytic agents discussed earlier, pharmacologic reperfusion typically involves adjunctive antiplatelet and antithrombotic drugs, as discussed subsequently.

Clear contraindications to the use of fibrinolytic agents include a history of cerebrovascular hemorrhage at any time, a nonhemorrhagic stroke or other cerebrovascular event within the past year, marked hypertension (a reliably determined systolic arterial pressure >180 mmHg and/or a diastolic pressure >110 mmHg) at any time during the acute presentation, suspicion of aortic dissection, and active internal bleeding (excluding menses). While advanced age is associated with an increase in hemorrhagic complications, the benefit of fibrinolytic therapy in the elderly appears to justify its use if no other contraindications are present and the amount of myocardium in jeopardy appears to be substantial.

Relative contraindications to fibrinolytic therapy, which require assessment of the risk-to-benefit ratio, include current use of anti-coagulants (international normalized ratio ≥2), a recent (<2 weeks) invasive or surgical procedure or prolonged (>10 min) cardiopulmonary resuscitation, known bleeding diathesis, pregnancy, a hemorrhagic ophthalmic condition (e.g., hemorrhagic diabetic retinopathy), active peptic ulcer disease, and a history of severe hypertension that is currently adequately controlled. Because of the risk of an allergic reaction, patients should not receive streptokinase if that agent had been received within the preceding 5 days to 2 years.

Allergic reactions to streptokinase occur in ~2% of patients who receive it. While a minor degree of hypotension occurs in 4–10% of patients given this agent, marked hypotension occurs, although rarely, in association with severe allergic reactions.

Hemorrhage is the most frequent and potentially the most serious complication. Because bleeding episodes that require transfusion are more common when patients require invasive procedures, unnecessary venous or arterial interventions should be avoided in patients receiving fibrinolytic agents. Hemorrhagic stroke is the most serious complication and occurs in ~0.5–0.9% of patients being treated with these agents. This rate increases with advancing age, with patients >70 years experiencing roughly twice the rate of intracranial hemorrhage as those <65 years. Large-scale trials have suggested that the rate of intracranial hemorrhage with tPA or rPA is slightly higher than with streptokinase.

INTEGRATED REPERFUSION STRATEGY

Evidence has emerged that suggests PCI plays an increasingly important role in the management of STEMI. Prior approaches that segregated the pharmacologic and catheter-based approaches to reperfusion have now been replaced with an integrated approach to triage and transfer of STEMI patients to receive PCI (Fig. 269-4). To achieve the degree of integration required to care for a patient with STEMI, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of emergency medical services and hospital-based activities.

Cardiac catheterization and coronary angiography should be carried out after fibrinolytic therapy if there is evidence of either (1) failure of reperfusion (persistent chest pain and ST-segment elevation >90 min), in which case a *rescue PCI* should be considered; or (2) coronary artery reocclusion (re-elevation of ST segments and/or recurrent chest pain) or the development of recurrent ischemia (such as recurrent angina in the early hospital course or a positive exercise stress test before discharge), in which case an *urgent PCI* should be considered. Routine angiography and *elective PCI* even in asymptomatic patients following administration of fibrinolytic therapy are used with less frequency, given the numerous technologic advances that have occurred in the catheterization laboratory and the increasing number of skilled interventionalists. Coronary artery bypass surgery should be reserved for patients whose coronary anatomy is unsuited to PCI but in whom revascularization appears to be advisable because of extensive jeopardized myocardium or recurrent ischemia.

HOSPITAL PHASE MANAGEMENT

CORONARY CARE UNITS

These units are routinely equipped with a system that permits continuous monitoring of the cardiac rhythm of each patient and hemodynamic monitoring in selected patients. Defibrillators, respirators, noninvasive transthoracic pacemakers, and facilities for introducing pacing catheters and flow-directed balloon-tipped catheters are also usually available. Equally important is the organization of a highly trained team of nurses who can recognize arrhythmias; adjust the dosage of antiarrhythmic, vasoactive, and anticoagulant drugs; and perform cardiac resuscitation, including electroshock, when necessary.

Patients should be admitted to a coronary care unit early in their illness when it is expected that they will derive benefit from the sophisticated and expensive care provided. The availability of electrocardiographic monitoring and trained personnel outside the coronary care unit has made it possible to admit lower-risk patients (e.g., those not hemodynamically compromised and without active arrhythmias) to "intermediate care units."

The duration of stay in the coronary care unit is dictated by the ongoing need for intensive care. If symptoms are controlled with oral therapy, patients may be transferred out of the coronary care unit. Also, patients who have a confirmed STEMI but who are considered to be at low risk (no prior infarction and no persistent chest discomfort, CHF, hypotension, or cardiac arrhythmias) may be safely transferred out of the coronary care unit within 24 h.

Activity Factors that increase the work of the heart during the initial hours of infarction may increase the size of the infarct. Therefore, patients with STEMI should be kept at bed rest for the first 6–12 h. However, in the absence of complications, patients should be encouraged, under supervision, to resume an upright posture by dangling their feet over the side of the bed and sitting in a chair within the first 24 h. This practice is psychologically beneficial and usually results in a reduction in the pulmonary capillary wedge pressure. In the absence of hypotension and other complications, by the second or third day, patients typically are ambulating in their room with increasing duration and frequency, and they may shower or stand at the sink to bathe. By day 3 after infarction, patients should be increasing their ambulation progressively to a goal of 185 m (600 ft) at least three times a day.

Diet Because of the risk of emesis and aspiration soon after STEMI, patients should receive either nothing or only clear liquids by mouth for the first 4–12 h. The typical coronary care unit diet should provide ≤30% of total calories as fat and have a cholesterol content of ≤300 mg/d. Complex carbohydrates should make up 50–55% of total calories. Portions should not be unusually large, and the menu should be enriched with foods that are high in potassium, magnesium, and fiber, but low in sodium. Diabetes mellitus and hypertriglyceridemia are managed by restriction of concentrated sweets in the diet.

Bowel Management Bed rest and the effect of the narcotics used for the relief of pain often lead to constipation. A bedside commode rather than a bedpan, a diet rich in bulk, and the routine use of a stool

softener such as dioctyl sodium sulfosuccinate (200 mg/d) are recommended. If the patient remains constipated despite these measures, a laxative can be prescribed. Contrary to prior belief, it is safe to perform a gentle rectal examination on patients with STEMI.

Sedation Many patients require sedation during hospitalization to withstand the period of enforced inactivity with tranquility. Diazepam (5 mg), oxazepam (15–30 mg), or lorazepam (0.5–2 mg), given three to four times daily, is usually effective. An additional dose of any of the above medications may be given at night to ensure adequate sleep. Attention to this problem is especially important during the first few days in the coronary care unit, where the atmosphere of 24-h vigilance may interfere with the patient's sleep. However, sedation is no substitute for reassuring, quiet surroundings. Many drugs used in the coronary care unit, such as atropine, H_2 blockers, and narcotics, can produce delirium, particularly in the elderly. This effect should not be confused with agitation, and it is wise to conduct a thorough review of the patient's medications before arbitrarily prescribing additional doses of anxiolytics.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

The use of antiplatelet and anticoagulant therapy during the initial phase of STEMI is based on extensive laboratory and clinical evidence that thrombosis plays an important role in the pathogenesis of this condition. The primary goal of treatment with antiplatelet and anticoagulant agents is to maintain patency of the infarct-related artery, in conjunction with reperfusion strategies. A secondary goal is to reduce the patient's tendency to thrombosis and, thus, the likelihood of mural thrombus formation or deep-venous thrombosis, either of which could result in pulmonary embolization. The degree to which antiplatelet and anticoagulant therapy achieves these goals partly determines how effectively it reduces the risk of mortality from STEMI.

As noted previously (see "Management in the Emergency Department" earlier), aspirin is the standard antiplatelet agent for patients with STEMI. The most compelling evidence for the benefits of antiplatelet therapy (mainly with aspirin) in STEMI is found in the comprehensive overview by the Antiplatelet Trialists' Collaboration. Data from nearly 20,000 patients with MI enrolled in 15 randomized trials were pooled and revealed a relative reduction of 27% in the mortality rate, from 14.2% in control patients to 10.4% in patients receiving antiplatelet agents.

Inhibitors of the $P2Y_{12}$ ADP receptor prevent activation and aggregation of platelets. The addition of the $P2Y_{12}$ inhibitor clopidogrel to background treatment with aspirin to STEMI patients reduces the risk of clinical events (death, reinfarction, stroke) and, in patients receiving fibrinolytic therapy, has been shown to prevent reocclusion of a successfully reperfused infarct artery. New $P2Y_{12}$ ADP receptor antagonists, such as prasugrel and ticagrelor, are more effective than clopidogrel in preventing ischemic complications in STEMI patients undergoing PCI, but are associated with an increased risk of bleeding. Glycoprotein IIb/IIIa receptor inhibitors appear useful for preventing thrombotic complications in patients with STEMI undergoing PCI.

The standard anticoagulant agent used in clinical practice is unfractionated heparin (UFH). The available data suggest that when UFH is added to a regimen of aspirin and a non-fibrin-specific thrombolytic agent such as streptokinase, additional mortality benefit occurs (about 5 lives saved per 1000 patients treated). It appears that the immediate administration of intravenous UFH, in addition to a regimen of aspirin and relatively fibrin-specific fibrinolytic agents (tPA, rPA, or TNK), helps to maintain patency of the infarct-related artery. This effect is achieved at the cost of a small increased risk of bleeding. The recommended dose of UFH is an initial bolus of 60 U/kg (maximum 4000 U) followed by an initial infusion of 12 U/kg per h (maximum 1000 U/h). The activated partial thromboplastin time during maintenance therapy should be 1.5–2 times the control value.

Alternatives to UFH for anticoagulation of patients with STEMI are the low-molecular-weight heparin (LMWH) preparations, a synthetic version of the critical pentasaccharide sequence (fondaparinux), and the direct antithrombin bivalirudin. Advantages of LMWHs include high bioavailability permitting administration subcutaneously, reliable anticoagulation without monitoring, and greater antiXa:IIa activity. Enoxaparin has been shown to reduce significantly the composite endpoints of death/nonfatal reinfarction and death/nonfatal reinfarction/urgent revascularization compared with UFH in STEMI patients who receive fibrinolysis. Treatment with enoxaparin is associated with higher rates of serious bleeding, but net clinical benefit—a composite endpoint that combines efficacy and safety—still favors enoxaparin over UFH. Interpretation of the data on fondaparinux is difficult because of the complex nature of the pivotal clinical trial evaluating it in STEMI (OASIS-6). Fondaparinux appears superior to placebo in STEMI patients not receiving reperfusion therapy, but its relative efficacy and safety compared with UFH is less certain. Owing to the risk of catheter thrombosis, fondaparinux should not be used alone at the time of coronary angiography and PCI but should be combined with another anticoagulant with antithrombin activity such as UFH or bivalirudin. Contemporary trials of bivalirudin used an open-label design to evaluate its efficacy and safety compared with UFH plus a glycoprotein IIb/IIIa inhibitor. Bivalirudin was associated with a lower rate of bleeding, largely driven by reductions in vascular access site hematomas ≥5 cm or the administration of blood transfusions.

Patients with an anterior location of the infarction, severe LV dysfunction, heart failure, a history of embolism, two-dimensional echocardiographic evidence of mural thrombus, or atrial fibrillation are at increased risk of systemic or pulmonary thromboembolism. Such individuals should receive full therapeutic levels of anticoagulant therapy (LMWH or UFH) while hospitalized, followed by at least 3 months of warfarin therapy.

BETA-ADRENOCEPTOR BLOCKERS

The benefits of beta blockers in patients with STEMI can be divided into those that occur immediately when the drug is given acutely and those that accrue over the long term when the drug is given for secondary prevention after an infarction. Acute intravenous beta blockade improves the myocardial O_2 supply-demand relationship, decreases pain, reduces infarct size, and decreases the incidence of serious ventricular arrhythmias. In patients who undergo fibrinolysis soon after the onset of chest pain, no incremental reduction in mortality rate is seen with beta blockers, but recurrent ischemia and reinfarction are reduced.

Thus, beta-blocker therapy after STEMI is useful for most patients (including those treated with an angiotensin-converting enzyme [ACE] inhibitor) except those in whom it is specifically contraindicated (patients with heart failure or severely compromised LV function, heart block, orthostatic hypotension, or a history of asthma) and perhaps those whose excellent long-term prognosis (defined as an expected mortality rate of <1% per year, patients <55 years, no previous MI, with normal ventricular function, no complex ventricular ectopy, and no angina) markedly diminishes any potential benefit.

INHIBITION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

ACE inhibitors reduce the mortality rate after STEMI, and the mortality benefits are additive to those achieved with aspirin and beta blockers. The maximum benefit is seen in high-risk patients (those who are elderly or who have an anterior infarction, a prior infarction, and/or globally depressed LV function), but evidence suggests that a short-term benefit occurs when ACE inhibitors are prescribed unselectively to all hemodynamically stable patients with STEMI (i.e., those with a systolic pressure >100 mmHg). The mechanism involves a reduction in ventricular remodeling after infarction (see "Ventricular Dysfunction" later) with a subsequent reduction in the risk of CHF. The rate of recurrent infarction may also be lower in patients treated chronically with ACE inhibitors after infarction.

Before hospital discharge, LV function should be assessed with an imaging study. ACE inhibitors should be continued indefinitely in patients who have clinically evident CHF, in patients in whom an imaging study shows a reduction in global LV function or a large regional wall motion abnormality, or in those who are hypertensive.

Angiotensin receptor blockers (ARBs) should be administered to STEMI patients who are intolerant of ACE inhibitors and who have either clinical or radiologic signs of heart failure. Long-term aldosterone blockade should be prescribed for STEMI patients without significant renal dysfunction (creatinine ≥2.5 mg/dL in men and ≥2.0 mg/dL in women) or hyperkalemia (potassium ≥5.0 mEq/L) who are already receiving therapeutic doses of an ACE inhibitor, have an LV ejection fraction ≤40%, and have either symptomatic heart failure or diabetes mellitus. A multidrug regimen for inhibiting the renin-angiotensin-aldosterone system has been shown to reduce both heart failure–related and sudden cardiac death–related cardiovascular mortality after STEMI, but has not been as thoroughly explored as ACE inhibitors in STEMI patients.

OTHER AGENTS

Favorable effects on the ischemic process and ventricular remodeling (see below) previously led many physicians to routinely use *intravenous nitroglycerin* (5–10 µg/min initial dose and up to 200 µg/min as long as hemodynamic stability is maintained) for the first 24–48 h after the onset of infarction. However, the benefits of routine use of intravenous nitroglycerin are less in the contemporary era where beta-adrenoceptor blockers and ACE inhibitors are routinely prescribed for patients with STEMI.

Results of multiple trials of different calcium antagonists have failed to establish a role for these agents in the treatment of most patients with STEMI. Therefore, the routine use of calcium antagonists cannot be recommended. Strict control of blood glucose in diabetic patients with STEMI has been shown to reduce the mortality rate. Serum magnesium should be measured in all patients on admission, and any demonstrated deficits should be corrected to minimize the risk of arrhythmias.

COMPLICATIONS AND THEIR MANAGEMENT

VENTRICULAR DYSFUNCTION

After STEMI, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident CHF in the months to years after infarction. Soon after STEMI, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct, i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone. Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the anterior wall and apex of the left ventricle and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates). In patients with an ejection fraction <40%, regardless of whether or not heart failure is present, ACE inhibitors or ARBs should be prescribed (see "Inhibition of the Renin-Angiotensin-Aldosterone System" earlier).

HEMODYNAMIC ASSESSMENT

Pump failure is now the primary cause of in-hospital death from STEMI. The extent of infarction correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S_3 and S_4 gallop sounds. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevated LV filling pressure and elevated pulmonary artery pressure are the characteristic hemodynamic findings, but these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 252).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S_3 gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure <90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. When this classification was established in 1967, the expected hospital mortality rate of patients in these classes was as follows: class I, 0–5%; class II, 10–20%; class III, 35–45%; and class IV, 85–95%. With advances in management, the mortality rate in each class has fallen, perhaps by as much as one-third to one-half.

Hemodynamic evidence of abnormal global LV function appears when contraction is seriously impaired in 20–25% of the left ventricle. Infarction of ≥40% of the left ventricle usually results in cardiogenic shock (Chap. 298). Positioning of a balloon flotation (Swan-Ganz) catheter in the pulmonary artery permits monitoring of LV filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence of CHF. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with STEMI have markedly elevated LV filling pressures (>22 mmHg) and normal cardiac indices (2.6–3.6 L/[min/m^2]), while others have relatively low LV filling pressures (<15 mmHg) and reduced cardiac indices. The former patients usually benefit from diuresis, while the latter may respond to volume expansion.

HYPOVOLEMIA

This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with STEMI in some patients. It may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with STEMI and hypotension before more vigorous forms of therapy are begun. Central venous pressure reflects RV rather than LV filling pressure and is an inadequate guide for adjustment of blood volume, because LV function is almost always affected much more adversely than RV function in patients with STEMI. The optimal LV filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally ~20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output plateaus, and further increases in LV filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

TREATMENT

Congestive Heart Failure

The management of CHF in association with STEMI is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (Chap. 252), except that the benefits of digitalis administration to patients with STEMI are unimpressive. By contrast, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. LV filling pressure falls and orthopnea and dyspnea improve after the intravenous administration of furosemide or other loop diuretics. These drugs should be used with caution, however, as they can result in a massive diuresis with associated decreases in plasma volume, cardiac output, systemic blood pressure, and, hence, coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, and intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of LV filling pressure. Vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction after STEMI, especially for the long term. (See "Inhibition of the Renin-Angiotensin-Aldosterone System" earlier.)

CARDIOGENIC SHOCK

Prompt reperfusion, efforts to reduce infarct size and treatment of ongoing ischemia and other complications of MI appear to have reduced the incidence of cardiogenic shock from 20 to about 7%. Only 10% of patients with this condition present with it on admission, while 90% develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of "piecemeal" necrosis extending outward from the original infarct zone. **The evaluation and management of cardiogenic shock and severe power failure after STEMI are discussed in detail in Chap. 298.**

RIGHT VENTRICULAR INFARCTION

Approximately one-third of patients with inferior infarction demonstrate at least a minor degree of RV necrosis. An occasional patient with inferoposterior LV infarction also has extensive RV infarction, and rare patients present with infarction limited primarily to the RV. Clinically significant RV infarction causes signs of severe RV failure (jugular venous distention, Kussmaul's sign, hepatomegaly **[Chap. 234]**) with or without hypotension. ST-segment elevations of right-sided precordial ECG leads, particularly lead V_4R, are frequently present in the first 24 h in patients with RV infarction. Two-dimensional echocardiography is helpful in determining the degree of RV dysfunction. Catheterization of the right side of the heart often reveals a distinctive hemodynamic pattern resembling constrictive pericarditis (steep right atrial "y" descent and an early diastolic dip and plateau in RV waveforms) **(Chap. 265)**. Therapy consists of volume expansion to maintain adequate RV preload and efforts to improve LV performance with attendant reduction in pulmonary capillary wedge and pulmonary arterial pressures.

ARRHYTHMIAS

(See also Chaps. 239 and 241) The incidence of arrhythmias after STEMI is higher in patients seen early after the onset of symptoms. The mechanisms responsible for infarction-related arrhythmias include autonomic nervous system imbalance, electrolyte disturbances, ischemia, and slowed conduction in zones of ischemic myocardium. An arrhythmia can usually be managed successfully if trained personnel and appropriate equipment are available when it develops. Since most deaths from arrhythmia occur during the first few hours after infarction, the effectiveness of treatment relates directly to the speed with which patients come under medical observation. The prompt management of arrhythmias constitutes a significant advance in the treatment of STEMI.

Ventricular Premature Beats Infrequent, sporadic ventricular premature depolarizations occur in almost all patients with STEMI and do not require therapy. Whereas in the past, frequent, multifocal, or early diastolic ventricular extrasystoles (so-called warning arrhythmias) were routinely treated with antiarrhythmic drugs to reduce the risk of development of ventricular tachycardia and ventricular fibrillation, pharmacologic therapy is now reserved for patients with sustained ventricular arrhythmias. Prophylactic antiarrhythmic therapy (either intravenous lidocaine early or oral agents later) is contraindicated for ventricular premature beats in the absence of clinically important ventricular tachyarrhythmias, because such therapy may actually increase the mortality rate. Beta-adrenoceptor blocking agents are effective in abolishing ventricular ectopic activity in patients with STEMI and in the prevention of ventricular fibrillation. As described earlier (see "Beta-Adrenoceptor Blockers"), they should be used routinely in patients without contraindications. In addition, hypokalemia and hypomagnesemia are risk factors for ventricular fibrillation in patients with STEMI; to reduce the risk, the serum potassium concentration should be adjusted to ~4.5 mmol/L and magnesium to about 2.0 mmol/L.

Ventricular Tachycardia and Fibrillation Within the first 24 h of STEMI, ventricular tachycardia and fibrillation can occur without prior warning arrhythmias. The occurrence of ventricular fibrillation can be reduced by prophylactic administration of intravenous lidocaine. However, prophylactic use of lidocaine has not been shown to reduce overall mortality from STEMI. In fact, in addition to causing possible noncardiac complications, lidocaine may predispose to an excess risk of bradycardia and asystole. For these reasons, and with earlier treatment of active ischemia, more frequent use of beta-blocking agents, and the nearly universal success of electrical cardioversion or defibrillation, routine prophylactic antiarrhythmic drug therapy *is no longer recommended*.

Sustained ventricular tachycardia that is well tolerated hemodynamically should be treated with an intravenous regimen of amiodarone (bolus of 150 mg over 10 min, followed by infusion of 1.0 mg/min for 6 h and then 0.5 mg/min). A less desirable but alternative regimen is procainamide (bolus of 15 mg/kg over 20–30 min; infusion of 1–4 mg/min). If ventricular tachycardia does not stop promptly, electroversion should be used **(Chap. 241)**. An unsynchronized discharge of 200–300 J (monophasic waveform; ~50% of these energies with biphasic waveforms) is used immediately in patients with ventricular fibrillation or when ventricular tachycardia causes hemodynamic deterioration. Ventricular tachycardia or fibrillation that is refractory to electroshock may be more responsive after the patient is treated with epinephrine (1 mg intravenously or 10 mL of a 1:10,000 solution via the intracardiac route) or amiodarone (a 75–150-mg bolus).

Ventricular arrhythmias, including the unusual form of ventricular tachycardia known as torsades des pointes **(Chaps. 247 and 249)**, may occur in patients with STEMI as a consequence of other concurrent problems (such as hypoxia, hypokalemia, or other electrolyte disturbances) or of the toxic effects of an agent being administered to the patient (such as digoxin or quinidine). A search for such secondary causes should always be undertaken.

Although the in-hospital mortality rate is increased, the long-term survival is excellent in patients who survive to hospital discharge after *primary* ventricular fibrillation; i.e., ventricular fibrillation that is a primary response to acute ischemia that occurs during the first 48 h and is not associated with predisposing factors such as CHF, shock, bundle branch block, or ventricular aneurysm. This result is in sharp contrast to the poor prognosis for patients who develop ventricular fibrillation *secondary* to severe pump failure. For patients who develop ventricular tachycardia or ventricular fibrillation late in their hospital course (i.e., after the first 48 h), the mortality rate is increased both in-hospital and during long-term follow-up. Such patients should be considered for electrophysiologic study and implantation of a cardioverter-defibrillator (ICD) **(Chap. 247)**. A more challenging issue is the prevention of sudden cardiac death from ventricular fibrillation late after STEMI in patients who have not exhibited sustained ventricular tachyarrhythmias during their index hospitalization. An algorithm for selection of patients who warrant prophylactic implantation of an ICD is shown in **Fig. 269-5**.

Accelerated Idioventricular Rhythm Accelerated idioventricular rhythm (AIVR, "slow ventricular tachycardia"), a ventricular rhythm with a rate of 60–100 beats/min, often occurs transiently during fibrinolytic therapy at the time of reperfusion. For the most part, AIVR, whether it occurs in association with fibrinolytic therapy or spontaneously, is benign and does not presage the development of classic ventricular tachycardia. Most episodes of AIVR do not require treatment if the patient is monitored carefully, as degeneration into a more serious arrhythmia is rare.

Supraventricular Arrhythmias Sinus tachycardia is the most common supraventricular arrhythmia. If it occurs secondary to another cause (such as anemia, fever, heart failure, or a metabolic derangement), the primary problem should be treated first. However, if it appears to be due to sympathetic overstimulation (e.g., as part of a hyperdynamic state), then treatment with a beta blocker is indicated. Other common arrhythmias in this group are atrial flutter and atrial fibrillation, which are often secondary to LV failure. Digoxin is usually the treatment of choice for supraventricular arrhythmias if heart failure is present. If heart failure is absent, beta blockers, verapamil, or diltiazem are suitable alternatives for controlling the ventricular rate, as they may also help to control ischemia. If the abnormal rhythm persists for >2 h with a ventricular rate >120 beats/min, or if tachycardia induces heart failure, shock, or ischemia (as manifested by recurrent

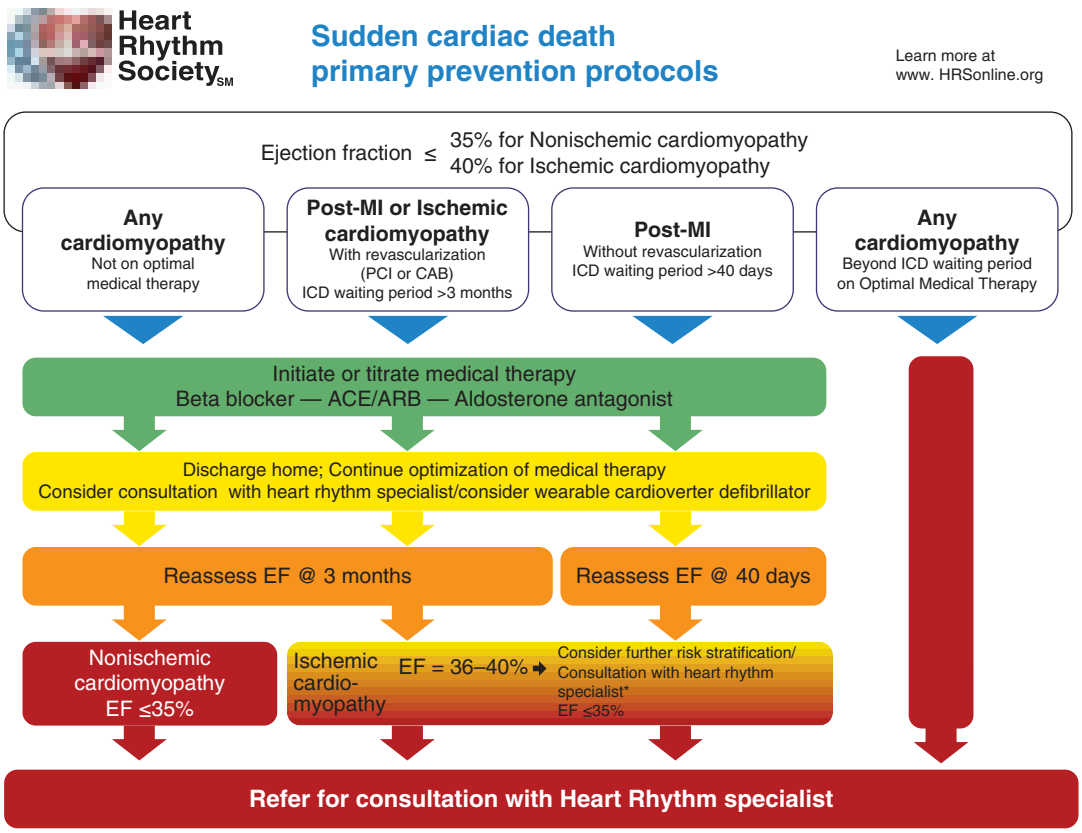

FIGURE 269-5 Algorithm for assessment of need for implantation of a cardioverter-defibrillator. The appropriate management is selected based on measurement of left ventricular ejection fraction, the timing following infarction, and whether revascularization has been performed. *(Reproduced from data at www.hrsonline.org.)*

pain or ECG changes), a synchronized electroshock (100–200 J monophasic waveform) should be used.

Accelerated junctional rhythms have diverse causes but may occur in patients with inferoposterior infarction. Digitalis excess must be ruled out. In some patients with severely compromised LV function, the loss of appropriately timed atrial systole results in a marked reduction of cardiac output. Right atrial or coronary sinus pacing is indicated in such instances.

Sinus Bradycardia Treatment of sinus bradycardia is indicated if hemodynamic compromise results from the slow heart rate. Atropine is the most useful drug for increasing heart rate and should be given intravenously in doses of 0.5 mg initially. If the rate remains <50–60 beats/min, additional doses of 0.2 mg, up to a total of 2.0 mg, may be given. Persistent bradycardia (<40 beats/min) despite atropine may be treated with electrical pacing. Isoproterenol should be avoided.

Atrioventricular and Intraventricular Conduction Disturbances (See also Chap. 239) Both the in-hospital mortality rate and the postdischarge mortality rate of patients who have complete atrioventricular (AV) block in association with anterior infarction are markedly higher than those of patients who develop AV block with inferior infarction. This difference is related to the fact that heart block in inferior infarction is commonly a result of increased vagal tone and/or the release of adenosine and therefore is transient. In anterior wall infarction, however, heart block is usually related to ischemic malfunction of the conduction system, which is commonly associated with extensive myocardial necrosis.

Temporary electrical pacing provides an effective means of increasing the heart rate of patients with bradycardia due to AV block. However, acceleration of the heart rate may have only a limited impact on prognosis in patients with anterior wall infarction and complete heart block in whom the large size of the infarct is the major factor determining outcome. It should be carried out if it improves hemodynamics. Pacing does appear to be beneficial in patients with inferoposterior infarction who have complete heart block associated with heart failure, hypotension, marked bradycardia, or significant ventricular ectopic activity. A subgroup of these patients, those with RV infarction, often respond poorly to ventricular pacing because of the loss of the atrial contribution to ventricular filling. In such patients, dual-chamber AV sequential pacing may be required.

External noninvasive pacing electrodes should be positioned in a "demand" mode for patients with sinus bradycardia (rate <50 beats/min) that is unresponsive to drug therapy, Mobitz II second-degree AV block, third-degree heart block, or bilateral bundle branch block (e.g., right bundle branch block plus left anterior fascicular block). Retrospective studies suggest that permanent pacing may reduce the long-term risk of sudden death due to bradyarrhythmias in the rare patient who develops combined persistent bifascicular and transient third-degree heart block during the acute phase of MI.

OTHER COMPLICATIONS

Recurrent Chest Discomfort Because recurrent or persistent ischemia often heralds extension of the original infarct or reinfarction in a new myocardial zone and is associated with a near tripling of mortality after STEMI, patients with these symptoms should be referred for prompt coronary arteriography and mechanical revascularization. Administration of a fibrinolytic agent is an alternative to early mechanical revascularization.

Pericarditis (See also Chap. 265) Pericardial friction rubs and/or pericardial pain are frequently encountered in patients with STEMI involving the epicardium. This complication can usually be managed with aspirin (650 mg four times daily). It is important to diagnose the chest pain of pericarditis accurately, because failure to recognize it may lead to the erroneous diagnosis of recurrent ischemic pain and/or infarct extension, with resulting inappropriate use of anticoagulants,

nitrates, beta blockers, or coronary arteriography. When it occurs, complaints of pain radiating to either trapezius muscle is helpful, because such a pattern of discomfort is typical of pericarditis but rarely occurs with ischemic discomfort. Anticoagulants potentially could cause tamponade in the presence of acute pericarditis (as manifested by either pain or persistent rub) and therefore should not be used unless there is a compelling indication.

Thromboembolism Clinically apparent thromboembolism complicates STEMI in ~10% of cases, but embolic lesions are found in 20% of patients in necropsy series, suggesting that thromboembolism is often clinically silent. Thromboembolism is considered to be an important contributing cause of death in 25% of patients with STEMI who die after admission to the hospital. Arterial emboli originate from LV mural thrombi, while most pulmonary emboli arise in the leg veins.

Thromboembolism typically occurs in association with large infarcts (especially anterior), CHF, and an LV thrombus detected by echocardiography. The incidence of arterial embolism from a clot originating in the ventricle at the site of an infarction is small but real. Two-dimensional echocardiography reveals LV thrombi in about one-third of patients with anterior wall infarction but in few patients with inferior or posterior infarction. Arterial embolism often presents as a major complication, such as hemiparesis when the cerebral circulation is involved or hypertension if the renal circulation is compromised. When a thrombus has been clearly demonstrated by echocardiographic or other techniques or when a large area of regional wall motion abnormality is seen even in the absence of a detectable mural thrombus, systemic anticoagulation should be undertaken (in the absence of contraindications), as the incidence of embolic complications appears to be markedly lowered by such therapy. The appropriate duration of therapy is unknown, but 3–6 months is probably prudent.

Left Ventricular Aneurysm The term *ventricular aneurysm* is usually used to describe *dyskinesis* or local expansile paradoxical wall motion. Normally functioning myocardial fibers must shorten more if stroke volume and cardiac output are to be maintained in patients with ventricular aneurysm; if they cannot, overall ventricular function is impaired. True aneurysms are composed of scar tissue and neither predispose to nor are associated with cardiac rupture.

The complications of LV aneurysm do not usually occur for weeks to months after STEMI; they include CHF, arterial embolism, and ventricular arrhythmias. Apical aneurysms are the most common and the most easily detected by clinical examination. The physical finding of greatest value is a double, diffuse, or displaced apical impulse. Ventricular aneurysms are readily detected by two-dimensional echocardiography, which may also reveal a mural thrombus in an aneurysm.

Rarely, myocardial rupture may be contained by a local area of pericardium, along with organizing thrombus and hematoma. Over time, this *pseudoaneurysm* enlarges, maintaining communication with the LV cavity through a narrow neck. Because a pseudoaneurysm often ruptures spontaneously, it should be surgically repaired if recognized.

POSTINFARCTION RISK STRATIFICATION AND MANAGEMENT

Many clinical and laboratory factors have been identified that are associated with an increase in cardiovascular risk after initial recovery from STEMI. Some of the most important factors include persistent ischemia (spontaneous or provoked), depressed LV ejection fraction (<40%), rales above the lung bases on physical examination or congestion on chest radiograph, and symptomatic ventricular arrhythmias. Other features associated with increased risk include a history of previous MI, age >75, diabetes mellitus, prolonged sinus tachycardia, hypotension, ST-segment changes at rest without angina ("silent ischemia"), an abnormal signal-averaged ECG, nonpatency of the infarct-related coronary artery (if angiography is undertaken), and persistent advanced heart block or a new intraventricular conduction abnormality on the ECG. Therapy must be individualized on the basis of the relative importance of the risk(s) present.

The goal of preventing reinfarction and death after recovery from STEMI has led to strategies to evaluate risk after infarction. In stable patients, submaximal exercise stress testing may be carried out before hospital discharge to detect residual ischemia and ventricular ectopy and to provide the patient with a guideline for exercise in the early recovery period. Alternatively, or in addition, a maximal (symptom-limited) exercise stress test may be carried out 4–6 weeks after infarction. Evaluation of LV function is usually warranted as well. Recognition of a depressed LV ejection fraction by echocardiography or radionuclide ventriculography identifies patients who should receive medications to inhibit the renin-angiotensin-aldosterone system. Patients in whom angina is induced at relatively low workloads, those who have a large reversible defect on perfusion imaging or a depressed ejection fraction, those with demonstrable ischemia, and those in whom exercise provokes symptomatic ventricular arrhythmias should be considered at high risk for recurrent MI or death from arrhythmia (Fig. 269-5). Cardiac catheterization with coronary angiography and/or invasive electrophysiologic evaluation is advised.

Exercise tests also aid in formulating an individualized exercise prescription, which can be much more vigorous in patients who tolerate exercise without any of the previously mentioned adverse signs. In addition, predischarge stress testing may provide an important psychological benefit, building the patient's confidence by demonstrating a reasonable exercise tolerance.

In many hospitals, a cardiac rehabilitation program with progressive exercise is initiated in the hospital and continued after discharge. Ideally, such programs should include an educational component that informs patients about their disease and its risk factors.

The usual duration of hospitalization for an uncomplicated STEMI is about 3–5 days. The remainder of the convalescent phase may be accomplished at home. During the first 1–2 weeks, the patient should be encouraged to increase activity by walking about the house and outdoors in good weather. Normal sexual activity may be resumed during this period. After 2 weeks, the physician must regulate the patient's activity on the basis of exercise tolerance. Most patients will be able to return to work within 2–4 weeks.

SECONDARY PREVENTION

Various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin) after STEMI is associated with a 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg orally daily). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.

The chronic routine use of oral beta-adrenoceptor blockers for at least 2 years after STEMI is supported by well-conducted, placebo-controlled trials.

Evidence suggests that warfarin lowers the risk of late mortality and the incidence of reinfarction after STEMI. Most physicians prescribe aspirin routinely for all patients without contraindications and add warfarin for patients at increased risk of embolism (see "Thromboembolism" earlier). Several studies suggest that in patients <75 years old a low dose of aspirin (75–81 mg/d) in combination with warfarin administered to achieve an international normalized ratio >2.0 is more effective than aspirin alone for preventing recurrent MI and embolic cerebrovascular accident. However, there is an increased risk of bleeding and a high rate of discontinuation of warfarin that has limited clinical acceptance of combination antithrombotic therapy. There is an increased risk of bleeding when warfarin is added to dual antiplatelet therapy **(see Chap. 267)**. However, patients who have had a stent implanted and have an indication for anticoagulation should receive dual antiplatelet therapies in combination with warfarin. Such patients should also receive a proton pump inhibitor to minimize the risk of gastrointestinal bleeding and should have regular monitoring

of their hemoglobin levels and stool hematest while on combination antithrombotic therapy.

Finally, risk factors for *atherosclerosis* **(Chap. 232)** should be discussed with the patient and, when possible, favorably modified.

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270 Percutaneous Coronary Interventions and Other Interventional Procedures

David P. Faxon, Deepak L. Bhatt

Percutaneous transluminal coronary angioplasty (PTCA) was first introduced by Andreas Gruentzig in 1977 as an alternative to coronary bypass surgery. The concept was initially demonstrated by Charles Dotter in 1964 in peripheral vessels. The development of a small inelastic balloon catheter by Gruentzig allowed expansion of the technique into smaller peripheral and coronary vessels. Initial coronary experience was limited to single-vessel coronary disease and discrete proximal lesions due to the technical limitations of the equipment. Advances in technology and greater operator experience allowed the procedure to grow rapidly with expanded use in patients with more complex lesions and multivessel disease. The introduction of coronary stents in 1994 was one of the major advances in the field. These devices reduced acute complications and reduced by half the significant problems of acute thrombosis and late restenosis (or recurrence of the stenosis). Further reductions in restenosis were achieved by the introduction of drug-eluting stents in 2003. These stents slowly release antiproliferative drugs directly into the plaque over a few months. Percutaneous coronary intervention (PCI) is the most common revascularization procedure in the United States and is performed more than twice as often as coronary artery bypass surgery: nearly 900,000 patients a year.

Interventional cardiology is a separate discipline in cardiology that requires a dedicated 1-year interventional cardiology fellowship following a 3-year general cardiology fellowship in order to obtain a separate board certification. The discipline has also expanded to include interventions for structural heart disease including treatment of congenital heart disease and valvular heart disease; it also includes interventions to treat peripheral vascular disease, including atherosclerotic and nonatherosclerotic lesions in the carotid, renal, aortic, and peripheral arterial and venous circulations.

TECHNIQUE

The initial procedure is performed in a similar manner as a diagnostic cardiac catheterization **(Chap. 237)**. Arterial access is obtained via the femoral or radial artery. To prevent thrombotic complications during the procedure, patients who are anticipated to need an angioplasty are given aspirin (325 mg) and may be given a platelet P2Y12 inhibitor such as clopidogrel (loading dose of 600 mg), prasugrel (loading dose of 60 mg), or ticagrelor (loading dose of 180 mg) before the procedure. Cangrelor, an IV P2Y12 inhibitor, is approved for use in patients who have not received an oral agent prior to the procedure. During the procedure, anticoagulation is achieved by administration of unfractionated heparin, enoxaparin (a low-molecular-weight heparin), or bivalirudin (a direct thrombin inhibitor). In patients with ST-elevation myocardial infarction, high-risk acute coronary syndrome, or a large thrombus in the coronary artery, an intravenous glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) may also be given, though cangrelor may be as effective with less bleeding risk.

Following placement of an introducing sheath into the artery, preformed guiding catheters are used to cannulate selectively the origins of the coronary arteries. Through the guiding catheter, a flexible, steerable guidewire is negotiated down the coronary artery lumen using fluoroscopic guidance; it is then advanced through the stenosis and into the vessel beyond. This guidewire then serves as a "rail" over which angioplasty balloons, stents, or other therapeutic devices can be advanced to enlarge the narrowed segment of coronary artery. The artery is usually dilated with a balloon catheter followed by placement of a stent. The catheters and introducing sheath are removed and the artery manually held or in the case of radial access use of an inflatable cuff. One of several femoral arterial closure devices can also be used to achieve hemostasis. Because PCI is performed under local anesthesia and mild sedation, it requires only a short (1-day) hospitalization or less.

Angioplasty works by stretching the artery and displacing the plaque away from the lumen, enlarging the entire vessel **(Figs. 270-1 and 270-2)**. The procedure rarely results in embolization of atherosclerotic material. Owing to inelastic elements in the plaque, the stretching of the vessel by the balloon results in small localized dissections that can protrude into the lumen and be a nidus for acute thrombus formation. If the dissections are severe, then they can obstruct the lumen or induce a thrombotic occlusion of the artery (acute closure). Stents have largely prevented this complication by holding the dissection flaps up against the vessel wall (Fig. 270-1).

Stents are currently used in >90% of coronary angioplasty procedures. Stents are wire meshes (usually made of stainless steel or other metals, such as cobalt chromium or nitinol) that are compressed over a deflated angioplasty balloon. When the balloon is inflated, the stent is enlarged to approximate the "normal" vessel lumen. The balloon is then deflated and removed, leaving the stent behind to provide a permanent scaffold in the artery. Owing to the design of the struts, these devices are flexible, allowing their passage through diseased and tortuous coronary vessels. Stents are rigid enough to prevent elastic recoil of the vessel and have dramatically improved the success and safety of the procedure as a result.

Drug-eluting stents further enhanced the efficacy of PCI. An antiproliferative agent is attached to the metal stent by use of a thin polymer coating. The antiproliferative drug elutes from the stent over a 1- to

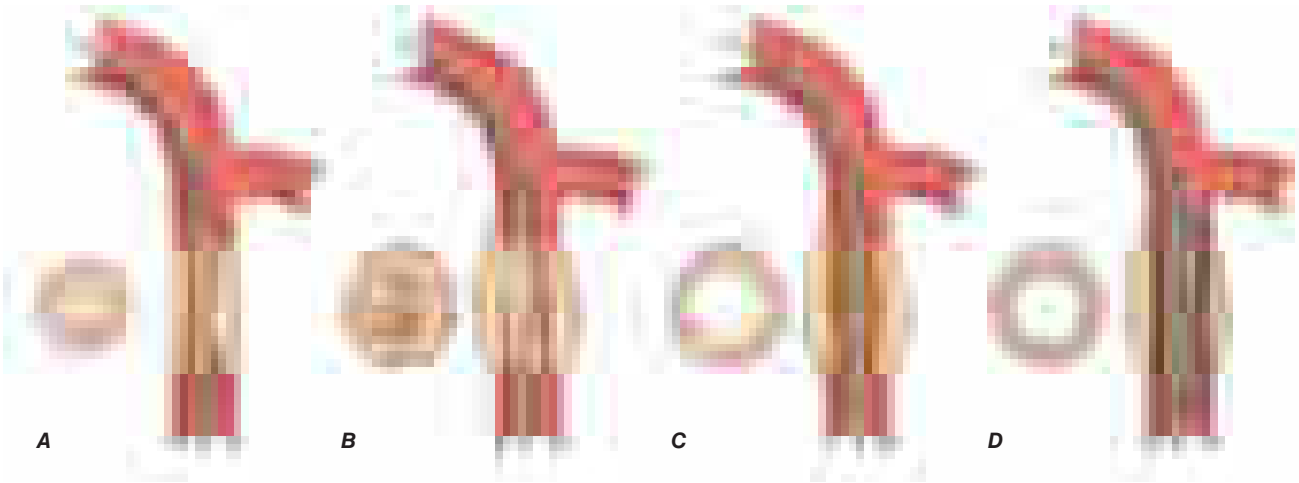


FIGURE 270-1 Schematic diagram of the primary mechanisms of balloon angioplasty and stenting. *A.* A balloon angioplasty catheter is positioned into the stenosis over a guidewire under fluoroscopic guidance. ***B.*** The balloon is inflated, temporarily occluding the vessel. ***C.*** The lumen is enlarged primarily by stretching the vessel, often resulting in small dissections in the neointima. ***D.*** A stent mounted on a deflated balloon is placed into the lesion and pressed against the vessel wall with balloon inflation (not shown). The balloon is deflated and removed, leaving the stent permanently against the wall acting as a scaffold to hold the dissections against the wall and prevent vessel recoil. *(Adapted from EJ Topol: Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2002.)*

3-month period or longer after implantation. Drug-eluting stents have been shown to reduce clinical restenosis by 50%, so that in uncomplicated lesions symptomatic restenosis occurs in 5–10% of patients. Not surprisingly, this led to the rapid acceptance of these devices; currently 80–90% of all stents implanted are drug-eluting. The first-generation devices were coated with either sirolimus or paclitaxel. Second-generation drug-eluting stents use newer agents such as everolimus, biolimus, and zotarolimus. These second-generation drug-eluting stents appear to be more effective with fewer complications, such as early or late stent thrombosis, than the first-generation devices and, therefore, have replaced the first-generation stents. Biodegradable polymers that are used to attach the drugs to the stents may be theoretically superior to permanent polymers in preventing late stent thrombosis. In addition, the everolimus-eluting biodegradable vascular scaffold (BVS) stent has been shown to be reasonably safe with gradual degradation over several years with improvement in vessel function. Additional bioresorbable stents are under investigation. Drug-coated balloons are covered with an antiproliferative drug that can also reduce restenosis, and are used primarily to treat in-stent restenosis.

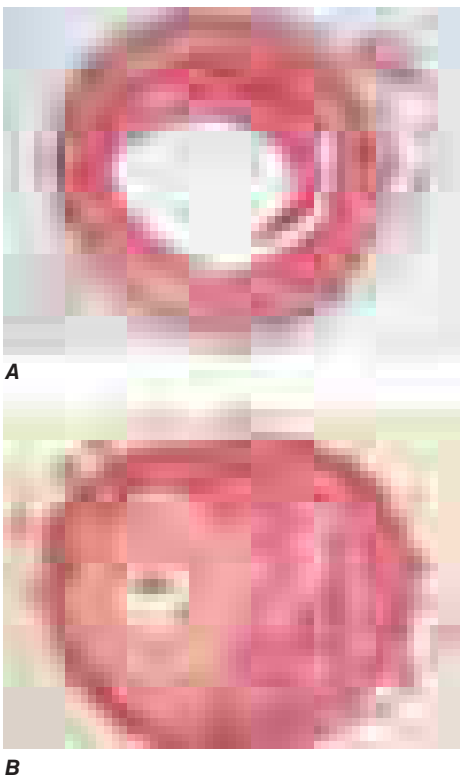


FIGURE 270-2 Pathology of acute effects of balloon angioplasty with intimal dissection and vessel stretching (***A***) and an example of neointimal hyperplasia and restenosis showing renarrowing of the vessel (***B***). *(Panel A from M Ueda et al: Eur Heart J 12:937, 1991; with permission. Panel B from CE Essed et al: Br Heart J 49:393, 1983; with permission.)*

Other interventional devices include atherectomy devices and thrombectomy catheters. These devices are designed to remove atherosclerotic plaque or thrombus and are used in conjunction with balloon dilatation and stent placement. Rotational atherectomy is the most commonly used adjunctive device and is modeled after a dentist's drill, with small round burrs of 1.25–2.5 mm at the tip of a flexible wire shaft. The burr is passed over the guidewire up to the stenosis and drills away atherosclerotic material. Because the atherosclerotic particles are ≤25 μm, they pass through the coronary microcirculation and rarely cause problems. The device is particularly useful in heavily calcified plaques that are resistant to balloon dilatation. Given the current advances in stents, rotational atherectomy is infrequently used. Orbital atherectomy is a newer approach to calcified lesions that also relies on a spinning burr. Directional atherectomy catheters that slice off the plaque and remove it are not used in the coronaries any longer but are used in peripheral artery disease. In acute ST-elevation myocardial infarction, specialized catheters without a balloon are used to aspirate thrombus in order to prevent embolization down the coronary vessel and to improve blood flow before angioplasty and stent placement. Current studies suggest that manual catheter thrombus aspiration should not be used routinely, but in certain cases of a large thrombus burden, can improve blood flow in primary PCI.

PCI of degenerated saphenous vein graft lesions has been associated with a significant incidence of distal embolization of atherosclerotic material, unlike PCI of native vessel disease. A number of distal protection devices have been shown to significantly reduce embolization and myocardial infarction in this setting. Most devices work by using a collapsible wire filter at the end of a guidewire that is expanded in the distal vessel before PCI. If atherosclerotic debris is dislodged, the basket captures the material, and at the end of the PCI, the basket is pulled into a delivery catheter and the debris safely removed from the patient.

SUCCESS AND COMPLICATIONS

A successful procedure (angiographic success), defined as a reduction of the stenosis to less than a 20% diameter narrowing, occurs in 95–99% of patients. Lower success rates are seen in patients with tortuous, small, or calcified vessels or chronic total occlusions. Chronic total

occlusions have the lowest success rates and their recanalization is significantly better if the occlusion is recent (within 3 months) or there are favorable anatomic features. Improvements in equipment and complex antegrade and retrograde techniques have increased the success rates of recanalization of chronic total occlusions to 70–80%.

Serious complications are rare but include a mortality rate of 0.1–0.3% for elective cases, a large myocardial infarction in <3%, and stroke in <0.1%. Patients who are elderly (>65 years), undergoing an emergent or urgent procedure, have chronic kidney disease, present with an ST-segment elevation myocardial infarction (STEMI), or are in shock have significantly higher risk. Scoring systems can help to estimate the risk of the procedure. Myocardial infarction during PCI can occur for multiple reasons including an acute occluding thrombus, severe coronary dissection, embolization of thrombus or atherosclerotic material, or closure of a side branch vessel at the site of angioplasty or stent placement. Most myocardial infarctions are small and only detected by a rise in the creatine phosphokinase (CPK) or troponin level after the procedure. Only those with significant enzyme elevations (more than five times the upper limit of normal) are associated with a less favorable long-term outcome. Coronary stents have largely prevented coronary dissections due to the scaffolding effect of the stent.

All types of stents are prone to stent thrombosis (1–3%), either acute (<24 h) or subacute (1–30 days), which can be ameliorated by greater attention to full initial stent deployment and the use of dual antiplatelet therapy (DAPT) (aspirin, plus a platelet $P2Y_{12}$ receptor blocker [clopidogrel, prasugrel, or ticagrelor]). Late (30 days–1 year) and very late stent thromboses (>1 year) occur very infrequently with stents but are slightly more common with first-generation drug-eluting stents, necessitating DAPT for up to 1 year or longer. Use of the second-generation stents is associated with lower rates of late and very late stent thromboses, and shorter durations of DAPT (6 months) are recommended. Premature discontinuation of DAPT, particularly in the first month after implantation, is associated with a significantly increased risk for stent thrombosis (three- to ninefold greater). Stent thrombosis results in death in 10–20% and myocardial infarction in 30–70% of patients. Elective surgery that requires discontinuation of antiplatelet therapy after drug-eluting stent implantation should be postponed until after 3 months and preferably after 6 months, if at all possible.

Restenosis, or renarrowing of the dilated coronary stenosis, is the most common complication of angioplasty and occurs in 20–50% of patients with balloon angioplasty alone, 10–30% of patients with bare metal stents, and 5–15% of patients with drug-eluting stents within the first year. The fact that stent placement provides a larger acute luminal area than balloon angioplasty alone reduces the incidence of subsequent restenosis. Drug-eluting stents further reduce restenosis through a reduction in excessive neointimal growth over the stent. If restenosis does not occur, the long-term outcome is excellent **(Fig. 270-3)**. Clinical restenosis is recognized by recurrence of angina or symptoms within 12 months of the procedure. Less frequently, patients with restenosis can present with non-ST-segment elevation myocardial infarction (NSTEMI) (10%) or STEMI (2%) as well. Very late stent thrombosis and restenosis after 1 year is more likely to be due to neoatherosclerosis than intimal hyperplasia seen within the first year. Clinical restenosis requires confirmation of a significant stenosis at the site of the prior PCI. *Target lesion revascularization* (TLR) or *target vessel revascularization* (TVR) is defined as angiographic restenosis with repeat PCI or coronary artery bypass grafting (CABG). By angiography, the incidence of restenosis is significantly higher than clinical restenosis (TLR or TVR) because many patients have mild restenosis that does not result in a recurrence of symptoms. The management of clinical restenosis is usually to repeat the PCI with balloon dilatation and placement of another drug-eluting stent. Once a patient has had restenosis, the risk of a second restenosis is further increased. The risk factors for restenosis are diabetes, myocardial infarction, long lesions, small-diameter vessels, and suboptimal initial PCI result.

INDICATIONS

The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines extensively review the indications for PCI in patients with stable angina, unstable angina, NSTEMI, and STEMI and should be referred to for a comprehensive discussion of the indications. Briefly, the two principal indications for coronary revascularization in patients with *chronic stable angina* **(Chap. 267)** are (1) to improve angina symptoms in patients who remain symptomatic despite adequate medical therapy and (2) to reduce mortality rates in patients with severe and extensive coronary disease. In patients with stable angina who are well controlled on medical therapy, studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials have shown that initial revascularization does not lead to better outcomes (death or MI) and can be safely delayed until symptoms worsen or evidence of severe ischemia on noninvasive testing occurs. When revascularization is indicated, the choice of PCI or CABG depends on a number of clinical and anatomic factors. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial compared PCI with the paclitaxel drug-eluting stent to CABG in 1800 patients with three-vessel coronary disease or left main disease. The study found no difference in death or myocardial infarction at 1 year, but repeat revascularization was significantly higher in the stent-treated group (13.5 vs 5.9%), while stroke was significantly higher in the surgical group (2.2 vs 0.6%). The primary endpoint of death, myocardial infarction, stroke, or revascularization was significantly better with CABG, particularly in those with the most extensive coronary artery disease such as three-vessel disease. The 5-year results confirm these findings. The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 patients with diabetes and multivessel disease and found a significantly lower primary endpoint of death, myocardial infarction, or stroke with CABG than PCI. Recent trials comparing PCI with CABG have shown similar

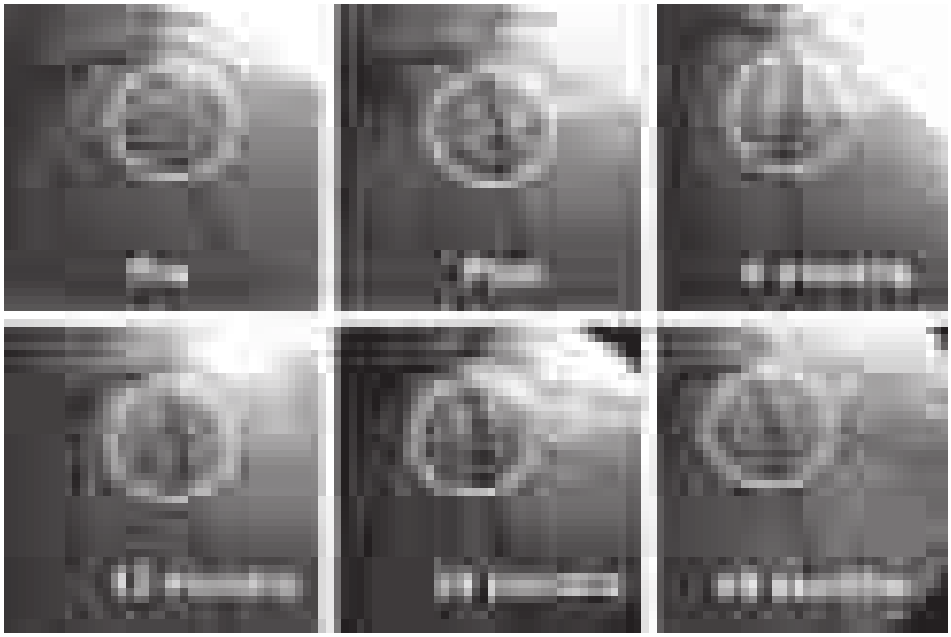


FIGURE 270-3 Long-term results from one of the first patients to receive a sirolimus-eluting stent from early Sao Paulo experience. *(From GW Stone, in D Baim [ed]: Cardiac Catheterization, Angiography and Intervention, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2006; with permission.)*

outcomes for those with less extensive disease, but a better outcome when the coronary disease is severe and extensive. These studies support CABG for those with the most severe left main and three-vessel disease or those with diabetes. Lesser degrees of multivessel disease in patients with or without diabetes have an equal outcome with PCI, including left main disease with favorable angiographic characteristics.

The choice of PCI versus CABG is also related to the anticipated procedural success and complications of PCI and the risks of CABG. For PCI, the characteristics of the coronary anatomy are critically important. The location of the lesion in the vessel (proximal or distal), the degree of tortuosity, and the size of the vessel are considered. In addition, the lesion characteristics, including the degree of the stenosis, the presence of calcium, lesion length, and presence of thrombus, are assessed. The most common reason to decide not to do PCI is that the lesion(s) felt to be responsible for the patient's symptoms are not treatable. This is most commonly due to the presence of a chronic total occlusion (>3 months in duration) with unfavorable characteristics. A lesion classification to characterize the likelihood of success or failure of PCI has been developed by the ACC/AHA. Lesions with the highest success are called type A lesions (such as proximal non-calcified subtotal lesions), and those with the lowest success or highest complication rate are type C lesions (such as chronic total occlusions). Intermediate lesions are classified as type B1 or B2 depending on the number of unfavorable characteristics. Approximately 25–30% of patients will not be candidates for PCI due to unfavorable anatomy, whereas only 5% of CABG patients will not be candidates for surgery due to coronary anatomy. The primary reason for being considered inoperable with CABG is the presence of severe comorbidities such as advanced age, frailty, severe chronic obstructive pulmonary disease (COPD), poor left ventricular function, or lack of suitable surgical conduits or poor distal targets for bypass.

Another consideration in choosing a revascularization strategy is the degree of revascularization. In patients with multivessel disease, bypass grafts can usually be placed to all vessels >2 mm with significant stenosis, whereas PCI may be able to treat only some of the lesions due to the presence of unfavorable anatomy. Assessment of the significance of intermediate lesions using fractional flow reserve (FFR) **(Chap. 237)** can assist in determining which lesions should be revascularized. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial showed a 30% reduction in adverse events when revascularization by PCI was restricted to those lesions that were hemodynamically significant (FFR ≤0.80) rather than when guided by angiography alone. Thus, complete revascularization of all functionally significant lesions should be favored and considered when choosing the optimal revascularization strategy. Given the multiple factors that need to be considered in choosing the best revascularization for an individual patient with multivessel disease, it is optimal to have a discussion among the cardiac surgeon, interventional cardiologist, and the physicians caring for the patient (so-called Heart Team) to weigh the choices properly.

Patients with acute coronary syndrome are at excess risk of short- and long-term mortality. Randomized clinical trials have shown that PCI is superior to intensive medical therapy in reducing mortality and myocardial infarction, with the benefit largely confined to those patients who are high risk. High-risk patients are defined as those with any one of the following: refractory ischemia, recurrent angina, positive cardiac-specific enzymes, new ST-segment depression, low ejection fraction, severe arrhythmias, or a recent PCI or CABG. PCI is preferred over surgical therapy in most high-risk patients with acute coronary syndromes unless they have severe multivessel disease or the culprit lesion responsible for the unstable presentation cannot be adequately treated. In STEMI, thrombolysis or PCI (primary PCI) are effective methods to restore coronary blood flow and salvage myocardium within the first 12 h after onset of chest pain. Because PCI is more effective in restoring flow than thrombolysis, it is preferred if readily available within 90 min of presentation to the hospital. PCI is also performed following thrombolysis to facilitate adequate reperfusion or as a rescue procedure in those who do not achieve reperfusion from thrombolysis, cannot be rapidly transferred to a hospital that can perform primary PCI, or in those who develop cardiogenic shock.

OTHER INTERVENTIONAL TECHNIQUES

STRUCTURAL HEART DISEASE

Interventional treatment for structural heart disease (adult congenital heart disease and valvular heart disease) is a significant and growing component of the field of interventional cardiology.

The most common adult congenital lesion to be treated with percutaneous techniques is closure of atrial septal defects **(Chap. 264)**. The procedure is done as in a diagnostic right heart catheterization with the passage of a catheter up the femoral vein into the right atrium. With echo and fluoroscopic guidance, the size and location of the defect can be accurately defined, and closure is accomplished using one of several approved devices. All devices use a left atrial and right atrial wire mesh or covered disk that are pulled together to capture the atrial septum around the defect and seal it off. The Amplatzer Septal Occluder device (AGA Medical, Minneapolis, Minnesota) is the most commonly used in the United States. The success rate in selected patients is 85–95%, and the device complications are rare and include device embolization, infection, or erosion. Closure of patent foramen ovale (PFO) is done in a similar way. PFO closure may be considered in patients who have had recurrent paradoxical stroke or transient ischemic attack (TIA) despite adequate medical therapy including anticoagulation or antiplatelet therapy. The CLOSURE I trial randomized 909 patients with cryptogenic stroke or TIA who had a PFO. Closure did not reduce the primary endpoint of death within 30 days or death following a neurologic cause during 2 years of follow-up or stroke/TIA within 2 years. Other trials have confirmed these findings. However, the 10-year follow up from the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial did suggest a benefit of closure in reducing the risk for recurrent cryptogenic stroke. The use in the treatment of migraine is not supported by the current data.

Similar devices can also be used to close patent ductus arteriosus and ventricular septal defects. Other congenital diseases that can be treated percutaneously include coarctation of the aorta, pulmonic stenosis, peripheral pulmonary stenosis, and other abnormal communications between the cardiac chambers or vessels.

The treatment of valvular heart disease is the most rapidly growing area in interventional cardiology. Until recently, the only available techniques were balloon valvuloplasty for the treatment of aortic, mitral, or pulmonic stenosis **(Chap. 256)**. Mitral valvuloplasty is the preferred treatment for symptomatic patients with rheumatic mitral stenosis who have favorable anatomy. The outcome in these patients is equal to that of surgical commissurotomy. The success is highly related to the echocardiographic appearance of the valve. The most favorable setting is commissural fusion without calcification or subchordal fusion and the absence of significant mitral regurgitation. Access is obtained from the femoral vein using a transseptal technique in which a long metal catheter with a needle tip is advanced from the femoral vein through the right atrium and atrial septum at the level of the foramen ovale into the left atrium. A guidewire is advanced into the left ventricle, and a balloon-dilatation catheter is negotiated across the mitral valve and inflated to a predetermined size to enlarge the valve. The most commonly used dilatation catheter is the Inoue balloon. The technique splits the commissural fusion and commonly results in a doubling of the mitral valve area. The success of the procedure in favorable anatomy is 95% and severe complications are rare (1–2%). The most common complications are tamponade due to puncture into the pericardium during the transseptal puncture or the creation of severe mitral regurgitation due to damage to the valve leaflets.

Severe mitral regurgitation can be treated percutaneously using the MitraClip (Abbott, Abbott Park, Illinois) device. The procedure involves the passage of a catheter into the left atrium using the transseptal technique. A special catheter with a metallic clip on the end is passed through the mitral valve and retracted to catch and clip together

the mid portion of the anterior and posterior mitral valve leaflets. The clip creates a double opening in the mitral valve and thereby reduces mitral regurgitation similar to the surgical Alfieri repair. In the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial, the device was less effective than surgical repair or replacement but was shown to be safe. Subsequent trials have shown it to be reasonably effective for patients who are not good candidates for surgical repair, particularly when the regurgitation is due to functional causes.

Severe aortic stenosis can be treated with balloon valvuloplasty as well. In this setting, the valvuloplasty balloon catheter is placed retrograde across the aortic valve from the femoral artery and briefly inflated to stretch open the valve. The success is much less favorable, with only 50% achieving an aortic valve area of >1 cm^2 and a restenosis rate of 25–50% after 6–12 months. This poor success rate has limited its use to patients who are not surgical candidates or as a bridge to surgery or transcatheter aortic valve replacement (TAVR). In this setting, the intermediate-term mortality rate of the procedure is high (10%). Repeat aortic valvuloplasty as a treatment for aortic valve restenosis has been reported.

Percutaneous TAVR has been shown to be an effective treatment for intermediate, high-risk, and inoperable patients with aortic stenosis. Currently, two valve models, the Edwards SAPIEN valve (Edwards Lifescience, Irvine, California) and the CoreValve ReValving system (Medtronic, Minneapolis, Minnesota) are available. In more than 50,000 cases worldwide since 2002, follow-up shows no evidence of restenosis or severe prosthetic valve dysfunction in the midterm, but long-term outcomes of 5–10 years are not yet available. The CoreValve is self-expanding, while the Edwards valve is balloon expanded. The cannulas are large (14–22 French), and retrograde access via the femoral artery is most commonly chosen, if possible. In patients with peripheral artery disease, access via the subclavian artery, aorta, or transapically through a surgical incision can be used. Following balloon valvuloplasty, the valve is positioned across the valve and deployed with post-deployment balloon inflation to ensure full contact with the aortic annulus. The success rate is >90%, and the 30-day mortality rate is 2–15% based on preoperative risk. The Placement of Aortic Transcatheter Valve (PARTNER) randomized trial of the Edwards valve showed a 55% reduction in 1-year mortality and major adverse events in the extreme-risk group randomized to TAVR compared with medical therapy. In separate randomized trials, moderate- and high-risk patients had similar outcomes to surgical valve replacement at 1 year. As a result, this valve is approved for both intermediate-risk, high-risk, and extreme-risk patients with severe aortic stenosis.

Aortic and mitral bioprosthetic valve degeneration can be treated with repeat surgery or, in high-risk patients, with a valve-in-valve procedure where a percutaneous valve is placed inside of the prior surgical valve. It has been shown to be effective for aortic and mitral valves.

Pulmonic stenosis can also be effectively treated with balloon valvuloplasty and percutaneously replaced with the Melody valve (Medtronic). Tricuspid valve interventions remain experimental.

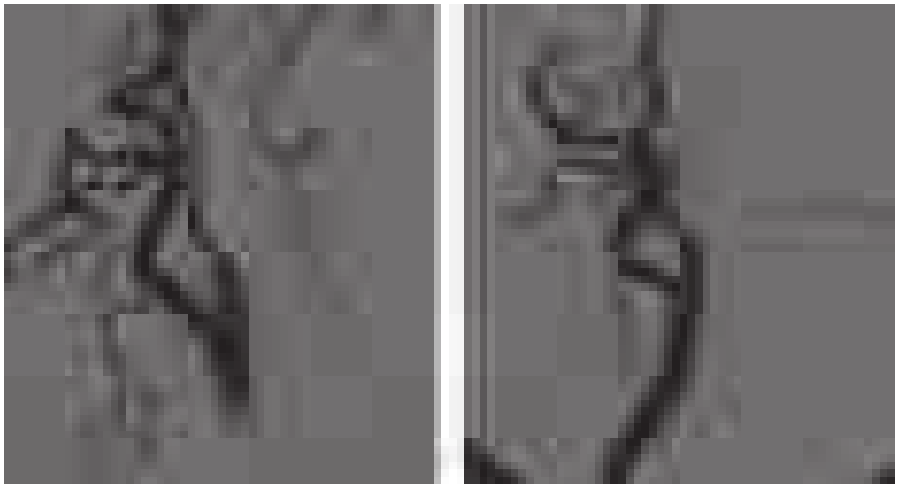
PERIPHERAL ARTERY INTERVENTIONS

The use of percutaneous interventions to treat symptomatic patients with arterial obstruction in the carotid, renal, aortic, and peripheral vessels is an effective alternative to vascular surgery. Randomized clinical trial data support the use of carotid stenting in patients at high risk of complications from carotid endarterectomy **(Fig. 270-4)**. Recent trials suggest similar outcomes with carotid stenting and carotid endarterectomy in patients at average risk, although depending on the patient's risk for periprocedural stroke or myocardial infarction, one procedure may be preferred over the other. The success rate of peripheral artery interventional procedures has been improving, including treatment for long segments of occlusive disease historically treated by peripheral bypass surgery **(Fig. 270-5)**. The use of drug-coated balloons and drug-eluting stents has shown to reduce restenosis when compared with balloon angioplasty alone. Peripheral intervention is increasingly part of the training of an interventional cardiologist, and most programs now require an additional year of training after the interventional cardiology training year. The techniques and outcomes are described in detail in the chapter on peripheral vascular disease **(Chap. 275)**.

CIRCULATORY SUPPORT TECHNIQUES

The use of circulatory support techniques is indicated for the management of patients with shock or hemodynamic instability and occasionally is needed in order to safely perform PCI on hemodynamically unstable patients. It also can be useful in helping to stabilize patients before surgical interventions. The most commonly used device is the percutaneous intraaortic balloon pump developed in the early 1960s. A 7- to 10-French, 25- to 50-mL balloon catheter is placed retrograde from the femoral artery into the descending aorta between the aortic arch and the abdominal aortic bifurcation. It is connected to a helium gas inflation system that synchronizes the inflation to coincide with early diastole with deflation by mid-diastole. As a result, it increases early diastolic pressure, lowers systolic pressure, and lowers late diastolic pressure through displacement of blood from the descending aorta (counterpulsation). This results in an increase in coronary blood flow and a decrease in afterload. It is contraindicated in patients with aortic regurgitation, aortic dissection, or severe peripheral artery disease. The major complications are vascular and thrombotic. Intravenous heparin is given in order to reduce thrombotic complications.

Another useful support device is the Impella (Abiomed, Danvers, Massachusetts). The Impella catheter is placed percutaneously from the femoral artery into the left ventricle. The catheter has a small microaxial pump at its tip that can pump up to 2.5–5 L/min from the left ventricle to the aorta. The smaller devices can be placed percutaneously but the larger devices need surgical access. Other support devices include TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania), which involves placement of a large 21-French catheter from the femoral vein through the right atrium into the left atrium using the transseptal technique and a catheter in the femoral artery. A centrifugal pump can deliver 5 L of blood per minute. It may be useful in patients in shock or with STEMI or very-high-risk PCI. Patients can also be placed on peripheral extracorporeal membrane oxygenation (ECMO) using large cannulas placed in the femoral artery and vein. This technique can be performed in the catheterization laboratory and is useful for support of patients with acute respiratory failure or cardiac failure.



A **B**

FIGURE 270-4 ***A.*** An example of a high-risk patient who requires carotid revascularization, but who is not a candidate for carotid endarterectomy. ***B.*** Carotid artery stenting resulted in an excellent angiographic result. *(From M Belkin, DL Bhatt: Circulation 119:2302, 2009; with permission.)*

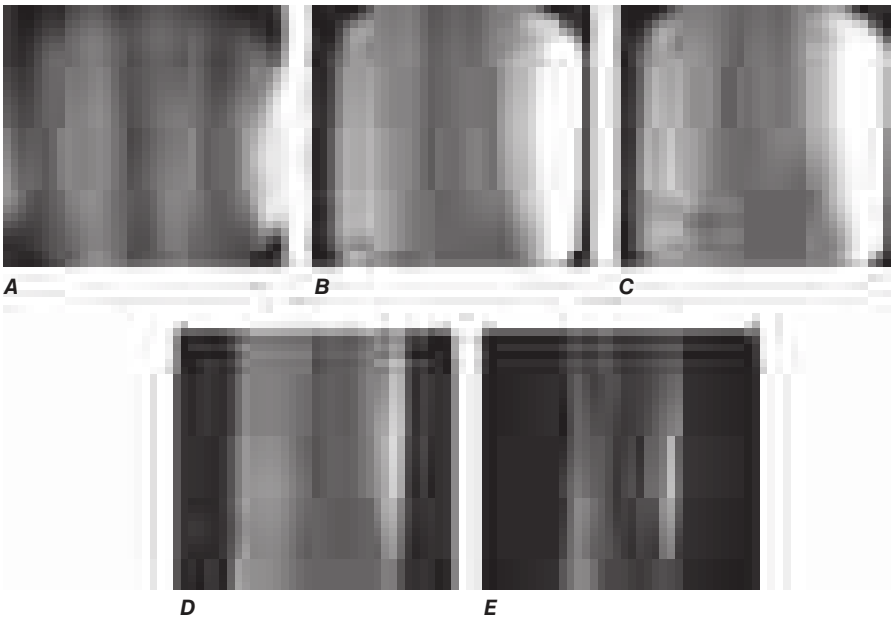


FIGURE 270-5 Peripheral interventional procedures have become highly effective at treating anatomic lesions previously amenable only to bypass surgery. *A.* Complete occlusion of the left superficial femoral artery. ***B.*** Wire and catheter advanced into subintimal space. ***C.*** Intravascular ultrasound positioned in the subintimal space to guide retrograde wire placement through the occluded vessel. ***D.*** Balloon dilation of the occlusion. ***E.*** Stent placement with excellent angiographic result. *(From A Al Mahameed, DL Bhatt: Cleve Clin J Med 73:S45, 2006; with permission. Copyright © 2006 Cleveland Clinic Foundation. All rights reserved.)*

INTERVENTIONS FOR PULMONARY EMBOLISM

The treatment of deep vein thrombosis is intravenous anticoagulation, with placement of an inferior vena cava filter if recurrent pulmonary emboli (PE) occur or anticoagulation is not possible. Postphlebitic syndrome is a serious condition due to chronic venous obstruction that can lead to chronic leg edema and venous ulcers. Preliminary studies suggest that mechanical treatments may have a role in treatment, and a large trial is ongoing.

PE should be treated with fibrinolytic agents if massive and in some cases if submassive. Surgical pulmonary embolectomy is an option for the treatment of massive PE with hemodynamic instability in patients who have contraindications for systemic fibrinolysis or those in whom it has failed. Catheter-based therapies for submassive and massive PEs are still evolving, but studies have shown promise. The techniques employed include the use of aspiration of the clot with a large catheter (10 French), intraclot infusion of a thrombolytic agent followed by aspiration, ultrasound-assisted catheter-directed thrombolysis, and use of rheolytic thrombectomy. Success for these techniques has been reported to be 80–90%, with major complications occurring in 2–4% of patients.

INTERVENTIONS FOR REFRACTORY HYPERTENSION

The recent recognition of the importance of the renal sympathetic nerves in modulating blood pressure has led to a technique to selectively denervate renal sympathetic nerves in patients with refractory hypertension. The procedure involves applying low-power radiofrequency treatment via a catheter along the length of both renal arteries. In the randomized Symplicity HTN-2 trial, renal denervation significantly reduced blood pressure compared with medical therapy. The Symplicity device (Medtronic, Minnesota) is approved in Europe, though the randomized and blinded U.S. Symplicity HTN-3 trial showed no effect. Further optimization of the technique is needed with evidence from randomized trials of efficacy before approval in the United States.

CONCLUSION

Interventional cardiology continues to expand its borders. Treatment for coronary artery disease, including complex anatomic subsets, continues to advance. Technological advances such as drug-eluting stents, now already in their second generation are improving the results of PCI. PCI is the treatment of choice for patients with acute coronary syndromes. For patients with stable coronary disease, PCI is effective in symptom alleviation. Use of a Heart Team is the best way to make decisions concerning which revascularization—PCI or CABG—is best for an individual patient. Treatment of peripheral and cerebrovascular disease can be effective with percutaneous techniques. Structural heart disease is increasingly being treated with percutaneous options, with a high likelihood that interventional approaches will compete with open-heart surgery in a significant proportion of cases in years to come.

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271 Hypertensive Vascular Disease

Theodore A. Kotchen

Hypertension is one of the leading causes of the global burden of disease. Elevated blood pressure affects more than one billion individuals and causes an estimated 9.4 million deaths per year. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease (PAD). It often is associated with additional cardiovascular disease risk factors,

and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

EPIDEMIOLOGY

Blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension vary among countries and among subpopulations within a country. Hypertension is present in all populations except for small numbers of individuals living in isolated societies. In industrialized societies, blood pressure increases steadily during the first two decades of life. In children and adolescents, blood pressure is associated with growth and maturation. Blood pressure "tracks" over time in children and between adolescence and young adulthood. In the United States, average systolic blood pressure is higher for men than for women during early adulthood, although among older individuals the age-related rate of rise is steeper for women. Consequently, among individuals aged ≥60 years, systolic blood pressures of women are higher than those of men. Among adults, diastolic blood pressure also increases progressively with age until ~55 years, after which it tends to decrease. The consequence is a widening of pulse pressure (the difference between systolic and diastolic blood pressure) beyond age 60.

In the United States, ~78 million adults have hypertension. Hypertension prevalence is 33.5% in non-Hispanic blacks, 28.9% in non-Hispanic whites, and 20.7% in Mexican Americans. The likelihood of hypertension increases with age, and among individuals aged ≥60 years, the prevalence is 65.4%. Recent evidence suggests that the prevalence of hypertension in the United States may be increasing, possibly as a consequence of increasing obesity. The prevalence of hypertension and stroke mortality rates is higher in the southeastern United States than in other regions. In African Americans, hypertension appears earlier, is generally more severe, and results in higher rates of morbidity and mortality from stroke, left ventricular hypertrophy, CHF, and end-stage renal disease (ESRD) than in white Americans. According to NHANES (National Health and Nutrition Examination Survey) data, in 2007–2010, 81.5% of those with hypertension were aware they had it, 74.9% were being treated, but only 52.5% were controlled.

Both environmental and genetic factors may contribute to regional and racial variations in hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. It has been estimated that 60% of hypertensives are >20% overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. The urine sodium-to-potassium ratio (an index of both sodium and potassium intakes) is a stronger correlate of blood pressure than is either sodium or potassium alone. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

GENETIC CONSIDERATIONS

Although specific genetic variants have been identified in rare Mendelian forms of hypertension (Table 271–5), these variants are not applicable to the vast majority (>98%) of patients with hypertension. For most individuals, it is likely that hypertension represents a polygenic disorder in which a combination of genes acts in concert with environmental exposures to make only a modest contribution to blood pressure. Furthermore, different subsets of genes may lead to different phenotypes associated with hypertension, e.g., obesity, dyslipidemia, insulin resistance.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Animal models (including selectively bred rats and congenic rat strains) have identified a number of genetic loci and genes associated with hypertension. Clinically, although replication has been a challenge, results of candidate gene studies and genome-wide association studies in large numbers of individuals have also identified a number of hypertension-related genes, several of which are involved in pathways that regulate arterial pressure, e.g., genes that encode components of the renin-angiotensin-aldosterone system, atrial natriuretic peptide, the beta-2 adrenoreceptor, and alpha adducin (associated with increased renal tubular reabsorption of sodium). Overall, identified genetic determinants account for ~1% of blood pressure variance, whereas based on family studies, heritability of hypertension is estimated to be in the range of 30–40%. One hypothesis to account for the "missing heritability" is that epigenetic modifications of DNA contribute to the heritability of blood pressure. Epigenetic processes are changes in gene expression that occur without changes in DNA sequence. In contrast to DNA sequence, the epigenome is relatively susceptible to modification by environmental exposures. Epigenetic dysregulation has emerged as a hallmark of several complex diseases, including hypertension. Several recent studies have described epigenetic modifications of specific genes associated with hypertension. However, current results of detailed genome-wide epigenetic modifications of DNA are limited and conflicting.

Preliminary evidence suggests that there may also be genetic determinants of target organ damage and vascular disease attributed to hypertension. Family studies indicate significant heritability of left ventricular mass, and there is considerable individual variation in the responses of the heart to hypertension. Family studies and variations in candidate genes associated with renal damage suggest that genetic factors also may contribute to hypertensive nephropathy. Specific genetic variants have been linked to CHD and stroke. In the future, it is possible that DNA and epigenetic analyses may predict individual risk for hypertension and target organ damage and will identify responders to specific classes of antihypertensive agents.

MECHANISMS OF HYPERTENSION

To provide a framework for understanding the pathogenesis and treatment options for hypertensive disorders, it is useful to understand factors involved in the regulation of both normal and elevated arterial pressure. Cardiac output and peripheral resistance are the two determinants of arterial pressure **(Fig. 271-1)**. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries (lumen diameter 100–400 μm) and arterioles.

INTRAVASCULAR VOLUME

Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume may initially expand and cardiac output may increase. However, many vascular beds have the capacity to autoregulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase, since

$$\text{Blood Flow} = \frac{\text{pressure across the vascular bed}}{\text{vascular resistance}}$$

The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output;

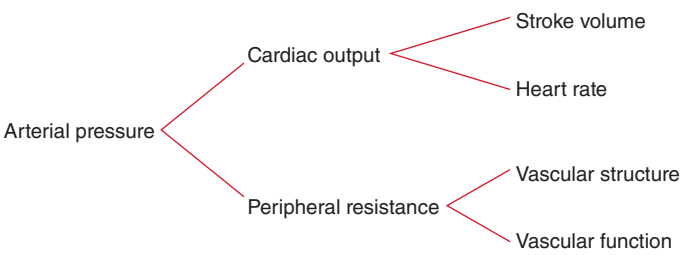

FIGURE 271-1 Determinants of arterial pressure.

however, over time, peripheral resistance increases and cardiac output reverts toward normal. Whether this hypothesized sequence of events occurs in the pathogenesis of hypertension is not clear. What is clear is that salt can activate a number of neural, endocrine/paracrine, and vascular mechanisms, all of which have the potential to increase arterial pressure. The effect of sodium on blood pressure is related to the provision of sodium with chloride; non-chloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this "pressure-natriuresis" phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance.

NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. ESRD is an extreme example of volume-dependent hypertension. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin.

AUTONOMIC NERVOUS SYSTEM

Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. Norepinephrine, epinephrine, and dopamine all play important roles in tonic and phasic cardiovascular regulation.

The activities of the adrenergic receptors are mediated by guanosine nucleotide-binding regulatory proteins (G proteins) and by intracellular concentrations of downstream second messengers. In addition to receptor affinity and density, physiologic responsiveness to catecholamines may be altered by the efficiency of receptor-effector coupling at a site "distal" to receptor binding. The receptor sites are relatively specific both for the transmitter substance and for the response that occupancy of the receptor site elicits. Based on their physiology and pharmacology, adrenergic receptors have been divided into two principal types: α and β. These types have been differentiated further into α_1, α_2, β_1, and β_2 receptors. Recent molecular cloning studies have identified several additional subtypes. α Receptors are occupied and activated more avidly by norepinephrine than by epinephrine, and the reverse is true for β receptors. α_1 Receptors are located on postsynaptic cells in smooth muscle and elicit vasoconstriction. α_2 Receptors are localized on presynaptic membranes of postganglionic nerve terminals that synthesize norepinephrine. When activated by catecholamines, α_2 receptors act as negative feedback controllers, inhibiting further norepinephrine release. In the kidney, activation of α_1-adrenergic receptors increases renal tubular reabsorption of sodium. Different classes of antihypertensive agents either inhibit α_1 receptors or act as agonists of α_2 receptors and reduce systemic sympathetic outflow. Activation of myocardial β_1 receptors stimulates the rate and strength of cardiac contraction and consequently increases cardiac output. β_1 Receptor activation also stimulates renin release from the kidney. Another class of antihypertensive agents acts by inhibiting β_1 receptors. Activation of β_2 receptors by epinephrine relaxes vascular smooth muscle and results in vasodilation.

Circulating catecholamine concentrations may affect the number of adrenoreceptors in various tissues. Downregulation of receptors may be a consequence of sustained high levels of catecholamines and provides an explanation for decreasing responsiveness, or tachyphylaxis, to catecholamines. For example, orthostatic hypotension frequently is observed in patients with pheochromocytoma, possibly due to the lack of norepinephrine-induced vasoconstriction with assumption of the upright posture. Conversely, with chronic reduction of neurotransmitter substances, adrenoreceptors may increase in number or be upregulated, resulting in increased responsiveness to the neurotransmitter. Chronic administration of agents that block adrenergic receptors may result in upregulation, and abrupt withdrawal of those agents may produce a condition of temporary hypersensitivity to sympathetic stimuli. For example, clonidine is an antihypertensive agent that is a centrally acting α_2 agonist that inhibits sympathetic outflow. Rebound hypertension may occur with the abrupt cessation of clonidine therapy, probably as a consequence of upregulation of α_1 receptors.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

In both normal-weight and obese individuals, hypertension often is associated with increased sympathetic outflow. Based on recordings of postganglionic muscle nerve activity (detected by a microelectrode inserted in a peroneal nerve in the leg), sympathetic outflow tends to be higher in hypertensive than in normotensive individuals. Sympathetic outflow is increased in obesity-related hypertension and in hypertension associated with obstructive sleep apnea. Baroreceptor activation via electrical stimulation of carotid sinus afferent nerves lowers blood pressure in patients with "resistant" hypertension. Drugs that block the sympathetic nervous system are potent antihypertensive agents, indicating that the sympathetic nervous system plays a permissive, although not necessarily a causative, role in the maintenance of increased arterial pressure.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. Blood pressure can be reduced by surgical excision of the tumor or by pharmacologic treatment with an α_1 receptor antagonist or with an inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis.

RENIN-ANGIOTENSIN-ALDOSTERONE

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells and released as active renin. Although human plasma contains two to five times more prorenin than renin, there is no evidence that prorenin contributes to the physiologic activity of this system. There are three primary stimuli for renin secretion: (1) decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole (macula densa), (2) decreased pressure or stretch within the renal afferent arteriole (baroreceptor mechanism), and (3) sympathetic nervous system stimulation of renin-secreting cells via β_1 adrenoreceptors. Conversely, renin secretion is inhibited by increased NaCl transport in the thick ascending limb of the loop of Henle, by increased stretch within the renal afferent arteriole, and by β_1 receptor blockade. In addition, angiotensin II directly inhibits renin secretion due to angiotensin II type 1 receptors on juxtaglomerular cells, and renin secretion increases in response to pharmacologic blockade of either angiotensin-converting enzyme (ACE) or angiotensin II receptors.

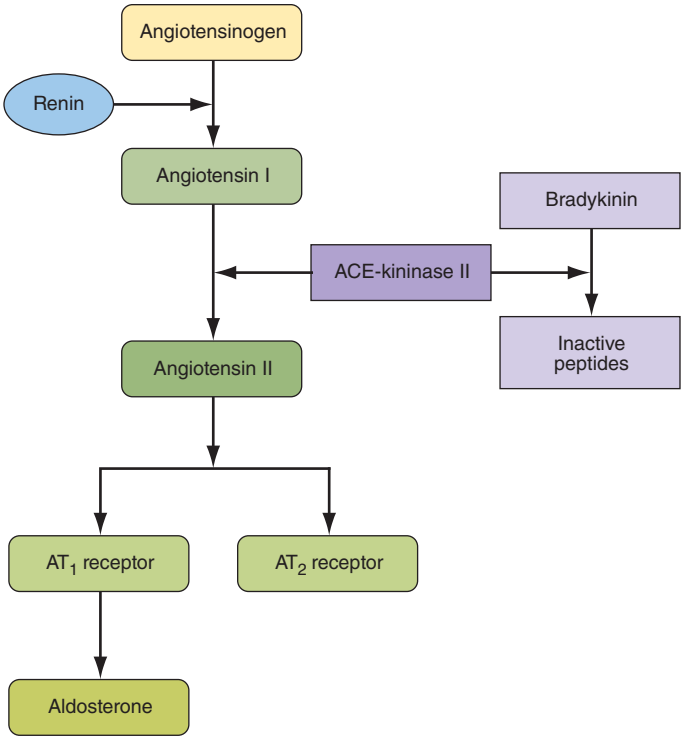

FIGURE 271-2 Renin-angiotensin-aldosterone axis. ACE, angiotensin-converting enzyme.

Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I (Fig. 271-2). A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same converting enzyme cleaves a number of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1 (AT_1) receptors on cell membranes, angiotensin II is a potent pressor substance, the primary tropic factor for the secretion of aldosterone by the adrenal zona glomerulosa. Independent of its hemodynamic effects, angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall. The angiotensin II type 2 (AT_2) receptor has the opposite functional effects of the AT_1 receptor. The AT_2 receptor induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. Experimental evidence suggests that the AT_2 receptor improves vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate. AT_1 receptor blockade induces an increase in AT_2 receptor activity.

Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal perfusion pressure, thereby stimulating renin secretion. Over time, possibly as a consequence of secondary renal damage, this form of hypertension may become less renin-dependent.

Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure, and consequently may be a target for pharmacologic therapy to prevent target organ damage.

Angiotensin II is the primary tropic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of adrenocorticotropic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important tropic factor for the chronic regulation of aldosterone.

Aldosterone is a potent mineralocorticoid that increases sodium reabsorption by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct (Chap. 303). Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis. Beyond its renal effects, aldosterone can exert deleterious effects on the cardiovascular system, including fibrosis, endothelial dysfunction, inflammation, and oxidative stress, as well as an overall increase in cardiovascular morbidity and mortality.

Cortisol also binds to the mineralocorticoid receptor but normally functions as a less potent mineralocorticoid than aldosterone because cortisol is converted to cortisone by the enzyme 11 β-hydroxysteroid dehydrogenase type 2. Cortisone has no affinity for the mineralocorticoid receptor. Primary aldosteronism is a compelling example of mineralocorticoid-mediated hypertension. In this disorder, adrenal aldosterone synthesis and release are independent of renin-angiotensin, and renin release is suppressed by the resulting volume expansion.

Mineralocorticoid receptors are expressed in a number of tissues in addition to the kidney, and mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, high circulating aldosterone levels stimulate cardiac fibrosis and left ventricular hypertrophy, and spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. Pathologic patterns of left ventricular geometry also have been associated with elevations of plasma aldosterone concentration in hypertensive patients. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Due to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria.

Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

VASCULAR MECHANISMS

Vascular radius and compliance of resistance arteries are important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size, and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and, hence, increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semirigid vascular system, a small increment in volume induces a relatively large increment of pressure.

An association between arterial stiffness and hypertension is well established. A stiffened vasculature is less able to buffer short-term alterations in flow. Although it has been assumed that arterial

stiffness is a manifestation of hypertension, recent evidence suggests that vascular stiffness may also represent a cause of hypertension. Noninvasive determination of pulse wave velocity between the carotid and femoral arteries is often interpreted as an index of arterial stiffness. Due to arterial stiffness, central blood pressures (aortic, carotid) may not correspond to brachial artery pressures. Ejection of blood into the aorta elicits a pressure wave that is propagated at a given velocity. The forward traveling wave generates a reflected wave that travels backward toward the ascending aorta. Although mean arterial pressure is determined by cardiac output and peripheral resistance, pulse pressure is related to the functional properties of large arteries and the amplitude and timing of the incident and reflected waves. Increased arterial stiffness results in increased pulse wave velocity of both incident and reflected waves. Due to the timing of these waves, the consequence is augmentation of aortic systolic pressure and a reduction of aortic diastolic pressure, i.e., an increase in pulse pressure. The aortic augmentation index, a surrogate index of arterial stiffening, is calculated as the ratio of central arterial pressure-to-pulse pressure. However, wave reflections are also influenced by left ventricular structure and function. Central blood pressure may be measured directly by placing a sensor in the aorta or noninvasively by radial tonometry using commercially available devices. Central blood pressure and the aortic augmentation index are strong, independent predictors of cardiovascular disease and all-cause mortality. Central blood pressure also appears to be more strongly associated with pre-clinical organ damage than brachial blood pressure.

Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH (pH_i). Three ion transport mechanisms participate in the regulation of pH_i: (1) Na^+-H^+ exchange, (2) Na^+-dependent HCO_3^--Cl^- exchange, and (3) cation-independent HCO_3^--Cl^- exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the Na^+-H^+ exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating Na^+-Ca^{2+} exchange and thereby increasing intracellular calcium. Second, increased pH_i enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased Na^+-H^+ exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases several vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 min of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension.

Currently, it is not known if the hypertension-related vascular abnormalities of ion transport and endothelial function are primary alterations or secondary consequences of elevated arterial pressure. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure–independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

IMMUNE MECHANISMS, INFLAMMATION, AND OXIDATIVE STRESS

Inflammation and alterations of the immune response have been implicated in the pathogenesis of vascular injury and hypertension for at least four decades. Patients with primary hypertension have increased circulating levels of autoantibodies. Both hypertension and aortic stiffness are associated with activation of innate and adaptive immunity. Many forms of hypertension in experimental animals are associated with an inflammatory component requiring T lymphocytes. Inflammation and exudative injury are closely coupled. Inflammation, vascular stretch, angiotensin II, and salt have all been shown to result in the generation of reactive oxygen species (ROS), which modify T cell function and further enhance inflammation. ROS also attenuate the effects of endogenous small-molecule vasodilators. ROS within the renal medulla is a key determinant of the set point of the renal pressure-natriuresis curve. Increasing evidence suggests that infiltration of T cells into the renal interstitium contributes to inflammation and oxidative stress. Renal medullary oxidative stress disrupts pressure-natriuresis and contributes to the development of hypertension in experimental models. Clinically, markers of oxidative stress have been described in both hypertensive and pre-hypertensive patients.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

HEART

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias, including atrial fibrillation. Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

BRAIN

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals aged >65 years. Treatment of hypertension decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension is associated with beta amyloid deposition, a major pathologic factor in dementia. In addition to actual blood pressure level, arterial stiffness and visit-to-visit blood pressure variability may be independently related to subclinical small vessel disease and subsequent cognitive decline. Hypertension-related cognitive impairment and dementia may also be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.

Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed *autoregulation* of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of

hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status. Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. It is important to distinguish hypertensive encephalopathy from other neurologic syndromes that may be associated with hypertension, e.g., cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

KIDNEY

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Conversely, hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Studies of hypertension-related renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and cardiovascular disease.

PERIPHERAL ARTERIES

In addition to contributing to the pathogenesis of hypertension, blood vessels are a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. In hypertensive patients, vascular disease is a major contributor to stroke, heart disease, and renal failure. Further, hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. An ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. In adults, there is a continuous, incremental risk of cardiovascular disease, stroke, and renal disease across levels of both systolic and diastolic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg. Similarly, results of a meta-analysis involving almost 1 million participants indicate that ischemic heart disease mortality, stroke mortality, and mortality from other vascular causes are directly related to the height of the blood pressure, beginning at 115/75 mmHg, without evidence of a threshold. Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mmHg increase in diastolic pressure. Among older individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than is diastolic blood pressure.

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure–related morbidity and mortality. Clinical criteria for defining hypertension generally have been based on the average of two or more seated blood pressure readings during each of two or more outpatient visits. One classification recommends blood pressure criteria for defining normal blood pressure, prehypertension, hypertension (stages I and II), and isolated systolic hypertension, which is frequent among the elderly **(Table 271-1)**. In children and adolescents, hypertension generally is defined as systolic and/or diastolic blood pressure consistently >95th percentile for age, sex, and height. Blood pressures between the 90th and 95th percentiles are considered prehypertensive and are an indication for lifestyle interventions.

Home blood pressure and average 24-h ambulatory blood pressure measurements are generally lower than clinic blood pressures. Because ambulatory blood pressure recordings yield multiple readings throughout the day and night, they provide a more comprehensive assessment of the vascular burden of hypertension than do a limited number of office readings. Increasing evidence suggests that home blood pressures, including 24-h blood pressure recordings, more reliably predict target organ damage than do office blood pressures. Blood pressure tends to be higher in the early morning hours, soon after waking, than at other times of day. Myocardial infarction and stroke are more common in the early morning hours. Nighttime blood pressures are generally 10–20% lower than daytime blood pressures, and an attenuated nighttime blood pressure "dip" may be associated with increased cardiovascular disease risk. Recommended criteria for a diagnosis of hypertension, based on 24-h blood pressure monitoring, are average awake blood pressure ≥135/85 mmHg and asleep blood pressure ≥120/75 mmHg. These levels approximate a clinic blood pressure of 140/90 mmHg.

Approximately 15–20% of patients with stage 1 hypertension based on office blood pressures have average ambulatory readings <135/85 mmHg, termed "white coat hypertension." Long-term outcomes of individuals with white coat hypertension are more similar to normotensive individuals than to individuals with sustained hypertension (elevation of both office and out-of-office blood pressures). To confirm hypertension, some authorities recommend ambulatory blood pressure monitoring in all individuals with elevated clinic blood pressure, and postponing therapy with careful follow-up in those individuals with normal out-of-office blood pressures who are at low cardiovascular risk. In contrast, the prognosis of "masked hypertension" (normal office blood pressure and elevated out-of-office blood pressure) is nearly equivalent to that of sustained hypertension.

TABLE 271-1 Blood Pressure Classification

BLOOD PRESSURE CLASSIFICATION	SYSTOLIC, mmHg	DIASTOLIC, mmHg
Normal	<120	*and* <80
Prehypertension	120–139	*or* 80–89
Stage 1 hypertension	140–159	*or* 90–99
Stage 2 hypertension	≥160	*or* ≥100
Isolated systolic hypertension	≥140	*and* <90

Source: Adapted from AV Chobanian et al: JAMA 289:2560, 2003.

CLINICAL DISORDERS OF HYPERTENSION

Depending on methods of patient ascertainment, ~80–95% of hypertensive patients are diagnosed as having primary, or "essential," hypertension. In the remaining 5–20% of hypertensive patients, a specific underlying disorder causing the elevation of blood pressure can be identified (**Tables 271-2 and 271-3**). In individuals with "secondary" hypertension, a specific mechanism for the blood pressure elevation is often more apparent.

PRIMARY HYPERTENSION

Primary hypertension tends to be familial and is likely to be the consequence of an interaction between environmental and genetic factors. The prevalence of primary hypertension increases with age, and individuals with relatively high blood pressures at younger ages are at increased risk for the subsequent development of hypertension. It is likely that primary hypertension represents a spectrum of disorders with different underlying pathophysiologies. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

When plasma renin activity (PRA) is plotted against 24-h sodium excretion, ~10–15% of hypertensive patients have high PRA and 25% have low PRA. High-renin patients may have a vasoconstrictor form of hypertension, whereas low-renin patients may have volume-dependent hypertension. Inconsistent associations between plasma aldosterone and blood pressure have been described in patients with primary hypertension. The association between aldosterone and blood pressure is more striking in African Americans, and PRA tends to be low in hypertensive African Americans. This raises the possibility that subtle increases in aldosterone may contribute to hypertension in at least some groups of patients who do not have overt primary aldosteronism. Furthermore, spironolactone, an aldosterone antagonist, may be a particularly effective antihypertensive agent for some patients with primary hypertension, including some patients with "drug-resistant" hypertension.

OBESITY AND THE METABOLIC SYNDROME

(See also Chap. 401) There is a well-documented association between obesity (body mass index >30 kg/m^2) and hypertension. Further, cross-sectional studies indicate a direct linear correlation between body weight (or body mass index) and blood pressure. Centrally located body fat is a more important determinant of blood pressure elevation than is peripheral body fat. In longitudinal studies, a direct correlation exists between change in weight and change in blood pressure over time. Sixty percent of hypertensive adults are >20% overweight. It has been established that 60–70% of hypertension in adults may be directly attributable to adiposity.

Hypertension and dyslipidemia frequently occur together and in association with resistance to insulin-stimulated glucose uptake. This clustering of risk factors is often, but not invariably, associated with obesity, particularly abdominal obesity. Insulin resistance also is associated with an unfavorable imbalance in the endothelial production of mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vessel tone. When these risk factors cluster, the risks for CHD, stroke, diabetes, and cardiovascular disease mortality are increased further.

TABLE 271-2 Systolic Hypertension with Wide Pulse Pressure

1. Decreased vascular compliance (arteriosclerosis)
2. Increased cardiac output
   a. Aortic regurgitation
   b. Thyrotoxicosis
   c. Hyperkinetic heart syndrome
   d. Fever
   e. Arteriovenous fistula
   f. Patent ductus arteriosus

TABLE 271-3 Secondary Causes of Systolic and Diastolic Hypertension

Renal	Parenchymal diseases, renal cysts (including polycystic kidney disease), renal tumors (including renin-secreting tumors), obstructive uropathy
Renovascular	Arteriosclerotic, fibromuscular dysplasia
Adrenal	Primary aldosteronism, Cushing's syndrome, 17α-hydroxylase deficiency, 11β-hydroxylase deficiency, 11-hydroxysteroid dehydrogenase deficiency (licorice), pheochromocytoma
Aortic coarctation	
Obstructive sleep apnea	
Preeclampsia/eclampsia	
Neurogenic	Psychogenic, diencephalic syndrome, familial dysautonomia, polyneuritis (acute porphyria, lead poisoning), acute increased intracranial pressure, acute spinal cord section
Miscellaneous endocrine	Hypothyroidism, hyperthyroidism, hypercalcemia, acromegaly
Medications	High-dose estrogens, adrenal steroids, decongestants, appetite suppressants, cyclosporine, tricyclic antidepressants, monoamine oxidase inhibitors, erythropoietin, nonsteroidal anti-inflammatory agents, cocaine
Mendelian forms of hypertension	See Table 271-4

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of nonobese, nondiabetic hypertensive persons are insulin resistant. The constellation of insulin resistance, abdominal obesity, hypertension, and dyslipidemia has been designated as the *metabolic syndrome*. As a group, first-degree relatives of patients with primary hypertension are also insulin resistant, and hyperinsulinemia (a surrogate marker of insulin resistance) may predict the eventual development of hypertension and cardiovascular disease. Although the metabolic syndrome may in part be heritable as a polygenic condition, the expression of the syndrome is modified by environmental factors, such as degree of physical activity and diet. Insulin sensitivity increases and blood pressure decreases in response to weight loss. The recognition that cardiovascular disease risk factors tend to cluster within individuals has important implications for the evaluation and treatment of hypertension. Evaluation of both hypertensive patients and individuals at risk for developing hypertension should include assessment of overall cardiovascular disease risk. Similarly, introduction of lifestyle modification strategies and drug therapies should address overall risk and not focus exclusively on hypertension.

RENAL PARENCHYMAL DISEASES

Virtually all disorders of the kidney may cause hypertension (Table 271-3), and renal disease is the most common cause of secondary hypertension. Hypertension is present in >80% of patients with chronic renal failure. In general, hypertension is more severe in glomerular diseases than in interstitial diseases such as chronic pyelonephritis. Conversely, hypertension may cause nephrosclerosis, and in some instances it may be difficult to determine whether hypertension or renal disease was the initial disorder. Proteinuria >1000 mg/d and an active urine sediment are indicative of primary renal disease. In either instance, the goals are to control blood pressure and retard the rate of progression of renal dysfunction.

RENOVASCULAR HYPERTENSION

Hypertension due to an occlusive lesion of a renal artery, renovascular hypertension, is a potentially curable form of hypertension. Two groups of patients are at risk for this disorder: older arteriosclerotic patients who have a plaque obstructing the renal artery, frequently at its origin, and patients with fibromuscular dysplasia. Atherosclerosis accounts for the large majority of patients with renovascular hypertension. Although fibromuscular dysplasia may occur at any age, it has a strong predilection for young white women. The lesions

of fibromuscular dysplasia are frequently bilateral and, in contrast to atherosclerotic renovascular disease, tend to affect more distal portions of the renal artery.

Renovascular hypertension should be considered in patients with other evidence of atherosclerotic vascular disease. Severe or refractory hypertension, recent loss of hypertension control or recent onset of moderately severe hypertension, and unexplained deterioration of renal function or deterioration of renal function associated with an ACE inhibitor should raise the possibility of renovascular hypertension. Approximately 50% of patients with renovascular hypertension have an abdominal or flank bruit, and the bruit is more likely to be hemodynamically significant if it lateralizes or extends throughout systole into diastole.

If renal artery stenosis is suspected and if the clinical condition warrants an intervention such as percutaneous transluminal renal angioplasty (PTRA), placement of a vascular endoprosthesis (stent), or surgical renal revascularization, imaging studies should be the next step in the evaluation. As a screening test, renal blood flow may be evaluated with a radionuclide [^{131}I]-orthoiodohippurate (OIH) scan, or glomerular filtration rate may be evaluated with a [^{99}mTc]-diethylenetriamine pentaacetic acid (DTPA) scan before and after a single dose of captopril (or another ACE inhibitor). In patients with normal, or nearly normal, renal function, a normal captopril renogram essentially excludes functionally significant renal artery stenosis; however, its usefulness is limited in patients with renal insufficiency (creatinine clearance <20 mL/min) or bilateral renal artery stenosis. Additional imaging studies are indicated if the scan is positive. Doppler ultrasound of the renal arteries produces reliable estimates of renal blood flow velocity and offers the opportunity to track a lesion over time. Positive studies usually are confirmed at angiography, whereas false-negative results occur frequently, particularly in obese patients. Gadolinium-contrast magnetic resonance angiography offers clear images of the proximal renal artery but may miss distal lesions. An advantage is the opportunity to image the renal arteries with an agent that is not nephrotoxic. Contrast arteriography remains the "gold standard" for evaluation and identification of renal artery lesions.

Some degree of renal artery obstruction may be observed in almost 50% of patients with atherosclerotic disease, and there are several approaches for evaluating the functional significance of such a lesion to predict the effect of vascular repair on blood pressure control and renal function. Each approach has varying degrees of sensitivity and specificity, and no single test is sufficiently reliable to determine a causal relationship between a renal artery lesion and hypertension. Functionally significant lesions generally occlude >70% of the lumen of the affected renal artery. On angiography, the presence of collateral vessels to the ischemic kidney suggests a functionally significant lesion. A lateralizing renal vein renin ratio (ratio >1.5 of affected side/contralateral side) has a 90% predictive value for a lesion that would respond to vascular repair; however, the false-negative rate for blood pressure control is 50–60%. Measurement of the pressure gradient across a renal artery lesion does not reliably predict the response to vascular repair.

In the final analysis, a decision concerning vascular repair vs medical therapy and the type of repair procedure should be individualized. If blood pressure is adequately controlled with medical therapy and renal function remains stable, there may be little impetus to pursue an evaluation for renal artery stenosis. Several recent randomized clinical trials have found that PTRA with stent placement in patients with arteriosclerotic renal artery stenosis offers no advantages to medical therapy in reducing cardiovascular events and mortality or in preserving kidney function. In addition, 5 of 7 trials found similar blood pressure control in the two groups of patients. These results suggest that laboratory evaluation for renal artery stenosis and stent placement should be considered only in those arteriosclerotic patients in whom medical therapy fails to control blood pressure or preserve renal function. Patients with long-standing hypertension, advanced renal insufficiency, or diabetes mellitus are less likely to benefit from renal vascular repair. The most effective medical therapies include an ACE inhibitor or an angiotensin II receptor blocker; however, these agents decrease glomerular filtration rate in a stenotic kidney owing to efferent renal arteriolar dilation. In the presence of bilateral renal artery stenosis or renal artery stenosis to a solitary kidney, progressive renal insufficiency may result from the use of these agents. Importantly, the renal insufficiency is generally reversible after discontinuation of the offending drug. Patients with fibromuscular disease have more favorable outcomes with vascular repair than do patients with atherosclerotic lesions, presumably owing to their younger age, shorter duration of hypertension, and less systemic disease.

PRIMARY ALDOSTERONISM

Excess aldosterone production due to primary aldosteronism is a potentially curable form of hypertension. In patients with primary aldosteronism, increased aldosterone production is independent of the renin-angiotensin system, and the consequences are sodium retention, hypertension, hypokalemia, and low PRA. The reported prevalence of this disorder varies from <2 to ~15% of hypertensive individuals. In part, this variation is related to the intensity of screening and the criteria for establishing the diagnosis.

History and physical examination provide little information about the diagnosis. The age at the time of diagnosis is generally the third through fifth decade. Hypertension is usually mild to moderate but occasionally may be severe; primary aldosteronism should be considered in all patients with refractory hypertension. Hypertension in these patients may be associated with glucose intolerance. Most patients are asymptomatic; however, infrequently, polyuria, polydipsia, paresthesias, or muscle weakness may be present as a consequence of hypokalemic alkalosis. Although aldosterone is a salt-retaining hormone, patients with primary aldosteronism rarely have edema. Renal dysfunction and cardiovascular disease are strikingly increased in patients with primary aldosteronism compared to those with primary hypertension.

In a hypertensive patient with unprovoked hypokalemia (i.e., unrelated to diuretics, vomiting, or diarrhea), the prevalence of primary aldosteronism approaches 40–50%. In patients on diuretics, serum potassium <3.1 mmol/L (<3.1 meq/L) also raises the possibility of primary aldosteronism; however, serum potassium is an insensitive and nonspecific screening test. Serum potassium is normal in ~25% of patients subsequently found to have an aldosterone-producing adenoma, and higher percentages of patients with other etiologies of primary aldosteronism are not hypokalemic.

The ratio of plasma aldosterone to PRA (PA/PRA) is a useful screening test. These measurements preferably are obtained in ambulatory patients in the morning. A ratio >30:1 in conjunction with a plasma aldosterone concentration >555 pmol/L (>20 ng/dL) reportedly has a sensitivity of 90% and a specificity of 91% for an aldosterone-producing adenoma. In a Mayo Clinic series, an aldosterone-producing adenoma subsequently was confirmed surgically in >90% of hypertensive patients with a PA/PRA ratio ≥20 and a plasma aldosterone concentration ≥415 pmol/L (≥15 ng/dL). There are, however, several caveats to interpreting the ratio. The cutoff for a "high" ratio is laboratory- and assay-dependent. Some anti-hypertensive agents may affect the ratio (e.g., aldosterone antagonists, angiotensin receptor antagonists, and ACE inhibitors may increase renin; aldosterone antagonists may increase aldosterone). Current recommendations are to withdraw aldosterone antagonists for at least 4–6 weeks before obtaining these measurements. Because aldosterone biosynthesis is potassium-dependent, hypokalemia should be corrected with oral potassium supplements prior to screening. With these caveats, the ratio has been reported to be useful as a screening test in measurements obtained with patients taking their usual antihypertensive medications except for aldosterone antagonists, which should be discontinued six weeks before testing. A high ratio in the absence of an elevated plasma aldosterone level is considerably less specific for primary aldosteronism since many patients with primary hypertension have low renin levels in this setting, particularly African Americans and elderly patients. In patients with renal insufficiency, the ratio may also be elevated because of decreased aldosterone clearance. In patients with an elevated PA/PRA ratio, the diagnosis of primary aldosteronism can be confirmed by demonstrating failure to suppress plasma aldosterone to

<200 pmol/L (<10 ng/dL) after IV infusion of 2 L of isotonic saline over 4 h; post-saline infusion plasma aldosterone values between 138 and 277 pmol/L (5–10 ng/dL) are not determinant. Alternative confirmatory tests include failure to suppress aldosterone (based on test-specific criteria) in response to an oral NaCl load, fludrocortisone, or captopril.

Several sporadic and familial adrenal abnormalities may culminate in the syndrome of primary aldosteronism, and appropriate therapy depends on the specific etiology. The two most common causes of sporadic primary aldosteronism are an aldosterone-producing adenoma and bilateral adrenal hyperplasia. Together, they account for >90% of all patients with primary aldosteronism. The tumor is almost always unilateral, and most often measures <3 cm in diameter. Most of the remainder of these patients have bilateral adrenocortical hyperplasia (idiopathic hyperaldosteronism). Rarely, primary aldosteronism may be caused by an adrenal carcinoma or an ectopic malignancy, e.g., ovarian arrhenoblastoma. Most aldosterone-producing carcinomas, in contrast to adrenal adenomas and hyperplasia, produce excessive amounts of other adrenal steroids in addition to aldosterone. Functional differences in hormone secretion may assist in the diagnosis of adenoma vs hyperplasia. Aldosterone biosynthesis is more responsive to ACTH in patients with adenoma and more responsive to angiotensin in patients with hyperplasia. Consequently, patients with adenoma tend to have higher plasma aldosterone in the early morning that decreases during the day, reflecting the diurnal rhythm of ACTH, whereas plasma aldosterone tends to increase with upright posture in patients with hyperplasia, reflecting the normal postural response of the renin-angiotensin-aldosterone axis. However, there is overlap in the ability of these measurements to discriminate between adenoma and hyperplasia. Rare familial forms of primary aldosteronism include glucocorticoid-remediable primary aldosteronism and familial aldosteronism types II and III. Genetic testing may assist in the diagnosis of these familial disorders.

Adrenal computed tomography (CT) should be carried out in all patients diagnosed with primary aldosteronism. High-resolution CT may identify tumors as small as 0.3 cm and is positive for an adrenal tumor 90% of the time. If the CT is not diagnostic, an adenoma may be detected by adrenal scintigraphy with 6 β-[I^{131}] iodomethyl-19-norcholesterol after dexamethasone suppression (0.5 mg every 6 h for 7 days); however, this technique has decreased sensitivity for adenomas <1.5 cm.

When carried out by an experienced radiologist, bilateral adrenal venous sampling for measurement of plasma aldosterone is the most accurate means of differentiating unilateral from bilateral forms of primary aldosteronism. The sensitivity and specificity of adrenal venous sampling (95 and 100%, respectively) for detecting unilateral aldosterone hypersecretion are superior to those of adrenal CT; success rates are 90–96%, and complication rates are <2.5%. One frequently used protocol involves sampling for aldosterone and cortisol levels in response to ACTH stimulation. An ipsilateral/contralateral aldosterone ratio >4, with symmetric ACTH-stimulated cortisol levels, is indicative of unilateral aldosterone production.

Hypertension generally is responsive to surgery in patients with adenoma but not in patients with bilateral adrenal hyperplasia. Unilateral adrenalectomy, often done via a laparoscopic approach, is curative in 40–70% of patients with an adenoma. Transient hypoaldosteronism may occur up to 3 months postoperatively, resulting in hyperkalemia, which should be treated with potassium-wasting diuretics and with fludrocortisone, if needed. Patients with bilateral hyperplasia should be treated medically. The drug regimen for these patients, as well as for patients with an adenoma who are poor surgical candidates, should include an aldosterone antagonist and, if necessary, other potassium-sparing diuretics.

Glucocorticoid-remediable hyperaldosteronism is a rare, monogenic autosomal dominant disorder characterized by moderate to severe hypertension, often occurring at an early age. These patients may have a family history of hemorrhagic stroke at a young age. Hypokalemia is usually mild or absent. Normally, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa, whereas ACTH stimulates cortisol production in the zona fasciculata. Owing to a chimeric gene on chromosome 8, ACTH also regulates aldosterone secretion by the zona fasciculata in patients with glucocorticoid-remediable hyperaldosteronism. The consequence is overproduction in the zona fasciculata of both aldosterone and hybrid steroids (18-hydroxycortisol and 18-oxocortisol) due to oxidation of cortisol. The diagnosis may be established by urine excretion rates of these hybrid steroids that are 20–30 times normal or by direct genetic testing. Therapeutically, suppression of ACTH with low-dose glucocorticoids corrects the hyperaldosteronism, hypertension, and hypokalemia. Aldosterone antagonists are also therapeutic options. Patients with familial aldosteronism types II and III are treated with aldosterone antagonists or adrenalectomy.

CUSHING'S SYNDROME

(See also Chap. 379) Cushing's syndrome is related to excess cortisol production due either to excess ACTH secretion (from a pituitary tumor or an ectopic tumor) or to ACTH-independent adrenal production of cortisol. Hypertension occurs in 75–80% of patients with Cushing's syndrome. The mechanism of hypertension may be related to stimulation of mineralocorticoid receptors by cortisol and increased secretion of other adrenal steroids. If clinically suspected based on phenotypic characteristics, in patients not taking exogenous glucocorticoids, laboratory screening may be carried out with measurement of 24-h excretion rates of urine-free cortisol or an overnight dexamethasone-suppression test. Late night salivary cortisol is also a sensitive and convenient screening test. Further evaluation is required to confirm the diagnosis and identify the specific etiology of Cushing's syndrome. Appropriate therapy depends on the etiology.

PHEOCHROMOCYTOMA

(See also Chap. 380) Catecholamine-secreting tumors are located in the adrenal medulla (pheochromocytoma) or in extra-adrenal paraganglion tissue (paraganglioma) and account for hypertension in ~0.05% of patients. If unrecognized, pheochromocytoma may result in lethal cardiovascular consequences. Clinical manifestations, including hypertension, are primarily related to increased circulating catecholamines, although some of these tumors may secrete a number of other vasoactive substances. In a small percentage of patients, epinephrine is the predominant catecholamine secreted by the tumor, and these patients may present with hypotension rather than hypertension. The initial suspicion of the diagnosis is based on symptoms and/or the association of pheochromocytoma with other disorders **(Table 271-4)**. Approximately 20% of pheochromocytomas are familial with autosomal dominant inheritance. Inherited pheochromocytomas may be associated with multiple endocrine neoplasia (MEN) type 2A and type 2B, von Hippel-Lindau disease, and neurofibromatosis (Table 271-4). Each of these syndromes is related to specific, identifiable germ-line mutations. Additionally, mutations of succinate dehydrogenase genes are associated with paraganglioma syndromes, generally characterized by head and neck paragangliomas. Laboratory testing consists of measuring catecholamines in either urine or plasma, e.g., 24-h urine metanephrine excretion or fractionated plasma-free metanephrines. The urine measurement is less sensitive but more specific. Genetic screening is available for evaluating patients and relatives suspected of harboring a pheochromocytoma associated with a familial syndrome. Surgical excision is the definitive treatment of pheochromocytoma and results in cure in ~90% of patients.

MISCELLANEOUS CAUSES OF HYPERTENSION

Independent of obesity, hypertension occurs in >50% of individuals with *obstructive sleep apnea*. The severity of hypertension correlates with the severity of sleep apnea. Approximately 70% of patients with obstructive sleep apnea are obese. Hypertension related to obstructive sleep apnea also should be considered in patients with drug-resistant hypertension and patients with a history of snoring. The diagnosis can be confirmed by polysomnography. In obese patients, weight loss may alleviate or cure sleep apnea and related hypertension. Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) administered during sleep is an effective therapy for obstructive sleep apnea. With CPAP or BiPAP, patients with apparently drug-resistant hypertension may be more responsive to antihypertensive agents.

TABLE 271-4 Rare Mendelian Forms of Hypertension

DISEASE	PHENOTYPE	GENETIC CAUSE
Glucocorticoid-remediable hyperaldosteronism	Autosomal dominant Absent or mild hypokalemia	Chimeric 11β-hydroxylase/aldosterone gene on chromosome 8
17α-hydroxylase deficiency	Autosomal recessive Males: pseudohermaphroditism Females: primary amenorrhea, absent secondary sexual characteristics	Random mutations of the *CYP17* gene on chromosome 10
11β-hydroxylase deficiency	Autosomal recessive Masculinization	Mutations of the *CYP11B1* gene on chromosome 8q21-q22
11β-hydroxysteroid dehydrogenase deficiency (apparent mineralocorticoid excess syndrome)	Autosomal recessive Hypokalemia, low renin, low aldosterone	Mutations in the 11β-hydroxysteroid dehydrogenase gene
Liddle's syndrome	Autosomal dominant Hypokalemia, low renin, low aldosterone	Mutation subunits of the epithelial sodium channel *SCNN1B* and *SCNN1C* genes
Pseudohypoaldosteronism type II (Gordon's syndrome)	Autosomal dominant Hyperkalemia, normal glomerular filtration rate	Linkage to chromosomes 1q31-q42 and 17p11-q21
Hypertension exacerbated in pregnancy	Autosomal dominant Severe hypertension in early pregnancy	Missense mutation with substitution of leucine for serine at codon 810 (MR_{L810})
Polycystic kidney disease	Autosomal dominant Large cystic kidneys, renal failure, liver cysts, cerebral aneurysms, valvular heart disease	Mutations in the *PKD1* gene on chromosome 16 and *PKD2* gene on chromosome 4
Pheochromocytoma	Autosomal dominant (a) Multiple endocrine neoplasia, type 2A Medullary thyroid carcinoma, hyperparathyroidism (b) Multiple endocrine neoplasia, type 2B Medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, alimentary ganglioneuromatoses, marfanoid habitus (c) von Hippel-Lindau disease Retinal angiomas, hemangioblastomas of the cerebellum and spinal cord, renal cell carcinoma (d) Neurofibromatosis type 1 Multiple neurofibromas, café-au-lait spots	 (a) Mutations in the *RET* protooncogene (b) Mutations in the *RET* protooncogene (c) Mutations in the *VHL* tumor-suppressor gene (d) Mutations in the *NF1* tumor-suppressor gene

Coarctation of the aorta is the most common congenital cardiovascular cause of hypertension **(Chap. 264)**. The incidence is 1–8 per 1000 live births. It is usually sporadic but occurs in 35% of children with Turner's syndrome. Even when the anatomic lesion is surgically corrected in infancy, up to 30% of patients develop subsequent hypertension and are at risk of accelerated coronary artery disease and cerebrovascular events. Patients with less severe lesions may not be diagnosed until young adulthood. Physical findings include diminished and delayed femoral pulses and a systolic pressure gradient between the right arm and the legs and, depending on the location of the coarctation, between the right and left arms. A blowing systolic murmur may be heard in the posterior left interscapular areas. The diagnosis may be confirmed by chest x-ray and transesophageal echocardiography. Therapeutic options include surgical repair and balloon angioplasty, with or without placement of an intravascular stent. Subsequently, many patients do not have a normal life expectancy but may have persistent hypertension, with death due to ischemic heart disease, cerebral hemorrhage, or aortic aneurysm.

Several additional endocrine disorders, including *thyroid diseases* and *acromegaly*, cause hypertension. Mild diastolic hypertension may be a consequence of hypothyroidism, whereas hyperthyroidism may result in systolic hypertension. *Hypercalcemia* of any etiology, the most common being primary hyperparathyroidism, may result in hypertension. Hypertension also may be related to a number of prescribed or over-the-counter *medications*.

MONOGENIC HYPERTENSION

In addition to glucocorticoid-remediable primary aldosteronism, a number of rare forms of monogenic hypertension have been identified (Table 271–4). These disorders may be recognized by their characteristic phenotypes, and in many instances the diagnosis may be confirmed by genetic analysis. Several inherited defects in adrenal steroid biosynthesis and metabolism result in mineralocorticoid-induced hypertension and hypokalemia. In patients with a 17α-hydroxylase deficiency, synthesis of sex hormones and cortisol is decreased **(Fig. 271-3)**. Consequently, these individuals do not mature sexually; males may present with pseudohermaphroditism and females with primary amenorrhea and absent secondary sexual characteristics. Because cortisol-induced negative feedback on pituitary ACTH production is diminished, ACTH-stimulated adrenal steroid synthesis proximal to the enzymatic block is increased. Hypertension and hypokalemia are consequences of increased synthesis of mineralocorticoids proximal to the enzymatic block, particularly desoxycorticosterone. Increased steroid production and, hence, hypertension may be treated with low-dose glucocorticoids. An 11β-hydroxylase deficiency results in a salt-retaining adrenogenital syndrome that occurs in 1 in 100,000 live births. This enzymatic defect results in decreased cortisol synthesis, increased synthesis of mineralocorticoids (e.g., desoxycorticosterone), and shunting of steroid biosynthesis into the androgen pathway. In the severe form, the syndrome may present early in life, including the newborn period, with virilization and ambiguous genitalia in females and penile enlargement in males, or in older children as precocious puberty and short stature. Acne, hirsutism, and menstrual irregularities may be the presenting features when the disorder is first recognized in adolescence or early adulthood. Hypertension is less common in the late-onset forms. Patients with an 11β-hydroxysteroid dehydrogenase deficiency have an impaired capacity to metabolize cortisol to its inactive metabolite, cortisone, and hypertension is related to activation of mineralocorticoid receptors by cortisol. This defect may be inherited or acquired, due to licorice-containing glycyrrhizin acid. The same substance is present in the paste of several brands of chewing tobacco. The defect in Liddle's syndrome **(Chaps. 49 and 379)** results from constitutive

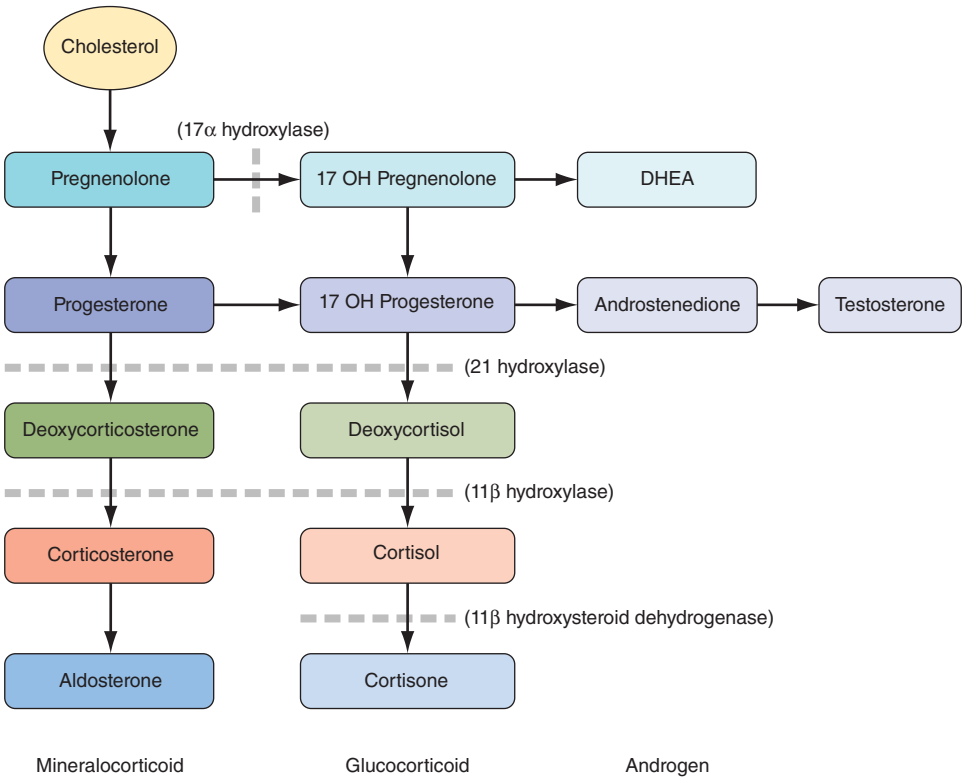

FIGURE 271-3 Adrenal enzymatic defects. DHEA, dehydroepiandrosterone.

activation of amiloride-sensitive ENaC on the distal renal tubule, resulting in excess sodium reabsorption; the syndrome is ameliorated by amiloride. Hypertension exacerbated in pregnancy **(Chap. 466)** may be due to activation of the mineralocorticoid receptor by progesterone.

APPROACH TO THE PATIENT

Hypertension

HISTORY AND PHYSICAL

The initial assessment of a hypertensive patient should include a complete history and physical examination to confirm a diagnosis of hypertension, screen for other cardiovascular disease risk factors, screen for secondary causes of hypertension, identify cardiovascular consequences of hypertension and other comorbidities, assess blood pressure–related lifestyles, and determine the potential for intervention. Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. **Table 271-5** lists salient features of the history and physical examination of the hypertensive patient.

Reliable measurements of blood pressure depend on attention to the details of the technique and conditions of the measurement. Proper training of observers, positioning of the patient, and selection of cuff size are essential. Owing to recent regulations preventing the use of mercury because of concerns about its potential toxicity, most office measurements are made with aneroid sphygmomanometers or with oscillometric devices. These instruments should be calibrated periodically, and their accuracy confirmed.

LABORATORY TESTING

Table 271-6 lists recommended laboratory tests in the initial evaluation of hypertensive patients. Repeat measurements of renal function, serum electrolytes, fasting glucose, and lipids may be obtained after the introduction of a new antihypertensive agent and then annually or more frequently if clinically indicated. More extensive laboratory testing is appropriate for patients with apparent drug-resistant hypertension or when the clinical evaluation suggests a secondary form of hypertension.

TREATMENT

Hypertension

LIFESTYLE INTERVENTIONS

Implementation of lifestyles that favorably affect blood pressure has implications for both the prevention and the treatment of hypertension. Health-promoting lifestyle modifications are recommended for individuals with prehypertension and as an adjunct to drug therapy

TABLE 271-5 Relevant History and Physical

History
Duration of hypertension
Previous therapies: responses and side effects
Family history of hypertension and cardiovascular disease
Dietary and psychosocial history
Other risk factors: weight change, dyslipidemia, smoking, diabetes, physical inactivity
Evidence of secondary hypertension: history of renal disease; change in appearance; muscle weakness; spells of sweating, palpitations, tremor; erratic sleep, snoring, daytime somnolence; symptoms of hypo- or hyperthyroidism; use of agents that may increase blood pressure
Evidence of target organ damage: history of TIA, stroke, transient blindness; angina, myocardial infarction, congestive heart failure; sexual function
Other comorbidities
Physical
Body habitus
Blood pressure in both arms
Supine and standing blood pressures
Funduscopic examination of retina
Quality of femoral and pedal pulses
Vascular and abdominal bruits
Cardiac rate and rhythm
Signs of congestive heart failure
Signs of secondary hypertension

Abbreviation: TIA, transient ischemic attack.

TABLE 271-6 Basic Laboratory Tests for Initial Evaluation

SYSTEM	TEST
Renal	Microscopic urinalysis, albumin excretion, serum BUN and/or creatinine
Endocrine	Serum sodium, potassium, calcium, TSH
Metabolic	Fasting blood glucose, total cholesterol, HDL and LDL (often computed) cholesterol, triglycerides
Other	Hematocrit, electrocardiogram

Abbreviations: BUN, blood urea nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

in hypertensive individuals. These interventions should address overall cardiovascular disease risk. Although the impact of lifestyle interventions on blood pressure is more pronounced in persons with hypertension, in short-term trials, weight loss and reduction of dietary NaCl have been shown to prevent the development of hypertension. In hypertensive individuals, even if these interventions do not produce a sufficient reduction in blood pressure to avoid drug therapy, the number of medications or doses required for blood pressure control may be reduced. Dietary modifications that effectively lower blood pressure are weight loss, reduced NaCl intake, increased potassium intake, moderation of alcohol consumption, and an overall healthy dietary pattern **(Table 271-7)**.

Prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk. In short-term trials, even modest weight loss can lead to a reduction of blood pressure and an increase in insulin sensitivity. Average blood pressure reductions of 6.3/3.1 mmHg have been observed with a reduction in mean body weight of 9.2 kg. Regular physical activity facilitates weight loss, decreases blood pressure, and reduces the overall risk of cardiovascular disease. Blood pressure may be lowered by 30 min of moderately intense physical activity, such as brisk walking, 6–7 days a week, or by more intense, less frequent workouts.

There is individual variability in the sensitivity of blood pressure to NaCl, and this variability may have a genetic basis. Several genetic loci have been associated with NaCl sensitivity. Based on results of meta-analyses, lowering of blood pressure by limiting daily NaCl intake to 4.4–7.4 g (75–125 meq) results in blood pressure reductions of 3.7–4.9/0.9–2.9 mmHg in hypertensive individuals and lesser reductions in normotensive individuals. Results of randomized clinical trials on the impact of sodium reduction on the incidence of cardiovascular events are conflicting; however, for obvious practical reasons, such studies are challenging and often are not sufficiently powered to detect differences in cardiovascular endpoints. Although reduced salt intakes are generally recommended for both the prevention and treatment of hypertension, overly rigorous salt restriction may have adverse cardiovascular outcomes in diabetic patients and in patients with CHF aggressively treated with diuretics. Potassium and calcium supplementation have inconsistent, modest antihypertensive effects, and, independent of blood pressure, potassium supplementation may be associated with reduced stroke mortality. Consuming three or more alcoholic drinks per day (a standard drink contains ~14 g ethanol) is associated with higher blood pressures, and a reduction of alcohol consumption is associated with a reduction of blood pressure. In patients with advanced renal disease, dietary protein restriction may have a modest effect in mitigating renal damage by reducing the intrarenal transmission of systemic arterial pressure.

TABLE 271-7 Lifestyle Modifications to Manage Hypertension

Weight reduction	Attain and maintain BMI <25 kg/m^2
Dietary salt reduction	<6 g NaCl/d
Adapt DASH-type dietary plan	Diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Moderation of alcohol consumption	For those who drink alcohol, consume ≤2 drinks/d in men and ≤1 drink/d in women
Physical activity	Regular aerobic activity, e.g., brisk walking for 30 min/d

Abbreviations: BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension (trial).

The DASH (Dietary Approaches to Stop Hypertension) trial convincingly demonstrated that over an 8-week period a diet high in fruits, vegetables, and low-fat dairy products lowers blood pressure in individuals with high-normal blood pressures or mild hypertension. Reduction of daily NaCl intake to <6 g (100 meq) augmented the effect of this diet on blood pressure. Fruits and vegetables are enriched sources of potassium, magnesium, and fiber, and dairy products are an important source of calcium.

PHARMACOLOGIC THERAPY

Lowering systolic blood pressure by 10–12 mmHg and diastolic blood pressure by 5–6 mmHg confers relative risk reductions of 35–40% for stroke and 12–16% for CHD within 5 years of the initiation of treatment. The risk of heart failure is reduced by >50%; although the benefit of blood pressure lowering on progression of renal failure is less apparent, hypertension control is the single most effective intervention for slowing the rate of progression of hypertension-related kidney disease.

There is considerable variation in individual responses to different classes of antihypertensive agents, and the magnitude of response to any single agent may be limited by activation of counter-regulatory mechanisms. Most available agents reduce systolic blood pressure by 7–13 mmHg and diastolic blood pressure by 4–8 mmHg when corrected for placebo effect. More often than not, combinations of agents, with complementary antihypertensive mechanisms, are required to achieve goal blood pressure reductions. Selection of antihypertensive agents and combinations of agents should be individualized, taking into account age, severity of hypertension, other cardiovascular disease risk factors, comorbid conditions, and practical considerations related to cost, side effects, and frequency of dosing **(Table 271-8)**.

Diuretics Low-dose thiazide diuretics may be used alone or in combination with other antihypertensive drugs. Thiazides inhibit the Na^+/Cl^- pump in the distal convoluted tubule and hence increase sodium excretion. In the long term, they also may act as vasodilators. Thiazides are safe, efficacious, inexpensive, and reduce clinical events. They provide additive blood pressure–lowering effects when combined with beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs). In contrast, addition of a diuretic to a calcium channel blocker is less effective. Usual doses of hydrochlorothiazide range from 6.25 to 50 mg/d. Owing to an increased incidence of metabolic side effects (hypokalemia, insulin resistance, increased cholesterol), higher doses generally are not recommended. Chlorthalidone is a diuretic structurally similar to hydrochlorothiazide, and like hydrochlorothiazide, it blocks sodium-chloride cotransport in the early distal tubule. However, chlorthalidone has a longer half-life (40–60 h vs 9–15 h) and an antihypertensive potency ~1.5–2.0 times that of hydrochlorothiazide. Potassium loss is also greater with chlorthalidone. Two potassium-sparing diuretics, amiloride and triamterene, act by inhibiting ENaC in the distal nephron. These agents are weak antihypertensive agents but may be used in combination with a thiazide to protect against hypokalemia. The main pharmacologic target for loop diuretics is the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. Loop diuretics generally are reserved for hypertensive patients with reduced glomerular filtration rates (reflected in serum creatinine >220 μmol/L [>2.5 mg/dL]), CHF, or sodium retention and edema for some other reason, such as treatment with a potent vasodilator, e.g., minoxidil.

Blockers of the Renin–Angiotensin System ACEIs decrease the production of angiotensin II, increase bradykinin levels, and reduce sympathetic nervous system activity. ARBs provide selective blockade of AT_1 receptors, and the effect of angiotensin II on unblocked AT_2 receptors may augment their hypotensive effect. Both classes

TABLE 271-8 Examples of Oral Drugs Used in Treatment of Hypertension

DRUG CLASS	EXAMPLES	USUAL TOTAL DAILY DOSE[a] (DOSING FREQUENCY/DAY)	OTHER INDICATIONS	CONTRAINDICATIONS/CAUTIONS
Diuretics				
Thiazides	Hydrochlorothiazide	6.25–50 mg (1–2)		Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
	Chlorthalidone	25–50 mg (1)		
Loop diuretics	Furosemide	40–80 mg (2–3)	CHF due to systolic dysfunction, renal failure	Diabetes, dyslipidemia, hyperuricemia, gout, hypokalemia
	Ethacrynic acid	50–100 mg (2–3)		
Aldosterone antagonists	Spironolactone	25–100 mg (1–2)	CHF due to systolic dysfunction, primary aldosteronism	Renal failure, hyperkalemia
	Eplerenone	50–100 mg (1–2)		
K^+ retaining	Amiloride	5–10 mg (1–2)		Renal failure, hyperkalemia
	Triamterene	50–100 mg (1–2)		
Beta blockers				Asthma, COPD, 2nd- or 3rd-degree heart block, sick-sinus syndrome
Cardioselective	Atenolol	25–100 mg (1)	Angina, CHF due to systolic dysfunction, post-MI, sinus tachycardia, ventricular tachyarrhythmias	
	Metoprolol	25–100 mg (1–2)		
Nonselective	Propranolol	40–160 mg (2)		
	Propranolol LA	60–180 (1)		
Combined alpha/beta	Labetalol	200–800 mg (2)		
	Carvedilol	12.5–50 mg (2)		
Alpha antagonists				
Selective	Prazosin	2–20 mg (2–3)	Prostatism	
	Doxazosin	1–16 mg (1)		
	Terazosin	1–10 mg (1–2)		
Nonselective	Phenoxybenzamine	20–120 mg (2–3)	Pheochromocytoma	
Sympatholytics				
Central	Clonidine	0.1–0.6 mg (2)		
	Clonidine patch	0.1–0.3 mg (1/week)		
	Methyldopa	250–1000 mg (2)		
	Reserpine	0.05–0.25 mg (1)		
	Guanfacine	0.5–2 mg (1)		
ACE inhibitors	Captopril	25–200 mg (2)	Post-MI, coronary syndromes, CHF with low ejection fraction, nephropathy	Acute renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
	Lisinopril	10–40 mg (1)		
	Ramipril	2.5–20 mg (1–2)		
Angiotensin II antagonists	Losartan	25–100 mg (1–2)	CHF with low ejection fraction, nephropathy, ACE inhibitor cough	Renal failure, bilateral renal artery stenosis, pregnancy, hyperkalemia
	Valsartan	80–320 mg (1)		
	Candesartan	2–32 mg (1–2)		
Renin inhibitors	Aliskiren	150–300 mg (1)	Diabetic nephropathy	Pregnancy
Calcium antagonists				
Dihydropyridines	Nifedipine (long-acting)	30–60 mg (1)		
Nondihydropyridines	Verapamil (long-acting)	120–360 mg (1–2)	Post-MI, supraventricular tachycardias, angina	2nd- or 3rd-degree heart block
	Diltiazem (long-acting)	180–420 mg (1)		
Direct vasodilators	Hydralazine	25–100 mg (2)		Severe coronary artery disease
	Minoxidil	2.5–80 mg (1–2)		

[a]At the initiation of therapy, lower doses may be preferable for elderly patients and for select combinations of antihypertensive agents.

Abbreviations: ACE, angiotensin-converting enzyme; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

of agents are effective antihypertensive agents that may be used as monotherapy or in combination with diuretics, calcium antagonists, and alpha blocking agents. ACEIs and ARBs improve insulin action and ameliorate the adverse effects of diuretics on glucose metabolism. Although the overall impact on the incidence of diabetes is modest, compared with amlodipine (a calcium antagonist), valsartan (an ARB) has been shown to reduce the risk of developing diabetes in high-risk hypertensive patients. ACEI/ARB combinations are less effective in lowering blood pressure than is the case when either class of these agents is used in combination with other classes of agents. In patients with vascular disease or a high risk of diabetes, combination ACEI/ARB therapy has been associated with more adverse events (e.g., cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure) without increases in benefit.

Side effects of ACEIs and ARBs include functional renal insufficiency due to efferent renal arteriolar dilation in a kidney with a stenotic lesion of the renal artery. Additional predisposing conditions to renal insufficiency induced by these agents include dehydration, CHF, and use of nonsteroidal anti-inflammatory drugs. Dry cough occurs in ~15% of patients, and angioedema occurs in <1% of patients taking ACEIs. Angioedema occurs most commonly in individuals of Asian origin and more commonly in African Americans than in whites. Hyperkalemia due to hypoaldosteronism is an occasional side effect of both ACEIs and ARBs.

An alternative approach to blocking the renin-angiotensin system has recently been introduced into clinical practice for the treatment of hypertension: direct renin inhibitors. Blockade of the renin-angiotensin system is more complete with renin inhibitors than with ACEIs or ARBs. Aliskiren is the first of a class of oral, nonpeptide

competitive inhibitors of the enzymatic activity of renin. Monotherapy with aliskiren seems to be as effective as an ACEI or ARB for lowering blood pressure, but not more effective. Further blood reductions may be achieved when aliskiren is used in combination with a thiazide diuretic or a calcium antagonist. Currently, aliskiren is not considered a first-line antihypertensive agent.

Aldosterone Antagonists Spironolactone is a nonselective aldosterone antagonist that may be used alone or in combination with a thiazide diuretic. It may be a particularly effective agent in patients with low-renin primary hypertension, resistant hypertension, and primary aldosteronism. In patients with CHF, low-dose spironolactone reduces mortality and hospitalizations for heart failure when given in addition to conventional therapy with ACEIs, digoxin, and loop diuretics. Because spironolactone binds to progesterone and androgen receptors, side effects may include gynecomastia, impotence, and menstrual abnormalities. These side effects are circumvented by a newer agent, eplerenone, which is a selective aldosterone antagonist.

Beta Blockers β-Adrenergic receptor blockers lower blood pressure by decreasing cardiac output owing to a reduction of heart rate and contractility. Other proposed mechanisms by which beta blockers lower blood pressure include a central nervous system effect and inhibition of renin release. Beta blockers are particularly effective in hypertensive patients with tachycardia, and their hypotensive potency is enhanced by co-administration with a diuretic. In lower doses, some beta blockers selectively inhibit cardiac β_1 receptors and have less influence on β_2 receptors on bronchial and vascular smooth muscle cells; however, there seems to be no difference in the antihypertensive potencies of cardioselective and nonselective beta blockers. Some beta blockers have intrinsic sympathomimetic activity, although it is uncertain whether this constitutes an overall advantage or disadvantage in cardiac therapy. Beta blockers without intrinsic sympathomimetic activity decrease the rate of sudden death, overall mortality, and recurrent myocardial infarction. In patients with CHF, beta blockers have been shown to reduce the risks of hospitalization and mortality. Overall, beta blockers may be less protective against cardiovascular and cerebrovascular endpoints, and some beta blockers may have less effect on central aortic pressure than other classes of antihypertensive agents. However, beta blockers remain appropriate therapy for hypertensive patients with concomitant heart disease and related comorbidities. Carvedilol and labetalol block both β receptors and peripheral α-adrenergic receptors. The potential advantages of combined β- and α-adrenergic blockade in treating hypertension remain to be determined. Nebivolol represents another class of cardioselective beta blockers that has additional vasodilator actions related to enhancement of nitric oxide activity. Whether this confers greater clinical effectiveness remains to be determined.

α-Adrenergic Blockers Postsynaptic, selective α-adrenoreceptor antagonists lower blood pressure by decreasing peripheral vascular resistance. They are effective antihypertensive agents used either as monotherapy or in combination with other agents. However, in clinical trials of hypertensive patients, alpha blockade has not been shown to reduce cardiovascular morbidity and mortality or to provide as much protection against CHF as other classes of antihypertensive agents. These agents are also effective in treating lower urinary tract symptoms in men with prostatic hypertrophy. Nonselective α-adrenoreceptor antagonists bind to postsynaptic and presynaptic receptors and are used primarily for the management of patients with pheochromocytoma.

Sympatholytic Agents Centrally acting α_2 sympathetic agonists decrease peripheral resistance by inhibiting sympathetic outflow. They may be particularly useful in patients with autonomic neuropathy who have wide variations in blood pressure due to baroreceptor denervation. Drawbacks include somnolence, dry mouth, and rebound hypertension on withdrawal. Peripheral sympatholytics decrease peripheral resistance and venous constriction by depleting nerve terminal norepinephrine. Although they are potentially effective antihypertensive agents, their usefulness is limited by orthostatic hypotension, sexual dysfunction, and numerous drug-drug interactions. Rebound hypertension is another concern with abrupt cessation of drugs with a short half-life.

Calcium Channel Blockers Calcium antagonists reduce vascular resistance through L-channel blockade, which reduces intracellular calcium and blunts vasoconstriction. This is a heterogeneous group of agents that includes drugs in the following three classes: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and 1,4-dihydropyridines (nifedipine-like). Used alone and in combination with other agents (ACEIs, beta blockers, α_1-adrenergic blockers), calcium antagonists effectively lower blood pressure; however, it is unclear if adding a diuretic to a calcium blocker results in a further lowering of blood pressure. Side effects of flushing, headache, and edema with dihydropyridine use are related to their potencies as arteriolar dilators; edema is due to an increase in transcapillary pressure gradients, not to net salt and water retention.

Direct Vasodilators Direct vasodilators decrease peripheral resistance and concomitantly activate mechanisms that defend arterial pressure, notably the sympathetic nervous system, the renin-angiotensin-aldosterone system, and sodium retention. Usually, they are not considered first-line agents but are most effective when added to a combination that includes a diuretic and a beta blocker. Hydralazine is a potent direct vasodilator that has antioxidant and nitric oxide–enhancing actions, and minoxidil is a particularly potent agent and is used most frequently in patients with renal insufficiency who are refractory to all other drugs. Hydralazine may induce a lupus-like syndrome, and side effects of minoxidil include hypertrichosis and pericardial effusion. Intravenous nitroprusside can be used to treat malignant hypertension and life-threatening left ventricular heart failure associated with elevated arterial pressure.

COMPARISONS OF ANTIHYPERTENSIVES

Based on pooling results from clinical trials, meta-analyses of the efficacy of different classes of antihypertensive agents suggest essentially equivalent blood pressure–lowering effects of the following six major classes of antihypertensive agents when used as monotherapy: thiazide diuretics, beta blockers, ACEIs, ARBs, calcium antagonists, and α_1 blockers. On average, standard doses of most antihypertensive agents reduce blood pressure by 8–10/4–7 mmHg; however, there may be subgroup differences in responsiveness. Younger patients may be more responsive to beta blockers and ACEIs, whereas patients aged >50 years may be more responsive to diuretics and calcium antagonists. There is a limited relationship between plasma renin and blood pressure response. Patients with high-renin hypertension may be more responsive to ACEIs and ARBs than to other classes of agents, whereas patients with low-renin hypertension are more responsive to diuretics and calcium antagonists. Hypertensive African Americans tend to have low renin and may require higher doses of ACEIs and ARBs than whites for optimal blood pressure control, although this difference is abolished when these agents are combined with a diuretic. Beta blockers also appear to be less effective than thiazide diuretics in African Americans than in non-African Americans. Early pharmacogenetic studies, utilizing a candidate gene approach, genome-wide scans, or integrated metabolomic and genetic profiles, have shown associations of gene polymorphisms with blood pressure responsiveness to specific antihypertensive drugs. However, the reported effects have generally been too small to affect clinical decisions, and associated polymorphisms remain to be confirmed. Currently, in practical terms, the presence of comorbidities often influences the selection of antihypertensive agents.

A meta-analysis of >30 randomized trials of blood pressure–lowering therapy indicates that for a given reduction in blood pressure, the major drug classes seem to produce similar overall net effects on total cardiovascular events. In both nondiabetic and diabetic hypertensive patients, most trials have failed to show significant

differences in cardiovascular outcomes with different drug regimens as long as equivalent decreases in blood pressure were achieved. For example, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that the occurrence of CHD and nonfatal myocardial infarction, as well as overall mortality, was virtually identical in hypertensive patients treated with either an ACEI (lisinopril), a diuretic (chlorthalidone), or a calcium antagonist (amlodipine). However, there is some evidence that beta blockers are inferior to other classes of agents for prevention of cardiovascular events, stroke, renal failure, and all-cause mortality, whereas calcium channel blockers may be inferior and diuretics but superior to other classes of agents for the prevention of heart failure.

However, in specific patient groups, ACEIs may have particular advantages, beyond that of blood pressure control, in reducing cardiovascular and renal outcomes. ACEIs and ARBs decrease intraglomerular pressure and proteinuria and may retard the rate of progression of renal insufficiency, not totally accounted for by their hypotensive effects, in both diabetic and nondiabetic renal diseases. In patients with type 2 diabetes, treatment with an ACEI, an ARB, or aliskiren decreases proteinuria and delays the progression of renal disease. In experimental models of hypertension and diabetes, renal protection with aliskiren is comparable to that with ACEIs and ARBs. However, in patients with type 2 diabetes, addition of aliskiren to an ACEI provides no additional protection against cardiovascular or renal disease and may be associated with more adverse outcomes. Among African Americans with hypertension-related renal disease, ACEIs appear to be more effective than beta blockers or dihydropyridine calcium channel blockers in slowing, although not preventing, the decline of glomerular filtration rate. The renoprotective effect of these renin-angiotensin blockers, compared with other antihypertensive drugs, is less obvious at lower blood pressures. In most patients with hypertension and heart failure due to systolic and/or diastolic dysfunction, the use of diuretics, ACEIs or ARBs, and beta blockers is recommended to improve survival. Independent of blood pressure, in both hypertensive and normotensive individuals, ACEIs attenuate the development of left ventricular hypertrophy, improve symptomatology and risk of death from CHF, and reduce morbidity and mortality rates in post-myocardial infarction patients. Similar benefits in cardiovascular morbidity and mortality rates in patients with CHF have been observed with the use of ARBs. ACEIs provide better coronary protection than do calcium channel blockers, whereas calcium channel blockers provide more stroke protection than do either ACEIs or beta blockers. Results of a large, double-blind, prospective clinical trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension [ACCOMPLISH Trial]) indicated that combination treatment with an ACEI (benazepril) plus a calcium antagonist (amlodipine) was superior to treatment with the ACEI plus a diuretic (hydrochlorothiazide) in reducing the risk of cardiovascular events and death among high-risk patients with hypertension. However, the combination of an ACEI and a diuretic has recently been shown to produce major reductions in morbidity and mortality in the very elderly.

After a stroke, combination therapy with an ACEI and a diuretic, but not with an ARB, has been reported to reduce the rate of recurrent stroke. Some of these apparent differences may reflect differences in trial design and/or patient groups.

There has been a recent resurgence of interest in two nonpharmacologic, antihypertensive therapies that interrupt sympathetic outflow: (1) device-based carotid baroreflex activation by electrical stimulation of the carotid sinus; and (2) endovascular radiofrequency ablation of the renal sympathetic nerves. Both have been suggested as potential options for resistant hypertension. Whereas renal denervation is a minimally invasive procedure, carotid baroreceptor stimulation is a surgical procedure, usually performed under general anesthesia that currently involves implanting electrodes on both the right and left carotid arteries. Both interventions inhibit sympathetic drive and decrease blood pressure by increasing the capacity of the kidney to excrete sodium and by decreasing renin release. Sustained activation of the baroreflex most likely lowers blood pressure by other mechanisms as well; however, clinical experience with this intervention is limited. Enthusiasm for renal denervation has been questioned by the results of Simplicity 3, a randomized, prospective clinical trial, comparing bilateral renal denervation with a sham procedure in 535 patients with resistant hypertension. At the end of six months there was no benefit of renal artery denervation on both office and ambulatory systolic blood pressures, the trial's primary endpoints. It remains to be seen whether these interventions will be adopted into clinical practice.

BLOOD PRESSURE GOALS OF ANTIHYPERTENSIVE THERAPY

Based on clinical trial data, the maximum protection against combined cardiovascular endpoints is achieved with pressures <135–140 mmHg for systolic blood pressure and <80–85 mmHg for diastolic blood pressure; however, treatment has not reduced cardiovascular disease risk to the level in non-hypertensive individuals. According to a recent meta-analysis, the magnitude of the proportional reduction of cardiovascular events is broadly consistent regardless of baseline co-morbidity, although the absolute benefit of blood pressure reduction is greater among individuals with the highest risk for cardiovascular events.

The degree of benefit derived from antihypertensive agents is related to the magnitude of the blood pressure reduction. Guidelines establishing blood pressure targets for hypertension control continue to evolve. An intensive blood pressure lowering strategy is superior to a less intensive strategy for prevention of stroke and myocardial infarction. For example, the SPRINT trial studied 9361 subjects aged >50 years at increased risk for cardiovascular evens. Intensive blood pressure control (systolic blood pressure <120 mmHg) reduced the risk of cardiovascular events and mortality by 25% compared with less intensive control (systolic blood pressure 135–139 mmHg). More intense control may also be associated with a higher incidence of adverse events (e.g., syncope, electrolyte abnormalities, deterioration of renal function), and recent studies suggest that the benefits of intensive blood-pressure lowering outweigh the risks. Nevertheless, the absolute impact of more intensive control is relatively small. In the final analysis, patients need to be carefully monitored, and clinical decision making should be individualized.

In diabetic patients, effective blood pressure control reduces the risk of cardiovascular events and death as well as the risk for microvascular disease (nephropathy, retinopathy). Various guidelines have been recommended for hypertension control in patients with type 2 diabetes (<140/90, <140/85, <130/80). One widely cited Action to Control Cardiovascular Risk in Diabetes clinical trial (ACCORD) failed to find superiority of intensive blood pressure lowering (<120 mmHg) over standard blood pressure control (<140 mmHg) in reducing the risk of the study's primary outcome (a composite endpoint of myocardial infarction, stroke, and cardiovascular death) in diabetic patients. However, that trial did demonstrate a significant reduction of stroke and left ventricular hypertrophy with more intensive therapy.

In patients with chronic renal insufficiency, a small, non-progressive increase in the serum creatinine concentration may occur with intensive blood pressure lowering. This generally reflects a hemodynamic response, not structural renal injury, indicating that intraglomerular pressure has been reduced. Blood pressure control should not be allowed to deteriorate in order to prevent the modest creatinine rise. Among older patients with isolated systolic hypertension, further lowering of diastolic blood pressure does not result in harm. However, relatively little information is available concerning the risk-versus-benefit ratio of intensive antihypertensive therapy in individuals >80 years of age, and in this population, gradual blood pressure reduction to a less aggressive target level of control may be appropriate (e.g., 130–150 mmHg).

To achieve recommended blood pressure goals, the majority of individuals with hypertension will require treatment with more than one drug. Three or more drugs frequently are needed in patients with diabetes and renal insufficiency. For most agents,

reduction of blood pressure at half-standard doses is only ~20% less than at standard doses. Appropriate combinations of agents at these lower doses may have additive or almost additive effects on blood pressure with a lower incidence of side effects.

The term *resistant hypertension* refers to patients with blood pressures persistently >140/90 mmHg despite taking three or more antihypertensive agents, including a diuretic. Resistant or difficult-to-control hypertension is more common in patients aged >60 years than in younger patients. Resistant hypertension may be related to "pseudoresistance" (high office blood pressures and lower home blood pressures), nonadherence to therapy, identifiable causes of hypertension (including obesity and excessive alcohol intake), and the use of any of a number of nonprescription and prescription drugs (Table 271-3). Rarely, in older patients, pseudohypertension may be related to the inability to measure blood pressure accurately in severely sclerotic arteries. This condition is suggested if the radial pulse remains palpable despite occlusion of the brachial artery by the cuff (Osler maneuver). The actual blood pressure can be determined by direct intra-arterial measurement. Evaluation of patients with resistant hypertension might include home blood pressure monitoring to determine if office blood pressures are representative of the usual blood pressure. A more extensive evaluation for a secondary form of hypertension should be undertaken if no other explanation for hypertension resistance becomes apparent.

HYPERTENSIVE EMERGENCIES

Probably due to the widespread availability of antihypertensive therapy, in the United States there has been a decline in the numbers of patients presenting with "crisis levels" of blood pressure. Most patients who present with severe hypertension are chronically hypertensive, and in the absence of acute end organ damage, precipitous lowering of blood pressure may result in significant morbidity and should be avoided. The key to successful management of severe hypertension is to differentiate hypertensive crises from hypertensive urgencies. The degree of target organ damage, rather than the level of blood pressure alone, determines the rapidity with which blood pressure should be lowered. **Tables 271-9 and 271-10** list a number of hypertension-related emergencies and recommended therapies.

Malignant hypertension is a syndrome associated with an abrupt increase of blood pressure in a patient with underlying hypertension or related to the sudden onset of hypertension in a previously normotensive individual. The absolute level of blood pressure is not as important as its rate of rise. Pathologically, the syndrome is associated with diffuse necrotizing vasculitis, arteriolar thrombi, and fibrin deposition in arteriolar walls. Fibrinoid necrosis has been observed in arterioles of kidney, brain, retina, and other organs. Clinically, the syndrome is recognized by progressive retinopathy (arteriolar spasm, hemorrhages, exudates, and papilledema), deteriorating renal function with proteinuria, microangiopathic hemolytic anemia, and encephalopathy. Historic inquiry should include questions about the use of monoamine oxidase inhibitors and recreational drugs (e.g., cocaine, amphetamines).

TABLE 271-9 Preferred Parenteral Drugs for Selected Hypertensive Emergencies

Hypertensive encephalopathy	Nitroprusside, nicardipine, labetalol
Malignant hypertension (when IV therapy is indicated)	Labetalol, nicardipine, nitroprusside, enalaprilat
Stroke	Nicardipine, labetalol, nitroprusside
Myocardial infarction/unstable angina	Nitroglycerin, nicardipine, labetalol, esmolol
Acute left ventricular failure	Nitroglycerin, enalaprilat, loop diuretics
Aortic dissection	Nitroprusside, esmolol, labetalol
Adrenergic crisis	Phentolamine, nitroprusside
Postoperative hypertension	Nitroglycerin, nitroprusside, labetalol, nicardipine
Preeclampsia/eclampsia of pregnancy	Hydralazine, labetalol, nicardipine

Source: Adapted from DG Vidt, in S Oparil, MA Weber (eds): *Hypertension*, 2nd ed. Philadelphia, Elsevier Saunders, 2005.

TABLE 271-10 Usual Intravenous Doses of Antihypertensive Agents Used in Hypertensive Emergencies[a]

ANTIHYPERTENSIVE AGENT	INTRAVENOUS DOSE
Nitroprusside	Initial 0.3 (μg/kg)/min; usual 2–4 (μg/kg)/min; maximum 10 (μg/kg)/min for 10 min
Nicardipine	Initial 5 mg/h; titrate by 2.5 mg/h at 5–15 min intervals; max 15 mg/h
Labetalol	2 mg/min up to 300 mg *or* 20 mg over 2 min, then 40–80 mg at 10-min intervals up to 300 mg total
Enalaprilat	Usual 0.625–1.25 mg over 5 min every 6–8 h; maximum 5 mg/dose
Esmolol	Initial 80–500 μg/kg over 1 min, then 50–300 (μg/kg)/min
Phentolamine	5–15 mg bolus
Nitroglycerin	Initial 5 μg/min, then titrate by 5 μg/min at 3–5-min intervals; if no response is seen at 20 μg/min, incremental increases of 10–20 μg/min may be used
Hydralazine	10–50 mg at 30-min intervals

[a]Constant blood pressure monitoring is required. Start with the lowest dose. Subsequent doses and intervals of administration should be adjusted according to the blood pressure response and duration of action of the specific agent.

Although blood pressure should be lowered rapidly in patients with hypertensive encephalopathy, there are inherent risks of overly aggressive therapy. In hypertensive individuals, the upper and lower limits of autoregulation of cerebral blood flow are shifted to higher levels of arterial pressure, and rapid lowering of blood pressure to below the lower limit of autoregulation may precipitate cerebral ischemia or infarction as a consequence of decreased cerebral blood flow. Renal and coronary blood flows also may decrease with overly aggressive acute therapy. The initial goal of therapy is to reduce mean arterial blood pressure by no more than 25% within minutes to 2 h or to a blood pressure in the range of 160/100–110 mmHg. This may be accomplished with IV nitroprusside, a short-acting vasodilator with a rapid onset of action that allows for minute-to-minute control of blood pressure. Parenteral labetalol and nicardipine are also effective agents for the treatment of hypertensive encephalopathy.

In patients with malignant hypertension without encephalopathy or another catastrophic event, it is preferable to reduce blood pressure over hours or longer rather than minutes. This goal may effectively be achieved initially with frequent dosing of short-acting oral agents such as captopril, clonidine, and labetalol.

Acute, transient blood pressure elevations that last days to weeks frequently occur after thrombotic and hemorrhagic strokes. Autoregulation of cerebral blood flow is impaired in ischemic cerebral tissue, and higher arterial pressures may be required to maintain cerebral blood flow. Although specific blood pressure targets have not been defined for patients with acute cerebrovascular events, aggressive reductions of blood pressure are to be avoided. With the increasing availability of improved methods for measuring cerebral blood flow (using CT technology), studies are in progress to evaluate the effects of different classes of antihypertensive agents on both blood pressure and cerebral blood flow after an acute stroke. Currently, in the absence of other indications for acute therapy, for patients with cerebral infarction who are not candidates for thrombolytic therapy, one recommended guideline is to institute antihypertensive therapy only for patients with a systolic blood pressure >220 mmHg or a diastolic blood pressure >130 mmHg. If thrombolytic therapy is to be used, the recommended goal blood pressure is <185 mmHg systolic pressure and <110 mmHg diastolic pressure. In patients with hemorrhagic stroke, there is no consistent evidence that acute reductions of systolic blood pressure to a more aggressive target than 140–179 mmHg improves functional outcome. The management of hypertension after subarachnoid hemorrhage is controversial.

Cautious reduction of blood pressure is indicated if mean arterial pressure is >130 mmHg.

In addition to pheochromocytoma, an adrenergic crisis due to catecholamine excess may be related to cocaine or amphetamine overdose, clonidine withdrawal, acute spinal cord injuries, and an interaction of tyramine-containing compounds with monoamine oxidase inhibitors. These patients may be treated with phentolamine or nitroprusside.

Treatment of hypertension in patients with acute aortic dissection is discussed in Chap. 274, and treatment of hypertension in pregnancy is discussed in Chap. 466.

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272 Renovascular Disease

Stephen C. Textor

The renal vasculature is unusually complex with rich arteriolar flow to the cortex in excess of metabolic requirements, consistent with its primary function as a filtering organ. After delivering blood to cortical glomeruli, the postglomerular circulation supplies deeper medullary segments that support energy-dependent solute transport at multiple levels of the renal tubule. These postglomerular vessels carry less blood, and high oxygen consumption leaves the deeper medullary regions at the margin of hypoxemia. Vascular disorders that commonly threaten the blood supply of the kidney include large-vessel atherosclerosis, fibromuscular diseases, and embolic disorders. **Microvascular injury, including inflammatory and primary hematologic disorders, is described in Chap. 311.**

The glomerular capillary endothelium shares susceptibility to oxidative stress, pressure injury, and inflammation with other vascular territories. Rates of urinary albumin excretion (UAE) are predictive of systemic atherosclerotic disease events. Increased UAE may develop years before cardiovascular events. UAE and the risk of cardiovascular events are both reduced with pharmacologic therapy such as statins. Experimental studies demonstrate functional changes and rarefaction of renal microvessels under conditions of accelerated atherosclerosis and/or compromise of proximal perfusion pressures with large-vessel disease **(Fig. 272-1)**.

MACROVASCULAR DISEASE

Large-vessel renal artery occlusive disease can result from extrinsic compression of the vessel, intimal dissection, fibromuscular dysplasia (FMD), or, most commonly, atherosclerotic disease. Any disorder that reduces perfusion pressure to the kidney can activate mechanisms that tend to restore renal pressures at the expense of developing systemic hypertension. Because restoration of perfusion pressures can reverse these pathways, renal artery stenosis is considered a specifically treatable "secondary" cause of hypertension.

Renal artery stenosis is common and often has only minor hemodynamic effects. FMD is reported in 3–5% of normal subjects presenting as potential kidney donors without hypertension. It may present clinically with hypertension in younger individuals (between age 15 and 50), most often women. FMD does not often threaten kidney function, but sometimes produces total occlusion and can be associated with renal artery aneurysms. Atherosclerotic renal artery stenosis (ARAS) is common in the general population (6.8% of a community-based sample above age 65). The prevalence increases with age and for patients with other vascular conditions such as coronary artery disease (18–23%) and/or peripheral aortic or lower extremity disease (>30%). If untreated, ARAS progresses in nearly 50% of cases over a 5-year period, sometimes to total occlusion. Intensive treatment of arterial blood pressure and statin therapy appear to slow these rates and improve clinical outcomes.

Critical levels of stenosis lead to a reduction in perfusion pressure that activates the renin-angiotensin system, reduces sodium excretion, and activates sympathetic adrenergic pathways. These events lead to systemic hypertension characterized by angiotensin dependence in the early stages, widely varying pressures, loss of circadian blood pressure (BP) rhythms, and accelerated target organ injury, including left ventricular hypertrophy and renal fibrosis. Renovascular hypertension can be treated with agents that block the renin-angiotensin system and other drugs that modify these pressor pathways. It can also be treated with restoration of renal blood flow by either endovascular or surgical revascularization. Most patients require continued antihypertensive drug therapy because revascularization alone rarely lowers BP to normal.

ARAS and systemic hypertension tend to affect both the post-stenotic and contralateral kidneys, reducing overall glomerular filtration rate (GFR) in ARAS. When kidney function is threatened by large-vessel disease primarily, it has been labeled ischemic nephropathy. Moderately reduced blood flow that develops gradually is associated with reduced GFR and limited oxygen consumption with preserved tissue oxygenation. Hence, kidney function often remains stable during medical therapy, sometimes for years. With more advanced disease, reductions in cortical perfusion and frank tissue hypoxia develop. Unlike FMD, ARAS develops in patients with other risk factors for atherosclerosis and is commonly superimposed upon preexisting small-vessel disease in the kidney resulting from hypertension, aging, and diabetes. Nearly 85% of patients considered for renal revascularization have stage 3–5 chronic kidney disease (CKD) with GFR <60 mL/min per 1.73 m^2. The presence of ARAS is a strong predictor of morbidity- and mortality-related cardiovascular events, independent of whether renal revascularization is undertaken.

Diagnostic approaches to renal artery stenosis depend partly on the specific clinical questions to be addressed. Noninvasive characterization of the renal vasculature may be achieved by several techniques, summarized in **Table 272-1**. Although activation of the renin-angiotensin system is a key step in developing renovascular hypertension, it is transient. Levels of renin activity are therefore subject to timing, the effects of drugs, and sodium intake, and do not reliably predict the response to vascular therapy. Renal artery velocities by Doppler ultrasound >200 cm/s generally predict hemodynamically important lesions (>60% vessel lumen occlusion), although some treatment trials require velocity >300 cm/s to avoid false positives. The renal resistive index has predictive value regarding the viability of the kidney.

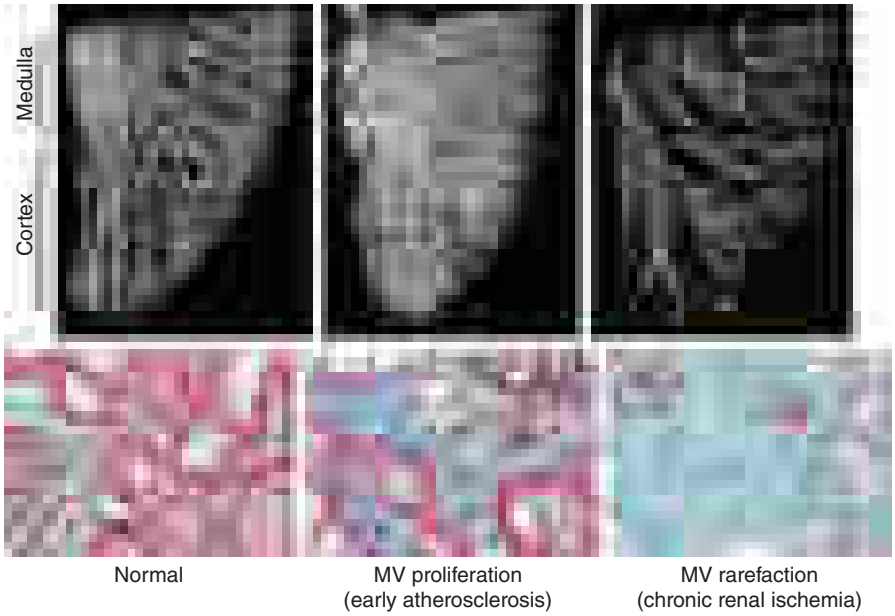

FIGURE 272-1 Examples of micro-CT images from vessels defined by radiopaque casts injected into the renal vasculature. These illustrate the complex, dense cortical capillary network supplying the kidney cortex that can either proliferate or succumb to rarefaction under the influence of atherosclerosis and/or occlusive disease. Changes in blood supply are followed by tubulointerstitial fibrosis and loss of kidney function. MV, microvascular. *(From LO Lerman, AR Chade: Curr Opin Nephrol Hyper 18:160, 2009, with permission.)*

It remains operator- and institution-dependent, however. Captopril-enhanced renography has a strong negative predictive value when entirely normal. Magnetic resonance angiography (MRA) is now less often used, as gadolinium contrast has been associated with nephrogenic systemic fibrosis. Contrast-enhanced computed tomography (CT) with vascular reconstruction provides excellent vascular images and functional assessment, but carries a small risk of contrast toxicity.

TREATMENT

Renal Artery Stenosis

While restoring renal blood flow and perfusion seems intuitively beneficial for high-grade occlusive lesions, revascularization procedures also pose hazards and expense. Patients with FMD are commonly younger females with otherwise normal vessels and a long life expectancy. These patients often respond well to percutaneous renal artery angioplasty. If BP can be controlled to goal levels and kidney function remains stable in patients with ARAS, it may be argued that medical therapy with follow-up for disease progression is equally effective. Multiple prospective randomized controlled trials have failed to identify compelling benefits for interventional procedures regarding short-term results of BP and renal function. Studies of cardiovascular outcomes including stroke, congestive heart failure, myocardial infarction, and end-stage renal failure, suggest a small mortality benefit for revascularized subjects without proteinuria. Medical therapy should include blockade of the renin-angiotensin system, attainment of goal BPs, cessation of tobacco, statins, and aspirin. Follow-up requires surveillance for progressive occlusion manifest by worsening renal function and/or loss of BP control. Renal revascularization is now often reserved for patients failing medical therapy or developing additional complications.

Techniques of renal revascularization are improving. With experienced operators, major complications occur in 5–9% of cases, including renal artery dissection, capsular perforation, hemorrhage, and occasional atheroembolic disease. Although not common, atheroembolic disease can be catastrophic and accelerate both hypertension and kidney failure, precisely the events that revascularization

TABLE 272-1 Summary of Imaging Modalities for Evaluating the Kidney Vasculature

Perfusion Studies to Assess Differential Renal Blood Flow			
Captopril renography with technetium ^{99m}Tc mertiatide (^{99m}Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dL (177 μmol/L)
Vascular Studies to Evaluate the Renal Arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available, suitable for follow-up studies	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Expensive, moderate volume of contrast required
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic, but concerns for gadolinium toxicity exclude use in GFR <30 mL/min/1.73 m^2; provides excellent images	Expensive; gadolinium excluded in renal failure, unable to visualize stented vessels
Intraarterial angiography	Shows location and severity of vascular lesion	Considered "gold standard" for diagnosis of large-vessel disease, usually performed simultaneous with planned intervention	Expensive, associated hazard of atheroemboli, contrast toxicity, procedure-related complications, e.g., dissection

Abbreviation: GFR, glomerular filtration rate.

TABLE 272-2 Clinical Factors That Determine the Role of Revascularization in Addition to Medical Therapy for Renal Artery Stenosis

Factors Favoring Medical Therapy and Revascularization for Renal Artery Stenosis
• Progressive decline in GFR during treatment of systemic hypertension
• Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
• Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
• Decline in the GFR during therapy with ACE inhibitors or ARBs
• Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain a cause
Factors Favoring Medical Therapy and Surveillance of Renal Artery Disease
• Controlled blood pressure with stable renal function (e.g., stable renal insufficiency)
• Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
• Very advanced age and/or limited life expectancy
• Extensive comorbidity that make revascularization too risky
• High risk for or previous experience with atheroembolic disease
• Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., interstitial nephritis, diabetic nephropathy)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate.

is intended to prevent. Although renal blood flow usually can be restored by endovascular stenting, recovery of renal function is limited to about 25% of cases, with no change in 50% and some deterioration evident in others. Patients with rapid loss of kidney function, sometimes associated with antihypertensive drug therapy, or with vascular disease affecting the entire functioning kidney mass are more likely to recover function after restoring blood flow. When hypertension is refractory to effective therapy, revascularization offers real benefits. Table 272-2 summarizes currently accepted guidelines for considering renal revascularization.

ATHEROEMBOLIC RENAL DISEASE

Emboli to the kidneys arise most frequently as a result of cholesterol crystals breaking free of atherosclerotic vascular plaque and lodging in downstream microvessels. Most clinical atheroembolic events follow angiographic procedures, often of the coronary vessels. It has been argued that nearly all vascular interventional procedures lead to plaque fracture and release of microemboli, but clinical manifestations develop only in a fraction of these. The incidence of clinical atheroemboli has been increasing with more vascular procedures and longer life spans. Atheroembolic renal disease is suspected in >3% of elderly subjects with end-stage renal disease (ESRD) and is likely underdiagnosed. It is more frequent in males with a history of diabetes, hypertension, and ischemic cardiac disease. Atheroemboli in the kidney are strongly associated with aortic aneurysmal disease and renal artery stenosis. Most clinical cases can be linked to precipitating events, such as angiography, vascular surgery, anticoagulation with heparin, thrombolytic therapy, or trauma. Clinical manifestations of this syndrome commonly develop between 1 and 14 days after an inciting event and may continue to develop for weeks thereafter. Systemic embolic disease manifestations, such as fever, abdominal pain, and weight loss, are present in less than half of patients, although cutaneous manifestations including livedo reticularis and localized toe gangrene may be more common. Worsening hypertension and deteriorating kidney function are common, sometimes reaching a malignant phase. Progressive renal failure can occur and require dialytic support. These cases often develop after a stuttering onset over many weeks and have an ominous prognosis. Mortality rate after 1 year reaches 38%, and although some may eventually recover sufficiently to no longer require dialysis, many do not.

Beyond the clinical manifestations above, laboratory findings include rising creatinine, transient eosinophilia (60–80%), elevated sedimentation rate, and hypocomplementemia (15%). Establishing this diagnosis can be difficult and is often by exclusion. Definitive diagnosis depends on kidney biopsy demonstrating microvessel occlusion with cholesterol crystals that leave a "cleft" in the vessel. Biopsies obtained from patients undergoing surgical revascularization of the kidney indicate that silent cholesterol emboli are frequently present before any further manipulation is performed.

No effective therapy is available for atheroembolic disease once it has developed. Withdrawal of anticoagulation is recommended. Late recovery of kidney function after supportive measures sometimes occurs, and statin therapy may improve outcome. The role of embolic protection devices in the renal circulation is unclear, but a few prospective trials have failed to demonstrate major benefits. These devices are limited to distal protection during the endovascular procedure and offer no protection from embolic debris developing after removal.

THROMBOEMBOLIC RENAL DISEASE

Thrombotic occlusion of renal vessels or branch arteries can lead to declining renal function and hypertension. It is difficult to diagnose and is often overlooked, especially in elderly patients. Thrombosis can develop as a result of local vessel abnormalities, such as local dissection, trauma, or inflammatory vasculitis. Local microdissections sometimes lead to patchy, transient areas of infarctions labeled "segmental arteriolar mediolysis." Although hypercoagulability conditions sometimes present as renal artery thrombosis, this is rare. It can also derive from distant embolic events, e.g., the left atrium in patients with atrial fibrillation or from fat emboli originating from traumatized tissue, most commonly large bone fractures. Cardiac sources include vegetations from subacute bacterial endocarditis. Systemic emboli to the kidneys may also arise from the venous circulation if right-to-left shunting occurs, e.g., through a patent foramen ovale.

Clinical manifestations vary depending on the rapidity of onset and extent of occlusion. Acute arterial thrombosis may produce flank pain, fever, leukocytosis, nausea, and vomiting. If kidney infarction results, enzymes such as lactate dehydrogenase (LDH) rise to extreme levels. If both kidneys are affected, renal function will decline precipitously with a drop in urine output. If a single kidney is involved, renal functional changes may be minor. Hypertension related to sudden release of renin from ischemic tissue can develop rapidly, as long as some viable tissue in the "peri-infarct" border zone remains. If the infarct zone demarcates precisely, the rise in BP and renin activity may resolve. Diagnosis of renal infarction may be established by vascular imaging with MRI, CT angiography, or arteriography (Fig. 272-2).

MANAGEMENT OF ARTERIAL THROMBOSIS OF THE KIDNEY

Options for interventions of newly detected arterial occlusion include surgical reconstruction, anticoagulation, thrombolytic therapy, endovascular procedures, and supportive care, particularly antihypertensive drug therapy. Application of these methods depends on the patient's overall condition, the precipitating factors (e.g., local trauma or systemic illness), the magnitude of renal tissue and function at risk, and the likelihood of recurrent events in the future. For unilateral disease, for example, arterial dissection with thrombosis, supportive care with anticoagulation may suffice. Acute, bilateral occlusion is potentially catastrophic, producing anuric renal failure. Depending on the precipitating event, surgical or thrombolytic therapies can sometimes restore kidney viability.

MICROVASCULAR INJURY ASSOCIATED WITH HYPERTENSION

ARTERIOLONEPHROSCLEROSIS

"Malignant" Hypertension Although BP rises with age, it has long been recognized that some individuals develop rapidly progressive BP elevations with target organ injury including retinal hemorrhages, encephalopathy, and declining kidney function. Placebo arms during the controlled trials of hypertension therapy identified progression to severe levels in 20% of subjects over 5 years. If untreated, patients

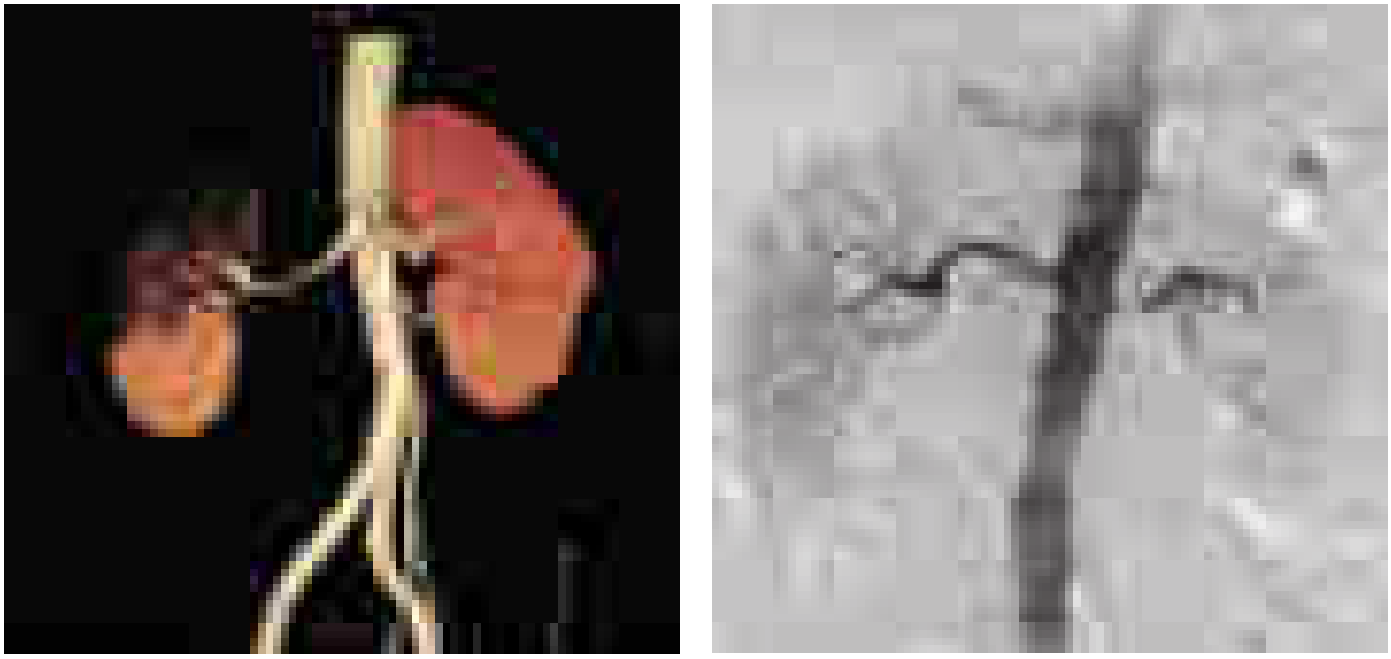

FIGURE 272-2 ***A.*** CT angiogram illustrating loss of circulation to the upper pole of the right kidney in a patient with fibromuscular disease and a renal artery aneurysm. Activation of the renin-angiotensin system produced rapidly developing hypertension. ***B.*** Angiogram illustrating high-grade renal artery stenosis affecting the left kidney. This lesion is often part of widespread atherosclerosis and sometimes is an extension of aortic plaque. This lesion develops in older individuals with preexisting atherosclerotic risk factors.

with target organ injury including papilledema and declining kidney function suffered mortality rates in excess of 50% over 6–12 months, hence the designation "malignant." Postmortem studies of such patients identified vascular lesions, designated "fibrinoid necrosis," with breakdown of the vessel wall, deposition of eosinophilic material including fibrin, and a perivascular cellular infiltrate. A separate lesion was identified in the larger interlobular arteries in many patients with hyperplastic proliferation of the vascular wall cellular elements, deposition of collagen, and separation of layers, designated the "onionskin" lesion. For many of these patients, fibrinoid necrosis led to obliteration of glomeruli and loss of tubular structures. Progressive kidney failure ensued and, without dialysis support, led to early mortality in untreated malignant-phase hypertension. These vascular changes could develop with pressure-related injury from a variety of hypertensive pathways, including but not limited to activation of the renin-angiotensin system and severe vasospasm associated with catecholamine release. Occasionally, endothelial injury is sufficient to induce microangiopathic hemolysis, as discussed below.

Antihypertensive therapy is the mainstay of therapy for malignant hypertension. With effective BP reduction, manifestations of vascular injury, including microangiopathic hemolysis and renal dysfunction, can improve over time. Whereas prior reports before the era of drug therapy suggested that 1-year mortality rates exceeded 90%, current survival over 5 years exceeds 50%.

Malignant hypertension is less common in Western countries, although it persists in parts of the world where medical care and antihypertensive drug therapy are less available. It most commonly develops in patients with treated hypertension who neglect to take medications or who may use vasospastic drugs, such as cocaine. Renal abnormalities typically include rising serum creatinine and occasionally hematuria and proteinuria. Biochemical findings may include evidence of hemolysis (anemia, schistocytes, and reticulocytosis) and changes associated with kidney failure. African-American males are more likely to develop rapidly progressive hypertension and kidney failure than are whites in the United States. Genetic polymorphisms for *APOL1* that are common in the African-American population predispose to subtle focal sclerosing glomerular disease, with severe hypertension developing at younger ages secondary to renal disease in this instance.

"Hypertensive Nephrosclerosis" Based on experience with malignant hypertension and epidemiologic evidence linking BP with long-term risks of kidney failure, it has long been assumed that lesser degrees of hypertension induce less severe, but prevalent, changes in kidney vessels and loss of kidney function. As a result, a large portion of patients reaching ESRD without a specific etiologic diagnosis are assigned the designation "hypertensive nephrosclerosis." Pathologic examination commonly identifies afferent arteriolar thickening with deposition of homogeneous eosinophilic material (hyaline arteriolosclerosis) associated with narrowing of vascular lumina. Clinical manifestations include retinal vessel changes associated with hypertension (arteriolar narrowing, arteriovenous crossing changes), left ventricular hypertrophy, and elevated BP. The role of these vascular changes in kidney function is unclear. Postmortem and biopsy samples from normotensive kidney donors demonstrate similar vessel changes associated with aging, dyslipidemia, and glucose intolerance. Although BP reduction does slow progression of proteinuric kidney diseases and is warranted to reduce the excessive cardiovascular risks associated with CKD, antihypertensive therapy does not alter the course of kidney dysfunction identified specifically as hypertensive nephrosclerosis.

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273 Deep Venous Thrombosis and Pulmonary Thromboembolism

Samuel Z. Goldhaber

EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death and disability as well as psychological illness and emotional distress. In the United States, the Surgeon General estimates that there are 100,000 to 180,000 deaths annually from PE and has declared that PE is the most common preventable cause of death among hospitalized patients. In a Canadian study, almost half of PE patients at 1 year had exercise limitation, decreased walking distance, or dyspnea, which lowered their quality of life. Survivors may suffer the complications of chronic thromboembolic pulmonary hypertension or postthrombotic syndrome. Chronic thromboembolic pulmonary hypertension causes breathlessness, especially with exertion. Postthrombotic syndrome (also known as *chronic venous insufficiency*) damages the venous valves of the leg and worsens the quality of life by causing ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes skin ulceration **(Fig. 273-1)**.

PATHOPHYSIOLOGY

Inflammation and Platelet Activation Virchow's triad of venous stasis, hypercoagulability, and endothelial injury leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called neutrophil extracellular traps. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in an environment of stasis, low oxygen tension, and upregulation of proinflammatory genes.

Prothrombotic States The two most common autosomal dominant genetic mutations are factor V Leiden, which causes resistance to the endogenous anticoagulant, activated protein C (which inactivates clotting factors V and VIII), and the prothrombin gene mutation, which increases the plasma prothrombin concentration **(Chaps. 61 and 113)**. Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors. Deficiencies of these inhibitors are associated with VTE but are rare. Antiphospholipid antibody syndrome is the most common acquired cause of thrombophilia and is associated with venous or arterial thrombosis. Other common predisposing factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, blood transfusion, long-haul air travel, air pollution, estrogen-containing contraceptives, pregnancy, postmenopausal hormone replacement, surgery, and trauma. Inflammation predisposes to thrombosis, and conditions such as psoriasis and inflammatory bowel disease have become recognized risk factors of VTE. Sedentary lifestyle is an increasingly prevalent etiology of fatal PE. A Japanese study found that each 2 h per day increment of television watching is associated with a 40% increased likelihood of fatal PE.

Embolization When deep venous thrombi **(Fig. 273-2)** detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle, and lodge in the pulmonary arterial circulation, thereby causing acute PE. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect. Many patients with PE have no evidence of DVT because the clot has already embolized to the lungs.

Physiology The most common gas exchange abnormalities are arterial hypoxemia and an increased alveolar-arterial O_2 tension gradient, which represents the inefficiency of O_2 transfer across the lungs. Anatomic dead space increases because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries.

Other pathophysiologic abnormalities include:

1. *Increased pulmonary vascular resistance* due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin. Release of vasoactive mediators can produce ventilation-perfusion mismatching at sites remote from the embolus, thereby accounting for discordance between a small PE and a large alveolar-arterial O_2 gradient.

FIGURE 273-1 Skin ulceration in the lateral malleolus from postthrombotic syndrome of the leg.

FIGURE 273-2 Deep venous thrombosis at autopsy.

2. *Impaired gas exchange* due to increased alveolar dead space from vascular obstruction, hypoxemia from alveolar hypoventilation relative to perfusion in the nonobstructed lung, right-to-left shunting, or impaired carbon monoxide transfer due to loss of gas exchange surface.
3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors.
4. *Increased airway resistance* due to constriction of airways distal to the bronchi.
5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant.

Pulmonary Hypertension, Right Ventricular (RV) Dysfunction, and RV Microinfarction Pulmonary artery obstruction and neurohumoral mediators cause a rise in pulmonary artery pressure and in pulmonary vascular resistance. When RV wall tension rises, RV dilation and dysfunction ensue, with release of the cardiac biomarker, brain natriuretic peptide, due to abnormal RV stretch. The interventricular septum bulges into and compresses an intrinsically normal left ventricle (LV). Diastolic LV dysfunction reduces LV distensibility and impairs LV filling. Increased RV wall tension also compresses the right coronary artery, limits myocardial oxygen supply, and precipitates right coronary artery ischemia and RV microinfarction, with release of cardiac biomarkers such as troponin. Underfilling of the LV may lead to a fall in LV cardiac output and systemic arterial pressure, with consequent circulatory collapse and death.

CLASSIFICATION OF PULMONARY EMBOLISM AND DEEP VENOUS THROMBOSIS

Pulmonary Embolism **Massive PE** accounts for 5–10% of cases, and is characterized by extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure. **Submassive PE** accounts for 20–25% of patients, and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers indicates a high risk of clinical deterioration. **Low-risk PE** constitutes about 65–75% of cases. These patients have an excellent prognosis.

Deep Venous Thrombosis **Lower extremity DVT** usually begins in the calf and propagates proximally to the popliteal vein, femoral vein, and iliac veins. Leg DVT is about 10 times more common than **upper extremity DVT,** which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase. **Superficial venous thrombosis** usually presents with erythema, tenderness, and a "palpable cord." Patients are at risk for extension of the thrombosis to the deep-venous system.

DIAGNOSIS

Clinical Evaluation PE is known as "the Great Masquerader." Diagnosis is difficult because symptoms and signs are nonspecific. The most common symptom is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness. This scenario presents a clinical clue to the possible coexistence of PE.

Hospitalization for syncope was associated with a 17% rate of newly diagnosed PE in an Italian multicenter study of 560 patients. Among those patients who had no alternative explanation for syncope, 25% had PE. Even when there was an alternative explanation for syncope, 13% had PE. When clinical suspicion was high according to the Wells Score or when the plasma D-dimer level was elevated, 42% had PE. PE in these patients was anatomically extensive, and 42% had thrombus in the main pulmonary artery.

With DVT, the most common symptom is a cramp or "charley horse" in the lower calf that persists and intensifies over several days.

TABLE 273-1 Clinical Decision Rules

Low Clinical Likelihood of Deep Venous Thrombosis (DVT) If Point Score Is Zero or Less; Moderate Likelihood If Score Is 1 to 2; High Likelihood If Score Is 3 or Greater	
CLINICAL VARIABLE	**DVT SCORE**
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	–2
High Clinical Likelihood of Pulmonary Embolism (PE) if Point Score Exceeds 4	
CLINICAL VARIABLE	**PE SCORE**
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Wells Point Score criteria help estimate the clinical likelihood of DVT and PE (Table 273-1). Patients with a low-to-moderate likelihood of DVT or PE should undergo initial diagnostic evaluation with D-dimer testing alone (see "Blood Tests") without obligatory imaging tests (Fig. 273-3). However, patients with a high clinical likelihood of VTE should skip D-dimer testing and undergo imaging as the next step in the diagnostic algorithm.

Clinical Pearls Not all leg pain is due to DVT, and not all dyspnea is due to PE (Table 273-2). Sudden, severe calf discomfort suggests a ruptured Baker's cyst. Fever and chills usually herald cellulitis rather than DVT. Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. Recurrent left thigh edema especially in young women raises the possibility of May-Thurner Syndrome, with right proximal iliac artery compression

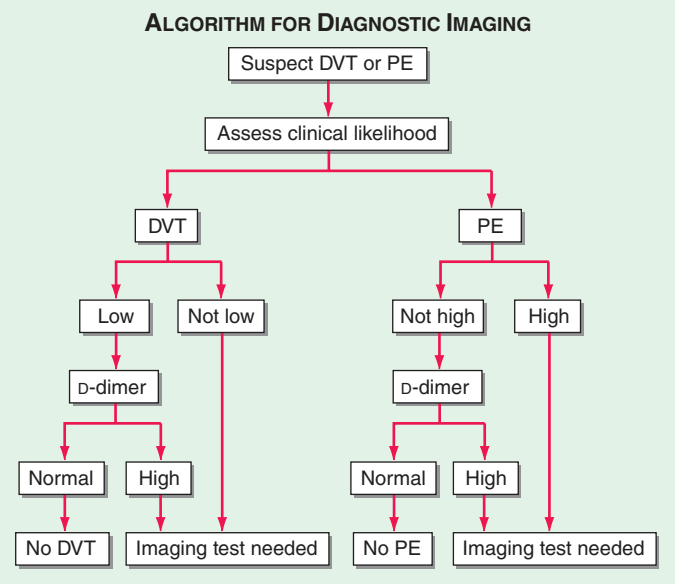

FIGURE 273-3 How to decide whether diagnostic imaging is needed. For assessment of clinical likelihood, see Table 273-1.

TABLE 273-2 Differential Diagnosis

Deep Venous Thrombosis (DVT)
Ruptured Baker's cyst
Muscle strain/injury
Cellulitis
Acute postthrombotic syndrome/venous insufficiency
Pulmonary Embolism (PE)
Pneumonia, asthma, chronic obstructive pulmonary disease
Congestive heart failure
Pericarditis
Pleurisy: "viral syndrome," costochondritis, musculoskeletal discomfort
Rib fracture, pneumothorax
Acute coronary syndrome
Anxiety

of the left proximal iliac vein. However, if a leg is diffusely edematous, DVT is unlikely. More probable is an acute exacerbation of venous insufficiency due to postthrombotic syndrome. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary infarction usually indicates a small PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves. *Nonthrombotic PE* etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize, such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

Nonimaging Diagnostic Modalities • **BLOOD TESTS** The quantitative *plasma D-dimer enzyme-linked immunosorbent assay (ELISA)* rises in the presence of DVT or PE because of the breakdown of fibrin by plasmin. Elevation of D-dimer indicates endogenous although often clinically ineffective thrombolysis. The sensitivity of the D-dimer is >80% for DVT (including isolated calf DVT) and >95% for PE. The D-dimer is less sensitive for DVT than for PE because the DVT thrombus size is smaller. A normal D-dimer is a useful "rule out" test. However, the D-dimer assay is not specific. Levels increase in patients with myocardial infarction, pneumonia, sepsis, cancer, and the postoperative state and those in the second or third trimester of pregnancy. Therefore, D-dimer rarely has a useful role among hospitalized patients, because levels are frequently elevated due to systemic illness.

ELEVATED CARDIAC BIOMARKERS Serum troponin and plasma heart-type fatty acid–binding protein levels increase because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

ELECTROCARDIOGRAM The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III (Chap. 235). This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V_1 to V_4.

Noninvasive Imaging Modalities • **VENOUS ULTRASONOGRAPHY** Ultrasonography of the deep-venous system relies on loss of vein compressibility as the primary diagnostic criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure on the ultrasound transducer. This creates the illusion of a "wink." With acute DVT, the vein loses its compressibility because of passive distention by acute thrombus. The diagnosis of acute DVT is even more secure when thrombus is directly visualized. It appears homogeneous and has low echogenicity (Fig. 273-4). The vein itself often appears mildly dilated, and collateral channels may be absent.

Venous flow dynamics can be examined with Doppler imaging. Normally, manual calf compression causes augmentation of the Doppler flow pattern. Loss of normal respiratory variation is caused by an obstructing DVT or by any obstructive process within the pelvis. For patients with a technically poor or nondiagnostic venous ultrasound, one should consider alternative imaging modalities for DVT, such as computed tomography (CT) and magnetic resonance imaging.

CHEST ROENTGENOGRAPHY A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include focal oligemia (Westermark's sign), a peripheral wedged-shaped density usually located at the pleural base (Hampton's hump), and an enlarged right descending pulmonary artery (Palla's sign).

CHEST CT CT of the chest with intravenous contrast is the principal imaging test for the diagnosis of PE (Fig. 273-5). "Thin-cut chest CT images" can provide exquisite detail, with ≤1 mm of resolution during a short breath hold. Sixth-order branches can be visualized with resolution superior to that of conventional invasive contrast pulmonary angiography. The CT scan also provides an excellent four-chamber view of the heart. RV enlargement on chest CT indicates an increased likelihood of death within the next 30 days compared with PE patients who have normal RV size. When imaging is extended distally below the chest to the knee, pelvic and proximal leg DVT also can be diagnosed by CT scanning. In patients without PE, the lung parenchymal images may establish alternative diagnoses not apparent on chest x-ray that explain the presenting symptoms and signs, such as pneumonia, emphysema, pulmonary fibrosis, pulmonary mass, and aortic pathology. Sometimes, asymptomatic early-stage lung cancer is diagnosed incidentally. Major efforts are underway to reduce radiation and contrast material requirements for chest CT. "Triple rule-out CT" utilizes ECG-synchronized acquisition, adjusts contrast material timing, and opacifies both the thoracic aorta and pulmonary artery circulation to exclude the three major causes of acute chest pain: PE, acute aortic syndrome, and acute coronary syndrome.

LUNG SCANNING Lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast. Small particulate aggregates of albumin labeled with a gamma-emitting radionuclide are injected intravenously and are trapped in the pulmonary capillary bed. The perfusion scan defect indicates absent or decreased blood flow, possibly due to PE. Ventilation scans, obtained with a radiolabeled inhaled gas such as xenon or krypton, improve the specificity of the perfusion scan. Abnormal ventilation scans indicate abnormal nonventilated lung, thereby providing possible explanations for perfusion defects other than acute PE, such as

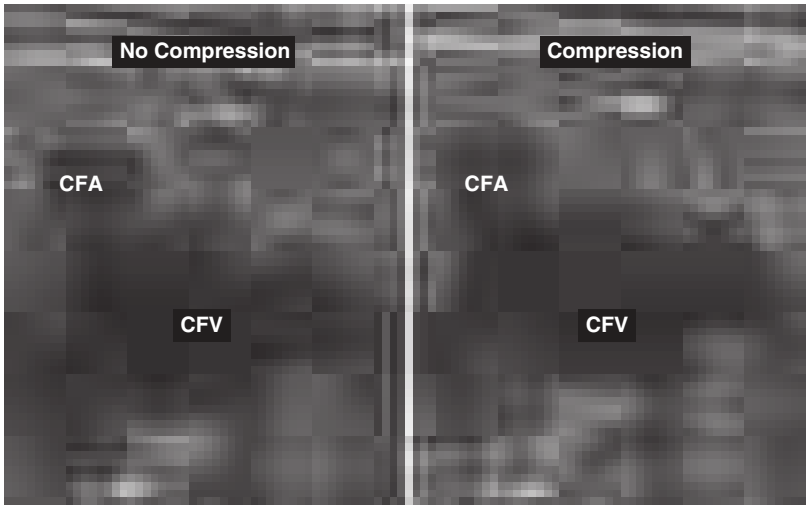

FIGURE 273-4 Venous ultrasound, with and without compression of the leg veins. CFA, common femoral artery; CFV, common femoral vein; GSV, great saphenous vein; LT, left.

FIGURE 273-5 Large bilateral proximal PE on a coronal chest CT image in a 54-year-old man with lung cancer and brain metastases. He had developed sudden onset of chest heaviness and shortness of breath while at home. There are filling defects in the main and segmental pulmonary arteries bilaterally (*white arrows*). Only the left upper lobe segmental artery is free of thrombus.

asthma and chronic obstructive pulmonary disease. A high-probability scan for PE is defined as two or more segmental perfusion defects in the presence of normal ventilation.

The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and, in contrast, is about 90% certain in patients with high-probability scans. Unfortunately, most patients have nondiagnostic scans, and fewer than one-half of patients with angiographically confirmed PE have a high probability scan. As many as 40% of patients with high clinical suspicion for PE but "low-probability" scans do, in fact, have PE at angiography.

MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING When ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE, but is not reliable for smaller segmental and subsegmental PE.

ECHOCARDIOGRAPHY Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is a very useful diagnostic tool for detecting conditions that may mimic PE, such as acute myocardial infarction, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion of the RV apex. One should consider transesophageal echocardiography when CT scanning facilities are not available or when a patient has renal failure or severe contrast allergy that precludes administration of contrast despite premedication with high-dose steroids. This imaging modality can identify saddle, right main, or left main PE.

Invasive Diagnostic Modalities • PULMONARY ANGIOGRAPHY

Chest CT with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis is planned. A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion ("cut-off") of vessels, segmental oligemia or avascularity, and a prolonged arterial phase with slow filling, and tortuous, tapering peripheral vessels.

CONTRAST PHLEBOGRAPHY Venous ultrasonography has virtually replaced contrast phlebography as the principal diagnostic test for suspected DVT.

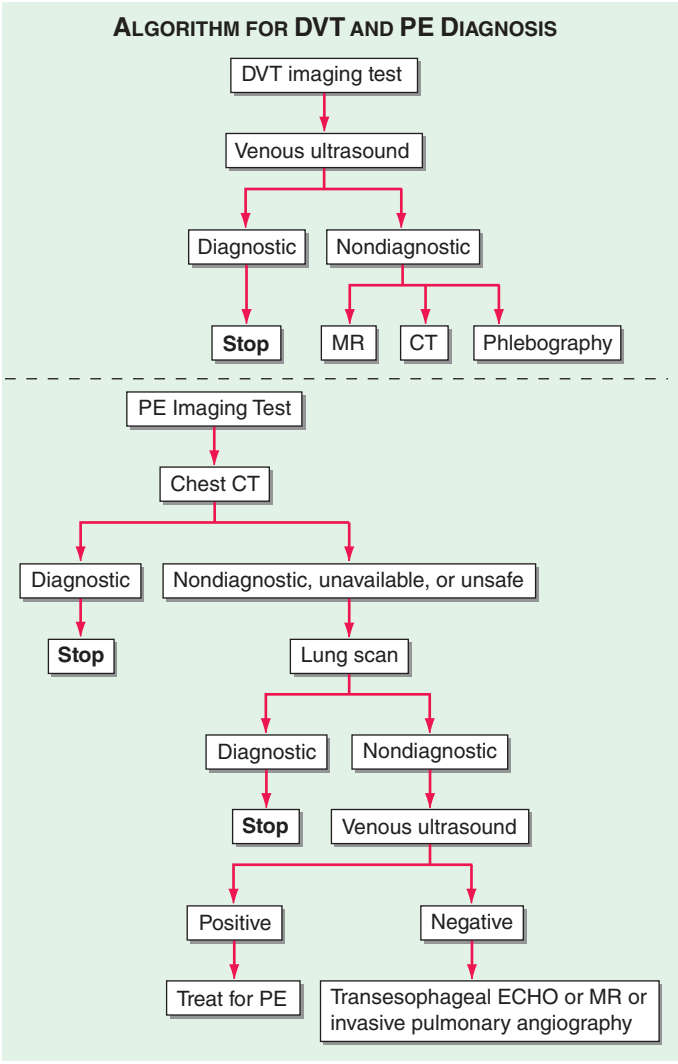

FIGURE 273-6 Imaging tests to diagnose DVT and PE. ECHO, echocardiography.

Integrated Diagnostic Approach An integrated diagnostic approach (Fig. 273-3) streamlines the workup of suspected DVT and PE **(Fig. 273-6)**.

TREATMENT

Deep Venous Thrombosis

PRIMARY THERAPY

Primary therapy consists of clot dissolution with pharmacomechanical therapy that usually includes low-dose catheter-directed thrombolysis. This approach is reserved for patients with extensive femoral, iliofemoral, or upper extremity DVT. The open vein hypothesis postulates that patients who receive primary therapy will sustain less long-term damage to venous valves, with consequent lower rates of postthrombotic syndrome. A National Heart, Lung, and Blood Institute–sponsored randomized controlled trial called ATTRACT (NCT00790335) is testing this hypothesis by randomizing femoral and iliofemoral DVT patients to conventional anticoagulation versus pharmacomechanical catheter-directed thrombolysis, and assessing the frequency of postthrombotic syndrome 2 years after randomization.

SECONDARY PREVENTION

Anticoagulation or placement of an inferior vena caval (IVC) filter constitutes *secondary prevention* of VTE. In 2016, the FDA approved a new retrievable IVC filter that is inserted at the bedside with

ultrasound visualization of the femoral or internal jugular vein (Angel® Filter) but without the need for any fluoroscopic or other radiological imaging.

For patients with swelling of the legs when acute DVT is diagnosed, below-knee graduated compression stockings may be prescribed, usually 30–40 mmHg, to lessen patient discomfort. They should be replaced every 3 months because they lose their elasticity. However, prescription of vascular compression stockings in asymptomatic newly diagnosed acute DVT patients does not prevent the development of postthrombotic syndrome.

TREATMENT

Pulmonary Embolism

RISK STRATIFICATION

Hemodynamic instability, RV dysfunction on echocardiography, RV enlargement on chest CT, or elevation of the troponin level due to RV microinfarction portend a high risk of an adverse clinical outcome despite anticoagulation. When RV function remains normal in a hemodynamically stable patient, a good clinical outcome is highly likely with anticoagulation alone **(Fig. 273-7)**.

ANTICOAGULATION

Effective anticoagulation is the foundation for successful treatment of DVT and PE. There are three major strategies: (1) the classical but waning strategy of parenteral anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux "bridged" to warfarin, (2) parenteral therapy switched after 5 days to a novel oral anticoagulant such as dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent), or (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both are anti-Xa agents) with a 3-week or 1-week loading dose, respectively, followed by a maintenance dose without parenteral anticoagulation. For patients with VTE in the setting of suspected or proven heparin-induced thrombocytopenia, one can choose between two parenteral direct thrombin inhibitors: argatroban and bivalirudin **(Table 273-3)**.

Unfractionated Heparin UFH anticoagulates by binding to and accelerating the activity of antithrombin, thus preventing additional thrombus formation. UFH is dosed to achieve a target activated partial thromboplastin time (aPTT) of 60–80 s. The most popular nomogram uses an initial bolus of 80 U/kg, followed by an initial infusion rate of 18 U/kg per h in patients with normal liver function. The major advantage of UFH is its short half-life, which is especially useful in patients in whom hour-to-hour control of the intensity of anticoagulation is desired. Heparin also has pleiotropic effects that may decrease systemic and local inflammation.

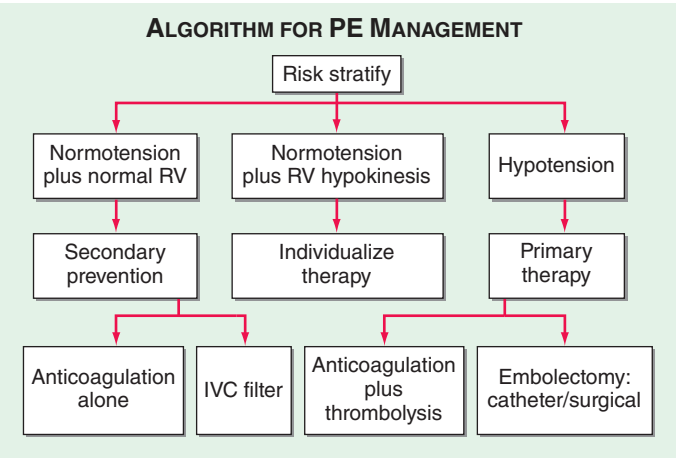

FIGURE 273-7 Acute management of pulmonary thromboembolism. RV, right ventricular; IVC, inferior vena cava.

TABLE 273-3 Anticoagulation of Venous Thromboembolism (VTE)

Non-Warfarin Anticoagulation
Unfractionated heparin, bolus and continuous infusion, to achieve activated partial thromboplastin time (aPTT) 2–3 times the upper limit of the laboratory normal, *or*
Enoxaparin 1 mg/kg twice daily with normal renal function, *or*
Dalteparin 200 U/kg once daily or 100 U/kg twice daily, with normal renal function, *or*
Tinzaparin 175 U/kg once daily with normal renal function, *or*
Fondaparinux weight-based once daily; adjust for impaired renal function
Direct thrombin inhibitors: argatroban or bivalirudin (with suspected or proven heparin-induced thrombocytopenia)
Rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily with the dinner meal thereafter
Apixaban 10 mg twice daily for 1 week, followed by 5 mg twice daily thereafter
Dabigatran 5 days of unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux followed by dabigatran 150 mg twice daily
Edoxaban 5 days of unfractionated heparin, LMWH, or fondaparinux followed by edoxaban 60 mg once daily with normal renal function, weight >60 kg, in the absence of potent P-glycoprotein inhibitors
Warfarin Anticoagulation
Requires 5–10 days of administration to achieve effectiveness as monotherapy
(Unfractionated heparin, LMWH, and fondaparinux are the usual immediately effective "bridging agents" used when initiating warfarin)
Usual start dose is 5 mg
Titrate to international normalized ratio (INR), target 2.0–3.0
Continue parenteral anticoagulation for a minimum of 5 days and until two sequential INR values, at least 1 day apart, achieve the target INR range

Low-Molecular-Weight Heparins These fragments of UFH exhibit less binding to plasma proteins and endothelial cells and consequently have greater bioavailability, a more predictable dose response, and a longer half-life than does UFH. No monitoring or dose adjustment is needed unless the patient is markedly obese or has chronic kidney disease.

Fondaparinux Fondaparinux, an anti-Xa pentasaccharide, is administered as a weight-based once-daily subcutaneous injection in a prefilled syringe. No laboratory monitoring is required. Fondaparinux is synthesized in a laboratory and, unlike LMWH or UFH, is not derived from animal products. It does not cause heparin-induced thrombocytopenia. The dose must be adjusted downward for patients with renal dysfunction.

Warfarin This vitamin K antagonist prevents carboxylation activation of coagulation factors II, VII, IX, and X. The full effect of warfarin requires at least 5 days, even if the prothrombin time, used for monitoring, becomes elevated more rapidly. If warfarin is initiated as monotherapy during an acute thrombotic illness, a paradoxical exacerbation of hypercoagulability increases the likelihood of thrombosis. Overlapping UFH, LMWH, fondaparinux, or parenteral direct thrombin inhibitors with warfarin for at least 5 days will nullify the early procoagulant effect of warfarin.

Warfarin dosing In an average-size adult, warfarin is often initiated in a dose of 5 mg. The prothrombin time is standardized by calculating the international normalized ratio (INR), which assesses the anticoagulant effect of warfarin **(Chap. 61)**. The target INR is usually 2.5, with a range of 2.0–3.0.

The warfarin dose is usually titrated empirically to achieve the target INR. Proper dosing is difficult because hundreds of drug-drug and drug-food interactions affect warfarin metabolism. Increasing age and systemic illness reduce the required warfarin dose. Pharmacogenomics may provide more precise initial dosing of warfarin. *CYP2C9* variant alleles impair the hydroxylation of S-warfarin, thereby lowering the dose requirement. Variants in the gene encoding the vitamin K

epoxide reductase complex 1 (*VKORC1*) can predict whether patients require low, moderate, or high warfarin doses. However, genetic testing is not used clinically to dose patients with warfarin.

Centralized anticoagulation clinics have improved the efficacy and safety of warfarin dosing. Patients can self-monitor their INR with a home point-of-care fingerstick machine and can occasionally be taught to self-dose their warfarin.

Warfarin can cause major hemorrhage, including intracranial hemorrhage, even when the INR remains within the desired therapeutic range. Warfarin can cause "off target" side effects such as alopecia or arterial vascular calcification. Some patients complain that warfarin makes them feel cold or fatigued.

Novel Oral Anticoagulants Novel oral anticoagulants (NOACs) are administered in a fixed dose, establish effective anticoagulation within hours of ingestion, require no laboratory coagulation monitoring, and have few of the drug-drug or drug-food interactions. Betrixaban, a direct factor Xa inhibitor, was approved by the FDA in 2017 for VTE prophylaxis in acutely ill medical patients during hospitalization and continuing for a total duration of 5 to 6 weeks. Rivaroxaban and apixaban, direct factor Xa inhibitors, are approved as monotherapy for acute and extended treatment of DVT and PE, without a parenteral "bridging" anticoagulant. Dabigatran, a direct thrombin inhibitor, and edoxaban, a factor Xa inhibitor, are approved for treatment of VTE after an initial 5-day course of parenteral anticoagulation.

Complications of Anticoagulants The most serious adverse effect of anticoagulation is hemorrhage. For life-threatening or intracranial hemorrhage due to heparin or LMWH, protamine sulfate can be administered. There is no specific reversal agent for bleeding caused by fondaparinux or factor Xa inhibitors. However, the dabigatran antibody, idarucizumab, is an effective and rapidly acting antidote for dabigatran that is now licensed for use. Andexanet is a universal anti-Xa antidote for betrixaban, rivaroxaban, apixaban, and edoxaban that is undergoing review by the FDA.

Major bleeding from warfarin is best managed with prothrombin complex concentrate. With less serious bleeding, fresh-frozen plasma or intravenous vitamin K can be used. Oral vitamin K is effective for managing minor bleeding or an excessively high INR in the absence of bleeding.

Duration of Anticoagulation For DVT isolated to an upper extremity or calf that has been provoked by surgery, trauma, estrogen, or an indwelling central venous catheter or pacemaker, 3 months of anticoagulation usually suffice. For an initial episode of provoked proximal leg DVT or PE, 3–6 months of anticoagulation used to be the classic teaching. However, the EINSTEIN CHOICE study found that patients with provoked VTE derived as great a risk reduction in recurrent VTE with extended duration anticoagulation as patients with unprovoked VTE. For patients with cancer and VTE, prescribe LMWH as monotherapy without warfarin and continue anticoagulation indefinitely unless the patient is rendered cancer-free.

Among patients with idiopathic, unprovoked VTE, the recurrence rate is high after cessation of anticoagulation. VTE that occurs during long-haul air travel is considered unprovoked. Unprovoked VTE may be caused by an exacerbation of an underlying inflammatory state and can be conceptualized as a chronic illness, with latent periods between flares of recurrent episodes. American College of Chest Physicians (ACCP) guidelines recommend considering anticoagulation for an indefinite duration with a target INR between 2 and 3 for patients with idiopathic VTE and a low bleeding risk. An alternative approach after the first 6 months of anticoagulation is to reduce the intensity of anticoagulation and to lower the target INR range to between 1.5 and 2. Another approach for patients at lower risk of recurrence, especially if there is an important reason to avoid long-term anticoagulation, is to consider low-dose aspirin after completing the initial period of standard anticoagulation.

Counterintuitively, the presence of genetic mutations such as heterozygous factor V Leiden and prothrombin gene mutation does not appear to increase the risk of recurrent VTE. However, patients with antiphospholipid antibody syndrome may warrant indefinite-duration anticoagulation, even if the initial VTE was provoked by trauma or surgery.

INFERIOR VENA CAVA FILTERS

The two principal indications for insertion of an IVC filter are (1) active bleeding that precludes anticoagulation and (2) recurrent venous thrombosis despite intensive anticoagulation. Prevention of recurrent PE in patients with right heart failure who are not candidates for fibrinolysis and prophylaxis of extremely high-risk patients are "softer" indications for filter placement. The filter itself may fail by permitting the passage of small- to medium-size clots. Large thrombi may embolize to the pulmonary arteries via collateral veins that develop.

Paradoxically, by providing a nidus for clot formation, filters increase the DVT rate, even though they usually prevent PE. Therefore, a common complication is recurrent DVT or caval thrombosis with marked leg swelling. Retrievable filters can now be placed for patients with an anticipated temporary bleeding disorder or for patients at temporary high risk of PE, such as individuals undergoing bariatric surgery who have a prior history of perioperative PE. The filters can be retrieved for months after insertion, unless thrombus forms and is trapped within the filter. The retrievable filter becomes permanent if it remains in place or if, for technical reasons such as rapid endothelialization, it cannot be removed.

MANAGEMENT OF MASSIVE PE

For patients with massive PE and hypotension, replete volume with 500 mL of normal saline. Additional fluid should be infused with extreme caution because excessive fluid administration exacerbates RV wall stress, causes more profound RV ischemia, and worsens LV compliance and filling by causing further interventricular septal shift toward the LV. Dopamine and dobutamine are first-line inotropic agents for treatment of PE-related shock. Maintain a low threshold for initiating these pressors. Often, a "trial-and-error" approach works best; other agents that may be effective include norepinephrine, vasopressin, or phenylephrine.

FIBRINOLYSIS

Successful fibrinolytic therapy rapidly reverses right heart failure and may result in a lower rate of death and recurrent PE by (1) dissolving much of the anatomically obstructing pulmonary arterial thrombus, (2) preventing the continued release of serotonin and other neurohumoral factors that exacerbate pulmonary hypertension, and (3) lysing much of the source of the thrombus in the pelvic or deep leg veins, thereby decreasing the likelihood of recurrent PE.

The preferred systemically administered fibrinolytic regimen is 100 mg of recombinant tissue plasminogen activator (tPA) prescribed as a continuous peripheral intravenous infusion over 2 h. The sooner thrombolysis is administered, the more effective it is. However, this approach can be used for at least 14 days after the PE has occurred. A popular off-label dosing regimen is 50 mg of TPA administered over 2 h. This lower dose is widely perceived to be associated with fewer bleeding complications.

Contraindications to fibrinolysis include intracranial disease, recent surgery, and trauma. The overall major bleeding rate is about 10%, including a 2–3% risk of intracranial hemorrhage. Careful screening of patients for contraindications to fibrinolytic therapy **(Chap. 269)** is the best way to minimize bleeding risk.

The only Food and Drug Administration–approved indication for PE fibrinolysis is massive PE. For patients with submassive PE, who have preserved systolic blood pressure but moderate or severe RV dysfunction, use of fibrinolysis remains controversial. Results of a 1006-patient European multicentered randomized trial of submassive PE, using the thrombolytic agent tenecteplase versus heparin alone, showed that death or hemodynamic collapse within 7 days of randomization was reduced by 56% in the tenecteplase group. However, hemorrhagic stroke occurred in 2% of tenecteplase patients versus 0.2% in patients who only received heparin.

PHARMACOMECHANICAL CATHETER-DIRECTED THERAPY

Many patients have relative contraindications to full-dose thrombolysis. Pharmacomechanical catheter-directed therapy usually combines physical fragmentation or pulverization of thrombus with catheter-directed low-dose thrombolysis. Mechanical techniques include catheter maceration and intentional embolization of clot more distally, suction thrombectomy, rheolytic hydrolysis, and low-energy ultrasound-facilitated thrombolysis. The dose of alteplase can be markedly reduced, usually to a range of 20–25 mg, instead of the peripheral intravenous systemic dose of 100 mg. In 2014, the FDA approved ultrasound-facilitated catheter-directed thrombolysis for acute massive and submassive PE. Using a total tPA dose of 24 mg, this approach decreased RV dilation, reduced pulmonary hypertension, decreased anatomic thrombus burden, and minimized intracranial hemorrhage. Lower doses and durations of TPA are currently being studied.

PULMONARY EMBOLECTOMY

The risk of major hemorrhage with systemically administered fibrinolysis has prompted a renaissance of interest in surgical embolectomy, an operation that had almost become extinct. More rapid referral before the onset of irreversible multisystem organ failure and improved surgical technique have resulted in a high survival rate.

PULMONARY THROMBOENDARTERECTOMY

Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients. Therefore, PE patients who have initial pulmonary hypertension (usually diagnosed with Doppler echocardiography) should be followed up at about 6 weeks with a repeat echocardiogram to determine whether pulmonary arterial pressure has normalized. Patients impaired by dyspnea due to chronic thromboembolic pulmonary hypertension should be considered for pulmonary thromboendarterectomy, which, when successful, can markedly reduce, and sometimes even cure, pulmonary hypertension **(Chap. 277)**. The operation requires median sternotomy, cardiopulmonary bypass, deep hypothermia, and periods of hypothermic circulatory arrest. The mortality rate at experienced centers is ~5%. Inoperable patients should be managed with pulmonary vasodilator therapy and balloon angioplasty of pulmonary arterial webs.

EMOTIONAL SUPPORT

Patients with VTE may feel overwhelmed when they learn that they are suffering from PE or DVT. Some have never previously encountered serious cardiovascular illness. They fear they will not be able to adapt to the new limitations imposed by anticoagulation. They worry about the health of their families and the genetic implications of their illness. Those who are advised to discontinue anticoagulation may feel especially vulnerable about the potential for suffering recurrent VTE. At Brigham and Women's Hospital, a physician-nurse–facilitated PE support group was initiated to address these concerns and has met monthly for >25 years. The nonprofit organization, North American Thrombosis Forum (*www.NATFonline.org*), has initiated other online support groups which garner worldwide participation.

PREVENTION OF VTE

Prevention of DVT and PE **(Table 273-4)** is of paramount importance because VTE is difficult to detect and poses a profound medical and economic burden. Low-dose UFH or LMWH is the most common form of in-hospital prophylaxis. Computerized reminder systems can increase the use of preventive measures and, at Brigham and Women's Hospital, have reduced the symptomatic VTE rate by >40%. Audits of hospitals to ensure that prophylaxis protocols are being used will also increase utilization of preventive measures. Duration of prophylaxis is an important consideration. Extended-duration prophylaxis with the novel anti-Xa agent, betrixaban, appears to be both effective and safe in medically ill patients during hospitalization, after hospital discharge, and is undergoing FDA review.

TABLE 273-4 Prevention of Venous Thromboembolism Among Hospitalized Patients

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Warfarin (target INR 2.0–3.0) Enoxaparin 40 mg daily Enoxaparin 30 mg bid Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily Rivaroxaban 10 mg daily, beginning 6-10 hours postoperatively Aspirin 81–325 mg daily Dabigatran 110 mg first day, then 220 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively Intermittent pneumatic compression (with or without pharmacologic prophylaxis)
Medically ill patients, during hospitalization	Unfractionated heparin 5000 units bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily
Medically ill patients, during and after hospitalization	Betrixaban 80 mg daily for 35–42 days
Anticoagulation contraindicated	Intermittent pneumatic compression devices (but whether graduated compression stockings are effective in medical patients remains uncertain)

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274 Diseases of the Aorta

Mark A. Creager, Joseph Loscalzo

The aorta is the conduit through which blood ejected from the left ventricle is delivered to the systemic arterial bed. In adults, its diameter is ~3 cm at the origin and in the ascending portion, 2.5 cm in the descending portion in the thorax, and 1.8–2 cm in the abdomen. The aortic wall consists of a thin intima composed of endothelium, subendothelial connective tissue, and an internal elastic lamina; a thick tunica media composed of smooth muscle cells and extracellular matrix; and an adventitia composed primarily of connective tissue enclosing the vasa vasorum and nervi vascularis. In addition to the conduit function of the aorta, its viscoelastic and compliant properties serve a buffering function. The aorta is distended during systole to allow a portion of the stroke volume and elastic energy to be stored, and it recoils during diastole so that blood continues to flow to the periphery. Owing to its continuous exposure to high pulsatile pressure and shear stress, the aorta is particularly prone to injury and disease resulting from mechanical trauma. The aorta is also more prone to rupture than is any other vessel, especially with the development of aneurysmal dilation, since its wall tension, as governed by Laplace's law (i.e., proportional to the product of pressure and radius), will be increased.

CONGENITAL ANOMALIES OF THE AORTA

Congenital anomalies of the aorta usually involve the aortic arch and its branches. Symptoms such as dysphagia, stridor, and cough may occur if an anomaly causes a ring around or otherwise compresses the esophagus or trachea. Anomalies associated with symptoms include double aortic arch, origin of the right subclavian artery distal to the left subclavian artery, and right-sided aortic arch with an aberrant left subclavian artery. A Kommerell's diverticulum is an anatomic remnant of a right aortic arch. Most congenital anomalies of the aorta do not cause symptoms and are detected during catheter-based procedures. The diagnosis of suspected congenital anomalies of the aorta typically is confirmed by computed tomographic (CT) or magnetic resonance (MR) angiography. Surgery is used to treat symptomatic anomalies.

Coarctation of the aorta **(Chap. 264)** typically occurs near the insertion of the ligamentum arteriosum, adjacent to the left subclavian artery. It may be associated with a bicuspid aortic valve, aortic arch hypoplasia, other congenital heart defects, and intracranial aneurysms. A pulse delay or pressure differential between the upper and lower extremities should raise suspicion of aortic coarctation. Imaging modalities, including echocardiography, CT and MR angiography are used to confirm the diagnosis. If untreated, hypertension develops in the arteries proximal to the coarctation. Treatment of hemodynamically significant aortic coarctation includes endovascular stent implantation if feasible or surgical repair.

AORTIC ANEURYSM

An *aneurysm* is defined as a pathologic dilation of a segment of a blood vessel. A *true aneurysm* involves all three layers of the vessel wall and is distinguished from a *pseudoaneurysm*, in which the intimal and medial layers are disrupted and the dilated segment of the aorta is lined by adventitia only and, at times, by perivascular clot. Aneurysms also may be classified according to their gross appearance. A *fusiform aneurysm* affects the entire circumference of a segment of the vessel, resulting in a diffusely dilated artery. In contrast, a *saccular aneurysm* involves only a portion of the circumference, resulting in an outpouching of the vessel wall. Aortic aneurysms also are classified according to location, i.e., abdominal versus thoracic. Aneurysms of the descending thoracic aorta are usually contiguous with infradiaphragmatic aneurysms and are referred to as *thoracoabdominal aortic aneurysms*.

ETIOLOGY

Aortic aneurysms result from conditions that cause degradation or abnormal production of the structural components of the aortic wall: elastin and collagen. The causes of aortic aneurysms may be broadly categorized as degenerative disorders, genetic or developmental diseases, vasculitis, infections, and trauma **(Table 274-1)**. Inflammation, oxidative stress, proteolysis, and biomechanical wall stress contribute to the degenerative processes that characterize most aneurysms of the abdominal and descending thoracic aorta. These are mediated by B cell and T cell lymphocytes, macrophages, inflammatory cytokines, and matrix metalloproteinases that degrade elastin and collagen and alter the tensile strength and ability of the aorta to accommodate pulsatile stretch. The associated histopathology demonstrates destruction of elastin and collagen, decreased vascular smooth muscle, in-growth of new blood vessels, and inflammation. Factors associated with degenerative aortic aneurysms include aging, cigarette smoking, hypercholesterolemia, hypertension, and male sex.

The most common pathologic condition associated with degenerative aortic aneurysms is *atherosclerosis*. Many patients with aortic aneurysms have coexisting risk factors for atherosclerosis, as well as atherosclerosis in other blood vessels.

TABLE 274-1 Diseases of the Aorta: Etiology and Associated Factors

Aortic aneurysm
Degenerative
Aging
Cigarette smoking
Hypercholesterolemia
Hypertension
Atherosclerosis
Genetic or developmental
Marfan's syndrome
Loeys-Dietz syndrome
Ehlers-Danlos syndrome type IV
Turner's syndrome
Familial
Bicuspid aortic valve
Chronic aortic dissection
Aortitis (see below)
Infective (see below)
Trauma
Acute aortic syndromes (aortic dissection, acute intramural hematoma, penetrating atherosclerotic ulcer)
Degenerative disorders (see above)
Genetic/developmental disorders (see above)
Hypertension
Aortitis (see below)
Pregnancy
Trauma
Aortic occlusion
Atherosclerosis
Thromboembolism
Aortitis
Vasculitis
Takayasu's arteritis
Giant cell arteritis
Rheumatic
Rheumatoid aortitis
HLA-B27–associated spondyloarthropathies
Behçet's syndrome
Cogan's syndrome
IgG4-related systemic disease
Idiopathic aortitis
Infective
Syphilis
Tuberculosis
Mycotic (*Salmonella*, staphylococcal, streptococcal, fungal)

Medial degeneration, previously designated *cystic medial necrosis*, is the histopathologic term used to describe the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material, such as proteoglycans. Medial degeneration characteristically affects the proximal aorta, results in circumferential weakness and dilation, and leads to the development of fusiform aneurysms involving the ascending aorta and the sinuses of Valsalva. This pathologic condition occurs in patients with Marfan's syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome type IV **(Chap. 406)**, hypertension, congenital bicuspid aortic valves, Turner's syndrome, and familial thoracic aortic aneurysm syndromes; sometimes it appears as an isolated condition in patients without any other apparent disease.

Familial clusterings of aortic aneurysms occur in 20% of patients, suggesting a hereditary basis for the disease. Mutations of the gene that encodes fibrillin-1 are present in patients with Marfan's syndrome. Fibrillin-1 is an important component of extracellular microfibrils, which support the architecture of elastic fibers and other connective tissue. Deficiency of fibrillin-1 in the extracellular matrix leads to excessive signaling by transforming growth factor β (TGF-β). Loeys-Dietz syndrome is caused by mutations in the genes that encode TGF-β receptors 1 (*TGFBR1*) and 2 (*TGFBR2*). Increased signaling by TGF-β and mutations of *TGFBR1*, *TGFBR2*, *TGFBR3*, as well as *TGFB2* and *TGFB3*, may cause thoracic aortic aneurysms. Mutations of *SMAD3*, which encodes a downstream signaling protein involved with TGF binding to its receptors, have been described in a syndrome of thoracic aortic aneurysm; craniofacial, skeletal, and cutaneous anomalies; and osteoarthritis. Mutations of the genes encoding the smooth muscle–specific alpha-actin (*ACTA2*), smooth muscle cell–specific myosin heavy chain 11 (*MHC11*), and myosin light chain kinase (*MYLK*) and mutations of *TGFBR2* and *SMAD3* have been reported in some patients with nonsyndromic familial thoracic aortic aneurysms. Mutations of type III procollagen have been implicated in Ehlers-Danlos type IV syndrome.

The infectious causes of aortic aneurysms include syphilis, tuberculosis, and other bacterial infections. *Syphilis* **(Chap. 177)** is a relatively uncommon cause of aortic aneurysm. Syphilitic periaortitis and mesoaortitis damage elastic fibers, resulting in thickening and weakening of the aortic wall. Approximately 90% of syphilitic aneurysms are located in the ascending aorta or aortic arch. *Tuberculous aneurysms* **(Chap. 173)** typically affect the thoracic aorta and result from direct extension of infection from hilar lymph nodes or contiguous abscesses as well as from bacterial seeding. Loss of aortic wall elasticity results from granulomatous destruction of the medial layer. A *mycotic aneurysm* is a rare condition that develops as a result of staphylococcal, streptococcal, *Salmonella*, or other bacterial or fungal infections of the aorta, usually at an atherosclerotic plaque. These aneurysms are usually saccular. Blood cultures are often positive and reveal the nature of the infective agent.

Vasculitides associated with aortic aneurysm include Takayasu's arteritis and giant cell arteritis, which may cause aneurysms of the aortic arch and descending thoracic aorta. Spondyloarthropathies such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, relapsing polychondritis, and reactive arthritis (formerly known as Reiter's syndrome) are associated with dilation of the ascending aorta. Aortic aneurysms occur in patients with Behçet's syndrome **(Chap. 357)**, Cogan's syndrome, and IgG4-related systemic disease. Aortic aneurysms also result from idiopathic aortitis. *Traumatic aneurysms* may occur after penetrating or nonpenetrating chest trauma and most commonly affect the descending thoracic aorta just beyond the site of insertion of the ligamentum arteriosum. Chronic aortic dissections are associated with weakening of the aortic wall that may lead to the development of aneurysmal dilatation.

THORACIC AORTIC ANEURYSMS

The clinical manifestations and natural history of thoracic aortic aneurysms depend on their location. Medial degeneration is the most common pathology associated with ascending aortic aneurysms, whereas atherosclerosis is the condition most frequently associated with aneurysms of the descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year. Thoracic aortic aneurysms associated with Marfan's syndrome or aortic dissection may expand at a greater rate. The risk of rupture is related to the size of the aneurysm and the presence of symptoms, ranging approximately from 2–3% per year for thoracic aortic aneurysms <4.0 cm in diameter to 7% per year for those >6 cm in diameter. Most thoracic aortic aneurysms are asymptomatic; however, compression or erosion of adjacent tissue by aneurysms may cause symptoms such as chest pain, shortness of breath, cough, hoarseness, and dysphagia. Aneurysmal dilation of the ascending aorta may cause congestive heart failure as a consequence of aortic regurgitation, and compression of the superior vena cava may produce congestion of the head, neck, and upper extremities.

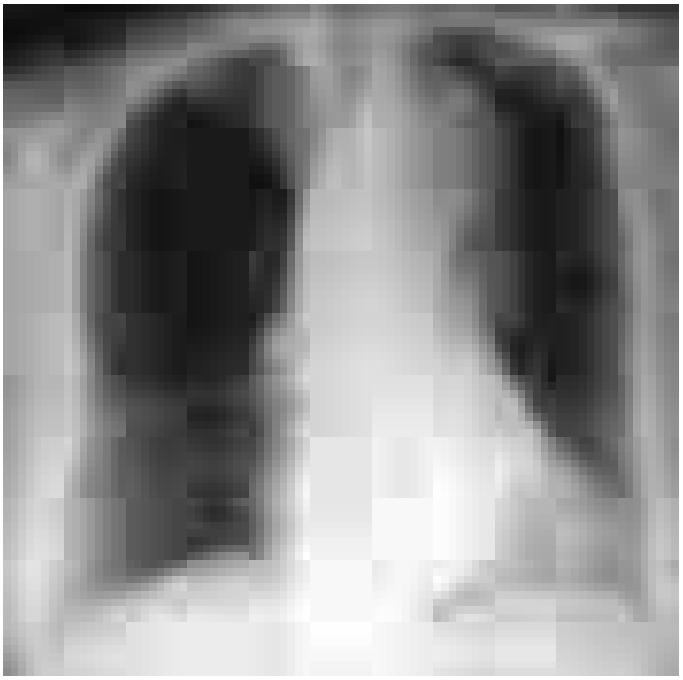

FIGURE 274-1 A chest x-ray of a patient with a thoracic aortic aneurysm.

A chest x-ray may be the first test that suggests the diagnosis of a thoracic aortic aneurysm **(Fig. 274-1)**. Findings include widening of the mediastinal shadow and displacement or compression of the trachea or left main stem bronchus. Echocardiography, particularly transesophageal echocardiography, can be used to assess the proximal ascending aorta and descending thoracic aorta. Contrast-enhanced CT, magnetic resonance imaging (MRI), and conventional invasive aortography are sensitive and specific tests for assessment of aneurysms of the thoracic aorta and involvement of branch vessels **(Fig. 274-2)**. In asymptomatic patients whose aneurysms are too small to justify surgery, noninvasive testing with either contrast-enhanced CT or MRI should be performed at least every 6–12 months to monitor expansion.

TREATMENT

Thoracic Aortic Aneurysms

β-Adrenergic blockers currently are recommended for patients with thoracic aortic aneurysms, particularly those with Marfan's syndrome, who have evidence of aortic root dilatation to reduce the rate of further expansion. Additional medical therapy should be given as necessary to control hypertension. Angiotensin receptor antagonists may reduce the rate of aortic dilation in patients with Marfan's syndrome by blocking TGF-β signaling. Clinical outcome trials have found that the rate of aortic root enlargement in patients with Marfan's syndrome was similar with atenolol and losartan. Operative repair with placement of a prosthetic graft is indicated

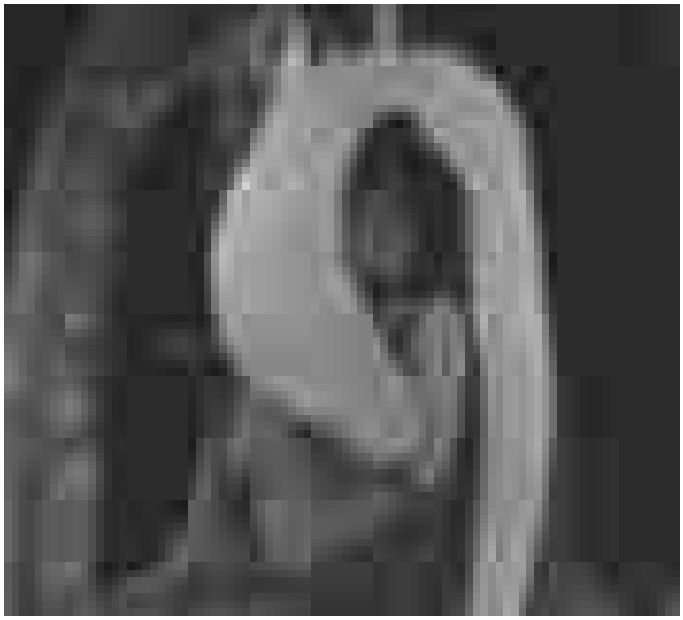

FIGURE 274-2 A magnetic resonance angiogram demonstrating a fusiform aneurysm of the ascending thoracic aorta. *(Courtesy of Dr. Michael Steigner, Brigham and Women's Hospital, Boston, MA, with permission.)*

in patients with symptomatic ascending thoracic aortic aneurysms and for most asymptomatic aneurysms, including those associated with bicuspid aortic valves, when the aortic root or ascending aortic diameter is ≥5.5 cm, or when the growth rate is >0.5 cm per year. Replacement of the ascending aorta >4.5 cm is reasonable in patients with bicuspid aortic valves undergoing aortic valve replacement because of severe aortic stenosis or aortic regurgitation. In patients with Marfan's syndrome, ascending thoracic aortic aneurysms of 4–5 cm should be considered for surgery. Operative repair is indicated for patients with degenerative descending thoracic aortic aneurysms when the diameter is >6 cm, and endovascular repair should be considered if feasible when the diameter is >5.5 cm. Repair is also recommended when the diameter of a descending thoracic aortic aneurysm has increased >1 cm per year.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms occur more frequently in males than in females, and the incidence increases with age. Cigarette smoking is a potent modifiable risk factor. Abdominal aortic aneurysms ≥4.0 cm may affect 1–2% men aged >50 years. At least 90% of all abdominal aortic aneurysms >4.0 cm are related to atherosclerotic disease, and most of these aneurysms are below the level of the renal arteries. Prognosis is related to both the size of the aneurysm and the severity of coexisting coronary artery and cerebrovascular disease. The risk of rupture increases with the size of the aneurysm: the 5-year risk for aneurysms <5 cm is 1–2%, whereas it is 20–40% for aneurysms >5 cm in diameter. The formation of mural thrombi within aneurysms may predispose to peripheral embolization.

An abdominal aortic aneurysm commonly produces no symptoms. It usually is detected on routine examination as a palpable, pulsatile, expansile, and nontender mass, or it is an incidental finding observed on an abdominal imaging study performed for other reasons. As abdominal aortic aneurysms expand, however, they may become painful. Some patients complain of strong pulsations in the abdomen; others experience pain in the chest, lower back, or scrotum. Aneurysmal pain is usually a harbinger of rupture and represents a medical emergency. More often, acute rupture occurs without any prior warning, and this complication is always life-threatening. Rarely, there is leakage of the aneurysm with severe pain and tenderness. Acute pain and hypotension occur with rupture of the aneurysm, which requires an emergency operation.

Abdominal radiography may demonstrate the calcified outline of the aneurysm; however, about 25% of aneurysms are not calcified and cannot be visualized by x-ray imaging. An abdominal ultrasound can delineate the transverse and longitudinal dimensions of an abdominal aortic aneurysm and may detect mural thrombus. Abdominal ultrasound is useful for serial documentation of aneurysm size and can be used to screen patients at risk for developing an aortic aneurysm. In one large study, ultrasound screening of men aged 65–74 years was associated with a risk reduction in aneurysm-related death of 42%. For this reason, screening by ultrasonography is recommended for men aged 65–75 years who have ever smoked. In addition, siblings or offspring of persons with abdominal aortic aneurysms, as well as individuals with thoracic aortic or peripheral arterial aneurysms, should be considered for screening for abdominal aortic aneurysms. CT with contrast and MRI are accurate noninvasive tests to determine the location and size of abdominal aortic aneurysms and to plan endovascular or open surgical repair **(Fig. 274-3)**. Contrast aortography may be used for the evaluation of patients with aneurysms, but the procedure carries a small risk of complications such as bleeding, allergic reactions, and atheroembolism. Since the presence of mural thrombi may reduce the luminal size, aortography may underestimate the diameter of an aneurysm.

TREATMENT

Abdominal Aortic Aneurysms

Statins are indicated to reduce the risk of cardiovascular events related to atherosclerosis. Medical therapies, such as β-adrenergic blockers and renin-angiotensin inhibitors, have not proven effective in reducing the rate of aneurysm growth. Operative repair of the aneurysm with insertion of a prosthetic graft or endovascular placement of an aortic stent graft (Fig. 274-3) is indicated for abdominal aortic aneurysms of any size that are expanding rapidly or are associated with symptoms. For asymptomatic aneurysms, abdominal aortic aneurysm repair is indicated if the diameter is ≥5.5 cm. In randomized trials of patients with abdominal aortic aneurysms <5.5 cm, there was no difference in the long-term (5- to 8-year) mortality rate between those followed with ultrasound surveillance and those undergoing elective surgical repair. Thus, serial noninvasive follow-up of smaller aneurysms (<5.5 cm) is an alternative to immediate repair. The decision to perform an open surgical operation or endovascular repair is based in part on the vascular anatomy and comorbid conditions. Endovascular repair of abdominal aortic aneurysms has a lower short-term morbidity rate, but a comparable long-term mortality rate with open surgical reconstruction. Long-term surveillance with CT or MR aortography is indicated after endovascular repair to detect leaks and possible aneurysm expansion.

In surgical candidates, careful preoperative cardiac and general medical evaluations (followed by appropriate therapy for complicating conditions) are essential. Preexisting coronary artery disease, congestive heart failure, pulmonary disease, diabetes mellitus, and advanced age add to the risk of surgery. With careful preoperative cardiac evaluation and postoperative care, the operative mortality rate approximates 1–2%. After acute rupture, the mortality rate of emergent operation is 45–50%. Endovascular repair with stent placement is an alternative approach to treat ruptured aneurysms and may be associated with a lower mortality rate.

ACUTE AORTIC SYNDROMES

The four major acute aortic syndromes are aortic rupture (discussed earlier), aortic dissection, intramural hematoma, and penetrating atherosclerotic ulcer. Aortic dissection is caused by a circumferential or, less frequently, transverse tear of the intima. It often occurs along the right lateral wall of the ascending aorta where the hydraulic shear stress is high. Another common site is the descending thoracic aorta just below the ligamentum arteriosum. The initiating event is either a primary intimal tear with secondary dissection into the media or

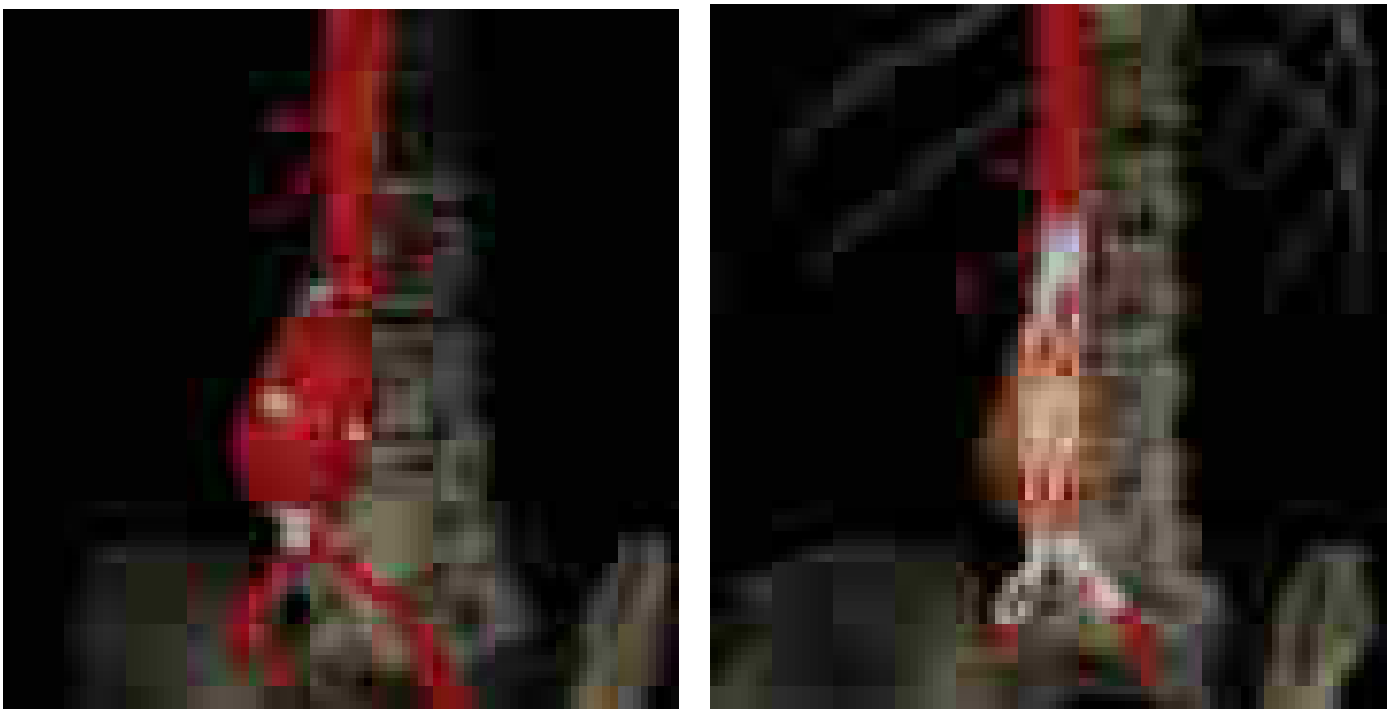

FIGURE 274-3 A computed tomographic angiogram depicting a fusiform abdominal aortic aneurysm before (*left*) and after (*right*) treatment with a bifurcated stent graft. *(Courtesy of Drs. Elizabeth George and Frank Rybicki, Brigham and Women's Hospital, Boston, MA, with permission.)*

a medial hemorrhage that dissects into and disrupts the intima. The pulsatile aortic flow then dissects along the elastic lamellar plates of the aorta and creates a false lumen. The dissection usually propagates distally down the descending aorta and into its major branches, but it may propagate proximally. Distal propagation may be limited by atherosclerotic plaque. In some cases, a secondary distal intimal disruption occurs, resulting in the reentry of blood from the false to the true lumen.

There are at least two important pathologic and radiologic variants of aortic dissection: intramural hematoma without an intimal flap and penetrating atherosclerotic ulcer. Acute intramural hematoma is thought to result from rupture of the vasa vasorum with hemorrhage into the wall of the aorta. Most of these hematomas occur in the descending thoracic aorta. Acute intramural hematomas may progress to dissection and rupture. Penetrating atherosclerotic ulcers are caused by erosion of a plaque into the aortic media, are usually localized, and are not associated with extensive propagation. They are found primarily in the middle and distal portions of the descending thoracic aorta and are associated with extensive atherosclerotic disease. The ulcer can erode beyond the internal elastic lamina, leading to medial hematoma, and may progress to false aneurysm formation or rupture.

Several classification schemes have been developed for thoracic aortic dissections. DeBakey and colleagues initially classified aortic dissections as type I, in which an intimal tear occurs in the ascending aorta but involves the descending aorta as well; type II, in which the dissection is limited to the ascending aorta; and type III, in which the intimal tear is located in the descending aorta with distal propagation of the dissection **(Fig. 274-4)**. Another classification (Stanford) is that of type A, in which the dissection involves the ascending aorta (proximal dissection), and type B, in which it is limited to the arch and/or descending aorta (distal dissection). From a management standpoint, classification of aortic dissections and intramural hematomas into type A or B is more practical and useful, since DeBakey types I and II are managed in a similar manner.

The factors that predispose to aortic dissection include those associated with medial degeneration and others that increase aortic wall stress (Table 274-1). Systemic hypertension is a coexisting condition in 70% of patients. Aortic dissection is the major cause of morbidity and mortality in patients with Marfan's syndrome **(Chap. 406)** or Loeys-Dietz syndrome, and similarly may affect patients with Ehlers-Danlos syndrome. The incidence also is increased in patients with inflammatory aortitis (i.e., Takayasu's arteritis, giant cell arteritis), congenital aortic valve anomalies (e.g., bicuspid valve), coarctation of

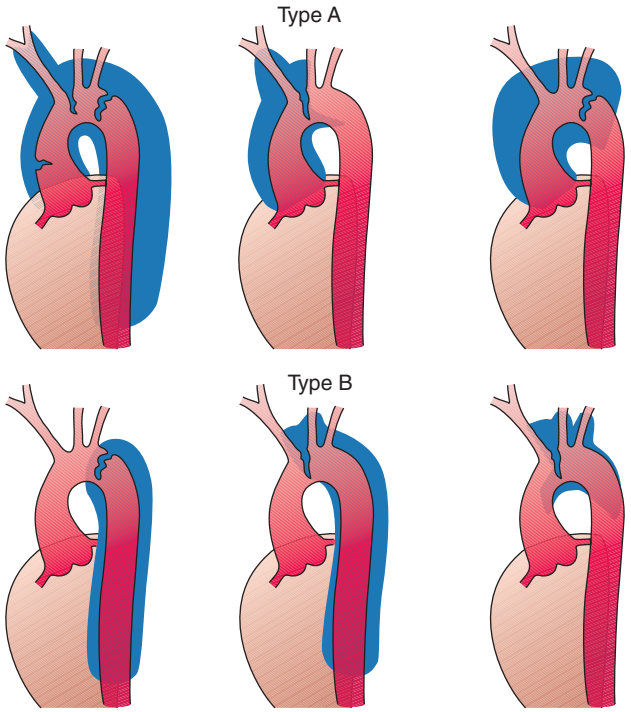

FIGURE 274-4 Classification of aortic dissections. Stanford classification: Type A dissections (*top*) involve the ascending aorta independent of site of tear and distal extension; type B dissections (*bottom*) involve transverse and/or descending aorta without involvement of the ascending aorta. DeBakey classification: Type I dissection involves ascending to descending aorta (*top left*); type II dissection is limited to ascending or transverse aorta, without descending aorta (*top center + top right*); type III dissection involves descending aorta only (*bottom left*). *(From DC Miller, in RM Doroghazi, EE Slater [eds]: Aortic Dissection. New York, McGraw-Hill, 1983, with permission.)*

the aorta, and a history of aortic trauma. In addition, the risk of dissection is increased in otherwise normal women during the third trimester of pregnancy. Aortic dissection also may occur as a consequence of weight lifting, cocaine use, or deceleration injury.

CLINICAL MANIFESTATIONS

The peak incidence of aortic dissection is in the sixth and seventh decades. Men are more affected than women by a ratio of 2:1. The presentations of aortic dissection and its variants are the consequences of intimal tear, dissecting hematoma, occlusion of involved arteries, and compression of adjacent tissues. Acute aortic dissection presents with the sudden onset of pain **(Chap. 11)**, which often is described as very severe and tearing and is associated with diaphoresis. The pain may be localized to the front or back of the chest, often the interscapular region, and typically migrates with propagation of the dissection. Other symptoms include syncope, dyspnea, and weakness. Physical findings may include hypertension or hypotension, loss of pulses, aortic regurgitation, pulmonary edema, and neurologic findings due to carotid artery obstruction (hemiplegia, hemianesthesia) or spinal cord ischemia (paraplegia). Bowel ischemia, hematuria, and myocardial ischemia have all been observed. These clinical manifestations reflect complications resulting from the dissection occluding the major arteries. Furthermore, clinical manifestations may result from the compression of adjacent structures (e.g., superior cervical ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection causing aneurysmal dilation, and include Horner's syndrome, superior vena cava syndrome, hoarseness, dysphagia, and airway compromise. Hemopericardium and cardiac tamponade may complicate a type A lesion with retrograde dissection. Acute aortic regurgitation is an important and common (>50%) complication of proximal dissection. It is the outcome of either a circumferential tear that widens the aortic root or a disruption of the annulus by a dissecting hematoma that tears a leaflet(s) or displaces it, inferior to the line of closure. Signs of aortic regurgitation include bounding pulses, a wide pulse pressure, a diastolic murmur often radiating along the right sternal border, and evidence of congestive heart failure. The clinical manifestations depend on the severity of the regurgitation.

In dissections involving the ascending aorta, the chest x-ray often reveals a widened superior mediastinum. A pleural effusion (usually left-sided) also may be present. This effusion is typically serosanguineous and not indicative of rupture unless accompanied by hypotension and falling hematocrit. In dissections of the descending thoracic aorta, a widened mediastinum may be observed on chest x-ray. In addition, the descending aorta may appear to be wider than the ascending portion. An electrocardiogram that shows no evidence of myocardial ischemia is helpful in distinguishing aortic dissection from myocardial infarction. Rarely, the dissection involves the right or, less commonly, left coronary ostium and causes acute myocardial infarction.

The diagnosis of aortic dissection can be established by noninvasive techniques such as echocardiography, CT, and MRI. Aortography is used less commonly because of the accuracy of these noninvasive techniques. Transthoracic echocardiography can be performed simply and rapidly and has an overall sensitivity of 60–85% for aortic dissection. For diagnosing proximal ascending aortic dissections, its sensitivity exceeds 80%; it is less useful for detecting dissection of the arch and descending thoracic aorta. Transesophageal echocardiography requires greater skill and patient cooperation, but is very accurate in identifying dissections of the ascending and descending thoracic aorta but not the arch, achieving 98% sensitivity and ~90% specificity. Echocardiography also provides important information regarding the presence and severity of aortic regurgitation and pericardial effusion. CT and MRI are both highly accurate in identifying the intimal flap and the extent of the dissection and involvement of major arteries; each has a sensitivity and specificity >90%. They are useful in recognizing intramural hemorrhage and penetrating ulcers. The relative utility of transesophageal echocardiography, CT, and MRI depends on the availability and expertise in individual institutions as well as on the hemodynamic stability of the patient, with CT and MRI obviously less suitable for unstable patients.

TREATMENT

Aortic Dissection

Medical therapy should be initiated as soon as the diagnosis is considered. The patient should be admitted to an intensive care unit for hemodynamic monitoring. Unless hypotension is present, therapy should be aimed at reducing cardiac contractility and systemic arterial pressure, and thus shear stress. For acute dissection, unless contraindicated, β-adrenergic blockers should be administered parenterally, using intravenous propranolol, metoprolol, or the short-acting esmolol to achieve a heart rate of ~60 beats/min. This should be accompanied by sodium nitroprusside infusion to lower systolic blood pressure to ≤120 mmHg. Labetalol **(Chap. 271)**, a drug with both β- and α-adrenergic blocking properties, also may be used as a parenteral agent in acute therapy for dissection.

The calcium channel antagonists verapamil and diltiazem may be used intravenously if nitroprusside or β-adrenergic blockers cannot be employed. The addition of a parenteral angiotensin-converting enzyme (ACE) inhibitor such as enalaprilat to a β-adrenergic blocker also may be considered. Isolated use of a direct vasodilator such as hydralazine is contraindicated because these agents can increase hydraulic shear and may propagate the dissection.

Emergent or urgent surgical correction is the preferred treatment for acute ascending aortic dissections and intramural hematomas (type A). Surgery involves excision of the intimal flap, obliteration of the false lumen, and placement of an interposition graft. Aortic valve repair or a composite valve-graft conduit is used if the aortic valve is disrupted. The overall in-hospital mortality rate after surgical treatment of patients with aortic dissection is reported to be 15–25%. The major causes of perioperative mortality and morbidity include myocardial infarction, paraplegia, renal failure, tamponade, hemorrhage, and sepsis. Thoracic endovascular aortic repair with an endoluminal stent graft is indicated for complicated type B dissections, including those characterized by propagation, compromise of major aortic branches, impending rupture, or continued pain. Other transcatheter techniques, such as fenestration of the intimal flaps and stenting of narrowed branch vessels to increase flow to compromised organs, are used in selected patients. Surgical correction is indicated for complicated type B dissections, particularly if endovascular repair is not feasible. Hybrid procedures consisting of both surgery and endovascular repair may be used when the dissection involves both the aortic arch and the descending thoracic aorta. For uncomplicated and stable distal dissections and intramural hematomas (type B), medical therapy is the preferred treatment. The in-hospital mortality rate of medically treated patients with type B dissection is ~10%. Long-term therapy for patients with aortic dissection and intramural hematomas (with or without surgery) consists of control of hypertension and reduction of cardiac contractility with the use of β-adrenergic blockers plus other antihypertensive agents, such as ACE inhibitors or calcium antagonists. Patients with chronic type B dissection and intramural hematomas should be followed on an outpatient basis every 6–12 months with contrast-enhanced CT or MRI to detect propagation or expansion. Patients with Marfan's syndrome are at high risk for postdissection complications. The long-term prognosis for patients with treated dissections is generally good with careful follow-up; the 10-year survival rate is ~60%.

CHRONIC ATHEROSCLEROTIC OCCLUSIVE DISEASE

Atherosclerosis may affect the thoracic and abdominal aorta. Occlusive aortic disease caused by atherosclerosis usually is confined to the distal abdominal aorta below the renal arteries. Frequently the disease extends to the iliac arteries **(Chap. 275)**. Claudication characteristically involves the buttocks, thighs, and calves and may be associated with impotence in males (Leriche's syndrome). The severity of the symptoms depends on the adequacy of collaterals. With sufficient collateral blood flow, a complete occlusion of the abdominal aorta may occur without the development of ischemic symptoms. The physical findings

include the absence of femoral and other distal pulses bilaterally and the detection of an audible bruit over the abdomen (usually at or below the umbilicus) and the common femoral arteries. Atrophic skin, loss of hair, and coolness of the lower extremities usually are observed. In advanced ischemia, rubor on dependency and pallor on elevation can be seen.

The diagnosis usually is established by physical examination and noninvasive testing, including leg pressure measurements, Doppler velocity analysis, pulse volume recordings, and duplex ultrasonography. The anatomy may be defined by MRI, CT, or conventional aortography, typically performed when one is considering revascularization. Catheter-based endovascular or operative treatment is indicated in patients with lifestyle-limiting or debilitating symptoms of claudication and patients with critical limb ischemia.

ACUTE AORTIC OCCLUSION

Acute occlusion in the distal abdominal aorta constitutes a medical emergency because it threatens the viability of the lower extremities; it usually results from an occlusive (saddle) embolus that almost always originates from the heart. Rarely, acute occlusion may occur as the result of in situ thrombosis in a preexisting severely narrowed segment of the aorta.

The clinical picture is one of acute ischemia of the lower extremities. Severe rest pain, coolness, and pallor of the lower extremities and the absence of distal pulses bilaterally are the usual manifestations. Diagnosis should be established rapidly by MRI, CT, or aortography. Emergency thrombectomy or revascularization is indicated.

AORTITIS

Aortitis, a term referring to inflammatory disease of the aorta, may be caused by large vessel vasculitides such as Takayasu's arteritis and giant cell arteritis, rheumatic and HLA-B27–associated spondyloarthropathies, Behçet's syndrome, antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides, Cogan's syndrome, Erdheim-Chester disease, IgG4-related systemic disease, and infections such as syphilis, tuberculosis, and *Salmonella*, or may be associated with retroperitoneal fibrosis. Aortitis may result in aneurysmal dilation and aortic regurgitation, occlusion of the aorta and its branch vessels, or acute aortic syndromes.

TAKAYASU'S ARTERITIS

(See also Chap. 356) This inflammatory disease often affects the ascending aorta and aortic arch, causing obstruction of the aorta and its major arteries. Takayasu's arteritis is also termed *pulseless disease* because of the frequent occlusion of the large arteries originating from the aorta. It also may involve the descending thoracic and abdominal aorta and occlude large branches such as the renal arteries. Aortic aneurysms also may occur. The pathology is a panarteritis characterized by mononuclear cells and occasionally giant cells, with marked intimal hyperplasia, medial and adventitial thickening, and, in the chronic form, fibrotic occlusion. The disease is most prevalent in young females of Asian descent but does occur in women of other geographic and ethnic origins and also in young men. During the acute stage, fever, malaise, weight loss, and other systemic symptoms may be evident. Elevations of the erythrocyte sedimentation rate and C-reactive protein are common. The chronic stages of the disease, which is intermittently active, present with symptoms related to large artery occlusion, such as upper extremity claudication, cerebral ischemia, and syncope. The process is progressive, and there is no definitive therapy. Glucocorticoids and immunosuppressive agents are effective in some patients during the acute phase. Biologically targeted agents are under investigation. Surgical bypass or endovascular intervention of a critically stenotic artery may be necessary.

GIANT CELL ARTERITIS

(See also Chap. 356) This vasculitis occurs in older individuals and affects women more often than men. Primarily large and medium-size arteries are affected. The pathology is that of focal granulomatous lesions involving the entire arterial wall; it frequently is associated with polymyalgia rheumatica. Obstruction of medium-size arteries (e.g., temporal and ophthalmic arteries) and major branches of the aorta and the development of aortitis and aortic regurgitation are important complications of the disease. High-dose glucocorticoid therapy should be administered early and then gradually tapered. Immunosuppressive therapy with methotrexate may allow reduction in steroid dosage and reduce the risk of relapse. Biologically targeted therapies are under investigation.

RHEUMATIC AORTITIS

Rheumatoid arthritis **(Chap. 351)**, ankylosing spondylitis **(Chap. 355)**, psoriatic arthritis **(Chap. 355)**, reactive arthritis (formerly known as Reiter's syndrome) **(Chap. 355)**, relapsing polychondritis, and inflammatory bowel disorders may all be associated with aortitis involving the ascending aorta. The inflammatory lesions usually involve the ascending aorta and may extend to the sinuses of Valsalva, the mitral valve leaflets, and adjacent myocardium. The clinical manifestations are aneurysm, aortic regurgitation, and involvement of the cardiac conduction system.

IDIOPATHIC AORTITIS

Idiopathic abdominal aortitis is characterized by adventitial and periaortic inflammation with thickening of the aortic wall. It is associated with abdominal aortic aneurysms and idiopathic retroperitoneal fibrosis. Affected individuals may present with vague constitutional symptoms, fever, and abdominal pain. Retroperitoneal fibrosis can cause ureteral obstruction and hydronephrosis. Glucocorticoids and immunosuppressive agents may reduce the inflammation.

INFECTIVE AORTITIS

Infective aortitis may result from direct invasion of the aortic wall by bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* or by fungi. These bacteria cause aortitis by infecting the aorta at sites of atherosclerotic plaque. Bacterial proteases lead to degradation of collagen, and the ensuing destruction of the aortic wall leads to the formation of a saccular aneurysm referred to as a mycotic aneurysm. Mycotic aneurysms have a predilection for the suprarenal abdominal aorta. The pathologic characteristics of the aortic wall include acute and chronic inflammation, abscesses, hemorrhage, and necrosis. Mycotic aneurysms typically affect the elderly and occur in men three times more frequently than in women. Patients may present with fever, sepsis, and chest, back, or abdominal pain; there may have been a preceding diarrheal illness. Blood cultures are positive in the majority of patients. Both CT and MRI are useful to diagnose mycotic aneurysms. Treatment includes antibiotic therapy and surgical removal of the affected part of the aorta and revascularization of the lower extremities with grafts placed in uninfected tissue.

Syphilitic aortitis is a late manifestation of luetic infection **(Chap. 177)** that usually affects the proximal ascending aorta, particularly the aortic root, resulting in aortic dilation and aneurysm formation. Syphilitic aortitis occasionally may involve the aortic arch or the descending aorta. The aneurysms may be saccular or fusiform and are usually asymptomatic, but compression of and erosion into adjacent structures may result in symptoms; rupture also may occur.

The initial lesion is an obliterative endarteritis of the vasa vasorum, especially in the adventitia. This is an inflammatory response to the invasion of the adventitia by the spirochetes. Destruction of the aortic media occurs as the spirochetes spread into this layer, usually via the lymphatics accompanying the vasa vasorum. Destruction of collagen and elastic tissues leads to dilation of the aorta, scar formation, and calcification. These changes account for the characteristic radiographic appearance of linear calcification of the ascending aorta.

The disease typically presents as an incidental chest radiographic finding 15–30 years after initial infection. Symptoms may result from aortic regurgitation, narrowing of coronary ostia due to syphilitic aortitis, compression of adjacent structures (e.g., esophagus), or rupture. Diagnosis is established by a positive serologic test, i.e., rapid plasmin reagin (RPR) or fluorescent treponemal antibody. Treatment includes penicillin and surgical excision and repair.

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275 Arterial Diseases of the Extremities

Mark A. Creager, Joseph Loscalzo

PERIPHERAL ARTERY DISEASE

Peripheral artery disease (PAD) is defined as a clinical disorder in which there is a stenosis or occlusion in the aorta or the arteries of the limbs. Atherosclerosis is the leading cause of PAD in patients >40 years old. Other causes include thrombosis, embolism, vasculitis, fibromuscular dysplasia, entrapment, cystic adventitial disease, and trauma. The highest prevalence of atherosclerotic PAD occurs in the sixth and seventh decades of life. As in patients with atherosclerosis of the coronary and cerebral vasculature, there is an increased risk of developing PAD in cigarette smokers and in persons with diabetes mellitus, hypercholesterolemia, hypertension, or renal insufficiency.

Pathology (See also Chap. 291e from HPIM 19e) Segmental lesions that cause stenosis or occlusion are usually localized to large and medium-size vessels. The pathology of the lesions includes atherosclerotic plaques with calcium deposition, thinning of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina, and thrombi composed of platelets and fibrin. The primary sites of involvement are the abdominal aorta and iliac arteries (30% of symptomatic patients), the femoral and popliteal arteries (80–90% of patients), and the more distal vessels, including the tibial and peroneal arteries (40–50% of patients). Atherosclerotic lesions occur preferentially at arterial branch points, which are sites of increased turbulence, altered shear stress, and intimal injury. Involvement of the distal vasculature is most common in elderly individuals and patients with diabetes mellitus.

Clinical Evaluation Fewer than 50% of patients with PAD are symptomatic, although many have a slow or impaired gait. The most common *symptom* is intermittent claudication, which is defined as a pain, ache, cramp, numbness, or a sense of fatigue in the muscles; it occurs during exercise and is relieved by rest. The site of claudication is distal to the location of the occlusive lesion. For example, buttock, hip, thigh, and calf discomfort occurs in patients with aortoiliac disease, whereas calf claudication develops in patients with femoral-popliteal disease. Symptoms are far more common in the lower than in the upper extremities because of the higher incidence of obstructive lesions in the former region. In patients with severe arterial occlusive disease in whom resting blood flow cannot accommodate basal nutritional needs of the tissues, critical limb ischemia may develop. Patients complain of rest pain or a feeling of cold or numbness in the foot and toes. Frequently, these symptoms occur at night when the legs are horizontal and improve when the legs are in a dependent position. With severe ischemia, rest pain may be persistent.

Important *physical findings* of PAD include decreased or absent pulses distal to the obstruction, the presence of bruits over the narrowed artery, and muscle atrophy. With more severe disease, hair loss, thickened nails, smooth and shiny skin, reduced skin temperature, and pallor or cyanosis are common physical signs. In patients with critical limb ischemia, ulcers or gangrene may occur. Elevation of the legs and repeated flexing of the calf muscles produce pallor of the soles of the feet, whereas rubor, secondary to reactive hyperemia, may develop when the legs are dependent. The time required for rubor to develop or for the veins in the foot to fill when the patient's legs are transferred from an elevated to a dependent position is related to the severity of the ischemia and the presence of collateral vessels. Patients with severe ischemia may develop peripheral edema because they keep their legs in a dependent position much of the time. Ischemic neuropathy can result in numbness and hyporeflexia.

Noninvasive Testing The history and physical examination are often sufficient to establish the diagnosis of PAD. An objective assessment of the presence and severity of disease is obtained by noninvasive techniques. Arterial pressure can be recorded noninvasively in the legs by placement of sphygmomanometric cuffs at the ankles and the use of a Doppler device to auscultate or record blood flow from the dorsalis pedis and posterior tibial arteries. Normally, systolic blood pressure in the legs and arms is similar. Indeed, ankle pressure may be slightly higher than arm pressure due to pulse-wave amplification. In the presence of hemodynamically significant stenoses, the systolic blood pressure in the leg is decreased. Thus, the ratio of the ankle and brachial artery pressures (termed the *ankle:brachial index*, or ABI) is 1.00–1.40 in normal individuals. ABI values of 0.91–0.99 are considered "borderline," and those <0.90 are abnormal and diagnostic of PAD. ABIs >1.40 indicate noncompressible arteries secondary to vascular calcification.

Other noninvasive tests include segmental pressure measurements, segmental pulse volume recordings, duplex ultrasonography (which combines B-mode imaging and Doppler flow velocity waveform analysis), transcutaneous oximetry, and stress testing (usually using a treadmill). Placement of pneumatic cuffs enables assessment of systolic pressure along the legs. The presence of pressure gradients between sequential cuffs provides evidence of the presence and location of hemodynamically significant stenoses. In addition, the amplitude of the pulse volume contour becomes blunted in the presence of significant PAD. Duplex ultrasonography is used to image and detect stenotic lesions in native arteries and bypass grafts.

Treadmill testing allows the physician to assess functional limitations objectively. Decline of the ABI immediately after exercise provides further support for the diagnosis of PAD in patients with equivocal symptoms and findings on examination.

Magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and conventional catheter-based angiography should not be used for routine diagnostic testing, but are performed before potential revascularization (Fig. 275-1). Each test is useful in defining the anatomy to assist planning for endovascular and surgical revascularization procedures.

Prognosis The natural history of patients with PAD is influenced primarily by the extent of coexisting coronary artery and

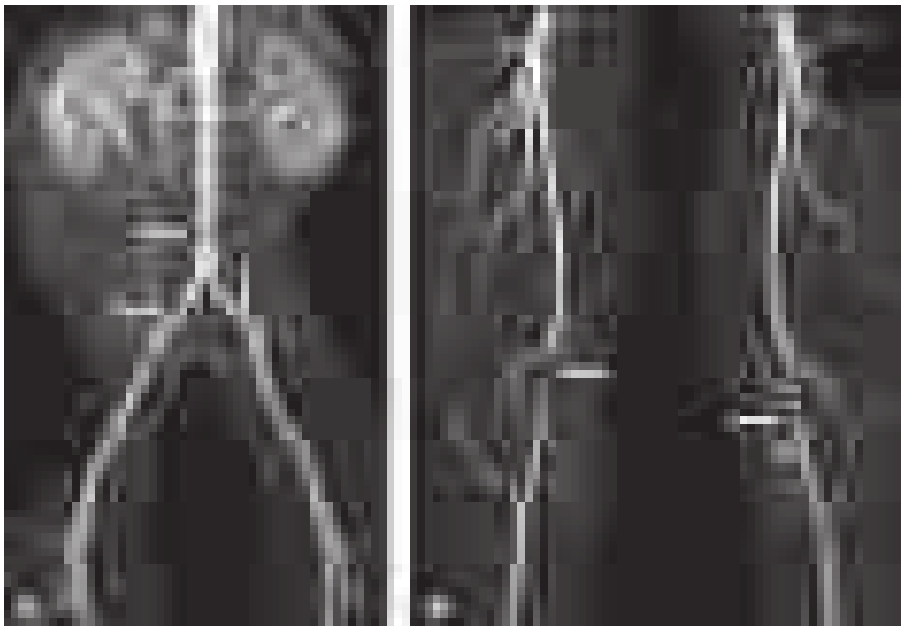

FIGURE 275-1 Magnetic resonance angiography of a patient with intermittent claudication, showing stenoses of the distal abdominal aorta and right common iliac artery (***A***) and stenoses of the right and left superficial femoral arteries (***B***). *(Courtesy of Dr. Edwin Gravereaux, with permission.)*

cerebrovascular disease. Approximately one-third to one-half of patients with symptomatic PAD have evidence of coronary artery disease (CAD) based on clinical presentation and electrocardiogram, and over one-half have significant CAD by coronary angiography. Patients with PAD have a 15–25% 5-year mortality rate and a two- to sixfold increased risk of death from coronary heart disease. Mortality rates are highest in those with the most severe PAD. Measurement of ABI is useful for detecting PAD and identifying persons at risk for future atherothrombotic events. The likelihood of symptomatic progression of PAD is lower than the chance of succumbing to CAD. Approximately 75–80% of nondiabetic patients who present with mild to moderate claudication remain symptomatically stable. Deterioration is likely to occur in the remainder, with ~1–2% of the group ultimately developing critical limb ischemia each year. Approximately 25–30% of patients with critical limb ischemia undergo amputation within 1 year. The prognosis is worse in patients who continue to smoke cigarettes or have diabetes mellitus.

TREATMENT

Peripheral Artery Disease

Patients with PAD should receive therapies to reduce the risk of associated cardiovascular events, such as myocardial infarction and death, and to improve limb symptoms, prevent progression to critical limb ischemia, and preserve limb viability. Risk factor modification and antiplatelet therapy should be initiated to improve cardiovascular outcomes. The importance of discontinuing cigarette smoking cannot be overemphasized. The physician must assume a major role in this lifestyle modification. Counseling and adjunctive drug therapy with the nicotine patch, bupropion, or varenicline increase smoking cessation rates and reduce recidivism. It is important to control blood pressure in hypertensive patients. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may reduce the risk of cardiovascular events in patients with symptomatic PAD. β-Adrenergic blockers do not worsen claudication and may be used to treat hypertension, especially in patients with coexistent CAD. Treatment of hypercholesterolemia with statins is advocated to reduce the risk of myocardial infarction, stroke, and death. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends high intensity statin treatment in patients with atherosclerotic disorders, including PAD. Platelet inhibitors, including aspirin and the ADP antagonist, clopidogrel, reduce the risk of adverse cardiovascular events in patients with atherosclerosis and are recommended for patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia or prior lower extremity revascularization. Outcomes with ticagrelor are similar to those with clopidogrel. The benefit of dual antiplatelet therapy with both aspirin and clopidogrel compared with aspirin alone in reducing cardiovascular morbidity and mortality rates in patients with PAD is uncertain. When added to other antiplatelet therapy, vorapaxar, a protease activated receptor-1 antagonist that inhibits thrombin-mediated platelet activation, decreases the risk of adverse cardiovascular events in patients with atherosclerosis, including PAD. It also reduces the risk of acute limb ischemia and peripheral revascularization; however, it is associated with an increased rate of moderate bleeding. The anticoagulant warfarin is as effective as antiplatelet therapy in preventing adverse cardiovascular events but causes more major bleeding; therefore, it is not indicated to improve outcomes in patients with chronic PAD. The combination of a low dose of the oral factor Xa inhibitor, rivaroxaban, and aspirin improves cardiovascular outcomes in patients with established atherosclerosis, including PAD, but is associated with increased risk of bleeding.

Therapies for intermittent claudication and critical limb ischemia include supportive measures, medications, exercise training, endovascular interventions, and surgery. Supportive measures include meticulous care of the feet, which should be kept clean and protected against excessive drying with moisturizing creams. Well-fitting and protective shoes are advised to reduce trauma. Elastic support hose should be avoided, as it reduces blood flow to the skin. In patients with critical limb ischemia, shock blocks under the head of the bed together with a canopy over the feet may improve perfusion pressure and ameliorate some of the rest pain.

Patients with claudication should be encouraged to exercise regularly and at progressively more strenuous levels. Supervised exercise training programs for 30- to 45-min sessions, three to five times per week for at least 12 weeks, prolong walking distance. The beneficial effect of supervised exercise training on walking performance in patients with claudication often is similar to or greater than that realized after a revascularization procedure. Structured home and community-based exercise programs are also effective. Pharmacologic treatment of PAD has not been as successful as the medical treatment of CAD (Chap. 267). In particular, vasodilators as a class have not proved to be beneficial. During exercise, peripheral

vasodilation occurs distal to sites of significant arterial stenoses. As a result, perfusion pressure falls, often to levels lower than that generated in the interstitial tissue by the exercising muscle. Drugs such as α-adrenergic blocking agents, calcium channel antagonists, and other vasodilators have not been shown to be effective in patients with PAD.

Cilostazol, a phosphodiesterase inhibitor with vasodilator and antiplatelet properties, increases claudication distance by 40–60% and improves measures of quality of life. The mechanism of action accounting for its beneficial effects is not known. Pentoxifylline, a substituted xanthine derivative, increases blood flow to the microcirculation and enhances tissue oxygenation. Although several placebo-controlled studies have found that pentoxifylline modestly increases the duration of exercise, its efficacy has not been confirmed in other clinical trials. Statins appeared effective for treatment of intermittent claudication in initial clinical trials, but more studies are needed to confirm the efficacy of this class of drugs.

There is no definitive medical therapy for critical limb ischemia. Vasodilator prostaglandins are not effective in relieving symptoms or preventing limb loss. Enthusiasm for therapy with angiogenic growth factors abated when clinical trials of intramuscular gene transfer of DNA encoding vascular endothelial growth factor, fibroblast growth factor, hepatocyte growth factor, or hypoxia-inducible factor 1α failed to demonstrate improvement in symptoms or outcomes in patients with intermittent claudication or critical limb ischemia. Most clinical trials of bone marrow–derived vascular progenitor cells to promote angiogenesis and preserve limb viability in patients with critical limb ischemia have failed to demonstrate benefit, though a meta-analysis of these trials suggested a modest reduction in the risk of amputation. This remains an active area of preclinical and clinical investigation.

REVASCULARIZATION

Revascularization procedures, including catheter-based and surgical interventions, are usually indicated for patients with disabling, progressive, or severe symptoms of intermittent claudication despite medical therapy in order to improve walking distance and functional capacity. These are also indicated in patients with critical limb ischemia to relieve pain and prevent limb loss. MRA, CTA, or conventional angiography should be performed to assess vascular anatomy in patients who are being considered for revascularization. Endovascular interventions include percutaneous transluminal balloon angioplasty (PTA) (including drug coated balloons), stent placement (including drug eluting stents), stent grafts, and atherectomy **(Chap. 270)**. When endovascular intervention is performed in conjunction with a supervised exercise program, walking distance improves more than with exercise training alone.

PTA and stenting of the iliac artery are associated with higher success rates than are PTA and stenting of the femoral and popliteal arteries. Approximately 90–95% of iliac PTAs are initially successful, and the 3-year patency rate is >75%. Patency rates may be higher if a stent is placed in the iliac artery. The initial success rate for femoral-popliteal PTA and stenting approximate 90% with 60% 3-year patency rates. Outcomes following stenting of longer femoral-popliteal lesions (>5–10 cm) generally are better than after PTA. Several clinical trials have found lower restenosis rates with drug-coated balloons than with PTA, and with drug eluting stents compared with bare metal stents. Patency rates are influenced by the severity and length of pretreatment stenoses; the prognosis of occlusive lesions is worse than that of nonocclusive stenotic lesions. Endovascular interventions of the infrapoplital, tibial, and peroneal arteries, often in conjunction with treatment of more proximal lesions, can be used to treat critical limb ischemia and prevent limb loss.

Several operative procedures are available for treating patients with aortoiliac and femoral-popliteal artery disease. The preferred operative procedure depends on the location and extent of the obstruction(s) and the general medical condition of the patient. Operative procedures for aortoiliac disease include aortobifemoral bypass, axillofemoral bypass, femoro-femoral bypass, and aortoiliac endarterectomy. The most frequently used procedure is the aortobifemoral bypass using knitted Dacron grafts. Immediate graft patency approaches 99%, and 5- and 10-year graft patency rates in survivors are >90% and 80%, respectively. Operative complications include myocardial infarction and stroke, infection of the graft, peripheral embolization, and sexual dysfunction from interruption of autonomic nerves in the pelvis. The operative mortality rate ranges from 1 to 3%, mostly due to ischemic heart disease.

Operative therapy for femoral-popliteal artery disease includes in situ and reverse autogenous saphenous vein bypass grafts, placement of polytetrafluoroethylene (PTFE) or other synthetic grafts, and thromboendarterectomy. The operative mortality rate ranges from 1 to 3%. The long-term patency rate depends on the type of graft used, the location of the distal anastomosis, and the patency of runoff vessels beyond the anastomosis. Patency rates of femoral-popliteal saphenous vein bypass grafts approach 90% at 1 year and 70–80% at 5 years. Five-year patency rates of infrapopliteal saphenous vein bypass grafts are 60–70%. In contrast, 5-year patency rates of infrapopliteal PTFE grafts are <30%.

Preoperative cardiac risk assessment may identify individuals who are especially likely to experience an adverse cardiac event during the perioperative period. Patients with angina, prior myocardial infarction, heart failure, diabetes, or renal insufficiency are among those at increased risk. Stress testing with treadmill exercise (if feasible), radionuclide myocardial perfusion imaging, or echocardiography permits further stratification of risk in these patients, particularly those with poor or unknown functional capacity **(Chap. 270)**. Patients with abnormal test results require close supervision and adjunctive management with anti-ischemic medications. Coronary angiography and coronary artery revascularization compared with optimal medical therapy do not improve outcomes in most patients undergoing peripheral vascular surgery, but cardiac catheterization should be considered in patients with unstable angina and angina refractory to medical therapy as well as those suspected of having left main or three-vessel CAD.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia is a hyperplastic disorder that affects medium-size and small arteries. It occurs predominantly in females and usually involves the renal and carotid arteries but can affect extremity vessels such as the iliac and subclavian arteries. The histologic classification includes intimal fibroplasia (also classified as focal), medial dysplasia (multifocal), and adventitial hyperplasia. Medial dysplasia is subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Medial fibroplasia is the most common type and is characterized by alternating areas of thinned media and fibromuscular ridges. The internal elastic lamina usually is preserved. The iliac arteries are the limb arteries most likely to be affected by fibromuscular dysplasia. It is identified angiographically by a "string of beads" appearance caused by thickened fibromuscular ridges contiguous with thin, less-involved portions of the arterial wall, which is typical of medial fibroplasia, or less commonly, as a focal tubular stenosis, and which is more typical of intimal fibroplasia. When limb vessels are involved, clinical manifestations are similar to those for atherosclerosis, including claudication and rest pain. PTA and surgical reconstruction have been beneficial in patients with debilitating symptoms or threatened limbs.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's disease) is an inflammatory occlusive vascular disorder involving small and medium-size arteries and veins in the distal upper and lower extremities. Cerebral, visceral, and coronary vessels may be affected rarely. This disorder develops most frequently in men <40 years of age. The prevalence is higher in Asians and individuals of Eastern European descent. Although the cause of thromboangiitis obliterans is not known, there is a definite relationship to cigarette smoking in patients with this disorder.

In the initial stages of thromboangiitis obliterans, polymorphonuclear leukocytes infiltrate the walls of the small and medium-size

arteries and veins. The internal elastic lamina is preserved, and a cellular, inflammatory thrombus develops in the vascular lumen. As the disease progresses, mononuclear cells, fibroblasts, and giant cells replace the neutrophils. Later stages are characterized by perivascular fibrosis, organized thrombus, and recanalization.

The clinical features of thromboangiitis obliterans often include a triad of claudication of the affected extremity, Raynaud's phenomenon, and migratory superficial vein thrombophlebitis. Claudication usually is confined to the calves and feet or the forearms and hands because this disorder primarily affects distal vessels. In the presence of severe digital ischemia, trophic nail changes, painful ulcerations, and gangrene may develop at the tips of the fingers or toes. The physical examination shows normal brachial and popliteal pulses but reduced or absent radial, ulnar, and/or tibial pulses. MRA, CTA, and conventional arteriography are helpful in making the diagnosis. Smooth, tapering segmental lesions in the distal vessels are characteristic, as are collateral vessels at sites of vascular occlusion. Proximal atherosclerotic disease is usually absent. The diagnosis can be confirmed by excisional biopsy and pathologic examination of an involved vessel.

There is no specific treatment except abstention from tobacco. The prognosis is worse in individuals who continue to smoke, but results are discouraging even in those who stop smoking. Arterial bypass of the larger vessels may be used in selected instances, as well as local debridement, depending on the symptoms and severity of ischemia. Antibiotics may be useful; anticoagulants and glucocorticoids are not helpful. If these measures fail, amputation may be required.

VASCULITIS

Other vasculitides may affect the arteries that supply the upper and lower extremities. **Takayasu's arteritis and giant cell (temporal) arteritis are discussed in Chap. 356.**

ACUTE LIMB ISCHEMIA

Acute limb ischemia occurs when arterial occlusion results in the sudden cessation of blood flow to an extremity. The severity of ischemia and the viability of the extremity depend on the location and extent of the occlusion and the presence and subsequent development of collateral blood vessels. Principal causes of acute arterial occlusion include embolism, thrombus in situ, arterial dissection, and trauma.

The most common sources of arterial emboli are the heart, aorta, and large arteries. Cardiac disorders that cause thromboembolism include atrial fibrillation; acute myocardial infarction; ventricular aneurysm; cardiomyopathy; infectious and marantic endocarditis; thrombi associated with prosthetic heart valves; and atrial myxoma. Emboli to the distal vessels may also originate from proximal sites of atherosclerosis and aneurysms of the aorta and large vessels. Less frequently, an arterial occlusion results paradoxically from a venous thrombus that has entered the systemic circulation via a patent foramen ovale or another septal defect. Arterial emboli tend to lodge at vessel bifurcations because the vessel caliber decreases at those sites; in the lower extremities, emboli lodge most frequently in the femoral artery, followed by the iliac artery, aorta, and popliteal and tibioperoneal arteries.

Acute arterial thrombosis in situ occurs most frequently in atherosclerotic vessels at the site of an atherosclerotic plaque or aneurysm and in arterial bypass grafts. Trauma to an artery may disrupt continuity of blood flow and cause acute limb ischemia via formation of an acute arterial thrombus or by disruption of an artery's integrity and extravasation of blood. Arterial occlusion may complicate arterial punctures and placement of catheters; it also may result from arterial dissection if the intimal flap obstructs the artery. Less common causes include thoracic outlet compression syndrome, which causes subclavian artery occlusion, and entrapment of the popliteal artery by abnormal placement of the medial head of the gastrocnemius muscle. Polycythemia and hypercoagulable disorders **(Chaps. 99 and 112)** are also associated with acute arterial thrombosis.

CLINICAL FEATURES

The symptoms of an acute arterial occlusion depend on the location, duration, and severity of the obstruction. Often severe pain, paresthesia, numbness, and coldness develop in the involved extremity within 1 h. Paralysis may occur with severe and persistent ischemia. Physical findings include loss of pulses distal to the occlusion, cyanosis or pallor, mottling, decreased skin temperature, muscle stiffening, loss of sensation, weakness, and/or absent deep tendon reflexes. If acute arterial occlusion occurs in the presence of an adequate collateral circulation, as is often the case in acute graft occlusion, the symptoms and findings may be less severe. In this situation, the patient complains about an abrupt decrease in the distance walked before claudication occurs or of modest pain and paresthesia. Pallor and coolness are evident, but sensory and motor functions generally are preserved. The clinical evaluation includes Doppler assessment of peripheral blood flow. The diagnosis of acute limb ischemia is usually apparent from the clinical presentation. In most circumstances, MRA, CTA, or catheter-based arteriography is used to confirm the diagnosis and demonstrate the location and extent of arterial occlusion.

TREATMENT

Acute Limb Ischemia

Once the diagnosis is made, the patient should be anticoagulated with intravenous heparin to prevent propagation of the clot and recurrent embolism. In cases of severe ischemia of recent onset, particularly when limb viability is jeopardized, immediate intervention to ensure reperfusion is indicated. Catheter-directed thrombolysis/thrombectomy, surgical thromboembolectomy, and arterial bypass procedures are used to restore blood flow to the ischemic extremity promptly, particularly when a large proximal vessel is occluded.

Intraarterial thrombolytic therapy with recombinant tissue plasminogen activator, reteplase, or tenecteplase is most effective when acute arterial occlusion is recent (<2 weeks) and caused by a thrombus in an atherosclerotic vessel, arterial bypass graft, or occluded stent. Thrombolytic therapy is also indicated when the patient's overall condition contraindicates surgical intervention or when smaller distal vessels are occluded, thus preventing surgical access. Meticulous observation for hemorrhagic complications is required during intraarterial thrombolytic therapy. Another endovascular approach to thrombus removal is percutaneous mechanical thrombectomy using devices that employ hydrodynamic forces or rotating baskets to fragment and remove the clot. These treatments may be used alone but usually are used in conjunction with pharmacologic thrombolysis. Surgical revascularization is preferred when restoration of blood flow must occur within 24 h to prevent limb loss or when symptoms of occlusion have been present for >2 weeks. Amputation is performed when the limb is not viable, as characterized by loss of sensation, paralysis, and the absence of Doppler-detected blood flow in both arteries and veins.

Long-term anticoagulation is indicated when acute limb ischemia is caused by cardiac thromboembolism. Emboli resulting from infective endocarditis, the presence of prosthetic heart valves, or atrial myxoma often require surgical intervention to remove the cause.

ATHEROEMBOLISM

Atheroembolism is another cause of limb ischemia. In this condition, multiple small deposits of fibrin, platelets, and cholesterol debris embolize from proximal atherosclerotic lesions or aneurysmal sites. Large protruding aortic atheromas are a source of emboli that may lead to limb ischemia, as well as stroke and renal insufficiency. Atheroembolism may occur after intraarterial procedures. Since atheroemboli to limbs tend to lodge in the small vessels of the muscle and skin and may not occlude the large vessels, distal pulses usually remain palpable. Patients complain of acute pain and tenderness at the site of embolization. Digital vascular occlusion may result in ischemia and the "blue toe" syndrome; digital necrosis and gangrene may develop **(Fig. 275-2)**. Localized areas of tenderness, pallor, and livedo reticularis (see below) occur at sites of emboli. Skin or muscle biopsy may demonstrate cholesterol crystals.

Ischemia resulting from atheroemboli is notoriously difficult to treat. Local foot care and occasionally amputation may be needed to

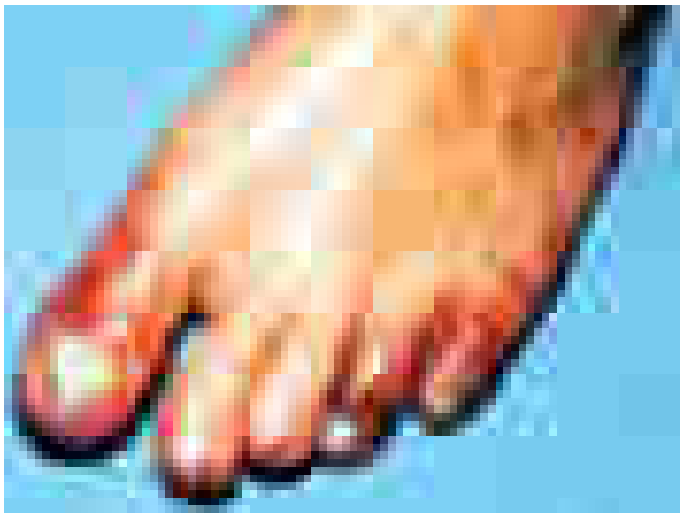

FIGURE 275-2 Atheroembolism causing cyanotic discoloration and impending necrosis of the toes ("blue toe" syndrome).

treat necrotic areas. Analgesics are indicated for pain relief. Usually neither surgical revascularization procedures nor thrombolytic therapy is helpful because of the multiplicity, composition, and distal location of the emboli. Therapy with antiplatelet drugs and statins improves cardiovascular outcome in patients with atherosclerosis, but it is not established whether either class of drugs prevents recurrent atheroembolism. Similarly, it is not known whether anticoagulant therapy is effective. Surgical intervention to remove or bypass the atherosclerotic vessel or aneurysm that causes the recurrent atheroemboli may be necessary.

THORACIC OUTLET COMPRESSION SYNDROME

This is a symptom complex resulting from compression of the neurovascular bundle (artery, vein, or nerves) at the thoracic outlet as it courses through the neck and shoulder. Cervical ribs, abnormalities of the scalenus anticus muscle, proximity of the clavicle to the first rib, or abnormal insertion of the pectoralis minor muscle may compress the subclavian artery, subclavian vein, and brachial plexus as these structures pass from the thorax to the arm. Depending on the structures affected, thoracic outlet compression syndrome is divided into arterial, venous, and neurogenic forms. Patients with neurogenic thoracic outlet compression may develop shoulder and arm pain, weakness, and paresthesias. Patients with arterial compression may experience claudication, Raynaud's phenomenon, and even ischemic tissue loss and gangrene. Venous compression may cause thrombosis of the subclavian and axillary veins; this is often associated with effort and is referred to as *Paget-Schroetter syndrome.*

APPROACH TO THE PATIENT

Thoracic Outlet Compression Syndrome

Examination of a patient with arterial thoracic outlet compression syndrome is often normal unless provocative maneuvers are performed. Occasionally, distal pulses are decreased or absent and digital cyanosis and ischemia may be evident.

Several maneuvers that support the diagnosis of arterial thoracic outlet compression syndrome may be used to precipitate symptoms, cause a subclavian artery bruit, and diminish arm pulses. These maneuvers include the abduction and external rotation test, in which the affected arm is abducted by 90° and the shoulder is externally rotated; the scalene maneuver (extension of the neck and rotation of the head to the side of the symptoms); the costoclavicular maneuver (posterior rotation of shoulders); and the hyperabduction maneuver (raising the arm 180°). A chest x-ray will indicate the presence of cervical ribs. Duplex ultrasonography, MRA, and contrast angiography can be performed during provocative maneuvers to demonstrate thoracic outlet compression of the subclavian artery. Neurophysiologic tests such as the electromyogram, nerve conduction studies, and somatosensory evoked potentials may be abnormal if the brachial plexus is involved, but the diagnosis of neurogenic thoracic outlet syndrome is not necessarily excluded if these tests are normal owing to their low sensitivity.

Most patients can be managed conservatively. They should be advised to avoid the positions that cause symptoms. Many patients benefit from shoulder girdle exercises. Surgical procedures such as removal of the first rib and resection of the scalenus anticus muscle are necessary occasionally for relief of symptoms or treatment of ischemia.

POPLITEAL ARTERY ENTRAPMENT

Popliteal artery entrapment typically affects young athletic men and women when the gastrocnemius or popliteus muscle compresses the popliteal artery and causes intermittent claudication. Thrombosis, embolism, or popliteal artery aneurysm may occur. The pulse examination may be normal unless provocative maneuvers such as ankle dorsiflexion and plantar flexion are performed. The diagnosis is confirmed by duplex ultrasound, CTA, MRA, or conventional angiography. Treatment involves surgical release of the popliteal artery or vascular reconstruction.

POPLITEAL ARTERY ANEURYSM

Popliteal artery aneurysms are the most common peripheral artery aneurysms. Approximately 50% are bilateral. Patients with popliteal artery aneurysms often have aneurysms of other arteries, especially the aorta. The most common clinical presentation is limb ischemia secondary to thrombosis or embolism. Rupture occurs less frequently. Other complications include compression of the adjacent popliteal vein or peroneal nerve. Popliteal artery aneurysm can be detected by palpation and confirmed by duplex ultrasonography. Repair is indicated for symptomatic aneurysms or when the diameter exceeds 2–3 cm, owing to the risk of thrombosis, embolism, or rupture.

ARTERIOVENOUS FISTULA

Abnormal communications between an artery and a vein, bypassing the capillary bed, may be congenital or acquired. Congenital arteriovenous fistulas are a result of persistent embryonic vessels that fail to differentiate into arteries and veins; they may be associated with birthmarks, can be located in almost any organ of the body, and frequently occur in the extremities. Acquired arteriovenous fistulas either are created to provide vascular access for hemodialysis or occur as a result of a penetrating injury such as a gunshot or knife wound or as complications of arterial catheterization or surgical dissection. An uncommon cause of arteriovenous fistula is rupture of an arterial aneurysm into a vein.

The clinical features depend on the location and size of the fistula. Frequently, a pulsatile mass is palpable, and a thrill and a bruit lasting throughout systole and diastole are present over the fistula. With long-standing fistulas, clinical manifestations of chronic venous insufficiency, including peripheral edema; large, tortuous varicose veins; and stasis pigmentation become apparent because of the high venous pressure. Evidence of ischemia may occur in the distal portion of the extremity. Skin temperature is higher over the arteriovenous fistula. Large arteriovenous fistulas may result in an increased cardiac output with consequent cardiomegaly and high-output heart failure (Chap. 252).

The diagnosis is often evident from the physical examination. Compression of a large arteriovenous fistula may cause reflex slowing of the heart rate (Nicoladoni-Branham sign). Duplex ultrasonography may detect an arteriovenous fistula, especially one that affects the femoral artery and vein at the site of catheter access. CTA and conventional angiography can confirm the diagnosis and are useful in demonstrating the site and size of the arteriovenous fistula.

Management of arteriovenous fistulas may involve surgery, radiotherapy, or embolization. Congenital arteriovenous fistulas are often difficult to treat because the communications may be numerous and extensive, and new communications frequently develop after ligation

of the most obvious ones. Many of these lesions are best treated conservatively using elastic support hose to reduce the consequences of venous hypertension. Occasionally, embolization with autologous material, such as fat or muscle, or with hemostatic agents, such as gelatin sponges or silicon spheres, is used to obliterate the fistula. Acquired arteriovenous fistulas are usually amenable to surgical treatment that involves division or excision of the fistula. Occasionally, autogenous or synthetic grafting is necessary to reestablish continuity of the artery and vein.

RAYNAUD'S PHENOMENON

Raynaud's phenomenon is characterized by episodic digital ischemia, manifested clinically by the sequential development of digital blanching, cyanosis, and rubor of the fingers or toes after cold exposure and subsequent rewarming. Emotional stress may also precipitate Raynaud's phenomenon. The color changes are usually well demarcated and are confined to the fingers or toes. Typically, one or more digits will appear white when the patient is exposed to a cold environment or touches a cold object **(Fig. 275-3*A*)**. The blanching, or pallor, represents the ischemic phase of the phenomenon and results from vasospasm of digital arteries. During the ischemic phase, capillaries and venules dilate, and cyanosis results from the deoxygenated blood that is present in these vessels. A sensation of cold or numbness or paresthesia of the digits often accompanies the phases of pallor and cyanosis.

With rewarming, the digital vasospasm resolves, and blood flow into the dilated arterioles and capillaries increases dramatically. This "reactive hyperemia" imparts a bright red color to the digits. In addition to rubor and warmth, patients often experience a throbbing, painful sensation during the hyperemic phase. Although the triphasic color response is typical of Raynaud's phenomenon, some patients may develop only pallor and cyanosis; others may experience only cyanosis.

TABLE 275-1 Classification of Raynaud's Phenomenon

Primary or idiopathic Raynaud's phenomenon
Secondary Raynaud's phenomenon
Collagen vascular diseases: scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis, mixed connective tissue disease, Sjögren's syndrome
Arterial occlusive diseases: atherosclerosis of the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome
Pulmonary hypertension
Neurologic disorders: intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome, complex regional pain syndrome
Blood dyscrasias: cold agglutinins, cryoglobulinemia, cryofibrinogenemia, myeloproliferative disorders, lymphoplasmacytic lymphoma
Trauma: vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing
Drugs and toxins: ergot derivatives, methysergide, β-adrenergic receptor blockers, bleomycin, vinblastine, cisplatin, gemcitabine, vinyl chloride

Raynaud's phenomenon is broadly separated into two categories: idiopathic, termed primary Raynaud's phenomenon, and secondary Raynaud's phenomenon, which is associated with other disease states or known causes of vasospasm **(Table 275-1)**.

Primary Raynaud's Phenomenon This appellation is applied when the secondary causes of Raynaud's phenomenon have been excluded. Over 50% of patients with Raynaud's phenomenon have the primary form. Women are affected about five times more often than men, and the age of presentation is usually between 20 and 40 years. The fingers are involved more frequently than the toes. Initial episodes

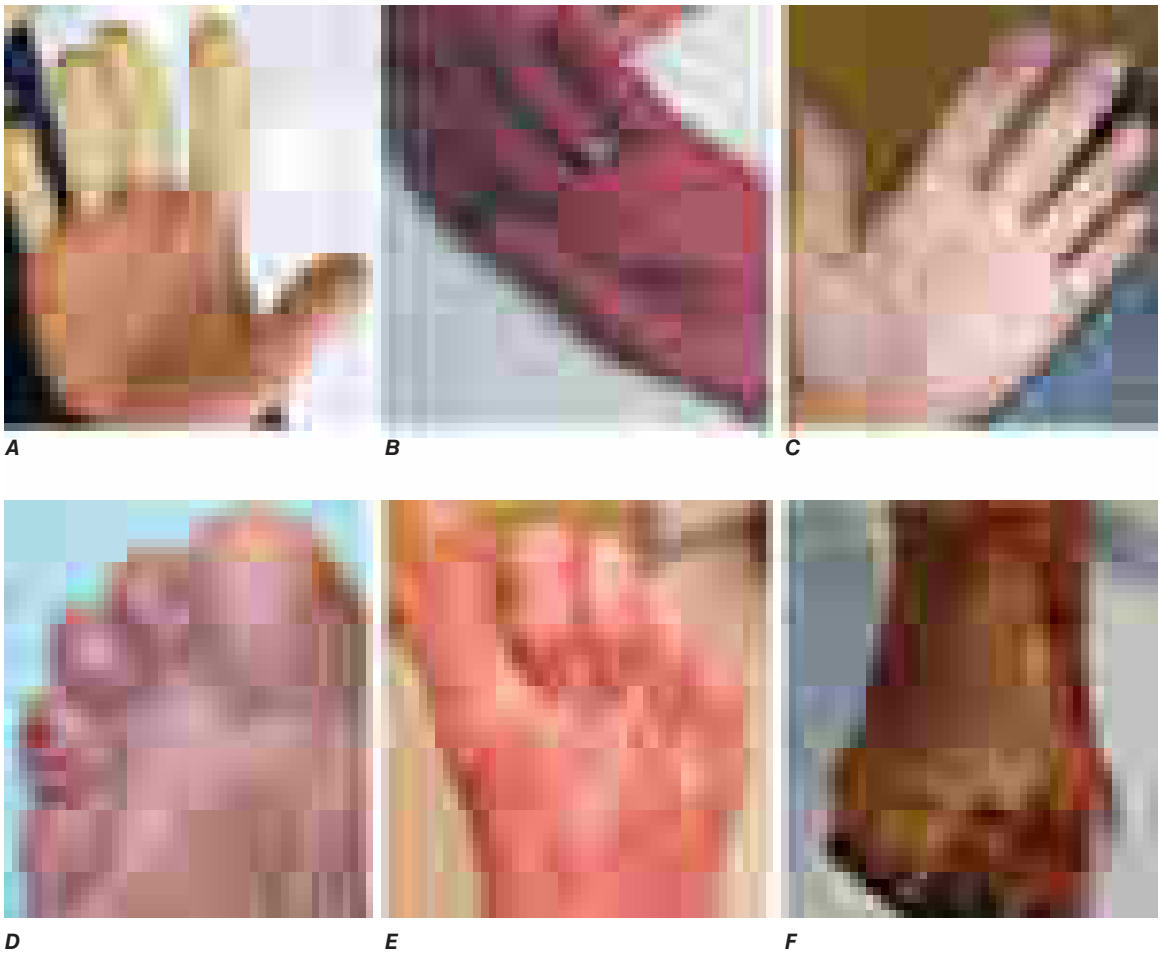

FIGURE 275-3 Vascular diseases associated with temperature: ***A.*** Raynaud's phenomenon; ***B.*** acrocyanosis; ***C.*** livedo reticularis; ***D.*** pernio; ***E.*** erythromelalgia; and ***F.*** frostbite.

may involve only one or two fingertips, but subsequent attacks may involve the entire finger and may include all the fingers. The toes are affected in 40% of patients. Although vasospasm of the toes usually occurs in patients with symptoms in the fingers, it may happen alone. Rarely, the earlobes, the tip of the nose, tongue, nipple, or penis are involved. Raynaud's phenomenon occurs frequently in patients who also have migraine headaches or variant angina. These associations suggest that there may be a common predisposing cause for the vasospasm.

Results of physical examination are often entirely normal; the radial, ulnar, and pedal pulses are normal. The fingers and toes may be cool between attacks and may perspire excessively. Nailfold capillaroscopy reveals normal superficial capillaries, which appear as regularly spaced hairpin loops. Thickening and tightening of the digital subcutaneous tissue (*sclerodactyly*) develop in 10% of patients. Angiography of the digits for diagnostic purposes is not indicated.

In general, patients with primary Raynaud's disease have milder clinical manifestations. Fewer than 1% of these patients lose a part of a digit. After the diagnosis is made, the disease improves spontaneously in ~15% of patients and progresses in about 30%.

Secondary Causes of Raynaud's Phenomenon Raynaud's phenomenon occurs in 80–90% of patients with systemic sclerosis (scleroderma) and is the presenting symptom in 30% **(Chap. 353)**. It may be the only symptom of scleroderma for many years. Abnormalities of the digital vessels may contribute to the development of Raynaud's phenomenon in this disorder. Ischemic fingertip ulcers may develop and progress to gangrene and autoamputation. About 20% of patients with systemic lupus erythematosus (SLE) have Raynaud's phenomenon **(Chap. 349)**. Occasionally, persistent digital ischemia develops and may result in ulcers or gangrene. In most severe cases, the small vessels are occluded by a proliferative endarteritis. Raynaud's phenomenon occurs in about 30% of patients with dermatomyositis or polymyositis **(Chap. 358)**. It frequently develops in patients with rheumatoid arthritis and may be related to the intimal proliferation that occurs in the digital arteries.

Atherosclerosis of the extremities is a common cause of Raynaud's phenomenon in men aged >50 years. Thromboangiitis obliterans is an uncommon cause of Raynaud's phenomenon but should be considered in young men, particularly those who are cigarette smokers. The development of cold-induced pallor in these disorders may be confined to one or two digits of the involved extremity. Occasionally, Raynaud's phenomenon may follow acute occlusion of large and medium-sized arteries by a thrombus or embolus. Embolization of atheroembolic debris may cause digital ischemia. The latter situation often involves one or two digits and should not be confused with Raynaud's phenomenon. In patients with thoracic outlet compression syndrome, Raynaud's phenomenon may result from diminished intravascular pressure, stimulation of sympathetic fibers in the brachial plexus, or a combination of both. Raynaud's phenomenon occurs in patients with primary pulmonary hypertension **(Chap. 277)**; this is more than coincidental and may reflect a neurohumoral abnormality that affects both the pulmonary and digital circulations.

A variety of blood dyscrasias may be associated with Raynaud's phenomenon. Cold-induced precipitation of plasma proteins, hyperviscosity, and aggregation of red cells and platelets may occur in patients with cold agglutinins, cryoglobulinemia, or cryofibrinogenemia. Hyperviscosity syndromes that accompany myeloproliferative disorders and lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia) should also be considered in the initial evaluation of patients with Raynaud's phenomenon.

Raynaud's phenomenon occurs often in patients whose vocations require the use of vibrating hand tools, such as chain saws or jackhammers. The frequency of Raynaud's phenomenon also seems to be increased in pianists and keyboard operators. Electric shock injury to the hands or frostbite may lead to the later development of Raynaud's phenomenon.

Several drugs have been causally implicated in Raynaud's phenomenon. They include ergot preparations, methysergide, β-adrenergic receptor antagonists, and the chemotherapeutic agents bleomycin, vinblastine, cisplatin, and gemcitabine.

TREATMENT

Raynaud's Phenomenon

Most patients with Raynaud's phenomenon experience only mild and infrequent episodes. These patients need reassurance and should be instructed to dress warmly and avoid unnecessary cold exposure. In addition to gloves and mittens, patients should protect the trunk, head, and feet with warm clothing to prevent cold-induced reflex vasoconstriction. Tobacco use is contraindicated.

Drug treatment should be reserved for severe cases. Dihydropyridine calcium channel antagonists such as nifedipine, isradipine, felodipine, and amlodipine decrease the frequency and severity of Raynaud's phenomenon. Diltiazem may be considered but is less effective. The postsynaptic α_1-adrenergic antagonist prazosin has been used with favorable responses; doxazosin and terazosin may also be effective. Phosphodiesterase type 5 inhibitors such as sildenafil, tadalafil, and vardenafil may improve symptoms in patients with secondary Raynaud's phenomenon, as occurs with systemic sclerosis. There is limited evidence that topical nitroglycerin preparations are effective. Digital sympathectomy is helpful in some patients who are unresponsive to medical therapy. Injection of botulinum toxin into the perivascular tissue of the wrist or palm improved ischemic manifestations of severe Raynaud's phenomenon in case series, but controlled clinical trials are lacking.

ACROCYANOSIS

In this condition, there is arterial vasoconstriction and secondary dilation of the capillaries and venules with resulting persistent cyanosis of the hands and, less frequently, the feet. Cyanosis may be intensified by exposure to a cold environment. Acrocyanosis may be categorized as primary or secondary to an underlying condition. In primary acrocyanosis, women are affected much more frequently than men, and the age of onset is usually <30 years. Generally, patients are asymptomatic but seek medical attention because of the discoloration. The prognosis is favorable, and pain, ulcers, and gangrene do not occur. Examination reveals normal pulses, peripheral cyanosis, and moist palms **(Fig. 275-3*B*)**. Trophic skin changes and ulcerations do *not* occur. The disorder can be distinguished from Raynaud's phenomenon because it is persistent and not episodic, the discoloration extends proximally from the digits, and blanching does not occur. Ischemia secondary to arterial occlusive disease can usually be excluded by the presence of normal pulses. Central cyanosis and decreased arterial oxygen saturation are not present. Patients should be reassured and advised to dress warmly and avoid cold exposure. Pharmacologic intervention is not indicated.

Secondary acrocyanosis may result from hypoxemia, vasopressor medications, connective tissue diseases, atheroembolism, antiphospholipid antibodies, cold agglutinins, or cryoglobulins and is associated with anorexia nervosa and postural orthostatic tachycardia syndrome. Treatment should be directed at the underlying disorder.

LIVEDO RETICULARIS

In this condition, localized areas of the extremities develop a mottled or rete (netlike) appearance of reddish to blue discoloration **(Fig. 275-3*C*)**. The mottled appearance may be more prominent after cold exposure. There are primary and secondary forms of livedo reticularis. The primary, or idiopathic, form of this disorder may be benign or associated with ulcerations. The benign form occurs more frequently in women than in men, and the most common age of onset is the third decade. Patients with the benign form are usually asymptomatic and seek attention for cosmetic reasons. These patients should be reassured and advised to avoid cold environments. No drug treatment is indicated. Primary livedo reticularis with ulceration is also called *atrophie blanche en plaque*. The ulcers are painful and may take months to heal. Secondary livedo reticularis can occur with atheroembolism (see above), SLE and other vasculitides, antiphospholipid antibodies, hyperviscosity,

cryoglobulinemia, and Sneddon's syndrome (ischemic stroke and livedo reticularis). Rarely, skin ulcerations develop.

PERNIO (CHILBLAINS)

Pernio is a vasculitic disorder associated with exposure to cold; acute forms have been described. Raised erythematous lesions develop on the lower part of the legs and feet in cold weather **(Fig. 275-3*D*)**. They are associated with pruritus and a burning sensation, and they may blister and ulcerate. Pathologic examination demonstrates angiitis characterized by intimal proliferation and perivascular infiltration of mononuclear and polymorphonuclear leukocytes. Giant cells may be present in the subcutaneous tissue. Patients should avoid exposure to cold, and ulcers should be kept clean and protected with sterile dressings. Sympatholytic drugs and dihydropyridine calcium channel antagonists may be effective in some patients.

ERYTHROMELALGIA

This disorder is characterized by burning pain and erythema of the extremities **(Fig. 275-3*E*)**. The feet are involved more frequently than the hands, and males are affected more frequently than females. Erythromelalgia may occur at any age but is most common in middle age. It may be primary (also termed erythermalgia) or secondary. Mutations in the *SCN9A* gene, which encodes the Nav1.7 voltage-gated sodium channel expressed in sensory and sympathetic nerves, has been described in inherited forms of erythromelalgia. The most common causes of secondary erythromelalgia are myeloproliferative disorders such as polycythemia vera and essential thrombocytosis. Less common causes include drugs, such as calcium channel blockers, bromocriptine, and pergolide; neuropathies; connective tissue diseases such as SLE; and paraneoplastic syndromes. Patients complain of burning in the extremities that is precipitated by exposure to a warm environment and aggravated by a dependent position. The symptoms are relieved by exposing the affected area to cool air or water or by elevation. Erythromelalgia can be distinguished from ischemia secondary to peripheral arterial disorders because the peripheral pulses are present. There is no specific treatment; aspirin may produce relief in patients with erythromelalgia secondary to myeloproliferative disease. Treatment of associated disorders in secondary erythromelalgia may be helpful.

FROSTBITE

In this condition, tissue damage results from severe environmental cold exposure or from direct contact with a very cold object. Tissue injury results from both freezing and vasoconstriction. Frostbite usually affects the distal aspects of the extremities or exposed parts of the face, such as the ears, nose, chin, and cheeks. Superficial frostbite involves the skin and subcutaneous tissue. Patients experience pain or paresthesia, and the skin appears white and waxy. After rewarming, there is cyanosis and erythema, wheal-and-flare formation, edema, and superficial blisters. Deep frostbite involves muscle, nerves, and deeper blood vessels. It may result in edema of the hand or foot, vesicles and bullae, tissue necrosis, and gangrene **(Fig. 275-3*F*)**.

Initial treatment is rewarming, performed in an environment where reexposure to freezing conditions will not occur. Rewarming is accomplished by immersion of the affected part in a water bath at temperatures of 40°–44°C (104°–111°F). Massage, application of ice water, and extreme heat are contraindicated. The injured area should be cleansed with soap or antiseptic, and sterile dressings should be applied. Analgesics are often required during rewarming. Antibiotics are used if there is evidence of infection. The efficacy of sympathetic blocking drugs is not established. After recovery, the affected extremity may exhibit increased sensitivity to cold.

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276 Chronic Venous Disease and Lymphedema

Mark A. Creager, Joseph Loscalzo

CHRONIC VENOUS DISEASE

Chronic venous diseases range from telangiectasias and reticular veins, to varicose veins, to chronic venous insufficiency with edema, skin changes, and ulceration. This section of the chapter will focus on identification and treatment of varicose veins and chronic venous insufficiency, since these problems are encountered frequently by the internist. The estimated prevalence of varicose veins in the United States is ~15% in men and 30% in women. Chronic venous insufficiency with edema affects ~7.5% of men and 5% of women, and the prevalence increases with age ranging from 2% among those <50 years of age to 10% of those 70 years of age. Approximately 20% of patients with chronic venous insufficiency develop venous ulcers.

VENOUS ANATOMY

Veins in the extremities can be broadly classified as either superficial or deep. The superficial veins are located between the skin and deep fascia. In the legs, these include the great and small saphenous veins and their tributaries. The great saphenous vein is the longest vein in the body. It originates on the medial side of the foot and ascends anterior to the medial malleolus and then along the medial side of the calf and thigh, and drains into the common femoral vein. The small saphenous vein originates on the dorsolateral aspect of the foot, ascends posterior to the lateral malleolus and along the posterolateral aspect of the calf, and drains into the popliteal vein. The deep veins of the leg accompany the major arteries. There are usually paired peroneal, anterior tibial, and posterior tibial veins in the calf, which converge to form the popliteal vein. Soleal tributary veins drain into the posterior tibial or peroneal veins, and gastrocnemius tributary veins drain into the popliteal vein. The popliteal vein ascends in the thigh as the femoral vein. The confluence of the femoral vein and deep femoral vein form the common femoral vein, which ascends in the pelvis as the external iliac and then common iliac vein, which converges with the contralateral common iliac vein at the inferior vena cava. Perforating veins connect the superficial and deep systems in the legs at multiple locations, normally allowing blood to flow from the superficial to deep veins. In the arms, the superficial veins include the basilic, cephalic, and median cubital veins and their tributaries. The basilic and cephalic veins course along the medial and lateral aspects of the arm, respectively, and these are connected via the median cubital vein in the antecubital fossa. The deep veins of the arms accompany the major arteries and include the radial, ulnar, brachial, axillary, and subclavian veins. The subclavian vein converges with the internal jugular vein to form the brachiocephalic vein, which joins the contralateral brachiocephalic vein to form the superior vena cava. Bicuspid valves are present throughout the venous system to direct the flow of venous blood centrally.

Pathophysiology of Chronic Venous Disease *Varicose veins* are dilated, bulging, tortuous superficial veins, measuring at least 3 mm in diameter. The smaller and less tortuous reticular veins are dilated intradermal veins, which appear blue-green, measure 1–3 mm in diameter, and do not protrude from the skin surface. Telangiectasias, or spider veins, are small, dilated veins, <1 mm in diameter, located near the skin surface, and form blue, purple, or red linear, branching, or spider-web patterns.

Varicose veins can be categorized as primary or secondary. Primary varicose veins originate in the superficial system and result from defective structure and function of the valves of the saphenous veins, intrinsic weakness of the vein wall, and high intraluminal pressure. Approximately one-half of these patients have a family history of varicose veins. Other factors associated with primary varicose veins include aging, pregnancy, hormonal therapy, obesity, and prolonged standing. Secondary varicose veins result from venous hypertension, associated with deep-venous insufficiency or deep-venous obstruction, and incompetent perforating veins that cause enlargement of superficial veins. Arteriovenous fistulas also cause varicose veins in the affected limb.

Chronic venous insufficiency is a consequence of incompetent veins in which there is venous hypertension and extravasation of fluid and blood elements into the tissue of the limb. It may occur in patients with varicose veins but usually is caused by disease in the deep veins. It also is categorized as primary or secondary. Primary deep-venous insufficiency is a consequence of an intrinsic structural or functional abnormality in the vein wall or venous valves leading to valvular reflux. Secondary deep-venous insufficiency is caused by obstruction and/or valvular incompetence from previous deep-vein thrombosis **(Chap. 273)**. Deep-venous insufficiency occurs following deep-vein thrombosis, as the delicate valve leaflets become thickened and contracted and can no longer prevent retrograde flow of blood and the vein itself becomes rigid and thick walled. Although most veins recanalize after an episode of thrombosis, the large proximal veins may remain occluded. Secondary incompetence develops in distal valves because high pressures distend the vein and separate the leaflets. Other causes of secondary deep-venous insufficiency include May-Thurner syndrome, where the left iliac vein is occluded or stenosed by extrinsic compression from the overlapping right common iliac artery; arteriovenous fistulas resulting in increased venous pressure; congenital deep-vein agenesis or hypoplasia; and venous malformations as may occur in Klippel-Trénaunay and Parkes-Weber syndromes.

Clinical Presentation Patients with venous varicosities are often asymptomatic but still concerned about the cosmetic appearance of their legs. Superficial venous thrombosis may be a recurring problem, and, rarely, a varicosity ruptures and bleeds. Symptoms in patients with varicose veins or venous insufficiency, when they occur, include a dull ache, throbbing or heaviness, or pressure sensation in the legs typically after prolonged standing; these symptoms usually are relieved with leg elevation. Additional symptoms may include cramping, burning, pruritus, leg swelling, and skin ulceration.

The legs are examined in both the supine and standing positions. Visual inspection and palpation of the legs in the standing position confirm the presence of varicose veins. The location and extent of the varicose veins should be noted. Edema, stasis dermatitis, and skin ulceration near the ankle may be present if there is superficial venous insufficiency and venous hypertension. Findings of deep-venous insufficiency include increased leg circumference, venous varicosities, edema, and skin changes. The edema, which is usually pitting, may be confined to the ankles, extend above the ankles to the knees, or involve the thighs in severe cases. Over time, the edema may become less pitting and more indurated. Dermatologic findings associated with venous stasis include hyperpigmentation, erythema, eczema, lipodermatosclerosis, *atrophie blanche*, and a phlebectasia corona. Lipodermatosclerosis is the combination of induration, hemosiderin deposition, and inflammation, and typically occurs in the lower part of the leg just above the ankle. Atrophie blanche is a white patch of scar tissue, often with focal telangiectasias and a hyperpigmented border; it usually develops near the medial malleolus. A phlebectasia corona is a fan-shaped pattern of intradermal veins near the ankle or on the foot. Skin ulceration may occur near the medial and lateral malleoli. A venous ulcer is often shallow and characterized by an irregular border, a base of granulation tissue, and the presence of exudate **(Fig. 276-1)**.

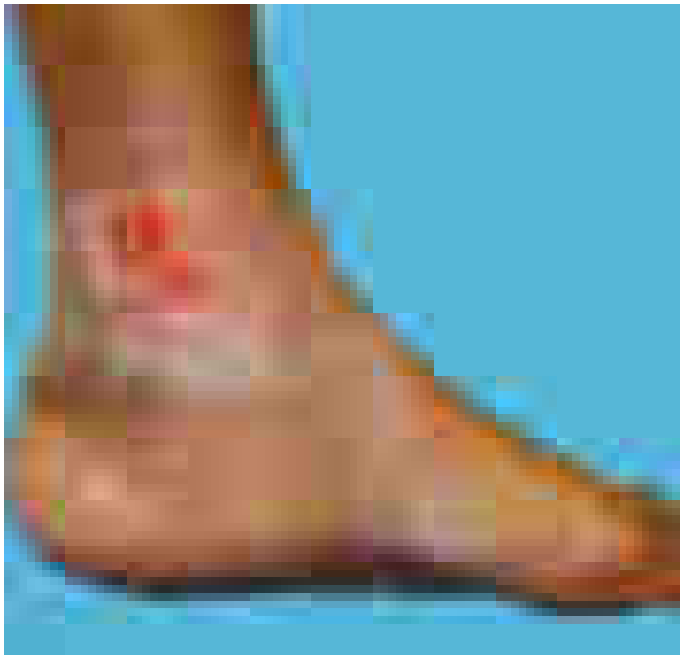


FIGURE 276-1 Venous insufficiency with active venous ulcer near the medial malleolus. *(Courtesy of Dr. Steven Dean, with permission.)*

Bedside maneuvers can be used to distinguish primary varicose veins from secondary varicose veins caused by deep-venous insufficiency. With the contemporary use of venous ultrasound (see below), however, these maneuvers are employed infrequently. The Brodie–Trendelenburg test is used to determine whether varicose veins are secondary to deep-venous insufficiency. As the patient is lying supine, the leg is elevated and the veins allowed to empty. Then, a tourniquet is placed on the proximal part of the thigh and the patient is asked to stand. Filling of the varicose veins within 30 s indicates that the varicose veins are caused by deep-venous insufficiency and incompetent perforating veins. Primary varicose veins with superficial venous insufficiency are the likely diagnosis if venous refilling occurs promptly after tourniquet removal. The Perthes test assesses the possibility of deep-venous obstruction. A tourniquet is placed on the midthigh after the patient has stood, and the varicose veins are filled. The patient is then instructed to walk for 5 min. A patent deep-venous system and competent perforating veins enable the superficial veins below the tourniquet to collapse. Deep-venous obstruction is likely to be present if the superficial veins distend further with walking.

Differential Diagnosis The duration of leg edema helps to distinguish chronic venous insufficiency from acute deep-vein thrombosis. Lymphedema, as discussed later in this chapter, is often confused with chronic venous insufficiency, and both may occur together. Other disorders that cause leg swelling should be considered and excluded when evaluating a patient with presumed venous insufficiency. Bilateral leg swelling occurs in patients with congestive heart failure, hypoalbuminemia secondary to nephrotic syndrome or severe hepatic disease, myxedema caused by hypothyroidism or pretibial myxedema associated with Graves' disease, and with drugs such as dihydropyridine calcium channel blockers and thiazolidinediones. Unilateral causes of leg swelling also include ruptured leg muscles, hematomas secondary to trauma, and popliteal cysts. Cellulitis may cause erythema and swelling of the affected limb. Leg ulcers may be caused by severe peripheral artery disease and critical limb ischemia; neuropathies, particularly those associated with diabetes; and less commonly, skin cancer, vasculitis, or rarely as a complication of hydroxyurea.

TABLE 276-1 CEAP (Clinical, Etiologic, Anatomic, Pathophysiologic) Classification

Clinical Classification
C0 No visible or palpable signs of venous disease
C1 Telangiectasias, reticular veins
C2 Varicose veins
C3 Edema without skin changes
C4 Skin changes, including pigmentation, eczema, lipodermatosclerosis, and atrophie blanche
C5 Healed venous ulcer
C6 Active venous ulcer
Etiologic Classification
Ec Congenital
Ep Primary
Es Secondary (postthrombotic)
En No venous etiology identified
Anatomic Classification
As Superficial veins
Ap Perforator veins
Ad Deep veins
An No venous location identified
Pathophysiologic Classification
Pr Reflux
Po Obstruction
Pr,o Reflux and obstruction
Pn No venous pathophysiology identifiable

Source: Data from B Eklöf et al: J Vasc Surg 40:1248, 2004.

The location and characteristics of venous ulcers help to differentiate these from other causes.

Classification of Chronic Venous Disease The CEAP (clinical, etiologic, anatomic, pathophysiologic) classification schema incorporates the range of symptoms and signs of chronic venous disease to characterize its severity. It also broadly categorizes the etiology as congenital, primary, or secondary; identifies the affected veins as superficial, deep, or perforating; and characterizes the pathophysiology as reflux, obstruction, both, or neither **(Table 276-1)**.

Diagnostic Testing The principal diagnostic test to evaluate patients with chronic venous disease is venous duplex ultrasonography. A venous duplex ultrasound examination uses a combination of B-mode imaging and spectral Doppler to detect the presence of venous obstruction and venous reflux in superficial and deep veins. Color-assisted Doppler ultrasound is useful to visualize venous flow patterns. Obstruction may be diagnosed by the absence of flow, the presence of an echogenic thrombus within the vein, or failure of the vein to collapse when a compression maneuver is applied by the sonographer, the last implicating the presence of an intraluminal thrombus. Venous reflux is detected by prolonged reversal of venous flow direction during a Valsalva maneuver, particularly for the common femoral vein or saphenofemoral junction, or after compression and release of a cuff placed on the limb distal to the area being interrogated.

Some vascular laboratories use air or strange gauge plethysmography to assess the severity of venous reflux and complement findings from the venous ultrasound examination. Venous volume and venous refilling time are measured when the legs are placed in a dependent position and after calf exercise to quantify the severity of venous reflux and the efficiency of the calf muscle pump to affect venous return.

Magnetic resonance, computed tomographic, and conventional venography are rarely required to determine the cause and plan treatment for chronic venous insufficiency unless there is suspicion for pathology that might warrant intervention. These modalities are used to identify obstruction or stenosis of the inferior vena cava and iliofemoral veins, as may occur in patients with previous proximal deep-vein thrombosis; occlusion of inferior vena cava filters; extrinsic compression from tumors; and May-Thurner syndrome.

TREATMENT

Chronic Venous Disease

SUPPORTIVE MEASURES

Varicose veins usually are treated with conservative measures. Symptoms often decrease when the legs are elevated periodically, prolonged standing is avoided, and elastic support hose are worn. External compression with elastic stockings or stretch bandages provides a counterbalance to the hydrostatic pressure in the veins. Although compression garments may improve symptoms, they do not prevent progression of varicose veins. Graduated compression stockings with pressures of 20–30 mmHg are suitable for most patients with simple varicose veins, although pressures of 30–40 mmHg may be required for patients with manifestations of venous insufficiency such as edema and ulcers.

Patients with chronic venous insufficiency also should be advised to avoid prolonged standing or sitting; frequent leg elevation is helpful. Graded compression therapy consisting of stockings or multilayered compression bandages is the standard of care for advanced chronic venous insufficiency characterized by edema, skin changes, or venous ulcers defined as CEAP clinical class C3–C6. Graduated compression stockings of 30–40 mmHg are more effective than lesser grades for healing venous ulcers. The length of stocking depends on the distribution of edema. Calf-length stockings are tolerated better by most patients, particularly elderly patients; for patients with varicose veins or edema extending to the thigh, thigh-length stockings or panty hose should be considered. Exercise training, including leg muscle strengthening, may improve calf muscle pump function and antegrade venous flow, and reduce the severity of chronic venous insufficiency. Overweight and obese patients should be advised to lose weight via caloric restriction and exercise.

In addition to a compression bandage or stocking, patients with venous ulcers also may be treated with low adherent absorbent dressings that take up exudates while maintaining a moist environment. Other types of dressings include hydrocolloid (an adhesive dressing composed of polymers such as carboxymethylcellulose that absorbs exudates by forming a gel), hydrogel (a nonabsorbent dressing comprising >80% water or glycerin that moisturizes wounds), foam (an absorbent dressing made with polymers such as polyurethane), and alginate (an absorbent, biodegradable dressing that is derived from seaweed), but there is little evidence that these are more effective than low-adherent absorbent dressings. The choice of specific dressing depends on the amount of drainage, presence of infection, and integrity of the skin surrounding the ulcer. Ulcers should be debrided of necrotic tissue. Antibiotics are not indicated unless the ulcer is infected. The multilayered compression bandage or graduated compression garment is then put over the dressing.

MEDICAL THERAPIES

There are no drugs approved by the U.S. Food and Drug Administration for the treatment of chronic venous insufficiency. Diuretics may reduce edema, but at the risk of volume depletion and compromise in renal function. Topical steroids may be used for a short period of time to treat inflammation associated with stasis dermatitis. Several herbal supplements, such as horse chestnut seed extract (aescin); flavonoids including diosmin, hesperidin, or the two combined as micronized purified flavonoid fraction; and French maritime pine bark extract, are touted to have venoconstrictive and anti-inflammatory properties. Although meta-analyses have suggested that aescin reduces edema, pruritus, and pain and that micronized purified flavonoid fraction in conjunction with compression therapy facilitates venous ulcer healing, there is insufficient evidence to recommend the general use of these substances in patients with chronic venous insufficiency.

INTERVENTIONAL AND SURGICAL THERAPIES

Ablative procedures, including endovenous thermal ablation, sclerotherapy, and surgery, are used to treat varicose veins in selected patients who have persistent symptoms, great saphenous vein incompetency, and complications of venous insufficiency including

dermatitis, edema, and ulcers. Ablative therapy may also be indicated for cosmetic reasons.

Endovenous thermal ablation procedures of the saphenous veins include endovenous laser therapy and radiofrequency ablation. To ablate the great saphenous vein, a catheter is placed percutaneously and advanced from the level of the knee to just below the saphenofemoral junction via ultrasound guidance. Thermal energy is then delivered as the catheter is pulled back. The heat injures the endothelium and media and promotes thrombosis and fibrosis, resulting in venous occlusion. Average 1- and 5-year occlusion rates exceed 90% following endovenous laser therapy and are slightly less after radiofrequency ablation. Deep-vein thrombosis of the common femoral vein adjacent to the saphenofemoral junction is an uncommon but potential complication of endovenous thermal ablation. Other adverse effects of thermal ablation procedures include pain, paresthesias, bruising, hematoma, and hyperpigmentation.

Sclerotherapy involves the injection of a chemical into a vein to cause fibrosis and obstruction. Sclerosing agents approved by the U.S. Food and Drug Administration include sodium tetradecyl sulfate, polidocanol, sodium morrhuate, and glycerin. The sclerosing agent is administered as a liquid or mixed with air or CO_2/O_2 to create a foam. It first is injected into the great saphenous vein or its affected tributaries, often with ultrasound guidance. Thereafter, smaller more distal veins and incompetent perforating veins are injected. Following completion of the procedure, elastic bandages are applied, or 30–40 mmHg compression stockings are worn for 1–2 weeks. Average 1- and 5-year occlusion rates are 81 and 74%, respectively, following sclerotherapy. Complications are uncommon and include deep-vein thrombosis, hematomas, damage to adjacent saphenous or sural nerves, and infection. Anaphylaxis is a very rare but severe complication.

Surgical therapy usually involves ligation and stripping of the great and small saphenous veins. The procedure is performed under general anesthesia. Incisions are made at the groin and the upper calf. The great saphenous vein is ligated below the saphenofemoral junction, and a wire is inserted into the great saphenous vein and advanced distally. The proximal part of the great saphenous vein is secured to the wire and retrieved, i.e., stripped, via the calf incision. Stripping of the great saphenous vein below the knee and stripping of the small saphenous vein usually are not performed because of the respective risks of saphenous and sural nerve injury. Complications of great saphenous vein ligation and stripping include deep -vein thrombosis, bleeding, hematoma, infection, and nerve injury. Recurrent varicose veins occur in up to 50% patients by 5 years, due to technical failures, deep-venous insufficiency, and incompetent perforating veins.

Stab phlebectomy is another surgical treatment for of varicose veins. A small incision is made alongside the varicose vein, and it is avulsed by means of a forceps or hook. This procedure may be performed in conjunction with saphenous vein ligation and stripping or thermal ablation. Subfascial endoscopic perforator surgery (SEPS) uses endoscopy to identify and occlude incompetent perforating veins. It also may be performed along with other ablative procedures.

Endovascular interventions, surgical bypass, and reconstruction of the valves of the deep veins are performed when feasible to treat patients with advanced chronic venous insufficiency who have not responded to other therapies. Catheter-based interventions, usually involving placement of endovenous stents, may be considered to treat some patients with chronic occlusions of the iliac veins. Technical success rates exceed 85% in most series, and long-term patency is achieved in ~75% of these patients. Iliocaval bypass, femoroiliac venous bypass, and femorofemoral crossover venous bypass are procedures used occasionally to treat iliofemoral vein occlusion; saphenopopliteal vein bypass can be used to treat chronic femoropopliteal vein obstruction. Long-term patency rates for venous bypass procedures generally exceed 60% and are associated with improvement in symptoms. Surgical reconstruction of the valves of the deep veins and valve transfer procedures are used to treat valvular incompetence. Valvuloplasty involves tightening the valve by commissural apposition. With valve transfer procedures, a segment of vein with a competent valve, such as a brachial or axillary vein, or adjacent saphenous or deep femoral vein, is inserted as an interposition graft in the incompetent vein. Both valvuloplasty and vein transfer operations result in ulcer healing in the majority of patients, although success rates are somewhat better with valvuloplasty.

Lymphedema Lymphedema is a chronic condition caused by impaired transport of lymph and characterized by swelling of one or more limbs and occasionally the trunk and genitalia. Fluid accumulates in interstitial tissues when there is an imbalance between lymph production and lymph absorption, a process governed in large part by Starling forces. Deficiency, reflux, or obstruction of lymph vessels perturbs the ability of the lymphatic system to reabsorb proteins that had been filtered by blood vessels, and the tissue osmotic load promotes interstitial accumulation of water. Persistent lymphedema leads to inflammatory and immune responses characterized by infiltration of mononuclear cells, fibroblasts, and adipocytes, leading to adipose and collagen deposition in the skin and subcutaneous tissues.

Lymphatic Anatomy Lymphatic capillaries are blind-ended tubes formed by a single layer of endothelial cells. The absent or widely fenestrated basement membrane of lymphatic capillaries allows access to interstitial proteins and particles. Lymphatic capillaries merge to form microlymphatic precollector vessels, which contain few smooth muscle cells. The precollector vessels drain into collecting lymphatic vessels, which comprise endothelial cells, a basement membrane, smooth muscle, and bileaflet valves. The collecting lymphatic vessels in term merge to form larger lymphatic conduits. Analogous to venous anatomy, there are superficial and deep lymphatic vessels in the legs, which communicate at the popliteal and inguinal lymph nodes. Pelvic lymphatic vessels drain into the thoracic duct, which ascends from the abdomen to the thorax and connects with the left brachiocephalic vein. Lymph is propelled centrally by the phasic contractile activity of lymphatic smooth muscle and facilitated by the contractions of contiguous skeletal muscle. The presence of lymphatic valves ensures unidirectional flow.

Etiology Lymphedema may be categorized as primary or secondary **(Table 276-2)**. The prevalence of primary lymphedema is ~1.15 per 100,000 persons <20 years of age. Females are affected more frequently than males. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or obstruction of the lymphatic vessels. There are three clinical subtypes: congenital lymphedema, which appears shortly after birth; lymphedema praecox, which has its onset at the time of puberty; and lymphedema tarda, which usually begins after age 35. Familial forms of congenital lymphedema (Milroy's disease) and lymphedema praecox (Meige's disease) may be inherited in an autosomal dominant manner with variable penetrance; autosomal or sex-linked recessive forms are less common. At least 19 genes are associated with inherited forms of lymphedema. Mutations in genes expressing vascular endothelial growth factor receptor 3 (*VEGFR3*), which is a determinant of lymphangiogenesis, cause Milroy's disease; and a mutation of the gene encoding *VEGF-C*, a ligand for *VEGFR3*, may cause a Milroy's disease-like phenotype. A mutation of the *LSC1* gene is associated with the cholestasis-lymphedema syndrome. Mutations in the *FOXC2* gene, which encodes a transcription factor that interacts with a signaling pathway involved in the development of lymphatic vessels, cause the lymphedema-distichiasis syndrome, in which lymphedema praecox occurs in patients who also have a double row of eyelashes. A mutation of *SOX18*, a transcription factor upstream of lymphatic endothelial cell differentiation, has been described in patients with lymphedema, alopecia, and telangiectasias (hypotrichosis, lymphedema, telangiectasia syndrome). Mutations of the *CCBE1* gene, which enhances the lymphangiogenic effects of VEGF-C, cause Hennekam lymphangiectasia-lymphedema syndrome, and *KIF11* gene mutations are associated with microcephaly-lymphedema syndrome. Mutations of the *GATA2* gene, which is involved in the development of lymphatic valves, cause lymphedema and a predisposition to acute myeloid leukemia. Patients

TABLE 276-2 Causes of Lymphedema

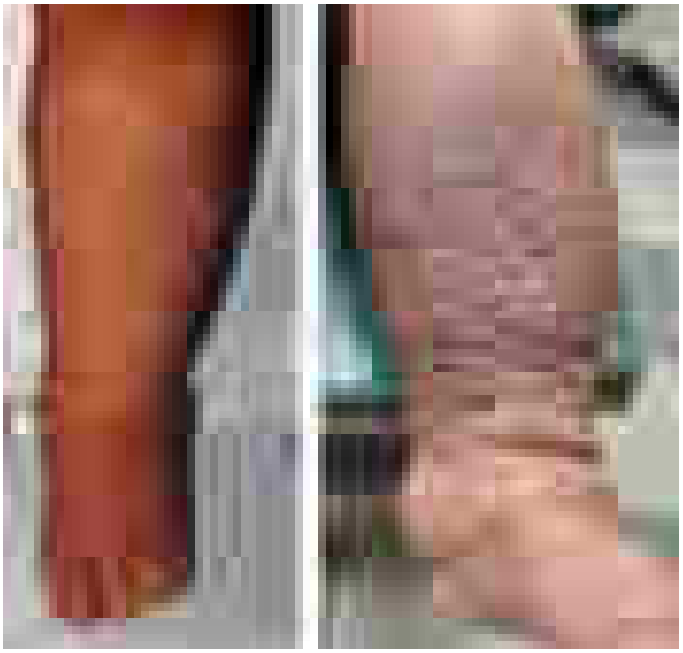
Primary
Sporadic (no identified cause)
Genetic disorders
Milroy's disease (*VEGFR3*, *VEGF-C*)
Meige's disease (gene mutation not established)
Lymphedema-distichiasis syndrome (*FOXC2*)
Cholestasis-lymphedema (*LSC1*)
Hennekam's lymphangiectasia-lymphedema syndrome (*LCCBE1*)
Emberger's syndrome-lymphedema and predisposition to AML (*GATA2*)
Microcephaly-lymphedema syndrome (*KIF11*)
Hypotrichosis-lymphedema-telangiectasia (*SOX18*)
Chromosomal aneuploidies
Turner's syndrome
Klinefelter's syndrome
Trisomy 13, 18, or 21
Other disorders associated with primary lymphedema
Noonan's syndrome
Klippel-Trénaunay syndrome
Parkes-Weber syndrome
Yellow nail syndrome
Intestinal lymphangiectasia syndrome
Lymphangiomyomatosis
Neurofibromatosis type 1
Secondary
Infection
Bacterial lymphangitis (*Streptococcus pyogenes*, *Staphylococcus aureus*)
Lymphogranuloma venereum (*Chlamydia trachomatis*)
Filariasis (*Wucheria bancrofti*, *Brugia malayi*, *B. timori*)
Tuberculosis
Neoplastic infiltration of lymph nodes
Lymphoma
Prostate
Others
Surgery or irradiation of axillary or inguinal lymph nodes for treatment of cancer
Iatrogenic
Lymphatic division (during peripheral bypass surgery, varicose vein surgery, or harvesting of saphenous veins)
Miscellaneous
Contact dermatitis
Podoconiosis
Rheumatoid arthritis
Pregnancy
Factitious

with a chromosomal aneuploidy, such as Turner's syndrome, Klinefelter's syndrome, or trisomy 18, 13, or 21, may develop lymphedema. Syndromic vascular anomalies associated with lymphedema also include Klippel-Trénaunay syndrome and Parkes-Weber syndrome. Other disorders associated with lymphedema include Noonan's syndrome, yellow nail syndrome, intestinal lymphangiectasia syndrome, lymphangiomyomatosis, and neurofibromatosis type 1.

Secondary lymphedema is an acquired condition that results from damage to or obstruction of previously normal lymphatic channels. Recurrent episodes of bacterial lymphangitis, usually caused by streptococci, are a very common cause of lymphedema. The most common etiology of secondary lymphedema worldwide is lymphatic filariasis and affecting >120 million children and adults and causing lymphedema and elephantiasis in 14 million of these affected individuals (Chap. 228). Recurrent bacterial lymphangitis by *Streptococcus* may result in chronic lymphedema. Other infectious causes include lymphogranuloma venereum and tuberculosis. A common acquired cause of lymphedema in tropical countries is podoconiosis, which results from barefoot exposure and absorption of silicate particles in soil derived from volcanic rock. In developed countries, the most common secondary cause of lymphedema is surgical excision or irradiation of axillary and inguinal lymph nodes for treatment of cancers, such as breast, cervical, endometrial, and prostate cancer, sarcomas, and malignant melanoma. Lymphedema of the arm occurs in 13% of breast cancer patients after axillary node dissection and in 22% after both surgery and radiotherapy. Lymphedema of the leg affects ~15% of patients with cancer after inguinal lymph node dissection. Tumors, such as prostate cancer and lymphoma, also can infiltrate and obstruct lymphatic vessels. Less common causes include contact dermatitis, rheumatoid arthritis, pregnancy, and self-induced or factitious lymphedema after application of tourniquets.

Clinical Presentation Lymphedema is generally a painless condition, but patients may experience a chronic dull, heavy sensation in the leg, and most often they are concerned about the appearance of the leg. Lymphedema of the lower extremity initially involves the foot and gradually progresses up the leg so that the entire limb becomes edematous (Fig. 276-2). In the early stages, the edema is soft and pits easily with pressure. Over time, subcutaneous adipose tissue accumulates, the limb enlarges further and loses its normal contour, and the toes appear square. Thickening of the skin is detected by Stemmer's sign, which is the inability to tent the skin at the base of the toes. Peau d'orange is a term used to describe dimpling of the skin, resembling that of an orange peel, caused by lymphedema. In the chronic stages, the edema no longer pits and the limb acquires a woody texture as the tissues become indurated and fibrotic. The International Society of Lymphology describes four clinical stages of lymphedema (Table 276-3).

Differential Diagnosis Lymphedema should be distinguished from other disorders that cause unilateral leg swelling, such as deep-vein thrombosis and chronic venous insufficiency. In the latter condition, the edema is softer, and there is often evidence of a stasis dermatitis, hyperpigmentation, and superficial venous varicosities, as described earlier. Other causes of leg swelling that resemble lymphedema are myxedema and lipedema. Lipedema usually occurs in women and is caused by accumulation of adipose tissue in the leg from the thigh to the ankle with sparing of the feet.



A *B*

FIGURE 276-2 ***A.*** Lymphedema characterized by swelling of the leg, nonpitting edema, and squaring of the toes. *(Courtesy of Dr. Marie Gerhard-Herman, with permission.)* ***B.*** Advanced chronic stage of lymphedema illustrating the woody appearance of the leg with acanthosis and verrucous overgrowths. *(Courtesy of Dr. Jeffrey Olin, with permission.)*

TABLE 276-3 Stages of Lymphedema
Stage 0 (or Ia)
A latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist for months or years before overt edema occurs.
Stage I
Early accumulation of fluid relatively high in protein content that subsides with limb elevation. Pitting may occur. An increase in proliferating cells may also be seen.
Stage II
Limb elevation alone rarely reduces tissue swelling, and pitting is manifest. Late in stage II, the limb may or may not pit as excess fat and fibrosis supervene.
Stage III
Lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, further deposition of fat and fibrosis, and warty overgrowths have developed.

Source: Adapted from The 2013 Consensus Document of the International Society of Lymphology: Lymphology 46:1, 2013.

Diagnostic Testing The evaluation of patients with lymphedema should include diagnostic studies to clarify the cause. Abdominal and pelvic ultrasound and computed tomography (CT) can be used to detect obstructing lesions such as neoplasms. Magnetic resonance imaging (MRI) of the affected limb may reveal a honeycomb pattern characteristic of lymphedema in the epifascial compartment and identify enlarged lymphatic channels and lymph nodes. MRI also is useful to distinguish lymphedema from lipedema. Lymphoscintigraphy and lymphangiography are rarely indicated, but either can be used to confirm the diagnosis or differentiate primary from secondary lymphedema. Lymphoscintigraphy involves the injection of radioactively labeled technetium-containing colloid into the distal subcutaneous tissue of the affected extremity, which is imaged with a scintigraphic camera to visualize lymphatic vessels and lymph nodes. Findings indicative of primary lymphedema include absent or delayed filling of the lymphatic vessels or dermal back flow caused by lymphatic reflux. Findings of secondary lymphedema include dilated lymphatic vessels distal to an area of obstruction. In lymphangiography, iodinated radiocontrast material is injected into a distal lymphatic vessel that has been isolated and cannulated. In primary lymphedema, lymphatic channels are absent, hypoplastic, or ectatic. In secondary lymphedema, lymphatic channels often appear dilated beneath the level of obstruction. The complexities of lymphatic cannulation and the risk of lymphangitis associated with the contrast agent limit the utility of lymphangiography. A novel technique of optical imaging with a near-infrared fluorescence dye may enable quantitative imaging of lymph flow.

TREATMENT

Lymphedema

Patients with lymphedema of the lower extremities must be instructed to take meticulous care of their feet and legs to prevent cellulitis and lymphangitis. Skin hygiene is important, and emollients can be used to prevent drying. Prophylactic antibiotics are often helpful, and fungal infection should be treated aggressively. Patients should be encouraged to participate in physical activity; frequent leg elevation can reduce the amount of edema. Psychosocial support is indicated to assist patients cope with anxiety or depression related to body image, self-esteem, functional disability, and fear of limb loss.

Physical therapy, including massage to facilitate lymphatic drainage, may be helpful. The type of massage used in decongestive physiotherapy for lymphedema involves mild compression of the skin of the affected extremity to dilate the lymphatic channels and enhance lymphatic motility. Multilayered, compressive bandages are applied after each massage session to reduce recurrent edema. After optimal reduction in limb volume by decongestive physiotherapy, patients can be fitted with graduated compression hose. Occasionally, intermittent pneumatic compression devices can be applied at home to facilitate reduction of the edema. Diuretics are contraindicated and may cause depletion of intravascular volume and metabolic abnormalities.

Liposuction in conjunction with decongestive physiotherapy may be considered to treat lymphedema, particularly postmastectomy lymphedema. Other surgical interventions are rarely used and often not successful in ameliorating lymphedema. Microsurgical lymphaticovenous anastomotic procedures have been performed to rechannel lymph flow from obstructed lymphatic vessels into the venous system. Limb reduction procedures to resect subcutaneous tissue and excessive skin are performed occasionally in severe cases of lymphedema to improve mobility.

Therapeutic lymphangiogenesis has been studied in rodent models of lymphedema. Overexpression of VEGF-C generates new lymphatic vessels and improves lymphedema in a murine model of primary lymphedema, and administration of recombinant VEGF-C or VEGF-D stimulated lymphatic growth in preclinical models of postsurgical lymphedema. There may be additional benefit when administered in conjunction with lymph node transfer. Clinical trials in patients with lymphedema are required to determine efficacy of gene transfer and cell-based therapies for lymphedema.

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277 Pulmonary Hypertension

Aaron B. Waxman, Joseph Loscalzo

Pulmonary hypertension (PH) is a spectrum of diseases involving the pulmonary vasculature, and defined as an elevation in pulmonary arterial pressures (mean pulmonary artery pressure [PAP] >22 mmHg or an estimated systolic PAP >36 mmHg). Pulmonary arterial hypertension (PAH) is a relatively rare form of PH and is characterized by symptoms of dyspnea, chest pain, and syncope. If left untreated, the disease carries a high mortality rate, with the most common cause

of death being decompensated right heart failure. There have been significant advances in this field in regard to understanding the pathogenesis, diagnosis, and classification of PAH. Despite these significant advances, there is still a substantial delay in diagnosis of up to 2 years. In many cases, patients whose primary complaint is exertional intolerance are frequently misdiagnosed with more common diseases such as asthma or chronic obstructive pulmonary disease. The availability of newer drugs has resulted in a radical change in the management of this disease with significant improvement in both quality of life and mortality. A delay in diagnosis results in an obvious delay in the initiation of appropriate treatment. Clinicians should be able to recognize the signs and symptoms of PH and to complete a systematic workup in at-risk patients. In this way, early diagnosis, prompt treatment, and improved outcomes for patients become achievable.

PATHOBIOLOGY

Vasoconstriction, vascular proliferation, thrombosis, and inflammation appear to underlie the development of PAH **(Fig. 277-1)**. Intimal proliferation and fibrosis, medial hypertrophy, and *in situ* thrombosis characterize the pathological findings in the pulmonary vasculature. Vascular remodeling at earlier stages may be confined to the small distal pulmonary arteries. As the disease advances, intimal proliferation and pathologic remodeling progress resulting in decreased compliance of the pulmonary vasculature. The outcome is a progressive increase in the right ventricular afterload or total pulmonary vascular resistance (PVR), and, thus, right ventricular work. In subjects with moderate to severe pulmonary vascular disease, as the resting PVR increases, there will be a corresponding increase in mean PAP until the cardiac output (CO) is compromised and starts to fall. With a decline in CO, the PAP will fall. As CO declines as a result of increased afterload and decreased contractility, tachycardia is a compensatory response. Tachycardia decreases filling time and, thus, preload, and results in a reduced fraction of stroke volume available to distend the pulmonary vascular tree.

Abnormalities in multiple molecular pathways and genes that regulate the pulmonary vascular endothelial and smooth muscle cells have been identified **(Table 277-1)**. These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxia-induced activation of hypoxia-inducible factor-1α, and activation of nuclear factor of activated T cells. As a result, there is a decrease in apoptosis of smooth muscle cells and the emergence of apoptosis-resistant endothelial cells that promote their accumulation and can obliterate the vascular lumen. In addition, thrombin deposition in the pulmonary vasculature from the prothrombotic state that develops as an independent abnormality or as a result of endothelial dysfunction may amplify the obliterative arteriopathy.

DIAGNOSIS AND CLASSIFICATION

The diagnosis of PH can be missed without a reasonable index of suspicion. PH symptoms are nonspecific, insidious, and overlap considerably with many common conditions, including asthma and other lung disease, and cardiac disease. Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and syncope are less common and associated with more advanced disease. In early phases of PAH, the physical examination is often unrevealing. As the

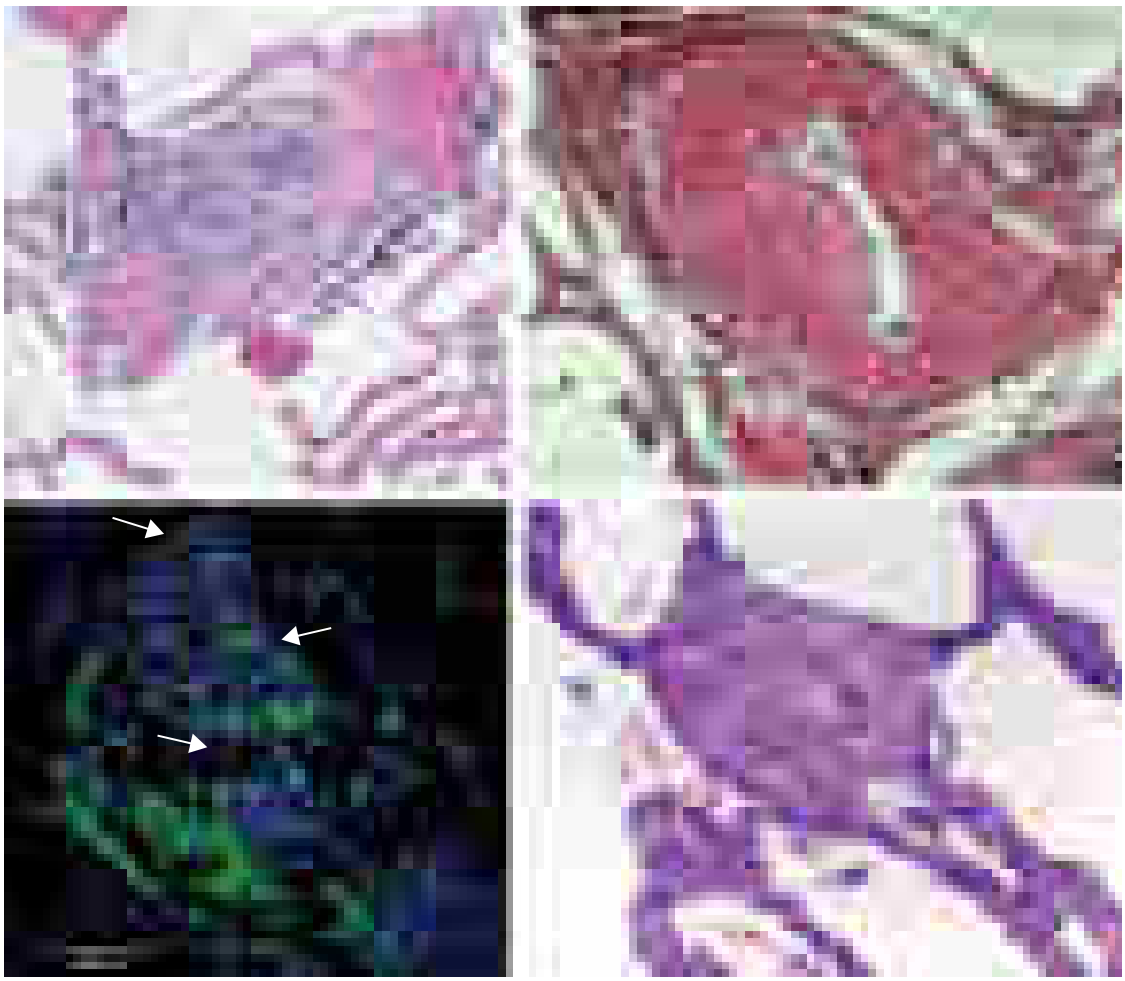


FIGURE 277-1. Panels on the left show examples of plexogenic pulmonary arteriopathy. These are obstructive and proliferative lesions of the small muscular pulmonary arteries, composed primarily of endothelial cells with intermixed inflammatory cells, myofibroblasts, and connective tissue components. The lower left panel demonstrates proliferating cells (red PCNA stain—*white arrows*). Panels on the right demonstrate medial hypertrophy of muscular pulmonary arteries. *(Photograph on the lower left is courtesy of Dr. Stephen Archer, Queen's University School of Medicine, Kingston, Ontario, Canada.)*

TABLE 277-1 Molecular Determinants of the Pathogenesis of Pulmonary Arterial Hypertension

Alterations in regulators of proliferation
• Growth factors
◦ PDGF
◦ FGF
◦ VEGF
◦ EGF
• TGF-β
• BMP
• Transcription factors
• MMPs
• Cytokines
• Chemokines
• Mitochondria
Alterations in inflammatory mediators
• Altered T-cell subsets
• Monocytes and macrophages
• IL-1β
• IL-6
• MCP-1
• RANTES
• Fractalkine
Alterations in vascular tone
• Endothelin
• Nitric oxide
• Serotonin
• Prostaglandin
• K^+ channels
• Ca^{2+} channels
Hypoxia induced remodeling
• HIF-1α
• ROS
• Mitochondria
Alterations in TGF-β signaling pathways
• BMPR2
• ALK1
• Endoglin
• Smad9
• TGF-β1

Abbreviations: ALK, anaplastic lymphoma kinase; BMP, bone morphogenic protein; EGF, epidermal-derived growth factor; FGF, fetal-derived growth factor; HIF-1α, hypoxia-inducible factor-1; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MMP, mucous membrane pemphigoid; PDGF, platelet-derived growth factor; ROS, reactive oxygen specie; TGFβ, transforming growth factor β; VEGF, vascular endothelial-derived growth factor.

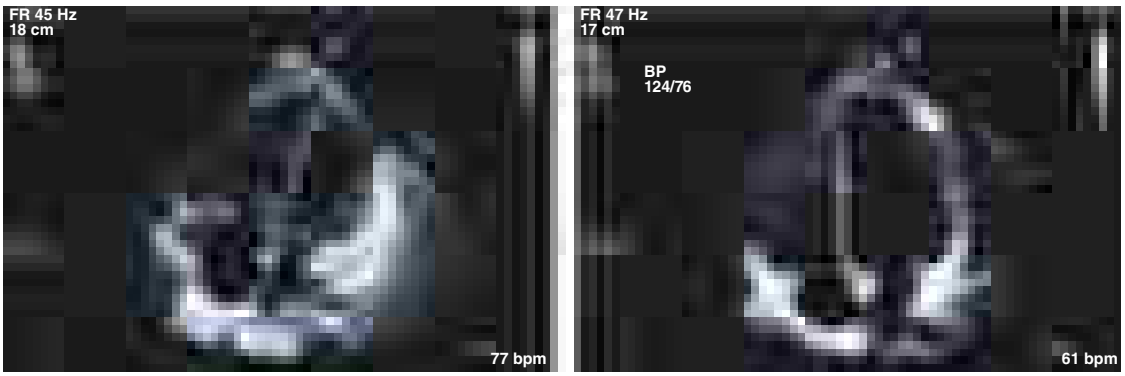
disease progresses there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P2 component of the second heart sound, a right-sided S3 or S4, and a holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are often concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma, and crackles on examination of the lungs and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.

Once clinical suspicion is raised, a systematic approach to diagnosis and assessment is essential. An echocardiogram with *bubble study* is the most important initial screening test. Echocardiography is also important for determining specific causes. All forms of PH may demonstrate a hypertrophied and dilated right ventricle **(Fig. 277-2)** with elevated estimated pulmonary artery systolic pressure. Important additional information can be gleaned about specific etiologies of PH, such as valvular disease, left ventricular systolic and diastolic function, intracardiac shunts, and other cardiac diseases.

Although the accuracy of Doppler echocardiography is often debated, a high quality echocardiogram that is absolutely normal may obviate the need for further evaluation for PH. An echocardiogram is a screening test, whereas invasive hemodynamic monitoring is the gold standard for diagnosis and assessment of disease severity. With a normal echocardiogram, there may still be some concern for PH; this is particularly true if there is unexplained dyspnea or hypoxemia. In this setting, it is reasonable to proceed to right heart catheterization (RHC) for definitive diagnosis. Alternatively, if the patient has a reasonable functional capacity, a cardiopulmonary exercise test may help to identify a true physiologic limitation as well as differentiate between cardiac and pulmonary causes of dyspnea. If this test is normal, there is no indication for a RHC.

If the echocardiogram or cardiopulmonary exercise test (CPET) suggests PH and the diagnosis is confirmed by catheterization, a reasonable effort must be made to establish the etiology because this will largely determine the therapeutic approach. A stepwise approach to evaluation is outlined below.

Chest imaging and lung function tests are essential because lung disease is an important cause of PH. Signs of PH that may be evident on chest radiograph include enlargement of the central pulmonary arteries, "vascular pruning," and cardiomegaly **(Fig. 277-3)**. High-resolution computed tomography (CT) may provide additional useful information. Classic findings of PH on CT include those found on chest radiograph: enlarged pulmonary arteries **(Fig. 277-4)**, peripheral pruning of the small vessels, and enlarged right ventricle and atrium. However, high-resolution CT may also reveal signs of venous congestion, including centrilobular ground glass infiltrate and thickened septal lines. In the absence of left heart disease, these findings suggest pulmonary venous disease, a rare cause of PAH that can be quite challenging to diagnose. CT is also critical for distinguishing co-morbid interstitial lung disease or emphysema.



A ***B***

FIGURE 277-2 Panel (***A***) is a representative echocardiogram showing the apical 4-chamber view from a patient with pulmonary hypertension demonstrating an enlarged right atrium and ventricle with some compression of the left side of the heart. Panel (***B***) is the same echocardiographic view showing a normal echocardiogram.

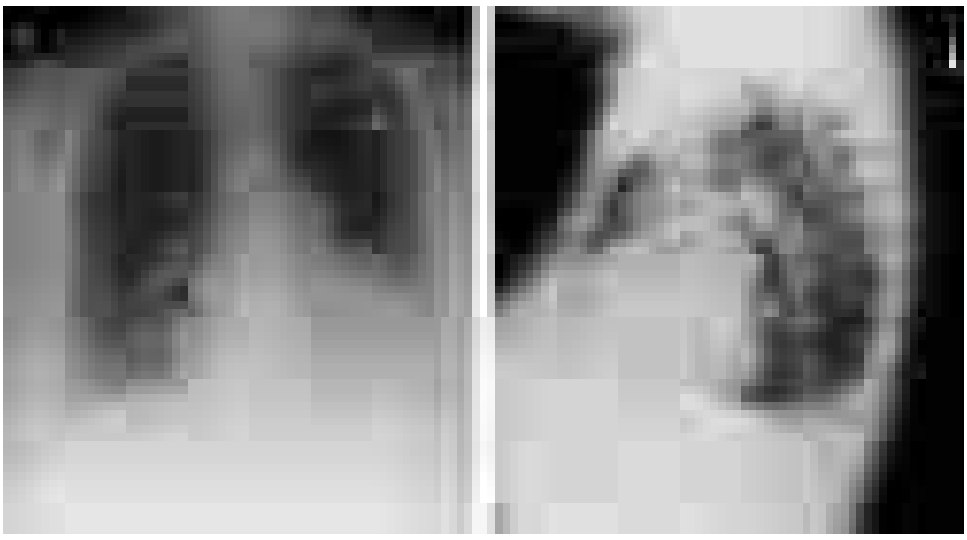


FIGURE 277-3 Postero-anterior (*left*) and lateral (*right*) chest radiograph showing enlarged pulmonary arteries (*black arrows*) and pruning of the distal pulmonary vasculature (*white arrows*) commonly seen with advanced pulmonary arterial hypertension.

CT angiograms are commonly used to evaluate acute thromboembolic disease and have demonstrated excellent sensitivity and specificity for that purpose. Ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning has been used for screening because of its high sensitivity and its role in qualifying patients for surgical intervention. The role of CT angiograms in the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) remains controversial, even with the advent of spiral CT. Although a negative $\dot{V}/\dot{Q}$ virtually rules out CTEPH, rare cases may be missed through the use of CT angiograms.

Pulmonary function tests are an important component of the evaluation. While an isolated reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) is the classic finding in PAH, results of pulmonary function tests may also suggest restrictive or obstructive lung diseases as the cause of dyspnea or PH. The 6-minute walk test is also important to evaluate the degree of exertional hypoxemia and limitation, and to monitor progression and response to therapy. Increasingly, sub-maximal and maximal exercise testing are being utilized for screening and characterization of disease because it provides a more objective measure of breathing efficiency (V_E/VCO_2 slope).

Sleep-disordered breathing is another important cause of mild PH, but a sleep study is generally necessary only when indicated by the patient's history. Nocturnal desaturation is a common finding in PH, even in the absence of sleep-disordered breathing. Thus, all patients should undergo nocturnal oximetry screening, regardless of whether classic symptoms of obstructive sleep apnea or obesity-hypoventilation syndrome are observed. Laboratory tests that are important for screening include an HIV test when clinically indicated. In addition, all patients should have antinuclear antibodies, rheumatoid factor, and anti-scl-70 antibodies assessed to screen for the most common rheumatologic diseases associated with PH. Liver function and hepatitis serology tests are important to screen for underlying liver disease. Finally, there is an increasing role for brain natriuretic peptide testing in the diagnosis and management of PH. Brain naturetic peptide (BNP) and the N-terminus of its pro-peptide (NT-proBNP) correlate with right ventricular (dys)function, hemodynamic severity, and functional status in PAH.

RHC with pulmonary vasodilator testing remains the gold standard both to establish the diagnosis of PH and to guide selection of appropriate medical therapy. The definition of precapillary PH or PAH requires (1) an increased mean PAP (mPAP >25 mmHg); (2) a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg; and (3) PVR >3 Wood units. Post capillary PH is differentiated from precapillary PH by the PCWP being ≥15 mmHg; this is further differentiated into passive, based on a transpulmonary gradient <12 mmHg, or reactive, based on a transpulmonary gradient >12 mmHg and an increased PVR. In either case, the CO may be normal or reduced.

Vasodilators with a short duration of action, such as inhaled nitric oxide (NO), or inhaled epoprostenol are preferred for vasodilator testing. A decrease in mPAP by ≥10 mmHg to an absolute level ≤40 mmHg without a decrease in CO is defined as a positive pulmonary vasodilator response, and responders are considered for long-term treatment with calcium channel blockers (CCB). Less than 15% of patients are deemed vasoreactive during testing, and even fewer exhibit long-term responsiveness to CCB. An acute vasodilator-induced reduction in PVR and mPAP predict better long-term survival even among those patients not treated with CCB. The diagnosis of PH is increasing in the older population, in part, because of increased awareness of this disease in the elderly and increased use of screening echocardiograms. Furthermore, the increased availability of oral and less complicated therapeutic options has encouraged the referral of older patients for evaluation and treatment.

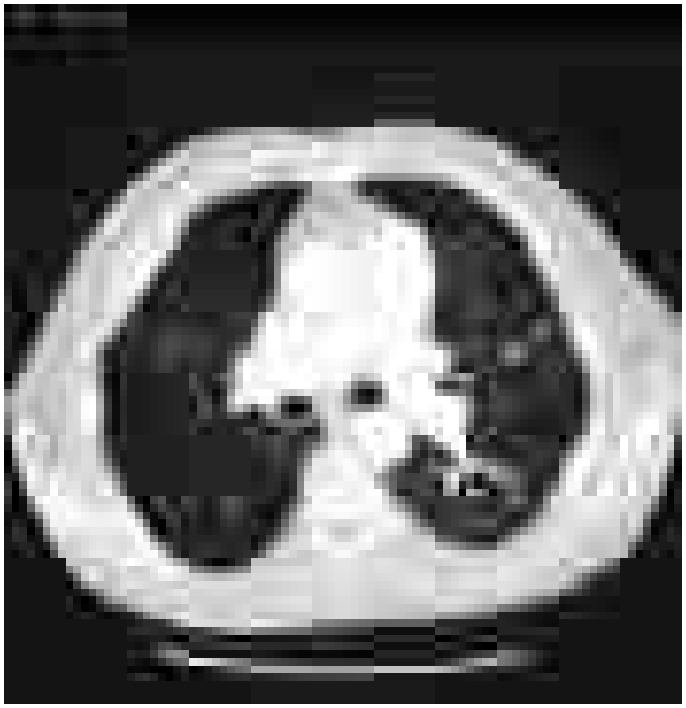


FIGURE 277-4 Representative computed tomographic scan of the chest demonstrating enlarged main pulmonary arteries. There is also a mosaic pattern evident in both lungs.

PULMONARY HYPERTENSION AS A COMORBID DISEASE

PAH is but one of a number of disease classifications that affect the pulmonary vascular bed. As understanding of the various contributing diseases has increased, classification systems have attempted to group these diseases by clinical features to aid in diagnosis. The World Health Organization (WHO) formulated a clinical classification of the various manifestations of PH, of which PAH is a subgroup, according to similarities in pathophysiologic mechanisms and clinical presentation. PH is a diverse mix of pathologies in which the only unifying theme is elevated PAP relative to left atrial pressure. The categorization of PH was designed by convenience for the purpose of facilitating novel treatments to be tested across different presentations. Efforts are underway

to define pulmonary vascular diseases based on molecular phenotyping that, in the future, may offer a guide for improved management decisions as precision medicine strategies continue to evolve.

The current classification system, last revised in 2013 during the Fifth World Symposium on Pulmonary Hypertension, recognizes five categories of PH, including PAH, PH due to left heart disease, PH due to chronic lung disease, PH associated with chronic thromboemboli, and a group of miscellaneous diseases that only rarely cause PH.

Pulmonary Arterial Hypertension WHO Group I PH, PAH, is a relatively rare cause of PH. PAH includes a group of diseases that result in pulmonary arterial precapillary remodeling marked by intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and classic plexiform lesions. PAH is defined as a sustained elevation in resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg, PVR > 240 dyne-s/cm^5, and PCWP or LVEDP of ≤15 mmHg based on a RHC. With a normal PCWP and an elevated mPAP, these diseases demonstrate an increased transpulmonary gradient (mPAP–PCWP) and increased PVR.

Idiopathic PAH (IPAH) is a progressive disease that leads to right heart failure and death. The National Institutes of Health registry, the first large registry of patients with PAH, reported that the average age at diagnosis was 36 years, with only 9% of patients with IPAH over the age of 60. However, more current clinical data suggest that the patient demographics are changing. The Pulmonary Hypertension Connection registry found that the average age of diagnosis for IPAH was 45 years, with 8.5% of patients older than 70 years at diagnosis. This finding is supported by data from the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) study, the largest cohort of PAH to date, which reported that the average age at diagnosis of IPAH was 44.9+/-0.6 years.

Other forms of PAH that deserve specific consideration are those associated with HIV, connective tissue disease, and portal hypertension. Although HIV is a rare cause of PAH, this form of PAH is indistinguishable from IPAH and is an important cause of mortality in the HIV-infected population. Importantly, there is no correlation between the stage of HIV infection and the development of PAH.

Among connective tissue diseases, the prevalence of PAH has been established only for systemic sclerosis, especially in those with limited cutaneous scleroderma. Although the average age of scleroderma onset is from 30 to 50 years old, patients who eventually develop scleroderma-associated PAH tend to be older at the time of scleroderma diagnosis. Outcomes of scleroderma are closely linked to the development of PAH and are associated with a poor prognosis, although modern therapies have improved outcomes.

Portopulmonary hypertension occurs in 2–10% of patients with established portal hypertension. Its occurrence appears to be independent of the cause of liver disease and is observed in patients with non-hepatic causes of portal hypertension. A hyperdynamic circulatory state is common, as in most patients with advanced liver disease; however, the same pulmonary vascular remodeling observed in other forms of PAH is seen in the pulmonary vascular bed in portopulmonary hypertension. It is important to distinguish this process from hepatopulmonary syndrome, which can also manifest with dyspnea and hypoxemia but is pathophysiologically distinct from portopulmonary hypertension in that abnormal vasodilation of the pulmonary vasculature leads to intrapulmonary shunting.

Pulmonary Hypertension Associated with Left Heart Disease WHO Group II PH includes patients with left heart systolic dysfunction, aortic and mitral valve disease, and heart failure with preserved ejection fraction (HFpEF). PH can develop as a result of each of these conditions. The hallmark of Group II PH is elevated left atrial pressure with resulting pulmonary venous hypertension. In general, the transpulmonary gradient and PVR remain normal. Although this phenomenon is well described in both left-sided valvular disease and left-sided systolic heart failure, studies suggest that HFpEF may carry a higher overall risk of PH.

Whatever the cause of elevated left atrial pressure (i.e., systolic or diastolic heart failure or valvular disease), the increased pulmonary venous pressure indirectly leads to a rise in pulmonary arterial pressure. The presence of PH portends a poor prognosis in all forms of heart failure. In particular, chronic pulmonary venous hypertension may lead to a reactive pulmonary arterial vasculopathy, seen as an elevated transpulmonary gradient (>12 mm Hg) and elevated PVR (>3 Wood units). Pathologically, this process is marked by pulmonary arteriolar remodeling with intimal fibrosis and medial hyperplasia akin to that seen in PAH.

Pulmonary Hypertension Associated with Lung Disease Intrinsic lung disease is the second most common cause of PH, although its actual prevalence is difficult to ascertain. PH has been observed in both chronic obstructive lung disease and interstitial lung disease. It can also be seen in diseases with mixed obstructive/restrictive physiology: bronchiectasis, cystic fibrosis, mixed obstructive restrictive disease marked by fibrosis in the lower lung zones, and emphysema predominantly in the upper lung zones. As in patients with left heart disease, PH associated with chronic lung disease is usually modest; however, some of these patients appear to have PH "out of proportion" to their parenchymal lung disease, suggesting intrinsic pulmonary arterial disease. These patients typically have more severe PH, with results of pulmonary function tests demonstrating a very low DLCO.

Although PH is described in most forms of interstitial lung disease, it has been most extensively studied in idiopathic pulmonary fibrosis; however, the individual studies have been small. Early echocardiographic data suggested that the prevalence of PH in interstitial lung diseases is high, but invasive hemodynamic monitoring suggests that the incidence is considerably lower than originally believed. The diagnosis of PH portends poor outcome in pulmonary fibrosis.

Also included in Group III PH is sleep-disordered breathing. Sleep apnea has long been associated with PH. However, PH associated with sleep-disordered breathing is generally mild.

PH Associated with Chronic Thromboembolic Disease The development of PH after chronic thromboembolic obstruction of the pulmonary arteries is well described, but its incidence is not known. The incidence of PH after a single pulmonary embolic event is thought to be quite low, and likely increases following recurrent embolism. The risk factors for developing CTEPH are unclear. Many patients have no history of clinical venous thromboembolism. The pathogenesis of CTEPH is poorly understood. Obstruction of the proximal pulmonary vasculature is important and often the dominant factor; however, additional pulmonary vascular remodeling occurs. Approximately 10–15% of patients will develop a disease very similar clinically and pathologically to PAH after resection of the proximal thrombus.

OTHER DISORDERS AFFECTING THE PULMONARY VASCULATURE

Sarcoidosis Patients with sarcoidosis can develop PH as a result of lung involvement, and those who present with progressive dyspnea and PH require a thorough evaluation. While many sarcoidosis patients with PH do not respond to therapy for PAH, there is a subset of patients with sarcoidosis and severe PH who do have a beneficial response to therapy.

Sickle Cell Disease Cardiovascular system abnormalities are prominent in the clinical spectrum of sickle cell disease, including PH. The etiology is multifactorial, including hemolysis, hypoxemia, thromboembolism, chronic high CO, and chronic liver disease. The presence of PH in patients with sickle cell disease is rare.

Schistosomiasis Globally, schistosomiasis is one of the most common causes of PH. The development of PH occurs in the setting of hepatosplenic disease and portal hypertension. Studies suggest that inflammation from the infection triggers the pulmonary vascular changes that occur. The diagnosis is confirmed by finding the parasite ova in the urine or stool of patients with symptoms, which can be difficult. The efficacy of therapies directed toward PH in these patients is unknown.

PHARMACOLOGIC TREATMENT OF PAH

Without treatment PAH is invariably fatal. There are a rapidly growing number of approved agents for PAH, including prostacyclin and prostacyclin analogues and agonists, NO pathway enhancers, and endothelin receptor antagonists (ERAs) that have improved the outlook dramatically. While there is no cure for PAH, current pharmacologic therapies improve morbidity, and in some cases, mortality.

PROSTANOIDS

In PAH, endothelial dysfunction and platelet activation cause an imbalance of arachidonic acid metabolites with reduced prostacyclin levels and increased thromboxane A_2 production. Prostacyclin (PGI_2) activates cyclic adenosine monophosphate (cAMP)-dependent pathways that mediate vasodilation. PGI_2 also has antiproliferative effects on vascular smooth muscle and inhibits platelet aggregation. Protein levels of prostacyclin synthase are decreased in pulmonary arteries of patients with PAH. This imbalance of mediators is addressed by the exogenous administration of prostanoids as therapy in advanced PAH.

Epoprostenol was the first prostanoid available for the management of PAH. Epoprostenol delivered as a continuous intravenous infusion improves functional capacity and survival in PAH. The efficacy of epoprostenol in WHO FC class 3 and 4 PAH patient was demonstrated in a clinical trial that showed improved quality of life, mPAP, PVR, 6-minute walk distance (MWD) and mortality. Treprostinil has a longer half-life than epoprostenol (~4 hours vs ~6 minutes), which allows for subcutaneous and continuous intravenous administration. Treprostinil has been shown to improve pulmonary hemodynamics, symptoms, exercise capacity, and, survival in PAH.

Inhaled prostacyclins provide the beneficial effects of infused prostacyclin therapy without the inconvenience and side effects (risk of infection and infusion site reactions) of infusion catheters. Both inhaled iloprost and treprostinil have been approved for patients with WHO FC class 3 and 4 PAH. The main advantage of treprostinil is less frequent administration. Inhaled formulations can be efficacious in moderately symptomatic patients with PAH and may be appropriate when used in combination with an oral medication. Phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil) increase cyclic guanosine monophosphate (cGMP) levels and activate cGMP-dependent signaling pathways that also mediate vasodilation and platelet inhibition. The addition of a phosphodiesterase-5 (PDE5) inhibitor, therefore, augments the pulmonary hemodynamic and functional capacity benefits of prostanoids in PAH.

Oral treprostinil (an extended release formulation) has been assessed in one randomized controlled trial in treatment-naïve and two-combination therapy randomized controlled trials. Oral treprostinil significantly improved 6MWD in comparison with placebo (+23 m in comparison with baseline, P=0.0125) but had no effect on clinical worsening. Both combination therapy trials, in which treprostinil was added on to background therapy with either a PDE5 inhibitor or an ETRA failed to meet their primary end point in 6MWD. As a result of improved exercise tolerance in the monotherapy trial, along with the established clinical efficacy of parenteral and inhaled treprostinil, however, the FDA-approved oral treprostinil for the treatment of WHO group 1 PAH. Oral treprostinil is dosed three times daily, and is slowly titrated to the (maximally) effective dose.

Selexipag is an oral nonprostanoid diphenylpyrazine derivative that binds the prostaglandin I_2 (IP) receptor with high affinity. The active metabolite of selexipag has a prolonged half-life in comparison with prostanoid analogues and permits twice daily dosing. The efficacy of selexipag has been evaluated in a phase 3 randomized controlled trial in patients with PAH in New York Heart Association (NYHA) FC II to III on background therapy with either an endothelin-1 (ET-1) receptor antagonist, sildenafil, or both. This trial represents the largest randomized placebo-controlled trial among patients with PAH ever completed, enrolling more than 1100 patients treated for a median of 1.4 years. Selexipeg significantly reduced the risk of hospitalization and the risk of disease progression by 43% (P<0.0001) compared to those who received placebo. There were no significant differences in mortality between the two study groups. The side effect profile was similar to the prostacyclins.

Endothelin Receptor Antagonists ERAs target ET-1, a potent endogenous vasoconstrictor and vascular smooth muscle mitogen that is elevated in PAH patients. Endothelin levels are increased coincident with increased PVR and mean PAP, and decreased CO and 6MWD.

ERAs block the binding of ET-1 to either endothelin receptor A (ET-A) and/or B (ET-B). ET-A receptors found on pulmonary artery smooth muscle cells (PASMC) mediate vasoconstriction. In the normal pulmonary vasculature, ET-B receptors are found on endothelial cells and mediate ET-1 clearance, as well as vasodilation via production of prostacyclin and NO. The three ERAs approved for use in the United States are bosentan and macitentan, non-selective receptor antagonists; and ambrisentan, a selective ET-A receptor antagonist.

Studies have shown that bosentan improves hemodynamics and exercise capacity and delays clinical worsening. The randomized, placebo controlled, phase III, Bosentan Randomized trial of Endothelin Antagonist THErapy (BREATHE)-1 trial comparing bosentan or placebo demonstrated improved symptoms, 6MWD, and WHO functional class. The Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients (EARLY) study comparing bosentan to placebo demonstrated improved PVR and 6MWD.

Several studies, including the phase III placebo-controlled Ambrisentan in Pulmonary Arterial Hypertension, (ARIES)-1 trial, demonstrate that ambrisentan improves exercise tolerance, WHO functional class, hemodynamics, and quality of life in patients with PAH. There are no trial data to evaluate if the selective ET-A receptor antagonism of ambrisentan has any advantage over the non-selective ET receptor antagonism of bosentan or macitentan.

Nitric Oxide Pathway Nitric oxide (NO) derived from endothelial cells activate guanylyl cyclase that, in turn, generates cGMP in vascular smooth muscle cells and platelets. cGMP is a second messenger that induces vasodilation through relaxation of the arterial smooth muscle cells and inhibits platelet activation. Phosphodiesterase type 5 enzymes metabolize cGMP. Therefore, cGMP phosphodiesterase type 5 (PDE5) inhibitors prolong the vasodilatory effect of NO, especially within the pulmonary arterial bed where high concentrations of cGMP are found. There are currently two PDE5 inhibitors used for the treatment of PAH, sildenafil and tadalafil. Both agents have been shown to improve hemodynamics and 6MWD.

Riociguate is a soluble guanylyl cyclase stimulator acting synergistically with endogenous NO, and also directly stimulating soluble guanylyl cyclase independent of NO availability. Riociguat significantly improved exercise capacity, pulmonary hemodynamics, WHO functional class, and time to clinical worsening in patients with PAH and CTEPH.

Combination Therapy Current guidelines recommend add-on therapy targeting a different pathway when there is an inadequate clinical response or clinical deterioration with monotherapy. Combination therapy has a number of hypothetical advantages. As multiple pathogenic pathways are identified, and the neoplastic nature of PAH is increasingly recognized, this approach may provide increased benefit. This same approach has been used successfully in other complex diseases such as HIV, cancer, and heart failure. Using combination therapy could provide synergy and added benefits, while at the same time allowing for lower doses and potentially decreased side effects. Data are increasingly supportive of initial combination therapy at the time of diagnosis.

A retrospective study from the French PAH network reported benefits of upfront triple combination therapy targeting the three currently available therapeutic pathways. They reviewed 19 patients with severe PAH who were initiated on bosentan, sildenafil, and intravenous epoprostenol therapy simultaneously at the time of diagnosis. Of the 19 patients, 18 had a significant improvement in walking distance and hemodynamics at 4 months compared with baseline. The beneficial effects were sustained to final follow-up evaluation for more than 2 years. More importantly, the 1-, 2-, and 3-year survival rates were 100%. Although these results are encouraging, the findings from this single-center, retrospective analysis need further validation.

TABLE 277-2 FDA-Approved Therapies for the Treatment of Pulmonary Arterial Hypertension (PAH)

GENERIC NAME	ROUTE OF ADMINISTRATION	DRUG CLASS	INDICATION
Epoprostenol	IV	Prostacyclin derivative	Treatment of PAH to improve exercise capacity
Iloprost	Inhaled	Prostacyclin derivative	Treatment of PAH to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration
Treprostinil	IV or SC	Prostacyclin derivative	Treatment of PAH to diminish symptoms associated with exercise
Treprostinil	Inhaled	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Treprostinil	Oral	Prostacyclin derivative	Treatment of PAH to improve exercise ability
Selexipeg	Oral	Selective IP receptor agonist	Treatment of PAH to improve a composite endpoint lack of clinical deterioration
Bosentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and to decrease clinical worsening
Ambrisentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and delay clinical worsening
Macitentan	Oral	Endothelin receptor antagonist	Treatment of PAH to improve a composite endpoint of delay of clinical worsening
Sildenafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise capacity and delay clinical worsening
Tadalafil	Oral	PDE5 inhibitor	Treatment of PAH to improve exercise ability
Riociguat	Oral	Soluble guanylyl cyclase stimulator	Treatment of PAH to improve exercise ability

Abbreviations: IV, intravenous; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; SC, subcutaneous.

The AMBITION trial compared de novo combination therapy to monotherapy in newly diagnosed patients. Patients were randomized to a combination of ambrisentan and tadalafil, ambrisentan monotherapy, or tadalafil monotherapy. Upfront combination therapy with ambrisentan and tadalafil was associated with a 50% lower risk of clinical worsening (composite of death, lung transplantation, hospitalization for PAH worsening, and worsening PAH) when compared with the monotherapy groups. This difference was driven primarily by the delay in time to first hospitalization. Importantly, initial combination therapy was not associated with an increase in adverse events.

Unmet and Future Research Needs in Pulmonary Hypertension Presently there are only three classes of therapy for patients with PAH and, even with therapy, the median survival for a person with PAH is only 5–6 years **(Table 277-2)**. While there are five subtypes of PH, currently approved therapies only address one subtype. Not only do we need to expand the treatment options for patients with PAH, but we also need to develop effective therapies for all patients with PH. Limited survival is, in part, a result of delay in diagnosis. Improved awareness among clinicians and patients could lead to more timely diagnosis that will affect the response to therapy and survival. PH needs to be diagnosed in a timely manner so that therapy can be initiated as soon as possible. Patients should also have the option of referral to a specialty center that focuses on treatment of patients with pulmonary vascular disease, which will ensure their access to state-of-the-art care and a multidisciplinary approach to care. Finally, there needs to be continued efforts at developing new therapies that target the increasingly complex and overlapping pathways involved in the various forms of PH.

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Section 1 Diagnosis of Respiratory Disorders

278 Approach to the Patient with Disease of the Respiratory System

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The majority of diseases of the respiratory system present with cough and/or dyspnea and fall into one of three major categories: (1) obstructive lung diseases; (2) restrictive disorders; and (3) abnormalities of the vasculature. Obstructive lung diseases are most common and primarily disorders of the airways, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and bronchiolitis. Diseases resulting in restrictive pathophysiology include parenchymal lung diseases, abnormalities of the chest wall and pleura, and neuromuscular disease. Pulmonary embolism, pulmonary hypertension, and pulmonary venoocclusive disease are all disorders of the pulmonary vasculature. Although many specific diseases fall into these major categories, both infective and neoplastic processes can affect the respiratory system and result in myriad pathologic findings, including those listed in the three categories above (Table 278-1).

Disorders can also be grouped according to gas exchange abnormalities, including hypoxemic, hypercarbic, or combined impairment; however, many respiratory disorders do not manifest as gas exchange abnormalities.

As with the evaluation of most patients, the approach to a patient with a respiratory system disorder begins with a thorough history and a focused physical examination. Many patients will subsequently undergo pulmonary function testing, chest imaging, blood and sputum analysis, a variety of serologic or microbiologic studies, and diagnostic procedures, such as bronchoscopy. This stepwise approach is discussed in detail below.

TABLE 278-1 Categories of Respiratory Disease

CATEGORY	EXAMPLES
Obstructive lung disease	Asthma
	Chronic obstructive pulmonary disease (COPD)
	Bronchiectasis
	Bronchiolitis
Restrictive pathophysiology—parenchymal disease	Idiopathic pulmonary fibrosis (IPF)
	Asbestosis
	Desquamative interstitial pneumonitis (DIP)
	Sarcoidosis
Restrictive pathophysiology—neuromuscular weakness	Amyotrophic lateral sclerosis (ALS)
	Guillain-Barré syndrome
	Myasthenia gravis
Restrictive pathophysiology—chest wall/pleural disease	Kyphoscoliosis
	Ankylosing spondylitis
	Chronic pleural effusions
Pulmonary vascular disease	Pulmonary embolism
	Pulmonary arterial hypertension (PAH)
	Pulmonary venoocclusive disease
	Vasculitis
Malignancy	Bronchogenic carcinoma (non-small-cell and small-cell lung cancer)
	Metastatic disease
Infectious diseases	Pneumonia
	Bronchitis
	Tracheitis

HISTORY

Dyspnea and Cough The cardinal symptoms of respiratory disease are dyspnea and cough (Chaps. 33 and 34). Dyspnea has many causes, some of which are not predominantly due to lung pathology. The words a patient uses to describe shortness of breath can suggest certain etiologies for dyspnea. Patients with obstructive lung disease often complain of "chest tightness" or "inability to get a deep breath," whereas patients with congestive heart failure more commonly report "air hunger" or a sense of suffocation.

The tempo of onset and the duration of a patient's dyspnea are likewise helpful in determining the etiology. Acute shortness of breath is usually associated with sudden physiological changes, such as laryngeal edema, bronchospasm, myocardial infarction, pulmonary embolism, or pneumothorax. Patients with COPD and idiopathic pulmonary fibrosis (IPF) experience a gradual progression of dyspnea on exertion, punctuated by acute exacerbations of shortness of breath. In contrast, most asthmatics do not have daily symptoms, but experience intermittent episodes of dyspnea, cough, and chest tightness that are usually associated with specific triggers, such as an upper respiratory tract infection or exposure to allergens.

Specific questioning should focus on factors that incite dyspnea as well as on any intervention that helps resolve the patient's shortness of breath. Asthma is commonly exacerbated by specific triggers, although this can also be true of COPD. Many patients with lung disease report dyspnea on exertion. Determining the degree of activity that results in shortness of breath gives the clinician a gauge of the patient's degree of disability. Many patients adapt their level of activity to accommodate progressive limitation. For this reason, it is important, particularly in older patients, to delineate the activities in which they engage and how these activities have changed over time. Dyspnea on exertion is often an early symptom of underlying lung or heart disease and warrants a thorough evaluation.

For cough, the clinician should inquire about the duration of the cough, whether or not it is associated with sputum production, and any specific triggers that induce it. Acute cough productive of phlegm is often a symptom of infection of the respiratory system, including processes affecting the upper airway (e.g., sinusitis, tracheitis), the lower airways (e.g., bronchitis, bronchiectasis), and the lung parenchyma (e.g., pneumonia). Both the quantity and quality of the sputum, including whether it is blood-streaked or frankly bloody, should be determined. Hemoptysis warrants urgent evaluation as delineated in Chap. 35.

Chronic cough (defined as that persisting for >8 weeks) is commonly associated with obstructive lung diseases, particularly asthma, COPD and chronic bronchiectasis, as well as "nonrespiratory" diseases, such as gastroesophageal reflux and postnasal drip. Diffuse parenchymal lung diseases, including IPF, frequently present as a persistent, nonproductive cough. All causes of cough are not respiratory in origin, and assessment should encompass a broad differential, including cardiac and gastrointestinal diseases as well as psychogenic causes.

Additional Symptoms Patients with respiratory disease may report wheezing, which is suggestive of airways disease, particularly asthma. Hemoptysis can be a symptom of a variety of lung diseases, including infections of the respiratory tract, bronchogenic carcinoma, and pulmonary embolism. In addition, chest pain or discomfort can be respiratory in origin. As the lung parenchyma is not innervated with pain fibers, pain in the chest from respiratory disorders usually results from either diseases of the parietal pleura (e.g., pneumothorax) or pulmonary vascular diseases (e.g., pulmonary hypertension). As many diseases of the lung can result in strain on the right side of the heart, patients may also present with symptoms of cor pulmonale, including abdominal bloating or distention and pedal edema (Chap. 252).

Additional History A thorough social history is an essential component of the evaluation of patients with respiratory disease. All patients should be asked about current or previous cigarette smoking, as this exposure is associated with many diseases of the respiratory system, including COPD, bronchogenic lung cancer, and select parenchymal lung diseases (e.g., desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis). For most of these disorders, increased cigarette smoke exposure (i.e., cigarette pack-years) increases the risk of disease. "Secondhand smoke" also increases risk for some respiratory disorders, so patients should also be asked about parents, spouses, or housemates who smoke. Possible inhalational exposures at work (e.g., asbestos, silica) or home (e.g., wood smoke, excrement from pet birds) should be explored **(Chap. 283)**. Travel predisposes to certain infections of the respiratory tract, most notably tuberculosis. Potential exposure to fungi is increased in specific geographic regions or climates (e.g., *Histoplasma capsulatum*), so exposures to these regions should be determined.

Associated symptoms of fever and chills should raise the suspicion of infective etiologies, both pulmonary and systemic. A comprehensive review of systems may suggest rheumatologic or autoimmune disease presenting with respiratory tract manifestations. Questions should focus on joint pain or swelling, rashes, dry eyes, dry mouth, or constitutional symptoms. In addition, carcinomas from a variety of primary sources commonly metastasize to the lung and cause respiratory symptoms. Finally, therapy for other conditions, including both irradiation and medications, can result in diseases of the chest.

Physical Examination The clinician's suspicion of respiratory disease often begins with patient's vital signs. The respiratory rate is informative, whether elevated (tachypnea) or depressed (hypopnea). In addition, pulse oximetry should be measured, as many patients with respiratory disease have hypoxemia, either at rest or with exertion.

The first step of the physical examination is inspection. Patients with respiratory disease may be in distress, using accessory muscles of respiration to breathe. Severe kyphoscoliosis can result in restrictive pathophysiology. Inability to complete a sentence in conversation is generally a sign of severe impairment and should result in an expedited evaluation of the patient.

Percussion of the chest is used to establish diaphragm excursion and lung size. In the setting of decreased breath sounds, percussion is used to distinguish between pleural effusions (dull to percussion) and pneumothorax (hyper-resonant note).

The role of palpation is limited in the respiratory examination. Palpation can demonstrate subcutaneous air in the setting of barotrauma. It can also be used as an adjunctive assessment to determine whether an area of decreased breath sounds is due to consolidation (increased tactile fremitus) or a pleural effusion (decreased tactile fremitus). To detect unilateral disorders of ventilation, the symmetry and degree of chest wall expansion can be assessed during a deep inspiration by placing one's thumbs together at the midline over the lower posterior chest while grasping the lateral rib cage.

The majority of the manifestations of respiratory disease present as abnormalities of auscultation. Wheezes are a manifestation of airway obstruction. While most commonly a sign of asthma, peribronchial edema in the setting of congestive heart failure can also result in diffuse wheezes, as can any other process that causes narrowing of small airways. Wheezes can be polyphonic, involving multiple different size airways (e.g., asthma) or monophonic, involving one size airway (e.g., bronchogenic carcinoma). For these reasons, clinicians must take care not to attribute all wheezing to asthma.

Rhonchi are a manifestation of obstruction of medium-sized airways, most often with secretions. In the acute setting, this manifestation may be a sign of viral or bacterial bronchitis. Chronic rhonchi suggest bronchiectasis or COPD. In contrast to expiratory wheezes and rhonchi, stridor is a high-pitched, focal inspiratory wheeze, usually heard over the neck as a manifestation of upper airway obstruction.

Crackles, or rales, are commonly a sign of alveolar disease. Processes that fill the alveoli with fluid may result in crackles, including pulmonary edema and pneumonia. Crackles in pulmonary edema are generally more prominent at the bases. Interestingly, diseases that result in fibrosis of the interstitium (e.g., IPF) also result in crackles that sound like Velcro being ripped apart. Although some clinicians make a distinction between "wet" and "dry" crackles, this distinction has not been shown to be a reliable way to differentiate among etiologies of respiratory disease.

One way to help distinguish between crackles associated with alveolar fluid and those associated with interstitial fibrosis is to assess for egophony. *Egophony* is the auscultation of the sound "AH" instead of "EEE" when a patient phonates "EEE." This change in note is due to abnormal sound transmission through consolidated parenchyma and is present in pneumonia but not in IPF. Similarly, areas of alveolar filling have increased whispered *pectoriloquy* as well as transmission of larger-airway sounds (i.e., bronchial breath sounds in a lung zone where vesicular breath sounds are expected).

The lack or diminution of breath sounds can also help determine the etiology of respiratory disease. Patients with emphysema often have a quiet chest with diffusely decreased breath sounds. A pneumothorax or pleural effusion may present with an area of absent breath sounds.

Other Systems Pedal edema, if symmetric, may suggest cor pulmonale; if asymmetric, it may be due to deep venous thrombosis and associated pulmonary embolism. Jugular venous distention may also be a sign of volume overload associated with right heart failure. *Pulsus paradoxus* is an ominous sign in a patient with obstructive lung disease, as it is associated with significant negative intrathoracic (pleural) pressures required for ventilation and impending respiratory failure.

As stated earlier, rheumatologic disease may manifest primarily as lung disease. Owing to this association, particular attention should be paid to joint and skin examination. Clubbing can be found in many lung diseases, including cystic fibrosis, IPF, and lung cancer. Cyanosis is seen in hypoxemic respiratory disorders that result in >5 g of deoxygenated hemoglobin/dL.

DIAGNOSTIC EVALUATION

The sequence of studies is dictated by the clinician's differential diagnosis, as determined by the history and physical examination. Acute respiratory symptoms are often evaluated with multiple tests performed at the same time in order to diagnose any life-threatening diseases rapidly (e.g., pulmonary embolism or multilobar pneumonia). In contrast, chronic dyspnea and cough can be evaluated in a more protracted, stepwise fashion.

Pulmonary Function Testing (See also Chap. 280) The initial pulmonary function test obtained is spirometry. This study is an effort-dependent test used to assess for obstructive pathophysiology as seen in asthma, COPD, and bronchiectasis. A diminished-forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) (often defined as <70%) is diagnostic of obstruction. In addition to measuring FEV_1 and FVC, the clinician should examine the flow-volume loop (which is less effort-dependent). A plateau of the inspiratory and expiratory curves suggests large-airway obstruction in extrathoracic and intrathoracic locations, respectively.

Spirometry with symmetric decreases in FEV_1 and FVC warrants further testing, including measurement of lung volumes and the diffusion capacity of the lung for carbon monoxide (D_{LCO}). A total lung capacity <80% of the patient's predicted value defines restrictive pathophysiology. Restriction can result from parenchymal disease, neuromuscular weakness, or chest wall or pleural diseases (Table 278-1). Restriction with impaired gas exchange, as indicated by a decreased D_{LCO}, suggests parenchymal lung disease. Additional testing, such as measurements of maximal inspiratory and expiratory pressures, can help diagnose neuromuscular weakness. Normal spirometry, normal lung volumes, and a low D_{LCO} should prompt further evaluation for pulmonary vascular disease.

Arterial blood gas testing is often helpful in assessing respiratory disease. Hypoxemia, while usually apparent with pulse oximetry, can be further evaluated with the measurement of arterial PO_2 and the calculation of an alveolar gas and arterial blood oxygen tension difference ($[A–a]DO_2$). Patients with diseases that cause ventilation-perfusion

mismatch or shunt physiology have an increased (A–a)DO_2 at rest. Arterial blood gas testing also allows the measurement of arterial P_{CO_2}. Hypercarbia can accompany disorders of ventilation, as seen in severe airway obstruction (e.g., COPD) or progressive restrictive physiology.

Chest Imaging **(See Chap. A12)** Most patients with disease of the respiratory system undergo imaging of the chest as part of the initial evaluation. Clinicians should generally begin with ultrasound of the chest or a plain chest radiograph, preferably posterior-anterior and lateral films. Ultrasound is often readily available and can help rapidly diagnose pneumothorax, pleural effusion, and consolidation of lung parenchyma. Chest radiographs give additional detail and can reveal findings including opacities of the parenchyma, blunting of the costophrenic angles, mass lesions, and volume loss. However, many diseases of the respiratory system, particularly those of the airways and pulmonary vasculature, are associated with a normal chest radiograph.

CT scan of the chest can also be useful to delineate parenchymal processes, pleural disease, masses or nodules, and large airways. If the test includes administration of contrast, the pulmonary vasculature can be assessed with particular utility for determination of pulmonary emboli. Intravenous contrast also allows lymph nodes to be examined in greater detail. When coupled with positron emission testing (PET), lesions of the chest can be assessed for metabolic activity; helping differentiate between malignancy and scar.

FURTHER STUDIES

Depending on the clinician's suspicion, a variety of other studies may be done. Concern about large-airway lesions may warrant bronchoscopy. This procedure may also be used to sample the alveolar space with bronchoalveolar lavage or to obtain nonsurgical lung biopsies. Blood testing may include assessment for hypercoagulable states in the setting of pulmonary vascular disease, serologic testing for infectious or rheumatologic disease, or assessment of inflammatory markers or leukocyte counts (e.g., eosinophils). Genetic testing is increasingly used for heritable lung diseases such as cystic fibrosis. Sputum evaluation for malignant cells or microorganisms may be appropriate. An echocardiogram to assess right- and left-sided heart function is often obtained. Finally, at times, a surgical lung biopsy is needed to diagnose certain diseases of the respiratory system. All of these studies will be guided by the preceding history, physical examination, pulmonary function testing, and chest imaging.

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279 Disturbances of Respiratory Function

Edward T. Naureckas, Julian Solway

The primary functions of the respiratory system—to oxygenate blood and eliminate carbon dioxide—require virtual contact between blood and fresh air, which facilitates diffusion of respiratory gases between blood and gas. This process occurs in the lung alveoli, where blood flowing through alveolar wall capillaries is separated from alveolar gas by an extremely thin membrane of flattened endothelial and epithelial cells, across which respiratory gases diffuse and equilibrate. Blood flow through the lung is unidirectional via a continuous vascular path along which venous blood absorbs oxygen from and loses CO_2 to inspired gas. The path for airflow, in contrast, reaches a dead end at the alveolar walls; thus the alveolar space must be ventilated tidally, with inflow of fresh gas and outflow of alveolar gas alternating periodically at the respiratory rate (RR). To provide an enormous alveolar surface area (typically 70 m^2) for blood-gas diffusion within the modest volume of a thoracic cavity (typically 7 L), nature has distributed both blood flow and ventilation among millions of tiny alveoli through multigenerational branching of both pulmonary arteries and bronchial airways. As a consequence of variations in tube lengths and calibers along these pathways as well as the effects of gravity, tidal pressure fluctuations, and anatomic constraints from the chest wall, the alveoli vary in their relative ventilations and perfusions. Not surprisingly, for the lung to be most efficient in exchanging gas, the fresh gas ventilation of a given alveolus must be matched to its perfusion.

For the respiratory system to succeed in oxygenating blood and eliminating CO_2, it must be able to ventilate the lung tidally and thus to freshen alveolar gas; it must provide for perfusion of the individual alveolus in a manner proportional to its ventilation; and it must allow adequate diffusion of respiratory gases between alveolar gas and capillary blood. Furthermore, it must accommodate several-fold increases in the demand for oxygen uptake or CO_2 elimination imposed by metabolic needs or acid-base derangement. Given these multiple requirements for normal operation, it is not surprising that many diseases disturb respiratory function. This chapter considers in some detail the physiologic determinants of lung ventilation and perfusion, elucidates how the matching distributions of these processes and rapid gas diffusion allow normal gas exchange, and discusses how common diseases derange these normal functions, thereby impairing gas exchange—or at least increasing the work required by the respiratory muscles or heart to maintain adequate respiratory function.

VENTILATION

It is useful to conceptualize the respiratory system as three independently functioning components: the lung, including its airways; the neuromuscular system; and the chest wall, which includes everything that is not lung or active neuromuscular system. Accordingly, the mass of the respiratory muscles is part of the chest wall, while the force these muscles generate is part of the neuromuscular system; the abdomen (especially an obese abdomen) and the heart (especially an enlarged heart) are, for these purposes, part of the chest wall. Each of these three components has mechanical properties that relate to its enclosed volume (or—in the case of the neuromuscular system—the respiratory system volume at which it is operating) and to the rate of change of its volume (i.e., flow).

Volume-Related Mechanical Properties—Statics Figure 279-1 shows the volume-related properties of each component of the respiratory system. Because of both surface tension at the air-liquid interface between alveolar wall lining fluid and alveolar gas and elastic recoil of the lung tissue itself, the lung requires a positive transmural pressure difference between alveolar gas and its pleural surface to stay inflated; this difference is called the *elastic recoil pressure* of the lung, and it increases with lung volume. The lung becomes rather stiff at high volumes, so that relatively small volume changes are accompanied by large changes in transpulmonary pressure; in contrast, the lung is compliant at lower volumes, including those at which tidal breathing normally occurs. At zero inflation pressure, even normal lungs retain some air in the alveoli. Because the small peripheral airways are tethered open by outward radial pull from inflated lung parenchyma attached to adventitia, as the lung deflates during exhalation, those small airways are pulled open progressively less, and eventually close, trapping some gas in the alveoli. This effect can be exaggerated with age and especially with obstructive airway diseases, resulting in gas trapping at quite large lung volumes.

The elastic behavior of the passive chest wall (i.e., in the absence of neuromuscular activation) differs markedly from that of the lung.

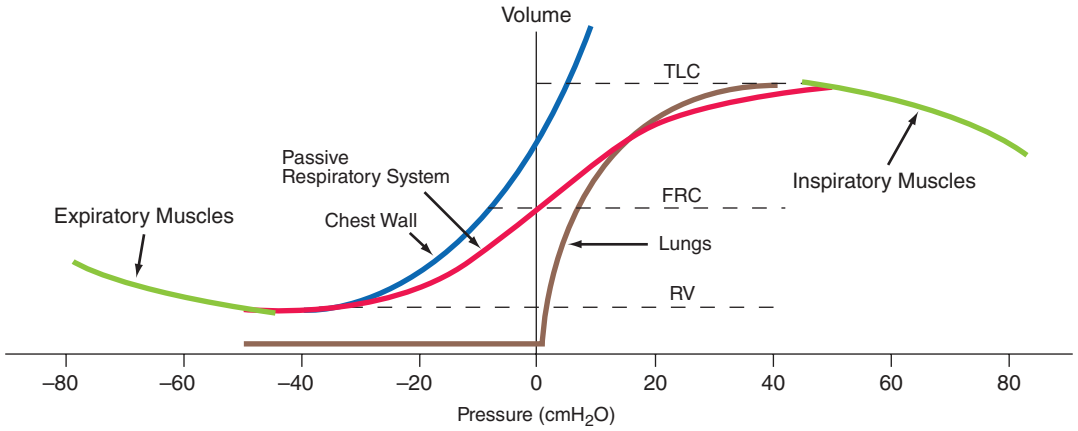

FIGURE 279-1 Pressure-volume curves of the isolated lung, isolated chest wall, combined respiratory system, inspiratory muscles, and expiratory muscles. FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity.

Whereas the lung tends toward full deflation with no distending (transmural) pressure, the chest wall encloses a large volume when pleural pressure equals body surface (atmospheric) pressure. Furthermore, the chest wall is compliant at high enclosed volumes, readily expanding even further in response to increases in transmural pressure. The chest wall also remains compliant at small negative transmural pressures (i.e., when pleural pressure falls slightly below atmospheric pressure), but as the volume enclosed by the chest wall becomes quite small in response to large negative transmural pressures, the passive chest wall becomes stiff due to squeezing together of ribs and intercostal muscles, diaphragm stretch, displacement of abdominal contents, and straining of ligaments and bony articulations. Under normal circumstances, the lung and the passive chest wall enclose essentially the same volume, the only difference being the volumes of the pleural fluid and of the lung parenchyma (normally both quite small in the absence of disease). For this reason and because the lung and chest wall function in mechanical series, the pressure required to displace the passive respiratory system (lungs plus chest wall) at any volume is simply the sum of the elastic recoil pressure of the lungs and the transmural pressure across the chest wall. When plotted against respiratory system volume, this relationship assumes a sigmoid shape, exhibiting stiffness at high lung volumes (imparted by the lung), stiffness at low lung volumes (imparted by the chest wall or sometimes by airway closure), and compliance in the middle range of lung volumes where normal tidal breathing occurs. In addition, a passive resting point of the respiratory system is attained when alveolar gas pressure equals body surface pressure (i.e., when the transrespiratory system pressure is zero). At this volume (called the *functional residual capacity* [FRC]), the outward recoil of the chest wall is balanced exactly by the inward recoil of the lung. As these recoils are transmitted through the pleural fluid, the lung is pulled both outward and inward simultaneously at FRC, and thus its pressure falls below atmospheric pressure (typically, -5 cmH_2O).

The normal passive respiratory system would equilibrate at the FRC and remain there were it not for the actions of the respiratory muscles. The inspiratory muscles act on the chest wall to generate the equivalent of positive pressure across the lungs and passive chest wall, while the expiratory muscles generate the equivalent of negative transrespiratory pressure. The maximal pressures these sets of muscles can generate vary with the lung volume at which they operate. This variation is due to length-tension relationships in striated muscle sarcomeres and to changes in mechanical advantage as the angles of insertion change with lung volume (Fig. 279-1). Nonetheless, under normal conditions, the respiratory muscles are substantially "overpowered" for their roles and generate more than adequate force to drive the respiratory system to its stiffness extremes, as determined by the lung (total lung capacity [TLC]) or by chest wall or airway closure (residual volume [RV]); the airway closure always prevents the adult lung from emptying completely under normal circumstances. The excursion between full and minimal lung inflation is called *vital capacity* (VC; **Fig. 279-2**) and is readily seen to be the difference between volumes at two unrelated stiffness extremes—one determined by the lung (TLC) and the other by the chest wall or airways (RV). Thus, although VC is easy to measure (see below), it provides little information about the intrinsic properties of the respiratory system. As will become clear, it is much more useful for the clinician to consider TLC and RV individually.

Flow-Related Mechanical Properties—Dynamics The passive chest wall and active neuromuscular system both exhibit mechanical behaviors related to the rate of change of volume, but these behaviors become quantitatively important only at markedly supraphysiologic breathing frequencies (e.g., during high-frequency mechanical ventilation), and thus will not be addressed here. In contrast, the dynamic airflow properties of the lung substantially affect its ability to ventilate and contribute importantly to the work of breathing, and these properties are often deranged by disease. Understanding dynamic airflow properties is, therefore, worthwhile.

As with the flow of any fluid (gas or liquid) in any tube, maintenance of airflow within the pulmonary airways requires a pressure gradient that falls along the direction of flow, the magnitude of which is determined by the flow rate and the frictional resistance to flow. During quiet tidal breathing, the pressure gradients driving inspiratory or expiratory flow are small owing to the very low frictional resistance of normal pulmonary airways (R_{aw}, normally <2 $cmH_2O/L/s$). However, during rapid exhalation, another phenomenon reduces flow below that which would have been expected if frictional resistance were the only impediment to flow. This phenomenon is called *dynamic airflow limitation*, and it occurs because the bronchial airways through which air is exhaled are collapsible rather than rigid **(Fig. 279-3)**. An important anatomic feature of the pulmonary airways is its treelike branching structure. While the individual airways in each successive generation, from most proximal (trachea) to most distal (respiratory bronchioles), are smaller than those of the parent generation, their number increases exponentially such that the summed cross-sectional area of the airways becomes very large toward the lung periphery. Because flow

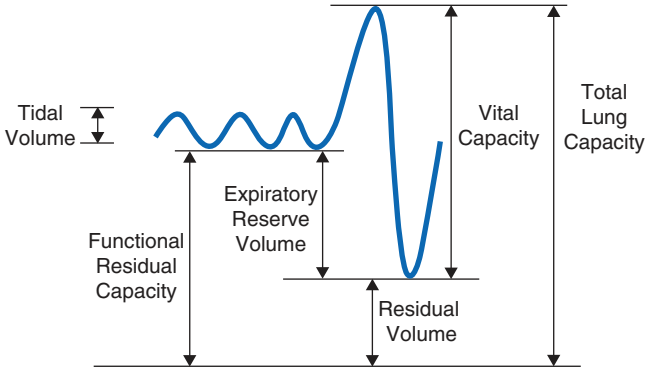

FIGURE 279-2 Spirogram demonstrating a slow vital capacity maneuver and various lung volumes.

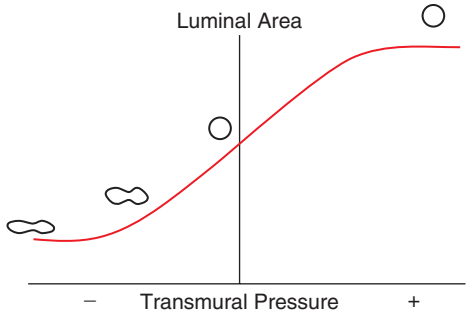

FIGURE 279-3 Luminal area versus transmural pressure relationship. Transmural pressure represents the pressure difference across the airway wall from inside to outside.

(volume/time) is constant along the airway tree, the velocity of airflow (flow/summed cross-sectional area) is much greater in the central airways than in the peripheral airways. During exhalation, gas leaving the alveoli must, therefore, gain velocity as it proceeds toward the mouth. The energy required for this "convective" acceleration is drawn from the component of gas energy manifested as its local pressure, which reduces intraluminal gas pressure, airway transmural pressure, airway size (Fig. 279-3), and flow. This phenomenon is the Bernoulli effect, the same effect that keeps an airplane airborne, generating a lifting force by decreasing pressure above the curved upper surface of the wing due to acceleration of air flowing over the wing. If an individual tries to exhale more forcefully, the local velocity increases further and reduces airway size further, resulting in no net increase in flow. Under these circumstances, flow has reached its maximum possible value, or its *flow limit*. Lungs normally exhibit such dynamic airflow limitation. This limitation can be assessed by spirometry, in which an individual inhales fully to TLC and then forcibly exhales to RV. One useful spirometric measure is the volume of air exhaled during the forced expiratory volume 1 s (FEV_1), as discussed later. Maximal expiratory flow at any lung volume is determined by gas density, airway cross-section and distensibility, elastic recoil pressure of the lung, and frictional pressure loss to the flow-limiting airway site. Under normal conditions, maximal expiratory flow falls with lung volume **(Fig. 279-4)**, primarily because of the dependence of lung recoil pressure on lung volume (Fig. 279-1). In pulmonary fibrosis, lung recoil pressure is increased at any lung volume, and thus the maximal expiratory flow is elevated when considered in relation to lung volume. Conversely, in emphysema, lung recoil pressure is reduced; this reduction is a principal mechanism by which maximal expiratory flows fall. Diseases that narrow the airway lumen at any transmural pressure (e.g., asthma or chronic bronchitis) or that cause excessive airway collapsibility (e.g., tracheomalacia) also reduce maximal expiratory flow.

The Bernoulli effect also applies during inspiration, but the more negative pleural pressures during inspiration lower the pressure outside of the airways, thereby increasing transmural pressure and promoting airway expansion. Thus, inspiratory airflow limitation seldom occurs due to diffuse pulmonary airway disease. Conversely, extrathoracic airway narrowing (e.g., due to a tracheal adenoma or post-tracheostomy stricture) can lead to inspiratory airflow limitation (Fig. 279-4).

The Work of Breathing In health, the elastic (volume change-related) and dynamic (flow-related) loads that must be overcome to ventilate the lungs at rest are small, and the work required of the respiratory muscles is minimal. However, the work of breathing can increase considerably due to a metabolic requirement for substantially increased ventilation, an abnormally increased mechanical load, or both. As discussed below, the rate of ventilation is primarily set by the need to eliminate carbon dioxide, and thus ventilation increases during exercise (sometimes by >20-fold) and during metabolic acidosis as a compensatory response. Naturally, the work rate required to overcome the elasticity of the respiratory system increases with both the depth and the frequency of tidal breaths, while the work required to overcome the dynamic load increases with total ventilation. A modest increase of ventilation is most efficiently achieved by increasing tidal volume but not RR, which is the normal ventilatory response to lower-level exercise. At higher levels of exercise, deep breathing persists, but RR also increases.

The work of breathing also increases when disease reduces the compliance of the respiratory system or increases the resistance to airflow. The former occurs commonly in diseases of the lung parenchyma (interstitial processes or fibrosis, alveolar filling diseases such as pulmonary edema or pneumonia, or substantial lung resection), and the latter occurs in obstructive airway diseases such as asthma, chronic bronchitis, emphysema, and cystic fibrosis. Furthermore, severe airflow obstruction can functionally reduce the compliance of the respiratory system by leading to dynamic hyperinflation. In this scenario, expiratory flows slowed by the obstructive airways disease may be insufficient to allow complete exhalation during the expiratory phase of tidal breathing; as a result, the "functional residual capacity (FRC)" from which the next breath is inhaled is greater than the static FRC. With repetition of incomplete exhalations of each tidal breath, the operating FRC becomes dynamically elevated, sometimes to a level that approaches TLC. At these high lung volumes, the respiratory system is much less compliant than at normal breathing volumes, and thus the elastic work of each tidal breath is also increased. The dynamic pulmonary hyperinflation that accompanies severe airflow obstruction causes patients to sense difficulty in inhaling—even though

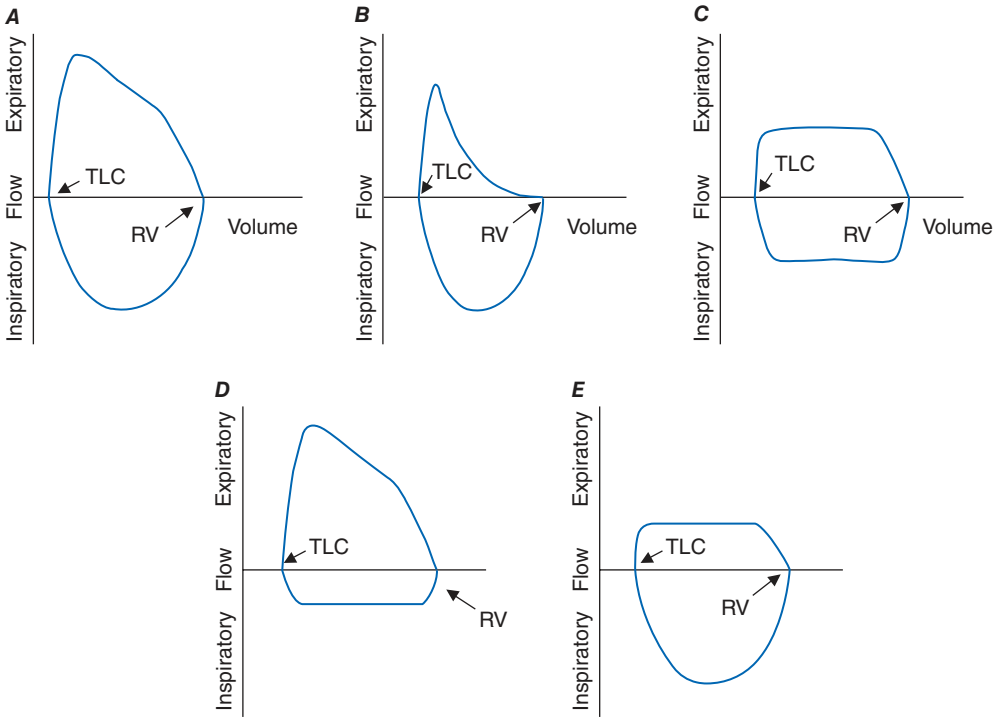

FIGURE 279-4 Flow-volume loops. ***A.*** Normal. ***B.*** Airflow obstruction. ***C.*** Fixed central airway obstruction (either above or below the thoracic inlet). ***D.*** Variable upper airway obstruction (above the thoracic inlet) ***E.*** Variable lower airway obstruction (below the thoracic inlet); RV, residual volume; TLC, total lung capacity.

the root cause of this pathophysiologic abnormality is expiratory airflow obstruction.

Adequacy of Ventilation As noted above, the respiratory control system that sets the rate of ventilation responds to chemical signals, including arterial CO_2 and oxygen tensions and blood pH, and to volitional needs, such as the need to inhale deeply before playing a long phrase on the trumpet. Disturbances in ventilation are discussed in Chap. 290. The focus of this chapter is on the relationship between ventilation of the lung and CO_2 elimination.

At the end of each tidal exhalation, the conducting airways are filled with alveolar gas that did not reach the mouth when expiratory flow stopped. During the ensuing inhalation, fresh gas immediately enters the airway tree at the mouth, but the gas first entering the alveoli at the start of inhalation is that same alveolar gas in the conducting airways that had just left the alveoli. Accordingly, fresh gas does not enter the alveoli until the volume of the conducting airways has been inspired. This volume is called the *anatomic dead space* (V_D). Quiet breathing with tidal volumes smaller than the anatomic dead space introduces no fresh gas into the alveoli at all; only that part of the inspired tidal volume (V_T) that is greater than the V_D introduces fresh gas into the alveoli. The dead space can be further increased functionally if some of the inspired tidal volume is delivered to a part of the lung that receives no pulmonary blood flow and thus cannot contribute to gas exchange (e.g., the portion of the lung distal to a large pulmonary embolus). In this situation, exhaled minute ventilation ($\dot{V}_E = V_T \times RR$) includes a component of dead space ventilation ($\dot{V}_D = V_D \times RR$) and a component of fresh gas alveolar ventilation ($\dot{V}_A = [V_T - V_D] \times RR$). CO_2 elimination from the alveoli is equal to $\dot{V}_A$ times the difference in CO_2 fraction between inspired air (essentially zero) and alveolar gas (typically ~5.6% after correction for humidification of inspired air, corresponding to 40 mmHg). In the steady state, the alveolar fraction of CO_2 is equal to metabolic CO_2 production divided by alveolar ventilation. Because, as discussed below, alveolar and arterial CO_2 tensions are equal, and because the respiratory controller normally strives to maintain arterial P_{CO_2} (Pa_{CO_2}) at ~40 mmHg, the adequacy of alveolar ventilation is reflected in Pa_{CO_2}. If the Pa_{CO_2} falls much below 40 mmHg, alveolar hyperventilation is present; if the Pa_{CO_2} exceeds 40 mmHg, alveolar hypoventilation is present. Ventilatory failure is characterized by extreme alveolar hypoventilation.

As a consequence of oxygen uptake of alveolar gas into capillary blood, alveolar oxygen tension falls below that of inspired gas. The rate of oxygen uptake (determined by the body's metabolic oxygen consumption) is related to the average rate of metabolic CO_2 production, and their ratio—the "respiratory quotient" ($R = \dot{V}_{CO_2}/\dot{V}_{O_2}$)—depends largely on the fuel being metabolized. For a typical American diet, R is usually around 0.85. Together, these phenomena allow the estimation of alveolar oxygen tension, according to the following relationship, known as the *alveolar gas equation*:

$$Pa_{O_2} = FI_{O_2} \times (P_{bar} - P_{H_2O}) - Pa_{CO_2}/R$$

The alveolar gas equation also highlights the influences of inspired oxygen fraction (FI_{O_2}), barometric pressure (P_{bar}), and vapor pressure of water (P_{H_2O} = 47 mmHg at 37°C) in addition to alveolar ventilation (which sets Pa_{CO_2}) in determining Pa_{O_2}. An implication of the alveolar gas equation is that severe arterial hypoxemia rarely occurs as a pure consequence of alveolar hypoventilation at sea level while an individual is breathing air. The potential for alveolar hypoventilation to induce severe hypoxemia with otherwise normal lungs increases as P_{bar} falls with increasing altitude.

GAS EXCHANGE

Diffusion For oxygen to be delivered to the peripheral tissues, it must pass from alveolar gas into alveolar capillary blood by diffusing through alveolar membrane. The aggregate alveolar membrane is highly optimized for this process, with a very large surface area and minimal thickness. Diffusion through the alveolar membrane is so efficient in the human lung that in most circumstances hemoglobin of a red blood cell becomes fully oxygen saturated by the time the cell has traveled just one-third the length of the alveolar capillary. Thus, the uptake of alveolar oxygen is ordinarily limited by the amount of blood transiting the alveolar capillaries rather than by the rapidity with which oxygen can diffuse across the membrane; consequently, oxygen uptake from the lung is said to be "perfusion limited" rather than diffusion limited. CO_2 also equilibrates rapidly across the alveolar membrane. Therefore, the oxygen and CO_2 tensions in capillary blood leaving a normal alveolus are essentially equal to those in alveolar gas. Only in rare circumstances (e.g., at high altitude or in high-performance athletes exerting maximal effort) is oxygen uptake from normal lungs diffusion limited. Diffusion limitation can also occur in interstitial lung disease if substantially thickened alveolar walls remain perfused.

Ventilation/Perfusion Heterogeneity As noted above, for gas exchange to be most efficient, ventilation to each individual alveolus (among the millions of alveoli) should match perfusion to its accompanying capillaries. Because of the differential effects of gravity on lung mechanics and blood flow throughout the lung and because of differences in airway and vascular architecture among various respiratory paths, there is minor ventilation/perfusion heterogeneity even in the normal lung; however, $\dot{V}/\dot{Q}$ heterogeneity can be particularly marked in disease. Two extreme examples are (1) ventilation of unperfused lung distal to a pulmonary embolus, in which ventilation of the physiologic dead space is "wasted" in the sense that it does not contribute to gas exchange; and (2) perfusion of nonventilated lung (a "shunt"), which allows venous blood to pass through the lung unaltered. When mixed with fully oxygenated blood leaving other well-ventilated lung units, shunted venous blood disproportionately lowers the mixed arterial Pa_{O_2} as a result of the nonlinear oxygen content versus Po_2 relationship of hemoglobin (Fig. 279-5). Furthermore, the resulting arterial hypoxemia is refractory to supplemental inspired oxygen. The reason is that (1) raising the inspired FI_{O_2} has no effect on alveolar gas tensions in nonventilated alveoli and (2) while raising inspired FI_{O_2} increases Pa_{CO_2} in ventilated alveoli, the oxygen content of blood exiting ventilated units increases only slightly, as hemoglobin will already have been nearly fully saturated and the solubility of oxygen in plasma is quite small.

A more common occurrence than the two extreme examples given above is a widening of the distribution of ventilation/perfusion ratios; such $\dot{V}/\dot{Q}$ heterogeneity is a common consequence of lung disease. In this circumstance, perfusion of relatively underventilated alveoli results in the incomplete oxygenation of exiting blood. When mixed with well-oxygenated blood leaving higher $\dot{V}/\dot{Q}$ regions, this partially reoxygenated blood disproportionately lowers arterial Pa_{O_2}, although to a lesser extent than does a similar perfusion fraction of blood leaving regions of pure shunt. In addition, in contrast to shunt regions, inhalation of supplemental oxygen raises the Pa_{O_2}, even in relatively underventilated low $\dot{V}/\dot{Q}$ regions, and so the arterial hypoxemia induced by $\dot{V}/\dot{Q}$ heterogeneity is typically responsive to oxygen therapy (Fig. 279-5).

In sum, arterial hypoxemia can be caused by substantial reduction of inspired oxygen tension, severe alveolar hypoventilation, perfusion of relatively underventilated (low $\dot{V}/\dot{Q}$) or completely unventilated (shunt) lung regions, and, in very unusual circumstances, by limitation of gas diffusion.

PATHOPHYSIOLOGY

Although many diseases injure the respiratory system, this system responds to injury in relatively few ways. For this reason, the pattern of physiologic abnormalities may or may not provide sufficient information by which to discriminate among conditions.

Figure 279-6 lists abnormalities in pulmonary function testing that are typically found in a number of common respiratory disorders and highlight the simultaneous occurrence of multiple physiologic abnormalities. The coexistence of some of these respiratory disorders results in more complex superposition of these abnormalities. Methods to measure respiratory system function clinically are described later in this chapter.

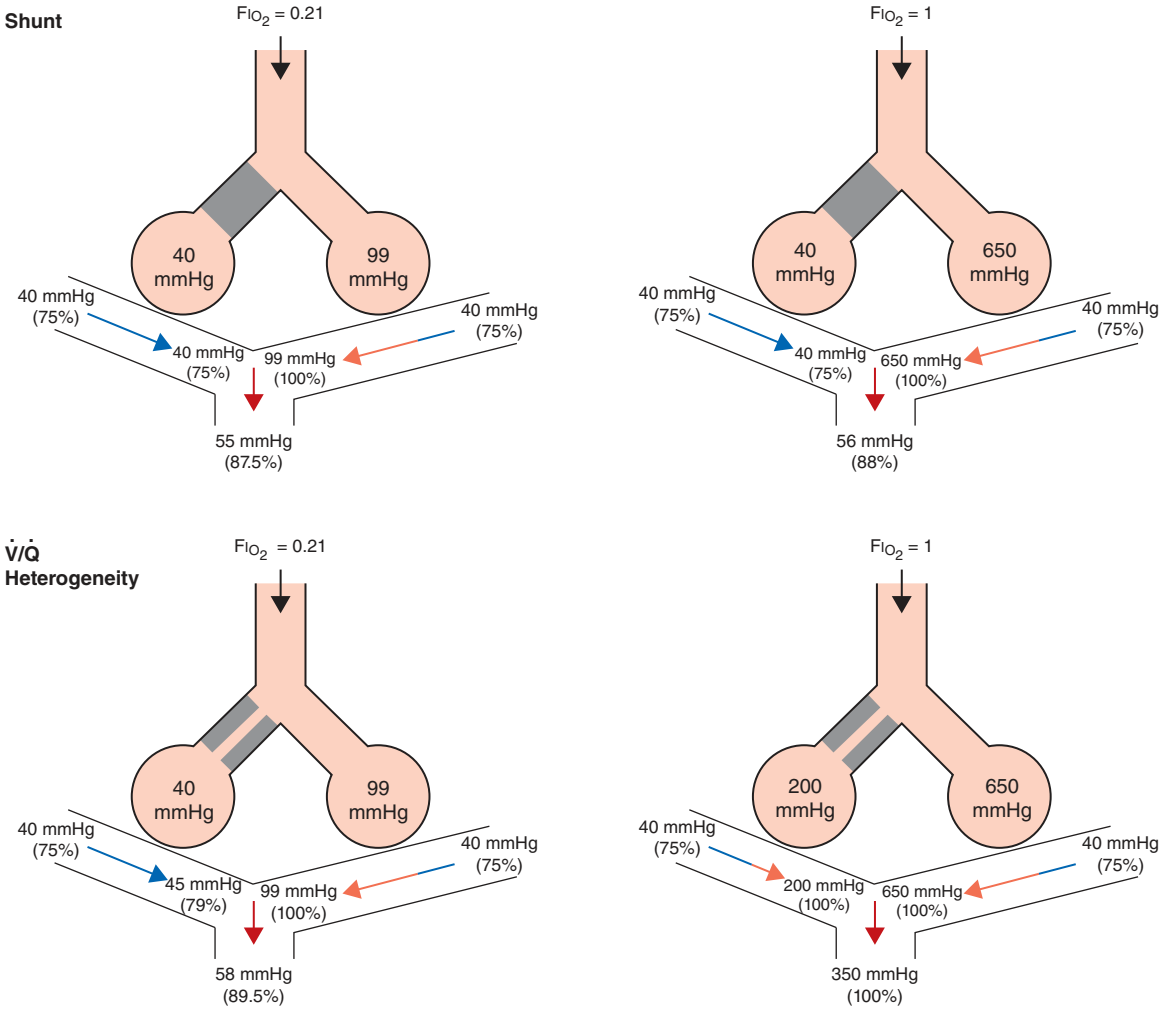

FIGURE 279-5 Influence of air versus oxygen breathing on mixed arterial oxygenation in shunt and ventilation/perfusion heterogeneity. Partial pressure of oxygen (mmHg) and oxygen saturations are shown for mixed venous blood, for end capillary blood (normal vs affected alveoli), and for mixed arterial blood. $F_{I_{O_2}}$, fraction of inspired oxygen; V̇/Q̇, ventilation/perfusion.

	Restriction due to increased lung elastic recoil (pulmonary fibrosis)	Restriction due to chest wall abnormality (moderate obesity)	Restriction due to respiratory muscle weakness (myasthenia gravis)	Obstruction due to airway narrowing (acute asthma)	Obstruction due to decreased elastic recoil (severe emphysema)
TLC	60%	95%	75%	100%	130%
FRC	60%	65%	100%	104%	220%
RV	60%	100%	120%	120%	310%
FVC	60%	92%	60%	90%	60%
FEV_1	75%	92%	60%	35% pre-b.d. 75% post-b.d.	35% pre-b.d. 38% post-b.d.
R_{aw}	1.0	1.0	1.0	2.5	1.5
$D_{L_{CO}}$	60%	95%	80%	120%	40%

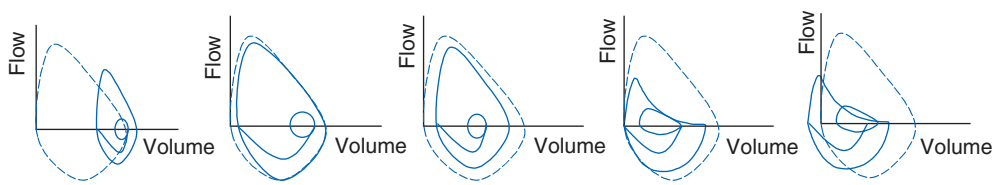

FIGURE 279-6 Common abnormalities of pulmonary function (see text). Pulmonary function values are expressed as a percentage of normal predicted values, except for R_{aw}, which is expressed as $cmH_2O/L/s$ (normal, <2 $cmH_2O/L/s$). The figures at the bottom of each column show the typical configuration of flow-volume loops in each condition, including the flow-volume relationship during tidal breathing. b.d., bronchodilator; $D_{L_{CO}}$, diffusion capacity of lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; R_{aw}, airways resistance; RV, residual volume; TLC, total lung capacity.

Ventilatory Restriction due to Increased Elastic Recoil—Example: Idiopathic Pulmonary Fibrosis Idiopathic pulmonary fibrosis raises lung recoil at all lung volumes, thereby lowering TLC, FRC, and RV as well as forced vital capacity (FVC). Maximal expiratory flows are also reduced from normal values but are elevated when considered in relation to lung volumes. Increased flow occurs both because the increased lung recoil drives greater maximal flow at any lung volume and because airway diameters are relatively increased due to greater radially outward traction exerted on bronchi by the stiff lung parenchyma. For the same reason, airway resistance is also normal. Destruction of the pulmonary capillaries by the fibrotic process results in a marked reduction in diffusing capacity (see below). Oxygenation is often severely reduced by persistent perfusion of alveolar units that are relatively underventilated due to fibrosis of nearby (and mechanically linked) lung. The flow-volume loop (see below) looks like a miniature version of a normal loop but is shifted toward lower absolute lung volumes and displays maximal expiratory flows that are increased for any given volume over the normal tracing.

Ventilatory Restriction due to Chest Wall Abnormality—Example: Moderate Obesity As the size of the average American continues to increase, this pattern may become the most common of pulmonary function abnormalities. In moderate obesity, the outward recoil of the chest wall is blunted by the weight of chest wall fat and the space occupied by intra-abdominal fat. In this situation, preserved inward recoil of the lung overbalances the reduced outward recoil of the chest wall, and FRC falls. Because respiratory muscle strength and lung recoil remain normal, TLC is typically unchanged (although it may fall in massive obesity) and RV is normal (but may be reduced in massive obesity). Mild hypoxemia may be present due to perfusion of alveolar units that are poorly ventilated because of airway closure in dependent portions of the lung during breathing near the reduced FRC. Flows remain normal, as does the diffusion capacity of the lung for carbon monoxide ($D_{L_{CO}}$), unless obstructive sleep apnea (which often accompanies obesity) and associated chronic intermittent hypoxemia have induced pulmonary arterial hypertension, in which case $D_{L_{CO}}$ may be low.

Ventilatory Restriction due to Reduced Muscle Strength—Example: Myasthenia Gravis In this circumstance, FRC remains normal, as both lung recoil and passive chest wall recoil are normal. However, TLC is low and RV is elevated because respiratory muscle strength is insufficient to push the passive respiratory system fully toward either volume extreme. Caught between the low TLC and the elevated RV, FVC, and FEV_1 are reduced as "innocent bystanders." As airway size and lung vasculature are unaffected, both R_{aw} and $D_{L_{CO}}$ are normal. Oxygenation is normal unless weakness becomes so severe that the patient has insufficient strength to reopen collapsed alveoli during sighs, with resulting atelectasis.

Airflow Obstruction due to Decreased Airway Diameter—Example: Acute Asthma During an episode of acute asthma, luminal narrowing due to smooth muscle constriction as well as inflammation and thickening within the small- and medium-sized bronchi raise frictional resistance and reduce airflow. "Scooping" of the flow-volume loop is caused by reduction of airflow, especially at lower lung volumes. Often, airflow obstruction can be reversed by inhalation of β_2-adrenergic agonists acutely or by treatment with inhaled steroids chronically. TLC usually remains normal (although elevated TLC is sometimes seen in long-standing asthma), but FRC may be dynamically elevated. RV is often increased due to exaggerated airway closure at low lung volumes, and this elevation of RV reduces FVC. Because central airways are narrowed, R_{aw} is usually elevated. Mild arterial hypoxemia is often present due to perfusion of relatively underventilated alveoli distal to obstructed airways (and is responsive to oxygen supplementation), but $D_{L_{CO}}$ is normal or mildly elevated.

Airflow Obstruction due to Decreased Elastic Recoil—Example: Severe Emphysema Loss of lung elastic recoil in severe emphysema results in pulmonary hyperinflation, of which elevated TLC is the hallmark. FRC is more severely elevated due to both loss of lung elastic recoil and dynamic hyperinflation—the same phenomenon as auto-PEEP (auto–positive end-expiratory pressure), which is the positive end-expiratory alveolar pressure that occurs when a new breath is initiated before the lung volume is allowed to return to FRC. RV is very severely elevated because of airway closure and because exhalation toward RV may take so long that RV cannot be reached before the patient must inhale again. Both FVC and FEV_1 are markedly decreased, the former because of the severe elevation of RV and the latter because loss of lung elastic recoil reduces the pressure driving maximal expiratory flow and also reduces tethering open of small intrapulmonary airways. The flow-volume loop demonstrates marked scooping, with an initial transient spike of flow attributable largely to expulsion of air from collapsing central airways at the onset of forced exhalation. Otherwise, the central airways remain relatively unaffected, so R_{aw} is normal in "pure" emphysema. Loss of alveolar surface and capillaries in the alveolar walls reduces $D_{L_{CO}}$; however, because poorly ventilated emphysematous acini are also poorly perfused (due to loss of their capillaries), arterial hypoxemia usually is not seen at rest until emphysema becomes very severe. However, during exercise, Pa_{O_2} may fall precipitously if extensive destruction of the pulmonary vasculature prevents a sufficient increase in cardiac output and mixed venous oxygen content falls substantially. Under these circumstances, any venous admixture through low $\dot{V}/\dot{Q}$ units has a particularly marked effect in lowering mixed arterial oxygen tension.

FUNCTIONAL MEASUREMENTS

Measurement of Ventilatory Function • LUNG VOLUMES Figure 279-2 demonstrates a spirometry tracing in which the volume of air entering or exiting the lung is plotted over time. In a slow vital capacity maneuver, the patient inhales from FRC, fully inflating the lungs to TLC, and then exhales slowly to RV; VC, the difference between TLC and RV, represents the maximal excursion of the respiratory system. Spirometry discloses relative volume changes during these maneuvers but cannot reveal the absolute volumes at which they occur. To determine absolute lung volumes, two approaches are commonly used: inert gas dilution and body plethysmography. In the former, a known amount of a nonabsorbable inert gas (usually helium or neon) is inhaled in a single large breath or is rebreathed from a closed circuit; the inert gas is diluted by the gas resident in the lung at the time of inhalation, and its final concentration reveals the volume of resident gas contributing to the dilution. A drawback of this method is that regions of the lung that ventilate poorly (e.g., due to airflow obstruction) may not receive much inspired inert gas and so do not contribute to its dilution. Therefore, inert gas dilution (especially in the single-breath method) often underestimates true lung volumes.

In the second approach, FRC is determined by measuring the compressibility of gas within the chest, which is proportional to the volume of gas being compressed. The patient sits in a body plethysmograph (a chamber usually made of transparent plastic to minimize claustrophobia) and, at the end of a normal tidal breath (i.e., when lung volume is at FRC), is instructed to pant against a closed shutter, thus periodically compressing air within the lung slightly. Pressure fluctuations at the mouth and volume fluctuations within the body box (equal but opposite to those in the chest) are determined, and from these measurements, the thoracic gas volume is calculated by means of Boyle's law. Once FRC is obtained, TLC and RV are calculated by adding the value for inspiratory capacity and subtracting the value for expiratory reserve volume, respectively (both values having been obtained during spirometry) (Fig. 279-2). The most important determinants of healthy individuals' lung volumes are height, age, and sex, but there is considerable additional normal variation beyond that accounted for by these parameters. In addition, race influences lung volumes; on average, TLC values are ~12% lower in African Americans and 6% lower in Asian Americans than in Caucasian Americans. In practice, a mean "normal" value is predicted by multivariate regression equations using height, age, and sex, and the patient's value is divided by the predicted value (often with "race correction" applied) to determine "percent predicted."

For most measures of lung function, 85–115% of the predicted value can be normal; however, in health, the various lung volumes tend to scale together. For example, if one is "normal big" with a TLC 110% of the predicted value, all other lung volumes and spirometry values will also approximate 110% of their respective predicted values. This pattern is particularly helpful in evaluating airflow, as discussed below.

AIR FLOW As noted above, spirometry plays a key role in lung volume determination. Even more often, spirometry is used to measure airflow, which reflects the dynamic properties of the lung. During an FVC maneuver, the patient inhales to TLC and then exhales rapidly and forcefully to RV; this method ensures that flow limitation has been achieved, so that the precise effort made has little influence on actual flow. The total amount of air exhaled is the FVC, and the amount of air exhaled in the first second is the FEV_1; the FEV_1 is a flow rate, revealing volume change per time. Like lung volumes, an individual's maximal expiratory flows should be compared with predicted values based on height, age, and sex. While the FEV_1/FVC ratio is typically reduced in airflow obstruction, this condition can also reduce FVC by raising RV, sometimes rendering the FEV_1/FVC ratio "artifactually normal" with the erroneous implication that airflow obstruction is absent. To circumvent this problem, it is useful to compare FEV_1 as a fraction of its predicted value with TLC as a fraction of its predicted value. In health, the results are usually similar. In contrast, even an FEV_1 value that is 95% of its predicted value may actually be relatively low if TLC is 110% of its respective predicted value. In this case, airflow obstruction may be present, despite the "normal" value for FEV_1.

The relationships among volume, flow, and time during spirometry are best displayed in two plots—the spirogram (volume vs time) and the flow-volume loop (flow vs volume) (Fig. 279-4). In conditions that cause airflow obstruction, the site of obstruction is sometimes correlated with the shape of the flow-volume loop. In diseases that cause lower airway obstruction, such as asthma and emphysema, flows decrease more rapidly with declining lung volumes, leading to a characteristic scooping of the flow-volume loop. In contrast, fixed upper-airway obstruction typically leads to inspiratory and/or expiratory flow plateaus (Fig. 279-4).

AIRWAYS RESISTANCE The total resistance of the pulmonary and upper airways is measured in the same body plethysmograph used to measure FRC. The patient is asked once again to pant, but this time against a closed and then opened shutter. Panting against the closed shutter reveals the thoracic gas volume as described above. When the shutter is opened, flow is directed to and from the body box, so that volume fluctuations in the box reveal the extent of thoracic gas compression, which in turn reveals the pressure fluctuations driving flow. Simultaneous measurement of flow allows the calculation of lung resistance (as flow divided by pressure). In health, R_{aw} is very low (<2 $cmH_2O/L/s$), and half of the detected resistance resides within the upper airway. In the lung, most resistance originates in the central airways. For this reason, airways resistance measurement tends to be insensitive to peripheral airflow obstruction.

RESPIRATORY MUSCLE STRENGTH To measure respiratory muscle strength, the patient is instructed to exhale or inhale with maximal effort against a closed shutter while pressure is monitored at the mouth. Pressures >±60 cmH_2O at FRC are considered adequate and make it unlikely that respiratory muscle weakness accounts for any other resting ventilatory dysfunction that is identified.

Measurement of Gas Exchange • DIFFUSING CAPACITY (DL_{CO})

This test uses a small (and safe) amount of carbon monoxide (CO) to measure gas exchange across the alveolar membrane during a 10-s breath hold. CO in exhaled breath is analyzed to determine the quantity of CO crossing the alveolar membrane and combining with hemoglobin in red blood cells. This "single-breath diffusing capacity" (DL_{CO}), value increases with the surface area available for diffusion and the amount of hemoglobin within the capillaries, and it varies inversely with alveolar membrane thickness. Thus, DL_{CO} decreases in diseases that thicken or destroy alveolar membranes (e.g., pulmonary fibrosis, emphysema), curtail the pulmonary vasculature (e.g., pulmonary hypertension), or reduce alveolar capillary hemoglobin (e.g., anemia). Single-breath diffusing capacity may be elevated in acute congestive heart failure, asthma, polycythemia, and pulmonary hemorrhage.

Arterial Blood Gases The effectiveness of gas exchange can be assessed by measuring the partial pressures of oxygen and CO_2 in a sample of blood obtained by arterial puncture. The oxygen content of blood (Ca_{O_2}) depends on arterial saturation ($\%O_2Sat$), which is set by Pa_{O_2}, pH, and Pa_{CO_2} according to the oxyhemoglobin dissociation curve. Ca_{O_2} can also be measured by oximetry (see below):

$$Ca_{O_2}\ (mL/dL) = 1.39\ (mL/dL) \times [hemoglobin](g) \times \%\ O_2\ Sat + 0.003\ (mL/dL/mmHg) \times Pa_{O_2}\ (mmHg)$$

If hemoglobin saturation alone needs to be determined, this task can be accomplished noninvasively with pulse oximetry.

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280 Diagnostic Procedures in Respiratory Disease

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The diagnostic modalities available for assessing the patient with suspected or known respiratory system disease include imaging studies and techniques for acquiring biologic specimens, some of which involve direct visualization of part of the respiratory system. Methods to characterize the functional changes developing as a result of disease, including pulmonary function tests and measurements of gas exchange, are discussed in Chap. 279.

IMAGING STUDIES

ROUTINE RADIOGRAPHY

Routine chest radiography, including both posteroanterior (PA) and lateral views, is an integral part of the diagnostic evaluation of diseases involving the pulmonary parenchyma, the pleura, and, to a lesser extent, the airways and the mediastinum (see Chaps. 278 and A12). Lateral decubitus views are useful for determining whether pleural abnormalities represent freely flowing fluid, whereas apical lordotic views can visualize disease at the lung apices better than the standard

PA view. Portable equipment is often used for acutely ill patients who cannot be transported to a radiology suite but are more difficult to interpret owing to several limitations: (1) the single anteroposterior (AP) projection obtained; (2) variability in over- and underexposure of film; (3) a shorter focal spot-film distance leading to lack of edge sharpness and loss of fine detail; and (4) magnification of the cardiac silhouette and other anterior structures by the AP projection. Common radiographic patterns and their clinical correlates are reviewed in Chap. A12.

Advances in computer technology have allowed the development of digital or computed radiography, which has several benefits: (1) immediate availability of the images; (2) significant postprocessing analysis of images to improve diagnostic information; and (3) ability to store images electronically and to transfer them within or between health care systems.

ULTRASOUND

Diagnostic ultrasound (US) produces images using echoes or reflection of the US beam from interfaces between tissues with differing acoustic properties. US is nonionizing and safe to perform on pregnant patients and children. It can detect and localize pleural abnormalities, guide percutaneous needle biopsy of peripheral lung, pleural, or chest wall lesions and identify septations within loculated pleural collections (i.e., for thoracentesis), improving the yield and safety of the procedure. Real-time imaging can be used to assess the movement of the diaphragm and can demonstrate changes in clinical condition. Availability of portable machines has allowed point of care (POC) ultrasound to provide rapid and accurate bedside diagnosis and monitoring of several common respiratory conditions, including pneumothorax, and pleural effusions. In experienced hands, POC ultrasound has higher sensitivity and specificity than chest radiography in detecting pleural effusions and pneumothorax, with an accuracy approaching computed tomography (CT). Pulmonary congestion may be quantified using lung US monitoring pulmonary congestion in heart failure patients in response to therapy.

NUCLEAR MEDICINE TECHNIQUES

Nuclear imaging depends on the selective uptake of various compounds by organs of the body. In thoracic imaging, these compounds are concentrated by one of three mechanisms: blood pool or compartmentalization (e.g., within the heart), physiologic incorporation (e.g., bone or thyroid) and capillary blockage (e.g., lung scan). Radioactive isotopes can be administered by either the IV or inhaled routes or both. When injected intravenously, albumin macroaggregates labeled with technetium-99m (^{99m}Tc) become lodged in pulmonary capillaries; the distribution of the trapped radioisotope follows the distribution of blood flow. When inhaled, radiolabeled xenon gas can be used to demonstrate the distribution of ventilation. Using these techniques, ventilation-perfusion lung scanning was a commonly used technique for the evaluation of pulmonary embolism. Pulmonary thromboembolism produces one or more regions of ventilation-perfusion mismatch (i.e., regions in which there is a defect in perfusion that follows the distribution of a vessel and that is not accompanied by a corresponding defect in ventilation [Chap. 273]). However, with advances in CT scanning, scintigraphic imaging has been largely replaced by CT angiography in patients with suspected pulmonary embolism.

Another common use of ventilation-perfusion scans is in patients with impaired lung function, who are being considered for lung resection. Many patients with bronchogenic carcinoma have coexisting chronic obstructive pulmonary disease (COPD), and the question arises as to whether or not a patient can tolerate lung resection. The distribution of the isotope(s) can be used to assess the regional distribution of blood flow and ventilation, allowing the physician to estimate the level of postoperative lung function.

COMPUTED TOMOGRAPHY

CT offers several advantages over routine chest radiography (Figs. 280-1*A, B* and 280-2*A, B*). First, the use of cross-sectional images allows distinction between densities that would be superimposed on plain radiographs. Second, CT is far better than routine radiographic studies at characterizing tissue density and providing accurate size assessment of lesions.

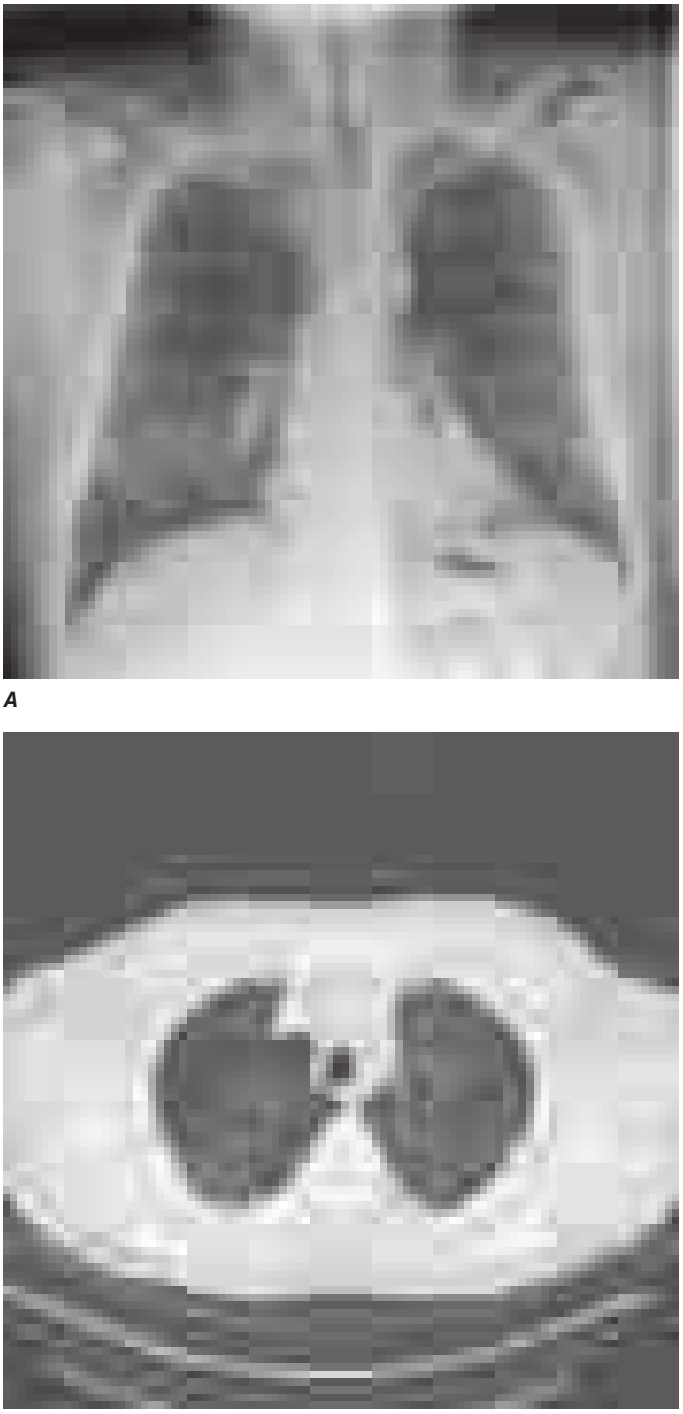
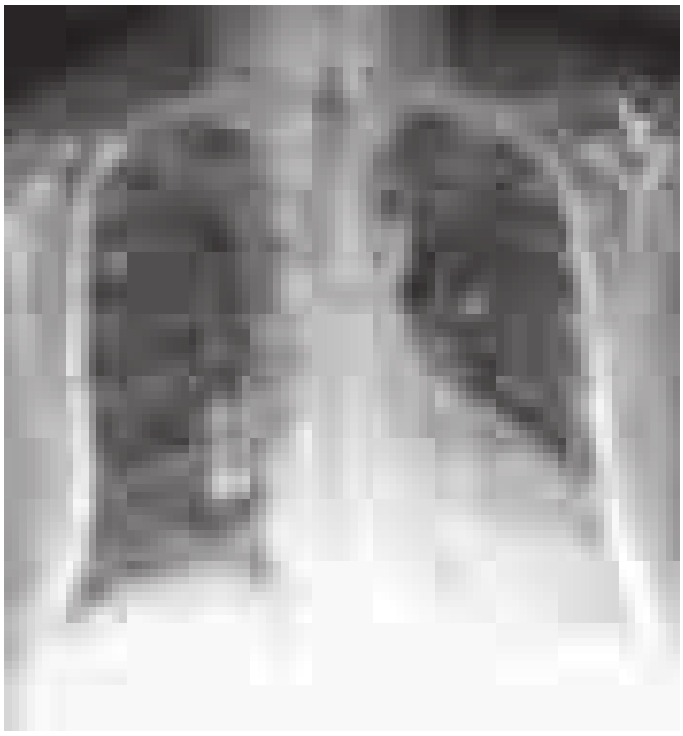
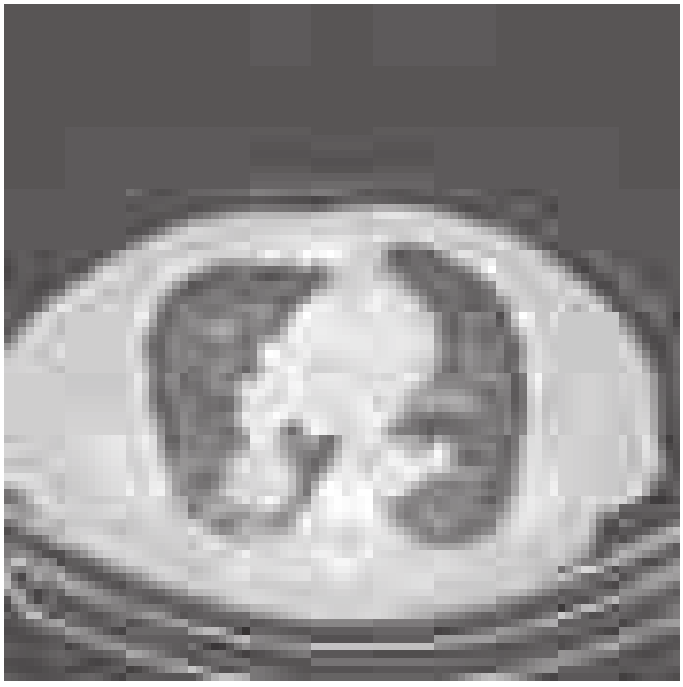


FIGURE 280-1 Chest x-ray (*A*) and computed tomography (CT) scan (*B*) from a patient with emphysema. The extent and distribution of emphysema are not well appreciated on plain film but clearly evident on the CT scan obtained.

CT is particularly valuable in assessing hilar and mediastinal disease (often poorly characterized by plain radiography), in identifying and characterizing disease adjacent to the chest wall or spine (including pleural disease), and in identifying areas of fat density or calcification in pulmonary nodules (Fig. 280-2). Its utility in the assessment of mediastinal disease has made CT an important tool in the staging of lung cancer (Chap. 74). With the additional use of contrast material, CT also makes it possible to distinguish vascular from nonvascular structures, which is particularly important in distinguishing lymph nodes and



A



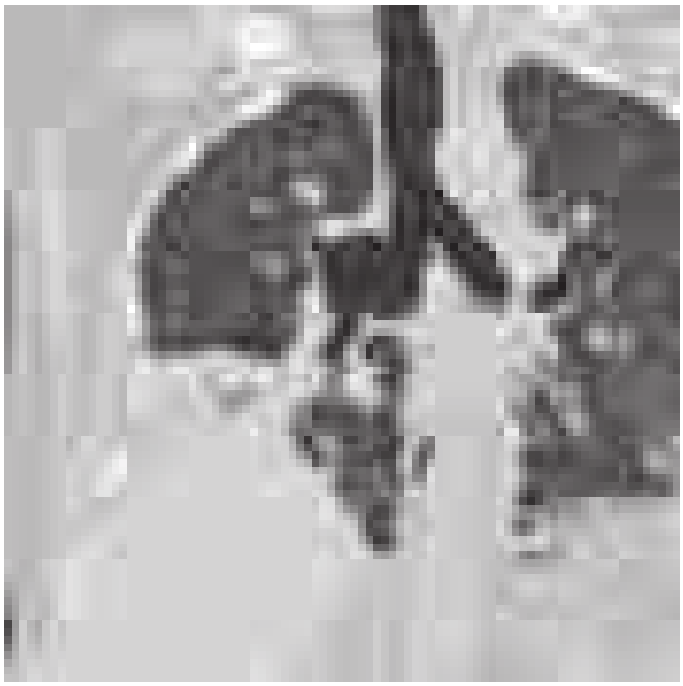
B

FIGURE 280-2 Chest x-ray (*A*) and computed tomography (CT) scan (*B*) demonstrating a right lower-lobe mass. The mass is not well appreciated on the plain film because of the hilar structures and known calcified adenopathy. CT is superior to plain radiography for the detection of abnormal mediastinal densities and the distinction of masses from adjacent vascular structures.

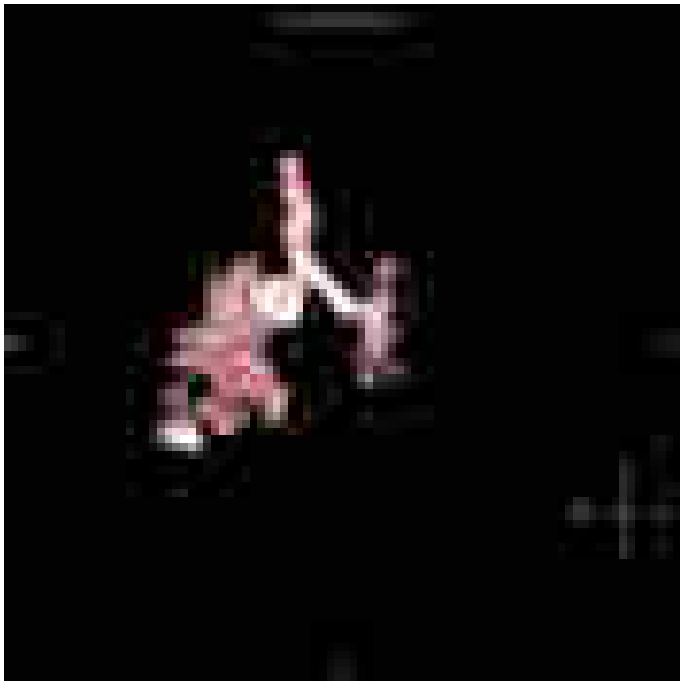
masses from vascular structures primarily in the mediastinum, and vascular disorders such as pulmonary embolism.

Helical CT and Multidetector CT Helical scanning is currently the standard method for thoracic CT. Helical CT technology results in faster scans with improved contrast enhancement and thinner collimation. Images are obtained during a single breath-holding maneuver that allows less motion artifact and collection of continuous data over a larger volume of lung than is possible with conventional CT. Data from the imaging procedure can be reconstructed in coronal or sagittal planes (Fig. 280-3*A*), as well as the traditional cross-sectional (axial) view.

Further refinements in detector technology have allowed production of scanners with additional detectors along the scanning axis (*z*-axis). These *multidetector CT* (MDCT) scanners can obtain multiple slices in a single rotation that are thinner and can be acquired in a shorter period of time. This results in enhanced resolution and increased image reconstruction ability. As the technology has progressed, higher numbers (currently up to 64) of detectors allow submillimeter spatial resolution



A



B

FIGURE 280-3 Spiral computed tomography (CT) with reconstruction of images in planes other than axial view. Spiral CT in a lung transplant patient with a dehiscence and subsequent aneurysm of the anastomosis. CT images were reconstructed in the sagittal view (***A***) and using digital subtraction to view images of the airways only (***B***), which demonstrate the exact location and extent of the abnormality.

to produce clearer final images, allowing this technique to essentially replace high-resolution CT (HRCT) in the evaluation of lung disease. The pattern of usual interstitial pneumonia (UIP) seen on MDCT (peripheral, basilar predominant honeycomb structure, and traction bronchiectasis), together with typical clinical presentation, and other causes are ruled out, the diagnosis of idiopathic pulmonary fibrosis (IPF) can be reliably diagnosed without histological confirmation. MDCT allows for even shorter breath holds, which are beneficial for all patients but especially children, the elderly, and the critically ill. It should be noted that despite the advantages of MDCT, there is an increase in radiation dose compared to single-detector CT to consider. However, using iterative reconstruction techniques, there is continued progress in reducing the radiation dose reported for CT scans of the thorax. Low dose MDCT is now a recommended screening procedure for lung cancer among persons who are aged 55–80 years with 30 pack year smoking history and currently smoke or quit within the past 15 years.

In MDCT, the additional detectors along the *z*-axis result in improved use of the contrast bolus. This and the faster scanning times and increased resolution have all led to improved imaging of the pulmonary vasculature and the ability to detect segmental and subsegmental emboli. CT pulmonary angiography (CTPA) also allows simultaneous detection of parenchymal abnormalities that may be contributing to a patient's clinical presentation. Secondary to these advantages and increasing availability, CTPA has rapidly become the test of choice for many clinicians in the evaluation of pulmonary embolism; compared with pulmonary angiography, it is considered equal in terms of accuracy and with less associated risks. A further development is the dual-source CT (DSCT), which uses two x-ray tubes and their corresponding detectors offset by 90°. These scanners can emphasize particular tissue characteristics and combine functional and morphological information, which may allow better detection of perfusion defects in the lung parenchyma. In addition, the newer generation DSCT systems allow high resolution scans of the thorax to be performed in <1 s, of particular interest for dyspneic patients who are unable to comply with breath hold instructions.

VIRTUAL BRONCHOSCOPY

The three-dimensional (3D) image of the thorax obtained by MDCT can be digitally stored, reanalyzed, and displayed as 3D reconstructions of the airways down to the sixth to seventh generation. Using these reconstructions, a "virtual" bronchoscopy can be performed **(Fig. 280-4)**.

FIGURE 280-4 Virtual bronchoscopic image of the trachea. The view projected is one that would be obtained from the trachea looking down to the carina. The left and right main stem airways are seen bifurcating from the carina.

Virtual bronchoscopy has been proposed as an adjunct to conventional bronchoscopy in several clinical situations: It can allow accurate assessment of the extent and length of an airway stenosis, including the airway distal to the narrowing; it can provide useful information about the relationship of the airway abnormality to adjacent mediastinal structures; and it allows preprocedure planning for therapeutic bronchoscopy to help ensure the appropriate equipment is available for the procedure.

Electromagnetic navigational bronchoscopy systems (EMN or ENB), using virtual bronchoscopy, have been developed to allow accurate navigation to peripheral pulmonary target lesions. Electromagnetic navigation bronchoscopy (ENB) uses technology similar to a car global positioning system (GPS) unit, which allows precise tracking of both position and orientation through the use of electromagnetic fields.

POSITRON EMISSION TOMOGRAPHIC SCANNING

Positron emission tomographic (PET) scanning involves injection of a radiolabeled glucose analogue, [^{18}F]-fluoro-2-deoxyglucose (FDG), which is taken up by metabolically active malignant cells. This technique has been used in the evaluation of solitary pulmonary nodules and in staging lung cancer. Detection or exclusion of mediastinal lymph node involvement and identification of extrathoracic disease can be achieved. The development of hybrid imaging allows the superimposition of PET and CT images, a technique known as functional–anatomical mapping. Hybrid PET/CT scans provide images that help pinpoint the abnormal metabolic activity to anatomical structures seen on CT and provide more accurate diagnoses than the two scans performed separately. FDG-PET can differentiate benign from malignant lesions as small as 1 cm and can be very useful in detection of distant metastases. However, false-negative findings can occur in lesions with low metabolic activity such as carcinoid tumors and bronchioloalveolar cell carcinomas, or in lesions <1 cm in which the required threshold of metabolically active malignant cells is not present for PET diagnosis. False-positive results can be seen due to FDG uptake in inflammatory conditions such as pneumonia and granulomatous diseases.

MAGNETIC RESONANCE IMAGING

Magnetic resonance (MR) provides poorer spatial resolution and less detail of the pulmonary parenchyma and, for these reasons, is not currently considered a substitute for CT in imaging the thorax. However, because of the high soft tissue contract available with MRI, this technology may be used to distinguish tumor from post-stenotic atelectasis and assess infiltration of the chest wall and/or mediastinum. In addition, for superior sulcus tumors, MRI can be valuable in preoperative planning to better visualize if/where the tumor is in contact with the spine. Further, "diffusion-weighted" MRI is an emerging technique that has been used to differentiate metastatic lymph nodes from healthy lymph nodes with sensitivity, specificity, and positive predictive values higher than PET/CT or CT alone. Finally, the use of hyperpolarized gas in conjunction with MR has led to the investigational use of MR for imaging the lungs, particularly in obstructive lung disease. Imaging performed during an inhalation and exhalation can provide dynamic information on lung function.

An advantage of MR is the use of nonionizing electromagnetic radiation. Additionally, MR is well suited to distinguish vascular from nonvascular structures without the need for contrast. Blood vessels appear as hollow tubular structures because flowing blood does not produce a signal on MRI. Therefore, MR can be useful in demonstrating pulmonary emboli, defining aortic lesions such as aneurysms or dissection, or other vascular abnormalities **(Fig. 280-5)** if radiation and IV contrast medium cannot be used. Gadolinium can be used as an intravascular contrast agent for MR angiography (MRA); however, synchronization of data acquisition with the peak arterial bolus is one of the major challenges of MRA. The flow of contrast medium from the peripheral injection site to the vessel of interest is affected by a number of factors including heart rate, stroke volume, and the presence of proximal stenotic lesions.

Disadvantages of MRI include less spatial resolution and longer study acquisition times compared with CT. MR examinations are

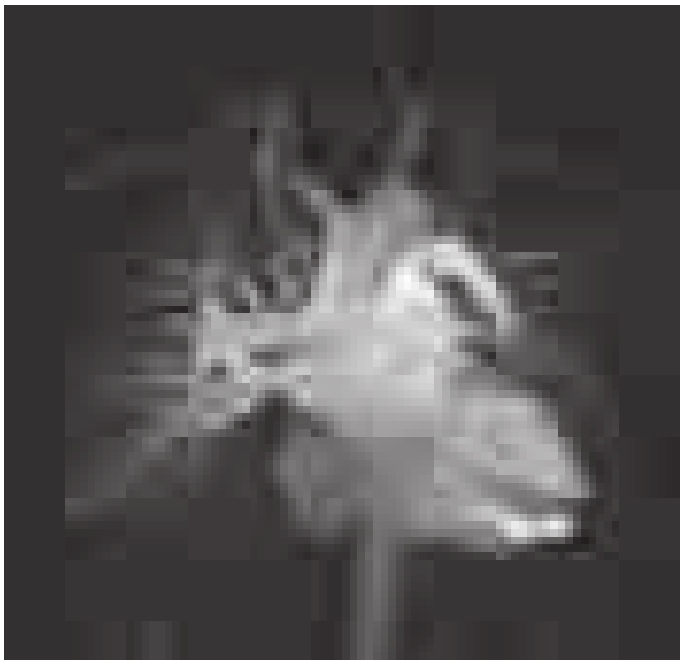


FIGURE 280-5 Magnetic resonance angiography image of the vasculature of a patient after lung transplant. The image demonstrates the detailed view of the vasculature that can be obtained using digital subtraction techniques. Images from a patient after lung transplant show the venous and arterial anastomosis on the right; a slight narrowing is seen at the site of the anastomosis, which is considered within normal limits and not suggestive of obstruction.

difficult to obtain among patients who cannot lie still or who cannot lay on their backs. MRI is generally avoided in unstable and/or ventilated patients and those with severe trauma because of the hazards of the MR environment and the difficulties in monitoring patients within the MR room. The presence of metallic foreign bodies, pacemakers, and intracranial aneurysm clips also preclude use of MRI.

PULMONARY ANGIOGRAPHY

The pulmonary arterial system can be visualized by pulmonary angiography, in which radiopaque contrast medium is injected through a catheter placed in the pulmonary artery. When performed in cases of pulmonary embolism, pulmonary angiography demonstrates the consequences of an intravascular thrombus—either a defect in the lumen of a vessel (a filling defect) or an abrupt termination (cutoff) of the vessel. Other, less common indications for pulmonary angiography include visualization of a suspected pulmonary arteriovenous malformation and assessment of pulmonary arterial invasion by a neoplasm. The risks associated with modern arteriography are small, generally of greatest concern in patients with severe pulmonary hypertension or chronic kidney disease. With advances in CT scanning, MDCT angiography (MDCTA) is replacing conventional angiography for the diagnosis of pulmonary embolism.

MEDICAL TECHNIQUES FOR OBTAINING BIOLOGIC SPECIMENS

COLLECTION OF BLOOD AND SERUM

Testing of blood and/or serum can be useful in situations where respiratory diseases are secondary to systemic illness. Collagen vascular disease is a frequent cause of diffuse interstitial lung disease (DILD) and serologic tests for autoantibodies may be helpful in determining if an autoimmune disorder is affecting the lungs. In addition, blood tests for inherited respiratory diseases are available. In patients presenting with COPD, a low level of α_1-antitrypsin (α_1AT) confirms α_1AT deficiency and further assessment with α_1AT protein phenotyping and/or α_1AT genotyping can be carried if needed. Beyond emphysema, next-generation sequencing has allowed development of respiratory gene panels that identify genes implicated in several different lung syndromes including cystic, fibrotic, and bronchiectatic diseases.

COLLECTION OF SPUTUM

Sputum can be collected either by spontaneous expectoration or induced (after inhalation of an irritating aerosol such as hypertonic saline). *Sputum induction* is used either because sputum is not spontaneously being produced or because of an expected higher yield of certain types of findings. Because sputum consists mainly of secretions from the tracheobronchial tree rather than the upper airway, the finding of alveolar macrophages and other inflammatory cells is consistent with a lower respiratory tract origin of the sample, whereas the presence of squamous epithelial cells in a "sputum" sample indicates contamination by secretions from the upper airways.

In addition to processing for routine bacterial pathogens by Gram's method and culture, sputum can be processed for a variety of other pathogens, including staining and culture for mycobacteria or fungi, culture for viruses, and staining for *Pneumocystis jiroveci*. In the specific case of sputum obtained for evaluation of *P. jiroveci* pneumonia, for example, sputum should be collected by induction rather than spontaneous expectoration, and an immunofluorescent stain should be used to detect the organisms. Traditional stains and cultures are now also being supplemented in some cases by immunologic techniques and by molecular biologic methods, including the use of polymerase chain reaction (PCR) amplification and DNA probes. Cytologic staining of sputum for malignant cells, using the traditional Papanicolaou method, allows noninvasive evaluation for suspected lung cancer.

PERCUTANEOUS NEEDLE ASPIRATION (TRANSTHORACIC)

A needle can be inserted through the chest wall into a pulmonary lesion to obtain an aspirate or tissue core for cytologic/histologic or microbiologic analysis. Aspiration can be performed to obtain a diagnosis or to decompress and/or drain a fluid collection. The procedure is usually carried out under CT or US guidance to assist positioning of the needle and assure localization in the lesion. The low potential risk of this procedure (intrapulmonary bleeding or creation of a pneumothorax with collapse of the underlying lung) in experienced hands is usually acceptable compared with the information obtained. However, a limitation of the technique is sampling error due to the small size of the tissue sample. Thus, findings other than a specific cytologic or microbiologic diagnosis are of limited clinical value.

THORACENTESIS

Sampling of pleural liquid by thoracentesis is commonly performed for diagnostic purposes or, in the case of a large effusion, for palliation of dyspnea. Diagnostic sampling, either by blind needle aspiration or after localization by US, allows the collection of liquid for microbiologic and cytologic studies. Analysis of the fluid obtained for its cellular composition and chemical constituents allows classification of the effusion and can help with diagnosis and treatment (Chap. 288).

BRONCHOSCOPY

Bronchoscopy is the process of direct visualization of the tracheobronchial tree. Although bronchoscopy is now performed almost exclusively with flexible fiberoptic instruments, rigid bronchoscopy, generally performed in an operating room on a patient under general anesthesia, still has a role in selected circumstances, primarily because of a larger suction channel and the fact that the patient can be ventilated through the bronchoscope channel. These situations include the retrieval of a foreign body and the suctioning of a massive hemorrhage, for which the small suction channel of the bronchoscope may be insufficient.

FLEXIBLE FIBEROPTIC BRONCHOSCOPY

This outpatient procedure is usually performed in an awake but sedated patient (conscious sedation). The bronchoscope is passed through either the mouth or the nose, between the vocal cords, and into the trachea. The ability to flex the scope makes it possible to visualize virtually all airways to the level of subsegmental bronchi. The bronchoscopist is able to identify endobronchial pathology, including tumors, granulomas, bronchitis, foreign bodies, and sites of bleeding. Samples from airway lesions can be taken by several methods,

including washing, brushing, and biopsy. Washing involves instillation of sterile saline through a channel of the bronchoscope and onto the surface of a lesion. A portion of the liquid is collected by suctioning through the bronchoscope, and the recovered material can be analyzed for cells (cytology) or organisms (by standard stains and cultures). Brushing or biopsy of the surface of the lesion, using a small brush or biopsy forceps at the end of a long cable inserted through a channel of the bronchoscope, allows recovery of cellular material or tissue for analysis by standard cytologic and histopathologic methods.

The bronchoscope can be used to sample material not only from the regions that can be directly visualized (i.e., the airways), but also from the more distal pulmonary parenchyma. With the bronchoscope wedged into a subsegmental airway, aliquots of sterile saline can be instilled through the scope, allowing sampling of cells and organisms from alveolar spaces. This procedure, called *bronchoalveolar lavage* (*BAL*), has been particularly useful for the recovery of fluid for culture. In addition, immunofluorescent staining with antibodies and/or nucleic acid analysis via PCR can facilitate more rapid diagnosis than culture techniques for some organisms. Cytology, cellular analysis, and examination of acellular components such as cytokines, viral particles, and microbial signatures are commonly performed.

Brushing and biopsy of the distal lung parenchyma can also be performed with the same instruments that are used for endobronchial sampling. These instruments can be passed through the scope into small airways. When biopsies are performed, the forceps penetrate the airway wall, allowing biopsy of peribronchial alveolar tissue. This procedure, called *transbronchial biopsy*, is used when there is either relatively diffuse disease or a localized lesion of adequate size. With the aid of fluoroscopic imaging, the bronchoscopist is able to determine not only whether and when the instrument is in the area of abnormality, but also the proximity of the instrument to the pleural surface. If the forceps are too close to the pleural surface, there is a risk of violating the visceral pleura and creating a pneumothorax; the other potential complication of transbronchial biopsy is pulmonary hemorrhage. The incidence of these complications is less than several percent.

TRANSBRONCHIAL NEEDLE ASPIRATION

Another procedure involves use of a hollow-bore needle passed through the bronchoscope for sampling of tissue adjacent to the trachea or a large bronchus. The needle is passed through the airway wall (transbronchial), and cellular material can be aspirated from mass lesions or enlarged lymph nodes, generally in a search for malignant cells. Mediastinoscopy has been considered the gold standard for mediastinal staging; however, transbronchial needle aspiration (TBNA) allows sampling from the lungs and surrounding lymph nodes without the need for surgery or general anesthesia.

ENDOBRONCHIAL ULTRASOUND (EBUS)–TRANSBRONCHIAL NEEDLE ASPIRATION (TBNA)

Further advances in needle aspiration techniques have been accomplished with the development of endobronchial ultrasound (EBUS). The technology uses an ultrasonic bronchoscope fitted with a probe that allows for needle aspiration of mediastinal and hilar lymph nodes guided by real-time US images. EBUS allows sampling of mediastinal lymph nodes and masses under direct vision to better identify and localize peribronchial and mediastinal pathology and offers access to more difficult-to-reach areas and smaller lymph nodes in the staging of malignancies. EBUS-TBNA has the potential to access the same paratracheal and subcarinal lymph node stations as mediastinoscopy, but also extends out to the hilar lymph nodes (levels 10 and 11).

Radial probe endobronchial ultrasound (RP-EBUS) produces a 360-degree ultrasound image of the surrounding lung parenchyma and has significantly improved the bronchoscopic diagnostic yield for peripheral pulmonary nodules, particularly for larger lesions (>2 cm). RP-EBUS can be combined with ENB (described above), to provide accurate navigational assistance to localize peripheral nodules and increase the diagnostic yield.

RP-EBUS has a superior safety profile compared with transthoracic approach, but limitations include a poor ultrasound signal for evaluating nodules that have a ground glass appearance on CT scan and a high reliance on the bronchoscopist's ability to navigate the branching architecture of the airways to position the probe near the nodule.

EMERGING BRONCHOSCOPIC TECHNIQUES

Additional techniques that can be performed using bronchoscopy include video/autofluorescence bronchoscopy (AFB), narrow band imaging (NBI), optical coherence tomography (OCT), and endomicroscopy using confocal fluorescent laser microscopy (CFM). AFB uses bronchoscopy with an additional light source to screen high-risk individuals and identify premalignant lesions (airway dysplasia) and carcinoma in situ. NBI capitalizes on the increased absorption of blue and green wavelengths of light by hemoglobin to enhance the visibility of vessels of the mucosa and differentiate between inflammatory versus malignant mucosal lesions. CFM uses a blue laser to induce fluorescence, and its high degree of resolution provides a real-time view of living tissue at an almost histologic resolution. OCT uses near-infrared light source and has spatial resolution advantages over CT and MRI. It can penetrate the airway wall up to three times deeper than CFM and is less susceptible to motion artifacts from cardiac pulsation and respiratory movements. However, careful assessment is required before these methods find a place in the evaluation strategy of early lung cancer and other lung diseases.

MEDICAL THORACOSCOPY

Medical thoracoscopy (or pleuroscopy) focuses on the diagnosis of pleural-based problems. The procedure is performed with a conventional rigid or a semi-rigid pleuroscope (similar in design to a bronchoscope and enabling the operator to inspect the pleural surface, sample and/or drain pleural fluid, or perform targeted biopsies of the parietal pleura). Medical thoracoscopy can be performed in the endoscopy suite or operating room with the patient under conscious sedation and local anesthesia. In contrast, video-assisted thoracoscopic surgery (VATS) requires general anesthesia and is only performed in the operating room. A common diagnostic indication for medical thoracoscopy is the evaluation of a pleural effusion or biopsy of presumed parietal pleural carcinomatosis. It can also be used to place a chest tube under visual guidance, or perform chemical or talc pleurodesis, a therapeutic intervention to prevent a recurrent pleural effusion (usually malignant) or recurrent pneumothorax.

The increasing availability of advanced bronchoscopic and pleuroscopic techniques has motivated the development of IP programs. IP can be defined as "the art and science of medicine as related to the performance of diagnostic and invasive therapeutic procedures, that which require additional training and expertise beyond that which required in a standard pulmonary medicine training program." IP physicians provide alternatives to surgery for patients with a wide variety of thoracic disorders and problems, including therapeutic interventions (see further reading).

SURGICAL TECHNIQUES FOR OBTAINING BIOLOGIC SPECIMENS

Evaluation and diagnosis of disorders of the chest commonly involve collaboration between pulmonologists and thoracic surgeons. Although procedures such as mediastinoscopy, VATS, and thoracotomy are performed by thoracic surgeons, there is overlap in many minimally invasive techniques that can be performed by a pulmonologist, an interventional pulmonologist, or a thoracic surgeon.

MEDIASTINOSCOPY AND MEDIASTINOTOMY

Proper staging of lung cancer is of paramount concern when determining a treatment regimen. Although CT and PET scanning are useful for determining the size and nature of mediastinal lymph nodes as part of the staging of lung cancer, tissue biopsy and histopathologic examination are often critical for the diagnosis of mediastinal masses or enlarged mediastinal lymph nodes. The two major surgical procedures used to obtain specimens from masses or nodes in the mediastinum are mediastinoscopy (via a suprasternal approach) and mediastinotomy

(via a parasternal approach). Both procedures are performed under general anesthesia by a qualified surgeon. In the case of suprasternal mediastinoscopy, a rigid mediastinoscope is inserted at the suprasternal notch and passed into the mediastinum along a pathway just anterior to the trachea. Tissue can be obtained with biopsy forceps passed through the scope, sampling masses or nodes that are in a paratracheal or pretracheal position (levels 2R, 2L, 3, 4R, 4L). Aortopulmonary lymph nodes (levels 5, 6) are not accessible by this route and thus are commonly sampled by parasternal mediastinotomy (the Chamberlain procedure). This approach involves a parasternal incision and dissection directly down to a mass or node that requires biopsy.

As an alternative to surgery, a bronchoscope can be used to perform TBNA to obtain tissue from the mediastinum, and, when combined with EBUS, can allow access to the same lymph node stations associated with mediastinoscopy, but also extend access out to the hilar lymph nodes (levels 10, 11). Finally, endoscopic ultrasound (EUS)–fine-needle aspiration (FNA) is a second procedure that complements EBUS-FNA in the staging of lung cancer. EUS-FNA is performed via the esophagus and is ideally suited for sampling lymph nodes in the posterior mediastinum (levels 7, 8, 9). Because US imaging cannot penetrate air-filled spaces, the area directly anterior to the trachea cannot accurately be assessed and is a "blind spot" for EUS-FNA. However, EBUS-FNA can visualize the anterior lymph nodes and can complement EUS-FNA. The combination of EUS-FNA and EBUS-FNA with the use of radial probes has made these techniques a clear nonoperative alternative for staging the mediastinum in thoracic malignancies.

VIDEO-ASSISTED THORACOSCOPIC SURGERY

VATS is the operative technique for the diagnosis and management of pleural as well as parenchymal lung disease. This procedure is performed in the operating room using single-lung ventilation with double-lumen endotracheal intubation and involves the passage of a rigid scope with a distal lens through a trocar inserted into the pleura. A high-quality image is shown on a monitor screen, allowing the operator to manipulate instruments passed into the pleural space through separate small intercostal incisions. With these instruments the operator can biopsy lesions of the pleura under direct visualization. In addition, this procedure is now used commonly to biopsy peripheral lung tissue or to remove peripheral nodules for both diagnostic and therapeutic purposes. This much less invasive procedure has largely supplanted the traditional "open lung biopsy" performed via thoracotomy. The decision to use medical thorascopy versus VATS technique is based on the clinical scenario with input from the consulting pulmonary and thoracic surgery providers. If a surgical technique is preferred, the decision to use a VATS technique versus performing an open thoracotomy is made by the thoracic surgeon and based on whether a patient can tolerate the single-lung ventilation that is required to allow adequate visualization of the lung. With further advances in instrumentation and experience, VATS can be used to perform procedures previously requiring thoracotomy, including stapled lung biopsy, resection of pulmonary nodules, lobectomy, pneumonectomy, pericardial window, or other standard thoracic surgical procedures, but allows them to be performed in a minimally invasive manner.

THORACOTOMY

Although frequently replaced by VATS, thoracotomy remains an option for the diagnostic sampling of lung tissue. It provides the largest amount of material, and it can be used to biopsy and/or excise lesions that are too deep or too close to vital structures for removal by VATS. The choice between VATS and thoracotomy needs to be made on a case-by-case basis.

TECHNIQUES ON BIOLOGIC SPECIMENS

Histopathologic examination of tissue samples and cytologic examination of aspirates or fluid are critical components in the diagnosis of many respiratory disorders. In the area of lung cancer, improved understanding of molecular changes and genetic mutations that drive cancer has allowed development of specific molecular tests that guide therapy (e.g., epidermal growth factor receptor [EGFR] mutations and anaplastic lymphoma kinase [ALK] fusions).

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Section 2 Diseases of the Respiratory System

281 Asthma

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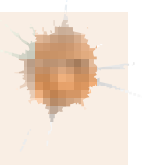

Asthma is a syndrome characterized by airflow obstruction that varies markedly, both spontaneously and with treatment. Asthmatics harbor a special type of inflammation in the airways that makes them more responsive than nonasthmatics to a wide range of triggers, leading to excessive narrowing with consequent reduced airflow and symptomatic wheezing and dyspnea. Narrowing of the airways is usually reversible, but in some patients with chronic asthma there may be an element of irreversible airflow obstruction. Asthma is a heterogeneous disease with several phenotypes recognized, but thus far these do not correspond well to specific pathogenic mechanisms (endotypes) or responses to therapy. The increasing global prevalence of asthma, the large burden it now imposes on patients, and the high health care costs have led to extensive research into its mechanisms and treatment.

PREVALENCE

Asthma is one of the most common chronic diseases globally and currently affects ~300 million people worldwide, with ~250,000 deaths annually. The prevalence of asthma has risen in affluent countries over the last 30 years but now appears to have stabilized, with ~10–12% of adults and 15% of children affected by the disease. In developing countries where the prevalence of asthma had been much lower, there is a rising prevalence, which is associated with increased urbanization. The prevalence of atopy and other allergic diseases has also increased over the same time, suggesting that the reasons for the increase are likely to be systemic rather than confined to the lungs. Most patients with asthma in affluent countries are atopic, with allergic sensitization to the house dust mite *Dermatophagoides pteronyssinus* and other environmental allergens, such as animal fur and pollens.

Asthma can present at any age, with a peak age of 3 years. In childhood, twice as many males as females are asthmatic, but by adulthood the sex ratio has equalized. Long-term studies that have followed children until they reach the age of 40 years suggest that many with asthma become asymptomatic during adolescence but that asthma returns in some during adult life, particularly in those with persistent symptoms and severe asthma. Adults with asthma, including those with onset during adulthood, rarely become permanently asymptomatic. The severity of asthma does not vary significantly within a given patient; those with mild asthma rarely progress to more severe disease, whereas those with severe asthma usually have severe disease at the onset.

Deaths from asthma are relatively uncommon, and in many affluent countries have been steadily declining over the last decade. A rise in asthma mortality seen in several countries during the 1960s was associated with increased use of short-acting inhaled β_2-adrenergic agonists (as rescue therapy), but there is now compelling evidence that the more widespread use of inhaled corticosteroids (ICS) in patients with persistent asthma is responsible for the decrease in mortality in recent years. Major risk factors for asthma deaths are poorly controlled disease with frequent use of bronchodilator inhalers, lack of or poor compliance with ICS therapy, and previous admissions to hospital with near-fatal asthma.

It has proved difficult to agree on a definition of asthma, but there is good agreement on the description of the clinical syndrome and disease pathology. Until the etiologic mechanisms of the disease are better understood, it will be difficult to provide an accurate definition.

RISK FACTORS AND TRIGGERS

Asthma is a heterogeneous disease with interplay between genetic and environmental factors. Several risk factors that predispose to asthma have been identified **(Table 281-1)**. These should be distinguished from triggers, which are environmental factors that worsen asthma in a patient with established asthma.

Atopy Atopy is the major risk factor for asthma, and non-atopic individuals have a very low risk of developing asthma. Patients with asthma commonly suffer from other atopic diseases, particularly allergic rhinitis, which may be found in >80% of asthmatic patients, and atopic dermatitis (eczema). Atopy may be found in 40–50% of the population in affluent countries, but only a proportion of atopic individuals becoming asthmatic. This observation suggests that some other environmental or genetic factor(s) predispose to the development of asthma in atopic individuals. The allergens that lead to sensitization are usually proteins that have protease activity, and the most common allergens are derived from house dust mites, cat and dog fur, cockroaches (in inner cities), grass and tree pollens, and rodents (in laboratory workers). Atopy is due to the genetically determined production of specific IgE antibody, with many patients showing a family history of allergic diseases.

TABLE 281-1 Risk Factors and Triggers Involved in Asthma

ENDOGENOUS FACTORS	ENVIRONMENTAL FACTORS
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections
Obesity	Air pollution (diesel particulates, nitrogen oxides)
Early viral infections	Diet
	Dampness and mold exposure
	Acetaminophen (paracetamol)
Triggers	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β-blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

Genetic Predisposition The familial association of asthma and a high degree of concordance for asthma in identical twins indicate a genetic predisposition to the disease; however, whether or not the genes predisposing to asthma are similar or in addition to those predisposing to atopy is not yet clear. It now seems likely that different genes may also contribute to asthma specifically, and there is increasing evidence that the severity of asthma is also genetically determined. Genetic screens with classical linkage analysis and single-nucleotide polymorphisms of various candidate genes indicate that asthma is polygenic, with each gene identified having a small effect that is often not replicated in different populations. This observation suggests that the interaction of many genes is important, and these may differ in different populations. The most consistent findings have been associations with polymorphisms of genes on chromosome 5q, including the T helper 2 (T_H2) cells interleukin (IL)-4, IL-5, IL-9, and IL-13, which are associated with atopy. There is increasing evidence for a complex interaction between genetic polymorphisms and environmental factors that will require very large population studies to unravel. Novel genes that have been associated with asthma, including *ADAM-33*, *DPP-10*, and *ORMDL3*, have also been identified by positional cloning, but their function in disease pathogenesis is not yet clear. Recent genome-wide association studies have identified further novel genes, such as ORMDL3, although their functional role is not yet clear. Genetic polymorphisms may also be important in determining the response to asthma therapy. For example, the Arg-Gly-16 variant in the β_2-receptor has been associated with reduced response to β_2-agonists, and repeats of an Sp1 recognition sequence in the promoter region of 5-lipoxygenase may affect the response to antileukotrienes. However, these effects are small and inconsistent and do not yet have any implications for asthma therapy.

It is likely that environmental factors in early life determine which atopic individuals become asthmatic. The increasing prevalence of asthma, particularly in developing countries, over the last few decades also indicates the importance of environmental mechanisms interacting with a genetic predisposition.

Epigenetic Mechanisms There is increasing evidence that epigenetic mechanisms may be important, particularly in the early development of asthma. DNA methylation and histone modification patterns may be influenced by diet, cigarette smoke exposure, and air pollution, and may affect genes involved in the pathogenesis of asthma. These epigenetic changes may occur in the fetus as a result of maternal environmental exposure.

Infections Although viral infections (especially Rhinovirus) are common as triggers of asthma exacerbations, it is uncertain whether they play a role in etiology. There is some association between respiratory syncytial virus infection in infancy and the development of asthma, but the specific pathogenesis is difficult to elucidate, as this infection is very common in children. Atypical bacteria, such as *Mycoplasma* and *Chlamydophila*, have been implicated in the mechanism of severe asthma, but thus far, the evidence is not very convincing of a true association. Living in damp houses with exposure to mold spores is now recognized to be a risk factor, and removal of these factors may improve asthma.

The observation that allergic sensitization and asthma were less common in children with older siblings first suggested that lower levels of infection may be a factor in affluent societies that increase the risks of asthma. This "hygiene hypothesis" proposes that lack of infections in early childhood preserves the T_H2 cell bias at birth, whereas exposure to infections and endotoxin results in a shift toward a predominant protective T_H1 immune response. Children brought up on farms who are exposed to a high level of endotoxin are less likely to develop allergic

sensitization than children raised on dairy farms. Intestinal parasite infection, such as hookworm, may also be associated with a reduced risk of asthma. While there is considerable epidemiologic support for the hygiene hypothesis, it cannot account for the parallel increase in T_H1-driven diseases such as diabetes mellitus over the same period.

Diet The role of dietary factors is controversial. Observational studies have shown that diets low in antioxidants such as vitamin C and vitamin A, magnesium, selenium, and omega-3 polyunsaturated fats (fish oil) or high in sodium and omega-6 polyunsaturates are associated with an increased risk of asthma. Vitamin D deficiency may also predispose to the development of asthma. However, interventional studies with supplementary diets have not supported an important role for these dietary factors. Obesity is also an independent risk factor for asthma, particularly in women, but the mechanisms are not yet clear.

Air Pollution Air pollutants such as sulfur dioxide, ozone, and diesel particulates may trigger asthma symptoms, but the role of different air pollutants in the etiology of the disease is not yet clear. Asthma had a much lower prevalence in East Germany compared to West Germany despite a much higher level of air pollution, but since reunification these differences have decreased as Eastern Germany has become more affluent. There is increasing evidence that exposure to road traffic pollution is associated with increased asthma symptoms, with the main culprits being diesel particulates and nitrogen dioxide. Indoor air pollution is also important with exposure to nitrogen oxides from cooking stoves and exposure to passive cigarette smoke. There is some evidence that maternal smoking is a risk factor for asthma, but it is difficult to dissociate this association from an increased risk of respiratory infections.

Allergens Inhaled allergens are common triggers of asthma symptoms and have also been implicated in allergic sensitization. Exposure to house dust mites in early childhood is a risk factor for allergic sensitization and asthma, but rigorous allergen avoidance has not shown any evidence for a reduced risk of developing asthma. The increase in house dust mites in centrally heated poorly ventilated homes with fitted carpets has been implicated in the increasing prevalence of asthma in affluent countries. Domestic pets, particularly cats, have also been associated with allergic sensitization, but early exposure to cats in the home may be protective through the induction of tolerance.

Occupational Exposure Occupational asthma is relatively common and may affect up to 10% of young adults. Over 300 sensitizing agents have been identified. Chemicals such as toluene diisocyanate and trimellitic anhydride, may lead to sensitization independent of atopy. Individuals may also be exposed to allergens in the workplace such as small animal allergens in laboratory workers and fungal amylase in wheat flour in bakers. Cleaners commonly develop occupational asthma owing to exposure to aerosols of cleaning liquids. Occupational asthma may be suspected when symptoms improve during weekends and holidays.

Obesity Asthma occurs more frequently in obese people (BMI >30 kg/m^2) and is often more difficult to control. Although mechanical factors may contribute, it may also be linked to the pro-inflammatory adipokines and reduced anti-inflammatory adipokines that are released from fat cells.

Other Factors Several other factors have been implicated in the etiology of asthma, including lower maternal age, duration of breastfeeding, prematurity and low birthweight, and inactivity, but are unlikely to contribute to the recent global increase in asthma prevalence. There is also an association with acetaminophen (paracetamol) consumption in childhood, which may be linked to increased oxidative stress.

Intrinsic Asthma A minority of asthmatic patients (~10%) have negative skin tests to common inhalant allergens and normal serum concentrations of IgE. These patients, with non-atopic or intrinsic asthma, usually show later onset of disease (adult-onset asthma), commonly have concomitant nasal polyps, and may be aspirin-sensitive. They usually have more severe, persistent asthma. Little is understood about mechanism, but the immunopathology in bronchial biopsies and sputum appears to be identical to that found in atopic asthma. There is recent evidence for increased local production of IgE in the airways, suggesting that there may be common IgE-mediated mechanisms; staphylococcal enterotoxins, which serve as "superantigens," have been implicated. Type-2 innate lymphoid cells (ILC2) may drive the eosinophilic inflammation in these non-allergic patients.

Asthma Triggers Several stimuli trigger airway narrowing, wheezing, and dyspnea in asthmatic patients. While the previous view held that these should be avoided, it is now seen as evidence for poor control and an indicator of the need to increase controller (preventive) therapy.

ALLERGENS Inhaled allergens activate mast cells with bound IgE directly leading to the immediate release of bronchoconstrictor mediators, resulting in the early response that is reversed by bronchodilators. Often, an experimental allergen challenge is followed by a late response when there is airway edema and an acute inflammatory response with increased eosinophils and neutrophils that are not very reversible with bronchodilators. The most common allergens to trigger asthma are *Dermatophagoides* species, and environmental exposure leads to low-grade chronic symptoms that are perennial. Other perennial allergens are derived from cats and other domestic pets, as well as cockroaches. Other allergens, including grass pollen, ragweed, tree pollen, and fungal spores, are seasonal. Pollens usually cause allergic rhinitis rather than asthma, but in thunderstorms the pollen grains are disrupted and the particles that may be released can trigger severe asthma exacerbations (thunderstorm asthma).

VIRUS INFECTIONS Upper respiratory tract virus infections such as rhinovirus, respiratory syncytial virus, and coronavirus are the most common triggers of acute severe exacerbations and may invade epithelial cells of the lower as well as the upper airways. The mechanism whereby these viruses cause exacerbations is poorly understood, but there is an increase in airway inflammation with increased numbers of eosinophils and neutrophils. There is evidence for reduced production of type I interferons by epithelial cells from asthmatic patients, resulting in increased susceptibility to these viral infections and a greater inflammatory response.

PHARMACOLOGIC AGENTS Several drugs may trigger asthma. Beta-adrenergic blockers commonly acutely worsen asthma, and their use may be fatal. The mechanisms are not clear but are likely mediated through increased cholinergic bronchoconstriction. All beta blockers need to be avoided and even selective β, β_2 blockers, or topical application (e.g., timolol eye drops) may be dangerous. Angiotensin-converting enzyme inhibitors are theoretically detrimental as they inhibit breakdown of kinins, which are bronchoconstrictors; however, they rarely worsen asthma, and the characteristic cough is no more frequent in asthmatics than in non-asthmatics. Aspirin may worsen asthma in some patients (aspirin-sensitive asthma is discussed under "Special Considerations").

EXERCISE Exercise is a common trigger of asthma, particularly in children. The mechanism is linked to hyperventilation, which results in increased osmolality in airway lining fluid and triggers mast cell mediator release, resulting in bronchoconstriction. Exercise-induced asthma (EIA) typically begins after exercise has ended, and recovers spontaneously within about 30 min. EIA is worse in cold, dry climates than in hot, humid conditions. It is, therefore, more common in sports such as cross-country running in cold weather, overland skiing, and ice hockey than in swimming. It may be prevented by prior administration of β_2-agonists and antileukotrienes, but is best prevented by regular treatment with ICS, which reduce the population of surface mast cells required for this response.

PHYSICAL FACTORS Cold air and hyperventilation may trigger asthma through the same mechanisms as exercise. Laughter may also be a trigger. Many patients report worsening of asthma in hot weather and when the weather changes. Some asthmatics become worse when exposed to strong smells or perfumes, but the mechanism of this response is uncertain.

FOOD AND DIET There is little evidence that allergic reactions to food lead to increased asthma symptoms, despite the belief of many patients that their symptoms are triggered by particular food constituents. Exclusion diets are usually unsuccessful at reducing the frequency of episodes. Some foods such as shellfish and nuts may induce anaphylactic reactions that may include wheezing. Patients with aspirin-induced asthma may benefit from a salicylate-free diet, but these are difficult to maintain. Certain food additives may trigger asthma. Metabisulfite, which is used as a food preservative, may trigger asthma through the release of sulfur dioxide gas in the stomach. Tartrazine, a yellow food-coloring agent, was believed to be a trigger for asthma, but there is little convincing evidence for this.

AIR POLLUTION Increased ambient levels of sulfur dioxide, ozone, diesel particulates and nitrogen oxides are associated with increased asthma symptoms.

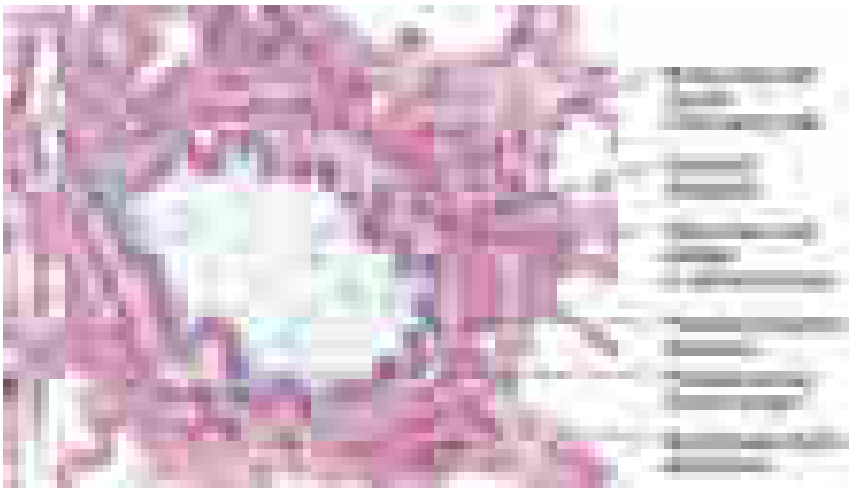

FIGURE 281-1 Histopathology of a small airway in fatal asthma. The lumen is occluded with a mucous plug, there is goblet cell metaplasia, and the airway wall is thickened, with an increase in basement membrane thickness and airway smooth muscle. *(Courtesy of Dr. J. Hogg, University of British Colombia.)*

OCCUPATIONAL FACTORS Several substances found in the workplace may act as sensitizing agents, as discussed above, but may also act as triggers of asthma symptoms. Occupational asthma is characteristically associated with symptoms at work with relief on weekends and holidays. If removed from exposure within the first 6 months of symptoms, there is usually complete recovery. More persistent symptoms lead to irreversible airway changes, and, thus, early detection and avoidance are important.

HORMONES Some women show premenstrual worsening of asthma, which can occasionally be very severe. The mechanisms are not completely understood, but are related to a fall in progesterone and in severe cases may be improved by treatment with high doses of progesterone or gonadotropin-releasing factors. Thyrotoxicosis and hypothyroidism can both worsen asthma, although the mechanisms are uncertain.

GASTROESOPHAGEAL REFLUX Gastroesophageal reflux is common in asthmatic patients as it is increased by bronchodilators. Although acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and antireflux therapy usually fails to reduce asthma symptoms in most patients.

STRESS Many asthmatics report worsening of symptoms with stress. Psychological factors can induce bronchoconstriction through cholinergic reflex pathways. Paradoxically, very severe stress such as bereavement usually does not worsen, and may even improve, asthma symptoms.

PATHOPHYSIOLOGY

Asthma is associated with a specific chronic inflammation of the mucosa of the lower airways. One of the main aims of treatment is to reduce this inflammation.

Pathology The pathology of asthma has been revealed through examining the lungs of patients who have died of asthma and from bronchial biopsies. The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells. The degree of inflammation is poorly related to disease severity and may even be found in atopic patients without asthma symptoms. This inflammation is usually reduced by treatment with ICS. There are also structural changes in the airways (often termed remodeling). A characteristic finding is thickening of the basement membrane due to subepithelial collagen deposition. This feature is also found in patients with eosinophilic bronchitis presenting as cough who do not have asthma and is, therefore, likely to be a marker of eosinophilic inflammation in the airway as eosinophils release fibrogenic mediators. The epithelium is often shed or friable, with reduced attachments to the airway wall and increased numbers of epithelial cells in the lumen. The airway wall itself may be thickened and edematous, particularly in fatal asthma. Another common finding in fatal asthma is occlusion of the airway lumen by a mucous plug, which is comprised of mucous glycoproteins secreted from goblet cells and plasma proteins from leaky bronchial vessels **(Fig. 281-1)**. There is also vasodilation and increased numbers of blood vessels (angiogenesis). Direct observation by bronchoscopy indicates that the airways may be narrowed, erythematous, and edematous. The pathology of asthma is remarkably uniform in different phenotypes of asthma, including atopic (extrinsic), non-atopic (intrinsic), occupational, aspirin-sensitive, and pediatric asthma. These pathologic changes are found in all airways, but do not extend to the lung parenchyma; peripheral airway inflammation is found particularly in patients with severe asthma. The involvement of airways may be patchy and this is consistent with bronchographic findings of uneven narrowing of the airways.

Airway Inflammation There is inflammation in the respiratory mucosa from the trachea to terminal bronchioles, but with a predominance in the bronchi (cartilaginous airways), but it is still uncertain how inflammatory cells interact and how inflammation translates into the symptoms of asthma **(Fig. 281-2)**. There is good evidence that the specific pattern of airway inflammation in asthma is associated with airway hyperresponsiveness (AHR), the physiologic abnormality of asthma, which is correlated with variable airflow obstruction. The pattern of inflammation in asthma is characteristic of allergic diseases, with similar inflammatory cells seen in the nasal mucosa in rhinitis. However, an indistinguishable pattern of inflammation is found in intrinsic asthma, and this may reflect local rather than systemic IgE production. Although most attention has focused on the acute

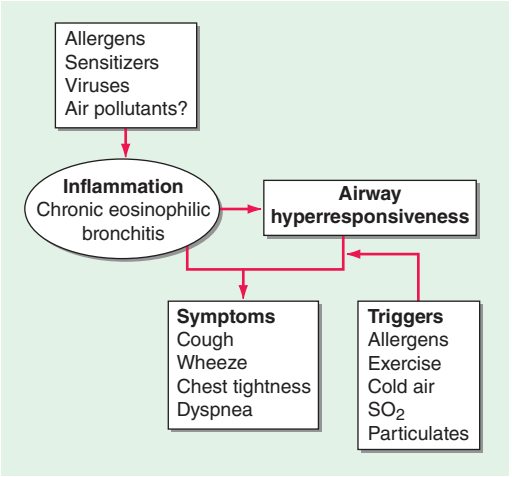

FIGURE 281-2 Inflammation in the airways of asthmatic patients leads to airway hyperresponsiveness and symptoms. SO_2, sulfur dioxide.

inflammatory changes seen in asthma, this is a chronic condition, with inflammation persisting over many years in most patients. The mechanisms involved in persistence of inflammation in asthma are still poorly understood. Superimposed on this chronic inflammatory state are acute inflammatory episodes, which correspond to exacerbations of asthma. Although the common pattern of inflammation in asthma is characterized by eosinophil infiltration, some patients with severe asthma show a neutrophilic pattern of inflammation that is less sensitive to corticosteroids. However, many inflammatory cells are involved in asthma with no key cell that is predominant **(Fig. 281-3)**.

MAST CELLS Mast cells are important in initiating the acute bronchoconstrictor responses to allergens and several other indirectly acting stimuli, such as exercise and hyperventilation (via osmolality changes), as well as fog. Activated mucosal mast cells are found at the airway surface in asthma patients and also in the airway smooth-muscle layer, whereas this is not seen in normal subjects or patients with eosinophilic bronchitis. Mast cells are activated by allergens through an IgE-dependent mechanism, and binding of specific IgE to mast cells renders them more sensitive to activation by physical stimuli such as osmolality. The importance of IgE in the pathophysiology of asthma has been highlighted by clinical studies with humanized anti-IgE antibodies, which inhibit IgE-mediated effects, reduce asthma symptoms, and reduce exacerbations. There are, however, uncertainties about the role of mast cells in more chronic allergic inflammatory events. Mast cells release several bronchoconstrictor mediators, including histamine, prostaglandin D_2, and cysteinyl-leukotrienes, but also several cytokines, chemokines, growth factors, and neurotrophins.

MACROPHAGES AND DENDRITIC CELLS Macrophages, which are derived from blood monocytes, may traffic into the airways in asthma and may be activated by allergens via low-affinity IgE receptors ($Fc_\varepsilon RII$). Macrophages have the capacity to initiate a type of inflammatory response via the release of a certain pattern of cytokines, but these cells also release anti-inflammatory mediators (e.g., IL-10) and, thus, their roles in asthma are uncertain. Dendritic cells are specialized macrophage-like cells in the airway epithelium, which are the major antigen-presenting cells. Dendritic cells take up allergens, process them to peptides, and migrate to local lymph nodes where they present the allergenic peptides to uncommitted T lymphocytes to program the production of allergen-specific T cells. Immature dendritic cells in the respiratory tract promote T_H2 cell differentiation and require cytokines such as IL-12 and tumor necrosis factor α (TNF-α), to promote the normally preponderant T_H1 response. The cytokine thymic stromal lymphopoietin (TSLP) released from epithelial cells in asthmatic patients instructs dendritic cells to release chemokines that attract T_H2 cells into the airways.

EOSINOPHILS Eosinophil infiltration is a characteristic feature of asthmatic airways. Allergen inhalation results in a marked increase in activated eosinophils in the airways at the time of the late reaction. Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals. Eosinophil recruitment involves adhesion of eosinophils to vascular endothelial cells in the airway circulation due to interaction between adhesion molecules, migration into the submucosa under the direction of chemokines, and their subsequent activation and prolonged survival. Blocking antibodies to IL-5 causes a profound and prolonged reduction in circulating and sputum eosinophils, but is not associated with reduced AHR or asthma symptoms, although in selected patients with steroid-resistant airway eosinophils, there is a reduction in exacerbations. Eosinophils may be important in release of growth factors involved in airway remodeling and in exacerbations but probably not in AHR.

NEUTROPHILS Increased numbers of activated neutrophils are found in sputum and airways of some patients with severe asthma and during exacerbations, although there is a proportion of patients even with mild or moderate asthma who have a predominance of neutrophils. The roles of neutrophils in asthma that are resistant to the anti-inflammatory effects of corticosteroids are currently unknown.

LYMPHOCYTES T lymphocytes play a very important role in coordinating the inflammatory response in asthma through the release of specific patterns of cytokines, resulting in the recruitment and survival of eosinophils and in the maintenance of a mast cell population in the airways. The naïve immune system and the immune system of asthmatics are skewed to express the T_H2 phenotype, whereas in normal airways T_H1 cells predominate. T_H2 cells, through the release of IL-5, are associated with eosinophilic inflammation and, through the release of IL-4 and IL-13, are associated with increased IgE formation. Natural killer $CD4^+$ T lymphocytes that express high levels of IL-4 have been described in some studies. Regulatory T cells (Treg) play an important role in determining the expression of other T cells, and there is evidence for a reduction in a certain subset of Tregs ($CD4^+CD25^+$) that express the transcription factor FOXP3 in asthma that is associated with increased T_H2 cells. Recently innate T cells (ILC2) without T cell receptors have been identified that release T_H2 cytokines and are regulated by epithelial cytokines such as IL-25 and IL-33 and may be predominant in non-allergic asthma.

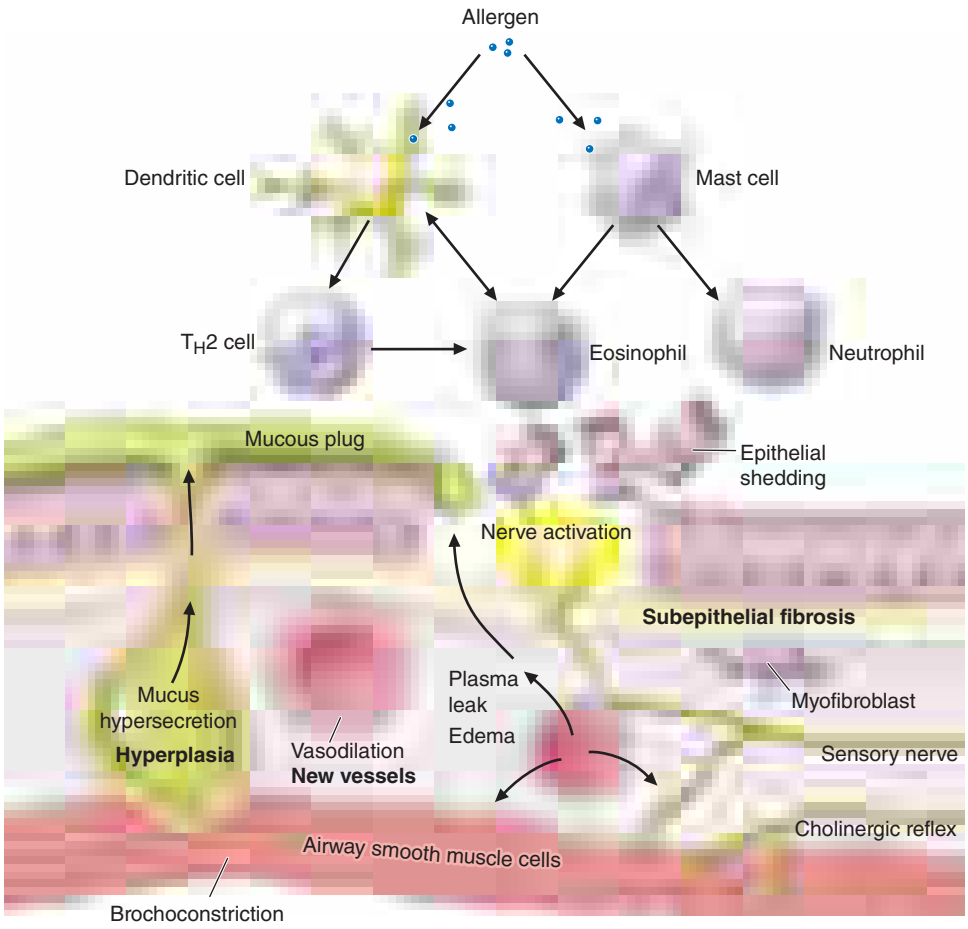

FIGURE 281-3 The pathophysiology of asthma is complex with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

STRUCTURAL CELLS Structural cells of the airways, including epithelial cells, fibroblasts, and airway smooth-muscle cells, are also important sources of inflammatory mediators such as cytokines and lipid mediators, in asthma. Indeed, because structural cells far outnumber inflammatory cells, they may become the major sources of mediators driving chronic inflammation in asthmatic airways. In addition, epithelial cells may have key roles in translating inhaled environmental signals into an airway inflammatory response, and are probably major target cells for ICS.

Inflammatory Mediators

Multiple inflammatory mediators have been implicated in asthma, and they may have a variety of effects on the airways that account for the pathologic features of asthma (Fig. 281-4). Mast cell-derived mediators, such as histamine, prostaglandin D_2, and cysteinyl-leukotrienes, contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells. Because each mediator has many effects, the role of individual mediators in the pathophysiology of asthma is not yet clear. Although the multiplicity of mediators makes it unlikely that preventing the synthesis or action of a single mediator will have a major impact in clinical asthma, recent clinical studies with antileukotrienes suggest that cysteinyl-leukotrienes have clinically important effects.

CYTOKINES Multiple cytokines regulate the chronic inflammation of asthma. The T_H2 cytokines IL-4, IL-5, IL-9, and IL-13 mediate allergic inflammation, whereas proinflammatory cytokines such as TNF-α and IL-1β amplify the inflammatory response and play a role in more severe disease. TSLP is an upstream cytokine released from epithelial cells of asthmatics that orchestrates the release of chemokines that selectively attract T_H2 cells. Some cytokines such as IL-10 and IL-12 are anti-inflammatory and may be deficient in asthma.

CHEMOKINES Chemokines are involved in attracting inflammatory cells from the bronchial circulation into the airways. Eotaxin (CCL11) is selectively attractant to eosinophils via CCR3 and is expressed by epithelial cells of asthmatics, whereas CCL17 (TARC) and CCL22 (MDC) from epithelial cells attract T_H2 cells via CCR4 (Fig. 281-5).

OXIDATIVE STRESS Activated inflammatory cells such as macrophages, eosinophils, and neutrophils produce reactive oxygen species. Evidence for increased oxidative stress in asthma is provided by the increased concentrations of 8-isoprostane (a product of oxidized arachidonic acid) in exhaled breath condensates and increased ethane (a product of lipid peroxidation) in the expired air of asthmatic patients. Increased oxidative stress is related to disease severity, it may amplify the inflammatory response, and may reduce responsiveness to corticosteroids.

NITRIC OXIDE Nitric oxide (NO) is produced by NO synthases in several cells in the airway, particularly airway epithelial cells and macrophages. The level of NO in the expired air of patients with asthma is higher than normal and is related to the eosinophilic inflammation. Increased NO may contribute to the bronchial vasodilation observed in asthma. Fractional exhaled NO (F_ENO) is increasingly used in the diagnosis and monitoring of asthmatic inflammation, although it is not yet used routinely in clinical practice.

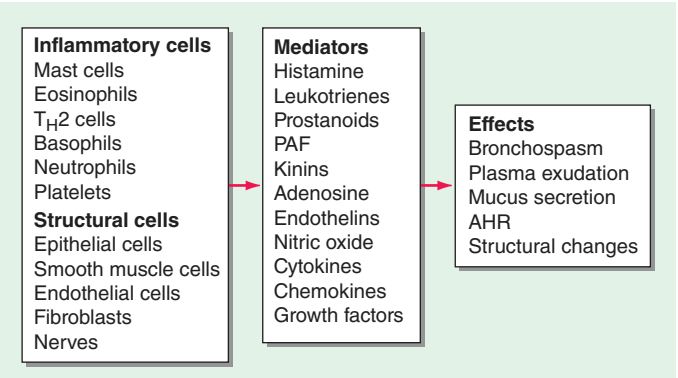

FIGURE 281-4 Many cells and mediators are involved in asthma and lead to several effects on the airways. AHR, airway hyperresponsiveness; PAF, platelet-activating factor.

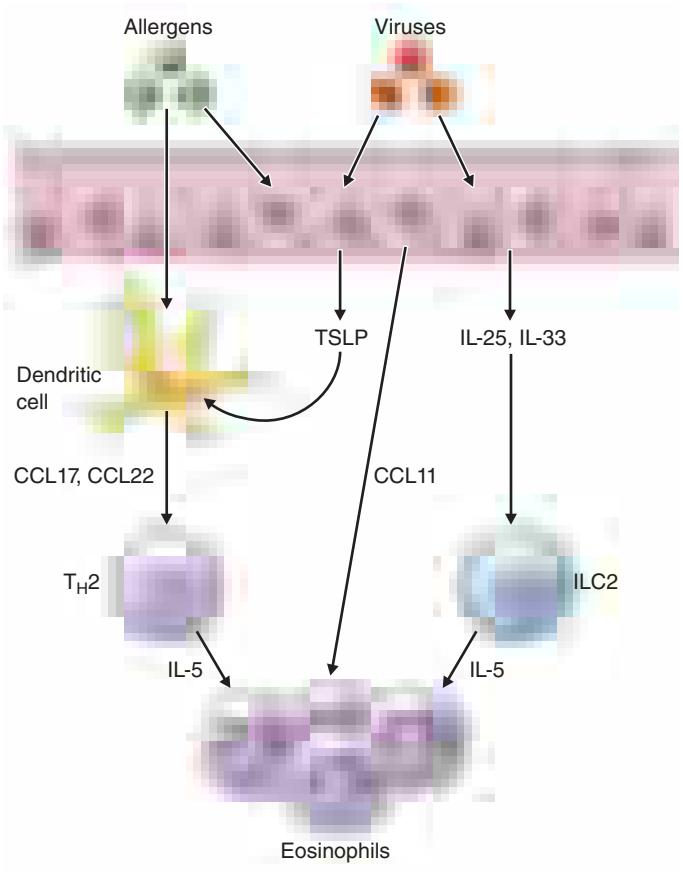

FIGURE 281-5 T lymphocytes in asthma. Allergen interacts with dendritic cells and releases thymus stimulated lymphopoietin (TSLP) which stimulate activated dendritic cells to release the chemokines CCL17 and CCL22, which attract T helper 2 (T_H2) lymphocytes. Allergens and viral infection may release interleukins (IL)-25 and -33 which recruit and activate type 2 innate lymphoid cells (ILC2). Both T_H2 and ILC2 cells release IL-5 and epithelial cells CCL11 (eotaxin), which together lead to recruitment of eosinophils into the airways.

TRANSCRIPTION FACTORS Proinflammatory transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1, are activated in asthmatic airways and orchestrate the expression of multiple inflammatory genes. More specific transcription factors that are involved include nuclear factor of activated T cells and GATA-3, which regulate the expression of T_H2 cytokines in T_H2 and ILC2 cells.

Effects of Inflammation

The chronic inflammatory response has several effects on the target cells of the airways, resulting in the characteristic pathophysiologic and remodeling changes associated with asthma. Asthma may be regarded as a disease with continuous inflammation and repair proceeding simultaneously, although the relationship between chronic inflammatory processes and asthma symptoms is often obscure.

AIRWAY EPITHELIUM Airway epithelial shedding may be important in contributing to AHR and may explain how several mechanisms, such as ozone exposure, virus infections, chemical sensitizers, and allergens (usually proteases), can lead to its development, as all of these stimuli may lead to epithelial disruption. Epithelial damage may contribute to AHR in a number of ways, including loss of its barrier function to allow penetration of allergens; loss of enzymes (such as neutral endopeptidase/neprilysin) that degrade certain peptide inflammatory mediators like bradykinin; loss of a relaxant factor (so-called epithelial-derived relaxant factor); and exposure of sensory nerves, which may lead to reflex neural effects on the airway.

FIBROSIS In all asthmatic patients, the basement membrane is apparently thickened due to subepithelial fibrosis with deposition of types III

and V collagen below the true basement membrane and is associated with eosinophil infiltration, presumably through the release of profibrotic mediators such as transforming growth factor-β. Mechanical manipulations can alter the phenotype of airway epithelial cells in a profibrotic fashion. In more severe patients, there is also fibrosis within the airway wall, which may contribute to irreversible narrowing of the airways.

AIRWAY SMOOTH MUSCLE In vitro airway smooth muscle from asthmatic patients usually shows no increased responsiveness to constrictors. Reduced responsiveness to β-agonists has also been reported in postmortem or surgically removed bronchi from asthmatics, although the number of β-receptors is not reduced, suggesting that β-receptors have been uncoupled. These abnormalities of airway smooth muscle may be secondary to the chronic inflammatory process. Inflammatory mediators may modulate the ion channels that serve to regulate the resting membrane potential of airway smooth-muscle cells, thus altering the level of excitability of these cells. In asthmatic airways there is also a characteristic hypertrophy and hyperplasia of airway smooth muscle, which is presumably the result of stimulation of airway smooth-muscle cells by various growth factors such as platelet-derived growth factor (PDGF) or endothelin-1 released from inflammatory or epithelial cells. Airway smooth-muscle cells from asthmatic patients also release multiple inflammatory mediators, particularly cytokines and chemokines.

VASCULAR RESPONSES There is increased airway mucosal blood flow in asthma, which may contribute to airway narrowing. There is an increase in the number of blood vessels in asthmatic airways as a result of angiogenesis in response to growth factors, particularly vascular-endothelial growth factor. Microvascular leakage from postcapillary venules in response to inflammatory mediators is observed in asthma, resulting in airway edema and plasma exudation into the airway lumen.

MUCUS HYPERSECRETION Increased mucus secretion contributes to the viscid mucous plugs that occlude asthmatic airways, particularly in fatal asthma. There is hyperplasia of submucosal glands that are confined to large airways and of increased numbers of epithelial goblet cells. IL-13 induces mucus hypersecretion in experimental models of asthma.

NEURAL REGULATION Various defects in autonomic neural control may contribute to AHR in asthma, but these are likely to be secondary to the disease, rather than primary defects. Cholinergic pathways, through the release of acetylcholine acting on muscarinic receptors, cause bronchoconstriction and may be activated reflexly in asthma. Inflammatory mediators may activate sensory nerves, resulting in reflex cholinergic bronchoconstriction or release of inflammatory neuropeptides. Inflammatory products may also sensitize sensory nerve endings in the airway epithelium such that the nerves become hyperalgesic. Neurotrophins, which may be released from various cell types in airways, including epithelial cells and mast cells, may cause proliferation and sensitization of airway sensory nerves. Airway nerves may also release neurotransmitters, such as substance P, which may have inflammatory effects.

Airway Remodeling Several changes in the structure of the airway are characteristically found in asthma, and these may lead to irreversible narrowing of the airways. Population studies have shown a greater decline in lung function over time than in normal subjects; however, most patients with asthma preserve normal or near-normal lung function throughout life if appropriately treated. This suggests that the accelerated decline in lung function occurs in a smaller proportion of asthmatics, and these are usually patients with more severe disease. There is some evidence that the early use of ICS may reduce the decline in lung function. The characteristic structural changes are increased airway smooth muscle, fibrosis, angiogenesis, and mucus hyperplasia.

Physiology Limitation of airflow is due mainly to bronchoconstriction (from mast cell mediators), but airway edema, vascular congestion, and luminal occlusion with exudate may contribute. This results in a reduction in forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC) ratio, and peak expiratory flow (PEF), as well as an increase in airway resistance. Early closure of peripheral airway results in lung hyperinflation (air trapping) and increased residual volume, particularly during acute exacerbations and in severe persistent asthma. In more severe asthma, reduced ventilation and increased pulmonary blood flow result in mismatching of ventilation and perfusion and in bronchial hyperemia. Ventilatory failure is very uncommon, even in patients with severe asthma, and arterial P_{CO_2} tends to be low due to increased ventilation.

Airway Hyperresponsiveness AHR is the characteristic physiologic abnormality of asthma and describes the excessive bronchoconstrictor response to multiple inhaled triggers that would have no effect on normal airways. The increase in AHR is linked to the frequency of asthma symptoms, and, thus, an important aim of therapy is to reduce AHR. Increased bronchoconstrictor responsiveness is seen with *direct* bronchoconstrictors such as histamine and methacholine, which contract airway smooth muscle, but is characteristically also seen with many *indirect* stimuli, which release bronchoconstrictors from mast cells or activate sensory nerves. Most of the triggers for asthma symptoms appear to act indirectly, including allergens, exercise, hyperventilation, fog (via mast cell activation), irritant dusts, and sulfur dioxide (via a cholinergic reflex).

CLINICAL FEATURES AND DIAGNOSIS

The characteristic symptoms of asthma are wheezing, dyspnea, and coughing, which are variable, both spontaneously and with therapy. Symptoms may be worse at night and patients typically awake in the early morning hours. Patients may report difficulty in filling their lungs with air. There is increased mucus production in some patients, with typically tenacious mucus that is difficult to expectorate. There may be increased ventilation and use of accessory muscles of ventilation. Prodromal symptoms may precede an attack, with itching under the chin, discomfort between the scapulae, or inexplicable fear (impending doom).

Typical physical signs are inspiratory, and to a greater extent expiratory, rhonchi throughout the chest, and there may be hyperinflation. Some patients, particularly children, may present with a predominant nonproductive cough ("cough-variant asthma"). There may be no abnormal physical findings when asthma is under control.

DIAGNOSIS

The diagnosis of asthma is usually apparent from the symptoms of variable and intermittent airways obstruction, but must be confirmed by objective measurements of lung function.

Lung Function Tests Simple spirometry confirms airflow limitation with a reduced FEV_1, FEV_1/FVC ratio, and PEF **(Fig. 281-6)**. Reversibility is demonstrated by a >12% and 200-mL increase in FEV_1 15 min after an inhaled short-acting β_2-agonist (SABA; such as inhaled albuterol 400 μg) or in some patients by a 2–4 week trial of oral corticosteroids (OCS) (prednisone or prednisolone 30–40 mg daily). Measurements of PEF twice daily may confirm the diurnal variations in airflow obstruction. Flow-volume loops show reduced peak flow and reduced maximum expiratory flow. Further lung function tests are rarely necessary, but whole body plethysmography shows increased airway resistance and may show increased total lung capacity and residual volume. Gas diffusion, measured by carbon monoxide transfer, is usually normal, but there may be a small increase in some patients.

Airway Responsiveness The increased AHR is normally measured by methacholine or histamine challenge with calculation of the provocative concentration that reduces FEV_1 by 20% (PC20). This is rarely useful in clinical practice, but can be used in the differential diagnosis of chronic cough and when the diagnosis is in doubt in the setting of normal pulmonary function tests. Occasionally exercise testing is done to demonstrate the post-exercise bronchoconstriction if there is a predominant history of EIA. Allergen challenge is rarely necessary

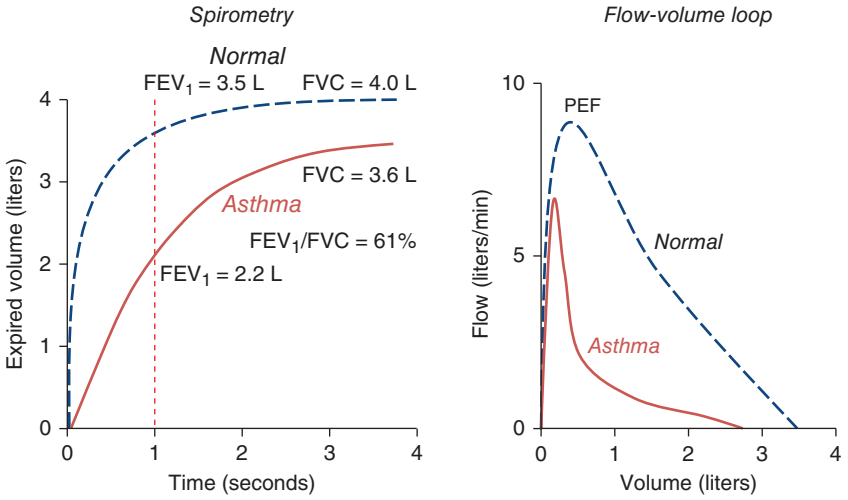

FIGURE 281-6 Spirometry and flow-volume loop in asthmatic compared to normal subject. There is a reduction in forced expiratory volume in 1 second (FEV_1) but less reduction in forced vital capacity (FVC), giving a reduced FEV_1/FVC ratio (<70%). The flow-volume loop shows reduced peak expiratory flow and a typical scalloped appearance indicating widespread airflow obstruction.

and should only be undertaken by a specialist if specific occupational agents are to be identified.

Hematologic Tests Blood tests are not usually helpful. Total serum IgE and specific IgE to inhaled allergens (radioallergosorbent test [RAST]) may be measured in some patients.

Imaging Chest roentgenography is usually normal but in more severe patients may show hyperinflated lungs. In exacerbations, there may be evidence of a pneumothorax. Lung shadowing usually indicates pneumonia or eosinophilic infiltrates in patients with bronchopulmonary aspergillosis (BPA). High-resolution CT may show areas of bronchiectasis in patients with severe asthma, and there may be thickening of the bronchial walls, but these changes are not diagnostic of asthma.

Skin Tests Skin prick tests to common inhalant allergens (house dust mite, cat fur, grass pollen) are positive in allergic asthma and negative in intrinsic asthma, but are not helpful in diagnosis. Positive skin responses may be useful in persuading patients to undertake allergen avoidance measures.

Exhaled NO Fractional exhaled nitric oxide (F_ENO) is now being used as a noninvasive test to measure eosinophilic airway inflammation. The typically elevated levels in asthma are reduced by ICS, so this may be a test of compliance with therapy. It may also be useful in demonstrating insufficient anti-inflammatory therapy and may be useful in down-titrating ICS. However, studies in unselected patients have not convincingly demonstrated improved clinical outcomes and it may be necessary to select patients who are poorly controlled.

Differential Diagnosis It is usually not difficult to differentiate asthma from other conditions that cause wheezing and dyspnea. Upper airway obstruction by a tumor or laryngeal edema can mimic severe asthma, but patients typically present with stridor localized to large airways. The diagnosis is confirmed by a flow-volume loop that shows a reduction in inspiratory as well as expiratory flow, and bronchoscopy to demonstrate the site of upper airway narrowing. Persistent wheezing in a specific area of the chest may indicate endobronchial obstruction with a foreign body. Left ventricular failure may mimic the wheezing of asthma but basilar crackles are present in contrast to asthma. Vocal cord dysfunction may mimic asthma and is thought to be a hysterical conversion syndrome.

Eosinophilic pneumonias and systemic vasculitis, including Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) and polyarteritis nodosa, may be associated with wheezing. Chronic obstructive pulmonary disease (COPD) is usually easy to differentiate from asthma as symptoms show less variability, never completely remit, and show much less (or no) reversibility to bronchodilators. Approximately 15% of COPD patients have features of asthma, with increased sputum eosinophils and a response to OCS; these patients probably have both diseases concomitantly.

TREATMENT

Asthma

The treatment of asthma is straightforward, with the majority of patients now managed by internists and family doctors with effective and safe therapies. There are several aims of therapy **(Table 281-2)**. Most of the emphasis has been placed on drug therapy, but several non-pharmacologic approaches have also been used. The main drugs for asthma can be divided into bronchodilators, which give rapid relief of symptoms mainly through relaxation of airway smooth muscle, and controllers, which inhibit the underlying inflammatory process.

BRONCHODILATOR THERAPIES

Bronchodilators act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma. This gives rapid relief of symptoms but has little or no effect on the underlying inflammatory process. Thus, bronchodilators are not sufficient to control asthma in patients with persistent symptoms. There are three classes of bronchodilator in current use: β_2-adrenergic agonists, anticholinergics, and theophylline; of these, β_2-agonists are by far the most effective.

β_2-Agonists β_2-Agonists activate β_2-adrenergic receptors, which are widely expressed in the airways. β_2-Receptors are coupled through a stimulatory G protein to adenylyl cyclase, resulting in increased intracellular cyclic adenosine monophosphate (AMP), which relaxes smooth muscle cells and inhibits certain inflammatory cells, particularly mast cells.

TABLE 281-2 Aims of Asthma Therapy

- Minimal (ideally no) chronic symptoms, including nocturnal
- Minimal (infrequent) exacerbations
- No emergency visits
- Minimal (ideally no) use of a required β_2-agonist
- No limitations on activities, including exercise
- Peak expiratory flow circadian variation <20%
- (Near) normal PEF
- Minimal (or no) adverse effects from medicine

Abbreviation: PEF, peak expiratory flow.

Mode of Action The primary action of β_2-agonists is to relax airway smooth-muscle cells of all airways, where they act as functional antagonists, reversing and preventing contraction of airway smooth-muscle cells by all known bronchoconstrictors. This generalized action is likely to account for their great efficacy as bronchodilators in asthma. There are also additional non-bronchodilator effects that may be clinically useful, including inhibition of mast cell mediator release, reduction in plasma exudation, and inhibition of sensory nerve activation. Inflammatory cells express small numbers of β_2-receptors, but these are rapidly down-regulated with β_2-agonist activation so that, in contrast to corticosteroids, there are no effects on inflammatory cells in the airways and there is no reduction in AHR.

Clinical Use β_2-Agonists are usually given by inhalation to reduce side effects. SABA, such as albuterol and terbutaline, have a duration of action of 3–6 h. They have a rapid onset of bronchodilatation and are, therefore, used as needed for symptom relief (relievers). Increased use of SABA indicates that asthma is not controlled. They are also useful in preventing EIA if taken prior to exercise. SABA are used in high doses by nebulizer or via a metered-dose inhaler (MDI) with a spacer. Long-acting β_2-agonists (LABA) include salmeterol and formoterol, both of which have a duration of action over 12 h and are given twice daily by inhalation; and indacaterol, olodaterol, and vilanterol, which are given once daily. LABA have replaced the regular use of SABA, but LABA should not be given in the absence of ICS therapy as they do not control the underlying inflammation. They do, however, improve asthma control and reduce exacerbations when added to ICS, which allows asthma to be managed with lower doses of corticosteroids. This observation has led to the widespread use of fixed combination inhalers that contain a corticosteroid and a LABA, which have proved to be highly effective in the control of asthma and prevention of exacerbations.

Side Effects Adverse effects are not usually a problem with β_2-agonists when given by inhalation. The most common side effects are muscle tremor and palpitations, which are seen more commonly in elderly patients. There is a small fall in plasma potassium due to increased uptake by skeletal muscle cells, but this effect does not usually cause any clinical problem.

Tolerance Tolerance is a potential problem with any agonist given chronically, but while there is down-regulation of β_2-receptors, this does not reduce the bronchodilator response as there is a large receptor reserve in airway smooth-muscle cells. By contrast, mast cells become rapidly tolerant, but their tolerance may be prevented by concomitant administration of ICS.

Safety The safety of β_2-agonists has been an important issue. There is an association between asthma mortality and the amount of SABA used, but careful analysis demonstrates that the increased use of rescue SABA reflects poor asthma control, which is a risk factor for asthma death. The slight excess in mortality that has been associated with the use of LABA is related to the lack of use of concomitant ICS, as the LABA therapy fails to suppress the underlying inflammation. This highlights the importance of always using an ICS when LABAs are given, which is most conveniently achieved by using a combination inhaler. Recent large safety studies have shown no adverse effects of LABA in adults or children.

Anticholinergics Muscarinic receptor antagonists, such as ipratropium bromide, prevent cholinergic nerve-induced bronchoconstriction and mucus secretion. They are less effective than β_2-agonists in asthma therapy as they inhibit only the cholinergic reflex component of bronchoconstriction, whereas β_2-agonists prevent all bronchoconstrictor mechanisms. Long-acting muscarinic antagonists (LAMA), including tiotropium bromide or glycopyrronium bromide, may be used as an additional bronchodilator in patients with asthma that is not controlled by maximal doses of ICS-LABA combinations, and improve lung function and further reduce exacerbations. High doses of short-acting anticholinergics may be given by nebulizer in treating acute severe asthma but should only be given following β_2-agonists, as they have a slower onset of bronchodilation.

Side effects are not usually a problem as there is little or no systemic absorption. The most common side effect is dry mouth; in elderly patients, urinary retention and glaucoma may also be observed.

Theophylline Theophylline was widely prescribed as an oral bronchodilator several years ago, especially as it was inexpensive. It has now fallen out of favor as side effects are common, and inhaled β_2-agonists are much more effective as bronchodilators. The bronchodilator effect is due to inhibition of phosphodiesterases in airway smooth-muscle cells, which increases cyclic AMP, but doses required for bronchodilatation commonly cause side effects that are mediated mainly by phosphodiesterase inhibition. There is increasing evidence that theophylline at lower doses has anti-inflammatory effects, and these are likely to be mediated through different molecular mechanisms. Theophylline activates the key nuclear enzyme histone deacetylase-2 (HDAC2), which is a critical mechanism for switching off activated inflammatory genes and may therefore reduce corticosteroid insensitivity in severe asthma.

Clinical Use Oral theophylline is usually given as a slow-release preparation once or twice daily as this gives more stable plasma concentrations than normal theophylline tablets. It may be used as an additional bronchodilator in patients with severe asthma when plasma concentrations of 10–20 mg/L are required, although these concentrations are often associated with side effects. Low doses of theophylline, giving plasma concentrations of 5–10 mg/L, have additive effects to ICS and are particularly useful in patients with severe asthma. Indeed, withdrawal of theophylline from these patients may result in marked deterioration in asthma control. At low doses, the drug is well tolerated. IV aminophylline (a soluble salt of theophylline) was used for the treatment of severe asthma but has now been largely replaced by high doses of inhaled SABA, which are more effective and have fewer side effects. Aminophylline is occasionally used (via slow IV infusion) in patients with severe exacerbations that are refractory to SABA.

Side Effects Oral theophylline is well absorbed and is largely inactivated in the liver. Side effects are related to plasma concentrations; measurement of plasma theophylline may be useful in determining the correct dose. The most common side effects are nausea, vomiting, and headaches and are due to phosphodiesterase inhibition. Diuresis and palpitations may also occur, and at high concentrations cardiac arrhythmias, epileptic seizures, and death may occur due to adenosine A_1-receptor antagonism. Theophylline side effects are related to plasma concentration and are rarely observed at plasma concentrations <10 mg/L. Theophylline is metabolized by CYP450 (CYP1A2) in the liver, and, thus, plasma concentrations may be elevated by drugs that block CYP450 such as erythromycin and allopurinol. Other drugs may also reduce clearance by other mechanisms leading to increased plasma concentrations **(Table 281-3)**.

CONTROLLER THERAPIES

Inhaled Corticosteroids ICS are by far the most effective controllers for asthma, and their early use has revolutionized asthma therapy.

Mode of Action ICS are the most effective anti-inflammatory agents used in asthma therapy, reducing inflammatory cell numbers and their activation in the airways. ICS reduce eosinophils in the airways and sputum, and numbers of activated T lymphocytes and surface mast cells in the airway mucosa. These effects may account for the reduction in AHR that is seen with chronic ICS therapy.

The molecular mechanism of action of corticosteroids involves several effects on the inflammatory process. The major effect of corticosteroids is to switch off the transcription of multiple activated genes that encode inflammatory proteins such as cytokines, chemokines, adhesion molecules, and inflammatory enzymes.

TABLE 281-3 Factors Affecting Clearance of Theophylline

Increased Clearance
• Enzyme induction (rifampicin, phenobarbitone, ethanol)
• Smoking (tobacco, marijuana)
• High-protein, low-carbohydrate diet
• Barbecued meat
• Childhood
Decreased Clearance
• Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zafirlukast)
• Congestive heart failure
• Liver disease
• Pneumonia
• Viral infection and vaccination
• High carbohydrate diet
• Old age

This effect involves several mechanisms, including inhibition of the transcription factors NF-κB, but an important mechanism is recruitment of HDAC2 to the inflammatory gene complex, which reverses the histone acetylation associated with increased gene transcription. Corticosteroids also activate anti-inflammatory genes such as mitogen-activated protein (MAP) kinase phosphatase-1, and increase the expression of β_2-receptors. Most of the metabolic and endocrine side effects of corticosteroids are also mediated through transcriptional activation.

Clinical Use ICS are by far the most effective controllers in the management of asthma and are beneficial in treating asthma of any severity and age. ICS are usually given twice daily, but some may be effective once daily in mildly symptomatic patients. ICS rapidly improve the symptoms of asthma, and lung function improves over several days. They are effective in preventing asthma symptoms, such as EIA and nocturnal exacerbations, but also prevent severe exacerbations. ICS reduce AHR, but maximal improvement may take several months of therapy. Early treatment with ICS appears to prevent irreversible changes in airway function that occur with chronic asthma. Withdrawal of ICS results in slow deterioration of asthma control, indicating that they suppress inflammation and symptoms, but do not cure the underlying condition. ICS are now given as first-line therapy for patients with persistent asthma, but if they do not control symptoms at low doses, it is usual to add a LABA as the next step.

Side Effects Local side effects include hoarseness (dysphonia) and oral candidiasis, which may be reduced with the use of a large-volume spacer device. There has been concern about systemic side effects from lung absorption, but many studies have demonstrated that ICS have minimal systemic effects **(Fig. 281-7)**. At the highest recommended doses, there may be some suppression of plasma and urinary cortisol concentrations, but there is no convincing evidence that long-term treatment leads to impaired growth in children or to osteoporosis in adults. Indeed effective control of asthma with ICS reduces the number of courses of OCS that are needed and, thus, reduces systemic exposure to ICS.

Systemic Corticosteroids Corticosteroids are used intravenously (hydrocortisone or methylprednisolone) for the treatment of acute severe asthma, although several studies now show that OCS are as effective and easier to administer. A course of OCS (usually prednisone or prednisolone 30–45 mg once daily for 5–10 days) is used to treat acute exacerbations of asthma; no tapering of the dose is needed. Approximately 1% of asthma patients may require maintenance treatment with OCS; the lowest dose necessary to maintain control needs to be determined. Systemic side effects, including truncal obesity, bruising, osteoporosis, diabetes, hypertension, gastric ulceration, proximal myopathy, depression, and cataracts, may be a major problem, and steroid-sparing therapies may be considered if side effects are a significant problem. If patients require maintenance treatment with OCS, it is important to monitor bone density so that preventive treatment with bisphosphonates or estrogen in postmenopausal women may be initiated if bone density is low. Intramuscular triamcinolone acetonide is a depot preparation that is occasionally used in noncompliant patients, but proximal myopathy is a major problem with this therapy.

Antileukotrienes Cysteinyl-leukotrienes are potent bronchoconstrictors; they cause microvascular leakage and increase eosinophilic inflammation through the activation of cys-LT_1-receptors. These inflammatory mediators are produced predominantly by mast cells and, to a lesser extent, eosinophils in asthma. Antileukotrienes, such as montelukast and zafirlukast, block cys-LT_1-receptors and provide modest clinical benefit in asthma. They are less effective than ICS in controlling asthma and have less effect on airway inflammation, but are useful as an add-on therapy in some patients not controlled with low doses of ICS, although less effective than a LABA. They are given orally once or twice daily and are well tolerated. Some patients show a better response than others to antileukotrienes, but this has not been convincingly linked to any genomic differences in the leukotriene pathway.

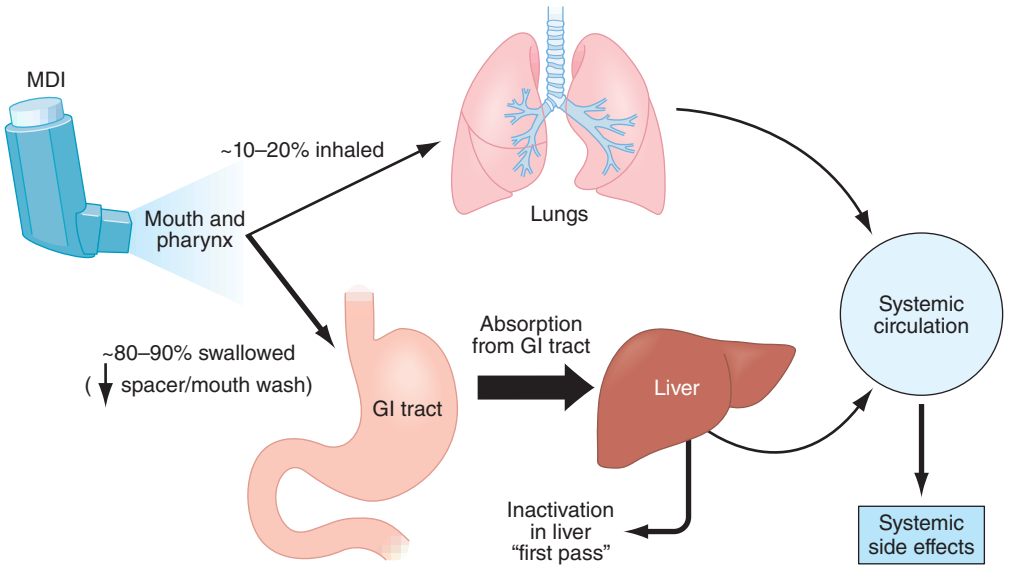

FIGURE 281-7 Pharmacokinetics of inhaled corticosteroids.

Cromones Cromolyn sodium and nedocromil sodium are asthma controller drugs that appear to inhibit mast cell and sensory nerve activation and are, therefore, effective in blocking trigger-induced asthma such as EIA and allergen- and sulfur dioxide-induced symptoms. Cromones have relatively little benefit in the long-term control of asthma due to their short duration of action (at least four times daily by inhalation). They are very safe and were popular in the treatment of childhood asthma, although now low doses of ICS are preferred as they are far more effective and have a proven safety profile.

Steroid-Sparing Therapies Various immunomodulatory treatments have been used to reduce the requirement for OCS in patients with severe asthma, who have serious side effects with this therapy. Methotrexate, cyclosporin A, azathioprine, gold, and IV gamma globulin have all been used as steroid-sparing therapies, but none of these treatments has any long-term benefit and each is associated with a relatively high risk of side effects.

Anti-IgE Omalizumab is a blocking antibody that neutralizes circulating IgE without binding to cell-bound IgE and, thus, inhibits IgE-mediated reactions. This treatment has been shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control. However, the treatment is very expensive and is only suitable for highly selected patients who are not controlled on maximal doses of inhaler therapy and have a circulating IgE within a specified range. Patients should be given a 3- to 4-month trial of therapy to show objective benefit. Omalizumab is usually given as a subcutaneous injection every 2–4 weeks and appears not to have significant side effects, although anaphylaxis is very occasionally seen.

Anti-IL-5 Antibodies that block IL-5 (mepolizumab, reslizumab) or its receptor (benralizumab) markedly reduce blood and tissue eosinophils and reduce exacerbations in patients who have persistently increased sputum eosinophils despite maximal ICS therapy.

Immunotherapy Specific immunotherapy using injected extracts of pollens or house dust mites has not been very effective in controlling asthma and may cause anaphylaxis. Side effects may be reduced by sublingual dosing. It is not recommended in most asthma treatment guidelines because of lack of evidence of clinical efficacy and potential anaphylaxis.

Alternative Therapies Nonpharmacologic treatments, including hypnosis, acupuncture, chiropraxis, breathing control, yoga, and speleotherapy, may be popular with some patients. However, placebo-controlled studies have shown that each of these treatments lacks efficacy and cannot be recommended. However, they are not detrimental and may be used as long as conventional pharmacologic therapy is continued.

Bronchial Thermoplasty Bronchial thermoplasty is a bronchoscopic treatment using thermal energy to ablate airway smooth muscle in accessible bronchi. It may reduce exacerbations and improve asthma control in highly selected patients not controlled on maximal inhaler therapy, particularly when there is no increase in inflammation.

Future Therapies It has proved very difficult to discover novel pharmaceutical therapies, particularly as current therapy with corticosteroids and β_2-agonists is so effective in the majority of patients. There is, however, a need for the development of new therapies for patients with refractory asthma who have side effects with systemic corticosteroids. Antagonists of specific mediators have little or no benefit in asthma, apart from antileukotrienes, which have rather weak effects, presumably reflecting the fact that multiple mediators are involved. Anti-TNF-α antibodies are not effective in severe asthma. Anti-IL-13 blocking antibodies have little clinical effect, but an antibody (dupilumab) against the common receptor for IL-4 and IL-13 (IL-4Rα) is more promising in reducing exacerbations and improving asthma control in severe asthma. Novel anti-inflammatory treatments that are in clinical development include inhibitors of phosphodiesterase-4, NF-κB, and p38 MAP kinase. However, these drugs, which act on signal transduction pathways common to many cells, have troublesome side effects, which may necessitate their delivery by inhalation. Safer and more effective immunotherapy using T cell peptide fragments of allergens or DNA vaccination are also being investigated. Bacterial products, such as CpG oligonucleotides that stimulate T_H1 immunity or Treg, are also currently under evaluation.

TABLE 281-4 Asthma Control

CHARACTERISTIC	CONTROLLED (ALL OF FOLLOWING)	PARTLY CONTROLLED	UNCONTROLLED
Daytime symptoms	None (≤2/week)	>2/week	Three of more features of partly controlled
Limitation of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (≤2/week)	>2/week	
Lung function (PEF or FEV_1)	Normal	<80% predicted or personal best (if known)	

MANAGEMENT OF CHRONIC ASTHMA

There are several aims of chronic therapy in asthma (Table 281-2). It is important to establish the diagnosis objectively using spirometry or PEF measurements at home. Triggers that worsen asthma control, such as allergens or occupational agents, should be avoided, whereas triggers, such as exercise and fog, which result in transient symptoms, provide an indication that more controller therapy is needed. It is important to assess asthma control, assessed by symptoms, night awakening, need for reliever inhalers, limitation of activity and lung function **(Table 281-4)**. Avoidance of side effects and expense of medications are also important. There are several validated questionnaires for quantifying asthma control, such as the Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Test (ACT).

Stepwise Therapy For patients with mild, intermittent asthma, a SABA is all that is required **(Fig. 281-8)**. However, use of a reliever medication more than twice a week indicates the need for regular controller therapy. The treatment of choice for all patients is an ICS given twice daily. It is usual to start with an intermediate dose (e.g., 200 [μg] bid of [beclomethasone dipropionate] BDP) or equivalent and to decrease the dose if symptoms are controlled after three months. If symptoms are not controlled, a LABA should be added, which is most conveniently given by switching to a combination inhaler.

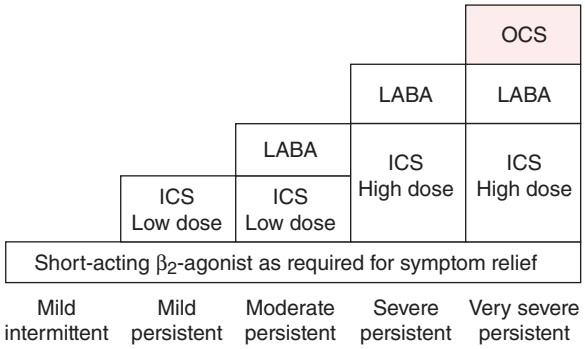

FIGURE 281-8 Stepwise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; OCS, oral corticosteroid.

The dose of controller should be adjusted accordingly, as judged by the need for a rescue inhaler. Low doses of theophylline or an antileukotriene may also be considered as an add-on therapy, but these are less effective than LABA. In patients with severe asthma, low-dose oral theophylline is also helpful, and when there is irreversible airway narrowing, the long-acting anticholinergic may be tried. If asthma is not controlled despite the maximal recommended dose of inhaled therapy, it is important to check adherence and inhaler technique. In these patients, maintenance treatment with an OCS may be needed and the lowest dose that maintains control should be used. Occasionally omalizumab and anti-IL-5 may be tried in steroid-dependent asthmatics who are not well controlled. Once asthma is controlled, it is important to slowly decrease therapy in order to find the optimal dose to control symptoms.

Education Patients with asthma need to understand how to use their medications and the difference between reliever and controller therapies. Education may improve adherence, particularly with ICS. All patients should be taught how to use their inhalers correctly. In particular, they need to understand how to recognize worsening of asthma and how to step up therapy accordingly. Written action plans have been shown to reduce hospital admissions and morbidity rates in adults and children, and are recommended particularly in patients with unstable disease who have frequent exacerbations.

ACUTE SEVERE ASTHMA

Exacerbations of asthma are feared by patients and may be life threatening. One of the main aims of controller therapy is to prevent exacerbations; in this respect, ICS and combination inhalers are very effective.

Clinical Features Patients are aware of increasing chest tightness, wheezing, and dyspnea that are often not or poorly relieved by their usual reliever inhaler. In severe exacerbations patients may be so breathless that they are unable to complete sentences and may become cyanotic. Examination usually shows increased ventilation, hyperinflation, and tachycardia. Pulsus paradoxus may be present, but this is rarely a useful clinical sign. There is a marked fall in spirometric values and PEF. Arterial blood gases on air show hypoxemia, and P_{CO_2} is usually low due to hyperventilation. A normal or rising P_{CO_2} is an indication of impending respiratory failure and requires immediate monitoring and therapy. A chest roentgenogram is not usually informative, but may show pneumonia or pneumothorax.

TREATMENT

Acute Severe Asthma

A high concentration of oxygen should be given by face mask to achieve oxygen saturation of >90%. The mainstay of treatment are high doses of SABA given either by nebulizer or via a MDI with a spacer. In severely ill patients with impending respiratory failure, IV β_2-agonists may be given. A nebulized anticholinergic may be added if there is not a satisfactory response to β_2-agonists alone, as there are additive effects. In patients who are refractory to inhaled therapies, a slow infusion of aminophylline may be effective, but it is important to monitor blood levels, especially if patients have already been treated with oral theophylline. Magnesium sulfate given intravenously or by nebulizer is effective when added to inhaled β_2-agonists, and is relatively well tolerated but is not routinely recommended. Prophylactic intubation may be indicated for impending respiratory failure, when the P_{CO_2} is normal or rises. For patients with respiratory failure, it is necessary to intubate and institute ventilation. These patients may benefit from a general anesthetic, such as halothane, if they have not responded to conventional bronchodilators. Sedatives should never be given as they may depress ventilation. Antibiotics should not be used routinely unless there are signs of pneumonia.

SPECIAL CONSIDERATIONS

Refractory Asthma Although most patients with asthma are easily controlled with appropriate medication, a small proportion of patients (~5%) are difficult to control despite maximal inhaled therapy. It is important to check adherence to therapy and inhaler technique. Some of these patients will require maintenance treatment with OCS. In managing these patients, it is important to investigate and correct any mechanisms that may be aggravating asthma. There are two major patterns of difficult asthma: some patients have persistent symptoms and poor lung function, despite appropriate therapy, whereas others may have normal or near normal lung function but intermittent, severe (sometimes life-threatening) exacerbations.

MECHANISMS The most common reason for poor control of asthma is poor adherence with medication, particularly ICS. Compliance with ICS may be low because patients do not feel any immediate clinical benefit or may be concerned about side effects. Adherence with ICS is difficult to monitor as there are no useful plasma measurements that can be made but measuring F_ENO may identify the problem. Compliance may be improved by giving the ICS as a combination with a LABA that gives symptom relief. Adherence with OCS may be measured by suppression of plasma cortisol and the expected concentration of prednisone/prednisolone in the plasma. There are several factors that may make asthma more difficult to control, including exposure to high, ambient levels of allergens or unidentified occupational agents. Severe rhinosinusitis may make asthma more difficult to control; upper airway disease should be vigorously treated. Drugs such as beta-adrenergic blockers, aspirin, and other cyclooxygenase (COX) inhibitors may worsen asthma. Some women develop severe premenstrual worsening of asthma, which is unresponsive to corticosteroids and requires treatment with progesterone or gonadotropin-releasing factors. Few systemic diseases make asthma more difficult to control, but hyper- and hypothyroidism may increase asthma symptoms and should be investigated if suspected.

Bronchial biopsy studies in refractory asthma may show the typical eosinophilic pattern of inflammation, whereas others have a predominantly neutrophilic pattern. There may be an increase in T_H1 cells, TH17 cells, and CD8 lymphocytes compared to mild asthma and increased expression of TNF-α. Structural changes in the airway, including fibrosis, angiogenesis, and airway smooth muscle thickening, are more commonly seen in these patients.

Corticosteroid-Resistant Asthma A few patients with asthma show a poor response to corticosteroid therapy and may have various molecular abnormalities that impair the anti-inflammatory action of corticosteroids. Complete resistance to corticosteroids is extremely uncommon and affects <1 in 1000 patients. It is defined by a failure to respond to a high dose of oral prednisone/prednisolone (40 mg once daily over 2 weeks), ideally with a 2-week run-in with matched placebo. More common is reduced responsiveness to corticosteroids where control of asthma requires OCS (corticosteroid-dependent asthma). In patients with poor responsiveness to corticosteroids, there is a reduction in the response of circulating monocytes and lymphocytes to the anti-inflammatory effects of corticosteroids in vitro and reduced skin blanching in response to topical corticosteroids. There are several mechanisms that have been described, including an increase in the alternatively spliced form of the glucocorticoid receptor (GR)-β, an abnormal pattern of histone acetylation in response to corticosteroids, a defect in IL-10 production, and a reduction in HDAC2 activity (as in COPD). These observations suggest that there are likely to be heterogeneous mechanisms for corticosteroid resistance; whether these mechanisms are genetically determined has yet to be decided.

Brittle Asthma Some patients show chaotic variations in lung function despite taking appropriate therapy. Some show a persistent pattern of variability and may require OCS or, at times, continuous infusion of β_2-agonists (type I brittle asthma), whereas others have generally normal or near-normal lung function but precipitous, unpredictable falls in lung function that may result in death (type 2 brittle asthma). These latter patients are difficult to manage as they do not

respond well to corticosteroids, and the worsening of asthma does not reverse well with inhaled bronchodilators. The most effective therapy is subcutaneous epinephrine, which suggests that the worsening is likely to be a localized airway anaphylactic reaction with edema. In some of these patients, there may be allergy to specific foods. These patients should be taught to self-administer epinephrine and should carry a medical warning accordingly.

TREATMENT

Refractory Asthma

Refractory asthma is difficult to control, by definition. It is important to check adherence and the correct use of inhalers and to identify and eliminate any underlying triggers. Low doses of theophylline may be helpful in some patients, and theophylline withdrawal has been found to worsen in many patients. Many of these patients will require maintenance treatment with OCS, and the minimal dose that achieves satisfactory control should be determined by careful dose titration. Steroid-sparing therapies are rarely effective. In some patients with allergic asthma, omalizumab is effective, particularly when there are frequent exacerbations. Anti-IL-5 may be useful if sputum eosinophils persist despite maximal ICS or OCS therapy. Anti-TNF therapy is not effective in severe asthma and should not be used. A few patients may benefit from infusions of β_2-agonists. New therapies are needed for these patients, who currently consume a disproportionate amount of health care spending.

Aspirin-Sensitive Asthma A small proportion (1–5%) of asthmatics become worse with aspirin and other COX inhibitors, although this is much more commonly seen in severe cases and in those patients with frequent hospital admission. Aspirin-sensitive asthma is a well-defined phenotype of asthma that is usually preceded by perennial rhinitis and nasal polyps in nonatopic patients with a late onset of the disease. Aspirin, even in small doses, characteristically provokes rhinorrhea, conjunctival injection, facial flushing, and wheezing. There is a genetic predisposition to increased production of cysteinyl-leukotrienes with functional polymorphism of *cys*-leukotriene C4 synthase. Asthma is triggered by COX inhibitors, but is persistent even in their absence. All nonselective COX inhibitors should be avoided, but selective COX2 inhibitors are safe to use when an anti-inflammatory analgesic is needed. Aspirin-sensitive asthma responds to usual therapy with ICS. Although antileukotrienes should be effective in these patients, they are no more effective than in allergic asthma. Occasionally, aspirin desensitization is necessary, but this should only be undertaken in specialized centers.

Asthma in the Elderly Asthma may start at any age, including in elderly patients. The principles of management are the same as in other asthmatics, but side effects of therapy may be a problem, including muscle tremor with β_2-agonists and more systemic side effects with ICS. Comorbidities are more frequent in this age group, and interactions with drugs such as β_2-blockers, COX inhibitors, and agents that may affect theophylline metabolism need to be considered. COPD is more likely in elderly patients and may coexist with asthma. A trial of OCS may be very useful in documenting the steroid responsiveness of asthma.

Pregnancy Approximately one-third of asthmatic patients who are pregnant improve during the course of a pregnancy, one-third deteriorate, and one-third are unchanged. It is important to maintain good control of asthma as poor control may have adverse effects on fetal development. Adherence may be a problem as there is often concern about the effects of antiasthma medications on fetal development. The drugs that have been used for many years in asthma therapy have now been shown to be safe and without teratogenic potential. These drugs include SABA, ICS, and theophylline; there is less safety information about newer classes of drugs such as LABA, antileukotrienes, and anti-IgE. If an OCS is needed, it is better to use prednisone rather than prednisolone as it cannot be converted to the active prednisolone by the fetal liver, thus protecting the fetus from systemic effects of the corticosteroid. There is no contraindication to breast-feeding when patients are using these drugs.

Cigarette Smoking Approximately 20% of asthmatics smoke, which may adversely affect asthma in several ways. Smoking asthmatics have more severe disease, more frequent hospital admissions, a faster decline in lung function, and a higher risk of death from asthma than nonsmoking asthmatics. There is evidence that smoking interferes with the anti-inflammatory actions of corticosteroids by reducing HDAC2, necessitating higher doses for asthma control. Smoking cessation improves lung function and reduces the steroid resistance, and, thus, vigorous smoking cessation strategies should be used. LABA and theophylline appear to overcome some of the steroid resistance; so, ICS-LABA combination therapy and low dose theophylline should be used. Some patients report a temporary worsening of asthma when they first stop smoking, possibly due to the loss of the bronchodilating effect of NO in cigarette smoke.

Surgery If asthma is well controlled, there is no contraindication to general anesthesia and intubation. Patients who are treated with OCS will have adrenal suppression and should be treated with an increased dose of OCS immediately prior to surgery. Patients with FEV1 <80% of their normal levels should also be given a boost of OCS prior to surgery. High-maintenance doses of corticosteroids may be a contraindication to surgery because of increased risks of infection and delayed wound healing.

Bronchopulmonary Aspergillosis BPA is uncommon and results from an allergic pulmonary reaction to inhaled spores of *Aspergillus fumigatus* and, occasionally, other *Aspergillus* species. A skin prick test to *A. fumigatus* is always positive, whereas serum *Aspergillus* precipitins are low or undetectable. Characteristically, there are fleeting eosinophilic infiltrates in the lungs, particularly in the upper lobes. Airways become blocked with mucoid plugs rich in eosinophils, and patients may cough up brown plugs and have hemoptysis. BPA may result in bronchiectasis, particularly affecting central airways, if not suppressed by corticosteroids. Asthma is controlled in the usual way by ICS, but it is necessary to give a course of OCS if any sign of worsening or pulmonary shadowing is found. Treatment with the oral antifungal itraconazole is beneficial in preventing exacerbations. Anti-IgE therapy may also be useful to reduce the need for OCS.

ASTHMA-COPD OVERLAP (ACO)

Although asthma and COPD are distinct syndromes with different clinical presentations and underlying inflammatory mechanisms, some patients with asthma have features of COPD (for example, asthmatics who smoke and severe asthmatics with irreversible airflow limitation) and some patients with COPD have features of asthma with more reversibility and increased airway and blood eosinophils. This may represent the coincidence of two common diseases, or these may be distinct phenotypes. ACO patients tend to have more symptoms and exacerbations. They may benefit from triple therapy with ICS, LABA, and LAMA.

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282 Hypersensitivity Pneumonitis and Pulmonary Infiltrates with Eosinophilia

Praveen Akuthota, Michael E. Wechsler

HYPERSENSITIVITY PNEUMONITIS

INTRODUCTION AND DEFINITION

Hypersensitivity pneumonitis (HP), also referred to as extrinsic allergic alveolitis, is a pulmonary disease that occurs due to inhalational exposure to a variety of antigens leading to an inflammatory response of the alveoli and small airways. Systemic manifestations such as fever and fatigue can accompany respiratory symptoms. Although sensitization to an inhaled antigen as manifested by specific circulating IgG antibodies is necessary for the development of HP, sensitization alone is not sufficient as a defining characteristic, because many sensitized individuals do not develop HP. The incidence and prevalence of HP are variable, depending on geography, occupation, avocation, and environment of the cohort being studied. As yet unexplained is the decreased risk of developing HP in smokers.

OFFENDING ANTIGENS

HP can be caused by any of a large list of potential offending inhaled antigens (Table 282-1). The various antigens and environmental conditions described to be associated with HP give rise to an expansive list of monikers given to specific forms of HP. Antigens derived from fungal, bacterial, mycobacterial, bird-derived, and chemical sources have all been implicated in causing HP.

Categories of individuals at particular risk in the United States include farmers, bird owners, industrial workers, and hot tub users. Farmer's lung occurs as a result of exposure to one of several possible sources of bacterial or fungal antigens such as grain, moldy hay, or silage. Potential offending antigens include thermophilic actinomycetes or *Aspergillus* species. Bird fancier's lung (also referred to by names corresponding to specific birds) must be considered in patients who give a history of keeping birds in their home and is precipitated by exposure to antigens derived from feathers, droppings, and serum proteins. Occupational exposure to birds may also cause HP, as is seen in poultry worker's lung. Chemical worker's lung is provoked by exposure to occupational chemical antigens such as diphenylmethane diisocyanate and toluene diisocyanate. Mycobacteria may cause HP rather than frank infection, a phenomenon observed in hot tub lung and in HP due to metalworking fluid.

PATHOPHYSIOLOGY

While much remains to be learned regarding the pathophysiology of HP, it has been established that HP is an immune-mediated condition that occurs in response to inhaled antigens that are small enough to deposit in distal airways and alveoli. From a lymphocyte perspective, HP has been categorized as a condition with a T_H1 inflammatory pattern. However, emerging evidence suggests that T_H17 lymphocyte subsets may be involved in the pathogenesis of the disease as well. Although the presence of precipitating IgG antibodies against specific antigens in HP suggests a prominent role for adaptive immunity in the pathophysiology of HP, innate immune mechanisms likely also make an important contribution. This is highlighted by the observation that Toll-like receptors and downstream signaling proteins such as MyD88 are activated in HP, leading to neutrophil recruitment. Although no clear genetic basis for HP has been established, in specific cohorts, polymorphisms in genes involved in antigen processing and presentation, including TAP1 and major histocompatibility complex type II, have been observed. In chronic HP, bone marrow-derived fibrocytes may contribute to lung inflammation and fibrosis.

TABLE 282-1 Examples of Hypersensitivity Pneumonitis

DISEASE	ANTIGEN	SOURCE
Farming/Food Processing		
Farmer's lung	Thermophilic actinomycetes (e.g., *Saccharopolyspora rectivirgula*); fungus	Grain, moldy hay, silage
Bagassosis	Thermophilic actinomycetes	Sugarcane
Cheese washer's lung	*Penicillium casei; Aspergillus clavatus*	Cheese
Coffee worker's lung	Coffee bean dust	Coffee beans
Malt worker's lung	*Aspergillus* species	Barley
Miller's lung	*Sitophilus granarius* (wheat weevil)	Wheat flour
Mushroom worker's lung	Thermophilic actinomycetes; mushroom spores	Mushrooms
Potato riddler's lung	Thermophilic actinomycetes; *Aspergillus* species	Moldy hay around potatoes
Tobacco grower's lung	*Aspergillus* species	Tobacco
Wine maker's lung	*Botrytis cinerea*	Grapes
Birds and Other Animals		
Bird fancier's lung (also named by specific bird exposures)	Proteins derived by parakeets, pigeons, budgerigars	Bird feathers, droppings, serum proteins
Duck fever	Duck feathers, serum proteins	Ducks
Fish meal worker's lung	Fish meal dust	Fish meal
Furrier's lung	Dust from animal furs	Animal furs
Laboratory worker's lung	Rat urine, serum, fur	Laboratory rats
Pituitary snuff taker's lung	Animal proteins	Pituitary snuff from bovine and porcine sources
Poultry worker's lung	Chicken serum proteins	Chickens
Turkey handling disease	Turkey serum proteins	Turkeys
Other Occupational and Environmental Exposures		
Chemical worker's lung	Isocyanates	Polyurethane foam, varnish, lacquer
Detergent worker's lung	*Bacillus subtilis* enzymes	Detergent
Hot tub lung	*Cladosporium* species; *Mycobacterium avium* complex	Contaminated water, mold on ceiling
Humidifier fever (and air conditioner lung)	Several microorganisms including: *Aureobasidium pullulans; Candida albicans*; thermophilic actinomycetes; *Mycobacterium* species; *Klebsiella oxytoca*; *Naegleria gruberi*	Humidifiers and air conditioners (contaminated water)
Machine operator's lung	*Pseudomonas* species; *Mycobacteria* species	Metal working fluid
Sauna taker's lung	*Aureobasidium* species; other antigens	Sauna water
Suberosis	*Penicillium glabrum; Chrysonilia sitophila*	Cork dust
Summer-type pneumonitis	*Trichosporon cutaneum*	House dust mites, bird droppings
Woodworker's lung	*Alternaria* species; *Bacillus subtilis*	Oak, cedar, pine, mahogany dusts

CLINICAL PRESENTATION

Given the heterogeneity among patients, variability in offending antigens, and differences in the intensity and duration of exposure to antigen, the presentation of HP is accordingly variable. Although these categories are not fully satisfactory in capturing this variability, HP has

been traditionally categorized as having *acute*, *subacute*, and *chronic* forms. Acute HP usually manifests itself 4–8 h following exposure to the inciting antigen, often intense in nature. Systemic symptoms, including fevers, chills, and malaise, are prominent and are accompanied by dyspnea. Symptoms resolve within hours to days if no further exposure to the offending antigen occurs. In subacute HP resulting from ongoing antigen exposure, the onset of respiratory and systemic symptoms is typically more gradual over the course of weeks. A similar presentation may occur as a culmination of intermittent episodes of acute HP. Although respiratory impairment may be quite severe, antigen avoidance generally results in resolution of the symptoms, but with a slower time course, on the order of weeks to months, than that seen with acute HP. Chronic HP can present with an even more gradual onset of symptoms than subacute HP, with progressive dyspnea, cough, fatigue, weight loss, and clubbing of the digits. The insidious onset of symptoms and frequent lack of an anteceding episode of acute HP make diagnosing chronic HP a challenge. Unlike with the other forms of HP, there can be an irreversible component to the respiratory impairment that is not responsive to removal of the responsible antigen from the patient's environment. The disease progression of chronic HP to lung fibrosis and hypoxemic respiratory failure can mirror that seen in idiopathic pulmonary fibrosis (IPF). Diagnostic uncertainty between these two entities is not uncommon. Fibrotic lung disease is a potential feature of chronic HP due to exposure to bird antigens, whereas an emphysematous phenotype may be seen in farmer's lung.

The categories of acute, subacute, and chronic HP are not completely sufficient in classifying HP. The HP Study Group found on cluster analysis that a cohort of HP patients is best described in bipartite fashion, with one group featuring recurrent systemic signs and symptoms and the other featuring more severe respiratory findings.

Concordant with the variability in the presentation of HP is the observed variability in outcome. HP that has not progressed to chronic lung disease has a more favorable outcome with likely resolution if antigen avoidance can be achieved. However, chronic HP resulting in lung fibrosis has a poorer prognosis, with patients with chronic pigeon breeder's lung having demonstrated a similar mortality as seen in IPF.

DIAGNOSIS

Although there is no set of universally accepted criteria for arriving at a diagnosis of HP, diagnosis depends foremost on establishing a history of exposure to an offending antigen that correlates with respiratory and systemic symptoms. A careful occupational and home exposure history should be taken and may be supplemented if necessary by a clinician visit to the work or home environment. Specific inquiries will be influenced by geography and the occupation of the patient. When HP is suspected by history, the additional workup is aimed at establishing an immunologic and physiologic response to inhalational antigen exposure with chest imaging, pulmonary function testing (PFT), serologic studies, bronchoscopy, and, on occasion, lung biopsy. Re-exposure to the offending environment may be performed to aid in confirming the diagnosis of HP.

Chest Imaging Chest x-ray findings in HP are nonspecific and can even lack any discernible abnormalities. In cases of acute and subacute HP, findings may be transient and can include ill-defined micronodular opacities or hazy ground-glass airspace opacities. Findings on chest x-ray will often resolve with removal from the offending antigen, although the time course of resolution may vary. With chronic HP, the abnormalities seen on the chest radiograph are frequently more fibrotic in nature and may be difficult to distinguish from IPF.

With the wide availability of high-resolution computed tomography (HRCT), this modality has become a common component in the diagnostic workup for HP. Although the HRCT may be normal in acute forms of HP, this may be due to lack of temporal correlation between exposure to the offending antigen and obtaining the imaging. Additionally, because of the transient nature of acute HP, HRCT is not always performed. In subacute forms of the disease, ground-glass airspace opacities are characteristic, as is the presence of centrilobular nodules. Expiratory images may show areas of air trapping that are likely caused by involvement of the small airways (Fig. 282-1). Reticular changes and traction bronchiectasis can be observed in chronic HP. Subpleural honeycombing similar to that seen in IPF may be present in advanced cases, although unlike in IPF, the lung bases are frequently spared.

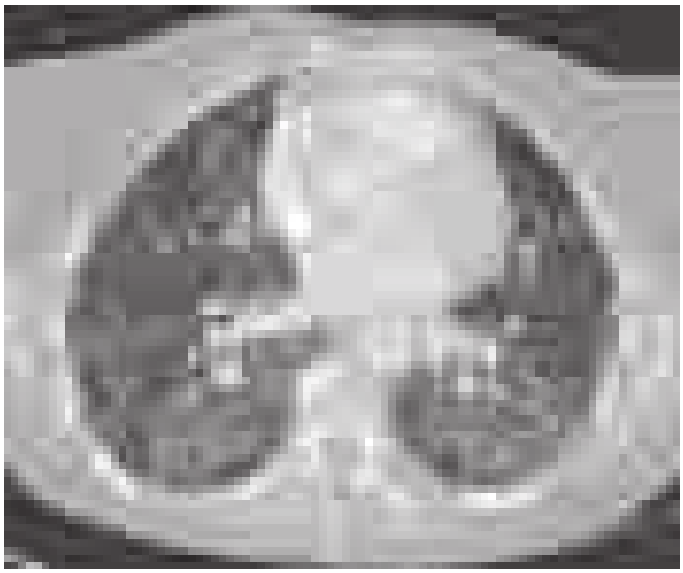

FIGURE 282-1 Chest computed tomography scan of a patient with subacute hypersensitivity pneumonitis in which scattered regions of ground-glass infiltrates in a mosaic pattern consistent with air trapping are seen bilaterally. This patient had bird fancier's lung. *(Courtesy of TJ Gross; with permission.)*

Pulmonary Function Testing Either restrictive or obstructive PFTs can be present in HP, so the pattern of PFT change is not useful in establishing the diagnosis of HP. However, obtaining PFTs is of use in characterizing the physiologic impairment of an individual patient and in gauging the response to antigen avoidance and/or corticosteroid therapy. Diffusion capacity for carbon monoxide may be significantly impaired, particularly in cases of chronic HP with fibrotic pulmonary parenchymal changes.

Serum Precipitins Assaying for precipitating IgG antibodies against specific antigens can be a useful adjunct in the diagnosis of HP. However, the presence of an immunologic response alone is not sufficient for establishing the diagnosis, because many asymptomatic individuals with high levels of exposure to antigen may display serum precipitins, as has been observed in farmers and in pigeon breeders. It should also be noted that panels that test for several specific serum precipitins often provide false-negative results, because they represent an extremely limited proportion of the universe of potential offending environmental antigens.

Bronchoscopy Bronchoscopy with bronchoalveolar lavage (BAL) may be used in the evaluation of HP. Although not a specific finding, BAL lymphocytosis is characteristic of HP. However, in active smokers, a lower threshold should be used to establish BAL lymphocytosis, because smoking will result in lower lymphocyte percentages. Most cases of HP have a CD4+/CD8+ lymphocyte ratio of <1, but again, this is not a specific finding and has limited utility in the diagnosis of HP.

Lung Biopsy Tissue samples may be obtained by a bronchoscopic approach using transbronchial biopsy, or more architecturally preserved specimens may be obtained by a surgical approach (video-assisted thoracoscopy or open approach). As is the case with BAL, histologic specimens are not absolutely necessary to establish the diagnosis of HP, but they can be useful in the correct clinical context. A common histologic feature in HP is the presence of noncaseating granulomas in the vicinity of small airways (Fig. 282-2). As opposed to pulmonary sarcoidosis, in which noncaseating granulomas are well defined, the granulomas seen in HP are loose and poorly defined in nature. Within the alveolar spaces and in the interstitium, a mixed

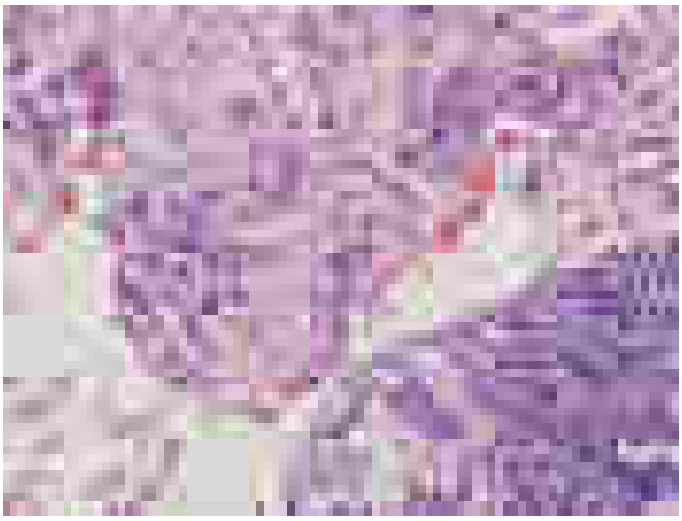

FIGURE 282-2 Open-lung biopsy from a patient with subacute hypersensitivity pneumonitis demonstrating a loose, nonnecrotizing granuloma made up of histiocytes and multinucleated giant cells. Peribronchial inflammatory infiltrate made up of lymphocytes and plasma cells is also seen. *(Courtesy of TJ Gross; with permission.)*

cellular infiltrate with a lymphocytic predominance is observed that is frequently patchy in distribution. Bronchiolitis with the presence of organizing exudate is also often observed. Fibrosis may be present as well, particularly in chronic HP. Fibrotic changes may be focal but can be diffuse and severe with honeycombing in advanced cases, similar to findings in IPF.

Clinical Prediction Rule Although not meant as a set of validated diagnostic criteria, a clinical prediction rule for predicting the presence of HP has been published by the HP Study Group. They identified six statistically significant predictors for HP, the strongest of which was exposure to an antigen known to cause HP. Other predictive criteria were the presence of serum precipitins, recurrent symptoms, symptoms occurring 4–8 h after antigen exposure, crackles on inspiration, and weight loss.

DIFFERENTIAL DIAGNOSIS

Differentiating HP from other conditions that cause a similar constellation of respiratory and systemic symptoms requires an increased index of suspicion based on obtaining a history of possible exposure to an offending antigen. Presentations of acute or subacute HP can be mistaken for respiratory infection. In cases of chronic disease, HP must be differentiated from interstitial lung disease, such as IPF or nonspecific interstitial pneumonitis (NSIP); this can be a difficult task even with lung biopsy. Given the presence of pulmonary infiltrates and noncaseating granulomas on biopsy, sarcoidosis is also a consideration in the differential diagnosis of HP. Unlike in HP, however, hilar adenopathy may be prominent on chest x-ray, organs other than the lung may be involved, and noncaseating granulomas in pathologic specimens tend to be well formed. Other inhalational syndromes, such as organic toxic dust syndrome (OTDS), can be misdiagnosed as HP. OTDS occurs with exposure to organic dusts, including those produced by grains or mold silage, but neither requires prior antigen sensitization nor is characterized by positive serum precipitins.

TREATMENT

Hypersensitivity Pneumonitis

The mainstay of treatment for HP is antigen avoidance, if possible. A careful exposure history must be obtained to attempt to identify the potential offending antigen and to identify the location where a patient is exposed. Once a potential antigen and location are identified, efforts should be made to modify the environment to minimize patient exposure. This may be accomplished with measures such as removal of birds, removal of molds, and improved ventilation. Personal protective equipment including respirators and ventilated helmets can be used but may not provide adequate protection for sensitized individuals. In some cases, fully avoiding specific environments may be necessary, although such a recommendation must be balanced against the effects to an individual's lifestyle or occupation. It is not uncommon for patients with HP due to exposure to household birds to be unwilling to remove them from the home.

Because acute HP is generally a self-limited disease after a discrete exposure to an offending antigen, pharmacologic therapy is generally not necessary. However, in so-called subacute and chronic forms of the disease, there is a role for glucocorticoid therapy. In patients with particularly severe symptoms as a result of subacute HP, antigen avoidance may be insufficient after establishing the diagnosis. Although glucocorticoids do not change the long-term outcome in these patients, they can accelerate the resolution of symptoms. While there is significant variability in the approach to glucocorticoid therapy by individual clinicians, prednisone therapy can be initiated at 0.5–1 mg/kg of ideal body weight per day (not to exceed 60 mg/d or alternative glucocorticoid equivalent) over a duration of 1–2 weeks, followed by a taper over the next 2–6 weeks. In chronic HP, a similar trial of corticosteroids may be used, although a variable component of fibrotic disease may be irreversible. In advanced cases of chronic HP with extensive lung fibrosis, lung transplantation may be necessary.

GLOBAL CONSIDERATIONS

As the ever-expanding list of antigens and exposures associated with the development of HP suggests, populations at risk for HP will vary globally based on specifics of local occupational, avocational, and environmental factors. Specific examples of geographically limited HP include summer-type pneumonitis seen in Japan and suberosis seen in cork workers in Portugal and Spain.

PULMONARY INFILTRATES WITH EOSINOPHILIA

Although eosinophils are normal constituents of the lungs, there are several pulmonary eosinophilic syndromes that are characterized by pulmonary infiltrates on imaging along with an increased number of eosinophils in lung tissue, in sputum, and/or in BAL fluid, with resultant increased respiratory symptoms and the potential for systemic manifestations. Because the eosinophil plays such an important role in each of these syndromes, it is often difficult to distinguish between them, but there are important clinical and pathologic differences as well as differences in prognosis and treatment paradigms.

CLASSIFYING PULMONARY INFILTRATES WITH EOSINOPHILIA AND GENERAL APPROACH

Because there are so many different diagnoses associated with pulmonary infiltrates with eosinophilia, the first step in classifying pulmonary eosinophilic syndromes is distinguishing between primary pulmonary eosinophilic lung disorders and those with eosinophilia that are secondary to a specific cause such as a drug reaction, an infection, a malignancy, or another pulmonary condition such as asthma. **Table 282-2** lists primary and secondary pulmonary eosinophilic disorders.

For each patient, a detailed history is of utmost importance and can help elucidate what the underlying disease is. Details regarding onset, timing, and precipitants of specific symptoms can help discern one diagnosis from another. History regarding pharmacologic, occupational, and environmental exposures is instructive, and family and travel history are crucial. In addition to details about the sinuses and lungs, it is important to inquire about systemic manifestations and assess for physical findings of cardiac, gastrointestinal (GI), neurologic, dermatologic, and genitourinary involvement, all of which may give clues to specific diagnoses. Once the details from history and physical are teased out, laboratory testing (including measurements of blood

TABLE 282-2 Pulmonary Infiltrates with Eosinophilia
Primary Pulmonary Eosinophilic Disorders
Acute eosinophilic pneumonia
Chronic eosinophilic pneumonia
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Hypereosinophilic syndrome
Pulmonary Disorders of Known Cause Associated with Eosinophilia
Asthma and eosinophilic bronchitis
Allergic bronchopulmonary aspergillosis
Bronchocentric granulomatosis
Drug/toxin reaction
Infection (Table 282-4)
Parasitic/helminthic disease
Nonparasitic infection
Lung Diseases Associated with Eosinophilia
Cryptogenic organizing pneumonia
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Pulmonary Langerhans cell granulomatosis
Malignant Neoplasms Associated with Eosinophilia
Leukemia
Lymphoma
Lung cancer
Adenocarcinoma of various organs
Squamous cell carcinoma of various organs
Systemic Disease Associated with Eosinophilia
Postradiation pneumonitis
Rheumatoid arthritis
Sarcoidosis
Sjögren's syndrome

eosinophils, cultures, and markers of inflammation), spirometry and radiographic imaging can help distinguish between different diseases. Often, however, BAL, transbronchial, or open lung biopsies are required. In many cases, biopsies or noninvasive diagnostic studies of other organs (e.g., echocardiogram, electromyogram, or bone marrow biopsy) can be helpful.

PATHOPHYSIOLOGY

Pathologically, the pulmonary eosinophilic syndromes are characterized by tissue infiltration by eosinophils (Fig. 282-2). In eosinophilic granulomatosis with polyangiitis (EGPA), extravascular granulomas and necrotizing vasculitis may occur in the lungs, as well as in the heart, skin, muscle, liver, spleen, and kidneys, and may be associated with fibrinoid necrosis and thrombosis.

The exact etiology of the various pulmonary eosinophilic syndromes is unknown; however, it is felt that these syndromes result from dysregulated eosinophilopoiesis or an autoimmune process because of the prominence of allergic features and the presence of immune complexes, heightened T cell immunity, and altered humoral immunity as evidenced by elevated IgE and rheumatoid factor. Because of its integral involvement in eosinophilopoiesis, interleukin 5 (IL-5) has been hypothesized to play an etiologic role. Monoclonal antibodies against IL-5 are now in clinical use for the treatment of eosinophilic asthma and are under investigation for conditions characterized by pulmonary infiltrates with eosinophilia. Antineutrophil cytoplasmic antibodies (ANCAs) are present in about half of patients with EGPA; binding of ANCAs to vascular walls likely contributes to vascular inflammation and injury as well as chemotaxis of inflammatory cells.

ACUTE EOSINOPHILIC PNEUMONIA

Acute eosinophilic pneumonia is a syndrome characterized by fevers, acute respiratory failure that often requires mechanical ventilation, diffuse pulmonary infiltrates, and pulmonary eosinophilia in a previously healthy individual **(Table 282-3)**.

TABLE 282-3 Diagnostic Criteria of Acute Eosinophilic Pneumonia
Acute febrile illness with respiratory manifestations of <1 month in duration
Hypoxemic respiratory failure
Diffuse pulmonary infiltrates on chest x-ray
Bronchoalveolar lavage eosinophilia >25%
Absence of parasitic, fungal, or other infection
Absence of drugs known to cause pulmonary eosinophilia
Quick clinical response to corticosteroids
Failure to relapse after discontinuation of corticosteroids

Clinical Features and Etiology At presentation, acute eosinophilic pneumonia is often mistaken for acute lung injury or acute respiratory distress syndrome (ARDS), until a BAL is performed and reveals >25% eosinophils. Although the predominant symptoms of acute eosinophilic pneumonia are cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain, physical examination findings include high fevers, basilar rales, and rhonchi on forced expiration. Acute eosinophilic pneumonia most often affects males between age 20 and 40 with no history of asthma. Although no clear etiology has been identified, several case reports have linked acute eosinophilic pneumonia to recent initiation of tobacco smoking or exposure to other environmental stimuli including dust from indoor renovations.

In addition to a suggestive history, the key to establishing a diagnosis of acute eosinophilic pneumonia is the presence of >25% eosinophilia on BAL fluid. While lung biopsies show eosinophilic infiltration with acute and organizing diffuse alveolar damage, it is generally not necessary to proceed to biopsy to establish a diagnosis. Although patients present with an elevated white blood cell count, in contrast to other pulmonary eosinophilic syndromes, acute eosinophilic pneumonia is often not associated with peripheral eosinophilia upon presentation. However, between 7 and 30 days of disease onset, peripheral eosinophilia often occurs with mean eosinophil counts of 1700. Erythrocyte sedimentation rate (ESR), C-reactive protein, and IgE levels are high but nonspecific, whereas HRCT is always abnormal with bilateral random patchy ground-glass or reticular opacities, and small pleural effusions in as many as two-thirds of patients. Pleural fluid is characterized by a high pH with marked eosinophilia.

Clinical Course and Response to Therapy Although some patients improve spontaneously, most patients require admission to an intensive care unit and respiratory support with either invasive (intubation) or noninvasive mechanical ventilation. However, what distinguishes acute eosinophilic pneumonia from both other cases of acute lung injury as well as some of the other pulmonary eosinophilic syndromes is the absence of organ dysfunction or multisystem organ failure other than respiratory failure. One of the characteristic features of acute eosinophilic pneumonia is the high degree of corticosteroid responsiveness and the excellent prognosis. Another distinguishing feature of acute eosinophilic pneumonia is that complete clinical and radiographic recovery without recurrence or residual sequelae occurs in almost all patients within several weeks of initiation of therapy.

CHRONIC EOSINOPHILIC PNEUMONIA

In contrast to acute eosinophilic pneumonia, chronic eosinophilic pneumonia is a more indolent syndrome that is characterized by pulmonary infiltrates and eosinophilia in both the tissue and blood. Most patients are female nonsmokers with a mean age of 45, and patients do not usually develop the acute respiratory failure and significant hypoxemia appreciated in acute eosinophilic pneumonia. Similar to EGPA, a majority have asthma, with many having a history of allergies.

Patients present with a subacute illness over weeks to months, with cough, low-grade fevers, progressive dyspnea, weight loss, wheezing, malaise, and night sweats, and a chest x-ray with migratory bilateral peripheral or pleural-based opacities. Although this "photographic negative pulmonary edema" appearance on chest x-ray and chest CT is pathognomonic of chronic eosinophilic pneumonia, <25% of patients present with this finding. Other radiographic findings

include atelectasis, pleural effusions, lymphadenopathy, and septal line thickening.

Almost 90% of patients have peripheral eosinophilia, with mean eosinophil counts of over 30% of total white blood cell count. BAL eosinophilia is also an important distinguishing feature with mean BAL eosinophil counts of ~60%. Both peripheral and BAL eosinophilia are very responsive to treatment with corticosteroids. Other laboratory features of chronic eosinophilic pneumonia include increased ESR, C-reactive protein, platelets, and IgE. Lung biopsy is also often not required to establish a diagnosis, but may show accumulation of eosinophils and histiocytes in the lung parenchyma and interstitium, as well as cryptogenic organizing pneumonia, but with minimal fibrosis. Nonrespiratory manifestations are uncommon, but arthralgias, neuropathy, and skin and GI symptoms have all been reported; their presence may suggest EGPA or a hypereosinophilic syndrome. Another similarity is the rapid response to corticosteroids with quick resolution of peripheral and BAL eosinophilia and improvement in symptoms. In contrast to acute eosinophilic pneumonia, though, >50% of patients relapse, and many require prolonged courses of corticosteroids for months to years.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

Previously known as allergic angiitis granulomatosis or Churg-Strauss syndrome, this complex syndrome is characterized by eosinophilic vasculitis that may involve multiple organ systems including the lungs, heart, skin, GI tract, and nervous system. Although EGPA is characterized by peripheral and pulmonary eosinophilia with infiltrates on chest x-ray, the primary features that distinguish EGPA from other pulmonary eosinophilic syndromes are the presence of eosinophilic vasculitis in the setting of asthma and involvement of multiple end organs (a feature it shares with hypereosinophilic syndrome). Although perceived to be quite rare, in the last few years, there has appeared to be an increased incidence of this disease, particularly in association with various asthma therapies, including leukotriene modifiers and anti-IGE therapy with omalizumab, possibly due to concurrent systemic corticosteroid withdrawal (*forme fruste* EGPA).

The primary features of EGPA include asthma, peripheral eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and presence of eosinophilic vasculitis. The mean age at diagnosis is 48 years, with a range of 14–74 years; the average length of time between diagnosis of asthma and vasculitis is 9 years. EGPA typically occurs in several phases. The prodromal phase is characterized by asthma and allergic rhinitis, and usually begins when the individual is in his or her twenties or thirties, typically persisting for many years. The eosinophilic infiltrative phase is characterized by peripheral eosinophilia and eosinophilic tissue infiltration of various organs including the lungs and GI tract. The third phase is the vasculitic phase and may be associated with constitutional signs and symptoms including fever, weight loss, malaise, and fatigue. This phasic progression supports the hypothesis that there is a pathophysiologic continuum between eosinophilic asthma, chronic eosinophilic asthma, and EGPA.

Similar to other pulmonary eosinophilic syndromes, constitutional symptoms are very common in EGPA and include weight loss of 10–20 lb, fevers, and diffuse myalgias and migratory polyarthralgias. Myositis may be present with evidence of vasculitis on muscle biopsies. In contrast to the eosinophilic pneumonias, EGPA involves many organ systems including the lungs, skin, nerves, heart, GI tract, and kidneys.

Symptoms and Clinical Manifestations • **RESPIRATORY** Most EGPA patients have asthma that arises later in life and in individuals who have no family history of atopy. The asthma can often be severe, and oral corticosteroids are often required to control symptoms but may lead to suppression of vasculitic symptoms. In addition to the more common symptoms of cough, dyspnea, sinusitis, and allergic rhinitis, alveolar hemorrhage and hemoptysis may also occur.

NEUROLOGIC Over three-fourths of EGPA patients have neurologic manifestations. Mononeuritis multiplex most commonly involves the peroneal nerve, but also involves the ulnar, radial, internal popliteal, and occasionally, cranial nerves. Cerebral hemorrhage and infarction may also occur and are important causes of death. Despite treatment, neurologic sequelae often do not completely resolve.

DERMATOLOGIC Approximately half of EGPA patients develop dermatologic manifestations. These include palpable purpura, skin nodules, urticarial rashes, and livedo.

CARDIOVASCULAR Granulomas, vasculitis, and widespread myocardial damage may be found on biopsy or at autopsy, and cardiomyopathy and heart failure may be seen in up to half of all patients but are often at least partially reversible. Acute pericarditis, constrictive pericarditis, myocardial infarction, and other electrocardiographic changes all may occur. The heart is a primary target organ in EGPA, and cardiac involvement often portends a worse prognosis.

GI GI symptoms are common in EGPA and likely represent an eosinophilic gastroenteritis characterized by abdominal pain, diarrhea, GI bleeding, and colitis. Ischemic bowel, pancreatitis, and cholecystitis have also been reported in association with EGPA and usually portend a worse prognosis.

RENAL Renal involvement is more common than once thought, and ~25% of patients have some degree of renal involvement. This may include proteinuria, glomerulonephritis, renal insufficiency, and rarely, renal infarct.

Lab Abnormalities Systemic eosinophilia is the hallmark laboratory finding in patients with EGPA and reflects the likely pathogenic role that the eosinophil plays in this disease. Eosinophilia >10% is one of the defining features of this illness and may be as high as 75% of the peripheral white blood cell count. It is present at the time of diagnosis in >80% of patients, but may respond quickly (often within 24 h) to initiation of systemic corticosteroid therapy. Even in the absence of systemic eosinophilia, tissue eosinophilia may be present.

Although not specific to EGPA, ANCAs are present in up to two-thirds of patients, mostly with a perinuclear staining pattern. Nonspecific lab abnormalities that may be present in patients with EGPA include a marked elevation in ESR, a normochromic normocytic anemia, an elevated IgE, hypergammaglobulinemia, and positive rheumatoid factor and antinuclear antibodies (ANA). Although BAL often reveals significant eosinophilia, this may be seen in other eosinophilic lung diseases. Similarly, PFT often reveals an obstructive defect similar to asthma.

Radiographic Features Chest x-ray abnormalities are extremely common in EGPA and consist of bilateral, nonsegmental, patchy infiltrates that often migrate and may be interstitial or alveolar in appearance. Reticulonodular and nodular disease without cavitation can be seen, as can pleural effusions and hilar adenopathy. The most common CT findings include bilateral ground-glass opacity and airspace consolidation that is predominantly subpleural. Other CT findings include bronchial wall thickening, hyperinflation, interlobular septal thickening, lymph node enlargement, and pericardial and pleural effusions. Angiography may be used diagnostically and may show signs of vasculitis in the coronary, central nervous system, and peripheral vasculature.

Treatment and Prognosis of EGPA Most patients diagnosed with EGPA have previously been diagnosed with asthma, rhinitis, and sinusitis, and have received treatment with inhaled or systemic corticosteroids. Because these agents are also the initial treatment of choice for EGPA patients, institution of these therapies in patients with EGPA who are perceived to have severe asthma may delay the diagnosis of EGPA because signs of vasculitis may be masked. Corticosteroids dramatically alter the course of EGPA: up to 50% of those who are untreated die within 3 months of diagnosis, whereas treated patients have a 6-year survival of >70%. Common causes of death include heart failure, cerebral hemorrhage, renal failure, and GI bleeding. Recent data suggest that clinical remission may be obtained in >90% of patients treated; ~25% of those patients may relapse, often due to corticosteroid tapering, with a rising eosinophil count heralding the relapse. Myocardial, GI, and renal involvement most often portend a poor prognosis.

In such cases, treatment with higher doses of corticosteroids or the addition of cytotoxic agents such as cyclophosphamide is often warranted. Although survival does not differ between those treated or untreated with cyclophosphamide, cyclophosphamide is associated with a reduced incidence of relapse and an improved clinical response to treatment. Other therapies that have been used successfully in the management of EGPA include azathioprine, methotrexate, rituximab, omalizumab, intravenous gamma globulin, and interferon α. Plasma exchange has not been shown to provide any additional benefit. Recent studies examining the efficacy of anti-IL-5 therapy compared with placebo have shown promise as safe and effective corticosteroid sparing agents that can reduce exacerbations.

HYPEREOSINOPHILIC SYNDROMES

Hypereosinophilic syndromes (HES) constitute a heterogeneous group of disease entities manifest by persistent eosinophilia >1500 eosinophils/μL in association with end organ damage or dysfunction, in the absence of secondary causes of eosinophilia. In addition to familial, undefined, and overlap syndromes with incomplete criteria, the predominant HES subtypes are the myeloproliferative and lymphocytic variants. The myeloproliferative variants may have acquired genetic abnormalities, including to platelet-derived growth factor receptor α (PDGFRα), attributed to a constitutively activated tyrosine kinase fusion protein (Fip1L1-PDGFRα) due to a chromosomal deletion on 4q12; this variant is often responsive to imatinib. Myeloproliferative HES may also be associated with mutations involving platelet-derived growth factor β (PDGFRβ), Janus kinase 2 (JAK2), and fibroblast growth factor receptor 1 (FGFR1). Chronic eosinophilic leukemia with demonstrable cytogenetic abnormalities and/or blasts on peripheral smear is often categorized with the myeloproliferative HES. Clinical and laboratory findings in myeloproliferative HES may include dysplastic peripheral eosinophils, increased serum vitamin B_{12}, increased tryptase, anemia, thrombocytopenia, splenomegaly, bone marrow cellularity >80%, spindle-shaped mast cells, and myelofibrosis. The evaluation for lymphocytic HES includes searching for abnormal T cell clonal populations.

Extrapulmonary Manifestations of HES More common in men than in women, HES occurs between the ages of 20 and 50 and is characterized by significant extrapulmonary involvement, including infiltration of the heart, GI tract, kidney, liver, joints, and skin. Cardiac involvement includes myocarditis and/or endomyocardial fibrosis, as well as a restrictive cardiomyopathy.

Pulmonary Manifestations of HES Similar to the other pulmonary eosinophilic syndromes, these HES are manifested by high levels of blood, BAL, and tissue eosinophilia. Lung involvement occurs in 40% of these patients and is characterized by cough and dyspnea, as well as pulmonary infiltrates. Although it is often difficult to discern the pulmonary infiltrates and effusions seen on chest x-ray from pulmonary edema resulting from cardiac involvement, CT scan findings include interstitial infiltrates, ground-glass opacities, and small nodules. HES are typically not associated with ANCA. IgE may be elevated in lymphocytic HES variants.

Course and Response to Therapy Unlike the other pulmonary eosinophilic syndromes, less than half of patients with these HES respond to corticosteroids as first-line therapy. Although other treatment options include hydroxyurea, cyclosporine, and interferon, the tyrosine kinase inhibitor imatinib has emerged as an important therapeutic option for patients with the myeloproliferative variant, particularly in individuals with the Fip1L1-PDGFRA gene fusion. Anti-IL-5 therapy with mepolizumab also holds promise for these patients and is currently being investigated.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is an eosinophilic pulmonary disorder that occurs in response to allergic sensitization to antigens from *Aspergillus* species fungi. The predominant clinical presentation of ABPA is an asthmatic phenotype, often accompanied by cough with production of brownish plugs of mucus. ABPA has also been well described as a complication of cystic fibrosis. A workup for ABPA may be beneficial in patients who carry a diagnosis of asthma but have proven refractory to usual therapy. ABPA is a distinct diagnosis from simple asthma, characterized by prominent peripheral eosinophilia and elevated circulating levels of IgE (>417 IU/mL). Establishing a diagnosis of ABPA also requires establishing sensitivity to *Aspergillus* antigens by skin test reactivity, positive serum precipitins for *Aspergillus*, and/or direct measurement of circulating specific IgG and IgE to *Aspergillus*. Central bronchiectasis is described as a classic finding on chest imaging in ABPA but is not necessary for making a diagnosis. Other possible findings on chest imaging include patchy infiltrates and evidence of mucus impaction.

Systemic glucocorticoids may be used in the treatment of ABPA that is persistently symptomatic despite the use of inhaled therapies for asthma. Courses of glucocorticoids should be tapered over 3–6 months, and their use must be balanced against the risks of prolonged steroid therapy. Antifungal agents such as fluconazole and voriconazole given over a 4-month course reduce the antigenic stimulus in ABPA and may therefore modulate disease activity in selected patients. The use of monoclonal antibody against IgE (omalizumab) has been described in treating severe ABPA, particularly in individuals with ABPA as a complication of cystic fibrosis.

ABPA-like syndromes have been reported as a result to sensitization to several non-*Aspergillus* species fungi. However, these conditions are substantially rarer than ABPA, which may be present in a significant proportion of patients with refractory asthma.

INFECTIOUS PROCESSES

Infectious etiologies of pulmonary eosinophilia are largely due to helminths and are of particular importance in the evaluation of pulmonary eosinophilia in tropical environments and in the developing world **(Table 282-4)**. These infectious conditions may also be considered in recent travelers to endemic regions. Loffler syndrome refers to transient pulmonary infiltrates with eosinophilia that occurs in response to passage of helminthic larvae through the lungs, most commonly larvae of *Ascaris* species (roundworm). Symptoms are generally self-limited and may include dyspnea, cough, wheeze, and hemoptysis. Loffler syndrome may also occur in response to hookworm infection with *Ancylostoma duodenale* or *Necator americanus*. Chronic *Strongyloides stercoralis* infection can lead to recurrent respiratory symptoms with

TABLE 282-4 Infectious Causes of Pulmonary Eosinophilia

Löffler Syndrome
Ascaris
Hookworm
Schistosomiasis
Heavy Parasite Burden
Strongyloidiasis
Direct Pulmonary Penetration
Paragonimiasis
Visceral larval migrans
Immunologic Response to Organisms in Lungs
Filariasis
Dirofilariasis
Cystic Disease
Echinococcus
Cysticercosis
Other Nonparasitic
Coccidioidomycosis
Basidiobolomycosis
Paracoccidioidomycosis
Tuberculosis

Source: Adapted from P Akuthota, PF Weller: Clin Microbiol Rev 25:649, 2012.

peripheral eosinophilia between flares. In immunocompromised hosts, including patients on glucocorticoids, a severe, potentially fatal, hyperinfection syndrome can result from *Strongyloides* infection. Paragonimiasis, filariasis, and visceral larval migrans can all cause pulmonary eosinophilia as well.

DRUGS AND TOXINS

A host of medications are associated with the development of pulmonary infiltrates with peripheral eosinophilia. Therefore, drug reaction must always be included in the differential diagnosis of pulmonary eosinophilia. Although the list of medications associated with pulmonary eosinophilia is ever expanding, common culprits include nonsteroidal anti-inflammatory medications and systemic antibiotics, most specifically nitrofurantoin. Additionally, various and diverse environmental exposures such as particulate metals, scorpion stings, and inhalational drugs of abuse may also cause pulmonary eosinophilia. Radiation therapy for breast cancer has been linked with eosinophilic pulmonary infiltration as well. The mainstay of treatment is removal of the offending exposure, although glucocorticoids may be necessary if respiratory symptoms are severe.

GLOBAL CONSIDERATIONS

In the United States, drug-induced eosinophilic pneumonias are the most common cause of eosinophilic pulmonary infiltrates. A travel history or evidence of recent immigration should prompt the consideration of parasite-associated disorders. Tropical eosinophilia is usually caused by filarial infection; however, eosinophilic pneumonias also occur with other parasites such as *Ascaris* spp., *Ancylostoma* spp., *Toxocara* spp., and *Strongyloides stercoralis*. Tropical eosinophilia due to *Wuchereria bancrofti* or *Wuchereria malayi* occurs most commonly in southern Asia, Africa, and South America and is treated successfully with diethylcarbamazine. In the United States, *Strongyloides* is endemic to the southeastern and Appalachian regions.

FURTHER READING

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283 Occupational and Environmental Lung Disease

John R. Balmes

Occupational and environmental lung diseases are difficult to distinguish from those of nonenvironmental origin. Virtually all major categories of pulmonary disease can be caused by environmental agents, and environmentally related disease usually presents clinically in a manner indistinguishable from that of disease not caused by such agents. In addition, the etiology of many diseases may be multifactorial; occupational and environmental factors may interact with other factors (such as smoking and genetic risk). It is often only after a careful exposure history is taken that the underlying workplace or general environmental exposure is uncovered.

Why is knowledge of occupational or environmental etiology so important? Patient management and prognosis are affected significantly by such knowledge. For example, patients with occupational asthma or hypersensitivity pneumonitis often cannot be managed adequately without cessation of exposure to the offending agent. Establishment of cause may have significant legal and financial implications for a patient who no longer can work in his or her usual job. Other exposed people may be identified as having the disease or prevented from getting it. In addition, new associations between exposure and disease may be identified (e.g., nylon flock worker's lung disease and diacetyl-induced bronchiolitis obliterans).

Although the exact proportion of lung disease due to occupational and environmental factors is unknown, a large number of individuals are at risk. For example, 15–20% of the burden of adult asthma and chronic obstructive pulmonary disease (COPD) has been estimated to be due to occupational factors.

HISTORY AND EXPOSURE ASSESSMENT

The patient's history is of paramount importance in assessing any potential occupational or environmental exposure. Inquiry into specific work practices should include questions about the specific contaminants involved, the presence of visible dusts, chemical odors, the size and ventilation of workspaces, the use of respiratory protective equipment, and whether co-workers have similar complaints. The temporal association of exposure at work and symptoms may provide clues to occupation-related disease. In addition, the patient must be questioned about alternative sources of exposure to potentially toxic agents, including hobbies, home characteristics, exposure to secondhand smoke, and proximity to traffic or industrial facilities. Short-term and long-term exposures to potential toxic agents in the distant past also must be considered.

Workers in the United States have the right to know about potential hazards in their workplaces under federal Occupational Safety and Health Administration (OSHA) regulations. Employers must provide specific information about potential hazardous agents in products being used through Safety Data Sheets as well as training in personal protective equipment and environmental control procedures. However, the introduction of new processes and/or new chemical compounds may change exposure significantly, and often only the employee on the production line is aware of the change. For the physician caring for a patient with a suspected work-related illness, a visit to the work site can be very instructive. Alternatively, an affected worker can request an inspection by OSHA. If reliable environmental sampling data are available, that information should be used in assessing a patient's exposure. Because chronic diseases may result from exposure over many years, current environmental measurements should be combined with work histories to arrive at estimates of past exposure.

LABORATORY TESTS

Exposures to inorganic and organic dusts can cause interstitial lung disease that presents with a restrictive pattern and a decreased diffusing capacity (Chap. 279). Similarly, exposures to a number of dusts or chemical agents may result in occupational asthma or COPD that is characterized by airway obstruction. Measurement of change in forced expiratory volume (FEV_1) before and after a working shift can be used to detect an acute bronchoconstrictive response.

The chest radiograph is useful in detecting and monitoring the pulmonary response to mineral dusts, certain metals, and organic dusts capable of inducing hypersensitivity pneumonitis. The International Labour Organisation (ILO) International Classification of Radiographs of Pneumoconioses classifies chest radiographs by the nature and size of opacities seen and the extent of involvement of the parenchyma. In general, small rounded opacities are seen in silicosis or coal worker's pneumoconiosis, and small linear opacities are seen in asbestosis. Although useful for epidemiologic studies and screening large numbers of workers, the ILO system can be problematic when applied to an individual worker's chest radiograph. With dusts causing rounded opacities, the degree of involvement on the chest radiograph may be extensive, whereas pulmonary function may be only minimally impaired. In contrast, in pneumoconiosis causing linear, irregular opacities like those seen in asbestosis, the radiograph may lead to underestimation of the severity of the impairment until relatively late in the disease. For patients with a history of asbestos exposure, conventional computed tomography (CT) is more sensitive for the detection of pleural thickening, and high-resolution CT (HRCT) improves the detection of asbestosis.

Other procedures that may be of use in identifying the role of environmental exposures in causing lung disease include skin prick testing or specific IgE antibody titers for evidence of immediate hypersensitivity to agents capable of inducing occupational asthma (flour antigens in bakers), specific IgG precipitating antibody titers for agents capable of causing hypersensitivity pneumonitis (pigeon antigen in bird handlers), and assays for specific cell-mediated immune responses (beryllium lymphocyte proliferation testing in nuclear workers or tuberculin skin testing in health care workers). Sometimes a bronchoscopy to obtain transbronchial biopsies of lung tissue may be required for histologic diagnosis (chronic beryllium disease [CBD]). Rarely, video-assisted thoracoscopic surgery to obtain a larger sample of lung tissue may be required to determine the specific diagnosis of environmentally induced lung disease (hypersensitivity pneumonitis or giant cell interstitial pneumonitis due to cobalt exposure).

DETERMINANTS OF INHALATIONAL EXPOSURE

The chemical and physical characteristics of inhaled agents affect both the dose and the site of deposition in the respiratory tract. Water-soluble gases such as ammonia and sulfur dioxide are absorbed in the lining fluid of the upper and proximal airways and thus tend to produce irritative and bronchoconstrictive responses. In contrast, nitrogen dioxide and phosgene, which are less soluble, may penetrate to the bronchioles and alveoli in sufficient quantities to produce acute chemical pneumonitis.

Particle size of air contaminants must also be considered. Because of their settling velocities in air, particles >10–15 μm in diameter do not penetrate beyond the nose and throat. Particles <10 μm in size are deposited below the larynx. These particles are divided into three size fractions on the basis of their size characteristics and sources. Particles ~2.5–10 μm (coarse-mode fraction) contain crustal elements such as silica, aluminum, and iron. These particles mostly deposit relatively high in the tracheobronchial tree. Although the total mass of an ambient sample is dominated by these larger respirable particles, the number of particles, and therefore the surface area on which potential toxic agents can deposit and be carried to the lower airways, is dominated by particles <2.5 μm (fine-mode fraction). These fine particles are created primarily by the burning of fossil fuels or high-temperature industrial processes resulting in condensation products from gases, fumes, or vapors. The smallest particles, those <0.1 μm in size, represent the ultrafine fraction and make up the largest number of particles; they tend to remain in the airstream and deposit in the lung only on a random basis as they come into contact with the alveolar walls. If they do deposit, however, particles of this size range may penetrate into the circulation and be carried to extrapulmonary sites. New technologies create particles of this size ("nanoparticles") for use in many commercial applications. Besides the size characteristics of particles and the solubility of gases, the actual chemical composition, mechanical properties, and immunogenicity or infectivity of inhaled material determine in large part the nature of the diseases found among exposed persons.

OCCUPATIONAL EXPOSURES AND PULMONARY DISEASE

Table 283-1 provides broad categories of exposure in the workplace and diseases associated with chronic exposure in those industries.

ASBESTOS-RELATED DISEASES

Asbestos is a generic term for several different mineral silicates, including chrysolite, amosite, anthophyllite, and crocidolite. In addition to workers involved in the production of asbestos products (mining, milling, and manufacturing), many workers in the shipbuilding and construction trades, including pipe fitters and boilermakers, were occupationally exposed because asbestos was widely used during the twentieth century for its thermal and electrical insulation properties. Asbestos also was used in the manufacture of fire-resistant textiles, in cement and floor tiles, and in friction materials such as brake and clutch linings.

TABLE 283-1 Categories of Occupational Exposure and Associated Respiratory Conditions

OCCUPATIONAL EXPOSURES	NATURE OF RESPIRATORY RESPONSES	COMMENT
Inorganic Dusts		
Asbestos: mining, processing, construction, ship repair	Fibrosis (asbestosis), pleural disease, cancer, mesothelioma	Virtually all new mining and construction with asbestos done in developing countries
Silica: mining, stone cutting, sandblasting, quarrying	Fibrosis (silicosis), progressive massive fibrosis (PMF), cancer, tuberculosis, chronic obstructive pulmonary disease (COPD)	Improved protection in United States; persistent risk in developing countries
Coal dust: mining	Fibrosis (coal worker's pneumoconiosis), PMF, COPD	Risk persists in certain areas of United States, increasing in countries where new mines open
Beryllium: processing alloys for high-tech industries	Acute pneumonitis (rare), chronic granulomatous disease, lung cancer (highly suspect)	Risk in high-tech industries persists
Other metals: aluminum, chromium, cobalt, nickel, titanium, tungsten carbide, or "hard metal" (contains cobalt)	Wide variety of conditions from acute pneumonitis to lung cancer and asthma	New diseases appear with new process development
Organic Dusts		
Cotton dust: milling, processing	Byssinosis (an asthma-like syndrome), chronic bronchitis, COPD	Increasing risk in developing countries with drop in United States as jobs shift overseas
Grain dust: elevator agents, dock workers, milling, bakers	Asthma, chronic bronchitis, COPD	Risk shifting more to migrant labor pool
Other agricultural dusts: fungal spores, vegetable products, insect fragments, animal dander, bird and rodent feces, endotoxins, microorganisms, pollens	Hypersensitivity pneumonitis (farmer's lung), asthma, chronic bronchitis	Important in migrant labor pool but also resulting from in-home exposures
Toxic chemicals: wide variety of industries; see Table 283-2	Asthma, chronic bronchitis, COPD, hypersensitivity pneumonitis, pneumoconiosis, and cancer	Reduced risk with recognized hazards; increasing risk for developing countries where controlled labor practices are less stringent
Other Environmental Agents		
Uranium and radon daughters, secondhand tobacco smoke, polycyclic aromatic hydrocarbons (PAHs), biomass smoke, diesel exhaust, welding fumes, wood finishing	Occupational exposures estimated to contribute to up to 10% of all lung cancers; chronic bronchitis, COPD, and fibrosis	In-home exposures important; in developing countries, biomass smoke is a major risk factor for COPD among women in these countries

Exposure to asbestos is not limited to persons who directly handle the material. Cases of asbestos-related diseases have been encountered in individuals with only bystander exposure, such as painters and electricians who worked alongside insulation workers in a shipyard. Community exposure resulted from the use of asbestos-containing mine and mill tailings as landfill, road surface, and playground material (e.g., Libby, MT, the site of a vermiculite mine in which the ore was contaminated with asbestos). Finally, exposure can occur from the disturbance of naturally occurring asbestos (e.g., from increasing residential development in the foothills of the Sierra Mountains in California).

Asbestos has largely been replaced in the developed world with synthetic mineral fibers such as fiberglass and refractory ceramic fibers, but it continues to be used in the developing world. The major health effects from exposure to asbestos are pleural and pulmonary fibrosis, cancers of the respiratory tract, and pleural and peritoneal mesothelioma.

Asbestosis is a diffuse interstitial fibrosing disease of the lung that is directly related to the intensity and duration of exposure. The disease resembles other forms of diffuse interstitial fibrosis **(Chap. 287)**. Usually, exposure has taken place for at least 10 years before the disease becomes manifest. The mechanisms by which asbestos fibers induce lung fibrosis are not completely understood but are known to involve oxidative injury due to the generation of reactive oxygen species by the transition metals on the surface of the fibers as well as from cells engaged in phagocytosis.

Past exposure to asbestos is specifically indicated by pleural plaques on chest radiographs, which are characterized by either thickening or calcification along the parietal pleura, particularly along the lower lung fields, the diaphragm, and the cardiac border. Without additional manifestations, pleural plaques imply only exposure, not pulmonary impairment. Benign pleural effusions also may occur. The fluid is typically a serous or bloody exudate. The effusion may be slowly progressive or may resolve spontaneously.

Irregular or linear opacities that usually are first noted in the lower lung fields are the chest radiographic hallmark of asbestosis. An indistinct heart border or a "ground-glass" appearance in the lung fields may be seen. HRCT may show distinct changes of subpleural curvilinear lines 5–10 mm in length that appear to be parallel to the pleural surface **(Fig. 283-1)**.

Pulmonary function testing in asbestosis reveals a restrictive pattern with a decrease in both lung volumes and diffusing capacity. There may also be evidence of mild airflow obstruction (due to peribronchiolar fibrosis).

Because no specific therapy is available for asbestosis, supportive care is the same as that given to any patient with diffuse interstitial fibrosis of any cause. In general, newly diagnosed cases will have resulted from exposures that occurred many years before.

Lung cancer **(Chap. 74)** is the most common cancer associated with asbestos exposure. The excess frequency of lung cancer (all histologic types) in asbestos workers is associated with a minimum latency of 15–19 years between first exposure and development of the disease. Persons with more exposure are at greater risk of disease. In addition, there is a significant interactive effect of smoking and asbestos exposure that results in greater risk than what would be expected from the additive effect of each factor.

Mesotheliomas **(Chap. 288)**, both pleural and peritoneal, are also associated with asbestos exposure. In contrast to lung cancers, these tumors do not appear to be associated with smoking. Relatively short-term asbestos exposures of ≤1–2 years, occurring up to 40 years in the past, have been associated with the development of mesotheliomas (an observation that emphasizes the importance of obtaining a complete environmental exposure history). Although the risk of mesothelioma is much less than that of lung cancer among asbestos-exposed workers, >2000 cases were reported in the United States per year at the start of the twenty-first century.

Because epidemiologic studies have shown that >80% of mesotheliomas may be associated with asbestos exposure, documented mesothelioma in a patient with occupational or environmental exposure to asbestos may be compensable.

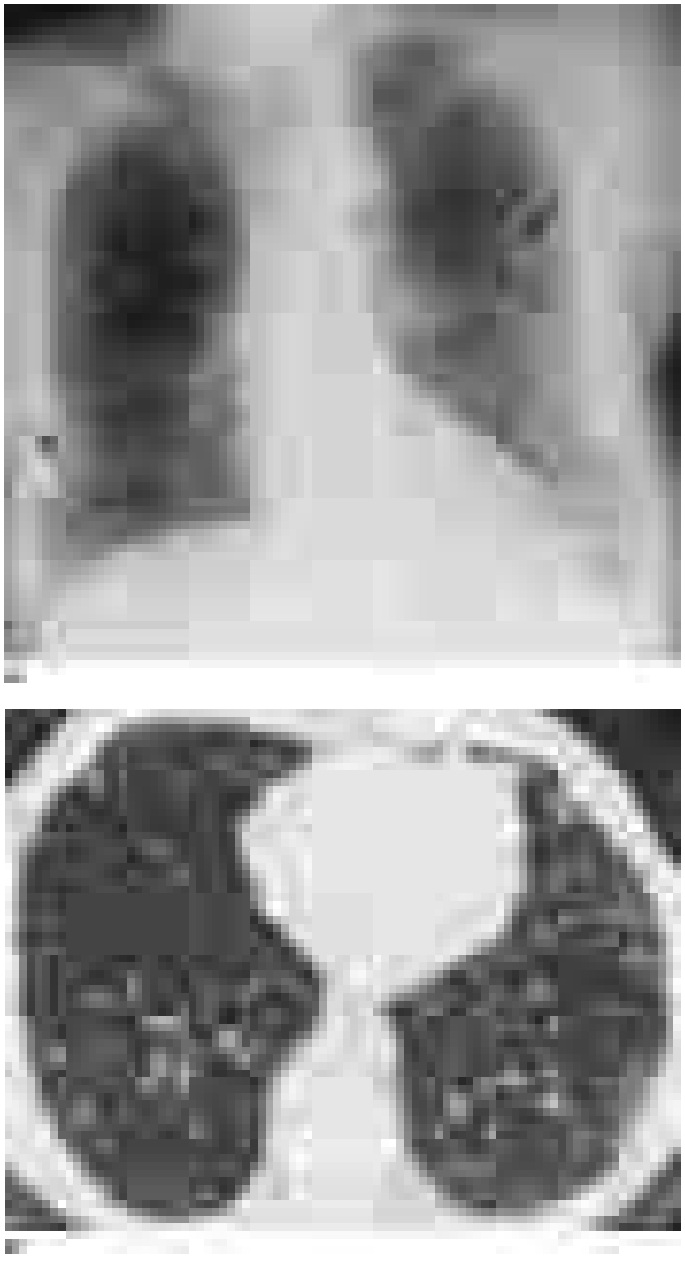

FIGURE 283-1 Asbestosis. ***A.*** Frontal chest radiograph shows bilateral calcified pleural plaques consistent with asbestos-related pleural disease. Poorly defined linear and reticular abnormalities are seen in the lower lobes bilaterally. ***B.*** Axial high-resolution computed tomography of the thorax obtained through the lung bases shows bilateral, subpleural reticulation (*black arrows*), representing fibrotic lung disease due to asbestosis. Subpleural lines are also present (*arrowheads*), characteristic of, though not specific for, asbestosis. Calcified pleural plaques representing asbestos-related pleural disease (*white arrows*) are also evident.

SILICOSIS

Despite being one of the oldest known occupational pulmonary hazards, *free silica* (SiO_2), or crystalline quartz, is still a major cause of disease. The major occupational exposures include mining; stonecutting; sand blasting; glass and cement manufacturing; foundry work; packing of silica flour; and quarrying, particularly of granite. Most often, pulmonary fibrosis due to silica exposure (silicosis) occurs in a dose-response fashion after many years of exposure.

Workers heavily exposed through sandblasting in confined spaces, tunneling through rock with a high quartz content (15–25%), or the manufacture of abrasive soaps may develop acute silicosis with as little as 10 months of exposure. The clinical and pathologic features of acute silicosis are similar to those of pulmonary alveolar proteinosis **(Chap. 287)**. The chest radiograph may show profuse miliary infiltration

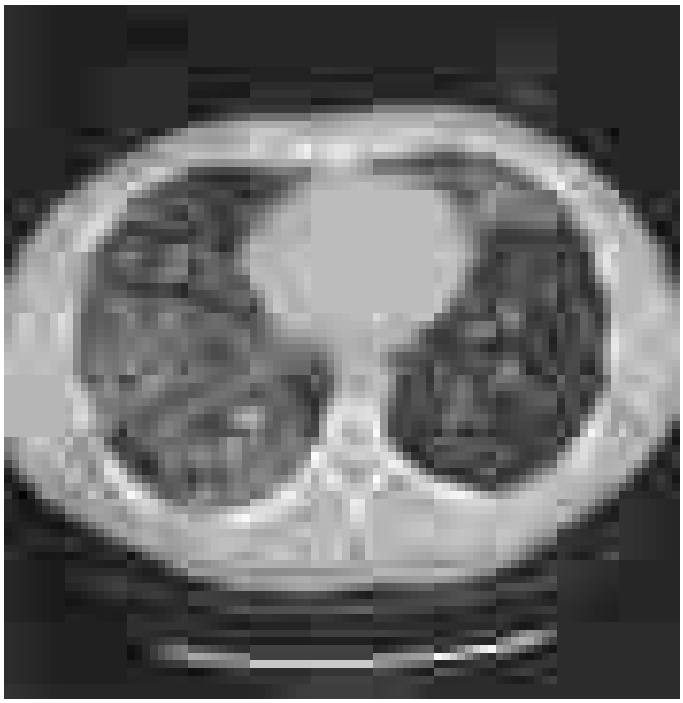

FIGURE 283-2 Acute silicosis. This high-resolution computed tomography scan shows multiple small nodules consistent with silicosis but also diffuse ground-glass densities with thickened intralobular and interlobular septa producing polygonal shapes. This has been referred to as "crazy paving."

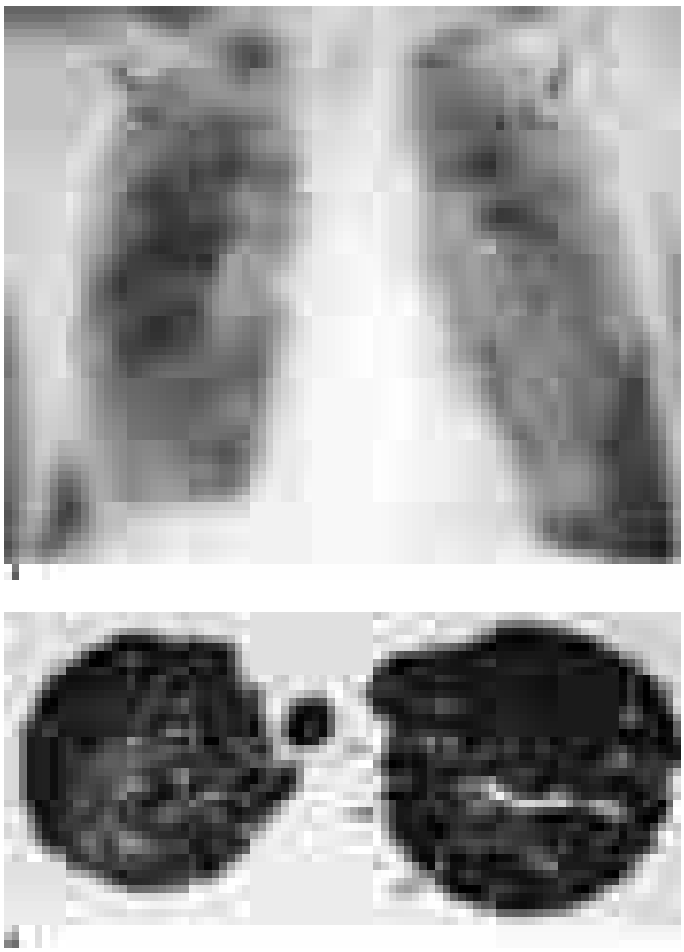

FIGURE 283-3 Chronic silicosis. *A.* Frontal chest radiograph in a patient with silicosis shows variably sized, poorly defined nodules (*arrows*) predominating in the upper lobes. ***B.*** Axial thoracic computed tomography image through the lung apices shows numerous small nodules, more pronounced in the right upper lobe. A number of the nodules are subpleural in location (*arrows*).

or consolidation, and there is a characteristic HRCT pattern known as "crazy paving" **(Fig. 283-2)**. The disease may be quite severe and progressive despite the discontinuation of exposure. Whole-lung lavage may provide symptomatic relief and slow the progression.

With long-term, less intense exposure, small rounded opacities in the upper lobes may appear on the chest radiograph after 15–20 years of exposure, usually without associated impairment of lung function (*simple silicosis*). Calcification of hilar nodes may occur in as many as 20% of cases and produces a characteristic "eggshell" pattern. Silicotic nodules may be identified more readily by HRCT **(Fig. 283-3)**. The nodular fibrosis may be progressive in the absence of further exposure, with coalescence and formation of nonsegmental conglomerates of irregular masses >1 cm in diameter (*complicated silicosis*). These masses can become quite large, and when this occurs, the term *progressive massive fibrosis* (PMF) is applied. Significant functional impairment with both restrictive and obstructive components may be associated with PMF.

Because silica causes alveolar macrophage dysfunction, patients with silicosis are at greater risk of acquiring lung infections that involve these cells as a primary defense (*Mycobacterium tuberculosis*, atypical mycobacteria and fungi). Because of the increased risk of active tuberculosis, the recommended treatment of latent tuberculosis in these patients is longer. Silica has immunoadjuvant properties and another potential clinical complication of silicosis is autoimmune connective tissue disorders such as rheumatoid arthritis and scleroderma. In addition, there are sufficient epidemiologic data that the International Agency for Research on Cancer lists silica as a probable lung carcinogen.

Other, less hazardous silicates include fuller's earth, kaolin, mica, diatomaceous earths, silica gel, soapstone, carbonate dusts, and cement dusts. The production of fibrosis in workers exposed to these agents is believed to be related either to the free silica content of these dusts or, for substances that contain no free silica, to the potentially large dust loads to which these workers may be exposed. Some silicates, including *talc* and *vermiculite*, may be contaminated with asbestos. Fibrosis of lung or pleura, lung cancer, and mesothelioma have been associated with chronic exposure to talc and vermiculite dusts.

COAL WORKER'S PNEUMOCONIOSIS (CWP)

Occupational exposure to *coal dust* can lead to CWP, which has enormous social, economic, and medical significance in every nation in which coal mining is an important industry. Simple radiographically identified CWP is seen in ~10% of all coal miners and in as many as 50% of anthracite miners with >20 years of work on the coal face. The prevalence of disease is lower in workers in bituminous coal mines.

With prolonged exposure to coal dust (i.e., 15–20 years), small, rounded opacities similar to those of silicosis may develop. As in silicosis, the presence of these nodules (*simple CWP*) usually is not associated with pulmonary impairment. In addition to CWP, coal dust can cause chronic bronchitis and COPD **(Chap. 286)**. The effects of coal dust are additive to those of cigarette smoking.

Complicated CWP is manifested by the appearance on the chest radiograph of nodules ≥1 cm in diameter generally confined to the upper half of the lungs. As in silicosis, this condition can progress to PMF that is accompanied by severe lung function deficits and associated with premature mortality. Despite improvements in technology to protect coal miners, cases of PMF still occur in the United States at a disturbing rate.

Caplan syndrome **(Chap. 351)**, first described in coal miners but subsequently in patients with silicosis, is the combination of pneumoconiotic nodules and seropositive rheumatoid arthritis. Silica is often present in anthracitic coal dust and its presence may contribute to risk of PMF.

CHRONIC BERYLLIUM DISEASE

Beryllium is a lightweight metal with tensile strength, good electrical conductivity, and value in the control of nuclear reactions through

its ability to quench neutrons. Although beryllium may produce an acute pneumonitis, it is far more commonly associated with a chronic granulomatous inflammatory disease that is similar to sarcoidosis (Chap. 360). Unless one inquires specifically about occupational exposures to beryllium in the manufacture of alloys, ceramics, or high-technology electronics in a patient with sarcoidosis, one may miss entirely the etiologic relationship to the occupational exposure. What distinguishes CBD from sarcoidosis is evidence of a specific cell-mediated immune response (i.e., delayed hypersensitivity) to beryllium.

The test that usually provides this evidence is the beryllium lymphocyte proliferation test (BeLPT). The BeLPT compares the in vitro proliferation of lymphocytes from blood or bronchoalveolar lavage in the presence of beryllium salts with that of unstimulated cells. Proliferation is usually measured by lymphocyte uptake of radiolabeled thymidine.

Chest imaging findings are similar to those of sarcoidosis (nodules along septal lines) except that hilar adenopathy is somewhat less common. As with sarcoidosis, pulmonary function test results may show restrictive and/or obstructive ventilatory deficits and decreased diffusing capacity. With early disease, both chest imaging studies and pulmonary function tests may be normal. Fiberoptic bronchoscopy with transbronchial lung biopsy usually is required to make the diagnosis of CBD. In a beryllium-sensitized individual, the presence of noncaseating granulomas or monocytic infiltration in lung tissue establishes the diagnosis. Accumulation of beryllium-specific CD4+ T cells occurs in the granulomatous inflammation seen on lung biopsy. Susceptibility to CBD is highly associated with human leukocyte antigen DP (HLA-DP) alleles that have a glutamic acid in position 69 of the β chain.

OTHER METALS

Aluminum and titanium dioxide have been rarely associated with a sarcoid-like reaction in lung tissue. Exposure to dust containing tungsten carbide, also known as "hard metal," may produce giant cell interstitial pneumonitis. Cobalt is a constituent of tungsten carbide and is the likely etiologic agent of both the interstitial pneumonitis and the occupational asthma that may occur. The most common exposures to tungsten carbide occur in tool and dye, saw blade, and drill bit manufacture. Diamond polishing may also involve exposure to cobalt dust. In patients with interstitial lung disease, one should always inquire about exposure to metal fumes and/or dusts. Especially when sarcoidosis appears to be the diagnosis, one should always consider possible CBD.

OTHER INORGANIC DUSTS

Most of the inorganic dusts discussed thus far are associated with the production of either dust macules or interstitial fibrotic changes in the lung. Other inorganic and organic dusts (see categories in Table 283-1), along with some of the dusts previously discussed, are associated with chronic mucus hypersecretion (chronic bronchitis), with or without reduction of expiratory flow rates. Cigarette smoking is the major cause of these conditions, and any effort to attribute some component of the disease to occupational and environmental exposures must take cigarette smoking into account. Most studies suggest an additive effect of dust exposure and smoking. The pattern of the irritant dust effect is similar to that of cigarette smoking, suggesting that small airway inflammation may be the initial site of pathologic response in those cases and continued exposure may lead to chronic bronchitis and COPD.

ORGANIC DUSTS

Some of the specific diseases associated with organic dusts are discussed in detail in the chapters on asthma (Chap. 281) and hypersensitivity pneumonitis (Chap. 282). Many of these diseases are named for the specific setting in which they are found, e.g., farmer's lung, malt worker's disease, and mushroom worker's disease. Often the temporal relation of symptoms to exposure furnishes the best evidence for the diagnosis. Three occupational exposures are singled out for discussion here because they affect the largest proportions of workers.

Cotton Dust (Byssinosis) Workers occupationally exposed to cotton dust (but also to flax, hemp, or jute dust) in the production of yarns for textiles and rope making are at risk for an asthma-like syndrome known as byssinosis. The risk of byssinosis is associated with both cotton dust and endotoxin levels in the workplace environment.

Byssinosis is characterized clinically as occasional (early-stage) and then regular (late-stage) chest tightness toward the end of the first day of the workweek ("Monday chest tightness"). Exposed workers may show a significant drop in FEV_1 over the course of a Monday workshift. Initially the symptoms do not recur on subsequent days of the week, but in a subset of workers, chest tightness may recur or persist throughout the workweek. After >10 years of exposure, workers with recurrent symptoms are more likely to have an obstructive pattern on pulmonary function testing.

Dust exposure can be reduced by the use of exhaust hoods, general increases in ventilation, and wetting procedures, but respiratory protective equipment may be required during certain operations. Regular surveillance of pulmonary function in cotton dust–exposed workers using spirometry before and after the workshift is required by OSHA. All workers with persistent symptoms or significantly reduced levels of pulmonary function should be moved to areas of lower risk of exposure.

Grain Dust Worldwide, many farmers and workers in grain storage facilities are exposed to grain dust. The presentation of obstructive airway disease in grain dust–exposed workers is virtually identical to the characteristic findings in cigarette smokers, i.e., persistent cough, mucus hypersecretion, wheeze and dyspnea on exertion, and reduced FEV_1 and FEV_1/FVC (forced vital capacity) ratio (Chap. 279).

Dust concentrations in grain elevators vary greatly but can be >10,000 $\mu g/m^3$ with many particles in the respirable size range. The effect of grain dust exposure is additive to that of cigarette smoking, with ~50% of workers who smoke having symptoms. Smoking grain dust–exposed workers are more likely to have obstructive ventilatory deficits on pulmonary function testing. As in byssinosis, endotoxin may play a role in grain dust–induced chronic bronchitis and COPD.

Farmer's Lung This condition results from exposure to moldy hay containing spores of thermophilic actinomycetes that produce a hypersensitivity pneumonitis (Chap. 282). A patient with acute farmer's lung presents 4–8 h after exposure with fever, chills, malaise, cough, and dyspnea without wheezing. The history of exposure is obviously essential to distinguish this disease from influenza or pneumonia with similar symptoms. In the chronic form of the disease, the history of repeated attacks after similar exposure is important in differentiating this syndrome from other causes of patchy fibrosis (e.g., sarcoidosis).

A wide variety of other organic dusts are associated with the occurrence of hypersensitivity pneumonitis (Chap. 282). For patients who present with hypersensitivity pneumonitis, specific and careful inquiry about occupations, hobbies, and other home environmental exposures is necessary to uncover the source of the etiologic agent.

TOXIC CHEMICALS

Exposure to toxic chemicals affecting the lung generally involves gases and vapors. A common accident is one in which the victim is trapped in a confined space where the chemicals have accumulated to harmful levels. In addition to the specific toxic effects of the chemical, the victim often sustains considerable anoxia, which can play a dominant role in determining whether the individual survives.

Table 283-2 lists a variety of toxic agents that can produce acute and sometimes life-threatening reactions in the lung. All these agents in sufficient concentrations have been demonstrated, at least in animal studies, to affect the lower airways and disrupt alveolar architecture, either acutely or as a result of chronic exposure. Some of these agents may be generated acutely in the environment (see below).

Firefighters and fire victims are at risk of *smoke inhalation*, an important cause of acute cardiorespiratory failure. Smoke inhalation kills more fire victims than does thermal injury. Carbon monoxide poisoning with resulting significant hypoxemia can be life-threatening (Chap. 450). Synthetic materials (plastic, polyurethanes), when burned, may release a variety of other toxic agents (such as cyanide and hydrochloric acid), and this must be considered in evaluating smoke

TABLE 283-2 Selected Common Toxic Chemical Agents That Affect the Lung

AGENT(s)	SELECTED EXPOSURES	ACUTE EFFECTS FROM HIGH OR ACCIDENTAL EXPOSURE	CHRONIC EFFECTS FROM RELATIVELY LOW EXPOSURE
Acid anhydrides	Manufacture of resin esters, polyester resins, thermoactivated adhesives	Nasal irritation, cough	Asthma, chronic bronchitis, hypersensitivity pneumonitis
Acid fumes: H_2SO_4, HNO_3	Manufacture of fertilizers, chlorinated organic compounds, dyes, explosives, rubber products, metal etching, plastics	Mucous membrane irritation, followed by chemical pneumonitis 2–3 days later	Bronchitis and suggestion of mildly reduced pulmonary function in children with lifelong residential exposure to high levels
Acrolein and other aldehydes	By-product of burning plastics, woods, tobacco smoke	Mucous membrane irritant, decrease in lung function	Upper respiratory tract irritation
Ammonia	Refrigeration; petroleum refining; manufacture of fertilizers, explosives, plastics, and other chemicals	Same as for acid fumes, but bronchiectasis also has been reported	Upper respiratory tract irritation, chronic bronchitis
Cadmium fumes	Smelting, soldering, battery production	Mucous membrane irritant, acute respiratory distress syndrome (ARDS)	Chronic obstructive pulmonary disease (COPD)
Formaldehyde	Manufacture of resins, leathers, rubber, metals, and woods; laboratory workers, embalmers; emission from urethane foam insulation	Same as for acid fumes	Nasopharyngeal cancer
Halides and acid salts (Cl, Br, F)	Bleaching in pulp, paper, textile industry; manufacture of chemical compounds; synthetic rubber, plastics, disinfectant, rocket fuel, gasoline	Mucous membrane irritation, pulmonary edema; possible reduced forced vital capacity (FVC) 1–2 years after exposure	Upper respiratory tract irritation, epistaxis, tracheobronchitis
Hydrogen sulfide	By-product of many industrial processes, oil, other petroleum processes and storage	Increase in respiratory rate followed by respiratory arrest, lactic acidosis, pulmonary edema, death	Conjunctival irritation, chronic bronchitis, recurrent pneumonitis
Isocyanates (TDI, HDI, MDI)	Production of polyurethane foams, plastics, adhesives, surface coatings	Mucous membrane irritation, dyspnea, cough, wheeze, pulmonary edema	Upper respiratory tract irritation, cough, asthma, hypersensitivity pneumonitis, reduced lung function
Nitrogen dioxide	Silage, metal etching, explosives, rocket fuels, welding, by-product of burning fossil fuels	Cough, dyspnea, pulmonary edema may be delayed 4–12 h; possible result from acute exposure: bronchiolitis obliterans in 2–6 weeks	Emphysema in animals, chronic bronchitis, associated with reduced lung function growth in children with lifelong residential exposure
Ozone	Arc welding, flour bleaching, deodorizing, emissions from copying equipment, photochemical air pollutant	Mucous membrane irritant, reduced pulmonary function transiently in children and adults, asthma exacerbation	Excess cardiopulmonary mortality rates, increased risk for new-onset asthma in children
Phosgene	Organic compound, metallurgy, volatilization of chlorine-containing compounds	Delayed onset of bronchiolitis and pulmonary edema	Chronic bronchitis
Sulfur dioxide	Manufacture of sulfuric acid, bleaches, coating of nonferrous metals, food processing, refrigerant, burning of fossil fuels, wood pulp industry	Mucous membrane irritant, epistaxis, bronchospasm (especially in people with asthma)	Chronic bronchitis

Abbreviations: HDI, hexamethylene diisocyanate; MDI, methylene diphenyl diisocyanate; TDI, toluene diisocyanate.

inhalation victims. Exposed victims may have some degree of lower respiratory tract inflammation and/or pulmonary edema.

Exposure to certain highly reactive, low-molecular-weight agents used in the manufacture of synthetic polymers, paints, and coatings (*diisocyanates* in polyurethanes, *aromatic amines* and *acid anhydrides* in epoxies) is associated with a high risk of occupational asthma. Although this occupational asthma manifests clinically as if sensitization has occurred, an IgE antibody–mediated mechanism is not necessarily involved. Hypersensitivity pneumonitis–like reactions also have been described in diisocyanate and acid anhydride–exposed workers.

Fluoropolymers such as Teflon, which at normal temperatures produce no reaction, become volatilized upon heating. The inhaled agents cause a characteristic syndrome of fever, chills, malaise, and occasionally mild wheezing, leading to the diagnosis of *polymer fume fever*. A similar self-limited, influenza-like syndrome—*metal fume fever*—results from acute exposure to fumes containing zinc oxide, typically from welding of galvanized steel. These inhalational fever syndromes may begin several hours after work and resolve within 24 h, only to return on repeated exposure.

Two other agents have been associated with potentially severe lung disease. Occupational exposure to nylon flock has been shown to induce a lymphocytic bronchiolitis, and workers exposed to diacetyl, which is used to provide "butter" flavor in the manufacture of microwave popcorn and other foods, have developed bronchiolitis obliterans (Chap. 287).

World Trade Center Disaster A consequence of the attack on the World Trade Center (WTC) on September 11, 2001, was relatively heavy exposure of a large number of firefighters and other rescue workers to the dust generated by the collapse of the buildings. Environmental monitoring and chemical characterization of WTC dust has revealed a wide variety of potentially toxic constituents, although much of the dust was pulverized cement. Possibly because of the high alkalinity of WTC dust, significant cough, wheeze, and phlegm production occurred among firefighters and cleanup crews. New cough and wheeze syndromes also occurred among local residents. Heavier exposure to WTC dust among New York City firefighters was associated with accelerated decline of lung function over the first year after the disaster. More recently, concerns have been raised about risk of interstitial lung disease, especially of a granulomatous nature.

OCCUPATIONAL RESPIRATORY CARCINOGENS

Exposures at work have been estimated to contribute to 10% of all lung cancer cases. In addition to asbestos, other agents either proven or suspected to be respiratory carcinogens include acrylonitrile, arsenic compounds, beryllium, bis(chloromethyl) ether, chromium (hexavalent), formaldehyde (nasal), isopropanol (nasal sinuses), mustard gas, nickel carbonyl (nickel smelting), polycyclic aromatic hydrocarbons (coke oven emissions and diesel exhaust), secondhand tobacco smoke, silica (both mining and processing), talc (possible asbestos contamination in both mining and milling), vinyl chloride (sarcomas), wood (nasal), and

uranium. Workers at risk of radiation-related lung cancer include not only those involved in mining or processing uranium but also those exposed in underground mining operations of other ores where radon daughters may be emitted from rock formations.

ASSESSMENT OF DISABILITY

Disability is the term used to describe the decreased ability to work due to the effects of a medical condition. Physicians are generally able to assess physiologic dysfunction, or *impairment*, but the rating of disability for compensation of loss of income also involves nonmedical factors such as the education and employability of the individual. The disability rating scheme differs with the compensation-granting agency. For example, the U.S. Social Security Administration requires that an individual be unable to do any work (i.e., *total* disability) before he or she will receive income replacement payments. Many state workers' compensation systems allow for payments for *partial* disability. In the Social Security scheme, no determination of cause is done, whereas work-relatedness must be established in workers' compensation systems.

For respiratory impairment rating, resting pulmonary function tests (spirometry and diffusing capacity) are used as the initial assessment tool, with cardiopulmonary exercise testing (to assess maximal oxygen consumption) used if the results of the resting tests do not correlate with the patient's symptoms. Methacholine challenge (to assess airway reactivity) can also be useful in patients with asthma who have normal spirometry when evaluated. Some compensation agencies (e.g., Social Security) have proscribed disability classification schemes based on pulmonary function test results. When no specific scheme is proscribed, the *Guidelines of the American Medical Association* should be used.

GENERAL ENVIRONMENTAL EXPOSURES

OUTDOOR AIR POLLUTION

In 1971, the U.S. government established national air quality standards for several pollutants believed to be responsible for excess cardiorespiratory diseases. Primary standards regulated by the U.S. Environmental Protection Agency (EPA) designed to protect the public health with an adequate margin of safety exist for sulfur dioxide, particulate matter, nitrogen dioxide, ozone, lead, and carbon monoxide. Standards for each of these pollutants are updated regularly through an extensive review process conducted by the EPA. (For details on current standards, go to *https://www.epa.gov/criteria-air-pollutants/naaqs-table%20*.

Pollutants are generated from both stationary sources (power plants and industrial complexes) and mobile sources (motor vehicles), and none of the regulated pollutants occurs in isolation. Furthermore, pollutants may be changed by chemical reactions after being emitted. For example, sulfur dioxide and particulate matter emissions from a coal-fired power plant may react in air to produce acid sulfates and aerosols, which can be transported long distances in the atmosphere. Oxides of nitrogen and volatile organic compounds from automobile exhaust react with sunlight to produce ozone. Although originally thought to be confined to Los Angeles, photochemically derived pollution ("smog") is now known to be a problem throughout the United States and in many other countries. Both acute and chronic effects of these exposures have been documented in large population studies.

The symptoms and diseases associated with air pollution are the same as conditions commonly associated with cigarette smoking. In addition, decreased growth of lung function and asthma have been associated with chronic exposure to only modestly elevated levels of traffic-related gases and respirable particles. Multiple population-based time-series studies within cities have demonstrated excess health care utilization for asthma and other cardiopulmonary conditions as well as increased mortality rates. Cohort studies comparing cities that have relatively high levels of particulate exposures with less polluted communities suggest excess morbidity and mortality rates from cardiopulmonary conditions in long-term residents of the former. The strong epidemiologic evidence that fine particulate matter is a risk factor for cardiovascular morbidity and mortality has prompted toxicologic investigations into the underlying mechanisms. The inhalation of fine particles from combustion sources probably generates oxidative stress followed by local injury and inflammation in the lungs that in turn lead to autonomic and systemic inflammatory responses that can induce endothelial dysfunction and/or injury. Recent research findings on the health effects of air pollutants has led to stricter U.S. ambient air quality standards for ozone, oxides of nitrogen, and particulate matter as well as greater emphasis on publicizing pollution alerts to encourage individuals with significant cardiopulmonary impairment to stay indoors during high-pollution episodes.

INDOOR EXPOSURES

Secondhand tobacco smoke (Chap. 448), radon gas, wood smoke, and other biologic agents generated indoors must be considered. Several studies have shown that the respirable particulate load in any household is directly proportional to the number of cigarette smokers living in that home. Increases in prevalence of respiratory illnesses, especially asthma, and reduced levels of pulmonary function measured with simple spirometry have been found in the children of smoking parents in a number of studies. Recent meta-analyses for lung cancer and cardiopulmonary diseases, combining data from multiple secondhand tobacco smoke epidemiologic studies, suggest an ~25% increase in relative risk for each condition, even after adjustment for major potential confounders.

Exposure to *radon gas* in homes is a risk factor for lung cancer. The main radon product (radon-222) is a gas that results from the decay series of uranium-238, with the immediate precursor being radium-226. The amount of radium in earth materials determines how much radon gas will be emitted. Levels associated with excess lung cancer risk may be present in as many as 10% of the houses in the United States. When smokers reside in the home, the problem is potentially greater, because the molecular size of radon particles allows them to attach readily to smoke particles that are inhaled. Fortunately, technology is available for assessing and reducing the level of exposure.

Other indoor exposures of concern are bioaerosols that contain antigenic material (fungi, cockroaches, dust mites, and pet danders) associated with an increased risk of atopy and asthma. Indoor chemical agents include strong cleaning agents (bleach, ammonia), formaldehyde, perfumes, pesticides, and oxides of nitrogen from gas appliances. Nonspecific responses associated with "tight-building syndrome," perhaps better termed "building-associated illness," in which no particular agent has been implicated, have included a wide variety of complaints, among them respiratory symptoms that are relieved only by avoiding exposure in the building in question. The degree to which "smells" and other sensory stimuli are involved in the triggering of potentially incapacitating psychological or physical responses has yet to be determined, and the long-term consequences of such environmental exposures are unknown.

GLOBAL CONSIDERATIONS

Indoor exposure to *household air pollution* from cooking or heating with solid fuels (wood, dung, crop residues, charcoal, coal) is estimated to be responsible for >4% of worldwide disability-adjusted life-years (DALYs) lost, due to acute lower respiratory infections in children, COPD and lung cancer in women, and cardiovascular disease among men. This burden of disease places exposure to household air pollution as the leading environmental hazard for poor health on a global scale.

Forty percent of the world's population uses solid fuel for cooking, heating, or baking. Kerosene (similar to diesel fuel) is often used for lighting and sometimes cooking. This occurs predominantly in the rural areas of developing countries. Because many families burn coal or biomass fuels in open stoves, which are highly inefficient, and inside homes with poor ventilation, women and young children are exposed on a daily basis to high levels of smoke. In these homes, 24-h mean levels of fine particulate matter have been reported to be 2–30 times higher than the National Ambient Air Quality Standard set by the U.S. EPA.

Epidemiologic studies have consistently shown associations between exposure to biomass smoke and both chronic bronchitis and COPD. Because of increased migration to the United States from developing countries, clinicians need to be aware of the chronic respiratory effects

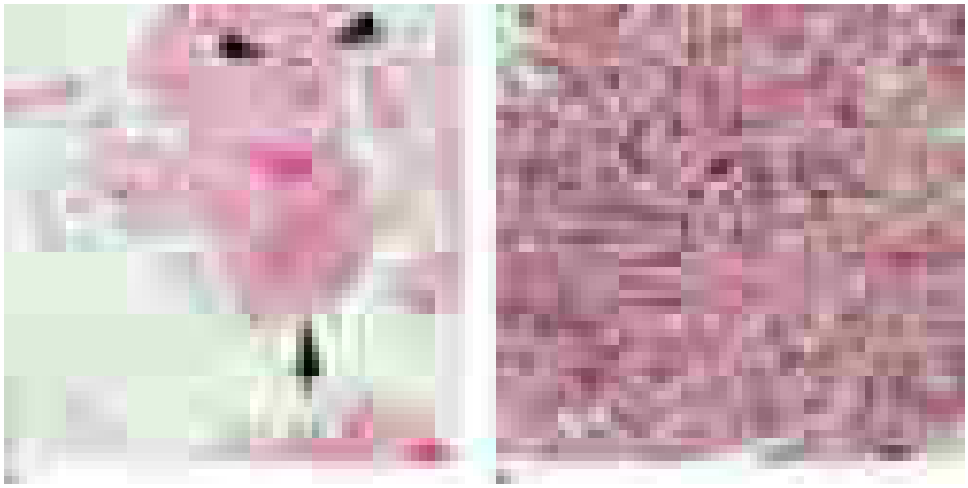

FIGURE 283-4 Histopathologic features of biomass smoke–induced interstitial lung disease. *A.* Anthracitic pigment is seen accumulating along alveolar septae (*arrowheads*) and within a pigmented dust macule (*single arrow*). ***B.*** A high-power photomicrograph contains a mixture of fibroblasts and carbon-laden macrophages.

of exposure to biomass smoke, which can include interstitial lung disease (Fig. 283-4). Evidence is beginning to emerge that improved stoves that reduce biomass smoke exposure can reduce risk of respiratory illness in both children and adults.

Household air pollution (HAP) from domestic use of solid fuels also contributes substantially to outdoor air pollution. Contributions from HAP, coal-fired power plants without emission scrubbers, and increased traffic congestion involving motor vehicles without pollution controls can lead to high concentrations of outdoor air pollution, especially fine particulate matter, in mega-cities in developing countries (e.g., Delhi).

ACKNOWLEDGMENT

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284 Bronchiectasis

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Bronchiectasis refers to an irreversible airway dilation that involves the lung in either a focal or a diffuse manner and that classically has been categorized as cylindrical or tubular (the most common form), varicose, or cystic.

ETIOLOGY

Bronchiectasis can arise from infectious or noninfectious causes (Table 284-1). Clues to the underlying etiology are often provided by the pattern of lung involvement. *Focal bronchiectasis* refers to bronchiectatic changes in a localized area of the lung and can be a consequence of obstruction of the airway—either extrinsic (e.g., due to compression by adjacent lymphadenopathy or parenchymal tumor mass) or intrinsic

TABLE 284-1 Major Etiologies of Bronchiectasis and Proposed Workup

PATTERN OF LUNG INVOLVEMENT	ETIOLOGY BY CATEGORY (EXAMPLES)	WORKUP
Focal	Obstruction (aspirated foreign body, tumor mass)	Chest imaging (chest x-ray and/or chest CT); bronchoscopy
Diffuse	Infection (bacterial, nontuberculous mycobacterial)	Sputum Gram's stain/culture; stains/cultures for acid-fast bacilli and fungi. If no pathogen is identified, consider bronchoscopy with bronchoalveolar lavage.
	Immunodeficiency (hypogammaglobulinemia, HIV infection, bronchiolitis obliterans after lung transplantation)	Complete blood count with differential; immunoglobulin measurement; HIV testing
	Genetic causes (cystic fibrosis, Kartagener's syndrome, α_1 antitrypsin deficiency)	Measurement of chloride levels in sweat (for cystic fibrosis), α_1 antitrypsin levels; nasal or respiratory tract brush/biopsy (for dyskinetic/immotile cilia syndrome); genetic testing
	Autoimmune or rheumatologic causes (rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease); immune-mediated disease (allergic bronchopulmonary aspergillosis)	Clinical examination with careful joint exam, serologic testing (e.g., for rheumatoid factor). Consider workup for allergic bronchopulmonary aspergillosis, especially in patients with refractory asthma.[a]
	Recurrent aspiration	Test of swallowing function and general neuromuscular strength
	Miscellaneous (yellow nail syndrome, traction bronchiectasis from postradiation fibrosis or idiopathic pulmonary fibrosis)	Guided by clinical condition
	Idiopathic	Exclusion of other causes

[a]Skin testing for *Aspergillus* reactivity; measurement of serum precipitins for *Aspergillus*, serum IgE levels, serum eosinophils, etc.

(e.g., due to an airway tumor or aspirated foreign body, a scarred/stenotic airway, or bronchial atresia from congenital underdevelopment of the airway). *Diffuse bronchiectasis* is characterized by widespread bronchiectatic changes throughout the lung and often arises from an underlying systemic or infectious disease process.

More pronounced involvement of the upper lung fields is most common in cystic fibrosis (CF) and is also observed in postradiation fibrosis, corresponding to the lung region encompassed by the radiation port. Bronchiectasis with predominant involvement of the lower lung fields usually has its source in chronic recurrent aspiration (e.g., due to esophageal motility disorders like those in scleroderma), end-stage fibrotic lung disease (e.g., traction bronchiectasis from idiopathic pulmonary fibrosis), or recurrent immunodeficiency-associated infections (e.g., hypogammaglobulinemia). Bronchiectasis resulting from infection by nontuberculous mycobacteria (NTM), most commonly the *Mycobacterium avium-intracellulare* complex (MAC), often preferentially affects the midlung fields. Congenital causes of bronchiectasis with predominant midlung field involvement include the dyskinetic/immotile cilia syndrome. Finally, predominant involvement of the central airways is reported in association with allergic bronchopulmonary aspergillosis (ABPA), in which an immune-mediated reaction to *Aspergillus* damages the bronchial wall. Congenital causes of central airway–predominant bronchiectasis resulting from cartilage deficiency include tracheobronchomegaly (Mounier-Kuhn syndrome) and Williams-Campbell syndrome.

In many cases, the etiology of bronchiectasis is not determined. In case series, as many as 25–50% of patients referred for bronchiectasis have idiopathic disease.

EPIDEMIOLOGY

The overall reported prevalence of bronchiectasis in the United States has recently increased, but the epidemiology of bronchiectasis varies greatly with the underlying etiology. For example, patients born with CF often develop significant clinical bronchiectasis in late adolescence or early adulthood, although atypical presentations of CF in adults in their thirties and forties are also possible. In contrast, bronchiectasis resulting from MAC infection classically affects nonsmoking women >50 years of age. In general, the incidence of bronchiectasis increases with age. Bronchiectasis is more common among women than among men.

In areas where tuberculosis is prevalent, bronchiectasis more frequently occurs as a sequela of granulomatous infection. Focal bronchiectasis can arise from extrinsic compression of the airway by enlarged granulomatous lymph nodes and/or from development of intrinsic obstruction as a result of erosion of a calcified lymph node through the airway wall (e.g., broncholithiasis). Especially in reactivated tuberculosis, parenchymal destruction from infection can result in areas of more diffuse bronchiectasis. Apart from cases associated with tuberculosis, an increased incidence of non-CF bronchiectasis with an unclear underlying mechanism has been reported as a significant problem in developing nations. It has been suggested that the high incidence of malnutrition in certain areas may predispose to immune dysfunction and development of bronchiectasis.

PATHOGENESIS AND PATHOLOGY

The most widely cited mechanism of infectious bronchiectasis is the "vicious cycle hypothesis," in which susceptibility to infection and poor mucociliary clearance result in microbial colonization of the bronchial tree. Some organisms, such as *Pseudomonas aeruginosa*, exhibit a particular propensity for colonizing damaged airways and evading host defense mechanisms. Impaired mucociliary clearance can result from inherited conditions such as CF or dyskinetic cilia syndrome, and it has been proposed that a single severe infection (e.g., pneumonia caused by *Bordetella pertussis* or *Mycoplasma pneumoniae*) can result in significant airway damage and poor secretion clearance. The presence of the microbes incites continued chronic inflammation, with consequent damage to the airway wall, continued impairment of secretions and microbial clearance, and ongoing propagation of the infectious/inflammatory cycle. Moreover, it has been proposed that mediators released directly from bacteria can interfere with mucociliary clearance.

Classic studies of the pathology of bronchiectasis from the 1950s demonstrated significant small-airway wall inflammation and larger-airway wall destruction as well as dilation, with loss of elastin, smooth muscle, and cartilage. It has been proposed that inflammatory cells in the small airways release proteases and other mediators, such as reactive oxygen species and proinflammatory cytokines, that damage the larger-airway walls. Furthermore, the ongoing inflammatory process in the smaller airways results in airflow obstruction. It is thought that antiproteases, such as α_1 antitrypsin, play an important role in neutralizing the damaging effects of neutrophil elastase and in enhancing bacterial killing. Bronchiectasis and emphysema have been observed in patients with α_1 antitrypsin deficiency.

Proposed mechanisms for noninfectious bronchiectasis include immune-mediated reactions that damage the bronchial wall (e.g., those associated with systemic autoimmune conditions such as Sjögren's syndrome and rheumatoid arthritis). *Traction bronchiectasis* refers to dilated airways arising from parenchymal distortion as a result of lung fibrosis (e.g., postradiation fibrosis or idiopathic pulmonary fibrosis).

CLINICAL MANIFESTATIONS

The most common clinical presentation is a persistent productive cough with ongoing production of thick, tenacious sputum. Physical findings often include crackles and wheezing on lung auscultation, and some patients with bronchiectasis exhibit clubbing of the digits. Mild to moderate airflow obstruction is often detected on pulmonary function tests, overlapping with that seen at presentation with other conditions, such as chronic obstructive pulmonary disease (COPD). Acute exacerbations of bronchiectasis are usually characterized by changes in the nature of sputum production, with increased volume and purulence. However, typical signs and symptoms of lung infection, such as fever and new infiltrates, may not be present.

DIAGNOSIS

The diagnosis is usually based on presentation with a persistent chronic cough and sputum production accompanied by consistent radiographic features. Although chest radiographs lack sensitivity, the presence of "tram tracks" indicating dilated airways is consistent with bronchiectasis. Chest CT is more specific for bronchiectasis and is the imaging modality of choice for confirming the diagnosis. CT findings include airway dilation (detected as parallel "tram tracks" or as the "signet-ring sign"—a cross-sectional area of the airway with a diameter at least 1.5 times that of the adjacent vessel), lack of bronchial tapering (including the presence of tubular structures within 1 cm from the pleural surface), bronchial wall thickening in dilated airways, inspissated secretions (e.g., the "tree-in-bud" pattern), or cysts emanating from the bronchial wall (especially pronounced in cystic bronchiectasis) **(Fig. 284-1)**.

FIGURE 284-1 Representative chest CT image of severe bronchiectasis. This patient's CT demonstrates many severely dilated airways, seen both longitudinally (*arrowhead*) and in cross-section (*arrow*).

APPROACH TO THE PATIENT

Bronchiectasis

The evaluation of a patient with bronchiectasis entails elicitation of a clinical history, chest imaging, and a workup to determine the underlying etiology. Evaluation of focal bronchiectasis almost always requires bronchoscopy to exclude airway obstruction by an underlying mass or foreign body. A workup for diffuse bronchiectasis includes analysis for the major etiologies (Table 284-1), with an initial focus on excluding CF. Pulmonary function testing is an important component of a functional assessment of the patient.

TREATMENT

Bronchiectasis

Treatment of infectious bronchiectasis is directed at the control of active infection and improvements in secretion clearance and bronchial hygiene so as to decrease the microbial load within the airways and minimize the risk of repeated infections.

ANTIBIOTIC TREATMENT

Antibiotics targeting the causative or presumptive pathogen (with *Haemophilus influenzae* and *P. aeruginosa* isolated commonly) should be administered in acute exacerbations, usually for a minimum of 7–10 days and perhaps for as long as 14 days. Decisions about treatment of NTM infection can be difficult, given that these organisms can be colonizers as well as pathogens and the prolonged treatment course often is not well tolerated. Consensus guidelines have advised that diagnostic criteria for true clinical infection with NTM should be considered in patients with symptoms and radiographic findings of lung disease who have at least two sputum samples positive on culture; at least one bronchoalveolar lavage (BAL) fluid sample positive on culture; a biopsy sample displaying histopathologic features of NTM infection (e.g., granuloma or a positive stain for acid-fast bacilli) along with one positive sputum culture; or a pleural fluid sample (or a sample from another sterile extrapulmonary site) positive on culture. MAC strains are the most common NTM pathogens, and the recommended regimen for HIV-negative patients infected with macrolide-sensitive MAC includes a macrolide combined with rifampin and ethambutol. Consensus guidelines recommend macrolide susceptibility testing for clinically significant MAC isolates.

BRONCHIAL HYGIENE

The numerous approaches used to enhance secretion clearance in bronchiectasis include hydration and mucolytic administration, aerosolization of bronchodilators and hyperosmolar agents (e.g., hypertonic saline), and chest physiotherapy (e.g., postural drainage, traditional mechanical chest percussion via hand clapping to the chest, or use of devices such as an oscillatory positive expiratory pressure flutter valve or a high-frequency chest wall oscillation vest). Pulmonary rehabilitation and a regular exercise program may assist with secretion clearance as well as with other aspects of bronchiectasis, including improved exercise capacity and quality of life. The mucolytic dornase (DNase) is recommended routinely in CF-related bronchiectasis but not in non-CF bronchiectasis, given concerns about lack of efficacy and potential harm in the non-CF population.

ANTI-INFLAMMATORY THERAPY

It has been proposed that control of the inflammatory response may be of benefit in bronchiectasis, and relatively small-scale trials have yielded evidence of alleviated dyspnea, decreased need for inhaled β-agonists, and reduced sputum production with inhaled glucocorticoids. However, no significant differences in lung function or bronchiectasis exacerbation rates have been observed. Risks of immunosuppression and adrenal suppression must be carefully considered with use of anti-inflammatory therapy in infectious bronchiectasis. Nevertheless, administration of oral/systemic glucocorticoids may be important in treatment of bronchiectasis due to certain etiologies, such as ABPA, or of noninfectious bronchiectasis due to underlying conditions, especially that in which an autoimmune condition is believed to be active (e.g., rheumatoid arthritis or Sjögren's syndrome). Patients with ABPA may also benefit from a prolonged course of treatment with the oral antifungal agent itraconazole.

REFRACTORY CASES

In select cases, surgery can be considered, with resection of a focal area of suppuration. In advanced cases, lung transplantation can be considered.

COMPLICATIONS

In more severe cases of infectious bronchiectasis, recurrent infections and repeated courses of antibiotics can lead to microbial resistance to antibiotics. In certain cases, combinations of antibiotics that have independent toxicity profiles may be necessary to treat resistant organisms.

Recurrent infections can result in injury to superficial mucosal vessels, with bleeding and, in severe cases, life-threatening hemoptysis. Management of massive hemoptysis usually requires intubation to stabilize the patient, identification of the source of bleeding, and protection of the nonbleeding lung. Control of bleeding often necessitates bronchial artery embolization and, in severe cases, surgery.

PROGNOSIS

Outcomes of bronchiectasis can vary widely with the underlying etiology and comorbid conditions and may also be influenced by the frequency of exacerbations and (in infectious cases) the specific pathogens involved (with worse outcomes associated with *P. aeruginosa* colonization). Increasing attention is being given to defining clinical phenotypes of bronchiectasis in light of clinical, radiographic, and microbial features and to developing screening tools for the assessment of quality of life and disease severity. In one study, the decline of lung function in patients with non-CF bronchiectasis was similar to that in patients with COPD, with the forced expiratory volume in 1 s (FEV_1) declining by 50–55 mL per year as opposed to 20–30 mL per year for healthy controls.

PREVENTION

Reversal of an underlying immunodeficient state (e.g., by administration of gamma globulin for immunoglobulin-deficient patients) and vaccination of patients with chronic respiratory conditions (e.g., influenza and pneumococcal vaccines) can decrease the risk of recurrent infections. Patients who smoke should be counseled about smoking cessation.

After resolution of an acute infection in patients with recurrences (e.g., ≥3 episodes per year), the use of suppressive antibiotics to minimize the microbial load and reduce the frequency of exacerbations has been proposed. Although there is less consensus about this approach in non-CF-associated bronchiectasis than in CF-related bronchiectasis, small studies have supported benefits of selected therapies. Possible suppressive treatments include (1) administration of an oral antibiotic (e.g., ciprofloxacin) daily for 1–2 weeks per month; (2) use of a rotating schedule of oral antibiotics (to minimize the risk of development of drug resistance); (3) administration of a macrolide antibiotic (see below) daily or three times per week (with mechanisms of possible benefit related to non-antimicrobial properties, such as anti-inflammatory effects and reduction of gram-negative bacillary biofilms); (4) inhalation of aerosolized antibiotics (e.g., tobramycin inhalation solution) for select patients on a rotating schedule (e.g., 30 days on, 30 days off), with the goal of decreasing the microbial load without eliciting the side effects of systemic drug administration; and (5) intermittent administration of IV antibiotics (e.g., "clean-outs") for patients with more severe bronchiectasis and/or resistant pathogens. In relation to macrolide therapy (point 3 above), a number of double-blind, placebo-controlled, randomized trials have been published in non-CF bronchiectasis and support a benefit of long-term macrolides (6–12 months of azithromycin or erythromycin) in decreasing rates of bronchiectasis exacerbation,

mucus production, and decline in lung function. However, two of these studies also reported increased macrolide resistance in commensal pathogens, dampening enthusiasm for universal use of macrolides in this setting and raising the question of whether there might be select non-CF bronchiectasis patients with higher morbidity for whom benefits of long-term macrolides might outweigh the risks of emergence of antibiotic resistance. In particular, development of macrolide-resistant NTM is a potential concern, making treatment of those pathogens much more difficult. Furthermore, patients with different patterns of microbial colonization may not all experience similar benefits with macrolide therapy. Therefore, before chronic macrolide therapy is considered, it is advisable to rule out NTM infection and carefully consider each patient's scenario closely, obtaining an electrocardiogram to rule out a prolonged QT interval that might place the patient at increased risk of arrhythmias.

In addition, ongoing consistent attention to bronchial hygiene can promote secretion clearance and decrease the microbial load in the airways.

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285 Cystic Fibrosis

Eric J. Sorscher

CLINICAL FEATURES

Cystic fibrosis (CF) is an autosomal recessive exocrinopathy affecting multiple epithelial tissues. The gene product responsible for CF (the cystic fibrosis transmembrane conductance regulator [CFTR]) serves as an anion channel in the apical (luminal) plasma membranes of epithelial cells and regulates volume and composition of exocrine secretion. An increasingly sophisticated understanding of CFTR molecular genetics and membrane protein biochemistry has facilitated CF drug discovery, with a number of new agents recently approved or advancing through the clinical testing phase.

Respiratory Manifestations The major morbidity and mortality associated with CF is attributable to respiratory compromise, characterized by copious hyperviscous and adherent pulmonary secretions that obstruct small and medium-sized airways. CF airway secretions are exceedingly difficult to clear, and a complex bacterial flora that includes *Staphylococcus aureus, Haemophilus influenzae*, and *Pseudomonas aeruginosa* (among other pathogens) is routinely cultured from CF sputum. Microbiome analysis has identified hundreds of other bacterial species in CF lungs, although their relationship to pulmonary failure remains to be determined. Robust pulmonary inflammation in the setting of inspissated mucus and chronic bacterial infection leads to collateral tissue injury and further aggravates respiratory decline. Organisms such as *P. aeruginosa* exhibit a stereotypic mode of pathogenesis; a sentinel and early colonization event often engenders lifelong pulmonary infection by the same genetic strain. Over a period of many years, *P. aeruginosa* evolves in CF lungs to adopt a mucoid phenotype (attributable to release of alginate exoproduct) that confers selective advantage for the pathogen and poor prognosis for the host. Strategies to eradicate *P. aeruginosa* early in the course of disease have been successful and are thought to improve prognosis significantly if sustained.

Pancreatic Findings The complete name of the disease, *cystic fibrosis of the pancreas*, refers to profound tissue destruction of the exocrine pancreas, with fibrotic scarring and/or fatty replacement, cyst proliferation, loss of acinar tissue, and ablation of normal pancreatic architecture. As in the lung, tenacious exocrine secretions (sometimes termed *concretions*) obstruct pancreatic ducts and impair production and flow of digestive enzymes to the duodenum. The sequelae of exocrine pancreatic insufficiency include chronic malabsorption, poor growth, fat-soluble vitamin insufficiency, high levels of serum immunoreactive trypsinogen (a diagnostic test used in newborn screening), and loss of pancreatic islet cell mass. CF-related diabetes mellitus is a manifestation in over 30% of adults with the disease and is likely multifactorial in nature (attributable to progressive destruction of the endocrine pancreas, insulin resistance due to stress hormones, and additional factors).

Other Organ System Damage As in CF lung and pancreas, thick and tenacious secretions compromise numerous other exocrine tissues. Obstruction of intrahepatic bile ducts and parenchymal fibrosis are commonly observed in pathologic specimens, with multilobular cirrhosis in 4–15% of patients with CF and significant hepatic insufficiency as a resulting manifestation among adults. Contents of the intestinal lumen are often difficult to excrete, leading to meconium ileus (a presentation in 10–20% of newborns with CF) or distal intestinal obstructive syndrome in older individuals. Men typically exhibit complete involution of the vas deferens and infertility (despite functioning spermatogenesis), and ~99% of males with CF are infertile. The etiology of this dramatic anatomic defect in the male genitourinary system is not understood but may represent a developmental abnormality secondary to improper secretion by the vas or associated structures. Abnormalities of female reproductive tract secretions are likely contributors to an increased incidence of infertility among women with the disease. Radiographic evidence of sinusitis occurs in most CF patients and is associated with pathogens similar to those recovered from lower airways, suggesting that the sinus may serve as a reservoir for bacterial seeding.

PATHOGENESIS

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) CFTR is an integral membrane protein that functions as an epithelial anion channel. The ~1480-amino-acid molecule encodes a passive conduit for chloride and bicarbonate transport across plasma membranes of epithelial tissues, with direction of ion flow dependent on the electrochemical driving force. Gating of CFTR involves conformational cycling between an open and closed configuration and is augmented by hydrolysis of adenosine triphosphate (ATP). Anion flux mediated by CFTR does not involve active transport against a concentration gradient but utilizes the energy provided from ATP hydrolysis as a central feature of ion channel mechanochemistry and gating.

CFTR is situated in the apical plasma membranes of acinar and other epithelial cells where it regulates the amount and composition of secretion by exocrine glands. In numerous epithelia, chloride and bicarbonate release is followed passively by the flow of water, allowing for mobilization and clearance of exocrine products. Along respiratory mucosa, CFTR is necessary to provide sufficient depth of the periciliary fluid layer (PCL), allowing normal ciliary extension and mucociliary transport. CFTR-deficient airway cells exhibit depleted PCL, causing ciliary collapse and failure to clear overlying mucus **(Video 285-1)**. In airway submucosal glands, CFTR is highly expressed in acini and may participate both in the formation of mucus and extrusion of glandular secretion onto the airway surface **(Fig. 285-1)**. In other exocrine glands characterized by abrogated mucus transport (e.g., pancreatic acini and ducts, as well as bile canaliculi, intestinal lumen), similar pathogenic mechanisms have been implicated. In these tissues, a driving force for apical chloride and/or bicarbonate secretion is believed to promote CFTR-mediated fluid and electrolyte release into the lumen, which

FIGURE 285-1 Extrusion of mucus secretion onto the epithelial surface of airways in cystic fibrosis (CF). ***A.*** Schematic of the surface epithelium and supporting glandular structure of the human airway. ***B.*** The submucosal glands of a patient with CF are filled with mucus, and mucopurulent debris overlies the airway surfaces, essentially burying the epithelium. ***C.*** A higher magnification view of a mucus plug tightly adhering to the airway surface, with *arrows* indicating the interface between infected and inflamed secretions and the underlying epithelium to which the secretions adhere. (Both ***B*** and ***C*** were stained with hematoxylin and eosin, with the colors modified to highlight structures.) Infected secretions obstruct airways and, over time, dramatically disrupt the normal architecture of the lung. ***D.*** CFTR is expressed in surface epithelium and serous cells at the base of submucosal glands in a porcine lung sample, as shown by the dark staining, signifying binding by CFTR antibodies to epithelial structures (aminoethylcarbazole detection of horseradish peroxidase with hematoxylin counterstain). *(From SM Rowe, S Miller, EJ Sorscher: N Engl J Med 352:1992, 2005.)*

confers proper rheology of mucins and other exocrine products. Failure of this mechanism disrupts normal hydration and transport of glandular secretion and is widely viewed as a proximate cause of obstruction, with concomitant tissue injury.

Pulmonary Inflammation and Remodeling The CF airway is characterized by an aggressive, unrelenting, neutrophilic inflammatory response with release of proteases and oxidants leading to airway remodeling and bronchiectasis. Intense pulmonary inflammation is largely driven by chronic respiratory infection. Macrophages and other cells resident in CF lungs augment elaboration of proinflammatory cytokines, which contribute to innate and adaptive immune reactivity. CFTR-dependent abnormalities of airway surface fluid composition (e.g., pH) have been reported as contributors to impaired bacterial killing in CF lungs. The role of CFTR as a direct mediator of inflammatory responsiveness and/or pulmonary remodeling represents an important and topical area of investigation.

MOLECULAR GENETICS

DNA sequencing of *CFTR* from patients (and others) worldwide has revealed almost 2000 allelic variants; several hundred of these have been well-characterized as disease-causing mutations. Distinguishing the single nucleotide transversions or other polymorphisms with causal relevance can sometimes present a significant challenge. The CFTR2 resource (*www.cftr2.org/*) delineates gene variants with a clear etiologic role.

CFTR defects known to elicit disease are often categorized based on molecular mechanism. For example, the common F508del mutation (nomenclature denotes omission of a single phenylalanine residue [F] at CFTR position 508) leads to a folding abnormality recognized by cellular quality control pathways. CFTR encoding F508del retains partial ion channel function, but protein maturation is arrested in the endoplasmic reticulum, and CFTR fails to arrive at the plasma membrane. Instead, F508del CFTR is misrouted and undergoes endoplasmic reticulum–associated degradation via the proteasome. CFTR mutations that disrupt protein maturation are termed class II defects and are by far the most common genetic abnormalities. F508del alone accounts for ~70% of defective *CFTR* alleles in the United States, where ~90% of individuals with CF carry at least one F508del mutation.

Other gene defects include CFTR ion channels properly trafficked to the apical cell surface but unable to open and/or gate. Such channel proteins include G551D (a glycine to aspartic acid replacement at CFTR position 551), which leads to an inability to transport Cl^- or HCO_3^- in the presence of ATP (a class III abnormality). Individuals with at least one G551D allele represent 4–5% of CF patients in North America. *CFTR* nonsense alleles such as G542X, R553X, and W1282X (premature termination codon replaces glycine, arginine, or tryptophan at positions 542, 553, or 1282, respectively) are among the common class I defects, in addition to large deletions or other major disruptions of the gene. The W1282X mutation, for example, is prevalent among individuals of Ashkenazi descent and is a predominant CF genotype in Israel. Additional categories of *CFTR* mutation include defects in the ion channel pore (class IV), RNA splicing (class V), and increased plasma membrane turnover (class VI) **(Fig. 285-2)**.

DIAGNOSIS

During the past decade, newborn screening has led to most CF diagnoses, with confirmation through *CFTR* mutation analysis and sweat electrolyte measurements as cardinal diagnostic tests. DNA-based evaluation typically surveys numerous disease-associated mutations; panels that identify on the order of 20–140 CFTR variants are available through a variety of public health laboratories and commercial sources. For difficult cases, complete *CFTR* exonic sequencing together with analysis of splice junctions and key regulatory elements can be obtained.

Sweat electrolytes following pilocarpine iontophoresis continue to comprise an essential diagnostic element, with levels of chloride markedly elevated in CF compared to non-CF individuals. The sweat test result is highly specific and served as a mainstay of diagnosis for many decades prior to availability of *CFTR* genotyping. Notably, hyperviscosity of eccrine sweat is not a clinical feature of the disease. Sweat ducts function to reabsorb chloride from a primary sweat secretion produced by the glandular coil. Malfunction of CFTR leads to diminished chloride uptake from the ductular lumen, and sweat

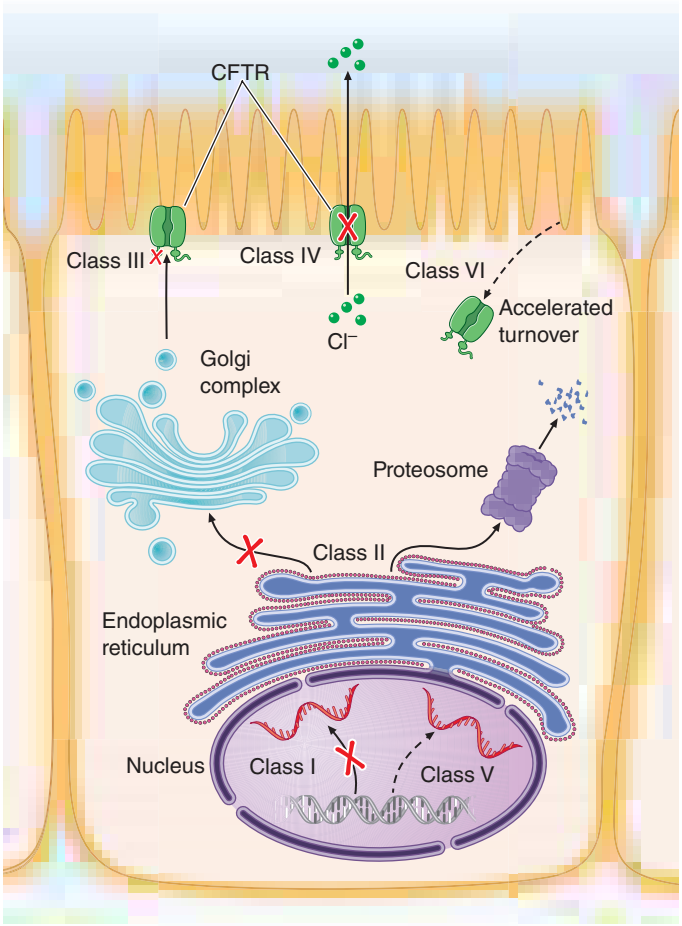

FIGURE 285-2 Categories of *CFTR* mutations. Classes of defects in the *CFTR* gene include the absence of synthesis (class I); defective protein maturation and premature degradation (class II); disordered gating/regulation, such as diminished adenosine triphosphate (ATP) binding and hydrolysis (class III); defective conductance through the ion channel pore (class IV); a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI). *(From SM Rowe, S Miller, EJ Sorscher: N Engl J Med 352:1992, 2005.)*

emerges on the skin with markedly elevated levels of chloride. For the unusual situation in which both *CFTR* genotype and sweat electrolytes are inconclusive, in vivo measurement of ion transport across the nasal airways can serve as a specific test for CF and is used by a number of referral centers. For example, elevated (sodium-dependent) transepithelial charge separation across airway epithelial tissue and persistent failure of isoproterenol-dependent chloride secretion (via CFTR) represent bioelectric findings specific for the disease. Measurements of CFTR activity in excised rectal mucosal biopsies can also be obtained.

COMPLEXITY OF A CF PHENOTYPE

CF classically presents in childhood with chronic productive cough, malabsorption including steatorrhea, and failure to thrive. The disease is most common among whites (~1 in 3300 live births) and much less frequent among African-American (~1 in 10,000) or Asian populations (~1 in 33,000). Several "severe" defects that impair CFTR activity (including F508del, G551D, and truncation alleles) are predictive of pancreatic insufficiency, which is clinically evident in 80–90% of individuals with CF. These few genotype-phenotype correlations notwithstanding, genotype is, in general, a poor predictor of overall respiratory prognosis.

A spectrum of CFTR-related diseases with features resembling classic CF has been well described. In addition to multiorgan involvement, forme frustes, such as isolated congenital bilateral absence of the vas deferens or pancreatitis (without other organ system findings), are strongly associated with *CFTR* mutations in at least one allele. Although CF is a classic monogenic disease, the importance of non-*CFTR* gene modifiers and proteins that regulate ion flux, inflammatory pathways, and airway remodeling has been increasingly appreciated as influencing clinical course. For example, the magnitude of transepithelial sodium reabsorption in CF airways, which helps control periciliary fluid depth and composition, is strongly influenced by CFTR and represents a molecular target for disease intervention.

THERAPEUTICS DIRECTED TOWARD CF SEQUELAE

Chronic Management Standard care for outpatients with CF is intensive, with regimens that include exogenous pancreatic enzymes taken with meals, nutritional supplementation, anti-inflammatory medication, bronchodilators, and chronic or periodic administration of oral or aerosolized antibiotics (e.g., as maintenance therapy for patients with *P. aeruginosa*). Recombinant DNAse aerosols (degraded DNA strands that contribute to mucus viscosity) and nebulized hypertonic saline (serves to augment PCL depth, activate mucociliary clearance, and mobilize inspissated airway secretions) are administered routinely. Chest physiotherapy several times each day is a standard means to promote clearance of airway mucus. Among adults with CF, malabsorption, chronic inflammation, and endocrine abnormalities can lead to poor bone mineralization, requiring treatment with vitamin D, calcium, and other measures. The time, complexity, and expense of home care are considerable and take a significant toll on patients and their families. Improved treatments directed toward nutritional deficits, pulmonary inflammation, mucostasis, and other sequelae therefore remain a high priority in the field.

Pulmonary Exacerbation Severe respiratory exacerbation is commonly managed by hospital admission for frequent chest physiotherapy and parenteral antibiotics directed against serious (and often multiply resistant) bacterial pathogens. Aggressive intervention in this setting can restore a large component of lung function, but ongoing and cumulative loss of pulmonary reserve reflects the natural history of the disease. Poor prognostic indicators such as sputum culture containing *Burkholderia cepacia* complex, mucoid *P. aeruginosa*, or atypical mycobacteria are rigorously monitored in the CF patient population. An increasing incidence of methicillin-resistant *S. aureus* has also been observed, although the clinical significance of this finding has not been fully elucidated. Typical inpatient antibiotic coverage includes combination drug therapy with an aminoglycoside and β-lactam for at least 14 days. Maximal improvement in lung function is often achieved by 8–10 days in this setting. Many families elect parenteral antibiotic treatment at home, and additional studies are needed to evaluate specific drug combinations, duration of therapy, and home versus inpatient management. Other CF respiratory sequelae that may require hospitalization include hemoptysis and pneumothorax. Hypersensitivity to *Aspergillus* (allergic bronchopulmonary aspergillosis) occurs in ~5% of individuals with the disease and should be suspected in the absence of a response to conventional treatment.

Considerations Regarding Lung Transplantation In the setting of end-stage CF pulmonary failure, lung transplantation is a viable therapeutic option with 5-year survival rates on the order of 60% and median survival >8 years. Determining the optimal timing for surgery presents a substantial challenge, particularly because overall prognosis for individuals with severe lung disease is sometimes difficult to predict, and mortality associated with transplantation can be significant. Forced expiratory volume in 1s (FEV_1) measurements <30% predicted, together with an assortment of other clinical parameters (hospitalization frequency, need for supplemental oxygen, etc.), are often used as thresholds for entry onto transplantation lists, although waiting periods for healthy donor lungs can be quite protracted. Based on clinical outcome and other features, CF patients and their families sometimes do not pursue this option. The decision is best approached through consultation with health care providers specializing in both CF clinical management and transplantation.

CFTR MODULATION

Potentiation of Mutant CFTR Gating A massive effort directed toward high-throughput drug analysis of large compound libraries (containing millions of individual agents) has identified novel and promising approaches to CF therapy. The approved compound ivacaftor, for example, robustly potentiates CFTR channel opening and stimulates ion transport. Ivacaftor overcomes the G551D CFTR gating defect, and individuals carrying this mutation exhibit pronounced improvement in lung function, weight gain, and other clinical benefit after only a few weeks of oral therapy. Remarkably, sweat chloride values are significantly reduced. Prior to ivacaftor, no clinical intervention of any sort had been shown to normalize the CF sweat abnormality. Partial function CFTR variants (in addition to G551D) for which ivacaftor has recently been approved include numerous other genotypes, with the list of registered indications expected to increase. Chronic administration studies of the drug are ongoing, and indicate significant benefit in terms of respiratory function and other clinical parameters. Ivacaftor has been viewed as the harbinger of a new era for CF therapeutics directed at treating the most fundamental causes of the disease.

Correction of the F508del Processing Abnormality Advancement of new drugs that address specific CFTR defects in protein folding and maturation has been bolstered by clinical studies of F508del rescue in combination with ivacaftor. Lumacaftor, the first FDA approved "corrector" molecule (as distinct from a CFTR gating "potentiator" such as ivacaftor) partially overcomes defective F508del CFTR biogenesis, and was discovered through compound library screening. The drug promotes cell surface localization of F508del protein. A dual formulation with ivacaftor confers improvement in pulmonary function among F508del homozygous individuals (~45% of the U.S. CF population). The combination of lumacaftor with ivacaftor has been associated with several important pharmacologic interactions, including those mediated by CYP3A, and diminished activity of oral contraceptives. A chest discomfort syndrome and dyspnea are also well-described.

Personalized Molecular Therapies The advent of CFTR modulators with robust clinical impact has engendered new optimism regarding care of patients with CF. It is clear that future interventions will be tailored to specific genotypic abnormalities. Drug screening campaigns and other research programs have identified agents capable of suppressing CFTR nonsense alleles, augmenting potentiator activity, and further promoting F508del correction. Efforts to apply emerging compounds in a fashion that will benefit the ~90% of CF subjects carrying at least one copy of F508del (i.e., with F508del or a different *CFTR* mutation on the second allele) comprise an essential priority for the future. Several new molecules in combination with ivacaftor or other CFTR modulators are under evaluation as part of multi-center efficacy trials for this purpose.

Progress in CF drug discovery is emblematic of what might be accomplished in numerous refractory inherited diseases using an approach grounded in molecular mechanism and unbiased compound library screening. Genetic manipulation (CFTR gene transfer, genome editing, etc.) represents an alternative strategy less dependent on the specific defect, and potentially applicable to diverse CF variants. Such an approach in CF will require efficient and safe in vivo delivery strategies, particularly those addressing clinically prominent lung disease.

Challenges to Precision CF Therapeutics Because hundreds of CF defects are very rare (or even "private," e.g., reported in only one individual or family), detailed molecular profiling (ion transport behavior, protein folding/biogenesis, response to emerging CFTR modulators, etc.) represents an essential scientific objective. In contrast to the classic and invaluable paradigm of tailored therapeutics (Fig. 285-2, and above), a sizable majority of CF variants do not fall into a single diagnostic category. F508del CFTR, for example, predominately displays abnormalities of maturational processing (class II), but also exhibits more subtle defects related to channel activity/gating (class III) and instability at the plasma membrane (class VI). Comprehensive molecular analysis for hundreds of rare CFTR variants will help guide therapeutics, and may be especially important given the high cost of drugs such as ivacaftor and lumacaftor. Expense of these compounds has often restricted third-party reimbursement to include only the specific genotypes for which FDA approval has been obtained. As a consequence, patient access to potentially efficacious agents (and off-label prescribing) is largely precluded. Moreover, clinical trials intended to expand drug label are difficult based on the small numbers of patients carrying ultra-rare alleles. Similar challenges to drug access have been noted in numerous other settings for which precision medicine has become a therapeutic priority.

CF QUALITY IMPROVEMENT

As a direct result of advances in basic research, new therapies have transformed CF from a disease typically leading to death in early childhood to a condition with frequent survival well into the fourth decade of life. It has also become increasingly clear that carefully specified approaches to patient management can have an impact on overall prognosis. For example, standardization of clinical intervention throughout the United States has led to remarkable benefit among the CF population. Well-defined measures for outpatient care are now established, including thresholds for hospital admission, antibiotic regimens, nutritional guidelines, periodicity of diagnostic tests, and other clinical parameters. These recommendations have become standard throughout specialized CF care centers and other accredited programs. The initiative has improved endpoints such as weight gain, body mass index, and pulmonary function. Information regarding standardized protocols for CF therapy can be accessed at *www.cff.org/treatments/cfcareguidelines/* or through a number of excellent reviews.

GLOBAL CONSIDERATIONS

Newborn screening for CF is universal throughout the United States, most of the Canadian provinces, Australia, New Zealand, and much of Europe, and will facilitate early CF intervention. Based on data indicating that early nutritional and other therapies can be beneficial, newborn diagnosis is expected to significantly promote health among those with the disease. Implementation of quality improvement measures and novel therapeutics worldwide has become an increasing imperative. For example, median survival among individuals with CF is ~20 years in much of Latin America (compared to >40 years in the United States). The less favorable prognosis is attributable in part to lack of widespread diagnostic testing (newborn screening, sweat and genetic evaluation) and insufficient access to leading-edge, interdisciplinary CF care. Efforts to apply state-of-the-art management to underdiagnosed and underserved CF patient populations are expected to improve outcomes and mitigate CF health disparities in the future.

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VIDEO 285-1 Initial video sequences describe establishment of the normal periciliary fluid layer bathing the surface airway epithelium, with spheres representing chloride and bicarbonate ions secreted through CFTR and across the apical (mucosal) respiratory surface. Later video sequences depict failure of CFTR anion transport and resulting depletion of the periciliary layer, "plastering" of cilia against the mucosal surface, and accumulation of mucus in the airway with resulting bacterial infection. *(Video courtesy of the Cystic Fibrosis Foundation.)*

286 Chronic Obstructive Pulmonary Disease

Edwin K. Silverman, James D. Crapo, Barry J. Make

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible (*http://www.goldcopd.com/*). COPD includes *emphysema*, an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement; *chronic bronchitis*, a clinically defined condition with chronic cough and phlegm; and *small airway disease*, a condition in which small bronchioles are narrowed and reduced in number. The classic definition of COPD requires the presence of chronic airflow obstruction, determined by spirometry, that usually occurs in the setting of noxious environmental exposures—most commonly cigarette smoking. Emphysema, chronic bronchitis, and small airway disease are present in varying degrees in different COPD patients. Patients with a history of cigarette smoking without chronic airflow obstruction may have chronic bronchitis, emphysema, and dyspnea. Although these patients are not included within the classic definition of COPD, they may have similar disease processes. Respiratory symptoms and other features of COPD can occur in subjects who do not meet a definition of COPD based only on airflow obstruction determined by spirometric thresholds of normality.

COPD is the third leading cause of death and affects >10 million persons in the United States. COPD is also a disease of increasing public health importance around the world. Estimates suggest that COPD will rise to the third most common cause of death worldwide by 2020.

PATHOGENESIS

Airflow limitation, a major physiologic change in COPD, can result from small airway disease and/or emphysema. Small airways may become narrowed by cells (hyperplasia and accumulation), mucus, and fibrosis, and extensive small airway destruction has been demonstrated to be a hallmark of advanced COPD. Although the precise biological mechanisms leading to COPD have not been determined, a number of key cell types, molecules, and pathways have been identified from cell-based and animal model studies. The pathogenesis of emphysema (shown in Fig. 286-1) is more clearly defined than the pathogenesis of

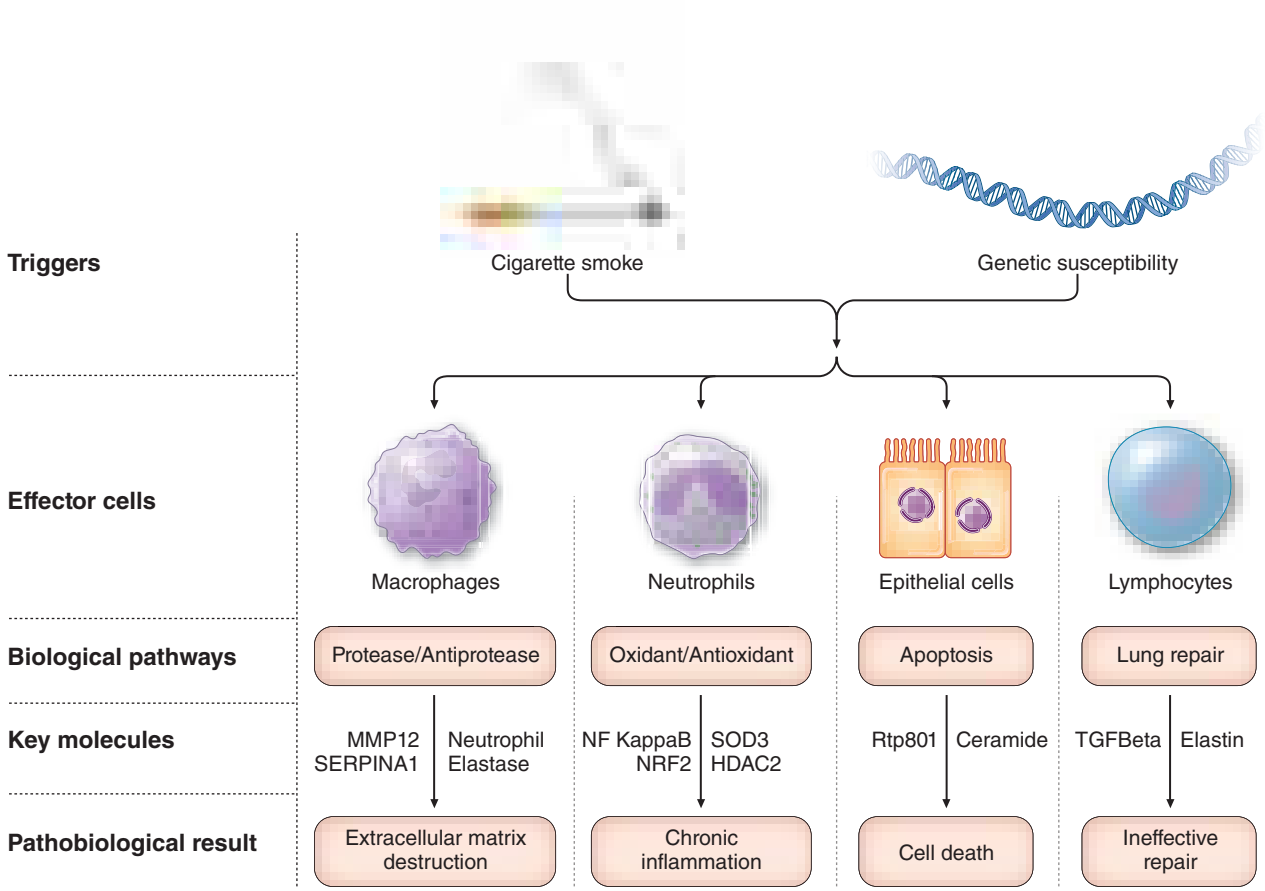

FIGURE 286-1 Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke in genetically susceptible individuals, lung epithelial cells and T and B lymphocytes recruit inflammatory cells to the lung. Biological pathways of protease-antiprotease imbalance, oxidant/antioxidant imbalance, apoptosis, and lung repair lead to extracellular matrix destruction, cell death, chronic inflammation, and ineffective repair. Although most of these biological pathways influence multiple pathobiological results, only a single relationship between pathways and results is shown. A subset of key molecules related to these biological pathways is listed.

small airway disease. Pulmonary vascular destruction occurs in concert with small airway disease and emphysema.

The dominant current paradigm for the pathogenesis of emphysema comprises a series of four interrelated events: (1) Chronic exposure to cigarette smoke in genetically susceptible individuals triggers inflammatory and immune cell recruitment within large and small airways and in the terminal air spaces of the lung. (2) Inflammatory cells release proteinases that damage the extracellular matrix supporting airways, vasculature, and gas exchange surfaces of the lung. (3) Structural cell death occurs through oxidant-induced damage, cellular senescence, and proteolytic loss of cellular-matrix attachments leading to extensive loss of smaller airways, vascular pruning, and alveolar destruction. (4) Disordered repair of elastin and other extracellular matrix components contributes to air space enlargement and emphysema.

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

Elastin, the principal component of elastic fibers, is a highly stable component of the extracellular matrix that is critical to the integrity of the lung. The elastase:antielastase hypothesis, proposed in the mid-1960s, postulated that the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction resulting in air space enlargement. This hypothesis was based on the clinical observation that patients with genetic deficiency in α_1 antitrypsin (α_1AT), the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema, and that instillation of elastases, including neutrophil elastase, into experimental animals, results in emphysema. The elastase:antielastase hypothesis remains a prevailing mechanism for the development of emphysema. However, a complex network of immune and inflammatory cells and additional proteinases that contribute to emphysema has subsequently been identified. Upon exposure to oxidants from cigarette smoke, lung macrophages and epithelial cells become activated, producing proteinases and chemokines that attract other inflammatory and immune cells. Oxidative stress is a key component of COPD pathobiology; the transcription factor NRF2, a major regulator of oxidant-antioxidant balance, and SOD3, a potent antioxidant, have been implicated in emphysema pathogenesis by animal models. Mitochondrial dysfunction in COPD may worsen oxidative stress. One mechanism of macrophage activation occurs via oxidant-induced inactivation of histone deacetylase-2 (HDAC2), shifting the balance toward acetylated or loose chromatin, exposing nuclear factor-kappaB sites, and resulting in transcription of matrix metalloproteinases and proinflammatory cytokines such as interleukin 8 (IL-8) and tumor necrosis factor α (TNF-α); this leads to neutrophil recruitment. CD8+ T cells are also recruited in response to cigarette smoke and release interferon-inducible protein-10 (IP-10, CXCL-7), which in turn leads to macrophage production of macrophage elastase (matrix metalloproteinase-12 [MMP-12]).

Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin serve as a macrophage chemokine, and proline-glycine-proline (generated by proteolytic cleavage of collagen) is a neutrophil chemokine—fueling this destructive positive feedback loop. Elastin degradation and disordered repair are thought to be primary mechanisms in the development of emphysema.

There is some evidence that autoimmune mechanisms may promote the progression of disease. Increased B cells and lymphoid follicles are present around the airways of COPD patients, particularly those with advanced disease. Antibodies have been found against elastin fragments as well; IgG autoantibodies with avidity for pulmonary epithelium and the potential to mediate cytotoxicity have been detected.

Concomitant cigarette smoke–induced loss of cilia in the airway epithelium and impaired macrophage phagocytosis predispose to bacterial infection with neutrophilia. In end-stage lung disease, long after smoking cessation, there remains an exuberant inflammatory response, suggesting that cigarette smoke–induced inflammation both initiates the disease and, in susceptible individuals, establishes a chronic process that can continue disease progression even after smoking cessation.

Cell Death Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms including excessive ceramide production and Rtp801 inhibition of mammalian target of rapamycin (mTOR), leading to cell death as well as inflammation and proteolysis. Involvement of mTOR and other senescence markers has led to the concept that emphysema resembles premature aging of the lung. Heterozygous gene-targeting of one of the leading genetic determinants of COPD identified by genome-wide association studies (GWAS), hedgehog interacting protein (*HHIP*), in a murine model leads to aging-related emphysema.

Ineffective Repair The ability of the adult lung to replace lost smaller airways and microvasculature and to repair damaged alveoli appears limited. Uptake of apoptotic cells by macrophages normally results in production of growth factors and dampens inflammation, promoting lung repair. Cigarette smoke impairs macrophage uptake of apoptotic cells, limiting repair. It is unlikely that the intricate and dynamic process of septation that is responsible for alveologenesis during lung development can be reinitiated in the adult human lung.

PATHOLOGY

Cigarette smoke exposure may affect the large airways, small airways (≤2 mm diameter), and alveoli. Changes in large airways cause cough and sputum production, while changes in small airways and alveoli are responsible for physiologic alterations. Airway inflammation, destruction, and the development of emphysema are present in most persons with COPD; however, they appear to be relatively independent processes, and their relative contributions to obstruction vary from one person to another. The early stages of COPD, based on the severity of airflow obstruction **(Table 286-1)**, appear to be primarily associated with medium and small airway disease with the majority of Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1 and GOLD 2 subjects demonstrating little or no emphysema. The early development of chronic airflow obstruction is driven by small airway disease. Advanced stages of COPD (GOLD 3 and 4) are typically characterized by extensive emphysema, although there are a small number of subjects with very severe (GOLD 4) obstruction with virtually no emphysema. The subjects at greatest risk of progression in COPD are those with both aggressive airway disease and emphysema. Thus, finding emphysema (by chest CT) either early or late in the disease process suggests enhanced risk for disease progression.

LARGE AIRWAYS

Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production that define chronic bronchitis, but these abnormalities are not related to airflow limitation. In response to cigarette smoking, goblet cells not only increase in number but in extent through the bronchial tree. Bronchi also undergo squamous metaplasia, predisposing to carcinogenesis and disrupting mucociliary clearance. Although not as prominent as in asthma, patients may have smooth-muscle hypertrophy and bronchial hyperreactivity leading to airflow limitation. Neutrophil influx has been associated with purulent sputum during respiratory tract

TABLE 286-1 GOLD Criteria for Severity of Airflow Obstruction in COPD

GOLD STAGE	SEVERITY	SPIROMETRY
I	Mild	FEV_1/FVC <0.7 and FEV_1 ≥80% predicted
II	Moderate	FEV_1/FVC <0.7 and FEV_1 ≥50% but <80% predicted
III	Severe	FEV_1/FVC <0.7 and FEV_1 ≥30% but <50% predicted
IV	Very severe	FEV_1/FVC <0.7 and FEV_1 <30% predicted

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Source: Reproduced with permission from the Global Strategy for Diagnosis, Management and Prevention of COPD 2014, © Global Initiative for Chronic Obstructive Lung Disease (GOLD), all rights reserved. Available from *http://www.goldcopd.org*.

infections. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

SMALL AIRWAYS

The major site of increased resistance in most individuals with COPD is in airways ≤2 mm diameter. Characteristic cellular changes include goblet cell metaplasia, with these mucus-secreting cells replacing surfactant-secreting Club cells. Smooth-muscle hypertrophy may also be present. Luminal narrowing can occur by fibrosis, excess mucus, edema, and cellular infiltration. Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around alveolar entrances. Narrowing and drop-out of small airways precede the onset of emphysematous destruction. Advanced COPD has been shown to be associated with a loss of many of the smaller airways and a similar significant loss of the lung microvasculature.

LUNG PARENCHYMA

Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Their walls become perforated and later obliterated with coalescence of the delicate alveolar structure into large emphysematous air spaces. Large numbers of macrophages accumulate in respiratory bronchioles of essentially all smokers. Bronchoalveolar lavage fluid from such individuals contains roughly five times as many macrophages as lavage from nonsmokers. Neutrophils and T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers.

Emphysema is classified into distinct pathologic types, which include centrilobular, panlobular, and paraseptal **(Fig 286-2)**. *Centrilobular emphysema*, the type most frequently associated with cigarette smoking, is characterized by enlarged air spaces found (initially) in association with respiratory bronchioles. Centrilobular emphysema is usually most prominent in the upper lobes and superior segments of lower lobes and is often quite focal. *Panlobular emphysema* refers to abnormally large air spaces evenly distributed within and across acinar units. Panlobular emphysema is commonly observed in patients with α_1AT deficiency, which has a predilection for the lower lobes. Paraseptal emphysema occurs in 10–15% of cases and is distributed along the pleural margins with relative sparing of the lung core or central regions. It is commonly associated with significant airway inflammation and with centrilobular emphysema.

PATHOPHYSIOLOGY

Persistent reduction in forced expiratory flow rates is the most typical finding in COPD. Increases in the residual volume and the residual volume/total lung capacity ratio, non-uniform distribution of ventilation, and ventilation-perfusion mismatching also occur.

AIRFLOW OBSTRUCTION

Airflow limitation, also known as airflow obstruction, is typically determined for clinical purposes by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity. Key parameters obtained from spirometry include the volume of air exhaled within the first second of the forced expiratory maneuver (FEV_1) and the total volume of air exhaled during the entire spirometric maneuver (forced vital capacity [FVC]). Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV_1/FVC. In contrast to asthma, the reduced FEV_1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common.

HYPERINFLATION

Lung volumes are also routinely assessed in pulmonary function testing. In COPD there is often "air trapping" (increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation (increased total lung capacity) late in the disease. Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases.

Despite compensating for airway obstruction, hyperinflation can push the diaphragm into a flattened position with a number of adverse effects. First, by decreasing the zone of apposition between the diaphragm and the abdominal wall, positive abdominal pressure during inspiration is not applied as effectively to the chest wall, hindering rib cage movement and impairing inspiration. Second, because the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, they are less capable of generating inspiratory pressures than normal. Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing. Fourth, the thoracic cage is distended beyond its normal resting volume and during tidal breathing the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation instead of gaining the normal assistance from the chest wall recoiling outward toward its resting volume.

GAS EXCHANGE

Although there is considerable variability in the relationships between the FEV_1 and other physiologic abnormalities in COPD, certain generalizations may be made. The partial pressure of oxygen in arterial blood Pao_2 usually remains near normal until the FEV_1 is decreased to ~50% of predicted, and even much lower FEV_1 values can be associated with a normal Pao_2, at least at rest. An elevation of arterial level of carbon dioxide ($Paco_2$) is not expected until the FEV_1 is <25% of predicted and even then may not occur. Pulmonary hypertension severe enough to cause cor pulmonale and right ventricular failure due to COPD typically occurs in individuals who have marked decreases in FEV_1 (<25% of predicted) and chronic hypoxemia (Pao_2 <55 mmHg); however, recent evidence suggests that some patients will develop significant pulmonary hypertension independent of COPD severity **(Chap. 277)**.

Non-uniform ventilation and ventilation-perfusion mismatching are characteristic of COPD, reflecting the heterogeneous nature of the disease process within the airways and lung parenchyma. Physiologic studies are consistent with multiple parenchymal compartments having different rates of ventilation due to regional differences in compliance and airway resistance. Ventilation-perfusion mismatching accounts for essentially all of the reduction in Pao_2 that occurs in COPD; shunting is minimal. This finding explains the effectiveness of modest elevations of

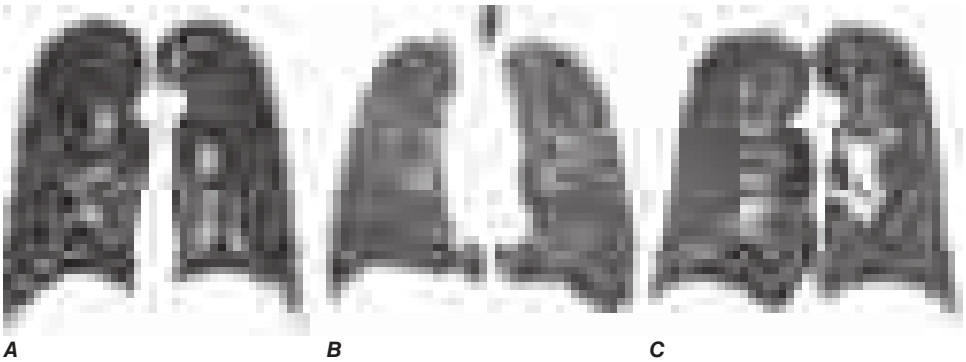

FIGURE 286-2 CT patterns of emphysema. ***A.*** Centrilobular emphysema with severe upper lobe involvement in a 68-year-old man with a 70 pack-year smoking history but forced expiratory volume (FEV_1) 81% predicted (GOLD spirometry grade 1); ***B.*** Panlobular emphysema with diffuse loss of lung parenchymal detail predominantly in the lower lobes in a 64-year-old man with severe α_1AT deficiency; and ***C.*** Paraseptal emphysema with marked airway inflammation in a 52-year-old woman with a 37 pack-year smoking history and FEV_1 40% predicted.

inspired oxygen in treating hypoxemia due to COPD and therefore the need to consider problems other than COPD when hypoxemia is difficult to correct with modest levels of supplemental oxygen.

RISK FACTORS

CIGARETTE SMOKING

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent longitudinal studies have shown accelerated decline in FEV_1 in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts, at least in part, for the higher prevalence rates of COPD with increasing age. The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males; however, the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

Although the causal relationship between cigarette smoking and the development of COPD has been absolutely proved, there is considerable variability in the response to smoking. Pack-years of cigarette smoking is the most highly significant predictor of FEV_1 **(Fig. 286-3)**, but only 15% of the variability in FEV_1 is explained by pack-years. This finding suggests that additional environmental and/or genetic factors contribute to the impact of smoking on the development of chronic airflow obstruction. Nonetheless, many patients with a history of cigarette smoking with normal spirometry have evidence for worse health-related quality of life, reduced exercise capacity, and emphysema and/or airway disease on chest CT evaluation; thus, they have not escaped the harmful effects of cigarette smoking. While they do not meet the classic definition of COPD based on population normals for FEV_1 and FEV_1/FVC, studies have shown that these subjects overall have a shift toward lower FEV_1 values, which is consistent with obstruction on an individual level.

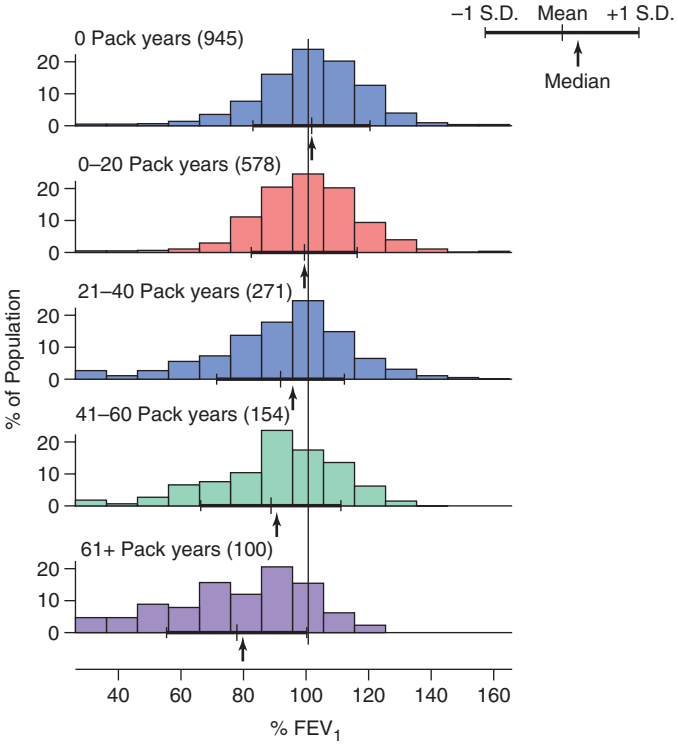

FIGURE 286-3 Distributions of forced expiratory volume in 1 s (FEV_1) values in a general population sample, stratified by pack-years of smoking. Means, medians, and ±1 standard deviation of percent predicted FEV_1 are shown for each smoking group. Although a dose-response relationship between smoking intensity and FEV_1 was found, marked variability in pulmonary function was observed among subjects with similar smoking histories. *(From B Burrows et al: Am Rev Respir Dis 115:95, 1977; with permission.)*

Although cigar and pipe smoking may also be associated with the development of COPD, the evidence supporting such associations is less compelling, likely related to the lower dose of inhaled tobacco by-products during cigar and pipe smoking. The impact of electronic cigarettes (e-cigarettes) on the development and progression of COPD has not yet been determined.

AIRWAY RESPONSIVENESS AND COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma **(Chap. 281)**. However, many patients with COPD also share this feature of airway hyperresponsiveness. In older subjects, there is considerable overlap between persons with a history of chronic asthma and smokers with COPD in terms of airway responsiveness, airflow obstruction, and pulmonary symptoms. The origin of asthma is viewed as an allergic disease while COPD is thought to primarily result from smoking-related inflammation and damage; however, they likely share common environmental and genetic factors and the chronic form in older subjects can present similarly. This is particularly true for childhood asthmatic subjects who become chronic smokers.

Longitudinal studies that compared airway responsiveness at the beginning of the study to subsequent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. A recent study from the Childhood Asthma Management Program identified four lung function trajectories in children with persistent asthma. Asthmatics with reduced lung function early in life were more likely to meet spirometric criteria for COPD in early adulthood. Patients with features of both asthma and COPD have been described as the asthma-COPD overlap syndrome. Both asthma and airway hyperresponsiveness are risk factors for COPD.

RESPIRATORY INFECTIONS

The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen following an individual episode of acute bronchitis or pneumonia. However, respiratory infections are important causes of COPD exacerbations, and recent results from the COPDGene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally, particularly among those individuals with better baseline lung function levels. The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess due to a lack of adequate longitudinal data, but recent studies have suggested that childhood pneumonia may lead to increased risk for COPD later in life.

OCCUPATIONAL EXPOSURES

Increased respiratory symptoms and airflow obstruction have been suggested to result from exposure to dust and fumes at work. Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been implicated as risk factors for chronic airflow obstruction. Although nonsmokers in these occupations can develop some reductions in FEV_1, the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain for most of these exposures. However, among coal miners, coal mine dust exposure was a significant risk factor for emphysema in both smokers and nonsmokers. In most cases, the magnitude of these occupational exposures on COPD risk is likely substantially less important than the effect of cigarette smoking.

AMBIENT AIR POLLUTION

Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased pollution in the urban settings. However, the relationship of air pollution to chronic airflow obstruction remains unproved.

Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD among women in those countries. However, in most populations, ambient air pollution is a much less important risk factor for COPD than cigarette smoking.

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero, tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions often observed in COPD remains uncertain.

GENETIC CONSIDERATIONS

Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe α_1AT deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

α_1 Antitrypsin Deficiency Many variants of the protease inhibitor (PI or *SERPINA1*) locus that encodes α_1AT have been described. The common M allele is associated with normal α_1AT levels. The S allele, associated with slightly reduced α_1AT levels, and the Z allele, associated with markedly reduced α_1AT levels, also occur with frequencies of >1% in most white populations. Rare individuals inherit null alleles, which lead to the absence of any α_1AT production through a heterogeneous collection of mutations. Individuals with two Z alleles or one Z and one null allele are referred to as Pi^Z, which is the most common form of severe α_1AT deficiency.

Although only ~1% of COPD patients are found to have severe α_1AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Pi^Z individuals often develop early-onset COPD, but the ascertainment bias in the published series of Pi^Z individuals—which have usually included many Pi^Z subjects who were tested for α_1AT deficiency because they had COPD—means that the fraction of Pi^Z individuals who will develop COPD and the age-of-onset distribution for the development of COPD in Pi^Z subjects remain unknown. Approximately 1 in 3000 individuals in the United States inherits severe α_1AT deficiency, but only a small minority of these individuals has been identified. The clinical laboratory test used most frequently to screen for α_1AT deficiency is measurement of the immunologic level of α_1AT in serum (see "Laboratory Findings").

A significant percentage of the variability in pulmonary function among Pi^Z individuals is explained by cigarette smoking; cigarette smokers with severe α_1AT deficiency are more likely to develop COPD at early ages. However, the development of COPD in Pi^Z subjects, even among current or ex-smokers, is not absolute. Among Pi^Z nonsmokers, impressive variability has been noted in the development of airflow obstruction. Asthma and male gender also appear to increase the risk of COPD in Pi^Z subjects. Other genetic and/or environmental factors likely contribute to this variability.

Specific treatment in the form of α_1AT augmentation therapy is available for severe α_1AT deficiency as a weekly IV infusion (see "Treatment," below).

The risk of lung disease in heterozygous Pi^{MZ} individuals, who have intermediate serum levels of α_1AT (~60% of Pi^{MM} levels), has been controversial. Several recent large studies have demonstrated that Pi^{MZ} subjects who smoke are likely at increased risk for the development of COPD. However, alpha-1 antitrypsin augmentation therapy is not recommended for use in Pi^{MZ} subjects.

Other Genetic Risk Factors Studies of pulmonary function measurements performed in general population samples have suggested that genetic factors other than PI type influence variation in pulmonary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated.

GWAS have identified >20 regions of the genome that contain COPD susceptibility loci, including a region near the *HHIP* gene on chromosome 4, a cluster of genes on chromosome 15 (including components of the nicotinic acetylcholine receptor and another gene, *IREB2*, related to mitochondrial iron regulation), and a region within a gene of unknown function (*FAM13A*). As with most other complex diseases, the risk associated with individual GWAS loci is modest, but these genetic determinants may identify important biological pathways related to COPD. Gene-targeted murine models for *HHIP*, *FAM13A*, and *IREB2* exposed to chronic cigarette smoke had altered emphysema susceptibility, suggesting that those genes are likely to be involved in COPD pathogenesis. A regulatory single nucleotide polymorphisms (SNP) upstream from the *HHIP* gene has been identified as one potential functional variant; the specific genetic determinants in the other COPD GWAS genomic regions have yet to be definitively identified.

NATURAL HISTORY

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth, and the baseline lung function of the individual; other environmental factors may have similar effects. Most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence, followed by a plateau in early adulthood, and then gradual decline with aging. Individuals appear to track in their quantile of pulmonary function based on environmental and genetic factors that put them on different tracks. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV_1. A graphic depiction of the natural history of COPD is shown as a function of the influences on tracking curves of FEV_1 in **Fig. 286-4**. Death or disability from COPD can result from a normal rate of decline after a reduced growth phase (curve *C*), an early initiation of pulmonary function decline after normal growth (curve *B*), or an accelerated decline after normal growth (curve *D*). Although accelerated rates of lung function decline have classically been associated with COPD, recent analyses of several population-based cohorts demonstrated that many subjects meeting the spirometric criteria for COPD had reduced growth but normal rates of lung function decline. The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. The absolute annual loss in FEV_1 tends to be highest in mild COPD and lowest in very severe COPD. Multiple genetic factors influence the level of pulmonary function achieved during growth; genetic determinants

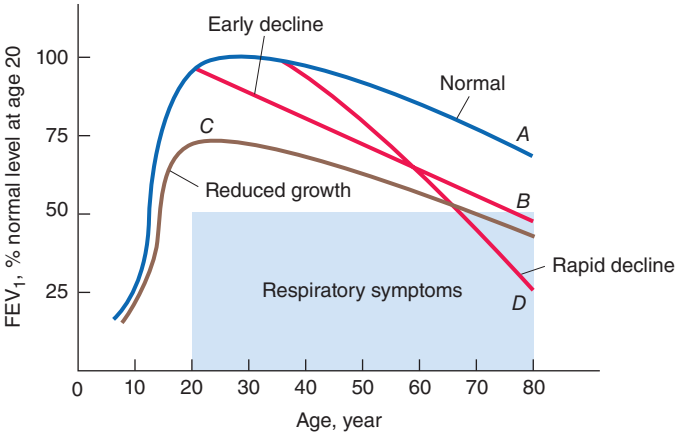

FIGURE 286-4 Hypothetical tracking curves of forced expiratory volume in 1 s (FEV_1) for individuals throughout their life spans. The normal pattern of growth and decline with age is shown by curve *A*. Significantly reduced FEV_1 (<65% of predicted value at age 20) can develop from a normal rate of decline after a reduced pulmonary function growth phase (curve *C*), early initiation of pulmonary function decline after normal growth (curve *B*), or accelerated decline after normal growth (curve *D*). *(From B Rijcken: Doctoral dissertation, p 133, University of Groningen, 1991; with permission.)*

likely also influence the rate of decline in response to smoking and potentially to other environmental factors as well.

CLINICAL PRESENTATION

HISTORY

The three most common symptoms in COPD are cough, sputum production, and exertional dyspnea. Many patients have such symptoms for months or years before seeking medical attention. Although the development of airflow obstruction is a gradual process, many patients date the onset of their disease to an acute illness or exacerbation. A careful history, however, usually reveals the presence of symptoms prior to the acute exacerbation. The development of exertional dyspnea, often described as increased effort to breathe, heaviness, air hunger, or gasping, can be insidious. It is best elicited by a careful history focused on typical physical activities and how the patient's ability to perform them has changed. Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for many patients with COPD. Conversely, activities that allow the patient to brace the arms and use accessory muscles of respiration are better tolerated. Examples of such activities include pushing a shopping cart or walking on a treadmill. As COPD advances, the principal feature is worsening dyspnea on exertion with increasing intrusion on the ability to perform vocational or avocational activities. In the most advanced stages, patients are breathless doing simple activities of daily living.

Accompanying worsening airflow obstruction is an increased frequency of exacerbations (described below). Patients may also develop resting hypoxemia and require institution of supplemental oxygen.

PHYSICAL FINDINGS

In the early stages of COPD, patients usually have an entirely normal physical examination. Current smokers may have signs of active smoking, including an odor of smoke or nicotine staining of fingernails. In patients with more severe disease, the physical examination of the lungs is notable for a prolonged expiratory phase and may include expiratory wheezing. In addition, signs of hyperinflation include a barrel chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in the characteristic "tripod" position to facilitate the actions of the sternocleidomastoid, scalene, and intercostal muscles. Patients may develop cyanosis, visible in the lips and nail beds.

Although traditional teaching is that patients with predominant emphysema, termed "pink puffers," are thin and noncyanotic at rest and have prominent use of accessory muscles, and patients with chronic bronchitis are more likely to be heavy and cyanotic ("blue bloaters"), current evidence demonstrates that most patients have elements of both chronic bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

Advanced disease may be accompanied by cachexia, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF-α). Such wasting is an independent poor prognostic factor in COPD. Some patients with advanced disease have paradoxical inward movement of the rib cage with inspiration (Hoover's sign), the result of alteration of the vector of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation.

Signs of overt right heart failure, termed *cor pulmonale*, are relatively infrequent since the advent of supplemental oxygen therapy.

Clubbing of the digits is not a sign of COPD, and its presence should alert the clinician to initiate an investigation for causes of clubbing. In this population, the development of lung cancer is the most likely explanation for newly developed clubbing.

LABORATORY FINDINGS

The hallmark of COPD is airflow obstruction (discussed above). Pulmonary function testing shows airflow obstruction with a reduction in FEV_1 and FEV_1/FVC **(Chap. 279)**. With worsening disease severity, lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity, and residual volume. In patients with emphysema, the diffusing capacity may be reduced, reflecting the lung parenchymal destruction characteristic of the disease. The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the GOLD spirometric severity classification (Table 286-1). Although the degree of airflow obstruction *generally* correlates with the presence and severity of respiratory symptoms, exacerbations, emphysema, and hypoxemia, the correlations are far from perfect. Thus, clinical features should be carefully assessed in each individual patient with COPD to determine the most appropriate therapies. It has been shown that a multifactorial index (BODE) incorporating airflow obstruction, exercise performance, dyspnea, and body mass index is a better predictor of mortality rate than pulmonary function alone. Recently, the GOLD added additional elements to their classification system incorporating respiratory symptoms and exacerbation history; these metrics are used to guide COPD treatment (see below).

Arterial blood gases and oximetry may demonstrate resting or exertional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial Pco_2 and pH. The change in pH with Pco_2 is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state. Knowledge of the arterial pH therefore allows the classification of ventilatory failure, defined as Pco_2 >45 mmHg, into acute or chronic conditions with acute respiratory failure being associated with acidemia. The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation. An elevated hematocrit suggests the presence of chronic hypoxemia, as does the presence of signs of right ventricular hypertrophy.

Radiographic studies may assist in the classification of the type of COPD. Obvious bullae, paucity of parenchymal markings, or hyperlucency on chest x-ray suggests the presence of emphysema. Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not provide information about chronicity of the changes. Chest computed tomography (CT) scan is the current definitive test for establishing the presence or absence of emphysema, the pattern of emphysema, and the presence of significant disease involving medium and large airways (Fig. 286-2). It also enables the discovery of coexisting interstitial lung disease and bronchiectasis, which are common complications in COPD. Smokers with COPD are at high risk for development of lung cancer, which can be identified on a chest CT scan. In advanced COPD, CT scans can help determine the possible value of surgical therapy (described below).

Recent guidelines have suggested testing for α_1AT deficiency in all subjects with COPD or asthma with chronic airflow obstruction. Measurement of the serum α_1AT level is a reasonable initial test. For subjects with low α_1AT levels, the definitive diagnosis of α_1AT deficiency requires PI type determination. This is typically performed by isoelectric focusing of serum or plasma, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles as well. Molecular genotyping of DNA can be performed for the common PI alleles (M, S, and Z).

TREATMENT

Chronic Obstructive Pulmonary Disease

STABLE PHASE COPD

The two main goals of therapy are to provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, improve health status) and reduce future risk (prevent disease progression, prevent and treat exacerbations, and reduce mortality). The institution of therapies should be based on symptom assessment, benefits of therapy, potential risks, and costs. **Figure 286-5** provides the currently suggested categories of COPD patients based on respiratory symptoms and risk for exacerbations. Response to therapy should be assessed, and decisions should be made whether or not to continue or alter treatment.

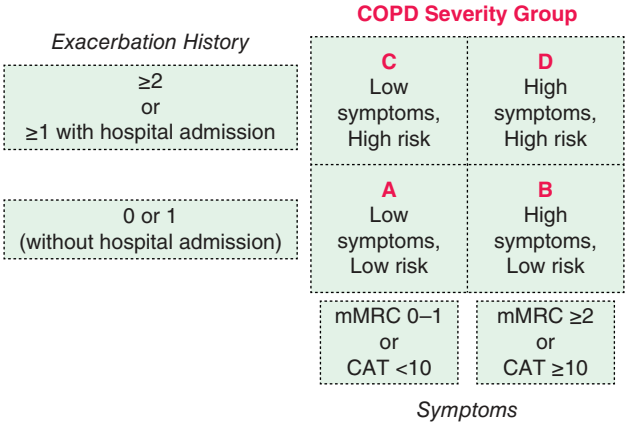

FIGURE 286-5 COPD severity assessment. COPD severity categories are based on respiratory symptoms (based on the mMRC or CAT scales) and annual frequency of COPD exacerbations. mMRC—Modified Medical Research Council Dyspnea Scale. Provides a single number for degree of breathlessness: 0—only with strenuous activity; 1—hurrying on level ground or walking up a slight hill; 2—walk slower than peers or stop walking at their own pace; 3—walking about 100 yards or after a few minutes on level ground; 4—too breathless to leave the house or when dressing. CAT—COPD Assessment Test. An 8-item COPD health status measure with Likert scale responses for questions about cough, phlegm, chest tightness, dyspnea on one flight of stairs, limitation in home activities, confidence in leaving the home, sleep and energy. Range of total score is 0–40. Both mMRC and CAT are available from Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. With permission from *http://goldcopd.org*.

Only three interventions—smoking cessation, oxygen therapy in chronically hypoxemic patients, and lung volume reduction surgery (LVRS) in selected patients with emphysema—have been demonstrated to improve survival of patients with COPD. There is suggestive, but not definitive, evidence that the use of inhaled corticosteroids (ICS) and muscarinic antagonists may reduce the mortality rate.

PHARMACOTHERAPY

Smoking Cessation (See also Chap. 448) It has been shown that middle-aged smokers who were able to successfully stop smoking experienced a significant improvement in the rate of decline in pulmonary function, often returning to annual changes similar to that of nonsmoking patients. In addition, smoking cessation improves survival. Thus, all patients with COPD should be strongly urged to quit smoking and educated about the benefits of quitting. An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation. There are three principal pharmacologic approaches to the problem: nicotine replacement therapy available as gum, transdermal patch, lozenge, inhaler, and nasal spray; bupropion; and varenicline, a nicotinic acid receptor agonist/antagonist. Current recommendations from the U.S. Surgeon General are that all adult, nonpregnant smokers considering quitting be offered pharmacotherapy, in the absence of any contraindication to treatment. Smoking cessation counseling is also recommended and free counseling is available through state Smoking QuitLines.

Bronchodilators In general, bronchodilators are the primary treatment for almost all patients with COPD and are used for symptomatic benefit and to reduce exacerbations. The inhaled route is preferred for medication delivery, because side effects are less than with systemic medication delivery. In symptomatic patients, both regularly scheduled use of long-acting agents and as-needed short-acting medications are indicated. **Figure 286-6** provides suggestions for prescribing inhaled medication therapy based on grouping patients by severity of symptoms and risk of exacerbations.

Anticholinergic Muscarinic Antagonists Short-acting ipratropium bromide improves symptoms with acute improvement in FEV_1. Long-acting muscarinic antagonists (LAMA, including aclidinium, glycopyrrolate, tiotropium, and umeclidinium) improve symptoms and reduce exacerbations. In a large randomized clinical trial, there was a trend toward reduced mortality rate in tiotropium-treated patients that approached statistical significance. Side effects are minor; dry mouth is the most frequent side effect.

Beta Agonists Short-acting beta agonists ease symptoms with acute improvements in lung function. Long-acting agents (LABA) provide symptomatic benefit and reduce exacerbations, though to a lesser extent than a LAMA. Currently available long-acting inhaled β agonists are arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol. The main side effects are tremor and tachycardia.

Combinations of Beta Agonist — Muscarinic Antagonist The combination inhaled β agonist and muscarinic antagonist therapy has

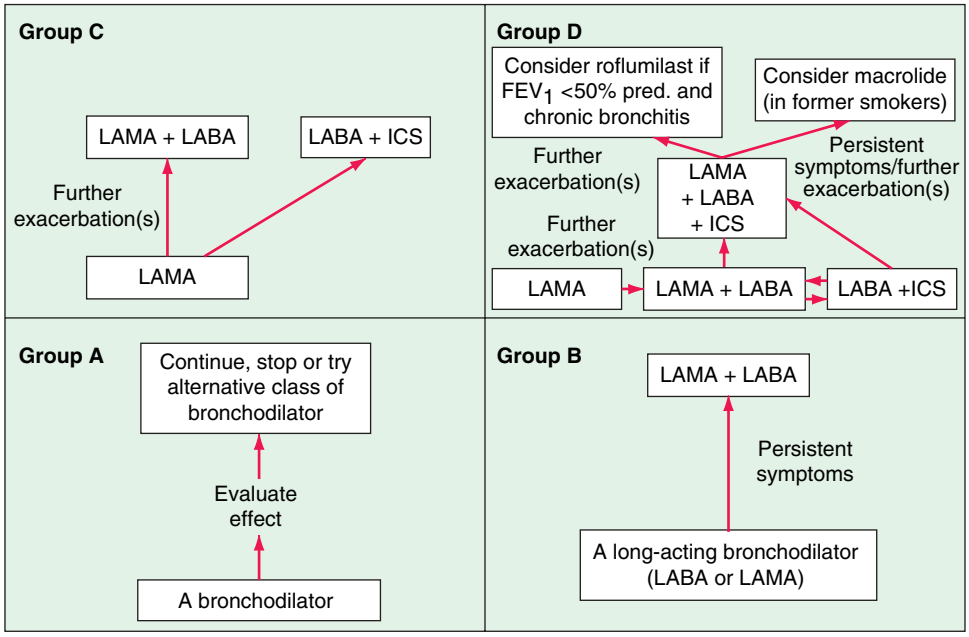

FIGURE 286-6 Medication therapy for stable COPD. Recommended pharmacologic treatment of stable COPD is based on respiratory symptoms and exacerbation frequency. Preferred treatment Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Reproduced with permission from *http://goldcopd.org*.

been demonstrated to provide improvement in lung function that is greater than either agent alone and reduces exacerbations.

Inhaled Corticosteroids The main role of ICS is to reduce exacerbations. Although one large trial and a meta-analysis demonstrated an apparent benefit from the regular use of inhaled glucocorticoids on the rate of decline of lung function, a number of other well-designed randomized trials have not. A meta-analysis and retrospective studies suggest a mortality benefit, but in a large randomized trial, differences in mortality rate approached, but did not reach, conventional criteria for statistical significance. Their use has been associated with increased rates of oropharyngeal candidiasis and pneumonia and in some studies an increased rate of loss of bone density. A trial of ICS should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients with features of asthma, such as eosinophilia. In stable patients, ICS withdrawal may be considered. Although ICS withdrawal does not lead to an increase in exacerbations, there may be a small decline in lung function.

Oral Glucocorticoids The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio. The chronic use of oral glucocorticoids is associated with significant side effects, including osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection. A recent study demonstrated that patients tapered off chronic low-dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function.

Theophylline Theophylline produces modest improvements in airflow and vital capacity, but is not first-line therapy due to side effects and drug interactions. Nausea is a common side effect; tachycardia and tremor have also been reported. Monitoring of blood theophylline levels is required to minimize toxicity.

PDE4 Inhibitors The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been demonstrated to reduce exacerbation frequency in patients with severe COPD, chronic bronchitis, and a prior history of exacerbations; its effects on airflow obstruction and symptoms are modest.

Antibiotics There are strong data implicating bacterial infection as a precipitant of a substantial portion of exacerbations. A randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimicrobial properties, administered daily to subjects with a history of exacerbation in the past 6 months demonstrated a reduced exacerbation frequency and longer time to first exacerbation in the macrolide-treated cohort (hazard ratio, 0.73).

Oxygen Supplemental O_2 is the only pharmacologic therapy demonstrated to unequivocally decrease mortality rates in patients with COPD. For patients with resting hypoxemia (resting O_2 saturation ≤88% in any patient or ≤89% with signs of pulmonary hypertension or right heart failure), the use of O_2 has been demonstrated to have a significant impact on mortality. Patients meeting these criteria should be on continuous oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

A recent study failed to demonstrate significant benefits to COPD patients with moderate hypoxemia at rest or with hypoxemia only with activity.

α_1AT Augmentation Therapy Specific treatment in the form of IV α_1AT augmentation therapy is available for individuals with severe α_1AT deficiency. Despite sterilization procedures for these blood-derived products and the absence of reported cases of viral infection from therapy, some physicians recommend hepatitis B vaccination prior to starting augmentation therapy. Although biochemical efficacy of α_1AT augmentation therapy has been shown, the benefits of α_1AT augmentation therapy are controversial. A recent randomized study suggested a reduction in emphysema progression in patients receiving α_1AT augmentation therapy. Eligibility for α_1AT augmentation therapy requires a serum α_1AT level <11 μ*M* (~50 mg/dL). Typically, Pi^Z individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Because only a fraction of individuals with severe α_1AT deficiency will develop COPD, α_1AT augmentation therapy is not recommended for severely α_1AT-deficient persons with normal pulmonary function and a normal chest CT scan.

NONPHARMACOLOGIC THERAPIES

Patients with COPD should receive the influenza vaccine annually. Pneumococcal vaccines and vaccination for *Bordetella pertussis* are recommended.

Pulmonary Rehabilitation This refers to a comprehensive treatment program that incorporates exercise, education, and psychosocial and nutritional counseling. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period.

Lung Volume Reduction Surgery In carefully selected patients with emphysema, surgery to remove the most emphysematous portions of lung improves exercise, lung function, and survival. The anatomic distribution of emphysema and post-rehabilitation exercise capacity are important prognostic characteristics. Patients with upper lobe–predominant emphysema and a low post-rehabilitation exercise capacity are most likely to benefit from LVRS.

Patients with an FEV_1 <20% of predicted and either diffusely distributed emphysema on CT scan or diffusing capacity of lung for carbon monoxide (DL_{CO}) <20% of predicted have increased mortality after the procedure, and thus are not candidates for LVRS.

Methods of achieving lung volume reduction by using bronchoscopic techniques are under investigation.

Lung Transplantation (See also Chap. 292) COPD is currently the second leading indication for lung transplantation. Current recommendations are that candidates for lung transplantation should have very severe airflow limitation, severe disability despite maximal medical therapy, and be free of significant comorbid conditions such as liver, renal, or cardiac disease.

EXACERBATIONS OF COPD

Exacerbations are a prominent feature of the natural history of COPD. Exacerbations are episodic acute worsening of respiratory symptoms, including increased dyspnea, cough, wheezing, and/or change in the amount and character of sputum. They may or may not be accompanied by other signs of illness, including fever, myalgias, and sore throat. The strongest single predictor of exacerbations is a history of a previous exacerbation. The frequency of exacerbations increases as airflow obstruction worsens; patients with severe (FEV_1 <50% predicted) or very severe airflow obstruction (FEV_1 <30% predicted) on average have 1–3 episodes per year. However, some individuals with very severe airflow obstruction do not have frequent exacerbations. Other factors, such as an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT, and gastroesophageal reflux, are also associated with increased risk of COPD exacerbations. Economic analyses have shown that >70% of COPD-related health care expenditures are due to emergency department visits and hospital care for COPD exacerbations; this translates to over $10 billion annually in the United States.

Precipitating Causes and Strategies to Reduce Frequency of Exacerbations A variety of stimuli may result in the final common pathway of airway inflammation and increased respiratory symptoms that are characteristic of COPD exacerbations. Studies suggest that acquiring a new strain of bacteria is associated with increased near-term risk of exacerbation and that bacterial infection/superinfection is involved in >50% of exacerbations. Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a significant minority of instances (20–35%), no specific precipitant can be identified.

Patient Assessment An attempt should be made to establish the severity of the exacerbation as well as the severity of preexisting COPD. The more severe either of these two components, the more likely that the patient will require hospital admission. The history should include quantification of the degree and change in dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient. The patient should be asked about fever; change in character of sputum; and associated symptoms such as wheezing, nausea, vomiting, diarrhea, myalgias, and chills. Inquiring about the frequency and severity of prior exacerbations can provide important information; the single greatest risk factor for hospitalization with an exacerbation is a history of previous hospitalization.

The physical examination should incorporate an assessment of the degree of distress of the patient. Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and the patient's mental status. The chest examination should establish the presence or absence of focal findings, degree of air movement, presence or absence of wheezing, asymmetry in the chest examination (suggesting large airway obstruction or pneumothorax mimicking an exacerbation), and the presence or absence of paradoxical motion of the abdominal wall.

Patients with severe underlying COPD, who are in moderate or severe distress, or those with focal findings should have a chest x-ray or chest CT scan. Approximately 25% of x-rays in this clinical situation will be abnormal, with the most frequent findings being pneumonia and congestive heart failure. Patients with advanced COPD, a history of hypercarbia, mental status changes (confusion, sleepiness), or those in significant distress should have an arterial blood-gas measurement. The presence of hypercarbia, defined as a Pco_2 >45 mmHg, has important implications for treatment (discussed below). In contrast to its utility in the management of exacerbations of asthma, measurement of pulmonary function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD. Pulmonary embolus (PE) should also be considered, as the incidence of PE is increased in COPD exacerbations.

The need for inpatient treatment of exacerbations is suggested by the presence of respiratory acidosis and hypercarbia, new or worsening hypoxemia, severe underlying disease and those whose living situation is not conducive to careful observation and the delivery of prescribed treatment.

TREATMENT OF ACUTE EXACERBATIONS

Bronchodilators Typically, patients are treated with inhaled β agonists and muscarinic antagonists. These may be administered separately or together, and the frequency of administration depends on the severity of the exacerbation. Patients are often treated initially with nebulized therapy, as such treatment is often easier to administer in those in respiratory distress. It has been shown, however, that conversion to metered-dose inhalers is effective when accompanied by education and training of patients and staff. This approach has significant economic benefits and also allows an easier transition to outpatient care. The addition of methylxanthines (theophylline) to this regimen can be considered, although convincing proof of its efficacy is lacking. If added, serum levels should be monitored in an attempt to minimize toxicity.

Antibiotics Patients with COPD are frequently colonized with potential respiratory pathogens, and it is often difficult to identify conclusively a specific species of bacteria responsible for a particular clinical event. Bacteria frequently implicated in COPD exacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In addition, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are found in 5–10% of exacerbations. The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above pathogens as well as the patient's clinical condition. Patients with moderate or severe exacerbations are usually treated with antibiotics, even in the absence of data implicating a specific pathogen.

In patients admitted to the hospital, the use of systemic glucocorticoids reduces the length of stay, hastens recovery, and reduces the chance of subsequent exacerbation or relapse. One study demonstrated that 2 weeks of glucocorticoid therapy produced benefit indistinguishable from 8 weeks of therapy. Current recommendations suggest 30–40 mg of oral prednisolone or its equivalent typically for a period of 5–10 days in outpatients. Hyperglycemia, particularly in patients with preexisting diagnosis of diabetes, is the most frequently reported acute complication of glucocorticoid treatment.

Oxygen Supplemental O_2 should be supplied to maintain oxygen saturation ≥90%. Studies have demonstrated that in patients with both acute and chronic hypercarbia, the administration of supplemental O_2 does not reduce minute ventilation. It does, in some patients, result in modest increases in arterial Pco_2, chiefly by altering ventilation-perfusion relationships within the lung. This should not deter practitioners from providing the oxygen needed to correct hypoxemia.

Mechanical Ventilatory Support The initiation of noninvasive positive-pressure ventilation (NIPPV) in patients with respiratory failure, defined as $Paco_2$ >45 mmHg, results in a significant reduction in mortality rate, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status, inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burns.

Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercarbia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. The goal of mechanical ventilation is to correct the aforementioned conditions. Factors to consider during mechanical ventilatory support include the need to provide sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure), which can result in patients having to generate significant respiratory effort to trigger a breath during a demand mode of ventilation. The mortality rate of patients requiring mechanical ventilatory support is 17–30% for that particular hospitalization. For patients aged >65 admitted to the intensive care unit for treatment, the mortality rate doubles over the next year to 60%, regardless of whether mechanical ventilation was required.

Following a hospitalization for COPD, about 20% of patients are re-hospitalized in the subsequent 30 days and 45% are hospitalized in the next year. Mortality following hospital discharge is about 20% in the following year.

FURTHER READING

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287 Interstitial Lung Disease

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Diffuse parenchymal lung diseases include a large number (>200) of heterogeneous conditions that affect the lung parenchyma with varying degrees of inflammation and fibrosis. While remodeling of the interstitial space, the region between the epithelium and endothelium, tends to be the dominant site of involvement for most of the interstitial lung diseases (ILDs), it is important to recognize the prominent role of the alveolar epithelium and endothelial cells (including both airways and vessels) in the pathogenesis of these interstitial lung disorders.

Despite the diverse array of conditions, most patients ultimately diagnosed with an ILD will come to medical attention with reports of progressive exertional dyspnea or a persistent dry cough. However, because some ILDs are part of multisystem disorders, some patients will be identified based on non-respiratory symptomatology (e.g., skin thickening in the setting of systemic sclerosis, **Chap. 353**) or physical examination findings (e.g., ulnar deviation of the fingers in the setting of rheumatoid arthritis [RA], **Chap. 351**). Additionally, ILDs can also be identified incidentally based on the results of abnormal pulmonary function tests, chest x-rays (CXRs), computed tomography (CT) studies of both the chest and abdomen (which can both visualize, at least a portion, of the lung parenchyma), and positron emission tomography (PET) scans. It is important to remember that ILDs can be associated with high rates of morbidity and mortality, and although prognosis depends on both disease extent and specificity, this fact makes these important disorders to recognize in a timely manner.

Owing to a variety of clinical presentations, as well as overlapping imaging and histopathologic findings **(Table 287-1)**, ILDs can be difficult to diagnose. A generally accepted central tenet of ILD diagnosis is that the combined weight of clinical data, laboratory studies, pulmonary function testing, imaging findings, and histopathology (if obtained) are jointly required to make a confident diagnosis. No single piece of data confers a diagnosis alone. For example, a lung biopsy demonstrating a usual interstitial pneumonia (UIP) pattern is helpful in diagnosing a patient with idiopathic pulmonary fibrosis (IPF) but can also be present in some connective tissue diseases (CTDs) (e.g., RA-associated ILD, **Chap. 351**). In light of this challenge, most ILD centers recommend a multidisciplinary approach to the diagnosis (and in some cases the management) of ILDs. An example of a multidisciplinary approach might include a conference attended by pulmonologists, rheumatologists, radiologists, and pathologists where all of the data generated on a patient can be discussed and reviewed jointly by those with unique sets of expertise in the care of patients with ILD.

While there are numerous ways to categorize the ILDs, one classic approach is to divide the ILDs into those of known and unknown

Table 287-1 Common Interstitial Lung Disease Findings

	IPF	NONSPECIFIC INTERSTITIAL PNEUMONIA	RESPIRATORY BRONCHIOLITIS ASSOCIATED ILD	SYSTEMIC SCLEROSIS ASSOCIATED ILD	SARCOIDOSIS
Clinical symptoms	Gradual onset of SOB, dry cough. Unusual in younger adults.	Subacute onset of SOB, dry cough. Frequently associated with other conditions.	Can be asymptomatic, or have SOB, and cough.	Gradual onset of SOB, dry cough. Fatigue, tightening of skin, exaggerated cold response, reflux, and difficulty swallowing.	Can be asymptomatic, or have SOB, and cough. Can also have fatigue, palpitations, eye, skin, and joint findings.
Physical examination findings	Frequent rales at lung bases, digital clubbing is common.	Frequent rales. Clubbing is less common.	Rales common. Clubbing is rare.	Can have rales in isolation. Also skin thickening, joint swelling, and telangiectasias.	Can be normal, rales may be present. Can have skin findings, joint pain, and enlarged lymph nodes.
Exposures	Idiopathic but many exposed to smoke. Genetic findings may explain >1/3 of the risk of the disease.	Can be idiopathic but should prompt consideration for associated conditions.	Strong association with smoking.	Mostly unknown, some debate about solvent and silicate exposures.	Mostly unknown, although silicate dusts thought to play a role in some cases.
HRCT findings	Bilateral subpleural reticular changes most prominent in lower, posterior lung zones. Traction bronchiectasis and honeycombing common. Classic UIP pattern is considered diagnostic.	Peripheral subpleural ground glass and reticular patterns. Traction bronchiectasis is common but honeycombing is rare. HRCT not diagnostic.	Diffuse patchy centrilobular ground glass nodules.	Can have UIP or NSIP patterns, also dilated esophagus, occasional mediastinal calcifications, and pulmonary vascular enlargement.	Can have mediastinal and hilar lymphadenopathy. Peribronchovascular reticular-nodular findings.
Histopathology	UIP pattern including fibroblastic foci, temporal and spatial heterogeneity, honeycombing.	Cellular or fibrotic pattern of NSIP. More uniform than a UIP pattern.	Respiratory bronchiolitis with adjacent inflammatory and fibrosing changes. Pigment laden macrophages.	Both UIP or NSIP patterns can occur.	Non-caseating granulomas.
Clinical course	50% 3–5 year mortality.	18% 5-year mortality.	25% 7-year mortality.	20–30% 10-year mortality.	Generally low but varies by state.

Abbreviations: HRCT, high resolution chest CT; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; SOB, shortness of breath; UIP, usual interstitial pneumonia

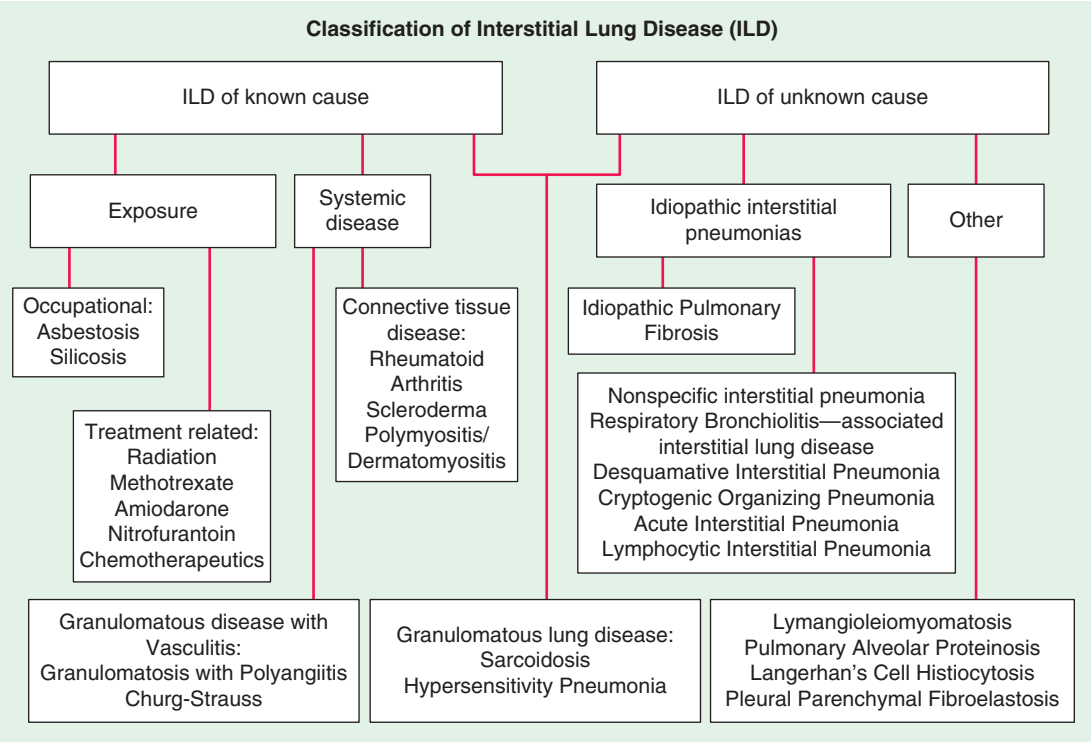

FIGURE 287-1 Classification of interstitial lung disease. This algorithm represents a common approach to sub-classifying the interstitial lung diseases. It is typical to divide the interstitial lung diseases into those of known and unknown causes (although it is important to note that genetic studies demonstrate that a significant portion of familial and idiopathic pulmonary fibrosis [classically described as diseases of unknown cause] may be explained, in part, by genetic factors). The idiopathic interstitial pneumonias were more precisely defined by a 2002 study as described in Am J Respir Crit Care Med 165:277, 2002, referenced in the Further Reading list.

causes (Fig. 287-1). Although even this approach has limitations (e.g., genetic studies demonstrate that a significant portion of familial and IPF [classically described as a diseases of unknown cause] may be explained, in part, by genetic factors), it is a useful place to start. Known causes of ILD include occupational exposures (e.g., asbestosis), medications (e.g., nitrofurantoin), and those related to an underlying systemic disease (e.g., cryptogenic organizing pneumonia [COP] in the setting of polymyositis). Unknown causes of ILD include groups of rare disorders often with classic presentations (e.g., a spontaneous pneumothorax in a young female with diffuse cystic changes on a chest CT might suggest lymphangioleiomyomatosis [LAM]) and the most common group of ILDs, the idiopathic interstitial pneumonias (IIPs). Granulomatous lung diseases straddle both known (e.g., hypersensitivity pneumonitis (HP) due to chronic bird exposure, Chap. 282), and unknown (e.g., sarcoidosis, Chap. 360) causes and are often separated due to their unique presentations, imaging findings, and diagnostic evaluation. Equally important to knowledge of disease classification is knowledge of disease prevalence. Although there is variability within different demographic groups, most studies demonstrate that IPF, sarcoidosis (Chap. 360), and ILDs related to CTDs (Chap. 406) as a group are among the most common forms of ILD.

DIAGNOSTIC APPROACH

The initial diagnostic approach to diffuse parenchymal lung disease is often broader than a focus on ILD and should include an evaluation for alternate causes including cardiovascular disease (e.g., heart failure, Chap. 253), diffuse infections (e.g., *pneumocystis* pneumonia, Chap. 215), and malignancy (e.g., bronchoalveolar cell carcinoma, Chap. 315 in HPIM 19e). This chapter will focus on the diagnostic evaluation that helps to distinguish among the various forms of ILD.

HISTORY

Age Age at presentation has a strong influence on the pretest probability that IPF, in particular, is present. For example, IPF occurs most commonly in patients aged >60 and is quite rare among patients aged <50. In fact, in patients aged >65 without strong evidence for an alternate diagnosis, atypical chest CT findings are still more likely to result in a histopathologic diagnosis of UIP (a pathologic hallmark of IPF) than they are to result in an alternate IIP diagnosis. Other common ILDs such as sarcoidosis, CTD associated ILD, and less common ILDs such as LAM, pulmonary Langerhans cell histiocytosis (PLCH) tend to present between the ages of 20 and 40.

Sex Although less influential than age, sex has some influence on likelihood of various ILDs. LAM (and related disorder tuberous sclerosis) (see Chap. 315 in HPIM 19e) is a disorder that is frequently diagnosed in young women. Many CTD-associated ILDs are more common among women, with the exception of RA associated ILD which is more common among men. IPF and occupational/exposure-related ILDs (likely due to work related exposures that tend to differ between men and women) are more common among men.

Duration of Symptoms Acute presentations (*days to weeks*) of ILD are unusual and are commonly misdiagnosed as more common diseases such as pneumonia, a COPD exacerbation, or heart failure. ILDs that can present acutely include eosinophilic pneumonia, acute interstitial pneumonia (AIP), HP, and granulomatosis with polyangiitis (GPA). An acute exacerbation of IPF as the initial presentation of this disease should also be a consideration given its prevalence. ILDs most commonly have a chronic indolent presentation (*months to years*) typified by IPF. However subacute presentations (*weeks to months*) can occur in most of the ILDs, but in the right context could suggest sarcoidosis, CTD associated ILD, drug-induced ILD, or COP.

Respiratory Symptoms Progressive dyspnea, most frequently noted with exertion, is the most common complaint in patients presenting with an ILD. Despite this fact, both research studies of general population samples and clinical experiences of asymptomatic patient referrals with abnormal chest CT imaging patterns have also demonstrated that some patients, even those with more extensive disease, may not report dyspnea. Cough, particularly a dry cough, is also common, and can be the most prominent symptom in patients with IPF. Cough is often reported in other ILDs, particularly those that have prominent airway involvement including sarcoidosis and HP. Cough with hemoptysis is rare and could suggest an ILD associated with diffuse alveolar

hemorrhage (DAH) (e.g., Goodpasture's syndrome), GPA, or LAM. Cough with hemoptysis could also suggest a secondary pulmonary infection that can be seen in patients with traction bronchiectasis and in those receiving immunosuppressive therapy. Chest pain is rare in most of the ILDs with the exception of sarcoidosis where chest discomfort is not uncommon. Fatigue is common to all of the ILDs.

Past Medical History The most pertinent history includes a personal history of a CTD or a history of symptoms commonly associated with a CTD (e.g., Raynaud's phenomena). It is also important to remember that ILD associated with a CTD can be the initial presenting symptom of the disease and can precede the development of additional symptomatology by many years. A history of malignancy is important; as some malignancies can be associated with dermatomyositis associated COP and sarcoid-like reactions. A history of asthma and allergic rhinitis might suggest a diagnosis of eosinophilic GPA.

Medications Many medications have been associated with ILD and to complicate matters further, many medications commonly used to treat inflammatory and granulomatous lung disease are also associated with ILD development (e.g., methotrexate, azathioprine, rituximab, and the tumor-necrosis factor-alpha blocking agents). Specific medications in many classes are also known to cause ILD, including antibiotics (e.g., nitrofurantoin), anti-arrhythmics (e.g., amiodarone) and many of the anti-neoplastic agents (e.g., bleomycin).

Family History A family history of ILD (of almost any type) is important to ascertain. The percentage of pulmonary fibrosis that is familial, as opposed to idiopathic, varies by study, with estimates ranging from <5% to as high as 20%. Despite this variability, most agree that the presence of a close relative with an IIP is among the strongest risk factors for IPF. Family studies have consistently noted familial aggregation of diverse forms of IIP (such as IPF, non-specific interstitial pneumonia [NSIP], and DIP running in the same family) and in some cases other forms of ILD. To date, the most well replicated genetic factors for pulmonary fibrosis (a promoter variant of a mucin gene [*MUC5B*]) and various genetic determinants known to influence telomere length (e.g., variants in the telomerase reverse transcriptase gene [*TERT*]) appear to be associated with both familial and idiopathic forms of pulmonary fibrosis similarly.

Social History A history of smoking is nearly always present in some forms of ILD (e.g., respiratory bronchiolitis and desquamative interstitial pneumonia [DIP]—sometimes referred by pathologists jointly as smoking related—ILD) where it is felt to be causative. A history of smoking is also noted in approximately three-quarters of IPF patients. Occupational and environmental exposure histories are also important to obtain as they might identify exposures known to cause pulmonary fibrosis (e.g., significant asbestos exposure) or HP (pigeon breeder's lung).

PHYSICAL EXAMINATION

End-inspiratory fine crackles, or rales, noted at the lung bases are found in most patients with IPF and may be one of the earliest signs of the disease. However, rales are nonspecific and can be found in many forms of ILD and other disorders. Wheezing is uncommon in most forms of ILD but can be present in some disorders, such as sarcoidosis, HP, and eosinophilic GPA. Signs of advanced disease include cyanosis, digital clubbing, and cor pulmonale.

LABORATORY STUDIES

Laboratory studies can be particularly helpful in the workup for an underlying CTD-associated ILD. As noted previously, these tests can reveal the presence of an underlying CTD as the cause of an ILD (e.g., a positive anti-cyclic citrullinated peptide [anti-CCP] antibody for RA) even when no other symptomatology or physical examination findings suggestive of the disorder are present. However, the cost-effectiveness and the extent of laboratory testing that should be ordered in various clinical contexts have yet to be determined (as there is a relatively long list of auto-antibody tests that could be ordered).

PULMONARY FUNCTION TESTS

Most forms of ILD will eventually result in a restrictive deficit on pulmonary function testing. A restrictive deficit is typified by a reduced total lung capacity (TLC), and symmetrically reduced measures of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). A reduction in the diffusing capacity of the lung for carbon monoxide (DLCO) is also common and may precede a reduction in lung volumes; however, there is more measurement variability in DLCO measurement and the test is less specific for ILD. A reduced FEV1 to FVC ratio, which is diagnostic of airway obstruction, is unusual in many forms of ILD but can be present as an isolated finding, or in conjunction with an additional restrictive deficit, in ILDs involving the airways such as sarcoidosis, HP, and LAM. Although pulmonary function testing is rarely diagnostic, reductions in lung function help to characterize the extent of disease, and evidence for decline in repeated measures of pulmonary function (e.g., FVC) have been correlated with an elevated rate of mortality.

CHEST IMAGING STUDIES

Chest X-Ray Findings on CXR can be the first clinical indication that an ILD might be present. For example, enlarged hilar lymph nodes and a pattern of central nodular opacities in the mid to upper lung zones can suggest sarcoidosis. A basilar reticular pattern, with small cystic spaces, in the absence of clinical evidence for heart failure, might suggest IPF. With a few exceptions, CXR alone rarely leads to a specific diagnosis.

Chest CT High resolution chest CT (HRCT) imaging is now considered to be standard of care in the initial evaluation of a patient with a suspected ILD. HRCT can be diagnostic for some ILDs (e.g., IPF) in right clinical context and may preclude the need for, and spare the patient the risk of, a lung biopsy. HRCT also helps to define the extent of the ILD, the presence of more concerning features suggestive of advanced disease (e.g., honeycombing), can provide information on coexisting diseases (e.g., emphysema and lung cancer), and when not diagnostic, can help to provide the most useful locations for obtaining lung biopsy specimens.

LUNG BIOPSY

Fiberoptic Bronchscopy Bronchoscopy can be helpful in establishing a specific ILD diagnosis, and can help to establish an alternate diagnosis, in select cases. Examination of serial lavage fluid can be helpful in establishing DAH which can be present in ILDs with vasculitis (e.g., GPA), and in some cases, cellular examination can suggest a specific diagnosis (eosinophilia >25% in chronic eosinophilic pneumonia or fat globules in macrophages in lipoid pneumonia). Trans-bronchial lung biopsies and lymph node biopsies (in sarcoidosis in particular) can lead to a confident diagnosis in patients with likely granulomatous lung disease (e.g., sarcoidosis and HP). However, in general, bronchoscopically obtained tissue samples are often felt to be insufficient to diagnose most of the IIPs. There is some preliminary evidence that bronchoscopically obtained cryobiopsies, which can result in yields larger than those obtained by transbronchial forceps biopsies, could improve the diagnostic yield of bronchoscopy; however, the precise role cryobiopsies in the diagnostic workup of ILD has yet to be clarified.

Surgical Lung Biopsy A surgically obtained lung biopsy specimen can help solidify the diagnosis of ILD. In many cases these are now obtained through a video-assisted thoracoscopic (VATS) approach (as compared to an open thoracotomy), which tends to reduce the length of operative times and hospital stays. The diagnostic yield of biopsies tends to be higher if obtained prior to treatment. The desire to obtain a surgical lung biopsy should be weighed against the risks which can include a short-term mortality rate of as high as 5%. These risks are reported to be higher in biopsies of patients ultimately diagnosed with IPF, and in those presenting acutely.

INDIVIDUAL FORMS OF ILD

The ILDs include a diverse group of lung pathologies that can be subclassified into those disorders of unknown cause (e.g., IIPs), and those

of known cause (e.g., sometimes referred to as secondary interstitial pneumonias [connective tissue disease-associated ILDs]) (see Fig. 287-1). Although this remains a useful approach to classifying this diverse group of disorders it is important to recognize that genetic studies are challenging this classic categorization. For example, numerous ILDs commonly listed as having an "unknown cause" have been determined to have significant genetic underpinnings (e.g., IPF and LAM), while the pathophysiologic processes that result in ILDs of "known cause" (e.g., connective tissue disease) remain incompletely understood. Diagnosis is based on combined information obtained from a patient's clinical presentation, measures of pulmonary function, imaging, immune serologies, and histopathology. It is important to remember that prognosis and treatment vary widely by disorder (and disease extent). In some cases, medical therapy that is felt to be effective for some ILDs has been proven to be harmful for others. Medical treatments range from immune modulators to anti-fibrotic medications while lung transplantation remains the standard of care for those with advanced and rapidly progressive ILDs.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

IDIOPATHIC PULMONARY FIBROSIS

Clinical Manifestations IPF is the most common ILD of unknown cause. Prevalence increases with age and is estimated at 50–200:100,000. IPF is commonly diagnosed in the fifth or sixth decade in life, affects men more than women, and is frequently associated with a history of smoking or other environmental exposures. IPF is a variably progressive disease that carries a poor prognosis with an estimated 50% 3–5-year survival.

HRCT Image Findings Chest CT findings include subpleural reticulation with a posterior basal predominance usually including more advanced fibrotic features, such as honeycombing and traction bronchiectasis. Collectively these imaging findings are referred to as a UIP pattern. The presence of extensive ground glass opacities, bronchovascular changes, micronodules, mosaic attenuation, or an upper lung predominance should raise suspicion for an alternative diagnosis **(Fig. 287-2)**.

Histopathology Diagnostic VATS biopsy findings include subpleural reticulation associated with honeycomb changes and fibroblast foci (subepithelial collections of myofibroblasts and collagen). These fibrotic changes alternate with areas of preserved normal alveolar architecture consistent with temporal and spatial heterogeneity **(Fig. 287-3)**. Collectively, these pathologic findings are referred to as UIP.

Treatment Historically, IPF was felt to be refractory to medical therapy with lung transplantation the only viable therapeutic option. This dogma changed in 2014 with large clinical trials that demonstrated that antifibrotic therapy (pirfenidone and nintedanib) can slow decline of lung function in IPF patients. Further meta-analyses have suggested that anti-fibrotic therapy may also improve survival. In contrast, treatment with immunosuppression, which had been commonly prescribed to many IPF patients, has now been demonstrated (in some cases) to

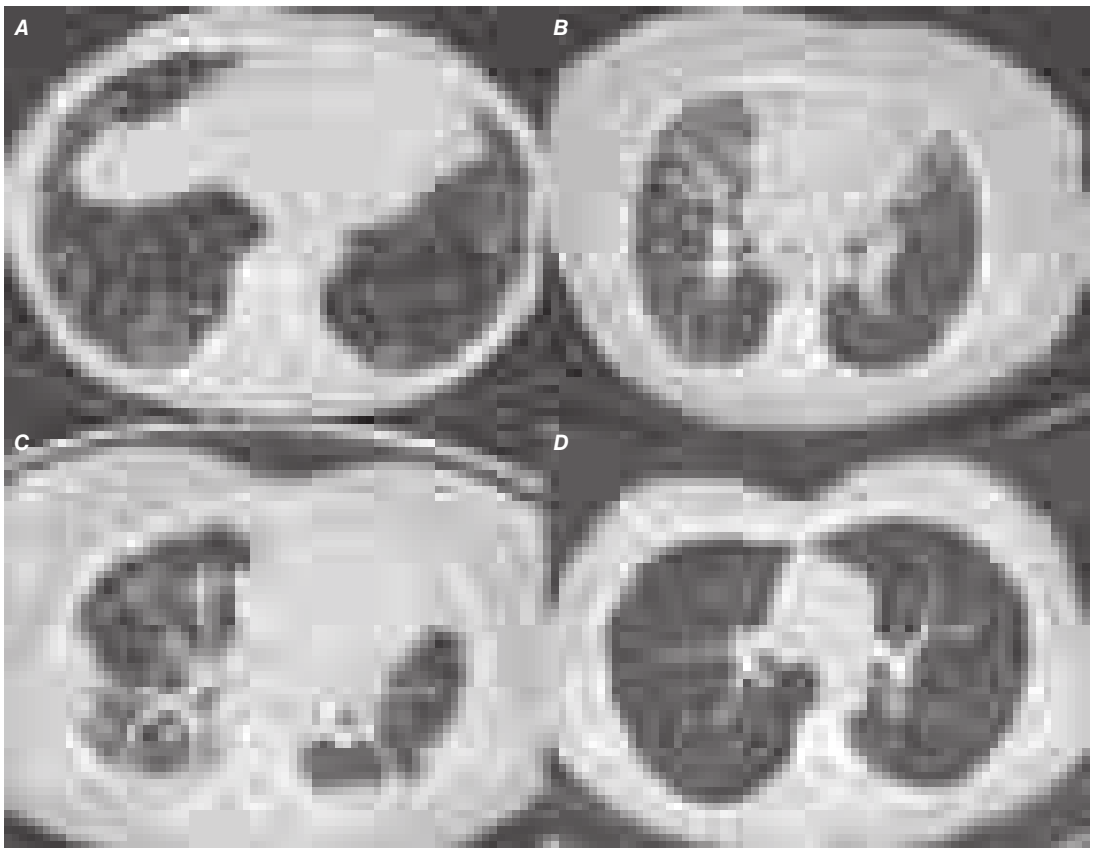

FIGURE 287-2 Chest CT imaging and interstitial lung disease. ***A***. Idiopathic pulmonary fibrosis (IPF): Classic findings of IPF (apparent on this image) include a posterior, basilar predominance of subpleural reticular markings and more advanced features of pulmonary fibrosis including traction bronchiectasis and honeycombing. This constellation of findings is often referred to as a usual interstitial pneumonia (UIP) pattern. ***B***. Non-specific interstitial pneumonia (NSIP): Chest CT findings of NSIP can overlap with those of a UIP pattern but tend to include a bilateral, symmetric pattern that presents with a greater percentage of ground-glass opacities than is apparent in a UIP pattern. Additional unique findings include more diffuse imaging abnormalities with a predominance not limited to the lung bases, imaging abnormalities that spare the subpleural regions, and thickening of the bronchovascular bundles (as is apparent in the right mid lung zone on this image). ***C***. Cryptogenic organizing pneumonia: Chest CT findings include patchy, sometimes migratory, subpleural consolidative opacities (as is apparent on this image) often with associated ground-glass opacities. Peribronchiolar, or perilobar opacities can be present and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen which can help to aid in the diagnosis. ***D***. Sarcoidosis: Sarcoidosis can present with varied imaging abnormalities but a pattern of mediastinal and hilar lymphadenopathy with a pattern of reticular-nodular opacities involving the bronchovascular bundles (apparent in this image) are common features. Additional findings can include diffuse small nodules in a miliary pattern, larger nodular opacities, extensive ground glass infiltrates and, mosaic attenuation suggestive of small airways involvement, and in more advanced cases, signs of pulmonary fibrosis.

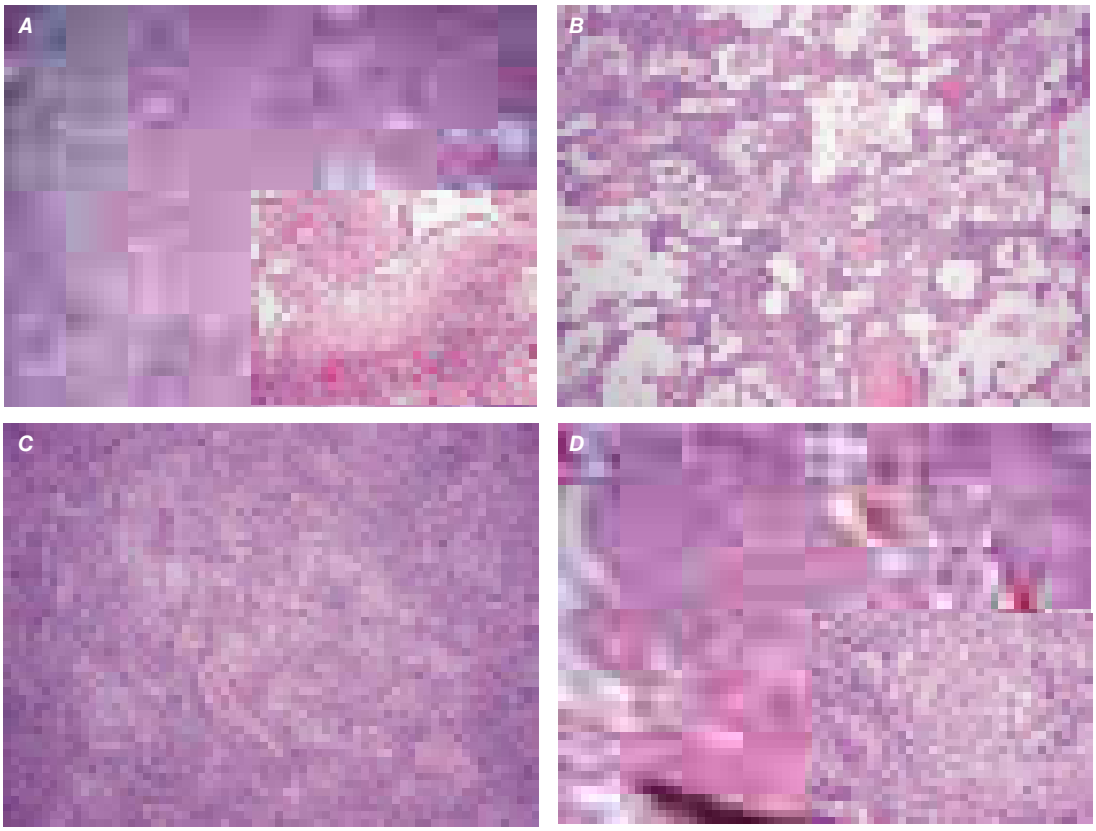

FIGURE 287-3 Histopathology of interstitial lung disease. ***A***. Idiopathic pulmonary fibrosis (IPF): Histopathologic findings include subpleural reticulation associated with honeycomb changes alternating with areas of preserved normal lung architecture referred to as temporal and spatial heterogeneity (as is apparent in the low power image above). Additional important diagnostic findings include fibroblast foci, which are subepithelial collections of myofibroblasts and collagen (as is apparent in the higher powered inset of this image). Collectively these pathologic findings are referred to as usual interstitial pneumonia (UIP). ***B***. Non-specific interstitial pneumonia (NSIP): Histopathologic findings of NSIP include varying amounts of interstitial inflammation and fibrosis with a uniform appearance (as is apparent in this image). Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular or fibrotic. ***C***. Cryptogenic organizing pneumonia (COP): Histopathologic findings of COP include patchy regions of organizing pneumonia with granulation tissue that commonly involves the small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (as is apparent in this image). ***D***. Sarcoidosis: The hallmark histopathologic feature of sarcoidosis is presence of granulomas (as are apparent numerously in the low powered image and more closely visualized in the higher powered inset image). Typically these are referred to as non-caseating which suggests the absence of necrosis. Caseating granulomas are rare in sarcoid and should prompt additional evaluation for an underlying infection. Because malignancy can result in a granulomatous reaction it is important to closely survey biopsy specimens with granulomatous involvement for additional signs of malignancy.

be associated with increased morbidity and mortality. Physical therapy and supplemental oxygen, when indicated, can improve exercise tolerance and reduce likelihood of developing pulmonary hypertension. Lung transplantation can extend survival and improve the quality of life in a subset of IPF patients who meet criteria to undergo transplant.

NON-SPECIFIC INTERSTITIAL PNEUMONIA

Clinical Manifestations Idiopathic NSIP is a distinct clinical entity with characteristic clinical, radiologic, and pathologic features; however, NSIP is also commonly observed in patients with connective tissue disease and less frequently with familial interstitial pneumonia, drug toxicity, and infection. Although the prevalence of NSIP is not well established, it is commonly diagnosed in non-smoking females in their fifth decade of life. Positive serologic tests for connective tissue disease are frequently observed. Idiopathic NSIP has a relatively good prognosis, with a 5-year survival >80%; patients with a predominant cellular NSIP pattern have a more favorable prognosis than those with a fibrosing NSIP pattern.

HRCT Image Findings Diffuse subpleural, symmetric, ground glass, and reticular opacities are common. Volume loss and traction bronchiectasis involving the lower lung zones can also be found. Occasionally subpleural sparing is noted, while peribronchiolar thickening and honeycombing are uncommon.

Histopathology Diagnostic lung biopsy findings include varying amounts of interstitial inflammation and fibrosis with a uniform appearance. Honeycomb changes are usually absent and fibroblast foci are rare. NSIP is often referred to histopathologically as being either predominantly cellular (and potentially more responsive to medical therapy) or fibrotic (and potentially less likely to resolve with medical therapy).

Treatment Pulmonary fibrosis associated with connective tissue disease is commonly treated with immunosuppression despite the paucity of randomized clinical trials to demonstrate efficacy. Idiopathic NSIP is often treated with oral steroids (prednisone), cytotoxic agents (mycophenolate, azathioprine, and cyclophosphamide), or biologics (rituximab). Oxygen therapy, pulmonary rehabilitation, and lung transplantation may be required in patients with progressive disease.

SMOKING-RELATED ILD

Although smoking-related ILDs including respiratory bronchiolitis with interstitial lung disease (RB-ILD), and DIP are frequently subclassified with the IIPs, these disorders (along with PLCH, an ILD with unique clinical, imaging and histopathologic manifestations) are commonly felt to be the result of active or prior tobacco smoke exposure. DIP has also been known to occur in children with familial pulmonary fibrosis (FPF). Smokers, particularly elderly smokers, frequently have radiologic (centrilobular) interstitial abnormalities. These interstitial abnormalities are often incidentally found on routine CXR or chest CT studies in asymptomatic, or minimally symptomatic individuals. Respiratory bronchiolitis is felt to correlate histopathologically with these imaging findings. However, in some cases these imaging findings

can progress to more advanced radiologic changes where more diffuse signs of interstitial pneumonia tend to be present.

Clinical Manifestations These disorders predominantly occur in active, and in many cases heavy, smokers who are typically between 40 and 50 years of age. In those ultimately diagnosed with RB-ILD or DIP, dyspnea and cough are relatively common and symptomatic wheezing is not rare. The prevalence of smoking-related ILDs is not well understood, but they are generally felt to account for <10% of the IIPs. While there is minimal data on the natural histories and prognoses of these conditions, prolonged survival can be expected in most patients with RB-ILD and death secondary to progressive ILD is felt to be rare.

HRCT Image Findings Prominent and common findings in RB-ILD include central bronchial wall thickening, peripheral bronchial wall thickening, centrilobular nodules, and ground-glass opacities. Septal lines and a reticular pattern are also not uncommon. Honeycombing is generally felt to be rare (and indicates a worse prognosis). Similar findings are noted in patients with DIP where diffuse (or patchy) bilateral symmetric ground-glass opacities tend to be even more prominent.

Histopathology Common features of RB-ILD include the accumulation of pigmented macrophages within the lumens of respiratory bronchioles and alveolar ducts, accompanied by chronic inflammation of the respiratory bronchiolar walls and both bronchiolar and peribronchiolar alveolar fibrosis causing architectural distortion. These features are patchy and confined to the peribronchiolar region. DIP tends to include similar changes but they have a more diffuse pattern characterized by pigmented macrophage accumulation, pneumocyte hyperplasia, and prominent interstitial thickening.

Treatment All patients with smoking-related ILD should be counseled to discontinue smoking and/or encouraged to enroll in a formal smoking cessation program. Small studies have evaluated, and patients are often treated with immunosuppressive (e.g., prednisone) and cytotoxic (e.g., azathioprine, and cyclophosphamide) agents and in some cases with bronchodilators. To date there is no strong evidence that these therapies result in significant improvements symptoms, measures of pulmonary function, or if they prevent clinical deterioration.

CRYPTOGENIC ORGANIZING PNEUMONIA

Clinical Manifestations COP typically involves patients in their 50–60s and often presents as a subacute flu-like illness, with cough, dyspnea, fever, and fatigue. Inspiratory rales are often present on examination and most patients are noted to have restrictive lung deficits on pulmonary function testing with hypoxemia. It is commonly mistaken for pneumonia. It is important to note that this syndrome can occur in isolation or can be secondary to an underlying connective tissue disease (e.g., polymyositis), medications, or can result from an underlying malignancy. Laboratory testing for various connective tissue diseases is helpful as they can both be diagnostic and suggest the need for prolonged medical therapy.

HRCT Image Findings The most common imaging findings include patchy, sometimes migratory, subpleural consolidative opacities often with associated ground-glass opacities. Peribronchiolar, or perilobar opacities can be present and sometimes a rim of subpleural sparing (often referred to as a reversed halo or atoll sign) can be seen which can aid in the diagnosis.

Histopathology Surgical lung biopsy specimens tend to reveal patchy regions of organizing pneumonia with granulation tissue that commonly involves the small airways, alveolar ducts, and alveoli with surrounding inflammation that can involve the alveolar walls (Fig. 287-2).

Treatment Corticosteroids can result in substantial clinical improvement in many patients but usually need to be continued for at least 6 months as relapse rates are high. Evidence is growing that alternate cytotoxic (e.g., mycophenolate, cyclophosphamide) or biologic (e.g., rituximab) therapies can be helpful in both treating the disease and reducing the need for steroids. In some patients with secondary forms of the disease, long-term therapy may be needed.

ACUTE OR SUBACUTE IIPS

ACUTE INTERSTITIAL PNEUMONIA (HAMMAN-RICH SYNDROME)

Clinical Manifestations AIP is a rare and often fatal lung disorder that is characterized by an acute onset of respiratory distress and hypoxemia. A prodromal period of symptoms consistent with an acute upper respiratory infection is common. The mortality rate within 6 months of presentation can be quite high (>50%) and recurrences are common. In those that recover, lung function improvement can be substantial. AIP can be difficult to distinguish from acute respiratory distress syndrome (ARDS) and an acute exacerbation of an unsuspected underlying pulmonary fibrotic process.

HRCT Image Findings The most common imaging findings are patchy bilateral ground-glass opacities. Dependent regions of air-space consolidation are also common.

Histopathology Similar to ARDS and acute exacerbations of underlying pulmonary fibrosis, AIP presents histopathologically as diffuse alveolar damage (DAD) demonstrated on a surgical lung biopsy.

Treatment Treatment is mostly supportive and often includes mechanical ventilation. There is no proven drug therapy for AIP. Glucocorticoids are often given but they are not clearly effective and have been demonstrated not to be beneficial in other forms of DAD (e.g., ARDS).

ACUTE EXACERBATIONS OF IIPS

Clinical Manifestations Acute exacerbations are not separate disorders, but rather an accelerated phase of lung injury that can occur in any ILD resulting in pulmonary fibrosis. Acute exacerbations are most commonly described, and most severe in, patients with known IPF. Acute exacerbations are characterized by an acute onset (<30 days) of respiratory distress and hypoxemia occurring in a patient with underlying pulmonary fibrosis not explained by an alternate cause (e.g., pneumonia, left heart failure). Reported mortality rates are very high (>85%) and mean survival periods range from as little as days to months.

HRCT Image Findings The most common imaging findings include patchy bilateral ground-glass opacities and dependent regions of air-space consolidation. Sometimes these new changes can be appreciated on the background of the imaging findings typified by the underlying IIP, although sometimes they obscure the preceding imaging findings.

Histopathology Acute exacerbations of underlying pulmonary fibrosis present histopathologically as DAD, although sometimes organizing pneumonia can also be demonstrated on a surgical lung biopsy.

Treatment Treatment is mostly supportive. Mechanical ventilation, when not being used as a bridge to lung transplantation, is controversial as the survival rate in these patients tends to be poor. There is some evidence that drug therapy (e.g., Nintedanib) may reduce the rate of acute exacerbations in patients with IPF. Drug therapy, in the context of an acute exacerbation is also controversial. Immunosuppressive (e.g., prednisone) and cytotoxic (e.g., cyclophosphamide) therapies are commonly used without proven benefit.

ILD ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

ILD is a common disease manifestation of many connective tissue diseases. Disease progression, response to therapy and survival is variable and associated with specific radiologic and histopathologic patterns. ILD occurs most commonly in patients with scleroderma (systemic sclerosis form, or SSc), RA, polymyositis/dermatomyositis, and less

frequently Sjögren syndrome and systemic lupus erythematosus (SLE). ILD may precede the development of extrapulmonary manifestations of a specific connective tissue disease or may present as part of a poorly defined connective tissue disease. In rare cases, lung manifestations may be the sole feature of the patient's clinical presentation.

SYSTEMIC SCLEROSIS

Clinical Manifestations (Chap. 353) ILD is the most common pulmonary manifestation of SSc. ILD occurs in about 50% of SSc patients with diffuse disease and in about 30% of patients with limited disease. Pulmonary hypertension can occur separately or concomitantly with ILD and is more frequent in patients with limited SSc.

HRCT Image Findings Similar imaging findings noted in both patients with NSIP and IPF can be present, although findings consistent with COP and DAD may also be present. Additional HRCT findings may include a dilated esophagus and pulmonary artery enlargement.

Histopathology Comparable to the imaging overlap, histopathologic changes commonly noted in patients with NSIP and IPF are frequently identified. Additionally, aspiration related to esophageal dysmotility is common in SSc, in these patients histopathologic findings consistent with COP and DAD may be observed.

Treatment Cyclophosphamide has a modest benefit in preservation of lung function and is associated with significant toxicity. Mycophenolate has recently been shown to have similar efficacy and improved tolerability. Clinical trials testing antifibrotic therapies (pirfenidone and nintedanib) are presently being conducted. Minimizing the risk of reflux by using high-dose proton pump inhibitors or antireflux surgery should be considered in SSc with progressive ILD. Lung transplantation can potentially be offered to select patients without significant aspiration or chest wall restriction.

RHEUMATOID ARTHRITIS

Clinical Manifestations (Chap. 351) A common extraarticular complication of RA is ILD. Although RA is more common in females, RA-ILD is more frequent in males and in patients with a history of tobacco exposure. In a small subset of patients, ILD is the first disease manifestation of RA. Clinically evident disease RA-ILD occurs in nearly 10% of the RA population; however, up to 40–50% of subjects have radiologic abnormalities on chest CT suggesting ILD in the context of RA may be under-diagnosed.

HRCT Image Findings The most common imaging pattern of ILD in patients with RA is a UIP pattern, although NSIP patterns are not uncommon. There is evidence that survival in patients with RA is decreased in those with a UIP pattern and among those with more extensive fibrosis in general.

Histopathology Histopathologic findings of UIP and NSIP are most common. Some studies suggest that UIP in the context of RA (as compared to IPF) may present with a reduced number of fibroblastic foci and an increased amount of germinal centers. Comparable to the imaging findings, UIP (and DAD) patterns in patients with RA are associated with reduced survival.

Treatment In contrast with SSc, there are no randomized clinical trials testing the role of immune suppression in RA-ILD. Extrapolating from the scleroderma experience, immunosuppresive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents have been used with variable success. Clinical trials testing antifibrotic therapies (pirfenidone and nintedanib) are presently being conducted. Lung transplantation is a viable therapeutic approach for eligible patients with progressive disease that is not responsive to medical therapy.

DERMATOMYOSITIS/POLYMYOSITIS

Clinical Manifestations (Chap. 358) The idiopathic inflammatory myopathies are disorders characterized by immune-mediated destruction and dysfunction of muscle, however this disorder can affect the skin, joints, cardiovascular system and lung. The prevalence of ILD associated with inflammatory myopathy varies by report, however ILD is present in up to 45% of patients with positive anti-synthetase antibodies. The anti-synthetase syndrome is characterized by positive anti-synthetase antibodies, myositis, fever, Raynaud phenomenon, mechanic's hands, arthritis, and progressive ILD. There is a subset of anti–Jo-1 antibody–positive individuals who can develop a rapidly progressive form of ILD consistent with an acute exacerbation. Some studies have suggested that ILD may be even more common in those with other antibodies (e.g., anti-PL-12). Dermatomyositis/polymyositis can occur as an isolated connective tissue disease or as a process associated with an underlying malignancy.

HRCT Image Findings Common imaging patterns of ILD in patients with dermatomyositis/polymyositis include those consistent with NSIP with or without evidence for COP. A UIP pattern can also occur. Some studies have suggested that a UIP pattern may be more common among those with anti-PL-12 antibodies.

Histopathology The antisynthetase syndrome is associated with multiple histopathologic subtypes including NSIP, COP, and UIP. DAD, a histopathologic pattern observed in AIP and acute exacerbations, is associated with rapidly progressive ILD in myositis patients.

Treatment Immunosuppresive (e.g., prednisone) and cytotoxic (e.g., mycophenolate, azathioprine, cyclophosphamide, and calcineurin inhibitors) agents are often used in patients with progressive ILD. Some patients (particularly those with less fibrosis) have been noted to improve or resolve their ILD in response to medical therapy. In small studies relapses have been more common in patients treated with prednisone alone. Patients who fail immune suppressive therapy can benefit from lung transplantation.

GRANULOMATOUS ILDS

The most common granulomatous ILD is sarcoidosis, a multisystem disorder of unknown cause where lung involvement is often the most dominant feature, will be discussed in Chap. 360. HP, a granulomatous reaction due to inhalation of organic (e.g., bird fancier's lung secondary to exposure to bird feathers) and inorganic (e.g., coal worker's pneumoconiosis secondary to exposure to coal dusts) dusts, is also an important and common cause of ILD and is discussed in Chap. 282.

Granulomatous Vasculitides (See Chap. 60) These disorders are characterized by blood vessels with inflammatory infiltrates associated granulomatous lesions with or without the presence of tissue necrosis. The lungs are commonly involved and a unique feature of these disorders is that hemoptysis can be a presenting symptom. Although laboratory testing is often helpful and can provide specific information, biopsies of involved tissue can be essential for making the diagnosis. Many of these disorders include additional systemic manifestations. GPA, also referred to as Wegener's disease, is an example of a granulomatous vasculitis that commonly affects the lung (including inflammatory infiltrates in small to medium sized vessels), the ears, nose, throat, and kidney (resulting in glomerulonephritis). Common imaging abnormalities of GPA include nodules, patchy ground glass, and consolidative opacities that can be migratory, and hilar lymphadenopathy. Eosinophilic GPA (EG, also referred to as Churg-Strauss syndrome) is another example of a granulomatous vasculitis that affects the lung (including eosinophilic infiltrates in small to medium sized vessels) that can result in numerous clinical manifestations but frequently includes chronic sinusitis, asthma, and peripheral blood eosinophilia. Common imaging abnormalities of EG include peripheral consolidative opacities that can be migratory and small pleural effusions.

GENETICS AND ILD

Studies of genetic epidemiology have led to important insights in our understanding of ILD. First, studies of families with FPF have demonstrated that unique IIPs can cosegregate with specific genetic

variants known to be associated with IPF. This suggests that many genetic variants appear to predispose to interstitial lung injury patterns more broadly than to unique diagnoses specifically. Second, most of the genetic variants known to be associated with FPF are also associated with more sporadic forms of the disease. Third, at least one of the genetic factors most strongly associated with FPF and IPF is both common and confers a large increase in the risk of these diseases. At least one copy of a mucin 5B (*MUC5B*) promoter variant is present in ~20% of Caucasian populations and 35–45% of patients with IPF and confers and approximate sixfold increase in the risk of this disease. Fourth, studies of general population samples demonstrate that imaging abnormalities suggestive of an early stage of pulmonary fibrosis in research participants without known ILD are not uncommon (occurring in ~7–9% of adults) and are also associated with the same genetic variants known to be associated with IPF (e.g., the *MUC5B* promoter variant). This latter finding suggests a path forward towards an early detection of IPF. Additional genetic findings demonstrating replicable associations with pulmonary fibrosis include numerous genetic variants in, and adjacent to, genes known to be involved in the regulation of telomere length (e.g., the *TERT* gene, the telomerase RNA component [*TERC*] gene, and the regulator of telomere elongation helicase 1 [*RTEL1*] gene) and surfactant protein genes (e.g., surfactant protein A2 [*SFTPA2*] gene).

Genetic studies have also provided some insights into other forms of ILD. Genome-wide association studies of sarcoidosis have demonstrated numerous variants in genes, and in genomic regions, that are associated with the disease. Some of these disease associated variants in sarcoidosis fall in human leukocyte antigen (*HLA*) regions, in regions of genes involved in immune regulation (e.g., interleukin 12B [*IL12B*]) in regions of genes that are less well understood (butroyrophilin-like 2 [*BTNL2*]) but also appear to be involved in T-cell activation. LAM is often associated with genetic variants in the tuberous sclerosis complex genes (e.g., *TSC1* and *TSC2*), consistent with the known evidence that this disease can occur in isolation but also in patients with known tuberous sclerosis. Many genetic factors for rare diseases such as Hermansky-Pudlak syndrome (a rare autosomal recessive disorder that results in pulmonary fibrosis but also includes oculocutaneous albinism, bleeding diatheses, and horizontal nystagmus) have also been discovered (e.g., *HSP1*, and *HSP3-7*).

GLOBAL CONSIDERATIONS

The prevalence, clinical presentation, and natural history of most ILDs in European countries resemble that described in the United States. However, as expected, there is growing evidence for racial differences in clinical (rate of acute exacerbations) or genetic (*MUC5B*) attributes between Caucasian and Asian populations. To date there are limited data on the prevalence of ILD in Hispanics, subjects of African descent and many other ethnic groups.

Acknowledgment

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FURTHER READING

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288 Disorders of the Pleura

Richard W. Light

PLEURAL EFFUSION

The pleural space lies between the lung and the chest wall and normally contains a very thin layer of fluid, which serves as a coupling system. A pleural effusion is present when there is an excess quantity of fluid in the pleural space.

Etiology Pleural fluid accumulates when pleural fluid formation exceeds pleural fluid absorption. Normally, fluid enters the pleural space from the capillaries in the parietal pleura and is removed via the lymphatics in the parietal pleura. Fluid also can enter the pleural space from the interstitial spaces of the lung via the visceral pleura or from the peritoneal cavity via small holes in the diaphragm. The lymphatics have the capacity to absorb 20 times more fluid than is formed normally. Accordingly, a pleural effusion may develop when there is excess pleural fluid formation (from the interstitial spaces of the lung, the parietal pleura, or the peritoneal cavity) or when there is decreased fluid removal by the lymphatics.

Diagnostic Approach Patients suspected of having a pleural effusion should undergo chest imaging to diagnose its extent. Chest ultrasound has replaced the lateral decubitus x-ray in the evaluation of suspected pleural effusions and as a guide to thoracentesis. When a patient is found to have a pleural effusion, an effort should be made to determine the cause **(Fig. 288-1)**. The first step is to determine whether the effusion is a transudate or an exudate. A *transudative pleural effusion* occurs when *systemic factors* that influence the formation and absorption of pleural fluid are altered. The leading causes of transudative pleural effusions in the United States are left ventricular failure and cirrhosis. An *exudative pleural effusion* occurs when *local factors* that influence the formation and absorption of pleural fluid are altered. The leading causes of exudative pleural effusions are bacterial pneumonia, malignancy, viral infection, and pulmonary embolism. The primary reason for making this differentiation is that additional diagnostic procedures are indicated with exudative effusions to define the cause of the local disease.

Transudative and exudative pleural effusions are distinguished by measuring the lactate dehydrogenase (LDH) and protein levels in the pleural fluid. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none:

1. Pleural fluid protein/serum protein >0.5
2. Pleural fluid LDH/serum LDH >0.6
3. Pleural fluid LDH more than two-thirds the normal upper limit for serum

These criteria misidentify ~25% of transudates as exudates. If one or more of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, the difference between the protein levels in the serum and the pleural fluid should be measured. If this gradient is >31 g/L (3.1 g/dL), the exudative categorization by these criteria can be ignored because almost all such patients have a transudative pleural effusion.

If a patient has an exudative pleural effusion, the following tests on the pleural fluid should be obtained: description of the appearance of the fluid, glucose level, differential cell count, microbiologic studies, and cytology.

Effusion Due to Heart Failure The most common cause of pleural effusion is left ventricular failure. The effusion occurs because the increased amounts of fluid in the lung interstitial spaces exit in part across the visceral pleura; this overwhelms the capacity of the lymphatics in the parietal pleura to remove fluid. In patients with heart failure, a diagnostic thoracentesis should be performed if the effusions are not bilateral and comparable in size, if the patient is febrile, or if the patient has pleuritic chest pain to verify that the patient has a

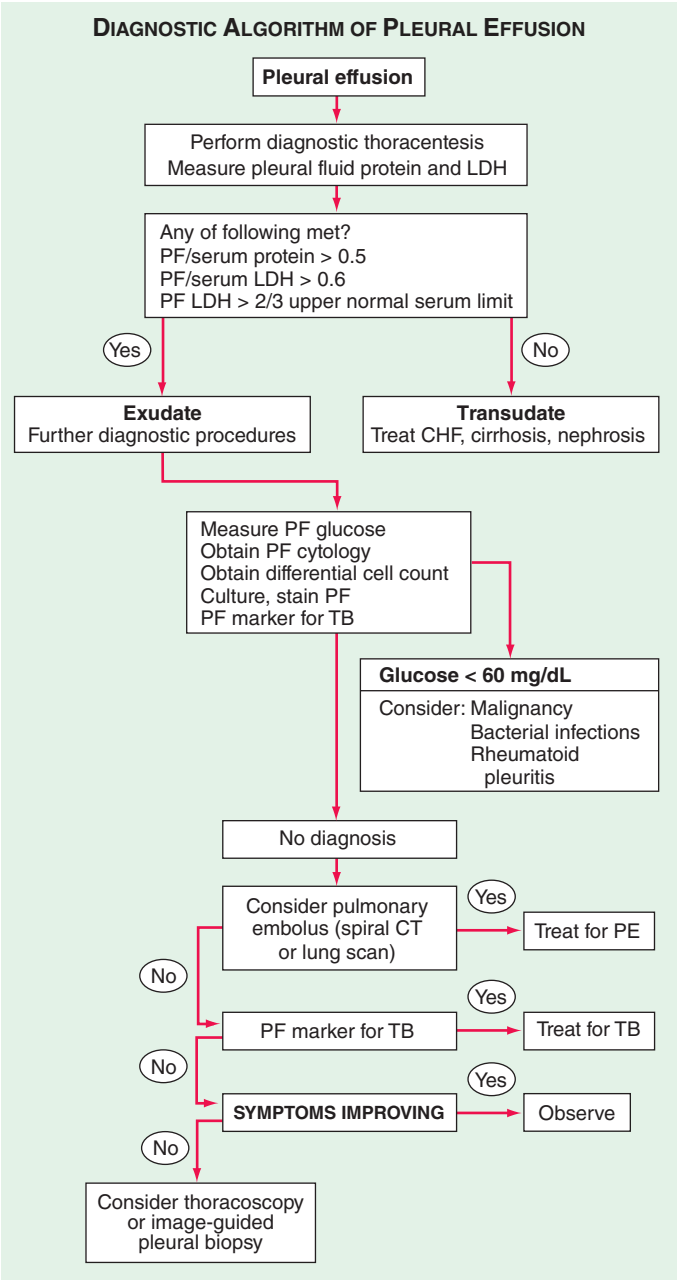

FIGURE 288-1 Approach to the diagnosis of pleural effusions. CHF, congestive heart failure; CT, computed tomography; LDH, lactate dehydrogenase; PE, pulmonary embolism; PF, pleural fluid; TB, tuberculosis.

transudative effusion. Otherwise the patient's heart failure is treated. If the effusion persists despite therapy, a diagnostic thoracentesis should be performed. A pleural fluid N-terminal pro-brain natriuretic peptide (NT-proBNP) >1500 pg/mL is virtually diagnostic that the effusion is secondary to congestive heart failure.

Hepatic Hydrothorax Pleural effusions occur in ~5% of patients with cirrhosis and ascites. The predominant mechanism is the direct movement of peritoneal fluid through small openings in the diaphragm into the pleural space. The effusion is usually right-sided and frequently is large enough to produce severe dyspnea.

Parapneumonic Effusion Parapneumonic effusions are associated with bacterial pneumonia, lung abscess, or bronchiectasis and are probably the most common cause of exudative pleural effusion in the United States. *Empyema* refers to a grossly purulent effusion.

Patients with aerobic bacterial pneumonia and pleural effusion present with an acute febrile illness consisting of chest pain, sputum production, and leukocytosis. Patients with anaerobic infections present with a subacute illness with weight loss, a brisk leukocytosis, mild anemia, and a history of some factor that predisposes them to aspiration.

The possibility of a parapneumonic effusion should be considered whenever a patient with bacterial pneumonia is initially evaluated. The presence of free pleural fluid can be demonstrated with a lateral decubitus radiograph, computed tomography (CT) of the chest, or ultrasound. If the free fluid separates the lung from the chest wall by >10 mm, a therapeutic thoracentesis should be performed. Factors indicating the likely need for a procedure more invasive than a thoracentesis (in increasing order of importance) include the following:

1. Loculated pleural fluid
2. Pleural fluid pH <7.20
3. Pleural fluid glucose <3.3 mmol/L (<60 mg/dL)
4. Positive Gram stain or culture of the pleural fluid
5. Presence of gross pus in the pleural space

If the fluid recurs after the initial therapeutic thoracentesis and if any of these characteristics is present, a repeat thoracentesis should be performed. If the fluid cannot be completely removed with the therapeutic thoracentesis, consideration should be given to inserting a chest tube and instilling the combination of a fibrinolytic agent (e.g., tissue plasminogen activator, 10 mg) and deoxyribonuclease (5 mg) or performing a thoracoscopy with the breakdown of adhesions. Decortication should be considered when these measures are ineffective.

Effusion Secondary to Malignancy Malignant pleural effusions secondary to metastatic disease are the second most common type of exudative pleural effusion. The three tumors that cause ~75% of all malignant pleural effusions are lung carcinoma, breast carcinoma, and lymphoma. Most patients complain of dyspnea, which is frequently out of proportion to the size of the effusion. The pleural fluid is an exudate, and its glucose level may be reduced if the tumor burden in the pleural space is high.

The diagnosis usually is made via cytology of the pleural fluid. If the initial cytologic examination is negative, thoracoscopy is the best next procedure if malignancy is strongly suspected. At the time of thoracoscopy, a procedure such as pleural abrasion should be performed to effect a pleurodesis. An alternative to thoracoscopy is CT- or ultrasound-guided needle biopsy of pleural thickening or nodules. Patients with a malignant pleural effusion are treated symptomatically for the most part, since the presence of the effusion indicates disseminated disease and most malignancies associated with pleural effusion are not curable with chemotherapy. The only symptom that can be attributed to the effusion itself is dyspnea. If the patient's lifestyle is compromised by dyspnea and if the dyspnea is relieved with a therapeutic thoracentesis, one of the following procedures should be considered: (1) insertion of a small indwelling catheter or (2) tube thoracostomy with the instillation of a sclerosing agent such as doxycycline (500 mg).

Mesothelioma Malignant mesotheliomas are primary tumors that arise from the mesothelial cells that line the pleural cavities; most are related to asbestos exposure. Patients with mesothelioma present with chest pain and shortness of breath. The chest radiograph reveals a pleural effusion, generalized pleural thickening, and a shrunken hemithorax. The diagnosis is usually established with image-guided needle biopsy or thoracoscopy.

Effusion Secondary to Pulmonary Embolization The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion is pulmonary embolism. Dyspnea is the most common symptom. The pleural fluid is almost always an exudate. The diagnosis is established by spiral CT scan or pulmonary arteriography (Chap. 273). Treatment of a patient with a pleural effusion secondary to pulmonary embolism is the same as it is for any patient with pulmonary emboli. If the pleural effusion increases in size after anticoagulation, the patient probably has recurrent emboli or another complication, such as a hemothorax or a pleural infection.

Tuberculous Pleuritis (See also Chap. 173) In many parts of the world, the most common cause of an exudative pleural effusion

is tuberculosis (TB), but tuberculous effusions are relatively uncommon in the United States. Tuberculous pleural effusions usually are associated with primary TB and are thought to be due primarily to a hypersensitivity reaction to tuberculous protein in the pleural space. Patients with tuberculous pleuritis present with fever, weight loss, dyspnea, and/or pleuritic chest pain. The pleural fluid is an exudate with predominantly small lymphocytes. The diagnosis is established by demonstrating high levels of TB markers in the pleural fluid (adenosine deaminase >40 IU/L or interferon γ >140 pg/mL). Alternatively, the diagnosis can be established by culture of the pleural fluid, needle biopsy of the pleura, or thoracoscopy. The recommended treatments of pleural and pulmonary TB are identical **(Chap. 173)**.

Effusion Secondary to Viral Infection Viral infections are probably responsible for a sizable percentage of undiagnosed exudative pleural effusions. In many series, no diagnosis is established for ~20% of exudative effusions, and these effusions resolve spontaneously with no long-term residua. The importance of these effusions is that one should not be too aggressive in trying to establish a diagnosis for the undiagnosed effusion, particularly if the patient is improving clinically.

Chylothorax A chylothorax occurs when the thoracic duct is disrupted and chyle accumulates in the pleural space. The most common cause of chylothorax is trauma (most frequently thoracic surgery), but it also may result from tumors in the mediastinum. Patients with chylothorax present with dyspnea, and a large pleural effusion is present on the chest radiograph. Thoracentesis reveals milky fluid, and biochemical analysis reveals a triglyceride level that exceeds 1.2 mmol/L (110 mg/dL). Patients with chylothorax and no obvious trauma should have a lymphangiogram and a mediastinal CT scan to assess the mediastinum for lymph nodes. The treatment of choice for most chylothoraxes is insertion of a chest tube plus the administration of octreotide. If these modalities fail, percutaneous transabdominal thoracic duct blockage effectively controls most chylothoraces. An alternative treatment is ligation of the thoracic duct. Patients with chylothoraxes should not undergo prolonged tube thoracostomy with chest tube drainage because this will lead to malnutrition and immunologic incompetence.

Hemothorax When a diagnostic thoracentesis reveals bloody pleural fluid, a hematocrit should be obtained on the pleural fluid. If the hematocrit is more than one-half of that in the peripheral blood, the patient is considered to have a hemothorax. Most hemothoraxes are the result of trauma; other causes include rupture of a blood vessel or tumor. Most patients with hemothorax should be treated with tube thoracostomy, which allows continuous quantification of bleeding. If the bleeding emanates from a laceration of the pleura, apposition of the two pleural surfaces is likely to stop the bleeding. If the pleural hemorrhage exceeds 200 mL/h, consideration should be given to angiographic coil embolization, thoracoscopy or thoracotomy.

Miscellaneous Causes of Pleural Effusion There are many other causes of pleural effusion **(Table 288-1)**. Key features of some of these conditions are as follows: If the pleural fluid amylase level is elevated, the diagnosis of esophageal rupture or pancreatic disease is likely. If the patient is febrile, has predominantly polymorphonuclear cells in the pleural fluid, and has no pulmonary parenchymal abnormalities, an intraabdominal abscess should be considered.

The diagnosis of an asbestos pleural effusion is one of exclusions. Benign ovarian tumors can produce ascites and a pleural effusion (Meigs' syndrome), as can the ovarian hyperstimulation syndrome. Several drugs can cause pleural effusion; the associated fluid is usually eosinophilic. Pleural effusions commonly occur after coronary artery bypass surgery. Effusions occurring within the first weeks are typically left-sided and bloody, with large numbers of eosinophils, and respond to one or two therapeutic thoracenteses. Effusions occurring after the first few weeks are typically left-sided and clear yellow, with predominantly small lymphocytes, and tend to recur. Other medical manipulations that induce pleural effusions include abdominal surgery; radiation therapy; liver, lung, or heart transplantation; and the intravascular insertion of central lines.

TABLE 288-1 Differential Diagnoses of Pleural Effusions

Transudative Pleural Effusions

1. Congestive heart failure
2. Cirrhosis
3. Nephrotic syndrome
4. Peritoneal dialysis
5. Superior vena cava obstruction
6. Myxedema
7. Urinothorax

Exudative Pleural Effusions

1. Neoplastic diseases
   a. Metastatic disease
   b. Mesothelioma
2. Infectious diseases
   a. Bacterial infections
   b. Tuberculosis
   c. Fungal infections
   d. Viral infections
   e. Parasitic infections
3. Pulmonary embolization
4. Gastrointestinal disease
   a. Esophageal perforation
   b. Pancreatic disease
   c. Intraabdominal abscesses
   d. Diaphragmatic hernia
   e. After abdominal surgery
   f. Endoscopic variceal sclerotherapy
   g. After liver transplant
5. Collagen vascular diseases
   a. Rheumatoid pleuritis
   b. Systemic lupus erythematosus
   c. Drug-induced lupus
   d. Sjögren syndrome
   e. Granulomatosis with polyangiitis (Wegener)
   f. Churg-Strauss syndrome
6. Post-coronary artery bypass surgery
7. Asbestos exposure
8. Sarcoidosis
9. Uremia
10. Meigs' syndrome
11. Yellow nail syndrome
12. Drug-induced pleural disease
    a. Nitrofurantoin
    b. Dantrolene
    c. Methysergide
    d. Bromocriptine
    e. Procarbazine
    f. Amiodarone
    g. Dasatinib
13. Trapped lung
14. Radiation therapy
15. Post-cardiac injury syndrome
16. Hemothorax
17. Iatrogenic injury
18. Ovarian hyperstimulation syndrome
19. Pericardial disease
20. Chylothorax

PNEUMOTHORAX

Pneumothorax is the presence of gas in the pleural space. A *spontaneous pneumothorax* is one that occurs without antecedent trauma to the thorax. A *primary spontaneous pneumothorax* occurs in the absence of underlying lung disease, whereas a *secondary pneumothorax* occurs in

its presence. A *traumatic pneumothorax* results from penetrating or nonpenetrating chest injuries. A *tension pneumothorax* is a pneumothorax in which the pressure in the pleural space is positive throughout the respiratory cycle.

Primary Spontaneous Pneumothorax Primary spontaneous pneumothoraxes are usually due to rupture of apical pleural blebs, small cystic spaces that lie within or immediately under the visceral pleura. Primary spontaneous pneumothoraxes occur almost exclusively in smokers; this suggests that these patients have subclinical lung disease. Approximately one-half of patients with an initial primary spontaneous pneumothorax will have a recurrence. The initial recommended treatment for primary spontaneous pneumothorax is simple aspiration. If the lung does not expand with aspiration or if the patient has a recurrent pneumothorax, thoracoscopy with stapling of blebs and pleural abrasion is indicated. Thoracoscopy or thoracotomy with pleural abrasion is almost 100% successful in preventing recurrences.

Secondary Pneumothorax Most secondary pneumothoraxes are due to chronic obstructive pulmonary disease, but pneumothoraxes have been reported with virtually every lung disease. Pneumothorax in patients with lung disease is more life-threatening than it is in normal individuals because of the lack of pulmonary reserve in these patients. Nearly all patients with secondary pneumothorax should be treated with tube thoracostomy. Most should also be treated with thoracoscopy or thoracotomy with the stapling of blebs and pleural abrasion. If the patient is not a good operative candidate or refuses surgery, pleurodesis should be attempted by the intrapleural injection of a sclerosing agent such as doxycycline.

Traumatic Pneumothorax Traumatic pneumothoraxes can result from both penetrating and nonpenetrating chest trauma. Traumatic pneumothoraxes should be treated with tube thoracostomy unless they are very small. If a hemopneumothorax is present, one chest tube should be placed in the superior part of the hemithorax to evacuate the air and another should be placed in the inferior part of the hemithorax to remove the blood. Iatrogenic pneumothorax is a type of traumatic pneumothorax that is becoming more common. The leading causes are transthoracic needle aspiration, thoracentesis, and the insertion of central intravenous catheters. Most can be managed with supplemental oxygen or aspiration, but if these measures are unsuccessful, a tube thoracostomy should be performed.

Tension Pneumothorax This condition usually occurs during mechanical ventilation or resuscitative efforts. The positive pleural pressure is life-threatening both because ventilation is severely compromised and because the positive pressure is transmitted to the mediastinum, resulting in decreased venous return to the heart and reduced cardiac output.

Difficulty in ventilation during resuscitation or high peak inspiratory pressures during mechanical ventilation strongly suggest the diagnosis. The diagnosis is made by physical examination showing an enlarged hemithorax with no breath sounds, hyperresonance to percussion, and shift of the mediastinum to the contralateral side. Tension pneumothorax must be treated as a medical emergency. If the tension in the pleural space is not relieved, the patient is likely to die from inadequate cardiac output or marked hypoxemia. A large-bore needle should be inserted into the pleural space through the second anterior intercostal space. If large amounts of gas escape from the needle after insertion, the diagnosis is confirmed. The needle should be left in place until a thoracostomy tube can be inserted.

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289 Disorders of the Mediastinum

Richard W. Light

The mediastinum is the region between the pleural sacs. It is separated into three compartments **(Table 289-1)**. The *anterior mediastinum* extends from the sternum anteriorly to the pericardium and brachiocephalic vessels posteriorly. It contains the thymus gland, the anterior mediastinal lymph nodes, and the internal mammary arteries and veins. The *middle mediastinum* lies between the anterior and posterior mediastina and contains the heart; the ascending and transverse arches of the aorta; the venae cavae; the brachiocephalic arteries and veins; the phrenic nerves; the trachea, the main bronchi, and their contiguous lymph nodes; and the pulmonary arteries and veins. The *posterior mediastinum* is bounded by the pericardium and trachea anteriorly and the vertebral column posteriorly. It contains the descending thoracic aorta, the esophagus, the thoracic duct, the azygos and hemiazygos veins, and the posterior group of mediastinal lymph nodes.

MEDIASTINAL MASSES

The first step in evaluating a mediastinal mass is to place it in one of the three mediastinal compartments, since each has different characteristic lesions (Table 289-1).

Computed tomography (CT) scanning is the most valuable imaging technique for evaluating mediastinal masses and is the only imaging technique that should be done in most instances. Barium studies of the gastrointestinal tract are indicated in many patients with posterior mediastinal lesions, because hernias, diverticula, and achalasia are readily diagnosed in this manner. An iodine-131 scan can efficiently establish the diagnosis of intrathoracic goiter.

A definite diagnosis can be obtained with mediastinoscopy or anterior mediastinotomy in many patients with masses in the anterior or middle mediastinal compartments. A diagnosis can be established without thoracotomy via percutaneous fine-needle aspiration biopsy or endoscopic transesophageal or endobronchial ultrasound-guided biopsy of mediastinal masses in most cases. An alternative way to establish the diagnosis is video-assisted thoracoscopy. In many cases, the diagnosis can be established and the mediastinal mass removed with video-assisted thoracoscopy.

ACUTE MEDIASTINITIS

Cases of acute mediastinitis are usually due to esophageal perforation, occur after median sternotomy for cardiac surgery, or are infections descending from the neck, oral cavity, or facial area. Patients with esophageal rupture are acutely ill with chest pain and dyspnea due to the mediastinal infection. The esophageal rupture can occur spontaneously or as a complication of esophagoscopy or the insertion of a Blakemore tube. Appropriate treatment consists of exploration of the mediastinum with primary repair of the esophageal tear and drainage of the pleural space and the mediastinum.

The incidence of mediastinitis after median sternotomy is 0.4–5.0%. Patients most commonly present with wound drainage. Other presentations include sepsis and a widened mediastinum. The diagnosis usually is established with mediastinal needle aspiration. Treatment includes immediate drainage, debridement, and parenteral antibiotic therapy, but the mortality rate still exceeds 20%.

CHRONIC MEDIASTINITIS

The spectrum of chronic mediastinitis ranges from granulomatous inflammation of the lymph nodes in the mediastinum to fibrosing mediastinitis. Most cases are due to histoplasmosis or tuberculosis, but sarcoidosis, silicosis, and other fungal diseases are at times causative. Patients with granulomatous mediastinitis are usually asymptomatic. Those with fibrosing mediastinitis usually have signs of compression of a mediastinal structure such as the superior vena cava or large airways,

TABLE 289-1 The Three Compartments of the Mediastinum

	ANTERIOR COMPARTMENT	MIDDLE COMPARTMENT	POSTERIOR COMPARTMENT
Anatomical boundaries	Manubrium and sternum anteriorly, pericardium, aorta, and brachiocephalic vessels posteriorly	Anterior mediastinum anteriorly, posterior mediastinum posteriorly	Pericardium and trachea anteriorly; vertebral column posteriorly
Contents	Thymus gland, anterior mediastinal lymph nodes, internal mammary arteries, and veins	Pericardium, heart, ascending and transverse arch of aorta, superior and inferior vena cavae, brachiocephalic arteries and veins, phrenic nerves, trachea, and main bronchi and their contiguous lymph nodes, pulmonary arteries, and veins	Descending thoracic aorta, esophagus, thoracic duct, azygos and hemiazygos veins, sympathetic chains, and the posterior group of mediastinal lymph nodes
Common abnormalities	Thymoma, lymphomas, teratomatous neoplasms, thyroid masses, parathyroid masses, mesenchymal tumors, giant lymph node hyperplasia, hernia through foramen of Morgagni	Metastatic lymph node enlargement, granulomatous lymph node enlargement, pleuropericardial cysts, bronchogenic cysts, masses of vascular origin	Neurogenic tumors, meningocele, meningomyelocele, gastroenteric cysts, esophageal diverticula, hernia through foramen of Bochdalek, extramedullary hematopoiesis

phrenic or recurrent laryngeal nerve paralysis, or obstruction of the pulmonary artery or proximal pulmonary veins. If veins or arteries are involved, the placement of stents has relieved the symptoms in many patients.

PNEUMOMEDIASTINUM

In this condition, there is gas in the interstices of the mediastinum. The three main causes are (1) alveolar rupture with dissection of air into the mediastinum; (2) perforation or rupture of the esophagus, trachea, or main bronchi; and (3) dissection of air from the neck or the abdomen into the mediastinum. Typically, there is severe substernal chest pain with or without radiation into the neck and arms. The physical examination usually reveals subcutaneous emphysema in the suprasternal notch and *Hamman's sign*, which is a crunching or clicking noise synchronous with the heartbeat and is best heard in the left lateral decubitus position. The diagnosis is confirmed with the chest radiograph. Usually no treatment is required, but the mediastinal air will be absorbed faster if the patient inspires high concentrations of oxygen. If mediastinal structures are compressed, the compression can be relieved with needle aspiration.

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290 Disorders of Ventilation

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DEFINITION AND PHYSIOLOGY

In health the arterial level of carbon dioxide ($Paco_2$) is maintained between 37 and 43 mmHg at sea level. All disorders of ventilation result in abnormal measurements of $Paco_2$. This chapter reviews chronic ventilatory disorders.

The continuous production of CO_2 by cellular metabolism necessitates its efficient elimination by the respiratory system. The relationship between CO_2 production and $Paco_2$ is described by the equation: $Paco_2 = (k)\ (\dot{V}co_2)/\dot{V}A$, where $\dot{V}co_2$ represents the carbon dioxide production, k is a constant and $\dot{V}A$ is fresh gas alveolar ventilation (see Chap. 279). $\dot{V}A$ can be calculated as minute ventilation × (1 – Vd/Vt), where the dead space fraction Vd/Vt represents the portion of a tidal breath that remains within the conducting airways at the conclusion of inspiration and so does not contribute to alveolar ventilation. As such, all disturbances of $Paco_2$ must reflect altered CO_2 production, minute ventilation, or dead space fraction.

Diseases that alter $\dot{V}co_2$ are often acute (sepsis, burns, or pyrexia, for example) and their contribution to ventilatory abnormalities and/or respiratory failure is reviewed elsewhere. Chronic ventilatory disorders typically involve inappropriate levels of minute ventilation or increased dead space fraction. Characterization of these disorders requires a review of the normal respiratory cycle.

The spontaneous cycle of inspiration and expiration is automatically generated in the brainstem. Two groups of neurons located within the medulla are particularly important: the dorsal respiratory group (DRG) and the ventral respiratory column (VRC). These neurons have widespread projections including the descending projections into the contralateral spinal cord where they perform many functions. They initiate activity in the phrenic nerve/diaphragm, project to the upper airway muscle groups and spinal respiratory neurons, and innervate the intercostal and abdominal muscles that participate in normal respiration. The DRG acts as the initial integration site for many of the afferent nerves relaying information about Pao_2, $Paco_2$, pH, and blood pressure from the carotid and aortic chemoreceptors and baroreceptors to the central nervous system (CNS). In addition, the vagus nerve relays information from stretch receptors and juxtapulmonary-capillary receptors in the lung parenchyma and chest wall to the DRG. The respiratory rhythm is generated within the VRC as well as the more rostrally located parafacial respiratory group (pFRG), which is particularly important for the generation of active expiration. One particularly important area within the VRC is the so called pre-Bötzinger complex. This area is responsible for the generation of various forms of inspiratory activity, and lesioning of the pre-Bötzinger complex leads to the complete cessation of breathing. The neural output of these medullary respiratory networks can be voluntarily suppressed or augmented by input from higher brain centers and the autonomic nervous system. During normal sleep there is an attenuated response to hypercapnia and hypoxemia resulting in mild nocturnal hypoventilation that corrects upon awakening.

Once neural input has been delivered to the respiratory pump muscles, normal gas exchange requires an adequate amount of respiratory muscle strength to overcome the elastic and resistive loads of the respiratory system (Fig. 290-1*A*) (also see Chap. 279). In health, the strength of the respiratory muscles readily accomplishes this and normal respiration continues indefinitely. Reduction in respiratory drive or neuromuscular competence or substantial increase in respiratory load can diminish minute ventilation, resulting in hypercapnia (Fig. 290-1*B*). Alternatively, if normal respiratory muscle strength is coupled with excessive respiratory drive, then alveolar hyperventilation ensues and leads to hypocapnia (Fig. 290-1*C*).

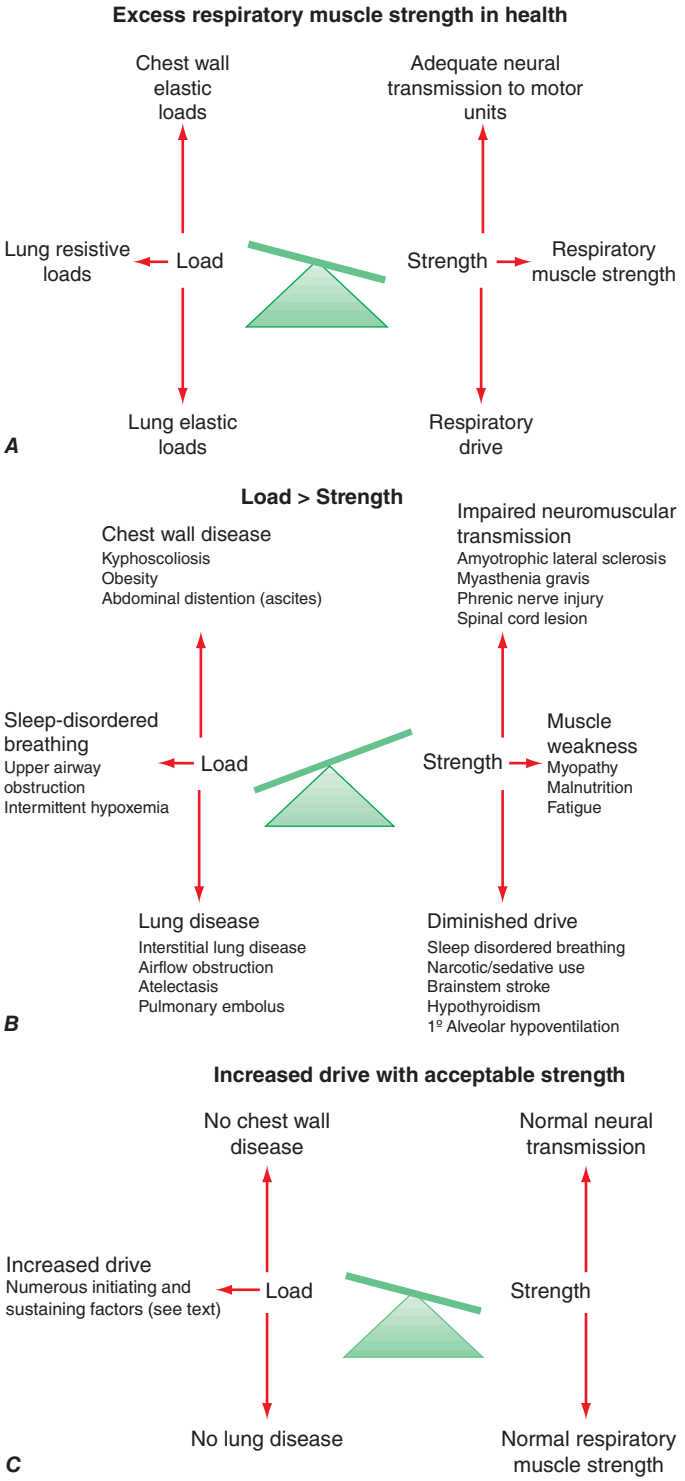

FIGURE 290-1 Examples of balance between respiratory system strength and load. ***A.*** Excess respiratory muscle strength in health. ***B.*** Load greater than strength. ***C.*** Increased drive with acceptable strength.

TABLE 290-1 Signs and Symptoms of Hypoventilation

Dyspnea during activities of daily living
Orthopnea in diseases affecting diaphragm function
Poor-quality sleep
Daytime hypersomnolence
Early morning headaches
Anxiety
Impaired cough in neuromuscular diseases

HYPOVENTILATION

CLINICAL FEATURES

Diseases that reduce minute ventilation or increase dead space fall into four major categories: parenchymal lung and chest wall disease, sleep disordered breathing, neuromuscular disease, and respiratory drive disorders (Fig. 290-1*B*). The clinical manifestations of hypoventilation syndromes are nonspecific (Table 290-1) and vary depending on the severity of hypoventilation, the rate at which hypercapnia develops, the degree of compensation for respiratory acidosis, and the underlying disorder. Patients with parenchymal lung or chest wall disease typically present with shortness of breath and diminished exercise tolerance. Episodes of increased dyspnea and sputum production are hallmarks of obstructive lung diseases such as COPD, whereas progressive dyspnea and cough are common in interstitial lung diseases. Excessive daytime somnolence, poor-quality sleep and snoring are common among patients with sleep-disordered breathing. Sleep disturbance and orthopnea are also described in neuromuscular disorders. As neuromuscular weakness progresses, the respiratory muscles, including the diaphragm, are placed at a mechanical disadvantage in the supine position due to the upward movement of the abdominal contents. New onset orthopnea is frequently a sign of reduced respiratory muscle force generation. More commonly however, extremity weakness or bulbar symptoms develop prior to sleep disturbance in neuromuscular diseases such as amyotrophic lateral sclerosis (ALS) or muscular dystrophy. Patients with respiratory drive disorders do not have symptoms distinguishable from other causes of chronic hypoventilation.

The clinical course of patients with chronic hypoventilation from neuromuscular or chest wall disease follows a characteristic sequence: An asymptomatic stage where daytime Pao_2 and $Paco_2$ are normal followed by nocturnal hypoventilation, initially during rapid eye movement (REM) sleep and later in non-REM sleep. Finally, if vital capacity drops further, daytime hypercapnia develops. Symptoms can develop at any point along this time-course and often depend on the pace of respiratory muscle functional decline. Regardless of cause, the hallmark of all alveolar hypoventilation syndromes is an increase in alveolar Pco_2 ($PAco_2$) and therefore in $Paco_2$. The resulting respiratory acidosis eventually leads to a compensatory increase in plasma bicarbonate concentration. The increase in $Paco_2$ results in an obligatory decrease in PAo_2, often resulting in hypoxemia. If severe, the hypoxemia manifests clinically as cyanosis and can stimulate erythropoiesis and so induce secondary erythrocytosis. The combination of chronic hypoxemia and hypercapnia may also induce pulmonary vasoconstriction, leading eventually to pulmonary hypertension, right ventricular hypertrophy, and right heart failure.

DIAGNOSIS

Elevated plasma bicarbonate in the absence of volume depletion is suggestive of hypoventilation. An arterial blood gas demonstrating elevated $Paco_2$ with a normal pH confirms chronic alveolar hypoventilation. The subsequent evaluation to identify an etiology should initially focus on whether the patient has lung disease or chest wall abnormalities. Physical examination, imaging studies (chest x-ray and/or CT scan) and pulmonary function tests are sufficient to identify most lung/chest wall disorders leading to hypercapnia. If these evaluations are unrevealing then the clinician should screen for obesity hypoventilation syndrome (OHS), the most frequent sleep disorder leading to chronic hypoventilation, which is typically accompanied by obstructive sleep apnea (OSA). Several screening tools have been developed to identify patients at risk for OSA. The Berlin Questionnaire has been validated in a primary care setting and identifies patients likely to have OSA. The Epworth Sleepiness Scale (ESS) and the STOP-Bang questionnaires have not been validated in outpatient primary care settings but are quick and easy to use. The ESS measures daytime sleepiness, with a score of ≥10 identifying individuals who warrant additional investigation. The STOP-Bang survey has been used in preoperative anesthesia

clinics to identify patients at risk of having OSA. In this population it has 93% sensitivity and 90% negative predictive value. Additionally, the STOP-Bang questionnaire has been validated as a screening tool for OSA in sleep and surgical clinics. The probability of moderate and severe OSA steadily increases with higher STOP-Bang scores.

If the ventilatory apparatus (lung, airways, chest wall) is not responsible for chronic hypercapnia then the focus should shift to respiratory drive and neuromuscular disorders. There is an attenuated increase in minute ventilation in response to elevated CO_2 and/or low O_2 in respiratory drive disorders. These diseases are difficult to diagnose and should be suspected when patients with hypercapnia are found to have normal respiratory muscle strength, normal pulmonary function, and normal alveolar-arterial Po_2 difference. Hypoventilation is more marked during sleep in patients with respiratory drive defects and polysomnography often reveals central apneas, hypopneas, or hypoventilation. Brain imaging (CT scan or MRI) can sometimes identify structural abnormalities in the pons or medulla that result in hypoventilation. Chronic narcotic use or significant hypothyroidism can depress the central respiratory drive and lead to chronic hypercapnia as well.

Respiratory muscle weakness has to be profound before lung volumes are compromised and hypercapnia develops. Typically physical examination reveals decreased strength in major muscle groups prior to the development of hypercapnia. Measurement of maximum inspiratory and expiratory pressures or forced vital capacity (FVC) can be used to monitor for respiratory muscle involvement in diseases with progressive muscle weakness. These patients also have increased risk for sleep-disordered breathing, including hypopneas, central and obstructive apneas, and hypoxemia. Nighttime oximetry and capnometry during polysomnography are helpful in better characterizing sleep disturbances in this patient population.

TREATMENT

Hypoventilation

Nocturnal non-invasive positive-pressure ventilation (NIPPV) has been used successfully in the treatment of hypoventilation and apneas, both central and obstructive, in patients with neuromuscular and chest wall disorders. Nocturnal NIPPV has been shown to improve daytime hypercapnia, prolong survival, and improve health-related quality of life when daytime hypercapnia is documented. ALS guidelines recommend consideration of nocturnal NIPPV if symptoms of hypoventilation exist and one of the following criteria is present: $Paco_2$ ≥45 mmHg; nocturnal oximetry demonstrates oxygen saturation ≤88% for 5 consecutive min; maximal inspiratory pressure <60 cmH_2O; FVC <50% predicted; sniff nasal pressure <40 cmH_2O. However, at present there is inconclusive evidence to support pre-emptive nocturnal NIPPV use in all patients with neuromuscular and chest wall disorders who demonstrate nocturnal but not daytime hypercapnia. Nevertheless, at some point, the institution of full-time ventilatory support with either pressure or volume-preset modes is required in progressive neuromuscular disorders. There is less evidence to direct the timing of this decision, but ventilatory failure requiring mechanical ventilation and chest infections related to ineffective cough are frequent triggers for the institution of full-time ventilatory support.

Treatment of chronic hypoventilation from lung or neuromuscular diseases should be directed at the underlying disorder. Pharmacologic agents that stimulate respiration, such as medroxyprogesterone and acetazolamide, have been poorly studied in chronic hypoventilation and should not replace treatment of the underlying disease process. Regardless of the cause, excessive metabolic alkalosis should be corrected, as plasma bicarbonate levels elevated out of proportion for the degree of chronic respiratory acidosis can result in additional hypoventilation. When indicated, administration of supplemental oxygen is effective in attenuating hypoxemia, polycythemia, and pulmonary hypertension. However, in some patients supplemental oxygen can worsen hypercapnia.

Phrenic nerve or diaphragm pacing is a potential therapy for patients with hypoventilation from high cervical spinal cord lesions or respiratory drive disorders. Prior to surgical implantation patients should have nerve conduction studies to ensure normal bilateral phrenic nerve function. Small case series suggest that effective diaphragmatic pacing can improve quality of life in these patients.

HYPOVENTILATION SYNDROMES

OBESITY HYPOVENTILATION SYNDROME

The diagnosis of OHS requires: BMI ≥30 kg/m^2 and chronic daytime alveolar hypoventilation, defined as $Paco_2$ ≥45 mmHg at sea level in the absence of other known causes of hypercapnia. In almost 90% of cases the sleep disordered breathing is in the form of OSA. Several international studies in different populations confirm that the overall prevalence of OSA syndrome, defined by an apnea hypopnea index ≥5 AND daytime sleepiness, is ~3–4% in middle-aged men and 2% in middle-aged women. Thus, the population at risk for the development of OHS continues to rise as the world-wide obesity epidemic persists. Although no population-based prevalence studies of OHS have been performed, some estimates suggest there may be as many as 500,000 individuals with OHS in the United States.

Some, but not all, studies suggest that severe obesity (BMI >40 kg/m^2) and severe OSA (AHI >30 events per h) are risk factors for the development of OHS. The pathogenesis of hypoventilation in these patients is the result of multiple physiologic variables and conditions including OSA, increased work of breathing, respiratory muscle impairment, ventilation-perfusion mismatching, and depressed central ventilatory responsiveness to hypoxemia and hypercapnia. These defects in central respiratory drive often improve with treatment which suggest that decreased ventilatory responsiveness is a consequence rather than a primary cause of OHS. The treatment of OHS is similar to that for OSA: weight reduction and nocturnal non-invasive positive pressure ventilation (NIPPV). There is evidence that weight loss alone lowers $Paco_2$ in patients with OHS. However, treatment with NIPPV should never be delayed while the patient attempts to lose weight. Continuous positive airway pressure (CPAP) improves daytime hypercapnia and hypoxemia in more than half of patients with OHS and concomitant OSA. Bi-level positive airway pressure should be reserved for patients not able to tolerate high levels of CPAP support or patients that remain hypoxemic despite resolution of obstructive respiratory events. NIPPV with bi-level PAP should be strongly considered if hypercapnia persists after several weeks of CPAP therapy with objectively proven adherence. Patients with OHS and no evidence of OSA are typically started on bi-level positive airway pressure, as are patients presenting with acute decompensated OHS. Finally, comorbid conditions that impair ventilation, such as chronic obstructive pulmonary disease, should be aggressively treated in conjunction with co-existing OHS.

CENTRAL HYPOVENTILATION SYNDROME

This syndrome can present later in life or in the neonatal period where it is often called Ondine's curse or congenital central hypoventilation syndrome (CCHS). Abnormalities in the gene encoding PHOX2b, a transcription factor with a role in neuronal development, have been implicated in the pathogenesis of CCHS. Regardless of the age of onset, these patients have absent respiratory response to hypoxia or hypercapnia, mildly elevated $Paco_2$ while awake, and markedly elevated $Paco_2$ during non-REM sleep. Interestingly these patients are able to augment their ventilation and "normalize" $Paco_2$ during exercise and during REM sleep. These patients typically require NIPPV or mechanical ventilation as therapy and should be considered for phrenic nerve or diaphragmatic pacing at centers with experience performing these procedures.

HYPERVENTILATION

CLINICAL FEATURES

Hyperventilation is defined as ventilation in excess of metabolic requirements (CO_2 production) leading to a reduction in $Paco_2$. The physiology of patients with chronic hyperventilation is poorly

understood and there is no typical clinical presentation. Symptoms can include dyspnea, paresthesias, tetany, headache, dizziness, visual disturbances, and atypical chest pain. Because symptoms can be so diverse, patients with chronic hyperventilation present to a variety of health care providers, including internists, neurologists, psychologists, psychiatrists, and pulmonologists.

It is helpful to think of hyperventilation as having initiating and sustaining factors. Some investigators believe that an initial event leads to increased alveolar ventilation and a drop in $Paco_2$ to ~20 mmHg. The ensuing onset of chest pain, breathlessness, paresthesia, or altered consciousness can be alarming. The resultant increase in minute volume to relieve these acute symptoms only serves to exacerbate symptoms that are often misattributed by the patient and health care workers to cardiopulmonary disorders. An unrevealing evaluation for causes of these symptoms often results in patients being anxious and fearful of additional attacks. It is important to note that **anxiety disorders and panic attacks are NOT synonymous with hyperventilation**. Anxiety disorders can be both an initiating and sustaining factor in the pathogenesis of chronic hyperventilation, but these are not necessary for the development of chronic hypocapnia.

DIAGNOSIS

Respiratory symptoms associated with acute hyperventilation can be the initial manifestation of systemic illnesses such as diabetic ketoacidosis. Causes of acute hyperventilation need to be excluded before a diagnosis of chronic hyperventilation is considered. Arterial blood gas sampling that demonstrates a compensated respiratory alkalosis with a near normal pH, low $Paco_2$, and low calculated bicarbonate are necessary to confirm chronic hyperventilation. Other causes of respiratory alkalosis, such as mild asthma, need to be diagnosed and treated before chronic hyperventilation can be considered. A high index of suspicion is required as increased minute ventilation can be difficult to detect on physical examination. Once chronic hyperventilation is established, a sustained 10% increase in alveolar ventilation is enough to perpetuate hypocapnia. This increase can be accomplished with subtle changes in the respiratory pattern, such as occasional sigh breaths or yawning 2–3 times per min.

TREATMENT

Hyperventilation

There are few well-controlled treatment studies of chronic hyperventilation owing to its diverse features and the lack of a universally accepted diagnostic process. Clinicians often spend considerable time identifying initiating factors, excluding alternative diagnoses, and discussing the patient's concerns and fears. In some patients, reassurance and frank discussion about hyperventilation can be liberating. Identifying and eliminating habits that perpetuate hypocapnia, such as frequent yawning or sigh breathing, can be helpful. Some evidence suggests that breathing exercises and diaphragmatic retraining may be beneficial for some patients. The evidence for using medications to treat hyperventilation is scant. Beta-blockers may be helpful in patients with sympathetically mediated symptoms such as palpitations and tremors.

Acknowledgment

We acknowledge Jan-Marino Ramirez for his careful critique and helpful suggestions.

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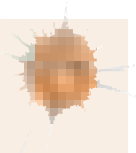
291 Sleep Apnea

Andrew Wellman, Susan Redline



Obstructive sleep apnea/hypopnea syndrome (OSAHS) and central sleep apnea (CSA) are both classified as sleep-related breathing disorders. OSAHS and CSA share some risk factors and physiological bases but also have unique features. Each disorder is associated with impaired ventilation during sleep and disruption of sleep, and each diagnosis requires careful elicitation of the patient's history, physical examination, and physiological testing. OSAHS, the more common disorder, causes daytime sleepiness, impairs daily function, and is a major contributor to cardiovascular disease in adults and to behavioral problems in children. CSA is less common and may occur in combination with obstructive sleep apnea, as a primary condition, or secondary to a medical condition (such as heart failure) or medication. Patients with CSA often report frequent awakenings and daytime fatigue and are at increased risk for heart failure and atrial fibrillation.

OBSTRUCTIVE SLEEP APNEA/HYPOPNEA SYNDROME

Definition OSAHS is defined on the basis of nocturnal and daytime symptoms as well as sleep study findings. Diagnosis requires the patient to have (1) either symptoms of nocturnal breathing disturbances (snoring, snorting, gasping, or breathing pauses during sleep) or daytime sleepiness or fatigue that occurs despite sufficient opportunities to sleep and is unexplained by other medical problems; and (2) five or more episodes of obstructive apnea or hypopnea per hour of sleep (the apnea-hypopnea index [AHI], calculated as the number of episodes divided by the number of hours of sleep) documented during a sleep study. OSAHS also may be diagnosed in the absence of symptoms if the AHI is >15 episodes/h. Each episode of apnea or hypopnea represents a reduction in breathing for at least 10 s and commonly results in a ≥3% drop in oxygen saturation and/or a brain cortical arousal. OSAHS severity is based on the frequency of breathing disturbances (AHI), the amount of oxyhemoglobin desaturation with respiratory events, the duration of apneas and hypopneas, the degree of sleep fragmentation, and the level of daytime sleepiness or functional impairment.

Pathophysiology During inspiration, intraluminal pharyngeal pressure becomes increasingly negative, creating a "suctioning" force. Because the pharyngeal airway has no bone or cartilage, airway patency is dependent on the stabilizing influence of the pharyngeal dilator muscles. Although these muscles are continuously activated during wakefulness, neuromuscular output declines with sleep onset. In patients with a collapsible airway, the reduction in neuromuscular output results in transient episodes of pharyngeal collapse (manifesting as an "apnea") or near collapse (manifesting as a "hypopnea"). The episodes of collapse are terminated when ventilatory reflexes are

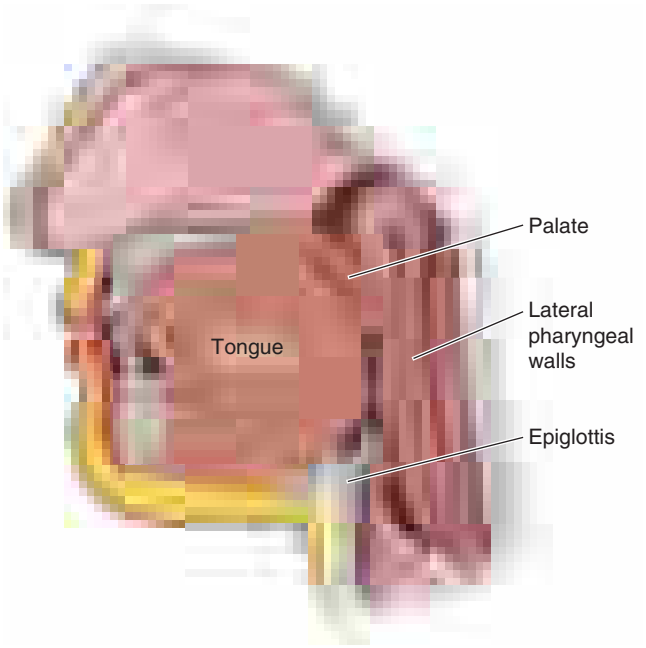


FIGURE 291-1 The structures causing airway collapse in OSAHS include the palate, the tongue, and/or the epiglottis. In addition, collapse can also occur due to the lateral pharyngeal walls.

activated and cause arousal, thus stimulating an increase in neuromuscular activity and opening of the airway. The airway may collapse at different sites, such as the soft palate (most common), tongue base, lateral pharyngeal walls, and/or epiglottis **(Fig. 291-1)**. OSAHS may be most severe during REM (rapid eye movement) sleep, when neuromuscular output to the skeletal muscles is particularly low, and in the supine position due to gravitational forces.

Individuals with a small pharyngeal lumen require relatively high levels of neuromuscular innervation to maintain patency during wakefulness and thus are predisposed to excessive airway collapsibility during sleep. The airway lumen may be narrowed with enlargement of soft tissue structures (tongue, palate, and uvula) due to fat deposition, increased lymphoid tissue, or genetic variation. Craniofacial factors such as mandibular retroposition or micrognathia, reflecting genetic variation or developmental influences, also can reduce lumen dimensions. In addition, lung volumes influence the caudal traction on the pharynx and consequently the stiffness of the pharyngeal wall. Accordingly, low lung volume in the recumbent position, which is particularly pronounced in the obese, contributes to collapse. A high degree of nasal resistance (e.g., due to nasal septal deviation or polyps) can contribute to airway collapse by increasing the negative intraluminal suction pressure. High-level nasal resistance also may trigger mouth opening during sleep, which breaks the seal between the tongue and the teeth and allows the tongue to fall posteriorly and occlude the airway.

Pharyngeal muscle activation is integrally linked to ventilatory drive. Thus, factors related to ventilatory control, particularly ventilatory sensitivity, arousal threshold, and neuromuscular responses to CO_2, contribute to the pathogenesis of OSAHS. A buildup in CO_2 during sleep activates both the diaphragm and the pharyngeal muscles, which stiffen the upper airway and can counteract inspiratory suction pressures and maintain airway patency to an extent that depends on the anatomic predisposition to collapse. However, pharyngeal collapse can occur when the ventilatory control system is overly sensitive to CO_2, with resultant wide fluctuations in ventilation and ventilatory drive and in upper airway instability. Moreover, increasing levels of CO_2 during sleep result in central nervous system arousal, causing the individual to move from a deeper to a lighter level of sleep or to awaken. A low arousal threshold (i.e., awaken to a low level of CO_2 or ventilatory drive) can preempt the CO_2-mediated process of pharyngeal muscle compensation and prevent airway stabilization. A high arousal threshold, conversely, may prevent appropriate termination of apneas, prolonging apnea duration, and exacerbating oxyhemoglobin desaturation severity. Finally, any impairment in the ability of the muscles to compensate during sleep can contribute to collapse of the pharynx. The relative contributions of risk factors vary among individuals. Approaches to the measurement of these factors in clinical settings, with consequent enhancement of "personalized" therapeutic interventions, are being actively investigated.

Risk Factors and Prevalence The major risk factors for OSAHS are obesity and male sex. Additional risk factors include mandibular retrognathia and micrognathia, a positive family history of OSAHS, genetic syndromes that reduce upper airway patency (e.g., Down syndrome, Treacher-Collins syndrome), adenotonsillar hypertrophy (especially in children), menopause (in women), and various endocrine syndromes (e.g., acromegaly, hypothyroidism).

Approximately 40–60% of cases of OSAHS are attributable to excess weight. Obesity predisposes to OSAHS through the narrowing effects of upper airway fat on the pharyngeal lumen. Obesity also reduces chest wall compliance and decreases lung volumes, resulting in a loss of caudal traction on upper airway structures. Obese individuals are at a fourfold or greater risk for OSAHS than their normal-weight counterparts. A 10% weight gain is associated with a >30% increase in AHI. Even modest weight loss or weight gain can influence the risk and severity of OSAHS. However, the absence of obesity does not exclude this diagnosis.

The prevalence of OSAHS is two- to fourfold higher among men than among women. Factors that predispose men to OSAHS include android patterns of obesity (resulting in upper-airway and abdominal fat deposition) and relatively greater pharyngeal length, which exacerbates collapsibility. Premenopausal women are relatively protected from OSAHS by the influence of sex hormones on ventilatory drive. The decline in sex differences in older age is associated with an increased OSAHS prevalence in women after menopause.

Variations in craniofacial morphology that reduce the size of the posterior airway space increase OSAHS risk. The contribution of hard-tissue structural features to OSAHS is most evident in nonobese patients. Identification of features such as retrognathia can influence therapeutic decision making.

OSAHS has a strong genetic basis, as evidenced by its significant familial aggregation and heritability. For a first-degree relative of a patient with OSAHS, the odds ratio of having OSAHS is approximately twofold higher than that for someone without an affected relative. Several genetic variants have been associated with prevalence of OSAHS or with related traits, such as duration of apneas and hypopneas and overnight levels of hypoxemia.

OSAHS prevalence varies with age, from 2 to 15% among middle-aged adults to >20% among elderly individuals. There is a peak due to lymphoid hypertrophy among children between the ages of 3 and 8 years; with airway growth and lymphoid tissue regression during later childhood, prevalence declines. Then, as obesity prevalence increases in middle life and women enter menopause, OSAHS again increases.

The prevalence of OSAHS is especially high among patients with diabetes or hypertension. Individuals of Asian ancestry appear to be at increased risk of OSAHS at relatively low levels of body mass index, possibly because of the influence of craniofacial risk factors that narrow the nasopharynx. In the United States, African Americans, especially children and young adults, are at higher risk for OSAHS than their Caucasian counterparts. In a majority of adults with OSAHS, the disorder is undiagnosed.

Course of the Disorder The precise onset of OSAHS is usually hard to identify. A person may snore for many years, often beginning in childhood, before OSAHS is identified. Weight gain may precipitate an increase in symptoms, which in turn may lead the patient to pursue an evaluation. OSAHS may become less severe with weight loss, particularly after bariatric surgery. Marked increases and decreases in the AHI are uncommon unless accompanied by weight change.

APPROACH TO THE PATIENT

Obstructive Sleep Apnea/Hypopnea Syndrome

An evaluation for OSAHS should be considered in patients with symptoms of OSAHS and one or more risk factors. Screening also should be considered in patients who report symptoms consistent with OSAHS and who are at high risk for OSAHS-related morbidities, such as hypertension, diabetes mellitus, and cardiac and cerebrovascular diseases.

SYMPTOMS AND HISTORY

When possible, a sleep history should be obtained with assistance from a bed partner or household member. Snoring is the most common complaint; however, its absence does not exclude the diagnosis, as pharyngeal collapse may occur without tissue vibration. Gasping or snorting during sleep may also be reported, reflecting termination of individual apneas with abrupt airway opening. Dyspnea is unusual, and its absence generally distinguishes OSAHS from paroxysmal nocturnal dyspnea, nocturnal asthma, and acid reflux with laryngospasm. Patients also may describe frequent awakening or sleep disruption, which is more common among women and older adults. The most common daytime symptom is excessive sleepiness, identified by a history of difficulty maintaining alertness or involuntary periods of dozing. However, many women preferentially report fatigue rather than sleepiness. Other symptoms include a dry mouth, nocturnal heartburn, diaphoresis of the chest and neck, nocturia, morning headaches, trouble concentrating, irritability, and mood disturbances. Although difficulty falling sleep and maintaining sleep are characteristics of insomnia disorders, they also may occur with OSAHS, especially in women. Several questionnaires that evaluate snoring frequency, self-reported apneas, and daytime sleepiness can facilitate OSAHS screening. The predictive ability of a questionnaire can be enhanced by a consideration of whether the patient is male or has risk factors such as obesity or hypertension.

PHYSICAL FINDINGS

Physical findings often reflect the etiologic factors for the disorder as well as comorbid conditions, particularly vascular disease. On examination, patients may exhibit hypertension and regional (central) obesity, as indicated by a large waist and neck circumference. The oropharynx may reveal a small orifice with crowding due to an enlarged tongue, a low-lying soft palate with a bulky uvula, large tonsils, a high-arched palate, and/or micro/retrognathia. Since nasal resistance can increase the propensity to pharyngeal collapse, the nasal cavity should be inspected for polyps, septal deviation, and other signs of obstruction. Because patients with heart failure are at increased risk for both OSAHS and CSA, a careful cardiac examination should be conducted to detect possible left- or right-sided cardiac dysfunction. Evidence of cor pulmonale suggests a comorbid cardiopulmonary condition; OSAHS alone is not thought to cause right-heart failure. A neurologic evaluation is needed to evaluate for conditions such as neuromuscular and cerebrovascular diseases, which increase OSAHS risk.

LABORATORY FINDINGS

Diagnostic Findings Since symptoms and signs do not accurately predict the severity of sleep-related breathing disturbances, specific diagnosis and categorization of OSAHS severity requires objective measurement of breathing during sleep. The gold standard for diagnosis of OSAHS is an overnight polysomnogram (PSG). A negative in-laboratory PSG usually rules out OSAHS. However, false-negative studies can result if the study did not collect representative information on the patient's usual sleep, particularly if there was insufficient REM sleep or inadequate supine sleep during testing. Home sleep tests that record only a few respiratory and cardiac channels commonly are used as a cost-effective means for diagnosing patients without significant comorbidity who have a high pretest probability of OSAHS. However, a home study may yield a false-negative result if sleep time is not accurately estimated or in individuals experiencing hypopneas with arousals rather than oxyhemoglobin desaturation. Further evaluation may therefore be required.

The key physiological information collected during a sleep study for OSAHS assessment includes measurement of breathing (changes in airflow, respiratory excursion), oxygenation (hemoglobin oxygen saturation), body position, and cardiac rhythm. In addition, PSGs and some home sleep studies measure sleep continuity and sleep stages (by electroencephalography, chin electromyography, electro-oculography, and actigraphy), limb movements (by leg sensors), and snoring intensity. This information is used to quantify the frequency and subtypes of abnormal respiratory events during sleep as well as associated changes in oxygen hemoglobin saturation, arousals, and sleep stage distributions. **Tables 291-1** and **291-2** define the respiratory events scored and the severity guidelines employed during a sleep study. **Fig. 291-2** shows examples of sleep-related respiratory events. A typical sleep study report provides quantitative data such as the AHI and the profile of oxygen saturation over the night (mean, nadir, time at low levels). Reports may also include the respiratory disturbance index, which includes the number of respiratory effort-related arousals in addition to the number of apneas plus hypopneas. In-laboratory, PSG also quantifies sleep latency (time from "lights off" to first sleep onset), sleep efficiency (percentage of time asleep relative to time in bed), arousal index (number of cortical arousals per hour of sleep), time in each sleep stage, and periodic limb movement index. OSAHS severity can be further characterized according to the degree of sleep fragmentation associated with respiratory disturbances. Relevant metrics include the frequency of cortical micro-arousals or awakenings per sleep hour (arousal index), reduction in sleep continuity (low sleep efficiency), reduction of time in deeper stages of sleep (stage N3 and REM sleep), and increases in light sleep (stage N1). The detection of autonomic arousals, such as surges in blood pressure, changes in heart rate, and abnormalities in cardiac rhythm, also provides relevant information on OSAHS severity.

Other Laboratory Findings Various imaging studies, including cephalometric radiography, MRI, CT, and fiberoptic endoscopy, can be used to identify anatomic risk factors for OSAHS. Cardiac testing may yield evidence of impaired systolic or diastolic ventricular function or abnormal cardiac structure. Overnight blood pressure monitoring often displays a "non-dipping" pattern (absence of the

TABLE 291-1 Respiratory Event Definitions

- *Apnea:* Cessation of airflow for ≥10 s during sleep, accompanied by:
  - Persistent respiratory effort (obstructive apneas, **Fig. 291-2A**), or
  - Absence of respiratory effort (central apneas, **Fig. 291-2B**)
- *Hypopnea:* A ≥30% reduction in airflow for at least 10 s during sleep that is accompanied by either a ≥3% desaturation or an arousal **(Fig. 291-2C)**
- *Respiratory effort-related arousal (RERA):* Partial obstruction that does not meet the criteria for hypopnea but provides evidence of increasing inspiratory effort (usually through pleural pressure monitoring) punctuated by an arousal **(Fig. 291-2D)**
- *Flow-limited breath:* A partially obstructed breath, typically within a hypopnea or RERA, identified by a flattened or "scooped-out" inspiratory flow shape **(Fig. 291-3)**

TABLE 291-2 Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS): Quantification and Severity Scale

- *Apnea-hypopnea index (AHI)*[a]*:* Number of apneas plus hypopneas per hour of sleep
- *Respiratory disturbance index (RDI):* Number of apneas plus hypopneas plus RERAs per hour of sleep
- *Mild OSAHS:* AHI of 5–14 events/h
- *Moderate OSAHS:* AHI of 15–29 events/h
- *Severe OSAHS:* AHI of ≥30 events/h

[a]Each level of AHI can be further quantified by level of sleepiness and associated hypoxemia.

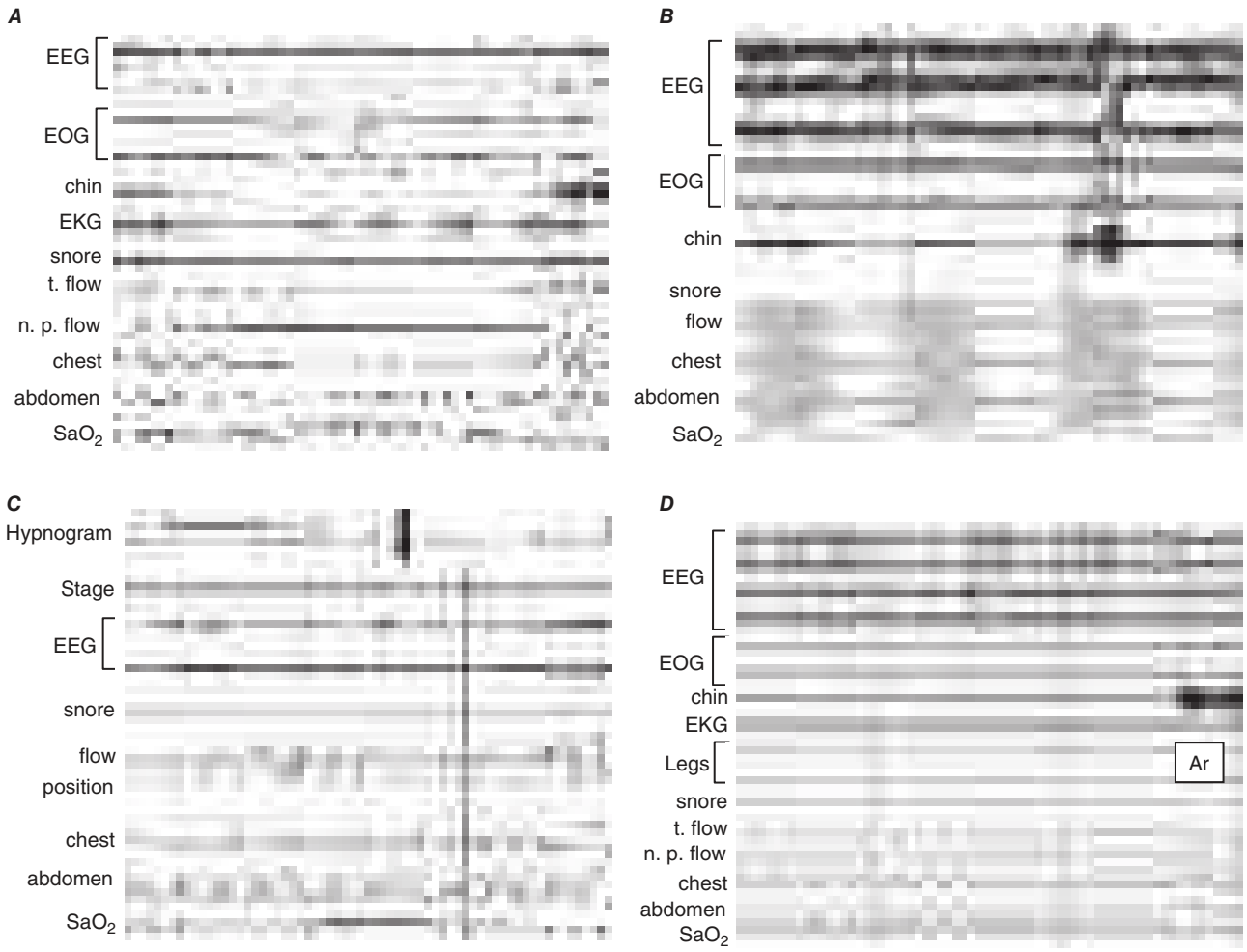


FIGURE 291-2 Obstructive apnea. ***A.*** There are 30 s of no airflow, as shown in the nasal pressure (n. p. flow) and thermistor-measured flow (t. flow). Note the presence of chest-abdomen paradox, indicating respiratory effort against an occluded airway. ***B.*** Central apnea in a patient with Cheyne-Stokes respiration due to congestive heart failure. The flat chest-abdomen tracings indicate the absence of inspiratory effort during the central apneas. ***C.*** Hypopnea. Partial obstruction of the pharyngeal airway can limit ventilation, leading to desaturation (a mild decrease in this patient, from 93 to 90%) and arousal. ***D.*** Respiratory effort-related arousal (RERA). Minimal flow reduction terminated by an arousal (Ar) without desaturation constitutes a RERA. EEG, electroencephalogram; EOG, electro-oculogram; EKG, electrocardiogram.

typical 10-mmHg fall of blood pressure during sleep compared to wakefulness). Arterial blood gas measurements made during wakefulness are usually normal. Waking hypoxemia or hypercarbia suggests coexisting cardiopulmonary disease or hypoventilation syndromes. Patients with severe nocturnal hypoxemia may have elevated hemoglobin values. A multiple sleep latency test or a maintenance of wakefulness test can be useful in quantifying sleepiness and helping to distinguish OSAHS from narcolepsy.

Health Consequences and Comorbidities OSAHS is a major contributor to cardiac, cerebrovascular, and metabolic disorders as well as to premature death. It is the most common medical cause of daytime sleepiness and negatively influences quality of life. This broad range of health effects is attributable to the impact of sleep fragmentation, cortical arousal, and intermittent hypoxemia on vascular, cardiac, metabolic, and neurologic functions. OSAHS-related respiratory events stimulate sympathetic overactivity, leading to acute blood pressure surges during sleep, endothelial damage, and nocturnal as well as daytime hypertension. OSAHS-related hypoxemia also stimulates release of acute-phase proteins and reactive oxygen species that exacerbate insulin resistance and lipolysis and cause an augmented prothrombotic and proinflammatory state. Inspiratory effort against an occluded airway causes large intrathoracic negative pressure swings, altering cardiac preload and afterload and resulting in cardiac remodeling and reduced cardiac function. Hypoxemia and sympathetic-parasympathetic imbalance also may cause electrical remodeling of the heart and myocyte injury.

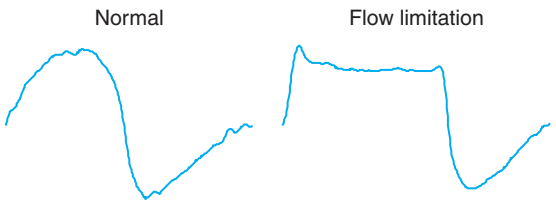


FIGURE 291-3 Example of flow limitation. The inspiratory flow pattern in a patient airway is rounded and peaks in the middle. In contrast, a partially obstructed airway exhibits an early peak followed by mid-inspiratory flattening, yielding a scooped-out appearance.

HYPERTENSION OSAHS can raise blood pressure to pre-hypertensive and hypertensive ranges, increase the prevalence of a non-dipping overnight blood pressure pattern, and increase the risk of resistant hypertension. Elevations in blood pressure are due to augmented sympathetic nervous system activation as well as alterations in the renin-angiotensin–aldosterone system and fluid balance. Treatment of OSAHS with nocturnal continuous positive airway pressure (CPAP) has been shown to reduce 24-h ambulatory blood pressure. Although the overall impact of CPAP on blood pressure levels is relatively modest (averaging 2–4 mmHg), larger improvements are observed among patients who have a high AHI, report daytime sleepiness, or who have resistant hypertension.

CARDIOVASCULAR, CEREBROVASCULAR, AND METABOLIC DISEASES Among the most serious health consequences of OSAHS is its impact on cardiac and metabolic functions. Strong epidemiologic evidence indicates that OSAHS significantly increases the risk of coronary artery disease, heart

failure with and without reduced ejection fraction, atrial and ventricular arrhythmias, atherosclerosis and coronary artery disease, stroke, and diabetes. Treatment of OSAHS has been shown to reduce several markers of cardiovascular risk, improve insulin resistance, decrease the recurrence rate of atrial fibrillation, and improve various outcomes in patients with active cardiovascular disease. Large-scale trials have not yet, however, demonstrated that OSAHS treatment with CPAP reduces cardiac event rates and prolongs survival, perhaps due to limited adherence with treatment among trial participants.

SLEEPINESS More than 50% of patients with moderate to severe OSAHS report daytime sleepiness. Patients with OSAHS symptoms have a twofold increased risk of occupational accidents. Individuals with elevated AHIs are involved in motor vehicle crashes as much as seven times more often than persons with normal AHIs. Randomized controlled trials have shown that treatment of OSAHS with nasal CPAP therapy alleviates sleepiness as measured by either questionnaire or objective testing in patients with both mild and more severe disease. However, the degree of improvement varies widely. Residual sleepiness may be due to several factors, including suboptimal treatment adherence, insufficient sleep time, other sleep disorders, or prior hypoxic-mediated damage in brain areas involved in alertness. Visceral adipose tissue, whose amounts are increased in patients with OSAHS, releases somnogenic cytokines that may contribute to sleepiness. Thus, even after treatment, it is important to assess and monitor patients for residual sleepiness and to evaluate the necessity of optimizing treatment adherence, improving sleep patterns, and identifying other disorders contributing to sleepiness. Careful and supervised use of alerting agents may be administered as adjunctive treatment in patients in whom sleepiness does not respond to CPAP alone.

QUALITY OF LIFE AND MOOD Reductions in health-related quality of life are common in patients with OSAHS, with the largest decrements on the physical and vitality subscales. Numerous studies, including a large-scale trial of minimally symptomatic patients, have shown that treatment with CPAP can improve these patient-reported outcomes. Depression, in particular symptoms of somatic depression (irritability, fatigue, lack of energy), is commonly reported in OSAHS and improves with CPAP.

TREATMENT

Obstructive Sleep Apnea/Hypopnea Syndrome

A comprehensive approach to the management of OSAHS is needed to reduce risk factors and comorbidities. The clinician should seek to identify and address lifestyle and behavioral factors as well as comorbidities that may be exacerbating OSAHS. As appropriate, treatment should aim to reduce weight; optimize sleep duration (7–9 h); regulate sleep schedules (with similar bedtimes and wake times across the week); encourage the patient to avoid sleeping in the supine position; treat nasal allergies; increase physical activity; eliminate alcohol ingestion (which impairs pharyngeal muscle activity) within 3 h of bedtime; and minimize use of sedating medications. Patients should be counseled to avoid drowsy driving.

CPAP is the standard medical therapy with the highest level of evidence for efficacy. Delivered through a nasal or nasal-oral mask, CPAP works as a mechanical splint to hold the airway open, thus maintaining airway patency during sleep. An overnight CPAP titration study, performed either in a laboratory or with a home "auto-titrating" device, is required to determine the optimal pressure setting that reduces the number of apneas/hypopneas during sleep, improves gas exchange, and reduces arousals. Rates of adherence to CPAP treatment are highly variable (average, 50–80%) and may be improved with support by a skilled health care team who can address side effects, help the patient "problem solve," and provide motivational education **(Table 291-3)**. Despite the limitations of CPAP, controlled studies have demonstrated its beneficial effect on blood pressure, alertness, mood, quality of life, and insulin sensitivity. Uncontrolled studies also indicate a favorable effect on cardiovascular outcomes, cardiac ejection fraction, atrial fibrillation recurrence, and mortality risk.

TABLE 291-3 Side Effects of Continuous Positive Airway Pressure (CPAP) and Their Treatments

SIDE EFFECT	TREATMENT
Nasal congestion	Provide heated humidification, administer saline/steroid nasal sprays
Claustrophobia	Change mask interface (e.g., to nasal prongs), promote habituation (i.e., practice breathing on CPAP while awake)
Difficulty exhaling	Temporarily reduce pressure, provide bilevel positive airway pressure
Bruised nasal ridge	Change mask interface, provide protective padding
Aerophagia	Administer antacids

Oral appliances for OSAHS work by advancing the mandible, thus opening the airway by repositioning the lower jaw and pulling the tongue forward. These devices generally work better when customized for patient use; maximal adaptation can take several weeks. Efficacy studies show that these devices can reduce the AHI by ≥50% in two-thirds of individuals, although these data are based largely on patients with mild OSAHS. Some patients with moderate or severe OSAHS respond to oral appliances as well, although no consistent predictors of success have been identified in these groups and thus follow-up PSG testing is recommended. Side effects of oral appliances include temporomandibular joint pain and tooth movement. Oral appliances are most often used for treating patients with mild OSAHS or patients who do not tolerate CPAP. However, since adherence to the use of oral appliances sometimes exceeds CPAP adherence, these devices are under investigation for treatment of more severe disease.

Upper airway surgery for OSAHS is less effective than CPAP and is mostly reserved for the treatment of patients who snore, have mild OSAHS, or cannot tolerate CPAP. Uvulopalatopharyngoplasty (removal of the uvula and the margin of the soft palate) is the most common surgery and, although results vary greatly, is generally less successful than treatment with oral appliances. Upper airway surgery is less effective in severe OSAHS and in obese patients. Success rates may be higher for multilevel surgery (involving more than one site/structure) performed by an experienced surgeon, but the selection of patients is an important factor and relies on careful targeting of culprit areas for surgical resection. Bariatric surgery is an option for obese patients with OSAHS and can improve not only OSAHS but also other obesity-associated health conditions. Other procedures that can decrease snoring but have minimal effects on OSAHS include injection of the soft palate (resulting in stiffening), radiofrequency ablation, laser-assisted uvulopalatoplasty, and palatal implants.

Upper airway neuro-stimulation is a recently tested alternative treatment for OSAHS. Unilateral stimulation of the hypoglossal nerve through a surgically implanted device was shown to significantly decrease the AHI and improve a number of patient-reported outcomes, such as sleepiness and quality of life, for a duration of at least 18 months after treatment. Initial studies enrolled patients with a BMI ≤32 kg/m^2, moderate OSAHS, absence of complete concentric pharyngeal collapse (considered to decrease surgical efficacy) and were unable to be treated successfully with CPAP. Additional research is underway to further evaluate longer-term effectiveness and potential utility of this treatment in other patient groups.

Supplemental oxygen can improve oxygen saturation, but there is little evidence that it improves OSAHS symptoms or the AHI in unselected patients.

CENTRAL SLEEP APNEA

CSA, which is less common than OSAHS, may occur in isolation or, more often, in combination with obstructive events in the form of "mixed" apneas. CSA is often caused by an increased sensitivity to p_{CO2}, which leads to an unstable breathing pattern that manifests

as hyperventilation alternating with apnea. A prolonged circulation delay between the pulmonary capillaries and carotid chemoreceptors is also a contributing cause; thus individuals with congestive heart failure are at risk for CSA. With prolonged circulation delay, there is a crescendo-decrescendo breathing pattern known as *Cheyne-Stokes respiration* (Fig. 291–2*B*). Other risk factors for CSA include opioid medications (which appear to have a dose-dependent effect on CSA) and hypoxia (e.g., breathing at high altitude). In some individuals, CPAP—particularly at high pressures—seems to induce central apnea; this condition is referred to as *complex sleep apnea*. Rarely, CSA may be caused by blunted chemosensitivity due to congenital disorders (congenital central hypoventilation syndrome) or acquired factors. CSA is an independent risk factor for the development of both heart failure and atrial fibrillation, possibly related to elevations in sympathetic nervous system activity that accompany this disorder. Patients with CSA may report symptoms of frequent awakenings as well as daytime fatigue. Treatment of CSA is difficult and depends on the underlying cause. Limited data suggest that supplemental oxygen can reduce the frequency of central apneas, particularly in patients with hypoxemia. Cheyne-Stokes respiration is treated by optimizing therapy for heart failure. At this time, there is no good evidence that CPAP, including *adaptive servoventilation* (a form of ventilatory support that attempts to regularize the breathing pattern) improves health outcomes in patients with Cheyne-Stokes respiration without OSAHS.

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292 Lung Transplantation

Elbert P. Trulock, III

Lung transplantation is a therapeutic consideration for many patients with nonmalignant end-stage lung disease, and it prolongs survival and improves quality of life in appropriately selected recipients. Since 1985 more than 51,000 adult lung transplants have been recorded worldwide, and annual volume has reached ~4000 transplants per year.

INDICATIONS

The indications for lung transplantation span the gamut of lung diseases, and the distribution reflects both the prevalence and prognosis of the diseases and the applicable organ allocation policies. According to international registry data, the most common indications in recent years have been idiopathic pulmonary fibrosis (IPF), ~30%; chronic obstructive pulmonary disease (COPD), ~27%; cystic fibrosis (CF), ~15%; α_1-antitrypsin deficiency emphysema, ~3%; and idiopathic pulmonary arterial hypertension (IPAH), ~2.5%. Other lung diseases have comprised the balance of primary indications, and retransplantation has accounted for ~3% of procedures. Since 2001, IPF has increased from ~15 to ~30%, and COPD has decreased from ~40 to ~27% among the indications.

REFERRAL AND RECIPIENT SELECTION

Transplantation should be considered when other therapeutic options have been exhausted and when the patient's prognosis is expected to improve as a result of the procedure. Survival rates after transplantation can be compared with predictive indices for the patient's disease, but each patient's individual clinical circumstances must be incorporated into the assessment. Moreover, quality of life is a primary motive for transplantation for many patients, and the prospect of improved quality-adjusted survival is often attractive even if the survival advantage itself is questionable.

Disease-specific consensus guidelines for referring patients for evaluation and for listing them for transplantation are summarized in **Table 292-1**. Candidates for lung transplantation are also thoroughly screened for comorbidities that might affect the outcome adversely. Conditions such as systemic hypertension, diabetes mellitus, gastroesophageal reflux, and osteoporosis are not unusual, but if uncomplicated and adequately managed, they do not disqualify patients from transplantation. The upper age limit is ~70–75 years at most centers, and the proportion of older recipients has been increasing. In 2014, 29% of adult recipients in the United States were ≥65 years old.

Standard exclusions include HIV infection, chronic active hepatitis B or C infection, uncontrolled or untreatable pulmonary or extrapulmonary infection, uncured malignancy, active cigarette smoking, drug or alcohol dependency, irreversible physical deconditioning, chronic nonadherence with medical care, significant disease of another vital organ (e.g., heart, liver, or kidney), and psychiatric or psychosocial situations that could substantially interfere with post-transplantation management. Other problems that may compromise the outcome constitute relative contraindications. Some typical issues are ventilator-dependent respiratory failure, extracorporeal life support, obesity, coronary artery disease, and previous thoracic surgical procedures. Chronic infection with antibiotic-resistant *Pseudomonas species, Burkholderia species, Aspergillus species,* or nontuberculous mycobacteria is a unique concern in some patients with CF. The potential impact of these and other factors has to be judged in clinical context to determine an individual candidate's suitability for transplantation.

WAITING LIST AND ORGAN ALLOCATION

Organ allocation policies are influenced by medical, ethical, geographical, and political factors, with systems varying from country to country. Regardless of the system, potential recipients are placed on a waiting list and must be matched for blood group compatibility and, with some latitude, for lung size with an acceptable donor. If the potential recipient is allosensitized with antibodies to any human leukocyte antigen (HLA), the donor also has to be HLA compatible.

Most lungs are procured from deceased donors after brain death, but only ~20% of brain-death organ donors yield either one or two lungs suitable for transplantation. Lungs from donors after circulatory death have been utilized to a limited extent (~2% of lung donors in the United States in 2014). Ex vivo lung perfusion is being used by some centers to assess donor lungs that are marginal for implantation by standard criteria; if the results of ex vivo testing are satisfactory, these lungs have been transplanted successfully.

In the United States, a lung allocation score (LAS) system has been used to prioritize patients on the waiting list since 2005. For the purposes of the LAS, patients are divided into four groups by diagnosis: A—COPD and emphysema; B—IPAH and other forms of pulmonary hypertension; C—cystic fibrosis and other forms of bronchiectasis; D—IPF and other interstitial diseases. The LAS is based on the patient's risk of death during 1 year on the waiting list and the patient's likelihood of survival for 1 year after transplantation. It can range from 0 to 100, and priority for transplantation is ranked from highest to lowest scores. Both the lung disease and its severity affect a patient's LAS; parameters in the LAS must be updated biannually, but can be submitted for recalculation whenever the patient's condition changes. Patients in group D usually have the highest scores, and those in group A, the lowest.

In recent years, the U.S. national waiting list typically has contained ~1500 patients with a median LAS of ~35–36. In 2014, 50% of the patients on the waiting list were in group D, and the median waiting time to transplantation was 3.7 months. The overall death rate (deaths per 100 waitlist years) on the waiting list was ~10, but the rate varied

TABLE 292-1 Disease-Specific Guidelines for Referral and Transplantation

Chronic Obstructive Pulmonary Disease
Referral for Evaluation
Progressive despite medications, oxygen, and pulmonary rehabilitation
FEV_1 <25%
Pao_2 <60 mmHg or $Paco_2$ >50 mmHg
BODE index 5–6
Listing for Transplantation
BODE index ≥7
FEV_1 <15–20%
Moderate to severe pulmonary hypertension
Three or more severe exacerbations in preceding year
One severe exacerbation with acute hypercapnic respiratory failure
Cystic Fibrosis/Bronchiectasis
Referral for Evaluation
FEV_1 <30% or rapidly declining despite optimal therapy
Pulmonary hypertension (in absence of hypoxemic exacerbation)
6-min walk distance <400 m
Clinical deterioration with increasing frequency of exacerbations, with
– An episode of acute respiratory failure requiring ventilatory support
– Increasing antibiotic resistance and poor recovery from exacerbations
– Worsening nutritional status despite adequate supplementation
– Refractory or recurrent pneumothorax
– Life-threatening hemoptysis despite bronchial artery embolization
Listing for Transplantation
Chronic hypoxemic or hypercapnic respiratory failure
Pulmonary hypertension
Rapid decline in lung function
Long-term noninvasive ventilator support
Frequent hospitalization
WHO functional class IV
Idiopathic Pulmonary Fibrosis
Referral for Evaluation
Pathologic or radiographic evidence of UIP or NSIP regardless of lung function
FVC <80% or DL_{CO} <40%
Dyspnea or functional limitation attributable to lung disease
Any oxygen requirement (rest or exercise)
Listing for Transplantation
Decrement in FVC ≥10% or in DL_{CO} >15% during 6 months of follow-up
Pulmonary hypertension
Desaturation to Sp_{O2} <88% during 6-min walk test
6-min walk test distance <250 m or decrement >50 m over 6 months
Hospitalization for acute exacerbation
Idiopathic Pulmonary Arterial Hypertension
Referral for Evaluation
NYHA functional class III or IV during escalating therapy
Use of parenteral therapy regardless of NYHA functional class
Rapidly progressive disease
Listing for Transplantation
NYHA functional class III or IV despite combination therapy with a prostanoid
Cardiac index <2 L/min/m^2 or right atrial pressure >15 mmHg
6-minute walk test distance <350 m
Progressive right heart failure or significant pericardial effusion or hemoptysis

Abbreviations: BODE—body-mass index (B), airflow obstruction (O), dyspnea (D), exercise capacity (E); FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DL_{CO}, diffusing capacity for carbon monoxide; HRCT, high resolution computed tomography; ICU, intensive care unit; NSIP, nonspecific interstitial pneumonitis; NYHA, New York Heart Association; $Paco_2$ and Pao_2, partial pressures of carbon dioxide and oxygen, respectively, in arterial blood; Sp_{O2}, arterial oxygen saturation by pulse oximetry; UIP, usual interstitial pneumonitis; WHO, World Health Organization

Source: Summarized from D. Weill et al: J Heart Lung Transplant 34:1, 2015. For BODE index, BR Celli et al: N Engl J Med 350:1005, 2004.

considerably by diagnostic group (e.g., A, ~4; B, ~11; C, ~12; D, ~18) and by LAS (e.g., 35–39, ~10; 40–49, ~22; ≥50, ~125). Because the LAS system prioritizes patients with the highest risk of death on the waiting list, many patients are now critically ill at the time of transplantation. In 2014, 25% of recipients were hospitalized (15% in intensive care), and 9% were being supported by mechanical ventilation, extracorporeal life support or both at the time of transplantation.

TRANSPLANT PROCEDURE

Bilateral transplantation is mandatory for CF and other forms of bronchiectasis because the risk of spillover infection from a remaining native lung precludes single-lung transplantation. Heart-lung transplantation is obligatory for Eisenmenger syndrome with complex anomalies that cannot be readily repaired in conjunction with lung transplantation and for concomitant end-stage lung and heart disease. However, cardiac replacement is not necessary for cor pulmonale because right ventricular function will recover when pulmonary vascular afterload is normalized by lung transplantation.

Either bilateral or single-lung transplantation is an option for other diseases unless there is a special consideration, but for all indications, bilateral transplantation is performed most often. In 2014, 68% of all transplants in the United States were bilateral (68% of transplants for COPD; 54% for IPF).

Living donor lobar transplantation has played a limited role in adult lung transplantation, but is rarely performed anymore; only three cases were recorded in the U.S. registry from 2010 through 2015. When performed, it usually has been reserved for teenagers or young adults with CF who were unlikely to survive the wait for a deceased organ donor.

POSTTRANSPLANTATION MANAGEMENT

Immunosuppression Induction therapy is increasingly utilized, and in 2014, ~65% of recipients in both the U.S. and international registries received an induction agent. The interleukin-2 receptor antagonist basiliximab has been the most widely used drug (~50% of recipients), but the antilymphocyte globulins and alemtuzumab have been used, as well. A three-drug maintenance immunosuppressive regimen that includes a calcineurin inhibitor (cyclosporine or tacrolimus), a purine synthesis antagonist (azathioprine or a mycophenolic acid precursor), and prednisone is traditional; the triad of tacrolimus, mycophenolate, and prednisone is the most commonly prescribed regimen. Subsequently, other drugs such as sirolimus or everolimus may be substituted for various reasons. Prophylaxis for *Pneumocystis jiroveci* pneumonia is standard, and prophylaxis against cytomegalovirus (CMV) infection and fungal infection is part of many protocols. The dose of cyclosporine, tacrolimus, sirolimus, or everolimus is adjusted by blood-level monitoring. All of these agents are metabolized by the hepatic cytochrome P450 system, and interactions with medications that affect this pathway can significantly alter their clearance and blood level.

Spirometry and Bronchoscopy Routine management focuses on monitoring of the allograft, regulating immunosuppressive therapy, and detecting problems or complications expeditiously. Regular contact with a nurse coordinator, physician follow-up, chest radiography, blood tests, and spirometry are customary. Surveillance bronchoscopy with bronchoalveolar lavage and transbronchial biopsies is employed by some programs to screen for occult acute cellular rejection (ACR) or infection, and bronchoscopy is the standard invasive procedure to investigate problems with the allograft. If recovery is uncomplicated, lung function rapidly improves and then stabilizes by 3–6 months after transplantation. Subsequently, the variation in spirometric measurements is small, and a sustained decline of ≥10–15% signals a potentially significant problem.

OUTCOMES

Survival Major registries publish survival rates (Table 292-2) and other outcomes annually (*www.ishlt.org; www.srtr.org*). In the international registry, for the cohort from 1990 to 2013, median survival for recipients with IPF was 4.7 years; IPAH, 5.7 years; COPD, 5.5 years; CF,

TABLE 292-2 Recipient Survival, by Pretransplantation Diagnosis

	SURVIVAL RATE, %					
DIAGNOSIS; TRANSPLANT TYPE	3 MONTHS	1 YEAR	3 YEARS	5 YEARS	10 YEARS	15 YEARS
Chronic obstructive pulmonary disease[a]						
Bilateral	93	86	71	59	37	16
Single	92	84	66	51	24	6
α_1-antitrypsin deficiency emphysema						
Bilateral	89	81	69	61	40	24
Single	88	78	62	52	29	13
Cystic fibrosis[a]	93	88	76	63	48	27
Idiopathic pulmonary fibrosis[a]						
Bilateral	89	82	66	55	34	16
Single	89	79	58	45	21	7
Idiopathic pulmonary arterial hypertension						
Bilateral	80	74	62	55	40	28
Single	71	62	52	41	24	15
Sarcoidosis	86	76	62	55	35	22

[a]Survival cohorts: 2009–2015 for 3 months, 1 year and 3 years; 1999–2008 for 5 years and 10 years; 1990–1998 for 15 years. For other diagnoses, cohort is 1990–2013 for all survival rates.

Source: Data from *www.ishlt.org/registries/slides.asp?slides=heartLungRegistry*. Accessed March 10, 2016.

8.6 years; and sarcoidosis, 6.1 years. Transplant procedure and recipient age also have a significant impact on outcome. Long-term survival has been significantly better after bilateral transplantation than after unilateral transplantation for all of the major indications. For recipients 18–49 years of age, the median survival is ~7.2 years, but it decreases to ~5.5 years for those 50–59 years old and to ~4.5 years for those ≥60 years old. In the U.S. registry, survival rates have been lowest for recipients who were in group D, were ≥65 years old, or had an LAS ≥60.

The causes of death depend on the time period after transplantation. In the first 30 days, the major causes have been infection (~19%), graft failure (~24%), cardiovascular events (~11%) and technical problems (~11%), and for the remainder of the first year, the main contributors have been infection (~37%) and graft failure (~17%). After the first year, bronchiolitis and other forms of late graft failure have accounted for ~40–45% of deaths and infection for ~16–20%.

Risk factors for mortality have been analyzed in the international and U.S. registries. In these analyses, factors associated with an increased risk of death in the first year after transplantation have included the following: recipients hospitalized at the time of transplantation; recipients supported by mechanical ventilation, extracorporeal membrane oxygenation, or dialysis at the time of transplantation; and recipients undergoing retransplantation; however, other factors have contributed, too. The mortality risk has also been higher at centers with an annual volume below ~30 transplants/year.

Function Regardless of the disease, successful transplantation impressively restores cardiopulmonary function. After bilateral transplantation, pulmonary function tests are typically normal; after unilateral transplantation, a mild abnormality characteristic of the remaining diseased lung is still apparent. Formal exercise testing usually demonstrates some impairment in maximum work rate and maximum oxygen uptake, but few recipients report any limitation to activities of daily living.

Quality of Life Both overall and health-related quality of life measurements have improved after transplantation. With multidimensional profiles, improvements have extended across most domains and have been sustained longitudinally unless chronic rejection or some other complication develops.

Cost The cost of transplantation depends on the health care system and economic factors that vary from country to country. In the United States in 2014, lung transplantation was covered by private insurance for 49% of recipients, Medicare for 36%, and other government-sponsored programs for 8.5%. In 2014, the average total of billed charges for a bilateral transplant for the period from 30 days before transplantation until 180 days after discharge from the transplant admission was $1,037,700. The total charge included the following components: all care during 30 days before transplantation, $30,700; organ procurement, $129,700; hospital transplant admission, $566,900; physician fees during transplant admission, $59,100; all inpatient and outpatient care for 180 days after discharge, $219,800; and all outpatient drugs, including immunosuppressants, for 180 days after discharge, $31,500. However, Medicare does not fully reimburse billed charges, and in the era from 2008 to 2012, the average Medicare cost from transplantation through the first posttransplant year was ~$240,000.

COMPLICATIONS

Lung transplantation can be complicated by a variety of problems (Table 292-3). The average length of stay after bilateral transplantation in the United States in 2014 was 29.5 days, and the rehospitalization rate in the first year has been ~50%, higher than after any other solid organ transplant except intestine.

Primary Graft Dysfunction Primary graft dysfunction (PGD), an acute lung injury, is a manifestation of multiple potential insults to the donor organ inherent in harvesting, preserving, and implanting it in the recipient. The principal clinical features are diffuse pulmonary infiltrates and hypoxemia within 72 h of transplantation; however, the presentation can be mimicked by pulmonary venous obstruction, hyperacute rejection, pulmonary edema, and pneumonia.

The severity is graded by a standardized system that is based on an edema pattern on chest radiograph and the Pa_{O2}/FiO_2 ratio (>300, grade 1; 200–300, grade 2; <200, grade 3). Up to 50% of recipients may have some degree of PGD, and ~10–20% have grade 3 PGD. The treatment follows the conventional, supportive paradigm for acute lung injury. Inhaled nitric oxide, inhaled epoprostenol, and extracorporeal membrane oxygenation have been used in severe cases. Retransplantation has also been performed, but when undertaken in the first 30 days, the 1-year survival rate has been only ~30%. Most recipients with mild PGD recover, but the mortality rate for severe PGD has been ~40–60%. PGD is also associated with longer postoperative ventilator support, longer intensive care unit and hospital stays, higher costs, and excess morbidity. Finally, severe (grade 3) PGD is a risk factor for the later development of chronic lung allograft dysfunction (CLAD).

Airway Complications The bronchial blood supply to the donor lung is disrupted during procurement. Bronchial revascularization during transplantation is technically feasible in some cases, but it is not widely practiced. Consequently, after implantation, the donor bronchus is dependent on retrograde bronchial blood flow from the pulmonary circulation and is vulnerable to ischemia.

The spectrum of airway problems includes anastomotic necrosis and dehiscence, occlusive granulation tissue, anastomotic or bronchial

TABLE 292-3 Major Potential Complications of Lung Transplantation and Immunosuppression

CATEGORY	COMPLICATION
Allograft	Primary graft dysfunction; anastomotic dehiscence or stenosis; ischemic airway injury with bronchostenosis or bronchomalacia; rejection; infection; recurrence of primary disease (sarcoidosis, lymphangioleiomyomatosis, giant cell interstitial pneumonitis, diffuse panbronchiolitis, pulmonary alveolar proteinosis, Langerhans cell histiocytosis)
Thoracic	Phrenic nerve injury/diaphragmatic dysfunction; recurrent laryngeal nerve injury/vocal cord dysfunction; cervical ganglia injury/Horner's syndrome; pneumothorax; pleural effusion; chylothorax; empyema
Cardiovascular	Intraoperative or perioperative air embolism; postoperative pericarditis; perioperative myocardial injury/infarction; venous thromboembolism; supraventricular dysrhythmias; systemic hypertension
Gastrointestinal	Esophagitis (especially *Candida*, herpes or cytomegalovirus [CMV]); gastroparesis; gastroesophageal reflux; diarrhea (*C. difficile*; medications, especially mycophenolate mofetil and sirolimus); colitis (*C. difficile*; CMV)
Hepatobiliary	Hepatitis (especially CMV or medications); acalculous cholecystitis
Renal	Calcineurin inhibitor nephropathy; hemolytic-uremic syndrome (thrombotic microangiopathy)
Neurologic	Perioperative stroke; tremors; seizures; reversible posterior leukoencephalopathy; headaches
Musculoskeletal	Steroid myopathy; rhabdomyolysis (cyclosporine + HMG co-A reductase inhibitor treatment); osteoporosis; avascular necrosis
Metabolic	Obesity; diabetes mellitus; hyperlipidemia; idiopathic hyperammonemia
Hematologic	Anemia; leukopenia; thrombocytopenia; thrombotic microangiopathy
Oncologic	Lymphoproliferative disease and lymphoma; skin cancers; other malignancies

stenosis, and bronchomalacia. The incidence has been in the range of 7–18%, but the associated mortality rate has been low. These problems usually can be managed bronchoscopically with techniques such as simple endoscopic debridement, laser photoresection, balloon dilation, and bronchial stenting.

Lung Allograft Dysfunction The transplanted lung is susceptible to a variety of conditions that can compromise graft function. Some of these, such as the various forms of rejection, are unique to transplantation, but others are not. Acute lung allograft dysfunction is most often caused by rejection or infection and may be completely reversible after diagnosis and treatment. CLAD can be the result of residual damage from an episode of acute allograft dysfunction, or it can develop separately in response to alloimmune and non-alloimmune injuries to the graft.

Acute Cellular Rejection ACR is caused by T lymphocyte interactions with donor alloantigens, mainly in the major histocompatibility complex (MHC), and its incidence is highest in the first 6–12 months after transplantation. In the years 2008–2013, ~18% of recipients in the U.S. registry had an episode of ACR during the first year.

ACR can be clinically silent or can be manifested by nonspecific symptoms or signs that may include cough, low-grade fever, dyspnea, hypoxemia, inspiratory crackles, interstitial infiltrates, and declining lung function; however, clinical impressions are not reliable. The diagnosis is confirmed by transbronchial biopsies showing the characteristic lymphocytic infiltrates around arterioles or bronchioles, and a standardized pathologic scheme is used to grade the biopsies (grades A0–4 and B0–4 for the arteriolar and bronchiolar components, respectively).

Minimal ACR (grade A1) on a surveillance biopsy in a clinically stable recipient is not treated always, but higher grades (≥A2) generally are treated regardless of the clinical situation. Treatment usually includes a short course of high-dose steroid therapy and adjustment of the maintenance immunosuppressive regimen. Most episodes respond to this approach; however, more intensive therapy is sometimes necessary for persistent or recurrent episodes.

Chronic Lung Allograft Dysfunction CLAD is the preferred term when lung function never reaches expected values because of an early complication or, more often, when there is a sustained decrement in lung function below previously normal baseline measurements. In the latter situation, two main forms of CLAD are recognized—bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), and both alloimmune and nonalloimmune fibroproliferative reactions can contribute to the pathogenesis. CLAD is the principal impediment to better long-term survival rates, and it is the source of substantial morbidity because of its impact on performance status and quality of life.

The distinguishing features of BOS and RAS are contrasted in Table 292-4. By definition, the decrement in lung function must persist for ≥3 weeks, and other causes of graft dysfunction must be excluded by an appropriate evaluation. Bronchoscopy with bronchoalveolar lavage and transbronchial biopsies is usually performed to exclude bronchostenosis, ACR, and infection. Transbronchial biopsies, however, are insensitive for detecting obliterative bronchiolitis in BOS and are nonspecific in RAS, and pathologic confirmation is not required for diagnosis.

BOS is the classic form of chronic rejection, and the prevalence approaches 50% by 5 years after transplantation. The severity is categorized by the decrement in FEV_1 from the average of the two best posttransplant values (20–35%, stage 1; 35–50%, stage 2; >50%, stage 3). Risk factors include PGD, ACR, humoral rejection and anti-HLA antibodies, viral infections (CMV pneumonia; community-acquired respiratory viral infections), airway colonization by *Pseudomonas aeruginosa* or *Aspergillus fumigatus*, and gastroesophageal reflux (GER).

BOS usually is treated with augmented immunosuppression, but there is no consensus about therapy. Strategies include adjustments to the maintenance drug regimen, the addition of azithromycin, and treatment with antilymphocyte globulin, photopheresis, or total lymphoid irradiation; antireflux surgery should be considered if GER is present. Although therapy may stabilize lung function, the overall results of treatment have been disappointing; median survival period after onset has been ~3–4 years. Retransplantation is a consideration if clinical

TABLE 292-4 Chronic Lung Allograft Dysfunction: Clinical Features of Bronchiolitis Obliterans Syndrome (BOS) and Restrictive Allograft Syndrome (RAS)

SYNDROME	PULMONARY FUNCTION	HRCT PATTERN	PATHOLOGY
BOS	Obstructive FEV_1 <80% of baseline	Air trapping usually present Minimal, if any, infiltrates ± bronchiectasis	Obliterative bronchiolitis Transbronchial biopsies insensitive
RAS	Restrictive TLC <90% of baseline, or FVC and FEV_1 <80% of baseline	Infiltrates usually present ± air trapping ± bronchiectasis	Parenchymal/pleural fibrosis ± obliterative bronchiolitis

Abbreviations: BOS, bronchiolitis obliterans syndrome; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; TLC, total lung capacity.

Source: Modified from GM Verleden et al: J Heart Lung Transplant 33:127, 2014.

circumstances and other comorbidities are not prohibitive, but survival rates have been inferior to that with primary transplantation.

RAS is less common than BOS, and occasionally the two forms coexist. Risk factors for RAS have not been delineated yet. Treatment usually includes a trial of steroid therapy and, in some cases, the same strategies that are used for BOS. Prognosis is worse than BOS, with a median survival ~1.5 years.

Humoral Rejection The role of antibody-mediated rejection is still evolving. Hyperacute rejection is caused by preformed HLA antibodies in the recipient, but it is minimized by pretransplantation antibody screening coupled with virtual or direct cross-matching with any potential donor. Donor-specific HLA antibodies develop after transplantation in ~35–50% of recipients, and their presence has been associated with an increased risk of both ACR and BOS and with poorer overall survival. Criteria for antibody-mediated rejection include graft dysfunction, serologic detection of donor-specific antibodies, and a pathologic pattern of graft injury with evidence of antibody deposition; however, few cases in lung transplantation fulfill all of these criteria. Nonetheless, episodes of acute lung allograft dysfunction occasionally have been attributed directly to antibody-mediated rejection. If treatment is indicated, potential therapies include plasmapheresis and administration of intravenous immune globulin, rituximab, bortezomib, and eculizumab.

Infection The lung allograft is especially susceptible to infection. In addition to a blunted immune response from the immunosuppressive drugs, other normal defenses are compromised: the cough reflex is diminished, and mucociliary clearance is impaired in the transplanted lung. The spectrum of infections includes both opportunistic and nonopportunistic pathogens.

Bacterial bronchitis or pneumonia can occur at any time, but it is very common in the perioperative period. Later, bronchitis occurs frequently in recipients with BOS, and *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* is often the culprit.

Community-acquired respiratory viruses (influenza, parainfluenza, respiratory syncytial virus, metapneumovirus and others) are the most common viral infections and are easily identified with viral multiplex PCR testing of a nasopharyngeal swab or washing. CMV infection has become less problematic with highly sensitive blood CMV PCR monitoring and with widespread prophylactic and preemptive protocols using valganciclovir. However, CMV viremia, pneumonia, hepatitis, and gastroenteritis/colitis still occur occasionally, and treatment with ganciclovir is generally effective unless resistance has developed. The most problematic fungal infections are caused by *Aspergillus* species. The spectrum encompasses simple pulmonary colonization, tracheobronchitis, invasive pulmonary aspergillosis, and disseminated aspergillosis, and the clinical scenario dictates treatment.

Other Complications Other potential complications are listed in Table 292-3. Many of them are related to side effects or toxicities of the immunosuppressive drugs, and the prevalence of some of them is high (hypertension—39% and 61%; renal dysfunction—16% and 45%; hyperlipidemia—24% and 47%; diabetes mellitus—13% and 34%; malignancy—4% and 22%, at 1 year and 5 years, respectively, in the U.S. registry). Management of these general medical problems is guided by standard practices, but the complex milieu of transplantation requires close collaboration and good communication among health care providers.

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Section 1 Respiratory Critical Care

293 Approach to the Patient with Critical Illness

John P. Kress, Jesse B. Hall

The care of critically ill patients requires a thorough understanding of pathophysiology and centers initially on the resuscitation of patients at the extremes of physiologic deterioration. This resuscitation is often fast-paced and occurs early, without a detailed awareness of the patient's chronic medical problems. While physiologic stabilization is taking place, intensivists attempt to gather important background medical information to supplement the real-time assessment of the patient's current physiologic conditions. Numerous tools are available to assist intensivists in the accurate assessment of pathophysiology and management of incipient organ failure, offering a window of opportunity for diagnosing and treating underlying disease(s) in a stabilized patient. Indeed, the use of invasive interventions such as mechanical ventilation and renal replacement therapy is commonplace in the intensive care unit (ICU). An appreciation of the risks and benefits of such aggressive and often invasive interventions is vital to ensure an optimal outcome. Nonetheless, intensivists must recognize when a patient's chances for recovery are remote or nonexistent and must counsel and comfort dying patients and their significant others. Critical care physicians often must redirect the goals of care from resuscitation and cure to comfort when the resolution of an underlying illness is not possible.

ASSESSMENT OF ILLNESS SEVERITY

In the ICU, illnesses are frequently categorized by degree of severity. Numerous severity-of-illness (SOI) scoring systems have been developed and validated over the past three decades. Although these scoring systems have been validated as tools to assess populations of critically ill patients, their utility in predicting individual patient outcomes is not clear. SOI scoring systems are important for defining populations of critically ill patients. Such systematic scoring allows effective comparison of groups of patients enrolled in clinical trials. In verifying a purported benefit of therapy, investigators must be confident that different groups involved in a clinical trial have similar illness severities. SOI scores are also useful in guiding hospital administrative policies, directing the allocation of resources such as nursing and ancillary care and assisting in assessments of quality of ICU care over time. Scoring system validations are based on the premise that age, chronic medical illnesses, and derangements from normal physiology are associated with increased mortality rates. All existing SOI scoring systems are derived from patients who have already been admitted to the ICU.

SOI scoring systems cannot be used to predict survival in individual patients. No established scoring systems that purport to direct clinicians' decision-making regarding criteria for admission to an ICU are available. Thus the use of SOI scoring systems to direct therapy and clinical decision-making cannot be recommended. Instead, these tools should be used as a source of important data to complement clinical bedside decision-making.

The most commonly utilized scoring systems are the SOFA (Sequential Organ Failure Assessment), the APACHE (Acute Physiology and Chronic Health Evaluation), and the SAPS (Simplified Acute Physiology Score) systems.

THE SOFA SCORING SYSTEM

The SOFA scoring system is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction **(Table 293-1)**. The score accounts for clinical interventions; it can be measured repeatedly (i.e., each day), and rising scores correlate well with increasing mortality. Patients with suspected infection can be predicted to have poor outcomes typical of sepsis if they have at least two of the following clinical criteria: respiratory rate >22, altered mental status, or systolic blood pressure <100 mmHg. Recently, a new bedside clinical score using two or more of the above clinical criteria has emerged and is termed quickSOFA (qSOFA). qSOFA is intended to screen patients for ICU admission from out-of-hospital, emergency department, and hospital ward settings.

THE APACHE II SCORING SYSTEM

The APACHE II system is the most commonly used SOI scoring system in North America. Age, type of ICU admission (after elective surgery

TABLE 293-1 Calculation of SOFA Score[a]

	SCORE				
SYSTEM	**0**	**1**	**2**	**3**	**4**
Respiration Pao_2/Fio_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, × $10^3/\mu L$	>150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP >70 mmHg	MAP <70 mmHg	Dopamine < 5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine <0.1 or norepinephrine <0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central Nervous System Glasgow Coma Scale[c]	15	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/dL				<500	<200

[a]Adapted from JL Vincent, R Moreno, J Takala, et al: Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 22(7):707, 1996. [b]Catecholamine doses are given as μg/kg per min for at least 1 h. [c] Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

vs nonsurgical or after emergency surgery), chronic health problems, and 12 physiologic variables (the worst values for each in the first 24 h after ICU admission) are used to derive a score. The predicted hospital mortality rate is derived from a formula that takes into account the APACHE II score, the need for emergency surgery, and a weighted, disease-specific diagnostic category **(Table 293-2)**. The relationship between APACHE II score and mortality risk is illustrated in **Fig. 293-1**. Updated versions of the APACHE scoring system (APACHE III and APACHE IV) have been published.

THE SAPS SCORING SYSTEM

The SAPS II score, used more frequently in Europe than in the United States, was derived in a manner similar to the APACHE score. This score is not disease-specific but rather incorporates three underlying disease variables: AIDS, metastatic cancer, and hematologic malignancy. SAPS 3, which utilizes a 1-h rather than a 24-h window for measuring physiologic derangement scores, was developed in 2005.

SHOCK

See also Chap. 296.

INITIAL EVALUATION

Shock, a common condition necessitating ICU admission or occurring in the course of critical care, is defined by the presence of multisystem end-organ hypoperfusion. Clinical indicators include reduced mean arterial pressure (MAP), tachycardia, tachypnea, cool skin and extremities, acute altered mental status, and oliguria. Hypotension is usually, though not always, present. The end result of multiorgan hypoperfusion is tissue hypoxia, often with accompanying lactic acidosis. Since the MAP is the product of cardiac output and systemic vascular resistance (SVR), reductions in blood pressure can be caused by decreases in cardiac output and/or SVR. Accordingly, once shock is contemplated, the initial evaluation of a hypotensive patient should include an early bedside assessment of the adequacy of cardiac output **(Fig. 293-2)**. Clinical evidence of *diminished* cardiac output includes a narrow pulse pressure (systolic BP minus diastolic BP)—a marker that correlates with stroke volume—and cool extremities with delayed capillary refill. Signs of *increased* cardiac output include a widened pulse pressure (particularly with a reduced diastolic pressure), warm extremities with bounding pulses, and rapid capillary refill. If a hypotensive patient has clinical signs of increased cardiac output, it can be inferred that the reduced blood pressure is from decreased SVR.

TABLE 293-2 Calculation of Acute Physiology and Chronic Health Evaluation II (APACHE II) Score[a]

Acute Physiology Score									
SCORE	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Rectal temperature (°C)	≥41	39.0–40.9		38.5–38.9	36.0–38.4	34.0–35.9	32.0–33.9	30.0–31.9	≤29.9
Mean blood pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate (beats/min)	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (breaths/min)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Arterial pH	≥7.70	7.60–7.69		7.50–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Oxygenation If FIO_2 >0.5, use (A – a) DO_2 If FIO_2 ≤ 0.5, use PaO_2	≥500	350–499	200–349		<200 >70	 61–70		 55–60	 <55
Serum sodium (meq/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium (meq/L)	≥7.0	6.0–6.9		5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9		<2.5
Serum creatinine (mg/dL)	≥3.5	2.0–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count (10^3/mL)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

Glasgow Coma Score[b,c]			
Eye Opening	*Verbal (Nonintubated)*	*Verbal (Intubated)*	*Motor Activity*
4—Spontaneous	5—Oriented and talks	5—Seems able to talk	6—Verbal command
3—Verbal stimuli	4—Disoriented and talks	3—Questionable ability to talk	5—Localizes to pain
2—Painful stimuli	3—Inappropriate words	1—Generally unresponsive	4—Withdraws from pain
1—No response	2—Incomprehensible sounds 1—No response		3—Decorticate 2—Decerebrate 1—No response

Points Assigned to Age and Chronic Disease	
Age, Years	*Score*
<45	0
45–54	2
55–64	3
65–74	5
≥75	6

Chronic Health (History of Chronic Conditions)[d]	*Score*
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

[a]The APACHE II score is the sum of the acute physiology score (vital signs, oxygenation, laboratory values), the Glasgow coma score, age, and chronic health points. The worst values during the first 24 h in the ICU should be used. [b]Glasgow coma score (GCS) = eye-opening score + verbal (intubated or nonintubated) score + motor score. [c]For GCS component of acute physiology score, subtract GCS from 15 to obtain points assigned. [d]Hepatic: cirrhosis with portal hypertension or encephalopathy; cardiovascular: class IV angina (at rest or with minimal self-care activities); pulmonary: chronic hypoxemia or hypercapnia, polycythemia, ventilator dependence; renal: chronic peritoneal or hemodialysis; immune: immunocompromised host.

Abbreviations: (A – a) DO_2, alveolar-arterial oxygen difference; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; WBC, white blood cell count.

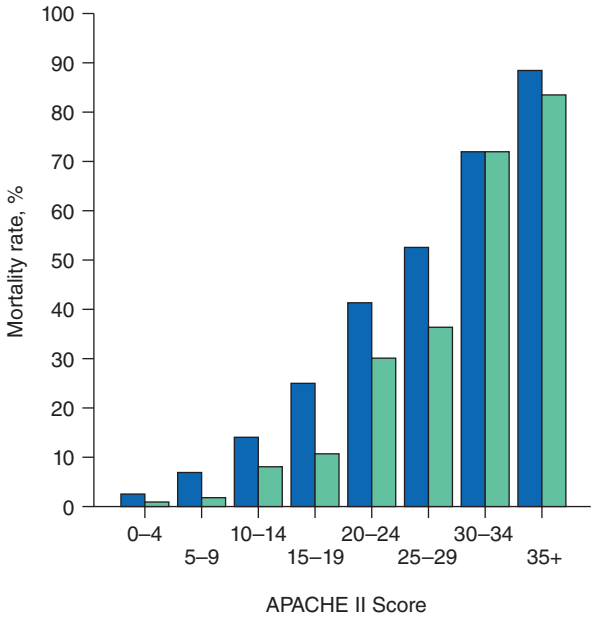

FIGURE 293-1 APACHE II survival curve. Blue, nonoperative; green, postoperative.

In hypotensive patients with signs of reduced cardiac output, an assessment of intravascular volume status is appropriate. A hypotensive patient with decreased intravascular volume status may have a history suggesting hemorrhage or other volume losses (e.g., vomiting, diarrhea, polyuria). Although evidence of a reduced jugular venous pressure (JVP) is often sought, static measures of right atrial pressure do not predict fluid responsiveness reliably; the *change* in right atrial pressure as a function of spontaneous respiration is a better predictor of fluid responsiveness **(Fig. 293-3)**. Patients with fluid-responsive (i.e., hypovolemic) shock also may manifest large changes in pulse pressure as a function of respiration *during* mechanical ventilation **(Fig. 293-4)**. A hypotensive patient with increased intravascular volume and cardiac dysfunction may have S_3 and/or S_4 gallops on examination, increased JVP, extremity edema, and crackles on lung auscultation. The chest x-ray may show cardiomegaly, widening of the vascular pedicle, Kerley B lines, and pulmonary edema. Chest pain and electrocardiographic changes consistent with ischemia may be noted **(Chap. 298)**.

In hypotensive patients with clinical evidence of increased cardiac output, a search for causes of decreased SVR is appropriate. The most common cause of high-cardiac-output hypotension is sepsis **(Chap. 297)**. Other causes include liver failure, severe pancreatitis, burns, trauma, anaphylaxis, thyrotoxicosis, and peripheral arteriovenous shunts.

In summary, the most common categories of shock are hypovolemic, cardiogenic, and high-cardiac-output with decreased SVR (high-output hypotension). Certainly more than one category can occur simultaneously (e.g., hypovolemic and septic shock).

The initial assessment of a patient in shock should take only a few minutes. It is important that aggressive resuscitation is instituted on the basis of the initial assessment, particularly since early resuscitation from septic and cardiogenic shock may improve survival (see below). If the initial bedside assessment yields equivocal or confounding data, more objective assessments such as ultrasound/echocardiography may be useful. In spontaneously breathing patients, inferior vena cava collapse seen on ultrasound predicts a fluid responsive state. Increasingly, ultrasound of the thorax and abdomen is used by intensivists as an extension of the physical examination to assess rapidly imputed filling volumes, adequacy of cardiac performance, and for indices of other specific conditions (e.g., pericardial tamponade, pulmonary embolus, pulmonary edema, pneumothorax). The goal of aggressive resuscitation is to reestablish adequate tissue perfusion and thus to prevent or minimize end-organ injury.

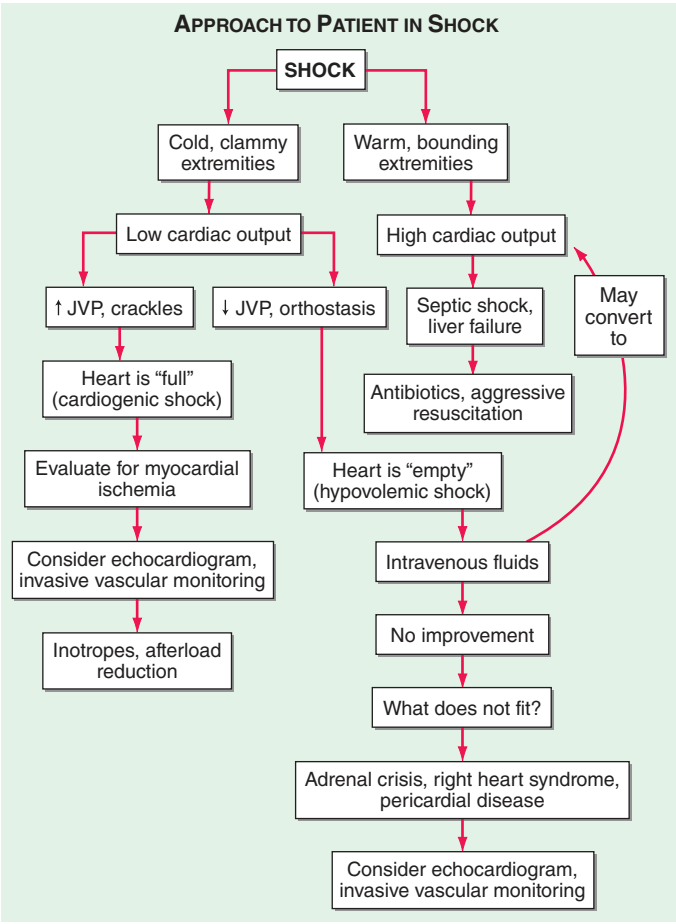

FIGURE 293-2 Approach to the patient in shock. JVP, jugular venous pressure.

MECHANICAL VENTILATORY SUPPORT

(See also Chap. 295) During the initial resuscitation of patients in shock, principles of advanced cardiac life support should be followed. As such patients may be obtunded and unable to protect the airway, an early assessment of the airway is mandatory. Early intubation and mechanical ventilation often are required. Reasons for the institution of endotracheal intubation and mechanical ventilation include acute hypoxemic respiratory failure and ventilatory failure, which frequently accompany shock. Acute hypoxemic respiratory failure may occur in patients with cardiogenic shock and pulmonary edema **(Chap. 298)** as well as in those who are in septic shock with pneumonia or acute respiratory distress syndrome (ARDS) **(Chaps. 294 and 297)**. Ventilatory failure often occurs as a consequence of an increased load on the respiratory system in the form of acute metabolic (often lactic) acidosis or decreased lung compliance due to pulmonary edema. Inadequate perfusion to respiratory muscles in the setting of shock may be another reason for early intubation and mechanical ventilation. Normally, the respiratory muscles receive a very small percentage of the cardiac output. However, in patients who are in shock with respiratory distress, the percentage of cardiac output dedicated to respiratory muscles may increase by tenfold or more. Lactic acid production from inefficient respiratory muscle activity presents an additional ventilatory load.

Mechanical ventilation may relieve the work of breathing and allow redistribution of a limited cardiac output to other vital organs. Patients demonstrate respiratory distress by an inability to speak full sentences, accessory use of respiratory muscles, paradoxical abdominal muscle activity, extreme tachypnea (>40 breaths/min), and decreasing respiratory rate despite an increasing drive to breathe due to exhaustion. When patients with shock are treated with mechanical ventilation, a major goal is for the ventilator to assume all or the majority of the work of breathing, facilitating a state of minimal respiratory muscle work. With the institution of mechanical ventilation for shock, further declines in MAP are frequently seen. The reasons include impeded venous return from positive-pressure ventilation, reduced endogenous

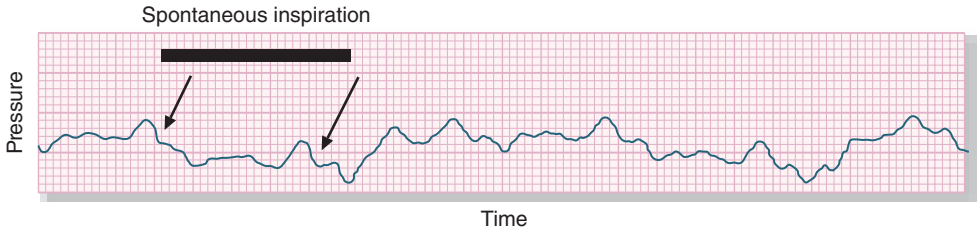

FIGURE 293-3 Right atrial pressure change during spontaneous respiration in a patient with shock whose cardiac output will increase in response to intravenous fluid administration. The right atrial pressure decreases from 7 mmHg to 4 mmHg. The horizontal bar marks the time of spontaneous inspiration.

catecholamine secretion once the stress associated with respiratory failure abates, and the actions of drugs used to facilitate endotracheal intubation (e.g., propofol, opiates). Patients with right heart dysfunction or preexiting pulmonary hypertension may also have diminished cardiac output related to the increases in right ventricular afterload resulting from positive pressure ventilation. Accordingly, hypotension should be anticipated during and following endotracheal intubation. Because many of these patients may be fluid responsive, IV volume administration should be considered. Figure 293-2 summarizes the diagnosis and treatment of different types of shock. **For further discussion of individual forms of shock, see Chaps. 296, 297, and 298.**

RESPIRATORY FAILURE

Respiratory failure is one of the most common reasons for ICU admission. In some ICUs, ≥75% of patients require mechanical ventilation during their stay. Respiratory failure can be categorized mechanistically on the basis of pathophysiologic derangements in respiratory function.

TYPE I: ACUTE HYPOXEMIC RESPIRATORY FAILURE

This type of respiratory failure occurs with alveolar flooding and subsequent intrapulmonary shunt physiology. Alveolar flooding may be a consequence of pulmonary edema, lung injury, pneumonia, or alveolar hemorrhage. Pulmonary edema can be further categorized as occurring due to elevated pulmonary microvascular pressures, as seen in heart failure and intravascular volume overload or ARDS ("low-pressure pulmonary edema," **Chap. 294**). This syndrome is defined by acute onset (≤1 week) of bilateral opacities on chest imaging that are not fully explained by cardiac failure or fluid overload and of shunt physiology requiring positive end-expiratory pressure (PEEP). Type I respiratory failure occurs in clinical settings such as sepsis, gastric aspiration, pneumonia, near-drowning, multiple blood transfusions, and pancreatitis. The mortality rate among patients with ARDS was traditionally very high (50–70%), although changes in patient care have led to mortality rates closer to 30% (see below).

It is well established that mechanical ventilation of patients with ARDS may propagate lung injury. As seen in **Fig. 293-5**, the pressure-volume relationship of the lung in ARDS is not linear. Alveoli may collapse at very low lung volumes. Animal studies have suggested that stretching and overdistention of injured alveoli during mechanical ventilation can further injure the lung. Concern over this alveolar overdistention, termed *ventilator-induced "volutrauma,"* led to a multicenter, randomized, prospective trial comparing traditional ventilator strategies for ARDS (large tidal volume: 12 mL/kg of ideal body weight) with a low tidal volume (6 mL/kg of ideal body weight). This study showed a dramatic reduction in mortality rate in the low-tidal-volume group from that in the high-tidal-volume group (31 versus 39.8%). Other studies have shown that large tidal volumes may lead to ARDS in patients who initially do not have this problem. Neuromuscular blockade and prone positioning have been shown to improve survival in those with severe ARDS. In addition, a "fluid-conservative" management strategy (maintaining a low central venous pressure [CVP] or pulmonary capillary wedge pressure [PCWP]) is associated with fewer days of mechanical ventilation than a "fluid-liberal" strategy (maintaining a relatively high CVP or PCWP) in ARDS. There is growing interest in avoiding intubation in patients with ARDS by the use of a variety of devices, such as masks, high flow oxygen delivery systems, and helmets for respiratory support; however, this is tempered by concern that higher tidal volumes during spontaneous breathing with these devices could result in progression of preexisting lung injury.

TYPE II RESPIRATORY FAILURE

This type of respiratory failure is a consequence of alveolar hypoventilation and results from the inability to eliminate carbon dioxide effectively. Mechanisms are categorized by impaired central nervous system (CNS) drive to breathe, impaired strength with failure of neuromuscular function in the respiratory system, and increased load(s) on the respiratory system. Reasons for diminished CNS drive to breathe include drug overdose, brainstem injury, sleep-disordered breathing, and severe hypothyroidism. Reduced strength can be due to impaired neuromuscular transmission (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis) or respiratory muscle weakness (e.g., myopathy, electrolyte derangements, fatigue).

The overall load on the respiratory system can be subclassified into resistive loads (e.g., bronchospasm), loads due to reduced lung compliance (e.g., alveolar edema, atelectasis, intrinsic positive end-expiratory pressure [auto-PEEP]—see below), loads due to reduced chest wall compliance (e.g., pneumothorax, pleural effusion, abdominal distention), and loads due to increased minute ventilation requirements (e.g., pulmonary embolus with increased dead-space fraction, sepsis).

The mainstays of therapy for type II respiratory failure are directed at reversing the underlying cause(s) of ventilatory failure. Noninvasive positive-pressure ventilation with a tight-fitting facial or nasal mask, with avoidance of endotracheal intubation, often stabilizes these patients. This approach has been shown to be beneficial in treating patients with exacerbations of chronic obstructive pulmonary disease; it has been tested less extensively in other kinds of respiratory failure but may be attempted nonetheless in the absence of contraindications (hemodynamic instability, inability to protect the airway, respiratory arrest).

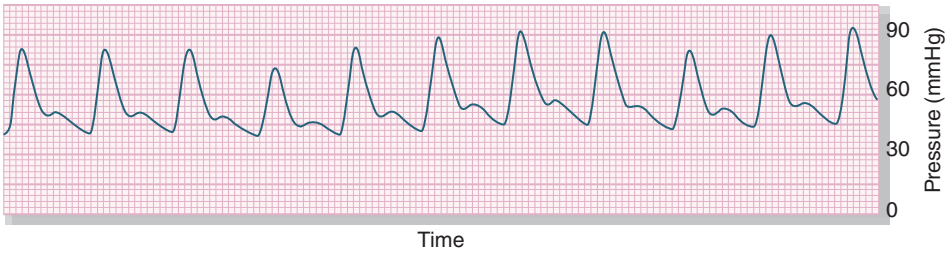

FIGURE 293-4 Pulse pressure change during mechanical ventilation in a patient with shock whose cardiac output will increase in response to intravenous fluid administration. The pulse pressure (systolic minus diastolic blood pressure) changes during mechanical ventilation in a patient with septic shock.

TYPE III RESPIRATORY FAILURE

This form of respiratory failure results from lung atelectasis. Because atelectasis occurs so commonly in the perioperative period, this form is also called *perioperative respiratory failure*. After general anesthesia, decreases in functional residual capacity lead to collapse of dependent lung units. Such atelectasis can be treated by frequent changes in position, chest physiotherapy, upright positioning, and control of incisional and/or abdominal

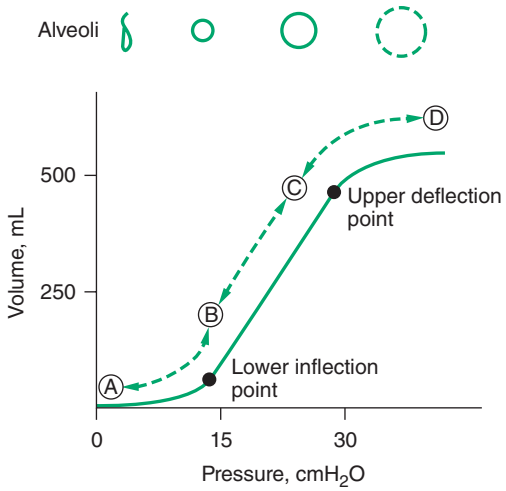

FIGURE 293-5 Pressure-volume relationship in the lungs of a patient with acute respiratory distress syndrome (ARDS). At the lower inflection point, collapsed alveoli begin to open and lung compliance changes. At the upper deflection point, alveoli become overdistended. The shape and size of alveoli are illustrated at the top of the figure.

pain. Noninvasive positive-pressure ventilation may also be used to reverse regional atelectasis.

TYPE IV RESPIRATORY FAILURE

This form results from hypoperfusion of respiratory muscles in patients in shock. Normally, respiratory muscles consume <5% of total cardiac output and oxygen delivery. Patients in shock often experience respiratory distress due to pulmonary edema (e.g., in cardiogenic shock), lactic acidosis, and anemia. In this setting, up to 40% of cardiac output may be distributed to the respiratory muscles. Intubation and mechanical ventilation can allow redistribution of the cardiac output away from the respiratory muscles and back to vital organs while the shock is treated.

CARE OF THE MECHANICALLY VENTILATED PATIENT

(See also Chap. 295) Whereas a thorough understanding of the pathophysiology of respiratory failure is essential for optimal patient care, recognition of a patient's readiness to be liberated from mechanical ventilation is likewise important. Several studies have shown that daily spontaneous breathing trials can identify patients who are ready for extubation. Accordingly, all intubated, mechanically ventilated patients should undergo daily screening of respiratory function. If oxygenation is stable (i.e., Pao_2/FIo_2 [partial pressure of oxygen/fraction of inspired oxygen] >200 and PEEP ≤5 cmH_2O), cough and airway reflexes are intact, and no vasopressor agents or sedatives are being administered, the patient has passed the screening test and should undergo a spontaneous breathing trial. This trial consists of a period of breathing through the endotracheal tube without ventilator support (continuous positive airway pressure [CPAP] of 5 cmH_2O with or without low level pressure support [e.g., 5 cmH_2O] and an open T-piece breathing system have all been validated) for 30–120 min. The spontaneous breathing trial is declared a failure and stopped if *any* of the following occur: (1) respiratory rate >35/min for >5 min, (2) O_2 saturation <90%, (3) heart rate >140/min or a 20% increase or decrease from baseline, (4) systolic blood pressure <90 mmHg or >180 mmHg, or (5) increased anxiety or diaphoresis. If, at the end of the spontaneous breathing trial, none of the above events has occurred and the ratio of the respiratory rate and tidal volume in liters (f/V_T) is <105, the patient can be extubated. Such protocol-driven approaches to patient care can have an important impact on the duration of mechanical ventilation and ICU stay. In spite of such a careful approach to liberation from mechanical ventilation, up to 10% of patients develop respiratory distress after extubation and may require resumption of mechanical ventilation. Many of these patients will require reintubation. The use of noninvasive ventilation in patients in whom extubation fails may be associated with worse outcomes than are obtained with immediate reintubation.

Mechanically ventilated patients frequently require sedatives and analgesics. Opiates are the mainstay of therapy for analgesia in mechanically ventilated patients. After adequate pain control has been ensured, additional indications for sedation include anxiolysis; treatment of subjective dyspnea; reduction of autonomic hyperactivity, which may precipitate myocardial ischemia; and reduction of total O_2 consumption (Vo_2). Non-benzodiazepine sedatives are preferred since benzodiazepines are associated with worse patient outcomes.

The neuromuscular blocking agent cisatracurium is occasionally used to facilitate mechanical ventilation in patients with profound ventilator dyssynchrony despite optimal sedation, particularly in the setting of severe ARDS. Use of these agents may result in prolonged weakness—a myopathy known as the *postparalytic syndrome*. For this reason, neuromuscular blocking agents typically are used as a last resort when aggressive sedation fails to achieve patient-ventilator synchrony. Because neuromuscular blocking agents result in pharmacologic paralysis without altering mental status, sedative-induced amnesia is mandatory when these agents are administered.

Amnesia can be achieved reliably with propofol and benzodiazepines such as lorazepam and midazolam. Outside the setting of pharmacologic paralysis, few data support the idea that amnesia is mandatory in all patients who require intubation and mechanical ventilation. Since many of these critical patients have impaired hepatic and renal function, sedatives and opiates may accumulate when given for prolonged periods. A nursing protocol–driven approach to sedation of mechanically ventilated patients or daily interruption of sedative infusions paired with daily spontaneous breathing trials has been shown to prevent excessive drug accumulation and shorten the duration of both mechanical ventilation and ICU stay.

MULTIORGAN SYSTEM FAILURE

Multiorgan system failure, which is commonly associated with critical illness, is defined by the simultaneous presence of physiologic dysfunction and/or failure of two or more organs. Typically, this syndrome occurs in the setting of severe sepsis, shock of any kind, severe inflammatory conditions such as pancreatitis, and trauma. The fact that multiorgan system failure occurs commonly in the ICU is a testament to our current ability to stabilize and support single-organ failure. The ability to support single-organ failure aggressively (e.g., by mechanical ventilation or by renal replacement therapy) has reduced rates of early mortality in critical illness. As a result, it is uncommon for critically ill patients to die in the initial stages of resuscitation. Instead, many patients succumb to critical illness later in the ICU stay, after the initial presenting problem has been stabilized.

Although there is debate regarding specific definitions of organ failure, several general principles governing the syndrome of multiorgan system failure apply. First, organ failure, no matter how it is defined, must persist beyond 24 h. Second, mortality risk increases with the accrual of failing organs. Third, the prognosis worsens with increased duration of organ failure. These observations remain true across various critical care settings (e.g., medical versus surgical).

MONITORING IN THE ICU

Because respiratory failure and circulatory failure are common in critically ill patients, monitoring of the respiratory and cardiovascular systems is undertaken frequently. Evaluation of respiratory gas exchange is routine in critical illness. The "gold standard" remains arterial blood-gas analysis, in which pH, Pao_2, partial pressure of carbon dioxide (Pco_2), and O_2 saturation are measured directly. With arterial blood-gas analysis, the two main functions of the lung—oxygenation of arterial blood and elimination of CO_2—can be assessed directly. In fact, the blood pH, which has a profound effect on the drive to breathe, can be assessed only by such sampling. Although sampling of arterial blood is generally safe, it may be painful and cannot provide continuous information. In light of these limitations, noninvasive monitoring of respiratory function is often employed.

PULSE OXIMETRY

The most commonly utilized noninvasive technique for monitoring respiratory function, pulse oximetry takes advantage of differences in the absorptive properties of oxygenated and deoxygenated hemoglobin. At wavelengths of 660 nm, oxyhemoglobin reflects light more effectively than does deoxyhemoglobin, whereas the reverse is true in the infrared spectrum (940 nm). A pulse oximeter passes both wavelengths of light through a perfused digit such as a finger, and the relative intensity of light transmission at these two wavelengths is recorded. From this information, the relative percentage of oxyhemoglobin is derived. Since arterial pulsations produce phasic changes in the intensity of transmitted light, the pulse oximeter is designed to detect only light of alternating intensity. This feature allows distinction of arterial and venous blood O_2 saturations.

RESPIRATORY SYSTEM MECHANICS

Respiratory system mechanics can be measured in patients during mechanical ventilation **(Chap. 295)**. When volume-controlled modes of mechanical ventilation are used, accompanying airway pressures can easily be measured as long as the patient is passive. The peak airway pressure is determined by two variables: airway resistance and respiratory system compliance. At the end of inspiration, inspiratory flow can be stopped transiently. This end-inspiratory pause (*plateau pressure*) is a static measurement, affected only by respiratory system compliance and not by airway resistance. Therefore, during volume-controlled ventilation, the difference between the peak (airway resistance + respiratory system compliance) and plateau (respiratory system compliance only) airway pressures provides a quantitative assessment of airway resistance. Accordingly, during volume-controlled ventilation, patients with increases in airway resistance typically have increased peak airway pressures as well as abnormally high gradients between peak and plateau airway pressures (typically >15 cmH_2O) at a constant inspiratory flow rate of 1 L/sec. The compliance of the respiratory system is defined by the change in volume of the respiratory system per unit change in pressure.

The respiratory system can be divided into two components: the lungs and the chest wall. Normally, respiratory system compliance is ~100 mL/cmH_2O. Pathophysiologic processes such as pleural effusions, pneumothorax, and increased abdominal girth all reduce chest wall compliance. Lung compliance may be reduced by pneumonia, pulmonary edema, interstitial lung disease, or auto-PEEP. Accordingly, patients with abnormalities in compliance of the respiratory system (lungs and/or chest wall) typically have elevated peak *and* plateau airway pressures but a normal gradient between these two pressures. Auto-PEEP occurs when there is insufficient time for emptying of alveoli before the next inspiratory cycle. Since the alveoli have not decompressed completely, alveolar pressure remains positive at the end of exhalation (*functional residual capacity*). This phenomenon results most commonly from obstruction of distal airways in disease processes such as asthma and COPD. Auto-PEEP with resulting alveolar overdistention may result in diminished lung compliance, reflected by abnormally increased plateau airway pressures. Modern mechanical ventilators allow breath-to-breath display of pressure and flow, permitting detection of problems such as patient-ventilator dyssynchrony, airflow obstruction, and auto-PEEP **(Fig. 293-6)**.

CIRCULATORY STATUS

Oxygen delivery (Qo_2) is a function of cardiac output and the content of O_2 in the arterial blood (Cao_2). The Cao_2 is determined by the hemoglobin concentration, the arterial hemoglobin saturation, and dissolved O_2 not bound to hemoglobin. For normal adults:

$$Qo_2 = 50\ \text{dL/min} \times (1.39 \times 15\ \text{g/dL [hemoglobin concentration]} \times 1.0\ \text{[hemoglobin \% saturation]} + 0.0031 \times 100\ [Pao_2])$$
$$= 50\ \text{dL/min (cardiac output)} \times 21.6\ \text{mL } O_2\ \text{per dL blood } (Cao_2)$$
$$= 1058\ \text{mL } O_2\ \text{per min}$$

It is apparent that nearly all of the O_2 delivered to tissues is bound to hemoglobin and that the dissolved O_2 (Pao_2) contributes very little to O_2 content in arterial blood or to O_2 delivery. Normally, the content of O_2 in mixed venous blood ($C\bar{v}o_2$) is 15.76 mL/dL since the mixed venous blood is 75% saturated. Therefore, the normal tissue extraction ratio for O_2 is $Cao_2 - C\bar{v}o_2/Cao_2$ ([21.16 – 15.76]/21.16) or ~25%. A pulmonary artery catheter allows measurements of O_2 delivery and the O_2 extraction ratio.

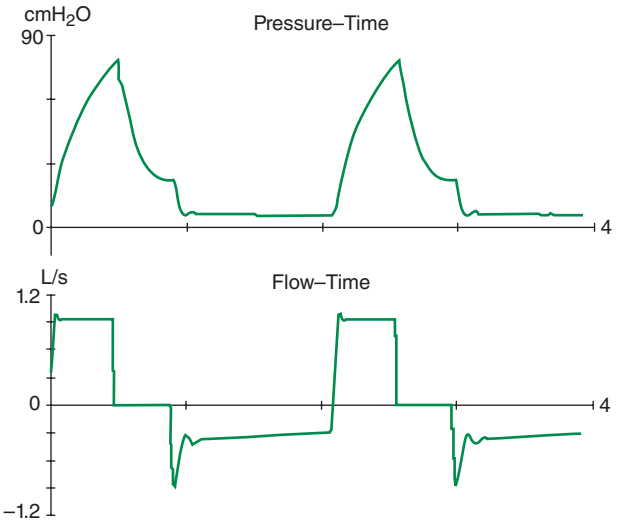

FIGURE 293-6 Increased airway resistance with auto-PEEP. The top waveform (airway pressure vs. time) shows a large difference between the peak airway pressure (80 cmH_2O) and the plateau airway pressure (20 cmH_2O). The bottom waveform (flow vs. time) demonstrates airflow throughout expiration (reflected by the flow tracing on the negative portion of the abscissa) that persists up to the next inspiratory effort.

Information on the venous O_2 saturation allows assessment of global tissue perfusion. A reduced venous O_2 saturation may be caused by inadequate cardiac output, reduced hemoglobin concentration, and/or reduced arterial O_2 saturation. An abnormally high Vo_2 may also lead to a reduced venous O_2 saturation if O_2 delivery is not concomitantly increased. Abnormally increased Vo_2 in peripheral tissues may be caused by problems such as fever, agitation, shivering, and thyrotoxicosis.

The pulmonary artery catheter originally was designed as a tool to guide therapy for acute myocardial infarction but has been used in the ICU for evaluation and treatment of a variety of other conditions, such as ARDS, septic shock, congestive heart failure, and acute renal failure. This device has never been validated as a tool associated with reduction in morbidity and mortality rates. Indeed, despite numerous prospective studies, mortality or morbidity rate benefits associated with use of the pulmonary artery catheter have never been reported in any setting. Accordingly, it appears that routine pulmonary artery catheterization is not indicated as a means of monitoring and characterizing circulatory status in most critically ill patients.

Static measurements of circulatory parameters (e.g., *CVP,* PCWP) do not provide reliable information on the circulatory status of critically ill patients. In contrast, dynamic assessments measuring the impact of breathing on the circulation are more reliable predictors of responsiveness to IV fluid administration. A decrease in CVP of >1 mmHg during inspiration in a spontaneously breathing patient may predict an increase in cardiac output after IV fluid administration. Similarly, a changing pulse pressure during mechanical ventilation of a passive patient has been shown to predict an increase in cardiac output after IV fluid administration, assuming the R-R interval is stable.

PREVENTION OF COMPLICATIONS OF CRITICAL ILLNESS

SEPSIS IN THE CRITICAL CARE UNIT

(See also Chap. 297) Sepsis, is defined as life-threatening organ dysfunction (i.e., an increase in Sequential Organ Failure Assessment [SOFA] of 2 points or more) caused by a dysregulated response to infection. Poor outcomes can be anticipated in patients with 2 or more of the following: respiratory rate >22 per min, altered mentation, systolic blood

pressure <100 mmHg. Sepsis is a leading cause of death in noncoronary ICUs in the United States, with case rates expected to increase as the population ages and a higher percentage of people are vulnerable to infection.

NOSOCOMIAL INFECTIONS IN THE ICU

Many therapeutic interventions in the ICU are invasive and predispose patients to infectious complications. These interventions include endotracheal intubation, indwelling vascular catheters, transurethral bladder catheters, and other catheters placed into sterile body cavities (e.g., tube thoracostomy, percutaneous intraabdominal drainage catheterization). The longer such devices remain in place, the more prone to these infections patients become. For example, ventilator-associated events such as ventilator-associated pneumonia correlate strongly with the duration of intubation and mechanical ventilation. Therefore, an important aspect of preventive care is the timely removal of invasive devices as soon as they are no longer needed. Moreover, multidrug-resistant organisms are commonplace in the ICU.

Infection control is critical in the ICU. Care bundles, which include measures such as frequent hand washing, are effective but underutilized strategies. Other components of care bundles, such as protective isolation of patients colonized or infected by drug-resistant organisms, are also commonly used. Silver-coated endotracheal tubes reportedly reduce the incidence of ventilator-associated pneumonia. Studies evaluating multifaceted, evidence-based strategies to decrease catheter-related bloodstream infections have shown improved outcomes with strict adherence to measures such as hand washing, full-barrier precautions during catheter insertion, chlorhexidine skin preparation, avoidance of the femoral site, and timely catheter removal.

DEEP-VENOUS THROMBOSIS (DVT)

(See also Chap. 273) All ICU patients are at high risk for this complication because of their predilection for immobility. Therefore, all should receive some form of prophylaxis against DVT. The most commonly employed forms of prophylaxis are subcutaneous low-dose heparin injections and sequential compression devices for the lower extremities. Observational studies report an alarming incidence of DVTs despite the use of these standard prophylactic regimens. Furthermore, heparin prophylaxis may result in heparin-induced thrombocytopenia, another nosocomial complication in critically ill patients.

Low-molecular-weight heparins such as enoxaparin are more effective than unfractionated heparin for DVT prophylaxis in high-risk patients (e.g., those undergoing orthopedic surgery) and are associated with a lower incidence of heparin-induced thrombocytopenia. Fondaparinux, a selective factor Xa inhibitor, is even more effective than enoxaparin in high-risk orthopedic patients.

STRESS ULCERS

Prophylaxis against stress ulcers is not necessary for all ICU patients. It should only be administered to high-risk patients, such as those with coagulopathy or respiratory failure. Histamine receptor-2 antagonists are preferred over proton pump inhibitors because the latter are associated with increased incidence of *C. difficile* colitis and pneumonia.

NUTRITION AND GLYCEMIC CONTROL

These are important issues that may be associated with respiratory failure, impaired wound healing, and dysfunctional immune response in critically ill patients. Early enteral feeding is reasonable, with some data suggesting that permissive underfeeding of nonprotein calories is not inferior to full goal feeding. Certainly, enteral feeding, if possible, is preferred over parenteral nutrition, which is associated with numerous complications, including hyperglycemia, fatty liver, cholestasis, and sepsis. When parenteral feeding is necessary to supplement enteral nutrition, delaying this intervention until day 8 in the ICU results in better recovery and fewer ICU-related complications. Tight glucose control is an area of controversy in critical care. Although one study showed a significant mortality benefit when glucose levels were aggressively normalized in a large group of surgical ICU patients, other studies of both medical and surgical ICU patients suggested that tight glucose control resulted in increased rates of mortality.

ICU-ACQUIRED WEAKNESS

ICU-acquired weakness occurs frequently in patients who survive critical illness, particularly those with SIRS and/or sepsis. Both neuropathies and myopathies have been described, most commonly after ~1 week in the ICU. The mechanisms behind ICU-acquired weakness syndromes are poorly understood, they are known to present with heterogeneous muscle pathophysiology. Intensive insulin therapy may reduce polyneuropathy in critical illness. Very early physical and occupational therapy in mechanically ventilated patients reportedly results in significant improvements in functional independence at hospital discharge as well as in reduced durations of mechanical ventilation and delirium.

ANEMIA

Studies have shown that most ICU patients are anemic as a result of chronic inflammation. Phlebotomy also contributes to ICU anemia. A large multicenter study involving patients in many different ICU settings challenged the conventional notion that a hemoglobin level of 100 g/L (10 g/dL) is needed in critically ill patients, with similar outcomes noted in those whose transfusion trigger was 7 g/dL. Red blood cell transfusion is associated with impairment of immune function and increased risk of infections as well as of ARDS and volume overload, all of which may explain the findings in this study. A conservative transfusion strategy has shown similar outcomes in septic shock, post-cardiac surgery, and post-hip surgery patients. A conservative transfusion strategy has been shown to enhance survival among patients with active upper gastrointestinal hemorrhage.

ACUTE KIDNEY FAILURE

(See also Chap. 304) Acute kidney failure occurs in a significant percentage of critically ill patients. The most common underlying etiology is acute tubular necrosis, usually precipitated by hypoperfusion and/or nephrotoxic agents. Currently, no pharmacologic agents are available for prevention of kidney injury in critical illness. Studies have shown convincingly that neither low-dose dopamine, fenoldapam nor vasopressin are *not* effective in protecting the kidneys from acute injury.

NEUROLOGIC DYSFUNCTION IN CRITICALLY ILL PATIENTS

DELIRIUM

(See also Chaps. 24 and 300) This state is defined by (1) an acute onset of changes or fluctuations in mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness (i.e., a state other than alertness). Delirium is reported to occur in a wide range of mechanically ventilated ICU patients and can be detected by the Confusion Assessment Method (CAM)-ICU or the Intensive Care Delirium Screening Checklist. These tools are used to ask patients to answer simple questions and perform simple tasks and can be used readily at the bedside. The differential diagnosis of delirium in ICU patients is broad and includes infectious etiologies (including sepsis), medications (particularly sedatives and analgesics), drug withdrawal, metabolic/electrolyte derangements, intracranial pathology (e.g., stroke, intracranial hemorrhage), seizures, hypoxia, hypertensive crisis, shock, and vitamin deficiencies (particularly thiamine). The etiology of a patient's ICU delirium impacts the prognosis. Those with persistent ICU delirium not related to sedatives have increases in length of hospital stay, time on mechanical ventilation, cognitive impairment at hospital discharge, and 6-month mortality rate. Interventions to reduce ICU delirium are limited. The sedative dexmedetomidine has been less strongly associated with ICU delirium than midazolam. In addition, very early physical and occupational therapy in mechanically ventilated patients has been demonstrated to reduce delirium.

ANOXIC CEREBRAL INJURY

(See also Chap. 301) This condition is common after cardiac arrest and often results in severe and permanent brain injury in survivors. Active cooling of patients after cardiac arrest is controversial, with some studies showing improved neurologic outcomes and others showing no

such improvement. Certainly patients suffering cardiac arrest should have a temperature targeted to no higher than 36°C.

STROKE

(See also Chap. 419) Stroke is a common cause of neurologic critical illness. Hypertension must be managed carefully, since abrupt reductions in blood pressure may be associated with further brain ischemia and injury. Acute ischemic stroke treated with tissue plasminogen activator (tPA) has an improved neurologic outcome when treatment is given within 4.5 h of onset of symptoms. The mortality rate is not reduced when tPA is compared with placebo, despite the improved neurologic outcome. The risk of cerebral hemorrhage is significantly higher in patients given tPA. No benefit is seen when tPA therapy is given beyond 4.5 h after symptom onset. Heparin has not been convincingly shown to improve outcomes in patients with acute ischemic stroke. Decompressive craniectomy is a surgical procedure that relieves increased intracranial pressure in the setting of space-occupying brain lesions or brain swelling from stroke; available evidence suggests that this procedure may improve survival among select patients (≤55 years or age), albeit at a cost of increased disability for some.

SUBARACHNOID HEMORRHAGE

(See also Chap. 419) Subarachnoid hemorrhage may occur secondary to aneurysm rupture and is often complicated by cerebral vasospasm, re-bleeding, and hydrocephalus. Vasospasm can be detected by either transcranial Doppler assessment or cerebral angiography; it is typically treated with the calcium channel blocker nimodipine, aggressive IV fluid administration, and therapy aimed at increasing blood pressure, typically with vasoactive drugs such as phenylephrine. The IV fluids and vasoactive drugs (hypertensive hypervolemic therapy) are used to overcome the cerebral vasospasm. Early surgical clipping or endovascular coiling of aneurysms is advocated to prevent complications related to re-bleeding. Hydrocephalus, typically heralded by a decreased level of consciousness, may require ventriculostomy drainage.

STATUS EPILEPTICUS

(See also Chap. 418) Recurrent or relentless seizure activity is a medical emergency. Cessation of seizure activity is required to prevent irreversible neurologic injury. Lorazepam is the most effective benzodiazepine for treating status epilepticus and is the treatment of choice for controlling seizures acutely. Phenytoin or fosphenytoin should be given concomitantly since lorazepam has a short half-life. Other drugs, such as gabapentin, carbamazepine, and phenobarbital, should be reserved for patients with contraindications to phenytoin (e.g., allergy or pregnancy) or ongoing seizures despite phenytoin.

BRAIN DEATH

(See also Chap. 301) Although deaths of critically ill patients usually are attributable to irreversible cessation of circulatory and respiratory function, a diagnosis of death also may be established by irreversible cessation of all functions of the entire brain, including the brainstem, even if circulatory and respiratory functions remain intact on artificial life support. Such a diagnosis requires demonstration of the absence of cerebral function (no response to any external stimulus) and brainstem functions (e.g., unreactive pupils, lack of ocular movement in response to head turning or ice-water irrigation of ear canals, positive apnea test [no drive to breathe]). Absence of brain function must have an established cause and be permanent without possibility of recovery; a sedative effect, hypothermia, hypoxemia, neuromuscular paralysis, and severe hypotension must be ruled out. If there is uncertainty about the cause of coma, studies of cerebral blood flow and electroencephalography should be performed.

WITHHOLDING OR WITHDRAWING CARE

(See also Chap. 9) Withholding or withdrawal of care occurs commonly in the ICU setting. The Task Force on Ethics of the Society of Critical Care Medicine reported that it is ethically sound to withhold or withdraw care if a patient or the patient's surrogate makes such a request or if the physician judges that the goals of therapy are not achievable. Since all medical treatments are justified by their expected benefits, the loss of such an expectation justifies the act of withdrawing or withholding such treatment; these two actions are judged to be fundamentally similar. An underlying stipulation derived from this report is that an informed patient should have his or her wishes respected with regard to life-sustaining therapy. Implicit in this stipulation is the need to ensure that patients are thoroughly and accurately informed regarding the plausibility and expected results of various therapies.

The act of informing patients and/or surrogate decision-makers is the responsibility of the physician and other health care providers. If a patient or surrogate desires therapy deemed futile by the treating physician, the physician is not obligated ethically to provide such treatment. Rather, arrangements may be made to transfer the patient's care to another care provider. Whether the decision to withdraw life support should be initiated by the physician or left to surrogate decision-makers alone is not clear. One study reported that slightly more than half of surrogate decision-makers preferred to receive such a recommendation, whereas the rest did not. Critical care providers should meet regularly with patients and/or surrogates to discuss prognosis when the withholding or withdrawal of care is being considered. After a consensus among caregivers has been reached, this information should be relayed to the patient and/or surrogate decision-maker. If a decision to withhold or withdraw life-sustaining care for a patient has been made, aggressive attention to analgesia and anxiolysis is needed.

FURTHER READING

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294 Acute Respiratory Distress Syndrome

Rebecca M. Baron, Bruce D. Levy

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. ARDS is caused by diffuse lung injury from many underlying medical and surgical disorders. The lung injury may be direct, as occurs in toxic inhalation, or indirect, as occurs in sepsis (Table 294-1). The clinical features of ARDS are listed in Table 294-2. By expert consensus, ARDS is defined by three categories based on the degrees of hypoxemia (Table 294-2). These stages of mild, moderate, and severe ARDS are associated with mortality risk and with the duration of mechanical ventilation in survivors.

The annual incidence of ARDS is estimated to be as high as 60 cases/100,000 population. Approximately 10% of all intensive care unit (ICU) admissions involve patients with ARDS.

TABLE 294-1 Clinical Disorders Commonly Associated with ARDS

DIRECT LUNG INJURY	INDIRECT LUNG INJURY
Pneumonia	Sepsis
Aspiration of gastric contents	Severe trauma
Pulmonary contusion	Multiple bone fractures
Near-drowning	Flail chest
Toxic inhalation injury	Head trauma
	Burns
	Multiple transfusions
	Drug overdose
	Pancreatitis
	Postcardiopulmonary bypass

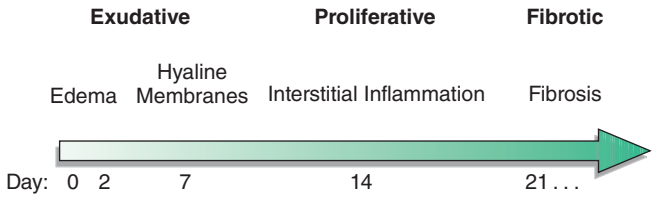

FIGURE 294-1 Diagram illustrating the time course for the development and resolution of ARDS. The exudative phase is notable for early alveolar edema and neutrophil-rich leukocytic infiltration of the lungs, with subsequent formation of hyaline membranes from diffuse alveolar damage. Within 7 days, a proliferative phase ensues with prominent interstitial inflammation and early fibrotic changes. Approximately 3 weeks after the initial pulmonary injury, most patients recover. However, some patients enter the fibrotic phase, with substantial fibrosis and bullae formation.

ETIOLOGY

While many medical and surgical illnesses have been associated with the development of ARDS, most cases (>80%) are caused by a relatively small number of clinical disorders: pneumonia and sepsis (~40–60%), followed in incidence by aspiration of gastric contents, trauma, multiple transfusions, and drug overdose. Among patients with trauma, the most frequently reported surgical conditions in ARDS are pulmonary contusion, multiple bone fractures, and chest wall trauma/flail chest, whereas head trauma, near-drowning, toxic inhalation, and burns are rare causes. The risks of developing ARDS are increased in patients with more than one predisposing medical or surgical condition.

Several other clinical variables have been associated with the development of ARDS. These include older age, chronic alcohol abuse, metabolic acidosis, pancreatitis, and severity of critical illness. Trauma patients with an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥16 **(Chap. 293)** have a 2.5-fold increased risk of developing ARDS.

CLINICAL COURSE AND PATHOPHYSIOLOGY

The natural history of ARDS is marked by three phases—exudative, proliferative, and fibrotic—that each have characteristic clinical and pathologic features **(Fig. 294-1)**.

Exudative Phase In this phase, alveolar capillary endothelial cells and type I pneumocytes (alveolar epithelial cells) are injured, with consequent loss of the normally tight alveolar barrier to fluid and macromolecules. Edema fluid that is rich in protein accumulates in the interstitial and alveolar spaces **(Fig. 294-2)**. Pro-inflammatory cytokines (e.g., interleukin 1, interleukin 8, and tumor necrosis factor α [TNF-α]) and lipid mediators (e.g., leukotriene B_4) are increased in this acute phase, leading to the recruitment of leukocytes (especially neutrophils) into the pulmonary interstitium and alveoli. In addition, condensed plasma proteins aggregate in the air spaces with cellular debris and dysfunctional pulmonary surfactant to form hyaline membrane whorls. Pulmonary vascular injury also occurs early in ARDS, with vascular obliteration by microthrombi and fibrocellular proliferation **(Fig. 294-3)**.

Alveolar edema predominantly involves *dependent* portions of the lung with diminished aeration. Collapse of large sections of dependent lung can contribute to decreased lung compliance. Consequently, intrapulmonary shunting and hypoxemia develop and the work of breathing increases, leading to dyspnea. The pathophysiologic alterations in alveolar spaces are exacerbated by microvascular occlusion that results in reductions in pulmonary arterial blood flow to ventilated portions of the lung (and thus in increased dead space) and in pulmonary hypertension. Thus, in addition to severe hypoxemia, hypercapnia secondary to an increase in pulmonary dead space can be prominent in early ARDS.

The exudative phase encompasses the first 7 days of illness after exposure to a precipitating ARDS risk factor, with the patient experiencing the onset of respiratory symptoms. Although usually presenting within 12–36 h after the initial insult, symptoms can be delayed by 5–7 days. Dyspnea develops, with a sensation of rapid shallow breathing and an inability to get enough air. Tachypnea and increased work of breathing result frequently in respiratory fatigue and ultimately in respiratory failure. Laboratory values are generally nonspecific and are primarily indicative of underlying clinical disorders. The chest radiograph usually reveals opacities consistent with pulmonary edema and often involves at least three-quarters of the lung fields (Fig. 294-2). While characteristic for ARDS, these radiographic findings are not specific and can be indistinguishable from cardiogenic pulmonary edema **(Chap. 298)**. Unlike the latter, however, the chest x-ray in ARDS may not demonstrate cardiomegaly, pleural effusions, or pulmonary vascular redistribution as is often present in pure cardiogenic pulmonary edema. If no ARDS risk factor is present, then some objective evaluation is required (e.g., echocardiography) to exclude a cardiac etiology for hydrostatic edema. Chest computed tomography (CT) in ARDS also reveals the presence of bilateral pulmonary infiltrates and demonstrates extensive heterogeneity of lung involvement **(Fig. 294-4)**.

Because the early features of ARDS are nonspecific, alternative diagnoses must be considered. In the differential diagnosis of ARDS, the most common disorders are cardiogenic pulmonary edema, bilateral pneumonia, and alveolar hemorrhage. Less common diagnoses to consider include acute interstitial lung diseases (e.g., acute interstitial pneumonitis; **Chap. 287**), acute immunologic injury (e.g., hypersensitivity pneumonitis; **Chap. 282**), toxin injury (e.g., radiation pneumonitis; **Chap. 71**), and neurogenic pulmonary edema **(Chap. 33)**.

Proliferative Phase This phase of ARDS usually lasts from day 7 to day 21. Most patients recover rapidly and are liberated from mechanical ventilation during this phase. Despite this improvement, many patients still experience dyspnea, tachypnea, and hypoxemia. Some patients develop progressive lung injury and early changes of

TABLE 294-2 Diagnostic Criteria for ARDS

SEVERITY: OXYGENATION[a]	ONSET	CHEST RADIOGRAPH	ABSENCE OF LEFT ATRIAL HYPERTENSION
Mild: 200 mmHg < Pao_2/Fio_2 ≤ 300 mmHg *Moderate:* 100 mmHg < Pao_2/Fio_2 ≤ 200 mmHg *Severe:* Pao_2/Fio_2 ≤ 100 mmHg	Acute: Within 1 week of a clinical insult or new or worsening respiratory symptoms.	Bilateral opacities consistent with pulmonary edema not fully explained by effusions, lobar/lung collapse, or nodules	Hydrostatic edema is not the primary cause of respiratory failure. If no ARDS risk factor is present, then some objective evaluation is required (e.g., echocardiography) to rule out hydrostatic edema

[a]As assessed on at least 5 cm H_2O of positive end expiratory pressure (PEEP).

Abbreviations: ARDS, acute respiratory distress syndrome; Fio_2, inspired O_2 percentage; Pao_2, arterial partial pressure of O_2; PCWP, pulmonary capillary wedge pressure.

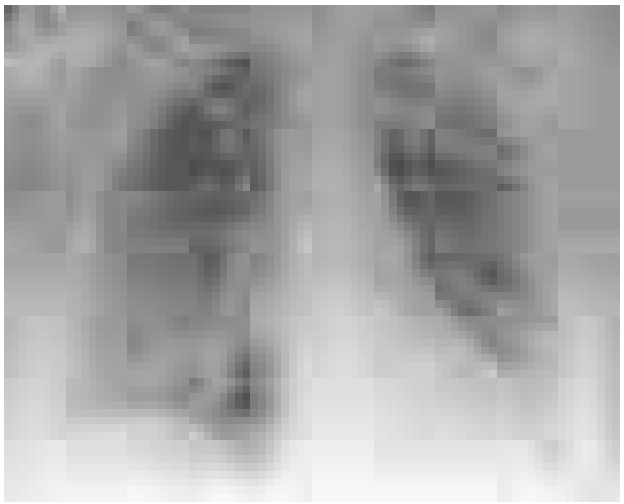

FIGURE 294-2 A representative anteroposterior chest x-ray in the exudative phase of ARDS shows bilateral opacities consistent with pulmonary edema that can be difficult to distinguish from left ventricular failure.

FIGURE 294-4 A representative CT scan of the chest during the exudative phase of acute respiratory distress syndrome (ARDS), in which *dependent* alveolar edema and atelectasis predominate.

pulmonary fibrosis during the proliferative phase. Histologically, the first signs of resolution are often evident in this phase, with the initiation of lung repair, the organization of alveolar exudates, and a shift from neutrophil- to lymphocyte-predominant pulmonary infiltrates. As part of the reparative process, type II pneumocytes proliferate along alveolar basement membranes. These specialized epithelial cells synthesize new pulmonary surfactant and differentiate into type I pneumocytes.

Fibrotic Phase While many patients with ARDS recover lung function 3–4 weeks after the initial pulmonary injury, some enter a

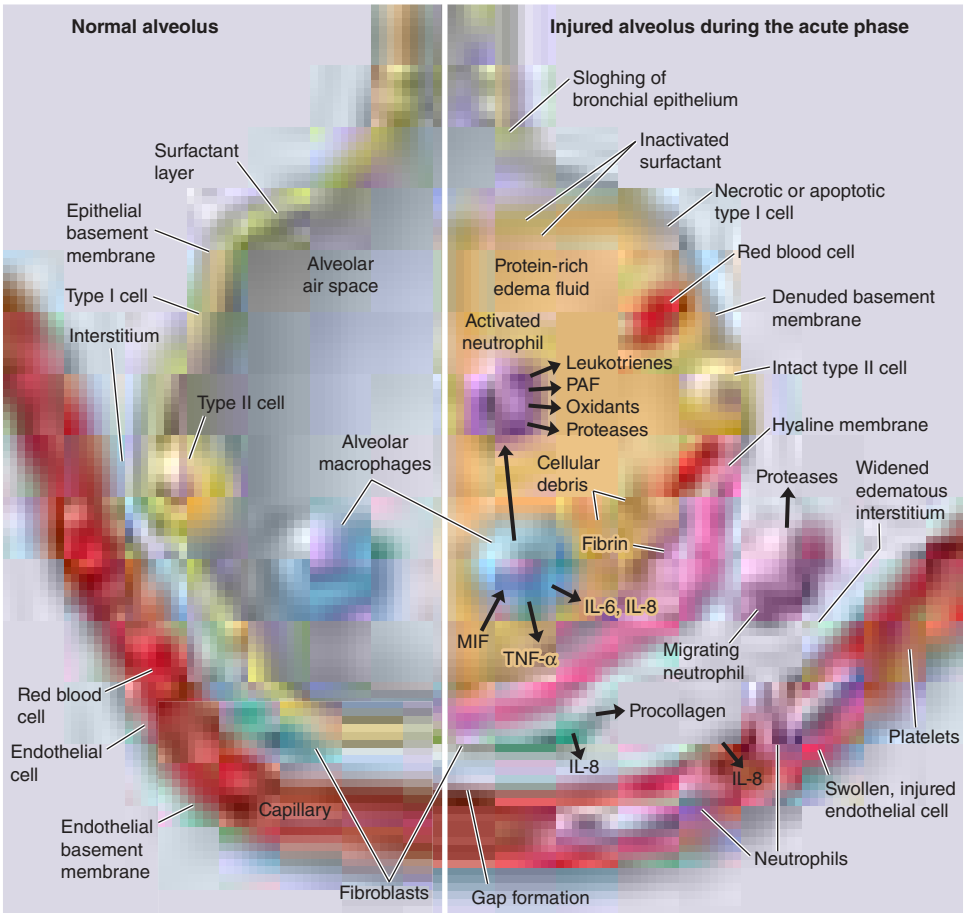

FIGURE 294-3 The normal alveolus (*left*) and the injured alveolus in the acute phase of acute lung injury and the acute respiratory distress syndrome (*right*). In the acute phase of the syndrome (*right*), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and transmigrating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting pro-inflammatory cytokines—i.e., interleukins 1, 6, 8 (IL-1, 6, 8) and tumor necrosis factor α (TNF-α)—that act locally to stimulate chemotaxis and activate neutrophils. IL-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu, including the IL-1-receptor antagonist, soluble TNF-α receptor, autoantibodies to IL-8, and cytokines such as IL-10 and IL-11 (not shown). The influx of protein-rich edema fluid into the alveolus can lead to the inactivation of surfactant. MIF, macrophage inhibitory factor. *(Adapted from LB Ware, MA Matthay: N Engl J Med 342:1334, 2000, with permission.)*

fibrotic phase that may require long-term support on mechanical ventilators and/or supplemental oxygen. Histologically, the alveolar edema and inflammatory exudates of earlier phases convert to extensive alveolar-duct and interstitial fibrosis. Marked disruption of acinar architecture leads to emphysema-like changes, with large bullae. Intimal fibroproliferation in the pulmonary microcirculation causes progressive vascular occlusion and pulmonary hypertension. The physiologic consequences include an increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space. Patients in this late phase experience a substantial burden of excess morbidity. Lung biopsy evidence for pulmonary fibrosis in any phase of ARDS is associated with increased mortality risk.

TREATMENT

Acute Respiratory Distress Syndrome

GENERAL PRINCIPLES

Recent reductions in ARDS mortality rates are largely the result of general advances in the care of critically ill patients **(Chap. 293)**. Thus, caring for these patients requires close attention to (1) the recognition and treatment of underlying medical and surgical disorders (e.g., pneumonia, sepsis, aspiration, trauma); (2) the minimization of unnecessary procedures and their complications; (3) standardized "bundled care" approaches for ICU patients, including prophylaxis against venous thromboembolism, gastrointestinal bleeding, aspiration, excessive sedation, prolonged mechanical ventilation, and central venous catheter infections; (4) prompt recognition of nosocomial infections; and (5) provision of adequate nutrition via the enteral route when feasible.

MANAGEMENT OF MECHANICAL VENTILATION

(See also Chap. 295) Patients meeting clinical criteria for ARDS frequently become fatigued from increased work of breathing and progressive hypoxemia, requiring mechanical ventilation for support.

Minimizing Ventilator-Induced Lung Injury Despite its life-saving potential, mechanical ventilation can aggravate lung injury. Experimental models have demonstrated that ventilator-induced lung injury can arise from at least two principal mechanisms: "volutrauma" from repeated alveolar overdistention from excess tidal volume and "atelectrauma" from recurrent alveolar collapse. As is evident from chest CT (Fig. 294-4), ARDS is a heterogeneous disorder, principally involving dependent portions of the lung with relative sparing of other regions. Because compliance differs in affected versus more "normal" areas of the lung, attempts to fully inflate the consolidated lung may lead to overdistention of and injury to the more normal areas. Ventilator-induced injury can be demonstrated in experimental models of acute lung injury, in particular with high-tidal-volume (V_T) ventilation.

A large-scale, randomized controlled trial sponsored by the National Institutes of Health and conducted by the ARDS Network compared low V_T ventilation (6 mL/kg of predicted body weight) to conventional V_T ventilation (12 mL/kg predicted body weight). Lower airway pressures were also targeted in the low tidal volume group (i.e., plateau pressure measured on the ventilator after a 0.5-s pause after inspiration) ≤30 cm H_2O versus ≤50 cm H_2O in the high tidal volume group. The mortality rate was significantly lower in the low V_T patients (31%) than in the conventional V_T patients (40%). This improvement in survival represents a substantial ARDS-mortality benefit.

Minimizing Atelectrauma by Prevention of Alveolar Collapse In ARDS, the presence of alveolar and interstitial fluid and the loss of surfactant can lead to a marked reduction of lung compliance. Without an increase in end-expiratory pressure, significant alveolar collapse can occur at end-expiration, with consequent impairment of oxygenation. In most clinical settings, positive end-expiratory pressure (PEEP) is adjusted to minimize F_{IO_2} (inspired O_2 percentage) and provide adequate P_{AO_2} (arterial partial pressure of O_2) without causing alveolar overdistention. Currently, there is no consensus on the optimal method to set PEEP, because numerous trials have proved inconclusive. Possible approaches include using the table of PEEP-F_{IO_2} combinations from the ARDS Network trial group, generating a static pressure-volume curve for the respiratory system and setting PEEP at the lower inflection point on this curve to maximize respiratory system compliance, and measuring esophageal pressures to estimate transpulmonary pressure (which may be particularly helpful in patients with a stiff chest wall). Until more data become available on how best to optimize PEEP settings in ARDS, clinicians can use these options or a practical approach to empirically measure "best PEEP" at the bed side to determine the optimal settings that best promotes alveolar recruitment, minimizes alveolar overdistention and hemodynamic instability, and provides adequate P_{AO_2} while minimizing F_{IO_2} **(Chap. 295)**.

Prone Positioning While several prior trials demonstrated that mechanical ventilation in the prone position improved arterial oxygenation without a mortality benefit, a recent trial demonstrated a significant reduction in 28-day mortality with prone positioning (32.8 to 16%) for patients with severe ARDS (P_{AO_2}/F_{IO_2} <150 mm Hg). Thus, many centers are increasing the use of prone positioning in severe ARDS, with the understanding that this maneuver requires a critical-care team that is experienced in "proning," as repositioning critically ill patients can be hazardous, leading to accidental endotracheal extubation, loss of central venous catheters, and orthopedic injury.

OTHER STRATEGIES IN MECHANICAL VENTILATION

Recruitment maneuvers that transiently increase PEEP to high levels to "recruit" atelectatic lung can increase oxygenation, but a mortality benefit has not been established. *Alternate modes of mechanical ventilation*, such as airway pressure release ventilation and high frequency oscillatory ventilation, have not been proven beneficial over standard modes of ventilation in ARDS management and in many cases require specialized expertise at the bedside. *Lung-replacement therapy with extracorporeal membrane oxygenation* (ECMO) was shown to improve mortality for patients with ARDS in the United Kingdom who were referred to an ECMO center (though only 75% of referred patients received ECMO) and thus may have utility in select adult patients with severe ARDS as a rescue therapy.

FLUID MANAGEMENT

(See also Chap. 293) Increased pulmonary vascular permeability leading to interstitial and alveolar edema fluid rich in protein is a central feature of ARDS. In addition, impaired vascular integrity augments the normal increase in extravascular lung water that occurs with increasing left atrial pressure. Maintaining a low left atrial filling pressure minimizes pulmonary edema and prevents further decrements in arterial oxygenation and lung compliance; improves pulmonary mechanics; shortens ICU stay and the duration of mechanical ventilation. Thus, aggressive attempts to reduce left atrial filling pressures with fluid restriction and diuretics should be an important aspect of ARDS management, limited only by hypotension and hypoperfusion of critical organs such as the kidneys.

NEUROMUSCULAR BLOCKADE

In severe ARDS, sedation alone can be inadequate for the patient-ventilator synchrony required for lung-protective ventilation. In a multicenter, randomized, placebo-controlled trial of early neuromuscular blockade (with cisatracurium besylate) for 48 h, patients with severe ARDS had increased survival and ventilator-free days without increasing ICU-acquired paresis. These promising findings support the early administration of neuromuscular blockade if needed to facilitate mechanical ventilation in severe ARDS.

GLUCOCORTICOIDS

Many attempts have been made to treat both early and late ARDS with glucocorticoids, with the goal of reducing potentially deleterious pulmonary inflammation. Few studies have shown any significant mortality benefit. Current evidence does *not* support the routine use of glucocorticoids in the care of ARDS patients.

TABLE 294-3 Evidence-Based Recommendations for ARDS Therapies

TREATMENT	RECOMMENDATION[a]
Mechanical ventilation	
Low tidal volume	A
Minimized left atrial filling pressures	B
High-PEEP or "open lung"	B[b]
Prone position	B[b]
Recruitment maneuvers	C
High-frequency ventilation	D
ECMO	B[b]
Early neuromuscular blockade	B[b]
Glucocorticoid treatment	D
Inhaled vasodilators (e.g., inhaled NO, inhaled epoprosteol)	C
Surfactant replacement, and other anti-inflammatory therapy (e.g., ketoconazole, PGE_1, NSAIDs)	D

[a]Key: A, recommended therapy based on strong clinical evidence from randomized clinical trials; B, recommended therapy based on supportive but limited clinical data; C, recommended only as alternative therapy on the basis of indeterminate evidence; D, not recommended on the basis of clinical evidence against efficacy of therapy. [b]As described in the text, there is no consensus on optimal PEEP setting in ARDS, but general consensus supports an open lung strategy that minimizes alveolar distention; prone positioning was shown to improve mortality in severe ARDS in one randomized controlled clinical trial; ECMO may be beneficial in select patients with severe ARDS; early neuromuscular blockade demonstrated a mortality benefit in one randomized controlled trial in patients with severe ARDS

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PEEP, positive end-expiratory pressure; PGE1, prostaglandin E_1.

OTHER THERAPIES

Clinical trials of surfactant replacement and multiple other medical therapies have proved disappointing. Pulmonary vasodilators such as inhaled nitric oxide and inhaled epoprostenol sodium can transiently improve oxygenation but have not been shown to improve survival or decrease time on mechanical ventilation.

RECOMMENDATIONS

Many clinical trials have been undertaken to improve the outcome of patients with ARDS; most have been unsuccessful in modifying the natural history. While results of large clinical trials must be judiciously applied to *individual* patients, evidence-based recommendations are summarized in **Table 294-3**, and an algorithm for the initial therapeutic goals and limits in ARDS management is provided in **Fig. 294-5**.

PROGNOSIS

Mortality In the recent report from the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) trial, hospital mortality estimates for ARDS range from 34.9% for mild ARDS, 40.3% for moderate ARDS, and 46.1% with severe ARDS. There is substantial variability, but a trend toward improved ARDS outcomes over time appears evident. Of interest, mortality in ARDS is largely attributable to nonpulmonary causes, with sepsis and nonpulmonary organ failure accounting for >80% of deaths. Thus, improvement in survival is likely secondary to advances in the care of septic/infected patients and those with multiple organ failure **(Chap. 293)**.

The major risk factors for ARDS mortality are nonpulmonary. Advanced age is an important risk factor. Patients aged >75 years have a substantially higher mortality risk (~60%) than those <45 (~20%). Moreover, patients >60 years of age with ARDS and sepsis have a threefold higher mortality risk than those <60. Other risk factors include preexisting organ dysfunction from chronic medical illness—in particular, chronic liver disease, cirrhosis, chronic alcohol abuse, chronic immunosuppression **(Chap. 293)**. Patients with ARDS arising from direct lung injury (including pneumonia, pulmonary contusion, and aspiration; Table 294-1) are nearly twice as likely to die as those with indirect causes of lung injury, while surgical and trauma patients with ARDS—especially those without direct lung injury—generally have a higher survival rate than other ARDS patients.

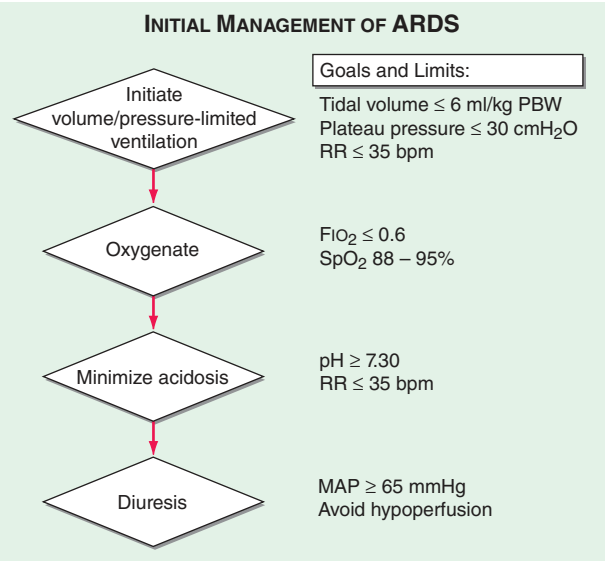

FIGURE 294-5 Algorithm for the initial management of ARDS. Clinical trials have provided evidence-based therapeutic goals for a stepwise approach to the early mechanical ventilation, oxygenation, and correction of acidosis and diuresis of critically ill patients with ARDS. F_{IO_2}, inspired O_2 percentage; MAP, mean arterial pressure; PBW, predicted body weight; RR, respiratory rate; Spo_2, arterial oxyhemoglobin saturation measured by pulse oximetry.

Increasing severity of ARDS, as defined by the consensus Berlin definition, predicts increased mortality. Surprisingly, there is little additional value in predicting ARDS mortality from other parameters of lung injury, including the level of PEEP (≥10 cm H_2O), respiratory system compliance (≤40 mL/cm H_2O), the extent of alveolar infiltrates on chest radiography, and the corrected expired volume per minute (≥10 L/min) (as a surrogate measure of dead space).

Functional Recovery in ARDS Survivors While it is common for patients with ARDS to experience prolonged respiratory failure and remain dependent on mechanical ventilation for survival, it is a testament to the resolving powers of the lung that the majority of patients who survive regain nearly normal lung function. Patients usually recover maximal lung function within 6 months. One year after endotracheal extubation, more than one-third of ARDS survivors have normal spirometry values and diffusion capacity. Most of the remaining patients have only mild abnormalities in pulmonary function. Unlike mortality risk, recovery of lung function is strongly associated with the extent of lung injury in early ARDS. Low static respiratory compliance, high levels of required PEEP, longer durations of mechanical ventilation, and high lung injury scores are all associated with less recovery of pulmonary function. Of note, when physical function is assessed 5 years after ARDS, exercise limitation and decreased physical quality of life are often documented despite normal or nearly normal pulmonary function. When caring for ARDS survivors, it is important to be aware of the potential for a substantial burden of psychological problems in patients and family caregivers, including significant rates of depression and posttraumatic stress disorder.

ACKNOWLEDGMENT

The authors acknowledge the contributions to this chapter by the previous authors, Drs. Augustine Choi and Steven D. Shapiro.

FURTHER READING

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WEBSITES

ARDS Support Center for patient-oriented education: *www.ards.org*
NHLBI ARDS Clinical Trials information: *www.ardsnet.org*
ARDS Foundation: *www.ardsusa.org*

295 Mechanical Ventilatory Support

Bartolome R. Celli

MECHANICAL VENTILATORY SUPPORT

Mechanical ventilation (MV) is used to assist or replace spontaneous breathing. It is implemented with special devices that can support ventilatory function and improve oxygenation through the application of high-oxygen-content gas and positive pressure. The primary indication for initiation of MV is respiratory failure, of which there are two basic types: (1) *hypoxemic*, which is present when arterial O_2 saturation (Sao_2) <90% occurs despite an increased inspired O_2 fraction and usually results from ventilation-perfusion mismatch or shunt; and (2) *hypercarbic*, which is characterized by elevated arterial carbon dioxide partial pressure (PCO_2) values (usually >50 mmHg) resulting from conditions that decrease minute ventilation or increase physiologic dead space such that alveolar ventilation is inadequate to meet metabolic demands. When respiratory failure is chronic, neither of the two types is obligatorily treated with MV, but when it is acute, MV may be lifesaving.

INDICATIONS

The most common reasons for instituting MV are acute respiratory failure with hypoxemia (acute respiratory distress syndrome, heart failure with pulmonary edema, pneumonia, sepsis, complications of surgery and trauma), which accounts for ~65% of all ventilated cases, and hypercarbic ventilatory failure—e.g., due to coma (15%), exacerbations of chronic obstructive pulmonary disease (COPD; 13%), and neuromuscular diseases (5%). The primary objectives of MV are to decrease the work of breathing, thus avoiding respiratory muscle fatigue, and to reverse life-threatening hypoxemia and progressive respiratory acidosis.

In some cases, MV is used as an adjunct to other forms of therapy. For example, it is used to reduce cerebral blood flow in patients with increased intracranial pressure. MV also is used frequently in conjunction with endotracheal intubation for airway protection to prevent aspiration of gastric contents in otherwise unstable patients during gastric lavage for suspected drug overdose or during gastrointestinal endoscopy. In critically ill patients, intubation and MV may be indicated before the performance of essential diagnostic or therapeutic studies if it appears that respiratory failure may occur during those maneuvers.

TYPES OF MECHANICAL VENTILATION

There are two basic methods of MV: noninvasive ventilation (NIV) and invasive (or conventional mechanical) ventilation (MV).

Noninvasive Ventilation NIV has gained acceptance because it is effective in certain conditions, such as acute or chronic respiratory failure, and is associated with fewer complications—namely, pneumonia and tracheolaryngeal trauma. NIV usually is provided with a tight-fitting face mask, a nasal mask similar to that used for treatment of sleep apnea and in some cases with the use of a helmet or a hood. NIV has proved highly effective in patients with respiratory failure arising from exacerbations of COPD. It is most frequently implemented as bilevel positive airway pressure ventilation or pressure-support ventilation (PSV). Both modes, which apply a preset positive pressure during inspiration and a lower pressure during expiration, are well tolerated by a conscious patient and optimize patient-ventilator synchrony. The major limitation to the widespread application of NIV has been patient intolerance: the interface required for NIV can cause both physical and psychological discomfort. In addition, NIV has had limited success in patients with acute hypoxemic respiratory failure, for whom endotracheal intubation and conventional MV remain the ventilatory method of choice.

The most important group of patients who benefit from a trial of NIV are those with COPD exacerbations and respiratory acidosis (pH <7.35). Several randomized trials have shown that, in patients with ventilatory failure characterized by blood pH levels between 7.25 and 7.35, NIV is associated with low failure rates (15–20%) and good outcomes (as judged by intubation rate, length of stay in intensive care, and—in some series—mortality rates). In more severely ill patients with a blood pH <7.25, the rate of NIV failure is inversely related to the severity of respiratory acidosis, with higher failure rates as the pH decreases. In patients with milder acidosis (pH >7.35), NIV is not better than conventional treatment that includes controlled oxygen delivery and pharmacotherapy for exacerbations of COPD (systemic glucocorticoids, bronchodilators, and, if needed, antibiotics).

NIV is not useful in the majority of cases of respiratory failure and is contraindicated in patients with the conditions listed in Table 295-1. NIV can delay lifesaving ventilatory support in those cases and, in fact, can actually result in aspiration or hypoventilation. Once NIV is initiated, patients should be monitored; a reduction in respiratory frequency and a decrease in the use of accessory muscles (scalene, sternomastoid, and intercostals) are good clinical indicators of therapeutic benefit. Arterial blood gases should be determined at least within hours of the initiation of therapy to ensure that NIV is having the desired effect. Lack of benefit within that time frame should alert the physician to the possible need for conventional MV.

Conventional MV Conventional MV is implemented once a cuffed tube is inserted into the trachea to allow conditioned gas (warmed, oxygenated, and humidified) to be delivered to the airways and lungs at pressures above atmospheric pressure. Care should be taken during intubation to avoid brain-damaging hypoxia. In most cases, the administration of mild sedation may facilitate the procedure. Opiates and benzodiazepines are good choices but can have a deleterious effect on hemodynamics in patients with depressed cardiac function or low systemic vascular resistance. Morphine can promote histamine release from tissue mast cells and may worsen bronchospasm in patients with asthma; fentanyl, sufentanil, and alfentanil are acceptable alternatives. Ketamine may increase systemic arterial pressure and has been associated with hallucinatory responses. The shorter-acting agents—etomidate and propofol—have been used for both induction and maintenance of anesthesia in ventilated patients because they have fewer adverse hemodynamic effects, but both are significantly more expensive than older agents. Great care must be taken to avoid the use of neuromuscular paralysis during intubation of

TABLE 295-1 Contraindications for Noninvasive Ventilation

Cardiac or respiratory arrest
Severe encephalopathy
Severe gastrointestinal bleed
Hemodynamic instability
Unstable angina and myocardial infarction
Facial surgery or trauma
Upper airway obstruction
High-risk aspiration and/or inability to protect airways
Inability to clear secretions

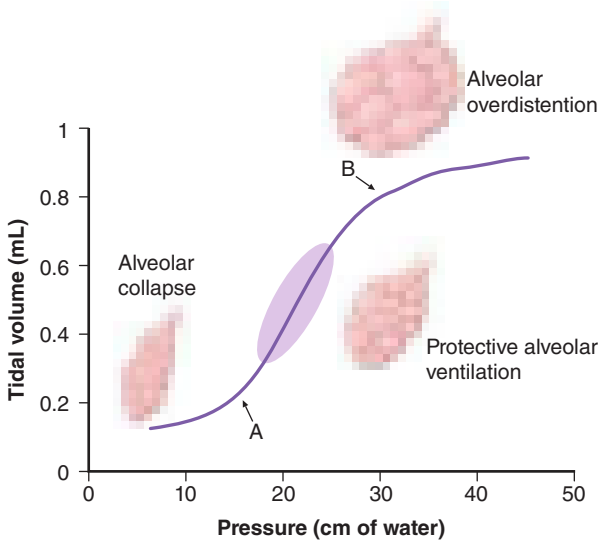

FIGURE 295-1 Hypothetical pressure-volume curve of the lung in a patient undergoing mechanical ventilation. Alveoli tend to close if the distending pressure falls below the lower inflection point A, whereas they overstretch if the pressure within them is higher than that of the upper inflection point B. Collapse and opening of ventilated alveoli are associated with poor outcomes in patients with acute respiratory failure. Protective ventilation (*purple shaded area*), using a lower tidal volume (6 mL/kg of ideal body weight) and maintaining positive end-expiratory pressure to prevent overstretching and collapse/opening of alveoli, has resulted in improved survival rates among patients receiving mechanical ventilatory support.

patients with renal failure, tumor lysis syndrome, crush injuries, medical conditions associated with elevated serum potassium levels, and muscular dystrophy syndromes; in particular, the use of agents whose mechanism of action includes depolarization at the neuromuscular junction, such as succinylcholine chloride, must be avoided.

PRINCIPLES OF MV

Once the patient has been intubated, the basic goals of MV are *to optimize oxygenation while avoiding ventilator-induced lung injury due to overstretch and collapse/re-recruitment*. This concept, known as the "protective ventilatory strategy" (see below and Fig. 295-1) is supported by evidence linking high airway pressures and volumes and overstretching of the lung as well as collapse/re-recruitment to poor clinical outcomes (barotrauma and volume trauma). Although normalization of pH through elimination of CO_2 is desirable, the risk of lung damage associated with the large volume and high pressures needed to achieve this goal has led to the acceptance of permissive hypercapnia. This condition is well tolerated when care is taken to avoid excess acidosis by pH buffering.

MODES OF VENTILATION

Mode refers to the manner in which ventilator breaths are triggered, cycled, and limited. The *trigger*, either an inspiratory effort or a time-based signal, defines what the ventilator senses to initiate an assisted breath. *Cycle* refers to the factors that determine the end of inspiration. For example, in volume-cycled ventilation, inspiration ends when a specific tidal volume is delivered. Other types of cycling include pressure cycling and time cycling. The *limiting factors* are operator-specified values, such as airway pressure, that are monitored by transducers internal to the ventilator circuit throughout the respiratory cycle; if the specified values are exceeded, inspiratory flow is terminated, and the ventilator circuit is vented to atmospheric pressure or the specified pressure at the end of expiration (positive end-expiratory pressure, or PEEP). Most patients are ventilated with assist-control ventilation (ACMV), intermittent mandatory ventilation (IMV), or PSV, with the latter two modes often used simultaneously (Table 295-2).

Assist-Control Ventilation ACMV is the most widely used mode of ventilation. In this mode, an inspiratory cycle is initiated either by the patient's inspiratory effort or, if none is detected within a specified time window, by a timer signal within the ventilator. Every breath delivered, whether patient- or timer-triggered, consists of the operator-specified tidal volume. Ventilatory rate is determined either by the patient or by the operator-specified backup rate, whichever is of higher frequency. ACMV is commonly used for initiation of MV because it ensures a backup minute ventilation in the absence of an intact respiratory drive and allows for synchronization of the ventilator cycle with the patient's inspiratory effort.

Problems can arise when ACMV is used in patients with tachypnea due to nonrespiratory or nonmetabolic factors, such as anxiety, pain, and airway irritation. Respiratory alkalemia may develop and trigger myoclonus or seizures. Dynamic hyperinflation leading to increased intrathoracic pressures (so-called auto-PEEP) may occur if the patient's respiratory mechanics are such that inadequate time is available for complete exhalation between inspiratory cycles. Auto-PEEP can limit venous return, decrease cardiac output, and increase airway pressures, predisposing to barotrauma.

Intermittent Mandatory Ventilation With this mode, the operator sets the number of mandatory breaths of fixed volume to be delivered by the ventilator; between those breaths, the patient can breathe spontaneously. In the most frequently used synchronized mode (SIMV), mandatory breaths are delivered in synchrony with the patient's inspiratory efforts at a frequency determined by the operator. If the patient fails to initiate a breath, the ventilator delivers a fixed-tidal-volume breath and resets the internal timer for the next inspiratory cycle. SIMV differs from ACMV in that only a preset number of breaths are ventilator-assisted.

SIMV allows patients with an intact respiratory drive to exercise inspiratory muscles between assisted breaths; thus it is useful for both supporting and weaning intubated patients. SIMV may be difficult to use in patients with tachypnea because they may attempt to exhale during the ventilator-programmed inspiratory cycle. Consequently, the airway pressure may exceed the inspiratory pressure limit, the ventilator-assisted breath will be aborted, and minute volume may drop below that programmed by the operator. In this setting, if the tachypnea represents a response to respiratory or metabolic acidosis, a change in ACMV will increase minute ventilation and help normalize the pH while the underlying process is further evaluated and treated.

Pressure-Support Ventilation This form of ventilation is patient-triggered, flow-cycled, and pressure-limited. It provides graded assistance and differs from the other two modes in that the operator sets the pressure level (rather than the volume) to augment every spontaneous respiratory effort. The level of pressure is adjusted by observing the patient's respiratory frequency. During PSV, the inspiration is terminated when inspiratory airflow falls below a certain level; in most ventilators, this flow rate cannot be adjusted by the operator. With PSV, patients receive ventilator assistance only when the ventilator detects an inspiratory effort. PSV is often used in combination with SIMV to ensure volume-cycled backup for patients whose respiratory drive is depressed. PSV is well tolerated by most patients who are being weaned from MV; PSV parameters can be set to provide full ventilatory support and can be withdrawn to load the respiratory muscles gradually.

Other Modes of Ventilation There are other modes of ventilation, each with its own acronym and each with specific modifications of the manner and duration in which pressure is applied to the airway and lungs and of the interaction between the mechanical assistance provided by the ventilator and the patient's respiratory effort. Although their use in acute respiratory failure is limited, the following modes have been used with varying levels of enthusiasm and adoption.

PRESSURE-CONTROL VENTILATION (PCV) This form of ventilation is time-triggered, time-cycled, and pressure-limited. A specified pressure is imposed at the airway opening throughout inspiration. Since the inspiratory pressure is specified by the operator, tidal volume and inspiratory flow rate are *dependent*, rather than *independent*, variables and are not operator-specified. PCV is the preferred mode of ventilation for patients in whom it is desirable to regulate peak airway

TABLE 295-2 Characteristics of the Most Commonly Used Forms of Mechanical Ventilation

VENTILATORY MODE	VARIABLES SET BY USER (INDEPENDENT)	VARIABLES MONITORED BY USER (DEPENDENT)	TRIGGER CYCLE LIMIT	ADVANTAGES	DISADVANTAGES
ACMV (assist-control ventilation)	Tidal volume Ventilator rate F_{IO_2} PEEP level Pressure limit	Peak, mean, and plateau airway pressures VE ABG I/E ratio	Patient effort Timer Pressure limit	Patient control Guaranteed ventilation	Potential hyperventilation Barotrauma and volume trauma Every effective breath generates a ventilator volume
IMV (intermittent mandatory ventilation)	Tidal volume Mandatory ventilator rate F_{IO_2} PEEP level Pressure limit Spontaneous breaths between assisted breaths	Peak, mean, and plateau airway pressures VE ABG I/E ratio	Patient effort Timer Pressure limit	Patient control Comfort from spontaneous breaths Guaranteed ventilation	Potential dysynchrony Potential hypoventilation
PSV (pressure-support ventilation)	Inspiratory pressure level F_{IO_2} PEEP Pressure limit	Tidal volume Respiratory rate VE ABG	Pressure limit Inspiratory flow	Patient control Comfort Assures synchrony	No timer backup Potential hypoventilation
NIV (noninvasive ventilation)	Inspiratory and expiratory pressure level F_{IO_2}	Tidal volume Respiratory rate VE ABG	Pressure limit Inspiratory flow	Patient control	Mask interface may cause discomfort and facial bruising Leaks are common Hypoventilation

Abbreviations: ABG, arterial blood gases; F_{IO_2}, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; I/E, inspiratory to expiratory time ratio; VE, minute ventilation.

pressures, such as those with preexisting barotrauma, and for post–thoracic surgery patients, in whom the shear forces across a fresh suture line should be limited. When PCV is used, minute ventilation is altered through changes in rate or in the pressure-control value, with consequent changes in tidal volume.

INVERSE-RATIO VENTILATION (IRV) This mode is a variant of PCV that incorporates the use of a prolonged inspiratory time with the appropriate shortening of the expiratory time. IRV has been used in patients with severe hypoxemic respiratory failure. This approach increases mean distending pressures without increasing peak airway pressures. It is thought to work in conjunction with PEEP to open collapsed alveoli and improve oxygenation. However, no clinical-trial data have shown that IRV improves outcomes.

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) CPAP is not a true support mode of ventilation because all ventilation occurs through the patient's spontaneous efforts. The ventilator provides fresh gas to the breathing circuit with each inspiration and sets the circuit to a constant, operator-specified pressure. CPAP is used to assess extubation potential in patients who have been effectively weaned and who require little ventilatory support and in patients with intact respiratory system function who require an endotracheal tube for airway protection.

Nonconventional Ventilatory Strategies Several nonconventional strategies have been evaluated for their ability to improve gas exchange and survival rates in severe hypoxemic respiratory failure. These strategies include high-frequency oscillatory ventilation (HFOV), airway pressure release ventilation (APRV), partial liquid ventilation (PLV) using perfluorocarbons and the administration of nitric oxide gas delivered through the airways. Although case reports and small uncontrolled cohort studies have shown benefit, randomized controlled trials have failed to demonstrate consistent improvements in outcome with these strategies.

Some "salvage" techniques have gained acceptance given recent positive clinical outcomes. A randomized trial of extracorporeal membrane oxygenation (ECMO) documented positive outcomes, although older studies had failed to document positive results. However, with the popularity of venous-venous access, and encouraging reports in small series and uncontrolled trials, the use of ECMO has increased world-wide. Guidelines for ECMO centers have been published, and if considered in patients with severe respiratory failure refractory to conventional therapy, the patient should be referred to a center familiar with the procedure. The second of these techniques, prone positioning, should be available in all units caring for these patients. Several multi-center randomized trials in patients with acute lung injury and refractory hypoxemia have shown that prone positioning improves ventilation-perfusion matching and provides short- and long-term survival advantage.

The design of new ventilator modes reflects attempts to improve patient-ventilator synchrony—a major practical issue during MV—by allowing patients to trigger the ventilator with their own effort while also incorporating flow algorithms that terminate the cycles once certain preset criteria are reached; this approach has greatly improved patient comfort. New modes of ventilation that synchronize not only the timing but also the levels of assistance to match the patient's effort have been developed. Proportional assist ventilation (PAV) and neurally adjusted ventilatory-assist ventilation (NAV) are two modes that are designed to deliver assisted breaths through algorithms incorporating not only pressure, volume, and time but also overall respiratory resistance as well as compliance (in the case of PAV) and neural activation of the diaphragm (in the case of NAV). Although these modes enhance patient-ventilator synchrony, their practical use in the everyday management of patients undergoing MV needs further study.

PROTECTIVE VENTILATORY STRATEGY

Whichever mode of MV is used in acute respiratory failure, the evidence from several important controlled trials indicates that a protective ventilation approach guided by the following principles (and summarized in Fig. 295-1) is safe and offers the best chance of a good outcome: (1) Set a target tidal volume close to 6 mL/kg of ideal body weight. (2) Prevent plateau pressure (static pressure in the airway at the end of inspiration) exceeding 30 cm H_2O. (3) Use the lowest possible fraction of inspired oxygen (F_{IO_2}) to keep the Sao_2 at ≥90%. (4) Adjust the PEEP to maintain alveolar patency while preventing overdistention and closure/reopening. With the application of these techniques, the

mortality rate among patients with acute hypoxemic respiratory failure has decreased to ~30% from close to 50% a decade ago.

PATIENT MANAGEMENT

Once the patient's gas exchange has been stabilized, definitive therapy for the underlying process responsible for respiratory failure is continued. Subsequent modifications in ventilator therapy must be provided in parallel with changes in the patient's clinical status. As improvement in respiratory function is noted, the first priority is to reduce the level of mechanical ventilatory support. Patients on full ventilatory support should be monitored frequently, with the goal of switching to a mode that allows for weaning as soon as possible. Protocols and guidelines that can be applied by paramedical personnel when physicians are not readily available have proved to be of value in shortening ventilator and intensive care unit (ICU) time, with very good outcomes. Patients whose condition continues to deteriorate after ventilatory support is initiated may require increased O_2, PEEP, or one of the alternative modes of ventilation.

GENERAL SUPPORT DURING VENTILATION

Patients for whom MV has been initiated usually require sedation and analgesia to maintain an acceptable level of comfort. Often, this treatment consists of a combination of a benzodiazepine and an opiate administered intravenously. Medications commonly used for this purpose include lorazepam, midazolam, diazepam, morphine, and fentanyl. Oversedation must be avoided in the ICU because most studies show that daily interruption of sedation in patients with improved ventilatory status results in a shorter time on the ventilator and a shorter ICU stay.

Immobilized patients receiving mechanical ventilatory support are at risk for deep venous thrombosis and decubitus ulcers. Venous thrombosis should be prevented with the use of subcutaneous heparin and/or pneumatic compression boots. Fractionated low-molecular-weight heparin appears to be equally effective for this purpose. To help prevent decubitus ulcers, frequent changes in body position and the use of soft mattress overlays and air mattresses are employed. Early mobilization is recommended for patients on MV, since this approach is associated with better outcomes. Prophylaxis against diffuse gastrointestinal mucosal injury is indicated for patients undergoing MV. Histamine-receptor (H_2-receptor) antagonists, antacids, and cytoprotective agents such as sucralfate have all been used and appear to be effective. Nutritional support by enteral feeding through either a nasogastric or an orogastric tube should be initiated and maintained whenever possible. Delayed gastric emptying is common in critically ill patients taking sedative medications but often responds to promotility agents such as metoclopramide. Parenteral nutrition is an alternative to enteral nutrition in patients with severe gastrointestinal pathology who need prolonged MV.

COMPLICATIONS OF MECHANICAL VENTILATION

Endotracheal intubation and MV have direct and indirect effects on the lung and upper airways, the cardiovascular and the gastrointestinal system. Pulmonary complications include barotrauma, nosocomial pneumonia, oxygen toxicity, tracheal stenosis, and deconditioning of respiratory muscles. Barotrauma and volutrauma overdistend and disrupt lung tissue; may be clinically manifest by pneumomediastinum, interstitial and subcutaneous emphysema, or pneumothorax; and can result in the liberation of cytokines from overdistended tissues, further promoting tissue injury. Clinically significant pneumothorax requires tube thoracostomy. Intubated patients are at high risk for ventilator-associated pneumonia as a result of aspiration from the upper airways through small leaks around the endotracheal tube cuff; the most common organisms responsible for this condition are *Pseudomonas aeruginosa*, enteric gram-negative rods, and *Staphylococcus aureus*. Given the high associated mortality rates, when suspected, early initiation of empirical antibiotics directed against likely pathogens is recommended. *Hypotension* resulting from elevated intrathoracic pressures with decreased venous return is almost always responsive to intravascular volume repletion. In patients who are judged to have respiratory failure on the basis of alveolar edema but in whom the cardiac or pulmonary origin of the edema is unclear, hemodynamic monitoring with a pulmonary arterial catheter may be of value in helping to clarify the cause of the edema. Gastrointestinal effects of positive-pressure ventilation include stress ulceration and mild to moderate cholestasis.

WEANING FROM MECHANICAL VENTILATION

The Decision to Wean It is important to consider discontinuation of MV once the underlying respiratory disease begins to reverse. Although the predictive capacities of multiple clinical and physiologic variables have been explored, the consensus from a ventilatory weaning task force cites the following conditions as indicating amenability to weaning: (1) Lung injury is stable or resolving; (2) gas exchange is adequate, with low PEEP (<8 cmH_2O) and F_{IO_2} (<0.5); (3) hemodynamic variables are stable, and the patient is no longer receiving vasopressors; and (4) the patient is capable of initiating spontaneous breaths. A "wean screen" based on these variables should be done at least daily. If the patient is deemed capable of beginning to wean, the recommendation is to perform a spontaneous breathing trial (SBT), whose value is supported by several randomized trials **(Fig. 295-2)**. The SBT involves an integrated patient assessment during spontaneous breathing with little or no ventilatory support. The SBT is usually implemented with a T-piece using 1–5 cmH_2O CPAP with 5–7 cmH_2O or PSV from the ventilator to offset resistance from the endotracheal tube. Once it is determined that the patient can breathe spontaneously, a decision must be made about the removal of the artificial airway, which should be undertaken only when it is concluded that the patient has the ability to protect the airway, is able to cough and clear secretions, and is alert enough to follow commands. In addition, other factors must be taken into account, such as the possible difficulty of replacing the tube if that maneuver is required. If upper airway difficulty is suspected, an evaluation using a "cuff-leak" test (assessing the presence of air movement around a deflated endotracheal tube cuff) is supported by current evidence. If the "cuff-leak test" suggests a risk of post-extubation stridor, the administration of systemic corticosteroids should be considered prior to extubation. Despite all precautions, ~10–15% of extubated patients require reintubation. Several studies suggest that NIV can be used to obviate reintubation, particularly in patients with ventilatory

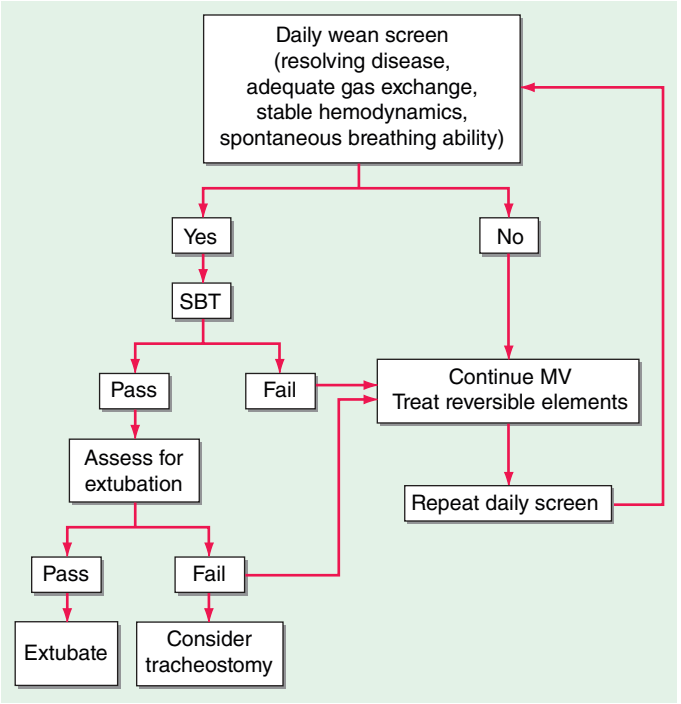

FIGURE 295-2 Flowchart to guide the daily approach to management of patients being considered for weaning off mechanical ventilation (MV). If attempts at extubation fail, a tracheostomy should be considered. SBT, spontaneous breathing trial.

failure secondary to COPD exacerbation or congestive heart failure; in this setting, earlier extubation with the use of prophylactic NIV has yielded good results.

Prolonged MV and Tracheostomy From 5 to 13% of patients undergoing MV will go on to require prolonged MV (>21 days). In these instances, critical care personnel must decide whether and when to perform a tracheostomy. This decision is individualized and is based on the risk and benefits of tracheostomy and prolonged intubation as well as the patient's preferences and expected outcomes. A tracheostomy is thought to be more comfortable, to require less sedation, and to provide a more secure airway and may also reduce weaning time. However, tracheostomy carries the risk of complications, which occur in 5–40% of these procedures and include bleeding, cardiopulmonary arrest, hypoxia, structural damage, pneumothorax, pneumomediastinum, and wound infection. In patients with long-term tracheostomy, complex complications include tracheal stenosis, granulation, and erosion of the innominate artery. In general, if a patient needs MV for >10–14 days, a tracheostomy, planned under optimal conditions, is indicated. Whether it is completed at the bedside or as an operative procedure depends on local resources and experience. Some 5–10% of patients are deemed unable to wean in the ICU. These patients may benefit from transfer to special units where a multidisciplinary approach, including nutrition optimization, physical therapy with rehabilitation, and slower weaning methods (including SIMV with PSV), results in successful weaning rates of up to 30%. Unfortunately, close to 2% of ventilated patients may ultimately become dependent on ventilatory support to maintain life. Most of these patients remain in chronic care institutions, although some with strong social, economic, and family support may live a relatively fulfilling life with at-home ventilation.

FURTHER READING

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Section 2 Shock and Cardiac Arrest

296 Approach to the Patient with Shock

Anthony F. Massaro

Shock is the clinical condition of organ dysfunction resulting from an imbalance between cellular oxygen supply and demand. This life-threatening condition is common in the intensive care unit (ICU). There are a multitude of heterogeneous disease processes that can lead to shock. The organ dysfunction seen in early shock is reversible with restoration of adequate oxygen supply. Left untreated, shock transitions from this reversible phase to an irreversible phase and death from multisystem organ dysfunction (MSOF). The clinician is required to identify the patient with shock promptly, make a preliminary assessment of the type of shock present, and initiate therapy to prevent irreversible organ dysfunction and death. In this chapter, we review a commonly used classification system that organizes shock into four major types based on the underlying physiologic derangement. We discuss the initial assessment utilizing the history, physical examination, and initial diagnostic testing to confirm the presence of shock and determine the type of shock causing the organ dysfunction. Finally, we will discuss key principles of initial therapy with the aim of reducing the high morbidity and mortality associated with shock.

PATHOPHYSIOLOGY OF SHOCK

The cellular oxygen imbalance of shock is most commonly related to impaired oxygen delivery in the setting of circulatory failure. Shock can also develop during states of increased oxygen consumption or impaired oxygen utilization. An example of the impaired oxygen utilization is cyanide poisoning, which causes uncoupling of oxidative phosphorylation. This chapter will focus on the approach to the patient with shock related to inadequate oxygen delivery.

In the setting of insufficient oxygen supply, the cell is no longer able to support aerobic metabolism. With adequate oxygen, the cell metabolizes glucose to pyruvate, which then enters the mitochondria where ATP is generated via oxidative phosphorylation. Without sufficient oxygen supply, the cell is forced into anaerobic metabolism, in which pyruvate is metabolized to lactate with much less ATP generation (per mole of glucose). Maintenance of the homeostatic environment of the cell is dependent on an adequate supply of ATP. ATP-dependent ion pumping systems, such as the Na+/K+ ATPase, consume 20–80% of the cell's energy. Inadequate oxygen delivery and subsequent decreased ATP disrupt the cell's ability to maintain osmotic, ionic, and intracellular pH homeostasis. Influx of calcium can lead to activation of calcium-dependent phospholipases and proteases, causing cellular swelling and death. In addition to direct cell death, cellular hypoxia can cause damage at the organ system level via leakage of the intracellular contents into the extracellular space activating inflammatory cascades and altering the microvascular circulation.

DETERMINANTS OF OXYGEN DELIVERY

Since shock is the clinical manifestation of inadequate oxygen delivery compared to cellular needs, we will review determinants of oxygen delivery (DO_2). Disease processes affecting any of the components of oxygen delivery have the potential to lead to the development of shock. Disturbances to key determinants of oxygen delivery form the basis of the four major shock types described below.

The two major components of DO_2 are cardiac output (CO) and arterial oxygen content (CaO_2):

$$DO_2 = CO \times CaO_2$$

The two components of CO are heart rate (HR) and stroke volume (SV), which can be substituted in the above equation as

$$DO_2 = (HR \times SV) \times CaO_2$$

The major determinants of SV are preload, afterload (systemic vascular resistance, SVR), and cardiac contractility. The relationship can be represented as

$$SV \ \alpha \ (\text{Preload} \times \text{contractility})/SVR$$

In this equation, preload refers to the myocardial fiber length before contraction (the ventricular end-diastolic volume). Contractility refers to the ability of the ventricle to contract independent of preload and afterload. The SVR represents the afterload, or the force against which the ventricle must contract.

The CaO_2 is composed of oxygen carried by convection with hemoglobin and oxygen dissolved in blood, given as

$$CaO_2 = (Hb \times 1.39 \times SaO_2) + (PaO_2 \times 0.03)$$

A disease process that affects these variables (HR, preload, contractility, SVR, SaO_2, or Hb) has the potential to reduce oxygen delivery and

cause cellular hypoxia. Each of the shock types described below has a distinctive physiologic hemodynamic profile corresponding with alterations in one of the variables affecting oxygen delivery described above.

CLASSIFICATION OF SHOCK

While there is a heterogeneous list of specific conditions that can cause shock, it is helpful to categorize these processes into four major shock types based on the primary physiologic derangement leading to reduced oxygen delivery and cellular hypoxia. The four major shock types are distributive, cardiogenic, hypovolemic, and obstructive. Table 296-1 outlines these major shock types as well as specific disease processes that can result in that physiologic derangement. Each shock type has a distinct hemodynamic profile (Table 296-2). Familiarity with the major shock types and their unique hemodynamic profile is essential so that when evaluating a patient presenting with shock, the clinician can use the history, physical examination, and laboratory testing to determine the type of shock present and promptly begin appropriate initial therapy to restore oxygen delivery.

Distributive Shock Distributive shock is the condition of reduced oxygen delivery where the primary physiologic disturbance is a reduction in SVR. It is unique among the types of shock in that there is a compensatory increase in CO (Table 296-2). The central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) are usually reduced. The most common cause of distributive shock is sepsis. Sepsis has recently been redefined as the dysregulated host response to infection resulting in life-threatening organ dysfunction. When this process is accompanied by persistent hypotension requiring vasopressor support, it is classified as septic shock. Other processes that are manifest as cellular hypoxia related to a primary reduction of SVR include pancreatitis, severe burns, and liver failure. Anaphylaxis is predominantly an IgE-mediated allergic reaction that can rapidly develop after exposure to an allergen (food, medication, or insect bite), in which there is a profound distributive type of shock possibly mediated through histamine release. In this setting, there is evidence of both venous and arterial vasodilation. Studies have demonstrated extravasation of up to 35% of the circulating blood volume within 10 min. Patients with severe brain or spinal cord injury may have a reduction of SVR related to disruption of the autonomic pathways that regulate vascular tone. In these patients, there is pooling of blood in the venous system with a resulting decreased venous return and decreased CO. A final category of patients who present with distributive shock are those with adrenal insufficiency. Adrenal insufficiency may be related to chronic steroid use, metastatic malignancy, adrenal hemorrhage, infection (tuberculosis, HIV), autoimmune adrenalitis, or amyloidosis. In conditions of stress (such as infection or surgery), the deficit may become apparent with an inability to increase cortisol leading to vasodilation as well as aldosterone deficiency-mediated hypovolemia.

TABLE 296-1 Pathophysiologic Classification of Shock

1. Distributive
   - a. Septic shock
   - b. Pancreatitis
   - c. Severe burns
   - d. Anaphylactic shock
   - e. Neurogenic shock
   - f. Endocrine shock
   - i. Adrenal crisis
2. Cardiogenic
   - a. Myocardial infarction
   - b. Myocarditis
   - c. Arrhythmia
   - d. Valvular
     - i. Severe aortic valve insufficiency
     - ii. Severe mitral valve insufficiency
3. Obstructive
   - a. Tension pneumothorax
   - b. Cardiac tamponade
   - c. Restrictive pericarditis
   - d. Pulmonary embolism
   - e. Aortic dissection
4. Hypovolemic
   - a. Hemorrhagic
   - b. GI losses
   - c. Burns
   - d. Polyuria
     - i. Diabetic ketoacidosis
     - ii. Diabetes insipidus

TABLE 296-2 Hemodynamic Characteristics of the Major Types of Shock

TYPE OF SHOCK	CVP	PCWP	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE
Distributive	↓	↓	↑	↓
Cardiogenic	↑	↑	↓	↑
Obstructive	↑	↓↑	↓	↑
Hypovolemic	↓	↓	↓	↑

Abbreviations: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure.

Cardiogenic Shock Cardiogenic shock is characterized by reduced oxygen delivery related to a reduction in CO owing to a primary cardiac problem. There is usually a compensatory increase in SVR in cardiogenic shock. When the cardiac process (e.g., myocardial infarction) affects the left ventricle (LV), there will be elevation of the PCWP and when it affects the right ventricle (RV), the CVP will be elevated. As detailed above, the CO (and accordingly the DO_2) can be reduced by alterations in the SV or HR. In cardiogenic shock, the SV may be reduced by processes that affect myocardial contractility (myocardial infarction, ischemic cardiomyopathies, and primary myocarditis) or mechanical valvular disease (acute mitral insufficiency or aortic insufficiency). Both bradyarrhythmias and tachyarrhythmias (from either an atrial or ventricular source) may have associated hemodynamic consequence with a reduction in CO.

Hypovolemic Shock Hypovolemic shock encompasses disease processes that reduce CO (and oxygen delivery) via a reduction in preload. In addition to the reduced CO, this shock type is characterized by an elevated SVR and low CVP and PCWP related to decreased intravascular volume. Any process causing a reduction in intravascular volume can cause shock of this type. Hypovolemic shock most commonly is related to hemorrhage, that may be external (secondary to trauma) or internal (most commonly upper or lower gastrointestinal [GI]) bleeding. Hypovolemic shock can also be seen with nonhemorrhagic processes. Examples include GI illnesses causing profound emesis or diarrhea, renal losses (osmotic diuresis associated with diabetic ketoacidosis or diabetes insipidus), or skin loss (severe burns, inflammatory conditions such as Stevens-Johnson).

Obstructive Shock Obstructive shock is also characterized by a reduction in oxygen delivery related to reduced CO, but in this case the etiology of the reduced CO is an extracardiac processes impairing blood flow. Processes that can impede venous return to the heart and reduce CO include tension pneumothorax (PTX), cardiac tamponade, and restrictive pericarditis. Similarly processes that obstruct cardiac outflow, such as pulmonary embolism (right heart) or aortic dissection (left heart), are included in this shock type category.

Mixed Shock The types of shock outlined in this classification scheme are not mutually exclusive; not uncommonly, a patient will present with more than one type of shock. The initial physiologic disturbance leading to reduced perfusion and cellular hypoxia in sepsis is distributive shock. In this setting, a sepsis-induced cardiomyopathy

can develop, which reduces myocardial contractility, thus producing a cardiogenic component to what now would be described as a mixed type of shock.

Undifferentiated Shock Upon initial presentation, many patients have undifferentiated shock in which the shock type and specific disease process are not apparent. Using the history, physical examination, and initial diagnostic testing (including hemodynamic monitoring), the clinician attempts to classify a patient with one of the types of shock outlined above so that proper therapy can be initiated to restore tissue perfusion and oxygen delivery.

The type of shock seen most commonly is dependent upon the clinical area of practice. In the medical ICU, the largest number of patients have distributive shock related to sepsis. A cardiac ICU will have a population weighted toward cardiogenic or obstructive types of shock. The emergency department will see more of a mix of patients with trauma patients presenting with hypovolemic shock and septic patients having a distributive pathophysiology.

STAGES OF SHOCK

Regardless of type, shock progresses through a continuum of three stages. These stages are compensated shock (preshock), shock (decompensated shock), and irreversible shock. During compensated shock, the body utilizes a variety of physiologic responses to counteract the initial insult and attempts to reestablish the adequate perfusion and oxygen delivery. At this point, there are no overt signs of organ dysfunction. Laboratory evaluation may demonstrate mild organ dysfunction (i.e., elevated creatinine or troponin) or a mild elevation of lactate. The specific compensatory response is determined by the initial pathophysiologic defect. In early sepsis with reduction in SVR, there is a compensatory rise in HR (and CO). With early hemorrhagic volume loss, there will be a compensatory increase in SVR. As the host compensatory responses are overwhelmed, the patient transitions into true shock with evidence organ dysfunction. Appropriate interventions to restore perfusion and oxygen delivery during these initial two phases of shock can reverse the organ dysfunction. If untreated the patient will progress to the third phase of irreversible shock. At this point, the organ dysfunction is permanent and often the patient progresses to MSOF.

EVALUATION OF THE PATIENT WITH SHOCK

The evaluation of the patient with shock utilizes the history, physical examination, and diagnostic testing toward two specific aims. The first aim is confirmation of the presence of shock. Given the reversible nature of the organ dysfunction in early shock, it is important that the clinician has a high clinical suspicion for this condition. The possibility of shock should be considered all patients presenting with new organ dysfunction. This early recognition of the presence of shock is an essential tenet of shock care **(Table 296-3)**. A second aim of the initial assessment (history, physical examination, and diagnostic testing) is to identify either a specific shock etiology or to determine the type of shock present. We will discuss the role of the history, physical examination, and diagnostic testing toward these specific aims. While the assessment of shock etiology is ongoing, the initiation of therapy should not be delayed until the final diagnosis is determined. Evaluation of shock etiology and initiation of therapy should be simultaneous.

History Obtaining a concise, focused history is essential. If the patient is unable to provide a history, ancillary information from anyone accompanying the patient should be obtained, and a brief chart review should be performed. As the history is being obtained, the clinician must be attentive to any details indicating new organ dysfunction.

TABLE 296-3 Key Principles in the Treatment of Shock

1. Recognize shock early
2. Assess for type of shock present
3. Initiate therapy simultaneous with the evaluation into the etiology of shock
4. Restoration of oxygen delivery is the aim of therapy
5. Identify etiologies of shock which require additional lifesaving interventions

The most easily identified new organ dysfunction from the history is the presence of a newly altered mental status or decrease in renal function (oliguria). In some cases, the type of shock (and the specific disease process) is apparent from the history. Patients with distributive shock from sepsis may present with fever and a history revealing of a focal site of infection. Anaphylactic distributive shock may be suggested by the onset of hives, dyspnea, and new facial edema after exposure to common allergens. Cardiogenic shock may be identified by the onset of exertional chest discomfort. The patient with significant arrhythmia may have an initial complaint of palpitations with syncope or presyncope. Hypovolemic shock may be identified in patients who present with a history of trauma (blunt or penetrating) or GI bleed (hematemesis, melena, or bright red blood per rectum). A patient with hypertension and tearing chest or back pain may be presenting with acute aortic dissection and obstructive type shock. Acute onset chest pain with dyspnea in the setting of immobility and or underlying malignancy raises concern for obstructive shock due to pulmonary embolism.

For most patients, the specific etiology will be less clear but the history can be helpful in raising the likelihood of a particular type of shock. As an example, a patient with a preexisting immune dysfunction or medication-induced neutropenia may present with hypoperfusion and new organ dysfunction, in which the clinician must have a high suspicion for septic shock. Similarly, a patient with extensive cardiac disease requires a higher suspicion for cardiogenic shock.

Physical Examination The physical examination should be conducted with the aim of answering two questions. Is shock present (either in compensated stage prior to overt evidence of organ dysfunction or decompensated indicated by the presence of new organ dysfunction)? Secondly, what type of shock is present (distributive, cardiogenic, hypovolemic, or obstructive)?

The physical examination findings present during the compensated phase of shock tend to be nonspecific. These include an elevation of the HR (with the body's attempt to increase CO) or tachypnea (to compensate for the developing metabolic acidosis). While nonspecific, the clinician should recognize these findings early as they may herald the development of end-organ dysfunction if perfusion and oxygen delivery are not restored. Shock is most commonly seen in the setting of circulatory failure. In most cases, this is manifest as hypotension (a mean arterial pressure [MAP] of <60 mmHg), but this finding is not always present. Many patients may have underlying conditions that cause longstanding low blood pressure without any evidence of organ dysfunction. Alternatively, patients with underlying hypertension may develop organ dysfunction at higher blood pressures.

The physical examination can confirm the presence of shock prior to the return of laboratory testing. The central nervous system (CNS), kidney, and skin are the organ systems most easily assessed for evidence of organ dysfunction. These organ systems are considered the "windows" through which we can identify organ dysfunction. Decreased oxygen delivery to the brain is manifest as confusion and encephalopathy. In the early stage of shock, the body will redirect blood flow to the CNS to maintain adequate perfusion. In the patient with shock and altered mental status, all the usual compensatory mechanisms have been outstripped by the magnitude of shock pathophysiology. New encephalopathy represents decompensated shock. To assess renal function during the physical examination, one should evaluate the patient's urine output since the time of presentation. If not already present, a urinary catheter should be placed for accurate hourly assessment of urine output. In patients with normal baseline renal function, oliguria (<0.5 mL/kg per h) may indicate shock. Finally, decreased capillary refill and cold and clammy skin are signs of hypoperfusion and shock.

Many components of the examination provide insight into hemodynamics and assist in elucidating the type of shock present. Evaluation of jugular venous pressure (JVP) and peripheral edema can provide insight into right-sided cardiac pressures. Pulmonary auscultation can identify signs of left-sided cardiac dysfunction. The physical examination may be used to differentiate shock with high CO (distributive) from that with low CO (cardiogenic shock, hypovolemic shock, and obstructive shock). Examination findings suggestive of high output

shock (distributive) include warm peripheral extremities, brisk capillary refill (<2 s), and bounding pulses. Alternatively, cool extremities, delayed poor capillary refill, or weak pulses would indicate low CO forms of shock. Among those with evidence of low CO, the examination can be used to distinguish between conditions with increased intravascular filling pressure (cardiogenic shock) and intravascular volume depletion (hypovolemic shock). The JVP may be elevated cardiogenic shock (with right-sided failure) and reduced (JVP <8 cm) in hypovolemic shock. The presence of cardiogenic shock would be further supported by an S3 gallop. One must remember, however, that it is well established that patients with chronic heart failure do not present with the classical findings of acute heart failure.

At times, the physical examination may identify the specific etiology of shock. This is particularly helpful in the patient who cannot provide a detailed history. The examination may demonstrate the site of an untreated infection (cellulitis, abscess, infected pressure injury, or focal). The examination may reveal a brady- or tachyarrhythmia leading to development of shock. Similarly, large ecchymosis may indicate a significant bleed related to trauma or spontaneous retroperitoneal bleeding. The rectal examination may reveal GI hemorrhage. Pulsus paradox and elevated JVP may suggest the presence of cardiac tamponade. Patients with a tension PTX may have a paucity of breath sounds over the affected side, deviation of the trachea away from the affected side, or subcutaneous emphysema.

Combinations of easily assessed examination components have been combined to create a scoring system to identify high risk patient populations. The shock index (SI) is defined as the HR/systolic blood pressure (SBP) with a normal SI being 0.5–0.7. An elevated SI (>0.9) has been proposed to be a more sensitive indicator of transfusion requirement and of patients with critical bleeding among those with hypovolemic (hemorrhagic) shock than either HR or BP alone. The SI may also identify patients at risk for postintubation hypotension. This concept of use of a clinical score to identify at-risk patients has been extended to patients with distributive shock from sepsis. The quick Sequential Organ Failure Assessment (qSOFA) score is a rapid assessment scale that assigns a point for SBP <100, respiratory rate >22, or altered mental status (Glasgow Coma Scale <15). A qSOFA ≥2 (with a concern for infection) is associated with a significantly greater risk of death or prolonged ICU stay. The Third International Consensus Definition of Sepsis has recommended the use of the qSOFA to identify the most acutely ill subset of patients with sepsis (longer length of stay, increased need for ICU admission, and higher in-hospital mortality).

Diagnostic Testing Laboratory evaluation should be initiated promptly in all patients with suspected shock. The laboratory evaluation is directed toward the dual aim of assessing the extent of end-organ dysfunction and of gaining insight into the possible etiology of shock. Table 296-4 outlines the recommended initial laboratory evaluation of the patient with undifferentiated shock.

BLOOD TESTS Evaluation of blood urea nitrogen (BUN), creatinine, and transaminases provide an assessment of the extent of end-organ dysfunction related to shock. Urine electrolytes with subsequent calculation of the fractional excretion of sodium (FENa) or fractional excretion of urea (FEUrea) may indicate states of hypovolemia or decreased effective circulating volume. Elevation of alkaline phosphatase may suggest biliary obstruction and may thereby identify a source of infection in patients with distributive shock. Elevation of cardiac enzymes can indicate a primary cardiac problem with myocyte damage related to ischemia, myocarditis, or a pulmonary embolism. An elevation of the white blood cell count may raise suspicion for an infective process, but this is certainly not diagnostic; an accompanying left shift may improve the sensitivity of this measure. While the extent of acidosis may be determined with a venous blood gas (VBG), if there is accompanying hypoxemia an arterial blood gas should be obtained. For patients with undifferentiated shock, there should always be a high index of suspicion for possible infection. Urinalysis and urine sediment should be sent to evaluate for pyuria. Blood cultures, urine cultures, and sputum cultures should be obtained. Radiographic evaluation should be directed to seek sources of infection suggested by the history and physical examination.

TABLE 296-4 Initial Laboratory Evaluation of Undifferentiated Shock

1. Lactate
2. Renal function tests
3. Liver function tests
4. Cardiac enzymes
5. Complete blood count (with differential)
6. PT, PTT, and INR
7. Urinalysis and urine sediment
8. Arterial blood gas
9. ECG

Abbreviations: INR, International normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Lactate measurement has a role in the diagnosis, risk stratification, and, potentially, the treatment of shock. Increased lactate (hyperlactemia) and lactic acidosis (hyperlactemia and pH <7.35) are common in shock. Lactate is a product of anaerobic glucose metabolism. In glycolysis, the enzyme phosphofuctokinase metabolizes glucose to pyruvate. Under aerobic conditions, the pyruvate is then converted (in the mitochondria) to acetyl CoA and enters the Krebs cycle with resulting ATP generation through oxidative phosphorylation. In the setting of cellular hypoxia, the Krebs (tricarboxylic acid) cycle cannot oxidize the pyruvate, and thus, the pyruvate is converted to lactate by the enzyme lactate dehydrogenase. Under normal conditions, lactate is produced from skeletal muscle, brain, skin, and intestine. In the setting of reduced oxygen delivery and cellular hypoxia, the amount of lactate produced from these tissues increases (and other tissue can begin to produce lactate). While most of the studies have been performed in patients with septic shock, there is evidence that elevated lactate correlates with a worse outcome. A recent systematic literature review evaluating the role of lactate measurement in a variety of critically ill populations supported the value of serial lactate measurements in the evaluation of critically ill patients and their response to therapy.

ECG The electrocardiogram (ECG) is an essential part of the evaluation of the patient with shock. There may be a bradycardia or tachycardic arrhythmia causing a reduction in CO. ST segment elevation myocardial infarction may be identified. The presence of the S1 Q3 T3 pattern would raise concerns for pulmonary embolism. Reduced voltage in the presence of electrical alternans raises the possibility of pericardial tamponade.

Echocardiography Echocardiography is increasingly used as an essential tool to help categorize shock, and it provides an assessment that is both rapid and noninvasive. Familiarity with basic echocardiographic techniques and interpretation is now expected in the critical care setting. Accordingly, competency standards have been proposed for critical care providers in both basic and advanced echocardiographic techniques. The bedside echocardiogam performed by the ICU team does not replace a formal examination performed by the echocardiography service.

The basic echocardiographic assessment for the shock patient is transthoracic echocardiography (TTE) utilizing both the two-dimensional (2D) and M mode. Standardized, focused echocardiography protocols such as the RACE protocol (rapid assessment for cardiac echocardiography) have been introduced to facilitate the assessment of cardiac function. It focuses the examination on LV function, RV function, and pericardium. It also can assess volume, but the use of echocardiography for volume assessment will be discussed in the section below.

The 2D mode can evaluate LV size, wall thickness, and ventricular function. Ventricular size and thickness can suggest longer standing cardiac processes. Evaluation of LV function through estimation of left ventricular ejection fraction (LVEF), and can identify shock with globally reduced LV function or regional wall motion abnormalities. Similarly, the assessment of RV function also examines RV size and wall thickness (to identify conditions such as elevated pulmonary pressures or suggest pulmonary embolism), and also evaluate the patient for pericardial tamponade. Two-dimensional echocardiography can

also be used to assess valve function, including acute processes, such as mitral valve rupture. Assessment of valvular function is often a process that requires a higher skilled practitioner. The performance of the bedside echocardiogram by the critical care practitioner does not replace formal assessment by a cardiologist.

INITIAL TREATMENT OF SHOCK

Since shock can progress rapidly to an irreversible stage, a key principle in shock management is to initiate treatment for circulatory shock simultaneous with efforts to elucidate shock etiology (Table 296-3). If the initial history, physical examination, and laboratory evaluation have identified the shock type or the specific etiology, then therapy is directed to reverse the underlying physiologic abnormality causing the hypoperfusion and reduced oxygen delivery. Details of the optimal care for the specific disease processes leading to shock may be found in other chapters of this text. As many patients will present with undifferentiated shock, in this section we will discuss treatment directed at the patient with undifferentiated shock. At the conclusion of this section, we will highlight etiologies of shock that require initiation of lifesaving specific therapy.

The development of shock is a medical emergency, and optimal therapy involves the involvement of a multidisciplinary team to allow the evaluation and initiation of therapy to begin simultaneously. Patients must be treated in a setting where adequate resources are available to support frequent reassessments and invasive monitoring. Most patients with shock should be cared for in an ICU setting.

A key early consideration is to ensure adequate intravenous access. Placement of a peripheral venous catheter (16G or 18G) will provide initial access for the aggressive volume resuscitation that is required for patients with distributive or hypovolemic shock. If there is concern for distributive shock with sepsis, this IV access will also permit prompt antibiotic administration. For patients with ongoing hypotension despite adequate volume resuscitation, placement of a central venous catheter (CVC) is indicated to provide therapy with vasopressors and inotropes. The CVC will provide a mechanism for hemodynamic monitoring (CVP) as well as a means to obtain central venous oxygen saturations ($ScvO_2$). The $ScvO_2$ is a surrogate of mixed venous oxygen saturation, and, thus, can provide insight into the adequacy of oxygen delivery. Central venous access using a sheath will provide an access point for placement of a Swan Ganz catheter if more detailed assessment of hemodynamic measurements are required (PCWP, CO, and SVR). If the patient presents critically ill or in the midst of cardiopulmonary arrest, the quickest method of obtaining central access will be through the use of an intraosseous device. Placement of an arterial line allows for intravascular measurement of blood pressure and continuous determination of MAP. In addition, it can provide insight into the adequacy of volume resuscitation through the measurement of systolic or pulse pressure variation. The arterial line will provide access for determination of arterial oxygen tension, which is helpful since peripheral oximetry measurements (SpO_2) can be unreliable in states of tissue hypoperfusion. The arterial line facilitates repeated measures of acid base status or lactate to assess the impact of treatment. All patients with shock should have a urinary catheter placed to permit hourly assessment of renal function as another potential indication of the adequacy of resuscitation

Volume Resuscitation Initial volume resuscitation has the aim of restoring tissue perfusion and is crucial to optimal shock therapy. Assessment of current intravascular volume status and determination of the optimal amount of volume resuscitation are challenging. The physiologic goal of volume resuscitation is to move the patient to the nonpreload-dependent portion of the Starling curve. Most patients with any of the four shock types will benefit from an increase in intravascular volume. For patients with distributive shock, the need for early aggressive volume replacement is well established. In the past, the use of early goal-directed therapy (EGDT) in septic shock targeted specific measures of CVP, MAP, and SvO_2 to guide volume resuscitation (and initiation of vasopressors and inotropes). More recent studies have demonstrated that targeted resuscitation using invasive monitoring is not required, but in all of these studies patients in the "usual care" arms of the study received early initial volume resuscitation. For patients with suspected septic shock, a minimum of 30 mL/kg is recommended by the Surviving Sepsis Campaign. While the need for volume resuscitation is most apparent for patients with distributive or hypovolemic shock, even patients with cardiogenic shock may benefit by cautious volume replacement. In these patients, there should be a careful assessment of volume status prior to volume administration.

In general, volume replacement therapy should be given as a bolus with a predefined endpoint to assess the effect of the volume resuscitation. Most commonly, the volume resuscitation will begin with crystalloid. In patients with hypovolemic shock due to ongoing hemorrhage, volume replacement with packed red blood cells is warranted. In cases of massive transfusion, platelets and fresh frozen plasma should be provided to offset the dilution of these components during volume replacement. Since hemoglobin is a key determinant of $CaCO_2$ red cell administration may be a part of volume replacement even without hemorrhage if hemoglobin content is <7 g/dL in order to optimize oxygen delivery.

Assessment of intravascular volume status (and the adequacy of volume resuscitation) begins with the physical examination (described above). The passive leg raise (PLR) test can predict responsiveness to additional intravenous fluid (IVF) by providing the patient with an endogenous volume bolus. While the patient is resting in a semirecumbent position at a 45-degree angle, the bed is placed in trendelenburg such that the patient's head becomes horizontal and the legs are extended at a 45-degree angle. There is then an immediate (within 1 min) assessment of changes in CO (or pulse pressure variation as a surrogate). It is important to emphasize that one does not merely look for changes in blood pressure; if the shock patient is mechanically ventilated there is the option of looking at changes in SV variation (or pulse pressure variation) during the respiratory cycle to assess volume responsiveness. A >12% SV variation suggests a volume-responsive state. This measurement requires that the patient be in a volume cycle mode of ventilation, without breath-to-breath variations in intrathoracic pressure and without arrhythmias. A final caveat to the use of these parameters to assess volume status is that these studies are performed on patients being ventilated with tidal volumes larger than currently used to minimize ventilator-induced lung injury.

There is also increased use of echocardiography to assist in determination of intravascular fluid status, with a variety of static and dynamic variables that the trained operator can assess. The most commonly used parameters to assess adequacy of volume resuscitation are inferior vena cava (IVC) diameter and IVC collapse. Alternatively, serial assessments of LV function can be performed while volume is being administered. Placement of a pulmonary artery catheter (PAC) is another tool for assessment of volume status. This more invasive measure involves placement of the PAC into the central venous circulation and through the right heart. Ports in the PAC (Swan Ganz catheter) allow for direct measurement of CVP, pulmonary artery (PA), and PCWPs. The PCWP is used as a surrogate for LA pressure. While studies have not identified a mortality or length-of-stay benefit with routine use of PA catheterization, there are cases where it may be beneficial. Patients with mixed shock (distributive and cardiogenic) or those with ongoing shock of unclear etiology are examples of situations in which it should be considered.

The need for continued volume replacement must be frequently reassessed. As the patient continues to receive treatment for shock, the initial proper strategy regarding volume management may change in light of development of processes that independently require a different volume management strategy. For patients who initially present with shock but then develop failure related to acute respiratory distress syndrome (ARDS) or renal failure, it may be reasonable to begin volume removal.

Vasopressor and Inotropic Support If intravascular volume status has been optimized with volume resuscitation but hypotension and inadequate tissue perfusion persist, then vasopressor and inotropic support should be initiated. The use of vasopressors and inotropes must be tailored to the primary physiologic disturbance. The clinician

must understand the receptor selectivity of various agents and that for some agents the selectivity may be dose-dependent. In patients with distributive shock, the aim is to increase the SVR. Norepinephrine is the first choice vasopressor: with potent α_1 and β_1 adrenergic effects. The α_1 causes vasoconstriction while β_1 has positive inotropic and chronotropic effects. At high doses, epinephrine has a similar profile (at lower doses the β effects predominate), but is associated with tachyarrhythmia, myocardial ischemia, decreased splanchnic blood flow, pulmonary hypertension, and acidosis. In distributive shock, vasopressin deficiency may be present. Vasopressin acts on the vasopressin receptor to reverse vasodilation and redistribute flow to the splanchnic circulation. In a randomized trial in patients with septic shock, the addition of low-dose vasopressin did not reduce all-cause 28-day mortality compared to norepinephrine. Vasopressin is safe and has a role as a second agent for hypotension in septic shock. Dopamine does not have a role as a first line agent in distributive shock. A randomized control study in patients with all cause circulatory shock did not show a survival benefit, but did reveal an increase in adverse events (arrhythmia). In this study, the subgroup of patients with cardiogenic shock had increased mortality. For patients with cardiogenic shock, dobutamine is the first line agent; it is a synthetic catecholamine with primarily β-mediated effects and minimal α adrenergic effects. The β_1 effect is manifest in increased inotropy and the β_2 effect leads to vasodilation with decreased afterload; it can be used with norepinephrine in patients with mixed distributive and cardiogenic shock.

OXYGENATION AND VENTILATION SUPPORT

In addition to the cellular hypoxia caused by the circulatory failure, patients with shock may present with hypoxemia. For patients with distributive shock, this may be related to a primary pulmonary process (pneumonia in a patient with septic shock). For patients with cardiogenic or obstructive shock, the hypoxemia may be related to LV dysfunction and elevations of PCWP. For patients with all types of shock, there can be development of ARDS and subsequent $\dot{V}/\dot{Q}$ mismatch and shunt. Supplemental oxygen should be initiated and titrated to maintain SpO_2 of 92–95%. This may require intubation and initiation of mechanical ventilation. If the patient requires intubation and initiation of mechanical ventilation, this should be provided promptly so as to minimize the duration of tissue hypoxia. Patients with shock may have high minute ventilatory needs to compensate for metabolic acidosis. As shock progresses, they may not be able to maintain adequate respiratory compensation, which may be a second indication to initiate mechanical ventilator support. If mechanical support is initiated, it is important to provide ventilation with lung-protective strategies focused on low tidal volume ventilation and optimization of positive end-expiratory pressure to minimize ventilator-induced lung injury. In addition, there should be daily sedation cessation to assess underlying neurologic function and minimize time on mechanical ventilation. There are currently little data to support the use of noninvasive ventilation in the setting of shock.

Antibiotic Administration Sepsis and septic shock are the most common cause of shock. For patients presenting with undifferentiated shock, if the diagnosis of septic shock is being entertained then broad spectrum antibiotics should be administered after obtaining appropriate cultures. For patients with sepsis, every hour delay in antibiotic administration is associated with an increase in mortality. While it is ideal to initiate antibiotics after appropriate cultures, the inability to obtain cultures should not delay the start of treatment. When sepsis is excluded as a cause of shock, an important aspect of antibiotic stewardship is to stop all antibiotics.

Specific Causes of Shock Requiring Tailored Intervention The initial evaluation (history, physical examination, and diagnostic testing) may have identified an etiology of shock that requires urgent lifesaving intervention in addition to the initial treatment steps outlined above. Patients with distributive shock secondary to anaphylaxis require removal of the inciting allergen, administration of epinephrine, and vascular support with intravenous fluid resuscitation and vasopressors. Adrenal insufficiency requires replacement with intravenous stress dose steroids. Cardiogenic shock patients with arrhythmia may require treatment as outlined in advanced cardiac life support algorithms or placement of an artificial pacemaker. In cases of acute ischemic events, consideration must be given to revascularization and temporary mechanical supportive measures. In the case of valve dysfunction, emergency surgery may be considered. Patients with hypovolemic shock due to hemorrhage may require surgical intervention in the case of trauma or endoscopic or interventional radiology procedures in the case of a GI source of blood loss. Among patients with obstructive shock, a tension PTX would necessitate immediate decompression. Proximal pulmonary embolism requires evaluation for thrombolytic therapy or surgical removal of the clot. Dissection of the ascending aorta may require surgical intervention.

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297 Sepsis and Septic Shock

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INTRODUCTION AND DEFINITIONS

Sepsis is a common and deadly disease. More than two millennia ago, Hippocrates wrote that sepsis was characterized by rotting flesh and festering wounds. Several centuries later, Galen described sepsis as a laudable event required for wound healing. Once the germ theory was proposed by Semmelweis, Pasteur, and others in the nineteenth century, sepsis was recast as a systemic infection referred to as "blood poisoning" and was thought to be due to pathogen invasion and spread in the bloodstream of the host. However, germ theory did not fully explain sepsis: many septic patients died despite successful removal of the inciting pathogen. In 1992, Bone and colleagues proposed that the host, not the germ, was responsible for the pathogenesis of sepsis. Specifically, they defined sepsis as a systemic inflammatory response to infection. Yet sepsis arose in response to many different pathogens, and septicemia was neither a necessary condition nor a helpful term. Thus, these investigators instead proposed the term *severe sepsis* to describe cases where sepsis was complicated by acute organ dysfunction and the term *septic shock* for a subset of sepsis cases that were complicated by hypotension despite adequate fluid resuscitation along with perfusion abnormalities.

In the past 20 years, research has revealed that many patients develop acute organ dysfunction in response to infection but without a measurable inflammatory excess (i.e., without the systemic inflammatory response syndrome [SIRS]). In fact, both pro- and anti-inflammatory responses are present along with significant changes in other pathways. To clarify terminology and reflect the current understanding of the pathobiology of sepsis, the Sepsis Definitions Task Force in 2016 proposed the Third International Consensus Definitions specifying that *sepsis* is a dysregulated host response to infection that leads to acute organ dysfunction. This definition distinguishes sepsis from uncomplicated infection that does not lead to organ dysfunction, a poor course,

TABLE 297-1 Definitions and Criteria for Sepsis and Septic Shock

CONDITION	DEFINITION	COMMON CLINICAL FEATURES	CRITERIA IN 1991/2003 ("SEPSIS-1"/"SEPSIS-2")	CRITERIA IN 2016 ("SEPSIS-3")
Sepsis	A life-threatening organ dysfunction caused by a dysregulated host response to infection	Include signs of infection, with organ dysfunction, plus altered mentation; tachypnea; hypotension; hepatic, renal, or hematologic dysfunction	Suspected (or documented) infection plus ≥2 systemic inflammatory response syndrome (SIRS) criteria[a]	Suspected (or documented) infection and an acute increase in ≥2 sepsis-related organ failure assessment (SOFA) points[b]
Septic shock	A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities lead to substantially increased mortality risk	Signs of infection, plus altered mentation, oliguria, cool peripheries, hyperlactemia	Suspected (or documented) infection plus persistent arterial hypotension (systolic arterial pressure, <90 mmHg; mean arterial pressure, <60 mmHg; or change in systolic by >40 mmHg from baseline	Suspected (or documented) infection plus vasopressor therapy needed to maintain mean arterial pressure at ≥65 mmHg and serum lactate >2.0 mmol/L despite adequate fluid resuscitation

[a]SIRS criteria include 1 point for each of the following (score range, 0–4): fever >38°C (>100.4°F) or <36°C (<96.8°F); tachypnea with >20 breaths per min; tachycardia with heart rate >90 beats per min; leukocytosis with white blood cell count >12,000/μL; leukopenia (<4000/μL) or >10% bands. [b]SOFA score is a 24-point measure of organ dysfunction that uses six organ systems (renal, cardiovascular, pulmonary, hepatic, neurologic, hematologic), where 0–4 points are assigned per organ system.

or death. In light of the wide variation in the ways that septic shock is identified in research, clinical, or surveillance settings, the Third International Consensus Definitions further specified that *septic shock* be defined as a subset of sepsis cases in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality risk.

To aid clinicians in identifying sepsis and septic shock at the bedside, new "Sepsis-3" clinical criteria for sepsis include (1) a suspected infection and (2) acute organ dysfunction, defined as an increase by two or more points from baseline (if known) on the sequential (or sepsis-related) organ failure assessment (SOFA) score (Table 297-1). Criteria for septic shock include sepsis plus the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg with a serum lactate concentration >2.0 mmol/L despite adequate fluid resuscitation.

ETIOLOGY

Sepsis can arise from both community-acquired and hospital-acquired infections. Of these infections, pneumonia is the most common source, accounting for about half of cases; next most common are intraabdominal and genitourinary infections. Blood cultures are typically positive in only one-third of cases, while many cases are culture negative at all sites. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common gram-positive isolates, while *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa* are the most common gram-negative isolates. In recent years, gram-positive infections have been reported more often than gram-negative infections, yet a 75-country point-prevalence study of 14,000 patients on intensive care units (ICUs) found that 62% of positive isolates were gram-negative bacteria, 47% were gram-positive bacteria, and 19% were fungi.

The many risk factors for sepsis are related to both the predisposition to develop an infection and, once infection develops, the likelihood of developing acute organ dysfunction. Common risk factors for increased risk of infection include chronic diseases (e.g., HIV infection, chronic obstructive pulmonary disease, cancers) and immunosuppression. Risk factors for progression from infection to organ dysfunction are less well understood but may include underlying health status, preexisting organ function, and timeliness of treatment. Age, sex, and race/ethnicity all influence the incidence of sepsis, which is highest at the extremes of age, higher in males than in females, and higher in blacks than in whites. The differences in risk of sepsis by race are not fully explained by socioeconomic factors or access to care, raising the possibility that other factors, such as genetic differences in susceptibility to infection or in the expression of proteins critical to the host response, may play a role.

EPIDEMIOLOGY

The incidences of sepsis and septic shock depend on how acute organ dysfunction and infection are defined as well as on which data sources are studied. Disparate estimates come from administrative data, prospective cohorts with manual case identification, and large electronic health-record databases. Organ dysfunction is often defined by the provision of supportive therapy, in which case epidemiologic studies count the "treated," rather than the actual, incidence. In the United States, recent cohort studies using administrative data suggest that upwards of 2 million cases of sepsis occur annually. Shock is present in ~30% of cases, resulting in an estimated 230,000 cases in a recent systematic review. An analysis of data (both clinical and administrative) from 300 hospitals in the United Healthcare Consortium estimated that septic shock occurred in 19 per 1000 hospitalized encounters. The incidences of sepsis and septic shock are also reported to be increasing (according to ICD9-CM diagnosis and procedure codes), with a rise of almost 50% in the past decade. However, the stability of objective clinical markers (e.g., provision of organ support, detection of bacteremia) over this period in a two-center validation study suggests that new ICD-9 coding rules, confusion over semantics (e.g., *septicemia* versus *severe sepsis*), rising capacity to provide intensive care, and increased case-finding confound the interpretation of serial trends. Studies from other high-income countries report rates of sepsis in the ICU similar to those in the United States.

While the data demonstrate that sepsis is a significant public-health burden in high-income countries, its impact on the populations of low- and middle-income countries is probably even more substantial because of the increased incidence of infectious diseases and the high prevalence of HIV in some parts of the developing world. Although there are fewer high-quality studies on sepsis in these countries, the available data support sepsis as a major public-health problem. For example, a study of one cohort in rural Uganda found an incidence of laboratory-confirmed sepsis tenfold that of current global sepsis estimates; as only a minority of patients with sepsis develop bacteremia, the incidence of sepsis in the cohort was probably even higher. Case–fatality rates in low- and middle-income countries are also higher than those in high-income countries, as exemplified by two observational cohorts in Brazil with mortality rates >40%.

PATHOGENESIS

For many years, the clinical features of sepsis were considered the result of an excessive inflammatory host response (SIRS). More recently, it has become apparent that infection triggers a much more complex, variable, and prolonged host response than was previously thought. The specific response of each patient depends on the pathogen (load and virulence) and the host (genetic composition and comorbidity), with different responses at local and systemic levels. The host response evolves over time with the patient's clinical course. Generally, proinflammatory reactions (directed at eliminating pathogens) are responsible for "collateral" tissue damage in sepsis, whereas anti-inflammatory responses are implicated in the enhanced susceptibility to secondary infections that occurs later in the course. These mechanisms can be characterized as an interplay between two "fitness costs": direct damage to organs by the pathogen and damage to organs stemming from the host's immune response. The host's ability to resist as well as tolerate both direct and immunopathologic damage will determine whether uncomplicated infection becomes sepsis.

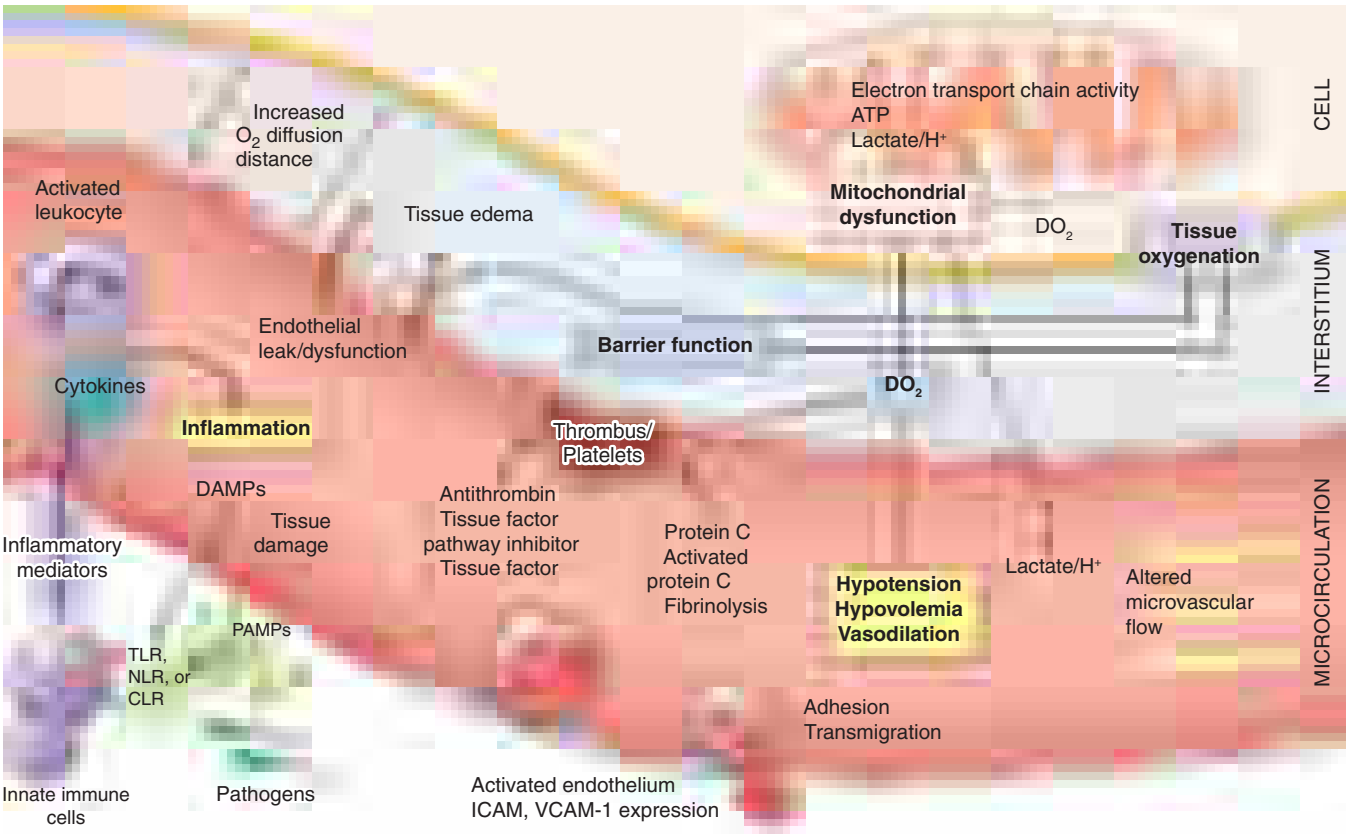

FIGURE 297-1 Select mechanisms implicated in the pathogenesis of sepsis-induced organ and cellular dysfunction. The host response to sepsis involves multiple mechanisms that lead to decreased oxygen delivery (DO_2) at the tissue level. The duration, extent, and direction of these interactions are modified by the organ under threat, host factors (e.g., age, genetic characteristics, medications), and pathogen factors (e.g., microbial load and virulence). The inflammatory response is typically initiated by an interaction between pathogen-associated molecular patterns (PAMPs) expressed by pathogens and pattern recognition receptors expressed by innate immune cells on the cell surface (Toll-like receptors [TLRs] and C-type lectin receptors [CLRs]), in the endosome (TLRs), or in the cytoplasm (retinoic acid inducible gene 1–like receptors and nucleotide-binding oligomerization domain–like receptors [NLRs]). The resulting tissue damage and necrotic cell death lead to release of damage-associated molecular patterns (DAMPs) such as uric acid, high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones. These molecules promote the activation of leukocytes, leading to greater endothelial dysfunction, expression of intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule 1 (VCAM-1) on the activated endothelium, coagulation activation, and complement activation. This cascade is compounded by macrovascular changes such as vasodilation and hypotension, which are exacerbated by greater endothelial leak tissue edema, and relative intravascular hypovolemia. Subsequent alterations in cellular bioenergetics lead to greater glycolysis (e.g., lactate production), mitochondrial injury, release of reactive oxygen species, and greater organ dysfunction.

Initiation of Inflammation Over the past decade, our knowledge of pathogen recognition has increased tremendously. Pathogens activate immune cells by an interaction with pattern recognition receptors (Fig. 297-1), of which four main classes are prominent: Toll-like receptors (TLRs), RIG-I-like receptors, C-type lectin receptors, and NOD-like receptors; the activity of the last group occurs partially in protein complexes called *inflammasomes*. The recognition of structures conserved across microbial species—so-called pathogen-associated molecular patterns (PAMPs)—by all these receptors results in upregulation of inflammatory gene transcription and initiation of innate immunity. A common PAMP is the lipid A moiety of lipopolysaccharide (LPS or endotoxin), which attaches to the LPS-binding protein on the surface of monocytes, macrophages, and neutrophils. LPS is transferred to and signals via TLR4 to produce and release cytokines such as tumor necrosis factor that grow the signal and alert other cells and tissues. Up to 10 TLRs have been identified in humans.

At the same time, these receptors also sense endogenous molecules released from injured cells—so-called damage-associated molecular patterns (DAMPs), such as high-mobility group protein B1, S100 proteins, and extracellular RNA, DNA, and histones. The release of DAMPs during sterile injuries such as those incurred during trauma gives rise to the concept that the pathogenesis of multiple-organ failure may be similar in sepsis and noninfectious critical illness. In addition to activating the proinflammatory cytokines, the inflammatory responses implicated in the pathogenesis of sepsis also activate the complement system, platelet-activating factor, arachidonic acid metabolites, and nitric oxide.

Coagulation Abnormalities Sepsis is commonly associated with coagulation disorders and frequently leads to disseminated intravascular coagulation. Abnormalities in coagulation are thought to isolate invading microorganisms and/or to prevent the spread of infection and inflammation to other tissues and organs. Excess fibrin deposition is driven by coagulation via tissue factor, a transmembrane glycoprotein expressed by various cell types; by impaired anticoagulant mechanisms, including the protein C system and antithrombin; and by compromised fibrin removal due to depression of the fibrinolytic system. Coagulation (and other) proteases further enhance inflammation via protease-activated receptors. In infections with endothelial predominance (e.g., meningococcemia), these mechanisms can be common and deadly.

Organ Dysfunction Although the mechanisms that underlie organ failure in sepsis are only partially known, impaired tissue oxygenation plays a key role. Several factors contribute to reduced oxygen delivery in sepsis and septic shock, including hypotension, reduced red-cell deformability, and microvascular thrombosis. Inflammation can cause dysfunction of the vascular endothelium, accompanied by cell death and loss of barrier integrity, giving rise to subcutaneous and body-cavity edema. An excessive and uncontrolled release of nitric oxide causes vasomotor collapse, opening of arteriovenous shunts, and pathologic shunting of oxygenated blood from susceptible tissues. In addition, mitochondrial damage due to oxidative stress and other mechanisms impairs cellular oxygen utilization. The slowing of oxidative metabolism, in parallel with impaired oxygen delivery, reduces cellular O_2 extraction. Yet energy (i.e., ATP) is still needed to support basal, vital cellular function, which derives from glycolysis and fermentation and thus yields H^+ and lactate. With severe or prolonged insult, ATP levels fall beneath a critical threshold, bioenergetic failure

ensues, toxic reactive oxygen species are released, and apoptosis leads to irreversible cell death and organ failure. The actual morphologic changes in sepsis-induced organ failure are also complex. Generally, organs such as the lung undergo extensive microscopic changes, while other organs may undergo rather few histologic changes. In fact, some organs (e.g., the kidney) may lack significant structural damage while still having significant tubular-cell changes that impair function.

Anti-Inflammatory Mechanisms The immune system harbors humoral, cellular, and neural mechanisms that may exacerbate the potentially harmful effects of the proinflammatory response. Phagocytes can switch to an anti-inflammatory phenotype that promotes tissue repair, while regulatory T cells and myeloid-derived suppressor cells further reduce inflammation. The so-called neuroinflammatory reflex may also contribute: sensory input is relayed through the afferent vagus nerve to the brainstem, from which the efferent vagus nerve activates the splenic nerve in the celiac plexus, with consequent norepinephrine release in the spleen and acetylcholine secretion by a subset of CD4+ T cells. The acetylcholine release targets α7 cholinergic receptors on macrophages, reducing proinflammatory cytokine release. Disruption of this neural-based system by vagotomy renders animals more vulnerable to endotoxin shock, while stimulation of the efferent vagus nerve or α7 cholinergic receptors attenuates systemic inflammation in experimental sepsis.

Immune Suppression Patients who survive early sepsis but remain dependent on intensive care occasionally demonstrate evidence of a suppressed immune system. These patients may have ongoing infectious foci despite antimicrobial therapy or may experience the reactivation of latent viruses. Multiple investigations have documented reduced responsiveness of blood leukocytes to pathogens in patients with sepsis; these findings were recently corroborated by post-mortem studies revealing strong functional impairments of splenocytes harvested from ICU patients who died of sepsis. Immune suppression was evident in the lungs as well as the spleen; in both organs, the expression of ligands for T cell–inhibitory receptors on parenchymal cells was increased. Enhanced apoptotic cell death, especially of B cells, CD4+ T cells, and follicular dendritic cells, has been implicated in sepsis-associated immune suppression and death. In a cohort of >1000 ICU admissions for sepsis, secondary infections developed in 14% of patients, and the associated genomic response at the time of infection was consistent with immune suppression, including impaired glycolysis and cellular gluconeogenesis. The most common secondary infections included catheter-related bloodstream infections, ventilator-associated infections, and abdominal infections. What is not yet understood is the optimal way to identify those sepsis patients who have hyperinflamed rather than immunosuppressed phenotypes. Similarly, it is unknown whether the dysfunctional immune system is driving organ dysfunction and secondary infections or whether the immune system itself is just another dysfunctional organ.

APPROACH TO THE PATIENT

Sepsis and Septic Shock

At the bedside, a clinician begins by asking, "Is this patient septic?" Consensus criteria for sepsis and septic shock agree on core diagnostic elements, including suspected or documented infection accompanied by acute, life-threatening organ dysfunction. If infection is documented, the clinician must determine the inciting cause and the severity of organ dysfunction, usually by asking: "What just happened?" Severe infection can be evident, but it is often quite difficult to recognize. Many infection-specific biomarkers and molecular diagnostics are under study to help discriminate sterile inflammation from infection, but these tools are not commonly used. The clinician's acumen is still crucial to the diagnosis of infection. Next, the primary physiologic manifestations of organ dysfunction can be assessed quickly at the bedside with a six-organ framework, yielding the SOFA score. Particular focus should then be placed on the presence or absence of shock, which constitutes a clinical emergency. The general manifestations of shock include arterial hypotension with evidence of tissue hypoperfusion (e.g., oliguria, altered mental status, poor peripheral perfusion, or hyperlactemia).

CLINICAL MANIFESTATIONS

The specific clinical manifestations of sepsis are quite variable, depending on the initial site of infection, the offending pathogen, the pattern of acute organ dysfunction, the underlying health of the patient, and the delay before initiation of treatment. The signs of both infection and organ dysfunction may be subtle. Guidelines provide a long list of potential warning signs of incipient sepsis (Table 297-1). Once sepsis has been established and the inciting infection is assumed to be under control, the temperature and white blood cell (WBC) count often return to normal. However, organ dysfunction typically persists.

Cardiorespiratory Failure Two of the most commonly affected organ systems in sepsis are the respiratory and cardiovascular systems. Respiratory compromise classically manifests as acute respiratory distress syndrome (ARDS), defined as hypoxemia and bilateral infiltrates of noncardiac origin that arise within 7 days of the suspected infection. ARDS can be classified by Berlin criteria as mild (PaO_2/FiO_2, 201–300 mmHg), moderate (101–200 mmHg), or severe (≤100 mmHg). A common competing diagnosis is hydrostatic edema secondary to cardiac failure or volume overload. Although traditionally identified by elevated pulmonary capillary wedge measurements from a pulmonary artery catheter (>18 mmHg), cardiac failure can be objectively evaluated on the basis of clinical judgment or focused echocardiography.

Cardiovascular compromise typically presents as hypotension. The cause can be frank hypovolemia, maldistribution of blood flow and intravascular volume due to diffuse capillary leakage, reduced systemic vascular resistance, or depressed myocardial function. After adequate volume expansion, hypotension frequently persists, requiring the use of vasopressors. In early shock, when volume status is reduced, systemic vascular resistance may be quite high with low cardiac output; after volume repletion, however, this picture may rapidly change to low systemic vascular resistance and high cardiac output.

Kidney Injury Acute kidney injury (AKI) is documented in >50% of septic patients, increasing the risk of in-hospital death by six- to eightfold. AKI manifests as oliguria, azotemia, and rising serum creatinine levels and frequently requires dialysis. The mechanisms of sepsis-induced AKI are incompletely understood. AKI may occur in up to 25% of patients in the absence of overt hypotension. Current mechanistic work suggests that a combination of diffuse microcirculatory blood-flow abnormalities, inflammation, and cellular bioenergetic responses to injury contribute to sepsis-induced AKI beyond just organ ischemia.

Neurologic Complications Typical central nervous system dysfunction presents as coma or delirium. Imaging studies typically show no focal lesions, and electroencephalographic findings are usually consistent with nonfocal encephalopathy. Sepsis-associated delirium is considered a diffuse cerebral dysfunction caused by the inflammatory response to infection without evidence of a primary central nervous system infection. Consensus guidelines recommend delirium screening with valid and reliable tools such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Critical-illness polyneuropathy and myopathy are also common, especially in patients with a prolonged course. For survivors of sepsis, neurologic complications can be severe. In a national (U.S.) representative prospective cohort of >1000 elderly patients with severe sepsis, moderate to severe cognitive impairment increased by 10.6 percentage points among patients who survived severe sepsis (odds ratio, 3.34; 95% confidence interval [CI], 1.53–7.25) over that among survivors of nonsepsis hospitalizations. Many of these limitations persisted for up to 8 years.

Additional Manifestations Many other abnormalities occur in sepsis, including ileus, elevated aminotransferase levels, altered glycemic control, thrombocytopenia and disseminated intravascular coagulation, adrenal dysfunction, and sick euthyroid syndrome. Adrenal

dysfunction in sepsis is widely studied and is thought to be related more to reversible dysfunction of the hypothalamic–pituitary axis or tissue glucocorticoid resistance than to direct damage to the adrenal gland. The diagnosis is difficult to establish. Recent clinical practice guidelines do not recommend use of the adrenocorticotropic hormone stimulation test or determination of the plasma cortisol level to detect relative glucocorticoid insufficiency.

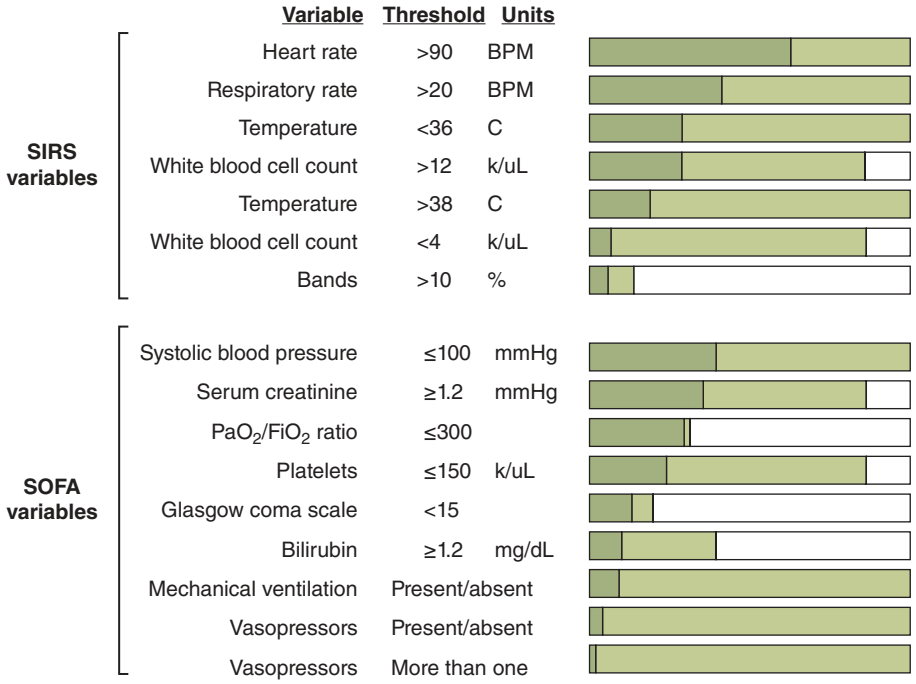

FIGURE 297-2 Distribution of SIRS and SOFA variables among infected patients at risk for sepsis, as documented in the electronic health record. Dark green bars represent the proportion of such patients with abnormal findings; light green bars, the proportion with normal findings; and white bars, the proportion with missing data. *(Adapted from CW Seymour et al: Assessment of clinical criteria for sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3]. JAMA 315:762, 2016.)*

DIAGNOSIS

Laboratory and Physiologic Findings

A variety of laboratory and physiologic changes are found in patients with suspected infection who are at risk for sepsis. In a 12-hospital cohort of electronic health records related to >70,000 encounters (Fig. 297-2), only tachycardia (heart rate, >90 beats per min) was present in >50% of encounters; the most common accompanying abnormalities were tachypnea (respiratory rate, >20 breaths per min), hypotension (systolic blood pressure, ≤100 mmHg), and hypoxia (SaO_2, ≤90%). Leukocytosis (WBC count, >12,000/μL) was present in fewer than one-third of patients and leukopenia (WBC count, <4000/μL) in fewer than 5%. Notably, many features that may identify acute organ dysfunction, such as platelet count, total bilirubin, or serum lactate level, are measured in only a small minority of at-risk encounters. If measured, metabolic acidosis with anion gap may be detected, as respiratory muscle fatigue occurs in sepsis-associated respiratory failure. Other, less common findings include serum hypoalbuminemia, troponin elevation, hypoglycemia, and hypofibrinogenemia.

Diagnostic Criteria There is no specific test for sepsis, nor is there a gold-standard method for determining whether a patient is septic. In fact, the definition of sepsis can be written as a logic statement:

sepsis = f (threat to life | organ dysfunction | dysregulated host response | infection),

where sepsis is the dependent variable, which in turn is a function of four independent variables linked in a causal pathway, with—from left to right—one conditional upon the other. There may be uncertainty about whether each variable exists, whether it can be measured, and whether the causal and conditional relationships hold. If we assume that organ dysfunction exists and can be measured, then attributing the marginal degradation in function to a dysregulated host response is not simple and requires the ability to determine preexisting dysfunction, other noninfectious contributions to organ dysfunction, and—ideally—the mechanism by which the host response to an infection causes organ dysfunction.

In order to sort through these complex details, clinicians need simple bedside criteria to operationalize the logic statement (Fig. 297-3). With this mandate, the Sepsis Definitions Task Force recommended that, once infection is suspected, clinicians consider whether it has caused organ dysfunction by determining a SOFA score. The SOFA score ranges from 0 to 24 points, with up to 4 points accrued across six organ systems. The SOFA score is widely studied in the ICU among patients with infection, sepsis, and shock. With ≥2 new SOFA points, the infected patient is considered septic and may be at ≥10% risk of in-hospital death.

Because the SOFA score requires multiple laboratory tests and may be costly to measure repeatedly, the quick SOFA (qSOFA) score was proposed as a clinical prompt to identify patients at high risk of sepsis outside the ICU, whether on the medical ward or in the emergency department. The qSOFA score ranges from 0 to 3 points, with 1 point each for systolic hypotension (≤100 mmHg), tachypnea (≥22 breaths/min), or altered mentation. A qSOFA score of ≥2 points has a predictive value for sepsis similar to that of more complicated measures of organ dysfunction. The qSOFA score is undergoing broader evaluation in other cohorts, in low-and middle-income settings, and in algorithms linked to clinical decision-making. Recent work has also shown that, although SIRS criteria may be fulfilled in sepsis, they sometimes are not and do not meaningfully contribute to the identification of patients with suspected infection who are at greater risk of a poor course, ICU admission, or death—outcomes more common among patients with sepsis than among those without.

As stated above, recent definitions have specified that septic shock is a subset of sepsis in which circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality risk, but the application of this definition as a criterion for enrollment of patients varies significantly in clinical trials, observational studies, and quality improvement work. For clarity, criteria are proposed for septic shock that include (1) sepsis plus (2) the need for vasopressor therapy to elevate mean arterial pressure to ≥65 mmHg, with (3) a serum lactate concentration >2.0 mmol/L after adequate fluid resuscitation.

The new definitions and diagnostic criteria were externally validated in >1 million encounters stored in electronic health records. Nevertheless, given the uncertainty around the diagnosis of sepsis, Sepsis-3 is undergoing both validation in prospective studies and incorporation into clinical practice and quality improvement initiatives.

Arterial lactate is a long-studied marker of tissue hypoperfusion, and hyperlactemia and delayed lactate clearance are associated with a greater incidence of organ failure and death in sepsis. In a study of >1200 patients with suspected infection, 262 (24%) of 1081 patients exhibited an elevated lactate concentration (≥2.5 mmol/L) even in the setting of normal systolic blood pressure (>90 mmHg) and were at elevated risk of 28-day in-hospital mortality. However, lactic acidosis may occur in the presence of alcohol intoxication, liver disease, diabetes mellitus, administration of total parenteral nutrition, or antiretroviral treatment, among other conditions. Furthermore, in sepsis, an elevated lactate concentration may simply be the manifestation of impaired clearance. These factors may confound the use of lactate as a stand-alone biomarker for the diagnosis of sepsis; thus it should be used in the context of other markers of infection and organ dysfunction.

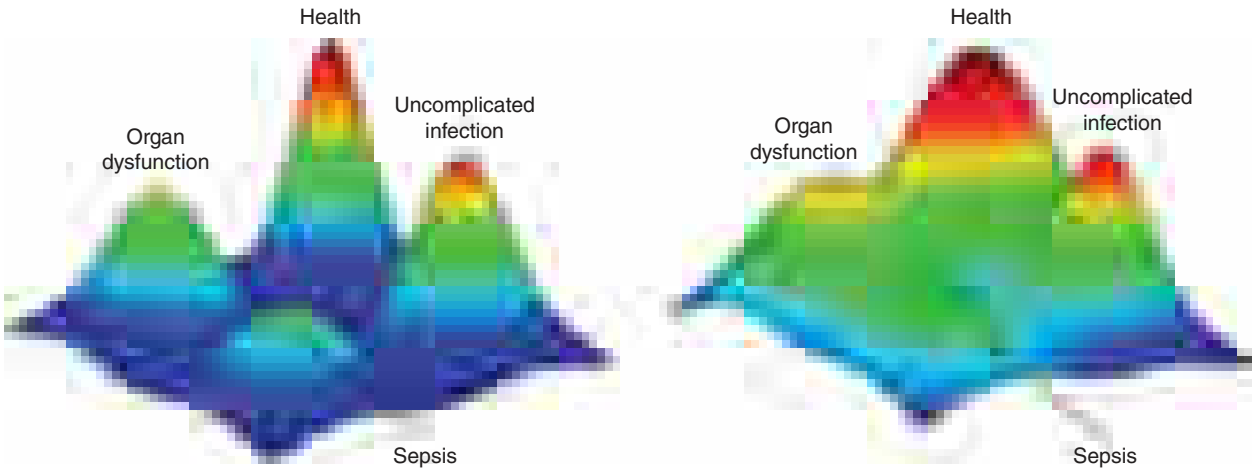

FIGURE 297-3 Schematic of the importance of accurate, easy-to-use criteria for sepsis and its components, infection and organ dysfunction. In the ideal case (*left*), criteria clearly distinguish sepsis patients from other patients with uncomplicated infection or organ dysfunction. The reality (*right*), however, is that existing criteria fail to make clear distinctions, leaving a significant proportion of patients in areas of uncertainty. *(Adapted from DC Angus et al: A framework for the development and interpretation of different sepsis definitions and clinical criteria. Crit Care Med 44:e113, 2016.)*

TREATMENT

Sepsis and Septic Shock

EARLY TREATMENT OF SEPSIS AND SEPTIC SHOCK

Recommendations for sepsis care begin with prompt diagnosis. Recognition of septic shock by a clinician constitutes an emergency in which immediate treatment can be life-saving. Up-to-date guidelines for treatment are derived from international clinical practice guidelines provided by the Surviving Sepsis Campaign. This consortium of critical care, infectious disease, and emergency medicine professional societies has issued three iterations of clinical guidelines for the management of patients with sepsis and septic shock **(Table 297-2)**.

The initial management of infection requires several steps: forming a probable diagnosis, obtaining samples for culture, initiating empirical antimicrobial therapy, and achieving source control. More than 30% of patients with severe sepsis require source control, mainly for abdominal, urinary, and soft-tissue infections. The mortality rate is lower among patients with source control than among those without, although the timing of intervention is debated. For empirical antibiotic therapy **(Table 297-3)**, the appropriate choice depends on the suspected site of infection, the location of infection onset (i.e., the community, a nursing home, or a hospital), the patient's medical history, and local microbial susceptibility patterns. In a single-center study of >2000 patients with bacteremia, the number of patients who needed to receive appropriate antimicrobial therapy in order to prevent one patient death was 4.0 (95% CI, 3.7–4.3).

Antibiotic delays may be deadly. For every 1-h delay among patients with sepsis, a 3–7% increase in the odds of in-hospital death is reported. Although meta-analyses report conflicting results, international clinical practice guidelines recommend the administration of appropriate broad-spectrum antibiotics within 1 h of recognition of severe sepsis or septic shock. Empirical antifungal therapy should be administered only to septic patients at high risk for invasive candidiasis.

The treatment elements listed above form the basis for two "bundles" of care: an initial management bundle to be completed within 3 h of presentation and a management bundle to be completed within 6 h. The initial management bundle includes (1) early administration of appropriate broad-spectrum antibiotics, (2) collection of blood for culture before antibiotic administration, and (3) measurement of serum lactate levels. The management bundle includes (1) an intravenous fluid bolus, (2) treatment with vasopressors for persistent hypotension or shock, and (3) re-measurement of serum lactate levels. Implementation of these two bundles has been associated with improved outcome in large multinational studies.

Other elements of the initial management bundle are cardiorespiratory resuscitation and mitigation of the immediate threats of uncontrolled infection. Early resuscitation requires a structured approach including the administration of IV fluids and vasopressors, with oxygen therapy and mechanical ventilation to support injured organs. The exact components required to optimize resuscitation, such as choice and amount of fluid, appropriate type and intensity of hemodynamic monitoring, and role of adjunctive vasoactive agents, all remain controversial, even after the completion and reporting of recent large randomized trials.

Evidence from an older study suggests that protocol-based, early goal-directed therapy (EGDT) may confer a greater survival advantage than clinical assessments of organ perfusion and management without a protocol. EGDT included an aggressive resuscitation protocol with specific hemodynamic thresholds for fluid administration, blood transfusion, and use of ionotropes. Given the many controversial features of this older single-center trial, the recent ProCESS trial compared protocol-based standard care with protocol-based EGDT and usual care in >31 emergency departments in the United States. Among 1341 patients, the 60-day in-hospital mortality rate for protocol-based standard care (18.2%) was similar to that for usual care (18.9%) and protocol-based EGDT (21%). The ARISE trial confirmed this finding, showing that, among 1600 patients with early septic shock at 51 centers in Australia and New Zealand, 90-day mortality was similar for EGDT and usual care. Finally, the ProMISe trial, which enrolled 1260 patients in 56 hospitals in England, found that EGDT offered no mortality benefit in early septic shock but did increase treatment intensity and cost. Multiple subsequent meta-analyses of the ProCESS, ARISE, and ProMISe trials confirmed that EGDT offers no mortality benefit while increasing health care utilization and ICU admission in well-resourced countries. Modified versions of EGDT were also tested in lower-resourced settings, with no change in outcome. Thus EGDT is no longer recommended as the primary strategy for early resuscitation in septic shock. Nonetheless, some form of resuscitation is considered essential, and a standardized approach, akin to the use of "trauma teams," has been advocated to ensure prompt care. The patient should be moved to an appropriate setting, such as the ICU, for ongoing care.

SUBSEQUENT TREATMENT OF SEPSIS AND SEPTIC SHOCK

After initial resuscitation, attention is focused on monitoring and support of organ function, avoidance of complications, and de-escalation of care when possible.

Monitoring Hemodynamic monitoring devices may clarify the primary physiologic manifestations in sepsis and septic shock. The clinical usefulness of these monitoring devices can be attributable to the device itself, the algorithm linked to the device, or the static/dynamic target of the algorithm. Decades ago, the standard care of shock patients included invasive devices like the pulmonary artery

TABLE 297-2 Elements of Care in Sepsis and Septic Shock: Recommendations Adapted from International Consensus Guidelines

Resuscitation
Sepsis and septic shock constitute an emergency, and treatment should begin right away.
Resuscitation with IV crystalloid fluid (30 mL/kg) should begin within the first 3 h.
Saline or balanced crystalloids are suggested for resuscitation.
If the clinical examination does not clearly identify the diagnosis, hemodynamic assessments (e.g., with focused cardiac ultrasound) can be considered.
In patients with elevated serum lactate levels, resuscitation should be guided towards normalizing these levels when possible.
In patients with septic shock requiring vasopressors, the recommended target mean arterial pressure is 65 mmHg.
Hydroxyethyl starches and gelatins are not recommended.
Norepinephrine is recommended as the first-choice vasopressor.
Vasopressin should be used with the intent of reducing the norepinephrine dose.
The use of dopamine should be avoided except in specific situations—e.g., in those patients at highest risk of tachyarrhythmias or relative bradycardia.
Dobutamine use is suggested when patients show persistent evidence of hypoperfusion despite adequate fluid loading and use of vasopressors.
Red blood cell transfusion is recommended only when the hemoglobin concentration decreases to <7.0 g/dL in the absence of acute myocardial infarction, severe hypoxemia, or acute hemorrhage.
Infection Control
So long as no substantial delay is incurred, appropriate samples for microbiologic cultures should be obtained before antimicrobial therapy is started.
IV antibiotics should be initiated as soon as possible (within 1 h); specifically, empirical broad-spectrum therapy should be used to cover all likely pathogens.
Antibiotic therapy should be narrowed once pathogens are identified and their sensitivities determined and/or once clinical improvement is evident.
If needed, source control should be undertaken as soon as is medically and logistically possible.
Daily assessment for de-esclation of antimicrobial therapy should be conducted.
Respiratory Support
A target tidal volume of 6 mL/kg of predicted body weight (compared with 12 mL/kg in adult patients) is recommended in sepsis-induced ARDS.
A higher PEEP rather than a lower PEEP is used in moderate to severe sepsis-induced ARDS.
In severe ARDS (PaO_2/FIO_2, <150 mmHg), prone positioning is recommended, and recruitment maneuvers and/or neuromuscular blocking agents for ≤48 h are suggested.
A conservative fluid strategy should be used in sepsis-induced ARDS if there is no evidence of tissue hypoperfusion.
Routine use of a pulmonary artery catheter is not recommended.
Spontaneous breathing trials should be used in mechanically ventilated patients who are ready for weaning.
General Supportive Care
Patients requiring a vasopressor should have an arterial catheter placed as soon as is practical.
Hydrocortisone is not suggested in septic shock if adequate fluids and vasopressor therapy can restore hemodynamic stability.
Continuous or intermittent sedation should be minimized in mechanically ventilated sepsis patients, with titration targets used whenever possible.
A protocol-based approach to blood glucose management should be used in ICU patients with sepsis, with insulin dosing initiated when two consecutive blood glucose levels are >180 mg/dL.
Continuous or intermittent renal replacement therapy should be used in patients with sepsis and acute kidney injury.
Pharmacologic prophylaxis (unfractionated heparin or low-molecular-weight heparin) against venous thromboembolism should be used in the absence of contraindications.
Stress ulcer prophylaxis should be given to patients with risk factors for gastrointestinal bleeding.
The goals of care and prognosis should be discussed with patients and their families.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit; PEEP, positive end-expiratory pressure.

Source: Adapted from A Rhodes et al: Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 45:486, 2017.

catheter (PAC), also known as the continuous $ScvO_2$ catheter. The PAC can estimate cardiac output and measure mixed venous oxygen saturation, among other parameters, to refine the etiology of shock and potentially influence patient outcomes. Recently, a Cochrane review of 2923 general-ICU patients (among whom the proportion of patients in shock was not reported) found no difference in mortality with or without PAC management, and the PAC therefore is no longer recommended for routine use. Instead, a variety of noninvasive monitoring tools, such as arterial pulse contour analysis (PCA) or focused echocardiography, can provide continuous estimates of parameters such as cardiac output, beat-to-beat stroke volume, and pulse pressure variation. These tools, along with passive leg-raise maneuvers or inferior vena cava collapsibility on ultrasound, can help determine a patient's volume responsiveness but require that a variety of clinical conditions be met (e.g., patient on mechanical ventilation, sinus rhythm); in addition, more evidence from larger randomized trials on the impact of these tools in daily management is needed.

Support Of Organ Function The primary goal of organ support is to improve delivery of oxygen to the tissues as quickly as possible. Depending on the underlying physiologic disturbance, this step may require administration of IV fluids or vasopressors, blood transfusions, or ventilatory support.

Many crystalloids can be used in septic shock, including 0.9% normal saline, Ringer's lactate, Hartmann's solution, and Plasma-Lyte. Because crystalloid solutions vary in tonicity and inorganic/organic anions, few of these preparations closely resemble plasma. Normal saline is widely used in the United States. Colloid solutions (e.g., albumin, dextran, gelatins, or hydroxyethyl starch) are the most widely used fluids in critically ill patients, with variability across ICUs and countries. A clinician's choice among colloids is influenced by availability, cost, and the desire to minimize interstitial edema. Many think that a greater intravascular volume is gained by use of colloids in shock, but the effects of colloids are modified by molecular weight and concentration as well as by vascular endothelial changes during inflammation. A network meta-analysis using direct and indirect comparisons in sepsis found evidence of higher mortality with starch than with crystalloids (relative risk [RR], 1.13; 95% CI, 0.99–1.30 [high confidence]) and no difference between albumin (RR, 0.83; 95% CI, 0.65, 1.04 [moderate confidence]) or gelatin (RR, 1.24; 95%CI, 0.61, 2.55 [very low confidence]) and crystalloids. In general, crystalloids are recommended on the basis of strong evidence as

TABLE 297-3 Initial Antimicrobial Therapy for Severe Sepsis with No Obvious Source in Adults with Normal Renal Function

CLINICAL CONDITION	ANTIMICROBIAL REGIMENS[a]
Septic shock (immunocompetent adult)	The many acceptable regimens include (1) piperacillin-tazobactam (3.375–4.5 g q6h), (2) cefepime (2 g q12h), or (3) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h). If the patient is allergic to β-lactam antibiotics, use (1) aztreonam (2 g q8h) or (2) ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q24h). Add vancomycin (loading dose of 25–30 mg/kg, then 15–20 mg/kg q8–12h) to each of the above regimens.
Neutropenia (<500 neutrophils/μL)	Regimens include (1) cefepime (2 g q8h), (2) meropenem (1 g q8h) or imipenem-cilastatin (0.5 g q6h) or doripenem (500 mg q8h), or (3) piperacillin-tazobactam (3.375 g q4h). Add vancomycin (as above) if the patient has a suspected central line–associated bloodstream infection, severe mucositis, skin/soft tissue infection, or hypotension. Add tobramycin (5–7 mg/kg q24h) plus vancomycin (as above) plus caspofungin (one dose of 70 mg, then 50 mg q24h) if the patient has severe sepsis/septic shock.
Splenectomy	Use ceftriaxone (2 g q24h, or—in meningitis—2 g q12h). If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin (as above). If the patient is allergic to β-lactam antibiotics, use levofloxacin (750 mg q24h) or moxifloxacin (400 mg q24h) plus vancomycin (as above).

[a]All agents are administered by the intravenous route.

Source: Adapted in part from DN Gilbert et al: *The Sanford Guide to Antimicrobial Therapy*, 47th ed, 2017; and from RS Munford: Sepsis and septic shock, in DL Kasper et al (eds). *Harrison's Principles of Internal Medicine*, 19th ed. New York, McGraw-Hill, 2015, p 1757.

first-line fluids for sepsis resuscitation, with specific caveats; their use is guided by resolution of hypotension, oliguria, altered mentation, and hyperlactemia. Only weak evidence supports the use of balanced crystalloids, and guidelines recommend against using hydroxyethyl starches for intravascular volume replacement.

When circulating fluid volume is adequate, vasopressors are recommended to maintain perfusion of vital organs. Vasopressors such as norepinephrine, epinephrine, dopamine, and phenylephrine differ in terms of half-life, β- and α-adrenergic stimulation, and dosing regimens. Recent evidence comes from the SOAP II trial, a double-blind randomized clinical trial at eight centers comparing norepinephrine with dopamine in 1679 undifferentiated ICU patients with shock, of whom 63% were septic. Although no difference was observed in 28-day mortality or in predefined septic-shock subgroup, arrhythmias were significantly greater with dopamine. These findings were confirmed in a subsequent meta-analysis. As a result, expert opinion and consensus guidelines recommend norepinephrine as the first-choice vasopressor in septic shock. Levels of the endogenous hormone vasopressin may be low in septic shock, and the administration of vasopressin can reduce the norepinephrine dose. Consensus guidelines suggest adding vasopressin (up to 0.03 U/min) in patients without a contraindication to norepinephrine, with the intent of raising mean arterial pressure or decreasing the norepinephrine dose. There may be select indications for use of alternative vasopressors—e.g., when tachyarrhythmias from dopamine or norepinephrine, limb ischemia from vasopressin, or other adverse effects dictate.

The transfusion of red blood cells to high thresholds (>10 g/dL) had been suggested as part of EGDT in septic shock. However, the recent Scandinavian TRISS trial in 1005 septic shock patients demonstrated that a lower threshold (7 g/dL) resulted in 90-day mortality rates similar to those with a higher threshold (9 g/dL) and reduced transfusions by almost 50%.

Significant hypoxemia (PaO_2, <60 mmHg; or SaO_2, <90%), hypoventilation (rising $PaCO_2$), increased work of breathing, and inadequate or unsustainable compensation for metabolic acidosis (pH <7.20) are common indications for mechanical ventilatory support. Endotracheal intubation protects the airway, and positive-pressure breathing allows oxygen delivery to metabolically active organs in favor of inspiratory muscles of breathing and the diaphragm. An experiment in dogs showed that the relative proportion of cardiac output delivered to respiratory muscles in endotoxic shock decreased by fourfold with spontaneous ventilation over that with mechanical ventilation. During intubation, patients in shock should be closely monitored for vasodilatory effects of sedating medications or compromised cardiac output due to increased intrathoracic pressure, both of which may cause hemodynamic collapse. With hemodynamic instability, noninvasive mask ventilation may be less suitable in patients experiencing sepsis-associated acute respiratory failure.

Adjuncts One of the great disappointments in sepsis management over the past 30 years has been the failure to convert advances in our understanding of the underlying biology into new therapies. Researchers have tested both highly specific agents and those with more pleotropic effects. The specific agents can be divided into those designed to interrupt the initial cytokine cascade (e.g., anti-LPS or anti-proinflammatory cytokine strategies) and those that interfere with dysregulated coagulation (e.g., antithrombin or activated protein C). Recombinant activated protein C (aPC) was one of the first agents approved by the U.S. Food and Drug Administration and was the most widely used. A large, randomized, double-blind, placebo-controlled, multicenter trial of aPC in severe sepsis (the PROWESS trial) was reported in 2001; the data suggested an absolute risk reduction of up to 6% among aPC-treated patients with severe sepsis. However, subsequent phase 3 trials failed to confirm this effect, and the drug was withdrawn from the market. It is no longer recommended in the care of sepsis or septic shock.

Many adjunctive treatments in sepsis and septic shock target changes in the innate immune response and coagulation cascade. Specific adjuncts like glucocorticoids in septic shock have continued to be widely used. A large negative clinical trial and a conflicting systematic review in 2009 extended the debate about whether glucocorticoids lower 28-day mortality or improve shock reversal. Most meta-analyses report no change in mortality but an increase in shock reversal with glucocorticoid treatment. The recent HYPRESS trial found no difference between patients with severe sepsis who were treated with glucocorticoids and control patients in terms of the development of shock or the mortality rate. These data and others led to a suggestion in international clinical practice guidelines against using IV hydrocortisone to treat septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If not, the guidelines suggest the administration of IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Among other adjuncts, IV immunoglobulin may be associated with potential benefit, but significant questions remain and such treatment is not part of routine practice. Despite a large number of observational studies suggesting that statin use mitigates the incidence or outcome of sepsis and severe infection, there are no confirmatory randomized controlled trials, and statins are not an element in routine sepsis care.

De-Escalation of Care Once patients with sepsis and septic shock are stabilized, it is important to consider which therapies are no longer required and how care can be minimized. The de-escalation of initial broad-spectrum therapy, which observational evidence indicates is safe, may reduce the emergence of resistant organisms as well as potential drug toxicity and costs. The added value of combination antimicrobial therapy over that of adequate single-agent antibiotic therapy in severe sepsis has not been established. Current guidelines recommend combination antimicrobial therapy only for neutropenic sepsis and sepsis caused by *Pseudomonas*. Large trials are under way in the United States to determine how serum biomarkers like procalcitonin can assist clinicians in minimizing antibiotic exposure, while European trials are indicating that this

biomarker may lead to a reduction in the duration of treatment and in daily defined doses in critically ill patients with a presumed bacterial infection.

PROGNOSIS

Before modern intensive care, sepsis and septic shock were highly lethal, with infection leading to compromise of vital organs. Even with intensive care, nosocomial mortality rates for septic shock often exceeded 80% as recently as 30 years ago. Now, the U.S. Burden of Disease Collaborators report that the primary risk factor for sepsis and septic shock—i.e., infection—is the fifth leading cause of years of productive life lost because of premature death. More than half of sepsis cases require ICU admission, representing 10% of all ICU admissions. However, with advances in training, surveillance, monitoring, and prompt initiation of supportive care for organ dysfunction, the mortality rate from sepsis and septic shock is now closer to 20% in many series. Although some data suggest that mortality trends are even lower, attention has been focused on the trajectory of recovery among survivors. Patients who survive to hospital discharge after sepsis remain at increased risk of death in the following months and years. Those who survive often suffer from impaired physical or neurocognitive dysfunction, mood disorders, and low quality of life. In many studies, it is difficult to determine the causal role of sepsis. However, an analysis of the Health and Retirement Study—a large longitudinal cohort study of aging Americans—suggested that severe sepsis significantly accelerated physical and neurocognitive decline. Among survivors, the rate of hospital readmission within 90 days after sepsis exceeds 40%.

PREVENTION

In light of the persistently high mortality risk in sepsis and septic shock, prevention may be the best approach to reducing avoidable deaths, but preventing sepsis is a challenge. The aging of the population, the overuse of inappropriate antibiotics, the rising incidence of resistant microorganisms, and the use of indwelling devices and catheters contribute to a steady burden of sepsis cases. The number of cases could be reduced by avoiding unnecessary antibiotic use, limiting use of indwelling devices and catheters, minimizing immune suppression when it is not needed, and increasing adherence to infection control programs at hospitals and clinics. To facilitate earlier treatment, such pragmatic work could be complemented by research into the earliest pathophysiology of infection, even when symptoms of sepsis are nascent. In parallel, the field of implementation science could inform how best to increase adoption of infection control in high-risk settings and could guide appropriate care.

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298 Cardiogenic Shock and Pulmonary Edema

David H. Ingbar, Holger Thiele

Cardiogenic shock (CS) and pulmonary edema are life-threatening high acuity conditions that require treatment as medical emergencies, usually in an intensive care unit (ICU) or cardiac intensive care unit (CICU). The most common joint etiology is severe left ventricular (LV) dysfunction from myocardial infarction (MI) that leads to pulmonary congestion and/or systemic hypoperfusion **(Fig. 298-1)**. **The pathophysiology of pulmonary edema and shock are discussed in Chaps. 33 and 296, respectively.**

CARDIOGENIC SHOCK

CS is a low cardiac output state resulting in life-threatening end-organ hypoperfusion and hypoxia. The clinical presentation is typically characterized by persistent hypotension (<90 mmHg systolic blood pressure [BP]) unresponsive to volume replacement and is accompanied by clinical features of peripheral hypoperfusion, such as elevated arterial lactate (>2 mmol/L). Objective hemodynamic parameters such as cardiac index or pulmonary capillary wedge pressure can help confirm the diagnosis, but are not mandatory. The in-hospital mortality rates range from 40 to 60%, depending on shock severity and the associated underlying cause. Acute MI with LV dysfunction remains the most frequent cause of CS with other causes listed in **Table 298-1**. Circulatory failure based on cardiac dysfunction may be caused by primary myocardial failure, most commonly secondary to acute MI **(Chap. 269)**, and less frequently by cardiomyopathy or myocarditis **(Chap. 254)**, cardiac tamponade **(Chap. 265)**, arrhythmias **(Chap. 249)**, or critical valvular heart disease **(Chap. 256)**.

Incidence The incidence of CS complicating acute MI has decreased to 5–10%, largely due to increasing use of early mechanical reperfusion therapy for acute MI. Shock is more common with ST-elevation MI (STEMI) than with non-STEMI **(Chap. 269)**.

LV failure accounts for ~80% of cases of CS complicating acute MI. Acute severe mitral regurgitation (MR), ventricular septal rupture (VSR), predominant right ventricular (RV) failure, and free wall rupture or tamponade account for the remainder. A recently recognized uncommon cause of transient CS is the Takotsubo syndrome.

Pathophysiology The understanding of the complex pathophysiology of CS has evolved over the past decades. In general, a profound depression of myocardial contractility results in a deleterious spiral of reduced cardiac output, low blood pressure, and ongoing myocardial ischemia, followed by further contractility reduction (Fig. 298-1). This vicious cycle usually leads to death if not interrupted. CS can result in both acute and subacute derangements to the entire circulatory system. Hypoperfusion of vital organs and extremities remains a clinical hallmark. Although ineffective stroke volume is the inciting event, inadequate circulatory compensation also may contribute to shock. Initial peripheral vasoconstriction may improve coronary and peripheral perfusion at the cost of increased afterload. However, over the course of CS systemic inflammation response triggered by acute cardiac injury often induces pathologic vasodilatation. Inflammatory cytokines, endothelial and inducible nitric oxide synthase may augment NO production, accompanied by peroxynitrite, which has a negative inotropic effect and is cardiotoxic. Lactic acidosis and hypoxemia contribute to the vicious circle, as severe acidosis reduces the efficacy of endogenous and exogenous catecholamines. During ICU support bleeding and/or

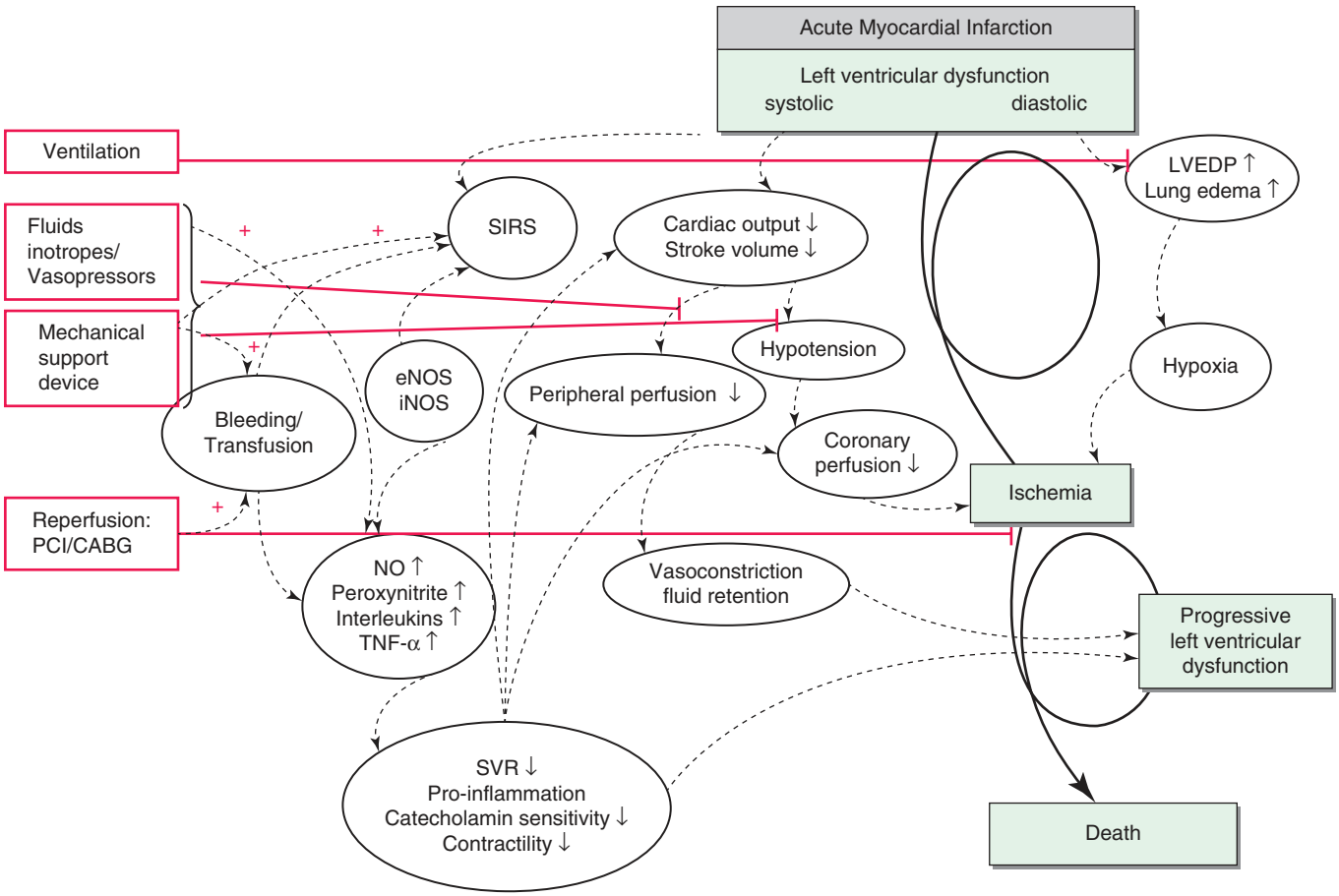

FIGURE 298-1 Pathophysiology of cardiogenic shock and potential treatment targets. The pathophysiological concept of the expanded cardiogenic shock spiral and treatment targets. CABG, coronary artery bypass grafting; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end diastolic pressure; NO, nitric oxide; PCI, percutaneous coronary intervention; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; TNF, tumor necrosis factor. *(Reproduced and adapted, with permission, from H Thiele et al: Shock in acute myocardial infarction: The Cape Horn for trials? Eur Heart J 31: 1828, 2010.)*

transfusions may trigger inflammation and are usually associated with higher mortality (Fig. 298-1).

Patient Profile In patients with MI, older age, prior MI, diabetes mellitus, anterior MI location, and multivessel coronary artery disease with extensive coronary artery stenoses are associated with an increased risk of CS. Shock associated with a first inferior MI should prompt a search for a mechanical cause or RV involvement. CS may rarely occur in the absence of significant stenosis, as seen in Takotsubo syndrome or fulminant myocarditis.

Timing Shock is present on admission in approximately one-quarter of MI patients who develop CS; one-quarter develop it rapidly thereafter, within 6 h of MI onset, and another quarter develop shock later on the first day. Later onset of CS may be due to reinfarction, marked infarct expansion, or mechanical complications.

Diagnosis For these unstable patients, supportive therapy must be initiated simultaneously with diagnostic evaluation **(Fig. 298-2)**. A focused history and physical examination should be performed along with an electrocardiogram (ECG), chest X-ray, arterial blood gas (ABG) analysis, lactate measurement, and blood specimens to the laboratory. Initial echocardiography is an invaluable tool to elucidate the underlying cause of CS.

CLINICAL FINDINGS Most patients initially are dyspneic, appear pale, apprehensive, and diaphoretic, and mental status may be altered. The pulse is typically weak and rapid or occasionally severe bradycardia due to high-grade heart block may be present. BP is typically reduced (<90 mmHg; or catecholamines required to maintain blood pressure >90 mmHg), but occasionally BP may be maintained by very high systemic vascular resistance. Tachypnea and jugular venous distention may be present. Typically there is a weak apical pulse and soft S_1, and an S_3 gallop may be audible. Acute, severe MR and VSR usually are associated with characteristic systolic murmurs **(Chap. 269)**. Crackles are audible in most patients with LV failure. Oliguria/anuria is common. Often CS patients require early mechanical ventilation (~80%) for management of acute hypoxemia, increased work of breathing, and hemodynamic instability; catecholamines often are required to maintain adequate blood pressure.

LABORATORY FINDINGS The white blood cell count and C-reactive protein typically are elevated. Renal function often is progressively impaired. Newer renal function markers such as Cystatin C or Neutrophil gelatinase-associated lipocalin (NGAL) do not add prognostic information over creatinine. Hepatic transaminases are elevated due to liver hypoperfusion in ~20% of patients and may be very high. The arterial lactate level is usually elevated to >2 mmol/L. ABGs usually demonstrate hypoxemia and anion gap metabolic acidosis. Glucose levels at admission are often elevated, a strong independent predictor for mortality. Cardiac markers, creatine kinase and its MB fraction, and troponins I and T are typically markedly elevated in acute MI.

ELECTROCARDIOGRAM In acute MI with CS, Q waves and/or ST elevation in multiple leads or left bundle branch block are usually present. Approximately one-half of MIs with CS are anterior infarctions. Global ischemia due to severe left main stenosis usually is accompanied by aVR lead ST segment elevation and ST depressions in multiple leads.

CHEST ROENTGENOGRAM The chest x-ray typically shows pulmonary vascular congestion and often pulmonary edema, but may be normal in up to a third of patients. The heart size is usually normal when CS results from a first MI, but may be enlarged when it occurs in a patient with a previous MI.

TABLE 298-1 Etiologies of Cardiogenic Shock (CS)[a] and Cardiogenic Pulmonary Edema

Etiologies of Cardiogenic Shock or Pulmonary Edema
Acute myocardial infarction/ischemia
Left ventricular failure
Ventricular septal rupture
Papillary muscle/chordal rupture–severe mitral regurgitation
Ventricular free wall rupture
Other conditions complicating large myocardial infarctions
Excess negative inotropic or vasodilator medications
Post-cardiac arrest
Post-cardiotomy
Refractory sustained supra or ventricular tachyarrhythmias
Refractory sustained bradyarrhythmias
Acute fulminant myocarditis
End-stage cardiomyopathy
Takotsubo syndrome/Apical ballooning syndrome
Hypertrophic cardiomyopathy with severe outflow obstruction
Aortic dissection with aortic insufficiency or tamponade
Severe valvular heart disease
Critical aortic or mitral stenosis
Acute severe aortic regurgitation or mitral regurgitation
Toxic/metabolic
β-blocker or calcium channel antagonist overdose
Hypertensive crisis
Post-cardiac arrest stunning
Myocardial depression in setting of septic shock or SIRS
Myocardial contusion
Other Etiologies of Cardiogenic Shock[b]
Right ventricular failure due to:
Acute myocardial infarction
Acute or decompensated chronic cor pulmonale
Pericardial tamponade
Toxic/metabolic
Severe acidosis, severe hypoxemia

[a]The etiologies of CS are listed. Most of these can cause pulmonary edema instead of shock or pulmonary edema with CS. [b]These cause CS but not pulmonary edema.

ECHOCARDIOGRAM An echocardiogram **(Chap. 236)** should be obtained promptly in patients with suspected/confirmed CS to help define its etiology. Echocardiography is able to delineate the extent of infarction/myocardium in jeopardy and the presence of mechanical complications such as VSR, MR, or cardiac tamponade. Furthermore, valvular obstruction or insufficiency, dynamic LV outflow tract obstruction, proximal aortic dissection with aortic regurgitation or tamponade may be seen, or indirect evidence for pulmonary embolism may be obtained **(Chap. 273) (Table 298-2)**.

PULMONARY ARTERY CATHETERIZATION The use of pulmonary artery catheter (PAC) hemodynamic monitoring is declining because clinical trials have shown no mortality benefit. However, hemodynamic data provided by a PAC can confirm the presence and severity of CS, involvement of the right ventricle, left-to-right shunting, pulmonary artery pressures and trans-pulmonary gradient, and the pulmonary and systemic vascular resistance. It can help in recognition of acute MR, decreased left atrial filling pressure, and secondary occult sepsis and to exclude left-to-right shunts. Equalization of diastolic pressures suggests cardiac tamponade, but echocardiogram is more definitive. The detailed hemodynamic profile can be used to individualize and monitor therapy and to provide prognostic information, such as cardiac index and cardiac power, can be obtained. The use of a PAC is currently recommended by the American Heart Association for potential utilization in cases of diagnostic or CS management uncertainty or in patients with severe CS who are unresponsive to initial therapy.

ADVANCED HEMODYNAMIC MONITORING Recently new central venous catheter systems linked to computer-based algorithms provide continuous monitoring of a variety of derived hemodynamic parameters, including cardiac output, stroke volume, stroke volume variation, and systemic vascular resistance. When combined with a femoral arterial catheter, calculated extravascular lung water and pulmonary permeability index can be monitored. The information allows for more rational therapy and assessment, but has not yet shown improved clinical outcomes in patients with shock or pulmonary edema **(Table 298-3)**.

CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY The definition of the coronary anatomy provides useful information and is immediately indicated in all patients with CS complicating MI for further reperfusion treatment. Furthermore, cardiac catheterization should also be considered for resuscitated cardiac arrest survivors without ST-segment elevation because ~70% of these patients have relevant coronary artery disease.

TREATMENT

Acute Myocardial Infarction

GENERAL MEASURES

In addition to the usual treatment of acute MI **(Chap. 269)**, initial therapy is aimed at maintaining adequate systemic and coronary perfusion by raising the blood pressure with vasopressors and adjusting volume status to a level that ensures optimum LV filling pressure (Fig. 298-2). There is some interpatient variability, but generally adequate perfusion occurs with a mean arterial BP of 60–65 mmHg or a systolic BP ~90 mmHg. Hypoxemia and acidosis need to be corrected; up to 90% of patients require ventilatory support, decreasing the stress from increased work of breathing (see "Pulmonary Edema," below) (Fig. 298-2). Moderate glucose control (≤180 mg/dL or 10.0 mmol/L) should be a goal and hypoglycemia must be avoided. Negative ionotropic agents should be discontinued. Bradyarrhythmias may require transvenous pacing. Recurrent ventricular tachycardia or rapid atrial fibrillation may require immediate treatment **(Chap. 241)**.

REPERFUSION-REVASCULARIZATION

Rapid revascularization of the infarct-related artery is the only evidence-based treatment strategy for mortality reduction in CS and forms the mainstay therapeutic intervention for CS due to MI (Fig. 298-2). In the SHOCK Trial 132 lives were saved per 1000 patients treated with early revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) compared with initial medical therapy. Outcome benefit correlates strongly with the time between symptom onset and reperfusion. In general, PCI with drug-eluting stents of the infarct-related artery is the preferred reperfusion strategy. Approximately 80% of CS patients present with multivessel coronary artery disease. The recent CULPRIT-SHOCK randomized trial showed that culprit lesion only PCI with possible staged revascularization led to a reduction in 30-day mortality or renal replacement therapy in comparison to immediate multivessel PCI. This reduction in the primary study endpoint was mainly driven by a 30-day mortality reduction. Currently, vascular access for diagnostic angiography and PIC via the radial artery is preferred when feasible over femoral arterial access due to its greater safety. CABG is currently performed in only 5% of cases mainly if coronary anatomy is not amenable to PCI.

VASOPRESSORS AND INOTROPES

Inotropic agents are theoretically appealing in CS treatment. However, current evidence is scarce. Vasoactive medications are often used in the management of patients with CS and all have important disadvantages, including increase in myocardial O_2 consumption, afterload, lethal arrhythmias, and possible myocardial cell death. As a consequence, catecholamines should be used in the lowest possible doses for the shortest possible time. Despite their frequent use, little clinical outcome data proves their benefit or is available

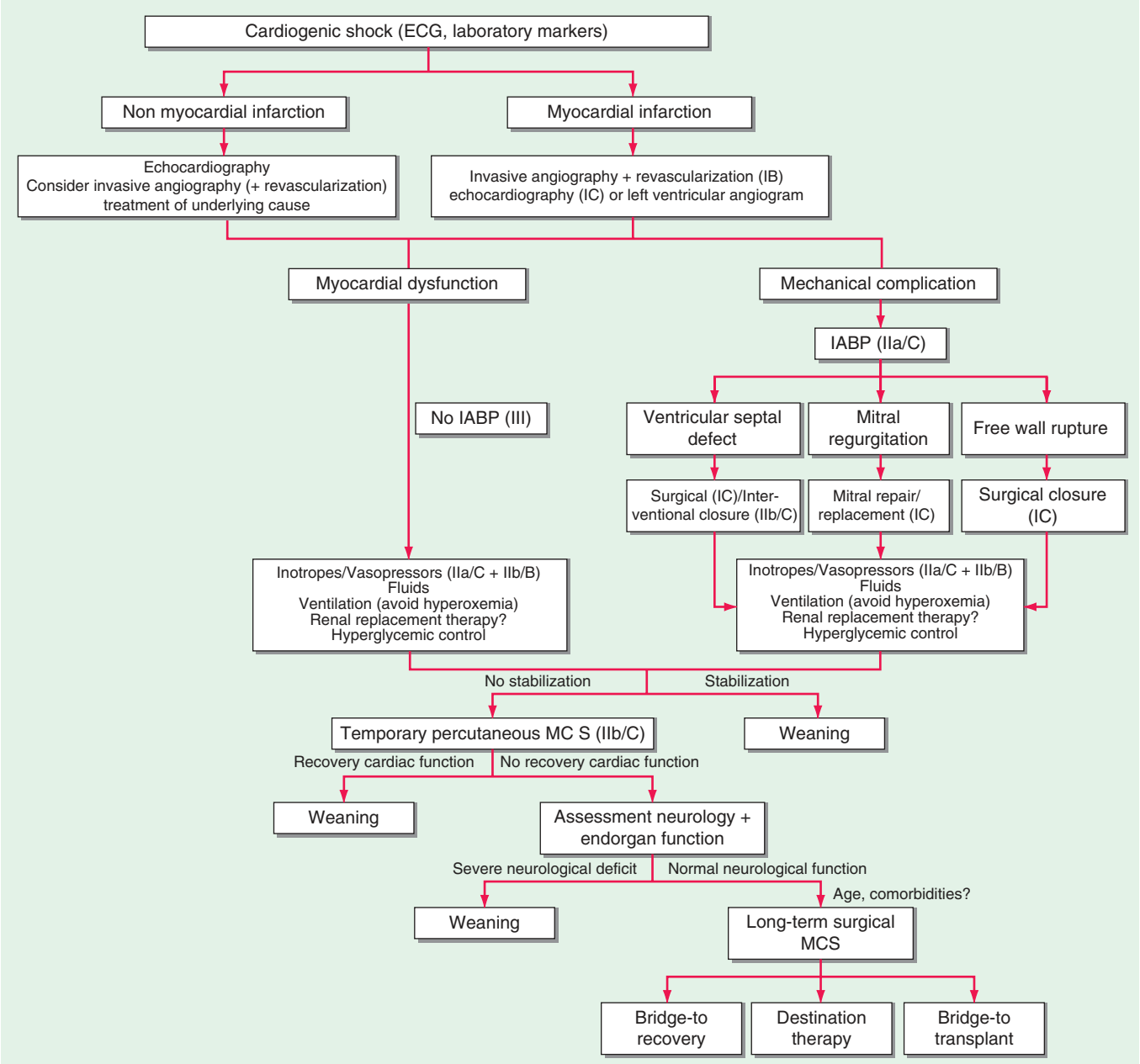

FIGURE 298-2 Emergency management of patients with cardiogenic shock. Treatment algorithm for patients with CS. The class of recommendation and level of evidence according to European Society of Cardiology guidelines is provided (see Further Reading citations Authors/Task Force members, S Windecker et al: Eur Heart J 35:2541, 2014, and P Ponikowski et al: Eur Heart J 37:2129, 2016). ECG, electrocardiogram; IABP, intraaortic balloon pump; MCS, mechanical circulatory support.

to guide the initial selection of vasoactive therapies in patients with CS. No vasopressor has been demonstrated to change outcome in large clinical trials. Norepinephrine is reasonable as the first line vasopressor based on randomized trials compared to dopamine. Norepinephrine was associated with fewer adverse events, including arrhythmias, compared to dopamine in a randomized trial of patients with several etiologies of circulatory shock and with improved survival in a pre-specified subgroup of CS patients. Norepinephrine dosing is usually begun at 2 to 4 μg/min and titrated upward based on blood pressure.

Dopamine's hemodynamic effects vary depending upon dose and there is interpatient variability in responses. Low doses stimulate renal dopaminergic receptors and with increasing dosage there is stimulation of first β-adrenergic receptors and then α adrenergic receptors. Dopamine should be avoided as first-line therapy for MI with CS based on hemodynamic and proarrhythmogenic effects.

Dobutamine is a synthetic sympathomimetic amine with positive inotropic action and minimal positive chronotropic activity at low doses (2.5 μg/kg per min), but moderate chronotropic activity at higher doses. Its vasodilating activity often precludes its use when a vasoconstrictor effect is required. Levosimendan may also be appealing despite a lack of randomized data, but was not beneficial for organ dysfunction in sepsis.

MECHANICAL CIRCULATORY SUPPORT

The most commonly used mechanical circulatory support (MCS) device has been the intraaortic balloon pump (IABP), which is inserted into the aorta via the femoral artery and provides passive hemodynamic support. However, routine IABP use in conjunction with early revascularization (predominantly with PCI) did not reduce either 30-day or 12-month mortality in the IABP-SHOCK II trial. IABP also had no benefit on secondary endpoints (arterial lactate, catecholamine doses, renal function, or intensive care severity of illness unit scores). IABP is no longer recommended for CS with LV failure.

Active MCS devices to support the left, right, or both ventricles can be placed percutaneously or surgically. Temporary percutaneous

TABLE 298-2 Utility of the Echocardiogram in Cardiogenic Shock or Pulmonary Edema

CLINICAL QUESTION	INFORMATION
Ventricular Function	Predominantly left, right or biventricular involvement
Etiology	**Acute Myocardial Infarction** • Extent of infarction/myocardium in jeopardy • Status of the non-culprit infarct zone • Presence of mechanical complications **Acute/Chronic Valvular Insufficiency/ Obstruction/Stenosis (Native/Prosthetic)** • Etiology: endocarditis; degenerative valve disease • Location and hemodynamic consequences **Dynamic Left Ventricular Tract Obstruction** **Takotsubo Syndrome** **Cardiac Tamponade** • Circumferential versus localized effusion • Route of pericardiocentesis if indicated **Acute Pulmonary Embolism** • Right ventricular function • Pulmonary artery pressure • Presence of clot in transition/Patent foramen ovale **Acute Aortic Syndrome** • Nature and extent of dissection • Degree of aortic insufficiency • Presence of pericardial effusion
Hemodynamics	Volume assessment by inferior vena cava diameter and inspiratory collapse Estimated pulmonary artery systolic pressure Estimated left atrial pressure
Therapeutic guidance	Guide vasoactive support Monitor response to therapy Mechanical circulatory support decisions Catheter position and guidance
Pulmonary	Pleural effusion Lung edema Pneumothorax Pulmonary infiltration

MCS can be used as bridge to recovery, to surgically implanted devices, to heart transplantation, or as a temporizing measure when the neurologic status is uncertain. Percutaneous MCS including the TandemHeart, Impella devices, and also venoarterial extracorporeal membrane oxygenation (VA-ECMO) have been used in patients not responding to standard treatment (catecholamines, fluids, and IABP) and also as a first-line treatment. Active percutaneous MCS results in better hemodynamic support compared to IABP. However, the appropriate role of MCS is uncertain as a positive impact on clinical outcomes or mortality has not yet been demonstrated in trials or metaanalyses.

Surgically implanted devices can support the circulation as bridging therapy for cardiac transplant candidates or as destination therapy (Chap. 255). Assist devices should be used selectively in suitable patients based on decisions by a multidisciplinary team with expertise in the selection, implantation, and management of MCS devices.

Prognosis The expected death rates for patients with MI complicated by CS range widely based on age, severity of hemodynamic abnormalities, severity of clinical hypoperfusion (arterial lactate, renal function), and performance of early revascularization. The recently introduced IABP-SHOCK II score predicts prognosis based on six readily available variables: age >73 years; prior stroke; glucose at admission >10.6 mmol/L (191 mg/dL); creatinine at admission >132.6 μmol/L (1.5 mg/dL); thrombolysis in myocardial infarction flow grade after PCI <3; and arterial blood lactate at admission >5 mmol/L. It also may help guide treatment strategies.

SHOCK SECONDARY TO RIGHT VENTRICULAR INFARCTION

Persistent CS due to predominant RV failure accounts for only 5% of CS complicating MI. It often results from proximal right coronary artery occlusion. The salient features are relatively high right atrial pressures, RV dilation and dysfunction, and only mildly or moderately depressed LV function. High right-sided pressures may be absent without volume loading. However, CS often has overlap combinations of both RV and LV ischemia, given a shared septum and the effect of ventricular interdependence on RV function. Management of isolated RV CS includes fluid administration to optimize right atrial pressure (10–15 mmHg); avoidance of excess fluids, which shift the interventricular septum into the LV; catecholamines; early reestablishment of infarct-artery flow; and MCS.

TABLE 298-3 Hemodynamic Patterns[a]

	RA, mmHg	RVS, mmHg	RVD, mmHg	PAS, mmHg	PAD, mmHg	PCW, mmHg	CI, (L/min)/m²	SVR, (dyn · s)/cm⁵
Normal values	<6	<25	0–12	<25	0–12	<6–12	≥2.5	(800–1600)
MI without pulmonary edema[b]	–	–	–	–	–	~13 (5–18)	~2.7 (2.2–4.3)	–
Pulmonary edema	↔↑	↔↑	↔↑	↑	↑	↑	↔↓	↑
Cardiogenic shock								
LV failure	↔↑	↔↑	↔↑	↔↑	↑	↑	↓	↔↑
RV failure[c]	↑	↓↔↑[d]	↑	↓↔↑[d]	↔↓↑[d]	↓↔↑[d]	↓	↑
Cardiac tamponade	↑	↔↑	↑	↔↑	↔↑	↔↑	↓	↑
Acute mitral regurgitation	↔↑	↑	↔↑	↑	↑	↑	↔↓	↔↑
Ventricular septal rupture	↑	↔↑	↑	↔↑	↔↑	↔↑	↑PBF ↓SBF	↔↑
Hypovolemic shock	↓	↔↓	↔↓	↓	↓	↓	↓	↑
Septic shock	↓	↔↓	↔↓	↓	↓	↓	↑	↓

[a]There is significant patient-to-patient variation. Pressure may be normalized if cardiac output is low. [b]Forrester et al classified nonreperfused MI patients into four hemodynamic subsets. (From JS Forrester et al: N Engl J Med 295:1356, 1976.) PCW pressure and CI in clinically stable subset 1 patients are shown. Values in parentheses represent range. [c]"Isolated" or predominant RV failure. [d]PCW and pulmonary artery pressures may rise in RV failure after volume loading due to RV dilation and right-to-left shift of the interventricular septum, resulting in impaired LV filling. When biventricular failure is present, the patterns are similar to those shown for LV failure.

Abbreviations: CI, cardiac index; MI, myocardial infarction; P/SBF, pulmonary/systemic blood flow; PAS/D, pulmonary artery systolic/diastolic; PCW, pulmonary capillary wedge; RA, right atrium; RVS/D, right ventricular systolic/diastolic; SVR, systemic vascular resistance.

Source: Table prepared with the assistance of Krishnan Ramanathan, MD.

MITRAL REGURGITATION

(See also Chap. 269) Acute severe MR due to papillary muscle dysfunction and/or rupture may complicate MI and result in CS and/or pulmonary edema. This complication most often occurs on the first day, with a second peak several days later. The diagnosis is confirmed by echocardiography (Table 298-2). Afterload reduction with IABP and, if tolerated, vasodilators to reduce pulmonary edema, is recommended as a bridge to surgery or interventional treatment. Mitral valve repair or reconstruction is the definitive therapy and should be performed early in the course in suitable candidates. Other options include percutaneous edge-to-edge repair which has been successful in small case series.

VENTRICULAR SEPTAL RUPTURE

(See also Chap. 269) VSR complicating MI is a relatively rare event associated with very high mortality if CS is present (>80%). The incidence of infarct-related VSR without reperfusion was 1–2% but has decreased to 0.2% in the era of reperfusion. VSR occurs a median of 24 h after infarction, but may occur up to 2 weeks later. Echocardiography demonstrates shunting of blood from the left to the right ventricle and may visualize the opening in the interventricular septum. Current guidelines recommend immediate surgical VSR closure, irrespective of the patient's hemodynamic status, to avoid further hemodynamic deterioration. IABP support as bridge to surgery is recommended. Given high mortality, suboptimal surgical results and many patients not being eligible for surgery, interventional percutaneous VSR umbrella device closure has been developed. Results of interventional VSR closure suggest a similar outcome as surgery. How to close the VSR should be based on a heart team decision.

FREE WALL RUPTURE

Myocardial rupture is a dramatic complication of MI that is most likely to occur during the first week after the onset of symptoms. The clinical presentation typically is a sudden loss of pulse, blood pressure, and consciousness but sinus rhythm on ECG (pulseless electrical activity) due to cardiac tamponade (Chap. 265). Free wall rupture may also result in CS due to subacute tamponade when the pericardium temporarily seals the rupture sites. Definitive surgical repair is required.

ACUTE FULMINANT MYOCARDITIS

(See also Chap. 254) Myocarditis can mimic acute MI with ST abnormalities or bundle branch block on the ECG and marked elevation of cardiac markers. Acute myocarditis causes CS in a small proportion of cases. These patients are typically younger than those with CS due to acute MI and often do not have typical ischemic chest pain. Echocardiography usually shows global LV dysfunction. Initial management is the same as for CS complicating acute MI but does not involve revascularization. Endomyocardial biopsy is recommended to determine the diagnosis and need for immunosuppressives for entities such as giant cell myocarditis. Refractory CS can be managed with MCS.

PULMONARY EDEMA

The etiologies and pathophysiology of pulmonary edema are discussed in Chap. 33.

Diagnosis Acute pulmonary edema usually presents with the rapid onset of dyspnea at rest, tachypnea, tachycardia, and severe hypoxemia. Crackles and wheezing due to alveolar flooding and airway compression from peribronchial cuffing may be audible. Release of endogenous catecholamines often causes hypertension.

It is often difficult to distinguish between cardiogenic and noncardiogenic causes of acute pulmonary edema. *Echocardiography* may identify systolic and diastolic ventricular dysfunction and valvular lesions. Electrocardiographic ST elevation and evolving Q waves are usually diagnostic of acute MI and should prompt immediate institution of MI protocols and coronary artery revascularization therapy (Chap. 269). Brain natriuretic peptide levels, when substantially elevated, support heart failure as the etiology of acute dyspnea with pulmonary edema (Chap. 252).

The use of a *Swan-Ganz catheter* permits measurement of pulmonary capillary wedge pressure (PCWP) and helps differentiate high-pressure (cardiogenic) from normal-pressure (non-cardiogenic) causes of pulmonary edema. PAC is indicated when the etiology of the pulmonary edema is uncertain, when edema is refractory to therapy, or when it is accompanied by hypotension. Data derived from use of a catheter often alter the treatment plan, but no impact on mortality rates has been demonstrated.

TREATMENT

Pulmonary Edema

The treatment of pulmonary edema depends on the specific etiology. As an acute, life-threatening condition, a number of measures must be applied immediately to support the circulation, gas exchange, and lung mechanics. Simultaneously, conditions that frequently complicate pulmonary edema, such as infection, acidemia, anemia, and acute kidney dysfunction, must be corrected.

SUPPORT OF OXYGENATION AND VENTILATION

Patients with acute cardiogenic pulmonary edema generally have an identifiable cause of acute LV failure—such as arrhythmia, ischemia/infarction, or myocardial decompensation (Chap. 252)—that may be rapidly treated, with improvement in gas exchange. In contrast, non-cardiogenic edema usually resolves much less quickly, and most patients require mechanical ventilation.

Oxygen Therapy Support of oxygenation is essential to ensure adequate O_2 delivery to peripheral tissues, including the heart. Generally the goal is O_2 saturation of ≥92%, but very high saturation (>98%) may be detrimental.

Positive-Pressure Ventilation Pulmonary edema increases the work of breathing and the O_2 requirements of this work, imposing a significant physiologic stress on the heart. When oxygenation or ventilation is not adequate in spite of supplemental O_2, positive-pressure ventilation by face or nasal mask or by endotracheal intubation should be initiated. Noninvasive ventilation (Chap. 295) can rest the respiratory muscles, improve oxygenation and cardiac function, and reduce the need for intubation. In refractory cases, mechanical ventilation can relieve the work of breathing more completely than can noninvasive ventilation. Mechanical ventilation with positive end-expiratory pressure can have multiple beneficial effects on pulmonary edema, as it: (1) decreases both preload and afterload, thereby improving cardiac function; (2) redistributes lung water from the intraalveolar to the extraalveolar space, where the fluid interferes less with gas exchange; and (3) increases lung volume to avoid atelectasis.

Renal Replacement Therapy For pulmonary edema patients with refractory volume overload, metabolic acidosis (pH <7.15–7.25), hypoxemia, and/or persistent hyperkalemia, renal replacement therapy should be considered. For patients who are hypotensive or requiring ionotropic support, continuous renal replacement therapy usually is better tolerated than intermittent hemodialysis.

REDUCTION OF PRELOAD

In most forms of pulmonary edema, the quantity of extravascular lung water is determined by a combination of the pulmonary capillary pressures (PCWP), the pulmonary vascular permeability, and the intravascular volume status.

Diuretics The "loop diuretics" furosemide, bumetanide, and torasemide are effective in most forms of pulmonary edema, even in the presence of hypoalbuminemia, hyponatremia, or hypochloremia. Furosemide is also a venodilator that rapidly reduces preload before any diuresis occurs, and is the diuretic of choice. The initial dose of furosemide should be ≤0.5 mg/kg, but a higher dose (1 mg/kg) is required in patients with renal insufficiency, chronic diuretic use, or hypervolemia or after failure of a lower dose. Combinations of

diuretics and/or continuous infusion are helpful to achieve the desired degree of diuresis in selected patients.

Nitrates Nitroglycerin and isosorbide dinitrate act predominantly as venodilators but have coronary vasodilating properties as well. Their onset is rapid and they are effectively administered by a variety of routes. Sublingual nitroglycerin (0.4 mg × 3 every 5 min) is first-line therapy for acute cardiogenic pulmonary edema. If pulmonary edema persists in the absence of hypotension, sublingual may be followed by IV nitroglycerin, commencing at 5–10 µg/min. IV nitroprusside (0.1–5 µg/kg per min) is a potent venous and arterial vasodilator. It is useful for patients with pulmonary edema and hypertension, but is not recommended in states of reduced coronary artery perfusion. It requires close monitoring and titration using an arterial catheter for continuous blood pressure measurement.

Morphine Given in 2- to 4-mg IV boluses, morphine is a transient venodilator that reduces preload while relieving dyspnea and anxiety. These effects can diminish stress, catecholamine levels, tachycardia, and ventricular afterload in patients with pulmonary edema and systemic hypertension. However, some registry trials showed increased mortality by use of morphine.

Angiotensin-Converting Enzyme (ACE) Inhibitors ACE inhibitors reduce both afterload and preload and are recommended for hypertensive patients. A low dose of a short-acting agent may be initiated and followed by increasing oral doses. In acute MI with heart failure, ACE inhibitors reduce short- and long-term mortality rates. The optimal starting point of ACE inhibitors has not been tested so far.

Other Preload-Reducing Agents IV recombinant brain natriuretic peptide (nesiritide) is a potent vasodilator with diuretic properties and is effective in the treatment of cardiogenic pulmonary edema. It should be reserved for refractory patients and is not recommended in the setting of ischemia or MI.

Physical Methods In nonhypotensive patients, venous return can be reduced by use of the sitting position with the legs dangling along the side of the bed.

Inotropic and Inodilator Drugs The sympathomimetic amines dopamine and dobutamine (see above) are potent inotropic agents. The bipyridine phosphodiesterase-3 inhibitors (inodilators), such as milrinone (50 µg/kg followed by 0.25–0.75 µg/kg per min), stimulate myocardial contractility while promoting peripheral and pulmonary vasodilation. Inodilators may be helpful in selected patients with cardiogenic pulmonary edema and severe LV dysfunction, but there is little published clinical data.

Digitalis Glycosides Once a mainstay of treatment because of their positive inotropic action **(Chap. 252)**, digitalis glycosides are rarely used at present. However, they may be useful for control of ventricular rate in patients with rapid ventricular response to atrial fibrillation or flutter and LV dysfunction with pulmonary edema, because they do not have the negative inotropic effects of other drugs that inhibit atrioventricular nodal conduction.

Intraaortic Balloon Counterpulsation IABP **(Chap. 255)** may be helpful in rare instances of acute MR from infective endocarditis, but is not typically used for pulmonary edema with CS.

Treatment of Tachyarrhythmias and Atrioventricular Resynchronization **(See also Chap. 247)** Sinus tachycardia or atrial fibrillation can result from elevated left atrial pressure and sympathetic stimulation. Tachycardia itself can limit LV filling time and raise left atrial pressure further. Although relief of pulmonary congestion will slow the sinus rate or ventricular response in atrial fibrillation, a primary tachyarrhythmia may require cardioversion. In patients with reduced LV function and without atrial contraction or with lack of synchronized atrioventricular contraction, placement of an atrioventricular sequential pacemaker should be considered **(Chap. 239)**.

Reduction in Pulmonary Vascular Permeability At present, no clinical therapies have been demonstrated as clinically effective to reduce the "leakiness" of the pulmonary capillaries.

Stimulation of Alveolar Fluid Clearance A variety of drugs and cellular therapies can stimulate alveolar epithelial ion transport and upregulate the clearance of alveolar solute and water, but this strategy has not been proven beneficial in clinical trials thus far.

SPECIAL CONSIDERATIONS

Risk of Iatrogenic Cardiogenic Shock In the treatment of pulmonary edema, vasodilators lower blood pressure, and their use, particularly in combination, may lead to hypotension, coronary artery hypoperfusion, and shock (Fig. 298-1). In general, patients with a *hypertensive* response to pulmonary edema tolerate and benefit from these medications. In normotensive patients, low doses of single agents should be instituted sequentially, as needed.

Acute Coronary Syndromes **(See also Chap. 269)** Acute STEMI complicated by pulmonary edema is associated with in-hospital mortality rates of 20–40%. After immediate stabilization, coronary artery blood flow must be reestablished rapidly. Early primary PCI is the method of choice; alternatively, a fibrinolytic agent should be administered. Early coronary angiography and revascularization by PCI or CABG also are indicated for patients with non-ST elevation acute coronary syndrome.

Extracorporeal Membrane Oxygenation (ECMO) For patients with acute, severe non-cardiogenic edema with a potential rapidly reversible cause, ECMO may be considered in highly selected patients as a temporizing supportive measure to achieve adequate gas exchange with current survival to discharge rates of 50–60%. Usually venovenous ECMO is used in this setting. ECMO can function as a bridge to transplantation or other interventions.

Unusual Types of Edema Specific etiologies of pulmonary edema may require particular therapy. Re-expansion pulmonary edema can develop after removal of long-standing pleural space air or fluid. These patients may develop hypotension or oliguria with pulmonary edema resulting from rapid fluid shifts into the lung. Diuretics and preload reduction are contraindicated, and intravascular volume repletion often is needed while supporting oxygenation and gas exchange.

High-altitude pulmonary edema often can be prevented by use of dexamethasone, calcium channel–blocking drugs, or long-acting inhaled β_2-adrenergic agonists. Treatment includes descent from altitude, bed rest, oxygen, and, if feasible, inhaled nitric oxide; nifedipine may also be effective.

For pulmonary edema resulting from upper airway obstruction, recognition of the obstructing cause is key, because treatment then is to relieve or bypass the obstruction.

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299 Cardiovascular Collapse, Cardiac Arrest, and Sudden Cardiac Death

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OVERVIEW AND DEFINITIONS (SEE TABLE 299-1)

Cardiovascular collapse is severe hypotension from acute dysfunction of the heart or peripheral vasculature causing hypotension with resulting cerebral hypoperfusion and loss of consciousness that can be the result of a cardiac arrhythmia, severe myocardial or valvular dysfunction, loss of vascular tone, and/or acute disruption of venous return. When an effective circulation is restored spontaneously, patients present with syncope (see Chap. 18). If spontaneous resolution does not occur, then cardiac arrest occurs, ultimately resulting in death if resuscitation attempts are unsuccessful or not initiated. Underlying etiologies for cardiovascular collapse include benign conditions such as vasovagal syncope, but also life-threatening conditions, including: ventricular tachyarrhythmias, severe bradycardia, severely depressed myocardial contractility, as with massive acute myocardial infarction (MI) or pulmonary embolus, and other catastrophic events interfering with cardiac function such as myocardial rupture with cardiac tamponade or papillary muscle rupture with torrential mitral regurgitation.

Sudden cardiac arrest (SCA) refers to an *abrupt* loss of cardiac function resulting in complete cardiovascular collapse due either to an acute life-threatening cardiac arrhythmia or abrupt loss of myocardial pump function that requires emergency medical intervention for restoration of effective circulation. Most SCAs occur outside the hospital, and fewer than 10% of these victims survive to be discharged from the hospital despite undergoing attempted resuscitation by emergency medical services (EMS). For those that die prior to hospital admission, a cardiovascular cause for the arrest is often presumed based upon the absence of evidence for a traumatic or other non-cardiac cause at the time of the arrest. If the patient does not survive an SCA, the death is classified as a sudden cardiac death (SCD). Deaths that occur during hospitalization or within 30 days after resuscitated cardiac arrest are usually counted as SCDs in epidemiologic studies.

SCD also includes a broader category of unexplained rapid deaths thought to be due to cardiac causes where resuscitation was not attempted. In epidemiologic studies, SCD is usually defined as an unexpected death without obvious extra-cardiac cause that occurs in association with a witnessed rapid collapse or within 1 h of the onset of symptoms. This definition is based on the presumption that rapid deaths are often due to an arrhythmia, an assumption that cannot always be validated. Approximately half of all SCDs are not witnessed, and in the United States, few deaths undergo autopsies, and non-cardiac conditions that evolve rapidly such as acute cerebral hemorrhage, aortic rupture, and pulmonary embolism cannot be excluded without an autopsy. Therefore, definitive information necessary to establish the cause of death is usually not available. In unwitnessed cases, the definition is often further expanded to include unexpected deaths where the subject was documented to be well when last observed within the preceding 24 h. This expanded definition further decreases the certainty that the death was due to an arrhythmia or cardiac causes. The majority of countries, including the United States, do not have national surveillance systems or reporting requirements for SCD; thus the true incidence and frequency of SCD and its different mechanisms can only be estimated.

EPIDEMIOLOGY

DEMOGRAPHICS

SCA and SCD are major public health problems that account for 15% of all deaths and comprise 50% of all cardiac deaths. In the United States alone, there are an estimated 350,000 EMS-attended out-of-hospital cardiac arrests and 210,000 SCDs in the adult population. The estimated societal burden of premature death due to SCD is 2 million years of potential life lost for men and 1.3 million years of potential life lost for women, which is greater than most other leading causes of death. Although cardiac pathology, particularly coronary heart disease (CHD), underlies the majority of SCD, up to two-thirds of all SCD occur as the first clinical expression of previously undiagnosed heart disease. SCD rates have declined but not as steeply as rates for CHD in general. Age, gender, race, and geographic region all influence the incidence of SCD. Rates of out-of-hospital cardiac arrest are lower in Asia (52.5 per 100,000 person-years) than Europe (86.4 per 100,000 person-years), North America (98.1 per 100,000 person-years), or Australia (111.9 per 100,000 person-years); and also vary within geographic regions of the United States. SCD is rare in individuals of younger than 35 years of age (1–3 per 100,000 per year), and increases markedly with age as the incidence of coronary artery disease (CAD), heart failure (HF), and other predisposing conditions also increase. Although absolute SCD

TABLE 299-1 Distinction between Cardiovascular Collapse, Cardiac Arrest, and Death

TERM	DEFINITION	QUALIFIERS	MECHANISMS
Cardiovascular collapse	Sudden loss of effective circulation due to cardiac and/or peripheral vascular factors that may reverse spontaneously (e.g., neurocardiogenic syncope, vasovagal syncope) or require interventions (e.g., cardiac arrest).	Broad term that includes cardiac arrest and transient events that characteristically revert spontaneously presenting as syncope.	Same as "Cardiac Arrest," plus vasodepressor syncope or other causes of transient loss of blood flow.
Cardiac arrest	Abrupt cessation of cardiac function resulting in loss of effective circulation which may be reversible by prompt emergency medical intervention, but will lead to death in its absence.	Rare spontaneous reversions; likelihood of successful intervention relates to mechanism of arrest, clinical setting, availability of emergency medical services, and prompt return of circulation.	Ventricular fibrillation, ventricular tachycardia, asystole, bradycardia, pulseless electrical activity, noncardiac mechanical factors (e.g., pulmonary embolism).
Sudden cardiac death	Sudden unexpected death attributed to cardiac arrest, which if witnessed occurs within one hour of symptom onset.	In unwitnessed cases, the definition is often expanded to include unexpected deaths where the subject was documented to be well within the preceding 24 h.	Same as Cardiac Arrest.

Source: Modified from RJ Myerburg, A Castellanos: Cardiovascular collapse, cardiac arrest, and sudden cardiac death, in *Harrison's Principles of Internal Medicine*, 19th ed, DL Kasper et al (eds). New York, McGraw-Hill Education, 2015, pp 1764–1771, Table 327-1.

rates increase with age, the proportion of deaths that are due to SCD decreases markedly as other causes of death increase.

Women have a lower incidence of SCD and SCA than men, and women are more likely to present with pulseless electrical activity (PEA) and to have their SCD occur at home as compared to men. Possibly related to these factors, the SCD rate has not declined as much for younger women compared to men in recent years. Black as opposed to white Americans have higher rates of SCD, are more likely to have unwitnessed arrests, to be found with PEA, and have worse rates of survival. Socioeconomic disparities, with resuscitation being less likely in low income neighborhoods, is likely a contributing factor, but does not appear to account for the entirety of the elevated SCD rate in blacks. Alternatively, individuals of Hispanic ethnicity appear to have lower rates of SCD, despite having a higher prevalence of cardiac risk factors. It also appears that the incidence of SCD may be relatively low among Asian populations as well, both within the United States and globally. These gender and racial differences in SCD/SCA incidence and survival are poorly understood and warrant further research.

RISK FACTORS (SEE FIG. 299-1)

The presence of overt structural heart disease and/or a certain types of inherited arrhythmia syndromes markedly elevates SCD risk (see Chaps. 249 and 250). Preexisting CHD and HF are the most prevalent predisposing cardiac conditions and are associated with four- to tenfold increases in SCD risk. Correspondingly, SCD shares many of the same risk factors with CHD and HF, including: hypertension, diabetes, hypercholesterolemia, obesity, and smoking. Diabetes is a particularly strong risk factor for SCD even in patients with established CHD. Hypertension and resultant left ventricular hypertrophy (LVH) appear to be particularly important markers of SCD risk in blacks, in whom the prevalence of these conditions is greater. Smoking markedly elevates risk, and smoking cessation lowers risk particularly among individuals who have not yet developed overt CHD. Serum cholesterol appears to be more strongly related to SCD at younger ages, and the benefits of cholesterol lowering on SCD incidence have not been firmly established. There also appears to be a genetic component to SCD risk that is distinct from that associated with other manifestations of atherosclerosis. A history of SCD among a first-degree relative is associated with an increased risk for SCD, and with the occurrence of ventricular fibrillation (VF) during acute MI, but is not associated with an increased risk for acute MI. These data suggest that genetic factors may predispose to fatal ventricular arrhythmia in the setting of ischemia, rather than to CHD in general.

Obstructive sleep apnea and seizure disorders are also associated with increased SCD risk, and the underlying mechanism is not clear, but may be due to hypoxia and/or suffocation-induced cardiac arrest. Atrial fibrillation also appears to be associated with an increased risk of SCD, which is partly, but not entirely, accounted for by its association with underlying heart disease. Patients with chronic kidney disease are also at higher SCD risk with annualized SCD rates approaching 5.5% in patients undergoing dialysis. Electrolyte shifts and LVH, which are common in this population, have been suggested to play a role. There are also potential dietary influences on SCD risk. Individuals with higher intakes of polyunsaturated fatty acids, particularly n-3 fatty acids, and other components of a Mediterranean-style diet have lower SCD risks in observational studies, possibly due to antiarrhythmic effects of dietary components. Low levels of alcohol intake may be beneficial, but heavy intake (>3 drinks/day) appears to elevate risk.

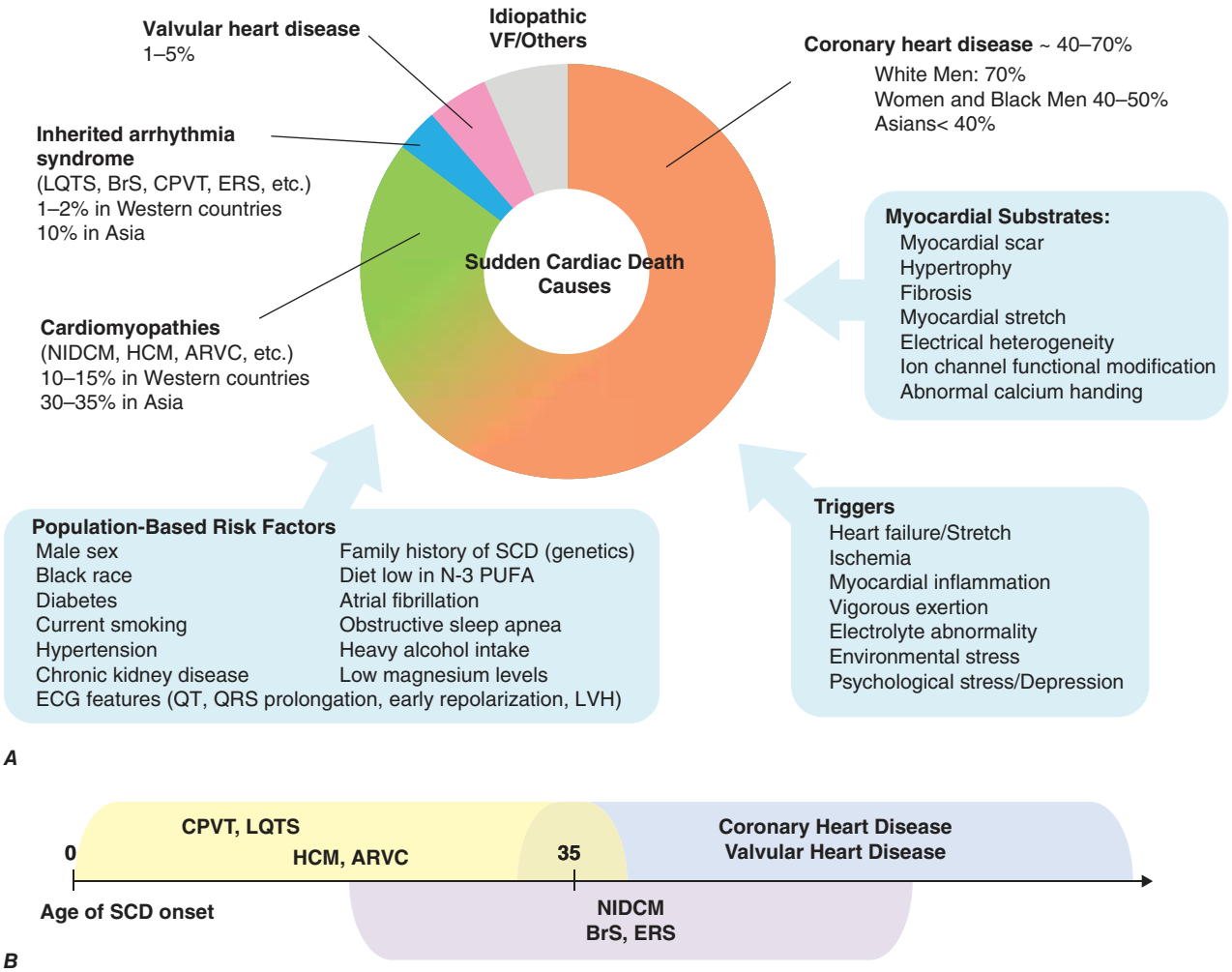


FIGURE 299-1 ***A.*** Proportionate causes, substrates, risk factors, and triggers of sudden cardiac death (SCD); and ***B.*** variation of causes by age of onset. *(Modified from M Hayashi et al: The spectrum of epidemiology underlying sudden cardiac death. Circ Res 116:1887, 2015.)*

PRECIPITATING FACTORS

SCD/SCA occurs with higher frequency at certain times, locations, and in association with certain activities and exposures. There are circadian variations in the incidence of SCD and cardiac arrest, with peaks in incidence in the morning hours and again in the later afternoon. There is also seasonal variability in SCD rates, which may be related to temperature and light exposure. Rates are highest during winter in the northern hemisphere and summer in the southern hemisphere. SCD rates also acutely peak during disasters such as earthquakes and terrorist attacks. SCA arrests are more likely to occur in certain locations as well, with notable clustering around train stations, airports, and other public places where there is significant population transit. SCD rates tend to be higher in urban areas and individuals that live near major roadways are at elevated SCD risk. There is also a well-recognized acute elevation in SCD risk that occurs during or shortly after bouts of vigorous exertion, and men appear to be more susceptible. Habitual exercise and training lowers this acute risk, but does not appear to eliminate it entirely. Exertion-associated SCDs are particularly tragic and highly publicized when they occur in highly trained athletes; however, the majority of such deaths actually occur in the general "non-athlete" population. The common thread amongst these precipitating factors is likely heightened autonomic tone, which can promote ischemia and has direct proarrhythmia and electrophysiologic actions that lower the threshold for VF.

CAUSES OF SUDDEN CARDIAC DEATH

UNDERLYING HEART DISEASE (FIG. 299-1)

Our understanding regarding the diseases which contribute to SCD is derived primarily from autopsy series and cardiac evaluations in cardiac arrest survivors, which are highly variable in level of detail. Despite the limitations of these data, it is generally accepted that SCD is most commonly associated with underlying CAD, although the proportion due to CAD varies markedly by age, race, and sex. It is estimated that ~70–75% of SCDs in white men are due to CAD, as compared to only 40–50% in women and blacks. The proportion of SCDs with underlying CAD may be even lower in Asian ethnicities. Recent data suggest that the proportion of SCDs with CAD may be declining in some parts of Europe (Fig. 299-2*A*) and the United States, and, at the same time, increasing in parts of Japan and other parts of Asia. Beyond CAD, non-ischemic cardiomyopathies (hypertrophic, dilated, and infiltrative) are the second most frequent cause of SCD in the United States and European countries. Other less common causes include valvular heart disease, myocarditis, myocardial hypertrophy (often from hypertension), and rare primary electrical heart diseases such as the long QT and Brugada syndrome. On average, 5–10% of SCA victims do not have a significant cardiac abnormality at the time of autopsy or after extensive premortem cardiac evaluation, and this also varies by gender and race. Before 35 years of age, atherosclerotic CAD accounts for a much smaller proportion of deaths, with hypertrophic cardiomyopathy (HCM), coronary artery anomalies, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and primary ion channelopathies accounting for a significant number of these deaths.

CARDIAC RHYTHMS AND SUDDEN DEATH

The initial rhythm found when EMS arrive at the scene of an out-of-hospital cardiac arrest is an important indication of the potential cause of the arrest and of the prognosis. In the early days of EMS systems, over half of victims were found in VF, giving rise to the hypothesis that ischmic VF or ventricular tachycardia (VT) degenerating to VF was the most common event. The proportion of cardiac arrests found in VF has decreased markedly since the 1970s, to only 20–25%, and

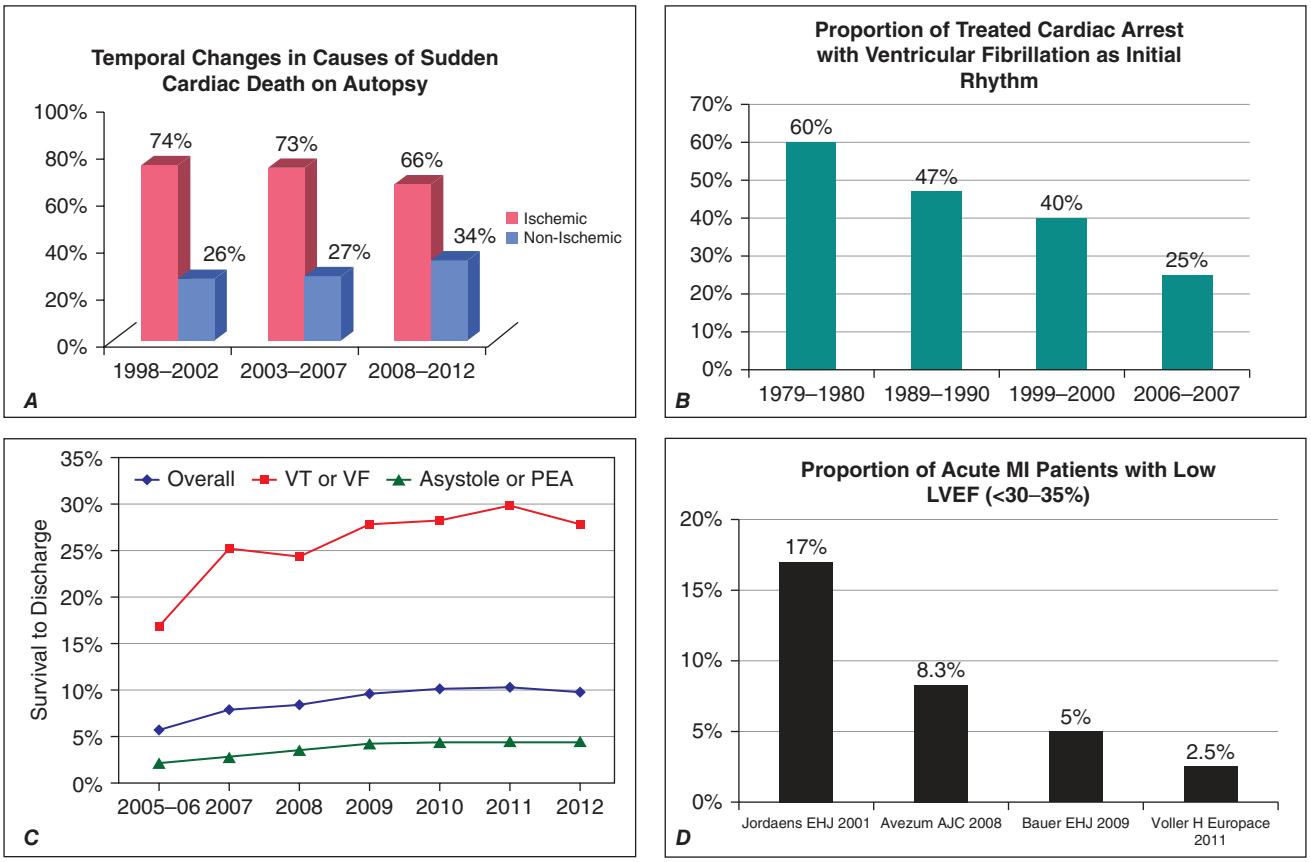


FIGURE 299-2 Changing epidemiology of sudden cardiac death/arrest. *A.* The proportion of sudden cardiac deaths attributable to coronary artery disease among individuals without a history of heart disease in Finland over time. Postmortem examinations are mandatory in Finland, which has the highest autopsy rate in Western World (*J Junttila et al: Circ Arrhythm Electrophysiol 2016*). ***B.*** Proportion of treated cardiac arrest with ventricular fibrillation as first recorded rhythm in Seattle, Washington, U.S. over time. *(Data from L Cobb et al: JAMA 288:3008, 2002, and G Nichol et al: JAMA 300:1423, 2008.)* ***C.*** Rates of overall survival and survival from shockable and nonshockable rhythms to hospital discharge among 70,027 out-of-hospital cardiac arrests across the United States from 2005 to 2012 (Cardiac Arrest to Enhance Survival Registry). (*From P Chan et al: Circulation 1876:1882, 2014.*) ***D.*** Proportion of myocardial infarction patients with left ventricular ejection fractions <30–35% in myocardial infarction registries over time.

PEA or asystole are now the most common scenarios (Fig. 299-2*B*). However, the vast majority of cardiac arrests are not monitored at the time of collapse, and since arrhythmias are inherently unstable once hemodynamic collapse occurs, the rhythm at the time of EMS arrival may not reflect the rhythm that initially precipitated the SCA. VF and primary bradycardias can degenerate quickly into asystole. VF as an initial rhythm still predominates in public locations or in other situations when there is a short time between collapse and arrival of EMS, suggesting that VF remains a common initial rhythm. However, there are also data to support an absolute decrease in VF incidence. Proposed explanations include decreases in underlying CHD incidence, increased used of beta blockers in CHD, and implantable cardioverter defibrillators (ICD) in high-risk patients. There also appears to be an increase of PEA incidence over the past several years, suggesting that the proportion of SCD due to abrupt hemodynamic collapse in the absence of preceding fatal arrhythmia may be increasing. Proposed explanations for these proportional changes in PEA versus VF include the aging of the population and the increased prevalence of end-stage cardiovascular disease and other severe comorbidities. These older, sicker patients may be more likely to have arrests in the home and to have acute precipitants leading to PEA (i.e., respiratory, metabolic, vascular), and/or be less likely to sustain VF up to the point of EMS arrival.

DISEASE SPECIFIC MECHANISMS

Coronary artery disease can cause SCD through a number of mechanisms (Table 299-2). The most common cause is acute MI or transient ischemia that leads to polymorphic VT and VF (see Chap. 250). Other primary mechanisms include severe bradyarrhythmias such as heart block with a slow escape rhythm, or PEA due to a massive MI or associated myocardial rupture. Areas of ventricular scar from prior infarcts increase the predisposition to reentrant VT, which often degenerates to VF. Once patients have suffered a MI, their risk of SCD elevates up to tenfold, with the highest absolute rates in the first 30 days after MI. The mechanisms underlying SCD vary at different time points after MI, with non-arrhythmic causes such as myocardial rupture and/or extensive reinfarction predominating early, within the first 1–2 months, and ischemic polymorphic VT and/or scar-related ventricular arrhythmias prevailing later. VT and sudden death can, and often does, occur years after an initial MI.

Cardiomyopathies and Other Forms of Structural Heart Disease Scar-mediated reentrant VT can also occur in a host of nonischemic cardiomyopathies in which replacement fibrosis and/or inflammatory ventricular infiltrates occur (Chap. 249). In congenital heart disease, surgical scars created during corrective surgery, such as those performed to correct ventricular septal defects in *tetralogy of Fallot*, can also serve as the substrate for ventricular reentry. Other common predisposing processes such as LVH, ventricular stretch due to fluid overload, and cardiomyocyte dysfunction can result in electrical heterogeneity and other electrophysiologic changes that predispose to ventricular arrhythmias, including ion channel alterations that prolong action potential duration, impair cellular calcium handling, and diminished cellular coupling. These processes occur in a wide variety of diseases associated with depressed ventricular function and/or hypertrophy, including CAD, valvular heart disease, myocarditis, and non-ischemic cardiomyopathies.

Absence of Structural Heart Disease In the absence of structural heart disease, VF can be due to an inherited ion channel abnormality, as in the long QT and Brugada syndromes (Chap. 250), rapid atrial fibrillation associated with the Wolff-Parkinson-White syndrome (Chap. 244), or drug toxicities, such as polymorphic VT due to drugs that prolong the QT interval (Chap. 250). PEA can result from pulmonary emboli, exsanguination, or the terminal phase of respiratory arrest.

MANAGEMENT OF CARDIAC ARREST

As the ability to predict SCA in the population is very limited, community approaches to reduce death focus on the rapid identification of victims and implementation of resuscitation measures by those

TABLE 299-2 Causes of Cardiovascular Collapse and Sudden Cardiac Arrest

CAUSE	PATHOPHYSIOLOGIC SUBSTRATE	RHYTHM PRESENTATION
Cardiac Causes		
Coronary artery disease Atherosclerotic, coronary spasm, congenital anomalies	Acute myocardial ischemia / Infarction, ventricular rupture, tamponade Ventricular scar from healed infarction	Polymorphic VT/VF Bradyarrhythmia Pulseless electrical activity Ventricular tachycardia Ventricular fibrillation
Cardiomyopathies Dilated, hypertrophic, ARVC, infiltrative disease, valvular disease with LV failure	Ventricular scar Ventricular hypertrophy Pump failure	Ventricular tachycardia Polymorphic VT/VF Pulseless electrical activity Bradyarrhythmia
Congenital heart disease (*tetralogy of Fallot*, VSD, others)	Ventricular scar from surgical repair Hypertrophy	Ventricular tachycardia Bradyarrhythmias Polymorphic VT/VF
Aortic stenosis	Obstruction to outflow Ventricular hypertrophy	Bradyarrhythmia Pulseless electrical activity Bradyarrhythmia Polymorphic VT/VF
Mitral valve prolapse/Mitral regurgitation	Pump failure Ventricular scar	Ventricular tachycardia Polymorphic VT/VF
Arrhythmia syndromes without structural heart disease: Genetic: Long QT Brugada CPVT Idiopathic VF, early repolarization Drug toxicities (acquired long QT, others) Electrolyte abnormalities (severe hypokalemia)	Abnormal cellular electrophysiology	Polymorphic VT/VF
Wolff-Parkinson-White Syndrome	Accessory atrioventricular connection	Preexcited AF/VF
Non-Cardiac Causes of Cardiovascular Collapse		
Pulmonary embolism		PEA
Stroke		PEA, bradyarrhythmia
Aortic dissection		PEA, VF
Exsanguination		PEA
Tension pneumothorax		PEA
Sepsis		PEA
Neurogenic		PEA, bradyarrhythmia
Drug overdose		PEA, bradyarrhythmia

Abbreviations: AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; LV, left ventricle; PEA, pulseless electrical activity; VF, ventricular fibrillation; VSD, ventricular septal defect; VT, ventricular tachycardia.

who first encounter the victim, most likely the lay public, who ideally summon EMS and initiate basic life support measures with chest compressions. The approach is codified in the "out-of-hospital chain of survival" which includes (1) initial evaluation and recognition of the SCA; (2) rapid initiation of cardiopulmonary resuscitation (CPR) with an emphasis on chest compressions; (3) defibrillation as quickly as possible usually with an automatic external defibrillation applied by the lay rescuer or EMT; (4) basic and advanced EMS; and (5) advanced life support and postcardiac arrest care. There have been major advances in each of these areas and survival rates to hospital discharge have increased from about 6% in 2005 to 10% in 2012, but much more progress is needed **(Fig. 299-2*C*)**.

The initial goal of resuscitation is to achieve the return of spontaneous circulation. Success is related to the time between collapse and initiation of resuscitation, decreasing markedly after 5 min, and the rhythm at the time of EMT arrival, being best for VT (25–30%), worse for VF and poor for PEA and asystole (<5%). Outcomes are also determined by the clinical state and comorbidities of the victim prior to the arrest, being worse for those with severe disease, such as cardiogenic shock, prior to arrest.

INITIAL EVALUATION AND INITIATION OF CPR

The rescuer should check for a response from the victim, shout for help, and call or ask someone else to call their local emergency number (e.g., 911), ideally on a cell phone that can be placed on speaker mode at the patient's side such that the responding dispatcher can provide instructions and queries to the rescuer. Consideration of aspiration or airway obstruction is important and if suspected a Heimlich maneuver may dislodge the obstructing body. A trained healthcare provider would also check for a pulse (taking no longer than 10 s so as not to delay initiation of chest compressions) and assess breathing. Gasping respirations and brief seizure activity are common during SCA and may be misinterpreted as breathing and responsiveness. Chest compressions should be initiated without delay and administered at a rate of 100–120/min depressing the sternum by 5 cm (2 in.) and allowing full chest recoil between compressions. Chest compressions generate forward cardiac output with sequential filling and emptying of the cardiac chambers, with competent valves maintaining forward direction of flow. Interruption of chest compressions should be minimized to reduce end organ ischemia. Ventilation may be administered with two breaths for every 30 compressions if a trained rescuer is present, but for lay rescuers without training, chest compressions alone ("hands only CPR") are more likely to be effectively applied and of similar benefit. If a second rescuer is present, they should be sent to seek out an automatic external defibrillator (AED), which are now widely available in many public areas.

RHYTHM-BASED MANAGEMENT (FIG. 299-3)

The rapidity with which defibrillation/cardioversion is achieved is an important predictor of outcome. A defibrillator, most often an AED, should be applied as soon as available. AEDs are easily used by lay rescuers and trained first responders, such as police officers and trained security guards. When the arrest is witnessed, the use of AEDs by lay responders can improve cardiac arrest survival rates. Once patches are applied to the chest, a brief pause in chest compressions is required to allow the AED to record the rhythm. An AED will advise a shock if the recorded rhythm meets criteria for VF or VT. Chest compressions are continued while the defibrillator is being charged. As soon as a diagnosis of VF or VT is established, a biphasic waveform shock of 150–200 J should be delivered. Chest compressions are resumed immediately and continue for 2 min until the next rhythm check. If VT/VF is still present, a second maximal energy shock is delivered. This sequence is continued until personnel to administer advanced life support are available, or return of spontaneous circulation is achieved. Electrocardiogram (ECG) rhythm strips produced by the AED should be retrieved, as the initial rhythm can be an important consideration in determining the cause of the arrest and to guide further therapy and evaluation if resuscitation is successful.

When advanced cardiac life support is available, an intravenous or intraosseous line is established for administration of medication and consideration given to placement of an advanced airway (endotracheal tube or supraglottic airway device). Epinephrine 1 mg every 3–5 min may be administered intravenously or intraosseously. If circulation is not restored or the patient is less than fully conscious despite return of circulation, confirmation that acidosis and hypoxia are adequately addressed should be assessed with arterial blood gas analysis. If metabolic acidosis persists after successful defibrillation and with adequate ventilation, 1 meq/kg $NaHCO_3$ may be administered.

The cardiac rhythm guides resuscitation when monitoring is available. VT is treated with external shocks synchronized to the QRS when VT is monomorphic, and asynchronous shocks for polymorphic VT or VF. If VT/VF recurs after one or more shocks, amiodarone 300 mg can be administered as a bolus via intravenous or intraosseous route in the hope that arrhythmia recurrence will be prevented after the next shock, followed by a 150 mg bolus if the arrhythmia recurs. If amiodarone fails, lidocaine can be administered.

Consideration of etiology should also guide therapy **(Chaps. 249 and 250)**. Commonly encountered causes of recurrent VT/VF may be due to ongoing myocardial ischemia or infarction that would benefit from emergent coronary angiography and revascularization, or QT prolongation causing the polymorphic VT *torsades des pointes* that may respond to administration of magnesium. Hyperkalemia should respond to administration of calcium, while other measures are implemented to reduce serum K.

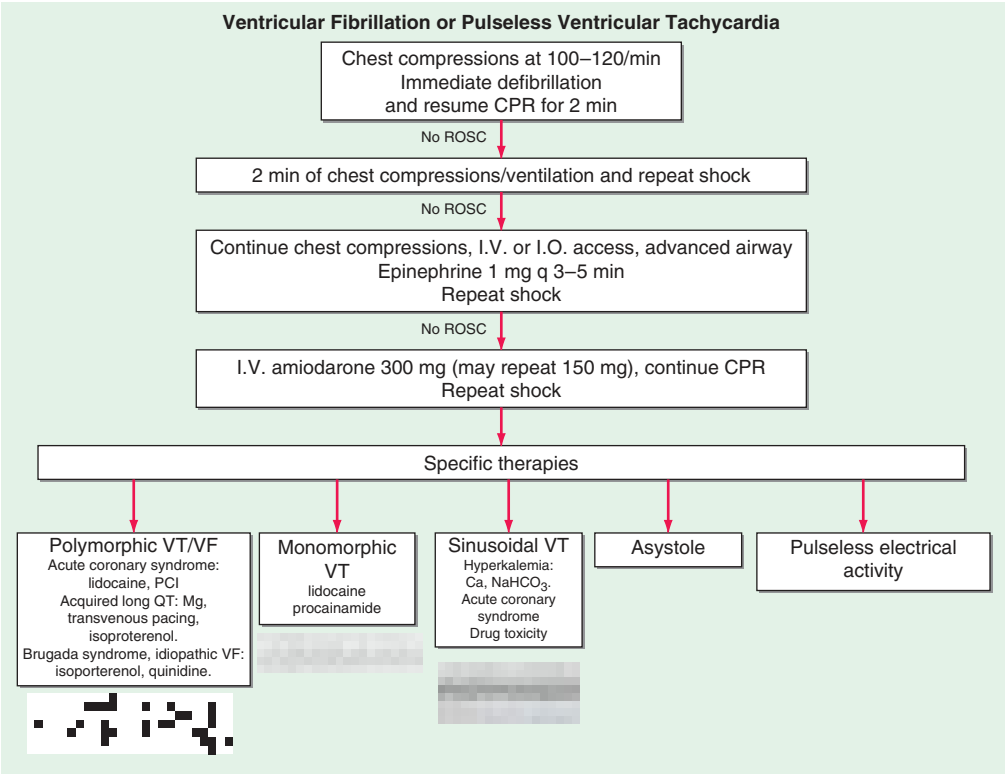
PEA/asystole should be managed with CPR, ventilation, and administration of epinephrine. Causes of PEA/asystole that require specific therapy should be considered including airway obstruction, hypoxia, hypovolemia, acidosis, hyperkalemia, hypothermia, toxins, cardiac tamponade, tension pneumothorax, pulmonary embolism, and MI. Naloxone should be administered if opiate overdose is suspected.

POSTCARDIAC ARREST ACUTE MANAGEMENT

Following restoration of effective circulation, the possibility of acute MI should be immediately assessed. More than 90% of patients who have ST elevation consistent with acute MI will be found to have a culprit coronary stenosis/occlusion and likely benefit from emergent coronary angiography with percutaneous angioplasty and stenting. Angiography should also be considered if an acute coronary syndrome is suspected, even if ST segment elevation is absent, as more than half of selected patients undergoing angiography for this concern are found to have a coronary lesion as a potential cause of the ACA. Decisions regarding which patients without ST segment elevation should undergo urgent angiography are complex and factors such as hemodynamic or electrical instability, evidence of ongoing ischemia, comorbidities, and overall prognosis are taken into consideration.

Hemodynamic instability is often present following resuscitation and further ischemic end organ damage is a major consideration. Optimizing ventilation with consideration of acidosis, hypoxemia, and electrolyte abnormalities is important. Maintaining systolic BP at >90 mmHg, mean BP >65 mmHg is desirable and may require administration of vasopressors and adjustment of volume status. Potentially treatable reversible causes including hyperkalemia, severe hypokalemia, and drug toxicity with QT prolongation causing *torsades des pointes* should be identified and treated **(Chap. 250)**.

After stable spontaneous circulation is achieved, brain injury due to ischemia and reperfusion is a major determinant of survival and accounts for over two-thirds of deaths. The probability of successful neurologic recovery decreases rapidly with time between collapse and restoration of circulation and is <30% at 5 min in the absence of bystander CPR. The time between collapse and restoration of circulation is generally imprecise and some patients have a period of hypotensive VT prior to complete collapse, such that a reported long period prior to arrival of rescuers does not always preclude a good recovery. Therapeutic hypothermia (targeted temperature management) has been shown to improve the likelihood of survival and neurologic recovery in patients who present with shockable (VT or VF) rhythms and is recommended for all cardiac arrest patients who remain comatose, regardless of presenting rhythm, who have lack of purposeful response to verbal commands following return of spontaneous circulation.



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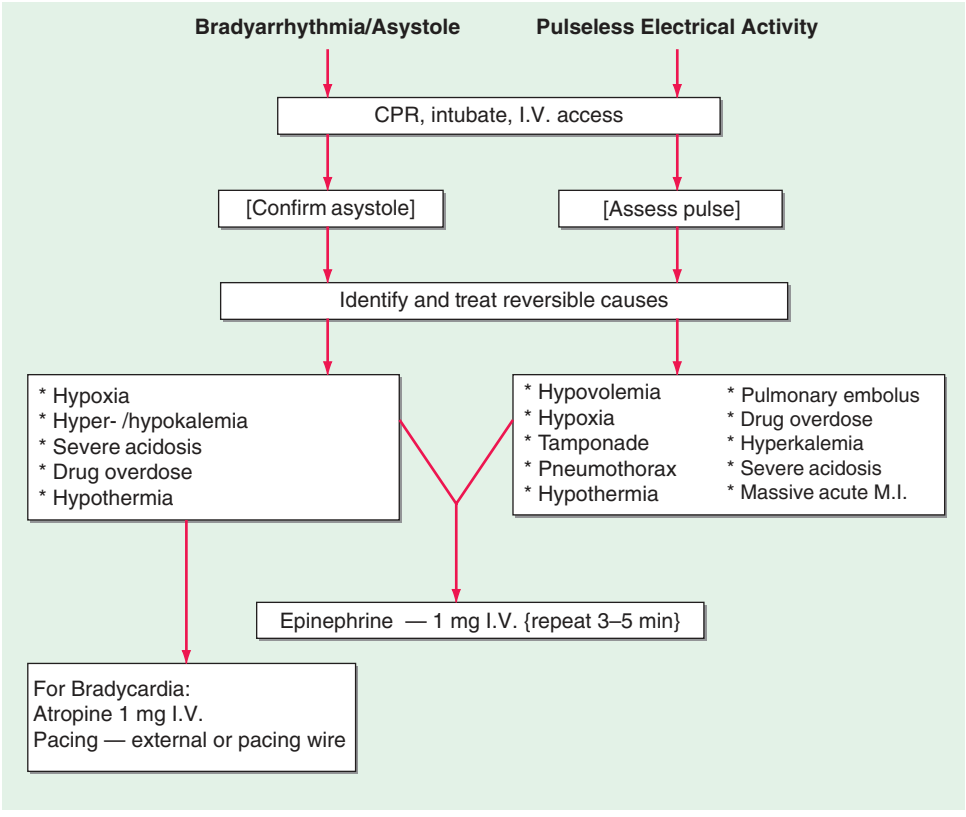

B

FIGURE 299-3 Algorithm for approach to cardiac arrest due to VT or VF (shockable rhythm). ***A.*** Chest compressions with ventilation and defibrillation or cardioversion should be initiated as soon as possible. Defibrillation should be repeated with minimal interruption of chest compressions. Once an intravenous or intraosseous access is established, administration of epinephrine defibrillation and amiodarone and defibrillation are performed. Further therapy can be guided by possible causes as suggested by the initial or recurrent cardiac rhythm as shown. i.v., intravenous; i.o., intraosseous; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention. ***B.*** Algorithm for approach to cardiac arrest due to bradyarrhythmias/asystole and pulseless electrical activity. Chest compressions with ventilation (and intubation) should be initiated as soon as possible, and i.v. access should be obtained. Once an intravenous or intraosseous access is established, administration of epinephrine is performed. At the same time, an investigation for potential reversible causes should be made and any such causes should be treated if present. For bradycardic rhythms, atropine 1 mg IV and external subcutaneous or transvenous pacing are also performed. Defibrillation should be repeated with minimal interruption of chest compressions. Once an intravenous or intraosseous access is established, administration of epinephrine is performed. Further therapy can be guided by possible causes. CPR, cardiopulmonary resuscitation; I.O., intraosseous; I.V., intravenous.

A constant target temperature of 32–36°C for at least 24 h is recommended. Shivering suppression with analgesics and sedatives may be needed. Induction of hypothermia should be started in-hospital, as no benefit was shown for implementation before hospital arrival, and administration of large volumes of cold saline for this purpose increased the risk of pulmonary edema. Brain injury is often accompanied by seizures and status epilepticus that may have further deleterious effects, warranting periodic or continuous electroencephalography (EEG) monitoring and treatment. A number of other therapies hoped to improve postarrest outcomes have been assessed, but have not been shown to be beneficial, including administration of corticosteroids, hemofiltration, and efforts to tightly control blood glucose.

Hypothermia and sedation preclude reliable prognostication for neurologic recovery. Functional neurologic assessment for neurologic recovery is generally deferred for at least 72 h after return to normothermia, typically 4–5 days after the cardiac arrest. Features that predict poor outcome include absence of pupillary reflex to light, status myoclonus, absence of EEG reactivity to external stimuli, and persistent burst suppression on EEG.

LONG-TERM MANAGEMENT AFTER SURVIVAL OF OUT-OF-HOSPITAL CARDIAC ARREST

For patients who survive cardiac arrest and have neurologic recovery, the likely underlying cause of the arrest guides further treatment. For arrests not due to an obvious non-cardiac cause, a full evaluation for the forms of structural heart disease outlined in Fig. 299-1 and Table 299-2 should be performed including an assessment for underlying CAD and ischemia as well as echocardiography and/or cardiac MRI to look for evidence of prior MI, valvular disease, nonischemic cardiomyopathies and to provide an assessment of left ventricular ejection fraction (LVEF). If the initial evaluation is not definitive or is suggestive of an inflammatory cardiomyopathy (i.e., sarcoidosis, myocarditis), a cardiac PET-scan and/or endomyocardial biopsy may also be performed. Patients without obvious structural abnormalities should undergo an evaluation for primary electrical disease (long-QT syndrome [LQTS], Brugada syndrome, early repolarization syndrome, or WPW). In cases where a heritable syndrome is suspected, further genetic evaluation should be considered. Diagnostic electrophysiology studies are warranted in selected patients to assess inducible arrhythmias, or perform provocative testing, such as with epinephrine challenge for LQTS, or sodium channel blocker (e.g., procainamide) challenge for Brugada syndrome.

Patients with shockable rhythms at arrest (VF and VT) that are not deemed to have been due to a transient reversible cause and have reasonable life expectancy should undergo insertion of an ICD for secondary prevention of SCA/SCD. Most of these patients will be found to have CAD. Patients with a VF arrest that occurs within the first 48 h of a documented acute MI generally do not require an ICD since they have a similar risk of sudden death over the next 5 years as infarct survivors who did not have a cardiac arrest. However, patients who have a large infarction with acutely depressed LV ejection fraction (e.g., <35%) have an increased risk for future development of life-threatening ventricular arrhythmias related to reentry in the infarct scar **(Chap. 247)**. The percentage of patients with such large infarcts has been declining due to improved treatment strategies for acute MI **(Fig. 299-2*D*)**. Implantation of an ICD early after MI in these patients does not, however, improve survival, in part because a significant number of sudden deaths in the first three months are due to recurrent myocardial ischemia or myocardial rupture, rather than arrhythmias. For patients with large infarcts a wearable defibrillator that will treat VT/VF if it occurs may be used, while left ventricular remodeling is taking place, followed by reevaluation of arrhythmia risk after the infarct is healed to determine if an ICD is warranted. Patients who experience VF in-hospital >48 h after MI or in the setting of myocardial ischemia without infarction may be at risk for recurrent VT/VF. These patients should be evaluated and optimally treated for ischemia. If there is evidence that clearly implicates ischemia immediately preceding the onset of VF without evidence of a prior MI, coronary revascularization may be adequate therapy. Others may warrant an ICD. When the cardiac arrest is due sustained monomorphic VT, a prior infarct scar is often present and the recurrence rate is significant regardless of whether the arrest occurred in association with elevated serum troponin. An ICD is usually warranted even if revascularization is also needed.

Patients who have cardiac arrest due to a treatable reversible cause, such as hyperkalemia, or drug toxicity with QT prolongation causing *torsades des pointes* **(Chap. 250)**, that can be adequately addressed and prevented by other means do not usually need an ICD. An ICD is usually recommended for cardiac arrest due to VT or VF without a clearly reversible cause, particularly when structural heart disease, such as hypertrophic or dilated cardiomyopathy, arrhythmogenic cardiomyopathy, cardiac sarcoidosis, or a cardiac syndrome associated with sudden death, including Brugada syndrome, or LQTS are present **(Chaps. 249 and 250)**. In patients with structural heart disease, it is important to recognize that life-threatening arrhythmias can be an indication of terminal, end-stage heart disease with minimal prospect for meaningful survival despite successful resuscitation, and ICDs will not alter the course of these patients and should not be implanted in this situation, unless there is a prospect for cardiac replacement therapy with future cardiac transplantation or a ventricular assist device.

PREVENTION OF SCD

Although advances in CPR and postresuscitation care have improved survival rates after cardiac arrest, 90% of patients will not survive to be discharged from the hospital. Of those that do survive, a proportion (~20%) are left with severe neurologic and/or physical disability. The majority of cardiac arrests do not occur in public places where AEDs and rapid defibrillation have the greatest impact. Patients who suffer an arrest at home also have longer EMS response times and are much less likely to be found in VF. Finally, 50% of cardiac arrests are not witnessed precluding effective resuscitation efforts. Thus, preventive efforts are critical to reducing mortality from cardiac arrest.

SCD RISK STRATIFICATION

The presence of overt structural heart disease and/or primary electrical heart disease is associated with an increased risk of SCD that varies with the severity and type of disease. For patients with structural heart disease, depressed left ventricular function is the best validated marker for risk, and clinical HF elevates risk further. After MI, SCD risk increases gradually as the LVEF decreases to 40% and then exponentially thereafter. In addition to LVEF and CHF, other potential markers of increased SCD risk in the setting of structural heart disease include unexplained syncope, sustained VT induced at electrophysiology study (EP study), left ventricular scar size and heterogeneity on cardiac magnetic resonance, markers of altered autonomic function and altered repolarization, and QRS prolongation. The majority of these tests, with the exception of the EP study in post-MI patients, broadly predict death from cardiovascular causes and are not able to discriminate patients who will die suddenly from those who will die of other cardiac causes. For instance, patients with the greatest degree of systolic HF and/or lowest LVEF, although at elevated risk for SCD, are more likely to die from HF. Although sustained VT at EP study does identify individuals at a higher risk of SCA versus non-SCA in certain subsets of patients, the sensitivity of the test is generally inadequate when LV function is significantly reduced.

PREVENTIVE THERAPIES FOR SCD IN HIGH-RISK POPULATIONS

Therapy with beta-adrenergic blockers has been demonstrated to reduce SCD risk in a multitude of settings including after MI, among patients with ischemic and nonischemic cardiomyopathy, and in LQTS. Angiotensin-converting enzyme inhibitors, aldosterone antagonists, and most recently angiotensin-receptor/neprilysin inhibitors have been associated with reductions in SCD in subsets of patients with structural heart disease, primarily ischemic and non-ischemic cardiomyopathy accompanied by HF. Coronary artery bypass grafting has also been associated with reductions in SCD risk, and revascularization in general may lower SCD risk through reduction in ischemic events and resultant improvements in left ventricular systolic function by reducing areas of hibernating myocardium.

For patients whose disease continues to confer substantial risk of sustained VT or VF on optimal medical therapy, an ICD is recommended (Table 299-3). The ICD indication in these patients is referred to as "primary prevention of sudden death." The indications for primary prevention ICDs vary depending on the type of underlying structural heart disease and its severity, and variable strength of evidence. In patients with a history of MI more than 40 days ago, primary prevention ICDs are indicated for those with Class II-III NYHA HF and LVEF <35%, and those who are NYHA functional Class I with LVEF <30%. Although, ICDs have not been found to be beneficial when implanted within 40 days of a MI, those with recent or old MI, nonsustained VT, LVEF <40% and inducible sustained VT at EP study also warrant an ICD.

TABLE 299-3 Implantable Cardioverter Defibrillator (ICD) Indications

	INDICATION	CLASS OF RECOMMENDATION*	LEVEL OF EVIDENCE**
Secondary Prevention			
All disease states VT or VF	ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.	CLASS I	A
	ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.	CLASS I	B
	ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.	CLASS IIa	C
Syncope	ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.	CLASS I	B
	ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom invasive and noninvasive have failed to determine a cause.	CLASS IIb	C
Primary Prevention			
Ischemic cardiomyopathy	ICD therapy ***is indicated*** in patients with LVEF ≤ 35% due to prior MI who are at least 40 days post-MI and are rare in NYHA functional Class II or III.	CLASS I	B
	ICD therapy ***is indicated*** in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤ 30%, and are in NYHA functional Class I.	CLASS I	A
	ICD therapy ***is indicated*** in patients with nonsustained VT due to prior MI, LVEF ≤ 40%, and inducible VF or sustained VT at electrophysiological study.	CLASS I	B
Non-ischemic cardiomyopathy	ICD therapy is ***indicated*** in patients with nonischemic DCM who have an LVEF ≤35% and who are in NYHA functional Class II or III.	CLASS I	B
	ICD implantation ***is reasonable*** for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM.	CLASS IIa	C
	ICD therapy ***can be considered*** in patients with non-ischemic heart disease and NYHA functional Class I.	CLASS IIb	C
Hypertrophic cardiomyopathy	ICD implantation ***is reasonable*** for patients with HCM who have one or more major risk factors for SCD.	CLASS IIa	C
Arrhythmogenic right ventricular dysplasia	ICD implantation ***is reasonable*** for the prevention of SCD in patients with ARVC who have one or more risk factors for SCD.	CLASS IIa	C
Brugada syndrome	ICD implantation ***is reasonable*** for patients with Brugada syndrome who have had syncope.	CLASS IIa	C
	ICD implantation ***is reasonable*** for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.	CLASS IIa	C
Long-QT syndrome	ICD implantation ***is reasonable*** to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers.	CLASS IIa	B
	ICD ***may be considered*** as primary therapy in patients long-QT syndrome who are deemed to be at very high risk, especially those with a contraindication to beta-blocker therapy.	CLASS IIb	B
Catecholaminergic polymorphic VT (CPVT)	ICD implantation ***is reasonable*** for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers.	CLASS IIa	C
Familial cardiomyopathy	ICD therapy ***may be considered*** in patients with a familial cardiomyopathy associated with SCD.	CLASS IIa	C
LV noncompaction	ICD therapy ***may be considered***.	CLASS IIa	C

CLASS OF RECOMMENDATION*		LEVEL OF EVIDENCE**		
CLASS I Procedure/treatment SHOULD be performed/ administered	CLASS IIa Additional studies with focused objectives needed. IT IS REASONABLE to perform procedure/administer treatment.	LEVEL A Multiple populations evaluated. Data derived from multiple randomized clinical trials or meta-analyses.	LEVEL B Limited populations evaluated. Data derived from a single randomized trial or nonrandomized studies.	LEVEL C Very limited populations evaluated. Only consensus opinion of experts, case studies, or standard of care.

Abbreviations: VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 299-4 Implantable Cardioverter Defibrillator (ICD) Not Indicated

Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least one year, even if they meet ICD implantation criteria.
Patients with incessant VT or VF.
Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.
Patients with drug-refractory New York Heart Association class IV congestive heart failure who are not candidates for cardiac transplantation or cardiac resynchronization therapy.
Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.
VF or VT is amenable to surgical or catheter ablation in patients without other disease predisposing to SCA (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).
Patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).

Adapted from: AE Epstein, JP DiMarco, KA Ellenbogen, et al: 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 127:e283–352, 2013.

Abbreviations: LV, left ventricular; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

In general, these criteria are not applied to patients who are within 90 days of myocardial revascularization, since some will experience improvement in ventricular function and older trial data suggested there was no benefit with ICDs in these patents. High-risk patients with low LVEFs may be considered for a wearable defibrillator with later reassessment of ventricular function and ICD placement.

ICDs for primary prevention of sudden death are also recommended for patients with diseases other than CAD, that put them at risk for SCD. ICDs are recommended for those with nonischemic DCM who have an LVEF ≤ 35% and who are in NYHA functional Class II or III and receiving medical therapy. Benefit is more likely in patients aged <60 years, as non-arrhythmia causes of death increase with age. For patients with LVEF <35%, HF, and left bundle branch block (LBBB) with QRS duration >150 ms cardiac resynchronization therapy also offers protection against SCD, particularly in patients with nonischemic cardiomyopathy. Primary prevention ICDs are also recommended in select high-risk patients with HCM, arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis, and Brugada syndrome and some patients with congenital LQTS with high-risk features or that have failed therapy with beta-adrenergic blocking agents. There are circumstances where an ICD is not indicated even if there is a significant sudden death risk (Table 299-4). Most notably, patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, should not undergo ICD placement.

THE CHALLENGE OF SCD PREVENTION (FIG. 299-4)

The Greatest Number of Sudden Deaths Occur in "Low Risk" Patients While patients with reduced left ventricular function and HF are at substantially elevated SCD risk, only ~20% of all SCDs occur in patients with poor left ventricular function. Most SCDs occur in individuals with preserved ventricular function who would not qualify for a primary prevention ICD. Although SCD rates are

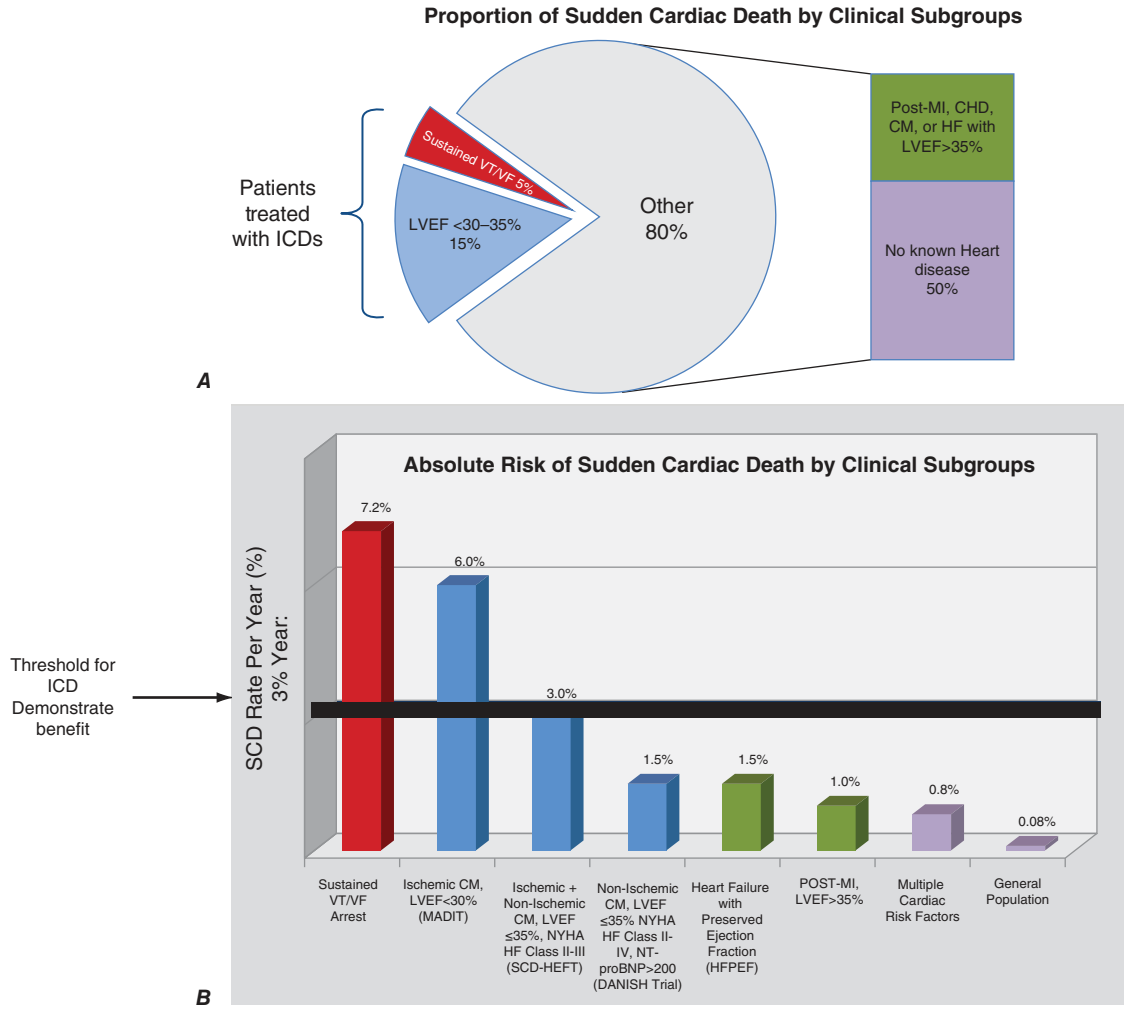

FIGURE 299-4 ***A.*** Proportion of sudden cardiac deaths that occur in clinical subgroups of the population treated and not treated with ICDs. ***B.*** Absolute risk on sudden cardiac death within clinical subgroups in comparison to the threshold of risk where ICDs demonstrated benefit.

elevated compared to the general population, the absolute SCD risk in patients with CHD or HF who have an LVEF >35% is not high enough to warrant consideration of ICD therapy. While the incidence of SCD is lower in patients with preserved LVEF, SCD accounts for a greater proportion of cardiac deaths, and active efforts are being made to advance SCD risk stratification in this segment of the population. However, at the present time, SCD prevention primarily involves cardiac risk factor modification and standard medical therapy for the underlying condition.

Preventing Sudden Death in the General Population Only about half of men and a third of women who suffer SCA are recognized to have heart disease prior to the event, and only half have warning symptoms prior to the event. SCD often occurs without warning as the first manifestation of cardiac disease. In order to prevent these SCDs, preventive interventions would need to be employed broadly to the general population. Although several risk scores have recently been developed with the intent to stratify SCD risk in low-risk populations, the clinical utility to date is limited by the low absolute incidence of SCD which is estimated to be only 50–90 per 100,000 in the general adult population. Therefore, current efforts aimed at preventing SCD in general populations primarily focus on modification of the SCD risk factors outlined previously. Individuals who adhere to a low risk, healthy lifestyle that includes avoidance of smoking, maintaining a healthy body weight, participating in moderate exercise, and a Mediterranean-type dietary pattern have markedly lower rates of SCD. A substantial number of SCDs are likely to be preventable thorough lifestyle modifications and treatment of risk factors.

Acknowledgment

The authors gratefully acknowledge the prior contributions of Agustin Castellanos and Robert J. Myerburg.

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Section 3 Neurologic Critical Care

300 Coma

S. Andrew Josephson, Allan H. Ropper, Stephen L. Hauser

Coma is among the most common neurologic emergencies encountered general medicine and requires an organized approach. It accounts for a substantial portion of admissions to emergency wards and occurs on all hospital services.

There exists a continuum of states of reduced alertness, the most severe form being coma, defined as a deep sleeplike state with eyes closed from which the patient cannot be aroused. Stupor refers to a higher degree of arousability in which the patient can be transiently awakened by vigorous stimuli, accompanied by motor behavior that leads to avoidance or withdrawal from uncomfortable or aggravating stimuli. Drowsiness simulates light sleep and is characterized by easy arousal and the persistence of alertness for brief periods. Stupor and drowsiness are usually accompanied by some degree of confusion **(Chap. 24)**. A precise narrative description of the level of arousal and of the type of responses evoked by various stimuli as observed at the bedside is preferable to use of ambiguous terms such as lethargy, semicoma, or obtundation.

Several conditions that render patients unresponsive and simulate coma are considered separately because of their special significance. The *vegetative state* signifies an awake-appearing but nonresponsive state often in a patient who has emerged from coma. In the vegetative state, the eyelids may open periodically, giving the appearance of wakefulness. Respiratory and autonomic functions are retained. Yawning, coughing, swallowing, and limb and head movements persist, but there are few, if any, meaningful responses to the external and internal environment. There are always accompanying signs that indicate extensive damage in both cerebral hemispheres, e.g., decerebrate or decorticate limb posturing and absent responses to visual stimuli (see below). In the closely related but less severe *minimally conscious state*, the patient displays rudimentary vocal or motor behaviors, often spontaneous, but some in response to touch, visual stimuli, or command. Cardiac arrest with cerebral hypoperfusion and head trauma are the most common causes of the vegetative and minimally conscious states **(Chap. 301)**.

The prognosis for regaining mental faculties once the vegetative state has supervened for several months is very poor, and after a year, almost nil; hence the term *persistent vegetative state*. Most reports of dramatic recovery, when investigated carefully, are found to yield to the usual rules for prognosis, but there have been rare instances in which recovery has occurred to a severely disabled condition and, in rare childhood cases, to an even better state. Patients in the minimally conscious state carry a better prognosis for some recovery compared to those in a persistent vegetative state, but even in these patients, dramatic recovery after 12 months is unusual.

The possibility of incorrectly attributing meaningful behavior to patients in the vegetative and minimally conscious states creates inordinate problems and anguish for families and physicians. On the other hand, the question of whether these patients lack any capability for cognition has been reopened by functional MRI studies that have demonstrated, in a small proportion of usually posttraumatic cases, meaningful cerebral activation in response to verbal and other stimuli

as discussed in more detail below. This finding suggests at a minimum that some of these patients could in the future be able to communicate their needs using technological advances and that further research could shed light on treatment approaches targeting areas of the brain and their connections that seem to be preserved in individual patients.

Apart from the above conditions, several syndromes that affect alertness are prone to be misinterpreted as stupor or coma. Clinicians should be aware of these pitfalls when diagnosing coma at the bedside. Akinetic mutism refers to a partially or fully awake state in which the patient is able to form impressions and think, as demonstrated by later recounting of events, but remains virtually immobile and mute. The condition results from damage in the regions of the medial thalamic nuclei or the frontal lobes (particularly lesions situated deeply or on the orbitofrontal surfaces) or from extreme hydrocephalus. The term abulia describes a milder form of akinetic mutism characterized by mental and physical slowness and diminished ability to initiate activity. It is also usually the result of damage to the medial frontal lobes and their connections **(Chap. 26)**.

Catatonia is a hypomobile and mute syndrome that occurs usually as part of a major psychosis, typically schizophrenia or major depression. Catatonic patients make few voluntary or responsive movements, although they blink, swallow, and may not appear distressed. There are nonetheless signs that the patient is responsive, although it may take a careful examination to demonstrate them. For example, eyelid elevation is actively resisted, blinking occurs in response to a visual threat, and the eyes move concomitantly with head rotation, all of which are inconsistent with the presence of a brain lesion causing unresponsiveness. It is characteristic but not invariable in catatonia for the limbs to retain the postures in which they have been placed by the examiner ("waxy flexibility," or catalepsy). With recovery, patients often have some memory of events that occurred during their catatonic stupor. Catatonia is superficially similar to akinetic mutism, but clinical evidence of cerebral damage such as hyperreflexia and hypertonicity of the limbs is lacking. The special problem of coma in brain death is discussed below.

The locked-in state describes an important type of pseudocoma in which an awake patient has no means of producing speech or volitional limb movement but retains voluntary vertical eye movements and lid elevation, thus allowing the patient to signal with a clear mind. The pupils are normally reactive. The usual cause is an infarction (e.g., basilar artery thrombosis) or hemorrhage of the ventral pons that transects all descending motor (corticospinal and corticobulbar) pathways. Another awake but de-efferented state occurs as a result of total paralysis of the musculature in severe cases of neuromuscular weakness such as in Guillain-Barré syndrome **(Chap. 439)**, critical illness neuropathy **(Chap. 301)**, and pharmacologic neuromuscular blockade.

THE ANATOMY AND PHYSIOLOGY OF COMA

Almost all instances of coma can be traced to either (1) widespread abnormalities of the cerebral hemispheres or to (2) reduced activity of a special thalamocortical alerting system termed the reticular activating system (RAS) which is diffusely located in the brainstem. The proper functioning of this system, its ascending projections to the cortex, and the cortex itself are required to maintain alertness and coherence of thought. In addition to structural damage of these two systems, suppression of reticulocerebral function can occur by drugs, toxins, or metabolic derangements such as hypoglycemia, anoxia, uremia, and hepatic failure; these types of metabolic causes of coma are far more common than structural injuries.

Coma Due to Cerebral Mass Lesions and Herniation Syndromes In addition to the fixed restriction of the skull, the cranial cavity is separated into compartments by infoldings of the dura. The two cerebral hemispheres are separated by the falx, and the anterior and posterior fossae by the tentorium. Herniation refers to displacement of brain tissue by an overlying or adjacent mass into a contiguous compartment that it normally does not occupy. Coma and many of its associated signs can be attributed to these tissue shifts, and certain clinical features are characteristic of specific configurations

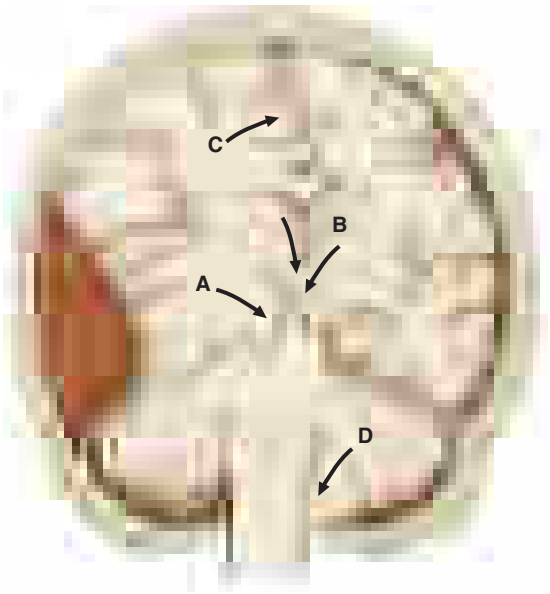
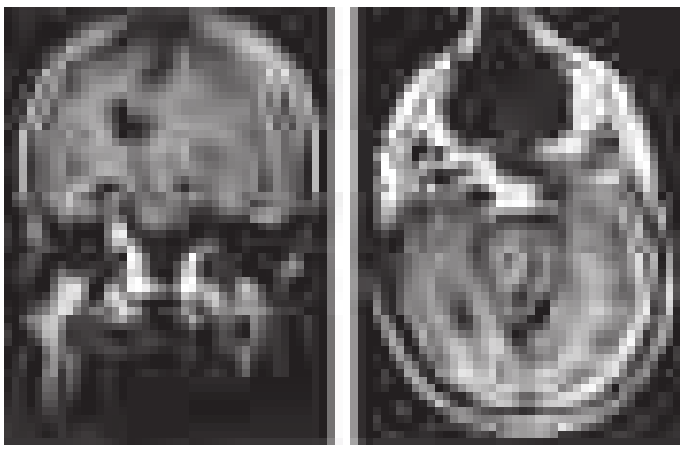


FIGURE 300-1 Types of cerebral herniation: (***A***) uncal; (***B***) central; (***C***) transfalcial; and (***D***) foraminal.

of herniation **(Fig. 300-1)**. They are in essence "false localizing" signs because they derive from compression of brain structures at a distance from the mass lesion that is the direct cause of coma.

In the most common form of herniation, brain tissue is displaced from the supratentorial to the infratentorial compartment through the tentorial opening; this is referred to as transtentorial herniation. Uncal transtentorial herniation refers specifically to impaction of the anterior medial temporal gyrus (the uncus) into the tentorial opening just anterior to and adjacent to the midbrain **(Fig. 300-1*A*)**. The uncus compresses the third nerve as the nerve traverses the subarachnoid space, causing enlargement of the ipsilateral pupil as the first sign (the fibers subserving parasympathetic pupillary function are located peripherally in the nerve). The coma that follows is due to compression of the midbrain (and therefore the RAS) against the opposite tentorial edge by the displaced parahippocampal gyrus **(Fig. 300-2)**. Lateral displacement of the midbrain may compress the opposite cerebral peduncle against the tentorial edge, producing a Babinski sign and hemiparesis contralateral to the hemiparesis that resulted from the mass (the Kernohan-Woltman sign). Herniation may also compress the anterior and posterior cerebral arteries as they pass over the tentorial



A ***B***

FIGURE 300-2 Coronal (*A*) and axial (*B*) magnetic resonance images from a stuporous patient with a left third nerve palsy as a result of a large left-sided subdural hematoma (seen as a gray-white rim). The upper midbrain and lower thalamic regions are compressed and displaced horizontally away from the mass, and there is transtentorial herniation of the medial temporal lobe structures, including the uncus anteriorly. The lateral ventricle opposite to the hematoma has become enlarged as a result of compression of the third ventricle.

reflections, with resultant brain infarction. These distortions may also entrap portions of the ventricular system, resulting in hydrocephalus.

Central transtentorial herniation denotes a symmetric downward movement of the thalamic structures through the tentorial opening with compression of the upper midbrain **(Fig. 300-1*B*)**. Miotic pupils and drowsiness are the heralding signs, in contrast to a unilaterally enlarged pupil of the uncal syndrome. Both uncal and central transtentorial herniations cause progressive compression of the brainstem and RAS, with initial damage to the midbrain, then the pons, and finally the medulla. The result is an approximate sequence of neurologic signs that corresponds to each affected level, with respiratory centers in the brainstem often spared until late in the herniation syndrome. Other forms of herniation include transfalcial herniation (displacement of the cingulate gyrus under the falx and across the midline, **Fig. 300-1*C***) and foraminal herniation (downward forcing of the cerebellar tonsils into the foramen magnum, **Fig. 300-1*D***), which causes early compression of the medulla, respiratory arrest, and death.

A direct relationship between the various configurations of transtentorial herniation and coma is not always found. Drowsiness and stupor can occur with moderate horizontal displacement of the diencephalon (thalamus), before transtentorial herniation is evident. This lateral shift may be quantified on axial images of computed tomography (CT) and magnetic resonance imaging (MRI) scans (Fig. 300-2). In cases of acutely enlarging masses, horizontal displacement of the pineal gland (often calcified in adults) of 3–5 mm is generally associated with drowsiness, 6–8 mm with stupor, and >9 mm with coma. Intrusion of the medial temporal lobe into the tentorial opening is also apparent on MRI and CT scans as obliteration of the cisterna that surrounds the upper brainstem.

Coma Due to Metabolic Disorders and Toxins (including Drug-induced) Many systemic metabolic abnormalities cause coma by interrupting the delivery of energy substrates (e.g., oxygen, glucose) or by altering neuronal excitability (drugs and alcohol, anesthesia, and epilepsy). These are some of the most common causes of coma in large case series. The metabolic abnormalities that produce coma may, in milder forms, induce an acute confusional state. Thus, in metabolic encephalopathies, clouded consciousness and coma are in a continuum.

Cerebral neurons are fully dependent on cerebral blood flow (CBF) and the delivery of oxygen and glucose. CBF is ~75 mL per 100 g/min in gray matter and 30 mL per 100 g/min in white matter (mean ~55 mL per 100 g/min); oxygen consumption is 3.5 mL per 100 g/min, and glucose utilization is 5 mg per 100 g/min. Brain stores of glucose are able to provide energy for ~2 min after blood flow is interrupted, and oxygen stores last 8–10 s after the cessation of blood flow. Simultaneous hypoxia and ischemia exhaust glucose more rapidly. The electroencephalogram (EEG) rhythm in these circumstances becomes diffusely slowed, typical of metabolic encephalopathies, and as substrate delivery worsens, eventually brain electrical activity ceases.

Unlike hypoxia-ischemia, which causes neuronal destruction, most metabolic disorders such as hypoglycemia, hyponatremia, hyperosmolarity, hypercapnia, hypercalcemia, and hepatic and renal failure cause only minor neuropathologic changes. The reversible effects of these conditions on the brain are not fully understood but may result from impaired energy supplies, changes in ion fluxes across neuronal membranes, and neurotransmitter abnormalities. In hepatic encephalopathy (HE), high ammonia concentrations lead to increased synthesis of glutamine in astrocytes with osmotic swelling, mitochondrial energy failure, production of reactive nitrogen and oxygen species, increases in the inhibitory neurotransmitter GABA, and synthesis of putative "false" neurotransmitters. Other factors, including coexisting inflammation and metabolic abnormalities, also contribute to the coma in some patients. Over time, development of a diffuse astrocytosis is typical of chronic HE. The mechanism of the encephalopathy of renal failure is also multifactorial. Unlike ammonia, urea does not produce central nervous system (CNS) toxicity, and contributors to uremic encephalopathy may include accumulation of neurotoxic substances such as creatinine, guanidine, and related compounds, depletion of catecholamines, altered glutamate and GABA tone, increases in brain calcium, inflammation with disruption of the blood brain barrier, and frequent coexisting vascular disease.

Coma and seizures are common accompaniments of large shifts in sodium and water balance in the brain. These changes in osmolarity arise from systemic medical disorders, including diabetic ketoacidosis, the nonketotic hyperosmolar state, and hyponatremia from any cause (e.g., water intoxication, excessive secretion of antidiuretic hormone, or atrial natriuretic peptides). Sodium levels <125 mmol/L induce confusion, and levels <119 mmol/L are typically associated with coma and convulsions, especially when these levels are achieved quickly. In hyperosmolar coma, the serum osmolarity is generally >350 mosmol/L. Hypercapnia depresses the level of consciousness in proportion to the rise in carbon dioxide (CO_2) in the blood. In all of these metabolic encephalopathies, the degree of neurologic change depends to a large extent on the rapidity with which the serum changes occur. The pathophysiology of other metabolic encephalopathies such as those due to hypercalcemia, hypothyroidism, vitamin B_{12} deficiency, and hypothermia are incompletely understood but must reflect derangements of CNS biochemistry, membrane function, or neurotransmitters.

Coma due to drugs and toxins are typically in large measure reversible and leave no residual damage provided there has not been cardiorespiratory failure. Many drugs and toxins are capable of depressing nervous system function. Some produce coma by affecting both the RAS and the cerebral cortex. The combination of cortical and brainstem signs, which occurs in certain drug overdoses, may lead to an incorrect diagnosis of structural brainstem disease. Overdose of medications that have atropinic actions produces signs such as dilated pupils, tachycardia, and dry skin; opiate overdose produces pinpoint pupils <1 mm in diameter. Some drug intoxications, such as with barbiturates, can mimic all of the signs of brain death, thus toxic etiologies must always be excluded prior to making a diagnosis of brain death.

Epileptic Coma Generalized electrical seizures are associated with coma, even in the absence of motor convulsions (nonconvulsive status epilepticus). As a result, consideration of EEG monitoring is essential in the workup of coma to exclude this treatable etiology. The self-limited coma that follows a seizure, the postictal state, may be due to exhaustion of energy reserves or effects of locally toxic molecules that are the by-product of seizures. The postictal state produces continuous, generalized slowing of the background EEG activity similar to that of metabolic encephalopathies. It typically lasts for a few minutes, but in some cases can be prolonged for hours or even rarely for days.

Coma Due to Widespread Damage to the Cerebral Hemispheres This category, comprising a number of unrelated disorders, results from extensive bilateral structural cerebral damage that simulates a metabolic disorder. Hypoxia-ischemia is perhaps the best characterized and one in which it is not possible initially to distinguish the acute reversible effects of oxygen deprivation of the brain from the subsequent effects of anoxic neuronal damage. Similar cerebral damage may be produced by disorders that occlude widespread small blood vessels throughout the brain; examples include cerebral malaria, thrombotic thrombocytopenic purpura, and hyperviscosity. Diffuse white matter damage from cranial trauma or inflammatory demyelinating diseases can cause a similar coma syndrome.

APPROACH TO THE PATIENT

Coma

A video examination of the comatose patient is shown in Chap. V4. Acute respiratory and cardiovascular problems should be attended to prior to neurologic assessment. In most instances, a complete medical evaluation, except for vital signs, funduscopy, and examination for nuchal rigidity, may be deferred until the neurologic evaluation has established the severity and nature of coma. **The approach to the patient with coma from cranial trauma is discussed in Chap. 435.**

HISTORY

The cause of coma may be immediately evident as in cases of trauma, cardiac arrest, or observed drug ingestion. In the remainder, certain points are useful: (1) the circumstances and rapidity with which neurologic symptoms developed; (2) antecedent symptoms (confusion, weakness, headache, fever, seizures, dizziness, double vision, or vomiting); (3) the use of medications, drugs, or alcohol; and (4) chronic liver, kidney, lung, heart, or other medical disease. Direct interrogation of family, observers, and ambulance technicians on the scene, in person or by telephone, is an important part of the evaluation when possible.

GENERAL PHYSICAL EXAMINATION

Fever suggests a systemic infection, bacterial meningitis, encephalitis, heat stroke, neuroleptic malignant syndrome, malignant hyperthermia due to anesthetics, or anticholinergic drug intoxication. Only rarely is fever attributable to a lesion that has disturbed hypothalamic temperature-regulating centers ("central fever") and this diagnosis should only be considered after an exhaustive search for other causes fails to reveal an explanation for fever. A slight elevation in temperature may follow vigorous convulsions. Hypothermia is observed with alcohol, barbiturate, sedative, or phenothiazine intoxication; hypoglycemia; peripheral circulatory failure; or extreme hypothyroidism. Hypothermia itself causes coma when the temperature is <31°C (87.8°F) regardless of the underlying etiology. Tachypnea may indicate systemic acidosis or pneumonia. Aberrant respiratory patterns that reflect brainstem disorders are discussed below. Marked hypertension suggests hypertensive encephalopathy, cerebral hemorrhage, large cerebral infarction, or head injury. Hypotension is characteristic of coma from alcohol or barbiturate intoxication, internal hemorrhage or myocardial infarction causing poor delivery of blood to the brain, sepsis, profound hypothyroidism, or Addisonian crisis. The funduscopic examination can detect increased intracranial pressure (ICP) (papilledema), subarachnoid hemorrhage (subhyaloid hemorrhages), and hypertensive encephalopathy (exudates, hemorrhages, vessel-crossing changes, papilledema). Cutaneous petechiae suggest thrombotic thrombocytopenic purpura, meningococcemia, or a bleeding diathesis associated with an intracerebral hemorrhage. Cyanosis and reddish or anemic skin coloration are other indications of an underlying systemic disease or carbon monoxide as responsible for the coma.

NEUROLOGIC EXAMINATION

The patient should first be observed without intervention by the examiner. Tossing about in the bed, reaching up toward the face, crossing legs, yawning, swallowing, coughing, or moaning reflect a drowsy state that is close to normal awakeness. Lack of restless movements on one side or an outturned leg suggests hemiplegia. Subtle, intermittent twitching movements of a foot, finger, or facial muscle may be the only sign of seizures. Multifocal myoclonus almost always indicates a metabolic disorder, particularly uremia, anoxia, drug intoxication, or rarely a prion disease **(Chap. 430)**. In a drowsy and confused patient, bilateral asterixis is a sign of metabolic encephalopathy or drug intoxication.

Decorticate rigidity and decerebrate rigidity, or "posturing," describe stereotyped arm and leg movements occurring spontaneously or elicited by sensory stimulation. Flexion of the elbows and wrists and supination of the arm (decorticate posturing) suggests bilateral damage rostral to the midbrain, whereas extension of the elbows and wrists with pronation (decerebrate posturing) indicates damage to motor tracts caudal to the midbrain. These localizations have been adapted from animal work and cannot be applied with precision to coma in humans. In fact, acute and widespread disorders of any type, regardless of location, frequently cause limb extension.

LEVEL OF AROUSAL

A sequence of increasingly intense stimuli is first used to determine the threshold for arousal and the motor response of each side of the body. The results of testing may vary from minute to minute, and serial examinations are useful. Tickling the nostrils with a cotton wisp is a moderate stimulus to arousal—all but deeply stuporous and comatose patients will move the head away and arouse to some degree. An even greater degree of responsiveness is present if the patient uses his hand to remove an offending stimulus. Pressure on the knuckles or bony prominences and pinprick stimulation are humane forms of noxious stimuli; pinching the skin causes unsightly ecchymoses and is generally not necessary but may be useful in eliciting abduction withdrawal movements of the limbs. Posturing in response to noxious stimuli indicates severe damage to the corticospinal system, whereas abduction-avoidance movement of a limb is usually purposeful and denotes an intact corticospinal system. Posturing may also be unilateral and coexist with purposeful limb movements, reflecting incomplete damage to the motor system.

BRAINSTEM REFLEXES

Given that the nuclei of the cranial nerves and the RAS are both located in the brainstem, assessment of brainstem function is essential to localization of the lesion in coma **(Fig. 300-3)**. Patients with preserved brainstem reflexes typically have a bihemispheric localization to coma, including toxic or drug intoxication, whereas patients with abnormal brainstem reflexes either have an RAS localization to their coma or are suffering from a herniation syndrome impacting the brainstem remotely from a cerebral mass lesion. The most important brainstem reflexes that are examined are pupillary size and reaction to light, spontaneous and elicited eye movements, corneal responses, and the respiratory pattern.

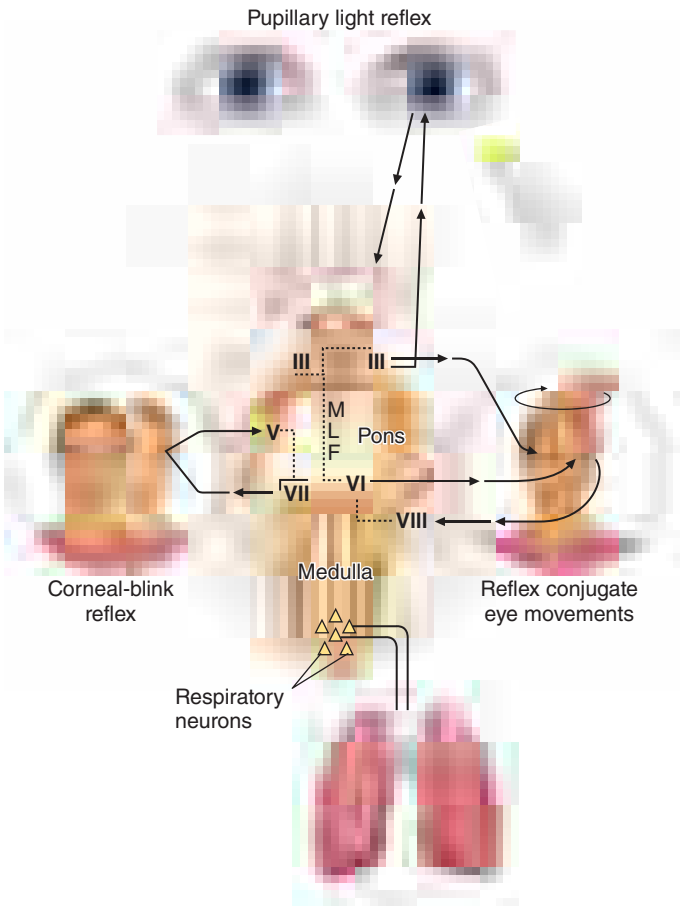


FIGURE 300-3 Examination of brainstem reflexes in coma. Midbrain and third nerve function are tested by pupillary reaction to light, pontine function by spontaneous and reflex eye movements and corneal responses, and medullary function by respiratory and pharyngeal responses. Reflex conjugate, horizontal eye movements are dependent on the medial longitudinal fasciculus (MLF) interconnecting the sixth and contralateral third nerve nuclei. Head rotation (oculocephalic reflex) or caloric stimulation of the labyrinths (oculovestibular reflex) elicits contraversive eye movements (for details see text).

Pupillary Signs Pupillary reactions are examined with a bright, diffuse light. Reactive and round pupils of midsize (2.5–5 mm) essentially exclude upper midbrain damage, either primary or secondary to compression. A response to light may be difficult to appreciate in pupils <2 mm in diameter, and bright room lighting mutes pupillary reactivity. One enlarged and poorly reactive pupil (>6 mm) signifies compression or stretching of the third nerve from the effects of a cerebral mass above. Enlargement of the pupil contralateral to a hemispheral mass may occur but is infrequent. An oval and slightly eccentric pupil is a transitional sign that accompanies early midbrain–third nerve compression. The most extreme pupillary sign, bilaterally dilated and unreactive pupils, indicates severe midbrain damage, usually from compression by a supratentorial mass. Ingestion of drugs with anticholinergic activity, the use of mydriatic eye drops, nebulizer treatments, and direct ocular trauma are among the causes of misleading pupillary enlargement.

Reactive and bilaterally small (1–2.5 mm) but not pinpoint pupils are seen in metabolic encephalopathies or in deep bilateral hemispheral lesions such as hydrocephalus or thalamic hemorrhage. Even smaller reactive pupils (<1 mm) characterize narcotic or barbiturate overdoses but also occur with extensive pontine hemorrhage. The response to naloxone and the presence of reflex eye movements (see below) assist in distinguishing between these. Unilateral miosis in coma has been attributed to dysfunction of sympathetic efferents originating in the posterior hypothalamus and descending in the tegmentum of the brainstem to the cervical cord. It is an occasional finding in patients with a large cerebral hemorrhage that affects the thalamus.

Ocular Movements The eyes are first observed by elevating the lids and observing the resting position and spontaneous movements of the globes. Horizontal divergence of the eyes at rest is normal in drowsiness. As coma deepens, the ocular axes may become parallel again.

Spontaneous eye movements in coma often take the form of conjugate horizontal roving. This finding alone exonerates extensive damage in the midbrain and pons and has the same significance as normal reflex eye movements (see below). Conjugate horizontal ocular deviation to one side indicates damage to the frontal lobe on the same side or less commonly the pons on the opposite side. This phenomenon is summarized by the following maxim: *The eyes look toward a hemispheral lesion and away from a brainstem lesion*. Seizures involving the frontal lobe drive the eyes to the opposite side, simulating a pontine destructive lesion. The eyes may occasionally turn paradoxically away from the side of a deep hemispheral lesion ("wrong-way eyes"). The eyes turn down and inward with thalamic and upper midbrain lesions, typically thalamic hemorrhage. "Ocular bobbing" describes brisk downward and slow upward movements of the eyes associated with loss of horizontal eye movements and is diagnostic of bilateral pontine damage, usually from thrombosis of the basilar artery. "Ocular dipping" is a slower, arrhythmic downward movement followed by a faster upward movement in patients with normal reflex horizontal gaze; it usually indicates diffuse cortical anoxic damage.

The oculocephalic reflexes, elicited by moving the head from side to side or vertically and observing eye movements in the direction opposite to the head movement, depend on the integrity of the ocular motor nuclei and their interconnecting tracts that extend from the midbrain to the pons and medulla (Fig. 300-3). The movements, called somewhat inappropriately "doll's eyes," are normally suppressed in the awake patient with intact frontal lobes. The ability to elicit them therefore reflects both reduced cortical influence on the brainstem and intact brainstem pathways. The opposite, an absence of reflex eye movements, usually signifies damage within the brainstem but can result from overdoses of certain drugs. In this circumstance, normal pupillary size and light reaction distinguishes most drug-induced comas from structural brainstem damage. Oculocephalic reflexes should never be elicited in patients with possible head or neck trauma, as vigorous head movements can precipitate or worsen a spinal cord injury.

Thermal, or "caloric," stimulation of the vestibular apparatus (oculovestibular response) provides a more intense stimulus for the oculocephalic reflex but provides essentially the same information. The test is performed by irrigating the external auditory canal with cold water in order to induce convection currents in the labyrinths. After a brief latency, the result is tonic deviation of both eyes to the side of cold-water irrigation. In comatose patients, nystagmus in the opposite direction may not occur. The acronym "COWS" has been used to remind generations of medical students of the direction of nystagmus—cold water opposite, warm water same—but since nystagmus is often absent in the opposite direction due to frontal lobe dysfunction in coma, this mnemonic does not often hold true.

When touching the cornea with a wisp of cotton, a response consisting of brief bilateral lid closure is normally observed. The corneal reflex depends on the integrity of pontine pathways between the fifth (afferent) and both seventh (efferent) cranial nerves; in conjunction with reflex eye movements, it is a useful test of pontine function. CNS-depressant drugs diminish or eliminate the corneal responses soon after reflex eye movements are paralyzed but before the pupils become unreactive to light. The corneal response may be lost for a time on the side of an acute hemiplegia.

Respiratory Patterns These are of less localizing value in comparison to other brainstem signs. Shallow, slow, but regular breathing suggests metabolic or drug depression. Cheyne-Stokes respiration in its typical cyclic form, ending with a brief apneic period, signifies bihemispheral damage or metabolic suppression and commonly accompanies light coma. Rapid, deep (Kussmaul) breathing usually implies metabolic acidosis but may also occur with pontomesencephalic lesions. Agonal gasps are the result of lower brainstem (medullary) damage and are recognized as the terminal respiratory pattern of severe brain damage. A number of other cyclic breathing variations have been described but are of lesser significance.

LABORATORY STUDIES AND IMAGING

The studies that are most useful in the diagnosis of coma are chemical-toxicologic analysis of blood and urine, cranial CT or MRI, EEG, and CSF examination. Arterial blood gas analysis is helpful in patients with lung disease and acid-base disorders. The metabolic aberrations commonly encountered in clinical practice are usually revealed by measurement of electrolytes, glucose, calcium, magnesium, osmolarity, and renal (blood urea nitrogen) and hepatic (NH_3) function. Toxicologic analysis may be necessary in any case of acute coma where the diagnosis is not immediately clear. However, the presence of exogenous drugs or toxins, especially alcohol, does not exclude the possibility that other factors, particularly head trauma, are also contributing to the clinical state. An ethanol level of 43 mmol/L (0.2 g/dL) in nonhabituated patients generally causes impaired mental activity; a level of >65 mmol/L (0.3 g/dL) is associated with stupor. The development of tolerance may allow some chronic alcoholics to remain awake at levels >87 mmol/L (0.4 g/dL).

The availability of CT and MRI has focused attention on causes of coma that are detectable by imaging (e.g., hemorrhage, tumor, or hydrocephalus). Resorting primarily to this approach, although at times expedient, is imprudent because most cases of coma (and confusion) are metabolic or toxic in origin. A normal CT scan does not exclude an anatomic lesion as the cause of coma; early bilateral hemisphere infarction, acute brainstem infarction, encephalitis, meningitis, mechanical shearing of axons as a result of closed head trauma, sagittal sinus thrombosis, hypoxic injury and subdural hematoma isodense to adjacent brain are some of the disorders that may not be detected. Sometimes imaging results can be misleading such as when small subdural hematomas or old strokes are found, but the patient's coma is due to intoxication.

The EEG **(Chap. 418)** provides clues in metabolic or drug-induced states but is rarely diagnostic. However, it is the essential test to reveal coma due to nonconvulsive seizures, and shows fairly characteristic patterns in herpesvirus encephalitis and prion (Creutzfeldt-Jakob) disease. The EEG may be further helpful in disclosing generalized slowing

of the background activity, a reflection of the severity of an encephalopathy. Predominant high-voltage slowing (δ or triphasic waves) in the frontal regions is typical of metabolic coma, as from hepatic failure, and widespread fast (β) activity implicates sedative drugs (e.g., benzodiazepines). A special pattern of "alpha coma," defined by widespread, variable 8- to 12-Hz activity, superficially resembles the normal α rhythm of waking but, unlike normal α activity, is not altered by environmental stimuli. Alpha coma results from pontine or diffuse cortical damage and is associated with a poor prognosis. Normal α activity on the EEG, which is suppressed by stimulating the patient, also alerts the clinician to the locked-in syndrome or to hysteria or catatonia.

Lumbar puncture should be performed if no cause is readily apparent, as examination of the CSF remains indispensable in the diagnosis of various forms of meningitis and encephalitis. An imaging study should be performed prior to lumbar puncture to exclude a large intracranial mass lesion which could lead to herniation with lumbar puncture. Blood cultures and administration of antibiotics should precede the imaging study if infectious meningitis is suspected **(Chap. 133)**.

DIFFERENTIAL DIAGNOSIS OF COMA

(Table 300-1) The causes of coma can be divided into three broad categories: cases without focal neurologic signs (e.g., metabolic and toxic encephalopathies); cases with prominent focal signs (e.g., stroke, cerebral hemorrhage); and meningitis syndromes, characterized by fever or stiff neck and an excess of cells in the spinal fluid (e.g., bacterial meningitis, subarachnoid hemorrhage, encephalitis). Causes of sudden coma include drug ingestion, cerebral hemorrhage, trauma, cardiac arrest, epilepsy, and basilar artery occlusion. Coma that appears subacutely is usually related to a preexisting medical or neurologic problem or, less often, to secondary brain swelling surrounding a mass such as tumor or cerebral infarction.

TABLE 300-1 Differential Diagnosis of Coma

1. Diseases that cause no focal brainstem or lateralizing neurologic signs (CT scan is often normal)
   a. Intoxications: alcohol, sedative drugs, opiates, etc.
   b. Metabolic disturbances: anoxia, hyponatremia, hypernatremia, hypercalcemia, diabetic acidosis, nonketotic hyperosmolar hyperglycemia, hypoglycemia, uremia, hepatic coma, hypercarbia, Addisonian crisis, hypo- and hyperthyroid states, profound nutritional deficiency
   c. Severe systemic infections: pneumonia, septicemia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome
   d. Shock from any cause
   e. Status epilepticus, nonconvulsive status epilepticus, postictal states
   f. Hyperperfusion syndromes including hypertensive encephalopathy, eclampsia, posterior reversible encephalopathy syndrome (PRES)
   g. Severe hyperthermia, hypothermia
   h. Concussion
   i. Acute hydrocephalus
2. Diseases that cause focal brainstem or lateralizing cerebral signs (CT scan is typically abnormal)
   a. Hemispheral hemorrhage (basal ganglionic, thalamic) or infarction (large middle cerebral artery territory) with secondary brainstem compression
   b. Brainstem infarction due to basilar artery thrombosis or embolism
   c. Brain abscess, subdural empyema
   d. Epidural and subdural hemorrhage, brain contusion
   e. Brain tumor with surrounding edema
   f. Cerebellar and pontine hemorrhage and infarction
   g. Widespread traumatic brain injury
   h. Metabolic coma (see above) in the setting of preexisting focal damage
3. Diseases that cause meningeal irritation with or without fever, and with an excess of WBCs or RBCs in the CSF
   a. Subarachnoid hemorrhage from ruptured aneurysm, arteriovenous malformation, trauma
   b. Infectious meningitis and meningoencephalitis
   c. Paraneoplastic and autoimmune meningitis
   d. Carcinomatous and lymphomatous meningitis

The diagnosis of coma due to cerebrovascular disease can be difficult **(Chap. 419)**. The most common diseases are (1) basal ganglia and thalamic hemorrhage (acute but not instantaneous onset, vomiting, headache, hemiplegia, and characteristic eye signs); (2) pontine hemorrhage (sudden onset, pinpoint pupils, loss of reflex eye movements and corneal responses, ocular bobbing, posturing, and hyperventilation); (3) cerebellar hemorrhage (occipital headache, vomiting, gaze paresis, and inability to stand and walk); (4) basilar artery thrombosis (neurologic prodrome or warning spells, diplopia, dysarthria, vomiting, eye movement and corneal response abnormalities, and asymmetric limb paresis); and (5) subarachnoid hemorrhage (precipitous coma after sudden severe headache and vomiting). The most common stroke, infarction in the territory of the middle cerebral artery, does not cause coma, but edema surrounding large infarctions may expand over several days and cause coma from mass effect.

The syndrome of acute hydrocephalus accompanies many intracranial diseases, particularly subarachnoid hemorrhage. It is characterized by headache and sometimes vomiting that may progress quickly to coma with extensor posturing of the limbs, bilateral Babinski signs, small unreactive pupils, and impaired oculocephalic movements in the vertical direction. At times, the coma may be featureless without lateralizing signs, although papilledema is often present.

BRAIN DEATH

This is a state of irreversible cessation of all cerebral and brainstem function with preservation of cardiac activity and maintenance of respiratory and somatic function by artificial means. Brain death is the only type of brain damage recognized as morally, ethically, and legally equivalent to death. Criteria have been advanced for the diagnosis of brain death, and it is essential to adhere to consensus standards as multiple studies have shown variability in local practice. Given the implications of such a diagnosis, clinicians must be thorough and precise in determining brain death. Established criteria are simple, can be assessed at the bedside, and allow no chance of diagnostic error. They contain two essential elements, after assuring that no confounding factors (e.g., hypothermia, drug intoxication) are present: (1) widespread cortical destruction that is reflected by deep coma and unresponsiveness to all forms of stimulation; (2) global brainstem damage demonstrated by absent pupillary light reaction, absent corneal reflexes, loss of oculovestibular reflexes, and destruction of the medulla, manifested by complete and irreversible apnea. Diabetes insipidus is usually present, but may only develop hours or days after the other clinical signs of brain death appear. The pupils are usually midsized but may be enlarged. Loss of deep tendon reflexes is not required because the spinal cord remains functional. Occasionally other reflexes that originate from the spine may be present and should not preclude a diagnosis of brain death.

Demonstration that apnea is due to medullary damage requires that the Pco_2 be high enough to stimulate respiration during a test of spontaneous breathing. Apnea testing can be done safely by the use of preoxygenation with 100% oxygen prior to and following removal of the ventilator. CO_2 tension increases ~0.3–0.4 kPa/min (2–3 mmHg/min) during apnea. Apnea is confirmed if no respiratory effort has been observed in the presence of a sufficiently elevated Pco_2. The apnea test is usually stopped if there is serious cardiovascular instability.

An isoelectric EEG may be used as an optional confirmatory test for total cerebral damage. Radionuclide brain scanning, cerebral angiography, or transcranial Doppler measurements may also be included to demonstrate the absence of blood flow when a confirmatory study is desired.

Some period of observation, usually 6–24 h, is recommended, during which the clinical signs of brain death are sustained. It is advisable to delay clinical testing for at least 24 h if a cardiac arrest has caused brain death or if the inciting disease is not known.

It is largely accepted in Western society that the ventilator can be disconnected from a brain-dead patient and that organ donation is subsequently possible. Good communication between the physician and the family is important with appropriate preparation of the family for brain death testing and diagnosis.

TREATMENT

Coma

The immediate goal in a comatose patient is prevention of further nervous system damage. Hypotension, hypoglycemia, hypercalcemia, hypoxia, hypercapnia, and hyperthermia should be corrected rapidly. An oropharyngeal airway is adequate to keep the pharynx open in a drowsy patient who is breathing normally. Tracheal intubation is indicated if there is apnea, upper airway obstruction, hypoventilation, or emesis, or if the patient is at risk for aspiration. Mechanical ventilation is required if there is hypoventilation or a need to induce hypocapnia in order to lower ICP. IV access is established, and naloxone and dextrose are administered if narcotic overdose or hypoglycemia is a possibility; thiamine is given along with glucose to avoid provoking Wernicke's encephalopathy in malnourished patients. In cases of suspected ischemic stroke including basilar thrombosis with brainstem ischemia, IV tissue plasminogen activator or mechanical embolectomy is often used after cerebral hemorrhage has been excluded and when the patient presents within established time windows for these interventions **(Chap. 420)**. Physostigmine may awaken patients with anticholinergic-type drug overdose but should be used only with careful monitoring; many physicians believe that it should only be used to treat anticholinergic overdose–associated cardiac arrhythmias. The use of benzodiazepine antagonists offers some prospect of improvement after overdose; however, these drugs are not commonly used empirically in part due to their tendency to provoke seizures. Certain other toxic and drug-induced comas have specific treatments such as fomepizole for ethylene glycol ingestion.

Administration of hypotonic intravenous solutions should be monitored carefully in any serious acute brain illness because of the potential for exacerbating brain swelling. Cervical spine injuries must not be overlooked, particularly before attempting intubation or evaluation of oculocephalic responses. Fever and meningismus indicate an urgent need for examination of the CSF to diagnose meningitis. Whenever acute bacterial meningitis is suspected, antibiotics including vancomycin and a third-generation cephalosporin should be administered along with dexamethasone, preferably after obtaining blood cultures **(see Chap. 133)**. **The management of raised ICP is discussed in Chap. 301.**

PROGNOSIS

Some patients, especially children and young adults, may have ominous early clinical findings such as abnormal brainstem reflexes and yet recover; ultra-early prognostication outside of brain death therefore is unwise. Metabolic comas have a far better prognosis than traumatic ones. All systems for estimating prognosis in adults should be taken as approximations, and medical judgments must be tempered by factors such as age, underlying systemic disease, and general medical condition. In an attempt to collect prognostic information from large numbers of patients with head injury, the Glasgow Coma Scale was devised; empirically, it has predictive value in cases of brain trauma **(see Chap. 435)**. For anoxic coma, clinical signs such as the pupillary and motor responses after 1 day, 3 days, and 1 week have been shown to have predictive value; however, some of these prediction rules are less reliable in the setting of therapeutic hypothermia and therefore serial examinations are advised in this setting. The absence of the cortical responses of the somatosensory evoked potentials has also been shown to be a strong indicator of poor outcome following hypoxic injury.

The uniformly poor outcome of persistent vegetative state has already been mentioned, but recent reports of a number of such patients displaying consistent cortical activation on functional MRI in response to salient stimuli have begun to alter the perception of such individuals. In one series, about 10% of vegetative patients (mainly following traumatic brain injury) could activate their frontal or temporal lobes in response to requests by an examiner to imagine certain visuospatial tasks. In one case, a rudimentary form of communication could be established. There are also reports in exceptional patients of improvement in cognitive function with the implantation of thalamic-stimulating electrodes or the use of novel activating agents including zolpidem. It is prudent to avoid generalizations from these findings, but the need for future studies of novel techniques to help communication and possibly recovery is needed.

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301 Severe Acute Encephalopathies and Critical Care Weakness

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Life-threatening neurologic illness may be caused by a primary disorder affecting any region of the neuraxis or may occur as a consequence of a systemic disorder such as hepatic failure, multisystem organ failure, or cardiac arrest **(Table 301-1)**. Neurologic critical care focuses on preservation of neurologic tissue and prevention of secondary brain injury caused by ischemia, hemorrhage, edema, herniation, and elevated intracranial pressure (ICP). Encephalopathy is a general term describing brain dysfunction that is diffuse, global, or multi-focal. Severe acute encephalopathies represent a group of various disorders due to different neurological or systemic etiologies, but that share the common themes of primary and secondary brain injury.

PATHOPHYSIOLOGY

Brain Edema Swelling, or edema, of brain tissue occurs with many types of brain injury. The two principal types of edema are vasogenic and cytotoxic. *Vasogenic edema* refers to the influx of fluid and solutes into the brain through an incompetent blood-brain barrier (BBB). In the normal cerebral vasculature, endothelial tight junctions associated with astrocytes create an impermeable barrier (the BBB), through which access into the brain interstitium is dependent upon specific transport mechanisms. The BBB may be compromised in ischemia, trauma, infection, and metabolic derangements. *Vasogenic edema* results from abnormal permeability of the BBB, and typically develops rapidly following injury. *Cytotoxic edema* results from cellular swelling, membrane breakdown, and ultimately cell death. Clinically significant brain edema usually represents a combination of vasogenic and cytotoxic components. Edema can lead to increased ICP as well as tissue shifts and brain displacement or herniation from focal processes **(Chap. 300)**. These tissue shifts can cause injury by mechanical distention and compression in addition to the ischemia of impaired perfusion consequent to the elevated ICP.

Ischemic Cascade and Cellular Injury When delivery of substrates, principally oxygen and glucose, is inadequate to sustain cellular function, a series of interrelated biochemical reactions known as the *ischemic cascade* is initiated **(see Fig. 419-2)**. The release of excitatory amino acids, especially glutamate, leads to influx of calcium

TABLE 301-1 Neurologic Disorders in Critical Illness

LOCALIZATION ALONG NEUROAXIS	SYNDROME
Central Nervous System	
Brain: Cerebral hemispheres	Global encephalopathy
	Delirium
	Sepsis
	Organ failure—hepatic, renal
	Medication related—sedatives, hypnotics, analgesics, H_2 blockers, antihypertensives
	Drug overdose
	Electrolyte disturbance—hyponatremia, hypoglycemia
	Hypotension/hypoperfusion
	Hypoxia
	Meningitis
	Subarachnoid hemorrhage
	Wernicke's disease
	Seizure—postictal or nonconvulsive status epilepticus
	Hypertensive encephalopathy
	Hypothyroidism—myxedema
	Focal deficits
	Ischemic stroke
	Tumor
	Abscess, subdural empyema
	Intraparenchymal hemorrhage
	Subdural/epidural hematoma
Brainstem/cerebellum	Mass effect and compression
	Basilar artery thrombosis
	Intraparenchymal hemorrhage
	Central pontine myelinolysis
Spinal cord	Mass effect and compression
	Disk herniation
	Epidural hematoma
	Ischemia—hypotension/embolic
	Epidural abscess
	Trauma
	Myelitis
Peripheral Nervous System	
Peripheral nerve	
Axonal	Critical illness polyneuropathy
	Neuromuscular blocking agent complications
	Metabolic disturbances, uremia, hyperglycemia
	Medication effects—chemotherapeutic, antiretroviral
Demyelinating	Guillain-Barré syndrome
	Chronic inflammatory demyelinating polyneuropathy
Neuromuscular junction	Prolonged effect of neuromuscular blockade
	Medication effects—aminoglycosides
	Myasthenia gravis, Lambert-Eaton syndrome, botulism
Muscle	Critical illness myopathy
	Cachectic myopathy
	Acute necrotizing myopathy
	Thick-filament myopathy
	Electrolyte disturbances—hypokalemia/hyperkalemia, hypophosphatemia
	Rhabdomyolysis

and sodium ions, which disrupt cellular homeostasis. An increased intracellular calcium concentration may activate proteases and lipases, which then lead to lipid peroxidation and free radical–mediated cell membrane injury. Cytotoxic edema ensues, and ultimately necrotic cell death and tissue infarction occur. This pathway to irreversible cell death is common to ischemic stroke, global cerebral ischemia, and traumatic brain injury.

Penumbra refers to areas of ischemic brain tissue that have not yet undergone irreversible infarction, implying that these regions are potentially salvageable if ischemia can be reversed. Factors that may exacerbate ischemic brain injury include systemic hypotension and hypoxia, which further reduce substrate delivery to vulnerable brain tissue, and fever, seizures, and hyperglycemia, which can increase cellular metabolism, outstripping compensatory processes. Clinically, these events are known as *secondary brain insults* because they lead to exacerbation of the primary brain injury. Prevention, identification, and treatment of secondary brain insults are fundamental goals of management.

An alternative pathway of cellular injury is *apoptosis*. This process implies programmed cell death, which may occur in the setting of ischemic stroke, global cerebral ischemia, traumatic brain injury, and possibly intracerebral hemorrhage. Apoptotic cell death can be distinguished histologically from the necrotic cell death of ischemia and is mediated through a different set of biochemical pathways; apoptotic cell death occurs without cerebral edema and therefore is often not seen on brain imaging. At present, interventions for prevention and treatment of apoptotic cell death remain less well defined than those for ischemia.

Cerebral Perfusion and Autoregulation Brain tissue requires constant perfusion in order to ensure adequate delivery of substrate. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of systemic blood pressures. Cerebral perfusion pressure (CPP), defined as the mean systemic arterial pressure (MAP) minus the ICP, provides the driving force for circulation across the capillary beds of the brain. *Autoregulation* refers to the physiologic response whereby cerebral blood flow (CBF) is regulated via alterations in cerebrovascular resistance in order to maintain perfusion over wide physiologic changes such as neuronal activation or changes in hemodynamic function. If systemic blood pressure drops, cerebral perfusion is preserved through vasodilation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion, resulting in fairly constant perfusion across a wide range of systemic blood pressures (Fig. 301-1). At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure. These autoregulatory changes occur in the microcirculation and are mediated by vessels below the resolution of those seen on angiography. CBF is also strongly influenced by pH and $Paco_2$. CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis because of pH related changes in cerebral vascular resistance. This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in both CBF and intracranial blood volume. Cerebral autoregulation is a complex process critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as traumatic brain injury and severe focal cerebral ischemia.

Cerebrospinal Fluid (CSF) and ICP The cranial contents consist essentially of brain, CSF, and blood. CSF is produced principally in the choroid plexus of each lateral ventricle, exits the brain via the foramens of Luschka and Magendie, and flows over the cortex to be absorbed into the venous system along the superior sagittal sinus. In adults, ~150 mL of CSF are contained within the ventricles and surrounding the brain and spinal cord; the cerebral blood volume is also ~150 mL. The bony skull offers excellent protection for the brain but allows little tolerance for additional volume. Significant increases in volume eventually result in increased ICP. Obstruction of CSF outflow, edema of cerebral tissue, or increases in volume from tumor or hematoma may increase ICP. Elevated ICP diminishes cerebral perfusion and

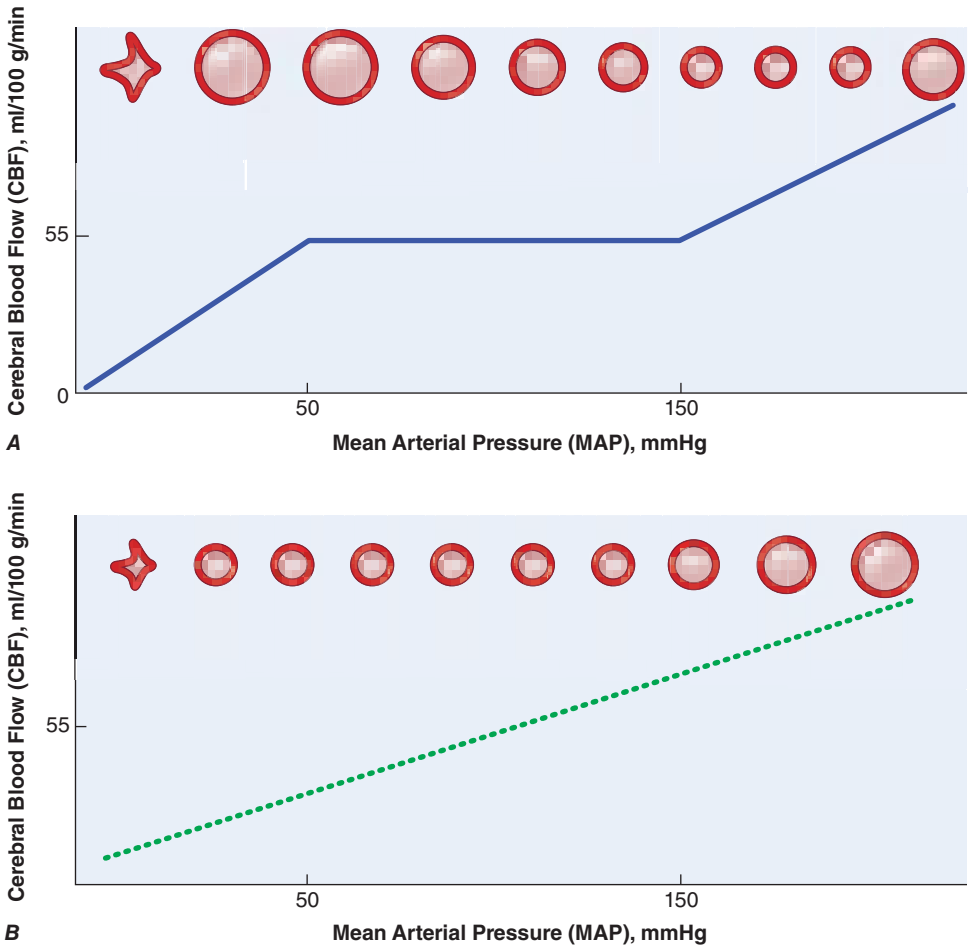

FIGURE 301-1 Pressure autoregulation of cerebral blood flow. In the normal state where autoregulation is intact ***A***, cerebral perfusion is constant over a wide range of systemic blood pressures (BP). This is mediated by dilation and constriction of small cerebral arterioles (round circles). Below the blood pressure threshold for maximal dilation, cerebral blood flow becomes pressure-dependent and decreases whereas above the threshold for maximum constriction cerebral blood flow increases with increasing systemic blood pressure. In severe brain injury, autoregulatory mechanisms may be impaired and cerebral blood flow becomes pressure-dependent throughout (***B***). At the extremes of BP there may be vascular collapse (very low BP) or forced vasodilation (very high BP).

can lead to tissue ischemia. Ischemia in turn may lead to vasodilation via autoregulatory mechanisms designed to restore cerebral perfusion. However, vasodilation also increases cerebral blood volume, which in turn then increases ICP, lowers CPP, and provokes further ischemia. This vicious cycle is commonly seen in traumatic brain injury, massive intracerebral hemorrhage, and large hemispheric infarcts with significant tissue shifts.

APPROACH TO THE PATIENT

Severe Brain Dysfunction

Critically ill patients with severe central nervous system (CNS) dysfunction require rapid evaluation and intervention in order to limit primary and secondary brain injury. Initial neurologic evaluation should be performed concurrent with stabilization of basic respiratory, cardiac, and hemodynamic parameters. Significant barriers may exist to neurologic assessment in the critical care unit, including endotracheal intubation and the use of sedative or paralytic agents to facilitate procedures.

An impaired level of consciousness is common in critically ill patients. The essential first task in assessment is to determine whether the cause of dysfunction is related to a diffuse, usually metabolic, process or whether a focal, usually structural, process is implicated. Examples of diffuse processes include metabolic encephalopathies related to organ failure, drug overdose, or hypoxia-ischemia. Focal processes include ischemic and hemorrhagic stroke and traumatic brain injury, especially with intracranial hematomas. Because these two categories of disorders have fundamentally different causes, treatments, and prognoses, the initial focus is on making this distinction rapidly and accurately. **The approach to the comatose patient is discussed in Chap. 300; etiologies are listed in Table 300-1.**

Minor focal deficits may be present on the neurologic examination in patients with metabolic encephalopathies. However, the finding of prominent focal signs such as pupillary asymmetry, hemiparesis, gaze palsy, or visual field deficit should suggest the possibility of a structural lesion. All patients with a decreased level of consciousness associated with focal findings should undergo an urgent neuroimaging procedure, as should all patients with coma of unknown etiology. Computed tomography (CT) scanning is usually the most appropriate initial study because it can be performed quickly in critically ill patients and demonstrates hemorrhage, hydrocephalus, and intracranial tissue shifts well. Magnetic resonance imaging (MRI) may provide more specific information in some situations, such as acute ischemic stroke (diffusion-weighted imaging [DWI]). Any suggestion of trauma from the history or examination should alert the examiner to the possibility of cervical spine injury and prompt an imaging evaluation using CT or MRI. Neurovascular imaging using CT or MRI angiography or venography is increasingly available and may suggest arterial occlusion or cerebral venous thrombosis.

Acute brainstem ischemia due to basilar artery thrombosis may cause brief episodes of spontaneous extensor posturing superficially

resembling generalized seizures. Coma of sudden onset, accompanied by these movements and cranial nerve abnormalities, necessitates emergency imaging. A noncontrast CT scan of the brain may reveal a hyperdense basilar artery indicating thrombus in the vessel, and subsequent CT or MR angiography can assess basilar artery patency.

Other diagnostic studies are best used in specific circumstances, usually when neuroimaging studies fail to reveal a structural lesion and the etiology of the altered mental state remains uncertain. Electroencephalography (EEG) can be important in the evaluation of critically ill patients with severe brain dysfunction. The EEG of metabolic encephalopathy typically reveals generalized slowing. One of the most important uses of EEG is to help exclude inapparent seizures, especially nonconvulsive status epilepticus. Untreated continuous or frequently recurrent seizures may cause neuronal injury, making the diagnosis and treatment of seizures crucial in this patient group. Lumbar puncture (LP) may be necessary to exclude infectious or inflammatory processes, and an elevated opening pressure may be an important clue to cerebral venous sinus thrombosis. In patients with coma or profound encephalopathy, it is preferable to perform a neuroimaging study prior to LP. If bacterial meningitis is suspected, an LP may be performed first or antibiotics may be empirically administered before the diagnostic studies are completed. Standard laboratory evaluation of critically ill patients should include assessment of serum electrolytes (especially sodium and calcium), glucose, renal and hepatic function, complete blood count, and coagulation. Serum or urine toxicology screens should be performed in patients with encephalopathy of unknown cause. EEG and LP are most useful when the mechanism of the altered level of consciousness is uncertain; they are not routinely performed for diagnosis in clear-cut cases of stroke or traumatic brain injury.

Monitoring of ICP can be an important tool in selected patients. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or traumatic brain injury, who are at significant risk for secondary brain injury due to elevated ICP and decreased CPP. Included are patients with the following: severe traumatic brain injury (Glasgow Coma Scale [GCS] score ≤8 **[Table 435-2]**); large tissue shifts from supratentorial ischemic or hemorrhagic stroke; or hydrocephalus from subarachnoid hemorrhage (SAH), intraventricular hemorrhage, or posterior fossa stroke. An additional disorder in which ICP monitoring can add important information is fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in the brain parenchyma, because ventriculostomy allows CSF drainage as a method of treating elevated ICP. However, parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications) **(Fig 301-2)**.

TREATMENT OF ELEVATED ICP

Elevated ICP may occur in a wide range of disorders, including head trauma, intracerebral hemorrhage, SAH with hydrocephalus, and fulminant hepatic failure. Because CSF and blood volume can be redistributed initially, by the time elevated ICP occurs, intracranial compliance is severely impaired. At this point, any small increase in the volume of CSF, intravascular blood, edema, or a mass lesion may result in a significant increase in ICP and a decrease in cerebral perfusion. This is a fundamental mechanism of secondary ischemic brain injury and constitutes an emergency that requires immediate attention. In general, ICP should be maintained at <20 mmHg and CPP should be maintained at ≥60 mmHg.

Interventions to lower ICP are ideally based on the underlying mechanism responsible for the elevated ICP **(Table 301-2)**. For example, in hydrocephalus from SAH, the principal cause of elevated ICP is impairment of CSF drainage. In this setting, ventricular drainage of CSF is likely to be sufficient and most appropriate. In head trauma and stroke, cytotoxic edema may be most responsible, and the use of osmotic agents such as mannitol or hypertonic saline becomes an appropriate early step. As described above, elevated ICP may cause tissue ischemia, and, if cerebral autoregulation is intact, the resulting vasodilation can lead to a cycle of worsening ischemia. Paradoxically, administration of vasopressor agents to increase mean arterial pressure may actually lower ICP by improving perfusion, thereby allowing autoregulatory vasoconstriction as ischemia is relieved and ultimately decreasing intracranial blood volume.

Early signs of elevated ICP include drowsiness and a diminished level of consciousness. Neuroimaging studies may reveal evidence of edema and mass effect. Hypotonic IV fluids should be avoided, and elevation of the head of the bed is recommended. Patients must be carefully observed for risk of aspiration and compromise of the airway as the level of alertness declines. Coma and unilateral

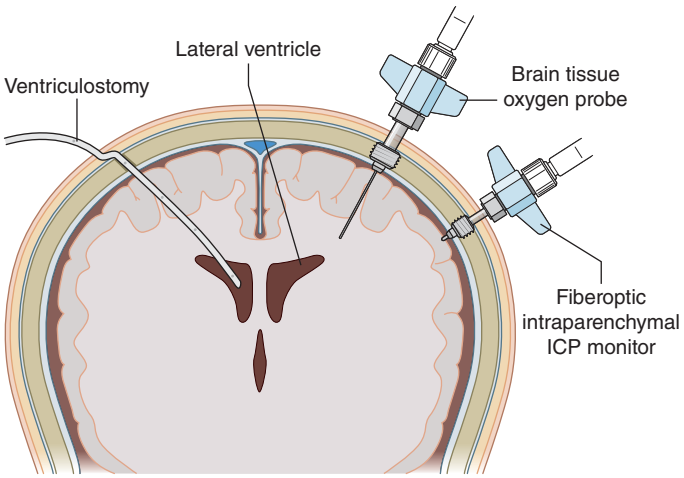

FIGURE 301-2 Intracranial pressure (ICP) and brain tissue oxygen monitoring. A ventriculostomy allows for drainage of cerebrospinal fluid to treat elevated ICP. Fiberoptic ICP and brain tissue oxygen monitors are usually secured using a screw-like skull bolt. Cerebral blood flow and microdialysis probes (not shown) may be placed in a manner similar to the brain tissue oxygen probe.

TABLE 301-2 Stepwise Approach to Treatment of Elevated Intracranial Pressure (ICP)[a]

Insert ICP monitor—ventriculostomy versus parenchymal device

General goals: maintain ICP <20 mmHg and CPP ≥60 mmHg. For ICP >20–25 mmHg for >5 min:

1. Elevate head of the bed; midline head position
2. Drain CSF via ventriculostomy (if in place)
3. Osmotherapy—mannitol 25–100 g q4h as needed (maintain serum osmolality <320 mosmol) or hypertonic saline (30 mL, 23.4% NaCl bolus)
4. Glucocorticoids—dexamethasone 4 mg q6h for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic and hemorrhagic stroke)
5. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before)
6. Hyperventilation—to $Paco_2$ 30–35 mmHg (short-term use or skip this step)
7. Pressor therapy—phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP ≥60 mmHg (maintain euvolemia to minimize deleterious systemic effects of pressors). May adjust target CPP in individual patients based on autoregulation status.
8. Consider second-tier therapies for refractory elevated ICP
   a. Decompressive craniectomy
   b. High-dose barbiturate therapy ("pentobarb coma")
   c. Hypothermia to 33°C

[a]Throughout ICP treatment algorithm, consider repeat head computed tomography to identify mass lesions amenable to surgical evacuation. May alter order of steps based on directed treatment to specific cause of elevated ICP.

Abbreviations: CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide.

pupillary changes are late signs and require immediate intervention. Emergent treatment of elevated ICP is most quickly achieved by intubation and hyperventilation, which causes vasoconstriction and reduces cerebral blood volume. To avoid provoking or worsening cerebral ischemia, hyperventilation, if used at all, is best administered only for short periods of time until a more definitive treatment can be instituted. Furthermore, the effects of hyperventilation on ICP are short-lived, often lasting only for several hours because of the buffering capacity of the cerebral interstitium, and rebound elevations of ICP may accompany abrupt discontinuation of hyperventilation. As the level of consciousness declines to coma, the ability to follow the neurologic status of the patient by examination lessens and measurement of ICP assumes greater importance. If a ventriculostomy device is in place, direct drainage of CSF to reduce ICP is possible. Finally, high-dose barbiturates, decompressive hemicraniectomy, and hypothermia are sometimes used for refractory elevations of ICP, although these have significant side effects and only decompressive hemicraniectomy has been shown to improve outcome in select patients.

SECONDARY BRAIN INSULTS

Patients with primary brain injuries, whether due to trauma or stroke, are at risk for ongoing secondary ischemic brain injury. Because secondary brain injury can be a major determinant of a poor outcome, strategies for minimizing secondary brain insults are an integral part of the critical care of all patients. Although elevated ICP may lead to secondary ischemia, most secondary brain injury is mediated through other clinical events that exacerbate the ischemic cascade already initiated by the primary brain injury. Episodes of secondary brain insults are usually not associated with apparent neurologic worsening. Rather, they lead to cumulative injury limiting eventual recovery, which manifests as a higher mortality rate or worsened long-term functional outcome. Thus, close monitoring of vital signs is important, as is early intervention to prevent secondary ischemia. Avoiding hypotension and hypoxia is critical, as significant hypotensive events (systolic blood pressure <90 mmHg) as short as 10 min in duration have been shown to adversely influence outcome after traumatic brain injury. Even in patients with stroke or head trauma who do not require ICP monitoring, close attention to adequate cerebral perfusion is warranted. Hypoxia (pulse oximetry saturation <90%), particularly in combination with hypotension, also leads to secondary brain injury. Likewise, fever and hyperglycemia both worsen experimental ischemia and have been associated with worsened clinical outcome after stroke and head trauma. Aggressive control of fever with a goal of normothermia is warranted but may be difficult to achieve with antipyretic medications and cooling blankets. The value of newer surface or intravascular temperature control devices for the management of refractory fever is under investigation. The use of IV insulin infusion is encouraged for control of hyperglycemia because this allows better regulation of serum glucose levels than SC insulin. A reasonable goal is to maintain the serum glucose level at <10.0 mmol/L (<180 mg/dL), although episodes of hypoglycemia appear equally detrimental and the optimal targets remain uncertain. New cerebral monitoring tools that allow continuous evaluation of brain tissue oxygen tension, CBF, and metabolism (via microdialysis) may further improve the management of secondary brain injury.

CRITICAL CARE DISORDERS OF THE CNS

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

This occurs from lack of delivery of oxygen to the brain because of extreme hypotension (hypoxia-ischemia) or hypoxia due to respiratory failure. Causes include myocardial infarction, cardiac arrest, shock, asphyxiation, paralysis of respiration, and carbon monoxide or cyanide poisoning. In some circumstances, hypoxia may predominate. Carbon monoxide and cyanide poisoning are sometimes termed *histotoxic hypoxia* because they cause a direct impairment of the respiratory chain.

Clinical Manifestations Mild degrees of pure hypoxia, such as occur at high altitudes, cause impaired judgment, inattentiveness, motor incoordination, and, at times, euphoria. However, with hypoxia-ischemia, such as occurs with circulatory arrest, consciousness is lost within seconds. If circulation is restored within 3–5 min, full recovery may occur, but if hypoxia-ischemia lasts beyond 3–5 min, some degree of permanent cerebral damage often results. Except in extreme cases, it may be difficult to judge the precise degree of hypoxia-ischemia, and some patients make a relatively full recovery after even 8–10 min of global cerebral ischemia. The brain is more tolerant to pure hypoxia than it is to hypoxia-ischemia. For example, a Pao_2 as low as 20 mmHg (2.7 kPa) can be well tolerated if it develops gradually, and normal blood pressure is maintained, whereas short durations of very low or absent cerebral circulation may result in permanent impairment.

Clinical examination at different time points after a hypoxic-ischemic insult (especially cardiac arrest) is useful in assessing prognosis for long-term neurologic outcome. The prognosis is better for patients with intact brainstem function, as indicated by normal pupillary light responses and intact oculocephalic (doll's eyes), oculovestibular (caloric), and corneal reflexes. Absence of these reflexes and the presence of persistently dilated pupils that do not react to light are grave prognostic signs. A low likelihood of a favorable outcome from hypoxic-ischemic coma is strongly suggested by an absent pupillary light reflex or extensor or absent motor response to pain on day 3 following the injury, excluding patients with metabolic disturbances and those treated with high-dose barbiturates or hypothermia, which confound interpretation of these signs. Electrophysiologically, the bilateral absence of the N20 component of the somatosensory evoked potential (SSEP) in the first several days also conveys a poor prognosis. Also, the presence of a burst-suppression pattern of myoclonic status epilepticus on EEG **(Fig 301-3)** or a nonreactive EEG is associated with a low likelihood of good functional outcome. A very elevated serum level (>33 μg/L) of the biochemical marker neuron-specific enolase (NSE) within the first 3 days is indicative of brain damage after resuscitation from cardiac arrest and predicts a poor outcome. Current approaches to prognostication after cardiac arrest encourage the use of a multimodal approach that includes these diagnostic tests, along with CT or MRI neuroimaging, in conjunction with clinical neurological assessment. Recent studies suggest that the administration of mild hypothermia after cardiac arrest (see "Treatment") may affect the time points when these clinical and electrophysiologic predictors become reliable in identifying patients with a very low likelihood of clinically meaningful recovery. For example, the false-positive rate for incorrect prediction of poor neurologic outcome may be as high as 21% (95% confidence interval [CI] 8–43%) for patients treated with mild hypothermia who exhibit 3-day motor function no better than extensor posturing. Thus, sufficient time from injury is important to ensure accuracy of prognostic assessment. Long-term consequences of hypoxic-ischemic encephalopathy include persistent coma or a vegetative state **(Chap. 300)**, dementia **(Chap. 25)**, visual agnosia **(Chap. 26)**, parkinsonism, choreoathetosis, cerebellar ataxia, myoclonus, seizures, and an amnestic state, which may be a consequence of selective damage to the hippocampus.

Pathology Principal histologic findings are extensive multifocal or diffuse laminar cortical necrosis **(Fig. 301-4)**, with frequent involvement of the hippocampus. The hippocampal CA1 neurons are vulnerable to even brief episodes of hypoxia-ischemia, perhaps explaining why selective persistent memory deficits may occur after brief cardiac arrest. Scattered small areas of infarction or neuronal loss may be present in the basal ganglia, hypothalamus, or brainstem. In some cases, extensive bilateral thalamic scarring may affect pathways that mediate arousal, and this pathology may be responsible for the persistent vegetative state. A specific form of hypoxic-ischemic encephalopathy, so-called watershed infarcts, occurs at the distal territories between the major cerebral arteries and can cause cognitive deficits, including visual agnosia, and weakness that is greater in proximal than in distal muscle groups.

Diagnosis Diagnosis is based on the history of a hypoxic-ischemic event such as cardiac arrest. Blood pressure <70 mmHg systolic or

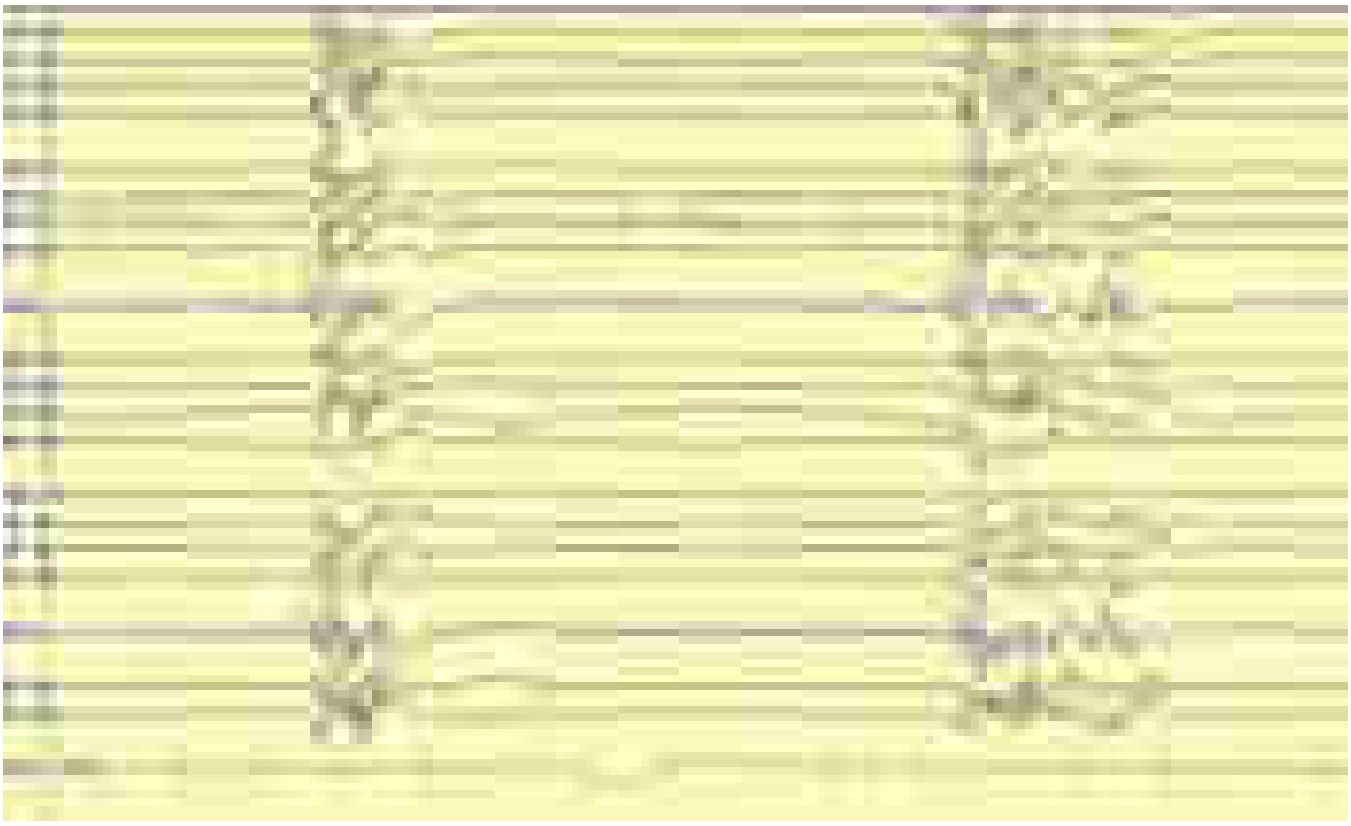

FIGURE 301-3 Electroencephalography (EEG) after cardiac arrest. A burst-suppression pattern is seen in a comatose patient with severe hypoxic-ischemic encephalopathy after cardiac arrest. In this patient, each burst on EEG was associated with a whole-body jerking movement leading to the clinical and electrophysiological diagnosis of myoclonic status epilepticus.

Pao_2 <40 mmHg is usually necessary, although both absolute levels and duration of exposure are important determinants of cellular injury. Carbon monoxide intoxication can be confirmed by measurement of carboxyhemoglobin and is suggested by a cherry red color of the venous blood and skin, although the latter is an inconsistent clinical finding.

TREATMENT

Hypoxic-Ischemic Encephalopathy

Treatment should be directed at restoration of normal cardiorespiratory function. This includes securing a clear airway, ensuring adequate oxygenation and ventilation, and restoring cerebral perfusion, whether by cardiopulmonary resuscitation, fluid, pressors, or cardiac pacing. Hypothermia may target the neuronal cell injury cascade and has substantial neuroprotective properties in experimental models of brain injury. In two trials, mild hypothermia (33°C) improved functional outcome in patients who remained comatose after resuscitation from a cardiac arrest. Treatment was initiated within minutes of cardiac resuscitation and continued for 12 h in one study and 24 h in the other. In a more recent study, targeted temperature management (TTM) to 33 or 36°C resulted in similar outcomes. Potential complications of hypothermia include coagulopathy and an increased risk of infection. Current guidelines recommend TTM for cardiac arrest patients who have no meaningful response to verbal commands after return of spontaneous circulation, with temperature maintained constant between 32 and 36°C for at least 24 h.

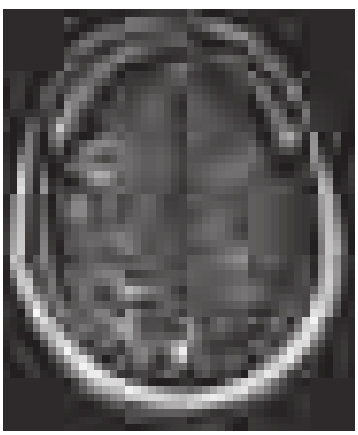

FIGURE 301-4 Cortical laminar necrosis in hypoxic-ischemic encephalopathy. T1-weighted postcontrast magnetic resonance imaging shows cortical enhancement in a watershed distribution consistent with laminar necrosis.

Severe carbon monoxide intoxication may be treated with hyperbaric oxygen. Anticonvulsants may be needed to control seizures, although these are not usually given prophylactically. Posthypoxic myoclonus may respond to oral administration of clonazepam at doses of 1.5–10 mg daily or valproate at doses of 300–1200 mg daily in divided doses. Myoclonic status epilepticus within 24 h after a primary circulatory arrest generally portends a very poor prognosis, even if seizures are controlled.

Carbon monoxide and cyanide intoxication can also cause a delayed encephalopathy. Little clinical impairment is evident when the patient first regains consciousness, but a parkinsonian syndrome characterized by akinesia and rigidity without tremor may develop. Symptoms can worsen over months, accompanied by increasing evidence of damage in the basal ganglia as seen on both CT and MRI.

POSTCARDIAC BYPASS BRAIN INJURY

CNS injuries following open heart or coronary artery bypass grafting (CABG) surgery are common and include acute encephalopathy, stroke, and a chronic syndrome of cognitive impairment. Hypoperfusion and embolic disease are frequently involved in the pathogenesis of these syndromes, although multiple mechanisms may be involved

in these critically ill patients who are at risk for various metabolic and polypharmaceutical complications.

The frequency of hypoxic injury secondary to inadequate blood flow intraoperatively has been markedly decreased by the use of modern surgical and anesthetic techniques. Despite these advances, some patients still experience neurologic complications from cerebral hypoperfusion or may suffer focal ischemia from carotid or focal intracranial stenoses in the setting of regional hypoperfusion. Postoperative infarcts in the border zones between vascular territories commonly are blamed on systemic hypotension, although these infarcts can also result from embolic disease.

Embolic disease is likely the predominant mechanism of cerebral injury during cardiac surgery as evidenced by diffusion-weighted MRI and intraoperative transcranial Doppler ultrasound studies. Thrombus in the heart itself as well as atheromas in the aortic arch can become dislodged during cardiac surgeries, releasing a shower of particulate matter into the cerebral circulation. Cross-clamping of the aorta, manipulation of the heart, extracorporeal circulation techniques ("bypass"), arrhythmias such as atrial fibrillation, and introduction of air through suctioning have all been implicated as potential sources of emboli.

This shower of microemboli results in a number of clinical syndromes. Occasionally, a single large embolus leads to an isolated large-vessel stroke that presents with obvious clinical focal deficits. When there is a high burden of very small emboli, an acute encephalopathy can occur postoperatively, presenting as either a hyperactive or hypoactive confusional state, the latter of which is frequently and incorrectly ascribed to depression or a sedative-induced delirium. When the burden of microemboli is lower, no acute syndrome is recognized, but the patient may suffer a chronic cognitive deficit.

METABOLIC ENCEPHALOPATHIES

Altered mental states, variously described as confusion, delirium, disorientation, and encephalopathy, are present in many patients with severe illness in an intensive care unit (ICU). Older patients are particularly vulnerable to delirium, a confusional state characterized by disordered perception, frequent hallucinations, delusions, and sleep disturbance. This is often attributed to medication effects, sleep deprivation, pain, and anxiety. The presence of delirium is associated with worsened outcome in critically ill patients, even in those without an identifiable CNS pathology such as stroke or brain trauma. In these patients, the cause of delirium is often multifactorial, resulting from organ dysfunction, sepsis, and especially the use of medications given to treat pain, agitation, or anxiety. Critically ill patients are often treated with a variety of sedative and analgesic medications, including opiates, benzodiazepines, neuroleptics, and sedative-anesthetic medications, such as propofol. In critically ill patients requiring sedation, use of the centrally acting α_2 agonist dexmedetomidine may reduce delirium and shorten the duration of mechanical ventilation compared to the use of benzodiazepines such as lorazepam or midazolam. The presence of family members in the ICU may also help to calm and orient agitated patients, and in severe cases, low doses of neuroleptics (e.g., haloperidol 0.5–1 mg) can be useful. Current strategies focus on limiting the use of sedative medications when this can be done safely.

In the ICU setting, several metabolic causes of an altered level of consciousness predominate. Hypercarbic encephalopathy can present with headache, confusion, stupor, or coma. Hypoventilation syndrome occurs most frequently in patients with a history of chronic CO_2 retention who are receiving oxygen therapy for emphysema or chronic pulmonary disease **(Chap. 290)**. The elevated $Paco_2$ leading to CO_2 narcosis may have a direct anesthetic effect, and cerebral vasodilation from increased $Paco_2$ can lead to increased ICP. Hepatic encephalopathy is suggested by asterixis and can occur in chronic liver failure or acute fulminant hepatic failure. Both hyperglycemia and hypoglycemia can cause encephalopathy, as can hypernatremia and hyponatremia. Confusion, impairment of eye movements, and gait ataxia are the hallmarks of acute Wernicke's disease (see below).

SEPSIS-ASSOCIATED ENCEPHALOPATHY

Pathogenesis In patients with sepsis, the systemic response to infectious agents leads to the release of circulating inflammatory mediators that appear to contribute to encephalopathy. Critical illness, in association with the systemic inflammatory response syndrome (SIRS), can lead to multisystem organ failure. This syndrome can occur in the setting of apparent sepsis, severe burns, or trauma, even without clear identification of an infectious agent. Many patients with critical illness, sepsis, or SIRS develop encephalopathy without obvious explanation. This condition is broadly termed *sepsis-associated encephalopathy*. Although the specific mediators leading to neurologic dysfunction remain uncertain, it is clear that the encephalopathy is not simply the result of metabolic derangements of multiorgan failure. The cytokines tumor necrosis factor, interleukin (IL)-1, IL-2, and IL-6 are thought to play a role in this syndrome.

Diagnosis Sepsis-associated encephalopathy presents clinically as a diffuse dysfunction of the brain without prominent focal findings. Confusion, disorientation, agitation, and fluctuations in level of alertness are typical. In more profound cases, especially with hemodynamic compromise, the decrease in level of alertness can be more prominent, at times resulting in coma. Hyperreflexia and frontal release signs such as a grasp or snout reflex **(Chap. 26)** can be seen. Abnormal movements such as myoclonus, tremor, or asterixis can occur. Sepsis-associated encephalopathy is quite common, occurring in the majority of patients with sepsis and multisystem organ failure. Diagnosis is often difficult because of the multiple potential causes of neurologic dysfunction in critically ill patients and requires exclusion of structural, metabolic, toxic, and infectious (e.g., meningitis or encephalitis) causes. The mortality rate of patients with sepsis-associated encephalopathy severe enough to produce coma approaches 50%, although this principally reflects the severity of the underlying critical illness and is not a direct result of the encephalopathy. Patients dying from severe sepsis or septic shock may have elevated levels of the serum brain injury biomarker S-100β and neuropathologic findings of neuronal apoptosis and cerebral ischemic injury. Successful treatment of the underlying critical illness almost always results in substantial improvement of the encephalopathy. However, although severe disability to the level of chronic vegetative or minimally conscious states is uncommon, long-term cognitive dysfunction clinically similar to dementia is being increasingly recognized in some survivors, especially in older patients.

OSMOTIC DEMYELINATION SYNDROME (CENTRAL PONTINE MYELINOLYSIS)

This disorder often presents in a devastating fashion as quadriplegia and pseudobulbar palsy although less severe presentations may occur. Predisposing factors include severe underlying medical illness or nutritional deficiency; most cases are associated with rapid correction of hyponatremia or with hyperosmolar states and clinical symptoms are usually identified a few days after sodium correction. Previously termed *central pontine myelinolysis*, the more accurate term *osmotic demyelination syndrome* is now preferred. The pathology consists of demyelination without inflammation in the base of the pons, with relative sparing of axons and nerve cells. MRI is useful in establishing the diagnosis **(Fig. 301-5)** and may also identify partial forms that present as confusion, dysarthria, and/or disturbances of conjugate gaze without quadriplegia. Occasional cases present with lesions outside of the brainstem. Therapeutic guidelines for the restoration of severe hyponatremia should aim for gradual correction, i.e., by ≤10 mmol/L (10 meq/L) within 24 h and 20 mmol/L (20 meq/L) within 48 h.

WERNICKE'S DISEASE

Wernicke's disease is a common and preventable disorder due to a deficiency of thiamine **(Chap. 326)**. In the United States, alcoholics account for most cases, but patients with malnutrition due to hyperemesis, starvation, renal dialysis, cancer, HIV/AIDS, or rarely gastric surgery are also at risk. The characteristic clinical triad is ophthalmoplegia, ataxia, and global confusion. However, only one-third of patients with acute Wernicke's disease present with the classic clinical triad. Most patients are profoundly disoriented, indifferent, and inattentive, although rarely they have an agitated delirium related to ethanol withdrawal. If the disease is not treated, stupor, coma, and death may ensue. Ocular motor abnormalities include horizontal nystagmus on

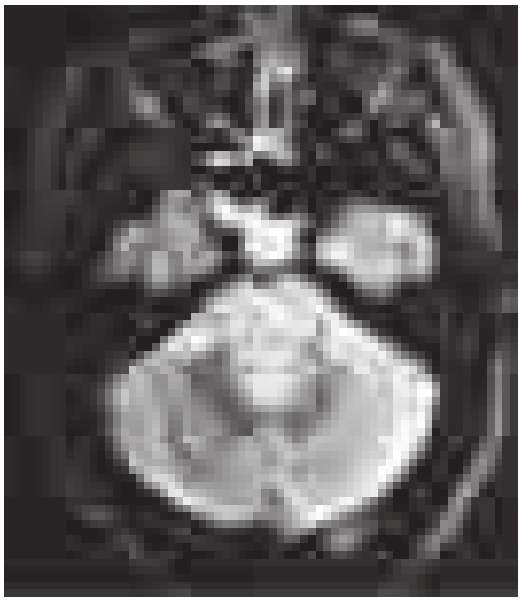

FIGURE 301-5 Osmotic demyelination syndrome. Axial T2-weighted magnetic resonance scan through the pons reveals a symmetric area of abnormal high signal intensity within the basis pontis (*arrows*).

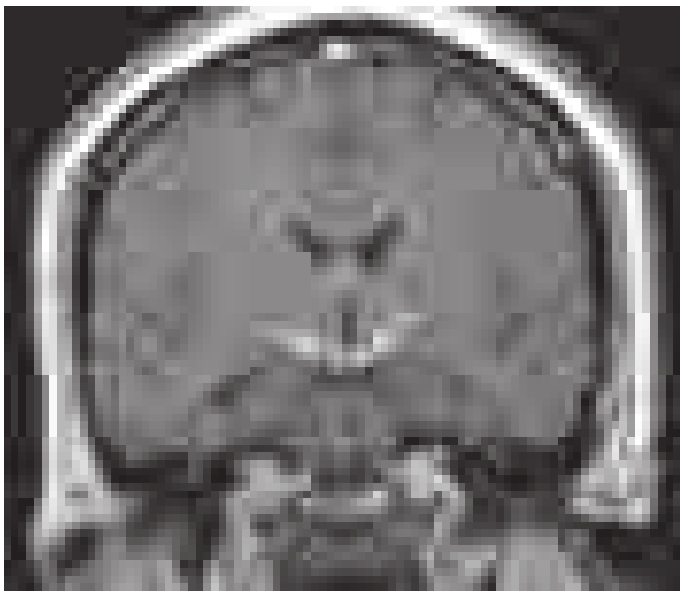

FIGURE 301-6 Wernicke's disease. Coronal T1-weighted postcontrast magnetic resonance imaging reveals abnormal enhancement of the mammillary bodies (*arrows*), typical of acute Wernicke's encephalopathy.

lateral gaze, lateral rectus palsy (usually bilateral), conjugate gaze palsies, and rarely ptosis. Gait ataxia probably results from a combination of polyneuropathy, cerebellar involvement, and vestibular paresis. The pupils are usually spared, but they may become miotic with advanced disease.

Wernicke's disease is usually associated with other manifestations of nutritional disease, such as polyneuropathy. Rarely, amblyopia or myelopathy occurs. Tachycardia and postural hypotension may be related to impaired function of the autonomic nervous system or to the coexistence of cardiovascular beriberi. Patients who recover show improvement in ocular palsies within hours after the administration of thiamine, but horizontal nystagmus may persist. Ataxia improves more slowly than the ocular motor abnormalities. Approximately half recover incompletely and are left with a slow, shuffling, wide-based gait and an inability to tandem walk. Apathy, drowsiness, and confusion improve more gradually. As these symptoms recede, an amnestic state with impairment in recent memory and learning may become more apparent (*Korsakoff's psychosis*). Korsakoff's psychosis is frequently persistent; the residual mental state is characterized by gaps in memory, confabulation, and disordered temporal sequencing.

Pathology Periventricular lesions surround the third ventricle, aqueduct, and fourth ventricle, with petechial hemorrhages in occasional acute cases and atrophy of the mammillary bodies in most chronic cases. There is frequently endothelial proliferation, demyelination, and some neuronal loss. These changes may be detected by MRI **(Fig. 301-6)**. The amnestic defect is related to lesions in the dorsal medial nuclei of the thalamus.

Pathogenesis Thiamine is a cofactor of several enzymes, including transketolase, pyruvate dehydrogenase, and α-ketoglutarate dehydrogenase. Thiamine deficiency produces a diffuse decrease in cerebral glucose utilization and results in mitochondrial damage. Glutamate accumulates due to impairment of α-ketoglutarate dehydrogenase activity and, in combination with the energy deficiency, may result in excitotoxic cell damage.

TREATMENT

Wernicke's Disease

Wernicke's disease is a medical emergency and requires immediate administration of thiamine, in a dose of 100 mg either IV or IM. The dose should be given daily until the patient resumes a normal diet and should be begun prior to treatment with IV glucose solutions. Larger doses, 100 mg four times a day or more, have been advocated by some. Glucose infusions may precipitate Wernicke's disease in a previously unaffected patient or cause a rapid worsening of an early form of the disease. For this reason, thiamine should be administered to all alcoholic patients requiring parenteral glucose.

HYPERPERFUSION DISORDERS (POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME)

Several seemingly diverse syndromes including hypertensive encephalopathy, eclampsia, postcarotid endarterectomy syndrome, and toxicity from calcineurin-inhibitor and other medications share the common pathogenesis of hyperperfusion likely due to endothelial dysfunction. Vasogenic edema is typically the primary process leading to neurologic dysfunction and this is thought to result from one of two mechanisms: exceeding the cerebral autoregulatory threshold leading to increased CBF and capillary leakage into the interstitium, or direct impairment of the BBB itself. The predilection of all of the hyperperfusion disorders to affect the posterior rather than anterior portions of the brain may be due to a lower threshold for autoregulatory breakthrough in the posterior circulation or a vasculopathy that is more common in these blood vessels.

These disorders of hyperperfusion can be divided into those caused primarily by increased pressure and those due to endothelial dysfunction from a toxic or autoimmune etiology **(Table 301-3)**. In reality, both of these processes likely play some role in each of these disorders. The clinical presentation of all of the hyperperfusion syndromes is similar with prominent headaches, seizures, or focal neurologic deficits. Headaches have no specific characteristics, range from mild to severe, and may be accompanied by alterations in consciousness ranging from confusion to coma. Seizures may be present, and these can be of multiple types depending on the severity and location of the edema. Nonconvulsive seizures have been described in hyperperfusion states; therefore, a low threshold for obtaining an electroencephalogram (EEG) in these patients should be maintained. The typical focal deficit in hyperperfusion states is cortical visual loss, given the tendency of the process to involve the occipital lobes. However, any focal deficit can occur depending on the area affected, as evidenced by patients who, after carotid endarterectomy, exhibit neurologic dysfunction referable to the ipsilateral newly reperfused hemisphere. It appears as if the rapidity of rise, rather than the absolute value of pressure, is the most important risk factor.

TABLE 301-3 Common Etiologies of Posterior Reversible Encephalopathy Syndrome

Disorders in which increased capillary pressure dominates the pathophysiology
Hypertensive encephalopathy, including secondary causes such as renovascular hypertension, pheochromocytoma, cocaine use, etc.
Postcarotid endarterectomy syndrome
Preeclampsia/eclampsia
Disorders in which endothelial dysfunction dominates the pathophysiology
Calcineurin-inhibitor toxicity (e.g. cyclosporine, tacrolimus)
Chemotherapeutic agent toxicity (e.g., cytarabine, azathioprine, 5-fluorouracil, cisplatin, methotrexate, tumor necrosis factor α antagonists)
HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count)
Hemolytic-uremic syndrome (HUS)

MRI classically exhibits the high T2 signal of edema primarily in the posterior occipital lobes, not respecting any single vascular territory **(Figure 301-7)**. CT is less sensitive but may show a pattern of patchy hypodensity in the involved territory. The term *posterior reversible encephalopathy syndrome* (PRES) is often used to describe these conditions; however, the clinical syndrome is not always reversible or limited just to the posterior brain regions. Vessel imaging may demonstrate narrowing of the cerebral vasculature, especially in the posterior circulation; whether this noninflammatory vasculopathy is a primary cause of the edema or occurs as a secondary phenomenon remains unclear. Other ancillary studies such as CSF analysis often yield nonspecific results. Many of the substances that have been implicated, such as cyclosporine, can cause this syndrome even at low doses or after years of treatment. Therefore, normal serum levels of these medications do not exclude them as inciting agents.

Treatment involves judicious lowering of the blood pressure with IV agents such as labetalol or nicardipine, removal of the offending medication, and treatment of an underlying medical condition such as eclampsia. If the blood pressure is very elevated, it is reasonable to lower the MAP by ~20% initially, as further lowering of the pressure may cause secondary ischemia and possibly infarction as pressure drops below the lower range of the patient's autoregulatory capability. Seizures must be identified and controlled, often necessitating continuous EEG monitoring. Anticonvulsants are effective when seizure activity is identified, but in the special case of eclampsia, there is evidence to support the use of magnesium sulfate for seizure control.

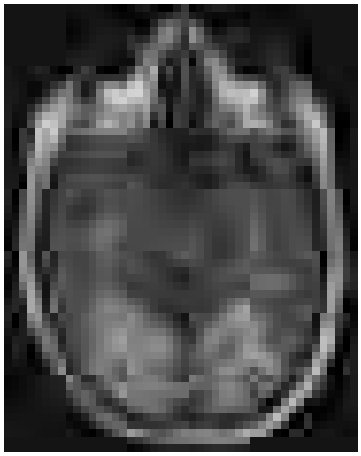

FIGURE 301-7 Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the brain in a patient taking cyclosporine after liver transplantation, who presented with seizures, headache, and cortical blindness. Increased signal is seen bilaterally in the occipital lobes predominantly involving the white matter, consistent with a hyperperfusion state secondary to calcineurin-inhibitor exposure.

POST-SOLID ORGAN TRANSPLANT BRAIN INJURY

Immunosuppressive medications are administered in high doses to patients after solid organ transplant, and many of these compounds have well-described neurologic complications. In patients with headache, seizures, or focal neurologic deficits taking calcineurin inhibitors, the diagnosis of hyperperfusion syndrome should be considered, as discussed above. This neurotoxicity occurs mainly with cyclosporine and tacrolimus and can present even in the setting of normal serum drug levels. Treatment primarily involves lowering the drug dosage or discontinuing the drug. Sirolimus has very few recorded cases of neurotoxicity and may be a reasonable alternative for some patients. Other examples of immunosuppressive medications and their neurologic complications include OKT3-associated akinetic mutism and the leukoencephalopathy seen with methotrexate, especially when it is administered intrathecally or with concurrent radiotherapy. In any solid organ transplant patient with neurologic complaints, a careful examination of the medication list is required to search for these possible drug effects.

Cerebrovascular complications of solid organ transplant are often first recognized in the immediate postoperative period. Border zone territory infarctions can occur, especially in the setting of systemic hypotension during cardiac transplant surgery. Embolic infarctions classically complicate cardiac transplantation, but all solid organ transplant procedures place patients at risk for systemic emboli. When cerebral embolization accompanies renal or liver transplantation surgery, a careful search for right-to-left shunting should include evaluation of the heart with agitated saline echocardiography (i.e., "bubble study"), as well as looking for intrapulmonary shunting. Renal and some cardiac transplant patients often have advanced atherosclerosis, providing a risk for stroke. Imaging with CT or MRI should be done when cerebrovascular complications are suspected to confirm the diagnosis and to exclude intracerebral hemorrhage, which most often occurs in the setting of coagulopathy secondary to liver failure or after cardiac bypass procedures.

Given that patients with solid organ transplants are chronically immunosuppressed, infections are a common concern **(Chap. 138)**. In any transplant patient with new CNS signs or symptoms such as seizure, confusion, or focal deficit, the diagnosis of a CNS infection should be considered and evaluated through imaging (usually MRI) and possibly lumbar puncture. The most common pathogens responsible for CNS infections in these patients vary based on time since transplant. In the first month posttransplant, common pathogens include the usual bacterial organisms associated with surgical procedures and indwelling catheters. Starting in the second month posttransplant, opportunistic infections of the CNS become more common, including *Nocardia* and *Toxoplasma* species as well as fungal infections such as aspergillosis. Viral infections that can affect the brain of the immunosuppressed patient, such as herpes simplex virus, cytomegalovirus, human herpesvirus type 6 (HHV-6), and varicella, also become more common after the first month posttransplant. Beyond 6 months, immunosuppressed posttransplant patients still remain at risk for these opportunistic bacterial, fungal, and viral infections but can also suffer late CNS infectious complications such as progressive multifocal leukoencephalopathy (PML) associated with JC virus **(Chap. 132)**, and Epstein-Barr virus–driven clonal expansions of B cells resulting in posttransplant lymphoproliferative disorder or CNS lymphoma **(Chap. 86)**.

CRITICAL CARE DISORDERS OF THE PERIPHERAL NERVOUS SYSTEM (PNS)

Critical illness with disorders of the PNS arises in two contexts: (1) primary neurologic diseases that require critical care interventions such as intubation and mechanical ventilation, and (2) secondary PNS manifestations of systemic critical illness, often involving multisystem organ failure. The former include acute polyneuropathies such as Guillain-Barré syndrome **(Chap. 439)**, neuromuscular junction disorders including myasthenia gravis **(Chap. 440)** and botulism **(Chap. 148)**, and primary muscle disorders such as polymyositis **(Chap. 358)**. The latter result either from the systemic disease itself or as a consequence

of interventions and as a group are often referred to as ICU acquired weakness (ICUAW).

General principles of respiratory evaluation in patients with PNS involvement, regardless of cause, include assessment of pulmonary mechanics, such as maximal inspiratory force (MIF) and vital capacity (VC), and evaluation of strength of bulbar muscles. Regardless of the cause of weakness, endotracheal intubation should be considered when the MIF falls to below –25 cmH_2O or the VC is <1 L. Also, patients with severe palatal weakness may require endotracheal intubation in order to prevent acute upper airway obstruction or recurrent aspiration. Arterial blood gases and oxygen saturation from pulse oximetry are used to follow patients with potential respiratory compromise from PNS dysfunction. However, intubation and mechanical ventilation should be undertaken based on clinical assessment rather than waiting until oxygen saturation drops or CO_2 retention develops from hypoventilation. Noninvasive mechanical ventilation may be considered initially in lieu of endotracheal intubation in myasthenia gravis but is generally insufficient in patients with severe bulbar weakness or ventilatory failure with hypercarbia. **Principles of mechanical ventilation are discussed in Chap. 295.**

NEUROPATHY

Although encephalopathy may be the most obvious neurologic dysfunction in critically ill patients, dysfunction of the PNS is also quite common. It is typically present in patients with prolonged critical illnesses lasting several weeks and involving sepsis; clinical suspicion is aroused when there is failure to wean from mechanical ventilation despite improvement of the underlying sepsis and critical illness. *Critical illness polyneuropathy* refers to the most common PNS complication related to critical illness; it is seen in the setting of prolonged critical illness, sepsis, and multisystem organ failure. Neurologic findings include diffuse weakness, decreased reflexes, and distal sensory loss. Electrophysiologic studies demonstrate a diffuse, symmetric, distal axonal sensorimotor neuropathy, and pathologic studies have confirmed axonal degeneration. The precise mechanism of critical illness polyneuropathy remains unclear, but circulating factors such as cytokines, which are associated with sepsis and SIRS, are thought to play a role. It has been reported that up to 70% of patients with the sepsis syndrome have some degree of neuropathy, although far fewer have a clinical syndrome profound enough to cause severe respiratory muscle weakness requiring prolonged mechanical ventilation or resulting in failure to wean. Aggressive glycemic control with insulin infusions appears to decrease the risk of critical illness polyneuropathy. Treatment is otherwise supportive, with specific intervention directed at treating the underlying illness. Although spontaneous recovery is usually seen, the time course may extend over weeks to months and necessitate long-term ventilatory support and care even after the underlying critical illness has resolved.

DISORDERS OF NEUROMUSCULAR TRANSMISSION

A defect in neuromuscular transmission may be a source of weakness in critically ill patients. Botulism **(Chap. 148)** may be acquired by ingesting botulinum toxin from improperly stored food or may arise from an anaerobic abscess from *Clostridium botulinum* (wound botulism). Infants can present with generalized weakness from gut-derived *Clostridium* infection, especially if they are fed honey. Diplopia and dysphagia are early signs of food-borne botulism. Treatment is mostly supportive, although use of antitoxin early in the course may limit the duration of the neuromuscular blockade. General ICU care is similar to patients with Guillain-Barré syndrome or myasthenia gravis with focused care to avoid ulcer formation at pressure points, deep venous thromboprophylaxis, and infection prevention. Public health officers should be rapidly informed when the diagnosis is made to prevent further exposure to others from the tainted food or source of wound botulism (such as injection drug use).

Undiagnosed myasthenia gravis **(Chap. 440)** may be a consideration in weak ICU patients; however, persistent weakness secondary to impaired neuromuscular junction transmission is almost always due to administration of drugs. A number of medications impair neuromuscular transmission; these include antibiotics, especially aminoglycosides, and beta-blocking agents. In the ICU, the nondepolarizing neuromuscular blocking agents (nd-NMBAs), also known as muscle relaxants, are most commonly responsible. Included in this group of drugs are such agents as pancuronium, vecuronium, rocuronium, and cisatracurium. They are often used to facilitate mechanical ventilation or other critical care procedures, but with prolonged use persistent neuromuscular blockade may result in weakness even after discontinuation of these agents hours or days earlier. Risk factors for this prolonged action of neuromuscular blocking agents include female sex, metabolic acidosis, and renal failure.

Prolonged neuromuscular blockade does not appear to produce permanent damage to the PNS. Once the offending medications are discontinued, full strength is restored, although this may take days. In general, the lowest dose of neuromuscular blocking agent should be used to achieve the desired result and, when these agents are used in the ICU, a peripheral nerve stimulator should be used to monitor neuromuscular junction function.

MYOPATHY

Critically ill patients, especially those with sepsis, frequently develop muscle weakness and wasting, often in the face of seemingly adequate nutritional support. *Critical illness myopathy* is an overall term that describes several different discrete muscle disorders that may occur in critically ill patients. The assumption has been that a catabolic myopathy may develop as a result of multiple factors, including elevated cortisol and catecholamine release and other circulating factors induced by the SIRS. In this syndrome, known as *cachectic myopathy*, serum creatine kinase levels and electromyography (EMG) are normal. Muscle biopsy shows type II fiber atrophy. Panfascicular muscle fiber necrosis may also occur in the setting of profound sepsis. This less common *acute necrotizing intensive care myopathy* is characterized clinically by weakness progressing to a profound level over just a few days. There may be associated elevations in serum creatine kinase and urine myoglobin. Both EMG and muscle biopsy may be normal initially but eventually show abnormal spontaneous activity and panfascicular necrosis with an accompanying inflammatory reaction. Acute rhabdomyolysis can occur from alcohol ingestion or from compartment syndromes.

A *thick-filament myopathy* may occur in the setting of glucocorticoid and nd-NMBA use. The most frequent scenario in which this is encountered is the asthmatic patient who requires high-dose glucocorticoids and nd-NMBA to facilitate mechanical ventilation. This muscle disorder is not due to prolonged action of nd-NMBAs at the neuromuscular junction but, rather, is an actual myopathy with muscle damage; it has occasionally been described with high-dose glucocorticoid use or sepsis alone. Clinically this syndrome is most often recognized when a patient fails to wean from mechanical ventilation despite resolution of the primary pulmonary process. Pathologically, there may be loss of thick (myosin) filaments. Thick-filament critical illness myopathy has a good prognosis. If patients survive their underlying critical illness, the myopathy invariably improves and most patients return to normal. However, because this syndrome is a result of true muscle damage, not just prolonged blockade at the neuromuscular junction, this process may take weeks or months, and tracheotomy with prolonged ventilatory support may be necessary. Some patients do have residual long-term weakness, with atrophy and fatigue limiting ambulation. At present, it is unclear how to prevent this myopathic complication, except by avoiding use of nd-NMBAs, a strategy not always possible. Monitoring with a peripheral nerve stimulator can help to avoid the overuse of these agents. However, this is more likely to prevent the complication of prolonged neuromuscular junction blockade than it is to prevent this myopathy.

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302 Subarachnoid Hemorrhage

J. Claude Hemphill, III, Wade S. Smith, Daryl R. Gress

Subarachnoid hemorrhage (SAH) renders the brain critically ill from both primary and secondary brain insults. Excluding head trauma, the most common cause of SAH is rupture of a saccular aneurysm. Other causes include bleeding from a vascular malformation (arteriovenous malformation or dural arteriovenous fistula) and extension into the subarachnoid space from a primary intracerebral hemorrhage. Some idiopathic SAHs are localized to the perimesencephalic cisterns and are benign; they probably have a venous or capillary source, and angiography is unrevealing.

SACCULAR ("BERRY") ANEURYSM

Autopsy and angiography studies have found that about 2% of adults harbor intracranial aneurysms, for a prevalence of 4 million persons in the United States; the aneurysm will rupture, producing SAH, in 25,000–30,000 cases per year. For patients who arrive alive at hospital, the mortality rate over the next month is about 45%. Of those who survive, more than half are left with major neurologic deficits as a result of the initial hemorrhage, cerebral vasospasm with infarction, or hydrocephalus. If the patient survives but the aneurysm is not obliterated, the rate of rebleeding is about 20% in the first 2 weeks, 30% in the first month, and about 3% per year afterward. Given these alarming figures, the major therapeutic emphasis is on preventing the predictable early complications of the SAH.

Unruptured, asymptomatic aneurysms are much less dangerous than a recently ruptured aneurysm. The annual risk of rupture for aneurysms <10 mm in size is ~0.1%, and for aneurysms ≥10 mm in size is ~0.5–1%; the surgical morbidity rate far exceeds these percentages. Aneurysm location may also factor into risk, with basilar bifurcation aneurysms appearing to have a somewhat higher rupture risk. Because of the longer length of exposure to risk of rupture, younger patients with aneurysms >10 mm in size may benefit from prophylactic treatment. As with the treatment of asymptomatic carotid stenosis, this risk-benefit ratio strongly depends on the complication rate of treatment.

Giant aneurysms, those >2.5 cm in diameter, occur at the same sites (see below) as small aneurysms and account for 5% of cases. The three most common locations are the terminal internal carotid artery, middle cerebral artery (MCA) bifurcation, and top of the basilar artery. Their risk of rupture is ~6% in the first year after identification and may remain high indefinitely. They often cause symptoms by compressing the adjacent brain or cranial nerves.

Mycotic aneurysms are usually located distal to the first bifurcation of major arteries of the circle of Willis. Most result from infected emboli due to bacterial endocarditis causing septic degeneration of arteries and subsequent dilation and rupture. Whether these lesions should be sought and repaired prior to rupture or left to heal spontaneously with antibiotic treatment remains controversial.

Pathophysiology Saccular aneurysms occur at the bifurcations of the large- to medium-sized intracranial arteries; rupture is into the subarachnoid space in the basal cisterns and sometimes into the parenchyma of the adjacent brain. Approximately 85% of aneurysms occur in the anterior circulation, mostly on the circle of Willis. About 20% of patients have multiple aneurysms, many at mirror sites bilaterally. As an aneurysm develops, it typically forms a neck with a dome. The length of the neck and the size of the dome vary greatly and are important factors in planning neurosurgical obliteration or endovascular embolization. The arterial internal elastic lamina disappears at the base of the neck. The media thins, and connective tissue replaces smooth-muscle cells. At the site of rupture (most often the dome), the wall thins, and the tear that allows bleeding is often ≤0.5 mm long. Aneurysm size and site are important in predicting risk of rupture. Those >7 mm in diameter and those at the top of the basilar artery and at the origin of the posterior communicating artery are at greater risk of rupture.

Clinical Manifestations Most unruptured intracranial aneurysms are completely asymptomatic. Symptoms are usually due to rupture and resultant SAH, although some unruptured aneurysms present with mass effect on cranial nerves or brain parenchyma. At the moment of aneurysmal rupture with major SAH, the intracranial pressure (ICP) suddenly rises. This may account for the sudden transient loss of consciousness that occurs in nearly half of patients. Sudden loss of consciousness may be preceded by a brief moment of excruciating headache, but most patients first complain of headache upon regaining consciousness. In 10% of cases, aneurysmal bleeding is severe enough to cause loss of consciousness for several days. In ~45% of cases, severe headache associated with exertion is the presenting complaint. The patient often calls the headache "the worst headache of my life"; however, the most important characteristic is sudden onset. Occasionally, these ruptures may present as headache of only moderate intensity or as a change in the patient's usual headache pattern. The headache is usually generalized, often with neck stiffness, and vomiting is common.

Although sudden headache in the absence of focal neurologic symptoms is the hallmark of aneurysmal rupture, focal neurologic deficits may occur. Anterior communicating artery or MCA bifurcation aneurysms may rupture into the adjacent brain or subdural space and form a hematoma large enough to produce mass effect. The deficits that result can include hemiparesis, aphasia, and mental slowness (abulia).

Occasionally, prodromal symptoms suggest the location of a progressively enlarging unruptured aneurysm. A third cranial nerve palsy, particularly when associated with pupillary dilation, loss of ipsilateral (but retained contralateral) light reflex, and focal pain above or behind the eye, may occur with an expanding aneurysm at the junction of the posterior communicating artery and the internal carotid artery. A sixth nerve palsy may indicate an aneurysm in the cavernous sinus, and visual field defects can occur with an expanding supraclinoid carotid or anterior cerebral artery (ACA) aneurysm. Occipital and posterior cervical pain may signal a posterior inferior cerebellar artery or anterior inferior cerebellar artery aneurysm (Chap. 419). Pain in or behind the eye and in the low temple can occur with an expanding MCA aneurysm. Thunderclap headache is a variant of migraine that simulates an SAH. Before concluding that a patient with sudden, severe headache has thunderclap migraine, a definitive workup for aneurysm or other intracranial pathology is required.

TABLE 302-1 Grading Scales for Subarachnoid Hemorrhage

GRADE	HUNT-HESS SCALE	WORLD FEDERATION OF NEUROSURGICAL SOCIETIES (WFNS) SCALE
1	Mild headache, normal mental status, no cranial nerve or motor findings	GCS[a] score 15, no motor deficits
2	Severe headache, normal mental status, may have cranial nerve deficit	GCS score 13–14, no motor deficits
3	Somnolent, confused, may have cranial nerve or mild motor deficit	GCS score 13–14, with motor deficits
4	Stupor, moderate to severe motor deficit, may have intermittent reflex posturing	GCS score 7–12, with or without motor deficits
5	Coma, reflex posturing or flaccid	GCS score 3–6, with or without motor deficits

[a]Glasgow Coma Scale; see **Table 435-1**.

Aneurysms can undergo small ruptures and leaks of blood into the subarachnoid space, so-called *sentinel bleeds*. Sudden unexplained headache at any location should raise suspicion of SAH and be investigated, because a major hemorrhage may be imminent.

The initial clinical manifestations of SAH can be graded using the Hunt-Hess or World Federation of Neurosurgical Societies classification schemes **(Table 302-1)**. For ruptured aneurysms, prognosis for good outcomes falls as the grade increases. For example, it is unusual for a Hunt-Hess grade 1 patient to die if the aneurysm is treated, but the mortality rate for grade 4 and 5 patients may be as high as 60%.

Delayed Neurologic Deficits There are four major causes of delayed neurologic deficits: rerupture, hydrocephalus, delayed cerebral ischemia (DCI), and hyponatremia.

1. *Rerupture*. The incidence of rerupture of an untreated aneurysm in the first month following SAH is ~30%, with the peak in the first 7 days. Rerupture is associated with a 50% mortality rate and poor outcome. Early treatment eliminates this risk.
2. *Hydrocephalus*. Acute hydrocephalus can cause stupor and coma and can be mitigated by placement of an external ventricular drain. More often, subacute hydrocephalus may develop over a few days or weeks and causes progressive drowsiness or slowed mentation with incontinence. Hydrocephalus is differentiated from cerebral vasospasm with a CT scan, CT angiogram, transcranial Doppler (TCD) ultrasound, or conventional x-ray angiography. Hydrocephalus may clear spontaneously or require temporary ventricular drainage. Chronic hydrocephalus may develop weeks to months after SAH and manifest as gait difficulty, incontinence, or impaired mentation. Subtle signs may be a lack of initiative in conversation or a failure to recover independence.
3. *Delayed cerebral ischemia*. Vasospasm is the narrowing of the arteries at the base of the brain following SAH. This may cause symptomatic ischemia and infarction in ~30% of patients and is the major cause of delayed morbidity and death. Signs of DCI appear 4–14 days after the hemorrhage, most often at 7 days. The severity and distribution of vasospasm determine whether infarction will occur.
   a. Vasospasm is believed to result from direct effects of clotted blood and its breakdown products on the arteries within the subarachnoid space. In general, the more blood that surrounds the arteries, the greater the chance of symptomatic vasospasm. Spasm of major arteries produces symptoms referable to the appropriate vascular territory **(Chap. 419)**. All of these focal symptoms may present abruptly, fluctuate, or develop over a few days. In most cases, focal spasm is preceded by a decline in mental status.
   b. Vasospasm can be detected reliably with conventional x-ray angiography, but this procedure is invasive and carries the risk of stroke and other complications. TCD ultrasound is based on the principle that the velocity of blood flow within an artery will rise as the lumen diameter is narrowed. By directing the probe along the MCA and proximal ACA, carotid terminus, and vertebral and basilar arteries on a daily or every-other-day basis, vasospasm can be reliably detected and treatments initiated to prevent cerebral ischemia (see below). CT angiography is another method that can detect vasospasm.
   c. Severe cerebral edema in patients with infarction from vasospasm may increase the ICP enough to reduce cerebral perfusion pressure. Treatment may include mannitol, hyperventilation, and for intractable cases hemicraniectomy; moderate hypothermia may have a role as well.
4. *Hyponatremia*. Hyponatremia may be profound and can develop quickly in the first 2 weeks following SAH. There is both natriuresis and volume depletion with SAH, so that patients become both hyponatremic and hypovolemic. Both atrial natriuretic peptide and brain natriuretic peptide have a role in producing this "cerebral salt-wasting syndrome." Typically, it clears over the course of 1–2 weeks and, in the setting of SAH, should not be treated with free-water restriction as this may increase the risk of stroke (see below).

Laboratory Evaluation and Imaging (Fig. 302-1) The hallmark of aneurysmal rupture is blood in the cerebrospinal fluid (CSF). More than 95% of cases have enough blood to be visualized on a high-quality noncontrast CT scan obtained within 72 h. If the scan fails to establish the diagnosis of SAH and no mass lesion or obstructive hydrocephalus is found, a lumbar puncture should be performed to establish the presence of subarachnoid blood. Lysis of the red blood cells and subsequent conversion of hemoglobin to bilirubin stains the spinal fluid yellow within 6–12 h. This xanthochromic spinal fluid

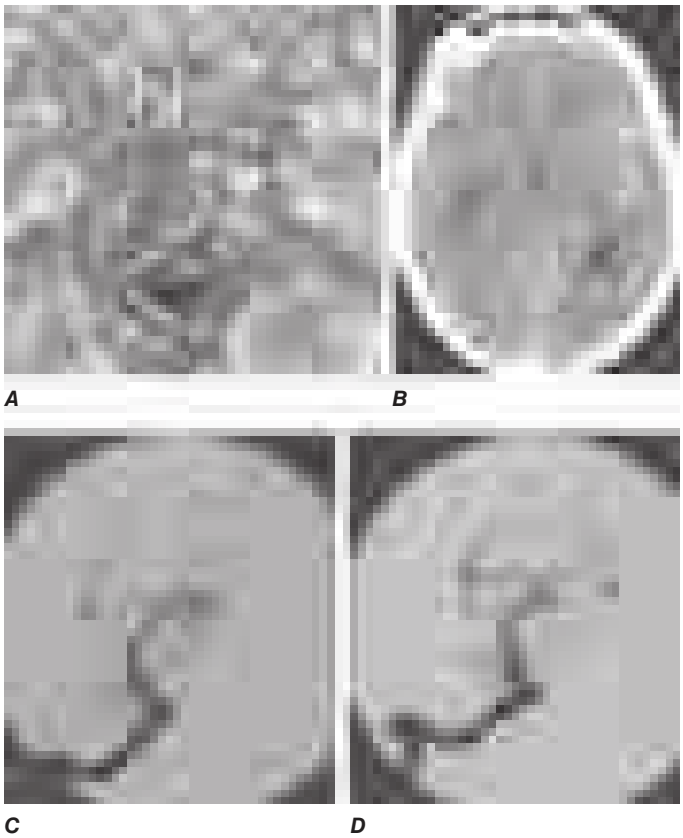

FIGURE 302-1 Subarachnoid hemorrhage. ***A.*** Computed tomography (CT) angiography revealing an aneurysm of the left superior cerebellar artery. ***B.*** Noncontrast CT scan at the level of the third ventricle revealing subarachnoid blood (*bright*) in the left sylvian fissure and within the left lateral ventricle. ***C.*** Conventional anteroposterior x-ray angiogram of the right vertebral and basilar artery showing the large aneurysm. ***D.*** Conventional angiogram following coil embolization of the aneurysm, whereby the aneurysm body is filled with platinum coils delivered through a microcatheter navigated from the femoral artery into the aneurysm neck.

peaks in intensity at 48 h and lasts for 1–4 weeks, depending on the amount of subarachnoid blood.

The extent and location of subarachnoid blood on a noncontrast CT scan help locate the underlying aneurysm, identify the cause of any neurologic deficit, and predict the occurrence of vasospasm. A high incidence of symptomatic vasospasm in the MCA and ACA has been found when early CT scans show subarachnoid clots >5 × 3 mm in the basal cisterns, or layers of blood >1 mm thick in the cerebral fissures. CT scans less reliably predict vasospasm in the vertebral, basilar, or posterior cerebral arteries.

Lumbar puncture prior to an imaging procedure is indicated only if a CT scan is not available at the time of the suspected SAH. Once the diagnosis of hemorrhage from a ruptured saccular aneurysm is suspected, four-vessel conventional x-ray angiography (both carotids and both vertebrals) is generally performed to localize and define the anatomic details of the aneurysm and to determine if other unruptured aneurysms exist **(Fig. 302-1*C*)**. At some centers, the ruptured aneurysm can be treated using endovascular techniques at the time of the initial angiogram as a way to expedite treatment and minimize the number of invasive procedures. CT angiography is an alternative method for locating the aneurysm and may be sufficient to plan definitive therapy.

Close monitoring (daily or twice daily) of electrolytes is important because hyponatremia can occur precipitously during the first 2 weeks following SAH (see above).

The electrocardiogram (ECG) frequently shows ST-segment and T-wave changes similar to those associated with cardiac ischemia. A prolonged QRS complex, increased QT interval, and prominent "peaked" or deeply inverted symmetric T waves are usually secondary to the intracranial hemorrhage. There is evidence that structural myocardial lesions produced by circulating catecholamines and excessive discharge of sympathetic neurons may occur after SAH, causing these ECG changes and a reversible cardiomyopathy sufficient to cause shock or congestive heart failure. Echocardiography reveals a pattern of regional wall motion abnormalities that follow the distribution of sympathetic nerves rather than the major coronary arteries, with relative sparing of the ventricular wall apex. The sympathetic nerves themselves appear to be injured by direct toxicity from the excessive catecholamine release. An asymptomatic troponin elevation is common. Serious ventricular dysrhythmias occurring in-hospital are unusual.

TREATMENT

Subarachnoid Hemorrhage

Early aneurysm repair prevents rerupture and allows the safe application of techniques to improve blood flow (e.g., induced hypertension) should vasospasm and DCI develop. An aneurysm can be "clipped" by a neurosurgeon or "coiled" by an endovascular surgeon. Surgical repair involves placing a metal clip across the aneurysm neck, thereby immediately eliminating the risk of rebleeding. This approach requires craniotomy and brain retraction, which is associated with neurologic morbidity. Endovascular techniques involve placing platinum coils, or other embolic material, within the aneurysm via a catheter that is passed from the femoral artery. The aneurysm is packed tightly to enhance thrombosis and over time is walled off from the circulation **(Fig. 302-1*D*)**. There have been two prospective randomized trials of surgery versus endovascular treatment for ruptured aneurysms: the first was the International Subarachnoid Aneurysm Trial (ISAT), which was terminated early when 24% of patients treated with endovascular therapy were dead or dependent at 1 year compared to 31% treated with surgery, a significant 23% relative reduction. After 5 years, risk of death was lower in the coiling group, although the proportion of survivors who were independent was the same in both groups. Risk of rebleeding was low, but more common in the coiling group. These results favoring coiling at 1 year were confirmed in a second trial, although the differences in functional outcome were no longer significant at 3 years. Because some aneurysms have a morphology that is not amenable to endovascular treatment, surgery remains an important treatment option. Newer endovascular techniques using balloon-assisted coiling or placement of flow-diverting stents are increasing the types of aneurysms amenable to endovascular intervention. Centers that combine both endovascular and neurosurgical expertise likely offer the best outcomes for patients, and there are reliable data showing that specialized aneurysm treatment centers can improve mortality rates.

The medical management of SAH focuses on protecting the airway, managing blood pressure before and after aneurysm treatment, preventing rebleeding prior to treatment, managing vasospasm and DCI, treating hydrocephalus, treating hyponatremia, limiting secondary brain insults, and preventing pulmonary embolus (PE).

Intracranial hypertension following aneurysmal rupture occurs secondary to subarachnoid blood, parenchymal hematoma, acute hydrocephalus, or loss of vascular autoregulation. Patients who are stuporous should undergo emergent ventriculostomy to measure ICP and to treat high ICP in order to prevent cerebral ischemia. Medical therapies designed to combat raised ICP (e.g., osmotic therapy and sedation) can also be used as needed. High ICP refractory to treatment is a poor prognostic sign.

Prior to definitive treatment of the ruptured aneurysm, care is required to maintain adequate cerebral perfusion pressure while avoiding excessive elevation of arterial pressure. If the patient is alert, it is reasonable to lower the systolic blood pressure to below 160 mmHg using nicardipine, labetalol, or esmolol. If the patient has a depressed level of consciousness, ICP should be measured and the cerebral perfusion pressure targeted to 60–70 mmHg. If headache or neck pain is severe, mild sedation and analgesia are prescribed. Extreme sedation is avoided if possible because it can obscure the ability to clinically detect changes in neurologic status. Adequate hydration is necessary to avoid a decrease in blood volume predisposing to brain ischemia.

Seizures are uncommon at the onset of aneurysmal rupture. The quivering, jerking, and extensor posturing that often accompany loss of consciousness with SAH are probably related to the sharp rise in ICP rather than seizures. However, anticonvulsants are sometimes given as prophylactic therapy because a seizure could theoretically promote rebleeding.

Glucocorticoids may help reduce the head and neck ache caused by the irritative effect of the subarachnoid blood. There is no good evidence that they reduce cerebral edema, are neuroprotective, or reduce vascular injury, and their routine use therefore is not recommended.

Antifibrinolytic agents are not routinely prescribed but may be considered in patients in whom aneurysm treatment cannot proceed immediately. They are associated with a reduced incidence of aneurysmal rerupture but may also increase the risk of DCI and deep-vein thrombosis (DVT). Several recent studies suggest that a shorter duration of use (until the aneurysm is secured or for the first 3 days) may decrease rerupture and be safer than found in earlier studies of longer duration treatment.

DCI due to vasospasm remains the leading cause of morbidity and mortality following aneurysmal SAH. Treatment with the calcium channel antagonist nimodipine (60 mg PO every 4 h) improves outcome, perhaps by preventing ischemic injury rather than reducing the risk of vasospasm. Nimodipine can cause significant hypotension in some patients, which may worsen cerebral ischemia in patients with vasospasm. Symptomatic cerebral vasospasm can also be treated by increasing the cerebral perfusion pressure by raising mean arterial pressure through plasma volume expansion and the judicious use of IV vasopressor agents, usually phenylephrine or norepinephrine. Raised perfusion pressure has been associated with clinical improvement in many patients, but high arterial pressure may promote rebleeding in unprotected aneurysms. Treatment with induced hypertension and hypervolemia generally requires monitoring of arterial and central venous pressures; it is best to infuse pressors through a central venous line as well. Volume expansion helps prevent hypotension and augments cardiac output.

A *B*

FIGURE 302-2 Vasospasm of the right middle cerebral artery. ***A.*** Catheter angiography demonstrates significant narrowing of the right middle cerebral artery (MCA). ***B.*** Because of symptomatic delayed cerebral ischemia, soft-balloon angioplasty was used to dilate the proximal portion of the main MCA stem.

If DCI due to vasospasm persists despite optimal medical therapy, intraarterial vasodilators and percutaneous transluminal angioplasty are considered **(Fig. 302-2)**. Vasodilatation by direct angioplasty appears to be permanent, allowing hypertensive therapy to be tapered sooner. The pharmacologic vasodilators (verapamil and nicardipine) do not last more than about 24 h, and therefore multiple treatments may be required until the subarachnoid blood is reabsorbed. Although intraarterial papaverine is an effective vasodilator, there is evidence that papaverine may be neurotoxic, so its use should generally be avoided.

Acute hydrocephalus can cause stupor or coma. It may clear spontaneously or require temporary ventricular drainage. When chronic hydrocephalus develops, ventricular shunting is the treatment of choice.

Free-water restriction is contraindicated in patients with SAH at risk for DCI because hypovolemia and hypotension may occur and precipitate cerebral ischemia. Many patients continue to experience a decline in serum sodium despite receiving parenteral fluids containing normal saline. Frequently, supplemental oral salt coupled with normal saline will mitigate hyponatremia, but often patients also require intravenous hypertonic saline. Care must be taken not to correct serum sodium too quickly in patients with marked hyponatremia of several days' duration, as the osmotic demyelination syndrome **(Chap. 301)** may occur.

All patients should have pneumatic compression stockings applied to prevent pulmonary embolism. Unfractionated heparin administered subcutaneously for DVT prophylaxis can be initiated within 1–2 days following endovascular treatment or craniotomy with surgical clipping and is a useful adjunct to pneumatic compression stockings. Treatment of PE depends on whether the aneurysm has been treated and whether or not the patient has had a craniotomy. Systemic anticoagulation with heparin is contraindicated in patients with ruptured and untreated aneurysms. It is a relative contraindication following craniotomy for several days, and it may delay thrombosis of a coiled aneurysm. If DVT or PE occurs within the first days following craniotomy, use of an inferior vena cava filter may be considered to prevent additional PEs, whereas systemic anticoagulation with heparin is preferred following successful endovascular treatment.

FURTHER READING

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303 Cellular and Molecular Biology of the Kidney

Alfred L. George, Jr., Eric G. Neilson

The kidney is one of the most highly differentiated organs in the body. At the conclusion of embryologic development, nearly 30 different cell types form a multitude of filtering capillaries and segmented nephrons enveloped by a dynamic interstitium. This cellular diversity modulates a variety of complex physiologic processes. Endocrine functions, the regulation of blood pressure and intraglomerular hemodynamics, solute and water transport, acid-base balance, and removal of drug metabolites are all accomplished by intricate mechanisms of renal response. This breadth of physiology hinges on the clever ingenuity of nephron architecture that evolved as complex organisms came out of water to live on land.

EMBRYOLOGIC DEVELOPMENT

Kidneys develop from intermediate mesoderm under the timed or sequential control of a growing number of genes, described in Fig. 303-1. The transcription of these genes is guided by morphogenic cues that invite two ureteric buds to each penetrate bilateral metanephric blastema, where they induce primary mesenchymal cells to form early nephrons. The two ureteric buds emerge from posterior nephric ducts and mature into separate collecting systems that eventually form a renal pelvis and ureter. Induced mesenchyme undergoes mesenchymal epithelial transitions to form comma-shaped bodies at the proximal end of each ureteric bud leading to the formation of S-shaped nephrons that cleft and enjoin with penetrating endothelial cells derived from sprouting angioblasts. Under the influence of vascular endothelial growth factor A (VEGF-A), these penetrating cells form capillaries with surrounding mesangial cells that differentiate into a glomerular filter for plasma water and solute. The ureteric buds branch and each branch produce a new set of nephrons. The number of branching events ultimately determines the total number of nephrons in each kidney. There are ~900,000 glomeruli in each kidney in normal birth weight adults and as few as 225,000 in low-birth-weight adults, with the latter producing numerous comorbid risks.

Glomeruli evolve as complex capillary filters with fenestrated endothelia under the guiding influence of VEGF-A and angiopoietin-1 secreted by adjacently developing podocytes. Epithelial podocytes facing the urinary space envelop the exterior basement membrane supporting these emerging endothelial capillaries. Podocytes are partially polarized and periodically slough into the urinary space by epithelial-mesenchymal transition, and to a lesser extent apoptosis, only to be replenished by migrating parietal epithelia from Bowman capsule. Impaired replenishment results in heavy proteinuria. Podocytes attach to the basement membrane by special foot processes and share a slit-pore membrane with their neighbor. The slit-pore membrane forms a filter for plasma water and solute by the synthetic interaction of nephrin, annexin-4, CD2AP, FAT, ZO-1, P-cadherin, podocin, TRPC6, PLCE1, and Neph 1-3 proteins. Mutations in many of these proteins also result in heavy proteinuria. The glomerular capillaries are embedded in a mesangial matrix shrouded by parietal and proximal tubular epithelia forming Bowman capsule. Mesangial cells have an embryonic lineage consistent with arteriolar or juxtaglomerular cells and contain contractile actin-myosin fibers. These mesangial cells make contact with glomerular capillary loops, and their local matrix holds them in condensed arrangement.

Between nephrons lies the renal interstitium. This region forms a functional space surrounding glomeruli and their downstream tubules, which are home to resident and trafficking cells such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The cortical and medullary peritubular capillaries, which siphon off solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitial fabric as well as a web of connective tissue that supports the kidney's emblematic architecture of folding tubules. The relational precision of these structures determines the unique physiology of the kidney.

Each nephron is partitioned during embryologic development into a proximal tubule, descending and ascending limbs of the loop of Henle, distal tubule, and the collecting duct. These classic tubular segments build from subsegments lined by highly unique epithelia serving regional physiology. All nephrons have the same structural components, but there are two types whose structures depend on their location within the kidney. The majority of nephrons are cortical, with glomeruli located in the mid-to-outer cortex. Fewer nephrons are juxtamedullary, with glomeruli at the boundary of the cortex and outer medulla. Cortical nephrons have short loops of Henle, whereas juxtamedullary nephrons have long loops of Henle. There are critical differences in blood supply as well. The peritubular capillaries surrounding cortical nephrons are shared among adjacent nephrons. By contrast, juxtamedullary nephrons depend on individual capillaries called *vasa recta* that run alongside the long loops of Henle. Cortical nephrons perform most of the glomerular filtration because there are more of them and because their afferent arterioles are larger than their respective efferent arterioles. The juxtamedullary nephrons, with

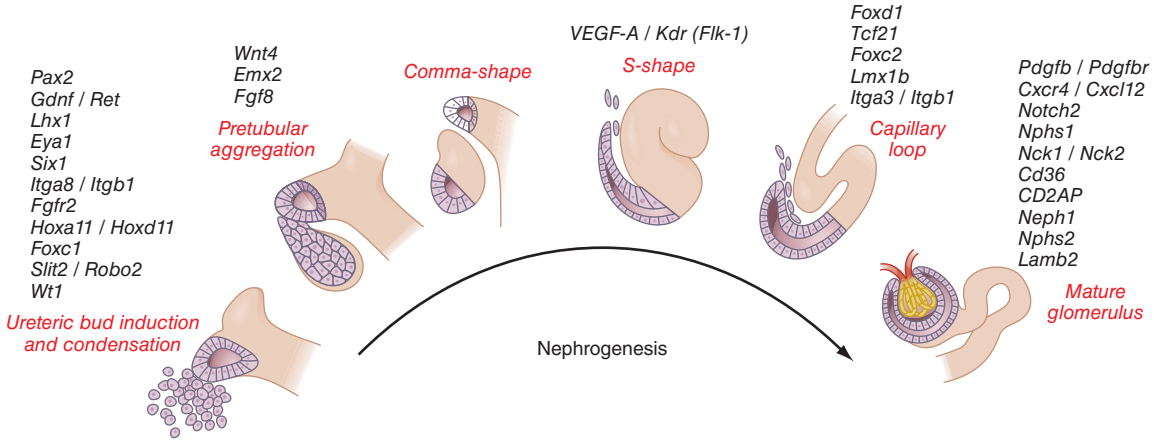


FIGURE 303-1 Genes controlling renal nephrogenesis. A growing number of genes have been identified at various stages of glomerulotubular development in the mammalian kidney. The genes listed have been tested in various genetically modified mice, and their location corresponds to the classical stages of kidney development postulated by Saxen in 1987.

longer loops of Henle, create an osmotic gradient for concentrating urine. How developmental instructions specify the differentiation of all these unique epithelia among various tubular segments is still unknown.

DETERMINANTS AND REGULATION OF GLOMERULAR FILTRATION

Renal blood flow normally drains ~20% of the cardiac output, or 1000 mL/min. Blood reaches each nephron through the afferent arteriole leading into a glomerular capillary where large amounts of fluid and solutes are filtered to form the tubular fluid. The distal ends of the glomerular capillaries coalesce to form an efferent arteriole leading to the first segment of a second capillary network (cortical peritubular capillaries or medullary vasa recta) surrounding the tubules **(Fig. 303-2*A*)**. Thus, nephrons have two capillary beds arranged in a series separated by the efferent arteriole that regulates the hydrostatic pressure in both capillary beds. The distal capillaries empty into small venous branches that coalesce into larger veins to eventually form the renal vein.

The hydrostatic pressure gradient across the glomerular capillary wall is the primary driving force for glomerular filtration. Oncotic pressure within the capillary lumen, determined by the concentration of unfiltered plasma proteins, partially offsets the hydrostatic pressure gradient and opposes filtration. As the oncotic pressure rises along the length of the glomerular capillary, the driving force for filtration falls to zero en route to the efferent arteriole. Approximately 20% of the renal plasma flow is filtered into Bowman space, and the ratio of glomerular filtration rate (GFR) to renal plasma flow determines the filtration fraction. Several factors, mostly hemodynamic, contribute to the regulation of filtration under physiologic conditions.

Although glomerular filtration is affected by renal artery pressure, this relationship is not linear across the range of physiologic blood pressures due to autoregulation of GFR. Autoregulation of glomerular filtration is the result of three major factors that modulate either afferent or efferent arteriolar tone: these include an autonomous vasoreactive (myogenic) reflex in the afferent arteriole, *tubuloglomerular feedback* (TGF), and angiotensin II-mediated vasoconstriction of the efferent arteriole. The myogenic reflex is a first line of defense against fluctuations in renal blood flow. Acute changes in renal perfusion pressure evoke reflex constriction or dilatation of the afferent arteriole in response to increased or decreased pressure, respectively. This phenomenon helps protect the glomerular capillary from sudden changes in systolic pressure.

TGF changes the rate of filtration and tubular flow by reflex vasoconstriction or dilatation of the afferent arteriole. TGF is mediated by specialized cells in the thick ascending limb of the loop of Henle called the *macula densa* that act as sensors of solute concentration and tubular fluid flow rate. With high tubular flow rates, a proxy for an inappropriately high filtration rate, there is increased solute delivery to the macula densa **(Fig. 303-2*B*)** that evokes vasoconstriction of the afferent arteriole causing GFR to return toward normal. One component of the soluble signal from the macula densa is adenosine triphosphate (ATP) released by the cells during increased NaCl reabsorption. ATP is metabolized in the extracellular space to generate adenosine, a potent vasoconstrictor of the afferent arteriole. During conditions associated with a fall in filtration rate, reduced solute delivery to the macula densa attenuates TGF, allowing afferent arteriolar dilatation and restoring GFR to normal levels. Angiotensin II and reactive oxygen species enhance, while nitric oxide (NO) blunts TGF.

The third component underlying autoregulation of GFR involves angiotensin II. During states of reduced renal blood flow, renin is released from granular cells within the wall of the afferent arteriole near the macula densa in a region called the juxtaglomerular apparatus (Fig. 303-2*B*). Renin, a proteolytic enzyme, catalyzes the conversion of angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE) **(Fig. 303-2*C*)**. Angiotensin II evokes vasoconstriction of the efferent arteriole, and the resulting increased glomerular hydrostatic pressure elevates GFR to normal levels.

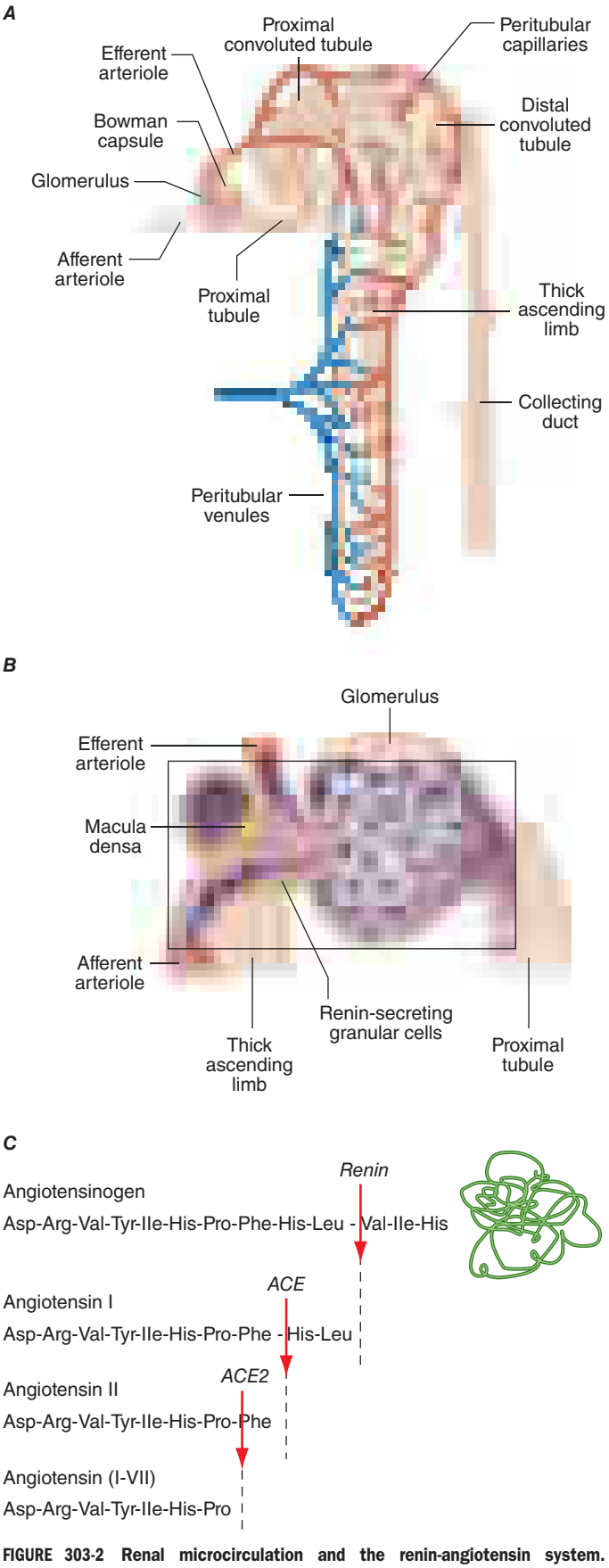


FIGURE 303-2 Renal microcirculation and the renin-angiotensin system. ***A.*** Diagram illustrating relationships of the nephron with glomerular and peritubular capillaries. ***B.*** Expanded view of the glomerulus with its juxtaglomerular apparatus including the macula densa and adjacent afferent arteriole. ***C.*** Proteolytic processing steps in the generation of angiotensins.

MECHANISMS OF RENAL TUBULAR TRANSPORT

The renal tubules are composed of highly differentiated epithelia that vary dramatically in morphology and function along the nephron (Fig. 303-3). The cells lining the various tubular segments form monolayers connected to one another by a specialized region of the adjacent lateral membranes called the *tight junction*. Tight junctions form an occlusive barrier that separates the lumen of the tubule from the interstitial spaces surrounding the tubule and also apportions the cell membrane into discrete domains: the apical membrane facing the tubular lumen and the basolateral membrane facing the interstitium. This regionalization allows cells to allocate membrane proteins and lipids asymmetrically. Owing to this feature, renal epithelial cells are said to be *polarized*. The asymmetric assignment of membrane proteins, especially proteins mediating transport processes, provides the machinery for directional movement of fluid and solutes by the nephron.

EPITHELIAL SOLUTE TRANSPORT

There are two types of epithelial transport. Movement of fluid and solutes sequentially across the apical and basolateral cell membranes (or vice versa) mediated by transporters, channels, or pumps is called *cellular transport*. By contrast, movement of fluid and solutes through the narrow passageway between adjacent cells is called *paracellular transport*. Paracellular transport occurs through tight junctions, indicating that they are not completely "tight" or occlusive. Indeed, some epithelial cell layers allow rather robust paracellular transport to occur (*leaky epithelia*), whereas other epithelia have more restrictive tight junctions (*tight epithelia*). In addition, because the ability of ions to flow through the paracellular pathway determines the electrical resistance across the epithelial monolayer, leaky and tight epithelia are also referred to as low- or high-resistance epithelia, respectively. The proximal tubule contains leaky epithelia, whereas distal nephron segments, such as the collecting duct, contain tight epithelia. Leaky epithelia are

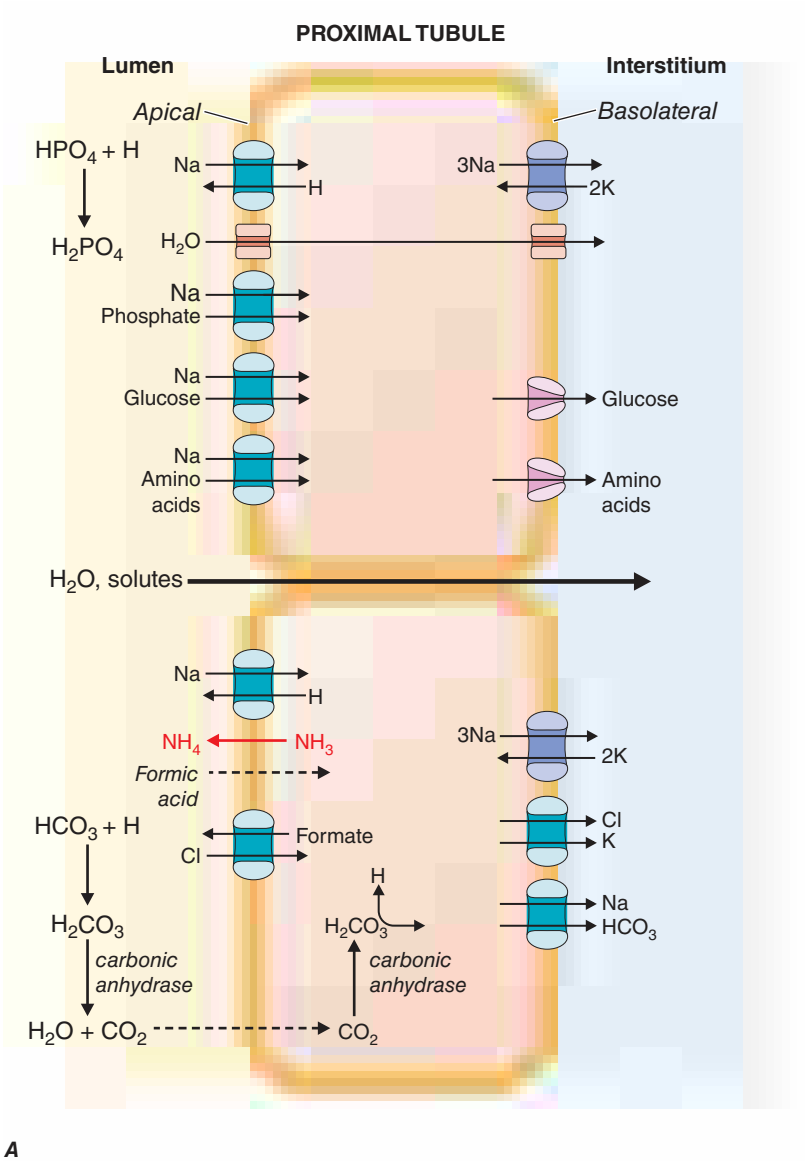
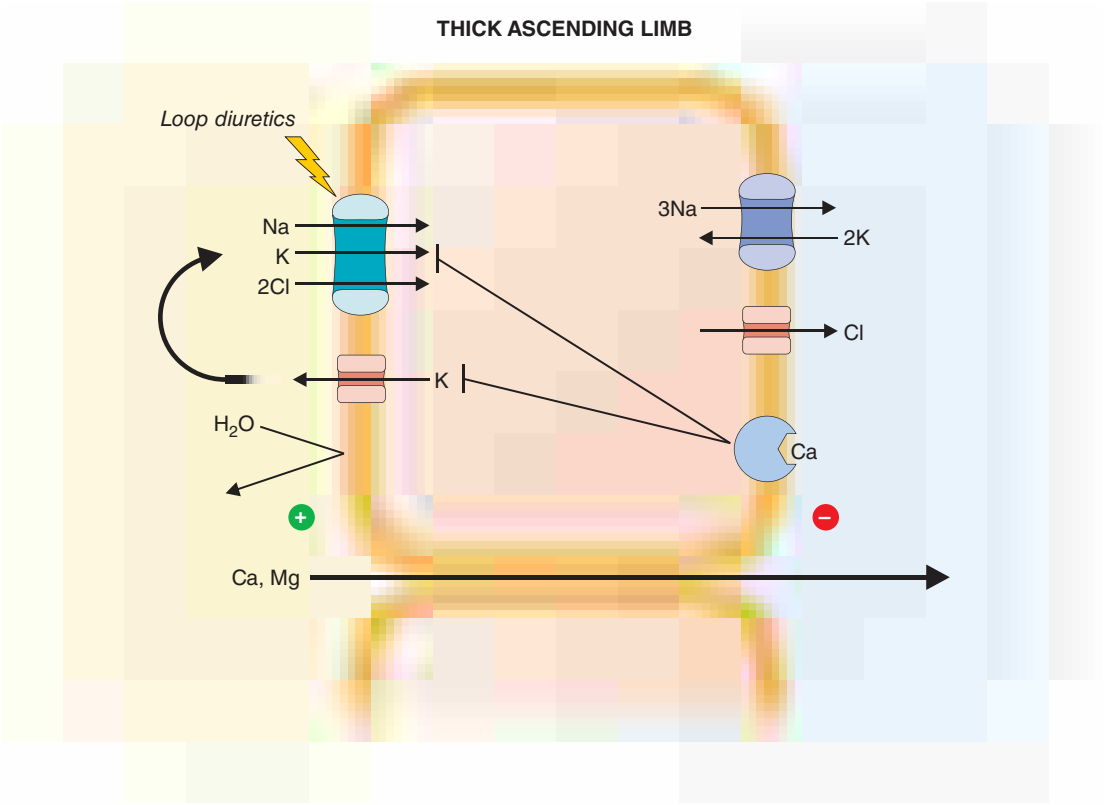
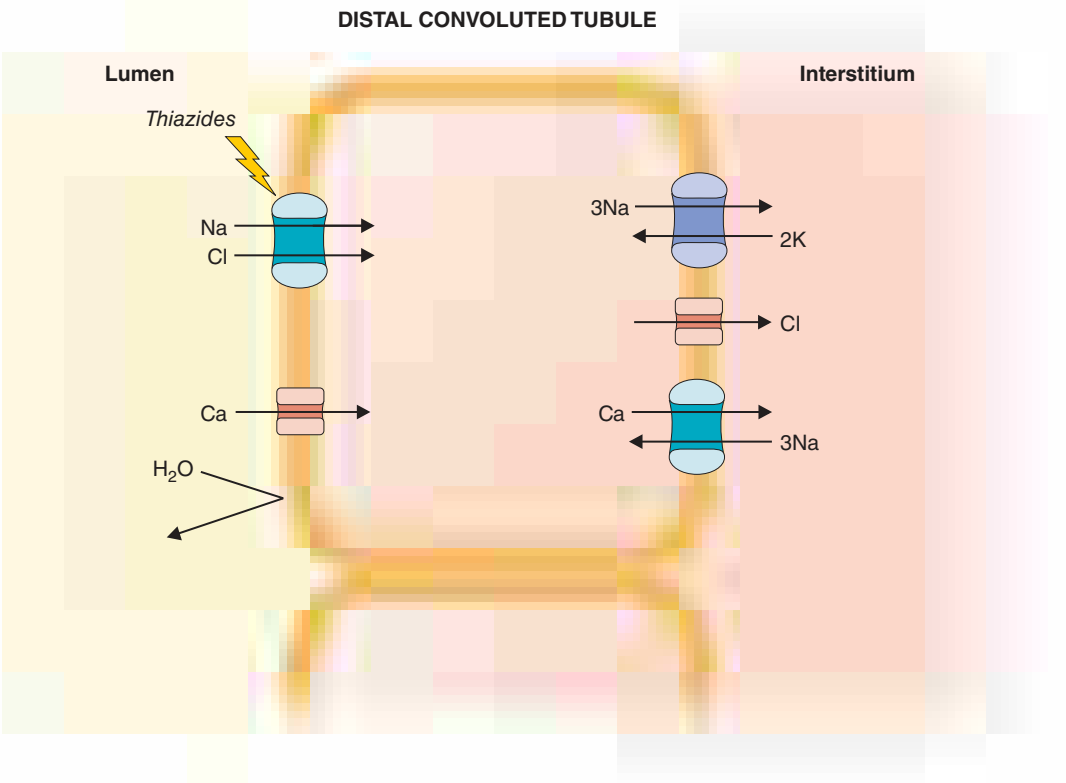


FIGURE 303-3 Transport activities of the major nephron segments. Representative cells from five major tubular segments are illustrated with the lumen side (apical membrane) facing left and interstitial side (basolateral membrane) facing right. ***A.*** Proximal tubular cells. ***B.*** Typical cell in the thick ascending limb of the loop of Henle. ***C.*** Distal convoluted tubular cell. ***D.*** Overview of entire nephron. ***E.*** Cortical collecting duct cells. ***F.*** Typical cell in the inner medullary collecting duct. The major membrane transporters, channels, and pumps are drawn with *arrows* indicating the direction of solute or water movement. For some events, the stoichiometry of transport is indicated by numerals preceding the solute. Targets for major diuretic agents are labeled. The actions of hormones are illustrated by *arrows with plus signs* for stimulatory effects and *lines with perpendicular ends* for inhibitory events. The *dashed line* indicates water impermeability of cell membranes in the thick ascending limb and distal convoluted tubule.



B



C

FIGURE 303-3 (*Continued*)

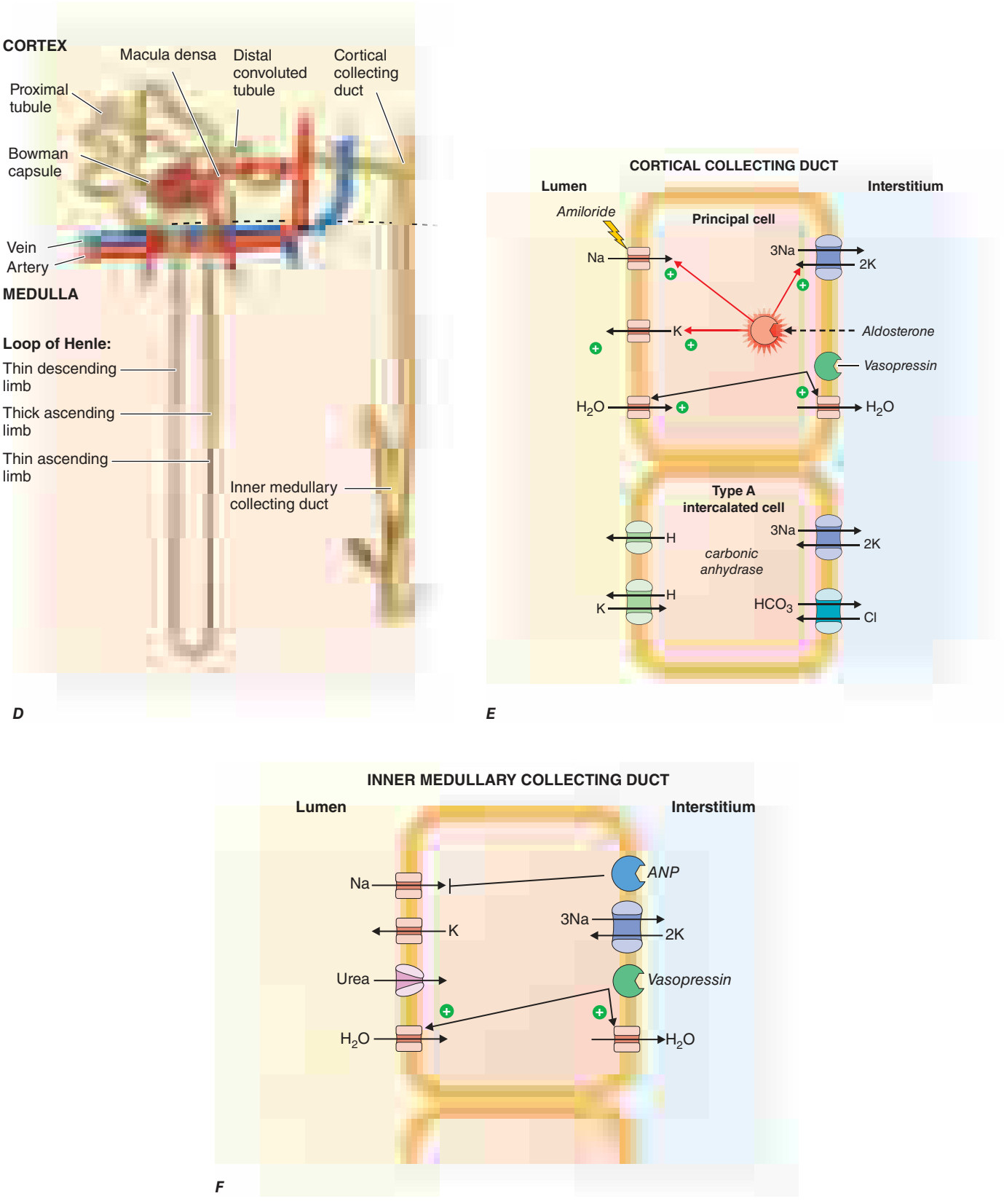


FIGURE 303-3 (*Continued*)

most well suited for bulk fluid reabsorption, whereas tight epithelia allow for more refined control and regulation of transport.

MEMBRANE TRANSPORT

Cell membranes are composed of hydrophobic lipids that repel water and aqueous solutes. The movement of solutes and water across cell membranes is made possible by discrete classes of integral membrane proteins, including channels, pumps, and transporters. These different mechanisms mediate specific types of transport activities, including *active transport* (pumps), *passive transport* (channels), *facilitated diffusion* (transporters), and *secondary active transport* (cotransporters). Active transport requires metabolic energy generated by the hydrolysis of ATP. Active transport pumps are ion-translocating ATPases, including the ubiquitous Na^+/K^+-ATPase, the H^+-ATPases, and Ca^{2+}-ATPases.

TABLE 303-1 Inherited Disorders Affecting Renal Tubular Ion and Solute Transport

DISEASE OR SYNDROME	GENE	OMIM[a]
Disorders Involving the Proximal Tubule		
Proximal renal tubular acidosis	Sodium bicarbonate cotransporter (*SLC4A4*, 4q21)	604278
Fanconi-Bickel syndrome	Glucose transporter, GLUT2 (*SLC2A2*, 3q26.2)	227810
Isolated renal glycosuria	Sodium glucose cotransporter (*SLC5A2*, 16p11.2)	233100
Cystinuria		
Type I	Cystine, dibasic and neutral amino acid transporter (*SLC3A1*, 2p16.3)	220100
Non-type I	Amino acid transporter, light subunit (*SLC7A9*, 19q13.1)	600918
Lysinuric protein intolerance	Amino acid transporter (*SLC7A7*, 4q11.2)	222700
Hartnup disorder	Neutral amino acid transporter (*SLC6A19*, 5p15.33)	34500
Hereditary hypophosphatemic rickets with hypercalcemia	Sodium phosphate cotransporter (*SLC34A3*, 9q34)	241530
Renal hypouricemia		
Type 1	Urate-anion exchanger (*SLC22A12*, 11q13)	220150
Type 2	Urate transporter, GLUT9 (*SLC2A9*, 4p16.1)	612076
Dent disease	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	300009
X-linked recessive nephrolithiasis with renal failure	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	310468
X-linked recessive hypophosphatemic rickets	Chloride channel, ClC-5 (*CLCN5*, Xp11.22)	307800
Disorders Involving the Loop of Henle		
Bartter's syndrome		
Type 1	Sodium, potassium chloride cotransporter (*SLC12A1*, 15q21.1)	241200
Type 2	Potassium channel, ROMK (*KCNJ1*, 11q24)	601678
Type 3	Chloride channel, ClC-Kb (*CLCNKB*, 1p36)	602023
with sensorineural deafness	Chloride channel accessory subunit, Barttin (*BSND*, 1p31)	602522
Autosomal dominant hypocalcemia with Bartter-like syndrome	Calcium-sensing receptor (*CASR*, 3q13.33)	601199
Familial hypocalciuric hypercalcemia	Calcium-sensing receptor (*CASR*, 3q13.33)	145980
Primary hypomagnesemia	Claudin-16 or paracellin-1 (*CLDN16* or *PCLN1*, 3q27)	248250
Isolated renal magnesium loss	Sodium potassium ATPase, γ_1-subunit (*ATP1G1*, 11q23)	154020
Disorders Involving the Distal Tubule and Collecting Duct		
Gitelman syndrome	Sodium chloride cotransporter (*SLC12A3*, 16q13)	263800
Primary hypomagnesemia with secondary hypocalcemia	Melastatin-related transient receptor potential cation channel 6 (*TRPM6*, 9q22)	602014
Pseudoaldosteronism (Liddle's syndrome)	Epithelial sodium channel β and γ subunits (*SCNN1B*, *SCNN1G*, 16p12.1)	177200
Recessive pseudohypoaldosteronism type 1	Epithelial sodium channel, α, β, and γ subunits (*SCNN1A*, 12p13; *SCNN1B*, *SCNN1G*, 16pp12.1)	264350
Pseudohypoaldosteronism type 2 (Gordon's hyperkalemia-hypertension syndrome)	Kinases WNK-1, WNK-4 (*WNK1*, 12p13; *WNK4*, 17q21.31)	145260
X-linked nephrogenic diabetes insipidus	Vasopressin V2 receptor (AVPR2, Xq28)	304800
Nephrogenic diabetes insipidus (autosomal)	Water channel, aquaporin-2 (*AQP2*, 12q13)	125800
Distal renal tubular acidosis		
autosomal dominant	Anion exchanger-1 (*SLC4A1*, 17q21.31)	179800
autosomal recessive	Anion exchanger-1 (*SLC4A1*, 17q21.31)	602722
with neural deafness	Proton ATPase, β1 subunit (*ATP6V1B1*, 2p13.3)	192132
with normal hearing	Proton ATPase, 116-kD subunit (*ATP6V0A4*, 7q34)	602722

[a]Online Mendelian Inheritance in Man database (*http://www.ncbi.nlm.nih.gov/Omim*).

Active transport creates asymmetric ion concentrations across a cell membrane and can move ions against a chemical gradient. The potential energy stored in a concentration gradient of an ion such as Na^+ can be used to drive transport through other mechanisms (secondary active transport). Pumps are often *electrogenic*, meaning they can create an asymmetric distribution of electrostatic charges across the membrane and establish a voltage or membrane potential. The movement of solutes through a membrane protein by simple diffusion is called passive transport. This activity is mediated by channels created by selectively permeable membrane proteins, and it allows solute or water to move across a membrane driven by favorable *concentration gradients* or *electrochemical potential*. Facilitated diffusion is a specialized type of passive transport mediated by simple transporters called *carriers* or *uniporters*. For example, hexose transporters such as GLUT2 mediate glucose transport by tubular cells. These transporters are driven by the concentration gradient for glucose that is highest in extracellular fluids and lowest in the cytoplasm due to rapid metabolism. Many other transporters operate by translocating two or more ions/solutes in concert either in the same direction (*symporters* or *cotransporters*) or in opposite directions (*antiporters* or *exchangers*) across the cell membrane. The movement of two or more ions/solutes may produce no net change in the balance of electrostatic charges across the membrane (*electroneutral*), or a transport event may alter the balance of charges (*electrogenic*). Several inherited disorders of renal tubular solute and water transport occur as a consequence of mutations in genes encoding a variety of channels, transporter proteins, and their regulators **(Table 303-1)**.

SEGMENTAL NEPHRON FUNCTIONS

Each anatomic segment of the nephron has unique characteristics and specialized functions enabling selective transport of solutes and water (Fig. 303-3). Through sequential events of reabsorption and secretion along the nephron, tubular fluid is progressively conditioned into urine. Knowledge of the major tubular mechanisms responsible for solute and water transport is critical for understanding hormonal regulation of kidney function and the pharmacologic manipulation of renal excretion.

PROXIMAL TUBULE

The proximal tubule is responsible for reabsorbing ~60% of filtered NaCl and water, as well as ~90% of filtered bicarbonate and most critical nutrients such as glucose and amino acids. The proximal tubule uses both cellular and paracellular transport mechanisms. The apical membrane of proximal tubular cells has an expanded surface area available for reabsorptive work created by a dense array of microvilli called the *brush border*, and leaky tight junctions enable high-capacity fluid reabsorption.

Solute and water pass through these tight junctions to enter the lateral intercellular space where absorption by the peritubular capillaries occurs. Bulk fluid reabsorption by the proximal tubule is driven by high oncotic pressure and low hydrostatic pressure within the peritubular capillaries. Cellular transport of most solutes by the proximal tubule is coupled to the Na^+ concentration gradient established by the activity of a basolateral Na^+/K^+-ATPase (Fig. 303-3*A*). This active transport mechanism maintains a steep Na^+ gradient by keeping intracellular Na^+ concentrations low. Solute reabsorption from the tubular lumen is coupled to the Na^+ gradient by Na^+-dependent transporters such as Na^+-glucose and Na^+-phosphate cotransporters present in apical membranes. In addition to the paracellular route, water reabsorption also occurs through the cellular pathway enabled by constitutively active water channels (aquaporin-1) present on both apical and basolateral membranes.

Proximal tubular cells reclaim nearly all filtered bicarbonate by a mechanism dependent on carbonic anhydrases. Filtered bicarbonate is first titrated by protons delivered to the lumen mainly by Na^+/H^+ exchange. The resulting carbonic acid (H_2CO_3) is metabolized by brush border carbonic anhydrase to water and carbon dioxide. Dissolved carbon dioxide then diffuses into the cell, where it is enzymatically hydrated by cytoplasmic carbonic anhydrase to re-form carbonic acid. Finally, intracellular carbonic acid dissociates into free protons and bicarbonate anions, and bicarbonate exits the cell through a basolateral Na^+/HCO_3^- cotransporter. This process is saturable, which can result in urinary bicarbonate excretion when plasma levels exceed the physiologically normal range (24–26 meq/L). Carbonic anhydrase inhibitors such as acetazolamide, a class of weak diuretic agents, block proximal tubule bicarbonate reabsorption and are useful for alkalinizing the urine.

The proximal tubule contributes to acid secretion by two mechanisms involving the titration of the urinary buffers ammonia (NH_3) and phosphate. Renal NH_3 is produced by glutamine metabolism in the proximal tubule. Subsequent diffusion of NH_3 out of the proximal tubular cell enables trapping of H^+, which is secreted by Na^+/H^+ exchange, in the lumen as ammonium ion (NH_4^+). Cellular K^+ levels inversely modulate proximal tubular ammoniagenesis, and in the setting of high serum K^+ from hypoaldosteronism, reduced ammoniagenesis promotes type IV renal tubular acidosis. Filtered hydrogen phosphate ion (HPO_4^{2-}) is also titrated in the proximal tubule by secreted H^+ to form $H_2PO_4^-$, and this reaction constitutes a major component of the urinary buffer referred to as titratable acid. Most filtered phosphate ion is reabsorbed by the proximal tubule through a sodium-coupled cotransport process that is regulated by parathyroid hormone (PTH).

Chloride is poorly reabsorbed throughout the first segment of the proximal tubule, and a rise in Cl^- concentration counterbalances the removal of bicarbonate anion from tubular fluid. In later proximal tubular segments, cellular Cl^- reabsorption is initiated by apical exchange of cellular formate for higher luminal concentrations of Cl^-. Once in the lumen, formate anions are titrated by H^+ (provided by Na^+/H^+ exchange) to generate neutral formic acid, which can diffuse passively across the apical membrane back into the cell where it dissociates a proton and is recycled. Basolateral Cl^- exit is mediated by a K^+/Cl^- cotransporter.

Reabsorption of glucose is nearly complete by the end of the proximal tubule. Cellular transport of glucose is mediated by apical Na^+-glucose cotransport coupled with basolateral, facilitated diffusion by a glucose transporter. This process is also saturable, leading to glycosuria when plasma levels exceed 180–200 mg/dL, as seen in untreated diabetes mellitus.

The proximal tubule possesses specific transporters capable of secreting a variety of organic acids (carboxylate anions) and bases (mostly primary amine cations). Organic anions transported by these systems include urate, dicarboxylic acid anions (succinate), ketoacid anions, and several protein-bound drugs not filtered at the glomerulus (penicillins, cephalosporins, and salicylates). Probenecid inhibits renal organic anion secretion and can be clinically useful for raising plasma concentrations of certain drugs like penicillin and oseltamivir. Organic cations secreted by the proximal tubule include various biogenic amine neurotransmitters (dopamine, acetylcholine, epinephrine, norepinephrine, and histamine) and creatinine. The ATP-dependent transporter P-glycoprotein is highly expressed in brush border membranes and secretes several medically important drugs, including cyclosporine, digoxin, tacrolimus, and various cancer chemotherapeutic agents. Certain drugs like cimetidine and trimethoprim compete with endogenous compounds for transport by the organic cation pathways. Although these drugs elevate serum creatinine levels, there is no actual change in GFR in this setting.

Calcium and phosphorus homeostasis depends upon normal functioning of the proximal tubule. Approximately 60–70% of filtered calcium and ~85% of filtered phosphorus (in the form of inorganic phosphate) are reabsorbed by the proximal tubule. Whereas calcium reabsorption is mostly by passive diffusion through the paracellular route, phosphate reabsorption is mediated by sodium-coupled cotransport. In addition to direct reabsorption, the proximal tubule contributes to systemic mineral balance by participating in specific endocrine pathways. Circulating 25-hydroxy vitamin D (calcidiol) is bioactivated by proximal tubular 1α-hydroxylase to produce 1,25-di-hydroxy vitamin D (calcitriol), the most active form of the hormone, that acts on the small intestine to promote calcium absorption. Phosphate balance is affected by circulating fibroblast growth hormone 23 (FGF23), a bone-derived hormone that interacts with its receptor (FGFR1) and co-receptor (Klotho) on proximal tubular cells to suppress sodium-phosphate cotransport and promote renal phosphate excretion. PTH stimulates proximal tubular 1α-hydroxylation of vitamin D while it suppresses sodium-phosphate cotransport. Derangements in PTH and FGF23 account for abnormal calcium and phosphate balance in chronic kidney disease.

The proximal tubule, through distinct classes of Na^+-dependent and Na^+-independent transport systems, reabsorbs amino acids efficiently. These transporters are specific for different groups of amino acids. For example, cystine, lysine, arginine, and ornithine are transported by a system comprising two proteins encoded by the *SLC3A1* and *SLC7A9* genes. Mutations in either *SLC3A1* or *SLC7A9* impair reabsorption of these amino acids and cause the disease cystinuria. Peptide hormones, such as insulin and growth hormone, β_2-microglobulin, albumin, and other small proteins, are taken up by the proximal tubule through a process of absorptive endocytosis and are degraded in acidified endocytic lysosomes. Acidification of these vesicles depends on a vacuolar H^+-ATPase and Cl^- channel. Impaired acidification of endocytic vesicles because of mutations in a Cl^- channel gene (*CLCN5*) causes low-molecular-weight proteinuria in Dent disease.

LOOP OF HENLE

The loop of Henle consists of three major segments: descending thin limb, ascending thin limb, and ascending thick limb. These divisions are based on cellular morphology and anatomic location, but also correlate with specialization of function. Approximately 15–25% of filtered NaCl is reabsorbed in the loop of Henle, mainly by the thick ascending limb. The loop of Henle has an important role in urinary concentration by contributing to the generation of a hypertonic medullary interstitium in a process called *countercurrent multiplication*. The loop of Henle is the site of action for the most potent class of diuretic agents (loop diuretics) and also contributes to reabsorption of calcium and magnesium ions.

The descending thin limb is highly water permeable owing to dense expression of constitutively active aquaporin-1 water channels. By contrast, water permeability is negligible in the ascending limb. In the thick ascending limb, there is a high level of secondary active NaCl

transport enabled by the $Na^+/K^+/2Cl^-$ cotransporter on the apical membrane in series with basolateral Cl^- channels and Na^+/K^+-ATPase (Fig. 303-3*B*). The $Na^+/K^+/2Cl^-$ cotransporter is the primary target for loop diuretics. Tubular fluid K^+ is the limiting substrate for this cotransporter (tubular concentration of K^+ is similar to plasma, about 4 meq/L), but transporter activity is maintained by K^+ recycling through an apical potassium channel. The cotransporter also enables reabsorption of NH_4^+ in lieu of K^+, and this leads to accumulation of both NH_4^+ and NH_3 in the medullary interstitium. An inherited disorder of the thick ascending limb, Bartter's syndrome, also results in a salt-wasting renal disease associated with hypokalemia and metabolic alkalosis. Loss-of-function mutations in one of five distinct genes encoding components of the $Na^+/K^+/2Cl^-$ cotransporter (*NKCC2*), apical K^+ channel (*KCNJ1*), basolateral Cl^- channel (*CLCNKB*, *BSND*), or calcium-sensing receptor (*CASR*) can cause Bartter's syndrome.

Potassium recycling also contributes to a positive electrostatic charge in the lumen relative to the interstitium that promotes divalent cation (Mg^{2+} and Ca^{2+}) reabsorption through a paracellular pathway. A Ca^{2+}-sensing, G-protein-coupled receptor (CaSR) on basolateral membranes regulates NaCl reabsorption in the thick ascending limb through dual signaling mechanisms using either cyclic AMP or eicosanoids. This receptor enables a steep relationship between plasma Ca^{2+} levels and renal Ca^{2+} excretion. Loss-of-function mutations in CaSR cause familial hypercalcemic hypocalciuria because of a blunted response of the thick ascending limb to extracellular Ca^{2+}. Mutations in *CLDN16* encoding paracellin-1, a transmembrane protein located within the tight junction complex, leads to familial hypomagnesemia with hypercalciuria and nephrocalcinosis, suggesting that the ion conductance of the paracellular pathway in the thick limb is regulated.

The loop of Henle contributes to urine-concentrating ability by establishing a *hypertonic medullary interstitium* that promotes water reabsorption by the downstream inner medullary collecting duct. *Countercurrent multiplication* produces a hypertonic medullary interstitium using two countercurrent systems: the loop of Henle (opposing descending and ascending limbs) and the vasa recta (medullary peritubular capillaries enveloping the loop). The countercurrent flow in these two systems helps maintain the hypertonic environment of the inner medulla, but NaCl reabsorption by the thick ascending limb is the primary initiating event. Reabsorption of NaCl without water dilutes the tubular fluid and adds new osmoles to medullary interstitial fluid. Because the descending thin limb is highly water permeable, osmotic equilibrium occurs between the descending limb tubular fluid and the interstitial space, leading to progressive solute trapping in the inner medulla. Maximum medullary interstitial osmolality also requires partial recycling of urea from the collecting duct.

DISTAL CONVOLUTED TUBULE

The distal convoluted tubule reabsorbs ~5% of the filtered NaCl. This segment is composed of a tight epithelium with little water permeability. The major NaCl-transporting pathway uses an apical membrane, electroneutral thiazide-sensitive Na^+/Cl^- cotransporter in tandem with basolateral Na^+/K^+-ATPase and Cl^- channels (Fig. 303-3C). Apical Ca^{2+}-selective channels (TRPV5) and basolateral Na^+/Ca^{2+} exchange mediate calcium reabsorption in the distal convoluted tubule. Ca^{2+} reabsorption is inversely related to Na^+ reabsorption and is stimulated by PTH. Blocking apical Na^+/Cl^- cotransport will reduce intracellular Na^+, favoring increased basolateral Na^+/Ca^{2+} exchange and passive apical Ca^{2+} entry. Loss-of-function mutations of *SLC12A3* encoding the apical Na^+/Cl^- cotransporter cause Gitelman syndrome, a salt-wasting disorder associated with hypokalemic alkalosis and hypocalciuria. Mutations in genes encoding WNK kinases, WNK-1 and WNK-4, cause pseudohypoaldosteronism type II (Gordon syndrome) characterized by familial hypertension with hyperkalemia. WNK kinases influence the activity of several tubular ion transporters. Mutations in this disorder lead to overactivity of the apical Na^+/Cl^- cotransporter in the distal convoluted tubule as the primary stimulus for increased salt reabsorption, extracellular volume expansion, and hypertension. Hyperkalemia may be caused by diminished activity of apical K^+ channels in the collecting duct, a primary route for K^+ secretion. Mutations in *TRPM6* encoding Mg^{2+} permeable ion channels also cause familial hypomagnesemia with hypocalcemia. A molecular complex of TRPM6 and TRPM7 proteins is critical for Mg^{2+} reabsorption in the distal convoluted tubule.

COLLECTING DUCT

The collecting duct modulates the final composition of urine. The two major divisions, the cortical collecting duct and inner medullary collecting duct, contribute to reabsorbing ~4–5% of filtered Na^+ and are important for hormonal regulation of salt and water balance. Cells in both segments of the collecting duct express vasopressin-regulated water channels (aquaporin-2 on the apical membrane, aquaporin-3 and -4 on the basolateral membrane). The antidiuretic hormone vasopressin binds to the V2 receptor on the basolateral membrane and triggers an intracellular signaling cascade through G-protein-mediated activation of adenylyl cyclase, resulting in an increase in the cellular levels of cyclic AMP. This signaling cascade stimulates the insertion of water channels into the apical membrane of collecting duct cells to promote increased water permeability. This increase in permeability enables water reabsorption and production of concentrated urine. In the absence of vasopressin, collecting duct cells are water impermeable, and urine remains dilute.

The cortical collecting duct contains *high-resistance epithelia* with two cell types. Principal cells are the main water, Na^+-reabsorbing, and K^+-secreting cells, and the site of action of aldosterone, K^+-sparing diuretics, and mineralocorticoid receptor antagonists such as spironolactone and eplerenone. The other cells are type A and B intercalated cells. Type A intercalated cells mediate acid secretion and bicarbonate reabsorption also under the influence of aldosterone. Type B intercalated cells mediate bicarbonate secretion and acid reabsorption.

Virtually all transport is mediated through the cellular pathway for both principal cells and intercalated cells. In principal cells, passive apical Na^+ entry occurs through an amiloride-sensitive, epithelial Na^+ channel (ENaC) with basolateral exit mediated by the Na^+/K^+-ATPase (Fig. 303-3*D*). This Na^+ reabsorptive process is tightly regulated by aldosterone and is physiologically activated by a variety of proteolytic enzymes that cleave extracellular domains of ENaC; plasmin in the tubular fluid of nephrotic patients, for example, activates ENaC, leading to sodium retention. Aldosterone enters the cell across the basolateral membrane, binds to a cytoplasmic mineralocorticoid receptor, and then translocates into the nucleus, where it modulates gene transcription, resulting in increased Na^+ reabsorption and K^+ secretion. Activating mutations in ENaC increase Na^+ reclamation and produce hypokalemia, hypertension, and metabolic alkalosis (Liddle's syndrome). The potassium-sparing diuretics amiloride and triamterene block ENaC, causing reduced Na^+ reabsorption.

Principal cells secrete K^+ through an apical membrane potassium channel. Several forces govern the secretion of K^+. Most importantly, the high intracellular K^+ concentration generated by Na^+/K^+-ATPase creates a favorable concentration gradient for K^+ secretion into tubular fluid. With reabsorption of Na^+ without an accompanying anion, the tubular lumen becomes negative relative to the cell interior, creating a favorable electrical gradient for secretion of potassium. When Na^+ reabsorption is blocked, the electrical component of the driving force for K^+ secretion is blunted, and this explains lack of excess urinary K^+ loss during treatment with potassium-sparing diuretics or mineralocorticoid receptor antagonists. K^+ secretion is also promoted by aldosterone actions that increase regional Na^+ transport, which favor more lumen electronegativity, and by increasing the number and activity of potassium channels. Fast tubular fluid flow rates that occur during volume expansion or diuretics acting "upstream" of the cortical collecting duct also increase K^+ secretion, as does the presence of relatively nonreabsorbable anions (including bicarbonate and semisynthetic penicillins) that contribute to the lumen-negative potential. Off-target effects of certain antibiotics, such as trimethoprim and pentamidine, block ENaCs and predispose to hyperkalemia, especially when renal K^+ handling is impaired for other reasons. Principal cells, as described below, also participate in water reabsorption by increased water permeability in response to vasopressin.

Intercalated cells do not participate in Na^+ reabsorption but, instead, mediate acid-base secretion. These cells perform two types of transport: active H^+ transport mediated by H^+-ATPase (proton pump), and Cl^-/HCO_3^- exchange. Intercalated cells arrange the two transport mechanisms on opposite membranes to enable either acid or base secretion. Type A intercalated cells have an apical proton pump that mediates acid secretion and a basolateral Cl^-/HCO_3^- anion exchanger for bicarbonate reabsorption (Fig. 303-3*E*). Aldosterone increases the number of H^+-ATPase pumps, sometimes contributing to the development of metabolic alkalosis. Secreted H^+ is buffered by NH_3 that has diffused into the collecting duct lumen from the surrounding interstitium. By contrast, type B intercalated cells have the Cl^-/HCO_3^- exchanger on the apical membrane to mediate bicarbonate secretion while the proton pump resides on the basolateral membrane to enable acid reabsorption. Under conditions of acidemia, the kidney preferentially uses type A intercalated cells to secrete the excess H^+ and generate more HCO_3^-. The opposite is true in states of bicarbonate excess with alkalemia where the type B intercalated cells predominate. An extracellular protein called *hensin* mediates this adaptation.

Inner medullary collecting duct cells share many similarities with principal cells of the cortical collecting duct. They have apical Na^+ and K^+ channels that mediate Na^+ reabsorption and K^+ secretion, respectively (Fig. 303-3*F*). Sodium reabsorption by inner medullary collecting duct cells is also inhibited by the natriuretic peptides called *atrial natriuretic peptide* or *renal natriuretic peptide* (urodilatin); the same gene encodes both peptides but uses different posttranslational processing of a common preprohormone to generate different proteins. Atrial natriuretic peptides are secreted by atrial myocytes in response to volume expansion, whereas urodilatin is secreted by renal tubular epithelia. Natriuretic peptides interact with either apical (urodilatin) or basolateral (atrial natriuretic peptides) receptors on inner medullary collecting duct cells to stimulate guanylyl cyclase and increase levels of cytoplasmic cGMP. This effect in turn reduces the activity of the apical Na^+ channel in these cells and attenuates net Na^+ reabsorption, producing natriuresis.

The inner medullary collecting duct transports urea out of the lumen, returning urea to the interstitium, where it contributes to the hypertonicity of the medullary interstitium. Urea is recycled by diffusing from the interstitium into the descending and ascending limbs of the loop of Henle.

HORMONAL REGULATION OF SODIUM AND WATER BALANCE

The balance of solute and water in the body is determined by the amounts ingested, distributed to various fluid compartments, and excreted by skin, bowel, and kidneys. *Tonicity*, the osmolar state determining the volume behavior of cells in a solution, is regulated by water balance **(Fig. 303-4*A*)**, and *extracellular blood volume* is regulated by Na^+ balance **(Fig. 303-4*B*)**. The kidney is a critical modulator of both physiologic processes.

WATER BALANCE

Tonicity depends on the variable concentration of *effective osmoles* inside and outside the cell causing water to move in either direction across its membrane. Classic effective osmoles, like Na^+, K^+, and their anions, are solutes trapped on either side of a cell membrane, where they collectively partition and obligate water to move and find equilibrium in proportion to retained solute; Na^+/K^+-ATPase keeps most K^+ inside cells and most Na^+ outside. Normal tonicity (~280 mosmol/L) is rigorously defended by osmoregulatory mechanisms that control water balance to protect tissues from inadvertent *dehydration* (cell shrinkage) or *water intoxication* (cell swelling), both of which are deleterious to cell function (Fig. 303-4*A*).

The mechanisms that control osmoregulation are distinct from those governing extracellular volume, although there is some shared physiology in both processes. While cellular concentrations of K^+ have a determinant role in any level of tonicity, the routine surrogate marker for assessing clinical tonicity is the concentration of serum Na^+. Any reduction in total body water, which raises the Na^+ concentration, triggers a brisk sense of thirst and conservation of water by decreasing renal water excretion mediated by release of vasopressin from the posterior pituitary. Conversely, a decrease in plasma Na^+ concentration triggers an increase in renal water excretion by suppressing the secretion of vasopressin. Whereas all cells expressing mechanosensitive TRPV1, 2, or 4 channels, among potentially other sensors, respond to changes in tonicity by altering their volume and Ca^{2+} concentration, only $TRPV^+$ neuronal cells connected to the organum vasculosum of the lamina terminalis are *osmoreceptive*. Only these cells, because of their neural connectivity and adjacency to a minimal blood-brain barrier, modulate the downstream release of vasopressin by the posterior lobe of the pituitary gland. Secretion is stimulated primarily by changing tonicity and secondarily by other nonosmotic signals such as variable blood volume, stress, pain, nausea, and some drugs. The release of vasopressin by the posterior pituitary increases linearly as plasma tonicity rises above normal, although this varies, depending on the perception of extracellular volume (one form of cross-talk between mechanisms that adjudicate blood volume and osmoregulation). Changing the intake or excretion of water provides a means for adjusting plasma tonicity; thus, osmoregulation governs water balance.

The kidneys play a vital role in maintaining water balance through the regulation of renal water excretion. The ability to concentrate urine to an osmolality exceeding that of plasma enables water conservation, whereas the ability to produce urine more dilute than plasma promotes excretion of excess water. For water to enter or exit a cell, the cell membrane must express aquaporins. In the kidney, aquaporin-1 is constitutively active in all water-permeable segments (e.g., proximal tubule, descending thin limb of the loop of Henle), whereas aquaporin-2, -3, and -4 in the collecting duct promote vasopressin-regulated water permeability. Net water reabsorption is ultimately driven by the osmotic gradient between dilute tubular fluid and a hypertonic medullary interstitium.

SODIUM BALANCE

The perception of *extracellular blood volume* is determined, in part, by the integration of arterial tone, cardiac stroke volume, heart rate, and the water and solute content of extracellular fluid. Na^+ and accompanying anions are the most abundant extracellular effective osmoles and together support a blood volume around which pressure is generated. Under normal conditions, this volume is regulated by sodium balance (Fig. 303-4*B*), and the balance between daily Na^+ intake and excretion is under the influence of *baroreceptors* in regional blood vessels and vascular hormone sensors modulated by atrial natriuretic peptides, the renin-angiotensin-aldosterone system, Ca^{2+} signaling, adenosine, vasopressin, and the neural adrenergic axis. If Na^+ intake exceeds Na^+ excretion (positive Na^+ balance), then an increase in blood volume will trigger a proportional increase in urinary Na^+ excretion. Conversely, when Na^+ intake is less than urinary excretion (negative Na^+ balance), blood volume will decrease and trigger enhanced renal Na^+ reabsorption, leading to decreased urinary Na^+ excretion.

The renin-angiotensin-aldosterone system is the best-understood hormonal system modulating renal Na^+ excretion. Renin is synthesized and secreted by granular cells in the wall of the afferent arteriole. Its secretion is controlled by several factors, including β_1-adrenergic stimulation to the afferent arteriole, input from the macula densa, and prostaglandins. Renin and ACE activity eventually produce angiotensin II that directly and indirectly promotes renal Na^+ and water reabsorption. Stimulation of proximal tubular Na^+/H^+ exchange by angiotensin II directly increases Na^+ reabsorption. Angiotensin II also promotes Na^+ reabsorption along the collecting duct by stimulating aldosterone secretion by the adrenal cortex. Constriction of the efferent glomerular arteriole by angiotensin II indirectly increases the filtration fraction and raises peritubular capillary oncotic pressure to promote tubular Na^+ reabsorption. Finally, angiotensin II inhibits renin secretion through a negative feedback loop. Alternative metabolism of angiotensin by ACE2 generates the vasodilatory peptide angiotensin 1-7 that acts through Mas receptors to counterbalance several actions of angiotensin II on blood pressure and renal function (Fig. 303-2*C*).

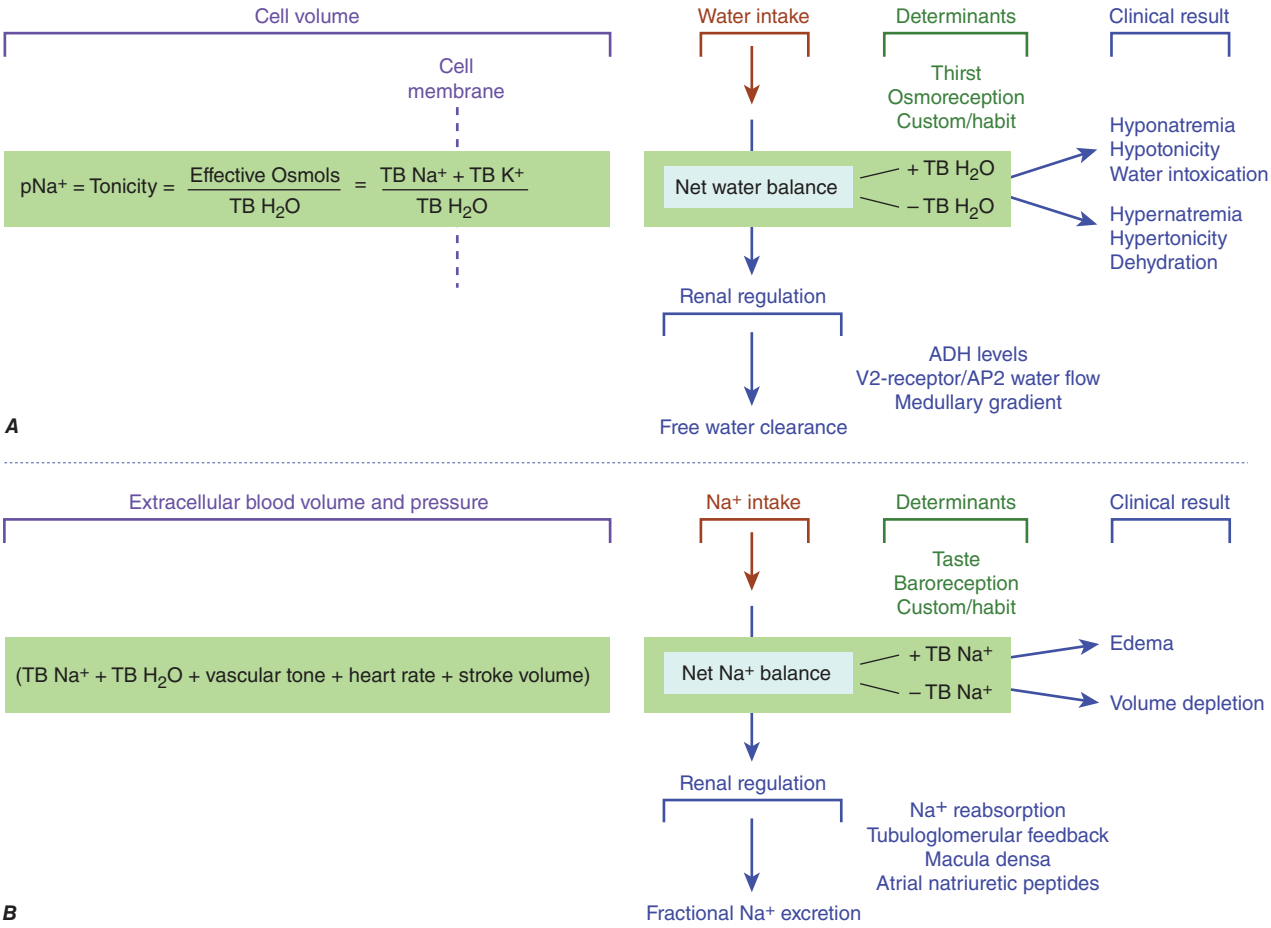


FIGURE 303-4 Determinants of sodium and water balance. ***A.*** Plasma Na^+ concentration is a surrogate marker for plasma tonicity, the volume behavior of cells in a solution. Tonicity is determined by the number of effective osmoles in the body divided by the total body H_2O (TB H_2O), which translates simply into the total body Na (TB Na^+) and anions outside the cell separated from the total body K (TB K^+) inside the cell by the cell membrane. Net water balance is determined by the integrated functions of thirst, osmoreception, Na reabsorption, vasopressin release, and the strength of the medullary gradient in the kidney, keeping tonicity within a narrow range of osmolality around 280 mosmol/L. When water metabolism is disturbed and total body water increases, hyponatremia, hypotonicity, and water intoxication occur; when total body water decreases, hypernatremia, hypertonicity, and dehydration occur. ***B.*** Extracellular blood volume and pressure are an integrated function of total body Na^+ (TB Na^+), total body H_2O (TB H_2O), vascular tone, heart rate, and stroke volume that modulates volume and pressure in the vascular tree of the body. This extracellular blood volume is determined by net Na balance under the control of taste, baroreception, habit, Na^+ reabsorption, macula densa/tubuloglomerular feedback, and natriuretic peptides. When Na^+ metabolism is disturbed and total body Na^+ increases, edema occurs; when total body Na^+ is decreased, volume depletion occurs. ADH, antidiuretic hormone; AQP2, aquaporin-2.

Aldosterone is synthesized and secreted by granulosa cells in the adrenal cortex. It binds to cytoplasmic mineralocorticoid receptors in the collecting duct principal cells that increase activity of ENaC, apical membrane K^+ channel, and basolateral Na^+/K^+-ATPase. These effects are mediated in part by aldosterone-stimulated transcription of the gene encoding serum/glucocorticoid-induced kinase 1 (SGK1). The activity of ENaC is increased by SGK1-mediated phosphorylation of Nedd4-2, a protein that promotes recycling of the Na^+ channel from the plasma membrane. Phosphorylated Nedd4-2 has impaired interactions with ENaC, leading to increased channel density at the plasma membrane and increased capacity for Na^+ reabsorption by the collecting duct.

Chronic exposure to aldosterone causes a decrease in urinary Na^+ excretion lasting only a few days, after which Na^+ excretion returns to previous levels. This phenomenon, called *aldosterone escape*, is explained by decreased proximal tubular Na^+ reabsorption following blood volume expansion. Excess Na^+ that is not reabsorbed by the proximal tubule overwhelms the reabsorptive capacity of more distal nephron segments. This escape may be facilitated by atrial natriuretic peptides that lose their effectiveness in the clinical settings of heart failure, nephrotic syndrome, and cirrhosis, leading to severe Na^+ retention and volume overload.

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304 Acute Kidney Injury

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Acute kidney injury (AKI) is defined by the impairment of kidney filtration and excretory function over days to weeks, resulting in the retention of nitrogenous and other waste products normally cleared by the kidneys. AKI is not a single disease but, rather, a designation for a heterogeneous group of conditions that share common diagnostic features: specifically, an increase in serum creatinine (SCr) concentration often associated with a reduction in urine volume. It is important to recognize that AKI is a clinical diagnosis and not a structural one. A patient may have AKI with or without injury to the kidney parenchyma. AKI can range in severity from asymptomatic and transient changes in laboratory parameters of glomerular filtration rate (GFR), to overwhelming and rapidly fatal derangements in effective circulating volume regulation and electrolyte and acid-base composition of the plasma.

EPIDEMIOLOGY

AKI complicates 5–7% of acute care hospital admissions and up to 30% of admissions to the intensive care unit. The incidence of AKI has grown by more than fourfold in the United States since 1988 and is estimated to have a yearly incidence of 500 per 100,000 population, higher than the yearly incidence of stroke. AKI is associated with a markedly increased risk of death in hospitalized individuals, particularly in those admitted to the ICU where in-hospital mortality rates may exceed 50%. AKI increases the risk for the development or worsening of chronic kidney disease (CKD). Patients who survive and recover from an episode of severe AKI requiring dialysis are at increased risk for the later development of dialysis-requiring end-stage kidney disease. AKI may be community-acquired or hospital-acquired. Common causes of community-acquired AKI include volume depletion, heart failure, adverse effects of medications, obstruction of the urinary tract, or malignancy. The most common clinical settings for hospital-acquired AKI are sepsis, major surgical procedures, critical illness involving heart or liver failure, and nephrotoxic medication administration.

AKI IN THE DEVELOPING WORLD

AKI is also a major medical complication in the developing world, where the epidemiology differs from that in developed countries due to differences in demographics, economics, environmental factors, and comorbid disease burden. While certain features of AKI are common in the developed and developing countries—particularly since urban centers of some developing countries increasingly resemble those in the developed world—many etiologies for AKI are region-specific such as envenomations from snakes, spiders, caterpillars, and bees; infectious causes such as malaria and leptospirosis; and crush injuries and resultant rhabdomyolysis from earthquakes.

ETIOLOGY AND PATHOPHYSIOLOGY

The causes of AKI have traditionally been divided into three broad categories: prerenal azotemia, intrinsic renal parenchymal disease, and postrenal obstruction **(Fig. 304-1)**.

PRERENAL AZOTEMIA

Prerenal azotemia (from "azo," meaning nitrogen, and "-emia," meaning in the blood) is the most common form of AKI. It is the designation for a rise in SCr or BUN concentration due to inadequate renal plasma flow and intraglomerular hydrostatic pressure to support normal glomerular filtration. The most common clinical conditions associated with prerenal azotemia are hypovolemia, decreased cardiac output, and medications that interfere with renal autoregulatory responses such as nonsteroidal anti-inflammatory drugs (NSAIDs) and inhibitors of angiotensin II **(Fig. 304-2)**. Prerenal azotemia may coexist with other forms of intrinsic AKI associated with processes acting directly on the renal parenchyma. Prolonged periods of prerenal azotemia may lead to ischemic injury, often termed acute tubular necrosis (ATN). By definition, prerenal azotemia involves no parenchymal damage to the kidney and is rapidly reversible once parenchymal blood flow and intraglomerular hemodynamics are restored.

Normal GFR is maintained in part by renal blood flow and the relative resistances of the afferent and efferent renal arterioles, which determine the glomerular plasma flow rate and the transcapillary hydraulic pressure gradient that drive glomerular ultrafiltration. Mild degrees of hypovolemia and reductions in cardiac output elicit compensatory

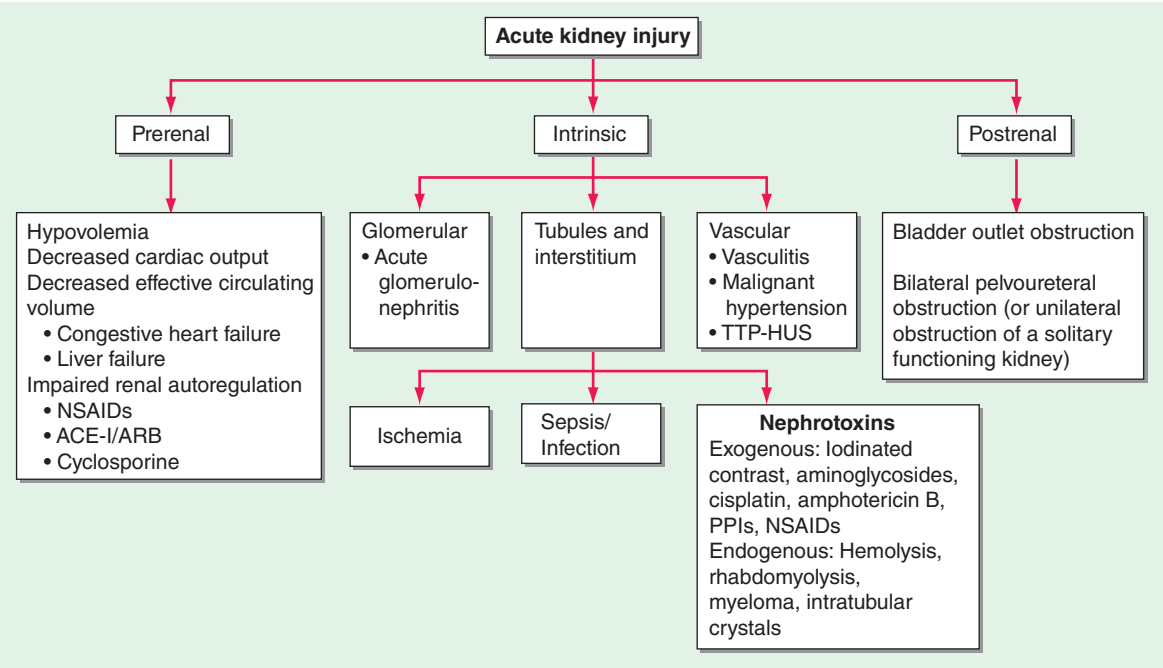

FIGURE 304-1 Classification of the major causes of acute kidney injury. ACE-I, angiotensin-converting enzyme inhibitor-I; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; TTP-HUS, thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome.

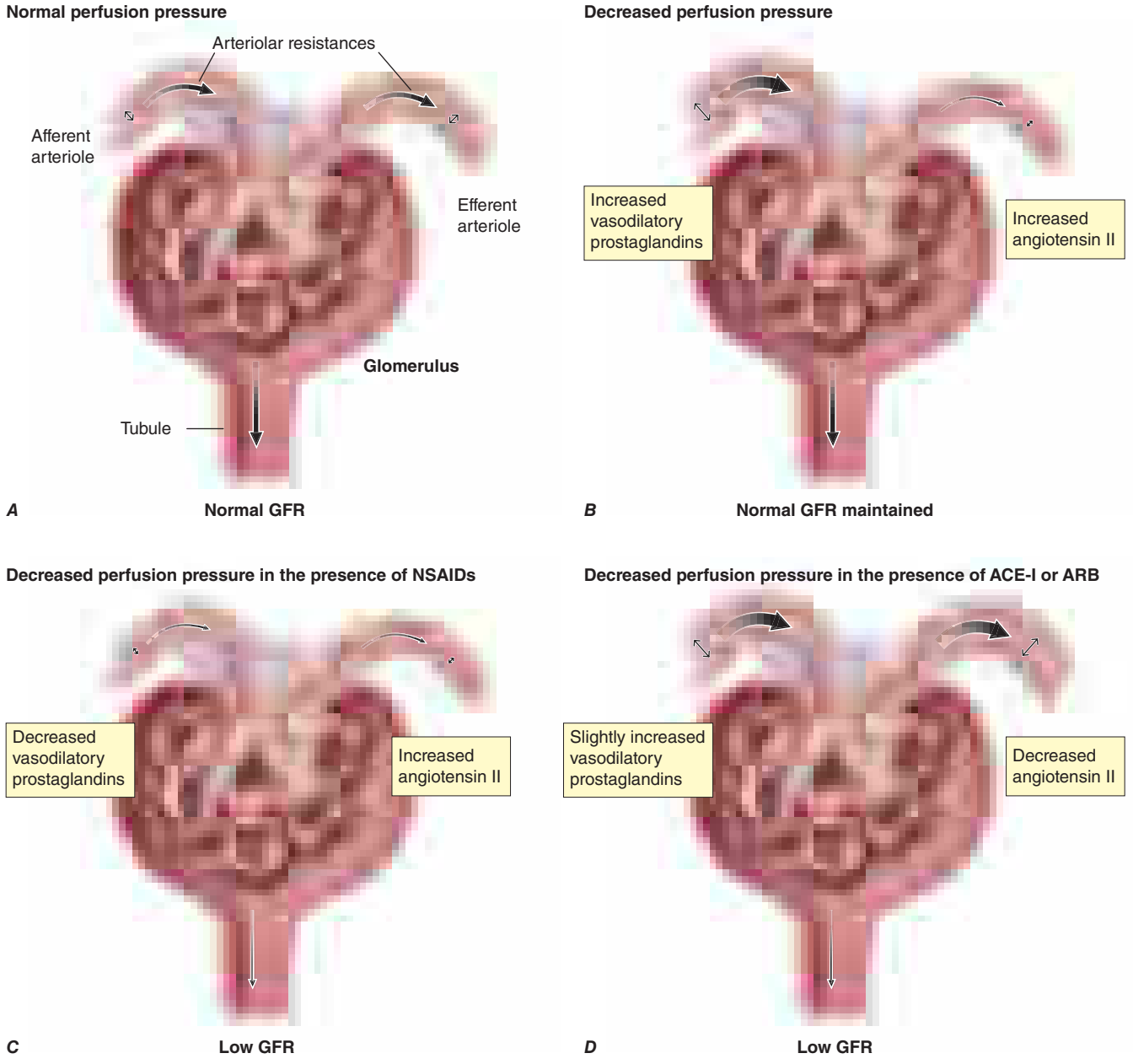

FIGURE 304-2 Intrarenal mechanisms for autoregulation of the glomerular filtration rate (GFR) under decreased perfusion pressure and reduction of the GFR by drugs. ***A.*** Normal conditions and a normal GFR. ***B.*** Reduced perfusion pressure within the autoregulatory range. Normal glomerular capillary pressure is maintained by afferent vasodilatation and efferent vasoconstriction. ***C.*** Reduced perfusion pressure with a nonsteroidal anti-inflammatory drug (NSAID). Loss of vasodilatory prostaglandins increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. ***D.*** Reduced perfusion pressure with an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin receptor blocker (ARB). Loss of angiotensin II action reduces efferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. *(From JG Abuelo: N Engl J Med 357:797-805, 2007; with permission.)*

renal physiologic changes. Because renal blood flow accounts for 20% of the cardiac output, renal vasoconstriction and salt and water reabsorption occur as homeostatic responses to decreased effective circulating volume or cardiac output in order to maintain blood pressure and increase intravascular volume to sustain perfusion to the cerebral and coronary vessels. Mediators of this response include angiotensin II, norepinephrine, and vasopressin (also termed antidiuretic hormone). Glomerular filtration can be maintained despite reduced renal blood flow by angiotensin II–mediated renal efferent vasoconstriction, which maintains glomerular capillary hydrostatic pressure closer to normal and thereby prevents marked reductions in GFR if renal blood flow reduction is not excessive.

In addition, a myogenic reflex within the afferent arteriole leads to dilation in the setting of low perfusion pressure, thereby maintaining glomerular perfusion. Intrarenal biosynthesis of vasodilator prostaglandins (prostacyclin, prostaglandin E_2), kallikrein and kinins, and possibly nitric oxide (NO) also increase in response to low renal perfusion pressure. Autoregulation is also accomplished by tubuloglomerular feedback, in which decreases in solute delivery to the macula densa (specialized cells within the distal tubule) elicit dilation of the juxtaposed afferent arteriole in order to maintain glomerular perfusion, a mechanism mediated, in part, by NO. There is a limit, however, to the ability of these counterregulatory mechanisms to maintain GFR in the face of systemic hypotension. Even in healthy adults, renal autoregulation usually fails once the systolic blood pressure falls below 80 mmHg.

A number of factors determine the robustness of the autoregulatory response and the risk of prerenal azotemia. Atherosclerosis, long-standing hypertension, and older age can lead to hyalinosis and myointimal hyperplasia, causing structural narrowing of the intrarenal arterioles and impaired capacity for renal afferent vasodilation. In CKD, renal afferent vasodilation may be operating at maximal capacity in order to maximize GFR in response to reduced functional

renal mass. Drugs can affect the compensatory changes evoked to maintain GFR. Nonsteroidal anti-inflammatory agents (NSAIDs) inhibit renal prostaglandin production, limiting renal afferent vasodilation. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) limit renal efferent vasoconstriction; this effect is particularly pronounced in patients with bilateral renal artery stenosis or unilateral renal artery stenosis (in the case of a solitary functioning kidney) because, as indicated above, efferent arteriolar vasoconstriction is needed to maintain GFR due to low renal perfusion. The combined use of NSAIDs with ACE inhibitors or ARBs poses a particularly high risk for developing prerenal azotemia.

Many individuals with advanced liver disease exhibit a hemodynamic profile that resembles prerenal azotemia in the setting of total-body volume overload. Systemic vascular resistance is markedly reduced due to primary arterial vasodilation in the splanchnic circulation, resulting ultimately in activation of vasoconstrictor responses similar to those seen in hypovolemia. AKI is a common complication in this setting, and it can be triggered by volume depletion and spontaneous bacterial peritonitis. A particularly poor prognosis is seen in the case of type 1 hepatorenal syndrome, in which AKI, defined as >two-fold increase in SCr to >2.5 mg/dL, within 2 weeks without an alternate cause (e.g., shock and nephrotoxic drugs), persists despite volume administration and withholding of diuretics. Type 2 hepatorenal syndrome is a less severe form characterized mainly by refractory ascites. The hepatorenal syndrome, defined as it is above, is difficult to distinguish from prerenal azotemia. An older way of characterizing hepatorenal was prerenal azotemia that would not improve, often leading to intrinsic renal AKI, unless a definitive procedure to improve hemodynamics, such as porto-systemic shunt placement or liver transplant, was performed. We still find this latter construct of use.

INTRINSIC AKI

The most common causes of intrinsic AKI are sepsis, ischemia, and nephrotoxins, both endogenous and exogenous **(Fig. 304-3)**. In many cases, prerenal azotemia advances to tubular injury. Although classically termed "acute tubular necrosis," human biopsy confirmation of tubular necrosis is, in general, often lacking in cases of sepsis and ischemia; indeed, processes such as inflammation, apoptosis, and altered regional perfusion may be important contributors pathophysiologically. ATN is also often diagnosed clinically without biopsy confirmation in settings such as sepsis with multiple alternate potential diagnoses, including drug-induced interstitial nephritis and immune complex glomerulonephritis. These and other causes of intrinsic AKI are considered to be less common and can be conceptualized anatomically according to the major site of renal parenchymal damage: glomeruli, tubulointerstitium, and vessels.

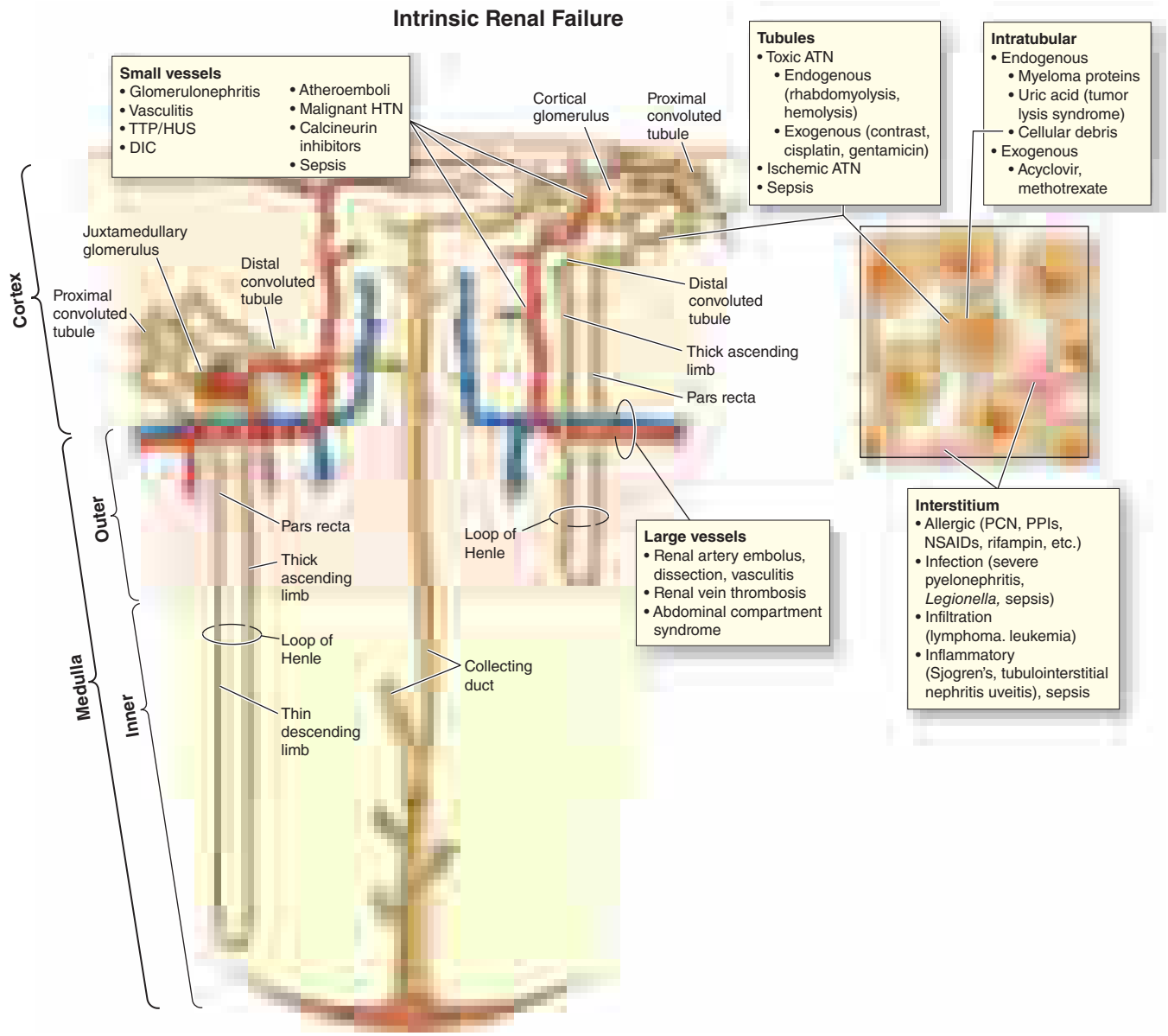

FIGURE 304-3 Major causes of intrinsic acute kidney injury. ATN, acute tubular necrosis; DIC, disseminated intravascular coagulation; HTN, hypertension; PCN, penicillin; PPI, proton pump inhibitors; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome; TINU, tubulointerstitial nephritis-uveitis.

SEPSIS-ASSOCIATED AKI

In the United States, more than one million cases of sepsis occur each year. AKI complicates more than 50% of cases of severe sepsis and greatly increases the risk of death. Sepsis is also a very important cause of AKI in the developing world. Decreases in GFR with sepsis can occur even in the absence of overt hypotension, although most cases of severe AKI typically occur in the setting of hemodynamic collapse requiring vasopressor support. While there is clearly tubular injury associated with AKI in sepsis as manifest by the presence of tubular debris and casts in the urine, postmortem examinations of kidneys from individuals with severe sepsis suggest that other factors, perhaps related to inflammation, mitochondrial dysfunction, and interstitial edema, must also be considered in the pathophysiology of sepsis-induced AKI.

The hemodynamic effects of sepsis—arising from generalized arterial vasodilation, mediated in part by cytokines that upregulate the expression of inducible NO synthase in the vasculature—can lead to a reduction in GFR. The operative mechanisms may be excessive efferent arteriole vasodilation, particularly early in the course of sepsis, or renal vasoconstriction from activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, vasopressin, and endothelin. Sepsis may lead to endothelial damage, which results in increased microvascular leukocyte adhesion and migration, thrombosis, permeability, increased interstitial pressure, reduction in local flow to tubules, and activation of reactive oxygen species, all of which may injure renal tubular cells.

ISCHEMIA-ASSOCIATED AKI

Healthy kidneys receive 20% of the cardiac output and account for 10% of resting oxygen consumption, despite constituting only 0.5% of the human body mass. The kidneys are also the site of one of the most hypoxic regions in the body, the renal medulla. The outer medulla is particularly vulnerable to ischemic damage because of the architecture of the blood vessels that supply oxygen and nutrients to the tubules. In the outer medulla enhanced leukocyte-endothelial interactions in the small vessels lead to inflammation and reduced local blood flow to the metabolically very active S3 segment of the proximal tubule, which depends on oxidative metabolism for survival. Mitochondrial dysfunction due to ischemia and mitochondrial release of reactive oxygen species also play a role in renal tubular injury. Ischemia alone in a normal kidney is usually not sufficient to cause severe AKI, as evidenced by the relatively low risk of severe AKI even after total interruption of renal blood flow during suprarenal aortic clamping or cardiac arrest. Clinically, AKI more commonly develops when ischemia occurs in the context of limited renal reserve (e.g., CKD or older age) or coexisting insults such as sepsis, vasoactive or nephrotoxic drugs, rhabdomyolysis, or the systemic inflammatory states associated with burns and pancreatitis. Prerenal azotemia and ischemia-associated AKI represent a continuum of the manifestations of renal hypoperfusion. Persistent preglomerular vasoconstriction may be a common underlying cause of the reduction in GFR seen in AKI; implicated factors for vasoconstriction include activation of tubuloglomerular feedback from enhanced delivery of solute to the macula densa following proximal tubule injury, increased basal vascular tone and reactivity to vasoconstrictive agents, and decreased vasodilator responsiveness. Other contributors to low GFR include backleak of filtrate across damaged and denuded tubular epithelium and mechanical obstruction of tubules from necrotic debris (Fig. 304-4).

Postoperative AKI Ischemia-associated AKI is a serious complication in the postoperative period, especially after major operations involving significant blood loss and intraoperative hypotension. The procedures most commonly associated with AKI are cardiac surgery with cardiopulmonary bypass (particularly for combined valve and bypass procedures), vascular procedures with aortic cross clamping, and intraperitoneal procedures. Severe AKI requiring dialysis occurs in ~1% of cardiac and vascular surgery procedures. The risk of severe AKI has been less well studied for major intraperitoneal procedures but appears to be of comparable magnitude. Common risk factors for postoperative AKI include underlying CKD, older age, diabetes mellitus, congestive heart failure, and emergency procedures. The pathophysiology of AKI following cardiac surgery is multifactorial. Major AKI risk factors are common in the population undergoing cardiac surgery. The use of nephrotoxic agents, including iodinated contrast for cardiac imaging prior to surgery, may increase the risk of AKI. Cardiopulmonary bypass is a unique hemodynamic state characterized by nonpulsatile flow and exposure of the circulation to extracorporeal circuits. Longer duration of cardiopulmonary bypass is a risk factor for AKI. In addition to ischemic injury from sustained hypoperfusion, cardiopulmonary bypass may cause AKI through a number of mechanisms including extracorporeal circuit activation of leukocytes and inflammatory processes, hemolysis with resultant pigment nephropathy (see below), and aortic injury with resultant atheroemboli. AKI from atheroembolic disease, which can also occur following percutaneous catheterization of the aorta, or spontaneously, is due to cholesterol crystal embolization resulting in partial or total occlusion of multiple small arteries within the kidney. Over time, a foreign body reaction can result in intimal proliferation, giant cell formation, and further narrowing of the vascular lumen, accounting for the generally subacute (over a period of weeks rather than days) decline in renal function.

Burns and Acute Pancreatitis Extensive fluid losses into the extravascular compartments of the body frequently accompany severe burns and acute pancreatitis. AKI is an ominous complication of burns, affecting 25% of individuals with >10% total body surface area involvement. In addition to severe hypovolemia resulting in decreased cardiac output and increased neurohormonal activation, burns and acute pancreatitis both lead to dysregulated inflammation and an increased risk of sepsis and acute lung injury, all of which may facilitate the development and progression of AKI. Individuals undergoing massive fluid resuscitation for trauma, burns, and acute pancreatitis can also develop the abdominal compartment syndrome, where markedly elevated intraabdominal pressures, usually >20 mmHg, lead to renal vein compression and reduced GFR.

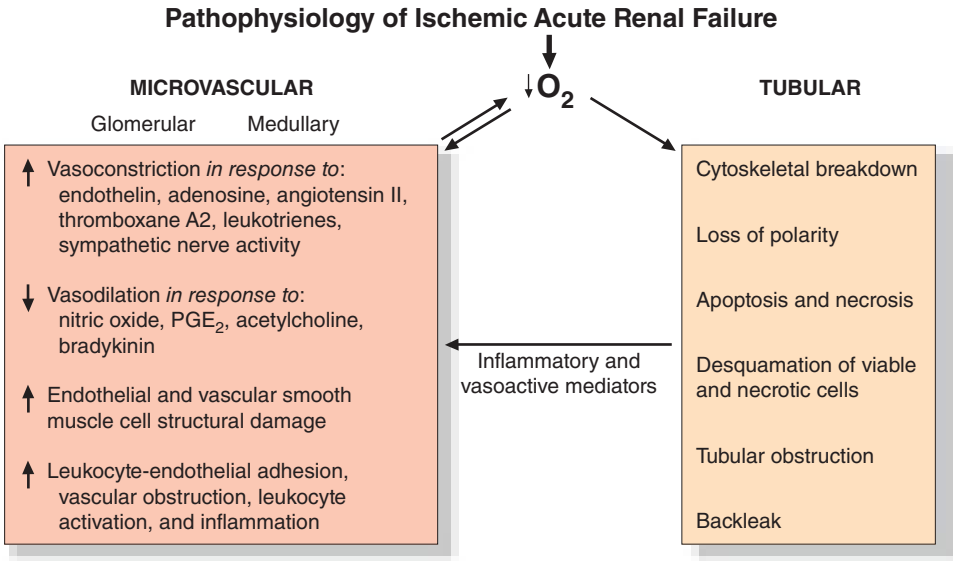

FIGURE 304-4 Interacting microvascular and tubular events contributing to the pathophysiology of ischemic acute kidney injury. PGE_2, prostaglandin E_2. *(From JV Bonventre, JM Weinberg: J Am Soc Nephrol 14:2199, 2003.)*

Diseases of the Microvasculature Leading to Ischemia Microvascular causes of AKI include the thrombotic microangiopathies (due to cocaine, certain chemotherapeutic agents, antiphospholipid antibody syndrome, radiation nephritis, malignant hypertensive nephrosclerosis, and thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome [TTP-HUS]), scleroderma, and atheroembolic disease. Large-vessel diseases associated with AKI include renal artery dissection, thromboembolism, or thrombosis, and renal vein compression or thrombosis.

NEPHROTOXIN-ASSOCIATED AKI

The kidney has very high susceptibility to nephrotoxic agents due to extremely high blood perfusion and concentration of circulating substances along the nephron where water is reabsorbed and in the medullary interstitium; this results in high-concentration exposure of toxins to tubular, interstitial, and endothelial cells. Nephrotoxic injury occurs in response to a number of pharmacologic compounds with diverse structures, endogenous substances, and environmental exposures. All structures of the kidney are vulnerable to toxic injury, including the tubules, interstitium, vasculature, and collecting system. As with other forms of AKI, risk factors for nephrotoxicity include older age, CKD, and prerenal azotemia. Hypoalbuminemia may increase the risk of some forms of nephrotoxin-associated AKI due to increased free circulating drug concentrations.

Contrast Agents Iodinated contrast agents used for cardiovascular and computed tomography (CT) imaging are a cause of AKI. The risk of AKI, or "contrast nephropathy," is negligible in those with normal renal function but increases in the setting of CKD, particularly diabetic nephropathy. The most common clinical course of contrast nephropathy is characterized by a rise in SCr beginning 24–48 h following exposure, peaking within 3–5 days, and resolving within 1 week. More severe, dialysis-requiring AKI is uncommon except in the setting of significant preexisting CKD, often in association with congestive heart failure or other coexisting causes for ischemia-associated AKI. Patients with multiple myeloma and renal disease are particularly susceptible. Low fractional excretion of sodium (FeNa) and relatively benign urinary sediment without features of tubular necrosis (see below) are common findings. Contrast nephropathy is thought to occur from a combination of factors, including (1) hypoxia in the renal outer medulla due to perturbations in renal microcirculation and occlusion of small vessels; (2) cytotoxic damage to the tubules directly or via the generation of oxygen-free radicals, especially because the concentration of the agent within the tubule is markedly increased; and (3) transient tubule obstruction with precipitated contrast material. Other diagnostic agents implicated as a cause of AKI are high-dose gadolinium used for magnetic resonance imaging (MRI) and oral sodium phosphate solutions used as bowel purgatives.

Antibiotics Several antimicrobial agents are commonly associated with AKI. *Vancomycin* may be associated with AKI, particularly when trough levels are high and when used in combination with other nephrotoxic antibiotics. *Aminoglycosides and amphotericin B* both cause tubular necrosis. Nonoliguric AKI (i.e., with a urine volume >400 mL/day) accompanies 10–30% of courses of aminoglycoside antibiotics, even when plasma levels are in the therapeutic range. Aminoglycosides are freely filtered across the glomerulus and then accumulate within the renal cortex, where concentrations can greatly exceed those of the plasma. AKI typically manifests after 5–7 days of therapy and can present even after the drug has been discontinued. Hypomagnesemia is a common finding.

Amphotericin B causes renal vasoconstriction from an increase in tubuloglomerular feedback as well as direct tubular toxicity mediated by reactive oxygen species. Nephrotoxicity from amphotericin B is dose and duration dependent. This drug binds to tubular membrane cholesterol and introduces pores. Clinical features of amphotericin B nephrotoxicity include polyuria, hypomagnesemia, hypocalcemia, and nongap metabolic acidosis.

Acyclovir can precipitate in tubules and cause AKI by tubular obstruction, particularly when given as an intravenous bolus at high doses (500 mg/m^2) or in the setting of hypovolemia. *Foscarnet, pentamidine, tenofovir*, and *cidofovir* are also frequently associated with AKI due to tubular toxicity. AKI secondary to acute interstitial nephritis can occur as a consequence of exposure to many antibiotics, including *penicillins, cephalosporins, quinolones, sulfonamides*, and *rifampin*.

Chemotherapeutic Agents *Cisplatin* and *carboplatin* are accumulated by proximal tubular cells and cause necrosis and apoptosis. Intensive hydration regimens have reduced the incidence of cisplatin nephrotoxicity, but it remains a dose-limiting toxicity. *Ifosfamide* may cause hemorrhagic cystitis and tubular toxicity, manifested as type II renal tubular acidosis (Fanconi's syndrome), polyuria, hypokalemia, and a modest decline in GFR. Antiangiogenesis agents, such as *bevacizumab*, can cause proteinuria and hypertension via injury to the glomerular microvasculature (thrombotic microangiopathy). Other antineoplastic agents such as mitomycin C and gemcitabine may cause thrombotic microangiopathy with resultant AKI.

Toxic Ingestions Ethylene glycol, present in automobile antifreeze, is metabolized to oxalic acid, glycolaldehyde, and glyoxylate, which may cause AKI through direct tubular injury and tubular obstruction. Diethylene glycol is an industrial agent that has caused outbreaks of severe AKI around the world due to adulteration of pharmaceutical preparations. The metabolite 2-hydroxyethoxyacetic acid (HEAA) is thought to be responsible for tubular injury. Melamine contamination of foodstuffs has led to nephrolithiasis and AKI, either through intratubular obstruction or possibly direct tubular toxicity. Aristolochic acid was found to be the cause of "Chinese herb nephropathy" and "Balkan nephropathy" due to contamination of medicinal herbs or farming. The list of environmental toxins is likely to grow and contribute to a better understanding of previously catalogued "idiopathic" chronic tubular interstitial disease, a common diagnosis in both the developed and developing world.

Endogenous Toxins AKI may be caused by a number of endogenous compounds, including myoglobin, hemoglobin, uric acid, and myeloma light chains. Myoglobin can be released by injured muscle cells, and hemoglobin can be released during massive hemolysis leading to pigment nephropathy. Rhabdomyolysis may result from traumatic crush injuries, muscle ischemia during vascular or orthopedic surgery, compression during coma or immobilization, prolonged seizure activity, excessive exercise, heat stroke or malignant hyperthermia, infections, metabolic disorders (e.g., hypophosphatemia, severe hypothyroidism), and myopathies (drug-induced, metabolic, or inflammatory). Pathogenic factors for AKI due to endogenous toxins include intrarenal vasoconstriction, direct proximal tubular toxicity, and mechanical obstruction of the distal nephron lumen when myoglobin or hemoglobin precipitates with Tamm-Horsfall protein (uromodulin, the most common protein in urine and produced in the thick ascending limb of the loop of Henle), a process favored by acidic urine. Tumor lysis syndrome may follow initiation of cytotoxic therapy in patients with high-grade lymphomas and acute lymphoblastic leukemia; massive release of uric acid (with serum levels often exceeding 15 mg/dL) leads to precipitation of uric acid in the renal tubules and AKI (Chap. 71). Other features of tumor lysis syndrome include hyperkalemia and hyperphosphatemia. The tumor lysis syndrome can also occasionally occur spontaneously or with treatment for solid tumors or multiple myeloma. Myeloma light chains can also cause AKI by direct tubular toxicity and by binding to Tamm-Horsfall protein to form obstructing intratubular casts. Hypercalcemia, which can also be seen in multiple myeloma, may cause AKI by intense renal vasoconstriction and volume depletion.

Other Causes of Acute Tubulointerstitial Disease Leading to AKI While many of the ischemic and toxic causes of AKI previously described result in tubulointerstitial disease, many drugs are also associated with the development of an allergic response characterized by an inflammatory infiltrate and often peripheral and urinary eosinophilia. Proton pump inhibitors and NSAIDS are commonly used drugs that have been associated with acute tubulointerstitial nephritis. AKI

may be also caused by severe infections and infiltrative malignant or nonmalignant (e.g., sarcoidosis) diseases.

Glomerulonephritis Diseases involving the glomerular podocytes, mesangial and endothelial cells can lead to AKI by compromising the filtration barrier and blood flow within the renal circulation. Although glomerulonephritis is a less common (~5%) cause of AKI, early recognition is particularly important because the diseases can respond to timely treatment with immunosuppressive agents or therapeutic plasma exchange, and the treatment may reverse the AKI.

POSTRENAL AKI

(See also Chap. 313) Postrenal AKI occurs when the normally unidirectional flow of urine is acutely blocked either partially or totally, leading to increased retrograde hydrostatic pressure and interference with glomerular filtration. Obstruction to urinary flow may be caused by functional or structural derangements anywhere from the renal pelvis to the tip of the urethra (Fig. 304-5). Normal urinary flow rate does not rule out the presence of partial obstruction, because the GFR is normally two orders of magnitude higher than the urinary flow rate and hence a preservation of urine output may be misleading in hiding the postrenal partial obstruction. For AKI to occur in individuals with two healthy functional kidneys, obstruction must affect both kidneys in order to observe large increases in SCr. Unilateral obstruction may cause AKI in the setting of significant underlying CKD or, in rare cases, from reflex vasospasm of the contralateral kidney. Bladder neck obstruction is a common cause of postrenal AKI which impacts both kidneys. This can be due to prostate disease (benign prostatic hypertrophy or prostate cancer), neurogenic bladder, or therapy with anticholinergic drugs. Obstructed Foley catheters can cause postrenal AKI if not recognized and relieved. Other causes of lower tract obstruction are blood clots, calculi, and urethral strictures. Ureteric obstruction can occur from intraluminal obstruction (e.g., calculi, blood clots, sloughed renal papillae), infiltration of the ureteric wall (e.g., neoplasia), or external compression (e.g., retroperitoneal fibrosis, neoplasia, abscess, or inadvertent surgical damage). The pathophysiology of postrenal AKI involves hemodynamic alterations triggered by an abrupt increase in intratubular pressures. An initial period of hyperemia from afferent arteriolar dilation is followed by intrarenal vasoconstriction from the generation of angiotensin II, thromboxane A2, and vasopressin, and a reduction in NO production. Secondary reductions in glomerular function are due to underperfusion of glomeruli and, possibly, changes in the glomerular ultrafiltration coefficient.

DIAGNOSTIC EVALUATION (TABLE 304-1)

By current definitions the presence of AKI is defined by an elevation in the SCr concentration or reduction in urine output. AKI is currently defined by a rise from baseline of at least 0.3 mg/dL within 48 h or at least 50% higher than baseline within 1 week, or a reduction in urine output to <0.5 mL/kg per h for longer than 6 h. As indicated above, it is important to recognize that given this definition, some patients with AKI will not have tubular or glomerular damage (e.g., prerenal azotemia). The distinction between AKI and CKD is important for proper diagnosis and treatment. The distinction is straightforward when a recent baseline SCr concentration is available, but more difficult in the many instances in which the baseline is unknown. In such cases, clues suggestive of CKD can come from radiologic studies (e.g., small, shrunken kidneys with cortical thinning on renal ultrasound, or evidence of renal osteodystrophy) or laboratory tests such as normocytic anemia in the absence of blood loss or secondary hyperparathyroidism with hyperphosphatemia and hypocalcemia, consistent with CKD. No set of tests, however, can rule out AKI superimposed on CKD because AKI is a frequent complication in patients with CKD, further complicating the distinction. Serial blood tests showing a continued substantial rise of SCr represents clear evidence of AKI. Once the diagnosis of AKI is established, its cause needs to be determined since the elevation of SCr or reduction in urine output can be due to a large number of physiological and pathophysiological processes.

HISTORY AND PHYSICAL EXAMINATION

The clinical context, careful history taking, and physical examination often narrow the differential diagnosis for the cause of AKI. Prerenal azotemia should be suspected in the setting of vomiting, diarrhea, glycosuria causing polyuria, and several medications including diuretics, NSAIDs, ACE inhibitors, and ARBs. Physical signs of orthostatic hypotension, tachycardia, reduced jugular venous pressure, decreased skin turgor, and dry mucous membranes are often present in prerenal azotemia. Congestive heart failure, liver disease, and nephrotic syndrome can be associated with reductions in renal blood flow and/or alterations in intrarenal hemodynamics leading to reduced GFR. Extensive vascular disease raises the possibility of renal artery disease, especially if kidneys are known to be asymmetric in size. Atheroembolic disease can be associated with livedo reticularis and other signs of emboli to the legs. The presence of sepsis is an important clue to causation although, as described above, the detailed pathophysiology may be multifactorial.

A history of prostatic disease, nephrolithiasis, or pelvic or paraaortic malignancy would suggest the possibility of postrenal AKI. Whether or not symptoms are present early during obstruction of the urinary tract depends on the location of obstruction. Colicky flank pain radiating to the groin suggests acute ureteric obstruction. Nocturia and urinary frequency or hesitancy can be seen in prostatic disease. Abdominal fullness and suprapubic pain can accompany bladder enlargement. Definitive diagnosis of obstruction requires radiologic investigations.

A careful review of all medications is imperative in the evaluation of an

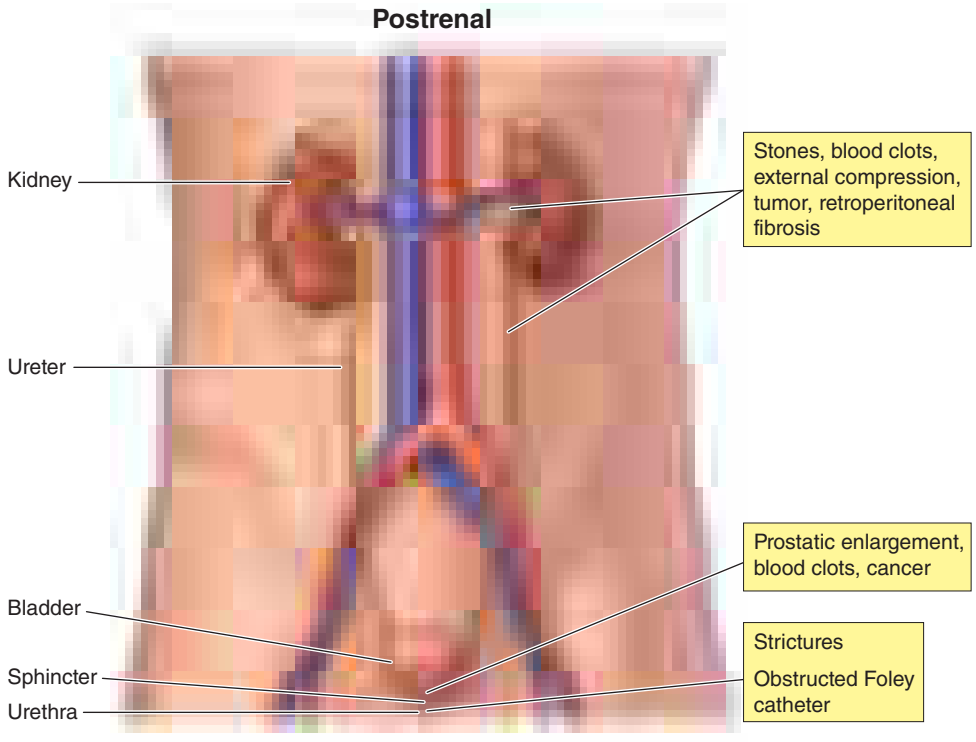

FIGURE 304-5 Anatomic sites and causes of obstruction leading to postrenal acute kidney injury.

TABLE 304-1 Major Causes, Clinical Features, and Diagnostic Studies for Prerenal and Intrinsic Acute Kidney Injury

ETIOLOGY	CLINICAL FEATURES	LABORATORY FEATURES	COMMENTS
Prerenal azotemia	History of poor fluid intake or fluid loss (hemorrhage, diarrhea, vomiting, sequestration into extravascular space); NSAID/ACE-I/ARB; heart failure; evidence of volume depletion (tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes), decreased effective circulatory volume (cirrhosis, heart failure)	BUN/creatinine ratio above 20, FeNa <1%, hyaline casts in urine sediment, urine specific gravity >1.018, urine osmolality >500 mOsm/kg	Low FeNa, high specific gravity and osmolality may not be seen in the setting of CKD, diuretic use; BUN elevation out of proportion to creatinine may alternatively indicate upper GI bleed or increased catabolism. Response to restoration of hemodynamics is most diagnostic.
Sepsis-associated AKI	Sepsis, sepsis syndrome, or septic shock. Overt hypotension not always seen in mild to moderate AKI	Positive culture from normally sterile body fluid; urine sediment often contains granular casts, renal tubular epithelial cell casts	FeNa may be low (<1%), particularly early in the course, but is usually >1% with osmolality <500 mOsm/kg
Ischemia-associated AKI	Systemic hypotension, often superimposed upon sepsis and/or reasons for limited renal reserve such as older age, CKD	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	
Nephrotoxin-Associated AKI: Endogenous			
Rhabdomyolysis	Traumatic crush injuries, seizures, immobilization	Elevated myoglobin, creatine kinase; urine heme positive with few red blood cells	FeNa may be low (<1%)
Hemolysis	Recent blood transfusion with transfusion reaction	Anemia, elevated LDH, low haptoglobin	FeNa may be low (<1%); evaluation for transfusion reaction
Tumor lysis	Recent chemotherapy	Hyperphosphatemia, hypocalcemia, hyperuricemia	
Multiple myeloma	Age >60 years, constitutional symptoms, bone pain	Monoclonal spike in urine or serum electrophoresis; low anion gap; anemia	Bone marrow or renal biopsy can be diagnostic
Nephrotoxin-Associated AKI: Exogenous			
Contrast nephropathy	Exposure to iodinated contrast	Characteristic course is rise in SCr within 1–2 d, peak within 3–5 d, recovery within 7 d	FeNa may be low (<1%)
Tubular injury	Aminoglycoside antibiotics, cisplatin, tenofovir, vancoycin, zoledronate, ethylene glycol, aristolochic acid, protein pump inhibitors, tacrolimus and melamine (to name a few)	Urine sediment often contains granular casts, renal tubular epithelial cell casts. FeNa typically >1%.	Can be oliguric or nonoliguric
Interstitial nephritis	Recent medication exposure (e.g., proton pump inhibitors, NSAIDs, antibiotics), can have fever, rash, arthralgias	Eosinophilia, sterile pyuria; often nonoliguric	Urine eosinophils have limited diagnostic accuracy; systemic signs of drug reaction often absent; kidney biopsy may be helpful
Other Causes of Intrinsic AKI			
Glomerulonephritis/vasculitis	Variable **(Chap. 308)** features include skin rash, arthralgias, sinusitis (AGBM disease), lung hemorrhage (AGBM, ANCA, lupus), recent skin infection or pharyngitis (poststreptococcal)	ANA, ANCA, AGBM antibody, hepatitis serologies, cryoglobulins, blood culture, decreased complement levels, ASO titer (abnormalities of these tests depending on etiology)	Kidney biopsy may be necessary
Interstitial nephritis	Nondrug-related causes include tubulointerstitial nephritis-uveitis (TINU) syndrome, *Legionella* infection	Eosinophilia, sterile pyuria; often nonoliguric	Urine eosinophils have limited diagnostic accuracy; kidney biopsy may be necessary
TTP/HUS	Neurologic abnormalities and/or AKI; recent diarrheal illness; use of calcineurin inhibitors; pregnancy or postpartum; spontaneous	Schistocytes on peripheral blood smear, elevated LDH, anemia, thrombocytopenia	"Typical HUS" refers to AKI with a diarrheal prodrome, often due to Shiga toxin released from *Escherichia coli* or other bacteria; "atypical HUS" is due to inherited or acquired complement dysregulation. "TTP-HUS" refers to sporadic cases in adults. Diagnosis may involve screening for ADAMTS13 activity, Shiga toxin–producing *E. coli*, genetic evaluation of complement regulatory proteins, and kidney biopsy.
Atheroembolic disease	Recent manipulation of the aorta or other large vessels; may occur spontaneously or after anticoagulation; retinal plaques, palpable purpura, livedo reticularis, GI bleed	Hypocomplementemia, eosinophiluria (variable), variable amounts of proteinuria	Skin or kidney biopsy can be diagnostic
Postrenal AKI	History of kidney stones, prostate disease, obstructed bladder catheter, retroperitoneal or pelvic neoplasm	No specific findings other than AKI; may have pyuria or hematuria	Imaging with computed tomography or ultrasound

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor-I; AGBM, antiglomerular basement membrane; AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; ARB, angiotensin receptor blocker; ASO, antistreptolysin O; BUN, blood urea nitrogen; CKD, chronic kidney disease; FeNa, fractional excretion of sodium; GI, gastrointestinal; LDH, lactate dehydrogenase; NSAID, nonsteroidal anti-inflammatory drug; TTP/HUS, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome.

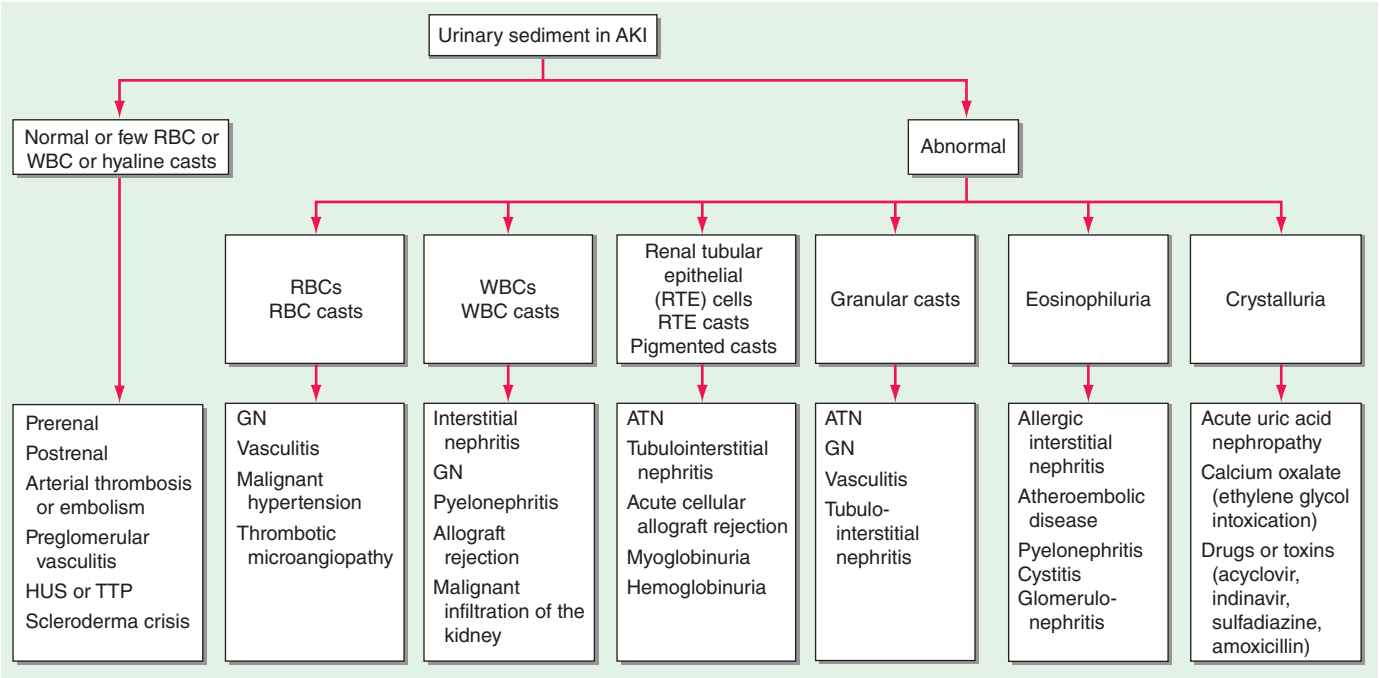

FIGURE 304-6 Interpretation of urinary sediment findings in acute kidney injury (AKI). ATN, acute tubular necrosis; GN, glomerulonephritis; HUS, hemolytic-uremic syndrome; RBCs, red blood cells; RTE, renal tubular epithelial; TTP, thrombotic thrombocytopenic purpura; WBCs, white blood cells. *(Adapted from L Yang, JV Bonventre: Diagnosis and clinical evaluation of acute kidney injury. In Comprehensive Nephrology, 4th ed. J Floege et al [eds]. Philadelphia, Elsevier, 2010.)*

individual with AKI. Not only are medications frequently a nephrotoxic cause of AKI, but doses of administered medications must be adjusted for reductions in kidney function. In this regard, it is important to recognize that reductions in true GFR are not reflected by equations which estimate GFR since those equations are dependent on SCr and the patient being in a steady state. With AKI, SCr will lag behind changes in filtration rate. Idiosyncratic reactions to a wide variety of medications can lead to allergic interstitial nephritis, which may be accompanied by fever, arthralgias, and a pruritic erythematous rash. The absence of systemic features of hypersensitivity, however, does not exclude the diagnosis of interstitial nephritis, and a kidney biopsy should be considered for definitive diagnosis.

AKI accompanied by palpable purpura, pulmonary hemorrhage, or sinusitis raises the possibility of systemic vasculitis with glomerulonephritis. A history of autoimmune disease, such as systemic lupus erythematosus, should lead to consideration of the possibility that the AKI is related to worsening of this underlying disease. Pregnancy should lead to the consideration of preeclampsia as a pathophysiological contributor to the AKI. A tense abdomen should prompt consideration of acute abdominal compartment syndrome, which requires measurement of bladder pressure. Signs of limb ischemia may be clues to the diagnosis of rhabdomyolysis.

URINE FINDINGS

Complete anuria early in the course of AKI is uncommon except in the following situations: complete urinary tract obstruction, renal artery occlusion, overwhelming septic shock, severe ischemia (often with cortical necrosis), or severe proliferative glomerulonephritis or vasculitis. A reduction in urine output (oliguria, defined as <400 mL/24 h) usually denotes more severe AKI (i.e., lower GFR) than when urine output is preserved. Oliguria is associated with worse clinical outcomes in AKI. Preserved urine output can be seen in nephrogenic diabetes insipidus characteristic of long-standing urinary tract obstruction, tubulointerstitial disease, or nephrotoxicity from cisplatin or aminoglycosides, among other causes. Red or brown urine may be seen with or without gross hematuria; if the color persists in the supernatant after centrifugation, then pigment nephropathy from rhabdomyolysis or hemolysis should be suspected.

The urinalysis and urine sediment examination are invaluable tools, but they require clinical correlation because of generally limited sensitivity and specificity **(Fig. 304-6) (Chap. A3)**. In the absence of preexisting proteinuria from CKD, AKI from ischemia or nephrotoxins leads to mild proteinuria (<1 g/d). Greater proteinuria in AKI suggests damage to the glomerular ultrafiltration barrier or excretion of myeloma light chains; the latter are not detected with conventional urine dipsticks (which detect albumin) and require the sulfosalicylic acid test or immunoelectrophoresis. Atheroemboli can cause a variable degree of proteinuria. Extremely heavy proteinuria ("nephrotic range," >3.5 g/d) can occasionally be seen in glomerulonephritis, vasculitis, or toxins/medications that can affect the glomerulus as well as the tubulointerstitium (e.g., NSAIDs). AKI can also complicate cases of minimal change disease, a cause of the nephrotic syndrome **(Chap. 303)**. If the dipstick is positive for hemoglobin but few red blood cells are evident in the urine sediment, then rhabdomyolysis or hemolysis should be suspected.

Prerenal azotemia may present with hyaline casts or an unremarkable urine sediment examination. Postrenal AKI may also lead to an unremarkable sediment, but hematuria and pyuria may be seen depending on the cause of obstruction. AKI from ATN due to ischemic injury, sepsis, or certain nephrotoxins has characteristic urine sediment findings: pigmented "muddy brown" granular casts and tubular epithelial cell casts. These findings may be absent in more than 20% of cases, however. Glomerulonephritis may lead to dysmorphic red blood cells or red blood cell casts. Interstitial nephritis may lead to white blood cell casts. The urine sediment findings overlap somewhat in glomerulonephritis and interstitial nephritis, and a diagnosis is not always possible on the basis of the urine sediment alone. Urine eosinophils have a limited role in differential diagnosis; they can be seen in interstitial nephritis, pyelonephritis, cystitis, atheroembolic disease, or glomerulonephritis. Crystalluria may be important diagnostically. The finding of oxalate crystals in AKI should prompt an evaluation for ethylene glycol toxicity. Abundant uric acid crystals may be seen in the tumor lysis syndrome.

BLOOD LABORATORY FINDINGS

Certain forms of AKI are associated with characteristic patterns in the rise and fall of SCr. Prerenal azotemia typically leads to modest rises in SCr that return to baseline with improvement in hemodynamic status. Contrast nephropathy leads to a rise in SCr within 24–48 h, peak within 3–5 days, and resolution within 5–7 days. In comparison, atheroembolic disease usually manifests with more subacute rises in

SCr, although severe AKI with rapid increases in SCr can occur in this setting. With many of the epithelial cell toxins such as aminoglycoside antibiotics and cisplatin, the rise in SCr is characteristically delayed for 3–5 days to 2 weeks after initial exposure.

A complete blood count may provide diagnostic clues. Anemia is common in AKI and is usually multifactorial in origin. It is not related to an effect of AKI solely on production of red blood cells because this effect in isolation takes longer to manifest. Peripheral eosinophilia can accompany interstitial nephritis, atheroembolic disease, polyarteritis nodosa, and Churg-Strauss vasculitis. Severe anemia in the absence of bleeding may reflect hemolysis, multiple myeloma, or thrombotic microangiopathy (e.g., hemolytic uremic syndrome [HUS] or TTP). Other laboratory findings of thrombotic microangiopathy include thrombocytopenia, schistocytes on peripheral blood smear, elevated lactate dehydrogenase level, and low haptoglobin content. Evaluation of patients suspected of having TTP or HUS includes measurement of levels of the von Willebrand factor cleaving protease (ADAMTS13) and testing for Shiga toxin–producing *Escherichia coli*. "Atypical HUS" constitutes the majority of adult cases of HUS; genetic testing is important because it is estimated that 60–70% of atypical HUS patients have mutations in genes encoding proteins that regulate the alternative complement pathway.

AKI often leads to hyperkalemia, hyperphosphatemia, and hypocalcemia. Marked hyperphosphatemia with accompanying hypocalcemia, however, suggests rhabdomyolysis or the tumor lysis syndrome. Serum creatine kinase and uric acid levels are often elevated in rhabdomyolysis, while tumor lysis syndrome shows normal or marginally elevated creatine kinase and markedly elevated serum uric acid. The anion gap may be increased with any cause of uremia due to retention of anions such as phosphate, hippurate, sulfate, and urate. The co-occurrence of an increased anion gap and an osmolal gap may suggest ethylene glycol poisoning, which may also cause oxalate crystalluria and oxalate deposition in kidney tissue. Low anion gap may provide a clue to the diagnosis of multiple myeloma due to the presence of unmeasured cationic proteins. Laboratory blood tests helpful for the diagnosis of glomerulonephritis and vasculitis include depressed complement levels and high titers of antinuclear antibodies (ANAs), antineutrophil cytoplasmic antibodies (ANCAs), antiglomerular basement membrane (Anti-GBM) antibodies, and cryoglobulins.

RENAL FAILURE INDICES

Several indices have been used to help differentiate prerenal azotemia from intrinsic AKI when the tubules are malfunctioning. The low tubular flow rate and increased renal medullary recycling of urea seen in prerenal azotemia may cause a disproportionate elevation of the BUN compared to creatinine. Other causes of disproportionate BUN elevation need to be kept in mind, however, including upper gastrointestinal bleeding, hyperalimentation, increased tissue catabolism, and glucocorticoid use.

The FeNa is the fraction of the filtered sodium load that is reabsorbed by the tubules, and is a measure of both the kidney's ability to reabsorb sodium as well as endogenously and exogenously administered factors that affect tubular reabsorption. As such, it depends on sodium intake, effective intravascular volume, GFR, diuretic intake, and intact tubular reabsorptive mechanisms. With prerenal azotemia, the FeNa may be <1%, suggesting avid tubular sodium reabsorption. In patients with CKD, a FeNa significantly >1% can be present despite a superimposed prerenal state. The FeNa may also be >1% despite hypovolemia due to treatment with diuretics. Low FeNa is often seen early in glomerulonephritis and other disorders and, hence, should not be taken as prima facie evidence of prerenal azotemia. Low FeNa is therefore suggestive, but not synonymous, with effective intravascular volume depletion, and should not be used as the sole guide for volume management. The response of urine output to crystalloid or colloid fluid administration may be both diagnostic and therapeutic in prerenal azotemia. In ischemic AKI, the FeNa is frequently >1% because of tubular injury and resultant inability to reabsorb sodium. Several causes of ischemia-associated and nephrotoxin-associated AKI can present with FeNa <1%, however, including sepsis (often early in the course), rhabdomyolysis, and contrast nephropathy.

The ability of the kidney to produce a concentrated urine is dependent upon many factors and reliant on good tubular function in multiple regions of the kidney. In the patient not taking diuretics and with good baseline kidney function, urine osmolality may be >500 mOsm/kg in prerenal azotemia, consistent with an intact medullary concentration gradient and elevated serum vasopressin levels causing water reabsorption resulting in concentrated urine. In elderly patients and those with CKD, however, baseline concentrating defects may exist, making urinary osmolality unreliable in many instances. Loss of concentrating ability is common in most forms of AKI that affect the tubules and interstitium, resulting in urine osmolality <350 mOsm/kg, but the finding is not specific.

RADIOLOGIC EVALUATION

Postrenal AKI should always be considered in the differential diagnosis of AKI because treatment is usually successful if instituted early. Simple bladder catheterization can rule out urethral obstruction. Imaging of the urinary tract with renal ultrasound or CT should be undertaken to investigate obstruction in individuals with AKI unless an alternate diagnosis is apparent. Findings of obstruction include dilation of the collecting system and hydroureteronephrosis. Obstruction can be present without radiologic abnormalities in the setting of volume depletion, retroperitoneal fibrosis, encasement with tumor, and also early in the course of obstruction. If a high-clinical index of suspicion for obstruction persists despite normal imaging, antegrade or retrograde pyelography should be performed. Imaging may also provide additional helpful information about kidney size and echogenicity to assist in the distinction between acute versus CKD. In CKD, kidneys are usually smaller unless the patient has diabetic nephropathy, HIV-associated nephropathy, or infiltrative diseases. Normal sized kidneys are expected in AKI. Enlarged kidneys in a patient with AKI suggests the possibility of acute interstitial nephritis or infiltrative diseases. Vascular imaging may be useful if venous or arterial obstruction is suspected, but the risks of contrast administration should be kept in mind. MRI with gadolinium-based contrast agents should be avoided if possible in severe AKI due to the possibility of inducing nephrogenic system fibrosis, a rare but serious complication seen most commonly in patients with end-stage renal disease.

KIDNEY BIOPSY

If the cause of AKI is not apparent based on the clinical context, physical examination, laboratory studies, and radiologic evaluation, kidney biopsy should be considered. The kidney biopsy can provide definitive diagnostic and prognostic information about acute kidney disease and CKD. The procedure is most often used in AKI when prerenal azotemia, postrenal AKI, and ischemic or nephrotoxic AKI have been deemed unlikely, and other possible diagnoses are being considered such as glomerulonephritis, vasculitis, interstitial nephritis, myeloma kidney, HUS and TTP, and allograft dysfunction. Kidney biopsy is associated with a risk of bleeding, which can be severe and organ- or life-threatening in patients with thrombocytopenia or coagulopathy.

NOVEL BIOMARKERS

BUN and creatinine are functional biomarkers of glomerular filtration rather than tissue injury biomarkers and, therefore, may be suboptimal for the diagnosis of actual parenchymal kidney damage. BUN and creatinine are also relatively slow to rise after kidney injury. Several novel biomarkers have been investigated and show promise for earlier and accurate diagnosis of AKI and for predicting AKI prognosis. In cases of oliguric AKI, the urinary flow rate in response to bolus intravenous furosemide 1.0–1.5 mg/kg can be used a prognostic test: urine output of less than 200 mL over 2 h after intravenous furosemide may identify patients at higher risk of progression to more severe AKI, and the need for renal replacement therapy. The severity or risk of progressive AKI may also be reflected in findings on urine microscopy. In one study involving review of fresh urine sediments by board-certified nephrologists, a greater number of renal tubular epithelial cells and/or granular casts in the urine sediment was associated with both the severity and worsening of AKI. Novel protein biomarkers of kidney injury have also

been identified in animal models of AKI and further tested in humans. *Kidney injury molecule-1* (KIM-1) is a type 1 transmembrane protein that is abundantly expressed in proximal tubular cells injured by ischemia or nephrotoxins such as cisplatin. KIM-1 is not expressed in appreciable quantities in the absence of tubular injury or in extrarenal tissues. KIM-1's functional role may be to confer phagocytic properties to tubular cells, enabling them to clear debris from the tubular lumen after kidney injury and also may reduce the inflammatory response to acute injury. KIM-1 can be detected shortly after ischemic or nephrotoxic injury in the urine and, therefore, may be an easily tested biomarker in the clinical setting. *Neutrophil gelatinase associated lipocalin* (NGAL, also known as lipocalin-2 or siderocalin) is another novel biomarker of AKI. NGAL was first discovered as a protein in granules of human neutrophils. NGAL can bind to iron siderophore complexes and may have tissue-protective effects in the proximal tubule. NGAL is highly upregulated after inflammation and kidney injury and can be detected in the plasma and urine within 2 h of cardiopulmonary bypass–associated AKI. In 2014, the U.S. Food and Drug Administration approved the marketing of a test based on the combination of the urinary concentrations of two cell-cycle arrest biomarkers, insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinase-2 (TIMP-2) as predictive biomarkers for higher risk of the development of moderate to severe AKI in critically ill patients. A number of other biomarkers are under investigation for early and accurate identification of AKI and for risk stratification to identify individuals at increased risk. The optimal use of novel AKI biomarkers in clinical settings is an area of ongoing investigation.

COMPLICATIONS OF AKI

The kidney plays a central role in homeostatic control of volume status, blood pressure, plasma electrolyte composition, and acid-base balance, and for excretion of nitrogenous and other waste products. Complications associated with AKI are, therefore, protean, and depend on the severity of AKI and other associated conditions. Mild to moderate AKI may be entirely asymptomatic, particularly early in the course.

UREMIA

Buildup of nitrogenous waste products, manifested as an elevated BUN concentration, is a hallmark of AKI. BUN itself poses little direct toxicity at levels <100 mg/dL. At higher concentrations, mental status changes and bleeding complications can arise. Other toxins normally cleared by the kidney may be responsible for the symptom complex known as uremia. Few of the many possible uremic toxins have been definitively identified. The correlation of BUN and SCr concentrations with uremic symptoms is extremely variable, due in part to differences in urea and creatinine generation rates across individuals.

HYPERVOLEMIA AND HYPOVOLEMIA

Expansion of extracellular fluid volume is a major complication of oliguric and anuric AKI, due to impaired salt and water excretion. The result can be weight gain, dependent edema, increased jugular venous pressure, and pulmonary edema; the latter can be life threatening. Pulmonary edema can also occur from volume overload and hemorrhage in pulmonary renal syndromes. AKI may also induce or exacerbate acute lung injury characterized by increased vascular permeability and inflammatory cell infiltration in lung parenchyma. Recovery from AKI can sometimes be accompanied by polyuria, which, if untreated, can lead to significant volume depletion. The polyuric phase of recovery may be due to an osmotic diuresis from retained urea and other waste products as well as delayed recovery of tubular reabsorptive functions.

HYPONATREMIA

Abnormalities in plasma electrolyte composition can be mild or life threatening. The dysfunctional kidney has limited ability to regulate electrolyte balance. Administration of excessive hypotonic crystalloid or isotonic dextrose solutions can result in hypoosmolality and hyponatremia, which, if severe, can cause neurologic abnormalities, including seizures.

HYPERKALEMIA

An important complication of AKI is hyperkalemia. Marked hyperkalemia is particularly common in rhabdomyolysis, hemolysis, and tumor lysis syndrome due to release of intracellular potassium from damaged cells. Muscle weakness may be a symptom of hyperkalemia. Potassium affects the cellular membrane potential of cardiac and neuromuscular tissues. The more serious complication of hyperkalemia is due to effects on cardiac conduction, leading to potentially fatal arrhythmias.

ACIDOSIS

Metabolic acidosis, usually accompanied by an elevation in the anion gap, is common in AKI, and can further complicate acid-base and potassium balance in individuals with other causes of acidosis, including sepsis, diabetic ketoacidosis, or respiratory acidosis.

HYPERPHOSPHATEMIA AND HYPOCALCEMIA

AKI can lead to hyperphosphatemia, particularly in highly catabolic patients or those with AKI from rhabdomyolysis, hemolysis, and tumor lysis syndrome. Metastatic deposition of calcium phosphate can lead to hypocalcemia. AKI-associated hypocalcemia may also arise from derangements in the vitamin D–parathyroid hormone–fibroblast growth factor-23 axis. Hypocalcemia is often asymptomatic but can lead to perioral paresthesias, muscle cramps, seizures, carpopedal spasms, and prolongation of the QT interval on electrocardiography. Calcium levels should be corrected for the degree of hypoalbuminemia, if present, or ionized calcium levels should be followed. Mild, asymptomatic hypocalcemia does not require treatment.

BLEEDING

Hematologic complications of AKI include anemia and bleeding, both of which are exacerbated by coexisting disease processes such as sepsis, liver disease, and disseminated intravascular coagulation. Direct hematologic effects from AKI-related uremia include decreased erythropoiesis and platelet dysfunction.

INFECTIONS

Infections are a common precipitant of AKI and also a dreaded complication of AKI. Impaired host immunity has been described in end-stage renal disease and may be operative in severe AKI.

CARDIAC COMPLICATIONS

The major cardiac complications of AKI are arrhythmias, pericarditis, and pericardial effusion. In addition, volume overload and uremia may lead to cardiac injury and impaired cardiac function. In animal studies cellular apoptosis and capillary vascular congestion as well as mitochondrial dysfunction have been described in the heart after renal ischemia reperfusion.

MALNUTRITION

AKI is often a severely hypercatabolic state, and therefore, malnutrition is a major complication.

PREVENTION AND TREATMENT OF AKI

The management of individuals with and at risk for AKI varies according to the underlying cause **(Table 304-2)**. Common to all are several principles. Optimization of hemodynamics, correction of fluid and electrolyte imbalances, discontinuation of nephrotoxic medications, and dose adjustment of administered medications are all critical. Common causes of AKI such as sepsis and ischemic ATN do not yet have specific therapies once injury is established, but meticulous clinical attention is needed to support the patient until (if) AKI resolves. The kidney possesses remarkable capacity to repair itself after even severe, dialysis-requiring AKI, when baseline renal function was intact. However, many patients with AKI, particularly when superimposed on preexisting CKD, do not recover fully and may remain dialysis dependent. It has become increasingly apparent that AKI predisposes to accelerated progression of CKD, and CKD is an important risk factor for AKI.

Prerenal Azotemia Prevention and treatment of prerenal azotemia require optimization of renal perfusion. The composition of replacement fluids should be targeted to the type of fluid lost.

TABLE 304-2 Management of Acute Kidney Injury

General Issues

1. Optimization of systemic and renal hemodynamics through volume resuscitation and judicious use of vasopressors
2. Elimination of nephrotoxic agents (e.g., ACE inhibitors, ARBs, NSAIDs, aminoglycosides) if possible
3. Initiation of renal replacement therapy when indicated

Specific Issues

1. Nephrotoxin-specific
   a. Rhabdomyolysis: aggressive intravenous fluids; consider forced alkaline diuresis
   b. Tumor lysis syndrome: aggressive intravenous fluids and allopurinol or rasburicase
2. Volume overload
   a. Salt and water restriction
   b. Diuretics
   c. Ultrafiltration
3. Hyponatremia
   a. Restriction of enteral free water intake, minimization of hypotonic intravenous solutions including those containing dextrose
   b. Hypertonic saline is rarely necessary in AKI. Vasopressin antagonists are generally not needed.
4. Hyperkalemia
   a. Restriction of dietary potassium intake
   b. Discontinuation of potassium-sparing diuretics, ACE inhibitors, ARBs, NSAIDs
   c. Loop diuretics to promote urinary potassium loss
   d. Potassium binding ion-exchange resin (sodium polystyrene sulfonate)
   e. Insulin (10 units regular) and glucose (50 mL of 50% dextrose) to promote entry of potassium intracellularly
   f. Inhaled beta-agonist therapy to promote entry of potassium intracellularly
   g. Calcium gluconate or calcium chloride (1 g) to stabilize the myocardium
5. Metabolic acidosis
   a. Sodium bicarbonate (if pH <7.2 to keep serum bicarbonate >15 mmol/L)
   b. Administration of other bases, e.g., THAM
   c. Renal replacement therapy
6. Hyperphosphatemia
   a. Restriction of dietary phosphate intake
   b. Phosphate binding agents (calcium acetate, sevelamer hydrochloride, aluminum hydroxide—taken with meals)
7. Hypocalcemia
   a. Calcium carbonate or calcium gluconate if symptomatic
8. Hypermagnesemia
   a. Discontinue Mg^{2+} containing antacids
9. Hyperuricemia
   a. Acute treatment is usually not required except in the setting of tumor lysis syndrome (see above)
10. Nutrition
    a. Sufficient protein and calorie intake (20–30 kcal/kg per day) to avoid negative nitrogen balance. Nutrition should be provided via the enteral route if possible.
11. Drug dosing
    a. Careful attention to dosages and frequency of administration of drugs, adjustment for degree of renal failure
    b. Note that serum creatinine concentration may overestimate renal function in the non–steady state characteristic of patients with AKI

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drug; THAM, tris (hydroxymethyl) aminomethane.

Severe acute blood loss should be treated with packed red blood cells. Isotonic crystalloid and/or colloid should be used for less severe acute hemorrhage or plasma loss in the case of burns and pancreatitis. Crystalloid solutions are less expensive and probably equally efficacious as colloid solutions. Hydroxyethyl starch solutions increase the risk of severe AKI and are contraindicated. Crystalloid has been reported to be preferable to albumin in the setting of traumatic brain injury. Isotonic crystalloid (e.g., 0.9% saline) or colloid should be used for volume resuscitation in severe hypovolemia, whereas hypotonic crystalloids (e.g., 0.45% saline) suffice for less severe hypovolemia and can also be used in the setting of hypernatremia. Excessive chloride administration from 0.9% saline may lead to hyperchloremic metabolic acidosis and may impair GFR. Bicarbonate-containing solutions (e.g., dextrose water with 150 mEq sodium bicarbonate) can be used if metabolic acidosis is a concern. Whether buffered crystalloid solutions containing bicarbonate or lactate offer advantages over normal saline for volume repletion in most critically ill patients is not yet established.

Optimization of cardiac function in AKI may require use of inotropic agents, preload- and afterload-reducing agents, antiarrhythmic drugs, and mechanical aids such as ventricular assist devices. Invasive hemodynamic monitoring to guide therapy may be necessary.

Cirrhosis and Hepatorenal Syndrome Fluid management in individuals with cirrhosis, ascites, and AKI is challenging because of the frequent difficulty in ascertaining intravascular volume status. Administration of intravenous fluids as a volume challenge may be required diagnostically as well as therapeutically. Excessive volume administration may, however, result in worsening ascites and pulmonary compromise in the setting of hepatorenal syndrome or AKI due to superimposed spontaneous bacterial peritonitis. Peritonitis should be ruled out by culture of ascitic fluid. Albumin may prevent AKI in those treated with antibiotics for spontaneous bacterial peritonitis. The definitive treatment of the hepatorenal syndrome is orthotopic liver transplantation. Bridge therapies that have shown promise include terlipressin (a vasopressin analog), combination therapy with octreotide (a somatostatin analog) and midodrine (an α_1-adrenergic agonist), and norepinephrine, in combination with intravenous albumin (25–50 g, maximum 100 g/d).

Intrinsic AKI Several agents have been tested and have failed to show benefit in the treatment of acute tubular injury. These include atrial natriuretic peptide, low-dose dopamine, endothelin antagonists, erythropoietin, loop diuretics, calcium channel blockers, α-adrenergic receptor blockers, prostaglandin analogs, antioxidants, antibodies against leukocyte adhesion molecules, and insulin-like growth factor, among many others. Most studies have enrolled patients with severe and well-established AKI, and treatment may have been initiated too late. Novel kidney injury biomarkers may provide an opportunity to test agents earlier in the course of AKI.

AKI due to acute glomerulonephritis or vasculitis may respond to immunosuppressive agents and/or plasmapheresis (Chap. 303). Allergic interstitial nephritis due to medications requires discontinuation of the offending agent. Glucocorticoids have been used, but not tested in randomized trials, in cases where AKI persists or worsens despite discontinuation of the suspected medication. AKI due to scleroderma (scleroderma renal crisis) should be treated with ACE inhibitors. Idiopathic TTP-HUS is a medical emergency and should be treated promptly with plasma exchange. Pharmacologic blockade of complement activation may be effective in atypical HUS.

Early and aggressive volume repletion is mandatory in patients with rhabdomyolysis, who may initially require 10 L of fluid per day. Alkaline fluids (e.g., 75 mmol/L sodium bicarbonate added to 0.45% saline) may be beneficial in preventing tubular injury and cast formation, but carry the risk of worsening hypocalcemia. Diuretics may be used if fluid repletion is adequate but unsuccessful in achieving urinary flow rates of 200–300 mL/h. There is no specific therapy for established AKI in rhabdomyolysis, other than dialysis in severe cases or general supportive care to maintain fluid and electrolyte balance and tissue perfusion. Careful attention must be focused on calcium and phosphate status because of precipitation in damaged tissue and release when the tissue heals.

Postrenal AKI Prompt recognition and relief of urinary tract obstruction can forestall the development of permanent structural damage induced by urinary stasis. The site of obstruction defines

the treatment approach. Transurethral or suprapubic bladder catheterization may be all that is needed initially for urethral strictures or functional bladder impairment. Ureteric obstruction may be treated by percutaneous nephrostomy tube placement or ureteral stent placement. Relief of obstruction is usually followed by an appropriate diuresis for several days. In rare cases, severe polyuria persists due to tubular dysfunction and may require continued administration of intravenous fluids and electrolytes for a period of time.

SUPPORTIVE MEASURES FOR AKI

Volume Management Hypervolemia in oliguric or anuric AKI may be life threatening due to acute pulmonary edema, especially because many patients have coexisting pulmonary disease, and AKI likely increases pulmonary vascular permeability. Fluid and sodium should be restricted, and diuretics may be used to increase the urinary flow rate. There is no evidence that increasing urine output itself improves the natural history of AKI, but diuretics may help to avoid the need for dialysis in some cases. In severe cases of volume overload, furosemide may be given as a bolus (200 mg) followed by an intravenous drip (10–40 mg/h), with or without a thiazide diuretic. In decompensated heart failure, stepped diuretic therapy was found to be superior to ultrafiltration in preserving renal function. Diuretic therapy should be stopped if there is no response. Dopamine in low doses may transiently increase salt and water excretion by the kidney in prerenal states, but clinical trials have failed to show any benefit in patients with intrinsic AKI. Because of the risk of arrhythmias and potential bowel ischemia, the risks of dopamine outweigh the benefits if used specifically for the treatment or prevention of AKI.

Electrolyte and Acid-Base Abnormalities The treatment of dysnatremias and hyperkalemia is described in Chap. 49. Metabolic acidosis is generally not treated unless severe (pH <7.20 and serum bicarbonate <15 mmol/L). Acidosis can be treated with oral or intravenous sodium bicarbonate (Chap. 51), but overcorrection should be avoided because of the possibility of metabolic alkalosis, hypocalcemia, hypokalemia, and volume overload. Hyperphosphatemia is common in AKI and can usually be treated by limiting intestinal absorption of phosphate using phosphate binders (calcium carbonate, calcium acetate, lanthanum, sevelamer, or aluminum hydroxide). Hypocalcemia does not usually require therapy unless symptoms are present. Ionized calcium should be monitored rather than total calcium when hypoalbuminemia is present.

Malnutrition Protein energy wasting is common in AKI, particularly in the setting of multisystem organ failure. Inadequate nutrition may lead to starvation ketoacidosis and protein catabolism. Excessive nutrition may increase the generation of nitrogenous waste and lead to worsening azotemia. Total parenteral nutrition requires large volumes of fluid administration and may complicate efforts at volume control. According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, patients with AKI should achieve a total energy intake of 20–30 kcal/kg per day. Protein intake should vary depending on the severity of AKI: 0.8–1.0 g/kg per day in noncatabolic AKI without the need for dialysis; 1.0–1.5 g/kg per day in patients on dialysis; and up to a maximum of 1.7 g/kg per day if hypercatabolic and receiving continuous renal replacement therapy. Trace elements and water-soluble vitamins should also be supplemented in AKI patients treated with dialysis and continuous renal replacement therapy.

Anemia The anemia seen in AKI is usually multifactorial and is not improved by erythropoiesis-stimulating agents, due to their delayed onset of action and the presence of bone marrow resistance in critically ill patients. Uremic bleeding may respond to desmopressin or estrogens, but may require dialysis for treatment in the case of long-standing or severe uremia. Gastrointestinal prophylaxis with proton pump inhibitors or histamine (H_2) receptor blockers is required. It is important to recognize, however, that protein pump inhibitors have been associated with AKI from interstitial nephritis, a relationship that is increasingly being recognized. Venous thromboembolism prophylaxis is important and should be tailored to the clinical setting; low-molecular-weight heparins and factor Xa inhibitors have unpredictable pharmacokinetics in severe AKI and should be avoided.

Dialysis Indications and Modalities (See also Chap. 306) Dialysis is indicated when medical management fails to control volume overload, hyperkalemia, or acidosis; in some toxic ingestions; and when there are severe complications of uremia (asterixis, pericardial rub or effusion, encephalopathy, uremic bleeding). The timing of dialysis is still a matter of debate. Late initiation of dialysis carries the risk of avoidable volume, electrolyte, and metabolic complications of AKI. On the other hand, initiating dialysis too early may unnecessarily expose individuals to intravenous lines and invasive procedures, with the attendant risks of infection, bleeding, procedural complications, and hypotension. The initiation of dialysis should not await the development of a life-threatening complication of renal failure. Many nephrologists initiate dialysis for AKI empirically when the BUN exceeds a certain value (e.g., 100 mg/dL) in patients without clinical signs of recovery of kidney function. The available modes for renal replacement therapy in AKI require either access to the peritoneal cavity (for peritoneal dialysis) or the large blood vessels (for hemodialysis, hemofiltration, and other hybrid procedures). Small solutes are removed across a semipermeable membrane down their concentration gradient ("diffusive" clearance) and/or along with the movement of plasma water ("convective" clearance). The choice of modality is often dictated by the immediate availability of technology and the expertise of medical staff.

Hemodialysis can be used intermittently or continuously and can be done through convective clearance, diffusive clearance, or a combination of the two. Vascular access is through the femoral, internal jugular, or subclavian veins. Hemodialysis is an intermittent procedure that removes solutes through diffusive and convective clearance. Hemodialysis is typically performed 3–4 h per day, three to four times per week, and is the most common form of renal replacement therapy for AKI. One of the major complications of hemodialysis is hypotension, particularly in the critically ill, which can perpetuate AKI by causing ischemic injury to the recovering organ.

Continuous intravascular procedures were developed in the early 1980s to treat hemodynamically unstable patients without inducing the rapid shifts of volume, osmolarity, and electrolytes characteristic of intermittent hemodialysis. Continuous renal replacement therapy (CRRT) can be performed by convective clearance (continuous venovenous hemofiltration [CVVH]), in which large volumes of plasma water (and accompanying solutes) are forced across the semipermeable membrane by means of hydrostatic pressure; the plasma water is then replaced by a physiologic crystalloid solution. CRRT can also be performed by diffusive clearance (continuous venovenous hemodialysis [CVVHD]), a technology similar to hemodialysis except at lower blood flow and dialysate flow rates. A hybrid therapy combines both diffusive and convective clearance (continuous venovenous hemodiafiltration [CVVHDF]). To achieve some of the advantages of CRRT without the need for 24-h staffing of the procedure, some physicians favor slow low-efficiency dialysis (SLED) or extended daily dialysis (EDD). In this therapy, blood flow and dialysate flow are higher than in CVVHD, but the treatment time is reduced to ≤12 h.

The optimal dose of dialysis for AKI is not clear. Daily intermittent hemodialysis and high-dose CRRT do not confer a demonstrable survival or renal recovery advantage, but care should be taken to avoid undertreatment. Studies have failed to show that continuous therapies are superior to intermittent therapies. If available, CRRT is often preferred in patients with severe hemodynamic instability, cerebral edema, or significant volume overload.

Peritoneal dialysis can be performed through a temporary intraperitoneal catheter, although it is rarely used in the United States for AKI in adults. Peritoneal dialysis has enjoyed widespread use internationally, particularly when hemodialysis technology is not as readily available. Dialysate solution is instilled into and removed from the peritoneal cavity at regular intervals in order to achieve diffusive and convective clearance of solutes across the peritoneal membrane; ultrafiltration of

water is achieved by the presence of an osmotic gradient across the peritoneal membrane achieved by high concentrations of dextrose in the dialysate solution. Because of its continuous nature, it is often better tolerated than intermittent procedures like hemodialysis in hypotensive patients. Peritoneal dialysis may not be sufficient for hypercatabolic patients due to inherent limitations in dialysis efficacy.

OUTCOME AND PROGNOSIS

The development of AKI is associated with a significantly increased risk of in-hospital and long-term mortality, longer length of stay, and increased costs. Prerenal azotemia, with the exception of the cardiorenal and hepatorenal syndromes, and postrenal azotemia carry a better prognosis than most cases of intrinsic AKI. The kidneys may recover even after severe, dialysis-requiring AKI. Survivors of an episode of AKI requiring temporary dialysis, however, are at extremely high risk for progressive CKD, and up to 10% may develop end-stage renal disease. Postdischarge care under the supervision of a nephrologist for aggressive secondary prevention of kidney disease is prudent. Patients with AKI are more likely to die prematurely after they leave the hospital even if their kidney function has recovered.

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305 Chronic Kidney Disease

Joanne M. Bargman, Karl L. Skorecki

Chronic kidney disease (CKD) encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). The risk of CKD progression is closely linked to both the GFR and the amount of albuminuria. **Figure 305-1** provides a staging of CKD stratified by the estimates of both of these parameters.

The dispiriting term *end-stage renal disease* represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation. These interventions are discussed in **Chaps. 306 and 307**. *End-stage renal disease* will be supplanted in this chapter by the term *stage 5 CKD*.

PATHOPHYSIOLOGY OF CKD

The pathophysiology of CKD involves two broad sets of mechanisms of damage: (1) initiating mechanisms specific to the underlying etiology (e.g., abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and (2) hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology and lead to further decline in kidney function (**Chap. 333e** from the 19th edition of *Harrison's*). The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short-term adaptations of hyperfiltration and hypertrophy to maintain GFR become maladaptive as the increased pressure and flow within the nephron predisposes to distortion of glomerular architecture, abnormal podocyte function, and disruption of the filtration barrier leading to sclerosis and dropout of the remaining nephrons **(Fig. 305-2)**. Increased intrarenal activity of the renin-angiotensin system (RAS) appears to contribute both to the initial compensatory hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis. This process explains why a reduction in renal mass from an isolated insult may lead to a progressive decline in renal function over many years **(Fig. 305-3)**.

IDENTIFICATION OF RISK FACTORS AND STAGING OF CKD

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR. Risk factors include small for gestation birth weight, childhood obesity, hypertension, diabetes mellitus, autoimmune disease, advanced age, African ancestry, a family history of kidney disease, a previous episode of acute kidney injury, and the presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract. It has been increasingly recognized that one or more episodes of acute kidney injury are associated with an increased risk of developing CKD.

Many rare inherited forms of CKD follow a Mendelian inheritance pattern, often as part of a systemic syndrome, with the most common in this category being autosomal dominant polycystic kidney disease. In addition, recent research in the genetics of predisposition to common complex diseases **(Chap. 456)** has revealed DNA sequence variants at a number of genetic loci that are associated with common forms of CKD. A striking example is the finding of allelic versions of the *APOL1* gene, of West African population ancestry, which contributes to the several-fold higher frequency of certain common etiologies of nondiabetic CKD (e.g., focal segmental glomerulosclerosis) observed among African and Hispanic Americans, in major regions of continental Africa and the global African diaspora. The prevalence in West African populations seems to have arisen as an evolutionary adaptation conferring protection from tropical pathogens. As in other common diseases with a heritable component, environmental triggers (such as a viral pathogen) transform genetic risk into disease.

To stage CKD, it is necessary to estimate the GFR rather than relying on serum creatinine concentration **(Table 305-1)**. Many laboratories now report an estimated GFR, or eGFR, using one of these equations. These equations are valid only if the patient is in steady state, that is, the serum creatinine is neither rising nor falling over days.

The normal annual mean decline in GFR with age from the peak GFR (~120 mL/min per 1.73 m^2) attained during the third decade of life is ~1 mL/min per year per 1.73 m^2, reaching a mean value of 70 mL/min per 1.73 m^2 at age 70, with considerable inter-individual variability. Although reduced GFR is expected with aging, the lower GFR signifies a true loss of kidney function with attendant consequences in terms of risk of CKD complications, and requirement for dose adjustment of medications. The mean GFR is lower in women than in men. For example, a woman in her eighties with a laboratory report of serum creatinine in the normal range may have a GFR of <50 mL/min per 1.73 m^2. Relatedly, even a mild elevation in serum creatinine concentration often signifies a substantial reduction in GFR in older individuals.

Measurement of albuminuria is also helpful for monitoring nephron injury and the response to therapy in many forms of CKD, especially chronic glomerular diseases. The cumbersome 24-h urine collection has been replaced by measurement of urinary albumin to creatinine ratio (UACR) in one and preferably several spot first-morning urine samples as a measure pointing to glomerular injury. Even in patients with negative conventional dipstick tests for elevated total protein excretion, UACR above 17 mg albumin/g creatinine in men and 25 mg albumin/g creatinine in women serves as a marker not only for early detection of primary kidney disease, but for systemic microvas-cular disease as well. The presence of albuminuria in general serves as a well-studied screening marker for the presence of systemic microvas-cular disease and endothelial dysfunction.

A Kidney Failure Risk (KFR) equation has been devised to predict the risk of progression to stage 5 dialysis-dependent kidney disease. The equation is available on many sites online (for example,

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

FIGURE 305-1 Kidney Disease Improving Global Outcome (KDIGO) classification of chronic kidney disease (CKD). Gradation of color from green to red corresponds to increasing risk and progression of CKD. GFR, glomerular filtration rate. *(Reproduced with permission from Kidney Int Suppl 3:5–14, 2013.)*

www.kidneyfailurerisk.com) and uses age, sex, region (North American or non-North American), GFR and the urine albumin/creatinine. It has been validated in several cohorts around the world, although the risk for progression appears to be greater in North America, accounting for the regional adjustment in the equation.

Stages 1 and 2 CKD are usually asymptomatic, such that the recognition of CKD occurs more often as a result of laboratory testing in clinical settings other than suspicion of kidney disease. Moreover, in the absence of the risk factors noted above, population-wide screening is not recommended. With progression to CKD stages 3 and 4, clinical and laboratory complications become more prominent. Virtually all organ systems are affected, but the most evident complications include anemia and associated easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23); and abnormalities in sodium, potassium, water, and acid-base homeostasis. Many patients, especially the elderly, will have eGFR values compatible with stage 2 or 3 CKD. However, the majority of these patients will show no further deterioration of renal function. The primary care physician is advised to recheck kidney function, and if it is stable and not associated with proteinuria, the patient can usually be

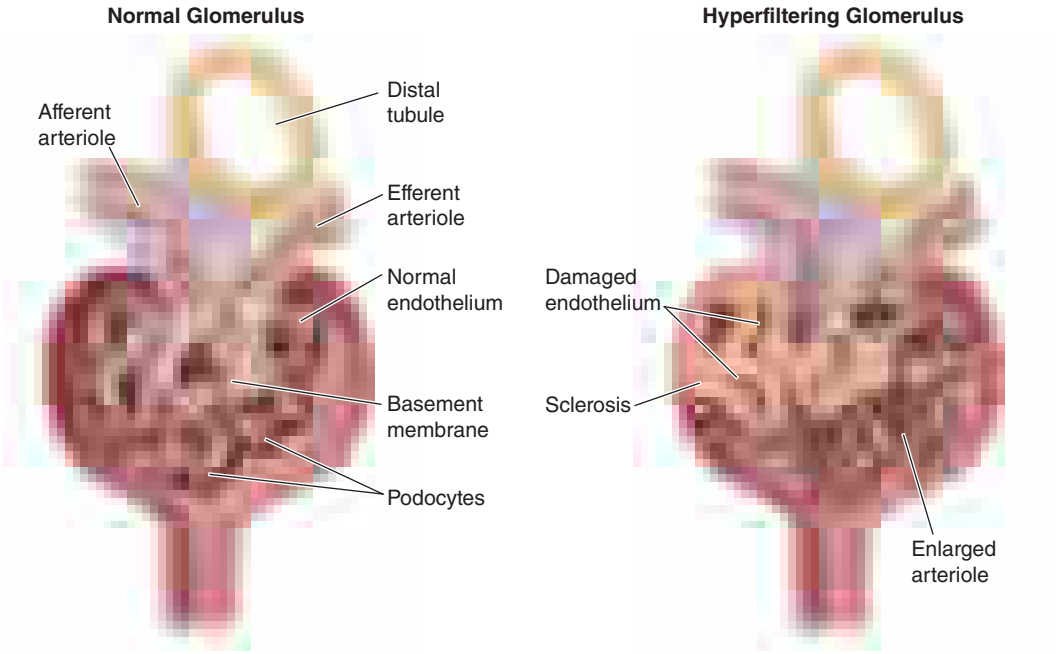

FIGURE 305-2 ***Left:*** Schema of the normal glomerular architecture. ***Right:*** Secondary glomerular changes associated with a reduction in nephron number, including enlargement of capillary lumens and focal adhesions, which are thought to occur consequent to compensatory hyperfiltration and hypertrophy in the remaining nephrons. *(Modified from JR Ingelfinger: N Engl J Med 348:99, 2003.)*

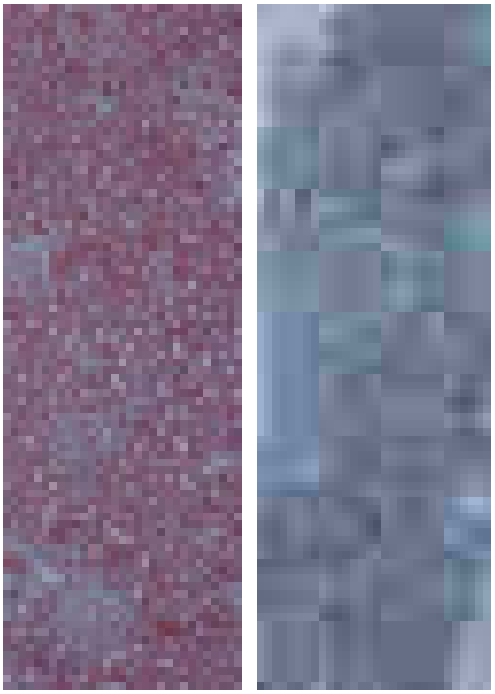

FIGURE 305-3 ***Left:*** Low-power photomicrograph of a normal kidney showing normal glomeruli and healthy tubulointerstitium without fibrosis. ***Right:*** Low-power photomicrograph of chronic kidney disease with sclerosis of many glomeruli and severe tubulointerstitial fibrosis (Masson trichrome, 40× magnification). *(Slides courtesy of the late Dr. Andrew Herzenberg.)*

followed with interval repeat testing without referral to nephrologist. However, caution should be exercised in terms of potential exposure to nephrotoxins or interventions that risk acute kidney injury (AKI) and also with respect to medication dose adjustment. If repeat testing shows declining GFR, albuminuria, or uncontrolled hypertension, referral to a nephrologist is appropriate. If the patient progresses to stage 5 CKD, toxins accumulate such that patients usually experience a marked disturbance in their activities of daily living, well-being, nutritional status, and water and electrolyte homeostasis, eventuating in the *uremic syndrome*.

ETIOLOGY AND EPIDEMIOLOGY

It has been estimated from population data that at least 6% of the adult population in the United States has CKD at stages 1 and 2. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. **Table 305-2** lists the five most frequent categories of causes of CKD, cumulatively accounting for >90% of the CKD disease burden worldwide. The relative contribution of each category varies among different geographic regions. The most frequent cause of CKD in North America and Europe is diabetic nephropathy, most often secondary to type 2 diabetes mellitus. Patients with newly diagnosed

TABLE 305-1 Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (S_{CR}), Age, Sex, Race, and Body Weight

1. Equation from the Modification of Diet in Renal Disease Study
Estimated GFR (mL/min per 1.73 m^2) = $1.86 \times (S_{Cr})^{-1.154} \times (age)^{-0.203}$
Multiply by 0.742 for women
Multiply by 1.21 for African ancestry
2. CKD-EPI Equation
$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$
Multiply by 1.018 for women
Multiply by 1.159 for African ancestry
where S_{Cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

TABLE 305-2 Leading Categories of Etiologies of CKD[a]

- Diabetic nephropathy
- Glomerulonephritis
- Hypertension-associated CKD (includes vascular and ischemic kidney disease and primary glomerular disease with associated hypertension)
- Autosomal dominant polycystic kidney disease
- Other cystic and tubulointerstitial nephropathy

[a]Relative contribution of each category varies with geographic region and race.

CKD often have hypertension. When no overt evidence for a primary glomerular or tubulointerstitial kidney disease process is present, CKD is frequently attributed to hypertension. However, it is now appreciated that such individuals can be considered in two categories. The first includes patients with a subclinical primary glomerulopathy, such as focal segmental or global glomerulosclerosis **(Chap. 308)**. The second includes patients in whom progressive nephrosclerosis and hypertension is the renal correlate of a systemic vascular disease, often also involving large- and small-vessel cardiac and cerebral pathology. This latter combination is especially common in the elderly, in whom chronic renal ischemia as a cause of CKD may be underdiagnosed. The increasing incidence of CKD in the elderly has been ascribed, in part, to decreased mortality rate from the cardiac and cerebral complications of atherosclerotic vascular disease, enabling a greater segment of the population to progress to more advanced stages of CKD. Nevertheless, it should be appreciated that the majority of patients with early stages of CKD succumb to cardiovascular and cerebrovascular complications before they progress to the more advanced stages of CKD. Indeed, even a minor decrement in GFR or the presence of albuminuria is now recognized as a major risk factor for cardiovascular disease.

PATHOPHYSIOLOGY AND BIOCHEMISTRY OF UREMIA

Although serum urea and creatinine concentrations are used to measure the excretory capacity of the kidneys, accumulation of these two molecules themselves does not account for the many symptoms and signs that characterize the uremic syndrome in advanced renal failure. Large numbers of toxins that accumulate when GFR declines have been implicated in the uremic syndrome. These include water-soluble, hydrophobic, protein-bound, charged, and uncharged nitrogen-containing non-volatile products of metabolism. It is thus evident that the serum concentrations of urea and creatinine should be viewed as being readily measured, but very incomplete surrogate markers for retained toxins, and monitoring the levels of urea and creatinine in the patient with impaired kidney function represents a vast oversimplification of the uremic state.

The uremic syndrome involves more than renal excretory failure. A host of metabolic and endocrine functions normally performed by the kidneys is also impaired, and this results in anemia, malnutrition, and abnormal metabolism of carbohydrates, fats, and proteins. Furthermore, plasma levels of many hormones, including PTH, FGF-23, insulin, glucagon, steroid hormones including vitamin D and sex hormones, and prolactin change with CKD as a result of reduced excretion, decreased degradation, or abnormal regulation. Finally, CKD is associated with increased systemic inflammation. Elevated levels of C-reactive protein are detected along with other acute-phase reactants, whereas levels of so-called negative acute-phase reactants, such as albumin and fetuin, decline. Thus, the inflammation associated with CKD is important in the *malnutrition-inflammation-atherosclerosis/calcification syndrome*, which contributes in turn to the acceleration of vascular disease and comorbidity associated with advanced kidney disease.

In summary, the pathophysiology of the uremic syndrome can be divided into manifestations in three spheres of dysfunction: (1) those consequent to the accumulation of toxins that normally undergo renal excretion; (2) those consequent to the loss of other kidney functions, such as fluid and electrolyte homeostasis and hormone regulation; and (3) progressive systemic inflammation and its vascular and nutritional consequences.

CLINICAL AND LABORATORY MANIFESTATIONS OF CKD AND UREMIA

Uremia leads to disturbances in the function of virtually every organ system. Chronic dialysis can reduce the incidence and severity of many of these disturbances, so that the florid manifestations of uremia have largely disappeared in the modern health setting. However, even optimal dialysis therapy is not completely effective as renal replacement therapy, because some disturbances resulting from impaired kidney function fail to respond to dialysis.

FLUID, ELECTROLYTE, AND ACID-BASE DISORDERS

Sodium and Water Homeostasis With normal renal function, tubular excretion of filtered sodium and water matches intake. Many forms of kidney disease (e.g., glomerulonephritis) disrupt this balance such that dietary intake of sodium exceeds its urinary excretion, leading to sodium retention and attendant extracellular fluid volume (ECFV) expansion. This expansion may contribute to hypertension, which itself can accelerate nephron injury. As long as water intake does not exceed the capacity for renal water clearance, the ECFV expansion will be isotonic and the patient will have a normal plasma sodium concentration. Hyponatremia is not commonly seen in CKD patients but, when present, often responds to water restriction. The patient with ECFV expansion (peripheral edema, sometimes hypertension poorly responsive to therapy) should be counseled regarding salt restriction. Thiazide diuretics have limited utility in stages 3–5 CKD, such that administration of loop diuretics, including furosemide, bumetanide, or torsemide, may also be needed. Resistance to loop diuretics in CKD often mandates use of higher doses than those used in patients with higher GFR. The combination of loop diuretics with metolazone may be helpful. Diuretic resistance with intractable edema and hypertension in advanced CKD may serve as an indication to initiate dialysis.

In addition to problems with salt and water excretion, some patients with CKD may instead have impaired renal conservation of sodium and water. When an extrarenal cause for fluid loss, such as gastrointestinal (GI) loss, is present, these patients may be prone to ECFV depletion because of the inability of the failing kidney to reclaim filtered sodium adequately. Furthermore, depletion of ECFV, whether due to GI losses or overzealous diuretic therapy, can further compromise kidney function through underperfusion, or a "prerenal" state, leading to acute-on-chronic kidney failure. In this setting, holding or adjusting the diuretic dose or even cautious volume repletion with normal saline may return the ECFV to normal and restore renal function to baseline.

Potassium Homeostasis In CKD, the decline in GFR is not necessarily accompanied by a parallel decline in urinary potassium excretion, which is predominantly mediated by aldosterone-dependent secretion in the distal nephron. Another defense against potassium retention in these patients is augmented potassium excretion in the GI tract. Notwithstanding these two homeostatic responses, hyperkalemia may be precipitated in certain settings. These include increased dietary potassium intake, hemolysis, hemorrhage, transfusion of stored red blood cells, and metabolic acidosis. Importantly, a host of medications can inhibit renal potassium excretion and lead to hyperkalemia. The most important medications in this respect include the RAS inhibitors and spironolactone and other potassium-sparing diuretics such as amiloride, eplerenone, and triamterene. The benefits of the RAS inhibitors in ameliorating the progression of CKD and its complications often favor their cautious and judicious use with very close monitoring of plasma potassium concentration.

Certain causes of CKD can be associated with earlier and more severe disruption of potassium-secretory mechanisms in the distal nephron, out of proportion to the decline in GFR. These include conditions associated with hyporeninemic hypoaldosteronism, such as diabetes, and renal diseases that preferentially affect the distal nephron, such as obstructive uropathy and sickle cell nephropathy.

Hypokalemia is not common in CKD and usually reflects markedly reduced dietary potassium intake, especially in association with excessive diuretic therapy or concurrent GI losses. The use of potassium supplements and potassium-sparing diuretics may be risky in patients with impaired renal function, and needs to be monitored closely.

Metabolic Acidosis Metabolic acidosis is a common disturbance in advanced CKD. The majority of patients can still acidify the urine, but they produce less ammonia and, therefore cannot excrete the normal quantity of protons. Hyperkalemia, if present, further depresses ammonia production. The combination of hyperkalemia and hyperchloremic metabolic acidosis is often present, even at earlier stages of CKD (stages 1–3), in patients with diabetic nephropathy or in those with predominant tubulointerstitial disease or obstructive uropathy.

With worsening renal function, the total urinary net daily acid excretion is usually limited to 30–40 mmol, and the anions of retained organic acids can then lead to an anion-gap metabolic acidosis. Thus, the non-anion-gap metabolic acidosis seen in earlier stages of CKD may be complicated by the addition of an anion-gap metabolic acidosis as CKD progresses. In most patients, the metabolic acidosis is mild; the pH is rarely <7.32 and can usually be corrected with oral sodium bicarbonate supplementation. Animal and human studies have suggested that even modest degrees of metabolic acidosis may be associated with the development of protein catabolism. Alkali supplementation may, in addition, attenuate the catabolic state and possibly slow CKD progression and is recommended when the serum bicarbonate concentration falls below 20–23 mmol/L. The concomitant sodium load mandates careful attention to volume status and the need for diuretic agents.

TREATMENT

Fluid, Electrolyte, and Acid-Base Disorders

Dietary salt restriction and the use of loop diuretics, occasionally in combination with metolazone, may be needed to maintain euvolemia. Water restriction is indicated only if there is a problem with hyponatremia.

Hyperkalemia often responds to dietary restriction of potassium, the use of kaliuretic diuretics, and avoidance of both potassium supplements (including occult sources, such as dietary salt substitutes) and dose reduction or avoidance of potassium-retaining medications (especially angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]). Kaliuretic diuretics promote urinary potassium excretion, whereas potassium-binding resins, such as calcium resonium, sodium polystyrene or patiromer can promote potassium loss through the GI tract and may reduce the incidence of hyperkalemia. Intractable hyperkalemia is an indication (although uncommon) to consider institution of dialysis in a CKD patient. The renal tubular acidosis and subsequent anion-gap metabolic acidosis in progressive CKD will respond to alkali supplementation, typically with sodium bicarbonate. Recent studies suggest that this replacement should be considered when the serum bicarbonate concentration falls below 20–23 mmol/L to avoid the protein catabolic state seen with even mild degrees of metabolic acidosis and to slow the progression of CKD.

DISORDERS OF CALCIUM AND PHOSPHATE METABOLISM

The principal complications of abnormalities of calcium and phosphate metabolism in CKD occur in the skeleton and the vascular bed, with occasional severe involvement of soft tissues. It is likely that disorders of bone turnover and disorders of vascular and soft tissue calcification are related to each other (Fig. 305-3).

Bone Manifestations of CKD The major disorders of bone disease can be classified into those associated with high bone turnover with increased PTH levels (including *osteitis fibrosa cystica*, the classic lesion of secondary hyperparathyroidism), osteomalacia due to reduced action of the active forms of vitamin D, and low bone turnover with low or normal PTH levels (adynamic bone disease) or most often combinations of the foregoing.

The pathophysiology of secondary hyperparathyroidism and the consequent high-turnover bone disease is related to abnormal mineral

metabolism through the following events: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of both FGF-23 by osteocytes and PTH and stimulates growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, resulting from suppression of calcitriol production by FGF-23 and by the failing kidney, as well as phosphate retention, also stimulate PTH production. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. These changes start to occur when the GFR falls below 60 mL/min.

FGF-23 is part of a family of phosphatonins that promotes renal phosphate excretion. Recent studies have shown that levels of this hormone, secreted by osteocytes, increase early in the course of CKD, even before phosphate retention and hyperphosphatemia. FGF-23 may defend normal serum phosphorus in at least three ways: (1) increased renal phosphate excretion; (2) stimulation of PTH, which also increases renal phosphate excretion; and (3) suppression of the formation of $1,25(OH)_2D_3$, leading to diminished phosphorus absorption from the GI tract. Interestingly, high levels of FGF-23 are also an independent risk factor for left ventricular hypertrophy and mortality in CKD, dialysis, and kidney transplant patients. Moreover, elevated levels of FGF-23 may indicate the need for therapeutic intervention (e.g., phosphate restriction), even when serum phosphate levels are within the normal range.

Hyperparathyroidism stimulates bone turnover and leads to *osteitis fibrosa cystica*. Bone histology shows abnormal osteoid, bone and bone marrow fibrosis, and in advanced stages, the formation of bone cysts, sometimes with hemorrhagic elements so that they appear brown in color, hence the term *brown tumor*. Clinical manifestations of severe hyperparathyroidism include bone pain and fragility, brown tumors, compression syndromes, and erythropoietin (EPO) resistance in part related to the bone marrow fibrosis. Furthermore, PTH itself is considered a uremic toxin, and high levels are associated with muscle weakness, fibrosis of cardiac muscle, and nonspecific constitutional symptoms.

Adynamic bone disease is increasing in prevalence, especially among diabetics and the elderly. It is characterized by reduced bone volume and mineralization and may result from excessive suppression of PTH production, chronic inflammation, or both. Suppression of PTH can result from the use of vitamin D preparations or from excessive calcium exposure in the form of calcium-containing phosphate binders or high-calcium dialysis solutions. Complications of adynamic bone disease include an increased incidence of fracture and bone pain and an association with increased vascular and cardiac calcification. Occasionally the calcium will precipitate in the soft tissues into large concretions termed "tumoral calcinosis" **(Fig. 305-4)**. Patients with adynamic bone disease often experience the most severe symptoms of musculoskeletal pain, owing to the inability to repair the microfractures that occur properly as a part of healthy skeletal homeostasis with regular physical activity. Osteomalacia is a distinct process, consequent to reduced production and action of $1,25(OH)_2D_3$, leading to non-mineralized osteoid.

Tumoral Calcinosis in a Dialysis Patient

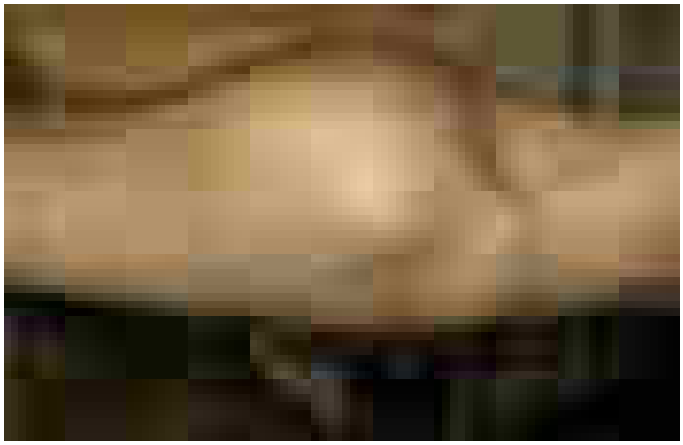

FIGURE 305-4 Tumoral calcinosis. This patient was on hemodialysis for many years and was nonadherent to dietary phosphorus restriction or the use of phosphate binders. He was chronically severely hyperphosphatemic. He developed an enlarging painful mass on his arm that was extensively calcified.

Calcium, Phosphorus, and the Cardiovascular System

Recent epidemiologic evidence has shown a strong association between hyperphosphatemia and increased cardiovascular mortality in patients with stage 5 and earlier stages of CKD. Hyperphosphatemia and hypercalcemia are associated with increased vascular calcification, but it is unclear whether the excessive mortality is mediated by this mechanism. Studies using computed tomography (CT) and electron-beam CT scanning show that CKD patients have calcification of the media in coronary arteries and even heart valves that appear to be orders of magnitude greater than that in patients without renal disease. The magnitude of the calcification is proportional to age and hyperphosphatemia and is also associated with low PTH levels and low bone turnover. It is possible that in CKD patients ingested calcium cannot be incorporated into bones with low turnover and, therefore, is deposited at extraosseous sites, such as the vascular bed and soft tissues. It is interesting in this regard that there is also an association between osteoporosis and vascular calcification in the general population. Finally, hyperphosphatemia can induce a change in gene expression in vascular cells to an osteoblast-like profile, leading to vascular calcification and even ossification.

Other Complications of Abnormal Mineral Metabolism

Calciphylaxis is a devastating condition seen almost exclusively in patients with advanced CKD. It is heralded by livedo reticularis and advances to patches of ischemic necrosis, especially on the legs, thighs, abdomen, and breasts **(Fig. 305-5)**. Pathologically, there is evidence of vascular occlusion in association with extensive vascular and soft tissue calcification. It appears that this condition is increasing in incidence. Originally it was ascribed to severe abnormalities in calcium and phosphorus control in dialysis patients, usually associated with advanced hyperparathyroidism. However, more recently, calciphylaxis has been seen with increasing frequency in the absence of severe hyperparathyroidism. Other etiologies have been suggested, including the increased use of oral calcium as a phosphate binder. Warfarin is commonly used in hemodialysis patients in whom most direct oral anticoagulants (DOACs) are contraindicated, and one of the effects of warfarin therapy is to decrease the vitamin K–dependent regeneration of matrix GLA protein. This latter protein is important in preventing vascular

Calciphylaxis

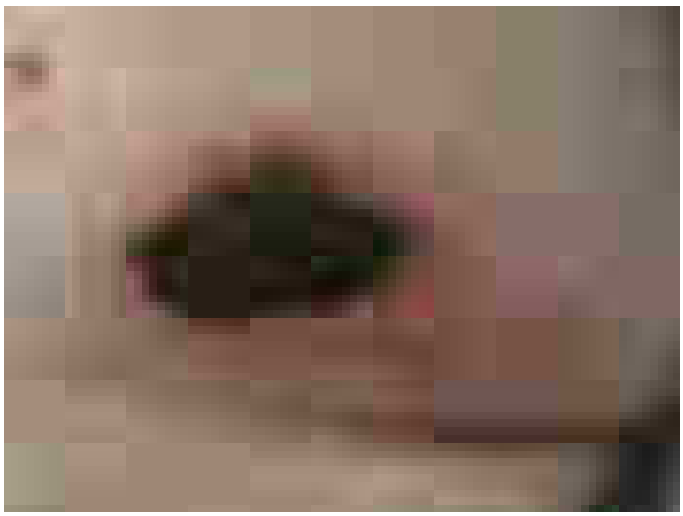

FIGURE 305-5 Calciphylaxis. This peritoneal dialysis patient was on chronic warfarin therapy for atrial fibrillation. She noticed a small painful nodule on the abdomen that was followed by progressive skin necrosis and ulceration of the anterior abdominal wall. She was treated with hyperbaric oxygen, intravenous thiosulfate, and discontinuation of warfarin, with slow resolution of the ulceration.

calcification. Thus, warfarin treatment is considered a risk factor for calciphylaxis, and if a patient develops this syndrome, this medication should be discontinued and replaced with another anticoagulant.

TREATMENT

Disorders of Calcium and Phosphate Metabolism

The optimal management of secondary hyperparathyroidism and *osteitis fibrosa* is prevention. Once the parathyroid gland mass is very large, it is difficult to control the disease. Careful attention should be paid to the plasma phosphate concentration in CKD patients, who should be counseled on a low-phosphate diet as well as the appropriate use of phosphate-binding agents. These are agents that are taken with meals and complex the dietary phosphate to limit its GI absorption. Examples of phosphate binders are calcium acetate and calcium carbonate. A major side effect of calcium-based phosphate binders is calcium accumulation and hypercalcemia, especially in patients with low-turnover bone disease. Sevelamer and lanthanum are non-calcium-containing polymers that also function as phosphate binders; they do not predispose CKD patients to hypercalcemia and may attenuate calcium deposition in the vascular bed.

Calcitriol exerts a direct suppressive effect on PTH secretion and also indirectly suppresses PTH secretion by raising the concentration of ionized calcium. However, calcitriol therapy may result in hypercalcemia and/or hyperphosphatemia through increased GI absorption of these minerals. Certain analogues of calcitriol are available (e.g., paricalcitol) that suppress PTH secretion with less attendant hypercalcemia.

Recognition of the role of the extracellular calcium-sensing receptor has led to the development of calcimimetic agents that enhance the sensitivity of the parathyroid cell to the suppressive effect of calcium. This class of drug, which includes cinacalcet, produces a dose-dependent reduction in PTH and plasma calcium concentration in some patients.

Current National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend a target PTH level between 150 and 300 pg/mL, recognizing that very low PTH levels are associated with adynamic bone disease and possible consequences of fracture and ectopic calcification.

CARDIOVASCULAR ABNORMALITIES

Cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD. The incremental risk of cardiovascular disease in those with CKD compared to the age- and sex-matched general population ranges from 10- to 200-fold, depending on the stage of CKD. As a result, most patients with CKD succumb to cardiovascular disease (Fig. 305-6) before ever reaching stage 5 CKD. Between 30 and 45% of those patients who do reach stage 5 CKD have advanced cardiovascular complications. Thus, the focus of patient care in earlier CKD stages should be directed to prevention of cardiovascular complications.

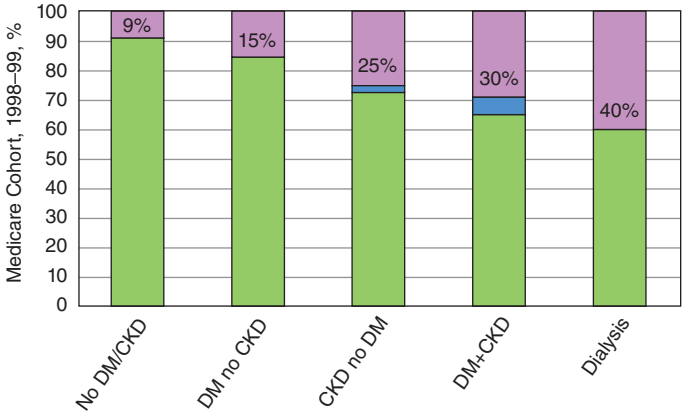

FIGURE 305-6 U.S. Renal Data System showing increased likelihood of dying rather than starting dialysis or reaching stage 5 chronic kidney disease (CKD). 1, Death; 2, ESRD; 3, event-free. DM; diabetes mellitus. *(Data from RN Foley et al: J Am Soc Nephrol 16:489–495, 2005.)*

Ischemic Vascular Disease The increased prevalence of vascular disease in CKD patients derives from both traditional ("classic") and nontraditional (CKD-related) risk factors. Traditional risk factors include hypertension, hypervolemia, dyslipidemia, sympathetic overactivity, and hyperhomocysteinemia. The CKD-related risk factors comprise anemia, hyperphosphatemia, hyperparathyroidism, increased FGF-23, sleep apnea, and generalized inflammation. The inflammatory state appears to accelerate vascular occlusive disease, and low levels of fetuin may permit more rapid vascular calcification, especially in the face of hyperphosphatemia. Other abnormalities seen in CKD may augment myocardial ischemia, including left ventricular hypertrophy and microvascular disease. In addition, hemodialysis, with its attendant episodes of hypotension and hypovolemia, may further aggravate coronary ischemia and repeatedly stun the myocardium. Interestingly, however, the largest increment in cardiovascular mortality rate in dialysis patients is not necessarily directly associated with documented acute myocardial infarction but, instead, is the result of congestive heart failure and sudden death.

Cardiac troponin levels are frequently elevated in CKD without evidence of acute ischemia. The elevation complicates the diagnosis of acute myocardial infarction in this population. Serial measurements may be needed. Therefore, the trend in levels over the hours after presentation may be more informative than a single, elevated level. Interestingly, consistently elevated levels are an independent prognostic factor for adverse cardiovascular events in this population.

Heart Failure Abnormal cardiac function secondary to myocardial ischemia, left ventricular hypertrophy, diastolic dysfunction, and frank cardiomyopathy, in combination with the salt and water retention often results in heart failure or even pulmonary edema. Heart failure can be a consequence of diastolic or systolic dysfunction, or both. A form of "low-pressure" pulmonary edema can also occur in advanced CKD, manifesting as shortness of breath and a "bat wing" distribution of alveolar edema fluid on the chest x-ray. This finding can occur even in the absence of ECFV overload and is associated with normal or mildly elevated pulmonary capillary wedge pressure. This process has been ascribed to increased permeability of alveolar capillary membranes as a manifestation of the uremic state, and it responds to dialysis. Other CKD-related risk factors, including anemia and sleep apnea, may contribute to the risk of heart failure.

Hypertension and Left Ventricular Hypertrophy Hypertension is one of the most common complications of CKD. It usually develops early during the course of CKD and is associated with adverse outcomes, including the development of ventricular hypertrophy and a more rapid loss of renal function. Left ventricular hypertrophy and dilated cardiomyopathy are among the strongest risk factors for cardiovascular morbidity and mortality in patients with CKD and are thought to be related primarily, but not exclusively, to prolonged hypertension and ECFV overload. In addition, anemia and the placement of an arteriovenous fistula for hemodialysis can generate a high cardiac output state and consequent heart failure.

The absence of hypertension may signify poor left ventricular function. Indeed, in epidemiologic studies of dialysis patients, low blood pressure actually carries a worse prognosis than does high blood pressure. This mechanism, in part, accounts for the "reverse causation" seen in dialysis patients, wherein the presence of traditional risk factors, such as hypertension, hyperlipidemia, and obesity, appear to portend a better prognosis. Importantly, these observations derive from cross-sectional studies of late-stage CKD patients and should not be interpreted to discourage appropriate management of these risk factors in CKD patients, especially at early stages. In contrast to the general population, it is possible that in late-stage CKD, low blood pressure, reduced body mass index, and hypolipidemia indicate the presence of an advanced malnutrition-inflammation state, with poor prognosis.

The use of exogenous erythropoiesis-stimulating agents can increase blood pressure and the requirement for antihypertensive drugs. Chronic ECFV overload is also a contributor to hypertension, and improvement in blood pressure can often be seen with the use of dietary sodium restriction, diuretics, and fluid removal with dialysis. Nevertheless, because of activation of the RAS and other disturbances in the balance of vasoconstrictors and vasodilators, some patients remain hypertensive despite careful attention to ECFV status.

TREATMENT

Cardiovascular Abnormalities

MANAGEMENT OF HYPERTENSION

The overarching goal of hypertension therapy in CKD is to prevent the extrarenal complications of high blood pressure, such as cardiovascular disease and stroke. Although a clear-cut generalizable benefit in slowing progression of CKD remains as yet unproven, the benefit for cardiac and cerebrovascular health is compelling. In all patients with CKD, blood pressure should be controlled to levels recommended by national guideline panels. In CKD patients with diabetes or proteinuria >1 g per 24 h, blood pressure should be reduced to <130/80 mmHg, if achievable without prohibitive adverse effects. Salt restriction should be the first line of therapy. When volume management alone is not sufficient, the choice of antihypertensive agent is similar to that in the general population. ACE inhibitors and ARBs appear to slow the rate of decline of kidney function in a manner that extends beyond reduction of systemic arterial pressure and that involves correction of the intraglomerular hyperfiltration and hypertension. Occasionally, introduction of ACE inhibitors and ARBs can actually precipitate an episode of acute kidney injury, especially when used in combination in patients with ischemic renovascular disease. Slight reduction of GFR (<30% of baseline) may signify a salutary reduction in intra-glomerular hypertension and hyperfiltration, and, if stable over time, can be tolerated with continued monitoring. Progressive decline in GFR should prompt discontinuation of these agents. The use of ACE inhibitors and ARBs may also be complicated by the development of hyperkalemia. Often the concomitant use of a combination of kaliuretic diuretics (e.g., furosemide with metolazone), or a potassium-lowering GI tract binder, such as patrimer, can improve potassium excretion in addition to improving blood pressure control. Potassium-sparing diuretics should be used with caution or avoided altogether in most patients.

The recent movement to even lower blood pressure targets in the general population may not be applicable to patients with CKD, who often lack autoregulation to maintain GFR in the face of low perfusion pressure. If a patient experiences sudden decline in kidney function with intensification of antihypertensive therapy, consideration should be given to reducing therapy.

MANAGEMENT OF CARDIOVASCULAR DISEASE

There are many strategies available to treat the traditional and nontraditional risk factors in CKD patients. Although these have proved effective in the general population, there is little evidence for their benefit in patients with advanced CKD, especially those on dialysis. Certainly hypertension, and dyslipidemia promote atherosclerotic disease and are treatable complications of CKD. Renal disease complicated by nephrotic syndrome is associated with a very atherogenic lipid profile and hypercoagulability, which increases the risk of occlusive vascular disease. Because diabetes mellitus and hypertension are the two most frequent causes of advanced CKD, it is not surprising that cardiovascular disease is the most frequent cause of death in dialysis patients. The role of "inflammation" may be quantitatively more important in patients with kidney disease, and the treatment of more traditional risk factors may result in only modest success. However, modulation of traditional risk factors may be the only weapon in the therapeutic armamentarium for these patients until the nature of inflammation in CKD and its treatment are better understood.

Pericardial Disease Chest pain with respiratory accentuation, accompanied by a friction rub, is diagnostic of pericarditis. Classic electrocardiographic abnormalities include PR-interval depression and diffuse ST-segment elevation. Pericarditis can be accompanied by pericardial effusion that is seen on echocardiography and can rarely lead to tamponade. However, the pericardial effusion can be asymptomatic, and pericarditis can be seen without significant effusion.

Pericarditis is observed in advanced uremia, and with the advent of timely initiation of dialysis, is not as common as it once was. It is now more often observed in underdialyzed, non-adherent patients than in those starting dialysis.

TREATMENT

Pericardial Disease

Uremic pericarditis is an absolute indication for the urgent initiation of dialysis or for intensification of the dialysis prescription in those already receiving dialysis. Because of the propensity to hemorrhage in pericardial fluid, hemodialysis should be performed without heparin. A pericardial drainage procedure should be considered in patients with recurrent pericardial effusion, especially with echocardiographic signs of impending tamponade. Non-uremic causes of pericarditis and effusion include viral, malignant, tuberculous, and autoimmune etiologies. It may also be seen after myocardial infarction and as a complication of treatment with the antihypertensive drug minoxidil.

HEMATOLOGIC ABNORMALITIES

Anemia A normocytic, normochromic anemia is observed as early as stage 3 CKD and is almost universal by stage 4. The primary cause is insufficient production of EPO by the diseased kidneys. Additional factors are reviewed in **Table 305-3**.

The anemia of CKD is associated with a number of adverse pathophysiologic consequences, including decreased tissue oxygen delivery and utilization, increased cardiac output, ventricular dilation, and ventricular hypertrophy. Clinical manifestations include fatigue and diminished exercise tolerance, angina, heart failure, decreased cognition and mental acuity, and impaired host defense against infection. In addition, anemia may play a role in growth restriction in children with CKD. Although many studies in CKD patients have found that anemia and resistance to exogenous erythropoietic-stimulating agents (ESA) are associated with a poor prognosis, the relative contribution to a poor outcome of the low hematocrit itself, versus inflammation as a cause of the anemia and ESA resistance, remains unclear.

TREATMENT

Anemia

The availability of recombinant human ESA has been one of the most significant advances in the care of renal patients since the introduction of dialysis and renal transplantation. Its routine use

TABLE 305-3 Causes of Anemia in CKD

Relative deficiency of erythropoietin
Diminished red blood cell survival
Bleeding diathesis
Iron deficiency due to poor dietary absorption and gastrointestinal blood loss
Hyperparathyroidism/bone marrow fibrosis
Chronic inflammation
Folate or vitamin B_{12} deficiency
Hemoglobinopathy
Comorbid conditions: hypo-/hyperthyroidism, pregnancy, HIV-associated disease, autoimmune disease, immunosuppressive drugs

has obviated the need for regular blood transfusions in severely anemic CKD patients, thus dramatically reducing the incidence of transfusion-associated infections and iron overload. Frequent blood transfusions in dialysis patients also lead to the development of alloantibodies that can sensitize the patient to donor kidney antigens and make renal transplantation more problematic.

Adequate bone marrow iron stores should be available before treatment with ESA is initiated. Iron supplementation is usually essential to ensure an optimal response to ESA in patients with CKD because the demand for iron by the marrow frequently exceeds the amount of iron that is immediately available for erythropoiesis (measured by percent transferrin saturation), as well as the amount in iron stores (measured by serum ferritin). For the CKD patient not yet on dialysis or the patient treated with peritoneal dialysis, oral iron supplementation should be attempted. If there is GI intolerance or poor GI absorption, the patient may have to undergo IV iron infusion. For patients on hemodialysis, IV iron can be administered during dialysis, keeping in mind that iron therapy can increase the susceptibility to bacterial infections, and that the adverse effects of free serum iron are still under investigation. In addition to iron, an adequate supply of other major substrates and cofactors for red cell production must be ensured, including vitamin B_{12} and folate. Anemia resistant to recommended doses of ESA in the face of adequate iron stores may be due to some combination of the following: acute or chronic inflammation, inadequate dialysis, severe hyperparathyroidism, chronic blood loss or hemolysis, chronic infection, or malignancy.

Randomized, controlled trials of ESA in CKD have failed to show an improvement in cardiovascular outcomes with this therapy. Indeed, there has been an indication that the use of ESA in CKD may be associated with an increased risk of stroke in those with type 2 diabetes, an increase in thromboembolic events, and perhaps a faster progression of renal decline. Therefore, any benefit in terms of improvement of anemic symptoms needs to be balanced against the potential cardiovascular risk. Although further studies are needed, it is quite clear that complete normalization of the hemoglobin concentration has not been demonstrated to be of incremental benefit to CKD patients. Current practice is to target a hemoglobin concentration of 100–115 g/L.

Abnormal Hemostasis Patients with later stages of CKD may have a prolonged bleeding time, decreased activity of platelet factor III, abnormal platelet aggregation and adhesiveness, and impaired prothrombin consumption. Clinical manifestations include an increased tendency to bleeding and bruising, prolonged bleeding from surgical incisions, menorrhagia, and GI bleeding. Interestingly, CKD patients also have a greater susceptibility to thromboembolism, especially if they have renal disease that includes nephrotic-range proteinuria. The latter condition results in hypoalbuminemia and renal loss of anticoagulant factors, which can lead to a thrombophilic state.

TREATMENT

Abnormal Hemostasis

Abnormal bleeding time and coagulopathy in patients with renal failure may be reversed temporarily with desmopressin (DDAVP), cryoprecipitate, IV conjugated estrogens, blood transfusions, and ESA therapy. Optimal dialysis will usually correct a prolonged bleeding time.

Given the coexistence of bleeding disorders and a propensity to thrombosis that is unique in the CKD patient, decisions about anticoagulation that have a favorable risk-benefit profile in the general population may not be applicable to the patient with advanced CKD. One example is warfarin anticoagulation for atrial fibrillation; the decision to anticoagulate should be made on an individual basis in the CKD patient because there appears to be a greater risk of bleeding complications.

Certain anticoagulants, such as fractionated low-molecular-weight heparin, may need to be avoided or dose-adjusted in these patients, with monitoring of factor Xa activity where available. It is often more prudent to use conventional unfractionated heparin, titrated to the measured partial thromboplastin time, in hospitalized patients requiring an alternative to warfarin anticoagulation. The new classes of oral anticoagulants are all, in part, renally eliminated and need to be avoided or dose adjusted in the face of decreased GFR (Chap. 114).

NEUROMUSCULAR ABNORMALITIES

Central nervous system (CNS), peripheral, and autonomic neuropathy as well as abnormalities in muscle structure and function are all well-recognized complications of CKD. Subtle clinical manifestations of uremic neuromuscular disease usually become evident at stage 3 CKD. Early manifestations of CNS complications include mild disturbances in memory and concentration and sleep disturbance. Neuromuscular irritability, including hiccups, cramps, and twitching, becomes evident at later stages. In advanced untreated kidney failure, asterixis, myoclonus, seizures, and coma can be seen.

Peripheral neuropathy usually becomes clinically evident after the patient reaches stage 4 CKD, although electrophysiologic and histologic evidence occurs earlier. Initially, sensory nerves are involved more than motor, lower extremities more than upper, and distal parts of the extremities more than proximal. The "restless leg syndrome" is characterized by ill-defined sensations of sometimes debilitating discomfort in the legs and feet relieved by frequent leg movement. Evidence of peripheral neuropathy without another cause (e.g., diabetes mellitus) is an indication for starting renal replacement therapy. Many of the complications described above will resolve with dialysis, although subtle nonspecific abnormalities may persist.

GASTROINTESTINAL AND NUTRITIONAL ABNORMALITIES

Uremic fetor, a urine-like odor on the breath, derives from the breakdown of urea to ammonia in saliva and is often associated with an unpleasant metallic taste (dysgeusia). Gastritis, peptic disease, and mucosal ulcerations at any level of the GI tract occur in uremic patients and can lead to abdominal pain, nausea, vomiting, and GI bleeding. These patients are also prone to constipation, which can be worsened by the administration of calcium and iron supplements. The retention of uremic toxins also leads to anorexia, nausea, and vomiting.

Protein restriction may be useful to decrease nausea and vomiting; however, it may put the patient at risk for malnutrition and should be carried out, if possible, in consultation with a registered dietitian specializing in the management of CKD patients. Weight loss and protein-energy malnutrition, a consequence of low protein and caloric intake, is common in advanced CKD and is often an indication for initiation of renal replacement therapy. Metabolic acidosis and the activation of inflammatory cytokines can promote protein catabolism. A number of indices are useful in nutritional assessment and include dietary history, including food diary and subjective global assessment; edema-free body weight; and measurement of urinary protein nitrogen appearance. Dual-energy x-ray absorptiometry is now widely used to estimate lean body mass versus fluid weight. Nutritional guidelines for patients with CKD are summarized in the "Treatment" section.

ENDOCRINE-METABOLIC DISTURBANCES

Glucose metabolism is impaired in CKD. However, fasting blood glucose is usually normal or only slightly elevated, and mild glucose intolerance does not require specific therapy. Because the kidney contributes to insulin removal from the circulation, plasma levels of insulin are slightly to moderately elevated in most uremic patients, both in the fasting and postprandial states. Because of this diminished renal degradation of insulin, patients on insulin therapy may need progressive reduction in dose as their renal function worsens. Many anti-hyperglycemic agents, including the gliptins, require dose reduction in renal failure, and some, such as metformin and sulfonylureas

are contraindicated when the GFR is less than half of normal. A recent exception is the class of drugs that inhibit sodium-glucose transport in the proximal tubule, resulting in glucose lowering, accompanied by striking reductions in kidney function decline and in cardiovascular events. The stabilization of GFR in many patients with this therapeutic intervention represents a major, important added beneficial effect of these drugs. Their long-term stabilizing effect on GFR and urine albumin excretion appears to result from correction of hyperfiltration early in type 2 diabetes mellitus *via* re-activation of the tubuloglomerular feedback loop. This represents a fortunate convergence of pathophysiology of glomerular hyperfiltration in diabetes with drug discovery.

In women with CKD, estrogen levels are low, and menstrual abnormalities, infertility, and inability to carry pregnancies to term are common. When the GFR has declined to ~40 mL/min, pregnancy is associated with a high rate of spontaneous abortion, with only ~20% of pregnancies leading to live births, and pregnancy may hasten the progression of the kidney disease itself. Women with CKD who are contemplating pregnancy should consult first with a nephrologist in conjunction with an obstetrician specializing in high-risk pregnancy. Men with CKD have reduced plasma testosterone levels, and sexual dysfunction and oligospermia may supervene. Sexual maturation may be delayed or impaired in adolescent children with CKD, even among those treated with dialysis. Many of these abnormalities improve or reverse with intensive dialysis or with successful renal transplantation.

DERMATOLOGIC ABNORMALITIES

Abnormalities of the skin are prevalent in progressive CKD. Pruritus is quite common and one of the most vexing manifestations of the uremic state. In advanced CKD, even on dialysis, patients may become more pigmented, and this is felt to reflect the deposition of retained pigmented metabolites, or *urochromes*. Although many of the cutaneous abnormalities improve with dialysis, pruritus is often tenacious. The first lines of management are to rule out unrelated skin disorders, such as scabies, and to treat hyperphosphatemia, which can cause itch. Local moisturizers, mild topical glucocorticoids, oral antihistamines, and ultraviolet radiation have been reported to be helpful.

A skin condition unique to CKD patients called *nephrogenic fibrosing dermopathy* consists of progressive subcutaneous induration, especially on the arms and legs. The condition is seen very rarely in patients with CKD who have been exposed to the magnetic resonance contrast agent gadolinium. Current recommendations are that patients with CKD stage 3 (GFR 30–59 mL/min) should minimize exposure to gadolinium, and those with CKD stages 4–5 (GFR <30 mL/min) should avoid the use of gadolinium agents unless it is medically necessary. However, no patient should be denied an imaging investigation that is critical to management, and under such circumstances, rapid removal of gadolinium by hemodialysis (even in patient's not yet receiving renal replacement therapy) shortly after the procedure may mitigate this sometimes devastating complication.

EVALUATION AND MANAGEMENT OF PATIENTS WITH CKD

INITIAL APPROACH

History and Physical Examination Symptoms and overt signs of kidney disease are often subtle or absent until renal failure supervenes. Thus, the diagnosis of kidney disease often surprises patients and may be a cause of skepticism and denial. Particular aspects of the history that are germane to renal disease include a history of hypertension (which can cause CKD or more commonly be a consequence of CKD), diabetes mellitus, abnormal urinalyses, and problems with pregnancy such as preeclampsia or early pregnancy loss. A careful drug history should be elicited. Drugs to consider include nonsteroidal anti-inflammatory agents, cyclooxygenase-2 (COX-2) inhibitors, antimicrobials, chemotherapeutic agents, antiretroviral agents, proton pump inhibitors, phosphate-containing bowel cathartics, and lithium. In evaluating the uremic syndrome, questions about appetite, weight loss, nausea, hiccups, peripheral edema, muscle cramps, pruritus, and restless legs are especially helpful. A family history of kidney disease, together with assessment of manifestations in other organ systems such as auditory, visual, and integumentary, may lead to the diagnosis of a heritable form of CKD (e.g., Alport or Fabry disease, cystinosis) or shared environmental exposure to nephrotoxic agents (e.g., heavy metals, aristolochic acid). It should be noted that clustering of CKD, sometimes of different etiologies, is often observed within families.

The physical examination should focus on blood pressure and target organ damage from hypertension. Thus, funduscopy and precordial examination should be carried out. Funduscopy is important in the diabetic patient, because it may show evidence of diabetic retinopathy, which is associated with nephropathy. Other physical examination manifestations of CKD include edema and sensory polyneuropathy. The finding of asterixis or a pericardial friction rub not attributable to other causes usually signifies the presence of the uremic syndrome.

Laboratory Investigation Laboratory studies should focus on a search for clues to an underlying causative or aggravating disease process and on the degree of renal damage and its consequences. Serum and urine protein electrophoresis, looking for multiple myeloma, should be obtained in all patients >35 years with unexplained CKD, especially if there is associated anemia and elevated, or even inappropriately normal, serum calcium concentration in the face of renal insufficiency. In the presence of glomerulonephritis, autoimmune diseases such as lupus and underlying infectious etiologies such as hepatitis B and C and HIV should be tested. Serial measurements of renal function should be obtained to determine the pace of renal deterioration and ensure that the disease is truly chronic rather than acute or subacute and hence potentially reversible. Serum concentrations of calcium, phosphorus, vitamin D, and PTH should be measured to evaluate metabolic bone disease. Hemoglobin concentration, iron, vitamin B_{12}, and folate should also be evaluated. A 24-h urine collection may be helpful, because protein excretion >300 mg may be an indication for therapy with ACE inhibitors or ARBs.

Imaging Studies The most useful imaging study is a renal ultrasound, which can verify the presence of two kidneys, determine if they are symmetric, provide an estimate of kidney size, and rule out renal masses and evidence of obstruction. Because it takes time for kidneys to shrink as a result of chronic disease, the finding of bilaterally small kidneys supports the diagnosis of CKD of long-standing duration. If the kidney size is normal, it is possible that the renal disease is acute or subacute. The exceptions are diabetic nephropathy (where kidney size is increased at the onset of diabetic nephropathy before CKD supervenes), amyloidosis, and HIV nephropathy, where kidney size may be normal in the face of CKD. Polycystic kidney disease that has reached some degree of renal failure will almost always present with enlarged kidneys with multiple cysts (Chap. 309). A discrepancy >1 cm in kidney length suggests either a unilateral developmental abnormality or disease process or renovascular disease with arterial insufficiency affecting one kidney more than the other. The diagnosis of renovascular disease can be undertaken with different techniques, including Doppler sonography, nuclear medicine studies, or CT or magnetic resonance imaging (MRI) studies. If there is a suspicion of reflux nephropathy (recurrent childhood urinary tract infection, asymmetric renal size with scars on the renal poles), a voiding cystogram may be indicated. However, in most cases, by the time the patient has CKD, the reflux has resolved, and even if still present, repair does not improve renal function. Radiographic contrast imaging studies are not particularly helpful in the investigation of CKD. Intravenous or intraarterial dye should be avoided where possible in the CKD patient, especially with diabetic nephropathy, because of the risk of radiographic contrast dye–induced renal failure. When unavoidable, appropriate precautionary measures include avoidance of hypovolemia at the time of contrast exposure, minimization of the dye load, and choice of radiographic contrast preparations with the least nephrotoxic potential. Additional measures thought to attenuate contrast-induced worsening of renal function include judicious administration of sodium bicarbonate–containing solutions and *N* acetylcysteine.

Kidney Biopsy In the patient with bilaterally small kidneys, renal biopsy is not advised because (1) it is technically difficult and has a greater likelihood of causing bleeding and other adverse consequences, (2) there is usually so much scarring that the underlying disease may not be apparent, and (3) the window of opportunity to render disease-specific therapy has passed. Other contraindications to renal biopsy include uncontrolled hypertension, active urinary tract infection, bleeding diathesis (including ongoing anticoagulation), and severe obesity. Ultrasound-guided percutaneous biopsy is the favored approach, but a surgical or laparoscopic approach can be considered, especially in the patient with a single kidney where direct visualization and control of bleeding are crucial. In the CKD patient in whom a kidney biopsy is indicated (e.g., suspicion of a concomitant or superimposed active process such as interstitial nephritis or in the face of accelerated loss of GFR), the bleeding time should be measured, and if increased, desmopressin should be administered immediately prior to the procedure.

A brief run of hemodialysis (without heparin) may also be considered prior to renal biopsy to normalize the bleeding time.

ESTABLISHING THE DIAGNOSIS AND ETIOLOGY OF CKD

The most important initial diagnostic step is to distinguish newly diagnosed CKD from acute or subacute renal failure, because the latter two conditions may respond to targeted therapy. Previous measurements of serum creatinine concentration are particularly helpful in this regard. Normal values from recent months or even years suggest that the current extent of renal dysfunction could be more acute, and hence reversible, than might otherwise be appreciated. In contrast, elevated serum creatinine concentration in the past suggests that the renal disease represents a chronic process. Even if there is evidence of chronicity, there is the possibility of a superimposed acute process (e.g., ECFV depletion, urinary infection or obstruction, or nephrotoxin exposure) supervening on the chronic condition. If the history suggests multiple systemic manifestations of recent onset (e.g., fever, polyarthritis, rash), it should be assumed that renal insufficiency is part of an acute systemic illness.

Although kidney biopsy can usually be performed in early CKD (stages 1–3), it is not always indicated. For example, in a patient with a history of type 1 diabetes mellitus for 15–20 years with retinopathy, nephrotic-range proteinuria, and absence of hematuria, the diagnosis of diabetic nephropathy is very likely and biopsy is usually not necessary. However, if there were some other finding not typical of diabetic nephropathy, such as hematuria or white blood cell casts, or absence of diabetic retinopathy, some other disease may be present and a biopsy may be indicated.

In the absence of a clinical diagnosis, kidney biopsy may be the only recourse to establish an etiology in early-stage CKD. However, as noted above, once the CKD is advanced and the kidneys are small and scarred, there is little utility and significant risk in attempting to arrive at a specific diagnosis. Genetic testing is increasingly entering the repertoire of diagnostic tests, since the patterns of injury and kidney morphologic abnormalities often reflect overlapping causal mechanisms, whose origins can sometimes be attributed to a genetic predisposition or cause.

TREATMENT

Chronic Kidney Disease

Treatments aimed at specific causes of CKD are discussed elsewhere. The optimal timing of both specific and nonspecific therapy is usually well before there has been a measurable decline in GFR and certainly before CKD is established. It is helpful to measure sequentially and plot the rate of decline of GFR in all patients. Any acceleration in the rate of decline should prompt a search for superimposed acute or subacute processes that may be reversible. These include ECFV depletion, uncontrolled hypertension, urinary tract infection, new obstructive uropathy, exposure to nephrotoxic agents (such as nonsteroidal anti-inflammatory drugs [NSAIDs] or radiographic dye), and reactivation or flare of the original disease, such as lupus or vasculitis.

SLOWING THE PROGRESSION OF CKD

There is variation in the rate of decline of GFR among patients with CKD. However, the following interventions should be considered in an effort to stabilize or slow the decline of renal function.

Reducing Intraglomerular Hypertension and Proteinuria Increased intraglomerular filtration pressures and glomerular hypertrophy develop as a response to loss of nephron number. This response is maladaptive, as it promotes the ongoing decline of kidney function even if the inciting process has been treated or spontaneously resolved. Control of glomerular hypertension is important in slowing the progression of CKD. Moreover, elevated blood pressure increases proteinuria by increasing its flux across the glomerular capillaries. Conversely, the renoprotective effect of antihypertensive medications is gauged through the consequent reduction of proteinuria. Thus, the more effective a given treatment is in lowering protein excretion, the greater the subsequent impact on protection from decline in GFR. This observation is the basis for the treatment guideline establishing 130/80 mmHg as a target blood pressure in proteinuric CKD patients.

Several controlled studies have shown that ACE inhibitors and ARBs are effective in slowing the progression of renal failure in patients with advanced stages of both diabetic and nondiabetic CKD, in large part through effects on efferent vasodilatation and the subsequent decline in glomerular hypertension. In the absence of an anti-proteinuric response with either agent alone, combined treatment with both ACE inhibitors and ARBs has been considered. The combination is associated with a greater reduction in proteinuria compared to either agent alone. Insofar as reduction in proteinuria is a surrogate for improved renal outcome, the combination would appear to be advantageous. However, there is a greater incidence of acute kidney injury and adverse cardiac events from such combination therapy. On balance, therefore, ACE inhibitor plus ARB therapy should be avoided. A progressive increase in serum creatinine concentration with these agents may suggest the presence of renovascular disease within the large or small arteries. Development of side effects may mandate the use of second-line antihypertensive agents instead of ACE inhibitors or ARBs. Among the calcium channel blockers, diltiazem and verapamil may exhibit superior antiproteinuric and renoprotective effects compared to the dihydropyridines. At least two different categories of response can be considered: one in which progression is strongly associated with systemic and intraglomerular hypertension and proteinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and ARBs are likely to be the first choice; and another in which proteinuria is mild or absent initially (e.g., adult polycystic kidney disease and other tubulointerstitial diseases), where the contribution of intraglomerular hypertension is less prominent and other antihypertensive agents can be useful for control of systemic hypertension.

SLOWING THE PROGRESSION OF DIABETIC NEPHROPATHY

See Chap. 397

MANAGING OTHER COMPLICATIONS OF CKD

Medication Dose Adjustment Although the loading dose of most drugs is not affected by CKD because renal elimination is not used in the calculation, the maintenance doses of many drugs will need to be adjusted. For those agents in which >70% excretion is by a nonrenal route, such as hepatic elimination, dose adjustment may not be needed. Some drugs that should be avoided include metformin, meperidine, and oral anti-hyperglycemics that are eliminated by the kidney. NSAIDs should be avoided because of the risk of further worsening of kidney function. Many antibiotics, antihypertensives, and antiarrhythmics may require a reduction in dosage or change in the dose interval. Several online Web-based databases for dose adjustment of medications according to stage of

CKD or estimated GFR are available (e.g., *http://www.globalrph.com/index_renal.htm*). Nephrotoxic radiocontrast agents and gadolinium should be avoided or used according to strict guidelines when medically necessary as discussed above.

PREPARATION FOR RENAL REPLACEMENT THERAPY

(See also Chap. 307) Temporary relief of symptoms and signs of impending uremia, such as anorexia, nausea, vomiting, lassitude, and pruritus, may sometimes be achieved with dietary protein restriction. However, this carries a risk of malnutrition, and thus plans for more long-term management should be in place.

Maintenance dialysis and kidney transplantation have extended the lives of hundreds of thousands of patients with CKD worldwide. Clear indications for initiation of renal replacement therapy for patients with CKD include uremic pericarditis, encephalopathy, intractable muscle cramping, anorexia, and nausea not attributable to reversible causes such as peptic ulcer disease, evidence of malnutrition, and fluid and electrolyte abnormalities, principally hyperkalemia or ECFV overload, that are refractory to other measures.

Recommendations for the Optimal Time for Initiation of Renal Replacement Therapy Because of the individual variability in the severity of uremic symptoms and renal function, it is ill-advised to assign an arbitrary urea nitrogen or creatinine level to the need to start dialysis. Moreover, patients may become accustomed to chronic uremia and deny symptoms, only to find that they feel better with dialysis and realize in retrospect how poorly they were feeling before its initiation.

Previous studies suggested that starting dialysis before the onset of severe symptoms and signs of uremia was associated with prolongation of survival. This led to the concept of "healthy" start and is congruent with the philosophy that it is better to keep patients feeling well rather than allowing them to become ill with uremia and then attempting to return them to better health with dialysis or transplantation. Although recent studies have not confirmed an association of early-start dialysis with improved patient survival, there may be merit in this approach for some patients. On a practical level, advanced preparation may help to avoid problems with the dialysis process itself (e.g., a poorly functioning fistula for hemodialysis or malfunctioning peritoneal dialysis catheter) and, thus, preempt the morbidity associated with resorting to the insertion of temporary hemodialysis access with its attendant risks of sepsis, bleeding, thrombosis, and association with accelerated mortality.

Patient Education Social, psychological, and physical preparation for the transition to renal replacement therapy and the choice of the optimal initial modality are best accomplished with a gradual approach involving a multidisciplinary team. Along with conservative measures discussed in the sections above, it is important to prepare patients with an intensive educational program, explaining the likelihood and timing of initiation of renal replacement therapy and the various forms of therapy available, and the option of nondialytic conservative care. The more knowledgeable that patients are about hemodialysis (both in-center and home-based), peritoneal dialysis, and kidney transplantation, the easier and more appropriate will be their decisions. Patients who are provided with education are more likely to choose home-based dialysis therapy. This approach is of societal benefit because home-based therapy is less expensive and is associated with improved quality of life. The educational programs should be commenced no later than stage 4 CKD so that the patient has sufficient time and cognitive function to learn the important concepts, make informed choices, and implement preparatory measures for renal replacement therapy.

Exploration of social support is also important. Early education of family members for selection and preparation of a home dialysis helper or a biologically or emotionally related potential living kidney donor should occur long before the onset of symptomatic renal failure.

Kidney transplantation **(Chap. 307)** offers the best potential for complete rehabilitation, because dialysis replaces only a small fraction of the kidneys' filtration function and none of the other renal functions, including endocrine and anti-inflammatory effects. Generally, kidney transplantation follows a period of dialysis treatment, although preemptive kidney transplantation (usually from a living donor) can be carried out if it is certain that the renal failure is irreversible.

IMPLICATIONS FOR GLOBAL HEALTH

In contrast to the natural decline and successful eradication of many devastating infectious diseases, there is rapid growth in the prevalence of metabolic and vascular disease in developing countries. Diabetes mellitus is becoming increasingly prevalent in these countries, perhaps due in part to change in dietary habits, diminished physical activity, and weight gain. Therefore, it follows that there will be a proportionate increase in vascular and renal disease. Health care agencies must plan for improved screening of high-risk individuals for early detection, prevention, and treatment plans in these nations and must start considering options for improved availability of renal replacement therapies.

There is also increasing recognition of endemic nephropathies in developing countries that particularly target young males working in agriculture. The extent of morbidity and mortality associated with these nephropathies is only starting to be appreciated. It is unclear what the cause is, but a combination of population genetic risk with endemic nephrotoxins, exposure to pesticides, NSAID use, and chronic volume depletion have all been suggested to contribute.

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306 Dialysis in the Treatment of Renal Failure

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Dialysis may be required for the treatment of either acute or chronic kidney disease (CKD). The use of continuous renal replacement therapies (CRRT) and prolonged intermittent renal replacement therapy (PIRRT)/slow low-efficiency dialysis (SLED) is specific to the management of acute renal failure and is discussed in **Chap. 304**. These modalities are performed continuously (CRRT) or over 6–12 h per session (PIRRT/SLED), in contrast to the 3–4 h of an intermittent hemodialysis session. **Advantages and disadvantages of CRRT and PIRRT/SLED are discussed in Chap. 304.**

Peritoneal dialysis is rarely used in developed countries for the treatment of acute renal failure because of the increased risk of infection and (as will be discussed in more detail below) less efficient clearance per unit of time. The focus of this chapter will be on the use of peritoneal and hemodialysis for end-stage renal disease (ESRD).

With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESRD have been prolonged. In the

United States alone, there are now ~675,000 patients with treated ESRD (kidney failure requiring dialysis or transplantation), the vast majority of whom require dialysis. Since 2000, the prevalence of treated ESRD has increased 74%, which reflects both a small increase in the incidence rate and marginally enhanced survival of patients receiving dialysis. The incidence rate for treated ESRD in the United States is 370 cases per million population per year; ESRD is disproportionately higher in African Americans (875 per million population per year) as compared with white Americans (285 per million population per year). In the United States, the leading cause of ESRD is diabetes mellitus, currently accounting for almost 45% of newly diagnosed cases of ESRD. Approximately 30% of patients have ESRD that has been attributed to hypertension, although it is unclear whether in these cases hypertension is the cause or a consequence of vascular disease or other unknown causes of kidney failure. Other prevalent causes of ESRD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy. A fraction of the excess incidence of ESRD in African Americans is likely related to transmission of high-risk alleles for the *APOL1* gene.

Globally, mortality rates for patients with ESRD are lowest in Europe and Japan but very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis has decreased slightly but remains extremely high, with a 5-year survival rate of ~40% for patients receiving dialysis. Deaths are due mainly to cardiovascular diseases and infections (~40 and 10% of deaths, respectively). Older age, male sex, nonblack race, diabetes mellitus, malnutrition, and underlying heart disease are important predictors of death.

TREATMENT OPTIONS FOR PATIENTS WITH ESRD

Commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative measures, persistent extracellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or estimated glomerular filtration rate (GFR) <10 mL/min per 1.73 m^2 (see Chap. 305 for estimating equations). Timely referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESRD treatment options, and management of the complications of advanced CKD, including hypertension, anemia, acidosis, and secondary hyperparathyroidism, is advisable. Recent data have suggested that a sizable fraction of ESRD cases result following episodes of acute renal failure, particularly among persons with underlying CKD. Furthermore, there is no benefit to initiating dialysis preemptively at a GFR of 10–14 mL/min per 1.73 m^2 compared to initiating dialysis for symptoms of uremia.

In ESRD, treatment options include hemodialysis (in center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD); or transplantation (Chap. 307). Although there are significant geographic variations and differences in practice patterns, in-center hemodialysis remains the most common therapeutic modality for ESRD (>90% of patients) in the United States. In contrast to hemodialysis, peritoneal dialysis is continuous, but much less efficient, in terms of solute clearance. While no large-scale clinical trials have been completed comparing outcomes among patients randomized to either hemodialysis or peritoneal dialysis, outcomes associated with both therapies are similar in most reports, and the decision of which modality to select is often based on personal preferences and quality-of-life considerations.

HEMODIALYSIS

Hemodialysis relies on the principles of solute diffusion across a semipermeable membrane. Movement of metabolic waste products takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the magnitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to laws of diffusion, the larger the molecule, the slower its rate of transfer across the membrane. A small molecule, such as urea (60 Da), undergoes substantial clearance, whereas a larger molecule, such as creatinine (113 Da), is cleared less efficiently. In addition to diffusive clearance, movement of waste products from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clearance occurs because of solvent drag, with solutes being swept along with water across the semipermeable dialysis membrane.

THE DIALYZER

There are three essential components to hemodialysis: the dialyzer, the composition and delivery of the dialysate, and the blood delivery system (Fig. 306-1). The dialyzer is a plastic chamber with the ability to perfuse blood and dialysate compartments simultaneously at very high flow rates. The hollow-fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capillary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle. Virtually all dialyzers now manufactured in the United States are "biocompatible" synthetic membranes derived from polysulfone or related compounds (versus older cellulose "bioincompatible" membranes that activated the complement cascade). The frequency of reprocessing and reuse of hemodialyzers and blood lines varies across the world. In general as the cost of disposable supplies has decreased, their use has increased. In the United States, reprocessing of dialyzers is now extremely rare. Formaldehyde, peracetic acid–hydrogen peroxide, glutaraldehyde, and bleach have all been used as reprocessing agents.

DIALYSATE

The potassium concentration of dialysate may be varied from 0 to 4 mmol/L depending on the predialysis serum potassium concentration. The use of 0 or 1 mmol/L potassium dialysate is becoming less common owing to data suggesting that patients who undergo treatments with very low potassium dialysate have an increased risk of sudden death, perhaps due to arrhythmias in the setting of potassium shifts. The usual dialysate calcium concentration is 1.25 mmol/L (2.5 mEq/L), although modification may be required in selected settings (e.g., higher dialysate calcium concentrations may be used in patients with hypocalcemia associated with secondary hyperparathyroidism or with "hungry bone syndrome" following parathyroidectomy). The usual dialysate sodium concentration is 136–140 mmol/L. In patients who frequently develop hypotension during their dialysis run, "sodium modeling" to counterbalance urea-related osmolar gradients may be employed. With sodium modeling, the dialysate sodium concentration is gradually lowered from the range of 145–155 mmol/L to isotonic concentrations (136–140 mmol/L) near the end of the dialysis treatment, typically declining either in steps or in a linear or exponential fashion. However, higher dialysate sodium concentrations and sodium modeling may predispose patients to positive sodium balance and increased thirst; thus, these strategies to ameliorate intradialytic hypotension may be undesirable in patients with hypertension or in patients with large interdialytic weight gains. Because patients are exposed to ~120 L of water during each dialysis treatment, water used for the dialysate is subjected to filtration, softening, deionization, and, ultimately, reverse osmosis to remove microbiologic contaminants and dissolved ions.

BLOOD DELIVERY SYSTEM

The blood delivery system is composed of the extracorporeal circuit and the dialysis access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate typically ranges from 250 to 450 mL/min, depending on the type and integrity of the vascular access. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal or *ultrafiltration*. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes,

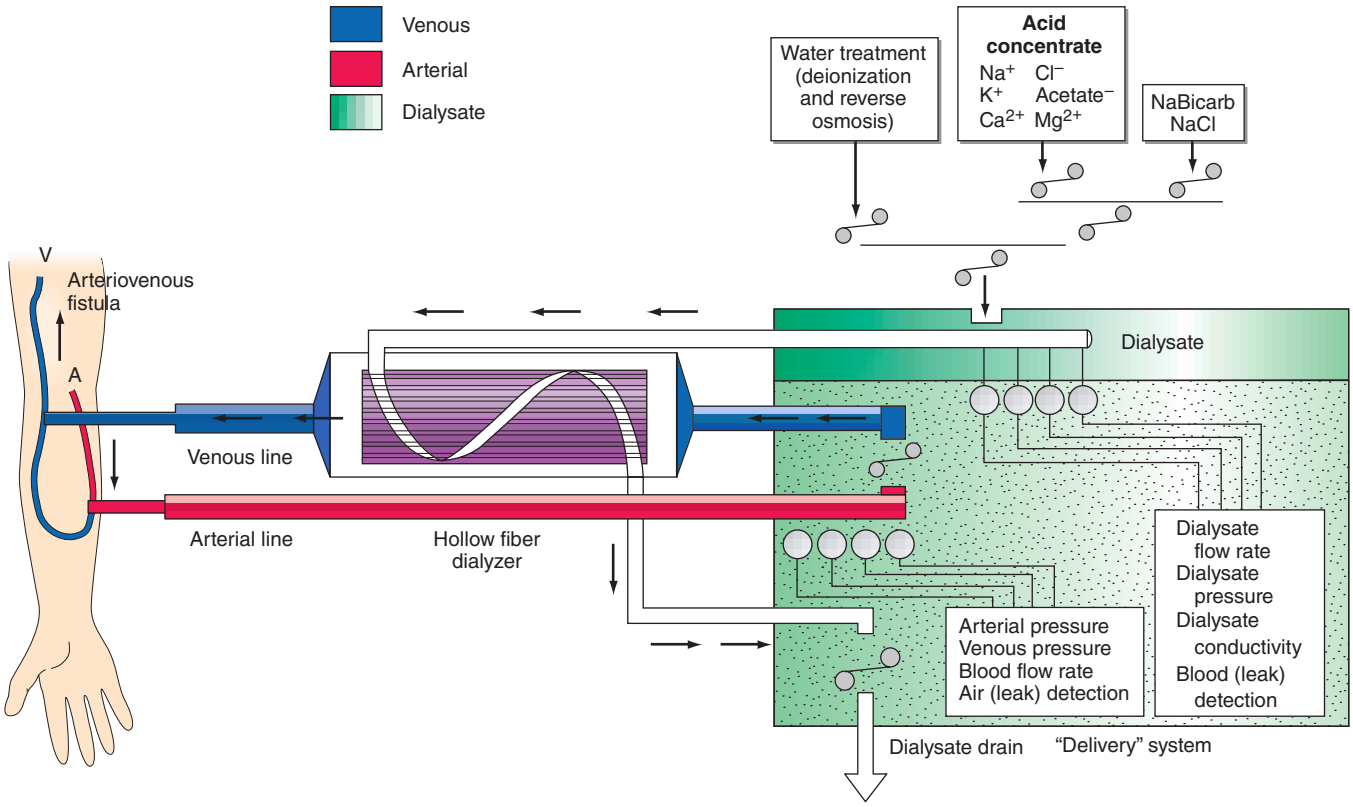

FIGURE 306-1 Schema for hemodialysis.

fluid removal can be varied. The dialysis solution delivery system dilutes the concentrated dialysate with water and monitors the temperature, conductivity, and flow of dialysate.

DIALYSIS ACCESS

The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a *hemodialysis (or vascular) access*. A native fistula created by the anastomosis of an artery to a vein (e.g., the Brescia-Cimino fistula, in which the cephalic vein is anastomosed end-to-side to the radial artery) results in arterialization of the vein. This facilitates its subsequent use in the placement of large needles (typically 15 gauge) to access the circulation. Fistulas have the highest long-term patency rate of all hemodialysis access options. For patients in whom fistulas fail to mature, or in patients whose vasculature does not allow creation of a successful fistula (i.e., poor arterial inflow or recipient veins of inadequate caliber), patients undergo placement of an arteriovenous graft (i.e., the interposition of prosthetic material, usually polytetrafluoroethylene, between an artery and a vein) or a tunneled hemodialysis catheter. In recent years, nephrologists, vascular surgeons, and health care policy makers in the United States have encouraged creation of arteriovenous fistulas in a larger fraction of patients (the "fistula first" initiative). Unfortunately, even when created, arteriovenous fistulas may not mature sufficiently to provide reliable access to the circulation, or they may thrombose early in their development.

The most important complication of arteriovenous grafts is thrombosis of the graft and graft failure, due principally to intimal hyperplasia at the anastomosis between the graft and recipient vein. When grafts (or fistulas) fail, catheter-guided angioplasty can be used to dilate stenoses; monitoring of venous pressures on dialysis and of access flow, although not routinely performed, may assist in the early recognition of impending vascular access failure. In addition to increased rates of access failure, grafts and (in particular) catheters are associated with much higher rates of infection than fistulas.

Intravenous large-bore catheters are often used in patients with acute renal failure and CKD. For persons on maintenance hemodialysis, tunneled catheters (either two separate catheters or a single catheter with two lumens) are often used when arteriovenous fistulas and grafts have failed or are not feasible due to anatomic considerations. These catheters are tunneled under the skin; the tunnel reduces bacterial translocation from the skin, resulting in a lower infection rate than with nontunneled temporary catheters. Most tunneled catheters are placed in the internal jugular veins; the external jugular, femoral, and subclavian veins may also be used.

Nephrologists, interventional radiologists, and vascular surgeons generally prefer to avoid placement of catheters into the subclavian veins; while flow rates are usually excellent, subclavian stenosis is a frequent complication and, if present, will likely prohibit permanent vascular access (i.e., a fistula or graft) in the ipsilateral extremity. Infection rates may be higher with femoral catheters. For patients with multiple vascular access complications and no other options for permanent vascular access, tunneled catheters may be the last "lifeline" for hemodialysis. Translumbar or transhepatic approaches into the inferior vena cava may be required if the superior vena cava or other central veins draining the upper extremities are stenosed or thrombosed.

GOALS OF DIALYSIS

The hemodialysis procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 250–450 mL/min, while dialysate flows in an opposite *counter-current* direction at 500–800 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer as well as dialyzer characteristics (i.e., its efficiency in removing solute). The *dose* of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single treatment, is further governed by patient size, residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions.

Since the landmark studies of Sargent and Gotch relating the measurement of the dose of dialysis using urea concentrations with morbidity in the National Cooperative Dialysis Study, the *delivered* dose of dialysis has been measured and considered as a quality assurance and improvement tool. While the fractional removal of urea nitrogen and derivations thereof are considered to be the standard methods by which "adequacy of dialysis" is measured, a large multicenter randomized clinical trial (the HEMO Study) failed to show a difference in mortality associated with a large difference in per-session urea clearance.

Current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a body water–indexed clearance × time product (Kt/V) >1.2 or 1.05, depending on whether urea concentrations are "equilibrated." For the majority of patients with ESRD, between 9 and 12 h of dialysis are required each week, usually divided into three equal sessions. Several studies have suggested that longer hemodialysis session lengths may be beneficial (independent of urea clearance), although these studies are confounded by a variety of patient characteristics, including body size and nutritional status. Hemodialysis "dose" should be individualized, and factors other than the urea nitrogen should be considered, including the adequacy of ultrafiltration or fluid removal and control of hyperkalemia, hyperphosphatemia, and metabolic acidosis. A randomized clinical trial comparing 6 versus 3 times per week hemodialysis (the "Frequent Hemodialysis Network Daily Trial") demonstrated improved control of hypertension and hyperphosphatemia, reduced left ventricular mass, and improved self-reported physical health with more frequent hemodialysis. Secondary analyses also demonstrated improvements in other metrics of health-related quality of life, including improved self-reported general health and a reduced "time to recovery" (time until usual activities can be resumed) among patients randomized to more frequent hemodialysis. A companion trial in which frequent nocturnal hemodialysis was compared to conventional hemodialysis at home showed no significant effect on left ventricular mass or self-reported physical health. Finally, an evaluation of the U.S. Renal Data System registry showed a significant increase in mortality and hospitalization for heart failure after the longer interdialytic interval that occurs over the dialysis "weekend."

COMPLICATIONS DURING HEMODIALYSIS

Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes mellitus. Numerous factors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, overzealous use of antihypertensive agents, and reduced cardiac reserve. Patients with arteriovenous fistulas and grafts may develop high-output cardiac failure due to shunting of blood through the dialysis access; on rare occasions, this may necessitate ligation of the fistula or graft. The management of hypotension during dialysis consists of discontinuing ultrafiltration, the administration of 100–250 mL of isotonic saline, or administration of salt-poor albumin. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Excessively rapid fluid removal (>13 mL/kg per h) should be avoided, as rapid fluid removal has been associated with adverse outcomes, including cardiovascular deaths. Additional maneuvers to prevent intradialytic hypotension include the performance of sequential ultrafiltration followed by dialysis, cooling of the dialysate during dialysis treatment, and avoiding heavy meals during dialysis. Midodrine, an oral selective α1 adrenergic agent, has been advocated by some practitioners, although there is insufficient evidence of its safety and efficacy to support its routine use.

Muscle cramps during dialysis are also a common complication. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively rapid volume removal or targeted removal below the patient's estimated dry weight often precipitate dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltration profiling, and the use of sodium modeling (see above).

Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported most frequently with the bioincompatible cellulosic-containing membranes. Dialyzer reactions can be divided into two types, A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis if the therapy is not promptly discontinued. Treatment with steroids or epinephrine may be needed if symptoms are severe. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialysis run and typically resolve over time with continued dialysis.

PERITONEAL DIALYSIS

In peritoneal dialysis, 1.5–3 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2–4 h. As with hemodialysis, metabolic byproducts are removed through a combination of convective clearance generated through ultrafiltration and diffusive clearance down a concentration gradient. The clearance of solutes and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. Absorption of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of peritoneal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs, and physical factors such as position and exercise.

FORMS OF PERITONEAL DIALYSIS

Peritoneal dialysis may be carried out as CAPD, CCPD, or a combination of both. In CAPD, dialysate is manually infused into the peritoneal cavity and exchanged three to five times during the day. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to an automated cycler that performs a series of exchange cycles while the patient sleeps. The number of exchange cycles required to optimize peritoneal solute clearance varies by the peritoneal membrane characteristics; as with hemodialysis, solute clearance should be tracked to ensure dialysis "adequacy."

Peritoneal dialysis solutions are available in volumes typically ranging from 1.5 to 3 L. The major difference between the dialysate used for peritoneal rather than hemodialysis is that the hypertonicity of peritoneal dialysis solutions drives solute and fluid removal, whereas solute removal in hemodialysis depends on concentration gradients, and fluid removal requires transmembrane pressure. Typically, dextrose at varying concentrations contributes to the hypertonicity of peritoneal dialysate. Icodextrin is a nonabsorbable carbohydrate that can be used in place of dextrose. Studies have demonstrated more efficient ultrafiltration with icodextrin than with dextrose-containing solutions. Icodextrin is typically used as the "last fill" for patients on CCPD or for the longest dwell in patients on CAPD. The most common additives to peritoneal dialysis solutions are heparin to prevent obstruction of the dialysis catheter lumen with fibrin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus.

ACCESS TO THE PERITONEAL CAVITY

Access to the peritoneal cavity is obtained through a peritoneal catheter. Catheters used for maintenance peritoneal dialysis are flexible, being made of silicone rubber with numerous side holes at the distal end. These catheters usually have two Dacron cuffs. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also prevents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the preperitoneal plane and ~2 cm from the skin surface.

The *peritoneal equilibrium test* is a formal evaluation of peritoneal membrane characteristics that measures the transfer rates of creatinine and glucose across the peritoneal membrane. Patients are classified as low, low–average, high–average, and high transporters. Patients with rapid equilibration (i.e., high transporters) tend to absorb more glucose and lose efficiency of ultrafiltration with long daytime dwells. High transporters also tend to lose larger quantities of albumin and

other proteins across the peritoneal membrane. In general, patients with rapid transporting characteristics require more frequent, shorter dwell time exchanges, nearly always obligating use of a cycler. Slower (low and low–average) transporters tend to do well with fewer exchanges. The efficiency of solute clearance also depends on the volume of dialysate infused. Larger volumes allow for greater solute clearance, particularly with CAPD in patients with low and low–average transport characteristics.

As with hemodialysis, the optimal dose of peritoneal dialysis is unknown. Several observational studies have suggested that higher rates of urea and creatinine clearance (the latter generally measured in L/week) are associated with lower mortality rates and fewer uremic complications. However, a randomized clinical trial (Adequacy of Peritoneal Dialysis in Mexico [ADEMEX]) failed to show a significant reduction in mortality or complications with a relatively large increment in urea clearance. In general, patients on peritoneal dialysis do well when they retain residual kidney function. Rates of technique failure increase with years on dialysis and have been correlated with loss of residual function to a greater extent than loss of peritoneal membrane capacity. For some patients in whom CCPD does not provide sufficient solute clearance, a hybrid approach can be adopted where one or more daytime exchanges are added to the CCPD regimen. While this approach can enhance solute clearance and prolong a patient's capacity to remain on peritoneal dialysis, the burden of the hybrid approach can be overwhelming.

COMPLICATIONS DURING PERITONEAL DIALYSIS

The major complications of peritoneal dialysis are peritonitis, catheter-associated nonperitonitis infections, weight gain and other metabolic disturbances, and residual uremia (especially among patients with little or no residual kidney function).

Peritonitis typically develops when there has been a break in sterile technique during one or more of the exchange procedures. Peritonitis is usually defined by an elevated peritoneal fluid leukocyte count ($100/mm^3$, of which at least 50% are polymorphonuclear neutrophils); these cutoffs are lower than in spontaneous bacterial peritonitis because of the presence of dextrose in peritoneal dialysis solutions and rapid bacterial proliferation in this environment without antibiotic therapy. The clinical presentation typically consists of pain and cloudy dialysate, often with fever and other constitutional symptoms. The most common culprit organisms are gram-positive cocci, including *Staphylococcus,* reflecting the origin from the skin. Gram-negative rod infections are less common; fungal and mycobacterial infections can be seen in selected patients, particularly after antibacterial therapy. Most cases of peritonitis can be managed either with intraperitoneal or oral antibiotics, depending on the organism; many patients with peritonitis do not require hospitalization. In cases where peritonitis is due to hydrophilic gram-negative rods (e.g., *Pseudomonas* sp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection. Nonperitonitis catheter-associated infections (often termed *tunnel infections*) vary widely in severity. Some cases can be managed with local antibiotic or silver nitrate administration, while others are severe enough to require parenteral antibiotic therapy and catheter removal.

Peritoneal dialysis is associated with a variety of metabolic complications. Albumin and other proteins can be lost across the peritoneal membrane in concert with the loss of metabolic wastes. Hypoproteinemia obligates a higher dietary protein intake in order to maintain nitrogen balance. Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentration of dextrose employed. Patients receiving peritoneal dialysis, particularly those with diabetes mellitus, are prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet, due to continuous removal of potassium and phosphorus—two major dietary components whose accumulation can be hazardous in ESRD.

LONG-TERM OUTCOMES IN ESRD

Cardiovascular disease constitutes the major cause of death in patients with ESRD. Cardiovascular mortality and event rates are higher in patients receiving dialysis than in patients posttransplantation, although rates are extraordinarily high in both populations. The underlying cause of cardiovascular disease is unclear but may be related to shared risk factors (e.g., diabetes mellitus, hypertension, atherosclerotic and arteriosclerotic vascular disease), chronic inflammation, massive changes in extracellular volume (especially with high interdialytic weight gains), inadequate treatment of hypertension, dyslipidemia, anemia, dystrophic (vascular) calcification, and, perhaps, alterations in cardiovascular dynamics during the dialysis treatment. Few studies have targeted cardiovascular risk reduction in ESRD patients; none have demonstrated consistent benefit. Two clinical trials of statin agents in ESRD demonstrated significant reductions in low-density lipoprotein (LDL) cholesterol concentrations but no significant reductions in death or cardiovascular events (Die Deutsche Diabetes Dialyse Studie [4D] and AURORA studies). The Study of Heart and Renal Protection (SHARP) which included patients on dialysis and others with nondialysis-requiring CKD showed a 17% reduction in the rate of major cardiovascular events or cardiovascular death with simvastatin-ezatamide treatment. Most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, inhibitors of the renin-angiotensin-aldosterone system, and β-adrenergic antagonists) in patients receiving dialysis based on the patients' cardiovascular risk profile, which appears to be increased by more than an order of magnitude relative to persons unaffected by kidney disease. Other complications of ESRD include a high incidence of infection, progressive debility and frailty, protein-energy malnutrition, and impaired cognitive function.

GLOBAL PERSPECTIVE

The incidence of ESRD is increasing worldwide with longer life expectancies and improved care of infectious and cardiovascular diseases. The management of ESRD varies widely by country and within country by region, and it is influenced by economic and other major factors. In general, peritoneal dialysis is more commonly performed in poorer countries owing to its lower expense and the high cost of establishing in-center hemodialysis units.

FURTHER READING

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307 Transplantation in the Treatment of Renal Failure

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Transplantation of the human kidney is the treatment of choice for advanced chronic renal failure. Worldwide, tens of thousands of these procedures have been performed with >180,000 patients bearing functioning kidney transplants in the United States today. When azathioprine and prednisone initially were used as immunosuppressive drugs in the 1960s, the results with properly matched familial donors were superior to those with organs from deceased donors: 75–90% compared with 50–60% graft survival rates at 1 year. During the 1970s and 1980s, the success rate at the 1-year mark for deceased-donor transplants rose progressively. Currently, deceased-donor grafts have a 92% 1-year survival and living-donor grafts have a 97% 1-year survival. Although there has been improvement in long-term survival, it has not been as impressive as the short-term survival, and currently the "average" ($t1/2$) life expectancy of a living-donor graft is around 14 years and that of a deceased-donor graft is close to 10 years.

Mortality rates after transplantation are highest in the first year and are age-related: 2% for ages 18–34 years, 3% for ages 35–49 years, and 6.8% for ages ≥50–60 years. These rates compare favorably with those in the chronic dialysis population even after risk adjustments for age, diabetes, and cardiovascular status. While the loss of kidney transplant due to acute rejection is currently rare, most allografts succumb at varying rates to a chronic process consisting of interstitial fibrosis, tubular atrophy, vasculopathy, and glomerulopathy, the pathogenesis of which is incompletely understood. Overall, transplantation returns most patients to an improved lifestyle and an improved life expectancy compared with patients on dialysis.

RECENT ACTIVITY AND RESULTS

In 2014 there were more than 12,328 deceased-donor kidney transplants and 5574 living-donor transplants in the United States, with the ratio of deceased to living donors remaining stable over the last few years. The backlog of patients with end-stage renal disease (ESRD) has been increasing every year, and it always lags behind the number of available donors. As the number of patients with end-stage kidney disease increases, the demand for kidney transplants continues to increase. As of 2015, there were 50,692 active adult candidates on the waiting list, and <18,000 patients were transplanted. This imbalance is set to worsen over the coming years with the predicted increased rates of obesity and diabetes worldwide. In an attempt to increase utilization of marginal kidneys while insuring longevity-matching, a new allocation system was developed and recently implemented. The main rule is that patients expected to survive the longest receive the allografts expected to last the longest. For this purpose, the Kidney Donor Profile Index (KDPI) score from 0 to 100% has been introduced to quantify the potential risk of graft failure after kidney transplant based on 10 donor factors. The lower KDPI values are associated with higher expected post-transplant survival. Hence, kidneys with KDPI <20% are allocated to the 20% of the potential recipients with the highest expected post-transplant survival. The kidneys with KDPI >85% (previously called expanded criteria donor or ECD kidneys) are usually used for older patients who are expected to fare less well on dialysis. Kidneys from donors after cardiac death (DCD) are also been used to overcome the increasing demand on the waiting list **(Table 307-1)**.

The overall results of transplantation are presented in **Table 307-2** as the survival of grafts and of patients. At the 1-year mark, graft survival is higher for living-donor recipients, most likely because those grafts are not subject to as much ischemic injury. The more effective drugs now in use for immunosuppression have almost equalized the risk of graft rejection in all patients for the first year. At 5 and 10 years, however, there has been a steeper decline in survival of those with deceased-donor kidneys.

TABLE 307-1 Definition of a Non-Heart-Beating Donor (Donation After Cardiac Death[a] [DCD])

I: Brought in dead
II: Unsuccessful resuscitation
III: Awaiting cardiac arrest
IV: Cardiac arrest after brainstem death
V: Cardiac arrest in a hospital patient

[a]Kidneys can be used for transplantation from categories II–V but are commonly only used from categories III and IV. The survival of these kidneys has not been shown to be inferior to that of deceased-donor kidneys.

Note: Kidneys can both have a KDPI >85 % and be DCD. High KDPI kidneys have been shown to have a poorer survival, and there is a separate shorter waiting list for those kidneys. They are generally utilized for patients for whom the benefits of being transplanted earlier outweigh the associated risks of using a lower quality kidney.

RECIPIENT SELECTION

There are few absolute contraindications to renal transplantation. The transplant procedure is relatively noninvasive, as the organ is generally placed in the inguinal fossa without entering the peritoneal cavity. Recipients without perioperative complications often can be discharged from the hospital in excellent condition within 5 days of the operation.

Virtually all patients with ESRD who receive a transplant have a higher life expectancy than do risk-matched patients who remain on dialysis. Even though diabetic patients and older candidates have a higher mortality rate than other transplant recipients, their survival is improved with transplantation compared with those remaining on dialysis. This global benefit of transplantation as a treatment modality poses substantial ethical issues for policy makers, as the number of deceased donor kidneys available is far from sufficient to meet the current needs of the candidates. The current standard of care is that the candidate should have a life expectancy of >5 years to be put on a deceased organ wait list. Even for living donation, the candidate should have >5 years of life expectancy. This standard has been established because the benefits of kidney transplantation over dialysis are realized only after a perioperative period in which the mortality rate is higher in transplanted patients than in dialysis patients with comparable risk profiles.

All candidates must have a thorough risk-versus-benefit evaluation before being approved for transplantation. In particular, an aggressive approach to diagnosis of correctable coronary artery disease, presence of latent or indolent infection (HIV, hepatitis B or C, tuberculosis), and neoplasm should be a routine part of the candidate workup. Most transplant centers consider overt AIDS and active hepatitis absolute contraindications to transplantation because of the high risk of opportunistic infection. Some centers are now transplanting individuals with hepatitis and even HIV infection under strict protocols to determine whether the risks and benefits favor transplantation over dialysis. Over the last few years, new direct acting hepatitis C antiviral medications have been introduced and have been shown to be very effective therapies both pre- and posttransplant. Those medications are reshaping our approach to patients with hepatitis C.

Among the few absolute "immunologic" contraindications to transplantation is the presence of antibodies against the donor kidney at the time of the anticipated transplant that can cause hyperacute rejection. Those harmful antibodies include natural antibodies against the ABO blood group antigens and antibodies against human leukocyte antigen (HLA) class I (A, B, C) or class II (DR, DQ, DP) antigens. These antibodies are routinely excluded by proper screening of the candidate's ABO compatibility and direct cytotoxic cross-matching of candidate serum with lymphocytes of the donor.

TISSUE TYPING AND CLINICAL IMMUNOGENETICS

Matching for antigens of the HLA major histocompatibility gene complex **(Chap. 343)** is an important criterion for selection of donors for renal allografts. Each mammalian species has a single chromosomal

TABLE 307-2 Mean Rates of Graft and Patient Survival for Kidneys Transplanted in the United States from 1998 to 2008[a]

	1-YEAR FOLLOW-UP		5-YEAR FOLLOW-UP		10-YEAR FOLLOW-UP	
	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %	GRAFTS, %	PATIENTS, %
Deceased donor	92	96	72	84	46	64
Living donor	96	99	81	91	59	77

[a]All patients transplanted are included, and the follow-up unadjusted survival data from the 1-, 5- , and 10-year periods are presented to show the attrition rates over time within the two types of organ donors.

Source: Data from Summary Tables, 2009 Annual Reports, Scientific Registry of Transplant Recipients.

region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other "minor" antigens may play crucial roles, in addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region that encodes major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are, therefore, suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment.

DONOR SELECTION

Donors can be deceased or volunteer living donors. When first-degree relatives are donors, graft survival rates at 1 year are 5–7% greater than those for deceased-donor grafts. The 5-year survival rates still favor a partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor. In addition, living donors provide the advantage of immediate availability. For both living and deceased donors, the 5-year outcomes are somewhat poorer if there is a complete (6/6) HLA mismatch.

The survival rate of living unrelated renal allografts is as high as that of perfectly HLA-matched cadaver renal transplants and comparable to that of kidneys from living relatives. This outcome is probably a consequence of both short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation. It is illegal in the United States to purchase organs for transplantation.

Living volunteer donors should be cleared of any medical conditions that may cause morbidity and mortality after kidney transplantation. Concern has been expressed about the potential risk to a volunteer kidney donor of premature renal failure after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet cell antibodies should be measured, and glucose tolerance tests should be performed in such donors to exclude a prediabetic state. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries, because the surgical procedure is difficult, and the ischemic time of the transplanted kidney is long when there are vascular abnormalities. Transplant surgeons commonly use a laparoscopic approach to isolate and remove the living donor's kidney. This operation has the advantage of less evident surgical scars, and, as there is less tissue trauma, laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who undergo an open nephrectomy.

Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV owing to possible transmission to the recipient, although under certain circumstances hepatitis C- and HIV-positive organs may be used in previously infected recipients. Increased risk of graft failure exists when the donor is elderly or has acute renal failure or when the kidney has a prolonged period of ischemia.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove deceased-donor kidneys and maintain them for up to 48 h on cold pulsatile perfusion or with simple flushing and cooling. Although generally an ischemic time of <24 h is preferred, this approach permits adequate time for typing, cross-matching, transportation, and selection problems to be solved.

PRESENSITIZATION

A positive cytotoxic cross-match of recipient serum with donor T lymphocytes indicates the presence of pre-formed donor specific anti-HLA class I antibodies and is usually predictive of an acute vasculitic event termed *hyperacute rejection*. This finding, along with ABO incompatibility, represents the only absolute immunologic contraindication for kidney transplantation. Recently, an increasing number of tissue typing laboratories have shifted to a flow cytometric-based crossmatch assay, which detects the presence of anti HLA antibodies that are not necessarily detected on a cytotoxic crossmatch assay and may not be an absolute contraindication to transplantation. The known sources of such sensitization are blood transfusion, a prior transplant, pregnancy, and vaccination/infection. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross-matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross-matches are performed accordingly. Flow cytometry detects binding of anti-HLA antibodies of candidate serum by recipient's lymphocytes. This highly sensitive test can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants.

For the purposes of crossmatching, donor T lymphocytes, which express class I but not class II antigens, are used as targets for detection of anti–class I (HLA-A and -B) antibodies that are expressed on all nucleated cells. Preformed anti–class II (HLA-DR and -DQ) antibodies against the donor also carry a higher risk of graft loss, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes, which express both class I and class II antigens, are used as targets in these assays. Furthermore, donor-specific HLA antibodies that fix complements have been shown to strongly correlate with antibody mediated rejection and worse long-term outcome.

Some non-HLA antigens restricted in expression to endothelium and monocytes have been described, but their clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these antigens is detectable only by cytotoxic T cells, an assay too cumbersome for routine use.

Desensitization before transplantation by reducing the level of anti-donor antibodies utilizing plasmapheresis and administration of pooled immunoglobulin, or both, has been useful in reducing the risk of hyperacute rejection following transplantation.

IMMUNOLOGY OF REJECTION

Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing proinflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct contact and

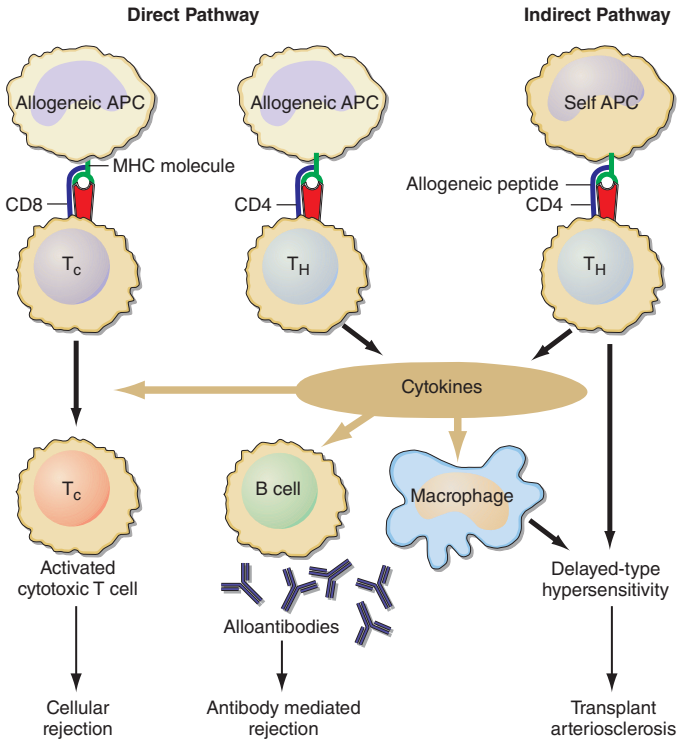

FIGURE 307-1 Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (TH) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, in contrast to other immunologic responses, there are two sets of T cell clones involved in rejection. In the direct pathway the class II MHC of donor allogeneic APCs is recognized by CD4 TH cells that bind to the intact MHC molecule, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells (TC). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T cell recognition of foreign antigens. Once TH cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, TC, and B cells. *(From MH Sayegh, LH Turka: N Engl J Med, 338:1813, 1998. Copyright 1998, Massachusetts Medical Society. All rights reserved.)*

lysis of donor target cells. Full T cell activation requires not only T cell receptor binding to the allo-antigens presented by self or donor HLA molecules (indirect and direct presentation respectively), but also engaging costimulatory molecules such as CD28 on T cells and CD80 and CD86 ligands on antigen presenting cells (Fig. 307-1). Signaling through both of these pathways induces activation of the kinase activity of calcineurin which, in turn, activates transcription factors leading to upregulation of multiple genes, including interleukin-2 (IL-2) and interferon gamma. IL-2 signals through the target of rapamycin (TOR) to induce cell proliferation in an autocrine fashion. There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, whereas identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, which can act as targets of humoral or cellular rejection responses, respectively.

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppressive therapy, as currently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are classically divided into induction and maintenance agents, and will be discussed in the following paragraphs. Those currently in clinical use are listed in Table 307-3.

INDUCTION THERAPY

Induction therapy is currently given to most kidney transplant recipients in the United States at the time of transplant to reduce the risk of early acute rejection and to minimize or eliminate the use of either steroids or calcineurin inhibitors and their associated toxicities. Induction therapy consists of antibodies that could be monoclonal or polyclonal, depletional or nondepletional.

Depleting Agents Anti-thymocyte globulin (ATG): peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas are injected into horses, rabbits, or goats to produce anti-lymphocyte serum, from which the globulin fraction is then separated. Those polyclonal antibodies induce lymphocyte depletion, and the immune system may take several months to recover.

Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. Alemtuzumab is directed to the CD52 protein, widely distributed on immune cells such as B and T cells, natural killer cells, macrophages, and some granulocytes.

Nondepleting Agents Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on T cells that have been recently activated. This approach is used as prophylaxis for acute rejection in the immediate

TABLE 307-3 Maintenance Immunosuppressive Drugs

AGENT	PHARMACOLOGY	MECHANISMS	SIDE EFFECTS
Glucocorticoids	Increased bioavailability with hypoalbuminemia and liver disease; prednisone/prednisolone generally used	Binds cytosolic receptors and heat shock proteins. Blocks transcription of IL-1, -2, -3, -6, TNF-α, and IFN-γ	Hypertension, glucose intolerance, dyslipidemia, osteoporosis
Cyclosporine (CsA)	Lipid-soluble polypeptide, variable absorption, microemulsion more predictable	Trimolecular complex with cyclophilin and calcineurin → block in cytokine (e.g., IL-2) production; however, stimulates TGF-β production	Nephrotoxicity, hypertension, dyslipidemia, glucose intolerance, hirsutism/hyperplasia of gums
Tacrolimus	Macrolide, well absorbed	Trimolecular complex with FKBP-12 and calcineurin → block in cytokine (e.g., IL-2) production; may stimulate TGF-β production	Similar to CsA, but hirsutism/hyperplasia of gums unusual, and diabetes more likely
Azathioprine	Mercaptopurine analogue	Hepatic metabolites inhibit purine synthesis	Marrow suppression (WBC > RBC > platelets)
Mycophenolate mofetil/sodium	Metabolized to mycophenolic acid	Inhibits purine synthesis via inosine monophosphate dehydrogenase	Diarrhea/cramps; dose-related liver and marrow suppression is uncommon
Sirolimus/Everolimus	Macrolide, poor oral bioavailability	Complexes with FKBP-12 and then blocks p70 S6 kinase in the IL-2 receptor pathway for proliferation	Hyperlipidemia, thrombocytopenia
Belatacept	Fusion protein, intravenous injections	Binds CD80 and CD86, prevents CD28 binding and T cell activation	Posttransplant Lymphoproliferative Disease (PTLD)

Abbreviations: FKBP-12, FK506 binding protein 12; IFN, interferon; IL, interleukin; RBC, red blood cells; TGF, transforming growth factor; TNF, tumor necrosis factor; WBC, white blood cells.

posttransplant period, and is effective at decreasing the early acute rejection rate with few adverse side effects.

The next step in the evolution of this therapeutic strategy, which has already been achieved in the short term in small numbers of immunologically well-matched patients, is the elimination of all maintenance immunosuppression therapy.

MAINTENANCE THERAPY

All kidney transplant recipients should receive maintenance immunosuppressive therapies except identical twins. The most frequently used combination is triple therapy with prednisone, a calcineurin inhibitor, and an antimetabolite; mTOR inhibitors can replace one of the last two agents. More recently, the FDA approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term CNI toxicity.

Antimetabolites *Azathioprine*, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans, but has given way to more effective agents. This agent can inhibit synthesis of DNA, RNA, or both. Azathioprine is administered in doses of 1.5–2 mg/kg per day. Reduction in the dose is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced. As inhibition of xanthine oxidase delays degradation, this combination is best avoided.

Mycophenolate mofetil or mycophenolate sodium, both of which are metabolized to mycophenolic acid, is now used in place of azathioprine in most centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces less bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection.

Steroids *Glucocorticoids* are important adjuncts to immunosuppressive therapy. Among all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200–300 mg prednisone is given immediately before or at the time of transplantation, and the dose is reduced to 30 mg within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Many centers now have protocols for early discontinuance or avoidance of steroids because of long-term adverse effects on bone, skin, and glucose metabolism. For treatment of acute rejection, methylprednisolone, 0.5–1 g IV, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year do not require large doses of prednisone; maintenance doses of 5–10 mg/d are the rule. A major effect of steroids is preventing the release of interleukin (IL) 6 and IL-1 by monocytes-macrophages.

Calcineurin Inhibitors *Cyclosporine* is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids and mycophenolate. Clinical results with tens of thousands of renal transplants have been impressive. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia, and diabetes), only nephrotoxicity presents a serious management problem and is further discussed below.

Tacrolimus (previously called FK506) is a fungal macrolide that has the same mode of action as cyclosporine as well as a similar side-effect profile; it does not, however, produce hirsutism or gingival hyperplasia. De novo diabetes mellitus is more common with tacrolimus. The drug was first used in liver transplantation and may substitute for cyclosporine entirely or as an alternative in renal patients whose rejections are poorly controlled by cyclosporine. An extended release formulation of tacrolimus is now available and is given once daily.

TOR Inhibitors *Sirolimus* (previously called rapamycin) is another fungal macrolide but has a different mode of action; i.e., it inhibits T cell growth factor signaling pathways, preventing the response to IL-2 and other cytokines. Sirolimus can be used in conjunction with cyclosporine or tacrolimus, or with mycophenolic acid, to avoid the use of calcineurin inhibitors.

Everolimus is another mTOR inhibitor with similar mechanism of action as *Sirolimus* but with better bioavailability.

Belatacept *Belatacept* is a fusion protein that binds costimulatory ligands (CD80 and CD86) present on antigen presenting cells, interrupting their binding to CD28 on T cells. This inhibition leads to T cell anergy and apoptosis. Belatacept is FDA-approved for kidney transplant recipients and is given monthly as an intravenous infusion. The 7 years follow-up of the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) showed higher patient and graft survival for the belatacept treated group compared to cyclosporine.

CLINICAL COURSE AND MANAGEMENT OF THE RECIPIENT

Adequate hemodialysis should be performed within 48 h of surgery as necessary, and care should be taken that the serum potassium level is not markedly elevated so that intraoperative cardiac arrhythmias can be averted. The diuresis that commonly occurs postoperatively must be carefully monitored. In some instances, it may be massive, reflecting the inability of ischemic tubules to regulate sodium and water excretion; with large diureses, large amounts of potassium may be lost. Most chronically uremic patients have some excess of extracellular fluid, and it is useful to maintain an expanded fluid volume in the immediate postoperative period. Acute tubular necrosis (ATN) due to ischemia may cause immediate oliguria or may follow an initial short period of graft function. Recovery usually occurs within 3 weeks, although periods as long as 6 weeks have been reported. Superimposition of rejection on ATN is common, and the differential diagnosis may be difficult without a graft biopsy. Cyclosporine therapy prolongs ATN, and some patients do not diurese until the dose is reduced drastically. Many centers avoid starting calcinenrins for the first several days, using ALG or a monoclonal antibody along with mycophenolic acid and prednisone until renal function is established. **Figure 307-2** illustrates an algorithm followed by many transplant centers for early posttransplant management of recipients at high or low risk of early renal dysfunction.

THE REJECTION EPISODE

Early diagnosis of rejection allows prompt institution of therapy to preserve renal function and prevent irreversible damage. Clinical evidence of rejection is rarely characterized by fever, swelling, and tenderness over the allograft. Rejection may present only with a rise in serum creatinine, with or without a reduction in urine volume. The focus should be on ruling out other causes of functional deterioration.

Doppler ultrasonography may be useful in ascertaining changes in the renal vasculature and in renal blood flow. Thrombosis of the renal vein occurs rarely; it may be reversible if it is caused by technical factors and intervention is prompt. Diagnostic ultrasound is the procedure of choice to rule out urinary obstruction or to confirm the presence of perirenal collections of urine, blood, or lymph. A rise in the serum creatinine level is a late marker of rejection, but it may be the only sign. Novel biomarkers are needed for early noninvasive detection of allograft rejection.

Calcineurin inhibitors (cyclosporine and tacrolimus) have an afferent arteriolar constrictor effect on the kidney, and may produce permanent vascular and interstitial injury after sustained high-dose therapy. This action will lead to a deterioration in renal function difficult to distinguish from rejection without a renal biopsy. Interstitial fibrosis, isometric tubular vacuolization, and thickening of arteriolar walls are suggestive of this side effect, but not diagnostic. Hence, if no rejection is detected on the biopsy, serum creatinine may respond to a reduction in dose. However, if cellular rejection activity is present in the biopsy, appropriate therapy is indicated. The first rejection episode is usually treated with IV administration of methylprednisolone, 500–1000 mg daily for 3 days. Failure to respond is an indication for antibody therapy, usually with antithymocyte globulin.

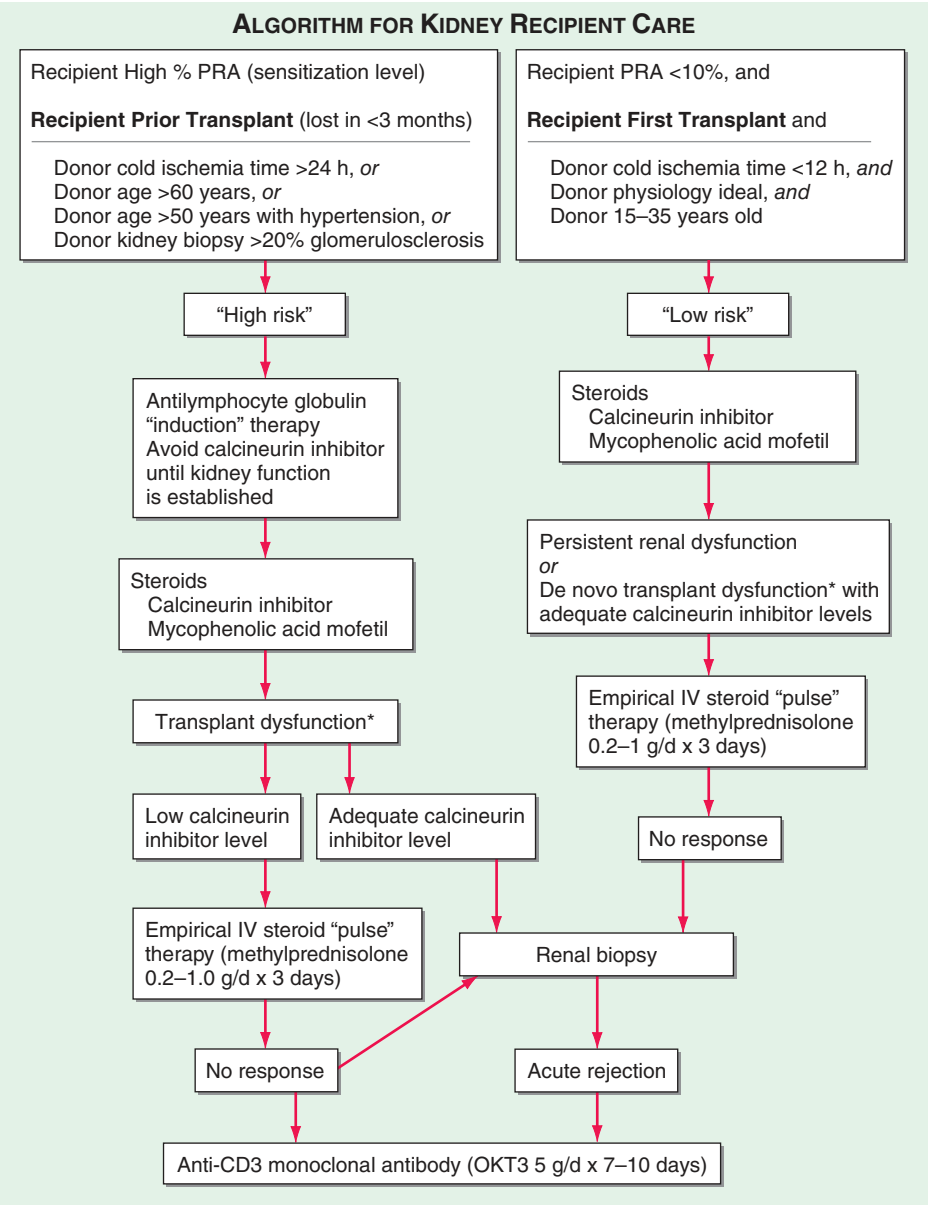

FIGURE 307-2 A typical algorithm for early posttransplant care of a kidney recipient. If any of the recipient or donor "high-risk" factors exist, more aggressive management is called for. Low-risk patients can be treated with a standard immunosuppressive regimen. Patients at higher risk of rejection or early ischemic and nephrotoxic transplant dysfunction are often induced with an antilymphocyte globulin to provide more potent early immunosuppression or to spare calcineurin nephrotoxicity. *When there is early transplant dysfunction, prerenal, obstructive, and vascular causes must be ruled out by ultrasonographic examination. The panel reactive antibody (PRA) is a quantitation of how much antibody is present in a candidate against a panel of cells representing the distribution of antigens in the donor pool. APC, antigen-presenting cell; MHC, major histocompatibility complex.

Evidence of antibody-mediated injury is present when endothelial injury and deposition of complement component c4d is detected by fluorescence labeling. This is usually accompanied by detection of the antibody in the recipient blood. The prognosis is poor, and aggressive use of plasmapheresis, immunoglobulin infusions, anti-CD20 monoclonal antibody (rituximab) to target B lymphocytes, bortezomib to target antibody producing plasma cells, and eculizumab to inhibit complement is indicated.

MANAGEMENT PROBLEMS

The typical times after transplantation when the most common opportunistic infections occur are shown in Table 307-4. Prophylaxis for cytomegalovirus (CMV) and Pneumocystis *Jirovecci* pneumonia is given for 6–12 months after transplantation.

The signs and symptoms of infection may be masked or distorted. Fever without obvious cause is common, and only after days or weeks may it become apparent that it has a viral or fungal origin. Bacterial infections are most common during the first month after transplantation. The importance of blood cultures in such patients cannot be overemphasized because systemic infection without obvious foci is common. Particularly ominous are rapidly occurring pulmonary lesions, which may result in death within 5 days of onset. When these lesions become apparent, immunosuppressive agents should be discontinued, except for maintenance doses of prednisone.

Aggressive diagnostic procedures, including transbronchial and open-lung biopsy, are frequently indicated. In the case of *Pneumocystis carinii* (Chap. 215) infection, trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice; amphotericin B has been used effectively in systemic fungal infections. Prophylaxis against *P. jirovecci* with daily or alternate-day low-dose TMP-SMX is very effective. Involvement of the oropharynx with *Candida* (Chap. 211) may be treated with local nystatin. Tissue-invasive fungal infections require treatment with systemic agents such as fluconazole. Small doses (a total of 300 mg) of amphotericin given over a period of 2 weeks may be effective in fungal infections refractory to fluconazole. Macrolide antibiotics, especially ketoconazole and erythromycin, and some calcium channel blockers (diltiazem, verapamil) compete with calcineurin inhibitors for P450 catabolism and cause elevated levels of these immunosuppressive drugs. Analeptics, such as phenytoin and carbamazepine, will increase catabolism to result in low levels. *Aspergillus* (Chap. 212), *Nocardia* (Chap. 169), and especially CMV (Chap. 190) infections also occur.

CMV is a common and dangerous DNA virus in transplant recipients. It does not generally appear until the end of the first posttransplant month. Active CMV infection is sometimes associated, or occasionally confused, with rejection episodes. Patients at highest risk for severe CMV disease are those without anti-CMV antibodies who receive a graft from a CMV antibody–positive donor (15% mortality). Valganciclovir is a cost-effective and bioavailable oral form of ganciclovir that has been proved effective in both prophylaxis and treatment of CMV disease.

TABLE 307-4 The Most Common Opportunistic Infections in Renal Transplant Recipients

Peritransplant (<1 month)	Late (>6 months)
Wound infections	*Aspergillus*
Herpesvirus	*Nocardia*
Oral candidiasis	BK virus (polyoma)
Urinary tract infection	Herpes zoster
Early (1–6 months)	Hepatitis B
Pneumocystis carinii	Hepatitis C
Cytomegalovirus	
Legionella	
Listeria	
Hepatitis B	
Hepatitis C	

Early diagnosis in a febrile patient with clinical suspicion of CMV disease can be made by determining CMV viral load in the blood. A rise in IgM antibodies to CMV is also diagnostic. Culture of CMV from blood may be less sensitive. Tissue invasion of CMV is common in the gastrointestinal tract and lungs. CMV retinopathy occurs late in the course, if untreated. Treatment of active CMV disease with valganciclovir is always indicated. In many patients immune to CMV, viral activation can occur with major immunosuppressive regimens.

The polyoma group (BK, JC, SV40) is another class of DNA viruses that can become dormant in kidneys and can be activated by immunosuppression. When reactivation occurs with BK, if left untreated, there is a 50% chance of progressive fibrosis and loss of the graft within 1 year by the activated virus. Risk of infection is associated with the overall degree of immunosuppression rather than the individual immunosuppressive drugs used. Renal biopsy is necessary for the diagnosis. There have been variable results with leflunomide, cidofovir, and quinolone anitibiotics (which are effective against polyoma helicase), but it is most important to reduce the immunosuppressive load.

The complications of glucocorticoid therapy are well known and include gastrointestinal bleeding, impairment of wound healing, osteoporosis, diabetes mellitus, cataract formation, and hemorrhagic pancreatitis. The treatment of unexplained jaundice in transplant patients should include cessation or reduction of immunosuppressive drugs if hepatitis or drug toxicity is suspected. Therapy in such circumstances often does not result in rejection of a graft, at least for several weeks. Acyclovir is effective in therapy for herpes simplex virus infections.

CHRONIC LESIONS OF THE TRANSPLANTED KIDNEY

Although 1-year transplant survival is excellent, most recipients experience progressive decline in kidney function over time thereafter. Chronic renal transplant dysfunction can be caused by recurrent disease, hypertension, cyclosporine or tacrolimus nephrotoxicity, chronic immunologic rejection, secondary focal glomerulosclerosis, or a combination of these pathophysiologies. Chronic vascular changes with intimal proliferation and medial hypertrophy are commonly found. Control of systemic and intrarenal hypertension with ACE inhibitors is thought to have a beneficial influence on the rate of progression of chronic renal transplant dysfunction. Renal biopsy can distinguish subacute cellular rejection from recurrent disease or secondary focal sclerosis.

MALIGNANCY

The incidence of tumors in patients on immunosuppressive therapy is 5–6%, or ~100 times greater than that in the general population in the same age range. The most common lesions are cancer of the skin and lips and carcinoma in situ of the cervix, as well as lymphomas such as non-Hodgkin's lymphoma. The risks are increased in proportion to the total immunosuppressive load administered and the time elapsed since transplantation. Surveillance for skin and cervical cancers is necessary.

OTHER COMPLICATIONS

Both chronic dialysis and renal transplant patients have a higher incidence of death from myocardial infarction and stroke than does the population at large, and this is particularly true in diabetic patients. Contributing factors are the use of glucocorticoids and sirolimus, as well as hypertension. Recipients of renal transplants have a high prevalence of coronary artery and peripheral vascular diseases. The percentage of deaths from these causes has been slowly rising as the numbers of transplanted diabetic patients and the average age of all recipients increase. More than 50% of renal recipient mortality is attributable to cardiovascular disease. In addition to strict control of blood pressure and blood lipid levels, close monitoring of patients for indications of further medical or surgical intervention is an important part of management.

Hypertension may be caused by (1) native kidney disease, (2) rejection activity in the transplant, (3) renal artery stenosis if an end-to-end anastomosis was constructed with an iliac artery branch, and (4) renal calcineurin inhibitor toxicity, which may improve with reduction in dose. Whereas ACE inhibitors may be useful, calcium channel blockers are more frequently used initially. Amelioration of hypertension to the range of 120–130/70–80 mmHg should be the goal in all patients.

Hypercalcemia after transplantation may indicate failure of hyperplastic parathyroid glands to regress. Aseptic necrosis of the head of the femur is probably due to preexisting hyperparathyroidism, with aggravation by glucocorticoid treatment. With improved management of calcium and phosphorus metabolism during chronic dialysis, the incidence of parathyroid-related complications has fallen dramatically. Persistent hyperparathyroid activity may require subtotal parathyroidectomy.

Although most transplant patients have robust production of erythropoietin and normalization of hemoglobin, *anemia* is commonly seen in the posttransplant period. Often the anemia is attributable to bone marrow–suppressant immunosuppressive medications such as azathioprine, mycophenolic acid, and sirolimus. Gastrointestinal bleeding is a common side effect of high-dose and long-term steroid administration. Many transplant patients have creatinine clearances of 30–50 mL/min and can be considered in the same way as other patients with chronic renal insufficiency for anemia management, including supplemental erythropoietin.

Chronic hepatitis, particularly when due to hepatitis B virus, can be a progressive, fatal disease over a decade or so. Patients who are persistently hepatitis B surface antigen–positive are at higher risk, according to some studies, but the presence of hepatitis C virus is also a concern when one embarks on a course of immunosuppression in a transplant recipient. However, the introduction of the new highly effective direct acting hepatitis C antiviral medications promises to reduce this risk significantly.

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308 Glomerular Diseases

Julia B. Lewis, Eric G. Neilson

Two human kidneys harbor nearly 1.8 million glomerular capillary tufts. Each glomerular tuft resides within Bowman's space. The capsule circumscribing this space is lined by parietal epithelial cells that transition into tubular epithelia forming the proximal nephron or migrate into the tuft to replenish podocytes. The glomerular capillary tuft derives from an afferent arteriole that forms a branching capillary bed embedded in mesangial matrix **(Fig. 308-1)**. This capillary network funnels into an efferent arteriole, which passes filtered blood into cortical peritubular capillaries or medullary vasa recta that supply and exchange with a folded tubular architecture. Hence the glomerular capillary tuft, fed and drained by arterioles, represents an arteriolar portal system. Fenestrated endothelial cells resting on a glomerular basement membrane (GBM) line glomerular capillaries. Delicate foot processes extending from epithelial podocytes shroud the outer surface of these capillaries, and adjacent podocytes interconnect to each other by slit-pore membranes forming a selective filtration barrier.

The glomerular capillaries filter 120–180 L/d of plasma water containing various solutes for reclamation or discharge by downstream tubules. Most large proteins and all cells are excluded from filtration by a physicochemical barrier governed by pore size and negative electrostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes **(Chap. 303)**. For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albumin has a negative charge, which would tend to repel the negatively charged GBM, it only has a physical radius of 3.6 nm, while pores in the GBM and slit-pore membranes have a radius of 4 nm. Consequently, variable amounts of albumin inevitably cross the filtration barrier to be reclaimed by megalin and cubilin receptors along the proximal tubule. Remarkably, humans with normal nephrons excrete on average 8–10 mg of albumin in daily voided urine, ~20–60% of total excreted protein. This amount of albumin, and other proteins, can rise to gram quantities following glomerular injury.

The breadth of diseases affecting the glomerulus is expansive because the microenvironment supporting the glomerular capillaries can be injured in a variety of ways, producing many different lesions. Some order to this vast subject is brought by grouping all of these diseases into a smaller number of clinical syndromes.

PATHOGENESIS OF GLOMERULAR DISEASE

There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called *idiopathic*. Specific or unique features of pathogenesis are mentioned with the description of each of the glomerular diseases later in this chapter.

Some glomerular diseases result from genetic mutations producing familial disease or a founder effect: congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations produce *focal segmental glomerulosclerosis* (*FSGS*) in adulthood; polymorphisms in the gene encoding apolipoprotein L1, *APOL1*, are a major risk for nearly 70% of African Americans with nondiabetic end-stage renal disease (ESRD), particularly FSGS; mutations in complement factor H associate with *membranoproliferative glomerulonephritis* (*MPGN*), C_3 glomerulopathies, or *atypical hemolytic uremic syndrome* (*aHUS*), type II partial lipodystrophy from mutations in genes encoding lamin A/C, or PPARγ cause a metabolic syndrome associated with MPGN, or C_3 glomerulopathies, which is sometimes accompanied by dense deposits and C3 nephritic factor; Alport's syndrome, from mutations in the genes encoding for the α3, α4, or α5 chains of type IV collagen, produces *split-basement membranes* with *glomerulosclerosis*; and lysosomal storage diseases, such as α-galactosidase A deficiency causing Fabry's disease and *N* acetylneuraminic acid hydrolase deficiency causing nephrosialidosis, produce FSGS.

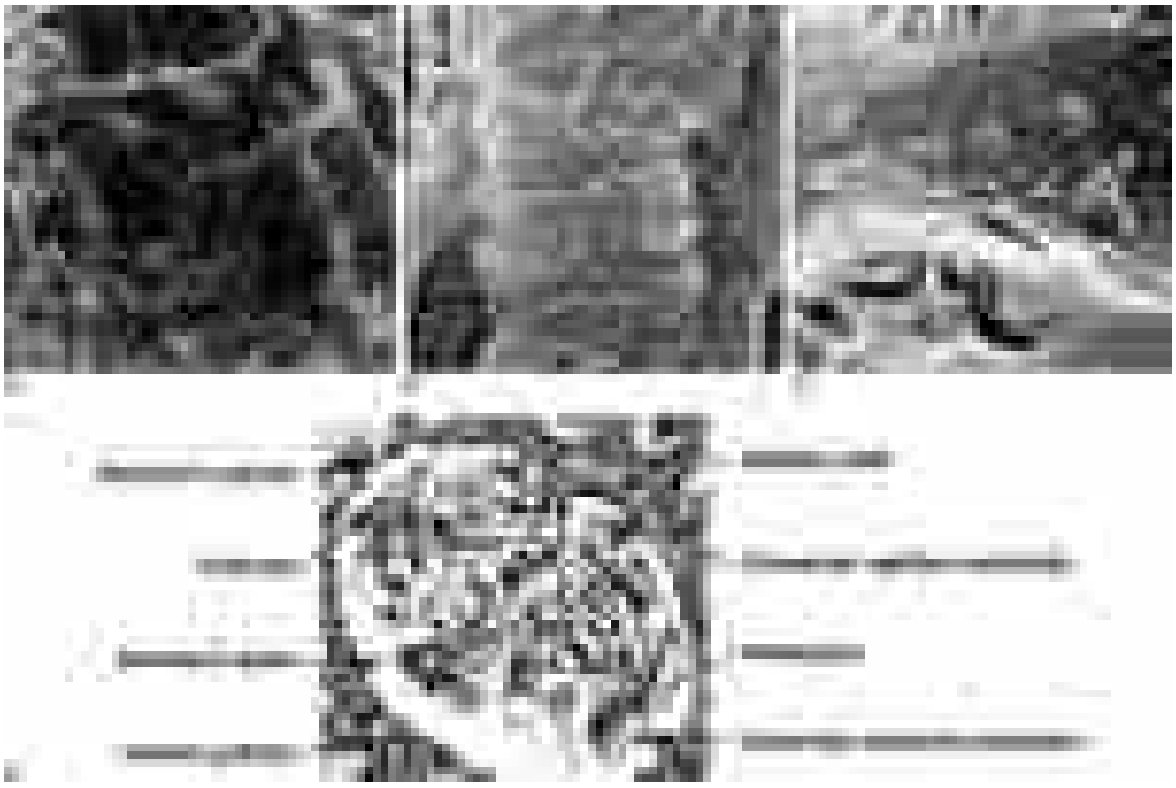


FIGURE 308-1 Glomerular architecture. ***A.*** The glomerular capillaries form from a branching network of renal arteries, arterioles, leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. *(From VH Gattone II et al: Hypertension 5:8, 1983.)* ***B.*** Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries (*arrow* shows foot process). ***C.*** Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary. ***D.*** The various normal regions of the glomerulus on light microscopy. *(A–C: Courtesy of Dr. Vincent Gattone, Indiana University; with permission.)*

Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to *chronic glomerulosclerosis*. *Malignant hypertension* can quickly complicate glomerulosclerosis with fibrinoid necrosis of arterioles and glomeruli, thrombotic microangiopathy, and acute renal failure. *Diabetic nephropathy* is an acquired sclerotic injury associated with thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end products, and reactive oxygen species.

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are unknown **(Fig. 308-2)**. Glomerular epithelial or mesangial cells may shed or express epitopes that mimic other immunogenic proteins made elsewhere in the body. Bacteria, fungi, and viruses can directly infect the kidney producing their own antigens. Autoimmune diseases like idiopathic *membranous glomerulonephritis* (*MGN*) or MPGN are confined to the kidney, whereas systemic inflammatory diseases like *lupus nephritis* or *granulomatosis with polyangiitis* spread to the kidney, causing secondary glomerular injury. *Antiglomerular basement membrane disease* producing Goodpasture's syndrome primarily injures both the lung and kidney because of the narrow distribution of the α3 NC1 domain of type IV collagen that is the target antigen.

Local activation of Toll-like receptors on glomerular cells, deposition of immune complexes, or complement injury to glomerular structures induces mononuclear cell infiltration, which subsequently leads to an adaptive immune response attracted to the kidney by local release of chemokines. Neutrophils, macrophages, and T cells are drawn by chemokines into the glomerular tuft, where they react with antigens and epitopes on or near somatic cells or their structures, producing more cytokines and proteases that damage the mesangium, capillaries, and/or the GBM. While the adaptive immune response is similar to that of other tissues, early T cell activation plays an important role in the mechanism of glomerulonephritis. Antigens presented by class II major histocompatibility complex (MHC) molecules on macrophages

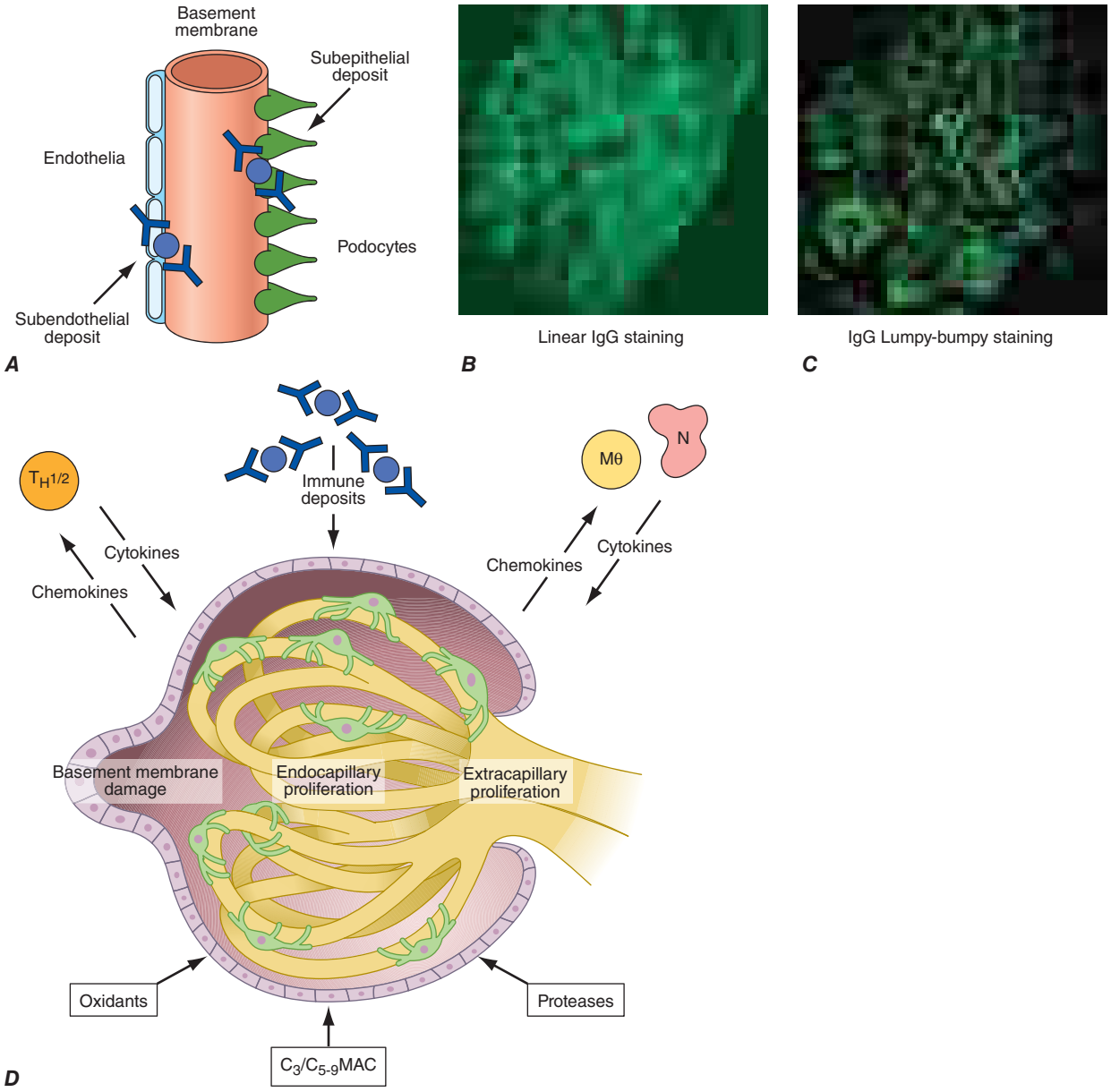


FIGURE 308-2 The glomerulus is injured by a variety of mechanisms. ***A.*** Preformed immune deposits can precipitate from the circulation and collect along the glomerular basement membrane (GBM) in the subendothelial space or can form in situ along the subepithelial space. ***B.*** Immunofluorescent staining of glomeruli with labeled anti-IgG demonstrating linear staining from a patient with anti-GBM disease or immune deposits from a patient with membranous glomerulonephritis. ***C.*** The mechanisms of glomerular injury have a complicated pathogenesis. Immune deposits and complement deposition classically draw macrophages and neutrophils into the glomerulus. T lymphocytes may follow to participate in the injury pattern as well. ***D.*** Amplification mediators as locally derived oxidants and proteases expand this inflammation, and, depending on the location of the target antigen and the genetic polymorphisms of the host, basement membranes are damaged with either endocapillary or extracapillary proliferation.

and dendritic cells in conjunction with associative recognition molecules engage the CD4/8 T cell repertoire.

Mononuclear cells by themselves can injure the kidney, but autoimmune events that damage glomeruli classically produce a humoral immune response. *Poststreptococcal glomerulonephritis, lupus nephritis,* and idiopathic *membranous nephritis* typically are associated with immune deposits along the GBM, while anti-GBM antibodies produce the linear binding of anti-GBM disease. Preformed circulating immune complexes can precipitate along the subendothelial side of the GBM, while other immune deposits form in situ on the subepithelial side. These latter deposits accumulate when circulating autoantibodies find their antigen trapped along the subepithelial edge of the GBM. Immune deposits in the glomerular mesangium may result from the deposition of preformed circulating complexes or in situ antigen-antibody interactions. Immune deposits stimulate the release of local proteases and activate the complement cascade, producing C_{5-9} attack complexes. In addition, local oxidants damage glomerular structures, producing proteinuria and effacement of the podocytes. Overlapping etiologies or pathophysiologic mechanisms can produce similar glomerular lesions, suggesting that downstream molecular and cellular responses often converge toward common patterns of injury.

PROGRESSION OF GLOMERULAR DISEASE

Persistent glomerulonephritis that worsens renal function is always accompanied by interstitial nephritis, renal fibrosis, and tubular atrophy **(see Fig. A3-27)**. What is not so obvious, however, is that renal failure in glomerulonephritis best correlates histologically with the appearance of tubulointerstitial nephritis rather than with the type of inciting glomerular injury.

Loss of renal function due to interstitial damage is explained hypothetically by several mechanisms. The simplest explanation is that urine flow is impeded by tubular obstruction as a result of interstitial inflammation and fibrosis. Thus, obstruction of the tubules with debris or by extrinsic compression functionally results in aglomerular nephrons. A second mechanism suggests that interstitial changes, including interstitial edema or fibrosis, alter tubular and vascular architecture and thereby compromise the normal tubular transport of solutes and water from tubular lumen to vascular space. This failure increases the solute and water content of the tubule fluid, resulting in isosthenuria and polyuria. Adaptive mechanisms related to tubuloglomerular feedback also fail, resulting in a reduction of renin output from the juxtaglomerular apparatus trapped by interstitial inflammation. Consequently, the local vasoconstrictive influence of angiotensin II on the glomerular arterioles decreases, and filtration drops owing to a generalized decrease in arteriolar tone. A third mechanism involves changes in vascular resistance due to damage of peritubular capillaries. The cross-sectional volume of these capillaries is decreased by interstitial inflammation, edema, or fibrosis. These structural alterations in vascular resistance affect renal function through two mechanisms. First, tubular cells are very metabolically active, and, as a result, decreased perfusion leads to tubular ischemic injury. Second, impairment of glomerular arteriolar outflow leads to increased intravascular hypertension in less-involved glomeruli; this selective intraglomerular hypertension aggravates and extends *mesangial sclerosis* and *glomerulosclerosis* to less-involved glomeruli. Regardless of the exact mechanism, early *acute tubulointerstitial nephritis* **(see Fig. A3-27)** suggests potentially recoverable renal function, whereas the development of *chronic interstitial fibrosis* prognosticates permanent loss **(see Fig. A3-30)**.

Persistent damage to glomerular capillaries spreads to the tubulointerstitium in association with proteinuria. There is a hypothesis that efferent arterioles leading from inflamed glomeruli carry forward inflammatory mediators, which induces downstream interstitial nephritis, resulting in fibrosis. Glomerular filtrate from injured glomerular capillaries adherent to Bowman's capsule may also be misdirected to the periglomerular interstitium. Most nephrologists believe, however, that proteinuric glomerular filtrate forming tubular fluid is the primary route to downstream tubulointerstitial injury, although none of these hypotheses are mutually exclusive.

The simplest explanation for the effect of proteinuria on the development of interstitial nephritis is that increasingly severe proteinuria, carrying activated cytokines and lipoproteins producing reactive oxygen species, triggers a downstream inflammatory cascade in and around epithelial cells lining the tubular nephron. These effects induce T lymphocyte and macrophage infiltrates in the interstitial spaces along with fibrosis and tubular atrophy.

Tubules disaggregate following direct damage to their basement membranes, leading to more interstitial fibroblasts and fibrosis at the site of injury; recent comprehensive evidence suggests that renal fibroblasts increase through several mechanisms: epithelial or endothelial-mesenchymal transitions (15%), bone marrow-derived fibrocytes (35%), and the proliferation of resident fibroblasts (50%). Transforming growth factor-β (TGF-β), fibroblast growth factor 2 (FGF-2), hypoxemia-inducible factor 1α (HIF-1α), and platelet-derived growth factor (PDGF) are particularly active in this transition. With persistent nephritis, fibroblasts multiply and lay down tenascin and a fibronectin scaffold for the polymerization of new interstitial collagen types I/III. These events form scar tissue through a process called fibrogenesis. In experimental studies, bone morphogenetic protein 7 and hepatocyte growth factor can reverse early fibrogenesis and preserve tubular architecture. When fibroblasts outdistance their survival factors, apoptosis occurs, and the permanent renal scar becomes acellular, leading to irreversible renal failure.

APPROACH TO THE PATIENT

Glomerular Disease

HEMATURIA, PROTEINURIA, AND PYURIA

Patients with glomerular disease usually have some hematuria with varying degrees of proteinuria. Hematuria is typically asymptomatic. As few as 3–5 red blood cells in the spun sediment from first-voided morning urine is suspicious. The diagnosis of glomerular injury can be delayed because patients will not realize they have *microscopic hematuria*, and only rarely with the exception of IgA nephropathy and sickle cell disease is *gross hematuria* present. When working up microscopic hematuria, perhaps accompanied by minimal proteinuria (<500 mg/24 h), it is important to exclude anatomic lesions, such as malignancy of the urinary tract, particularly in older men. Microscopic hematuria may also appear with the onset of benign prostatic hypertrophy, interstitial nephritis, papillary necrosis, hypercalciuria, renal stones, cystic kidney diseases, or renal vascular injury. However, when red blood cell casts **(see Fig. A3-34)** or dysmorphic red blood cells are found in the sediment, glomerulonephritis is likely. A mean of 8–10 mg/24 h of albumin appears in the urine in the absence of kidney disease. In early nephropathy, such as in diabetic nephropathy, proteinuria increases to 30–300 mg/24 h and is called microalbuminuria and represents the presence of renal disease. Greater than 300 mg/24 h of albuminuria represents frank proteinuria and more advanced renal disease **(Table 308-1)**.

TABLE 308-1 Urine Assays for Albuminuria/Proteinuria

	24-h ALBUMIN[a] (mg/24 h)	ALBUMIN[a]/CREATININE RATIO (mg/g)	DIPSTICK PROTEINURIA	24-h URINE PROTEIN[b] (mg/24 h)
Normal	8–10	<30	–	<150
Microalbuminuria	30–300	30–300	–/Trace/1+	–
Proteinuria	>300	>300	Trace–3+	>150

[a]Albumin detected by radioimmunoassay. [b]Albumin represents 20–60% of the total protein excreted in the urine.

Sustained proteinuria >1–2 g/24 h is also commonly associated with glomerular disease. Patients often will not know they have proteinuria unless they become edematous or notice foaming urine on voiding. *Sustained proteinuria* has to be distinguished from lesser amounts of so-called *benign proteinuria* in the normal population. (Table 308-1). This latter class of proteinuria is nonsustained, generally <1 g/24 h, and is sometimes called *functional* or *transient proteinuria*. Fever, exercise, obesity, sleep apnea, emotional stress, and congestive heart failure can explain transient proteinuria. Proteinuria only seen with upright posture is called *orthostatic proteinuria* and has a benign prognosis. Isolated proteinuria sustained over multiple clinic visits is found in many glomerular lesions. Proteinuria in most adults with glomerular disease is *nonselective*, containing albumin and a mixture of other serum proteins, whereas in children with *minimal change disease* (MCD), the proteinuria is *selective* and composed largely of albumin.

Some patients with inflammatory glomerular disease, such as acute poststreptococcal glomerulonephritis or MPGN, have *pyuria* characterized by the presence of considerable numbers of leukocytes. This latter finding has to be distinguished from urine infected with bacteria.

CLINICAL SYNDROMES

Various forms of glomerular injury can also be parsed into several distinct syndromes on clinical grounds **(Table 308-2)**. These syndromes, however, are not always mutually exclusive. There is an *acute nephritic syndrome* producing 1–2 g/24 h of proteinuria, hematuria with red blood cell casts, pyuria, hypertension, fluid retention, and a rise in serum creatinine associated with a reduction in glomerular filtration. If glomerular inflammation develops slowly, the serum creatinine will rise gradually over many weeks, but if the serum creatinine rises quickly, particularly over a few days, acute nephritis is sometimes called *rapidly progressive glomerulonephritis* (RPGN); the histopathologic term *crescentic glomerulonephritis* is the pathologic equivalent of the clinical presentation of RPGN. When patients with RPGN present with lung hemorrhage from Goodpasture's syndrome, antineutrophil cytoplasmic antibodies (ANCA)-associated small-vessel vasculitis, lupus erythematosus, or cryoglobulinemia, they are often diagnosed as having a *pulmonary-renal syndrome*. *Nephrotic syndrome* describes the onset of heavy proteinuria (>3.0 g/24 h), hypertension, hypercholesterolemia, hypoalbuminemia, edema/anasarca, and microscopic hematuria; if only large amounts of proteinuria are present without clinical manifestations,

TABLE 308-2 Patterns of Clinical Glomerulonephritis

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Acute Nephritic Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
Lupus nephritis[a]	+/++	++/+++	+
Antiglomerular basement membrane disease[a]	++	++/+++	–
IgA nephropathy[a]	+/++	+++[c]	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Membranoproliferative glomerulonephritis[a]	++	++/+++	–
C_3 Glomerulopathies	++	++/+++	-
Mesangioproliferative glomerulonephritis	+	+/++	–
Pulmonary-Renal Syndromes			
Goodpasture's syndrome[a]	++	++/+++	–
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+/++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
Nephrotic Syndromes			
Minimal change disease	++++	–	–
Focal segmental glomerulosclerosis	+++/++++	+	–
Membranous glomerulonephritis	++++	+	–
Diabetic nephropathy	++/++++	–/+	–
AL and AA amyloidosis	+++/++++	+	+/++
Light-chain deposition disease	+++	+	–
Fibrillary-immunotactoid disease	+++/++++	+	+
Fabry's disease	+	+	–
Basement Membrane Syndromes			
Anti-GBM disease[a]	++	++/+++	–
Alport's syndrome	++	++	–
Thin basement membrane disease	+	++	–
Nail-patella syndrome	++/+++	++	–

(*Continued*)

TABLE 308-2 Patterns of Clinical Glomerulonephritis (Continued)

GLOMERULAR SYNDROMES	PROTEINURIA	HEMATURIA	VASCULAR INJURY
Glomerular Vascular Syndromes			
Atherosclerotic nephropathy	+	+	+++
Hypertensive nephropathy[b]	+/++	+/++	++
Cholesterol emboli	+/++	++	+++
Sickle cell disease	+/++	+++[c]	+++
Thrombotic microangiopathies	++	++	+++
Antiphospholipid syndrome	++	++	+++
ANCA small-vessel vasculitis[a]			
Granulomatosis with polyangiitis (Wegener's)	+/++	++/+++	++++
Microscopic polyangiitis	+/++	++/+++	++++
Churg-Strauss syndrome	+++	++/+++	++++
Henoch-Schönlein purpura[a]	+/++	++/+++	++++
Cryoglobulinemia[a]	+/++	++/+++	++++
AL and AA amyloidosis	+++/++++	+	+/++
Infectious Disease–Associated Syndromes			
Poststreptococcal glomerulonephritis[a]	+/++	++/+++	–
Subacute bacterial endocarditis[a]	+/++	++	–
HIV	+++	+/++	–
Hepatitis B and C	+++	+/++	–
Syphilis	+++	+	–
Leprosy	+++	+	–
Malaria	+++	+/++	–
Schistosomiasis	+++	+/++	–

[a]Can present as rapidly progressive glomerulonephritis (RPGN); sometimes called crescentic glomerulonephritis. [b]Can present as a malignant hypertensive crisis producing an aggressive fibrinoid necrosis in arterioles and small arteries with microangiopathic hemolytic anemia. [c]Can present with gross hematuria.

Abbreviations: AA, amyloid A; AL, amyloid L; ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane.

the condition is sometimes called *nephrotic-range proteinuria*. The glomerular filtration rate (GFR) in these patients may initially be normal or, rarely, higher than normal, but with persistent hyperfiltration and continued nephron loss, it typically declines over months to years. Patients with a *basement membrane syndrome* either have genetically abnormal basement membranes (Alport's syndrome) or an autoimmune response to basement membrane collagen IV (Goodpasture's syndrome) associated with microscopic hematuria, mild to heavy proteinuria, and hypertension with variable elevations in serum creatinine. *Glomerular–vascular syndrome* describes patients with vascular injury producing hematuria and moderate proteinuria. Affected individuals can have vasculitis, thrombotic microangiopathy, antiphospholipid syndrome, or, more commonly, a systemic disease such as atherosclerosis, cholesterol emboli, hypertension, sickle cell anemia, and autoimmunity. *Infectious disease–associated syndrome* is most important if one has a global perspective. Save for subacute bacterial endocarditis (SBE) in the Western Hemisphere, malaria, and schistosomiasis may be the most common causes of glomerulonephritis throughout the world, closely followed by HIV and chronic hepatitis B and C. These infectious diseases produce a variety of inflammatory reactions in glomerular capillaries, ranging from nephrotic syndrome to acute nephritic injury, and urinalyses that demonstrate a combination of hematuria and proteinuria.

These six general categories of syndromes are usually determined at the bedside with the help of a history and physical examination, blood chemistries, renal ultrasound, and urinalysis. These initial studies help frame further diagnostic workup that typically involves testing of the serum for the presence of various proteins (HIV and hepatitis B and C antigens), antibodies (anti-GBM, antiphospholipid, antistreptolysin O [ASO], anti-DNAse, antihyaluronidase, ANCA, anti-DNA, cryoglobulins, anti-HIV, and anti-hepatitis B and C antibodies) or depletion of complement components (C_3 and C_4). The bedside history and physical examination can also help determine whether the glomerulonephritis is isolated to the kidney (*primary glomerulonephritis*) or is part of a systemic disease (*secondary glomerulonephritis*).

When confronted with an abnormal urinalysis and elevated serum creatinine, with or without edema or congestive heart failure, one must consider whether the glomerulonephritis is *acute* or *chronic*. This assessment is best made by careful history (last known urinalysis or serum creatinine during pregnancy or insurance physical, evidence of infection, or use of medication or recreational drugs); the size of the kidneys on renal ultrasound examination; and how the patient feels at presentation. Chronic glomerular disease often presents with decreased kidney size. Patients who quickly develop renal failure are fatigued and weak and often have uremic symptoms associated with nausea, vomiting, fluid retention, and somnolence. Primary glomerulonephritis presenting with renal failure that has progressed slowly, however, can be remarkably asymptomatic, as are patients with acute glomerulonephritis without much loss in renal function. Once this initial information is collected, selected patients who are clinically stable, have adequate blood clotting parameters, and are willing and able to receive treatment are encouraged to have a renal biopsy.

RENAL PATHOLOGY

A renal biopsy in the setting of glomerulonephritis quickly identifies the type of glomerular injury and often suggests a course of treatment. The biopsy is processed for light microscopy using stains for *hematoxylin and eosin* (*H&E*) to assess cellularity and architecture, *periodic acid–Schiff* (*PAS*) to stain carbohydrate moieties in the membranes of the glomerular tuft and tubules, *Jones-methenamine silver* to enhance basement membrane structure, *Congo red* for amyloid deposits, and *Masson's trichrome* to identify collagen deposition and assess the degree of glomerulosclerosis and interstitial fibrosis. Biopsies are also processed for direct immunofluorescence using conjugated antibodies against IgG, IgM, and IgA to detect the presence of "lumpy-bumpy" immune deposits or "linear" IgG or IgA antibodies bound to GBM, antibodies against trapped complement proteins (C_3 and C_4), or specific antibodies against

a relevant antigen. High-resolution electron microscopy can clarify the principal location of immune deposits and the status of the basement membrane.

Each region of a renal biopsy is assessed separately. By light microscopy, glomeruli (ideally 20) are reviewed individually for discrete lesions; <50% involvement is considered *focal*, and >50% is *diffuse*. Injury in each glomerular tuft can be *segmental,* involving a portion of the tuft, or *global,* involving most of the glomerulus. Glomeruli having *proliferative* characteristics show increased cellularity. When cells in the capillary tuft proliferate, it is called *endocapillary*, and when cellular proliferation extends into Bowman's space, it is called *extracapillary. Synechiae* are formed when epithelial podocytes attach to Bowman's capsule in the setting of glomerular injury; *crescents*, which in some cases may be the extension of synechiae, develop when fibrocellular/fibrin collections fill all or part of Bowman's space; and *sclerotic* glomeruli show acellular, amorphous accumulations of proteinaceous material throughout the tuft with loss of functional capillaries and normal mesangium. Since *age-related glomerulosclerosis* is common in adults, one can estimate the background percentage of sclerosis by dividing the patient's age in half and subtracting 10. Immunofluorescent and electron microscopy can detect the presence and location of *subepithelial, subendothelial, or mesangial* immune deposits, or *reduplication* or *splitting* of the basement membrane. In the other regions of the biopsy, the vasculature surrounding glomeruli and tubules can show *angiopathy, vasculitis*, the presence of *fibrils*, or *thrombi*. The tubules can be assessed for adjacency to one another; separation can be the result of edema, tubular dropout, or collagen deposition resulting from interstitial fibrosis. Interstitial fibrosis is an ominous sign of irreversibility and progression to renal failure.

ACUTE NEPHRITIC SYNDROMES

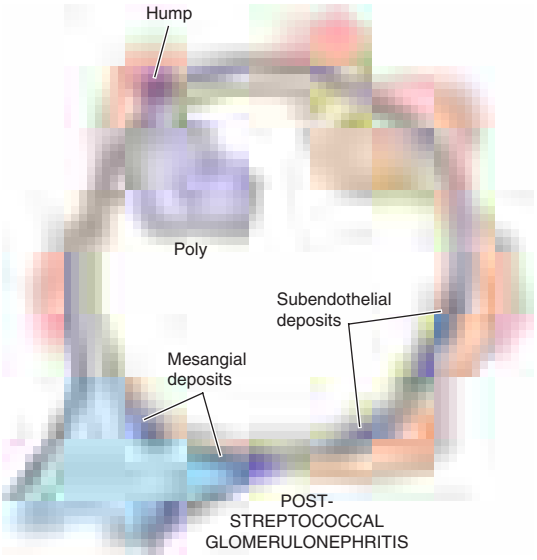
Acute nephritic syndromes classically present with hypertension, hematuria, red blood cell casts, pyuria, and mild to moderate proteinuria. Extensive inflammatory damage to glomeruli causes a fall in GFR and eventually produces uremic symptoms with salt and water retention, leading to edema and hypertension.

POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Poststreptococcal glomerulonephritis is prototypical for *acute endocapillary proliferative glomerulonephritis*. The incidence of poststreptococcal glomerulonephritis has dramatically decreased in developed countries and in these locations is typically sporadic. Acute poststreptococcal glomerulonephritis in underdeveloped countries is epidemic and usually affects children between the ages of 2 and 14 years, but in developed countries is more typical in the elderly, especially in association with debilitating conditions. It is more common in males, and the familial or cohabitant incidence is as high as 40%. Skin and throat infections with particular M types of streptococci (nephritogenic strains) antedate glomerular disease; M types 47, 49, 55, 2, 60, and 57 are seen following impetigo and M types 1, 2, 4, 3, 25, 49, and 12 with pharyngitis. Poststreptococcal glomerulonephritis due to impetigo develops 2–6 weeks after skin infection and 1–3 weeks after streptococcal pharyngitis.

The renal biopsy in poststreptococcal glomerulonephritis demonstrates hypercellularity of mesangial and endothelial cells, glomerular infiltrates of polymorphonuclear leukocytes, granular subendothelial immune deposits of IgG, IgM, C_3, C_4, and C_{5-9}, and subepithelial deposits (which appear as "humps") **(see Fig. A3-6)**. **(See Glomerular Schematic 1.)** Poststreptococcal glomerulonephritis is an immune-mediated disease involving putative streptococcal antigens, circulating immune complexes, and activation of complement in association with cell-mediated injury. Many candidate antigens have been proposed over the years; candidates from nephritogenic streptococci of interest at the moment are: a cationic cysteine proteinase known as streptococcal pyrogenic exotoxin B (SPEB) that is generated by proteolysis of a zymogen precursor (zSPEB), and NAPlr, the nephritis-associated plasmin receptor. These two antigens have biochemical affinity for plasmin, bind as complexes facilitated by this relationship, and activate the alternate complement pathway. The nephritogenic antigen, SPEB, has been demonstrated inside the subepithelial "humps" on biopsy.

Glomerular schematic 1



The classic presentation is an acute nephritic picture with hematuria, pyuria, red blood cell casts, edema, hypertension, and oliguric renal failure, which may be severe enough to appear as RPGN. Systemic symptoms of headache, malaise, anorexia, and flank pain (due to swelling of the renal capsule) are reported in as many as 50% of cases. Five percent of children and 20% of adults have proteinuria in the nephrotic range. In the first week of symptoms, 90% of patients will have a depressed CH_{50} and decreased levels of C_3 with normal levels of C_4. Positive rheumatoid factor (30–40%), cryoglobulins and circulating immune complexes (60–70%), and ANCA against myeloperoxidase (10%) are also reported. Positive cultures for streptococcal infection are inconsistently present (10–70%), but increased titers of ASO (30%), anti-DNAse (70%), or antihyaluronidase antibodies (40%) can help confirm the diagnosis. Consequently, the diagnosis of poststreptococcal glomerulonephritis rarely requires a renal biopsy. A subclinical disease is reported in some series to be 4–5 times as common as clinical nephritis, and these latter cases are characterized by asymptomatic microscopic hematuria with low serum C_3 complement levels.

Treatment is supportive, with control of hypertension, edema, and dialysis as needed. Antibiotic treatment for streptococcal infection should be given to all patients and their cohabitants. There is no role for immunosuppressive therapy, even in the setting of crescents. Recurrent poststreptococcal glomerulonephritis is rare despite repeated streptococcal infections. Early death is rare in children but does occur in the elderly. Overall, the prognosis is good, with permanent renal failure being reported as very uncommon in the past (<1%) but with recent reports of an increased risk of chronic kidney disease in adulthood. Complete resolution of the hematuria and proteinuria in the majority of children occurs within 3–6 weeks of the onset of nephritis but 3–10% of children may have persistent microscopic hematuria, nonnephrotic proteinuria, or hypertension. The prognosis in elderly patients is worse with a high incidence of azotemia (up to 60%), nephrotic-range proteinuria, and ESRD.

SUBACUTE BACTERIAL ENDOCARDITIS

Endocarditis-associated glomerulonephritis is typically a complication of SBE, particularly in patients who remain untreated for a long time, have negative blood cultures, or have right-sided endocarditis. Common comorbidities are valvular heart disease, intravenous drug use, hepatitis C, and diabetes mellitus. Glomerulonephritis is unusual in acute bacterial endocarditis because it takes 10–14 days to develop immune complex–mediated injury, by which time the patient has been treated, often with emergent surgery. Grossly, the kidneys in SBE have subcapsular hemorrhages with a "flea-bitten" appearance, and microscopy on renal biopsy reveals focal proliferation around foci of necrosis associated with abundant mesangial, subendothelial, and subepithelial

immune deposits of IgG, IgM, and C_3. Commonly patients present with a clinical picture of RPGN and have crescents on biopsy. Embolic infarcts or septic abscesses may also be present. The pathogenesis hinges on the renal deposition of circulating immune complexes in the kidney with complement activation. Patients present with gross or microscopic hematuria, pyuria, and mild proteinuria, acute kidney injury or, RPGN with rapid loss of renal function. A normocytic anemia, elevated erythrocyte sedimentation rate, hypocomplementemia, high titers of rheumatoid factor, type III cryoglobulins, circulating immune complexes, and ANCAs may be present. Levels of serum creatinine may be elevated at diagnosis, but with modern therapy there is little progression to chronic renal failure. Primary treatment is eradication of the infection with 4–6 weeks of antibiotics, and if accomplished expeditiously, the prognosis for renal recovery is good. ANCA-associated vasculitis sometimes accompanies or is confused with SBE and should be ruled out, as the treatment is different.

As variants of persistent bacterial infection in blood-associated glomerulonephritis, postinfectious glomerulonephritis can occur in patients with ventriculoatrial and ventriculoperitoneal shunts; pulmonary, intraabdominal, pelvic, or cutaneous infections; and infected vascular prostheses. In developed countries, a significant proportion of cases afflict adults, especially the immunocompromised, and the predominant organism is *Staphylococcus*. The clinical presentation of these conditions is variable and includes proteinuria, microscopic hematuria, acute renal failure, and hypertension. Serum complement levels are low, and there may be elevated levels of C-reactive proteins, rheumatoid factor, antinuclear antibodies, and cryoglobulins. Renal lesions include MPGN, diffuse proliferative and exudative glomerulonephritis (DPGN), or mesangioproliferative glomerulonephritis, sometimes leading to RPGN. Treatment focuses on eradicating the infection, with most patients treated as if they have endocarditis. The prognosis is guarded.

LUPUS NEPHRITIS

Lupus nephritis is a common and serious complication of systemic lupus erythematosus (SLE) and most severe in African-American female adolescents. Thirty to 50% of patients will have clinical manifestations of renal disease at the time of diagnosis, and 60% of adults and 80% of children develop renal abnormalities at some point in the course of their disease. Lupus nephritis results from the deposition of circulating immune complexes, which activate the complement cascade leading to complement-mediated damage, leukocyte infiltration, activation of procoagulant factors, and release of various cytokines. In situ immune complex formation following glomerular binding of nuclear antigens, particularly necrotic nucleosomes, also plays a role in renal injury. The presence of antiphospholipid antibodies may also trigger a thrombotic microangiopathy in a minority of patients.

The clinical manifestations, course of disease, and treatment of lupus nephritis are closely linked to renal pathology. The most common clinical sign of renal disease is proteinuria, but hematuria, hypertension, varying degrees of renal failure, and active urine sediment with red blood cell casts can all be present. Although significant renal pathology can be found on biopsy even in the absence of major abnormalities in the urinalysis, most nephrologists do not biopsy patients until the urinalysis is convincingly abnormal. The extrarenal manifestations of lupus are important in establishing a firm diagnosis of systemic lupus because, while serologic abnormalities are common in lupus nephritis, they are not diagnostic. Anti-dsDNA antibodies that fix complement correlate best with the presence of renal disease. Hypocomplementemia is common in patients with acute lupus nephritis (70–90%) and declining complement levels may herald a flare. Although urinary biomarkers of lupus nephritis are being identified to assist in predicting renal flares, renal biopsy is the only reliable method of identifying the morphologic variants of lupus nephritis.

The World Health Organization (WHO) workshop in 1974 first outlined several distinct patterns of lupus-related glomerular injury; these were modified in 1982. In 2004 the International Society of Nephrology in conjunction with the Renal Pathology Society again updated the classification. This latest version of lesions seen on biopsy **(Table 308-3)** forms the basis for modern treatment recommendations. Class I nephritis describes normal glomerular histology by any technique or normal light microscopy with minimal mesangial deposits on immunofluorescent or electron microscopy. Class II designates mesangial immune complexes with *mesangial proliferation*. Both class I and II lesions are typically associated with minimal renal manifestation and normal renal function; nephrotic syndrome is rare. Patients with lesions limited to the renal mesangium have an excellent prognosis and generally do not need therapy for their lupus nephritis.

TABLE 308-3 Classification for Lupus Nephritis

Class I	Minimal mesangial	Normal histology with mesangial deposits
Class II	Mesangial proliferation	Mesangial hypercellularity with expansion of the mesangial matrix
Class III	Focal nephritis	Focal endocapillary ± extracapillary proliferation with focal subendothelial immune deposits and mild mesangial expansion
Class IV	Diffuse nephritis	Diffuse endocapillary ± extracapillary proliferation with diffuse subendothelial immune deposits and mesangial alterations
Class V	Membranous nephritis	Thickened basement membranes with diffuse subepithelial immune deposits; may occur with class III or IV lesions and is sometimes called mixed membranous and proliferative nephritis
Class VI	Sclerotic nephritis	Global sclerosis of nearly all glomerular capillaries

Note: Revised in 2004 by the International Society of Nephrology-Renal Pathology Society Study Group.

The subject of lupus nephritis is presented under acute nephritic syndromes because of the aggressive and important proliferative lesions seen in class III–V renal diseases. Class III describes *focal lesions with proliferation or scarring*, often involving only a segment of the glomerulus **(see Fig. A3-12)**. Class III lesions have the most varied course. Hypertension, an active urinary sediment, and proteinuria are common with nephrotic-range proteinuria in 25–33% of patients. Elevated serum creatinine is present in 25% of patients. Patients with mild proliferation involving a small percentage of glomeruli respond well to therapy with steroids alone, and fewer than 5% progress to renal failure over 5 years. Patients with more severe proliferation involving a greater percentage of glomeruli have a far worse prognosis and lower remission rates. Treatment of those patients is the same as that for class IV lesions. Many nephrologists believe that class III lesions are simply an early presentation of class IV disease. Others believe severe class III disease is a discrete vasculitic lesion requiring aggressive therapy. Class IV describes *global, diffuse proliferative lesions* involving the vast majority of glomeruli. Patients with class IV lesions commonly have high anti-DNA antibody titers, low serum complement, hematuria, red blood cell casts, proteinuria, hypertension, and decreased renal function; 50% of patients have nephrotic-range proteinuria. Patients with crescents on biopsy often have a rapidly progressive decline in renal function **(see Fig. A3-12)**. Without treatment, this aggressive lesion has the worst renal prognosis. However, if a remission—defined as a return to near-normal renal function and proteinuria ≤330 mg/dL per day—is achieved with treatment, renal outcomes are excellent. Current evidence suggests that inducing a remission with administration of high-dose steroids and either cyclophosphamide or mycophenolate mofetil for 2–6 months, followed by maintenance therapy with lower doses of steroids and mycophenolate mofetil or azathioprine, best balances the likelihood of successful remission with the side effects of therapy. There is no consensus on use of high-dose intravenous methylprednisolone versus oral prednisone, monthly intravenous cyclophosphamide versus daily oral cyclophosphamide, or other immunosuppressants such as cyclosporine, tacrolimus, rituximab, or belimumab. Nephrologists tend to avoid prolonged use of cyclophosphamide in patients of childbearing age without first banking eggs or sperm.

The class V lesion describes subepithelial immune deposits producing a *membranous pattern*; a subcategory of class V lesions is associated with proliferative lesions and is sometimes called *mixed membranous and proliferative disease* **(see Fig. A3-11)**; this category of injury is treated like class IV glomerulonephritis. Sixty percent of patients present with nephrotic syndrome or lesser amounts of proteinuria. Patients with lupus nephritis class V, like patients with *idiopathic membranous nephropathy* (IMN), are predisposed to renal-vein thrombosis and other thrombotic complications. A minority of patients with class V will present with hypertension and renal dysfunction. There are conflicting data on the clinical course, prognosis, and appropriate therapy for patients with class V disease, which may reflect the heterogeneity of this group of patients. Patients with severe nephrotic syndrome, elevated serum creatinine, and a progressive course will probably benefit from therapy with steroids in combination with other immunosuppressive agents. Therapy with inhibitors of the renin-angiotensin system also may attenuate the proteinuria. Antiphospholipid antibodies present in lupus may result in glomerular microthromboses and complicate the course in up to 20% of lupus nephritis patients. The renal prognosis is worse despite anticoagulant therapy.

Patients with any of the above lesions also can transform to another lesion; hence patients often require reevaluation, including repeat renal biopsy. Lupus patients with class VI lesions have >90% *sclerotic glomeruli* and ESRD with interstitial fibrosis. As a group, ~20% of patients with lupus nephritis will reach end-stage disease, requiring dialysis or transplantation. Patients with lupus nephritis have a markedly increased mortality compared with the general population. Renal transplantation in renal failure from lupus, usually performed after ~6 months of inactive disease, results in allograft survival rates comparable to patients transplanted for other reasons.

ANTIGLOMERULAR BASEMENT MEMBRANE DISEASE

Patients who develop autoantibodies directed against glomerular basement antigens frequently develop a glomerulonephritis termed *antiglomerular basement membrane* (*anti-GBM*) *disease*. When they present with lung hemorrhage and glomerulonephritis, they have a pulmonary-renal syndrome called *Goodpasture's syndrome*. The target epitopes for this autoimmune disease lie in the quaternary structure of α3 NC1 domain of collagen IV. Indeed, anti-GBM disease may be considered an autoimmune "conformeropathy" that involves the perturbation of quaternary structure of the α 345NC1 hexamer. MHC-restricted T cells initiate the autoantibody response because humans are not tolerant to the epitopes created by this quaternary structure. The epitopes are normally sequestered in the collagen IV hexamer and can be exposed by infection, smoking, oxidants, or solvents. Goodpasture's syndrome appears in two age groups: in young men in their late twenties and in men and women in their sixties and seventies. Disease in the younger age group is usually explosive, with hemoptysis, a sudden fall in hemoglobin, fever, dyspnea, and hematuria. Hemoptysis is largely confined to smokers, and those who present with lung hemorrhage as a group do better than older populations who have prolonged, asymptomatic renal injury; presentation with oliguria is often associated with a particularly bad outcome. The performance of an urgent kidney biopsy is important in suspected cases of Goodpasture's syndrome to confirm the diagnosis and assess prognosis. Renal biopsies typically show *focal or segmental necrosis* that later, with aggressive destruction of the capillaries by cellular proliferation, leads to crescent formation in Bowman's space **(see Fig. A3-14)**. As these lesions progress, there is concomitant interstitial nephritis with fibrosis and tubular atrophy.

The presence of anti-GBM antibodies and complement is recognized on biopsy by linear immunofluorescent staining for IgG (rarely IgA). In testing serum for anti-GBM antibodies, it is particularly important that the α3 NC1 domain of collagen IV alone be used as the target. This is because nonnephritic antibodies against the α1 NC1 domain are seen in paraneoplastic syndromes and cannot be discerned from assays that use whole basement membrane fragments as the binding target. Between 10 and 15% of sera from patients with Goodpasture's syndrome also contain ANCA antibodies against myeloperoxidase. This subset of patients has a vasculitis-associated variant, which has a surprisingly good prognosis with treatment. Prognosis at presentation is worse if there are >50% crescents on renal biopsy with advanced fibrosis, if serum creatinine is >5–6 mg/dL, if oliguria is present, or if there is a need for acute dialysis. Although frequently attempted, most of these latter patients will not respond to plasmapheresis and steroids. Patients with advanced renal failure who present with hemoptysis should still be treated for their lung hemorrhage, as it responds to plasmapheresis and can be lifesaving. Treated patients with less severe disease typically respond to 8–10 treatments of plasmapheresis accompanied by oral prednisone and cyclophosphamide in the first 2 weeks. Kidney transplantation is possible, but because there is risk of recurrence, experience suggests that patients should wait for 6 months and until serum antibodies are undetectable.

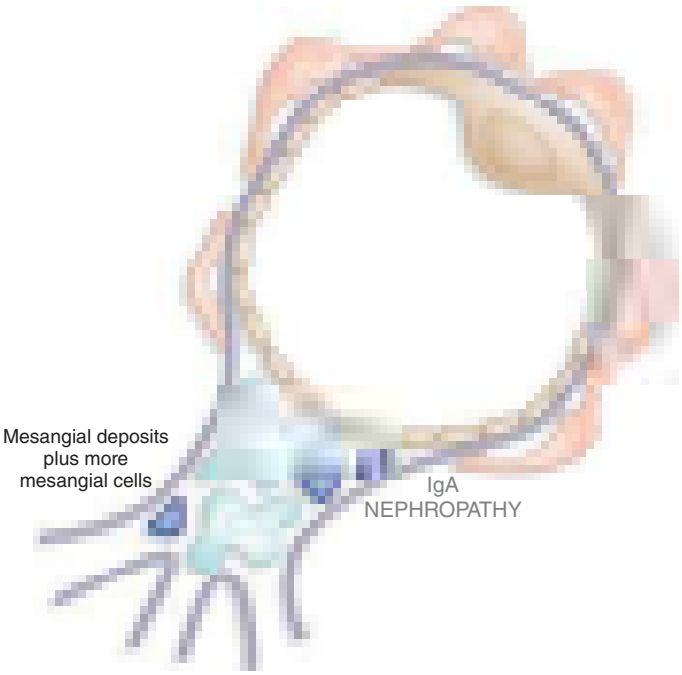
IgA NEPHROPATHY

Berger first described the glomerulonephritis now termed *IgA nephropathy*. It is classically characterized by episodic hematuria associated with the deposition of IgA in the mesangium. IgA nephropathy is one of the most common forms of glomerulonephritis worldwide. There is a male preponderance, a peak incidence in the second and third decades of life, and rare familial clustering. There are geographic differences in the prevalence of IgA nephropathy, with 30% prevalence along the Asian and Pacific Rim and 20% in southern Europe, compared to a much lower prevalence in northern Europe and North America. It was initially hypothesized that variation in detection, in part, accounted for regional differences. With clinical care in nephrology becoming more uniform, this variation in prevalence more likely reflects true differences among racial and ethnic groups.

IgA nephropathy is predominantly a sporadic disease but susceptibility to it has been shown uncommonly to have a genetic component depending on geography and the existence of "founder effects." Familial forms of IgA nephropathy are more common in northern Italy and eastern Kentucky. No single causal gene has been identified. Clinical and laboratory evidence suggests close similarities between Henoch-Schönlein purpura and IgA nephropathy. Henoch-Schönlein purpura is distinguished clinically from IgA nephropathy by prominent systemic symptoms, a younger age (<20 years old), preceding infection, and abdominal complaints. Deposits of IgA are also found in the glomerular mesangium in a variety of systemic diseases, including chronic liver disease, Crohn's disease, gastrointestinal adenocarcinoma, chronic bronchiectasis, idiopathic interstitial pneumonia, dermatitis herpetiformis, mycosis fungoides, leprosy, ankylosing spondylitis, relapsing polychondritis, and Sjögren's syndrome. IgA deposition in these entities is not usually associated with clinically significant glomerular inflammation or renal dysfunction and thus is not called IgA nephropathy.

IgA nephropathy is an immune complex–mediated glomerulonephritis defined by the presence of diffuse mesangial IgA deposits often associated with mesangial hypercellularity. **(See Glomerular Schematic 2.)** IgM, IgG, C_3, or immunoglobulin light chains may be codistributed with IgA. IgA deposited in the mesangium is typically polymeric and of the IgA1 subclass, the pathogenic significance of which is not clear. Abnormalities have been described in IgA production by plasma cells; in IgA clearance, by the liver and in mesangial IgA clearance and receptors for IgA. Currently, however, abnormalities in the *O* glycosylation of the hinge region of primarily polymeric IgA1 seem to best account for the pathogenesis of sporadic IgA nephropathy. Synthesis of poorly galactosylated IgA1 results in exposure of N-acetyl-galactosomine in truncated IgA1 hinge regions which is recognized by IgG or IgA1 antibodies leading to formation of immune complexes in the circulation or in situ after glomerular deposition of galactose-deficient IgA1. The galactose-deficient IgA1 may evade liver catabolism and preferentially deposit in the mesangium. A second hit, such as a viral or other antigen exposure, may be necessary for disease manifestation. Despite the presence of elevated serum IgA levels in 20–50% of patients, and IgA deposition in skin biopsies in 15–55% of patients, a renal biopsy is necessary to confirm the diagnosis. Although the immunofluorescent pattern of IgA on renal biopsy defines IgA nephropathy in the proper

Glomerular schematic 2



clinical context, a variety of histologic lesions may be seen on light microscopy **(see Fig. A3-8)**, including DPGN; *segmental sclerosis*; and, rarely, *segmental necrosis with cellular crescent formation*, which typically presents as RPGN.

The two most common presentations of IgA nephropathy are recurrent episodes of macroscopic hematuria during or immediately following an upper respiratory infection often accompanied by proteinuria or persistent asymptomatic microscopic hematuria. Nephrotic syndrome is uncommon. Proteinuria can also first appear late in the course of the disease. Rarely patients present with acute renal failure and a rapidly progressive clinical picture. IgA nephropathy is a benign disease for the majority of patients, and 5–30% of patients may go into a complete remission, with others having hematuria but well preserved renal function. In the minority of patients who have progressive disease, progression is slow, with renal failure seen in only 25–30% of patients with IgA nephropathy over 20–25 years. This risk varies considerably among populations. Cumulatively, risk factors for the loss of renal function identified thus far account for <50% of the variation in observed outcome but include the presence of hypertension or proteinuria, the absence of episodes of macroscopic hematuria, male sex, older age of onset, and extensive glomerulosclerosis or interstitial fibrosis on renal biopsy. Several analyses in large populations of patients found persistent proteinuria for 6 months or longer to have the greatest predictive power for adverse renal outcomes.

There is no agreement on optimal treatment. Both large studies that include patients with multiple glomerular diseases and small studies of patients with IgA nephropathy support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function. In patients with persistent proteinuria after ACE inhibitor therapy, steroid treatment or other immunosuppressives have demonstrated conflicting results. Tonsillectomy and fish oil have also been suggested in small studies to benefit select patients. When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

ANCA SMALL-VESSEL VASCULITIS

A group of patients with small-vessel vasculitis (arterioles, capillaries, and venules; rarely small arteries) and glomerulonephritis have serum ANCA; the antibodies are of two types, anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) **(Chap. 356)**; Lamp-2 antibodies have also been reported experimentally as potentially pathogenic. ANCA are produced with the help of T cells and activate leukocytes and monocytes, which together damage the walls of small vessels. Endothelial injury also attracts more leukocytes and extends the inflammation. Granulomatosis with polyangiitis, microscopic polyangiitis, Churg-Strauss syndrome, and renal-limited vasculitis belong to this group because they are ANCA-positive and have a *pauci-immune glomerulonephritis* with few immune complexes in small vessels and glomerular capillaries. Patients with any of these diseases can have any combination of the above serum antibodies, but anti-PR3 antibodies are more common in granulomatosis with polyangiitis and anti-MPO antibodies are more common in microscopic polyangiitis or Churg-Strauss. Although each of these diseases has some unique clinical features, most features do not predict relapse or progression, and as a group, they are generally treated in the same way. Once diagnosed ANCA monitoring has limited value, but targeted determination of ANCA levels may be useful if a relapse is clinically suspected. Since mortality is high without treatment, virtually all patients receive urgent treatment. Induction therapy usually includes glucocorticoids and either cyclophosphamide or rituximab. Plasmapheresis is recommended in rapidly progressive renal failure or pulmonary hemorrhage. Monthly "pulse" IV cyclophosphamide to induce remission of ANCA-associated vasculitis is as effective as daily oral cyclophosphamide but may be associated with increased relapses. Steroids are tapered soon after acute inflammation subsides, and patients are maintained on cyclophosphamide or less toxic agents such as azathioprine, methotrexate, or rituximab for up to a year to minimize the risk of relapse.

Granulomatosis with Polyangiitis Patients with this disease classically present with fever, purulent rhinorrhea, nasal ulcers, sinus pain, polyarthralgias/arthritis, cough, hemoptysis, shortness of breath, microscopic hematuria, and 0.5–1 g/24 h of proteinuria; occasionally there may be cutaneous purpura and mononeuritis multiplex. Presentation without renal involvement is termed *limited granulomatosis with polyangiitis*, although some of these patients will show signs of renal injury later. Chest x-ray often reveals nodules and persistent infiltrates, sometimes with cavities. Biopsy of involved tissue will show a small-vessel vasculitis and adjacent noncaseating granulomas. Renal biopsies during active disease demonstrate *segmental necrotizing glomerulonephritis* without immune deposits and have been classified as focal, mixed, crescentic or sclerotic **(see Fig. A3-13)**. The disease is more common in patients exposed to silica dust and those with α_1-antitrypsin deficiency, which is an inhibitor of PR3. Relapse after achieving remission is common and is more common in patients with granulomatosis with polyangiitis than the other ANCA-associated vasculitis, necessitating diligent follow-up care. Although associated with an unacceptable high mortality rate without treatment, the greatest threat to patients, especially elderly patients in the first year of therapy, is from adverse events, which are often secondary to treatment, rather than active vasculitis. Patients should also be monitored long term for malignancy after immunosuppressive therapy.

Microscopic Polyangiitis Clinically, these patients look somewhat similar to those with granulomatosis with polyangiitis, except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy, where the vasculitis in microscopic polyangiitis is without granulomas. Some patients will also have injury limited to the capillaries and venules.

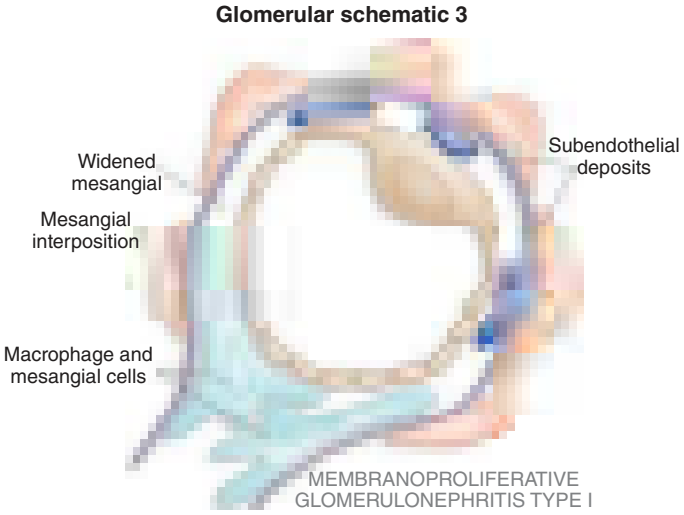
Churg-Strauss Syndrome When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of Churg-Strauss syndrome is considered. Hypergammaglobulinemia, elevated levels of serum IgE, or the presence of rheumatoid factor sometimes accompanies the allergic state. Lung inflammation, including fleeting cough and pulmonary infiltrates, often precedes the systemic manifestations of disease by years; lung manifestations are rarely absent. A third of patients may have exudative pleural effusions associated with eosinophils. Small-vessel vasculitis and *focal segmental necrotizing glomerulonephritis* can be seen on renal biopsy, usually absent eosinophils or granulomas. The cause of Churg-Strauss syndrome is autoimmune, but the inciting factors are unknown.

TABLE 308-4 Membranoproliferative Glomerulonephritis: Immunoglobulin-Mediated
Type I Disease—Most Common
Idiopathic
Subacute bacterial endocarditis
Systemic lupus erythematosus
Hepatitis C and cryoglobulinemia
Mixed cryoglobulinemia
Hepatitis C
Cancer: lung, breast and ovary (germinal)
Type II Disease
Idiopathic
Dense Deposit Disease (immunoglobulin-mediated)
Type III Disease
Idiopathic
C_3 Glomerulopathy: C_3 Dominant, Non-Immunoglobulin-mediated
Dense Deposit Disease (C_3 dominant)
Idiopathic
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway
C_3 Glomerulonephritis
Specific genetic mutations and/or autoantibodies to alternate complement pathway factors or regulatory factors of alternate complement pathway

C_3 Glomerulopathies C_3 glomerulopathy is a recent disease classification that is defined by the glomerular accumulation of C_3 with little or no immunoglobulin and encompasses dense deposit disease (DDD), formerly MPGN type II (see below), and C_3 glomerulonephritis (C_3GN), **(Table 308-4)**. DDD is defined morphologically with dense deposits forming ribbons in the GBM. In the absence of this specific morphology the entity is categorized as C_3GN. Both are associated with the presence of a complement mutation believed to cause the renal pathology, including mutations in the complement factor H regulatory proteins (CFHR's) genes. DDD is primarily a disease of children and young adults while the other C_3 glomerulopathies are reported to present in an older age group (mean age 30). By definition kidneys with C_3 glomerulopathy show sole or dominant staining for C_3 but can have variable light microscopy with mesangial proliferative or membranoproliferative patterns seen most commonly. Morphologically, many cases are not distinguishable from recovering post-infections GN. Patients with DDD present with proteinuria and/or hematuria with nephrotic range proteinuria in up to 2/3 of patients. Partial lipodystrophy and Drusen bodies in the retina may also be present. Prognosis is poor with 50% of patients progressing to ESRD. C_3GN patients are clinically less well defined but ~2/3 have hematuria and 1/3 proteinuria. In addition to renal biopsy serological and genetic evaluation may be indicated including measurement of C_3 levels which are typically low with normal C_4 levels, C_3 nephritic factor, Factor H, paraprotein detection and specific CFHR genetic mutations. The optimal therapies remain undefined but include inhibition of the renin-angiotensin system, anticoagulants, steroids and other immunosuppressants. Increasing evidence suggests a benefit of therapy with eculizumab, a monoclonal antibody directed at C_5 which is activated by C_3.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is sometimes called *mesangiocapillary glomerulonephritis* or *lobar glomerulonephritis*. It is an immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia. MPGN is rare in African Americans, and idiopathic disease usually presents in childhood or young adulthood. MPGN has been subdivided pathologically into type I, type II, and type III disease. *Type I MPGN* is commonly associated with persistent hepatitis C infections, autoimmune diseases like lupus or cryoglobulinemia, or neoplastic diseases (Table 308-4). A minority of cases of MPGN type I have C_3 but not immunoglobulin deposits on biopsy and are best considered as in the category of a C_3 glomerulopathy. *Types II and III MPGN* can be idiopathic, and immunoglobulin-mediated disease (driven by the classical complement pathway) but the majority of cases formerly defined as MPGN type II and III are non-immunoglobulin-mediated and driven by the alternate complement pathway.



Type I MPGN, the most proliferative of the three types, shows mesangial proliferation with lobular segmentation on renal biopsy and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes called *tram-tracking* **(see Fig. A3-9). (See Glomerular Schematic 3.)** Subendothelial deposits with low serum levels of C_3 are typical, although 50% of patients have normal levels of C_3 and occasional intramesangial deposits. Low serum C_3 and a dense thickening of the GBM containing ribbons of dense deposits and C_3 characterize type II MPGN, *dense deposit disease* **(see Fig. A3-10)**. Classically, the glomerular tuft has a lobular appearance; intramesangial deposits are rarely present and subendothelial deposits are generally absent. Proliferation in type III MPGN is less common than the other two types and is often focal; mesangial interposition is rare, and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

Classic type I MPGN is secondary to glomerular deposition of circulating immune complexes or their in situ formation. Patients with MPGN present with proteinuria, hematuria, and pyuria (30%); systemic symptoms of fatigue and malaise that are most common in children with type I disease; or an acute nephritic picture with RPGN and a speedy deterioration in renal function in up to 25% of patients. Low serum C_3 levels are common. Fifty percent of patients with MPGN develop ESRD 10 years after diagnosis, and 90% have renal insufficiency after 20 years. Nephrotic syndrome, hypertension, and renal insufficiency all predict poor outcome. In the presence of proteinuria, treatment with inhibitors of the renin-angiotensin system is prudent. Evidence for treatment with dipyridamole, Coumadin (warfarin), or cyclophosphamide is not strongly established. There is some evidence supporting the efficacy of treatment of *primary MPGN* with steroids, particularly in children, as well as reports of efficacy with plasma exchange and other immunosuppressive drugs. If defects in the complement pathway are found, treatment with eculizumab is of hypothetical but unproven benefit. In *secondary MPGN*, treating the associated infection, autoimmune disease, or neoplasms is of demonstrated benefit. In particular, pegylated interferon and ribavirin are useful in reducing viral load. Although all primary renal diseases can recur over time in transplanted renal allografts, patients with MPGN are well known to be at risk for not only a histologic recurrence but also a clinically significant recurrence with loss of graft function.

MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

Mesangioproliferative glomerulonephritis is characterized by expansion of the mesangium, sometimes associated with mesangial hypercellularity; thin, single contoured capillary walls; and mesangial immune deposits. Clinically, it can present with varying degrees of proteinuria and, commonly, hematuria. Mesangioproliferative disease may be seen in IgA nephropathy, *Plasmodium falciparum* malaria, resolving postinfectious glomerulonephritis, and class II nephritis from lupus, all of which can have a similar histologic appearance. With these secondary entities excluded, the diagnosis of *primary mesangioproliferative glomerulonephritis* is made in <15% of renal biopsies. As an immune-mediated renal lesion with deposits of IgM, C1q, and C_3, the clinical course is variable. Patients with isolated hematuria may have a very benign course, and those with heavy proteinuria occasionally progress to renal failure. There is little agreement on treatment, but some clinical reports suggest benefit from use of inhibitors of the renin-angiotensin system, steroid therapy, and even cytotoxic agents.

NEPHROTIC SYNDROME

Nephrotic syndrome classically presents with heavy proteinuria, minimal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure. Multiple studies have noted that the higher the 24-h urine protein excretion, the more rapid is the decline in GFR.

Therapies for various causes of nephrotic syndrome are noted under individual disease headings below. In general, all patients with hypercholesterolemia secondary to nephrotic syndrome should be treated with lipid-lowering agents because they are at increased risk for cardiovascular disease. Edema secondary to salt and water retention can be controlled with the judicious use of diuretics, avoiding intravascular volume depletion. Venous complications secondary to the hypercoagulable state associated with nephrotic syndrome can be treated with anticoagulants. The losses of various serum binding proteins, such as thyroid-binding globulin, lead to alterations in functional tests. Lastly, proteinuria itself is hypothesized to be nephrotoxic, and treatment of proteinuria with inhibitors of the renin-angiotensin system can lower urinary protein excretion.

MINIMAL CHANGE DISEASE

MCD, sometimes known as *nil lesion*, causes 70–90% of nephrotic syndrome in childhood but only 10–15% of nephrotic syndrome in adults. MCD usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of nonsteroidal anti-inflammatory agents; significant interstitial nephritis often accompanies cases associated with nonsteroidal drug use. MCD on renal biopsy shows no obvious glomerular lesion by light microscopy and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium **(see Fig. A3-1). (See Glomerular Schematic 4.)** Electron microscopy, however, consistently demonstrates an effacement of the foot processes supporting the epithelial podocytes with weakening of slit-pore membranes. The pathophysiology of this lesion is uncertain. Most agree there is a circulating cytokine, perhaps related to a T cell response that alters capillary charge and podocyte integrity. The evidence for cytokine-related immune injury is circumstantial and is suggested by the presence of preceding allergies, altered cell-mediated immunity during viral infections, and the high frequency of remissions with steroids.

MCD presents clinically with the abrupt onset of edema and nephrotic syndrome accompanied by acellular urinary sediment. Average urine protein excretion reported in 24 h is 10 g with severe hypoalbuminemia. Less common clinical features include hypertension (30% in children, 50% in adults), microscopic hematuria (20% in children, 33% in adults), atopy or allergic symptoms (40% in children, 30% in adults), and decreased renal function (<5% in children, 30% in adults). The appearance of acute renal failure in adults is often seen more commonly in patients with low serum albumin and intrarenal edema

Glomerular schematic 4

(nephrosarca) that is responsive to intravenous albumin and diuretics. This presentation must be distinguished from acute renal failure secondary to hypovolemia. Acute tubular necrosis and interstitial inflammation are also reported. In children, the abnormal urine principally contains albumin with minimal amounts of higher-molecular-weight proteins, and is sometimes called *selective proteinuria*. Although up to 30% of children have a spontaneous remission, all children today are treated with steroids; only children who are nonresponders are biopsied in this setting. Primary responders are patients who have a complete remission (<0.2 mg/24 h of proteinuria) after a single course of prednisone; steroid-dependent patients relapse as their steroid dose is tapered. Frequent relapsers have two or more relapses in the 6 months following taper, and steroid-resistant patients fail to respond to steroid therapy. Adults are not considered steroid-resistant until after 4 months of therapy. Ninety to 95% of children will develop a complete remission after 8 weeks of steroid therapy, and 80–85% of adults will achieve complete remission, but only after a longer course of 20–24 weeks. Patients with steroid resistance may have FSGS on repeat biopsy. Some hypothesize that if the first renal biopsy does not have a sample of deeper corticomedullary glomeruli, then the correct diagnosis of FSGS may be missed.

Relapses occur in 70–75% of children after the first remission, and early relapse predicts multiple subsequent relapses, as do high levels of basal proteinuria. The frequency of relapses decreases after puberty. There is an increased risk of relapse following the rapid tapering of steroids in all groups. Relapses are less common in adults but are more resistant to subsequent therapy. Prednisone is first-line therapy, either given daily or on alternate days. Other immunosuppressive drugs, such as cyclophosphamide, chlorambucil, and mycophenolate mofetil, are saved for frequent relapsers, steroid-dependent patients, or steroid-resistant patients. Cyclosporine can induce remission, but relapse is also common when cyclosporine is withdrawn. The long-term prognosis in adults is less favorable when acute renal failure or steroid resistance occurs.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS refers to a pattern of renal injury characterized by segmental glomerular scars that involve some but not all glomeruli; the clinical findings of FSGS largely manifest as proteinuria. When the secondary causes of FSGS are eliminated **(Table 308-5)**, the remaining patients are considered to have primary FSGS. The incidence of this disease is increasing, and it now represents up to one-third of cases of nephrotic syndrome in adults and one-half of cases of nephrotic syndrome in African Americans, in whom it is seen more commonly. The pathogenesis of FSGS is probably multifactorial. Possible mechanisms include a T cell–mediated circulating permeability factor, increased soluble urokinase receptor levels, TGF-β–mediated cellular proliferation and

TABLE 308-5 Focal Segmental Glomerulosclerosis

Primary focal segmental glomerulosclerosis
Secondary focal segmental glomerulosclerosis
Viruses: HIV/hepatitis B/parvovirus
Hypertensive nephropathy
Reflux nephropathy
Cholesterol emboli
Drugs: Heroin/analgesics/bisphosphonates/ecstasy
Oligomeganephronia
Renal dysgenesis
Alport's syndrome
Sickle cell disease
Lymphoma
Radiation nephritis
Familial podocytopathies
NPHS1 mutation/nephrin
NPHS2 mutation/podocin
TRPC6 mutation/cation channel
ACTN4 mutation/actinin
α-Galactosidase A deficiency/Fabry's disease
N acetylneuraminic acid hydrolase deficiency/nephrosialidosis

matrix synthesis, and podocyte abnormalities associated with genetic mutations. Risk polymorphisms at the *APOL1* locus encoding apolipoprotein L1 expressed in podocytes substantially explain the increased burden of FSGS among African Americans with or without HIV-associated disease.

The pathologic changes of FSGS are most prominent in glomeruli located at the corticomedullary junction **(see Fig. A3-2)**, so if the renal biopsy specimen is from superficial tissue, the lesions can be missed, which sometimes leads to a misdiagnosis of MCD. In addition to focal and segmental scarring, other variants have been described, including cellular lesions with *endocapillary hypercellularity* and heavy proteinuria; *collapsing glomerulopathy* **(see Fig. A3-3)** with segmental or global glomerular collapse and a rapid decline in renal function; a hilar stalk lesion **(see Fig. A3-4)**; or the *glomerular tip lesion* **(see Fig. A3-5)**, which may have a better prognosis. **(See Glomerular Schematic 5.)**

FSGS can present with hematuria, hypertension, any level of proteinuria, or renal insufficiency. Nephrotic-range proteinuria, African-American race, and renal insufficiency are associated with a poor outcome, with 50% of patients reaching renal failure in 6–8 years. FSGS rarely remits spontaneously, but treatment-induced remission of proteinuria significantly improves prognosis. Treatment of patients with *primary FSGS* should include inhibitors of the renin-angiotensin system. Based on retrospective studies, patients with nephrotic-range proteinuria can be treated with steroids but respond far less often and after a longer course of therapy than patients with MCD. Proteinuria remits in only 20–45% of patients receiving a course of steroids over 6–9 months. Limited evidence suggests the use of cyclosporine in steroid-responsive patients helps ensure remissions. Relapse frequently occurs after cessation of cyclosporine therapy, and cyclosporine itself can lead to a deterioration of renal function due to its nephrotoxic effects. A role for other agents that suppress the immune system such as rituximab or mycophenolate mofetil has not been firmly established. Primary FSGS recurs in 25–40% of patients given allografts at ESRD, leading to graft loss in half of those cases. In recurrent post-transplant FSGS many patients will achieve a full or partial remission with plasmapheresis. The treatment of *secondary FSGS* typically involves treating

Glomerular schematic 5

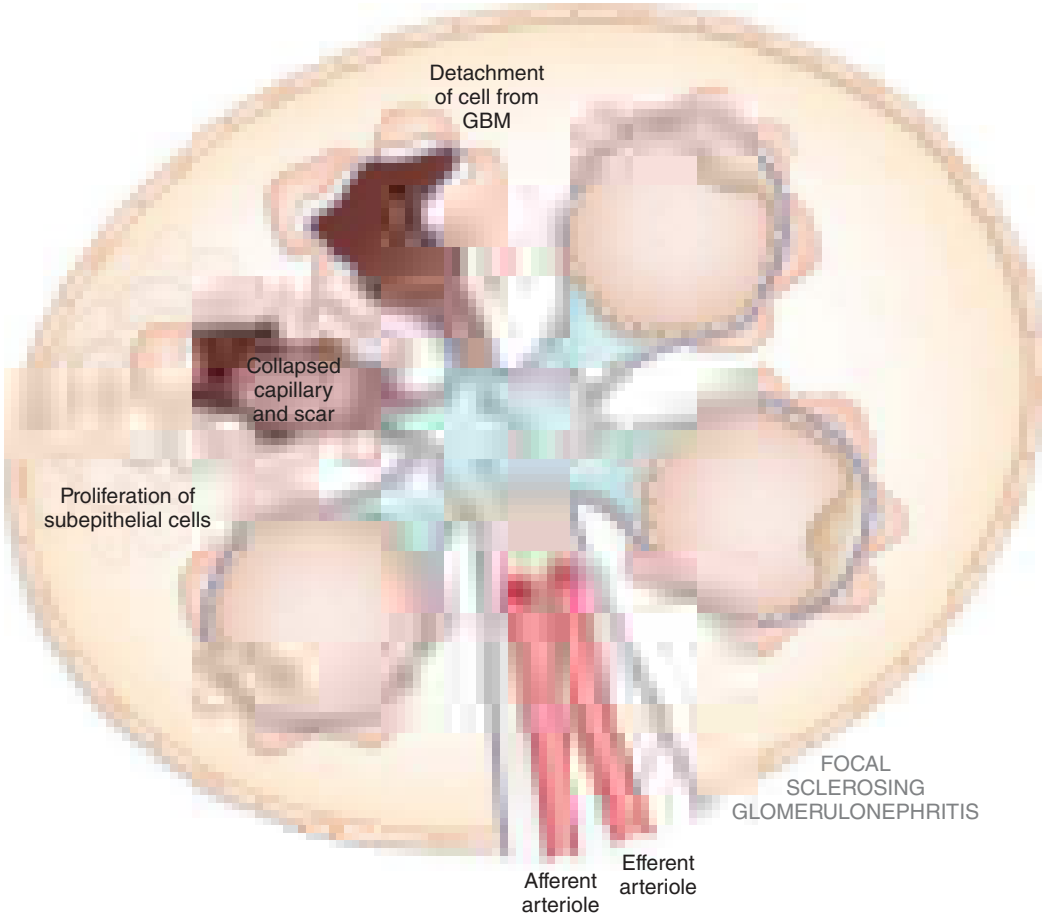


TABLE 308-6 Membranous Glomerulonephritis

Primary/idiopathic membranous glomerulonephritis
Secondary membranous glomerulonephritis
Infection: Hepatitis B and C, syphilis, malaria, schistosomiasis, leprosy, filariasis
Cancer: Breast, colon, lung, stomach, kidney, esophagus, neuroblastoma
Drugs: Gold, mercury, penicillamine, nonsteroidal anti-inflammatory agents, probenecid
Autoimmune diseases: Systemic lupus erythematosus, rheumatoid arthritis, primary biliary cirrhosis, dermatitis herpetiformis, bullous pemphigoid, myasthenia gravis, Sjögren's syndrome, Hashimoto's thyroiditis
Other systemic diseases: Fanconi's syndrome, sickle cell anemia, diabetes, Crohn's disease, sarcoidosis, Guillain-Barré syndrome, Weber-Christian disease, angiofollicular lymph node hyperplasia

the underlying cause and controlling proteinuria. There is no role for steroids or other immunosuppressive agents in secondary FSGS.

MEMBRANOUS GLOMERULONEPHRITIS

MGN, or *membranous nephropathy* as it is sometimes called, accounts for ~20% of cases of nephrotic syndrome in adults, with a peak incidence between the ages of 30 and 50 years and a male to female ratio of 2:1. IMN is rare in childhood and the most common cause of nephrotic syndrome in the elderly. In 20–30% of cases, MGN is secondary and is associated with a malignancy (solid tumors of the breast, lung, colon), infection (hepatitis B, syphilis, malaria, schistosomiasis), rheumatologic disorders like lupus, rheumatoid arthritis, IgG4 diseases or drug exposure **(Table 308-6)**.

Uniform thickening of the basement membrane along the peripheral capillary loops is seen by light microscopy on renal biopsy **(see Fig. A3-7)**; this thickening needs to be distinguished from that seen in diabetes and amyloidosis. **(See Glomerular Schematic 6.)** Immunofluorescence demonstrates diffuse granular deposits of IgG and C_3, and electron microscopy typically reveals electron-dense subepithelial deposits. While different stages (I–V) of progressive membranous lesions have been described, some published analyses indicate the degree of tubular atrophy or interstitial fibrosis is more predictive of progression than is the stage of glomerular disease. The presence of subendothelial deposits or the presence of tubuloreticular inclusions strongly points to a diagnosis of membranous lupus nephritis, which may precede the extrarenal manifestations of lupus. In 70% of cases of IMN, autoantibodies against the M-type phospholipase A_2 receptor circulate and bind to a conformational epitope present in the PLA2R on human podocytes, producing characteristic in situ deposits. 5–10% of IMN patients alternatively have autoantibodies to thrombospondin type-1 domain containing 7A. Both antigens co-localize within glomerular subepithelial deposits with IgG4 (PLA2R). Other renal diseases do not involve these autoantibodies. In most cases of secondary membranous nephropathy, these autoantibodies are absent with rare reports of autoantibodies to PLA2R in membranous glomerulopathy associated with hepatitis B and sarcoidosis. Circulating deposits and glomerular deposits of these autoantibodies have correlated with the likelihood of a spontaneous remission, severity of IMN, and the response to therapy. Eighty percent of patients with MGN present with nephrotic syndrome and nonselective proteinuria. Microscopic hematuria is seen but less commonly than in IgA nephropathy or FSGS. Spontaneous remissions occur in 20–33% of patients and often occur late in the course which make treatment decisions difficult. Low or absent levels of autoantibodies to PLA2R assist in predicting both spontaneous and treatment associated remissions. One-third of patients continue to have relapsing nephrotic syndrome but maintain normal renal function, and approximately another third of patients develop renal failure or die from the complications of nephrotic syndrome. Male gender, older age, hypertension, and the persistence of proteinuria are associated with worse prognosis. Although thrombotic complications are a feature of all nephrotic syndromes, MGN has the highest reported incidences of renal vein thrombosis, pulmonary embolism, and deep-vein thrombosis. Prophylactic anticoagulation is controversial but has been recommended for patients with severe or prolonged proteinuria in the absence of risk factors for bleeding.

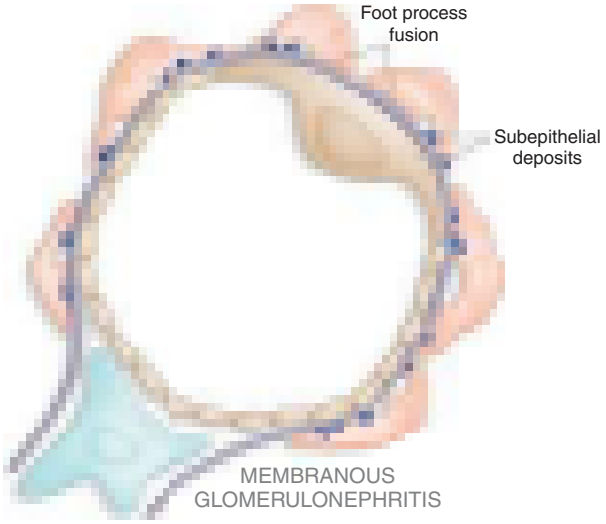
In addition to the treatment of edema, dyslipidemia, and hypertension, inhibition of the renin-angiotensin system is recommended. Therapy with immunosuppressive drugs is also recommended for patients with primary MGN and persistent proteinuria (>3.0 g/24 h). The choice of immunosuppressive drugs for therapy is controversial, but current recommendations are to treat with steroids and cyclophosphamide, chlorambucil, mycophenolate mofetil, or cyclosporine or rituximab, an anti-CD20 antibody directed at B cells.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the single most common cause of chronic renal failure in the United States, accounting for 45% of patients receiving renal replacement therapy, and is a rapidly growing problem worldwide. The dramatic increase in the number of patients with diabetic nephropathy reflects the epidemic increase in obesity, metabolic syndrome, and type 2 diabetes mellitus. Approximately 40% of patients with types 1 or 2 diabetes develop nephropathy, but due to the higher prevalence of type 2 diabetes (90%) compared to type 1 (10%), the majority of patients with diabetic nephropathy have type 2 disease. Renal lesions are more common in African-American, Native American, Polynesian, and Maori populations. Risk factors for the development of diabetic nephropathy include hyperglycemia, hypertension, dyslipidemia, smoking, a family history of diabetic nephropathy, and gene polymorphisms affecting the activity of the renin-angiotensin-aldosterone axis.

Within 1–2 years after the onset of clinical diabetes, morphologic changes appear in the kidney. Thickening of the GBM is a sensitive indicator for the presence of diabetes but correlates poorly with the presence or absence of clinically significant nephropathy. The composition of the GBM is altered notably with a loss of heparan sulfate moieties that form the negatively charged filtration barrier. This change results in increased filtration of serum proteins into the urine, predominately negatively charged albumin. The expansion of the mesangium due to the accumulation of extracellular matrix correlates with the clinical manifestations of diabetic nephropathy **(see stages in Fig. A3-20)**. This expansion in mesangial matrix is associated with the development of *mesangial sclerosis*. Some patients also develop eosinophilic, PAS^+ nodules called *nodular glomerulosclerosis* or *Kimmelstiel-Wilson nodules*. Immunofluorescence microscopy often reveals the nonspecific deposition of IgG (at times in a linear pattern) or complement staining without immune deposits on electron microscopy. Prominent vascular changes are frequently seen with hyaline and hypertensive arteriosclerosis. This is associated with varying degrees of chronic glomerulosclerosis and

Glomerular schematic 6



tubulointerstitial changes. Renal biopsies from patients with types 1 and 2 diabetes are largely indistinguishable.

These pathologic changes are the result of a number of postulated factors. Multiple lines of evidence support an important role for increases in glomerular capillary pressure (intraglomerular hypertension) in alterations in renal structure and function. Direct effects of hyperglycemia on the actin cytoskeleton of renal mesangial and vascular smooth-muscle cells as well as diabetes-associated changes in circulating factors such as atrial natriuretic factor, angiotensin II, and insulin-like growth factor (IGF) may account for this. Sustained glomerular hypertension increases matrix production, alterations in the GBM with disruption in the filtration barrier (and hence proteinuria), and glomerulosclerosis. A number of factors have also been identified that alter matrix production, including the accumulation of advanced glycosylation end products, circulating factors including growth hormone, IGF-I, angiotensin II, connective tissue growth factor, TGF-β, and dyslipidemia.

The natural history of diabetic nephropathy in patients with types 1 and 2 diabetes is similar. However, since the onset of type 1 diabetes is readily identifiable and the onset of type 2 diabetes is not, a patient newly diagnosed with type 2 diabetes may present with *advanced diabetic nephropathy*. At the onset of diabetes, renal hypertrophy and glomerular hyperfiltration are present. The degree of glomerular hyperfiltration correlates with the subsequent risk of clinically significant nephropathy. In the ~40% of patients with diabetes who develop diabetic nephropathy, the earliest manifestation is an increase in albuminuria detected by sensitive radioimmunoassay. Albuminuria in the range of 30–300 mg/24 h is called *microalbuminuria* (Table 308-1). Microalbuminuria appears 5–10 years after the onset of diabetes. It is currently recommended to test patients with type 1 disease for microalbuminuria 5 years after diagnosis of diabetes and yearly thereafter and, because the time of onset of type 2 diabetes is often unknown, to test type 2 patients at the time of diagnosis of diabetes and yearly thereafter.

Patients with small increases in albuminuria increase their levels of urinary albumin excretion, typically reaching dipstick positive levels of proteinuria (>300 mg albuminuria) 5–10 years after the onset of early albuminuria. Microalbuminuria is a potent risk factor for cardiovascular events and death in patients with type 2 diabetes. Many patients with type 2 diabetes and microalbuminuria succumb to cardiovascular events before they progress to proteinuria or renal failure. Proteinuria in frank diabetic nephropathy can be variable, ranging from 500 mg to 25 g/24 h, and is often associated with nephrotic syndrome. More than 90% of patients with type 1 diabetes and nephropathy have diabetic retinopathy, so the absence of retinopathy in type 1 patients with proteinuria should prompt consideration of a diagnosis other than diabetic nephropathy; only 60% of patients with type 2 diabetes with nephropathy have diabetic retinopathy. There is a significant correlation between the presence of retinopathy and the presence of Kimmelstiel-Wilson nodules **(see Fig. A3-20)**. Also, characteristically, patients with advanced diabetic nephropathy have normal to enlarged kidneys, in contrast to many other glomerular diseases where kidney size is usually decreased. Using the above epidemiologic and clinical data, and in the absence of other clinical or serologic data suggesting another disease, diabetic nephropathy is usually diagnosed without a renal biopsy. After the onset of proteinuria, renal function inexorably declines, with 50% of patients reaching renal failure over another 5–10 years; thus, from the earliest stages of microalbuminuria, it usually takes 10–20 years to reach ESRD. However, up to 20–25% of patients with type 2 diabetes and chronic kidney disease have never had albuminuria documented. It is not known if this represents an altered natural history of diabetic nephropathy or another kidney disease that happens to occur in a patient with diabetes. Once renal failure appears, survival on dialysis is shorter for patients with diabetes compared to other dialysis patients. Survival is best for patients who receive a transplant from a living related donor.

Good evidence supports the benefits of blood sugar and blood pressure control as well as inhibition of the renin-angiotensin system in retarding the progression of diabetic nephropathy. In patients with type 1 diabetes, intensive control of blood sugar clearly prevents the development or progression of diabetic nephropathy. The evidence for benefit of intensive blood glucose control in patients with type 2 diabetes is less certain, with current studies reporting conflicting results.

Controlling systemic blood pressure decreases renal and cardiovascular adverse events in this high-risk population. The vast majority of patients with diabetic nephropathy require three or more antihypertensive drugs including ACE inhibitors or angiotensin receptor blockers (ARB) to achieve this goal. Drugs that inhibit the renin-angiotensin system, independent of their effects on systemic blood pressure, have been shown in numerous large clinical trials to slow the progression of diabetic nephropathy at early (microalbuminuria) and late (proteinuria with reduced glomerular filtration) stages. Since angiotensin II increases efferent arteriolar resistance and, hence, glomerular capillary pressure, one key mechanism for the efficacy of inhibitors of the renin angiotensin system is reducing glomerular hypertension. Evidence suggests increased risk for cardiovascular adverse events with little evidence of efficacy in some patients with a combination of two drugs (ACE inhibitors, ARBs, or renin inhibitors) that suppress several components of the renin-angiotensin system. Ongoing trials are examining the hypotheses that other agents may be of benefit including sodium glucose transport 2 inhibitors, endothelin antagonists, and aldosterone antagonists.

GLOMERULAR DEPOSITION DISEASES

Plasma cell dyscrasias producing excess light chain immunoglobulin sometimes lead to the formation of glomerular and tubular deposits that cause heavy proteinuria and renal failure; the same is true for the accumulation of serum amyloid A protein fragments seen in several inflammatory diseases. This broad group of proteinuric patients has *glomerular deposition disease*.

Light Chain Deposition Disease The biochemical characteristics of nephrotoxic light chains produced in patients with light chain malignancies often confer a specific pattern of renal injury; that of either *cast nephropathy* **(see Fig. A3-17)**, which causes renal failure but not heavy proteinuria or amyloidosis, or light chain deposition disease **(see Fig. A3-16)**, which produces nephrotic syndrome with renal failure. These latter patients produce kappa light chains that do not have the biochemical features necessary to form amyloid fibrils. Instead, they self-aggregate and form granular deposits along the glomerular capillary and mesangium, tubular basement membrane, and Bowman's capsule. When predominant in glomeruli, nephrotic syndrome develops, and about 70% of patients progress to dialysis. Light-chain deposits are not fibrillar and do not stain with Congo red, but they are easily detected with anti–light chain antibody using immunofluorescence or as granular deposits on electron microscopy. A combination of the light chain rearrangement, self-aggregating properties at neutral pH, and abnormal metabolism probably contribute to the deposition. Treatment for light chain deposition disease is treatment of the primary disease and, if possible, autologous stem cell transplantation.

Renal Amyloidosis Most *renal amyloidosis* is either the result of primary fibrillar deposits of immunoglobulin light chains known as amyloid L (AL), or secondary to fibrillar deposits of serum amyloid A (AA) protein fragments **(Chap. 108)**. Even though both occur for different reasons, their clinicopathophysiology is quite similar and will be discussed together. Amyloid infiltrates the liver, heart, peripheral nerves, carpal tunnel, upper pharynx, and kidney, producing restrictive cardiomyopathy, hepatomegaly, macroglossia, and heavy proteinuria sometimes associated with renal vein thrombosis. In systemic AL amyloidosis, also called *primary amyloidosis,* light chains produced in excess by clonal plasma cell dyscrasias are made into fragments by macrophages so they can self-aggregate at acid pH. A disproportionate number of these light chains (75%) are of the *lambda* class. About 10% of these patients have overt myeloma with lytic bone lesions and infiltration of the bone marrow with >30% plasma cells; nephrotic syndrome is common, and about 20% of patients progress to dialysis. AA amyloidosis is sometimes called *secondary amyloidosis* and also presents as nephrotic syndrome. It is due to deposition of β-pleated sheets of

serum amyloid A protein, an acute phase reactant whose physiologic functions include cholesterol transport, immune cell attraction, and metalloproteases activation. Forty percent of patients with AA amyloid have rheumatoid arthritis, and another 10% have ankylosing spondylitis or psoriatic arthritis; the rest derive from other lesser causes. Less common in Western countries but more common in Mediterranean regions, particularly in Sephardic and Iraqi Jews, is familial Mediterranean fever (FMF). FMF is caused by a mutation in the gene encoding pyrin, whereas Muckle-Wells syndrome, a related disorder, results from a mutation in cryopyrin; both proteins are important in the apoptosis of leukocytes early in inflammation; such proteins with pyrin domains are part of a pathway called the *inflammasome*. Receptor mutations in tumor necrosis factor receptor 1 (TNFR1)-associated periodic syndrome also produce chronic inflammation and secondary amyloidosis. Fragments of serum amyloid A protein increase and self-aggregate by attaching to receptors for advanced glycation end products in the extracellular environment; nephrotic syndrome is common, and about 40–60% of patient's progress to dialysis. AA and AL amyloid fibrils are detectable with Congo red or in more detail with electron microscopy **(see Fig. A3-15)**. Serum-free light chain nephelometry assays are useful in the early diagnosis and follow-up of disease progression. Biopsy of involved liver or kidney is diagnostic 90% of the time when the pretest probability is high; abdominal fat pad aspirates are positive about 70% of the time, but apparently less so when looking for AA amyloid. Amyloid deposits are distributed along blood vessels and in the mesangial regions of the kidney. The treatment for primary amyloidosis, melphalan, and autologous hematopoietic stem cell transplantation can delay the course of disease in about 30% of patients. Secondary amyloidosis is also relentless unless the primary disease can be controlled. Some new drugs in development that disrupt the formation of fibrils may be available in the future.

Fibrillary-Immunotactoid Glomerulopathy Fibrillary-immunotactoid glomerulopathy is a rare (<1.0% of renal biopsies), morphologically defined disease characterized by glomerular accumulation of nonbranching randomly arranged fibrils. Some classify amyloid and nonamyloid fibril-associated renal diseases all as fibrillary glomerulopathies with immunotactoid glomerulopathy reserved for nonamyloid fibrillary disease not associated with a systemic illness. Others define fibrillary glomerulonephritis as a nonamyloid fibrillary disease with fibrils 12–24 nm and immunotactoid glomerulonephritis with fibrils >30 nm. In either case, fibrillar/microtubular deposits of oligoclonal or oligotypic immunoglobulins and complement appear in the mesangium and along the glomerular capillary wall. Congo red stains are negative. The cause of this "nonamyloid" glomerulopathy is mostly idiopathic; reports of immunotactoid glomerulonephritis describe an occasional association with chronic lymphocytic leukemia or B cell lymphoma. Both disorders appear in adults in the fourth decade with moderate to heavy proteinuria, hematuria, and a wide variety of histologic lesions, including DPGN, MPGN, MGN, or mesangioproliferative glomerulonephritis. Nearly half of patients develop renal failure over a few years. There is no consensus on treatment of this uncommon disorder. The disease has been reported to recur following renal transplantation in a minority of cases.

FABRY'S DISEASE

Fabry's disease is an X-linked inborn error of globotriaosylceramide metabolism secondary to deficient lysosomal α-galactosidase A activity, resulting in excessive intracellular storage of globotriaosylceramide. Affected organs include the vascular endothelium, heart, brain, and kidneys. Classically, Fabry's disease presents in childhood in males with acroparesthesias, angiokeratoma, and hypohidrosis. Over time male patients develop cardiomyopathy, cerebrovascular disease, and renal injury, with an average age of death around 50 years of age. Hemizygotes with hypomorphic mutations sometimes present in the fourth to sixth decade with single-organ involvement. Rarely, dominant-negative α-galactosidase A mutations or female heterozygotes with unfavorable X inactivation present with mild single-organ involvement. Rare females develop severe manifestations including renal failure but do so later in life than males. Renal biopsy reveals enlarged glomerular visceral epithelial cells packed with small clear vacuoles containing globotriaosylceramide; vacuoles may also be found in parietal and tubular epithelia **(see Fig. A3-18)**. These vacuoles of electron-dense materials in parallel arrays (zebra bodies) are easily seen on electron microscopy. Ultimately, renal biopsies reveal FSGS. The nephropathy of Fabry's disease typically presents in the third decade as mild to moderate proteinuria, sometimes with microscopic hematuria or nephrotic syndrome. Urinalysis may reveal oval fat bodies and birefringent glycolipid globules under polarized light (Maltese cross). Renal biopsy is necessary for definitive diagnosis. Progression to renal failure occurs by the fourth or fifth decade. Treatment with inhibitors of the renin-angiotensin system is recommended. Treatment with recombinant α-galactosidase A clears microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin. In patients with advanced organ involvement including chronic kidney disease, progression of disease occurs despite enzyme replacement therapy. Variable responses to enzyme therapy may be due to the occurrence of neutralizing antibodies or differences in uptake of the enzyme. Graft and patient survival following renal transplantation in patients with Fabry's are similar to other causes of ESRD.

PULMONARY-RENAL SYNDROMES

Several diseases can present with catastrophic hemoptysis and glomerulonephritis associated with varying degrees of renal failure. The usual causes include Goodpasture's syndrome, granulomatosis with polyangiitis, microscopic polyangiitis, Churg-Strauss vasculitis, and, rarely, Henoch-Schönlein purpura or cryoglobulinemia. Each of these diseases can also present without hemoptysis and are discussed in detail earlier in "Acute Nephritic Syndromes." **(See Glomerular Schematic 7.)** Pulmonary bleeding in this setting is life-threatening and often results in airway intubation, and acute renal failure requires dialysis. Diagnosis is difficult initially because biopsies and serologic testing take time. Treatment with plasmapheresis and methylprednisolone is often empirical and temporizing until results of testing are available.

BASEMENT MEMBRANE SYNDROMES

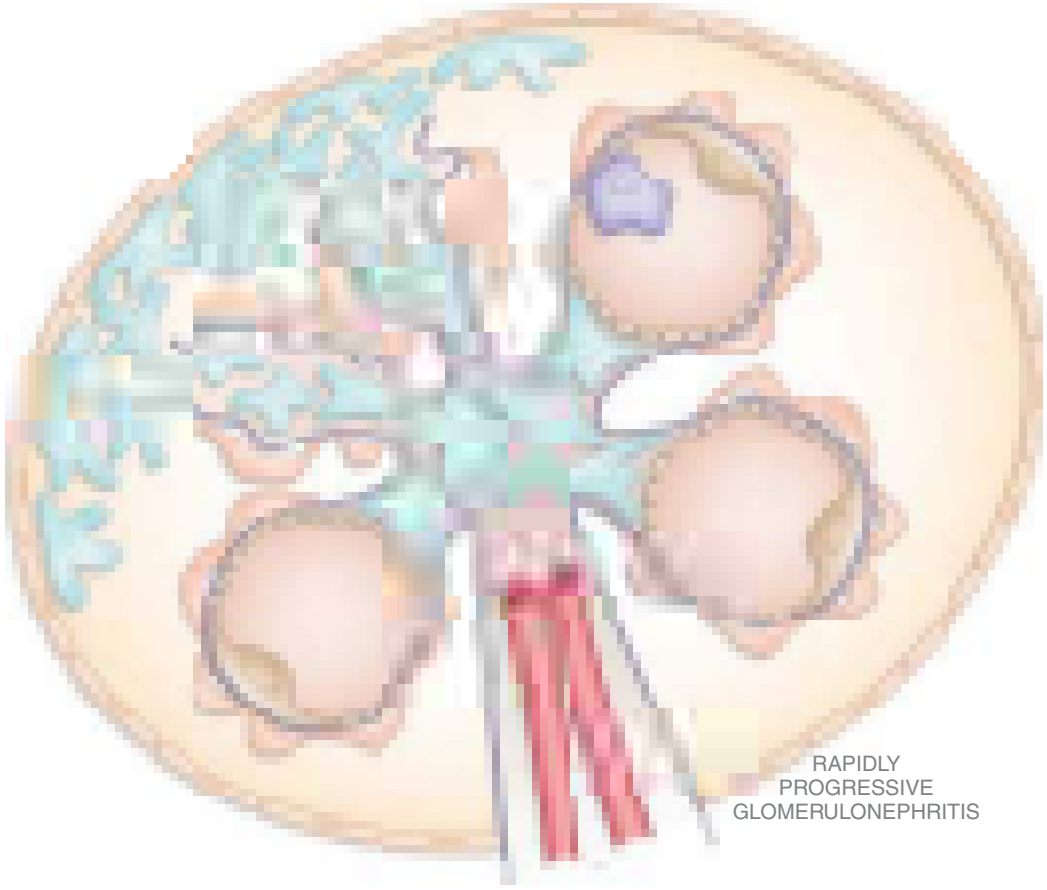
All kidney epithelia, including podocytes, rest on basement membranes assembled into a planar surface through the interweaving of collagen IV with laminins, nidogen, and sulfated proteoglycans. Structural abnormalities in GBM associated with hematuria are characteristic of several familial disorders related to the expression of collagen IV genes. The extended family of collagen IV contains six chains, which are expressed in different tissues at different stages of embryonic development. All epithelial basement membranes early in human development are composed of interconnected triple-helical protomers rich in α1.α1.α2(IV) collagen. Some specialized tissues undergo a developmental switch replacing α1.α1.α2(IV) protomers with an α3.α4.α5(IV) collagen network; this switch occurs in the kidney (glomerular and tubular basement membrane), lung, testis, cochlea, and eye, while an α5.α5.α6(IV) network appears in skin, smooth muscle, and esophagus and along Bowman's capsule in the kidney. This switch probably occurs because the α3.α4.α5(IV) network is more resistant to proteases and ensures the structural longevity of critical tissues. When basement membranes are the target of glomerular disease, they produce moderate proteinuria, some hematuria, and progressive renal failure.

ANTI-GBM DISEASE

Autoimmune disease where antibodies are directed against the α3 NC1 domain of collagen IV produces an *anti-GBM disease* often associated with RPGN and/or a pulmonary-renal syndrome called *Goodpasture's syndrome*. Discussion of this disease is covered earlier in "Acute Nephritic Syndromes."

ALPORT'S SYNDROME

Classically, patients with Alport's syndrome develop hematuria, thinning and splitting of the GBMs, mild proteinuria (<1–2 g/24 h), which appears late in the course, followed by chronic glomerulosclerosis leading to renal failure in association with sensorineural deafness.



Some patients develop lenticonus of the anterior lens capsule, "dot and fleck" retinopathy, and rarely, mental retardation or leiomyomatosis. Approximately 85% of patients with Alport's syndrome have an X-linked inheritance of mutations in the α5(IV) collagen chain on chromosome Xq22–24. Female carriers have variable penetrance depending on the type of mutation or the degree of mosaicism created by X inactivation. Fifteen percent of patients have autosomal recessive disease of the α3(IV) or α4(IV) chains on chromosome 2q35–37. Rarely, some kindred have an autosomal dominant inheritance of dominant-negative mutations in α3(IV) or α4(IV) chains.

Pedigrees with the X-linked syndrome are quite variable in their rate and frequency of tissue damage leading to organ failure. Seventy percent of patients have the juvenile form with nonsense or missense mutations, reading frame shifts, or large deletions and generally develop renal failure and sensorineural deafness by age 30. Patients with splice variants, exon skipping, or missense mutations of α-helical glycines generally deteriorate after the age of 30 (adult form) with mild or late deafness. Early severe deafness, lenticonus, or proteinuria suggests a poorer prognosis. Usually females from X-linked pedigrees have only microhematuria, but up to 25% of carrier females have been reported to have more severe renal manifestations. Pedigrees with the autosomal recessive form of the disease have severe early disease in both females and males with asymptomatic parents.

Clinical evaluation should include a careful eye examination and hearing tests. However, the absence of extrarenal symptoms does not rule out the diagnosis. Since α5(IV) collagen is expressed in the skin, some X-linked Alport's patients can be diagnosed with a skin biopsy revealing the lack of the α5(IV) collagen chain on immunofluorescent analysis. Patients with mutations in α3(IV) or α4(IV) require a renal biopsy. Genetic testing can be used for the diagnosis of Alport's syndrome and the demonstration of the mode of inheritance. Early in their disease, Alport's patients typically have thin basement membranes on renal biopsy **(see Fig. A3-19)**, which thicken over time into multilamellations surrounding lucent areas that often contain granules of varying density—the so-called split basement membrane. In any Alport's kidney, there are areas of thinning mixed with splitting of the GBM. Tubules drop out, glomeruli scar, and the kidney eventually succumbs to interstitial fibrosis. All affected members of a family with X-linked Alport's syndrome should be identified and followed, including mothers of affected males. Primary treatment is control of systemic hypertension and use of ACE inhibitors to slow renal progression. Although patients who receive renal allografts usually develop anti-GBM antibodies directed toward the collagen epitopes absent in their native kidney, overt Goodpasture's syndrome is rare and graft survival is good.

THIN BASEMENT MEMBRANE DISEASE

Thin basement membrane disease (TBMD) characterized by persistent or recurrent hematuria is not typically associated with proteinuria, hypertension, or loss of renal function or extrarenal disease. Although not all cases are familial (perhaps a founder effect), it usually presents in childhood in multiple family members and is also called *benign familial hematuria*. Cases of TBMD have genetic defects in type IV collagen but in contrast to Alport behave as an autosomal dominant disorder that in ~40% of families segregates with the *COL(IV) α3/COL(IV) α4* loci. Mutations in these loci can result in a spectrum of disease ranging from TBMD to autosomal dominant or recessive Alport's. The GBM shows diffuse thinning compared to normal values for the patient's age in otherwise normal biopsies **(see Fig. A3-19)**. The vast majority of patients have a benign course.

NAIL-PATELLA SYNDROME

Patients with nail-patella syndrome develop iliac horns on the pelvis and dysplasia of the dorsal limbs involving the patella, elbows, and nails, variably associated with neural-sensory hearing impairment, glaucoma, and abnormalities of the GBM and podocytes, leading to

hematuria, proteinuria, and FSGS. The syndrome is autosomal dominant, with haploinsufficiency for the *LIM* homeodomain transcription factor LMX1B; pedigrees are extremely variable in the penetrance for all features of the disease. LMX1B regulates the expression of genes encoding α3 and α4 chains of collagen IV, interstitial type III collagen, podocin, and CD2AP that help form the slit-pore membranes connecting podocytes. Mutations in the LIM domain region of *LMX1B* associate with glomerulopathy, and renal failure appears in as many as 30% of patients. Proteinuria or isolated hematuria is discovered throughout life, but usually by the third decade, and is inexplicably more common in females. On renal biopsy there is focal sclerosing glomerulonephritis with specific lucent damage to the lamina densa of the GBM, an increase in collagen III fibrils along glomerular capillaries and in the mesangium, and damage to the slit-pore membrane, producing heavy proteinuria not unlike that seen in congenital nephrotic syndrome. Patients with renal failure do well with transplantation.

GLOMERULAR-VASCULAR SYNDROMES

A variety of diseases result in classic vascular injury to the glomerular capillaries. Most of these processes also damage blood vessels elsewhere in the body. The group of diseases discussed here lead to vasculitis, renal endothelial injury, thrombosis, ischemia, and/or lipid-based occlusions.

ATHEROSCLEROTIC NEPHROPATHY

Aging in the developed world is commonly associated with the occlusion of coronary and systemic blood vessels. The reasons for this include obesity, insulin resistance, smoking, hypertension, and diets rich in lipids that deposit in the arterial and arteriolar circulation, producing local inflammation and fibrosis of small blood vessels. When the renal arterial circulation is involved, the glomerular microcirculation is damaged, leading to *chronic nephrosclerosis*. Patients with GFRs <60 mL/min have more cardiovascular events and hospitalizations than those with higher filtration rates. Several aggressive lipid disorders can accelerate this process, but most of the time atherosclerotic progression to chronic nephrosclerosis is associated with poorly controlled hypertension. Approximately 10% of glomeruli are normally sclerotic by age 40, rising to 20% by age 60 and 30% by age 80. Serum lipid profiles in humans are greatly affected by *apolipoprotein E* polymorphisms; the E4 allele is accompanied by increases in serum cholesterol and is more closely associated with atherogenic profiles in patients with renal failure. Mutations in E2 alleles, particularly in Japanese patients, produce a specific renal abnormality called *lipoprotein glomerulopathy* associated with glomerular lipoprotein thrombi and capillary dilation.

HYPERTENSIVE NEPHROSCLEROSIS

Systemic hypertension causes permanent damage to the kidneys in about 6% of patients with elevated blood pressure. As many as 27% of patients with end-stage kidney disease have hypertension as a primary cause. Although there is not a clear correlation between the extent or duration of hypertension and the risk of end-organ damage, *hypertensive nephrosclerosis* is fivefold more frequent in African Americans than whites. Risk alleles associated with *APOL1*, a functional gene for apolipoprotein L1 expressed in podocytes, substantially explains the increased burden of ESRD among African Americans. Associated risk factors for progression to end-stage kidney disease include increased age, male gender, race, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and preexisting renal injury. Kidney biopsies in patients with hypertension, microhematuria, and moderate proteinuria demonstrate arteriolosclerosis, chronic nephrosclerosis, and interstitial fibrosis in the absence of immune deposits **(see Fig. A3-21)**. Today, based on a careful history, physical examination, urinalysis, and some serologic testing, the diagnosis of chronic nephrosclerosis is usually inferred without a biopsy. Recent studies suggest, in the absence of diabetes, adults with hypertension and cardiovascular risk factors benefit from achieving a systolic BP <120 mmHg compared to <140 mmHg. In the presence of kidney disease, most patients begin antihypertensive therapy with two drugs, classically a thiazide diuretic and an ACE inhibitor; most will require three drugs. There is strong evidence in African Americans with hypertensive nephrosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in renal function independent of effects on systemic blood pressure. Malignant acceleration of hypertension complicates the course of chronic nephrosclerosis, particularly in the setting of scleroderma or cocaine use **(see Fig. A3-24)**. The hemodynamic stress of malignant hypertension leads to fibrinoid necrosis of small blood vessels, thrombotic microangiography, a nephritic urinalysis, and acute renal failure. In the setting of renal failure, chest pain, or papilledema, the condition is treated as a hypertensive emergency.

CHOLESTEROL EMBOLI

Aging patients with clinical complications from atherosclerosis sometimes shower cholesterol crystals into the circulation—either spontaneously or, more commonly, following an endovascular procedure with manipulation of the aorta—or with use of systemic anticoagulation. Spontaneous emboli may shower acutely or shower subacutely and somewhat more silently. Irregular emboli trapped in the microcirculation produce ischemic damage that induces an inflammatory reaction. Depending on the location of the atherosclerotic plaques releasing these cholesterol fragments, one may see cerebral transient ischemic attacks; livedo reticularis in the lower extremities; Hollenhorst plaques in the retina with visual field cuts; necrosis of the toes; and acute glomerular capillary injury leading to FSGS sometimes associated with hematuria, mild proteinuria, and loss of renal function, which typically progresses over a few years. Occasional patients have fever, eosinophilia, or eosinophiluria. A skin biopsy of an involved area may be diagnostic. Since tissue fixation dissolves the cholesterol, one typically sees only residual, biconvex clefts in involved vessels **(see Fig. A3-22)**. There is no therapy to reverse embolic occlusions, and steroids do not help. Controlling blood pressure and lipids and cessation of smoking are usually recommended for prevention.

SICKLE CELL DISEASE

Although individuals with SA-hemoglobin are usually asymptomatic, most will gradually develop hyposthenuria due to subclinical infarction of the renal medulla, thus predisposing them to volume depletion. There is an unexpectedly high prevalence of sickle trait among dialysis patients who are African American. Patients with homozygous SS-sickle cell disease and less commonly SC-sickle cell disease develop chronic vasoocclusive disease in many organs. Polymers of deoxygenated SS-hemoglobin distort the shape of red blood cells. These cells attach to endothelia and obstruct small blood vessels, producing frequent and painful sickle cell crises over time. Vessel occlusions in the kidney produce glomerular hypertension, FSGS, interstitial nephritis, and renal infarction associated with hyposthenuria, microscopic hematuria, and even gross hematuria; some patients also present with MPGN. Renal function can be overestimated due to the increased tubular secretion of creatinine seen in many patients with SS-sickle cell. By the second or third decade of life, persistent vasoocclusive disease in the kidney leads to varying degrees of renal failure, and some patients end up on dialysis. Their prognosis on dialysis is poor and anemia management with erythropoiesis-stimulating agents complicated. Treatment is directed to reducing the frequency of painful crises and administering ACE inhibitors in the hope of delaying a progressive decline in renal function. In sickle cell patients undergoing renal transplantation, renal graft survival is comparable to African Americans in the general transplant population.

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura (TTP) and *hemolytic-uremic syndrome* (HUS) represent a spectrum of thrombotic microangiopathies. TTP and HUS share the general features of idiopathic thrombocytopenic purpura, hemolytic anemia, fever, renal failure, and neurologic disturbances. When patients, particularly children, have more evidence of renal injury, their condition tends to be called HUS. In adults with neurologic disease, it is considered to be TTP. In adults there is often a mixture of both, which is why they are often referred to as having TTP/HUS. On examination of kidney tissue, there is evidence of *glomerular capillary endotheliosis* associated with platelet thrombi, damage to the

capillary wall, and formation of fibrin material in and around glomeruli (see Fig. A3-23). These tissue findings are similar to what is seen in preeclampsia/HELLP (*h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count syndrome), malignant hypertension, and the antiphospholipid syndrome. TTP/HUS is also seen in pregnancy; with the use of oral contraceptives or quinine; in renal transplant patients given OKT3 for rejection; in patients taking the calcineurin inhibitors, cyclosporine and tacrolimus, or in patients taking the antiplatelet agents, ticlopidine and clopidogrel; or following HIV infection.

Although there is no agreement on how much they share a final common pathophysiology, two general groups of patients are recognized: childhood HUS associated with enterohemorrhagic diarrhea and TTP/HUS in adults. Childhood HUS is caused by a toxin released by *Escherichia coli* 0157:H7 and occasionally by *Shigella dysenteriae*. This shiga toxin (verotoxin) directly injures endothelia, enterocytes, and renal cells, causing apoptosis, platelet clumping, and intravascular hemolysis by binding to the glycolipid receptors (Gb3). These receptors are more abundant along endothelia in children compared to adults. Shiga toxin also inhibits the endothelial production of ADAMTS13. In familial cases of adult TTP/HUS, there is a genetic deficiency of the ADAMTS13 metalloprotease that cleaves large multimers of von Willebrand's factor. Absent ADAMTS13, these large multimers cause platelet clumping and intravascular hemolysis. An antibody to ADAMTS13 is found in many sporadic cases of adult TTP/HUS, but not all; many patients also have antibodies to the thrombospondin receptor on selected endothelial cells in small vessels or increased levels of plasminogen-activator inhibitor 1 (PAI-1). Patients can be tested for ADAMTS13 activity and, if low, the presence of antibodies to ADAMTS13 distinguishes the deficiency from the immune-mediated disease. Some children with complement protein deficiencies express atypical HUS (aHUS), which can be treated with liver transplant. The treatment of adult TTP/HUS with ADAMTS13 antibodies is daily plasmapheresis, which can be lifesaving. Plasmapheresis with fresh frozen plasma is given until the platelet count rises, but in relapsing patients it normally is continued well after the platelet count improves, and in resistant patients twice-daily exchange may be helpful. Most patients respond within 2 weeks of daily plasmapheresis. Since TTP/HUS often has an autoimmune basis, there is an anecdotal role in relapsing patients for using splenectomy, steroids, immunosuppressive drugs, bortezomib, or rituximab, an anti-CD20 antibody. Patients without antibodies and a genetic deficiency of ADAMTS13 production can potentially be treated with fresh frozen plasma alone. Patients with childhood HUS from infectious diarrhea are not given antibiotics, because antibiotics are thought to accelerate the release of the toxin and the diarrhea is usually self-limited. No intervention appears superior to supportive therapy in children with postdiarrheal HUS.

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (SEE CHAP. 350)

GLOBAL CONSIDERATIONS

INFECTIOUS DISEASE–ASSOCIATED SYNDROMES

A number of infectious diseases will injure the glomerular capillaries as part of a systemic reaction producing an immune response or from direct infection of renal tissue. Evidence of this immune response is collected by glomeruli in the form of immune deposits that damage the kidney, producing moderate proteinuria and hematuria. A high prevalence of many of these infectious diseases in developing countries results in infection-associated renal disease being the most common cause of glomerulonephritis in many parts of the world.

Poststreptococcal Glomerulonephritis This form of glomerulonephritis is one of the classic complications of streptococcal infection. The discussion of this disease can be found earlier, in the section "Acute Nephritic Syndromes."

Subacute Bacterial Endocarditis Renal injury from persistent bacteremia absent the continued presence of a foreign body, regardless of cause, is treated presumptively as if the patient has endocarditis. The discussion of this disease can be found earlier, in the section "Acute Nephritic Syndromes."

Human Immunodeficiency Virus Renal disease is an important complication of HIV disease. The risk of development of ESRD is much higher in HIV-infected African Americans than in HIV-infected whites. About 50% of HIV-infected patients with kidney disease have HIV-associated nephropathy (HIVAN) on biopsy. The lesion in HIVAN is FSGS, characteristically revealing a collapsing glomerulopathy (see Fig. A3-3) with visceral epithelial cell swelling, microcystic dilatation of renal tubules, and tubuloreticular inclusion. Renal epithelial cells express replicating HIV virus, but host immune responses also play a role in the pathogenesis. HIVAN develops almost exclusively in patients of black race origin who have the APOL1 variant. HIVICK, HIV immune complex kidney disease is a group of immune complex-mediated glomerular lesions seen in HIV patients, and on biopsy can look like a constellation of other glomerular lesions, including postinfectious glomerulonephritis, MGN, MPGN, DPGN, MCD, and IgA nephropathy. The HIVICK effect is a complication of active HIV viremia.

HIV patients with FSGS typically present with nephrotic-range proteinuria and hypoalbuminemia, but unlike patients with other etiologies for nephrotic syndrome, they do not commonly have hypertension, edema, or hyperlipidemia. Renal ultrasound also reveals large, echogenic kidneys despite the finding that renal function in some patients declines rapidly. Treatment with inhibitors of the renin-angiotensin system decreases the proteinuria. Effective antiretroviral therapy benefits both the patient and the kidney and improves survival of HIV-infected patients with HIVAN and in some cases HIVICK-associated chronic kidney disease or ESRD. In HIV-infected patients not yet on therapy, the presence of HIVAN is an indication to initiate therapy. Following the introduction of antiretroviral therapy, survival on dialysis for the HIV-infected patient has improved dramatically. Renal transplantations in HIV-infected patients without detectable viral loads or histories of opportunistic infections provide a better survival benefit over dialysis. Following transplantation, patient and graft survival are similar to the general transplant population despite frequent rejections.

Hepatitis B and C Typically, infected patients present with microscopic hematuria, nonnephrotic or nephrotic-range proteinuria, and hypertension. There is a close association between hepatitis B infection and polyarteritis nodosa with vasculitis appearing generally in the first 6 months following infection. Renal manifestations include renal artery aneurysms, renal infarction, and ischemic scars. Alternatively, the hepatitis B carrier state can produce a MGN with predominant IgG1 deposition that is more common in children than adults, or MPGN that is more common in adults than in children. Renal histology is indistinguishable from idiopathic MGN, type I or type 3 MPGN. Viral antigens most commonly, HBeAG, are found in the renal deposits. Cryoglobulinemic glomerulonephritis has also been reported. There are no good treatment guidelines, but interferon α-2b and antiviral agents which consist of either nucleotide or nucleoside reverse transcription inhibitors have been used to some effect. Children have a good prognosis, with 60–65% achieving spontaneous remission within 4 years. In contrast, 30% of adults have renal insufficiency and 10% have renal failure 5 years after diagnosis.

Up to 30% of patients with chronic hepatitis C infection have some renal manifestations. Patients often present with type II mixed cryoglobulinemia, nephrotic syndrome, microscopic hematuria, abnormal liver function tests, depressed C3 levels, anti–hepatitis C virus (HCV) antibodies, and viral RNA in the blood. The renal lesions most commonly seen, in order of decreasing frequency, are cryoglobulinemic glomerulonephritis, MGN, and type I MPGN but PAN, IgA and FSGS have been reported. With the availability of direct-acting antivirals, including ledipasvir/sofosbuvir which can achieve a viral remission in >95% of patients, the prevalence of glomerular disease in HCV patients should decline. These drugs are currently the treatment of choice for patients with HCV-related MPGN or PAN.

Other Viruses Other viral infections are occasionally associated with glomerular lesions, but cause and effect are not well established.

These viral infections and their respective glomerular lesions include: cytomegalovirus producing MPGN or FSGS; influenza and anti-GBM disease; measles-associated endocapillary proliferative glomerulonephritis, with measles antigen in the capillary loops and mesangium; parvovirus causing mild proliferative or mesangioproliferative glomerulonephritis or FSGS; mumps and mesangioproliferative glomerulonephritis; Epstein-Barr virus producing MPGN, diffuse proliferative nephritis, or IgA nephropathy; dengue hemorrhagic fever causing endocapillary proliferative glomerulonephritis; Hanta virus and mesangial proliferative glomerulonephritis and coxsackievirus producing *focal glomerulonephritis* or DPGN.

Syphilis Secondary syphilis, with rash and constitutional symptoms, develops weeks to months after the chancre first appears and occasionally presents with the nephrotic syndrome from MGN caused by subepithelial immune deposits containing treponemal antigens. Other lesions have also rarely been described including interstitial syphilitic nephritis. The diagnosis is confirmed with nontreponemal and treponemal tests for *Treponema pallidum*. The renal lesion responds to treatment with penicillin or an alternative drug, if allergic. Additional testing for other sexually transmitted diseases is an important part of disease management.

Leprosy Despite aggressive eradication programs, ~400,000 new cases of leprosy appear annually worldwide. The diagnosis is best made in patients with multiple skin lesions accompanied by sensory loss in affected areas, using skin smears showing paucibacillary or multibacillary infection (WHO criteria). Leprosy is caused by infection with *Mycobacterium leprae* and can be classified by Ridley-Jopling criteria into various types: tuberculoid, borderline tuberculoid, mid-borderline and borderline lepromatous, and lepromatous. Renal involvement in leprosy is related to the quantity of bacilli in the body, and the kidney is one of the target organs during splanchnic localization. In some series, all cases with borderline lepromatous and lepromatous types of leprosy have various forms of renal involvement including FSGS, mesangioproliferative glomerulonephritis, or renal amyloidosis; much less common are the renal lesions of DPGN and MPGN. Treatment of the infection with multi-drug therapy can reduce the incidence of renal disease or produce remission of the renal disease.

Malaria There are 300–500 million incident cases of malaria each year worldwide, and the kidney is commonly involved. Glomerulonephritis is due to immune complexes containing malarial antigens that are implanted in the glomerulus. In malaria from *P. falciparum*, mild proteinuria is associated with subendothelial deposits, mesangial deposits, and mesangioproliferative glomerulonephritis that usually resolve with treatment. In quartan malaria from infection with *Plasmodium malariae*, children are more commonly affected and renal involvement is more severe. Transient proteinuria and microscopic hematuria can resolve with treatment of the infection. However, resistant nephrotic syndrome with progression to renal failure over 3–5 years does happen, as <50% of patients respond to steroid therapy. Affected patients with nephrotic syndrome have thickening of the glomerular capillary walls, with subendothelial deposits of IgG, IgM, and C_3 associated with a sparse membranoproliferative lesion. The rare mesangioproliferative glomerulonephritis reported with *Plasmodium vivax* or *Plasmodium ovale* typically has a benign course. Acute kidney injury can often complicate these glomerulopathies.

Schistosomiasis Schistosomiasis affects >300 million people worldwide and primarily involves the urinary and gastrointestinal tracts. Glomerular involvement varies with the specific strain of schistosomiasis; *Schistosoma mansoni* is most commonly associated with clinical renal disease, and the glomerular lesions can be classified: Class I is a *mesangioproliferative glomerulonephritis*; class II is an *extracapillary proliferative glomerulonephritis*; class III is a *membranoproliferative glomerulonephritis*; class IV is a *focal segmental glomerulonephritis*; and class V is *amyloidosis*. Classes I–II often remit with treatment of the infection, but classes III and IV lesions are associated with IgA immune deposits and progress despite antiparasitic and/or immunosuppressive therapy.

Other Parasites Renal involvement with toxoplasmosis infections is rare. When it occurs, patients present with nephrotic syndrome and have a histologic picture of MPGN. Fifty percent of patients with leishmaniasis will have mild to moderate proteinuria and microscopic hematuria, but renal insufficiency is rare. Acute DPGN, MGN, and mesangioproliferative glomerulonephritis have all been observed on biopsy. Filariasis and trichinosis are caused by nematodes and are sometimes associated with glomerular injury presenting with proteinuria, hematuria, and a variety of histologic lesions that typically resolve with eradication of the infection.

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309 Polycystic Kidney Disease and Other Inherited Disorders of Tubule Growth and Development

Jing Zhou, Martin R. Pollak

The polycystic kidney diseases are a group of genetically heterogeneous disorders and a leading cause of kidney failure. The autosomal dominant form of polycystic kidney disease (ADPKD) is the most common life-threatening monogenic disease, affecting 12 million people worldwide. The autosomal recessive form of polycystic kidney disease (ARPKD) is rarer but affects the pediatric population. Kidney cysts are often seen in a wide range of syndromic diseases. Recent studies have shown that defects in the structure or function of the primary cilia may underline this group of genetic diseases collectively termed *ciliopathies* **(Table 309-1)**.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Etiology and Pathogenesis (Fig. 309-1) ADPDK is characterized by progressive formation of epithelial lined cysts in the kidney. Although cysts only occur in 5% of the tubules in the kidney, the enormous growth of these cysts ultimately leads to the loss of normal surrounding tissues and loss of renal function. The cellular defects in ADPKD that have been known for a long time are increased cell proliferation and fluid secretion, decreased cell differentiation, and abnormal extracellular matrix. ADPKD is caused by mutations in *PKD1* and *PKD2* which, respectively, code for polycystin-1 (PC1) and polycystin-2 (PC2). PC1 is a large 11- transmembrane protein that functions like a G-protein coupled receptor. PC2 is a calcium-permeable six transmembrane protein that structurally belongs to the transient

TABLE 309-1 Inherited Diseases Commonly Associated with a Cystic Phenotype

DISEASE	MODE OF INHERITANCE	RENAL ABNORMALITIES	OTHER CLINICAL FEATURES	GENES
Autosomal dominant polycystic kidney disease	AD	Cortical and medullary cysts	Liver, pancreatic cysts, hypertension, subarachnoid hemorrhage	*PKD1, PKD2*
Autosomal recessive polycystic kidney disease	AR	Distal and collecting duct cysts	Oligohydramnios if severe, hypertension, ascending cholangitis, liver fibrosis	*PKHD1*
Medullary cystic kidney (Autosomal dominant tubulointerstital kidney disease)	AD	Small fibrotic kidneys; medullary cysts	In adults, gout	*UMOD* *MUC1* *REN*
Nephronophthisis	AR	Small fibrotic kidneys; medullary cysts	Growth retardation, anemia, (visual loss, liver fibrosis, cerebellar ataxia if associated with another syndrome)	*NPHP1-20, IQCB1, CEP290, GLIS2, RPGRIP1L, NEK8, SDCCAG8, TMEM67, TTC21B*
Senior-Loken syndrome	AR	Renal cysts	Juvenile nephronophthisis, Leber amaurosis	*NPHP1-6, SDCCAG8*
Leber congenital amaurosis	AR	Renal cysts	Visual impairment in first year of life; pigmentary retinopathy	*GUCY2D, RPE65, LCA3-14* (including *LCA10, CEP290*)
Meckel-Gruber syndrome	AR	Cortical and medullary cysts	CNS anomalies, polydactyly, congenital heart defects	*MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, TCTN2, B9D1, B9D2, NPHP3*
Bardet-Biedl syndrome	AR	Renal cysts	Obesity, polydactyly, retinitis pigmentosa, anosmia, congenital heart defects, mental retardation	*BBS1, 2, ARL6, BBS4,5, MKKS, BBS7, TTC8, BBS9, 10, TRIM32, BBS12, MKS1, CEP290, C2ORF86; modifiers MKS1, MKS3, CCDC28B*
Oral-facial-digital syndrome type I	AR	Renal cysts	Oral cavity, face, and digit anomalies; CNS abnormalities; cystic kidney disease; X-linked with male lethality, primary ciliary dyskinesia	*OFD1*
Cranioectodermal dysplasia (Sensenbrenner syndrome)	AR	Renal cysts	Skeletal dysplasia; thoracic deformities; polydactyly; renal cysts; retinitis pigmentosa	*IFT80*
Tuberous sclerosis	AD	Renal cysts	Angiomyolipomas; renal cell carcinoma Facial angiofibromas; CNS hamartomas	*TSC1, TSC2*
Von Hippel-Lindau disease	AD	Renal cysts	Renal cell carcinoma, retinal angiomas; CNS hemangioblastomas; pheochromocytomas	*VHL*

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system.

receptor potential (TRP) cation channel family. PC1 and PC2 are widely expressed in almost all tissues and organs. PC1 expression is high in development and low in the adult, whereas PC2 expression is relatively constant. PC1/2 are found on the primary cilium, a hair-like structure present on the apical membrane of a cell, in addition to the cell membranes and cell-cell junctions of tubular epithelial cells. Defects in the primary cilia are linked to a wide spectrum of human diseases, collectively termed ciliopathies. The most common phenotype shared by many ciliopathies is kidney cysts. PC1 and PC2 bind to each other via their respective C-terminal tails to form a receptor-channel complex and regulate each other's function. The PC1/2 protein complex serves as a mechanosensor or chemical sensor and regulates calcium and G-protein signaling. The PC1/2 protein complex may also directly regulate a number of cellular functions including the cell cycle, the actin cytoskeleton, planar cell polarity (PCP), and cell migration. This protein complex has also been implicated in regulating a number of signaling pathways, including Wnt, mammalian target of rapamycin (mTOR), STAT3, cMET, phosphoinositide 3-kinase (PI3K/Akt), G protein–coupled receptor (GPCR), and epidermal growth factor receptor (EGFR), as well as in the localization and activity of cystic fibrosis transmembrane conductance regulator (CFTR). One hypothesis is that loss of ciliary function of PC1 and PC2 leads to aberrant calcium signaling and a subsequent increase of adenylyl cyclase activity and decrease of phosphodiesterase activity, which, in turn, causes increased cellular cAMP. Increased cAMP promotes protein kinase A activity, among other effectors, and, in turn, leads to cyst growth by promoting proliferation and fluid secretion of cyst-lining cells through chloride and aquarporin channels in ADPKD kidneys.

ADPKD is inherited as an autosomal dominant trait with complete penetrance, but variable expressivity. The disease affects all ethnic groups worldwide with an estimated prevalence of 1:1000 to 1:400. Only half of the patients with ADPKD are clinically diagnosed during their lifetime. ADPKD is genetically heterogeneous. The first disease gene (*PKD1*) was localized to the region of the alpha-globin gene on chromosome 16p13 in 1985, and a second disease gene (*PKD2*) locus was mapped to chromosome 4q21-q23 in 1993. Mutations of *PKD1* and *PKD2* are responsible for ~85% and ~15% of ADPKD cases, respectively. However, patients with *PKD2* mutations may be >15% because they tend to have milder clinical disease and, as a result, under-diagnosed. Embryonic lethality of *Pkd1* and *Pkd2* knockout mice suggest human homozygotes may be lethal, thus not clinically recognized.

PKD1 is comprised of 46 exons occupying ~52 kb of genomic DNA. It produces a ~14 kb transcript that encodes polycystin-1, a protein of ~4300 amino acids. A feature of the *PKD1* gene is that the 5′ three-quarters of *PKD1* have been duplicated at six other sites on chromosome 16p, and many of them produce mRNA transcripts, which provides a major challenge for genetic analysis of the duplicated region. *PKD2* is a single-copy gene with 15 exons producing a ~5.3 kb mRNA transcript that encodes polycystin-2, a protein of 968 amino acids. A third gene *GANAB*, encoding the glucosidase IIa subunit, was recently reported to cause ADPKD, but patients with mutations in this gene all appear to have polycystic liver disease, and their kidney disease is milder than that in classic ADPKD.

In ADPKD patients, every cell carries a germline mutant allele of either *PKD1* or *PKD2*. However, cysts develop in only a small fraction of the nephrons. Cysts are thought to originate from clonal growth of single cells that have received a somatic "second hit" mutation in the "normal" allele of the *PKD1* or *PKD2* gene. Accumulating evidence in mouse models now shows that partial loss of function of the second allele of *Pkd1* in a proliferative environment is sufficient for cystogenesis, suggesting that a critical amount of *PKD1* is needed in a cell. Somatic inactivation of the second allele of *Pkd1* in adult mice results

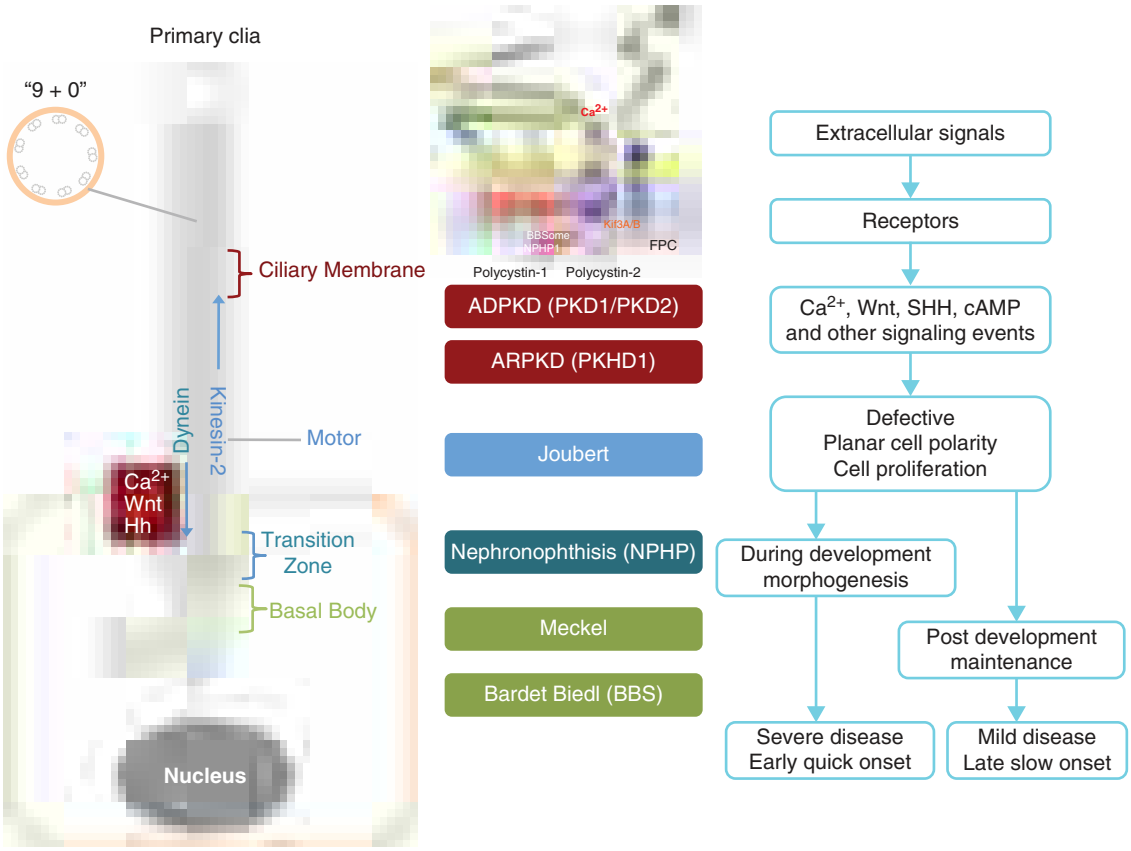

FIGURE 309-1 Scheme of the primary cilium and cystic kidney disease proteins. ***Left:*** a scheme of the primary cilium. Primary cilia share a "9+0" organization of microtubule doublets. Proteins are transported into the cilium by motor protein kinesin 2 and transported out of the cilium by dynein. The cilium is connected to the basal body through the transition zone. ***Middle:*** topology of ADPKD and ARPKD proteins polycystin 1, polycystin 2, and FPC are shown. Localization of disease proteins in the cilium, the transition zone and the basal body are color coded. ***Right:*** potential disease mechanisms due to cilium mediated signaling events.

in very slow onset of cyst development in the kidney, but a "third hit" such as an additional genetic or epigenetic event, the inactivation of a growth suppressor gene, the activation of a growth promoting gene(s), or an event like renal injury that activates the developmental program, may promote rapid cyst formation.

Clinical Manifestations ADPKD is characterized by the progressive bilateral formation of renal cysts. Focal renal cysts are typically detected in affected subjects aged <30 years. Hundreds to thousands of cysts are usually present in the kidneys of most patients in the fifth decade **(Fig. 309-2)**. Enlarged kidneys can each reach a fourfold increase in length, and weigh up to 20 times the normal weight. The clinical presentations of ADPKD are highly variable. While many patients are asymptomatic until the fourth to fifth decade of life and are diagnosed by incidental discoveries of hypertension or abdominal masses, back or flank pain is a frequent symptom in ~60% of patients with ADPKD. The pain may result from renal cyst infection, hemorrhage, or nephrolithiasis. Gross hematuria resulting from cyst rupture occurs in ~ 40% of patients during the course of their disease, and many of them will have recurrent episodes. Flank pain and hematuria may coexist if the cyst that ruptures is connected with the collecting system. Proteinuria is usually a minor feature of ADPKD. Infection is the second most common cause of death for patients with ADPKD. Up to half of patients with ADPKD will have one or more episodes of renal infection during their lifetime. An infected cyst and acute pyelonephritis are the most common renal infections often due to gram-negative bacteria, which are associated with fever and flank pain, with or without bacteremia. These complications and renal insufficiency often correlate with structural abnormality of the renal parenchyma. Kidney stones occur in ~20% of patients with ADPKD. Different from the general population, more than half of the stones in patients with ADPKD are composed of uric acid, with the remainder due to calcium oxalate. Distal acidification defects, abnormal ammonium transport, low urine pH, and hypocitraturia may be important in the pathogenesis of renal stones in ADPKD. Renal cell carcinoma is a rare complication of ADPKD with no apparent increased frequency compared to the general population. However, in ADPKD these tumors are more often bilateral at presentation, multicentric, and sarcomatoid in type. Radiological imaging is often not helpful in distinguishing cyst infection and cyst hemorrhage because of their complexity. CT scan and magnetic resonance imaging (MRI) are often useful in distinguishing a malignancy from a complex cyst. Cardiovascular complications are the major cause of mortality in patients with ADPKD. Hypertension is common, and typically occurs before any reduction in glomerular filtration rate (GFR). Hypertension is a risk factor for both cardiovascular and kidney disease progression in ADPKD. Notably, some normotensive patients with ADPKD may also have left ventricular hypertrophy. Hypertension in ADPKD may result from the increased activation of the renin-angiotensin-aldosterone system, increased sympathetic nerve activity, and impaired endothelial cilium function-dependent relaxation of small resistant blood vessels.

The progression of ADPKD has striking inter- and intrafamilial variability. The disease can present as early as *in utero*, but end-stage renal disease (ESRD) typically occurs in late middle age. Risk factors include early diagnosis of ADPKD, hypertension, gross hematuria, multiple pregnancies, and large kidney size. Liver cysts derived from the biliary epithelia are the most common extrarenal complication. Polycystic liver disease associated with ADPKD is different from autosomal dominant polycystic liver disease (ADPLD), which is caused by mutations in at least two distinct genes (*PRKCSH* and *SEC63*) and does not progress to renal failure. Massive polycystic liver disease occurs almost exclusively in women with ADPKD, particularly those with multiple pregnancies. Heterozygous loss-of-function variants in *PKHD1*, *ALG8*, *GANAB*, and *SEC61B* are now found in ADPLD. *ALG8*, *GANAB*, and *SEC61B*, all encode ER proteins that are involved in the same pathway as GIIβ and SEC63, and each appears to affect PC1 biogenesis.

FIGURE 309-2 Photograph showing a kidney from a patient with autosomal dominant polycystic kidney disease. The kidney has been cut open to expose the parenchyma and internal aspects of cysts.

Intracranial aneurysm (ICA) occurs four to five times more frequent in APDKD patients than that seen in the general population and cause high mortality. The disease gene products PC1 and PC2 may be directly responsible for defects in arterial smooth muscle cells and myofibroblasts. The focal nature and the natural history of ICA in ADPKD remain unclear. A family history of ICA is a risk factor of aneurysm rupture in ADPKD, whether hypertension and cigarette smoking are independent risk factors is not clear. About 20–50% of patients may experience "warning headaches" preceding the index episode of subarachnoid hemorrhage due to ruptured ICA. A CT scan is generally used as the first diagnostic test. A lumbar puncture may be used to confirm the diagnosis. The role of radiological screening for ICA in asymptomatic patients with ADPKD remains unclear. ADPKD patients with a positive family history of ICAs may undergo pre-symptomatic screening of ICAs by MR angiography. Other vascular abnormalities in ADPKD patients include diffuse arterial dolichoectasias of the anterior and posterior cerebral circulation, which can predispose to arterial dissection and stroke. Mitral valve prolapse occurs in up to 30% of patients with ADPKD, and tricuspid valve prolapse is less common. Other valvular abnormalities occurring with increased frequency in ADPKD patients include insufficiency of the mitral, aortic, and tricuspid valves. Most patients are asymptomatic but some may progress and require valve replacement. The prevalence of colonic diverticulae and abdominal wall hernias are also increased in ADPKD patients.

Diagnosis Diagnosis is typically made from a positive family history consistent with autosomal dominant inheritance and multiple kidney cysts bilaterally. Renal ultrasonography is often used for presymptomatic screening of at-risk subjects and for evaluation of potential living-related kidney donors from ADPKD families. The presence of *at least two renal cysts (unilateral or bilateral)* is sufficient for diagnosis among at-risk subjects between 15 and 29 years of age with a sensitivity value of 96% and specificity value of 100%. The presence of *at least two cysts in each kidney* and *at least four cysts in each kidney*, respectively, are required for the diagnosis among at-risk subjects aged 30–59 years and aged ≥60 years with a sensitivity value of 100% and specificity value of 100%. This is because there is an increased frequency of developing simple renal cysts with age. Conversely, in subjects aged between 30 and 59 years the absence of *at least two cysts in each kidney*, which is associated with a false negative rate of 0%, can be used for disease exclusion. These criteria have a lower sensitivity for patients with a *PKD2* mutation because a late onset of ADPKD2. CT scan and T2-MRI, with and without contrast enhancement, are more sensitive than ultrasonography and can detect cysts of smaller size. However, a CT scan exposes the patient to radiation and radiocontrast, which may cause serious allergic reactions and nephrotoxicity in patients with renal insufficiency. T2-MRI, with gadolinium as a contrast agent, has minimal renal toxicity and can detect cysts of only 2–3 mm in diameter. However, a large majority of cysts may still be below the detection level. Genetic testing by linkage analyses and mutational analyses are available for ambiguous cases. Because of the large size of *PKD1* gene and the presence of multiple highly homologous pseudogenes, mutational analysis of *PKD1* gene is difficult and costly. Application of new technologies such as paired-end next generation sequencing with multiplexing individually bar-coded long range PCR libraries may reduce the costs and improve the sensitivity for clinical genetic testing.

TREATMENT

Autosomal Dominant Polycystic Kidney Disease

No specific treatment to prevent cyst growth or the decline of renal function has been approved by U.S. Food and Drug Administration. Blood pressure control to a target of 140/90 mmHg is recommended according to the guidelines from the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VIII report) for reducing cardiovascular complications in ADPKD and renal disease progression. More rigorous blood pressure control does not equal greater clinical benefits. Maintaining a target systolic blood pressure to 110 mmHg in patients with moderate or advanced disease may increase the risk of renal disease progression by reducing renal blood flow. Lipid-soluble antibiotics against common gram-negative enteric organisms include trimethoprim-sulfamethoxazole, quinolones, and chloramphenicol, and are preferred for cyst infection because most renal cysts are not connected to glomerular filtration and antibiotics that are capable to penetrate the cyst walls are likely to be more effective. Treatment often requires 4–6 weeks. The treatment of kidney stones in ADPKD includes standard measures such as analgesics for pain relief, and hydration to ensure adequate urine flow. Management of chronic flank, back, or abdominal pain due to renal enlargement may include both pharmacologic (non-narcotic and narcotic analgesics) and non-pharmacological (transcutaneous electrical nerve stimulation, acupuncture, and biofeedback). Occasionally surgical decompression of cysts may be necessary. More than half of ADPKD patients eventually require peritoneal dialysis, hemodialysis, or kidney transplantation. Peritoneal dialysis may not be suitable for some patients with massively enlarged polycystic kidneys due to the small intraabdominal space for efficient peritoneal exchange of fluid and solutes and increased chance of abdominal hernia and back pain. Patients with very large polycystic kidneys and recurrent renal cyst infection may require pretransplant nephrectomy or bilateral nephrectomy to accommodate the allograft and reduce the pain.

Specific treatment strategies to ADPKD have focused on slowing renal disease progression and lowering cardiovascular risk. For the latter, the main approach is to control blood pressure by inhibiting the renin-angiotensin-aldosterone system. The HALT PKD trial was set to evaluate the impact of intensive blockade of the renin-angiotensin-aldosterone system, and levels of blood pressure control on progressive renal disease. This trial found that rigorous blood-pressure control could slow cyst growth. Most approaches target the

slowing of renal disease progression by inhibiting cell proliferation and fluid secretion. Several clinical trials have been conducted targeting cell proliferation: sirolimus and everolimus, inhibitors of the mammalian target of rapamycin (mTOR) pathway; OPC31260 and tolvaptan, which inhibits cyclic adenosine monophosphate (cAMP) pathways by antagonizing the activation of vasopressin V2 receptor (V2R) in collecting ducts and reduces cell proliferation by decreasing renal cAMP levels; and somatostatin analogues, which reduces cAMP levels by binding to several G-protein coupled receptors. The TAMPO and ALADIN trials showed that V2R antagonists and somatostatin analogues (octreotide-LAR groups) respectively slowed the decline of renal function. Some side effects, such as liver function impairment, polydipsia, and diarrhea, have been observed for tolvaptan and cholecystitis for octreotide-LAR. A recent report also showed that tolvaptan reduces renal pain. DIPAK, a small multi-center European study, showed that nerve block may be used to relieve pain in ADPKD patients suffering with refractory chronic pain. A combination of different growth inhibitors may enhance efficacy and reduce side effects.

Additional preclinical studies in animal models include the use of inhibitors to nonreceptor tyrosine kinase Src, B-raf, cyclin-dependent kinase (CDK), transcription factors STAT3 and STAT6 (pyrimethamine and leflunomide), purinergic receptors, hepatocyte growth factor receptor, glucosylceramide, and agonists to peroxisome proliferator-activated receptor-gamma (PPARγ) receptors (thiazolidodinediones). Recently, several microRNAs have been identified that mediate disease progression, which may prove to be a new therapeutic target. Food restriction in mouse models of the disease was reported to reduce cyst area, kidney fibrosis, inflammation, and injury. Branched chain amino acids appear to enhance cyst development in a mouse model.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

Genetic Considerations ARPKD is a significant hereditary renal disease in childhood, with an estimated prevalence of 1 in 20,000 live births. A carrier frequency of up to 1:70 has been reported. Mutations in a single gene, *PKHD1*, are responsible for all the clinical presentations of ARPKD. *PKHD1*, localized on human chromosome region 6p21.1-6p12.2, is one of the largest genes in the genome, occupies ~450 kb of DNA, and contains at least 86 exons. It produces multiple alternatively spliced transcripts. The largest transcript encodes fibrocystin/polyductin (FPC), which is a large receptor-like integral membrane protein of 4074 amino acids. FPC has a single transmembrane, a large N-terminal extracellular region, and a short intracellular cytoplasmic domain. FPC is localized on the primary cilia of epithelia cells of cortical and medullary collecting ducts and cholangiocytes of bile ducts, similar to polycystins and several other ciliopathy proteins. FPC is also expressed on the basal body and plasma membrane. The large extracellular domain of FPC is presumed to bind to an as yet unknown ligand(s), and is involved in cell-cell and cell-matrix interactions. FPC interacts with ADPKD protein PC2, and may also participate in regulation of the mechanosensory function of the primary cilia, calcium signaling, and PCP, suggesting a common mechanism underlying cystogenesis between ADPKD and ARPKD. FPC is also found on the centrosomes and mitotic spindle, and may regulate centrosome duplication and mitotic spindle assembly during cell division. A large number of various mutations have been found throughout *PKHD1*, and are unique to individual families. Most patients are compound heterozygotes for *PKHD1* mutations. Patients with two truncation mutations appear to have an earlier onset of the disease.

Clinical Features Classic ARPKD is generally diagnosed in utero or within the neonatal period, and characterized by greatly enlarged echogenic kidneys in diseased fetuses. Reduced fetal urine production may contribute to oligohydroaminos and pulmonary hypoplasia. About 30% of affected neonates die shortly after birth due to respiratory insufficiency. Close to 60% of mortality occurs within the first month of life. In the classic group, most patients are born with renal insufficiency and ESRD. However, infants often have a transient improvement in their GFR; death from renal insufficiency at this stage is rare. Some patients are diagnosed after the neonatal stage, which form the older group. Morbidity and mortality in this group often involve systemic hypertension, progressive renal insufficiency, and liver manifestations. The hallmarks of ARPKD liver disease are biliary dysgenesis due to a primary ductal plate malformation with associated periportal fibrosis, namely congenital hepatic fibrosis (CHF) and dilatation of intrahepatic bile ducts (Caroli disease). CHF and Caroli disease can then lead to portal hypertension exhibiting hepatosplenomegaly, variceal bleeding, and cholangitis. Some patients with the diagnosis of ARPKD at 1 year of age with nephromegaly exhibit slowly declining renal function over 20 years with only minimally enlarged kidneys at ESRD, and markedly atrophic kidneys following renal transplantation. The slow progression of renal disease is likely due to increasing fibrosis rather than the development of cysts. Systemic hypertension is common in all ARPKD patients, even those with normal renal function.

Diagnosis Ultrasonography, CT, and MRI all can be used for diagnosis. Ultrasonography reveals large, echogenic kidneys with poor corticomedullary differentiation. The diagnosis can be made in utero after 24 weeks of gestation in severe cases. Macrocysts generally are not common at birth in ARPKD patients. The absence of renal cysts in either parent, particularly if they are >40 years of age on ultrasonography helps distinguish ARPKD from ADPKD in older patients. Clinical, laboratory, or radiographic evidence of hepatic fibrosis, hepatic pathology demonstrating characteristic ductal plate abnormalities, family history of affected siblings, or parental consanguinity suggestive of autosomal recessive inheritance is helpful. The lack of mutational hot spots and the large and complex genomic structure of *PKHD1* make molecular diagnosis difficult, however, presymptomatic screen of other at-risk members in a family with already identified ARPKD mutations is straightforward and inexpensive.

TREATMENT

Autosomal Recessive Polycystic Kidney Disease

There is no specific therapy for ARPKD. Appropriate neonatal intensive care, blood pressure control, dialysis, and kidney transplantation increase survival into adulthood. Complications of hepatic fibrosis may necessitate liver transplantation. Patients with severe Caroli disease may need porto-systemic shunting. Upcoming therapies may target abnormal cell signaling mechanisms, as described above for ADPKD.

OTHER DISEASES CHARACTERIZED BY LARGE KIDNEY CYSTS

TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is a rare autosomal dominant syndrome caused by mutations in one of two genes, *TSC1*, encoding hamartin, or, *TSC2*, encoding tuberin. Published estimates of prevalence vary widely, but it certainly occurs in <1:5,000 births. Kidney cysts are a frequent feature of this condition, as are two other abnormalities of kidney growth, renal cell carcinoma and renal angiomyolipomas. TS is a syndrome affecting multiple organ systems. Other features of TS include benign growths in the nervous system, eyes, heart, lung, liver, and the skin. Essentially all TS patients have such skin lesions, and a large proportion of patients have neurologic and cognitive manifestations. The *TSC2* gene is adjacent to *PKD1* in the human genome. Some patients have deletions in their genomic DNA that inactivate these two genes. Such individuals may have manifestations of both ADPKD and TS.

The most common kidney finding in TS is the presence of angiomyolipomas. These growths tend to be multiple and bilateral. While they are usually benign, they may bleed. Surgical removal is often recommended as a prophylactic measure in people with angiomyolipomas >4 cm in diameter. The cysts in TS are radiographically similar to those

seen in ADPKD. In contrast to ADPKD, there is a clearly increased risk of renal cell carcinoma in TS patients. Regular periodic imaging is recommended in TS patients with kidney involvement to screen for the development of renal cell carcinoma. These cysts may rarely become large and hemorrhagic, occasionally requiring nephrectomy when nephron-sparing surgery is not possible.

Although not common, TS may lead to significant chronic kidney disease (CKD) and progress to end-stage kidney failure. Patients with TS and CKD typically have an unremarkable urine sediment and only minimal to mild amounts of proteinuria.

Mechanistically, the *TSC1* and *TSC2* gene products tuberin and hamartin interact physically. This protein complex is localized to the base of the cilia and inhibits intracellular signaling processes mediated by mTOR (mammalian target of rapamycin), leading to abnormal growth in a number of tissues. Investigation of mTOR inhibitors as therapy for TS is ongoing. There is increasing optimism that this class of drugs will become commonplace for prevention of the renal and non-renal manifestations of TS.

VON HIPPEL-LINDAU DISEASE

Von Hippel-Lindau disease (VHL) is an inherited cancer syndrome with renal manifestations. VHL is an autosomal dominant condition caused by mutations in the VHL tumor-suppressor gene. VHL is localized to the primary cilia and is necessary for the formation of primary cilia. Like many autosomal dominant cancer syndromes, VHL is recessive at the cellular level: a somatic mutation in the second VHL allele leads to loss of VHL in the cell and abnormal growth. Kidney manifestations of VHL include multiple bilateral kidney cysts, and renal cell carcinomas. Kidney cysts and carcinoma affects the majority of VHL patients. Non-renal features of VHL include pheochromocytomas, cerebellar hemangioblastomas, and retinal hemangiomas. While much rarer than ADPKD, it is important for this entity to be considered in the differential diagnosis of an individual with newly recognized kidney cysts.

In these patients, annual screening of the kidneys by imaging with CT or MRI scanning is recommended for early detection of renal cell carcinomas. Increasingly, nephron-sparing surgical approaches are being used for removal of cancerous lesions in order to preserve kidney function.

OTHER INHERITED DISEASES OF TUBULE GROWTH AND DEVELOPMENT

ADPKD is by far the most common adult onset single gene form of adult onset kidney disease. The large cysts that are sometimes seen in VHL and TS are similar in appearance to the cysts seen in ADPKD. A variety of other inherited disorders affecting primarily tubule and renal interstitial function can lead to CKD and eventual end-stage kidney disease in the absence of large tubule-derived cysts.

Inherited diseases affecting the tubulointerstitial compartment of the kidney can lead to secondary glomerular stress and glomerulosclerosis with some degree of concomitant proteinuria. Similarly, disorders of glomerular function will typically lead to secondary interstitial fibrosis and tubule atrophy. From a clinical perspective, therefore, distinguishing between a genetic disease of the renal tubules and a disease of the glomerulus may not be easy, particularly in the absence of a gross phenotype such as large kidney cysts.

AUTOSOMAL DOMINANT INTERSTITIAL KIDNEY DISEASE (MEDULLARY CYSTIC KIDNEY DISEASE)

The medullary cystic kidney diseases (MCKD) are autosomal dominant disorders. The term autosomal dominant tubulointerstitial kidney disease (ADTKD) is replacing MCKD as the preferred designation. Despite the old nosology, kidney cysts are not invariably present. Older literature often grouped MCKD together with the childhood-onset disorders known as the nephronophthises, but these are distinct clinical and genetic entities.

ADTKD-MUC1 Patients with medullary cystic kidney disease type I (MCKD I) have mutations in the mucin 1 gene *MUC1*. In contrast to MCKD II patients, individuals with MCKD I do not have elevated uric acid levels. The disease-causing *MUC1* mutations that have been reported all alter a highly repetitive region within the *MUC1* gene, leading to a large "neoprotein" fragment that may lead to toxic effects on the kidney tubule.

Clinically, patients with MCKD I exhibit slowly progressive CKD in adulthood, with only minimal amounts of increased urine protein and occasional renal cysts seen on ultrasound examination. Kidney histology shows tubulointerstitial fibrosis and tubular atrophy. The mechanisms by which *MUC1* mutations cause human kidney disease are not known. Disease does not recur in transplanted kidneys.

ADTKD-UMOD ADTKD-IUMOD (also called MCKD II) is caused by mutations in the *UMOD* gene, which encodes the protein uromodulin, also known as Tamm-Horsfall protein. Uromodulin is also found on the centrosome, the mitotic spindle, and the primary cilia; it colocalizes with nephrocystin-1 and KIF3A on the cilia. *UMOD* mutations also cause the conditions that have been referred to as familial juvenile hyperuricemic nephropathy (HNFJ1) and glomerulocystic kidney disease (GCKD), although it is not clear that these different names represent clearly distinct disorders. The term *uromodulin-associated kidney disease* (or UAKD) has been suggested as a better name for MCKD II and the various other related *UMOD*-associated diseases. Despite the name, kidney cysts are not a common feature of MCKD II. MCKD II should be suspected clinically in patients with a family history of late onset kidney disease, benign urine sediments, absence of significant proteinuria, and hyperuricemia. Large genome-wide association studies have suggested that certain common non-coding sequence variants in *UMOD* are associated with a moderately increased risk of CKD in the general population. *UMOD*-associated disease is often associated with gout.

Other Forms of Familial Tubulointerstitial Kidney Disease A small number of families have been identified with autosomal dominant tubulointerstitial kidney disease and hyperuricemia who lack *UMOD* mutations. Some of these families carry disease-segregating mutations in the renin gene *REN* (disease designation ADTKD-REN). ADKTKD-REN patients demonstrate hyporeninemia with mild hyperkalemia, and often have hyperuricemia and gout. There are other families who lack mutations in *UMOD, MUC1,* or *REN* mutation. Thus, mutations in other yet-to-be identified genes are able to produce similar interstitial kidney disease, both with and without hyperuricemia.

Kidney biopsies in patients with any of various forms of MCKD typically show interstitial fibrosis. These histologic features are not diagnostic of any particular genetic entity, and the specific diagnosis must be made by other means. Genetic tests for alterations in specific genes are increasingly available in the clinical setting.

Those patients with autosomal dominant interstitial kidney disease, *UMOD* or *REN* mutations, with hyperuricemia and gout should be treated similarly to others with these findings, with uric-acid lowering agents, such as allopurinol or febuxostat.

NEPHRONOPHTHISIS

A large and growing number of genetically distinct but related set of autosomal recessive disorders are referred to as nephronophthisis, or nephronophthisis-related ciliopathies. These entities should not be confused with the adult onset autosomal dominant MCKD discussed above, despite the often confusing nomenclature seen in older medical literature. Each of the individual forms of nephronophthisis is quite rare, but together this category constitutes the most common inherited childhood form of kidney failure requiring kidney replacement therapy.

Like ADPKD and ARPKD, the various genetically heterogeneous entities that fall under the category of nephronophthisis (NPHP) are disorders of ciliary function. Mutations in >90 genes have been identified that lead to NPHP under an autosomal recessive pattern of inheritance. Some of these gene defects cause limited kidney disease, while many cause ciliopathies characterized by multiple organ involvement. The various forms of NPHP share common features, including tubulointerstitial fibrosis, corticomedullary cysts, and progressive CKD,

leading to renal failure. Proteinuria is absent or mild, and the urine sediment is not active.

NPHP is often divided into infantile, juvenile, and adolescent forms. The juvenile form is the most frequent, and usually caused by mutations in the *NPHP2* gene. The infantile form, usually caused by *NPHP2* mutations, is associated with end-stage kidney failure in early childhood. Patients with the adolescent form of NPHP typically develop end–stage kidney failure in early adulthood. Hypertension, if present, tends to be a late finding in the course of the NPHPs. The products of the NPHP genes are referred to as nephrocystins. *NPHP1* through *NPHP20* have been reported; some are referred to by other names, as well.

NPHP can present as an isolated finding, or be part of several multi-organ syndromes. Neurologic abnormalities are present in a significant number of patients. Bone and liver abnormities are seen in some NPHP patients. Senior-Loken syndrome is defined by the presence of NPHP with retinitis pigmentosa. Joubert syndrome is defined by multiple neurologic findings, including hypoplasia of the cerebellar vermis. Some forms of this genetically heterogeneous syndrome include NPHP as a component.

The multisystem disease Bardet-Biedl syndrome (BBS) is defined clinically by a spectrum of features, including truncal obesity, cognitive impairment, retinal dystrophy, polydactyly, developmental urogenital abnormalities, and kidney cysts. The kidney phenotype is NPHP-like, with small cysts deriving from the tubules, tubulointerstitial and often secondary glomerular disease, and urine concentrating defects. There are 19 BBS genes cloned. BBS follows autosomal recessive inheritance. Like ADPKD, ARPKD, and NPHP, BBS is a disease of abnormal ciliary function.

The multiple genes and gene products (nephrocystins) that are responsible for NPHP are expressed in cilia, basal bodies, and the centrosomes of kidney tubules cells. It has been hypothesized that all of the NPHP gene defects lead to a clinical phenotype by interfering with the regulation of PCP.

There are no specific clinical tests that define nephronophthisis. Genetic diagnosis is possible, cumbersome because of the large number of genes that can be responsible, but increasingly feasible due to new DNA sequencing technologies. There are no specific therapies for NPHP. Rather, therapy is aimed at treating signs of these diseases as well as those systemic abnormalities seen with all CKDs. Chronic dialysis or kidney transplantation are eventually required for NPHP-affected individuals.

KARYOMEGALIC TUBULOINTERSTITIAL NEPHRITIS

Karyomegalic tubulointerstitial nephritis is an exceptionally rare form of kidney disease with adult-onset progressive kidney failure. Kidney biopsy shows chronic tubulointerstitial nephritis, as well as interstitial fibrosis. This is a recessive disorder caused by inheritance of two mutant copies of the *FAN1* gene. *FAN1* encodes a component of a DNA repair machinery complex. Individuals with two mutant *FAN1* gene are genetically sensitized to the effect of DNA damage. Kidney histology shows karyomegaly in addition to the non-specific findings of interstitial fibrosis and tubular atrophy.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney (MSK) is often grouped together with inherited disorders of the kidney affecting tubule growth and development, although it is usually a sporadic finding rather than an inherited phenotype. MSK is caused by developmental malformation and cystic dilatation of the renal collecting ducts. The medullary cysts seen in this entity can be quite variable in size.

MSK is usually a benign entity. The diagnosis of MSK is often made incidentally. In the past, the diagnosis of MSK was often made by intravenous pyelography (IVP). CT urography, which has replaced IVPs for much routine kidney imaging, is not as sensitive in detecting MSK.

MSK is associated with an increased frequency of calcium phosphate and calcium oxalate kidney stones. Altered flow characteristics in the kidney tubules may lead to the development of formation of a nidus for stone formation. Kidney stones in this group are treated the same as are kidney stones in the general population. MSK patients also often exhibit reduced kidney concentrating ability and an increased frequency of urinary tract infections.

CAKUT

The structural abnormalities known as CAKUT (Congenital Abnormalities of the Kidney and Urinary Tract) are a group of etiologically and phenotypically heterogeneous disorders. Some form of CAKUT is estimated to occur in up to 1 in 500 live births. Specific abnormalities classified as part of the CAKUT spectrum include kidney hypoplasia, kidney agenesis, ureteropelvic junction obstruction, and vesicoureteral reflux.

CAKUT can be the cause of clinically significant problems in both adults and children. However, it is a major contributor to kidney failure in children, accounting for more than one-third of end-stage kidney disease in this group.

CAKUT is typically a sporadic finding, but can also cluster in families. Familial forms can be observed as parts of multisystem developmental syndromes. A growing list of specific genes have been identified which when mutated lead to syndromic forms of CAKUT. For example, the branchio-oto-renal syndrome, characterized by developmental abnormalities in the neck, ears, and kidney, can be caused by mutations in the *EYA1* and *SIX1* genes. Mutations in the *PAX2* transcription factor gene can cause the autosomal dominant renal coloboma syndrome, characterized by optic nerve malformations and hypoplastic kidneys. Recent work has demonstrated that a non-trivial fraction of children with CKD have an unsuspected genomic imbalance, often disrupting genes known to relevant to CAKUT and kidney development. It is not uncommon for such genetic lesions that affect both kidney and neurocognitive function.

In many instances, CAKUT is caused by environmental influences rather than genetic alterations. For example, renal tubular dysgenesis, defined by altered tubule development, can be caused by prenatal exposure of angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

MITOCHONDRIAL DISEASE

Inherited disorders of the mitochondrial genome (discussed elsewhere in this text [see also Chap. 472]) commonly affect kidney function. Thirteen of the genes involved in encoding components of the mitochondrial respiratory chain are located on the mitochondrial genome that is inherited maternally. The remainder of these components is encoded by the nuclear genome. These defects of oxidative phosphorylation may affect multiple organs and tissues.

Neuromuscular disease is the best recognized part of this complex phenotype. Kidney disease is now recognized as a common component, as well. Tubulointerstitial disease may be seen on kidney biopsy, and progression to kidney failure may occur. Glomerular involvement, manifest as proteinuria and glomerulosclerosis, can also develop. Changes in proximal tubule activity are the most common renal phenotype. Patients may have several defects in proximal tubule transport, including the Fanconi syndrome. Some patients may also have acidosis, hypophosphatemic rickets, hypercalciuria, glycosuria, and tubular proteinuria. Decreased urine concentrating ability is common.

GLOBAL CONSIDERATIONS

The disorders discussed above are all seen worldwide. In addition, a previously unrecognized epidemic of kidney disease is leading to very high rates of kidney failure in and near the western coast of Central America. This mesoamerican nephropathy is particularly common in Nicaragua and El Salvador. Mesoamerican nephropathy patients do not have significant proteinuria, suggesting that this is a disease of the kidney tubules and interstitium. The cause is unknown, but some have suggested that a combination of toxic environmental factors and heat stress underlie the development of this kidney disease, which has a striking male predominance. However, the fact that in many families, a large fraction of the men are affected with kidney disease has suggested that a strong genetic component is involved, as well.

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310 Tubulointerstitial Diseases of the Kidney

Laurence H. Beck, Jr., David J. Salant

Inflammation or fibrosis of the renal interstitium and atrophy of the tubular compartment are common consequences of diseases that target the glomeruli or vasculature. Distinct from these secondary phenomena, however, are a group of disorders that primarily affect the tubules and interstitium, with relative sparing of the glomeruli and renal vessels. Such disorders are conveniently divided into acute and chronic tubulointerstitial nephritis (TIN) **(Table 310-1)**.

Acute TIN most often presents with acute renal failure **(Chap. 304)**. The acute nature of this group of disorders may be caused by aggressive inflammatory infiltrates that lead to tissue edema, tubular cell injury, and compromised tubular flow, or by frank obstruction of the tubules with casts, cellular debris, or crystals. There is sometimes flank pain due to distention of the renal capsule. Urinary sediment is often active with leukocytes and cellular casts, but depends on the exact nature of the disorder in question.

The clinical features of chronic TIN are more indolent and may manifest with disorders of tubular function, including polyuria from impaired concentrating ability (nephrogenic diabetes insipidus), defective proximal tubular reabsorption leading to features of Fanconi's syndrome (glycosuria, phosphaturia, aminoaciduria, hypokalemia, and type II renal tubular acidosis [RTA] from bicarbonaturia), or non-anion-gap metabolic acidosis and hyperkalemia (type IV RTA) due to impaired ammoniagenesis, as well as progressive azotemia (rising creatinine and blood urea nitrogen [BUN]). There is often modest proteinuria (rarely >2 g/d) attributable to decreased tubular reabsorption of filtered proteins; however, nephrotic-range albuminuria may occur in some conditions due to the development of secondary focal segmental glomerulosclerosis (FSGS). Renal ultrasonography may reveal changes of "medical renal disease," such as increased echogenicity of the renal parenchyma with loss of corticomedullary differentiation, prominence of the renal pyramids, and cortical scarring in some conditions. The predominant pathology in chronic TIN is interstitial fibrosis with patchy mononuclear cell infiltration and widespread tubular atrophy, luminal dilation, and thickening of tubular basement membranes. Because of the nonspecific nature of the histopathology, biopsy specimens rarely provide a specific diagnosis. Thus, diagnosis relies on careful analysis of history, drug or toxin exposure, associated symptoms, and imaging studies.

TABLE 310-1 Classification of the Causes of Tubulointerstitial Diseases of the Kidney

Acute Tubulointerstitial Disorders

Acute Interstitial Nephritis

Therapeutic agents

- Antibiotics (β-lactams, sulfonamides, quinolones, vancomycin, erythromycin, linezolid, minocycline, rifampin, ethambutol, acyclovir)
- Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors
- Diuretics (rarely thiazides, loop diuretics, triamterene)
- Anticonvulsants (phenytoin, valproate, carbamazepine, phenobarbital)
- Miscellaneous (proton pump inhibitors, H_2 blockers, captopril, mesalazine, indinavir, allopurinol, lenalidomide)

Infection

- Bacteria (*Streptococcus, Staphylococcus, Legionella, Salmonella, Brucella, Yersinia, Corynebacterium diphtheriae*)
- Viruses (EBV, CMV, hantavirus, polyomavirus, HIV)
- Miscellaneous (*Leptospira, Rickettsia, Mycoplasma, Histoplasma*)

Autoimmune

- Tubulointerstitial nephritis with uveitis (TINU)
- Sjögren's syndrome
- Systemic lupus erythematosus
- Granulomatous interstitial nephritis
- IgG4-related systemic disease
- Idiopathic autoimmune interstitial nephritis

Acute obstructive disorders

- Light chain cast nephropathy ("myeloma kidney")
- Acute phosphate nephropathy
- Acute urate nephropathy

Chronic Tubulointerstitial Disorders

- Vesicoureteral reflux/reflux nephropathy
- Sickle cell disease
- Chronic exposure to toxins or therapeutic agents
- Analgesics, especially those containing phenacetin
- Lithium
- Heavy metals (lead, cadmium)
- Aristolochic acid (Chinese herbal and Balkan endemic nephropathies)
- Calcineurin inhibitors (cyclosporine, tacrolimus)

Metabolic Disturbances

- Hypercalcemia and/or nephrocalcinosis
- Hyperuricemia
- Prolonged hypokalemia
- Hyperoxaluria
- Cystinosis **(see Chap. 309)**

Cystic and Hereditary Disorders (see Chap. 309)

- Polycystic kidney disease
- Nephronophthisis
- Adult medullary cystic disease
- Medullary sponge kidney

Miscellaneous

- Aging
- Chronic glomerulonephritis
- Chronic urinary tract obstruction
- Ischemia and vascular disease
- Radiation nephritis (rare)

Abbreviations: CMV, cytomegalovirus; COX, cyclooxygenase; EBV, Epstein-Barr virus.

ACUTE INTERSTITIAL NEPHRITIS

In 1897, Councilman reported on eight cases of acute interstitial nephritis (AIN) in the Medical and Surgical Reports of the Boston City Hospital; three as a postinfectious complication of scarlet fever and two from diphtheria. Later, he described the lesion as "an acute inflammation of the kidney characterized by cellular and fluid exudation in the interstitial tissue, accompanied by, but not dependant on, degeneration of the epithelium; the exudation is not purulent in character, and the lesions may be both diffuse and focal." Today AIN is far more often encountered as an allergic reaction to a drug (Table 310-1). Immune-mediated AIN may also occur as part of a known autoimmune syndrome, but in some cases there is no identifiable cause despite features suggestive of an immunologic etiology (Table 310-1).

ALLERGIC INTERSTITIAL NEPHRITIS

Although biopsy-proven AIN accounts for no more than ~15% of cases of unexplained acute renal failure, this is likely a substantial underestimate of the true incidence. This is because potentially offending medications are more often identified and empirically discontinued in a patient noted to have a rising serum creatinine, without the benefit of a renal biopsy to establish the diagnosis of AIN.

Clinical Features The classic presentation of AIN, namely, fever, rash, peripheral eosinophilia, and oliguric renal failure occurring after 7–10 days of treatment with methicillin or another β-lactam antibiotic, is the exception rather than the rule. More often, patients are found incidentally to have a rising serum creatinine or present with symptoms attributable to acute renal failure (Chap. 304). Atypical reactions can occur, most notably nonsteroidal anti-inflammatory drug (NSAID)-induced AIN, in which fever, rash, and eosinophilia are rare, but acute renal failure with heavy proteinuria is common. A particularly severe and rapid-onset AIN may occur upon reintroduction of rifampin after a drug-free period. More insidious reactions to the agents listed in Table 310-1 may lead to progressive tubulointerstitial damage. Examples include proton pump inhibitors and, rarely, sulfonamide and 5-aminosalicylate (mesalazine and sulfasalazine) derivatives and antiretrovirals. It is not clear if the recent association of proton pump inhibitors with incident chronic kidney disease involves an intermediate step of prolonged, subclinical interstitial nephritis.

Diagnosis Finding otherwise unexplained renal failure with or without oliguria and exposure to a potentially offending agent usually points to the diagnosis. Peripheral blood eosinophilia adds supporting evidence but is present in only a minority of patients. Urinalysis reveals pyuria with white blood cell casts and hematuria. Urinary eosinophils are neither sensitive nor specific for AIN; therefore, testing is not recommended. Renal biopsy is generally not required for diagnosis but reveals extensive interstitial and tubular infiltration of leukocytes, including eosinophils.

TREATMENT

Allergic Interstitial Nephritis

Discontinuation of the offending agent often leads to reversal of the renal injury. However, depending on the duration of exposure and degree of tubular atrophy and interstitial fibrosis that has occurred, the renal damage may not be completely reversible. Glucocorticoid therapy may accelerate renal recovery, but does not appear to impact long-term renal survival. It is best reserved for those cases with severe renal failure in which dialysis is imminent or if renal function continues to deteriorate despite stopping the offending drug (Fig. 310-1 and Table 310-2).

SJÖGREN'S SYNDROME

Sjögren's syndrome is a systemic autoimmune disorder that primarily targets the exocrine glands, especially the lacrimal and salivary glands, and thus results in symptoms, such as dry eyes and mouth, that constitute the "sicca syndrome" (Chap. 354). TIN with a predominant lymphocytic infiltrate is the most common renal manifestation of Sjögren's syndrome and can be associated with distal RTA, nephrogenic diabetes insipidus, and moderate renal failure. Diagnosis is strongly supported by positive serologic testing for anti-Ro (SS-A) and anti-La (SS-B) antibodies. A large proportion of patients with Sjögren's syndrome also have polyclonal hypergammaglobulinemia. Treatment is initially with glucocorticoids, although patients may require maintenance therapy with azathioprine or mycophenolate mofetil to prevent relapse (Fig. 310-1 and Table 310-2).

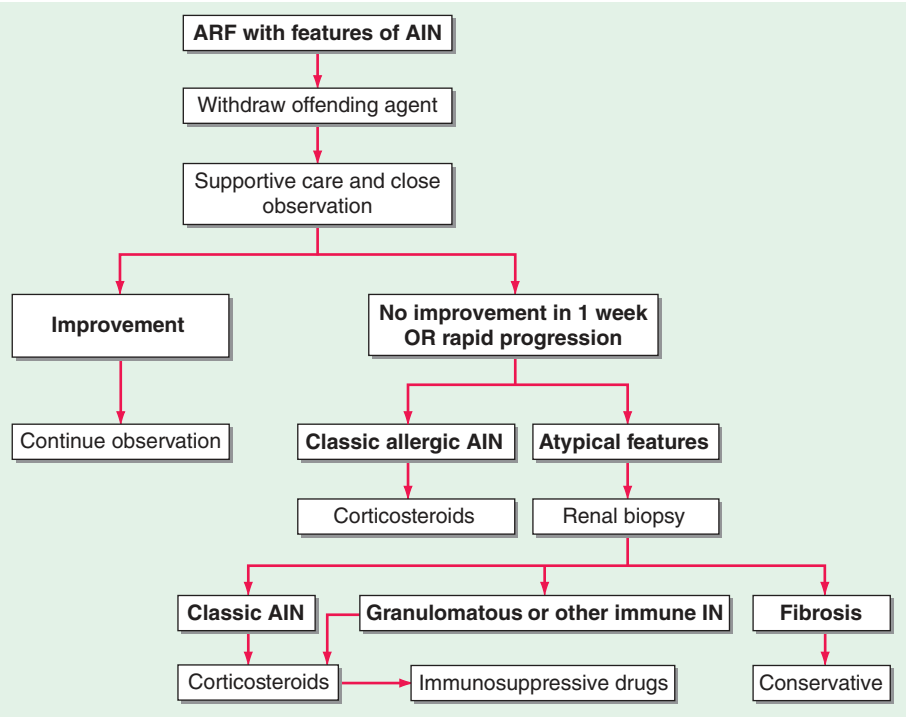

FIGURE 310-1 Algorithm for the treatment of allergic and other immune-mediated acute interstitial nephritis (AIN). ARF, acute renal failure; IN, interstitial nephritis. See text for immunosuppressive drugs used for refractory or relapsing AIN. *(Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.)*

TUBULOINTERSTITIAL NEPHRITIS WITH UVEITIS (TINU)

TINU is a systemic autoimmune disease of unknown etiology. It accounts for fewer than 5% of all cases of AIN, affects females three times more often than males, and has a median age of onset of 15 years. Its hallmark feature, in addition to a lymphocyte-predominant interstitial nephritis (Fig. 310-2), is a painful anterior uveitis, often bilateral and accompanied by blurred vision and photophobia. Diagnosis is often confounded by the fact that the ocular symptoms precede or accompany the renal disease in only one-third of cases. Additional extrarenal features include fever, anorexia, weight loss, abdominal pain, and arthralgia. The presence of such symptoms as well as elevated creatinine, sterile pyuria, mild proteinuria, features of Fanconi's syndrome, and elevated erythrocyte sedimentation rate should raise suspicion for this disorder. Serologies suggestive of the more common autoimmune diseases are usually negative, and TINU is often a diagnosis of exclusion after other causes of uveitis and renal disease, such as Sjögren's syndrome, Behçet's disease, sarcoidosis, and systemic lupus erythematosus, have been considered. Clinical symptoms are typically self-limited in children, but are more apt to follow a

TABLE 310-2 Indications for Corticosteroids and Immunosuppressives in Interstitial Nephritis

Absolute Indications
• Sjögren's syndrome
• Sarcoidosis
• SLE interstitial nephritis
• Adults with TINU
• Idiopathic and other granulomatous interstitial nephritis
Relative Indications
• Drug-induced or idiopathic AIN with:
Rapid progression of renal failure
Diffuse infiltrates on biopsy
Impending need for dialysis
Delayed recovery
• Children with TINU
• Postinfectious AIN with delayed recovery (?)

Abbreviations: AIN, acute interstitial nephritis; SLE, systemic lupus erythematosus; TINU, tubulointerstitial nephritis with uveitis.

Source: Modified from S Reddy, DJ Salant: Ren Fail 20:829, 1998.

relapsing course in adults. The renal and ocular manifestations generally respond well to oral glucocorticoids, although maintenance therapy with agents such as methotrexate, azathioprine, or mycophenolate may be necessary to prevent relapses (Fig. 310-1 and Table 310-2).

SYSTEMIC LUPUS ERYTHEMATOSUS

An interstitial mononuclear cell inflammatory reaction often accompanies the glomerular lesion in most cases of class III or IV lupus nephritis **(Chap. 308)**, and deposits of immune complexes can be identified in tubule basement membranes in ~50% of cases. Occasionally, however, the tubulointerstitial inflammation predominates and may manifest with azotemia and type IV RTA rather than features of glomerulonephritis.

GRANULOMATOUS INTERSTITIAL NEPHRITIS

Some patients may present with features of AIN but follow a protracted and relapsing course. Renal biopsy in such patients reveals a more chronic inflammatory infiltrate with granulomas and multinucleated giant cells. Most often, no associated disease or cause is found; however, some of these cases may have or subsequently develop the pulmonary, cutaneous, or other systemic manifestations of *sarcoidosis* such as hypercalcemia. Most patients experience some improvement in renal function if treated early with glucocorticoids before the development of significant interstitial fibrosis and tubular atrophy (Table 310-2). Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal. Other immunosuppressive agents may be required for those who relapse frequently upon steroid withdrawal (Fig. 310-1). Tuberculosis should be ruled out before starting treatment because this too is a rare cause of granulomatous interstitial nephritis.

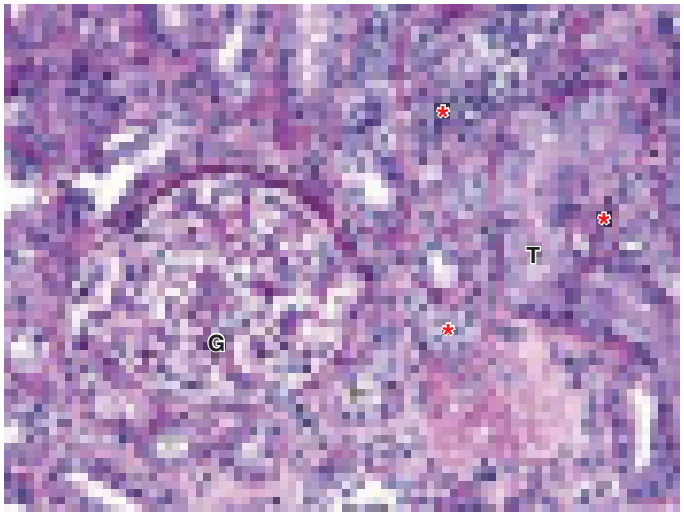

FIGURE 310-2 Acute interstitial nephritis (AIN) in a patient who presented with acute iritis, low-grade fever, erythrocyte sedimentation rate of 103, pyuria and cellular casts on urinalysis, and a newly elevated serum creatinine of 2.4 mg/dL. Both the iritis and AIN improved after intravenous methylprednisolone. This PAS-stained renal biopsy shows a mononuclear cell interstitial infiltrate (*asterisks*) and edema separating the tubules (T) and a normal glomerulus (G). Some of the tubules contain cellular debris and infiltrating inflammatory cells. The findings in this biopsy are indistinguishable from those that would be seen in a case of drug-induced AIN. PAS, Periodic acid–Schiff.

IgG4-RELATED SYSTEMIC DISEASE

A form of AIN characterized by a dense inflammatory infiltrate containing IgG4-expressing plasma cells can occur as a part of a syndrome known as IgG4-related systemic disease. Autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, and a chronic sclerosing sialadenitis (mimicking Sjögren's syndrome) may variably be present as well. Fibrotic lesions that form pseudotumors in the affected organs soon replace the initial inflammatory infiltrates and often lead to biopsy or excision for fear of true malignancy. Although the involvement of IgG4 in the pathogenesis is not understood, glucocorticoids have been successfully used as first-line treatment in this group of disorders, once they are correctly diagnosed.

IDIOPATHIC AIN

Some patients present with typical clinical and histologic features of AIN but have no evidence of drug exposure or clinical or serologic features of an autoimmune disease. The presence in some cases of autoantibodies to a tubular antigen, similar to that identified in rats with an induced form of interstitial nephritis, suggests that an autoimmune response may be involved. Like TINU and granulomatous interstitial nephritis, idiopathic AIN is responsive to glucocorticoid therapy but may follow a relapsing course requiring maintenance treatment with another immunosuppressive agent (Fig. 310-1 and Table 310-2). Recently, cases have been identified in which autoantibodies that may be important in disease pathogenesis were seen to target antigens expressed by collecting duct or proximal tubular brush border.

INFECTION-ASSOCIATED AIN

AIN may also occur as a local inflammatory reaction to microbial infection (Table 310-1) and should be distinguished from acute bacterial pyelonephritis **(Chap. 130)**. Acute bacterial pyelonephritis does not generally cause acute renal failure unless it affects both kidneys or causes septic shock. Presently, infection-associated AIN is most often seen in immunocompromised patients, particularly renal transplant recipients with reactivation of polyomavirus BK **(Chaps. 138 and 307).**

CRYSTAL DEPOSITION DISORDERS AND OBSTRUCTIVE TUBULOPATHIES

Acute renal failure may occur when crystals of various types are deposited in tubular cells and interstitium or when they obstruct tubules. Oliguric acute renal failure, often accompanied by flank pain from tubular obstruction, may occur in patients treated with sulfadiazine for toxoplasmosis, indinavir and atazanavir for HIV, and intravenous acyclovir for severe herpesvirus infections. Urinalysis reveals "sheaf of wheat" sulfonamide crystals, individual or parallel clusters of needle-shaped indinavir crystals, or red-green birefringement needle-shaped crystals of acyclovir. This adverse effect is generally precipitated by hypovolemia and is reversible with saline volume repletion and drug withdrawal. Distinct from the obstructive disease, a frank AIN from indinavir crystal deposition has also been reported.

Acute tubular obstruction is also the cause of oliguric renal failure in patients with *acute urate nephropathy*. It typically results from severe hyperuricemia from tumor lysis syndrome in patients with lympho- or myeloproliferative disorders treated with cytotoxic agents, but also may occur spontaneously before the treatment has been initiated **(Chap. 71)**. Uric acid crystallization in the tubules and collecting system leads to partial or complete obstruction of the collecting ducts, renal pelvis, or ureter. A dense precipitate of birefringent uric acid crystals is found in the urine, usually in association with microscopic or gross hematuria.

Prophylactic allopurinol reduces the risk of uric acid nephropathy but is of no benefit once tumor lysis has occurred. Once oliguria has developed, attempts to increase tubular flow and solubility of uric acid with alkaline diuresis may be of some benefit; however, emergent treatment with hemodialysis or rasburicase, a recombinant urate oxidase, is usually required to rapidly lower uric acid levels and restore renal function.

Calcium oxalate crystal deposition in tubular cells and interstitium may lead to permanent renal dysfunction in patients who survive ethylene glycol intoxication, in patients with enteric hyperoxaluria from ileal resection or small-bowel bypass surgery, and in patients with hereditary hyperoxaluria **(Chap. 312)**. *Acute phosphate nephropathy* is an uncommon but serious complication of oral Phosphosoda used as a laxative or for bowel preparation for colonoscopy. It results from calcium phosphate crystal deposition in tubules and interstitium and occurs especially in subjects with underlying renal impairment and hypovolemia. Consequently, Phosphosoda should be avoided in patients with chronic kidney disease.

LIGHT CHAIN CAST NEPHROPATHY

Patients with multiple myeloma may develop acute renal failure in the setting of hypovolemia, infection, or hypercalcemia or after exposure to NSAIDs or radiographic contrast media. The diagnosis of light chain cast nephropathy (LCCN)—commonly known as *myeloma kidney*—should be considered in patients who fail to recover when the precipitating factor is corrected or in any elderly patient with otherwise unexplained acute renal failure.

In this disorder, filtered monoclonal immunoglobulin light chains (Bence-Jones proteins) form intratubular aggregates with secreted Tamm-Horsfall protein in the distal tubule. Casts, in addition to obstructing the tubular flow in affected nephrons, incite a giant cell or foreign body reaction and can lead to tubular rupture, resulting in interstitial fibrosis **(Fig. 310-3)**. Although LCCN generally occurs in patients with known multiple myeloma and a large plasma cell burden, the disorder should also be considered as a possible diagnosis in patients who have known monoclonal gammopathy even in the absence of frank myeloma. Filtered monoclonal light chains may also cause less pronounced renal manifestations in the absence of obstruction, due to direct toxicity to proximal tubular cells and intracellular crystal formation. This may result in isolated tubular disorders such as RTA or full Fanconi's syndrome.

Diagnosis Clinical clues to the diagnosis include anemia, bone pain, hypercalcemia, and an abnormally narrow anion gap due to hypoalbuminemia and hypergammaglobulinemia. Urinary dipsticks detect albumin but not immunoglobulin light chains; however, laboratory detection of increased amounts of protein in a spot urine specimen and a negative dipstick result are highly suggestive that the urine contains Bence-Jones protein. Serum and urine should both be sent for protein electrophoresis and for immunofixation for the detection and identification of a potential monoclonal band. A sensitive method is available to detect urine and serum free light chains.

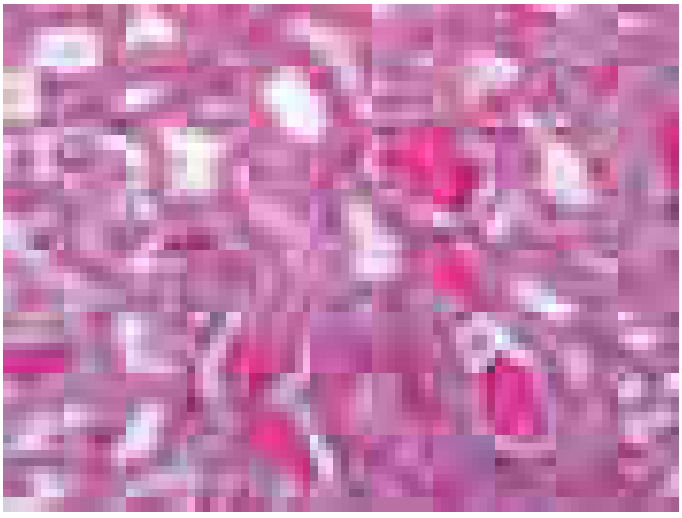

FIGURE 310-3 Histologic appearance of myeloma cast nephropathy. A hematoxylin-eosin–stained kidney biopsy shows many atrophic tubules filled with eosinophilic casts (consisting of Bence-Jones protein), which are surrounded by giant cell reactions. *(Courtesy of Dr. Michael N. Koss, University of Southern California Keck School of Medicine; with permission.)*

TREATMENT

Light Chain Cast Nephropathy

The goals of treatment are to correct precipitating factors such as hypovolemia and hypercalcemia, discontinue potential nephrotoxic agents, and treat the underlying plasma cell dyscrasia **(Chap. 107)**; plasmapheresis to remove light chains is of questionable value for LCCN.

LYMPHOMATOUS INFILTRATION OF THE KIDNEY

Interstitial infiltration by malignant B lymphocytes is a common autopsy finding in patients dying of chronic lymphocytic leukemia and non-Hodgkin's lymphoma; however, this is usually an incidental finding. Rarely, such infiltrates may cause massive enlargement of the kidneys and oliguric acute renal failure. Although high-dose glucocorticoids and subsequent chemotherapy often result in recovery of renal function, the prognosis in such cases is generally poor.

CHRONIC TUBULOINTERSTITIAL DISEASES

Improved occupational and public health measures, together with the banning of over-the-counter phenacetin-containing analgesics, has led to a dramatic decline in the incidence of chronic interstitial nephritis (CIN) from heavy metal—particularly lead and cadmium—exposure and analgesic nephropathy in North America. Today, CIN is most often the result of renal ischemia or secondary to a primary glomerular disease **(Chap. 308)**. Other important forms of CIN are the result of developmental anomalies or inherited diseases such as reflux nephropathy or sickle cell nephropathy and may not be recognized until adolescence or adulthood. Although it is impossible to reverse damage that has already occurred, further deterioration may be prevented or at least slowed in such cases by treating glomerular hypertension, a common denominator in the development of secondary FSGS and progressive loss of functioning nephrons. Therefore, awareness and early detection of patients at risk may prevent them from developing end-stage renal disease (ESRD).

VESICOURETERAL REFLUX AND REFLUX NEPHROPATHY

Reflux nephropathy is the consequence of vesicoureteral reflux (VUR) or other urologic anomalies in early childhood. It was previously called *chronic pyelonephritis* because it was believed to result from recurrent urinary tract infections (UTIs) in childhood. VUR stems from abnormal retrograde urine flow from the bladder into one or both ureters and kidneys because of mislocated and incompetent ureterovesical valves **(Fig. 310-4)**. Although high-pressure sterile reflux may impair normal growth of the kidneys, when coupled with recurrent UTIs in early childhood, the result is patchy interstitial scarring and tubular atrophy. Loss of functioning nephrons leads to hypertrophy of the remnant glomeruli and eventual secondary FSGS. Reflux nephropathy often goes unnoticed until early adulthood when chronic kidney disease is detected during routine evaluation or during pregnancy. Affected adults are frequently asymptomatic, but may give a history of prolonged bed-wetting or recurrent UTIs during childhood, and exhibit variable renal insufficiency, hypertension, mild to moderate proteinuria, and unremarkable urine sediment. When both kidneys are affected, the disease often progresses inexorably over several years to ESRD, despite the absence of ongoing urinary infections or reflux. A single affected kidney may go undetected, except for the presence of hypertension. Renal ultrasound in adults characteristically shows asymmetric small kidneys with irregular outlines, thinned cortices, and regions of compensatory hypertrophy (Fig. 310-4).

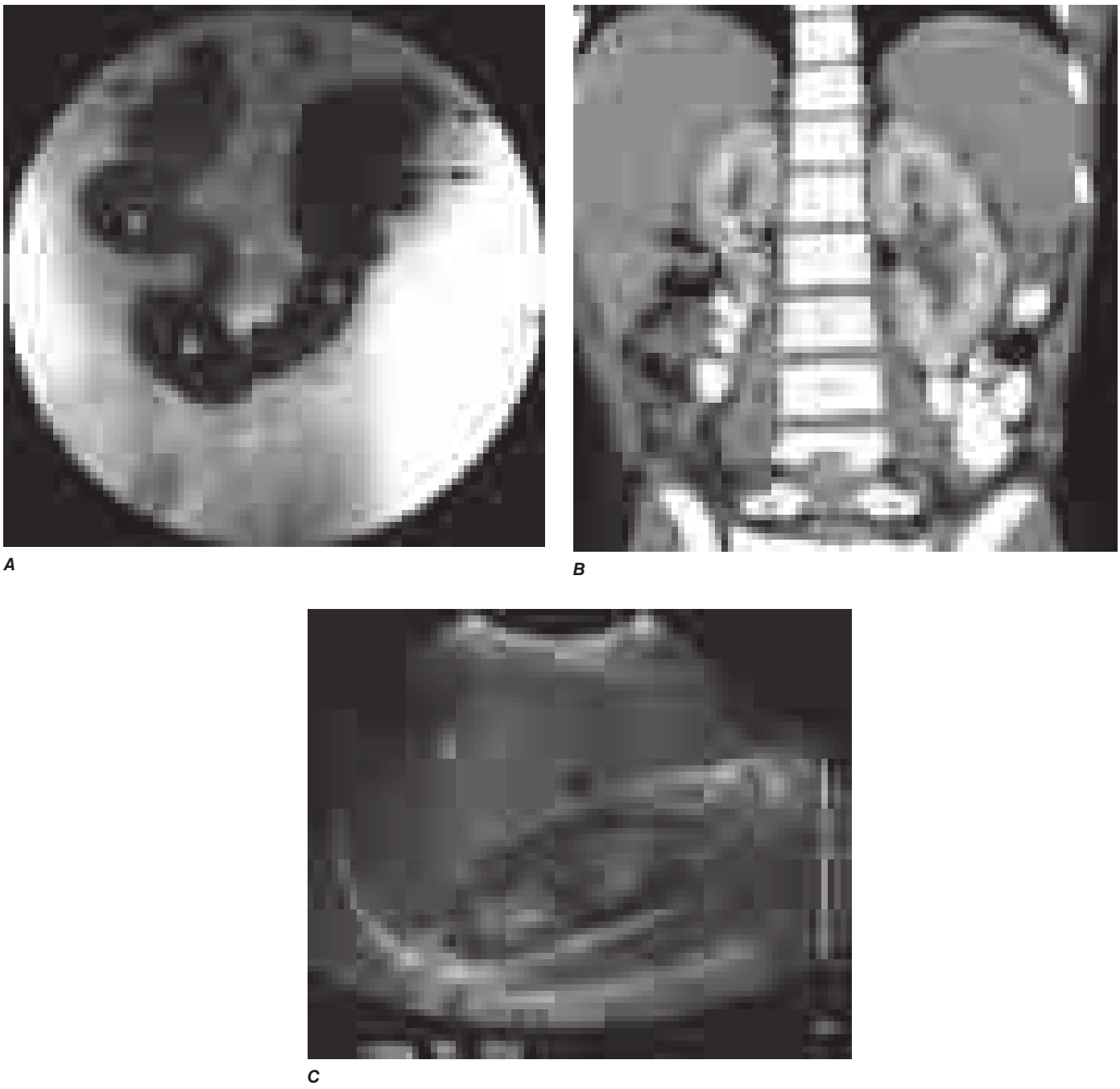

FIGURE 310-4 Radiographs of vesicoureteral reflux (VUR) and reflux nephropathy. *A.* Voiding cystourethrogram in a 7-month-old baby with bilateral high-grade VUR evidenced by clubbed calyces (*arrows*) and dilated tortuous ureters (U) entering the bladder (B). ***B.*** Abdominal computed tomography scan (coronal plane reconstruction) in a child showing severe scarring of the lower portion of the right kidney (*arrow*). ***C.*** Sonogram of the right kidney showing loss of parenchyma at the lower pole due to scarring (*arrow*) and hypertrophy of the mid-region (*arrowhead*). *(Courtesy of Dr. George Gross, University of Maryland Medical Center; with permission.)*

TREATMENT

Vesicoureteral Reflux and Reflux Nephropathy

Maintenance of sterile urine in childhood has been shown to limit scarring of the kidneys. Surgical reimplantation of the ureters into the bladder to restore competency is indicated in young children with persistent high-grade reflux, but is ineffective and is not indicated in adolescents or adults after scarring has occurred. Aggressive control of blood pressure with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and other agents is effective in reducing proteinuria and may significantly forestall further deterioration of renal function.

SICKLE CELL NEPHROPATHY

The pathogenesis and clinical manifestations of sickle cell nephropathy are described in Chap. 311. Evidence of tubular injury may be evident in childhood and early adolescence in the form of polyuria due to decreased concentrating ability or type IV RTA years before there is significant nephron loss and proteinuria from secondary FSGS. Early recognition of these subtle renal abnormalities or development of microalbuminuria in a child with sickle cell disease may warrant consultation with a nephrologist and/or therapy with low-dose ACEIs. Papillary necrosis may result from ischemia due to sickling of red cells in the relatively hypoxemic and hypertonic medullary vasculature and present with gross hematuria and ureteric obstruction by sloughed ischemic papillae (Table 310-3).

TABLE 310-3 Major Causes of Papilary Necrosis
Analgesic nephropathy
Sickle cell nephropathy
Diabetes with urinary tract infection
Prolonged NSAID use (rare)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

TUBULOINTERSTITIAL ABNORMALITIES ASSOCIATED WITH GLOMERULONEPHRITIS

Primary glomerulopathies are often associated with damage to tubules and interstitium. This may occasionally be due to the same pathologic process affecting the glomerulus and tubulointerstitium, as is the case with immune-complex deposition in lupus nephritis. More often, however, chronic tubulointerstitial changes occur as a secondary consequence of prolonged glomerular dysfunction. Potential mechanisms by which glomerular disease might cause tubulointerstitial injury include proteinuria-mediated damage to the epithelial cells, activation of tubular cells by cytokines and complement, or reduced peritubular blood flow leading to downstream tubulointerstitial ischemia, especially in the case of glomeruli that are globally obsolescent due to severe glomerulonephritis. It is often difficult to discern the initial cause of injury by renal biopsy in a patient who presents with advanced renal disease in this setting.

ANALGESIC NEPHROPATHY

Analgesic nephropathy results from the long-term use of compound analgesic preparations containing phenacetin (banned in the United States since 1983), aspirin, and caffeine. In its classic form, analgesic nephropathy is characterized by renal insufficiency, papillary necrosis (Table 310-3) attributable to the presumed concentration of the drug to toxic levels in the inner medulla, and a radiographic constellation of small, scarred kidneys with papillary calcifications best appreciated by computed tomography **(Fig. 310-5)**. Patients may also have polyuria due to impaired concentrating ability and non-anion-gap metabolic acidosis from tubular damage. Shedding of a sloughed necrotic papilla can cause gross hematuria and ureteric colic due to ureteral obstruction. Individuals with ESRD as a result of analgesic nephropathy are at increased risk of a urothelial malignancy compared to patients with other causes of renal failure. Recent cohort studies in individuals with normal baseline renal function suggest that the moderate chronic use of current analgesic preparations available in the United States, including acetaminophen and NSAIDs, does not seem to cause the constellation of findings known as analgesic nephropathy, although volume-depleted individuals and those with chronic kidney disease are at higher risk of NSAID-related renal toxicity. Nonetheless, it is recommended that heavy users of acetaminophen and NSAIDs be screened for evidence of renal disease.

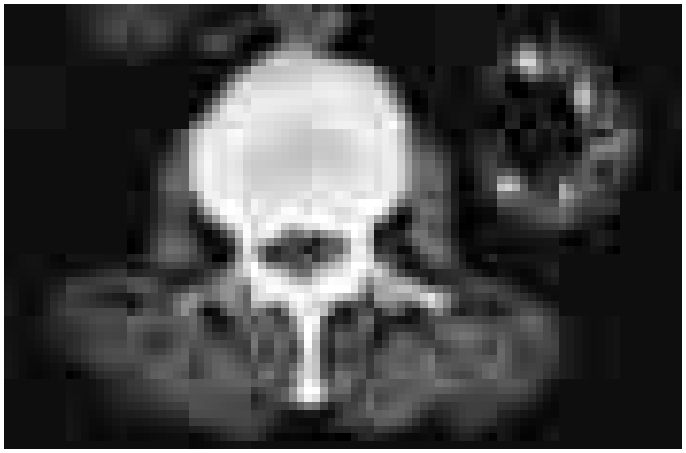

FIGURE 310-5 Radiologic appearance of analgesic nephropathy. A noncontrast computed tomography scan shows an atrophic left kidney with papillary calcifications in a garland pattern. *(Reprinted by permission from Macmillan Publishers, Ltd., MM Elseviers et al: Kidney International 48:1316, 1995.)*

ARISTOLOCHIC ACID NEPHROPATHY

Two seemingly unrelated forms of CIN, Chinese herbal nephropathy and Balkan endemic nephropathy, have recently been linked by the underlying etiologic agent aristolochic acid and are now collectively termed aristolochic acid nephropathy (AAN). In Chinese herbal nephropathy, first described in the early 1990s in young women taking traditional Chinese herbal preparations as part of a weight-loss regimen, one of the offending agents has been identified as aristolochic acid, a known carcinogen from the plant *Aristolochia*. Multiple *Aristolochia* species have been used in traditional herbal remedies for centuries and continue to be available despite official bans on their use in many countries. Molecular evidence has also implicated aristolochic acid in Balkan endemic nephropathy, a chronic TIN found primarily in towns along the tributaries of the Danube River and first described in the 1950s. Although the exact route of exposure is not known with certainty, contamination of local grain preparations with the seeds of *Aristolochia* species seems most likely. Aristolochic acid, after prolonged exposure, produces renal interstitial fibrosis with a relative paucity of cellular infiltrates. The urine sediment is bland, with rare leukocytes and only mild proteinuria. Anemia may be disproportionately severe relative to the level of renal dysfunction. Definitive diagnosis of AAN requires two of the following three features: characteristic histology on kidney biopsy; confirmation of aristolochic acid ingestion; and detection of aristolactam-DNA adducts in kidney or urinary tract tissue. These latter lesions represent a molecular signature of aristolochic acid–derived DNA damage and often consist of characteristic A:T-to-T:A transversions. Due to this mutagenic activity, AAN is associated with a very high incidence of upper urinary tract urothelial cancers, with risk related to cumulative dose. Surveillance with computed tomography, ureteroscopy, and urine cytology is warranted, and consideration should be given to bilateral nephroureterectomy once a patient has reached ESRD.

KARYOMEGALIC INTERSTITIAL NEPHRITIS

Karyomegalic interstitial nephritis is an unusual form of slowly progressive chronic kidney disease with mild proteinuria, interstitial fibrosis, tubular atrophy, and oddly enlarged nuclei of proximal tubular epithelial cells. It has been linked to mutations in *FAN1*, a nuclease involved in DNA repair, which may render carriers of the mutation susceptible to environmental DNA-damaging agents.

LITHIUM-ASSOCIATED NEPHROPATHY

The use of lithium salts for the treatment of manic-depressive illness may have several renal sequelae, the most common of which is nephrogenic diabetes insipidus manifesting as polyuria and polydipsia. Lithium accumulates in principal cells of the collecting duct by entering through the epithelial sodium channel (ENaC), where it inhibits glycogen synthase kinase 3β and downregulates vasopressin-regulated aquaporin water channels. Less frequently, chronic TIN develops after prolonged (>10–20 years) lithium use and is most likely to occur in patients who have experienced repeated episodes of toxic lithium levels. Findings on renal biopsy include interstitial fibrosis and tubular atrophy that are out of proportion to the degree of glomerulosclerosis or vascular disease, a sparse lymphocytic infiltrate, and small cysts or dilation of the distal tubule and collecting duct that are highly characteristic of this disorder. The degree of interstitial fibrosis correlates with both duration and cumulative dose of lithium. Individuals with lithium-associated nephropathy are typically asymptomatic, with minimal proteinuria, few urinary leukocytes, and normal blood pressure. Some patients develop more severe proteinuria due to secondary FSGS, which may contribute to further loss of renal function.

TREATMENT

Lithium-Associated Nephropathy

Renal function should be followed regularly in patients taking lithium, and caution should be exercised in patients with underlying renal disease. The use of amiloride to inhibit lithium entry via ENaC

has been effective to prevent and treat lithium-induced nephrogenic diabetes insipidus, but it is not clear if it will prevent lithium-induced CIN. Once lithium-associated nephropathy is detected, the discontinuation of lithium in attempt to forestall further renal deterioration can be problematic, as lithium is an effective mood stabilizer that is often incompletely substituted by other agents. Furthermore, despite discontinuation of lithium, chronic renal disease in such patients is often irreversible and can slowly progress to ESRD. The most prudent approach is to monitor lithium levels frequently and adjust dosing to avoid toxic levels (preferably <1 meq/L). This is especially important because lithium is cleared less effectively as renal function declines. In patients who develop significant proteinuria, ACEI or ARB treatment should be initiated.

CALCINEURIN-INHIBITOR NEPHROTOXICITY

The calcineurin inhibitor (CNI) immunosuppressive agents cyclosporine and tacrolimus can cause both acute and chronic renal injury. Acute forms can result from vascular causes such as vasoconstriction or the development of thrombotic microangiopathy, or can be due to a toxic tubulopathy. Chronic CNI-induced renal injury is typically seen in solid organ (including heart-lung and liver) transplant recipients and manifests with a slow but irreversible reduction of glomerular filtration rate, with mild proteinuria and arterial hypertension. Hyperkalemia is a relatively common complication and is caused, in part, by tubular resistance to aldosterone. The histologic changes in renal tissue include patchy interstitial fibrosis and tubular atrophy, often in a "striped" pattern. In addition, the intrarenal vasculature often demonstrates hyalinosis, and focal glomerulosclerosis can be present as well. Similar changes may occur in patients receiving CNIs for autoimmune diseases, although the doses are generally lower than those used for organ transplantation. Dose reduction or CNI avoidance appears to mitigate the chronic tubulointerstitial changes, but may increase the risk of rejection and graft loss.

HEAVY METAL (LEAD) NEPHROPATHY

Heavy metals, such as lead or cadmium, can lead to a chronic tubulointerstitial process after prolonged exposure. The disease entity is no longer commonly diagnosed, because such heavy metal exposure has been greatly reduced due to the known health risks from lead and the consequent removal of lead from most commercial products and fuels. Nonetheless, occupational exposure is possible in workers involved in the manufacture or destruction of batteries, removal of lead paint, or manufacture of alloys and electrical equipment (cadmium) in countries where industrial regulation is less stringent. In addition, ingestion of moonshine whiskey distilled in lead-tainted containers has been one of the more frequent sources of lead exposure.

Early signs of chronic lead intoxication are attributable to proximal tubule dysfunction, particularly hyperuricemia as a result of diminished urate secretion. The triad of "saturnine gout," hypertension, and renal insufficiency should prompt a practitioner to ask specifically about lead exposure. Unfortunately, evaluating lead burden is not as straightforward as ordering a blood test; the preferred methods involve measuring urinary lead after infusion of a chelating agent or by radiographic fluoroscopy of bone. Several recent studies have shown an association between chronic low-level lead exposure and decreased renal function, although either of these two factors may have been the primary event. In those patients who have CIN of unclear origin and an elevated total body lead burden, repeated treatments of lead chelation therapy have been shown to slow the decline in renal function.

METABOLIC DISORDERS

Disorders leading to excessively high or low levels of certain electrolytes and products of metabolism can also lead to chronic kidney disease if untreated.

CHRONIC URIC ACID NEPHROPATHY

The constellation of pathologic findings that represent *gouty nephropathy* are very uncommon nowadays and are more of historical interest than clinical importance, as gout is typically well managed with allopurinol and other agents. However, there is emerging evidence that hyperuricemia is an independent risk factor for the development of chronic kidney disease, perhaps through endothelial damage. The complex interactions of hyperuricemia, hypertension, and renal failure are still incompletely understood.

Presently, gouty nephropathy is most likely to be encountered in patients with severe tophaceous gout and prolonged hyperuricemia from a hereditary disorder of purine metabolism **(Chap. 410)**. This should be distinguished from juvenile hyperuricemic nephropathy, a form of medullary cystic kidney disease caused by mutations in uromodulin (UMOD) **(Chap. 309)** and now grouped into the larger category of autosomal dominant tubulointerstitial kidney disease. Histologically, the distinctive feature of gouty nephropathy is the presence of crystalline deposits of uric acid and monosodium urate salts in the kidney parenchyma. These deposits not only cause intrarenal obstruction but also incite an inflammatory response, leading to lymphocytic infiltration, foreign-body giant cell reaction, and eventual fibrosis, especially in the medullary and papillary regions of the kidney. Since patients with gout frequently suffer from hypertension and hyperlipidemia, degenerative changes of the renal arterioles may constitute a striking feature of the histologic abnormality, out of proportion to the other morphologic defects. Clinically, gouty nephropathy is an insidious cause of chronic kidney disease. Early in its course, glomerular filtration rate may be near normal, often despite morphologic changes in medullary and cortical interstitium, proteinuria, and diminished urinary concentrating ability. Treatment with allopurinol and urine alkalinization is generally effective in preventing uric acid nephrolithiasis and the consequences of recurrent kidney stones; however, gouty nephropathy may be intractable to such measures. Furthermore, the use of allopurinol in asymptomatic hyperuricemia has not been consistently shown to improve renal function.

HYPERCALCEMIC NEPHROPATHY

(See also Chap. 403) Chronic hypercalcemia, as occurs in primary hyperparathyroidism, sarcoidosis, multiple myeloma, vitamin D intoxication, or metastatic bone disease, can cause tubulointerstitial disease and progressive renal failure. The earliest lesion is a focal degenerative change in renal epithelia, primarily in collecting ducts, distal tubules, and loops of Henle. Tubular cell necrosis leads to nephron obstruction and stasis of intrarenal urine, favoring local precipitation of calcium salts and infection. Dilation and atrophy of tubules eventually occur, as do interstitial fibrosis, mononuclear leukocyte infiltration, and interstitial calcium deposition (nephrocalcinosis). Calcium deposition may also occur in glomeruli and the walls of renal arterioles.

Clinically, the most striking defect is an inability to maximally concentrate the urine, due to reduced collecting duct responsiveness to arginine vasopressin and defective transport of sodium and chloride in the loop of Henle. Reductions in both glomerular filtration rate and renal blood flow can occur, both in acute and in prolonged hypercalcemia. Eventually, uncontrolled hypercalcemia leads to severe tubulointerstitial damage and overt renal failure. Abdominal x-rays may demonstrate nephrocalcinosis as well as nephrolithiasis, the latter due to the hypercalciuria that often accompanies hypercalcemia.

Treatment consists of reducing the serum calcium concentration toward normal and correcting the primary abnormality of calcium metabolism **(Chap. 403)**. Renal dysfunction of acute hypercalcemia may be completely reversible. Gradual progressive renal insufficiency related to chronic hypercalcemia, however, may not improve even with correction of the calcium disorder.

HYPOKALEMIC NEPHROPATHY

Patients with prolonged and severe hypokalemia from chronic laxative or diuretic abuse, surreptitious vomiting, or primary aldosteronism may develop a reversible tubular lesion characterized by vacuolar degeneration of proximal and distal tubular cells. Eventually, tubular atrophy and cystic dilation accompanied by interstitial fibrosis may ensue, leading to irreversible chronic kidney disease. Timely correction of the hypokalemia will prevent further progression, but persistent hypokalemia can cause ESRD.

GLOBAL PERSPECTIVE

The causes of acute and CIN vary widely across the globe. Analgesic nephropathy continues to be seen in countries where phenacetin-containing compound analgesic preparations are readily available. Adulterants in unregulated herbal and traditional medicaments pose a threat of toxic interstitial nephritis, as exemplified by aristolochic acid contamination of herbal slimming preparations. Contamination of food sources with toxins, such as the recent outbreak of nephrolithiasis and acute renal failure from melamine contamination of infant milk formula, poses a continuing risk. Large-scale exposure to aristolochic acid remains prevalent in many Asian countries where traditional herbal medicine use is common. Although industrial exposure to lead and cadmium has largely disappeared as a cause of CIN in developed nations, it remains a risk for nephrotoxicity in countries where such exposure is less well controlled. New endemic forms of chronic kidney disease continue to be described. Most notable is the nephropathy found among Pacific coastal plantation workers in Central America that is estimated to have claimed 20,000 lives thus far due to the development of end-stage kidney disease. This entity has been named Mesoamerican nephropathy, although similar pathophysiologic mechanisms may also be at play in other regional forms of chronic kidney disease in Sri Lanka and southern India. Although a variety of etiologic factors have been proposed, the most likely cause appears to be related to repetitive episodes of heat exposure, dehydration or volume depletion, and consequent metabolic changes leading to uricosuria and elevated levels of vasopressin. Global warming and regional temperature variability have been proposed as contributors to these newly described forms of kidney disease.

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311 Vascular Injury to the Kidney

Ronald S. Go, Nelson Leung

The renal circulation is complex and is characterized by a highly perfused arteriolar network, reaching cortical glomerular structures adjacent to lower-flow vasa recta that descend into medullary segments. Disorders of the larger vessels, including renal artery stenosis and atheroembolic disease, are discussed elsewhere **(Chap. 322)**. This chapter examines primary disorders of the renal microvessels, many of which are associated with thrombosis and hemolysis.

THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy (TMA) is a pathologic lesion characterized by endothelial cell injury in the terminal arterioles and capillaries. Platelet and hyaline thrombi causing partial or complete occlusion are integral to the histopathology of TMA. TMA is usually accompanied by microangiopathic hemolytic anemia (MAHA) with its typical features of thrombocytopenia and schistocytes, but not always. In the kidney, TMA is characterized by swollen endocapillary cells (endotheliosis), fibrin thrombi, platelet plugs, arterial intimal fibrosis, and a membranoproliferative pattern in the glomerulus. Fibrin thrombi may extend into the arteriolar vascular pole, producing glomerular collapse and at times cortical necrosis. In kidneys that recover from acute TMA, secondary focal segmental glomerulosclerosis may develop. Diseases associated with this lesion include thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), malignant hypertension, scleroderma renal crisis, antiphospholipid syndrome, preeclampsia/HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, HIV infection, and radiation nephropathy. TMA can also be seen in myeloproliferative neoplasm (MPN)-related glomerulopathy and POEMS (polyneuropathy, endocrinopathy, organomegaly, monoclonal gammopathy and skin changes) syndrome which are not associated with MAHA.

HEMOLYTIC-UREMIC SYNDROME/THROMBOTIC THROMBOCYTOPENIC PURPURA

HUS and TTP are the prototypes for MAHA. Historically, HUS and TTP were distinguished mainly by their clinical and epidemiologic differences. TTP develops more commonly in adults and was thought to have more neurologic complications while HUS occurs more frequently in children, particularly when associated with hemorrhagic diarrhea. However, atypical HUS (aHUS) can have its first appearance in adulthood, and better testing has revealed that neurologic involvement is as common in HUS as in TTP. Currently, HUS and TTP can be differentiated etiologically and treated according to their specific pathophysiologic features.

Hemolytic-Uremic Syndrome HUS is loosely defined by the presence of MAHA and renal impairment. At least four variants are recognized. The most common is Shiga toxin–producing *Escherichia coli* (STEC) HUS, which is also known as D^+ (diarrhea-associated) HUS or enterohemorrhagic *E. coli* (EHEC) HUS. Most cases involve children <5 years of age, but adults also are susceptible, as evidenced by a 2011 outbreak in northern Europe. Diarrhea, often bloody, precedes MAHA within 1 week in >80% of cases. Abdominal pain, cramping, and vomiting are frequent, whereas fever is typically absent. Neurologic symptoms, including dysphasia, hyperreflexia, blurred vision, memory deficits, encephalopathy, perseveration, and agraphia, often develop, especially in adults. Seizures and cerebral infarction can occur in severe cases. STEC HUS is caused by the Shiga toxins (Stx1 and Stx2), which are also referred to as *verotoxins*. These toxins are produced by certain strains of *E. coli* and *Shigella dysenteriae*. In the United States and Europe, the most common STEC strain is O157:H7, but HUS has been reported with other strains ($O157/H^-$, $O111:H^-$, $O26:H11/H^-$, O145:H28, and O104:H4). After entry into the circulation, Shiga toxin binds to the glycolipid surface receptor globotriaosylceramide (Gb3), which is richly expressed on cells of the renal microvasculature. Upon binding, the toxin enters the cells, inducing inflammatory cytokines (interleukin 8 [IL-8], monocyte chemotactic protein 1 [MCP-1], and stromal cell–derived factor 1 [SDF-1]) and chemokine receptors (CXCR4 and CXCR7); this action results in platelet aggregation and the microangiopathic process. *Streptococcus pneumoniae* can also cause HUS. Certain strains produce a neuraminidase that cleaves the N-acetylneuraminic acid moieties normally covering the Thomsen-Friedenreich antigen on platelets and endothelial cells. Exposure of this cryptic antigen to preformed IgM results in severe MAHA.

Atypical HUS or complement medicated HUS is the result of complement dysregulation. The complement dysregulation can be congenital or acquired. The affected patients often have a low C3 and a normal C4 levels characteristic of alternative pathway activation. Factor H deficiency, the most common defect, has been linked to families with aHUS. Factor H competes with factor B to prevent the formation of C3bBb and acts as a cofactor for factor I, which proteolytically degrades C3b. More than 70 mutations of the factor H gene have been identified. Most are missense mutations that produce abnormalities in the

C-terminus region, affecting its binding to C3b but not its concentration. Other mutations result in low levels or the complete absence of the protein. Deficiencies in other complement-regulatory proteins, such as factor I, factor B, membrane cofactor protein (CD46), C3, complement factor H–related protein 1 (CFHR1), CFHR3, CFHR5, and thrombomodulin, have also been reported. Finally, an autoimmune variant of aHUS has been discovered. DEAP (deficiency of CFHR plasma proteins and CFH autoantibody positive) HUS occurs when an autoantibody to factor H is formed. DEAP HUS is often associated with a deletion of an 84-kb fragment of the chromosome that encodes for CFHR1 and CFHR3. The autoantibody blocks the binding of factor H to C3b and surface-bound C3 convertase. Renal injury is often severe resulting in end stage renal disease. The severity of the renal injury and recurrence after kidney transplant depend on the complement regulatory protein.

Thrombotic Thrombocytopenic Purpura Traditionally, TTP is characterized by the pentad: MAHA, thrombocytopenia, neurologic symptoms, fever, and renal failure. The pathophysiology of TTP involves the accumulation of ultra-large multimers of von Willebrand factor as a result of the absence or markedly decreased activity of the plasma protease ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. TTP is now defined as MAHA associated with ADAMTS13 activity of (<5–10%). These ultra-large multimers form clots and shear erythrocytes, resulting in MAHA; however, the absence of ADAMTS13 alone may not by itself produce TTP. Often, an additional inflammatory trigger (such as infection, surgery, pancreatitis, or pregnancy) is required to initiate clinical TTP. This may be mediated by human neutrophil peptides that inhibit cleavage of von Willebrand factor by ADAMTS13.

Data from the Oklahoma TTP/HUS Registry suggest an incidence rate of 2.9 cases/10^6 patients in the United States. The median age of onset is 40 years. The incidence is more than nine times higher among blacks than among non-blacks. Like that of systemic lupus erythematosus, the incidence of TTP is nearly three times higher among women than among men. If untreated, TTP has a mortality rate exceeding 90%. Even with modern therapy, 20% of patients die within the first month from complications of microvascular thrombosis.

The classic form of TTP is idiopathic TTP, which is the result of a severe deficiency in ADAMTS13. In the past, TTP had traditionally been associated with infection, malignancy, and intense inflammation (e.g., pancreatitis), but ADAMTS13 activity is typically not decreased in these conditions and therefore should be not considered TTP. In idiopathic TTP, the formation of an autoantibody to ADAMTS13 (IgG or IgM) either increases its clearance or inhibits its activity. Upshaw-Schülman syndrome is a hereditary condition characterized by congenital deficiency of ADAMTS13. TTP in these patients can start within the first weeks of life but in some instances may not present until adulthood, especially during pregnancy. Both environmental and genetic factors are thought to influence the development of TTP. Plasma transfusion is an effective strategy for prevention and treatment.

Drug-induced TMA is a recognized complication of treatment with some chemotherapeutic agents, immunosuppressive agents, and quinine. Two different mechanisms are now recognized. Toxic or endothelial damage (pathologically similar to that of HUS) is the main cause of the TMA that develops in association with chemotherapeutic agents (e.g., mitomycin C, gemcitabine) and immunosuppressive agents (cyclosporine, interferon, sirolimus, and tacrolimus). This process is usually dose-dependent. Alternatively, TMA may develop as a result of drug-induced autoantibodies. This form is less likely to be dose-dependent and can, in fact, occur after a single dose in patients with previous exposure. ADAMTS13 deficiency is found in fewer than half of patients with clopidogrel-associated TTP. Quinine appears to induce autoantibodies to granulocytes, lymphocytes, endothelial cells, and platelet glycoprotein Ib/IX or IIb/IIIa complexes, but not to ADAMTS13. Quinine-associated TTP is more common among women. TMA has also been reported with drugs that inhibit vascular endothelial growth factor, such as bevacizumab; the mechanism is not completely understood.

TREATMENT

HUS/TTP

Treatment should be based on pathophysiology. Autoantibody-mediated TTP and DEAP HUS respond to the combination of plasma exchange and prednisone. In addition to removing the autoantibodies, plasma exchange with fresh-frozen plasma replaces ADAMTS13. Twice-daily plasma exchanges with administration of rituximab may be effective in refractory cases. Plasma infusion is usually sufficient to replace the ADAMTS13 in Upshaw-Schülman syndrome. Plasma exchange should be considered if larger volumes are necessary. Drug-induced TMA secondary to endothelial damage typically does not respond to plasma exchange and is treated primarily by discontinuing use of the agent and providing supportive care. Similarly, STEC HUS should be treated with supportive measures as plasma exchange has not been found to be effective. Antimotility agents and antibiotics increase the incidence of HUS among children, but azithromycin was recently found to decrease the duration of bacterial shedding by adults. Plasma infusion/exchange is effective in certain types of aHUS as it replaces complement-regulatory proteins. Eculizumab is a monoclonal antibody to C5 that is approved for use in aHUS which has been shown to abort MAHA and improve renal function. Antibiotics and washed red cells should be given in neuraminidase-associated HUS, and plasmapheresis may be helpful. However, plasma and whole-blood transfusion should be avoided since these products contain IgM, which may exacerbate MAHA. Finally, combined factor H and ADAMTS13 deficiency have been reported. The affected patients are generally less responsive to plasma infusion, a result illustrating the complexity of the management of these cases.

HEMATOPOIETIC STEM CELL TRANSPLANTATION–ASSOCIATED THROMBOTIC MICROANGIOPATHY (HSCT-TMA)

HSCT-TMA develops after HSCT, with an incidence of ~8%. Etiologic factors include conditioning regimens, immunosuppression, infections, and graft-versus-host disease. Other risk factors include female sex and human leukocyte antigen (HLA)–mismatched donor grafts. HSCT-TMA usually occurs within the first 100 days of HSCT. Table 311-1 lists definitions of HSCT-TMA currently used for clinical trials. Diagnosis may be difficult since thrombocytopenia, anemia, and renal insufficiency are common after HSCT. HSCT-TMA carries a high mortality rate (75% within 3 months). The majority of patients have >10% ADAMTS13 activity, and plasma exchange is beneficial in <25% of patients. Discontinuation of calcineurin inhibitors and treatment of infections or sinusoidal obstruction syndrome (if present)

TABLE 311-1 Criteria for Establishing Microangiopathic Kidney Injury Associated with Hematopoietic Stem Cell Transplantation

INTERNATIONAL WORKING GROUP	BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK TOXICITY COMMITTEE
4% schistocytes in the blood	RBC fragmentation and at least 2 schistocytes per high-power field
De novo, prolonged, or progressive thrombocytopenia	Concurrent increase in LDH concentration above baseline
A sudden and persistent increase in LDH concentration	Negative direct and indirect Coombs test
Decrease in hemoglobin level or increased RBC transfusion requirement	Concurrent renal and/or neurologic dysfunction without other explanations
Decrease in haptoglobin concentration	

Note: These features underscore the need to identify pathways of hemolysis and thrombocytopenia that accompany deterioration of kidney function.

Abbreviations: LDH, lactate dehydrogenase; RBC, red blood cell.

are recommended. Treatment with rituximab and defibrotide may also be helpful, but clinical trial data are lacking.

HIV-RELATED TMA

HIV-related TMA is a complication encountered mainly before widespread use of highly active antiretroviral therapy. It is seen in patients with advanced AIDS and low CD4+ T cell counts although it can be the first manifestation of HIV infection. The presence of MAHA, thrombocytopenia, and renal failure are suggestive, but renal biopsy is required for diagnosis since other renal diseases are also associated with HIV infection. Thrombocytopenia may prohibit renal biopsy in some patients. The mechanism of injury is unclear, although HIV can induce apoptosis in endothelial cells. ADAMTS13 activity is not reduced in these patients. Cytomegalovirus co-infection may also be a risk factor. Effective antiviral therapy is key, while plasma exchange should be limited to patients who have evidence of TTP.

RADIATION NEPHROPATHY

Either local or total body irradiation can produce microangiopathic injury. The kidney is one of the most radiosensitive organs, and injury can result with as little as 4–5 Gy. Such injury is characterized by renal insufficiency, proteinuria, and hypertension usually developing ≥6 months after radiation exposure. Renal biopsy reveals classic TMA with damage to glomerular, tubular, and vascular cells, but systemic evidence of MAHA is uncommon. Because of its high incidence after allogeneic HSCT, radiation nephropathy is often referred to as *bone marrow transplant nephropathy*. No specific therapy is available, although observational evidence supports renin-angiotensin system blockade.

SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS)

Kidney involvement is common (up to 52%) in patients with widespread scleroderma, with 20% of cases resulting directly from scleroderma renal crisis. Other renal manifestations in scleroderma include transient (prerenal) or medication-related forms of acute kidney injury (e.g., associated with *D*-penicillamine, nonsteroidal anti-inflammatory drugs, or cyclosporine). Scleroderma renal crisis occurs in 12% of patients with diffuse systemic sclerosis but in only 2% of those with limited systemic sclerosis. Scleroderma renal crisis is the most severe manifestation of renal involvement, and is characterized by accelerated hypertension, a rapid decline in renal function, nephrotic range proteinuria, and hematuria. Retinopathy and encephalopathy may accompany the hypertension. Salt and water retention with microvascular injury can lead to pulmonary edema. Cardiac manifestations, including myocarditis, pericarditis, and arrhythmias, denote an especially poor prognosis. Although MAHA is present in more than half of patients, coagulopathy is rare.

The renal lesion in scleroderma renal crisis is characterized by arcuate artery intimal and medial proliferation with luminal narrowing. This lesion is described as "onion-skinning" and can be accompanied by glomerular collapse due to reduced blood flow. Histologically, scleroderma renal crisis is indistinguishable from malignant hypertension, with which it can coexist. Fibrinoid necrosis and thrombosis are common. Before the availability of angiotensin-converting enzyme (ACE) inhibitors, the mortality rate for scleroderma renal crisis was >90% at 1 month. Introduction of renin-angiotensin system blockade has lowered the mortality rate to 30% at 3 years. Nearly two-thirds of patients with scleroderma renal crisis may require dialysis support, with recovery of renal function in 50% (median time, 1 year). Glomerulonephritis and vasculitis associated with antineutrophil cytoplasmic antibodies and systemic lupus erythematosus have been described in patients with scleroderma. An association has been found with a speckled pattern of antinuclear antibodies and with antibodies to RNA polymerases I and III. Anti-U3-RNP may identify young patients at risk for scleroderma renal crisis. Anticentromere antibody, in contrast, is a negative predictor of this disorder. Because of the overlap between scleroderma renal crisis and other autoimmune disorders, a renal biopsy is recommended for patients with atypical renal involvement, especially if hypertension is absent.

Treatment with ACE inhibition is the first-line therapy unless contraindicated. The goal of therapy is to reduce systolic and diastolic blood pressure by 20 mmHg and 10 mmHg, respectively, every 24 h until blood pressure is normal. Additional antihypertensive therapy may be given once the dose of drug for ACE inhibition is maximized. Both ACE inhibitors and angiotensin II receptor antagonists are effective, although data suggest that treatment with ACE inhibitors is superior. ACE inhibition alone does not prevent scleroderma renal crisis, but it does reduce the impact of hypertension. Intravenous iloprost has been used in Europe for blood pressure management and improvement of renal perfusion. Kidney transplantation is not recommended for 2 years after the start of dialysis since delayed recovery may occur.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (Chap. 350) can be either primary or secondary to systemic lupus erythematosus. It is characterized by a predisposition to systemic thrombosis (arterial and venous) and fetal morbidity mediated by antiphospholipid antibodies—mainly anticardiolipin antibodies (IgG, IgM, or IgA), lupus anticoagulant, or anti-β-2 glycoprotein I antibodies (antiβ2GPI). Patients with both anticardiolipin antibodies and antiβ2GPI appear to have the highest risk of thrombosis. The vascular compartment within the kidney is the main site of renal involvement. Arteriosclerosis is commonly present in the arcuate and intralobular arteries. In the intralobular arteries, fibrous intimal hyperplasia characterized by intimal thickening secondary to intense myofibroblastic intimal cellular proliferation with extracellular matrix deposition is frequently seen along with onion-skinning. Arterial and arteriolar fibrous and fibrocellular occlusions are present in more than two-thirds of biopsy samples. Cortical necrosis and focal cortical atrophy may result from vascular occlusion. TMA is commonly present in renal biopsies, although signs of MAHA and platelet consumption are usually absent. TMA is especially common in the catastrophic variant of antiphospholipid syndrome. In patients with secondary antiphospholipid syndrome, other glomerulopathies may be present, including membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis, and pauci-immune crescentic glomerulonephritis.

Large vessels can be involved in antiphospholipid syndrome and may form the proximal nidus near the ostium for thrombosis of the renal artery. Renal vein thrombosis can occur and should be suspected in patients with lupus anticoagulant who develop nephrotic-range proteinuria. Progression to end-stage renal disease can occur, and a thrombosis may form in the vascular access and the renal allografts. Hypertension is common. Treatment entails lifelong anticoagulation. Glucocorticoids may be beneficial in accelerated hypertension. Immunosuppression and plasma exchange may be helpful for catastrophic episodes of antiphospholipid syndrome but by themselves do not reduce recurrent thrombosis.

HELLP SYNDROME

HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is a dangerous complication of pregnancy associated with microvascular injury. Occurring in 0.2–0.9% of all pregnancies and in 10–20% of women with severe preeclampsia, this syndrome carries a mortality rate of 7.4–34%. Most commonly developing in the third trimester, 10% of cases occur before week 27 and 30% post-partum. Although a strong association exists between HELLP syndrome and preeclampsia, nearly 20% of cases are not preceded by recognized preeclampsia. Risk factors include abnormal placentation, family history, and elevated levels of fetal mRNA for FLT1 (vascular endothelial growth factor receptor 1) and endoglin. Patients with HELLP syndrome have higher levels of inflammatory markers (C-reactive protein, IL-1Ra, and IL-6) and soluble HLA-DR than do those with preeclampsia alone.

Renal failure occurs in half of patients with HELLP syndrome, although the etiology is not well understood. Limited data suggest that renal failure is the result of both preeclampsia and acute tubular necrosis. Renal histologic findings are those of TMA with endothelial cell swelling and occlusion of the capillary lumens, but luminal thrombi are typically absent. However, thrombi become more common in severe eclampsia and HELLP syndrome. Although renal failure is

common, the organ that defines this syndrome is the liver. Subcapsular hepatic hematomas sometimes produce spontaneous rupture of the liver and can be life-threatening. Neurologic complications such as cerebral infarction, cerebral and brainstem hemorrhage, and cerebral edema are other potentially life-threatening complications. Nonfatal complications include placental abruption, permanent vision loss due to Purtscher-like (hemorrhagic and vaso-occlusive vasculopathy) retinopathy, pulmonary edema, bleeding, and fetal demise.

Many features are shared by HELLP syndrome and MAHA. Diagnosis of HELLP syndrome is complicated by the fact that aHUS and TTP also can be triggered by pregnancy and complement mutations are common (30–40%) among patients with HELLP syndrome. Patients with antiphospholipid syndrome also have an elevated risk of HELLP syndrome. A history of MAHA before pregnancy is of diagnostic value. Serum levels of ADAMTS13 activity are reduced (by 30–60%) in HELLP syndrome but not to the levels seen in TTP (<5%). Determination of the ratio of lactate dehydrogenase to aspartate aminotransferase may be helpful. This ratio is 13:1 in patients with HELLP syndrome and preeclampsia as opposed to 29:1 in patients without preeclampsia. Other markers, such as antithrombin III (decreased in HELLP syndrome but not in TTP) and D-dimer (elevated in HELLP syndrome but not in TTP), may also be useful. HELLP syndrome usually resolves spontaneously after delivery, although a small percentage of HELLP cases occur post-partum. Glucocorticoids may decrease inflammatory markers, although two randomized controlled trials failed to show much benefit. Plasma exchange should be considered if hemolysis is refractory to glucocorticoids and/or delivery, especially if TTP has not been ruled out.

Myeloproliferative Neoplasm-Related Glomerulopathy While MAHA is often present in TMA, this is not true for all lesions. Two conditions are now recognized to present with renal TMA but no evidence of systemic MAHA. The first is MPN-related glomerulopathy. MPN represents a group of clonal disorders that includes chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia not otherwise specified, chronic neutrophilic leukemia, and unclassifiable MPN. These patients present with renal impairment and nephrotic range proteinuria. MPN-related glomerulopathy usually occurs late in the course of the hematologic condition as median time from diagnosis of MPN to glomerulopathy was 7.2 years. Renal biopsy shows mesangial expansion, hypercellularity, mesangial and segmental sclerosis, luminal hyalinosis, loss of overlying podocytes, and adhesions to Bowman's capsule and duplication of glomerular basement membranes. Foot process effacement ranges from 30 to 95%. Arteriosclerosis is common and ranges from mild to severe. Arteriolar hyalinosis can also be seen. Extremedullary hematopoiesis can sometimes be seen especially in patients with myelofibrosis. MPGN-related glomerulopathy may develop while patients are on treatment with hydroxyurea and JAK2 inhibitors. No standard treatment is available. RAS blockade and corticosteroids have been tried with mixed results.

POEMS Syndrome POEMS syndrome is a systemic disease characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Peripheral neuropathy with severe motorsensory deficit is the hallmark of the disease. Another characteristic is that >95% of monoclonal light chain is of the lambda isotype. IgA also makes up about 50% of the monoclonal protein. Organomegaly can involve any organ and often presents as lymphadenopathy. In the kidney, the hypertrophy frequently is unilateral. One study suggests the difference in kidney size is due to unilateral contraction; however, a volumemetric study showed that enlargement is responsible for the difference in kidney size in some patients. Glomerulomegaly is not uncommon. Lobular appearance, endothelial cell swelling, hypercellularity, mesangiolysis, microaneurysm, and glomerular enlargement are reminiscent of membranoproliferative glomerulonephritis. Most patients present with mild to moderate renal impairment and low grade proteinuria. Progression to end stage renal disease is rare.

SICKLE CELL NEPHROPATHY

Renal complications in sickle cell disease result from occlusion of the vasa recta in the renal medulla. The low partial pressure of oxygen and high osmolarity predispose to hemoglobin S polymerization and erythrocyte sickling. Sequelae include hyposthenuria, hematuria, and papillary necrosis (which can also occur in sickle trait). The kidney responds by increases in blood flow and glomerular filtration rate mediated by prostaglandins. This dependence on prostaglandins may explain the greater reduction of glomerular filtration rate by nonsteroidal anti-inflammatory drugs in these patients than in others. The glomeruli are typically enlarged. Intracapillary fragmentation and phagocytosis of sickled erythrocytes are thought to be responsible for the membranoproliferative glomerulonephritis–like lesion, and focal segmental glomerulosclerosis is seen in more advanced cases. Proteinuria is present in 20–30%, and nephrotic-range proteinuria is associated with progression to renal failure. ACE inhibitors reduce proteinuria, although data are lacking on prevention of renal failure. Patients with sickle cell disease are also more prone to acute renal failure. The cause is thought to reflect microvascular occlusion associated with nontraumatic rhabdomyolysis, high fever, infection, and generalized sickling. Chronic kidney disease is present in 12–20% of patients. Despite the frequency of renal disease, hypertension is uncommon in patients with sickle cell disease.

RENAL VEIN THROMBOSIS

Renal vein thrombosis either can present with flank pain, tenderness, hematuria, rapid decline in renal function, and proteinuria or can be silent. Occasionally, renal vein thrombosis is identified during a workup for pulmonary embolism. The left renal vein is more commonly involved, and two-thirds of cases are bilateral. Etiologies can be divided into three broad categories: endothelial damage, venous stasis, and hypercoagulability. Homocystinuria, endovascular intervention, and surgery can produce vascular endothelial damage. Dehydration, which is more common among male patients, is a common cause of stasis in the pediatric population. Stasis also can result from compression and kinking of the renal veins from retroperitoneal processes such as retroperitoneal fibrosis and abdominal neoplasms. Thrombosis can occur throughout the renal circulation, including the renal veins, with antiphospholipid syndrome. Renal vein thrombosis can also be secondary to nephrotic syndrome, particularly membranous nephropathy. Other hypercoagulable states less commonly associated with renal vein thrombosis include proteins C and S, antithrombin deficiency, factor V Leiden, disseminated malignancy, and oral contraceptives. Severe nephrotic syndrome may also predispose patients to renal vein thrombosis.

Diagnostic screening can be performed with Doppler ultrasonography, which is more sensitive than ultrasonography alone. Computed tomography angiography is ~100% sensitive. Magnetic resonance angiography is another option but is more expensive. Treatment for renal vein thrombosis consists of anticoagulation and therapy for the underlying cause. Endovascular thrombolysis may be considered in severe cases. Occasionally, nephrectomy may be undertaken for life-threatening complications. Vena caval filters are often used to prevent migration of thrombi.

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312 Nephrolithiasis

Gary C. Curhan

Nephrolithiasis, or kidney stone disease, is a common, painful, and costly condition. Each year, billions of dollars are spent on nephrolithiasis-related activity, with the majority of expenditures on surgical treatment of existing stones. While a stone may form due to crystallization of lithogenic factors in the upper urinary tract, it can subsequently move into the ureter and cause renal colic. Although nephrolithiasis is rarely fatal, patients who have had renal colic report that it is the worst pain they have ever experienced. The evidence on which to base clinical recommendations is not as strong as desired; nonetheless, most experts agree that the recurrence of most, if not all, types of stones can be prevented with careful evaluation and targeted recommendations. Preventive treatment may be lifelong; therefore, an in-depth understanding of this condition must inform the implementation of tailored interventions that are most appropriate for and acceptable to the patient.

There are several types of kidney stones. It is clinically important to identify the stone type, which informs prognosis and selection of the optimal preventive regimen. Calcium oxalate stones are most common (~75%); next, in order, are calcium phosphate (~15%), uric acid (~8%), struvite (~1%), and cystine (<1%) stones. Many stones are a mixture of crystal types (e.g., calcium oxalate and calcium phosphate) and also contain protein in the stone matrix. Rarely, stones are composed of medications, such as acyclovir, atazanavir, and triamterene. Stones that form as a result of an upper tract infection, if not appropriately treated, can have devastating consequences and lead to end-stage renal disease. Consideration should be given to teaching practitioners strategies to prevent recurrence of all stone types and the related morbidity.

EPIDEMIOLOGY

Nephrolithiasis is a global disease. Data suggest an increasing prevalence, likely due to Westernization of lifestyle habits (e.g., dietary changes, increasing body mass index). National Health and Nutrition Examination Survey data for 2007–2010 indicate that up to 19% of men and 9% of women will develop at least one stone during their lifetime. The prevalence is ~50% lower among black individuals than among whites. The incidence of nephrolithiasis (i.e., the rate at which previously unaffected individuals develop their first stone) also varies by age, sex, and race. Among white men, the peak annual incidence is ~3.5 cases/1000 at age 40 and declines to ~2 cases/1000 by age 70. Among white women in their thirties, the annual incidence is ~2.5 cases/1000; the figure decreases to ~1.5/1000 at age 50 and beyond. In addition to the medical costs associated with nephrolithiasis, this condition also has a substantial economic impact, as those affected are often of working age. Once an individual has had a stone, the prevention of a recurrence is essential. Published recurrence rates vary by the definitions and diagnostic methods used. Some reports have relied on symptomatic events, while others have been based on imaging. Most experts agree that radiographic evidence of a second stone should be considered to represent a recurrence, even if the stone has not yet caused symptoms.

ASSOCIATED MEDICAL CONDITIONS

Nephrolithiasis is a systemic disorder. Several conditions predispose to stone formation, including gastrointestinal malabsorption (e.g., Crohn's disease, gastric bypass surgery), primary hyperparathyroidism, obesity, type 2 diabetes mellitus, and distal renal tubular acidosis. A number of other medical conditions are more likely to be present in individuals with a history of nephrolithiasis, including hypertension, gout, cardiovascular disease, cholelithiasis, reduced bone mineral density, and chronic kidney disease.

Although nephrolithiasis does not directly cause upper urinary tract infections (UTIs), a UTI in the setting of an obstructing stone is a urologic emergency ("pus under pressure") and requires urgent intervention to reestablish drainage.

PATHOGENESIS

In the consideration of the processes involved in crystal formation, it is helpful to view urine as a complex solution. A clinically useful concept is *supersaturation* (the point at which the concentration product exceeds the solubility product). However, even though the urine in most individuals is supersaturated with respect to one or more types of crystals, the presence of inhibitors of crystallization prevents the majority of the population from continuously forming stones. The most clinically important inhibitor of calcium-containing stones is urine citrate. While the calculated supersaturation value does not perfectly predict stone formation, it is a useful guide as it integrates the multiple factors that are measured in a 24-h urine collection.

Recent studies have changed the paradigm for the site of initiation of stone formation. Renal biopsies of stone formers have revealed calcium phosphate in the renal interstitium. It is hypothesized that this calcium phosphate deposits at the thin limb of the loop of Henle, and then extends down to the papilla and erodes through the papillary epithelium, where it provides a site for deposition of calcium oxalate and calcium phosphate crystals. The majority of calcium oxalate stones grow on calcium phosphate at the tip of the renal papilla (*Randall's plaque*). Tubular plugs of calcium phosphate may be the initiating event in calcium phosphate stone development. Thus, the process of stone formation may begin years before a clinically detectable stone is identified. The processes involved in interstitial deposition are under active investigation.

RISK FACTORS

Risk factors for nephrolithiasis can be categorized as dietary, nondietary, or urinary. These risk factors vary by stone type and by clinical characteristics.

Dietary Risk Factors Patients who develop stones often change their diet; therefore, studies that retrospectively assess diet may be hampered by recall bias. Some studies have examined the relation between diet and changes in the lithogenic composition of the urine, often using calculated supersaturation. However, the composition of the urine does not perfectly predict risk, and not all components that modify risk are included in the calculation of supersaturation. Thus, dietary associations are best investigated by prospective studies that examine actual stone formation as the outcome. Dietary factors that are associated with an increased risk of nephrolithiasis include animal protein, oxalate, sodium, sucrose, and fructose. Dietary factors associated with a lower risk include calcium, potassium, and phytate.

CALCIUM The role of dietary calcium deserves special attention. Although in the distant past dietary calcium had been suspected of increasing the risk of stone disease, several prospective observational studies and a randomized controlled trial have demonstrated that higher dietary calcium intake is related to a *lower* risk of stone formation. The reduction in risk associated with higher calcium intake may be due to a reduction in intestinal absorption of dietary oxalate that results in lower urine oxalate. Low calcium intake is contraindicated as it increases the risk of stone formation and may contribute to lower bone density in stone formers.

Despite similar bioavailability, supplemental calcium may increase the risk of stone formation. The discrepancy between the risks from dietary calcium and calcium supplements may be due to the timing of supplemental calcium intake or to higher total calcium consumption leading to higher urinary calcium excretion.

OXALATE Urinary oxalate is derived from both endogenous production and absorption of dietary oxalate. Owing to its low and often variable bioavailability, much of the oxalate in food may not be readily absorbed. However, absorption may be higher in stone formers. Although observational studies demonstrate that dietary oxalate is only a weak risk factor for stone formation, urinary oxalate is a strong risk factor for calcium oxalate stone formation, and efforts to avoid high oxalate intake should thus be beneficial.

OTHER NUTRIENTS Several other nutrients have been studied and implicated in stone formation. Higher intake of animal protein may lead to increased excretion of calcium and uric acid as well as to decreased urinary excretion of citrate, all of which increase the risk of stone formation. Higher sodium and sucrose intake increases calcium excretion independent of calcium intake. Higher potassium intake decreases calcium excretion, and many potassium-rich foods increase urinary citrate excretion due to their alkali content. Other dietary factors that have been inconsistently associated with lower stone risk include magnesium and phytate.

Vitamin C supplements are associated with an increased risk of calcium oxalate stone formation in men, possibly because of raised levels of oxalate in urine. Thus, male calcium oxalate stone formers should be advised to avoid vitamin C supplements. Although high doses of supplemental vitamin B_6 may be beneficial in selected patients with type 1 primary hyperoxaluria, the risk is not reduced in other patients.

FLUIDS AND BEVERAGES The risk of stone formation increases as urine volume decreases. When the urine output is <1 L/d, the risk of stone formation more than doubles. Fluid intake is the main determinant of urine volume, and the importance of fluid intake in preventing stone formation has been demonstrated in observational studies and in a randomized controlled trial. Observational studies have found that coffee, tea, beer, wine, and orange juice are associated with a reduced risk of stone formation. Sugar-sweetened beverage consumption may increase risk.

Nondietary Risk Factors Age, race, body size, and environment are important risk factors for nephrolithiasis. The incidence of stone disease is highest in middle-aged white men, but stones can form in infants as well as in the elderly. There is geographic variability, with the highest prevalence in the southeastern United States. Weight gain increases the risk of stone formation, and the increasing prevalence of nephrolithiasis in the United States may be due in part to the increasing prevalence of obesity. Environmental and occupational influences that may lead to lower urine volume, such as working in a hot environment or lack of ready access to water or a bathroom, are important considerations.

Urinary Risk Factors • **URINE VOLUME** As mentioned above, lower urine volume results in higher concentrations of lithogenic factors and is a common and readily modifiable risk factor. A randomized trial has demonstrated the effectiveness of higher fluid intake in increasing urine volume and reducing the risk of stone recurrence.

URINE CALCIUM Higher urine calcium excretion increases the likelihood of formation of calcium oxalate and calcium phosphate stones. While the term *hypercalciuria* is often used, there is no widely accepted cutoff that distinguishes between normal and abnormal urine calcium excretion. In fact, the relation between urine calcium and stone risk appears to be continuous; thus, the use of an arbitrary threshold should be avoided. Levels of urine calcium excretion are higher in individuals with a history of nephrolithiasis; however, the mechanisms remain poorly understood. Greater gastrointestinal calcium absorption is one important contributor, and greater bone turnover (with a resultant reduction in bone mineral density) may be another. Primary renal calcium loss, with lower serum calcium concentrations and elevated serum levels of parathyroid hormone (PTH) (and a normal 25-hydroxy vitamin D level), is rare.

URINE OXALATE Higher urine oxalate excretion increases the likelihood of calcium oxalate stone formation. As for urine calcium, no definition for "abnormal" urine oxalate excretion is widely accepted. Given that the relation between urine oxalate and stone risk is continuous, simple dichotomization of urine oxalate excretion is not helpful in assessing risk. The two sources of urine oxalate are endogenous generation and dietary intake. Dietary oxalate is the major contributor and also the source that can be modified. Notably, higher dietary calcium intake reduces gastrointestinal oxalate absorption and thereby reduces urine oxalate.

URINE CITRATE Urine citrate is a natural inhibitor of calcium-containing stones; thus, lower urine citrate excretion increases the risk of stone formation. Citrate reabsorption is influenced by the intracellular pH of proximal tubular cells. Metabolic acidosis, including that due to higher animal flesh intake, will lead to a reduction in citrate excretion by increasing reabsorption of filtered citrate. However, a notable proportion of patients have lower urine citrate for reasons that remain unclear.

URINE URIC ACID Higher urine levels of uric acid—a risk factor for uric acid stone formation—are found in individuals with excess purine consumption and rare genetic conditions that lead to overproduction of uric acid. This characteristic does not appear to be associated with the risk of calcium oxalate stone formation.

URINE pH Urine pH influences the solubility of some crystal types. Uric acid stones form only when the urine pH is consistently ≤5.5 or lower, whereas calcium phosphate stones are more likely to form when the urine pH is ≥6.5 or higher. Cystine is more soluble at higher urine pH. Calcium oxalate stones are not influenced by urine pH.

Genetic Risk Factors The risk of nephrolithiasis is more than twofold greater in individuals with a family history of stone disease. This association is likely due to a combination of genetic predisposition and similar environmental exposures. While a number of rare monogenic disorders cause nephrolithiasis, the genetic contributors to common forms of stone disease remain to be determined.

The two most common and well-characterized rare monogenic disorders that lead to stone formation are primary hyperoxaluria and cystinuria. *Primary hyperoxaluria* is an autosomal recessive disorder that causes excessive endogenous oxalate generation by the liver, with consequent calcium oxalate stone formation and crystal deposition in organs. Intraparenchymal calcium oxalate deposition in the kidney can eventually lead to renal failure. *Cystinuria* is an autosomal recessive disorder that causes abnormal reabsorption of filtered basic amino acids. The excessive urinary excretion of cystine, which is poorly soluble, leads to cystine stone formation. Cystine stones are visible on plain radiographs and often manifest as staghorn calculi or multiple bilateral stones. Repeat episodes of obstruction and instrumentation can cause a reduction in the glomerular filtration rate (GFR).

APPROACH TO THE PATIENT

Nephrolithiasis

Evidence-based guidelines for the evaluation and treatment of nephrolithiasis have been recently published. Although there is limited evidence for several aspects, there are standard approaches to patients with acute and chronic presentations that can reasonably guide the clinical evaluation.

It typically requires weeks to months (and often much longer) for a kidney stone to grow to a clinically detectable size. Although the passage of a stone is a dramatic event, stone formation and growth are characteristically clinically silent. A stone can remain asymptomatic in the kidney for years or even decades before signs (e.g., hematuria) or symptoms (e.g., pain) become apparent. Thus, it is important to remember that the onset of symptoms, typically attributable to a stone moving into the ureter, does not provide insight into when the stone actually formed. The factors that induce stone movement are unknown.

CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

There are two common presentations for individuals with an acute stone event: renal colic and painless gross hematuria. *Renal colic* is a misnomer because pain typically does not subside completely; rather, it varies in intensity. When a stone moves into the ureter, the discomfort often begins with a sudden onset of unilateral flank pain.

The intensity of the pain can increase rapidly, and there are no alleviating factors. This pain, which is accompanied often by nausea and occasionally by vomiting, may radiate, depending on the location of the stone. If the stone lodges in the upper part of the ureter, pain may radiate anteriorly; if the stone is in the lower part of the

ureter, pain can radiate to the ipsilateral testicle in men or the ipsilateral labium in women. Occasionally, a patient has gross hematuria without pain.

Other diagnoses may be confused with acute renal colic. If the stone is lodged at the right ureteral pelvic junction, symptoms may mimic those of acute cholecystitis. If the stone blocks the ureter as it crosses over the right pelvic brim, symptoms may mimic acute appendicitis, whereas blockage at the left pelvic brim may be confused with acute diverticulitis. If the stone lodges in the ureter at the ureterovesical junction, the patient may experience urinary urgency and frequency. In female patients, the latter symptoms may lead to an incorrect diagnosis of bacterial cystitis; the urine will contain red and white blood cells, but the urine culture will be negative. An obstructing stone with proximal infection may present as acute pyelonephritis. A UTI in the setting of ureteral obstruction is a medical emergency that requires immediate restoration of drainage by placement of either a ureteral stent or a percutaneous nephrostomy tube. Other conditions to consider in the differential diagnosis include muscular or skeletal pain, *herpes zoster*, duodenal ulcer, abdominal aortic aneurysm, gynecologic conditions, ureteral stricture, and ureteral obstruction by materials other than a stone, such as a blood clot or sloughed papilla. Extraluminal processes can lead to ureteral compression and obstruction; however, because of the gradual onset, these conditions do not typically present with renal colic.

DIAGNOSIS AND INTERVENTION

Serum chemistry findings are typically normal, but the white blood cell count may be elevated. Examination of the urine sediment will usually reveal red and white blood cells and occasionally crystals **(Fig. 312-1)**. The absence of hematuria does not exclude a stone, particularly when urine flow is completely obstructed by a stone.

The diagnosis is often made on the basis of the history, physical examination, and urinalysis. Thus, it may not be necessary to wait for radiographic confirmation before treating the symptoms. The diagnosis is confirmed by an appropriate imaging study—preferably helical computed tomography (CT), which is highly sensitive, allows visualization of uric acid stones (traditionally considered "radiolucent"), and does not require radiocontrast **(Fig. 312-2)**. Helical CT detects stones as small as 1 mm that may be missed by other imaging modalities.

Typically, helical CT reveals a ureteral stone or evidence of recent passage (e.g., perinephric stranding or hydronephrosis), whereas a plain abdominal radiograph (kidney/ureter/bladder, or KUB) can miss a stone in the ureter or kidney, even if it is radiopaque, and does not provide information on obstruction. Abdominal ultrasound offers the advantage of avoiding radiation and provides information on hydronephrosis, but it is not as sensitive as CT and images only the kidney and possibly the proximal segment of the ureter; thus most ureteral stones are not detectable by ultrasound.

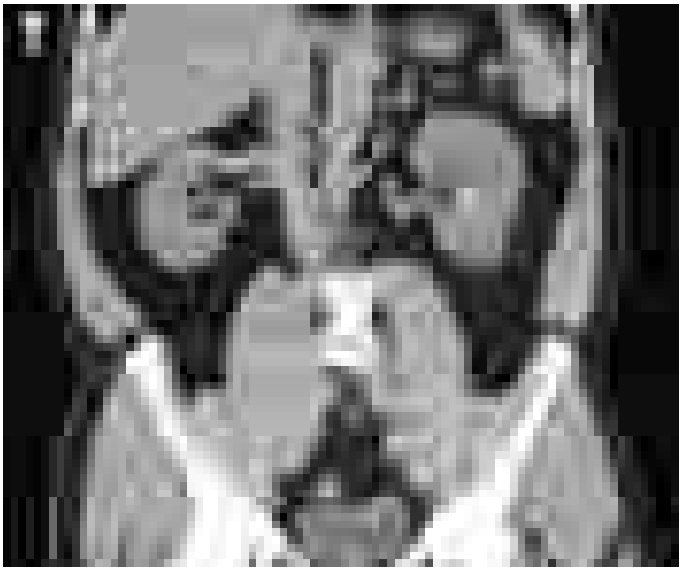

FIGURE 312-2 Coronal noncontrast CT image from a patient who presented with left-sided renal colic. An obstructing calculus, present in the distal left ureter at the level of S1, measures 10 mm in maximal dimension. There is severe left hydroureteronephrosis and associated left perinephric fat stranding. In addition, there is a nonobstructing 6-mm left renal calculus in the interpolar region. *(Image courtesy of Dr. Stuart Silverman, Brigham and Women's Hospital.)*

Many patients who experience their first episode of colic seek emergent medical care. Randomized trials have demonstrated that parenterally administered nonsteroidal anti-inflammatory drugs (such as ketorolac) are just as effective as opioids in relieving symptoms and have fewer side effects. Excessive fluid administration has not been shown to be beneficial; therefore, the goal should be to maintain euvolemia. If the pain can be adequately controlled and the patient is able to take fluids orally, hospitalization can be avoided. Use of an alpha blocker may increase the rate of spontaneous stone passage.

Urologic intervention should be postponed unless there is evidence of UTI, a low probability of spontaneous stone passage (e.g., a stone measuring ≥6 mm or an anatomic abnormality), or intractable pain. A ureteral stent may be placed cystoscopically, but this procedure typically requires general anesthesia, and the stent can be quite

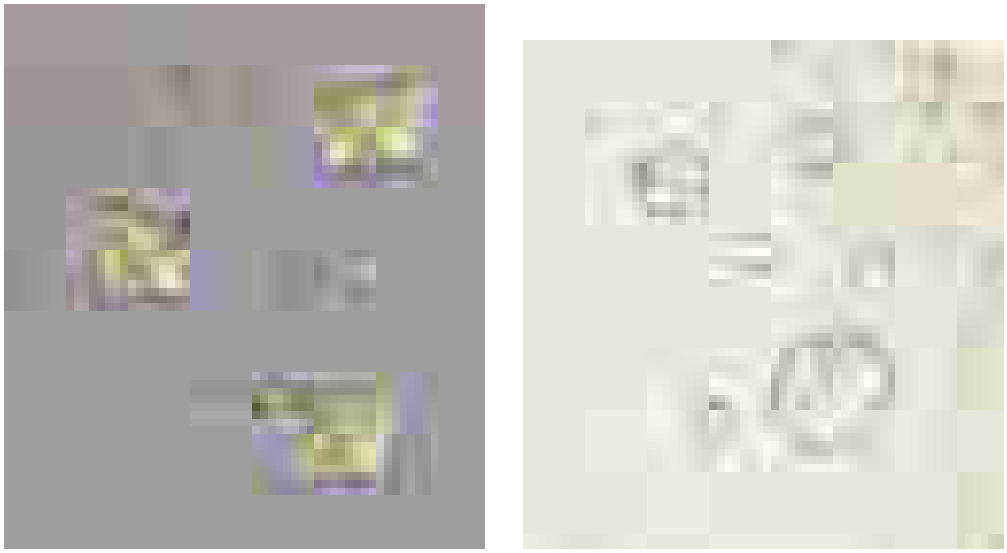

FIGURE 312-1 Urine sediment from a patient with calcium oxalate stones (*left*) and a patient with cystine stones (*right*). Calcium oxalate dihydrate crystals are bipyramidally shaped, and cystine crystals are hexagonal. *(Left panel image courtesy of Dr. John Lieske, Mayo Clinic.)*

uncomfortable, may cause gross hematuria, and may increase the risk of UTI.

If an intervention is indicated, the selection of the most appropriate intervention is determined by the size, location, and composition of the stone; the urinary tract anatomy; and the experience of the urologist. Extracorporeal shockwave lithotripsy (ESWL), the least invasive option, uses shock waves generated outside the body to fragment the stone, but is being used less frequently. An endourologic approach, now more frequently used than ESWL, can remove a stone by basket extraction or laser fragmentation. For large upper-tract stones, percutaneous nephrostolithotomy has the highest likelihood of rendering the patient stone-free. Advances in urologic approaches and instruments have nearly eliminated the need for open surgical procedures such as ureterolithotomy or pyelolithotomy.

EVALUATION FOR STONE PREVENTION

More than half of first-time stone formers will have a recurrence within 10 years. A careful evaluation is indicated to identify predisposing factors, which can then be modified to reduce the risk of new stone formation. It is appropriate to proceed with an evaluation even after the first stone if the patient is interested because recurrences are common and are usually preventable with inexpensive lifestyle modifications or other treatments.

HISTORY

A detailed history, obtained from the patient and from a thorough review of medical records, should include the number and frequency of episodes (distinguishing stone passage from stone formation) and previous imaging studies, interventions, evaluations, and treatments. Inquiries about the patient's medical history should cover UTIs, bariatric surgery, gout, hypertension, and diabetes mellitus. A family history of stone disease may reveal a genetic predisposition. A complete list of current prescription and over-the-counter medications as well as vitamin and mineral supplements is essential. The review of systems should focus on identifying possible etiologic factors related to low urine volume (e.g., high insensible losses) and gastrointestinal malabsorption as well as on ascertaining how frequently the patient voids during the day and overnight.

A large body of compelling evidence has demonstrated the important role of diet in stone disease. Thus, the dietary history should encompass information on usual dietary habits (meals and snacks), calcium intake, consumption of high-oxalate foods (spinach, rhubarb, potatoes), and fluid intake (including amount of specific beverages typically consumed). Amount and frequency of use of vitamin and mineral supplements should be carefully assessed.

PHYSICAL EXAMINATION

The physical examination should assess weight, blood pressure, costovertebral angle tenderness, and lower-extremity edema as well as signs of other systemic conditions such as primary hyperparathyroidism and gout.

LABORATORY EVALUATION

If not recently measured, the following serum levels should be determined: electrolytes (to uncover hypokalemia or renal tubular acidosis), creatinine, calcium, and uric acid. The PTH level should be measured if indicated by high-normal or elevated serum and urine calcium concentrations. Often, 25-hydroxy vitamin D is measured in concert with PTH to investigate the possible role of secondarily elevated PTH levels in the setting of vitamin D insufficiency.

The urinalysis, including examination of the sediment, can provide useful information. In individuals with asymptomatic residual renal stones, red and white blood cells are frequently present in urine. If there is concern about the possibility of an infection, a urine culture should be performed. The sediment may also reveal crystals (Fig. 312-1), which may help identify the stone type and also provide prognostic information, as crystalluria is a strong risk factor for new stone formation.

The results from 24-h urine collections serve as the cornerstone on which therapeutic recommendations are based. Recommendations on lifestyle modification should be deferred until urine collection is complete. As a baseline assessment, patients should collect at least two 24-h urine samples while consuming their usual diet and usual volume of fluid. The following factors should be measured: total volume, calcium, oxalate, citrate, uric acid, sodium, potassium, phosphorus, pH, and creatinine. When available, the calculated supersaturation is also informative. There is substantial day-to-day variability in the 24-h excretion of many relevant factors; therefore, obtaining values from two collections is important before committing a patient to long-term lifestyle changes or medication. The interpretation of the 24-h urine results should take into account that the collections are usually performed on a weekend day when the patient is staying at home; an individual's habits may differ dramatically (beneficially or detrimentally) at work or outside the home. Specialized testing, such as calcium loading or restriction, is not recommended as it does not influence clinical recommendations.

Stone composition analysis is essential if a stone or fragment is available; patients should be encouraged to retrieve passed stones. The stone type cannot be determined with certainty from 24-h urine results, but pure uric acid stones can be identified by low Hounsfield units on CT.

IMAGING

The "gold standard" diagnostic test is helical CT without contrast. If not already performed during an acute episode, a low-dose CT should be considered to definitively establish the baseline stone burden. A suboptimal imaging study may not detect a residual stone that, if subsequently passed, would be mistaken for a new stone. In this instance, the preventive medical regimen might be unnecessarily changed as the result of a preexisting stone.

Recommendations for follow-up imaging should be tailored to the individual patient. While CT provides the best information, the radiation dose is higher than from other modalities; therefore, CT should be performed only if the results will lead to a change in clinical recommendations. Although they are less sensitive, renal ultrasound or a KUB examinaion is typically used to minimize radiation exposure, with recognition of the limitations.

PREVENTION OF NEW STONE FORMATION

Recommendations for preventing stone formation depend on the stone type and the results of metabolic evaluation. After remediable secondary causes of stone formation (e.g., primary hyperparathyroidism) are excluded, the focus should turn to modification of the urine composition to reduce the risk of new stone formation. The urinary constituents are continuous variables, and the associated risk is continuous; thus, there are no definitive thresholds. Dichotomization into "normal" and "abnormal" can be misleading and should be avoided.

For all stone types, consistently diluted urine reduces the likelihood of crystal formation. The urine volume should be at least 2 L/d. Because of differences in insensible fluid losses and fluid intake from food sources, the required total fluid intake will vary from person to person. Rather than specify how much to drink, it is more helpful to educate patients about how much *more* they need to drink in light of their 24-h urine volume. For example, if the daily urine volume is 1.5 L, then the patient should be advised to drink at least 0.5 L more per day in order to increase the urine volume to the goal of 2 L/day.

RECOMMENDATIONS FOR SPECIFIC STONE TYPES

Calcium Oxalate Risk factors for calcium oxalate stones include higher urine calcium, higher urine oxalate, and lower urine citrate. This stone type is insensitive to pH in the physiologic range.

Individuals with higher urine calcium excretion tend to absorb a higher percentage of ingested calcium. Nevertheless, dietary calcium restriction is not beneficial and, in fact, is likely to be harmful (see

"Dietary Risk Factors," above). In a randomized trial in men with high urine calcium and recurrent calcium oxalate stones, a diet containing 1200 mg of calcium and a low intake of sodium and animal protein significantly reduced subsequent stone formation from that with a low-calcium diet (400 mg/d). Excessive calcium intake (>1200 mg/d) should be avoided.

A thiazide diuretic, in doses higher than those used to treat hypertension, can substantially lower urine calcium excretion. Several randomized controlled trials have demonstrated that thiazide diuretics, most commonly chlorthalidone, can reduce calcium oxalate stone recurrence by ~50%. When a thiazide is prescribed, dietary sodium restriction is essential to obtain the desired reduction in urinary calcium excretion and minimize urinary potassium losses. While bisphosphonates may reduce urine calcium excretion in some individuals, there are no data on whether this class of medication can reduce stone formation; therefore, bisphosphonates cannot be recommended solely for stone prevention at present but they can be used to treat those individuals with low bone density.

A reduction in urine oxalate will in turn reduce the supersaturation of calcium oxalate. In patients with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production.

Oxalate is a metabolic end product; therefore, any dietary oxalate that is absorbed will be excreted in the urine. Reducing absorption of exogenous oxalate involves two approaches. First, the avoidance of foods that contain high amounts of oxalate, such as spinach, rhubarb, almonds, and potatoes, is prudent. However, extreme oxalate restriction has not been demonstrated to reduce stone recurrence and could be harmful to overall health, given other health benefits of many foods that are erroneously considered to be high in oxalate. Controversy exists regarding the most clinically relevant measure of the oxalate content of foods (e.g., bioavailability). Notably, the absorption of oxalate is reduced by higher calcium intake; therefore, individuals with higher-than-desired urinary oxalate should be counseled to consume adequate calcium. Oxalate absorption can be influenced by the intestinal microbiota, depending on the presence of oxalate-degrading bacteria. Currently, however, there are no available therapies to alter the microbiota that beneficially affect urinary oxalate excretion over the long term.

Citrate is a natural inhibitor of calcium oxalate and calcium phosphate stones. Higher-level consumption of foods rich in alkali (i.e., fruits and vegetables) can increase urine citrate. For patients with lower urine citrate in whom dietary modification does not adequately increase urine citrate, the addition of supplemental alkali (typically potassium citrate or bicarbonate) will lead to an increase in urinary citrate excretion. Sodium salts, such as sodium bicarbonate, while successful in raising urine citrate, are typically avoided due to the adverse effects of sodium on urine calcium excretion. Urine pH in the physiologic range does not influence calcium oxalate stone formation.

Past reports suggested that higher levels of urine uric acid may increase the risk of calcium oxalate stones, but more recent studies do not support this association. However, allopurinol reduced stone recurrence in one randomized controlled trial in patients with calcium oxalate stones and high urine uric acid levels. The lack of association between urine uric acid level and calcium oxalate stones suggests that a different mechanism underlies the observed beneficial effect of allopurinol.

Additional dietary modifications may be beneficial in reducing stone recurrence. Restriction of nondairy animal protein (e.g., meat, chicken, seafood) is a reasonable approach and may result in higher excretion of citrate and lower excretion of calcium. In addition, reducing sodium intake to <2.5 g/d may decrease urinary excretion of calcium. Sucrose and fructose intake should be minimized.

For adherence to a dietary pattern that is more manageable for patients than manipulating individual nutrients, the DASH (Dietary Approaches to Stop Hypertension) diet provides an appropriate and readily available option. Randomized trials have conclusively shown the DASH diet to reduce blood pressure. At present, only data from observational studies are available, but these demonstrate a strong and consistent inverse association between the DASH diet and risk of stone formation.

Calcium Phosphate Calcium phosphate stones share risk factors with calcium oxalate stones, including higher concentrations of urine calcium and lower concentrations of urine citrate, but additional factors deserve attention. Higher urine phosphate levels and higher urine pH (typically ≥6.5) are associated with an increased likelihood of calcium phosphate stone formation. Calcium phosphate stones are more common in patients with distal renal tubular acidosis and primary hyperparathyroidism.

There are no randomized trials on which to base preventive recommendations for calcium phosphate stone formers, so the interventions are focused on modification of the recognized risk factors. Thiazide diuretics (with sodium restriction) may be used to reduce urine calcium, as described above for calcium oxalate stones. In patients with low urine citrate levels, alkali supplements (e.g., potassium citrate or bicarbonate) may be used to increase these concentrations. However, the urine pH of these patients should be monitored initially because supplemental alkali can raise urine pH, thereby potentially increasing the risk of stone formation. Because these patients tend to have a urinary acidification defect, reducing the urine pH is not an option. Reduction of dietary phosphate may be beneficial by reducing urine phosphate excretion.

Uric Acid The two main risk factors for uric acid stones are persistently low urine pH and higher uric acid excretion. Urine pH is the predominant influence on uric acid solubility; therefore, the mainstay of prevention of uric acid stone formation entails increasing urine pH. Alkalinizing the urine can be readily achieved by increasing the intake of foods rich in alkali (e.g., fruits and vegetables) and reducing the intake of foods that produce acid (e.g., animal flesh). If necessary, supplementation with bicarbonate or citrate salts (preferably potassium-based) can be used to reach the recommended pH goal of 6.5 throughout the day and night.

Urine uric acid excretion is determined by uric acid generation. Uric acid is the end product of purine metabolism; thus, reduced consumption of purine-containing foods can lower urine uric acid excretion. It is noteworthy that the serum uric acid level is dependent on the fractional excretion of uric acid and therefore does not provide information on urine uric acid excretion. For example, an individual with high uric acid generation and concurrent high fractional excretion of uric acid will have high urine uric acid excretion with a normal (or even low) serum uric acid level. If alkalinization of the urine alone is not successful and if dietary modifications do not reduce urine uric acid sufficiently, then the use of a xanthine oxidase inhibitor, such as allopurinol or febuxostat, can reduce urine uric acid excretion by 40–50%.

Cystine Cystine excretion is not easily modified. Long-term dietary cystine restriction is not feasible and is unlikely to be successful; thus the focus for cystine stone prevention is on increasing cystine solubility. This goal may be achieved by treatment with medication that covalently binds to cystine (tiopronin or penicillamine) and a medication that raises urine pH. Tiopronin is the preferred choice due to its better adverse event profile. The preferred alkalinizing agent to achieve a urine pH of 7.5 is potassium citrate or bicarbonate as sodium salts may increase cystine excretion. As with all stone types, and especially in patients with cystinuria, maintaining a high urine volume is an essential component of the preventive regimen.

Struvite Struvite stones, also known as *infection stones* or *triple-phosphate stones*, form only when the upper urinary tract is infected with urease-producing bacteria such as *Proteus mirabilis, Klebsiella pneumoniae*, or *Providencia* species. Urease produced by these bacteria hydrolyzes urea and may elevate the urine pH to a supraphysiologic level (>8.0). Struvite stones may grow quickly and fill the renal pelvis (*staghorn calculi*).

Struvite stones require complete removal by a urologist. New stone formation can be avoided by the prevention of UTIs. In patients with recurrent upper UTIs (e.g., some individuals with surgically altered

urinary drainage or spinal cord injury), the urease inhibitor acetohydroxamic acid can be considered; however, this agent should be used with caution because of potential side effects.

LONG-TERM FOLLOW-UP

In general, the preventive regimens described above do not cure the underlying pathophysiologic process. Thus these recommendations typically need to be followed for the patient's lifetime, and it is essential to tailor recommendations in a way that is acceptable to the patient. Because the memory of the acute stone event fades and patients often return to old habits (e.g., insufficient fluid intake), long-term follow-up, including repeat 24-h urine collections, is important to ensure that the preventive regimen has been implemented and has resulted in the desired reduction in the risk of new stone formation.

Follow-up imaging should be planned thoughtfully. Many patients with recurrent episodes of renal colic that lead to emergency room visits often undergo repeat CT studies. While CT does provide the best information, the radiation dose is substantially higher than that with plain abdominal radiography (KUB). Small stones may be missed by KUB, and ultrasound has a limited ability to determine size and number of stones. Minimizing radiation exposure should be a goal of the long-term follow-up plan and must be balanced against the gain in diagnostic information.

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TABLE 313-1 Common Mechanical Causes of Urinary Tract Obstruction

URETER	BLADDER OUTLET	URETHRA
Congenital		
Ureteropelvic junction narrowing or obstruction	Bladder neck obstruction	Posterior urethral valves
Ureterovesical junction narrowing or obstruction and reflux	Ureterocele	Anterior urethral valves
Ureterocele		Stricture
Retrocaval ureter		Meatal stenosis
		Phimosis
Acquired Intrinsic Defects		
Calculi	Benign prostatic hyperplasia	Stricture
Inflammation	Cancer of prostate	Tumor
Infection	Cancer of bladder	Calculi
Trauma	Calculi	Trauma
Sloughed papillae	Diabetic neuropathy	Phimosis
Tumor	Spinal cord disease	
Blood clots	Anticholinergic drugs and α-adrenergic antagonists	
Acquired Extrinsic Defects		
Pregnant uterus	Carcinoma of cervix, colon	Trauma
Retroperitoneal fibrosis		
Aortic aneurysm	Trauma	
Uterine leiomyomata		
Carcinoma of uterus, prostate, bladder, colon, rectum		
Lymphoma		
Pelvic inflammatory disease, endometriosis		
Accidental surgical ligation		

313 Urinary Tract Obstruction

Julian L. Seifter

Obstruction to the flow of urine, with attendant stasis and elevation in urinary tract pressure, impairs renal and urinary conduit functions and is a common cause of acute and chronic kidney disease (obstructive nephropathy). Early recognition and prompt treatment of urinary tract obstruction (UTO) can prevent or reverse devastating effects on kidney structure and function, and decrease susceptibility to hypertension, infection, and stone formation. Chronic obstruction may lead to permanent loss of renal mass (renal atrophy) and excretory capability. Since obstructive disease may be secondary to serious underlying inflammatory, vascular, or malignant disease, familiarity with clinical findings, appropriate diagnostic testing, and therapeutic approach is of great importance to the clinician.

ETIOLOGY

Obstruction to urine flow can result from *intrinsic* or *extrinsic mechanical blockade* as well as from *functional defects* not associated with fixed occlusion of the urinary drainage system. Mechanical obstruction can occur at any level of the urinary tract, from within the renal tubules, or the renal calyces to the external urethral meatus (obstructive uropathy). Normal points of narrowing, such as the ureteropelvic and ureterovesical junctions, bladder neck, and urethral meatus, are common sites of obstruction. When lower UTO is above the level of the bladder, unilateral dilatation of the ureter (*hydroureter*) and renal pyelocalyceal system (*hydronephrosis*) occurs; lesions at or below the level of the bladder cause bilateral involvement.

Common forms of obstruction are listed in Table 313-1. Childhood causes include *congenital malformations*, such as narrowing of the ureteropelvic junction (UPJ) and abnormal insertion of the ureter into the bladder, the most common cause. Vesicoureteral reflux in the absence of urinary tract infection or bladder neck obstruction often resolves with age. Reinsertion of the ureter into the bladder is indicated if reflux is severe and unlikely to improve spontaneously, if renal function deteriorates, or if urinary tract infections recur despite chronic antimicrobial therapy. Vesicoureteral reflux may cause prenatal hydronephrosis and, if severe, can lead to recurrent urinary infections, hypertension and renal scarring in childhood. Posterior urethral valves are the most common cause of bilateral hydronephrosis in boys. In adults, UTO is due mainly to *acquired defects*. Pelvic tumors, calculi, and urethral stricture predominate. Ligation of, or injury to, the ureter during pelvic or colonic surgery can lead to hydronephrosis which, if unilateral, may remain undetected. Obstructive uropathy may also result from extrinsic neoplastic (carcinoma of cervix or colon) or inflammatory disorders. Lymphomas and pelvic or colonic neoplasms with retroperitoneal involvement are causes of ureteral obstruction. As many as 50% of men aged >40 years may have lower urinary tract symptoms associated with benign prostatic hypertrophy, but these symptoms may occur without bladder outlet obstruction.

Functional impairment of urine flow occurs when voiding is altered by abnormal pontine or sacral centers of micturition control. It may be asymptomatic or associated with lower urinary tract symptoms such as frequency, urgency, and postmicturition incontinence, nocturia, straining to void, slow stream, hesitancy, or a feeling of incomplete emptying. A history should be sought for trauma, back injury, surgery, diabetes, neurologic or psychiatric conditions, and medications. Causes include neurogenic bladder, often with adynamic ureter, and vesicoureteral reflux. Reflux in children may result in severe unilateral or bilateral hydroureter and hydronephrosis. Overflow urinary incontinence combined with fecal incontinence may require an urgent evaluation for cauda equina syndrome. Urinary retention may be the consequence of α-adrenergic and anticholinergic agents, as well as opiates. Hydronephrosis in pregnancy is due to relaxational effects of progesterone on smooth muscle of the renal pelvis, as well as ureteral compression by the enlarged uterus, more often on the right side.

Diagnostic tools to identify anatomic obstruction include urinary flow measurements and a postvoid residual. Bladder volume may be readily assessed by bedside ultrasound. Cystourethroscopy and urodynamic studies may be reserved for the symptomatic patient to assess the filling phase (cystometry), pressure-volume relationship of the bladder, bladder compliance, and capacity. Pressure-flow analysis evaluates bladder contractility and bladder outlet resistance during voiding. Bladder obstruction is characterized by high pressures in women, whereas in men, a diagnosis of bladder outlet obstruction is based on flow rate and voiding pressures. A voiding cystourethrogram may be useful in evaluating incomplete emptying and bladder neck and urethral pathology.

CLINICAL FEATURES AND PATHOPHYSIOLOGY

The pathophysiology and clinical features of UTO are summarized in **Table 313-2**. Flank *pain*, the symptom that most commonly leads to medical attention, is due to distention of the collecting system or renal capsule. Pain severity is influenced more by the rate at which distention develops than by the degree of distention. Acute supravesical obstruction, as from a stone lodged in a ureter **(Chap. 312)**, is associated with excruciating, sometimes intermittent, pain, known as *renal colic*. This pain often radiates to the lower abdomen, testes, or labia. By contrast, more insidious causes of obstruction, such as chronic narrowing of the UPJ, may produce little or no pain and yet result in total destruction of the affected kidney. Flank pain that occurs only with micturition is pathognomonic of vesicoureteral reflux.

Obstruction of urine flow results in an increase in hydrostatic pressures proximal to the site of obstruction. It is this buildup of pressure that leads to the accompanying pain, the distention of the collecting system in the kidney, and elevated intratubular pressures that initiate tubular dysfunction. In the first days of obstruction, the dilatation of the poorly compliant collecting system may be minimal. As the increased hydrostatic pressure is expressed in the urinary space of the glomeruli, further filtration decreases or stops completely.

Azotemia develops when overall excretory function is impaired, often in the setting of bladder outlet obstruction, bilateral renal pelvic or ureteric obstruction, or unilateral disease in a patient with a solitary functioning kidney. Complete bilateral obstruction should be suspected when acute renal failure is accompanied by anuria. Any patient with renal failure otherwise unexplained, or with a history of nephrolithiasis, hematuria, diabetes mellitus, prostatic enlargement, pelvic surgery, trauma, or tumor should be evaluated for UTO.

In the acute setting, partial, bilateral obstruction may mimic prerenal azotemia with a high blood urea nitrogen-to-creatinine ratio, concentrated urine and sodium retention. Renal vascular resistance may be increased. However, with more prolonged obstruction, symptoms of *polyuria* and *nocturia* commonly accompany partial UTO and result from loss of medullary hypertonicity with diminished renal concentrating ability. Failure to produce urine free of salt (natriuresis) is due to downregulation of salt reabsorption in the proximal tubule and of transport proteins including the Na^+, K^+ adenosine triphosphatase (ATPase), NaK_2Cl cotransporter (NaK_2Cl) in the thick ascending limb, and the epithelial Na^+ channel (ENaC) in collecting duct cells. In addition to direct effects on renal transport mechanisms, increased prostaglandin E_2 (PGE_2) (due to induction of cyclooxygenase-2 [COX-2]), angiotensin II (with its downregulation of Na^+ transporters), and atrial or B-type natriuretic peptides (ANP or BNP) (due to volume expansion in the azotemic patient) contribute to decreased salt reabsorption along the nephron.

Dysregulation of aquaporin-2 water channels in the collecting duct contributes to the polyuria. The defect usually does not improve with administration of vasopressin and is therefore a form of acquired nephrogenic diabetes insipidus.

Wide fluctuations in urine output in a patient with azotemia should always raise the possibility of intermittent or partial UTO. If fluid intake is inadequate, severe dehydration and hypernatremia may develop. However, as with other causes of poor renal function, excesses of salt and water intake may result in edema and hyponatremia.

Partial bilateral UTO often results in *acquired distal renal tubular acidosis, hyperkalemia*, and *renal salt wasting*. The H^+-ATPase, situated on the apical membrane of the intercalated cells of the collecting duct, is critical for distal H^+ secretion. The trafficking of intracellular H^+ pumps from the cytoplasm to the cell membrane is disrupted in UTO. The decreased function of the ENaC, in the apical membrane of neighboring collecting duct principal cells, contributes to decreased Na^+ reabsorption (salt-wasting), and, therefore, decreased K^+ secretion via K^+ channels. Ammonium (NH_4^+) excretion important to the elimination of H^+ is impaired. These defects in tubule function are often accompanied by renal tubulointerstitial damage. Azotemia with hyperkalemia and metabolic acidosis should prompt consideration of UTO.

The renal interstitium becomes edematous and infiltrated with mononuclear inflammatory cells early in UTO. Later, interstitial fibrosis and atrophy of the papillae and medulla occur and precede these processes in the cortex. The increase in angiotensin II noted in UTO contributes to the inflammatory response and fibroblast accumulation through mechanisms involving profibrotic cytokines. With time, this process leads to chronic kidney damage.

UTO must always be considered in patients with urinary tract infections or urolithiasis. Urinary stasis encourages the growth of organisms. Urea-splitting bacteria are associated with magnesium ammonium phosphate (struvite) calculi that may take on a staghorn appearance. *Hypertension* is frequent in acute and subacute unilateral obstruction and is usually a consequence of increased release of renin by the involved kidney. Chronic kidney disease from bilateral UTO, often associated with extracellular volume expansion, may result in significant hypertension. *Erythrocytosis*, an infrequent complication of obstructive uropathy, is secondary to increased erythropoietin production.

TABLE 313-2 Pathophysiology of Bilateral Ureteral Obstruction

HEMODYNAMIC EFFECTS	TUBULE EFFECTS	CLINICAL FEATURES
Acute		
↑ Renal blood flow ↓ GFR ↓ Medullary blood flow ↑ Vasodilator prostaglandins, nitric oxide	↑ Ureteral and tubule pressures ↑ Reabsorption of Na^+, urea, water	Pain (capsule distention) Azotemia Oliguria or anuria
Chronic		
↓ Renal blood flow ↓↓ GFR ↑ Vasoconstrictor prostaglandins ↑ Renin-angiotensin production	↓ Medullary osmolarity ↓ Concentrating ability Structural damage; parenchymal atrophy ↓ Transport functions for Na^+, K^+, H^+	Azotemia Hypertension AVP-insensitive polyuria Natriuresis Hyperkalemic, hyperchloremic acidosis
Release of Obstruction		
Slow ↑ in GFR (variable)	↓ Tubule pressure ↑ Solute load per nephron (urea, NaCl) Natriuretic factors present	Postobstructive diuresis Potential for volume depletion and electrolyte imbalance due to losses of Na^+, K^+, PO_4^{2-}, Mg^{2+}, and water

Abbreviations: AVP, arginine vasopressin; GFR, glomerular filtration rate.

DIAGNOSIS

A history of difficulty in voiding, pain, infection, or change in urinary volume is common. Evidence for distention of the kidney or urinary bladder can often be obtained by palpation and percussion of the abdomen. A careful rectal and genital examination may reveal enlargement or nodularity of the prostate, abnormal rectal sphincter tone, or a rectal or pelvic mass.

Urinalysis may reveal hematuria, pyuria, and bacteriuria. The urine sediment is often normal, even when obstruction leads to marked

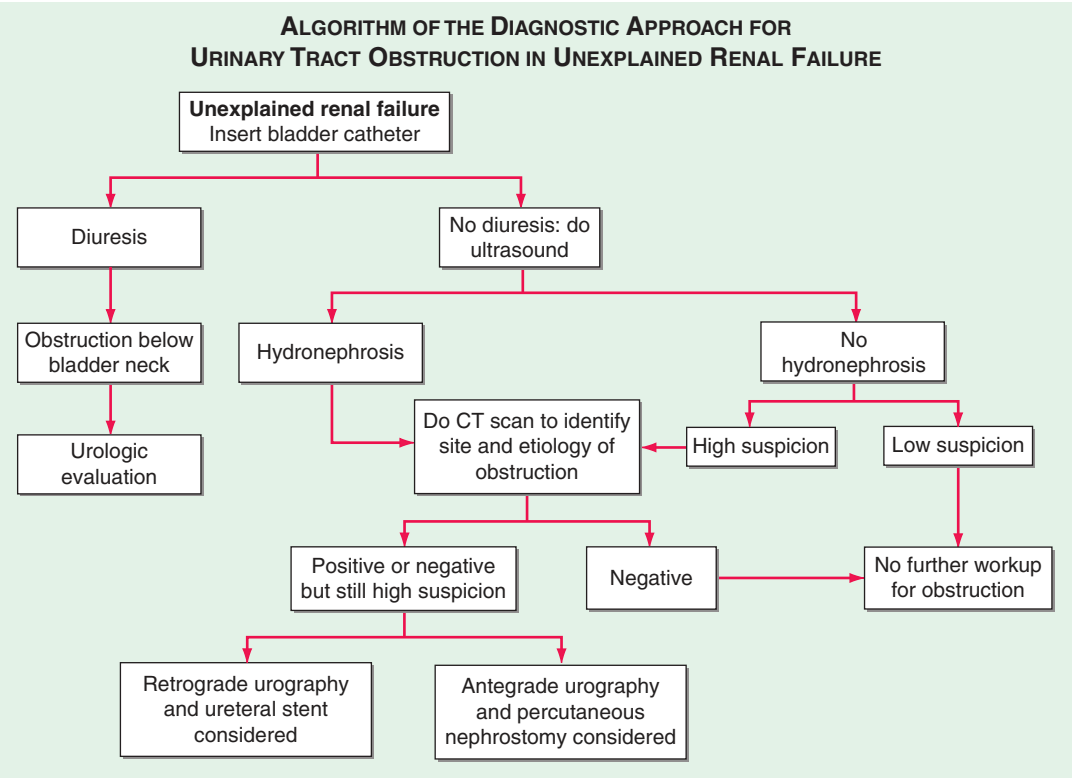

FIGURE 313-1 Diagnostic approach for urinary tract obstruction in unexplained renal failure. CT, computed tomography.

azotemia and extensive structural damage. An abdominal scout film, although insensitive, may detect nephrocalcinosis or a radiopaque stone. As indicated in Fig. 313-1, if UTO is suspected, a bladder catheter should be inserted. Abdominal ultrasonography should be performed to evaluate renal and bladder size, as well as pyelocalyceal contour. Ultrasonography is ~90% specific and sensitive for detection of hydronephrosis. False-positive results are associated with diuresis, renal cysts, or the presence of an extrarenal pelvis, a normal congenital variant. Congenital UPJ obstruction may be mistaken for renal cystic disease. Hydronephrosis may be absent on ultrasound when obstruction is less than 48 h in duration or associated with volume contraction, staghorn calculi, retroperitoneal fibrosis, or infiltrative renal disease. Duplex Doppler ultrasonography may detect an increased resistive index in urinary obstruction.

Recent advances in technology have led to alternatives and have largely replaced the once standard intravenous urogram in the further evaluation of UTO. The high-resolution multidetector row computed tomography (CT) scan in particular has advantages of visualizing the retroperitoneum, as well as identifying both intrinsic and extrinsic sites of obstruction. Noncontrast CT scans improve visualization of the urinary tract in the patient with renal impairment and are safer for patients at risk for contrast nephropathy. Magnetic resonance urography is a promising technique but, at this time, not superior to the CT scan and carries the risk of certain gadolinium agents in patients with renal insufficiency. CT scanning may define the site of obstruction, identify and characterize kidney stones, and demonstrate dilatation of the calyces, renal pelvis, and ureter above the obstruction. The ureter may be tortuous in chronic obstruction. Radionuclide scans are able to give differential renal function but give less anatomic detail than CT scans. Furosemide is sometimes given to increase detection with imaging, and to distinguish functional from anatomic obstruction. The increase in urinary flow may bring out the pain of an acute obstructive process.

To facilitate visualization of a suspected lesion in a ureter or renal pelvis, *retrograde* or *antegrade urography* should be attempted. These procedures do not carry risk of contrast-induced acute kidney injury in patients with renal insufficiency. The retrograde approach involves catheterization of the involved ureter under cystoscopic control, whereas the antegrade technique necessitates percutaneous placement of a catheter into the renal pelvis. Although the antegrade approach may provide immediate decompression of a unilateral obstructing lesion, many urologists initially attempt the retrograde approach unless the catheterization is unsuccessful.

Voiding cystourethrography is of value in the diagnosis of vesicoureteral reflux and bladder neck and urethral obstructions. Postvoiding films reveal residual urine. Endoscopic visualization by the urologist often permits precise identification of lesions involving the urethra, prostate, bladder, and ureteral orifices.

TREATMENT

Urinary Tract Obstruction

UTO complicated by infection requires immediate relief of obstruction to prevent development of generalized sepsis and progressive renal damage. Sepsis necessitates prompt urologic intervention. Drainage may be achieved by nephrostomy, ureterostomy, or ureteral, urethral, or suprapubic catheterization. Prolonged antibiotic treatment may be necessary. Chronic or recurrent infections in a poorly functioning obstructed kidney may necessitate nephrectomy. When infection is not present, surgery is often delayed until acid-base, fluid, and electrolyte status is restored. Nevertheless, the site of obstruction should be ascertained as soon as feasible. Elective relief of obstruction is usually recommended in patients with urinary retention, recurrent urinary tract infections, persistent pain, or progressive loss of renal function. Benign prostatic hypertrophy may be treated medically with α-adrenergic blockers and 5α-reductase inhibitors. Renal colic may be treated with anti-inflammatory medication as edema often contributes to an obstructing ureteral stone, and α-adrenergic blockers may also be of benefit. Use of opiates in patients with decreased renal function may be dangerous and should be used with caution. Functional obstruction secondary to neurogenic bladder may be decreased with the combination of frequent voiding and cholinergic drugs.

PROGNOSIS

With relief of obstruction, the prognosis regarding return of renal function depends largely on whether irreversible renal damage has occurred. When obstruction is not relieved, the course will depend mainly on whether the obstruction is complete or incomplete and bilateral or unilateral, as well as whether or not urinary tract infection is also present. Complete obstruction with infection can lead to total destruction of the kidney within days. Partial return of glomerular filtration rate may follow relief of complete obstruction of 1 and 2 weeks' duration, but after 8 weeks of obstruction, recovery is unlikely. In the absence of definitive evidence of irreversibility, every effort should be made to decompress the obstruction in the hope of restoring renal function at least partially. A renal radionuclide scan, performed after a prolonged period of decompression, may be used to predict the reversibility of renal dysfunction.

POSTOBSTRUCTIVE DIURESIS

Relief of bilateral, but not unilateral, complete obstruction commonly results in polyuria, which may be massive. The urine is usually hypotonic and may contain large amounts of sodium chloride, potassium, phosphate, and magnesium. The natriuresis is due in part to the correction of extracellular volume expansion, the increase in natriuretic factors accumulated during the period of renal failure, and depressed salt and water reabsorption when urine flow is reestablished. The retained urea is excreted with improved GFR, resulting in an osmotic diuresis which increases the urine volume of electrolyte-free water. The urinary concentrations of sodium and potassium that when added are less than the serum sodium is evidence of electrolyte free-water excretion. In the majority of patients, this diuresis results in the *appropriate* excretion of the excesses of retained salt and water. When extracellular volume and composition return to normal, the diuresis usually abates spontaneously. Occasionally, iatrogenic expansion of extracellular volume is responsible for, or sustains, the diuresis observed in the postobstructive period. Replacement with intravenous fluids in amounts less than urinary losses usually prevents this complication. More aggressive fluid management is required in the setting of hypovolemia, hypotension, or disturbances in serum electrolyte concentrations.

The loss of electrolyte-free water with urea may result in hypernatremia. Measured urinary output and serum and urine sodium, potassium and osmolal concentrations should guide the use of appropriate intravenous replacement. Often replacement with 0.45% saline is required. Relief of obstruction may be followed by urinary salt and water losses severe enough to provoke profound dehydration and vascular collapse. In these patients, decreased tubule reabsorptive capacity is probably responsible for the marked diuresis. Appropriate therapy in such patients includes intravenous administration of salt-containing solutions to replace sodium and volume deficits.

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Section 1 Disorders of the Alimentary Tract

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ANATOMIC CONSIDERATIONS

The gastrointestinal (GI) tract extends from the mouth to the anus and is composed of several organs with distinct functions. Specialized sphincters that assist in gut compartmentalization separate the organs. The gut wall is organized into distinct layers that contribute to regional activities. The mucosa is a barrier to luminal contents or a site for fluid and nutrient transfer. Gut smooth muscle in association with the enteric nervous system mediates propulsion from one region to the next. Many GI organs possess a serosal layer that provides a supportive foundation and permits external input.

Interactions with other systems serve the needs of the gut and the body. Pancreaticobiliary conduits deliver bile and enzymes into the duodenum. The vascular supply is modulated by GI activity. Lymphatic channels assist in gut immune activities. Intrinsic nerves provide the controls for propulsion and fluid regulation. Extrinsic neural input provides volitional or involuntary control that is specific for each gut region.

FUNCTIONS OF THE GI TRACT

The GI tract serves two main functions—assimilating nutrients and eliminating waste. In the mouth, food is processed, mixed with salivary amylase, and delivered to the gut lumen. The esophagus propels the bolus into the stomach; the lower esophageal sphincter prevents oral reflux of gastric contents. The squamous esophageal mucosa protects against significant diffusion or absorption. Aboral esophageal contractions coordinate with relaxation of the upper and lower esophageal sphincters on swallowing.

The stomach triturates and mixes the food bolus with pepsin and acid. Gastric acid also sterilizes the upper gut. The proximal stomach serves a storage function by relaxing to accommodate the meal. Phasic contractions in the distal stomach propel food residue against the pylorus, where it is ground and thrust proximally for further mixing before it is emptied into the duodenum. The stomach secretes intrinsic factor for vitamin B_{12} absorption.

Most nutrient absorption occurs in the small intestine. The intestinal mucosal villus architecture provides maximal surface area for absorption and is endowed with specialized enzymes and transporters. Triturated food from the stomach mixes with pancreatic juice and bile in the duodenum. Pancreatic juice contains enzymes for carbohydrate, protein, and fat digestion as well as bicarbonate to optimize the pH for enzyme activation. Bile secreted by the liver and stored in the gallbladder is essential for lipid digestion. The proximal intestine is optimized for rapid absorption of most nutrients and minerals, whereas the ileum is better suited for absorbing vitamin B_{12} and bile acids. Bile contains by-products of erythrocyte degradation, toxins, medications, and cholesterol for fecal evacuation. Small intestinal motor function delivers indigestible residue into the colon for processing. The ileocecal junction is a sphincteric structure that prevents coloileal reflux, maintaining small-intestinal sterility.

The colon prepares waste for evacuation. The colonic mucosa dehydrates the stool, decreasing daily volumes of 1000–1500 mL in the ileum to 100–200 mL expelled from the rectum. The colon possesses a dense bacterial colonization that ferments undigested carbohydrates and short-chain fatty acids. Additional roles for the gut microbiome include modulation of immune and physiologic activity. Transit in the esophagus takes seconds and times in the stomach and small intestine range from minutes to a few hours, but colon propagation requires more than 1 day in most individuals. Colon contractions exhibit a to-and-fro character that promotes fecal desiccation. The proximal colon mixes and absorbs fluid, while the distal colon exhibits peristaltic contractions and mass movements to expel the stool. The colon terminates in the anus, which possesses volitional and involuntary controls to permit fecal retention until it can be released in a convenient setting.

EXTRINSIC MODULATION OF GUT FUNCTION

GI function is modified by influences outside the gut. Unlike other organs, the gut is in continuity with the outside environment. Protective mechanisms are vigilant against damage from foods, medications, toxins, and infectious organisms. Mucosal immune mechanisms include epithelial and lamina propria lymphocyte and plasma cell populations supported by lymph node chains to prevent noxious agents from entering the circulation. Antimicrobial peptides secreted by intestinal Paneth cells also defend against luminal pathogens. All drugs and toxins absorbed into the bloodstream are filtered and detoxified in the liver via the portal venous circulation. Although intrinsic nerves control most basic gut activities, extrinsic neural input modulates many functions. Many GI reflexes involve extrinsic vagus or splanchnic nerve pathways. The brain-gut axis alters function in regions not under volitional regulation. As an example, stress has potent effects on gut motor, secretory, and sensory functions.

OVERVIEW OF GI DISEASES

GI diseases develop as a result of abnormalities within or outside of the gut and range in severity from those that produce mild symptoms and no long-term morbidity to those with intractable symptoms or adverse outcomes. Diseases may be localized to one organ or exhibit diffuse involvement at many sites.

CLASSIFICATION OF GI DISEASES

GI diseases are manifestations of alterations in nutrient assimilation or waste evacuation or in the activities supporting these main functions.

Impaired Digestion and Absorption Diseases of the stomach, intestine, biliary tree, and pancreas can disrupt digestion and absorption. The most common intestinal maldigestion syndrome, lactase deficiency, produces gas and diarrhea after ingestion of dairy products and has no adverse outcomes. Other intestinal enzyme deficiencies produce similar symptoms after ingestion of other simple sugars. Conversely, celiac disease, bacterial overgrowth, infectious enteritis, Crohn's ileitis, and radiation damage, which affect digestion and/or absorption more diffusely, produce anemia, dehydration, electrolyte disorders, or malnutrition. Gastric hypersecretory conditions such as Zollinger-Ellison syndrome damage the intestinal mucosa, impair pancreatic enzyme activation, and accelerate transit due to excess gastric acid. Biliary obstruction from stricture or neoplasm impairs fat digestion. Impaired pancreatic enzyme release in chronic pancreatitis or pancreatic cancer decreases intraluminal digestion and can lead to malnutrition.

Altered Secretion Selected GI diseases result from dysregulation of gut secretion. Gastric acid hypersecretion occurs in Zollinger-Ellison syndrome, G cell hyperplasia, retained antrum syndrome, and some individuals with duodenal ulcers. Conversely, patients with atrophic gastritis or pernicious anemia release little or no gastric acid. Inflammatory and infectious small-intestinal and colonic diseases produce fluid loss through impaired absorption or enhanced secretion. Common intestinal and colonic hypersecretory conditions cause diarrhea and include acute bacterial or viral infection, chronic *Giardia* or cryptosporidia infections, small-intestinal bacterial overgrowth, bile salt diarrhea,